Studies towards the Total Synthesis of Limnophilaspiroketone and the Synthesis of α-Modified Enones of Natural Product Derived Model Compound Limno-CP

Dissertation

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Simon Lindner
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Diese Arbeit wurde angeleitet von: Dr. Sabine Amslinger

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Prüfungsausschuss:
Prof. Dr. O. Reiser
Prof. Dr. B. König
Prof. Dr. J. Heilmann
Prof. Dr. A. Buschauer (Vorsitz)

Meiner lieben Familie

CONTENTS

ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetonate
AQN	Anthraquinone
ARE	Antioxidant-response element
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
*i*Bu	*iso*-Butyl
*n*Bu	*n*-Butyl
*t*Bu	*tert*-Butyl
Bz	Benzoyl
COX-2	Cyclooxygenase-2
Cul3	Cullin 3
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DHQ	Hydroquinine
DHQD	Hydroquinidine
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DTT	Dithiothreitol
EDC	1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDTA	Ethylenediaminetetraacetic acid
ERK	Extracellular-signal-regulated kinase
Et	Ethyl
EtOH	Ethanol
GCL	Glutamate cysteine ligase

Glu	Glucose
GPx	Glutathione peroxidase
GSH	Glutathione
GST	Glutathione transferase
Hex	Hexyl
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HO-1	Heme oxygenase-1
ICAM-1	Intercellular adhesion molecule-1
IκB	Inhibitor of κB
IKK	IκB kinase
IL	Interleukin
iNOS	Inducible NO synthase
IR	Infrared
JNK	c-Jun NH_2-terminal kinase
Keap1	Kelch-like ECH-associated protein 1
LDA	Lithium diisopropylamide
MAPK	Mitogen-activated protein kinase
*m*CPBA	*meta*-Chloroperoxy benzoic acid
MeCN	Acetonitrile
Me	Methyl
MeOH	Methanol
MOM	Methoxymethyl
µw	Microwave
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NF-κB	Nuclear factor-kappa B
NFSI	*N*-Fluorobenzenesulfonimide
NIS	*N*-Iodosuccinimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NQO1	NAD(P)H:quinone oxidoreductase 1
Nrf2	Nuclear factor-erythroid-2-related factor 2

Nu	Nucleophile
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PHN	Phenanthryl
PI3K	Phosphatidylinositol 3-kinase
PKC	Protein kinase C
PPTS	Pyridinium *para*-toluenesulfonate
Pr	Propyl
*i*Pr	*iso*-Propyl
*n*Pr	*n*-Propyl
Py	Pyridine
RNA	Ribonucleic acid
mRNA	Messenger ribonucleic acid
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TfOH	Trifluoromethanesulfonic acid, Triflic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethyl-ethane-1,2-diamine
TMS	Trimethylsilyl
TNF-α	Tumor necrosis factor-α
*p*TsOH	*para*-Toluenesulfonic acid
Ub	Ubiquitin
UGT	UDP-glucuronosyl transferase

1. INTRODUCTION

1.1. α,β-Unsaturated carbonyl compounds and inflammation

Natural products with an α,β-unsaturated carbonyl substructure are ubiquitous in nature. In the wide world of plants many dietary phytochemicals possess α,β-unsaturated carbonyl substructures – such compounds are commonly referred to as Michael acceptors.

From the first endeavors to reduce the global burden of cancer, they have been in the spot light of research. Basically, strong oxidants such as hydroxyl radical, lipid peroxidation derivatives or peroxynitrous acid can cause DNA damage resulting in mutagenesis and tumor formation. Michael acceptors are capable of trapping those radicals directly or inducing anti-oxidant enzymes. Therefore, they are reported to retain chemopreventive potential and to exhibit chemoprotective properties.[1]

Besides their role in carcinogenesis, α,β-unsaturated compounds have also been closely related to the pathogenesis of inflammation-associated disorders.[2] Many mechanisms have been discussed to account for their ability to intervene in the multistage process of inflammation, but the analysis of inflammation-associated signal-transduction pathways has revealed intracellular signaling cascades to be a common molecular target for anti-inflammatory phytochemicals. However, numerous events are involved in relaying intracellular signals, and their highly sophisticated interplay is the prerequisite for the fine-tuning of cellular homeostasis. Abnormal stimulation or silencing of upstream signal transducers can result in pathogenic processes. In order to restore normal signaling mechanisms or to prevent malignant processes, phytochemicals can act as modifiers of signal transduction pathways to elicit their beneficial effects.

In this regard, two major redox-sensitive transcription factors, nuclear factor-kappa B (NF-κB) and nuclear factor-erythroid-2-related factor 2 (Nrf2), have been discussed as the most frequently addressed target molecules.[3] Hence, modulating the function of these transcription factors can prevent such malignant aberration and potentiate detoxification processes and cellular anti-oxidative defense mechanisms.

Oxidative stress is closely linked to inflammation – a state in which a greater amount of oxidants is produced than can be scavenged. Under physiological conditions a certain oxidant production is normal, and efficient scavenging mechanisms are available. However, if these mechanisms break down or if they are overwhelmed by excess of oxidants, the cellular antioxidant capacity is insufficient turning into inflammatory processes. Most important oxidants include reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as superoxide anion, hydroxyl radical, nitric oxide, peroxynitrous acid, lipid peroxyl and alkoxyl radicals, but also α-oxo-aldehydes and 4-hydroxyalkenals.

Generation of oxidative stress is the predominant trigger for the activation of NF-κB, which in turn upregulates pro-inflammatory gene expression.[4] NF-κB, classically a heterodimer of p65 and p50 proteins, represents a prominent transcription factor, which is ubiquitous in eucaryotic cells and plays a pivotal role mediating pleiotropic effects of various external and internal stimuli.[5] It plays a central role in general inflammatory as well as immune responses. Normally, NF-κB is kept inactive in the cytoplasm by binding to the inhibitor IκBα (Figure 1). IκBα itself is controlled by a family of mitogen-activated protein kinases (MAPKs) such as IκB kinase (IKK), extracellular-signal-regulated kinase 1/2 (ERK1/2) or p38, which activate the dimeric complex by phosphorylation of serine residues on IκBα. Subsequent ubiquitination and degradation of IκBα by the 26S proteasome liberates NF-κB, which then translocates to the nucleus where it binds to specific promoter regions of the DNA. Subsequently, the transcription of pro-inflammatory genes is activated encoding enzymes such as inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2), various cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1). Thus, an aberrant overexpression of NF-κB is closely related to inflammation-associated processes.

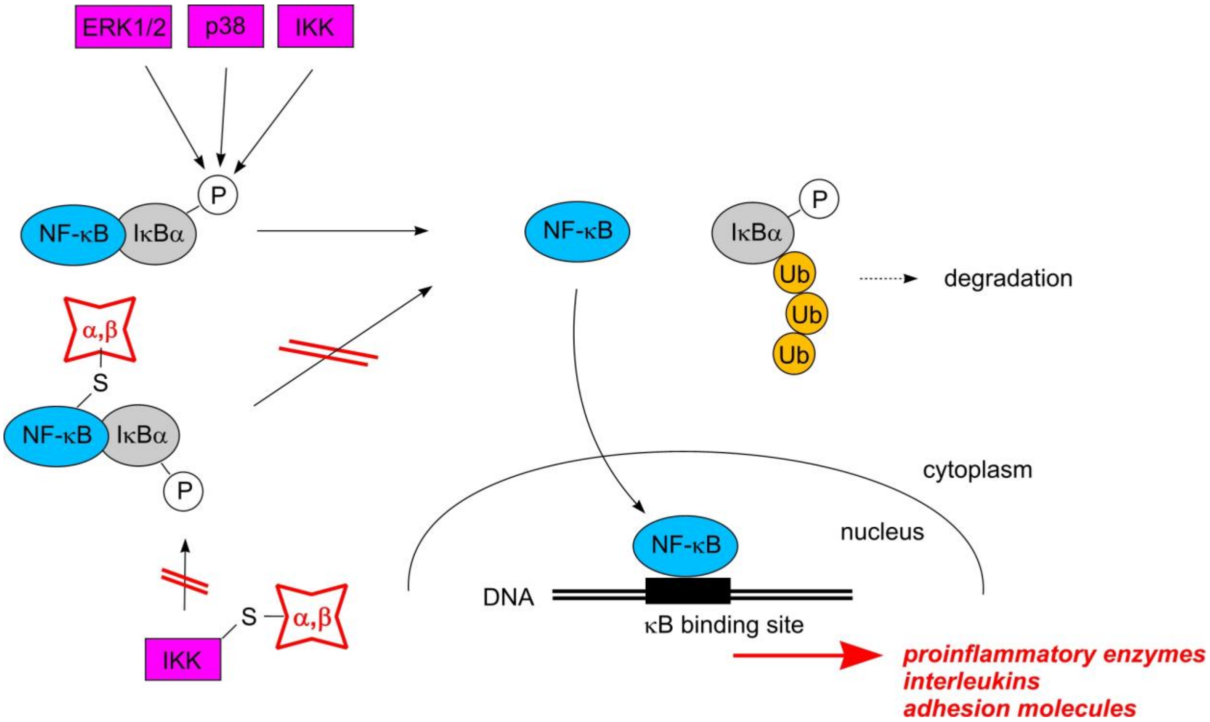


Figure 1: Expression of pro-inflammatory compounds through NF-κB activation

Cellular protection against oxidative toxicities is mediated by the Keap1/Nrf2/ARE pathway. The transcription factor Nrf2 plays a crucial role in the regulation of the genes of detoxifying or antioxidant proteins.[6] Transcriptional induction leads to the expression of several cytoprotective proteins, also known as phase 2 enzymes. Classically, they catalyze the conjugation of activated xenobiotics to increase their solubility and facilitate their excretion. But in a broader sense, other functionally diverse proteins can be included, which all commonly result in cytoprotection against electrophiles and oxidants. Amongst them, glutathione transferase (GST) and glutathione peroxidase (GPx) are the most prominent examples since the most abundant electron-donor glutathione (GSH) is used as substrate for the conjugation with 4-hydroxyalkenal and toxic products of lipid peroxidation in the case of GST and for the scavenging of peroxides in the case of GPx. Glutamate cysteine ligase (GCL) catalyzes the synthesis of GSH, and heme oxygenase-1 (HO-1) generates carbon monoxide and biliverdin/bilirubin, which are also important direct antioxidants. Further members of the group of functionally diverse phase 2 enzymes, which are regulated by Nrf2, are UDP-glucuronosyl transferase (UGT), NAD(P)H:quinone oxidoreductase-1 (NQO1), ferritin and thioredoxin.

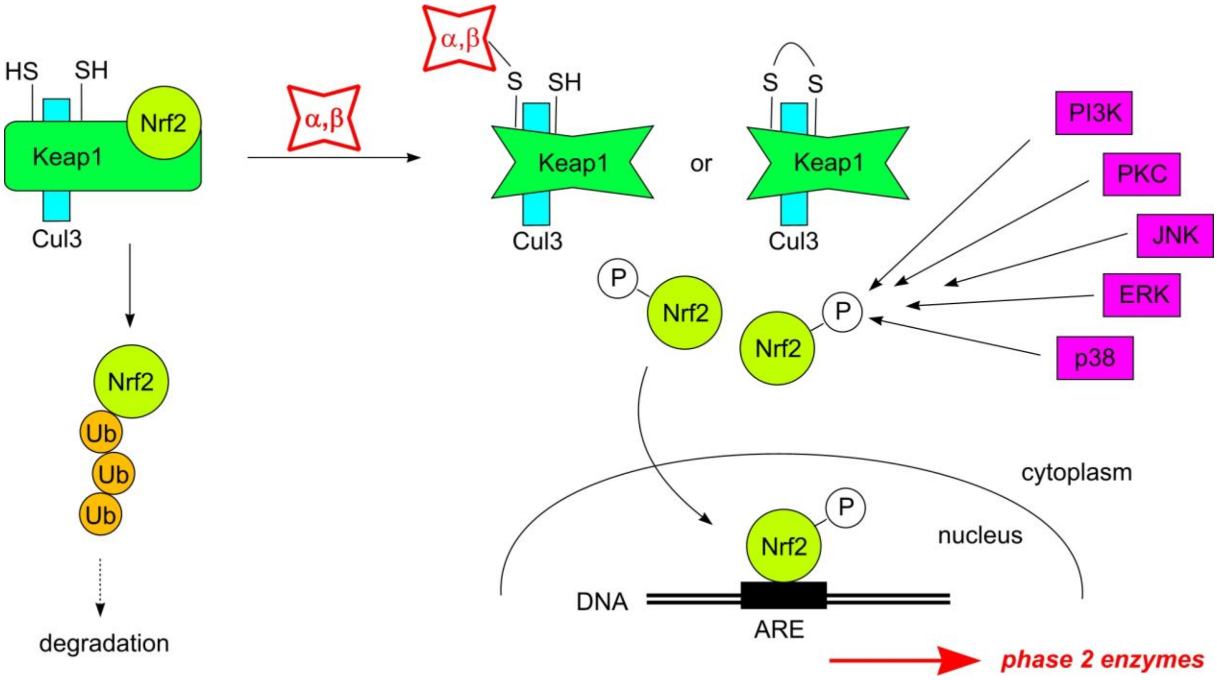


Figure 2: Induction of phase 2 enzymes through Nrf2 activation

The induction of phase 2 enzymes proceeds via a common molecular mechanism (Figure 2). In resting cells Nrf2 is sequestered in the cytoplasm forming a complex with the repressor Kelch-like ECH-associated protein 1 (Keap1). Keap1 is a zinc metalloprotein, which is anchored to the actin cytosceleton. Associated with Cullin 3 (Cul3) it binds Nrf2 tightly presenting it for ubiquitination and proteosomal degradation. Covalent modification or oxidation of highly reactive cysteine residues of Keap1, which serve as critical sensors for inducers, results in conformational changes diminishing the affinity of Keap1 for Nrf2.[7] Phosphorylation of Nrf2 by protein kinases such as phosphatidylinositol 3-kinase (PI3K), protein kinase C (PKC), c-Jun NH_2-terminal kinase (JNK), extracellular-signal-regulated kinase (ERK) or p38 are believed to facilitate the dissociation of the complex. Nrf2 is released and migrates to the nucleus where it binds as heterodimeric complex with small MAF transcription factors to the antioxidant-response element (ARE) of the DNA to stimulate gene expression.[8]

α,β-unsaturated carbonyl compounds are potential reaction partners for nucleophiles, which add to the electrophilic β-carbon of the unsaturated system. For that reason, they can act as potent inducing agents as they can form Michael adducts with critical cysteine residues, which are located at the periphery of Keap1 leading to the release of Nrf2 and subsequent induction of anti-inflammatory and cytoprotective phase 2 enzymes (Figure 2). Additionally, modification of cysteine residues at the p50 subunit of NF-κB by α,β-unsaturated compounds can stabilize the NF-κB-IκBα complex, which prevents the dissociation and translocation of NF-κB to the nucleus (Figure 1). Moreover, IKK can also be targeted abrogating phosphorylation of IκBα. Suppression of NF-κB mediated induction of pro-inflammatory genes is therefore another effective pathway for chemopreventive phytochemicals.

Furthermore, in combination with phenol substituents α,β-unsaturated compounds do not only have Michael acceptor activity, they also have significant relevance as antioxidants. The antioxidant activity can be attributed to excellent radical scavenging properties of phenolic Michael systems. They can undergo oxidation either enzymatically or spontaneously to form phenoxyl radicals and quinones, which are again electrophilic Michael systems. Quinone derivatives can in turn oxidize sulfhydryl groups of Keap1 leading to disulfide bond formation and subsequent oxidative activation of the Keap1-Nrf2 complex. Formation of disulfide bridges can also be mediated by ROS, which are formed upon reduction of quinones via redox-cycling. In the aforementioned cases the phenol moiety rather participates in the interaction with the cysteine residues than the Michael system.

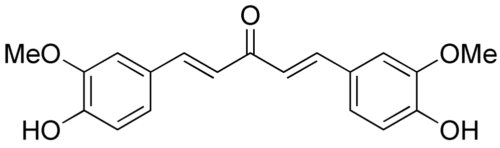
Consequently, phenolic Michael acceptors can be referred to as indirect antioxidants as they can promote the upregulation of cytoprotective enzymes resulting in antioxidative effects. Being redox active themselves, phenolic Michael acceptors can also be considered as potent direct antioxidants. Due to this dual protective role, phenolic Michael acceptors can be designated as bifunctional antioxidants.[9]

Multiple beneficial effects are closely related to the structural features of α,β-unsaturated compounds. Phytochemicals containing phenolic Michael acceptors are very attractive for their use as anti-inflammatory agents. Modulation of the activity of transcription factors provides a unique strategy and a promising novel therapeutic approach for the treatment or prevention of inflammatory disorders.

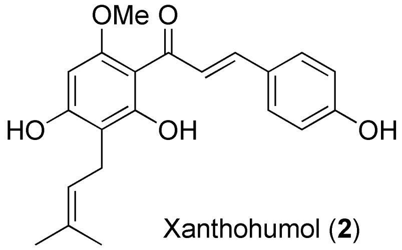
1.2. Examples of α,β-unsaturated phytochemicals for therapeutic applications

Extracts of plants are widely used in the traditional medicine of various cultures for their beneficial effects in the prevention and therapy of cancer and inflammatory disorders. Hence, numerous in-vitro assays and in-vivo studies have been performed to identify their biologically active ingredients and to investigate their molecular mode of action. Some representative examples of α,β-unsaturated phytochemicals are given (Figure 3).

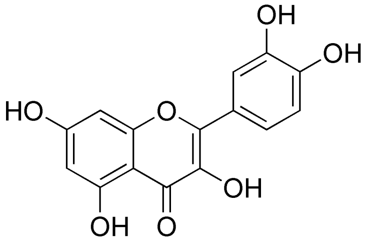
Curcumin, the yellow ingredient from turmeric (*Curcuma longa* L.), has been extensively used for the examination of its therapeutic potential. Curcumin has been reported to react with NF-κB directly via thiol modification and to inhibit its activation by interfering with IκBα degradation.[10] The blockade of IκB degradation is a frequently addressed approach to attenuate NF-κB activation.[11-16] Extraction of the total RNA of liver and small intestine of mice, which were given a single dose of curcumin, revealed a great number of induced genes, which were identified to be Nrf2-dependant.[17] In addition, high levels of Nrf2 and increased expression of GST and NQO1 was observed in benzo[*a*]pyrene-treated mice.[18] The up-regulation of the phase 2 enzyme HO-1 through Nrf2 activation was found in different types of cultured cells [19-23] and in liver.[24] Furthermore, enhanced expression of GST P1 mRNA[25] and GCL on mRNA and protein level[26] was reported. Various studies with curcumin analogues such as demethoxy- and bis-demethoxycurcumin have also been performed.[27,28] To date, several clinical trials are on-going using curcumin as drug or dietary supplement for the treatment of various cancer types, ulcerative colitis, osteoarthritis or Alzheimer’s disease.



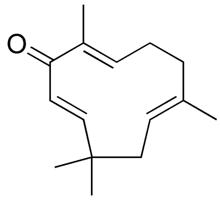
Curcumin (**1**)



Xanthohumol (**2**)



Quercetin (**3**)



Zerumbone (**4**)

Figure 3: Biologically active phytochemicals with an α,β-unsaturated carbonyl substructure

Chalcones have shown to be excellent anti-inflammatory and antioxidant compounds providing a broad structural diversity. Xanthohumol, a prenylchalcone derived from hops (*Humulus lupulus* L.), is just one out of many different chalcone derivatives. It exhibits potent chemopreventive activity by Nrf2 mediated induction of NQO1.[29] It was also reported to modify cysteine residues of IKK and NF-κB, which leads to the suppression of the NF-κB activation pathway (Figure 1).[30]

Quercetin, a member of the flavonoid family, proved to protect cells from oxidative stress-induced death with high efficacy. The up-regulation of Nrf2 and enhanced expression of HO-1 was observed.[31] HO-1 up-regulation was also reported to protect human hepatocytes from ethanol-induced oxidative stress.[32] An increased Nrf2 mRNA and protein level as well as inhibited ubiquitination and proteosomal degradation of Nrf2 was found resulting in an enhanced NQO1 activity.[33]

Zerumbone is a sesquiterpene compound present in tropical ginger (*Zingiber zerumbet* Smith). In presence of several proinflammatory stimuli, zerumbone effectively suppresses NF-κB-IKK signaling by attenuating IκB degradation in RAW264.7 murine macrophages.[34] It is also a potent inducer for phase 2 enzymes such as GCL, GPx and HO-1 in rat liver epithelial cells via the Nrf2-pathway[35] and abolishes NF-κB and IKK activation induced by various stimuli.[36]

1.3. Fine tuning the Michael acceptor activity

The beneficial effects of many Michael acceptors on inflammatory disorders are undisputable. However, other concerns such as cytotoxicity have to be taken into account if α,β-unsaturated compounds are supposed to be implemented in therapeutic applications and drug discovery. Since nature uses many different nucleophiles to trigger biological effects, other off-target pathways may be equally affected leading to cell damage and cytotoxic side effects. With respect to such severe consequences α,β-unsaturated compounds have always been controversial in drug development. Thus, tailormade compounds are needed to gain enhanced Michael acceptor specificity.[37]

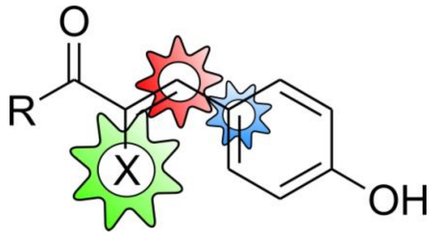


Figure 4: Introduction of substituents X in α-position of the α,β-unsaturated carbonyl substructure enables the fine tuning of its reactivity

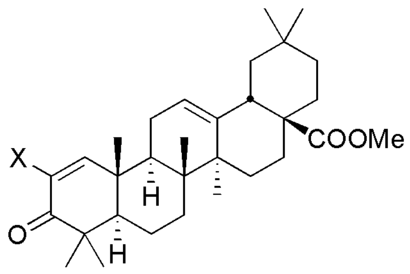
This can be achieved by fine tuning the reactivity of the α,β-unsaturated carbonyl unit. However, effective control of the chemical behavior of the enone entity affords an acurate analysis of its underlying reactivity. Several experimental and theoretical studies revealed intriguing correlations between the physicochemical properties of the enone substructure and the observed reactivity. Measurement of ^{13}C NMR chemical shifts of the β-carbon of a series of drug-like molecules was used to determine the electrophilicity of the reactive center.[38] Together with biological testing the results allowed the compounds to be classified as Michael acceptors, redoxactive or photoisomerizable substrates. Increased electrophilicity favored the Michael addition pathway, whereas decreased electrophilicity favored photoisomerization processes. In a model system with prostaglandines the proposed Michael addition reactivities, which were based on ^{13}C NMR studies, could be confirmed by calculated LUMO coefficients and net atom charges.[39] An interesting study showed that the tendency of 30 plant phenylpropenoids and synthetic analogues to release electrons linearly correlates with the potency to induce NAD(P)H:quinone oxidoreductase-1 (NQO1).[40] The electron-releasing power was expressed by calculated E_{HOMO} values. It was found that a smaller E_{HOMO} value, meaning a lower reduction potential, results in a greater inducer potency. E_{HOMO} and E_{LUMO} values were also used to establish structure-activity relationships with synthetic chalcones.[41]

Compounds with high E_{HOMO} values proved to be better electron donors and effective radical scavengers.

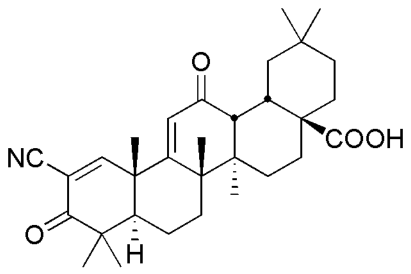
These examples show that NMR spectroscopic analyses and in silico methods can serve as powerful tools to predict the reactivity of α,β-unsaturated carbonyl compounds with respect to their anti-inflammatory, antioxidant or radical scavenging properties, and facilitate the rational design of biologically active molecules.

The reactivity of the enone substructure is predominantly determined by the substitution pattern of the carbon-carbon double bond. Pharmaceutically active natural products often exhibit phenolic substituents on the β-carbon such as in chalcones or flavonoids. Substitution at the α-position, however, is not frequently observed. Nevertheless, the introduction of different substituents X at the α-position of an α,β-unsaturated compound should also have a strong influence on the reactivity of the Michael acceptor (Figure 4). Depending on the nature of the substituent X, the electronic properties of the enone system can be adjusted. In that way, enones could be directed to display specific reactivities such as Michael addition or radical scavenging. This concept opens up the possibility to create a library of variable Michael acceptors with fine tuned activity as a versatile tool to control biological function.

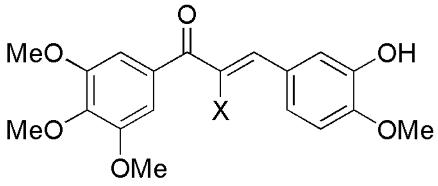
In the literature this approach has not been explored extensively. A few examples indicate that variation of the substituents in α-position of α,β-unsaturated compounds can have a strong impact on biological activity of the examined compounds (Figure 5). Honda et al. showed that stepwise introduction of substituents in oleanane triterpenoids **5-10** resulted in changes of biological activity.[42] Compounds were screened for inhibition of NO-production induced by interferon-γ in mouse macrophages. In particular, the α-cyano-substituted derivative **7** proved to exhibit high potency, which could be even augmented by a further semisynthetic triterpenoid derived from oleanolic acid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (**11**). The conjugate nucleophilic addition to one of the Michael systems was found to proceed selectively and reversibly using dithiothreitol (DTT).[43] In another example Lawrence et al. described the effect of different α-substituents on the biological activity of chalcones **12-14** exhibiting antimitotic properties caused by inhibition of tubulin polymerization. A high potency of the fluoro-derivative **12** in contrast to the ethyl ester **14** or nitrile substituted compound **13** was observed.[44]



X = Cl **5** COOH **8**
Br **6** COOMe **9**
CN **7** CONH$_2$ **10**



CDDO (**11**)

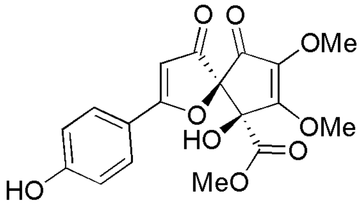


X = F **12**
CN **13**
COOEt **14**

Figure 5: Literature precedents of α-substituted enones to increase biological activity

1.4. Limnophilaspiroketone as a point for inspiration

In this study a natural product, called limnophilaspiroketone (**15**), served as starting point for subsequent investigations (Figure 6).



Limnophilaspiroketone (**15**)

Figure 6: Natural product limnophilaspiroketone (**15**)

Limnophilaspiroketone (**15**) was isolated from aerial parts of *Limnophila geoffrayi* Bon. (Scrophulariaceae) collected in Thailand (Figure 7). This edible plant is considered as a vegetable in northeastern parts of Thailand and is also used as an antidote for the detoxification of poisons.[45] Moreover, it is applied for its antipyretic, expectorant and galactogogue properties in the local traditional medicine. Interestingly, limnophilaspiroketone was isolated as a racemate although racemic natural products are rarely observed.

Figure 7: Pictures of *Limnophila geoffrayi* Bon.

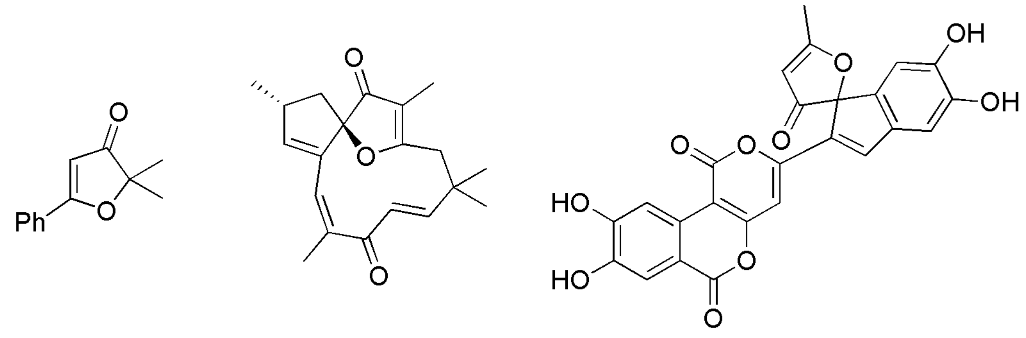
Until now no report on its biological activity is available. But, due to its structural features, limnophilaspiroketone represents an attractive molecule for the investigation of its prospective biological activity. Containing two orthogonal α,β-unsaturated carbonyl moieties and a phenolic substituent, this natural product is an interesting compound in terms of potential Michael acceptor and antioxidant activity. Moreover, there is no substituent in α-position of the α,β-unsaturated carbonyl unit in the 3(2*H*)-furanone part of the molecule. In case biological activity can be explored, further derivatization on the α-carbon is possible, which allows for the fine tuning of the reactivity of the enone subunit and the successive refinement of biological activity.

1.5. Natural products with a 3(2*H*)-furanone moiety

3(2*H*)-Furanones represent an important subgroup of α,β-unsaturated compounds. A great number of natural products contain this structural entity and display interesting properties in terms of biological activity. A few selected examples are presented herein.

The first example of naturally occurring 3(2*H*)-furanone was bullatenone (**16**), isolated from *Myrtus bullata* Banks & Sol. in 1954 by Brandt (Figure 8).[46] However, the structure was not assigned correctly until 1958 when Parker et al. revised its previously assumed structure and also accomplished its total synthesis.[47]

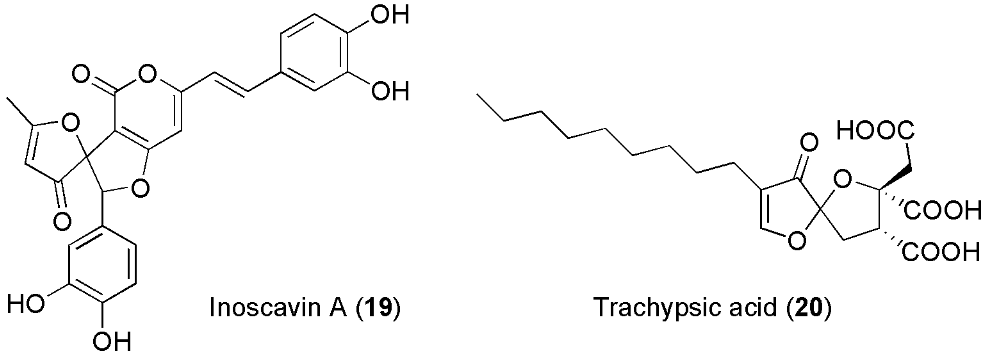
The 1-oxaspiro[4.4]non-2-ene-4-one motif, which is also present in limnophilaspiroketone (**15**), can be found in jatrophone (**17**), a macrocyclic tumor inhibitor from *Jatropha gossypiifolia* L.[48] Synthetic access to this natural product was provided by Smith III[49] and Hegedus.[50] The first asymmetric synthesis of optically active (+)-jatrophone was done in the Wiemer group.[51] Other important natural products with similar spirocyclic core structures can be found in the family of phelligridins, for instance phelligridin E (**18**), which was isolated from ethanolic extracts of *Phellinus igniarius* Quél.[52]



Bullatenone (**16**) Jatrophone (**17**) Phelligridin E (**18**)

Figure 8: Bullatenone (**16**) and naturally occurring spirocyclic 3(2*H*)-furanones

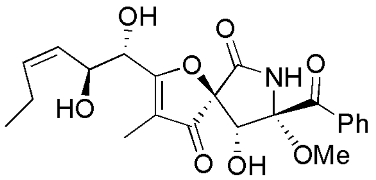
Another 3(2*H*)-furanone of this class, inoscavin A (**19**), contains a spirocyclic core structure with a furan heterocycle (Figure 9). The same framework is present in trachypsic acid (**20**), a metabolite produced by *Talaromyces trachyspermus* SANK 12191 (Shear) Stolk & Samson that inhibits tumor cell heparase.[53]



Inoscavin A (**19**) Trachypsic acid (**20**)

Figure 9: Spirocyclic 3(2*H*)-furanones with a furan unit

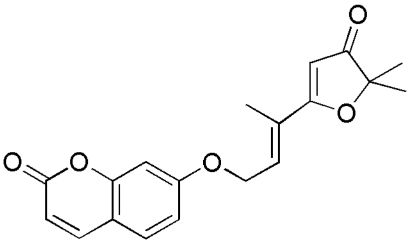
Pseurotins are a class of natural products with a 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione unit (Figure 10). A γ-lactam is attached at the spiro-carbon of the 3(2*H*)-furanone. Pseurotin A (**21**), isolated from the fermentation broth of *Pseudeurotium ovalis* Stolk,[54,55] has shown apomorphin-antagonistic activity,[56] chitin synthase[57] and monoamine oxidase inhibitory activity,[58] cell differentiation inducing activity[59] as well as inhibitory effect on immunoglobuline E production.[60] Due to the densely functionalized core structure of pseurotin A, its total synthesis posed significant challenges. It was achieved by Hayashi[61] and by Tadano[62] almost simultaneously.



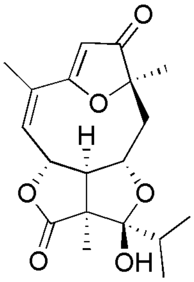
Pseurotin A (**21**)

Figure 10: Spirocyclic 3(2*H*)-furanone with a lactam unit

Apart from the previous mentioned 3(2*H*)-furanones, a broad variety of other compounds are known. Geiparvarin (**22**) for instance, isolated from the leaves of *Geijera parviflora* Lindl., was first synthesized by Jerris and Smith.[63] Besides the 3(2*H*)-furanone entity it contains a coumarin fragment and displays significant anti-tumor activity (Figure 11). Eremantholides such as eremantholide A (**23**) from *Eremanthus elaeagnus* Schultz-Bip. are germacranolide sesquiterpene lactones with a 3(2*H*)-furanone moiety as part of a complex polycyclic ring system.[64] The trypanocidal,[65] anti-inflammatory[66] and anti-tumor[67] activity of these natural products have prompted many researchers to complete total syntheses of eremantholide A (**23**).[68-70]



Geiparvarin (**22**)

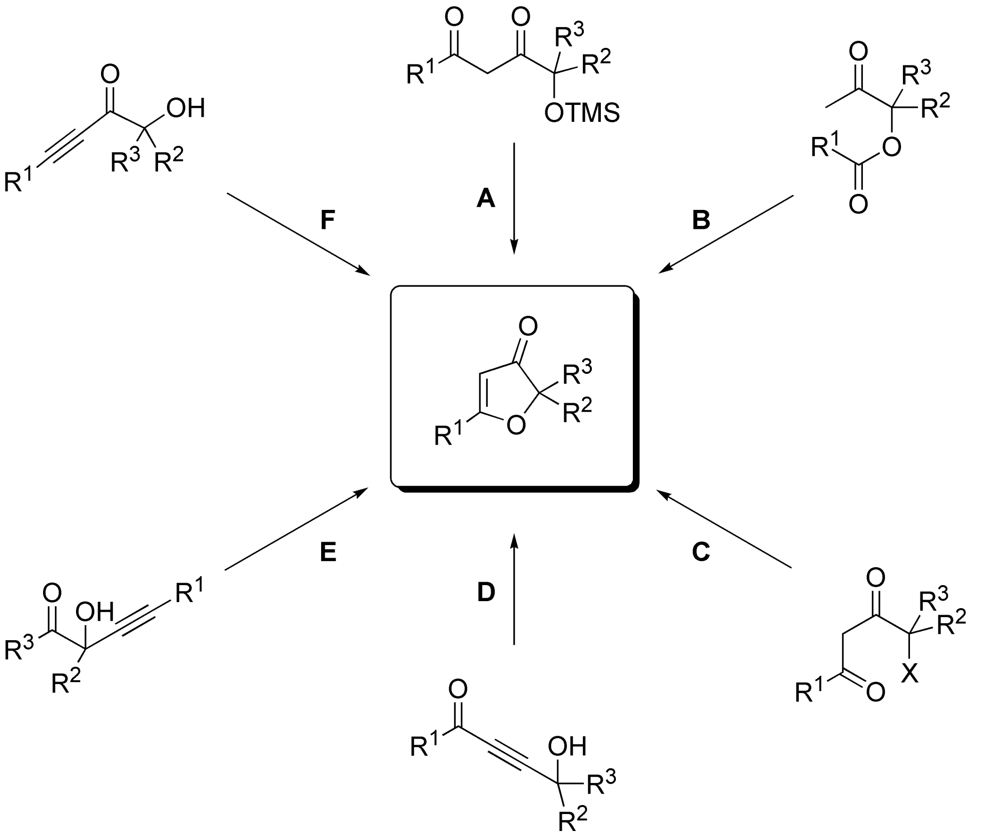


Eremantholide A (**23**)

Figure 11: 3(2*H*)-Furanones without spirocyclic core structure

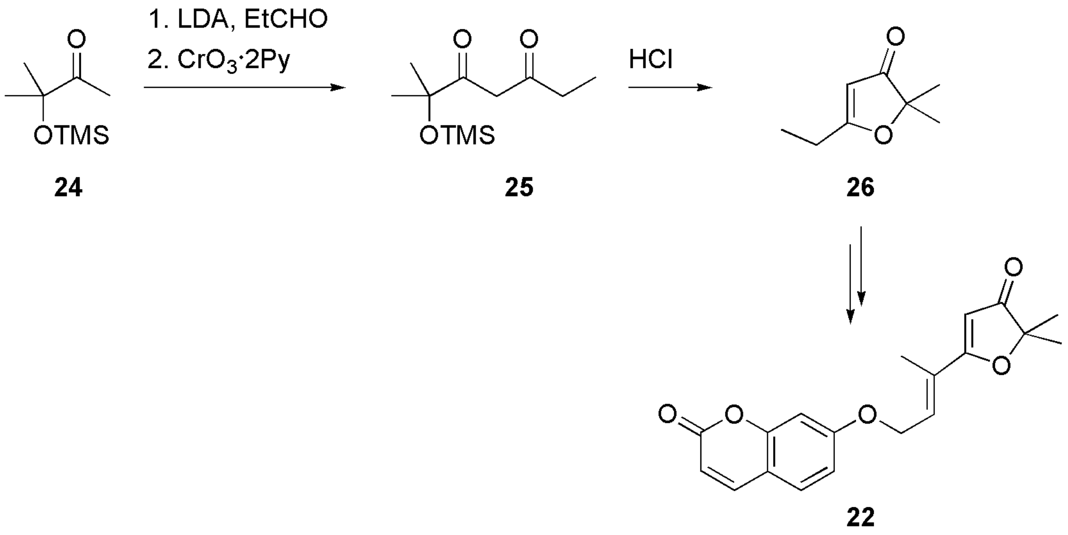
1.6. Approaches for the synthesis of 3(2*H*)-furanones

Numerous strategies for the construction of 3(2*H*)-furanones are available to date. Classical methods have been frequently applied, but in the last decades transition-metal catalyzed approaches have gained more and more importance. These achievements greatly expand and further complement the hitherto existing pool of available methodologies. The most important strategies providing synthetic access to the 3(2*H*)-furanone core are discussed below (Scheme 1). The importance of the different pathways is underlined by selected examples, which have been employed in the synthesis of natural products.



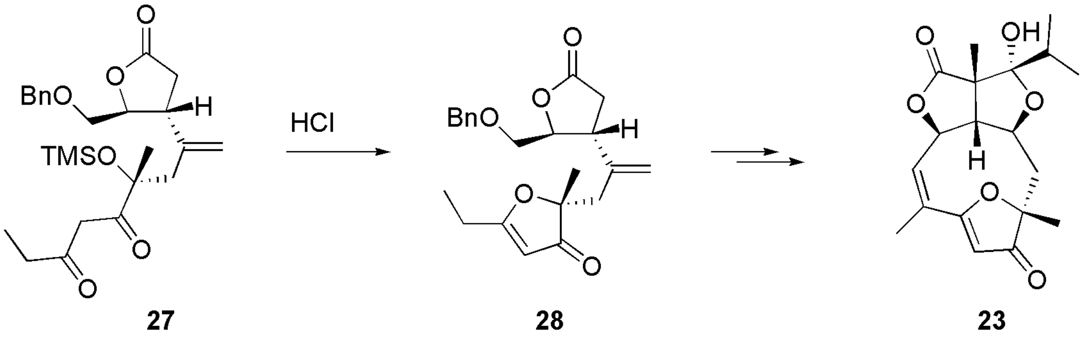
Scheme 1: Synthetic strategies for the construction of 3(2*H*)-furanones

α'-Hydroxy 1,3-diketones have been widely used as precursors for spirocyclic and various other 3(2*H*)-furanones (Scheme 1, **pathway A**). As they are prone to cyclize under acidic or basic conditions, they are ideal substrates giving the desired product directly. Seminal works on the conversion of α'-hydroxy 1,3-diketones under acidic conditions were reported by Sher et al.[71] This generally applicable and simple reaction was successfully implemented in several natural product syntheses. The 3(2*H*)-furanone core of geiparvarin (**22**), for example, was established in this way by Smith et al. (Scheme 2).[63] Aldol reaction, oxidation with Collins' reagent and acid catalyzed cyclization-dehydration afforded the furanone **26** from TMS protected α'-hydroxy 1,3-diketone precursor **24**. Subsequent steps including the coupling of the coumarin motif yielded the natural product **22**.



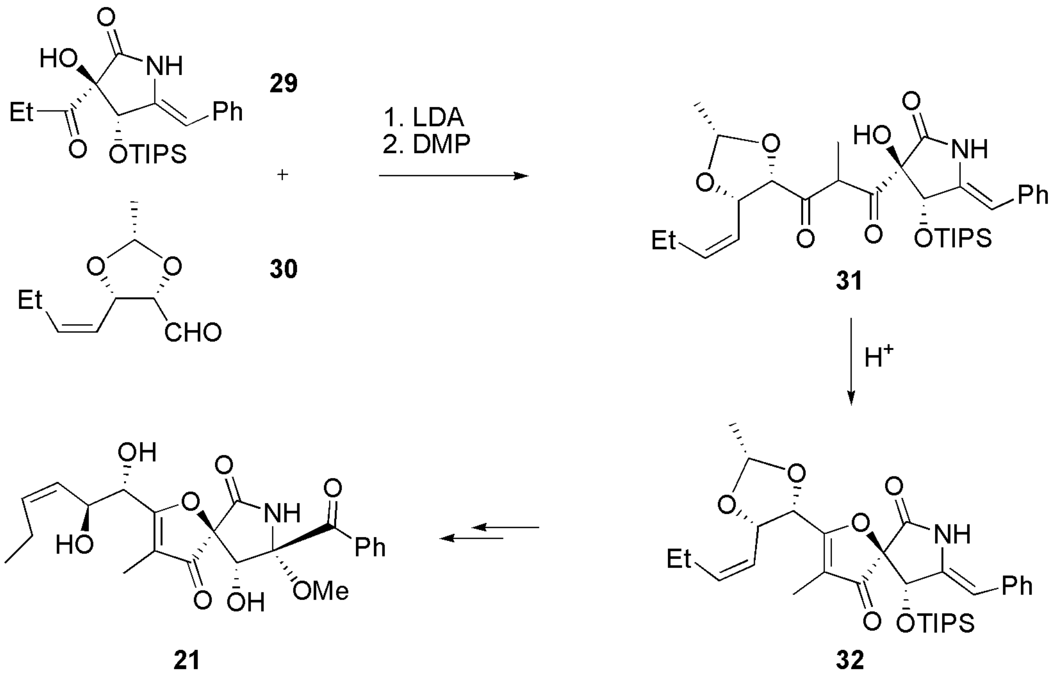
Scheme 2: Synthesis of geiparvarin (**22**) by Smith et al.[63]

This particular method was also applied in the total synthesis of eremantholide A (**23**) by Boeckman and coworkers (Scheme 3).[68] γ-Lactone **27** was treated with mild acid to effect the ring closure to furanone **28**. Further steps included the installation of the hemiacetal followed by the ring closure of the macrocycle to yield eremantholide A (**23**).



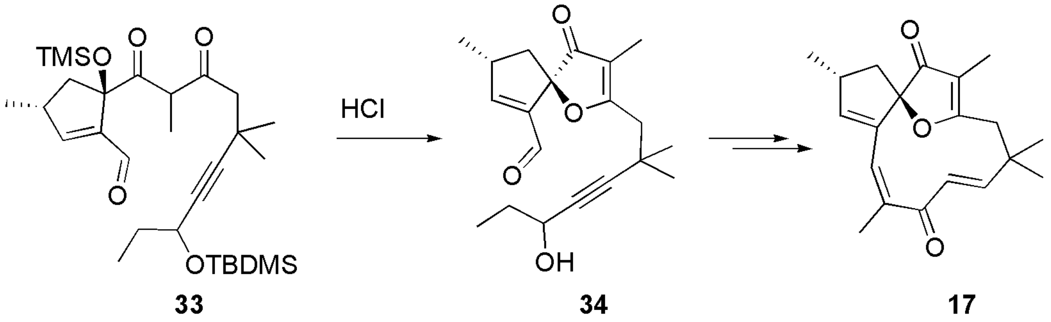
Scheme 3: Synthesis of eremantholide A (**23**) by Boeckman et al.[68]

Spirocyclic furanones have also been generated using this method. Pseurotin A (**21**) was synthesized from benzylidene-γ-lactam **29**, which was coupled with aldehyde **30**.[61] Oxidation and purification by thin layer chromatography yielded the spirocyclic 3(2*H*)-furanone **32** directly. From this stage of the synthesis the natural product was obtained just in additional four remaining steps (Scheme 4).



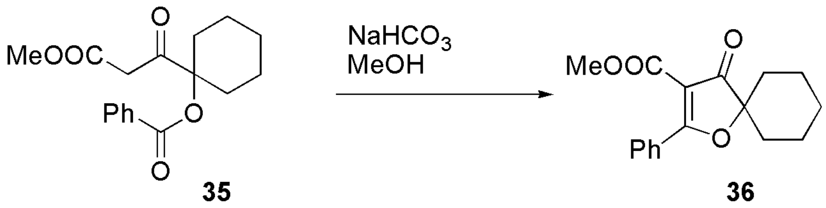
Scheme 4: Synthesis of pseurotin A (**21**) by Hayashi et al.[61]

In the synthesis of jatrophone (**17**) α'-hydroxy 1,3-diketone **33** served as precursor for the generation of the spirocyclic framework. Closure of the macrocycle in **34** gave access to the natural product (Scheme 5).[49]



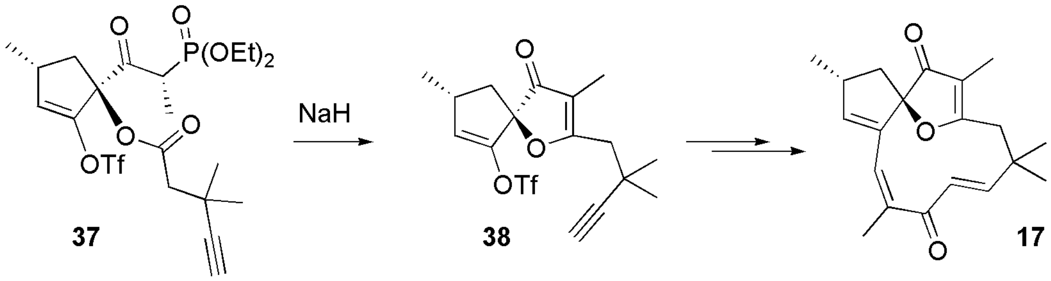
Scheme 5: Synthesis of jatrophone (**17**) by Smith et al.[49]

α-Acyloxy ketones have proven to be versatile building blocks for the generation of 3(2*H*)-furanones (Scheme 1, **pathway B**). Under basic conditions they react intramolecularly to build up the cyclic ring structure. Among various examples also spirofuranones have been accessed. Ester **35**, for instance, undergoes a Knoevenagel type condensation upon treatment with $NaHCO_3$ to afford highly substituted 3(2*H*)-furanone **36** (Scheme 6).[72]



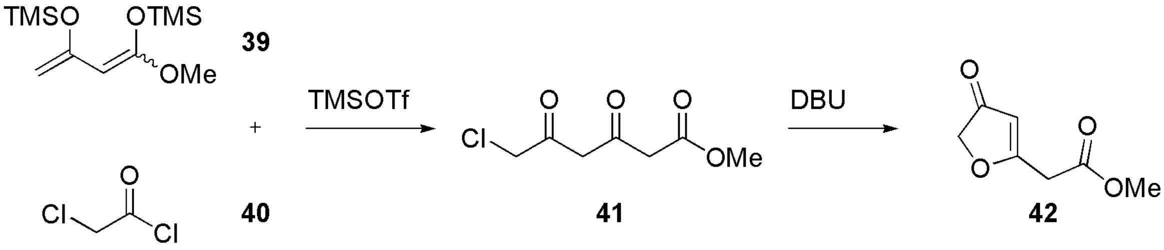
Scheme 6: Synthesis of 3(2*H*)-furanones from α-acyloxy ketones[72]

An analogous route towards 3(2*H*)-furanones was established by Wiemer and coworkers.[51] They used γ-(acyloxy)-β-ketophosphonate **37**, which undergoes a Horner-Wadsworth-Emmons-type condensation to afford the heterocyclic structure **38**.[73] Applying this strategy in natural product synthesis gave access to jatrophone (**17**) (Scheme 7).



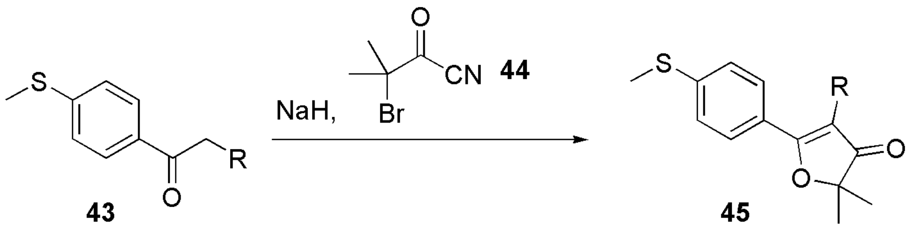
Scheme 7: Synthesis of jatrophone (**17**) by Wiemer et al.[51]

Further developments have been made to provide convenient access to 3(2*H*)-furanones. The heterocyclic products are also available from α-halo-1,3-diketones (Scheme 1, **pathway C**). This strategy has been used in the cyclization of 6-halo-1,3,5-trioxo compound **41**, which can be easily obtained from α-chloroacetic acid chloride (**40**) and 1,3-bis(trimethylsilyloxy)-1,3-butadiene **39** to form furanone **42** (Scheme 8).[74,75]



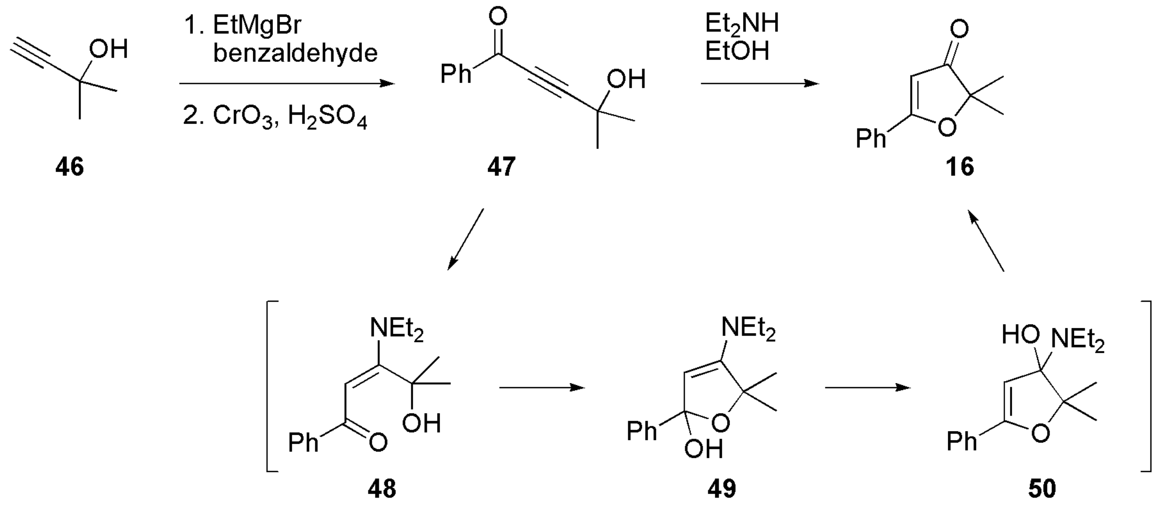
Scheme 8: Synthesis of 3(2*H*)-furanones from α-halo-1,3-diketones[74,75]

An efficient and practical one-pot synthesis was established using 1,2-diarylethanones **43** and 2-bromoisobutyryl cyanide (**44**) (Scheme 9).[76] By choosing the soft isobutyryl cyanide as electrophile C-acylation was observed predominantly. With excess base ring closure happened spontaneously to yield furanones **45**.



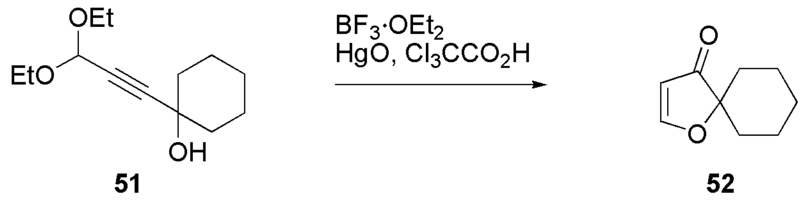
Scheme 9: One-pot synthesis of 3(2*H*)-furanones from 2-bromoisobutyryl cyanide and 1,2-diarylethanones[76]

4-Hydroxy-alk-2-ynones are extensively investigated as starting materials for their conversion to 3(2*H*)-furanones (Scheme 1, **pathway D**). Various methodologies are reported. An early example used diethylamine to mediate the ring closure in the total synthesis of bullatenone (**16**) (Scheme 10).[47]



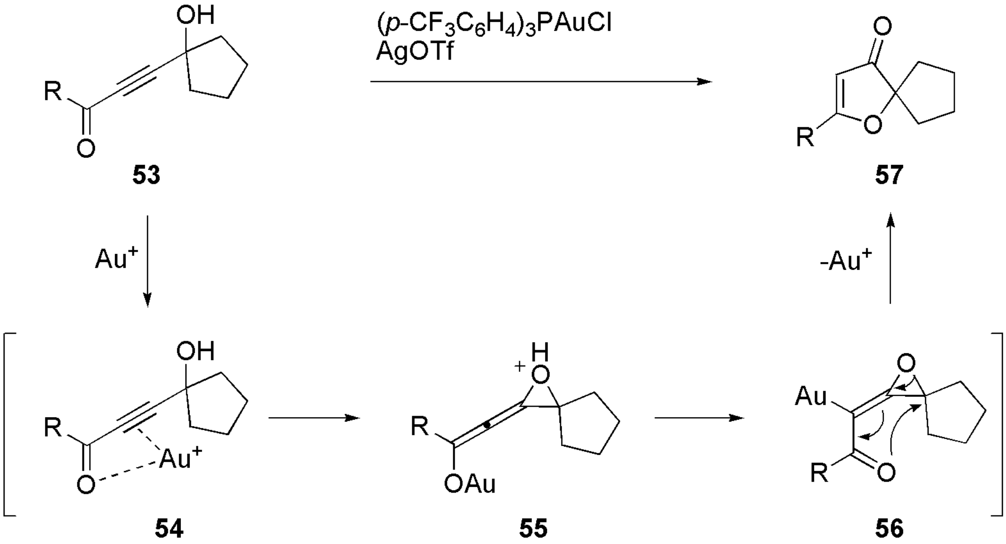
Scheme 10: Synthesis of 3(2*H*)-furanones from 4-hydroxy-alk-2-ynones[47]

4-Hydroxy-alk-2-ynones **47** was available from propargyl alcohol **46** via Grignard reaction and subsequent oxidation with Collins' reagent. It was assumed that diethylamine attacks at the β-carbon of the triple bond followed by ring closure, "oxotropic rearrangement" of the cyclic intermediate and final extrusion of diethylamine (intermediates **48** to **50**) to afford bullatenone (**16**). 25 years later, the total synthesis of bullatenone (**16**) was once again addressed using polymeric Hg/Nafion-H reagent, which gave the natural product in quantitative yield.[77] The corresponding acetals of 4-hydroxy-alk-2-ynones were successfully converted into 3(2*H*)-furanones using H_2SO_4 in MeOH.[78] From starting material **51** the spirocyclic furanone **52** was obtained with $BF_3{\cdot}OEt_2$ in presence of catalytic amounts of mercuric oxide and trichloroacetic acid (Scheme 11).[79]



Scheme 11: Synthesis of 3(2*H*)-furanone **52** from acetal **51**[79]

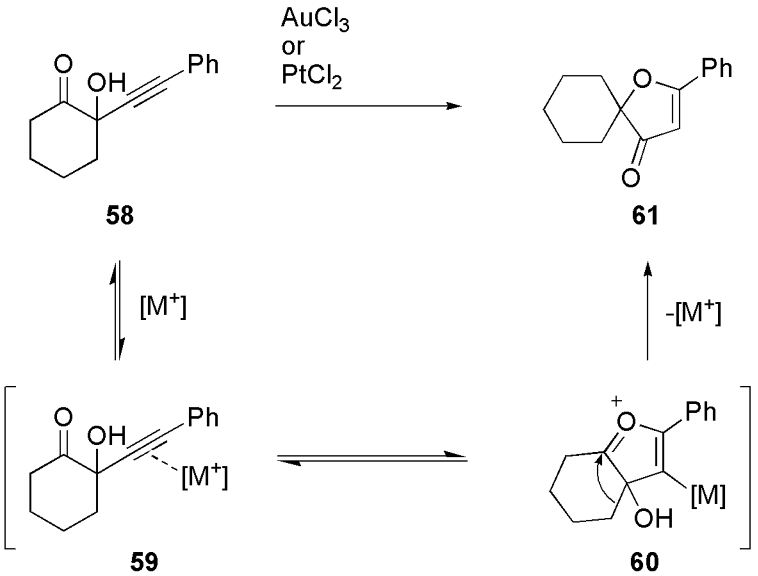
In principle, 4-hydroxy-alk-2-ynones can be considered as α-hydroxy-1,3-diketone equivalents since the latter can be easily obtained by hydration of the triple bond. However, as the reaction mechanisms do not imperatively run through the intermediate diketone species, 4-hydroxy-alk-2-ynones are categorized separately. Recently, a transition metal catalyzed approach using the combination of (p-$CF_3C_6H_4$)$_3$PAuCl and AgOTf was reported to be a powerful catalyst system to mediate the intramolecular cyclization of γ-hydroxyalkynone **53** to generate 3(2*H*)-furanone **57** under very mild conditions (Scheme 12).[80]



Scheme 12: Transition metal catalyzed approach to 3(2*H*)-furanones from 4-hydroxy-alk-2-ynones[80]

The following mechanism was proposed: Initial π-coordination of the active gold species and subsequent intramolecular Michael addition gives rise to a transient epoxide intermediate, which cyclizes to yield the desired product (intermediates **54** to **56**).

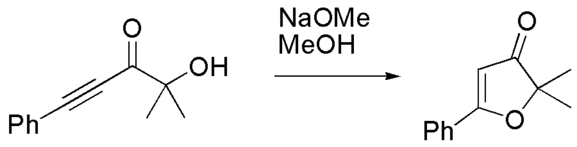
Another transition-metal catalyzed synthesis of 3(2*H*)-furanones was accomplished by Kirsch and coworkers (Scheme 1, **pathway E**).[81] They performed a $AuCl_3$- or $PtCl_2$-catalyzed domino reaction of alkinyl carbonyl compound **58**, which undergoes a heterocyclization - 1,2-migration cascade (Scheme 13). Initiated by the π-activation of the triple bond by the transition metal (intermediate **59**), this reaction is believed to proceed via an oxonium ion **60**, which triggers a subsequent 1,2-shift to afford the final product **61**.



Scheme 13: Synthesis of 3(2*H*)-furanones by a heterocyclization – 1,2-migration cascade[81]

Shortly after this publication, an extension of this methodology to access nitrogen-containing heterocycles such as pyrrolones, indolizines and indolizinones was reported by Sarpong and coworkers.[82]

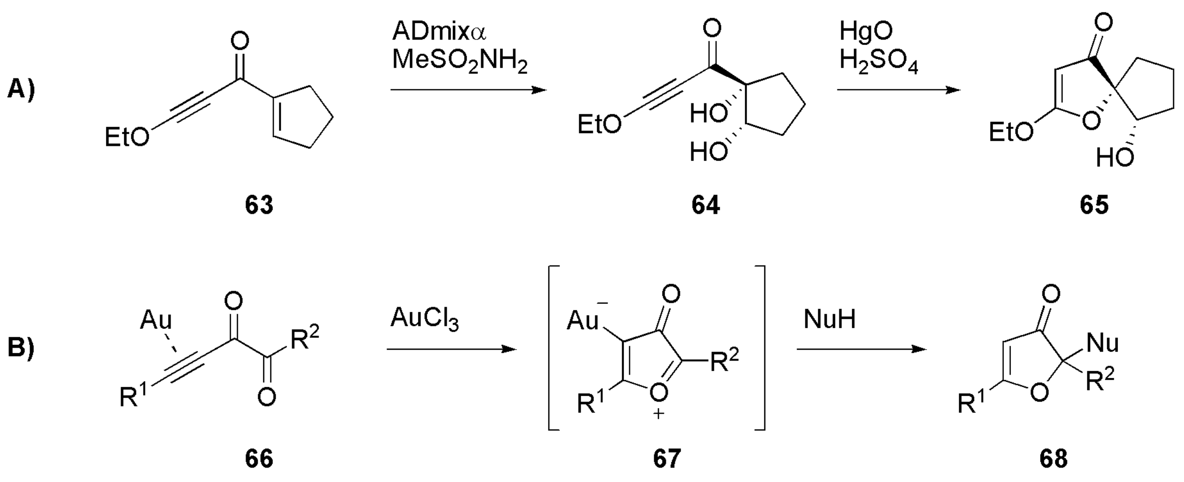
1-Hydroxy alk-3-ynones are also important building blocks for the synthesis of 3(2*H*)-furanones (Scheme 1, **pathway F**). Baldwin et al. showed in their seminal work on rules for ring closure that alkyne **62** readily cyclizes to yield bullatenone (**16**) under basic conditions (Scheme 14).[83]



62 **16**

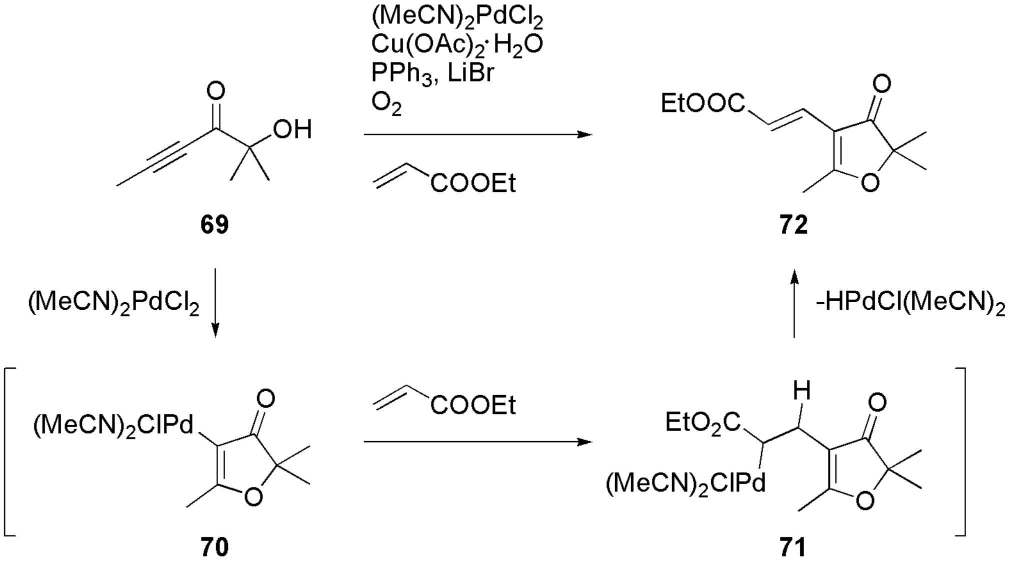
Scheme 14: Synthesis of 3(2*H*)-furanones from 1-hydroxy alk-3-ynones[83]

1-Hydroxy alk-3-ynone **64** can be generated in situ in an enantioselective way from enynone **63** via asymmetric dihydroxylation reaction. In presence of HgO it cyclizes spontaneously to the desired product **65** (Scheme 15, A).[84] Alternatively, a gold catalyzed cyclization of 2-oxo-3-butynoates or disubstituted diones **66** in presence of oxygen nucleophiles offers a straightforward route towards 3(2*H*)-furanones **68** (Scheme 15, B).[85]



Scheme 15: Synthesis of 3(2*H*)-furanones from enynones[84] and from 2-oxo-3-butynoates[85]

A striking process for the synthesis of 3(2*H*)-furanones was developed by Gouverneur et al. (Scheme 16).[86] This reaction involves a Wacker-Heck sequence, which is initiated by the activation of the triple bond in alkyne **69** by the transition metal followed by 5-*endo* ring closure to give palladium intermediate **70**. Further Heck-type carbopalladation with ethyl acrylate affords intermediate **71**, which undergoes β-elimination to release the final furanone **72**. After reductive elimination of the palladium hydride species, Pd(0) is reoxidized with molecular oxygen.



Scheme 16: Synthesis of 3(2*H*)-furanones via a Wacker-Heck sequence[86]

The broad pool of available methodologies renders the synthesis of many naturally occurring compounds possible. In this way, highly complex structures can be accessed in sufficient amounts in order to fully elucidate their biological effects. Consequently, quantities of biologically active compounds are provided, which might be powerful candidates for medicinal applications. Many α,β-unsaturated carbonyl compounds have shown to possess chemoprotective, anti-inflammatory and antioxidative effects. Therefore, the synthesis of the α,β-unsaturated 3(2*H*)-furanone limnophilaspiroketone (**15**) and related natural product analogues is envisioned and discussed herein.

2. AIM OF THE PRESENT STUDY

This work is aimed to explore a novel and straight forward strategy towards the total synthesis of limnophilaspiroketone (**15**).

From a synthetic point of view this natural product reveals several challenges to overcome. Firstly, the formation of the spirocyclic framework affords a deliberate retrosynthetic analysis, which is a prerequisite for the feasibility of the planned pathway. Secondly, the stereoselective introduction of substituents forming quaternary stereocenters still poses a common problem in asymmetric synthesis although a broad pool of concepts using various chiral ligands and catalysts is available to date. And furthermore, the highly oxygenated natural product calls for ambitious methodologies for the introduction of multiple oxygen functionalities in a very condensed framework.

Due to its structural features, limnophilaspiroketone (**15**) represents also an attractive molecule from a biological point of view. Containing two orthogonal α,β-unsaturated carbonyl moieties and a phenol substituent, this natural product is a promising structure in terms of potential Michael acceptor and antioxidant activity.

For an investigation of the appropriate synthetic route towards the 3(2*H*)-furanone framework a natural product derived simplified model compound is envisioned, which should be easy to synthesize.

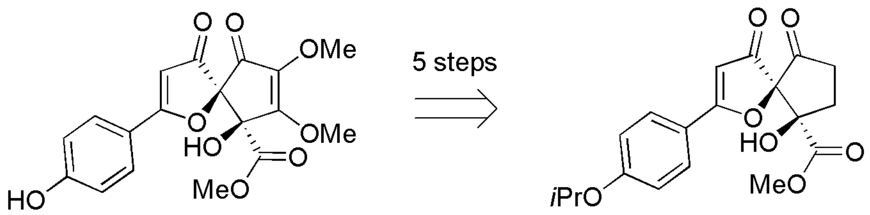
Moreover, a library of α-modified enones of this model compound is supposed to be generated via simple low step transformations from one common precursor. For 3(2*H*)-furanones the influence of the substituent in α-position of the α,β-unsaturated carbonyl system on the chemical reactivity against nucleophiles has not been studied so far. Thus, experiments are planned to elucidate potential Michael acceptor activities.

3. RESULTS AND DISCUSSION

3.1. Retrosynthetic approach towards the total synthesis of limnophilaspiroketone

Aiming for an effective and streamlined synthesis, particularly protecting-group-free reaction sequences as well as redox and atom economic transformations were envisioned in the retrosynthetic analysis of limnophilaspiroketone (**15**).

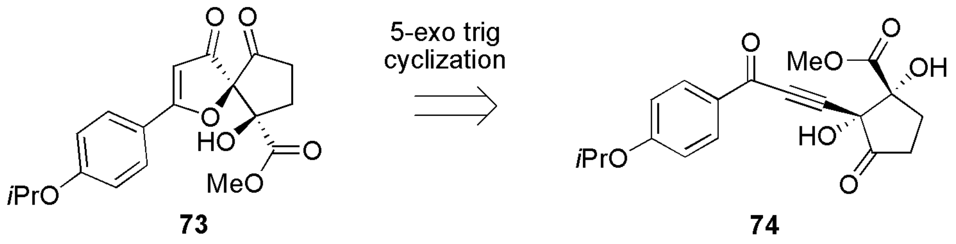
The envisaged approach considers a late-step introduction of the two methoxy substituents attached at the α,β-unsaturated carbonyl moiety (Scheme 17). This seems to be advantageous since it directly establishes the correct functionality found in the final product. Although the methoxy groups should be only slightly reactive, this alleviates the need to carry them through the synthesis and circumvents the possibility to interfere in other crucial steps. In detail, they can be introduced for example by an iodination, oxidation, methylation, methoxylation sequence according to a known procedure[87] from the saturated ketone **73**. Deprotection of the phenol moiety affords the correct structure of the natural product.



15 **73**

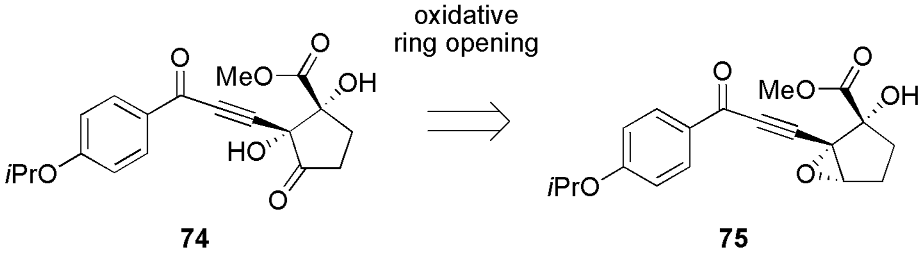
Scheme 17: Late-step introduction of the methoxy substituents and deprotection of the phenolic moiety to give the final natural product

The formation of the spirocyclic framework represents the key step in the design of the proposed synthesis. For the generation of the 3(2*H*)-furanone an example of a 5-exo trig cyclization was chosen (Scheme 18).[47] During this transformation four consecutive reaction steps take place representing a very step efficient and straightforward transformation. This method allows for an elegant installation of the desired framework and does not interfere in the previously established stereochemistry by racemization or epimerization processes. Furthermore, the synthesis of the corresponding cyclization precursor **74** seems to be facile and convenient.



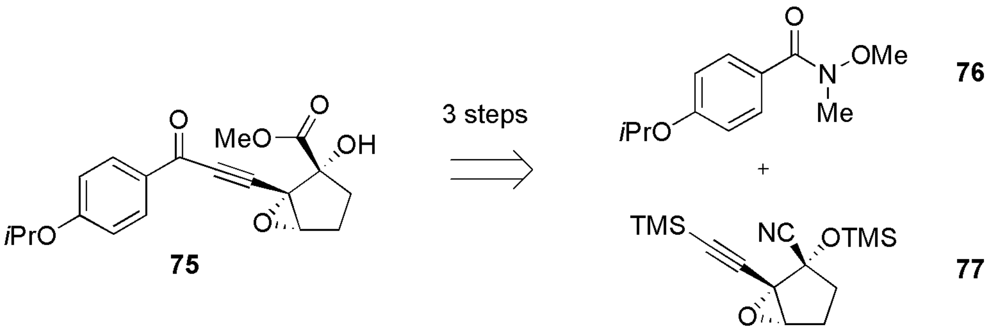
Scheme 18: 5-exo trig cyclization for the formation of the spirocyclic 3(2*H*)-furanone

The required alcohol functionality in the precursor **74**, which is essential for this cyclization process, could be established by a DMSO mediated oxidative ring opening reaction of epoxide **75** first examined by Trost in the synthesis of taxanes (Scheme 19).[88] It is expected to proceed in a highly regioselective manner. This example can also be referred to as an efficient step since it combines two separate procedures, namely an acid or base induced ring opening reaction and subsequent oxidation of the secondary alcohol. Moreover, it minimizes the use of reagents and environmentally critical oxidants.



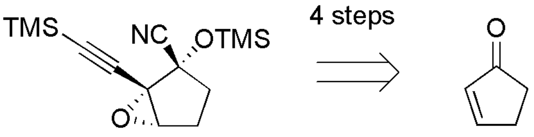
Scheme 19: Oxidative ring opening of the epoxide to form the α-hydroxy ketone motif

Epoxide **75** could be derived from acetylene **77** and the corresponding Weinreb amide of protected *p*-hydroxy benzoic acid **76**, which could be connected via simple alkyne addition after deprotection of the acetylene **77**. Hydrolysis of the nitrile in methanolic solution would yield the desired methyl ester. The masking of the phenol motif in the acid derivative **76** is an inevitable measure. The use of an aldehyde as coupling partner instead of a Weinreb amide is also attractive, however, this affords a further step for the reoxidation of the generated diastereomeric alcohol. Alternatively, the acid chloride would also form the desired product, but it is commonly avoided due to its high reactivity resulting in unspecific product formation.



Scheme 20: Combination of the phenolic part and the acetylenic fragment

The synthesis commences with simple cyclopent-2-enone (**78**), which serves as starting material for the synthesis of the corresponding acetylene **77** (Scheme 21). α-Iodination and subsequent Sonogashira coupling with TMS acetylene, asymmetric epoxidation and cyanohydrin reaction would afford the intermediate **77** in 4 steps. At first glance, it might appear that two protecting groups are included. But, as both TMS groups are imperatively necessary to allow the attachment of the alkyne and the cyanohydrin reaction to proceed, no additional steps for the introduction of the TMS groups are required. As a consequence, the differentiation between both TMS groups is a major challenge if the carbon based silyl group has to be selectively removed in presence of the silyl ether. To achieve this, a new methodology has to be developed.



77 **78**

Scheme 21: Planned synthesis of acetylenic fragment from simple cyclopentenone

In total, this retrosynthetic plan aimes for an efficient synthesis of limnophilaspiroketone (**15**) in about 14 consecutive steps. Non-strategic redox reactions, functional group interconversions and protecting group manipulations are supposed to be kept at a minimum leading to a short and streamlined synthesis.

3.2. Synthesis of the chiral cyclopentyl building block 77

The cyclopentyl part in the spirocyclic framework is characterized by a highly functionalized substitution pattern. Not only the degree of substitution, but also the chiral nature of this building block renders the synthesis nontrivial. To start with cyclopent-2-enone (**78**) is a versatile starting point since it allows various transformations on the α,β-unsaturated carbonyl function (Figure 12).

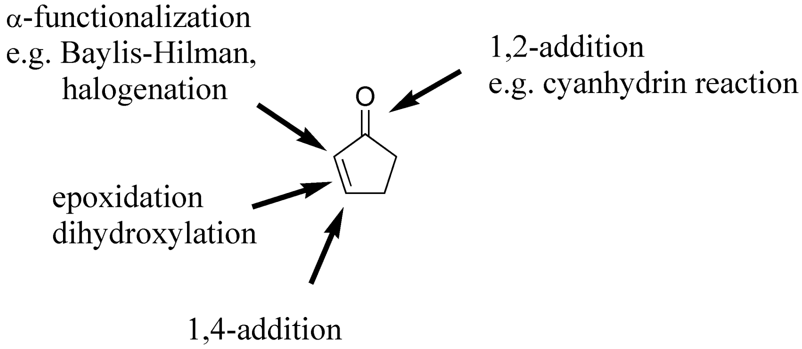
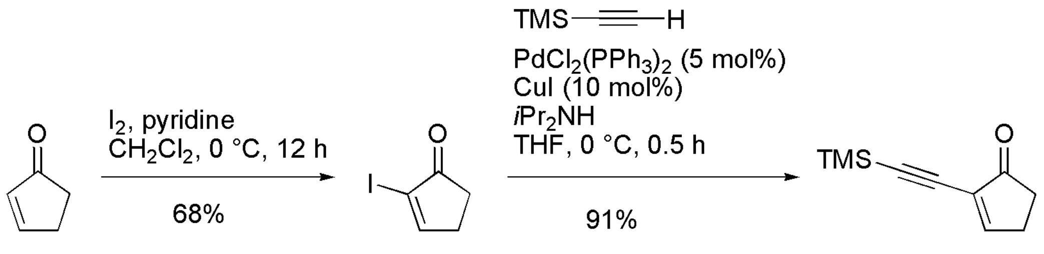


Figure 12: Considered reactions for the functionalization of cyclopentenone

A Baylis-Hilman type reaction was considered to address the α-functionalization at the α,β-unsaturated carbonyl moiety. As this necessarily implies a Michael addition mechanism, the conjugate 1,4-addition is also a suitable possibility for chemical modifications. 1,2-addition reactions such as a cyanohydrin reaction allow for an introduction of nucleophiles to the carbonyl group. Furthermore, the double bond is suitable for an epoxidation or dihydroxylation reaction, which can also be accomplished asymmetrically. However, a method has to be found to overcome the unfavorable electron deficient character of the double bond. Generally, an increased ring strain in a 5-membered ring in contrast to a 6-membered ring might be a drawback and a limiting factor for many reactions resulting in moderate reaction yields.

3.2.1. Introduction of an acetylene functionality

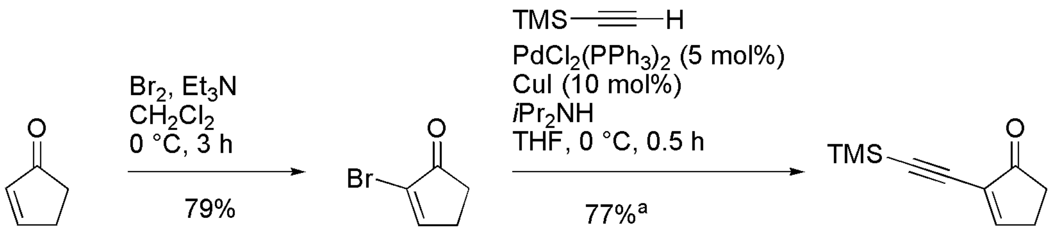
Since decades, the discovery of new methodologies for C-C bond formation has been in the focus of many research groups providing the possibility to build up complex carbon based structures. Amongst the C-C bond forming reactions the well known Sonogashira cross-coupling of acetylenes with aryl or vinyl halides is widely used in natural product synthesis since acetylenes represent an important intermediate in organic synthesis. To introduce the desired acetylene functionality, a prefunctionalization of cylopentenone (**78**) was required (Scheme 22).



78 **79** **80**

Scheme 22: Iodination and Sonogashira cross coupling to yield acetylene **80**

For this purpose a literature known direct iodination of cyclopent-2-enone (**78**) was performed.[89] Subsequent Sonogashira cross coupling reaction[90] with TMS acetylene proceeded smoothly to give the desired alkyne **80** in 91% yield. Alternatively, the same procedure was investigated using the corresponding 2-bromo-cyclopent-2-enone (**81**), which is easily available in one step from the common starting material **78** by bromination and HBr elimination. However, the cross coupling reaction turned out to be more critical and did not proceed as cleanly as in the previous case (Scheme 23).



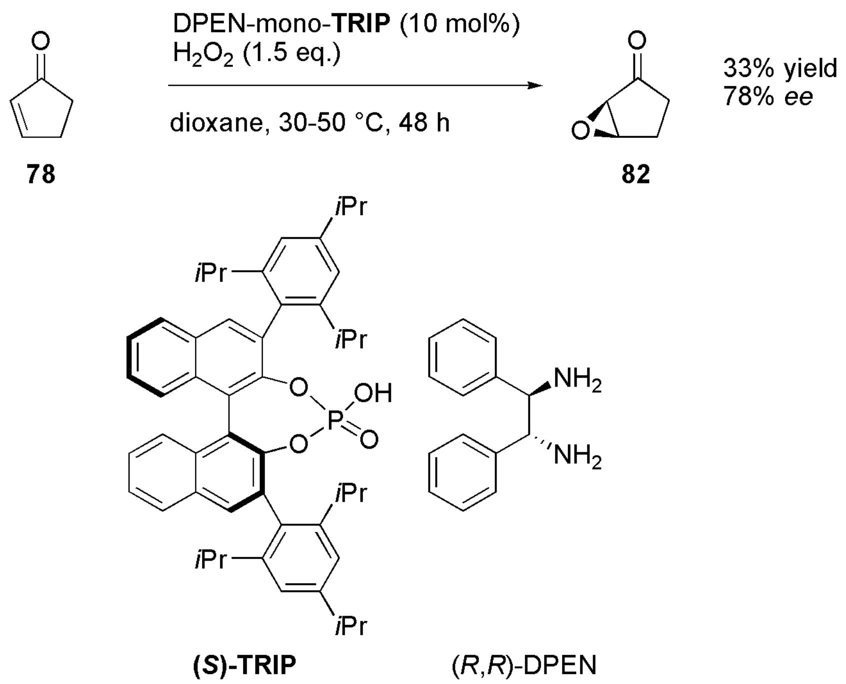
78 **81** **80**

Scheme 23: Bromination and Sonogashira cross coupling. [a]estimated by NMR

3.2.2. *Asymmetric epoxidation reactions*

Achiral versions of epoxidation reactions on cyclic α,β-unsaturated ketones using nucleophilic reagents such as H_2O_2 or *t*-BuOOH are widely used. Diastereoselective epoxidation reactions on chiral substrates are also often applied. These reactions proceed under substrate control, in which the inherent stereochemistry directs the newly formed epoxide to the desired direction. Numerous methods are reported on enantioselective epoxidation reactions of α,β-unsaturated ketones. Unfortunately, most cyclic enones have shown to be insufficient substrates for these methods giving only poor enantioselectivities. Prominent examples are the Julia-Colonna epoxidation using polyamino acids as chiral ligands[91] or chiral phase transfer catalysts with alkaloid derived quaternary ammonium salts such as cinchona derivatives.[92-97] Further examples using guanidine ligands[98,99] and chiral peroxide oxidants[100,101] were reported.

