Enantioselective Gold-Catalyzed Desymmetrization of 1,4-Diyne Species and Its Application on Naturally Occurring Compound Synthesis

Inaugural-Dissertation

zur Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultät

der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Jhen-Kuei Yu

aus Keelung

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Aus dem Institut für Organische Chemie und Makromolekulare Chemie

der Heinrich-Heine-Universität Düsseldorf

Gedruckt mit der Genehmigung der
Mathematisch-Naturwissenschaftlichen Fakultät
der Heinrich-Heine-Universität Düsseldorf

Berichterstatter:
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Tag der mündlichen Prüfung: 24.10.2023

Heinrich Heine
Universität
Düsseldorf

Mathematisch-
Naturwissenschaftliche
Fakultät

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Certificate

Mr M.Sc. Jhen Kuei Yu, born in Keelung, Taiwan,has proven his scientific qualification in an ordinary procedure of promotion in the Faculty of Mathematics and Natural Sciences at Heinrich Heine University with a doctoral thesis about

Enantioselective Gold-Catalyzed Desymmetrization of 1,4-Diyne Species and Its Application on Naturally Occurring Compound Synthesis

and also in an oral examination and obtained the final grade:

magna cum laude

The title „Dr. rer. nat." can only be used after submission of the statutory copies of the doctoral thesis, as well as the receipt of the doctoral degree certificate.

As representative of the dean

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Jhen-Kuei Yu

Acknowledgement

I would like to express my sincere gratitude to Prof. Dr. Czekelius, my supervisor, for his invaluable suggestions and unwavering support during my doctoral research. His generous encouragement and expert guidance were instrumental in successfully completing this research and crafting my dissertation.

Furthermore, I would like to extend my appreciation to Prof. Dr. Pietruszka for his invaluable contribution as member of my thesis evaluation committee. The insightful feedback and constructive suggestions have significantly enriched my research and thesis.

I would also like to convey thanks to all the lab partners who ever worked with me in the laboratory. Their kind encouragement and assistance have been greatly appreciated.

Additionally, I am grateful to my friends and family who have stood by me through those highs and lows in this journey. Your unwavering support and understanding have allowed me to pursue my passion without any concerns.

There are numerous individuals who deserve sincere appreciation for being a part of this enlightening journey with me. For either good or bad, big or small, I firmly believe that each one of you was a divine arrangement from above. Thus I am profoundly grateful to those serendipitous angels who crossed those paths with me throughout this remarkable expedition.

Preface

This doctoral thesis is composed in a cumulative manner that contains context from two published essays and unpublished results.

In chapter 1, a bismuth-catalyzed functionalization for 1,4-diyne species and the importance of this compound with respect to the stereoselective quaternary center construction *via* gold catalysis was described.

In chapter 2, the unpublished result of 3-alkoxy-1,4-diyne desymmetrization *via a* gold-catalyzed cyclization was discussed.

In chapter 3, the published results of "Insights into the Gold-Catalyzed Cycloisomerization of 3-Allyl-1,4-diynes for the Synthesis of Bicyclic Hydrocarbons" were included in this dissertation. (Cumulative part)

In chapter 4, the essay is currently under review, titled "A Comprehensive Approach to C3a-Arylated Hydroindole-related Alkaloids Utilizing Asymmetric Gold Catalysis: Formal Synthesis of (+)-Gracilamine and Other Enantiomerically Pure Crinine Alkaloids" were represented in this dissertation. (Cumulative part)

Abstract

In this dissertation, an extensive application of 1,4-diyne substrates featuring quaternary centers in synthetic chemistry has been demonstrated. It begins by describing the preparation and functionalization of these substrates, highlighting their unique chemical properties. With readily available 1,4-diyne substrates prepared using self-developed methodology, their reactivity in the presence of cationic gold complexes is investigated.

Various gold-catalyzed intramolecular cyclic functionalizations on the alkyne group are explored, both in chiral and achiral fashion, including alkyne hydroxylation (Chapter 2), enyne isomerization (Chapter 3), and alkyne hydroamination (Chapter 4). These investigations not only provide insights into the mild gold-catalyzed cyclization of diverse substrates but also shed light on the mechanistic details of the processes.

Furthermore, based on the knowledge and success gained from the enantioselective intramolecular hydroamination, the dissertation describes a diversity-oriented formal total synthesis of a wide range of naturally occurring compounds in the Amaryllidaceae family (Chapter 4). This work showcases the exploration of novel chemical substrates and provides mechanistic insights while facilitating the synthesis of these valuable natural products.

Abbreviation

ACC	1-Aminocyclopropanecarboxylic acid
Ac	Acetyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-Bi-2-naphthol
MeOBIPHEP	2,2′-Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Boc	*tert*-butyloxycarbonyl
Bn	Benzyl
Bu	Butyl
Cat.	Catalyst
cal.	Calorie
Cbz	Benzyl carbamate
CuAAC	Copper-catalysed azide–alkyne cycloaddition
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DFT	Density-functional theory
DMAP	4-Dimethylaminopyridine
DIPEA	*N*,*N*-Diisopropylethylamine
DPPA	Diphenylphosphoryl azide
dppe	1,2-Bis(diphenylphosphino)ethane
dppm	1,1-Bis(diphenylphosphino)methane

DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric Ratio
DTBM	Bis-(3,5-di-*tert*-butyl-4-methoxyphenyl
ee	Enantiomeric excess
Hex	Hexanes
HOMO	Highest occupied molecular orbital
HRMS	High-resolution mass spectrometry
HSAB	Hard soft acid base
Im^{t}Pent	2,5-Di-*tert*-pentyl-1,3-dihydro-2H-imidazol-2-ylidene
IR	Infrared
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
MRSA	Methicillin-resistant staphylococcus aureus
M.S.	Molecular sieves
mw	Microwave
N.D.	None determined
NMDA	*N*-Methyl-d-aspartate receptor
NMR	Nuclear magnetic resonance
N-mal	*N*-Maleinimidate
Nu	Nucleophile
N.R.	No reaction
Pin	Pinacol
Piv	Pivaloyl

Ka	Acid dissociation constant
PMB	*para*-Methoxybenzyl
pmdba	Bis(4-methoxybenzylidene)acetone
Ph	Phenyl
PyBox	Pyridine-2,6-bisoxazolines
PHOX	Phosphinooxazolines
PyOx	Pyridine oxazoline
R_F	Retention factor
SET	Single electron transfer
TADDOL	$\alpha,\alpha,\alpha',\alpha'$-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol.
TBA	Tetrabutylammonium
TBS	*tert*-Butyldimethylsilyl
TBADT	Tetra-n-butylammonium decatungstate
TBAF	Tetra-n-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TEA	Trimethylamine
tert	Tertiary
Temp.	Temperature
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
THF	Tetrahydrofuran

Ts	Toluenesulfonyl
TRIP	3,3′-Bis-(2,4,6-triisopropyl-phenyl)-1,1′-binaphthyl-2,2′-diyl-hydrogenphosphate
Segphos	5,5′-Bis-(diphenylphosphino)-4,4′-bis-1,3-benzodioxol
SOMO	Singly occupied molecular orbital
VREF	Vancomycin-resistant enterococcus faecium
XPhos	2-Dicyclohexylphosphin-2′,4′,6′-triisopropylbiphenyl
δ	Chemical shift

Table of Content

Chapter 1. Introduction and the method development for 1,4-diyne synthesis

In 1957, a worldwide drug injury known as the "Thalidomide tragedy" happened due to the cognitive deficits of the chemical inequivalent of stereoisomers.[1] Thalidomide, a medication initially developed by Chemie Grünenthal GmbH to treat morning sickness in pregnant women, was prescribed to thousands of pregnant females worldwide. Unfortunately, it was later discovered that the racemization of enantiopure thalidomide could occur *in vivo*, and the racemic mixture of thalidomide is known to cause severe congenital disabilities in babies whose mothers had taken the drug during pregnancy, including limb deformities, such as missing or shortened arms and legs, as well as damage to the eyes, ears, heart, and other organs. It is estimated that between 10,000 and 20,000 infants were born with these congenital disabilities as a result of drug misuse and ignorance of stereochemistry. It resulted in significant compensation being paid to affected families by the drug manufacturers, and in some countries, the drug was banned altogether. This disaster is considered one of the most significant drug-related tragedies in history and remains a cautionary tale about the importance of thorough inspecting and monitoring of new medications. Thus, the "Thalidomide tragedy" led to widespread outrage and changes in the process of new drug examination and approval for launch.[2]

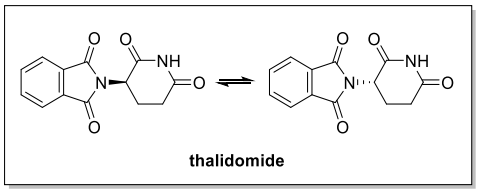


Figure 1. Configuration of thalidomide

Additionally, in the modern progress of synthetic chemistry, stereochemistry arouses considerable attention in chemical society. Stereoisomers own pretty similar configurations, but it exhibits different chemical properties from one another, especially when interacting with biological systems.[3] According to the dimensional arrangements and relevant position of atoms, the different chemical properties of stereoisomers could be facile envisioned, considering the biological objective is frequently chiral such as peptides or polysaccharides. Found by Louis Pasteur in 1857, the metabolic system of microorganisms reacts differently to (+)- and (–)-tartaric acid in speed, the first example indicating the chemical inequivalent of stereoisomers.[4] About 30 years later, another observation was made by the Italian chemist Arnaldo Piuttihe that (*R*)- and

(*S*)-asparagine have a significant difference in taste.[5] The chemical receptor on the palate is a series of proteins on the surface of the cells and mediates the effects of chemical messages. The different flavor of asparagine enantiomers is an essential finding that indicates chirality has a substantial impact on receptor-mediated biological activities.

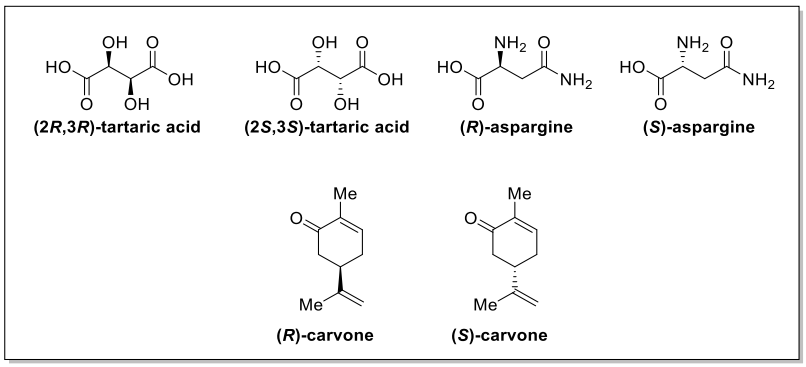


Figure 2. Absolute configuration of tartaric acid, aspargine, and carvone in both enantiomeric series.

Moreover, as a chiral monoterpene ketone, carvone is one of the most versatile terpenes used in the cosmetic and food additive industry.[6a, 6b] The enantiomers of carvone exist in many different essential oils from plants, such as spearmint, ginger grass, dill, and caraway. The different ratios between the enantiomers could cause distinctive odors due to the various chemical affinity to the olfactory receptors. Not only the smell but the influence on the central nervous system would react differently to the carvone enantiomers, which has been proved recently in preliminary animal experimentation.[6c, 6d]

In spite of the examples mentioned above of which the stereoisomer can easily be differentiated for bioactivity even without satisfactory identification by a spectrometer or any other explicit measurement, they still inspire the progress nowadays of enantioselective synthesis, which allows more and more organic compounds to be developed and examined in an ironclad manner to assure the safety of the chemical usage in human society or sometimes even ecosystems.

In the development of modern chemistry, the progress in pharmaceutical chemistry is an important branch that synergizes the studies on small molecular synthesis.[7] In order to cater to the need for novel medicine development, the enantioselective synthesis of small molecules becomes noticeable.[8] Stereochemistry is an issue that only exists in the molecules containing a stereogenic center, which can be defined as a carbon center that gives a new stereoisomer while interchanging any two adjacent groups.[9] To match the description above, a stereogenic carbon center must meet

the criteria of sp^3–hybridization and four different connected groups. In principle, among all classes of the stereogenic carbon center, the one with the carbon-hydrogen bonding is easier to approach because hydrogen, the smallest functional group, as a neighboring group could be beneficial in the process of differentiating the Re- or Si- face in terms of stereoselective bond formation. On the other hand, a quaternary carbon center attaching to four similar primary bondings requires higher activation energy to construct the molecule due to the steric hindrance from the crowded surrounding.[10] Therefore, in this dissertation, we will focus on constructing all-carbon-based stereogenic centers and try to conquer the difficulties of stereoselective synthesis of fully substituted stereogenic centers by utilizing the powerful synthetic tool "gold catalysis".

1-1 Cationic gold catalysis

1-1-1 Properties of gold

The discovery of elemental gold could date back to the prehistoric age. Almost in all sorts of ancient civilizations, humankind has developed a shared appetite for gold because of its appealing shiny color and its rarity.[11] One of the most noticeable chemical properties of gold is its high resistance to oxidation and corrosion. This fact is due to its low reactivity with other elements, which means it is relatively unaffected by air or water exposure, allowing it to preserve its shiny appearance for a more extended period. Gold is also highly malleable and ductile, which gives it a wide range of operability when it comes to sophisticated metalworking. Furthermore, high thermal and electrical conductivity are some other unique properties to describe elemental gold.[12] Concluding the abovementioned reasons, it is legitimate that gold has been regarded as a symbol of wealth and royalty in all kinds of civilizations for a long history; for example: in the Greek myth of King Midas, the golden mask of Tutankhamun, etc.[13,14] The reason that people insatiably adore this metal could be attributed to its stability and shiny appearance, which were both initially caused by the relativistic effect.[15] In the model of general atomic orbital, the heavier a nucleus is, the faster its electrons travel to maintain the atomic radius. To exemplify, the 1s electron of a gold atom has to travel at 65% of light speed to prevent the electron configuration from collapsing. Traveling at such a high speed makes the relativistic effect more pronounced that the mass of the electron will increase and lead to the contraction of the atomic orbital. The contraction of the 6s orbital on the gold atomic orbital directly led to the inertness of gold and minimized the energy gap between 6s and 5d, indirectly causing the shiny yellow color.[15]

1-1-2 Reactivity of gold cation

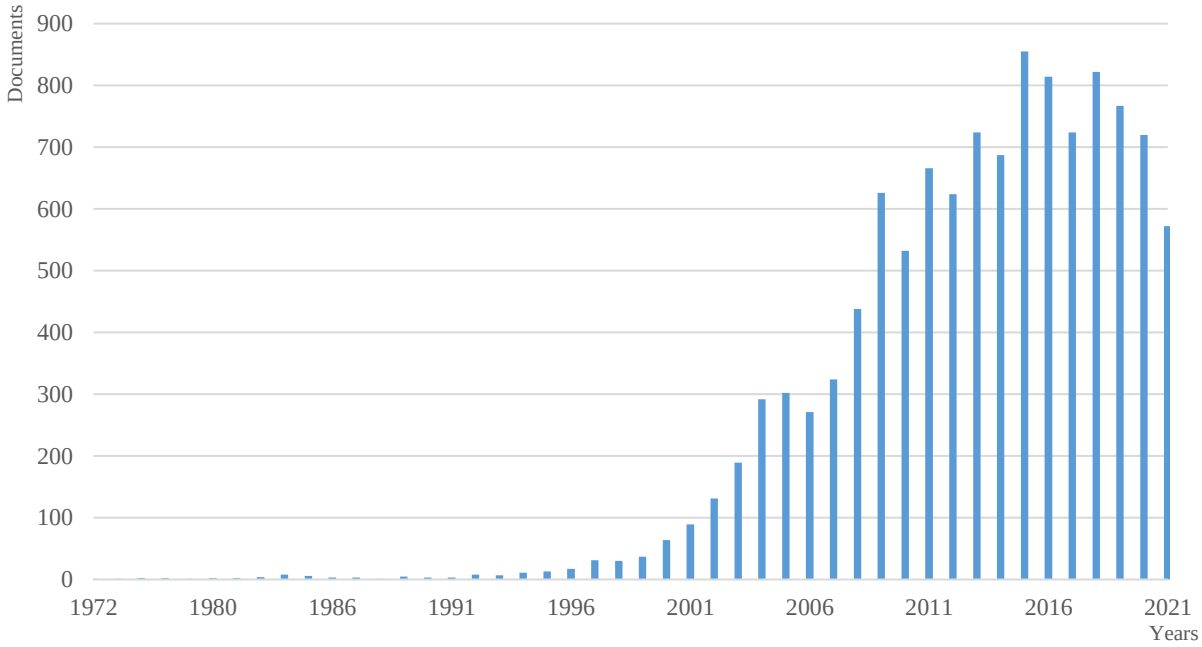


Figure 3. The statistics data of gold catalysis related scientific reports

Gold had been considered one of the most unreactive metals for centuries; however, the situation has been changed in the 1970s when a series of investigations of gold catalysis was reported by Prof. Bond[16], Prof. Haruta[17], and Prof. Hutchings.[18] Those works demonstrated the activity of gold nanoparticles for promoting the unsaturated species in various reactions such as alkene isomerization, carbon monoxide oxidation at low-temperature, and so on. Since these pioneering discoveries had been reported, chemists were aware that gold has massive potential in terms of catalysis.[19] Considering gold has an electronic configuration as $[Xe]4f^{14}5d^{10}6s^{1}$, even though it is exceptionally stable due to the aforementioned relativistic effect, gold can still be oxidized, and the most common oxidative state is gold(I) and gold(III) cations. The intense relativistic contractions of the 6s and 6p orbitals in gold draw the valence electrons much closer to the nucleus. The contraction of valence orbitals explains the higher ionization energy of gold compared to other elements in group 11, which in turn contributes to the increased Lewis acidity of cationic gold complexes. This observation is consistent with the relatively strong electronegativity of gold (2.54 for Au compared to 1.93 for Ag).[20] On the contrary, the expansion of 5d and 4f orbitals can be as well attributed to the influence of relativistic effects, whereby electrons occupying these orbitals are better shielded by the electrons in the contracted s and

p orbitals.[21] Hence there will be a weaker nuclear attraction for 5d and 4f orbitals, which results in the soft Lewis acidic nature of gold(I) species reacting preferentially with "soft" species (such as unsaturated compounds) and being less oxophilic according to the hard and soft Lewis acids and bases theory (HSAB).[22] Based on the mentioned reason, the gold cation is particularly good for the η^2-complexes formation in the presence of unsaturated hydrocarbons, which was reflected in the activation of highly strained cyclic alkene isomerization published by de Meijere and co-workers in 1976.[23] Similar to other metallic cations, the gold cation was applied to the aldol-type reaction as a Lewis acid by Prof. Ito, and co-workers in 1986.[24] Despite gold-catalyzed aldol reaction could achieve a pretty good result in terms of yield and stereoselectivity, it is not price-competitive with other naturally abundant Lewis acids. Thus, in the modern development of gold catalysis, aldol-type reactions could be rarely found; however, more and more different types of reactions catalyzed by gold cation were revealed in the late 19 century, for instance: hydration of alkynes[25], coupling reactions[26], and so on. In 2000, a critical breakthrough happened in the development of homogenous gold catalysis, a novel type of gold-catalyzed C−C bond formation reported by Hashmi and co-workers.[27] Since then, people have begun to explore the novel gold-catalyzed bond formation of the more sophisticated substrates. Herein, the synthesis disclosed in this dissertation encompasses three major topics, each focused on the cationic gold-catalyzed ring closure and its stereoselectivity.[28]

In modern chemistry development, the majority of the cationic gold-catalyzed chemical transformations focused on redox reactions[29] and nucleophilic additions[28] to unsaturated systems. Intrinsically, gold-catalyzed reactions are initiated and activated by the coordination of cationic gold to unsaturated π orbitals, which would render susceptible electrophilicity and allow for various types of bond formation to occur.[28a,e] As an alkynophilic Lewis acid, cationic gold has an exaggerated affinity to alkyne species; besides, acetylene was generally considered an endothermic compound with high kinetic reactivity and a strong thermodynamic driving force.[28a] According to these promising reasons, a plethora of scientific research on alkyne functionalization *via* homogeneous gold catalysis was published recently.[28] Among all the alkyne species, diynes provide diverse reactivities allowing the accomplishment of more complicated organic synthesis and the possibility of domino bond formation. Besides, the research area of diyne substrate has not been fully developed so far. Thus, in the following section, the importance of diynes and their

synthesis will be discussed. In addition, multiple chemical transformations of diyne species in the presence of cationic gold will be disclosed in this dissertation.

1-2 Importance of 1,4-diyne species and development of novel 1,4-diynes.

1-2-1 Construction of quaternary carbon center and desymmetrization

Nowadays, the construction of molecular complexity is trending in modern synthetic chemistry, especially in the field of bioactive molecule synthesis.[30] Numerous scientific reports in recent decades indicate that molecules exhibiting significant bioactivities usually carry a quaternary carbon center to provide certain molecular complexity.[31] Because of the structural diversity and conformational constraints, a molecule featuring quaternary carbon centers conventionally has better outcomes in the bioactivity tests. For example, upon interacting with targeting protein, the spirocyclic compounds tend to have a minor conformational entropy penalty that needs to be compensated compared to monocyclic compounds.[32] Based on that, the recent progress in developing pharmaceutically active molecules appears to have an increased occurrence in spiro scaffolds.[33]

Other than spiro compounds, there are more examples of bioactive molecules featuring quaternary carbon centers that significantly impact our daily life. Hydrocodone and fluticasone are commercially available medicine listed as the most used prescribed drugs in the U.S. market.[34] Hydrocodone, an immensely potent pain reliever, is typically administered to address intense symptoms. Sharing a structural similarity to morphine, it surpasses even more effective in mitigating severe discomfort.[35] Fluticasone, the manufactured steroid, on the other hand, is a versatile medicine that helps patients in need fight against topical and nasal inflammation.[36]

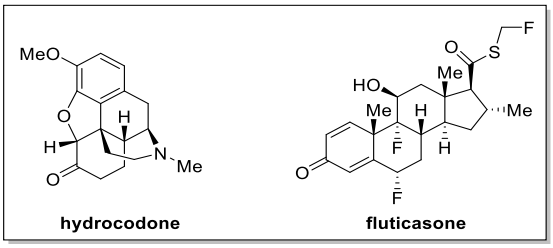


Figure 4. Structure of natural products bearing quaternary center: hydrocodone and fluticasone

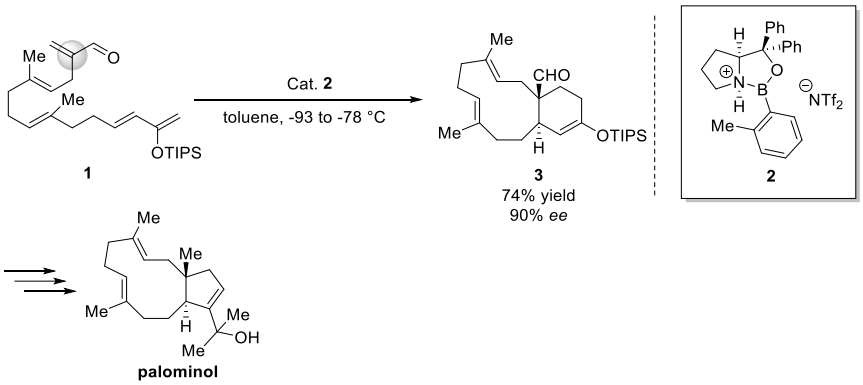
The significant market share of the prescribed medicines containing quaternary carbon centers also suggests that compounds bearing quaternary carbon centers often have promising bioactivities

compared to compounds without quaternary carbon. Thus, an efficient method for building up quaternary stereocenters is highly demanded.[37] Even if molecules bearing quaternary stereocenters have been proven essential to pharmaceutical progression and used in medical treatment, up to now, affirmative methodologies for constructing molecules containing chiral quaternary carbon stereocenters are still the minority.[10] Because the exasperating steric hindrance and problematic chirality embedding have been inevitable and harassing the synthetic chemists for many years, so far, most of the synthesis methods for these kinds of molecules rely on the enantiopure precursors to prevent the uncertainty of the stereochemistry issue on the quaternary stereocenters.[38] In essence, reliable methods for constructing such structural motifs are highly desirable. Thus, in recent years chemists have been devoted to developing valid synthetic methods for the enantioselective construction of quaternary carbon stereocenters. All in all, the possible way to produce enantioselective quaternary carbon stereocenters could be classified into three categories: (1) kinetic resolution reaction of racemic compounds featuring quaternary stereocenters. (2) bond-formation on highly substituted sp^2-hybridized prochiral carbon center (3) desymmetrization of the substrate including a prochiral quaternary carbon.[39]

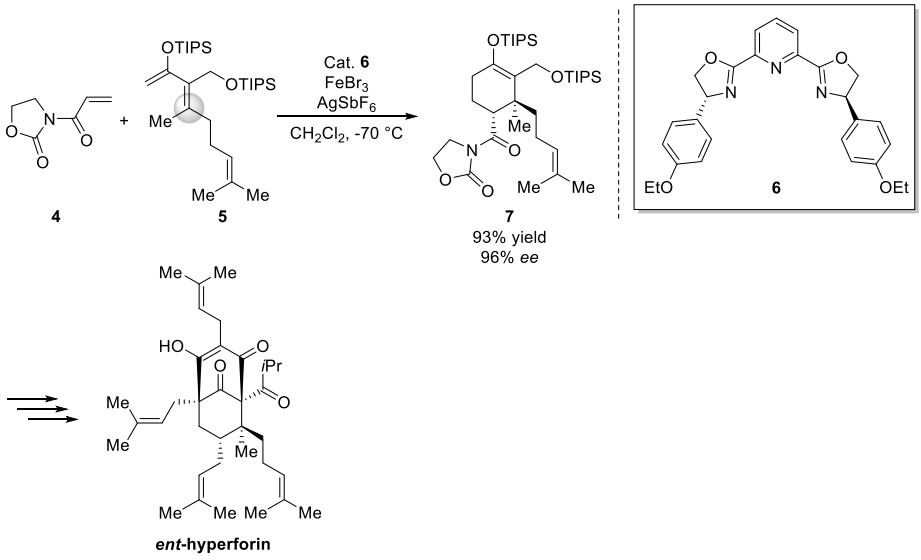
Although there are elegant and inspiring kinetic resolution methods of the quaternary carbon center reported in recent decades, intrinsically, those methods are for separating enantiomers; therefore, it has an obvious limitation with respect to the yield and makes this method less efficient. Hence, this type of method is not included within the scope of our discussion in this dissertation. As aforementioned, the quaternary stereocenters are known to be very sterically hindered. Therefore unlike other chiral center construction, a bond formation to achieve quaternary stereocenters construction requires a higher activation energy which enhances its difficulty. Besides, compared to tertiary stereocenters, the similarity of the substituent on prochiral quaternary centers makes the enantioselectivity an ordeal to achieve. In spite of many thorny problems in the way of quaternary stereocenters establishment, there were some remarkable breakthroughs that had been found and applied in the field of naturally occurring product synthesis already.

For example, the versatile Diels-Alder reaction was often utilized for the establishment of molecular complexity, and it was applied in the field of quaternary stereocenters construction in natural product syntheses.[40] In 2006, the catalytic enantioselective intramolecular Diels-Alder

reaction was accomplished by Snyder's and Corey's research groups. The intramolecular cyclization of polyene aldehyde **1** in the presence of chiral oxazaborolidinium catalyst **2** was examined in their research (Scheme 1).[41] With the assistance of Lewis-acidic catalyst **2**, the energy barrier between the lowest unoccupied molecular orbital (LUMO) of the *α,β*-unsaturated aldehyde and the highest occupied molecular orbital (HOMO) of the electron-rich Mukaiyama-type diene motif would be decreased and facilitate the thermally allowed [4+2] cycloaddition. Furthermore, the stereochemistry was structurally controlled by the proper oxazaborolidine catalyst **2**, resulting in macrocyclic product **3** in good yield with 90% enantiomeric excess. In addition, cycloadduct **3** could be elaborated to afford various dolabellane diterpenes, including the naturally occurring product palominol.

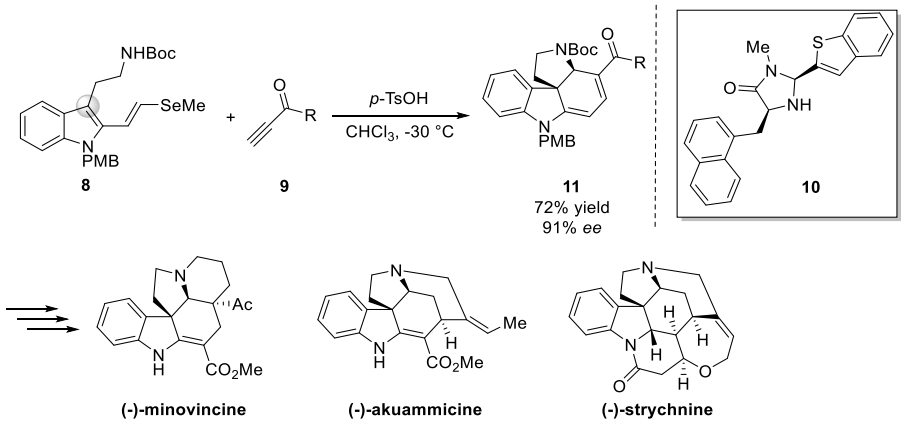


Scheme 1. Key step for quaternary stereocenter construction in the total synthesis of palominol[41]



Scheme 2. Key step for quaternary stereocenter construction in the total synthesis of *ent*-hyperforin[42]

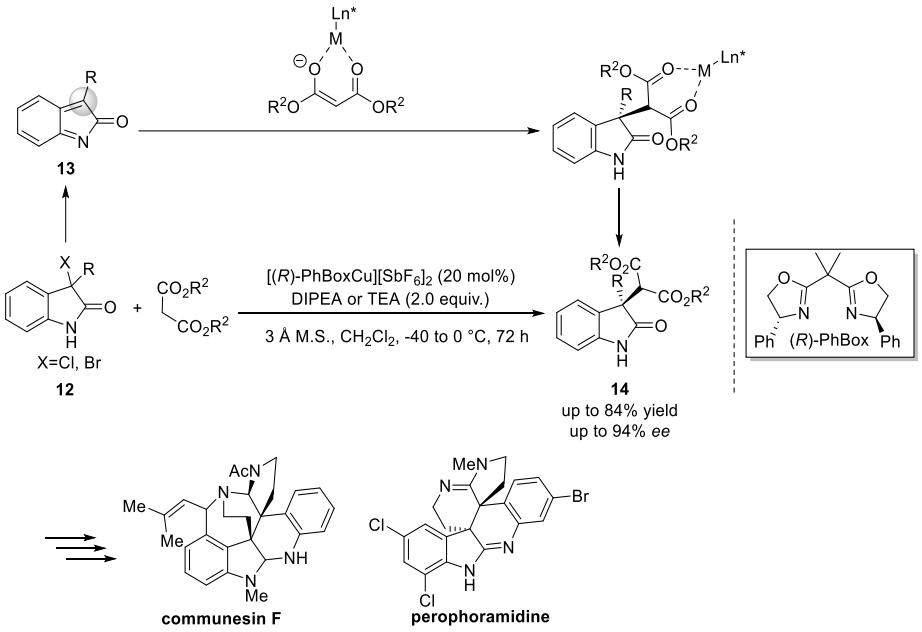
Moreover, in 2010, the asymmetric synthesis of naturally occurring *ent*-hyperforin was established and reported by Shibasaki and co-workers, employing an enantioselective Diels-Alder reaction (Scheme 2).[42] Rather than intramolecular cycloaddition, the intermolecular Diels-Alder reaction for the quaternary center could be achieved in the presence of the chiral iron complex *in situ* generated from $FeBr_3$ and the pyridine bisoxazoline ligand (4-OEt-PyBOX) **6**. The [4+2] cycloaddition between electron-deficient dienophile **4** and Mukaiyama-type diene **5** can successfully take place in a chiral manner with the guidance of the chiral pyridine bisoxazoline iron complex. Besides, the chiral quaternary center generated in this chemical transformation subsequently played a critical role in selectively evolving other stereocenters for the following synthetic process of *ent*-hyperforin syntheses.



Scheme 3. Key step for quaternary stereo center construction in the total synthesis of (−)-minovincine, (−)-akuammicine, and (−)-strychnine[43]

Among the various dienophiles in the Diels-Alder cycloaddition, the alkynyl ketone **9** is unique. As a dienophile, it could preserve the unsaturation and allow cascade bond formation when the cycloaddition is complete. This property helps improve the efficiency of molecular complexity construction in many cases. To exemplify, the synthesis of indole-based natural products disclosed by MacMillan's research group in 2013 indicates the potential of alkynyl ketone **9** in quaternary stereocenter construction *via* Diels-Alder cycloaddition (Scheme 3).[43] Activated by the chiral secondary amine organocatalyst **10** incorporating *para*-toluenesulfonic acid, the cycloaddition between methylselanylvinyl indol **8** and alkynyl ketone **9** was accomplished in a more eco-friendly manner since the metal-free process was applied at low temperature. The *in situ* generated iminium ion in the catalytic cycle would significantly reduce the energy barrier by lowering the LUMO of alkyne and facilitating the reaction rate of the cycloaddition. The corresponding *α,β*-unsaturated

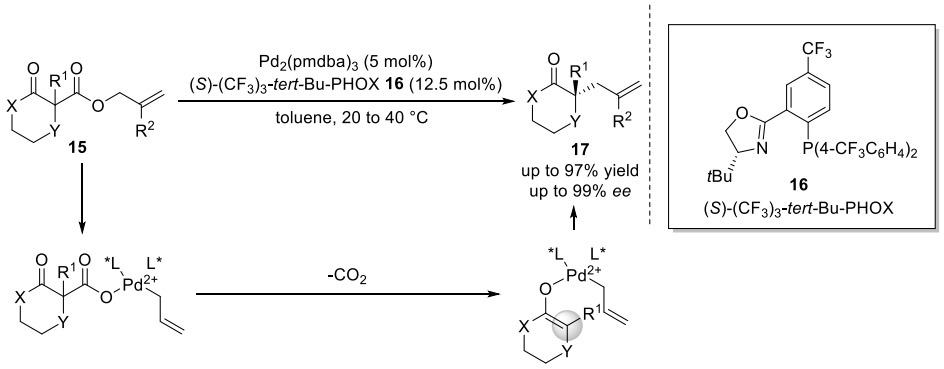
iminium ion intermediate forming in the [4+2] cycloaddition would allow the domino bond formation and accomplish the following construction of the second pyrrolidine motif in compound **11**. With a reactive Boc-protected amine, the intramolecular aza-Michael addition could take place on to the *α,β*-unsaturated iminium ion. The concept of mediating the domino Diels-Alder/aza-Michael reaction as the key step has later on been exploited in the syntheses of various indole-based natural products such as (−)-minovincine, (−)-akuammicine, and (−)-strychnine.



Scheme 4. Critical step for quaternary stereo center construction in the total synthesis of **Communesin F** and **Perphoramidine**[49]

Indole, a ubiquitous motif in naturally occurring alkaloids and their derivatives are encountered in a wide range of biologically active compounds.[44] Thus, a considerable amount of scientific research has been devoted to the enantioselective construction of indole derivatives, especially 3,3-disubstituted indoles bearing a quaternary center. Therefore, the indole-based diene **8** used in the domino Diels-Alder/aza-Michael reaction is a representative paradigm of 3,3-disubstituted indole synthesis for its related bioactive compound exploration. Besides, mechanistically this reaction manifests the advantage of the enriched electron density provided by indole for the 3,3-disubstituted indole synthesis.[43] On the other hand, oxindole as a primary metabolite of indole in the methanogenesis cycle is as essential with respect to pharmaceutical applications.[45] Although there are mechanistic differences in the reactivity of indole and oxindole, the reactive 3-position

is crucial in both cases. This highly reactive position plays a pivotal role in determining the stereochemistry of molecules in both series.[46] Based on the oxindole backbone, the quaternary center construction could be achieved in various ways. However, nucleophilic addition or substitution is used most frequently.[47] Intrinsically, oxindole could be easily deprotonated and allows facile nucleophilic addition to occur in order to construct 3,3-disubstituted oxindole. On the contrary, nucleophilic substitution for enantioselective bond formation on C(3)-substituted oxindoles is relatively rare. In 2007, Stoltz and co-workers reported a method for nucleophilic substitution to build up 3,3-disubstituted oxindoles **14** by alkylation of malonate nucleophiles. In collaboration with tertiary amine, 3-substituted-3-halo oxindole **12** and malonate would presumably be deprotonated. Through an eliminative process, the 3-substituted indolone **13** intermediates undergo a reaction with deprotonated malonate nucleophiles, leading to the formation of 3,3-disubstituted oxindoles.[48] In addition, enantioselective bond installation on a fully substituted sp^2 carbon center could be achieved with the chiral bisoxazoline copper complex as a catalyst which aggregates to the pronucleophile for providing the chiral environment and thereby facilitating the deprotonation of the malonate. Moreover, the polycyclic naturally occurring alkaloids such as communesin F, and perophoramidine were accessible based on this discovery (Scheme 4).[49]



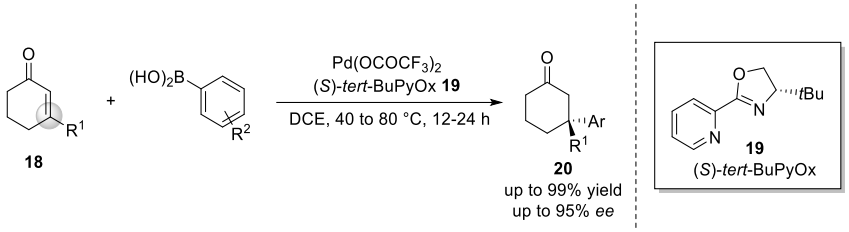
Scheme 5. The asymmetric Tsuji-Trost allylation for quaternary stereo center construction[52b]

Similar to the above-mentioned 3,3-disubstituted indole formation, α-trisubstituted ketones come into public attention in the society of organic synthesis chemists because of the versatility and the configurational complexity provided by the quaternary center it carries.[50] Thus, the tetra substituted enolates, as its precursor, were frequently used in quaternary carbon center formation in the related complex molecule synthesis. Despite the problematic steric hindrance resulting in a limited range of electrophiles to cope with, the well-established palladium-catalyzed allylic

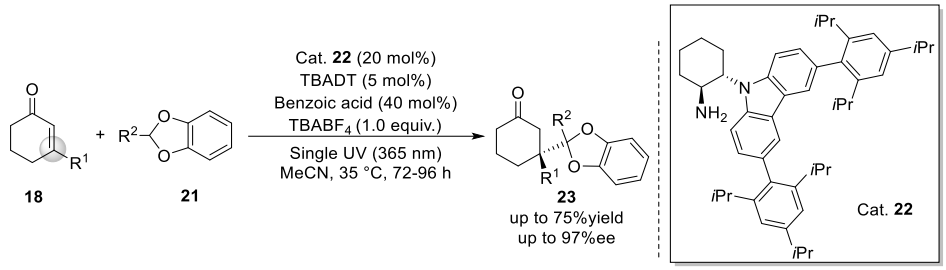
alkylation has been developed by Tsuji and Trost. to realize the functionalization of substituted enolates.[51] Nowadays, this method has been regarded as a reliable method for forging quaternary stereocenters.[52] The central concept of this catalytic allylation involves the oxidative metal addition to generate the π-allyl palladium intermediate following the nucleophilic attack from enolate nucleophiles.[52c] Besides, due to the preferential oxophilicity, the palladium cation tends to coordinate to the enolate motif, which makes the quaternary center construction an intramolecular process and minimizes the energy barrier caused by the steric issue. In the early-stage development of this method, people were focused on the highly substituted prochiral alkenes for thermodynamically more stable allyl palladium intermediate. Unfortunately, the reactivity of a germinal, doubly substituted π-allyl palladium intermediate has not been found helpful for a quaternary carbon construction so far. On the contrary, a heavily substituted prochiral enolate **15** could afford the allylated product bearing a quaternary center with excellent yield and even stereoselectivity.[52b] In 2004, the first attempt of asymmetric Tsuji-Trost allylation was reported by Stoltz and co-workers. Applying chiral phosphine ligand **16**, product **17** was obtained in excellent yield and enantiomeric excess by the catalysis of palladium complex (Scheme 5). Stemming from this triumphal progress, a significant amount of scientific research attempted to explore and broaden the substrate tolerance for this type of reaction and, of course, fulfill the enantioselective construction of the quaternary center.[52]

Other than the specialized indole systems and enolate allylation, catalytic asymmetric conjugate addition has a broad spectrum of achievable compound classes that were as well applied for the quaternary stereocenter construction.[53, 54] With proper activation, carbon-based nucleophiles is able to successfully add to the *β*-substituted *α,β*-unsaturated carbonyl acceptors, generating a quaternary stereocenter in the resulting product. The addition of prochiral Michael acceptor 3-methyl-2-cyclohexen-1-one (**18**) is the most iconic example, which has already been tested by multiple research groups.[53] The steric hindrance caused by the *β*-methyl group dramatically enhances the difficulty of nucleophilic addition; therefore, without the assisting metallic Lewis acid, this conjugate addition is unrealistic. On the contrary, with the proper activation from transition metal complexes such as Cu and Pd, which could presumably bind to both unsaturated carbonyl acceptors and nucleophiles, the bond formation was allowed to happen in an approximately intramolecular manner. According to the achievement reported in the past in this field, copper-catalyzed conjugate additions require highly reactive organometallic nucleophiles

such as diorganozinc, triorganoaluminium, and organomagnesium reagents.[53e] The requirement for air- and moisture-sensitive nucleophiles present a challenge as it necessitates strictly anhydrous reaction conditions. However, this reliance on such conditions can cause inconvenience from a practical standpoint. On the other hand, catalyzed by Pd complexes cooperating with chiral ligand **19**, the enantioselective conjugated addition on 3-methyl-2-cyclohexen-1-one (**18**) with commercially available aryl boronic acids was tested and reported by Stoltz and co-workers in 2011(Scheme 6).[53b] From the perspective of convenience, the less expeditious procedure of Pd-catalyzed conjugate addition of aryl boronic acids is in comparison much more valuable method for quaternary stereocenters generation. Based on these pioneering discoveries, more and more successful examples of asymmetric conjugate addition for embedding the quaternary stereocenters onto a cyclohexanone backbone were found in the past decade.[53, 54]



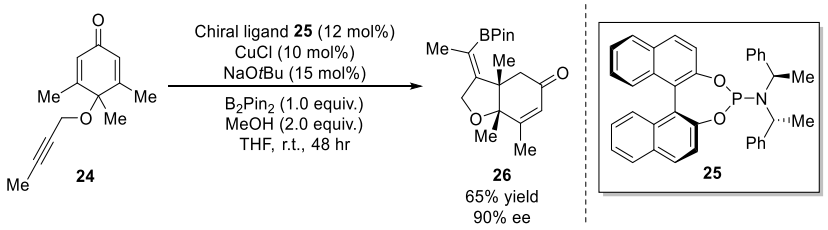
Scheme 6. The asymmetric 1,4-addition to highly substituted sp^2-carbon for quaternary stereo center construction[53b]



Scheme 7. The asymmetric radical addition for quaternary stereo center construction[55]

For the same issue of quaternary stereocenters generation on β-substituted α,β-unsaturated carbonyl acceptors, Melchiorre and co-workers have proposed a different entry point to solve this synthetic problem (Scheme 7).[55] Traditionally, organic bond formation relies on polar reactivity to address the challenging enantioselective quaternary stereocenters establishment. Despite the metal-catalyzed conjugate addition on β-disubstituted Michael acceptor has already attained an outstanding achievement, there are still some limitations it cannot overcome. The primary challenge lies in the cautious reaction conditions, which are not suitable for large-scale industrial

production. Additionally, the substrate tolerance is restricted by the reactivity that the nucleophiles can offer, imposing limitations on the range of applicable substrates. In contrast, the long incipient carbon-carbon bond in the early stage of radical additions to a highly substituted unsaturated ketone is less suffocated due to the steric hindrance. Intrinsically, the nature of radical reactivity is particularly suitable for forging structurally complicated fragments. Meanwhile, the technique of emerging photoredox catalysis for radical generation from air-stable precursors has become more mature recently; therefore, the novel methodology combines the effective radical generation strategy and the proper catalyst design for radical stabilization and stereoselectivity-control during the quaternary stereocenters formation was invented by Melchiorre *et al.* In their work, a designed chiral primary amine **22** was used as a catalyst to produce catalytically active iminium ions *in situ*. Theoretically, electrically neutral radical traps are a common but effective measurement for prolonging the lifetime of olefinic radical species. However, in a cationic iminium activation model, the radical intermediate generated in the radical addition is unstable and prone to undergo a *β*-scission retro process. In order to overcome this dilemma, a redox-active, electron-rich moiety was attached to the primary amine in catalyst **22**. With the specialized catalyst, a rapid single electron transfer (SET) from the electron pool side chain to α-iminyl radical could push the reaction further and produce the desired product **23** in a chiral manner.[55]

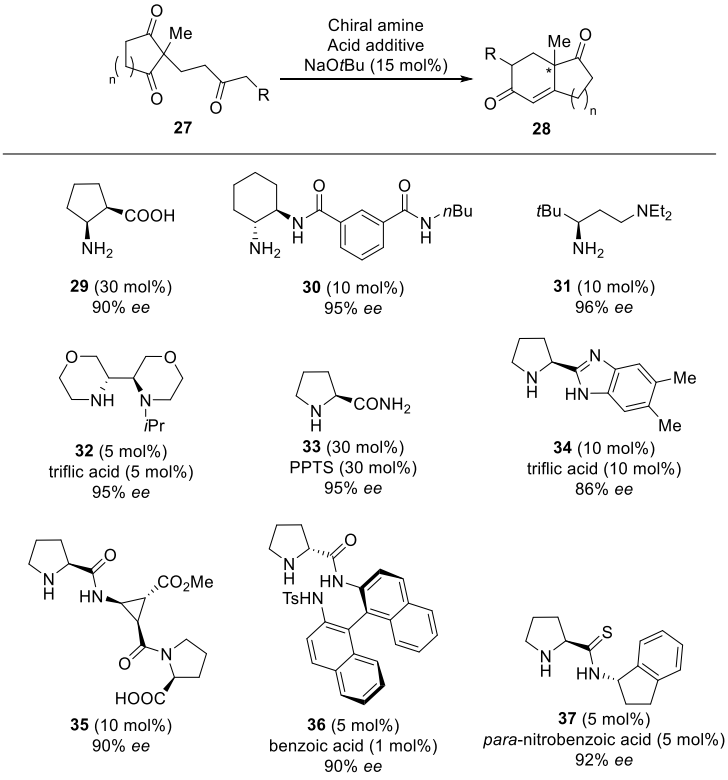


Scheme 8. Methodology for quaternary stereocenter construction *via* desymmetrization of cyclohexadieneone **24**[56]

According to the reactivity mentioned above of *α,β*-unsaturated carbonyl compounds, it has been proven that *α,β*-unsaturated carbonyl compounds are versatile substrates that have a broad tolerance to other sorts of chemical transformation.[53-55] Thus, the desymmetrization of symmetric *α,β*-unsaturated carbonyl compounds such as cyclohexadieneone utilizing well-established methods for enantioselective bond formation is emerging. Disclosure by Tian, Lin and co-workers, an intramolecular cyclization of symmetric *β*-methyl *α,β*-unsaturated cyclohexenone **24** bearing a prochiral quaternary center could be accomplished *via* tandem copper-catalyzed borylation/Michael addition to give tetrahydrobenzofuran derivatives **26** (Scheme 8). Initiated by

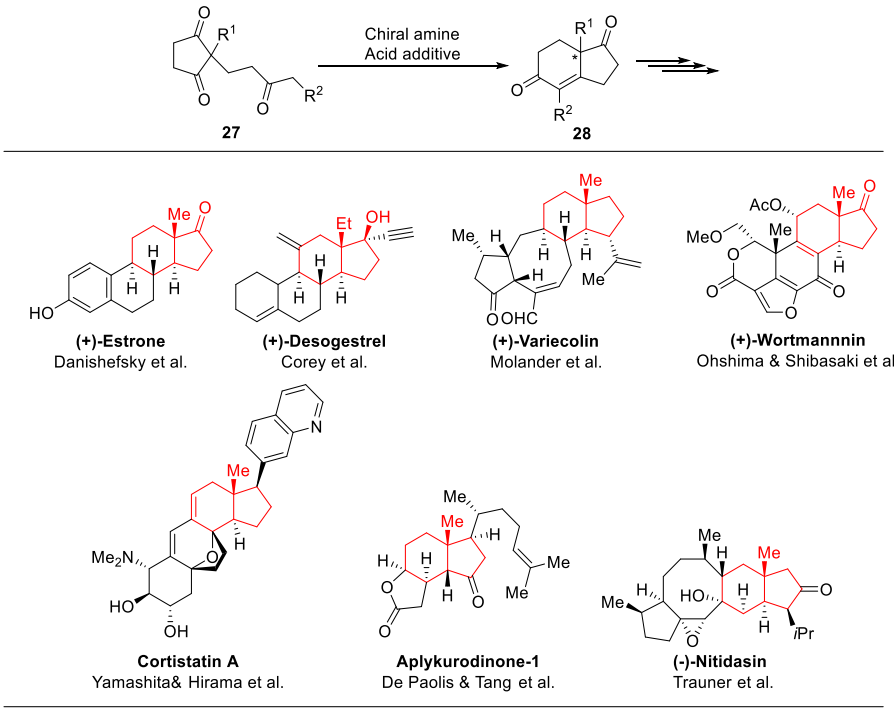
the copper-activated alkyne borylation, the corresponding organocopper nucleophile would allow the following 1,4-addition on *α,β*-unsaturated carbonyl to occur.[56] Provided by the chiral phosphite-based ligand **25**, the addition was affected by the chiral environment and proceeded in an enantioselective manner. In this cascade bond-forming process, two consecutive stereocenters were generated in two entirely different ways. With an intramolecular nucleophilic attack, the addition to a congested sp^2 prochiral center could be addressed; however, it is highly restricted structurally concerning the nucleophilicity and the steric hindrance. On the contrary, the prochiral center could be easily transferred into the chiral center without actual bond formation on itself. Through this example, minuscule benefits of desymmetrization were visualized compared to other methods for forging quaternary stereocenters. (1) The task could be simplified with a pre-existing quaternary carbon center because quaternary center generation is no longer an interference while solving the enantiofacial differentiating issue. (2) The bond formation is located on the reactive site away from the crowded quaternary center to avoid the steric obstacle in the process of bonding establishment. In comparison, the concept of desymmetrization has broad feasibility in terms of substrate tolerance, which is compatible with various types of reactions.[57]

Table 1. Collective results of chiral Hajos−Parrish ketone synthesis[59-64]



For instance, given the versatility of symmetric 1,3-diketones bearing a prochiral quaternary carbon center, symmetric 1,3-diketones could afford various chemical transformations to improvise the chirality onto the pre-existing quaternary stereocenter. Among all the extensive scientific investigations on the enantioselective desymmetrization of prochiral 1,3-diketones, the aldol-type reactions were mentioned in different aspects of organic synthesis research.[58] Among those related research, the stereoselective syntheses of Hajos-Parrish ketone **28** and Wieland-Miescher ketone **39** are the most representative examples of chemically transforming an achiral quaternary center into a chiral quaternary stereocenter *via* a desymmetrization procedure.[59] Due to the multiple utilities of these chiral building blocks, multiple research groups provided their solution for these enantiopure ketone syntheses.

Table 2. Naturally occurring product synthesis based on chiral Hajos−Parrish ketone building block[65-71]

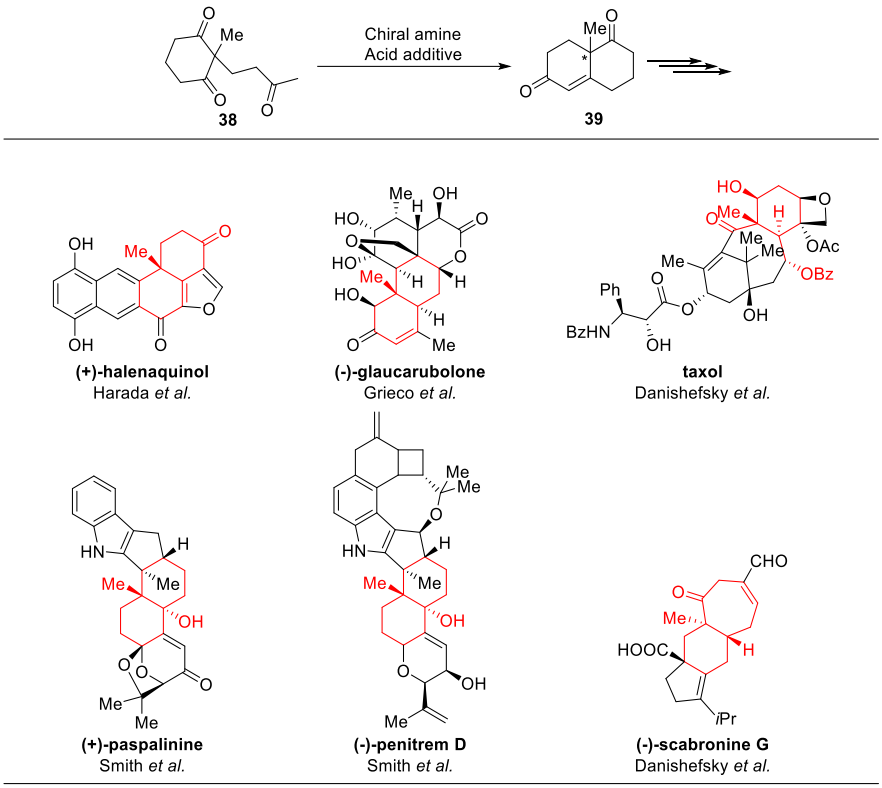


Proposed and accomplished in 1971 by Hajos, Parrish *et al.*, the concept of intramolecular aldol-type condensation of symmetric triketone **27** in the presence of primary or secondary amine catalyst initiates the intramolecular cyclization to occur and establish the indene-1,5-dione skeleton.[59a] The reaction is efficient and fond of various substrates; hence there is extensive research on bioactive compound synthesis based on Hajos-Parrish ketone discovered and calls for profound stereoselective synthetic methods. Herein, the collective results were organized to

display the previous effort that has been devoted to the chiral bifunctional organocatalysts for the enantioselective Hajos-Parrish ketone construction. Featuring hydrogen bond donating or accepting functional groups, the bifunctional catalysts such as primary amine catalyst **29**,[60] **30**,[61] **31**,[62] morpholine derivative **32**,[63] and pyrrolidines **33**-**37**,[64] were used by different working groups, respectively (Table 1). According to the substrates, the effect of the acidic additives and the catalyst usage were also listed in the table. Mechanistically, the chiral amine catalyst will undergo the Stork enamine synthesis on a sterically less hindered ketone group in the substrate. Regarding the nucleophilicity building up in the process of corresponding enamine generation in the catalytic cycle, the intramolecular aldol-reaction is imperative. Therefore, under the guidance of the hydrogen bonding provided by the chiral catalyst, the structurally favored enantiomeric imine intermediate would form presumably. Last but not least, the amine catalyst could be liberated for the next catalytic cycle by facile imine hydrolysis. With the blooming progress of chiral Hajos-Parrish ketone syntheses, an extensive range of naturally occurring products such as (+)-estrone,[65] (+)-desogestrel,[66] (+)-variecolin,[67] (+)-wortmannin,[68] cortistatin A,[69] aplykurodinone-1,[70] and (−)-nitidasin[71] which have a Hajos-Parrish ketone as a core building block could then be accomplished in more efficient ways (Table 2).

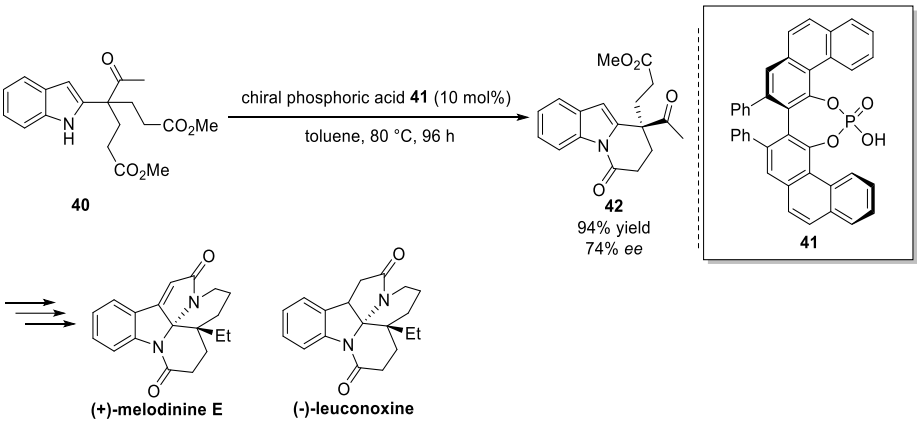
Along with Hajos-Parrish ketones **28** and their analogs, the reactivity of Wieland-Miescher ketones **39** bearing chiral quaternary stereocenters in the sense of its production is alike. In addition, these two ketones share similar stereochemistry, which was broadly applied in various natural product syntheses as a chiral building block. Despite the achiral synthesis of Wieland-Miescher ketones being discovered earlier than Hajos-Parrish ketones in 1950, stereoselective synthesis was underappreciated by the time, and enantiopure Wieland-Miescher ketones were not investigated.[59b] Nevertheless, twenty-seven years later, the idea of the asymmetric synthesis method found in Hajos-Parrish ketones formation was implanted in Wieland-Miescher ketones synthesis.[72] Additionally, concerning the demand for a broad range of naturally occurring compound synthesis, the Wieland-Miescher ketones in both enantiomeric series are accessible from catalytic enantioselective desymmetrization of triketone **38**. Since then, the research on the Wieland-Miescher ketones-related synthesis never faded. A list of naturally occurring product synthesis elaborated from the Wieland-Miescher ketone synthesis was exemplified in Table 3, such as (+)-halenaquinol,[73] (+)-paspalinine,[74] (−)-glaucarubolone,[75] taxol,[76] (−)-penitrem D,[77] and (−)-scabronine G (Table 3).[78]

Table 3. Naturally occurring product synthesis based on chiral Wieland−Miescher ketone building block[73-78]

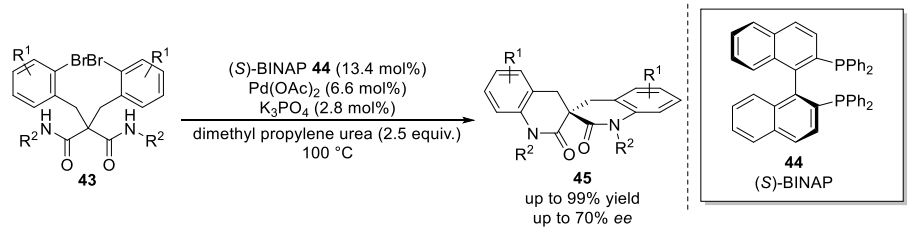


Apart from symmetric diketones, prochiral diesters are interesting target molecules known for asymmetric transesterification and lactamization. For instance: In 2015, Higuchi, Kawasaki and co-workers demonstrated the enantioselective total synthesis of (+)-melodinine E and (−)-leuconoxine.[79] Employing the concept of desymmetric lactamization of diester **40**, chiral phosphoric acid **41** was applied as a Brønsted acid catalyst which allowed the enantioselective ring closure to occur (Scheme 9). Along with the chiral lactam synthesis, the Buchwald-Hartwig reaction is a well-established strategy for this purpose.[80] By exploiting the palladium-catalyzed intramolecular *N*-arylation, it became possible to achieve a chiral desymmetrization of prochiral 1,3-diamides. A noteworthy demonstration of this method was observed in 2009, when a fascinating synthesis of C2-symmetric spirobi(3,4-dihydro-2-quinolone) derivatives **45** was accomplished (Scheme 10).[81] The synthetic route commenced with symmetric malonamides **43**, which were doubly *N*-arylated and featured *O*-bromoarylmethyl groups. Different from the diketone and diester, the diamine reacts as a nucleophilic site affording the ligand exchange after the oxidative insertion to the aryl functional group. Interfered by a chiral phosphine-based ligand **44**, the enantiomeric excess could reach 70%. Based on this preliminary result reported by Sasai

and co-workers, more and more research is devoted to improving the performance of stereoselectivity. The latest findings reveal that the chiral copper catalyst exhibits a superior ability to mitigate racemic background reactions compared to palladium. This effect is achieved by reducing the coordinating ability to diamide, thereby resulting in enhanced catalytic performance. According to the latest achievement in this field, Cai and co-workers recently published the result of the enantioselective desymmetrization of substituted 2-benzyl-2-(2-iodobenzyl)malonamides **46** (Scheme 11).[82] The utilization of the approved Cu(I) complex with chiral 1,2-diamine **47** has been demonstrated as the optimal environment for the enantioselective synthesis of six-membered quinolinone derivatives **48**. Remarkably, this approach achieves yields ranging from 52% to 98%, with enantiomeric excess (*ee*) values of up to 80%, representing the most successful outcome to date.



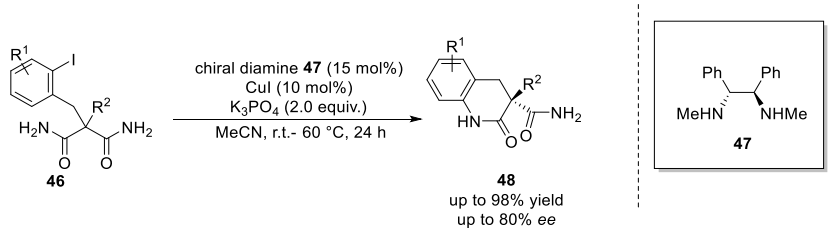
Scheme 9. The desymmetrization of prochiral diester for **(+)-melodinine E** and **(−)-leucinoxine** synthesis[80]



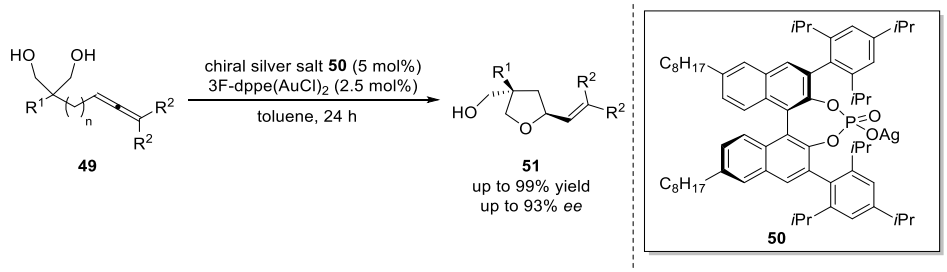
Scheme 10. Asymmetric Buchwald-Hartwig reaction for chiral spirobis(3,4-dihydro-2-quinolone) **45** synthesis[81]

From the easily accessible malonates derivatives or active methylene compounds, symmetric diols **49** bearing a quaternary carbon center can be prepared by facile procedures. Alcohol, as a common nucleophile, could afford a vast spectrum of reactivity; among all different reaction types, esterification is the most used method for preparing optically active alcohols bearing quaternary stereocenters. Along with the concept of the transesterification in the prochiral diester

desymmetrization, the chemically identical enantiotopic hydroxy groups could stereoselectively proceed with esterification with the assistance of chiral catalysts such as Lewis acid, enzyme, amine, etc., to embed the chirality in the quaternary center. Apart from that, miscellaneous reactions utilizing the chiral metal complexes for intramolecular C−O bond formations are alternative asymmetric reactions for bringing chirality to prochiral diols. For example, a gold-catalyzed intramolecular hydrofunctionalization of allenes **49** reported by Toste and co-workers exhibits the anion-induced enantioselective desymmetrization of diol substrates **49** (Scheme 12).[83] After intensive optimization, they found that intramolecular hydroalkoxylation could occur on the activated allene motif in the presence of 5 mol% of (*R*)-C8-TriP-derived silver salt **50** and 2.5 mol % 3-F-dppe(AuCl)$_2$, to result in multi-substituted tetrahydrofuran derivatives **51** in satisfying stereoselectivity. In addition, symmetric unsaturated hydrocarbons such as diene and diyne have been used in the desymmetrization reactions forging the quaternary stereocenters for a long time and accomplishing the synthesis of some eye-catching compounds.



Scheme 11. Modified asymmetric Buchwald-Hartwig reaction[82]

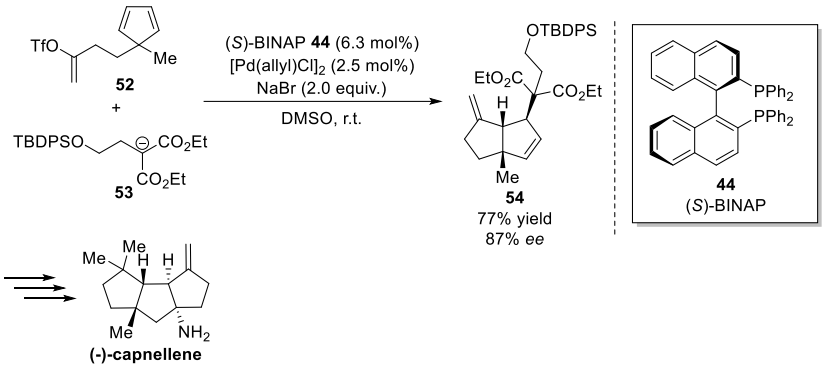


Scheme 12. Gold-catalyzed allene hydrooxylation for quaternary stereo center construction[83]

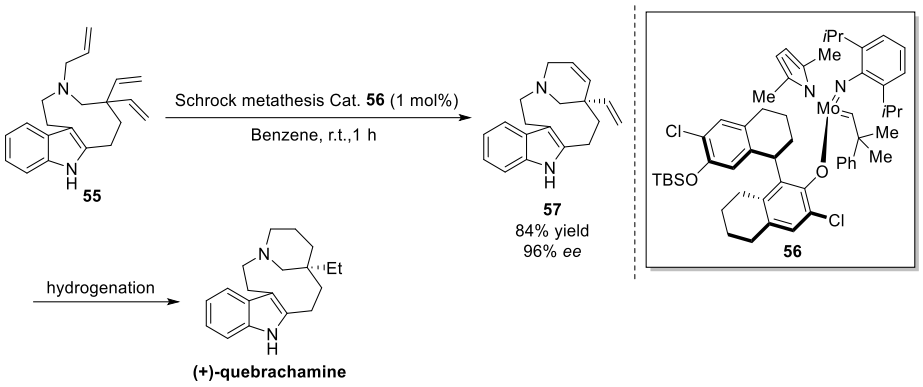
Apart from typical nucleophilic addition or substitution, the reaction between alkenes could also be exploited in asymmetric synthesis, even naturally occurring product synthesis. Driven by a strong interest in synthesizing (−)-capnellene, Shibasaki and his team have successfully devised an intramolecular Heck/Tsuji-Trost tandem reaction for desymmetrizing prochiral dienes **52** (Scheme 13).[84] By utilizing an enantiopure (*S*)-BINAP **44** palladium complex, the prochiral

cyclopentadiene **52** undergoes an enantioselective intramolecular Heck coupling, resulting in the formation of a cationic bicyclooctene intermediate. Subsequent to the Tsuji-Trost type allylation step, the generated allylic cation can be easily captured by the nucleophilic carbanion **53**. This efficient reaction leads to the formation of the desired bicyclooctane **54**, exhibiting a satisfying enantiomeric excess meeting the desired stereochemical requirements. Furthermore, building upon the successful asymmetric synthesis of bicyclooctane **54**, the total synthesis of (−)-capnellene was accomplished.

In 2006, Hoveyda and his team achieved another significant milestone in the synthesis of (+)-quebrachamine. Their pioneering work involved the catalytic enantioselective ring-closing metathesis of enol ethers, leading to the creation of quaternary carbon stereogenic centers during the cyclization process.[85a] Since the publication of these groundbreaking studies, researchers have been eager to employ these methodologies in diverse natural product syntheses.[85b,85c] To address the need for total synthesis and enhance efficiency, Schrock, Hoveyda, and their colleagues developed a potent molybdenum-based chiral catalyst **56** (Scheme 14).[85d] This catalyst demonstrated the feasibility of total synthesis for (+)-quebrachamine, featuring a quaternary stereocenter. With just 1 mol% of the molybdenum complex **56**, the enantioselective desymmetrization of indole-based triene **55** could be completed within one hour, yielding the crucial intermediate **57** for the synthesis of (+)-quebrachamine with a remarkable enantiomeric excess of 96% (96% *ee*).



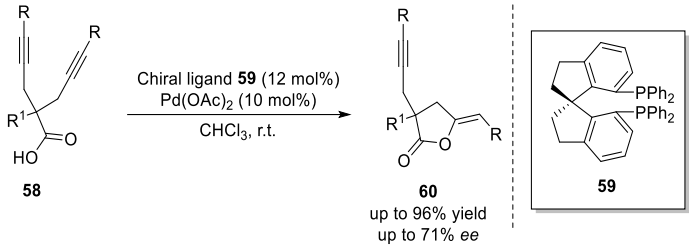
Scheme 13. The asymmetric intramolecular Heck reaction in the total synthesis of (−)-capnellene[84]



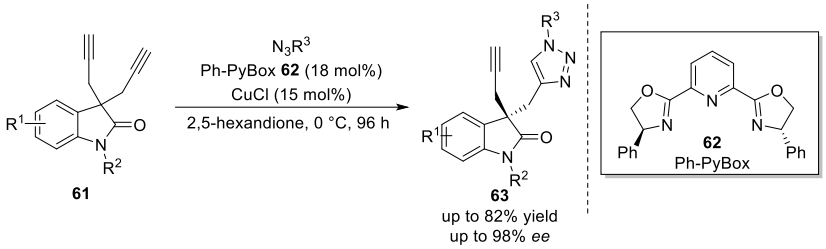
Scheme 14. The asymmetric metathesis of dialkene in the total synthesis of (+)-quebrachamine.[85d]

In the past, prochiral diynes were not generally utilized for the synthesis of naturally occurring products, unlike other symmetric compound classes mentioned above. Despite the feasibility of desymmetrization and creating quaternary stereocenters, their potential in this area remained underdeveloped. For example, the desymmetrization of *α,α*-disubstituted diynoic acids **58** catalyzed by chiral Pd complex **59** reported by Sridharan, Sasai, and co-workers exhibits excellent stereoselectivity controlled in this 5-*exo*-dig cyclization to compound **60** (Scheme 15).[86] Besides, with appropriate modifications, the prochiral diyne desymmetrization *via* enantioselective intramolecular alkyne hydrofunctionalization was successfully demonstrated by Hennecke's[87] and Sadow's[88] research group. On the other hand, the intermolecular reaction for the purpose of quaternary stereocenters building up *via* a prochiral diyne desymmetrization was verified by the investigation of the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC). In 2013, the first enantioselective desymmetrization of prochiral oxindole-based 1,6-heptadiyne **61** was described by Zhou *et al.* In this work, 10 mol% Ph-PyBox **62** as ligand incorporating copper chloride could afford the 1,6-heptadiynes desymmetrization in a chiral fashion (Scheme 16).[89] In addition, after an intensive optimization, the overreacting ditriazole side product could be minimized. Establishing upon the success of the CuAAC prochiral diyne desymmetrization demonstrated, an increasing number of research groups are dedicating their efforts to this field and carrying out inspiring investigations continuously. Noticeably, among all the research on prochiral diyne desymmetrization, 1,4-diynes have rarely been discussed.[90] In principle, symmetric diynes have great potential to be a class of versatile substrates for valuable organic compound formation. However, the linear configuration enhances the difficulties in enantioselective bond formation. Furthermore, the synthetic methodologies available for diynes containing a prochiral quaternary

carbon center are extremely limited, particularly in the case of 1,4-diynes synthesis so far. Therefore, the following section will focus on the previous result of 1,4-diynes synthesis and its reactivity. Additionally, the development of bismuth-catalyzed 1,4-diyne functionalization for a broader range of 1,4-diyne species synthesis will also be described.



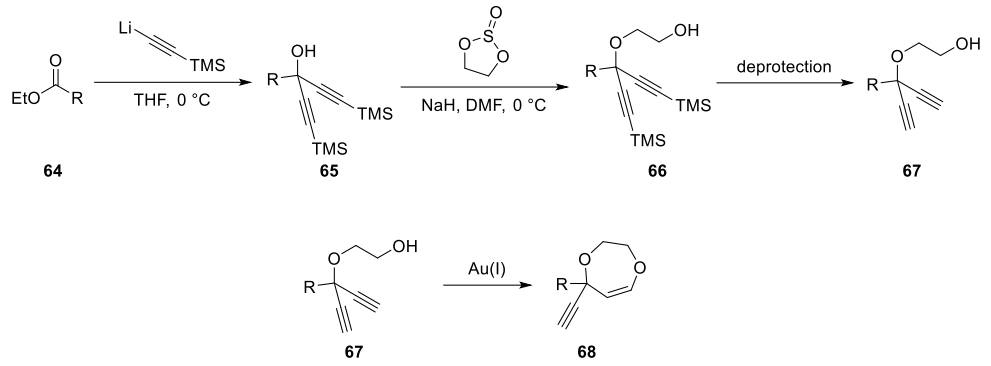
Scheme 15. Desymmetrization of prochiral diynes bearing a quaternary center *via* intramolecular bond formation[86]



Scheme 16. Desymmetrization of prochiral diynes bearing a quaternary center *via* intermolecular bond formation.[89]

1-2-2 Development of novel 1,4-diyne species

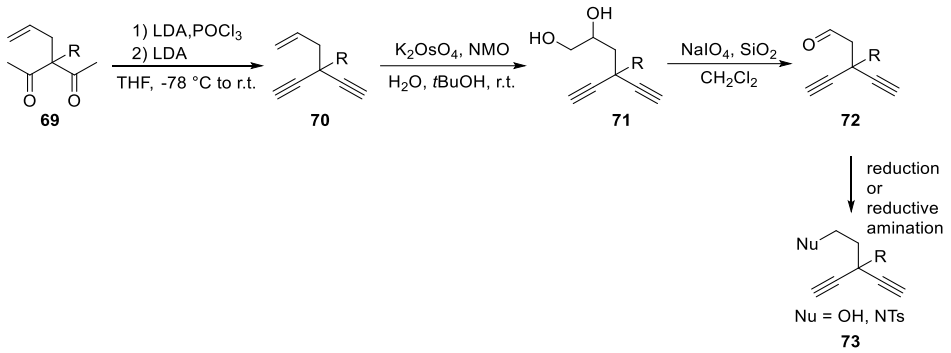
Alkynes incorporating a highly reactive functional group that allows various types of chemical transformations and provides a wide spectrum of available compounds.[91] Moreover, the widespread adoption of desymmetrization techniques in synthesizing complex molecules with quaternary carbons is currently mainstreaming. This trend indeed creates a substantial demand for symmetric diyne substrates. In the literature survey, the synthesis and reactions of 1,5- and 1,6-diynes have been discussed frequently.[93] Contrarily, the research on 1,4-diyne compounds has remained relatively dormant for an extended period. This chapter will focus on the previously published 1,4-diyne synthesis and our investigation of novel synthesis methodology for 1,4-diyne derivatives.



Scheme 17. Synthesis of 1,4-diyne substrates and its application.[95]

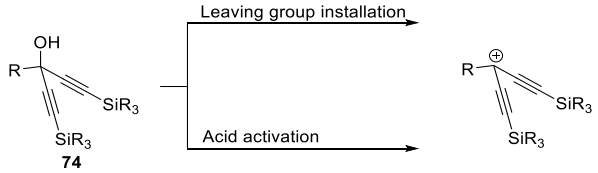
In 2004, a practical procedure for 3-substituted 3-hydroxy-l,4-diynes species **65** was established and reported by Tanner and co-workers, who successfully installed the alkynyl group twice onto an ester substrate **64** utilizing lithium acetylide (Scheme 17).[94] In 2009, our research team developed a series of procedures for the synthesis of 2-((3-alkyl-penta-1,4-diyn-3-yl)oxy)ethan-1-ol (**67**) on the basis of the previous 3-hydroxy-l,4-diyne **65** syntheses. Subsequently, we explored the application of gold-catalyzed *endo*-cyclizations, leading to the formation of seven-membered heterocycles **68**.[95] The abnormal *anti*-Markovnikov intramolecular addition to alkyne has been suggested by the stereoelectronic interaction of the σ(C−Au)-orbital with the σ*(C−O)-orbital. Other than the unique reactivity in terms of gold-catalyzed seven-membered ring closure, it also causes the limitation of substrate tolerance.[96] Because of the interaction between σ*(C−O)-orbital and σ(C−Au)-orbital, the C−O bonding is weakened and prone to undergo a rearrangement instead. Therefore, our research group established in 2011 the first synthetic method for 1,4-diynes baring a quaternary center to avoid the rearrangement and tried to broaden the applicability of our method. The concept of symmetrical 1,4-diynes feathering a quaternary center synthesis is about transforming a 3,3-disubstituted acetylacetone **69** into a 3,3-disubstituted 1,4-diyne **70-73** (Scheme 18). The synthesis of 1,4-diynes begins with an Ullmann coupling of penta-2,4-dione to generate the 3-aryl-penta-2,4-dione. Followed by a *C*-selective allylation on 3-position, a 3-allyl-3-aryl-1,4-diyne (**70**) could be readily prepared. Later on, the acidic α-proton on the acetyl functional group could be easily deprotonated by non-nucleophilic bases such as LDA, which allows *O*-phosphorylation to occur and form a vinyl phosphate intermediate. To the vinyl phosphate intermediate, the second equivalent of the base was added to initiate the elimination and generate symmetric 1,4-diyne **70** as the product. The versatile allyl group could contribute to different heteroatom nucleophiles installation such as alcohol, amine, etc. With a quaternary center,

the stereoelectronic interaction no longer influences the regioselectivity in the furan or pyrrolidine ring closure, and the 3,3-dialkyl-1,4-diynes **73** becomes more stable than 3-alkyl-3-oxyalkanol-1,4-diyne (**67**).



Scheme 18. Synthesis of 1,4-diyne substrates with a quaternary center in the previous work from our group[96]

This previously discovered synthesis pathway for 3,3-dialkyl-1,4-diynes is feasible, however inconvenient. Hence, we tried to find another possibility for the synthesis of such 3,3-double-substituted 1,4-diynes and tried to broaden the substrate scope. In order to develop a novel synthesis for 3,3-di-substituted 1,4-diynes **73**, the 3-substituted-3-hydroxyl-l,4-diynes **74** would be an equivalent starting point. Other than the derivation relying on the nucleophilicity of the hydroxy group shown in the synthesis of 2-((3-alkyl-penta-1,4-diyn-3-yl)oxy)ethan-1-ol (**67**), it conversely provides possibilities of substitution on the propargylic carbon as well. Thus, we looked into the propargylic substitution of selected penta-1,4-diyn-3-ols **74** and tried to develop a more straightforward method for synthesizing 3,3-double-substituted-1,4-diynes **73** (Scheme 19).

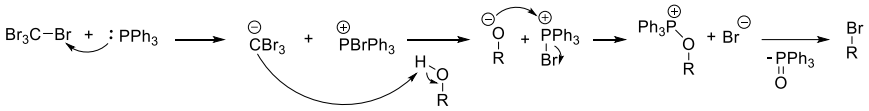


Scheme 19. Concept of possible propargylic substitution for the 1,4-diyne substrate synthesis

Inherently, the hydroxy group is not considered an optimal leaving group for substitution reactions. However, it can be transferred into an appropriate leaving group or activated as a leaving group in the presence of acid. The following section will delve into both aspects, providing a detailed discussion and presenting preliminary results related to the propargylic substitution on 3-substituted-3-hydroxyl-l,4-diynes **74**.

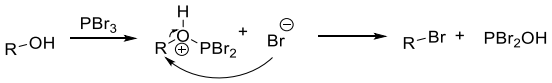
1-2-2-1 Leaving group installation

For the purpose of installing a substituent directly to 3-substituted-3-hydroxyl-l,4-diynes **74**, it requires an exceedingly reactive leaving group. Thus transforming the hydroxyl group into leaving group is our primary task for the investigation of the propargylic substitution. In order to convert the hydroxy group to a promising leaving group such as bromide, two well-established methods, (1) Appel reaction[97] and (2) Hell-Volhard-Zelinsky halogenation[98], are frequently used.



Scheme 20. The general idea of Appel's reaction to converting alcohol into bromide[97]

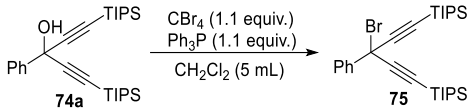
The Appel reaction is a widely used method for the conversion of alcohols into relevant alkyl bromides (Scheme 20).[97] The chemical transformation begins with the reaction between triphenylphosphine and tetrahalomethane. This leads to the formation of a tribromocarbanion, which then facilitates the deprotonation of the alcohol. Due to the oxophilic nature of triphenylphosphonium bromide, an oxyphosphonium intermediate is involuntarily generated. Subsequently, the intermediate undergoes spontaneous substitution with a halide nucleophile, resulting in a corresponding alkyl halide. Alongside the desired product, phosphine oxide is produced as a byproduct due to the high tendency of phosphine oxidation. This oxidation reaction serves as the driving force for the overall process, making it advantageous for overcoming steric hindrance challenges and enabling the halogenation of alcohols with conformational obstacles.



Scheme 21. The general idea of Hell-Volhard-Zelinsky halogenation[98]

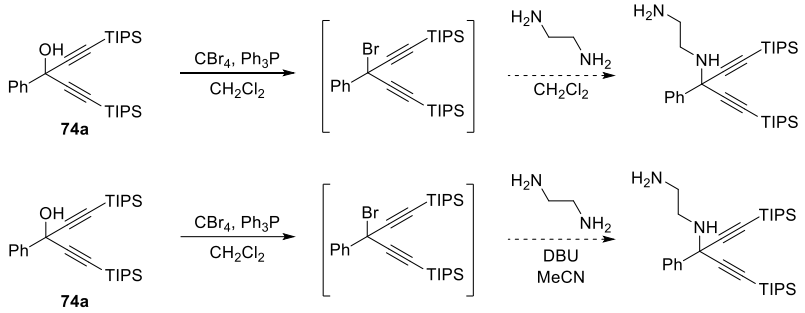
On the other hand, the Hell-Volhard-Zelinsky halogenation is a well-established procedure for bromination by using tribromophosphine as a bromine resource. While initially developed for the bromination of carboxylic acids, the concept has been successfully extended to alcohols in recent years, resulting in favorable outcomes (Scheme 21).[98] Despite the success of Hell-Volhard-Zelinsky halogenation in converting alcohols to bromides has been proven that the byproduct phosphoric acid as a side product might weaken the nucleophile and constrain the scope of applicable substrates. Furthermore, this reaction's compatibility with one-pot synthesis methods

is also compromised. Considering these limitations, our investigation will commence with the Appel reaction using selected substrates, 3-phenyl-3-hydroxyl-l,4-diynes **74a** (Scheme 22).



Scheme 22. The bromination of compound **74** *via* Appel halogenation

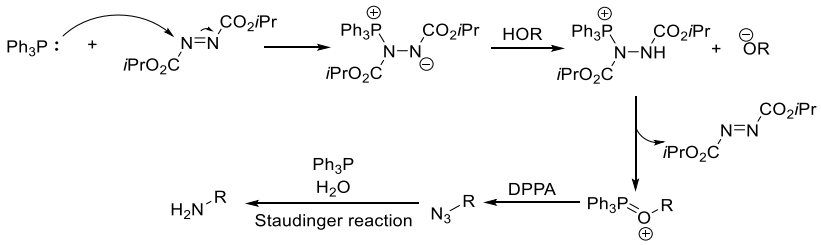
To prevent the occurrence of unnecessary side reactions such as alkyne transformation, silyl-protected alkyne **74a** was used to carry out the bromination under Appel's condition (Scheme 23, top). To a dried round bottom flask equipped with a magnetic stir bar, a solution of triphenylphosphine (1.10 equiv.) and tetrabromomethane (1.10 equiv.) in anhydrous dichloromethane (5 mL) was prepared. After 30 min stirring under the protection of N_2, 1 gram of 3-phenyl-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (**74a**) was added to the reaction mixture, and the reaction was stirred at room temperature. Within 3 hours, the complete consumption of starting material could be observed by TLC. To our delight, the Appel reaction seems to occur on 1,4-diyn-3-ol successfully. The analysis of crude TLC and NMR implies that the alcohol is converted into other species, which are less polar and have a similar pattern in the ^{1}H-NMR spectrum; however, the isolation of the product is problematic due to the instability of the corresponding alkyl halide. From flash column chromatography on the silica stationary phase, we could merely attain 3-phenyl-3-hydroxy-l,4-diyns **74a**, although the recovery yield is pretty good.



Scheme 23. The one-pot bromination/amine substitution of compound **74a**

To prevent alkyl bromide **75** from decomposition, we thus tried a one-pot Appel/substitution reaction. By employing *in situ* alkyl bromide generation, the subsequent substitution can proceed directly, mitigating the risk of decomposition. As a nucleophile, the diamine was treated to the reaction mixture, while the resulting TLC indicated the accomplishment of Appel bromination.

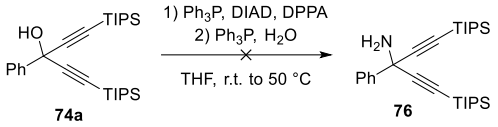
The reaction mixture was stirred for another 24 hours at room temperature after adding ethylenediamine. Unfortunately, upon TLC analysis no evidence of substitution occurring on the alkyl bromide. Recognizing the potential influence of the solvent in the substitution process, we decided to switch to MeCN as the solvent, which revealed the completion of bromination (Scheme 23, bottom). In order to increase nucleophilicity and neutralize the resulting hydrobromic acid, we introduced 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as an organic base in the subsequent experiment. However, no substitution was observed through TLC analysis after 24 hours of reaction time. Significantly, we observed the formation of white precipitation during the reaction, which could potentially be the ammonium salt corresponding to the product. To address this uncertainty, we carefully collected a representative portion of the reaction crude mixture, comprising both the solution and the solid precipitation. These samples were then prepared in suitable solvents for analysis by mass spectrometry and nuclear magnetic resonance spectrometry (NMR). To our disappointment, the obtained results did not indicate any evidence of the desired formation of the ammonium salt.



Scheme 24. The general idea of Mitsunobu amination[99]

Upon analysis, it was confirmed that despite the lack of immediate substitution following the Appel bromination, the feasibility of carrying out Appel bromination on 1,4-diyn-3-ol substrate **74a** was indeed established. Therefore, we decided to continue the investigation on propargylic functionalization by continuously testing Mitsunobu amination (Scheme 24).[99] Mitsunobu reaction principally shares a similar concept with Appel/substitution reaction in converting alcohol into the other functional group driven by the oxidation of phosphines. Diisopropyl azodicarboxylate plays the same role as tetrabromomethane in Appel halogenation, which procures the formation of oxyphosphonium intermediate. Similar to the bromide used in the Appel reaction, diphenyl phosphoryl azide was utilized as an amino nucleophile to facilitate the subsequent S_N2 reaction in the Mitsunobu amination. This reaction resulted in a notable inversion of the conformation. The resulting azide was eventually reacted with an additional equivalent of

phosphine to initiate the Staudinger reaction, enabling the formation of the desired primary amine **76**.



Scheme 25. The result of Mitsunobu amination of compound **74**

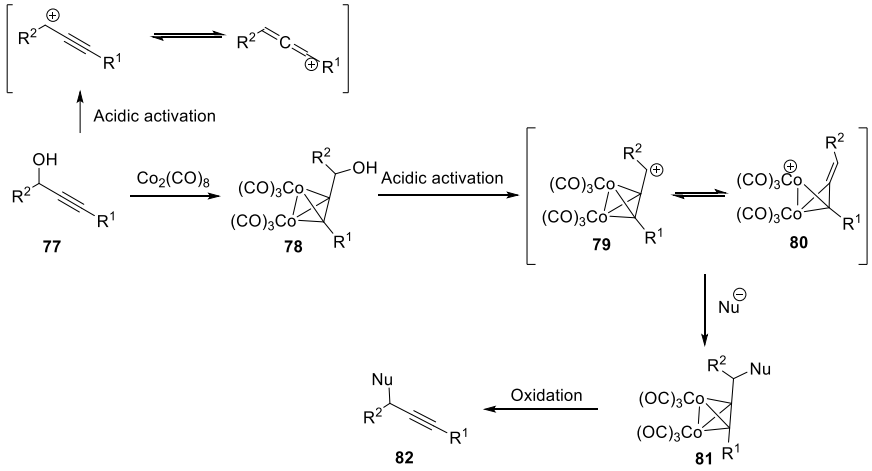
Undertaking the concept of the Mitsunobu reaction we carried out the reaction in anhydrous THF to evaluate the practicability of our 1,4-diyne **74a** (Scheme 25). Unfortunately, an unexpectedly low reactivity was observed after keeping the reaction stirring at 50 °C for three days. The analysis of TLC indicates only a trace amount of propargylic alcohol was reacted, and the resulting mass spectrum is not orientated to an expected primary amine **76** either.

In summary, the leaving group installation on 3-substituted 3-hydroxl-l,4-diyns **74a** is in general accessible; however, the reactivity of corresponding alkyl bromide to the following substitution is disappointing. The unenforceable isolation of the labile propargylic bromide, to a certain extent, increases the difficulty and limits the exploration of this reaction within the range of one-pot synthesis.

1-2-2-2 Lewis acid activation

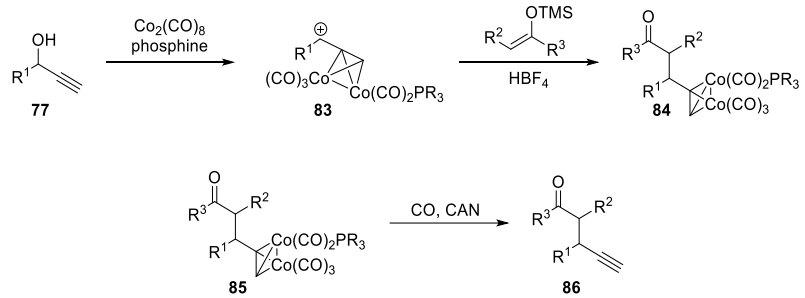
In contrast, propargylic bromination utilizing Lewis acid-activated carbocation formation offers several advantages, including tunable reactivity and ignorable intermediate purification. The Nicholas reaction, a renowned propargylic substitution method, has found extensive applications in organic synthesis. This reaction utilizes dicobalt hexacarbonyl to coordinate with the alkyne functional group, forming a cobalt complex **78**. The presence of this complex facilitates the formation of acidic intermediates, promoting the substitution process (Scheme 26).[100] Meanwhile, the alkyne motif is protected from isomerization preventing the reaction from unwanted addition to occur to the mesomeric allenyl cation. Moreover, the complexation from cobalt provides additional stabilization to the corresponding carbon cation **79** and approves further bond formation. Since the property of alkyne was altered by the cobalt, the nucleophile demanding S_N1 reaction is no longer a limitation to the propargyl alcohol **77**. When the propargyl replacement was finished, the cobalt protective group could be oxidatively removed. With a broad range of nucleophiles,

including carbon atom nucleophiles and other electron-rich heteroatoms, the Nicholas propargylic replacement could be performed.



Scheme 26. The general idea of propargylic replacement under Nicolas' condition[100]

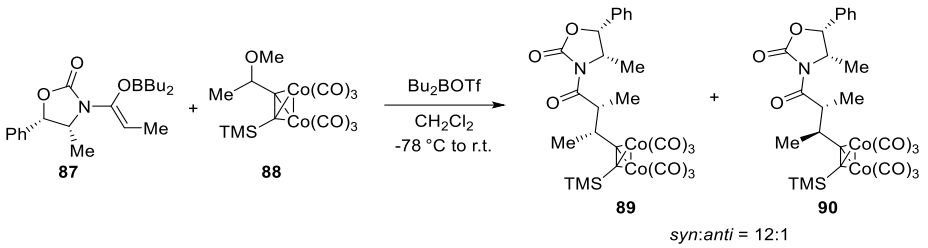
In 1993, a stereoselective propargylation with Mukaiyama-type silyl enol ether was published by Nicholas (Shceme 27).[101] The propargylic alcohol **77** was activated by the cobalt complex and provided an approach to the stereoselective propargylium $Co_2(CO)_5PR_3^+$ complexes **83**. The stabilized carbon cation could allow the silyl enol ether to comply with the bond formation on the propargylic position under the activation of tetraflourboric acid. Besides, the phosphine ligand offered a steric hindrance contributing to the selectivity, while the steric centers were formed in compound **84**. After finalizing the reaction by oxidative workup for removing cobalt protection on alkyne, the substituted pent-4-yn-1-one **85** could be generated in moderate diastereoselectivity.



Scheme 27. The first example of cobalt-mediated propargylic substitution report by Nicolas[101]

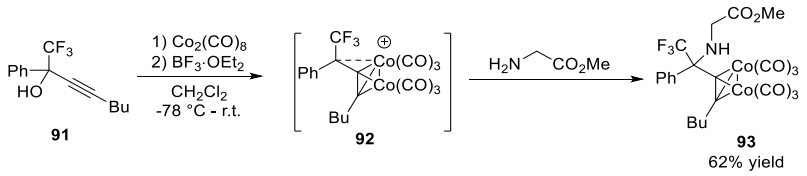
The propargyl $Co_2(CO)_6$ complexes are, in general, pretty stable and allow purification, which is often used in pure form with or without the protection of terminal alkynes. Apart from silyl enol ester, boron enolates are powerful carbon nucleophiles frequently used in different reactions too.

Its derivatives from Evans' chiral oxazolidinones **87** were proven to be reactive to isolated cobalt stabilized carbocations **88** in 1987 (Scheme 28).[102] In the presence of dibutyl-boron triflate, a mixture of *syn*- and *ant*- products **89** and **90** could be afforded in 80 % yield with a satisfying 12:1 diastereoisomeric ratio.

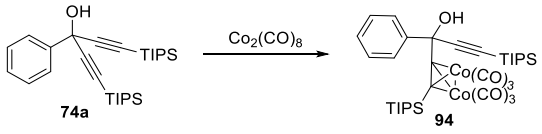


Scheme 28. Utilizing Evans' chiral oxazolidinones for chiral propargylic substitution under Nicolas' condition[102]

Considering the electron-withdrawing ability through an inductive effect on compound **91**, the reactivity and synthesis of α-trifluoromethyl propargylium $Co_2(CO)_6^+$ complex **93** were intriguing. The literature reported by Bonnet-Delpon and Gruselle demonstrated the potential for preparing CF_3-substituted propargylium $Co_2(CO)_6^+$ complex **93** and its reactivity (Scheme 29).[103] Besides, the carbon-nitrogen bond formation indicates a wide range of nucleophiles that could be afforded with cobalt-stabilized propargylium salt efficiently other than carbon nucleophiles. Given a great desire to install a side chain to replace the hydroxyl group on 3-substituted-3-hydroxl-l,4-diyns **74**; therefore, we tried to implement this task by following the Nicholas propargylic replacement (scheme 30).



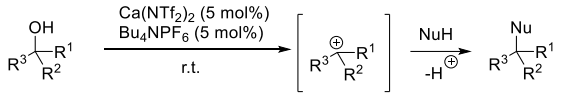
Scheme 29. Example indicates the broad substrate tolerance of Nicholas propargylic replacement[103]



Scheme 30. Our trial experiment on a propargylic replacement under Nicholas' condition

According to the literature-known procedure, we proceeded with the test reaction by treating 3-phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (**74a**) to cobalt carbonyl in anhydrous dichloromethane at room temperature. Moreover, the second equivalent of cobalt carbonyl was

added to identify if both alkynes would get involved in the complexation. The resulting TLC indicates the complete conversion of the complexation could be achieved in 2 hours under N_2 atmosphere, and no matter how much cobalt carbonyl was added, the resulting TLC indicates one kind of complex formation only. The rationale for the single complex being produced could be the bulkiness that prohibits the complexation of the second alkyne. With this convincible observation, we then cooled down the solution to -78 °C. At such a temperature, boron trifluoride etherate, and various nucleophiles were added to the reacting mixture; for example, allyltrimethylsilane, 1,2-diaminotheane, etc. Although the Nicholas propargylic replacement was widely used in organic synthesis, it has never been used in constructing quaternary carbon centers; thus, amino and carbon nucleophiles were utilized for testing the possibility of quaternary carbon establishment in this work. Unfortunately, none of the nucleophiles we tried could lead to a successful propargylic replacement under the catalysis of the cobalt complex. To elaborate, the highly steric hindered reacting center could be the main reason for the failure of substitution.

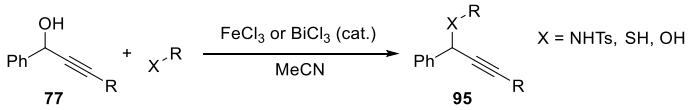


Scheme 31. Lewis acid-catalyzed cation formation for S_N1 substitution[104]

Other than Nicholas's reaction, there are different methods using Lewis acid for activating alcohols and facilitating the substitution. For instance, Niggemann *et al.* disclosed the carbon cation generation *via* calcium activation of tertiary alcohol in the recent decade. It offers evidence that the hydroxy group's leaving ability could be dramatically promoted when a proper Lewis acid was involved (Scheme 31).[104] Compared to the commonly used Nicholas propargylic substitution, a stoichiometric amount of metal reagent is no longer required, and the complicated procedures for the propargylic complexes preparation are not necessary for the Lewis acid-activated cation evolving process. Several propargylic substitution reactions *via* transition metal catalysis were published in recent years, indicating that unprotected alkyne is not necessarily a problem. A literature survey found that the ruthenium-catalyzed process is the most versatile among all the relative reactions.

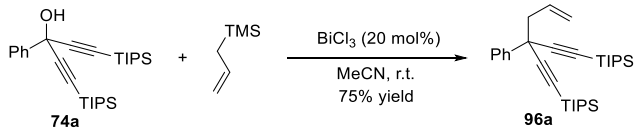
Nevertheless, a terminal alkyne group is required in such methods which restrict the substrate scope. Otherwise, efficient rhenium [(dppm)$ReOCl_3$] and gold [$NaAuCl_4 \cdot 2H_2O$] catalyzed nucleophilic substitution of propargylic alcohols have been reported by Toste[105] and Campagne,

respectively.[106] Both methods were elegant; however, the barrier to access and cost of such catalysts are high.



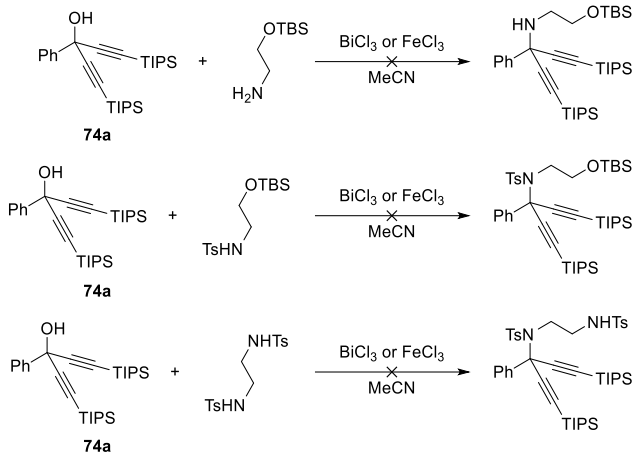
Scheme 32. Reported Lewis acid-catalyzed propargylic replacement[107, 108]

In 2006, a groundbreaking concept was introduced by Zhan and colleagues involving the substitution of propargylic alcohols **77** (Scheme 32).[107, 108] Various nucleophiles were tested to approve the feasibility of a wide range of propargylic functionalization that is affordable to fulfill compound **95**. This innovative approach proved to be highly effective due to the low toxicity, low cost, and relative insensitivity to ambient conditions associated with using various nucleophiles. Through this method, we could achieve this advance by introducing a variety of nucleophiles to propargylic alcohol using affordable Lewis acids such as $BiCl_3$ and $FeCl_3$, which makes a significant improvement compared to those previous methods limited by toxicity, cost, and sensitivity to ambient conditions.



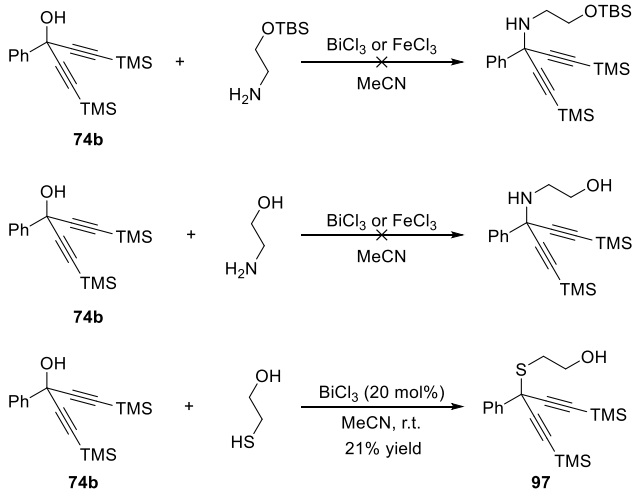
Scheme 33. Lewis acid-catalyzed propargylic allylation on 3-hydroxy-1,4-diyne **74a**

In addition to the impressive outcome mentioned, an experiment was conducted to assess the efficacy of bismuth-catalyzed propargylic substitution on 3-hydroxy-3-substituted-1,4-diyne **74a**. The 1,4-diyne substrate and allyltrimethylsilane were dissolved in anhydrous acetonitrile and subjected to $BiCl_3$ in catalytic amounts at room temperature. Encouragingly, the resulting allylated-compound **96a** was successfully obtained in a yield of 75% after stirring for three hours under N_2 atmosphere (Scheme 33). However, the substitution did not work with heteroatom nucleophiles such as 1,2-diaminoethane and ethane-1,2-dithiol under the same conditions.



Scheme 34. The test of various nucleophiles for the propargylic substitution on 3-hydroxy-1,4-diyne **74a**

In order to clarify the bizarre situation of heteroatom nucleophiles when it has been applied to the propargylic substitution on 3-hydroxy-1,4-diyne **74a**, different amino nucleophiles were tried in the presence of the catalytic amounts of iron chloride and bismuth chloride in acetonitrile. As illustrated in the scheme, the amino or hydroxyl group was protected to avoid unwanted side reactions. The tosylated-substrate was tested regarding the higher acidity of the amide group, which would benefit the elimination process. Disappointedly, all experiments give nothing but negative results as no conversion was observed (Scheme 34).



Scheme 35. The test of various nucleophiles for the propargylic substitution on 3-hydroxyl-1,4-diyne

The purpose of using the TIPS protecting group in the Lewis acid-activated propargylic substitution is to prevent the reactive terminal alkyne from self-aggregation or S_N1 prime side reactions. However, the unexpectedly low reactivity while heteroatom nucleophiles were applied

made us reconsider the protective group selection for the terminal alkyne. The bulky protecting group such as TIPS might enhance the difficulty of eventuating the collision between two reactants and direct to no reaction occurring. Hence, the propargylic substitution on the 3-hydroxyl-3-substituted 1,4-diyne was again tested with TMS-protected diyne **74b**. On the other hand, less bulky nucleophiles were selected as reaction partners, such as aminoethanol and mercaptoethanol. Thiol nucleophile gratifyingly showed propargylic substitution to afford substituted product **97** in 21% yield, but the amine still did not respond to the activated propargylic alcohol. 2-((3-phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl)thio)ethan-1-ol (**97**) product was noticed pretty unstable after purification *via* flash column chromatography on silica stationary phase. Besides, the compound was found particularly unstable at elevated temperatures. Thus, the proton NMR spectrum was the only characterization data we could provide for this product. Moreover, the removal of the silyl protective group was attempted for 2-((3-phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl)thio)ethan-1-ol (**97**), however the resulting terminal 1,4-diyne is extremely labile, which is almost impossible to purify (Scheme 35).

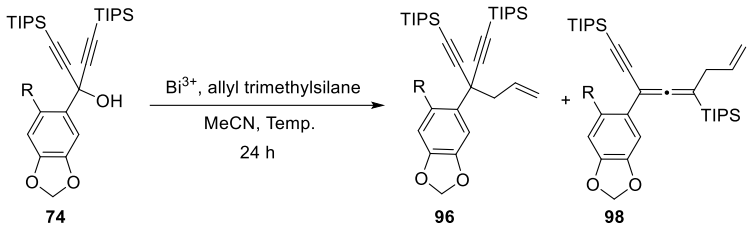
The success of thiol substitution on TMS-protected 3-hydroxy-3-phenyl-1,4-diyne (**74b**) provides evidence supporting that bulkiness indeed matters in this reaction. Furthermore, the allylation was a considerable success and fulfilled the transformation of tertiary alcohol into a quaternary carbon center with excellent yield.

1-2-2-3 Substrate scope of bismuth(III)-catalyzed propargylic replacement

Based on the promising preliminary results of propargylic allylation in the presence of bismuth chloride, we herein tried to improve the efficiency of this reaction by optimizing the reaction conditions, the selected 3-(benzo[*d*][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (**74c**) was dissolved in anhydrous MeCN, and various bismuth(III) catalysts were screened at ambient temperature (Table 4, entries 1-3). To our surprise, bismuth triflate as a catalyst exhibited an entirely different reactivity, which does not allow the desired allylated product to form. Other than that, in most cases, the desired allylated diyne could be observed along with the allylated allene as a side product. In terms of yield and regioselectivity, similar results were obtained even though different bismuth(III) sources were used in the reaction. Furthermore, the reaction temperature and solvents were also investigated, and the results indicate the limitation of this reaction concerning chemical selectivity (Table 4, entries 3-5). In addition, the result of the

brominated substrate **74d** indicates that the bulkiness of the substrate is not highly related to the chemoselectivity, which could allow a broad substrate tolerance (Table 4, entry 6). Through the optimization, we are therefore capable of deciding the optimized condition for this reaction that employing bismuth chloride as a catalyst and utilizing anhydrous MeCN as solvent at room temperature gives in the best result.

Table 4. Optimization of the bismuth(III)-catalyzed propargylic allylation.[a]

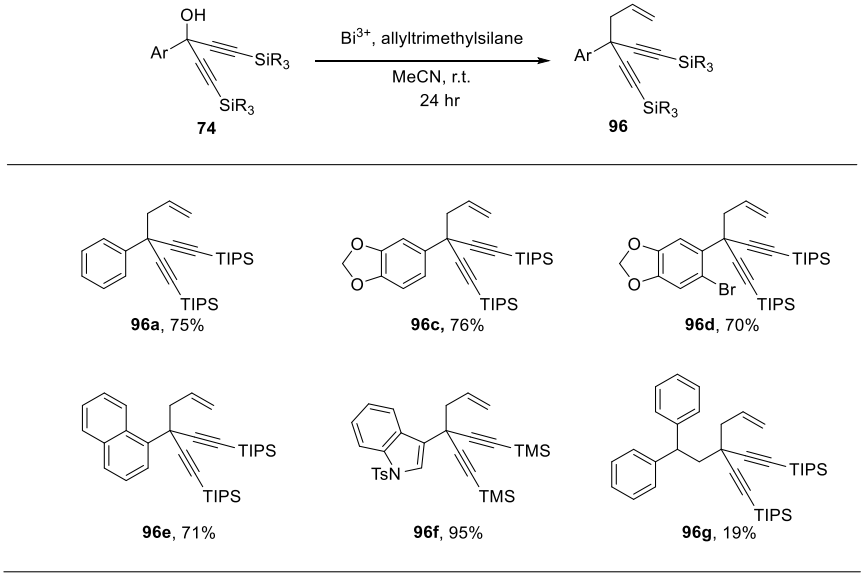


entry	R	Bi^{3+}	Temp. (°C)	Ratio of isomer (**96**:**98**)[b]	Yield in total (%)[c]
1	H	$Bi(NO_3)_3$	r.t.	2.6:1	n.d.[e]
2	H	$Bi(OTf)_3$	r.t.	n.d.[d]	n.d.[e]
3	H	$BiCl_3$	r.t.	2.6:1	97
4	H	$BiCl_3$	50	2.5:1	n.d.[e]
5	H	$BiCl_3$	-20	2.6:1	96
6	Br	$BiCl_3$	r.t.	2.7:1	96

[a] Unless noted otherwise the reactions were carried out by using diyne starting material (1 mmol), bismuth (III) catalyst (20 mol %), in anhydrous acetonitrile (0.2 M) under N_2 atmosphere.[b] the ratio is determined by NMR analysis of crude mixture. [c] isolated yield. [d] no desired product was observed. [e] not determined.

In the reaction, we observed and isolated the allene side product **98**, which could merely be generated from the S_N1' reaction. In other words, when the propargylic cation was formed, it could delocalize through the conjugated π system and allow the nucleophiles to attach to both active sites. Furthermore, due to the presence of the 1,4-diyne system, the cationic species can potentially migrate to both ends of the terminal position of the alkyne functional group. This condition increased the likelihood of allene side product formation. This phenomenon explains the unsuccessful propargylic allylation on TMS-protected substrates and emphasizes the importance of employing bulky TIPS groups to prevent such undesired reactions.

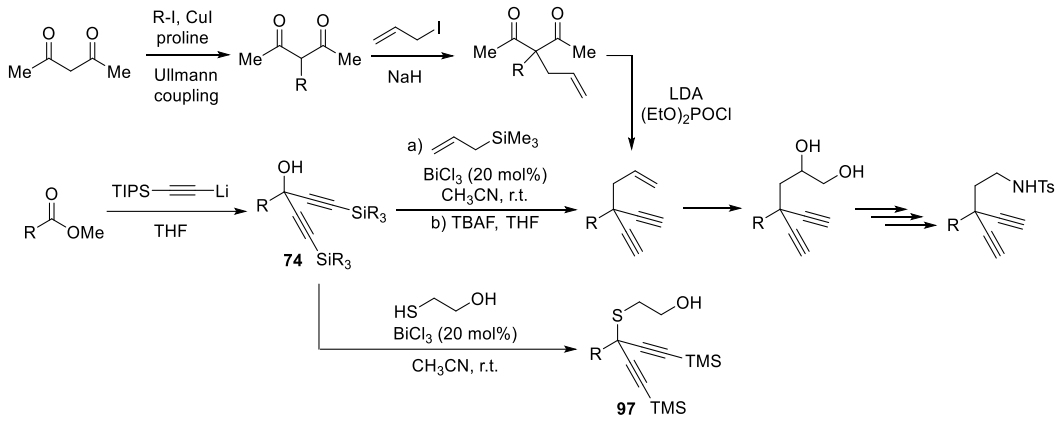
Table 5. The substrate scope of bismuth(III)-catalyzed propargylic allylation.



After confirming the occurrence of a side reaction primarily attributed to the nature of the substrates, we have decided to investigate the substrate tolerance of propargylic allylation. This exploration aims to establish the universality and applicability of this methodology across a range of substrates. During the substrate scope screening, a range of 3-aryl-substituted-3-hydroxyl-1,4-diynes **74** was successfully converted to 3-aryl-substituted-3-allyl-1,4 diynes **96** in similar yield and selectivity (Table 5). Noticeably, the indolyl substituted substrate could provide additional stabilization to the carbon cation, allowing excellent regioselectivity towards the compound **96f** formation even with a less sterically hindered TMS-protecting group (Table 5, substrate **96f**). On the other hand, the alkyl-substituted substrate **74g** could only provide moderate conversion to the allylated compound **96g** due to worse regioselectivity caused by the extra stabilization at the propargylic position. Overall, this bismuth-catalyzed propargylic allylation is universal and capable of tolerating a broad range of substrates; however, the efficiency dropped when the alkyl group was present at 3-position even though no elimination side product was observed in any case (Table 5, substrate **96g**). An additional stabilization, such as the benzylic system, is required to maintain the proficiency of this propargylic allylation.

1-3 Summary

In summary, we have successfully developed a novel synthesis method that enables the transformation of a hydroxy group into other functional groups on 3-hydroxy-1,4-diynes **74** *via* a Lewis acid-catalyzed propargylic replacement. By employing 20 mol% bismuth chloride as the catalyst, the hydroxy group undergoes carbocation evolution, allowing for the addition of nucleophiles such as allyl trimethyl silane or thiol.



Scheme 36. 1,4-Diyne synthesis *via* bismuth(III)-catalyzed propargylic replacement

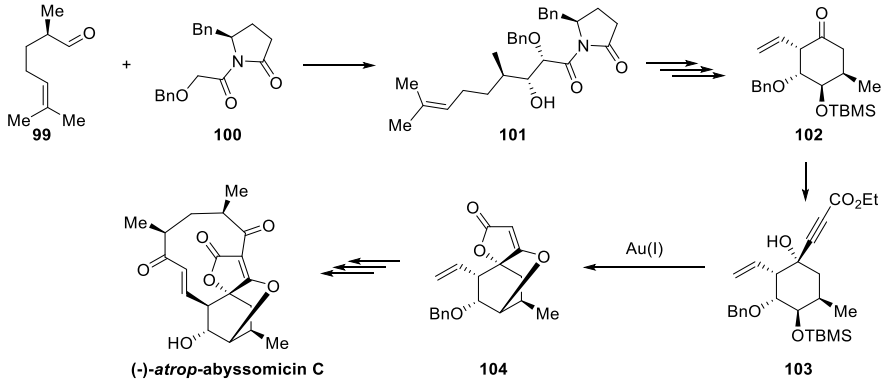
Given the widespread interest in the 1,4-diyne system, the synthesis described in this section offers an efficient method for producing various 1,4-diynes. Compared to previously reported hazardous and expeditious procedures starting with penta-2,4-dione, the bismuth-catalyzed allylation presented here allows for the synthesis of allylated-diynes in satisfactory yields over three steps. Additionally, the successful utilization of thiol nucleophiles in this chemical transformation demonstrates the potential for diverse derivatization of the 1,4-diyne system through propargylic substitution. This convenient method for symmetric 1,4-diyne substrates bearing a quaternary center paves the way for subsequent desymmetrization approaches aimed at constructing chiral quaternary centers (Scheme 36).

Chapter 2. Desymmetrization of 3-alkoxy-1,4-diynes *via* gold-catalyzed cyclization

2-1 Introduction

2-1-1 Gold-catalyzed cyclization as a critical step in the synthesis of polyketides

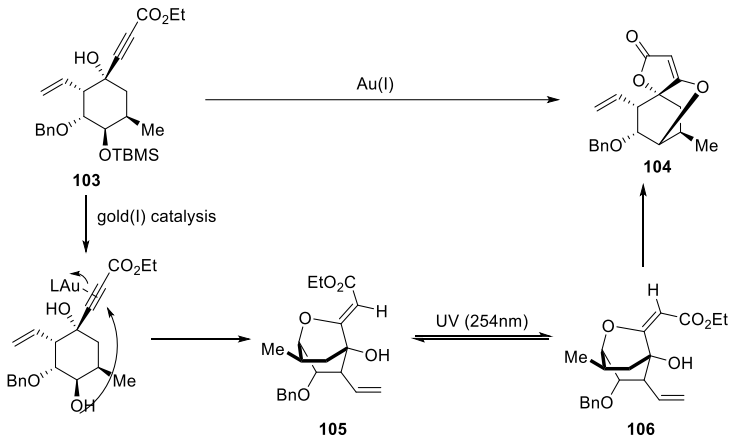
Polyketides are a class of secondary metabolites produced by bacteria, fungi, plants, and animals that is necessary for the development and growth of organisms.[109] Structurally, it usually has multiple oxygen-containing heterocycles as an omnipresent motif, and it is frequently used in pharmaceutical development, especially antibiotics.[110] To support the thriving progress in recent pharmaceutical research, the demand for corresponding methodologies for the oxygen-containing heterocycles construction is booming.[111] Among all the well-known consequential methodologies of heterocyclic compound formation, homogeneous gold catalysis could be one of the most iconic and indispensable methods for diverse carbon-heteroatom bond formation.[112] In addition, the enantioselective method of homogeneous gold catalysis is an exciting issue in the recent progress of small molecular synthesis. By employing prosperous evolvement in homogeneous gold catalysis, recently, we have an increasing number of scientific research applying it to assist the construction of significant skeletons in complex naturally occurring products.



Scheme 37. Total synthesis of (−)-*atrop*-abyssomicin C reported by Saicic[116]

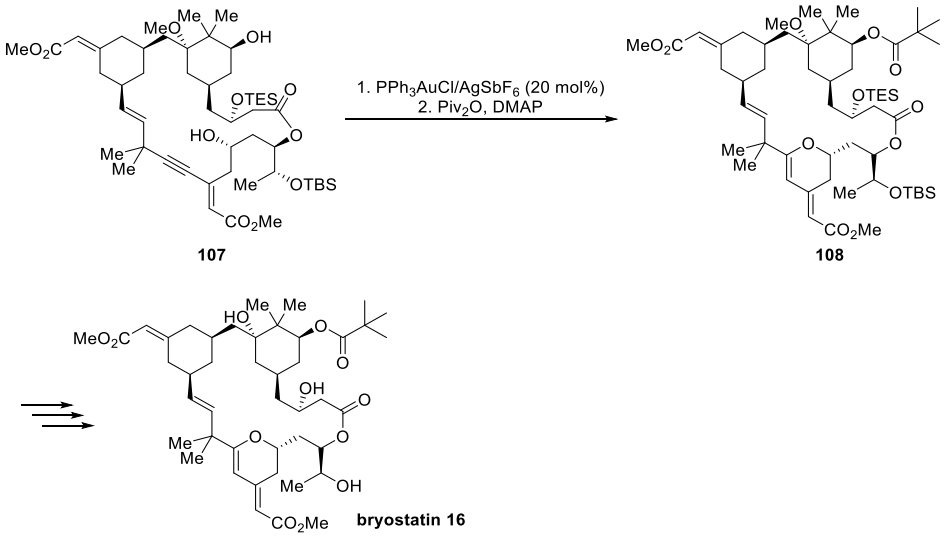
In 2004, the isolation of abyssomicin C was achieved by Süssmuth and co-workers.[113] It was found to positively inhibit the biosynthesis process of tetrahydrofolate in *Staphylococcus aureus* and assist humans in resisting the infection from gram-positive bacteria.[114] Abyssomicin C has a complex molecular architecture and impressive bioactivities, making it and its congeners an interesting and challenging synthetic target for synthetic scientists. Among all the reports of

abyssomicin C and its congeners, an insight for structural discussion was proposed by Nicolaou; especially, the discussion of the atropisomerism issue caused by the restriction of the free bond rotation in the eleven-membered ring motif.[115] On top of that, Saicic et al. reported an enantioselective synthesis of (−)-*atrop*-abyssomicin C in 2013 (Scheme 37).[116] The synthesis began with an aldol reaction of aldehyde **99** and Evans' oxazolidinone **100** to fulfill the enantiopure intermediate **101** formation. The following cyclohexane backbone **102** construction was then accomplished *via* a series of chemical transformations, including a novel organocatalytic Tsuji-Trost reaction with catalytic amounts of $(Ph_3P)_4Pd$ and pyrrolidine.[51] A simple 1,2 addition of acetylide on the corresponding ketone will lead to propargylic alcohol **103** readily prepared for further cyclization. Besides, the eleven-membered ring formation was done by a highly efficient Nozaki-Hiyama-Kishi reaction after the highly strained multiple ring intermediate **104** was finished with the vinyl functional group for further cyclization.[117] Among all the steps, the tricyclic spirotetronate unit formation was the most challenging part due to the apparent increase of the ring strain, which could be accomplished by gold catalysis with a catalytic amount of $(PPh_3)AuNTf_2$ in isopropanol. Unfortunately, in this cyclization, the *Z*-isomer **105** is favored. Because the *E*-isomer **106** is required for the following esterification, an isomerization could be initiated by irradiation with UV light in the presence of sodium isopropoxide as the catalyst. In this total synthesis, the gold-catalyzed intramolecular alkyne functionalization accentuates the broadness of the feasible substrates showing the possibility of a highly distorted multi-ring structure establishment (Scheme 38).[116]



Scheme 38. The gold-catalyzed cyclization for the highly strained core structure in (−)-*atrop*-abyssomicin C [116]

Other than that, in 2008, the total synthesis of bryostatin 16, another polyketide exhibiting exceptional biological activity, was reported by Trost (Scheme 39).[118] This macrocycle was accomplished in a well-designed and exquisite way that fulfills the atom-economical and selectivity-requirement chemically and sterically. Noticeably, in the process of this total synthesis, the 4-ethylidene-3,4-dihydro-2*H*-pyran motif in compound **108** was accomplished by utilizing gold-catalyzed intramolecular alkyne functionalization. In this reaction, a cationic gold catalyst was used on a highly functionalized macromolecule **107**; however, the chemoselectivity and diastereoselectivity are exceedingly satisfying. This provides additional evidence that cationic gold catalysis is versatile, but the preferential carbophilic activation is undoubtedly superior. Thus, it is a reliable method that could be used in the late stage of a complex molecule synthesis which will not bring a substantial impact concerning the overall efficiency. All in all, gold catalysis is a powerful synthetic tool, and it has been proven that it could play a critical role in the process of polyketide synthesis.



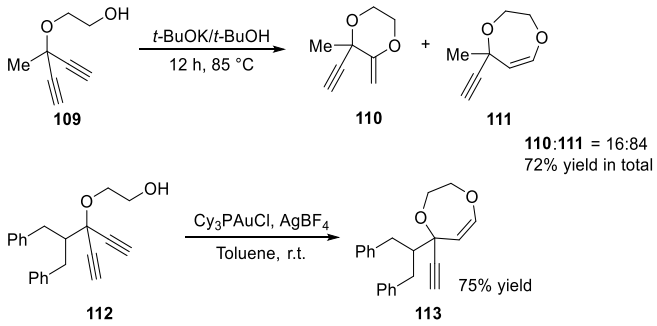
Scheme 39. Total synthesis of bryostatin 16 reported by Trost[118]

2-1-2 Previous results of gold-catalyzed alkynol isomerization

The ubiquitous furan and pyran moiety are the representative features of the polyketides which support their unique chemical properties. From the furan or pyran formation perspective *via* gold-catalyzed cyclization, unsaturated alkanols were considered essential substrates intuitively and practically. On the one hand, the alkynol could beautifully accomplish the furan or pyran ring closure by employing the cationic gold activation based on its strong carbophilicity and Lewis

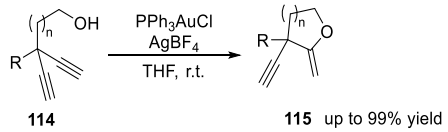
acidity; on the other hand, the alkyne functional group provides the corresponding reactive methylene moiety, which could provide further functionalization to afford the more complicated structure establishment in polyketides synthesis as well.[111-116, 118]

In 1998, the isomerization of 3-oxyalkanol-1,4-diyne **109** was reported by Schlosser. At elevated temperatures, the deprotonation of the hydroxy group could be achieved and trigger the occurrence of cyclization. Theoretically, the six-membered ring product **110** is thermodynamically more favored; however, an unusual *endo*-selectivity for seven-membered ring formation of product **111** was observed as the primary product in this cyclization (Scheme 40).[119]



Scheme 40. The previous result on 1,4-diyne desymmetrization *via* intramolecular alkyne functionalization[95,119]

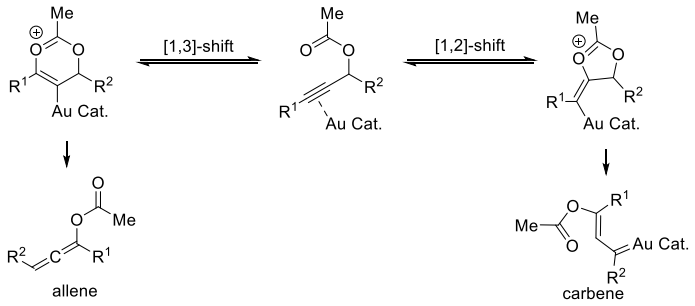
Evoked by the mysterious results, our desire for the detail of this abnormal cyclization was encouraged. In 2009, the transformations of 3-oxyalkanol-1,4-diynes **112** featuring an internal nucleophile in the presence of a gold catalyst were reported by our research group.[95] This investigation pointed out that gold catalysis not only allows mild conditions but improves the regioselectivity on the intramolecular alkyne hydroxylation to give unusual seven-membered rings **113**. The gold catalysis overall improves the reactivity of 3-oxyalkanol-1,4-diynes **112** for isomerization, but a specific requirement of the substrate was observed.



Scheme 41. The previous result on gold-catalyzed 1,4-diyne desymmetrization[96]

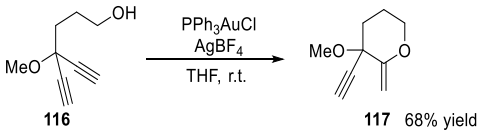
Unlike the 3-oxyalkanol-1,4-diyne **109** and **112**, a quaternary center in 3-aryl-3-alkanol-1,4-diyne **114** could effectively prohibit the stereoelectronic effect and lead to a favored 5-*exo*-dig cyclization (Scheme 41).[96] In addition, the substrate tolerance has no longer been limited by the

rearrangement caused by the C−O bond cleavage. Regardless, in the presence of gold(I) complex the 3-ethynyl-3-substituted-2-methylenetetrahydrofuran **115** could be afforded with an excellent yield.



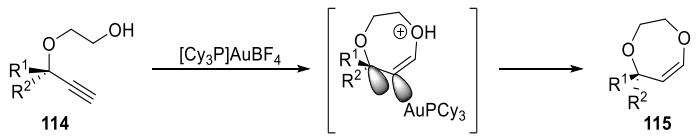
Scheme 42. Illustration of sigmatropic rearrangement activated by cationic gold complex[120]

In 2007, Nolan *et al*. tried to organize and deduce the plausible mechanism for [1,2]- or [1,3] -rearrangement of propargyl carboxylates *via* gold catalysis (Scheme 42).[120] In summary, the reactivity could be affected by the reaction condition, catalyst, and of particular importance, the structure of the substrate. To clarify the mechanism of the regioselectivity of the 2-methylenetetrahydrofuran **115** and 5-ethynyl-5-substituted-2,3-dihydro-5H-1,4-dioxepine (**113**) formations in detail, we thereby initiate an insight mechanism investigation.



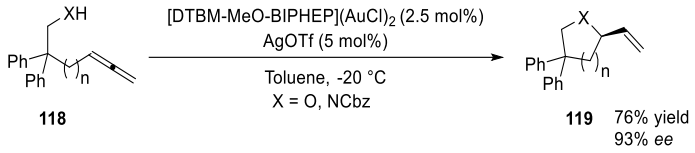
Scheme 43. Designed substrate for interpreting the chemoselectivity caused by the stereoelectronic effect[96]

Along with the *exo*-selective cyclization on the 4-ethynyl-4-methoxyhex-5-yn-1-ol (**116**) the inductive effect of the oxygen atom at the 3-position could be excluded because the inductive polarization on the alkyne functional group would not be too much different (Scheme 43).[95,96] This ascertainment suggests that the remarkable regioselectivity could originate from the stereoelectronic interaction of the σ(C−Au)-orbital with the σ*(C−O) -orbital (Scheme 44).[121]



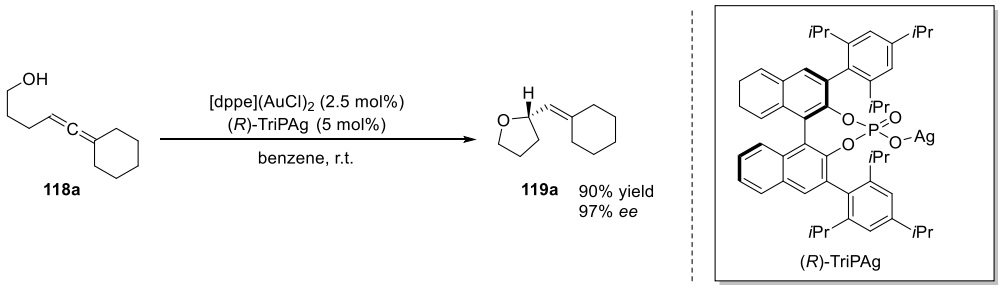
Scheme 44. Illustration of the stereoelectronic effect of the heteroatom substituent on the propargylic position[121]

In the cyclization process, we have created a chiral center which brings an enantioselectivity issue to the fore. In the past, there has been a convincing number of publications that revealed the feasibility of enantioselective gold(I) catalysis. For instance, Widenhoefer and co-workers demonstrated the intramolecular hydroalkoxylation of γ- and δ-hydroxyallenes **118** in 2007 (Scheme 45).[122] Using a gold complex of MeO-BIPHEP derivative, the enantioselectivity can be controlled successfully at -20 ^{o}C.



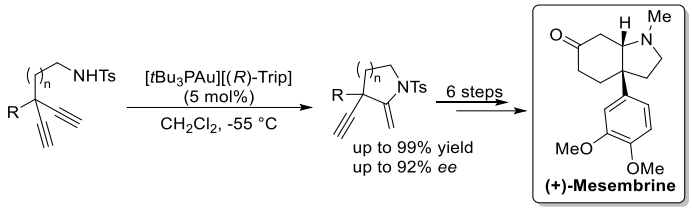
Scheme 45. Enantioselective gold(I)-catalyzed intramolecular cyclization of terminal allene[122]

According to the inspiring achievement on the enantioselective gold(I)-catalyzed cyclization on hydroxyallenes, same activation concept has been used in the asymmetric intramolecular alkyne hydroamination and resulted in moderate enantioselectivity for the formation of compound class **119**.[122b] The reactivity of different ligands, such as carbene-type ligands, has been evaluated as well, but none of them is compatible with the DTBM-MeO-BIPHEP derivative in this specific case. Considering both hydroalkoxylation and hydroamination could be achieved stereoselectively utilizing MeO-BIPHEP gold complex, the broad tolerance of substrate scope indicates that it has a significant contribution in differentiating the stereochemistry as the cyclization occur. However, excellent stereoselectivity is not universal with this linear complex. For example: Unlike terminal allene, an internal allene would plausibly extrude the ligand and affect the stereoselective outcome. An appropriate rationale for the disappointing selectivity control would be the congenital disadvantage of the gold(I) catalysis toward the enantioselectivity control. The linear conformation of the gold(I) complex makes chiral induction unfavorable. The chiral ligand hardly has a chance to approach the reacting center, especially with a stiff structure.