For the first time the group of List systematically addressed the enantioselective epoxidation of cyclic enones and provided a promising solution to this problem.[102] Using catalytic diamine salts (10 mol%) in combination with hydrogen peroxide (1.5 eq.) at 30 - 50 °C in dioxane for 20 - 48 h, various cyclic enones could be successfully epoxidized to the corresponding α,β-epoxyketones. However, in contrast to 2-cyclohexenones and 2-cycloheptenones, 2-cyclopentenone (**78**) exhibited lower reactivity giving the corresponding epoxide **82** in 33% yield and 78% enantiomeric excess (Scheme 24). Moreover, α-substituted enones were unreactive under these conditions.

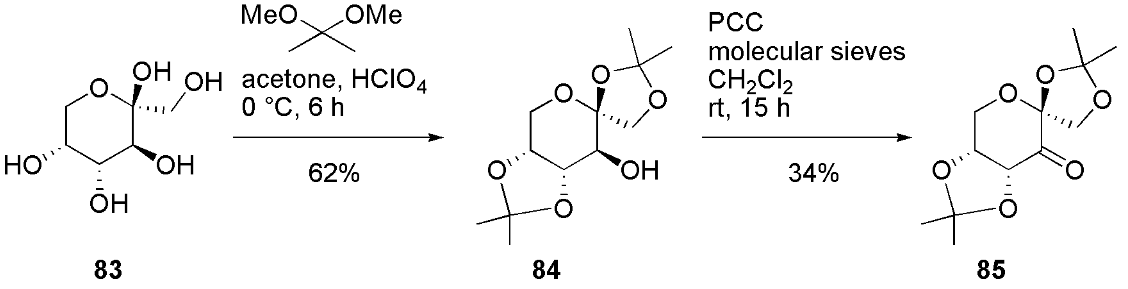


Scheme 24: Catalytic asymmetric epoxidation of 2-cyclopentenone (**78**) by List et al.[102]

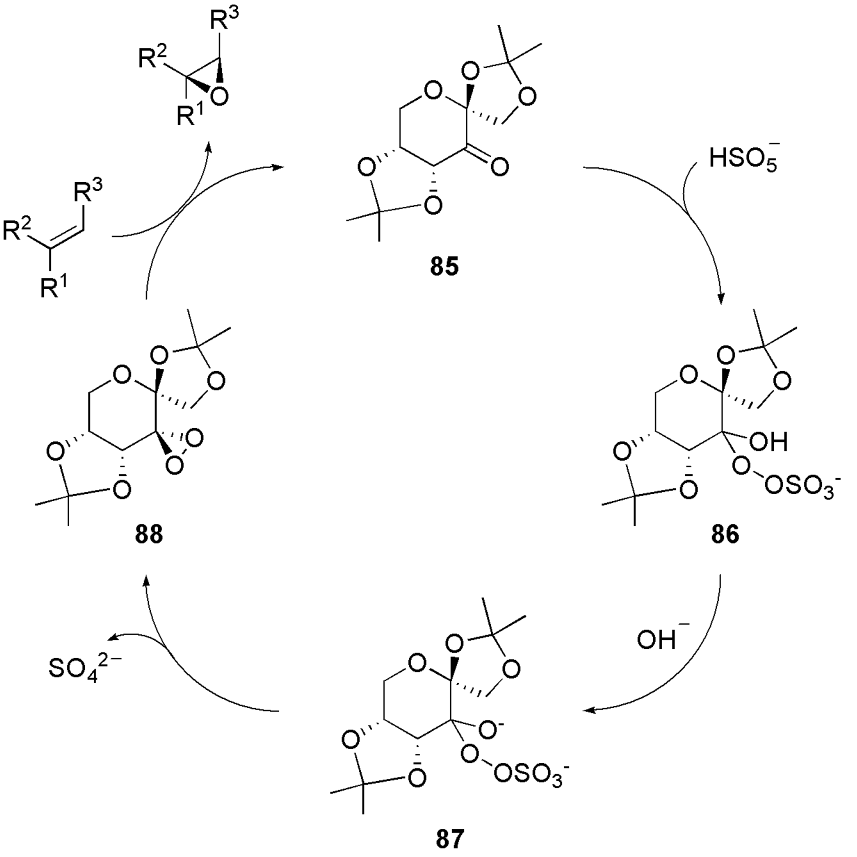
Although there are powerful methodologies for the enantioselective epoxidation of electron deficient cyclic olefins available, no solution exists for α-substituted 2-cyclopentenones.

Due to the lack of satisfactory methods, the focus was initially laid on chiral ketones as catalysts. The Shi asymmetric epoxidation using a chiral fructose-derived ketone catalyst in presence of oxone as the oxidant appeared to be the most promising approach since it has shown to have a very broad substrate scope.[103] A wide variety of olefins including trisubstituted olefins,[104] enynes,[105] electron deficient alkenes such as α,β-unsaturated esters[106] and even an example of an α,β-unsaturated ketone[107] yielded high enantioselectivities.

Although different chiral catalysts were used in these precedents, the investigations started with the standard catalyst **85** since it is most frequently applied and can be easily synthesized. It was prepared according to a known literature procedure[108] in a simple two step sequence starting from cheap D-fructose (**83**). Ketalization and subsequent oxidation of the remaining alcohol function afforded the chiral ketone **85** (Scheme 25).



Scheme 25: Preparation of the Shi catalyst **85** from D-fructose (**83**)[108]



Scheme 26: Proposed mechanism of the Shi epoxidation

The Shi epoxidation is based on the reaction of chiral ketone **85** with oxone ($KHSO_5 \cdot ½KHSO_4 \cdot ½K_2SO_4$) leading to intermediate **86** (Scheme 26). Basic conditions are required to facilitate the deprotonation to the corresponding anion **87**, which subsequently forms the catalytically active dioxirane **88**. Dioxirane **88** reacts with olefins to yield the corresponding enantioenriched epoxides. Since the ketone **85** is regenerated, it can be used in catalytic amounts.

The stereochemical outcome of this epoxidation reaction can be rationalized by analyzing the possible transition states (Figure 13). Two different transition state geometries are possible: A spiro transition state (**A-D**) where the olefin is orientated in a perpendicular position to the dioxirane, and a planar transition state (**E-H**) where dioxirane and olefin are arranged in the same plane. Transition states **B-D** and **E-G** are disfavored by destabilizing steric interactions. Transition states **A** and **H** are sterically favored.

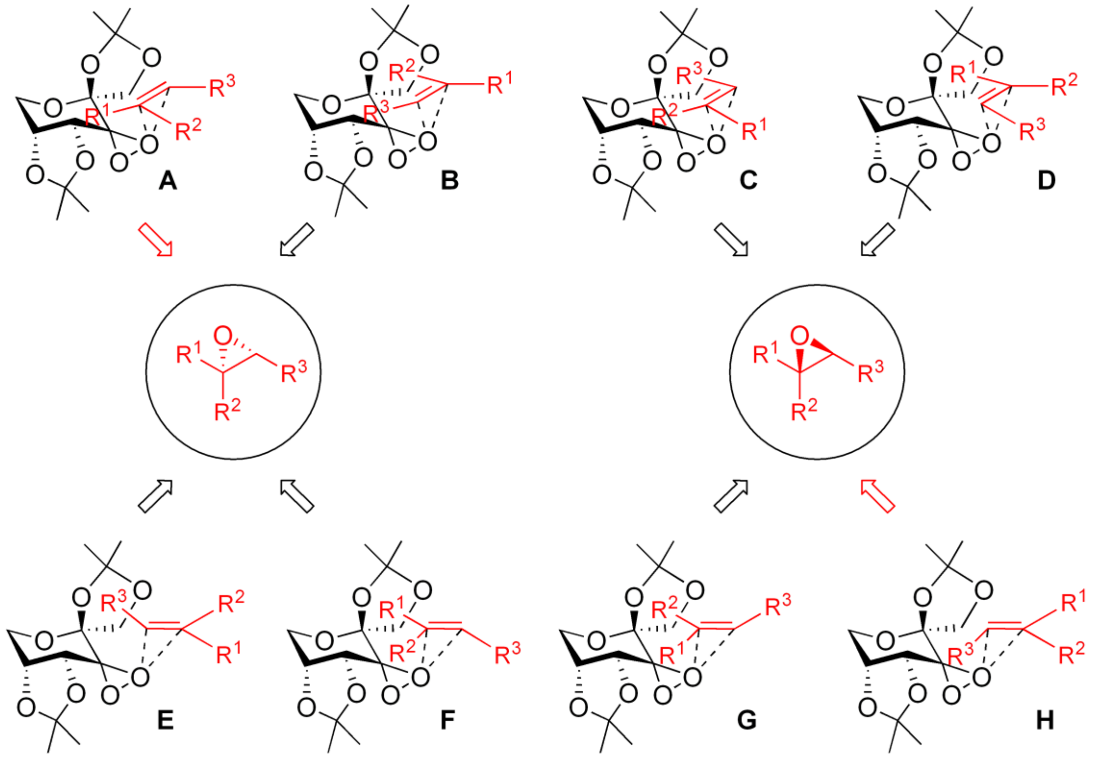


Figure 13: Spiro transition states (top row) and planar transition states (bottom row) in the asymmetric epoxidation of trisubstituted olefins using the Shi catalyst **85**

As the favored transition states (**A** and **H**) result in the opposite stereoisomer, electronic factors have to be considered for a valuable prediction. Due to stabilizing interactions of an oxygen lone pair with the π* orbital of the alkene, the spiro transition state should be preferred over the competing planar transition state where these interactions are geometrically not feasible (Figure 14). Furthermore, the alkyne substituent on the α-substituted 2-cyclopentenone **80** should lower the energy of the π* orbital and therefore strengthen the secondary orbital interactions.

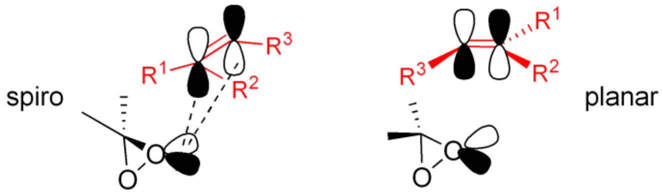
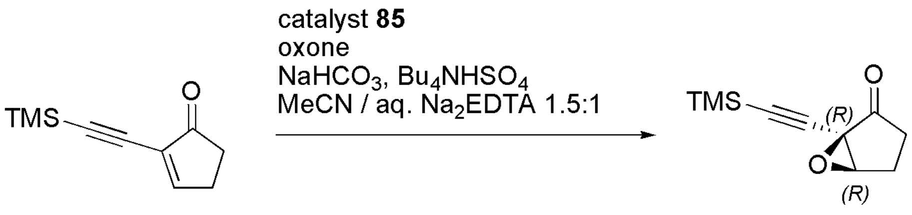


Figure 14: Electronic aspects of possible transition states for the epoxidation of olefins

Taken all together, the sterically and electronically favored spiro transition state **A** should result in the formation of the (2*R*, 3*R*)-configured epoxycyclopentanone derivative **89** when olefin **80** is used as a substrate for the asymmetric Shi epoxidation (Scheme 26).



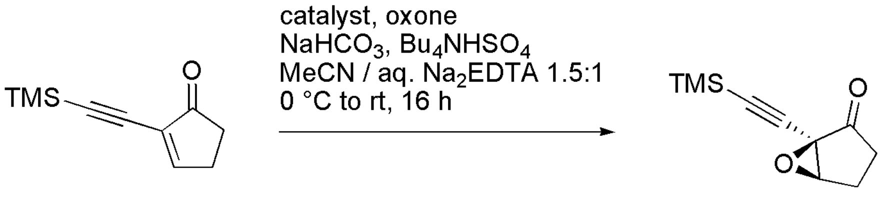
80

(*R*,*R*)-**89**

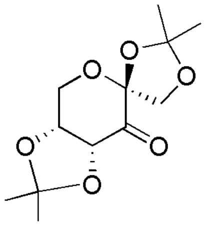
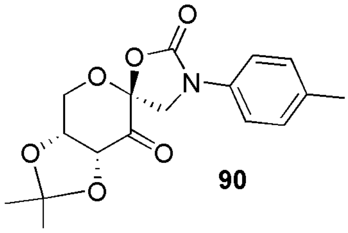
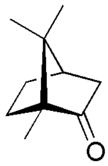
Scheme 26: Expected stereochemical outcome of the asymmetric Shi epoxidation on 2-cyclopentenone derivative **80** using chiral catalyst **85**

Alkyne substituted 2-cyclopentenone **80** was subjected to the epoxidation reaction. The desired product was obtained in 73% yield when chiral ketone **85** was used (Table 1, entry 1). Unfortunately, the expected stereochemical preference was not observed, instead, the epoxycyclopentanone **89** was just isolated as a racemic mixture. Since the reactivity appeared to be sufficient, the commercially available oxazolidinone containing chiral ketone **90** was applied. A better sterical differentiation of the olefin substituents was envisaged in that way. However, catalyst **90** was found to be ineffective giving lower yields and no stereoinduction. The same was found with D-camphor (**91**), which was also used instead of the fructose-derived catalysts **85** and **90** (Table 1, entries 2 and 3).

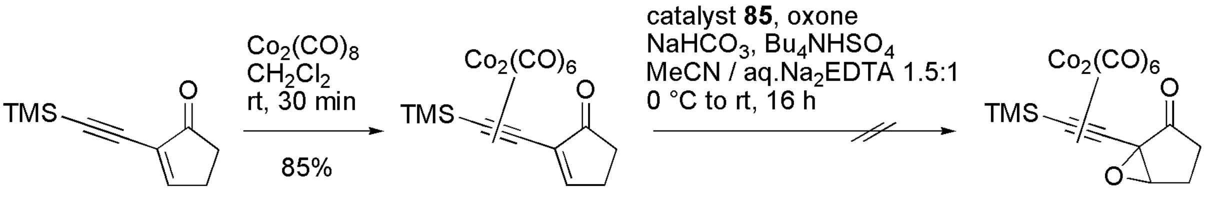
Table 1: Shi epoxidation reactions on 2-cyclopentenone **80** with different chiral ketones



80 **89**

entry	catalyst	yield 89 [%]	*ee* [%]
1	 **85**	73	0
2	 **90**	46	0
3	 **91**	17	0

Moreover, the acetylene substituent was protected with $Co_2(CO)_8$ to increase the steric bulk in the olefin. Subsequent asymmetric Shi epoxidation with ketone **85** failed, no conversion was observed. When the reaction time and the reaction temperature were increased, only polymerization products were observed (Scheme 27).

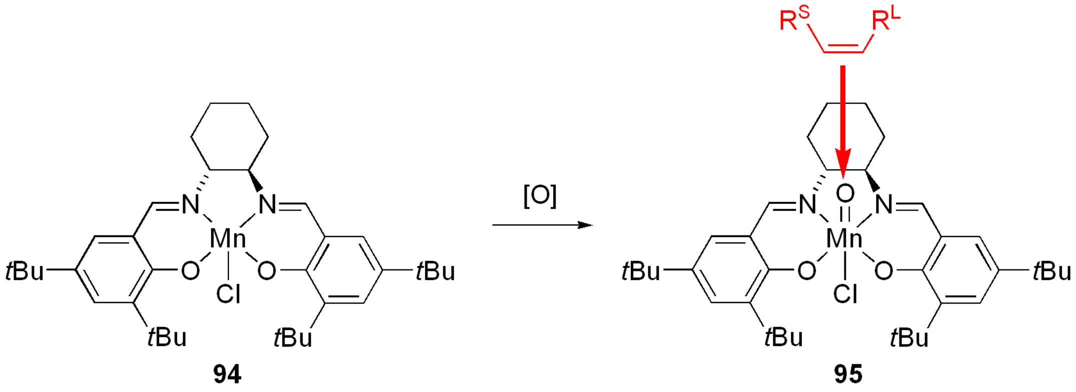


80 **92** **93**

Scheme 27: Protection of the alkyne moiety in cyclopentenone **80** and subsequent Shi epoxidation

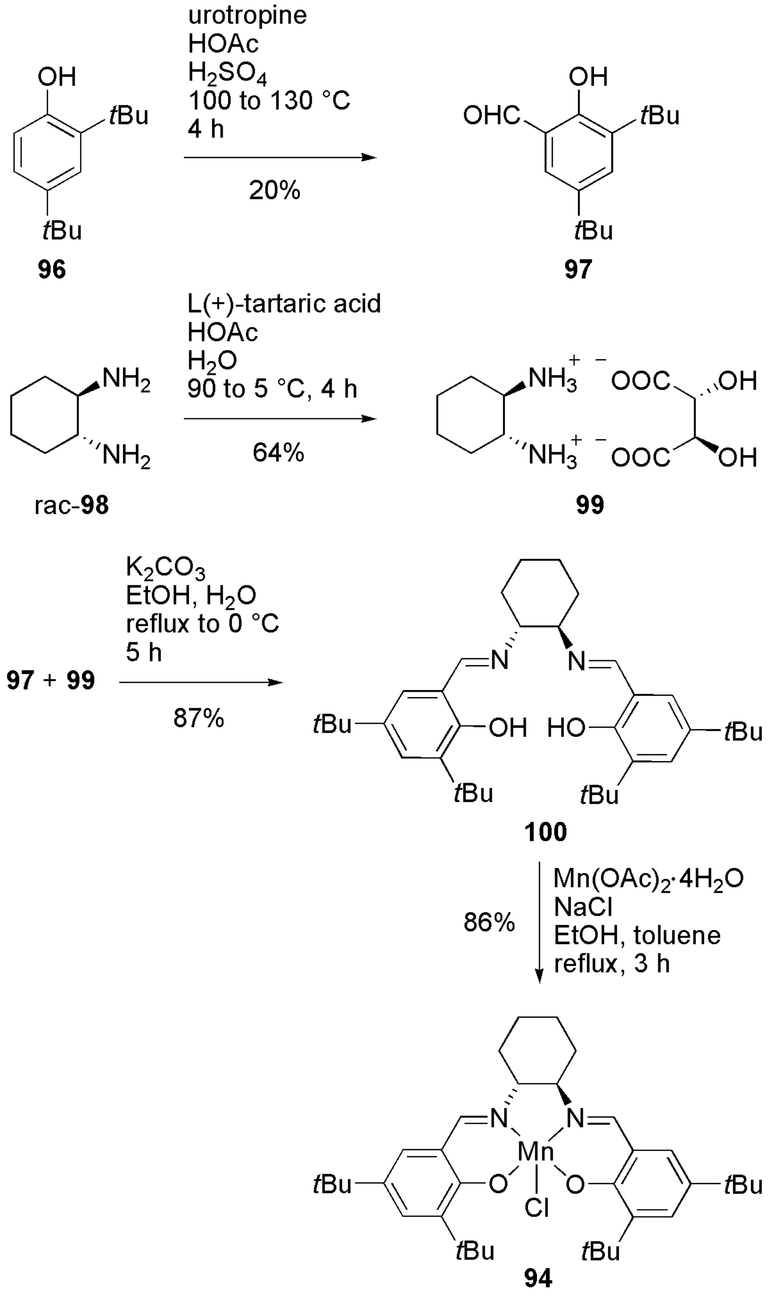
Epoxidation reactions on electron deficient olefins are generally slow. Being electrophilic in nature, dioxiranes might be consumed unproductively by reacting with oxone to form the corresponding ketone or by decomposition during prolonged reaction times. Nevertheless, significant conversion was observed giving the product in 73% yield in the case of catalyst **85**. This observation can be explained by a competing dioxirane formation with the ketone present in the substrate. This leads to an effective epoxidation catalyzed by the substrate itself being substrate and catalyst in one. However, no chiral induction is expected in this case. This indicates that well designed catalysts are required to effectively epoxidize ketones as shown in an intriguing example by Shi.[107] The development of novel sugar based chiral catalysts with an enlarged substrate scope including ketones is strongly desired.

Encouraged by a remarkable result by Adam[109] who was able to convert isoflavones to the corresponding epoxides using Jacobsen's chiral Mn(III)-salen catalyst **94**, the focus of the epoxidation of α-substituted 2-cyclopentenone **80** was shifted to this methodology. The Jacobsen asymmetric epoxidation has proven to be a versatile tool for a wide range of olefins. Although *cis*-disubstituted olefins are typically better substrates giving excellent enantioselectivities, it was also successfully applied with various other alkenes. The proposed mechanism is thought to proceed through the catalytically active manganese(V)oxo species **95**, which is formed in the presence of an oxidant.[110] The bulky *tert*-butyl groups at the backbone of the catalyst restrict the trajectory of the attacking olefin forcing it to approach the oxygen via the chiral diamine backbone. High selectivity can be explained by the maximization of stereochemical interaction between the ligand and incoming substrate in the transition state (Scheme 28).



Scheme 28: Jacobsen catalyst **94** and the enantiofacial bias of its catalytically active species **95**

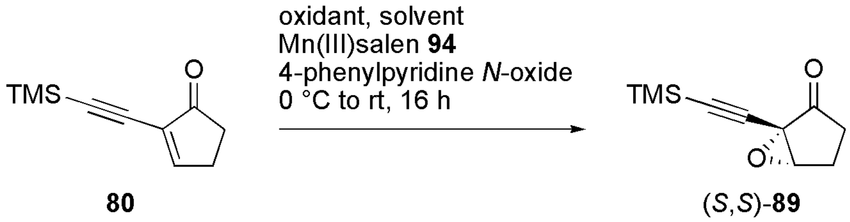
The chiral catalyst **94** was prepared in four steps from racemic *trans*-1,2-diaminocyclohexane (**98**) and 2,4-di-*tert*-butyl-phenol (**96**).[111] The phenol **96** was formylated to obtain the corresponding salicylaldehyde **97**. Efficient resolution of *trans*-1,2-diaminocyclohexane (**98**) with L(+)-tartaric acid gave enantiomerically pure (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (**99**), which was then coupled to the salicylaldehyde **97** to afford the resulting salen ligand **100**. A final complexation reaction with Mn(OAc)$_2$ in presence of NaCl yielded the desired chiral catalyst **94** (Scheme 29).



Scheme 29: Synthesis of the (*R*,*R*)-salen-Mn(III)-complex **94** for the asymmetric Jacobsen epoxidation

The epoxidation of α-substituted 2-cyclopentenone **80** with NaOCl as oxidant, (*R*,*R*)-salen-Mn(III)-complex **94** and 4-phenylpyridine *N*-oxide in a biphasic solution of CH_2Cl_2 and aqueous Na_2HPO_4-buffer was successful to give the desired product (*S*,*S*)-**89** in 60% yield (Table 2). The enantiomeric excess was determined to be 90%. In optimization studies it was shown that the concentration of the oxidant has a substantial impact on the conversion. Best results were obtained when a 2 M solution of NaOCl was used. The addition of the Lewis basic 4-phenylpyridine *N*-oxide turned out to be beneficial for a good conversion. Other oxidants such as iodosobenzene, dimethyldioxirane (DMDO) and hydrogen peroxide were screened exhibiting inferior results compared to NaOCl.

Table 2: Jacobsen epoxidation reactions on 2-cyclopentenone **80** using different oxidants



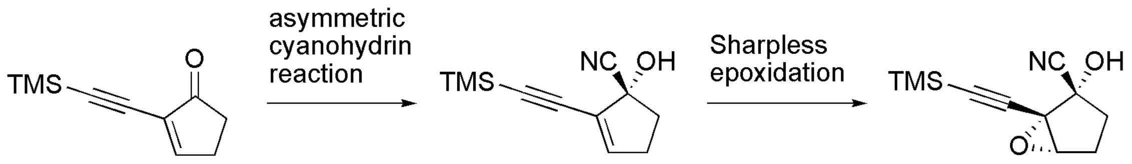
entry	oxidant	solvent	yield [%]	*ee* [%]
1	NaOCl	CH_2Cl_2 / aq. Na_2HPO_4	60	90
2	PhIO	MeCN	9	59
3	DMDO	CH_2Cl_2	16	19
4	H_2O_2	H_2O / MeCN	-	-

The absolute stereochemistry of the obtained epoxyketone **89** was determined at a later stage of the synthesis. X-ray crystallographic investigations on downstream intermediates allowed to deduce the correct stereochemistry of the product to be the (*S*,*S*)-enantiomer (see chapter 3.3.1, p. 41).

The asymmetric epoxidation of 2-cyclopentenone derivatives has been an unsatisfying issue so far. Especially, α-substituted cyclic enones as substrates represented an unresolved problem. With this achievement the first enantioselective epoxidation of an α-substituted 2-cyclopentenone compound succeeded giving the corresponding 2,3-epoxycyclopentanone in high *ee* and good yield.

3.2.3. Asymmetric cyanohydrin reactions

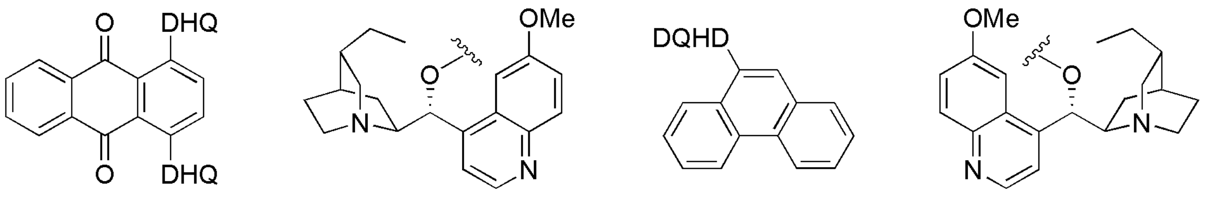
Subsequent investigations concentrated on the asymmetric cyanohydrin reaction. This approach should render further transformations possible, which lead to the envisaged chiral building block in a very elegant way. Initial experiments focused on the conversion of α-substituted 2-cyclopentenone **80** to a chiral cyanohydrin **101**, which results in the formation of an allylic alcohol. Allylic alcohols are excellent substrates for the well known titanium alkoxide mediated Sharpless asymmetric epoxidation. Using chiral tartrate esters and alkyl hydroperoxides, enantioenriched epoxy alcohol **102** should be obtained (Scheme 30).



80 **101** **102**

Scheme 30: Approach towards the chiral building block **102**

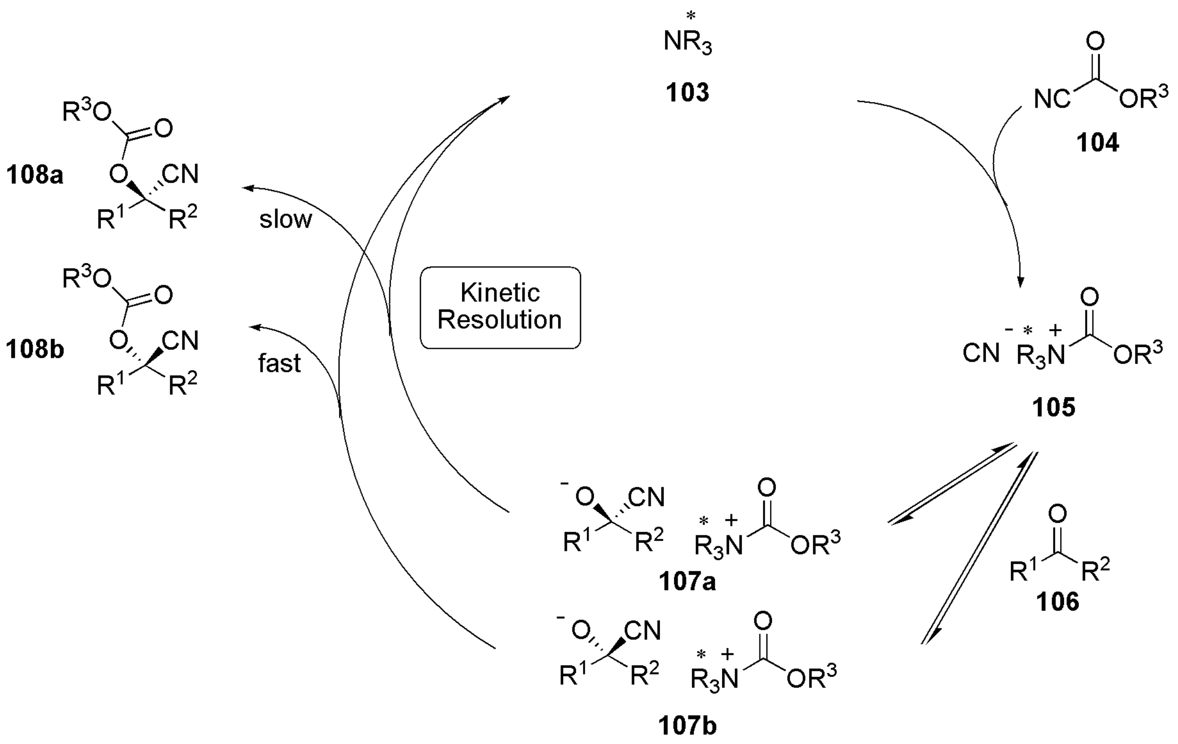
The cyanation of ketones is more challenging compared to the cyanation of aldehydes. The steric hindrance to cyanide attack and the lower electrophilicity of the carbonyl group are typically the main drawbacks. However, powerful methods have been developed in the last decades to overcome these problems and were reviewed elsewhere.[112-114] Aromatic ketones and aliphatic methyl and ethyl ketones are excellent substrates for many privileged catalysts. Ketones such as the aromatic indanone and tetralone were frequently used as model substrates, however, simple cyclic ketones such as cyclopentenone were little addressed so far. Small differences in sterics and electronics adjacent to the carbonyl group require enhanced stereodifferentiating properties of the catalyst. Encouraged by a chiral Lewis base-catalyzed asymmetric cyanation reported by Deng,[115] attention was drawn to this promising concept since α,α-disubstituted cyclopentanone and cyclohexanone derivatives could be converted to the corresponding cyanohydrins in excellent enantioselectivities using modified cinchona alkaloids as Lewis base catalysts (Figure 15).



$AQN(DHQ)_2$ DHQ(dihydroquinyl) PHN-DHQD DHQD(dihydroquinidyl)

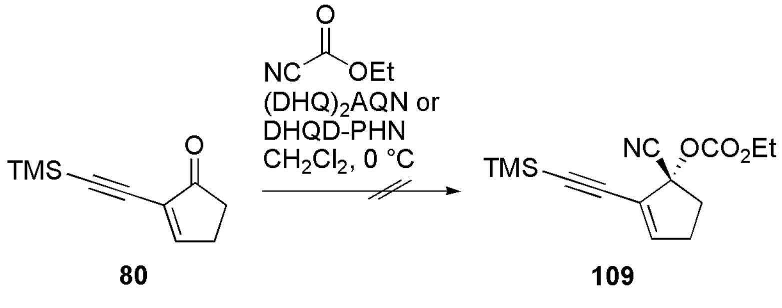
Figure 15: Cinchona alkaloids as chiral ligands for the cyanation of ketones

Ethyl cyanoformate as cyanide source was employed. As the commonly used TMSCN is relatively expensive and highly toxic, ethyl cyanoformate reveals beneficial properties and is therefore more attractive. A proposed mechanism of this reaction is shown in scheme 31.



Scheme 31: Proposed mechanism of the cyanation of ketones with alkaloid derived chiral catalysts by Deng et al.

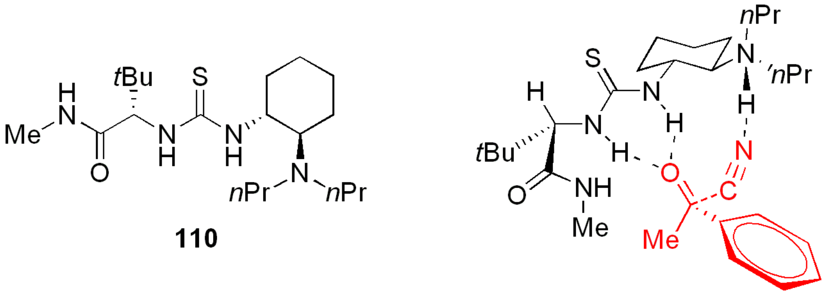
In the first step the cyanoformate **104** forms a chiral ion complex **105** with the chiral tertiary amine **103**. Two diastereomeric intermediates **107a** and **107b** are generated with the ketone **106** undergoing fast interconversion between each other. Transfer of the alkoxycarbonyl group from the *N*-acyl ammonium to the alkoxide at different rates gives rise to the optically enriched products **108a** and **108b**, respectively. The *ee* is therefore determined by a kinetic resolution in the last step.



Scheme 32: Cyanation with ethyl cyanoformate and chiral cinchona alkaloid ligands

α-Substituted 2-cyclopentenone **80** showed no clean reaction upon treatment with ethyl cyanoformate and $(DHQ)_2AQN$ or DHQD-PHN (Scheme 32). At low temperatures the reactivity was too low giving no conversion, upon slow warming to 0 °C the starting material started to react nonspecifically to form many by-products. A non-chiral version with DABCO instead of the alkaloid derived catalyst revealed a competing 1,4-addition. Additionally, cleavage of the TMS group was observed to set the highly reactive terminal alkyne free, which resulted in the formation of polymerization products. These observations indicate that alkynes and α,β-unsaturated subunits are not well tolerated by this approach.

A more versatile strategy with a broader substrate scope including α,β-unsaturated derivatives was reported by Jacobsen,[116] namely a thiourea catalyzed cyanosilylation reaction. Thiourea derived ligand **110** was developed, which proved to be general for a wide range of ketones (Figure 16). In presence of TMSCN and trifluoroethanol α-bromo-2-cyclohexenone, for instance, was converted to the corresponding cyanohydrin exclusively. Hence, the applicability of this method for cyclic α,β-unsaturated ketones is well exemplified. A cooperative mechanism, in which the thiourea activates the ketone and the tertiary amine activates the in situ formed HCN simultaneously, is thought to be the mode of activation.[117]



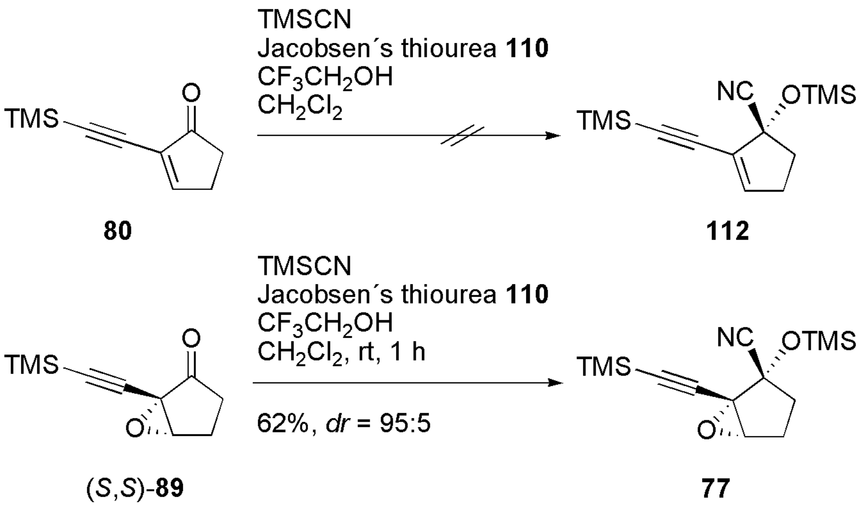
110

111

Figure 16: Thiourea ligand **110** for the cyanosilylation by Jacobsen et al. and the proposed transition state **111** for the addition of HCN to acetophenone

Investigations on the cyanosilylation of α-substituted 2-cyclopentenone **80** showed no product formation (Scheme 33). The conversion was low even at elevated temperatures. Several activation agents were tested in an achiral approach. The chiral thiourea catalyst **110** was omitted and the ineffective trifluoroethanol was replaced by various additives. Thiourea, ZnI$_2$, 4-phenyl pyridine *N*-oxide, CsF, HMPA, DMF, DMSO, Et$_3$N and Ph$_3$PO showed no beneficial effects. Llittle conversion was detected using Me$_3$NO, however, not giving preparatively useful results. Ammonium salts such as Et$_4$NCN and Et$_4$NF turned out to be powerful activating agents giving multiple decomposition products spontaneously.

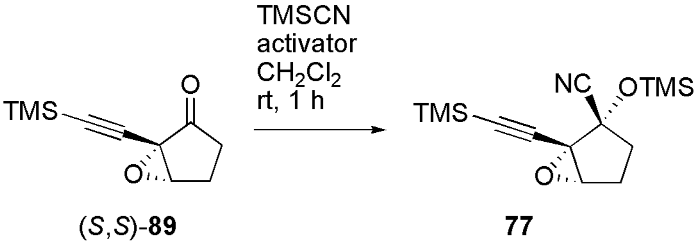
When the Jacobsen protocol was applied to α-substituted 2,3-epoxycyclopentanone (*S*,*S*)-**89**, a rapid and highly selective formation of the corresponding TMS protected epoxy cyanohydrin **77** as a single product was observed (Scheme 33).



Scheme 33: Cyanosilylation reactions on 2-cyclopentenone **80** and 2,3-epoxycyclopentanone (*S*,*S*)-**89** using Jacobsen’s protocol

Surprisingly enough, this reaction proceeds extremely regioselectively while the epoxide moiety remains untouched, and with a very good diastereomeric ratio of 95:5. Interestingly, when the chiral catalyst **110** was replaced simply by thiourea, the diastereoselectivity was even better, albeit at the expense of reactivity. By the use of Et_4NCN instead of thiourea the yield could even be raised to 72% with a still excellent diastereomeric ratio of 98:2 (Table 3).

Table 3: Optimization of the cyanosilylation reaction of 2,3-epoxycyclopentanone (*S*,*S*)-**89**

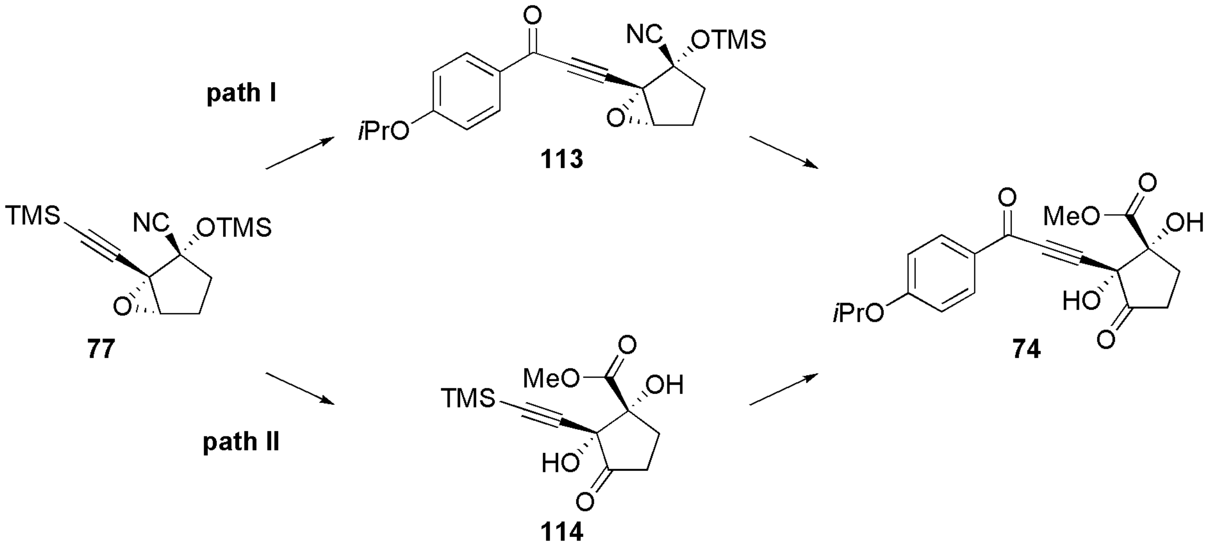


entry	activator	yield [%]	*dr*
1	catalyst **110**, CF_3CH_2OH	62	95:5
2	thiourea, CF_3CH_2OH	44	>99:1
3	Et_4NCN	72	98:2

The obtained results are in accordance with the findings of Aljarilla et al.,[118] who investigated the Bu_4NCN-catalyzed cyanosilylation of cyclic α,β-epoxyketones. However, obtained diastereoselectivities are in the case of the formation of **77** significantly higher. Even more interestingly, depending on the ringsize, reverse diastereoselectivities are obtained. Cyanosilylation of five-membered epoxyketones gave mainly the *syn* diastereomer, whereas the cyanosilylation of six-, seven- and eight-membered epoxyketones yielded mainly the *anti* diastereomer with respect to the epoxide moiety. This could be confirmed by the stereochemical assignment of the product, which was done after deprotection of the TMS ether (see chapter 3.3.1, p. 41) giving the *syn* diastereomer predominantly.

3.3. Subsequent transformations on the chiral building block 77

Careful strategic considerations were necessary to successfully accomplish further transformations on the chiral building block **77**. Stability and reactivity of the different functional groups under various reaction conditions have to be taken into account. Thus, several possibilities arise from this stage of the synthesis to proceed.



Scheme 34: Possible routes towards cyclization precursor **74**

The combination of the chiral building block **77** with a benzoic acid derivative can proceed via addition of the terminal acetylene to the carbonyl function (path I, Scheme 34). This requires the removal of the TMS protecting group prior to the coupling step. Particularly the TMS ether plays a pivotal role in this context since its stability is strongly limited, even though it is essential for the stability of the cyanohydrin preventing a retro cyanation reaction under basic conditions, which would reinstall the ketone moiety with concomitant loss of the stereochemical information.

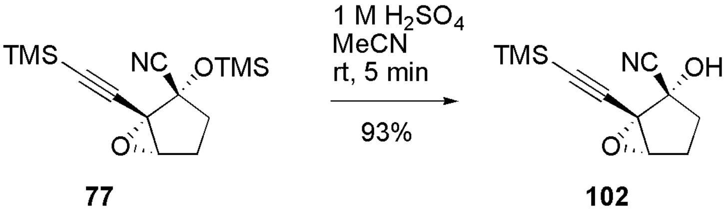
On the other hand, further transformations on the chiral building block **77** prior to the coupling step, namely the hydrolysis of the nitrile to give the methyl ester and oxidative ring opening of the epoxide, would give rise to α-hydroxyketone **114** (path II, Scheme 34). In this way, the differentiation of both TMS groups is circumvented. However, two acidic protons in direct proximity of the carbonyl group may interfere with the coupling step, which is typically done under basic conditions. Alternatively, the coupling step can also be carried out prior to the oxidative ring opening.

Both strategies were pursued in parallel. The results are described in the following.

3.3.1. Differentiation of the TMS ether and TMS acetylene

Amongst the frequently used silyl ethers the TMS ether is most susceptible to hydrolysis with either acid or base. A TMS acetylene is much more stable and tolerates acidic and to some extent also basic conditions. Hence, the selective deprotection of a TMS ether in presence of the TMS acetylene should be quite easy. The reverse way however, the selective deprotection of a TMS acetylene in presence of a TMS ether, is a rather difficult endeavor and has not been reported. No literature precedent could be found.

Indeed, deprotection of the TMS ether **77** using a 1 M aqueous solution of H_2SO_4 in MeCN in a ratio of 1:1 proceeded smoothly to give the corresponding 2,3-epoxyalcohol **102** in 93% after recrystallization from diethyl ether and pentane (Scheme 35).



Scheme 35: Cleavage of the TMS ether to generate the free alcohol **102**

The crystal structure of the alcohol **102** reveals the anticipated *syn* configuration of the alcohol functionality with respect to the epoxide with the nitrile pointing to the opposite direction. The absolute configuration was determined to correspond to the (1*S*, 2*S*, 3*S*)-isomer (Figure 17).

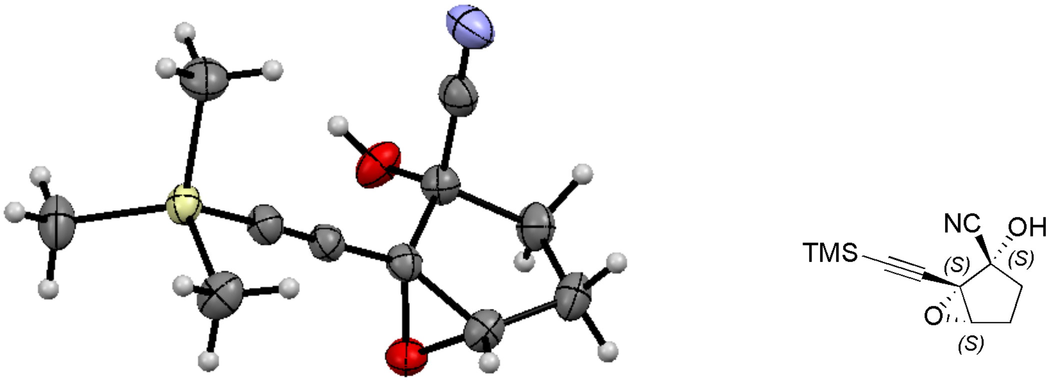
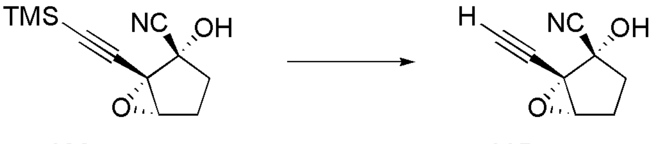


Figure 17: Ortep plot of alcohol **102**

Furthermore, the deprotection of the TMS acetylene from 2,3-epoxyalcohol **102** was investigated. Silyl groups are easily cleaved by fluoride ion, which is attributed to the high affinity of the fluoride ion for silicon. Treatment of the alcohol with TBAF as trihydrate or as an anhydrous solution in THF resulted in a fast conversion, however, all attempts to isolate the product **115** failed (Table 4, entries 1 and 2).[119] This could be traced back to the mild basicity of fluoride in aqueous solutions and the even higher basicity of “naked” fluoride in anhydrous solutions, which might deprotonate the alcohol and lead to a back-reaction to the corresponding 2,3-epoxyketone **89**. Under basic conditions polymerization products between the ketone and the deprotected terminal alkyne might have been formed. The same observations were made using K_2CO_3 in anhydrous MeOH, another frequently used method for the deprotection of TMS acetylenes (Table 4, entry 3).[119] Hence, the focus was shifted to a silver mediated deprotection reaction, which allows a TMS cleavage under non-basic conditions with catalytic amounts of $AgNO_3$.[120] In this way, the deprotected acetylene **115** could be obtained in 54% yield (Table 4, entry 4).

Table 4: Deprotection of the TMS acetylene **102**

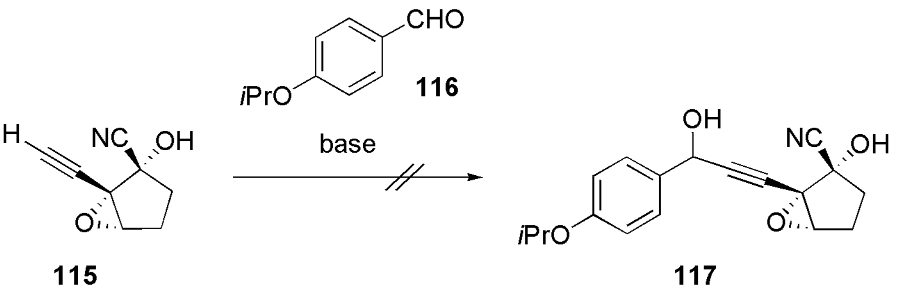


102 **115**

entry	conditions	yield [%]
1	TBAF·3H_2O, THF, 0 °C, 10 min	multiple products
2	TBAF anhydrous, THF, 0 °C, 10 min	multiple products
3	K_2CO_3, MeOH, 0 °C, 10 min	multiple products
4	$AgNO_3$, acetone/H_2O, rt, 16 h	54[a]

[a] estimated by NMR

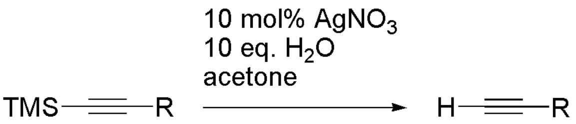
Unfortunately, the planned coupling step with protected *p*-hydroxybenzaldehyde **116** with various bases such as LDA, *n*-butyl lithium or KOH failed (Scheme 36). The very low stability of the unprotected cyanohydrin **115** towards bases made further steps impossible.



Scheme 36: Unsuccessful coupling of alcohol **115** with *p*-hydroxybenzaldehyde **116**

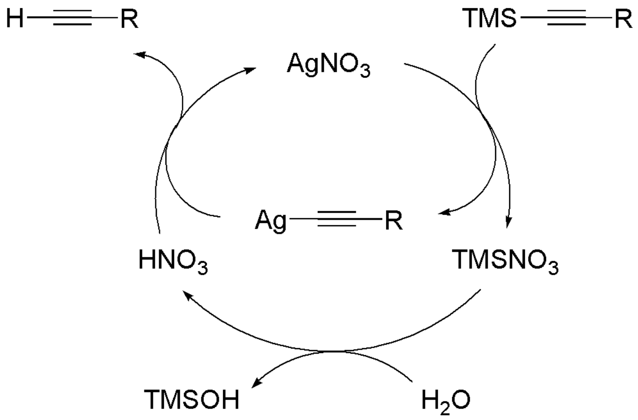
Previous observations clearly emphasize the inevitable necessity of a protected alcohol functionality. Thus, a novel methodology is required to selectively cleave the TMS acetylene in presence of a TMS ether if further protecting group manipulations are supposed to be avoided.

Since neither basic nor acidic conditions are tolerated, a very mild procedure is essential for the envisaged selectivity. Based on the previous results, studies were concentrated on the previously applied reaction using literature conditions with catalytic amounts of $AgNO_3$ in acetone and H_2O as a co-solvent (Scheme 37).



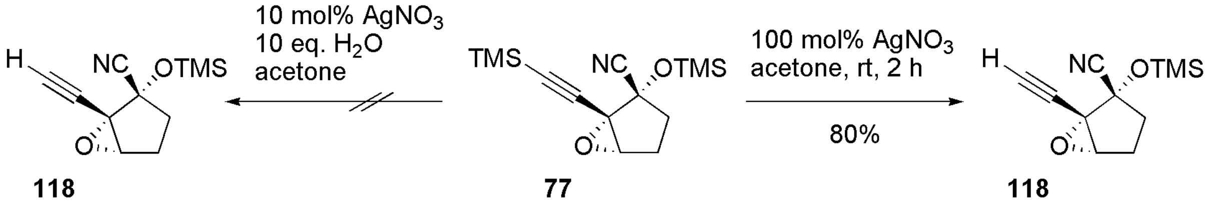
Scheme 37: Literature conditions for the deprotection of TMS acetylenes[120]

It was found to be effective for the cleavage of the TMS acetylene. However, a concomitant cleavage of the TMS ether was also observed. This can be explained by the in situ formation of nitric acid if H_2O is present in the reaction mixture (Scheme 38).



Scheme 38: Proposed mechanism for the Ag-catalyzed cleavage of TMS acetylenes

Consequently, if the reaction is carried out under anhydrous conditions, the catalytic cycle would be interrupted as $TMSNO_3$ cannot be hydrolyzed. Necessarily, the reaction would have to be performed stoichiometrically in $AgNO_3$. Indeed, using waterfree conditions and one equivalent of $AgNO_3$, the selective cleavage of the TMS acetylene **77** was achieved keeping the silyl ether nonchanged (Scheme 39). Aqueous workup with a saturated solution of NH_4Cl gave the deprotected acetylene **118** as single product in 80% yield after extraction. Further purification was not necessary due to the high purity of the isolated material.



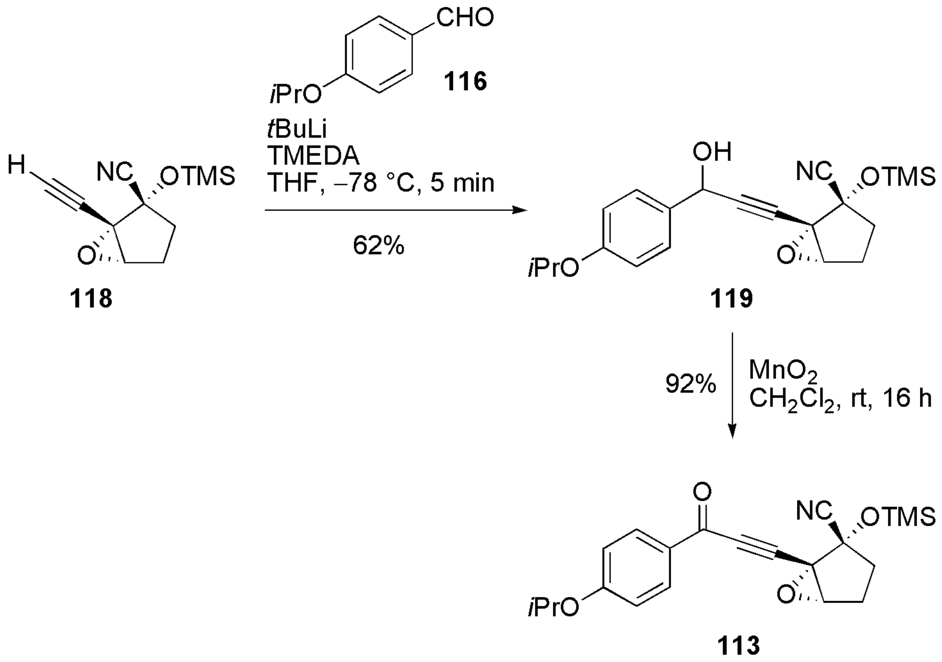
Scheme 39: Selective cleavage of the TMS acetylene in presence of a TMS ether to yield **118**

Using improved reaction conditions of a literature procedure,[120] a selective deprotection of a TMS alkyne in presence of a TMS ether was achieved for the first time. This provides a novel and powerful tool for challenging applications in the synthesis of complex molecules.

Further improvements of this reaction procedure using catalytic amounts of $AgNO_3$ in buffered aqueous media should be considered and remain to be explored.

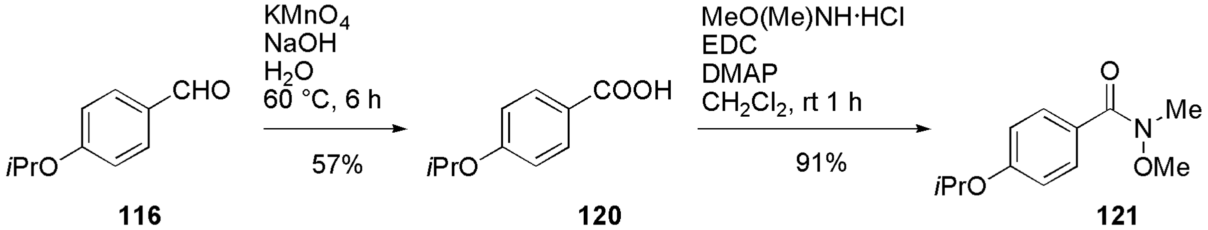
3.3.2. Coupling reactions with benzaldehyde and benzoic acid derivatives

Because of its acidity, the acetylene hydrogen can be abstracted with bases. However, the addition of the terminal alkyne to a carbonyl function under basic conditions is strongly limited by the stability of the TMS ether. Various bases have been screened to identify an appropriate reagent, which effectively deprotonates the alkyne, but which does not interfere with the other functional groups in the molecule. Isopropyl protected *p*-hydroxybenzaldehyde **116** was used as reactant for the coupling experiments. Upon treatment with $CsOH{\cdot}H_2O$, NaO*t*Bu or *n*-butyl lithium multiple decomposition products were observed since they do not only deprotonate the alkyne, but also unspecifically attack the silyl ether, the nitrile or the epoxide moiety due to their significant nucleophilicity. The non-nucleophilic amine base DBU showed no conversion, which can be simply traced back to its insufficient basicity in THF. Sterically demanding bases like LiHMDS and LDA revealed initial product formation, however, the formation of many by-products did not make the reactions synthetically useful. Better results were obtained using *t*-butyl lithium in presence of TMEDA as complexation reagent for the lithium ion. After extensive optimization, it was possible to isolate the crude propargylic alcohol **119** in 62% yield as a mixture of diastereomers with the TMS ether remaining intact. Subsequent oxidation of the alcohol using an excess of MnO_2 in CH_2Cl_2 afforded the corresponding ketone **113** as single stereoisomer in 92% yield (Scheme 40).



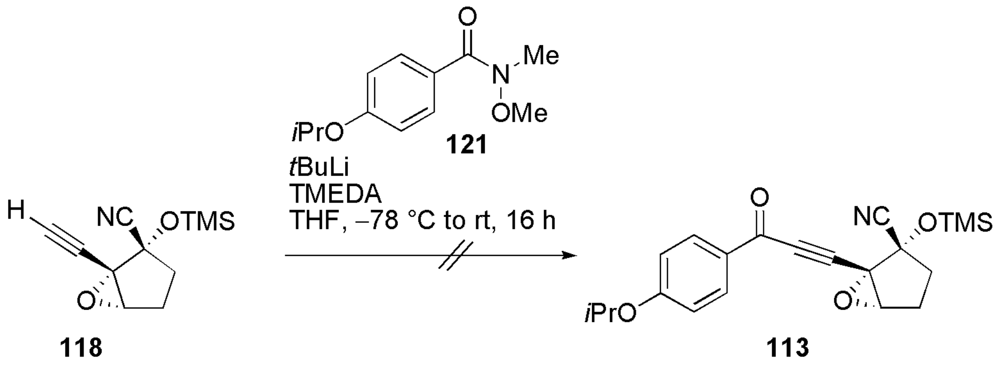
Scheme 40: Reaction of terminal alkyne **118** with benzaldehyde **116** and subsequent oxidation of the alcohol **119**

Aiming for a further improvement of the coupling reaction, the Weinreb amide **121** of isopropyl protected *p*-hydroxy benzoic acid as reaction partner was envisaged. With respect to the principles of efficiency this approach would save one step directly establishing the desired carbonyl functionality. The amide was prepared from the corresponding aldehyde **116** by oxidation and subsequent treatment with *N*,*O*-dimethylhydroxylamine hydrochloride (Scheme 41).



Scheme 41: Synthesis of the Weinreb amide **121** from isopropyl protected *p*-hydroxy-benzaldehyde **116**

In contrast to the aldehyde **116** the Weinreb amide **121** proved to be not reactive enough in the coupling reaction with terminal acetylene **118**. No product formation was observed in this case (Scheme 42). Further examinations with the appropriate ester or anhydride should be carried out to further enhance the accomplished results.



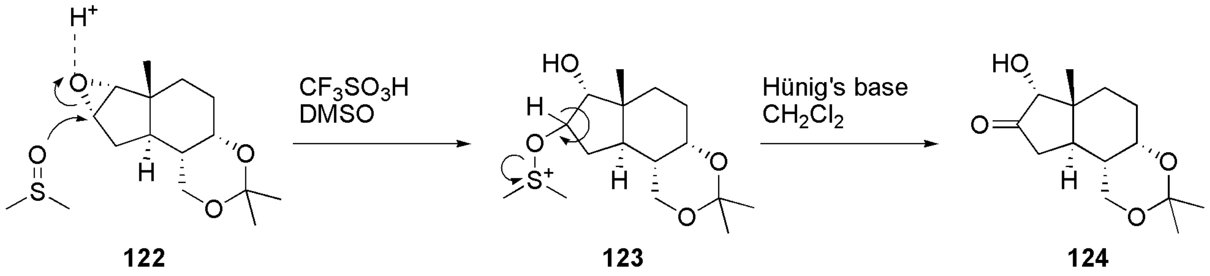
Scheme 42: Attempted reaction of terminal alkyne **118** with Weinreb amide **121**

3.3.3. Ring opening reactions on the epoxide

To evaluate whether the ring opening of the epoxide or the hydrolysis of the nitrile moiety in compound **77** prior to the coupling step with aldehyde **116** is superior to the present synthetic route (see chapter 3.3, p. 40), further investigations focused on ring opening reactions and were examined on the epoxide **102**. Special attention has to be drawn to the stereochemical outcome of the reaction since the *syn* orientation of both hydroxy groups attached at the quaternary stereocenters must remain intact during this transformation where sterical and electronical factors play a crucial role. Under basic conditions the attack of hydroxide should predominantly occur at the secondary carbon due to minimized steric interactions giving the product with the correct stereochemical orientation. All attempts, however, to open the epoxide under basic conditions failed. Reactions were performed in buffered solutions in the pH range from 8 to12 (Scheme 44). In the lower pH range (8 to 10) a retro-cyanation reaction to the corresponding ketone **89** was observed predominantly, in even more basic media (pH > 10) different reaction products of unknown structure were obtained.

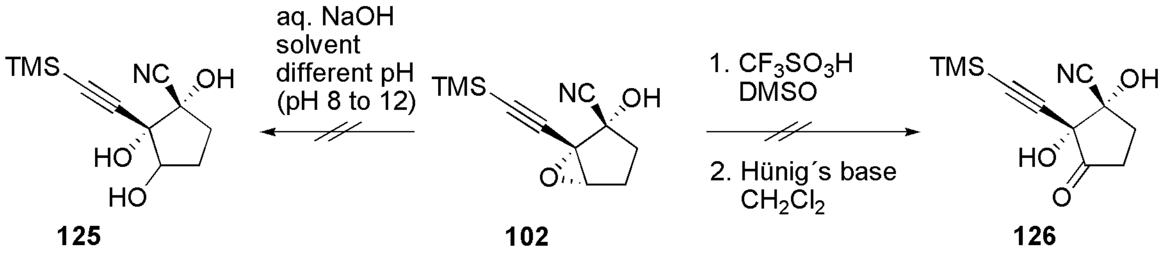
Under acidic conditions the more stable carbenium ion should be formed as a proton activates the epoxide prior to the attack of H_2O. Since tertiary carbon centers stabilize a charged intermediate better than secondary carbon centers, the attack at the higher substituted carbon should be favored. However, sterical interactions should have also a strong impact on the product formation. Thus, the outcome of the reaction cannot be unambiguously predicted. During experiments on the hydrolysis of the nitrile under acidic conditions, ring-opened products were formed, however, only as an inseparable mixture of multiple products (see chapter 3.3.4, p. 49).

A highly elegant way to solve this synthetic problem was reported by Trost[88] using a DMSO mediated oxidative ring opening reaction (Scheme 43). The key step is initiated by the activation of the epoxide **122** with triflic acid followed by a nucleophilic attack of DMSO. High regioselectivity was observed as the steric interactions were minimized. Upon treatment with Hünig's base the α-hydroxyketone **124** was installed with simultaneous loss of dimethylsulfide.



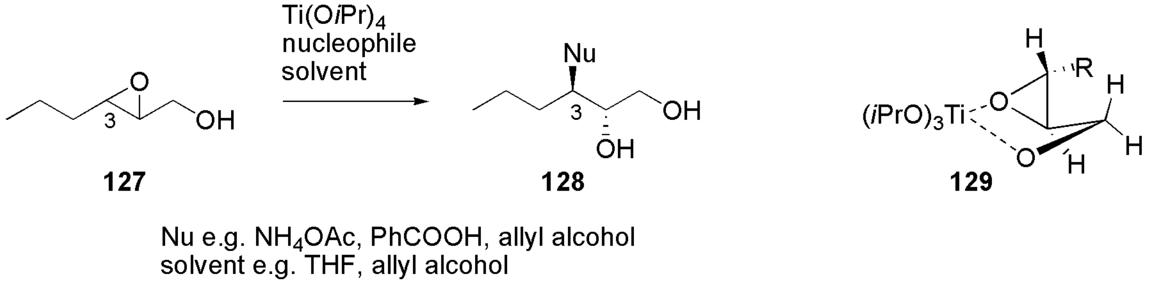
Scheme 43: Oxidative ring opening reported by Trost[88]

Treatment of epoxide **102** with triflic acid in DMSO resulted in a fast and quantitative consumption of the starting material. Addition of Hünig's base, however, was incompatible with the cyanohydrin moiety. Experiments to trap the ring-opened structure prior to the oxidation step failed as well. Upon careful neutralization a back-reaction was observed restoring the epoxide starting material again. Alternatively, the Lewis acid $Mg(OTf)_2$ instead of a Brønstedt acid was used to activate the epoxide. Chelation of the epoxide and the vicinal hydroxy group with $Mg(OTf)_2$ was supposed to suppress the cyanide elimination as well as to enhance the regioselectivity of the nucleophilic attack. Unfortunately, $Mg(OTf)_2$ turned out to be ineffective, no conversion could be observed.



Scheme 44: Ring opening reactions under basic and oxidative conditions

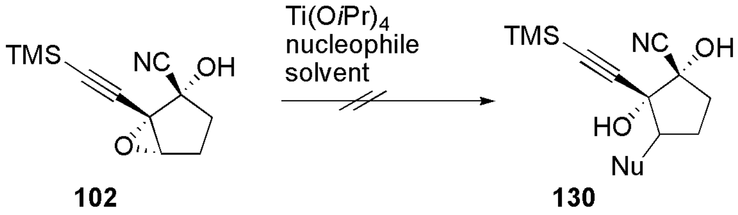
Sharpless has reported the highly regioselective titanium isopropoxide-mediated ring opening of 2,3-epoxy alcohols with various nucleophiles.[121] The efficient coordination of the alcohol with the metal center in a bidentate manner (see **129**, Scheme 45) is thought to be the determining factor for the strong preference of the nucleophiles to attack at C3 of the epoxy alcohol (Scheme 45).



Scheme 45: Regioselective ring opening of 2,3-epoxy alcohols with nucleophiles by Sharpless et al.[121]

However, no 2,3-epoxyalcohols of cyclic compounds as substrates were examined in the literature precedents. In the present study acetate, benzoic acid and allyl alcohol were used as nucleophiles to open the epoxide (Table 5). No conversion was observed with acetate and benzoic acid. Upon warming slow decomposition of the starting material **102** occurred over time. With allyl alcohol the starting material was partially converted to ketone **89**, which lacks the cyanohydrin unit. As epoxides in general are poor Lewis bases, cyclic epoxy alcohols in particular might be even worse substrates for an effective coordination by the Lewis acid. Consequently, the nucleophiles such as acetate, benzoic acid and allyl alcohol do not undergo a ring opening reaction with the non-activated substrate.

Table 5: Ti(O*i*Pr)$_4$-mediated ring opening reactions using different nucleophiles



entry	conditions	product
1	NH_4OAc, THF, rt, 24 h	no conversion
2	benzoic acid, THF, rt, 24 h	no conversion
3	allyl alcohol, rt, 1 h	ketone **89**

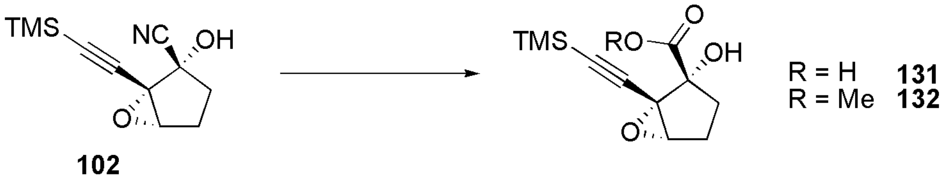
3.3.4. Hydrolysis and protecting group manipulations on the cyanohydrin

The low stability of the cyanohydrin **102** has shown to be a great drawback for many applications, which have been addressed so far. Although important steps have been accomplished such us the selective deprotection of the TMS acetylene or the coupling step with benzaldehyde **116** and *t*-butyl lithium in presence of the silyl ether, many reactions with a potential for an effective and straightforward synthesis did not proceed as the cyanohydrin **102** did not tolerate the required reaction conditions. Hence, a solution to this problem is desired to enable further steps in the proposed synthesis.

Two possibilities can be considered to enhance the stability of this functional group. The acidic hydrolysis of the nitrile to the corresponding α-hydroxy carboxylic acid or the corresponding ester transforms the very good leaving group CN to a stable substituent. Even more advantageous, it directly establishes the correct functionality found in the final natural product. Alternatively, a more stable protecting group can be introduced to mask the alcohol preventing the observed deprotonation under basic conditions and subsequent loss of the nitrile group.

Various conditions were used to hydrolyze the nitrile to the carboxylic acid **131** or the corresponding ester **132**, respectively (Table 6). With 4 M HCl no conversion was observed, under stronger acidic conditions using concentrated HCl in aqueous media or an anhydrous saturated solution of HCl in MeOH similar product mixtures were obtained in different ratios. The isolation and analysis of the obtained products was critical, nevertheless, no hydrolysis product could be identified, instead, ring-opened products were generated presumably by the nucleophilic addition of methanol or chloride (Table 6, entries 1-3). Since the removal of the silyl ether proceeds in 1 M sulfuric acid in acetonitrile, it is desirable to not only cleave the protecting group, but also to hydrolyze the nitrile in one single step. However, a 1 M solution of H_2SO_4 in MeCN turned out to be ineffective as the conversion was low after 22 h. Best results were achieved using a 3 M solution of H_2SO_4 instead, unfortunately, the resulting products could not be separated. NMR and IR data indicated that also ring-opened products were formed since no characteristic carbonyl signals, but broad OH signals were obtained. Harsher reaction conditions lead to the decomposition of the starting material (Table 6, entries 4-6). Further experiments using PPTS or *p*TsOH in dry MeOH did not show any product formation after 22 h, slow decomposition was observed in the case of *p*TsOH if longer reaction times were applied. Moreover, the reaction with triflic acid resulted in a mixture of unidentified compounds (Table 6, entries 7-9).

Table 6: Hydrolysis experiments with nitrile **102**



entry	conditions	product
1	4 M HCl / dioxane 1:1, reflux, 22 h	no conversion
2	aq. conc. HCl / MeOH / dioxane 1:1:1, reflux, 22 h	multiple products
3	anhydr. sat. HCl in MeOH, reflux, 22 h	multiple products
4	1 M H_2SO_4 / MeCN 1:1, reflux, 22 h	low conversion
5	3 M H_2SO_4 / MeCN 1:1, reflux, 22 h	multiple products
6	5 M H_2SO_4 / MeCN 2:1, reflux, 22 h	decomposition
7	PPTS (1.0 eq.), MeOH, reflux, 22 h	no conversion
8	*p*TsOH (0.1 eq.), MeOH, rt, 22 h	no conversion
9	TfOH (1.0 eq.), MeOH, reflux, 22 h	multiple products

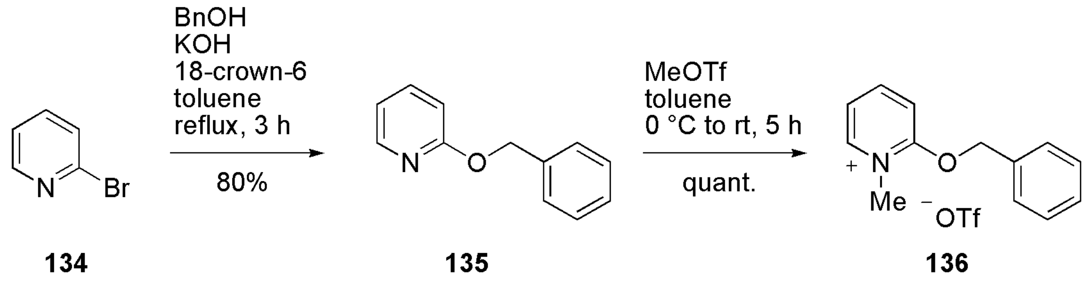
None of the performed experiments gave satisfying results. The hydrolyzed product was not found, instead, competing epoxide opening reactions occurred due to the higher reactivity of the epoxide in contrast to the nitrile. Under acidic conditions the activation of the epoxide for a subsequent addition of a nucleophile prevails over the hydrolysis of the nitrile. The hydrolysis under basic conditions was not carried out due to the instability of the cyanohydrin. An interesting biocatalytic approach towards α-hydroxy carboxylic acids was reported[122] using bacterial cells of *Rhodococcus erythropolis* NCIMB 11540. Having a highly active nitrile hydratase / amidase enzyme system present, enantiopure cyanohydrins could be converted to the carboxylic acids in high yields and without racemization. Since both enzymes are not commercially available, this bioorganic strategy could not be pursued although it represents an alternative to chemical procedures, which provides access to the desired α-hydroxy carboxylic acid as the crucial intermediate in the envisioned synthetical route.

Alternatively, a new protection strategy was used since previous approaches have shown to be insufficient. The choice of the appropriate protecting group for the alcohol is determined by the orthogonality to the present functional groups in the substrate. Various protecting groups were taken into consideration. As one possibility the benzyl group was chosen since it can be easily introduced under mild conditions and removed by hydrogenation in presence of a palladium catalyst (Table 7).

Table 7: Attempted benzylation of alcohol **102**

entry	conditions	product
1	BnBr, $NaHCO_3$, DMF, rt	decomposition
2	BnBr, Ag_2O, DMF, rt	decomposition
3	BnOH, $Bi(OTf)_3$, CCl_4, rt, 24 h	no conversion
4	BnCl, $Ni(acac)_2$, reflux, 24 h	decomposition
5	Bn-trichloroacetimidate, TfOH, CH_2Cl_2, rt, 30 min	trace **133**
6	Bn-trichloroacetimidate, TfOH, THF, rt	polymerization
7	Bn-trichloroacetimidate, TfOH, Et_2O, rt, 30 min	trace **133**
8	Bn-trichloroacetimidate, TMSOTf, CH_2Cl_2, rt, 30 min	trace **133**
9	Bn-trichloroacetimidate, $Sc(OTf)_3$, toluene, rt, 24 h	no conversion
10	2-Benzyloxy-1-methylpyridinium triflate, MgO, $C_2H_4Cl_2$, rt, 24 h	ketone **89**

The benzyl protecting group is often introduced under basic conditions. As expected this was not successful because of the base-labile cyanohydrin functionality (Table 7, entry 1). Metal catalyzed methods using Ag_2O,[123] $Bi(OTf)_3$[124] or $Ni(acac)_2$[125] gave either unspecific product mixtures, or no conversion was observed (Table 7, entries 2-4). Benzyl-trichloroacetimidate allows for the benzylation under acidic conditions.[126,127] Different solvents in combination with triflic acid were tested such as dichloromethane and diethyl ether, which gave traces of the desired protected alcohol **133**. However, the conversion was too low to be preparatively useful (Table 7, entries 5 and 7). In THF polymerization occurred to give a colorless highly viscous gel (Table 7, entry 6). With TMSOTf the conversion could not be significantly increased (Table 7, entry 8), $Sc(OTf)_3$[128] showed to be ineffective to catalyze the protection reaction (Table 7, entry 9). Another reagent which allows for a benzylation under neutral conditions is 2-benzyloxy-1-methylpyridinium triflate (**136**).[129] It was prepared from 2-bromopyridine (**134**) in two steps via a literature known procedure (Scheme 46).[130]

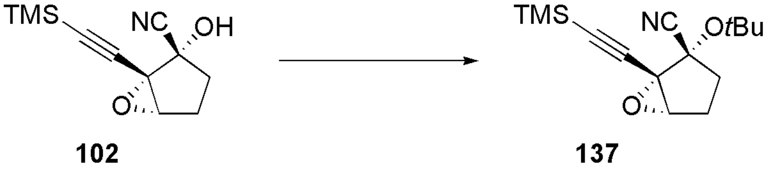


Scheme 46: Synthesis of 2-benzyloxy-1-methylpyridinium triflate (**136**)

Unfortunately, in presence of MgO as acid scavenger a retro-cyanation reaction was observed to yield ketone **89** predominantly (Table 7, entry 10). Although this method was also successfully tested on tertiary alcohols, it did not undergo the introduction of the benzyl group to the tertiary alcohol in substrate **102**. As a conclusion, the protection of the tertiary alcohol in the densely functionalized framework proved to be challenging since the alcohol functionality is shielded by a sterically demanding environment, which prevents an effective formation of the ether bond.

Thus, isobutylene was envisaged for the protection of **102** as *t*-butyl ether because it can be used as a gas and might alleviate the protection process. Moreover, *t*-butyl ethers are stable to most reagents except strong acids.

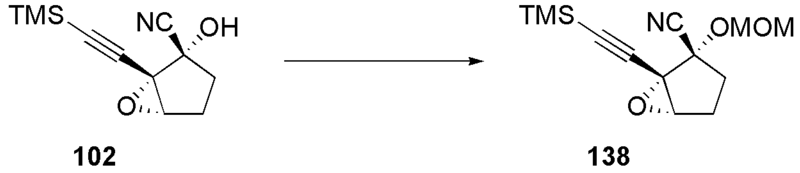
Table 8: Experiments on the protection of alcohol **102** as *t*-butyl ether **137**



entry	conditions	product
1	Isobutylene, PPTS, CH_2Cl_2, rt, 1 h	no conversion
2	Isobutylene, Amberlyst 15, CH_2Cl_2, rt, 1 h	ketone **89**
3	$Mg(ClO_4)_2$, Boc_2O, CH_2Cl_2, reflux, 24 h	conversion low trace **137** + ketone **89**

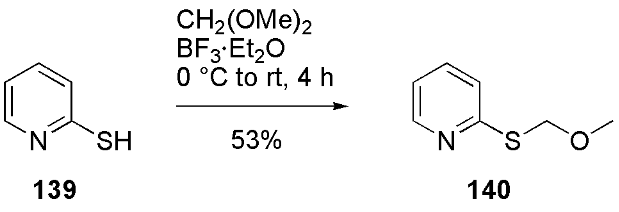
When isobutylene was bubbled through the alcohol **102** containing mixture in presence of PPTS, no conversion was observed. Using Amberlyst 15,[131] a polymer-bound acidic catalyst, ketone **89** was formed exclusively (Table 8, entries 1 and 2). Boc_2O in combination with anhydrous magnesiumperchlorate was reported to give the *t*-butyl ether, not as expected the corresponding Boc-derivative.[132] In fact, traces of the *t*-butyl ether were observed alongside with ketone **89**. However, the reactivity was low leaving the starting material widely unconsumed (Table 8, entry 3). As noticed similarly to the previous approach, the *t*-butyl group turned out to be too bulky for an efficient protection strategy. Thus, the rather slim methoxymethyl (MOM) group was chosen.

Table 9: Experiments on the protection of alcohol **102** as MOM ether **138**



entry	conditions	product
1	$CH_2(OMe)_2$, *p*TsOH, LiBr, reflux, 24 h	no conversion
2	$CH_2(OMe)_2$, $Sc(OTf)_3$, $CHCl_3$, reflux, 24 h	no conversion
3	$CH_2(OMe)_2$, P_2O_5, $CHCl_3$, rt, 1 h	ketone **89**
4	MOM-2-pyridylsulfide, NaOAc, AgOTf, THF, rt, 24 h	trace **138** + ketone **89**

The introduction of the methoxymethyl moiety under acidic conditions can be carried out using $CH_2(OMe)_2$ and a Lewis or Brønstedt acid. When p*ara*-toluenesulfonic acid was used, however, it was found to be ineffective to catalyze the desired transformation and no conversion was observed (Table 9, entry 1).[133] Scandium triflate showed the same behavior (Table 9, entry 2).[134] On the contrary, catalytic amounts of P_2O_5 gave the ketone **89** as single product (Table 9, entry 3).[135] MOM-2-pyridylsulfide (**140**) was reported to protect alcohols under very mild conditions.[136] The observed conversion was very low, but analytical data indicate that traces of the MOM ether were generated with a simultaneous formation of ketone **89**. The reagent was synthesized from 2-mercaptopyridine (**139**) and dimethoxymethane in one step (Scheme 47).[136]



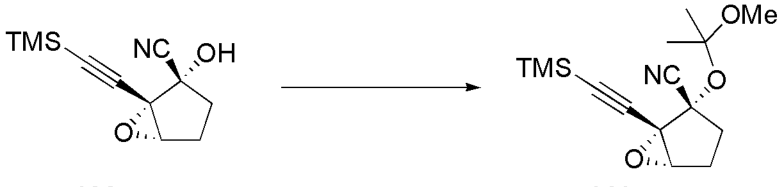
Scheme 47: Synthesis of MOM-2-pyridylsulfide (**140**)

Since the hydroxy group is poorly accessible for the introduction of a suitable protecting group, it can be expected that in turn it does not notably interfere in the downstream synthesis once the nitrile is hydrolyzed. Hence, a short-term protecting group was envisioned just for the hydrolysis of the nitrile. For that purpose, the synthesis of 1-methyl-1-methoxyethyl ether

141 was attempted. This protecting group is highly sensitive to acids, but more stable to bases. This strategy would allow for the mild hydrolysis of the nitrile under basic conditions and subsequent easy and quick removal of the protection group by an acidic workup procedure.