Scheme 46. Enantioselective gold(I)-catalyzed intramolecular cyclization of internal allene[123]

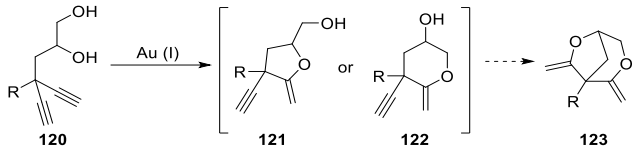
To accommodate the various requirements asking from the substrate scope, a solution was provided by Toste *et al*. showing that gold complex incorporating chiral counteranions such as (*R*)-TriPAg could afford successful enantioselective intramolecular hydroalkoxylation of internal allenes in 2007 (Scheme 46).[123] The advantage of anion-induced gold catalysis is obvious. The ionic interaction is intensive but could endure a modest deformation which allows the chiral anion to be embedded with the reacting center in the transition state. The satisfactory selectivity of intramolecular hydroalkoxylation of allene **118a** sufficiently verifies the theory.



Scheme 47. Previous work on enantioselective gold(I)-catalyzed intramolecular alkyne hydroamination and its application on the total synthesis[124]

On the basis of this successful anion-induced enantioselective gold(I)-catalyzed intramolecular allene hydrofunctionalization, an extended application for 1,4-diyne desymmetrization was established in our group in 2012 (Scheme 47).[124] Similar to allene, alkyne could as well allow η-complexation and activate the reactivity of alkyne, meanwhile the chiral anion gets involved for inducing the stereoselectivity by shielding the sterically disfavored alkyne. In this approach, a series of pyrrolidine-like products could be afforded with excellent yield and enantioselectivity. Upon the successful enantioselective formation of the alkynyl methylene pyrrolidine, the total synthesis of enantiopure (+)-mesembrine was established in our group in 2016 (Scheme 47).[125] (+)-mesembrine is a natural product featuring a pyrrolidine substructure that was successfully synthesized based on the anion-induced enantioselective desymmetrization strategy. On the other hand, the cyclohexanone motif found in (+)-mesembrine is accessible *via* a three-steps process including ester installation, hydrogenation, and tandem reductive deprotection/cyclization established in the previous work. Around this self-developed gold(I)-catalyzed desymmetrization of 1,4-diyne, a concise synthesis of (+)-mesembrine was built. Furthermore, the synthesis of the whole series of naturally occurring alkaloids sharing the C3a-arylated hydroindole backbone was described in this dissertation. More details on this topic will be further elaborated in chapter 4.

2-2 Result and discussion



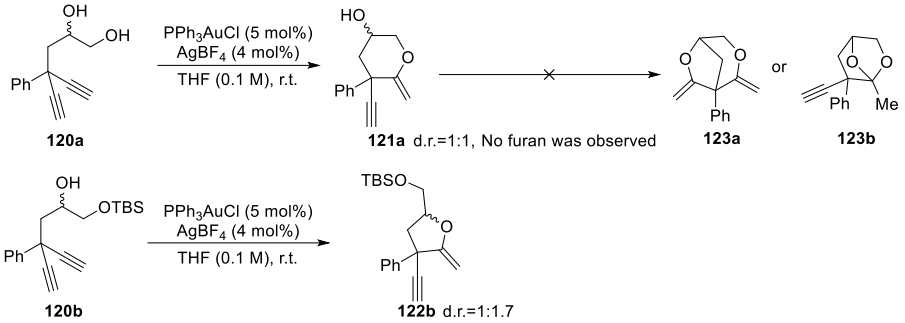
Scheme 48. Our motivation on the possible gold-catalyzed domino cyclization

Since building molecular complexity is trending in modern chemistry development, especially in homogeneous cationic metal catalysis, diol species **120** providing more than one possibility to form chemical bonding, has become an eye-catching substrate. Besides, the other secondary hydroxy group would bring versatility to this molecule with respect to stereochemistry. Subsequently, the resulting chemoselectivity remains unclear, presumably making it an appropriate substrate for diverse orientation synthesis. Based on the aforementioned reasons and the knowledge learned from the previous gold-catalyzed intramolecular 1,4-diyne functionalization, we herein tested out the cyclization of 1,4-diyne substrate featuring a diol functional group intramolecularly as a nucleophilic reacting site in the presence of a cationic gold catalyst (Scheme 48). In this chapter, preliminary results of hydroxy-substituted furan **121** or pyran **122** formation will be displayed and disclosed the process of the method development for building up the cyclic compound in a chiral fashion. Meanwhile, the feasibility of the domino reactivity the diol functional group may provide was explored.

2-2-1 Investigation of the regioselectivity and stereoselectivity of 1,4-diyne bearing 1,2-diol nucleophiles

Our investigation was initiated by testing the regioselectivity of the cyclization with selected 4-ethynyl-4-phenylhex-5-yne-1,2-diol (**120a**). The reaction conditions of the methylene furan formation in the previous study were employed for this intramolecular cyclization. The transformation is quite efficient and complete conversion can be achieved within 1 hour. The only compound generated could be isolated by column chromatography on neutral aluminum oxide stationary phase. The isolated compound appears to be the 3-hydroxy pyran which suggests the six-membered ring closure is favored and indicates the following cyclization for bicyclic compound formation is inhibited by the obstructive conformation. Later on, the reactivity of the secondary alcohol was tested by blocking the primary alcohol with a silyl-protecting group in the same reacting condition. The resulting furan product suggests the secondary alcohol is reactive;

however, in the non-protected case, the reactivity of the secondary hydroxyl group is far less than primary alcohol owing to steric hindrance.

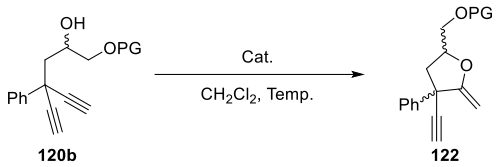


Scheme 49. The first attempt to clarify the regioselectivity of gold-catalyzed cyclization of compound **120**

In an initial attempt, the formation of 6-methylenetetrahydro-2*H*-pyran-3-ol (**121a**) demonstrated the remarkable reactivity and regioselectivity of the gold-catalyzed cycloisomerization. However, the stereoselectivity aspect exhibited certain limitations. Since the diol starting material has an existing chiral center, the quaternary stereogenic center generated in the desymmetrization would connive the problematic diastereoselectivity. Furthermore, cascade bond formation leading to the bicyclic compound **123a** or **123b** was not observed under any conditions. As previously mentioned, diastereoselectivity in the pyran ring formation was minimal. However, in the formation of the furan ring **122b** from the secondary alcohol **120b**, a diastereomer ratio of 1 to 1.7 was achieved (Scheme 49).

In order to achieve the stereoselective synthesis of heterocycles through homogeneous gold-catalyzed alkyne functionalization, our primary task was optimizing diastereoselectivity. The diastereoselectivity originates from the selective functionalization of the alkyne, which can be geometrically differentiated based on the steric configuration of the nucleophilic site due to the presence of a nearby pre-existing chiral center. Therefore, our optimization efforts will begin with the formation of methylene furan, taking into consideration the directly attached chiral center of the secondary hydroxy group, which could potentially facilitate the distinction in conformation.

Table 6. Optimization of gold(I)-catalyzed intramolecular cyclization of protected diol **120b**[a]



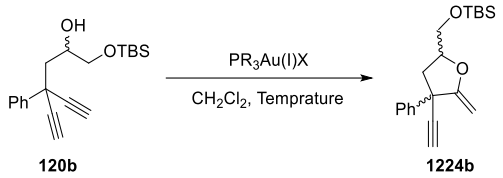
Entry	Cat.	Protecting group	Temp. (°C)	Time (hr)	Yield (%)[b]	d.r.[b]
1	Wilkinson's Cat	TBS	r.t.	24	N.R.	N.D.
2	Ph_3PAuBF_4	TBS	r.t.	1	63	2:1
3	$Ph_3PgAuSbF_6$	TBS	r.t.	1	trace	n.d.
4	$Ph_3PAuOTf$	TBS	r.t.	1	trace	n.d.
5	Ph_3PAuBF_4	TBS	0	1	79	2:1
6[c]	Ph_3PAuBF_4	TBS	0	1	56	2.2:1
7	Ph_3PAuBINOLPhosphate	TBS	0	1	74	2.4:1
8	Ph_3PAuDiphenylphosphate	TBS	0	1	71	2.2:1
9	Cy_3PAgBF_4	TBS	0	1	18	1:1
10	tBu$_3$PAgBF_4	TBS	0	1	40	1.5:1
11	Ph_3PAuBF_4	TBDPS (**120c**)	0 to r.t.	24	N.R.	N.D.

[a] Unless noted otherwise the reactions were carried out by using diyne starting material (0.2 mmol), gold(I) catalyst (5 mol %), and silver salt (4 mol%) in anhydrous solvent (0.1 M) under N_2 atmosphere. [b] Quantified by NMR spectroscopy with triphenylmethane as internal standard. [c] Reaction was carried out at 0.02 M.

The research continued by employing different cationic gold catalysts to the protected diol in CH_2Cl_2 to examine the selectivity because the better diastereoselectivity in the first attempt shows (Table 6). The reaction progressed with different counterions at room temperature, and it appears that tetrafluoroborate and phosphates allow moderate yield and diastereoselectivity; on the other hand, the highly reactive triflate and hexafluoroantimonate give no reactivity at all (Table 6, entries 2-8). The lower temperature result in the diminution of unwanted side reactions but brings no benefits to the diastereoselectivity (Table 6, entries 5-10), and the concentration seems to be orthogonal with the reactivity (Table 6, entry 6). Even though the diastereoselectivity in general is not good after the extensive screening of ligand and counter anion, a noteworthy point has been discovered that the bulkiness of the counter ion has a slightly positive influence on selectivity and reactivity. In addition, the sterically hindered ligand leads to worse selectivity. Theoretically, the stereoselectivity is based on the conformation of the transition state, and usually, the more sterically restricted transition state would have a larger impact on the energy barrier in the stage of forming, which brings in better selectivity. Thus, the linear configuration of the gold(I) catalyst is

a denunciation regarding the selectivity control by ligand. In line with the idea of influencing the energy barrier by increasing the steric hindrance in the transition state, the reactivity of a bulky substrate such as *tert*-butyldiphenylsilyl protected 4-ethynyl-4-phenylhex-5-yne-1,2-diol (**120c**) has been evaluated (Table 6, entry 11). However, an unexpectedly low reactivity was observed at room temperature for 24 hours. On the other hand, Wilkinson's catalyst, as a rhodium catalyst, possesses a square planar configuration and a similar reactivity on alkyne activation as a cationic gold catalyst, which disappointed us by failing to afford any cyclization as well.

Table 7. Optimization of stereoselective gold(I)-catalyzed intramolecular cyclization of protected diol **120b**[a]



120b **1224b**

Entry	X^-	R_3P	Temp. (°C)	Time (d)	Yield(%)[b]	d.r.[b]
1	TriPAg(S)	tBu_3P	-55	3	70	1.3:1
2	TriPAg(S)	Ph_3P	-55	3	28	1.2:1

[a] Unless noted otherwise the reactions were carried out by using diyne starting material (0.2 mmol), gold(I) catalyst (5 mol %), silver salt (4 mol%) in anhydrous solvent (0.1 M) under N_2 atmosphere. [b] Quantified by NMR with triphenylmethane as internal standard.

The chiral counterion 3,3′-(triisopropylphenyl)binol phosphate (TriP) has been found to exert excellent enantioselectivity for intramolecular amination of diynes in previous work, which is also a proper candidate for alkynol cyclization. As a chiral anion of gold catalyst TriP has a bulky side chain that could possibly bring better selectivity. Using this chiral catalyst could reach the recurrence of the concept to achieve alkynol cyclization in good diastereoselectivity; besides, the enantioselectivity might be realized due to the kinetic resolution pathway, which could possibly be induced by the chiral catalyst as well. Unfortunately, the outcome didn't match our expectations. The diastereoselectivity gets worse when the chiral anion (TriP) involves in the reaction, no matter whether triphenylphosphine or tri-*tert*-butyl phosphine served as a ligand. But the difference in reactivity is noticeable that tri-*tert*-butyl phosphine could lead to better yield (Table 7).

2-2-2 Hydrogen bonding and alkaline-earth-metal effect

Depending on the result of optimization, we realized the alkyne could be activated by gold(I) catalysis very efficiently; however, for improving the selectivity, an inferior reactivity is what we

pursue. The gold(I) complex is sensitive to ambient conditions, which means it is strenuous to regulate the Lewis acidity of the gold(I) complex. In response to the limitation of regulating the reactivity of gold catalyst, we therefore switch our focus to the modification of the nucleophilicity of the hydroxy group. Due to the nature of the bulky silyl protecting group, it would block the bonding ability of oxygen atoms and even the nearby secondary alcohol and make the modification of reactivity on the hydroxy group difficult. In order to evaluate the feasibility of affording better diastereoselectivity by adding an additive that would bind to the hydroxy group, we had to utilize the non-protected diol as a module. By introducing modifications, the reactivity of diols can be regulated through the addition of compounds that exhibit strong interactions with the hydroxy group, such as hydrogen bonding and complexation.

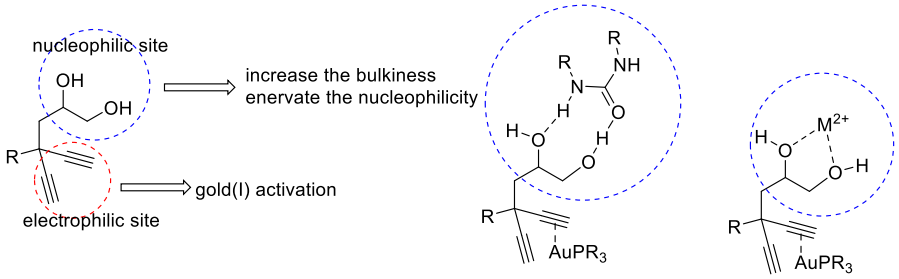
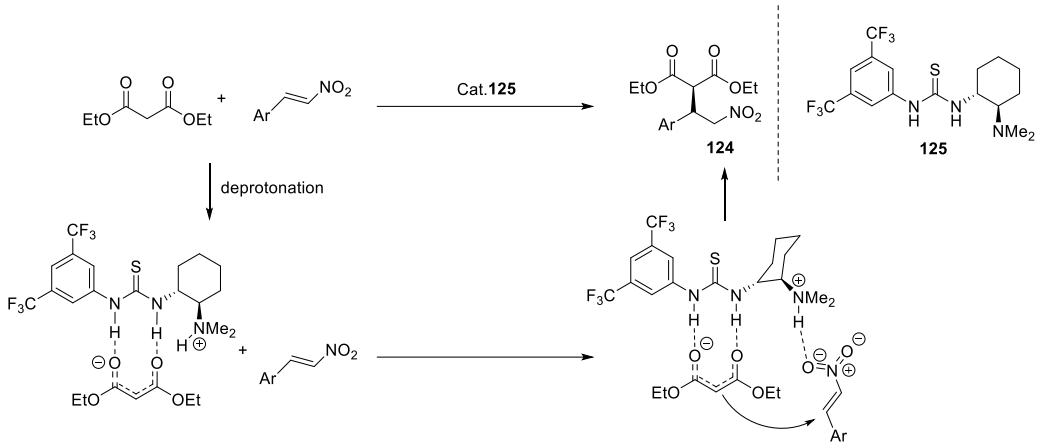


Figure 5. Illustration of the concept utilizing hydrogen bonding or metal coordination to improve the selectivity in the gold(I)-catalyzed cyclization.

Hydrogen bonding is a significant intermolecular interaction that has been applied to enantioselective synthesis for a long time. The development of non-covalent organocatalysts counts on this vital interaction between a hydrogen atom and an electronegative atom. Etter's group proposed the module of hydrogen bond-directed transformation in 1990.[126] Cocrystallization analysis of diaryl ureas and carbonyl compounds was conducted to investigate the pattern of hydrogen bond-directed molecular recognition and gain insights into the host and guest molecules involved in the interactions. This inspiring result leads to the development of bifunctional organocatalysts such as thiourea, squaramide, and so on (Figure 5).[127]

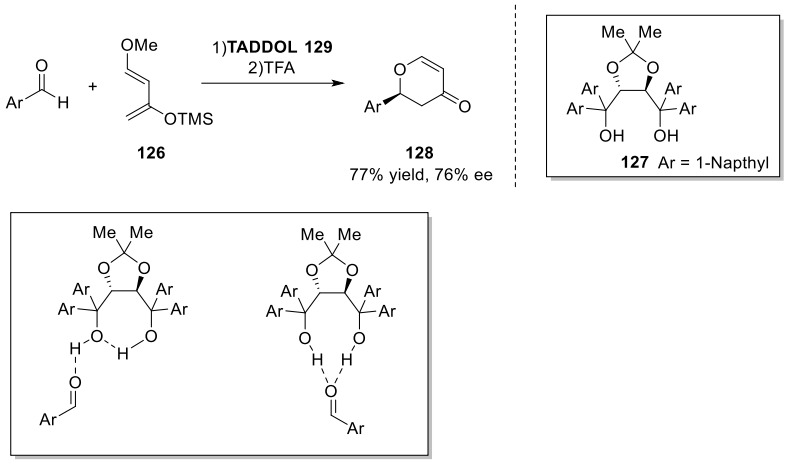


Scheme 50. Example of the stereoselective bond formation *via* bifunctional organocatalysis and its hydrogen bonding model[128]

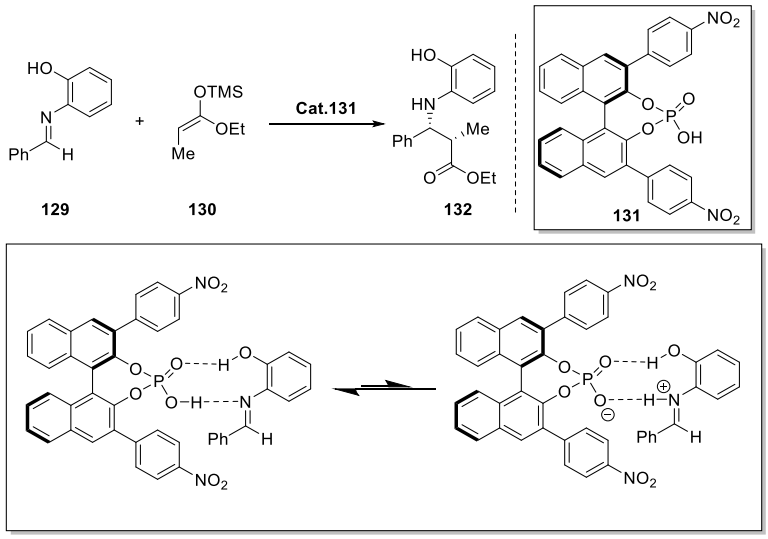
For example, thiourea catalyst **125**, which was reported by Takemoto's group, has shown impressive enantioselectivity in the Michael addition of a malonic ester to nitroolefin for the synthesis of compound **124** (Scheme 50).[128] The mechanism in detail was then proven by Pápai's group through theoretical calculation.[129] Their result of density functional theory (DFT) calculations provides solid evidence that hydrogen bonding indeed is involved in the reaction and helps to define the transition state, which has the lowest activation energy barrier. Since then, more and more results have been published and exhibited the effect of hydrogen bonding in chemical transformation, particularly stereoselectivity. Among all the functional groups, diol undoubtfully is a noticeable functional group in the hydrogen bonding-directed transformation. The most representative example is the *α,α,α′,α′*-tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL) catalyst **127**.[130] For example, the hetero-Diels-Alder reaction between benzaldehyde and Danishefsky's diene **126** was reported by Ding in 2006, including the investigation of the mechanism (Scheme 51).[131]

When the hydrogen bond is formed, the reaction is presumably activated by decreasing the LUMO energy level of benzaldehyde, and the two possible transition states were illustrated as single hydrogen-bond and double hydrogen-bond activation. The excellent selectivity indicated one of the activation models is dominating the reaction, and the result of a computational structure optimization, which was done by Ding's group, suggests that single hydrogen bond activation was favored. From the aspect of pKa values, TADDOL analogs show the influence of the polarity of the hydroxy group from the considerable intramolecular hydrogen bond. In other words, the

tendency of the single hydrogen bond complexes is higher, in general, because the increasing acidity of the hydroxy group is induced by an intramolecular hydrogen bond.



Scheme 51. Example of the stereoselective bond formation *via* bifunctional organocatalysis and its hydrogen bonding model[131]

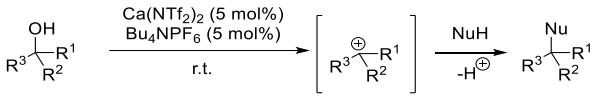


Scheme 52. Example of the stereoselective bond formation *via* BINOL-based phosphoric acid-catalyzed Mannich-type addition and its hydrogen bonding model[134]

Another main subclass of organocatalysis, Brønsted acid catalysis, shares a very similar concept of hydrogen bond-directed enantioselectivity inducing with hydrogen-bonding catalysts.[132] Phosphoric acid derivatives are the most iconic Brønsted acid catalysts, which contain both the Brønsted acidic site and Lewis basic site. The least property not only approves the Brønsted acid-associated proton transfers but plays a crucial role in the transition state, which decides the orientation of electrophilic and nucleophilic components.[133] A classic Mannich-type addition with

imine **129** and Mukaiyama-type nucleophile **130** in the presence of phosphoric acid **131** was published by Akiyama (Scheme 52).[134] Though the proton transfer from phosphoric acid to the imine gives in the more stable ion pair iminium complex, the computational calculation suggests that the double hydrogen bonding activation is the right transition state responsible for the extraordinary enantiomeric excess.

In addition, the hydroxy group is known as a suitable electron donor to the alkaline-earth-metal, wherefore alleviating the nucleophilicity by adding alkaline-earth-metallic acid is a reasonable alternative for the diastereoselectivity improvement. The strong affinity between alkaline-earth-metal and oxygen could be explained by the HSAB Theory, which makes the alkaline-earth-metal alkoxide such a stable complex that it could be extensively applied to different types of reactions. In 2013, the collective prospect of calcium-based Lewis acid catalysis was reviewed by Niggemann (Scheme 53).[104c] In this report, the calcium-activated carbon cation formation reaction from alcohol has been pointed out. This outcome proves that calcium salts have a great affinity to the hydroxyl group and could provide a robust intermolecular interaction which was also mentioned in chapter 2 for the propargylic replacement.

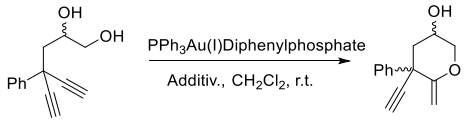


Scheme 53. Example of Lewis acid-activated hydroxy group substitution[104c]

Based on the understanding of the intermolecular interactions of alcohol in the literature survey, the hypothesis was proposed that the reactivity of the diol functional group is possible to be regulated by additives providing strong interaction with a hydroxy group. In order to verify the hypothesis and improve the selectivity, we continued the investigation of the influence of the additive by using silver(I) diphenyl phosphate. After the silver chloride precipitation was observed, it provided a conjugated Brønsted base as a bifunctional counter ion of gold catalyst, which could possibly engage in the hydrogen bonding activation while the cyclization occurs. The performance of the methylene tetrahydropyranol **121a** formation is good in yield; however, the stereoselectivity wasn't improved by the intervention of diphenyl phosphate as a counter ion (Table 8, entry 1). A similar result could be observed in the experiment with diphenyl urea as well, which was regarded as a convincing hydrogen bonding resource in genera (Table 8, entry 2). Since the concept of regulating the reactivity and selectivity by hydrogen bonding has failed, calcium chloride was used

as an alkaline-earth-metalic acid to test if the Lewis acid could truly slow down the reaction and direct the cyclization with a better stereoselectivity (Table8, entry 3). The frustrating result showed very low reactivity when calcium chloride was treated as an additive. The resulting TLC shows a trace amount of product was formed, which was unable to be isolated by flash column chromatography.

Table 8. Optimization of stereo selective gold(I)-catalyzed intramolecular cyclization of unprotected diol **120a**[a]



120a **121a**

Entry	Additive	Time (h)	Yield(%)[b]	d.r.[b]
1	-	1	70	1:1.2
2	Diphenyl urea	1	67	1:1.3
3	$CaCl_2$	24	trace	N.D.

[a] Unless noted otherwise the reactions were carried out by using diyne starting material (0.2 mmol), gold(I) catalyst (5 mol %), silver salt (4 mol%) in anhydrous solvent (0.1 M) under N_2 atmosphere. [b] Quantified by NMR spectroscopy with triphenylmethane as internal standard.

2-3 Summary

In this section, the preliminary results of our reactivity testing on the substrate in the presence of a cationic gold(I) catalyst were presented. Our initial findings show that achieving high chemoselectivity, which is improvised from the thermodynamic stability of the product, with the ring strain playing a crucial role in enabling excellent selectivity. However, we have also found that controlling stereoselectivity can be a significant challenge in this type of reaction. To overcome this issue, an extensive screening process involving the careful selection of catalysts and additives is necessary. By identifying the optimal combination of these factors, we hope to achieve the desired level of stereoselectivity in our reactions. Overall, our results suggest that achieving both high chemoselectivity and stereoselectivity in this reaction is a complex process that requires a thorough understanding of the underlying mechanisms and careful selection of reaction conditions. We believe that our ongoing research will shed further light on these crucial factors and contribute to developing more efficient and selective catalytic processes in the future.

Chapter 3. Gold-catalyzed isomerization of enynes (cumulative part)

3-1 Enantioselective cyclopropanation

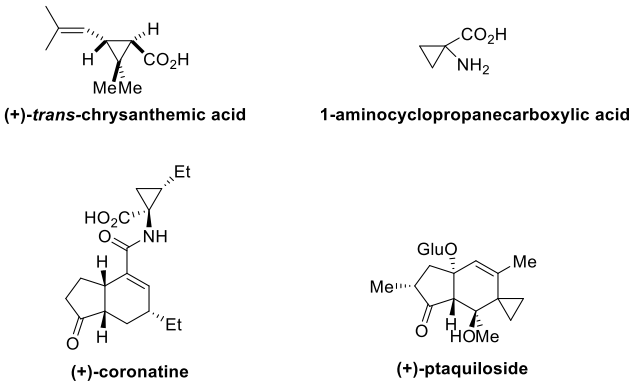


Figure 6. Bioactive compound bearing a cyclopropane motif

Cyclopropane, the smallest subset of cycloalkanes, has become an interesting research topic in the chemistry society since the synthesis method was first reported in 1882 by August Freund.[135] The unusual chemical structure leads to a shorter bond length and enhances the π-character of C−C bonds. The higher bonding energy of the C−H bond resulted in significant kinetic stability under intensive ring strain (27 kcal/mol).[136] Due to the conformational restriction, the cyclopropane has a pronounced stereoelectronic and directing effect, which has frequently been utilized as versatile probes for chemo- and stereoselectivity.[137] The unique physical and chemical properties make cyclopropane formation a noticeable issue in organic synthesis. In addition, cyclopropane subunits exist in many valuable compounds for pharmaceuticals, including terpenes, pheromones, fatty acid metabolites, and amino acids.[138] As a fundamental structural element, cyclopropane can also be found in various naturally occurring products. For example: From the pyrethrum flowers, (+)-*trans*-chrysanthemic acid was isolated and used as the defense mechanism against the insect.[139] Based on the unique property, the whole concept of developing bio-inspired pyrethroids insecticides is concerned with this aspect. In 2019, 1-aminocyclopropanecarboxylic acid (ACC) was issued a notice of an experimental permit as a pesticide by the United States Environmental Protection Agency. As an intermediate of biosynthesis of the plant hormones ethylene, ACC also has been found to exhibit agonistic activity against the *N*-methyl-d-aspartate receptor (NMDA) receptor.[140] Not merely the simple monocyclopropane derivatives, the (+)-coronatine, which includes a hexahydroinden-1-one motif, is also found in the culture broth of

Pseudomonas syringae.[141] Moreover, the bioactivity of (+)-ptaquiloside has been investigated and reported in the prospect of their convincible therapeutic potential.[142]

Among all sorts of cyclopropane derivatives, the bicyclo[*n*.1.0]alkane plays a significant role in pharmaceutical and synthetic chemistry. In bioactive agents and naturally occurring compounds, the prevalent system of bicyclo[*n*.1.0]alkane could be easily found. For example, the bicycle [3.1.0]hexanes are present in isodebromolaurinterol, a natural compound isolated from Chinese red algae, which is regarded as an antibiotic-related substance.[143] From the *Senecio arguments,* a perennial herb extensively distributed in northeast China, Korea, the Peninsula, far east of Russia, and Mongolia, not only the bicycle[3.1.0]hexanes but bicycle[4.1.0]hexanes derivatives could be isolated, such as chromolaevane dione and (23*Z*)-cycloart-23-*en*-3b,25-diol.[144]

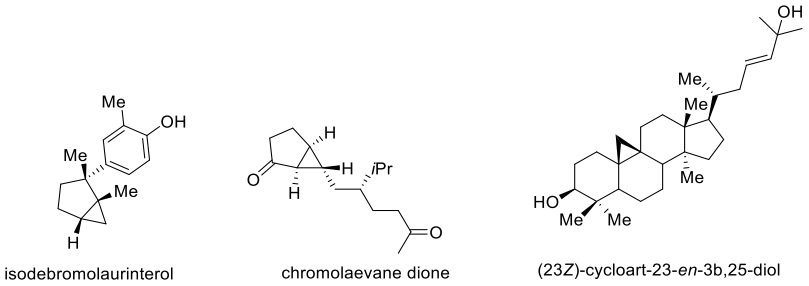
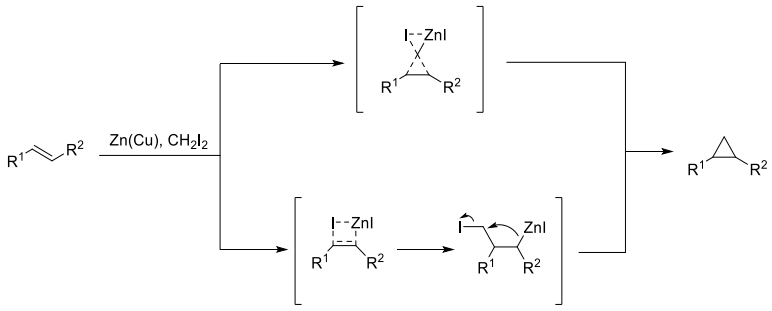


Figure 7. Bioactive compound bearing the [*n*,1.0] bicyclic structure

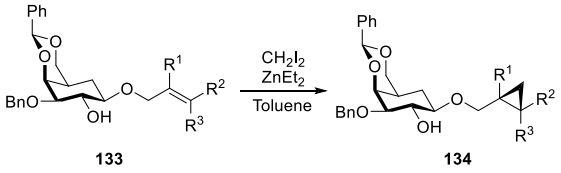
Since the cyclopropane derivatives have shown promising bioactivities in many cases, the enantioselective synthesis of cyclopropane derivatives becomes an important task in organic synthesis. The first systematic synthesis method for cyclopropane is the Simmons-Smith cyclopropanation, which was discovered in 1958 (Scheme 54).[145] The reaction involves a zinc carbenoid formation by exposing diiodomethane to the zinc−copper couple Zn(Cu) and (2+1) olefin cyclization to afford cyclopropanes in high yields. However, the variations in surface features of the zinc−copper alloy would cause the inconsistency of the results; thus, a modified method utilizing $IZnCH_2I$ complex was provided by mixing diazomethane with zinc iodide in the ether as a resource of zinc carbenoid was discovered by Wittig and Schwarzenbach.[146] The most widely adopted method for the generation of the zinc carbenoid nowadays has been reported by Furukawa.[147] The treatment of diiodomethane with $ZnEt_2$ offered a zinc carbenoid, which is of particular active to electron-rich olefins and substrates containing Lewis basic directing groups. However, the substrate is limited according to the electronic property of olefins. In an attempt to

overcome such a restriction, several elegant solutions have been reported, such as the superior cyclopropanation properties of a carbenoid generated from $ZnEt_2$ and $ClCH_2I$ reported by Denmark and Edwards in 1991,[148] further activated by a ligand-exchange process of the zinc carbenoid reported by Shi,[149] and the discovery of enhanced reactivity of phosphoric acid-derived zinc carbenoids reported by Charette.[150]



Scheme 54. Possible pathways for Simmons-Smith cyclopropanation[145]

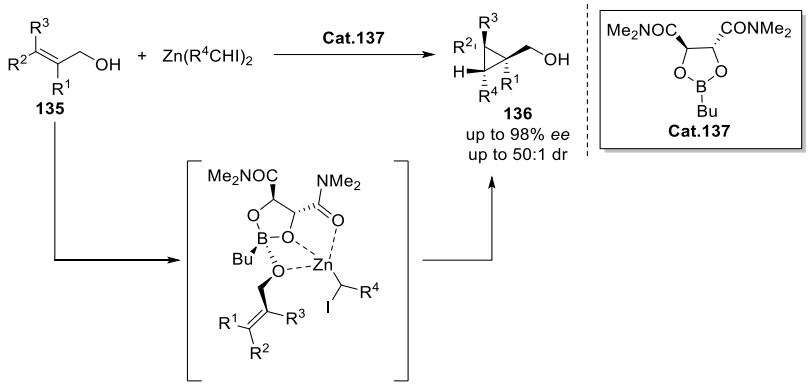
In the research field of biological compounds, chiral compounds are the majority providing active results. It could be visualized because the living organism is basically assembled from a bunch of chiral chemicals on the molecular scale. Cyclopropanes are indeed not an exception to this rule. Therefore, in recent decades synthetic methods for enantioselective cyclopropanation have become an essential challenge in organic synthesis chemistry. Although the mechanistic details of the Simmons-Smith are not completely clear, the broad spectrum of accessible substrates for Simmons-Smith reaction and the stereospecificity with respect to the alkene geometry are advantages that bring up the development of the enantioselective Simmons-Smith reaction (scheme 54).[145c] Based on the systematic Simmons-Smith method for (2+1) cycloaddition, extensive auxiliary-based cyclopropanation has been established to embed the chirality in cyclopropane derivatives and produce enantiopure compound for bioactivity inspection.



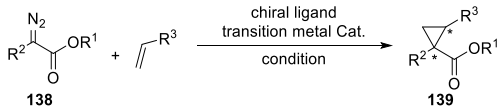
Scheme 55. The stereoselective Simmons-Smith cyclopropanation assisted by chiral auxiliary[151]

The synthesis of chiral cyclopropylmethanols as a representative paradigm and a considerable number of auxiliary-based enantioselective Simmons-Smith cyclopropanation were reported in the

past few years. The pioneering work was reported in 2008 by Iglesias-Guerra and co-workers (Scheme 55). [151] With the assistance of chiral monosaccharide derivatives **133**, cyclopropanation could occur to the allylic group in an enantiomeric manner. After extensive optimization, alkenyl *β*-d-galactopyranosides were found to be a reliable template for such enantioselective cyclopropanation to afford the formation of cyclopropane **134**. Thereafter, a diverse range of chiral auxiliaries has been tested and successfully embedded the chirality to the corresponding cyclopropylmethanol derivatives such as chiral allylic ethers, allylic amines, allylic alcohol, enamines, and enol ethers. Besides, the concept could be applied to alkenes bearing ketals, *α,β*-unsaturated carbonyl groups, and entirely unfunctionalized alkene as well. Unlike the broad substrate tolerance the chiral auxiliary-based cyclopropanation has, the catalytic Simmons-Smith cyclopropanation has been limited by its substrates tolerance; however, it is a more atom-economic method for the enantioselective cyclopropanation. In 1994, a designed dioxaborolane ligand **137** was utilized in the (2+1) cyclopropanation on allylic alcohol **135** by Charette and Juteau, which allows the generation of cyclopropane **136** to be accomplished in a stereoselective manner (Scheme 56).[152] Prepared from tetramethyltartaric acid diamide and butylboronic acid *in situ*, a stoichiometric amount of chiral dioxaborolane ligand **137** was required to conduct this classical Simmons-Smith cyclopropanation.



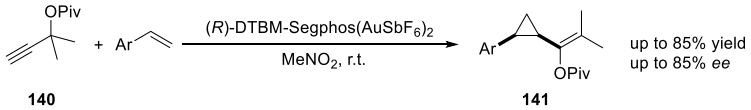
Scheme 56. Example of enantioselective cyclopropanations under Simmons-Smith's condition[152]



Scheme 57. The general idea of transition metal-catalyzed cyclopropanation using diazo compounds [153-155]

Other than zinc carbenoid, the diazo compounds **138** as a diacceptor play a role in the field of (2+1) cyclization as well (Scheme 57).[153-155] With different transition metal catalysts, the

cyclopropanation for cyclopropane **139** synthesis could be accomplished but elaborate through different pathways.[153] For instance, the mechanism of rhodium-catalyzed cyclopropanation could be rationalized based on the structural analysis and the stereoselectivity in different cases, although the definitive evidence is insufficient. Herein, we try to explain the mechanism according to the verified information found in the literature survey.[154] Between the diazo functional group and ruthenium catalyst, the coordination presumably allows the formation of the zwitterionic complex. This complexation would cause the emission of nitrogen gas to generate the metal carbene species for the subsequent intermolecular bond formation. Without direct coordination of the olefin to the metal, the concerted addition of the metal carbenoid to the olefin would then finish the whole cyclopropanation process. Noticeably, with this method, the substrate tolerance is broadened because diverse carbenoids could be used in this type of chemical transformation. Even thermodynamically unfavored electron-deficient carbine could be afforded. On the other hand, the cyclopropanation with the diazo compound could also be accomplished *via* a cobalt-catalyzed reaction which elaborates through a different pathway.[155] In the presence of a cobalt catalyst, the substrate tolerance is again expanded because electron-deficient alkenes could also be included. Found and verified by Bruin *et al.*, the unique reactivity was attributed to the radical character of the low-spin planar Co(II) complex.[154b] The resulting metal carbenoids with radical carbon character were produced by the metallic radical activation of diazo compounds, which generally could be described as one-electron-reduced Fischer-type carbenes. Upon carbene formation at Co(II) center, electron transfer from the metal center to the carbene moiety results in a cobalt(III) carbene radical intermediate. The unpaired electron in the p-orbital of the carbenoid will then result in the cobalt(III) carbenoid intermediate. Unlike usual Fischer-type carbenes, which have an entirely unoccupied p-orbital, the carbon p-orbital of the cobalt carbene radical intermediates has a singly occupied molecular orbital (SOMO) which makes it less electron deficient. This explains the increased reactivity of cobalt(III) carbene radical intermediates towards electron-deficient olefins and their decreased tendency to undergo unexpected carbene−carbene dimerization reactions.[155c, 155d]



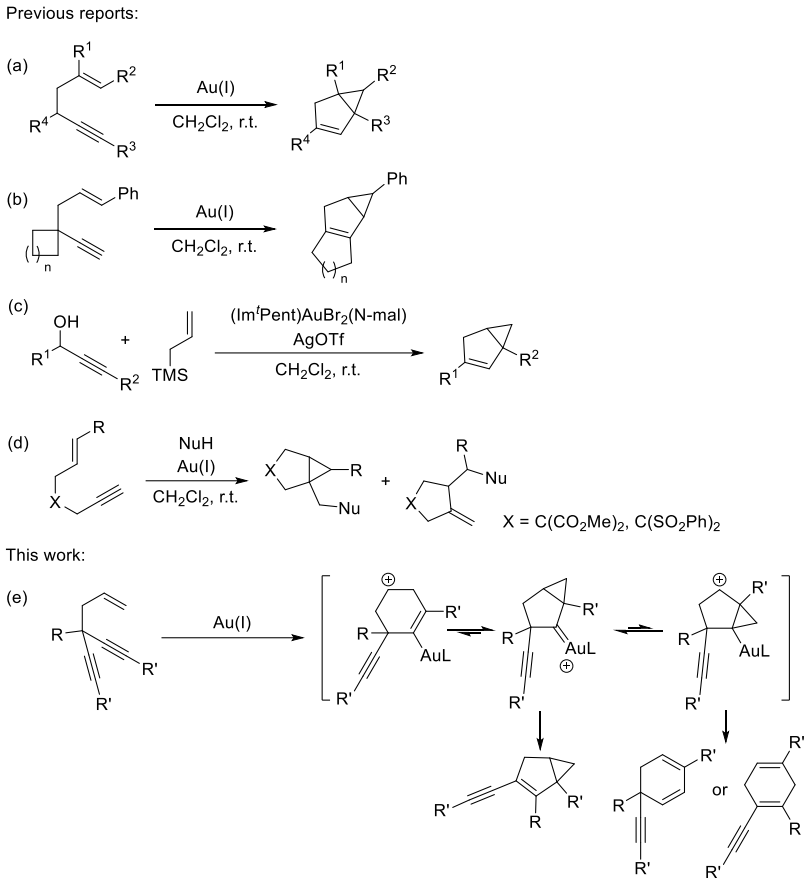
Scheme 58. Gold(I)-catalyzed stereoselective olefin cyclopropanation[156]

Other than typical (2+1) cyclization with active metal carbenoid species, the activated alkyne **140** could react to styrene and afford cyclopropanation to occur and fulfill the formation of vinylcyclopropane **141** in the presence of a Lewis acid catalyst; for example, homogeneous gold catalysis in this case (Scheme 58).[156] Considering the nature of the gold complexes, the enyne isomerization oftentimes can be initiated by the η-complexation, which increases the electrophilicity of the alkyne group and allows the corresponding carbon cation to generate. The resulting cation is either been trapped by other nucleophiles, or the pronounced back donation from the gold carbene would participate and fulfill the cyclopropanation. With assistance from the chiral ligand, enantioselective cyclopropanation is also feasible. Different from concerted (2+1) cycloaddition with metal carbenes, gold-catalyzed enyne isomerization provides a broader range of substrate tolerance at meanwhile diminish the convoluted procedure for manipulating the metallic radical species. Therefore in this dissertation, based on the previous discovery of the gold-catalyzed enyne isomerization, the reactivity of 3-allylated-1,4-diynes was explored.

3-2 Gold-catalyzed cycloisomerization of 1,5-enynes and 1,6-enynes

Along with the success of the intermolecular enyne isomerization, the intramolecular enyne isomerization for the [n,1,0] bicyclic formation was inspected, and multiple research results show the ring strain is not inhibiting this intramolecular enyne isomerization from happening no matter 1,5-enyne or 1,6-enyne was used. Besides, during the isomerization, driven by the thermal dynamic stability, the cationic intermediate will undergo a rearrangement process to stabilize the cation depending on the structure of the substrate, which gives in a wide diversity of possible unsaturated hydrocarbon products.

In this work, the reactivity of the 3-allylated-1,4-diynes in the presence of cationic gold(I) complex was investigated. In general, the enyne isomerization gives very similar reactivity to the 1,5-enyne isomerization. However, our 3-allylated-1,4-diynes has a quaternary center which will not allow the hydrogen shift to liberate the catalyst. Instead, the aryl group would get involved and stabilize the carbene intermediate and afford 1,2-aryl shift to finish the catalytic cycle and liberate the free gold(I) cation for the next catalytic cycle. Although the quaternary center was destroyed in this case, the cyclopropane still featured two consecutive chiral centers; therefore, the enantioselective cyclization was tested.



Scheme 59. Overview of gold-catalyzed 1,n-enyne cycloisomerizations

In the process of exploring the substrate scope, we noticed the diversity of this chemical transformation. In order to clarify this substrate-dependent chemoselectivity, we carefully isolated all the products and analyzed their structures while the aryl group was exchanged with alkyl group (Scheme 59). Toward differently substituted substrates, the specific mechanism was assigned. Furthermore, the reaction with isotope-labeled 1,4-diynes was conducted to rule out once more the suspicious hydrogen shift, which was dominant in the previously reported enyne isomerization; however not take place in our reaction. With our method, a broad range of novel cyclic hydrocarbons can be afforded, including bicycle[3.1.0]hexanes, bicyclo[3.1.0]hexane-fused pleiadiene, cyclohexa-1,3-diene, cyclohexa-1,4-diene, and 5,9-methanobenzo[8]-annulene.

3-3 Publication

European Journal of Organic Chemistry

Supporting Information

Insights into the Gold-Catalyzed Cycloisomerization of 3-Allyl-1,4-diynes for the Synthesis of Bicyclic Hydrocarbons

Jhen-Kuei Yu and Constantin Czekelius*

Author Contributions

J.-K.Y. Data curation:Lead; Investigation:Lead; Writing – review & editing:Lead

Table of Contents

I. General information

All solvents and reagents used were purchased from commercial suppliers as reagent grade. They were used without further purification unless otherwise noted. Starting materials and catalysts, which were not commercially available, were synthesized by previously reported methods. The methods for preparing anhydrous solvents and reagents were referred to Purification of Laboratory Chemicals, Sixth Edition (ISBN: 978-1-85617-567-8). Dichloromethane, tetrahydrofuran, and toluene were dried using the Solvent Purification System MP SPS-800 by M.Braun. For reactions requiring an inert atmosphere, the glassware was dried in a compartment dryer at 120 °C, and then standard Schlenk techniques were used to work under a dry nitrogen atmosphere. Rotary evaporators combined with vacuum pumps were used for the removal of volatiles under reduced pressure. Analytical thin-layer chromatography (TLC) was performed on precoated alumina-backed silica gel plates (Macherey-Nagel, 0.2 mm thickness silica gel 60 with fluorescence indicator UV_{254}), which were developed using UV fluorescence and $KMnO_4$ stain solution. Flash chromatography was performed on silica gel (Macherey-Nagel, silica 60 M, 0.04-0.063 mm). IR spectra were measured as thin films on a NaCl single crystal with a JASCO PS 4000 spectrometer, and only selected peaks are shown. ^{1}H-NMR spectra were recorded on a Bruker Advance III 300 MHz spectrometer, ^{13}C-NMR spectra were recorded at 75 MHz, and ^{31}P-NMR spectra were recorded at 121 MHz. The coupling constants *J* are given in Hertz (Hz) and chemical shifts (δ) in ppm. Chemical shifts were reported in δ ppm referenced to trace amounts of chloroform δ($CHCl_3$) = 7.26 ppm in ^{1}H-spectra and to the signal of deuterated chloroform δ($CDCl_3$) = 77.16 ppm in ^{13}C-spectra. The enantiomeric excess of the products was determined using a Hitachi LaChrome High-Performance Liquid Chromatography (HPLC) system equipped with DAICEL CHIRALPAK® IC™ (4.6 x 250 mm) column using *n*-hexane as eluent. The samples were filtered through syringe filters (25 mm, 0.45 µm PTFE membrane or 13 mm, 0.2 µm PTFE membrane) prior to analysis.

II. Experimental procedures

Procedures for the synthesis of starting materials

The allylated 1,4-diyne starting materials **1a, 1b, 1c, 1d, 1e, 1i** were prepared according to previous work and confirmed by ^{1}H-NMR.[1]

The preparations of new substances are described independently, such as **1f**, **1g**, **1h**, **1j**, **1k**, **1l**, **1m**, **1n**. The required precursors were prepared by following literature-known procedures.[2]

Procedures for the synthesis of catalysts

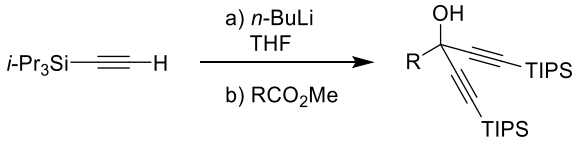
The racemic gold complexes were synthesized from $(Me_2S)AuCl$ by using phosphine ligands such as triphenylphosphine[3a], tri-*t*-butylphosphine[3b], tri-*n*-butylphosphine[3c], triphenylphosphite[3d], and tris(4-methoxy-3,5-dimethylphenyl)phosphine. The chiral complexes (*R*)-DTBM-MeO-Biphep$(AuCl)_2$[4b], (*R*)-DTBM-Garphos$(AuCl)_2$[4c], (*R*)-BTFM-Garphos$(AuCl)_2$[4c], (*R*)-Tol-Garphos$(AuCl)_2$, (*R*)-DTBM-Segphos$(AuCl)_2$[4d], and (*S*)-DM-Segphos$(AuCl)_2$[4e] were prepared via a modified procedure reported by Puddephat *et al*.[4a]

Silver (I) (*S*)TRIP-phosphate was prepared according to the method by Toste *et al.*[5]

Procedure for the synthesis of compounds 1f, 1g, 1l, and 1m

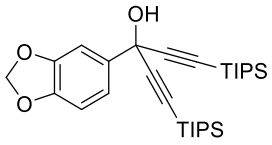
The corresponding esters were prepared according to literature-known procedures and the results are consistent with the data reported.[2a-2d]

General procedure for the dialkynylation of esters (GP 1)



In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, triisopropylsilylacetylene (2.20 equiv.) was dissolved in anhydrous THF (0.2 M). To this solution, *n*-BuLi (2.5 M, 2.20 equiv.) was added at 0 °C. The mixture was stirred at this temperature for 30 min and then treated with the methyl carboxylate (1.00 equiv.) under protection of N_2. The reaction mixture was stirred for 6 hr and allowed to warm to room temperature. Aqueous workup was committed when complete conversion was observed by TLC. The product was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent, the crude product was purified via flash column chromatography on silica gel (eluent EtOAc/Hex) to produce the substituted penta-1,4-diyn-3-ols.

3-(Benzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



Under protection of N_2, triisopropylsilylacetylene (12.9 mL, 57.7 mmol), *n*-BuLi (2.5 M, 23.1 mL, 57.7 mmol) and methyl benzo[d][1,3]dioxole-5-carboxylate (4.72 g, 26.2 mmol) were added to the reaction flask according to **GP 1** and purified by flash column chromatography (EtOAc : Hex = 1: 20, R_F = 0.43) to produce **3-(benzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)-penta-1,4-diyn-3-ol** as a yellowish oil (13.3 g, 99%).

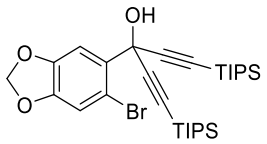
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.32 (d, *J* = 1.9 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 5.98 (s, 2H), 2.75(s, 1H), 1.11-0.92 (m, 42H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 147.9, 147.7, 136.0, 120.0, 107.9, 107.2, 107.1, 101.4, 86.5, 65.5, 18.7, 11.3.

IR (NaCl) ṽ (cm^{-1}): 3412, 2943, 2891, 2865, 2144, 1722, 1622, 1609, 1504, 1487, 1463, 1443, 1383, 1365, 1280, 1256, 1194, 1158, 1105, 1074, 1040, 1018, 996, 939, 919, 882, 810, 761, 722, 677.

HRMS (ESI): calc'd. for $C_{30}H_{49}O_3Si_2$, **[M+H]$^+$** 513.3215; found 513.3216.

3-(6-Bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



Under protection of N_2, triisopropylsilylacetylene (2.47 mL, 11.0 mmol), *n*-BuLi (2.5 M, 4.40 mL, 11.0 mmol) and methyl benzo[d][1,3]dioxole-5-carboxylate (1.30 g, 5.00 mmol) were added to the reaction flask according to **GP 1** and purified by flash column chromatography (EtOAc : Hex = 1: 20, R_F = 0.36) to produce **3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)-penta-1,4-diyn-3-ol** as a pale yellow powder (2.75 g, 93%).

m.p. = 67.6 °C

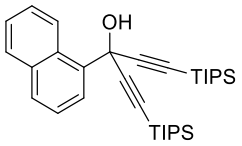
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (s, 1H), 7.06 (s, 1H), 6.00 (s, 2H), 3.47 (s, 1H), 1.27-1.02 (m, 42H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 148.2, 147.1, 132.9, 114.8, 112.6, 108.9, 105.5, 102.2, 87.3, 65.9, 18.7, 11.4.

IR(NaCl) ṽ (cm^{-1}): 3518, 2943, 2891, 2865, 1504, 1479, 1240, 1108, 1038, 996, 882, 677.

HRMS(ESI): calc'd. for $C_{30}H_{46}BrO_2Si_2$, **[M-OH]$^+$** 573.2214; found 573.2215.

3-(Naphthalen-1-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



Under protection of N_2, triisopropylsilylacetylene (10.5 mL, 46.8 mmol), *n*-BuLi (2.5 M, 18.7 mL, 46.8 mmol), and methyl 1-naphthoate (3.97 g, 21.3 mmol) were added to the reaction flask according to **GP 1** and purified by flash column chromatography (EtOAc : Hex = 1: 20, R_F = 0.54) to produce **3-(naphthalen-1-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol** as a colorless oil (10.9 g, 99%).

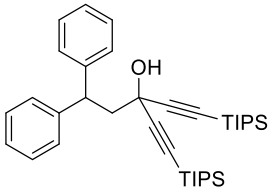
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.05-8.89 (m, 1H), 8.16 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.87-7.76 (m, 2H), 7.55-7.38 (m, 3H), 2.97 (s, 1H), 1.09-1.01 (m, 42H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 136.1, 134.6, 130.0, 129.9, 128.5, 127.3, 125.7, 125.5, 124.7, 124.2, 107.2, 87.7, 65.9, 18.7, 11.3.

IR(NaCl) ṽ (cm^{-1}): 3586, 3445, 3053, 2948, 2866, 1506, 1463, 1376, 1360, 1309, 1253, 1163, 1101, 1051, 1006, 928, 883, 805, 739, 671.

HRMS(ESI): calc'd. for $C_{33}H_{49}Si_2$, **[M-OH]$^+$** 501.3367; found 501.3379.

3-(2,2-Diphenylethyl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



Under protection of N_2, triisopropylsilylacetylene (2.06 mL, 9.24 mmol), *n*-BuLi (2.5 M, 3.70 mL, 9.24 mmol) and methyl 3,3-diphenylpropanoate (1.01 g, 4.20 mmol) were added to the reaction flask according to **GP 1** and purified by flash column chromatography (EtOAc : Hex = 1: 20, R_F = 0.58) to produce **3-(2,2-diphenylethyl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol** as a colorless oil (2.38 g, 99%).

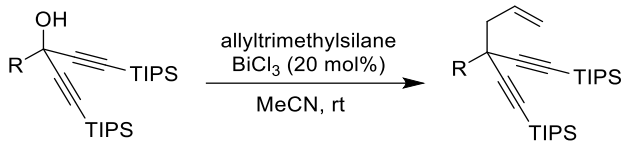
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.22 (m, 8H), 7.20-7.12 (m, 2H), 4.63 (t, *J* = 6.8 Hz, 1H), 2.79 (d, *J* = 6.8 Hz, 2H), 2.05 (s, 1H), 1.13-1.02 (m, 42H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 144.9, 128.8, 128.1, 126.5, 107.4, 85.3, 64.7, 48.7, 48.1, 18.8, 11.3.

IR (NaCl) ṽ (cm^{-1}): 3550, 3444, 2947, 2865, 1460, 1375, 1244, 1063, 1000, 920, 883, 745, 672.

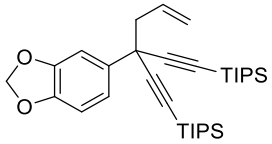
HRMS (ESI): calc'd. for $C_{37}H_{56}NaO_2Si_2$, **[M+Na]$^+$** 595.3762; found 595.3756.

General procedure for propargylic allylation (GP 2)



In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, the penta-1,4-diyn-3-ol (1.00 equiv.) was dissolved in anhydrous MeCN (0.2 M). To the solution, bismuth chloride (20 mol%) and allyltrimethylsilane (3.00 equiv.) were added at ambient temperature. The mixture was stirred at this temperature for 24 hr under protection of N_2. Aqueous workup was committed when complete conversion was observed by TLC. The product was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent, the crude product was purified via flash column chromatography on silica gel (eluent hexane/methylene chloride) to produce the allylated silyl-protected diyne.

(3-Allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



Under protection of N_2, 3-(benzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (5.59 g, 10.9 mmol), bismuth chloride (708 mg, 2.18 mmol), and allyltrimethylsilane (5.23 mL, 32.7 mmol) were dissolved in anhydrous MeCN (55 mL) according to **GP 2** and the product was purified by flash column chromatography (DCM : Hex = 1 : 30, R_F = 0.58) to produce **(3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)** as a yellowish oil (4.16 g, 70%).

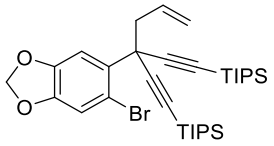
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23-7.16 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.96 (s, 2H), 5.87 (ddt, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.12-4.98 (m, 2H), 2.61 (dt, *J* = 7.1, 1.2 Hz, 2H), 1.13-1.03 (m, 42H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 147.5, 146.7, 136.1, 133.5, 120.0, 118.7, 108.0, 107.8, 107.6, 101.2, 84.2, 51.7, 42.1, 18.8, 11.4.

IR (NaCl) ṽ (cm^{-1}): 2943, 2892, 2865, 2171, 1504, 1488, 1464, 1438, 1242, 1042, 1017, 994, 942, 918, 882, 811, 678.

HRMS (ESI): calc'd. for $C_{33}H_{53}O_2Si_2$, **[M+H]$^+$** 537.3579; found: 537.3576.

(3-Allyl-3-(6-bromobenzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



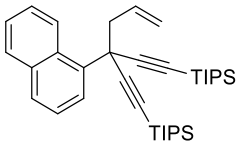
Under protection of N_2, 3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (531 mg, 900 µmol), bismuth chloride (58.5 mg, 180 µmol), and allyltrimethylsilane (0.44 mL, 2.70 mmol) were dissolved in anhydrous MeCN (5 mL) according to **GP 2** and the product was purified by flash column chromatography (DCM : Hex = 1: 30, R_F = 0.49) to produce **(3-allyl-3-(6-bromobenzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triiso-propyl-silane)** as a colorless oil (387 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.06 (s, 1H), 5.98 (s, 2H), 5.89 (ddt, *J* = 17.1, 10.0, 7.1 Hz, 1H), 5.18-5.03 (m, 2H), 3.04 (dt, *J* = 7.1, 1.2 Hz, 2H), 1.16-1.06 (m, 42H).
^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 147.6, 147.1, 133.5, 131.4, 118.6, 115.1, 112.6, 110.7, 106.9, 102.0, 86.1, 45.4, 43.3, 18.8, 11.5.

IR (NaCl) ṽ (cm^{-1}): 2943, 2891, 2865, 2167, 1505, 1478, 1380, 1235, 1114, 1071, 1041, 1017, 995, 938, 918, 882, 831, 784, 741, 678.

HRMS (ESI): calc'd. for $C_{33}H_{55}BrNO_2Si_2$, **[M+NH$_4$]$^+$** 632.2949; found 632.2951.

(3-Allyl-3-(naphthalen-1-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



Under protection of N_2, 3-(naphthalen-1-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (2.59 g, 5.00 mmol), bismuth chloride (325 mg, 1.00 mmol), and allyltrimethylsilane (2.43 mL, 15.0 mmol) were dissolved in anhydrous MeCN (25 mL) according to **GP 2** and the product was purified by flash column chromatography (DCM : Hex = 1: 30, R_F = 0.51) to produce **(3-allyl-3-(naphthalen-1-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)** as a yellowish oil (1.92 g, 71%).

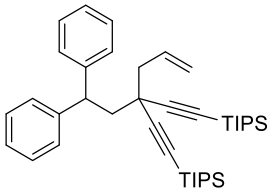
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.05-8.95 (m, 1H), 8.10 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.89-7.82 (m, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.51-7.39 (m, 3H), 6.00 (ddt, *J* = 16.6, 10.5, 7.1 Hz, 1H), 5.14-4.98 (m, 2H), 3.05 (dt, *J* = 7.1, 1.3 Hz, 2H), 1.12-1.06 (m, 42H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 136.0, 134.8, 133.9, 130.2, 129.0, 128.9, 126.6, 125.5, 125.4, 125.1, 125.0, 118.4, 108.3, 85.9, 47.5, 42.1, 18.8, 11.5.

IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3285, 3080, 2983, 2925, 1597, 1459, 1360, 1337, 1169, 1112, 1092, 1046, 990, 916, 813, 757, 714, 660.

HRMS (ESI): calc'd. for $C_{36}H_{55}Si_2$, **$[M+H]^+$** 543.3837; found 543.3838.

(3-Allyl-3-(2,2-diphenylethyl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



Under protection of N_2, 3-(2,2-diphenylethyl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (573 mg, 1.00 mmol), bismuth chloride (65.0 mg, 200 µmol), and allyltrimethylsilane (1.94 mL, 12.0 mmol) were dissolved in anhydrous MeCN (5 mL) according to **GP 2** and the product was purified by flash column chromatography (DCM:Hex = 1:50, R_F = 0.51) to produce **(3-allyl-3-(2,2-diphenylethyl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)** as a colorless oil (113 mg, 19%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.17 (m, 8H), 7.16-7.08 (m, 2H), 5.94 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.08-5.01 (m, 1H), 4.95 (dq, *J* = 17.3 1.7 Hz, 1H) 4.60 (t, *J* = 6.3 Hz, 1H), 2.49 (d,

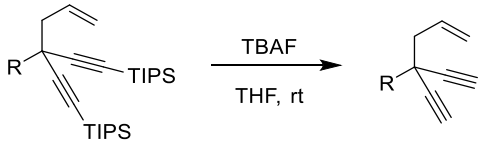
J = 6.3 Hz, 2H), 2.27 (d, *J* = 7.1, 2H), 1.26-0.81 (m, 42H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 145.8, 134.1, 128.5, 128.2, 126.2, 118.3, 109.0, 83.3, 48.9, 47.2, 46.1, 37.5, 18.8, 11.4.

IR (NaCl) ṽ (cm^{-1}): 2942, 2891, 2865, 2164, 1494, 1463, 1063, 1031, 1016, 995, 918, 883, 815, 742, 699.

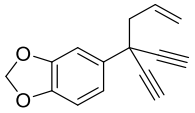
HRMS (ESI): calc'd. for $C_{40}H_{61}Si_2$, **[M+H]$^+$** 597.4306; found 597.4303.

General procedure for desilylation (GP 3)



In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, the allylated silyl-protected diyne (1.00 equiv.) was dissolved in anhydrous THF (0.1 M). To the solution, tetrabutylammonium fluoride (2.50 equiv.) was added at 0 °C under protection of N_2. The mixture was stirred for 18 hr allowing to warm to room temperature. Aqueous workup was committed when complete conversion was observed by TLC. The product was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent, the crude product was purified via flash column chromatography on silica gel (eluent hexane/methylene chloride) to produce the allylated terminal diyne.

5-(3-Ethynylhex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole (1f)



Under protection of N_2, (3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (269 mg, 0.50 mmol) and TBAF (327 mg, 1.25 mmol) were dissolved in anhydrous THF (5 mL) according to **GP 3** and the product was purified by flash column chromatography (DCM : Hex = 1: 10, R_F = 0.66) to produce **5-(3-ethynylhex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole** as a yellowish oil (108 mg, 96%).

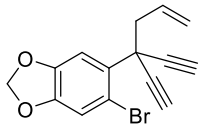
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20-7.13 (m, 2H), 6.81-6.71 (m, 1H), 5.97 (s, 2H), 5.85 (ddt, *J* = 17.4, 10.3, 7.1 Hz, 1H), 5.20-5.02 (m, 2H), 2.68 (dt, *J* = 7.1, 1.2 Hz, 2H), 2.53 (s, 2H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 147.8, 147.1, 134.6, 132.8, 119.9, 119.3, 107.9, 107.4, 101.4, 84.2, 72.3, 50.3, 39.9.

IR (NaCl) ṽ (cm^{-1}): 3293, 3077, 3014, 2980, 2898, 1504, 1484, 1438, 1099, 1039, 994, 934, 864, 811, 732, 709.

HRMS (ESI): calc'd. for $C_{15}H_{13}O_2$, **[M+H]$^+$** 225.0910; found: 225.0906.

5-Bromo-6-(3-ethynylhex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole (1g)



Under protection of N_2, (3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)-bis(triisopropylsilane) (1.07 g, 1.74 mmol) and TBAF (1.14 g, 4.34 mmol) were dissolved in anhydrous THF (17 mL) according to **GP 3** and the product was product was purified by flash column chromatography (DCM : Hex = 1: 10, R_F = 0.62) to produce **5-bromo-6-(3-ethynylhex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole** as a yellowish oil (509 mg, 96%).

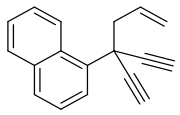
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.07 (s, 1H), 5.99 (s, 2H), 5.83 (ddt, *J* = 17.3, 10.2 7.1 Hz, 1H), 5.20-5.06 (m, 2H), 3.07 (dt, *J* = 7.1, 1.2 Hz, 2H), 2.60 (s, 2H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 147.9, 147.3, 132.7, 130.2, 119.3, 115.3, 112.6, 110.4, 102.2, 83.3, 73.6, 44.5, 41.1.

IR (NaCl) ṽ (cm^{-1}): 3294, 3079, 3011, 2981, 2899, 1640, 1620, 1504, 1479, 1440, 1403, 1379, 1335, 1236, 1114, 1038, 991, 931, 870, 825, 732.

HRMS (ESI): calc'd. for $C_{15}H_{12}BrO_2$, **[M+H]$^+$** 303.0015; found: 303.0008.

1-(3-Ethynylhex-5-en-1-yn-3-yl)naphthalene (1m)



Under protection of N_2, (3-allyl-3-(naphthalen-1-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (1.38 g, 2.60 mmol) and TBAF (1.70 g, 6.50 mmol) were dissolved in anhydrous THF (26 mL) according to **GP 3** and the product was purified by flash column chromatography (DCM : Hex = 1: 10, R_F = 0.58) to produce **1-(3-ethynylhex-5-en-1-yn-3-yl)naphthalene** as a yellowish oil (592 mg, 99%).

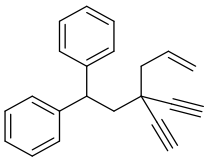
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.03 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.90(dd, *J* = 7.5, 1.4 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.60-7.39 (m, 3H), 5.97 (ddt, *J* = 17.2, 10.0, 6.9 Hz, 1H), 5.21-5.06 (m, 2H), 3.13 (dt, *J* = 7.0, 1.3 Hz, 2H), 2.66 (s, 2H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): = 134.9, 134.7, 133.2, 130.0, 129.5, 129.4, 125.8, 125.6, 125.5, 125.4, 125.1, 119.1, 84.5, 73.6, 46.3, 39.8.

IR (NaCl) ṽ (cm^{-1}): 3055, 2947, 2865, 2167, 1462, 1389, 1251, 1162, 1065, 996, 913, 884, 770, 672.

HRMS (ESI): calc'd. for $C_{18}H_{15}$, **$[M+H]^+$** 231.1168; found: 231.1166.

(3,3-Diethynylhex-5-ene-1,1-diyl)dibenzene (1l)



Under protection of N_2, (3-allyl-3-(2,2-diphenylethyl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (264 mg, 44.2 µmol) and TBAF (288 mg, 1.10 mmol) were dissolved in anhydrous THF (4 mL) according to **GP 3** and the product was purified by column chromatography (DCM : Hex = 1:50, R_F = 0.62) to produce **(3,3-diethynylhex-5-ene-1,1-diyl)dibenzene** as a colorless oil (124 mg, 99%).

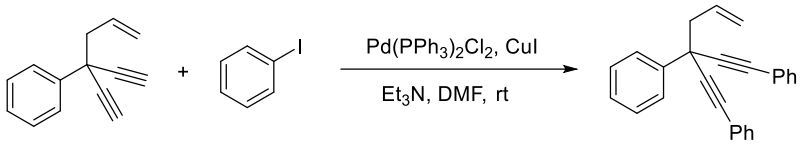
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.21 (m, 8H), 7.21-7.11 (m, 2H), 5.94 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.20-5.11 (m, 1H), 5.07 (d, *J* = 17.1, 1.6 Hz, 1H), 4.50 (t, *J* = 6.6 Hz, 1H), 2.51 (d, *J* = 6.6 Hz, 2H), 2.39 (d, *J* = 7.2, 2H), 2.15 (s, 2H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): 145.2, 133.2, 128.5, 128.3, 126.4, 119.0, 84.4, 71.4, 71.4, 48.6, 46.7, 46.1, 34.9.

IR (NaCl) ṽ (cm-1): 3292, 3084, 3061, 3027, 2949, 2918, 1641, 1600, 1584, 1494, 1473, 1451, 1439, 1289, 1271, 1031, 993, 921, 744, 701.

HRMS (ESI): calc'd. for $C_{22}H_{20}Na$, **[M+Na]$^+$** 307.1457; found: 307.1452.

Synthesis of (3-ethynylhex-5-en-1-yn-3-yl)benzene (1h)



In a dried and nitrogen-flushed Schlenk flask equipped with magnetic stir bar (3-ethynylhex-5-en-1-yn-3-yl)benzene (1.00 equiv. 901 mg, 5.00 mmol) was dissolved in triethylamine (30 mL, 0.17 M). Iodobenzene (4.00 equiv. 2.28 mL, 20.0 mmol) was added and the whole solution was degassed by bubbling N_2 through it for 30 min. At 0 °C, bis(triphenylphosphine)palladium(II) dichloride (5 mol%, 175 mg, 250 µmol) and copper iodide (10 mol%, 95.2 mg, 500 µmol) were added to the solution under N_2. Within 10 minutes, a grey precipitate was formed, which could be dissolved by an additional 10 mL of DMF. The reaction mixture was stirred vigorously for 24 hr allowing it to warm to room temperature. Aqueous workup with saturated NH_4Cl (aq.) was committed when complete conversion was observed by TLC. The mixture was extracted with DCM three times. The combined organic phases were washed with brine three times and dried over Na_2SO_4. The organic layer was collected and the volatiles were removed under reduced pressure. The crude product was purified by column chromatography (DCM : Hex = 1 : 30, R_F = 0.28) to afford **(3-(phenylethynyl)hex-5-en-1-yne-1,3-diyl)dibenzene** as a colorless oil (951 mg, 57%).

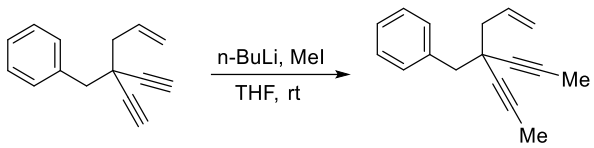
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89-7.78 (m, 2H), 7.60-7.48 (m, 4H), 7.46-7.37 (m, 2H), 7.37-7.28(m,7H), 6.03 (ddt, *J* = 16.3, 10.9, 7.2 Hz, 1H), 5.21 (dd, *J* = 1.2, 1.0 Hz, 1H), 5.19-5.14 (m, 1H), 2.88 (dt, *J* = 7.2, 1.2 Hz, 2H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 142.1, 133.6, 132.0, 132.0, 128.6, 128.5, 128.4, 128.4, 127.5, 126.8, 126.7, 123.2, 119.0, 90.0, 84.2, 51.1, 41.5.

IR (NaCl) ṽ (cm^{-1}): 3079, 3060, 3032, 2979, 2913, 1598, 1490, 1443, 917, 755, 690.

HRMS (APCI) calc'd. for $C_{26}H_{21}$, **[M+H]$^+$** 333.1638; found: 333.1635.

Synthesis of (2,2-diethynylpent-4-en-1-yl)benzene (1j)



In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar (2,2-diethynylpent-4-en-1-yl)benzene (1.00 equiv. 440 mg, 2.27 mmol) was dissolved in anhydrous THF (11 mL, 0.2 M). To the solution *n*-BuLi (2.40 equiv. 2.16 mL of 2.5 M solution in hexanes, 5.44 mmol) was added at 0 °C. After stirring at this temperature, iodomethane (2.40 equiv. 339 µL, 5.44 mmol) was then added to the reaction solution. The mixture was stirred for 6 h allowing to warm to rt. Aqueous workup was committed when complete conversion was observed by TLC. The mixture was extracted with EtOAc three times. The combined organic phases were washed with brine and dried over Na_2SO_4. The organic layer was collected and the volatiles were removed under reduced pressure. The crude product was purified via column chromatography on silica gel (DCM: Hex = 1**:** 50, R_F = 0.60) to afford **(2,2-di(prop-1-yn-1-yl)pent-4-en-1-yl)benzene** as a yellowish oil (409 mg, 83%).

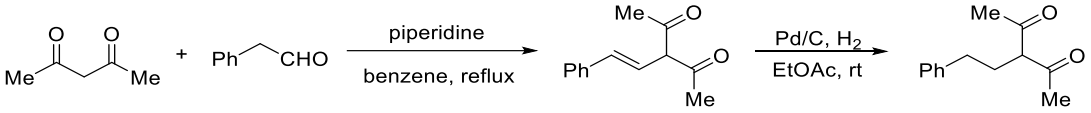
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.14 (m, 5H), 6.04 (ddt, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.23-5.05 (m, 2H), 2.89 (s, 2H), 2.38 (dt, *J* = 7.1, 1.28 Hz, 2H), 1.80 (s, 6H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 137.3, 134.6, 131.0, 127.7, 126.8, 118.2, 80.6, 78.8, 47.4, 46.1, 36.3, 3.8.

IR (NaCl) ṽ (cm^{-1}): 3075, 3064, 3031, 3008, 2978, 2946, 2918, 2855, 1641, 1604, 1496, 1454, 1439, 993, 916, 753, 699.

HRMS (ESI) calc'd. for $C_{17}H_{18}$, **$[M+H]^+$** 223.1481; found 223.1480.

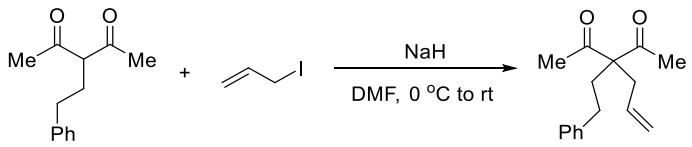
Synthesis of 3-phenethylpentane-2,4-dione



A mixture of acetylacetone (1.10 equiv. 19.0 mmol, 1.95 mL), phenylacetaldehyde (1.00 equiv. 17 mmol, 2.21 mL), piperidine (20 mol%, 3.4 mmol, 0.34 mL), and acetic acid (20 mol%, 3.4 mmol, 0.24 mL) was dissolved in benzene (15 mL, 1.1 M) in a round-bottom flask equipped with a magnetic stir bar. By using a Dean-Stark apparatus, the reaction mixture was refluxed for 18 h and monitored by TLC. The mixture was diluted with Et_2O (50 mL) and H_2O (25 mL). The organic layer was separated and washed with H_2O (25 mL), 1 M HCl (2×25 mL), and a saturated solution of $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4. After filtration and removal of the solvent, the crude product was purified via column chromatography on silica gel (EtOAc: Hex = 1**:** 10, R_F = 0.58) to afford **3-styrylpentane-2,4-dione** as a light yellow oil.

In a round-bottom flask equipped with a magnetic bar, the 3-styrylpentane-2,4-dione (1.00 equiv. 8.31 mmol, 1.68 g) was dissolved in EtOAc (0.17 M, 50 mL) and then treated with Pd/C (10.0%, 168 mg). The mixture was hydrogenated at 1 atm of hydrogen using a balloon. Purification proceeded when complete conversion was observed by TLC analysis. The volatiles were removed under reduced pressure and the crude product was purified via column chromatography on silica gel (EtOAc : Hex = 1 **:** 20, R_F = 0.19) to afford **3-phenethylpentane-2,4-dione** as a pale yellow oil. The results are consistent with the data reported.[2e, 2f]

Synthesis of 3-allyl-3-phenethyl-pentane-2,4-dione



In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, 3-phenethylpentane-2,4-dione (1.00 equiv. 734 mg, 3.59 mmol) was dissolved in dry DMF (14 mL, 0.25 M). Sodium hydride (60% in mineral oil, 1.00 equiv. 144 mg, 3.59 mmol) was added to this solution at 0 °C. The mixture was stirred at this temperature for 30 min and 30 min at room temperature until evolution of hydrogen gas had ceased. The mixture was then treated with allyl iodide (1.10 equiv. 362 µL, 3.95 mmol) at 0 °C and stirred for 2 h allowing to warm to rt. Aqueous workup with saturated NaCl (aq.) was committed when completion of the reaction was observed by TLC. The mixture was extracted with EtOAc three times. The combined organic phases were

washed with brine three times and dried over Na_2SO_4. The organic layer was collected and the volatiles were removed under reduced pressure. The crude product was purified via column chromatography on silica gel (EtOAc : Hex = 1**:** 20, R_F = 0.34) to afford **3-allyl-3-alkylpentane-2,4-dione** as a colorless oil (564 mg, 64%).

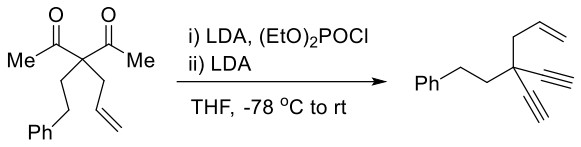
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.26 (m, 2H), 7.24-7.11(m, 3H), 5.57 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.24-5.08 (m, 2H), 2.75 (dt, *J* = 7.3, 1.3 Hz, 2H), 2.43-2.32 (m, 2H), 2.23-2.14 (m, 2H), 2.13 (s, 6H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 206.3, 141.4, 132.3, 128.7, 128.4, 126.4, 119.3, 70.5, 35.1, 32.8, 30.2, 27.2.

IR (NaCl) ṽ (cm^{-1}): 2954, 2925, 2858, 1716, 1698, 1455, 1358, 1182, 1151, 921, 753, 699.

HRMS (ESI): calc'd. for $C_{16}H_{21}O_2$, **$[M+H]^+$** 245.1536; found: 245.1535.

Dialkynylation of 3-allyl-3-phenethyl-pentane-2,4-dione (1k)



(a) In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, diisopropylamine (2.40 equiv. 580 µL, 4.14 mmol) was dissolved in dry THF (14 mL, 0.3 M). *n*-BuLi (2.20 equiv., 1.52 mL of 2.5 M solution in hexanes, 3.80 mmol) was added to this solution at -78 °C. The mixture was stirred at this temperature for 30 min and another 30 min at 0 °C. This mixture was treated with a solution of allylated dione (1.00 equiv. 423 mg, 1.73 mmol) in dry THF (6 mL, 0.4 M) at -78 °C and stirred at this temperature for 1 h. Diethyl chlorophosphate (2.10 equiv. 0.78 mL, 3.63 mmol) was added to this solution at -78 °C. The mixture was stirred for 3 h allowing to warm to rt.

(b) In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, diisopropylamine (4.80 equiv. 1.17 mL, 8.30 mmol)) was dissolved in dry THF (41 mL, 0.2 M). *n*-BuLi (4.40 equiv. 3.04 mL, 2.5 M solution in hexanes, 7.61 mmol) was added to this solution at -78 °C. The mixture was stirred at this temperature for 30 min and 30 min at 0 °C. This mixture was treated with the reaction mixture from a) at -78 °C and stirred for 24 h allowing to warm to rt. Aqueous workup was committed when completion of the reaction was observed by TLC. The mixture was extracted with diethyl ether three times. The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration and removal of solvent, the crude

product was purified via column chromatography on silica gel (DCM : Hex = 1 : 30, R_F = 0.36) to afford **(3,3-diethynylhex-5-en-1-yl)benzene** as a colorless oil (153 mg, 42 %).

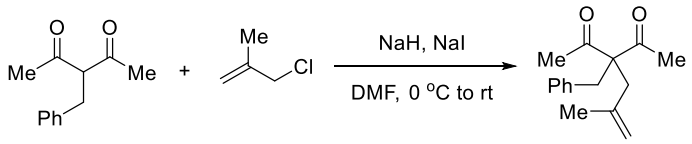
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.25 (m, 2H), 7.25-7.14 (m, 3H), 6.07-5.94 (m, 1H), 5.21 (t, *J* = 1.2 Hz, 1H), 5.16 (ddt, *J* = 7.6, 2.1, 1.2 Hz, 1H), 2.99- 2.91 (m, 2H), 2.52 (dt, *J* = 7.2, 1.2 Hz, 2H), 2.35 (s, 2H), 1.97-1.89 (m, 2H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 141.8, 133.1, 128.6, 128.6, 126.1, 119.0, 84.7, 70.8, 45.9, 42.8, 35.1, 31.9.

IR (NaCl) ṽ (cm^{-1}): 3295, 3082, 3063, 3027, 2979, 2953, 2922, 2863, 1507, 1497, 1455, 1438, 1221, 993, 815, 700, 643.

HRMS (APCI): calc'd. for $C_{16}H_{17}$, **$[M+H]^+$** 209.1325; found: 209.1326.

Synthesis of 3-benzyl-3-(2-methylallyl)pentane-2,4-dione



In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, 3-benzylpentane-2,4-dione (1.00 equiv. 1.94 g, 10.0 mmol.) was dissolved in dry DMF (20 mL, 0.50 M). Sodium hydride (60% in mineral oil, 1.0 equiv., 400 mg, 10.0 mmol) was added to this solution at 0 °C. The mixture was stirred at this temperature for 30 min and 30 min at room temperature until evolution of hydrogen gas had ceased. The mixture was then treated with 3-chloro-2-methylprop-1-ene (1.20 equiv. 1.20 mL, 12.0 mmol) and sodium iodide (1.20 equiv. 1.80 g, 12.0 mmol) under N_2 at 0 °C. The reaction mixture was stirred for 24 hr allowing to warm to room temperature. Aqueous workup with saturated NaCl (aq.) was committed when completion of the reaction was observed by TLC. The mixture was extracted with EtOAc three times. The combined organic phases were washed with brine three times and dried over Na_2SO_4. The organic layer was collected and the volatiles were removed under reduced pressure. The crude product was purified via column chromatography on silica gel (EtOAc: Hex = 1**:** 20, R_F = 0.24) to afford **3-benzyl-3-(2-methylallyl)pentane-2,4-dione** as slightly yellowish oil (1.91 g, 78%).

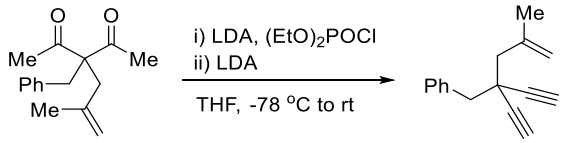
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25-7.16 (m, 3H), 7.05-6.96 (m, 2H), 4.91 (hept, *J* = 1.2 Hz, 1H), 4.63 (tq, *J* = 1.7, 0.9 Hz, 1H), 3.37(s, 2H), 2.59 (s, 2H), 2.14 (s, 6H), 1.68 (dd, *J* = 1.4, 0.7 Hz, 3H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 206.8, 140.9, 136.5, 129.8, 128.5, 127.0, 113.6, 71.3, 37.8, 37.1, 27.7, 24.9.

IR (NaCl) ṽ (cm^{-1}): 3084, 3065, 3031, 3002, 2971, 2926, 2857, 1718, 1697, 1651, 1496, 1454, 1375, 1358, 1175, 1146, 1081, 898, 759, 701. 503.

HRMS (ESI): calc'd. for $C_{16}H_{21}O_2$, **$[M+H]^+$** 245.1536; found: 245.1540.

Dialkynylation of 3-benzyl-3-(2-methylallyl)pentane-2,4-dione (1n)



(a) In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, diisopropylamine (2.40 equiv. 2.62 mL, 18.7 mmol) was dissolved in dry THF (62 mL, 0.3 M). *n*-BuLi (2.20 equiv. 6.88 mL, 2.5 M solution in hexanes, 17.2 mmol) was added to this solution at -78 °C. The mixture was stirred at this temperature for 30 min and another 30 min at 0 °C. This mixture was treated with a solution of allylated dione (1.00 equiv. 1.90 g, 7.8 mmol) in dry THF (20 mL, 0.4 M) at -78 °C and stirred at this temperature for 1 h. Diethyl chlorophosphate (2.10 equiv. 2.44 mL, 16.4 mmol) was added to this solution at -78 °C. The mixture was stirred for 3 h allowing to warm to rt.

(b) In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, diisopropylamine (4.80 equiv. 5.24 mL, 37.3 mmol) was dissolved in dry THF (187 mL, 0.2 M). *n*-BuLi (4.40 equiv. 13.8 mL, 2.5 M solution in hexanes, 34.3 mmol) was added to this solution at -78 °C. The mixture was stirred at this temperature for 30 min and 30 min at 0 °C. This mixture was treated with the reaction mixture from a) at -78 °C and stirred for 24 h allowing to warm to rt. Aqueous workup was committed when completion of the reaction was observed by TLC. The mixture was extracted with diethyl ether three times. The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration and removal of the solvent, the crude product was purified via column chromatography on silica gel (DCM: Hex = 1**:** 30, R_F = 0.39) to afford **(2,2-diethynyl-4-methylpent-4-en-1-yl)benzene** as slightly yellowish oil (1.34 g, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.36 (m, 2H), 7.35-7.27 (m, 3H), 5.01-4.92 (m, 2H), 3.00 (s, 2H), 2.47 (s, 2H), 2.33 (s, 2H), 1.95 (s, 3H).

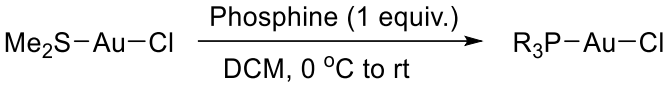
^{13}C NMR{1 H} (75 MHz, $CDCl_3$): δ = 141.3, 136.2, 131.1, 127.8, 127.2, 115.8, 84.9, 72.1, 48.9, 47.7, 36.0, 24.3.

IR (NaCl) ṽ (cm^{-1}): 3294, 3072, 3032, 2949, 2923, 1495, 1452, 1439, 1092, 900, 700, 644.

HRMS (APCI) calc'd. for $C_{16}H_{17}$, **$[M+H]^+$** 209.1325; found: 209.1323.

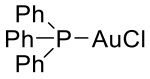
Synthesis of catalysts

General procedure for the preparation of chloro(phosphine)gold(I) and chloro(phosphite)gold(I) complexes (GP 4) [3,4]



In the glovebox chloro(dimethyl sulfide)gold(I) (1.00 equiv.) and phosphine (1.00 equiv.) were weight in a Schlenk flask equipped with magnetic stir bar. The mixture was then dissolved in dry DCM (0.04 M) at 0 °C. The mixture was stirred for 24 h allowing to warm to rt. The reaction solution was filtered through a pad of neutral aluminum oxide and the filter cake was washed three times with DCM. After removal of the volatiles from the combined filtrate under inert conditions the gold complex was isolated. The results are consistent with the data reported.

Chloro(triphenylphosphine)gold(I)

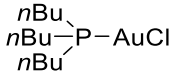


Chloro(dimethyl sulfide)gold(I) (295 mg, 1.00 mmol) and triphenylphosphine (262 mg, 1.00 mmol) were dissolved in dry DCM (25 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **chloro(triphenylphosphine) gold (I)** as a white solid (416 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57-7.50 (m, 9H), 7.49-7.43 (m, 6H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 33.42 (s).

Chloro(tri-*n*-butylphosphine)gold(I)

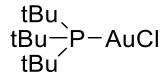


Chloro(dimethyl sulfide)gold(I) (295 mg, 1.00 mmol) and tri-*n*-butylphosphine (0.25 mL, 1.00 mmol) were dissolved in dry DCM (25 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **chloro(tri-*n*-butylphosphine)gold (I)** as a colorless oil (289 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73-1.82 (m, 6H), 1.51-1.61 (m, 6H), 1.46 (m, 6H), 0.94 (m, 9H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 22.1 (s).

Chloro(tri-*t*-butylphosphine)gold(I)

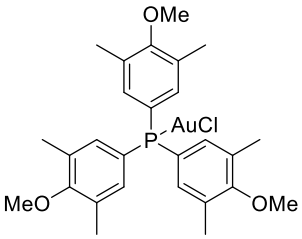


Chloro(dimethyl sulfide)gold(I) (295 mg, 1.00 mmol) and tri-*t*-butylphosphine (202 mg, 1.00 mmol) were dissolved in dry DCM (25 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **chloro(tri-*t*-butylphosphine)gold (I)** as a white solid (317 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, J = 13.9 Hz, 27H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 90.6 (s).

Chloro(tris(4-methoxy-3,5-dimethylphenyl)phosphine)gold(I)

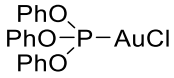


Chloro(dimethyl sulfide)gold(I) (147 mg, 500 µmol) and tris(4-methoxy-3,5-dimethylphenyl)phosphine (218 mg, 500 µmol) were dissolved in dry DCM (13 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **chloro(tris(4-methoxy-3,5-dimethylphenyl)phosphine) gold (I)** as a white solid (267 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 13.3 Hz, 6H), 3.75 (s, 9H), 2.26 (d, *J* = 0.7 Hz, 18H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 31.0 (s).

Chloro(triphenylphosphite)gold(I)

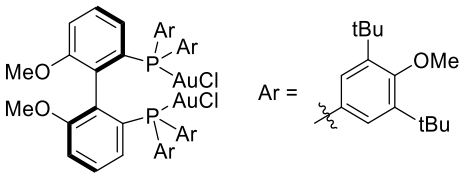


Chloro(dimethyl sulfide)gold(I) (295 mg, 1.00 mmol) and triphenylphosphite (310 mg, 1.00 mmol) were dissolved in dry DCM (25 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **chloro(triphenylphosphite)gold(I)** as a slightly grey solid (299 mg, 55%).[3d]

1H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.31 (m, 6H), 7.29-7.12 (m, 9H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 110.4 (s).

(*R*)-DTBM-MeO-Biphep(AuCl)$_2$

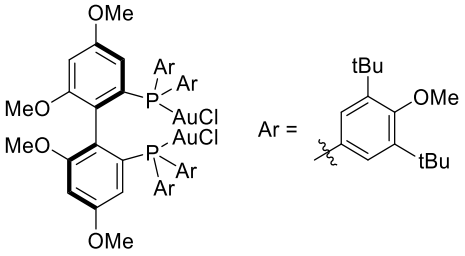


Chloro(dimethyl sulfide)gold(I) (58.8 mg, 200 µmol) and (*R*)-DTBM-MeO-Biphep (58.3 mg, 100 µmol) were dissolved in dry DCM (10 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **(*R*)-DTBM-MeO-Biphep(AuCl)$_2$** as a white solid (133 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (td, *J* = 8.1, 2.5 Hz, 2H), 7.39 (d, *J* = 13.9 Hz, 4H), 7.11 (d, *J* = 13.9 Hz, 4H), 6.96 (ddd, *J* = 10.7, 7.8, 0.9 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 3.72 (s, 6H), 3.69 (s, 6H), 2.72 (s, 6H), 1.33 (d, *J* = 1.1 Hz, 72H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 22.2 (s).

(*R*)-DTBM-Garphos(AuCl)$_2$

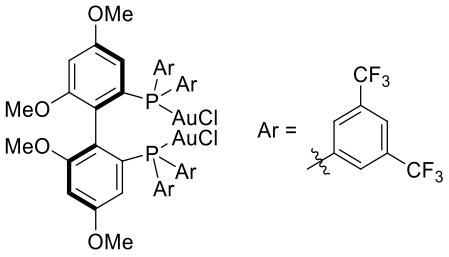


Chloro(dimethyl sulfide)gold(I) (29.5 mg, 100.0 µmol) and (*R*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine (62.5 mg, 50.0 µmol) were dissolved in dry DCM (5 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **(*R*)-DTBM-Garphos(AuCl)$_2$** as a white solid (61.5 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 13.7 Hz, 4H), 7.16 (d, *J* = 13.7 Hz, 4H), 6.47 (d, *J* = 2.3 Hz, 2H), 6.35 (dd, *J* = 11.8, 2.3 Hz, 2H), 3.68 (s, 6H), 3.67 (s, 6H), 3.64 (s, 6H), 2.71 (s, 6H), 1.34 (d, *J* = 2.3, 72H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 23.0 (s).

(*R*)-BTFM-Garphos(AuCl)$_2$



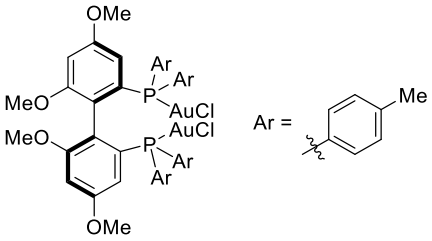
Chloro(dimethyl sulfide)gold(I) (29.5 mg, 100 µmol) and (*R*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl) bis(bis(3,5-bis(trifluoromethyl)phenyl)phosphine) (61.2 mg, 50.0 µmol) were dissolved in dry DCM (5 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **(*R*)-BTFM-Garphos(AuCl)$_2$** as a white solid (54.1 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14-7.99 (m, 8H), 7.92(d, *J* = 12.5 Hz, 4H), 6.52 (d, 2.0 Hz, 2H), 6.45 (dd, *J* = 12.2, 2.0 Hz, 2H), 3.73 (s, 6H), 3.05 (s, 6H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 26.5 (s).

^{19}F{1 H} NMR (282 MHz, $CDCl_3$): δ =-62.8 (s), -63.0 (s).

(*R*)-Tol-Garphos(AuCl)$_2$

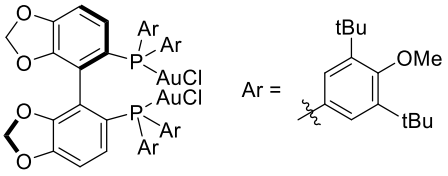


Chloro(dimethyl sulfide)gold(I) (58.8 mg, 200 µmol) and (*R*)-(4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(di-p-tolylphosphine) (69.9 mg, 100 µmmol) were dissolved in dry DCM (10 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **(*R*)-Tol-Garphos(AuCl)$_2$** as a white solid (97.4 mg, 84%).[4c]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.27 (m, 8H), 7.24-7.11 (m, 8H), 6.50 (d, *J* = 2.3 Hz, 2H), 6.44 (dd, *J* = 12.0, 2.3 Hz, 2H), 3.73 (s, 6H), 3.00 (s, 6H), 2.37 (d, *J* = 10.3 Hz, 12H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 22.9 (s).

(*R*)-DTBM-Segphos(AuCl)$_2$

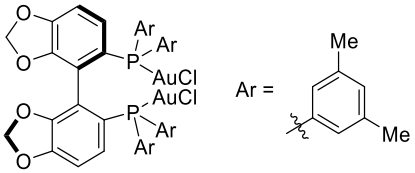


Chloro(dimethyl sulfide)gold(I) (29.5 mg, 100 µmol) and (*R*)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (59.0 mg, 50.0 µmol) were dissolved in dry DCM (5 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **(*R*)-DTBM-Segphos(AuCl)$_2$** as a white solid (69.8 mg, 85%).[4d]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 13.5 Hz, 4H), 7.33 (d, *J* = 13.5 Hz, 4H), 6.92-6.75 (m, 4H), 5.54 (d, *J* = 1.6, 2H), 4.47 (d, *J* = 1.6, 2H), 3.76 (s, 6H), 3.65 (s, 6H), 1.39 (s, 36H), 1.30 (s, 36H).

^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 27.3 (s).

(*S*)-DM-Segphos(AuCl)$_2$

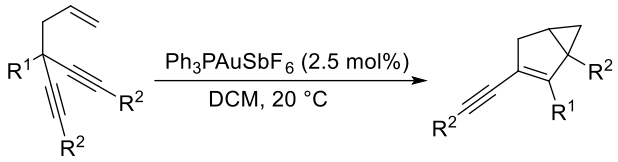


Chloro(dimethyl sulfide)gold(I) (58.8 mg, 200 µmol) and (*S*)-5,5′−bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole (72.3 mg, 100 µmol) were dissolved in dry DCM (10 mL) according to **GP 4**. Removal of the solvent under reduced pressure gave **(*S*)-DM-Segphos(AuCl)$_2$** as a yellow solid (97.6 mg, 82%).[4e]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 15.0, 4H), 7.08 (s, 2H), 7.00 (s, 4H), 6.95 (s, 2H), 6.91 (dd, *J* = 8.2, 1.3 Hz, 2H), 6.77 (dd, *J* = 11.7, 8.2 Hz, 2H), 5.71 (d, *J* = 1.5, 2H), 4.93 (d, *J* = 1.5, 2H), 2.30 (s, 12H), 2.27 (s, 12H).

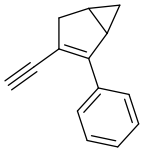
^{31}P{1 H} NMR (121 MHz, $CDCl_3$): δ = 23.6 (s).

Procedure for the synthesis of racemic 3-ethynyl-2-arylbicyclo[3.1.0]hexanes (GP 5)



In the glovebox a Schlenk flask equipped with a magnetic stir bar was charged with the gold (I) complex (2.5 mol%) and the silver (I) salt (2.5 mol%). The mixture of salts was dissolved in anhydrous dichloromethane (7.50 mM) at room temperature and the solution kept stirring at this temperature for 30 min. In a dry round-bottom flask, a solution of the diyne starting material (1.0 equiv.) in anhydrous dichloromethane (150 mM) was prepared and then it was transferred to the Schlenk flask with the gold catalyst under nitrogen at 20 °C. The reaction mixture was stirred at this temperature for the whole duration of the reaction. When completion of the reaction was indicated by NMR analysis, the mixture was directly purified via column chromatography and concentrated under reduced pressure by keeping the bath temperature at 20 °C.

3-Ethynyl-2-phenylbicyclo[3.1.0]hex-2-ene (2a)



A solution of (3-ethynylhex-5-en-1-yn-3-yl)benzene (54.0 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1.00 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.54) to afford 3-ethynyl-2-phenylbicyclo[3.1.0]hex-2-ene **2a** as a colorless oil in (41.0 mg, 76%).

The enantioselective synthesis of compound **2a** was done in the presence of (*R*)-DTBM-MeO-Biphep$(AuCl)_2$ (10.4 mg, 9.00 µmol) and silver tetrafluoroborate (2.9 mg, 15.0 µmol). According to **GP 5** the compound was synthesized and purified (27.5 mg, 51%). The enantiomeric excess was checked by HPLC with a chiral stationary phase (Daicel Chiralpak IC, flow 0.8 mL/min., *n*-hexane, ʎ = 254 nm)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76-7.67 (m, 2H), 7.34-7.13 (m, 3H), 3.35 (t, *J* = 1.0 Hz, 1H), 3.09 (dd, *J* = 18.1, 7.3 Hz, 1H), 2.80 (dd, *J* = 18.1, 3.1 Hz, 1H), 2.08 (ddtd, *J* = 7.4, 6.3, 3.0, 0.8

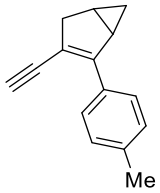
Hz, 1H), 1.61(ddddd, *J* = 8.3, 7.4, 6.3, 4.3, 1.1 Hz, 1H), 0.90 (td, *J* = 7.6, 4.3 Hz, 1H), 0.17 (td, *J* = 4.3, 3.0 Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 144.3, 135.9, 128.2, 127.9, 127.6, 126.8, 121.3, 83.9, 81.9, 38.7, 29.5, 16.5, 14.0, 1.2.

IR (NaCl) ṽ (cm^{-1}): 3288, 3063, 3038, 2989, 2902, 2833, 2091, 15978 1494, 1444, 761, 692.

HRMS (ESI) calc'd. for $C_{14}H_{13}$, **[M+H]$^+$** 181.1012; found: 181.1013.

3-Ethynyl-2-(*p*-tolyl)bicyclo[3.1.0]hex-2-ene (2b)



A solution of 1-(3-ethynylhex-5-en-1-yn-3-yl)-4-methylbenzene (58.3 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.54) to afford 3-ethynyl-2-(p-tolyl)bicyclo[3.1.0]hex-2-ene **2b** as a colorless oil (44.9 mg, 77%).

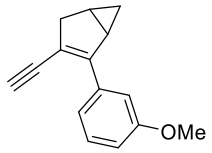
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.1 Hz, 2H), 7.13 (dt, *J* = 8.1 Hz, 2H), 3.40 (t, *J* = 0.8, 1H), 3.15 (dd, *J* = 18.1, 7.2 Hz, 1H), 2.84 (dd, *J* = 18.1 3.0 Hz, 1H), 2.34 (s, 3H), 2.13 (ddtd, *J* = 7.3, 6.3, 2.9, 0.8 Hz, 1H), 1.66 (ddddd, *J* = 8.2, 7.3, 6.3, 4.3, 1.0 Hz, 1H), 0.95 (td, *J* = 7.6, 4.3 Hz, 1H), 0.22 (td, *J* = 4.3, 2.9 Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 144.4, 137.8, 133.2, 128.9, 126.8, 120.3, 83.6, 82.1, 38.7, 29.4, 21.4, 16.5, 13.9.

IR (NaCl) ṽ (cm^{-1}): 3294, 3064, 3032, 2989, 2902, 2832, 2088, 1510, 1437, 817.

HRMS (ESI) calc'd. for $C_{15}H_{15}$ **[M+H]$^+$** 195.1168; found: 195.1170.

3-Ethynyl-2-(3-methoxyphenyl)bicyclo[3.1.0]hex-2-ene (2c)



A solution of 1-(3-ethynylhex-5-en-1-yn-3-yl)-3-methoxybenzene (63.1 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (DCM : Hex = 1: 15, R_F = 0.47) to afford 3-ethynyl-2-(3-methoxyphenyl)bicyclo[3.1.0]hex-2-ene **2c** as a colorless oil (47.3 mg, 75%).

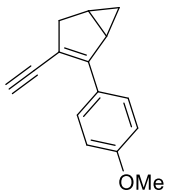
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.34 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 6.87 (ddd, *J* = 8.0, 2.6, 1.6 Hz, 1H), 3.86 (s, 3H), 3.51 (t, *J* = 0.8, 1H), 3.20 (dd, *J* = 18.1, 7.3 Hz, 1H), 2.91 (dd, *J* = 18.1 3.1 Hz, 1H), 2.20 (ddtd, *J* = 7.2, 6.1, 3.1, 0.8 Hz, 1H), 1.73 (ddddd, *J* = 8.1, 7.2, 6.1, 4.3, 1.0 Hz, 1H), 1.02 (td, *J* = 7.6, 4.2 Hz, 1H), 0.29 (td, *J* = 4.3, 3.1Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 159.4, 144.3, 137.2, 129.4, 121.6, 119.4, 113.9, 112.2, 184.2, 82.0, 55.3, 38.7, 29.5, 16.5, 14.0.

IR (NaCl) ṽ (cm^{-1}): 3288, 3065, 3039, 2991, 2905, 2833, 2083, 1599, 1568.81, 1287, 1214.

HRMS (APCI) calc'd. for $C_{15}H_{15}O$, **$[M+H]^+$** 211.1117; found: 211.1116.

3-Ethynyl-2-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene (2d)



A solution of 1-(3-ethynylhex-5-en-1-yn-3-yl)-4-methoxybenzene (63.1 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (DCM : Hex = 1: 15, R_F = 0.43) to afford 3-ethynyl-2-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene **2d** as a colorless oil (44.8 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H),

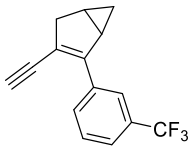
3.40 (t, *J* = 1.0 Hz, 1H), 3.14 (dd, *J* = 18.0, 7.3 Hz, 1H), 2.83 (dd, *J* = 18.0 3.0 Hz, 1H), 2.12 (ddtd, *J* = 7.3, 6.3, 3.0, 1.0 Hz, 1H), 1.73 (ddddd, *J* = 8.1, 7.3, 6.3, 4.3, 1.0 Hz, 1H), 0.94 (td, *J* = 7.6, 4.3 Hz, 1H), 0.22 (td, *J* = 4.3, 3.0 Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 159.3, 144.0, 128.8, 128.2, 119.1, 113.6, 83.4, 82.4, 55.4, 38.7, 29.4, 16.5, 13.8.

IR (NaCl) ṽ (cm^{-1}): 3284, 3029, 2988, 2900, 2832, 2087, 1510, 1437, 814, 774.

HRMS (EI) calc'd. for $C_{15}H_{14}O$, **[M]$^+$** 210.1045; found: 210.1042.

3-Ethynyl-2-(3-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene (2e)



A solution of 1-(3-ethynylhex-5-en-1-yn-3-yl)-3-trifluoromethylbenzene (74.5 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.49) to afford 3-ethynyl-2-(3-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene **2e** as a colorless oil (51.4 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08-8.04 (m, 1H), 7.95 (dt, *J* = 8.0, 1,7 Hz, 1H), 7.53-7.37 (m, 3H), 3.48 (t, *J* = 1.0 Hz, 1H), 3.17 (dd, *J* = 18.1, 7.1 Hz, 1H), 2.89 (dd, *J* = 18.1 3.0 Hz, 1H), 2.17 (ddtd, *J* = 7.1, 6.1, 3.0, 1.0 Hz, 1H), 1.72 (ddddd, *J* = 8.2, 7.1, 6.1, 4.3, 1.0 Hz, 1H), 1.01 (td, *J* = 7.7, 4.3 Hz, 1H), 0.25 (td, *J* = 4.3, 3.0 Hz, 1H).

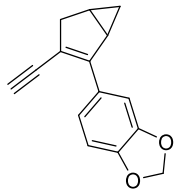
^{13}C {1 H} NMR (75 MHz, $CDCl_3$): δ = 142.7, 136.6, 130.8, 130.4, 129.9, 128.7, 124.3, 123.6, 123.4, 84.9, 81.3, 38.6, 29.6, 16.6, 14.1.

^{19}F {1 H} NMR (282 MHz, $CDCl_3$): δ = -62.8.

IR (NaCl) ṽ (cm^{-1}): 3305, 3072, 3045, 2994, 2905, 1712, 1329, 1166, 1126, 803, 700.

HRMS (APCI): calc'd for $C_{15}H_{12}F_3$, **[M+H]$^+$** 249.0886; found 249.0886.

5-(3-Ethynylbicyclo[3.1.0]hex-2-en-2-yl)benzo[d][1,3]dioxole (2f)



A solution of 5-(3-ethynylhex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole (102 mg, 45.0 µmol) in dry DCM (3 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (5.7 mg, 11 µmol) and silver hexafluoroantimonate (3.8 mg, 11 µmol) in DCM (1.5 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (DCM : Hex = 1: 20, R_F = 0.41) to afford 5-(3-ethynylbicyclo[3.1.0]hex-2-en-2-yl)benzo[d][1,3]dioxole **2f** as a colorless oil (79.2 mg, 78%).

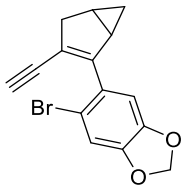
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 1.8 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 5.95 (s, 2H), 3.43 (t, *J* = 1.0 Hz, 1H), 3.11 (dd, *J* = 18.0, 7.3 Hz, 1H), 2.80 (dd, *J* = 18.0, 3.0 Hz, 1H), 2.11 (ddtd, *J* = 7.3, 6.3, 3.0, 1.0 Hz, 1H), 1.63 (ddddd, *J* = 8.1, 7.3, 6.3, 4.2, 1.0 Hz, 1H), 0.94 (td, *J* = 7.6, 4.2 Hz, 1H), 0.21 (q, *J* = 4.0 Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 147.5, 147.2, 143.8, 130.3, 121.0, 119.8, 108.0, 107.3, 101.2, 84.1, 82.1, 39.0, 29.4, 16.5, 13.8.

IR (NaCl) ṽ (cm^{-1}): 3289, 3067, 3039, 2989, 2898, 2831, 2778, 1503, 1490, 1445, 1254, 1225, 1039, 928, 913, 807, 744.

HRMS (EI) calc'd. for $C_{15}H_{12}O_2$, **[M+H]$^+$** 225.0910; found: 225.0907.

5-Bromo-6-(3-ethynylbicyclo[3.1.0]hex-2-en-2-yl)benzo[d][1,3]dioxole (2g)



A solution of 5-bromo-6-(3-ethynylhex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole (90.9 mg, 30.0 mmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (DCM : Hex = 1: 10, R_F = 0.34) to afford 5-bromo-6-(3-

ethynylbicyclo[3.1.0]hex-2-en-2-yl)benzo[d][1,3]dioxole **2g** as a colorless oil (78.2 mg, 86%).

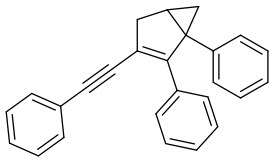
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (s, 1H), 6.69 (s, 1H), 5.96 (s, 2H), 3.06 (t, *J* = 1.0 Hz, 1H), 3.03 (dd, *J* = 19.3, 7.2 Hz, 1H), 2.77 (dd, *J* = 19.3, 3.2 Hz, 1H), 2.08 (ddtd, *J* = 7.1, 6.1, 3.1, 0.9 Hz, 1H), 1.73 (ddddd, *J* = 8.1, 7.1, 6.1, 4.3, 0.9 Hz, 1H), 0.93 (td, *J* = 7.6, 4.3 Hz, 1H), 0.37 (td, *J* = 4.3, 3.0 Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 147.9, 147.4, 147.2, 130.9, 125.7, 113.0, 110.2, 101.9, 81.9, 80.0, 40.4, 27.4, 15.3, 14.5.

IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3291, 3060, 2987, 2898, 2834, 1475, 1415, 1332, 1234, 1124, 1036, 986, 937, 863, 815, 796, 727.

HRMS (ESI) calc'd. for $C_{15}H_{11}BrO_2$, **$[M+H]^+$** 303.0015; Found: 303.0008.

1,2-Diphenyl-3-(phenylethynyl)bicyclo[3.1.0]hex-2-ene (2h)



A solution of (3-(phenylethynyl)hex-5-en-1-yne-1,3-diyl)dibenzene (99.7 mg, 30.0 mmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (DCM : Hex = 1 : 40, R_F = 0.34) to afford 1,2-diphenyl-3-(phenylethynyl)bicyclo[3.1.0]hex-2-ene **2h** as a colorless oil (65.8 mg, 66%).

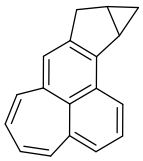
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00-7.90 (m, 2H), 7.52-7.43 (m, 2H), 7.42-7.18 (m, 11H), 3.41 (dd, *J* = 18.1, 7.0 Hz, 1H), 3.02 (dd, *J* = 18.1, 1.0 Hz, 1H), 1.90 (dddd, *J* = 8.1, 6.9, 4.5, 1.0 Hz, 1H), 1.62 (dd, *J* = 8.1, 4.3 Hz, 1H), 0.83 (t, *J* = 4.5 Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 142.8, 140.5, 136.3, 131.4, 129.4, 128.3, 128.2, 128.1, 127.9, 127.1, 126.6, 125.0, 123.7, 97.7, 87.7, 44.2, 38.7, 23.8, 21.9.

IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3056, 3028, 2896, 2833, 1598, 1491, 1439, 755, 688.

EA Anal. calc'd for $C_{26}H_{20}$: C, 93.94; H, 6,06. Found: C, 94.16; H, 6.17.

9,9a,10,10a-Tetrahydrocyclohepta[de]cyclopropa[4,5]cyclopenta[1,2-a]naphthalene (2m)



A solution of 1-(3-ethynylhex-5-en-1-yn-3-yl)naphthalene (69.1 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (3.8 mg, 7.5 µmol) and silver hexafluoroantimonate (2.5 mg, 7.5 µmol) in DCM (1 mL) according to **GP 5**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexanes, R_F = 0.51) to afford 6,6a,7,7a-tetrahydrocyclopropa[a]naphtho[1,8-gh]azulene **2m** as an orange oil (36.6 mg, 53%).

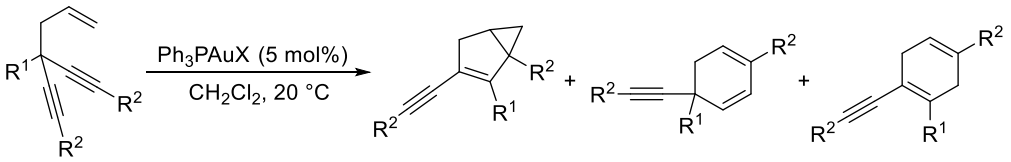
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03-6.90 (m, 2H), 6.73 (s, 1H), 6.60-6.51 (m, 1H), 6.10-5.95 (m, 2H), 5.44-5.30 (m, 2H), 3.05 (dd, *J* = 17.4, 6.7 Hz, 1H), 2.88 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.27 (tdd, *J* = 7.9, 3.2, 2.0 Hz, 1H), 1.96-1.83 (m,1H), 1.06 (td, *J* = 7.9, 4.2 Hz, 1H), 0.10 (td, *J* = 4.2, 3.2 Hz, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 144.9, 140.1, 139.9, 139.2, 138.1, 137.2, 136.7, 135.5, 127.3, 126.9, 126.8, 126.2, 124.6, 123.5, 35.1, 24.4, 18.0, 16.4.

IR (NaCl) ṽ (cm^{-1}): 3864, 3745, 3031, 2986, 2902, 2841, 2368, 1925, 1728, 1594, 1575, 1517, 1432, 1358, 1317, 1254, 1206, 1156, 1025.

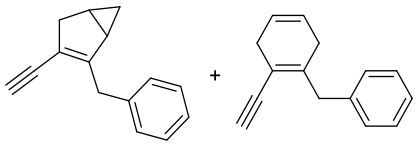
HRMS (ESI) calc'd. for $C_{18}H_{15}$, **$[M+H]^+$** 231.1166 ; Found: 231.1168.

Procedure for the synthesis of racemic 3-ethynyl-2-alkylbicyclo[3.1.0]hexanes (GP 6)



In the glovebox, a Schlenk flask equipped with a magnetic stir bar was charged with the gold (I) complex (6 mol%) and the silver (I) salt (5 mol%). The mixture of salts was dissolved in anhydrous dichloromethane (15.0 mM) at room temperature and the solution kept stirring at this temperature for 30 min. In a dry round-bottom flask, a solution of the diyne starting material (1.00 equiv.) in anhydrous dichloromethane (150 mM) was prepared and then it was transferred to the Schlenk flask with the gold catalyst under nitrogen at 20 °C. The reaction mixture was stirred at this temperature for the whole duration of the reaction. When completion of the reaction was indicated by TLC analysis, the mixture was directly purified via column chromatography.

2-Benzyl-3-ethynylbicyclo[3.1.0]hex-2-ene (2i) and ((2-ethynylcyclohexa-1,4-dien-1-yl)methyl)benzene (4i)



A solution of (2,2-diethynylpent-4-en-1-yl)benzene (58.3 mg, 30.0 mmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (8.9 mg, 18 µmol) and silver tetrafluoroborate (2.9 mg, 15 µmol) in DCM (1 mL) according to **GP 6**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.54) to afford 2-benzyl-3-ethynylbicyclo[3.1.0]hex-2-ene **2j** with small amounts of ((2-ethynylcyclohexa-1,4-dien-1-yl)methyl)benzene **4j** (22.4 mg, yield of **2j** : 31%, yield of **4j** : 7%) as a colorless oil. The ratio of both isomers was determined by ^{1}H-NMR.

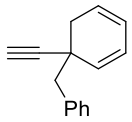
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.10 (m, 5H+5H'), 5.75-5.50 (m, 2H'), 3.68 (s, 2H'), 3.55 (d, *J* = 14.4 Hz, 1H), 3.46 (d, *J* = 14.4 Hz, 1H), 3.23 (t, *J* = 1.0Hz, 1H), 3.08 (s, 1H'), 2.90 (br t, *J* = 8.5 Hz, 2H'), 2.60 (br t, *J* = 5.6 Hz, 2H'), 2.54 (dd, *J* = 18.6, 7.1 Hz, 1H), 2.24 (dd, *J* = 18.6, 3.1 Hz, 1H), 1.95 (tt, *J* = 6.4, 3.0 Hz, 1H), 1.53-1.43 (m, 1H), 0.85-0.75 (m, 1H), 0.22 (td, *J* = 4.3, 3.0 Hz, 1H).

^{13}C{1 H} NMR (major isomer **2j**, 75 MHz, $CDCl_3$): δ = 149.7, 139.5, 128.9, 128.7, 128.6, 128.5, 126.3, 122.1, 81.3, 80.5, 38.1, 36.5, 26.6, 16.0, 14.1.

IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3290, 3062, 3028, 2989, 2900, 2829, 2092, 1602, 1495, 1453, 1437, 1028, 701, 648.

HRMS (APCI): calc'd for $C_{15}H_{15}$, **$[M+H]^+$** 195.1168; found 195.1169.

((1-Ethynylcyclohexa-2,4-dien-1-yl)methyl)benzene (3i)



A solution of (2,2-diethynylpent-4-en-1-yl)benzene (58.3 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine)gold(I) (8.9 mg, 18 µmol) and silver hexafluoroantimonate (5.2 mg, 15 µmol) in DCM (1 mL) according to **GP 6**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.39) to afford ((1-ethynylcyclohexa-2,4-dien-1-yl)methyl)benzene **3i** as a colorless oil (32.6 mg, 56%).

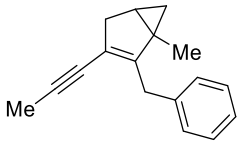
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36-7.22 (m, 5H), 6.04- 5.92 (m, 2H), 5.87- 5.74 (m, 1H), 5.70-5.61(m, 1H), 2.93 (d, *J* = 12.9 Hz, 1H), 2.75 (d, *J* = 12.9, 1H), 2.49 (ddd, *J* = 17.5, 3.5, 2.2 Hz, 1H), 2.34 (ddd, *J* = 17.5, 5.2, 1.1 Hz, 1H), 2.21(s, 1H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 137.0, 131.5, 130.9, 127.8, 126.7, 124.9, 123.8, 123.5, 89.0, 70.6, 43.2, 35.5, 34.6.

IR (NaCl) ṽ (cm^{-1}): 3298, 3037, 2919, 2870, 2850, 2821, 1496, 1454, 913, 748.

EA Anal. calc'd for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.57; H, 7.45.

2-Benzyl-1-methyl-3-(prop-1-yn-1-yl)bicyclo[3.1.0]hex-2-ene (2j)



A solution of (2,2-diethynylpent-4-en-1-yl)benzene (66.7 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine) gold(I) (8.9 mg, 18 µmol) and silver tetrafluoroborate (2.9 mg, 15 µmol) in DCM (1 mL) according to **GP 6**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexanes, R_F = 0.43) to afford 2-benzyl-1-methyl-3-(prop-1-yn-1-yl)bicyclo[3.1.0]hex-2-ene **2j** as a colorless oil (16.3 mg, 24%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.10 (m, 5H), 3.53-3.40 (m, 2H), 2.51 (dd, *J* = 18.3, 7.5 Hz, 1H), 2.13 (d, *J* = 18.3 Hz, 1H), 2.07 (s, 3H), 1.32 (s, 3H), 1.29-1.19 (m, 1H), 0.64 (dd, *J* = 7.5, 4.0 Hz, 1H), 0.15 (t, *J* = 4.0 Hz, 1H).

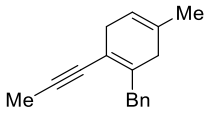
^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 144.6, 140.1, 128.7, 128.4, 126.9, 126.0, 90.7, 75.3, 37.9,

36.5, 32.4, 22.8, 21.1, 18.0, 4.8.

IR (NaCl) ṽ (cm^{-1}): 3059, 3027, 2981, 2950, 2915, 2896, 2863, 2831, 1602, 1494, 1453, 1440, 1377, 1029, 803, 748, 700, 678.

HRMS (ESI): calc'd. for $C_{17}H_{19}$, **[M+H]$^+$** 223.1481; found 223.1481.

((1-Ethynylcyclohexa-2,4-dien-1-yl)methyl)benzene (4j)



A solution of (2,2-diethynylpent-4-en-1-yl)benzene (66.7 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine) gold(I) (8.9 mg, 18 µmol) and silver hexafluoroantimonate (5.2 mg, 15 µmol) in DCM (1 mL) according to **GP 6**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.36) to afford ((1-ethynylcyclohexa-2,4-dien-1-yl)methyl)benzene **4k** as a colorless oil (32.0 mg, 48%).

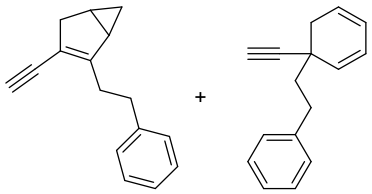
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.10 (m, 5H), 5.30 (tq, *J* = 3.3, 1.6 Hz, 1H), 3.65 (s, 2H) 2.76 (br t, *J* = 7.6 Hz, 2H), 2.58 (br t, *J* = 7.6 Hz, 2H), 2.02 (s, 3H), 1.73-1.62 (m, 3H).

^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ = 140.2, 139.2, 130.7, 128.8, 128.4, 126.1, 117.9, 114.1, 87.3, 79.9, 41.3, 36.3, 30.5, 22.8, 4.6.

IR (NaCl) ṽ (cm^{-1}): 3026, 2915, 2855, 1604, 1492, 1444, 1381, 1070, 1029, 926, 886, 799, 725, 704.

HRMS (ESI): calc'd. for $C_{17}H_{19}$, **[M+H]$^+$** 223.1481; found 223.1482.

3-Ethynyl-2-phenethylbicyclo[3.1.0]hex-2-ene (2k) and (2-(1-ethynylcyclohexa-2,4-dien-1-yl)ethyl)benzene (3k)



A solution of (2,2-diethynylpent-4-en-1-yl)benzene (62.5 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine) gold(I) (8.9 mg, 18 µmol) and silver tetrafluoroborate (2.9 mg, 15 µmol) in DCM (1 mL) according to **GP 6**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.54) to afford 3-ethynyl-2-phenethylbicyclo[3.1.0]hex-2-ene **2k** with a small amount of (2-(1-ethynylcyclohexa-2,4-dien-1-yl)ethyl)benzene **3k** (24.4 mg, yield of **2k** : 33%, yield of **3k** : 6%) as a colorless oil. The ratio of both isomers was determined by ^{1}H-NMR.

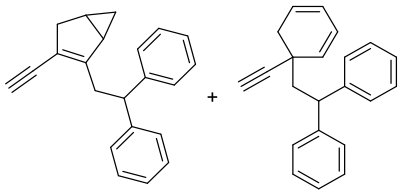
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.13 (m, 5H+5H'), 5.99-5.91 (m, 2H'), 5.83-5.65 (m, 2H'), 3.20 (s, 1H), 2.84-2.65 (m, 2H+4H'), 2.60 (d, *J* = 6.8 Hz, 1H), 2.52 (d, *J* = 8.8 Hz, 1H), 2.50 (d, *J* = 10.2 Hz, 1H), 2.41 (dd, *J* = 4.7, 1.3 Hz, 1H'), 2.33 (dd, *J* = 18.2, 3.1 Hz, 1H+1H'), 2.23 (s, 1H'), 1.90 (dq, *J* = 6.5, 3.3 Hz), 1.50 (dddd, *J* = 8.2, 6.4, 4.2, 0.9 Hz, 1H), 0.79 (td, *J* = 7.6, 4.2 Hz, 1H), -0.05 (td, *J* = 4.2, 2.9 Hz, 1H).

^{13}C{1 H} NMR (major isomer **2k**, 75 MHz, $CDCl_3$): δ = 150.5, 141.7, 128.5, 128.5, 128.4, 126.0, 121.8, 81.7, 80.5, 38.6, 34.4, 31.6, 26.6, 15.9, 14.0.

IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3300, 3084, 3062, 3027, 2988, 2940, 2923, 2895, 2857, 2827, 2092, 1603, 1496, 1454, 1437, 1427.

HRMS (APCI): calc'd. for $C_{16}H_{17}$, **$[M+H]^+$** 209.1325; found 209.1327.

2-(2,2-Diphenylethyl)-3-ethynylbicyclo[3.1.0]hex-2-ene (2l) and (2-(1-ethynylcyclohexa-2,4-dien-1-yl)ethane-1,1-diyl)dibenzene (3l)



A solution of (2,2-diethynylpent-4-en-1-yl)benzene (81.0 mg, 28.5 mol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine) gold(I) (8.9 mg, 18 µmol) and silver tetrafluoroborate (2.9 mg, 15 µmol) in DCM (1 mL) according to **GP 6**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.47) to afford 2-(2,2-diphenylethyl)-3-ethynylbicyclo[3.1.0]hex-2-ene **2l** with a small amount of (2-(1-ethynylcyclohexa-2,4-dien-1-yl)ethane-1,1-diyl)dibenzene **3l** (27.8 mg, yield of **2l** : 28%, yield of **3l** : 6%) as a colorless oil. The ratio of both isomers was determined by ^{1}H-NMR.

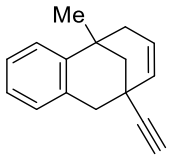
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.08 (10H+10H'), 5.88 (ddd, *J* = 9.4, 4.3, 2.2 Hz, 1H'), 5.78 (dd, *J* = 9.4, 5.1 Hz, 1H'), 5.55 (dt, *J* = 9.4, 4.3 Hz, 1H'), 5.48 (d, *J* = 9.4 Hz, 1H'), 4.40 (t, *J* = 6.6 Hz, 1H'), 4.12 (t, *J* = 8.37, 1H), 3.26 (s, 1H), 3.01 (dd, *J* = 14.1, 8.6 Hz, 1H), 2.90 (dd, *J* = 14.1, 8.6 Hz, 1H), 2.52-2.27 (m, 1H+3H'), 2.22 (s, 1H') 2.21-2.02 (m, 1H+1H'), 1.82 (td, *J* = 6.3, 2.9, 1.0 Hz, 1H), 1.73 (qd, *J* = 6.9, 4.1 Hz, 1H), 0.64 (td, *J* = 7.6, 4.1 Hz, 1H), -0.41 (q, *J* = 3.9 Hz, 1H).

^{13}C{1 H} NMR (isomer **2l** and **3l**, 75 MHz, $CDCl_3$): δ = 149.0, 146.1, 145.4, 144.4, 144.0, 131.6, 128.6, 128.53, 128.51, 128.47, 128.4, 128.24, 128.19, 128.14, 128.10, 128.0, 126.4, 126.3, 126.2, 125.1, 123.5, 123.2, 123.1, 89.0, 82.1, 80.6, 70.2, 50.0, 48.3, 43.4, 38.5, 36.1, 35.3, 35.2, 26.4, 15.5, 13.9.

IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3297, 3060, 3027, 2896, 1599, 1494, 1450, 1438, 1073, 1031, 913, 794, 742, 700.

HRMS (ESI): calc'd. for $C_{22}H_{21}$, **$[M+H]^+$** 285.1638; found 285.1638.

9-Ethynyl-5-methyl-5,6,9,10-tetrahydro-5,9-methanobenzo[8]annulene (5n)



A solution of (3-ethynylhex-5-en-1-yn-3-yl)benzene (62.5 mg, 30.0 µmol) in dry DCM (2 mL) was added to a Schlenk flask with a solution of chloro(triphenylphosphine) gold(I) (8.9 mg, 18 µmol) and silver hexafluoroantimonate (5.2 mg, 15 µmol) in DCM (1 mL) according to **GP 6**. The crude mixture was directly purified by flash column chromatography on silica (100% *n*-hexane, R_F = 0.39) to afford 9-ethynyl-5-methyl-5,6,9,10-tetrahydro-5,9-methanobenzo[8]annulene **5n** as a colorless oil (25.0 mg, 40%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1H), 7.12 (td, *J* = 7.5, 1.5 Hz, 1H), 7.03 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.68-5.54 (m, 2H), 3.21 (d, *J* = 16.4 Hz, 1H), 2.95 (dd, *J* = 16.4, 2.2 Hz, 1H), 2.24 (s, 1H), 2.21 (d, *J* = 15.6 Hz, 1H), 2.08-1.90 (m, 3H), 1.42 (s, 3H).

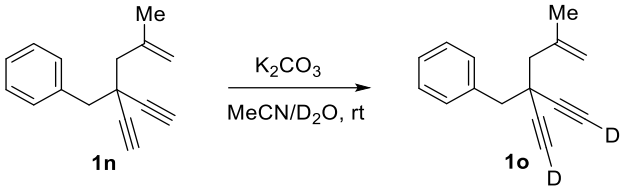
^{13}C{1 H} NMR (75 MHz, $CDCl_3$): δ =143.7, 134.1, 130.7, 128.9, 126.6, 126.4, 126.2, 125.8, 90.5, 68.3, 43.8, 43.2, 42.4, 34.1, 32.6, 28.6.

IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3295, 3060, 3026, 2956, 2925, 2871, 2837, 2823, 1489, 1457, 1430, 763, 744.

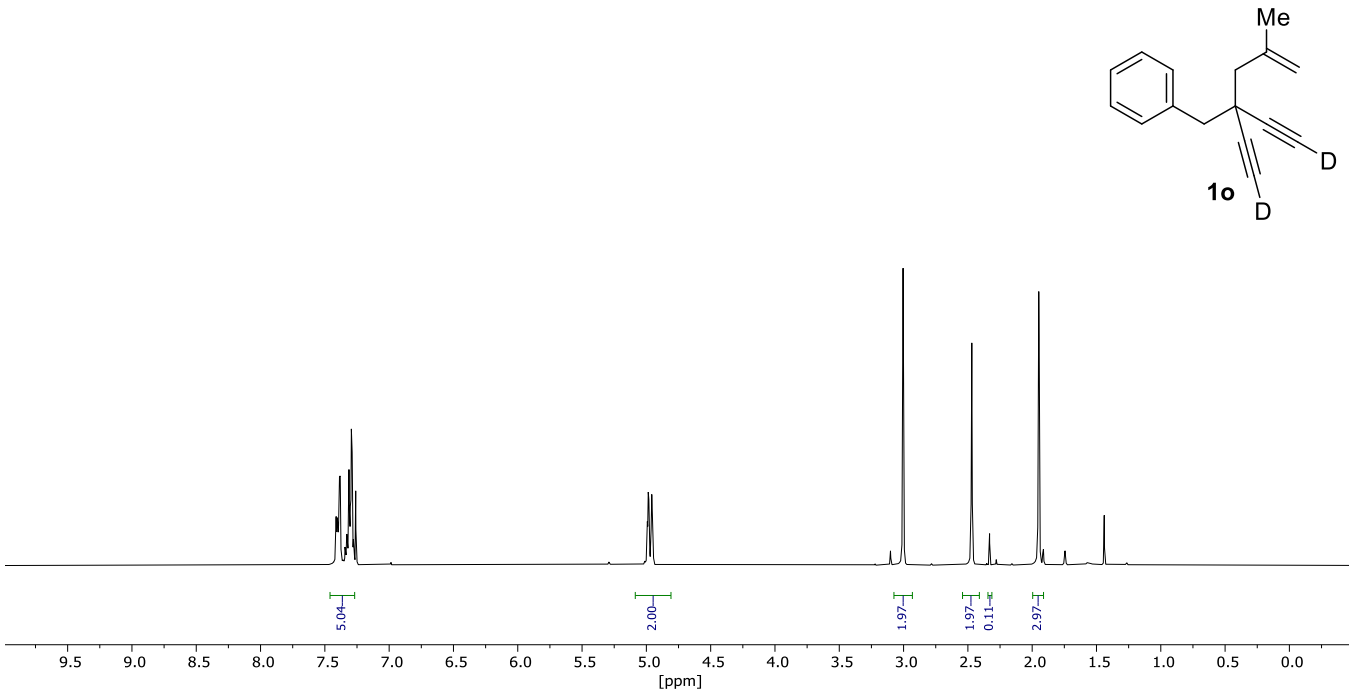
HRMS (APCI): calc'd. for $C_{16}H_{17}$, **$[M+H]^+$** 209.1325; found 209.1326.