Unfortunately, all attempts to generate the desired ether **141** failed. Both, *p*TsOH and $POCl_3$ in 2-methoxypropene[137] gave no conversion (Table 10, entries 1 and 2). The same result was observed with 2,2-dimethoxypropane as a solvent (Table 10, entry 3).[138]

Table 10: Experiments on the synthesis of 1-methyl-1-methoxyethyl ether **141**

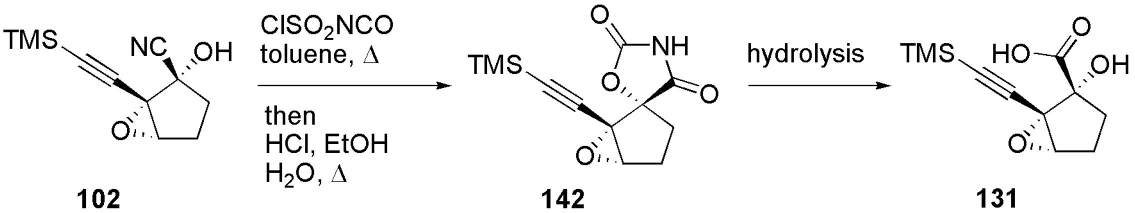


102 **141**

entry	conditions	product
1	CH_2=C(Me)OMe, *p*TsOH, reflux, 24 h	no conversion
2	CH_2=C(Me)OMe, $POCl_3$, reflux, 24 h	no conversion
3	$CMe_2(OMe)_2$, *p*TsOH, reflux, 24 h	no conversion

Although it was not possible to improve the stability of the cyanohydrin so far, several synthetic problems in the studies towards the total synthesis of limnophilaspiroketone (**15**) could be solved. An important step included the enantioselective epoxidation of an α-substituted cyclopentenone derivative, which was achieved for the first time in high enantioselectivity and good yield. A subsequent diastereoselective cyanohydrin reaction was accomplished. Both key steps allow for the formation of quaternary stereocenters with the correct absolute configuration. The selective deprotection of a TMS acetylene in the presence of a TMS ether was carried out. The differentiation between both protecting groups has not been reported so far and represents a general and valuable tool in organic synthesis. It enabled the coupling of the terminal acetylene to a benzaldehyde derivative and provided access to an important intermediate in the proposed synthetic route. However, problems arised from the instability of the cyanohydrin moiety in compound **102**. Since it turned out to be very base labile, ring opening reactions on the epoxide did not succeed. Further complications in downstream transformations such as the cyclization reaction under basic conditions can also be expected. Unfortunately, hydrolysis experiments on the nitrile and protecting group manipulations on the tertiary alcohol, which could have improved the stability of the cyanohydrin, were not successful. Nevertheless, a solution to this drawback has to be found since the stability of the cyanohydrin is a prerequisite for further steps in the total synthesis. Thus, a new concept has to be figured out to overcome this problem.

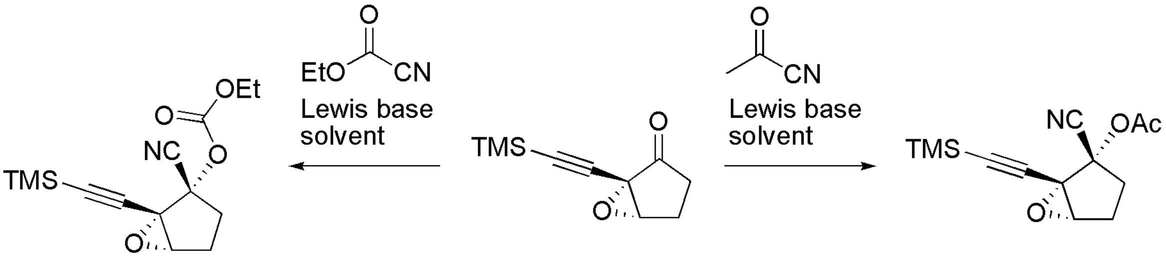
One possibility would be the use of chlorosulfonyl isothiocyanate, which is known to react with cyanohydrins to give 2,4-oxazolidinediones.[139] This approach would provide a useful route to the preparation of α-hydroxy carboxylic acid derivative **131** (Scheme 48).



102 **142** **131**

Scheme 48: Possible preparation of α-hydoxy carboxylic acid derivative **131** via oxazolidinedione **142**

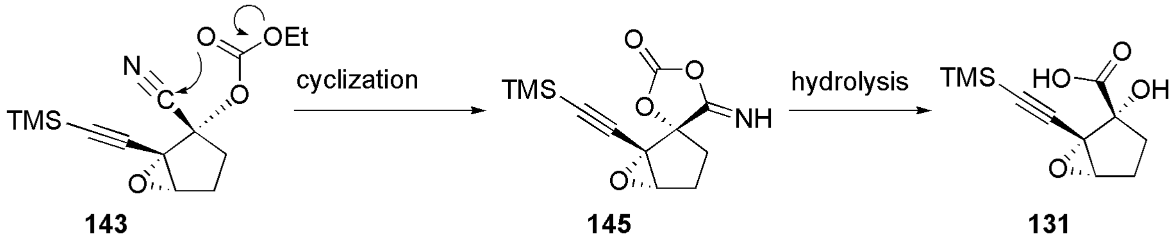
Alternatively, the use of different cyanide sources for the diastereoselective cyanohydrin reaction such as acyl cyanides or cyano formates enables the direct introduction of a protecting group at the alcohol oxygen. In that way, acetyl cyanide should give in presence of catalytic amounts of a Lewis base the acetylated cyanohydrin **144**.[140] Ethyl cyanoformate should result in the installation of the corresponding carbonate **143** (Scheme 49).



143 (*S*,*S*)-**89** **144**

Scheme 49: Possible cyanohydrin reaction with ethyl cyanoformate and acetyl cyanide

Moreover, from carbonate **143** a cyclization to the corresponding dioxolane **145** might be possible, which would give the α-hydroxy carboxylic acid **131** upon hydrolysis (Scheme 50).



Scheme 50: Possible cyclization of carbonate **143** and subsequent hydrolysis

Efforts have to be made to evaluate these strategies, and the feasibility of the proposed transformations remains to be explored in the future.

3.4. Limno-CP – a natural product derived model substrate

To gain information on the chemical reactivity on the one hand and on biological properties of 3(2*H*)-furanones on the other hand, the synthesis of the natural product derived model compound Limno-CP (**146**) (CP from cyclopentyl) was envisioned. It comprises the spirocyclic framework with the 3(2*H*)-furanone subunit and the phenolic substituent, which is also present in the natural product. The 5-membered ring, which is attached at the spiro carbon containing the second α,β-unsaturated carbonyl moiety, and all the rest of the substituents, however, are replaced by a simple cyclopentane ring. Consequently, an achiral simplified scaffold was generated (Figure 18).

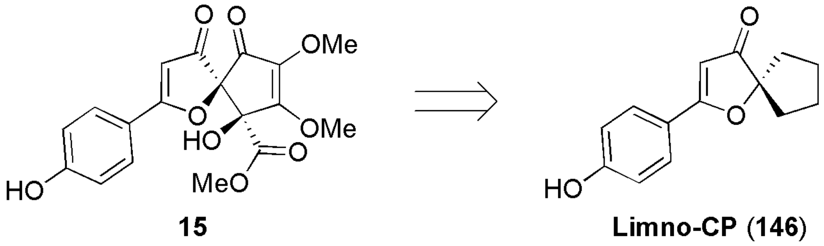


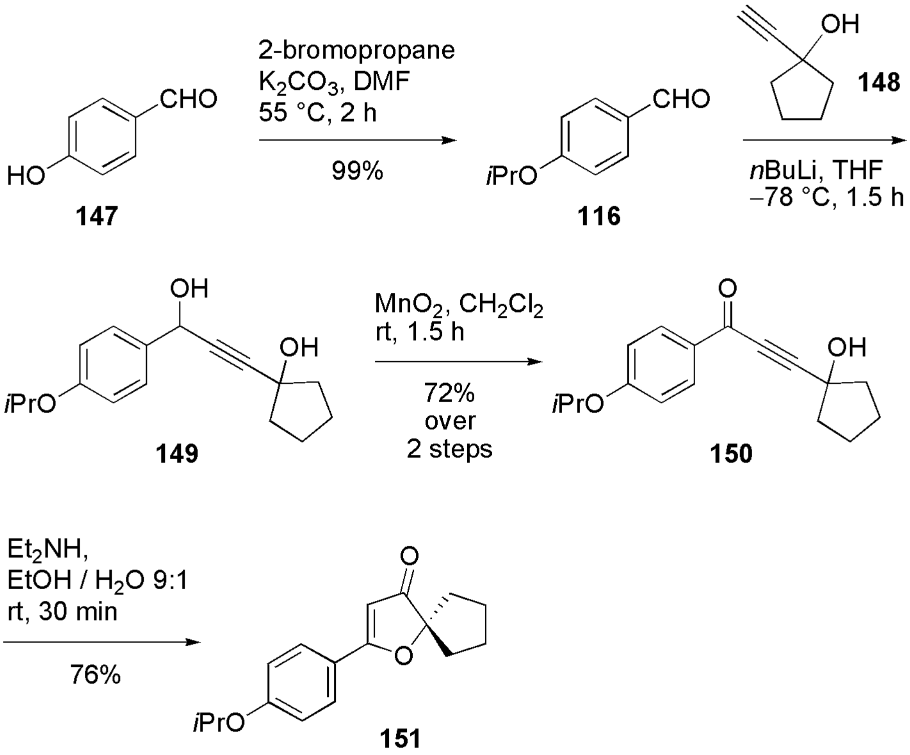
Figure 18: Design of the natural product derived model substrate Limno-CP (**146**)

This compound can be produced in a fast and straightforward reaction sequence. As discussed in the introductory part of this work (see chapter 1.6, p. 12) the spirocyclic framework can be installed via different ways. In this approach the 5-exo-trig cyclization of a 4-hydroxy-alk-2-ynone was envisioned, which was already applied by Parker et al.[47] in the total synthesis of bullatenone (**16**). The synthesis of the model compound focuses on the optimization of the reaction conditions, which are required for the formation of the spirocyclic 3(2*H*)-furanone moiety. The results from these experiments can then also be used for the synthesis of the natural product. Additionally, the investigations can provide a further insight into the mechanistic details of this reaction.

3.4.1. Synthesis of iPr-Limno-CP

The synthesis of *i*Pr-Limno-CP is closely related to a report by Shin et al., who applied this reaction sequence on similar compounds for the preparation of novel COX-2 inhibitors.[141] However, this methodology has never been applied to phenolic substrates. Therefore, the extension of this approach to phenolic substrates is envisioned in this study.

To start with, *p*-hydroxybenzaldehyde (**147**) was protected as isopropyl ether (Scheme 51).[142] This protecting group was chosen since it can be selectively removed in presence of methoxy groups using boron trichloride. Methoxy functionalities are not prone to cleavage under these conditions. The orthogonal behavior is particularly important for the synthesis of methoxy substituted natural product limnophilaspiroketone (**15**). Furthermore isopropyl ethers are stable under physiological conditions and give rise to a second set of biologically interesting compounds, which can be implemented into biological testing.



Scheme 51: Synthesis of *i*Pr-Limno-CP **151**

Protected *p*-hydroxybenzaldehyde **116** was coupled to lithiated 1-ethynylcyclopentanol (**148**) to afford diol **149**. Subsequent oxidation of the crude diol **149** with excess of MnO_2 yielded ketone **150** in 72% yield over two steps. Until this stage of the reaction sequence no purification by column chromatography was required. A diethylamine mediated cyclization of the propargylic alcohol **150** in ethanol/water 9:1 gave the spiroketone **151** in 76% yield after a final recrystallization. With inexpensive starting materials and commercially available standard reagents a facile synthesis of spiroketone **151** was achieved in four steps and very good total yield of 54%. All together, only two column chromatographic separations and one recrystallization were necessary for the whole sequence.

3.4.2. Investigations on the formation of the spirocyclic framework

Investigations were done to elucidate the underlying cyclization mechanism. Although a possible mechanism was proposed by Parker in the course of the total synthesis of bullatenone,[47] the rational remains rather vague since no sound experiments were carried out to verify the assumptions.

When literature conditions[141] were applied, only poor yields were obtained initially (Table 11, entries 1-2). When H_2O was added to the solvent, the product formation was significantly higher. A qualitative correlation based on un-optimized results is depicted in figure 19.

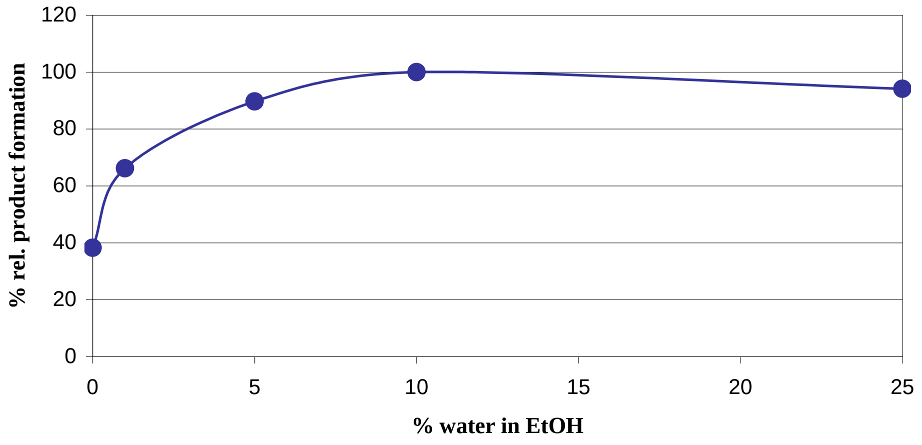


Figure 19: The crucial role of H_2O. The conversion is strongly dependant on the H_2O content in the solvent

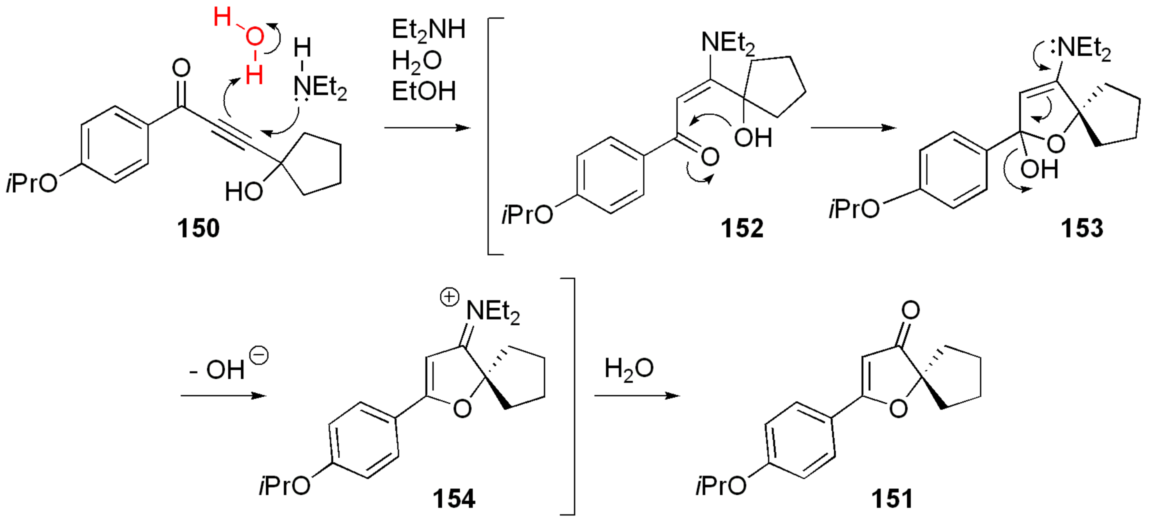
An optimum in the product formation is achieved when 10% H_2O is used in ethanol. The impact of the solvent has not been discussed in previous reports, however, the outcome of the reaction is strongly influenced by the H_2O content of the solvent.

Only poor product formation was observed if diethylamine was replaced by triethylamine or if it was omitted at all (Table 11, entries 4-5).

Table 11: Formation of *i*Pr-Limno-CP under various conditions

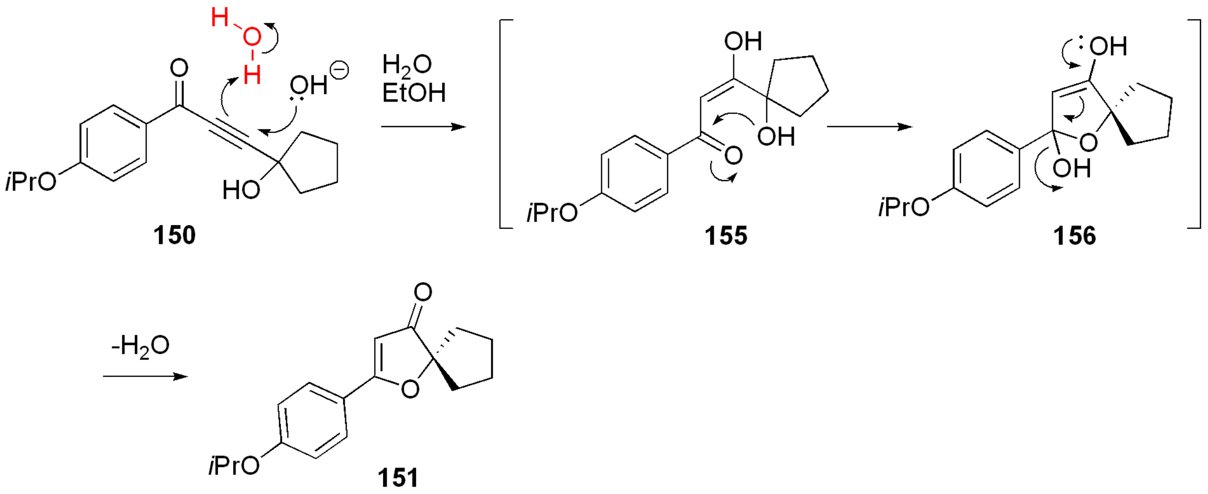
entry	Nuc / Base	solvent	T	time [h]	yield [%]
1	$HNEt_2$	EtOH 100%	rt	0.5	26
2	$HNEt_2$	EtOH 100%	reflux	4	35
3	$HNEt_2$	$EtOH/H_2O$ 9:1	rt	0.5	90
4	-	$EtOH/H_2O$ 9:1	reflux	4	7
5	NEt_3	$EtOH/H_2O$ 9:1	reflux	4	8
6	KOH	$EtOH/H_2O$ 9:1	rt	0.5	35
7	KOH	$EtOH/H_2O$ 9:1	reflux	4	90

These results indicate that $HNEt_2$ acts as a nucleophile adding to the electrophilic carbon of the acetylene unit while H_2O is needed as proton source for the addition process. Ring closure of intermediate **152** and subsequent loss of hydroxide in **153** lead to the formation of an iminium species **154**, which is finally hydrolyzed to give the final product **151**. The proposed mechanism is shown in scheme 52.



Scheme 52: Reaction mechanism for the formation of *i*Pr-Limno-CP (**151**)

Interestingly, the presence of H_2O alone is insufficient to catalyze this reaction, with strong bases, however, significant product formation was observed (Table 11, entries 6-7), albeit reflux conditions are required. In this case, the product **151** is formed via attack of hydroxide, ring closure and elimination of H_2O giving the 3(2*H*)-furanone scaffold directly (Scheme 53).



Scheme 53: Reaction mechanism for the formation of *i*Pr-Limno-CP (**151**) with KOH

To summarize, the synthesis of the model compound *i*Pr-Limno-CP (**151**) could be accomplished successfully. The 5-exo-trig cyclization of precursor **150** has not only proven to be a powerful methodology for the installation of the 3(2*H*)-furanone moiety, it also enabled the synthesis of the model compound in a multi-gram scale in 76% yield. The results from the experiments revealed interesting aspects of the reaction mechanism, which have not been discussed in the literature so far. Most importantly, the presence of water turned out to be essential for a sufficient conversion since it acts as a proton source for the addition of diethylamine to the triple bond. A nucleophile is imperatively required to mediate the reaction. $HNEt_2$ has shown to be the better nucleophile than hydroxide since it effectively catalyzes the cyclization at room temperature within 30 minutes, whereas reflux conditions are necessary in the case of KOH to yield the same result.

Starting from *i*Pr-Limno-CP (**151**), the synthesis of different α-substituted derivatives was envisioned.

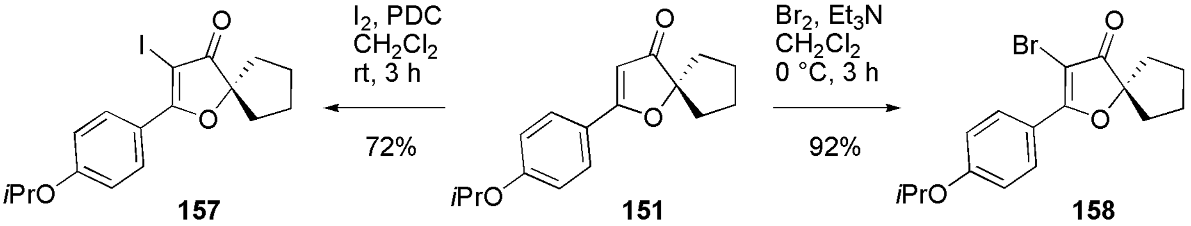
3.5. Synthesis of α-substituted derivatives of Limno-CP

The preparation of α-substituted 3(2*H*)-furanones from one common precursor has not been systematically studied in the literature. Single examples are known as intermediates for various target molecules. However, to minimize synthetic work, it is highly desirable to gain access to many α-substituted derivatives in simple one step modifications from one common precursor instead of finding different routes to every single derivative. Thus, one to three step transformations were envisaged for the generation of α-substituted 3(2*H*)-furanones from *i*Pr-Limno-CP as starting material. This approach facilitates the generation of a library of such spirocyclic α-modified 3(2*H*)-furanones, which can be used for the analysis of their biological properties.

3.5.1. Introduction of halogens

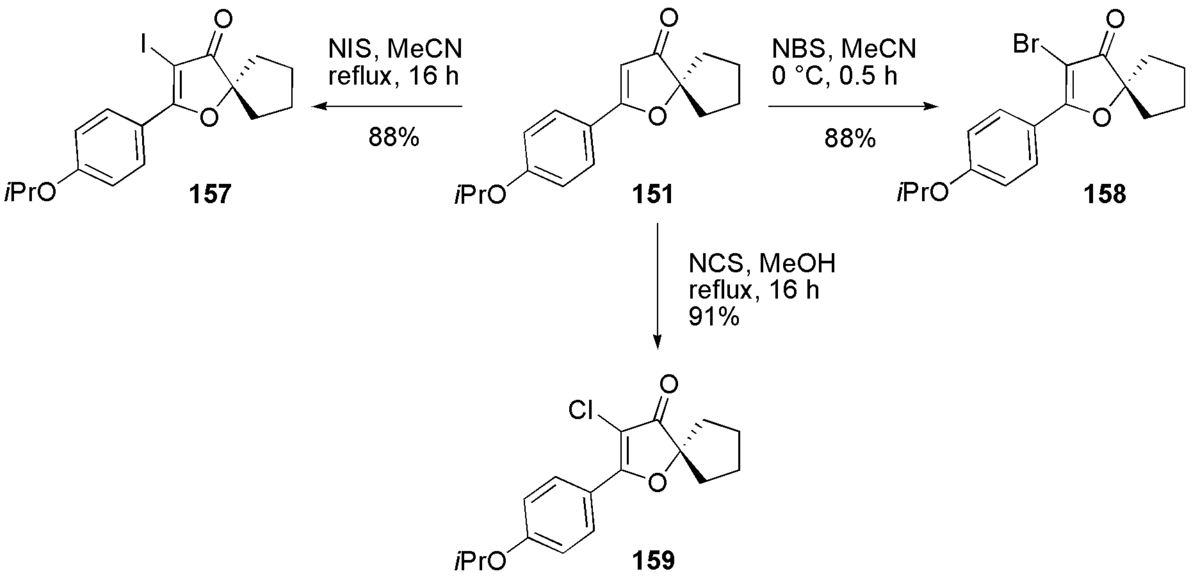
A few examples of α-halogen-3(2*H*)-furanones are reported in the literature. For the synthesis of phosphodiesterase 10-inhibitors a bromo-substituted 2,2-dimethyl-3(2*H*)-furanone derivative was prepared.[143] In the group of Kirsch a protocol for the construction of iodo-3(2*H*)-furanones was established[144] and also α-fluoro, α-chloro and α-bromo derivatives are known as part of a steroidal framework with anti-inflammatory activity.[145] Furthermore, an α-fluoro-3(2*H*)-furanone, very similar to this target molecule, was described.[146]

The α-bromo- and α-iodo-3(2*H*)-furanones are of particular interest since they are suitable starting materials for a further functionalization via metalation procedures such as palladium catalyzed coupling or bromine-lithium exchange reactions. Using common reaction procedures, α-bromo-3(2*H*)-furanone **158** was obtained in 92% yield via a bromination-HBr elimination pathway.[147] Likewise, the corresponding α-iodo derivative **157** was prepared in 72% yield using iodine and catalytic amounts of PDC (Scheme 54).[148]



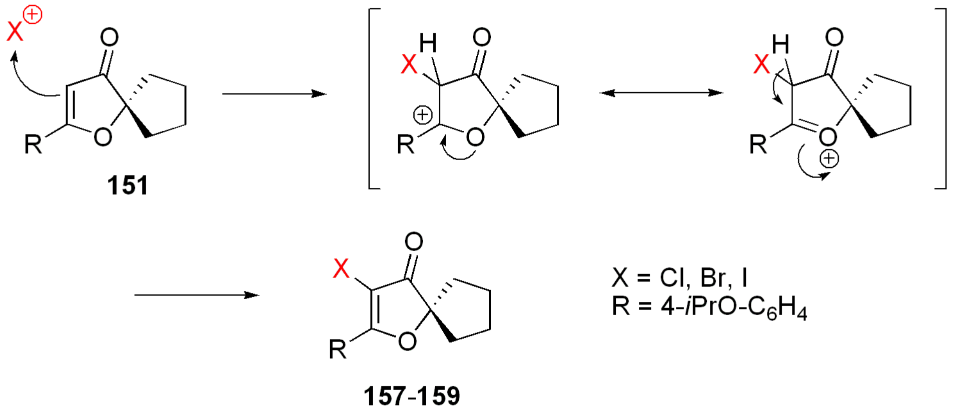
Scheme 54: Bromination and iodination of *i*Pr-Limno-CP (**151**)

Inspired by the high susceptibility of 3(2*H*)-pyrrolones towards electrophiles,[149] a similar reactivity was anticipated for the corresponding 3(2*H*)-furanone even though the electron donating properties of oxygen are less prominent than in the case of nitrogen. Nevertheless, the additional electron donating effect of the phenol substituent and the electron withdrawing properties of the carbonyl moiety should lead to a partial negative charge at the α-carbon of the α,β-unsaturated carbonyl subunit, which might be sufficient for a reaction with electrophilic reagents. Indeed, α-Br- **158** and α-I-derivative **157** were accessible with *N*-halosuccinimides as electrophilic halogen sources in very good yields of 88%. In the same manner, α-chloro-3(2*H*)-furanone **159** was obtained in 91% yield using NCS in methanol (Scheme 55).



Scheme 55: Bromination, iodination and chlorination of *i*Pr-Limno-CP (**151**) with *N*-halosuccinimides

The underlying mechanism can be explained as depicted in scheme 56. Addition of the halogen electrophile results in the formation of a positive charge, which can be stabilized by the oxygen and the phenol substituent. Subsequent deprotonation restores the α,β-unsaturated carbonyl motif to give the α-substituted compound. No additional base is required to induce the deprotonation step, the reaction proceeds smoothly without a significant formation of any side-products.

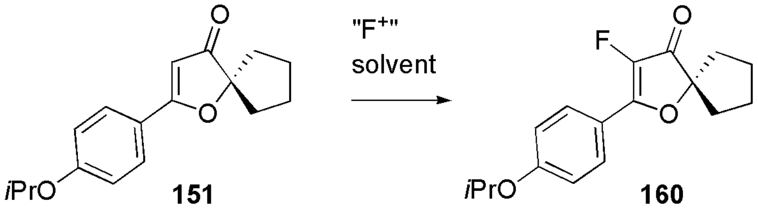


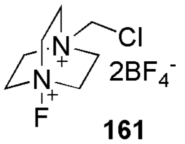
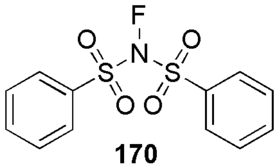
Scheme 56: General mechanism for the halogenation of *i*Pr-Limno-CP (**151**) with *N*-halosuccinimides

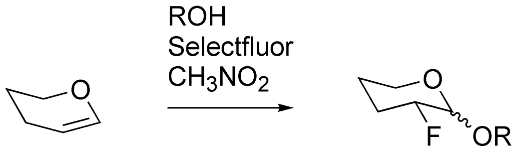
The generation of an α-fluoro derivative has shown to be exceedingly more challenging. Nonetheless, the synthesis of fluorine-containing organic compounds has gained intensified attention in medicinal chemistry in the recent decades since many beneficial features can be attributed to the chemical properties of fluorine.[150] The strong C-F bond can be utilized to increase the metabolic stability of the compounds. Fluorinated substructures substantially modulate the lipophilicity of the compounds, which is important for their capability to translocate cell membranes. Due to its similar size, hydrogen can be replaced by fluorine without notable steric differences. In contrast to steric parameters, the reactivity significantly differs from that of hydrogen. Fluorine is the most electronegative element and can therefore influence the reactivity of adjacent functional groups. Therefore, the implementation of fluorine into *i*Pr-Limno-CP (**151**) is an attractive approach since it might have a strong impact on the reactivity of the α,β-unsaturated carbonyl substructure. Two examples of α-fluoro 3(2*H*)-furanones are reported in the literature,[145,146] however, the introduction of fluorine was done prior to the formation of the furanone framework.

Based on the previous results with *N*-halosuccinimides, studies focused on electrophilic fluorinating reagents. Commercially available Selectfluor (**161**) is widely used[151] since it is one of the most reactive reagents to date. It is safe, nontoxic, exceptionally stable and as non-hygroscopic crystalline solid very easy to handle. However, its use is very much limited to polar solvents. In acetonitrile, DMF or acetone only complex mixtures were obtained at 0 °C (Table 12, entries 1, 3 and 4). Less polar solvents such as THF, chloroform, toluene or ethyl acetate gave the desired product, but only with very low conversions (Table 12, entries 5-8). When methanol was used as solvent, the addition of methanol to the β-position of the α,β-unsaturated carbonyl subunit was detected amongst other side-products (Table 12, entry 2). Similar observations were taken advantage of in the glycosylation of glycals (Scheme 57).[152]

Table 12: Fluorination experiments with electrophilic fluorine sources

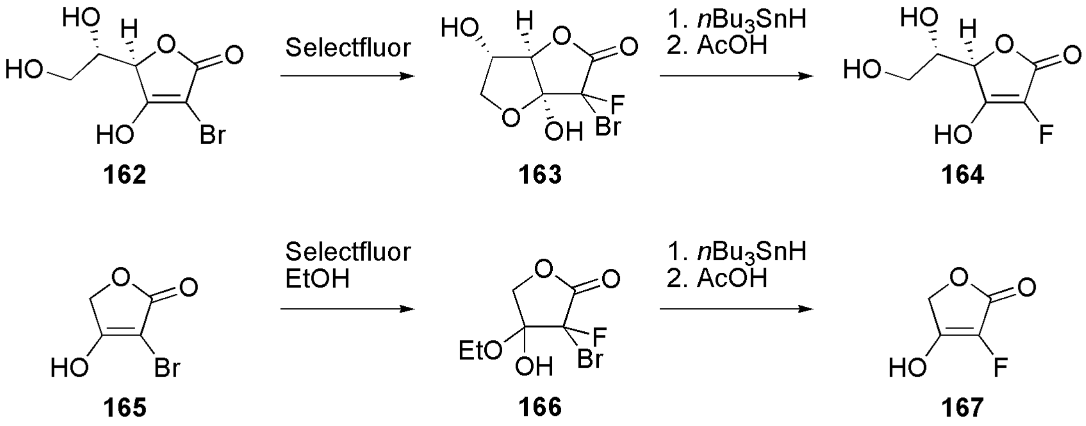


entry	electrophile	solvent	T	t	yield
1	 **161**	MeCN	0 °C	1 h	complex mixture
2		MeOH	0 °C	1 h	complex mixture
3		DMF	0 °C	1 h	complex mixture
4		acetone	0 °C	1 h	complex mixture
5		THF	reflux	16 h	trace
6		$CHCl_3$	reflux	16 h	trace
7		toluene	reflux	16 h	trace
8		EtOAc	reflux	16 h	trace
9	 **170**	MeCN	0 °C	1 h	complex mixture
10		MeOH	0 °C	1 h	complex mixture
11		THF	reflux	16 h	5%
12		toluene	reflux	16 h	complex mixture



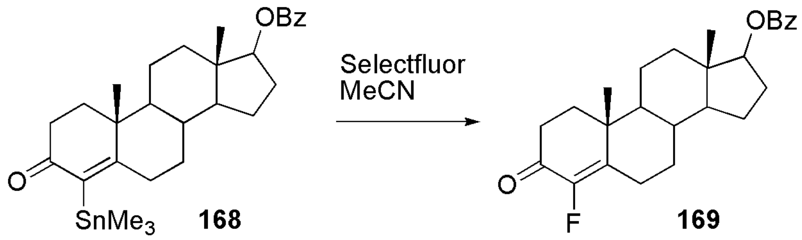
Scheme 57: Glycosylation of glycals with selectfluor in presence of alcohols

In presence of alcohols fluorinated derivatives of L-ascorbic acid **164**[153] and tetronic acid **167**[154] were synthesized from corresponding bromo precursors **162** and **165** (Scheme 58).



Scheme 58: Synthesis of fluorinated L-ascorbic acid **164** and tetronic acid **167** from corresponding α-bromo precursors **162** and **165**

In presence of an alcohol and Selectfluor the fluorinated addition products **163** and **166** were formed. Metal-bromine exchange was achieved with *n*Bu$_3$SnH, subsequent treatment with AcOH afforded the α-fluorinated enones **164** and **167**. Stannanes such as **168** were also used as precursors for the fluorination with Selectfluor via a metal-fluorine exchange reaction, another important strategy towards vinyl fluorides (Scheme 59).[155]



Scheme 59: Fluorination strategy from stannanes

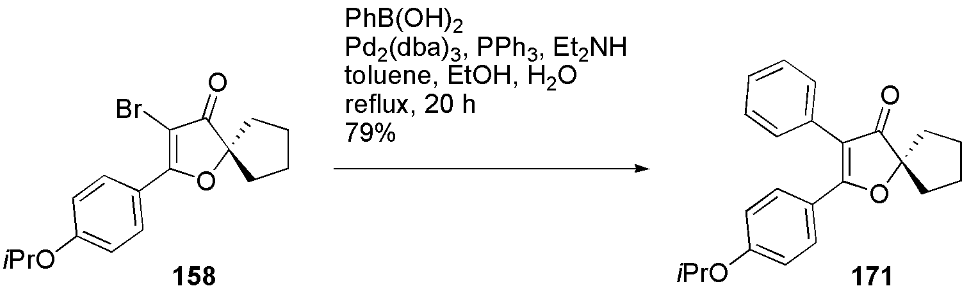
Unfortunately, fluorination experiments starting from α-bromo derivative **158** with Selectfluor in ethanol gave only complex product mixtures. All attempts to synthesize the stannane from the corresponding α-bromo derivative **158** failed. The metalation approach is discussed in detail in chapter 3.5.4.

To circumvent solubility problems, *N*-fluorobenzenesulfonimide (NFSI) (**170**) was used. This reagent can also be applied in more non-polar solvents. In refluxing THF the α-fluoro derivative **160** could be obtained after 16 h in 5% isolated yield (Table 12, entry 11). 87% of unreacted starting material was reisolated. If the reaction time was exceeded, bisfluorinated by-products were formed, which were inseparable due to very similar R_f values. In methanol, acetonitrile or toluene complex product mixtures were formed (Table 12, entries 9, 10 and 12).

The lack of other suitable methodologies to form sp^2-carbon-fluorine bonds directly has fueled the research on transition-metal-mediated reactions.[156] Pd^{IV} intermediates from electrophilic fluorine sources have shown to be powerful precursors to aryl fluorides,[157-160] whereas Pd^{II} in 16 electron configuration is not an adequate intermediate as reductive elimination is disfavored. Also a 14 electron Pd^{II} complex has been reported using *t*BuBrettPhos and nucleophilic fluoride to catalyze the formation of aryl fluorides.[161] Among other metals silver salts have been employed to fluorination reactions from aryl stannanes and boronic acids.[162,163] Gold-mediated sp^2-C-F bond constructions have been applied, but only from alkynes as starting materials using gold(I) N-heterocyclic carbene complexes,[164,165] from β-hydroxy-α,α-difluoroynones in presence of gold(I) chloride[166] or from propargyl acetates as starting materials.[167,168]

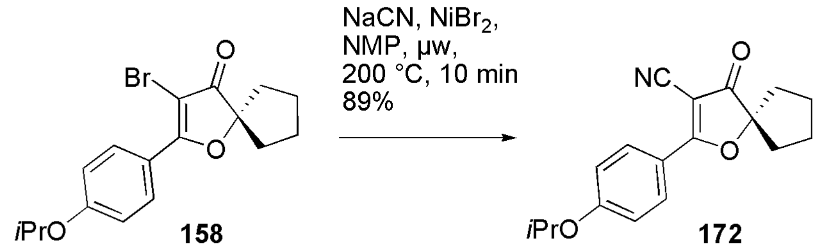
3.5.2. Introduction of carbon based substituents

The α-bromo-3(2*H*)-furanone **158** provides many possibilities for the formation of carbon-carbon bonds. For example, the olefinic halide represents a starting material for a palladium catalyzed Suzuki coupling reaction, which has also been used by Shin et al. for the synthesis of COX-2 inhibitors.[141] Under slightly different reaction conditions[169] the corresponding α-phenyl derivative **171** was amenable from the halide precursor in 79% yield (Scheme 60).



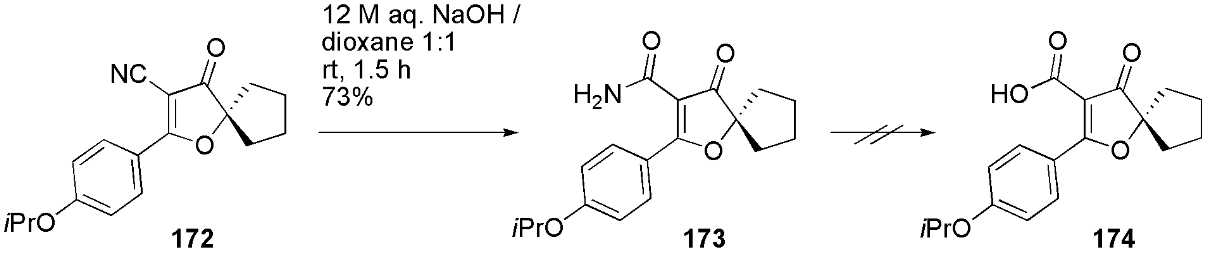
Scheme 60: Suzuki coupling reaction of derivative **158**

A microwave assisted cyanation reaction serves as a fast and efficient way for the preparation of nitrile **172** from bromide **158**.[170] This reaction is catalyzed by nickel cyanide, which is formed via *in situ* transmetalation from two equivalents of sodium cyanide and one equivalent of nickel bromide. The use of *N*-methyl-2-pyrrolidone (NMP) as solvent is required as the reaction is performed at an elevated temperature of 200 °C. However, in contrast to conventional heating, this can be done in a very easy and safe manner using a standard laboratory microwave instrument. Even more advantageous, it significantly enhances the reaction rate to obtain the nitrile **172** after 10 minutes in 89% yield (Scheme 61).



Scheme 61: Microwave assisted cyanation of α-bromo-3(2*H*)-furanone **158**

An alternative route towards similar spirocyclic α-CN-3(2*H*)-furanones via condensation of benzoic acid derivatives with α,β-acetylenic γ-hydroxy nitriles was published recently.[171] Nitrile **172** should be a direct precursor for carboxylic acid derivatives. Indeed, nitrile **172** could be hydrolyzed in basic media to give the corresponding amide **173** in 73% yield (Scheme 62).[172]



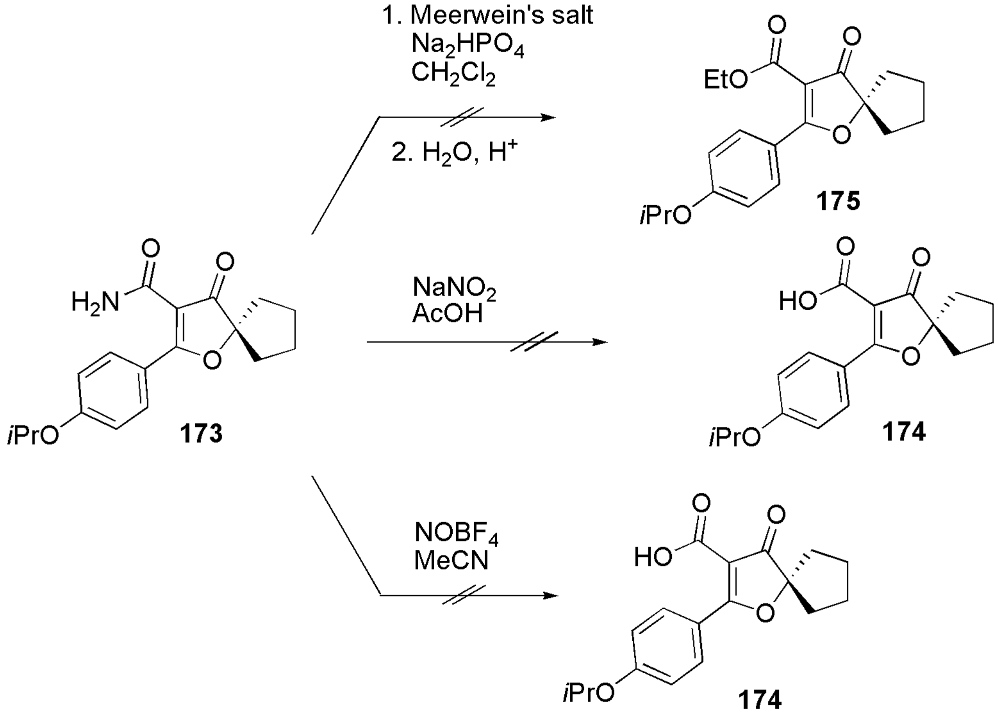
Scheme 62: Hydrolysis of nitrile **172** to the corresponding amide **173**

To obtain the corresponding carboxylic acid **174** directly from the nitrile **172**, prolonged reaction times and elevated temperatures have been applied since the hydrolysis of the amide to the carboxylic acid is much slower than the partial hydrolysis of the nitrile to the amide. However, amide **173** proved to be stable under basic conditions. Addition of H_2O_2 accelerated the first hydrolysis step, but had no impact on the second step (Table 13, entries 6 and 7). Thus, strong acids were applied to afford the carboxylic acid **174**. Unfortunately, with HCl, H_2SO_4, H_3PO_4 or HBr partial cleavage of the isopropyl ether was observed instead, and product mixtures of the starting material, the amide and their deprotected phenol analogues were obtained (Table 13, entries 1-4). With glacial acetic acid, amide **173** was formed as single product (Table 13, entry 5).

Table 13: Hydrolysis experiments towards carboxylic acid **174** from nitrile **172**

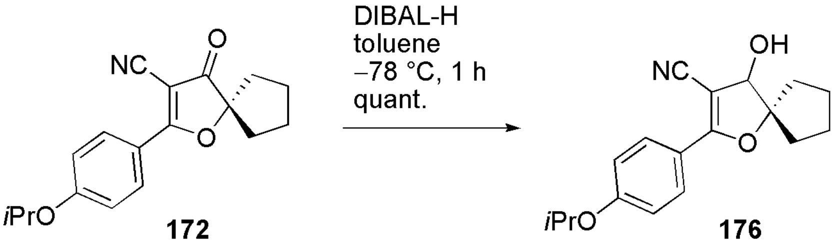
entry	reagents	conditions	product
1	conc. HCl	reflux, 24 h	mixture of *i*PrO-protected amide **173**, *i*PrO-protected nitrile **172**, deprotected amide **205**, deprotected nitrile **203**
2	H_2SO_4 98%	reflux, 24 h	
3	H_3PO_4 100%	reflux, 24 h	
4	HBr 48%	reflux, 24 h	
5	glacial acetic acid	reflux, 24 h	amide **173**
6	12 M NaOH	rt, 1.5 h	amide **173**
7	12 M NaOH + H_2O_2	rt, 5 min	amide **173**

The formation of the carboxylic acid **174** from the nitrile **172** via hydrolysis under acidic or basic conditions was not successful. Hence, further investigations concentrated on alternative methodologies towards **174**. Triethyloxonium tetrafluoroborate, commonly known as Meerwein´s salt, has proven to convert amides to the corresponding imidate esters, which yield the ethyl esters upon hydrolysis in dilute acid.[173] In the present study however, no conversion was observed under various reaction conditions. Further methodologies were applied such as the reaction of amide with $NaNO_2$ in acetic acid[174] or with nitrosonium tetrafluoroborate in MeCN,[175] albeit without significant conversion (Scheme 63).



Scheme 63: Unsuccessful reactions towards carboxylic acid derivatives **174** and **175**

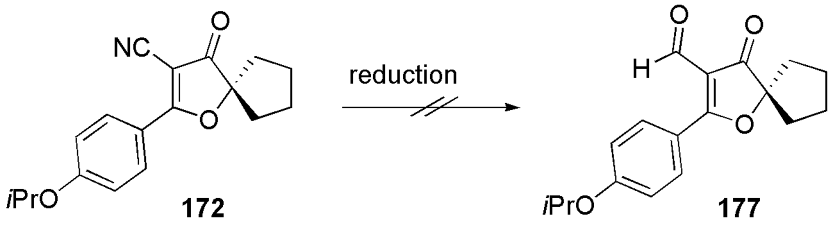
From nitrile **172** other transformations should be possible to gain more structural diversity within the library of Limno-CP derivatives. Reduction experiments were carried out to establish an aldehyde functionality. In this matter, chemoselectivity issues have to be taken into account since the carbonyl group as well as the electron deficient double bond are prone to react with many reducing agents. Indeed, DIBAL-H, a very common reagent for the reduction of nitriles, gave the corresponding allylic alcohol **176** solely (Scheme 64).



Scheme 64: Reduction of nitrile **172** to the corresponding allylic alcohol **176**

Since DIBAL-H gave the undesired product, the focus was shifted to metal catalyzed hydrogenations (Table 14). Raney nickel has been widely used for the conversion of nitriles to aldehydes or amines. Activated Raney-nickel in combination with formic acid[176] or glacial acetic acid[177] generates H_2 in situ and catalyzes the reduction of the nitrile at the same time. Unfortunately, no conversion was observed even under relatively harsh conditions. Addition of H_2 to the reaction mixture directly also failed. The same was observed when Raney-nickel was replaced by palladium on charcoal in ethyl acetate.

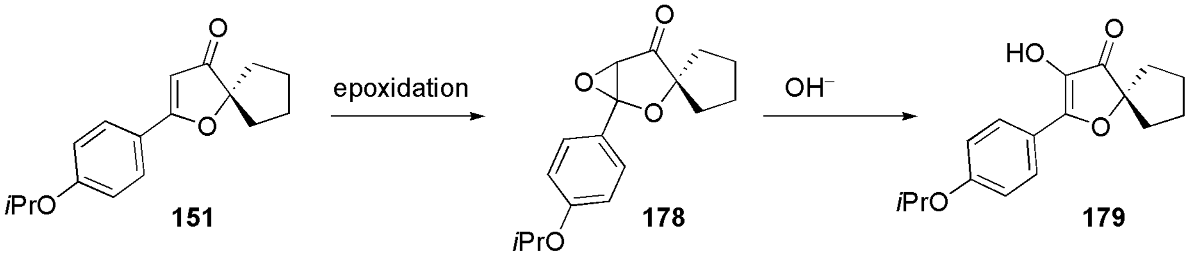
Table 14: Metal catalyzed hydrogenation reactions



entry	catalyst	conditions	product
1	Raney-Ni	75% HCOOH/EtOH 1:1, reflux, 24 h	no conversion
2	Raney-Ni	AcOH, pyridine, $Na_3PO_4 \cdot 12\ H_2O$, reflux, 24 h	no conversion
3	Raney-Ni	H_2, EtOH, reflux, 24 h	no conversion
4	Pd / C	H_2, EtOAc, reflux, 24 h	no conversion

3.5.3. Introduction of oxygen based substituents

For the introduction of an alcohol functionality different epoxidation reactions on the double bond of the α,β-unsaturated carbonyl moiety were performed. However, β-oxo enol ethers are poor substrates for electrophilic as well as for nucleophilic epoxidation reagents since the electron-donating substituent on the one side and the electron-withdrawing carbonyl group on the other side of the C-C double bond result in an extended conjugated system. Hence, only a few epoxides of β-oxo enol ethers are known. Moreover, they tend to rearrange to the corresponding 2-hydroxy-2-enones easily. Exactly this tendency to rearrange, however, should be utilized in this study. Under basic conditions the newly formed α,β-epoxy ketone **178** should therefore give the corresponding α-hydroxy 3(2*H*)-furanone **179** directly by deprotonation. Alternatively, the hydrolysis of the epoxide to its corresponding diol followed by H_2O elimination should yield the alcohol **179** in two consecutive steps (Scheme 65).

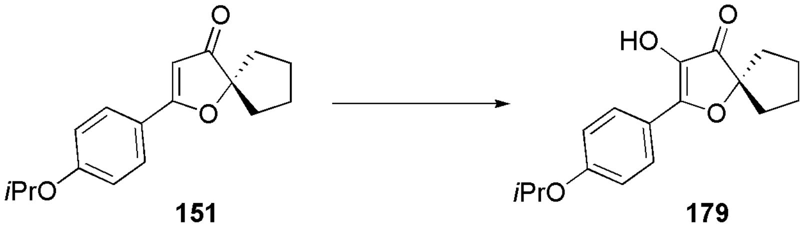


Scheme 65: Strategy towards the α-hydroxy-3(2*H*)-furanone **179** via an epoxidation reaction

In the group of Adam et al. the epoxidation of β-oxo enol ethers with dimethyldioxirane (DMDO) was investigated, which gave the products in quantitative yield.[178] However, isolation and purification was not possible as the epoxides decomposed once they were warmed above 0 °C.

In this study various epoxidation reagents were tested. The epoxidation of *i*Pr-Limno-CP (**151**) with DMDO showed initially a good reactivity, but several products were formed, which could not be isolated. With *m*CPBA[179] no conversion was observed, just unreacted starting material could be reisolated. The well known Weitz-Scheffer epoxidation,[180] which gives usually good results for electron deficient olefins, showed promising product formation and gave α-hydroxy Limno-CP (**179**) in 32% (Table 15).

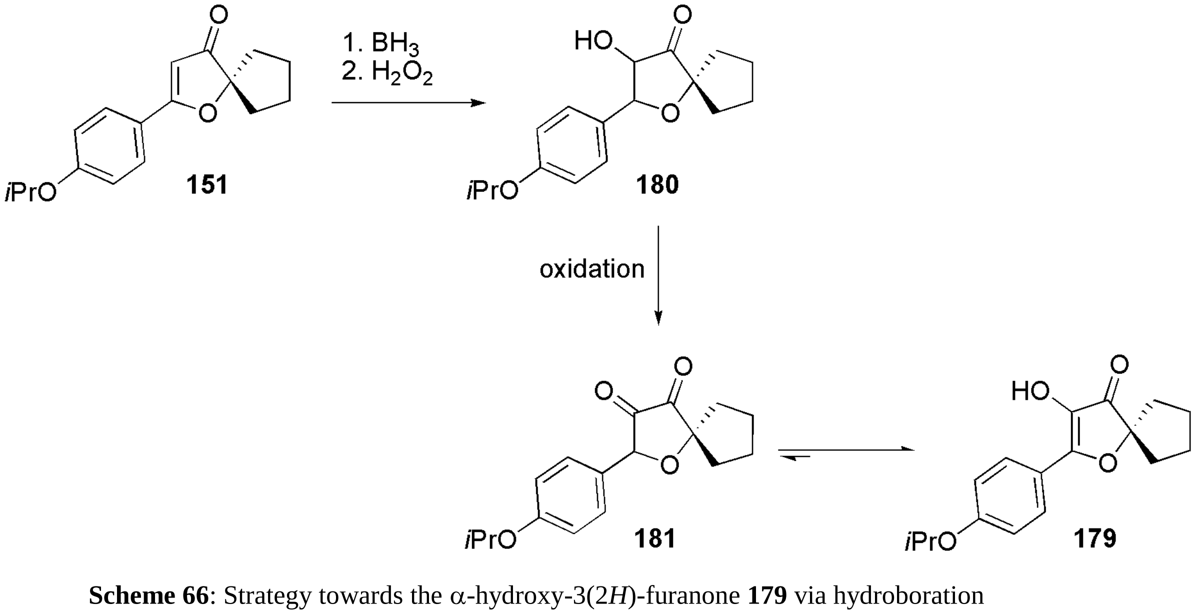
Table 15: Epoxidation reactions on *i*Pr-Limno-CP (**151**)



entry	reagent	conditions	product
1	DMDO (0.07 M in acetone)	CH_2Cl_2, −78 °C, 1 h	product mixture
2	*m*CPBA	CH_2Cl_2, 0 °C to rt, 16 h	-
3	H_2O_2	NaOH, MeOH, 0 °C to rt, 2.5 h	32%[a]

[a] estimated by NMR

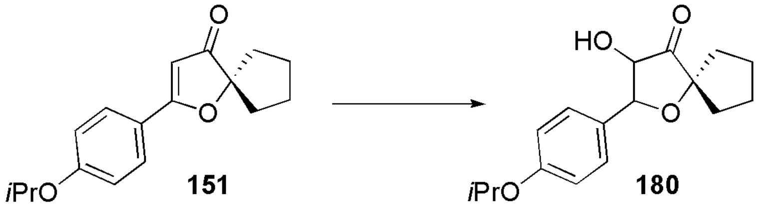
Alternatively, hydroboration and subsequent oxidation of the hydroboranes with hydrogen peroxide to the corresponding saturated α-hydroxy ketone **180** was envisaged. Upon further oxidation the 1,2-diketone **181** would be formed, which would tautomerize to the desired unsaturated alcohol **179** (Scheme 66).



Scheme 66: Strategy towards the α-hydroxy-3(2*H*)-furanone **179** via hydroboration

Steric and electronic aspects favor the addition of the borane at the α-position of the enone. Being electrophilic in nature, the borane adds to the nucleophilic carbon of the double bond. As steric hindrance is also minimized, only the anti-Markovnikov regioisomer can be expected. To achieve the desired transformation, various reagents were applied (Table 16). With $NaBH_4$ and iodine BH_3 is formed in situ.[181] BH_3·THF-complex was used as well as pinacol borane and 9-BBN. In general, the reactivity of the starting material was low towards the borane reagents. This might be attributed to the electron deficient nature of the double bond, which is a poor substrate for an electrophilic addition reaction. Prolonged reaction times and high temperatures resulted in complex mixtures of inseparable products.

Table 16: Hydroboration reactions on *i*Pr-Limno-CP (**151**)

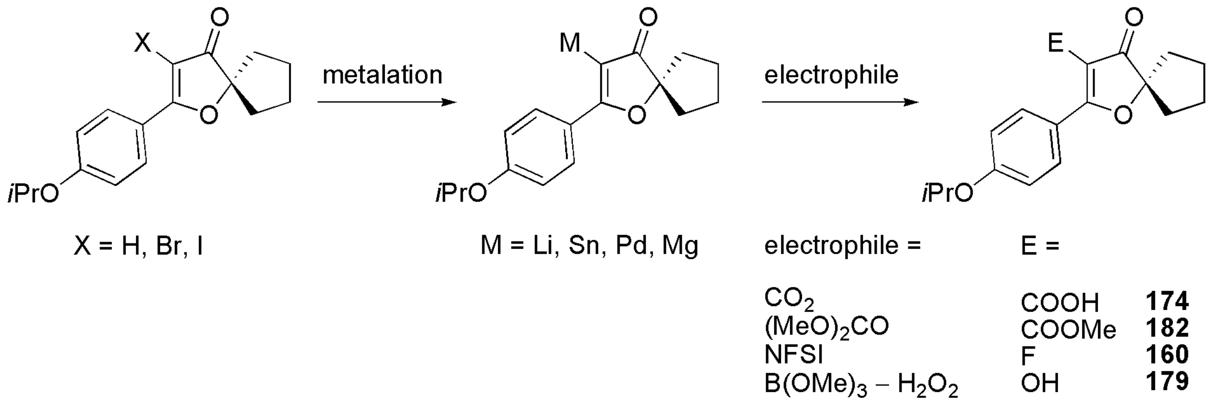


entry	reagent	conditions	product
1	$NaBH_4$, I_2	THF, 0 °C to rt, 16 h	no conversion
2	BH_3·THF	THF, 0 °C to rt, 16 h	no conversion
3	pinacol borane	THF, 0 °C to rt, 16 h	no conversion
4	9-BBN	THF, 0 °C to rt, 16 h	no conversion

Unfortunately, the synthesis of α-hydroxy *i*Pr-Limno-CP (**179**) from the unsubstituted derivative **151** could not be accomplished in simple one or two step modifications. In the literature, however, spirocyclic α-hydroxy 3(2*H*)-furanones are known as part of steroids.[182,183] But, steroid spiro enones were generated from prednisolone as starting material, which has already the alcohol functionality incorporated. Therefore, no additional manipulations for the introduction of the hydroxy functionality were required.

3.5.4. Metalation approaches

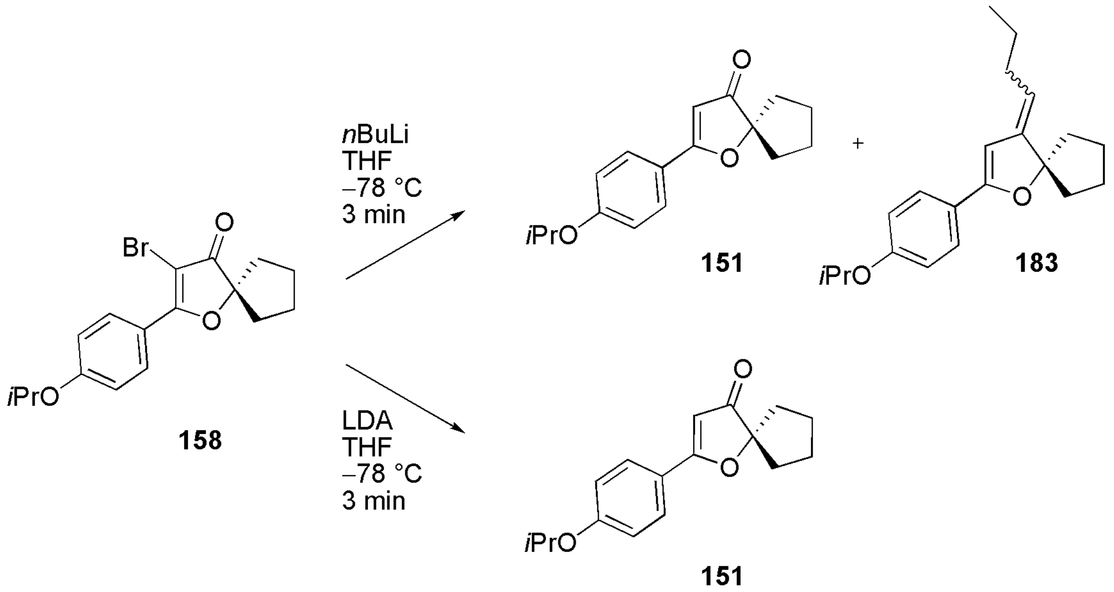
In order to gain access to a broad variety of α-modified Limno-CP derivatives, a more versatile strategy was envisioned, which should allow for an easy and more general introduction of substituents. If it is possible to attach a metal center to the α-position of the α,β-unsaturated carbonyl substructure, it should be possible to trap the metalated species with electrophiles (Scheme 67).



Scheme 67: Planned introduction of substituents via metalation approaches

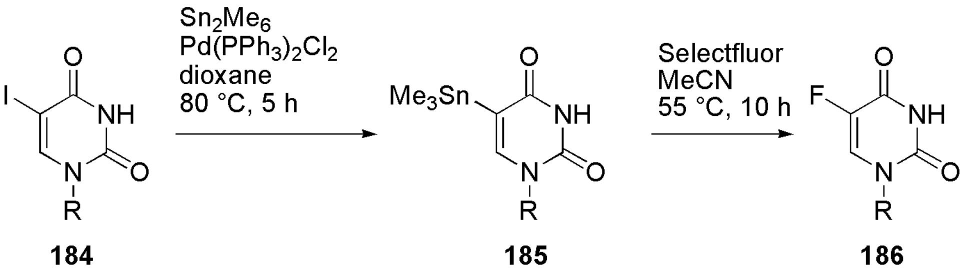
Via this approach the carboxylic acid **174** should be accessible using CO_2 as electrophile, whereas dimethyl carbonate would give the methyl ester **182**. The fluorinated derivative **160** should be obtained with electrophilic fluorine reagents such as NFSI **170**, even the hydroxy substituted compound **179** could be synthesized using methyl borate and hydrogen peroxide. In principle, any conceivable derivative could be synthesized provided that an adequate electrophile is available.

The present studies concentrated first on the lithiation of the α-bromo *i*Pr-Limno-CP derivative (**158**) via a bromine lithium exchange reaction. Adding *n*BuLi to a solution of the starting material at –78 °C, however, turned out to be problematic since an unspecific product formation occurred. Even in very low concentrations as well as at temperatures of –120 °C, which can be achieved in solvent mixtures like THF:Et_2O:hexanes 4:1:1, a substitution of the lithiated intermediate failed. As main products the dehalogenated compound **151** and a very unpolar product, which was identified to be the dehalogenated 1,2-addition product **183** in later studies (see chapter 3.6.1, p.78), were formed. Apparently, the protonation of the α-lithiated compound is very fast and superior to the addition of other electrophiles. Moreover, competing reaction pathways such as the addition of the butyl anion to the α,β-unsaturated carbonyl moiety gives rise to 1,2-addition products. This reaction was sought to be suppressed by the use of other lithiation reagents. Unfortunately, LDA gave even more dehalogenated product **151** instead, *t*BuLi and PhLi lead to decomposition of the starting material (Scheme 68).



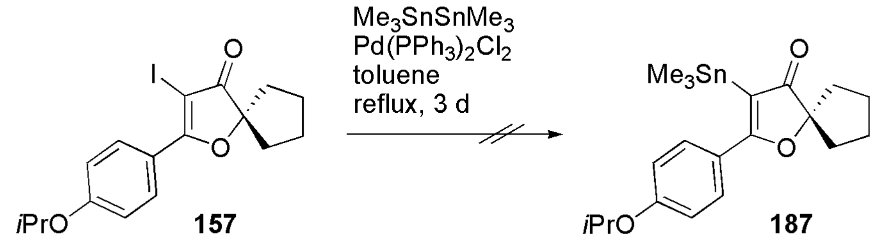
Scheme 68: Lithiation by bromine lithium exchange from derivative **158**

Since a bromine lithium exchange failed, the access to stannylated *i*Pr-Limno-CP via lithiation and subsequent stannylation with tributyltin chloride became impossible. As mentioned previously, stannanes, however, are important precursors of fluorinated compounds (Scheme 69).[184]



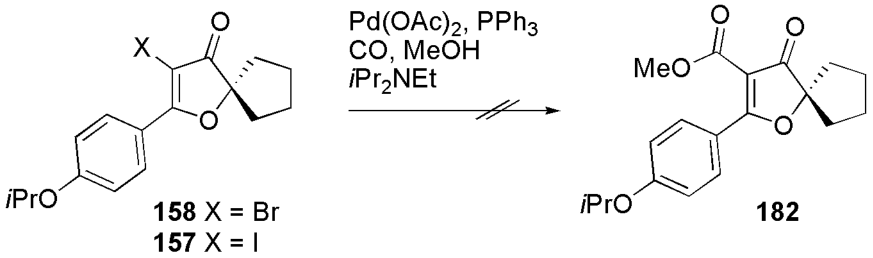
Scheme 69: Known stannylation regime for the synthesis of fluorinated nucleotide **186**[184]

Encouraged by the successful palladium catalyzed Suzuki coupling of α-bromo *i*Pr-Limno-CP (**158**) with phenylboronic acid, a palladium mediated stannylation was envisaged. When hexamethylditin and a Pd^{II} catalyst were applied, which is in accordance with literature conditions, the reactivity of α-iodo *i*Pr-Limno-CP (**157**) turned out to be low. Only a very low conversion was observed. Extended reaction times under reflux conditions gave only inseparable product mixtures (Scheme 70).



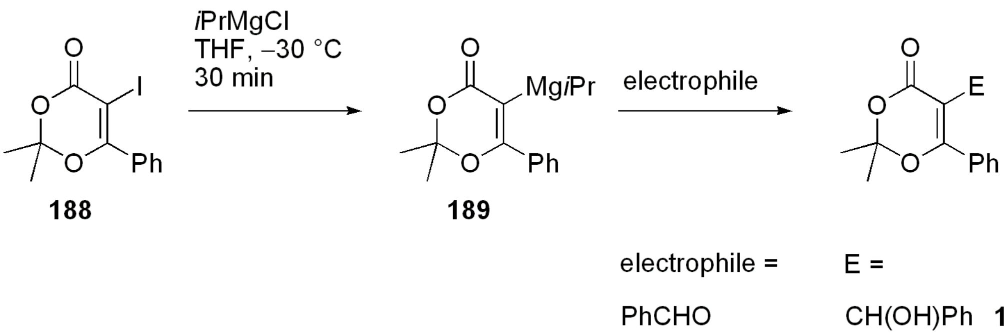
Scheme 70: Pd-catalyzed stannylation of derivative **157**

Palladium was also used to achieve a metal catalyzed carbonylation.[185] Carbon monoxide was used in presence of a Pd^{II} catalyst and MeOH to convert α-bromo (**158**) or α-iodo *i*Pr-Limno-CP (**157**) to the corresponding methyl ester **182**. But, also in this case, the reaction did not occur at ambient temperature and with elevated temperatures the formation of multiple products was detected (Scheme 71).



Scheme 71: Pd-catalyzed carbonylation of derivatives **157** and **158**

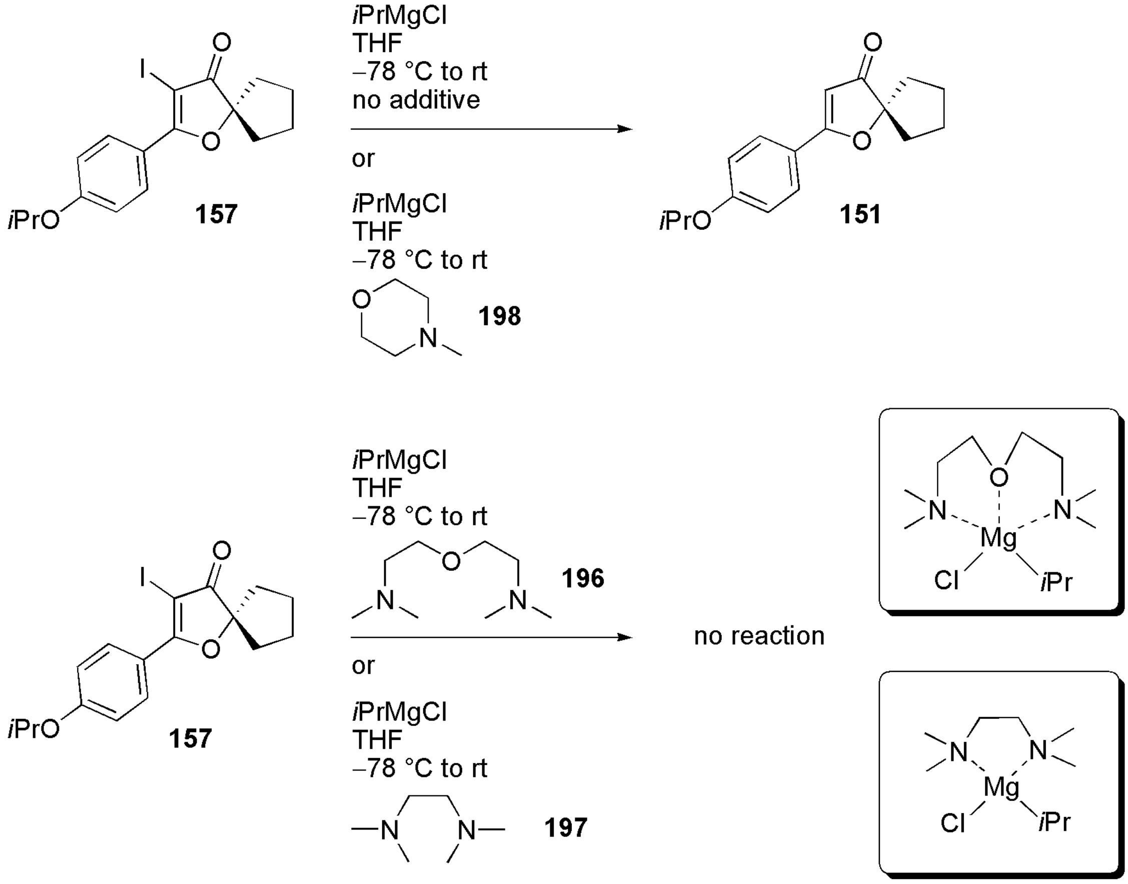
The group of Knochel has investigated the use of isopropyl magnesiumchloride for the metalation of halide **188** (Scheme 72).[186] With various electrophiles a wide range of substituted 1,3-dioxin-4-ones **190** to **195** were synthesized.



electrophile =	E =	
PhCHO	CH(OH)Ph	**190**
PhCOCl	COPh	**191**
Me$_3$SnCl	SnMe$_3$	**192**
PhSSPh	SPh	**193**
Allyl bromide	Allyl	**194**
ZnBr$_2$	ZnBr	**195**

Scheme 72: Derivatization approach of halide **188** via Grignard reagent **189** by Knochel et. al.[186]

Isopropyl magnesiumchloride was prepared from 2-chloropropane via Grignard reaction in 77% yield.[187] The solution of *i*PrMgCl was determined to be 1.4 M using a literature known titration method.[188] Upon addition of the magnesium reagent to α-iodo *i*Pr-Limno-CP (**157**) in THF at −40 °C immediate dehalogenation was observed. The corresponding α-bromo *i*Pr-Limno-CP (**158**) was not as reactive as its α-iodo counterpart and gave multiple products upon warming to room temperature. According to the literature, the reactivity of the magnesium reagent could be successfully regulated in presence of complexing agents. In this study the metalation process was suppressed completely with the tridentate ligand bis[2-(*N*,*N*-dimethylamino)ethyl] ether (**196**)[189] as well as with the bidentate chelator 1,2-bis(dimethylamino)ethane (**197**). With the monodentate ligand *N*-methyl morpholine (**198**) little conversion occurred, albeit only the dehalogenated *i*Pr-Limno-CP (**151**) was observed instead of the metalated compound (Scheme 73).



Scheme 73: Attempted synthesis of Grignard reagents in presence of complexing agents

A direct deprotonation of a 2(5*H*)-furanone was applied by Takeda et al. in the total synthesis of tetronolide with *t*BuLi.[190] Hence, a lithiation by abstraction of a proton with alkyl lithium reagents was investigated. In this study *t*BuLi as well as PhLi gave only decomposition products. LDA was found to be too weak resulting in no conversion. LDA was also reported to undergo a Baylis-Hilman type reaction with pyranones.[191] This reactivity has not been described in the literature so far with 3(2*H*)-furanones. Indeed, when literature conditions were used to perform the analogous reaction with *i*Pr-Limno-CP derivatives, no conversion was observed.

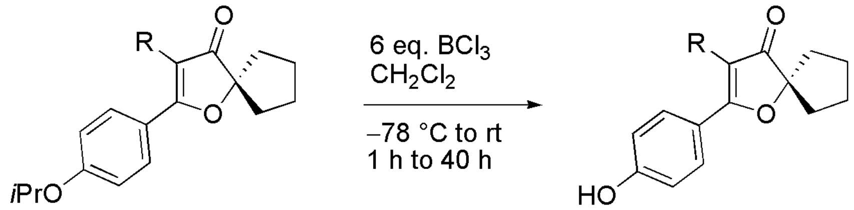
Fast protonation of metalated species has shown to be a general drawback of this approach competing with the coupling reaction with electrophiles to form α-substituted *i*Pr-Limno-CP derivatives. Hence, no α-modified product was obtained with either lithium, tin, palladium or magnesium reagents.

In total, eight differently substituted *i*Pr-Limno-CP derivatives could be generated in simple one to three step modifications from one common precursor. To complete the synthesis of natural product analogues, the removal of the isopropyl protecting group was required.

3.5.5. Deprotection reactions

For the regeneration of the phenol moiety from the masked isopropyl ethers a general protocol was found, which could be applied for each derivative similarly. Six equivalents of BCl_3 in dichloromethane were necessary to achieve a complete deprotection. The phenol derivatives were obtained in excellent yields (Table 17).

Table 17: Deprotection of *i*Pr-Limno-CP derivatives



entry	starting material	R	time	yield	product
1	**151**	H	16 h	99%	**146**
2	**160**	F	3 h	98%	**199**
3	**159**	Cl	16 h	95%	**200**
4	**158**	Br	16 h	93%	**201**
5	**157**	I	1 h	82%	**202**
6	**172**	CN	40 h	98%	**203**
7	**171**	Ph	16 h	94%	**204**
8	**173**	$CONH_2$	16 h	84%	**205**

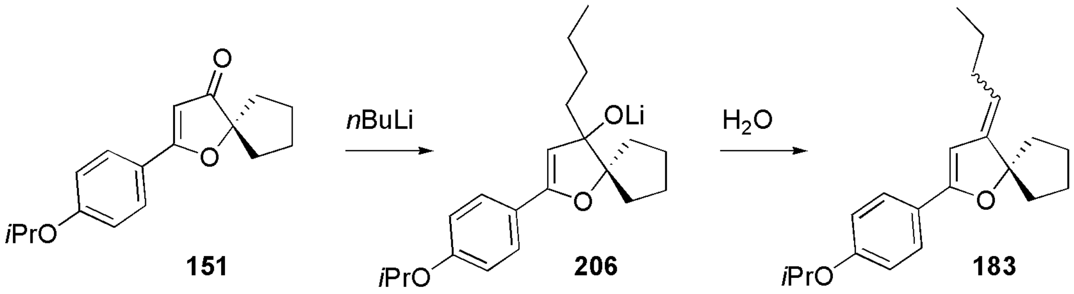
During the reaction, a white polymer emerges, which is hard to separate from the product. Furthermore, the solubility of the product is limited to DMSO, EtOH and to some extent EtOAc, which complicates the extraction of the product from the heterogeneous reaction mixture. Nevertheless, it was found that the polymer can be effectively dissolved by the addition of THF. Removal of the solvents and final extraction of the product from an aqueous solution with large amounts of EtOAc succeeded to isolate the deprotected compounds.

3.6. 1,2- versus 1,4-addition of nucleophiles

The evaluation of the reactivity of the synthesized *i*Pr-Limno-CP derivatives towards different nucleophiles is of central importance if Michael activity in biological systems is discussed. Although data of biological assays show a certain activity, the cellular pathway remains unclear as the observed effect may be triggered by different mechanisms at the same time and connot be unambiguously traced back to a 1,4-addition process. In turn, if it can be demonstrated by chemical experiments that the compounds undergo 1,4-addition, it might offer valuable clues which molecular pathway is taking place under physiological conditions. Hence, a proof of concept is desired if 1,4-addition is claimed to be the predominant activation process. The reactivity of the *i*Pr-Limno-CP derivatives against various nucleophiles is discussed in the following chapter.

3.6.1. 1,2-addition

In the course of the derivatization experiments *i*Pr-Limno-CP (**151**) has shown to react readily with alkyl lithium reagents. When *n*BuLi was added to a solution of unsubstituted 3(2*H*)-furanone **151** at −78 °C, a very unpolar compound was formed immediately. By thorough NMR spectroscopic and mass spectrometric analysis the product was identified to be the 3-butylidene-2,3-dihydrofurane **183**. Mechanistically, this unexpected reaction outcome can be explained by a 1,2-addition of the butyl anion and subsequent H_2O elimination to form the alkylidene motif (Scheme 74).



Scheme 74: Formation of alkylidene compound **183** from *i*Pr-Limno-CP (**151**)

This reaction proceeds very fast and quantitatively giving the product in 87% yield after aqueous workup as a mixture of *E* and *Z* isomers in very high purity (Figure 20). A full characterization of the compound has to be done quickly after isolation since the product is not stable at ambient temperature and decomposes within 30 minutes. Even at −20 °C slow decomposition processes are taking place. Fortunately, the product does not require further purification as the crude material is already sufficiently pure.

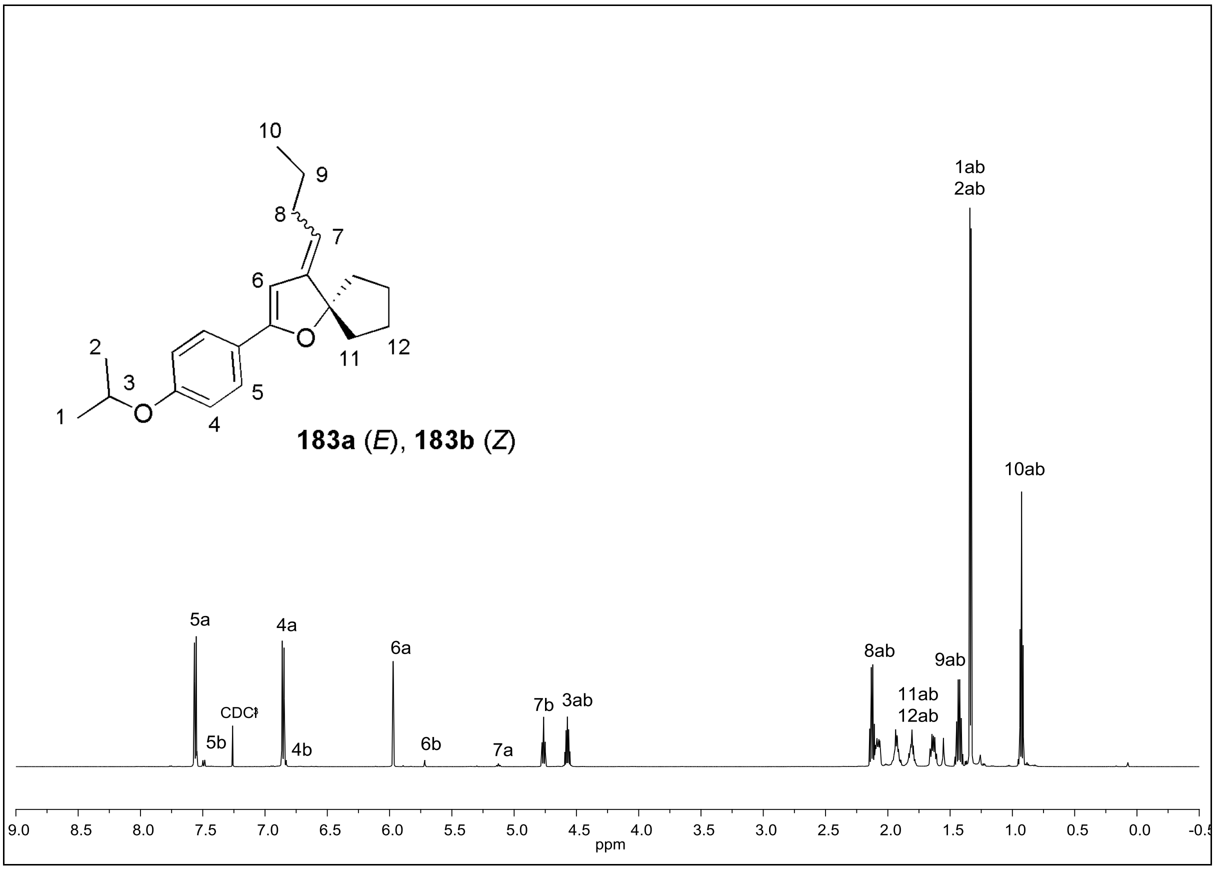


Figure 20: Crude ^{1}H NMR spectrum of alkylidene compounds **183a** and **183b** directly after aqueous workup

The ^{1}H NMR spectrum clearly shows the presence of *E* and *Z* isomers of the alkylidene product **183**. For reasons of clarity the isomers are assigned with **a** and **b** since the *E/Z* nomenclature changes depending on which substituent X is attached at the olefinic carbon (Figure 21).