III. Mechanistic studies

Deuteration of substrate 1n

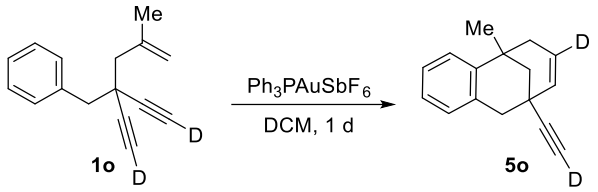


The deuteration protocol followed a literature-known procedure.[6] Diyne **1n** (1.00 equiv. 125 mg, 60.0 µmol) was weighed in a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar. Anhydrous acetonitrile (2 mL) was added. To this solution, potassium carbonate (3 equiv. 124 mg, 180 µmol) and deuterium oxide (1 mL) were added. The mixture was stirred at ambient temperature for 24 hr. The resulting crude reaction mixture was diluted with Et_2O and transferred to a separating funnel. The organic layer was separated, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. ^1H NMR analysis showed that 95% alkyne had been deuterated. The material was used without further purification.

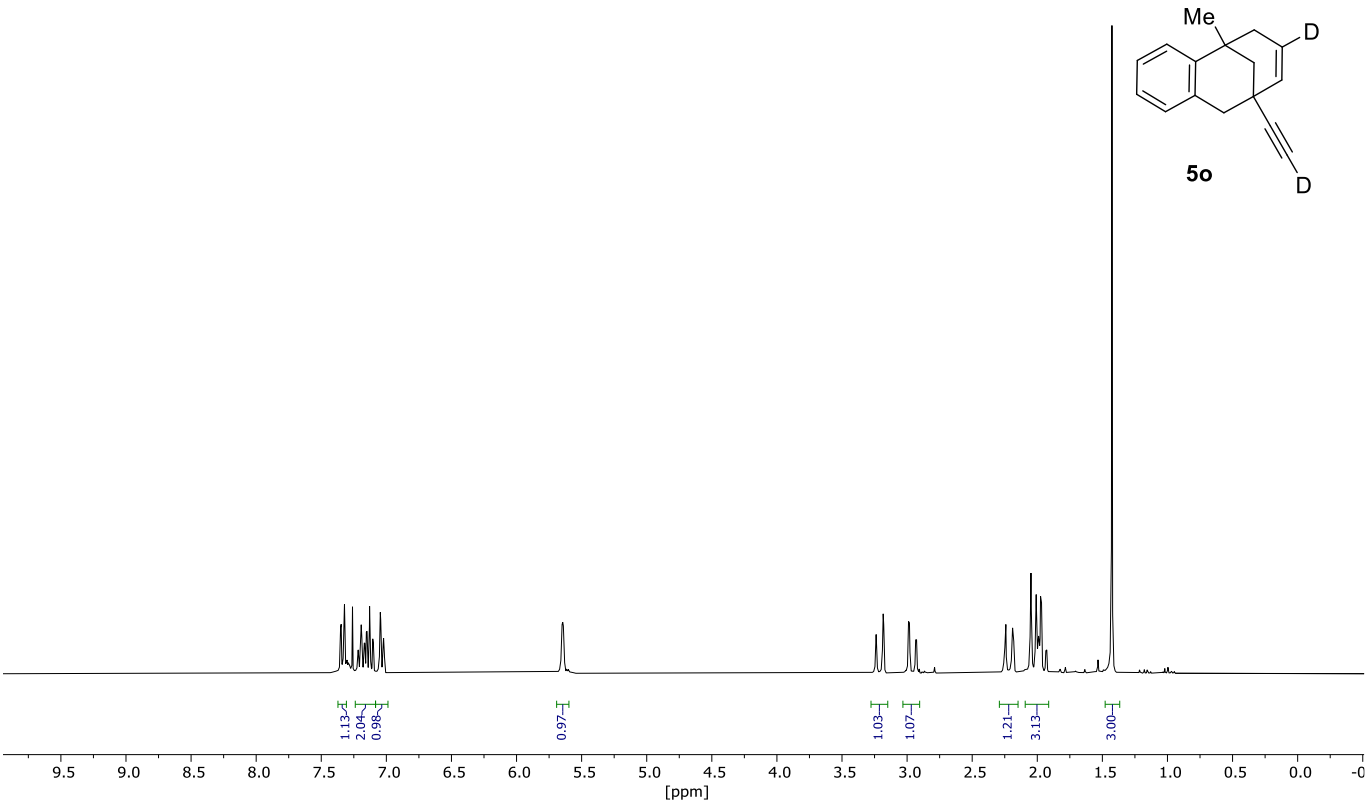


^1H NMR (300MHz, $CDCl_3$) of compound **1o**

Cyclization of deuterated substrate 1o

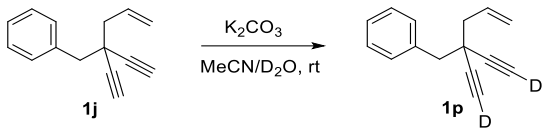


The 95%-deuterated substrate **1o** (1.00 equiv. 63.1 mg, 30.0 µmol) was treated with the gold catalyst in a dried Schlenk flask equipped with a magnetic stir bar according to **GP5**. The reaction mixture was stirred at rt for the whole process of the reaction. When completion of the reaction was indicated by TLC analysis, the mixture was directly purified via column chromatography giving deuterated product **5o** (25.5 mg, 40%).

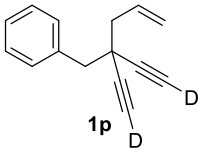


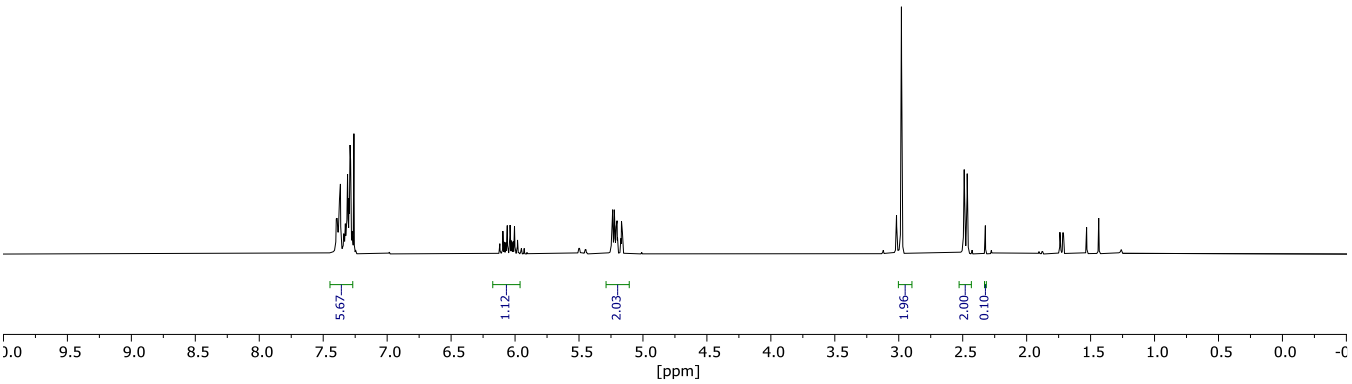
^{1}H NMR (300MHz, $CDCl_3$) of compound **5o**

Deuteration of substrate 1j



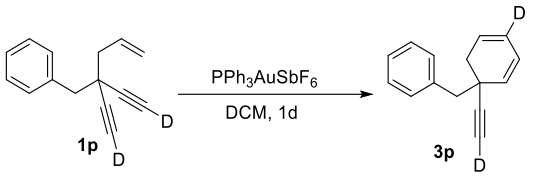
The deuteration was conducted following a literature-known procedure.[6] Diyne **1j** (1 equiv. 117 mg, 60.0 µmol) was weighed in a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar. Anhydrous acetonitrile (2.00 mL) was added. To this solution, potassium carbonate (3 equiv. 124 mg, 180 µmol) and deuterium oxide (1.00 mL) were added. The mixture was stirred at ambient temperature for 24 hr. The resulting crude reaction mixture was diluted with Et_2O and transferred to a separating funnel. The organic layer was separated, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. ^1H NMR analysis showed that 95% alkyne had been deuterated. The material was used without further purification.





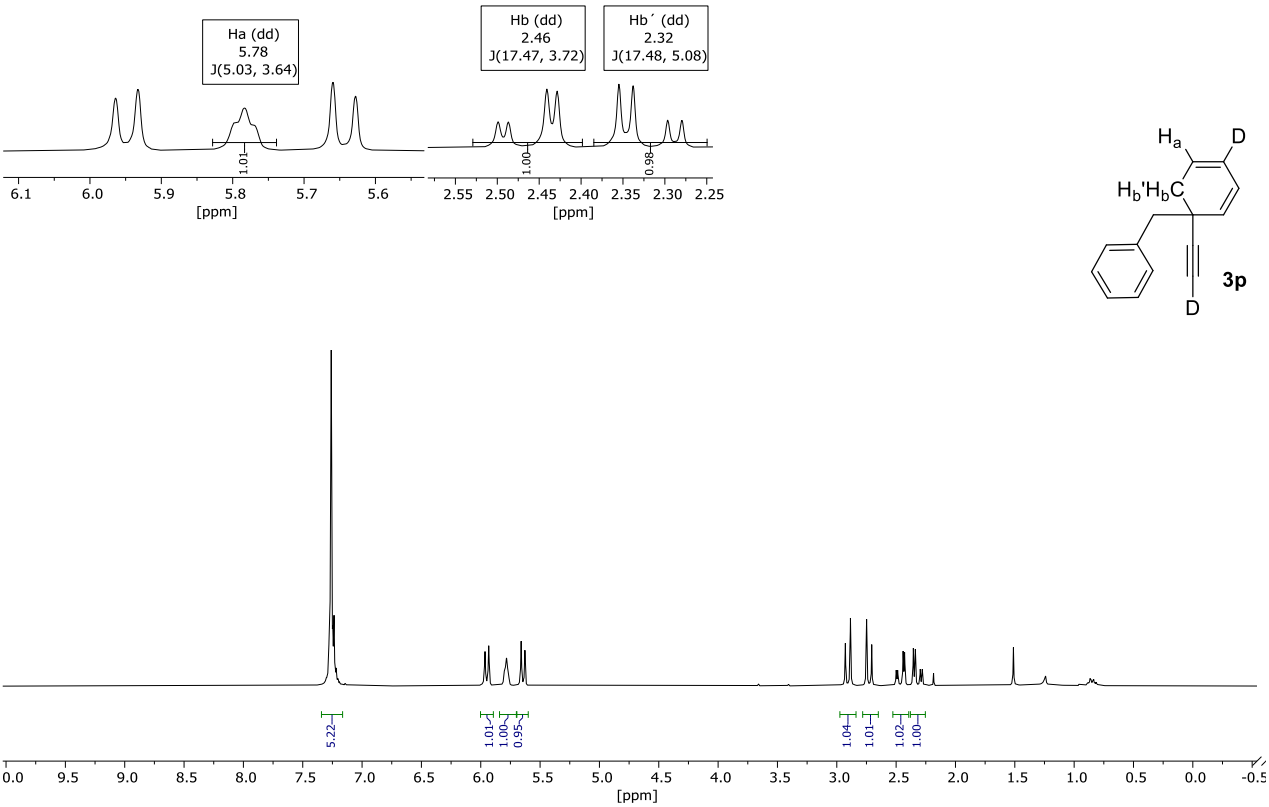
^1H NMR (300MHz, $CDCl_3$) of compound **1p**

Cyclization of deuterated substrate 1p

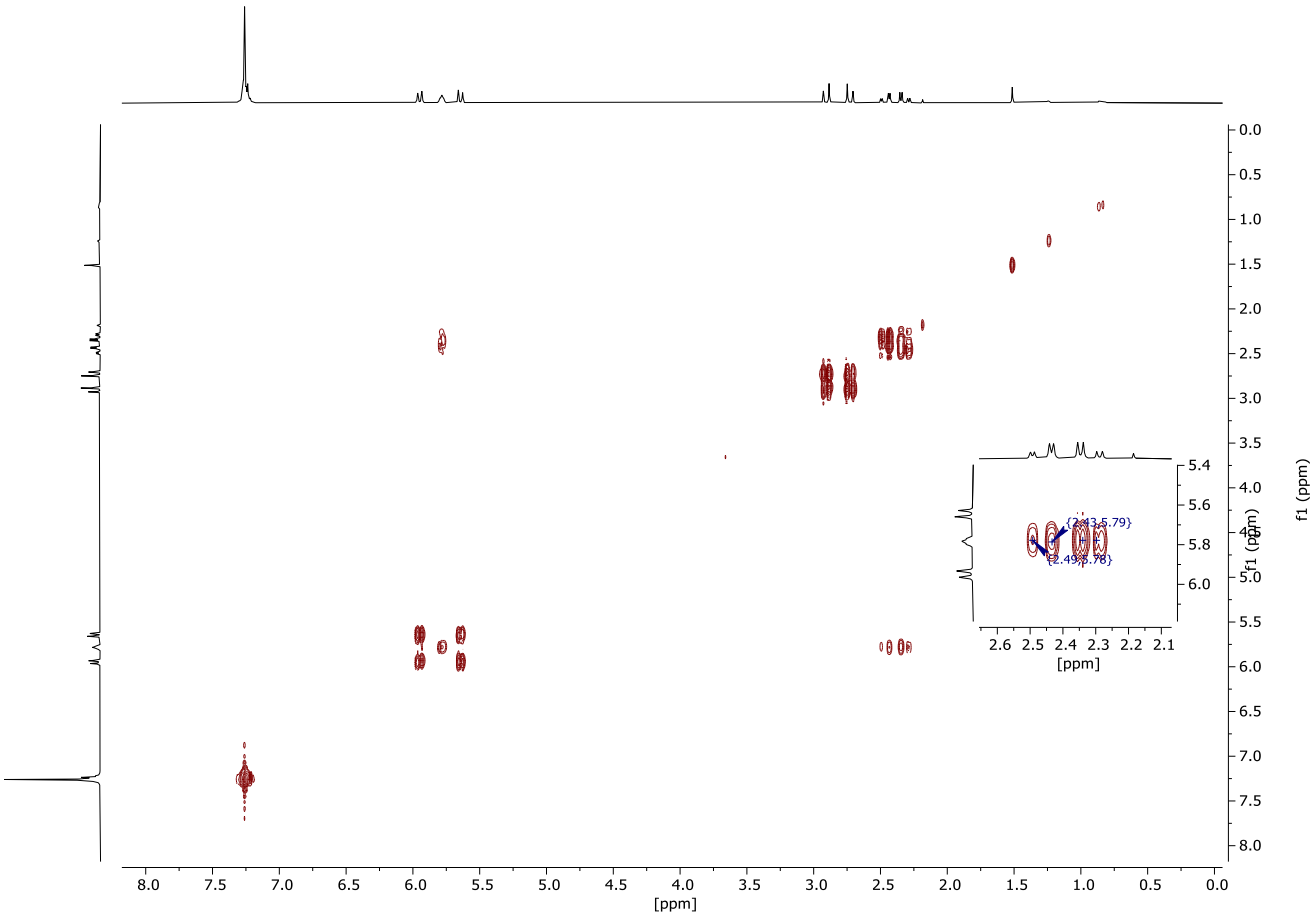


The 95%-deuterated substrate **1p** (1.00 equiv. 58.9 mg, 30.0 µmol) was treated with the gold catalyst in a dried Schlenk flask equipped with a magnetic stir bar according to **GP5**. The reaction mixture was stirred at rt for the whole process of the reaction. When completion of the reaction was indicated by TLC analysis, the mixture was directly purified via column chromatography giving **3p** (30.1 mg, 51%).

The position of the deuterium atom was validated by ^{1}H NMR and COSY analysis.

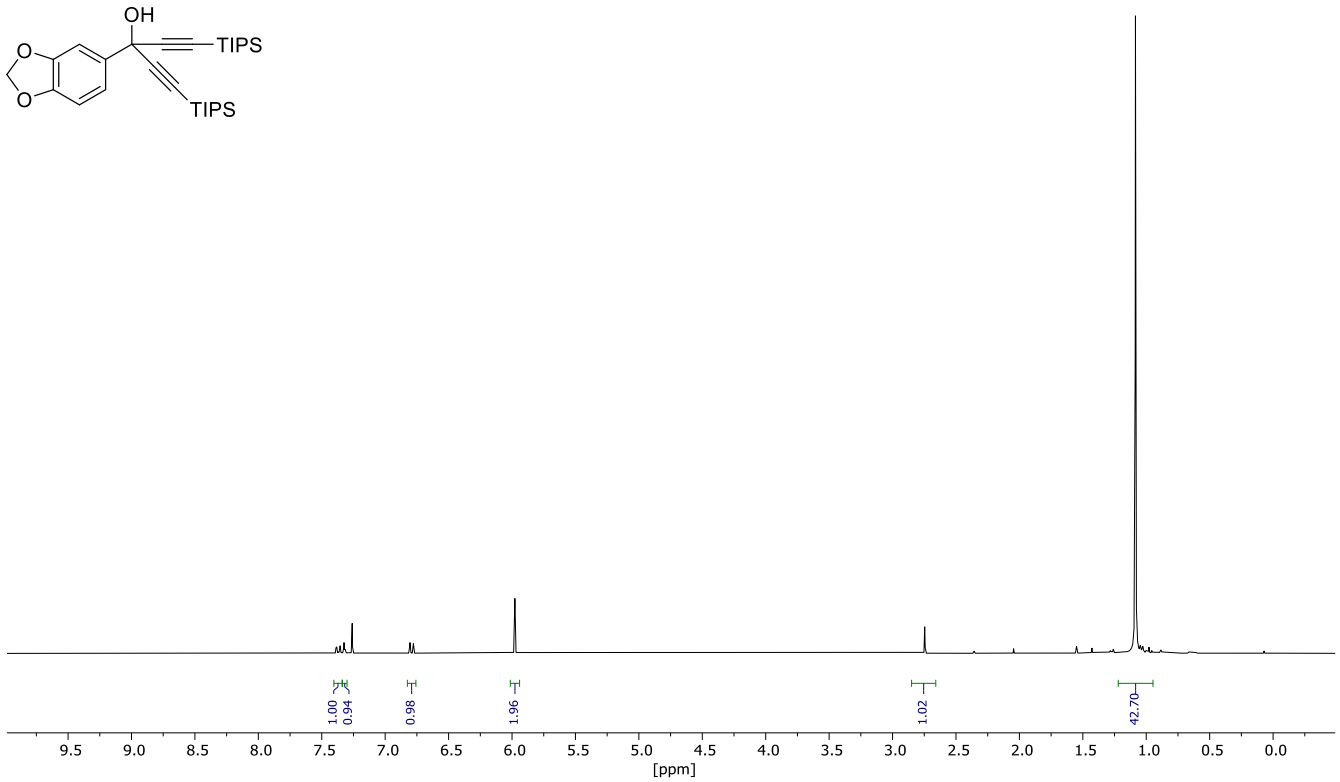


^{1}H NMR (300MHz, $CDCl_3$) of compound **3p**

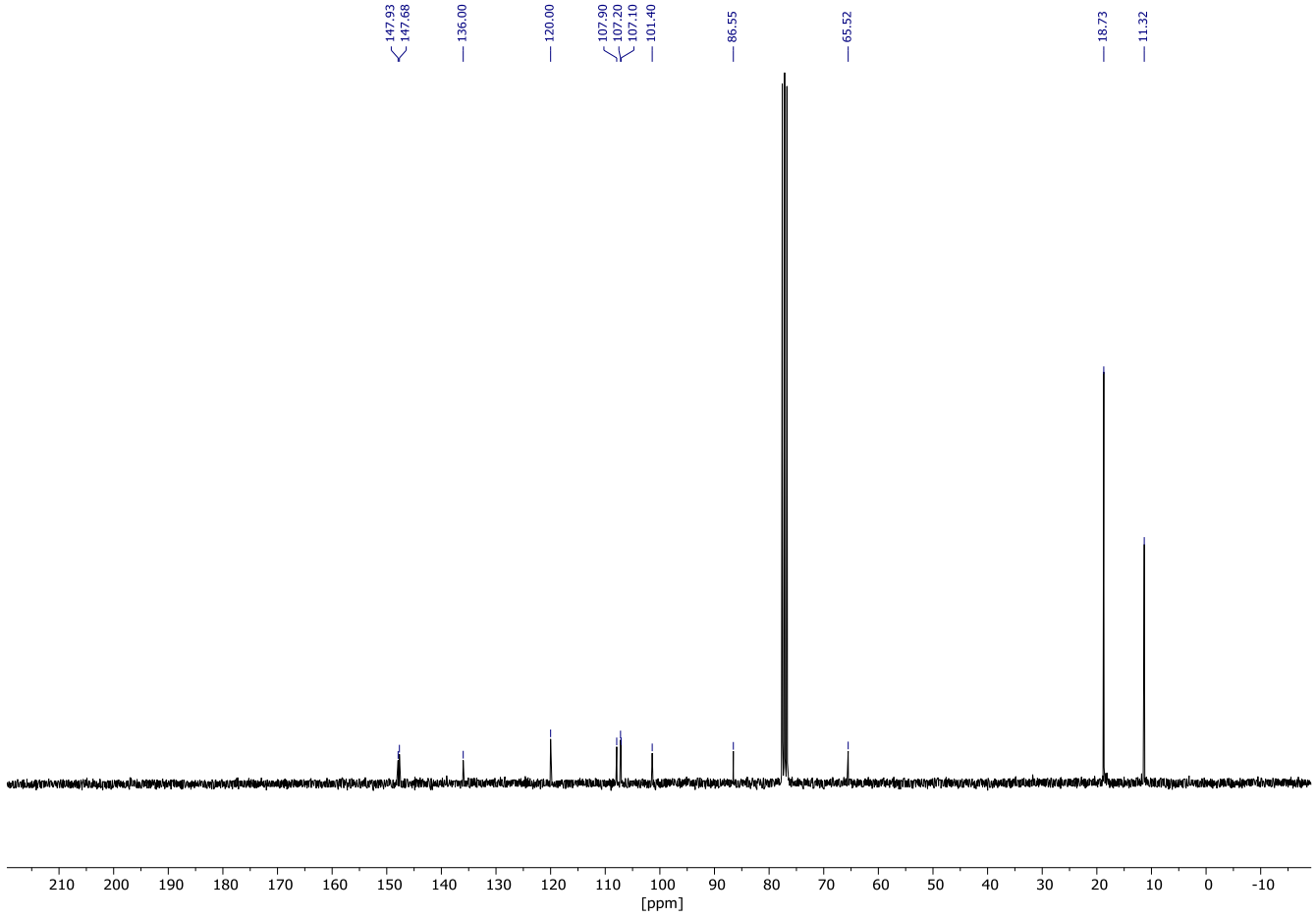


COSY (300MHz, $CDCl_3$) spectrum of compound **3p**

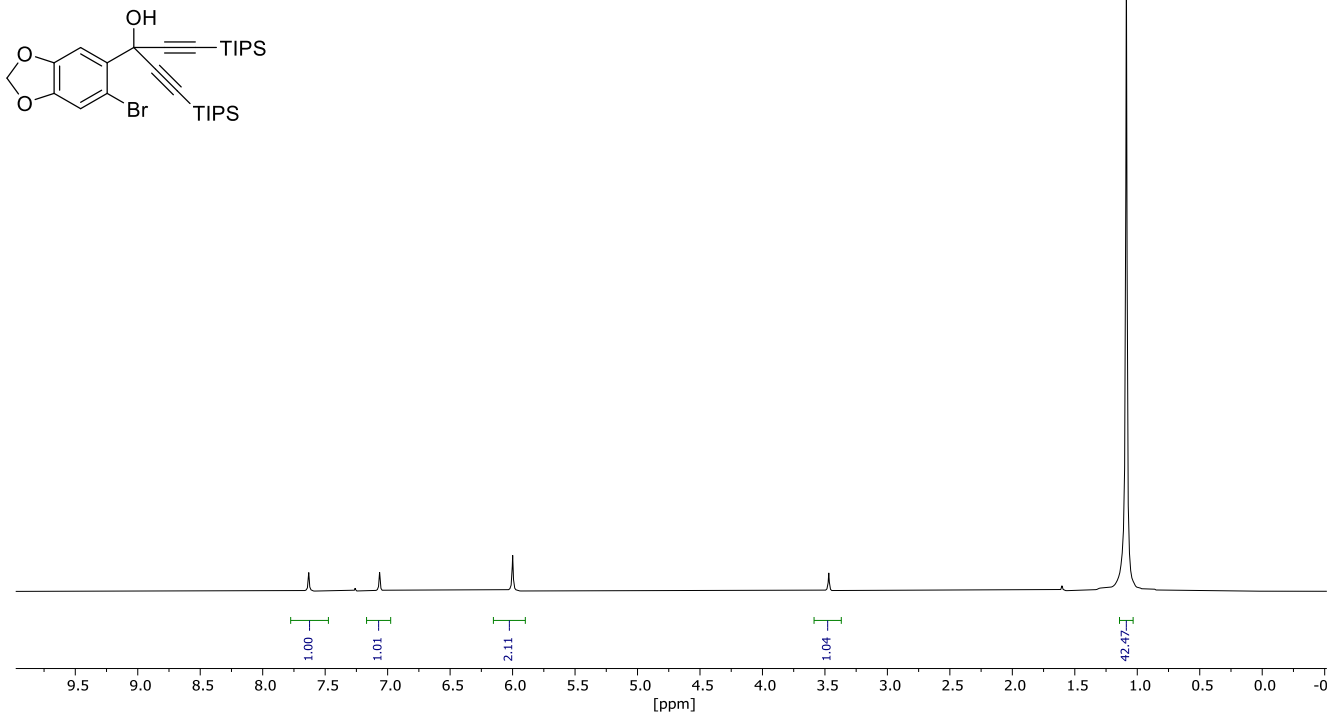
IV. NMR spectra and HPLC chromatograms for new compounds



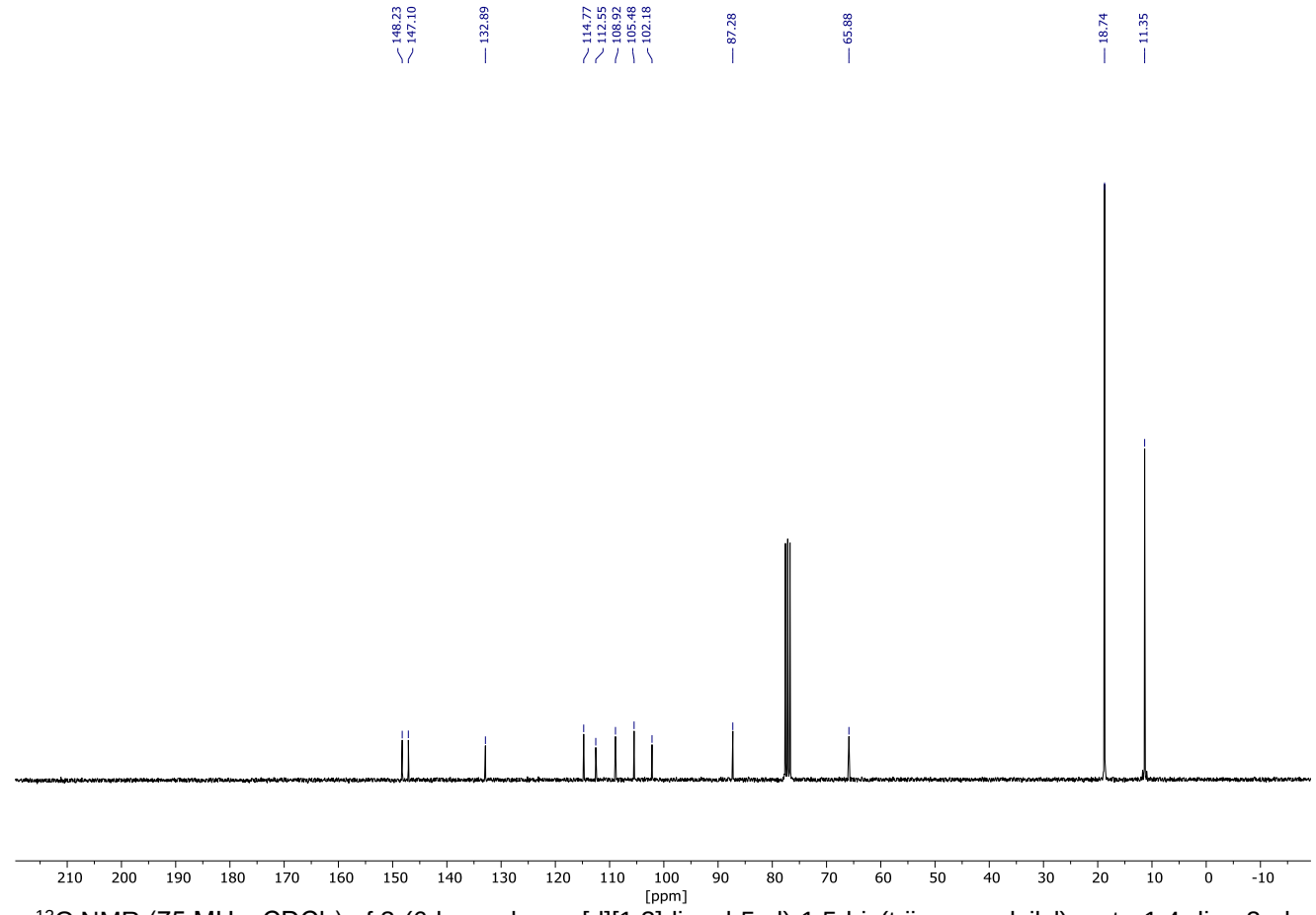
^{1}H NMR (300 MHz, $CDCl_3$) of 3-(benzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



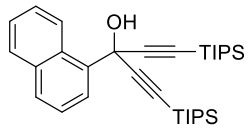
^{13}C NMR (75 MHz, $CDCl_3$) of 3-(benzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol

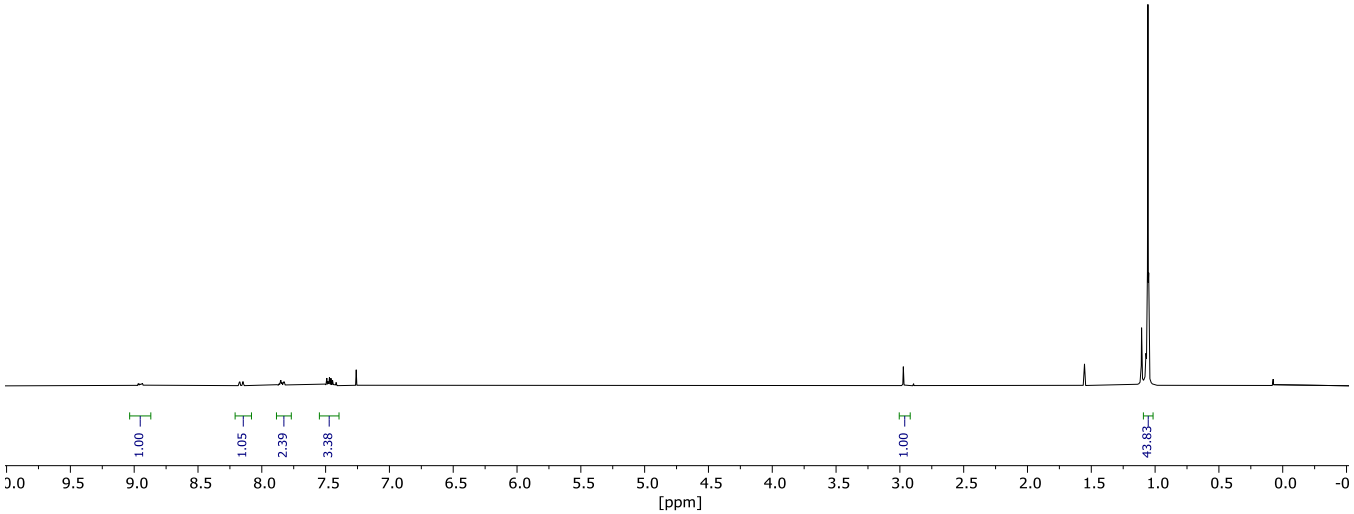


^{1}H NMR (300 MHz, $CDCl_3$) of 3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol

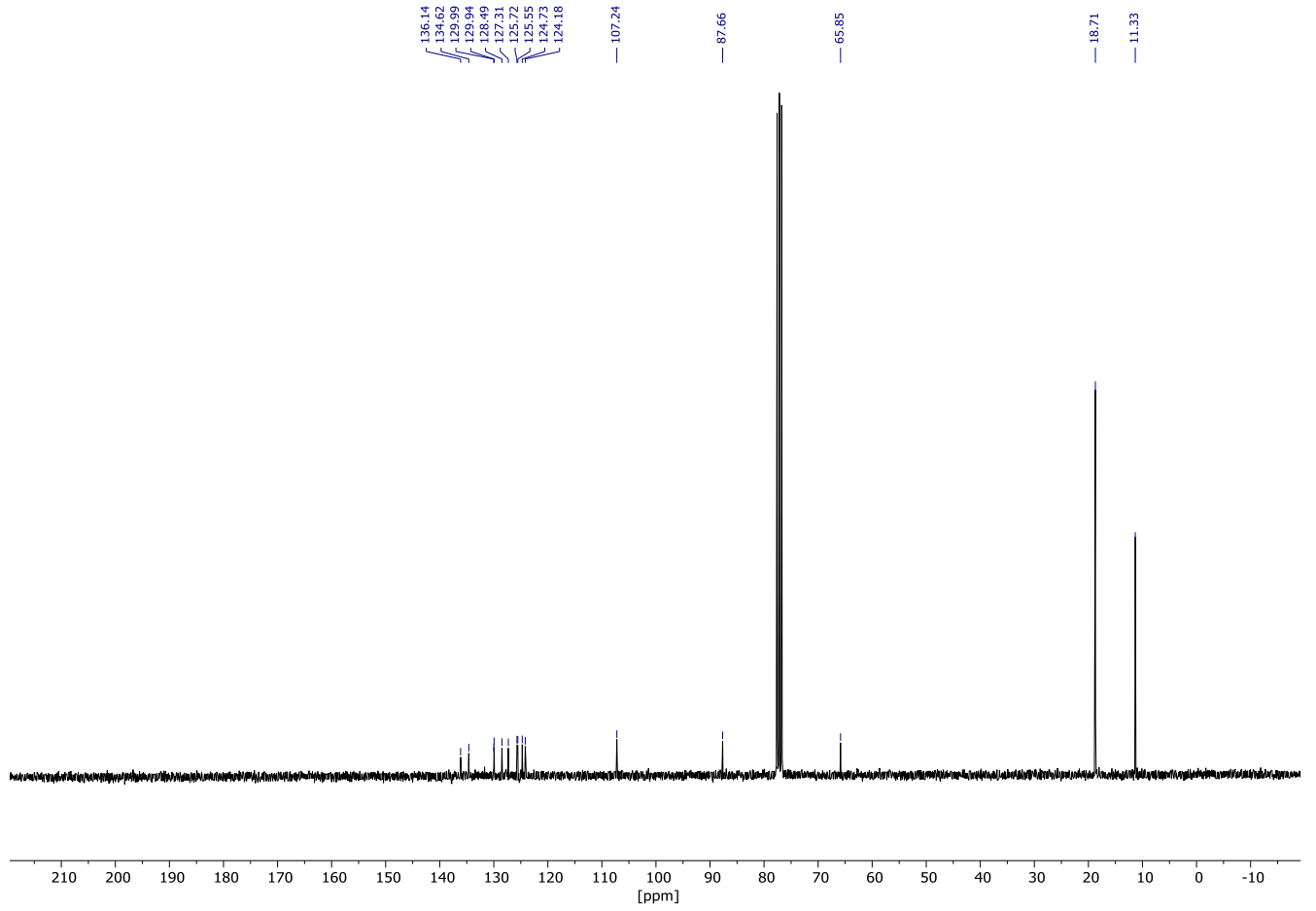


^{13}C NMR (75 MHz, $CDCl_3$) of 3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol

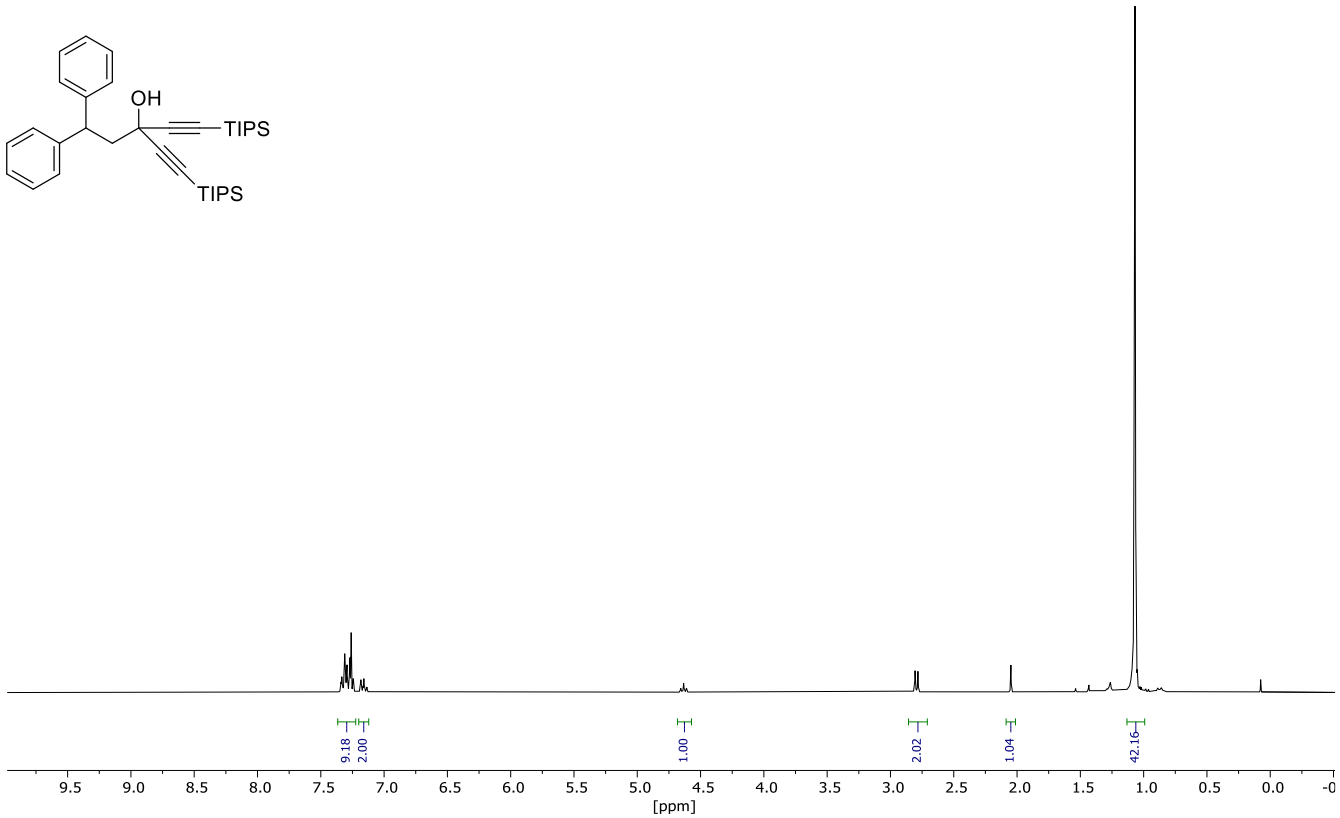




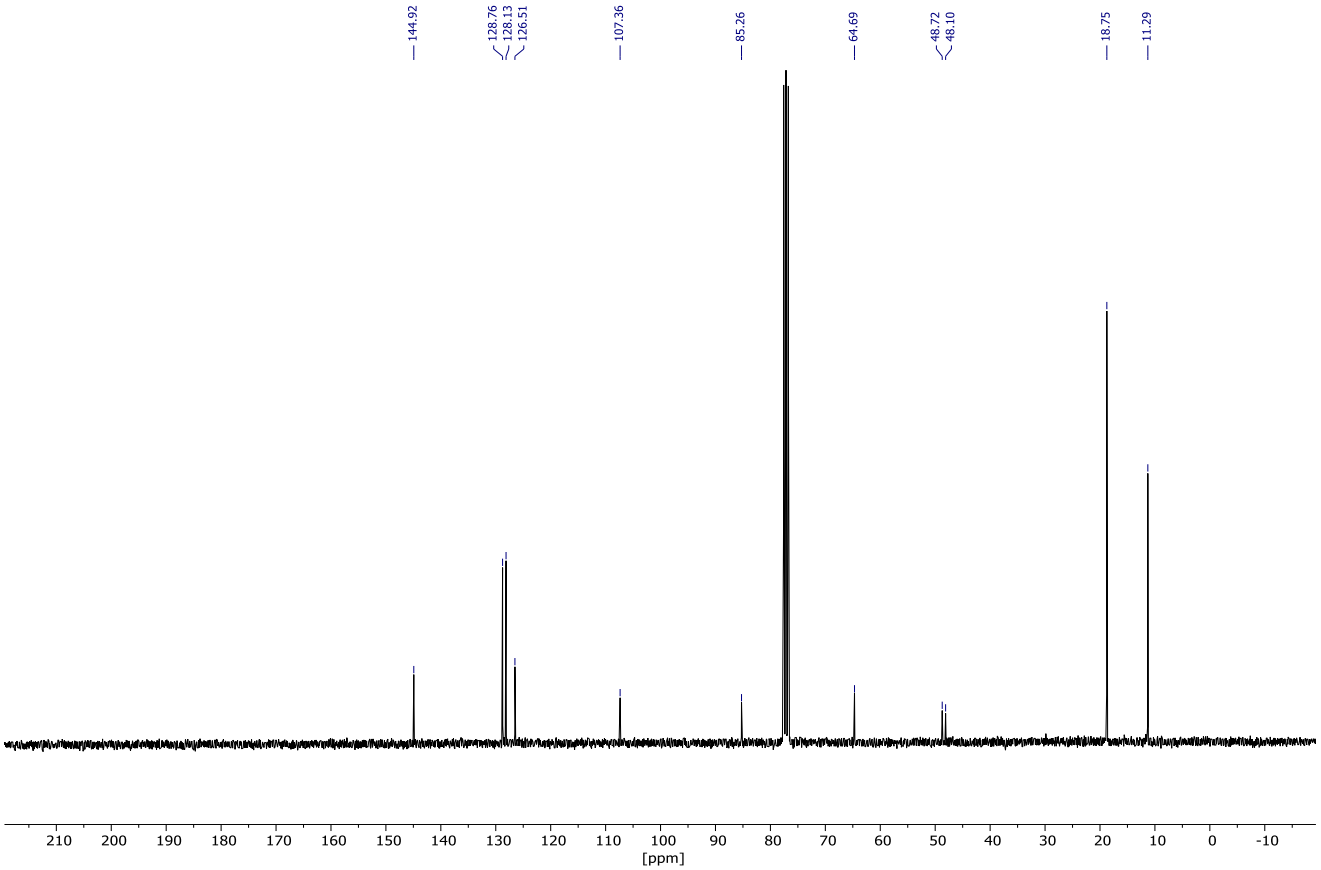
^{1}H NMR (300 MHz, $CDCl_3$) of 3-(naphthalen-1-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



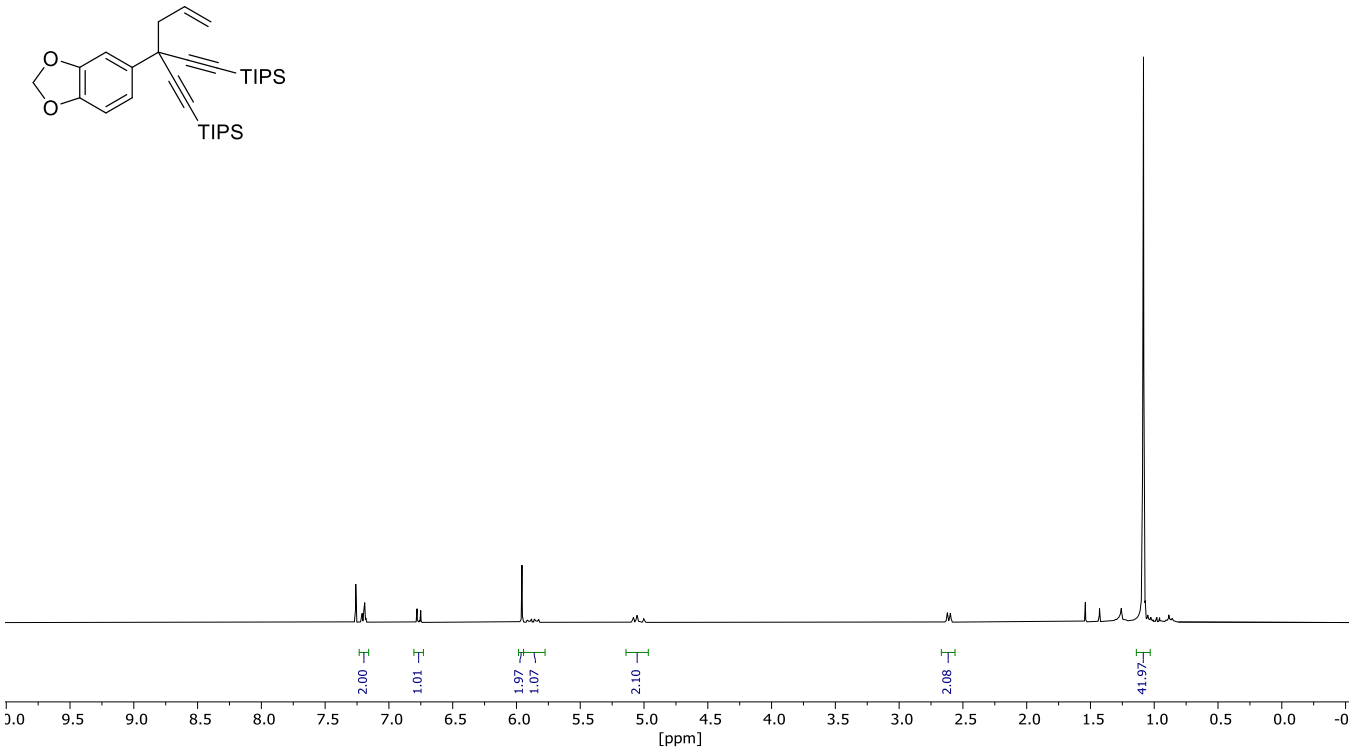
^{13}C NMR (75 MHz, $CDCl_3$) of 3-(naphthalen-1-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



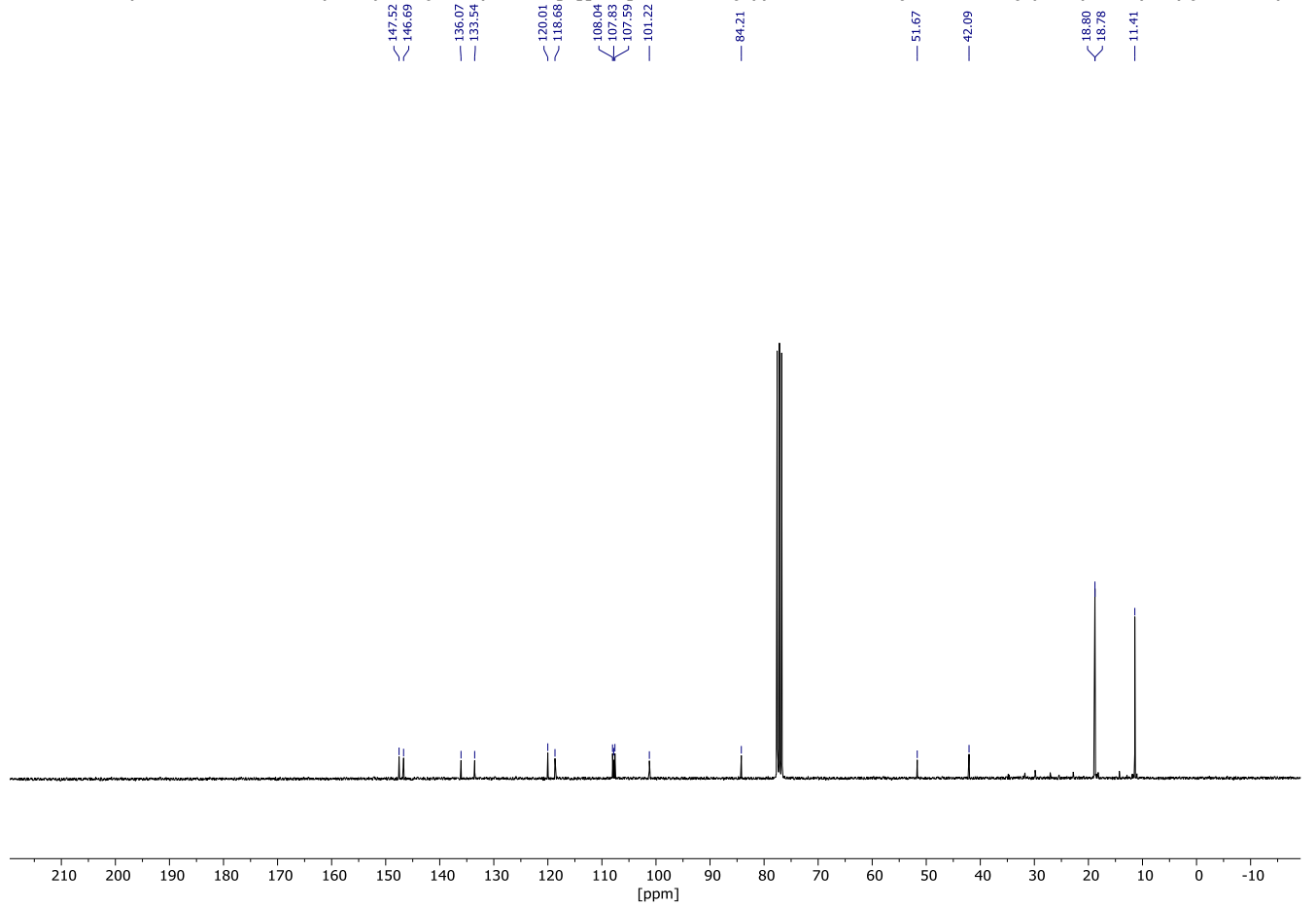
^{1}H NMR (300 MHz, $CDCl_3$) of 3-(2,2-diphenylethyl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



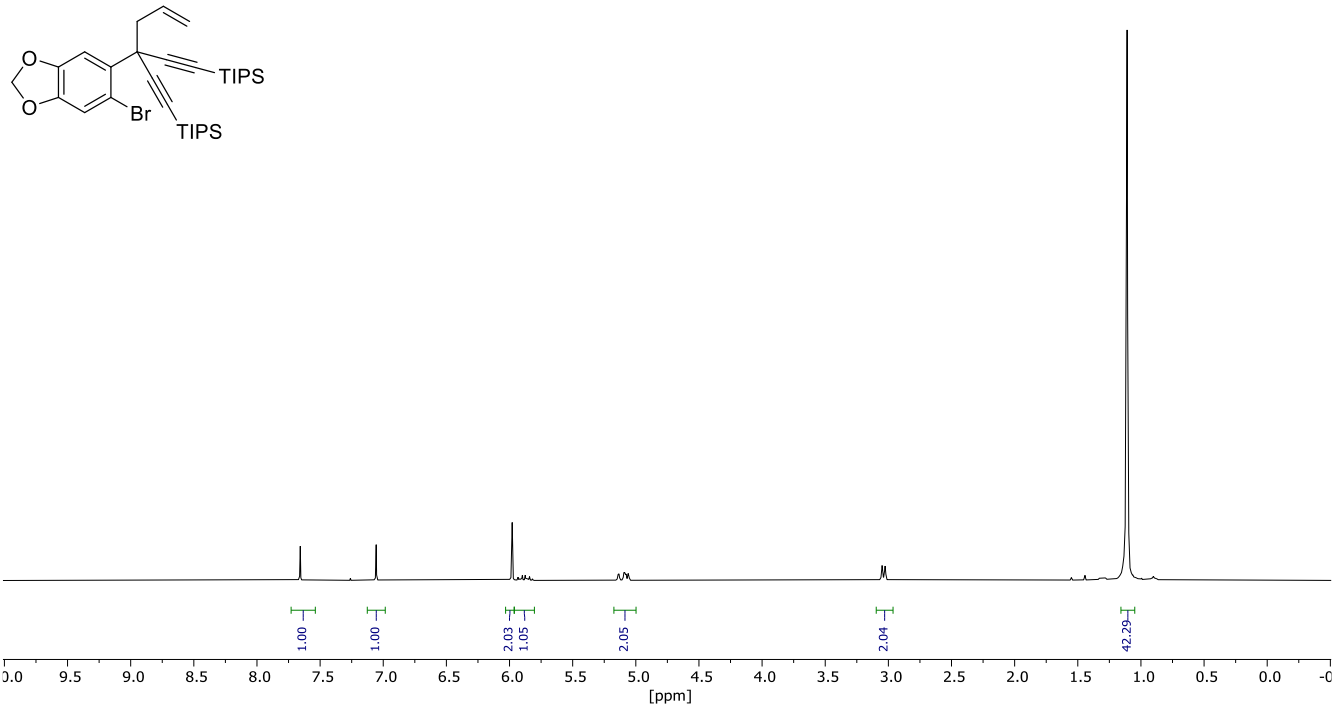
^{13}C NMR (75 MHz, $CDCl_3$) of 3-(2,2-diphenylethyl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol



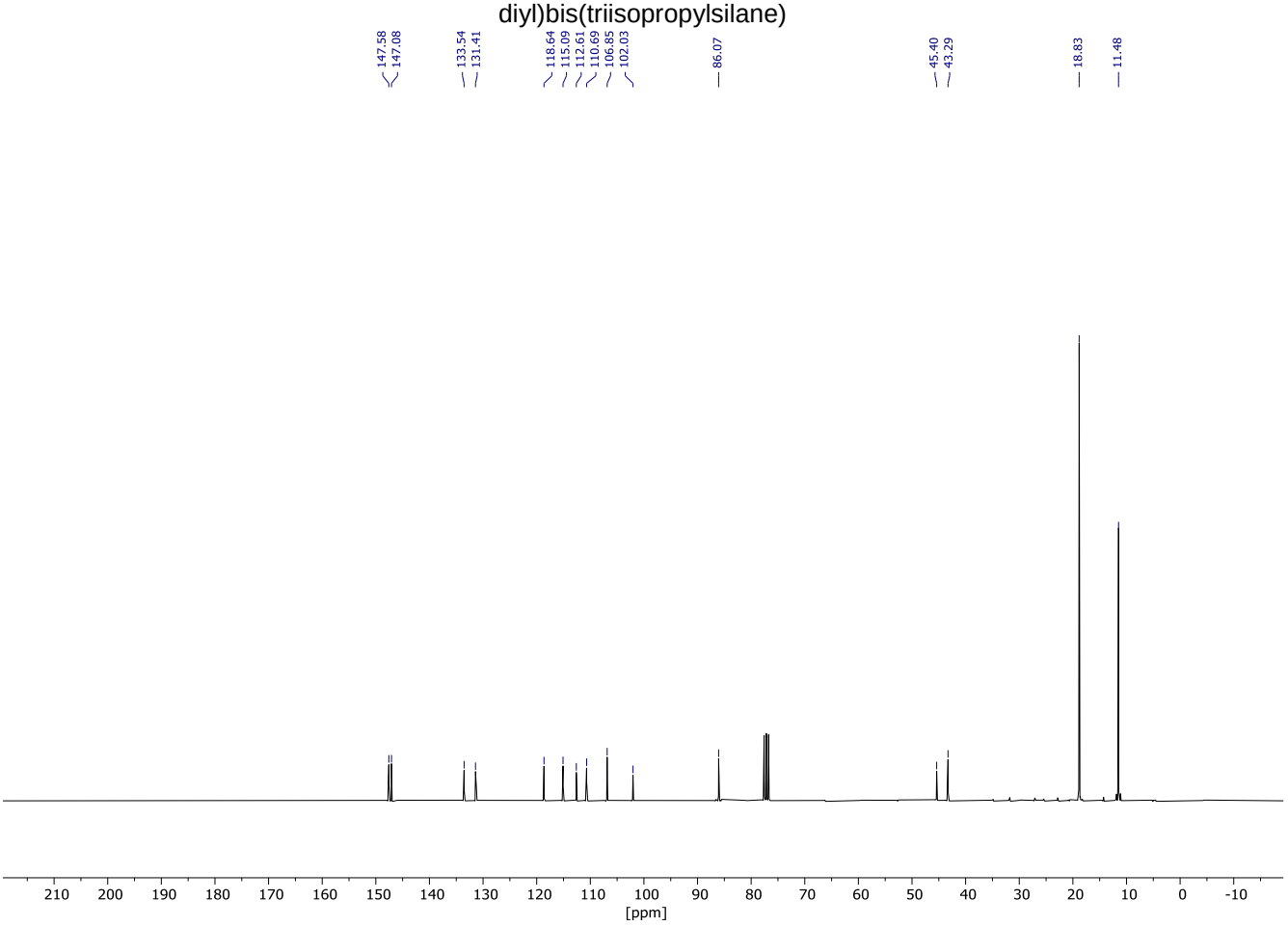
^{1}H NMR (300 MHz, $CDCl_3$) of (3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



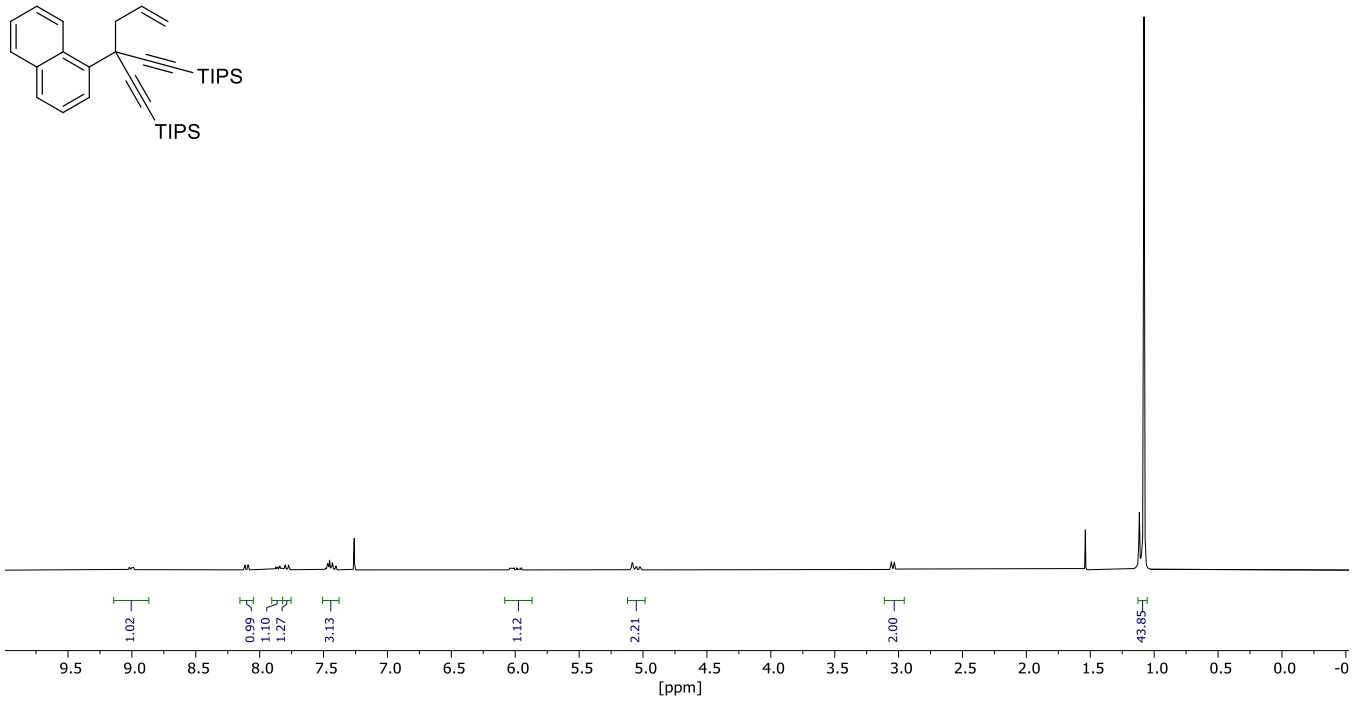
^{13}C NMR (75 MHz, $CDCl_3$) of (3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



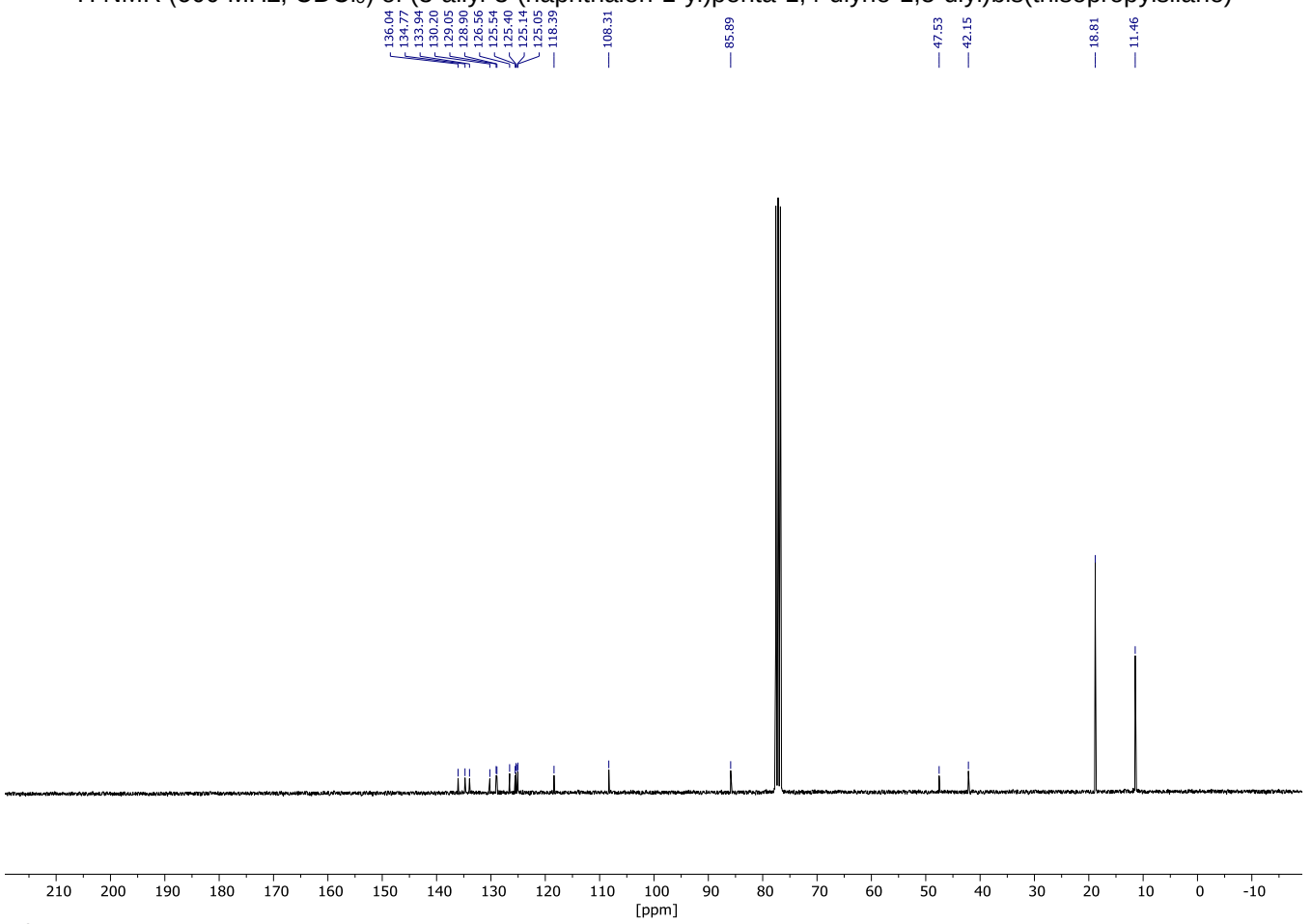
^{1}H NMR (300 MHz, $CDCl_3$) of (3-allyl-3-(6-bromobenzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



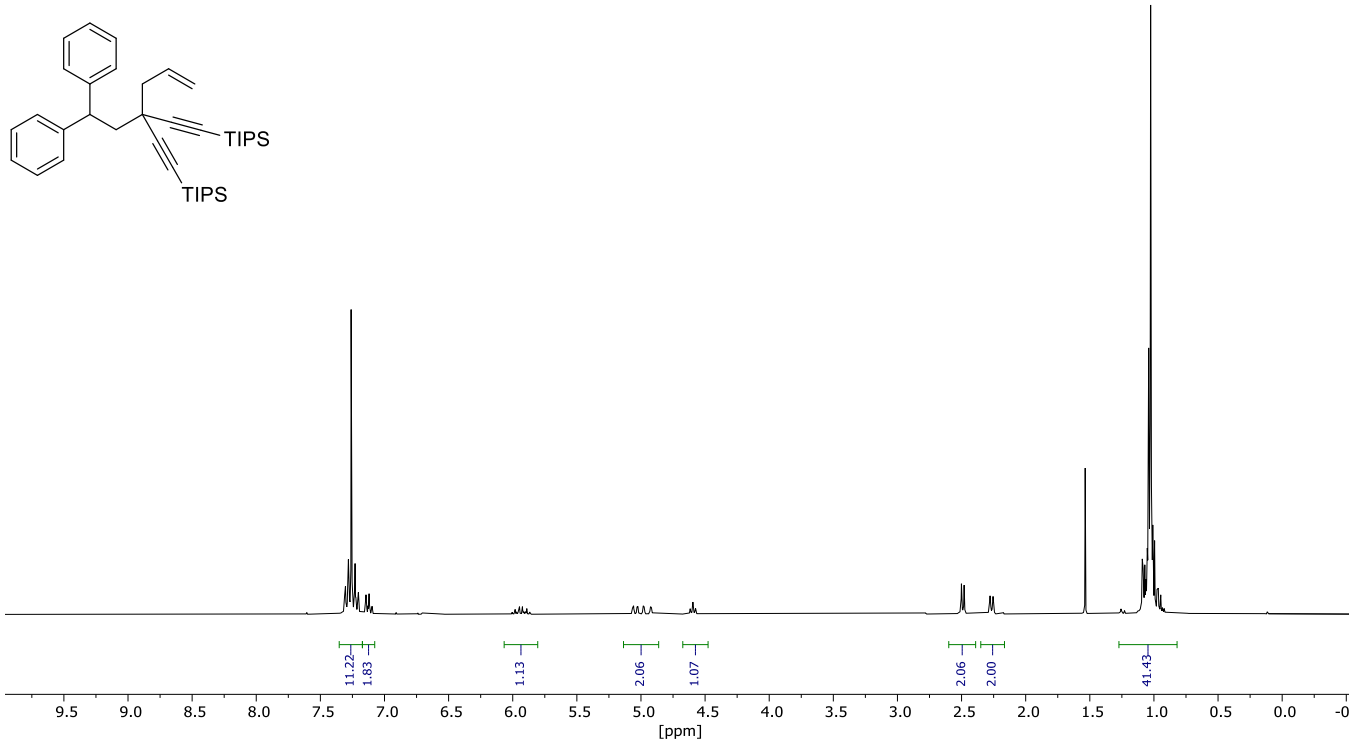
^{13}C NMR (75 MHz, $CDCl_3$) of (3-allyl-3-(6-bromobenzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



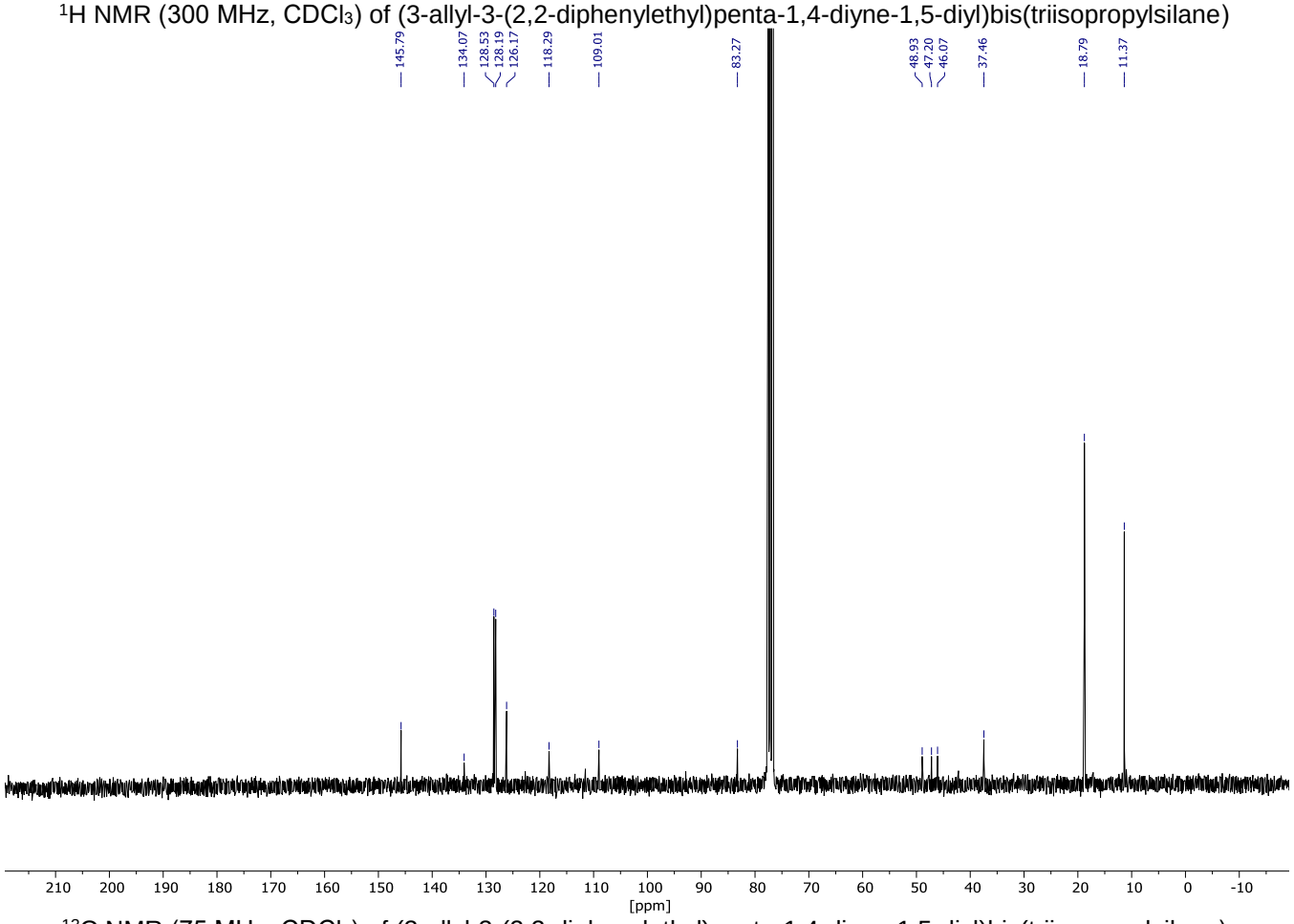
^{1}H NMR (300 MHz, $CDCl_3$) of (3-allyl-3-(naphthalen-1-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



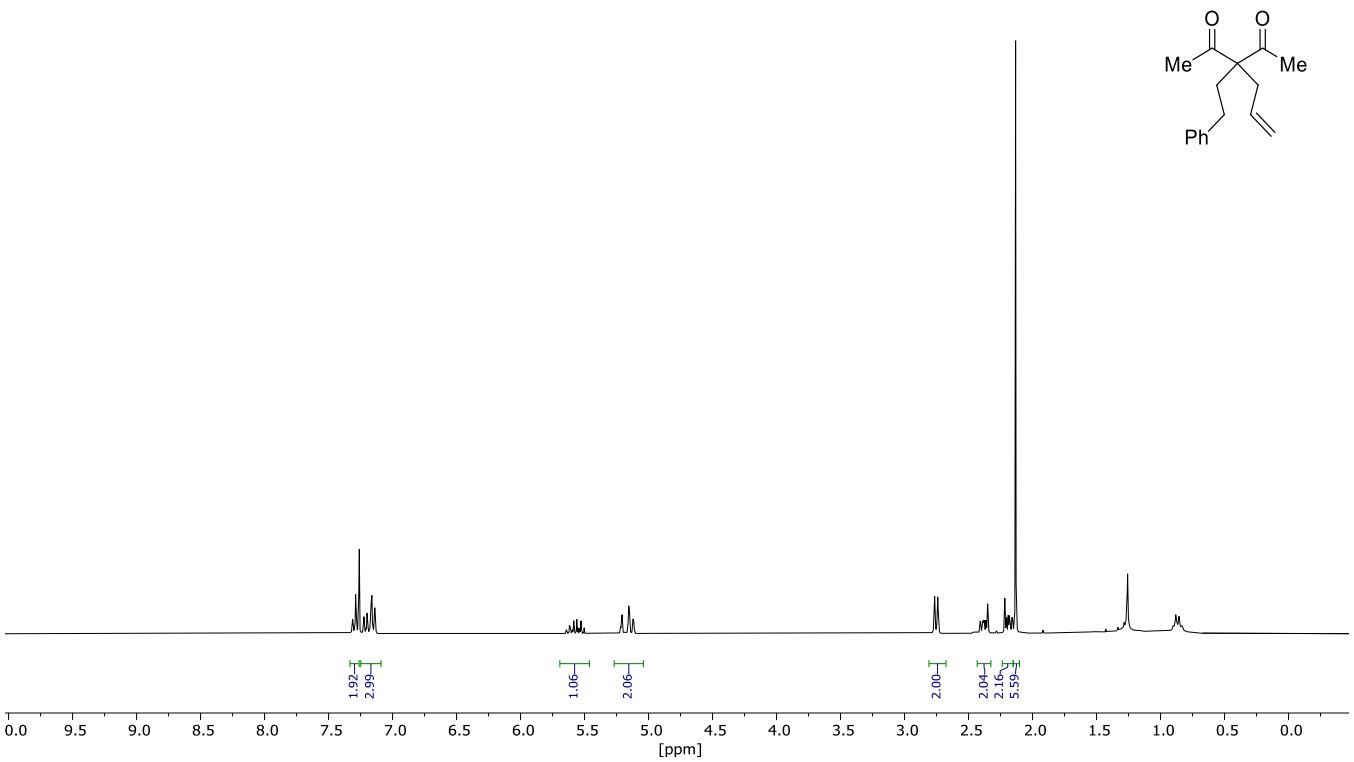
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of (3-allyl-3-(naphthalen-1-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



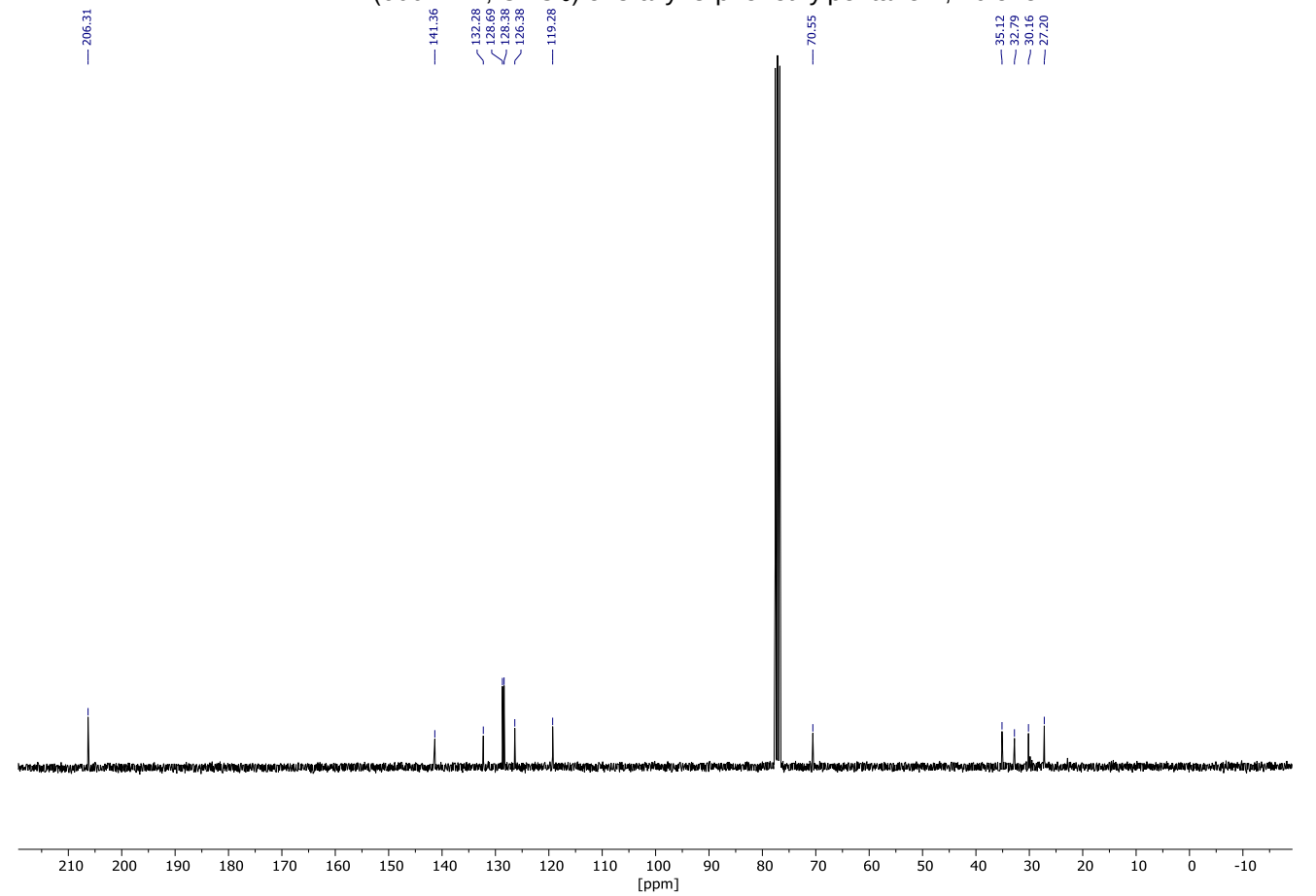
^{1}H NMR (300 MHz, $CDCl_3$) of (3-allyl-3-(2,2-diphenylethyl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



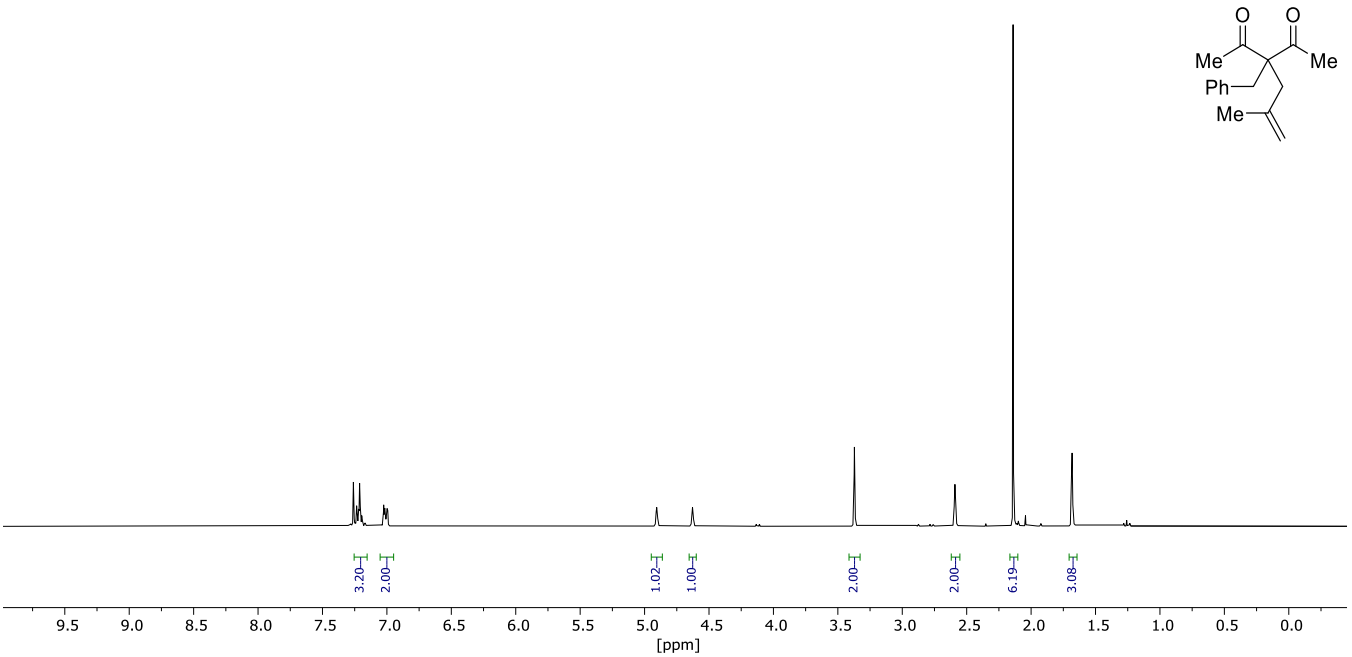
^{13}C NMR (75 MHz, $CDCl_3$) of (3-allyl-3-(2,2-diphenylethyl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane)



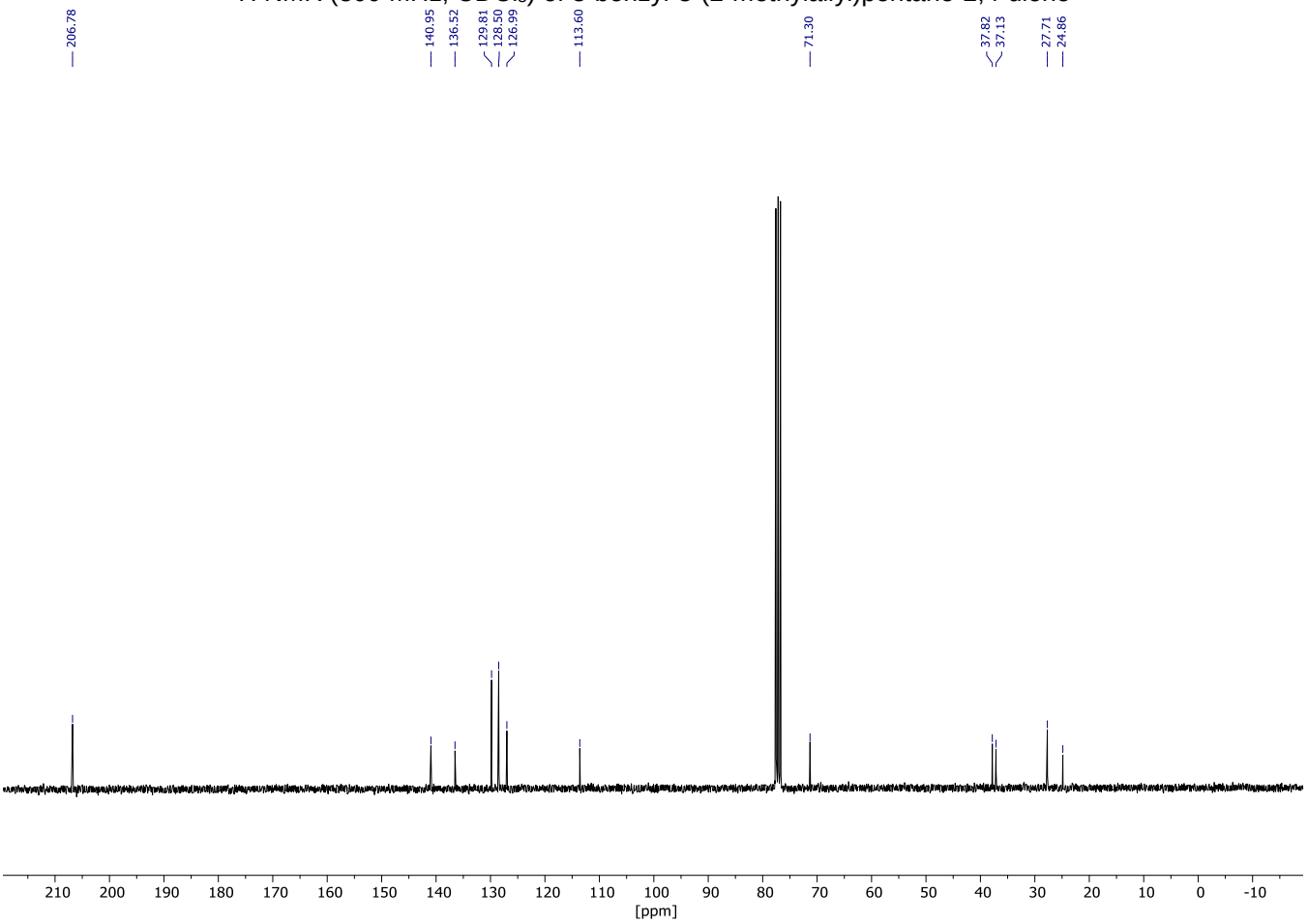
^{1}H NMR (300 MHz, $CDCl_3$) of 3-allyl-3-phenethylpentane-2,4-dione



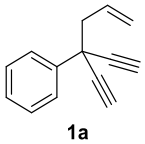
^{13}C NMR (75 MHz, $CDCl_3$) of 3-allyl-3-phenethylpentane-2,4-dione



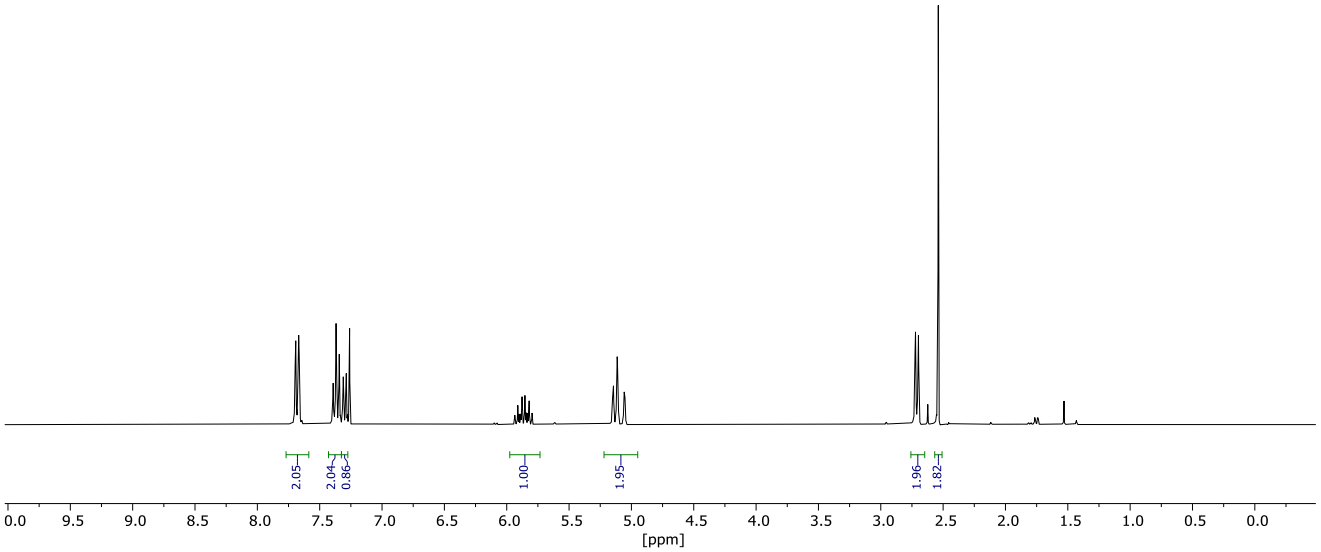
^{1}H NMR (300 MHz, $CDCl_3$) of 3-benzyl-3-(2-methylallyl)pentane-2,4-dione



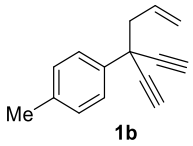
^{13}C NMR (75 MHz, $CDCl_3$) of 3-benzyl-3-(2-methylallyl)pentane-2,4-dione



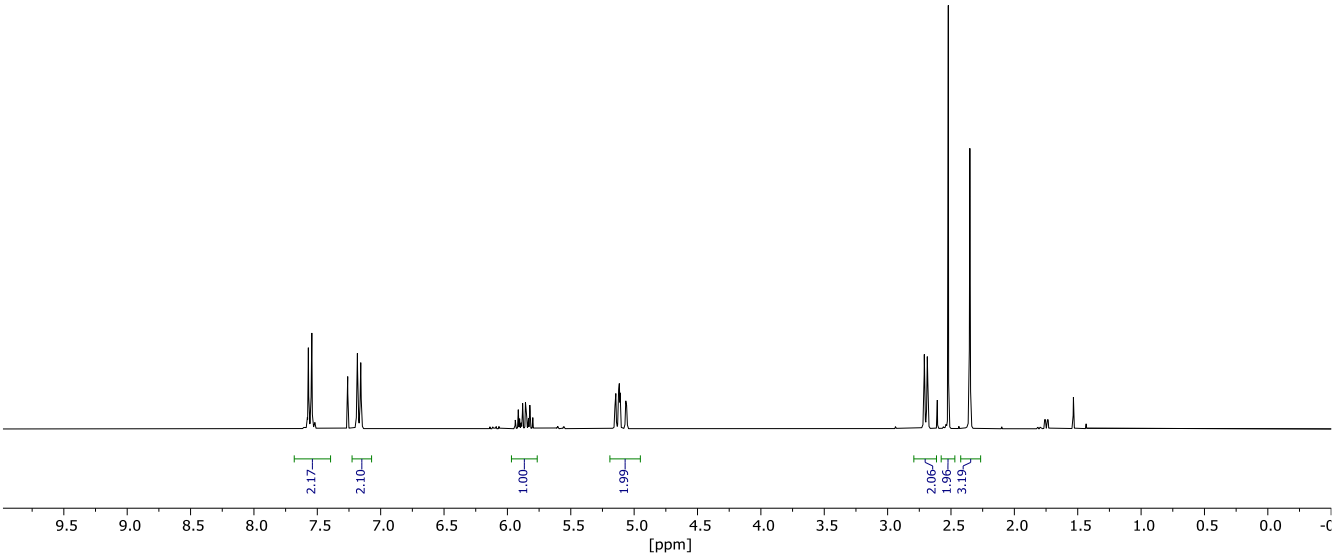
1a



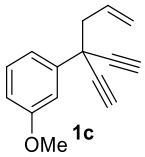
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1a**

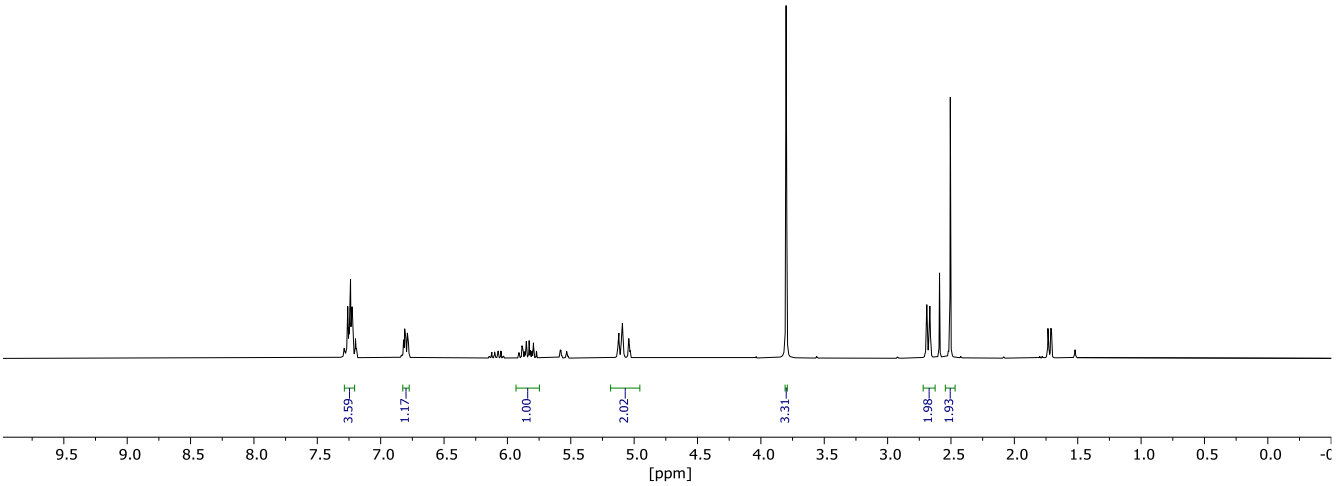


1b

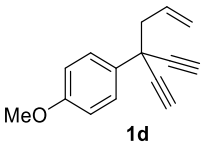


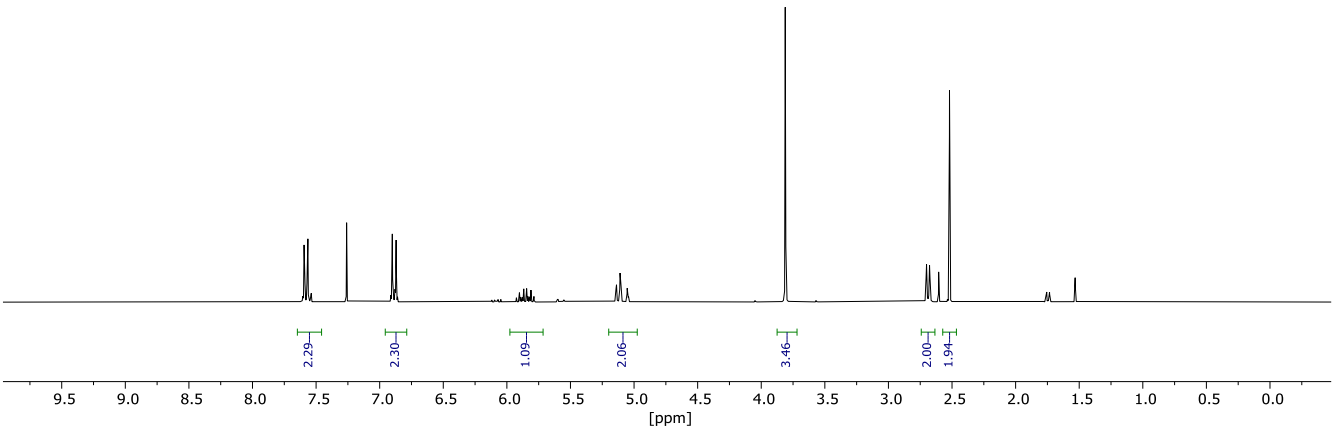
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1b**



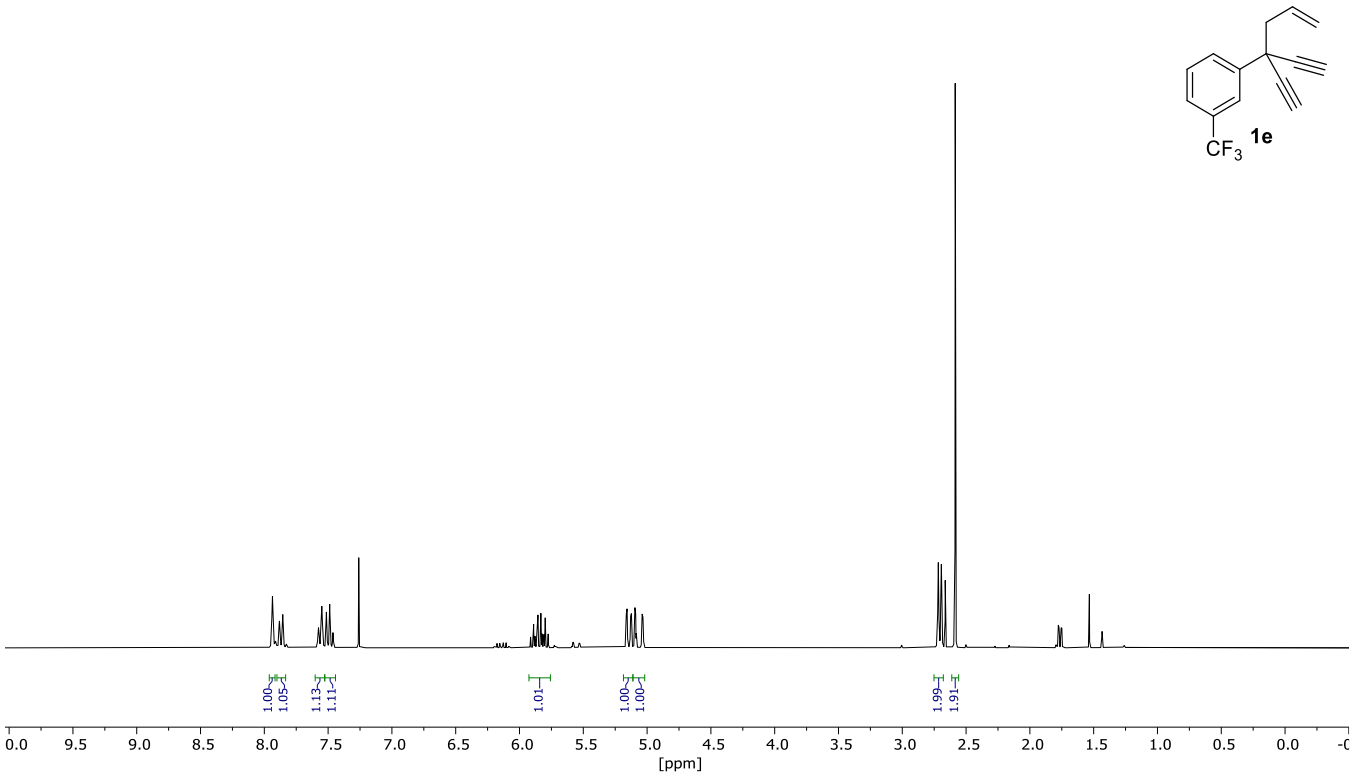


^{1}H NMR (300 MHz, $CDCl_3$) of compound **1c**

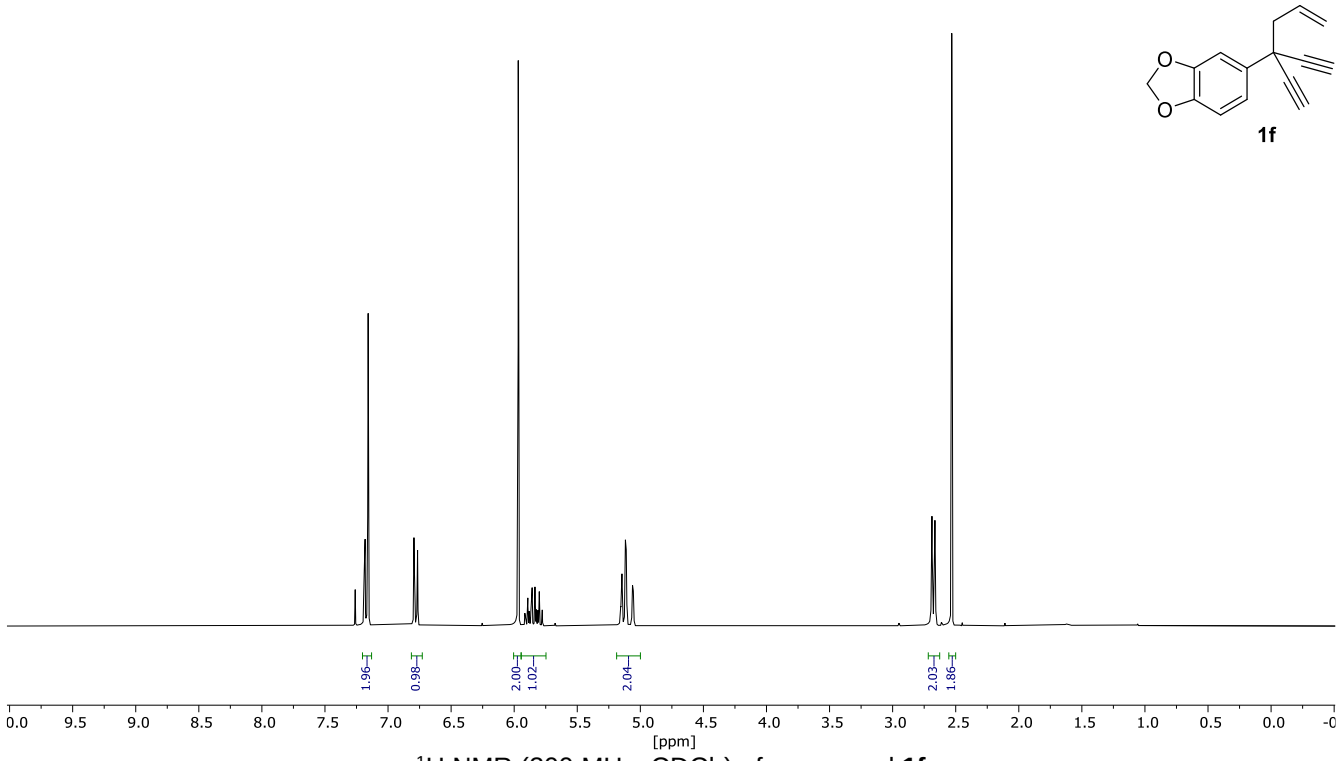




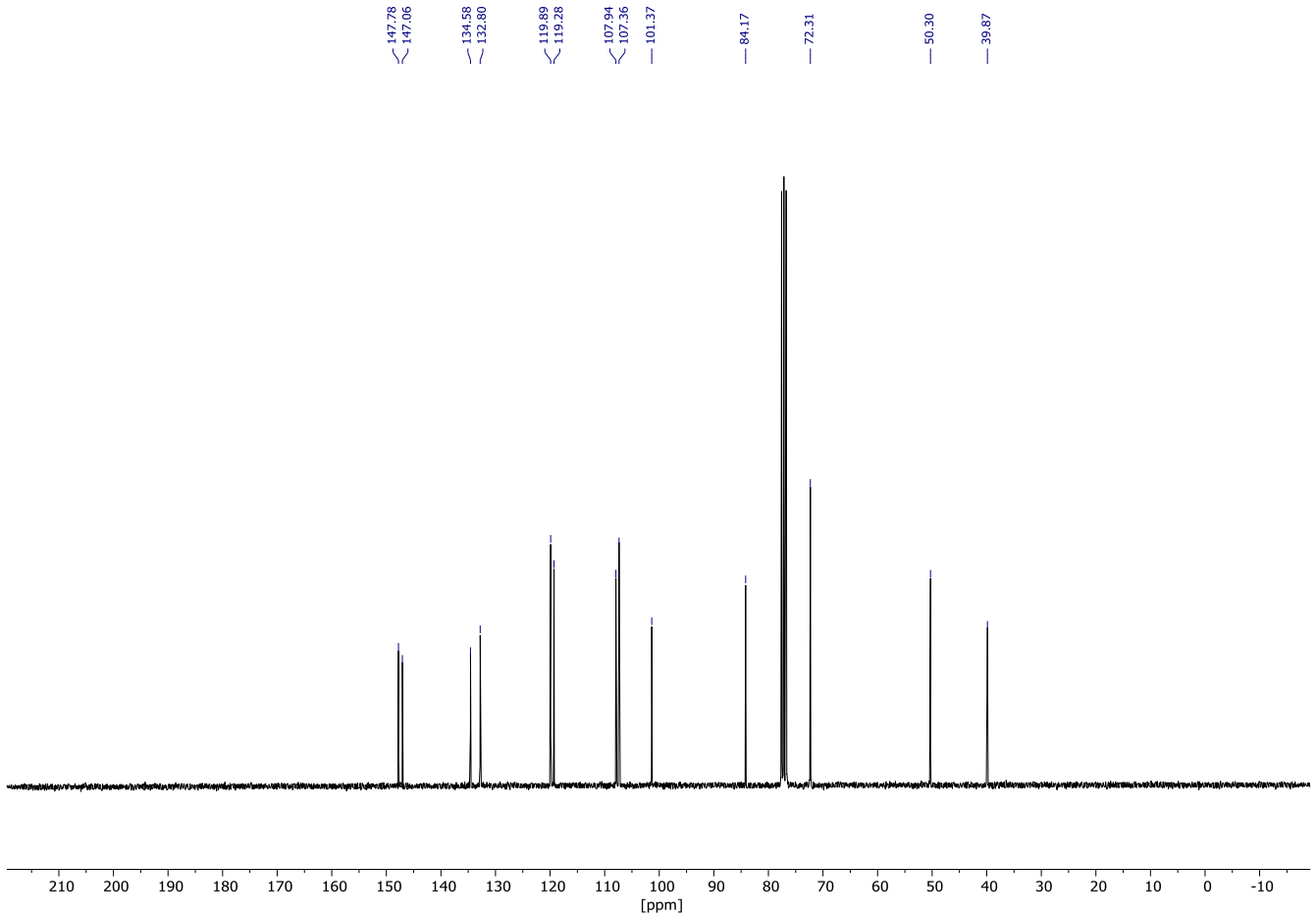
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1d**



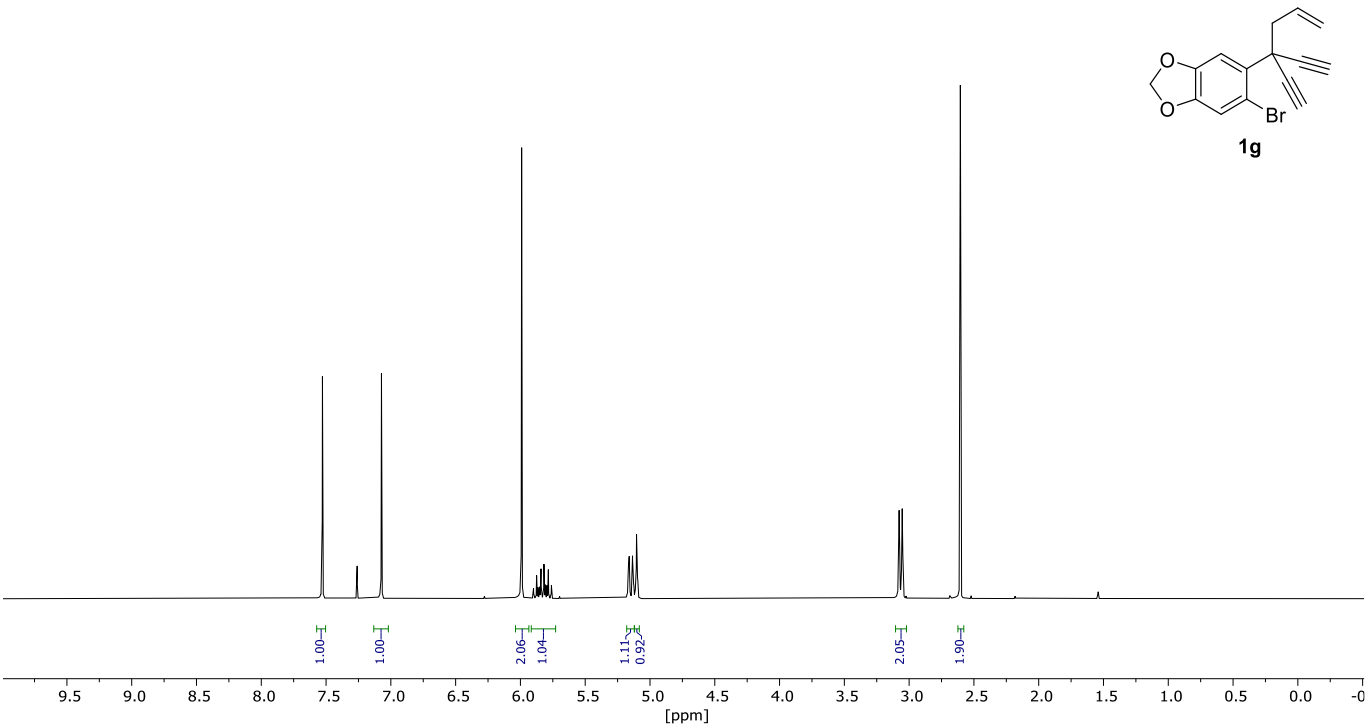
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1e**



^{1}H NMR (300 MHz, $CDCl_3$) of compound **1f**

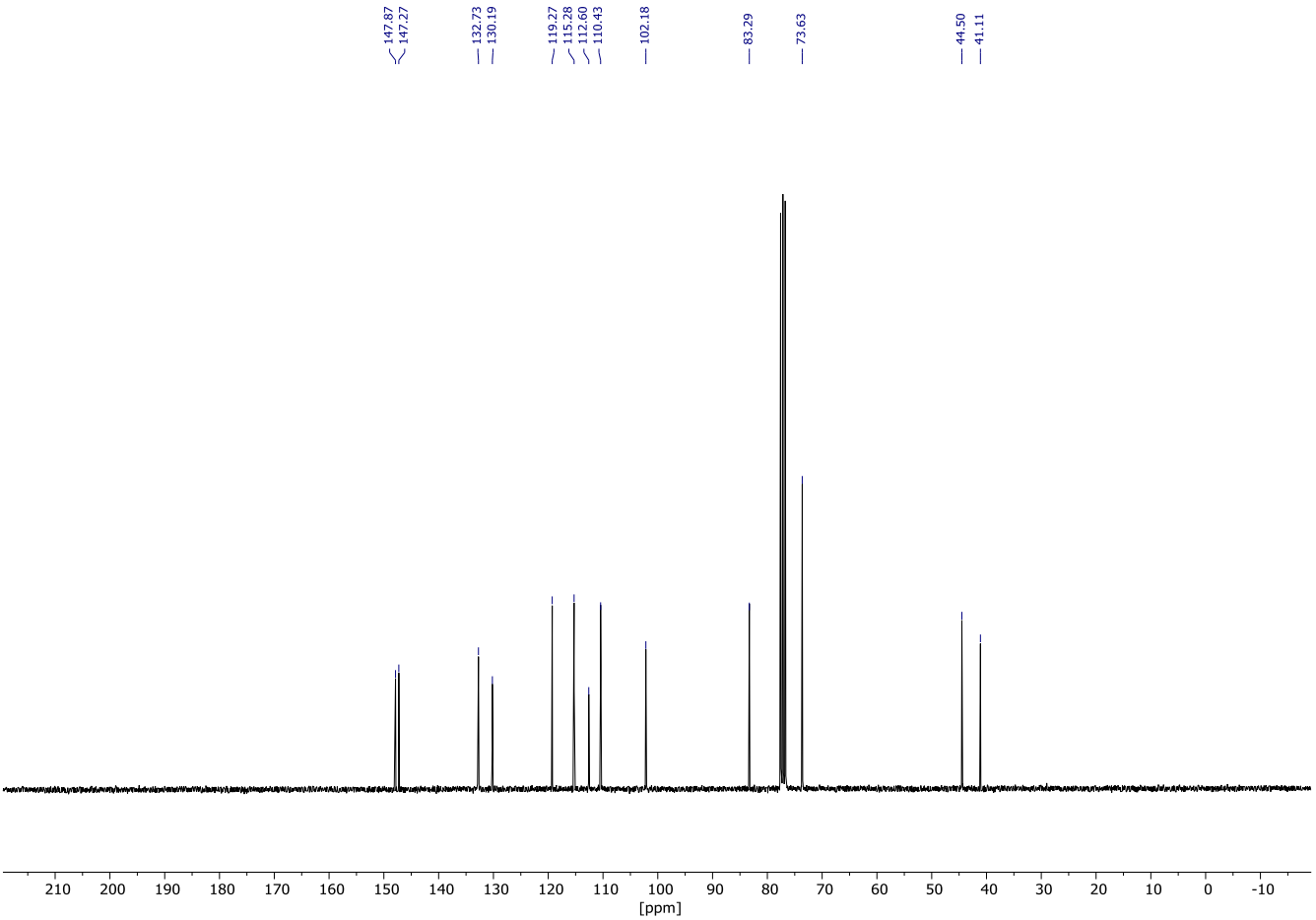


^{13}C NMR (75 MHz, $CDCl_3$) of compound **1f**

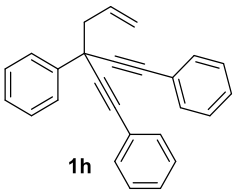


1g

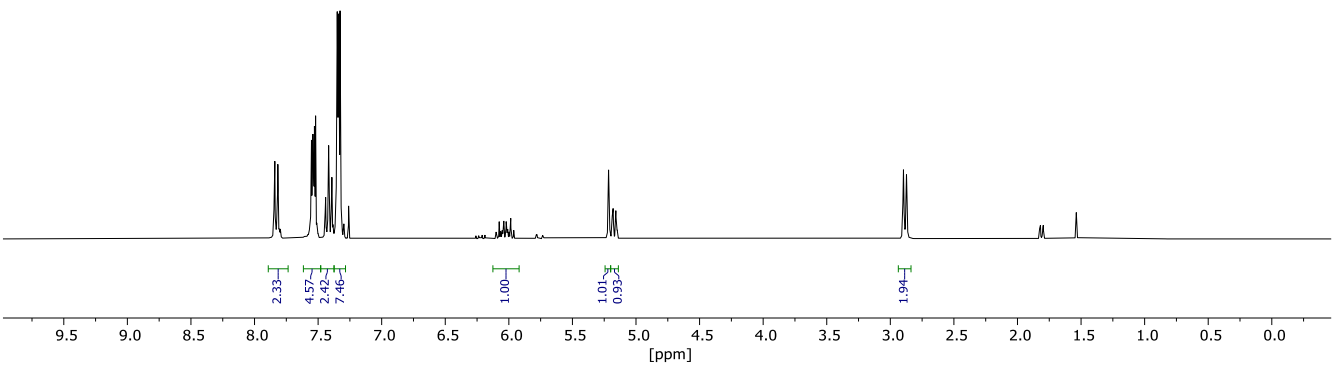
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1g**



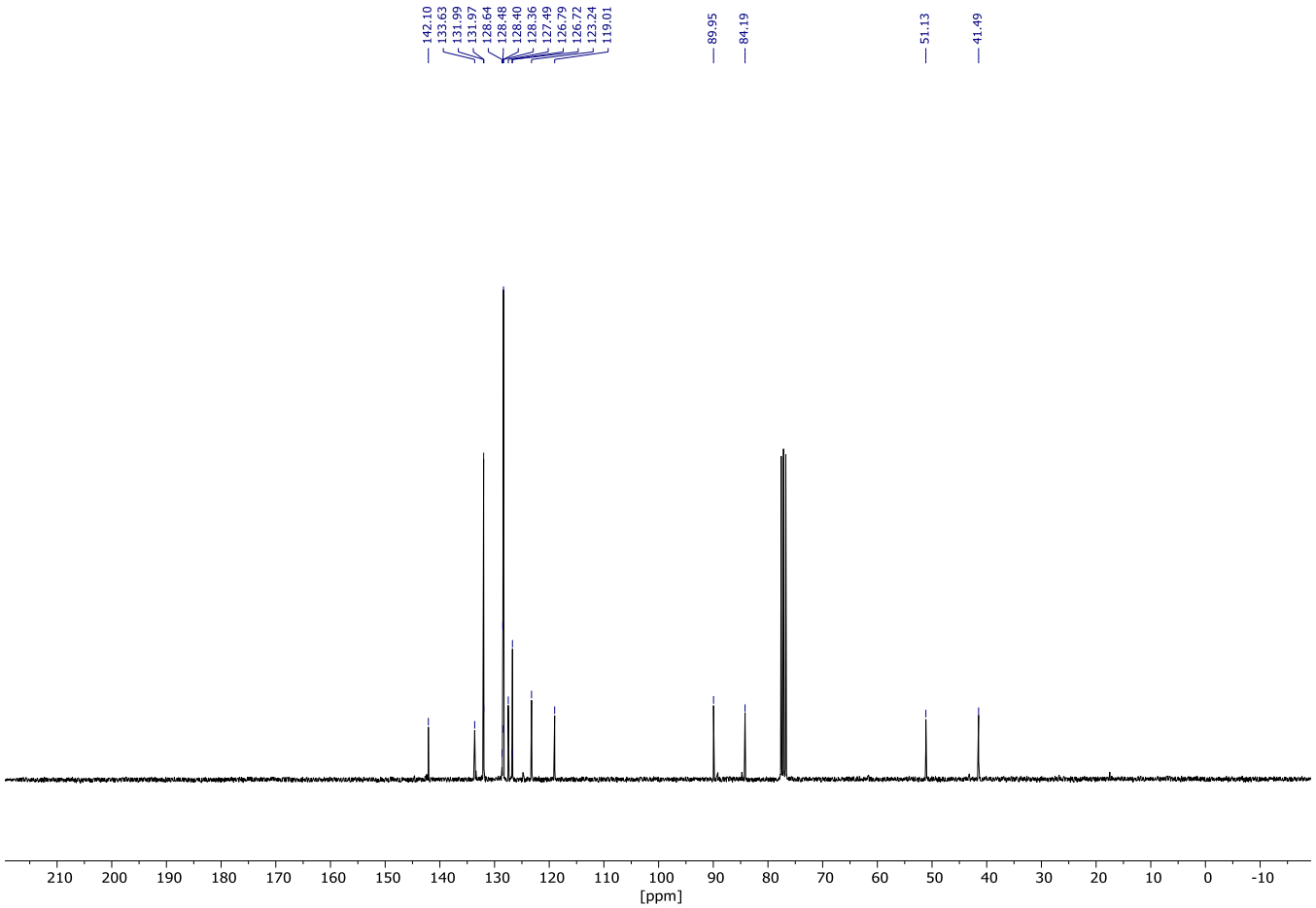
^{13}C NMR (75 MHz, $CDCl_3$) of compound **1g**



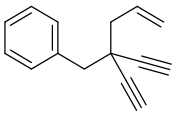
1h



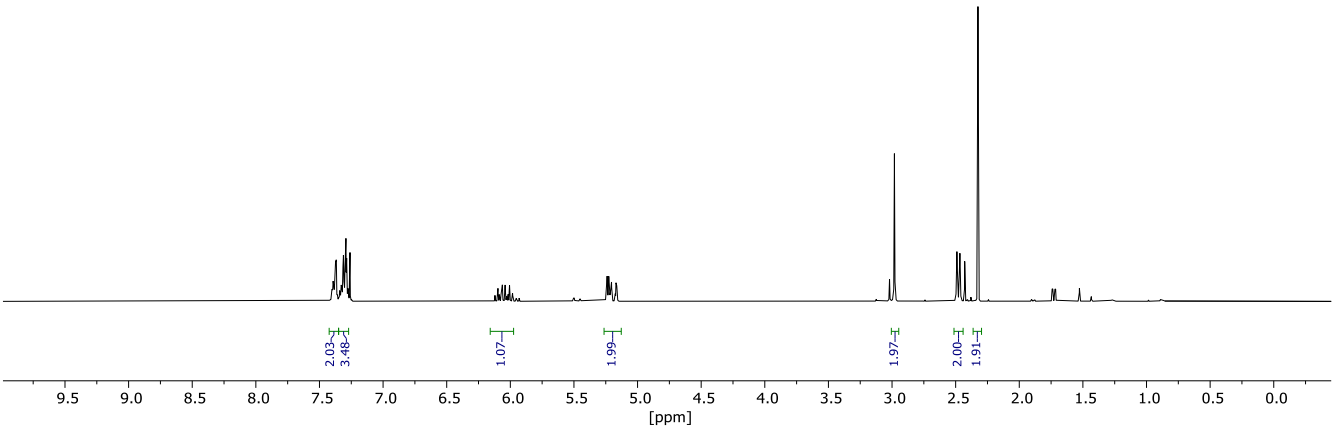
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1h**



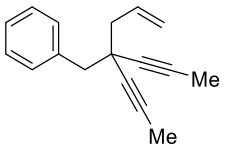
^{13}C NMR (75 MHz, $CDCl_3$) of compound **1h**



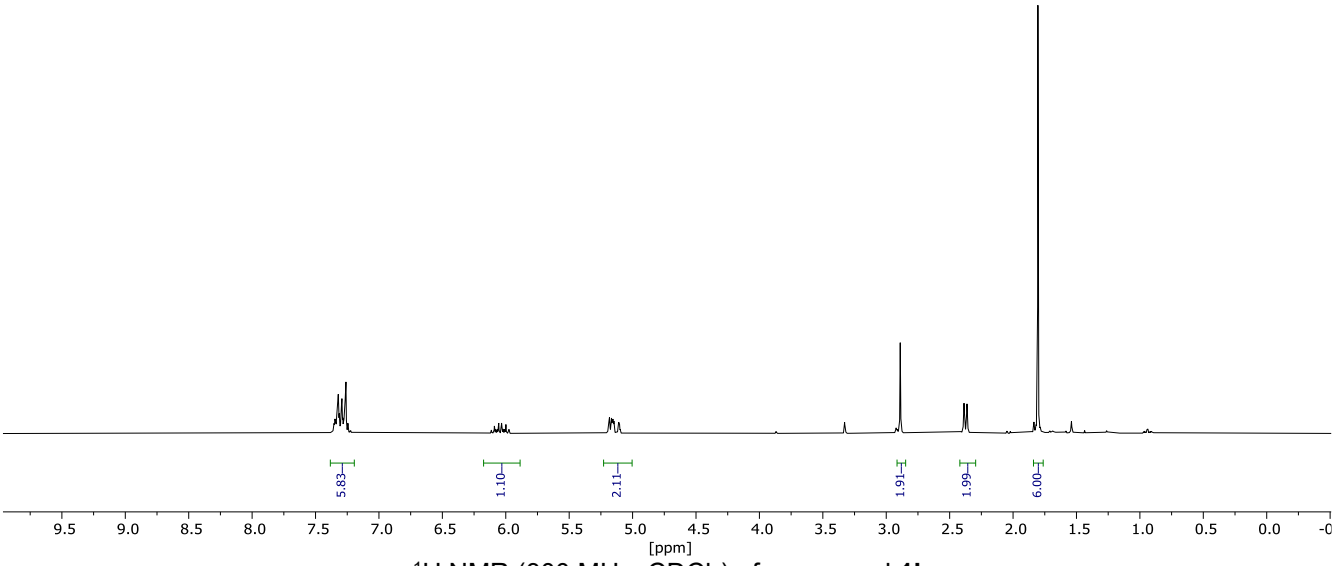
1i



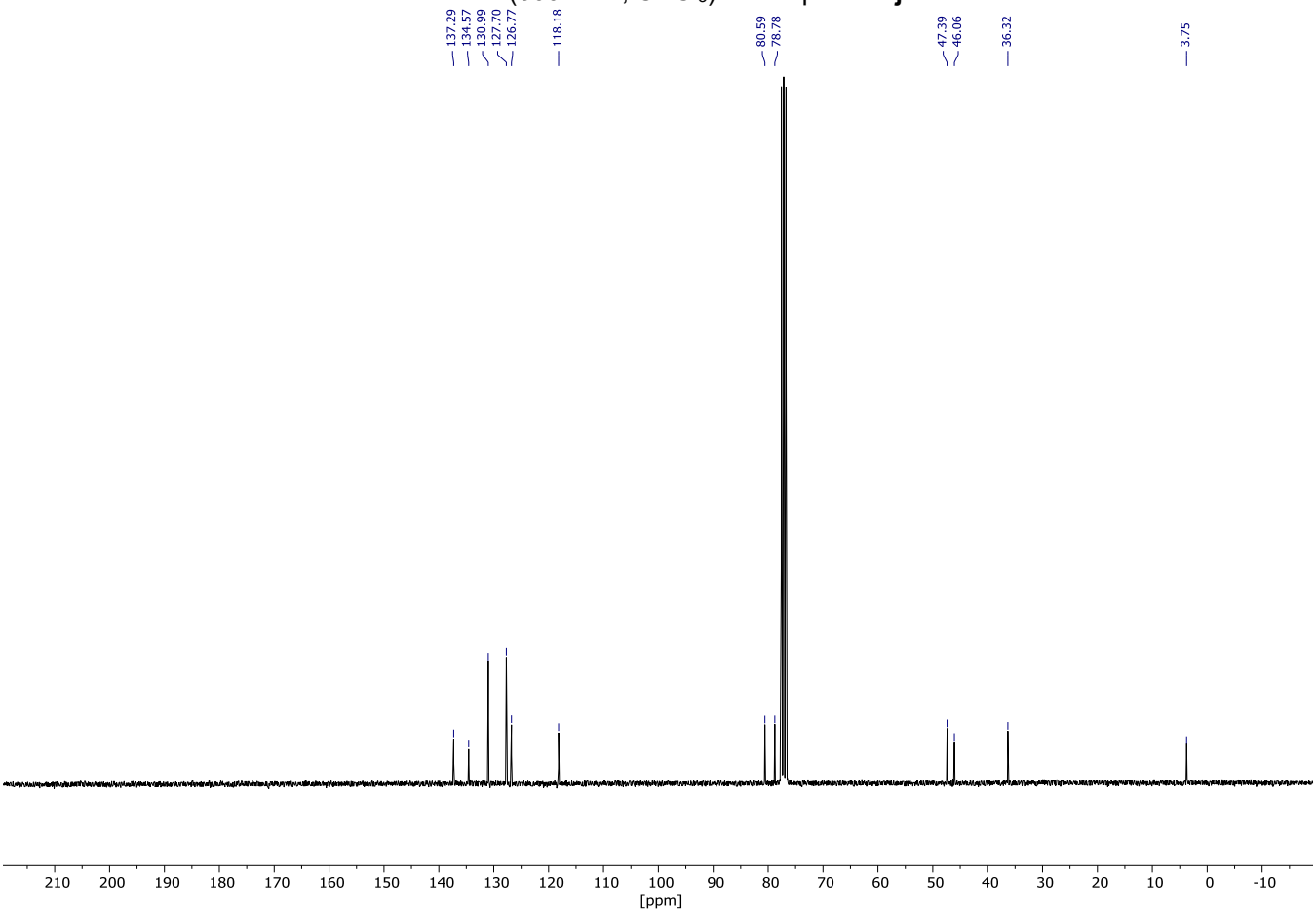
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1i**



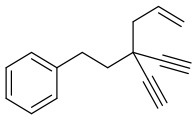
1j



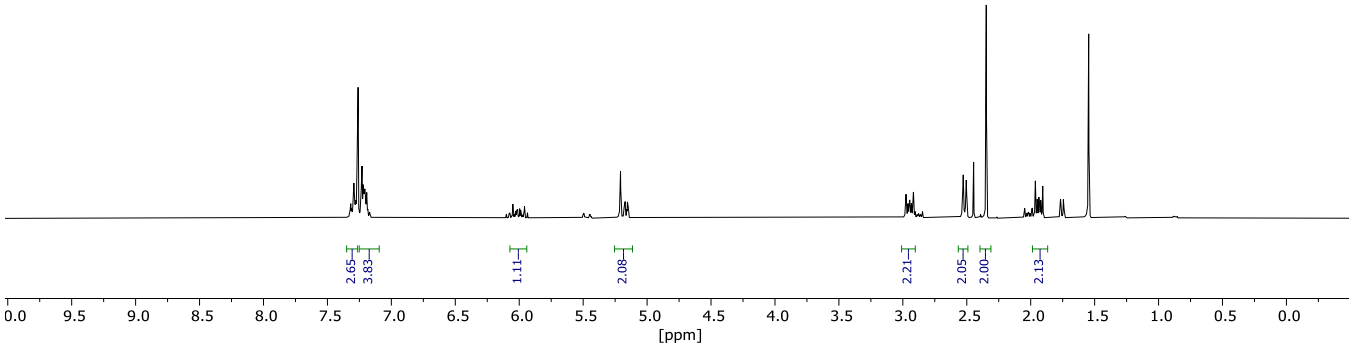
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1j**



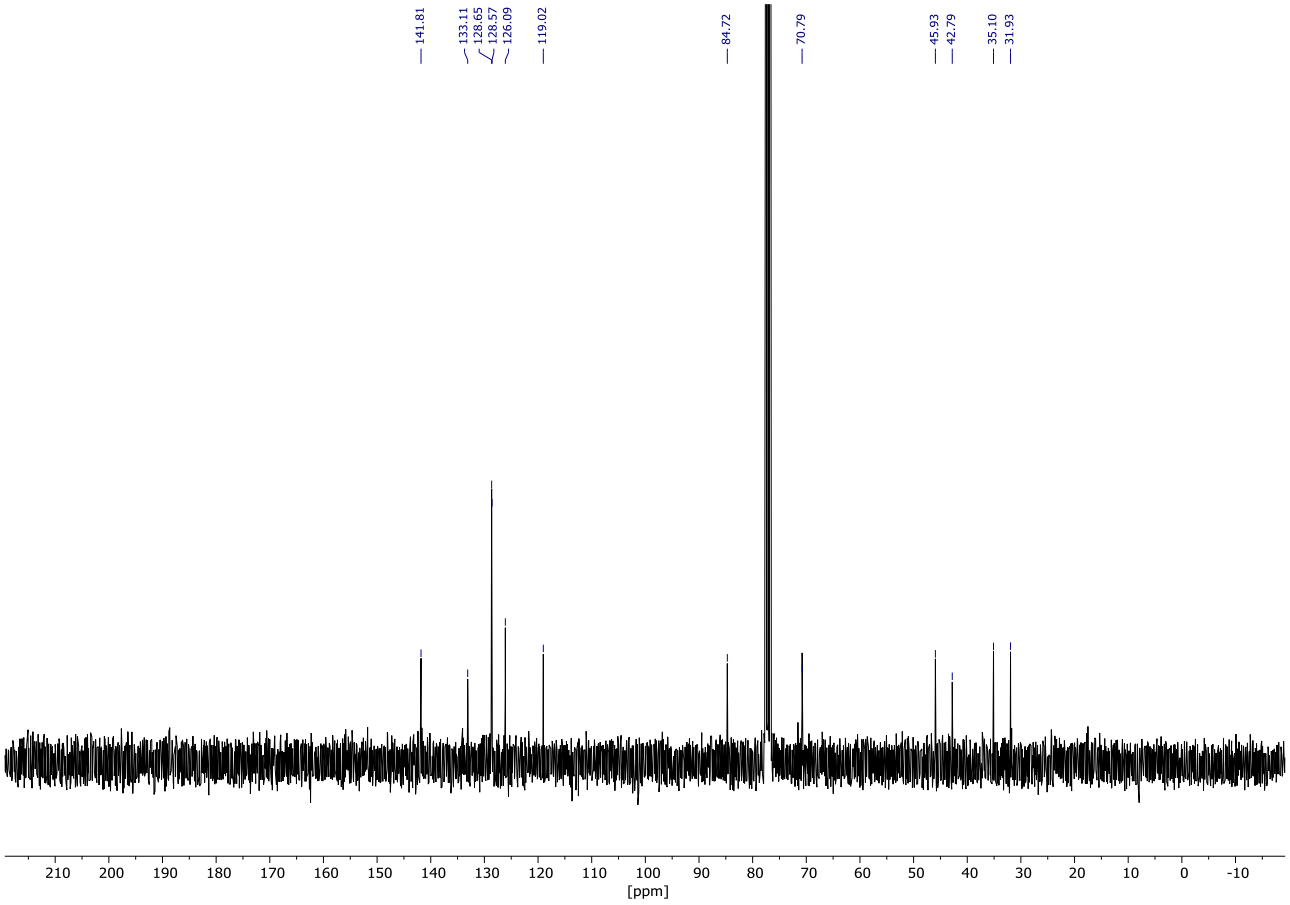
^{13}C NMR (75 MHz, $CDCl_3$) of compound **1j**