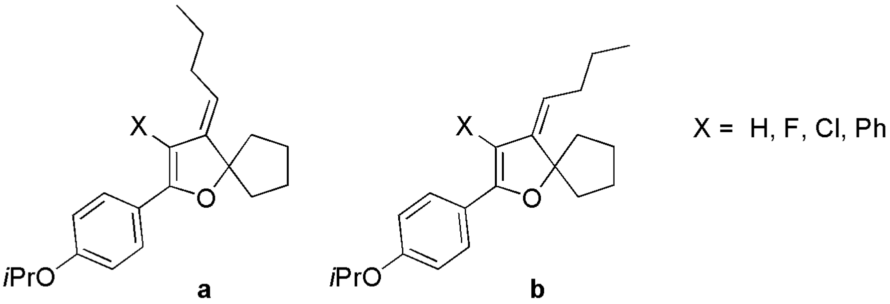
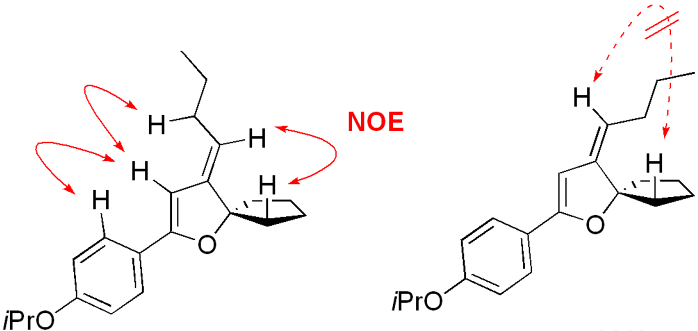


Figure 21: *E* and *Z* isomers of alkylidene compounds are assigned with **a** and **b**

The stereochemistry of the C-C double bond was determined by 2D NMR techniques including NOESY and ROESY. In figure 22 the important NOEs are depicted for the unsubstituted derivatives **183a** and **183b**.



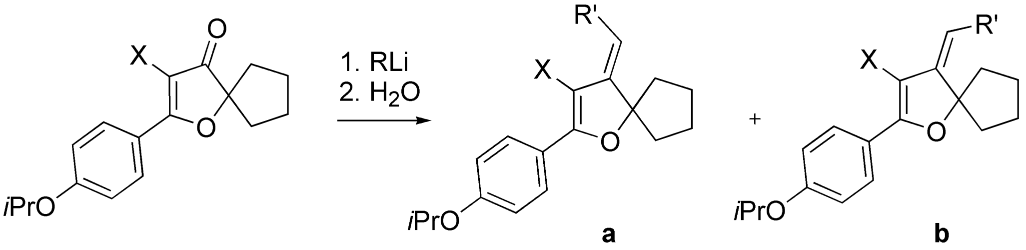
183a **183b**

Figure 22: Determination of the correct stereochemistry by means of NOE experiments

A significant cross peak was detected between the proton of the cyclopentyl ring and the olefinic proton in the isomer **183a**. This indicates the close distance of these protons to each other, which is only possible in the depicted double bond geometry of isomer **183a**. In the case of isomer **183b** a cross peak cannot be found since the olefinic proton is directed off the cyclopentyl ring. An **a**/**b** ratio of 95/5 was observed for the unsubstituted derivative **183**. It can be assumed that the trajectory of the attacking nucleophile is not the determining factor for the stereochemical outcome of this reaction since the spatial environment is more or less identical for both sides of the carbonyl plane. The stereochemical preference for the isomer **a** might rather be attributed to the H_2O elimination mode minimizing the steric repulsion between the butyl group and the cyclopentyl ring.

The transformation of the carbonyl group of 3(2*H*)-furanones to an olefin with alkyl lithium reagents has not been described so far. Alternatively, this is commonly done under Wittig conditions. Hence, the scope of this reaction was further investigated (Table 18). With hexyl lithium the corresponding hexylidene derivatives **207a** and **207b** were formed in 91% yield and an **a**/**b** ratio of 95/5 (Table 18, entry 2). The addition reaction with MeLi, which leads to the formation of the exomethylene group in **208**, did not proceed cleanly, however, the product was formed in 38% yield as determined from a mixture by use of an internal standard (Table 18, entry 3). As negative control PhLi and *t*BuLi were used. Since the elimination process cannot occur due to the lack of cleavable protons, the failure of the reaction was anticipated. Indeed, only complex mixtures were obtained (Table 18, entries 4 and 5). In the reactions of *n*BuLi with α-fluoro- **160**, α-chloro- **159** and α-phenyl-substituted derivative **171**, where X is inert to the reaction conditions, the corresponding products could be detected, albeit in different **a**/**b** ratios (Table 18, entries 6,7 and 12). This observation does not allow for a simple explanation. Especially in the case of fluorine being similar in size to hydrogen, steric effects have to be excluded for the decreased isomeric ratio. Hence, electronic effects can be assumed to play a pivotal role. Interestingly, the alkylidene products **210a** and **210b** from the reaction of *n*BuLi with α-chloro derivative **159** showed the reverse isomeric ratio as in the case of the other derivatives (Table 18, entry 7). In this case the bigger spatial demand of chlorine might be the reason for the opposite stereochemical preference. α-Bromo *i*Pr-Limno-CP (**158**) and α-iodo *i*Pr-Limno-CP (**157**) yielded only dehalogenated product **151** as well as the dehalogenated alkylidene derivative **183a** (Table 18, entries 8 and 9). This is in accordance with the results obtained in the metalation experiments and can explain why no metalated species were detected (see chapter 3.6.4, p. 74). In the case of α-nitrile *i*Pr-Limno-CP (**172**) the competing addition of the butyl anion to the nitrile is believed to be the preferred reaction over the formation of the alkylidene product (Table 18, entry 10). With the amide **173** only a low conversion was observed, which can be explained by the deprotonation of the amide-NH_2 unit (Table 18, entry 11).

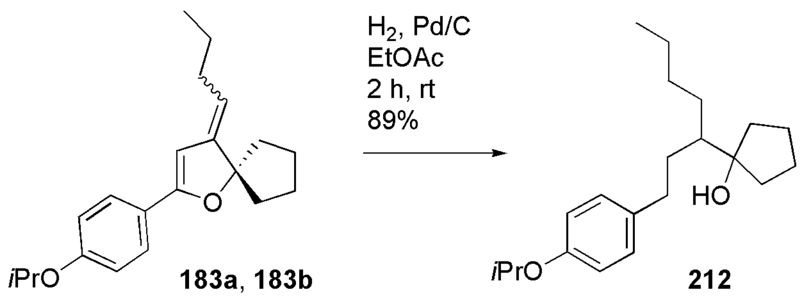
Table 18: Reaction of *i*Pr-Limno-CP derivatives with alkyl lithium reagents[a]



entry	X	starting material	RLi	conversion	products	yield, a/b[b]
1	H	**151**	*n*BuLi	quant.	**183a**, **183b**	87%,[c] 95/5
2	H	**151**	*n*HexLi	quant.	**207a**, **207b**	91%,[c] 95/5
3	H	**151**	MeLi	94%	**208**	38%
4	H	**151**	PhLi	quant.	-[d]	-
5	H	**151**	*t*BuLi	quant.	-[d]	-
6	F	**160**	*n*BuLi	quant.	**209a**, **209b**	52%, 65/35
7	Cl	**159**	*n*BuLi	quant.	**210a**, **210b**	86%, 10/90
8	Br	**158**	*n*BuLi	quant.	**183a**, **151**[e]	-
9	I	**157**	*n*BuLi	89%	**183a**, **151**[f]	-
10	CN	**172**	*n*BuLi	quant.	-[g]	-
11	$CONH_2$	**173**	*n*BuLi	< 5%	not det.[h]	-
12	Ph	**171**	*n*BuLi	quant.	**211a**, **211b**	33%, 60/40

[a] R' contains (n-1) C-atoms from R.
[b] Determined by ^{1}H NMR with hexamethyldisilane as internal standard.
[c] Isolated yield.
[d] Complex mixture.
[e] 67% **151**, 15% **183a**.
[f] 44% **151**, 22% **183a**, 11% **157**.
[g] Addition products to the nitrile group.
[h] Not determined.

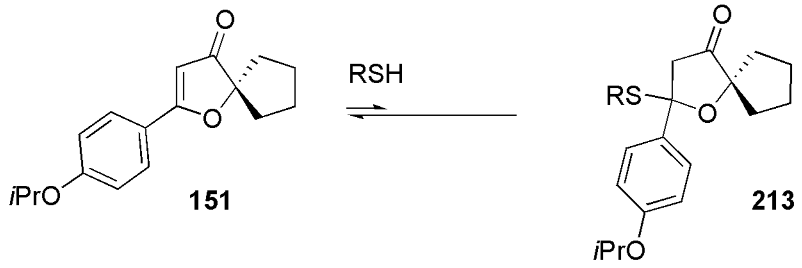
Since storage of the alkylidene compounds is precluded due to their severe lability, a consecutive reaction was searched, which might render this transformation synthetically useful. Various electrophilic and nucleophilic reagents such as *p*TsOH, *N*-halosuccinimides, iodine or NaOMe were tested, but all attempts to trap the dihydrofuran failed. In contrast, hydrogenation using H_2 and Pd/C in ethyl acetate succeeded. Not only both double bonds were hydrogenated readily, but also the benzyl ether was cleaved as it is well known from the deprotection of benzyl protected alcohols. The saturated tertiary alcohol **212** was received in 89% yield as the only product (Scheme 75).



Scheme 75: Hydrogenation of alkylidene compounds **183a** and **183b**

3.6.2. 1,4-addition

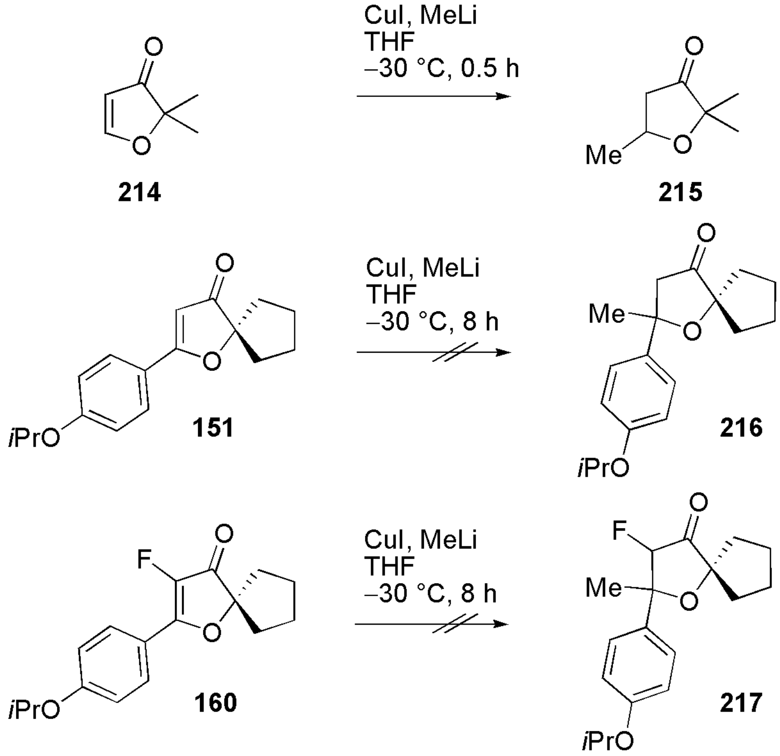
To evaluate the reactivity of *i*Pr-Limno-CP (**151**) with respect to a 1,4-addition pathway, various thiols were examined. The study started with naturally occurring thiols such as glutathione (GSH) or cysteine in MeOH. Chalcones have shown to undergo effectively 1,4-additions in presence of triethylamine.[192] Under the same conditions the addition to *i*Pr-Limno-CP (**151**) did not succeed. DMSO was used as solvent with variable amounts of H_2O, however, the use of aqueous solvent mixtures is very much restricted due to solubility problems of *i*Pr-Limno-CP. Dithiothreitol (DTT) was used in combination with a heterogeneous tungsten catalyst[193] as well as thiophenol and DBU in THF.[194] All attempts to perform a 1,4-addition with thiols failed. When butandithiol with catalytic amounts of *p*TsOH in benzene was used, conversion was observed once. Unfortunately, this reaction could not be reproduced revealing the high sensitivity to very small alterations in the reaction conditions, which shifts the equilibrium back to the left side (Scheme 76).



Scheme 76: Addition of thiols to *i*Pr-Limno-CP (**151**)

Investigations focused then on the classical 1,4-addition with lithium dimethylcuprate (Gilman cuprate). As a test substrate 2,2-dimethyl-3(2*H*)-furanone (**214**) was chosen,[195] which could be fully converted to its conjugate addition product **215** within minutes at –30 °C. Under the same conditions the 1,4-addition to *i*Pr-Limno-CP (**151**) or α-fluoro *i*Pr-Limno-CP

(**160**), however, showed no conversion within 8 hours at −30 °C. Warming to 0 °C resulted in a slow decomposition of the starting material (Scheme 77).



Scheme 77: 1,4-addition of Gilman cuprate to 2,2-dimethyl-3(2*H*)-furanone (**214**) and *i*Pr-Limno-CP derivatives **151** and **160**

Unfortunately, no 1,4-addition to *i*Pr-Limno-CP (**151**) and its fluoro derivative **160** has been achieved so far. Evidence for a feasible 1,4-addition pathway remains to be produced to underline the results from biological tests.

3.6.3. NMR analysis of the substitution effects on the Michael acceptor activity

The impact of the substituents at the α-position of the α,β-unsaturated carbonyl moiety on the electronic properties of the Michael system can be estimated in comparing the ^{13}C NMR chemical shifts (Table 19). Especially, the β-carbon is of particular importance since it is the reactive center in a possible 1,4-addition. Its reactivity can be strongly influenced by its electrophilic nature. Indeed, the ^{13}C NMR chemical shift of the β-carbon could be significantly altered by the introduction of an adjacent functional group. In the case of α-fluoro Limno-CP (**199**) the effect is quite significant. From 183.0 ppm for the unsubstituted compound **146** the value could be shifted to 166.8 ppm. To the other direction only a small field shift to 185.3 ppm was achieved in the case of isopropyl protected nitrile **172**.

Table 19: ^{13}C NMR chemical shifts of *i*Pr-Limno-CP derivatives

X	**R**[a]	**compound**	**C=O**[b]	**α-C**	**β-C**
H	O*i*Pr	**151**	205.7	98.8	183.6
F	O*i*Pr	**160**	193.4[c]	140.5[d]	167.2[e]
Cl	O*i*Pr	**159**	199.2	104.9	175.6
Br	O*i*Pr	**158**	200.0	92.2	176.9
I	O*i*Pr	**157**	202.5	62.8	179.1
CN	O*i*Pr	**172**	199.6	86.5	185.3
$CONH_2$	O*i*Pr	**173**	193.0	95.1	179.7
Ph	O*i*Pr	**171**	204.3	113.6	178.3
H	OH	**146**	203.8	97.3	183.0
F	OH	**199**	191.6[f]	139.4[g]	166.8[h]
Cl	OH	**200**	197.5	103.1	175.4
Br	OH	**201**	198.5	90.8	176.7
I	OH	**202**	201.9	63.3	178.8
CN	OH	**203**	199.0	84.8	185.1
$CONH_2$	OH	**205**	191.6	93.6	178.5
Ph	OH	**204**	202.8	112.3	177.9

[a] 4-Substituent on the aromatic ring.
[b] Carbonyl carbon of 3(2*H*)-furanone.
[c] d, $^{2}J_{CF}$ = 10.1 Hz.
[d] d, $^{1}J_{CF}$ = 259.3 Hz.
[e] d, $^{2}J_{CF}$ = 13.7 Hz.
[f] d, $^{2}J_{CF}$ = 10.1 Hz.
[g] d, $^{1}J_{CF}$ = 256.5 Hz.
[h] d, $^{2}J_{CF}$ = 14.0 Hz.

Compared to literature known Michael acceptors, the reactivity of Limno-CP derivatives is rather moderate. Typically, enone systems with chemical shifts of 120-170 ppm show intermediate to high reactivities in conjugate additions. Nonetheless, 2,2-dimethyl-3(2*H*)-furanone (**214**), which readily reacts with cuprates in a 1,4-fashion, exhibits a ^{13}C NMR chemical shift of 176.2 ppm for its β-carbon. This shows that at least isopropyl protected α-fluoro Limno-CP (**160**) with a more up-field β-carbon chemical shift of 167.2 ppm should be reactive enough for a Michael addition pathway. However, a conjugate addition was not observed experimentally. This can be explained by an increased steric hindrance in the β-position since the large phenyl group may interfere with the attacking nucleophile and inhibit the formation of a new bond with the β-carbon. Consequently, the prediction of a potential

Michael acceptor activity can not only be based on ^{13}C NMR chemical shifts. Particularly, if further demanding substituents are present, steric considerations are equally important and have to be taken into account.

Despite of the low reactivity of Limno-CP derivatives towards conjugate addition, a modulation of the electronic properties of the Michael system was successfully achieved. With ^{13}C NMR chemical shifts of 185.3 to 166.8 ppm for the β-carbon the compounds are ranged at the top of other literature known biologically active compounds. Even though no Michael addition was observed experimentally, the low reactivity towards nucleophilic addition might even be beneficial in biological systems since cytotoxic side effects are suppressed gaining a higher selectivity for a certain target molecule.

In summary, the reactivity of the synthesized *i*Pr-Limno-CP derivatives towards different nucleophiles was investigated. It was shown that isopropyl protected Limno-CP (**151**) readily reacts with alkyl lithium reagents such as *n*BuLi, *n*HexLi and MeLi in a 1,2-addition-elimination reaction to yield the corresponding alkylidene compounds. *i*Pr-Limno-CP derivatives **160**, **159** and **171**, which are substituted with inert functional groups at the α-position of the α,β-unsaturated carbonyl moiety, also react with butyl lithium in a 1,2-fashion. In contrast, the reactivity of *i*Pr-Limno-CP derivatives with respect to a 1,4-addition was low. Neither thiols nor cuprates afforded 1,4-addition products. NMR spectroscopic analysis showed that Limno-CP derivatives cannot be considered as typical Michael acceptors. Nevertheless, it could be demonstrated that the introduction of α-substituents had a significant effect on the ^{13}C NMR chemical shifts of the β-carbon as the reactive center of the enone system.

4. SUMMARY

Compounds which possess an α,β-unsaturated carbonyl moiety have been extensively investigated for their chemopreventive and cytoprotective potential. Especially, Michael acceptors with phenol substituents are reported to exhibit anti-inflammatory and antioxidative activities.

NF-κB and Nrf2 are important transcription factors of a complex signaling network, which mediate a multitude of different biological functions. However, they are also implicated in the pathogenesis of many inflammation-associated disorders and can therefore be addressed as molecular targets to alter or prevent undesired malignant events.

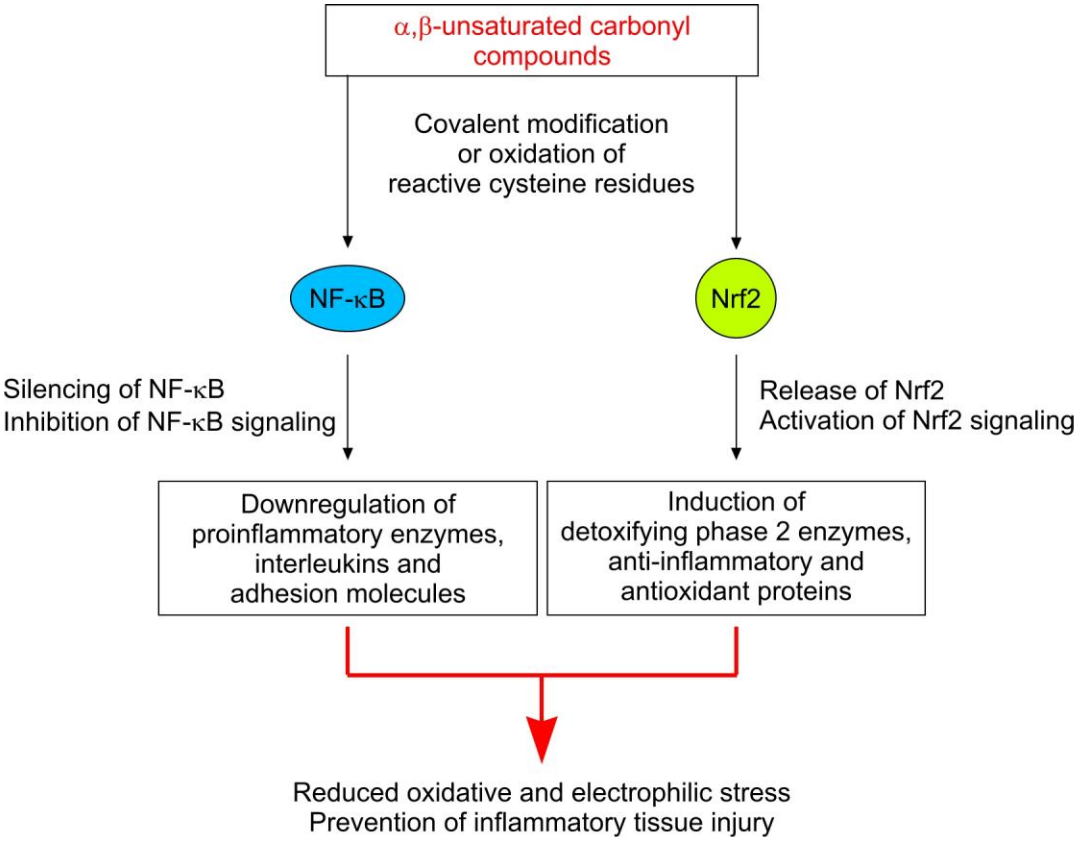
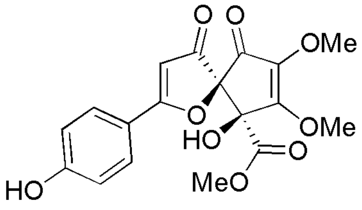


Figure 23: Effect of α,β-unsaturated carbonyl compounds on NF-κB and Nrf2 mediated signaling

Reactive cystein residues which are present in the transcription factors act as critical sensors for inducers and are involved in the fine-tuning of cellular homeostasis. Covalent modification or oxidation of the sulfhydryl groups by phenolic Michael acceptors results in an activation of anti-inflammatory Nrf2 and silencing of pro-inflammatory NF-κB respectively. Suppression of NF-κB leads to down-regulation of pro-inflammatory enzymes, interleukins and adhesion molecules. Activation of Nrf2 induces the expression of detoxifying phase 2 enzymes and other antioxidant and cytoprotective proteins. The modulation of the function of the transcription factors can abrogate oxidative and electrophilic stress as well as inflammatory tissue injury (Figure 23).

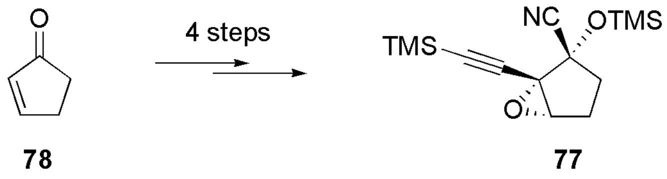


Limnophilaspiroketone (**15**)

Figure 24: Natural product limnophilaspiroketone (**15**)

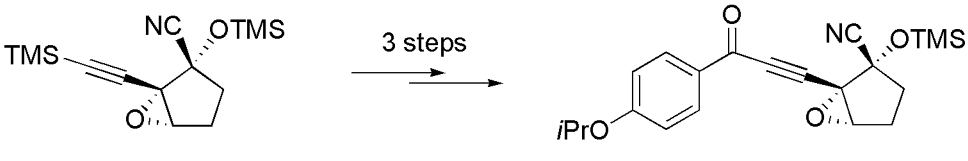
In this context the natural product limnophilaspiroketone (**15**), which belongs to the class of phenolic α,β-unsaturated 3(2*H*)-furanones, was chosen as an attractive molecule for the investigation of its biological activity (Figure 24). Therefore, the total synthesis of limnophilaspiroketone (**15**) was envisioned in the present study.

The synthesis started with simple cyclopent-2-enone (**78**), which could be converted into the chiral building block **77** in four steps. An enantioselective epoxidation and diastereoselective cyanohydrin reaction was applied to establish the desired stereochemistry (Scheme 78). Both key steps allowed for the formation of two quaternary stereocenters with the correct absolute configuration.



Scheme 78: Synthesis of chiral building block **77**

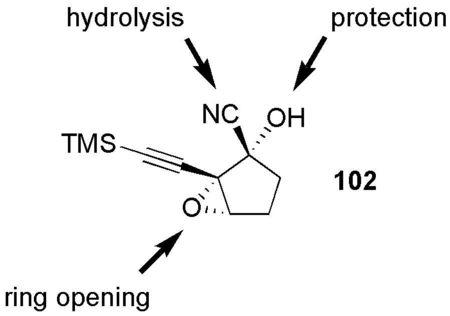
The key intermediate **113** was obtained from chiral building block **77** in three steps (Scheme 79), which included a selective deprotection of the TMS acetylene in presence of a TMS ether. With improved reaction conditions of a literature procedure[120] a valuable and general strategy for the differentiation of both protecting groups was developed.



77 **113**

Scheme 79: Synthesis of ketone **113** from chiral building block **77**

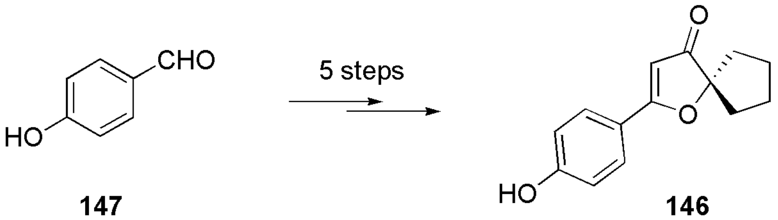
Further experiments focused on ring opening reactions on the epoxide **102** (Figure 25). The instability of the cyanohydrin moiety, however, has shown to be a general drawback. To improve the stability of the cyanohydrin, investigations concentrated on the hydrolysis of the nitrile and on the introduction of an appropriate protecting group on the tertiary alcohol. The hydrolysis of the nitrile, however, could not be achieved under various reaction conditions. The protection of the alcohol as benzyl, *t*-butyl, MOM and 1-methyl-1-methoxyethyl ether was attempted, but could not be accomplished, presumably due to a high steric hindrance in the substrate.



102

Figure 25: Attempted transformations on the cyanohydrin **102**

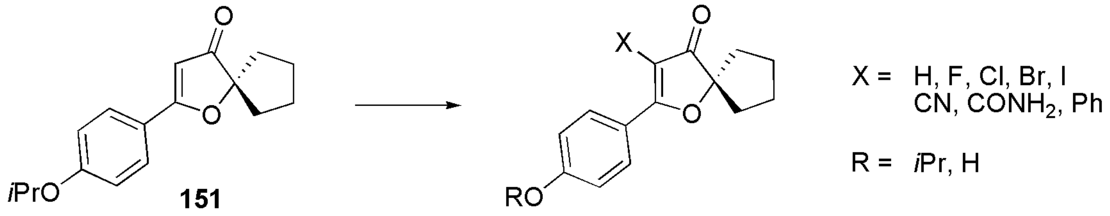
The synthesis of Limno-CP (**146**), a simplified natural product derived model compound, was carried out successfully. It was obtained from *p*-hydroxybenzaldehyde (**147**) in five steps in an overall yield of 54% (Scheme 80). Investigations on the formation of the spirocyclic framework revealed deeper insights in the mechanistic details of this cyclization reaction.



147 **146**

Scheme 80: Synthesis of Limno-CP (**146**)

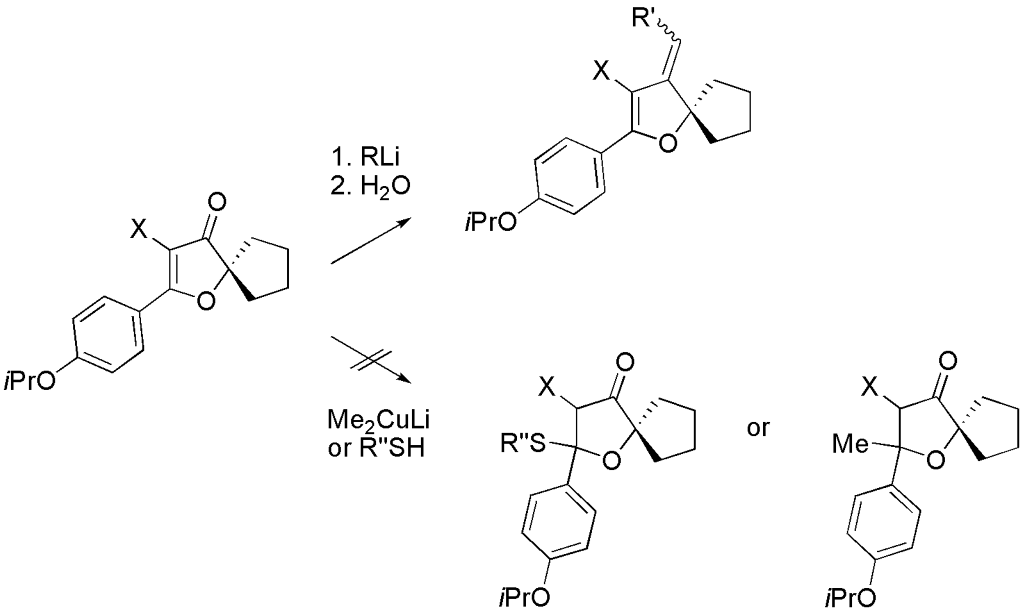
In order to gain Michael acceptor specificity, tailor-made compounds are needed. This can be achieved by fine tuning the reactivity of the α,β-unsaturated carbonyl unit. Thus, the introduction of various substituents in α-position was envisaged, which should have a strong influence on the electronic properties, and therefore on the reactivity of the enone moiety. From *i*Pr-protected Limno-CP (**151**) a library of 16 different, in α-position substituted compounds was synthesized (Scheme 81).



Scheme 81: Synthesis of differently substituted Limno-CP derivatives

NMR spectroscopic analysis was used to determine the electrophilicity of the β-carbon of the α,β-unsaturated carbonyl subunit. It could be demonstrated that the introduction of halogen, cyano, phenyl and amide substituents at the α-position has induced changes in the ^{13}C NMR chemical shifts of the β-carbon of the enone moiety.

The altered electronic properties of the enone entity could not be correlated to the observed reactivity towards nucleophiles. The ^{13}C NMR chemical shifts of the Limno-CP derivatives are not in the range of other typical Michael acceptors, furthermore, the sterically demanding phenyl substituent presumably suppresses an effective addition reaction. Hence, a 1,4-addition reaction with thiols or organocuprates was not observed (Scheme 82). In contrast, with Limno-CP derivatives bearing chemically inert substituents X alkyl lithium reagents effectively added in a 1,2-fashion to the carbonyl group, which lead to the corresponding alkylidene compounds.



Scheme 82: Reaction of *i*Pr-Limno-CP derivatives towards various nucleophiles. RLi = *n*BuLi, *n*HexLi and MeLi for X = H, and *n*BuLi for X = F, Cl, Ph. R’ contains (n-1) C-atoms from R.

So far no systematic studies on the biological properties of spirocyclic 3(2*H*)-furanones exist, especially, the influence of the substituents in α-position of the α,β-unsaturated carbonyl subunit on potential Michael acceptor and antioxidant activity is still not known. Test systems in which the activity in biological systems is measured depending on the nature of the substituents are on the way. The obtained results will give an insight into potential applications of 3(2*H*)-furanones in drug design.

5. EXPERIMENTAL PART

5.1. General methods and materials

All reagents were purchased from commercial sources and were used without further purification. Solvents of high purity were used and dried if waterfree conditions were necessary. The glassware was heated at 110 °C before use, all reactions were carried out under nitrogen atmosphere and monitored by TLC on silica gel plates 60 F_{254} by MERCK. Spots were detected under UV light (λ = 254 and 366 nm) or visualized by staining with vanillin-sulfuric acid (6 g vanillin in 100 mL 95% ethanol and 1 mL conc. sulfuric acid). Column chromatography was performed on silica gel Geduran Si 60 (0.063-0.200 mm) by MERCK.

Melting points were determined on a Büchi SMP 20 apparatus as well as on a MPA 100 Optimelt instrument (Stanford Research Systems).

^{1}H NMR spectra were recorded on a Avance 300 (300 MHz), Avance 400 (400 MHz) and Avance III 600 (600 MHz) spectrometer (Bruker BioSpin GmbH). Chemical shifts are referenced to $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm) or D_2O (4.79 ppm). Data are reported as follows: Chemical shifts δ in ppm, multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, m = multiplet, dt = doublet of a triplet, dd = double doublet, ddd = doublet of a double doublet), coupling constant (Hz).

^{13}C NMR spectra were recorded on a Bruker Avance 300 (75 MHz), Avance 400 (100 MHz) and Avance III 600 (150 MHz) spectrometer. Chemical shifts δ are referenced to $CDCl_3$ (77.0 ppm) or DMSO-d_6 (39.4 ppm) and are given in ppm.

^{19}F-NMR spectra were recorded on a Bruker Avance 300 (282 MHz) spectrometer. Chemical shifts δ are given in ppm.

IR spectroscopy was carried out on a Specac Golden Gate Diamond Single Reflection ATR System Excalibur Series FTS3000MX by BIO-RAD. Samples were measured as neat compounds. The wave numbers are reported in cm^{-1}.

Mass spectra were measured on Finnigan MAT SSQ 710 A, Finnigan MAT 95 or Thermoquest Finnigan TSQ 7000 instruments. Mass fragments are given, the values in brackets represent the peak intensities relative to the basic peak (100%). The molecular formula was proven by high resolution mass spectrometry (HR-MS).

Elemental analysis was performed by the micro analytic section of the University of Regensburg on a Vario EL III instrument.

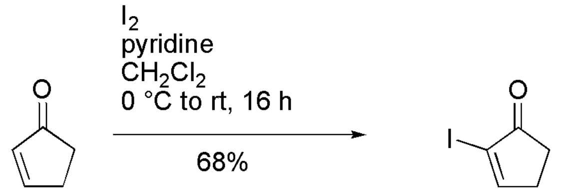
X-ray data were obtained from the crystallography laboratory of the University of Regensburg using a Stoe Imaging Plate Diffraction System (IPDS) (Stoe & Cie GmbH).

Optical rotation was determined on a Krüss Optronic polarimeter at room temperature at a wavelength of λ = 589 nm (Na-D) in a 0.05 dm cell. The concentration is given in g/100 mL.

Gas chromatography was performed on a Fisons GC 8000 instrument using a CP-Chiralsil-DEX-CP column (column 110 °C, FID 250 °C).

5.2. Experimental procedures

2-Iodo-cyclopent-2-enone (79)[89]



78

79

C_5H_5IO
M = [208.00]

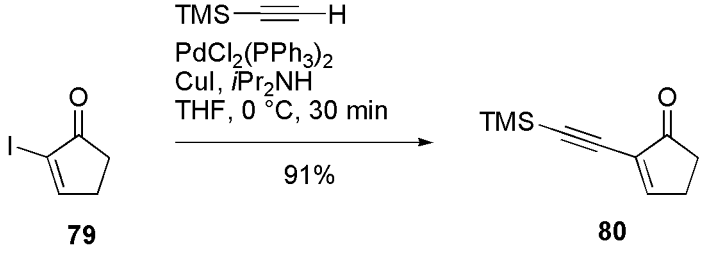
Iodine (3.09 g, 12.2 mmol 1.0 eq.) dissolved in 75 mL CH_2Cl_2 was added dropwise to a solution of cyclopentenone (**78**) (1.00 g, 12.2 mmol, 1.0 eq.) in 75 mL CH_2Cl_2 and pyridine (0.521 mL, 6.58 mmol, 0.54 eq.) at 0 °C. The mixture was stirred for 16 h during which time the mixture was allowed to warm to room temperature. It was diluted with Et_2O (100 mL) and washed successively with H_2O (100 mL), 1 M HCl (100 mL), H_2O (100 mL), saturated aqueous NaS_2O_3 solution (100 mL) and brine (100 mL). The mixture was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was recrystallized from Et_2O–pentane to afford 2-iodo-cyclopent-2-enone (**79)** as yellow crystals (1.72 g, 8.29 mmol, 68%).

R_f = 0.82 (SiO_2, hexanes–EtOAc, 1:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.49–2.52 (m, 2H, CH_2), 2.76–2.78 (m, 2H, CH_2), 8.02 (t, J = 2.8 Hz, 1H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.9, 31.2, 102.9, 169.4, 203.9.

2-Trimethylsilanylethynyl-cyclopent-2-enone (80)



$C_{10}H_{14}OSi$
M = [178.08]

2-Iodo-cyclopent-2-enone (**79**) (1.50 g, 7.21 mmol, 1.0 eq.), trimethylsilylacetylene (1.20 mL, 8.65 mmol, 1.2 eq.), bis(triphenylphosphine)palladium(II)-dichloride (0.253 g, 0.361 mmol, 0.05 eq.) and CuI (0.137 g, 0.721 mmol, 0.1 eq.) were taken up in 20 mL anhydrous THF at 0 °C. *i*Pr_2NH (3.1 mL, 22 mmol, 3.0 eq.) was added and the solution was stirred for 30 minutes at 0 °C turning from yellow to black during the reaction. The reaction mixture was partitioned between Et_2O (20 mL) and 1 M HCl (20 mL) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (SiO_2, hexanes–Et_2O, 3:1) to yield the pure acetylene **80** as brown crystals (1.17 g, 6.56 mmol, 91%).

$R_f = 0.59$ (SiO_2, hexanes–EtOAc, 3:1); Mp 40 °C.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.22$ (s, 9H, TMS), 2.44–2.47 (m, 2H, CH_2), 2.68–2.73 (m, 2H, CH_2), 7.81 (t, $J = 3.0$ Hz, 1H, CH).

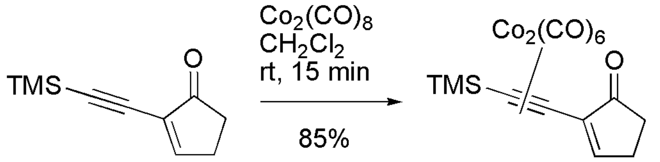
^{13}C NMR (100 MHz, $CDCl_3$): $\delta = –0.2$, 27.2, 34.0, 95.0, 101.9, 130.2, 166.2, 205.4.

IR (neat): 2975, 2161, 1703, 1595, 1439, 1295, 1274, 1049, 1010, 929, 834, 790, 757, 701, 663 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 178.1 (14) [M^+], 164.1 (14), 163.1 (100) [M^+-CH_3].

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{10}H_{14}SiO$: 178.0814; found: 178.0810.

2-Trimethylsilanylethynyl-cyclopent-2-enone-dicobalthexacarbonyl (92)



80 **92**

$C_{16}H_{14}Co_2O_7Si$
M = [464.23]

To a solution of the alkyne **80** (50.0 mg, 0.281 mmol, 1.0 eq.) in 2 mL anhydrous CH_2Cl_2 was added dicobalt octacarbonyl (0.149 g, 0.435 mmol, 1.55 eq.) at ambient temperature. After 15 minutes the solvent was removed *in vacuo* and the crude product was purified by column chromatography (SiO_2, hexanes–EtOAc, 20:1) to yield the protected alkyne **92** as black solid (0.111 g, 0.239 mmol, 85%).

R_f = 0.71 (SiO_2, hexanes–EtOAc, 5:1); Mp > 400 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.34 (s, 9H, TMS), 2.59–2.62 (m, 2H, CH_2), 2.67–2.70 (m, 2H, CH_2), 7.66 (t, J = 2.9 Hz, 1H, CH).

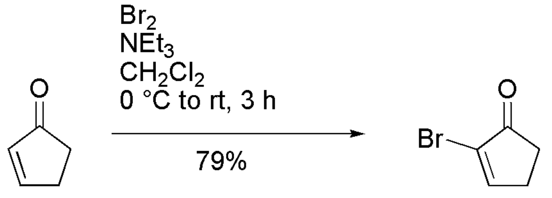
^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.7, 27.0, 35.3, 83.4, 91.3, 144.3, 160.6, 199.8, 203.8.

IR (neat): 2963, 2911, 2088, 1992, 1848, 1711, 1644, 1544, 1406, 1288, 1241, 1187, 1059, 996, 928, 837, 755, 694, 608, 496, 450 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 435.8 (10) [M^+-CO], 407.9 (31) [M^+-2CO], 379.9 (35) [M^+-3CO], 351.9 (30) [M^+-4CO], 323.9 (100) [M^+-5CO], 295.9 (65) [M^+-6CO], 237.0 (27), 178.1 (10) [M^+-$Co_2(CO)_6$], 163.0 (78) [M^+-CH_3], 83.9 (48), 49.0 (48).

Anal. Calcd for $C_{16}H_{14}Co_2O_7Si$: C, 41.40; H, 3.04. Found: C, 41.47; H, 3.14.

2-Bromo-cyclopent-2-enone (81)



78 **81**

C_5H_5BrO
M = [161.00]

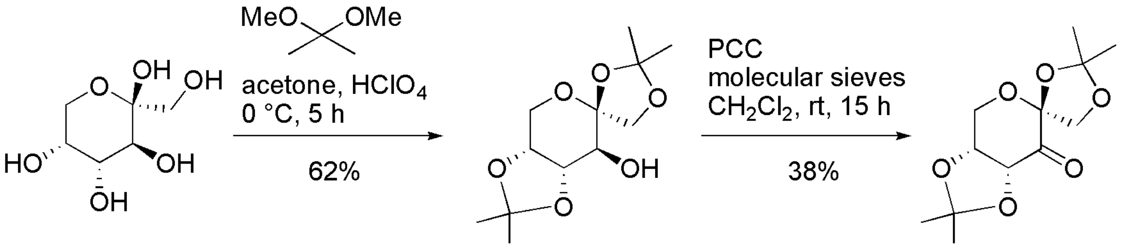
To an ice cold solution of cyclopent-2-enone (**78**) (5.10 mL, 60.9 mmol, 1.0 eq.) in 30 mL anhydrous CH_2Cl_2 was added dropwise a solution of bromine (3.12 mL, 60.9 mmol, 1.0 eq.) in 30 mL CH_2Cl_2. After stirring for 10 minutes at 0 °C, a solution of triethylamine (12.7 mL, 91.4 mmol, 1.5 eq.) in 30 mL CH_2Cl_2 was added slowly at this temperature. The mixture was allowed to warm to ambient temperature. After 3 hours the mixture was filtered through a pad of Celite and the solvent was evaporated. Purification of the crude product by flash column chromatography (SiO_2, hexanes–EtOAc 9:1) afforded 2-bromo-cyclopent-2-enone (**81**) (7.74 g, 48.1 mmol, 79%).

$R_f = 0.50$ (SiO_2, hexanes–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.52–2.54$ (m, 2H, CH_2), 2.68–2.72 (m, 2H, CH_2), 7.78 (t, $J = 2.9$ Hz, 1H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.0, 32.4, 126.2, 161.8, 201.8$.

1,2:4,5-Di-O-isopropylidene-D-erythro-2,3-hexodiulo-2,6-pyranose (85)[108]



83 **84** **85**

$C_{12}H_{18}O_6$
M = [258.27]

D-Fructose (**83**) (9.00 g, 50.0 mmol, 1.7 eq.) and dimethoxypropane (3.61 mL, 29.4 mmol, 1.0 eq.) were dissolved in 175 mL acetone. The mixture was cooled in an ice bath for 15 minutes, then $HClO_4$ (2.00 mL, 35.3 mmol, 1.2 eq.) was added in one portion. The resulting suspension was stirred at 0 °C for 5 hours. The mixture was neutralized with concentrated aqueous NH_3 solution and the solvent was removed *in vacuo*. The remaining white solid was dissolved in 100 mL CH_2Cl_2 and washed with brine (2 × 25 mL), dried over $MgSO_4$ and concentrated to approximately 40 mL. Recrystallization from boiling hexane (100 mL) yielded the alcohol **84** as fine white needles.

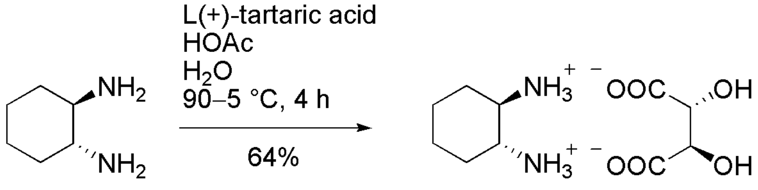
The obtained alcohol **84** (1.00 g, 3.84 mmol, 1.0 eq.) and freshly powdered 3Å molecular sieves (1.40 g) were suspended in 12 mL anhydrous CH_2Cl_2. PCC (2.07 g, 9.61 mmol, 2.5 eq.) was added portionwise over 10 minutes and the mixture was stirred at room temperature for 15 hours. Diethyl ether (20 mL) was added with vigorous stirring and the mixture was filtered through a pad of Celite. The brown filtrate was concentrated to dryness and the remaining solid was purified by column chromatography (SiO_2, hexanes–EtOAc, 1:1). The isolated product was recrystallized from boiling hexane to yield catalyst **85** (0.377 g, 1.46 mmol, 38%) as white needles.

$R_f = 0.67$ (SiO_2, hexanes–EtOAc, 1:1); $[\alpha]_D^{20}$ –121.5 (*c* 1.00, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 6H, CH_3), 1.46 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 3.99 (d, $J = 9.5$ Hz, 1H, 1-CH), 4.12 (d, $J = 13.5$ Hz, 1H, 6-CH), 4.39 (dd, J = 13.5, 2.2 Hz, 1H, 6-CH), 4.54 (ddd, $J = 5.6, 2.1, 0.8$ Hz, 1H, 5-CH), 4.61 (d, $J = 9.5$ Hz, 1H, 1-CH), 4.73 (d, J = 5.6 Hz, 1H, 4-CH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.98$, 26.03, 26.5, 27.1, 60.0, 70.0, 75.9, 77.9, 104.1, 110.6, 113.8, 196.9.

(*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate (99)[111]



rac-**98**

99

$C_{10}H_{20}N_2O_6$
M = [264.28]

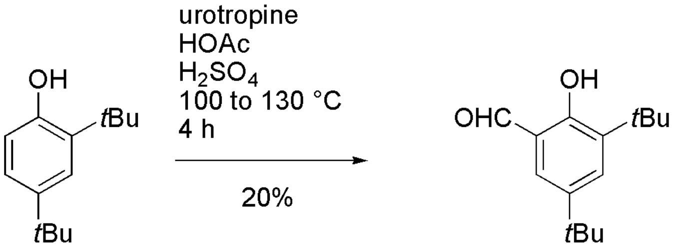
A 250 mL flask was charged with 50 mL H_2O and L(+)-tartaric acid (15.0 g, 0.100 mol, 1.0 eq.). The mixture was stirred vigorously and racemic *trans*-1,2-diaminocyclohexane (**98**) (23.8 mL, 0.200 mol, 2.0 eq.) was added carefully in one portion. When the slurry was completely dissolved, glacial acetic acid (10 mL) was added. During the addition the temperature rose to 90 °C. The mixture was allowed to cool to 5 °C within 3 hours with stirring. This temperature was maintained for another hour and the precipitate was collected by filtration and washed with ice cold water (10 mL) and methanol (4 × 10 mL). The product was dried at 45 °C under reduced pressure to yield the tartrate **99** as white crystals (16.9 g, 64.0 mmol, 64%).

$[\alpha]_D^{20}$ 12.2 (*c* 1.00, H_2O).

^{1}H NMR (300 MHz, D_2O): δ = 1.28–1.54 (m, 4H, CH_2), 1.72–1.84 (m, 2H, CH_2), 2.10–2.14 (m, 2H, CH_2), 3.30–3.35 (m, 2H, CH, NCH), 4.30 (s, 2H, CH, OCH).

^{13}C NMR (75 MHz, D_2O): δ = 22.8, 29.4, 52.2, 73.9, 178.5.

3,5-Di-*tert*-butylsalicylaldehyde (97)[111]



96

97

$C_{15}H_{22}O_2$
M = [234.33]

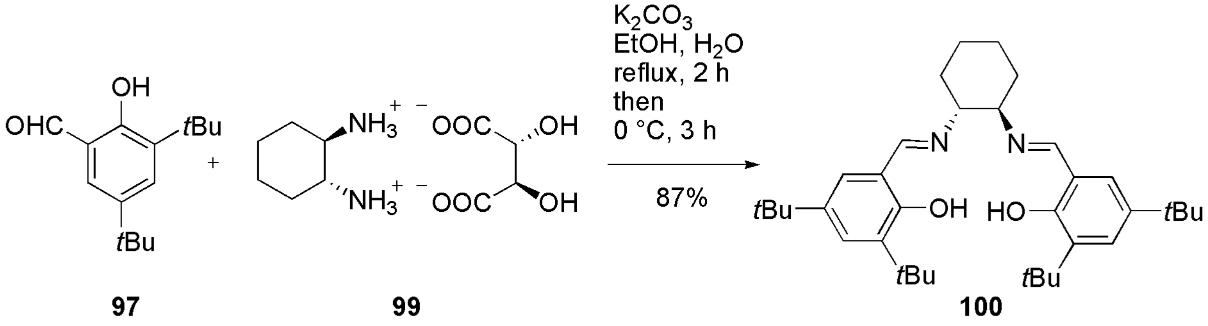
2,4-Di-*tert*-butylphenol (**96**) (63.0 g, 0.305 mol, 1.0 eq.) and urotropine (85.6 g, 0.611 mol, 2.0 eq.) were dissolved in 150 mL glacial acetic acid. The mixture was heated to 130 °C and maintained at that temperature for 3 hours. Then, the mixture was cooled to 80 °C and 150 mL of a 33% (w/w) aqueous solution of H_2SO_4 was added. The mixture was refluxed for another hour. The mixture was allowed to cool to room temperature and extracted with Et_2O (3 × 100 mL). The combined organic layers were concentrated and 50 mL MeOH was added to the crude product. Precipitation was completed in an ice bath and the product was collected by vacuum filtration. Recrystallization from MeOH afforded the aldehyde **97** as yellowish solid (14.3 g, 61.0 mmol, 20%).

R_f = 0.59 (SiO_2, hexanes–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9H, CH_3, *t*Bu), 1.43 (s, 9H, CH_3, *t*Bu), 7.35 (d, *J* = 2.5 Hz, 1H, CH, Ar), 7.59 (d, *J* = 2.4 Hz, 1H, CH, Ar), 9.87 (s, 1H, COH), 11.65 (s, 1H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.2, 31.3, 34.2, 35.0, 120.0, 127.8, 131.9, 137.6, 141.6, 159.1, 197.4.

(*R*,*R*)-*N*,*N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (100)[111]



$C_{36}H_{54}N_2O_2$
M = [546.83]

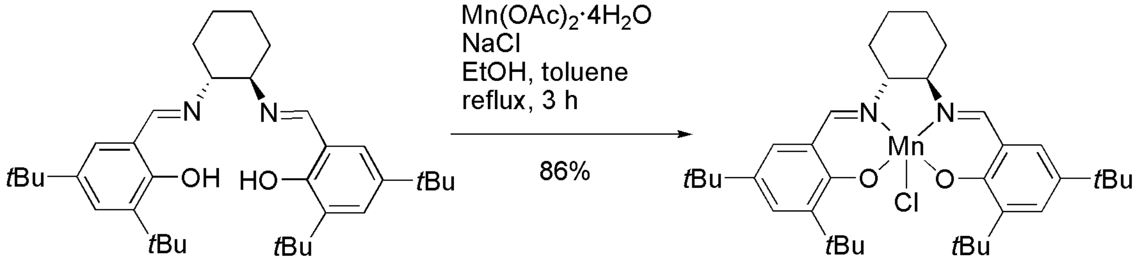
The mono-(+)-tartrate salt **99** (8.00 g, 30.3 mmol, 1.0 eq.) and K_2CO_3 (8.37 g, 60.5 mmol, 2.0 eq.) were dissolved in 40 mL H_2O. The mixture was stirred until dissolution was complete, then 160 mL EtOH were added. The reaction mixture was heated to reflux and a solution of aldehyde **97** (14.2 g, 60.5 mmol, 2.0 eq.) in 67 mL EtOH was added dropwise within 30 minutes. The resulting solution was refluxed for 2 hours. 40 mL H_2O was added and the mixture was cooled to 0 °C and maintained at that temperature for 3 hours. The yellow solid was collected by vacuum filtration and washed with 25 mL EtOH. The crude product was taken up with 135 mL CH_2Cl_2 and the organic solution was washed with H_2O (2 × 80 mL) and brine (120 mL) and finally dried over $MgSO_4$. The solvent was removed to yield the pure salen ligand **100** (14.4 g, 26.3 mmol, 87%) as yellow solid.

R_f = 0.76 (SiO_2, hexanes–EtOAc, 10:1); $[\alpha]_D^{20}$ –323.4 (*c* 1.00, CH_2Cl_2).

1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 18H, CH_3, *t*Bu), 1.41 (s, 18H, CH_3, *t*Bu), 1.41–1.50 (m, 2H, CH_2), 1.68–1.79 (m, 2H, CH_2), 1.86–1.97 (m, 4H, CH_2), 3.28–3.37 (m, 2H, NCH), 6.99 (d, *J* = 2.4 Hz, 1H, CH, Ar), 7.30 (d, *J* = 2.4 Hz, 1H, CH, Ar), 8.31 (s, 2H, CH, N=CH), 13.73 (s, 2H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 29.4, 31.4, 33.3, 34.0, 34.9, 72.4, 117.8, 126.0, 126.7, 136.3, 139.8, 158.0, 165.8.

(*R*,*R*)-*N*,*N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride (94)[111]



100 **94**

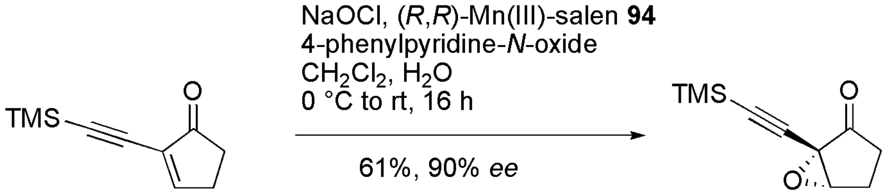
$C_{36}H_{52}ClMnN_2O_2$
M = [635.20]

A solution of manganese acetate tetrahydrate (13.4 g, 54.9 mmol, 3.0 eq.) in 100 mL EtOH was heated to reflux and a solution of the salen ligand **100** (10.0 g, 18.3 mmol, 1.0 eq.) in 50 mL toluene was added dropwise within 45 minutes at this temperature. The mixture was refluxed for 2 hours, then air was bubbled through the mixture using a simple commercially available aquarium pump for another hour under reflux conditions. Then, brine (20 mL) was added and the solution was cooled to ambient temperature, washed with H_2O (3 × 120 mL) and brine (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the black residue was taken up with 60 mL CH_2Cl_2 and 60 mL heptane. After careful removal of CH_2Cl_2 by rotary evaporation, the resulting slurry was stirred for 1 hour in an ice bath. Vacuum filtration and drying under high vacuum at 60 °C afforded catalyst **94** (9.99 g, 15.7 mmol, 86%) as black crystals.

The complex does not exhibit an interpretable NMR spectrum because of its paramagnetic nature.

MS (ESI): *m/z* = 599.3 $[M\text{-}Cl]^+$.

(1*S*,5*S*)-1-Trimethylsilanylethynyl-6-oxa-bicyclo[3.1.0]hexan-2-one (89)



80

(*S*,*S*)-**89**

$C_{10}H_{14}O_2Si$

M = [194.30]

To a stirred solution of ketone **80** (2.10 g, 11.8 mmol, 1.0 eq.), (*R*,*R*)-Mn(III)-salen complex **94** (0.749 g, 1.18 mmol, 0.1 eq.) and 4-phenylpyridine-*N*-oxide (0.404 g, 2.36 mmol, 0.2 eq.) in 25 mL CH_2Cl_2 was added a 2 M aqueous solution of NaOCl (0.05 M in Na_2HPO_4, pH = 11.3 adjusted with 1 M aqueous HCl) (88.4 mL, 0.177 mol, 15 eq.) at 0 °C. The mixture was allowed to warm to ambient temperature while stirring was continued for 16 hours. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. After evaporation of the solvent the crude material was purified by column chromatography (SiO_2, hexanes–EtOAc 10:1). The epoxide **89** (1.40 g, 7.19 mmol, 61%, 90% *ee*, determined by GC) was obtained as colorless oil.

R_f = 0.5 (SiO_2, hexanes–EtOAc, 5:1); $[\alpha]_D^{20}$ –8.0 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 9H, TMS), 2.03–2.43 (m, 4H, CH_2), 4.14 (s, 1H, CH).

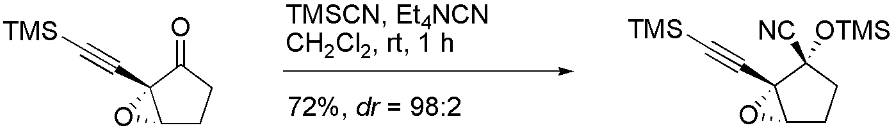
^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.4, 22.2, 30.7, 54.4, 66.3, 93.8, 96.0, 204.2.

IR (neat): 2961, 2180, 1752, 1393, 1251, 1076, 1053, 995, 843, 761, 674, 632, 537, 497, 412 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 194.1 (55) [M^+], 179.0 (97) [M^+-CH_3], 151.0 (29), 137.0 (41), 123.0 (32), 109.0 (75), 75.0 (100).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{10}H_{14}SiO_2$: 194.0763; found: 194.0760.

(1*S*,2*S*,5*S*)-1-Trimethylsilanylethynyl-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (77)



89 **77**

$C_{14}H_{23}NO_2Si_2$
M = [293.51]

To a solution of ketone **89** (0.170 g, 0.875 mmol, 1.0 eq.) in 4.4 mL anhydrous CH_2Cl_2 was added TMSCN (0.219 mL, 1.75 mmol, 2.0 eq.) at room temperature. Then, a solution of Et_4NCN (13.7 mg, 87.5 µmol, 0.1 eq.) in 4.4 mL CH_2Cl_2 was added. The mixture was stirred for 1 hour at ambient temperature. The solvent was removed and the crude product was taken up with diethylether (10 mL), washed with water (2 × 10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes–EtOAc 20:1) to obtain cyanohydrin **77** (0.185 g, 0.630 mmol, 72%, *dr* = 98:2, determined by GC) as colorless oil.

R_f = 0.3 (SiO_2, hexanes–EtOAc, 5:1); $[\alpha]_D^{20}$ –6.8 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.21 (s, 9H, TMS), 0.30 (s, 9H, OTMS), 1.75 (ddd, *J* = 12.7, 10.9, 7.7, 1H, CH), 1.95 (dddd, *J* = 14.4, 10.7, 7.6, 1.1, 1H, CH), 2.10–2.20 (m, 2H, CH), 3.72 (s, 1H, CH, epox).

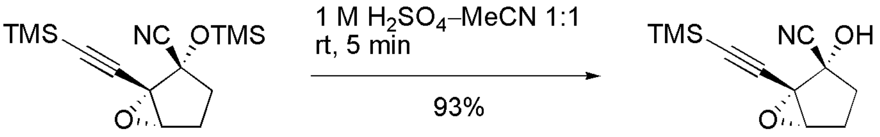
^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.5, 1.2, 24.4, 33.9, 56.2, 59.3, 63.0, 94.7, 96.2, 119.1.

IR (neat): 2962, 2176, 1399, 1399, 1253, 1194, 1153, 1045, 984, 946, 843, 760, 705, 632, 588, 545, 500, 416 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 278.1 (12), 179.1 (16), 75.1 (18), 73.1 (100).

HRMS (EI-MS) *m/z* (M^+) calcd. for $C_{14}H_{23}NO_2Si_2$: 293.1267; found: 293.1267.

(1*S*,2*S*,5*S*)-2-Hydroxy-1-trimethylsilanylethynyl-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (102)



77

102

$C_{11}H_{15}NO_2Si$
M = [221.33]

TMS ether **77** (0.500 g, 1.70 mmol, 1.0 eq.) was dissolved in 25 mL MeCN and 25 mL of a 1 M solution of aqueous H_2SO_4 were added. The mixture was stirred at room temperature for 5 minutes, diluted with EtOAc (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude material was recrystallized from diethylether–pentane to give the alcohol **102** (0.351 g, 1.58 mmol, 93%) as colorless crystals.

R_f = 0.3 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.23 (s, 9H, TMS), 1.77 (ddd, *J* = 13.3, 11.0, 7.9 Hz, 1H, CH), 1.97–2.05 (m, 1H, CH), 2.19 (dd, *J* = 14.7, 7.9 Hz, 1H, CH), 2.87 (s, 1H, CH), 3.82 (s, 1H, CH, epox).

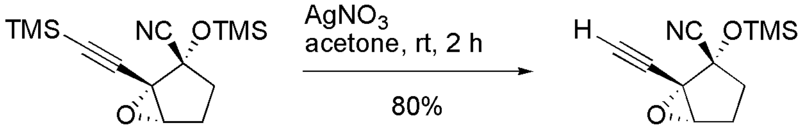
^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.5, 24.7, 32.6, 59.3, 64.0, 76.0, 94.5, 96.0, 118.3.

IR (neat): 3351, 2962, 2178, 1418, 1386, 1313, 1246, 1198, 1122, 1094, 1041, 982, 927, 907, 838, 759, 701, 654, 600, 551, 499 cm^{-1}.

MS (CI, NH_3): *m/z* = 212.1 [$M+NH_4^+$-HCN].

Anal. Calcd for $C_{11}H_{15}NO_2Si$: C, 59.69; H, 6.83; N, 6.33. Found: C, 59.78; H, 6.80; N, 6.04.

(1*S*,2*S*,5*S*)-1-Ethynyl-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (118)



77

118

$C_{11}H_{15}NO_2Si$
M = [221.33]

To a solution of the TMS protected alkyne **77** (0.550 g, 1.87 mmol, 1.0 eq.) in 50 mL anhydrous acetone was added $AgNO_3$ (0.446 g, 2.62 mmol, 1.4 eq.). The reaction flask was covered with aluminium foil and the reaction mixture was stirred for 2 hours in the dark at ambient temperature. Saturated aqueous NH_4Cl solution (50 mL) was added and the mixture was extracted with EtOAc (5 × 30 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield the pure deprotected acetylene **118** (0.332 g, 1.50 mmol, 80%) as brownish solid.

R_f = 0.6 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.29 (s, 9H, OTMS), 1.76 (ddd, J = 12.7, 10.8, 7.6 Hz, 1H, CH), 1.97 (dddd, J = 14.4, 10.3, 7.7, 1.1 Hz, 1H, CH), 2.21-2.13 (m, 2H, CH), 2.61 (s, 1H, CH, alkyne), 3.74 (s, 1H, CH, epox).

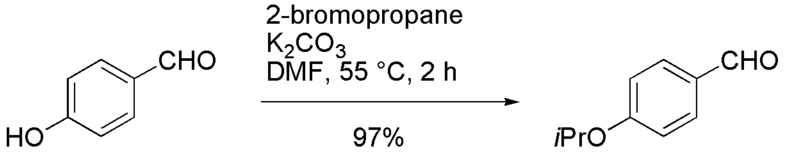
^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.2, 24.5, 33.4, 59.0, 62.4, 75.3, 76.3, 76.9, 118.9.

IR (neat): 3256, 2964, 2126, 1440, 1397, 1314, 1254, 1195, 1137, 1045, 984, 931, 841, 758, 724, 697, 636, 605, 573, 520, 475, 429 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 206.0 (34) [M^+-CH_3], 179.1 (20), 154.0 (46), 151.1 (34), 129.0 (27), 126.1 (23), 101.1 (21), 84.0 (31), 75.1 (45), 73.1 (100).

HRMS (EI-MS) m/z (M^+) calcd. for $C_{11}H_{14}NO_2Si$: 220.0794; found: 220.0795.

4-Isopropoxybenzaldehyde (116)[142]



147 **116**

$C_{10}H_{12}O_2$
M = [164.20]

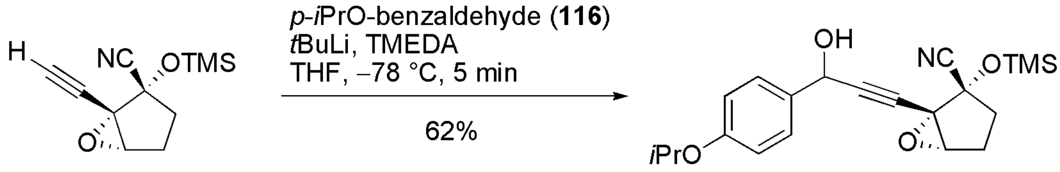
2-Bromopropane (45.3 g, 0.368 mol, 4.5 eq.) and K_2CO_3 (37.3 g, 0.270 mmol, 3.3 eq.) were added to a solution of *p*-hydroxybenzaldehyde (**147)** (10 g, 81.9 mmol, 1.0 eq.) in 90 mL DMF. The mixture was stirred for 2 hours at 55 °C, then cooled to ambient temperature and quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with H_2O (5 × 100 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* yielded the protected benzaldehyde **116** as yellowish liquid (13.0 g, 79.4 mmol, 97%).

R_f = 0.6 (SiO_2, hexanes–EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, J = 6.1 Hz, 6H, CH_3, *i*Pr), 4.67 (sept, J = 6.1 Hz, 1H, CH, *i*Pr), 6.97 (d, J = 8.8 Hz, 2H, CH, Ar), 7.82 (d, J = 8.9 Hz, 2H, CH, Ar), 9.87 (s, 1H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 70.2, 115.5, 129.4, 131.9, 163.1, 190.7.

(1*S*,2*S*,5*S*)-1-[3-Hydroxy-3-(4-isopropoxy-phenyl)-prop-1-ynyl]-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (119)



118 **119**

$C_{21}H_{27}NO_4Si$
M = [385.53]

To a solution of the terminal alkyne **118** (0.250 g, 1.13 mmol, 1.0 eq.) and TMEDA (0.187 mL, 1.24 mmol, 1.1 eq.) in 25 mL anhydrous THF was added a 1.6 M solution of *t*BuLi in pentane (0.777 mL, 1.24 mmol, 1.1 eq.) dropwise at –78 °C. Aldehyde **116** (0.185 g, 1.13 mmol, 1.0 eq.) was added and after 5 minutes the mixture was diluted with 25 mL saturated NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product **119** (yellow oil, 62%) can be used without further purification. A purified example of the product (column chromatography, SiO_2, hexanes–EtOAc, 5:1) showed the following analytical data:

R_f = 0.4 (SiO_2, hexanes–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9H, TMS, diast. 0.27), 1.33 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.72–1.83 (m, 1H, CH), 1.92–2.03 (m, 1H, CH), 2.14–2.22 (m, 1H, CH), 3.75 (s, 1H, CH, epox, diast. 3.76), 4.56 (sept, *J* = 6.1 Hz, 1H, *i*Pr), 5.48 (s, 1H, C*H*OH, diast. 5.50), 6.89 (d, *J* = 8.7 Hz, CH, Ar), 7.47 (d, *J* = 8.7 Hz, CH, Ar).

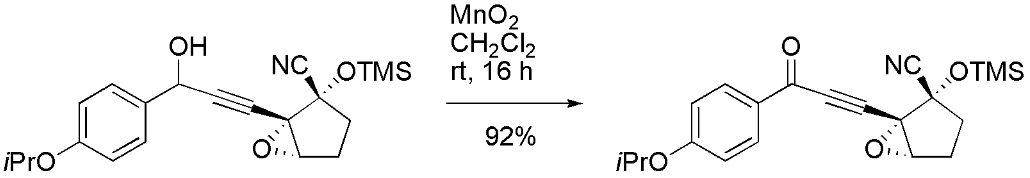
^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.1, 21.9, 24.5, 33.4, 59.3, 62.6, 64.2, 69.9, 77.2, 77.9, 87.9, 115.9, 119.1, 128.3, 131.5, 158.2.

IR (neat): 3443, 2977, 1751, 1610, 1509, 1449, 1384, 1302, 1244, 1194, 1150, 1119, 1069, 1043, 1009, 955, 921, 843, 758, 732, 632, 569, 474 cm^{-1}.

MS (ESI): *m/z* = 367.9 [MH^+-H_2O], 403.0 [M+NH_4^+].

Anal. Calcd for $C_{18}H_{20}NO_3Si$: C, 66.23; H, 6.18; N, 4.29. Found: C, 64.92; H, 7.18; N, 2.99.

(1*S*,2*S*,5*S*)-1-[3-(4-Isopropoxy-phenyl)-3-oxo-prop-1-ynyl]-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (113)



119 **113**

$C_{21}H_{25}NO_4Si$

M = [383.51]

A suspension of alcohol **119** (75.0 mg, 0.195 mmol, 1.0 eq.) and MnO_2 (0.169 g, 1.95 mmol, 10 eq.) in 2 mL anhydrous CH_2Cl_2 was stirred at ambient temperature for 16 hours. The suspension was filtered through a pad of Celite and the solvent was removed under reduced pressure to yield the pure ketone **113** (68.6 mg, 0.179 mmol, 92%).

R_f = 0.6 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.30 (s, 9H, TMS), 1.37 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.78–1.89 (m, 1H, CH), 2.00–2.12 (m, 1H, CH), 2.21–2.29 (m, 2H, CH), 3.90 (s, 1H, CH, epox), 4.67 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.93 (d, *J* = 8.9 Hz, 2H, CH, Ar), 8.15 (d, *J* = 8.9 Hz, 2H, CH, Ar).

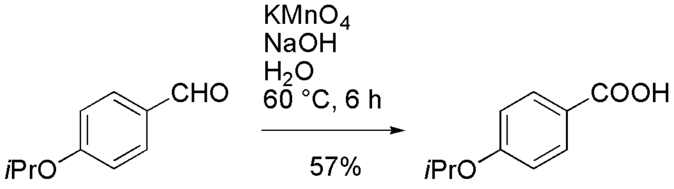
^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.1, 21.9, 24.8, 33.3, 59.1, 63.0, 70.4, 77.1, 83.4, 84.4, 115.3, 118.9, 129.1, 132.3, 163.5, 174.9.

IR (neat): 2978, 2221, 1752, 1640, 1594, 1506, 1314, 1251, 1161, 1106, 1065, 1043, 1001, 926, 869, 842, 755, 688, 632, 578, 470 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 383.1 (57) [M$^+$], 326.1 (62), 121.0 (100), 73.1 (86).

HRMS (EI-MS) *m/z* (M$^+$) calcd. for $C_{21}H_{25}NO_4Si$: 383.1553; found: 383.1552.

4-Isopropoxybenzoic acid (120)



116

120

$C_{10}H_{12}O_3$
M = [180.20]

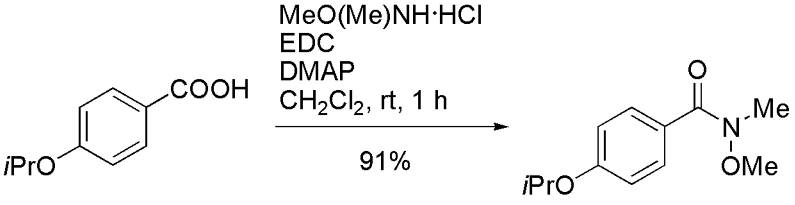
Benzaldehyde **116** (5.00 g, 30.5 mmol, 1.0 eq.) and NaOH (48.7 mg, 1.22 mmol, 0.04 eq.) were suspended in 60 mL H_2O. A solution of $KMnO_4$ (3.61 g, 22.8 mmol, 0.75 eq.) in 100 mL H_2O was added slowly at room temperature and the mixture was heated to 60 °C for 6 hours. The hot solution was filtered and acidified to pH 3 by addition of concentrated HCl. The filtrate was cooled in an ice bath, and the precipitate was collected by vacuum filtration and washed with cold H_2O (10 mL). The crude product was recrystallized from methylcyclohexane to yield benzoic acid **120** (3.13 g, 17.4 mmol, 57%) as white crystals.

R_f = 0.12 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 4.66 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.91 (d, *J* = 8.9 Hz, 2H, CH, Ar), 8.04 (d, *J* = 8.9 Hz, 2H, CH, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 70.1, 115.1, 121.1, 132.4, 162.5, 171.6.

N-methoxy-*N*-methyl-4-(isopropoxy)-benzamide (121)



120 **121**

$C_{12}H_{17}NO_3$
M = [223.27]

A solution of benzoic acid **120** (0.500 g, 2.77 mmol, 1.0 eq.) in 15 mL anhydrous CH_2Cl_2 was treated with *N*,*O*-dimethylhydroxylamine hydrochloride (0.406 g, 4.16 mmol, 1.5 eq.), EDC (0.797 g, 4.16 mmol, 1.5 eq.) and DMAP (0.508 g, 4.16 mmol, 1.5 eq.) and the mixture was stirred at ambient temperature for one hour. Brine (15 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed successively with a 5% solution of HCl (15 mL) and brine (15 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatographic purification (SiO_2, CH_2Cl_2–EtOAc, 3:1) afforded the Weinreb amide **121** (0.564 g, 2.52 mmol, 91%) as white solid.

R_f = 0.70 (SiO_2, CH_2Cl_2–EtOAc, 2:1); Mp 51 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.1 Hz, 6H,CH_3, *i*Pr), 3.35 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 4.60 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.86 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.70 (d, *J* = 8.9 Hz, 2H, CH, Ar).

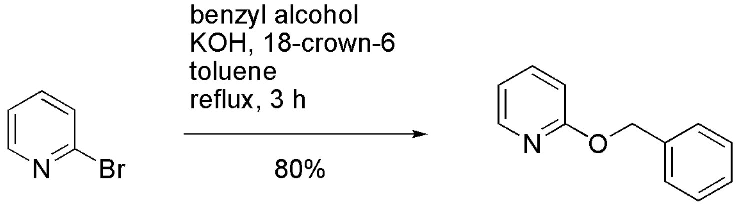
^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 33.9, 60.8, 69.8, 114.7, 125.5, 130.5, 159.9, 169.4.

IR (neat): 2978, 2935, 1633, 1604, 1508, 1462, 1420, 1372, 1299, 1248, 1180, 1106, 1063, 977, 950, 888, 840, 792, 755, 684, 617, 559, 505 cm^{-1}.

MS (ESI): *m/z* = 224.1 [MH^+].

HRMS (EI-MS) *m/z* (M^+) calcd. for $C_{12}H_{17}NO_3+Na^+$: 246.1101; found: 246.1103.

2-Benzyloxypyridine (135)[130]



134 **135**

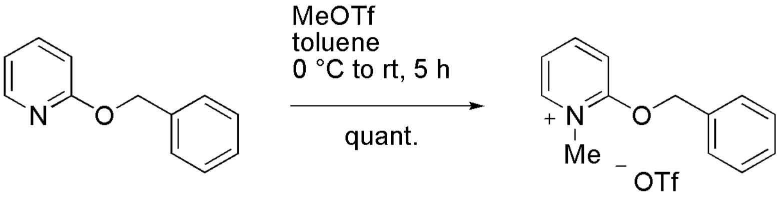
$C_{12}H_{11}NO$
M = [185.22]

Benzyl alcohol (1.00 g, 9.25 mmol, 1.0 eq.), 2-bromopyridine (**134**) (1.08 mL, 11.1 mmol, 1.2 eq.), powdered KOH (1.66 g, 29.6 mmol, 3.2 eq.) and 18-crown-6 (0.122 g, 0.462 mmol, 0.05 eq.) in 10 mL anhydrous toluene were refluxed for 3 hours with azeotropic removal of H_2O (Dean-Stark apparatus). H_2O (10 mL) was added and the mixture was extracted with toluene (3 × 10 mL). The organic layer was washed with brine (30 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was purified by distillation under reduced pressure. 2-Benzyloxypyridine (**135**) was obtained as colorless liquid (1.37 g, 7.40 mmol, 80%).

R_f = 0.68 (SiO_2, hexanes–EtOAc, 5:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 5.39 (s, 2H, CH_2), 6.81 (d, J = 8.3 Hz, 1H, CH, Ar), 6.87–6.91 (m, 1H, CH, Ar), 7.29–7.41 (m, 3H, CH, Ar), 7.46–7.49 (m, 2H, CH, Ar), 7.56–7.62 (m, 1H, CH, Ar), 8.19 (dd, J = 5.0, 1.3 Hz, 1H, CH, Ar).

2-Benzyloxy-1-methyl-pyridinium triflate (136)[129]



135 **136**

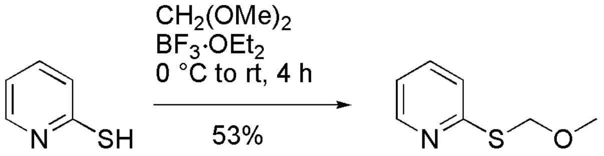
$C_{14}H_{14}F_3NO_4S$
M = [349.33]

MeOTf (0.746 mL, 6.80 mmol, 1.05 eq.) was added to an ice cold solution of 2-benzyloxypyridine (**135**) (1.20 g, 6.49 mmol, 1.0 eq.) in 6.5 mL anhydrous toluene. The ice bath was removed and the mixture was stirred for 5 hours. The solvent was removed under reduced pressure to obtain triflate **136** as white solid in quantitative yield (2.26 g, 6.49 mmol, 100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.04 (d, *J* = 6.3 Hz, CH_3), 5.53 (d, *J* = 3.5 Hz, 2H, CH_2), 7.34–7.49 (m, 6H, CH, Ar), 7.66 (d, *J* = 8.8 Hz, 1H, CH, Ar), 8.27–8.34 (m, 1H, CH, Ar), 8.46–8.48 (m, 1H, CH, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.0, 74.5, 112.1, 119.0, 128.5, 129.1, 129.6, 132.4, 143.8, 148.0, 159.6.

2-Methoxymethylsulfanylpyridine (140)[136]



139 **140**

C_7H_9NOS
M = [155.22]

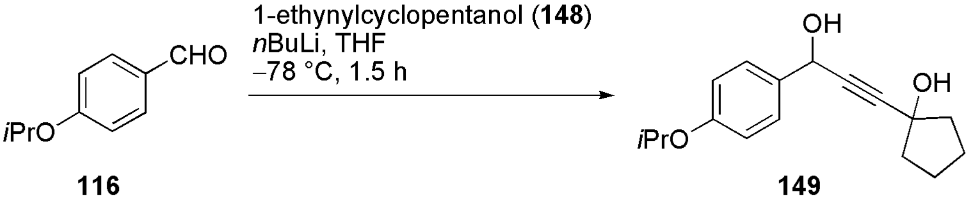
To a solution of 2-mercaptopyridine (**139**) (2.50 g, 22.5 mmol, 1.0 eq.) in 10 mL dimethoxymethane was added boron trifluoride diethyl etherate (3.13 mL, 24.7 mmol, 1.1 eq.) at 0 °C. The mixture was allowed to warm to ambient temperature and it was stirred for 4 hours. $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was purified by distillation under reduced pressure. Methoxymethylsulfanylpyridine (**140**) was obtained as clear yellow oil (1.85 g, 11.9 mmol, 53%).

R_f = 0.43 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.30 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 6.90–6.94 (m, 1H, CH, Ar), 7.17–7.20 (m, 1H, CH, Ar), 7.38–7.43 (m, 1H, CH, Ar), 8.35–8.37 (m, 1H, CH, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6, 73.6, 120.1, 122.8, 136.3, 149.5, 157.7.

1-[3-Hydroxy-3-(4-isopropoxy-phenyl)-prop-1-ynyl]-cyclopentanol (149)



$C_{17}H_{22}O_3$
M = [274.35]

To a suspension of 1-ethynylcyclopentanol (**148**) (5.00 g, 45.4 mmol, 1.3 eq.) in 100 mL THF was added dropwise a 1.6 M solution of *n*BuLi in *n*-hexane (45.8 mL, 73.3 mmol, 2.1 eq.) at −78 °C. After stirring for 30 minutes aldehyde **116** (5.64 g, 34.4 mmol, 1.0 eq.) was added dropwise and the solution was allowed to warm to room temperature. After 1.5 hours the solvent was removed and the residue dissolved in H_2O (100 mL). The solution was neutralized with 1 M HCl and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with H_2O (100 mL), dried ($MgSO_4$) and the solvent evaporated. Crude diol **149** (yellow solid, 8.82 g) was used without further purification. A purified example (SiO_2, hexanes–EtOAc, 4:1) of the product showed the following analytical data:

R_f = 0.1 (SiO_2, hexanes–EtOAc, 4:1); Mp 108 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.67–1.88 (m, 4H, CH_2), 1.90–2.00 (m, 4H, CH_2), 2.46 (s, 1H, OH), 2.78 (s, 1H, OH), 4.54 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 5.41 (s, 1H, CH, C*H*OH), 6.86 (d, *J* = 8.7 Hz, 2H, CH, Ar), 7.41 (d, *J* = 8.6 Hz, 2H, CH, Ar).

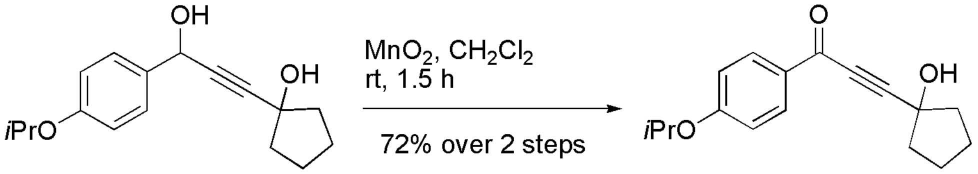
^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 23.4, 42.2, 64.1, 69.9, 74.4, 83.0, 90.2, 115.8, 128.1, 132.6, 157.9.

IR (neat): 3273, 2973, 2870, 1609, 1506, 1381, 1240, 1180, 1122, 994, 958, 844, 812, 728, 631, 597, 567, 530 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 274.2 (100) [M$^+$], 214.1 (33), 185.1 (66), 157.0 (48), 147.0 (36), 121.0 (82), 120.1 (68), 107.0 (64), 95.1 (32), 55.1 (24).

HRMS (EI) *m/z* (M$^+$) calcd for $C_{17}H_{22}O_3$: 274.1569; found: 274.1567.

3-(1-Hydroxy-cyclopentyl)-1-(4-isopropoxy-phenyl)-propynone (150)



149 **150**

$C_{17}H_{20}O_3$
M = [272.34]

A suspension of 8.82 g crude diol **149** and an excess of MnO_2 (27.8 g, 0.320 mol, 7.0 eq.) in 200 mL CH_2Cl_2 were stirred for 1.5 hours at ambient temperature. The suspension was filtered through a pad of Celite, evaporated to dryness and the product purified by flash column chromatography (SiO_2, hexanes–EtOAc, 6:1) to give ketone **150** as yellow solid (6.76 g, 24.8 mmol, 72% over two steps).

R_f = 0.4 (SiO_2, hexanes–EtOAc, 5:1); Mp 82 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.77–1.95 (m, 4H, CH_2), 2.03–2.19 (m, 5H, CH_2, OH), 4.66 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.91 (d, *J* = 8.9 Hz, 2H, CH, Ar), 8.07 (d, *J* = 8.9 Hz, 2H, CH, Ar).

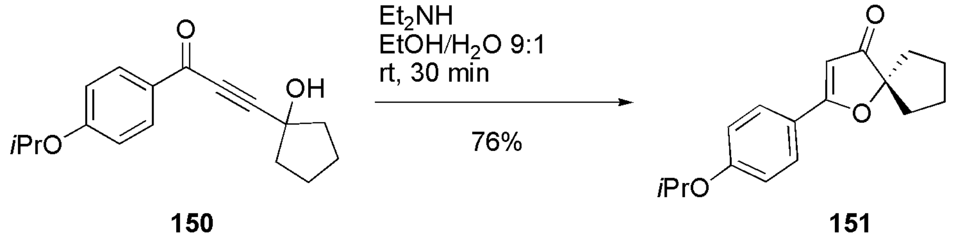
^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 23.6, 42.4, 70.3, 74.4, 81.1, 96.4, 115.1, 129.5, 132.1, 163.1, 176.5.

IR (neat): 3339, 2973, 2208, 1618, 1583, 1505, 1385, 1318, 1260, 1170, 1106, 1003, 946, 844, 757, 692, 632, 575 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 272.2 (68) [M^+], 201.2 (40), 173.1 (100), 121.1 (66).

HRMS (EI) *m/z* (M^+) calcd for $C_{17}H_{20}O_3$: 272.1412; found: 272.1411.

2-(4-Isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (151)



$C_{17}H_{20}O_3$
M = [272.34]

To a solution of ketone **150** (1.86 g, 6.83 mmol, 1.0 eq.) in 35 mL EtOH–H_2O 9:1 was added dropwise diethylamine (0.750 g, 10.3 mmol, 1.5 eq.) at room temperature. After 30 minutes the solvent was removed and the crude product purified by flash column chromatography (SiO_2, hexanes–EtOAc, 20:1). Recrystallization from hexanes yielded *i*Pr-Limno-CP (**151**) as light yellow crystals (1.42 g, 5.21 mmol, 76%).

R_f = 0.45 (SiO_2, hexanes–EtOAc, 3:1); Mp 93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.90-2.14 (m, 8H, CH_2), 4.65 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 5.88 (s,1H, CH), 6.94 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.75 (d, *J* = 8.9 Hz, 2H, CH, Ar).

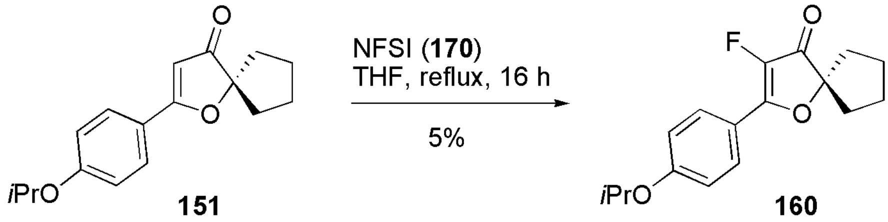
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 25.7, 37.1, 70.2, 98.2, 98.8, 115.6, 121.3, 129.1, 161.6, 183.6, 205.7.

IR (neat): 2972, 1674, 1603, 1562, 1499, 1429, 1366, 1298, 1253, 1182, 1109, 1074, 1051, 948, 893, 820, 666 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 272.1 (40) [M^+], 231.1 (62), 189.0 (100), 118.0 (86).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{17}H_{20}O_3$: 272.1412; found: 272.1410.

3-Fluoro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (160)



$C_{17}H_{19}FO_3$
M = [290.33]

A solution of furanone **151** (300 mg, 1.10 mmol, 1.0 eq.) and *N*-fluorobenzenesulfonimide (**170**) (382 mg, 1.21 mmol, 1.1 eq.) in 30 mL anhydrous THF was heated under reflux for 16 hours. The solution was evaporated in presence of SiO_2 and purified by flash column chromatography (SiO_2 (dryload), hexanes–EtOAc, 20:1 to 5:1) to obtain α-fluoro-furanone **160** as a white solid (17.0 mg, 58.6 µmol, 5%). Additionally, 261 mg (0.958 mmol, 87%) of starting material **151** could be reisolated.

R_f = 0.36 (SiO_2, hexanes–EtOAc, 5:1); Mp 94 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.96-2.11 (m, 8H, CH_2), 4.66 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.97 (d, *J* = 9.0 Hz, 2H, CH, Ar), 7.90 (d, *J* = 9.0 Hz, 2H, CH, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.5, 37.3, 70.2, 96.2 (d, *J* = 7.1 Hz), 115.7, 119.4 (d, *J* = 5.1 Hz), 129.3 (d, *J* = 6.6 Hz), 140.5 (d, *J* = 259.3 Hz), 161.6 (d, *J* = 1.8 Hz), 167.2 (d, *J* = 13.7 Hz), 193.4 (d, *J* = 10.1 Hz).

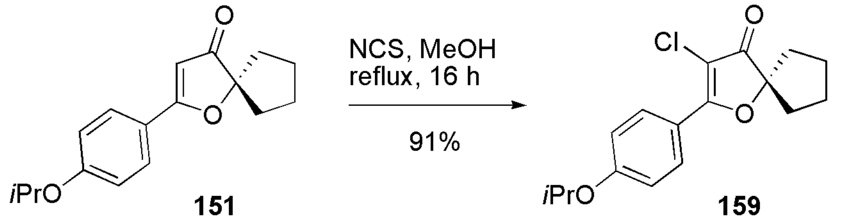
^{19}F NMR (282 MHz, $CDCl_3$): δ = –181.0.

IR (neat): 2970, 1701, 1616, 1566, 1511, 1432, 1404, 1385, 1306, 1259, 1178, 1153, 1118, 948, 885, 837, 745, 647, 632, 517, 490, 445 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 290.1 (34) [M^+], 249.1 (12), 220.0 (16), 207.0 (100), 136.0 (11), 121.0 (12).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{17}H_{19}FO_3$: 290.1318; found: 290.1321.

3-Chloro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (159)



$C_{17}H_{19}ClO_3$
M = [306.78]

A stirred solution of furanone **151** (200 mg, 0.734 mmol, 1.0 eq.) and *N*-chlorosuccinimide (118 mg, 0.881 mmol, 1.2 eq.) in 10 mL MeOH was refluxed for 16 hours. After removal of the solvent and addition of saturated aqueous $NaHCO_3$ solution (10 mL) the mixture was extracted with EtOAc (5 × 10 mL), the organic layer washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated. Purification by flash column chromatography (SiO_2, hexanes–EtOAc, 10:1) gave α-chloro-furanone **159** (204 mg, 0.665 mmol, 91%) as light yellow crystals.

R_f = 0.62 (SiO_2, hexanes–EtOAc, 5:1); Mp 94 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.95-2.18 (m, 8H, CH_2), 4.66 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.97 (d, *J* = 9.0 Hz, 2H, CH, Ar), 8.15 (d, *J* = 9.0 Hz, 2H, CH, Ar).

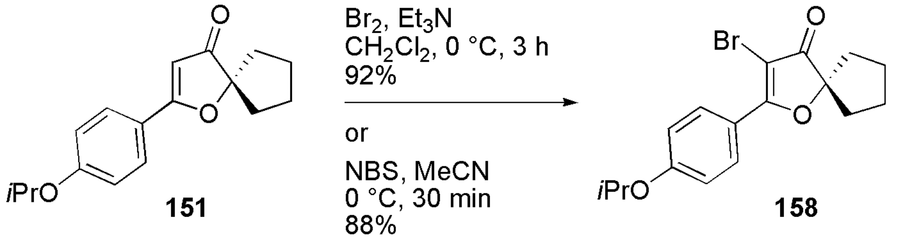
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.5, 37.4, 70.2, 96.8, 104.9, 115.4, 120.4, 130.3, 161.7, 175.6, 199.1.

IR (neat): 2977, 1698, 1603, 1561, 1501, 1428, 1351, 1298, 1261, 1188, 1086, 949, 926, 834, 747, 631, 445 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 306.1 (24) [M^+], 265.1 (12), 225.0 (31), 223.0 (100), 152.0 (18), 121.0 (14).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{17}H_{19}ClO_3$: 306.1023; found: 306.1025.

3-Bromo-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (158)



$C_{17}H_{19}BrO_3$
M = [351.23]

Method A: To a stirred solution of furanone **151** (500 mg, 1.84 mmol, 1.0 eq.) in 20 mL MeCN was added at 0 °C *N*-bromosuccinimide (359 mg, 2.02 mmol, 1.1 eq.) in portions. After 30 minutes saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed. Recrystallization from EtOAc gave α-bromo-furanone **158** (570 mg, 1.62 mmol, 88%) as white crystals.

Method B: A solution of furanone **151** (500 mg, 1.84 mmol, 1.0 eq.) in 15 mL CH_2Cl_2 was treated with a solution of bromine (293 mg, 1.84 mmol, 1.0 eq.) in 5 mL CH_2Cl_2 at 0 °C. After 20 minutes a solution of triethylamine (557 mg, 5.51 mmol, 3.0 eq.) in 3 mL CH_2Cl_2 was added dropwise to the mixture. The solution was stirred for 1 hour at 0 °C and 2 hours at room temperature, before it was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated. Purification by flash column chromatography (SiO_2, hexanes–EtOAc, 10:1) afforded α-bromo-furanone **158** (592 mg, 1.69 mmol, 92%).

R_f = 0.58 (SiO_2, hexanes–EtOAc, 5:1); Mp 94 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.95-2.18 (m, 8H, CH_2), 4.66 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.97 (d, *J* = 9.1 Hz, 2H, CH, Ar), 8.19 (d, *J* = 9.1 Hz, 2H, CH, Ar).

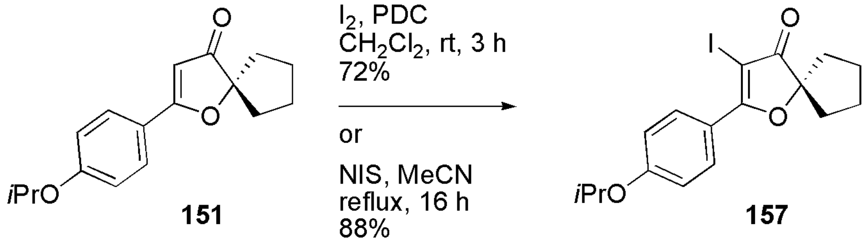
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.5, 37.5, 70.2, 92.2, 96.8, 115.3, 120.7, 130.5, 161.6, 176.9, 200.0.

IR (neat): 2954, 1696, 1601, 1556, 1497, 1425, 1347, 1293, 1256, 1187, 1106, 1070, 951, 919, 831, 746 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 350.0 (26) [M$^+$], 309.0 (15), 269.0 (84), 267.0 (84), 145.0 (100), 121.0 (29).

HRMS (EI-MS) *m/z* (M$^+$) calcd for $C_{17}H_{19}BrO_3$: 350.0518; found: 350.0512.

3-Iodo-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (157)



$C_{17}H_{19}IO_3$
M = [398.24]

Method A: A stirred solution of furanone **151** (100 mg, 0.367 mmol, 1.0 eq.) and *N*-iodosuccinimide (90.9 mg, 0.404 mmol, 1.1 eq.) in 10 mL MeCN was refluxed for 16 hours. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed. Recrystallization from EtOAc gave α-iodo-furanone **157** (592 mg, 1.49 mmol, 88%) as light yellow crystals.

Method B: To a solution of furanone **151** (50 mg, 0.18 mmol, 1.0 eq.) in 1.2 mL CH_2Cl_2 was added iodine (70 mg, 0.28 mmol, 1.5 eq.) and pyridinium dichromate (21 mg, 55 µmol, 0.3 eq.). The reaction flask was covered with aluminium foil and the mixture stirred for 3 hours at room temperature. Remaining solids were filtered off and the filtrate washed with H_2O (2 mL), saturated aqueous $Na_2S_2O_3$ solution (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated. Purification by flash column chromatography (SiO_2, hexanes–EtOAc, 10:1) afforded α-iodo-furanone **157** (52 mg, 0.13 mmol, 72%).

R_f = 0.57 (SiO_2, hexanes–EtOAc, 5:1); Mp 135 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.95-2.16 (m, 8H, CH_2), 4.66 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.96 (d, *J* = 9.0 Hz, 2H, CH, Ar), 8.21 (d, *J* = 9.0 Hz, 2H, CH, Ar).

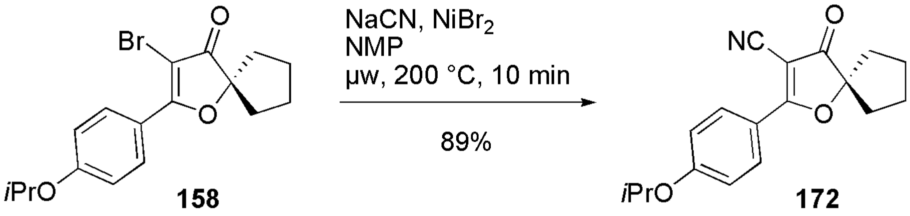
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.4, 37.6, 62.8, 70.2, 96.4, 115.2, 121.2, 130.9, 161.6, 179.1, 202.5.

IR (neat): 2955, 1677, 1599, 1545, 1491, 1422, 1342, 1291, 1253, 1175, 1107, 1060, 950, 915, 832, 747 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 398.0 (37) [M^+], 357.0 (14), 315.0 (62), 145.0 (100), 121.0 (17).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{17}H_{19}IO_3$: 398.0379; found: 398.0379.

2-(4-Isopropoxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carbonitrile (172)



$C_{18}H_{19}NO_3$
M = [297.35]

In a microwave glass tube with a magnetic stirring bar was placed α-bromo-furanone **158** (0.200 g, 0.569 mmol, 1.0 eq.), NaCN (55.8 mg, 1.14 mmol, 2.0 eq.) and $NiBr_2$ (0.124 g, 0.569 mmol, 1.0 eq.) in 4 mL *N*-methylpyrrolidinone. The sealed reaction vessel was put into the cavity of a CEM Discover S microwave synthesis system reactor using a non-contact, infrared sensor for temperature control and heated up to 200 °C. Once the temperature was reached the brown mixture was held at 200 °C for 10 minutes. Then, the green mixture was allowed to cool down to room temperature, diluted with H_2O (2 mL) and extracted with EtOAc (3 × 5 mL). The organic layer was washed with H_2O (5 × 5 mL), dried ($MgSO_4$) and the solvent evaporated. Purification by flash column chromatography (SiO_2, hexanes–EtOAc, 8:1) gave nitrile **172** as white crystals (0.151 g, 0.507 mmol, 89%).

R_f = 0.6 (SiO_2, hexanes–EtOAc, 5:1); Mp 126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.95-2.20 (m, 8H, CH_2), 4.69 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 7.00 (d, *J* = 9.1 Hz, 2H, CH, Ar), 8.19 (d, *J* = 9.0 Hz, 2H, CH, Ar).

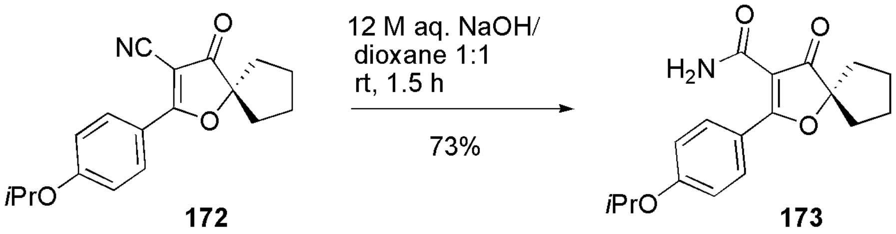
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.6, 37.3, 70.7, 86.5, 100.2, 113.4, 115.9, 119.0, 131.0, 163.6, 185.3, 199.6.

IR (neat): 2984, 2221, 1706, 1603, 1578, 1504, 1429, 1387, 1314, 1261, 1190, 1156, 1127, 1102, 951, 842, 758 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 297.2 (21) [M^+], 255.2 (7), 214.1 (100), 143.1 (20), 121.0 (9).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{18}H_{19}NO_3$: 297.1365; found: 297.1362.

2-(4-Isopropoxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carboxylic acid amide (173)



$C_{18}H_{21}NO_4$
M = [315.36]

Nitrile **172** (0.100 g, 0.336 mmol, 1.0 eq.) was dissolved in 9 mL of a 1:1 solution of 12 M NaOH–dioxane and stirred at room temperature for 1.5 hours. After dilution with 1 M HCl (5 mL) and extraction with EtOAc (3 × 10 mL), the organic layer was washed with brine (30 mL), dried ($MgSO_4$) and the solvent evaporated. Recrystallization from EtOAc gave amide **173** as white crystals (77.4 mg, 0.246 mmol, 73%).

R_f = 0.47 (SiO_2, hexanes–EtOAc, 5:1); Mp 175 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.84-1.94 (m, 6H, CH_2), 2.07-2.18 (m, 2H, CH_2), 4.63 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.03 (s, 1H, NH), 6.89 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.92 (d, *J* = 8.9 Hz, 2H, CH, Ar), 9.28 (s, 1H, NH).

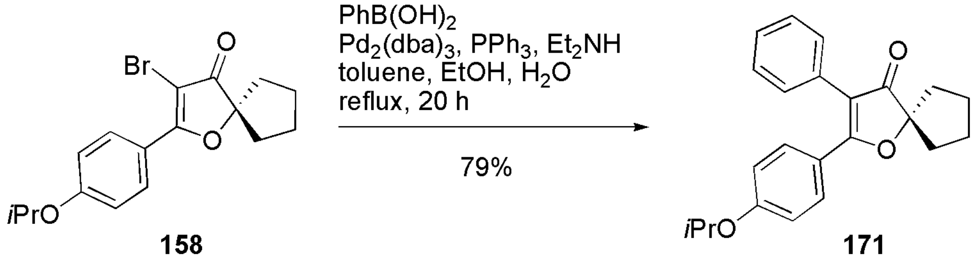
^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 25.4, 36.7, 69.8, 95.1, 99.7, 114.3, 130.4, 131.3, 161.2, 179.7, 189.0, 193.0.

IR (neat): 3321, 3183, 2966, 1597, 1483, 1245, 1184, 1121, 1045, 947, 931, 855, 830, 792, 652, 608, 545, 480 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 315.2 (47) [M^+], 272.2 (23), 232.1 (100), 138.0 (86), 121.0 (73), 95.0 (33).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{18}H_{21}NO_4$: 315.1471; found: 315.1467.

2-(4-Isopropoxy-phenyl)-3-phenyl-1-oxa-spiro[4.4]non-2-en-4-one (171)



158

171

$C_{23}H_{24}O_3$
M = [348.43]

α-Bromo-furanone **158** (20 mg, 57 µmol, 1.0 eq.) was dissolved in 0.32 mL toluene and 0.10 mL EtOH. $Pd_2(dba)_3$ (2.6 mg, 2.9 µmol, 0.05 eq.), PPh_3 (1.5 mg, 5.7 µmol, 0.1 eq.) and $PhB(OH)_2$ (8.3 mg, 68 µmol, 1.2 eq.) were added. After stirring for 10 minutes 7.5 µL diethylamine and 0.10 mL H_2O were added and the mixture refluxed for 20 hours. The solution was diluted with EtOAc (3 mL) and washed successively with 0.2 M NaOH (2 mL), 0.05 M HCl (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$) and the solvent removed. Purification by flash column chromatography (SiO_2, hexanes–EtOAc, 6:1) afforded α-phenyl-furanone **171** as colorless crystals (16 mg, 45 µmol, 79%).

R_f = 0.33 (SiO_2, toluene–MeOH, 99:1); Mp 119 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.1 Hz, 6H, CH_3, *i*Pr), 1.92–2.21 (m, 8H, CH_2), 4.57 (sept, J = 6.1 Hz, 1H, CH, *i*Pr), 6.80 (d, J = 9.0 Hz, 2H, CH, Ar), 7.27–7.39 (m, 5H, CH, Ar), 7.59 (d, J = 9.0 Hz, 2H, CH, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 25.7, 37.5, 70.0, 96.8, 113.6, 115.1, 121.9, 127.3, 128.6, 129.7, 130.3, 130.6, 160.8, 178.3, 204.3.

IR (neat): 2969, 1686, 1603, 1486, 1384, 1252, 1168, 1106, 1045, 948, 835, 695, 623, 514, 447 cm^{-1}.

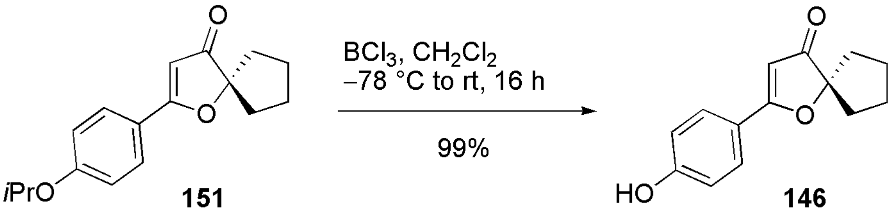
MS (EI, 70 eV): *m/z* (%) = 348.2 (98) [M$^+$], 307.2 (75), 265.1 (100), 194.1 (58), 165.0 (24), 121.0 (18).

HRMS (EI-MS) *m/z* (M$^+$) calcd for $C_{23}H_{24}O_3$: 348.1725; found: 348.1727.

Deprotection of isopropyl ethers:

The protected furanone (8.0 – 20 mg, 28 µmol – 57 µmol, 1.0 eq.) was dissolved in 0.5 mL anhydrous CH_2Cl_2 and 6.0 eq. of a 1 M solution of BCl_3 in *n*-hexane were added slowly at −78 °C to the solution. The solution was warmed to room temperature and stirred until the reaction was complete (1 to 40 hours). THF (0.5 mL) and 1 M HCl (0.5 mL) were added and the solvent removed. The residue was taken up in EtOAc (10 mL) and H_2O (10 mL), extracted with EtOAc (3 × 10 mL) and the organic layer dried ($MgSO_4$). Absorption on SiO_2 was done from a solution of EtOH and purification achieved by flash column chromatography (SiO_2 (dryload), hexanes–EtOAc–EtOH, 40:10:1 and/or $CHCl_3$–EtOH, 25:1) to yield the deprotected furanones.

2-(4-Hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (146)



$C_{14}H_{14}O_3$
M = [230.26]

10 mg (37 µmol) of **151** gave after 16 hours reaction time 8.4 mg (36 µmol, 99%) of **146** as white solid.

R_f = 0.15 (SiO_2, hexanes–EtOAc, 5:1); Mp 231 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.73–1.94 (m, 8H, CH_2), 6.13 (s, 1H, CH), 6.90 (d, *J* = 8.7 Hz, 2H, CH, Ar), 7.77 (d, *J* = 8.7 Hz, 2H, CH, Ar), 10.44 (s,1H, OH).

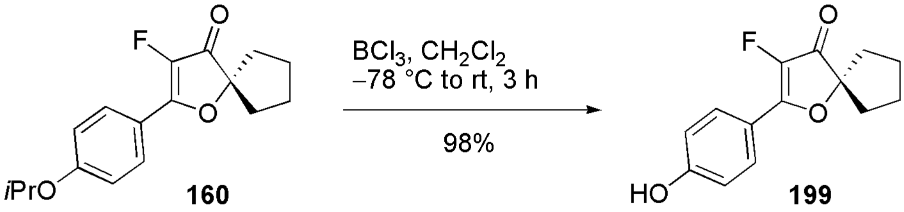
^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.1, 36.4, 97.3, 97.4, 115.7, 119.3, 129.2, 161.7, 183.0, 203.8.

IR (neat): 2918, 2728, 2609, 1638, 1548, 1501, 1431, 1366, 1234, 1161, 1051, 895, 789, 592 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 230.1 (26) [M^+], 189.0 (86), 118.0 (100), 89.1 (13), 44.0 (16), 40.1 (32).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{14}H_{14}O_3$: 230.0943; found: 230.0944.

3-Fluoro-2-(4-hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (199)



$C_{14}H_{13}FO_3$
M = [248.25]

8.0 mg (28 µmol) of **160** gave after 3 hours reaction time 6.7 mg (27 µmol, 98%) of **199** as white solid.

R_f = 0.33 (SiO_2, hexanes–EtOAc, 2:1); Mp 208 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.80–1.99 (m, 8H, CH_2), 6.98 (d, *J* = 8.8 Hz, 2H, CH, Ar), 7.78 (d, *J* = 8.8 Hz, 2H, CH, Ar), 10.61 (s,1H, OH).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 24.8, 36.5, 95.5 (d, *J* = 7.6 Hz), 116.2, 117.1 (d, *J* = 5.0 Hz), 129.2 (d, *J* = 6.2 Hz), 139.4 (d, *J* = 256.5 Hz), 162.0 (d, *J* = 1.2 Hz), 166.8 (d, *J* = 14.0 Hz), 191.6 (d, *J* = 10.1 Hz).

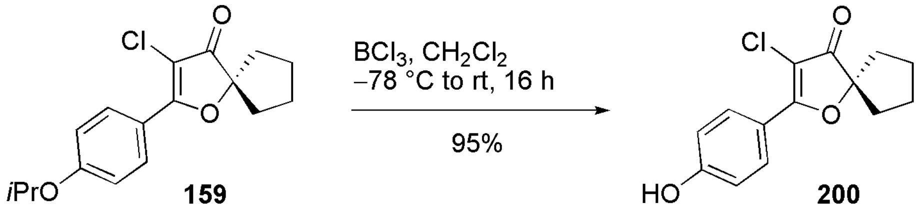
^{19}F NMR (282 MHz, DMSO-d_6): δ = −181.5.

IR (neat): 3121, 2946, 1675, 1563, 1508, 1414, 1285, 1154, 1107, 961, 843, 743, 581, 512, 413 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 248.2 (47) [M$^+$], 220.2 (18), 207.1 (100), 136.1 (23), 121.1 (29).

HRMS (EI-MS) *m/z* (M$^+$) calcd for $C_{14}H_{13}FO_3$: 248.0849; found: 248.0853.

3-Chloro-2-(4-hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (200)



$C_{14}H_{13}ClO_3$
M = [264.70]

10 mg (33 µmol) of **159** gave after 16 hours reaction time 8.2 mg (31 µmol, 95%) of **200** as white solid.

R_f = 0.43 (SiO_2, hexanes–EtOAc, 2:1); Mp 209 °C.

^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.81–2.00 (m, 8H, CH$_2$), 6.98 (d, *J* = 8.9 Hz, 2H, CH, Ar), 8.03 (d, *J* = 8.9 Hz, 2H, CH, Ar), 10.65 (s,1H, OH).

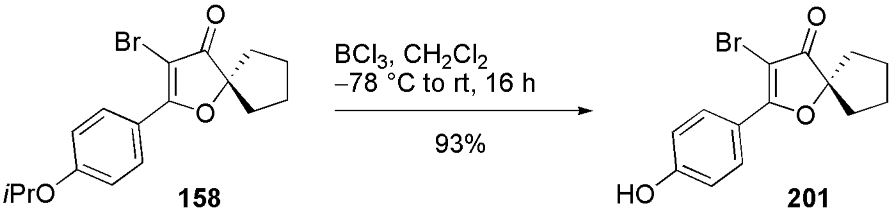
^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 24.9, 36.7, 96.1, 103.0, 115.9, 118.3, 130.2, 162.1, 175.3, 197.5.

IR (neat): 3139, 2924, 1670, 1606, 1552, 1489, 1370, 1284, 1170, 1095, 933, 837, 744, 659, 505, 450 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 264.1 (35) [M$^+$], 225.0 (30), 223.0 (100) [M$^+$-C$_3$H$_5$], 152.0 (33), 145.1 (16), 121.0 (24).

HRMS (EI-MS) *m/z* (M$^{\bullet+}$) calcd for $C_{14}H_{13}ClO_3$: 264.0553; found: 264.0548.

3-Bromo-2-(4-hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (201)



$C_{14}H_{13}BrO_3$
M = [309.16]

20 mg (57 µmol) of **158** gave after 16 hours reaction time 16 mg (53 µmol, 93%) of **201** as white solid.

R_f = 0.48 (SiO$_2$, hexanes–EtOAc, 2:1); Mp 216 °C.

^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.75–2.03 (m, 8H, CH$_2$), 6.97 (d, *J* = 8.9 Hz, 2H, CH, Ar), 8.07 (d, *J* = 8.9 Hz, 2H, CH, Ar), 10.63 (s, 1H, OH).

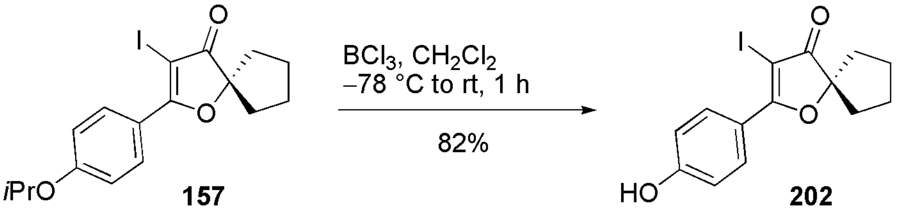
^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 24.9, 36.8, 90.8, 96.0, 115.7, 118.7, 130.5, 162.0, 176.7, 198.5.

IR (neat): 3158, 2958, 1666, 1603, 1552, 1484, 1361, 1281, 1235, 1171, 1079, 921, 846, 747, 665, 597, 438 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 308.0 (32) [M$^+$], 268.9 (79), 267.0 (82), 145.0 (100), 121.0 (28).

HRMS (EI-MS) *m/z* (M$^+$) calcd for $C_{14}H_{13}BrO_3$: 308.0048; found: 308.0047.

2-(4-Hydroxy-phenyl)-3-iodo-1-oxa-spiro[4.4]non-2-en-4-one (202)



$C_{14}H_{13}IO_3$
M = [356.16]

20 mg (50 µmol) of **157** gave after 1 hour reaction time 15 mg (41 µmol, 82%) of **202** as white solid.

R_f = 0.43 (SiO_2, hexanes–EtOAc, 2:1); Mp 201 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.76–1.98 (m, 8H, CH_2), 6.96 (d, *J* = 8.8 Hz, 2H, CH, Ar), 8.08 (d, *J* = 8.8 Hz, 2H, CH, Ar), 10.55 (s,1H, OH).

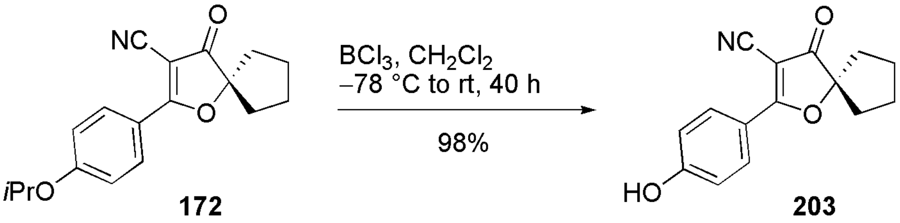
^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.0, 36.9, 63.3, 95.5, 115.5, 119.6, 130.8, 161.7, 178.8, 201.9.

IR (neat): 3139, 2923, 1656, 1600, 1545, 1476, 1352, 1279, 1231, 1168, 1070, 915, 841, 746, 665, 594, 523, 450 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 355.9 (65) [M^+], 314.9 (80), 145.0 (100), 121.0 (17).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{14}H_{13}IO_3$: 355.9909; found: 355.9902.

2-(4-Hydroxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carbonitrile (203)



$C_{15}H_{13}NO_3$
M = [255.27]

10 mg (34 µmol) of **172** gave after 40 hours reaction time 8.4 mg (33 µmol, 98%) of **203** as white solid.

R_f = 0.35 (SiO_2, hexanes–EtOAc, 2:1); Mp 255 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.82–2.07 (m, 8H, CH_2), 7.04 (d, *J* = 8.9 Hz, 2H, CH, Ar), 8.05 (d, *J* = 8.9 Hz, 2H, CH, Ar), 11.09 (s,1H, OH).

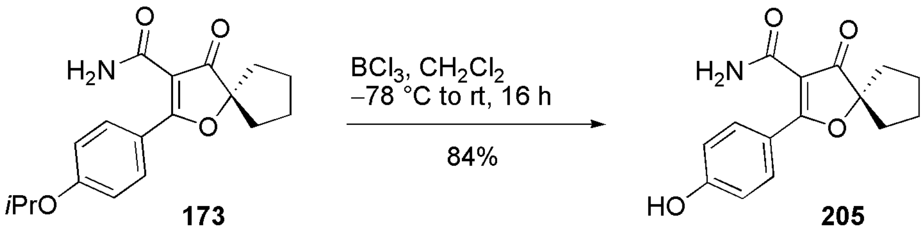
^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 24.9, 36.5, 84.8, 99.8, 113.7, 116.4, 117.3, 131.0, 164.2, 185.1, 199.0.

IR (neat): 3200, 2972, 2231, 1701, 1605, 1559, 1505, 1382, 1286, 1170, 1117, 956, 845, 707, 665, 575, 510 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 255.1 (20) [M$^+$], 214.1 (100) [M$^+$-C_3H_5], 143.0 (45), 121.0 (13).

HRMS (EI-MS) *m/z* (M$^+$) calcd for $C_{15}H_{13}NO_3$: 255.0895; found: 255.0889.

2-(4-Hydroxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carboxylic acid amide (205)



$C_{15}H_{15}NO_4$
M = [273.28]

10 mg (32 µmol) of **173** gave after 16 hours reaction time 7.3 mg (27 µmol, 84%) of **205** as white solid.

R_f = 0.09 (SiO_2, hexanes–EtOAc, 5:1); Mp 190 °C.

^1H NMR (300 MHz, DMSO-d$_6$): δ = 1.80–1.99 (m, 8H, CH_2), 6.75 (d, *J* = 8.7 Hz, 2H, CH, Ar), 7.68 (d, *J* = 8.7 Hz, 2H, CH, Ar), 9.00 (s, 1H, NH), 9.28 (s, 1H, NH), 10.01 (s,1H, OH).

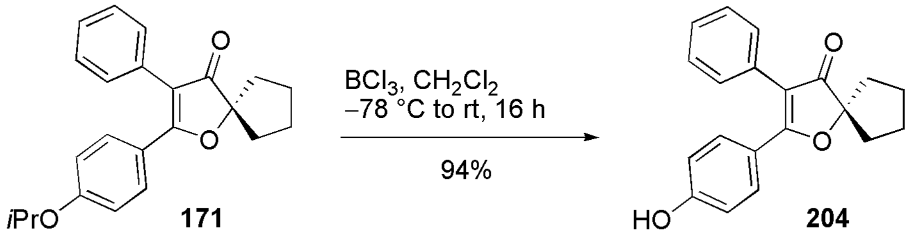
^{13}C NMR (300 MHz, DMSO-d$_6$): δ = 24.9, 36.1, 93.5, 97.4, 113.9, 129.7, 131.1, 160.6, 178.5, 187.1, 191.6.

IR (neat): 3283, 3057, 2962, 1610, 1581, 1452, 1274, 1244, 1024, 1000, 934, 789, 710, 636, 605, 525, 480, 440 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 273.1 (38) [M$^+$], 232.0 (49) [M$^+$-C_3H_5], 138.0 (43), 121.0 (100), 93.0 (37), 65.1 (44).

HRMS (EI-MS) *m/z* (M$^+$) calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.0994.

2-(4-Hydroxy-phenyl)-3-phenyl-1-oxa-spiro[4.4]non-2-en-4-one (204)



$C_{20}H_{18}O_3$
M = [306.36]

10 mg (29 µmol) of **171** gave after 16 hours reaction time 8.3 mg (27 µmol, 94%) of **204** as white solid.

R_f = 0.45 (SiO_2, hexanes–EtOAc, 2:1); Mp 221 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.79–2.04 (m, 8H, CH_2), 6.77 (d, *J* = 8.8 Hz, 2H, CH, Ar), 7.22–7.25 (m, 2H, CH, Ar), 7.29–7.46 (m, 5H, CH, Ar), 10.35 (s, 1H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.2, 36.8, 95.8, 112.3, 115.4, 119.8, 127.2, 128.4, 129.4, 130.0, 130.6, 161.0, 177.9, 202.8.

IR (neat): 3260, 2919, 1670, 1604, 1562, 1483, 1397, 1287, 1219, 1168, 1052, 841, 701, 594, 524, 450 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 306.1 (48) [M^+], 265.1 (100) [M^+-C_3H_5], 194.1 (51), 121.0 (16).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{20}H_{18}O_3$: 306.1256; found: 306.1252.

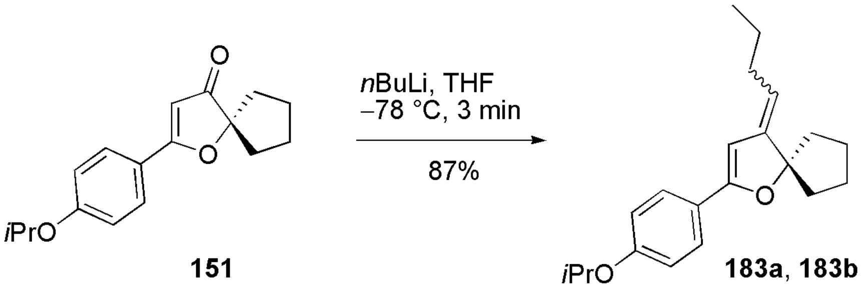
Reactions with alkyl lithium reagents:

With nBuLi:

To a stirred solution of 3(2*H*)-furanone (5.0 – 20 mg, 14 – 73 µmol, 1.0 eq.) in 1.0 mL anhydrous THF was added 1.0 eq. of a 1.6 M solution of *n*BuLi in *n*-hexane dropwise at −78 °C. Then H_2O (0.5 mL) was added, the mixture warmed to room temperature, diluted with saturated aqueous $NaHCO_3$ solution (0.5 mL) and extracted with EtOAc (3 × 1.0 mL). The organic layer was washed with brine (3 mL), dried ($MgSO_4$) and the solvent evaporated to give the dihydrofuran, which decomposes within hours even at –20 °C. The yield was determined by dissolving the crude material in 600 µL of a 3.77 mM solution of hexamethyldisilane (internal standard) in $CDCl_3$ or a 1.89 mM solution of hexamethyldisilane in $CDCl_3$–benzene-d_6 1:1 in the case of phenyl compound **211a**, **211b**. Yields of compounds

183a, **183b** and **207a**, **207b** are isolated yields of homogeneous materials without internal standard, but were verified by using the internal standard.

4-Butylidene-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-ene (183a, 183b)



151

183a, **183b**

$C_{21}H_{28}O_2$
M = [312.45]

20 mg (73 µmol, 1.0 eq.) of **151** gave 20 mg (64 µmol, 87%, **a**/**b** 95:5) of **183a**, **183b** as a colorless oil.

R_f = 0.97 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): **183a**: δ = 0.93 (t, *J* = 7.3 Hz, 3H, CH_3, Bu), 1.34 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.43 (sext, *J* = 7.3 Hz, 2H, CH_2, Bu), 1.61-1.66 (m, 2H, CH_2), 1.78-1.85 (m, 2H, CH_2), 1.90-1.96 (m, 2H, CH_2), 2.06-2.10 (m, 2H, CH_2), 2.13 (q, *J* = 7.3 Hz, 2H, CH_2, Bu), 4.57 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 4.76 (dt, *J* = 7.4, 0.7 Hz, 1H, CH, Bu), 5.97 (d, *J* = 0.8 Hz, 1H, CH), 6.85 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.56 (d, *J* = 8.9 Hz, 2H, CH, Ar); **183b**: δ = 0.93 (t, *J* = 7.3 Hz, 3H, CH_3, Bu), 1.34 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.43 (sext, *J* = 7.3 Hz, 2H, CH_2, Bu), 1.61-1.66 (m, 2H, CH_2), 1.78-1.85 (m, 2H, CH_2), 1.90-1.96 (m, 2H, CH_2), 2.06-2.10 (m, 2H, CH_2), 2.13 (q, *J* = 7.3 Hz, 2H, CH_2, Bu), 4.57 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 5.13 (t, *J* = 8.0 Hz, 1H, CH, Bu), 5.72 (s, 1H, CH), 6.85 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.49 (d, *J* = 8.9 Hz, 2H, CH, Ar).

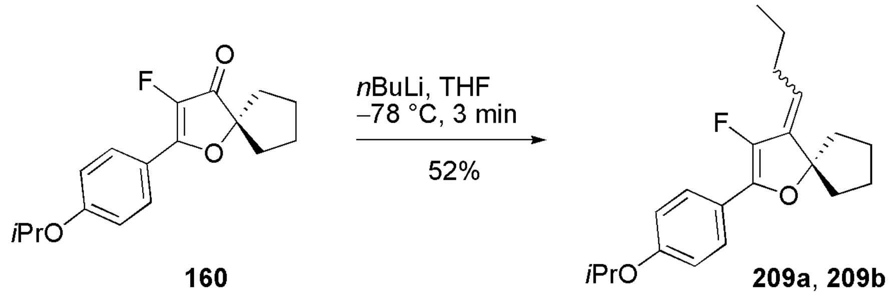
^{13}C NMR (150 MHz, $CDCl_3$): **183a**: δ = 13.8, 22.0, 23.4, 24.9, 31.5, 42.4, 69.9, 96.3, 97.5, 110.7, 115.6, 123.9, 126.8, 147.7, 158.4, 159.0.

IR (neat): 2927, 1609, 1504, 1245, 1119, 1058, 953, 833, 770, 638, 601 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 312.3 (56) [M$^+$], 283.2 (100), 241.2 (21), 121.0 (40).

HRMS (EI-MS) *m/z* (M$^+$) calcd for $C_{21}H_{28}O_2$: 312.2089; found: 312.2087.

4-Butylidene-3-fluoro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-ene (209a, 209b)



160

209a, **209b**

$C_{21}H_{27}FO_2$
M = [330.44]

7.7 mg (27 µmol, 1.0 eq.) of **160** gave 4.6 mg (14 µmol, 52%, **a**/**b** 65:35) of **209a**, **209b.**

R_f = 0.81 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): **209a**: δ = 0.93 (t, *J* = 7.4 Hz, 3H, CH_3, Bu), 1.34 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.41-1.49 (m, 2H, CH_2, Bu), 1.58-1.68 (m, 3H, CH_2), 1.77-2.02 (m, 5H, CH_2), 2.34 (q, *J* = 7.5 Hz, 1H, CH_2, Bu), 4.58 (sept, *J* = 6.0 Hz, 1H, CH, *i*Pr), 4.80 (t, *J* = 8.0 Hz, 1H, CH, Bu), 6.89 (d, *J* = 9.0 Hz, 2H, CH, Ar), 7.62 (d, *J* = 8.9 Hz, 2H, CH, Ar); **209b**: δ = 0.96 (t, *J* = 7.4 Hz, 3H, CH_3, Bu), 1.34 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.41-1.49 (m, 2H, CH_2, Bu), 1.58-1.68 (m, 3H, CH_2), 1.77-2.02 (m, 5H, CH_2), 2.14 (q, *J* = 7.5 Hz, 1H, CH_2, Bu), 4.57 (sept, *J* = 6.0 Hz, 1H, CH, *i*Pr), 5.16 (t, *J* = 8.1 Hz, 1H, CH, Bu), 6.89 (d, *J* = 9.0 Hz, 2H, CH, Ar), 7.59 (d, *J* = 8.9 Hz, 2H, CH, Ar).

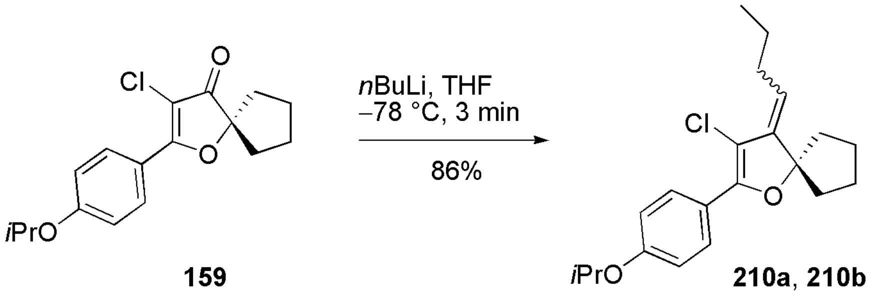
^{13}C NMR (150 MHz, $CDCl_3$): **209a**, **209b**: δ = 13.6, 13.8, 22.0, 23.7, 23.8, 24.5, 25.0, 29.3, 29.4, 39.9, 42.5, 69.9, 93.9 (d, *J* = 6.2 Hz), 94.6 (d, *J* = 8.4 Hz), 111.9 (d, *J* = 4.0 Hz), 112.6 (d, *J* = 7.6 Hz), 115.6, 122.0 (d, *J* = 5.8 Hz), 126.8 (d, *J* = 6.3 Hz), 127.0 (d, *J* = 6.9 Hz), 137.8 (d, *J* = 12.8 Hz), 137.9 (d, *J* = 14.8 Hz), 138.2 (d, *J* = 19.5 Hz), 141.1 (d, *J* = 21.2 Hz), 142.5 (d, *J* = 255.8 Hz), 143.8 (d, *J* = 257.5 Hz), 157.8, 158.0.

^{19}F NMR (282 MHz, $CDCl_3$): **209a**, **209b**: δ = 174.4, 170.7.

MS (EI, 70 eV): m/z (%) = 330.2 (81) [M^+], 301.2 (100), 259.1 (23), 121.0 (29).

HRMS (EI-MS) m/z (M^+) calcd for $C_{21}H_{27}FO_2$: 330.1995; found: 330.1993.

4-Butylidene-3-chloro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-ene (210a, 210b)



159

210a, **210b**

$C_{21}H_{27}ClO_2$
M = [346.89]

5.0 mg (16 µmol, 1.0 eq.) of **159** gave 4.9 mg (14 µmol, 86%, **a**/**b** 10:90) of **210a**, **210b**.

R_f = 0.61 (SiO_2, hexanes–EtOAc, 5:1).

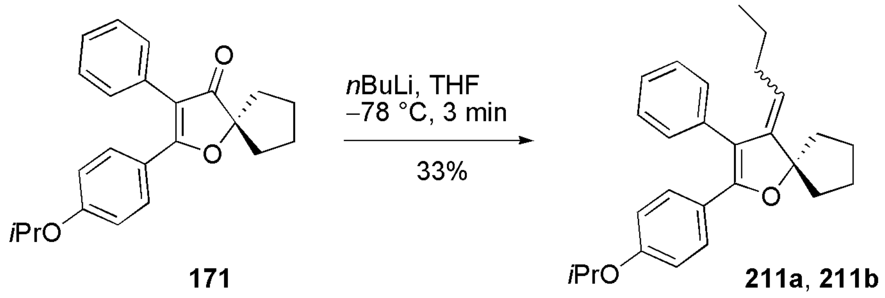
^{1}H NMR (600 MHz, $CDCl_3$): **210a**: δ = 0.95 (t, *J* = 7.4 Hz, 3H, CH_3, Bu), 1.34 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.47 (sext, *J* = 7.4 Hz, 2H, CH_2, Bu), 1.79–2.10 (m, 8H, CH_2), 2.58 (q, *J* = 7.5 Hz, 2H, CH_2, Bu), 4.59 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 4.88 (t, *J* = 7.9 Hz, 1H, CH, Bu), 6.89 (d, *J* = 9.0 Hz, 2H, CH, Ar), 7.86 (d, *J* = 9.0 Hz, 2H, CH, Ar); **210b**: δ = 0.96 (t, *J* = 7.4 Hz, 3H, CH_3, Bu), 1.34 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.47 (sext, *J* = 7.4 Hz, 2H, CH_2, Bu), 1.79–2.10 (m, 8H, CH_2), 2.16 (q, *J* = 7.3 Hz, 2H, CH_2, Bu), 4.59 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 5.26 (t, *J* = 8.1 Hz, 1H, CH, Bu), 6.89 (d, *J* = 9.0 Hz, 2H, CH, Ar), 7.86 (d, *J* = 9.0 Hz, 2H, CH, Ar).

^{13}C NMR (150 MHz, $CDCl_3$): **210b**: δ = 13.9, 22.0, 23.9, 25.2, 29.2, 40.0, 69.8, 95.3, 104.9, 114.4, 115.3, 122.5, 128.5, 143.3, 150.5, 158.4.

MS (EI, 70 eV): *m/z* (%) = 346.2 (76) [M^+], 317.1 (100), 121.0 (46).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{21}H_{27}ClO_2$: 346.1700; found: 346.1696.

4-Butylidene-2-(4-isopropoxy-phenyl)-3-phenyl-1-oxa-spiro[4.4]non-2-ene (211a, 211b)



$C_{27}H_{32}O_2$
M = [388.54]

5.0 mg (14 µmol, 1.0 eq.) of **171** gave 1.8 mg (4.7 µmol, 33%, **a**/**b** 60:40) of **211a**, **211b**.

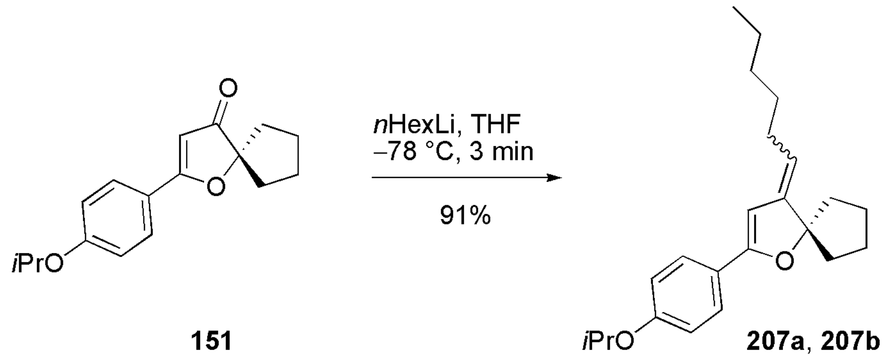
^{1}H NMR (600 MHz, $CDCl_3$–benzene-d_6, 1:1): **211a**: δ = 0.61 (t, *J* = 7.4 Hz, 3H, CH_3, Bu), 1.01 or 1.03 or 1.05 (d, *J* = 6.0 Hz, 6H, CH_3, *i*Pr), 1.07–1.16 (m, 2H, CH_2, Bu), 1.50–1.54 (m, 2H, CH_2, Bu), 1.57–1.65 (m, 2H, CH_2), 1.67–1.76 (m, 2H, CH_2), 1.86–1.98, (m, 2H, CH_2), 2.13–2.18 (m, 2H, CH_2), 4.16 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 4.74 (t, *J* = 7.9 Hz, 1H, CH, Bu), 6.49 or 6.52 or 6.54 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.06–7.29 (m, 7H, CH, Ar); **211b**: δ = 0.78 (t, *J* = 7.4 Hz, 3H, CH_3, Bu), 1.01 or 1.03 or 1.05 (d, *J* = 6.0 Hz, 6H, CH_3, *i*Pr), 1.19–1.26 (m, 2H, CH_2, Bu), 1.57–1.65 (m, 2H, CH_2), 1.67–1.76 (m, 2H, CH_2), 1.86–1.98, (m, 2H, CH_2), 1.99–2.04 (m, 2H, CH_2, Bu), 2.13–2.18 (m, 2H, CH_2), 4.11 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 4.83 (t, *J* = 8.0 Hz, 1H, CH, Bu), 6.49 or 6.52 or 6.54 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.06–7.29 (m, 7H, CH, Ar).

MS (EI, 70 eV): *m/z* (%) = 388.3 (89) [M^+], 359.2 (100), 121.0 (91).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{27}H_{32}O_2$: 388.2402; found: 388.2404.

With nHexLi:

4-Hexylidene-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-ene (207a, 207b)



151

207a, **207b**

$C_{23}H_{32}O_2$
M = [340.50]

To a stirred solution of furanone **151** (5.0 mg, 18 µmol, 1.0 eq.) in 0.5 mL anhydrous THF was added dropwise a 2.45 M solution of *n*HexLi in *n*-hexane (9.0 µL, 22 µmol, 1.2 eq.) at –78 °C. Workup and isolation see *n*BuLi-case. Furans **207a**, **207b** were obtained as a colorless oil (6.2 mg, 18 µmol, 91%, **a**/**b** 95:5).

R_f = 0.88 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): **207a**: δ = 0.90 (t, *J* = 7.0 Hz, 3H, CH_3, Hex), 1.30–1.34 (m, 10H, CH_3, *i*Pr, CH_2, Hex), 1.38–1.43 (m, 2H, CH_2, Hex), 1.60–1.66 (m, 2H, CH_2), 1.77–1.84 (m, 2H, CH_2), 1.89–1.97 (m, 2H, CH_2), 2.06-2.10 (m, 2H, CH_2), 2.14 (q, *J* = 7.4 Hz, 2H, CH_2, Hex), 4.57 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 4.76 (dt, *J* = 7.3, 0.3 Hz, 1H, CH, Hex), 5.96 (d, *J* = 0.6 Hz, 1H, CH), 6.85 (d, *J* = 8.8 Hz, 2H, CH, Ar), 7.56 (d, *J* = 8.8 Hz, 2H, CH, Ar); **207b**: δ = 0.90 (t, *J* = 7.0 Hz, 3H, CH_3, Hex), 1.30–1.34 (m, 10H, CH_3, *i*Pr, CH_2, Hex), 1.38–1.43 (m, 2H, CH_2, Hex), 1.60–1.66 (m, 2H, CH_2), 1.77–1.84 (m, 2H, CH_2), 1.89–1.97 (m, 2H, CH_2), 2.06–2.10 (m, 2H, CH_2), 2.14 (q, *J* = 7.4 Hz, 2H, CH_2, Hex), 4.57 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 5.12 (t, *J* = 8.0 Hz, 1H, CH, Hex), 5.71 (s, 1H, CH), 6.85 (d, *J* = 8.8 Hz, 2H, CH, Ar), 7.49 (d, *J* = 8.8 Hz, 2H, CH, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): **207a**: δ = 14.1, 22.0, 22.6, 24.9, 29.5, 30.0, 31.5, 42.4, 69.9, 96.2, 97.5, 111.0, 115.6, 123.9, 126.8, 147.5, 158.4, 158.9.

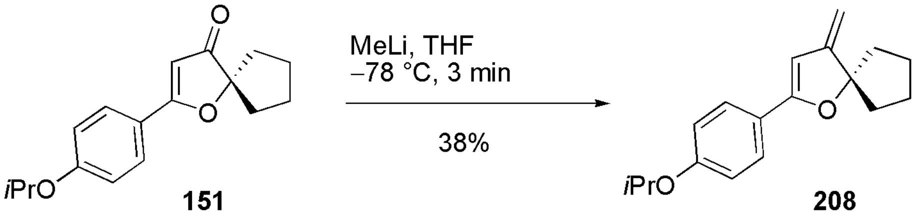
IR (neat): 2924, 1608, 1503, 1245, 1179, 1119, 1057, 952, 834, 770, 637, 601 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 340.3 (38) [M^+], 284.2 (20), 283.2 (100) [M^+-C_4H_9], 241.1 (19), 163.1 (17), 121.0 (35).

HRMS (EI-MS) *m/z* (M^+) calcd for $C_{23}H_{32}O_2$: 340.2402; found: 340.2397.

With MeLi:

2-(4-Isopropoxy-phenyl)-4-methylene-1-oxa-spiro[4.4]non-2-ene (208)



$C_{18}H_{22}O_2$
M = [270.37]

To a stirred solution of furanone **151** (75 mg, 18 µmol, 1.0 eq.) in 0.5 mL anhydrous THF was added dropwise a 1.6 M solution of MeLi in Et_2O (12 µL, 18 µmol, 1.0 eq.) at −78 °C. Workup and isolation see *n*BuLi-case. Furan **208** was obtained in 38% yield (1.9 mg, 7.0 µmol).

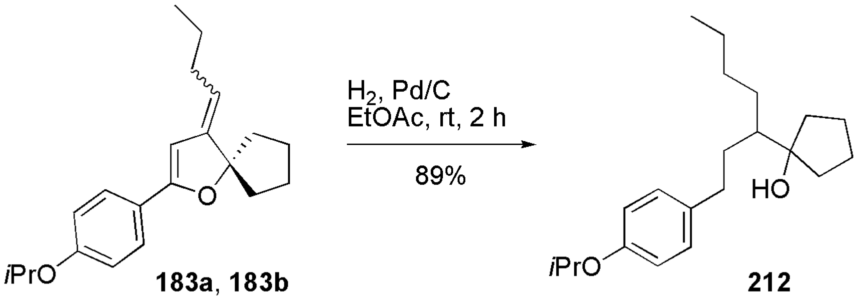
R_f = 0.92 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.1 Hz, 6H, CH_3, *i*Pr), 1.65–2.15 (m, 8H, CH_2), 4.38 (s, 1H, CH, Me), 4.58 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 4.69 (s, 1H, CH, Me), 5.88 (s, 1H, CH), 6.86 (d, *J* = 8.9 Hz, 2H, CH, Ar), 7.55 (d, *J* = 8.9 Hz, 2H, CH, Ar).

With PhLi and tBuLi:

The reactions of 1.0 eq. furanone **151** with 1.0 eq. of a 1.8 M solution of PhLi in Bu_2O and 1.0 eq. of a 1.6 M solution of *t*BuLi in pentane, respectively, were carried out as described in the *n*BuLi case. No defined addition product was observed.

1-{1-[2-(4-Isopropoxy-phenyl)-ethyl]-pentyl}-cyclopentanol (212)



$C_{21}H_{34}O_2$
M = [318.49]

To a stirred solution of furans **183a**, **183b** (20 mg, 64 µmol, 1.0 eq.) in 0.5 mL anhydrous EtOAc was added 10% Pd/C (6.8 mg, 6.4 µmol, 0.1 eq.) at room temperature. The mixture was stirred under H_2-atmosphere for 2 hours. Filtration and evaporation of the solvent gave pure tertiary alcohol **212** as a colorless oil (18 mg, 57 µmol, 89%).

R_f = 0.61 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.1 Hz, 3H, CH_3), 1.31–1.35 (m, 11H, CH_3, *i*Pr), 1.40–1.44 (m, 1H), 1.53–1.66 (m, 9H), 1.76–1.83 (m, 3H), 2.54 (ddd, *J* = 13.8, 10.8, 6.1 Hz, 1H, CH, Bz), 2.69 (ddd, *J* = 13.8, 11.0, 5.3 Hz, 1H, CH, Bz), 4.57 (sept, *J* = 6.1 Hz, 1H, CH, *i*Pr), 6.81 (d, *J* = 8.6 Hz, 2H, CH, Ar), 7.09 (d, *J* = 8.6 Hz, 2H, CH, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.1, 23.3, 23.8, 30.8, 31.2, 33.5, 34.3, 38.6, 38.7, 47.2, 69.9, 86.2, 115.9, 129.2, 135.0, 155.9.

IR (neat): 3421, 2928, 1509, 1239, 632, 536, 497 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 318.2 (6) [M^+], 162.1 (100), 120.0 (74), 107.0 (43).

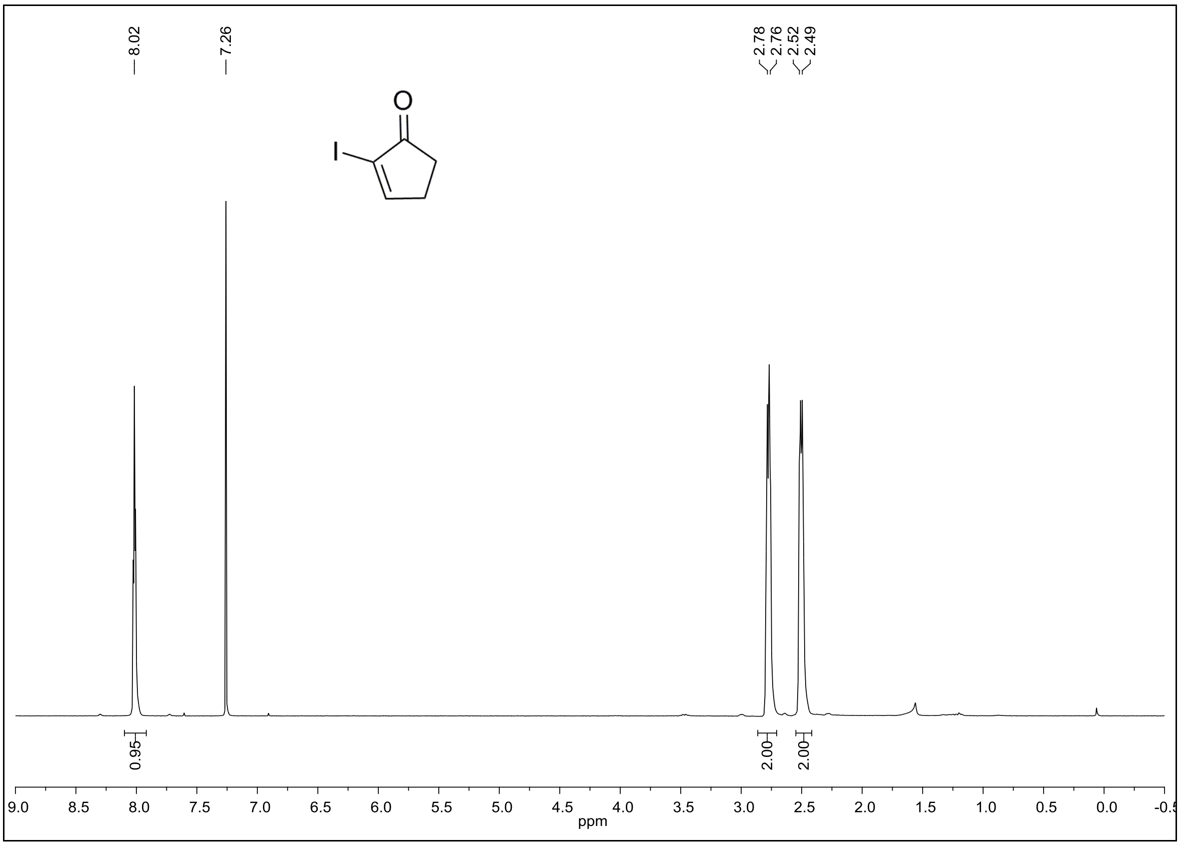
HRMS (EI-MS) *m/z* (M^+) calcd for $C_{21}H_{34}O_2$: 318.2559; found: 318.2559.

6. APPENDIX

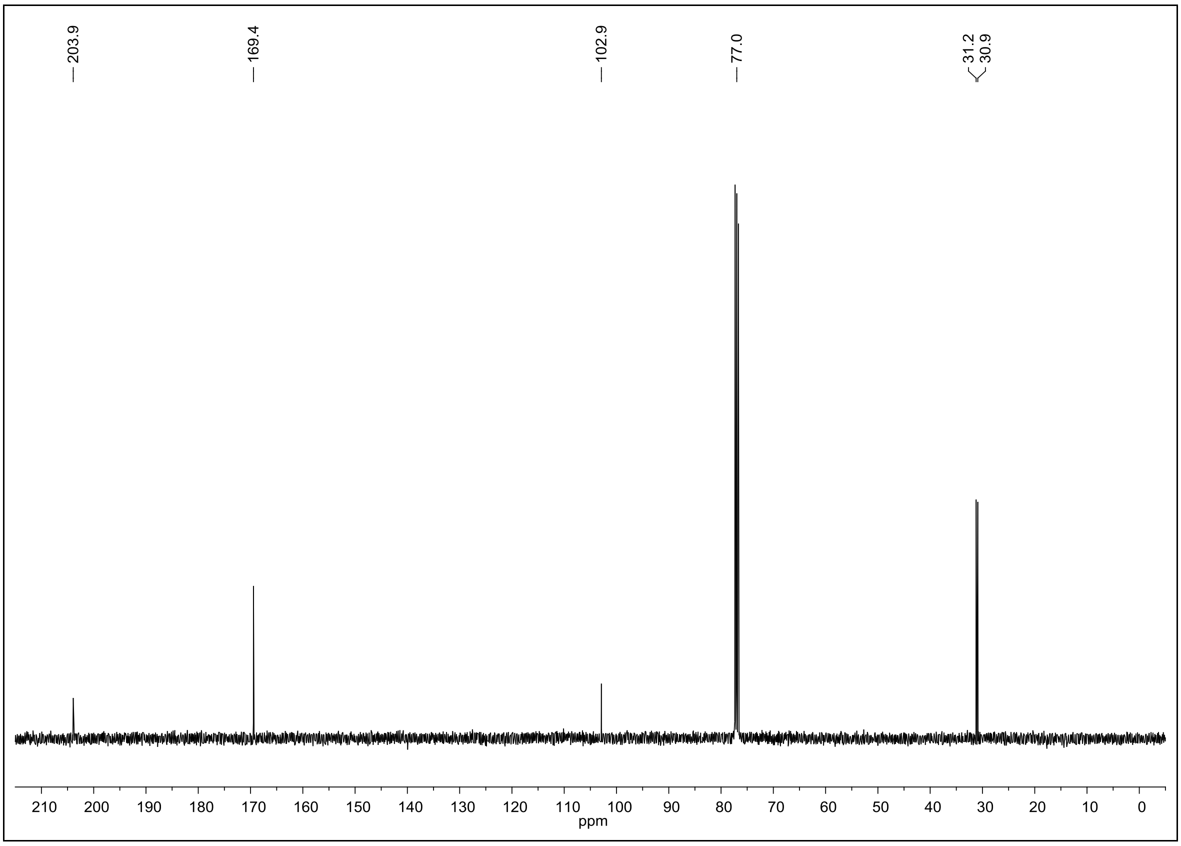
6.1. NMR spectra

2-Iodo-cyclopent-2-enone (79)

^{1}H NMR

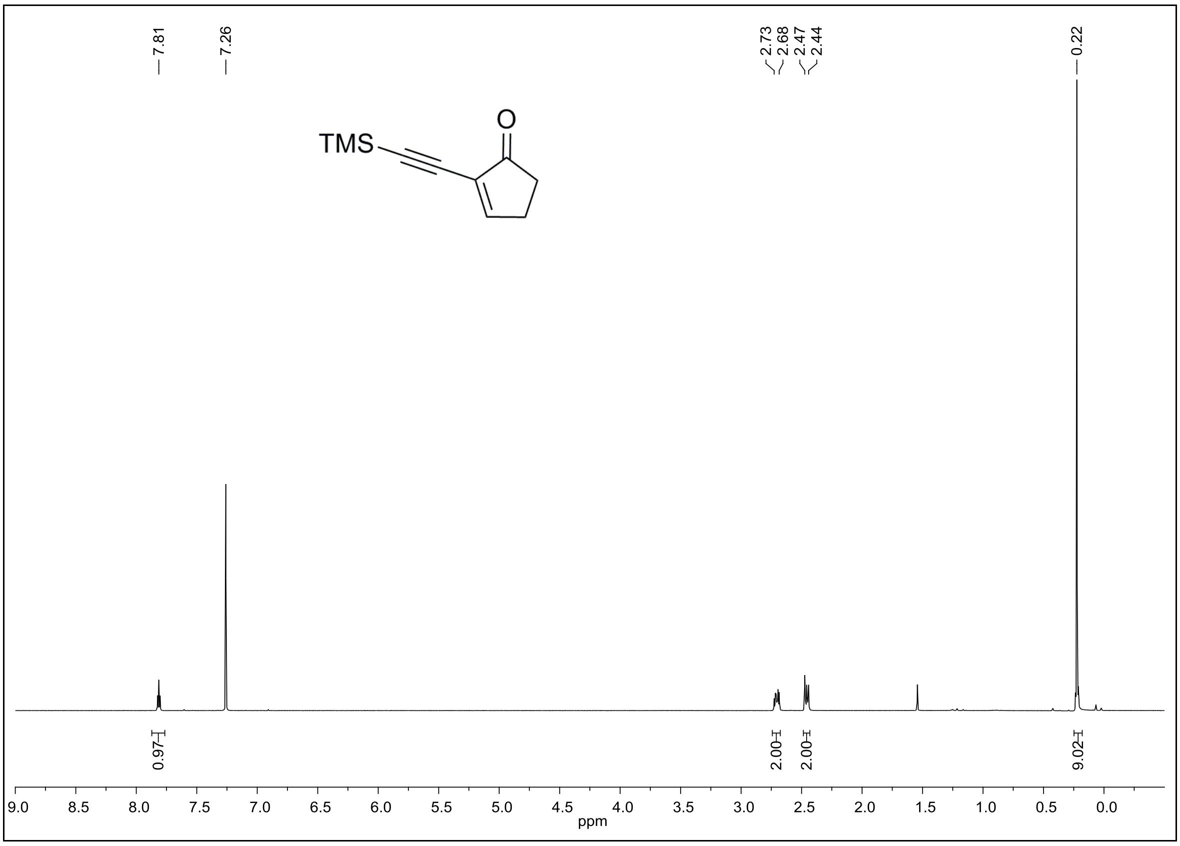


^{13}C NMR

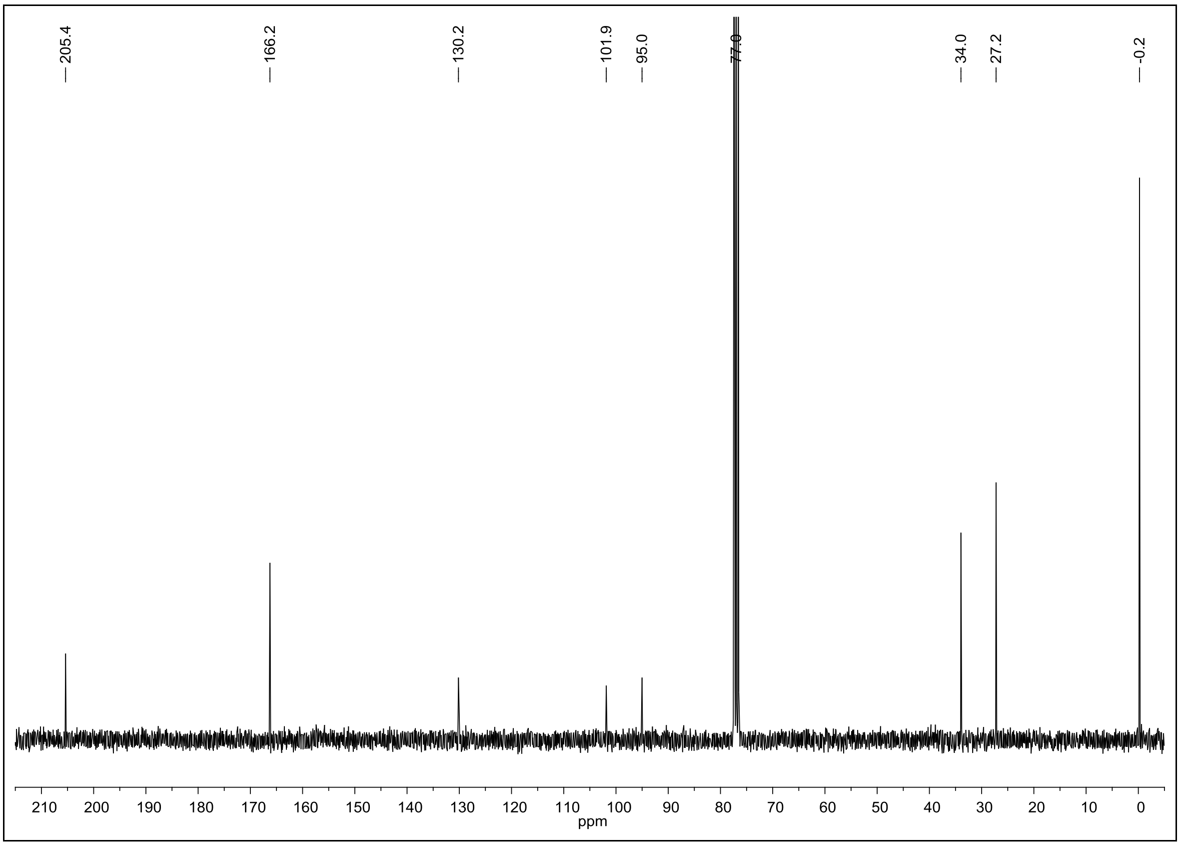


2-Trimethylsilanylethynyl-cyclopent-2-enone (80)

^{1}H NMR

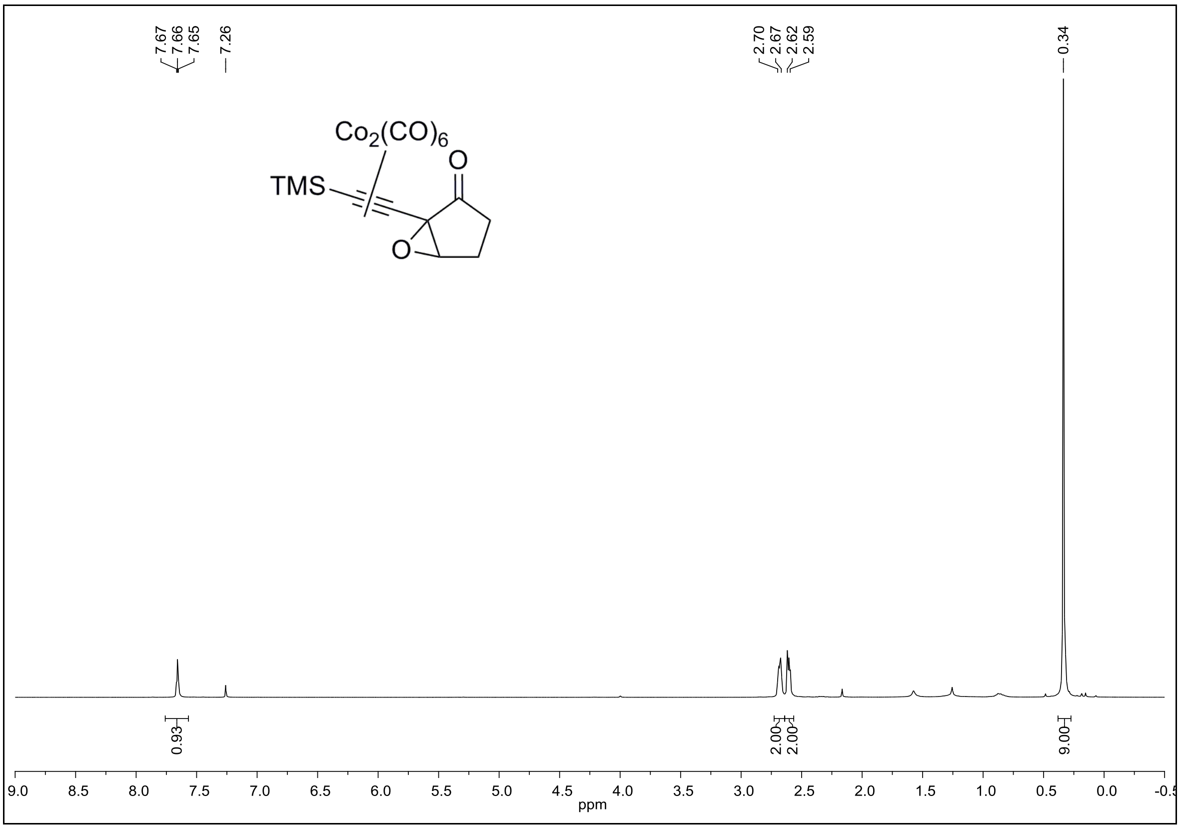


^{13}C NMR

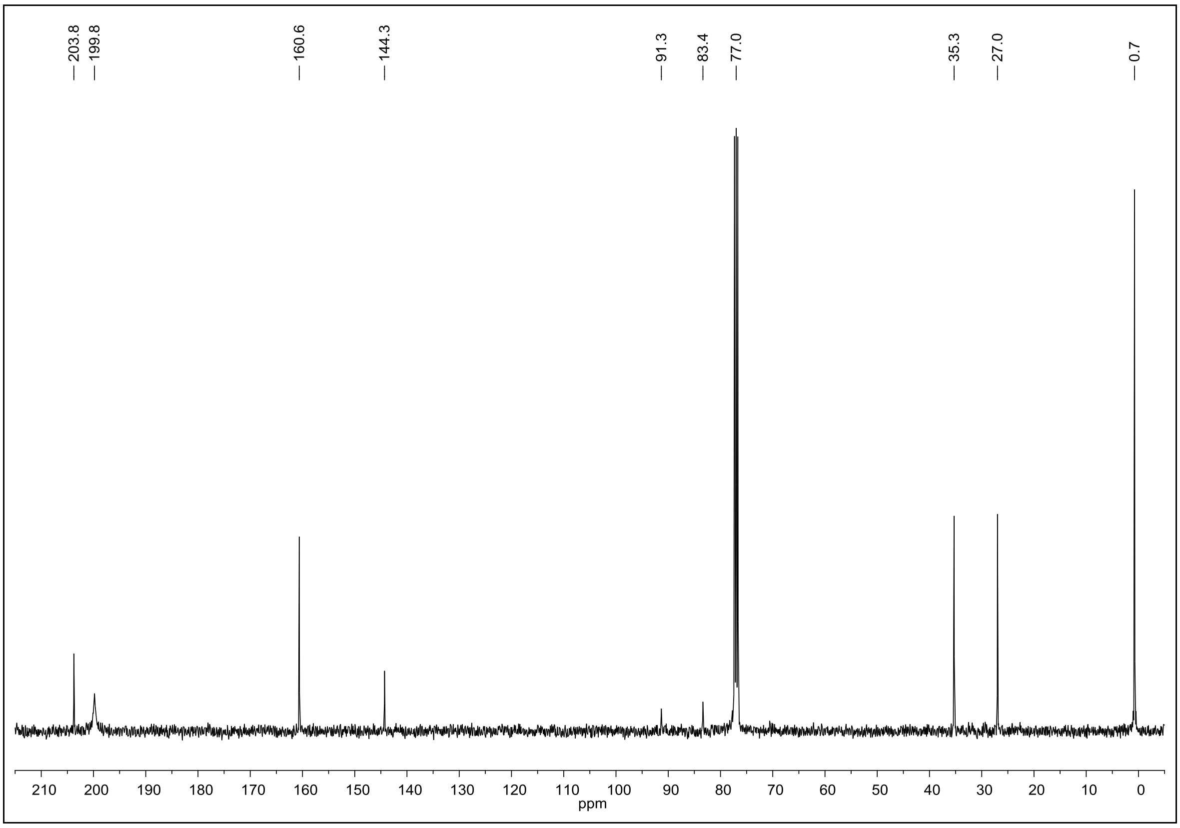


2-Trimethylsilanylethynyl-cyclopent-2-enone-dicobalthexacarbonyl (92)