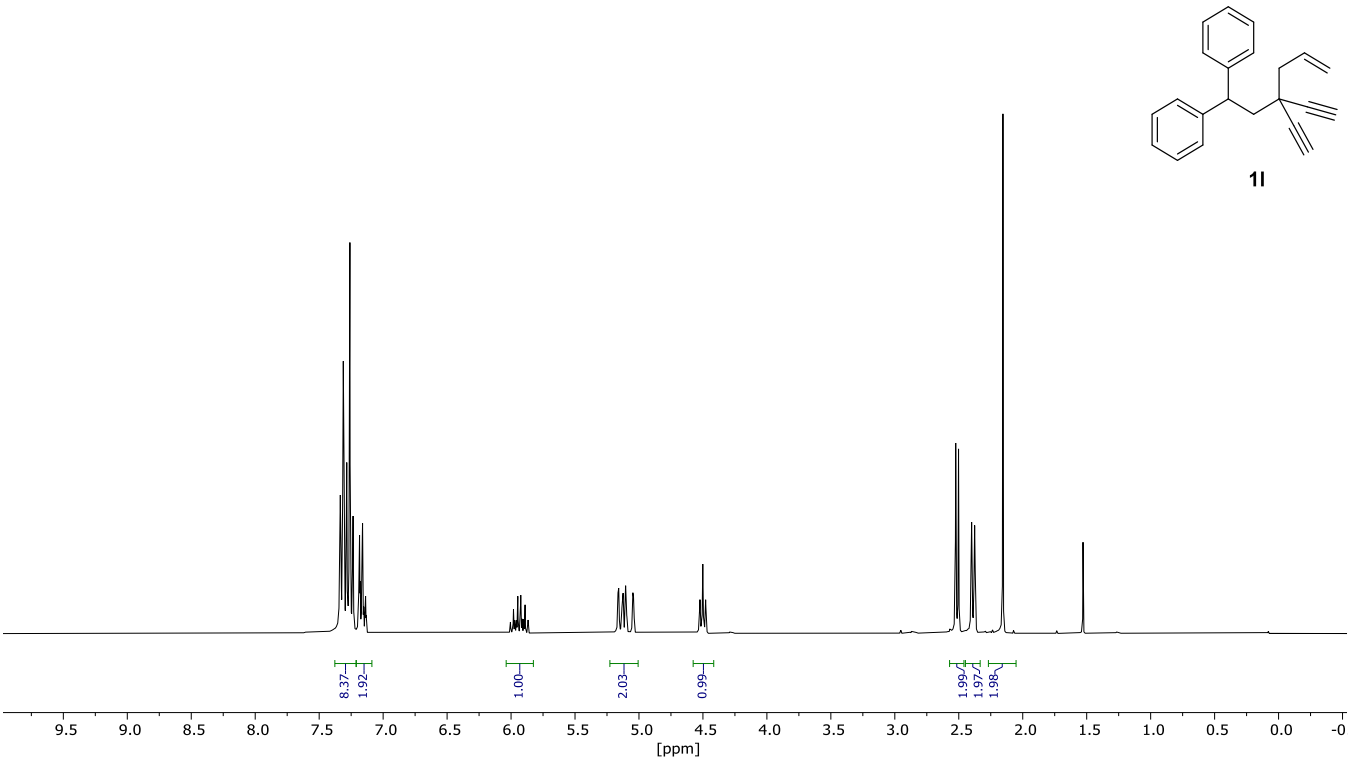
1k



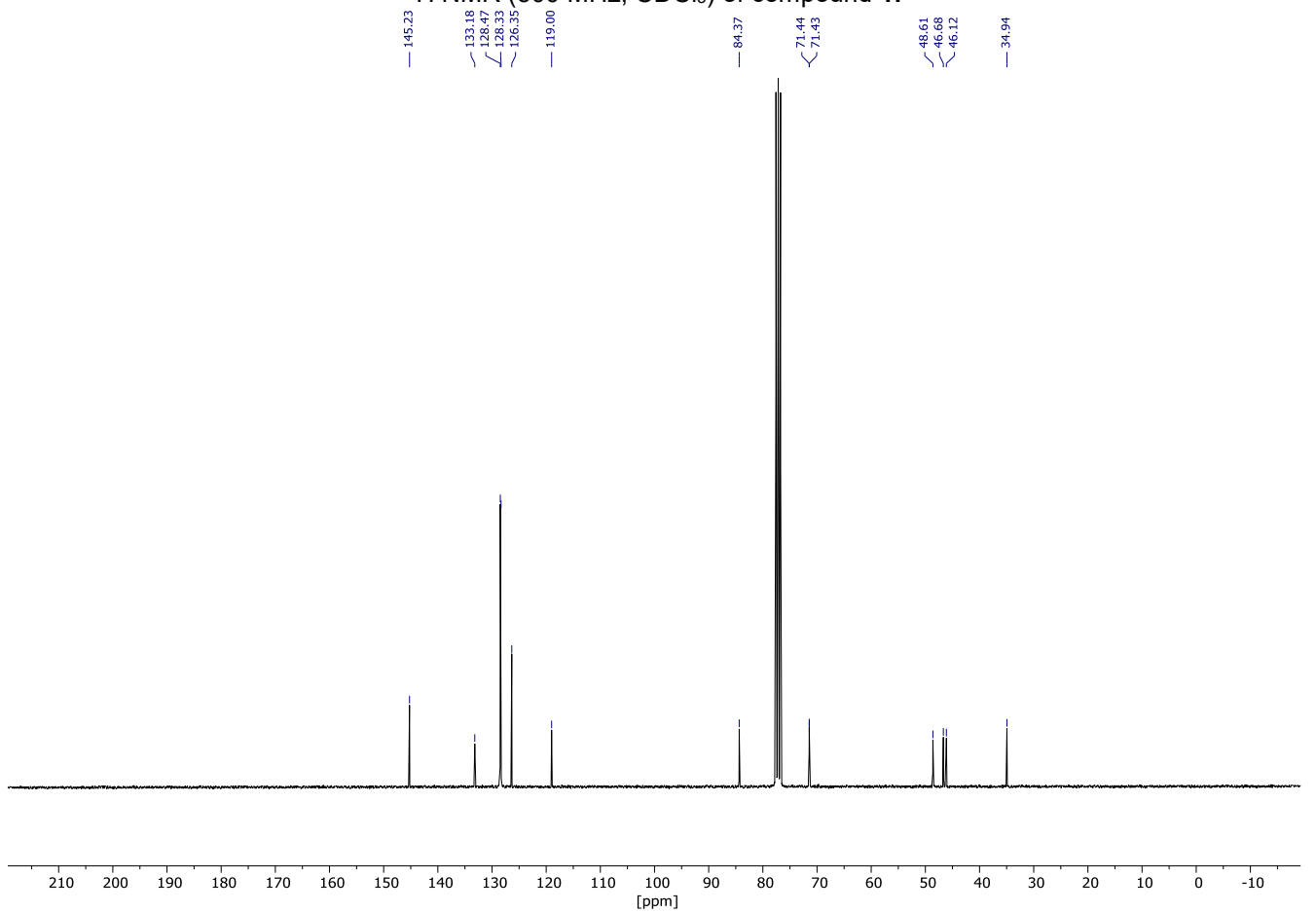
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1k**



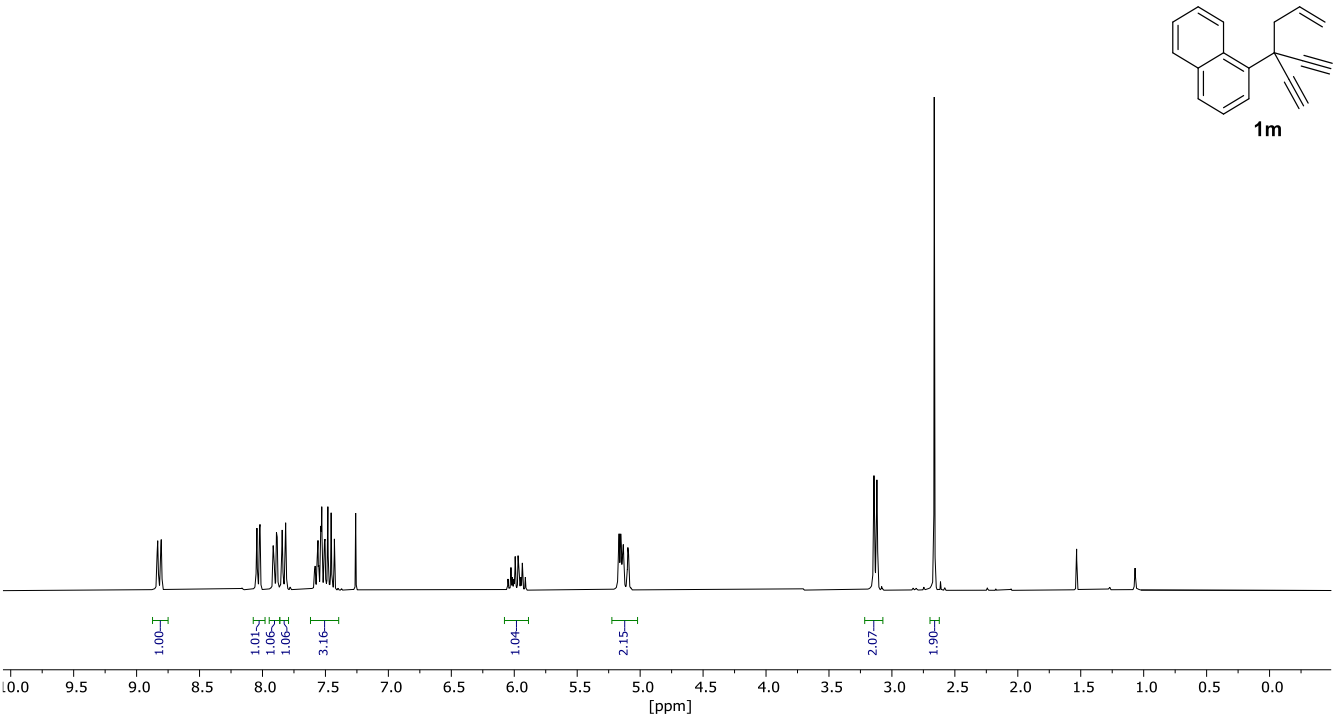
^{13}C NMR (75 MHz, $CDCl_3$) of compound **1k**



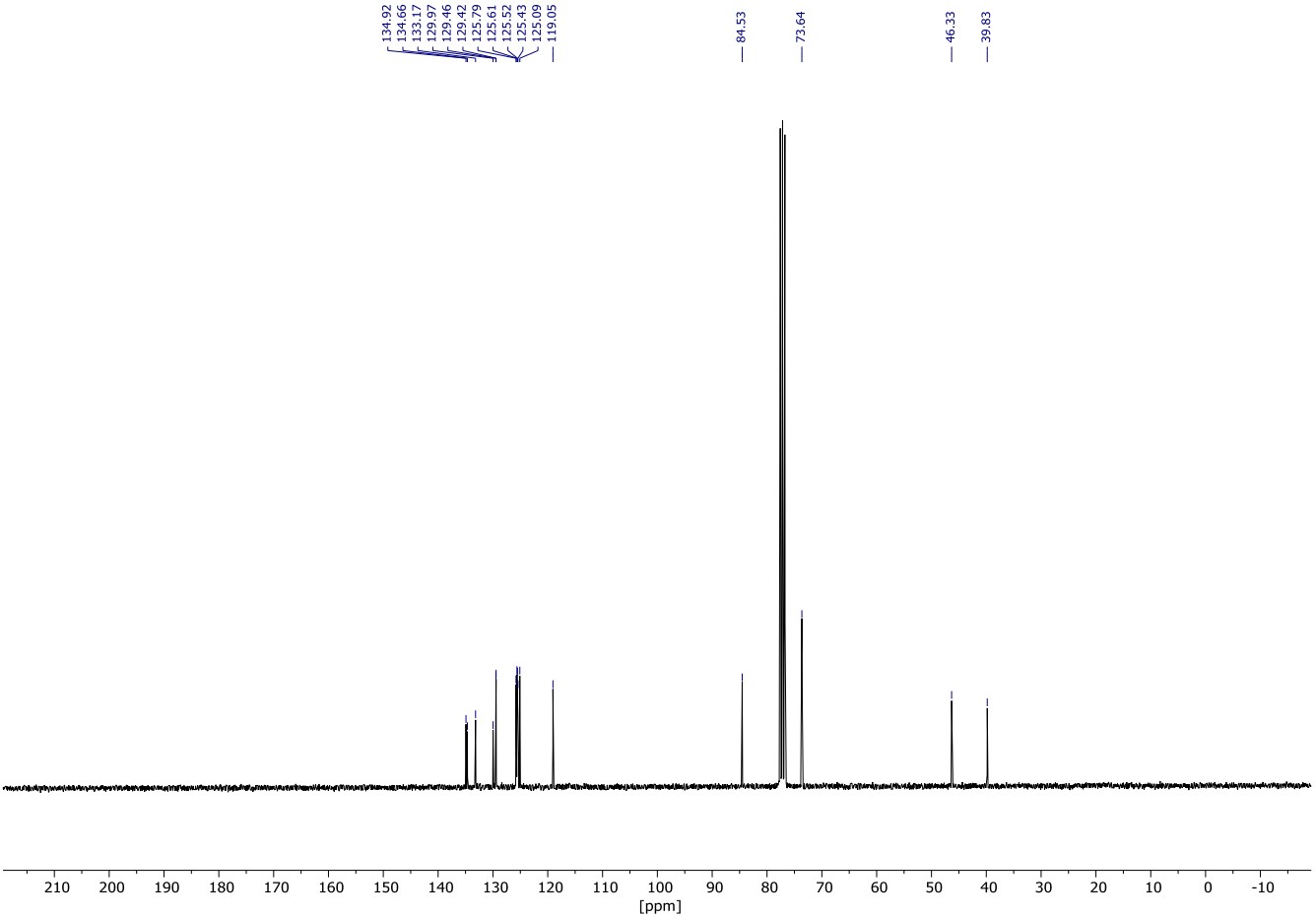
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1l**



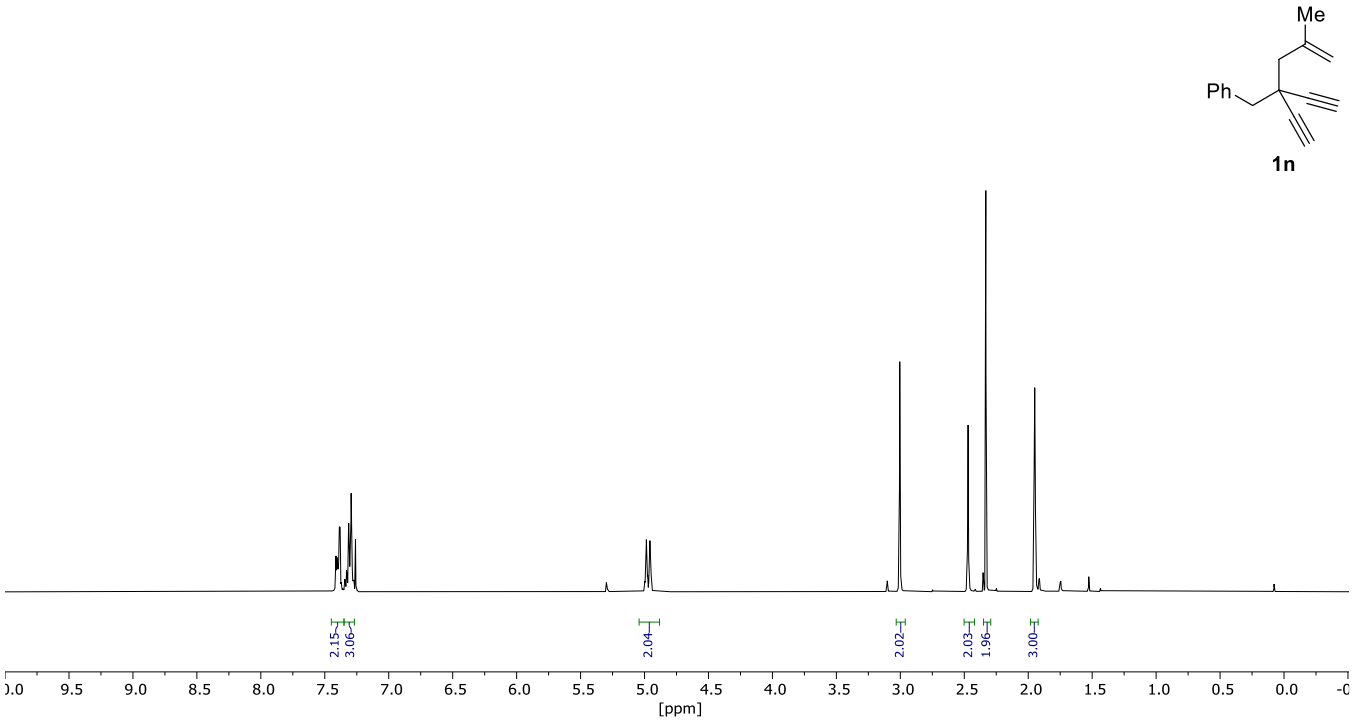
^{13}C NMR (75 MHz, $CDCl_3$) of compound **1l**



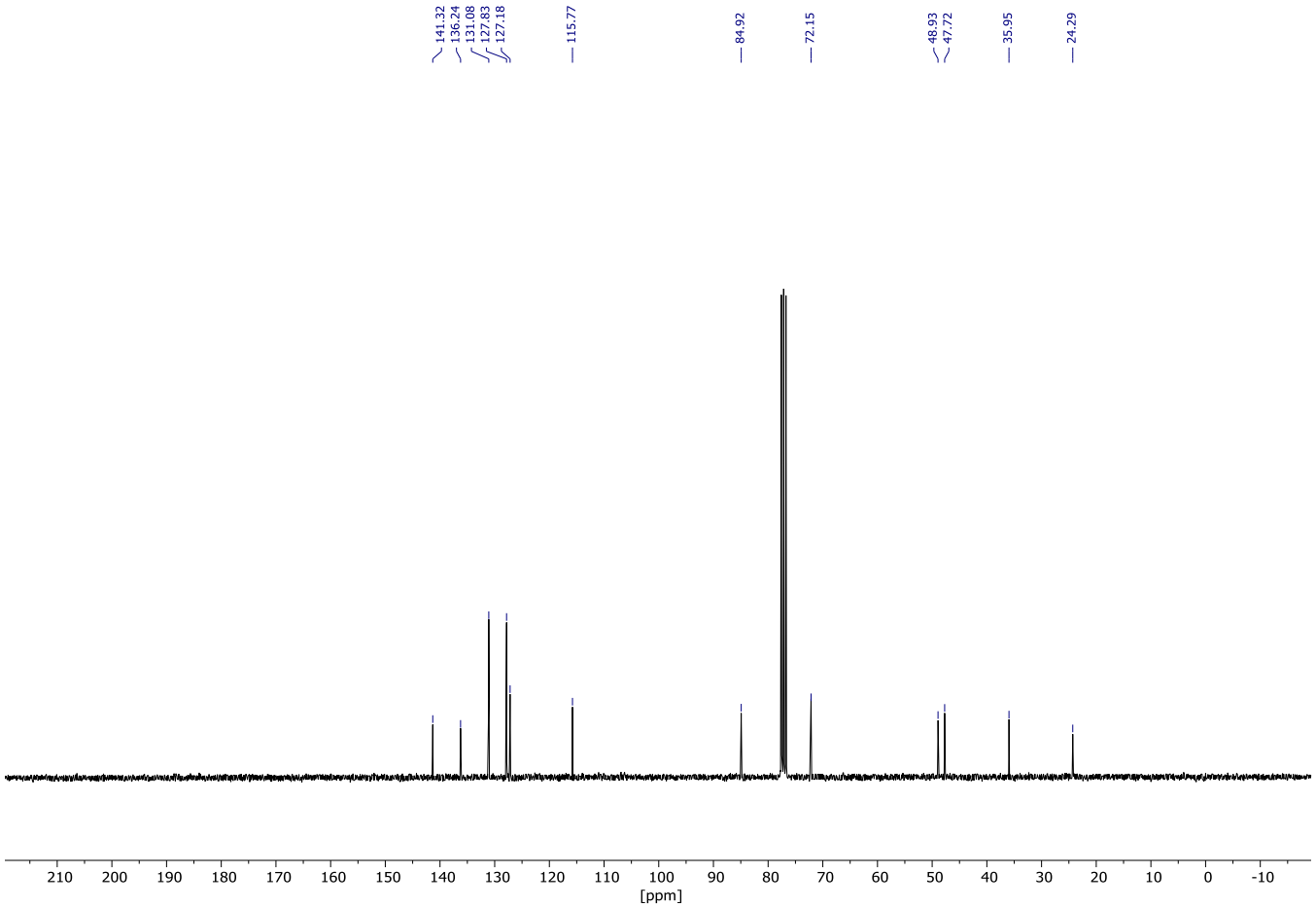
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1m**



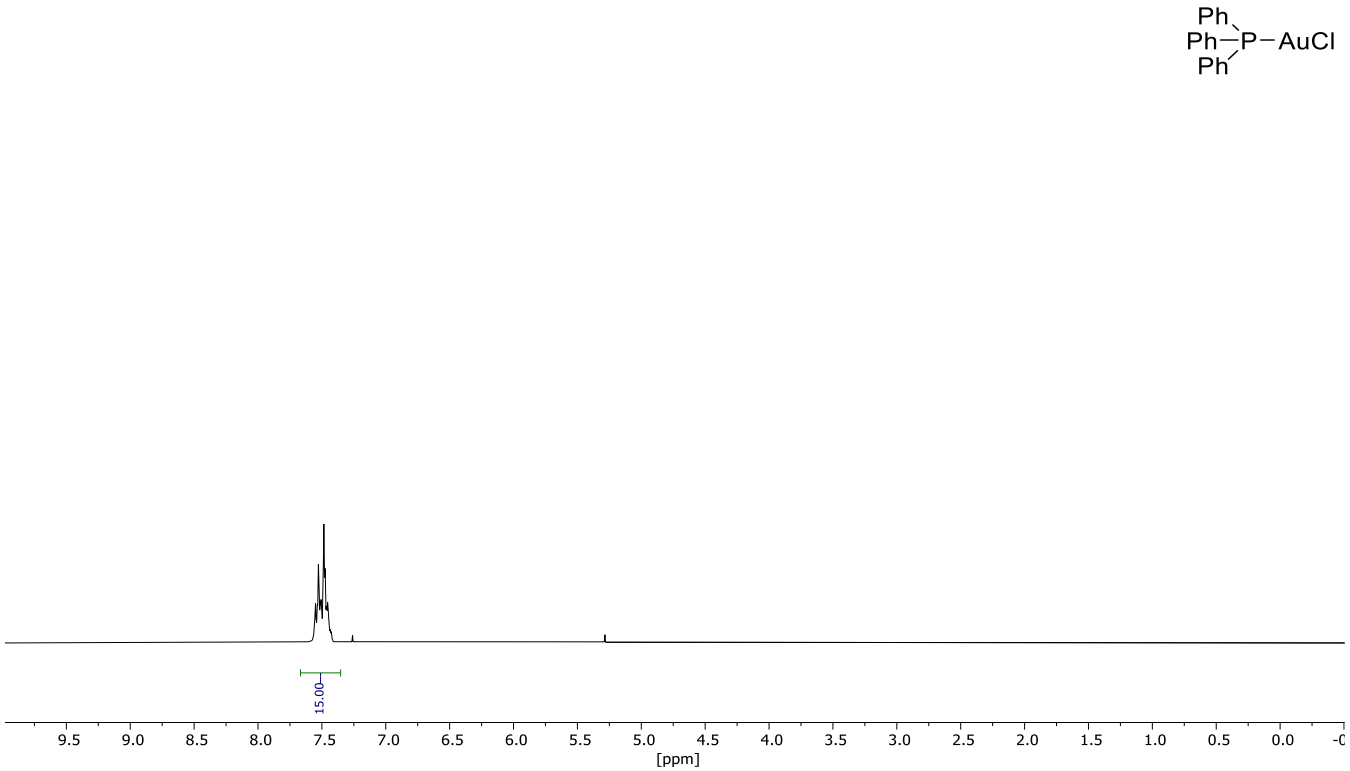
^{13}C NMR (75 MHz, $CDCl_3$) of compound **1m**



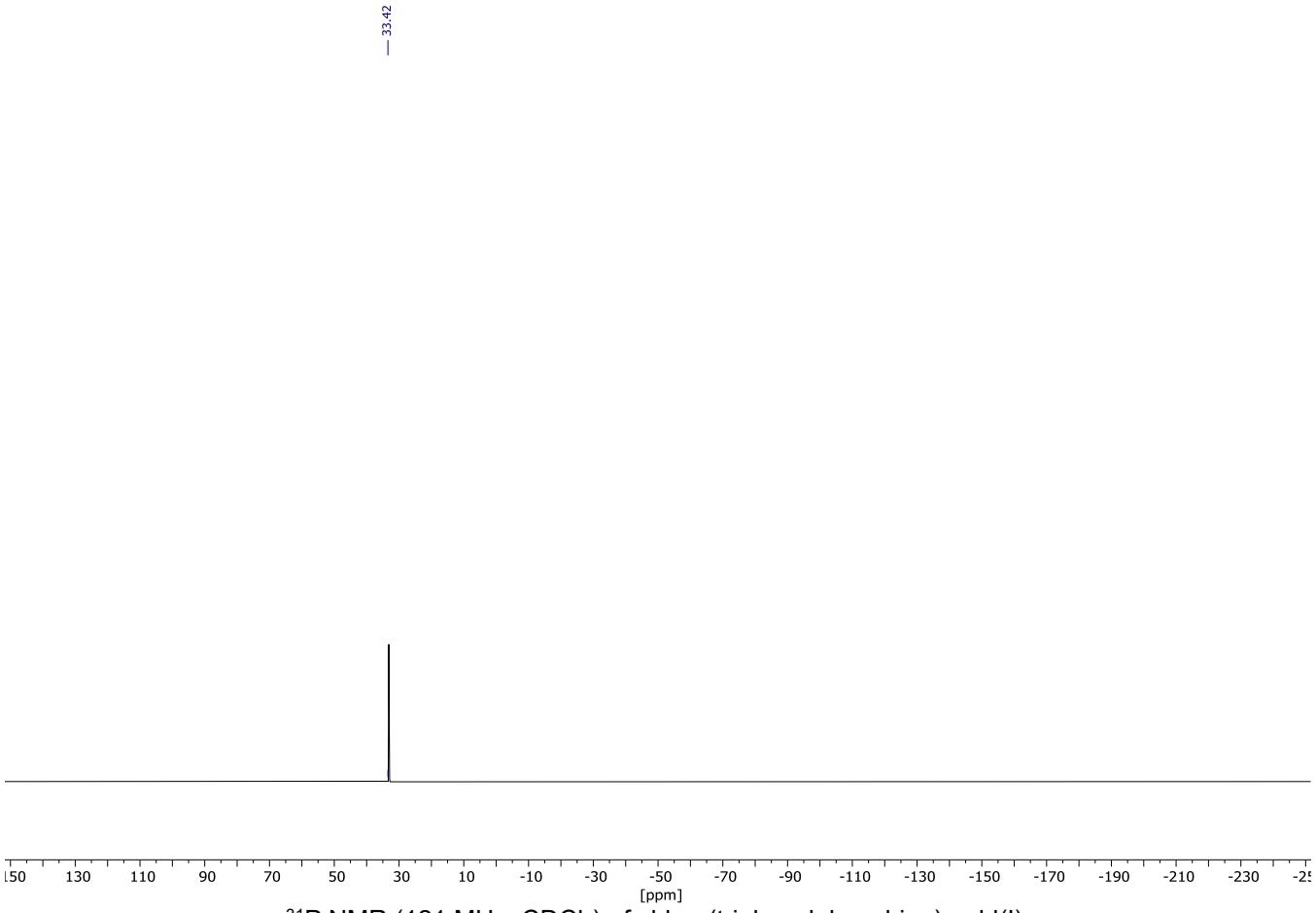
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1n**



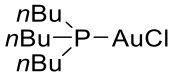
^{13}C NMR (75 MHz, $CDCl_3$) of compound **1n**

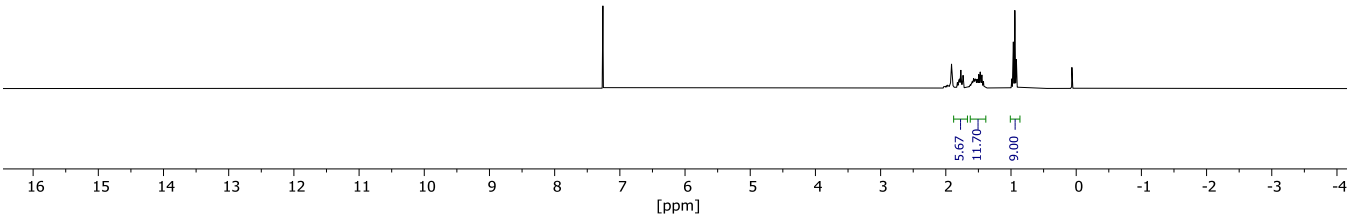


^{1}H NMR (300 MHz, $CDCl_3$) of chloro(triphenylphosphine) gold(I)

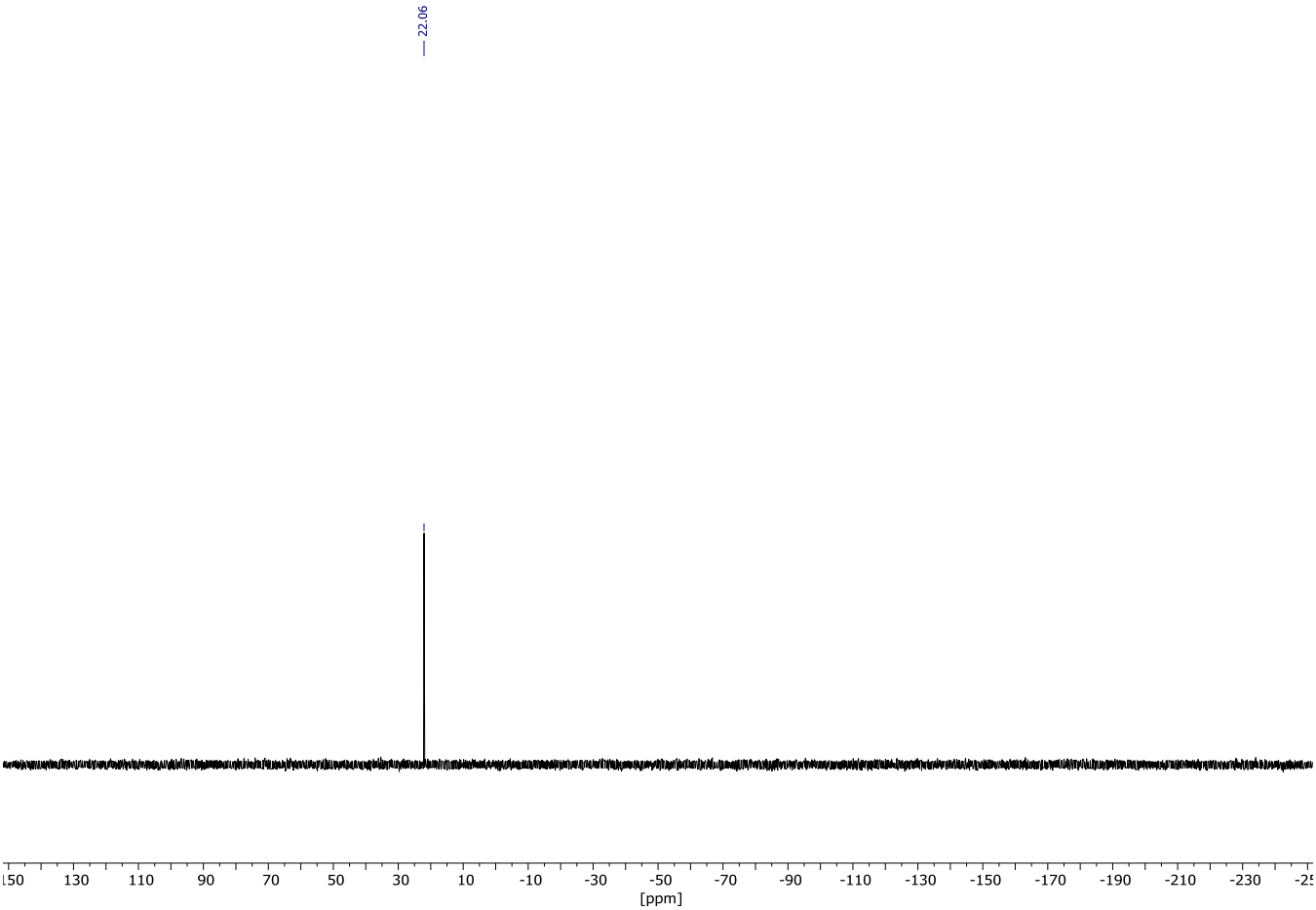


^{31}P NMR (121 MHz, $CDCl_3$) of chloro(triphenylphosphine) gold(I)

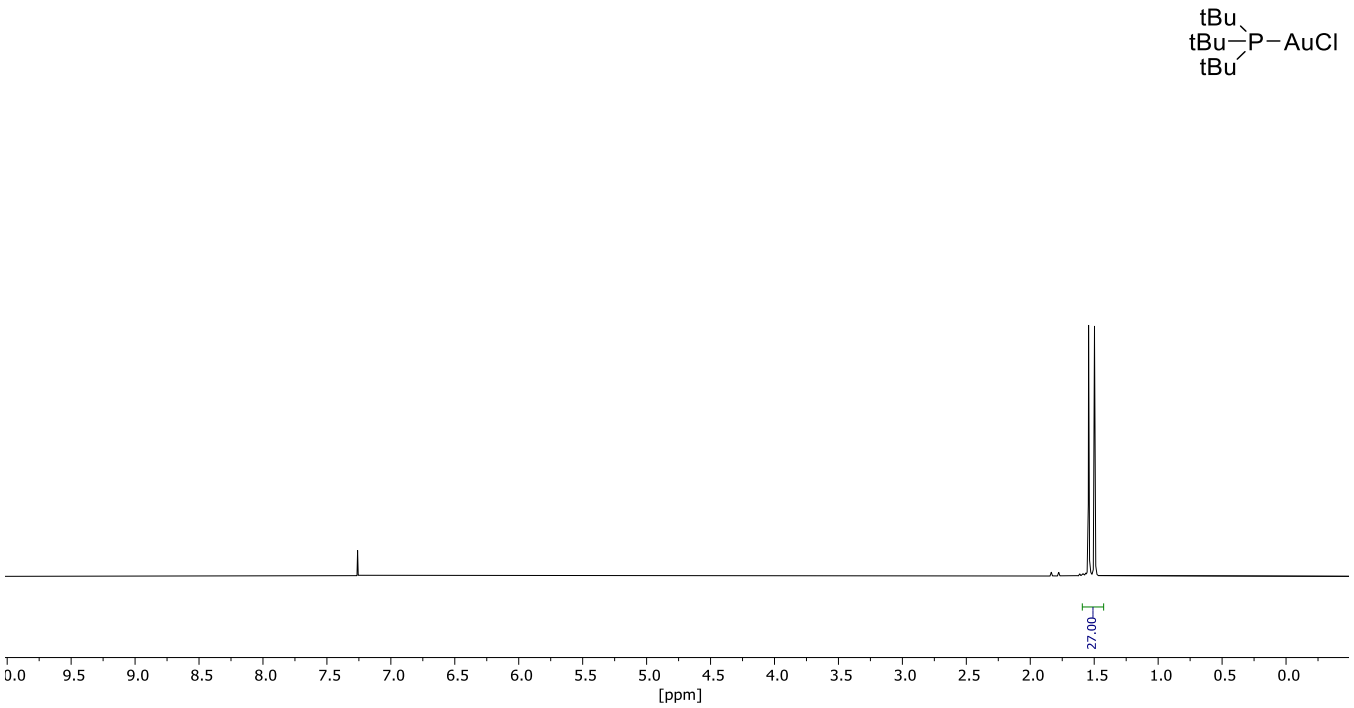




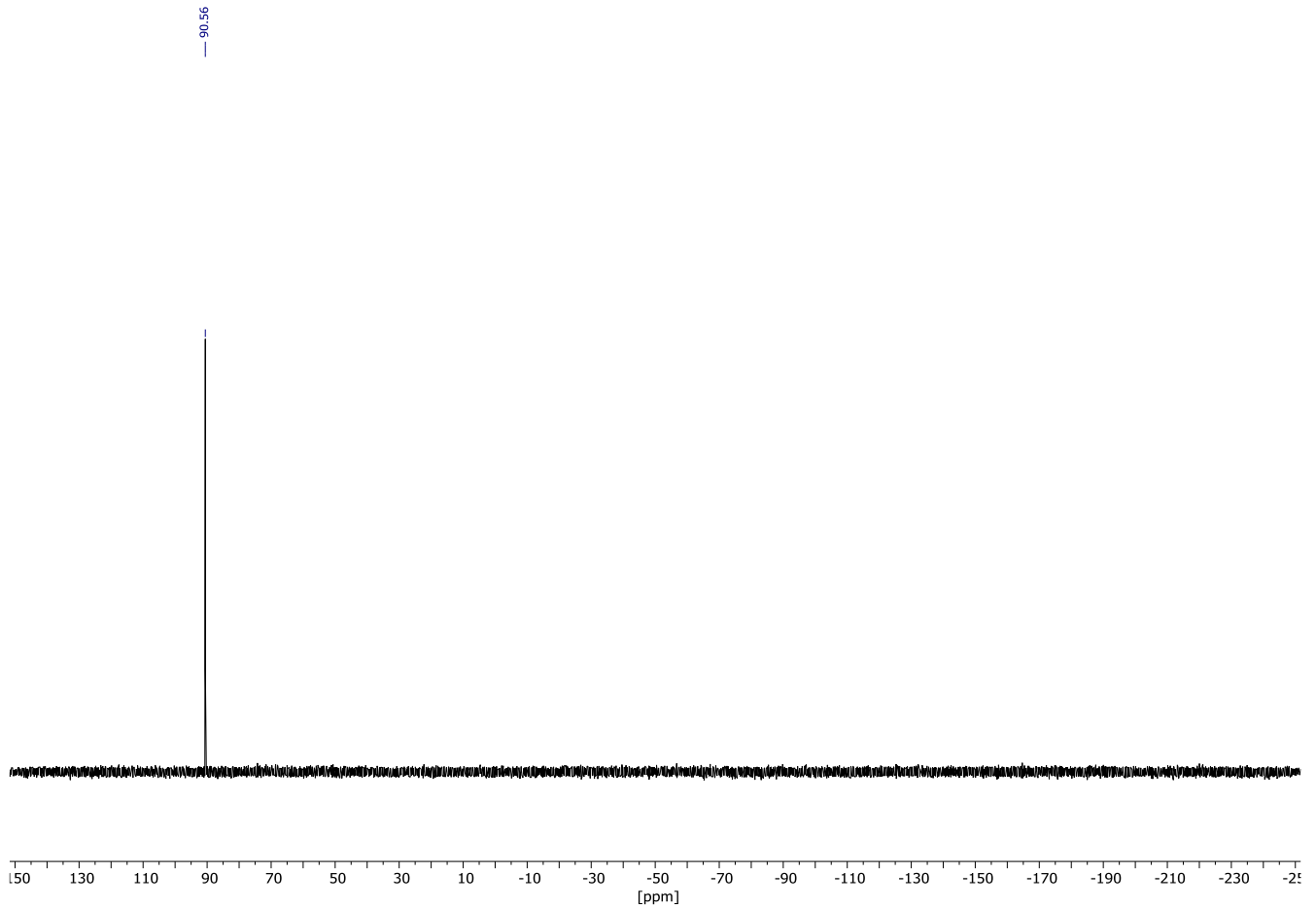
^{1}H NMR (300 MHz, $CDCl_3$) of chloro(tri-*n*-butylphosphine) gold(I)



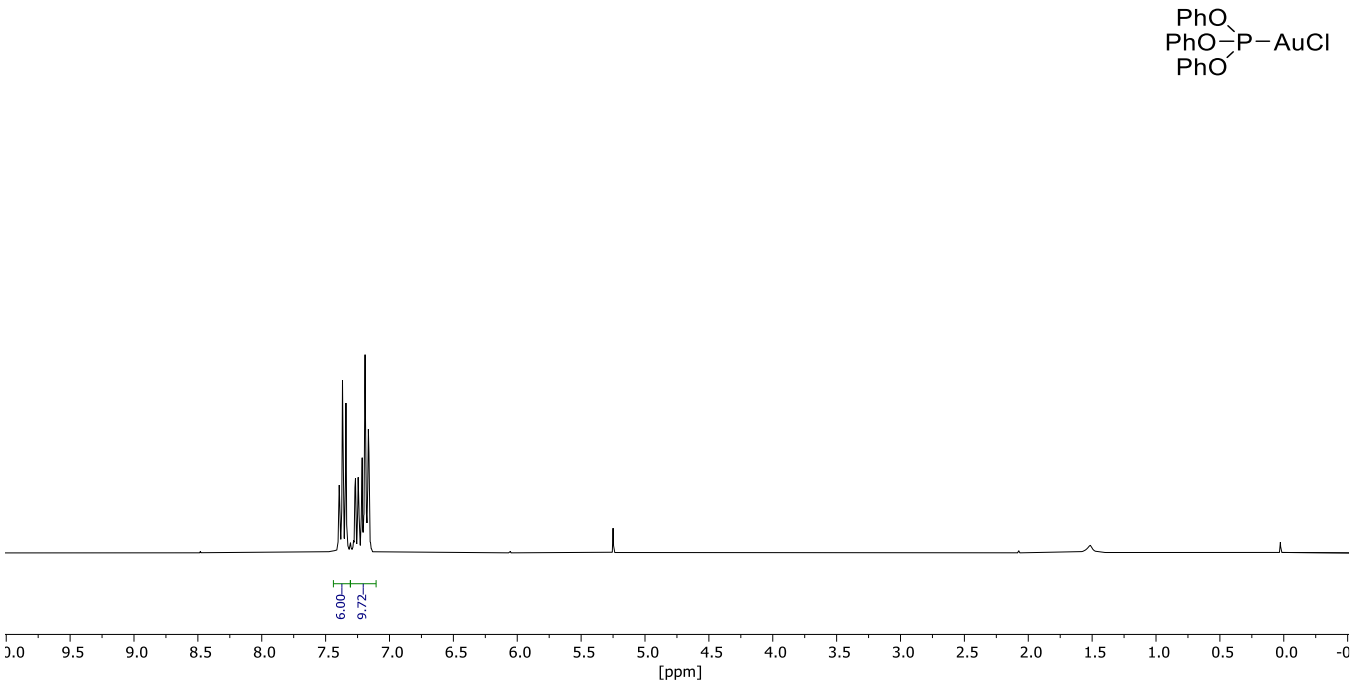
^{31}P NMR (121 MHz, $CDCl_3$) of chloro(tri-*n*-butylphosphine) gold(I)



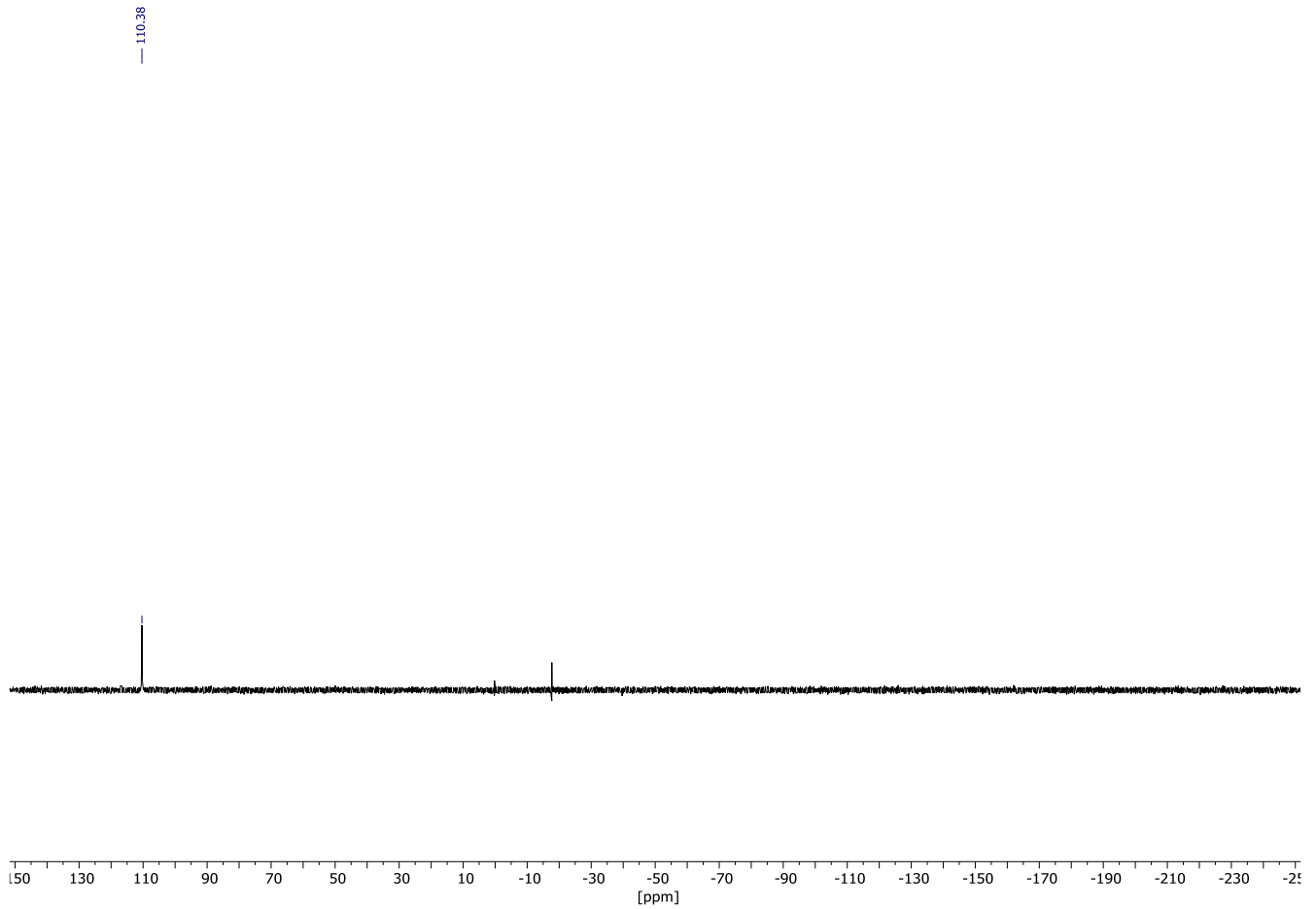
^{1}H NMR (300 MHz, $CDCl_3$) of chloro(tri-*t*-butylphosphine) gold(I)



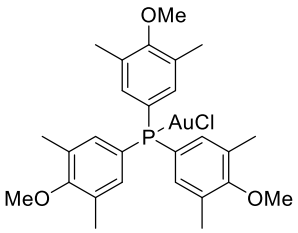
^{31}P NMR (121 MHz, $CDCl_3$) of chloro(tri-*t*-butylphosphine) gold(I)

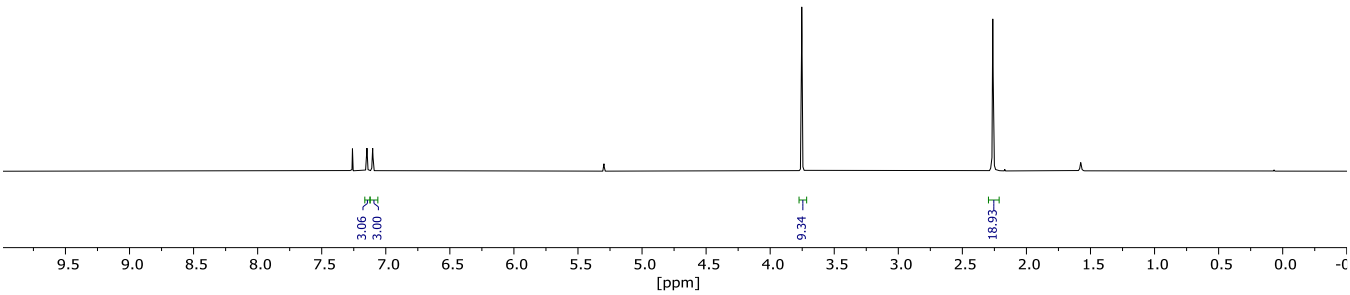


^{1}H NMR (300 MHz, $CDCl_3$) of chloro(triphenylphosphite) gold(I)

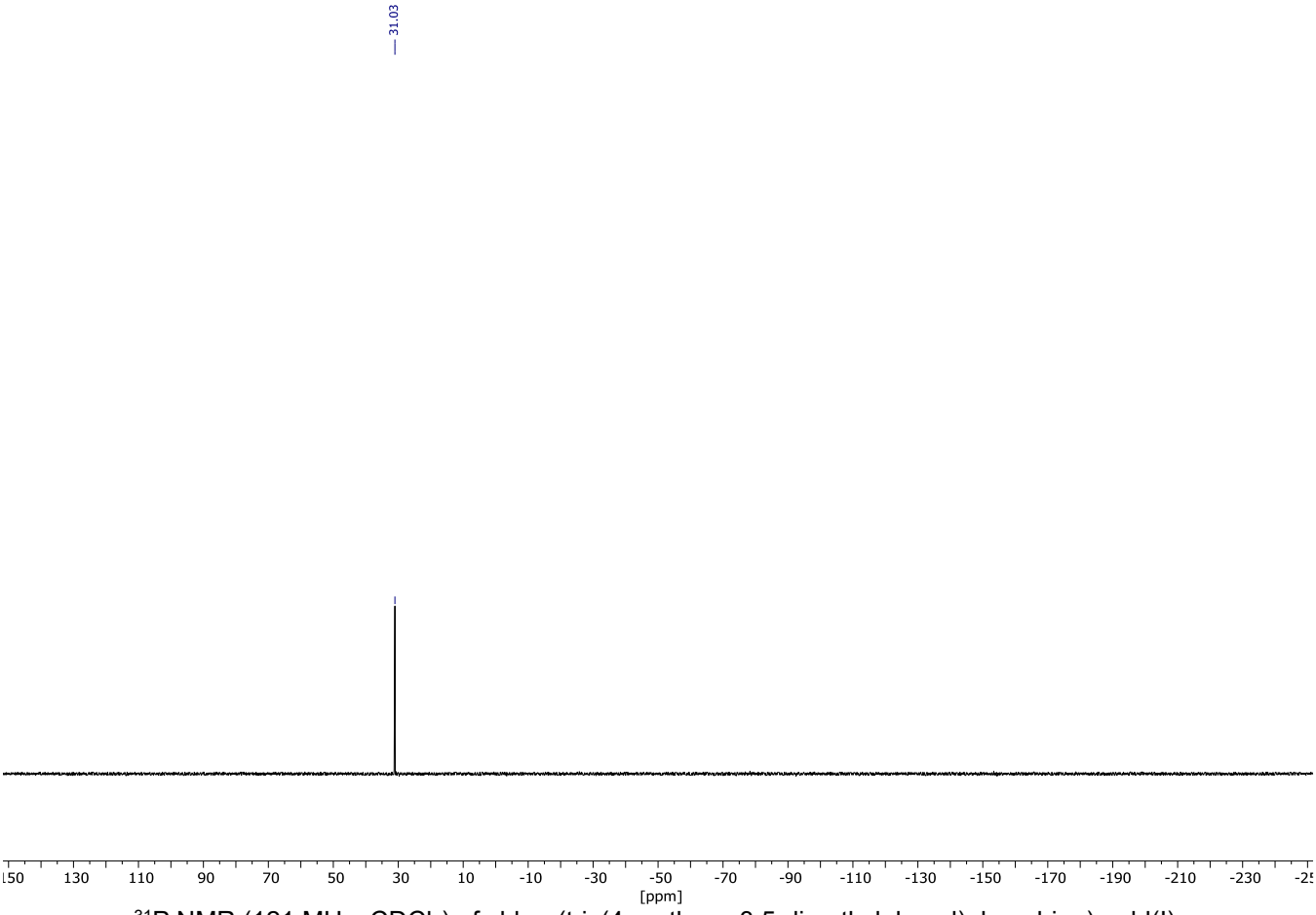


^{31}P NMR (121 MHz, $CDCl_3$) of chloro(triphenylphosphite) gold(I)

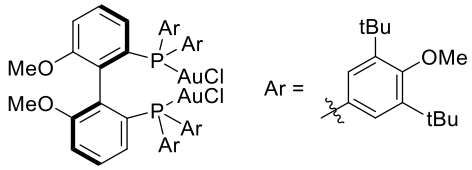




^{1}H NMR (300 MHz, $CDCl_3$) of chloro(tris(4-methoxy-3,5-dimethylphenyl)phosphine) gold(I)

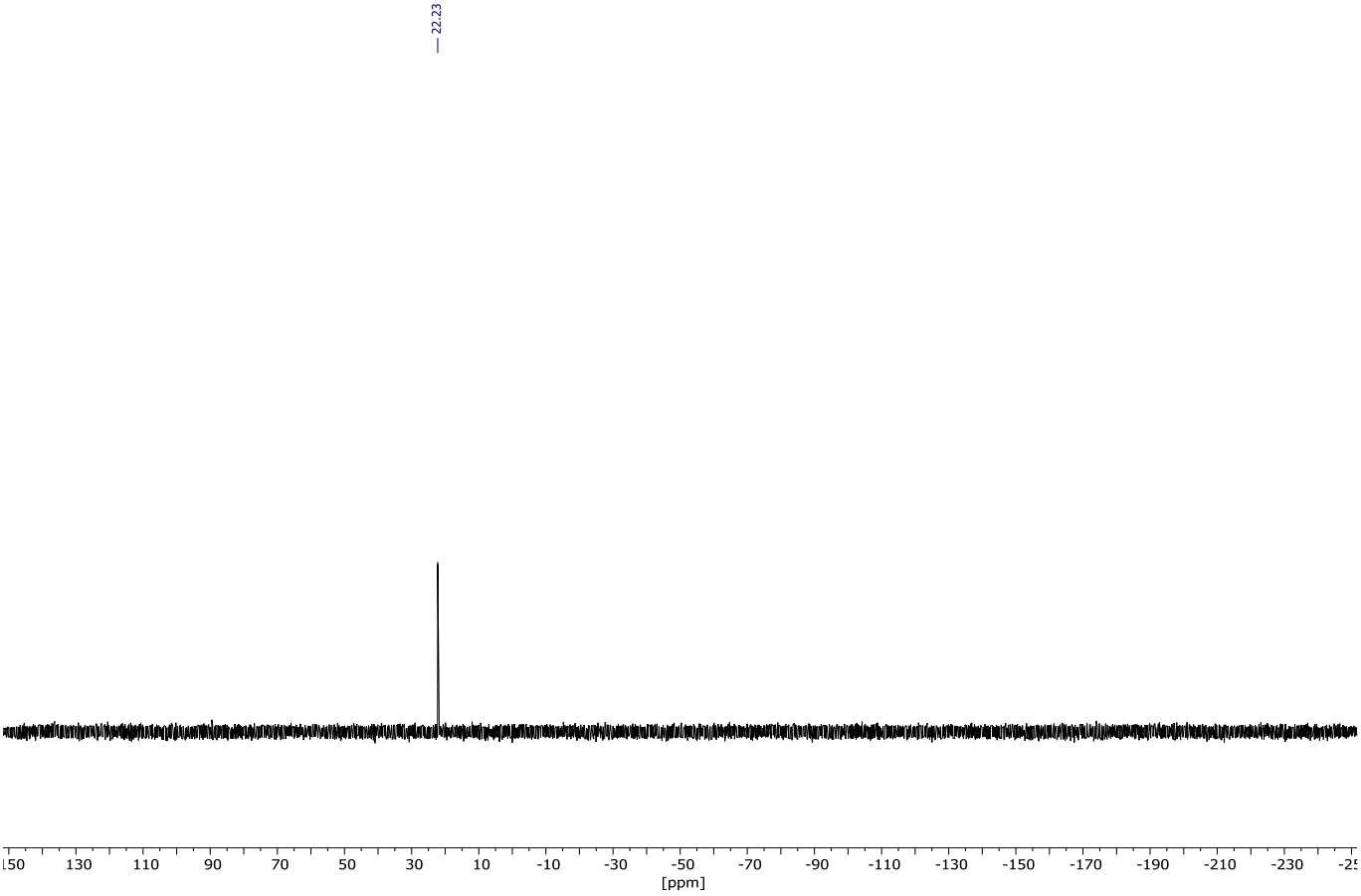


^{31}P NMR (121 MHz, $CDCl_3$) of chloro(tris(4-methoxy-3,5-dimethylphenyl)phosphine) gold(I)

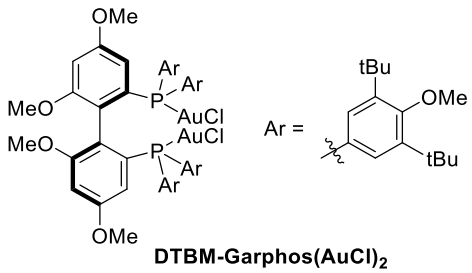


DTBM-MeO-Biphep(AuCl)$_2$

^{1}H NMR (300 MHz, $CDCl_3$) of DTBM-MeO-Biphep(AuCl)$_2$

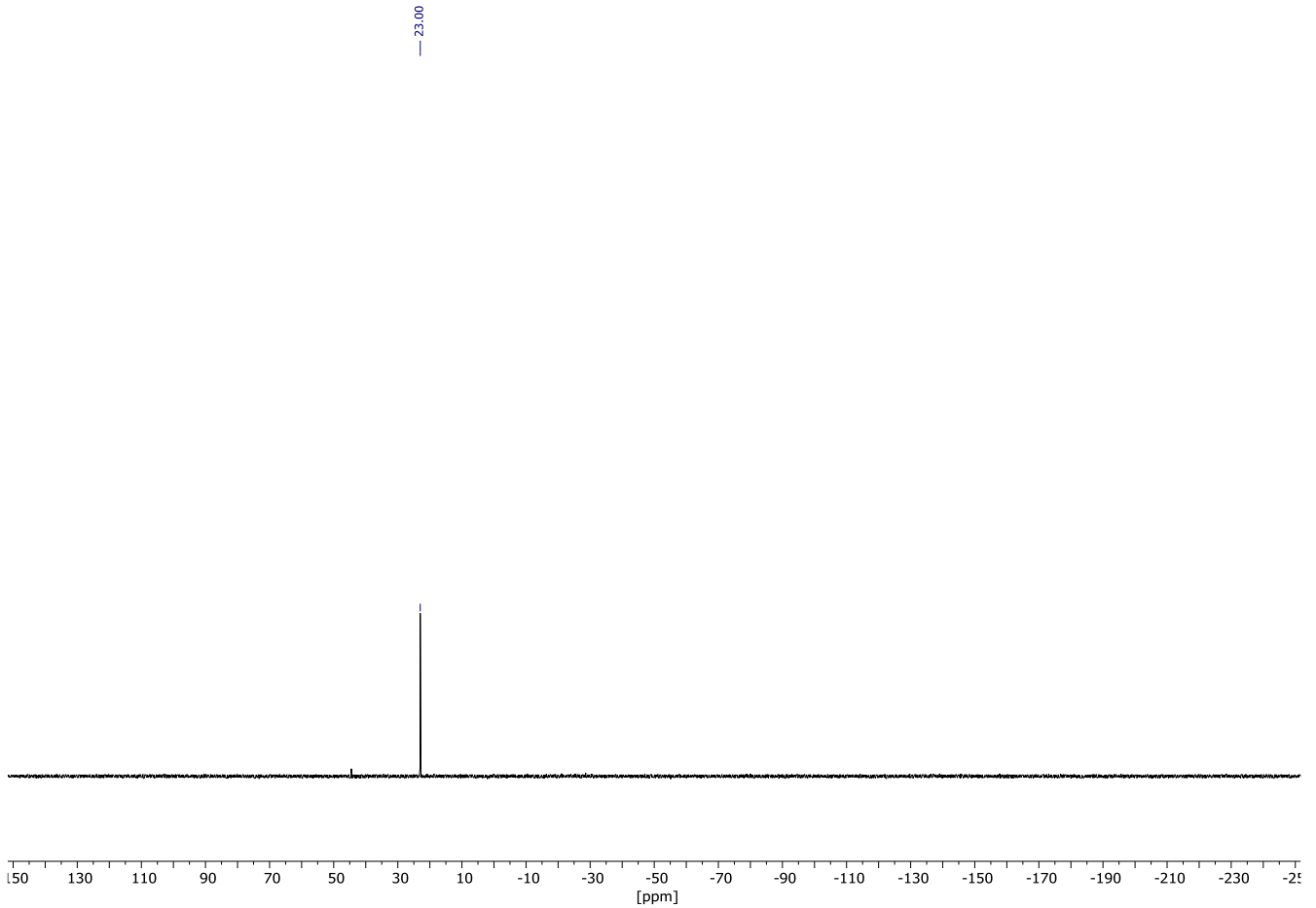


^{31}P NMR (121 MHz, $CDCl_3$) of DTBM-MeO-Biphep(AuCl)$_2$

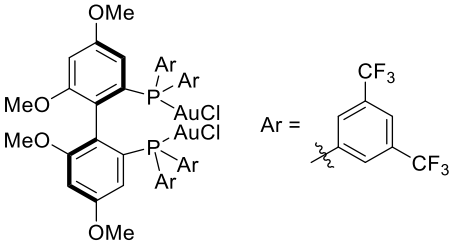


DTBM-Garphos(AuCl)$_2$

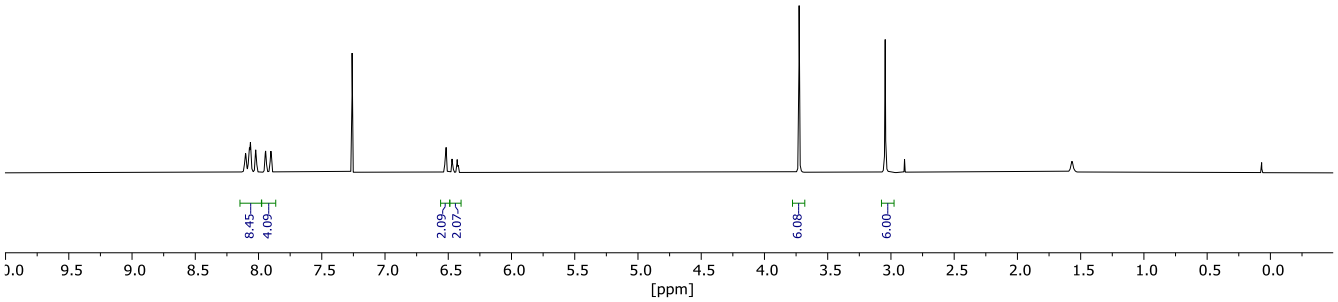
^{1}H NMR (300 MHz, $CDCl_3$) of DTBM-Garphos(AuCl)$_2$



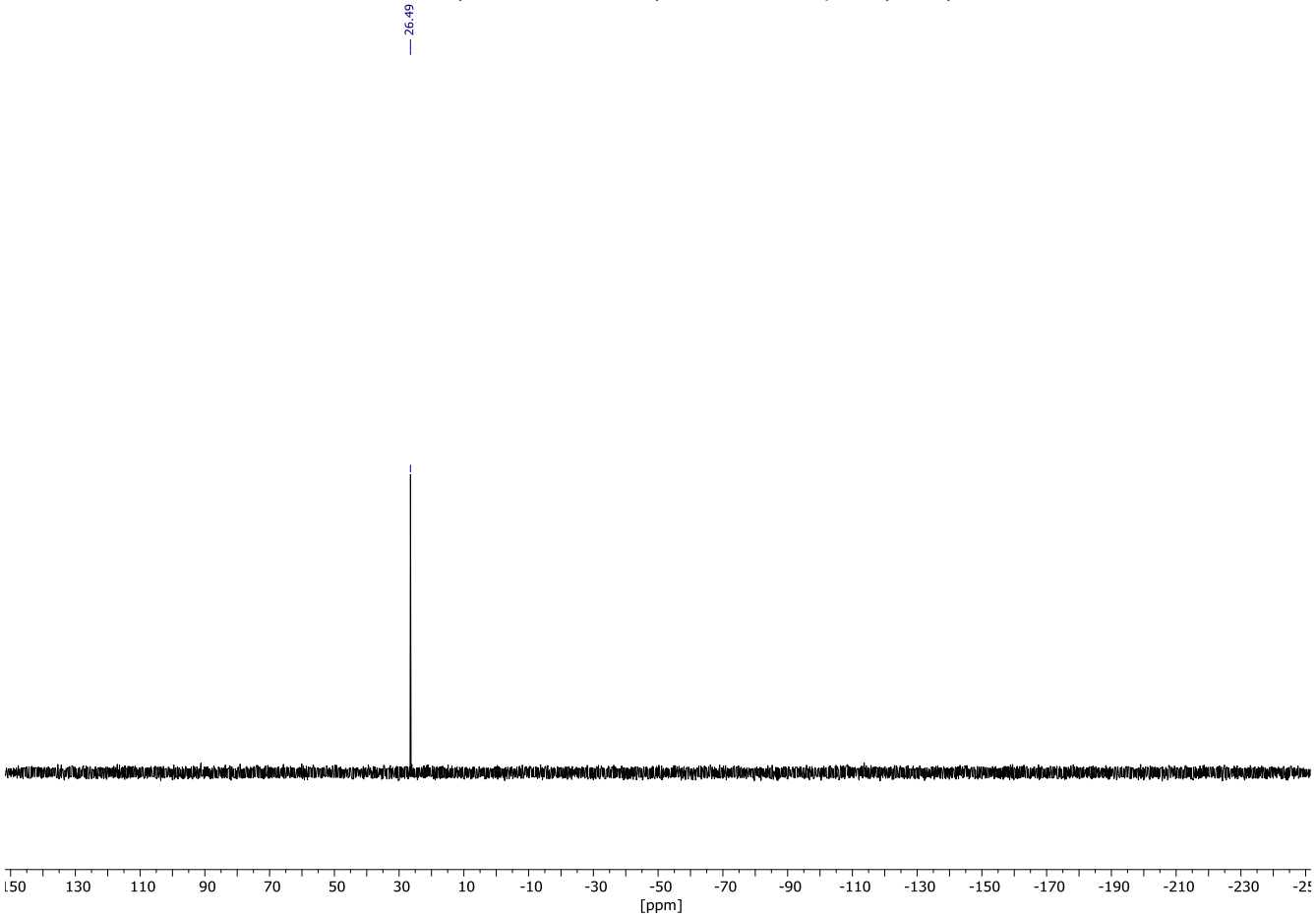
^{31}P NMR (121 MHz, $CDCl_3$) of DTBM-Garphos(AuCl)$_2$



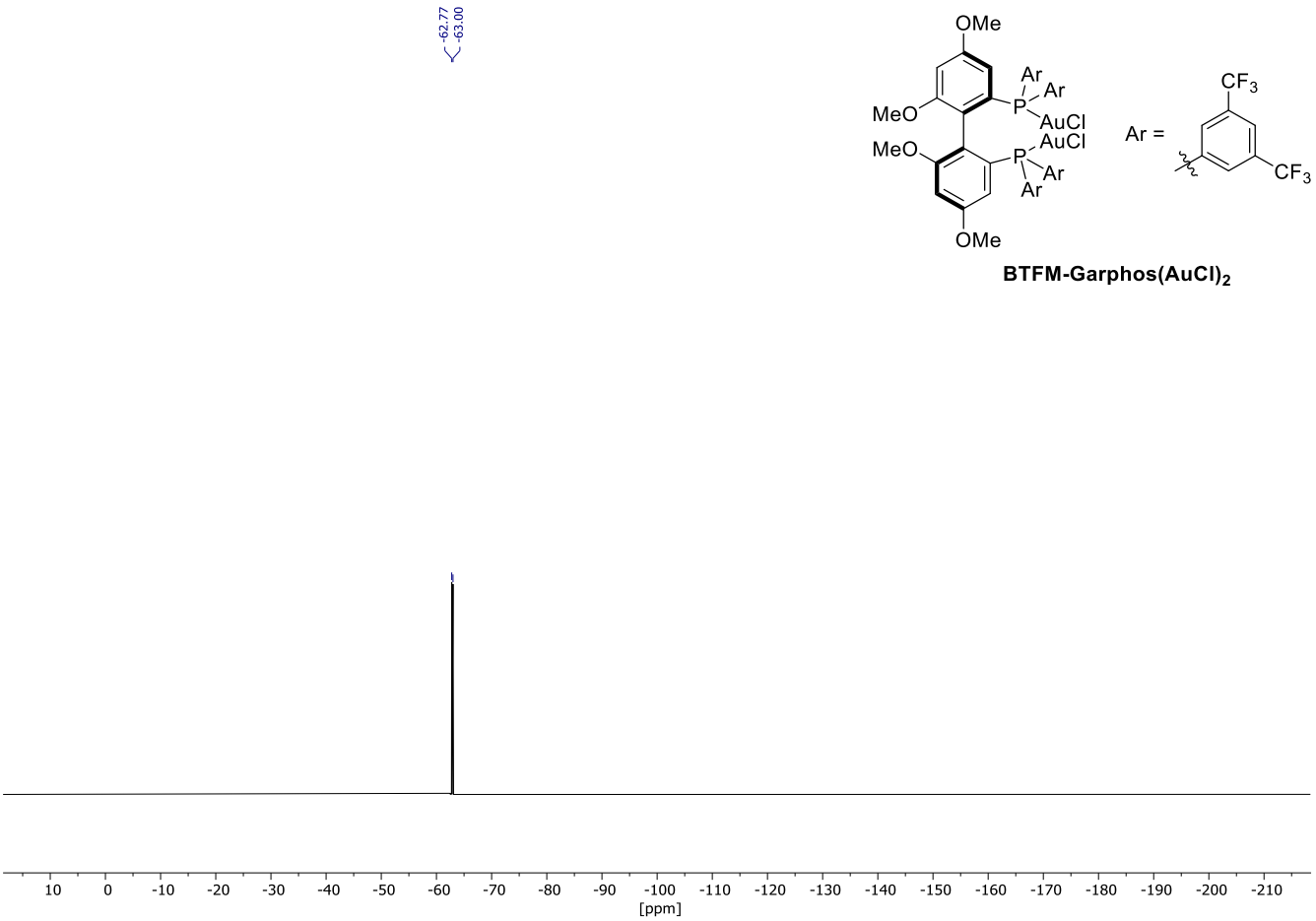
BTFM-Garphos(AuCl)$_2$



^{1}H NMR (300 MHz, $CDCl_3$) of BTFM-Garphos(AuCl)$_2$

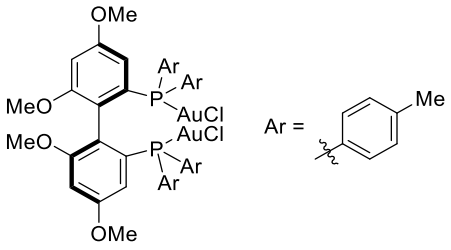


^{31}P NMR (121 MHz, $CDCl_3$) of BTFM-Garphos(AuCl)$_2$

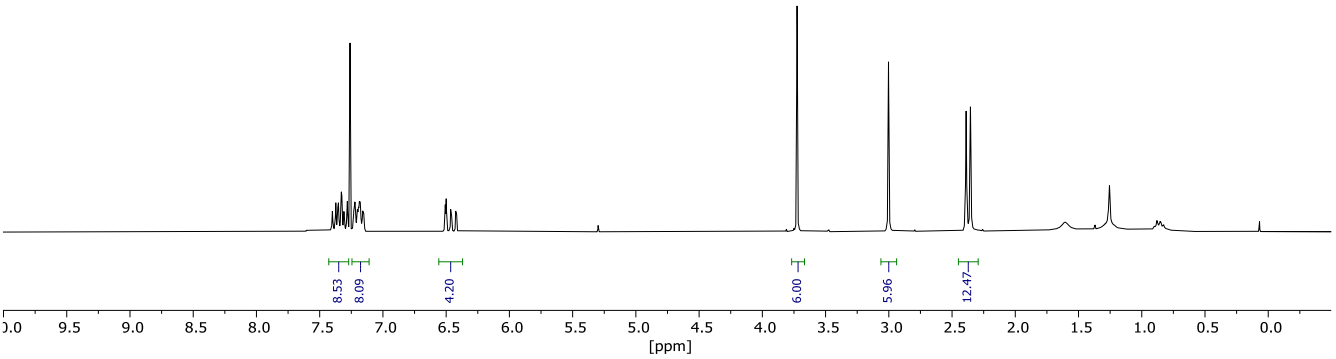


BTFM-Garphos(AuCl)$_2$

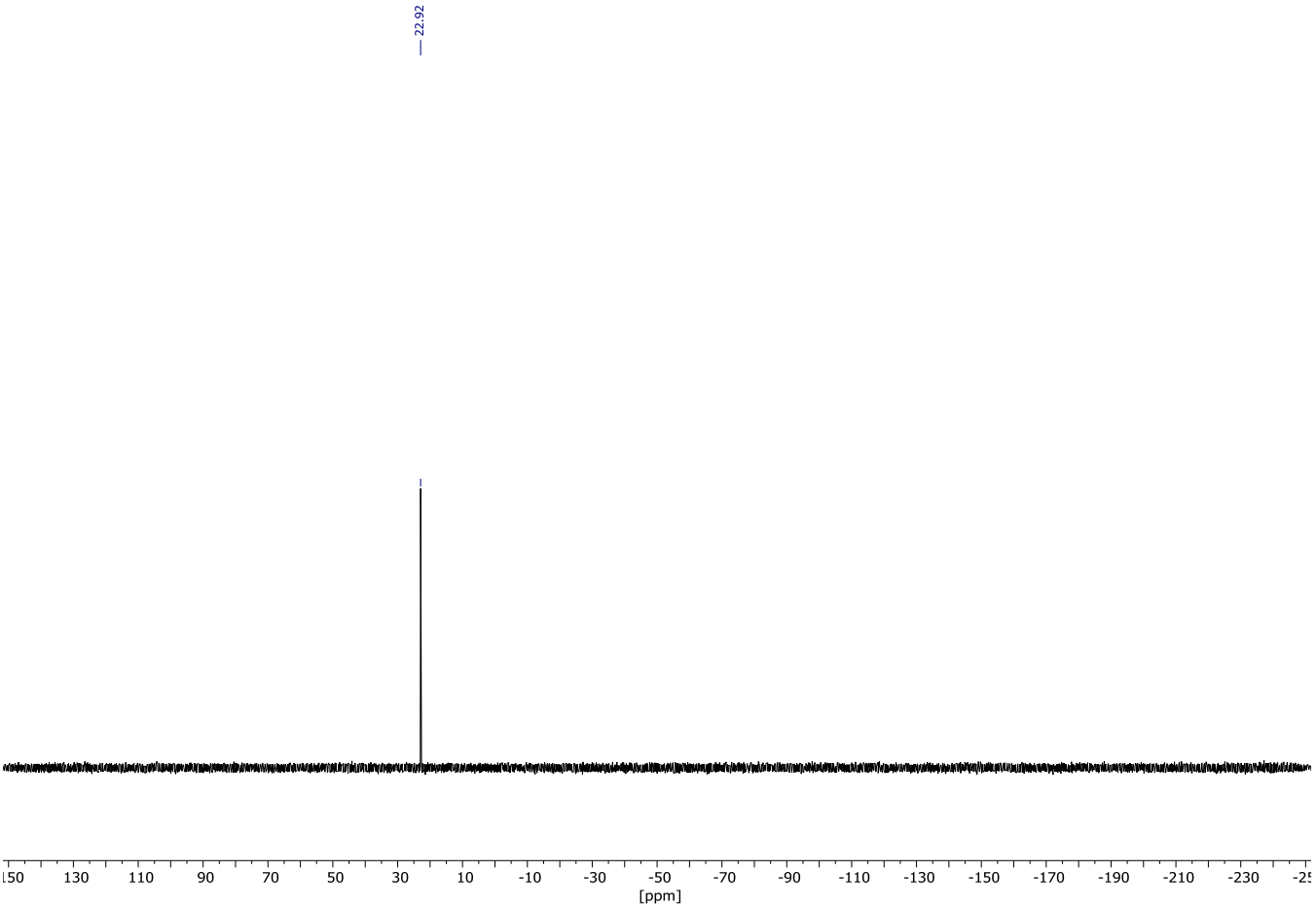
^{19}F NMR (282 MHz, $CDCl_3$) of BTFM-Garphos(AuCl)$_2$



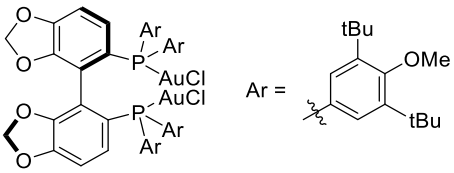
Tol-Garphos(AuCl)$_2$



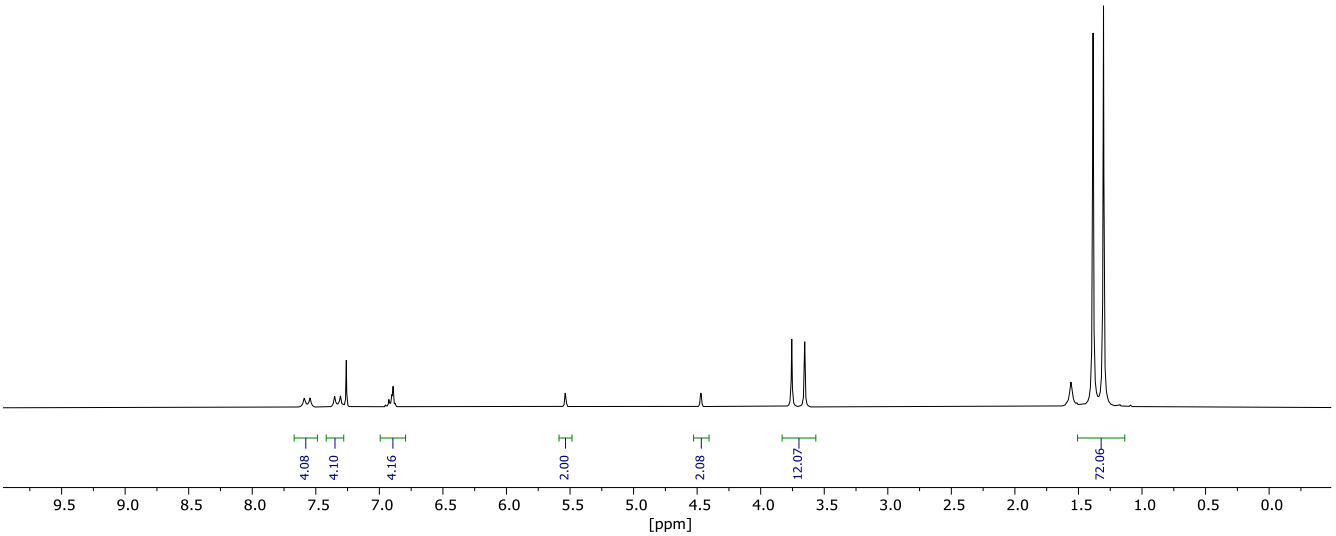
^{1}H NMR (300 MHz, $CDCl_3$) of Tol-Garphos(AuCl)$_2$



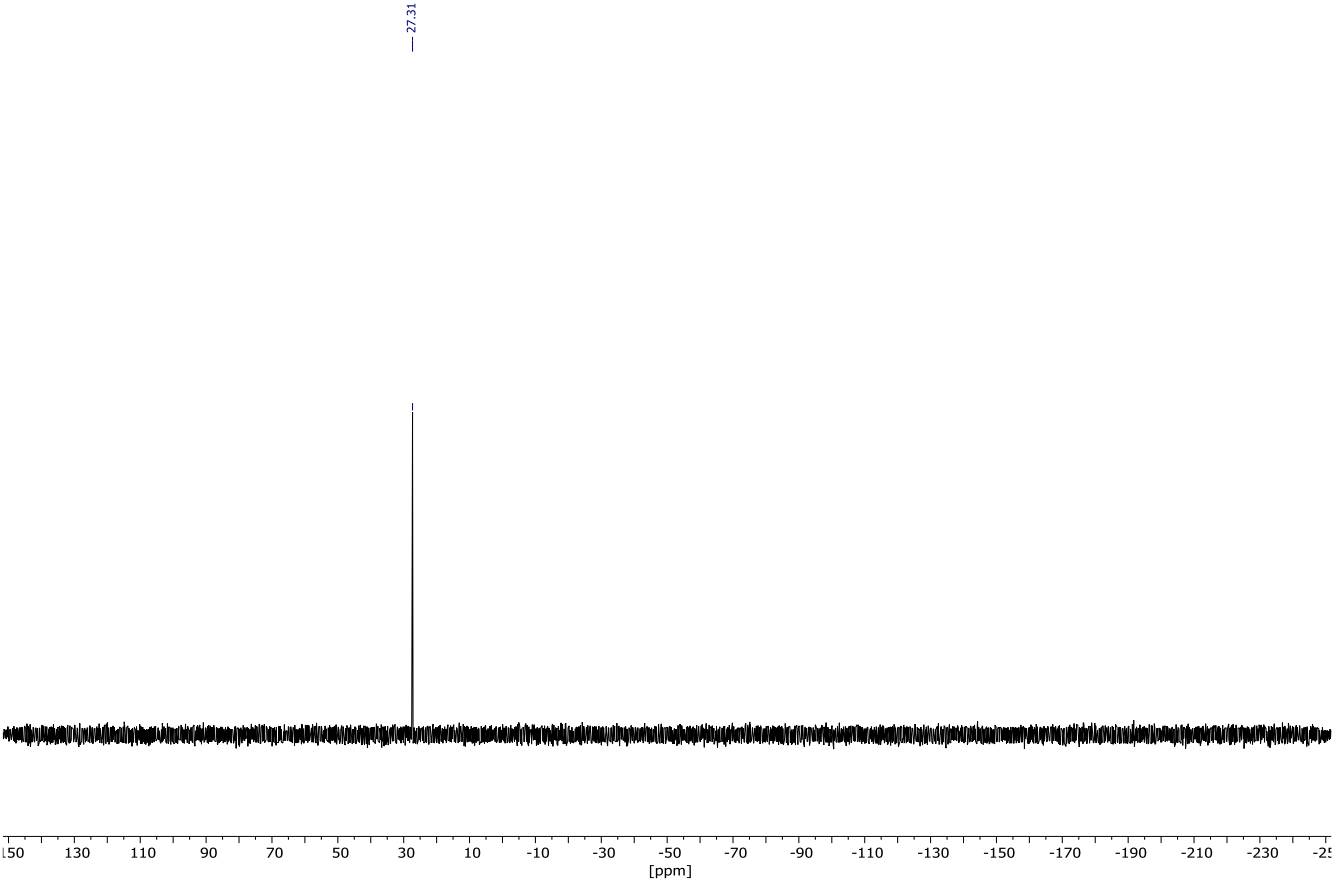
^{31}P NMR (121 MHz, $CDCl_3$) of Tol-Garphos(AuCl)$_2$



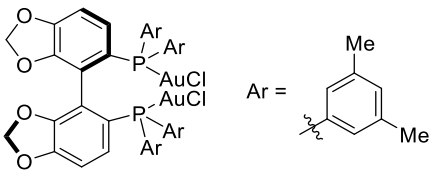
DTBM-Segphos(AuCl)$_2$



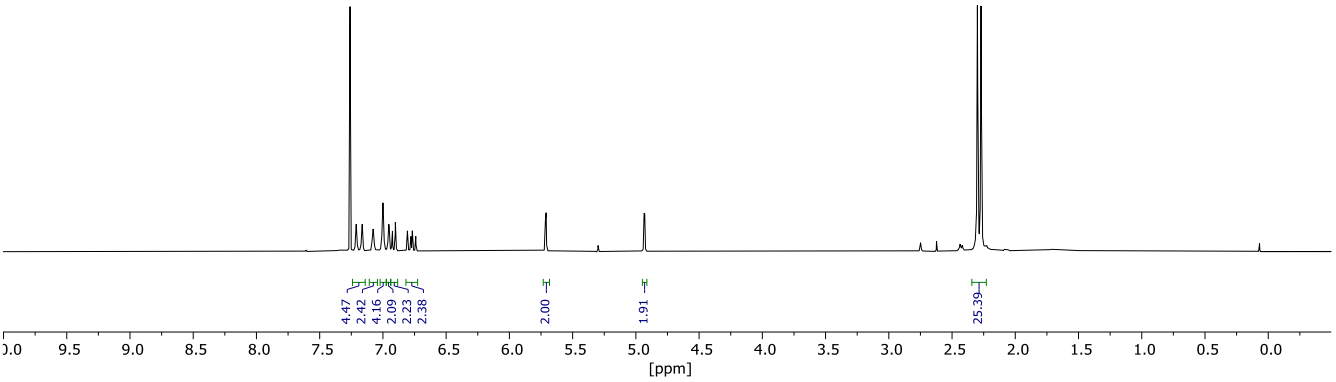
^{1}H NMR (300 MHz, $CDCl_3$) of DTBM-Segphos(AuCl)$_2$



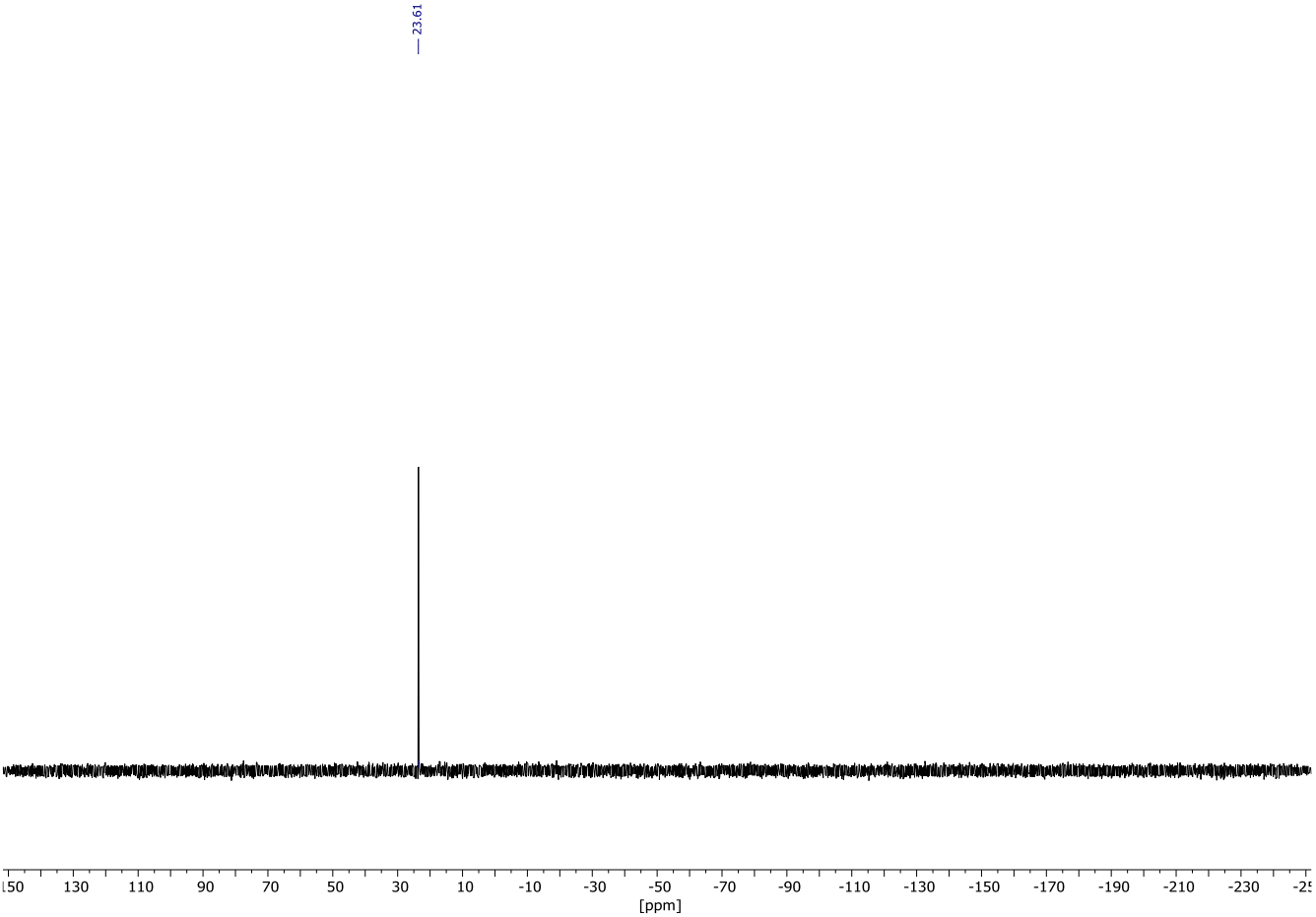
^{31}P NMR (121 MHz, $CDCl_3$) of DTBM-Segphos(AuCl)$_2$



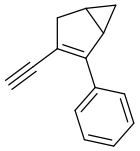
DM-Segphos(AuCl)$_2$



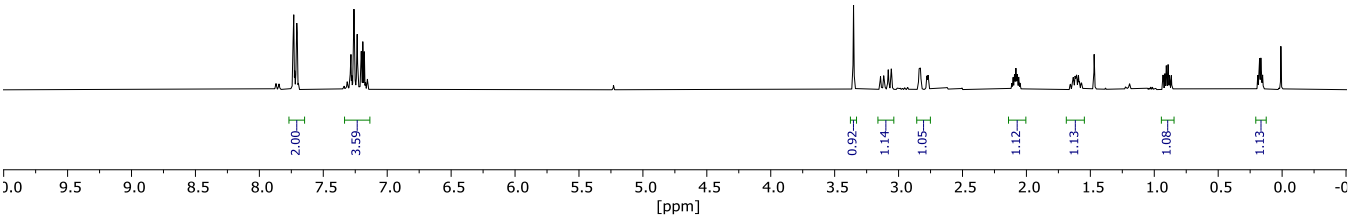
^{1}H NMR (300 MHz, $CDCl_3$) of DM-Segphos(AuCl)$_2$



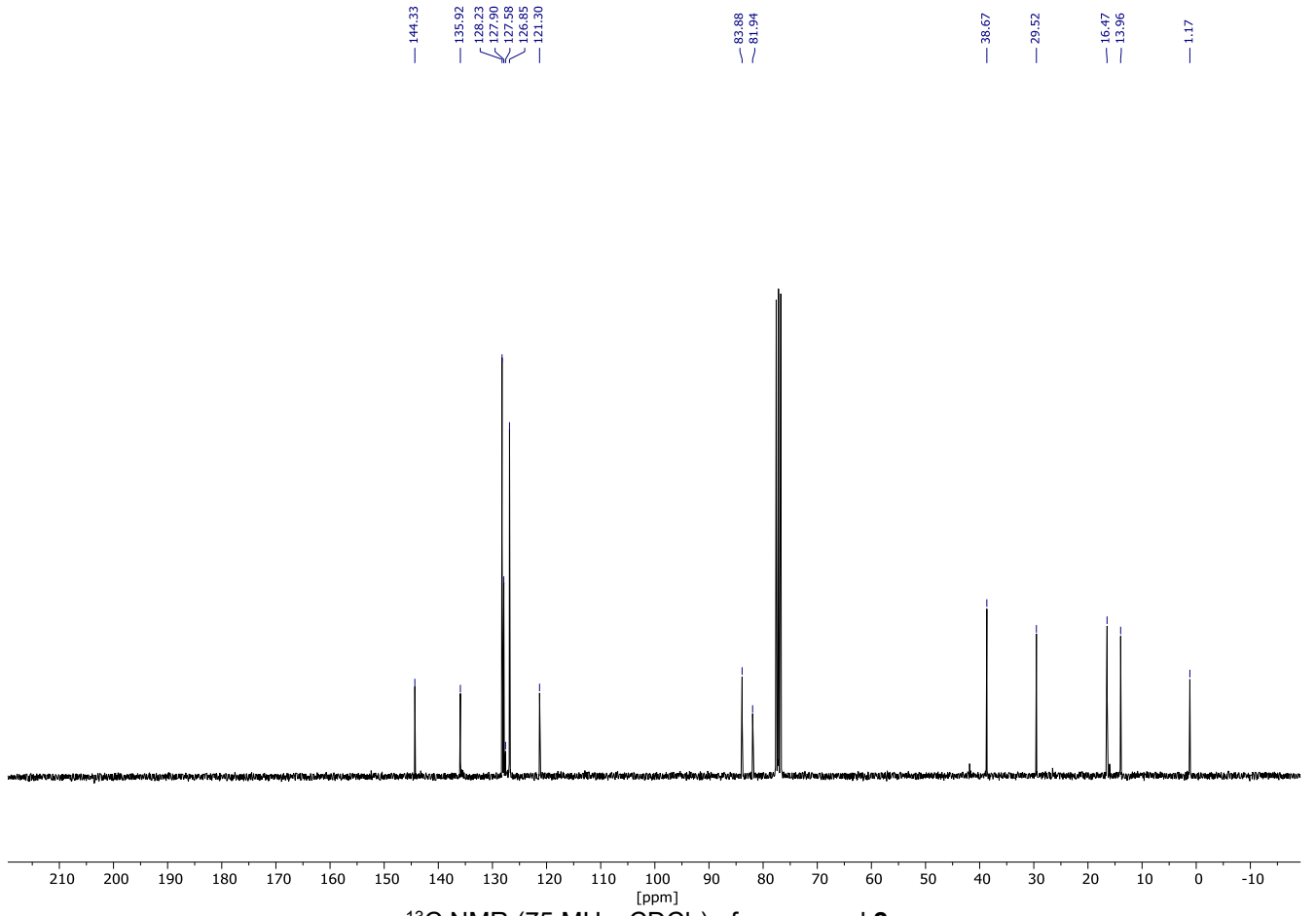
^{31}P NMR (121 MHz, $CDCl_3$) of DM-Segphos(AuCl)$_2$



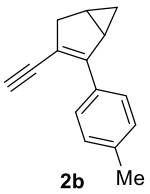
2a



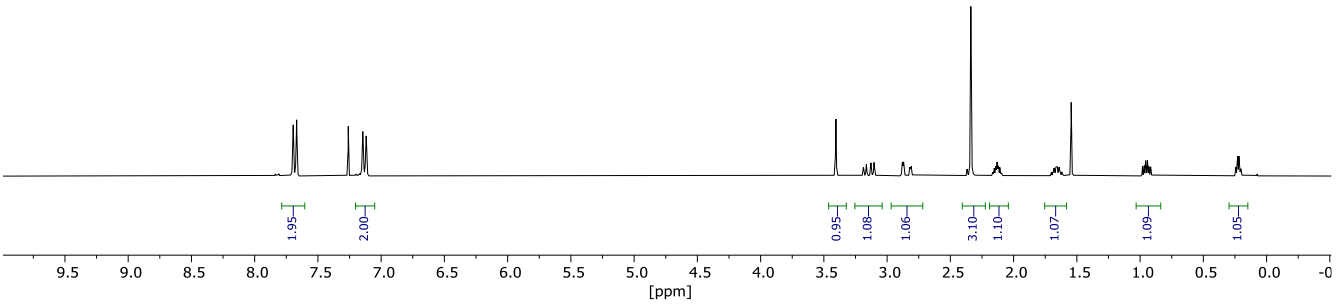
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2a**



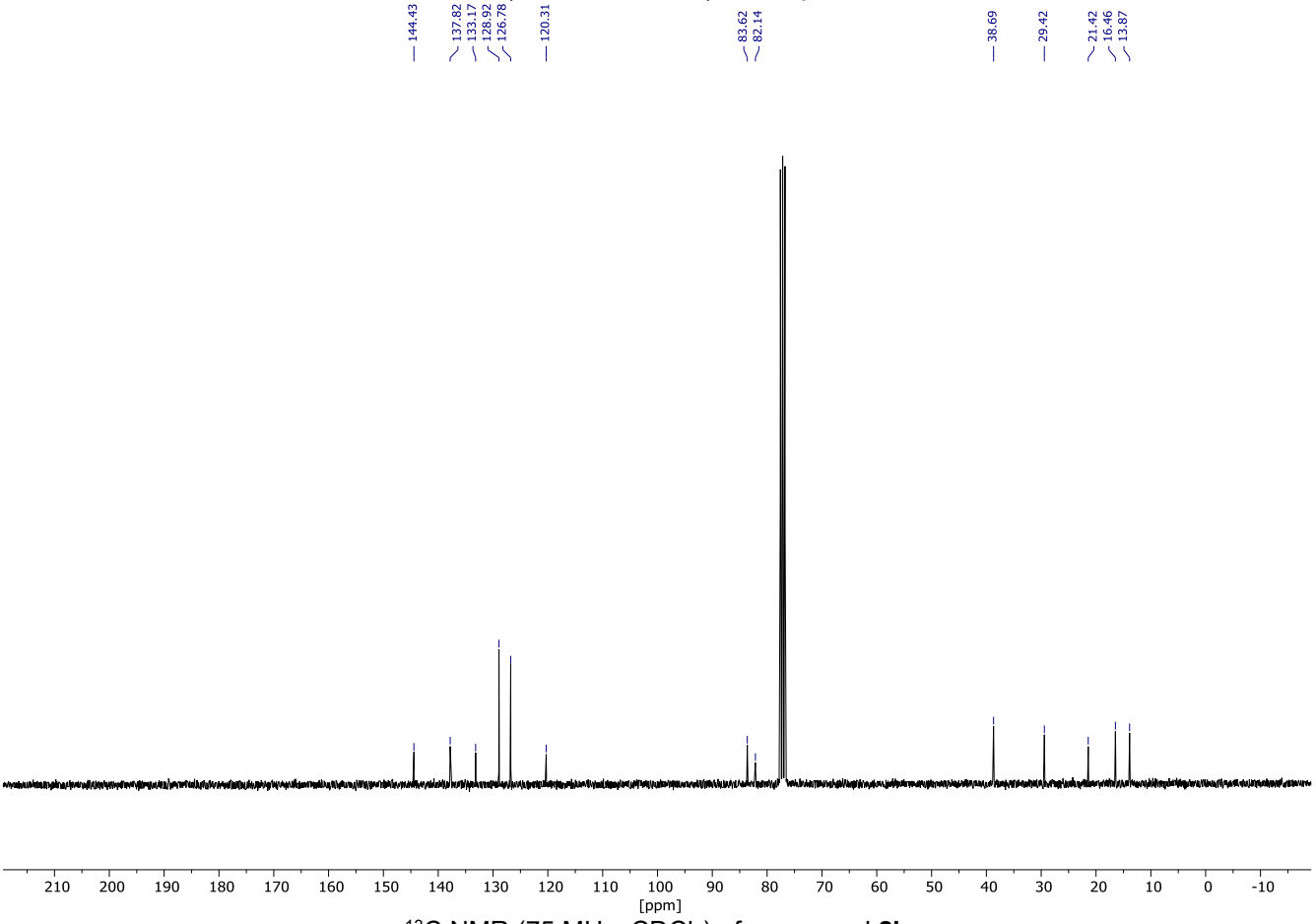
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2a**



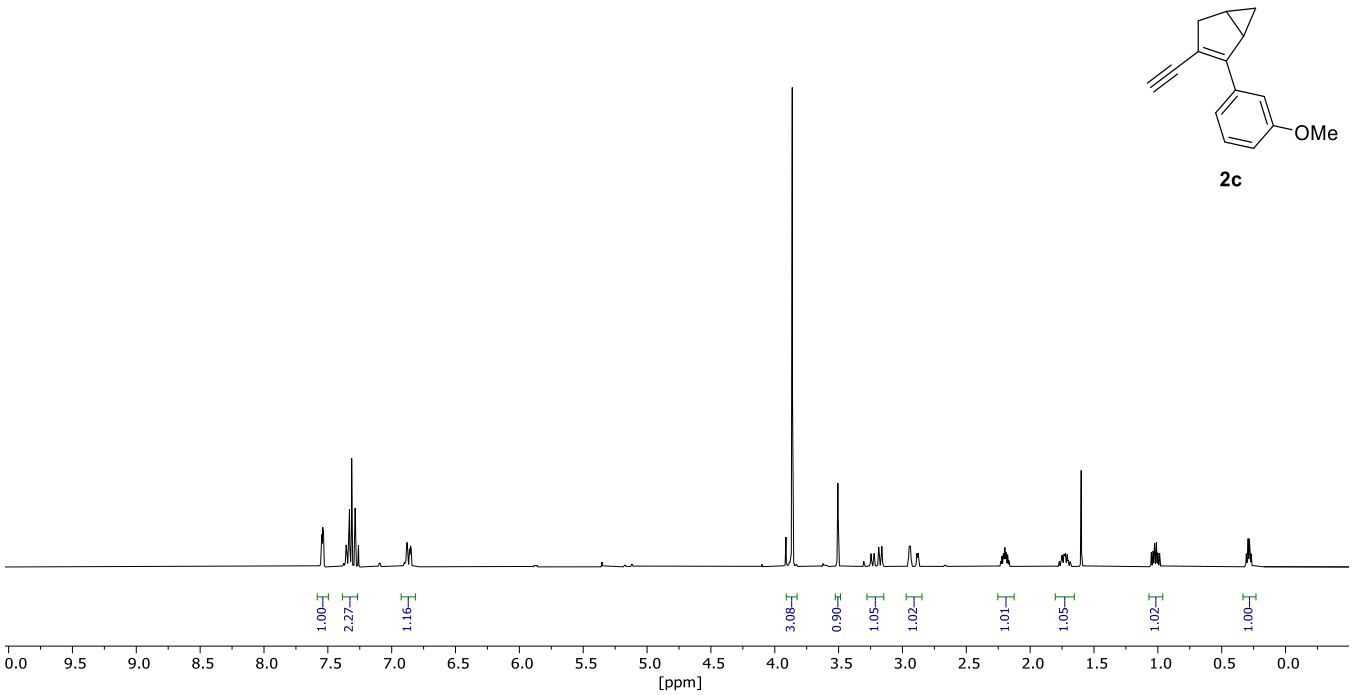
2b



^{1}H NMR (300 MHz, $CDCl_3$) of compound **2b**

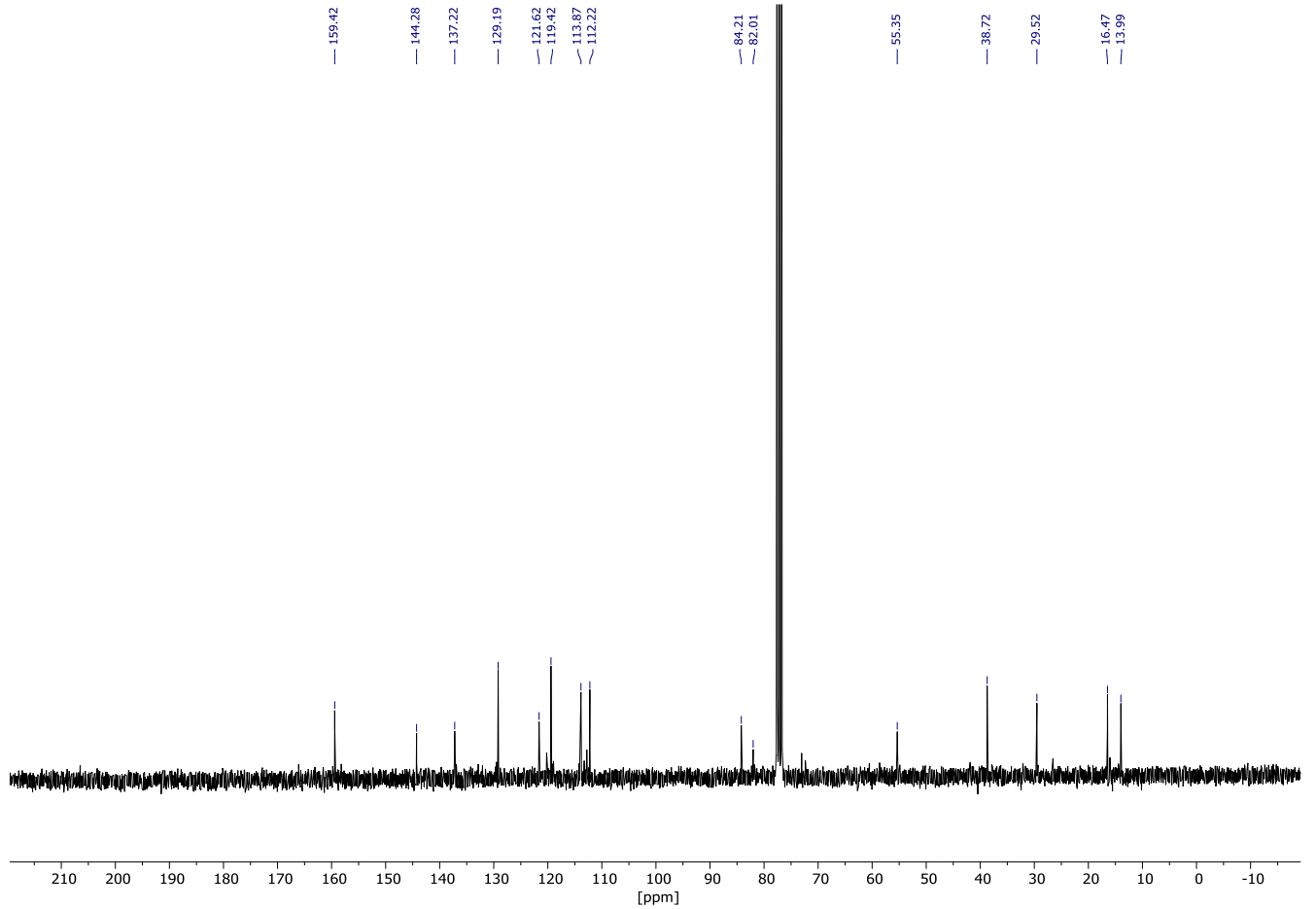


^{13}C NMR (75 MHz, $CDCl_3$) of compound **2b**

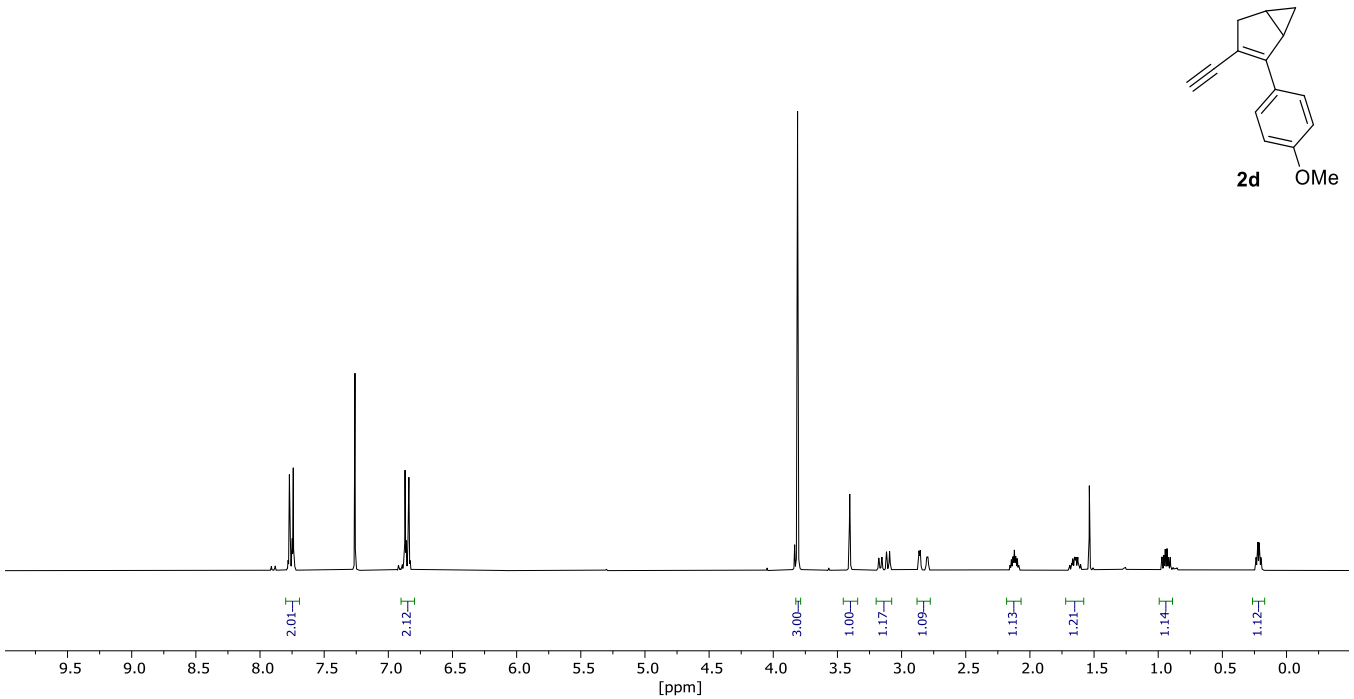


2c

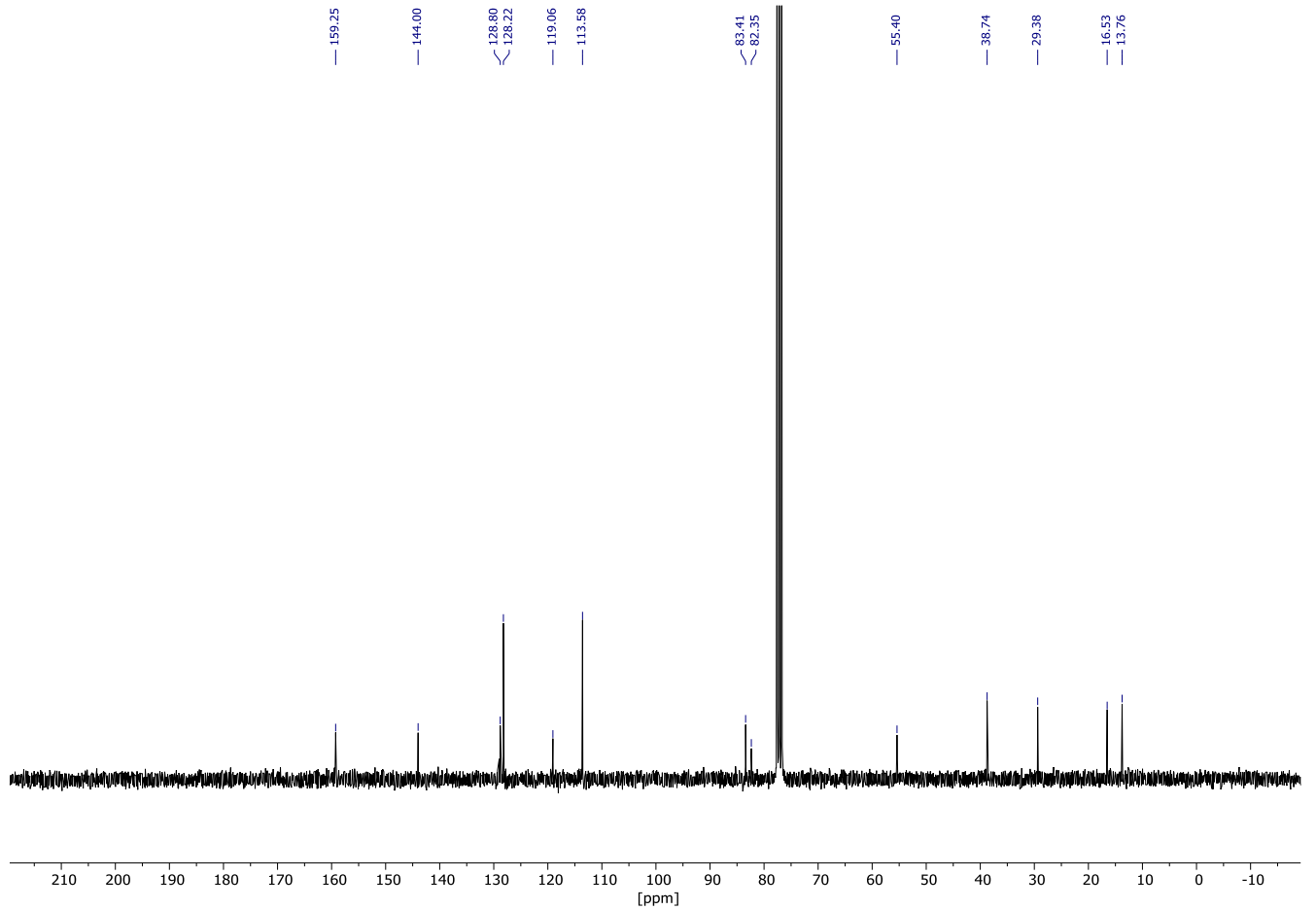
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2c**



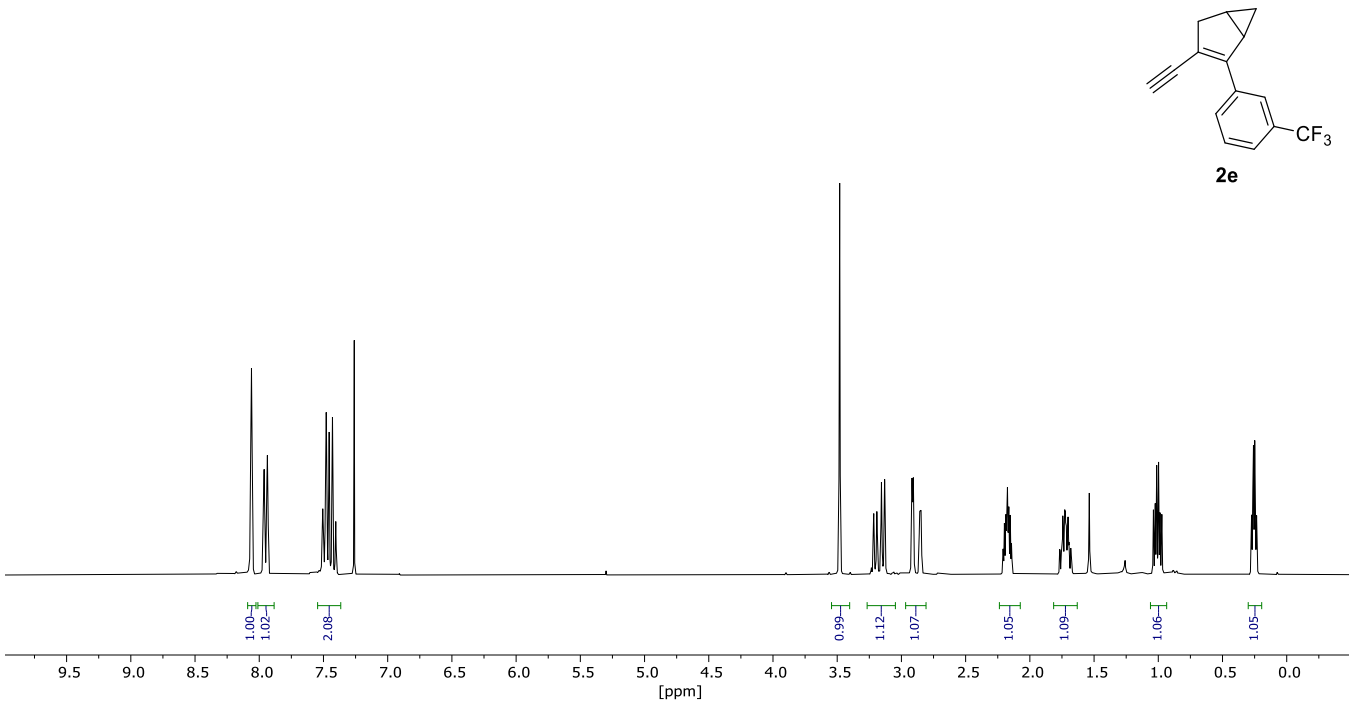
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2c**



^{1}H NMR (300 MHz, $CDCl_3$) of compound **2d**

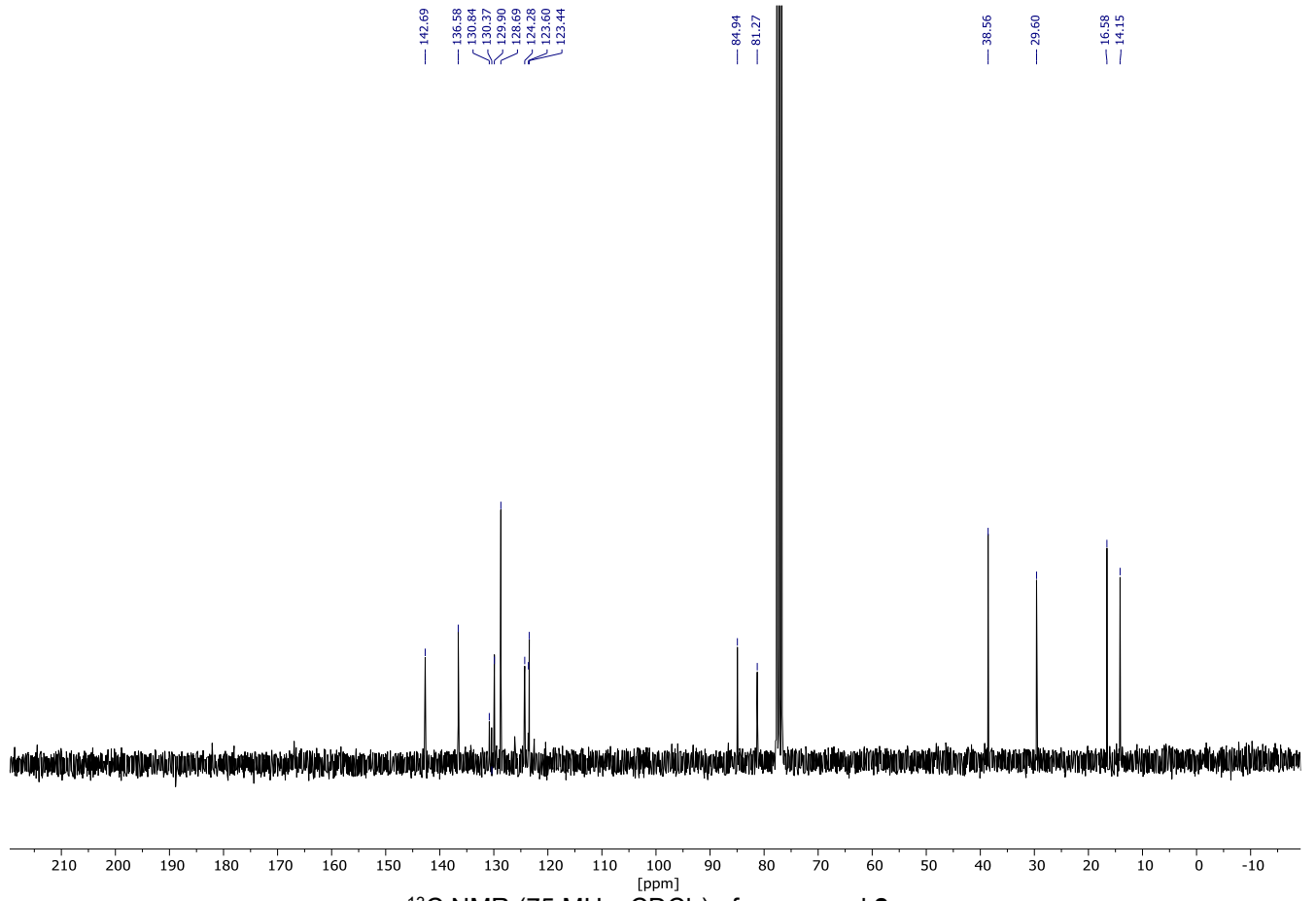


^{13}C NMR (75 MHz, $CDCl_3$) of compound **2d**

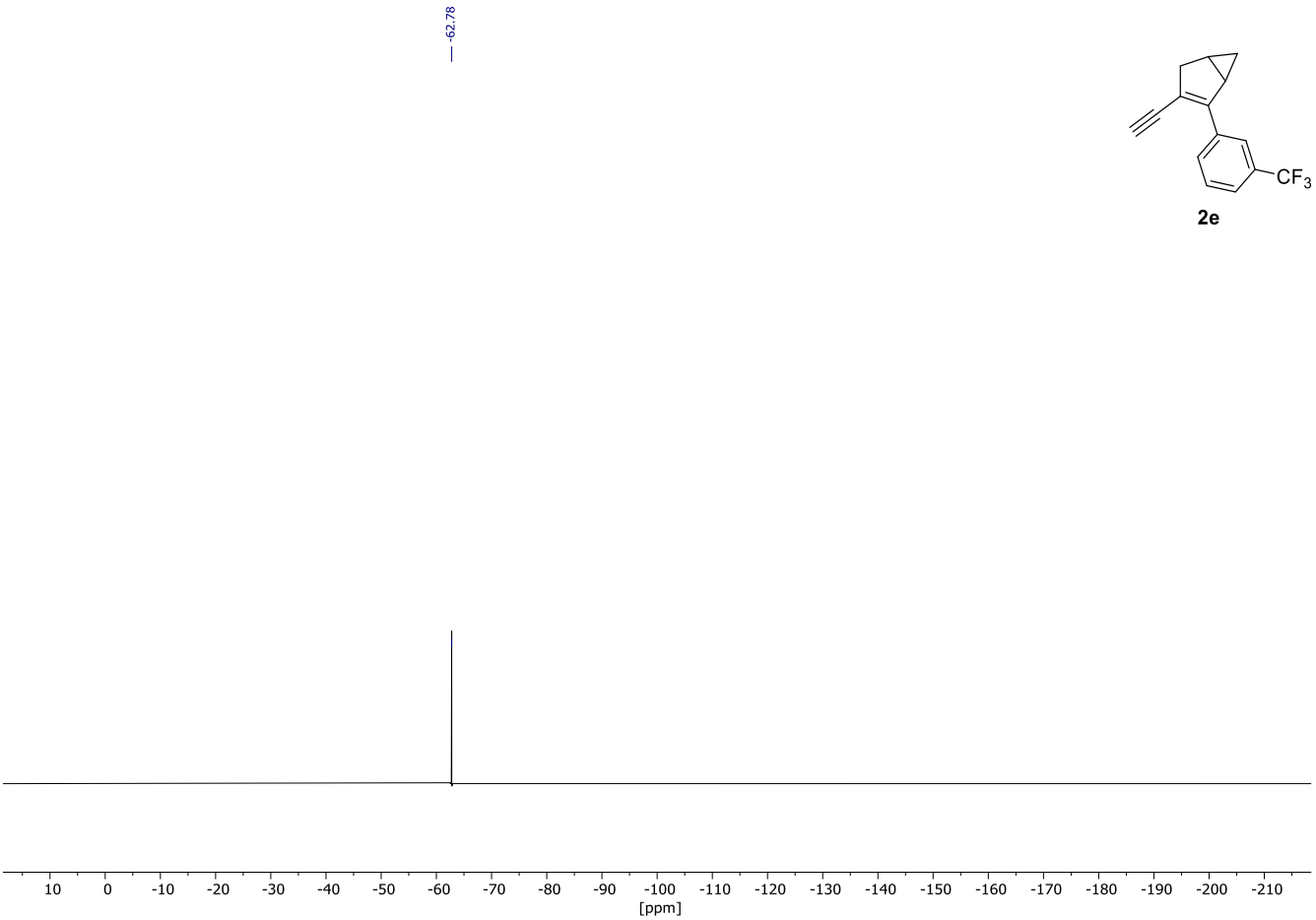


2e

^{1}H NMR (300 MHz, $CDCl_3$) of compound **2e**

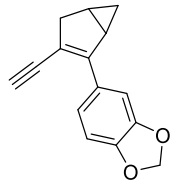


^{13}C NMR (75 MHz, $CDCl_3$) of compound **2e**

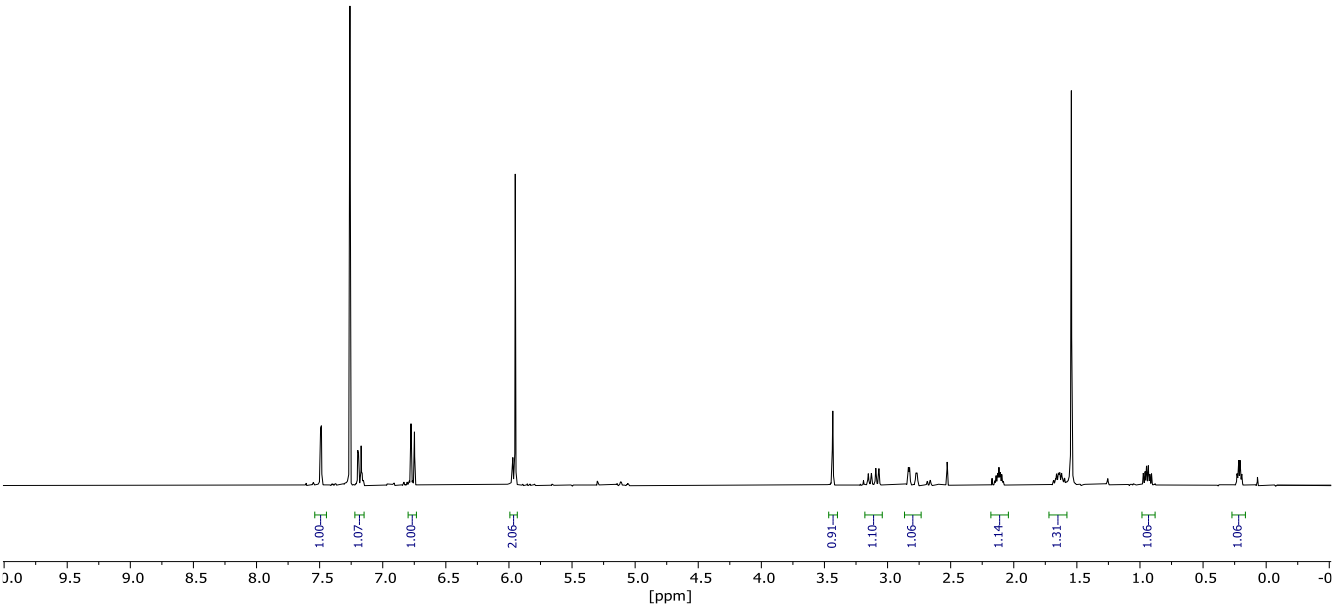


2e

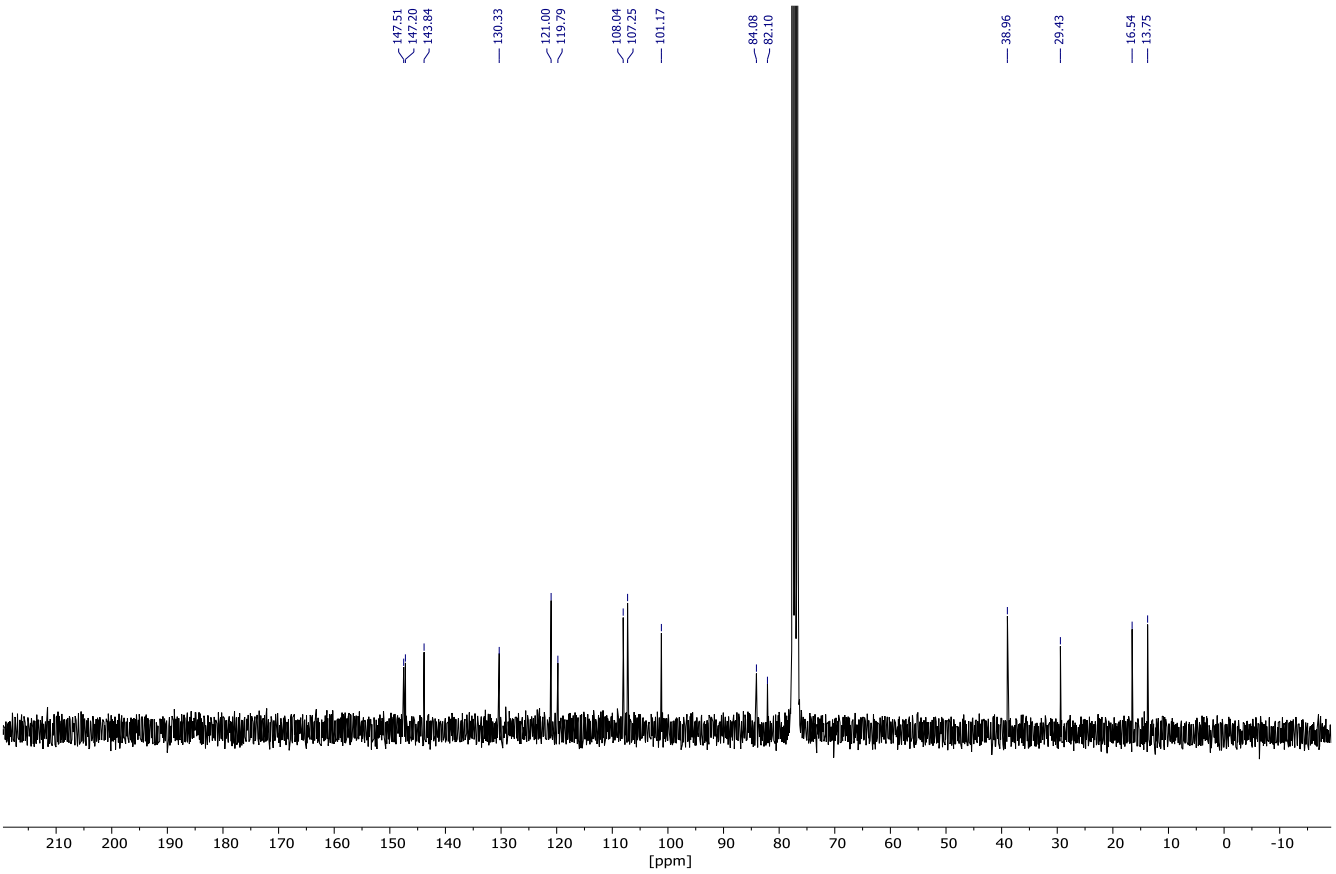
^{19}F NMR (282 MHz, $CDCl_3$) of compound **2e**