^{1}H NMR

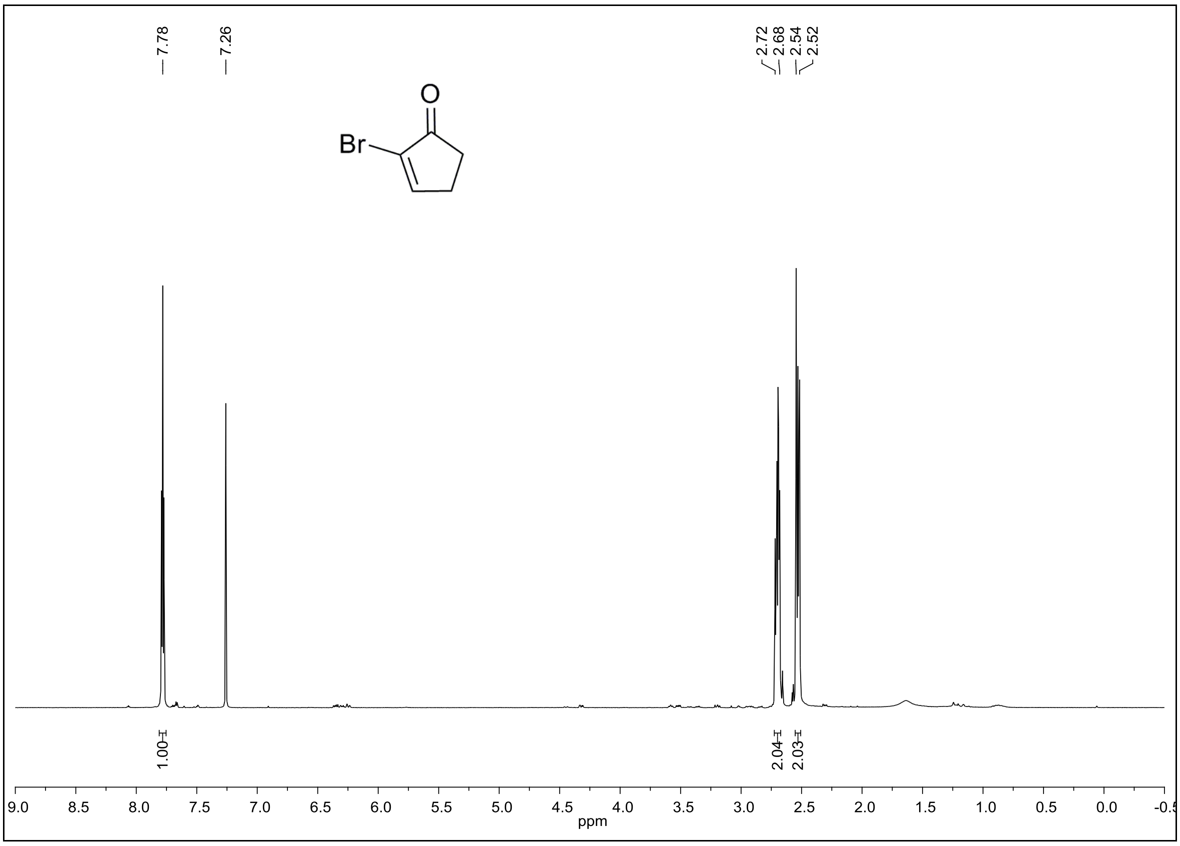


^{13}C NMR

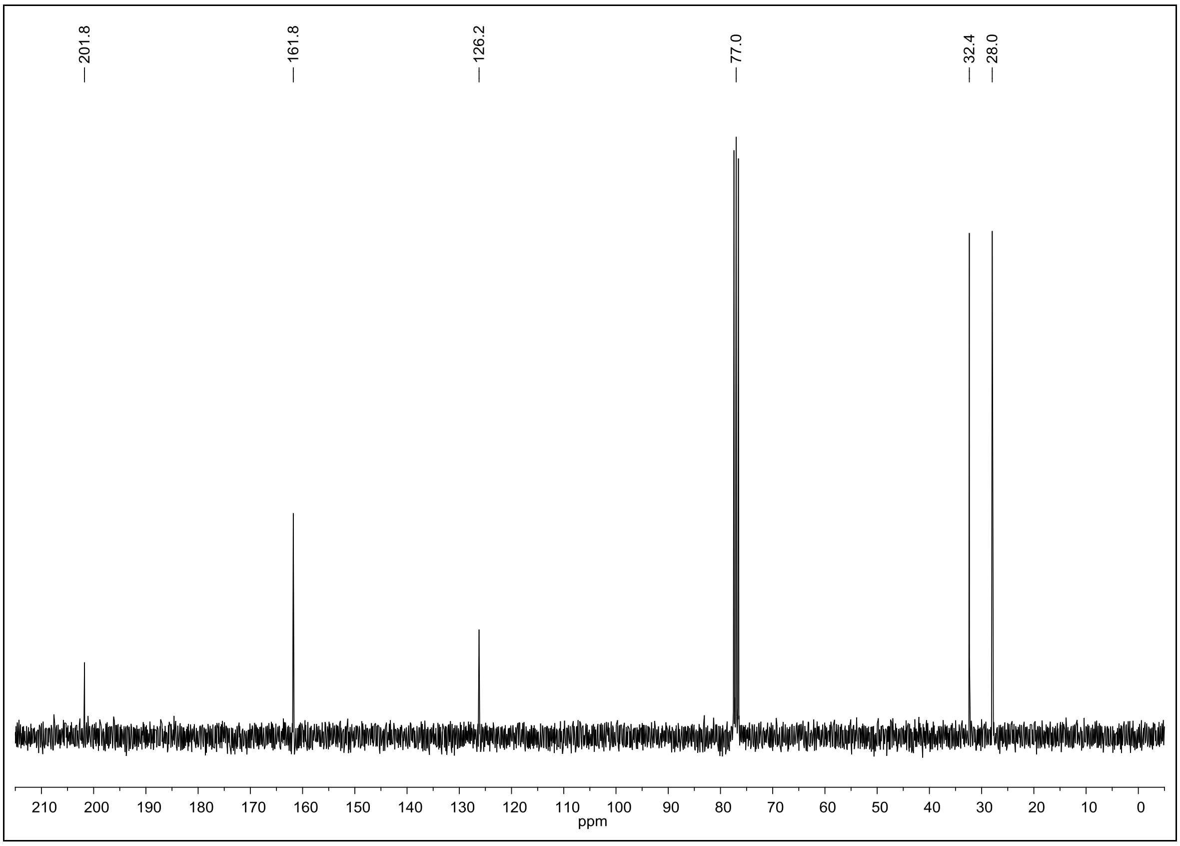


2-Bromo-cyclopent-2-enone (81)

^{1}H NMR

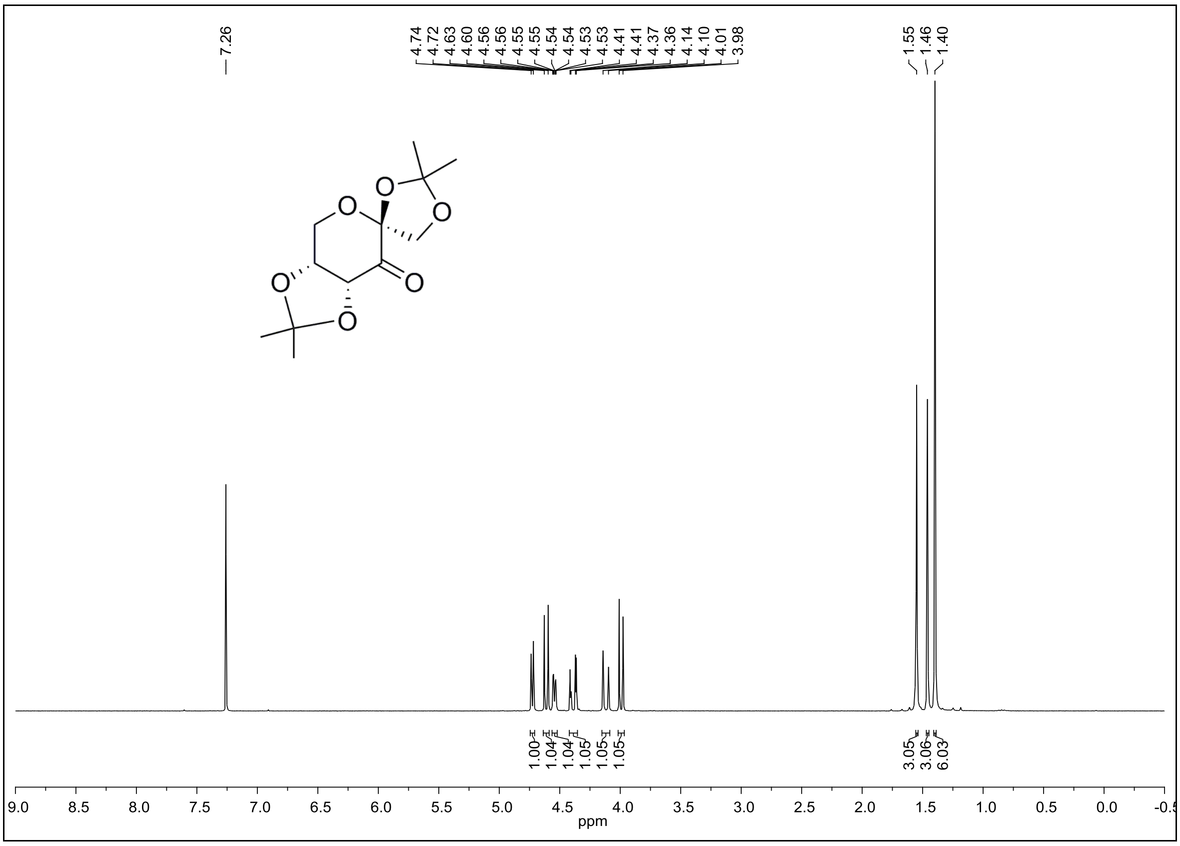


^{13}C NMR

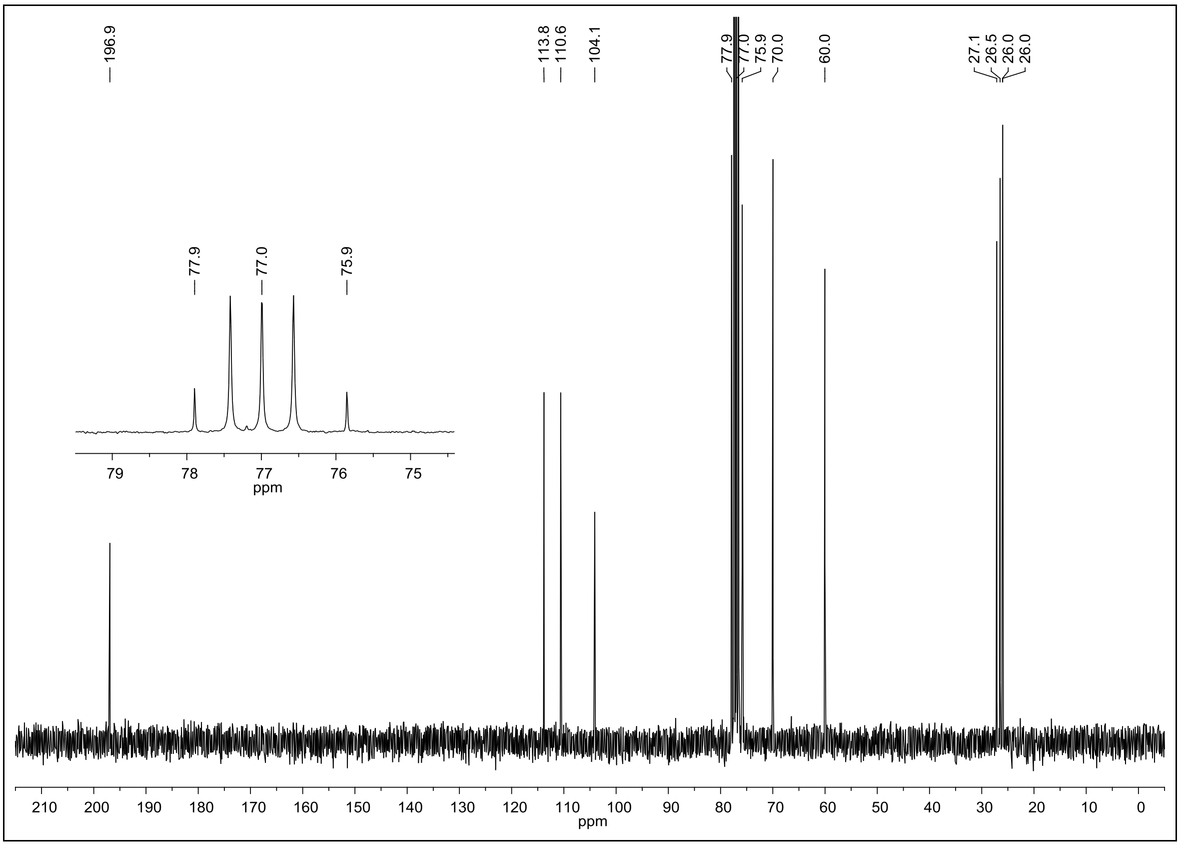


1,2:4,5-Di-O-isopropylidene-D-erythro-2,3-hexodiulo-2,6-pyranose (85)

^{1}H NMR

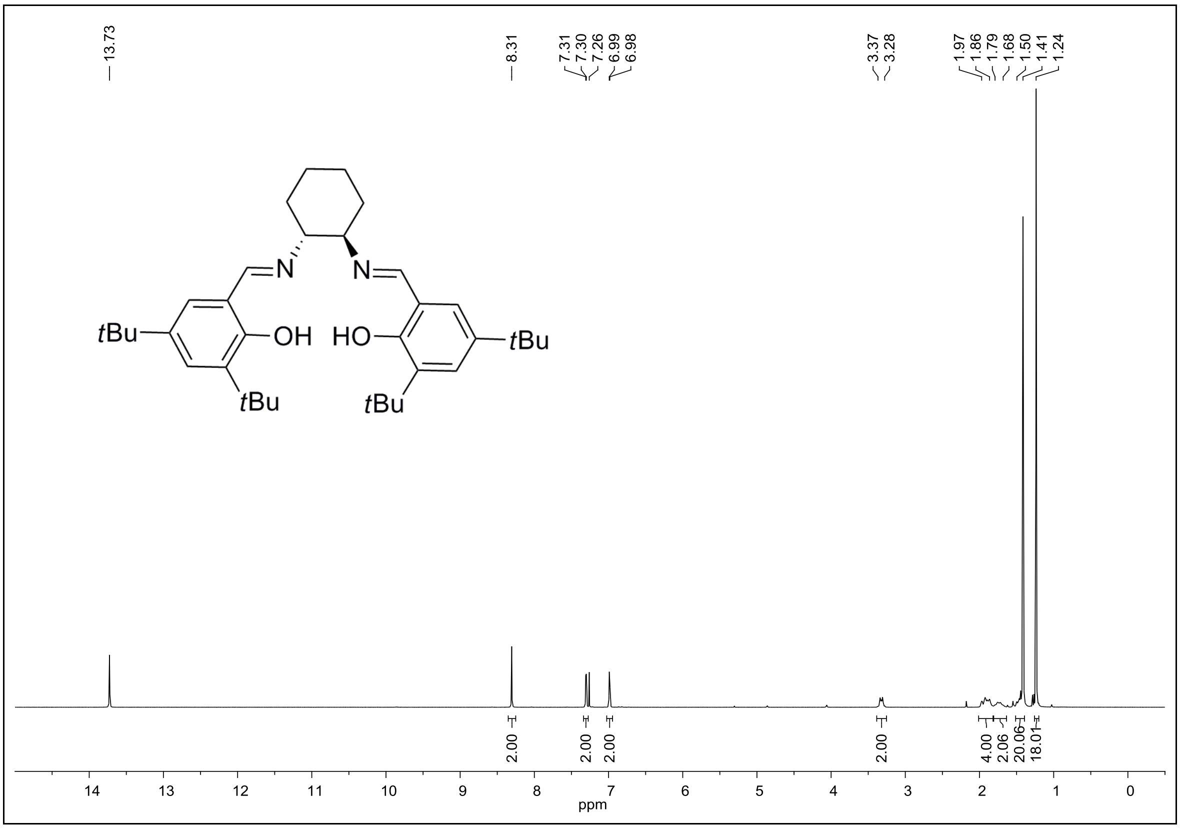


^{13}C NMR

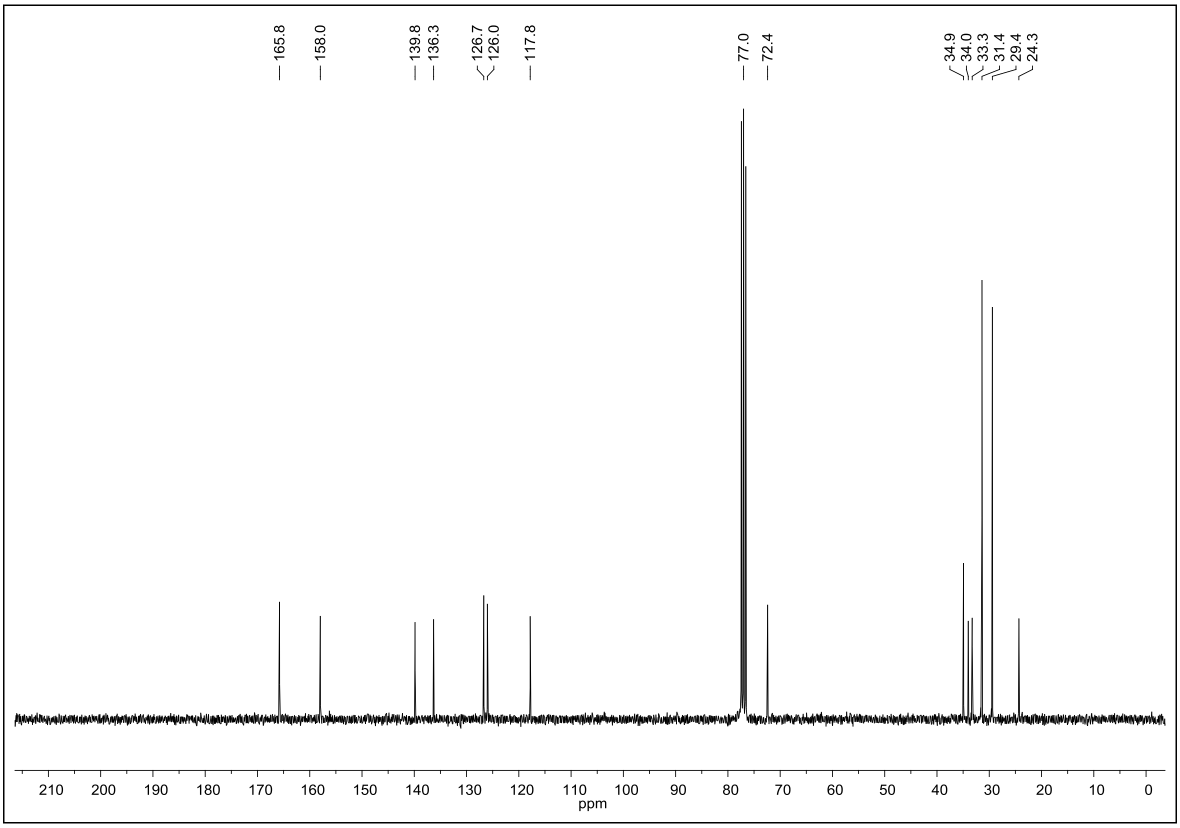


(*R*,*R*)-*N*,*N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (100)

^{1}H NMR

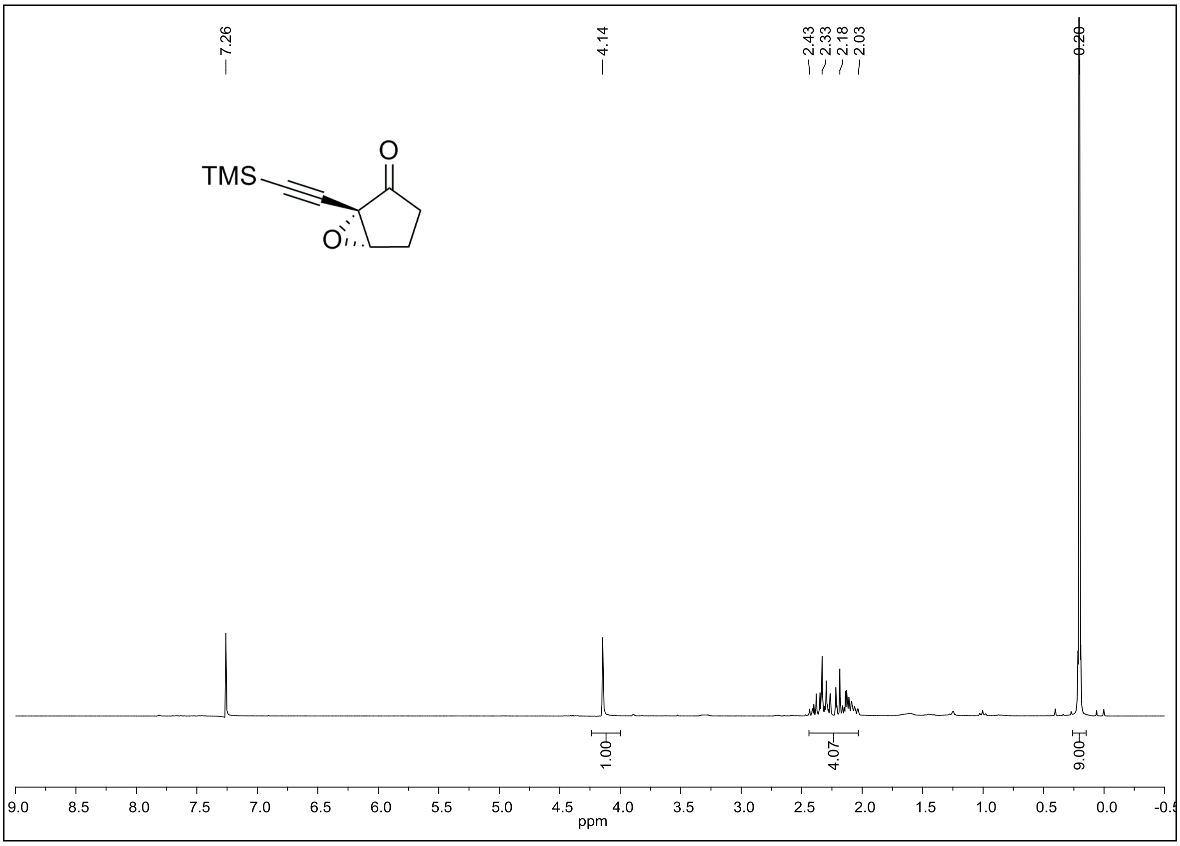


^{13}C NMR

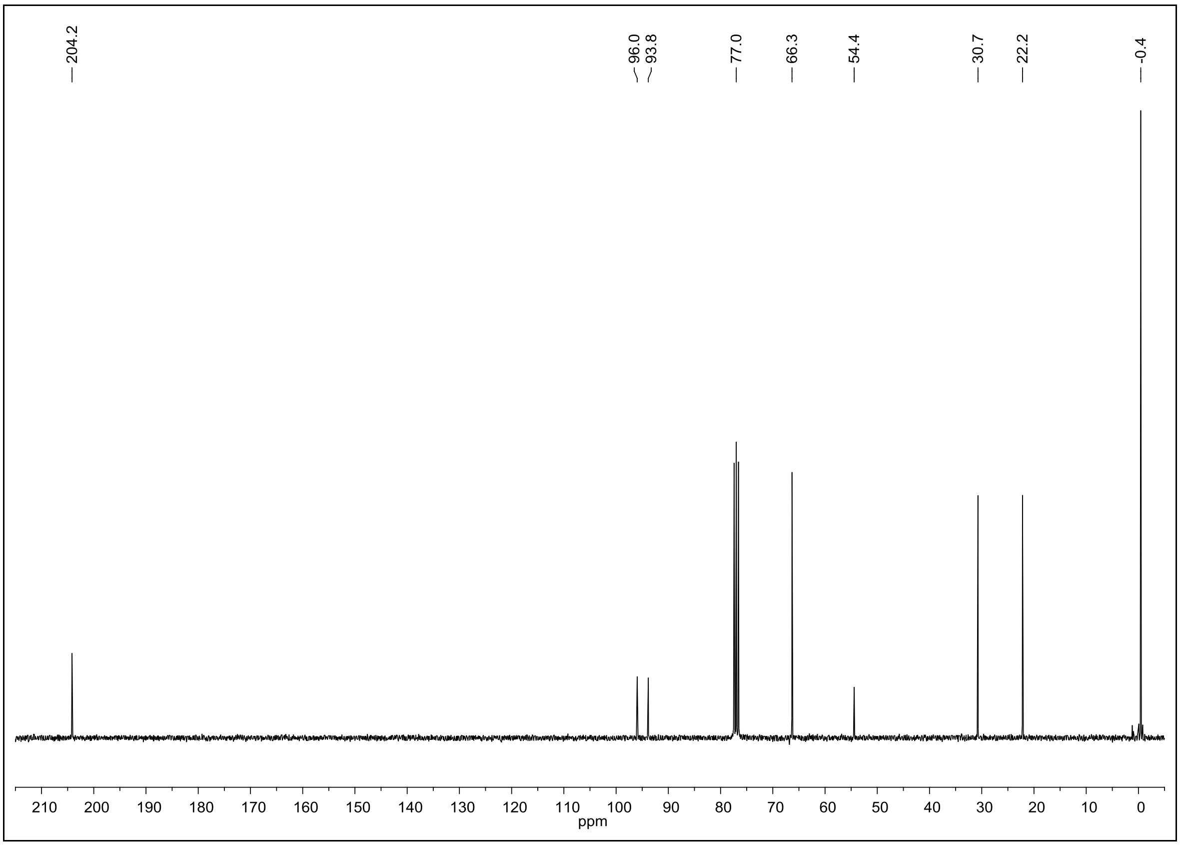


(1*S*,5*S*)-1-Trimethylsilanylethynyl-6-oxa-bicyclo[3.1.0]hexan-2-one (89)

^{1}H NMR

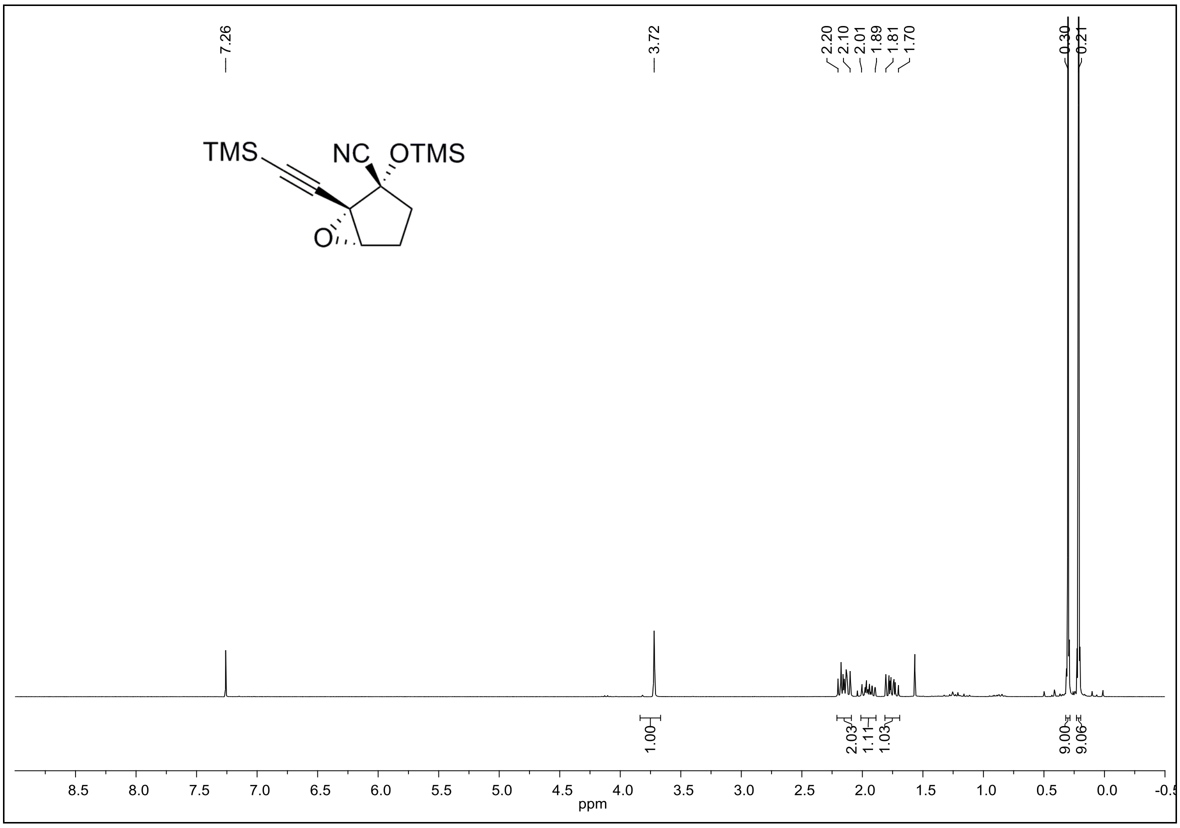


^{13}C NMR

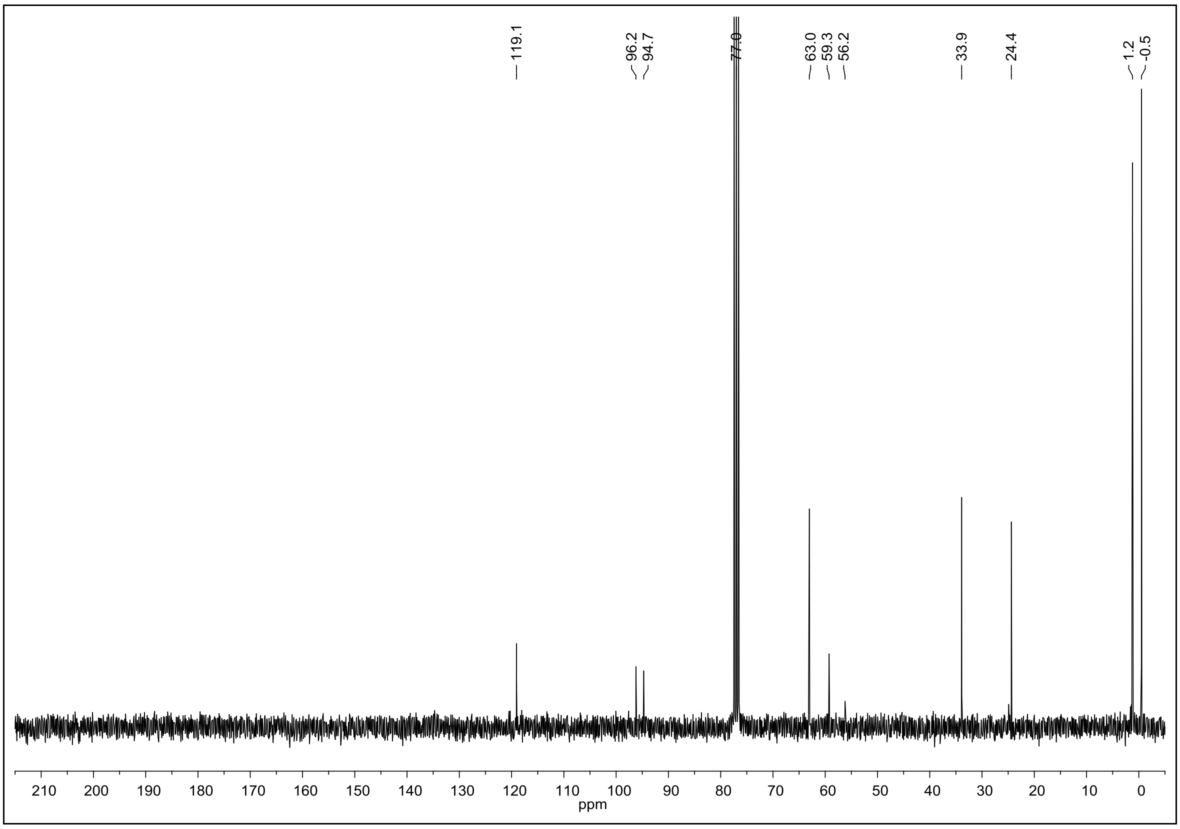


(1*S*,2*S*,5*S*)-1-Trimethylsilanylethynyl-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (77)

^{1}H NMR

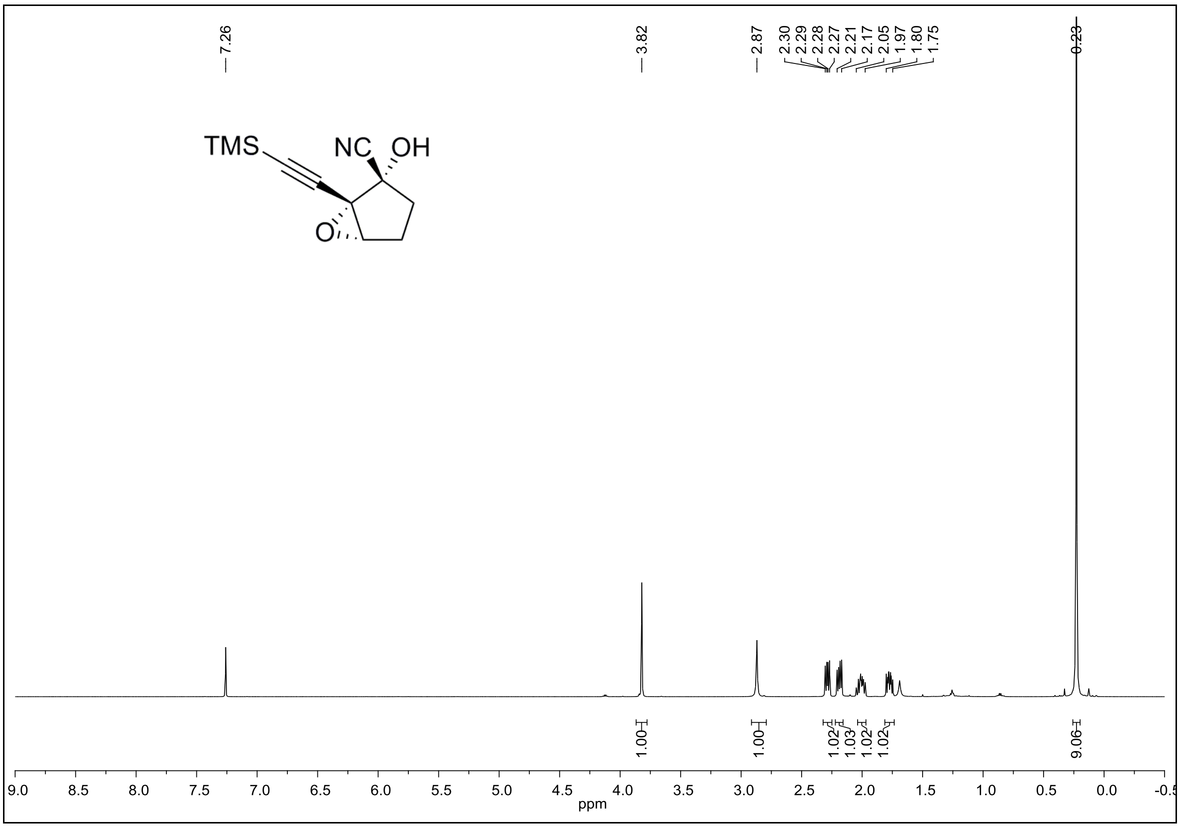


^{13}C NMR

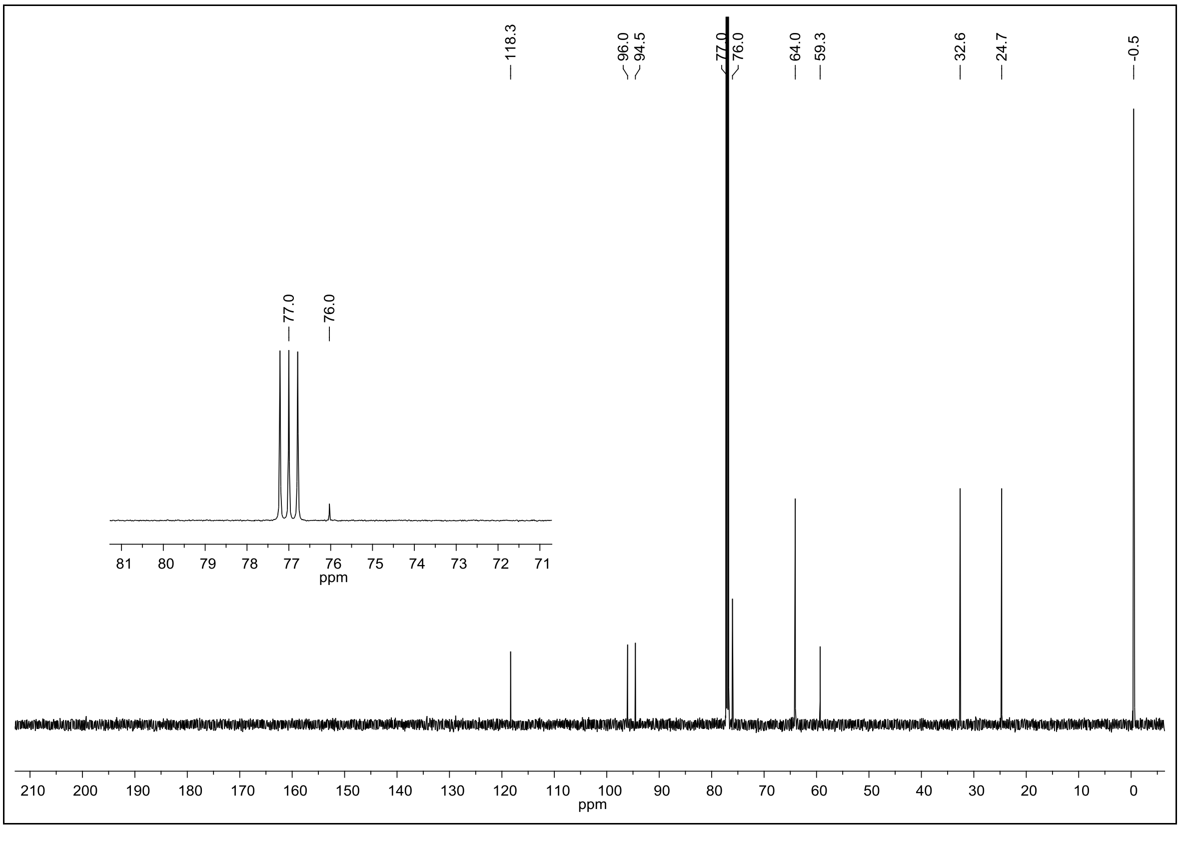


(1*S*,2*S*,5*S*)-2-Hydroxy-1-trimethylsilanylethynyl-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (102)

^{1}H NMR

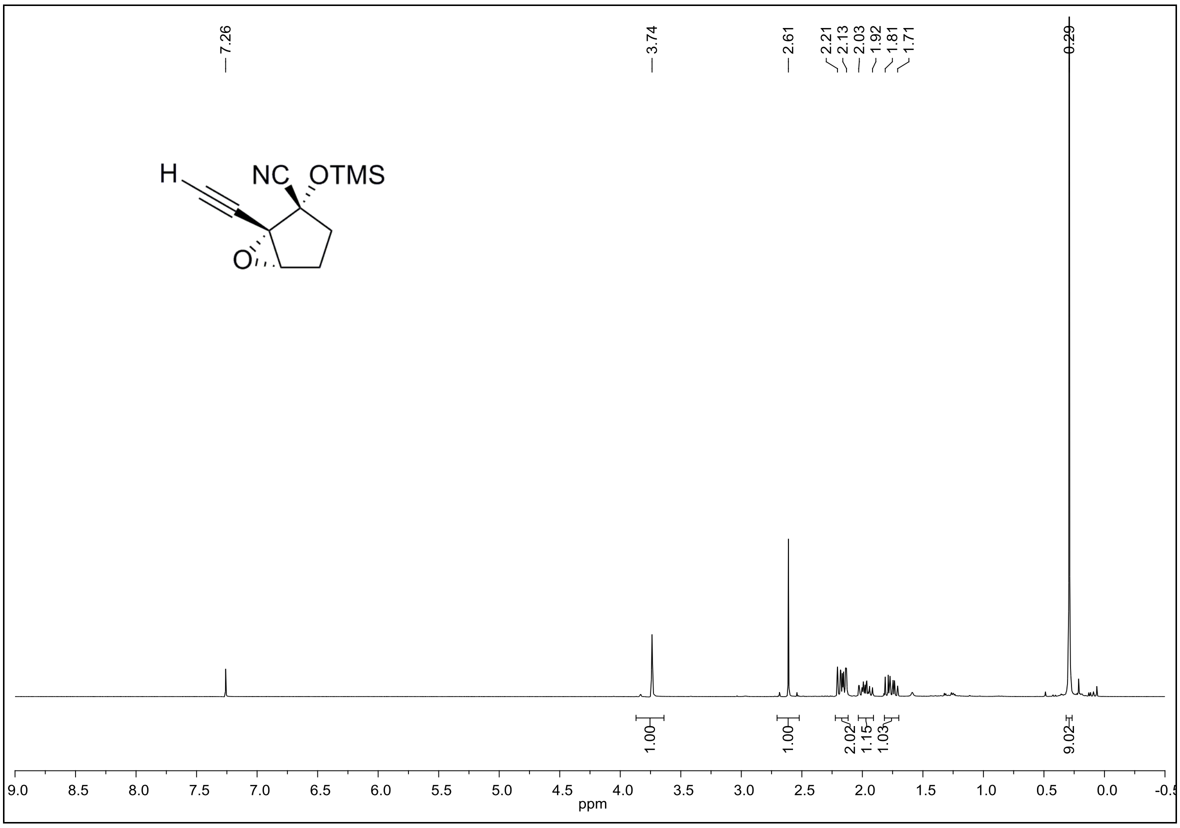


^{13}C NMR

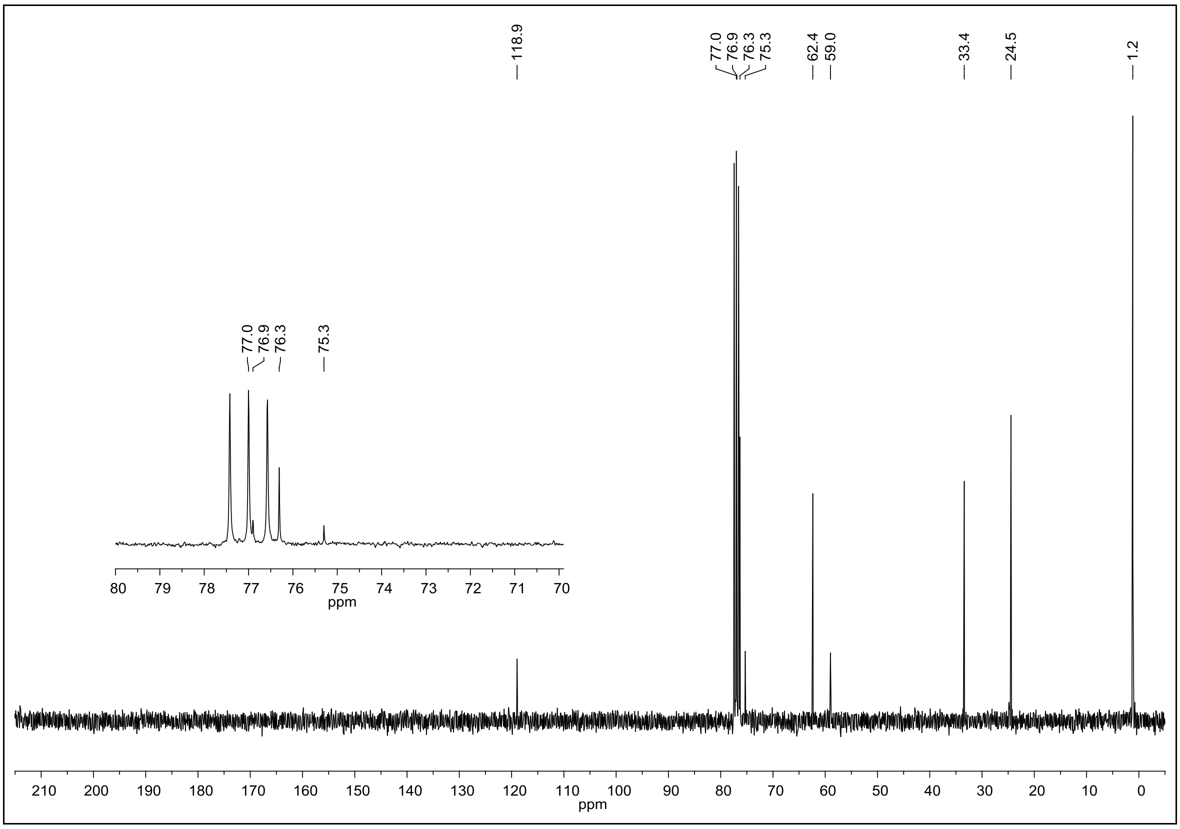


(1*S*,2*S*,5*S*)-1-Ethynyl-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (118)

^{1}H NMR

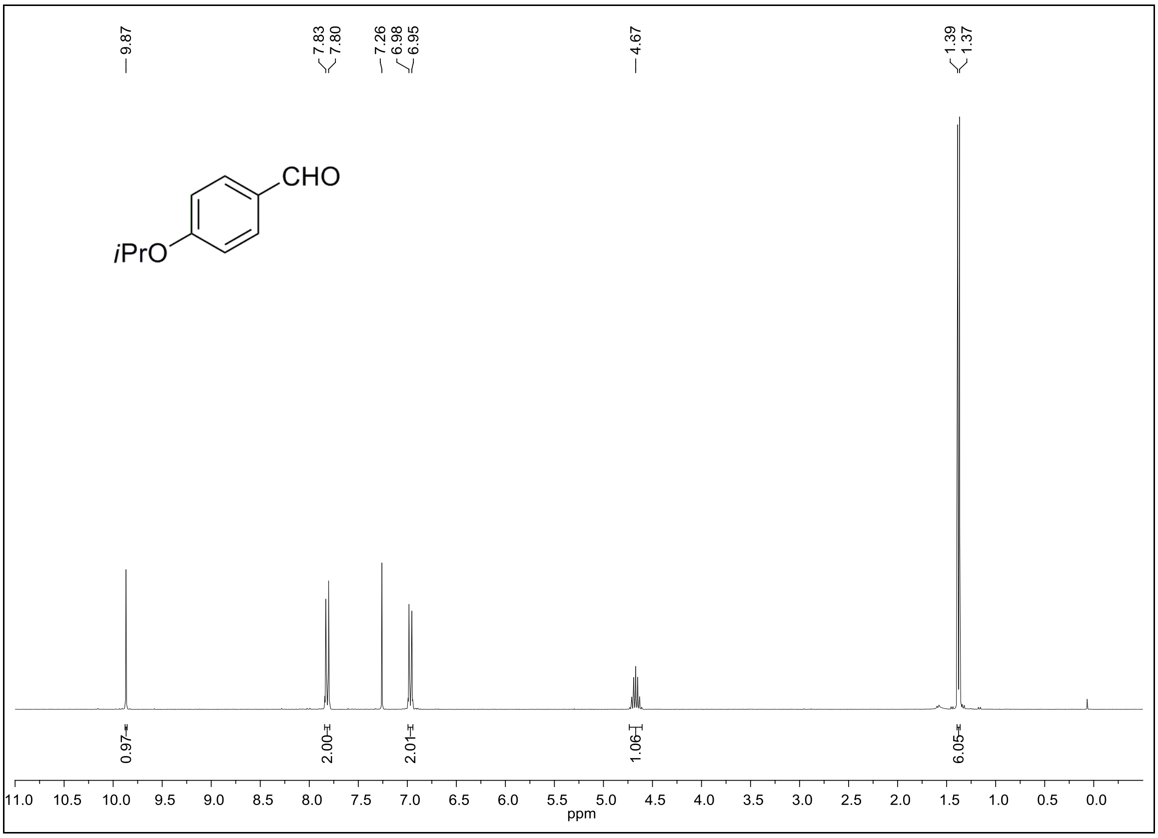


^{13}C NMR

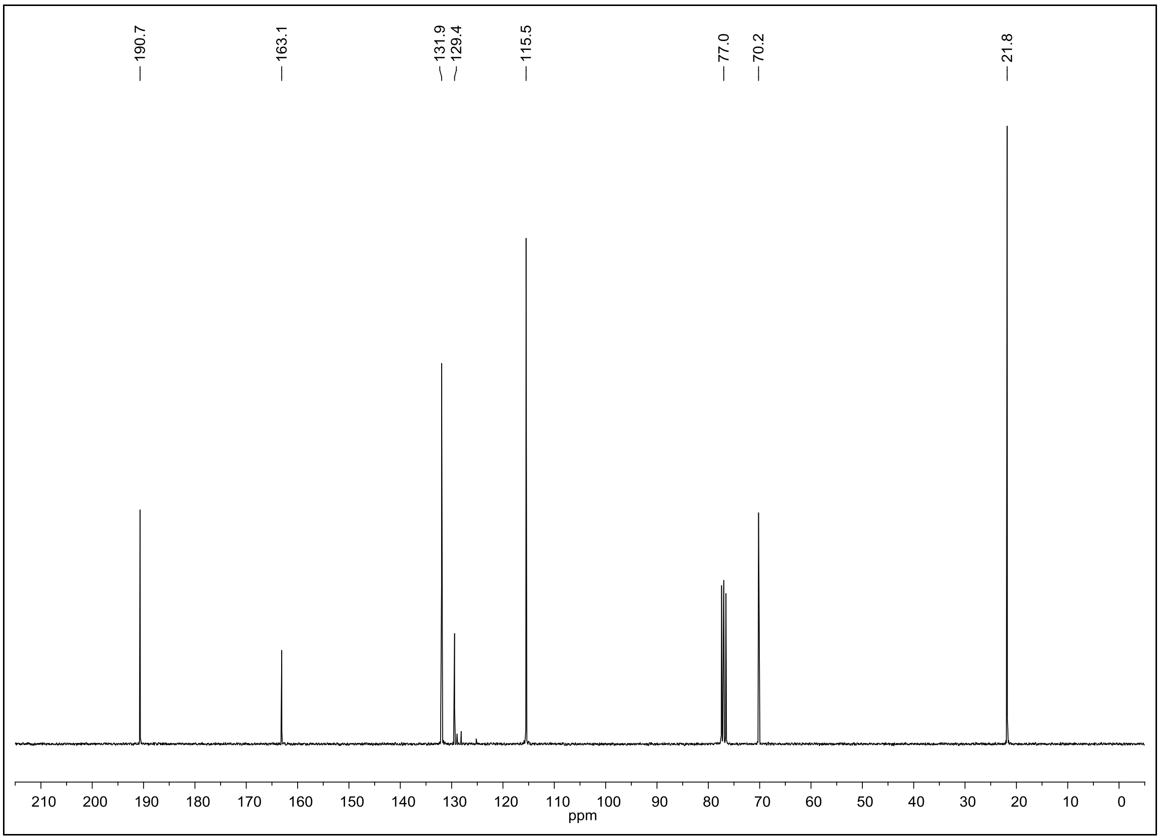


4-Isopropoxybenzaldehyde (116)

^{1}H NMR

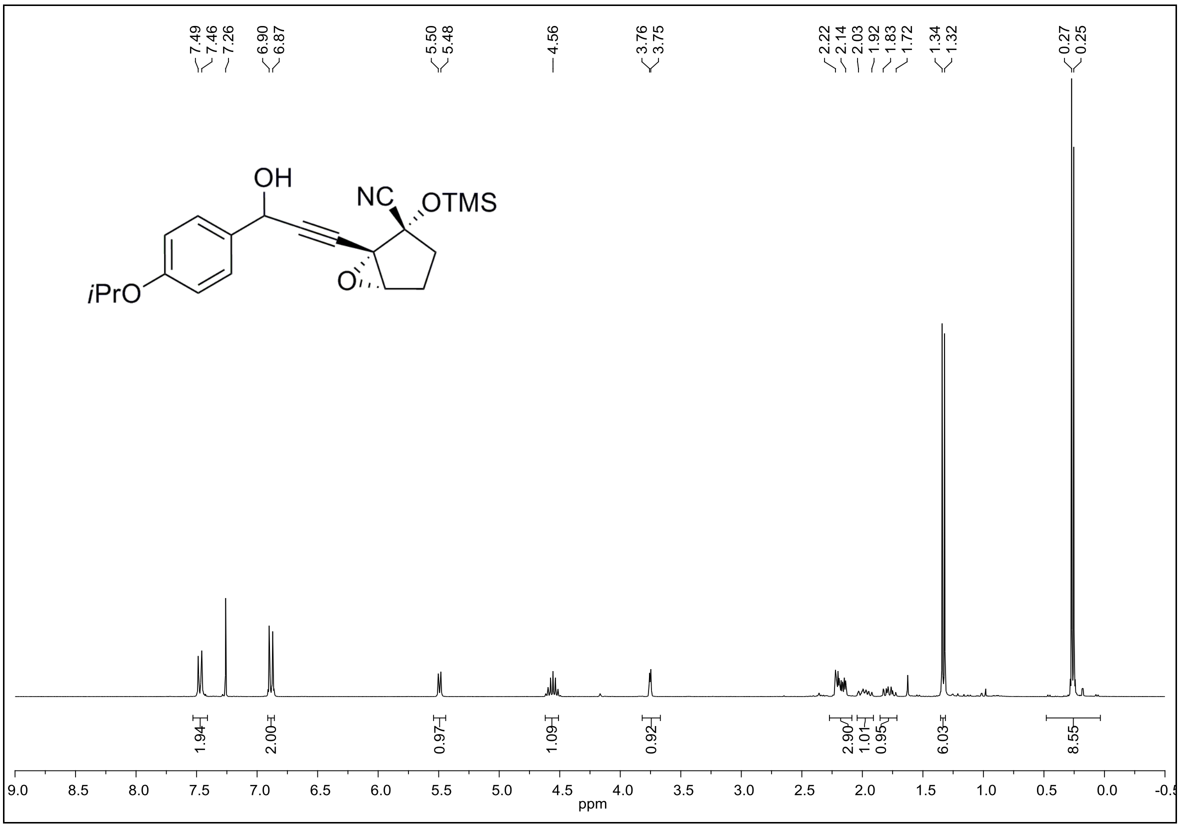


^{13}CNMR

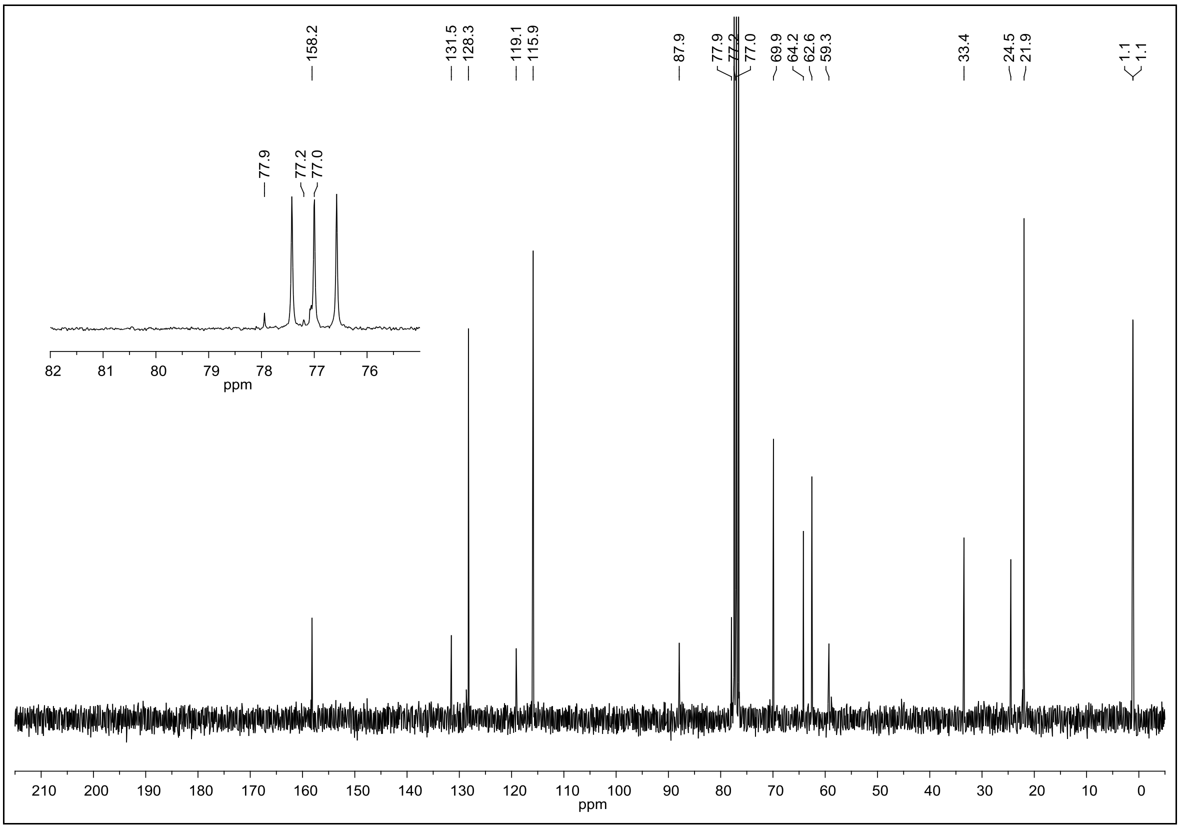


(1*S*,2*S*,5*S*)-1-[3-Hydroxy-3-(4-isopropoxy-phenyl)-prop-1-ynyl]-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (119)

^{1}H NMR

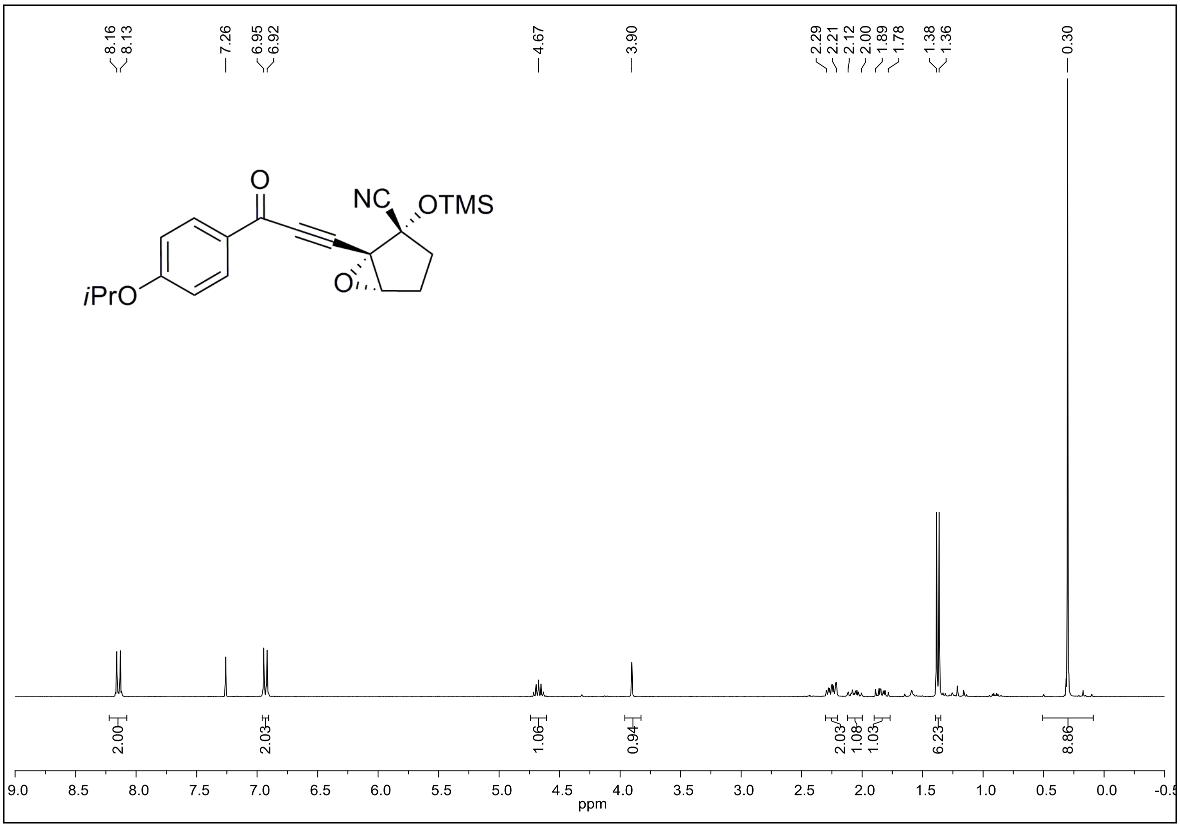


^{13}C NMR

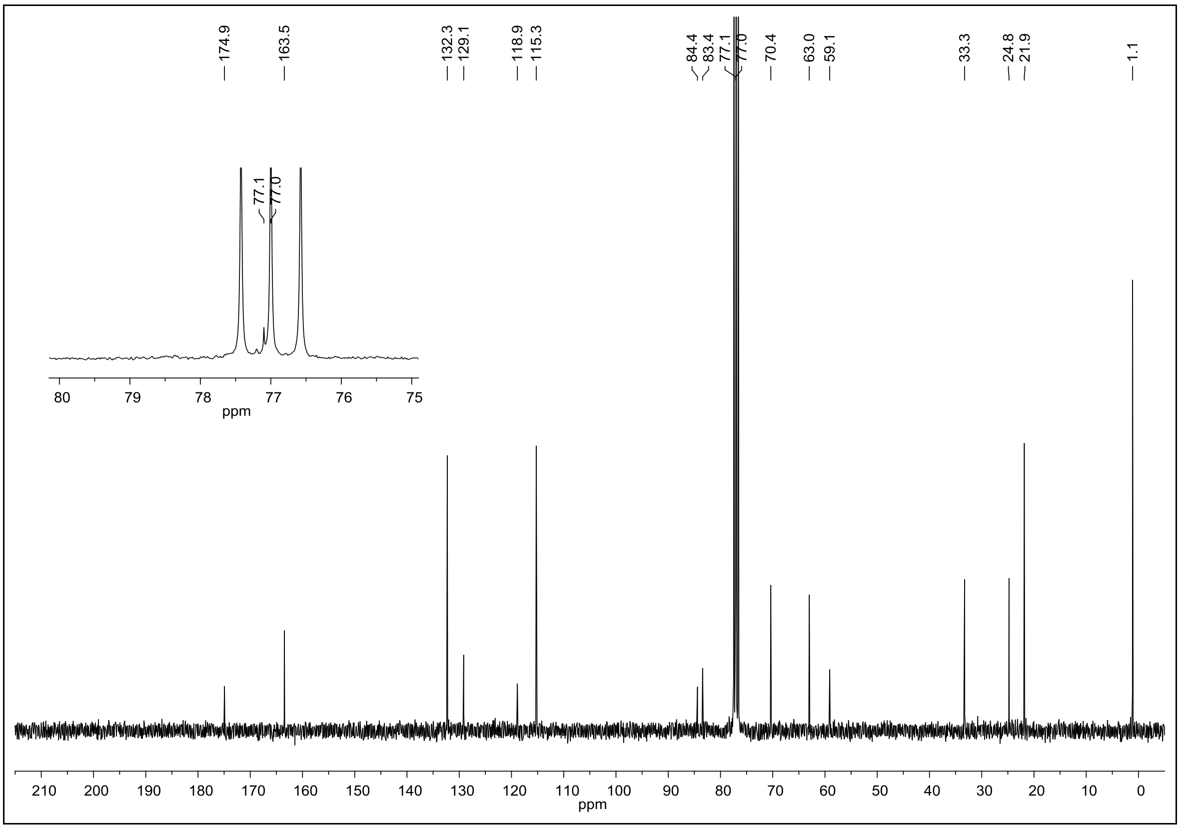


(1*S*,2*S*,5*S*)-1-[3-(4-Isopropoxy-phenyl)-3-oxo-prop-1-ynyl]-2-trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (113)

^{1}H NMR

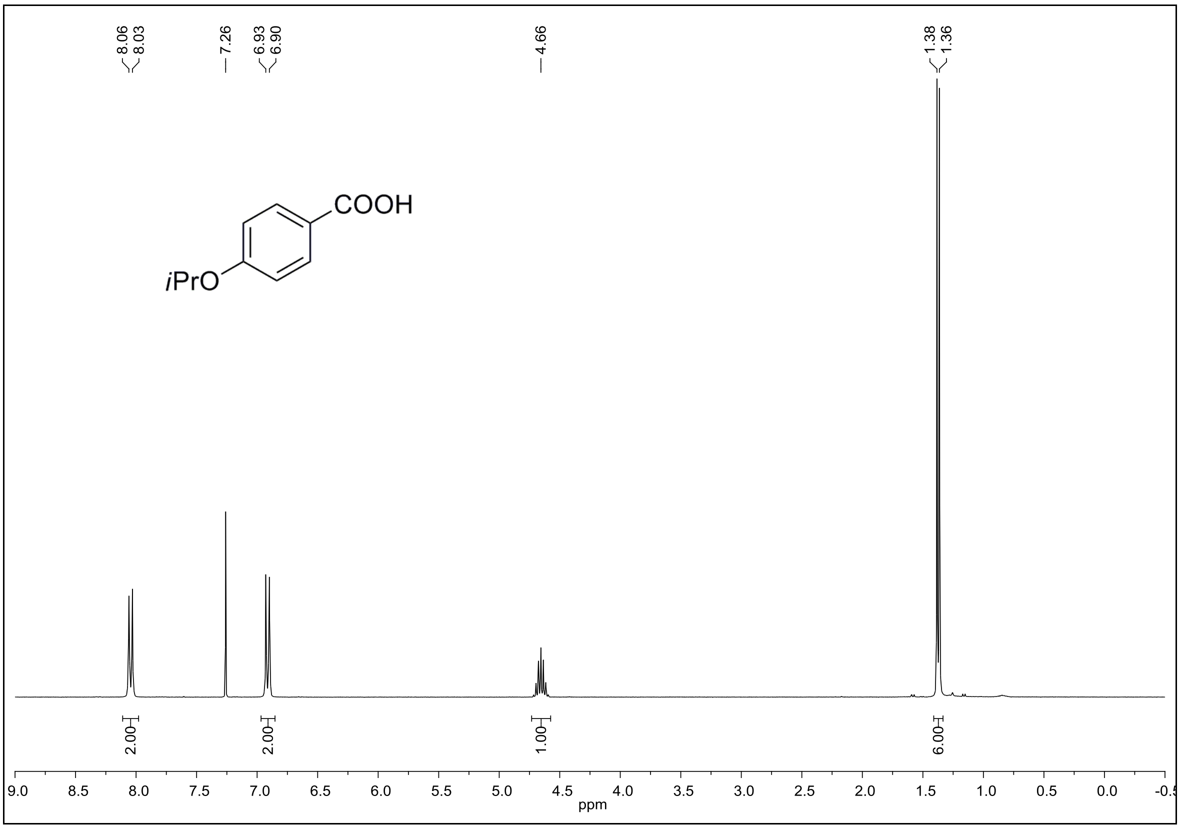


^{13}C NMR

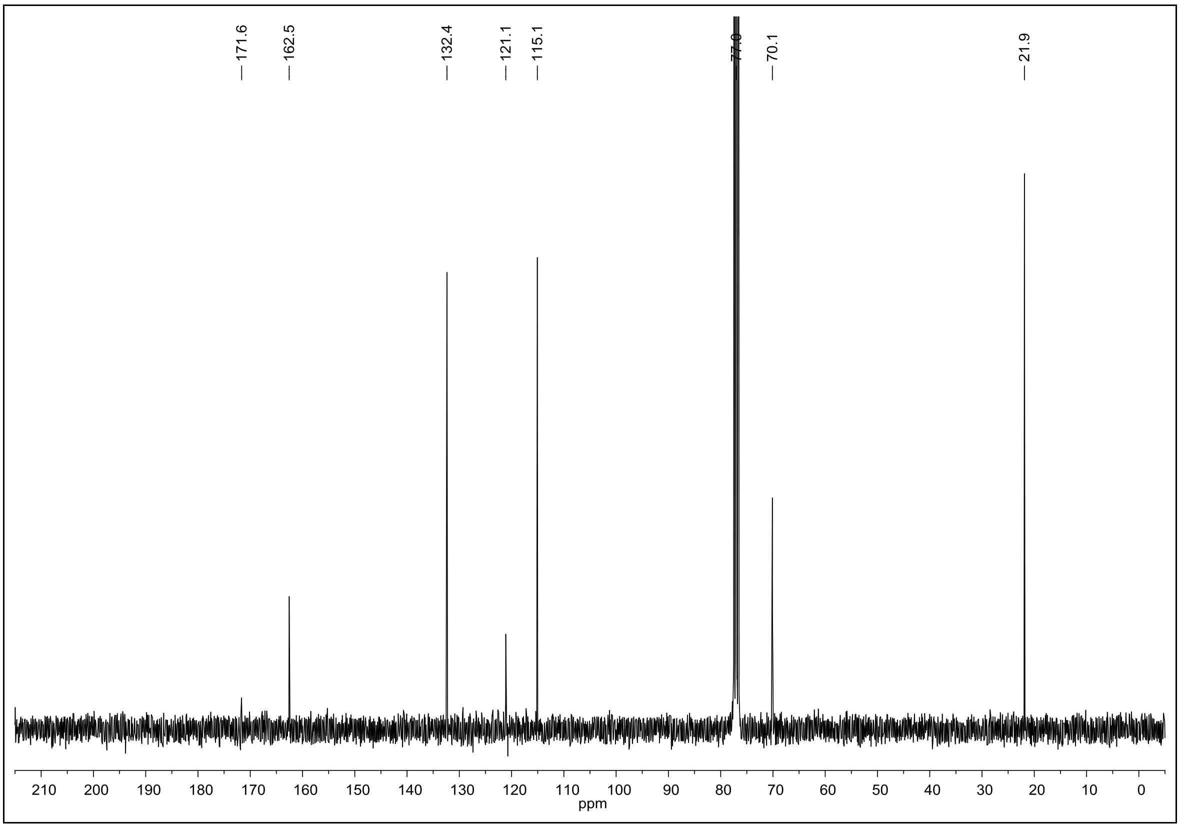


4-Isopropoxybenzoic acid (120)

^{1}H NMR

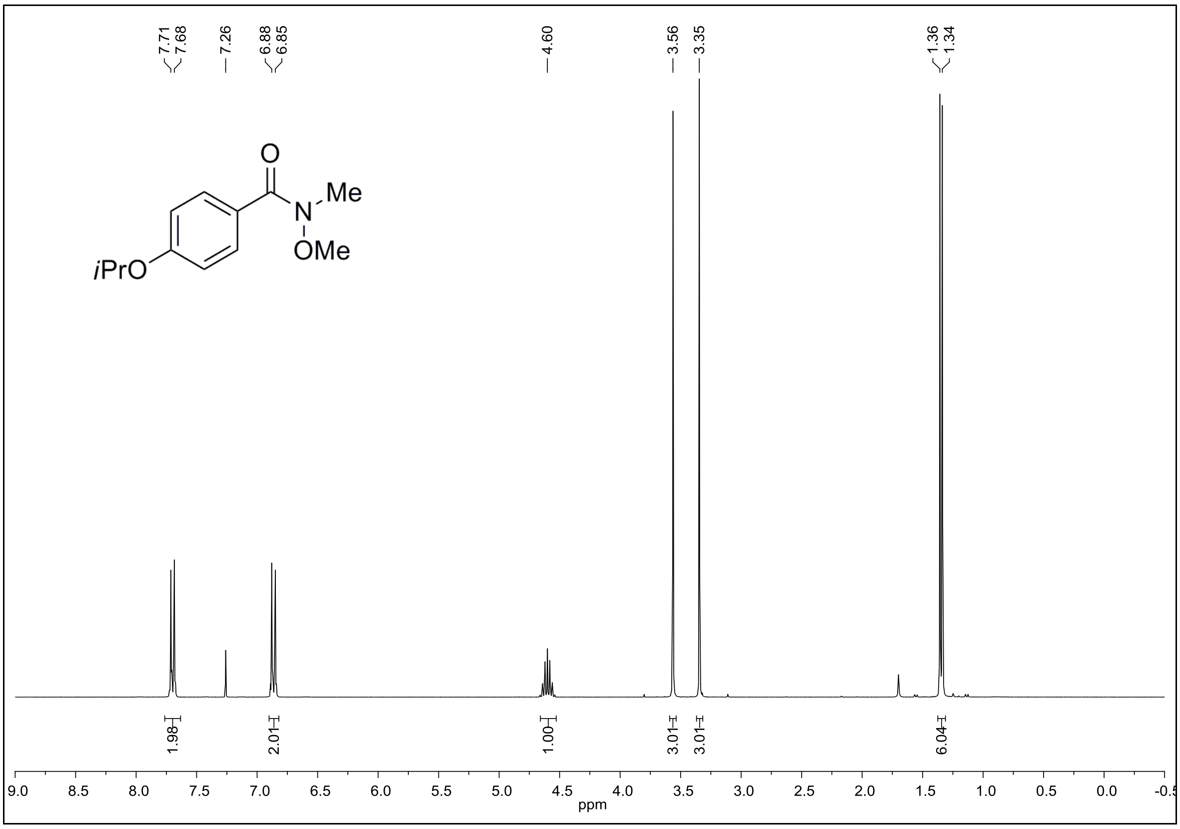


^{13}C NMR

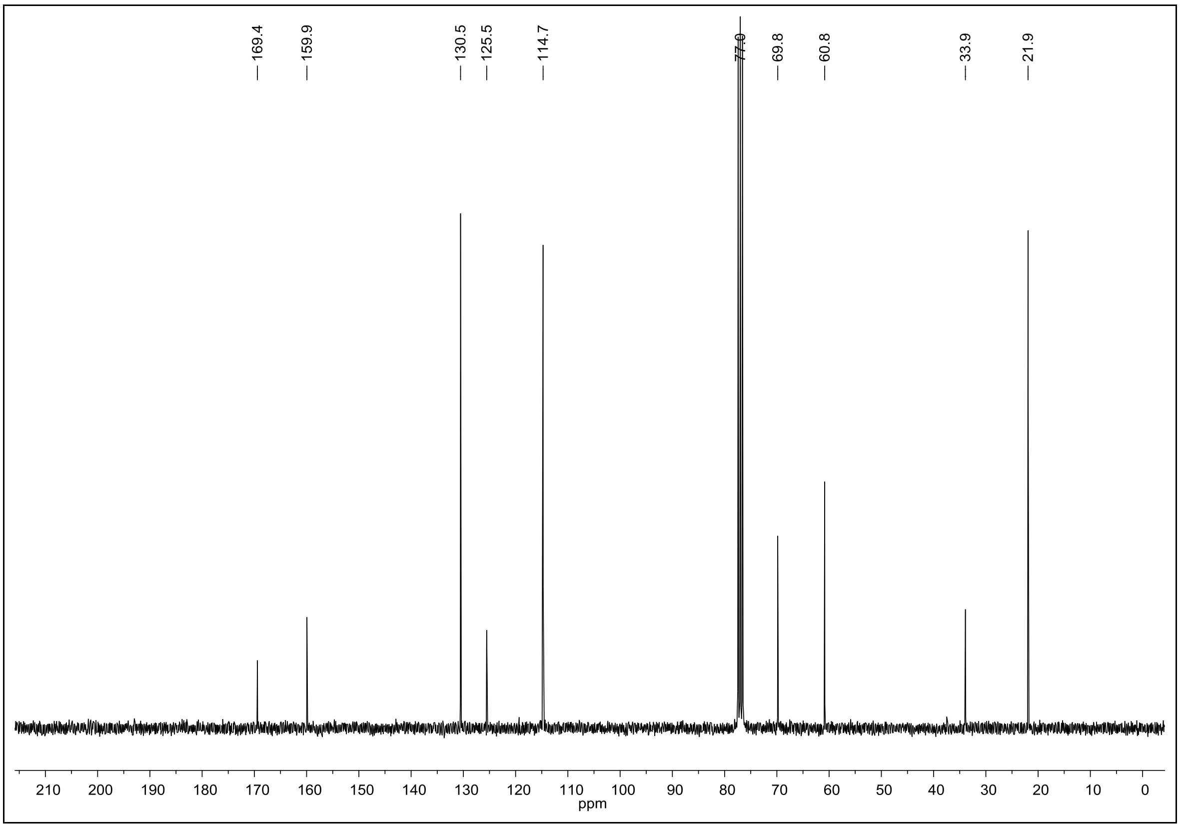


***N*-methoxy-*N*-methyl-4-(isopropoxy)-benzamide (121)**

^{1}H NMR

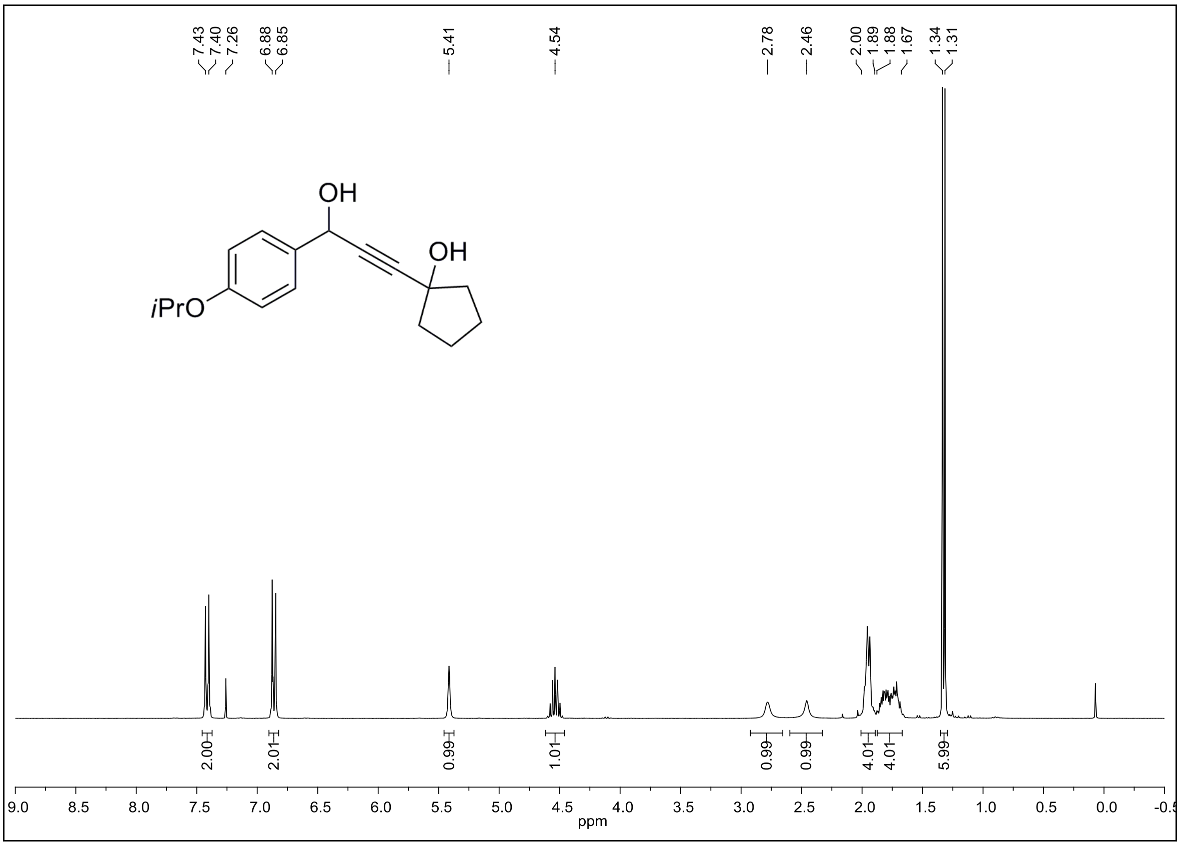


^{13}C NMR

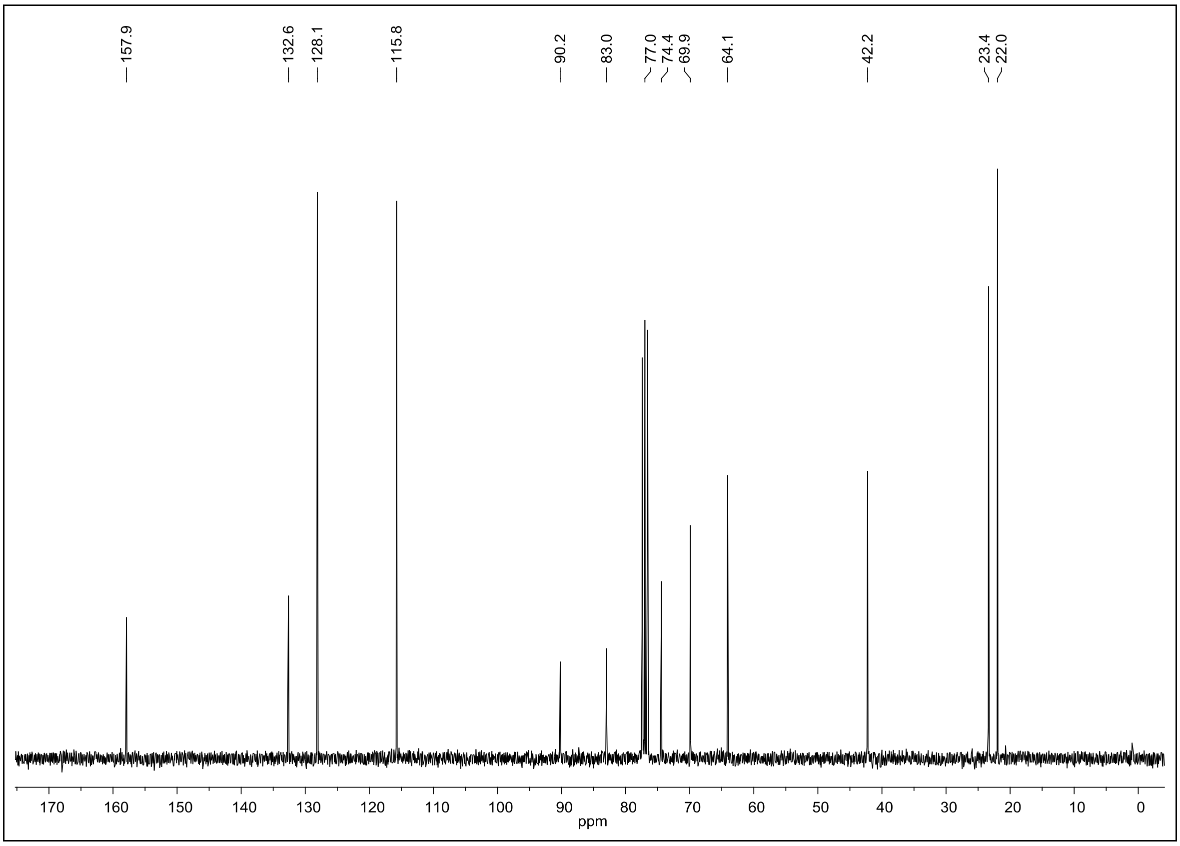


1-[3-Hydroxy-3-(4-isopropoxy-phenyl)-prop-1-ynyl]-cyclopentanol (149)