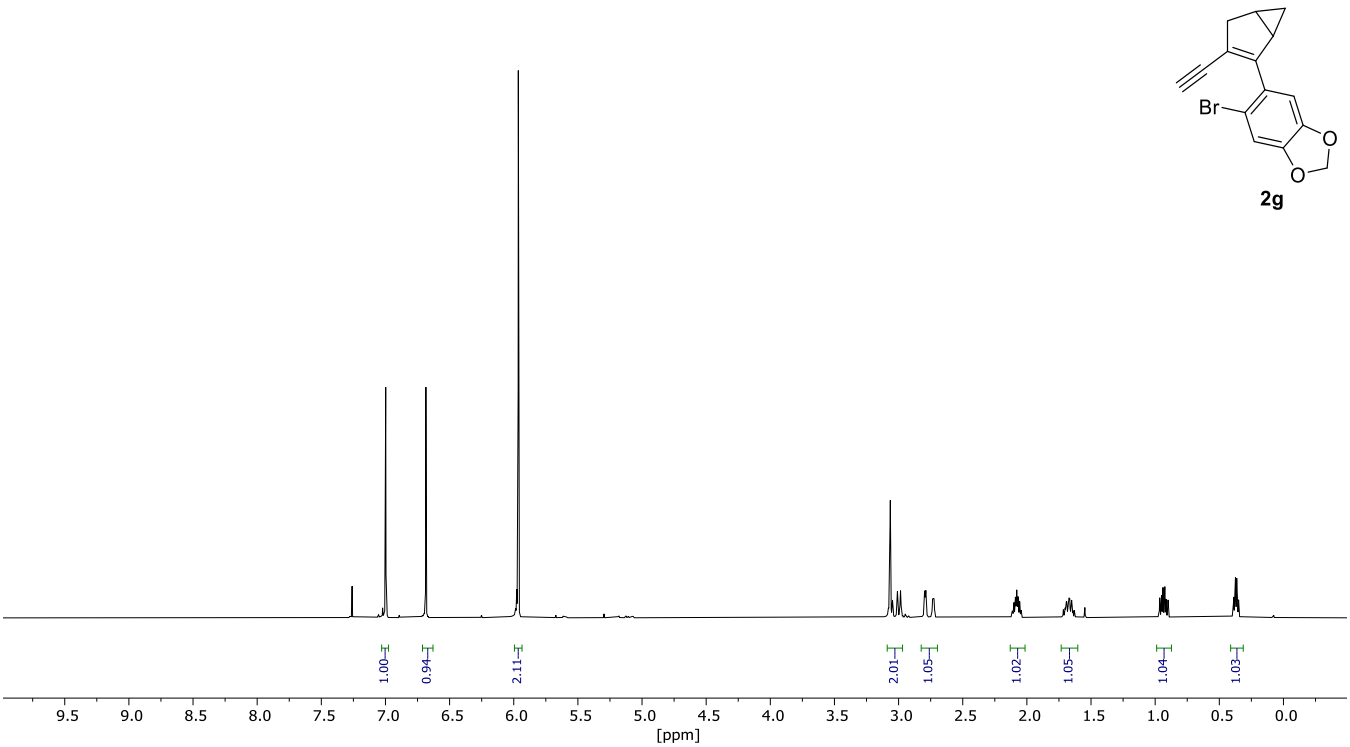
2f



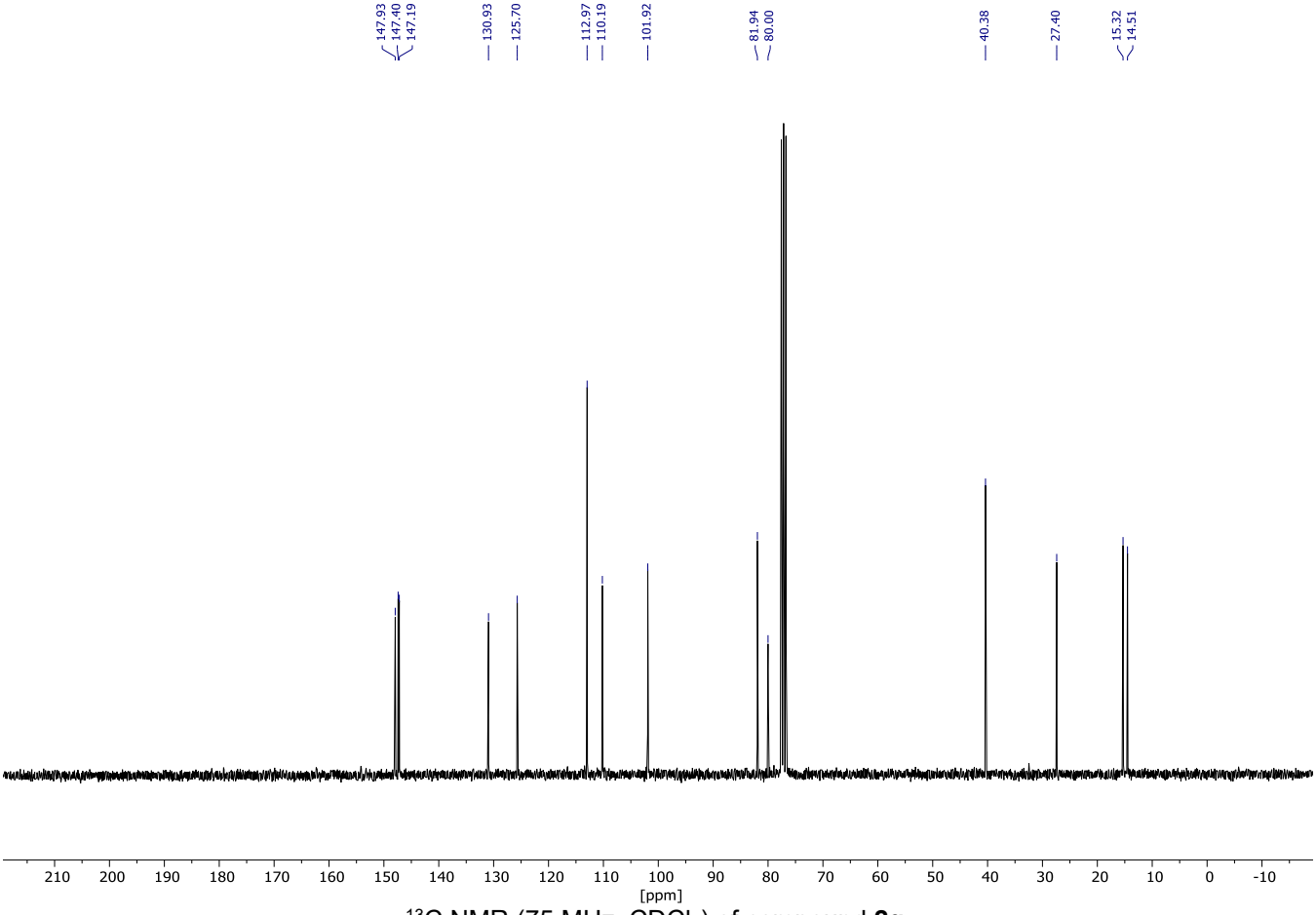
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2f**



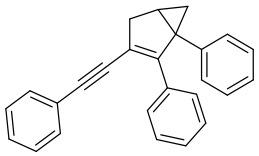
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2f**



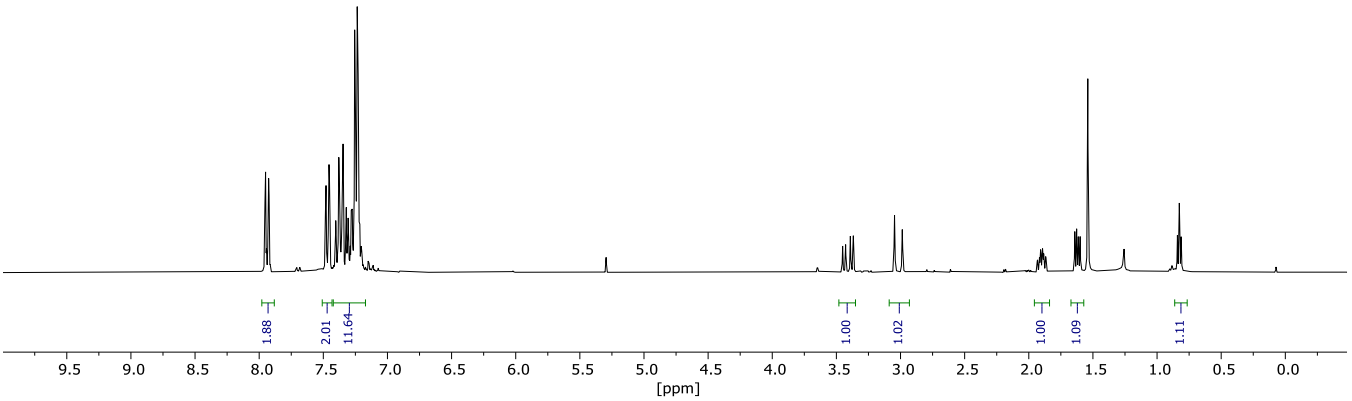
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2g**



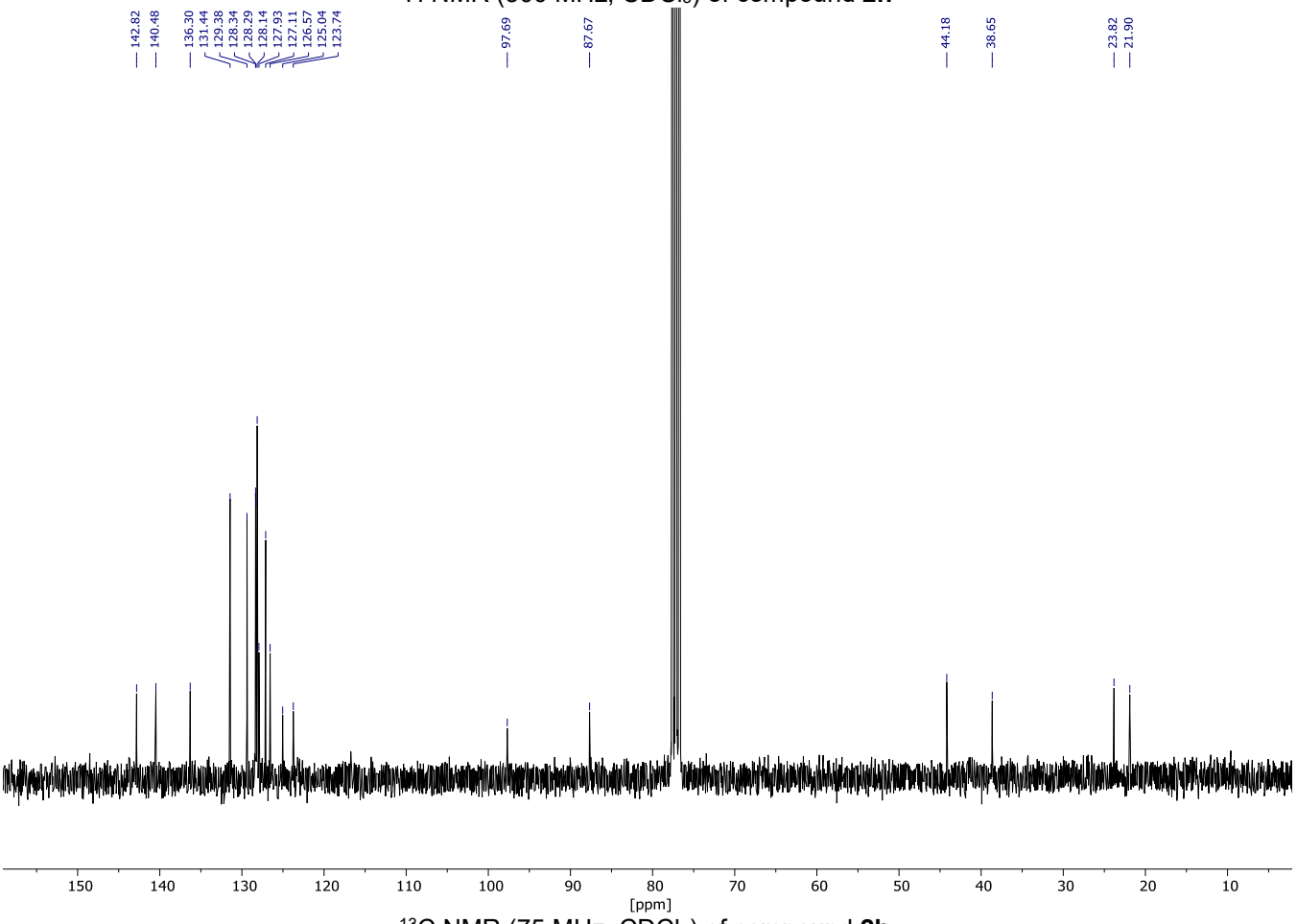
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2g**



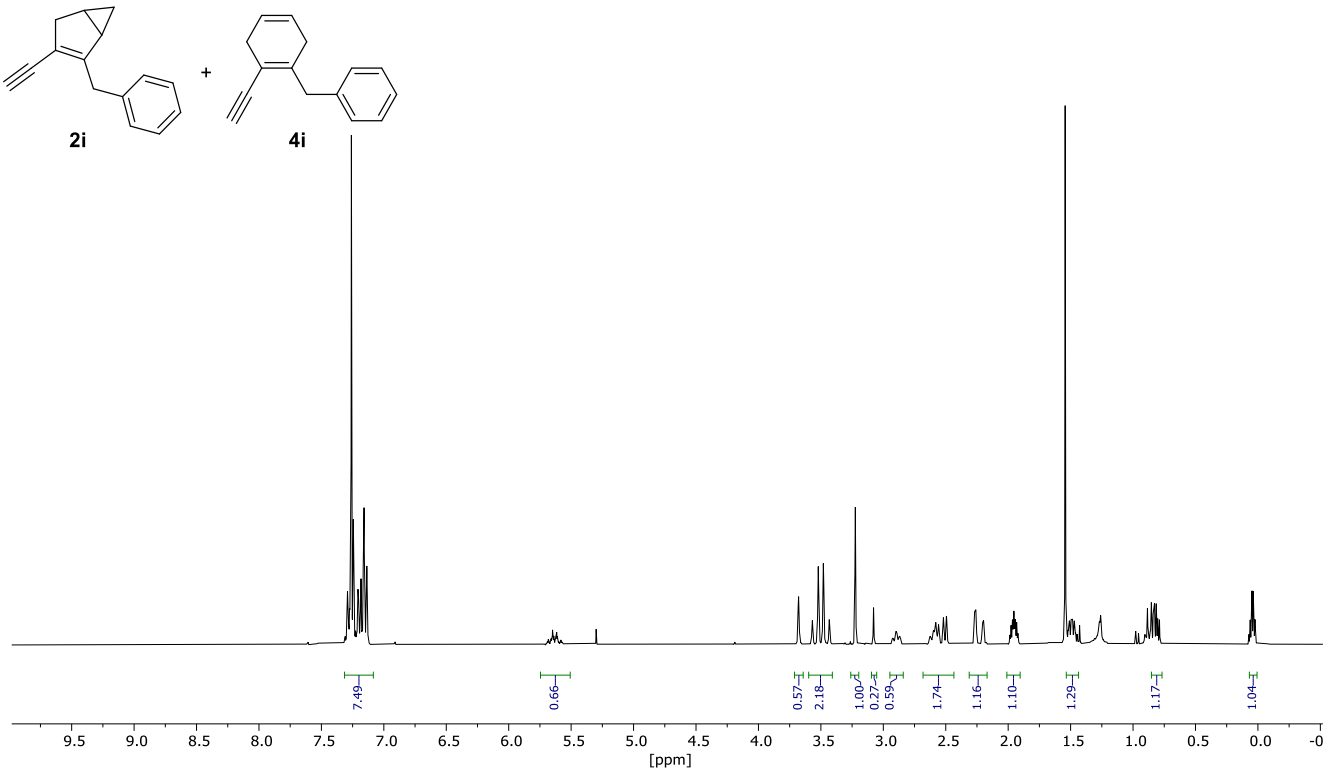
2h



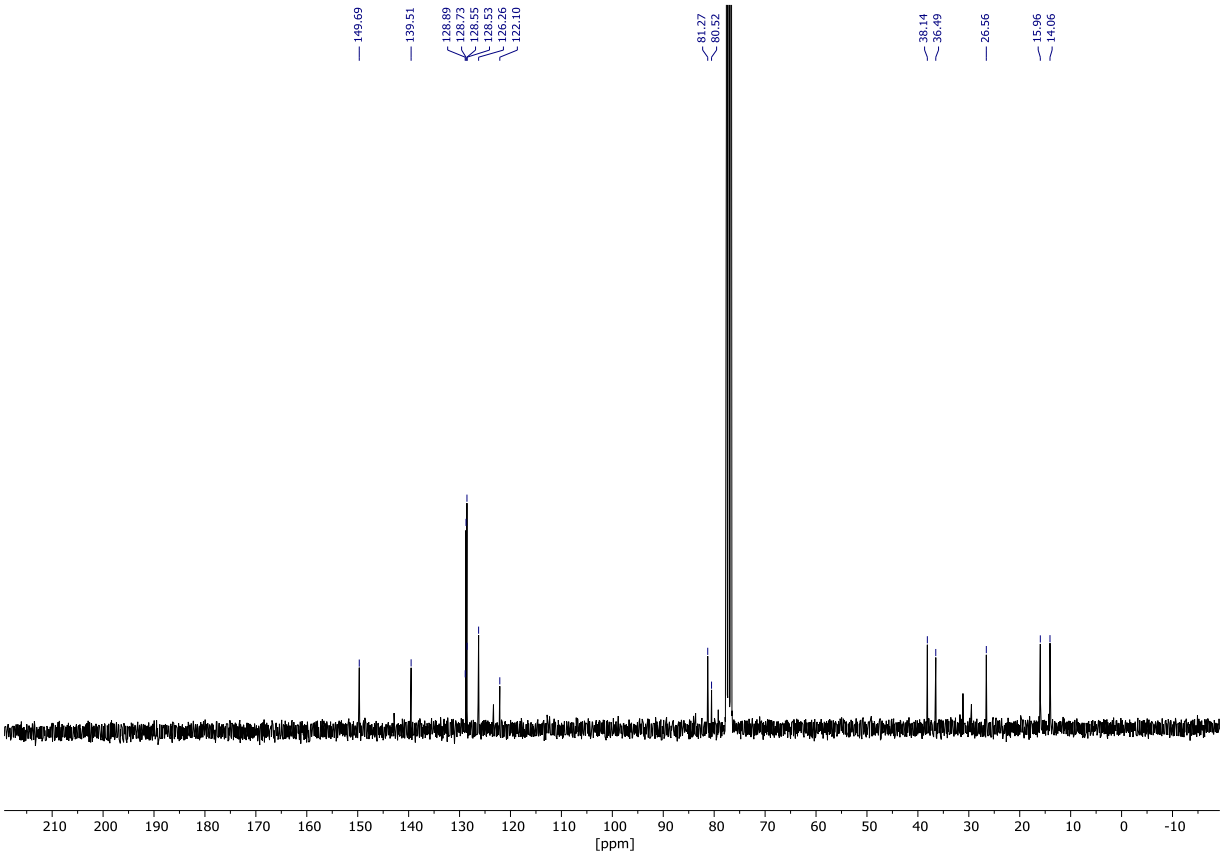
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2h**



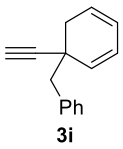
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2h**



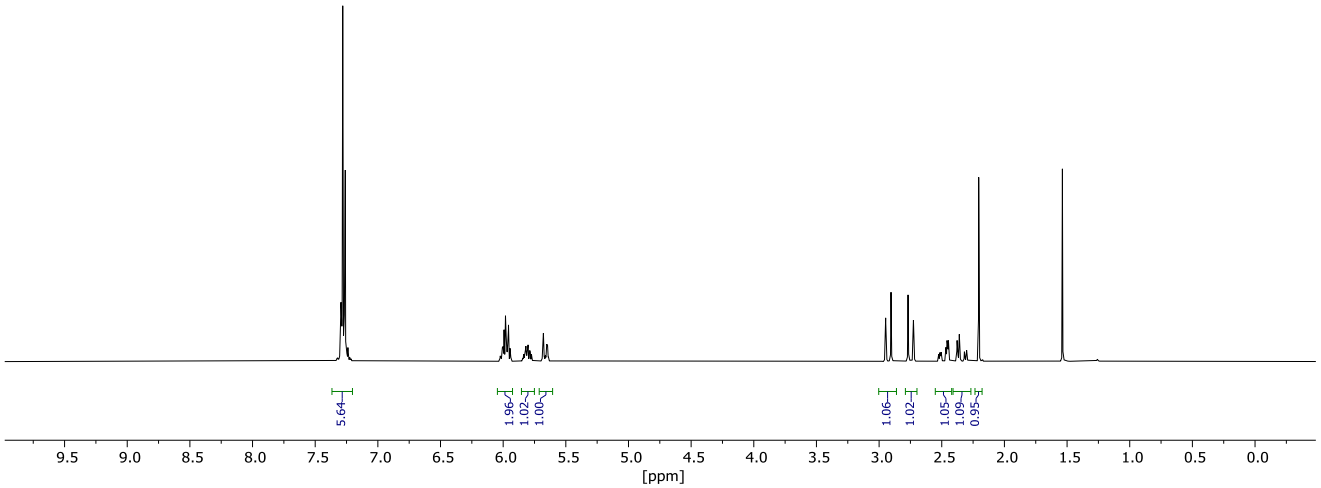
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2i+4i**



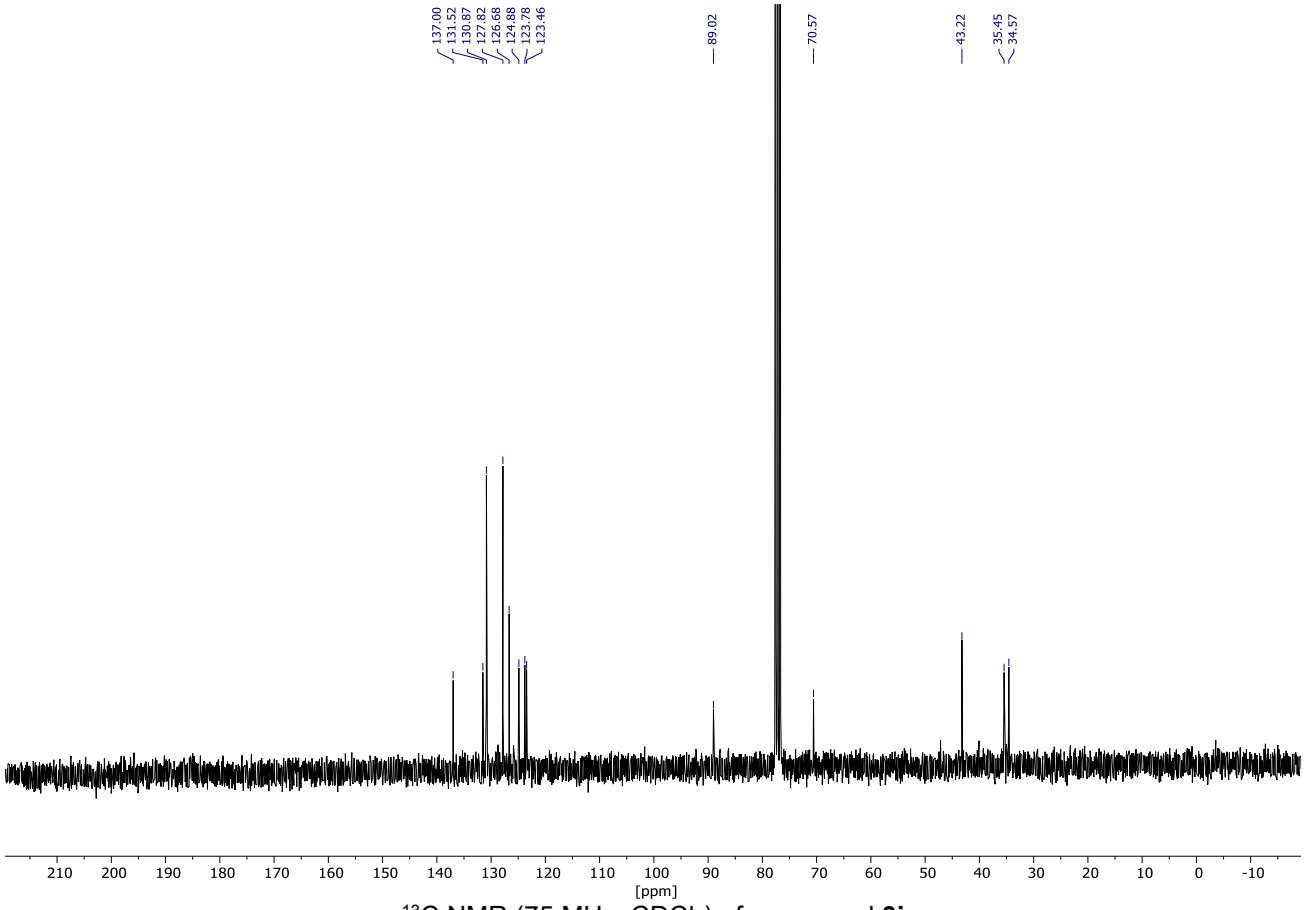
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2i+4i**



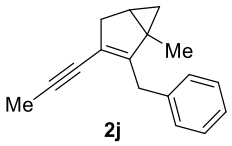
3i



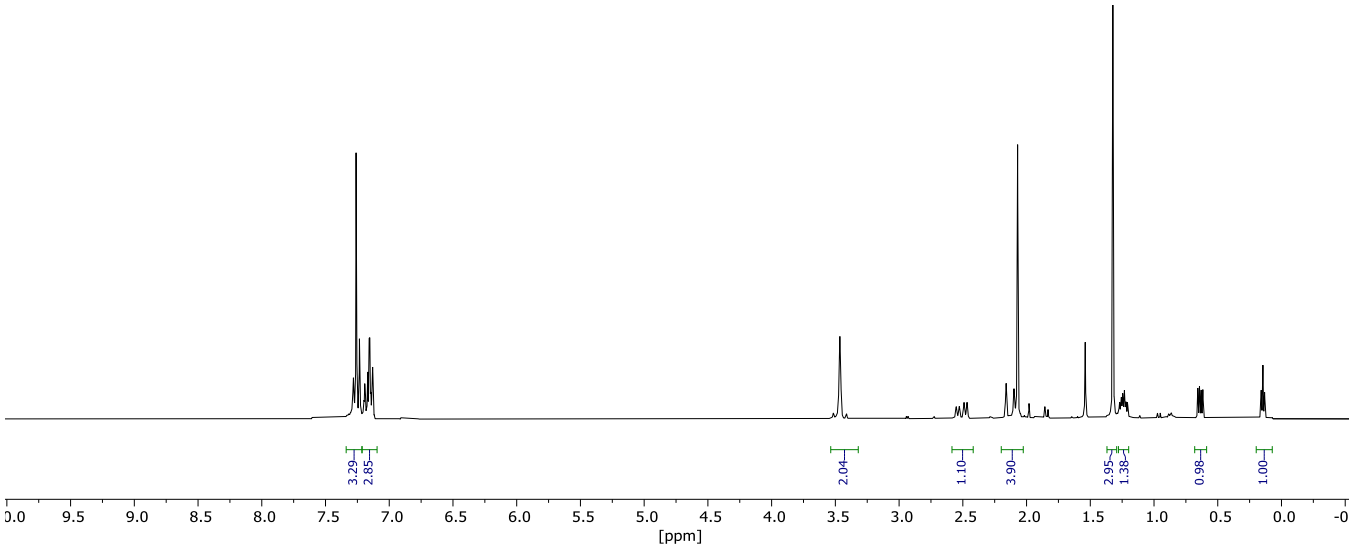
^{1}H NMR (300 MHz, $CDCl_3$) of compound **3i**



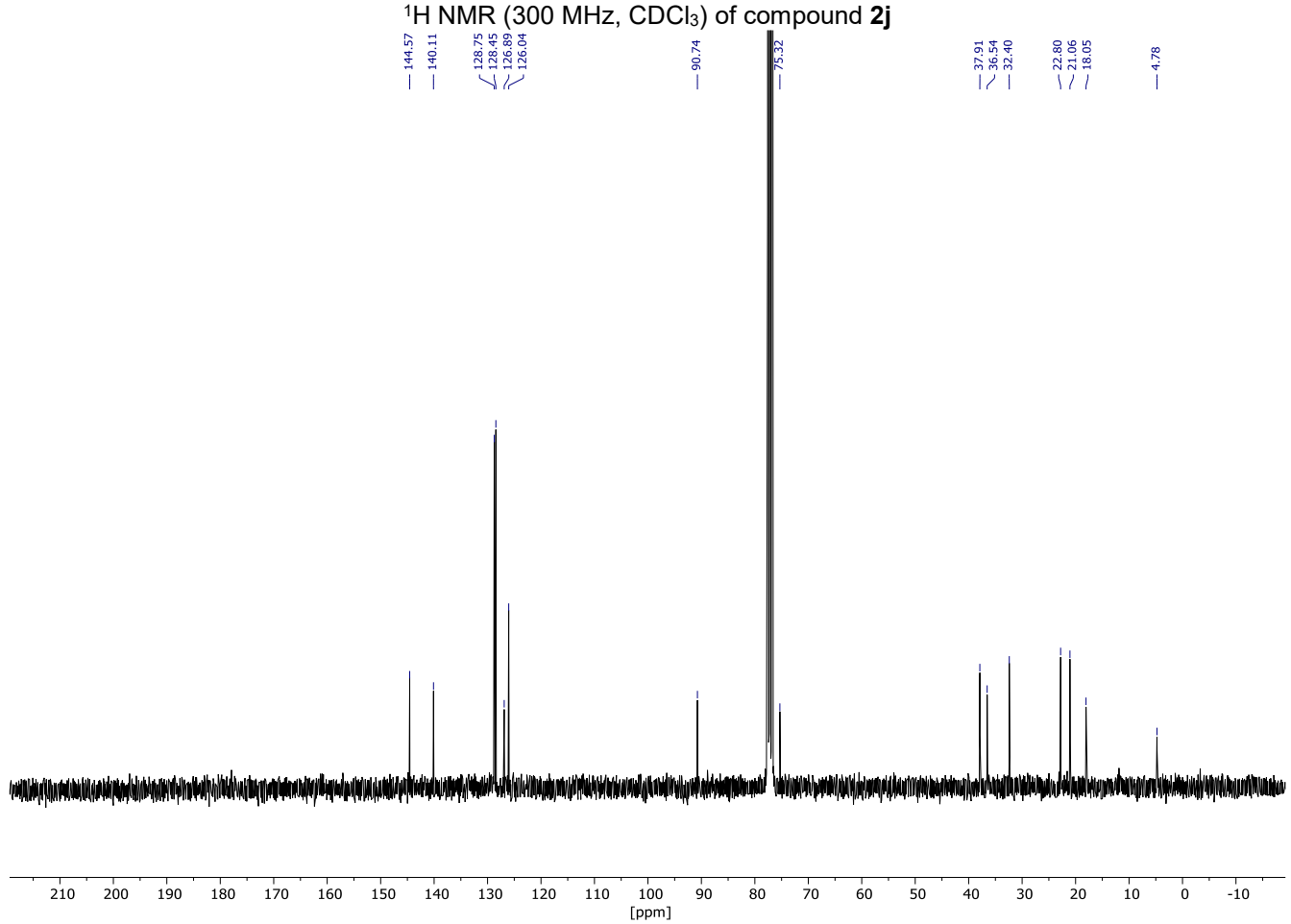
^{13}C NMR (75 MHz, $CDCl_3$) of compound **3i**



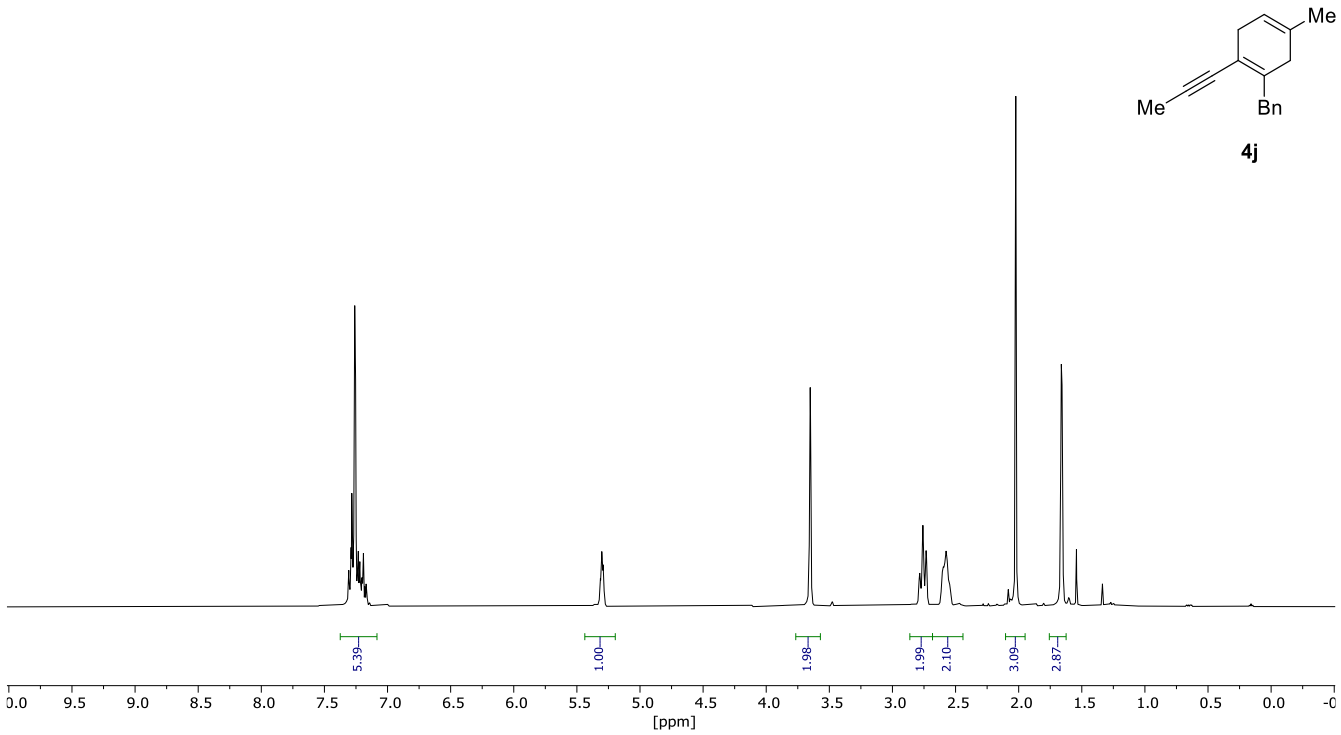
2j



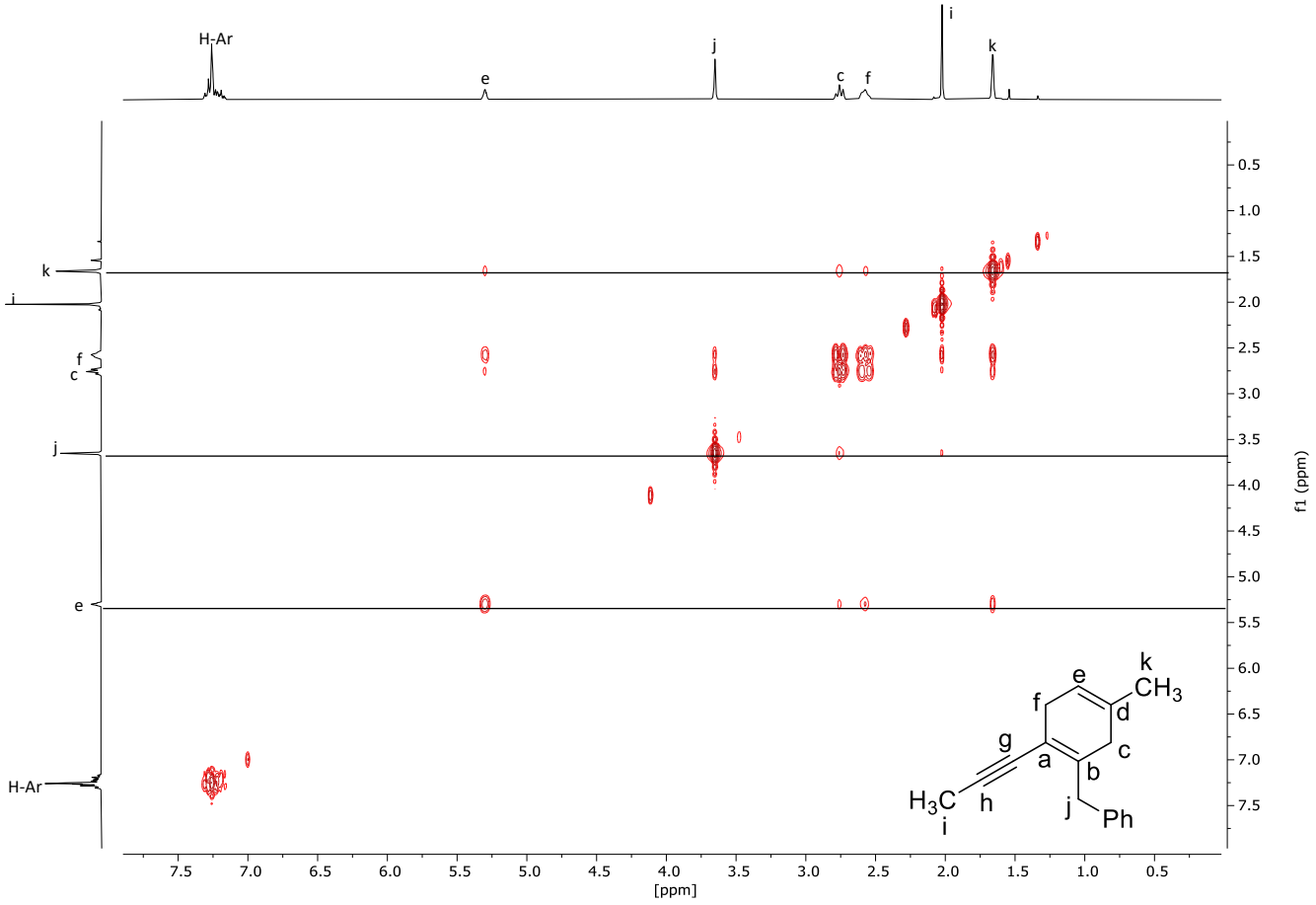
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2j**



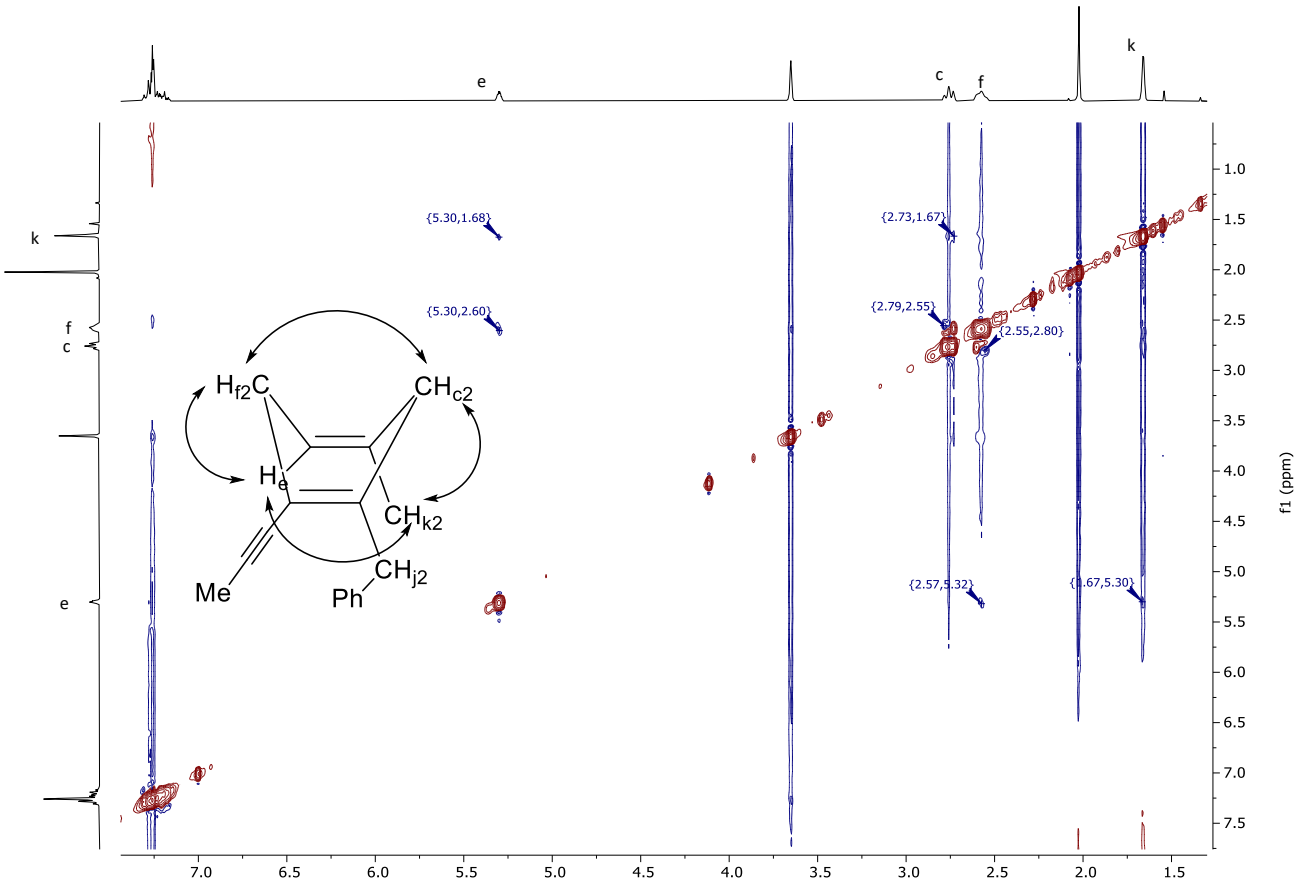
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2j**



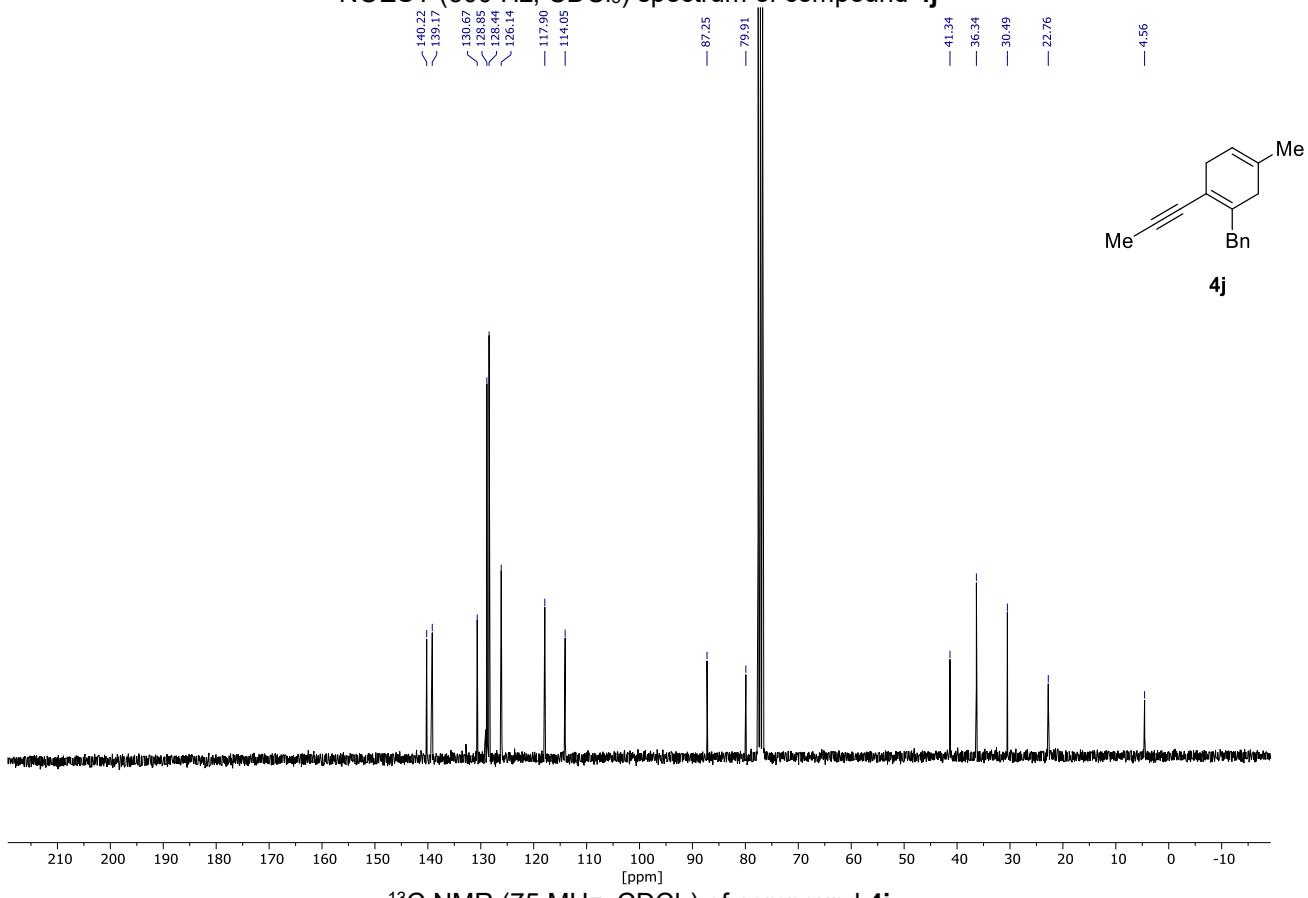
^{1}H NMR (300 MHz, $CDCl_3$) of compound **4j**



COSY (300 Hz, $CDCl_3$) spectrum of compound **4j**

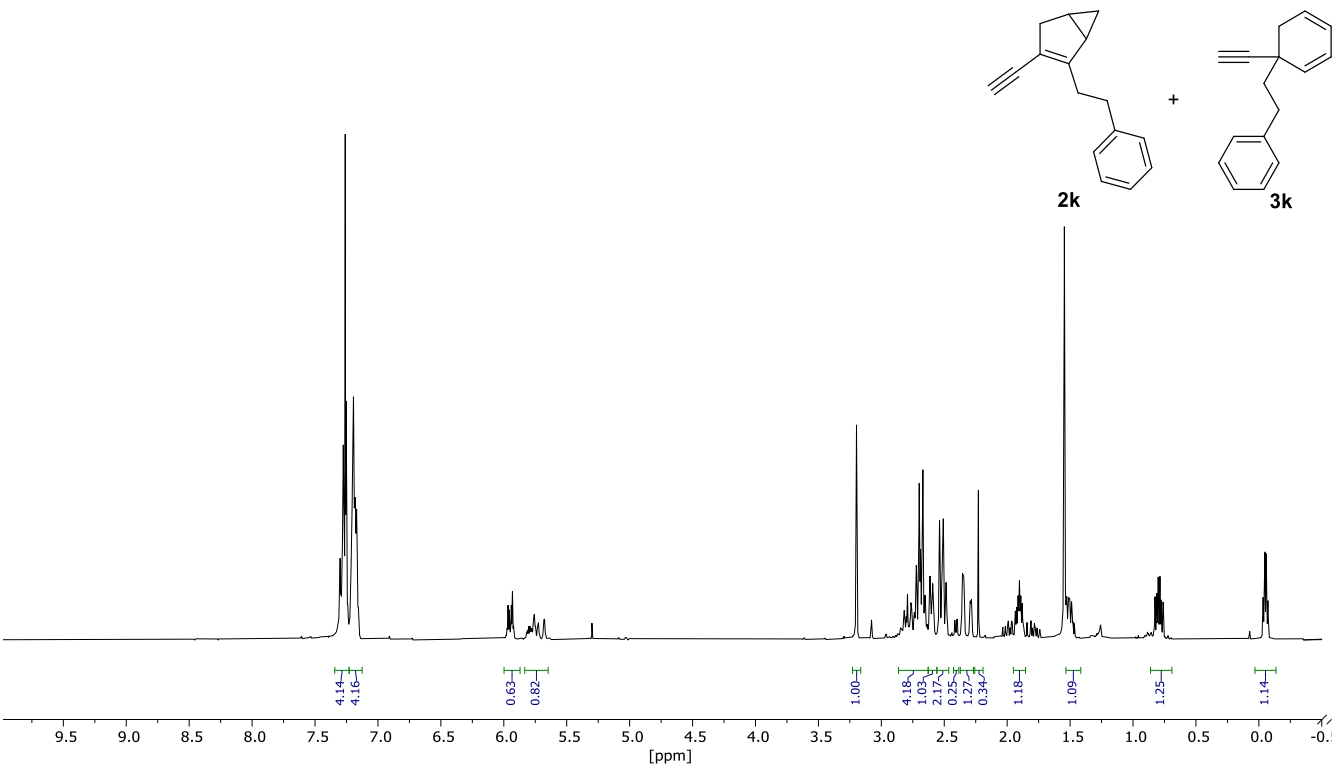


NOESY (300 Hz, $CDCl_3$) spectrum of compound **4j**

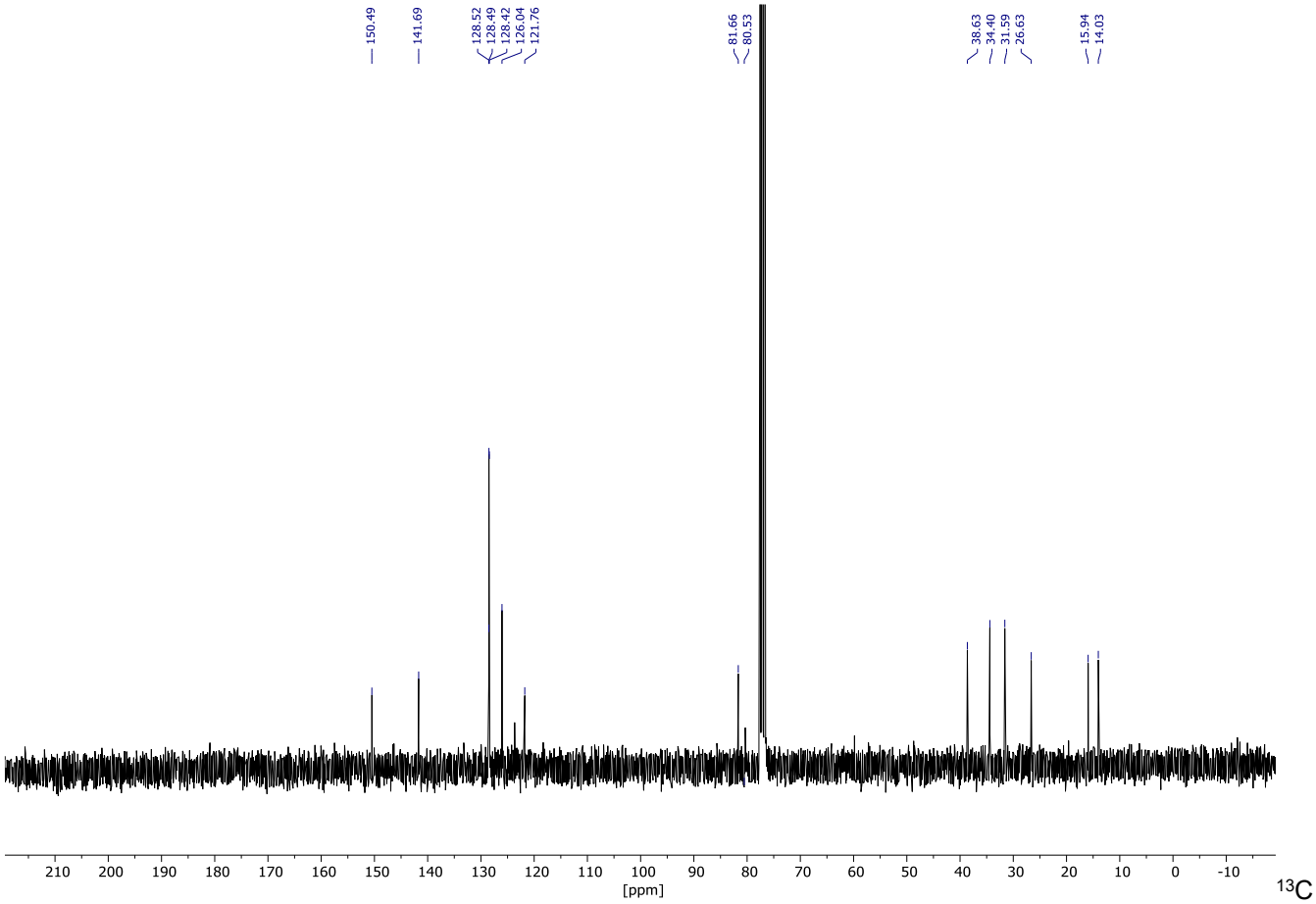


4j

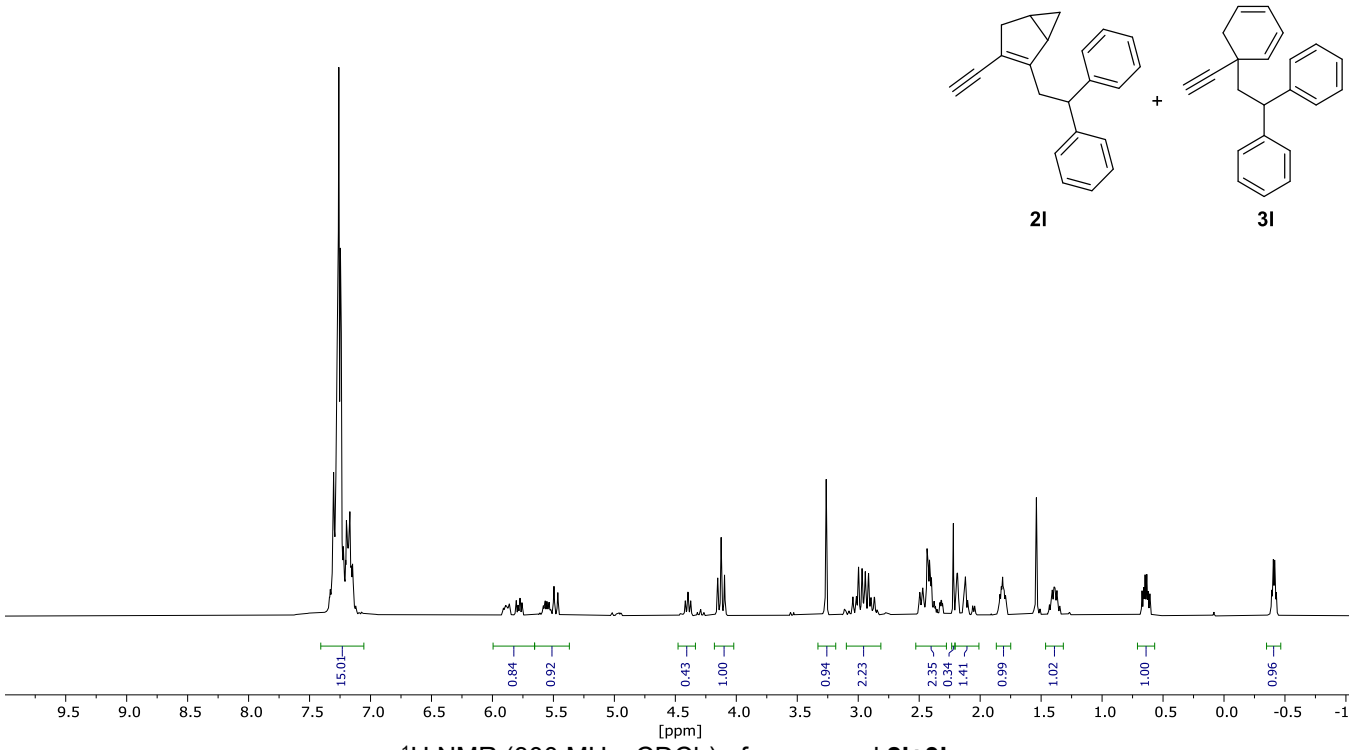
^{13}C NMR (75 MHz, $CDCl_3$) of compound **4j**



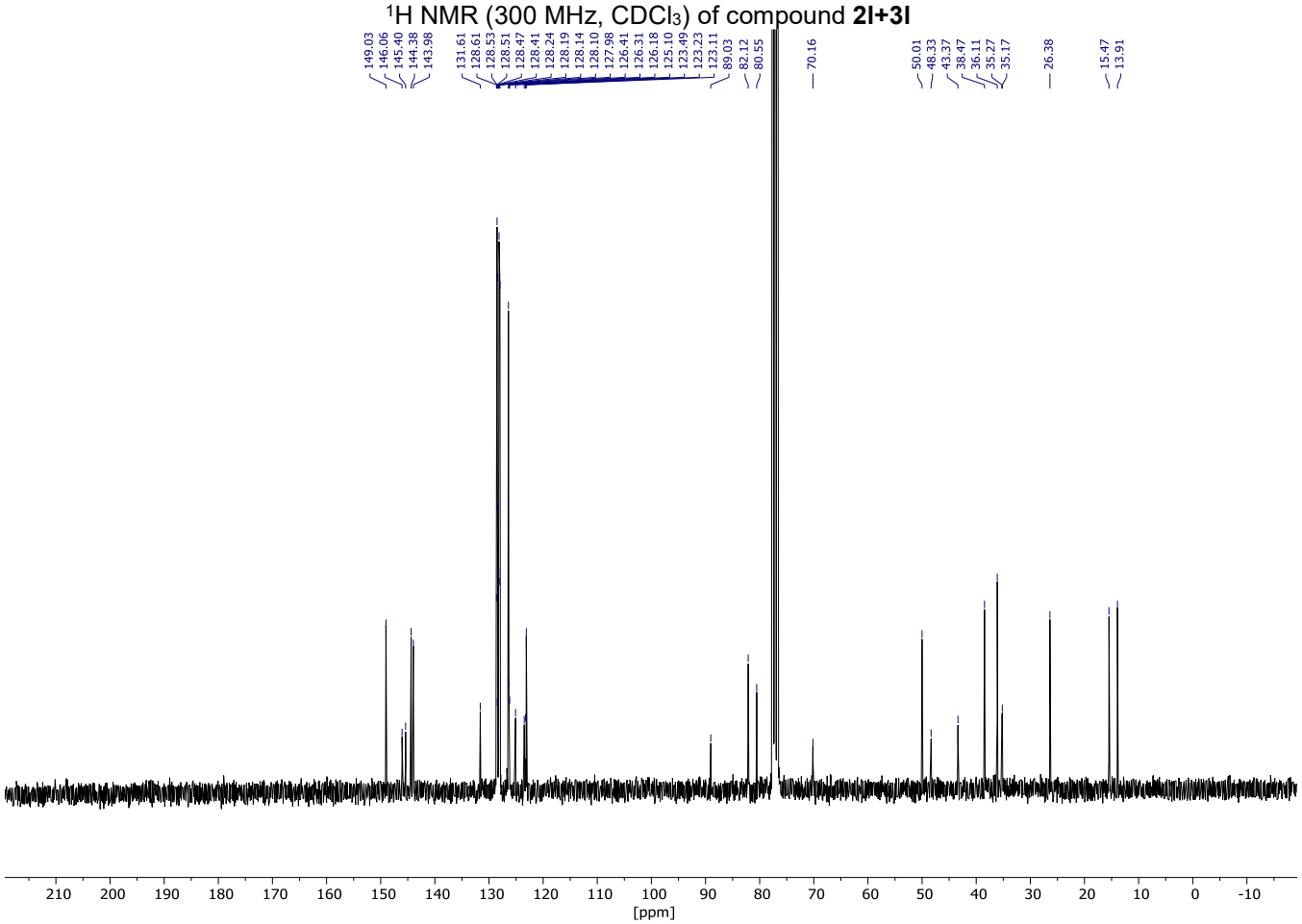
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2k+3k**



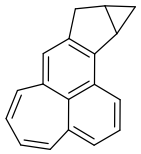
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2k+3k**



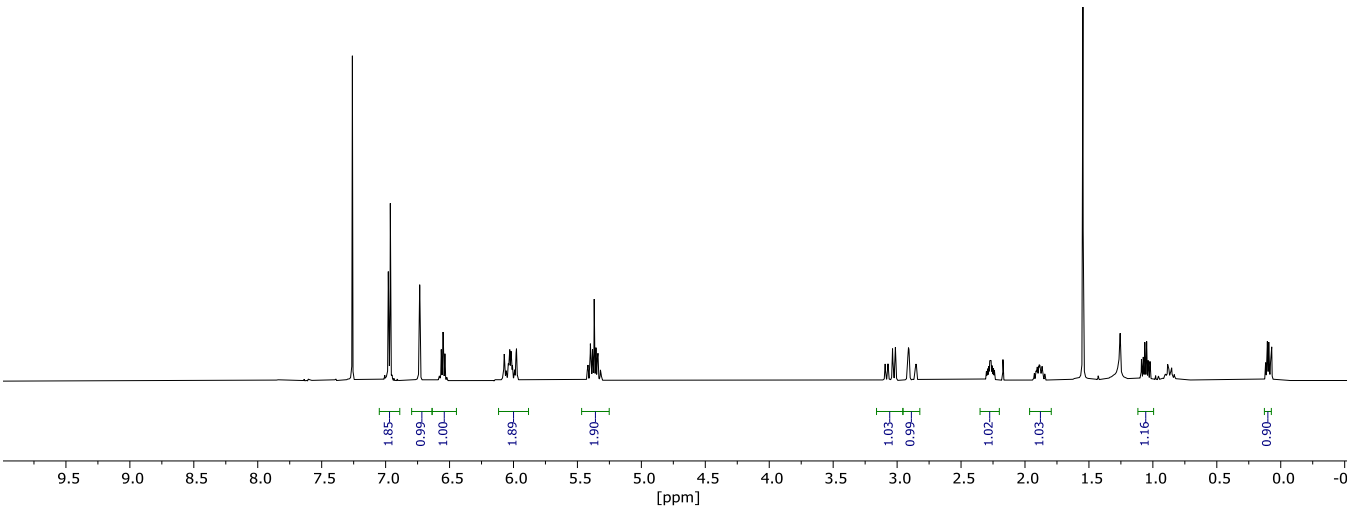
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2l+3l**



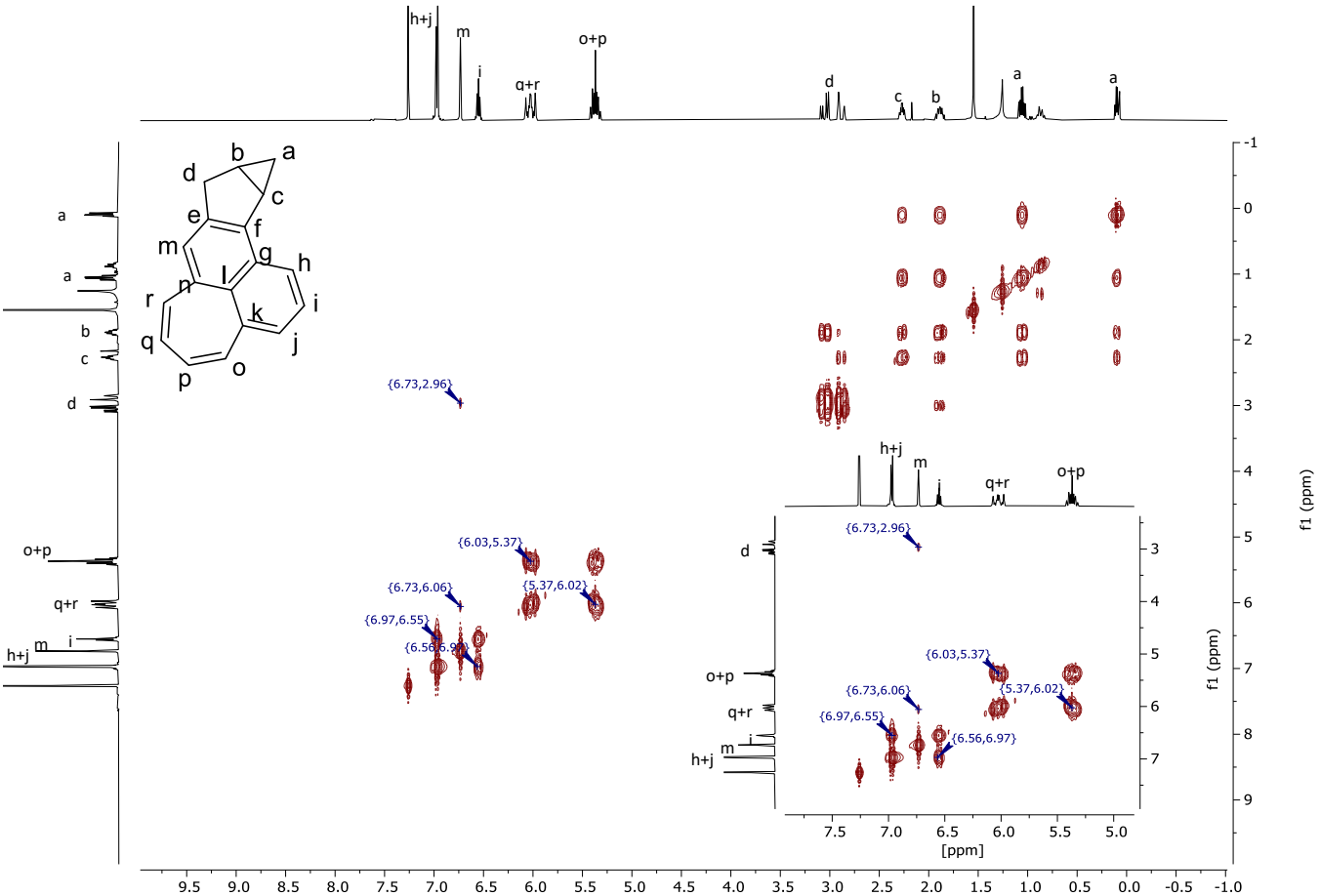
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2l+3l**



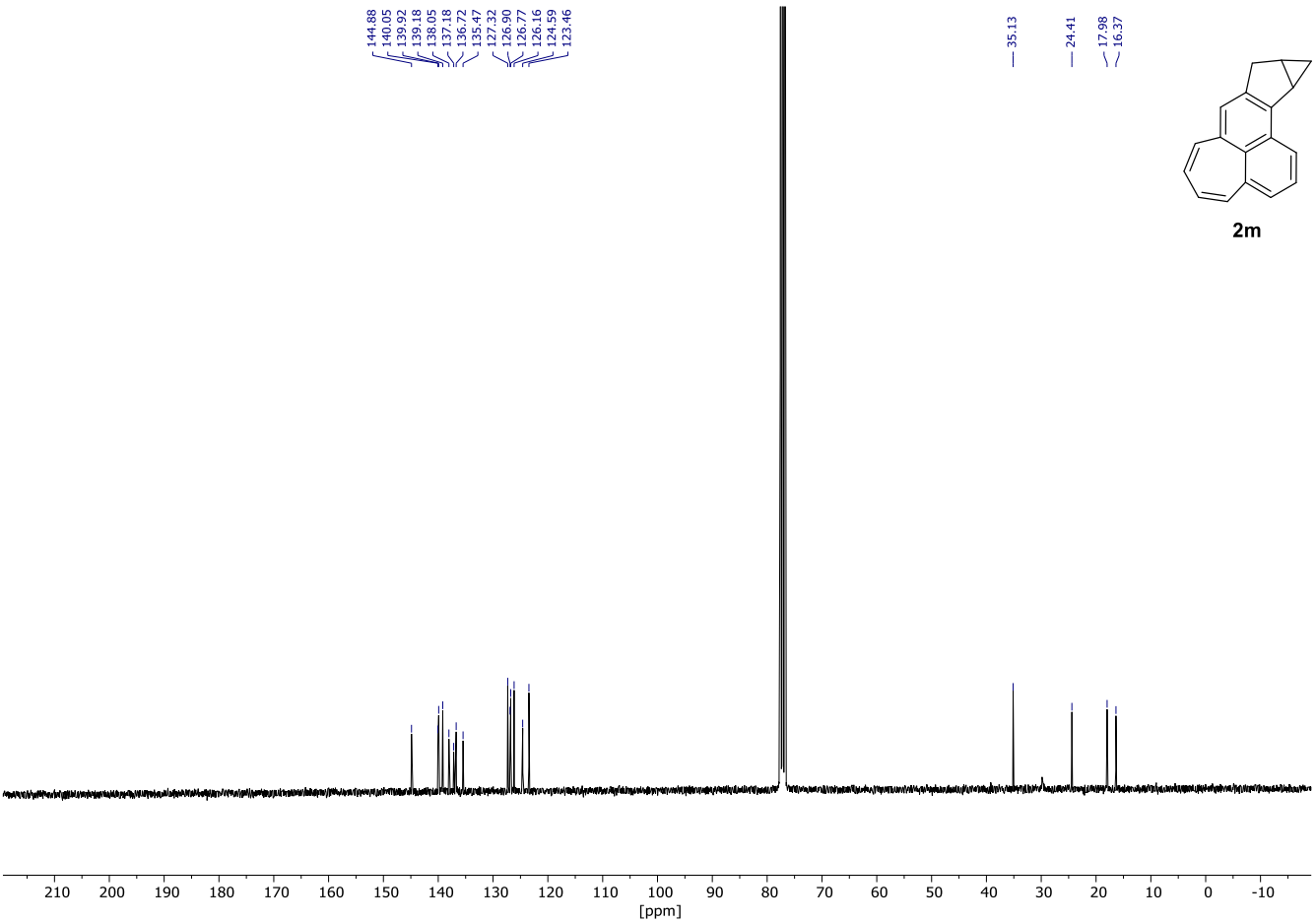
2m



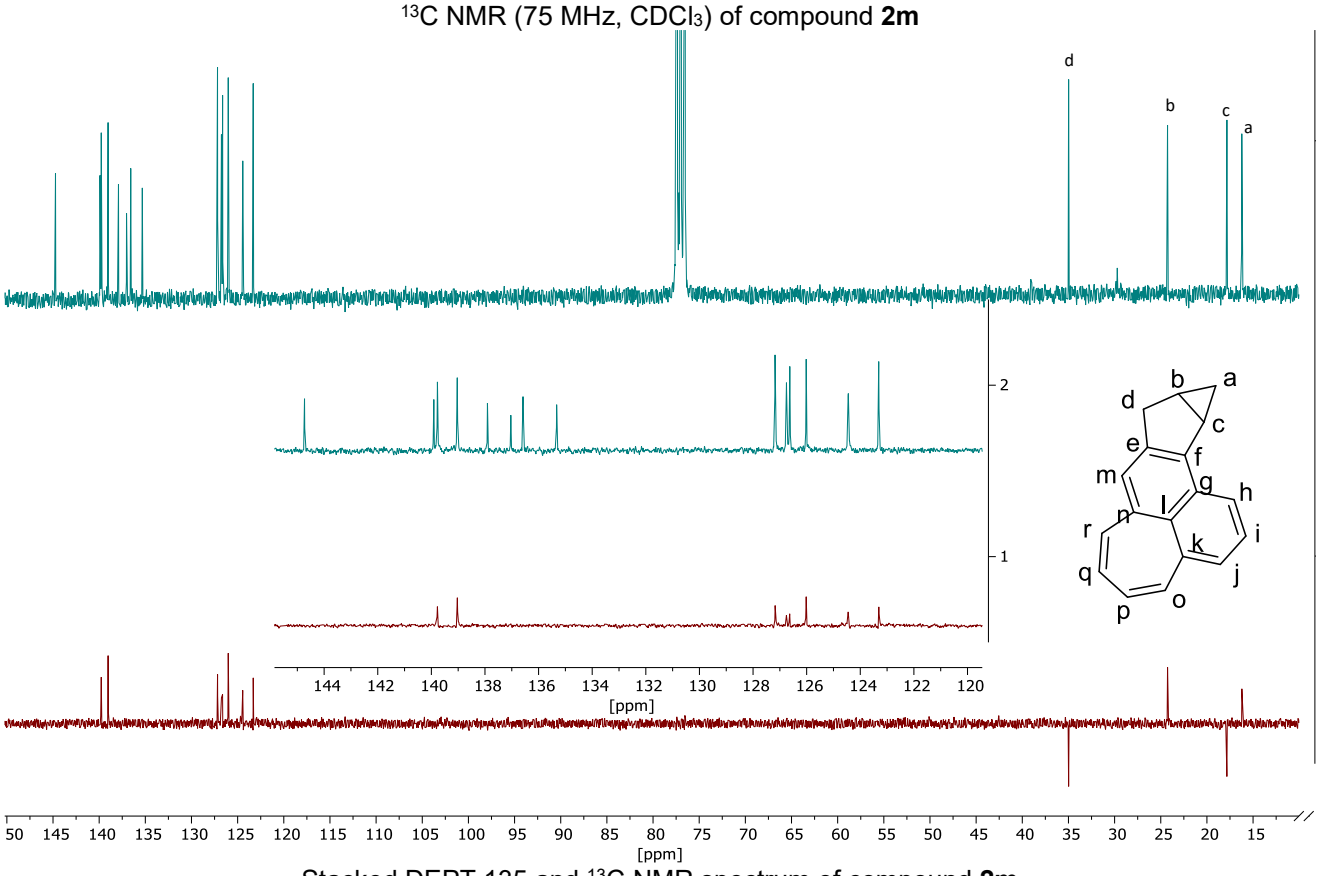
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2m**



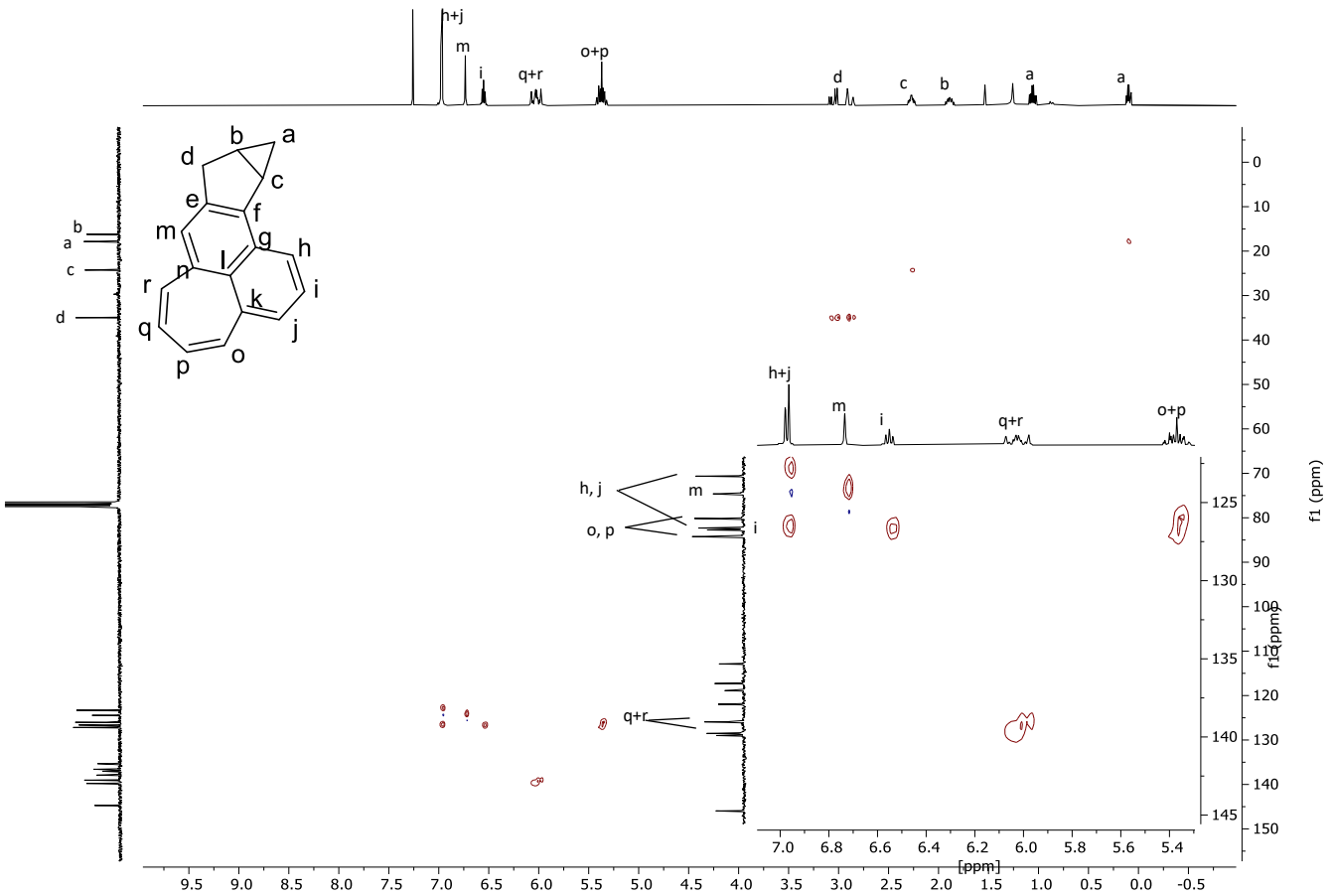
COSY (300 MHz, $CDCl_3$) spectrum of compound **2m**



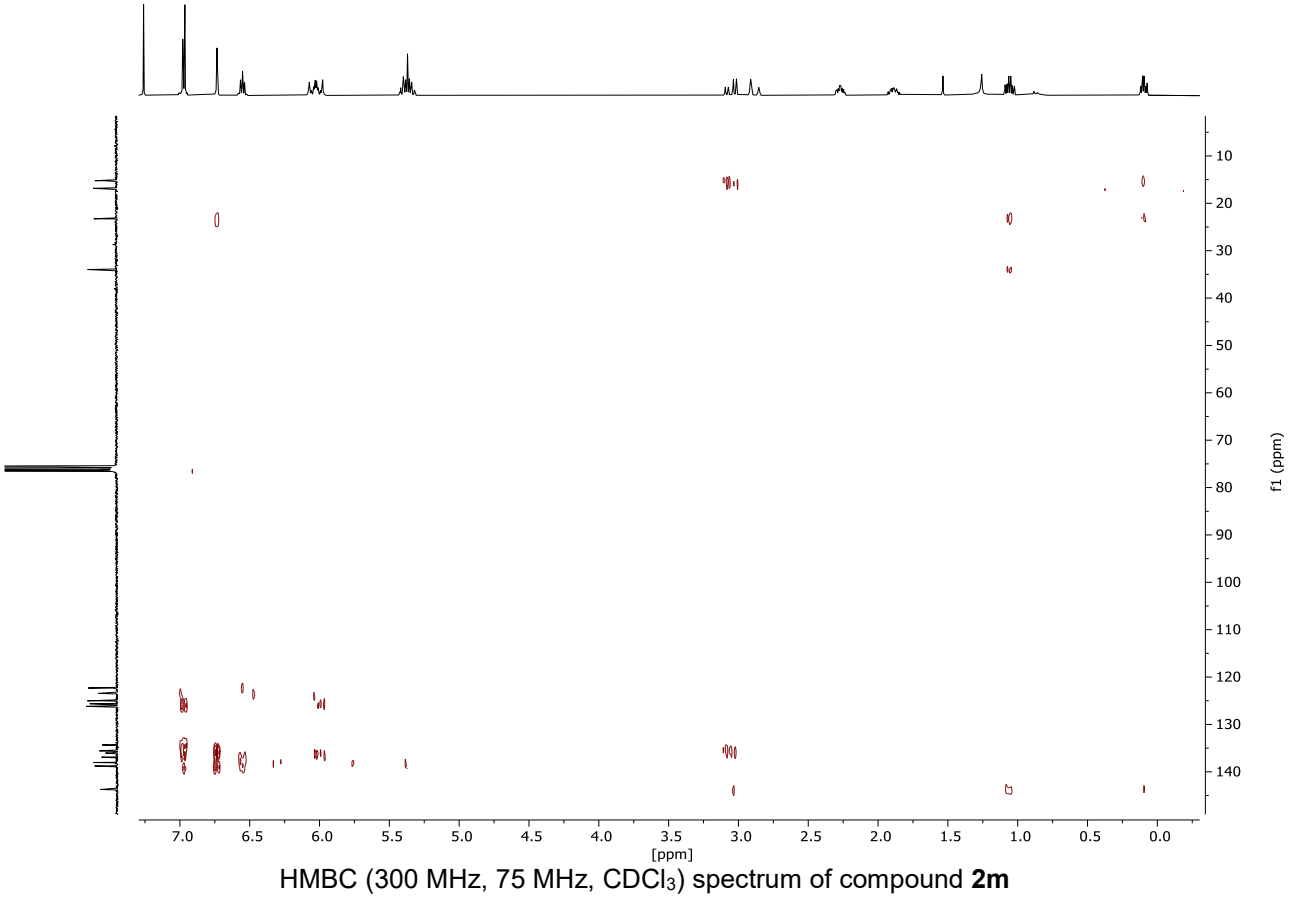
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2m**



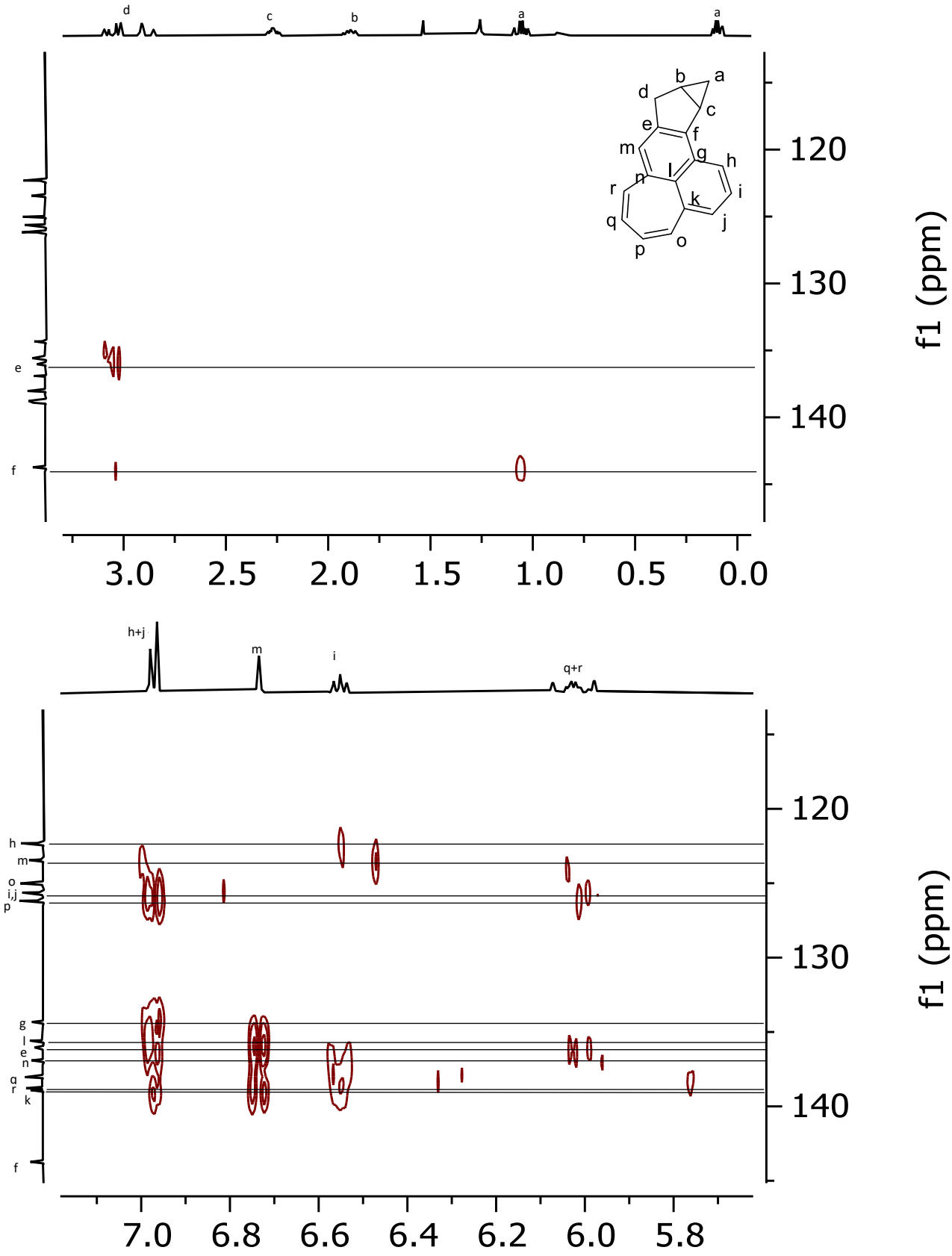
Stacked DEPT 135 and ^{13}C NMR spectrum of compound **2m**



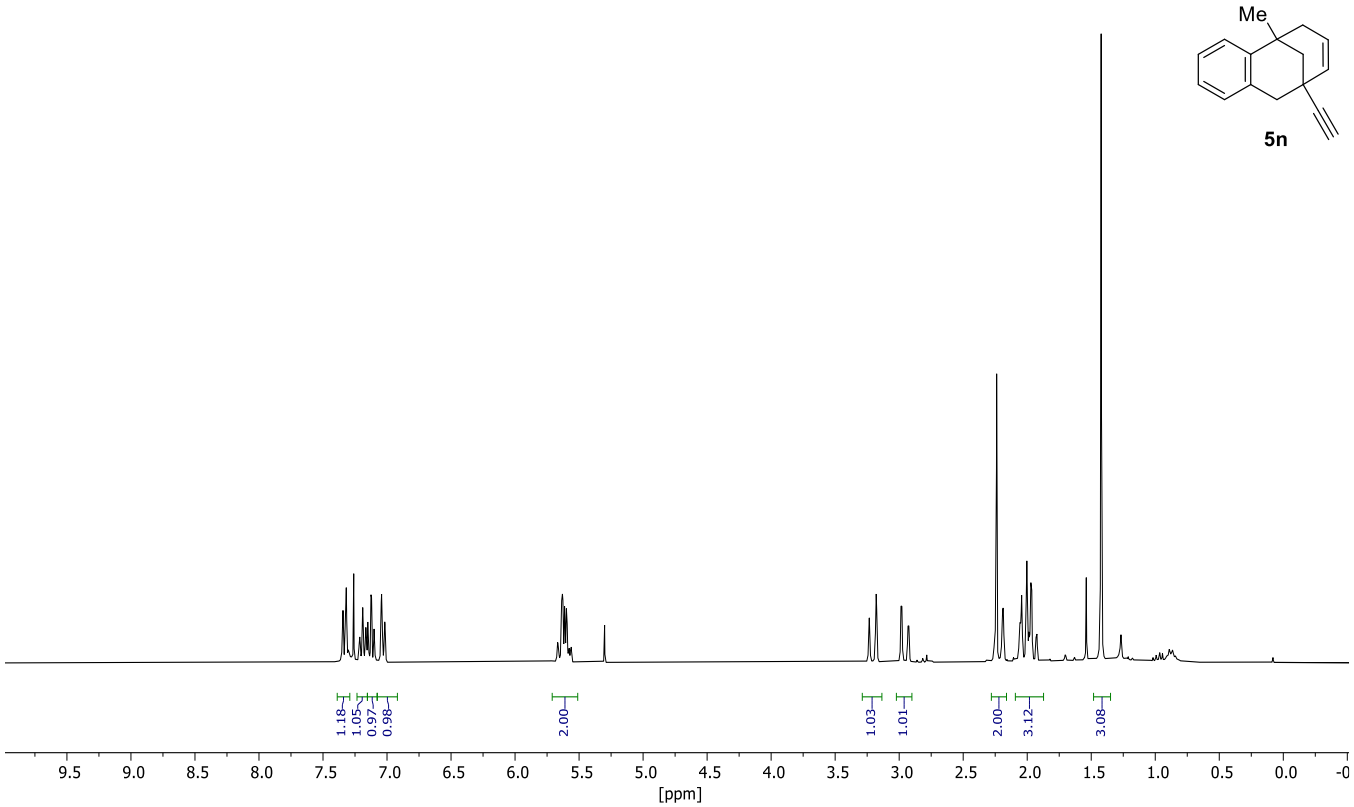
HSQC (300 MHz, 75 MHz, $CDCl_3$) spectrum of compound **2m**



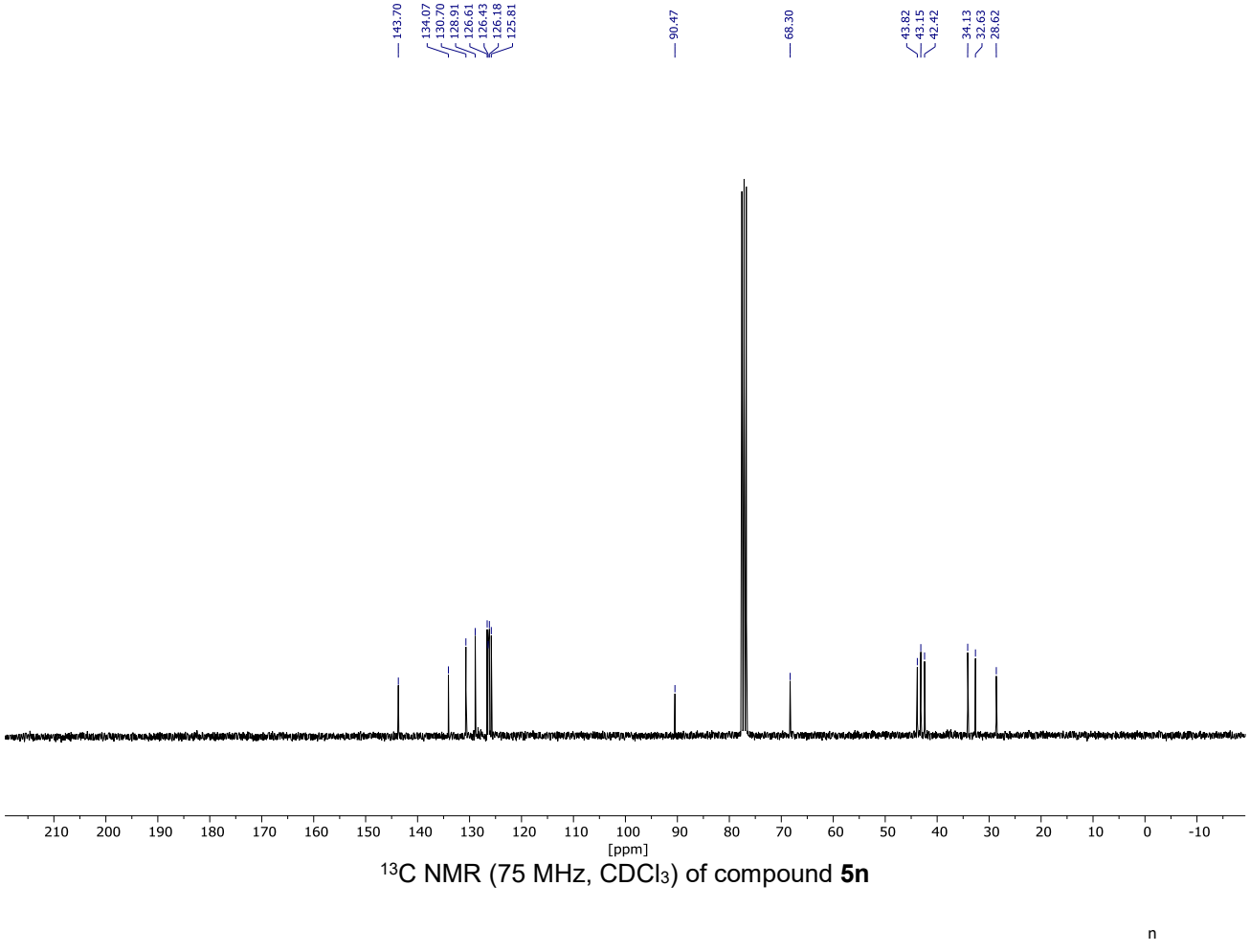
HMBC (300 MHz, 75 MHz, $CDCl_3$) spectrum of compound **2m**



HMBC (300 MHz, 75 MHz, $CDCl_3$) spectrum of compound **2m**

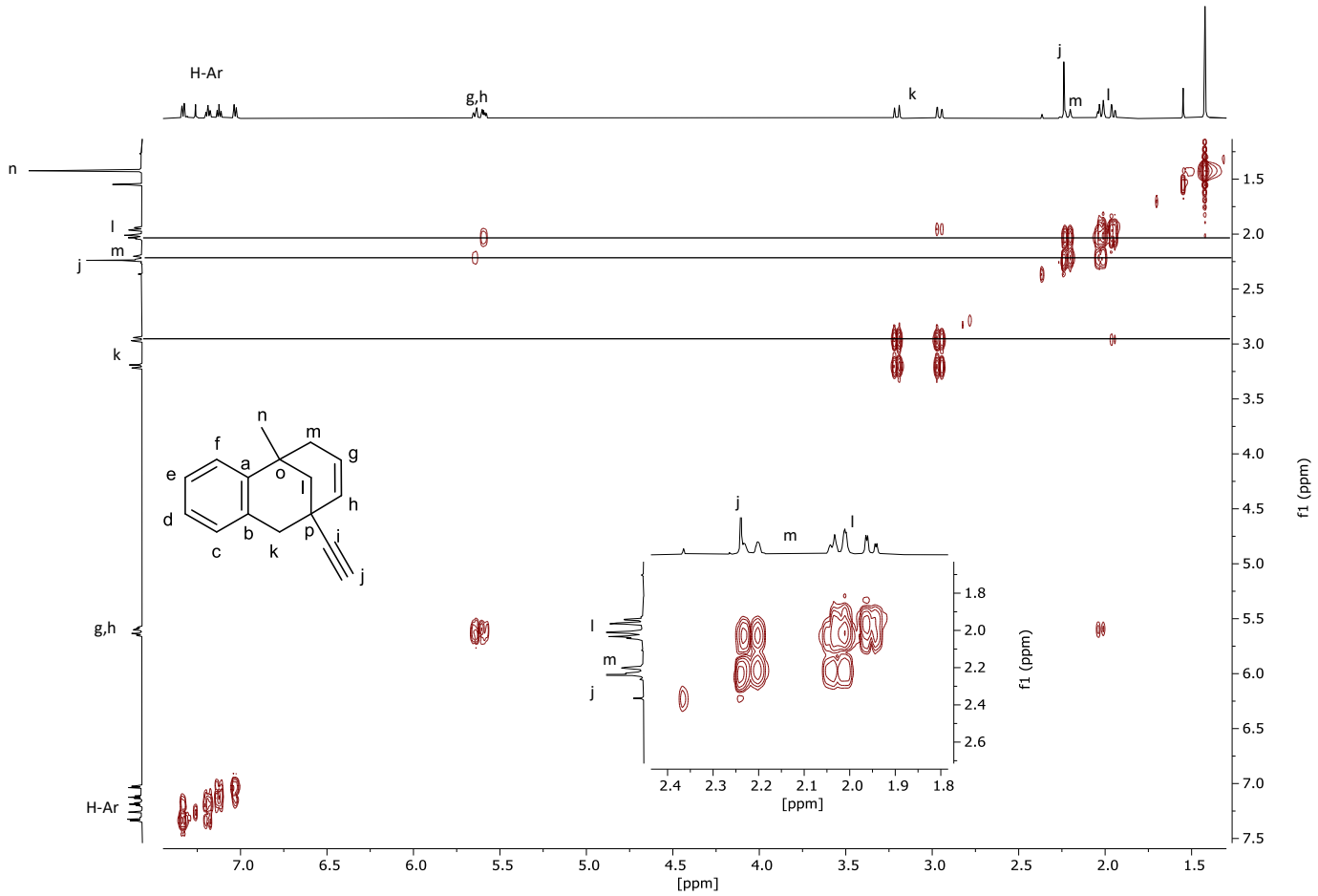


^{1}H NMR (300 MHz, $CDCl_3$) of compound **5n**

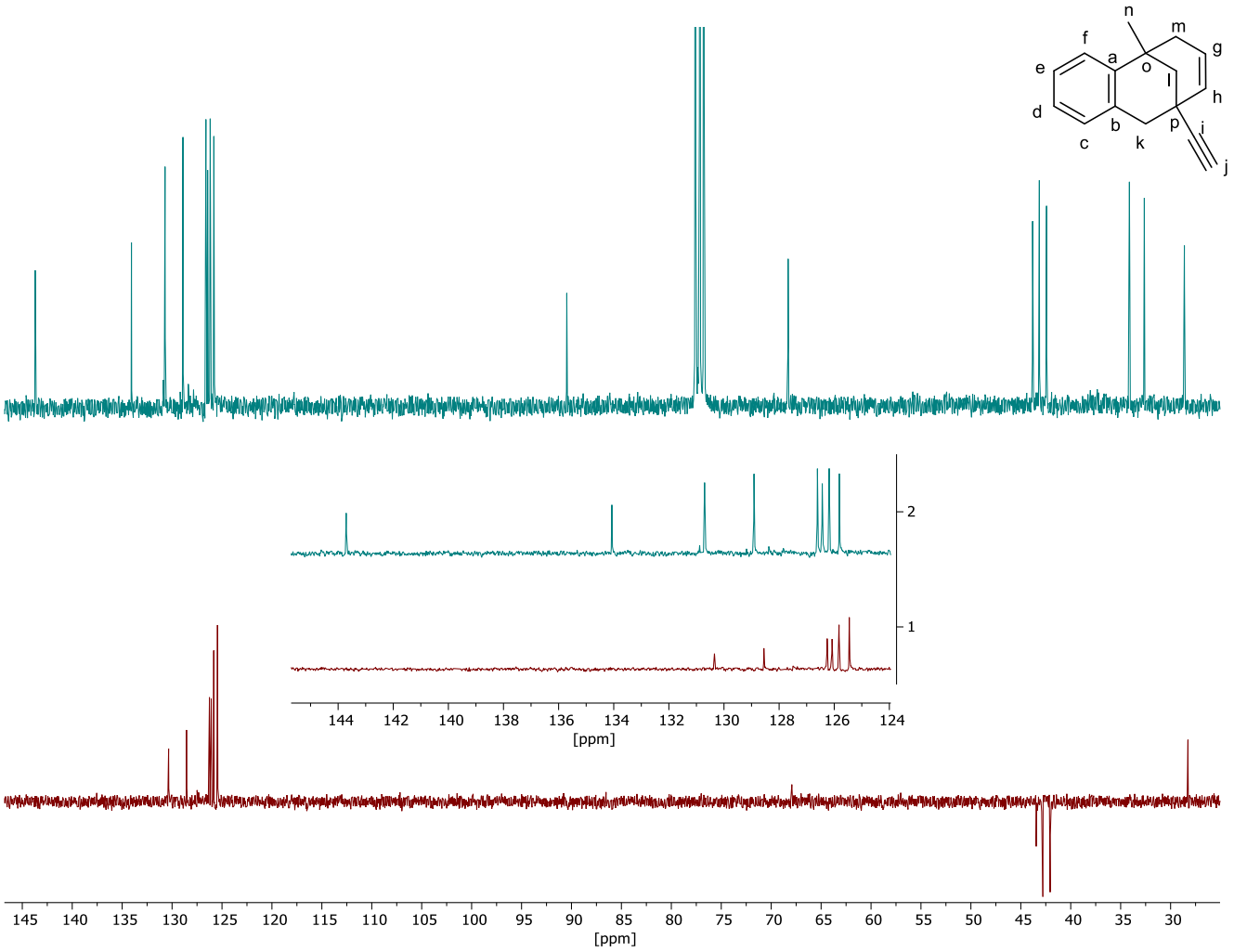


^{13}C NMR (75 MHz, $CDCl_3$) of compound **5n**

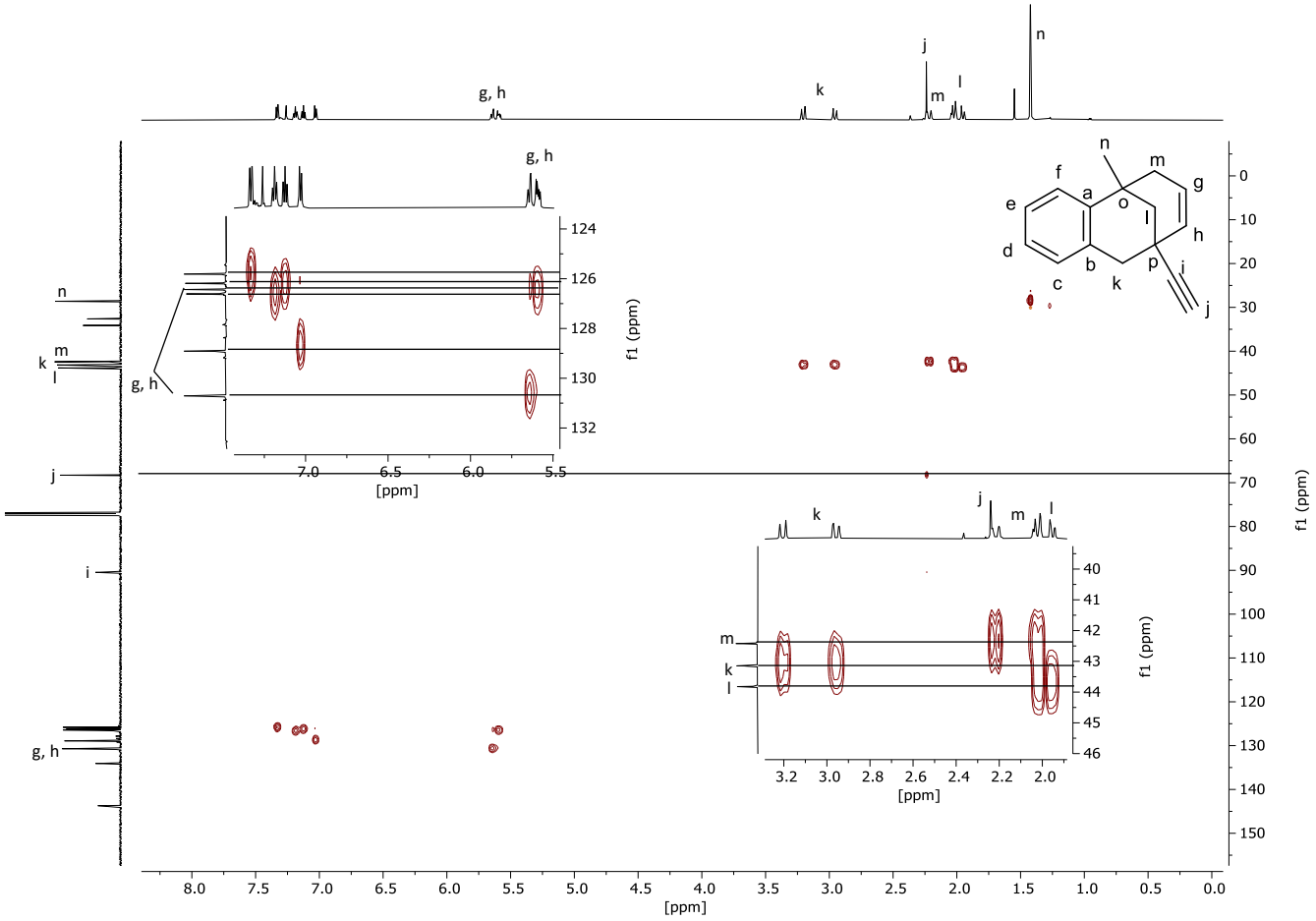
n



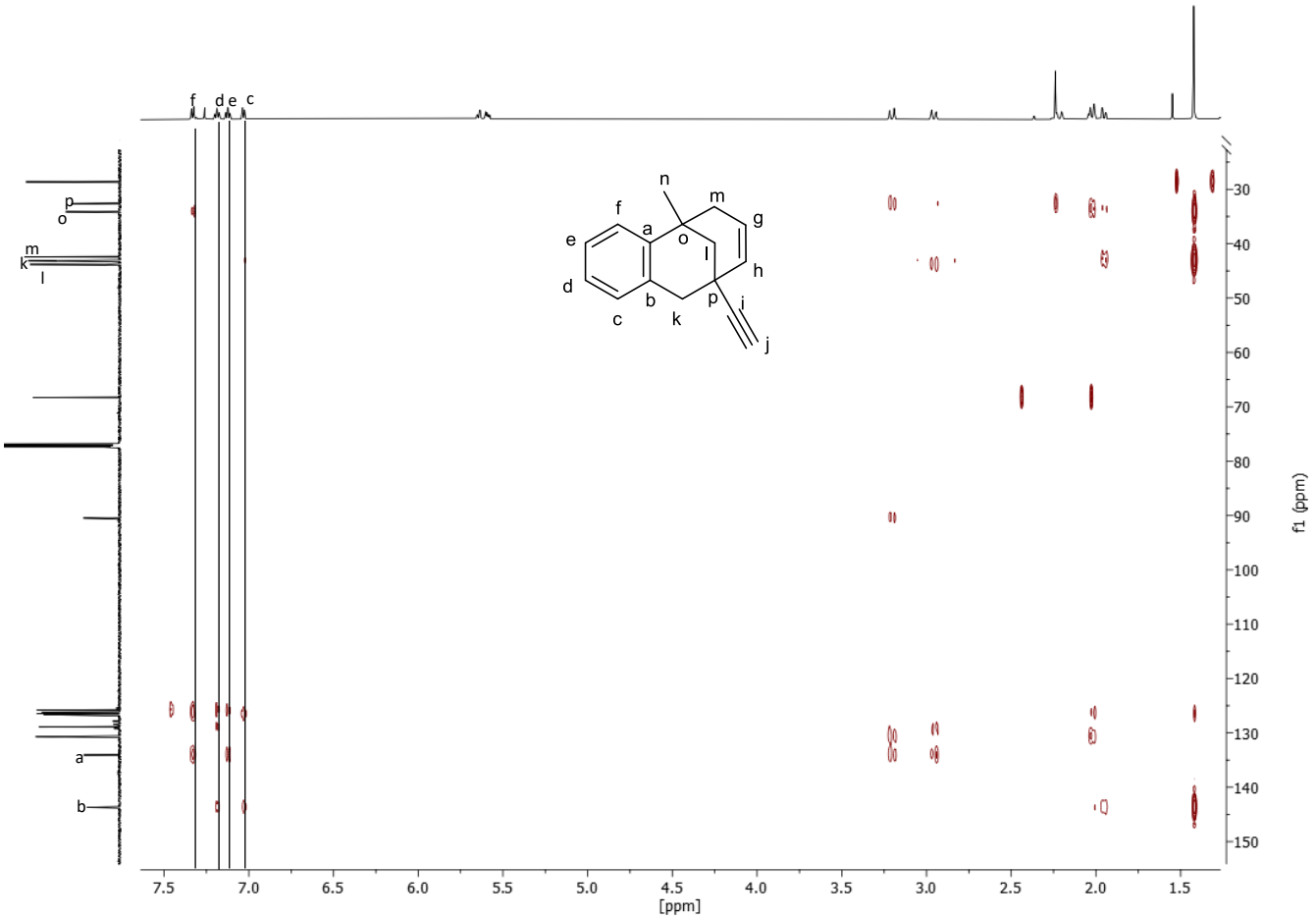
COSY (600 MHz, $CDCl_3$) spectrum of compound **5n**



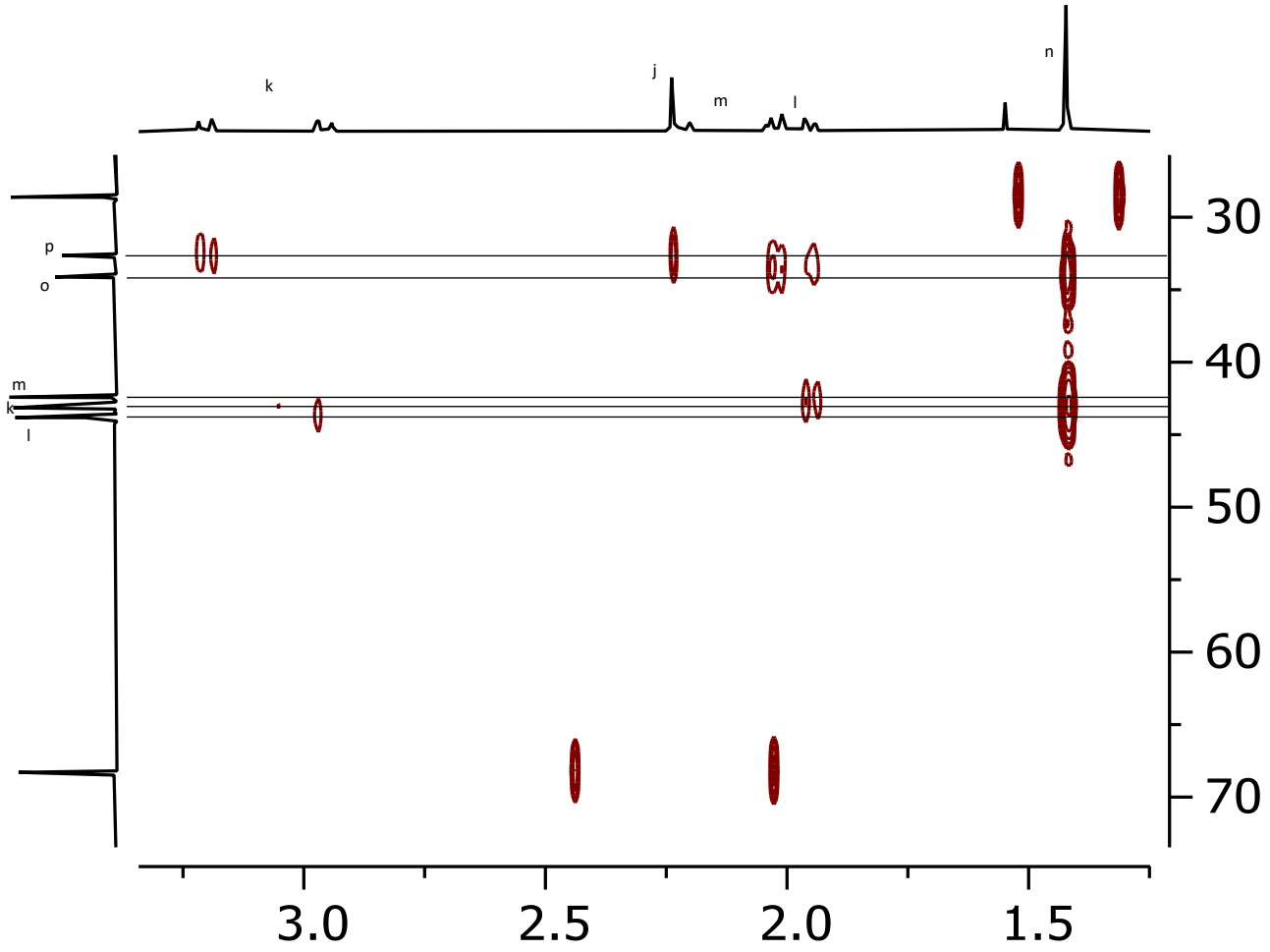
Stacked DEPT 135 and ^{13}C NMR spectrum of compound **5n**



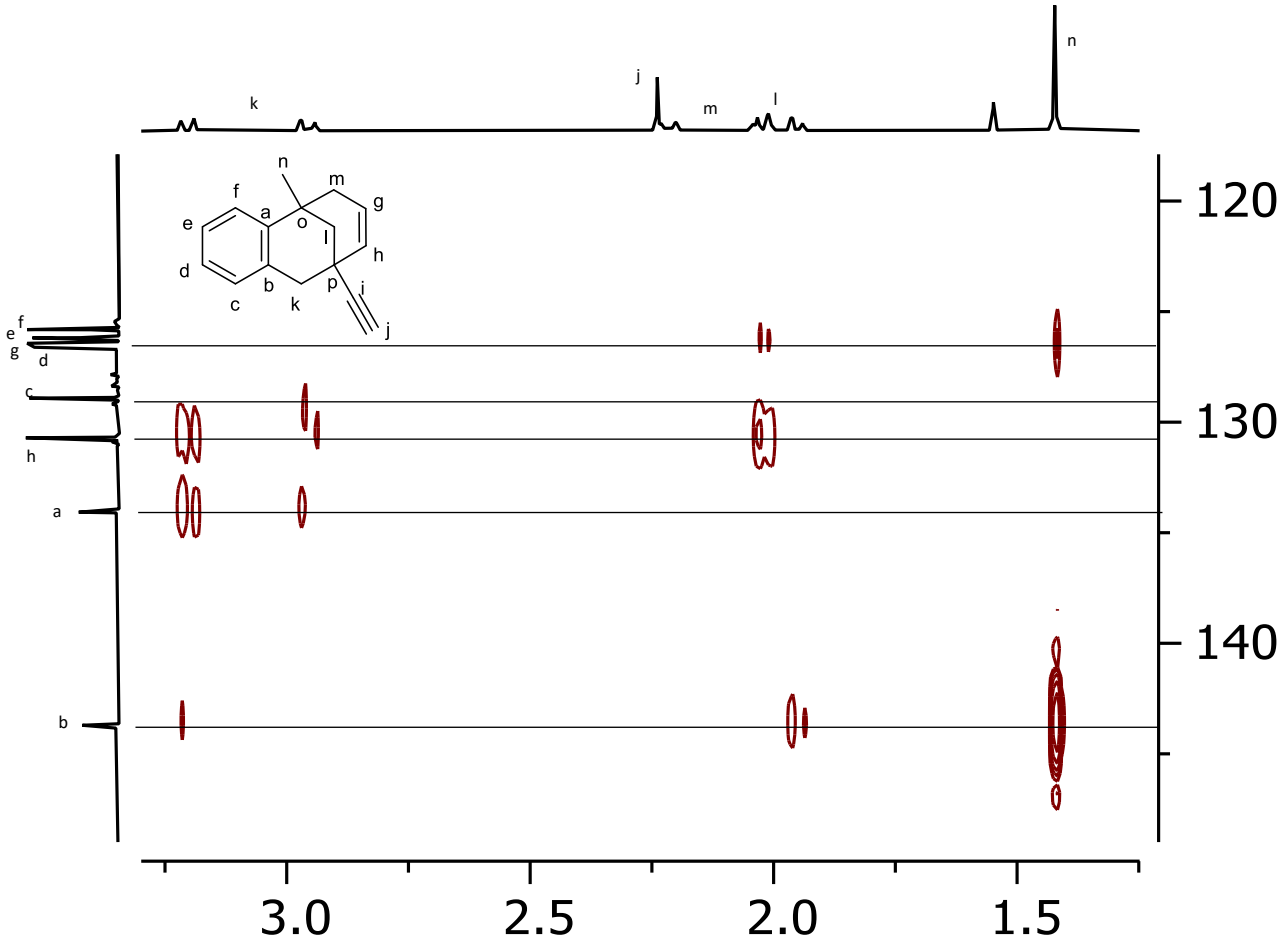
HSQC (600 MHz, 151 MHz, $CDCl_3$) spectrum of compound **5n**



HMBC (600 MHz, 151 MHz, $CDCl_3$) spectrum of compound **5n**



HMBC (600 MHz, 151 MHz, $CDCl_3$) spectrum of compound **5n**



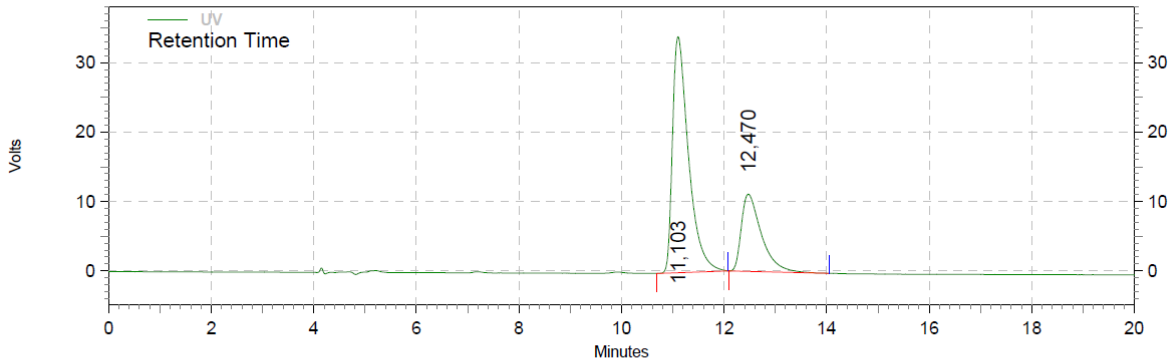
HMBC (600 MHz, 151 MHz, $CDCl_3$) spectrum of compound **5n**

HPLC traces of 3-ethynyl-2-phenylbicyclo[3.1.0]hex-2-ene (2a)

Enantioselective synthesis of 3-ethynyl-2-phenylbicyclo[3.1.0]hex-2-ene (**2a**) with (*R*)-DTBM-MeO-Biphep(AuCl)$_2$

ChiralPak IC, *n*-hexane 100%, Flow: 0.8 mL/min

Acquired: 22.09.2020 10:22:43
Printed: 23.09.2020 17:47:07



UV Results

Retention Time	Area	Area %	Height	Height %
11,103	2946461	70,90	136017	75,35
12,470	1209218	29,10	44490	24,65

Racemic reference

ChiralPak IC, *n*-hexane 100%, Flow: 0.8 mL/min

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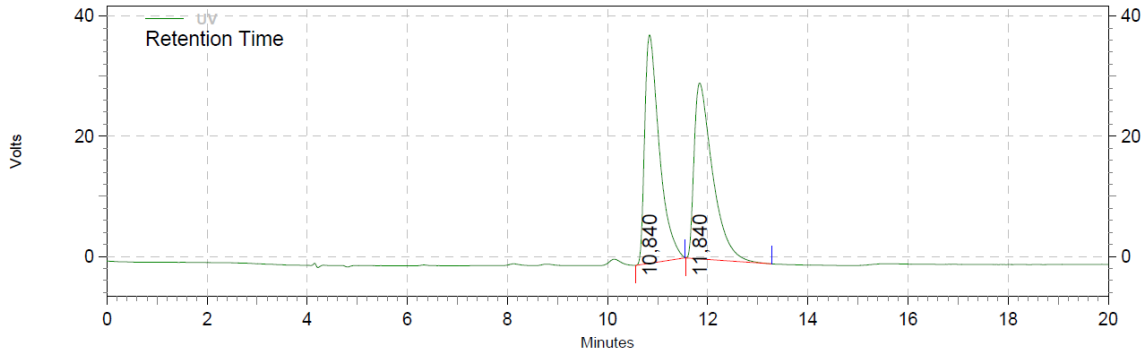

UV Results

Retention Time	Area	Area %	Height	Height %
10,840	3087882	50,70	151887	56,46
11,840	3003178	49,30	117108	43,54

VI. References

[1] R. Rüttinger, J. Leutzow, M. Wilsdorf, K. Wilckens, C. Czekelius, *Org. Lett.* **2011,** *13*, 224-227.

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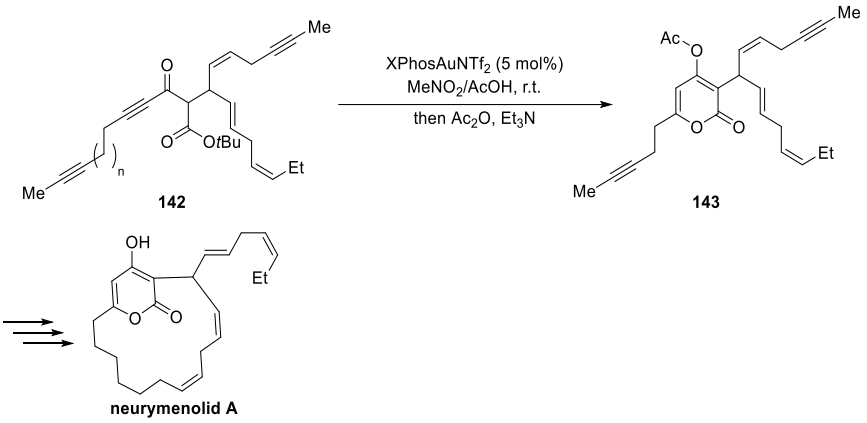
Chapter 4. Formal synthesis of enantiopure crinine type alkaloid *via* anion-induced enantioselective gold-catalyzed cyclization (cumulative part)

4-1 Building molecular complexity through gold-catalyzed intramolecular alkyne hydrofunctionalization

As aforementioned, being a versatile synthetic tool, gold catalysis is nowadays often utilized for complex molecular construction such as the synthesis of polyketides, which was elaborated in Chapter 2. Apart from polyketides, the wide substrate scope of gold catalysis and the preferential chemoselectivity could actually allow diverse chemical transformations in different types of naturally occurring product synthesis, providing a predictable and reliable solution to compound complexity construction.[28c, 157]

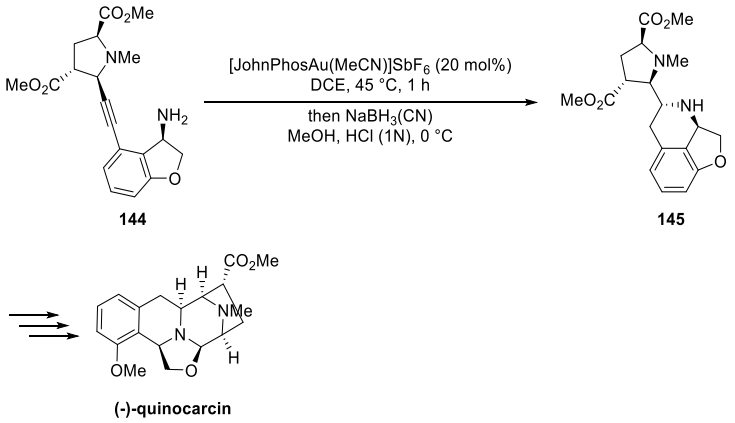


Scheme 60. Total synthesis of neurymenolide A exploiting gold-catalyzed cyclization as a critical step[158]

For instance, the first total synthesis of Neurymenolide A reported by Fürstner *et al.* is a dedicated example. Isolated from the red alga *Neurymenia fraxinifolia* on Fiji island, neurymenolide A exhibits considerable activity against methicillin-resistant staphylococcus aureus (MRSA) and vancomycin-resistant enterococcus faecium (VREF). Besides, promising cytotoxicity against 12 different cancer cell lines was also observed, making it an appealing naturally occurring product to synthesize. The synthesis commenced with an eicosapentaenoic acid derivative **142** and employed an unconventional cationic gold catalysis to achieve the crucial 4-hydroxy-2-pyrones moiety formation in intermediate **143** (Scheme 60).[158] Along with this synthesis, the merit of cationic gold catalysis was accentuated that the strong affinity between the

gold(I) complex and alkyne functional group of the pyrones formation can be accomplished in a highly efficient manner.

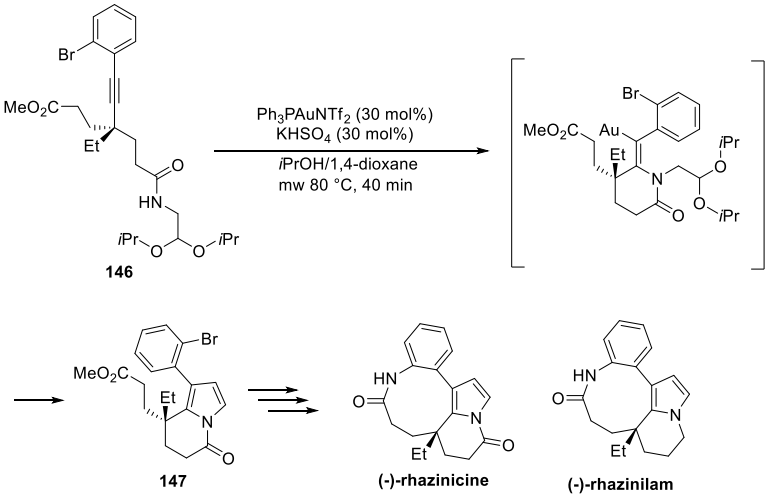
Another example of antitumor antibiotic (−)-quinocarcin total synthesis was fulfilled and reported by Ohno *et al.* in 2012 (Scheme 61).[159] The synthesis was divided into two parts, including pyrrolidine formation and tetrahydroisoquinoline scaffold construction. Beginning with the chiral *α*-substituted butyrolactone, the desired pyrrolidine **144** can be prepared without diminishing the configurational integrity. Besides, the alkyne functional group was inserted, which allows the installation of functionalized arenes under Sonogashira's condition, for the following tetrahydroisoquinoline scaffold construction for intermediate **145** was carried out under the assistance of the cationic gold-catalyzed hydroamination. Although the regioselectivity is not ideal, the substrate demanding regioselectivity control was achieved by exploiting the nature of ring strain in a multi-cyclic system. Their work shows the possibility of utilizing cationic gold catalysis in the molecular complexity building up again. On the other hand, describe the adaptability which makes it such an ideal synthesis method in a result-oriented task.



Scheme 61. Total synthesis of (−)-quinocarcin exploiting gold-catalyzed cyclization as a key step[159]

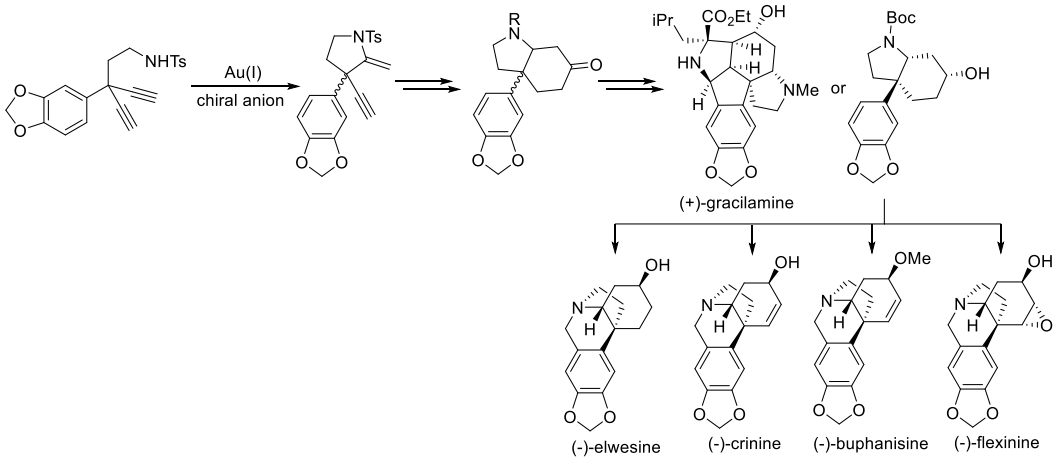
The total synthesis of (−)-rhazinilam and the first asymmetric total synthesis of (−)-rhazinicine were reported by Tokuyama in 2013 (Scheme 62).[160] By employing a gold-catalyzed cascade reaction, the construction of the per-substituted indolizinone skeleton **147** can be achieved through an intramolecular amide to alkyne addition of linear substrate **146** and followed by an intramolecular olefination driven by the liberation of the gold cation. The mild and highly selective reactivity of gold-catalyzed cyclization allows this total synthesis to be accomplished without involving any protecting group. By means of this synthesis, the scope and generality of the

gold-catalyzed cascade reaction were demonstrated. Meanwhile, further applications of gold-catalyzed cascade reactions for enhancing the molecular complexity of heterocyclic skeletons are flourishing in the modern development of organic synthesis.



Scheme 62. Total synthesis of (−)-rhazinicine exploiting gold-catalyzed cyclization as a key step[160]

4-2 Synthesis of Amaryllidaceae alkaloid that contains C3a-Arylated Hydroindole motif



Scheme 63. An overview of the formal total synthesis of crinine-type alkaloids in this dissertation.

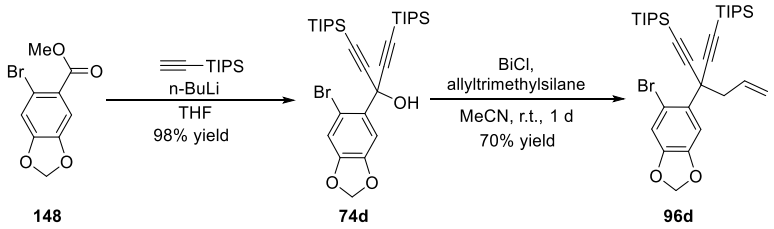
A wide array of alkaloids has been extracted from the Amaryllidaceae plant family, many of which possess significant pharmaceutical value. Among these naturally occurring compounds, the C3a-arylated hydroindole moieties found in Amaryllidaceae alkaloids are particularly intriguing. With the development of a reliable synthetic method, a diverse range of derivatives can be accessed, offering the opportunity to explore their bioactivity in the context of new drug discovery.

Additionally, studying the metabolism mechanisms of these chemicals in the human body can be facilitated by synthesizing and evaluating these derivatives.

This chapter presents the results of anion-induced enantioselective gold-catalyzed alkyne hydroamination, showcasing the successful formation of enantioselective pyrrolidine as a template for the synthesis of related crinine-type alkaloids. Furthermore, building upon the achievement of this gold-catalyzed desymmetrization for chiral quaternary center construction, a substantial number of Amaryllidaceae alkaloids formal synthesis was described (Scheme 63).

4-3 Unpublished results

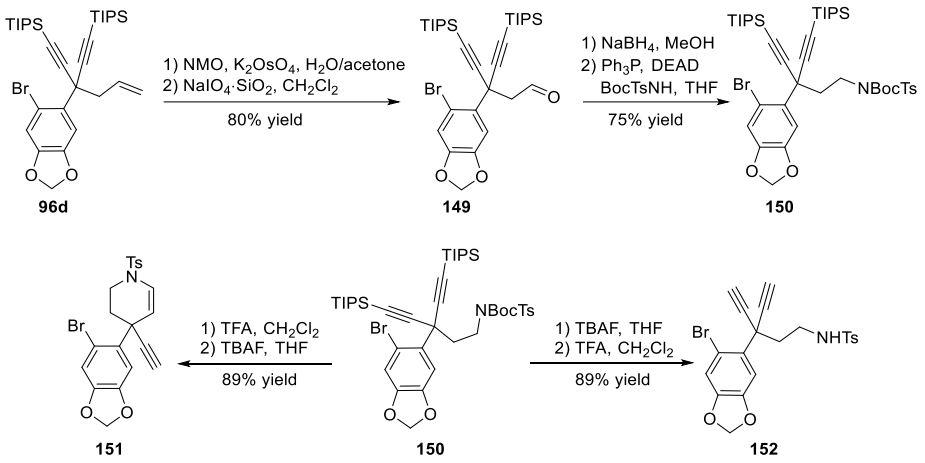
In the regard of targeting molecules synthesis such as crinines and (+)-gracilamine, although the C3a-arylated hydroindole synthesis is known to be feasible based on the experience of previously reported (+)-mesembrine synthesis[125], the challenge lies in the functionalization of arene moiety is inevitable. Thus, the synthesis was initiated with the *ortho*-brominated ester **148** in order to simplify the arene functionalization in the later stage.



Scheme 64. Self-developed bismuth(III)-catalyzed propargylic replacement of brominated substrate **74d**

With a promising synthetic strategy (see chapter 4-4), the journey of naturally occurring alkaloid formal synthesis commence with the assembly of the sulfonamido-1,4-diyne intermediate. In the previous research from 2011, our research group established a multi-steps procedure for synthesizing such 1,4-diynes species, including Ullmann coupling, selective *C*-allylation, and enol phosphate elimination. While this method proven practical, an opportunity for more direct propargylic functionalization emerged in the form of bismuth(III)-catalyzed allylation of 3-aryl-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ols **74d** was disclosed in 2022 which was as well shown in chapter 2 (Scheme 64). The further attempt to predigest the synthesis led to the exploration of bismuth(III)-catalyzed propargylic replacement was tested using functionalized vinyl amine nucleophiles such as trimethyl(vinyloxy)silane enamines. Unfortunately, these reagents predominantly underwent self-aggregation rather than participating in the intended

propargylic replacement. This deleterious side reaction was prohibited only under specific substrates involving the sulfonamide protecting group, but subsequent synthetic route complications and suboptimal overall efficiency still dissent to this approach.



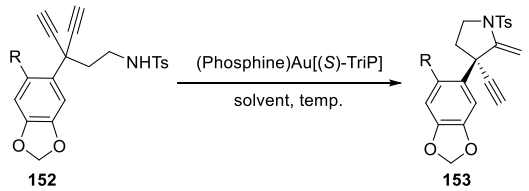
Scheme 65. Preparation of the brominated symmetric 3-aminoalkyl-1,4-diyne precursor **152**

Having the allylated-diyne **96d** readily for the further transformation of the alkene moiety into an amine nucleophile, a multi-steps procedure was established and illustrated in Scheme 65. Employing Upjohn's conditions, the alkene functional group will undergo a dihydroxylation with a remarkable 89% yield. Subsequently, oxidative cleavage proceeded to produce aldehyde **149** in an impressive 90% yield, utilizing sodium periodate on silica gel. However, the subsequent one-pot reductive amination of this compound proven challenging, as attested by previous research, a tandem approach involving sequential reduction and Mitsunobu amination was applied, yielding sulfonamide **150** with a two-step overall 75% yield. Eventually, the removal of the carbamate and silyl protecting groups provides the 3-alkylamine-1,4-diyne **152** in an overall 89% yield. It is noteworthy that careful compliance to the deprotection sequence is imperative to prevent the unwanted reactivity of the terminal alkyne moiety for thermally induced nucleophilic attack by the unprotected Sulfonamide, thereby forming compound **151**, which was cyclized in a six-*endo*-dig manner. (Scheme 65, bottom).

With the brominated substrate **152,** the reactivity and stereoselectivity were thereby tested in the presence of gold(I) complex incorporating chiral anion (*S*)-TriP for the methylene pyrrolidine formation. Since the *ortho*-substituted substrate might have a different pattern in its transition state, various phosphine ligands were tested to ensure the bulkiness is not significantly influencing the

stereochemistry. To our disappointment, the enantioselectivity of the cyclized-pyrrolidine observed at ambient temperature was not very tempting, although the ligand screening indicates the bulkiness from phosphine is necessary (Table 9, entries 1-3). Along with the experience from the non-brominated substrate (Table 9, entries 5-6), the lower temperature is particularly important to achieve satisfying enantioselectivity. Therefore, this cyclization was also tested at -30 ℃ and -55 ℃. Unfortunately, as the reaction temperature dropped, the emerging solubility issue caused low reactivity. When the reaction proceeded at -55 ℃, no conversion was observed after 72 h; on the other hand, when the reaction was carried out at -30 ℃, only 5% conversion was obtained (Table 9, entry 4). Even though the enantioselectivity slightly improved to 23 % *ee*, it is not good enough for fulfilling the enantiopure synthesis of naturally occurring alkaloids. Thus, the synthesis plan of crinines type alkaloid and (+)-gracilamine has to accommodate the cyclization of non-brominated 3-aminoalkyl-1,4-diyne and seek for an alternative arene functionalization method. The details of final result and discussion is included in chapter 4-4.

Table 9. Optimization of stereoselective gold(I)-catalyzed intramolecular cyclization of brominated substrate **152**[a]



152 **153**

Entry	R	R_3P	solvent	temp. (℃)	Time (h)	Yield (%)[b]	ee
1	Br	Ph_3P	CH_2Cl_2	r.t.	8	78	8
2	Br	JohnPhos	CH_2Cl_2	r.t.	8	97	6
3	Br	tBu_3P	CH_2Cl_2	r.t.	8	85	14
4	Br	tBu_3P	$CHCl_3$	-30 ℃	72	5	23
5	H	tBu_3P	$CHCl_3$	-55 ℃	72	98(76)	77
6[c]	H	tBu_3P	$CHCl_3$	-55 ℃	72	99(74)	75

[a] Unless noted otherwise the reactions were carried out by using diyne starting material (0.2 mmol), gold(I) catalyst (5 mol %), silver salt (4 mol%) in anhydrous solvent (0.1 M) under N_2 atmosphere. [b] isolated yield. [c] *t*-Bu_3PAu(*R*)-TriP was used as catalyst..

4-4 Publication

A Comprehensive Approach to C3a-Arylated Hydroindole-related Alkaloids Utilizing Asymmetric Gold Catalysis: Formal Synthesis of (+)-Gracilamine and Other Enantiomerically Pure Crinine Alkaloids

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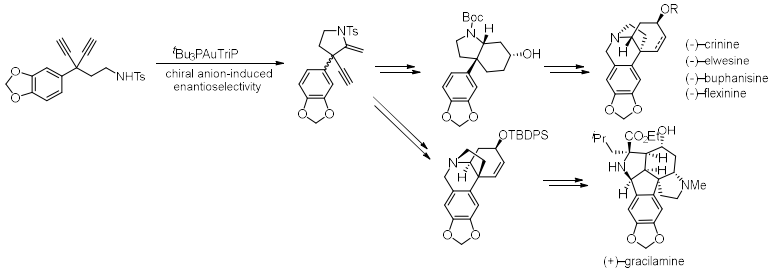
Institute for Organic Chemistry and Macromolecular Chemistry, Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, D-40225 Düsseldorf, Germany



Supporting Information Placeholder

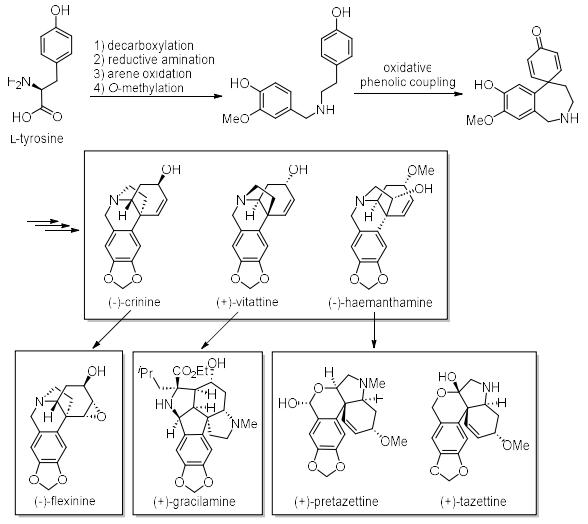
ABSTRACT: A diversity-oriented total synthesis for *Amaryllidaceae* alkaloids incorporating the frequently found C3a-arylated hydro-indole moiety has been developed. Chiral anion-induced gold(I) catalysis was employed for the cyclization of 1,4-diynes to the pyrrolidine and the installation of the all-carbon quaternary stereocenter. Using this methodology both enantiomeric series of crinine type alkaloids in high enantiopurity are accessible. The formal synthesis of a wide range of *Amaryllidaceae* alkaloids is described such as (+)-vitattine, (-)-*epi*-vitattine, (-)-elwesein, (-)-*epi*-elwesein, (-)-crinine, (-)-*epi*-crinine, (-)-buphanisine, (-)-flexinine, and (+)-gracilamine.

Introdution

Amaryllidaceae alkaloids are a family of naturally occurring compounds that have been frequently utilized for pharmacological, medicinal, and agricultural applications.[1] Due to their complex architecture and great potential in many aspects, these alkaloids are appealing molecules which caught significant attention among chemists.[1,2] In particular, the multi-cyclic structures sharing the same C3a-arylated hydroindole moiety with its chiral all-carbon quaternary stereocenter represents a challenge to their synthesis, for which more recently synthetic methodology was developed.[3,4] Originating from L-tyrosine, the biosynthesis of these natural products generally evolve through an oxidative *para-para* phenolic coupling and an intramolecular Michael addition as key steps (Figure 1).[5] These alkaloids display a wide range of bioactivity, including anti-bacterial, anti-malarial, anti-plasmodial, anti-viral as well as apoptosis-inducing properties.[6]

Among *Amaryllidaceae* alkaloids, (+)-gracilamine is one of the most eye-catching representatives incorporating a sophisticated pentacyclic structure with seven consecutive stereocenters. Isolated by Ünver and Kaya in 2005, this alkaloid was collected from *Galanthus gracilis* found in Turkey.[7] Due to the limited natural source of this compound and its great potential with respect to medicinal purposes, many research groups have addressed the total syntheses of gracilamine.[8]

Figure 1. The biosynthesis of crinines

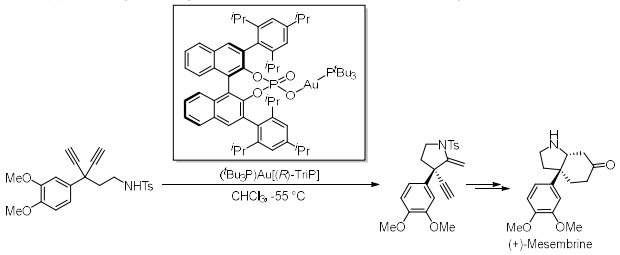


In 2017, the first enantioselective synthesis was reported by Xie's and Zhou's research groups utilizing the kinetic resolution of racemic *epi*-vitattine for the chiral quaternary center construction.[9] An entirely different approach based on an oxidative phenolic coupling was published by Nagasawa and co-workers in 2018.[10] In their work, an enantioselective aza-Friedel–Crafts reaction was applied to establish the desired configuration. In the same year, the

synthesis of the enantiomeric (-)-gracilamine starting from an enantiopure azabicyclic heptanone scaffold undergoing a stereoselective ring opening and a series of ring assembly steps was accomplished by the Pandey group.[11]

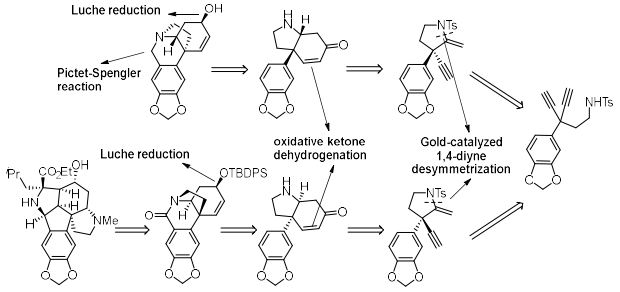
In 2012, our research group reported the asymmetric formation of pyrrolidines utilizing the chiral anion-induced gold(I)-catalyzed desymmetrization of amido-1,4-diynes.[12a] Herein, we found that tri(*tert*-butylphosphine)gold(I) 3,3′-bis(2,4,6-triisopropylphenyl)-BINOL-phosphate (TriP) is capable of selectively activating one of the alkynyl functional groups and allowing intramolecular bond formation (Scheme 1). At low temperatures up to 92% ee were observed in this challenging transformation. The synthetic applicability of the new method was exemplified in the total synthesis of (+)-mesembrine.[4b] From the 3-ethynyl-2-methylenepyrrolidine intermediate formed upon enantioselective cyclization, a second ring closure by the reactive enamide and subsequent reductions steps served for the construction of the C3a-arylated hydroindole skeleton of (+)-mesembrine.

Scheme 1. Previously reported (+)-mesembrine synthesis *via* gold (I)-catalyzed cycloisomerization of 1,4-diynes



Retrosynthetically, the pyrrolate motif of gracilamine could arise from an intramolecular (3+2)-cycloaddition involving an azomethine ylide originating from L-leucine (Figure 2).[8] The common method for azomethine ylide formation requires an aldehyde precursor, which could be derived from the known silyl-protected (+)-*epi*-vitattine.[8a,9] As for the 1-azabicyclo[3.2.1]octane motif in (-)-crinine and (+)-*epi*-vitattine, the Pictet-Spengler cyclization would be suitable for our purpose.[5c,13] The cyclohexenol could be easily afforded by a regioselective ketone reduction under Luche's condition.[14] A closely related, fused cyclohexanone would be accessible by a sequence as previously reported in our (+)-mesembrine total synthesis.[4b] However, a cyclic ketone dehydrogenation needs to be included in this case in order to restore the reactive α,β-unsaturated ketone for the last (3+2) cyclization.[12b,15] As described, the optically active pyrrolidine motive would be prepared enantioselectively by intramolecular 1,4-diyne hydroamidation in the presence of the chiral ^{t}Bu$_3$PAu(I)TriP complex (Scheme 1).[12a]

Figure 2. Retrosynthesis analysis for (+)-gracilamine and (-)-crinine

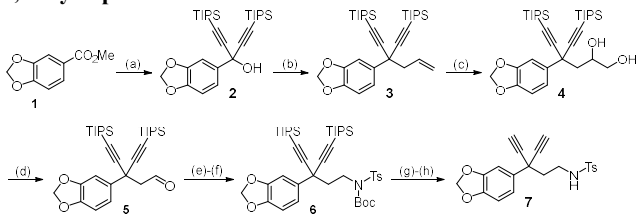


Result and discussion

Beginning with the synthesis of sulfonamido-1,4-diyne **7**, the formal synthesis of crinines was initiated (Scheme 2). In 2011, our research group reported the preparation of such 1,4-diynes requiring an Ullmann coupling, *C*-selective allylation and enol phosphate elimination.[14] This method is practical but can be significantly simplified as we found a more straightforward bismuth(III)-catalyzed propargylic allylation of 3-aryl-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ols in 2022 (Scheme 2, step b).[16] Optimization of this reaction to suppress allene formation resulted in 70% yield of the enediyne (see supporting information).

After preparation of the allylated diyne substrate **3** the alkene was transformed into an amine by a sequence of established methods (Scheme 2). Under Upjohn's condition,[17] the alkene moiety was converted into 1,2-diol **4** in 98% yield, which was then transformed into the corresponding aldehyde **5** in 95% yield by an oxidative cleavage process in the presence of sodium periodate on silica gel. Later on, reduction and following Mitsunobu amination in a consecutive fashion provided sulfonamide **6** in 84% yield over two steps.[12b] Finally, the removal of the carbamate and silyl protecting groups was conducted to provide 3-aminoethyl-1,4-diyne **7** in 92% yield over two steps. Notably, the order of deprotection steps is crucial in order to prevent the terminal alkyne species from being attacked by the nitrogen nucleophile in a thermally initiated intramolecular cyclization.

Scheme 2. Preparation of the symmetric 3-aminoalkyl-1,4-diyne precursor



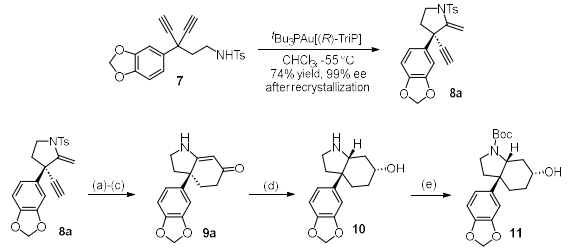
(a) (Triisopropylsilyl)acetylene, *n*-BuLi, THF, 0 °C to rt, 98%; (b) Allyltrimethylsilane, $BiCl_3$, MeCN, 70%; (c) NMO, K_2OsO_4, Acetone/H_2O, 89%; (d) $NaIO_4$ on silica gel, CH_2Cl_2, 95%; (e) $NaBH_4$, MeOH, 98% (f) BocTsNH, PPh_3, DEAD, THF, 86%; (g) TBAF, THF, 94%; (h) TFA, CH_2Cl_2, 98%.

With 1,4-diyne **7** readily in hand, the asymmetric pyrrolidine ring closure was investigated in the presence of gold (I) complexes incorporating the chiral anion (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL-phosphate ((*R*)-TriP). Pyrrolidine **8a** was obtained in 99% yield at -55 °C with 75% ee (Scheme 3, top).[12b] After simple recrystallization from ethyl acetate, the pyrrolidine intermediate was isolated in enantiomerically pure form.

In a related fashion to the (+)-mesembrine synthesis, the construction of the fused cyclohexenone moiety in compound **9a** was accomplished in a three-step process, including propynoate formation, alkyne hydrogenation, and domino reductive detosylation/cyclization reaction in a satisfying overall yield (Scheme 3, step a-c).[12b] Using the strong, bulky DIBAL-*H* reducing agent, both the ketone and enamine function in compound **9a** could be reduced at once without precautionary measures, giving the product in excellent diastereoselectivity (Scheme 3, step d). In comparison to the previously reported aminoketone reduction by Stevens and coworkers, the enamine moiety in compound **9a** presumably leads to

a more rigid, conformation of the bicyclic framework resulting higher selectivity.[18]

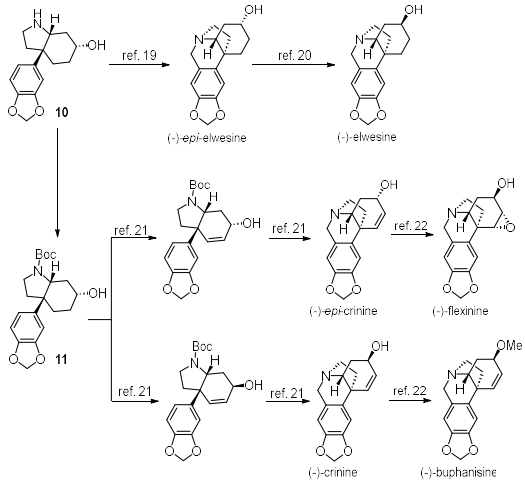
Scheme 3. Construction of the enantiomerically pure C3a-arylated hydroindole



(a) *n*-BuLi, then $ClCO_2Et$, −78 °C to rt, 96%; (b) 85 bar H_2, Pd/C, 99%; (c) $NaC_{10}H_8$, THF, –78 °C, 84%; (d) DIBAL-*H*, toluene, –78 °C to rt, 85%; (e) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 99%.

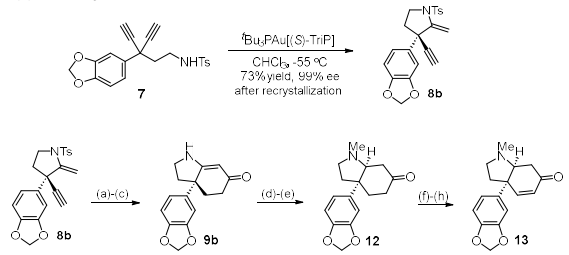
The amino alcohol intermediate **10** obtained in this way is of particular importance as it provides access to different naturally occurring products. For example, (-)-*epi*-elwesine can be prepared by a Pictet-Spengler cyclization from this intermediate, accomplished by Landais and co-workers in 2014.[19] Furthermore, epimerization of the cyclohexanol motif was achieved under Mitsunobu's condition to result in (-)-elwesine by Sánchez and co-workers in 1983.[20] Likewise, Boc-protected C3a-arylated hydroindole **11** can be easily prepared which could serve as a common template for the synthesis of crinine-type natural products including (-)-crinine, (-)-*epi*-crinine, (-)-buphanisine, and (-)-flexinine, respectively (Scheme 4).[21,22]

Scheme 4. Formal syntheses of various crinine-type natural occurring compounds



In order to demonstrate the applicability of the developed methodology for both enantiomeric series of *Amaryllidaceae* alkaloids, the enantiomeric pyrrolidine isomer **8b** was synthesized utilizing the (*S*)-configured catalyst and cyclized in the identical way to give compound **9b** as a precursor for the formal synthesis of (+)-gracilamine. The reduction of the highly polarized β-aminoenone moiety was investigated, however this enone proved surprisingly unreactive. To accomplish reduction, we chose to install a methyl group on the amine. On one hand, methyl group installation is inevitable in the context of the (+)-gracilamine synthesis; on the other hand, the methyl group serves as a protective moiety for which is precedence in the successful enamine reduction we found in the (+)-mesembrine synthesis (Scheme 5, step d). This way, selective enone reduction could be achieved under Birch´s conditions without affecting the aromatic ring to afford formation of compound **12** (Scheme 5, step e). The regioselective reinstallation of a new double bond in enone **13** was accomplished in a three-step oxidative process involving silyl enol ether formation, α-selenation, and selenoxide elimination (Scheme 5, step f-h).

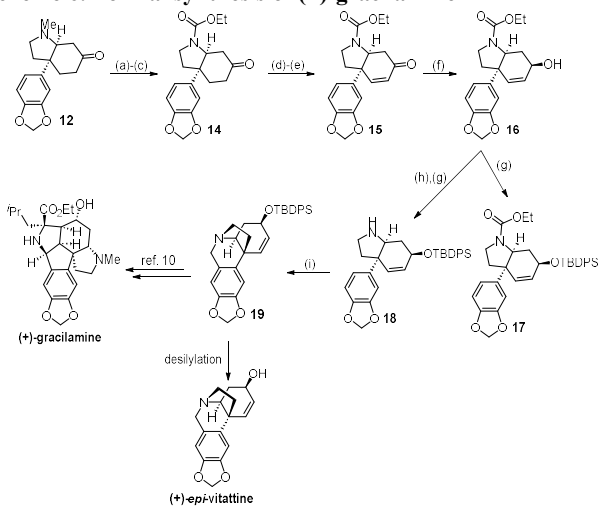
Scheme 5. Anion-induced enantioselective cyclization by gold(I) catalysis



(a) *n*-BuLi, then $ClCO_2Et$, −78 °C to rt, 96%; (b) H_2 (85 bar), Pd/C, 99%; (c) $NaC_{10}H_8$, THF, –78 °C, 84%; (d) MeI, NaH, THF; (e) Li, NH_3, THF, –78 °C, 74% (two steps); (f) TMSOTf, DIPEA, CH_2Cl_2, –78 °C to rt; (g) PhSeBr, CH_2Cl_2, –78 °C to rt; (h) *t*BuOOH, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 77% (3 steps).

In order to pave the ground for the final (3+2) cycloaddition giving the second pyrrolidine ring, the functionalization of the electron-rich aromatic ring was investigated. Neither formylation nor bromination of methylated enone **13** were successful despite many attempts. The reason could be attributed to the tertiary amine which effectively coordinates to the required Lewis acid or disadvantageously interacts with any other electrophiles in the later phase of this total synthesis. Thus, the methyl group was exchanged by a carbamate protecting group giving cyclohexanone **14** (Scheme 6, step a-c).[23] Ketone oxidation could be achieved in two steps, giving enone **15** under Saegusa's conditions instead of the aforementioned selenoxide elimination since this reaction is not hampered any more by the amine coordinating to the palladium catalyst (Scheme 6, step d-e).

Scheme 6. Formal synthesis of (+)-gracilamine



(a) Ethylene glycol, *p*-TsOH, toluene, reflux; (b) $ClCO_2Et$, K_2CO_3, benzene, rt; (c) HCl (2M), acetone, rt, 86% (3 steps); (d) TMSOTf, DIPEA, CH_2Cl_2, -78 °C; (e) $Pd(OAc)_2$, MeCN, 88% (two steps); (f) $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$, MeOH, 0 °C to rt, 71%; (g) TBDPSCl, imidazole, CH_2Cl_2, rt, 96% (h) NaOH, EtOH, 70 °C, 90%; (i) Eschenmoser's salt, benzene, 80 °C, 86%.

A diastereoselective reduction of enone **15** under Luche's conditions was successfully accomplished, providing the desired diastereomer **16** in 71% yield (Scheme 6, step f).[14] Next, we investigated the final ring-closure under Bischler-Napieralski's condition. To prevent unwanted lactonization a silyl protective group was installed (Scheme 6, step g).[24] However, despite many attempts using Lewis acids such as phosphoryl chloride, triflic anhydride, $Zn(OTf)_2$, $SnCl_4$, $TiCl_4$, boron trifluoride etherate etc. we could not identify suitable reaction conditions for this transformation. We therefore removed the carbamate by basic saponification (Scheme 6, step h) and conducted a Pictet-Spengler cyclization with Eschenmoser's salt giving tricyclic intermediate **19** and completing the formal synthesis of (+)-*epi*-vitattine (Scheme 6, step i).[14] Likewise, also the formal synthesis of gracilamine was thereby completed by the preparation of compound **19** since it was shown by Zhou and co-workers that (+)TBDPS-*epi*-vitattine can be transformed into the natural product *via* 1,3-dipolar cycloaddition with isoleucine ethyl ester after the disassembly of the pyrrolidine ring.[10]

In conclusion, a series of formal syntheses towards multiple enantiopure alkaloids such as (+)-gracilamine have been accomplished from bicyclic intermediate **10** and tricyclic intermediate **19**. A gold(I)-catalyzed 1,4-diyne desymmetrization was utilized as a key step for the construction of the C3a-aryl-hydroindole core, and the stereochemistry was controlled by the governance of a chiral phosphate anion (TriP). The key intermediates for the crinine-type natural products synthesis were accessed for the opposite enantiomeric series, showcasing the applicability of this methodology for diverse natural product synthesis.

Experimental section

Methyl benzo[d][1,3]dioxole-5-carboxylate (1) In a dried and nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar and reflux condenser, 1,3-benzodioxole-5-carboxylic acid (4.98 g, 30.0 mmol, 1.00 equiv.) was dissolved in anhydrous methanol (70 mL). To the solution, concentrated sulfuric acid (5.14 mL, 95.9 mmol, 3.20 equiv.) was added slowly. The reaction mixture was heated to reflux for 24 hours. After completion of the reaction was confirmed by TLC, the reaction mixture was cooled to 0 °C. 100 mL of ice water was added to the mixture; then, the mixture was filtered and washed with a water-methanol mixture (2:1). The solid was dried to yield **methyl benzo[d][1,3]dioxole-5-carboxylate (1)** as a white solid (4.11 g, 22.8 mmol, 76%). A minor amount of product was extracted with EtOAc three times from the filtrate. The organic fractions were collected and further purified by flash column chromatography on silica gel (EtOAc:n-hexanes = 1:20, RF = 0.45) to recover the desired methyl benzo[d][1,3]dioxole-5-carboxylate (1) (5.30 g, 29.4 mmol, 98%). ^{1}H NMR (300 MHz, CDCl3): δ = 7.31 (s, 1H), 7.08 (s, 1H), 6.04 (s, 2H), 3.88 (s, 3H). The results are consistent with the data reported.

3-(Benzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (2) In a dried and nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, triisopropylsilylacetlyene (14.2 mL, 62.4 mmol, 2.20 equiv.) was dissolved in anhydrous THF (125 mL). To the solution, *n*-BuLi (2.5 M, 25.0 mL, 62.5 mmol, 2.20 equiv.) was added at 0 °C. The mixture was stirred at this temperature for 30 min, then treated with methyl 1,3-benzodioxole-5-carboxylate (5.11 g, 28.4 mmol, 1.00 equiv.) under N_2 atmosphere. The reaction mixture was stirred for 1 h while being allowed to warm to room temperature. Aqueous workup was committed by slowly adding water to the reaction mixture after complete conversion was observed by TLC. The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent the crude product was purified via flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:20, R_F = 0.36) to produce **3-(benzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (2)** as a yellowish oil (14.4 g, 28.1 mmol, 99%); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.37 (dd, J = 8.1, 1.9 Hz, 1H), 7.32 (d, J = 1.9 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 5.98 (s, 2H), 2.75(s, 1H), 1.11-0.92 (m, 42H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.8, 147.5, 135.9, 119.9, 107.8, 107.1, 107.0, 101.3, 86.4, 65.4, 18.6, 11.2; **IR** (NaCl) ṽ (cm^{-1}): 3412, 2943, 2891, 2865, 2144, 1722, 1622, 1609, 1504, 1487, 1463, 1443, 1383, 1365, 1280, 1256, 1194, 1158, 1105, 1074, 1040, 1018, 996, 939, 919, 882, 810, 761, 722, 677; **HRMS (ESI):** calc'd. for $C_{30}H_{49}O_3Si_2$, **$[M+H]^+$** 513.3215; found 513.3216.

(3-Allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (3) and (3-(benzo[d][1,3]dioxol-5-yl)octa-3,4,7-trien-1-yne-1,5-diyl)bis(triisopropylsilane) In a dried and nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, (3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (15.1 g, 29.4 mmol, 1.00 equiv.) was dissolved in anhydrous MeCN (150 mL). To the solution, bismuth chloride (1.91 g, 5.88 mmol, 20.0 mol%) and allyltrimethyl silane (14.1 mL, 88.2 mmol, 3.00 equiv.) were added at ambient temperature. The mixture was stirred at this temperature for 24 h under N_2 atmosphere Aqueous workup was committed by slowly adding water to the reaction mixture after complete conversion was observed by TLC. The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent, the crude product was purified via flash column chromatography on silica gel (*n*-hexane 100%, R_F = 0.46) to produce the **(3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triiso-propylsilane) (3)** as a colorless oil (11.9 g, 22.2 mmol, 76%) and **(3-(benzo[d][1,3]dioxol-5-yl)octa-3,4,7-trien-1-yne-1,5-diyl)bis(triisopropylsilane)** as a colorless oil (1.30 g, 2.43 mmol, 22%). **(3-Allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane): ^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.23-7.16 (m, 2H), 6.77 (d, J = 8.7 Hz, 1H), 5.96 (s, 2H), 5.87 (ddt, J = 17.3, 10.3, 7.1 Hz, 1H), 5.12-4.98 (m, 2H), 2.61 (dt, J = 7.1, 1.2 Hz, 2H), 1.13-1.03 (m, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 146.4, 145.6, 134.9, 132.4, 118.9, 117.5, 106.9, 106.7, 106.5, 100.1, 83.1, 50.5, 40.9, 17.7, 17.6, 10.3; **IR**(NaCl) ṽ (cm^{-1}): 2943, 2892, 2865, 2171, 1504, 1488, 1464, 1438, 1242, 1042, 1017, 994, 942, 918, 882, 811, 678; **HRMS**(ESI): calc'd. for $C_{33}H_{53}O_2Si_2$, **$[M+H]^+$** 537.3579 found 537.3576; **(3-(Benzo[d][1,3]dioxol-5-yl)octa-3,4,7-trien-1-yne-1,5-diyl)bis(triiso-propylsilane): ^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.06 (dd, J = 8.1, 1.6 Hz, 1H), 7.00 (d, J = 1.6 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.02-5.83 (m, 3H), 5.11 (dq, J = 17.0, 1.5, 1H), 5.02 (dq, J = 10.0, 1.2 Hz, 1H), 2.92 (dq, J = 6.6, 1.4 Hz, 2H), 1.22-0.99 (m, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 212.4, 147.7, 146.3, 136.1, 128.9, 119.0, 115.8, 108.1, 105.9, 101.1, 101.0, 98.8, 95.0, 89.7, 34.9, 18.8, 18.7, 11.7, 11.4; **IR** (NaCl) ṽ (cm^{-1}): 2943, 2890, 2865, 2143, 1905, 1504, 1487, 1463, 1441, 1251, 1214, 1104, 1042, 1016, 995,

941, 916, 882, 863, 811, 717, 678; **HRMS** (ESI): calc'd. for $C_{33}H_{53}O_2Si_2$, **[M+H]**$^+$ 537.3579 found 537.3579.

4-(Benzo[d][1,3]dioxol-5-yl)-6-(triisopropylsilyl)-4-((triisopropylsilyl)ethynyl)hex-5-yne-1,2-diol (4) In a round bottom flask equipped with a magnetic stirring bar, (3-allyl-3-(benzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (1.53 g, 2.86 mmol, 1.00 equiv.) was dissolved in acetone/water mixture (1:1; 0.5 M). Potassium osmate(VI) dihydrate (12.3 mg, 0.29 mmol, 1.00 mol%,) and 4-methyl-morpholine-4-oxide monohydrate (1.26 g, 8.58 mmol, 3.00 equiv.) were added to this solution at ambient temperature. The mixture was stirred for 48 h at room temperature vigorously. Acidic work up with HCl (1N) was committed after complete conversion was observed by TLC. The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent the crude product was purified via column chromatography on silica gel (EtOAc:*n*-hexane = 1:9, R_F = 0.21) to afforded **4-(benzo[d][1,3]dioxol-5-yl)-6-(triisopropylsilyl)-4-((triisopropylsilyl)ethynyl)hex-5-yne-1,2-diol (4)** as a yellowish oil (1.45 g, 2.54 mmol, 89%); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.21 (dd, J = 8.1, 1.9 Hz, 1H), 7.19 (d, J = 1.9 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.97 (s, 2H), 4.22 (dddt, J = 8.5, 5.9, 4.1, 2.1 Hz, 1H), 3.59 (ddd, J = 10.8, 7.0, 3.5 Hz 1H), 3.47 (dd, J = 11.4, 5.8 Hz, 1H), 3.26 (d, J = 2.1 Hz, 1H), 2.14 (dd, J = 14.1, 8.6 Hz, 1H), 2.05 (td, J = 6.1, 5.6 Hz, 3.0 Hz, 1H), 1.94 (dd, J = 14.1, 2.1 Hz, 1H), 1.09 (d, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.8, 146.9, 135.8, 119.5, 108.5, 108.0, 107.4, 107.1, 101.3, 85.8, 70.3, 66.6, 50.5, 40.2, 18.6, 11.2; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3550 3427, 2943, 2891, 2866, 2167, 1504, 1488, 1464, 1438, 1246, 1132, 1105, 1071, 1041, 1018, 996, 939, 882, 811, 679; **HRMS** (ESI): calc'd. for $C_{33}H_{55}O_4Si_2$, **[M+H]**$^+$ 571.3633 found 571.3630.

3-(Benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-ynal (5) In a round bottom flask equipped with a magnetic stirring bar, a solution of 4-(benzo[d][1,3]dioxol-5-yl)-6-(triisopropylsilyl)-4-((triisopropylsilyl)ethynyl)hex-5-yne-1,2-diol (4.00 g, 7.01 mmol, 1.00 equiv.) in anhydrous dichloromethane (70 mL, 0.1 M) was prepared. $NaIO_4$ adsorbed on silica gel (15.1 g; 0.613 mmol/g, 9.11 mmol, 1.30 equiv.) was added to the solution. The mixture was stirred vigorously for 18 h at ambient temperature. The reaction mixture was filtered and washed with dichloromethane, when complete conversion was observed by TLC. The filtrate was evaporated and the residue was further purified via column chromatography on silica gel (EtOAc:*n*-hexane = 1:9, R_F = 0.67) to afforded **3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)-ethynyl)pent-4-ynal (5)** as a violet oil (3.60 g, 6.68 mmol, 95%); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 9.96 (t, J = 2.7 Hz, 1H), 7.24-7.16 (m, 2H), 6.80 (dd, J = 7.8, 0.7 Hz, 1H), 5.98 (s, 2H), 2.78 (d, J = 2.7, 2H), 1.08 (s, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 200.4, 147.9, 147.2, 134.5, 119.6, 108.2, 107.0, 106.2, 101.3, 86.4, 57.9, 37.9, 18.6, 11.2; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 2943, 2893, 2866, 2168, 1730, 1504, 1488, 1464, 1248, 1104, 1041, 996, 938, 882, 812, 678; **HRMS**(ESI): calc'd. for $C_{32}H_{54}NO_3Si_2$, **[M+NH$_4$]**$^+$ 556.3637 found 556.3632.

3-(Benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol In a dried, nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, 3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-ynal (7.86 g, 14.6 mmol, 1.00 equiv.) was dissolved in dry methanol (146 mL, 0.1 M) and cooled to 0 °C. At this temperature, $NaBH_4$ (1.11 g, 29.2 mmol, 2.00 equiv.) was added to the solution slowly which was stirred for 30 min under nitrogen atmosphere. Acidic work up with HCl (1N) was committed when complete conversion was observed by TLC, and the pH value was adjusted to 2 precisely. The reaction mixture was stirred for another 30 min allowing to warm to ambient temperature. The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent the crude product was purified via column chromatography on silica gel (EtOAc:*n*-hexane = 1:9, R_F : 0.36) to afforded **3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)-ethynyl)pent-4-yn-1-ol** as a yellowish oil (7.76 g, 14.3 mmol, 98%); **^{1}H NMR** (300 MHz, CDCl3): δ = 7.24-7.16 (m, 2H), 6.78 (dd, J = 7.6, 0.9 Hz, 1H), 5.97 (s, 2H), 3.96 (t, J = 6.0 Hz, 2H), 2.21 (br s, 1H), 2.16 (t, J = 6.0 Hz, 2H), 1.09 (s, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.7, 146.8, 136.1, 119.5, 108.0, 107.9, 107.1, 101.2, 85.1, 60.9, 49.4, 40.1, 18.6, 11.2; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3410, 2956, 2943, 2891, 2866, 2164, 1504, 1488, 1464, 1244, 1041, 996, 882, 811, 678; **HRMS** (ESI): calc'd. for $C_{32}H_{56}NO_3Si_2$, **[M+NH$_4$]**$^+$ 558.3793 found 558.3783.

***tert*-Butyl (3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-yl)(tosyl)carbamate (6)** In a dried, nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, 3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol (3.10 g, 5.73 mmol, 1.00 equiv.) was dissolved in anhydrous THF (57 mL, 0.1 M). At ambient temperature, triphenylphosphine (2.23 g, 8.60 mmol, 1.50 equiv.) and *tert*-butyl 4-toluenensulfonyl-carbamate (1.71 g, 6.30 mmol, 1.10 equiv.) were added to the solution under N_2-atmosphere. To the reaction mixture, diethyl azodicarboxylate solution (3.99 mL, 40%wt in toluene, 8.60 mmol, 1.5 equiv.) was added dropwise and the reaction was allowed to stir at ambient temperature for 3 h. Acidic workup was committed with 2M $HCl_{(aq)}$ when complete conversion was observed by TLC. The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent the crude product was purified via column chromatography on silica gel (EtOAc:*n*-hexane = 10:90, R_F = 0.43) to afford **tert-butyl (3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-yl)(tosyl)carbamate (6)** as a yellowish viscous product (3.92 g, 4.94 mmol, 86%); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.5 Hz, 2H), 7.32-7.21 (m, 4H), 6.78 (d, J = 8.5 Hz, 1H), 5.96 (s, 2H), 4.15-4.00 (m, 2H), 2.42 (s, 3H), 2.34-2.22 (m, 2H), 1.31 (s, 9H), 1.11 (s, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 150.6, 147.6, 146.8, 143.9, 137.5, 135.8, 129.2, 127.9, 119.7, 107.9, 107.3, 106.9, 101.2, 84.7, 83.8, 45.2, 44.8, 40.0, 27.9, 21.6, 18.7, 11.3; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 2956, 2943, 2891, 2865, 1732, 1504, 1487, 1463, 1368, 1288, 1245, 1173, 1156, 1104, 1089, 1040, 996, 966, 937, 882, 812, 719, 677; **HRMS** (ESI): calc'd. for $C_{44}H_{67}NO_6SSi_2$, **[M+H]**$^+$ 794.4300 found 794.4300.

***tert*-Butyl (3-(benzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)(4-toluenesulfonyl)carbamate** In a dried, nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, the solution of *tert*-butyl (3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-yl)-(4-toluenesulfonyl)carbamate (3.49 g, 4.39 mmol, 1.00 equiv.) in THF (44 mL, 0.1 M)

was prepared. To this solution, TBAF (3.54 g, 11.0 mmol, 2.50 equiv.) was added at ambient temperature. The reaction mixture was stirred at this temperature for 16 h. The aqueous workup proceeded after complete conversion was observed by TLC. The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent the crude product was purified via column chromatography on silica gel (*n*-hexane:EtOAc:CH_2Cl_2 = 80:10:10, R_F = 0.50) to afford ***tert*-butyl (3-(benzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-(4-toluenesulfonyl)carbamate** as a yellowish viscous product (1.99 g, 4.13 mmol, 94%); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.25-7.18 (m, 2H), 6.80 (dd, J = 7.8, 0.8 Hz, 1H), 5.98 (s, 2H), 4.13-4.03 (m, 2H), 2.59 (s, 2H), 2.43 (s, 3H), 2.41-2.32 (m, 2H), 1.34 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 150.7, 147.9, 147.2, 144.2, 137.2, 134.2, 129.3, 127.9, 119.6, 108.0, 107.1, 101.3, 84.3, 83.1, 72.6, 44.6, 44.4, 37.9, 27.9, 21.6; **IR** (NaCl) ṽ (cm^{-1}): 2943, 2890, 2865, 2168, 1732, 1504, 1487, 1463, 1368, 1288, 1245, 1173, 1156, 1104, 1089, 1040, 996, 966, 937, 882, 812, 719, 678; **HRMS** (ESI): calc'd. for $C_{26}H_{28}NO_6S$, **[M+H]$^+$** 482.1632 found 482.1631.

***N*-(3-(Benzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-4-methylbenzenesulfonamide (7)** In a round bottom flask equipped with a magnetic stir bar, *tert*-butyl (3-(benzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)(4-toluenesulfonyl)carbamate (5.09 g, 10.6 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (106 mL, 0.1 M). To this solution, TFA (8.09 mL, 106 mmol, 10.0 equiv.) was added at ambient temperature dropwise. The reaction mixture was stirred at this temperature for 12 h. The aqueous workup was done after complete conversion was observed by TLC. The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent the crude product was purified via column chromatography on silica gel (*n*-hexane:EtOAc:CH_2Cl_2 = 8:1:1, R_F = 0.51) to afford the ***N*-(3-(benzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-4-methylbenzenesulfonamide (7)** as a colorless solid (3.97 g, 10.4 mmol, 98%); **m.p.**: 107−108 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0, 2H), 7.07 (dd, J = 8.3, 2.0 Hz, 2H), 7.03 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.97 (s, 2H), 4.65 (t, J = 6.3 Hz, 1H), 3.23 (dt, J = 7.6, 6.3 Hz, 2H), 2.52 (s, 2H), 2.44 (s, 3H), 2.08 (t, J = 6.3 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.9, 147.3, 143.5, 136.9, 133.9, 129.7, 127.2, 119.4, 108.0, 106.9, 101.4, 83.4, 72.9, 44.9, 40.3, 38.1, 21.5; **IR** (NaCl) ṽ (cm^{-1}): 3289, 2960, 2928, 2893, 1504, 1487, 1437, 1327, 1247, 1160, 1093, 1038, 933, 862, 813, 730, 664; **HRMS** (ESI): calc'd. for $C_{21}H_{20}NO_4S$, **[M+H]$^+$** 382.1108 found 382.1113.

(*S*)-3-(Benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)-pyrrolidine (8a) In a round bottom Schlenk flask equipped with a magnetic stir bar, a solution of diyne starting material (1.46 g, 3.83 mmol, 1.0 equiv.) was prepared in anhydrous chloroform (33 mL). In another Schlenk flask equipped with a magnetic stir bar a solution of *tert*-Bu_3PAu[(R)TriP] gold catalyst was freshly prepared by mixing tri-(*tert*-butylphosphin)-gold(I)-chlorid (99.9 mg, 230 µmol, 6.00 mol%) with Ag[(*R*)TriP] (165 mg, 192 µmol, 5.00 mol%) in anhydrous chloroform (5 mL) under argon atmosphere. At -55 °C the solution of the gold catalyst was transferred to the Schlenk-flask with the diyne starting material. The reaction mixture was stirred at this temperature for 72 h. When completion of the reaction was indicated by TLC analysis, the catalyst was quenched by adding triethylamine and stirring continued for 30 min at -55 °C. The reaction mixture was warmed to room temperature. The volatiles were then removed under reduced pressure and the residue directly purified by flash column chromatography on neutral aluminum oxide (*n*-hexane:EtOAc:CH_2Cl_2 = 80:10:10, R_F = 0.46 on silica gel) to afford the crude product as a colorless crystalline material (1.45 g, 3.80 mmol, 99%, 75% ee) which was recrystallized from boiling ethyl acetate to afford enantiopure **(*S*)-3-(benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)-pyrrolidine (8a)** in 74% overall yield. Enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK IC, 4.6 × 250 mm, eluent = *n*-hexane:isopropanol = 60:40, 0.6 mL·min^{-1} , λ = 254 nm); **[α]$_D^{20}$**: +109 (c = 0.100, CH_2Cl_2); **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.74 (d, J = 8.1 Hz, 2H), 6.72 (d, J = 8.1 Hz, 2H), 6.69 (d, J = 1.9 Hz, 1H), 6.61 (dd, J = 8.1, 1.9 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 5.72 (d, J = 1.4 Hz, 1H), 5.23 (q, J = 1.3 Hz, 2H), 4.53 (d, J = 1.4 Hz, 1H), 3.54 (ddd, J = 9.5, 6.6, 5.7 Hz, 1H), 3.39 (ddd, J = 9.5, 6.6, 5.7 Hz, 1H), 1.88 (s, 3H), 1.84-1.62 (m, 3H); **^{13}C NMR** (75 MHz, C_6D_6): δ = 148.9, 148.1, 147.2, 143.4, 134.9, 134.3, 129.2, 120.7, 108.1, 107.6, 101.0, 93.8, 84.8, 73.14, 73.11, 51.0, 48.0, 38.6, 21.1; **IR** (NaCl) ṽ (cm^{-1}): 3285, 2893, 1644, 1600, 1485, 1439, 1345, 1242, 1164, 1096, 1036, 993, 931, 859, 809, 742; **HRMS** (ESI): calc'd. for $C_{21}H_{20}NO_4S$, **[M+H]$^+$** 382.1108 found 382.1114.

Methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate In a dry round bottom flask equipped with a magnetic stir bar, the pyrrolidine starting material (754 mg, 1.98 mmol, 1.00 equiv.) was dissolved in anhydrous THF (20 mL, 0.1 M). To the solution, *n*-BuLi (1.25 mL, 1.6 M, 2.00 mmol, 1.02 equiv.) was added at -78 °C. The reaction mixture was stirred for 2 h allowing it to warm to -20 °C. To this solution, methyl chloroformate (0.15 mL, 2.18 mmol, 1.10 equiv.) was added at this temperature. The reaction mixture was stirred for 3 h under N_2-atmosphere. The aqueous workup proceeded when complete conversion was observed by TLC. The aqueous phase was extracted with EtOAc three times and the combined organic layers were evaporated under reduced pressure. The residue was further purified by flash column chromatography on neutral aluminum oxide (EtOAc:*n*-hexane = 15:85, R_F = 0.32 on silica gel) to afford **methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate** as a colorless, viscous oil (835 mg, 1.90 mmol, 96%); **[α]$_D^{20}$**: +36.4 (c = 0.100, $CHCl_3$); **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.74 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 6.58 (dd, J = 8.1, 1.9 Hz, 1H), 6.53 (d, J = 1.9 Hz, 1H), 6.33 (d, J = 8.1 Hz, 1H), 5.69 (d, J = 1.7 Hz, 1H), 5.21 (s, 2H), 4.42 (d, J = 1.7 Hz, 1H), 3.54-3.29 (m, 2H), 3.18(s, 3H), 1.94 (s, 3H), 1.75-1.54 (m, 2H); **^{13}C NMR** (75 MHz, C_6D_6): δ = 153.4, 148.4, 147.7, 147.6, 144.0, 134.5, 132.8, 129.6, 127.9, 121.0, 108.0, 107.9, 101.3, 94.9, 87.7, 77.3, 52.0, 51.1, 48.1, 38.1, 21.3; **IR** (NaCl) ṽ (cm^{-1}): 2954, 2923, 2235, 1715, 1646, 1597, 1504, 1487, 1436, 1344, 1263, 1219, 1186, 1167, 1091, 1038, 995, 932, 859, 812, 772, 751, 707, 658; **HRMS** (ESI): calc'd. for $C_{23}H_{22}NO_6S$, **[M+H]$^+$** 440.1162 found 440.1169.

Methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate In a dry flask equipped with magnetic stir bar, methyl (*R*)-3-(3-(benzo[d][1,3]di-

oxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate (292 mg, 668 µmol, 1,00 equiv.) was dissolved in a mixture of methanol and tetrahydrofuran (1:1, 6.6 mL, 0.100 M). Palladium on carbon was added to the solution (35.5 mg, 5 wt%). The reaction was carried out in an autoclave at 85 bar hydrogen pressure for 18 h. The reaction residue was filtered through a Celite pad and the filter cake was washed three time with CH_2Cl_2. The solvent was removed from the collected filtrate under reduced pressure to afford **methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)-pyrrolidin-3-yl)propiolate** as a colorless crystalline product (293 mg, 661 µmol, 99%); **[α]$_D^{20}$**: +19.7 (c = 0.100, CH_2Cl_2); **m.p.**: 116-117 °C; **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.54 (d, J = 8.2 Hz, 2H), 6.63 (d, J = 8.2 Hz, 2H), 6.29 (d, J = 2.0 Hz, 1H), 6.23 (d, J = 8.2, 1H), 6.06 (d, J = 8.2, 2.0 Hz, 1H), 5.68 (d, J = 1.4 Hz, 1H), 5.26 (d, J = 1.4 Hz, 1H), 5.22 (d, J = 1.4 Hz, 1H), 4.21 (d, J = 1.4 Hz, 1H), 3.52 (ddd, J = 9.8, 7.6, 2.3 Hz, 1H), 3.26 (s, 3H), 3.03 (td, J = 9.8, 5.9 Hz, 1H), 2.01-1.93(m, 1H) 1.90 (s, 3H), 1.51 (ddd, J = 12.8, 5.9, 2.3 Hz, 1H), 1.19 (ddd, J = 12.8, 10.21, 7.6 Hz, 1H); **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.9, 149.5, 148.0, 145.6, 143.4, 135.0, 129.1, 127.7, 119.9, 107.9, 107.8, 100.9, 92.6, 53.5, 51.1, 47.6, 34.4, 32.4, 29.9, 21.2; **IR** (NaCl) ṽ (cm^{-1}): 3075, 3027, 2952, 2892, 1727, 1641, 1606, 1492, 1440, 1397, 1346, 1238, 1169, 1101, 1038, 997, 934, 861, 813, 753, 718, 657; **HRMS**(ESI): calc'd. for $C_{23}H_{26}NO_6S$, **[M+H]$^+$** 444.1475 found 444.1483.

(*R*)-3a-(Benzo[d][1,3]dioxol-5-yl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (9a) Sodium naphthalenide was prepared in a dry round bottom flask equipped with magnetic stir bar. Under N_2-atmosphere naphthalene (335 mg, 2.61mmol, 6.07 equiv.) was dissolved in dry THF (3 mL, 0.87 M) and sodium (52.0 mg, 2.26 mmol, 5.12 equiv.) was added to the solution. The mixture was stirred at ambient temperature for 2 h until the solution became deep green. In another dry round bottom flask equipped with magnetic stir bar, the pyrrolidine starting material (190 mg, 428 µmol, 1.00 equiv.) was dissolved in dry THF (2 mL). The solution was cooled down to -78 °C and the $NaC_{10}H_8$ solution (1.89 mL, 3.31 equiv.) was added at this temperature. After complete conversion was observed by TLC the reaction was quenched with sat. $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc three times. The organic solutions were combined, dried over Na_2SO_4, and the volatiles removed under reduced pressure. The residue was further purified by flash column chromatography on neutral aluminum oxide (CH_2Cl_2:MeOH = 97:3, R_F = 0.16 on silica gel) to afford **(*R*)-3a-(benzo[d][1,3]dioxol-5-yl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (9a)** as a yellowish solid (92.6 mg, 360 µmol, 84%); **[α]$_D^{20}$**: +183 (c = 0.100, CH_2Cl_2); **m.p.**:164-165 °C (decomp.); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.90-6.75 (m, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.13 (br s, 1H), 5.94 (q, J = 1.4 Hz, 2H), 5.34 (s, 1H), 3.42 (ddd, J = 10.4, 7.9, 2.3 Hz, 1H), 3.17 (td, J = 10.4, 5.2 Hz, 1H), 2.44-2.32 (m, 1H), 2.26 (dd, J = 11.9, 5.2 Hz, 1H), 2.20-2.02 (m, 3H), 2.02-1.87 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 197.2, 172.6, 148.0, 146.7, 134.8, 120.4, 108.1, 107.6, 101.3, 95.3, 51.4, 44.9, 40.3, 36.1, 33.6; **IR** (NaCl) ṽ (cm^{-1}): 3177, 3031, 2945, 2882, 1623, 1577, 1504, 1487, 1436, 1287, 1232, 1195, 1038, 934, 918, 814, 730; **HRMS** (ESI): calc'd. for $C_{15}H_{16}NO_3$, **[M+H]$^+$** 258.1125 found 258.1130.

(3a*R*,6*R*,7a*R*)-3a-(Benzo[d][1,3]dioxol-5-yl)octahydro-1*H*-indol-6-ol (10) In a dry round bottom flask equipped with a magnetic stir bar, the indol-6-one starting material (92.6 mg, 360 µmol, 1.00 equiv.) was dissolved in anhydrous toluene (3.6 mL). To the solution, DIBAL-H solution (900 µL ,900 µmol, 2.5 equiv. 1 M in toluene) was slowly added at -78 °C under N_2-atmosphere. The reaction was stirred at -78 °C for 10 h and then allowed to warm up to room temperature for another 12 h. After complete conversion was observed by TLC, the reaction was quenched with 1 M HCl solution. The aqueous solution was made alkaline by adding saturated Na_2CO_3 solution carefully at 0 °C and then extracted with dichloromethane three times. The organic solutions were combined and the volatiles removed under reduced pressure. The residue was further purified by flash column chromatography on neutral aluminum oxide (CH_2Cl_2:MeOH = 10:1:, R_F = 0.34 on silica gel). The prepurified product was dissolved in a minimal amount of methanol and the product recrystallized by adding diethyl ether to afford **(3a*R*,6*R*,7a*R*)-3a-(benzo[d][1,3]dioxol-5-yl)octahydro-1*H*-indol-6-ol (10)** as a white solid (79.9 mg, 360 µmol, 85%); **[α]$_D^{23}$**: -67.4 (c = 0.01, $CHCl_3$) The literature-known optical rotation for the enantiomer of this compound is **[α]$_D$** = +63.4° (c = 0.009, $CHCl_3$).[2]; **m.p.**: 89-90 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.88–6.71 (m, 3H), 5.94 (s, 2H), 3.97 (br s, 1H), 3.74 (br s, 1H), 3.16 (dt, J = 10.3, 8.2 Hz, 1H), 3.02(td, J = 10.3, 3.4Hz, 1H), 2.29 (td, J = 14.1, 3.4 Hz, 1H), 2.09–1.65 (m, 7H), 1.41 (tt, J = 13.1, 2.4 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.9, 145.7, 139.6, 119.5, 108.0, 107.6, 101.1, 66.9, 60.7, 46.6, 43.0, 42.0, 31.8, 29.6, 26.8; **IR** (NaCl) ṽ (cm^{-1}): 3418, 3310, 2930, 2881, 1507, 1488, 1433, 1232, 1039, 934, 916, 807,731; **HRMS** (ESI): calc'd. for $C_{15}H_{20}NO_3$, **[M+H]$^+$** 262.1438 found 262.1442. Analytical results are consist with literature data.[19]

***tert*-Butyl (3a*R*,6*R*,7a*R*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxyoctahydro-1H-indole-1-carboxylate (11)** In a dry round bottom flask equipped with a magnetic stir bar, the amino alcohol starting material (26.1 mg, 100 µmol, 1.00 equiv.) was dissolved in anhydrous dichloromethane (2 mL). To the solution di-*tert*-butyl dicarbonate (25.3 µL, 110 µmol, 1.10 equiv.), triethylamine (15.3 µL, 110 µmol, 1.10 equiv.), and 4-dimethylaminopyridine (2.44 mg, 20.0 µmol, 0.20 equiv.) were added under N_2-atmosphere. The reaction was stirred for 2 h at ambient temperature. Aqueous work up was done with KOH solution (3 M, 20 mL), after complete conversion was observed by TLC. The aqueous phase was extracted with EtOAc three times, the combined organic layers were dried over Na_2SO_4, and the volatiles under reduced pressure. The residue was further purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 40:60, R_F = 0.33) to afford ***tert*-butyl (3a*R*,6*R*,7a*R*)-3a-(benzo[d]-[1,3]dioxol-5-yl)-6-hydroxyoctahydro-1*H*-indole-1-carboxylate (11)** as a colorless oil-like substance (35.8 mg, 99.0 µmol, 99%); **[α]$_D^{20}$**: -37.6 (c = 0.100, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.85-6.65 (m, 3H), 5.93 (s, 2H), 4.34-4.18 (m, 1H), 3.77-3.58 (m, 1H), 3.35 (t), 3.13-2.97 (m, 1H), 2.51-2.28 (m, 2H), 2.19-2.09 (m, 1H), 1.96-1.78 (m, 2H), 1.69-1.58 (m, 3H), 1.45(s, 9H) (only the major amide rotamer was characterized); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.9, 145.8, 140.8, 118.4, 108.0, 106.5, 101.0, 79.4, 68.3, 59.0, 43.2, 38.0, 33.1, 31.4, 28.6 (only the major amide rotamer was characterized); **IR** (NaCl) ṽ (cm^{-1}): 3393, 2969, 2936, 2892, 1740, 1676, 1496, 1485, 1411, 1371, 1238, 1174, 1163, 1109, 1040; **HRMS** (ESI): calc'd. for $C_{20}H_{28}NO_5$, **[M+H]$^+$** 362.1962 found 362.1959.

(*R*)-3-(Benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-tosylpyrrolidine (8b) In a round bottom Schlenk flask equipped with a magnetic stir bar, a solution of diyne starting material (839 mg,

2.20 mmol, 1.0 equiv.) was prepared in anhydrous chloroform (18 mL). In another Schlenk flask equipped with a magnetic stir bar a solution of *tert*-Bu_3PAu[(*S*)TriP] gold catalyst was freshly prepared by mixing tri-(*tert*-butylphosphin)-gold(I)-chlorid (57.3 mg, 230 µmol, 6.00 mol%) with Ag[(*S*)TriP] (94.5 mg, 192 µmol, 5.00 mol%) in anhydrous chloroform (4 mL) under argon atmosphere. At -55 °C the solution of the gold catalyst was transferred to the Schlenk-flask with the diyne starting material. The reaction mixture was stirred at this temperature for 72 h. When completion of the reaction was indicated by TLC analysis, the catalyst was quenched by adding triethylamine and stirring continued for 30 min at -55 °C. The reaction mixture was then allowed to warm to room temperature. The volatiles were removed under reduced pressure and the residue directly purified by flash column chromatography on neutral aluminum oxide with 6% water (Hex:EtOAc:CH_2Cl_2 = 80:10:10, R_F = 0.46 on silica gel) to afford the crude product as a colorless crystalline material (822 mg, 2.15 mmol, 98%, 77% ee) which was recrystallized from boiling ethyl acetate to afford enantiopure **(*R*)-3-(benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)pyrrolidine (8b)** in 73% overall yield. The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK IC, 4.6 × 250 mm, eluent: *n*-hexane:isopropanol (60:40), 0.6 mL·min^{-1} , λ = 254 nm); **[α]$_D^{20}$**: -107 (c = 0.100, CH_2Cl_2); **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.74 (d, J = 8.1 Hz, 2H), 6.72 (d, J = 8.1 Hz, 2H), 6.69 (d, J = 1.9 Hz, 1H), 6.61 (dd, J = 8.1, 1.9 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 5.72 (d, J = 1.4 Hz, 1H), 5.23 (q, J = 1.3 Hz, 2H), 4.53 (d, J = 1.4 Hz, 1H), 3.54 (ddd, J = 9.5, 6.6, 5.7 Hz, 1H), 3.39 (ddd, J = 9.5, 6.6, 5.7 Hz, 1H), 1.88 (s, 3H), 1.84-1.62 (m, 3H). The data are consistent with **(*S*)-3-(benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)pyrrolidine (8a)**.

Methyl (*S*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate In a dry round bottom flask equipped with a magnetic stir bar, the pyrrolidine starting material (302 mg, 792 µmol, 1.0 equiv.) was dissolved in anhydrous THF (8 mL, 0.1 M). To the solution, *n*-BuLi (544 µL, 1.6 M, mmol, 1.1 equiv.) was added at -78 °C. The reaction mixture was stirred for 30 min and then allowed to warm to room temperature. The solution was cooled again to -78 °C and treated with methyl chloroformate (59.9 µL, 871 µmol, 1.1 equiv.). The reaction mixture was stirred for 3 h allowing it to warm to room temperature. The aqueous workup proceeded when complete conversion was observed by TLC. The aqueous phase was extracted with EtOAc three times, the combined organic solutions were dried over Na_2SO_4 and the volatiles removed under reduced pressure. The residue was purified by flash column chromatography on neutral aluminum oxide with 6% water (EtOAc:*n*-hexane = 10:90, R_F = 0.32 on silica gel) to afford **methyl (*S*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate** as a colorless viscose product (334 mg, 760 µmol, 98%); **[α]$_D^{20}$**: -35.3 (c = 0.100, $CHCl_3$); **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.74 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 6.58 (dd, J = 8.1, 1.9 Hz, 1H), 6.53 (d, J = 1.9 Hz, 1H), 6.33 (d, J = 8.1 Hz, 1H), 5.69 (d, J = 1.7 Hz, 1H), 5.21 (s, 2H), 4.42 (d, J = 1.7 Hz, 1H), 3.54-3.29 (m, 2H), 3.18(s, 3H), 1.94 (s, 3H), 1.75-1.54 (m, 2H). The data are consistent with **methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)propiolate**.

Methyl (*S*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate In a dry 20 mL vial equipped with a magnetic stir bar, methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate (229 mg, 522 µmol, 1.00 equiv.) was dissolved in a mixture of methanol and tetrahydrofuran (1:1, 5.2 mL, 0.1 M). Palladium on carbon was added to the solution (28.0 mg, 5.00 wt%). The reaction was carried out in an autoclave at 85 bar hydrogen pressure for 18 h. The reaction residue was filtered through a Celite pad and the filter cake was washed three time with CH_2Cl_2. The solvent was removed from the collected filtrate under reduced pressure to afford **methyl (*S*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate** as a colorless crystalline product (229 mg, 516 µmol, 99%); **[α]$_D^{20}$**: -18.6 (c = 0.110, CH_2Cl_2); **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.54 (d, J = 8.2 Hz, 2H), 6.63 (d, J = 8.2 Hz, 2H), 6.29 (d, J = 2.0 Hz, 1H), 6.23 (d, J = 8.2, 1H), 6.06 (d, J = 8.2, 2.0 Hz, 1H), 5.68 (d, J = 1.4 Hz, 1H), 5.26 (d, J = 1.4 Hz, 1H), 5.22 (d, J = 1.4 Hz, 1H), 4.21 (d, J = 1.4 Hz, 1H), 3.52 (ddd, J = 9.8, 7.6, 2.3 Hz, 1H), 3.26 (s, 3H), 3.03 (td, J = 9.8, 5.9 Hz, 1H), 2.01-1.93(m, 1H) 1.90 (s, 3H), 1.51 (ddd, J = 12.8, 5.9, 2.3 Hz, 1H), 1.19 (ddd, J = 12.8, 10.21, 7.6 Hz, 1H). The data are consistent with **methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)pyrrolidin-3-yl)propiolate**.

(*S*)-3a-(Benzo[d][1,3]dioxol-5-yl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (9b) Sodium naphthalenide was prepared in a dry round bottom flask equipped with magnetic stir bar. Under N_2-atmosphere, napthalene (335 mg, 2.61 mmol, 5.05 equiv.) was dissolved in THF (3 mL, 0.9 M) and sodium (50.0 mg, 2.20 mmol, 4.26 equiv.) was added. The mixture was stirred at ambient temperature for 2 h until the solution become deep green. In another dry round bottom flask equipped with magnetic stir bar the pyrrolidine starting material (229 mg, 516 µmol, 1.00 equiv.) was dissolved in dry THF (2 mL, 0.26 M). The solution was cooled down to −78 °C and the $NaC_{10}H_8$ solution (2.12 mL, 3.00 equiv.) was added at this temperature. After complete conversion was observed by TLC, the reaction was quenched with sat. $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc three times. The combined organic solutions were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on neutral aluminum oxide with 6% water (CH_2Cl_2:MeOH = 97:3, R_F = 0.16 on silica gel) to afford **(*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (9b)** as a yellowish solid (114 mg, 444 µmol, 86%); **[α]$_D^{20}$**: -184 (c = 0.100, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.90-6.75 (m, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.13 (br s, 1H), 5.94 (q, J = 1.4 Hz, 2H), 5.34 (s, 1H), 3.42 (ddd, J = 10.4, 7.9, 2.3 Hz, 1H), 3.17 (td, J = 10.4, 5.2 Hz, 1H), 2.44-2.32 (m, 1H), 2.26 (dd, J = 11.9, 5.2 Hz, 1H), 2.20-2.02 (m, 3H), 2.02-1.87 (m, 1H). The data are consistent with **(*R*)-3a-(benzo[d][1,3]dioxol-5-yl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (9a)**.

(3a*S*,7a*S*)-3a-(Benzo[d][1,3]dioxol-5-yl)octahydro-6*H*-indol-6-one (12) In a dry round bottom flask equipped with magnetic stir bar, the pyrrolidine (101 mg, 0.393 mmol, 1.00 equiv.) was dissolved in anhydrous THF (4 mL). To the solution, sodium hydride (60% in mineral oil, 17.2 mg, 0.430 mmol, 1.10 equiv.) was added at -20 °C. The reaction mixture was stirred for 30 min at this temperature, then methyl iodide (26.7 µL, 0.432 mmol, 1.10 equiv.) was added. The reaction mixture was allowed to warm to ambient temperature and stirred for another 3 h. When completion of the reaction was indicated by TLC analysis, aqueous workup was done.

The product was extracted with EtOAc three times from the aqueous phase. The combined organic phases were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by a filter column on neutral aluminum oxide. The crude product was dissolved in a mixture of anhydrous *tert*-butanol (81.9 mg, 1.09 mmol, 2.80 equiv.) and THF (6 mL). The solution was cooled to -78 °C and liquid ammonia (≈ 35 mL) was condensed into the reaction solution. A piece of lithium (5.5 mg, 0.780 mmol, 2.00 equiv.) was added to the reaction solution which was then stirred for 45 min. Ammonia was evaporated and the solution was diluted with a mixture of water and brine. The aqueous phase was extracted with EtOAc three times, the combined organic phases were washed with brine and dried over Na_2SO_4. The residue was purified by column chromatography on silica gel (CH_2Cl_2:MeOH = 40:1, R_F = 0.32) to afford **(3a*S*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)octahydro-6*H*-indol-6-one (12)** as a slightly yellowish solid (78.4 mg, 287 µmol, 74 %); **[α]$_D^{22}$**: -67.3 (c = 0.133, CH_2Cl_2); **m.p.**: 76-77 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.87-6.74 (m, 2H), 6.71 (d, J = 8.1 Hz, 1H), 5.89 (s, 1H), 3.05 (ddd, J = 9.3, 7.2, 3.5 Hz, 1H), 2.84 (t, J = 3.5 Hz, 1H), 2.51 (d, J = 3.5 Hz, 2H), 2.43-1.91 (m, 10H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 211.3, 148.0, 145.8, 141.7, 118.7, 108.0, 107.0, 101.1, 70.5, 54.8, 47.7, 40.4, 38.9, 36.2, 35.4; **IR** (NaCl) ṽ (cm^{-1}): 2946, 2851, 2783, 1717, 1506, 1455, 1434, 1234, 1177, 1038, 933, 853, 811; **HRMS** (ESI): calc'd. for $C_{16}H_{20}NO_3$, **[M+H]$^+$** 274.1438 found 274.1443.

(3a*R*,7a*S*)-3a-(Benzo[d][1,3]dioxol-5-yl)-1-methyl-1,2,3,3a,7,7a-hexahydro-6*H*-indol-6-one (13) In a dry round bottom flask equipped with magnetic stir bar, the cyclohexanone (187 mg, 690 µmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (7 mL). To the solution diisopropylethylamine (0.721 mL, 4.14 mmol, 6.00 equiv.) and trimethylsilyl triflate (376 µL, 2.07 mmol, 3.00 equiv.) were added at -78 °C. The reaction was stirred for another 24 h at room temperature. After complete conversion was observed by ^{1}H-NMR the reaction was quenched with sat. $NaHCO_3$ solution and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic solutions were evaporated under reduced pressure. Without further purification the silyl enol ether intermediate was dissolved in anhydrous CH_2Cl_2 (7 mL) and cooled down to -78 °C. At this temperature phenylselenyl bromide (183 mg, 759 µmol, 1.10 equiv.) was added to the reaction under N_2-atmosphere. The reaction was slowly warmed up to ambient temperature and was kept stirring for another 16 h. The resulting mixture was concentrated under reduced pressure and the residue was simply purified by a filter column to remove the excess amount of phenylselenyl bromide. The diastereomeric mixture of the selenoether intermediate was again dissolved in CH_2Cl_2 (14 mL), and *tert*-butyl hydroperoxide (1.38 mL, 5 M in decane, 6.90 mmol, 10.00 equiv.) was slowly added to the solution at 0 °C. The reaction was allowed to warm to ambient temperature and then kept stirring for 72 h to afford full conversion. After complete conversion was observed by TLC the reaction was quenched with 1 M NaS_2O_4 solution. The aqueous phase was extracted with CH_2Cl_2 three times and the combined organic solutions evaporated under reduced pressure. The residue was purified by flash column chromatography on neutral aluminum oxide with 6% water (EtOAc:*n*-hexane = 50:50 , R_F = 0.16 on silica gel) to afford **(3a*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-1-methyl-1,2,3,3a,7,7a-hexahydro-6*H*-indol-6-one (13)** as a white greasy substance (144 mg, 531 µmol, 77%); **[α]$_D^{20}$**: -128.6 (c = 0.100, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.93-6.73 (m, 3H), 6.69 (dd, J = 10.1, 2.1 Hz, 1H), 6.08 (d, J = 10.1 Hz, 1H), 5.96 (s, 2H), 3.30 (td, J = 8.8, 2.4 Hz, 1H), 2.70-2.11 (m, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 197.5, 153.7, 148.3, 146.7, 137.4, 126.6, 120.1, 108.3, 107.4, 101.4, 74.0, 56.2, 51.2, 40.2, 38.9, 36.3. **IR** (NaCl) ṽ (cm^{-1}): 2954, 2901, 2856, 2784, 1685, 1494, 1443, 1400, 1347, 1240, 1201, 1116, 1038, 813; **HRMS** (ESI): calc'd. for $C_{16}H_{18}NO_3$, **[M+H]$^+$** 272.1281 found 272.1283.

Ethyl (3a*S*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-oxooctahydro-1*H*-indole-1-carboxylate (14) In a dry round bottom flask equipped with magnetic stir bar, the methylamine (144.2 mg, 528 µmol, 1.00 equiv.) was dissolved in anhydrous toluene (5 mL). To the solution, ethylene glycol (36.0 mg, 580 µmol, 1.10 equiv.) and *p*-toluenesulfonic acid (99.93 mg, 580 µmol, 1.10 equiv.) were added. The reaction mixture was heated until reflux and the water generated in situ removed using a Dean-Stark apparatus for 8 h. After complete conversion was observed by TLC, the reaction was quenched with sat. $NaHCO_3$ solution and the aqueous phase was extracted with dichloromethane three times. The combined organic phases were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was directly submitted to amide formation. For this it was dissolved in benzene (5 mL). To the solution, potassium carbonate (146 mg, 1.06 mmol, 2.00 equiv.) and ethyl chloroformate (75.4 µL, 792 µmol, 1.50 equiv.) were added at room temperature. The reaction mixture was heated to reflux for 24 h. After complete conversion was observed by TLC, the reaction mixture was filtered and the filter was washed three times with dichloromethane (30 mL). The combined filtrate was concentrated and purified through a filter column (EtOAc:*n*-hexane = 50:50, R_F=0.46). The collected product was concentrated under reduced pressure and then dissolved in acetone (5 mL). To this solution hydrochloric acid solution was added (2 M, 5 mL). The mixture was stirred at ambient temperature for 8 h. After complete conversion was observed by TLC the reaction was quenched with sat. Na_2CO_3 solution and the aqueous phase was extracted with EtOAc three times. The combined organic phases were evaporated in vacuo to afford **ethyl (3a*S*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-oxooctahydro-1*H*-indole-1-carboxylate (14)** as a slightly yellow viscous oil (150.3 mg, 454 µmol, 86%); **[α]$_D^{20}$**: +37.8 (c = 0.100, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.88-6.66 (m, 3H), 5.95 (s, 2H), 4.53 (br s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.47 (m, 2H), 2.93 (dd, J = 15.7, 6.00 Hz, 1H), 2.69 (br s, 1H), 2.43-2.04 (m, 6H), 1.25 (td, J = 7.1, 2.9 Hz, 3H) (only the major amide rotamer was characterized); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 210.2, 155.0, 148.2, 146.4, 138.8, 118.7, 108.2, 106.6, 101.2, 61.3, 44.7, 36.5, 33.5, 14.7 (only the major amide rotamer was characterized); **IR** (NaCl) ṽ (cm^{-1}): 2897, 2362, 2331, 1693, 1496, 1420, 1337, 1234, 1114, 1033, 926, 809; **HRMS** (ESI): calc'd. for $C_{18}H_{22}NO_5$, **[M+H]$^+$** 332.1492 found 332.1494.

Ethyl (3a*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (15) To a solution of the cyclohexanone (150 mg, 454 µmol, 1.00 equiv.) in CH_2Cl_2 (4.5 mL) were added DIPEA (0.554 mL, 3.18 mmol, 7.00 equiv.) and trimethylsilyl triflate (0.247 mL, 1.36 mmol, 3.00 equiv.) at −78 °C. Then, the reaction temperature was allowed to increase to −40 °C over the period of 10 h. Following quenching with saturated aqueous Na_2CO_3 solution at −40 °C, the mixture was extracted with cold EtOAc, and the combined organic phases were washed with brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure giving the enol silyl ether intermediate that was used without further purification in the next step. To a solution of this enol silyl ether in acetonitrile (4.5 mL) was added $Pd(OAc)_2$ in portions (153 mg, 681 µmol, 1.5 equiv.) at 0 °C. The resulting mixture was stirred at room temperature for 10 h and then filtered through a Celite pad. The filtrate

was collected, concentrated, and purified through a filter column (EtOAc:*n*-hexane = 40:60, R_F = 0.34) to afford the **ethyl (3a*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (15)** as a colorless oil (131.6 mg, 400 µmol, 88%); **[α]$_D^{20}$**: +158 (c = 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.93-6.76 (m, 3H), 6.66 (dd, J = 10.3, 0.8 Hz, 1H), 6.22 (dd, J = 10.3, 0.8 Hz, 1H), 5.98 (s, 2H), 4.32-4.02 (m, 3H), 3.98-3.69 (m, 1H), 3.39-2.92 (m, 2H), 2.69-2.38 (m, 2H), 2.15- 1.97 (m, 1H), 1.25 (t, J = 7.1, 3H) (only the major amide rotamer was characterized); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 148.6, 147.3, 133.5, 120.1, 108.6, 107.1, 101.6, 63.4, 50.7, 14.8 (only the major amide rotamer was characterized); **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 2980, 2896, 2360, 1690, 1496, 1415, 1342, 1241, 1118, 1035, 930, 864, 812, 747; **HRMS** (ESI): calc'd. for $C_{18}H_{20}NO_5$, **[M+H]$^+$** 330.1336 found 330.1337.

Ethyl (3a*R*,6*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (16) and ethyl (3a*R*,6*S*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate To a solution of the cyclohexenone (132 mg, 400 µmol, 1.00 equiv.) in anhydrous MeOH (4 mL) $CeCl_3 \cdot 7\ H_2O$ (298 mg, 800 µmol, 2.00 equiv.) and sodium tetrahydroborate (16.6 mg, 440 µmol, 1.10 equiv.) were added at 0 °C. Then, the reaction temperature was allowed to increase to ambient temperature over the period of 1 h. After complete conversion was observed by TLC, the reaction was quenched with sat. NH_4Cl solution and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic phases were dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified through flash chromatography on silica gel to afford the major diastereomer **ethyl (3a*R*,6*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (16)** (EtOAc:*n*-hexane = 20:80, R_F = 0.27) as a colorless oil (94.1 mg, 284 µmol, 71%) and the minor diastereomer **ethyl (3a*R*,6*S*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate** (EtOAc:*n*-hexane = 20:80, R_F = 0.33) as a colorless oil (30.5 mg, 92.0 µmol, 23%); **Ethyl (3a*R*,6*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate** (major diastereomer **16**): **[α]$_D^{20}$**: +166 (c = 0.167, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.83-6.68 (m, 3H), 5.96 (dd, J = 10.1, 3.1 Hz, 1H), 5.92 (s, 2H), 5.67 (dd, J = 10.1, 1.7 Hz, 1H), 4.35-4.24 (m, 1H), 4.22-3.95 (m, 3H), 3.59 (s, 1H), 3.51-3.637 (m, 1H), 2.36 (ddd, J = 13.5, 7.6, 6.3 Hz, 2H), 2.25-1.91 (m, 3H), 1.23 (t, J = 7.1, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 155.4, 148.1, 146.4, 137.5, 132.8, 130.8, 119.7, 108.2, 107.3, 101.2, 101.19, 101.16, 64.6, 61.9, 61.2, 50.1, 45.4, 36.1, 32.9, 14.8 (both of amide rotamers were included); **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3408, 2979, 2893, 1678, 1506, 1487, 1469, 1432, 1382, 1349, 1336, 1237, 1172, 1125, 1077, 1039, 933, 811, 756; **HRMS** (ESI): calc'd. for $C_{18}H_{22}NO_5$, **[M+H]$^+$** 332.1492 found 332.1494.

Ethyl (3a*R*,6*S*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (minor diastereomer): **[α]$_D^{20}$**: +113 (c = 0.167, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.97-6.82 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.02 (dd, J = 10.1, 1.3 Hz, 1H), 5.92 (s, 2H), 5.55 (dd, J = 10.1, 1.3 Hz, 1H), 4.35-4.22 (m, 1H), 4.22-4.04 (m, 2H), 3.97 (d, J = 12.9 Hz, 1H), 3.88-3.60 (m, 1H), 3.33-3.10 (m, 1H), 2.77-2.41 (m, 1H), 2.41-2.13 (m, 2H), 1.83 (ddd, J = 12.4, 6.0, 2.2 Hz, 1H), 1.60 (t, J = 11.4 Hz, 1H), 1.24 (t, J = 7.1, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 155.5, 155.0, 148.0, 146.5, 137.0, 132.8, 132.3, 120.3, 108.1, 107.6, 101.2, 101.2, 63.3, 62.6, 62.2, 61.3, 61.1, 50.9, 50.0, 46.1, 45.7, 36.7, 36.2, 31.9, 30.9, 14.8 (both of amide rotamers were included); **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3396, 2973, 2890, 1679, 1496, 1426, 1237, 1122, 1037, 931, 810, 750; **HRMS** (ESI): calc'd. for $C_{18}H_{22}NO_5$, **[M+H]$^+$** 332.1492 found 332.1492.

Ethyl (3a*R*,6*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-((*tert*-butyldiphenylsilyl)oxy)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (17) To a solution of the secondary alcohol (94.1 mg, 284 µmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (3 mL) were added imidazole (38.7 mg, 568 µmol, 2.00 equiv.) and TBDPSCl (82.7 µL, 312 µmol, 1.10 equiv.) at ambient temperature. The reaction mixture was stirred for 5 h. After complete conversion was observed by TLC, aqueous workup was done and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic phases were dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc:*n*-hexane = 10:90, R_F = 0.36) to afford **ethyl (3a*R*,6*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-((*tert*-butyldiphenylsilyl)oxy)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (17)** as a colorless oil (155.3 mg, 273 µmol, 96%); **[α]$_D^{20}$**: +104 (c = 0.167, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.79-7.65 (m, 4H+4H'), 7.51-7.33 (m, 6H+6H'), 6.82-6.62 (m, 3H+3H'), 5.90 (s, 2H+2H'), 5.81-5.45 (m, 2H+2H'), 4.47-4.25 (m, 1H+1H'), 4.20-3.87 (m, 3H+3H'), 3.71-3.42 (m, 2H), 2.43-1.87 (m, 4H+4H'), 1.24 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H'), 1.09(s, 9H), 1.07 (s, 9H'); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 154.9, 154.6, 148.0, 146.3, 146.2, 138.5, 138.0, 136.0, 135.95, 135.89, 135.6, 134.9, 134.6, 134.2, 134.0, 132.6, 132.3, 131.1, 130.9, 129.8, 129.75, 129.71, 129.6, 127.7, 127.66, 119.6, 119.4, 108.1, 108.0, 107.4, 107.3, 101.14, 101.11, 66.7, 65.5, 61.6, 61.5, 60.9, 60.8, 60.5, 50.4, 49.5, 45.4, 45.0, 36.9, 35.5, 34.9, 32.1, 27.0, 19.24, 19.22, 14.8 (both of amide rotamers were included); **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3063, 2954, 2889, 1694, 1481, 1424, 1385, 1342, 1239, 1113, 1047, 933, 867, 814, 746, 702, 613; **HRMS** (ESI): calc'd. for $C_{34}H_{40}NO_5Si$, **[M+H]$^+$** 570.2670 found 570.2672.

(3a*R*,6*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-((*tert*-butyldiphenylsilyl)oxy)-2,3,3a,6,7,7a-hexahydro-1*H*-indole (18) To a solution of the carbamate (69.3 mg, 209 µmol, 1.00 equiv.) in EtOH (2 mL), sodium hydroxide (83.6 mg, 2.09 mmol, 10.0 equiv.) was added and the solution was heated to 70 °C for 3 days. After complete conversion was observed by TLC, aqueous workup was done, and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic phases were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was submitted for silyl protection without further purification. For this, it was dissolved in anhydrous CH_2Cl_2 (2 mL). To this solution, imidazole (28.5 mg, 418 µmol, 2.00 equiv.) and TBDPSCl (60.9 µL, 230 µmol, 1.10 equiv.) were added at ambient temperature. The reaction mixture was stirred for 5 h. After complete conversion was observed by TLC, aqueous workup was done, and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic phases were dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH = 20:1, R_F = 0.42) to afford **(3a*R*,6*R*,7a*S*)-3a-(benzo[d][1,3]dioxol-5-yl)-6-((*tert*-butyldiphenylsilyl)oxy)-2,3,3a,6,7,7a-hexahydro-1*H*-indole (18)** as a colorless oil (89.6 mg, 180 µmol, 86%); **[α]$_D^{20}$**: +54.2 (c = 0.133, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.74-7.56 (m, 4H), 7.52-7.35(m, 6H), 6.81-6.62 (m, 3H), 5.94-5.68 (m, 4H), 4.29 (dd, J = 5.3, 3.8 Hz, 1H), 4.13 (s, 1H), 3.75(dd, J = 11.1, 8.0 Hz, 1H), 3.60 (br s, 1H), 3.29 (td, J = 11.1, 6.4 Hz, 1H), 2.77 (td, J = 13.0, 8.0, Hz, 1H), 2.29 (dd, J = 15.7, 3.8 Hz, 1H), 2.10 (dd, J = 13.0, 6.4 Hz, 1H), 1.73 (ddd, J = 15.7, 4.3, 2.5 Hz, 1H), 1.06 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 148.3, 147.2, 135.8, 135.6, 135.0, 132.7, 132.5, 131.7, 130.6, 130.1, 129.5, 128.2, 127.6, 120.2, 108.4, 107.2, 101.4, 101.3, 63.9, 62.8, 49.6, 44.1, 38.5, 27.6, 27.1, 26.7, 19.0; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3429, 3188, 2937, 2893, 2862, 2656, 1495, 1432, 1395, 1241, 1108, 1040, 990, 932, 869, 816, 750,

703; **HRMS** (ESI): calc'd. for $C_{31}H_{36}NO_3Si$, **[M+H]**$^+$ 498.2459 found 498.2463.

(3*R*,4a*S*,5*R*,11b*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-4,4a-dihydro-3*H*,6*H*-5,11b-ethano[1,3]dioxolo[4,5-j]phenanthridine (19) To a solution of the secondary amine (49.8 mg, 100 µmol, 1.00 equiv.) in anhydrous THF (3 mL) *N*,*N*-dimethylmethaniminium iodide (20.4 mg, 110 µmol, 1.10 equiv.) was added. The reaction mixture was heated to 60 °C and stirred at this temperature for 3 days. After complete conversion was observed by TLC, aqueous workup was done and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic phases were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH = 25:1, R_F = 0.32) to afford **(3*R*,4a*S*,5*R*,11b*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4,4a-dihydro-3*H*,6*H*-5,11b-ethano[1,3]dioxolo[4,5-j]phenanthridine (19)** as a yellowish oil (43.8 mg, 85.9 µmol, 86%); **[α]$_D^{20}$**: +24.6 (c = 0.500, $CHCl_3$). The literature-known optical rotation for the title compound is **[α]$_D^{26}$ =** +22.8 (c = 0.500, $CHCl_3$) [3]; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.70–7.66 (m, 4H), 7.44–7.34 (m, 6H), 6.73 (s, 1H), 6.43 (s, 1H), 6.26 (dd, J = 10.2, 2.4 Hz, 1H), 5.87–5.84 (m, 2H), 5.70 (d, J = 10.2 Hz, 1H), 4.43–4.39 (m, 1H), 4.31 (d, J = 16.9 Hz, 1H), 3.72 (d, J = 16.9 Hz, 1H), 3.47–3.39 (m, 1H), 3.04–3.00 (m, 1H), 2.91–2.85 (m, 1H), 2.17–1.97 (m, 3H), 1.79–1.70 (m, 1H), 1.08 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 146.2, 145.8, 138.8, 136.0, 135.9, 134.2, 134.1, 132.6, 129.8, 128.0, 125.8, 107.0, 102.9, 100.9, 69.4, 66.7, 62.1, 53.4, 45.0, 44.5, 34.8, 27.1, 19.3; **IR** (NaCl) ṽ (cm^{-1}): 3070, 3046, 3030, 2956, 2931, 2888, 2857, 1503, 1482, 1445, 1427, 1393, 1362, 1329, 1312, 1250, 1233, 1145, 1111, 1092, 1041, 1000, 909, 884, 851, 841, 821, 703; **HRMS** (ESI): calc'd. for $C_{32}H_{36}NO_3Si$, **[M+H]**$^+$ 510.2459 found 510.2462. Analytical data are consistent with literature.[9]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Results of the mechanism study, experimental procedures, characterization data and spectra for all compounds (PDF)

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ACKNOWLEDGMENT

The CeMSA@HHU (**C**enter for **M**olecular and **S**tructural **A**nalytics @ **H**einrich **H**eine **U**niversity) is gratefully acknowledged for recording the mass-spectrometric and the NMR-spectroscopic data.

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A Comprehensive Approach to C3a-Arylated Hydroindole-related Alkaloids Utilizing Asymmetric Gold Catalysis: Formal Synthesis of (+)-Gracilamine and Other Enantiomerically Pure Crinine Alkaloids

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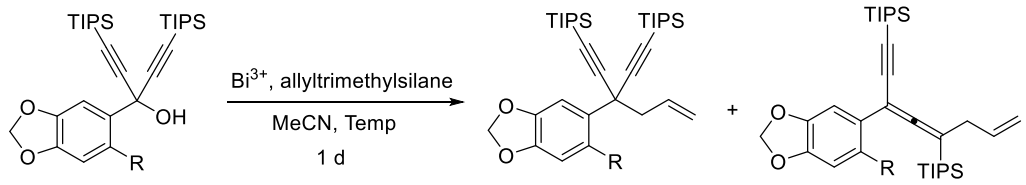
I. General information

All solvents and reagents used were purchased from commercial suppliers as reagent grade. They were used without further purification unless otherwise noted. Starting materials and catalysts, which were not commercially available, were synthesized by previously reported methods. The methods for preparing anhydrous solvents and reagents were referred to Purification of Laboratory Chemicals, Sixth Edition (ISBN: 978-1-85617-567-8). Dichloromethane, tetrahydrofuran, and toluene were dried using the Solvent Purification System MP SPS-800 by M.Braun. For reactions requiring an inert atmosphere, the glassware was dried in a compartment dryer at 120 °C, and then standard Schlenk techniques were used to work under a dry nitrogen atmosphere. Rotary evaporators combined with vacuum pumps were used for the removal of volatiles under reduced pressure. Analytical thin-layer chromatography (TLC) was performed on precoated alumina-backed silica gel plates (Macherey-Nagel, 0.2 mm thickness silica gel 60 with fluorescence indicator UV254), which were developed using UV fluorescence and $KMnO_4$ stain solution. Flash chromatography was performed on silica gel (Macherey-Nagel, silica 60 M, 0.04-0.063 mm). IR spectra were measured as thin films on a NaCl single crystal with a JASCO FT-IR 6200 spectrometer and only selected peaks are shown. ^{1}H-NMR spectra were recorded on a Bruker Advance III 300 MHz spectrometer, ^{13}C-NMR spectra were recorded at 75 MHz. The coupling constants *J* are given in Hertz (Hz) and chemical shifts (δ) in ppm. Chemical shifts were reported in δ ppm referenced to trace amounts of chloroform $\delta(CHCl_3)$ = 7.26 ppm in ^{1}H-spectra and to the signal of deuterated chloroform $\delta(CDCl_3)$ = 77.16 ppm in ^{13}C-spectra. In some cases, while d-benzene was used for measuring the chemical shifts were referenced to trace amounts of benzene $\delta(C_6H_6)$ = 7.15 ppm in ^{1}H-spectra and to the signal of deuterated b $\delta(C_6D_6)$ = 128 ppm in ^{13}C-spectra. The enantiomeric excess of the products was determined using a Hitachi LaChrome High-Performance Liquid Chromatography (HPLC) system equipped with DAICEL CHIRALPAK® IC™ (4.6 x 250 mm) column using *n*-hexane/isopropanol mixture as eluents. The samples were filtered through syringe filters (25 mm, 0.45 μm PTFE membrane or 13 mm, 0.2 μm PTFE membrane) prior to analysis.

II. Bismuth-catalyzed propargylic substitution

Table1. Optimization of the bismuth(III)-catalyzed propargyl allylation[1]

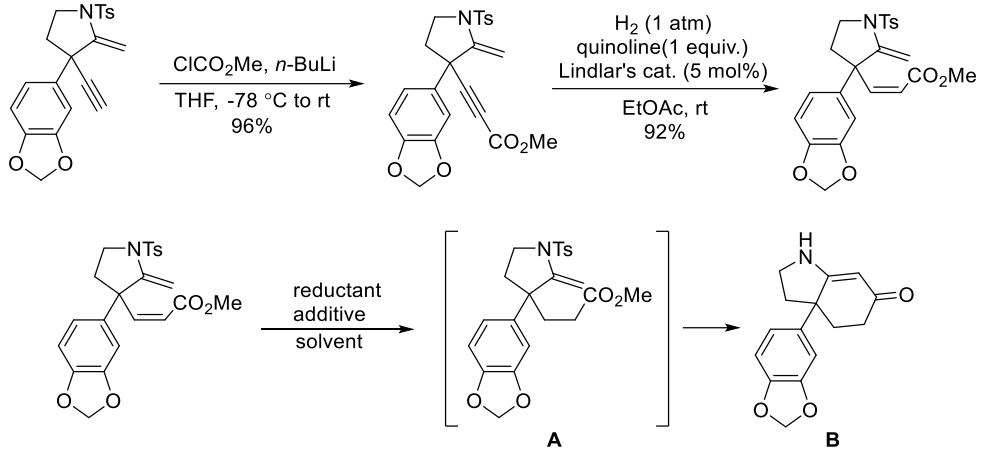


entry	R	Bi^{3+}	Temp [°C]	Ratio of isomer (A:B)[b]	Yield [%][c]
1	H	$Bi(NO_3)_3$	rt	2.6:1	n.d.[e]
2	H	$Bi(OTf)_3$	rt	n.d.[d]	n.d.[e]
3	H	$BiCl_3$	rt	2.6:1	97
4	H	$BiCl_3$	50	2.5:1	n.d.[e]
5	H	$BiCl_3$	-20	2.6:1	96
6	Br	$BiCl_3$	rt	2.7:1	96

[a] Unless otherwise noted, the reactions were carried out by using diyne starting material (1 mmol), bismuth (III) catalyst (20 mol %), in anhydrous acetonitrile (0.2 M) under N_2 atmosphere.[b] The ratio is determined by NMR analysis of the crude mixture. [c] Isolated yield. [d] No desired product was observed. [e] Not determined.

III. Reductive deprotection of the *p*-toluenesulfonamide

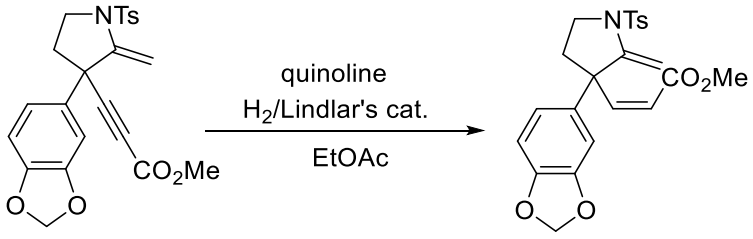
Table 2. Optimization of the reductive detosylation with different reductants



entry	reductant/ solvent	additive	yield of **A** [%]	yield of **B** [%]
1	$NaC_{10}H_8$/THF	-	n.d.	full conversion
2	SmI_2/THF	DABCO/H_2O	full conversion	n.d.
3	Mg/MeOH (sonication)	PPh_3	n.d.	decomp.
4	Mg/MeOH (sonication)	PPh_3/Na_2CO_3	n.r.	n.r.

In the reductive detosylation/cyclization, the preservation of the *α,β*-unsaturated ketone function could be convenient for the following synthesis, thus selective reduction for the removal of the *p*-toluenesulfonyl protecting group was tried. First of all, the propiolate group was successfully reduced. In the presence of quinoline and poisoned Pd catalyst the *syn*-hydrogenation proceeds efficiently in EtOAc at 1 bar H_2 atmosphere. In a dried and nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, the solution of methyl (*Z*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluene-sulfonyl)-pyrrolidin-3-yl)acrylate in THF was prepared. In another dried and nitrogen-flushed Schlenk-flask, sodium naphthalene (3.00 equiv.) was freshly prepared and transferred to the solution of *p*-toluenesulfonyl-protected pyrrolidine at ambient temperature. The resulting product was isolated by column chromatography and its structure confirmed by ^{1}H-NMR. The unsaturated double bond was reduced together with the sulfonate group at once and then the cyclization spontaneously happened to produce the hexahydro-indol-6-one as the only product. In addition, the well-established instantaneous sulfonamide reduction with samarium iodide (10.0 equiv.) was tried as well along with DABCO (20.0 equiv.) and H_2O (30.0 equiv.) as additives under the protection of N_2.[2] Furthermore, reduction employing sonication in the presence of magnesium metal in methanol was applied for this selective reduction. In this case, the resulting TLC and NMR analysis indicated no conversion in the presence of additional base. In summary, no procedure could be identified for selective cleavage of the sulfonamide in the presence of the *α,β*-unsaturated ester.

Methyl (*Z*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-(4-toluenesulfonyl)-pyrrolidin-3-yl)acrylate



In a dry round bottom flask equipped with a magnetic stir bar, the Lindlar catalyst (10.6 mg, 5.00 mol%) and quinoline (0.01 mL, 100 µmol, 1.00 equiv.) were mixed in anhydrous EtOAc (2 mL) and stirred for 30 min. The methyl 3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)propiolate (43.9 mg, 100 µmol, 1.00 equiv.) was dissolved in 1 mL of EtOAc and then added to the poisoned catalyst solution. The reaction mixture was exposed to H_2 atmosphere (1 atm) and the mixture was allowed to stir for 2 hours. After complete conversion was observed by TLC, the reaction mixture was filtered, and the filtrate was then purified by flash column chromatography on neutral aluminum oxide (EtOAc:*n*-hexane = 15:85, R_F = 0.42) to afford **methyl (*Z*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-(4-toluenesulfonyl)-pyrrolidin-3-yl)acrylate** as a colorless oil (40.7 mg, 92.2 µmol, 92%).

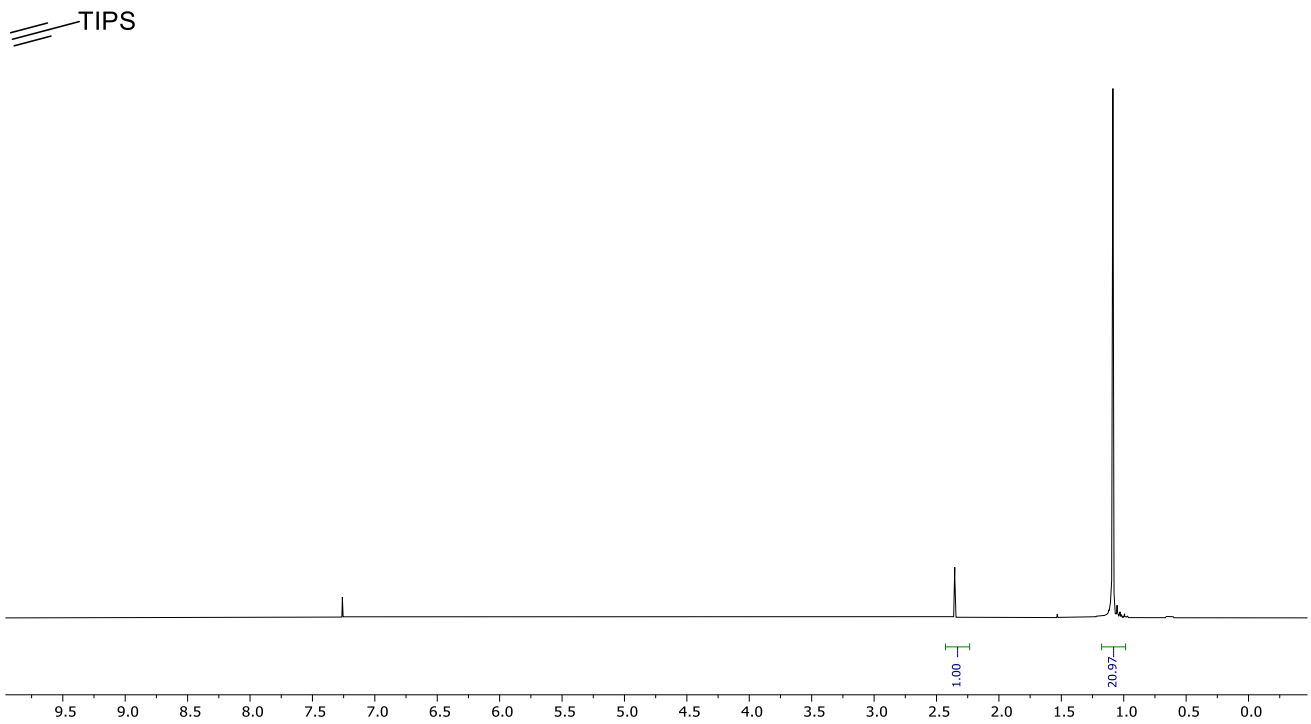
^{1}H NMR (300 MHz, C_6D_6): δ = 7.65 (m, 2H), 6.68 (m, 2H), 6.46 (d, J = 1.9 Hz, 1H), 6.25 (d, J = 8.2, 1H), 6.22 (d, J = 8.2, 1.9 Hz, 1H), 5.74 (d, J = 1.6 Hz, 1H), 5.65 (d, J = 12.6, 1H), 5.53 (d, J = 12.6, 1H), 5.22 (d, J = 1.4 Hz, 1H), 5.21 (d, J = 1.4 Hz, 1H), 4.47 (d, J = 1.6 Hz, 1H), 3.64 (ddd, J = 9.7, 7.7, 2.2 Hz, 1H), 3.10 (s, 3H), 3.10-3.04 (m, 1H), 2.11 (ddd, J = 12.6, 5.9, 2.1 Hz, 1H), 2.01-1.94 (m, 1H), 1.90 (s, 3H).

^{13}C NMR (75 MHz, C_6D_6): δ = 165.6, 149.1, 147.8, 146.9, 146.7, 135.5, 135.3, 129.4, 121.6, 121.2, 108.8, 107.5, 100.9, 93.2, 57.2, 50.8, 48.1, 36.4, 21.2.

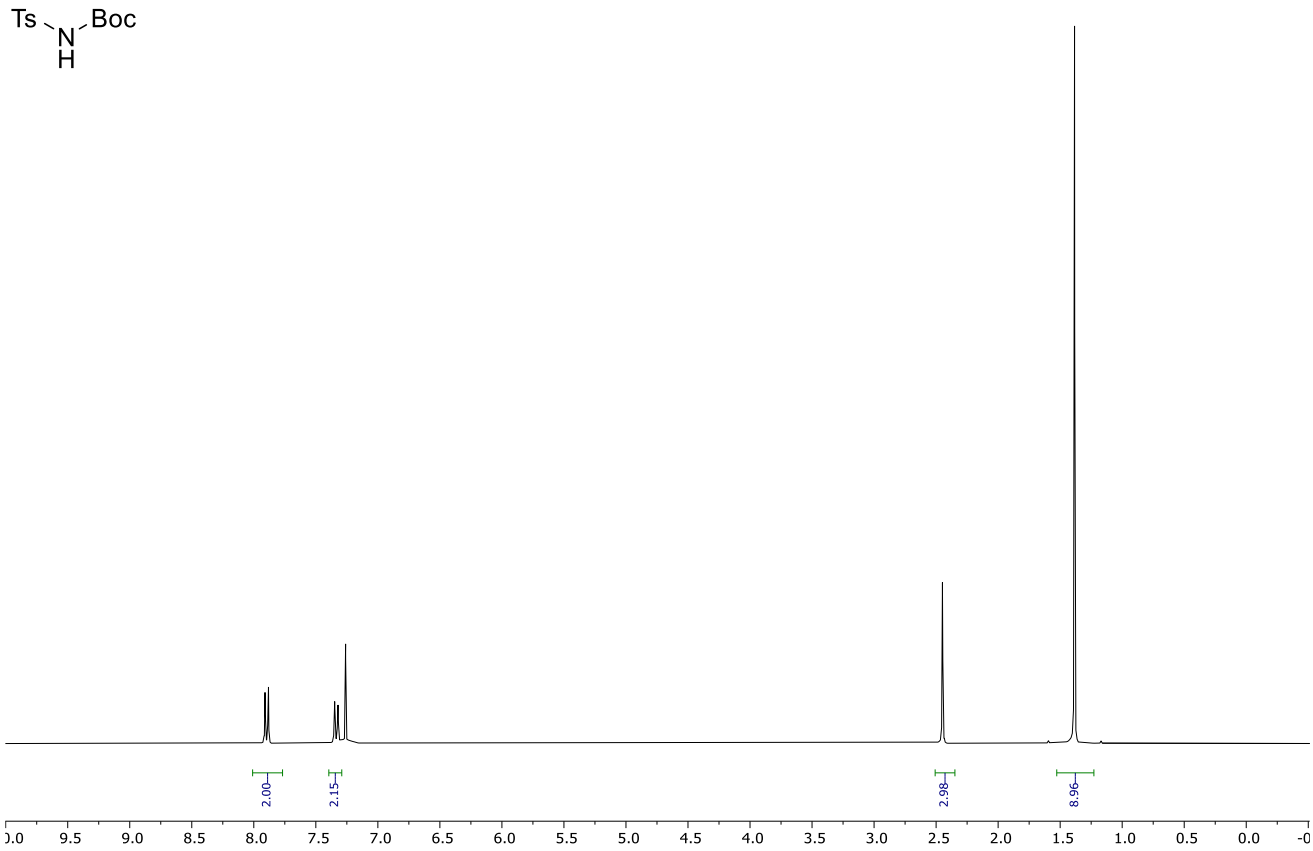
IR (NaCl) $\tilde{\nu}$ (cm^{-1}): 3075, 3017, 2952, 1727, 1641, 1606, 1492, 1440, 1397, 1346, 1238, 1169, 1101, 1038, 997, 934, 861, 813, 753, 718, 657.

HRMS (ESI): calc'd. for $C_{23}H_{24}O_6S$, **[M+H]**$^{+}$ 442.1319 found 442.1325.

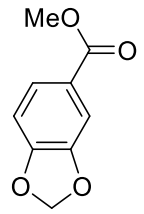
IV. NMR spectra and HPLC chromatograms of the new products

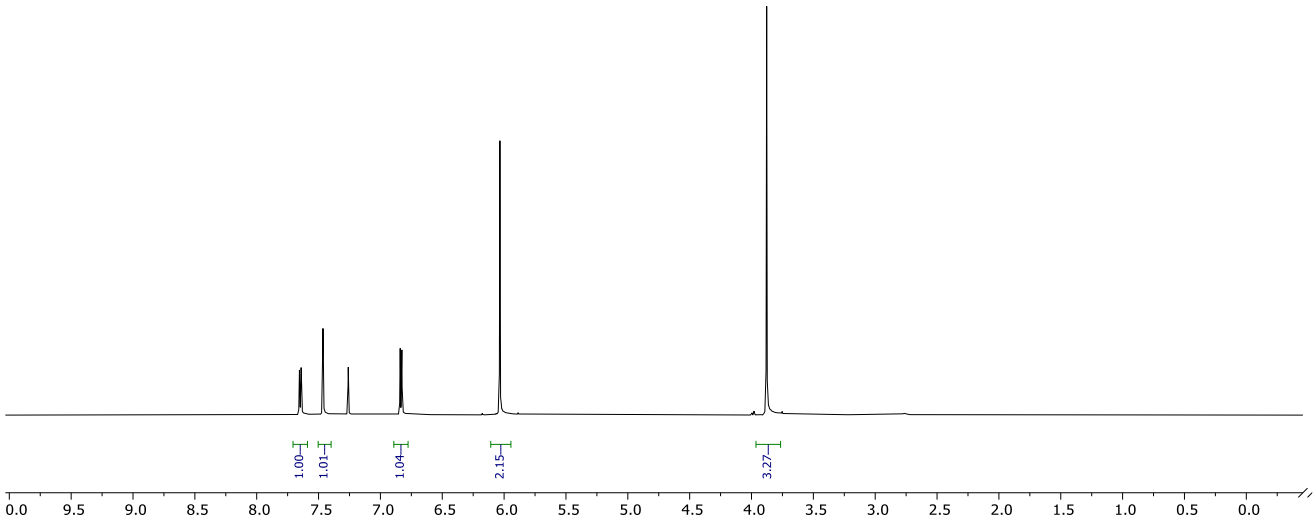


^{1}H NMR (300 MHz, $CDCl_3$) of ethynyltriisopropylsilane

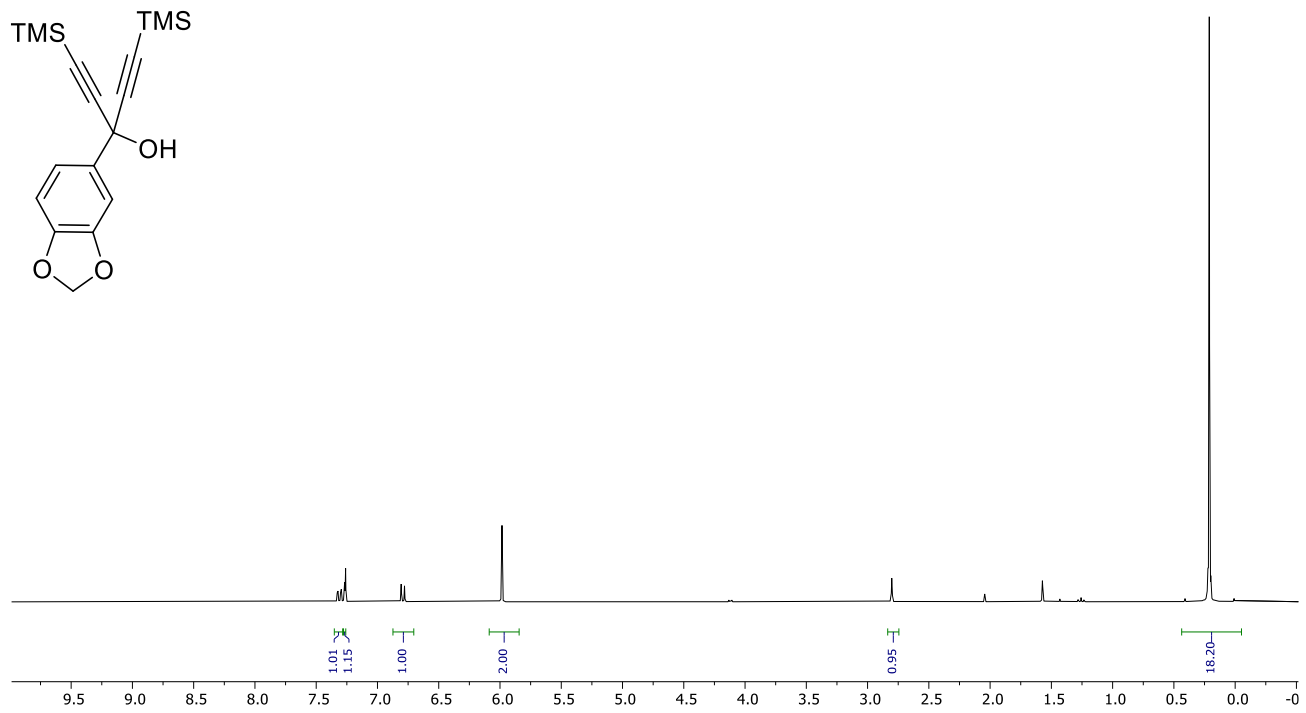


^{1}H NMR (300 MHz, $CDCl_3$) of *tert*-butyl tosylcarbamate

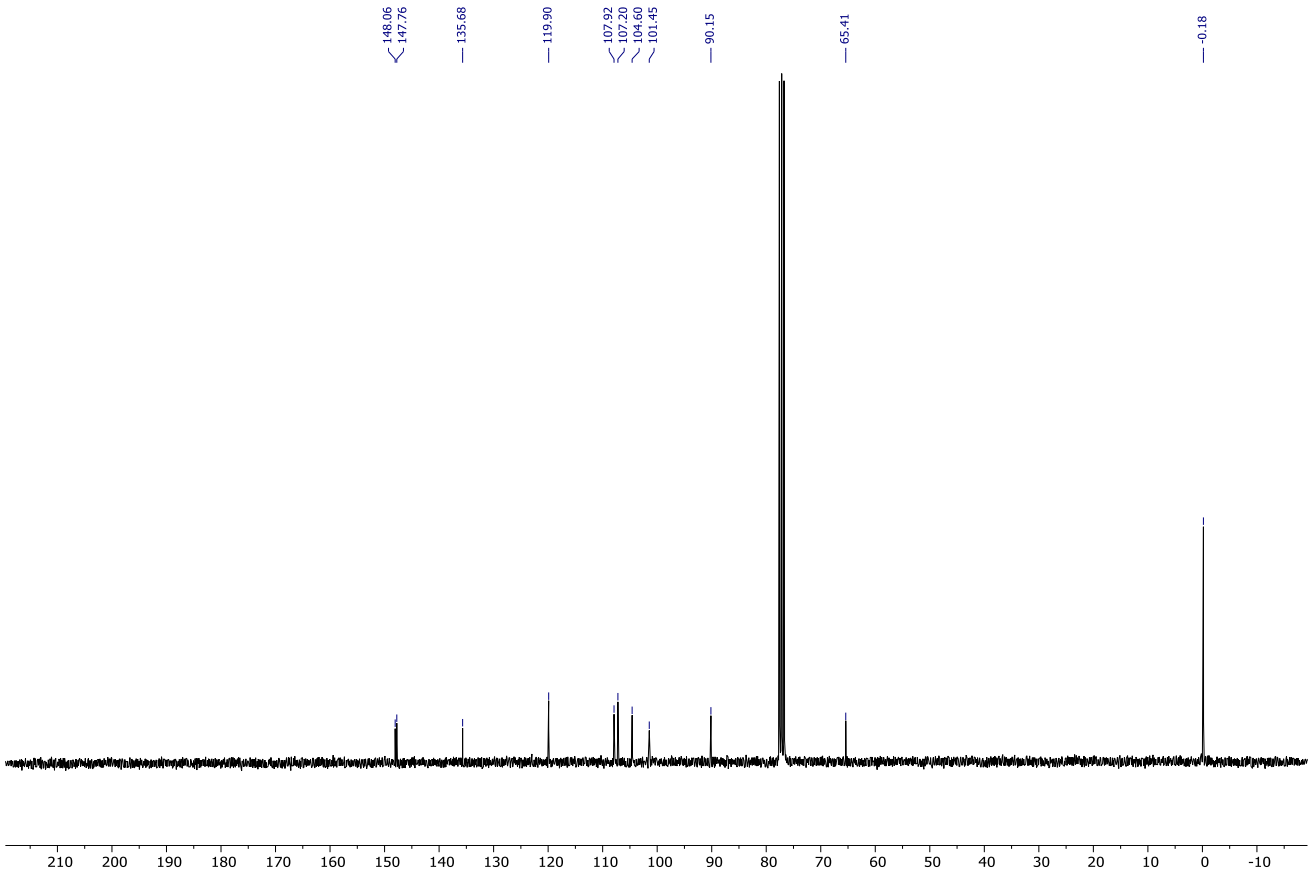




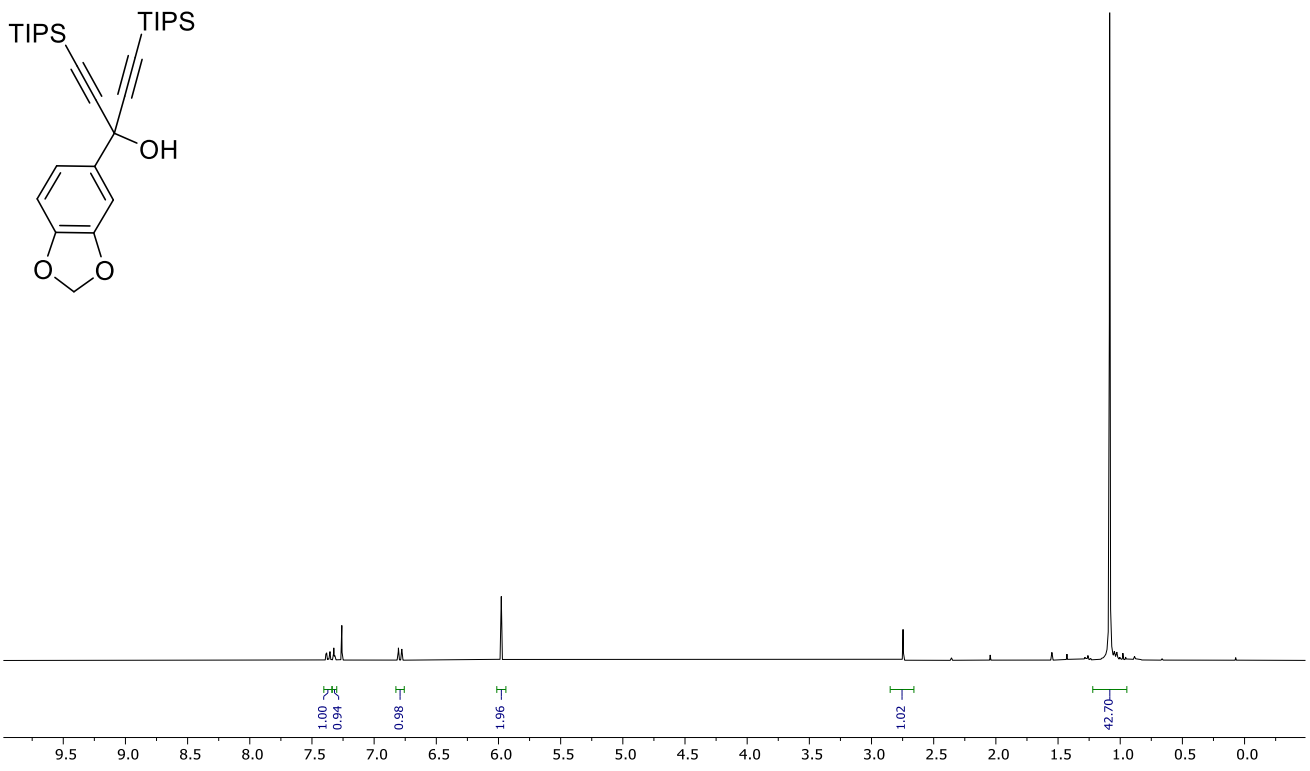
^{1}H NMR (300 MHz, $CDCl_3$) of compound **1**



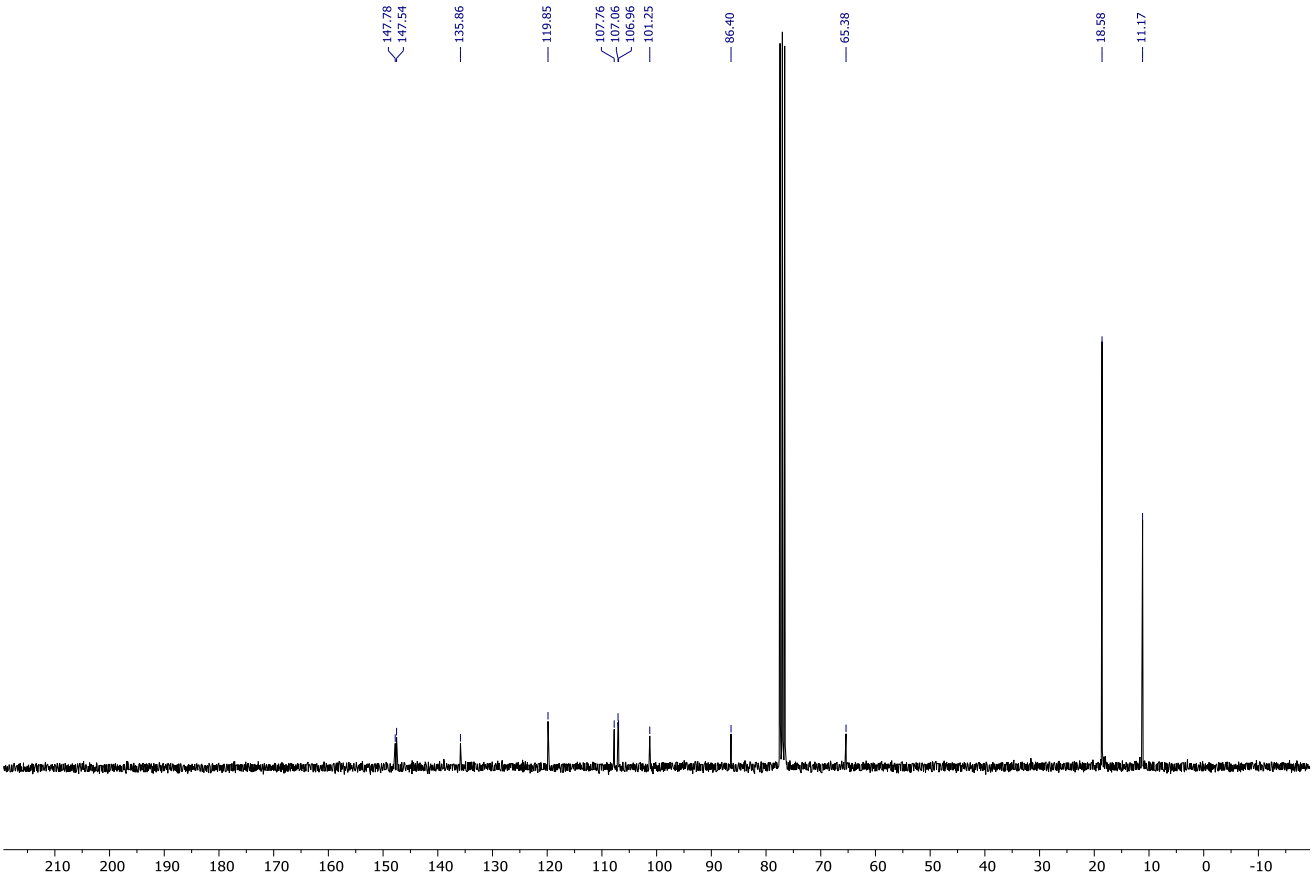
^{1}H NMR (300 MHz, $CDCl_3$) of **3-(benzo[d][1,3]dioxol-5-yl)-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol**



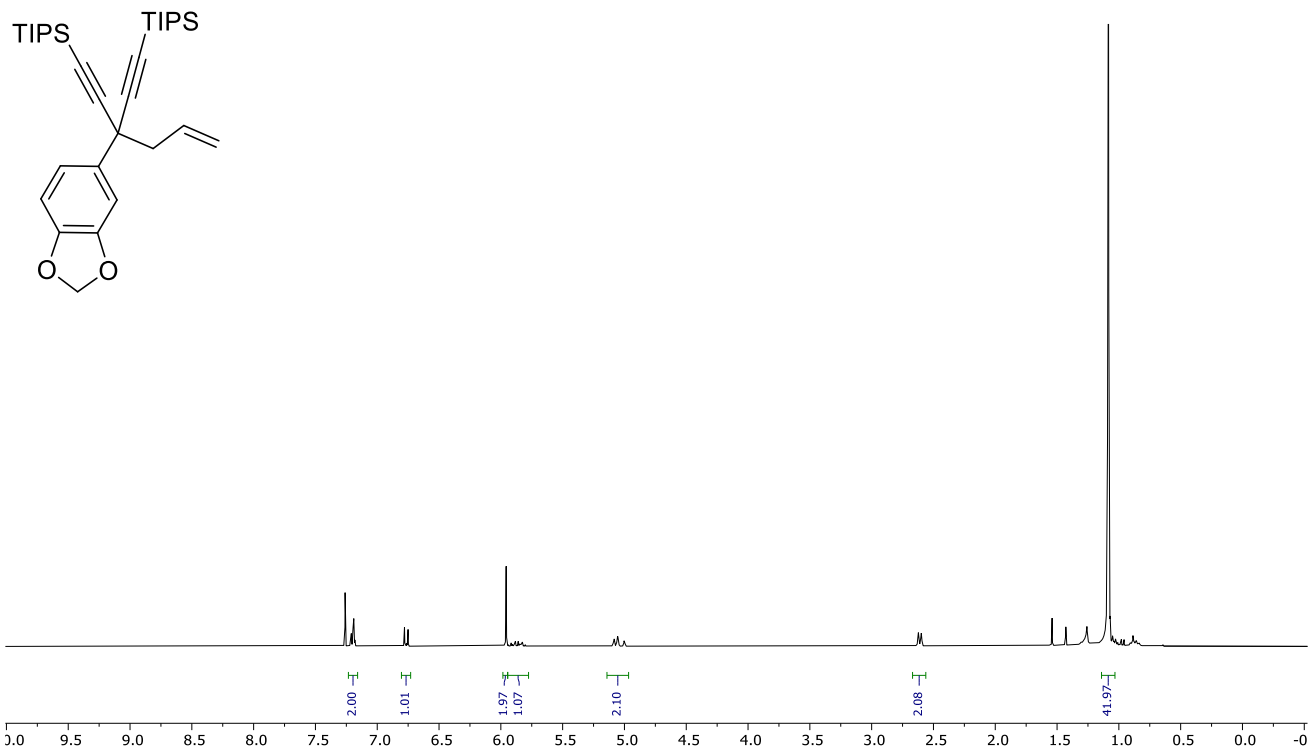
^{13}C NMR (75 MHz, $CDCl_3$) of **3-(benzo[d][1,3]dioxol-5-yl)-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol**



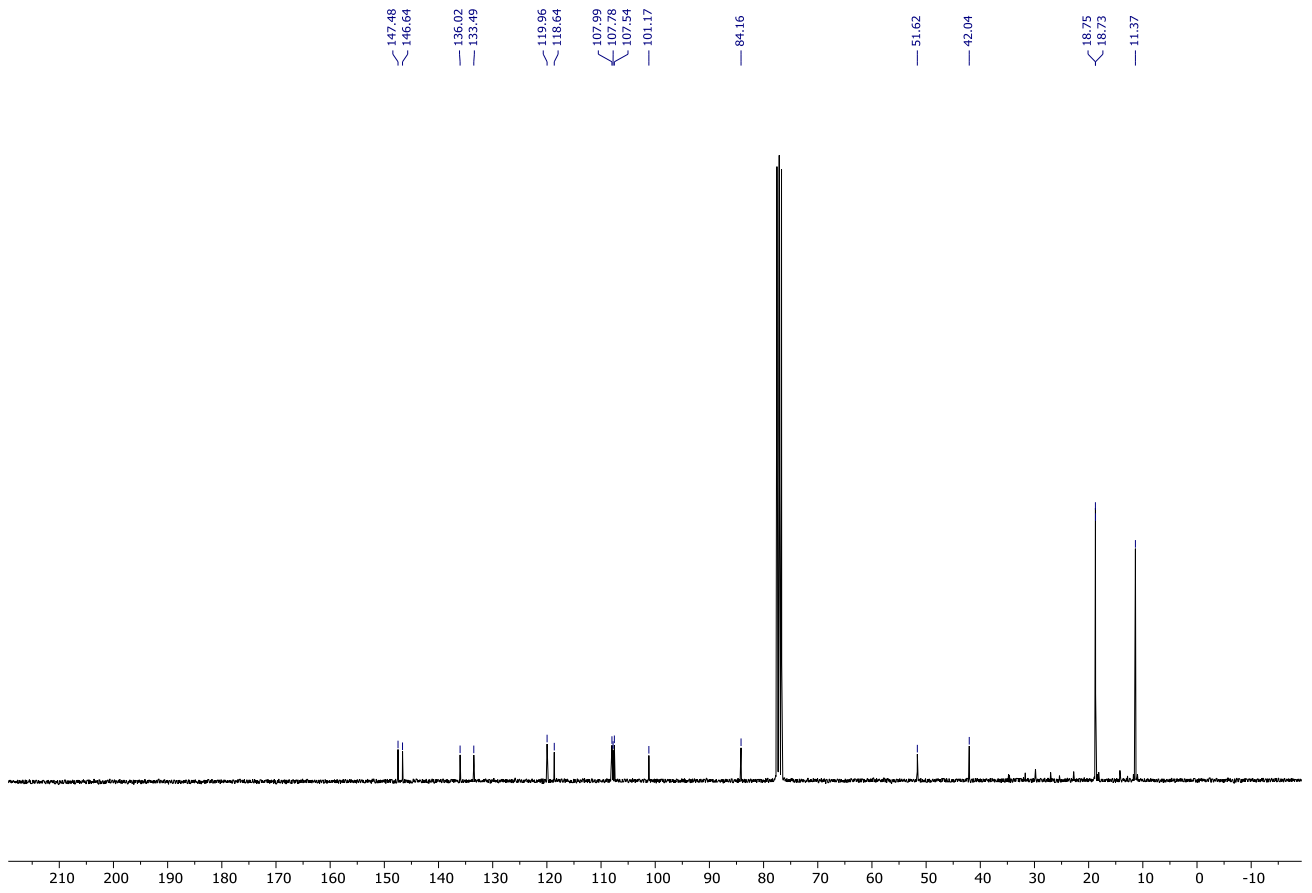
^{1}H NMR (300 MHz, $CDCl_3$) of compound **2**



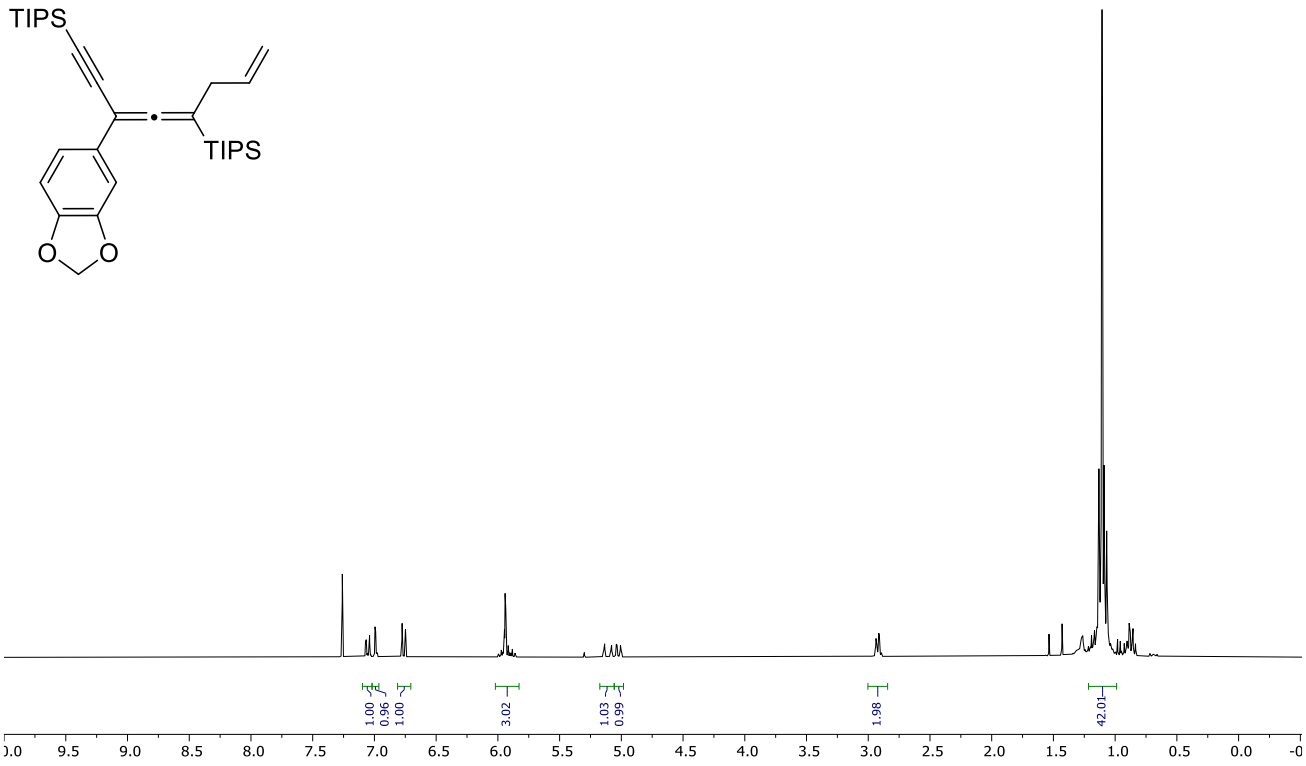
^{13}C NMR (75 MHz, $CDCl_3$) of compound **2**