^{1}H NMR

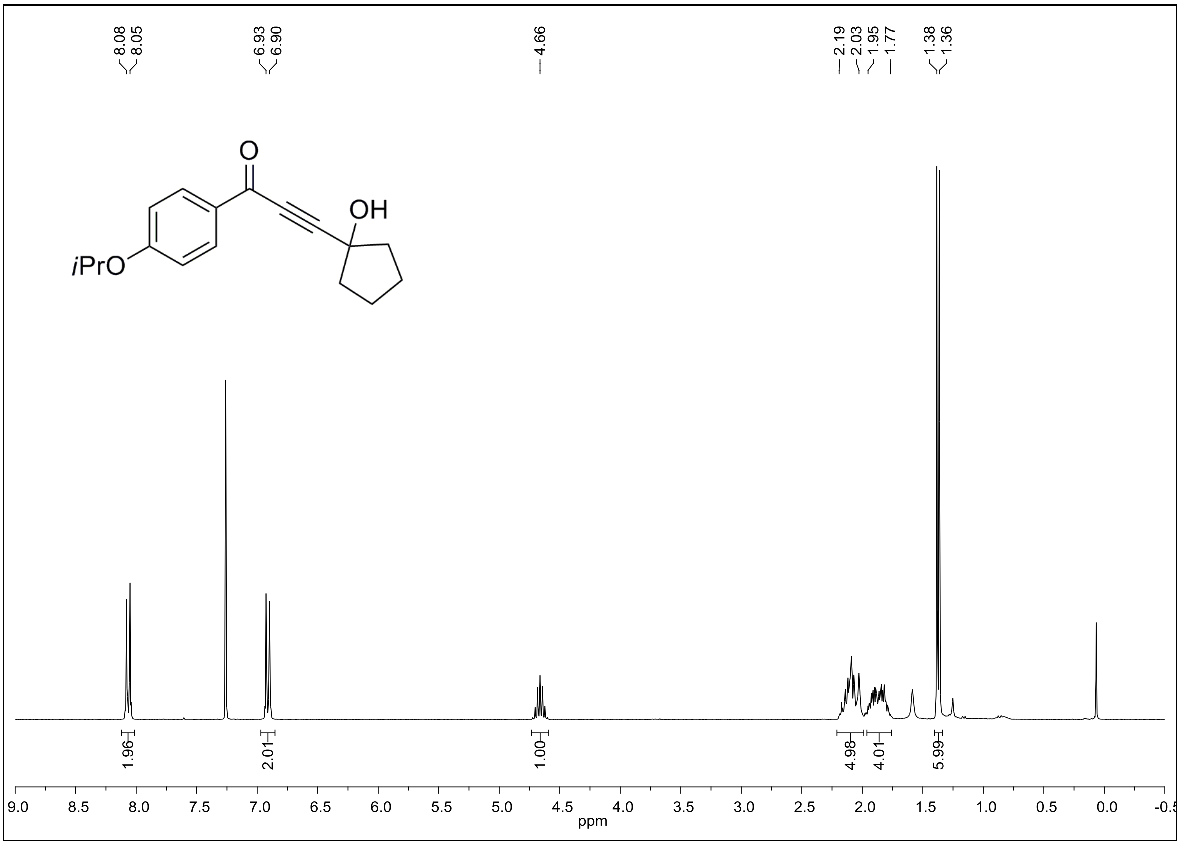


^{13}C NMR

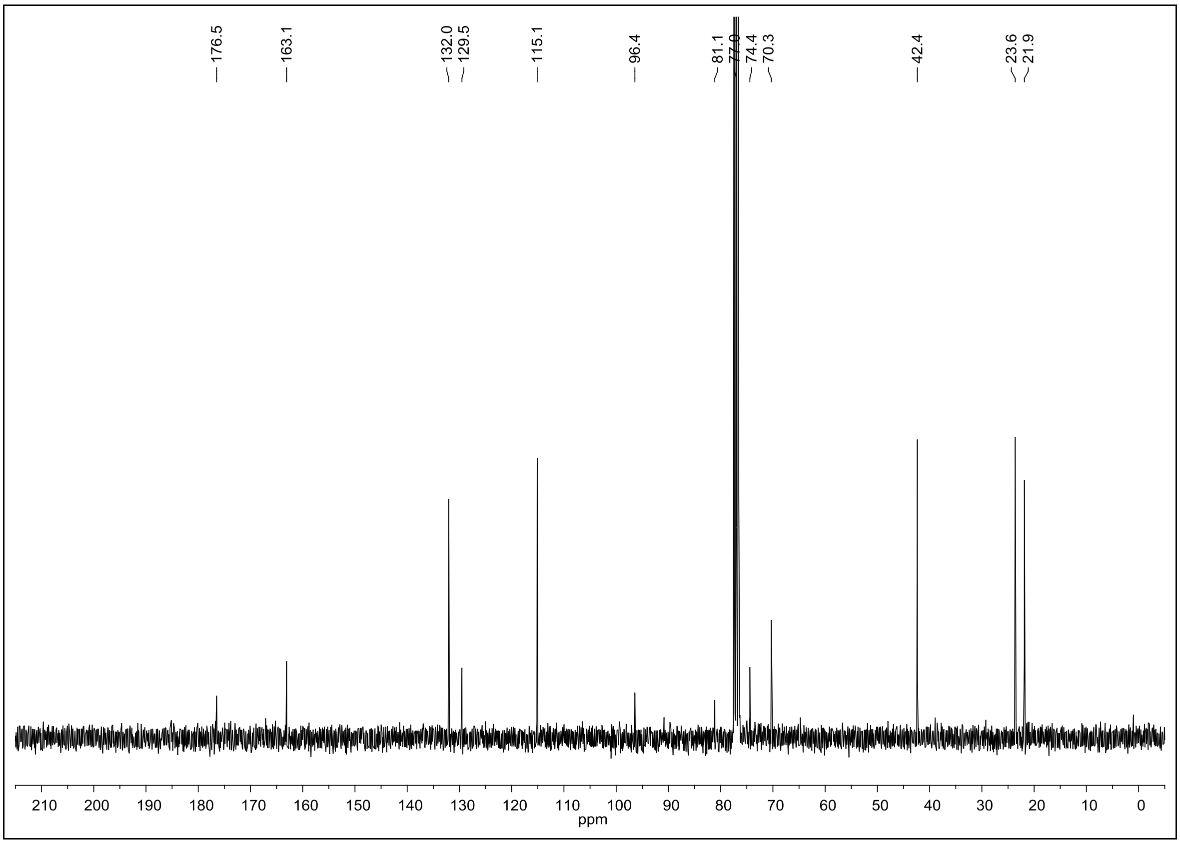


3-(1-Hydroxy-cyclopentyl)-1-(4-isopropoxy-phenyl)-propynone (150)

^{1}H NMR

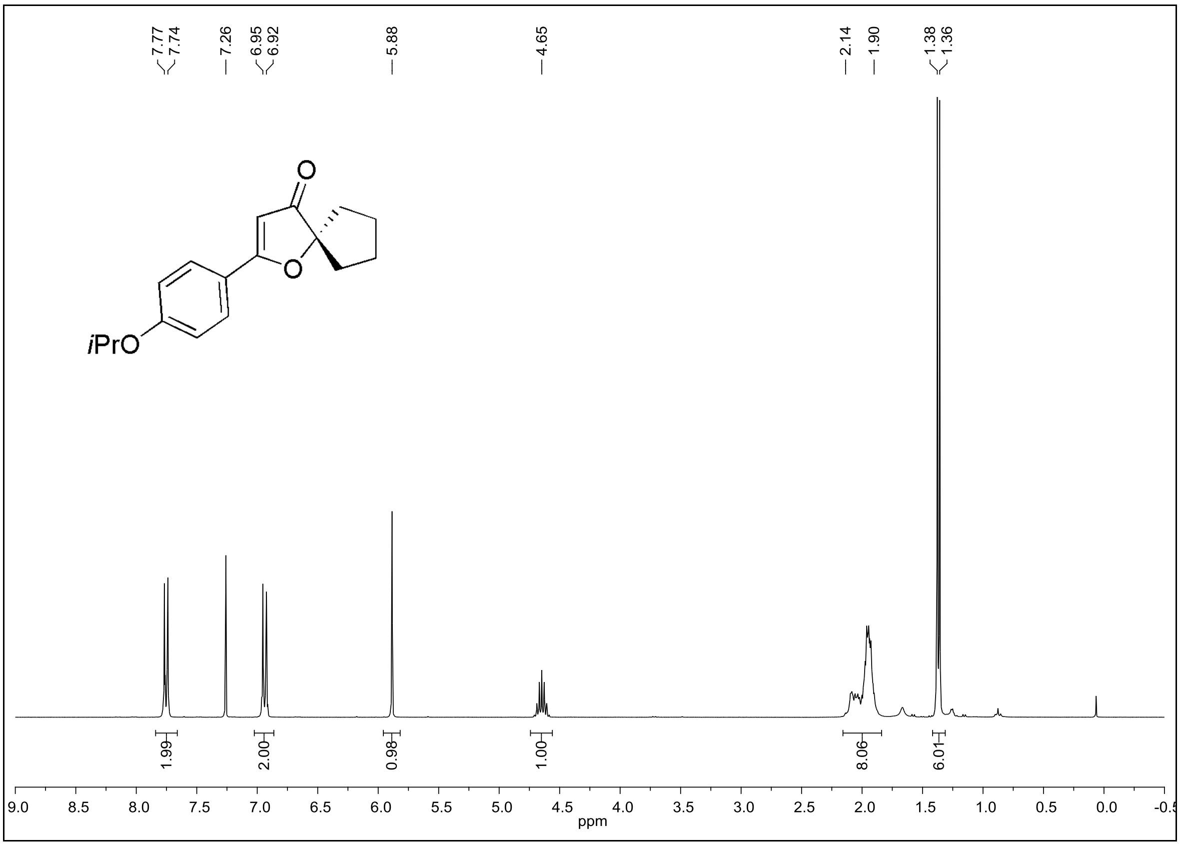


^{13}C NMR

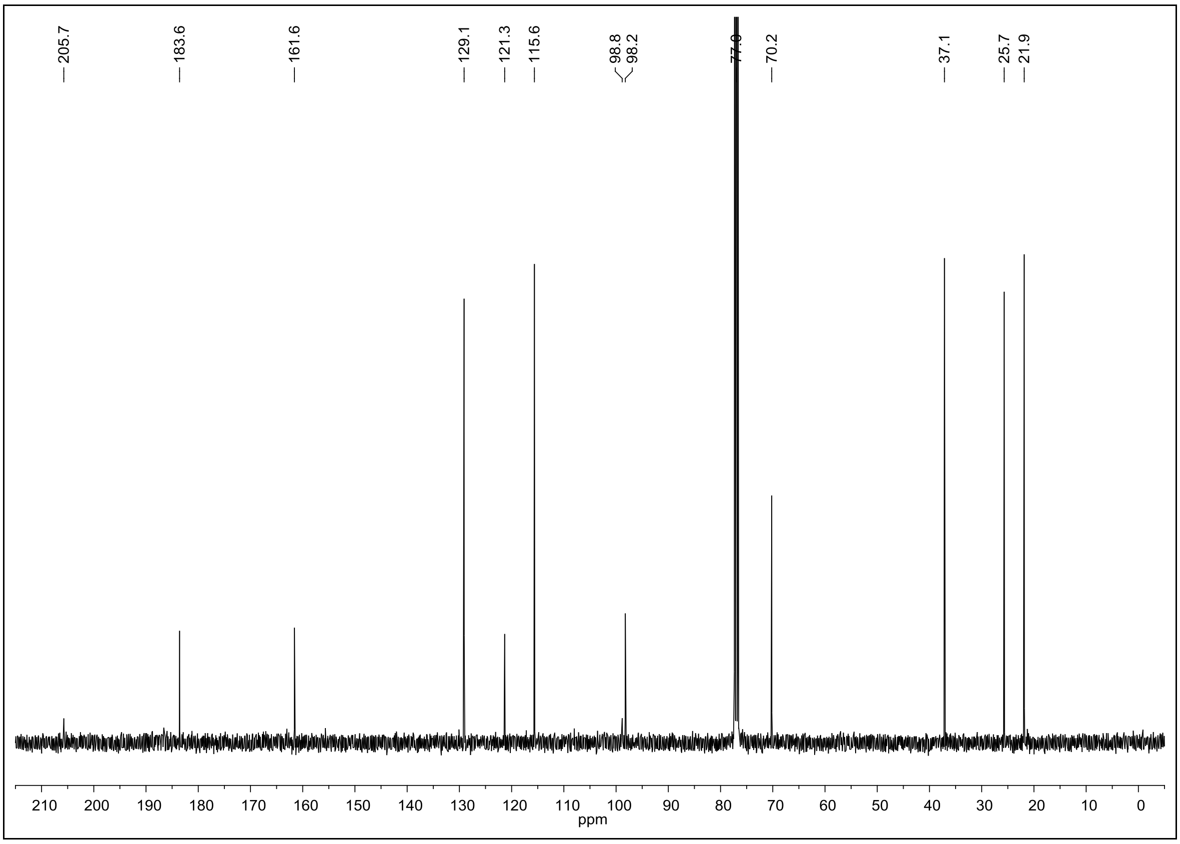


2-(4-Isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (151)

^{1}H NMR

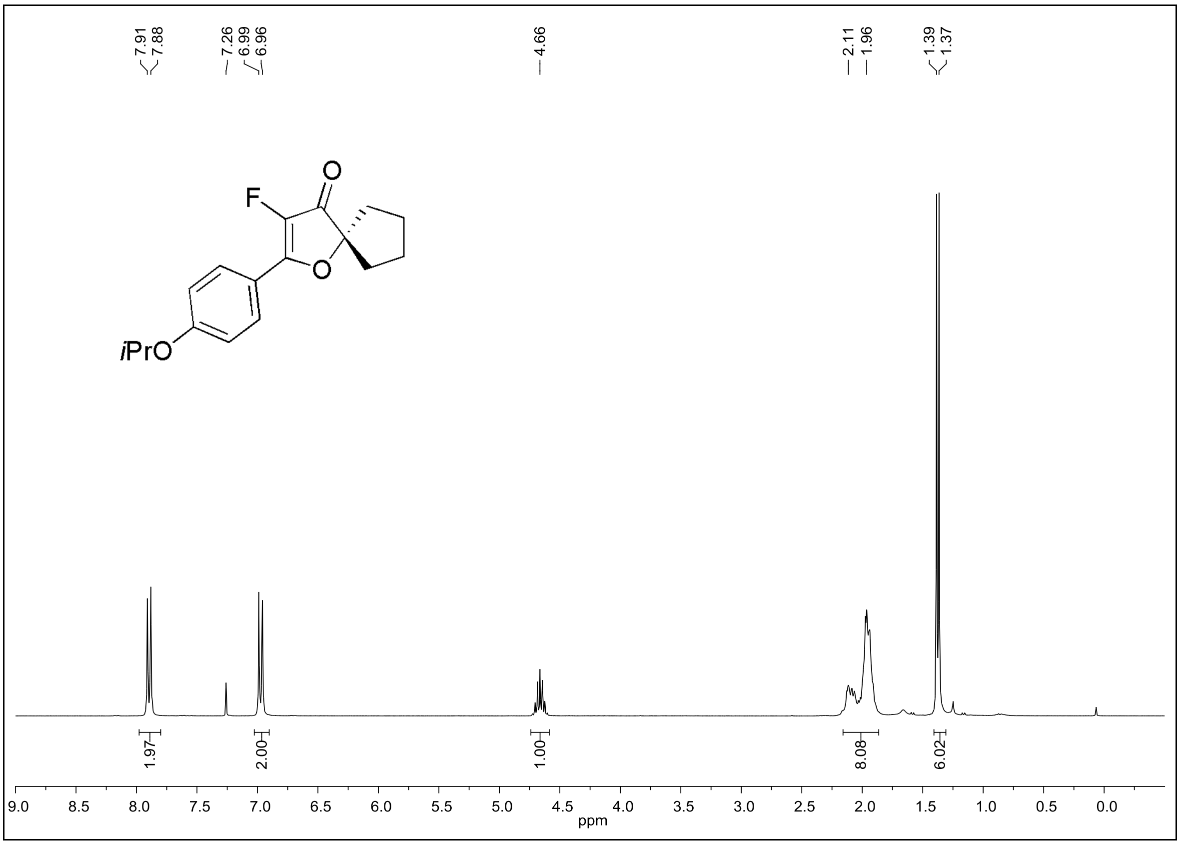


^{13}C NMR

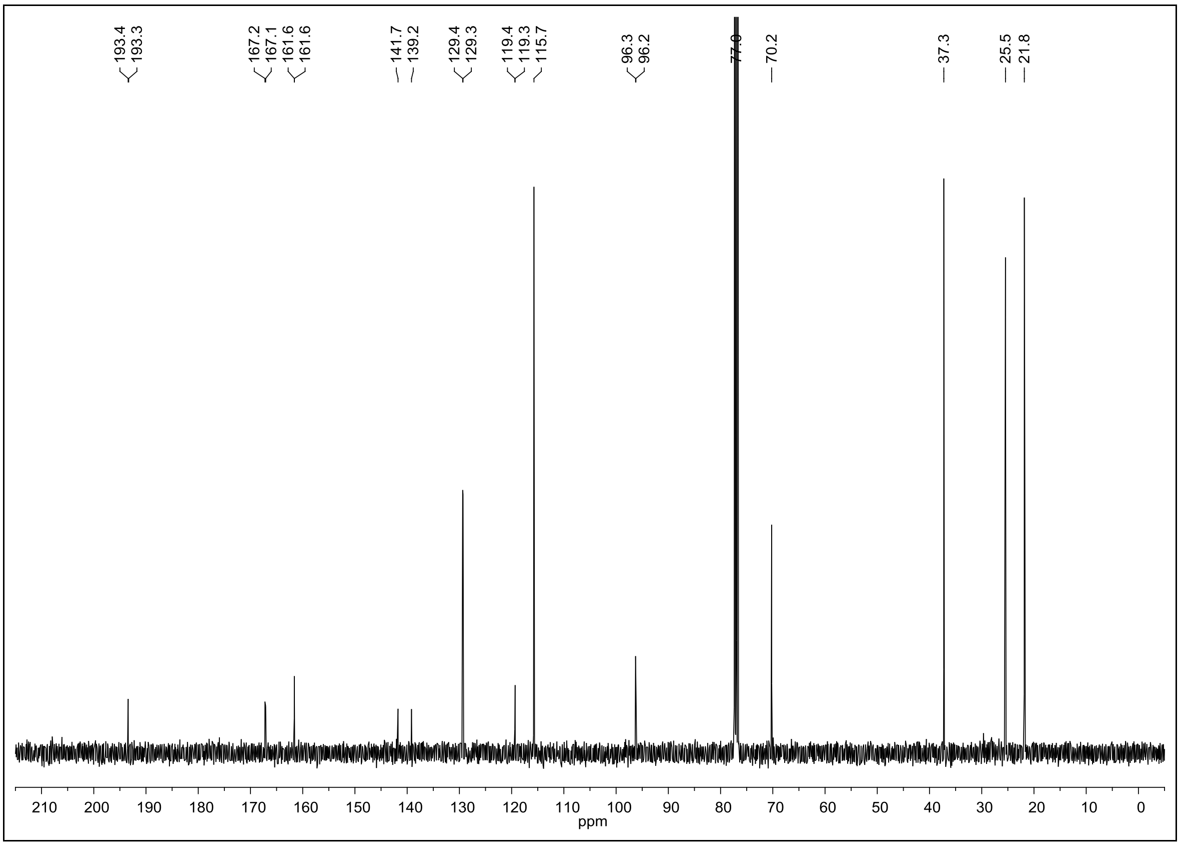


3-Fluoro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (160)

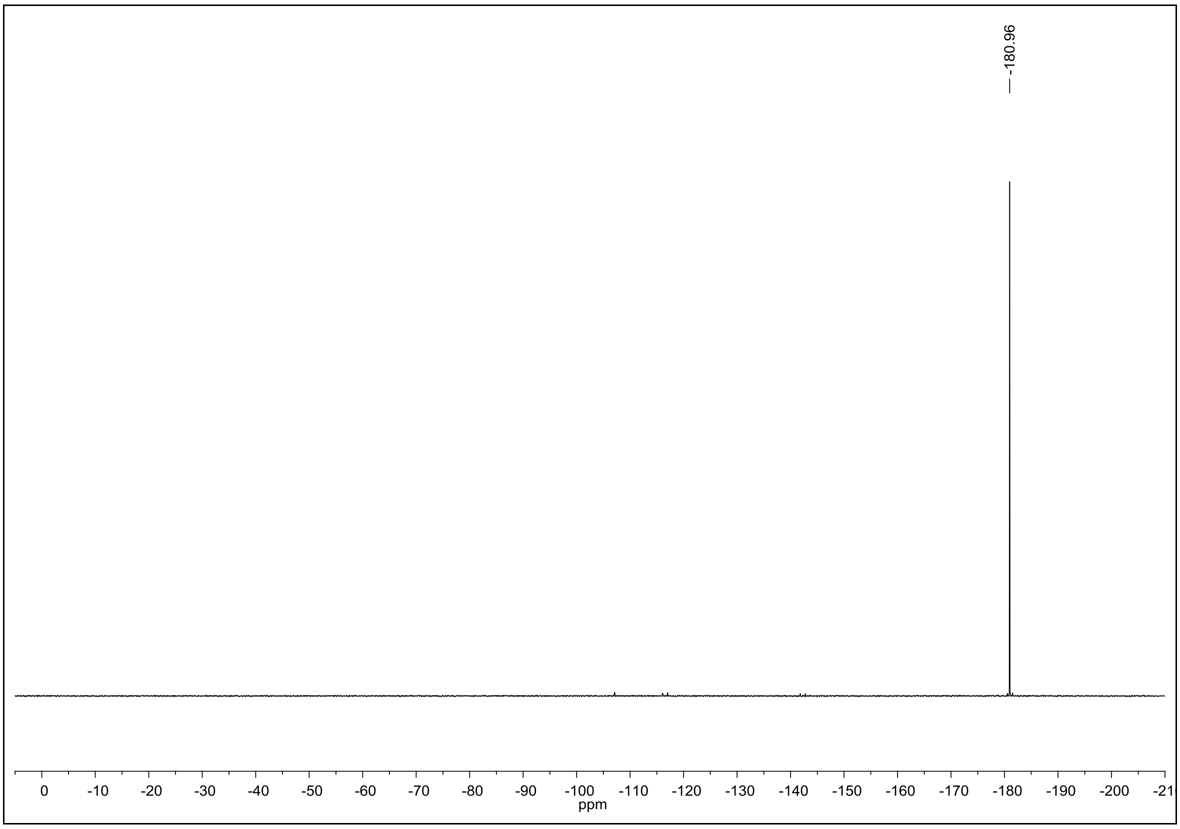
^{1}H NMR



^{13}C NMR



^{19}F NMR


-180.96
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-30
-40
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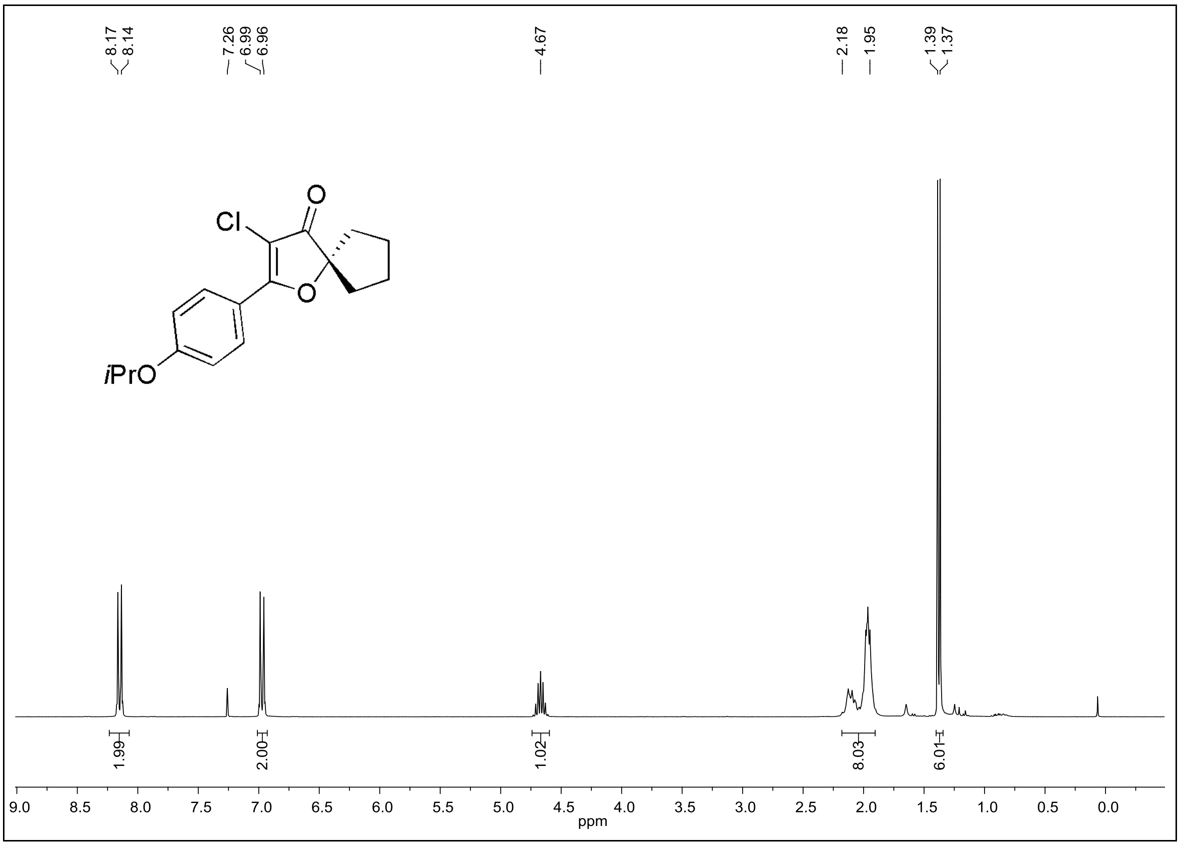
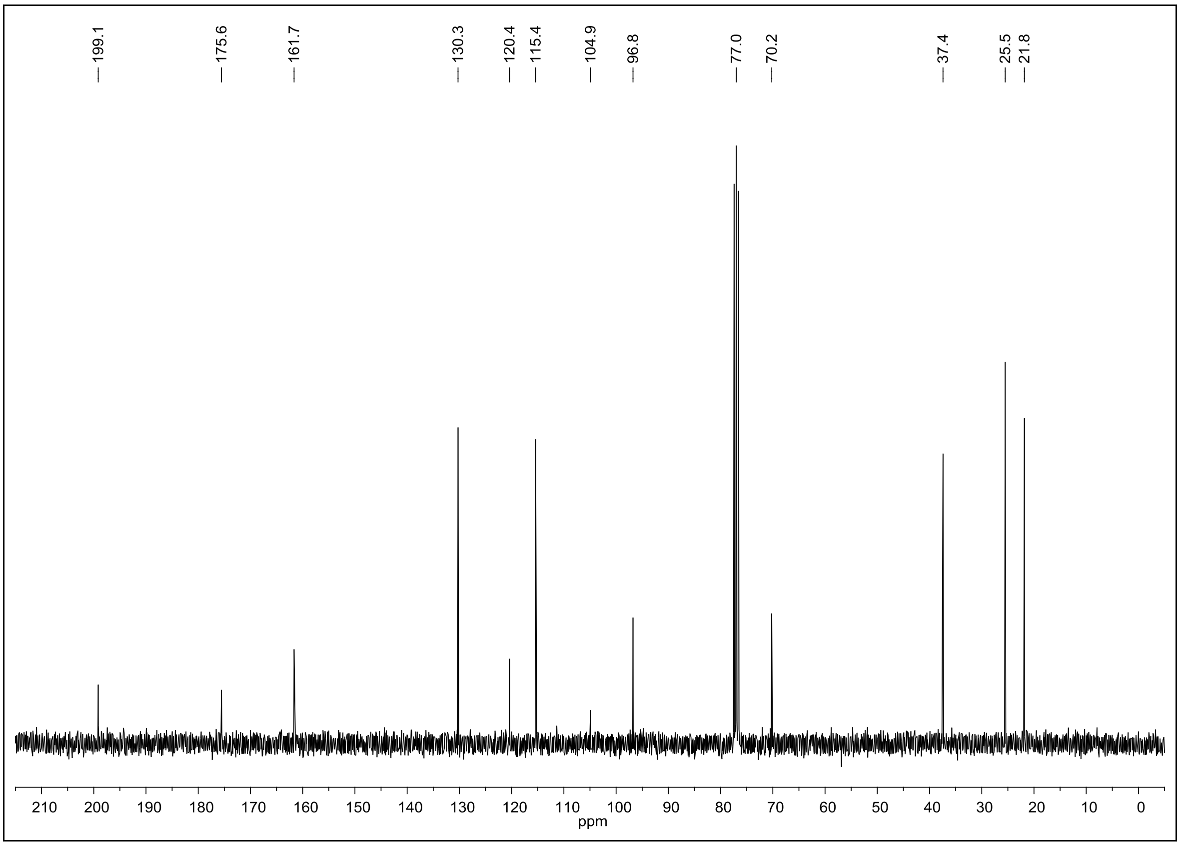
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-21
ppm

3-Chloro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (159)

^{1}H NMR

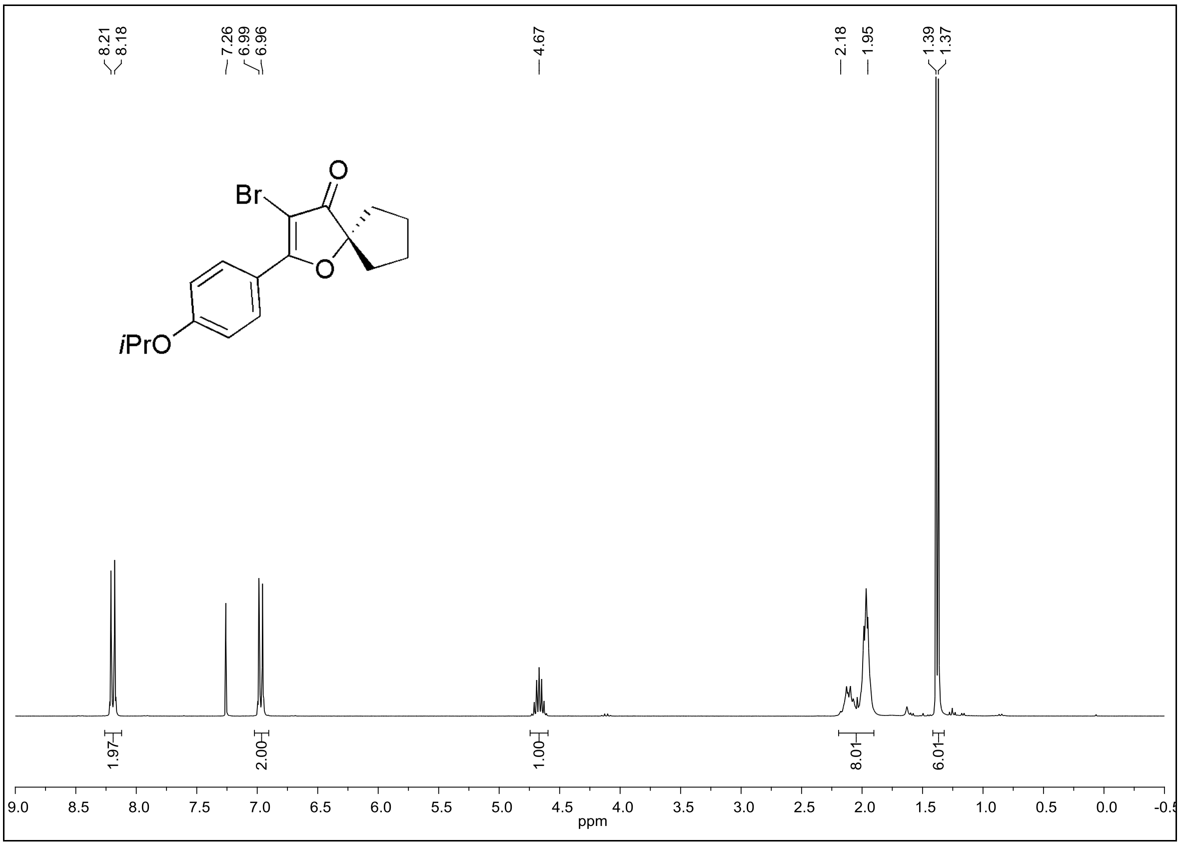


^{13}C NMR

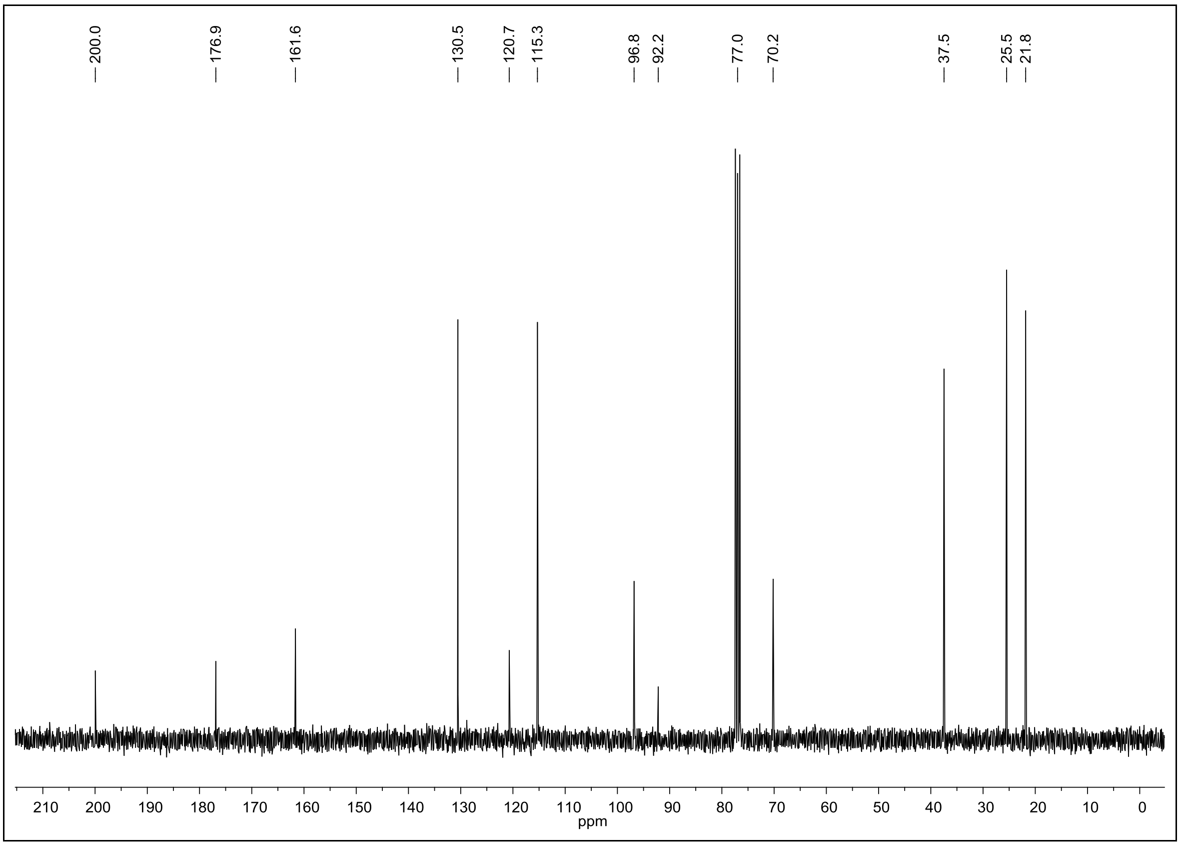


3-Bromo-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (158)

^{1}H NMR

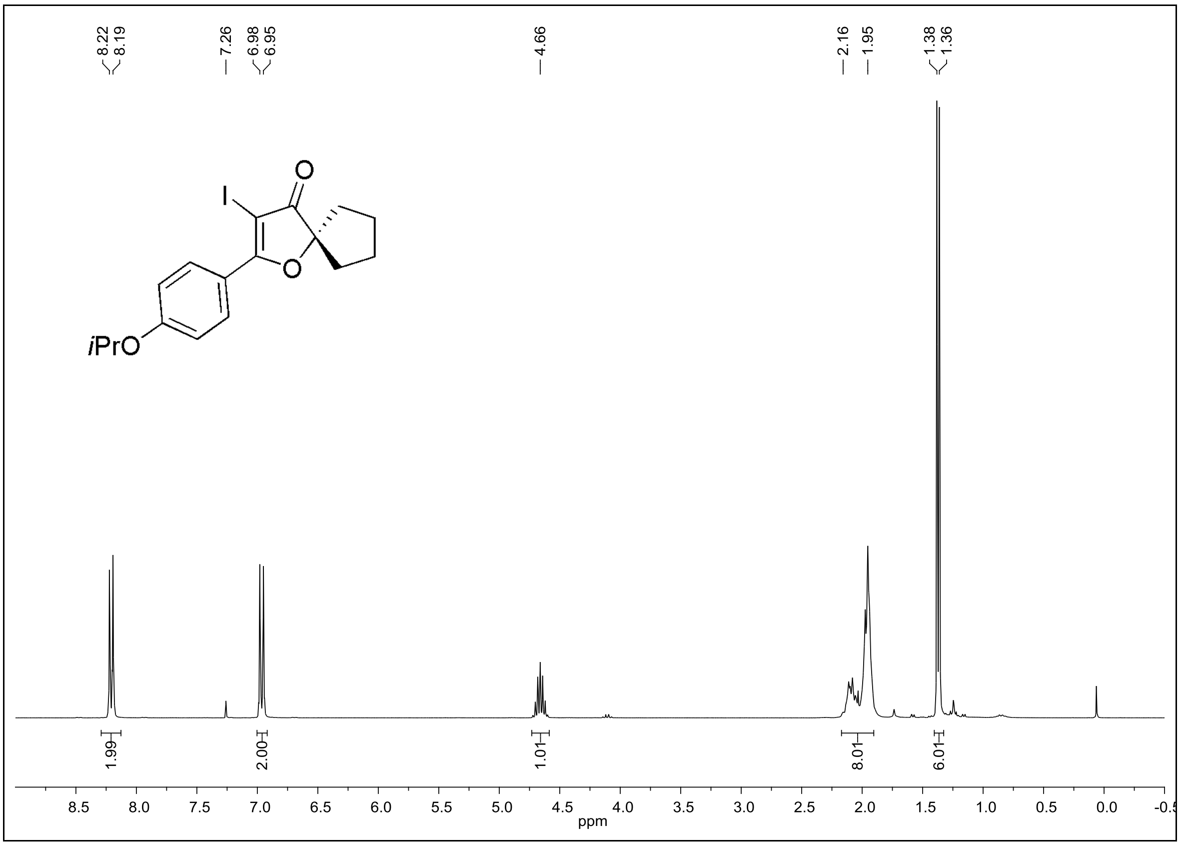


^{13}C NMR

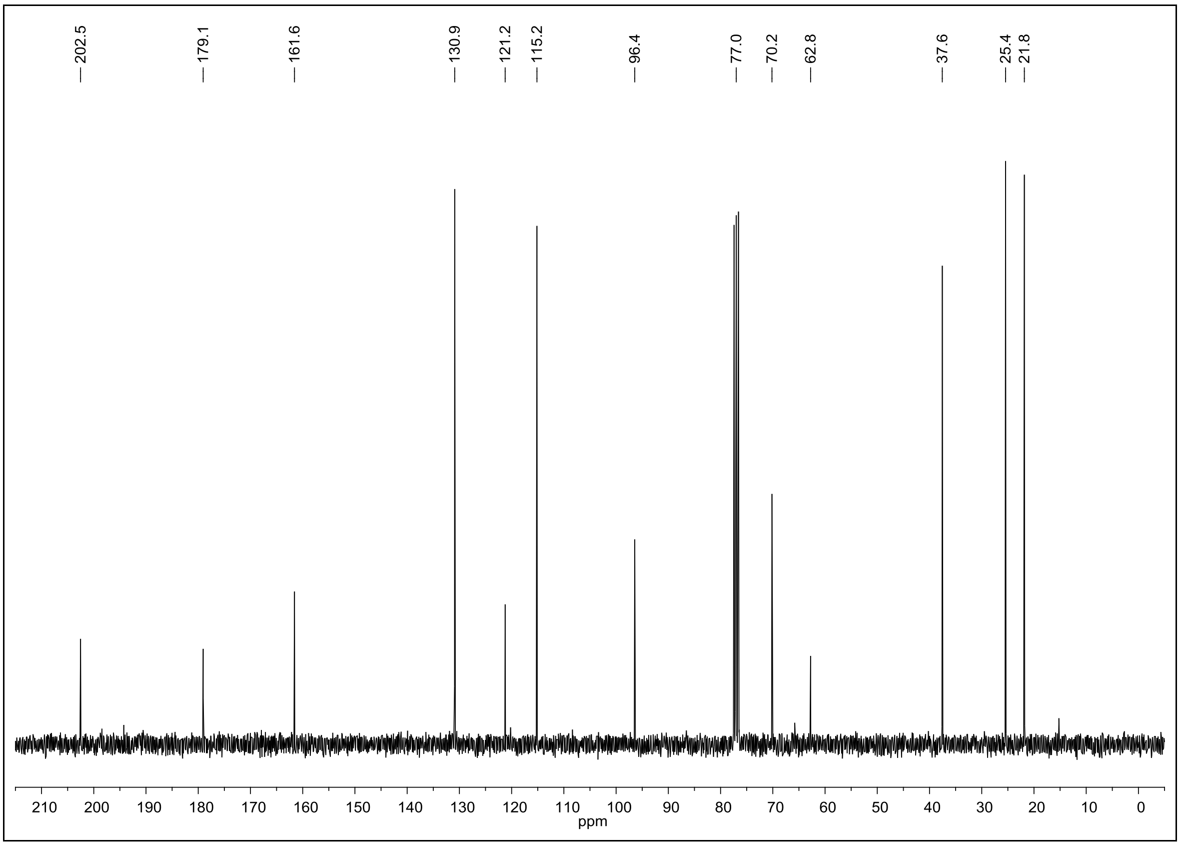


3-Iodo-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (157)

^{1}H NMR

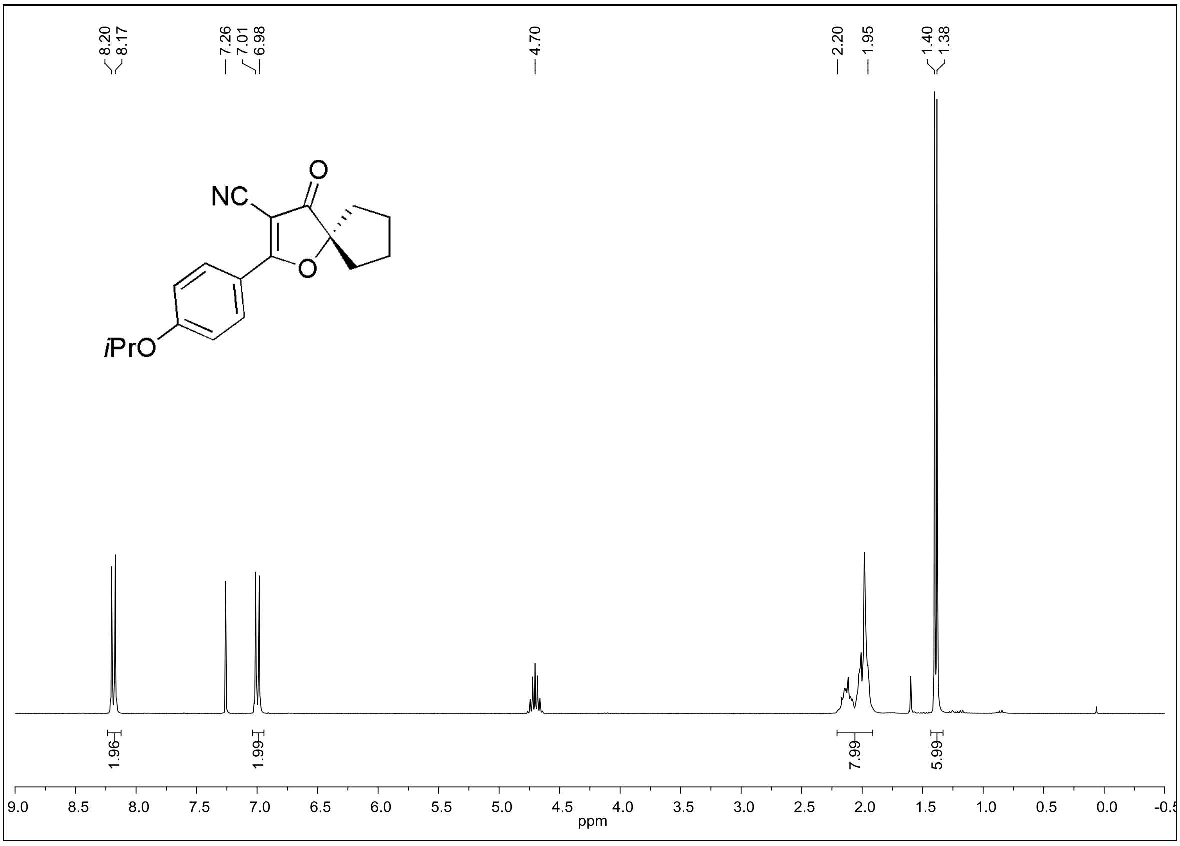


^{13}C NMR

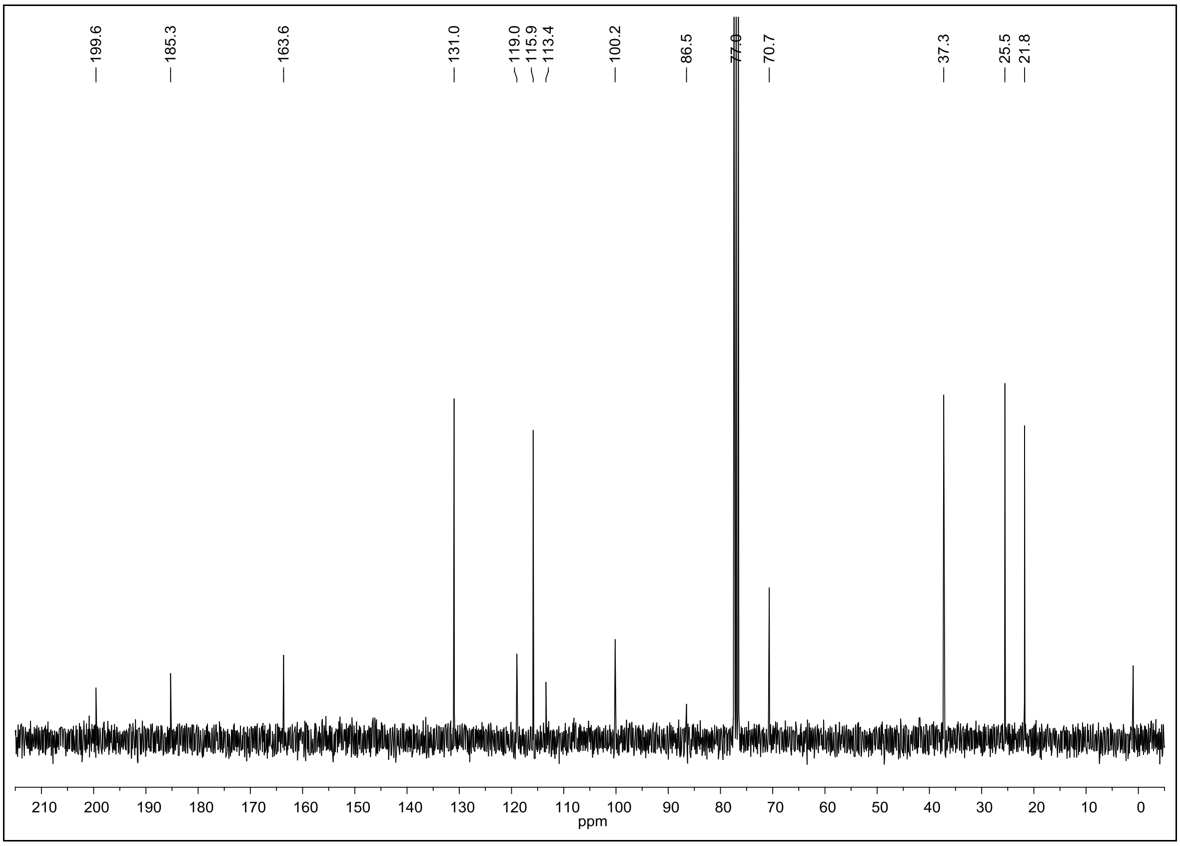


2-(4-Isopropoxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carbonitrile (172)

^{1}H NMR

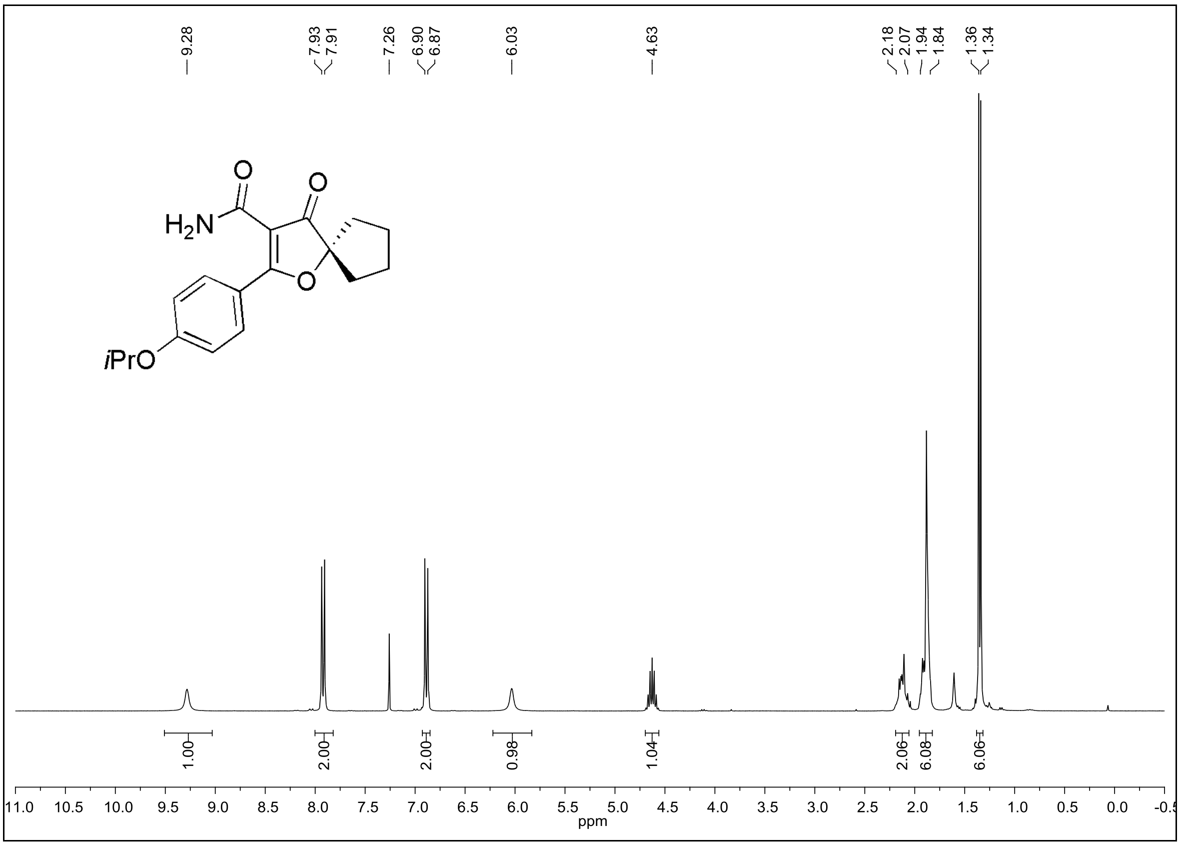


^{13}C NMR

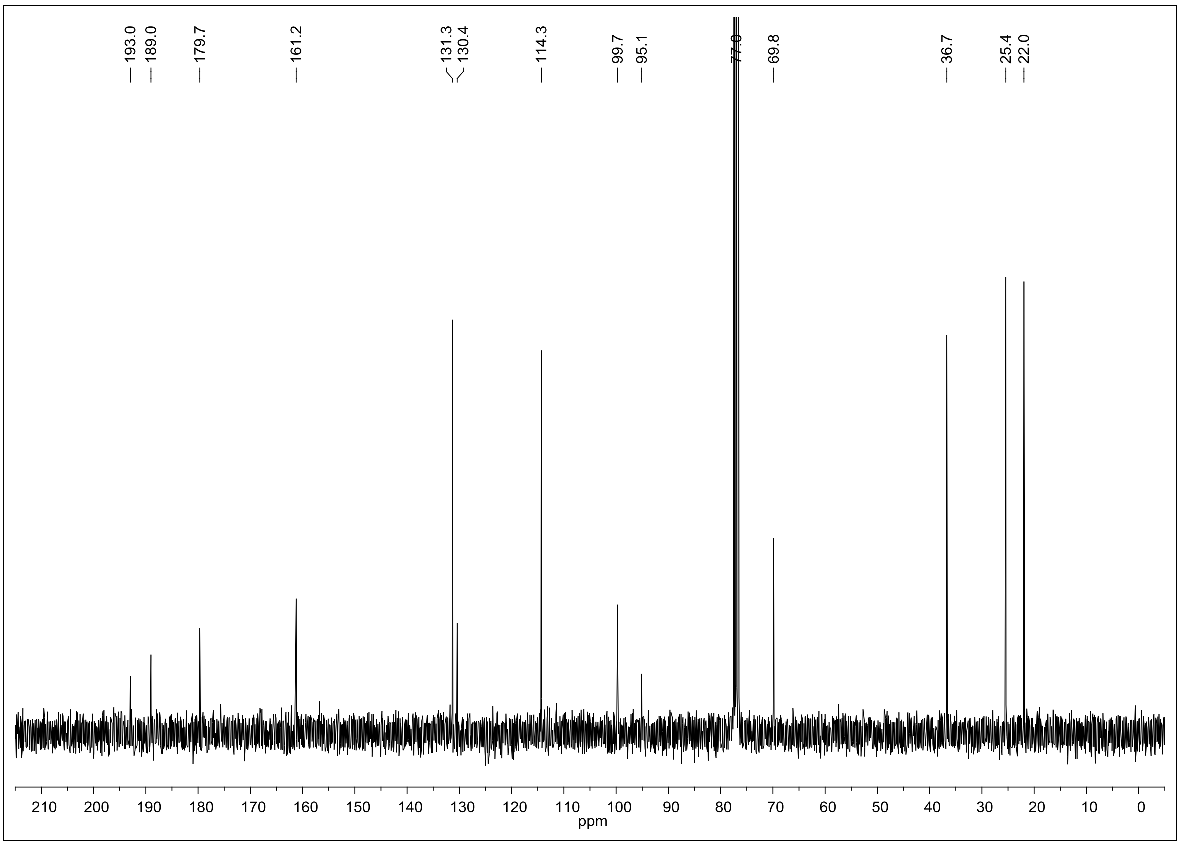


2-(4-Isopropoxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carboxylic acid amide (173)

^{1}H NMR

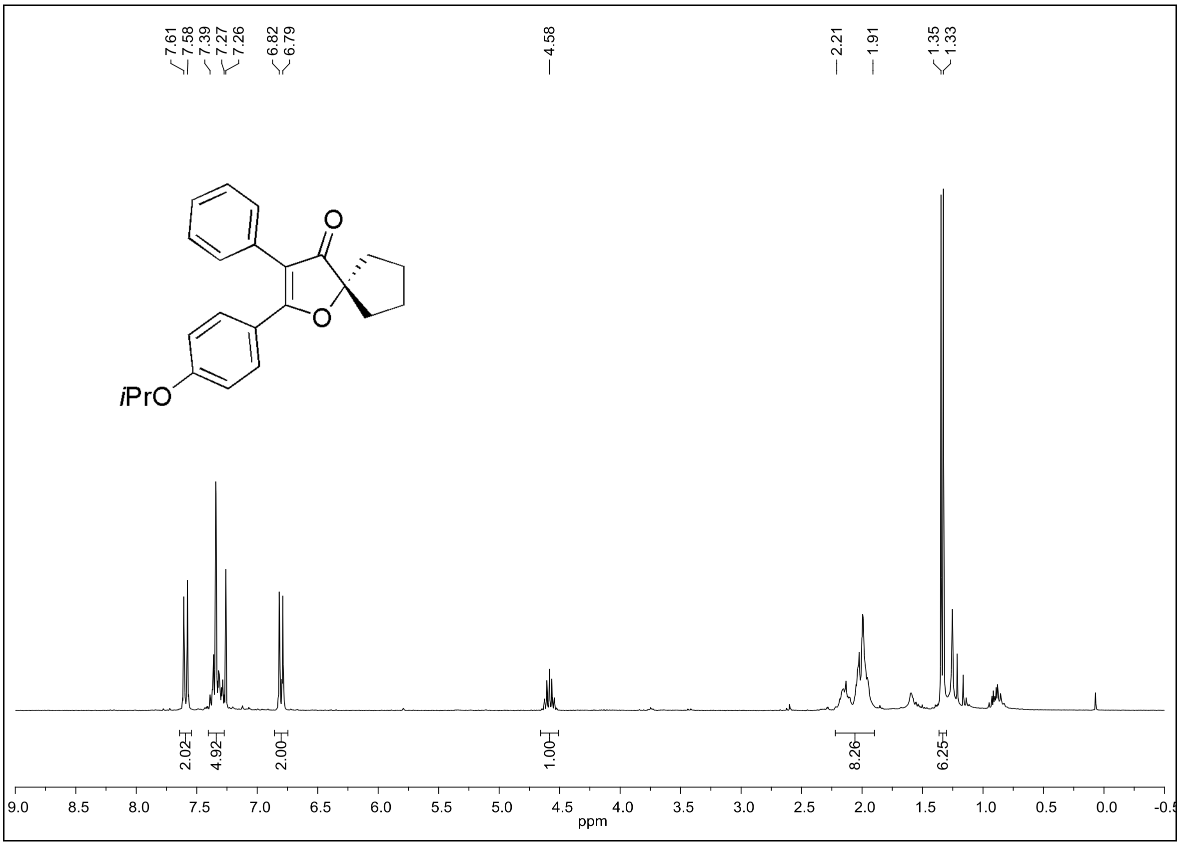


^{13}C NMR

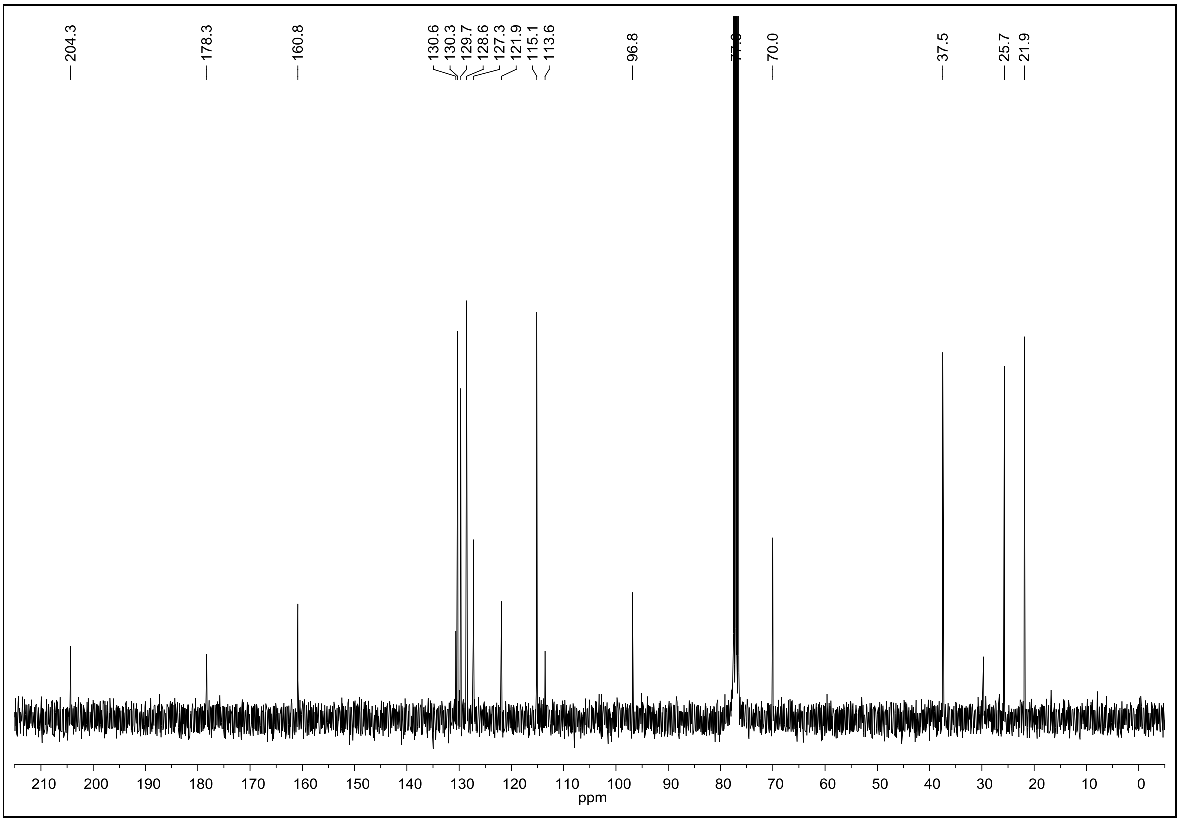


2-(4-Isopropoxy-phenyl)-3-phenyl-1-oxa-spiro[4.4]non-2-en-4-one (171)

^{1}H NMR

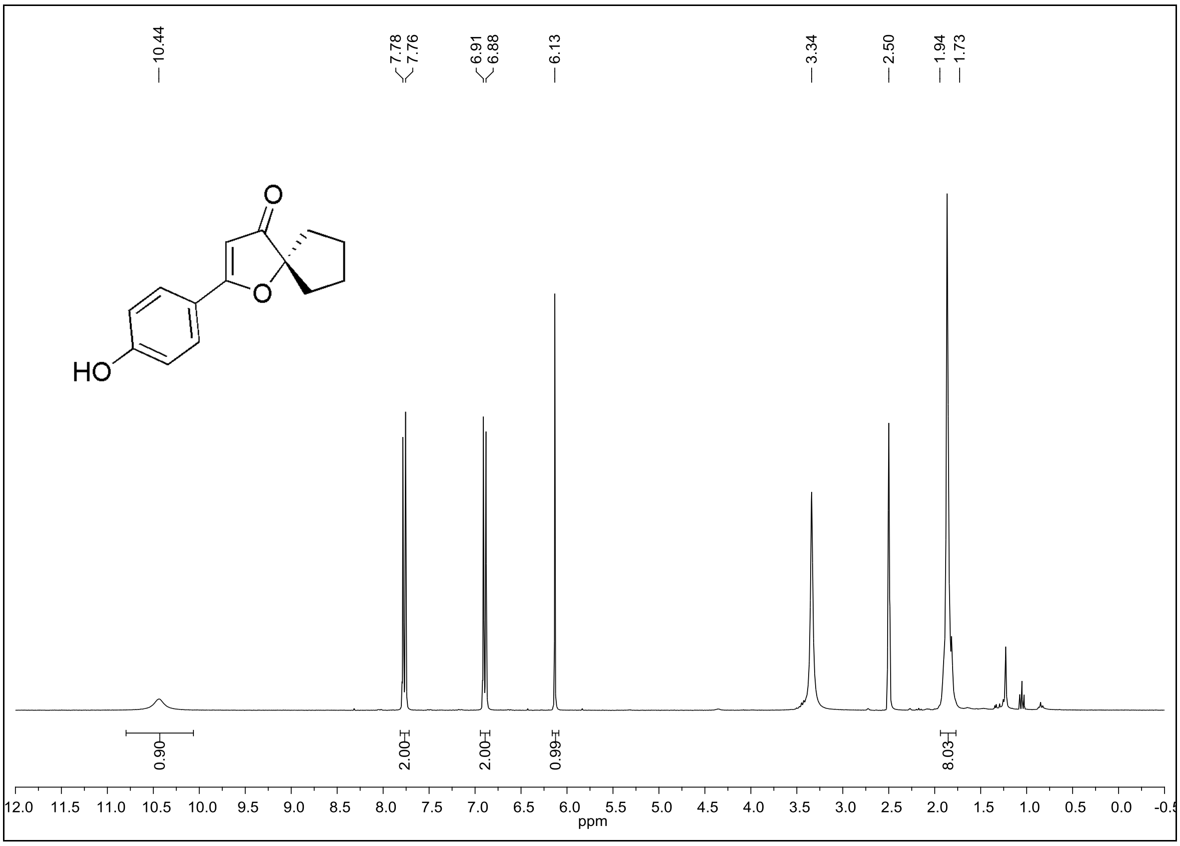


^{13}C NMR

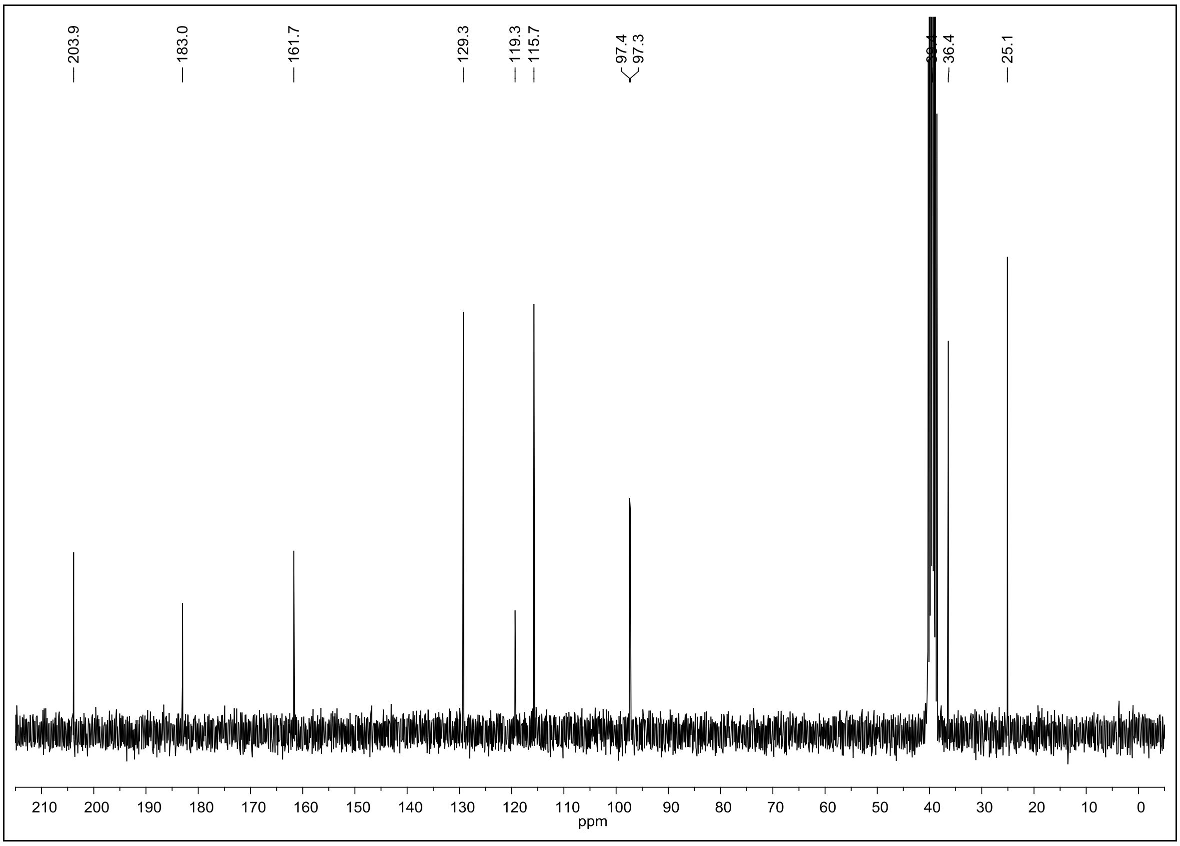


2-(4-Hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (146)

^{1}H NMR

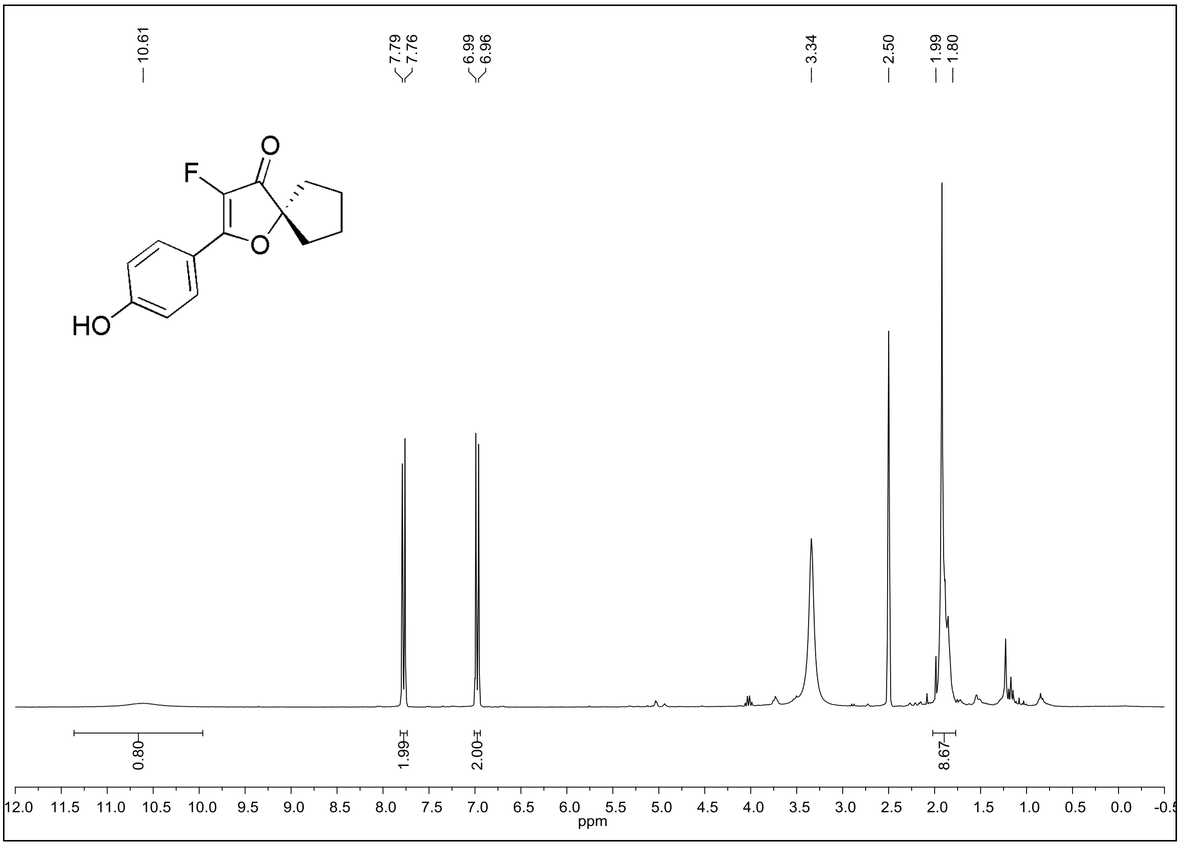


^{13}C NMR

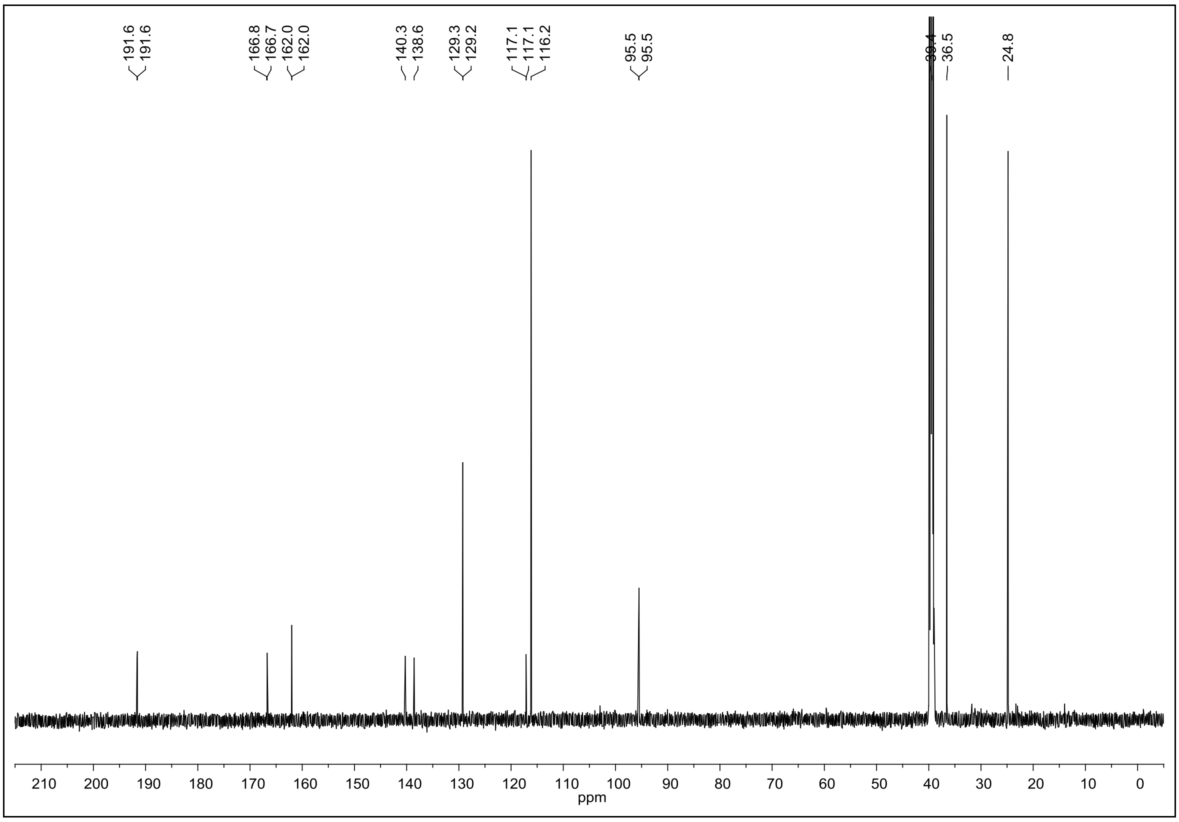


3-Fluoro-2-(4-hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (199)

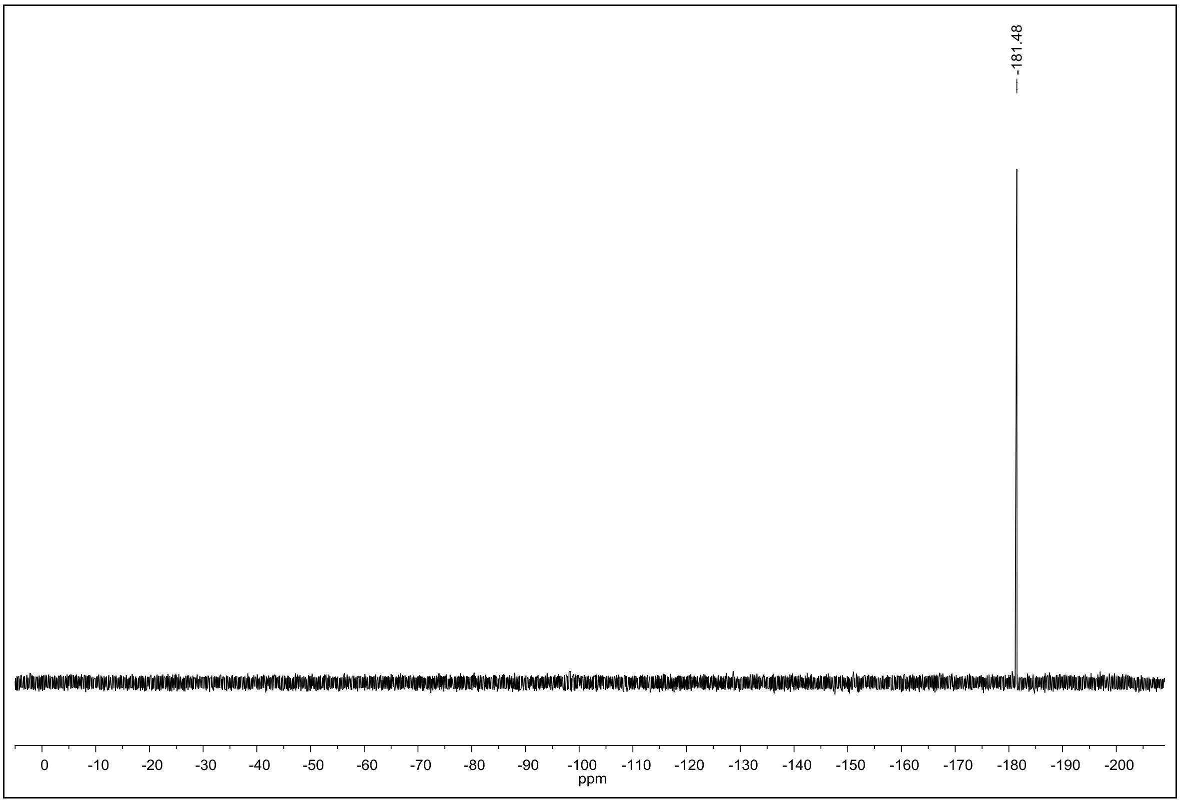
^{1}H NMR



^{13}C NMR



^{19}F NMR


-181.48
0
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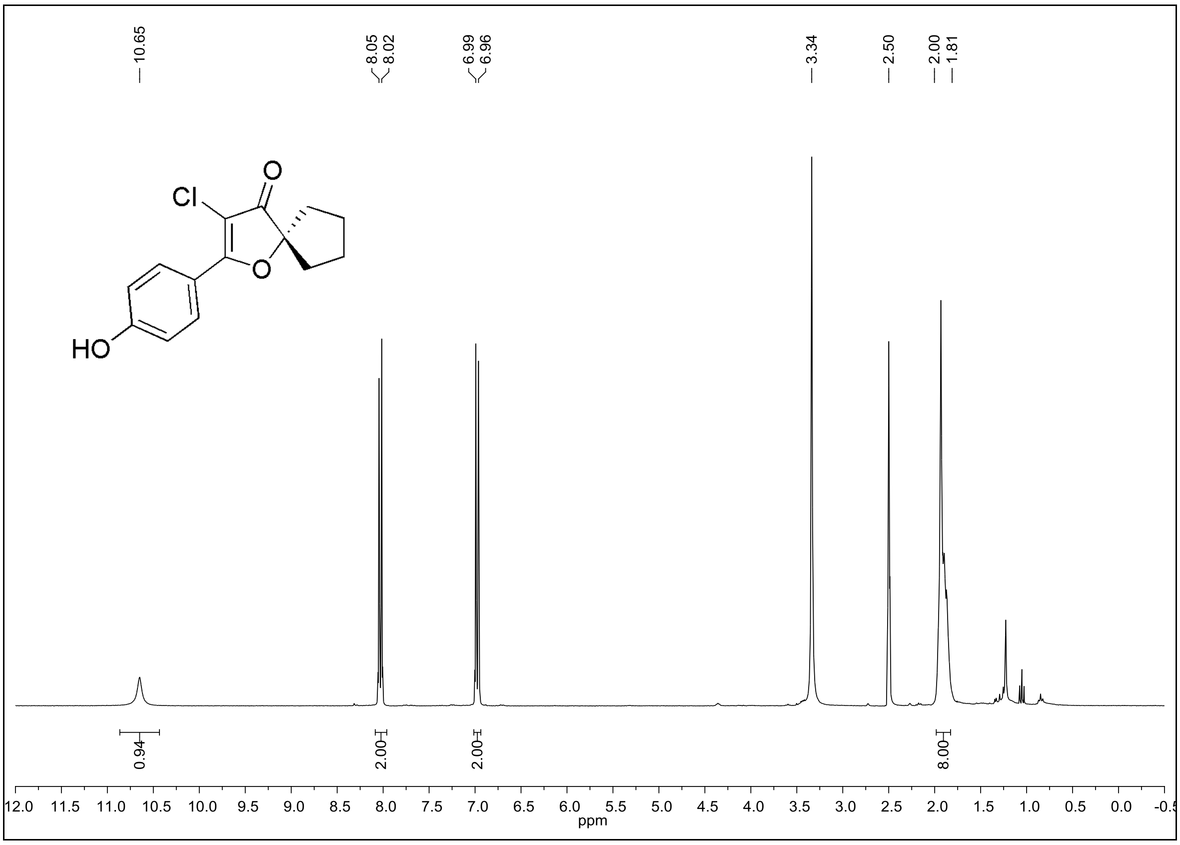
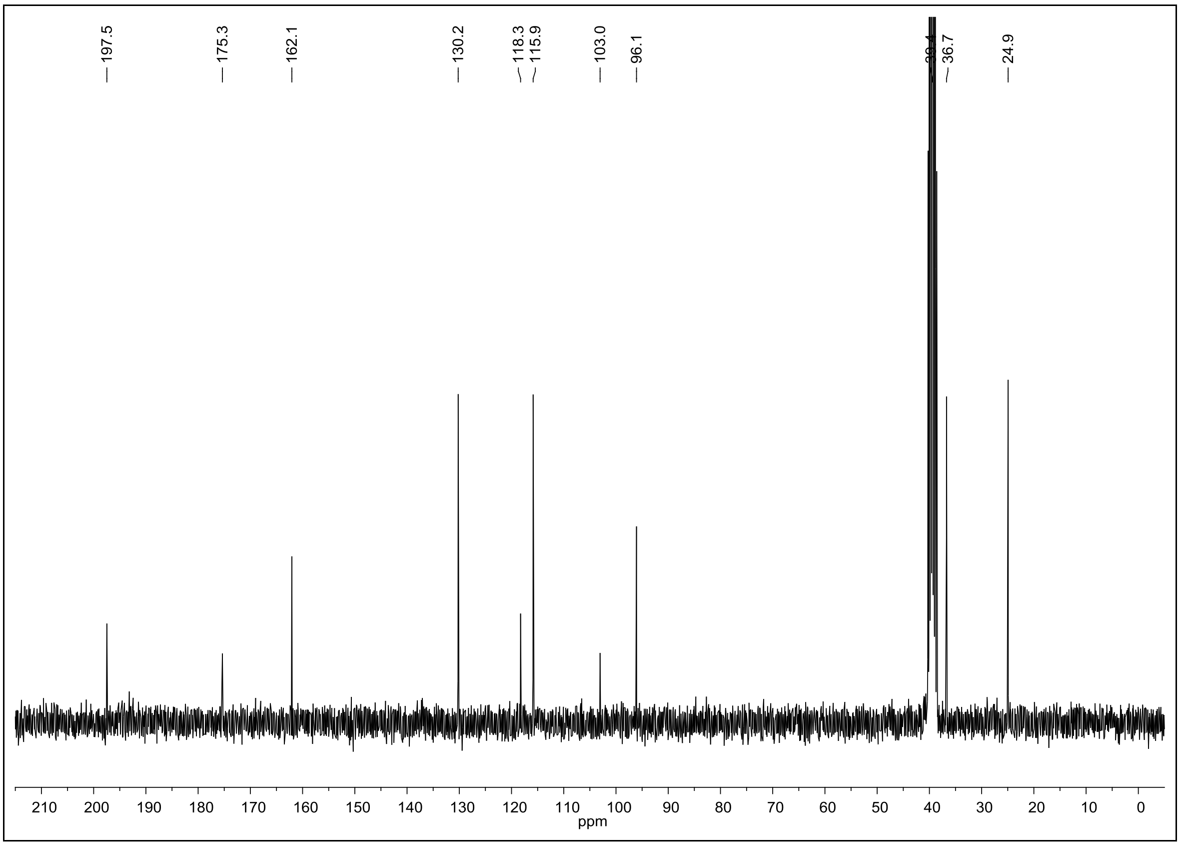
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
ppm