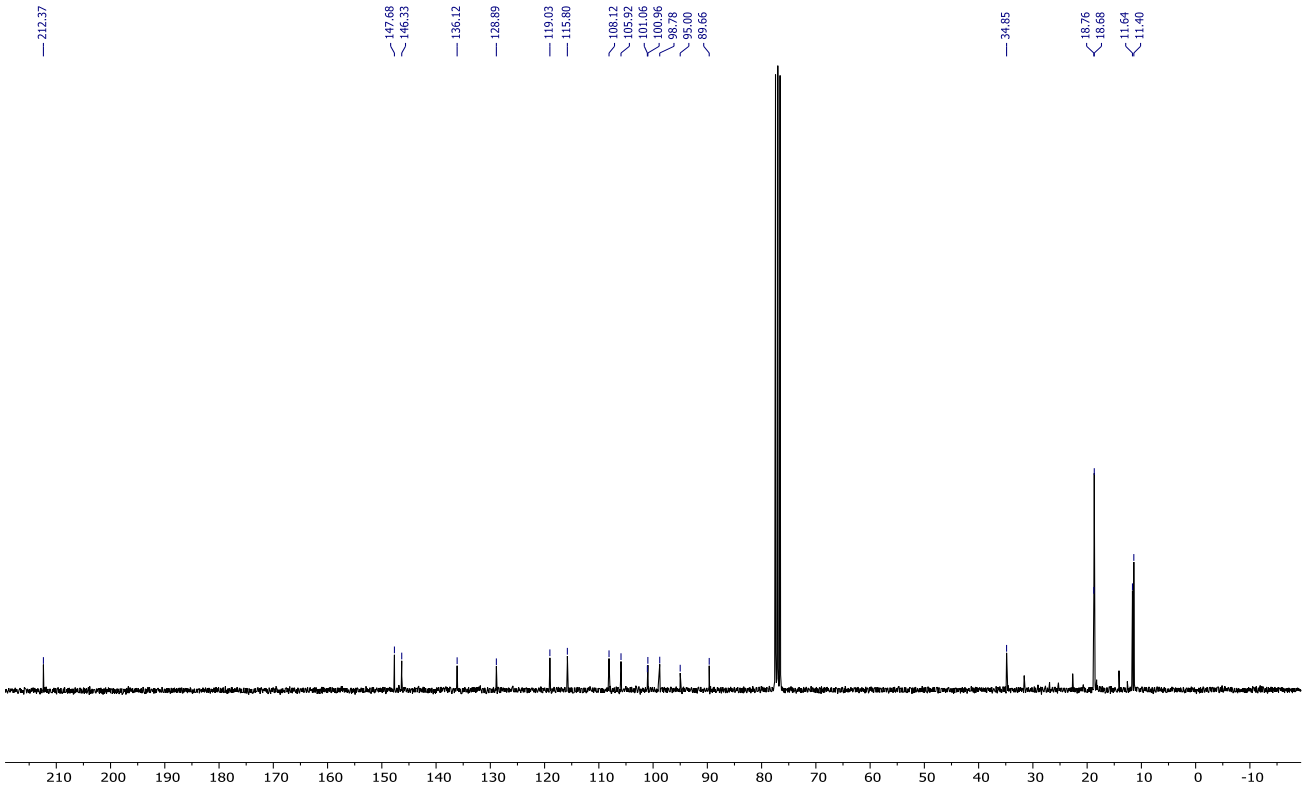
^{1}H NMR (300 MHz, $CDCl_3$) of compound **3**



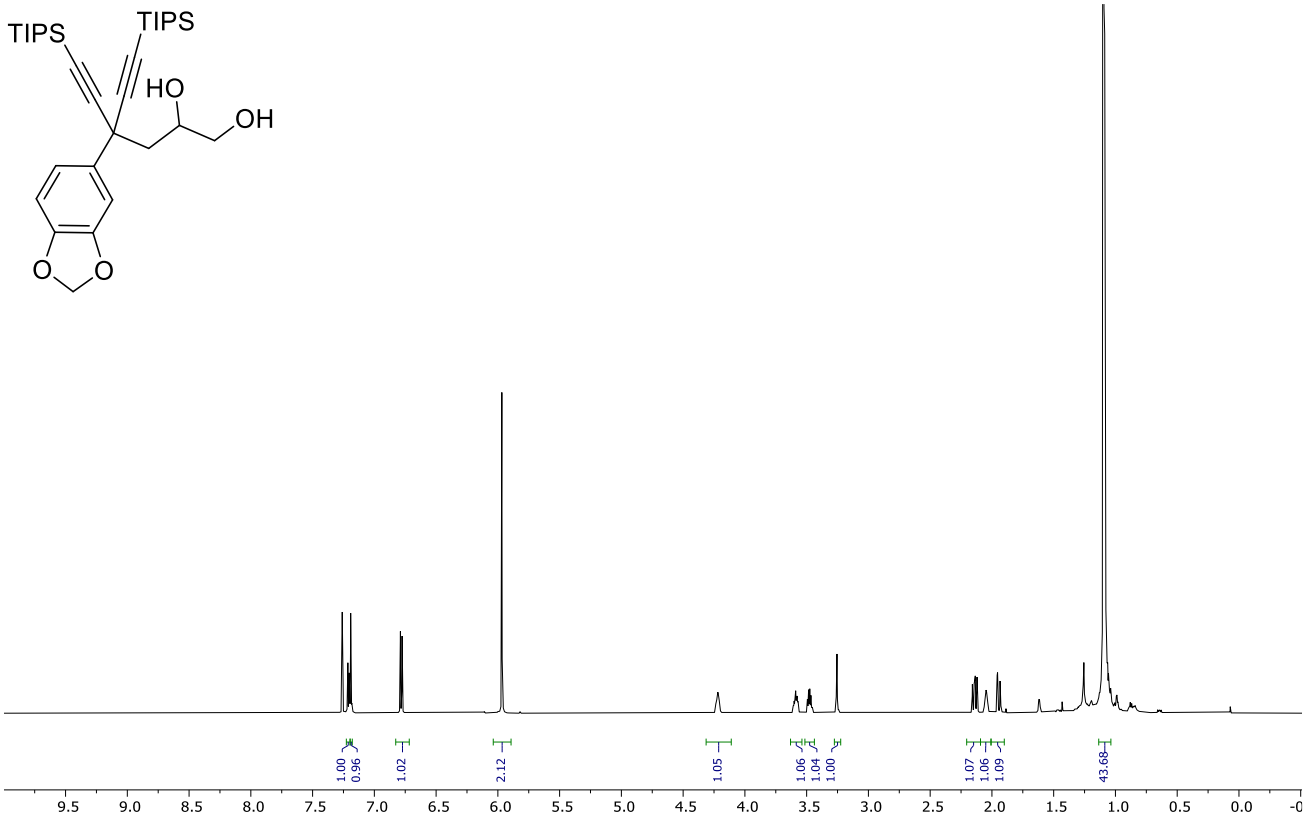
^{13}C NMR (75 MHz, $CDCl_3$) of compound **3**



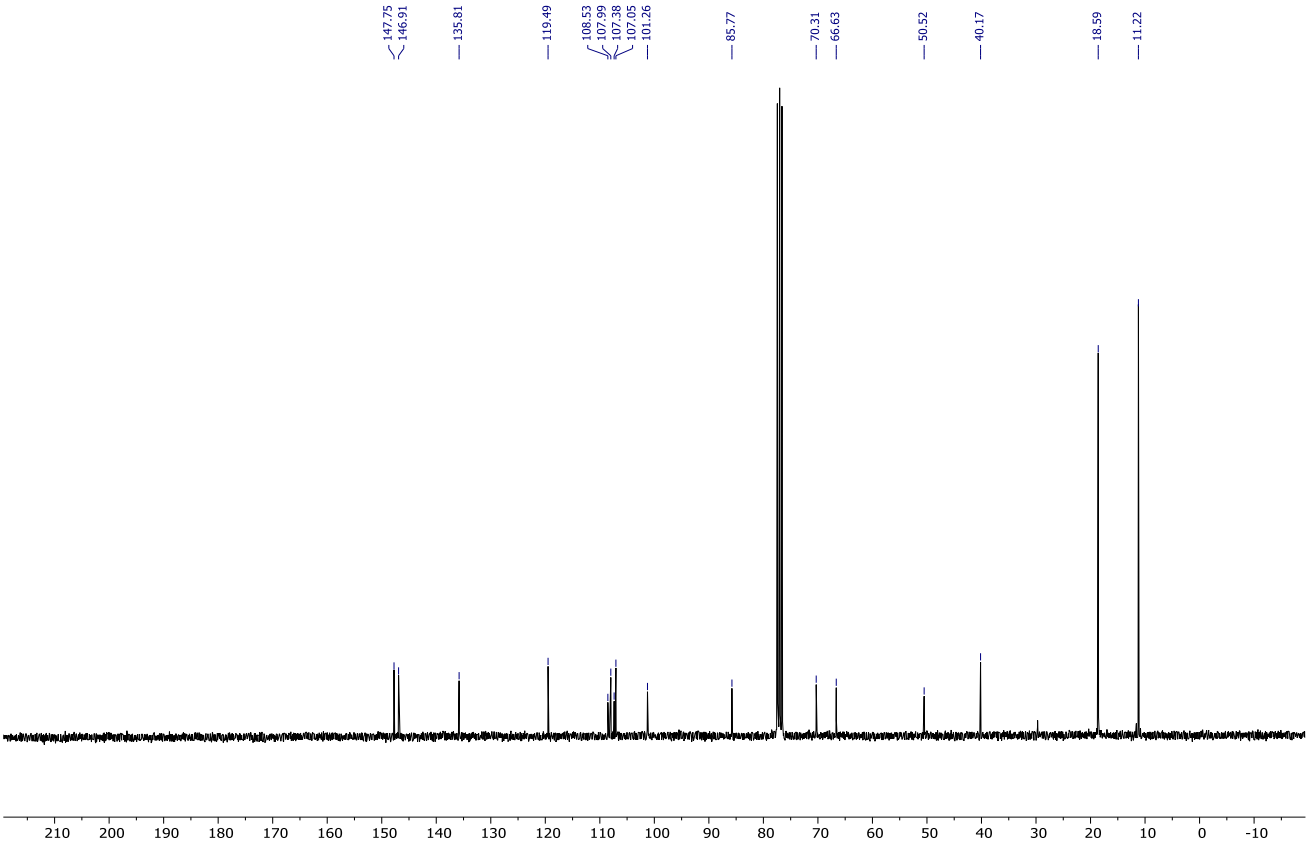
^{1}H NMR (300 MHz, $CDCl_3$) of **(3-(benzo[d][1,3]dioxol-5-yl)octa-3,4,7-trien-1-yne-1,5-diyl)bis(triisopropylsilane)**



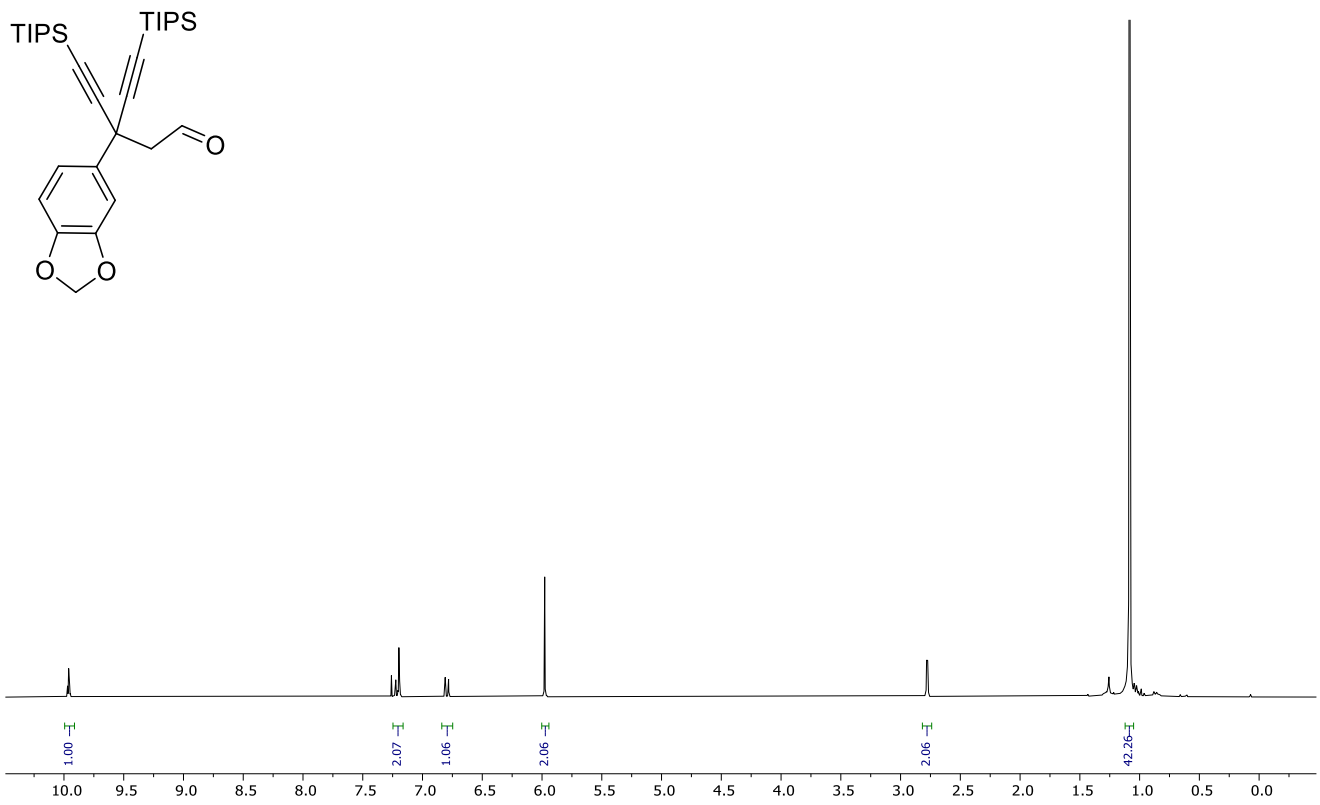
^{13}C NMR (75 MHz, $CDCl_3$) of **(3-(benzo[d][1,3]dioxol-5-yl)octa-3,4,7-trien-1-yne-1,5-diyl)bis(triisopropylsilane)**



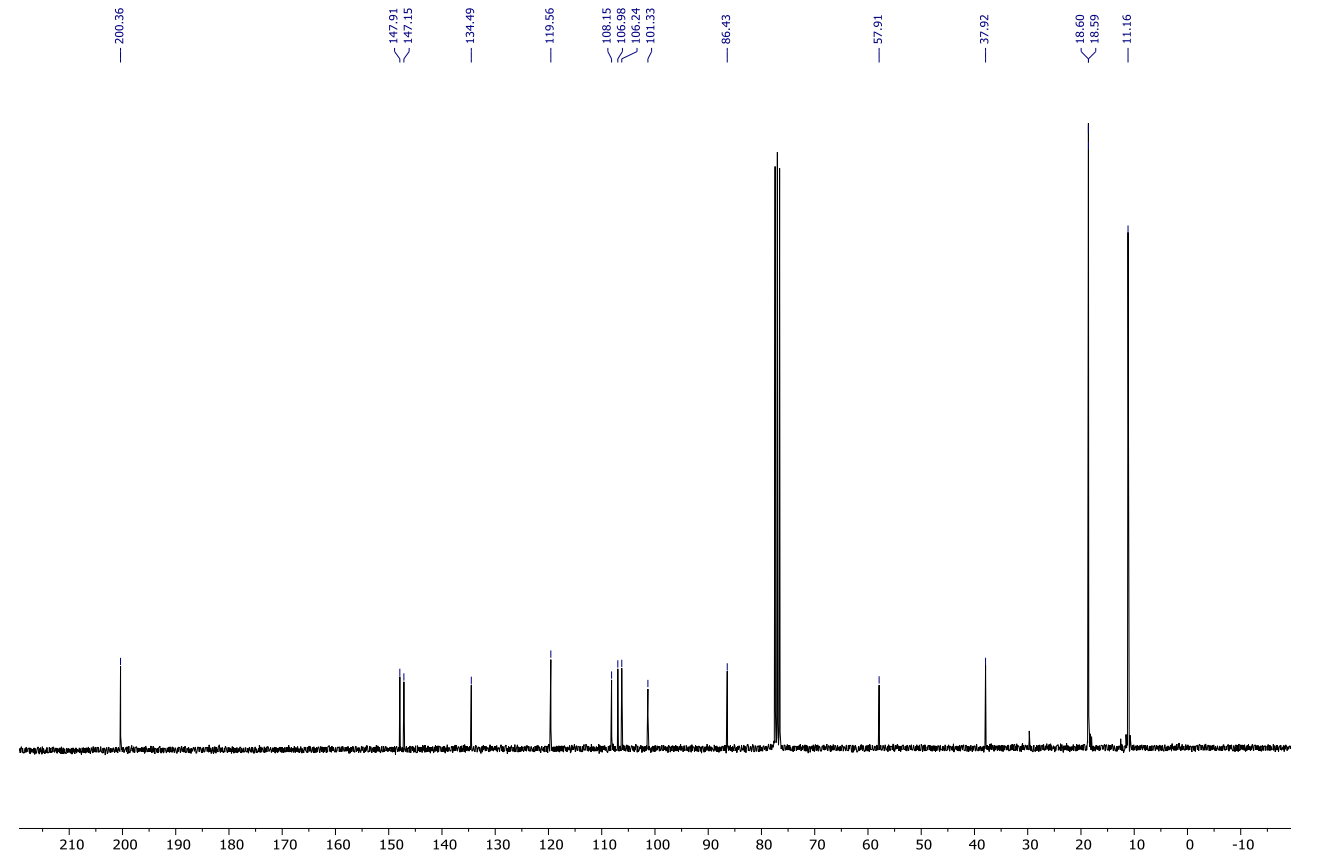
^{1}H NMR (300 MHz, $CDCl_3$) of compound **4**



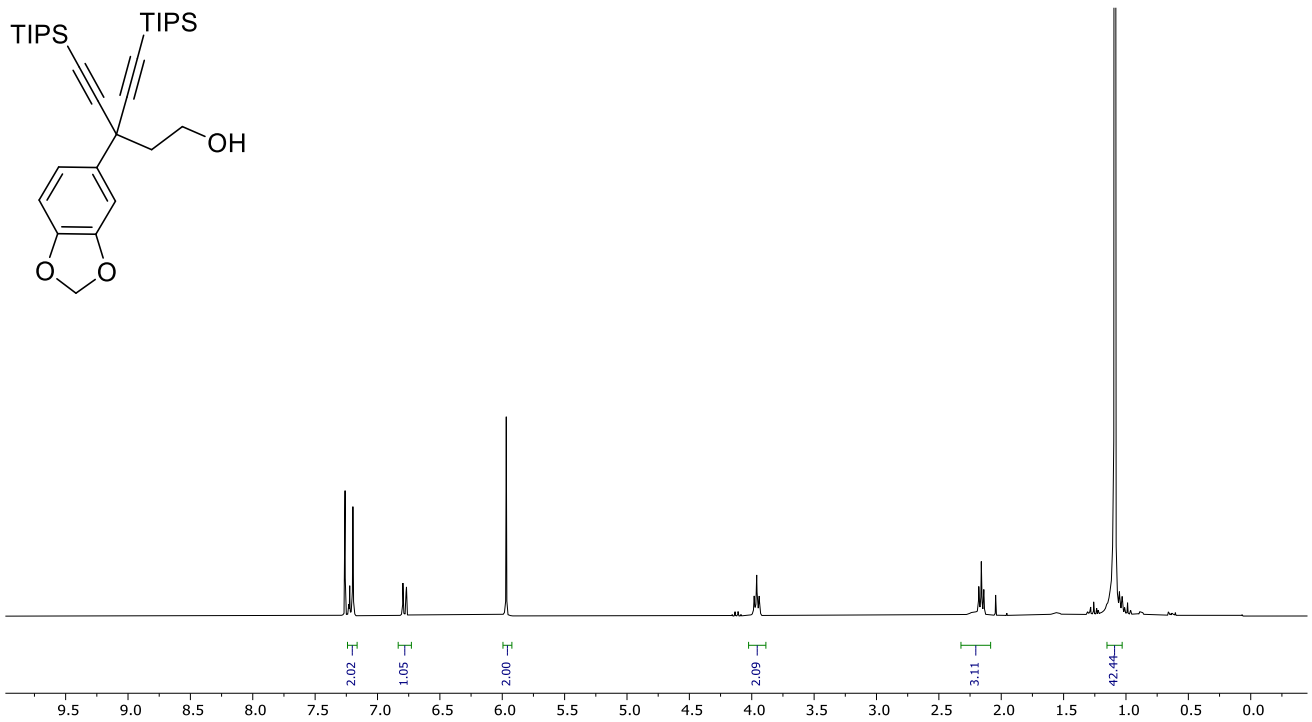
^{13}C NMR (75 MHz, $CDCl_3$) of compound **4**



^{1}H NMR (300 MHz, $CDCl_3$) of compound **5**

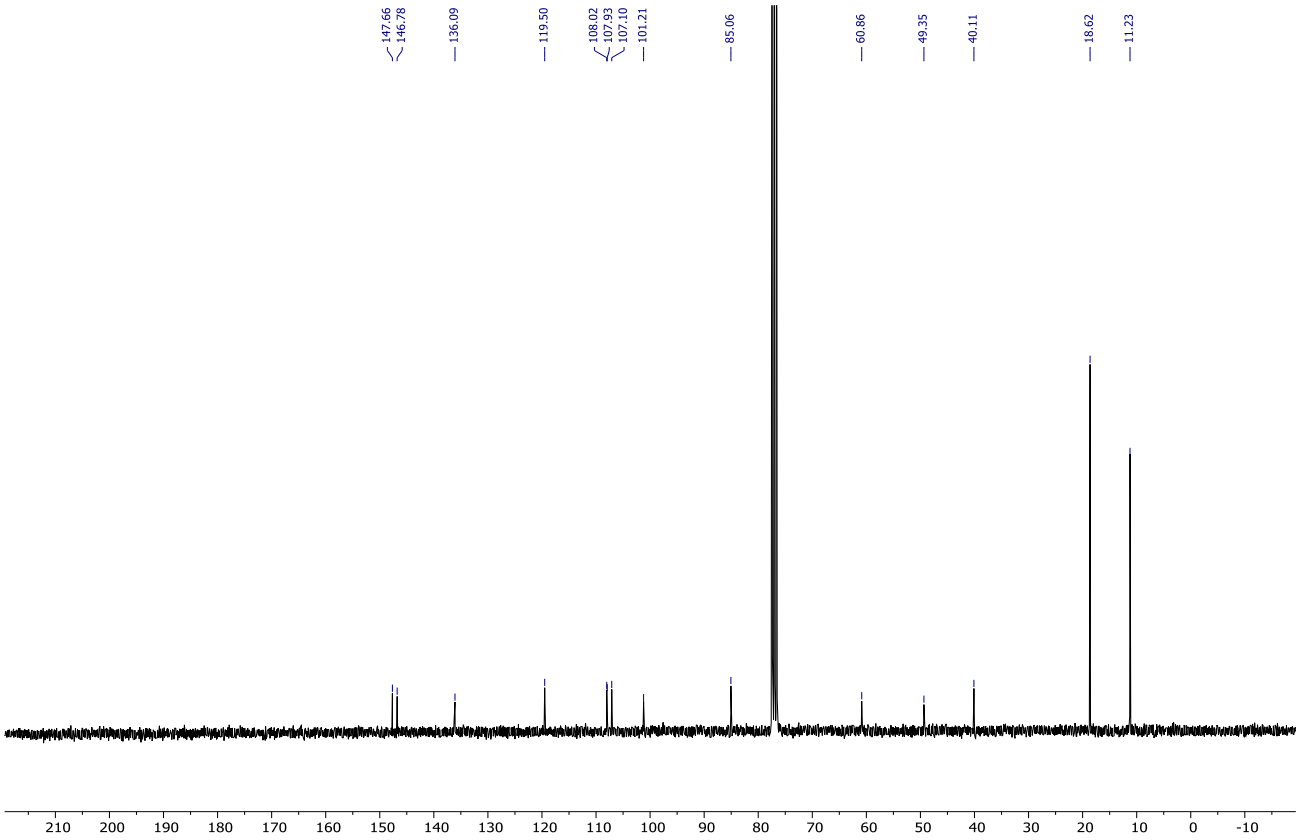


^{13}C NMR (75 MHz, $CDCl_3$) of compound **5**



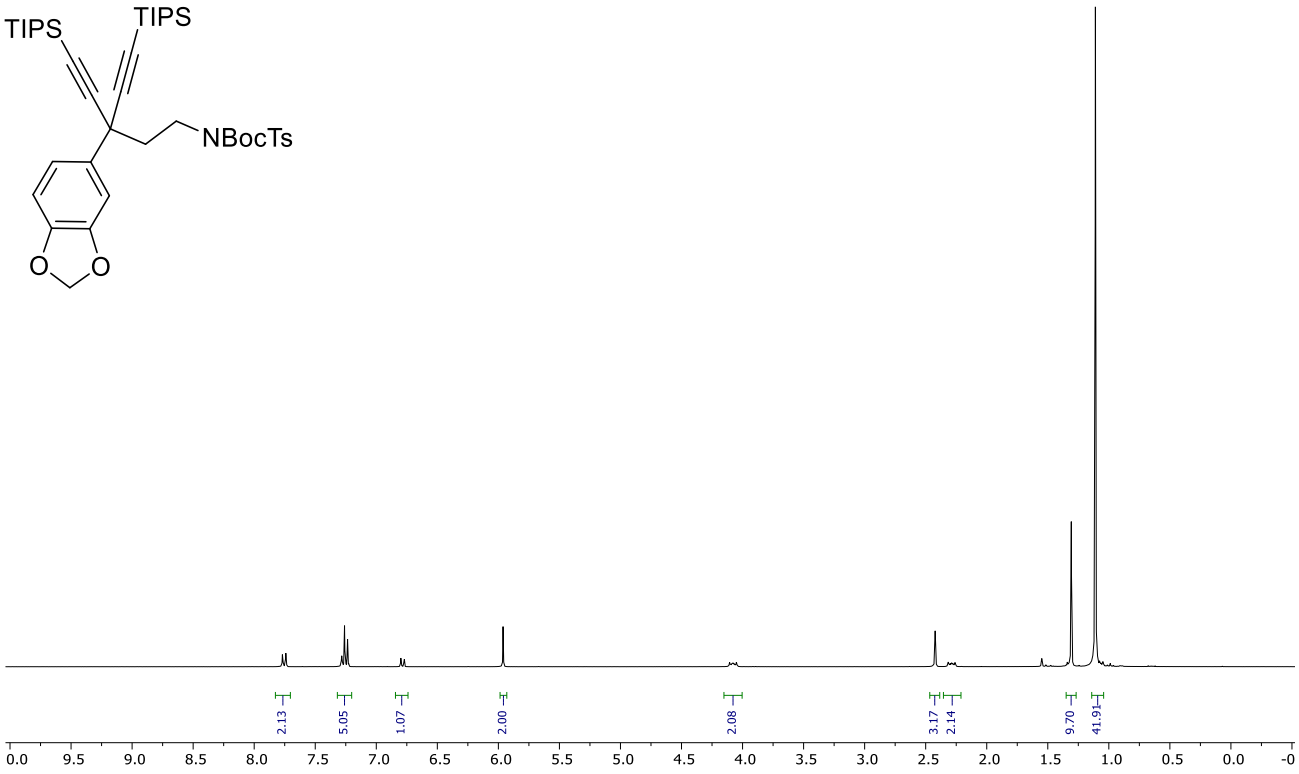
^{1}H NMR (300 MHz, $CDCl_3$) of

3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol

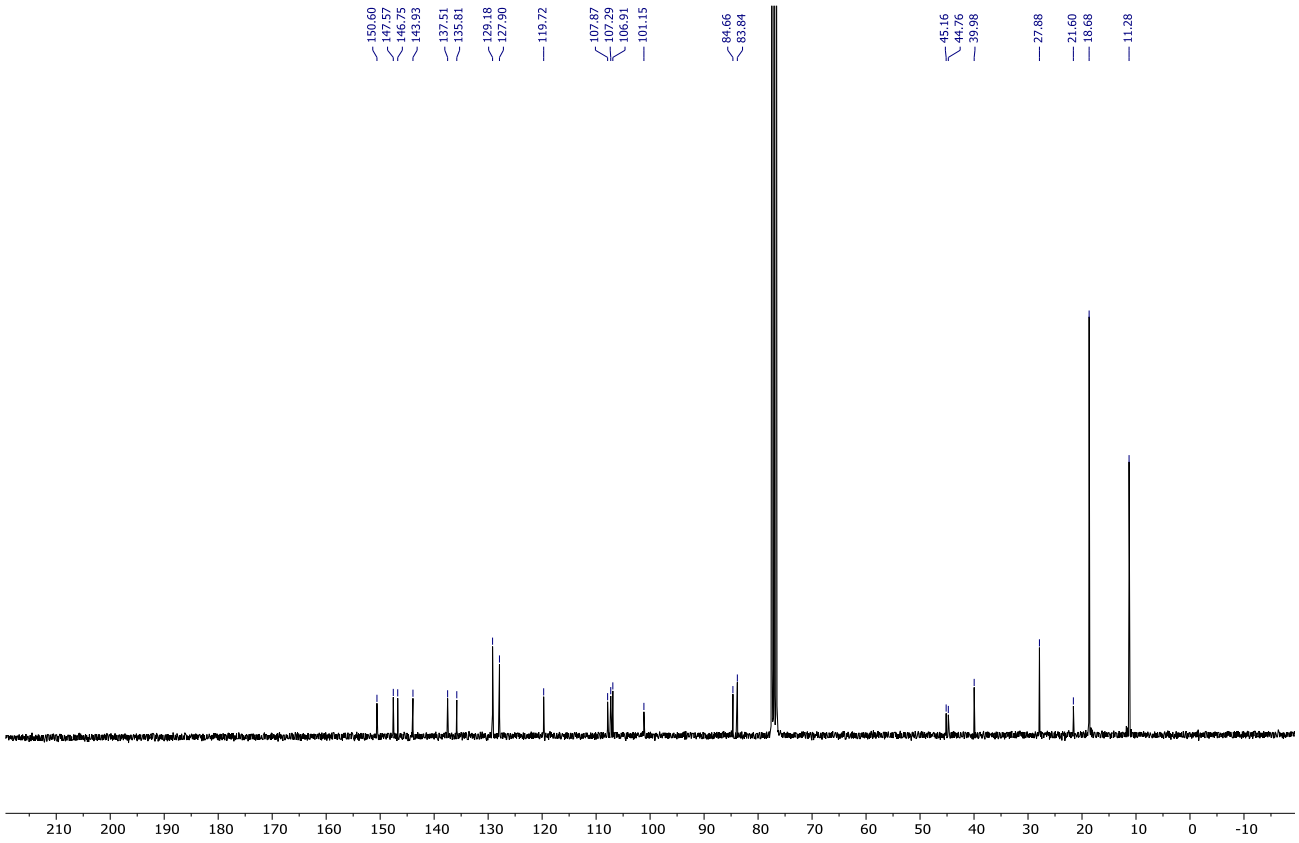


^{13}C NMR (75 MHz, $CDCl_3$) of

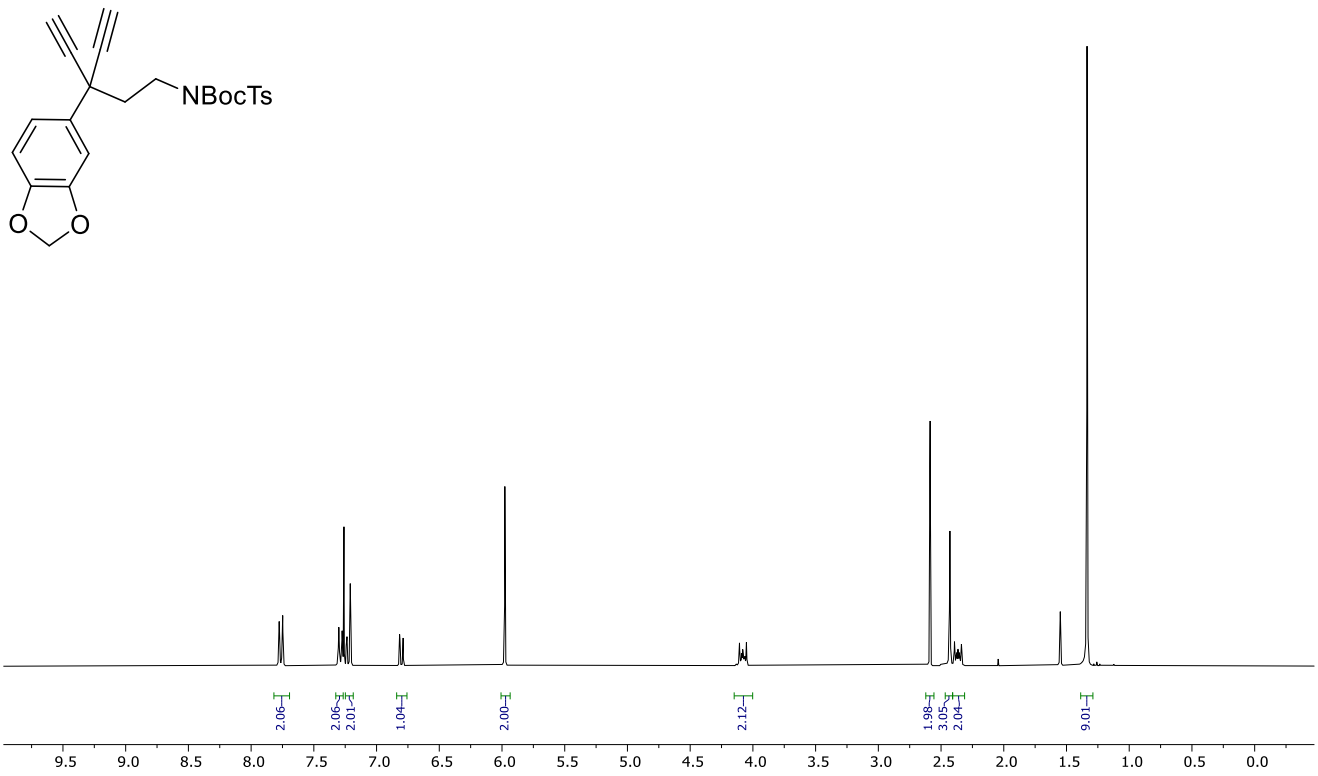
3-(benzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol



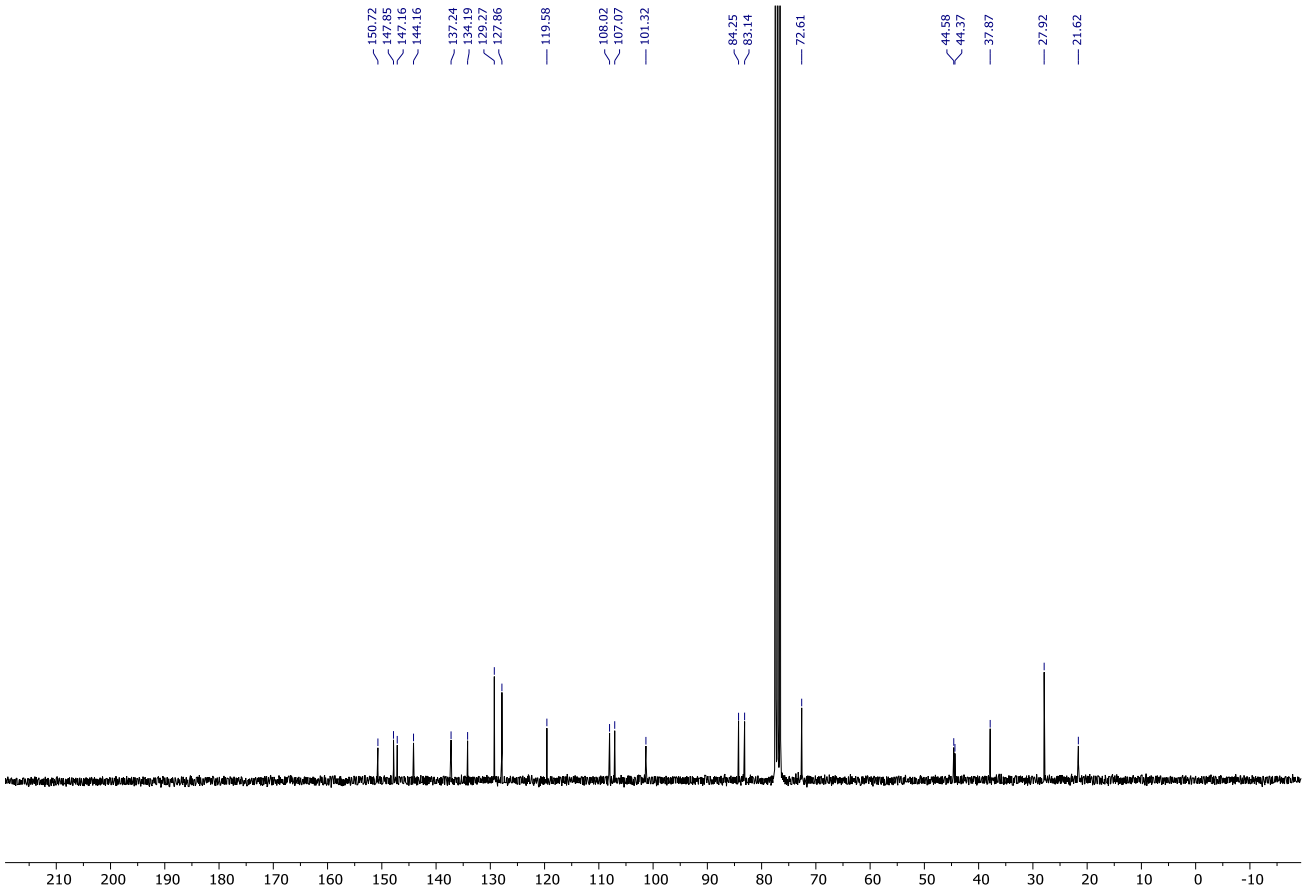
^{1}H NMR (300 MHz, $CDCl_3$) of compound **6**



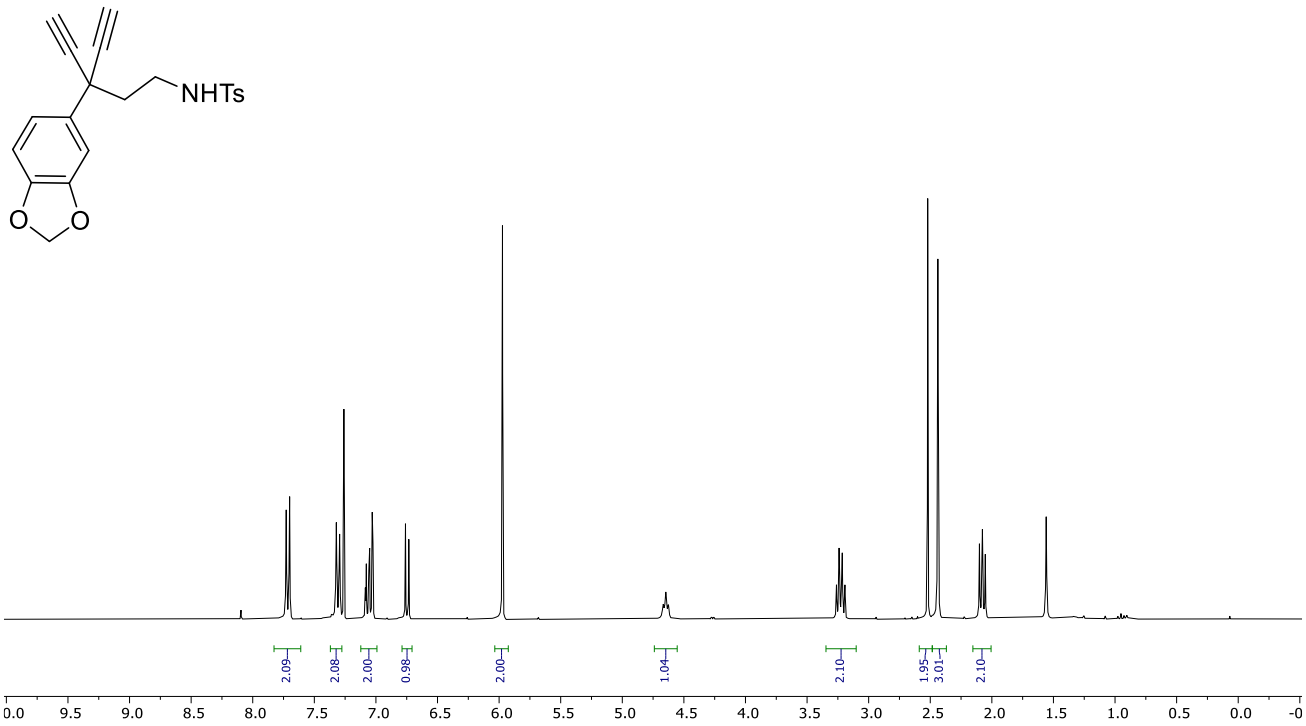
^{13}C NMR (75 MHz, $CDCl_3$) of compound **6**



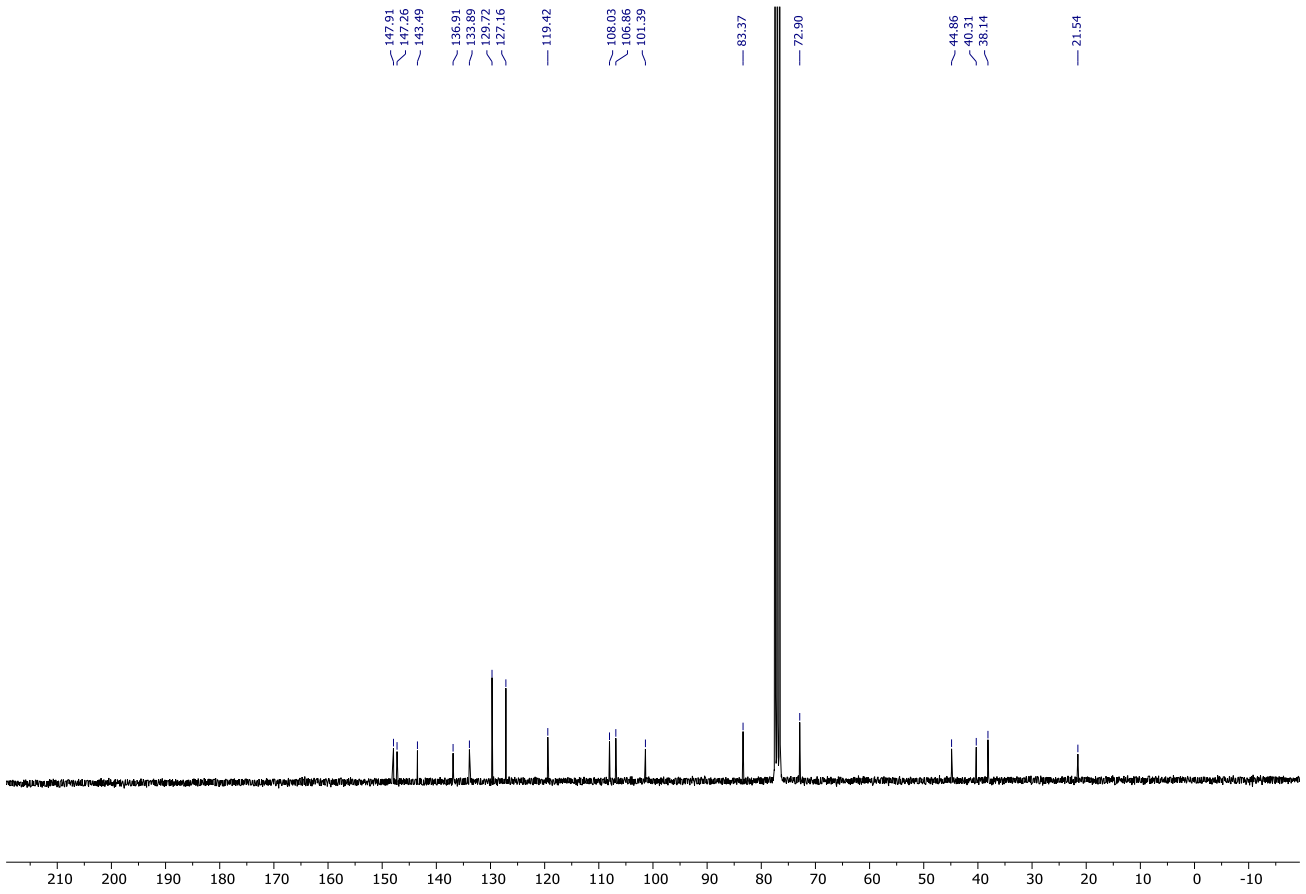
^{1}H NMR (300 MHz, $CDCl_3$) of ***tert*-butyl (3-(benzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)(tosyl)carbamate**



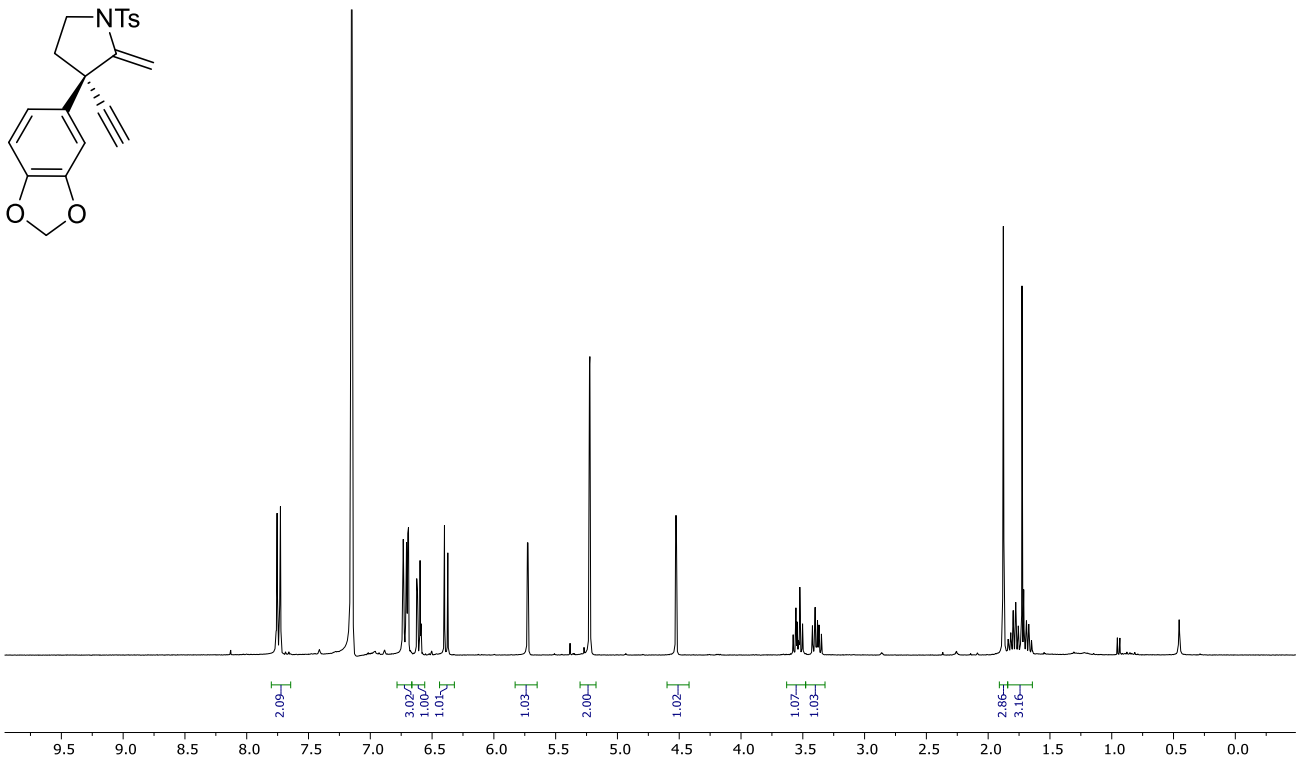
^{13}C NMR (75 MHz, $CDCl_3$) of ***tert*-butyl (3-(benzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)(tosyl)carbamate**



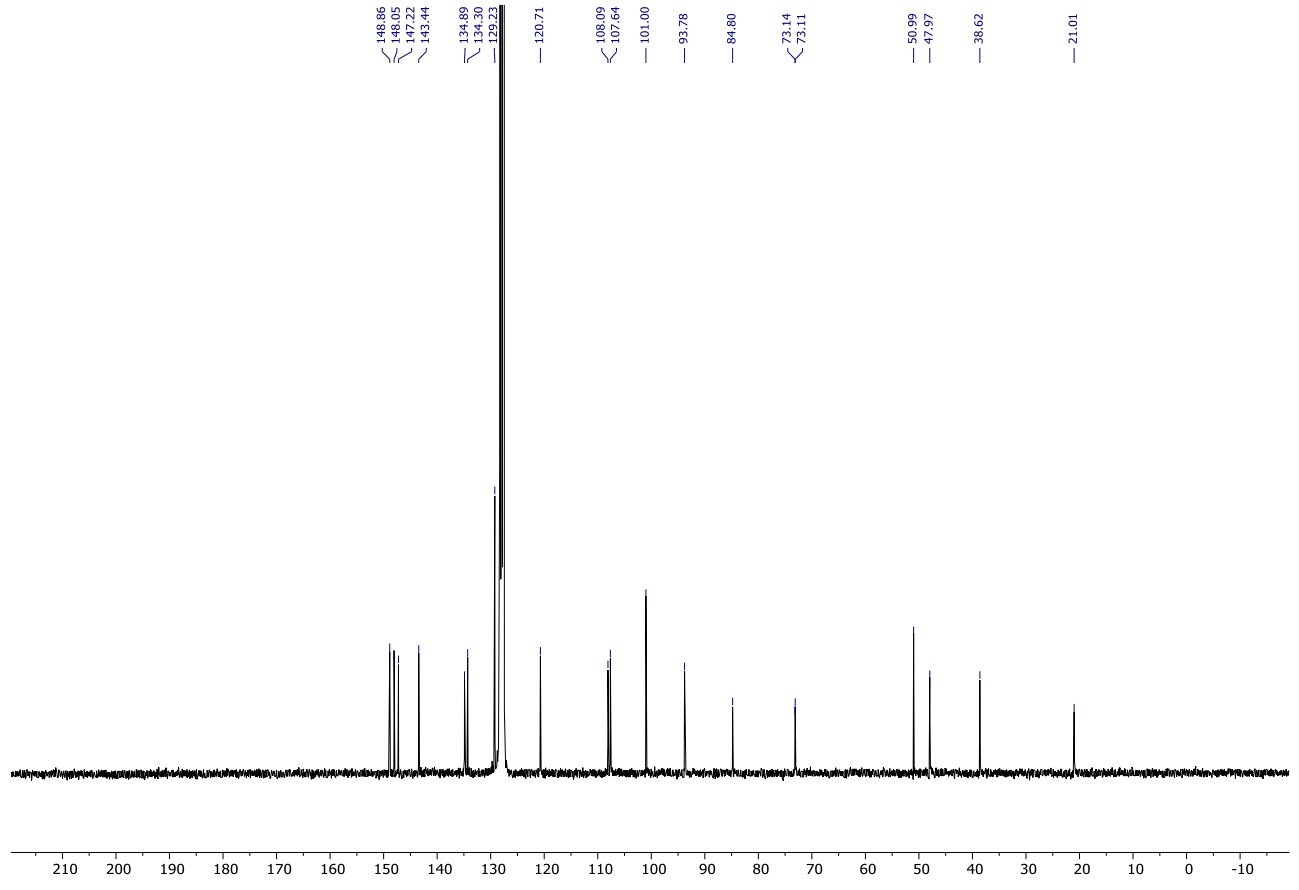
^{1}H NMR (300 MHz, $CDCl_3$) of **compound 7**



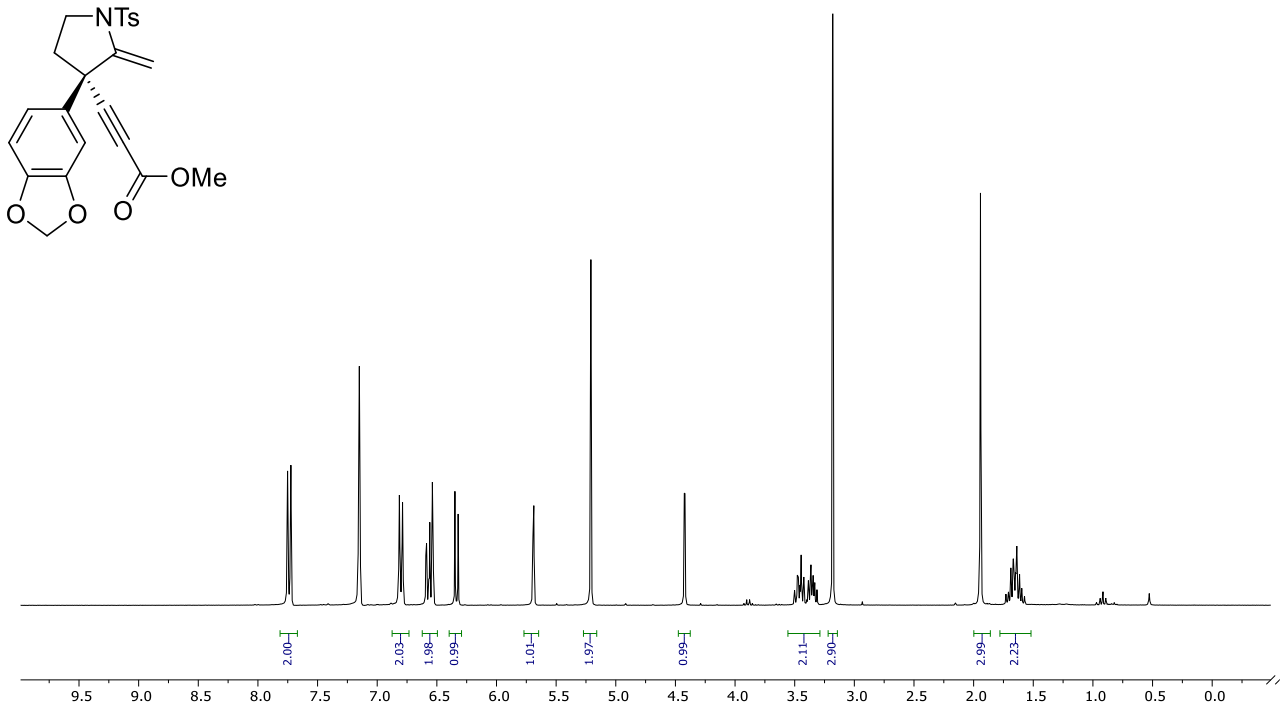
^{13}C NMR (75 MHz, $CDCl_3$) **of compound 7**



^{1}H NMR (300 MHz, C_6D_6) of compound **8a**

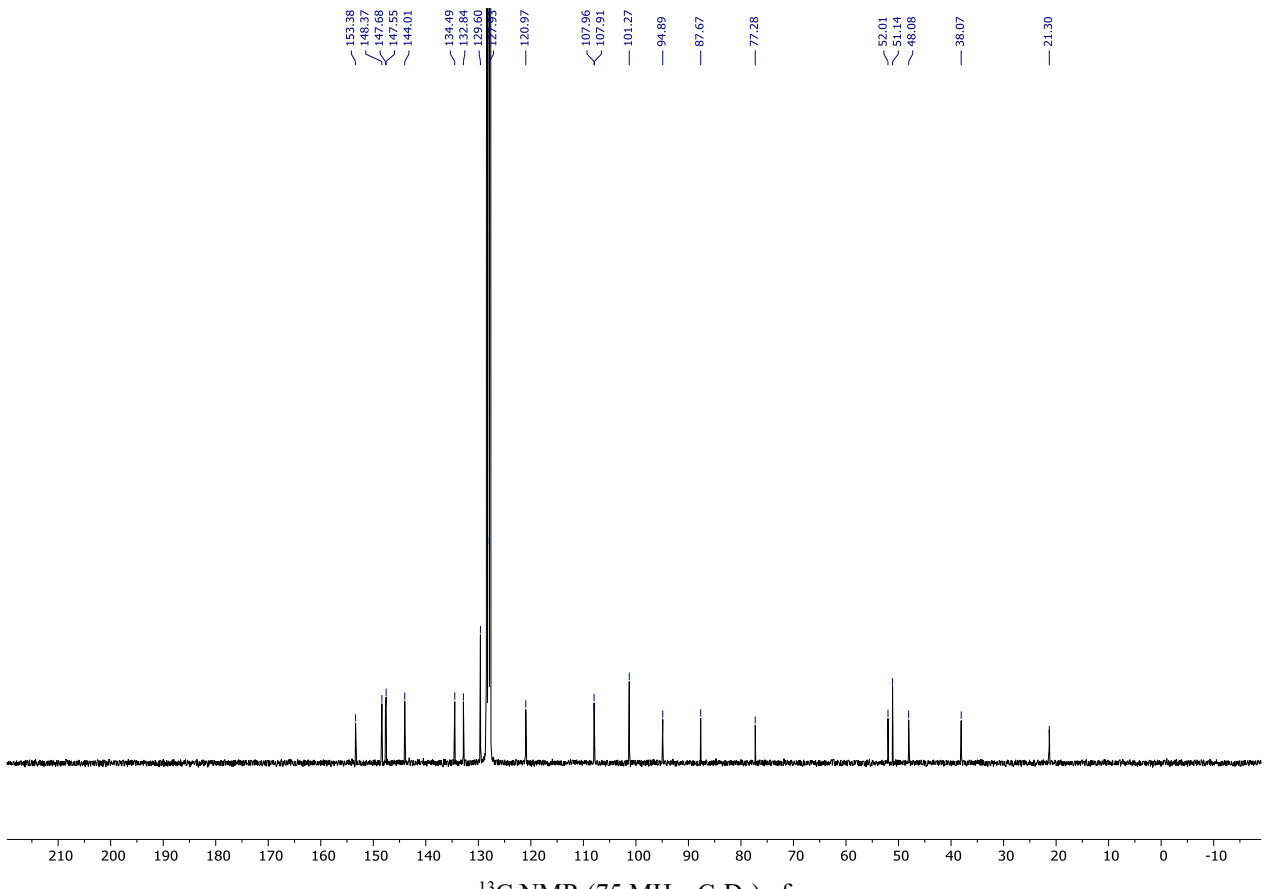


^{13}C NMR (75 MHz, C_6D_6) of compound **8a**



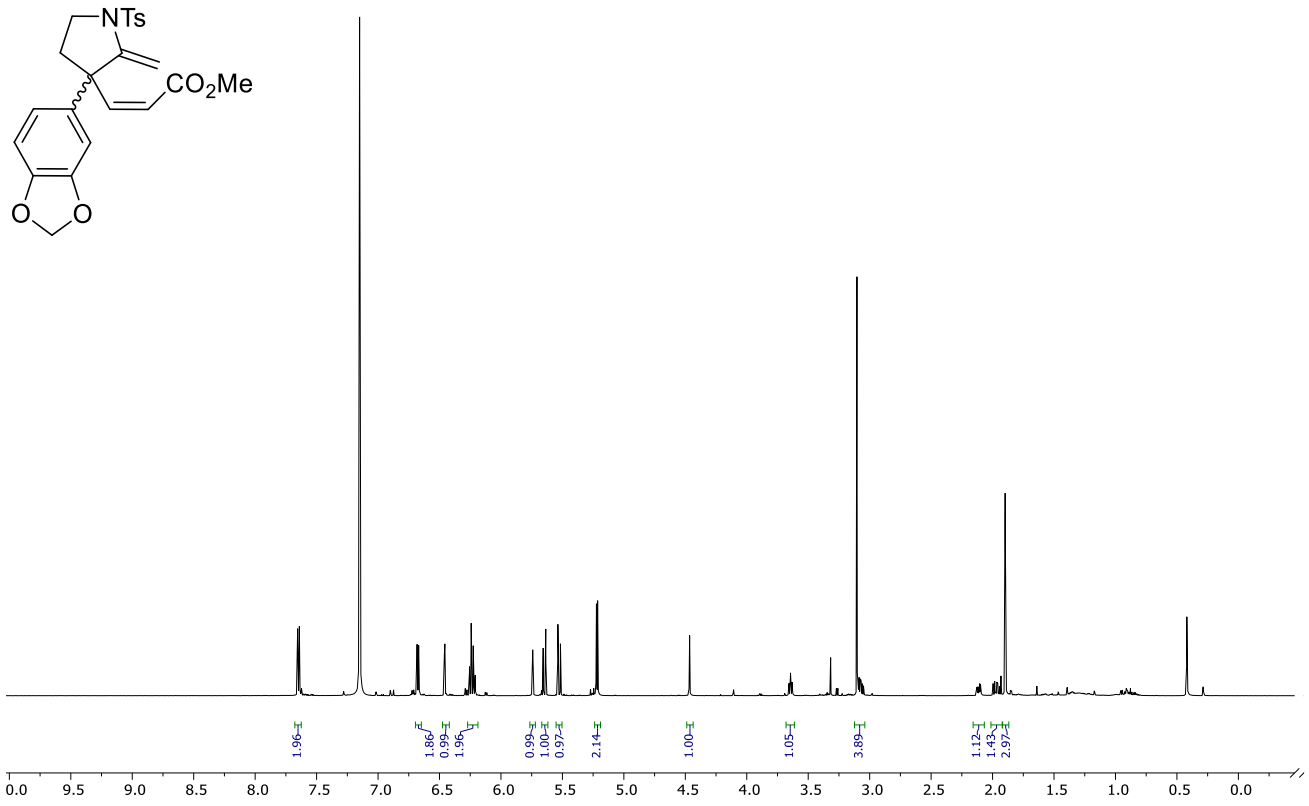
^{1}H NMR (300 MHz, C_6D_6) of

methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)propiolate

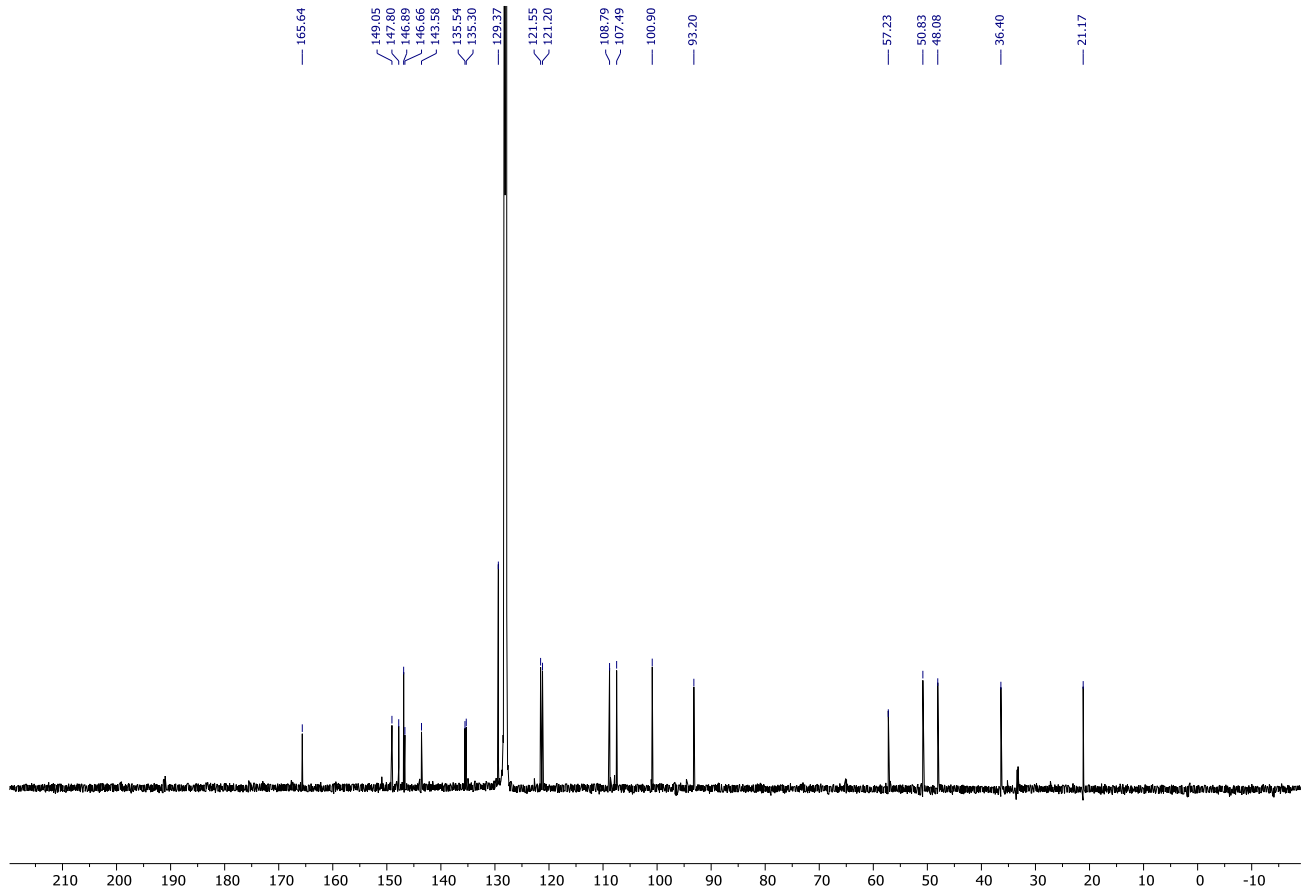


^{13}C NMR (75 MHz, C_6D_6) of

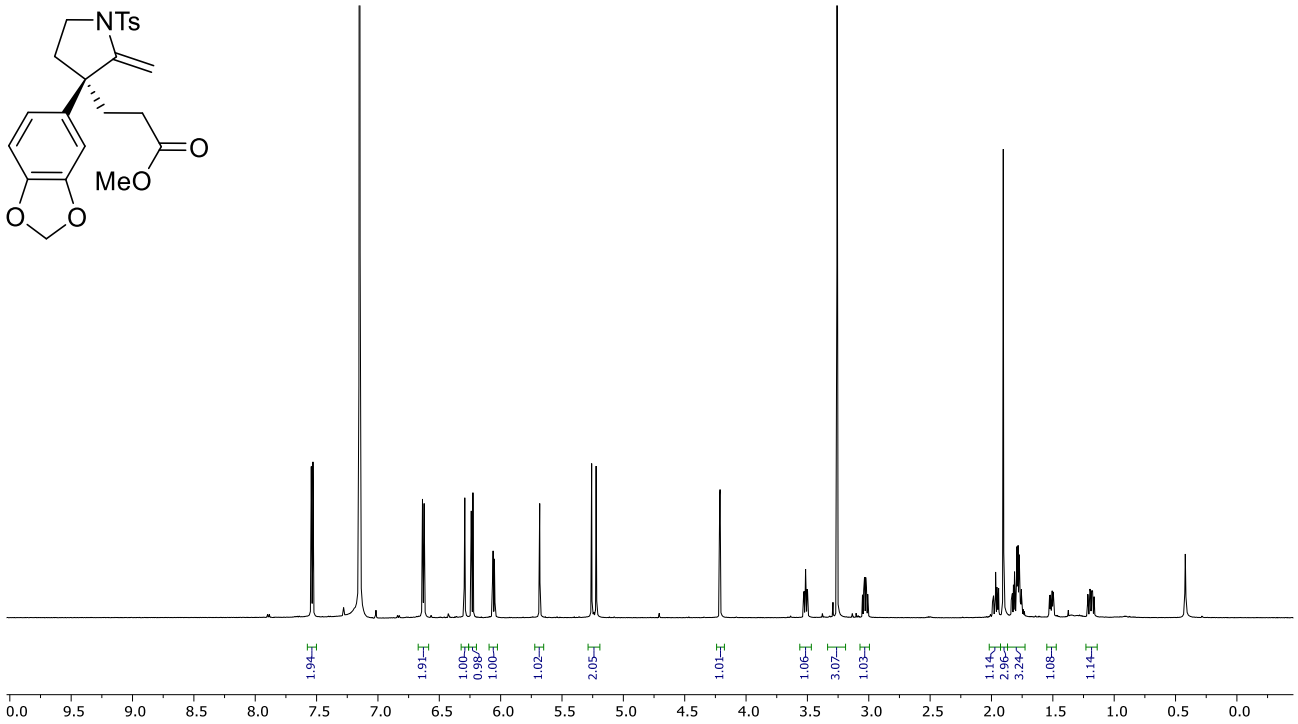
methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)propiolate



^{1}H NMR (300 MHz, C_6D_6) of **methyl (*Z*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)acrylate**

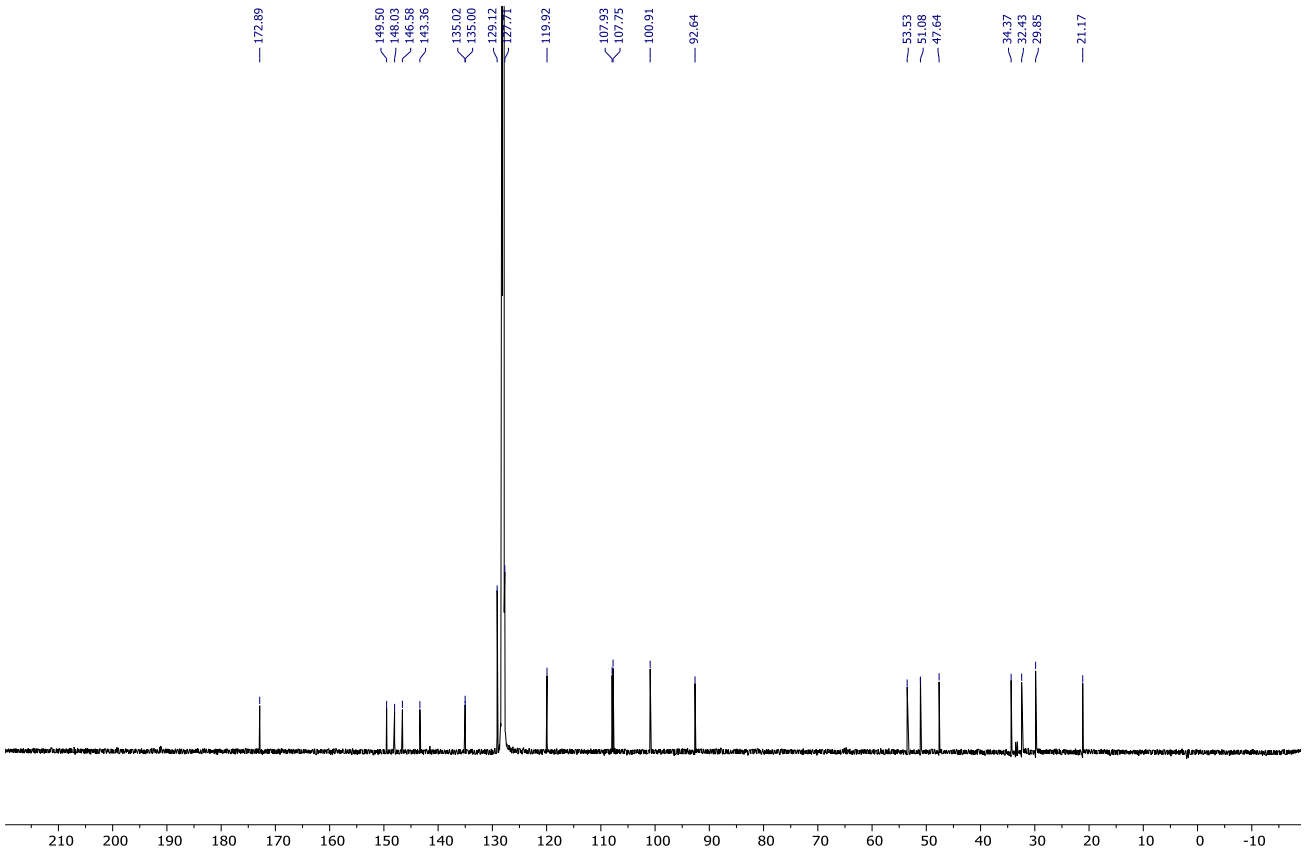


^{13}C NMR (75 MHz, C_6D_6) of **methyl (*Z*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)acrylate**



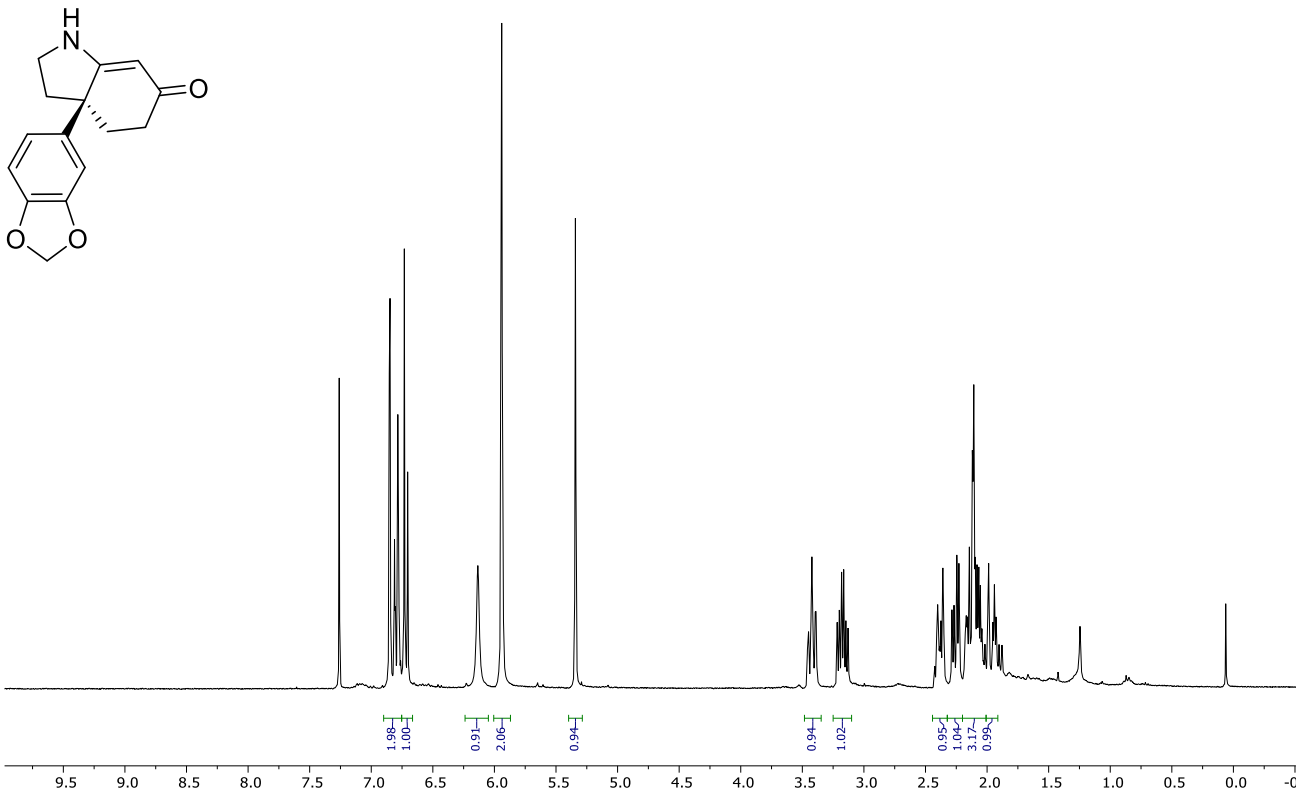
^{1}H NMR (300 MHz, C_6D_6) of

methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)propanoate

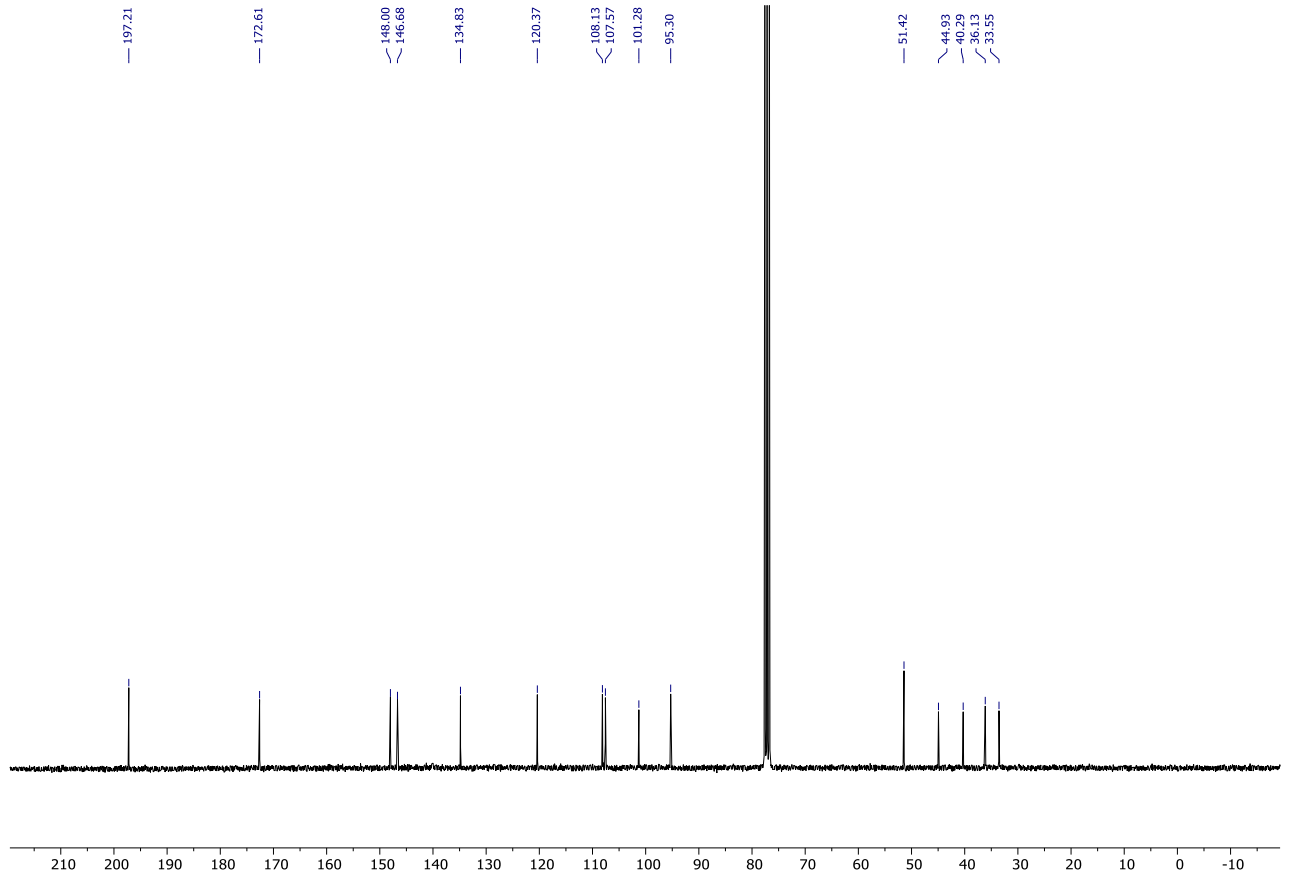


^{13}C NMR (75 MHz, C_6D_6) of

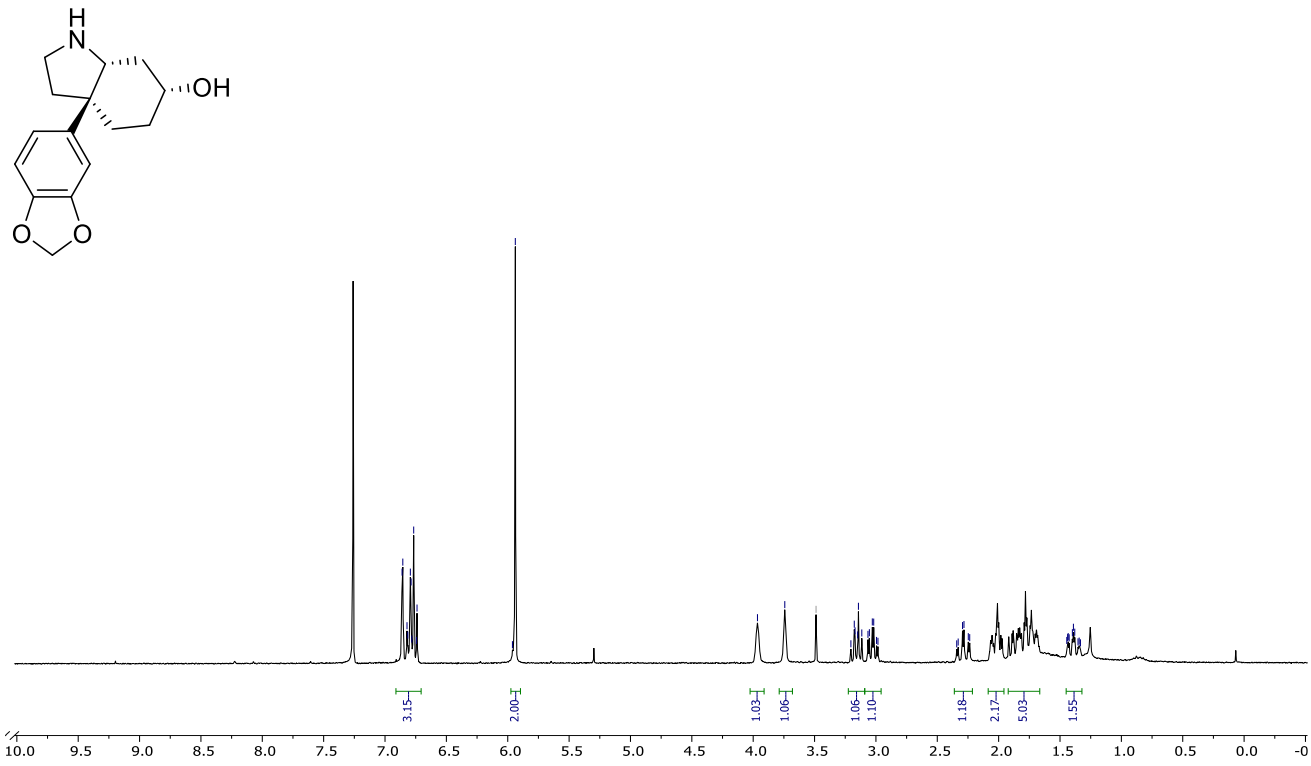
methyl (*R*)-3-(3-(benzo[d][1,3]dioxol-5-yl)-2-methylene-1-tosylpyrrolidin-3-yl)propanoate



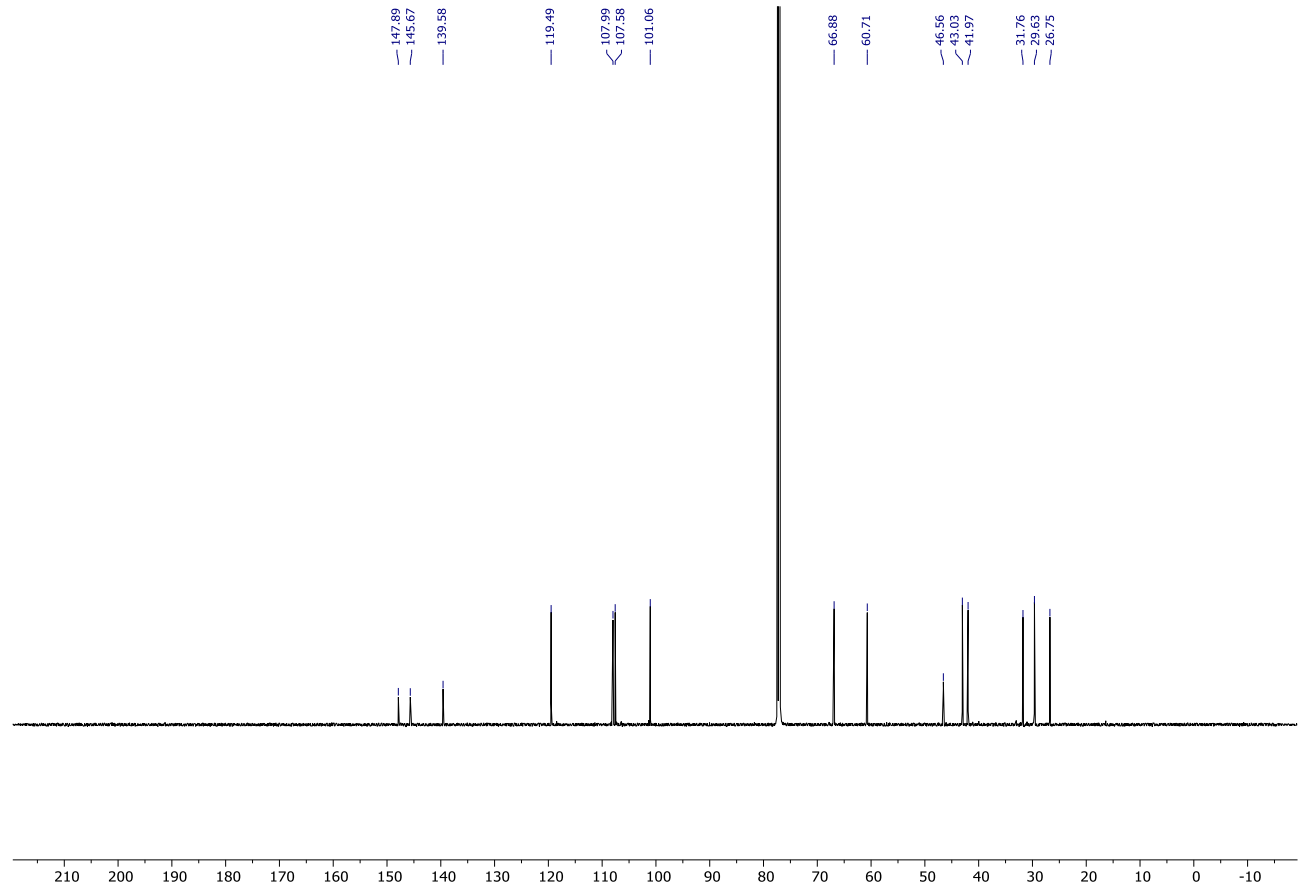
^{1}H NMR (300 MHz, $CHCl_3$) of compound **9a**



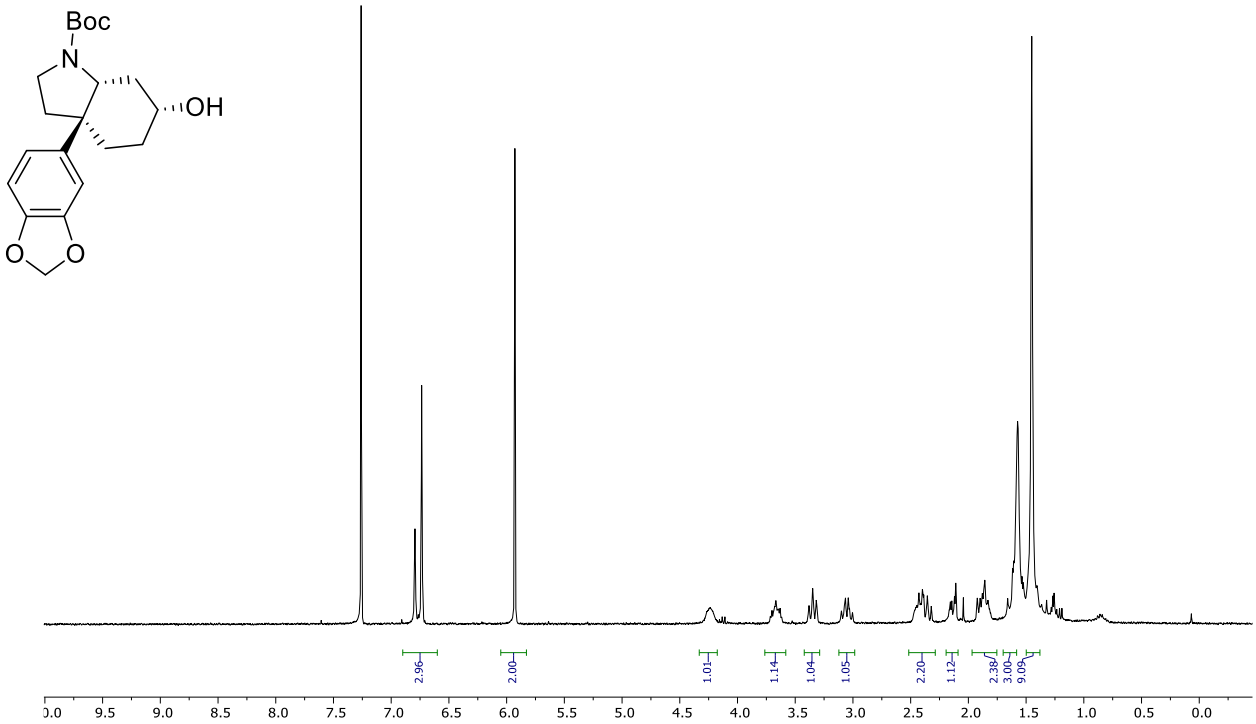
^{13}C NMR (75 MHz, $CHCl_3$) of compound **9a**



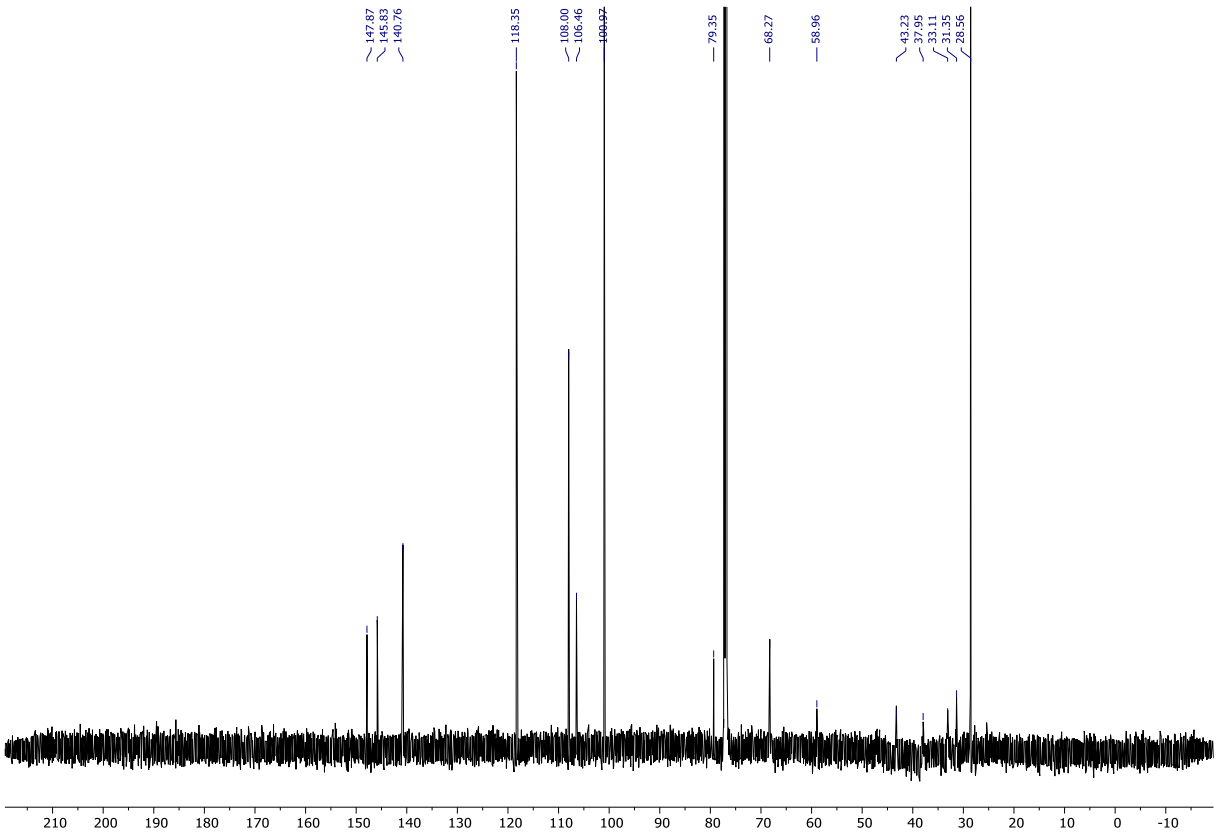
^{1}H NMR (300 MHz, $CHCl_3$) of compound **10**



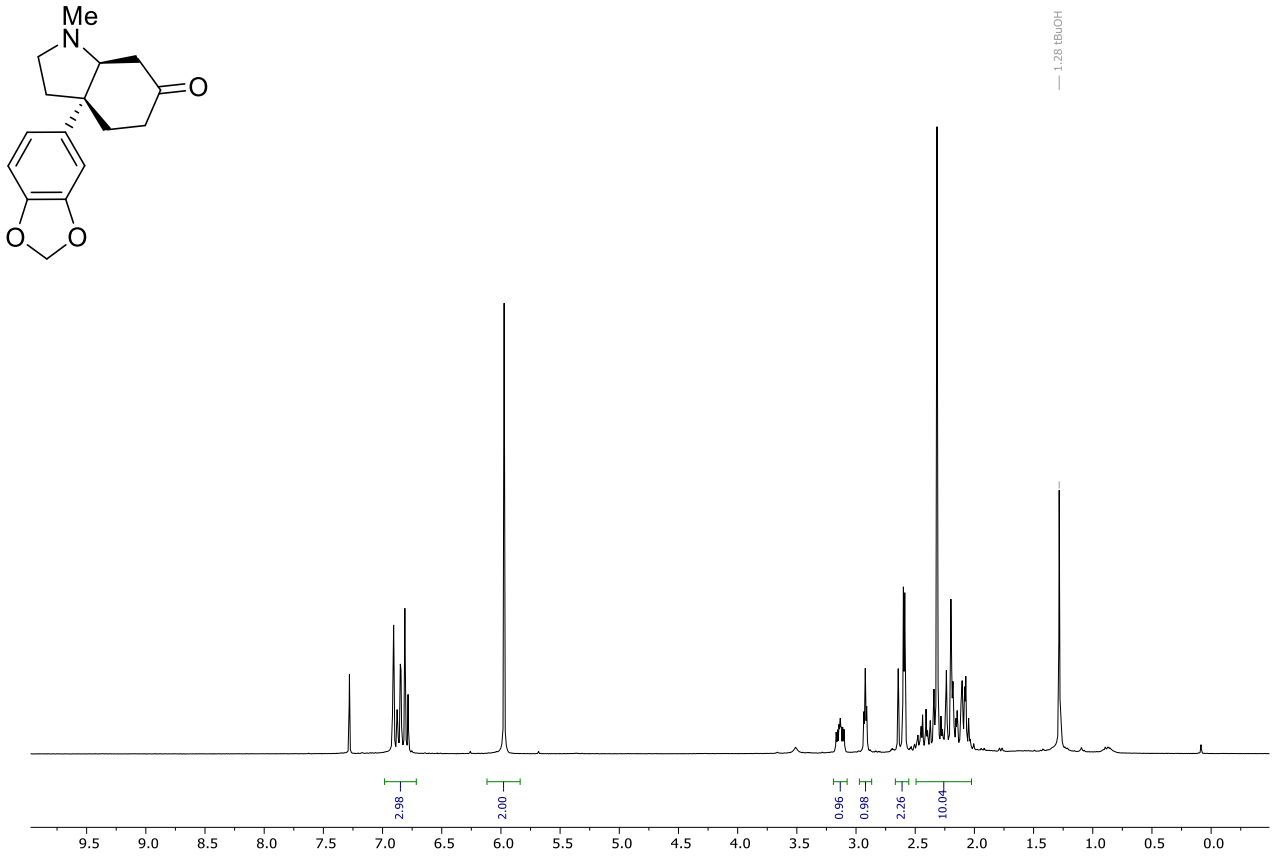
^{13}C NMR (75 MHz, $CHCl_3$) of compound **10**



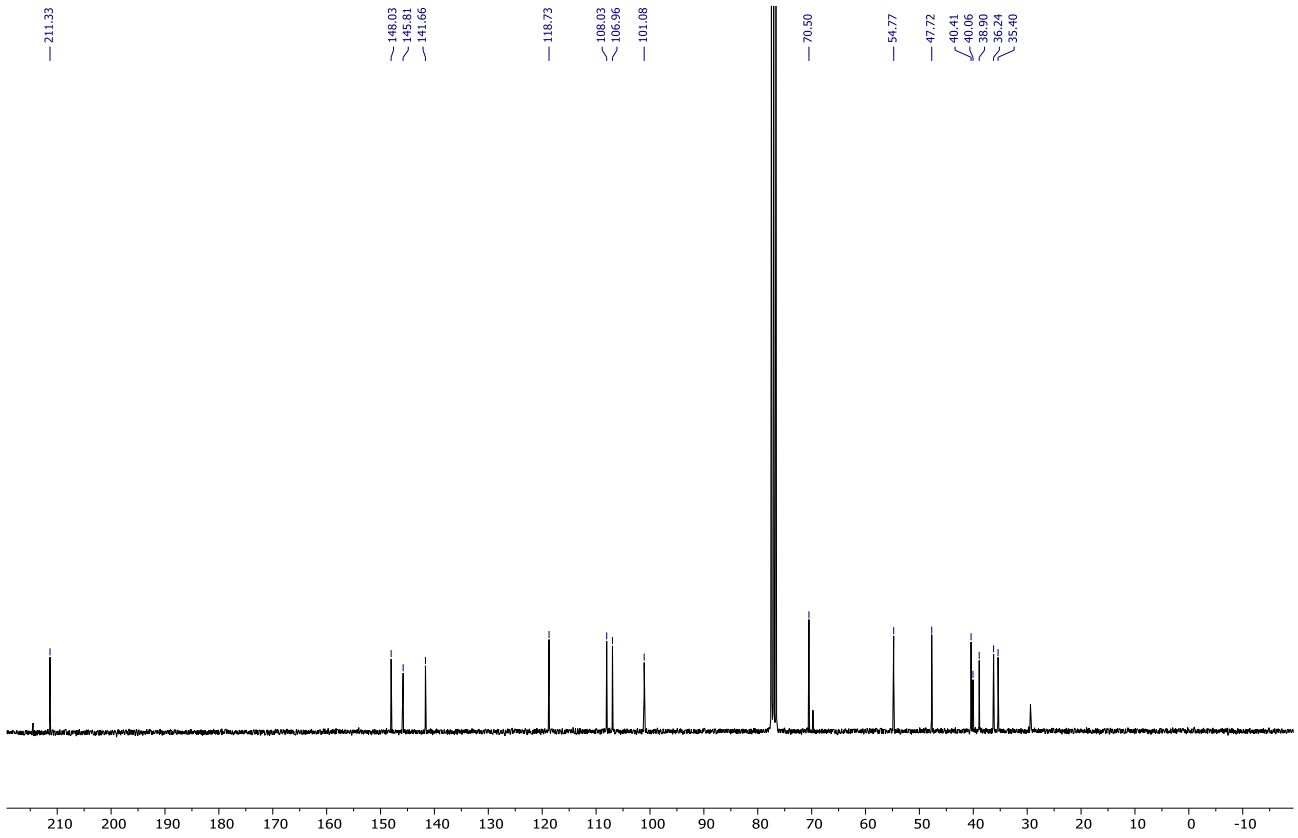
^{1}H NMR (300 MHz, $CHCl_3$) of compound **11**



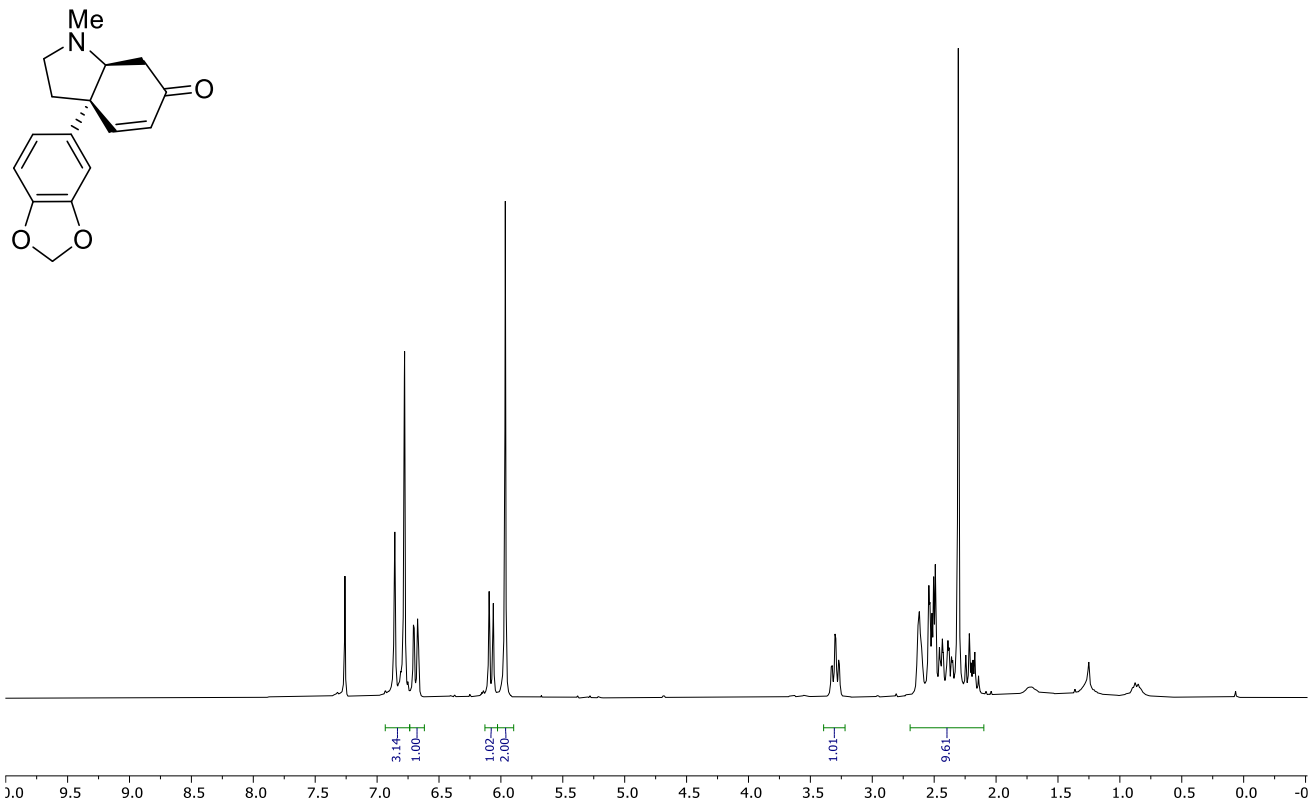
^{13}C NMR (75 MHz, $CHCl_3$) of compound **11**



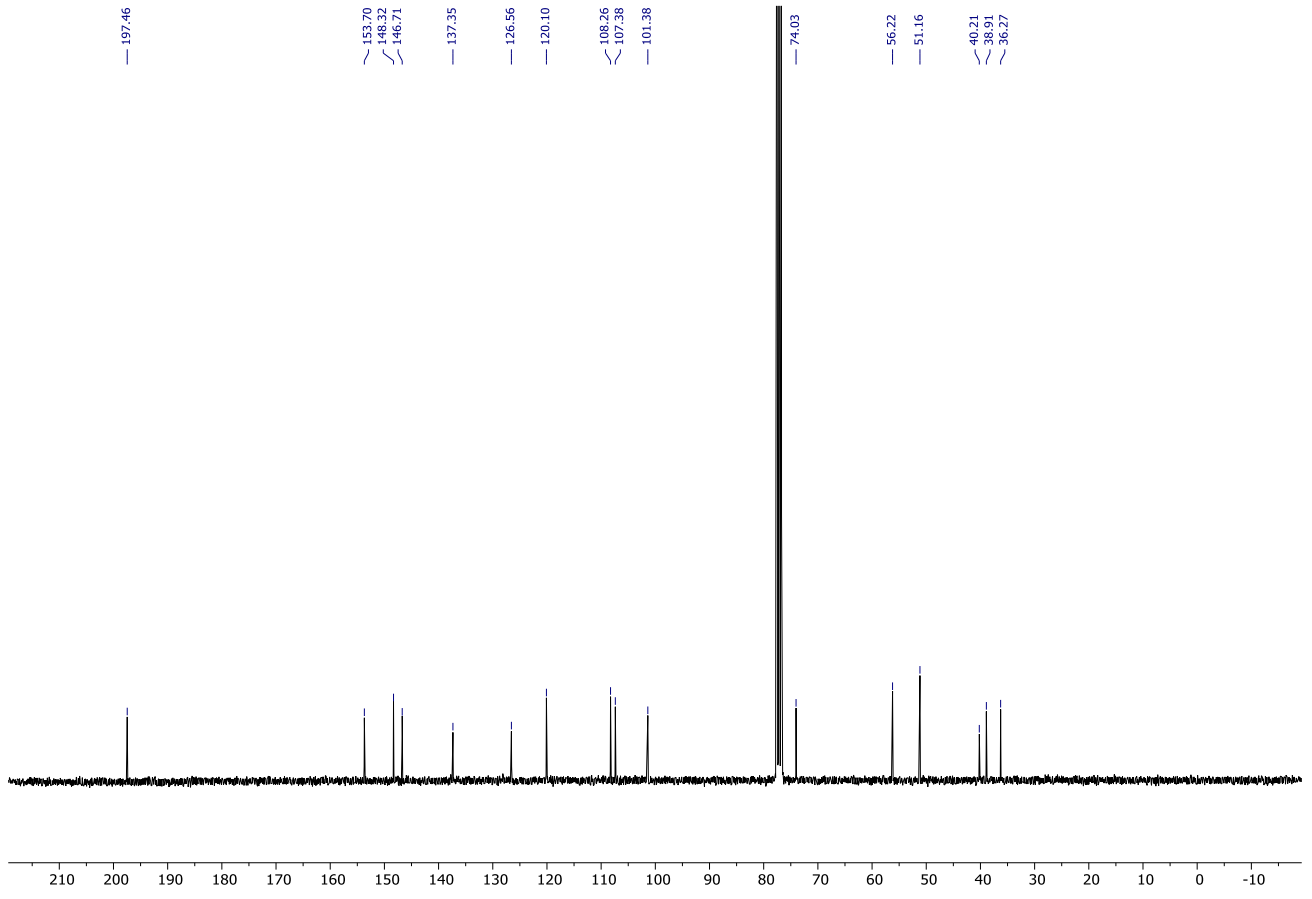
^{1}H NMR (300 MHz, $CHCl_3$) of compound **12**



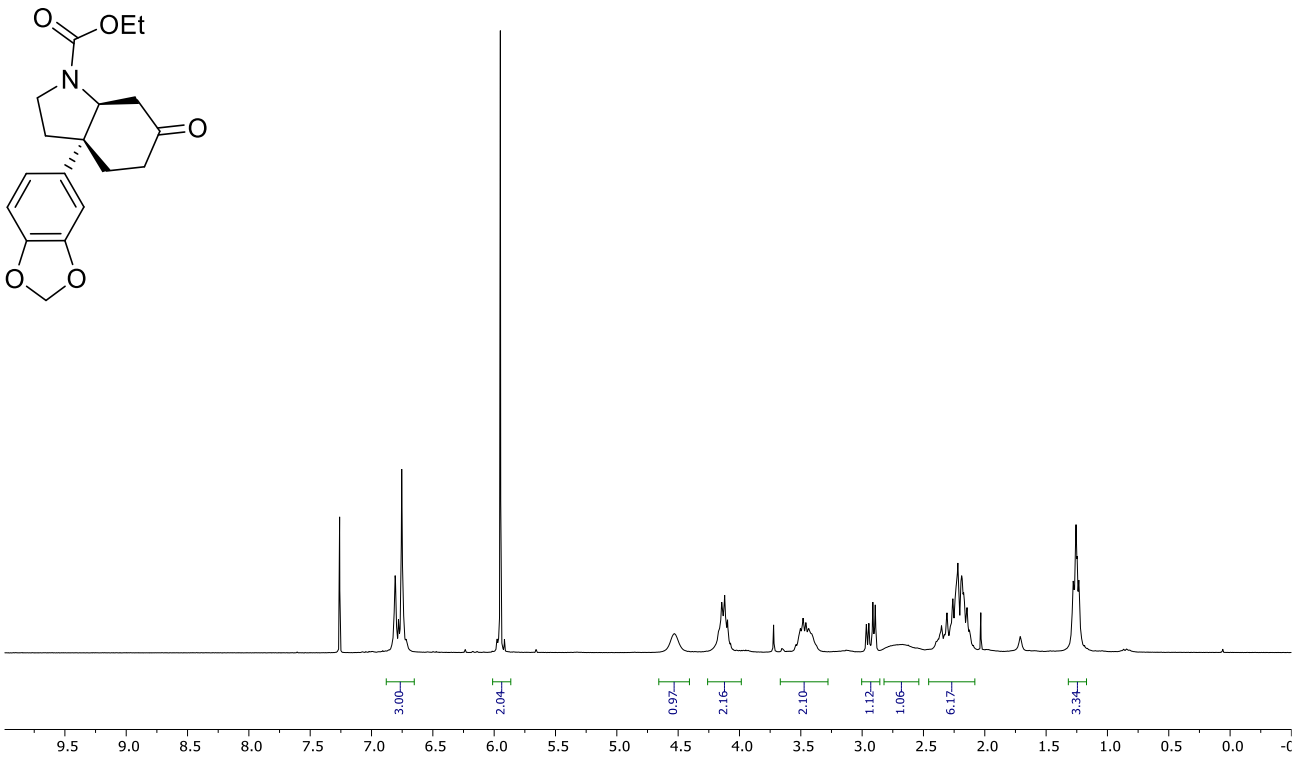
^{13}C NMR (75 MHz, $CHCl_3$) of compound **12**



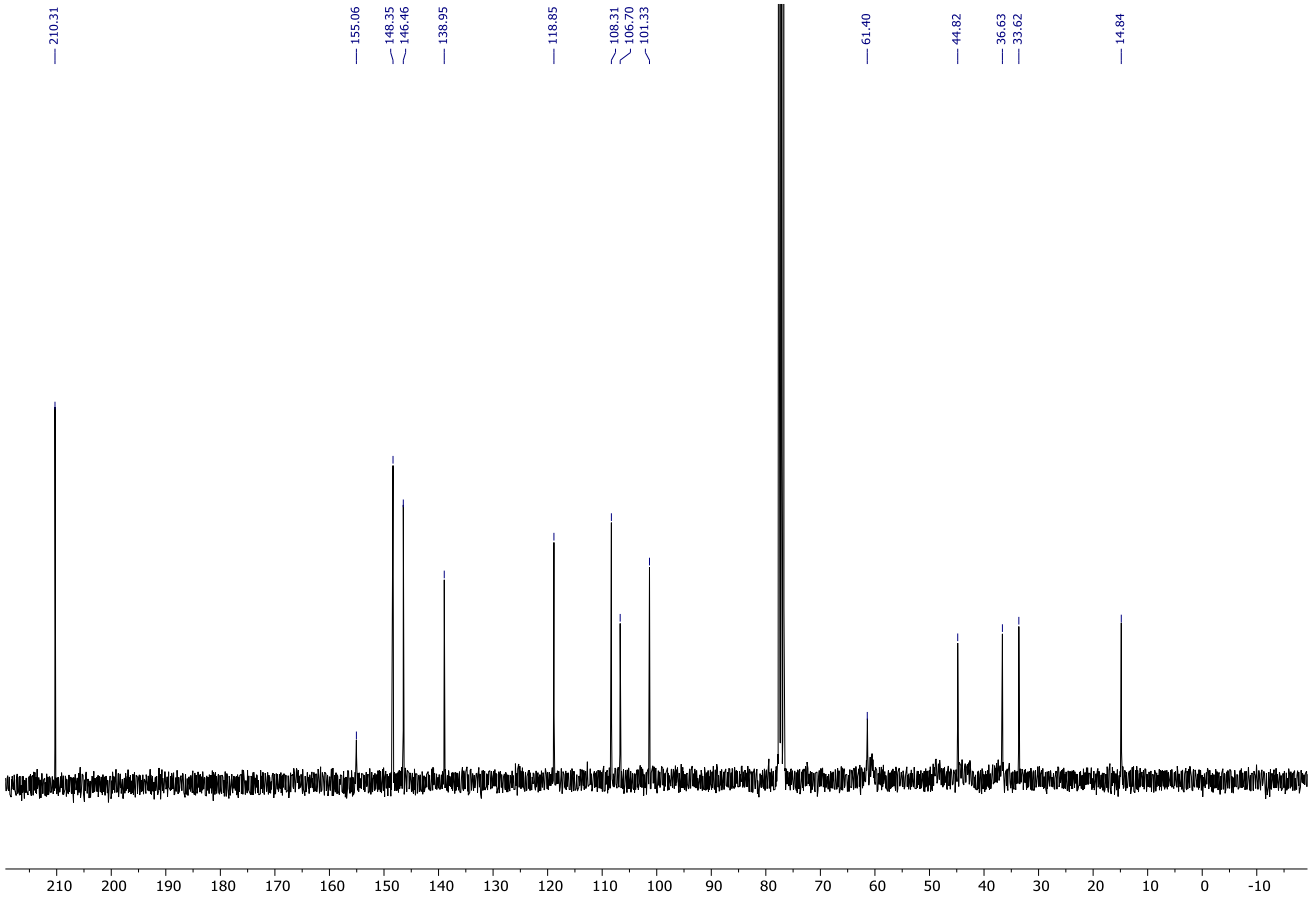
^{1}H NMR (300 MHz, $CHCl_3$) of compound **13**



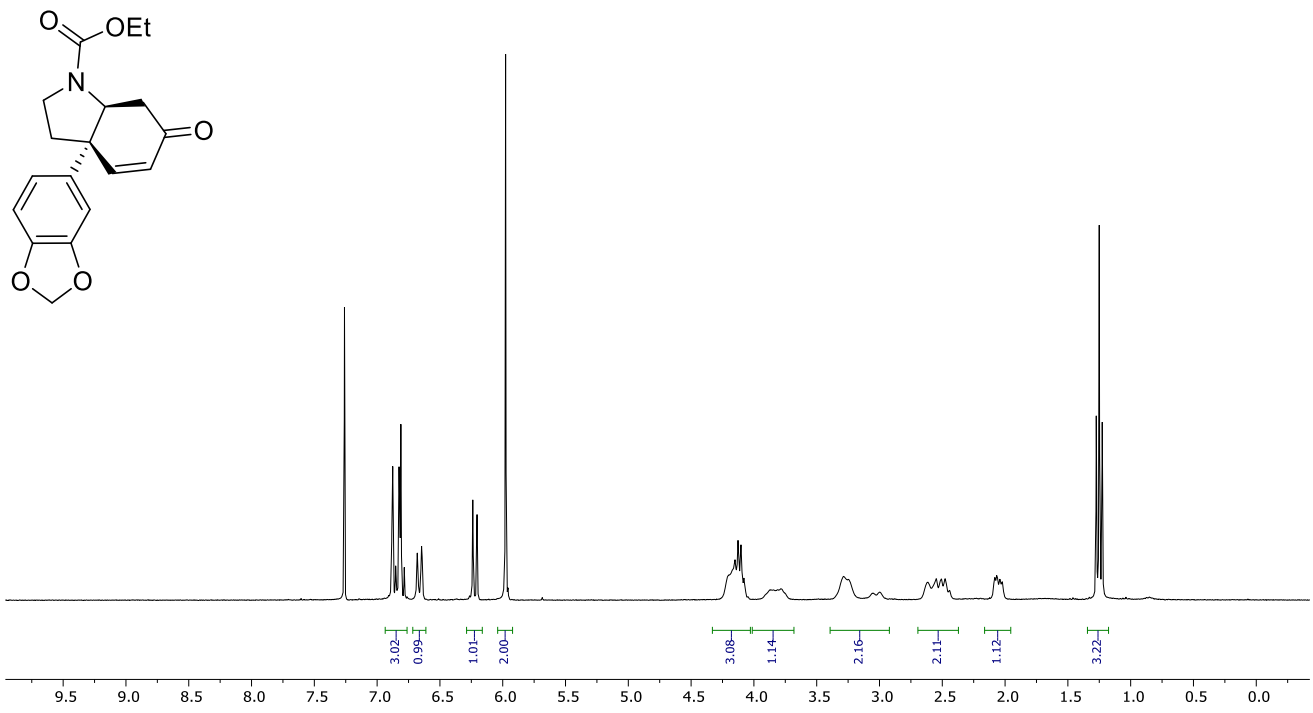
^{13}C NMR (75 MHz, $CHCl_3$) of compound **13**



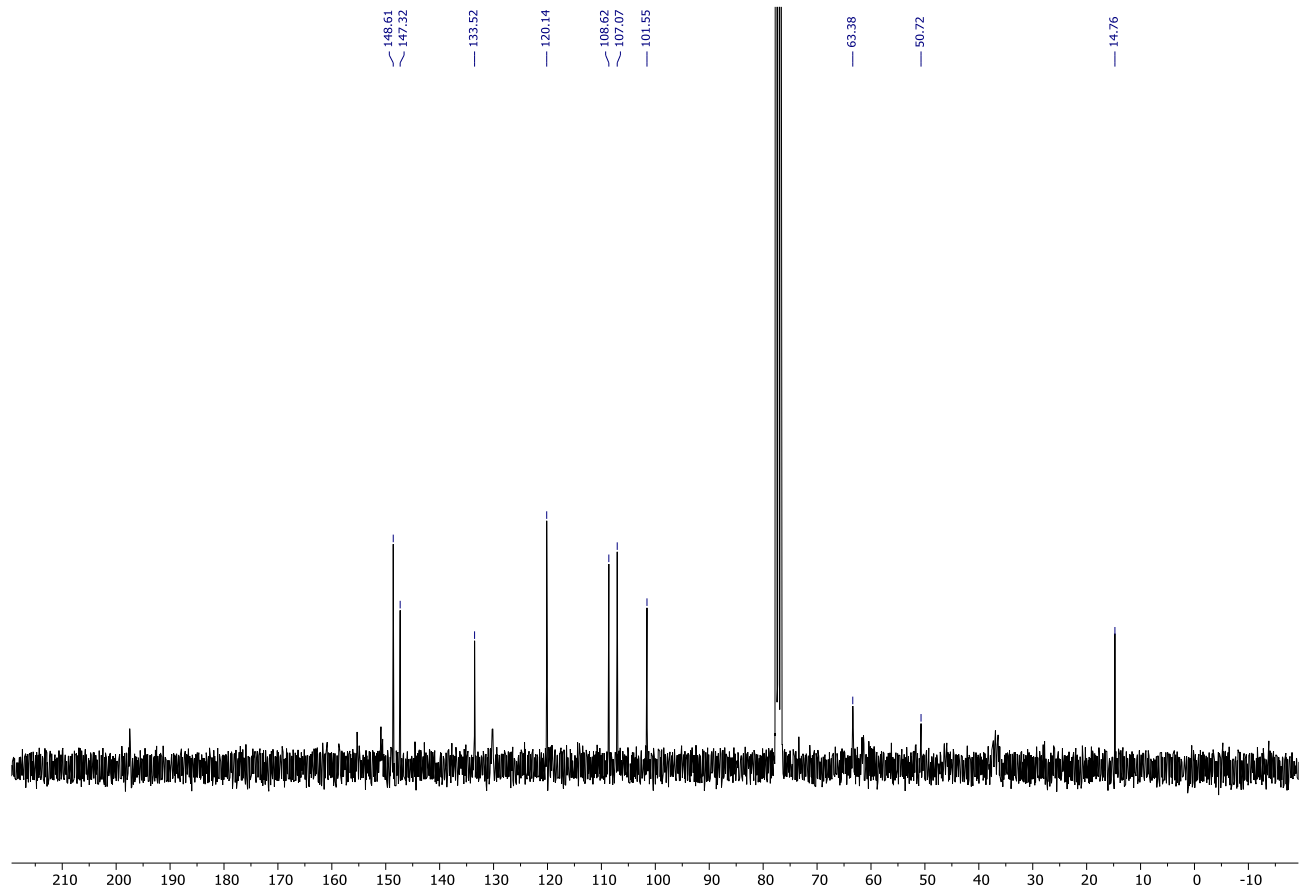
^{1}H NMR (300 MHz, $CHCl_3$) of compound **14**



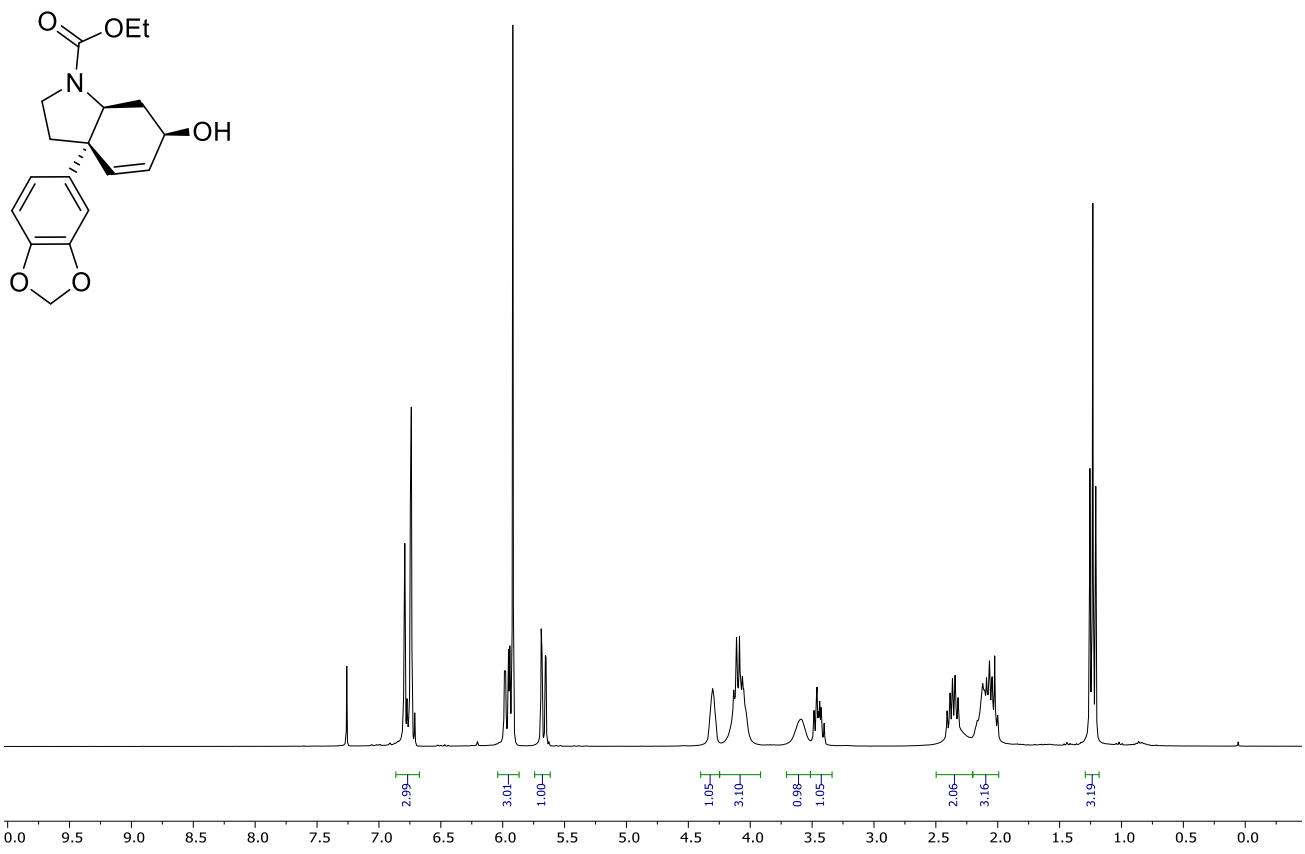
^{13}C NMR (75 MHz, $CHCl_3$) of compound **14**



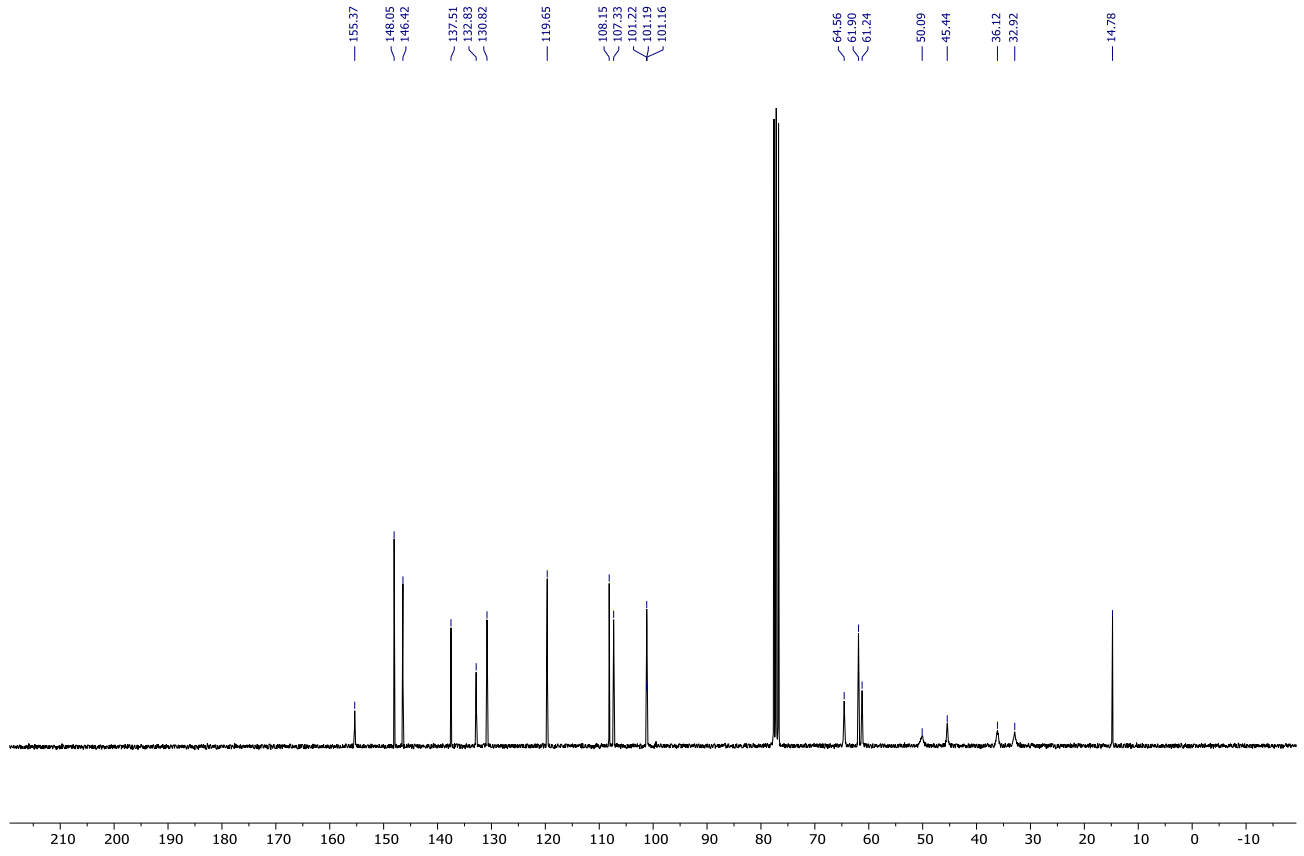
^{1}H NMR (300 MHz, $CHCl_3$) of compound **15**



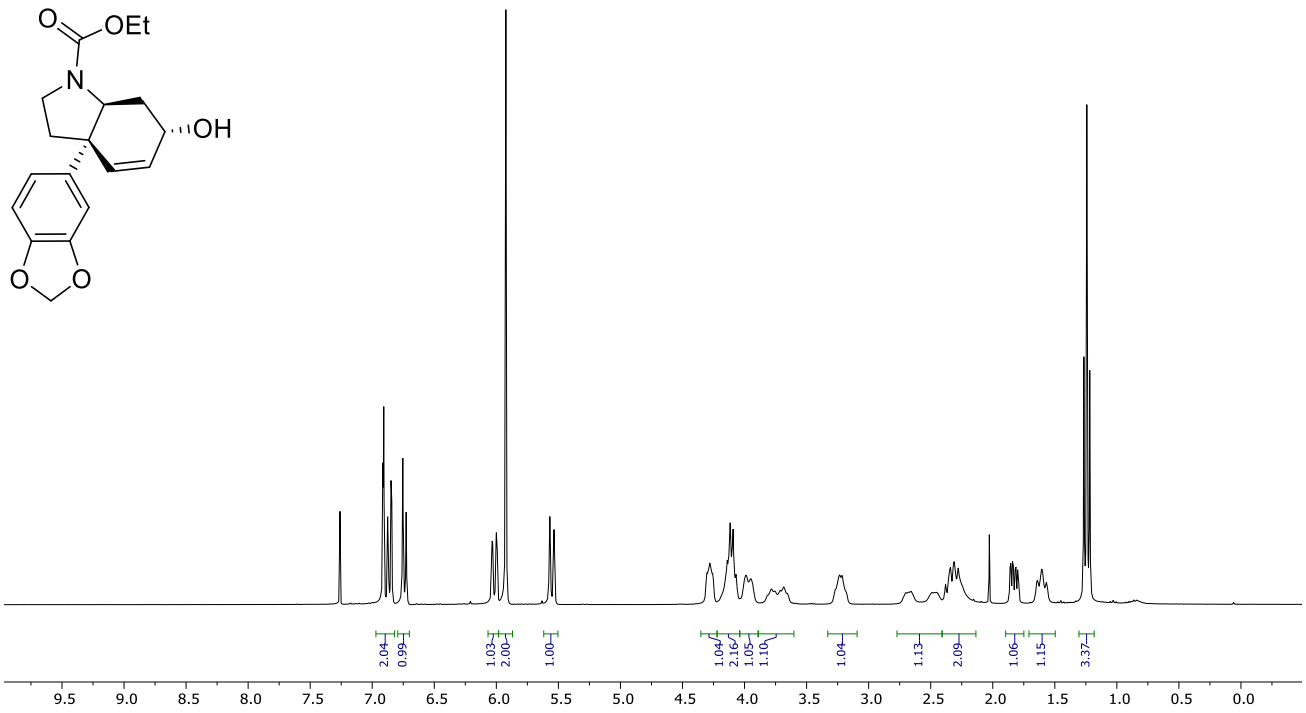
^{13}C NMR (75 MHz, $CHCl_3$) of compound **15**