3-Chloro-2-(4-hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (200)

^{1}H NMR

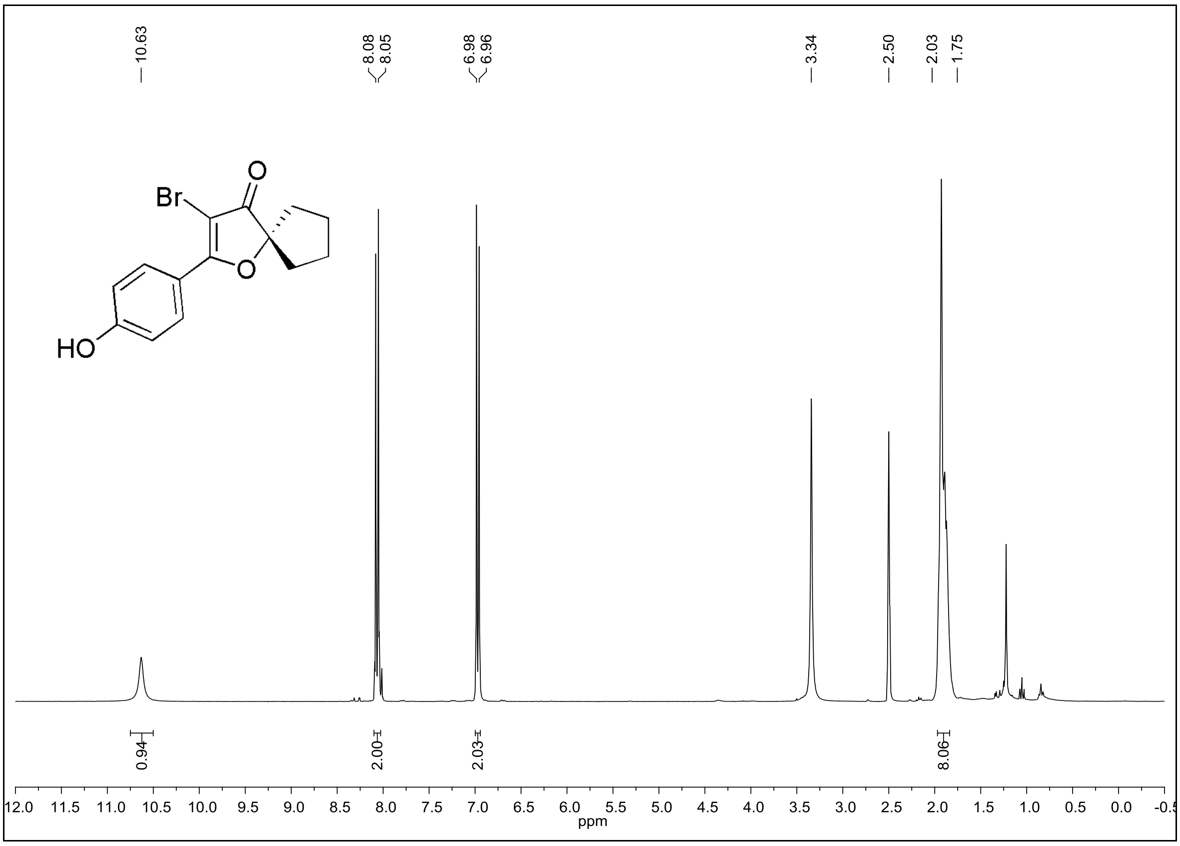


^{13}C NMR

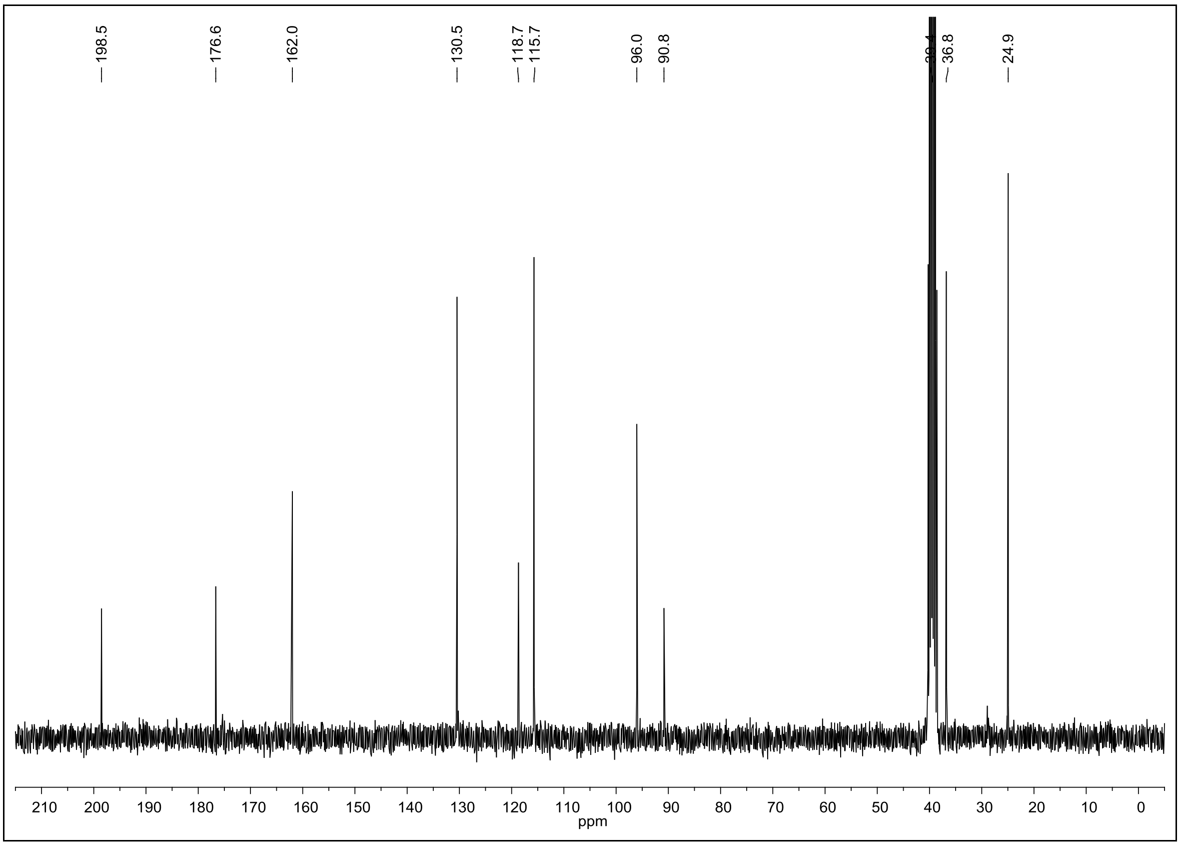


3-Bromo-2-(4-hydroxy-phenyl)-1-oxa-spiro[4.4]non-2-en-4-one (201)

^{1}H NMR

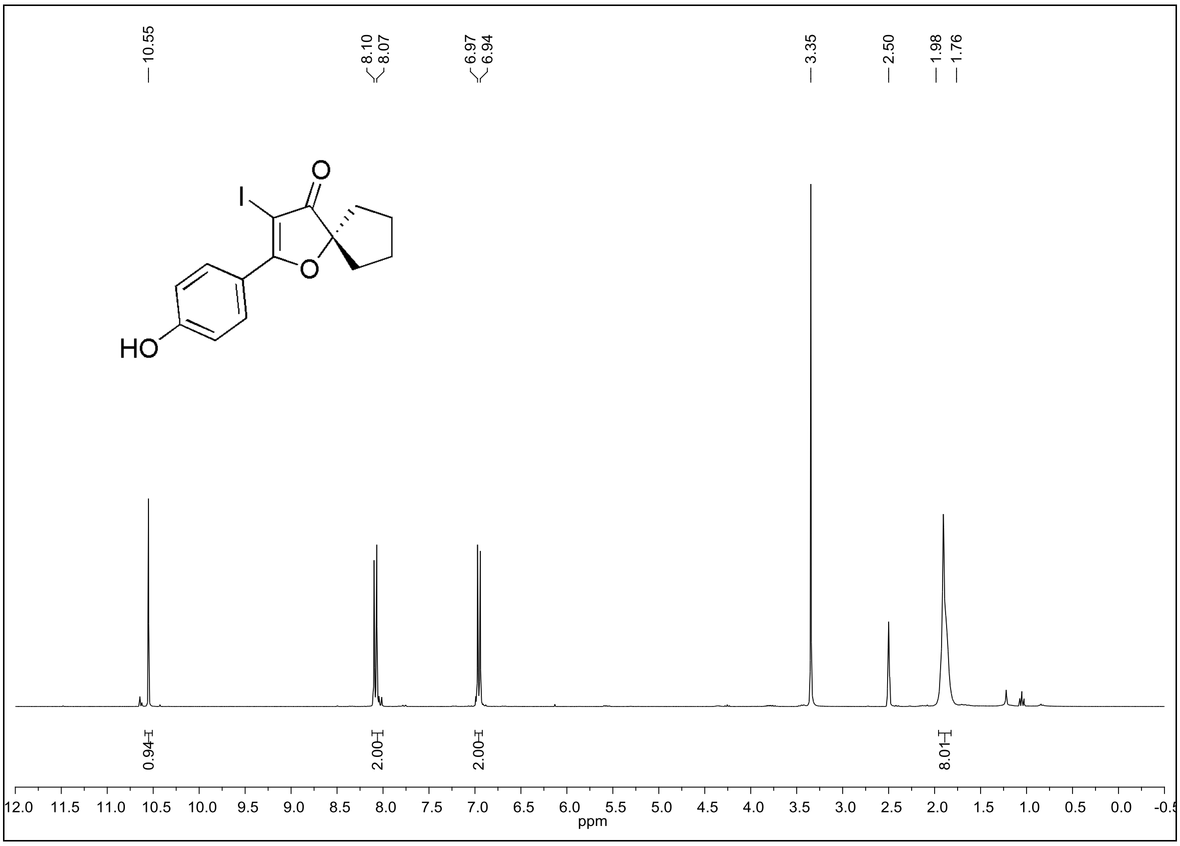


^{13}C NMR

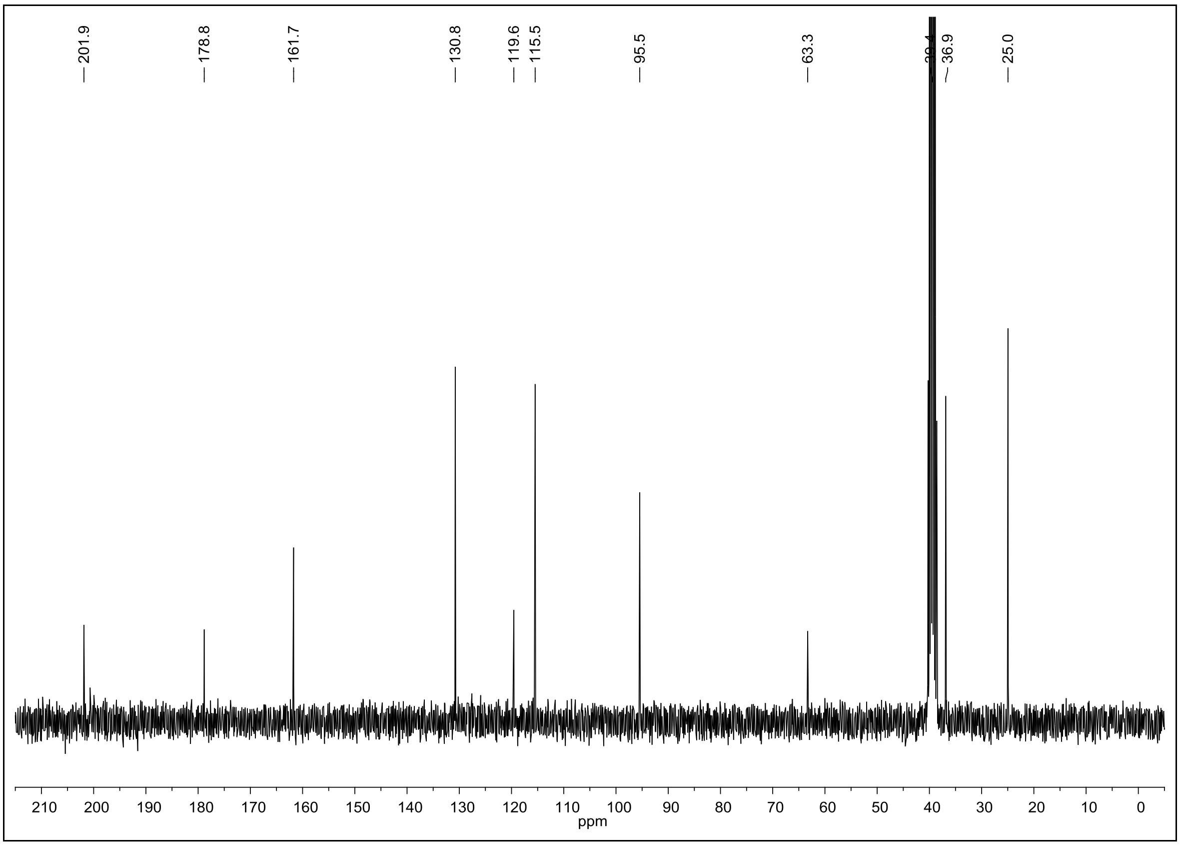


2-(4-Hydroxy-phenyl)-3-iodo-1-oxa-spiro[4.4]non-2-en-4-one (202)

^{1}H NMR

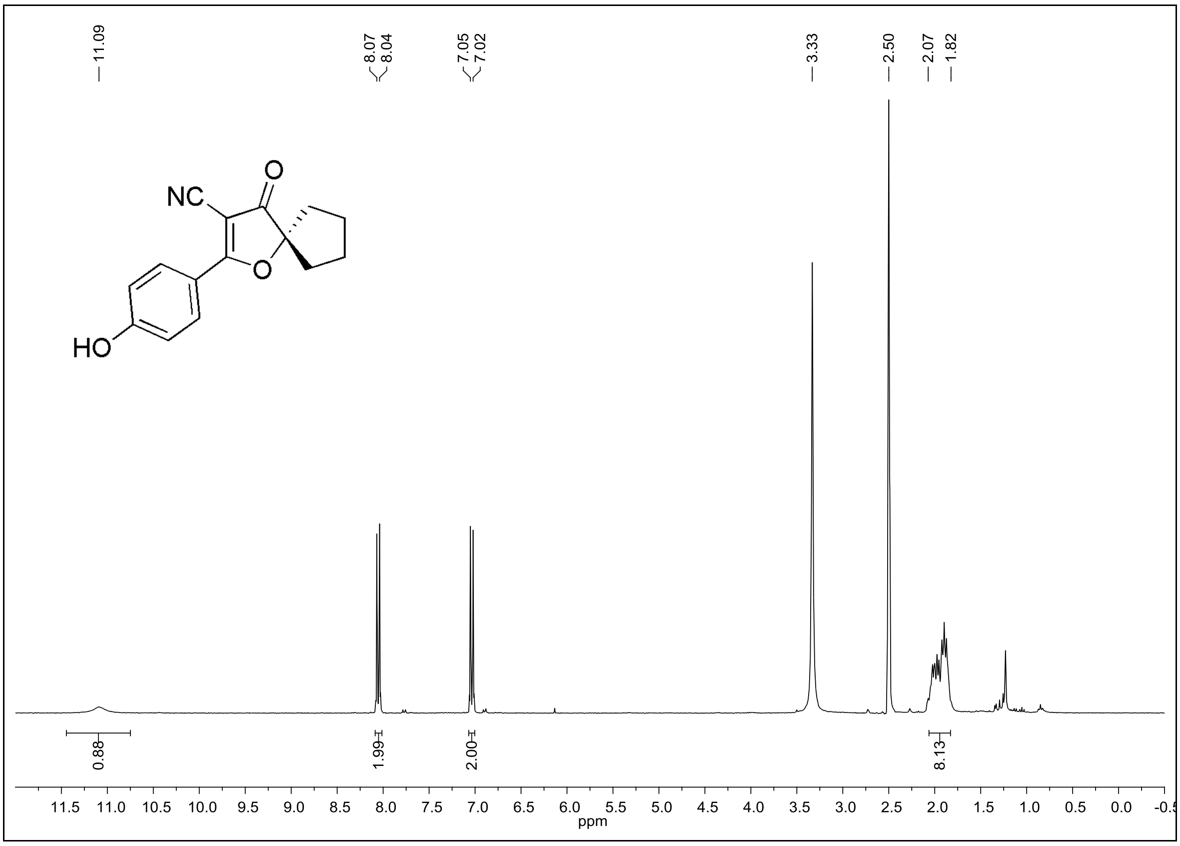


^{13}C NMR

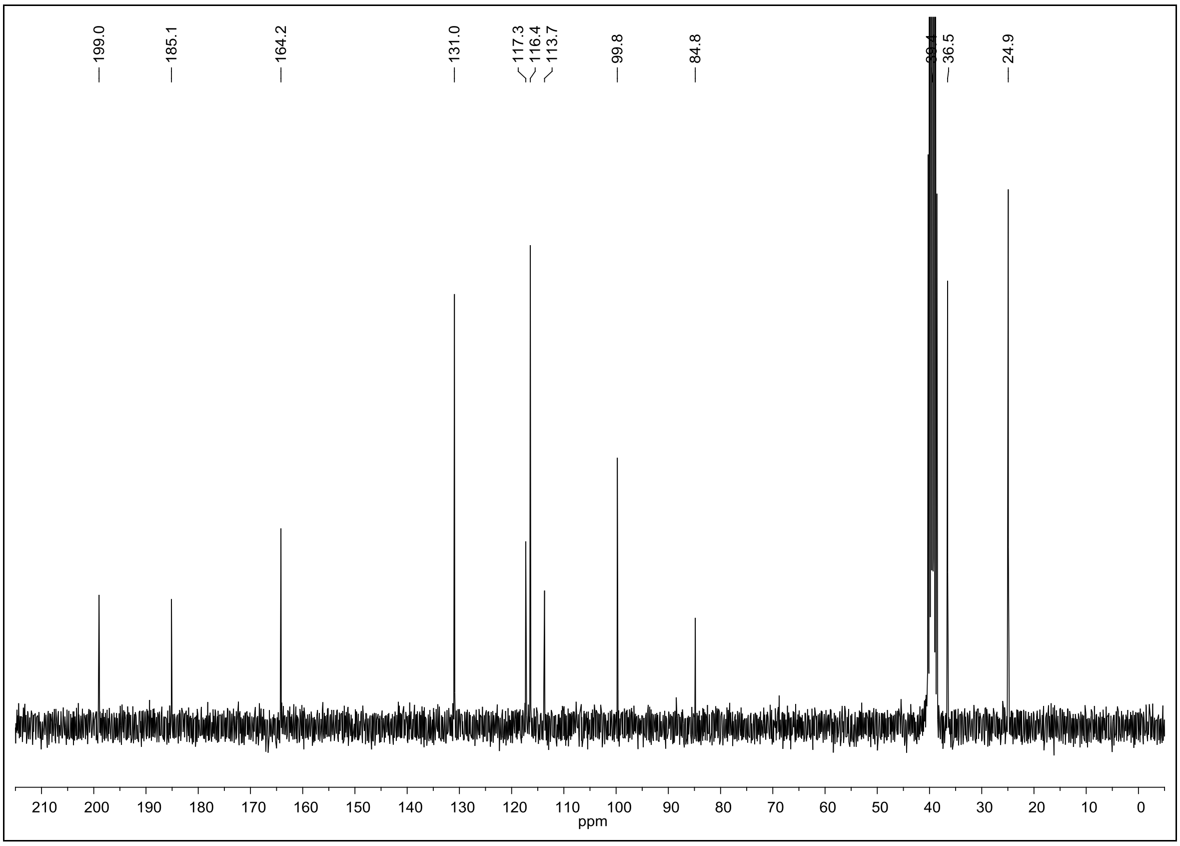


2-(4-Hydroxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carbonitrile (203)

^{1}H NMR

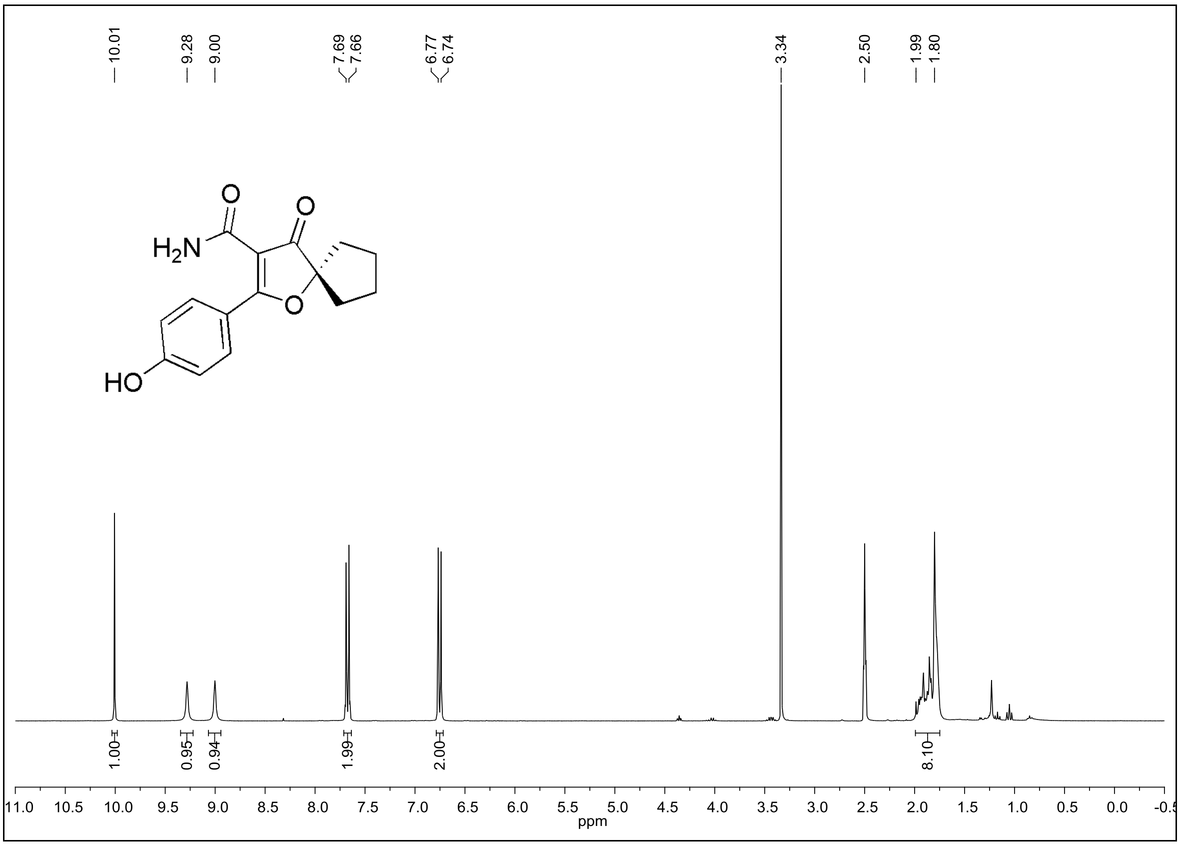


^{13}C NMR

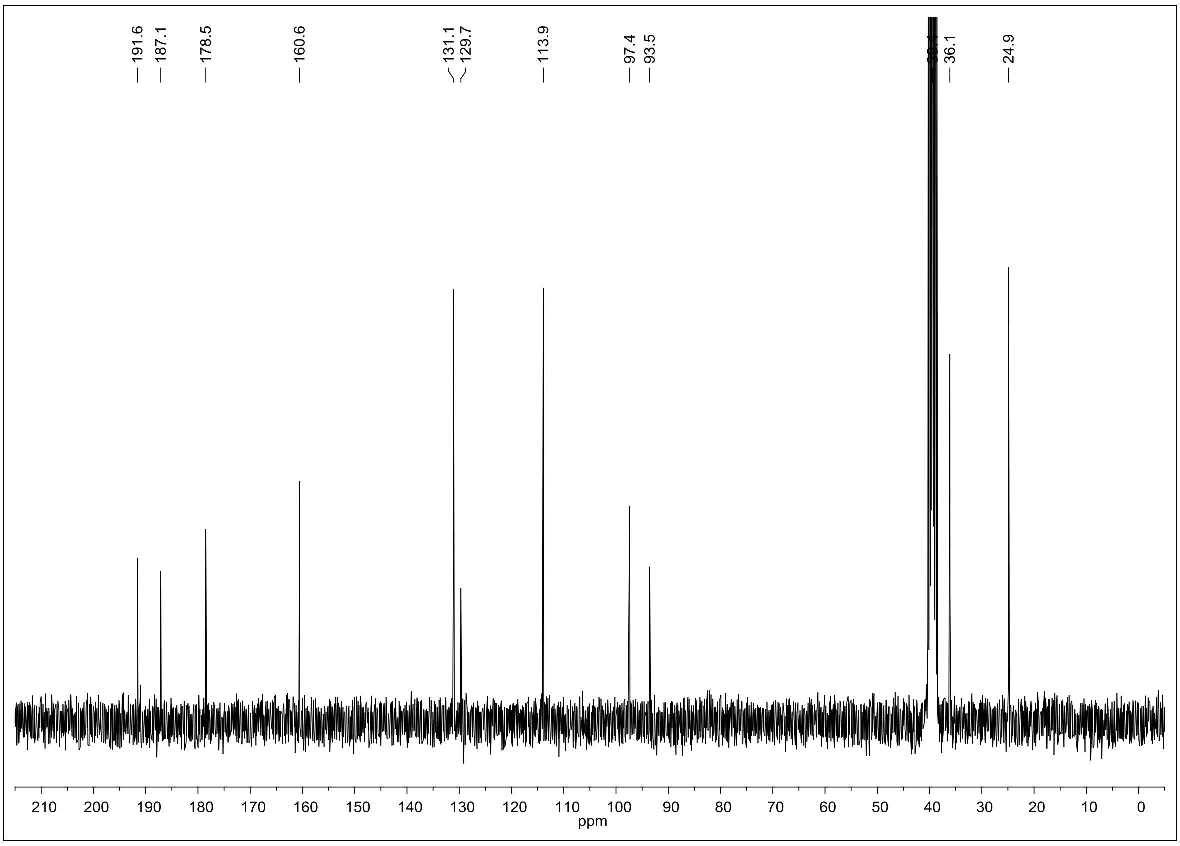


2-(4-Hydroxy-phenyl)-4-oxo-1-oxa-spiro[4.4]non-2-ene-3-carboxylic acid amide (205)

^{1}H NMR

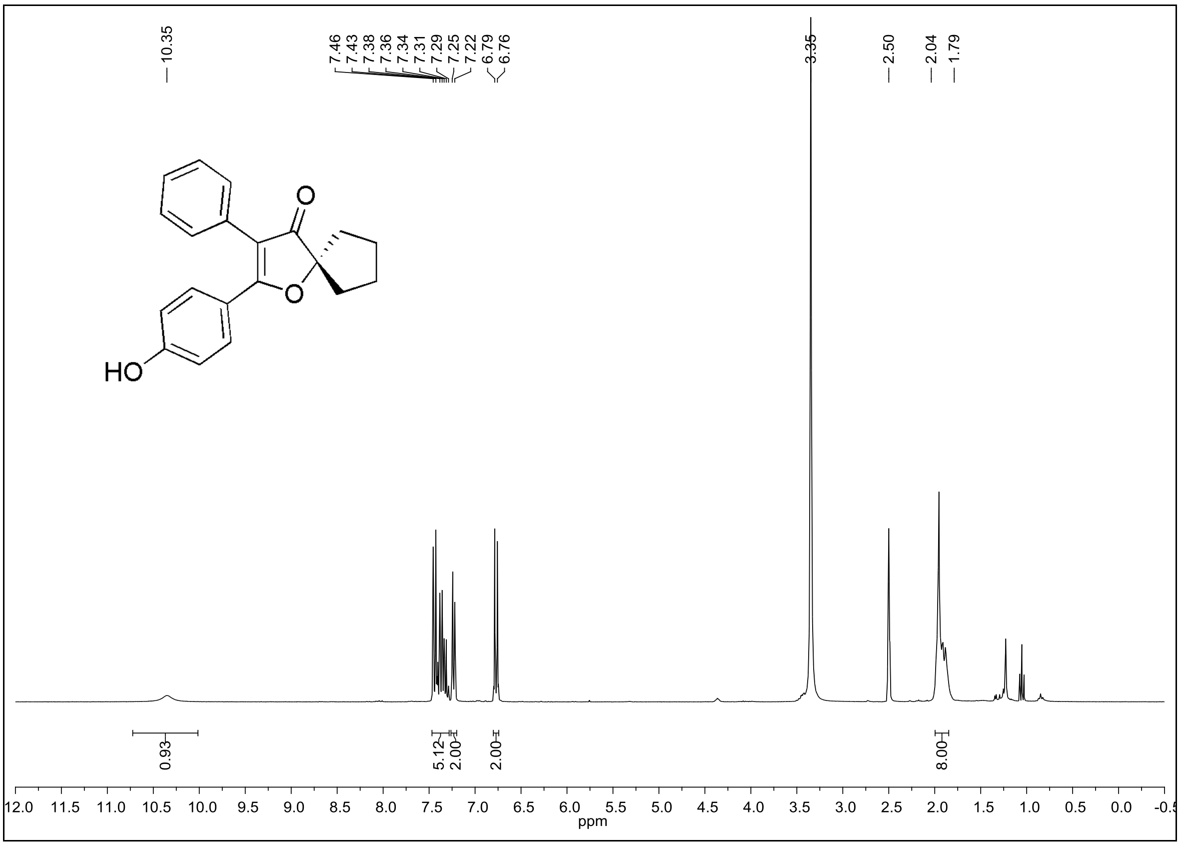


^{13}C NMR

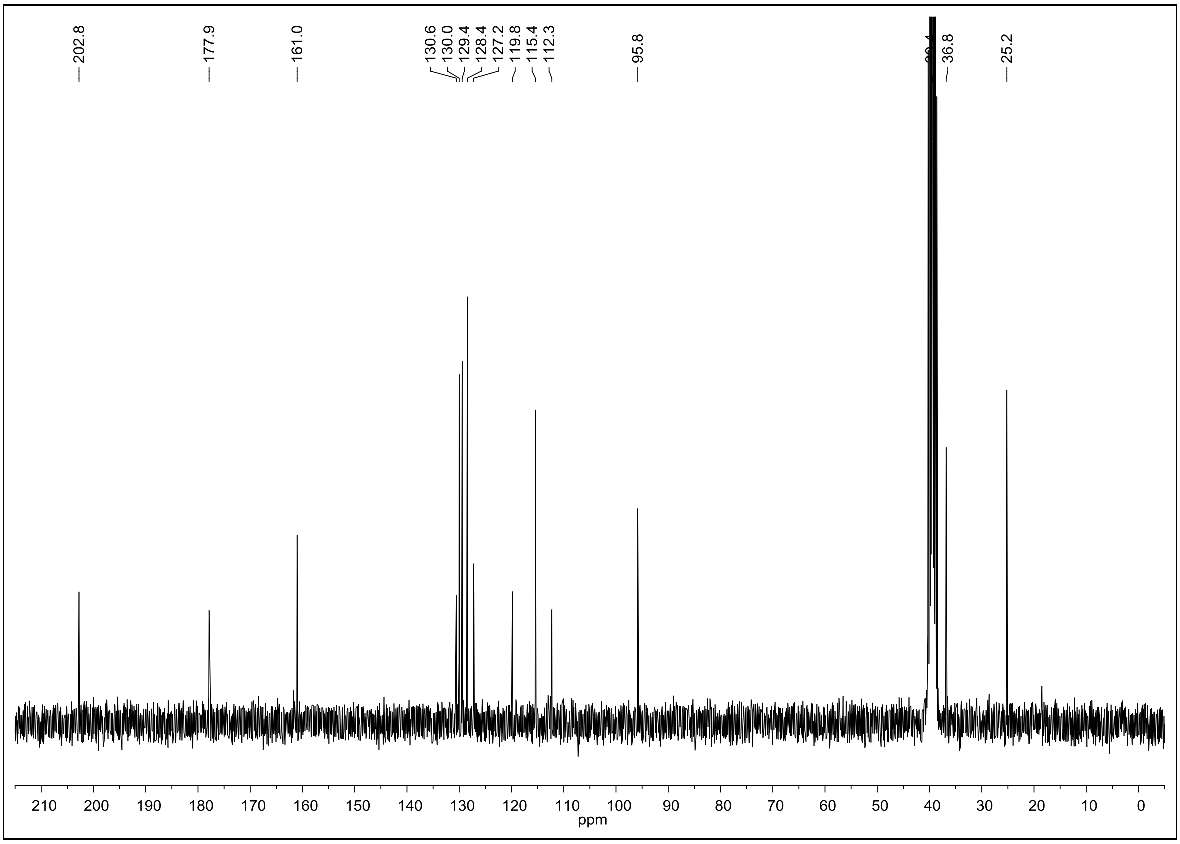


2-(4-Hydroxy-phenyl)-3-phenyl-1-oxa-spiro[4.4]non-2-en-4-one (204)

^{1}H NMR

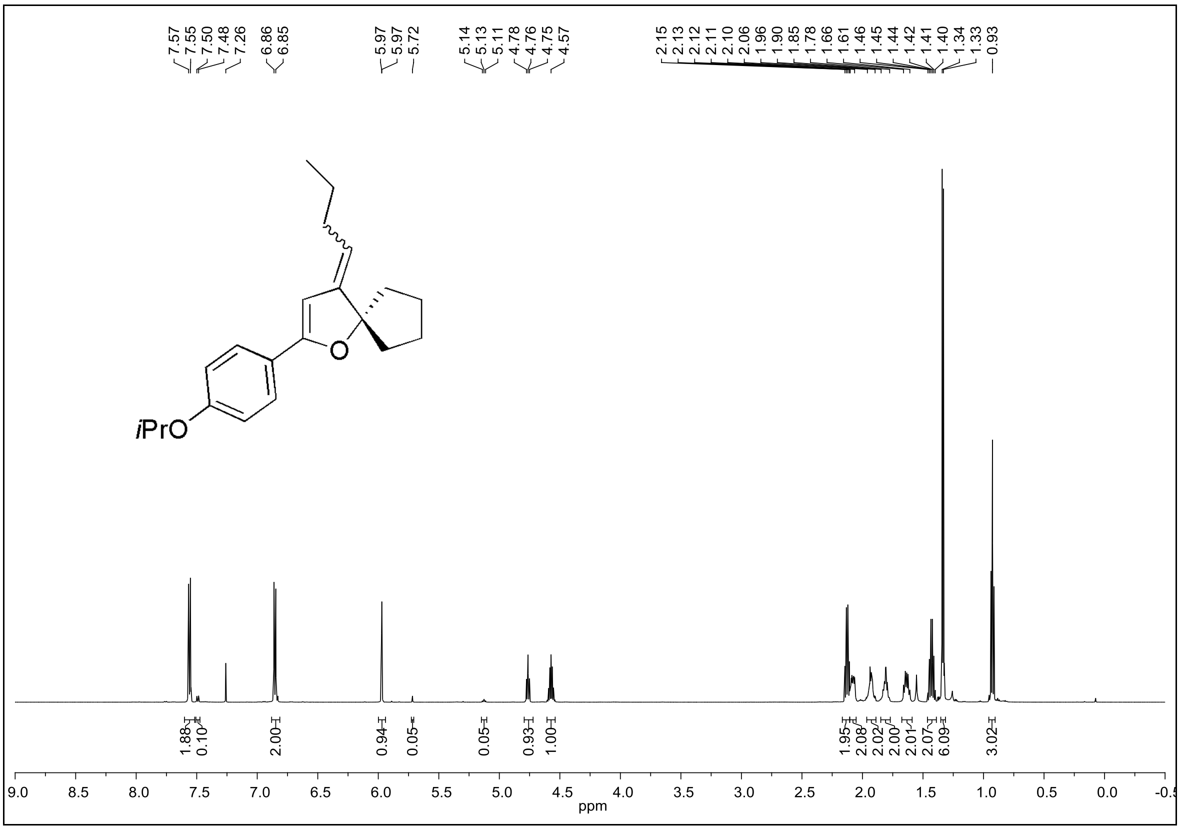


^{13}C NMR

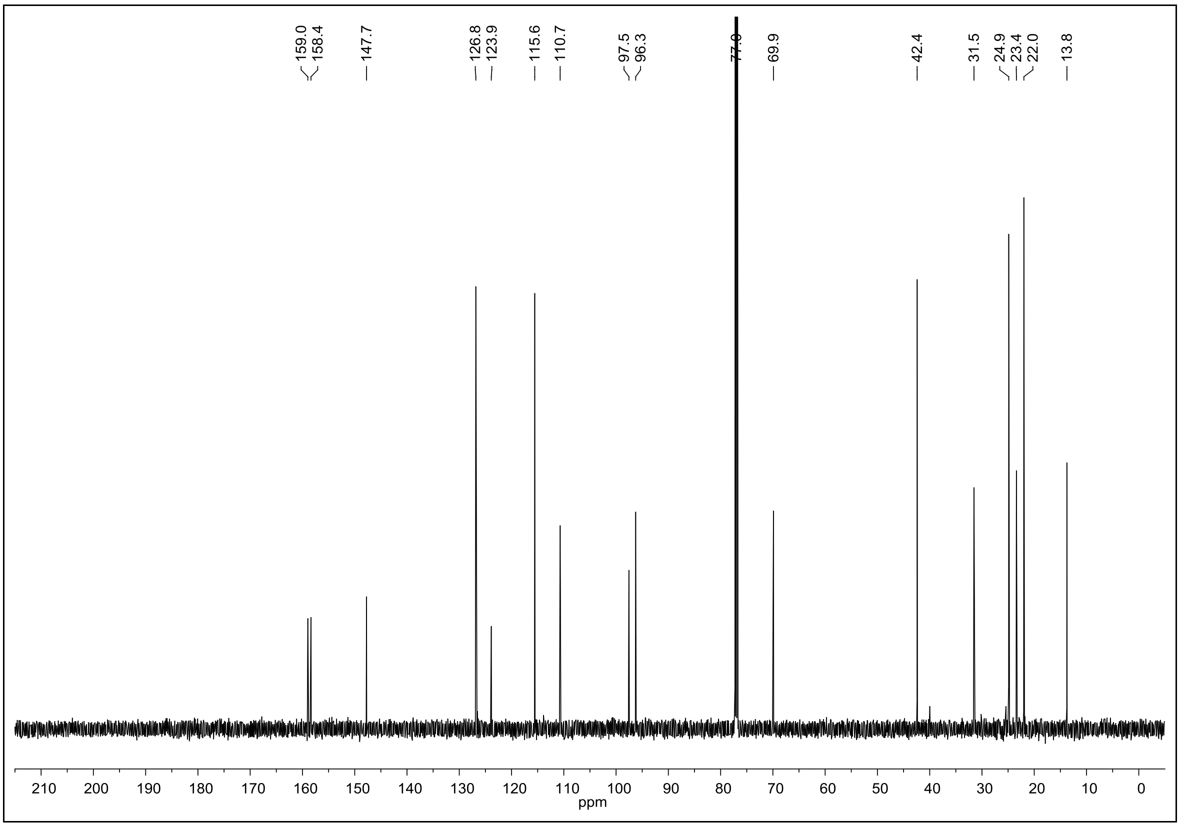


4-Butylidene-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-ene (183a, 183b)

^{1}H NMR

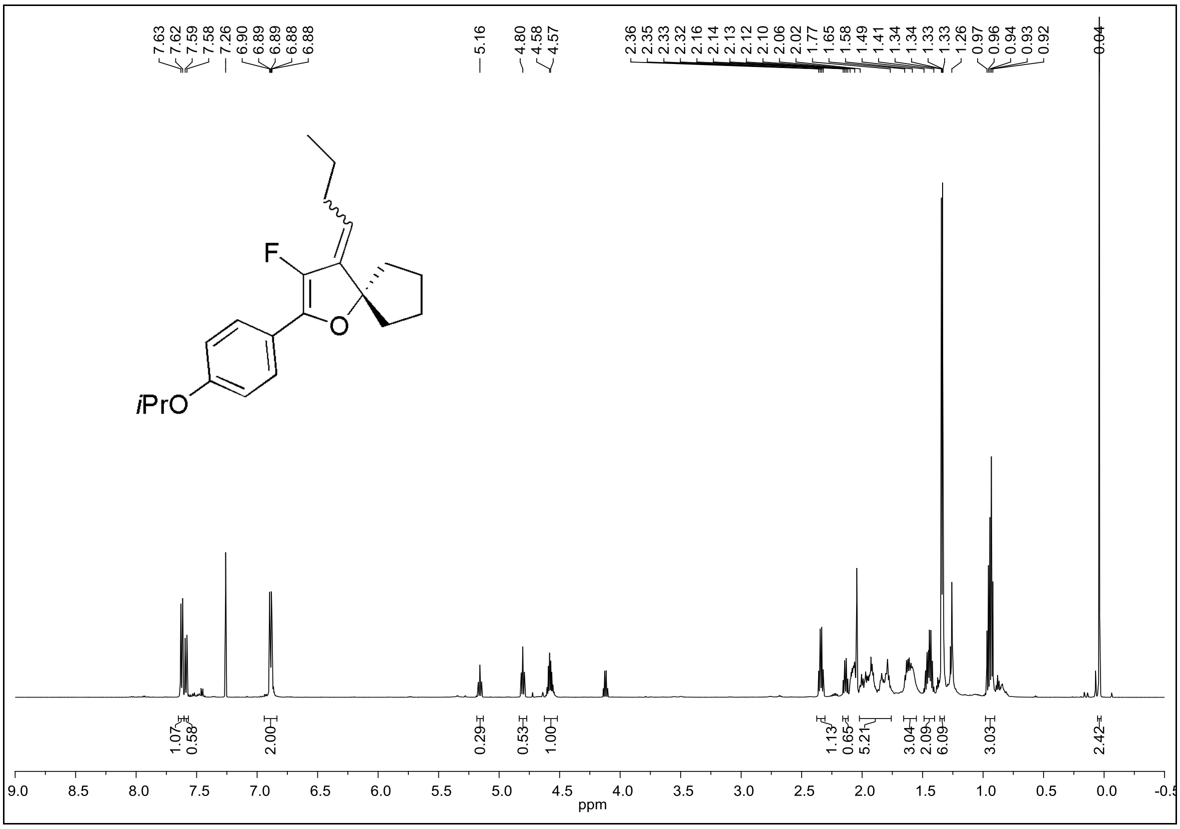


^{13}C NMR



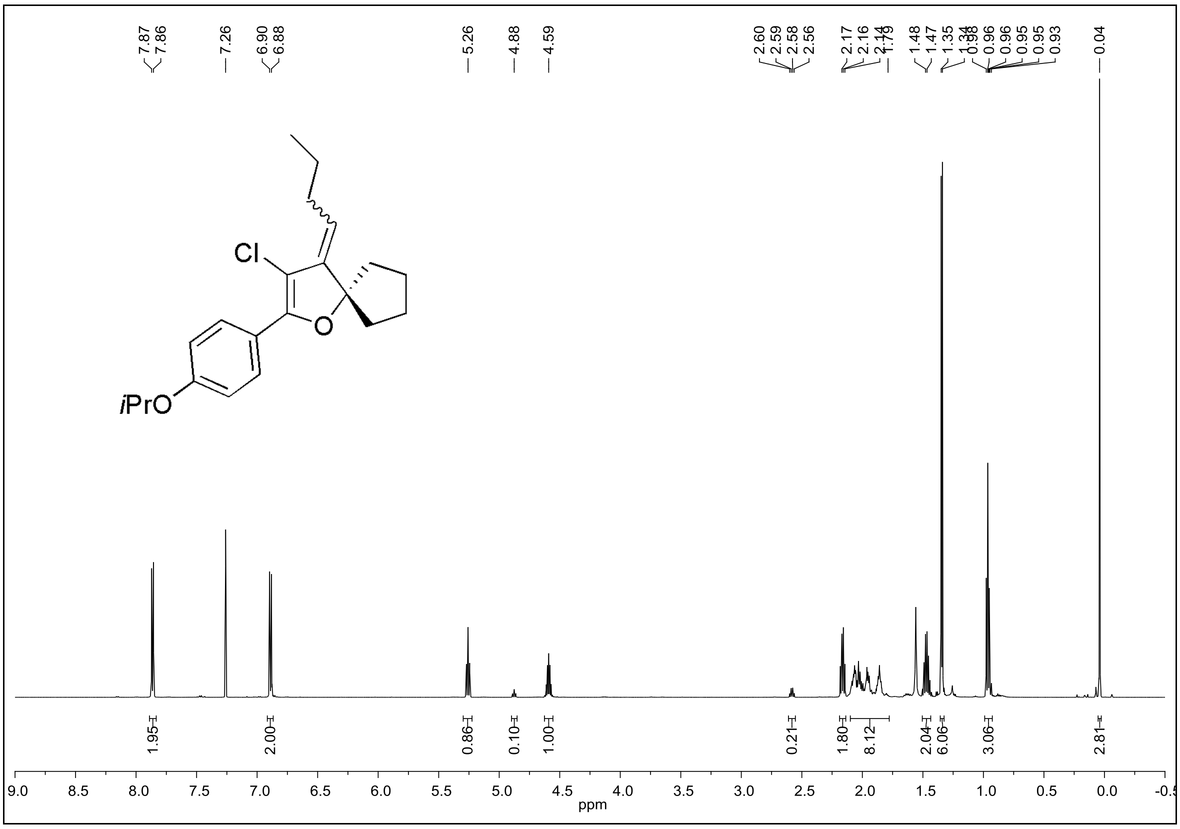
4-Butylidene-3-fluoro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-ene (209a, 209b)

^{1}H NMR



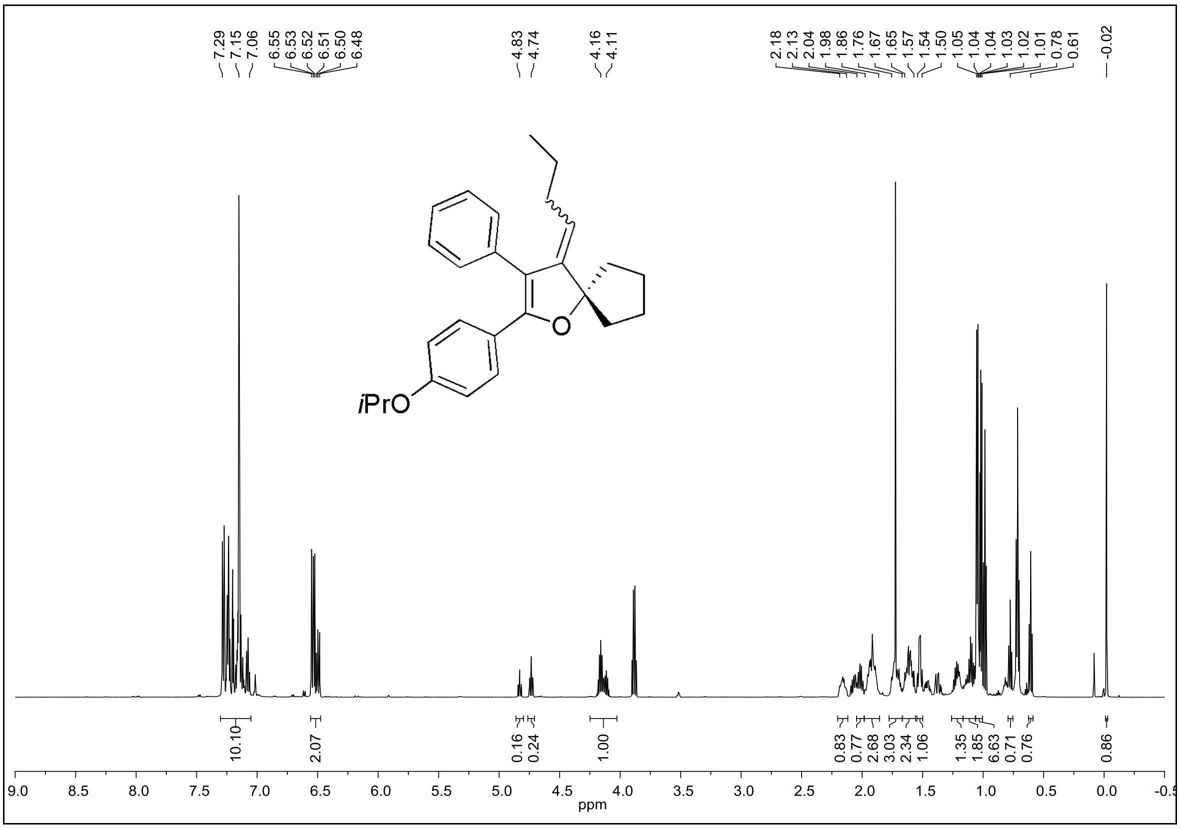
4-Butylidene-3-chloro-2-(4-isopropoxy-phenyl)-1-oxa-spiro[4.4]non-2-ene (210a, 210b)

^{1}H NMR



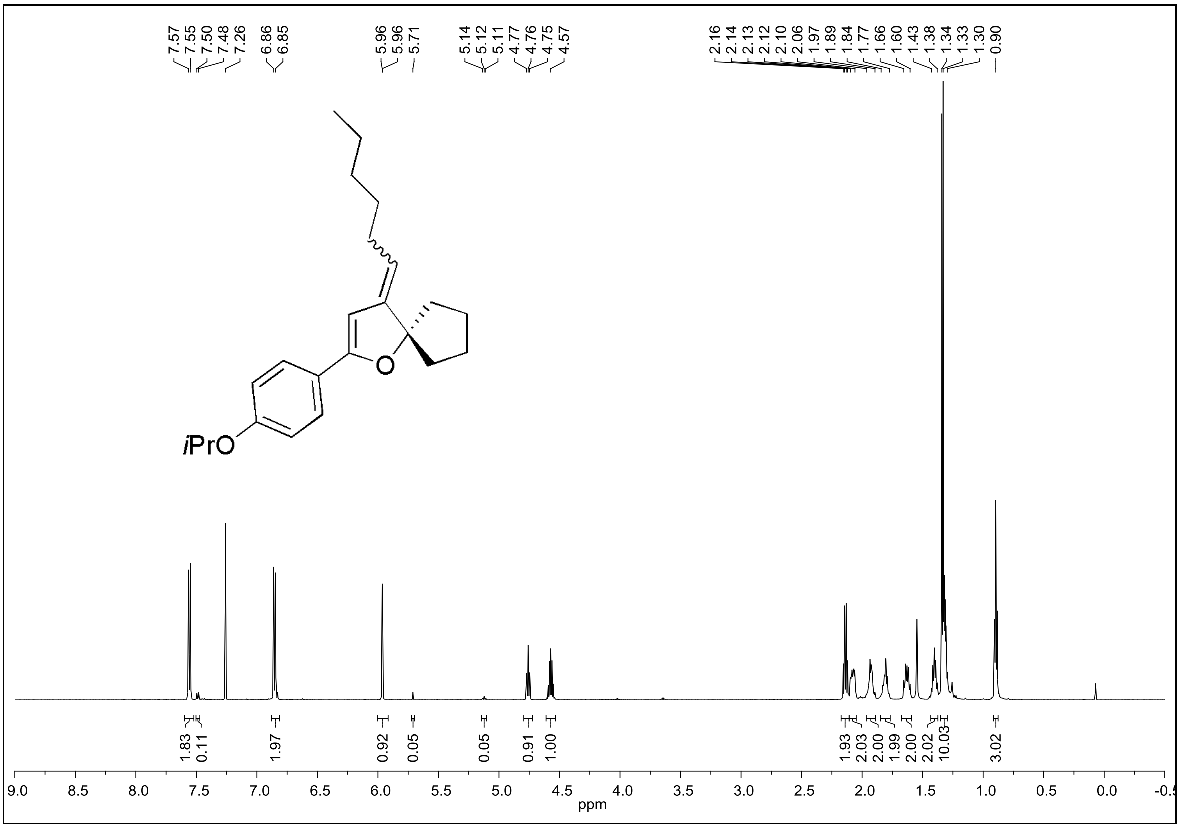
4-Butylidene-2-(4-isopropoxy-phenyl)-3-phenyl-1-oxa-spiro[4.4]non-2-ene (211a, 211b)

^{1}H NMR

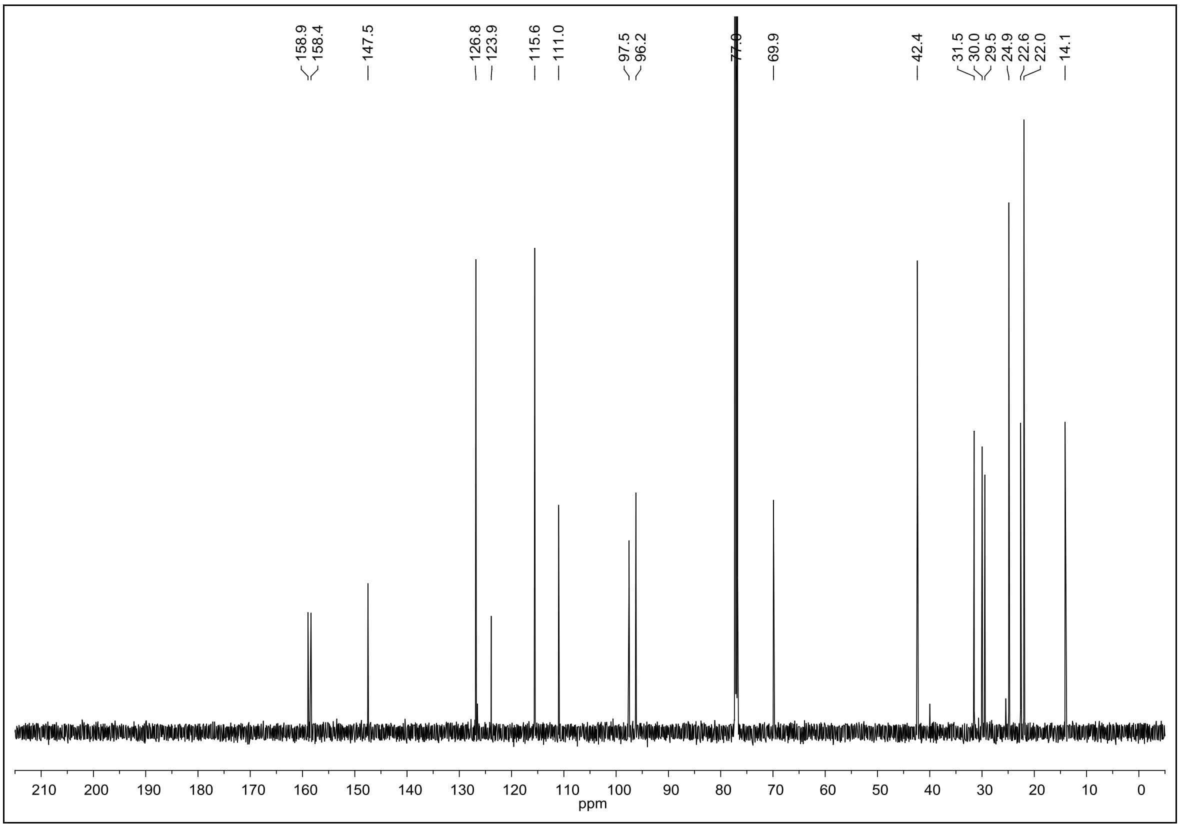


4-Hexylidene-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-ene (207a, 207b)

^{1}H NMR

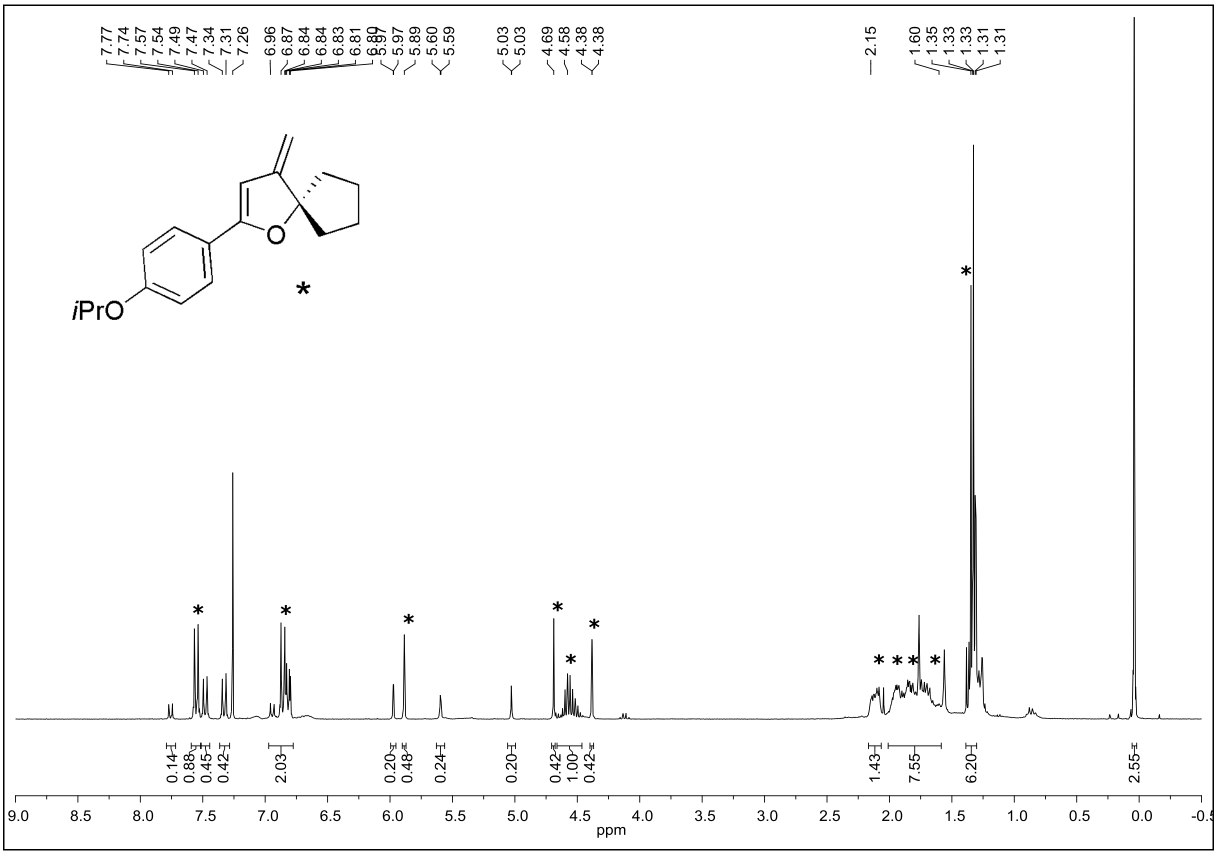


^{13}C NMR



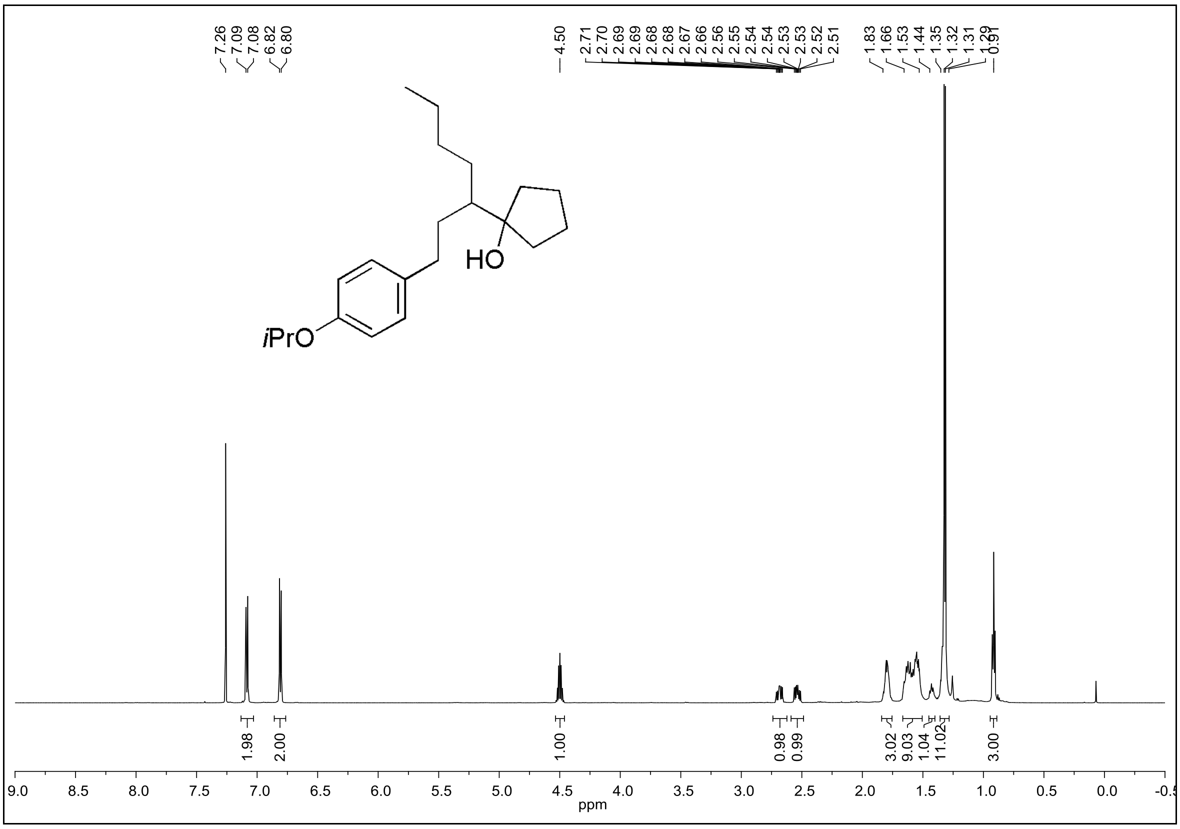
2-(4-Isopropoxy-phenyl)-4-methylene-1-oxa-spiro[4.4]non-2-ene (208)

^{1}H NMR

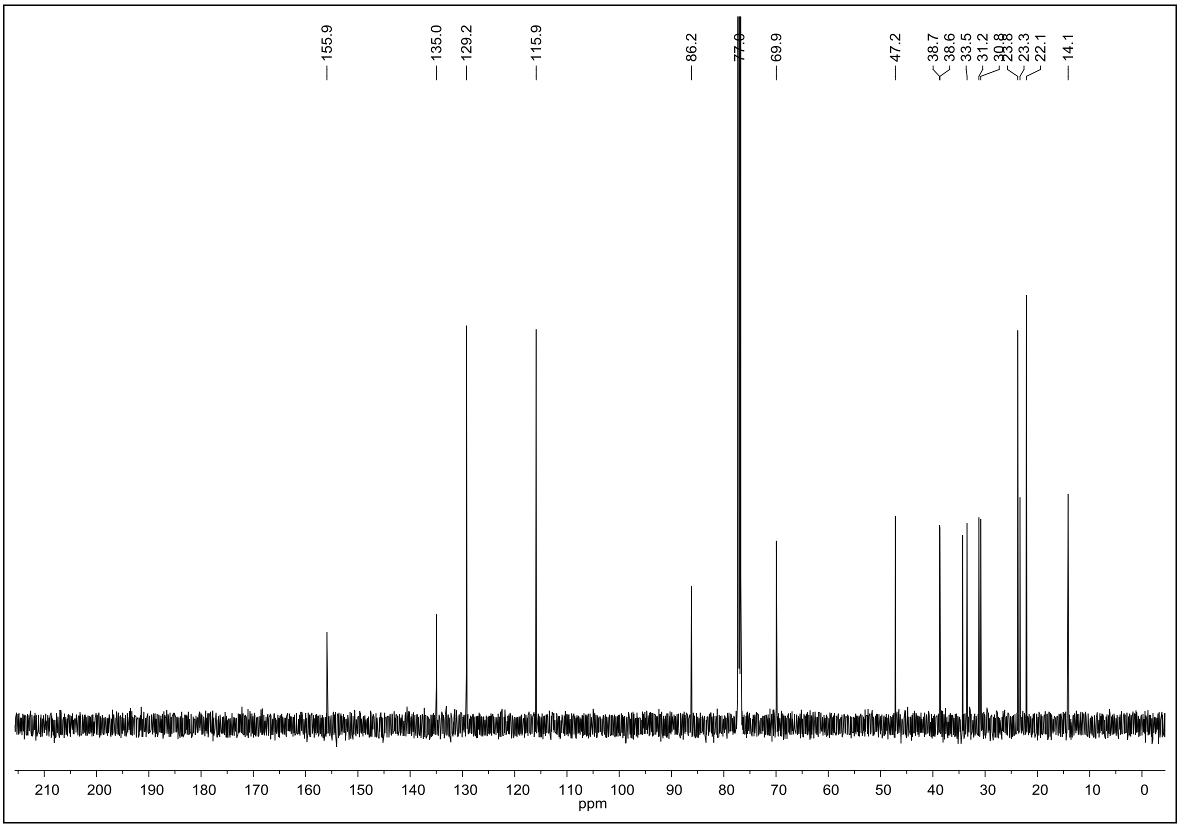


1-{1-[2-(4-Isopropoxy-phenyl)-ethyl]-pentyl}-cyclopentanol (212)

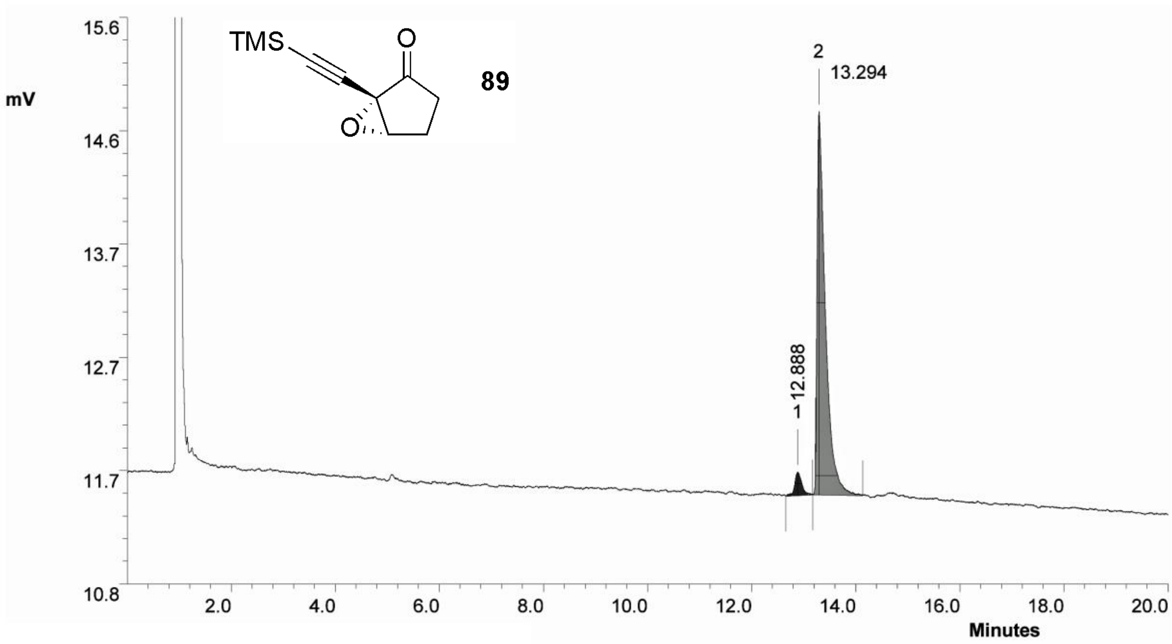
^{1}H NMR



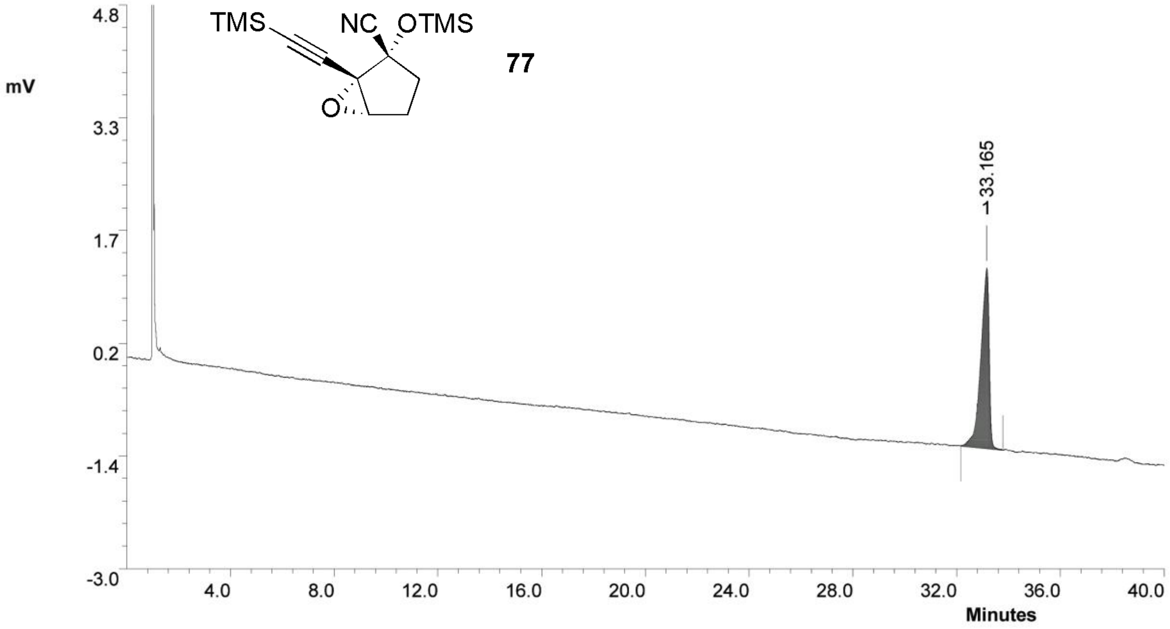
^{13}C NMR



6.2. GC spectra

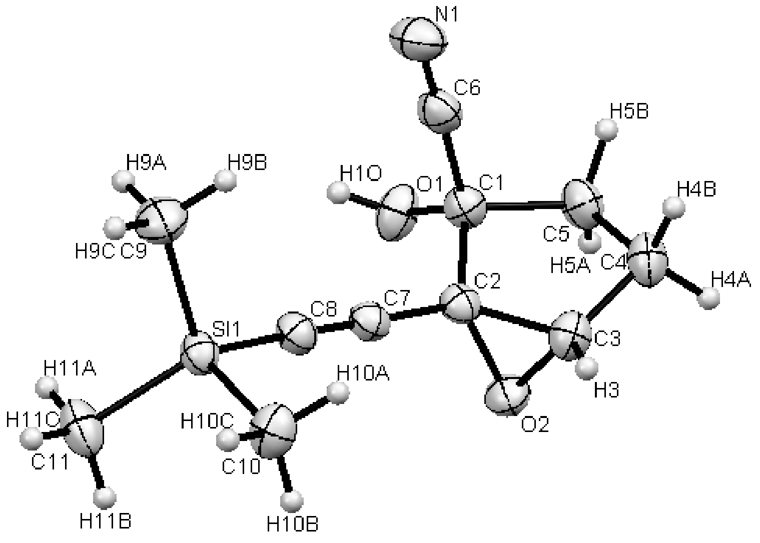


Peak	Retention time	Area	Area%
1	12.888	1.933	5.11
2	13.294	35.924	94.89



Peak	Retention time	Area	Area%
1	33.165	56.503	100

6.3. X-ray data



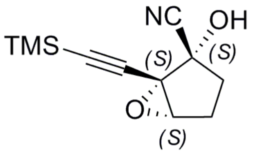


Table 20. Crystal data and structure refinement for **102**.

Crystal Data	
Empirical formula	$C_{11}H_{15}NO_2Si$
Formula weight	221.33
Crystal size	0.4214 × 0.2658 × 0.1386 mm
Crystal description	prism
Crystal colour	colorless
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.49140(8) Å α = 90°
	b = 10.67865(15) Å β = 90°
	c = 17.9430(2) Å γ = 90°
Volume	1243.80(3) $Å^3$
Z, Calculated density	4, 1.182 Mg/m^3
Absorption coefficient	1.527 mm^{-1}
F_{000}	472

Data Collection	
Measurement device type	Xcalibur, Ruby, Gemini ultra
Measurement method	\w scans
Temperature	123 K
Wavelength	1.54184 Å
Monochromator	graphite
θ range for data collection	4.82 to 72.94°
Index ranges	$-7 \leq h \leq 7$, $-12 \leq k \leq 13$, $-22 \leq l \leq 21$
Reflections collected / unique	9139 / 2441 [R_{int} = 0.0291]
Reflections greater I>2\s(I)	2391
Absorption correction	Analytical
Max. and min. transmission	0.818 and 0.597

Refinement	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	
Data / restraints / parameters	2441 / 0 / 142
Goodness-of-fit on F^2	1.065
Final R indices [$I>2\sigma(I)$]	R1 = 0.0253, wR2 = 0.0685
R indices (all data)	R1 = 0.0259, wR2 = 0.0689
Absolute structure parameter	0.00(2)
Largest diff. peak and hole	0.188 and -0.169 e/Å^3

Table 21: Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (A^2 × 10^3) for **102**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	**y**	**z**	**U(eq)**
Si(1)	3139(1)	9579(1)	8196(1)	29(1)
O(1)	38(2)	11059(1)	11159(1)	39(1)
O(2)	-740(2)	8370(1)	10726(1)	34(1)
N(1)	-2492(2)	12339(1)	9697(1)	47(1)
C(1)	-1491(2)	10605(1)	10674(1)	30(1)
C(2)	-871(2)	9437(1)	10233(1)	27(1)
C(3)	-2578(2)	8534(1)	10276(1)	33(1)
C(4)	-4349(2)	9096(2)	10695(1)	37(1)
C(5)	-3378(2)	10179(2)	11131(1)	37(1)
C(6)	-2078(2)	11589(1)	10124(1)	35(1)
C(7)	580(2)	9518(1)	9623(1)	28(1)
C(8)	1711(2)	9594(1)	9092(1)	30(1)
C(9)	2516(3)	11054(2)	7698(1)	45(1)
C(10)	2160(3)	8191(1)	7687(1)	40(1)
C(11)	5951(2)	9444(2)	8367(1)	43(1)
H(1O)	820(30)	11507(19)	10927(11)	46
H(3)	-2850	7957	9849	39
H(4A)	-4974	8476	11037	45
H(4B)	-5420	9406	10348	45
H(5A)	-2949	9896	11633	45
H(5B)	-4373	10875	11187	45
H(9A)	3042	11768	7983	55
H(9B)	1019	11129	7644	55
H(9C)	3158	11043	7204	55
H(10A)	659	8249	7640	48
H(10B)	2521	7430	7962	48
H(10C)	2782	8162	7189	48
H(11A)	6419	10162	8662	52
H(11B)	6235	8668	8640	52
H(11C)	6683	9432	7889	52

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CURRICULUM VITAE

Simon Lindner

geboren am 13.03.1982 in Regensburg

Beruflicher Werdegang

Seit Aug.2011	Anstellung in der Radiopharmazie der Klinik und Poliklinik für Nuklearmedizin, Klinikum der LMU München
Okt.2007 - Nov.2011	Promotionsstudium am Institut für Organische Chemie der Universität Regensburg bei Dr. Sabine Amslinger zum Thema *„Studies towards the Total Synthesis of Limnophilaspiroketone and the Synthesis of α-Modified Enones of Natural Product Derived Model Compound Limno-CP“*
Sep.2007	Diplom (1.6), Abschluss: Dipl. Chem. Univ.
Jan.2007 - Sep.2007	Diplomarbeit am Institut für Organische Chemie der Universität Regensburg bei Dr. Sabine Amslinger zum Thema *„Untersuchungen zur Totalsynthese des Naturstoffs Limnophilaspiroketon“*
Sep.2005 - Sep.2007	Hochschulstudium der Chemie mit Fachrichtung Medizinische Chemie, Organische Chemie, Analytische und Bioanalytische Chemie an der Universität Regensburg
Okt.2002 - Sep.2005	Grundstudium der allgemeinen Chemie an der Universität Regensburg
Sep.2001 - Jun.2002	Zivildienst im Rettungsdienst der Malteser
1992 - 2001	Albertus - Magnus - Gymnasium Regensburg
1988 - 1992	Grundschule Sinzing

Stipendien

Jan.2008 - Dez.2009	Promotionsstipendium der Stiftung Stipendien-Fonds des Verbandes der Chemischen Industrie

Publikationen und Präsentationen

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2. Poster: 3rd EuCheMS Chemistry Congress 2010, Nürnberg
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   Lindner, S. K.; Amslinger, S., Natural product derived α,β-unsaturated compounds as tool box to fine tune biological activity: synthesis and biological evaluation.

Referenzen

Dr. Sabine Amslinger
Universität Regensburg
Institut für Organische Chemie
Universitätsstraße 31
93053 Regensburg

Prof. Dr. Oliver Reiser
Universität Regensburg
Institut für Organische Chemie
Universitätsstraße 31
93053 Regensburg

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