^{1}H NMR (300 MHz, $CHCl_3$) of compound **16**

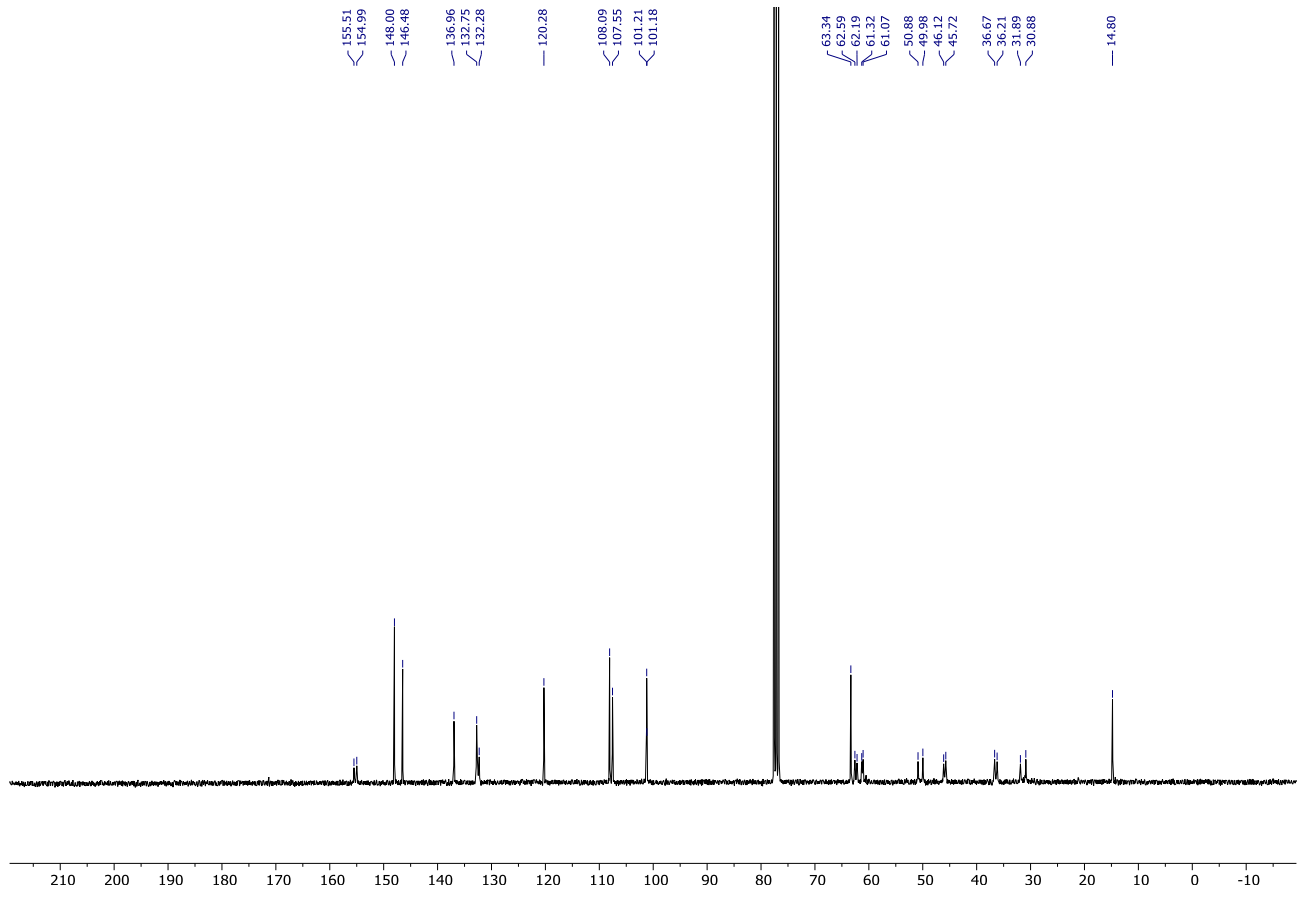


^{13}C NMR (75 MHz, $CHCl_3$) of compound **16**



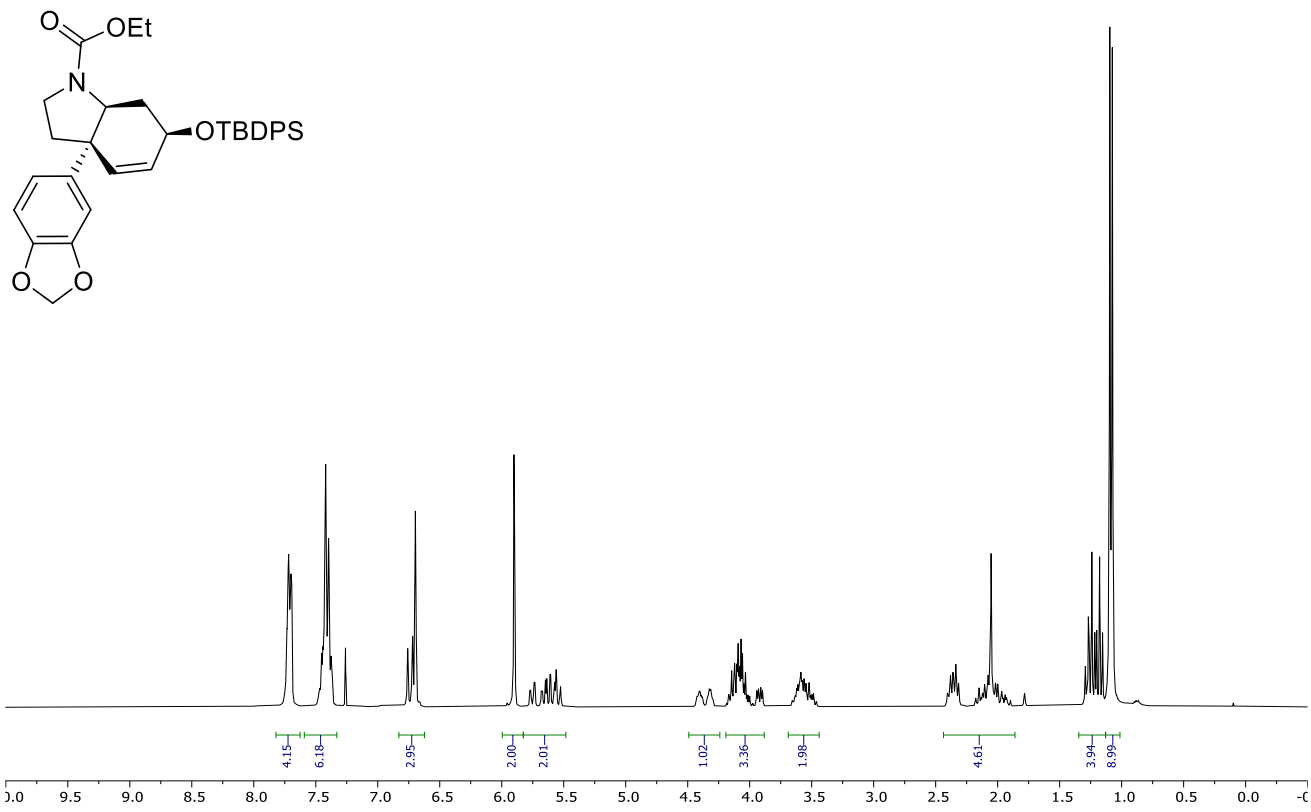
^{1}H NMR (300 MHz, $CHCl_3$) of

ethyl (3aR,6S,7aS)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate

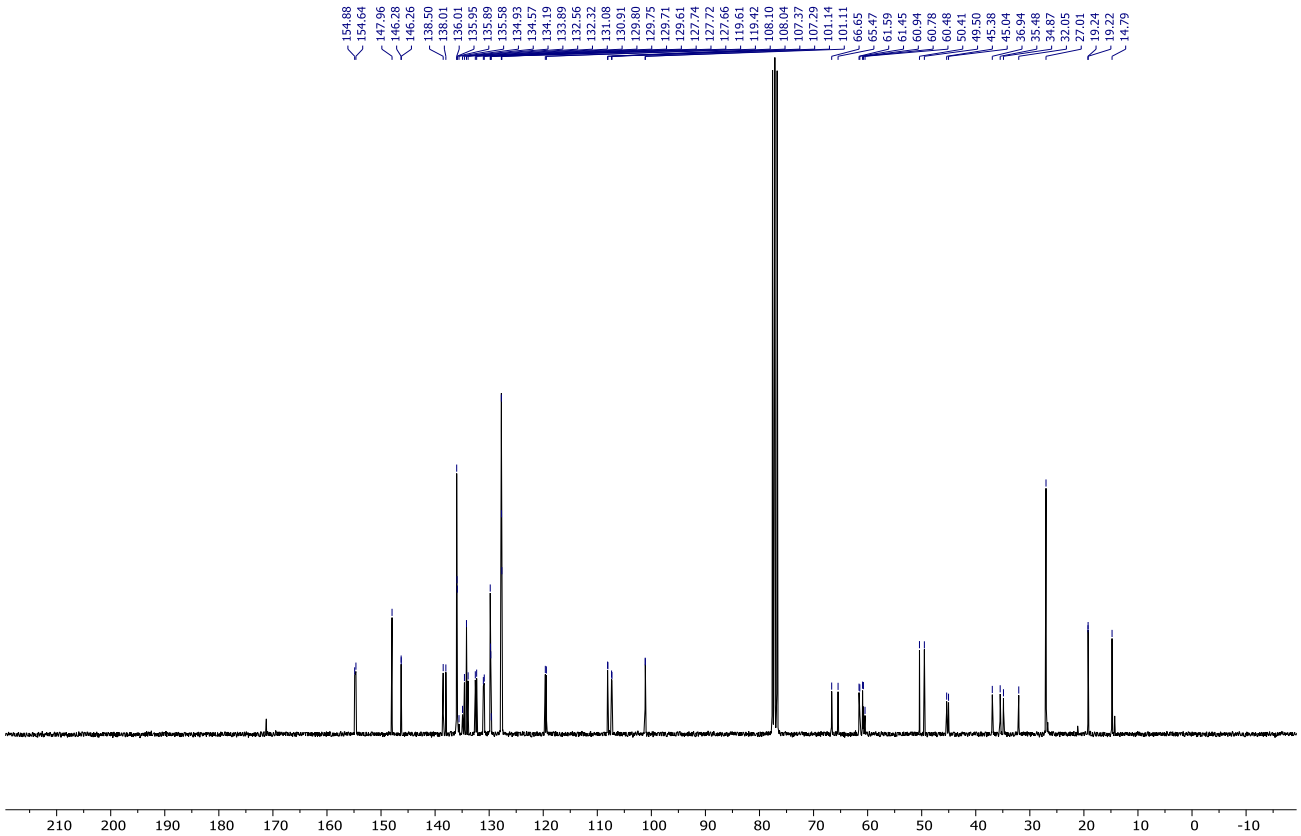


^{13}C NMR (75 MHz, $CHCl_3$) of

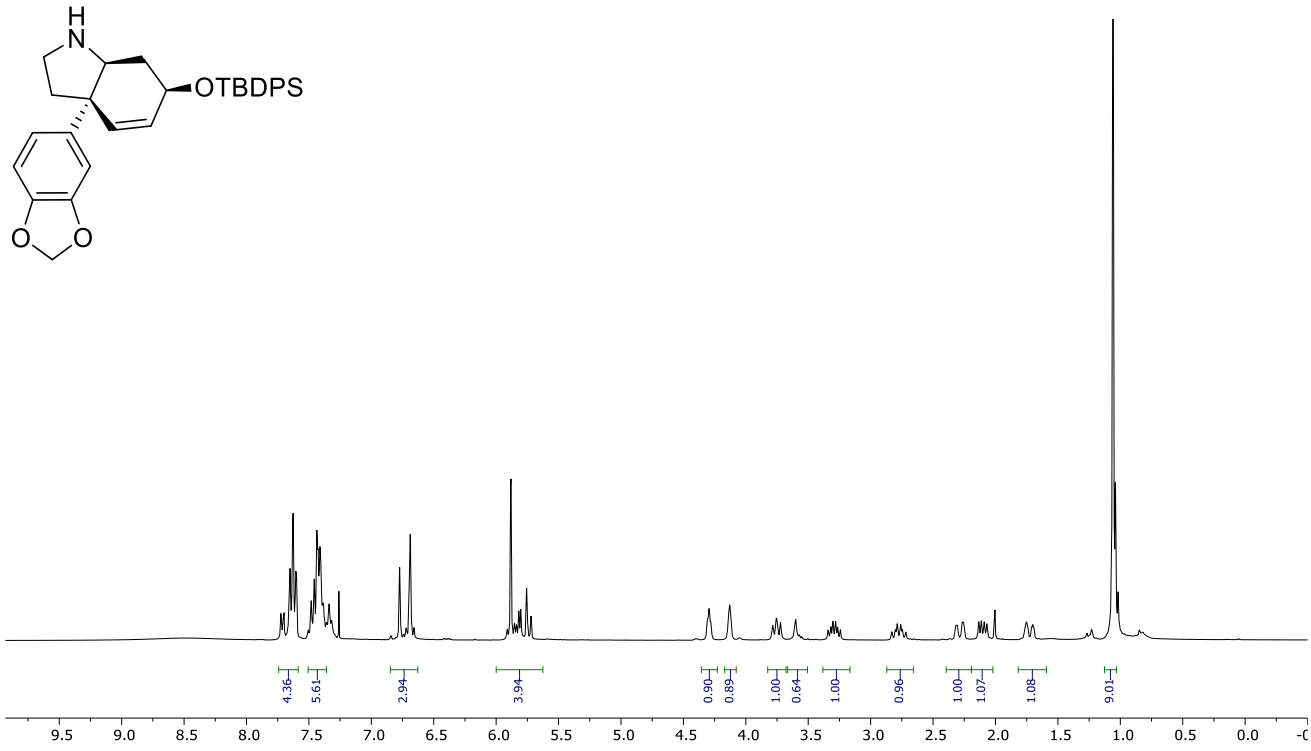
ethyl (3aR,6S,7aS)-3a-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate



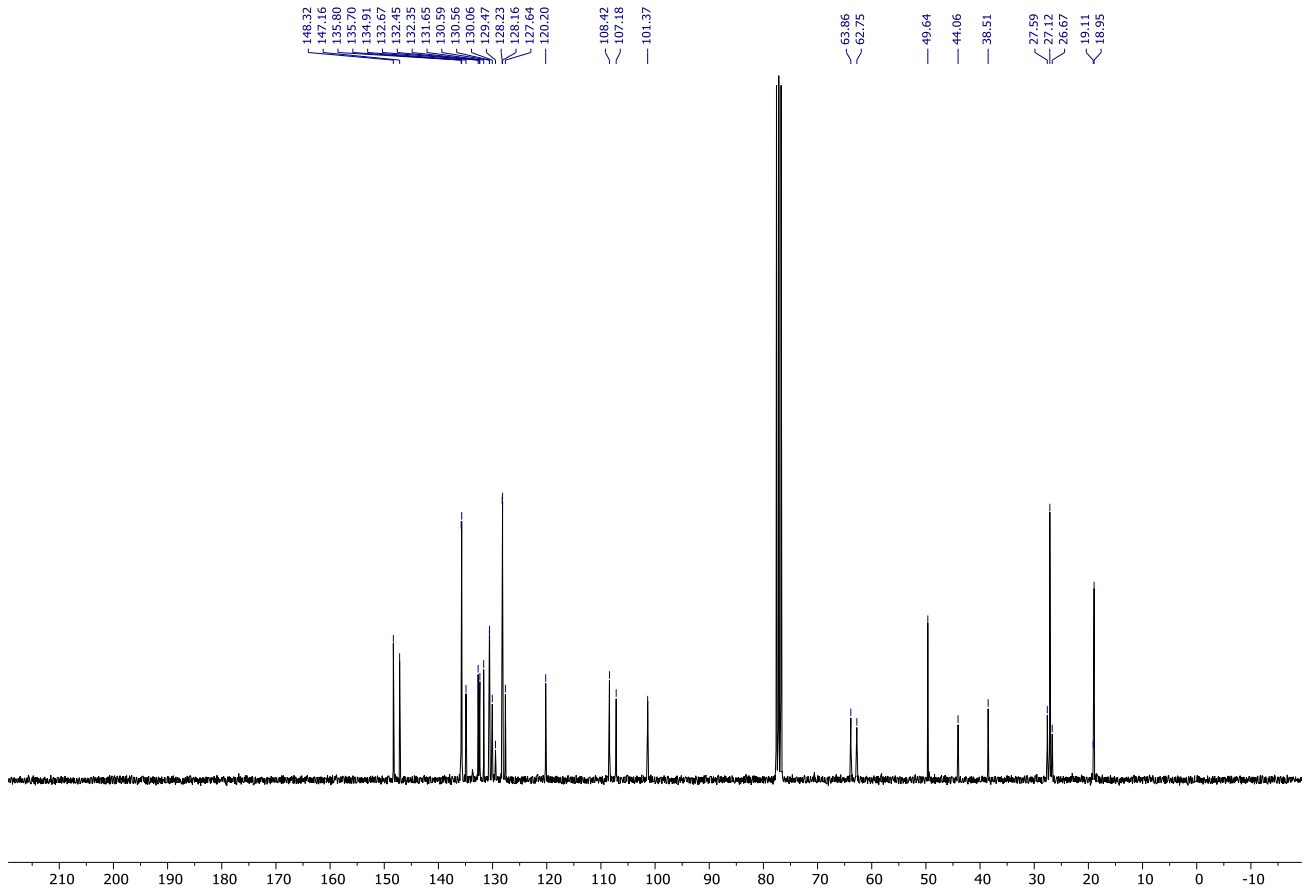
^{1}H NMR (300 MHz, $CHCl_3$) of compound **17**



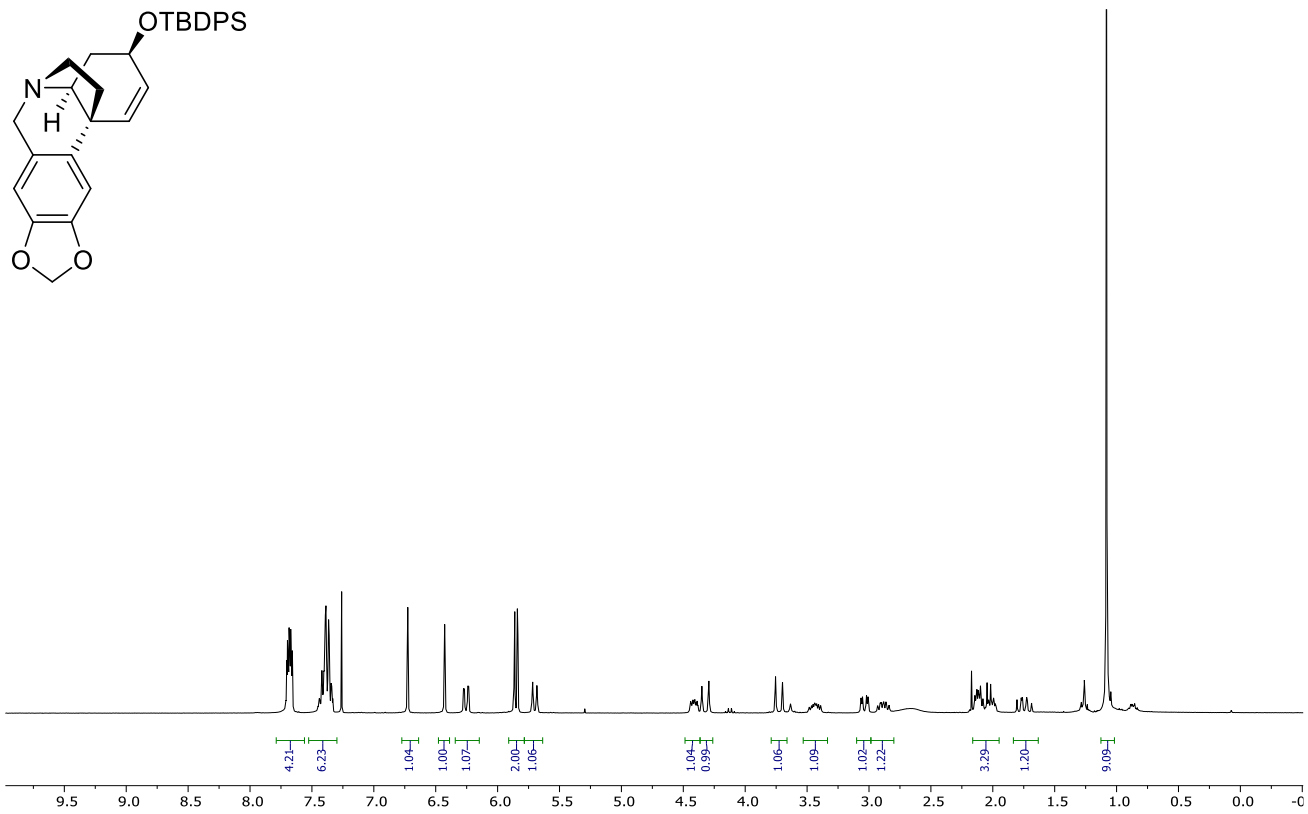
^{13}C NMR (75 MHz, $CHCl_3$) of compound **17**



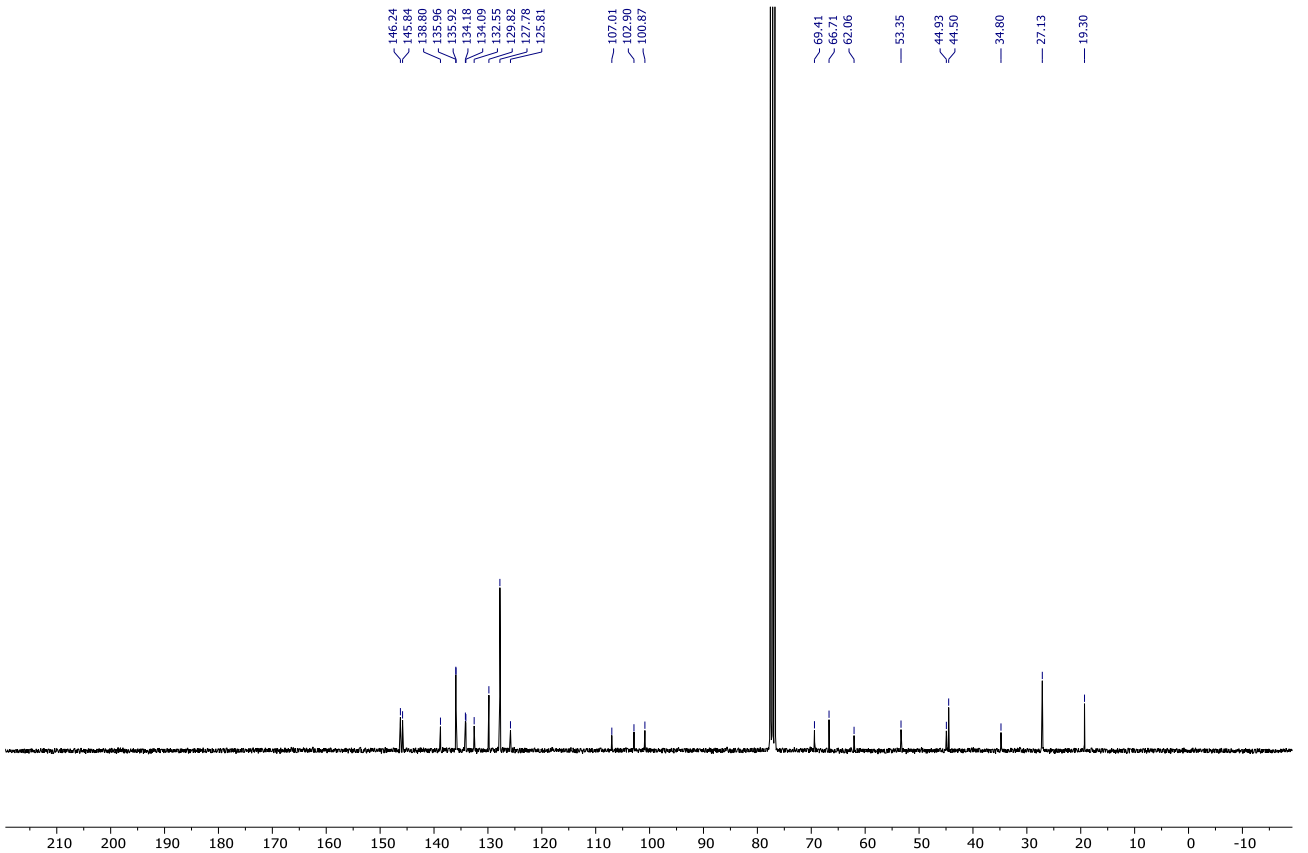
^{1}H NMR (300 MHz, $CHCl_3$) of compound **18**



^{13}C NMR (75 MHz, $CHCl_3$) of compound **18**



^{1}H NMR (300 MHz, $CHCl_3$) of compound **19**



^{13}C NMR (75 MHz, $CHCl_3$) of compound **19**

HPLC trace of racemic 3-(benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)pyrrolidine (compound 8b)

Area % Report

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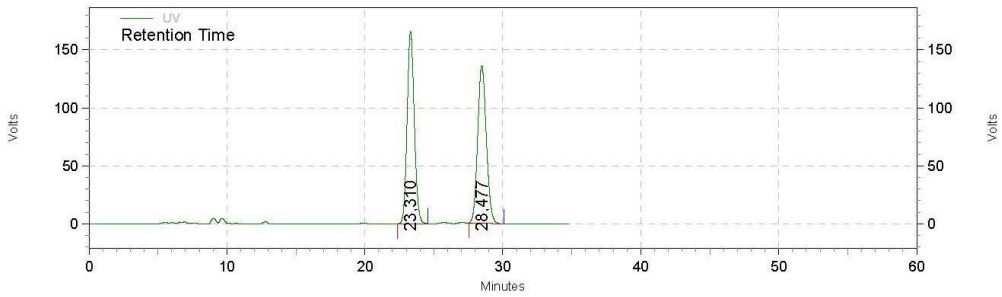

UV Results

Retention Time	Area	Area %	Height	Height %
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HPLC trace of (*R*)-3-(benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)pyrrolidine (compound 8b, before recrystallization)

ChiralPak IC, *n*-hexane/isopropanol = 60/40, Flow: 0.6 mL/min

Area % Report

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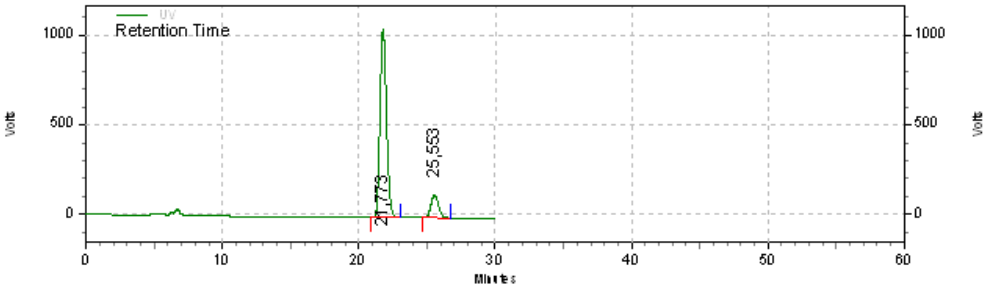

UV Results

Retention Time	Area	Area %	Height	Height %
21,773	139552824	87,63	4207531	89,12
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HPLC trace of (*R*)-3-(benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)pyrrolidine (compound 8b, after recrystallization)

ChiralPak IC, *n*-hexane/isopropanol = 60/40, Flow: 0.6 mL/min

Area % Report

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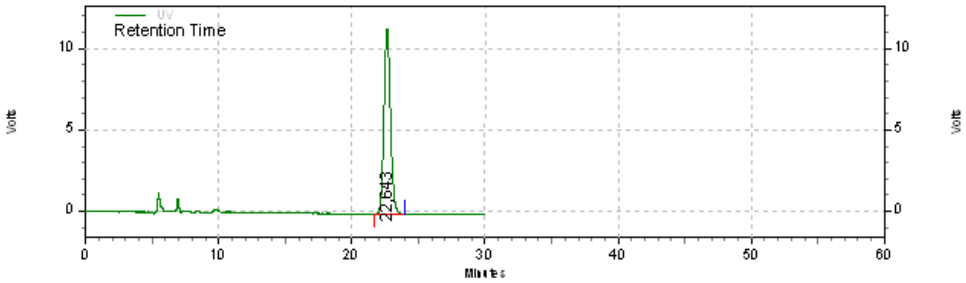

UV Results

Retention Time	Area	Area %	Height	Height %
22,643	1539703	100,00	45475	100,00

HPLC trace of (*S*)-3-(benzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)pyrrolidine (compound 8a, before recrystallization)

Area % Report

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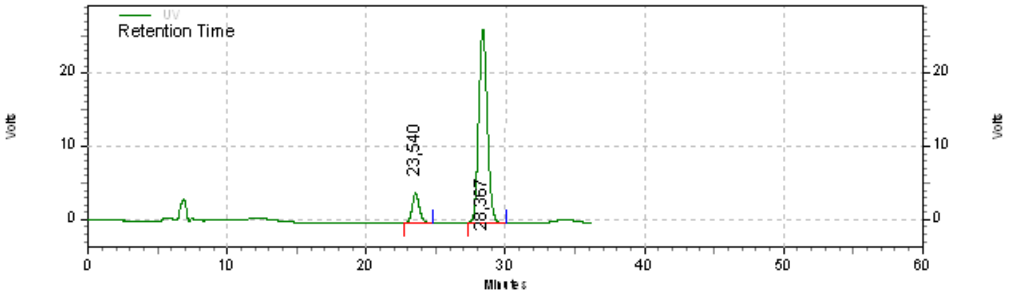

UV Results

Retention Time	Area	Area %	Height	Height %
23,540	581337	11,36	16204	13,31
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HPLC trace of (*S*)-3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-(4-toluenesulfonyl)pyrrolidine (compound 8a after recrystallization)

Area % Report

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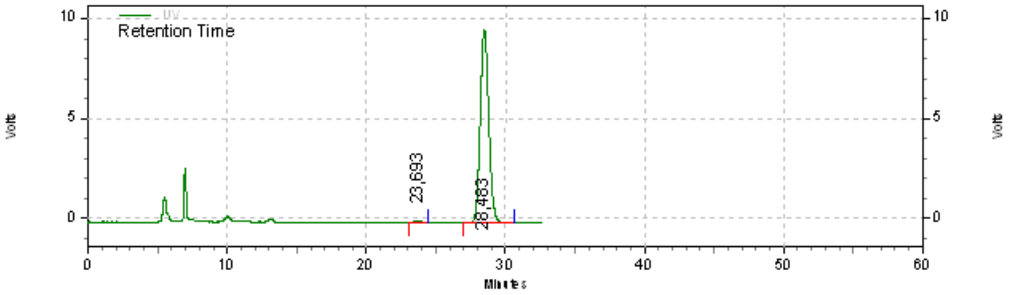


UV Results

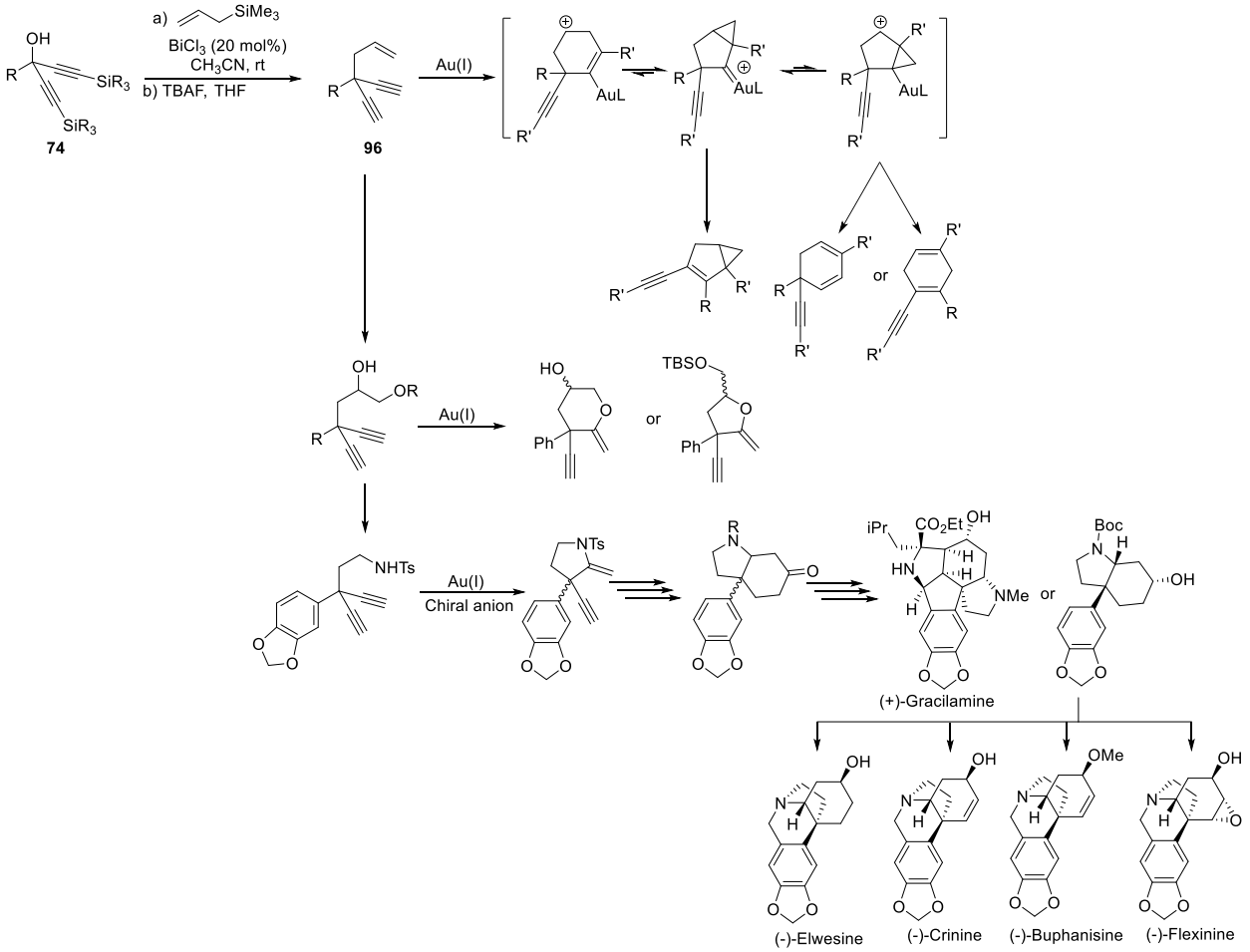
Retention Time	Area	Area %	Height	Height %
23,693	11547	0,70	319	0,82
28,483	1648940	99,30	38705	99,18

V. References

(1) Yu, J.-K.; Czekelius, C. *Eur. J. Org. Chem.* **2022**, *2022*, e202200027.
(2) Ankner, T.; Hilmersson, G. *Tetrahedron Lett.* **2007**, *48*, 5707.

Chapter 5. Conclusion

In this dissertation, our research has focused on investigating the reactivity of 1,4-diyne substrates, particularly through bismuth-catalyzed propargylic replacement and gold-catalyzed enyne isomerization. Furthermore, we have demonstrated the synthetic applications of homogeneous cationic gold catalysis, such as cyclopropanation, intramolecular hydroxylation, intramolecular hydroamination and its significant role in synthesizing enantiopure Amaryllidaceae alkaloids. The remarkable versatility of 1,4-diyne compounds enables a wide range of possible derivations, showcasing their potential for diverse applications.



Scheme 66. An overview of gold-catalyzed desymmetrization of 1,4-diyne species and its application on naturally occurring compound synthesis

Our research began with exploring 3-hydroxy-1,4-diyne **74** as a substrate, which exhibited propargylic allylation in the presence of Lewis acids such as bismuth chloride. Other than that, the feasibility of vinylamine for the propargylic substitution was inspected, which could only work when a sulfonamide protective group was attached. Additionally, we investigated the use of different heteroatom nucleophiles such as thiol. The result indicates heteroatom nucleophiles is capable of affording similar reactions with iron chloride as the Lewis acid catalyst instead of bismuth chloride (Chapter 1).

This Lewis acid directed propargylic substitution significantly simplifies the procedure for allylated-diyne substrate synthesis and facilitates the following research on the reactivity of 1,4-diyne featuring a propargylic quaternary center in the presence of gold(I) complexes. For example, The reactivity of the resulting 3-allylated-1,4-diyne **96** from propargylic substitution was further evaluated in the presence of a cationic gold(I) complex, which led to the formation of diverse unsaturated cyclic hydrocarbons, elucidating the intricacies of cationic rearrangement. To uncover the insights into the underlying mechanism, designed isotope-labeled-material was applied to the gold-catalyzed cyclization. The detailed information provided by that helps us understand better regarding the substrate-dependent reactivity. To summarize, the main reason for the diverse reactivity of this gold(I)-catalyzed enyne isomerization of allylated-1,4-diyne is the subtle changes in the cationic transition state when the substituent pattern change. According to the substituent pattern, the various reactivity was illustrated in this dissertation, which demonstrates a broad range of affordable compounds that could be achieved with this method (Chapter 3).

Apart from the allyl group, the alkene functional group can be transformed into other nucleophiles, exemplified by the dihydroxylation reaction. The gold-catalyzed cyclization of diol substrates was also investigated, demonstrating promising chemoselectivity. However, achieving complete chirality control proven challenging due to the presence of a pre-existing chiral center on the secondary alcohol. Preliminary results indicated that additives exploiting hydrogen bonding and Lewis acid coordination had limited influence on selectivity control. (Chapter 2)

Last but not least, the transformation converting diol functional group into a sulfonamide nucleophile was proceed on the basis of previous-developed multi-steps procedure. The resulting 3-alkylamine-1,4,-diyne is verified to afford the gold(I)-catalyzed intramolecular hydroamination

to occur in an enantioselective manner induced by a BINOL derivative chiral anion. Through enantioselective cyclization, enantiopure 3-ethynyl-2-methylenepyrrolidine was obtained, which was facile transfer into a C3a-arylated hydroindole backbone for further functionalization to achieve various naturally occurring alkaloids according to previously established procedures from (+)-mesembrine synthesis. Serving as a versatile template existing in various Amaryllidaceae alkaloids, the functionalization of C3a-arylated hydroindole was described in this dissertation which provides access to a wide spectrum of Amaryllidaceae alkaloids synthesis in both enantiomeric series including elwesine, crinine, buphanisine, flexnine, gracilamine, and more. (Chapter 4)

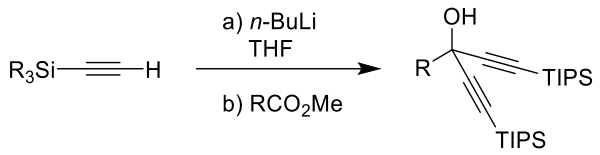
Chapter 6. Experimental section

6-1 General information

All solvents and reagents used were purchased from commercial suppliers as reagent grade. They were used without further purification unless otherwise noted. Starting materials and catalysts, which were not commercially available, were synthesized by previously reported methods. The methods for preparing anhydrous solvents and reagents were referred to Purification of Laboratory Chemicals, Sixth Edition (ISBN: 978-1-85617-567-8). Dichloromethane, tetrahydrofuran, and toluene were dried using the Solvent Purification System MP SPS-800 by M.Braun. For reactions requiring an inert atmosphere, the glassware was dried in a compartment dryer at 120 ℃, and then standard Schlenk techniques were used to work under a dry nitrogen atmosphere. Rotary evaporators combined with vacuum pumps were used for the removal of volatiles under reduced pressure. Analytical thin-layer chromatography (TLC) was performed on precoated alumina-backed silica gel plates (Macherey-Nagel, 0.2 mm thickness silica gel 60 with fluorescence indicator UV_{254}), which were developed using UV fluorescence and $KMnO_4$ stain solution. Flash chromatography was performed on silica gel (Macherey-Nagel, silica 60 M, 0.04-0.063 mm). IR spectra were measured as thin films on a NaCl single crystal with a JASCO FT-IR 6200 spectrometer, and only selected peaks were shown. ^{1}H-NMR spectra were recorded on a Bruker Advance III 300 MHz spectrometer, ^{13}C-NMR spectra were recorded at 75 MHz, and ^{31}P-NMR spectra were recorded at 121 MHz. The coupling constants *J* are given in Hertz (Hz) and chemical shifts (δ) in ppm. Chemical shifts were reported in δ ppm referenced to trace amounts of chloroform δ($CHCl_3$) = 7.26 ppm in ^{1}H-spectra and to the signal of deuterated chloroform δ($CDCl_3$) = 77.16 ppm in ^{13}C-spectra. In some cases, while *d*-benzene was used for measuring the chemical shift were referenced to trace amounts of benzene δ(C_6D_5H) = 7.15 ppm in ^{1}H-spectra and to the signal of deuterated benzene δ(C_6D_5H) = 128 ppm in ^{13}C-spectra. The enantiomeric excess of the products was determined using a Hitachi LaChrome High-Performance Liquid Chromatography (HPLC) system equipped with DAICEL CHIRALPAK® IC™ (4.6 x 250 mm) column using *n*-hexane as eluent. The samples were filtered through syringe filters (25 mm, 0.45 μm PTFE membrane or 13 mm, 0.2 μm PTFE membrane) prior to analysis.

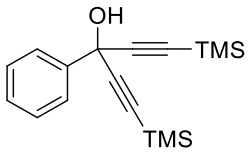
6-2 Experimental procedures

General procedure for the synthesis of substituted penta-1,4-diyn-3-ols (GP1)



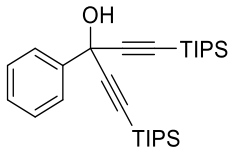
In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, trialkyl-silylacetylene (2.20 equiv.) was dissolved in anhydrous THF (0.2 M). To this solution, *n*-BuLi (2.5 M, 2.20 equiv.) was added at 0 °C. The mixture was stirred at this temperature for 30 min and then treated with the methyl carboxylate (1.00 equiv.) under N_2 atmosphere. The reaction mixture was stirred for 6 hr and allowed to warm to room temperature. Aqueous workup was committed when complete conversion was observed by TLC. The product was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent, the crude product was purified *via* flash column chromatography on silica gel (eluent EtOAc/*n*-hexan) to produce the substituted penta-1,4-diyn-3-ols.

3-Phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (74b)



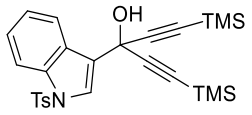
Under N_2 atmosphere, trimethylsilylacetylene (9.33 mL, 66.0 mmol), *n*-BuLi (2.5 M, 26.4 mL, 66.0 mmol) and methyl benzoate (4.17 mL, 30.0 mmol) were added to the reaction flask and the reaction was proceeded according to **GP 1**. The purification was done by flash column chromatography (EtOAc:*n*-hexane = 1:20, R_F = 0.36) to produce **3-phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (74b)** as a yellowish oil (8.93 g, 29.7 mmol, 99%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.86-7.75 (m, 2H), 7.45-7.30 (m, 3H), 2.81 (s, 1H), 0.22 (s, 18H).

3-Phenyl-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (74a)



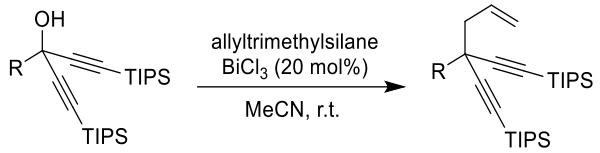
Under N_2 atmosphere, triisopropylsilylacetylene (4.93 mL, 22.0 mmol), *n*-BuLi (2.5 M, 8.80 mL, 22.0 mmol), and methyl benzoate (1.39 mL, 10.0 mmol) were added to the reaction flask and the reaction was proceeded according to **GP 1**. The purification was done by flash column chromatography (EtOAc: *n*-hexane = 1: 20, R_F = 0.46) to produce **3-Phenyl-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (74a)** as a yellowish oil (4.64 g, 9.90 mmol, 99%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.90-7.81 (m, 2H), 7.43-7.29 (m, 3H), 2.82 (s, 1H), 1.09 (s, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.9, 128.7, 128.4, 126.2, 107.2, 86.7, 65.8, 18.7, 11.3; **IR** (NaCl) ṽ (cm^{-1}): 3582, 3450, 2947, 2866, 1460, 1377, 1320, 1173, 1023, 948, 883, 770, 675; **HRMS** (ESI): calc'd. for $C_{29}H_{47}Si_2$ **[M-OH]$^+$** 451.3212 found 451.3211.

3-(1-*para*-Toluenesulfonyl-1*H*-indol-3-yl)-1,5-bis(trmethylsilyl)penta-1,4-diyn-3-ol (74f)



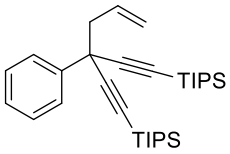
Under N_2 atmosphere, trimethylsilylacetlyene (390 µL, 2.70 mmol), *n*-BuLi (2.5M, 1.10 mL, 2.70 mmol), and methyl 1-*para*-toluenesulfonyl-1*H*-indole-3-carboxylate (408 mg, 1.20 mmol) were added to the reaction flask and the reaction was proceeded according to **GP 1**. The purification was done by flash column chromatography (EtOAc:*n*-hexane = 1: 10, R_F = 0.37) to produce **3-(1-*para*-toluenesulfonyl-1*H*-indol-3-yl)-1,5-bis(trmethylsilyl)penta-1,4-diyn-3-ol (74f)** as a colorless oil (562 mg, 1.14 mmol, 95%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.99-7.88 (m, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.78 (s, 1H), 7.32 (ddd, J = 8.4, 7.3, 1.4 Hz, 1H), 7.35-7.15 (m, 3H), 2.83 (s, 1H), 2.36 (s, 3H), 0.21 (s, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 145.2, 135.8, 135.3, 130.0, 127.2, 127.0, 124.9, 124.4, 123.2, 123.1, 121.6, 113.5, 89.7, 60.5, 21.6, -0.38; **IR** (NaCl) ṽ (cm^{-1}): 3501, 2961, 2910, 1446, 1373, 1256, 1178, 1119, 1024, 986, 910, 849, 753, 691, 668; **HRMS** (ESI)**:** calc'd. for $C_{26}H_{30}NO_2SSi_2$ **[M-OH]$^+$** 476.1530 found 476.1531.

General procedure for propargylic allylation (GP 2)



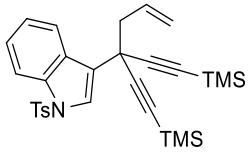
In a dried and nitrogen-flushed Schlenk flask equipped with a magnetic stir bar, the penta-1,4-diyn-3-ol (1.00 equiv.) was dissolved in anhydrous MeCN (0.2 M). To the solution, bismuth chloride (20 mol%) and allyl trimethyl silane (3.00 equiv.) was added at ambient temperature. The mixture was stirred at this temperature for 24 h under the N_2 atmosphere. Aqueous workup was committed when complete conversion was observed by TLC. The product was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent, the crude product was purified *via* flash column chromatography on silica gel (eluent methylene chloride/*n*-hexane) to produce the allylated silyl-protected diyne.

(3-Allyl-3-phenylpenta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (96a)



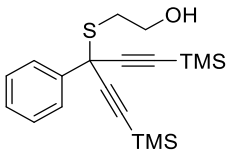
Under N_2 atmosphere, 3-phenyl-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (1.00 g, 2.14 mmol), bismuth chloride (138 mg, 42.8 μmol), and allyltrimethylsilane (1.04 mL, 6.42 mmol) were dissolved in anhydrous MeCN (10 mL) according to **GP 2**, and the product was purified by flash column chromatography (CH_2Cl_2:*n*-hexane = 1: 50, R_F = 0.58) to produce **(3-allyl-3-phenylpenta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (96a)** as a colorless oil (898 mg, 1.82 mmol, 85%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.75-7.66 (m, 2H), 7.38-7.21 (m, 3H), 5.90 (ddt, J = 7.11, 10.3, 17.3 Hz 1H), 5.12-4.96 (m, 2H), 2.64 (dt, 7.1, 1.2 Hz, 2H), 1.11 – 1.04 (m, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.9, 133.5, 128.1, 127.1, 126.6, 118.5, 107.9, 84.1, 77.5, 77.0, 76.6, 51.5, 42.3, 18.7, 11.3; IR (NaCl) ṽ (cm^{-1}): 2947, 2866, 2170, 1460, 1064, 995, 913, 885, 760, 672; **HRMS** (ESI): calc'd. for $C_{32}H_{56}NSi_2$ **$[M+NH_4]^+$** 510.3946 found 510.3956.

1-*para*-Toluenesulfonyl-3-(1-(trimethylsilyl)-3-((trimethylsilyl)ethynyl)hex-5-en-1-yn-3-yl)-1*H*-indole (96f)



3-(1-Toluenesulfonyl-1*H*-indol-3-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (585 mg, 1.18 mmol, 1.00 equiv.), bismuth chloride (76.7 mg, 236 μmol) and, allyltrimethylsilane (572 μL, 3.54 mmol) was dissolved in anhydrous MeCN (6 mL) under N_2 atmosphere according to **GP 2**, and the product was purified by flash column chromatography (EtOAc:*n*-hexane = 1:20, R_F = 0.43) to produce **1-toluenesulfonyl-3-(1-(trimethylsilyl)-3-((trimethylsilyl)ethynyl)hex-5-en-1-yn-3-yl)-1*H*-indole (96f)** as a yellowish oil (496 mg, 957 μmol, 81%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.18 (dt, J = 7.7, 1.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.33 (ddd, J = 8.4, 7.4, 1.3 Hz), 7.16 (d, J = 8.4 Hz, 2H), 7.05 (ddd, 8.4, 7.4, 1.0 Hz, 1H), 5.66 (ddt, J = 17.1, 10.1, 7.2 Hz, 1H), 5.12 (dq, J = 17.1, 1.4 Hz, 1H) 5.04-4.93 (m, 2H), 2.98-2.79 (m, 2H), 2.35 (s, 3H), 0.31 – 0.15 (m, 18 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 154.0, 145.7, 144.5, 134.4, 132.1, 132.0, 129.9, 129.4, 127.2, 125.0, 124.5, 119.0, 116.8, 101.6, 101.5, 101.2, 100.9, 95.5, 67.8, 38.5, 21.7, -0.12; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3075, 2960, 2906, 2141, 1594, 1455, 1408, 1362, 1254, 1167, 1086, 1049, 994, 939, 917, 849, 756, 701, 665; **HRMS** (ESI): calc'd. for $C_{29}H_{36}NO_2SSi_2$, **[M+H]$^+$** 518.2000 found 518.2000.

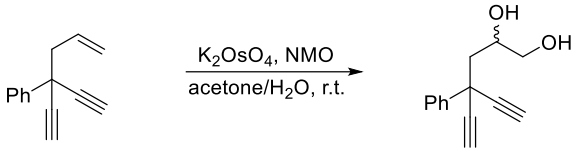
2-((3-Phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl)thio)ethan-1-ol (97)



Under N_2 atmosphere, 3-phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (301 mg, 1.00 mmol), bismuth chloride (65.0 mg, 200 μmol), and 2-mercaptoethan-1-ol (210 μL, 3.00 mmol) were dissolved in anhydrous MeCN (5 mL) according to **GP 2**, and the product was purified by flash column chromatography (CH_2Cl_2:*n*-Hexane = 1:50, R_F = 0.51) to produce **2-((3-phenyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl)thio)ethan-1-ol (97)** as a colorless oil (75.7 mg, 210 μmol, 21%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 5.3, 1H), 7.55-7.49 (m, 1H), 7.46-7.23 (m,

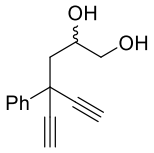
3H), 5.90 (ddt, J = 7.11, 10.3, 17.3 Hz 1H), 5.12-4.96 (m, 2H), 3.92 (td, J = 6.0, 0.8 Hz, 1H), 3.75 (tdd, J = 5.8, 3.2 0.8 Hz, 1H), 3.16 (td, J = 5.9, 0.7 Hz, 1H), 2.91 (tdd, J = 6.6, 2.4 0.8 Hz, 1H), 2.07 (s, br, 1H), 0.34-0.23 (m, 18H) other characterization data in not avalible due to the instability of the compound.

Procedure for the dihydroxylation of allylated diynes



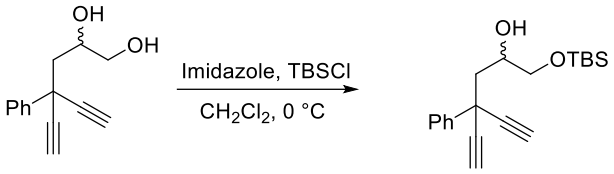
(3-Ethynylhex-5-en-1-yn-3-yl)benzene (260 mg, 1.40 mmol, 1.00 equiv.) was dissolved in acetone/water (1:1; 3 mL). Potassium osmate(VI) dihydrate (3 mg, 0.5 mol%) and 4-methyl-morpholine-4-oxide monohydrate (203 mg, 1.70 mmol, 1.20 equiv.) were added to this solution at ambient temperature. The mixture was stirred for 6 hr at this temperature. Acidic work up with 1 N HCl was committed when a complete conversion was observed by TLC. The product was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent, the crude product was purified *via* column chromatography on silica gel (EtOAc:*n*-hexane = 1:1, R_F = 0.33) to afforded **4-ethynyl-4-phenylhex-5-yne-1,2-diol (120a)** as a colorless oil (246 mg, 1.15 mmol, 82% yield).

4-Ethynyl-4-phenylhex-5-yne-1,2-diol (120a)



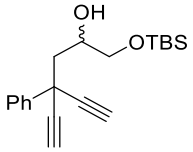
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79-7.65 (m, 2H), 7.49-7.29 (m, 3H), 4.32-4.08 (m, 1H), 3.60 (ddd, J = 11.2, 3.6, 2.5 Hz, 1H), 3.48 (dd, J = 11.2, 6.8 Hz, 1H), 2.63 (d, J = 7.2 Hz, 2H), 2.22 (dd, J = 14.2, 8.1 Hz, 2H), 2.05 (dd, J = 14.2, 2.6 Hz, 2H).

Procedure for silyl protection of 4-ethynyl-4-phenylhex-5-yne-1,2-diol



In a dried and nitrogen-flushed Schlenk-flask equipped with magnetic stir bar, 4-ethynyl-4-phenylhex-5-yne-1,2-diol (1.00 g, 4.60 mmol, 1.00 equiv.) and imidazole (636 mg, 9.30 mmol, 2.00 equiv.) was dissolved in dry CH_2Cl_2 (5 mL). TBSCl (703 mg, 4.60 mmol, 1 equiv.) were added to this solution at 0 °C. The mixture was stirred at this temperature for 6 h. Aqueous work up was committed by slowly adding water to the reaction mixture when the complete conversion was observed by TLC. The mixture was extracted with CH_2Cl_2 three times. The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration and removal of solvent the crude product was further purified *via* column chromatography (EtOAc:*n*-Hexane =1:19, R_F = 0.22) on silica gel to afford **1-((*tert*-butyldimethylsilyl)oxy)-4-ethynyl-4-phenylhex-5-yn-2-ol (120b)** as a colorless oil (771 mg, 2.35 mmol, 51%).

1-((*tert*-Butyldimethylsilyl)oxy)-4-ethynyl-4-phenylhex-5-yn-2-ol (120b)

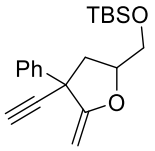


^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.66 (m, 2H), 7.42-7.26 (m, 2H), 4.08-3.97 (m, 1H), 3.55 (dd, J = 10.0, 4.7 Hz, 1H), 3.46 (dd, J = 10.0, 6.7 Hz, 1H), 2.58 (d, J = 3.0 Hz, 2H), 2.24-2.06 (m, 2H), 0.88 (s, 9H), 0.04 (d, J = 0.6 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ =140.9, 128.6, 127.7, 126.2, 84.6, 84.1, 72.6, 72.4, 69.8, 66.9, 49.0, 38.3, 25.9, 18.3, -5.4; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3575, 3306, 2954, 2857, 1499, 1471, 1448, 1362, 1255, 1032, 1006, 939,893, 782, 756; **HRMS** calc'd. for $C_{20}H_{29}O_2Si$, **$[M+H]^+$** 329.1931; found 329.1934

Procedure for five-membered ring enclosure of 4-diethynylbutane1,2-diol

In the glovebox, a Schlenk-flask equipped with a magnetic stir bar was filled with chloro(triphenylphosphine) gold(I) (20.7 mg, 35.0 μmol, 5 mol%) and silver tetrafluoroborate (5.50 mg, 30.0 μmol, 4 mol%). The mixture of salts was suspended in anhydrous dichloromethane (1 mL) at room temperature and keep stirring at this temperature for 30 min. In a dry round bottom flask, a solution of diyne 1-((*tert*-butyldimethylsilyl)oxy)-4-ethynyl-4-phenylhex-5-yn-2-ol **(120b)** (230 mg, 700 μmol 1.0 equiv.) in anhydrous dichloromethane (4 mL) was prepared, and then it was transferred to the Schlenk-flask with gold catalyst under nitrogen atmosphere at 0 ℃. The reaction mixture was stirred at 0 ℃ for 1 hour. After complete conversion was indicated by TLC analysis, the mixture was directly purified *via* column chromatography (EtOAc: *n*-Hexane = 1:40, R_F = 0.49) on neutral aluminum oxide (with 6% of water) to afford ***tert*-butyl((4-ethynyl-5-methylene-4-phenyltetrahydrofuran-2-yl)methoxy)dimethylsilane (122b)** as a colorless oil (172 mg, 532 μmol, 76%).

***tert*-Butyl((4-ethynyl-5-methylene-4-phenyltetrahydrofuran-2-yl)methoxy)dimethylsilane (122b)**

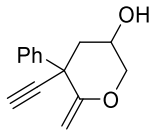


^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62-7.53 (m, 2H), 7.51-7.42 (m, 2H'), 7.31-7.11 (m, 3H+3H'), 4.57 (dddt, *J* = 11.6, 9.2, 6.1, 4.0 Hz, 1H), 4.44 (dd, *J* = 1.9, 0.8 Hz, 1H'), 4.27 (dd, *J* = 2.1, 0.8 Hz, 1H), 4.18 (d, *J* = 1.9 Hz, 1H'), 4.11-3.96 (m, 1H'), 3.85-3.63 (m, 2H+2H'), 3.55 (d, *J* = 2.1 Hz, 1H),.2.52 (s, 2H'), 2.40-2.34 (m, 2H), 0.86-0.79 (m, 9H+9H'), 0.03-(- 0.03), (m, 6H+6H'); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 167.4, 164.6, 142.4, 141.0, 128.5, 128.2, 127.9, 127.9, 127.3, 127.3, 126.5, 105.8, 86.6, 85.6, 83.3, 82.6, 80.5, 79.6, 77.5, 77.1, 77.0, 76.6, 73.4, 71.4, 64.4, 63.8, 50.0, 49.5, 45.4, 44.6, 25.9, 18.4, -5.2, -5.3 (both diastereomer were included); **IR** (NaCl) ṽ (cm^{-1}): 2954, 2929, 2885, 2858, 1740, 1496, 1471, 1448, 1389, 1362, 1256, 1110, 1005, 942, 838, 780, 755, 698; **HRMS** calc'd. for $C_{20}H_{29}O_2Si$, **[M+H]$^+$** 329.1931; found 329.1935.

Procedure for six-membered ring enclosure of 4-diethynylbutane1,2-diol

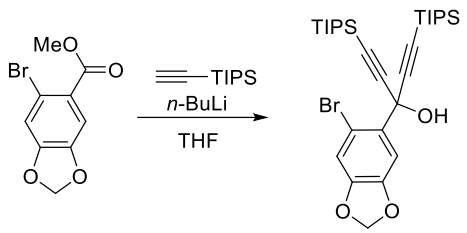
In the glovebox, a Schlenk-flask equipped with a magnetic stir bar was treated with chloro(triphenylphosphine) gold(I) (12.4 mg, 25.0 μmol, 5 mol%) and silver tetrafluoroborate (4.00 mg, 20.0 μmol, 4 mol%). The mixture of salts was suspended in anhydrous dichloromethane (1 mL) at room temperature and kept stirring at this temperature for 30 min. In a dry round bottom flask, a solution of diyne 4-ethynyl-4-phenylhex-5-yne-1,2-diol **(120b)** (107 mg, 500 μmol, 1.00 equiv.) in anhydrous dichloromethane (4 mL) was prepared, and then it was transferred to the Schlenk-flask with gold catalyst under the nitrogen atmosphere at 0 ℃. The reaction mixture was stirred at 0 ℃ for 1 hour. After complete conversion, was indicated by TLC analysis, the mixture was directly purified *via* column chromatography (EtOAc:*n*-hexane= 1:20, R_F = 0.41) on neutral aluminum oxide (with 6% of water) to afford **5-ethynyl-6-methylene-5-phenyltetrahydro-2H-pyran-3-ol (121a)** as a colorless oil (71.7mg, 335 μmol, 67%).

5-ethynyl-6-methylene-5-phenyltetrahydro-2H-pyran-3-ol (121a)



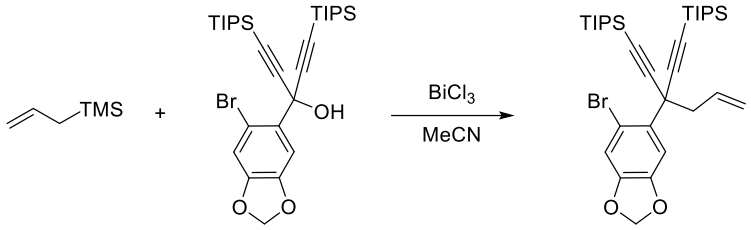
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74-7.65 (m, 2H), 7.64-7.57 (m ,2H'), 7.40-7.19 (m, 3H+3H'), 4.93 (dd, J = 5.1, 3.6 Hz, 1H), 4.26-4.19 (m, 1H'), 3.93 (d, J = 6.4 Hz, 1H), 3.87 (d, J = 6.6 Hz, 1H'), 3.81 (dt, J = 6.4, 3.2 Hz, 1H), 2.60 (ddd, J = 12.7, 5.2, 2.8 Hz, 1H), 2.52 (s, 1H), 2.45 (d, J = 12.7 Hz, 1H+1H'), 2.16-2.02 (m, 1H+1H'), 1.65 (s, 2H'), 1.57 (s, 1H+1H').; **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.9, 128.1, 128.0, 127.5, 127.2, 127.1, 125.9, 111.4, 90.4, 85.9, 77.2, 76.3, 72.5, 70.8, 54.5, 48.4, 15.3 (both diastereomer were included); **IR** (NaCl) ṽ (cm^{-1}): 3464, 3284, 2943, 1739, 1494, 1448, 1380, 1236, 1159, 1120, 1035, 975, 865, 755, 699, 636; **HRMS** calc'd. for $C_{14}H_{15}O_2$, **$[M+H]^+$** 215.1067; found 215.1068.

3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (74d)



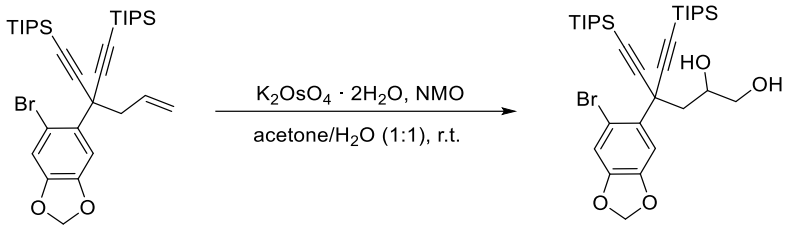
In a dried and nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, the triisopropylsilylacetlyene (2.50 mL, 11.0 mmol, 2.20 equiv.) was dissolved in anhydrous THF (25 mL). To the solution, *n*-BuLi (2.5 M, 4.40 mL, 11.0 mmol, 2.20 equiv.) was added at 0 °C. The mixture was stirred at this temperature for 30 min then treated with methyl 6-bromo-2*H*-1,3-benzodioxole-5-carboxylate (1.30 g, 5.00 mmol, 1.00 equiv.) under N_2 atmosphere. The reaction mixture was stirred for 1 h and allowed to warm to room temperature. Aqueous work up was committed by slowly adding water to the reaction mixture at 0 °C after a complete conversion was observed. The product in the aqueous phase was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent the crude product was purified *via* flash column chromatography (EtOA:*n*-hexane = 1:20, R_F = 0.33) on silica gel to afford **3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (74d)** as yellowish oil (2.91 g, 4.91 mmol, 98%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.56 (s, 1H), 6.99 (s, 1H), 5.92 (s, 2H), 3.39 (s, 1H), 1.06-0.95 (m, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 148.1, 147.0 132.8, 114.6, 112.4, 108.8, 105.3, 102.0, 87.1, 65.7, 18.6, 11.2; **IR**(NaCl) ṽ (cm^{-1}): 3518, 2942, 2890, 2864, 1504, 1479, 1240, 1107, 1038, 996, 882, 676; **HRMS**(ESI): calc'd. for $C_{30}H_{46}BrO_2Si_2$, **[M-OH]$^+$** 573.2214 found 573.2215

(3-allyl-3-(6-bromobenzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (96d)



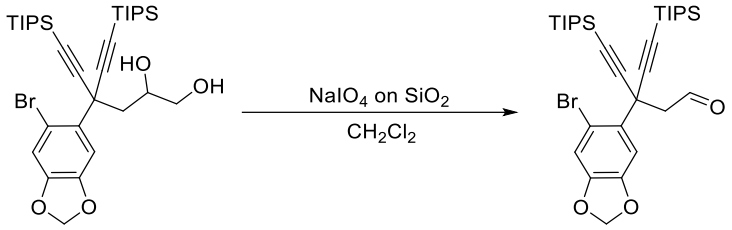
In a dried and nitrogen-flushed Schlenk-flask equipped with magnetic stir bar, in anhydrous MeCN (5 mL) a solution of 3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1,5-bis(triisopropylsilyl)penta-1,4-diyn-3-ol (530 mg, 0.90 mmol, 1.00 equiv.) was prepared. To this solution, bismuth chloride (65.0 mg, 0.18 mmol, 20 mol%) and allyltrimethylsilane (0.43 mL, 2.7 mmol, 3.00 equiv.) were added at ambient temperature. The mixture was stirred at this temperature for 24 h under N_2 atmosphere. Aqueous work up was committed by slowly adding water to the reaction mixture after a complete conversion was observed by TLC. The product in the aqueous phase was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent, the crude product was purified *via* flash column chromatography (*n*-hexane 100%, R_F = 0.48) on silica gel to produce the **(3-allyl-3-(6-bromobenzo[d][1,3]dioxol-5-yl)penta-1,4-diyne-1,5-diyl)bis(triisopropylsilane) (96d)** as a colorless oil (388 mg, 0.63 mmol, 70%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.06 (s, 1H), 5.98 (s, 2H), 5.89 (ddt, J = 17.1, 10.0, 7.1 Hz, 1H), 5.18-5.03 (m, 2H), 3.04 (dt, J = 7.1, 1.2 Hz, 2H), 1.16-1.06 (m, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.4, 146.9 133.4, 131.3, 118.5, 114.9, 112.5, 110.5, 106.7, 101.9, 85.9, 45.3, 43.1, 18.7, 11.3; **IR**(NaCl) ṽ (cm^{-1}): 2943, 2891, 2865, 2167, 1505, 1478, 1380, 1235, 1114, 1071, 1041, 1017, 995, 938, 918, 882, 831, 784, 741, 678; **HRMS**(ESI): calc'd. for $C_{33}H_{55}BrNO_2Si_2$, **$[M+NH_4]^+$** 632.2949 found 632.2951.

4-(6-bromobenzo[d][1,3]dioxol-5-yl)-6-(triisopropylsilyl)-4-((triisopropylsilyl)ethynyl)hex-5-yne-1,2-diol



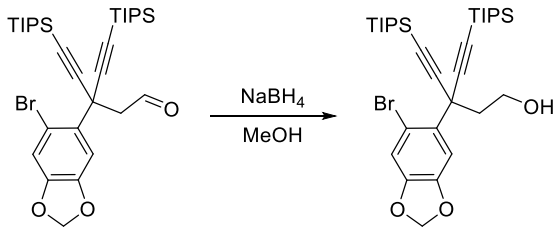
In a round bottom flask equipped with a magnetic stirring bar, allylated diyne (2.08 g, 3.37 mmol, 1.00 equiv.) was dissolved in acetone/water (1:1; 0.5 M). Potassium osmate(VI) dihydrate (14.6 mg, 0.34 mmol, 1 mol%) and 4-methyl-morpholine-4-oxide monohydrate (1.47 g, 10.2 mmol, 3.00 equiv.) were added to this solution at ambient temperature. The mixture was stirred for 48 hr at room temperature. Acidic work up with 1N HCl was committed at 0°C while a complete conversion was observed by TLC. The product in aqueous was extracted with EtOAc three times. The combined organic phases were dried over Na_2SO_4. After filtration and removal of solvent, the crude product was purified *via* column chromatography (EtOAc:*n*-hexane = 1:9, R_F = 0.19) on silica gel to afford **4-(6-bromobenzo[d][1,3]dioxol-5-yl)-6-(triisopropylsilyl)-4-((triisopropylsilyl)ethynyl)hex-5-yne-1,2-diol** as a lilac oil (1.95 g, 3.00 mmol, 89%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.06 (s, 1H), 6.00 (s, 2H), 4.29 (ddt, J = 7.7, 5.6, 3.3 Hz, 1H), 3.69-3.46 (m, 2H), 3.26 (d, J = 2.3 Hz, 1H), 2.52 (dd, J = 14.1, 8.4 Hz, 1H), 2.25 (dd, J = 14.1, 2.2 Hz, 1H), 2.04 (dd, J = 7.3, 5.4 Hz, 1H), 1.10 (d, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.7, 147.2, 131.1, 115.2, 112.5, 109.8, 107.0, 106.5, 102.1, 87.7, 87.5, 70.6, 66.7, 44.6, 41.5, 18.7, 18.6, 11.3; **IR**(NaCl) $\tilde{\nu}$ (cm^{-1}): 3546, 3427, 2943, 2891, 2865, 1505, 1480, 1380, 1236, 1116, 1071, 1040, 1018, 996, 936, 919, 883, 871, 741, 678; **HRMS**(ESI): calc'd. for $C_{33}H_{57}BrNO_4Si_2$, **$[M+NH_4]^+$** 666.3004 found 666.2999.

3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-ynal (149)



In a round bottom flask equipped with a magnetic stirring bar, a solution of diol (1.95 g, 3.00 mmol, 1.00 equiv.) in dry dichloromethane (30 mL) was prepared. $NaIO_4$ adsorbed on silica gel (6.48 g; 0.613 mmol·g^{-1}, 3.90 mmol, 1.30 equiv.) was added to the solution. The mixture was stirred vigorously for 18 h at room temperature. After complete conversion, the reaction residue was washed with dichloromethane. The filtrate was evaporated and the residue was further purified *via* column chromatography (EtOAc:*n*-hexane = 1:9, R_F = 0.68) on silica gel to afford **3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-ynal (149)** as a violet oil (1.68 g, 2.71 mmol, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.01-9.95 (m, 1H), 7.65 (s, 1H), 7.07 (s, 1H), 6.00 (s, 2H), 3.19 (d, J= 2.6, 2H), 1.08 (s, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 200.6, 148.2, 147.5, 130.0, 115.3, 112.8, 110.0, 105.2, 102.3, 88.3, 52.4, 39.3, 18.8, 11.4; **IR** (NaCl) ṽ (cm^{-1}): 2943, 2891, 2866, 2737, 2168, 1729, 1505, 1481, 1381, 1236, 1115, 1072, 1039, 996, 935, 883, 679; **HRMS** (ESI): calc'd. for $C_{32}H_{50}BrO_3Si_2$, **[M+H]$^+$** 617.2476 found 617.2461.

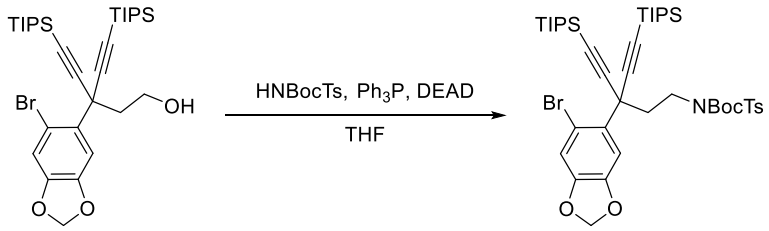
3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol



In a dried, nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, the aldehyde (1.67 g, 2.70 mmol, 1.00 equiv.) was dissolved in dry methanol (26 mL) and cooled to 0 °C. At this temperature, $NaBH_4$ (205 mg, 5.41 mmol, 2.00 equiv.) was added to the solution slowly under N_2 atmosphere. After complete conversion within 30 min the reaction was quenched with 1N

hydrochloric acid until pH = 2 was reached. The reaction mixture was stirred for another 30 min then extracted with EtOAc three times. The organic phase was washed with brine and dried over Na_2SO_4. The filtrate was condensed under the reduced pressure and the residue was further purified *via* column chromatography (EtOAc:*n*-hexane = 1:9, R_F = 0.38) on silica gel to afford **3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol** as a yellowish oil (1.54 g, 2.48 mmol, 92%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.06 (s, 1H), 5.99 (s, 2H), 4.03 (t, J = 5.8 Hz, 2H), 2.50 (J = 5.8 Hz, 2H), 2.05 (s, 1H), 1.18-0.93 (m, 42H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.6, 147.2, 131.4, 115.1, 112.5, 109.8, 106.8, 102.0, 87.0, 61.0, 43.4, 18.7, 11.3; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3416, 2943, 2891, 2865, 2164, 1504, 1480, 1380, 1236, 1114, 1069, 1040, 1017, 997, 936, 883, 870, 758, 678; **HRMS** (ESI): calc'd. for $C_{32}H_{55}BrNO_3Si_2$, **$[M+H]^+$** 636.2898 found 636.2902

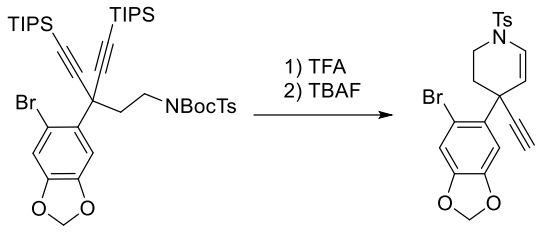
(3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-n-((triisopropylsilyl)ethynyl)pent-4-yn-1-yl)(toluenesulfonyl) *tert*-butyl carbamate (150)



In a dried, nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, the alcohol (1.40 g, 2.23 mmol, 1.00 equiv.) was dissolved in anhydrous THF (22 mL). At ambient temperature, triphenylphosphine (0.91 g, 3.34 mmol, 1.5 equiv.) and protected amine (0.69 g, 2.45 mmol, 1.1 equiv) were added to the solution under N_2 atmosphere. To the reaction mixture, the diethyl azodicarboxylate solution (1.55 mL, 3.34 mmol, 1.5 eq, 40%wt in toluene) was added dropwise. After complete conversion within 3 h, the acidic work up was proceeded with 2N $HCl_{(aq)}$. The aqueous phase was extracted with EtOAc three times. The combined organic phase was concentrated under reduced pressure. The residue was purified *via* flash column chromatography (EtOAc:*n*-hexane= 1:9, R_F = 0.43) on silica gel to afford **(3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-n-((triisopropylsilyl)ethynyl)pent-4-yn-1-yl)(toluenesulfonyl) *tert*-butyl carbamate (150)** as a yellowish viscous product (1.59 g, 1.83 mmol, 82%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.2 Hz, 2H), 7.70 (s, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.06 (s, 1H), 5.99 (s, 2H), 4.21-4.04 (m, 2H), 2.67-2.55 (m, 2H), 2.42 (s, 3H), 1.34 (s, 9H), 1.12 (s, 42H); **^{13}C**

NMR (75 MHz, $CDCl_3$): δ = 150.6, 147.6, 147.1, 143.9, 137.5, 131.1, 129.2, 128.0, 115.1, 112.6, 110.1, 105.5, 102.0, 86.8, 83.9, 44.6, 41.3, 39.2, 27.9, 21.6, 18.7, 11.3; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 2943, 2891, 2865, 2164, 1732, 1505, 1479, 1368, 1283, 1236, 1173, 1156, 1039, 883, 758, 676; **HRMS** (ESI): calc'd. for $C_{44}H_{70}BrN_2O_6SSi_2$, **$[M+NH_4]^+$** 889.3671 found 889.3666

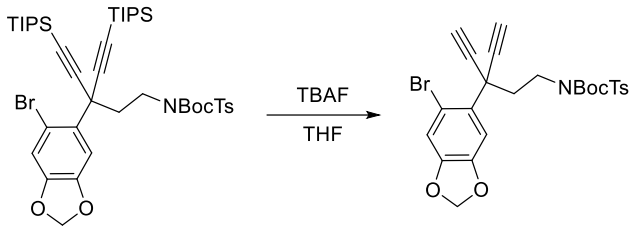
***N*-(3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-4-methylbenzenesulfonamide (151)**



In a dried, nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, the tosylcarbamate (1.66 g, 1.90 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (19 mL). To the solution, TFA (4.35 mL, 57.0 mmol, 30.0 equiv.) was added at ambient temperature. The reacting mixture was stirred for 5 h at this temperature. Saturated sodium carbonate solution was added to quench the reaction after the full conversion was observed by TLC analysis. The aqueous solution was extracted with EtOAc three times. The collection of organic phases was condensed under reduced pressure was dissolved in THF (19 mL, 0.1 M), then treated with TBAF (1.53 g, 4.75 mmol, 2.50 equiv.) at 0 °C. The reaction mixture was stirred under N_2 atmosphere for another 5 h allowed to warm to room temperature. The reaction mixture was subjected to saturated NaCl solution when the full conversion was observed by TLC analysis. The aqueous phase was extracted with EtOAc three times. The combined extracts were dried over Na_2SO_4. The filtrate was condensed under the reduced pressure and the residue was further purified *via* flash column chromatography (n-hexane:EtOAc:CH_2Cl_2 = 4:1:1, R_F = 0.53) on neutralized silica gel to afford ***N*-(3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-4-methylbenzenesulfonamide (151)** as a white solid (779 mg, 1.69 mmol, 89%). **m.p.** : 176-177 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.3 Hz, 2H), 7.31 (d J = 8.3 Hz, 2H), 7.07(s, 1H), 6.99 (s, 1H), 6.85 (d, J = 8.3 Hz, 1H), 5.99-5.89 (m, 2H), 5.09 (d, J = 8.3 Hz, 1H), 3.56 (ddd, J = 12.4, 9.0, 3.3 Hz, 1H), 3.32 (ddd, J = 12.4, 7.4, 3.4 Hz, 1H), 2.55 (ddd, J = 13.3, 9.0, 3.4 Hz, 1H), 2.45 (s, 1H), 2.43 (s, 3H), 2.00 (ddd, 13.3, 7.4, 3.3 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.4, 147.0, 144.0, 135.1, 133.0,

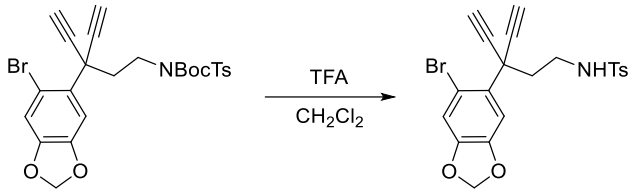
129.8, 129.5, 127.6, 127.0, 125.6, 115.2, 112.4, 111.2, 110.6, 101.9, 86.3, 73.9, 40.9, 38.9, 32.2, 21.6; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3293, 3091, 3056, 3024, 2978, 2921, 2893, 1644, 1503, 1478, 1350, 1276, 1235, 1168, 1122, 1093, 1038, 1013, 931, 756, 709, 685, 653; **HRMS** (ESI): calc'd. for $C_{21}H_{19}BrNO_4S$, **[M+H]**$^+$ 460.0213 found 460.0217.

***tert*-Butyl (3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl) (toluenesulfonyl) carbamate**



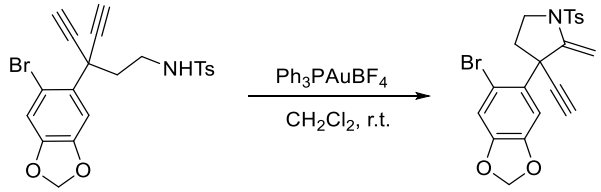
In a dried, nitrogen-flushed Schlenk-flask equipped with a magnetic stir bar, the tosylcarbamate (1.74 g, 1.99 mmol, 1.00 equiv.) was dissolved in anhydrous THF (20 mL, 0.1 M). To the solution, TBAF (1.60 g, 4.98 mmol, 2.50 equiv.) was added at ambient temperature. The reaction mixture was stirred at this temperature for 18 h. Aqueous work up was proceeded by slowly adding water to the reaction mixture after complete conversion was observed by TLC. The aqueous phase was extracted with EtOAc three times and the combined organic solution was condensed under reduced pressure. The residue was further purified *via* flash column chromatography (*n*-hexanes:EtOAc:CH_2Cl_2 = 8:1:1, R_F = 0.48) on silica gel to afford ***tert*-Butyl (3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl) (toluenesulfonyl)carbamate** as a white crystalline product (1.08 g, 1.93 mmol, 97%). **^{1}H NMR** (300 MHz, CDCl3): δ = 7.81 (d, J = 8.4 Hz, 2H), 7.59 (s, 1H), 7.30 (d, 8.4 Hz, 2H), 7.09 (s, 1H), 6.01 (s, 2H), 4.18-4.05 (m, 2H), 2.74-2.63 (m, 4H), 2.43 (s, 3H), 1.36 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 150.7, 147.9, 147.3, 144.1, 137.2, 129.8, 129.3, 128.0, 115.4, 112.7, 109.8, 102.1, 84.2, 82.1, 74.1, 44.2, 39.2, 39.0, 28.0, 21.6, 18.1, 13.4; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3289, 2978, 2939, 2868, 1730, 1505, 1479, 1368, 1356, 1288, 1238, 1172, 1156, 1144, 1088, 1038, 757, 717, 673; **HRMS** (ESI): calc'd. for $C_{26}H_{27}BrNO_6S$, **[M+H]**$^+$ 560.0737 found 560.0732

***N*-(3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-4-methylbenzenesulfonamide (152)**



In a round bottom flask equipped with a magnetic stir bar, the tosylcarbamate (1.0 g, 1.78 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (18 mL). To the solution, TFA (4.08 mL, 53.4 mmol, 30.0 equiv.) was added at ambient temperature. The reaction mixture was stirred at this temperature for 18 h. Aqueous work up was proceeded by slowly adding water to the reaction mixture after complete conversion was observed by TLC. The aqueous phase was extracted with EtOAc three times and the combined organic solution was condensed under reduced pressure. The residue was further purified by flash column chromatography (n-hexanes:EtOAc:CH_2Cl_2 = 8:1:1, R_F = 0.48) on silica gel to afford ***N*-(3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-4-methylbenzenesulfonamide (152)** as a white crystalline product (754 mg, 1.64 mmol, 92%). **m.p.** : 148-149 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.3 Hz, 2H), 7.46 (s, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.04 (s, 1H), 6.00 (s, 2H), 4.71 (t, J = 6.2 Hz, 1H), 3.30 (ddd, J = 7.9, 7.1, 6.2 Hz, 2H), 2.59 (s, 2H), 2.47-2.36 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.0, 146.4, 142.4, 136.0, 128.7, 128.6, 126.2, 114.3, 111.5, 108.7, 101.2, 81.4, 73.3, 39.4, 38.5, 38.4, 20.6; **IR** (NaCl) ṽ (cm^{-1}): 3374, 3285, 3024, 2981, 2893, 1504, 1479, 1327, 1238, 1159, 1093, 1037, 661 ;**HRMS** (ESI): calc'd. for $C_{21}H_{19}BrNO_4S$, **$[M+H]^+$** 460.0213 found 460.0216

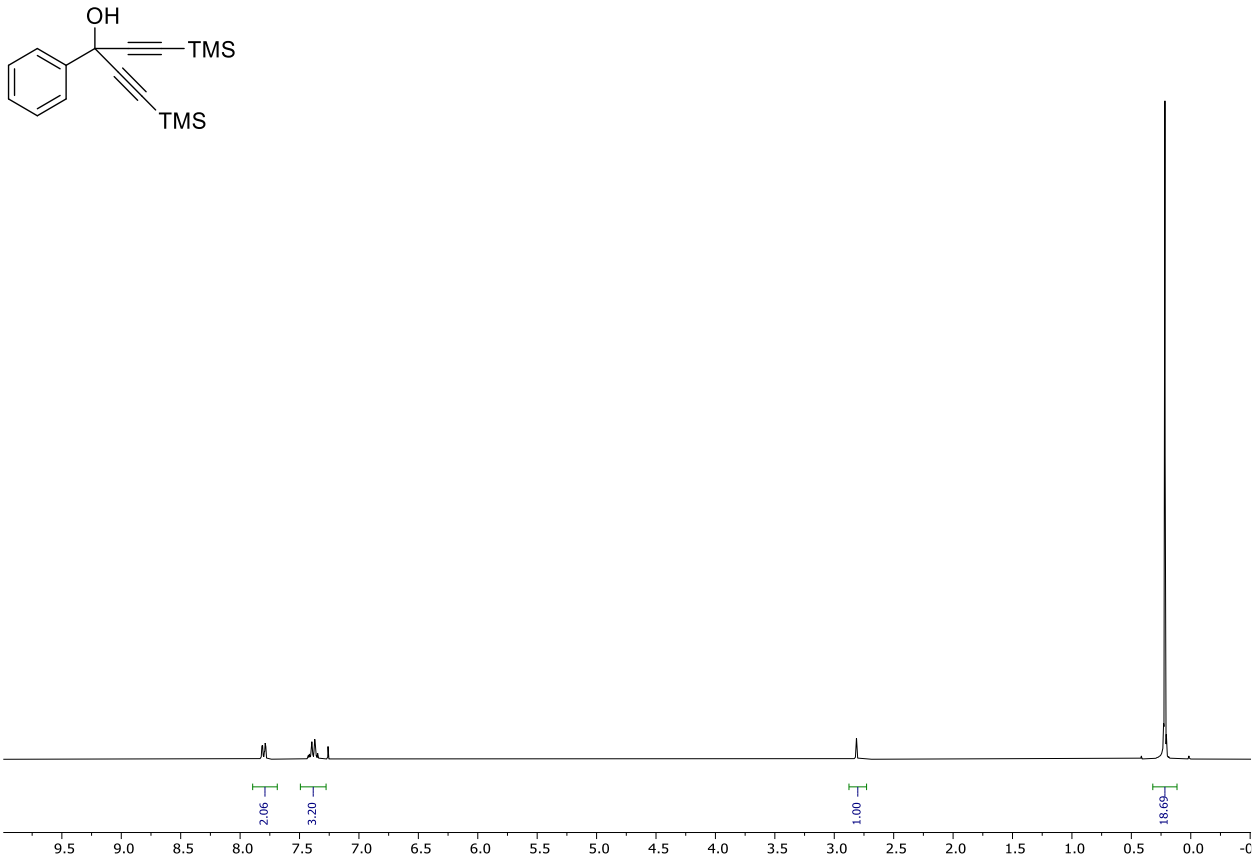
(rac)-3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-toluenesulfonyl pyrrolidine (153)



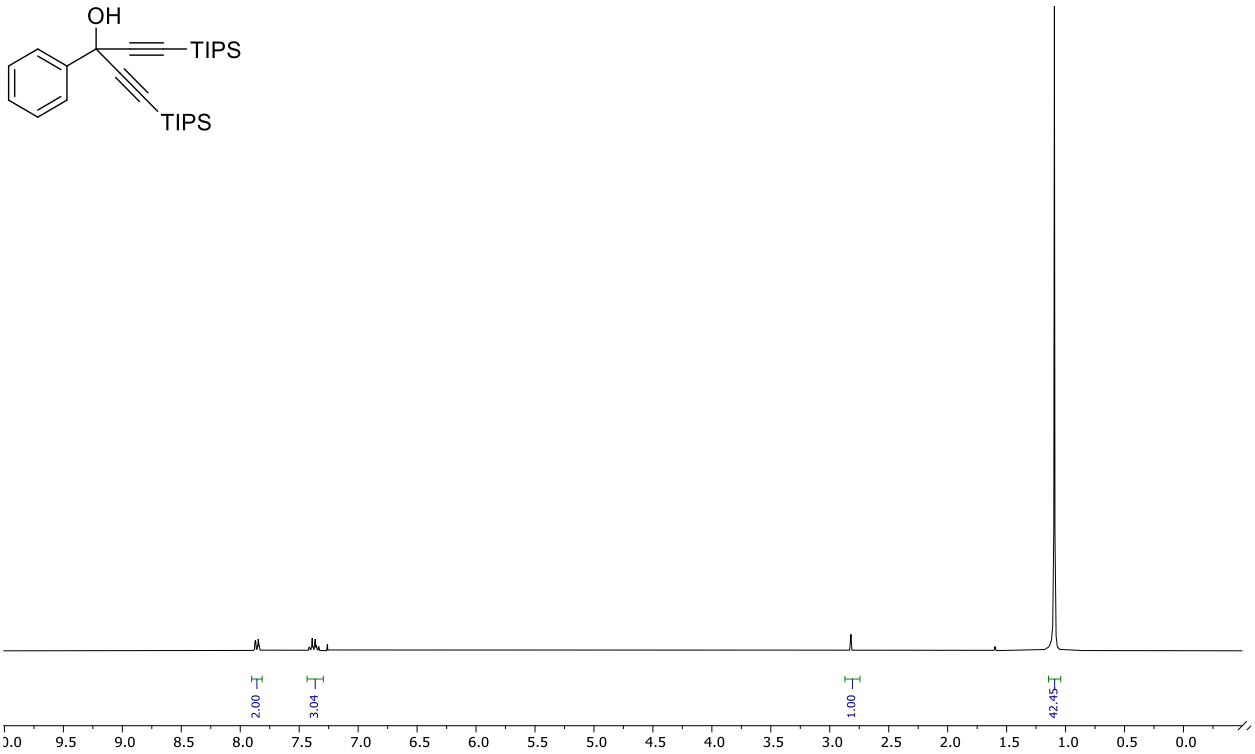
In the glovebox, a Schlenk-flask equipped with a magnetic stir bar was treated with chloro(triphenylphosphine) gold(I) (12.4 mg, 25.0 μmol, 5 mol%) and silver tetrafluoroborate (4.00 mg, 20.0 μmol, 4 mol%). The mixture of salts was suspended in anhydrous dichloromethane

(1 mL) at room temperature and kept stirring at this temperature for 30 min. In a dry round bottom flask, a solution of *N*-(3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)-4-methylbenzenesulfonamide (230 mg, 500 μmol, 1.00 equiv.) in anhydrous dichloromethane (4 mL) was prepared, and then it was transferred to the Schlenk-flask with gold catalyst under the nitrogen atmosphere at 0 ℃. The reaction mixture was stirred for 1 hour and allowed to warm up to ambient temperature. After complete conversion was indicated by TLC analysis, the mixture was directly purified *via* column chromatography (*n*-hexane:EtOAc:CH_2Cl_2 = 70:20:10 R_F = 0.46) on neutral aluminum oxide (with 6% of water) to afford **(rac)-3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynyl-2-methylene-1-toluenesulfonyl pyrrolidine (153)** as a colorless crystalline (225 mg, 490 μmol, 98%). **m.p. =** 162-163 ℃; **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.77 (d, J = 8.3 Hz, 2H), 6.83 (s, 1H), 6.81-6.71 (m, 2H), 5.72 (d, J = 1.7 Hz, 1H), 5.10 (dd, J = 7.8, 1.4, 2H), 5.02 (d, J = 10.1, 1.4 Hz, 2H), 4.69 (d, J = 1.7 Hz, 1H) , 3.62 (ddd, J = 9.6, 7.3, 5.2 Hz, 1H), 3.31 (ddd, J = 9.6, 7.3, 6.6 Hz, 1H), 2.76 (ddd, J = 12.2, 6.6, 5.2 Hz, 1H), 1.92 (s, 3H), 1.91 (s, 1H), 1.81 (dt, J = 12.2, 7.3, 1H); **^{13}C NMR** (75 MHz, C_6D_6): δ = 147.9, 147.1, 147.0, 143.8, 135.1, 131.0, 129.4, 115.4, 113.8, 110.6, 101.6, 93.2, 84.2, 74.4, 74.3, 52.6, 48.2, 35.5, 21.1; **IR** (NaCl) $\tilde{\nu}$ (cm^{-1}): 3293, 3056, 3016, 2960, 2921, 2893, 1644, 1503, 1479, 1343,1237, 1166, 1120, 1092, 1038, 994, 931, 868, 814, 754, 657; **HRMS** (ESI): calc'd. for $C_{21}H_{19}BrNO_4S$, **$[M+H]^+$** 460.0213 found 460.0216

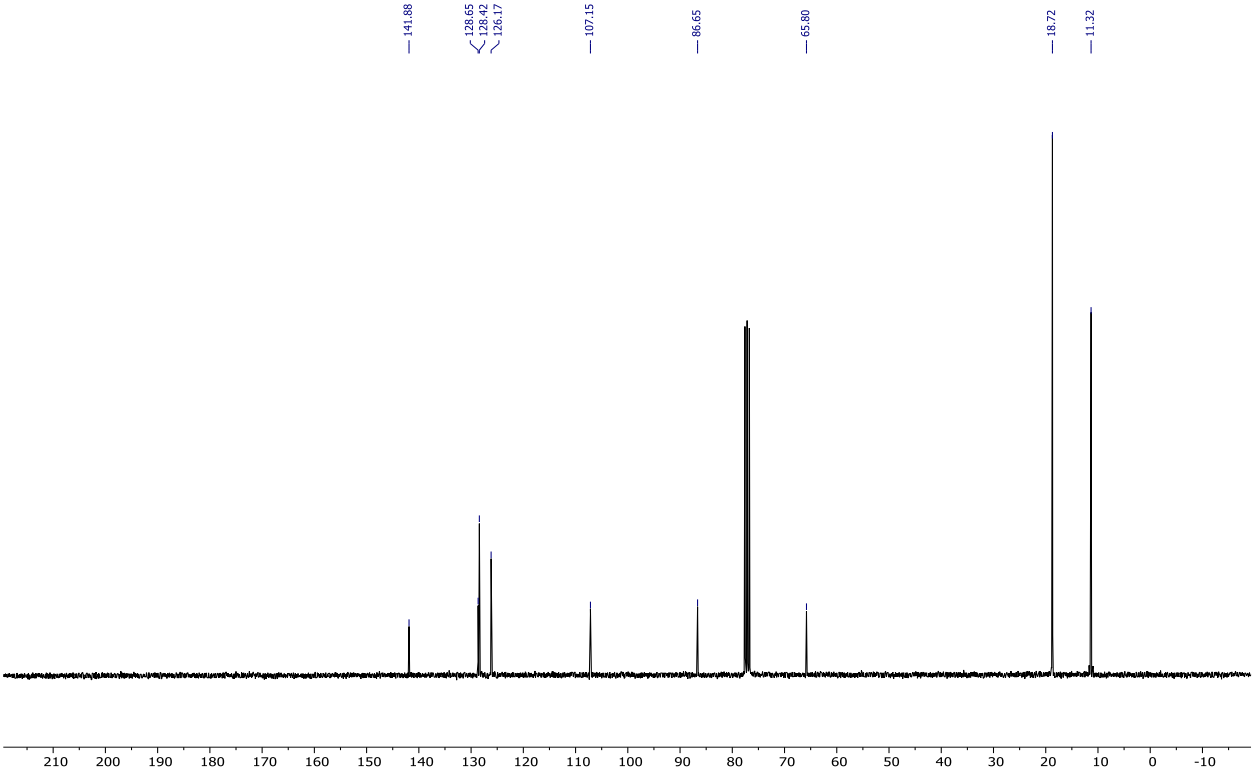
6-3 NMR Spectra and HPLC Trace For New Compounds



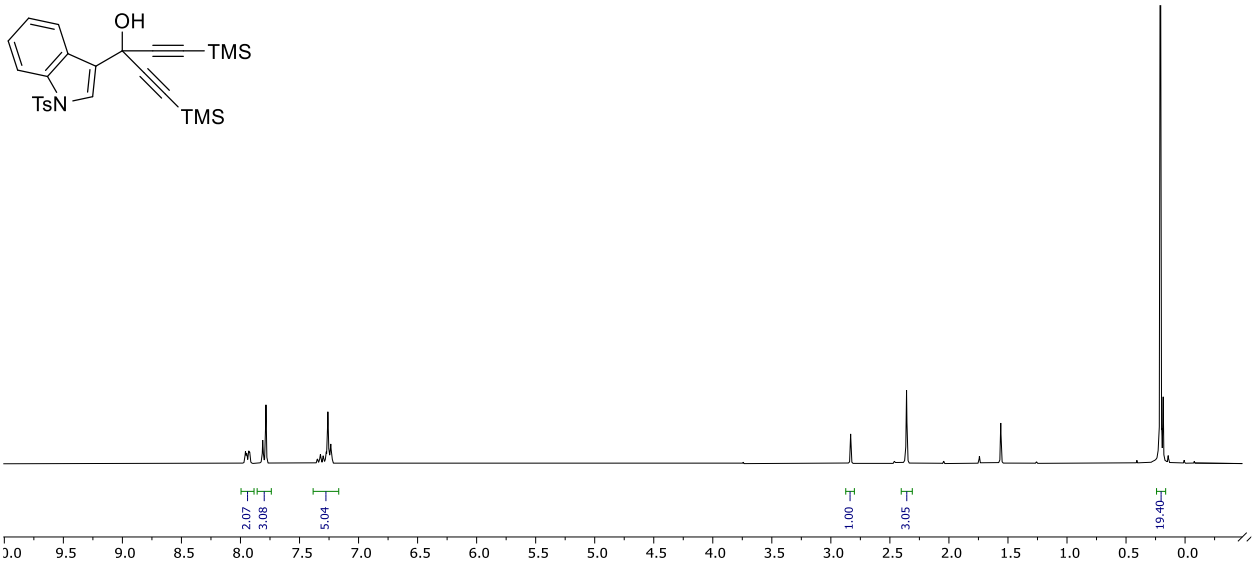
^{1}H NMR (300 MHz, $CDCl_3$) of compound **74b**



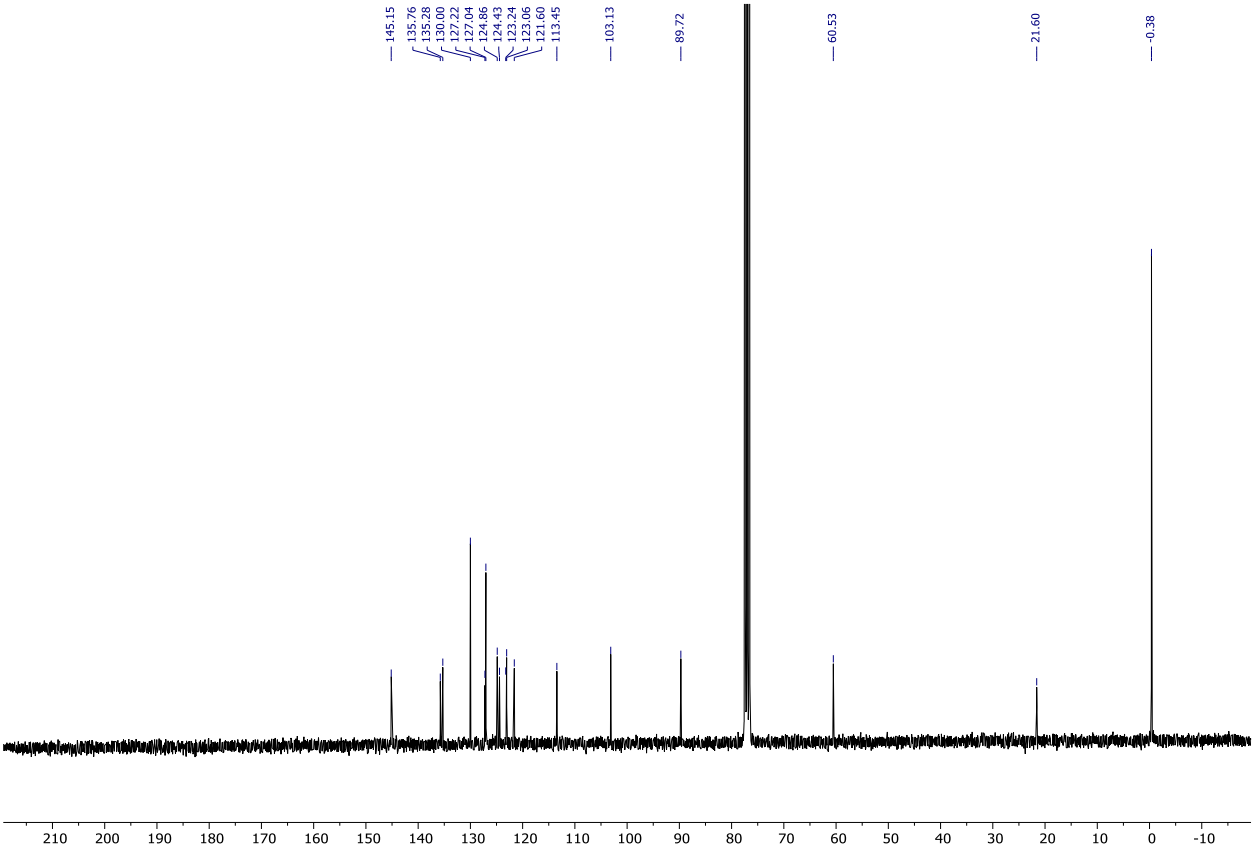
^{1}H NMR (300 MHz, $CDCl_3$) of compound **74a**



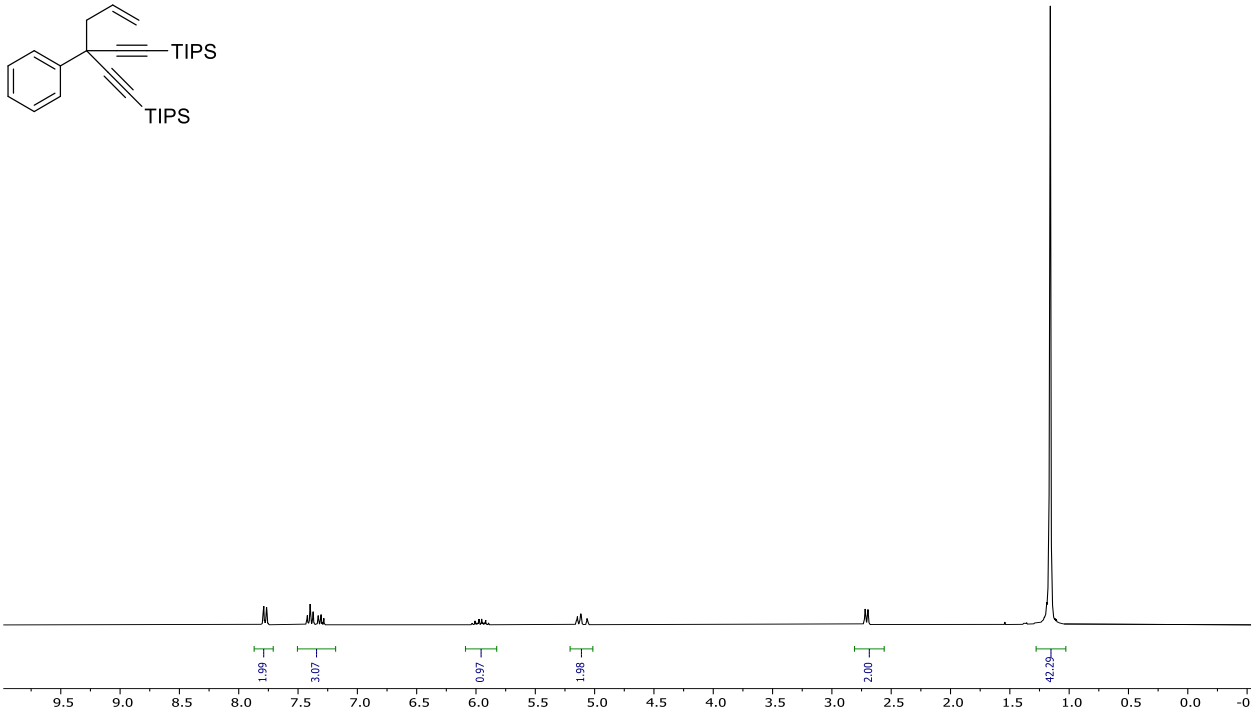
^{13}C NMR (75 MHz, $CDCl_3$) of compound **74a**



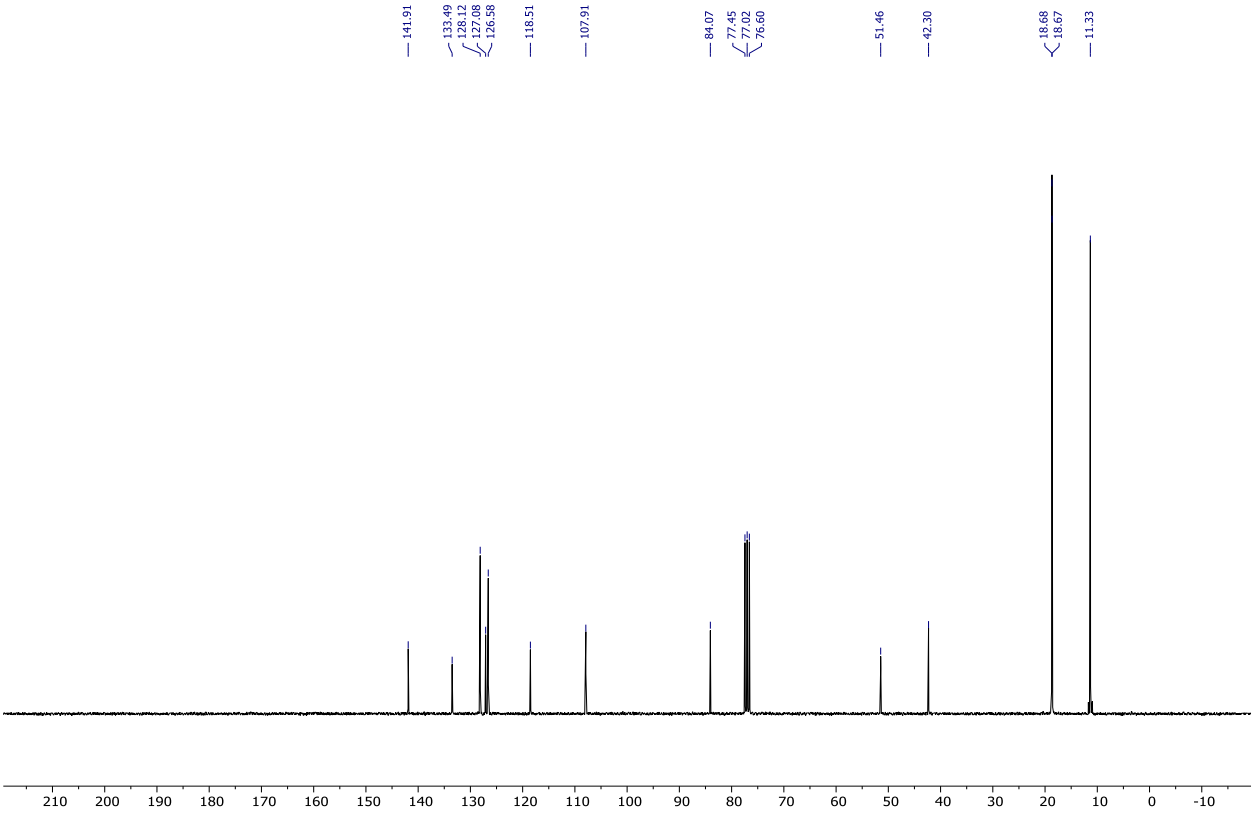
^{1}H NMR (300 MHz, $CDCl_3$) of compound **74f**



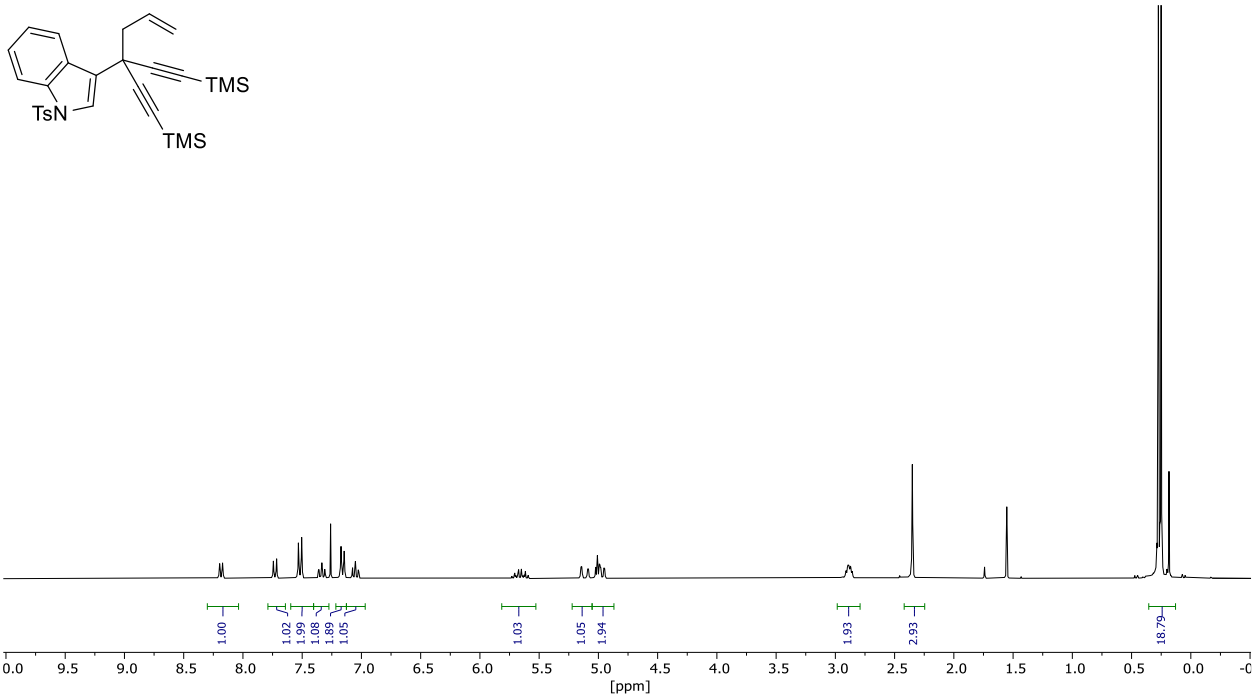
^{13}C NMR (75 MHz, $CDCl_3$) of compound **74f**



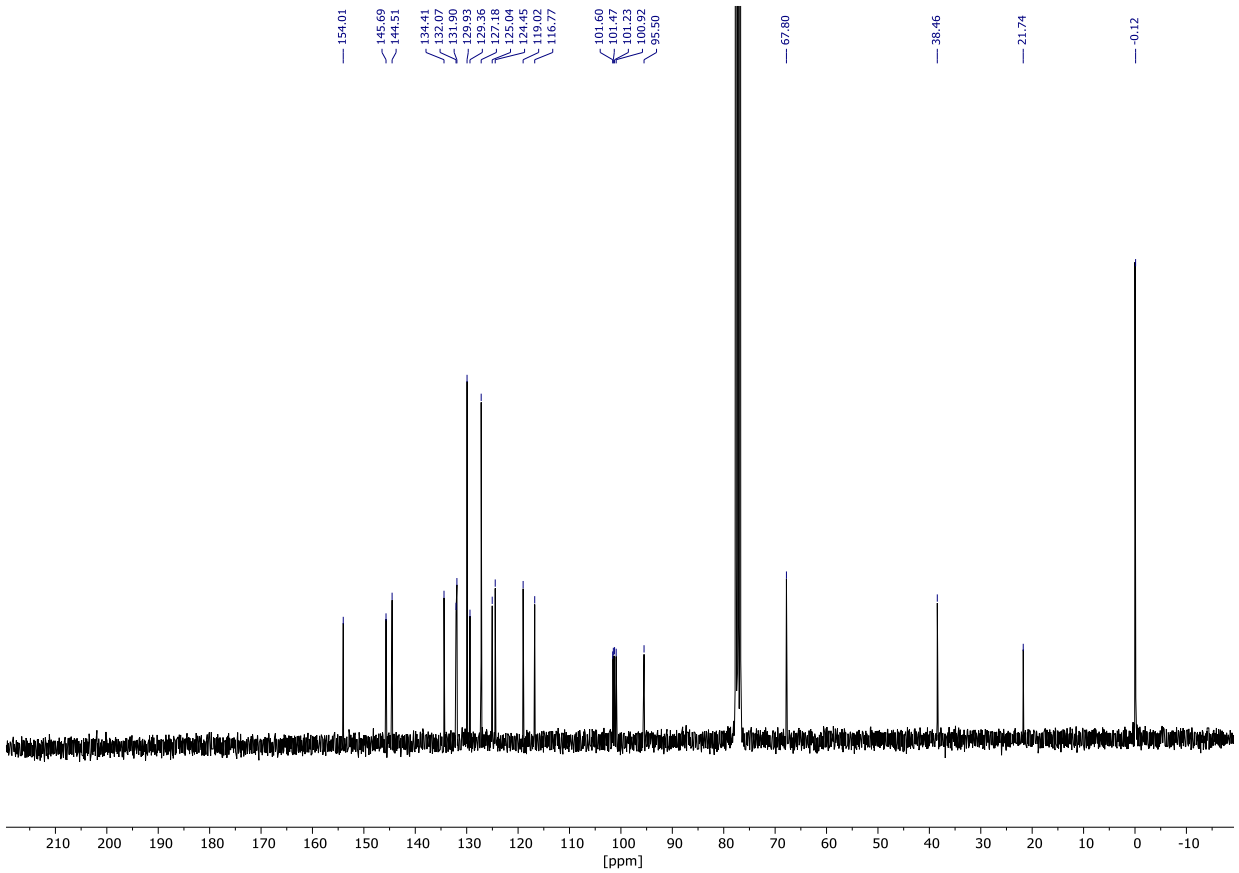
^{1}H NMR (300 MHz, $CDCl_3$) of compound **96a**



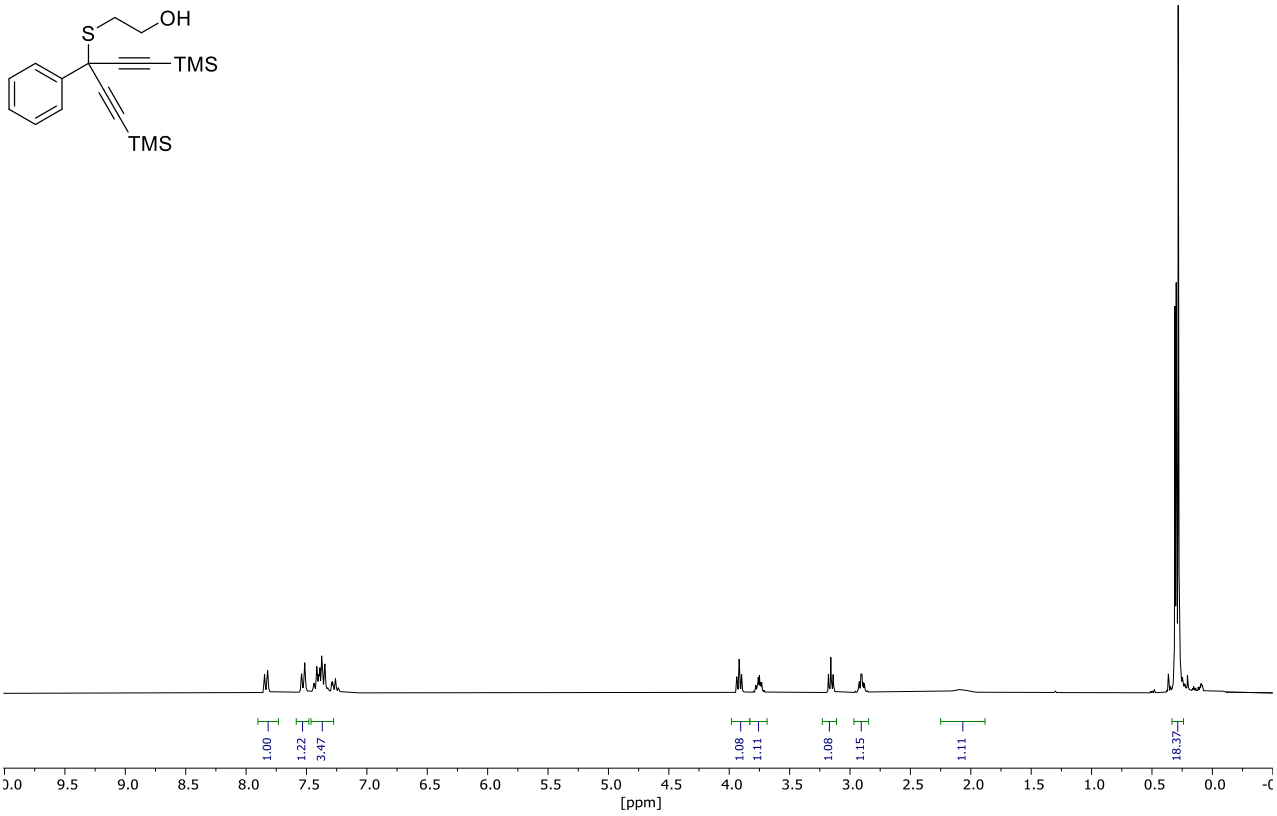
^{13}C NMR (75 MHz, $CDCl_3$) of compound **96a**



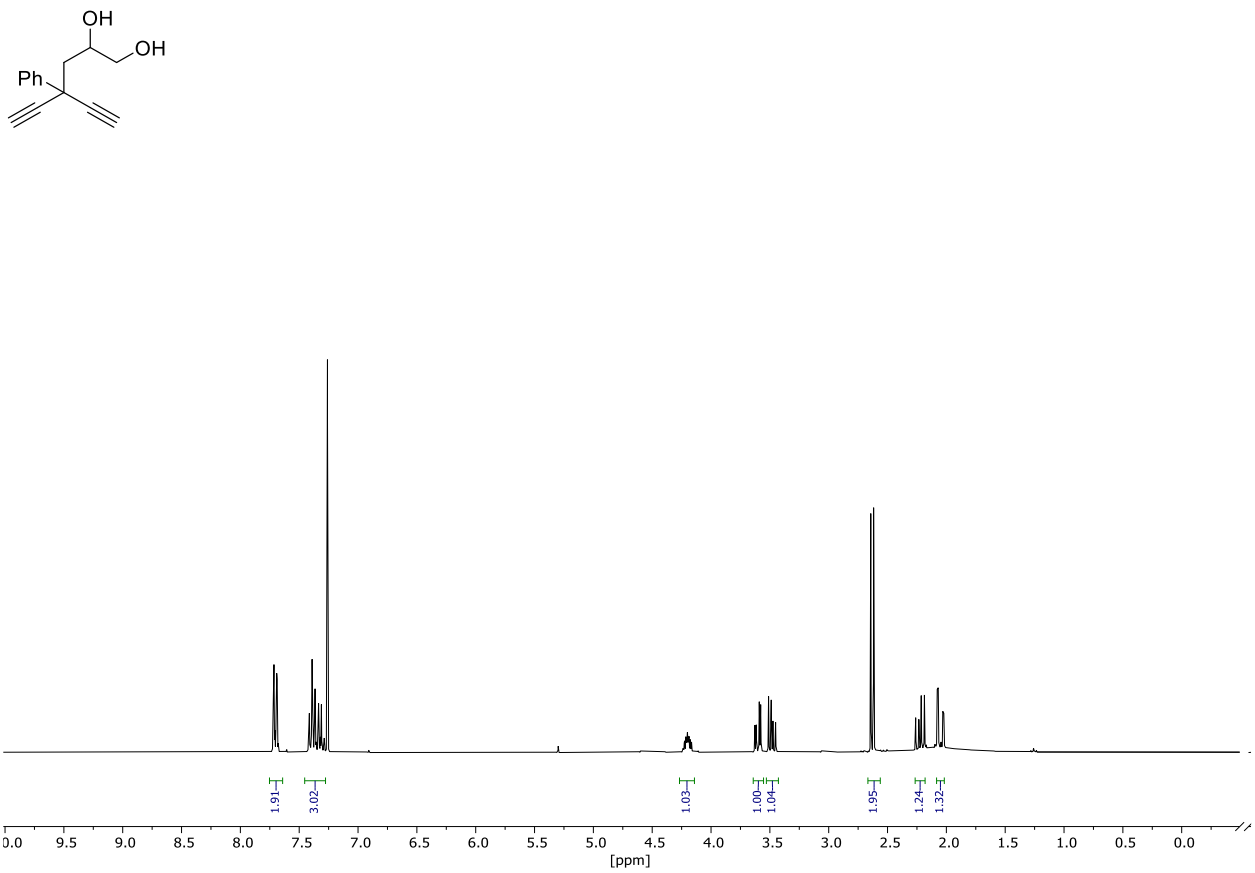
^{1}H NMR (300 MHz, $CDCl_3$) of compound **96f**



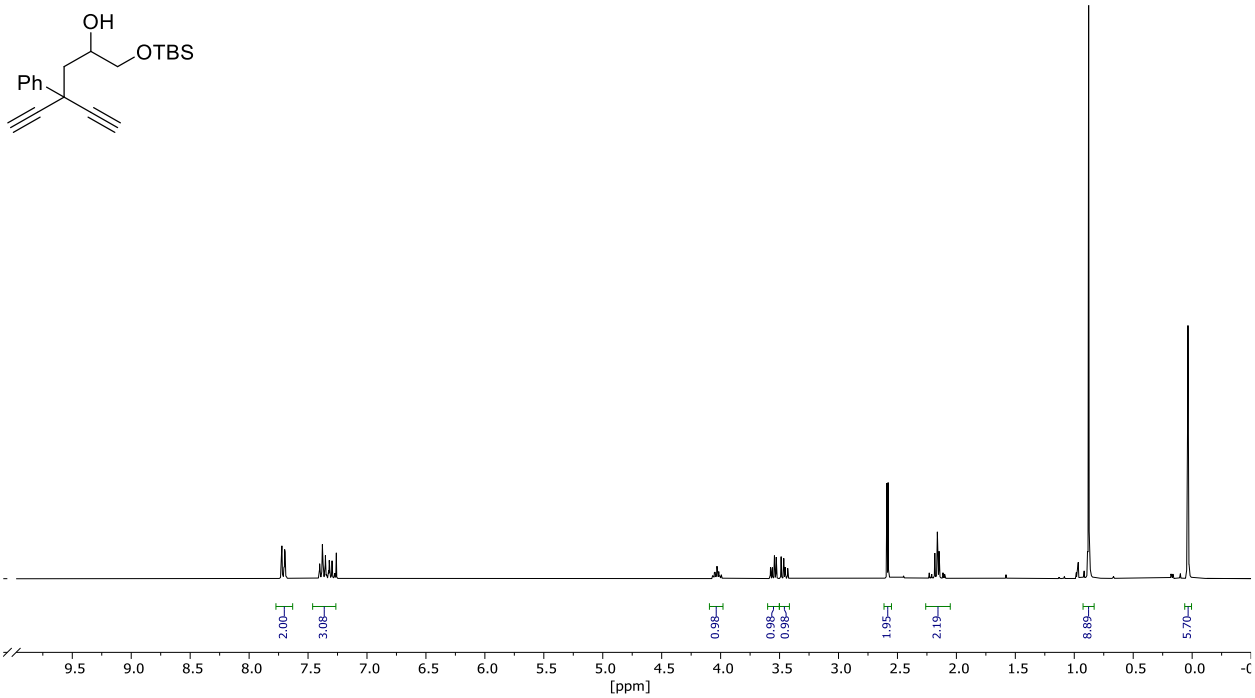
^{13}C NMR (75 MHz, $CDCl_3$) of compound **96f**



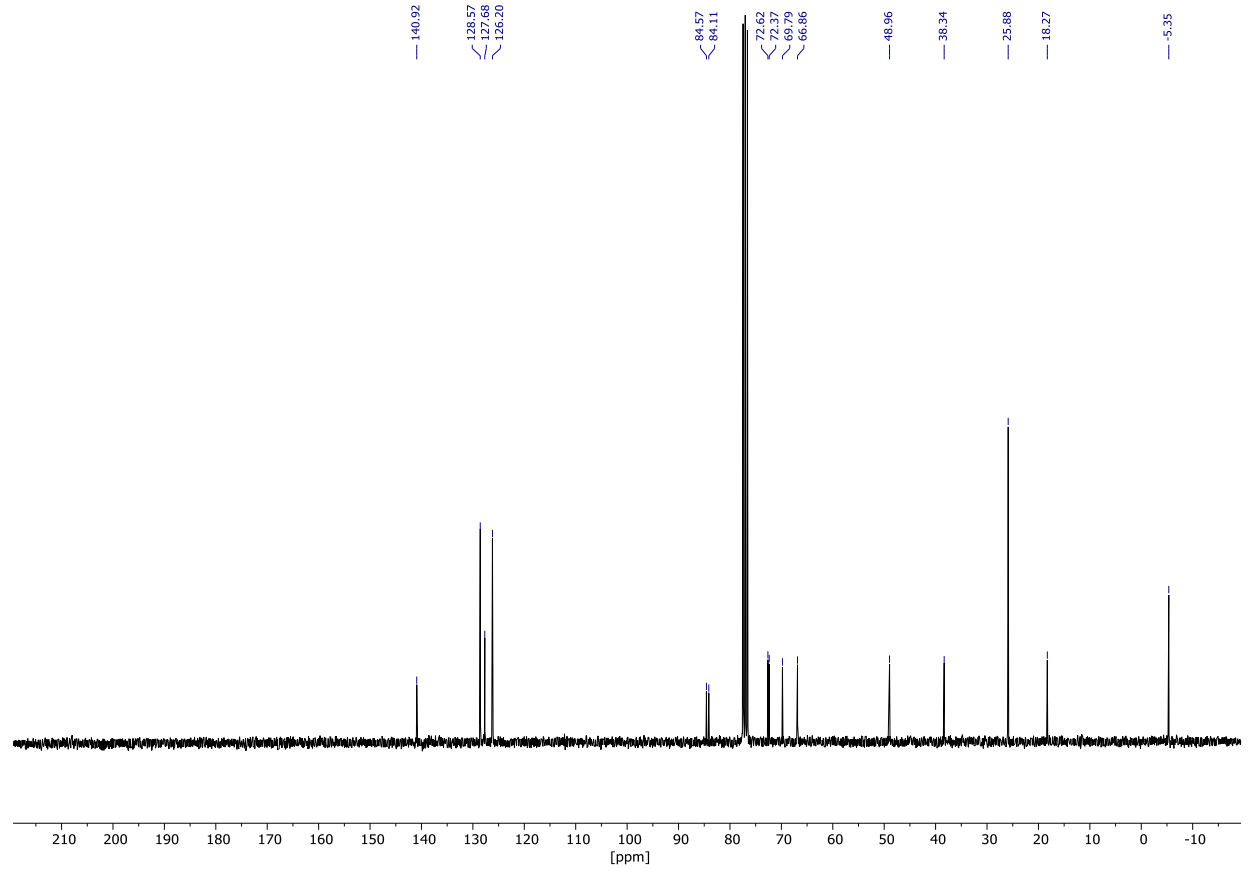
^{1}H NMR (300 MHz, $CDCl_3$) of compound **97**



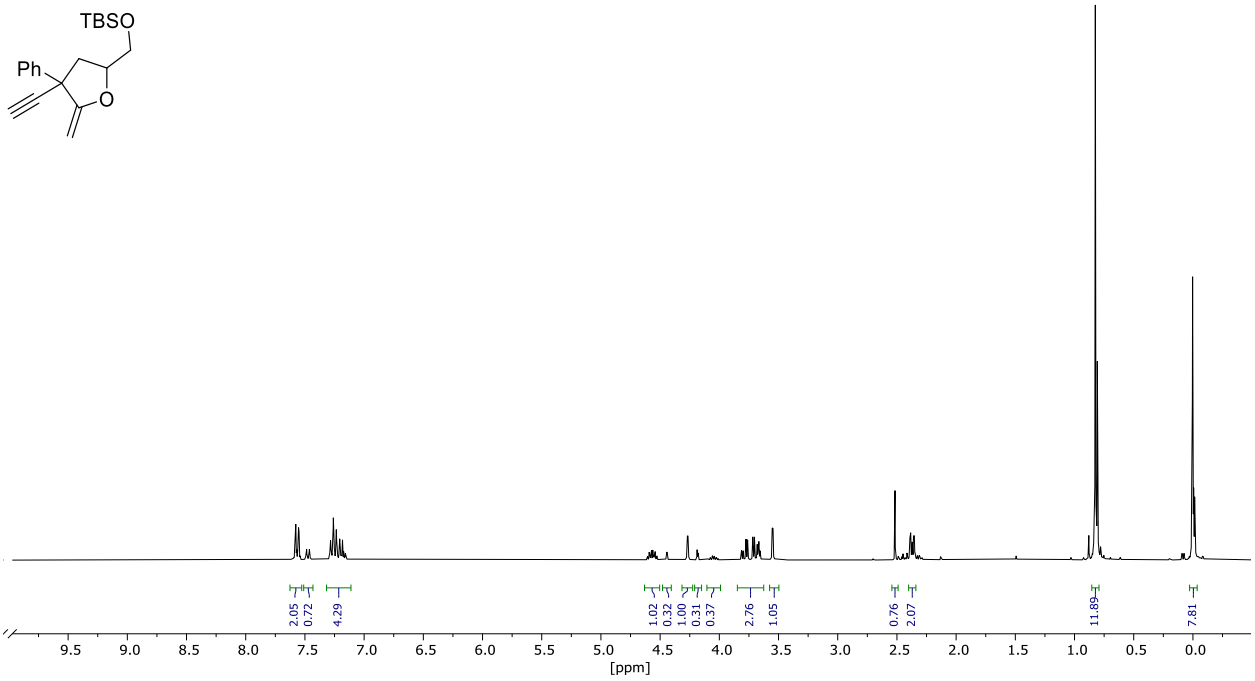
^{1}H NMR (300 MHz, $CDCl_3$) compound **120a**



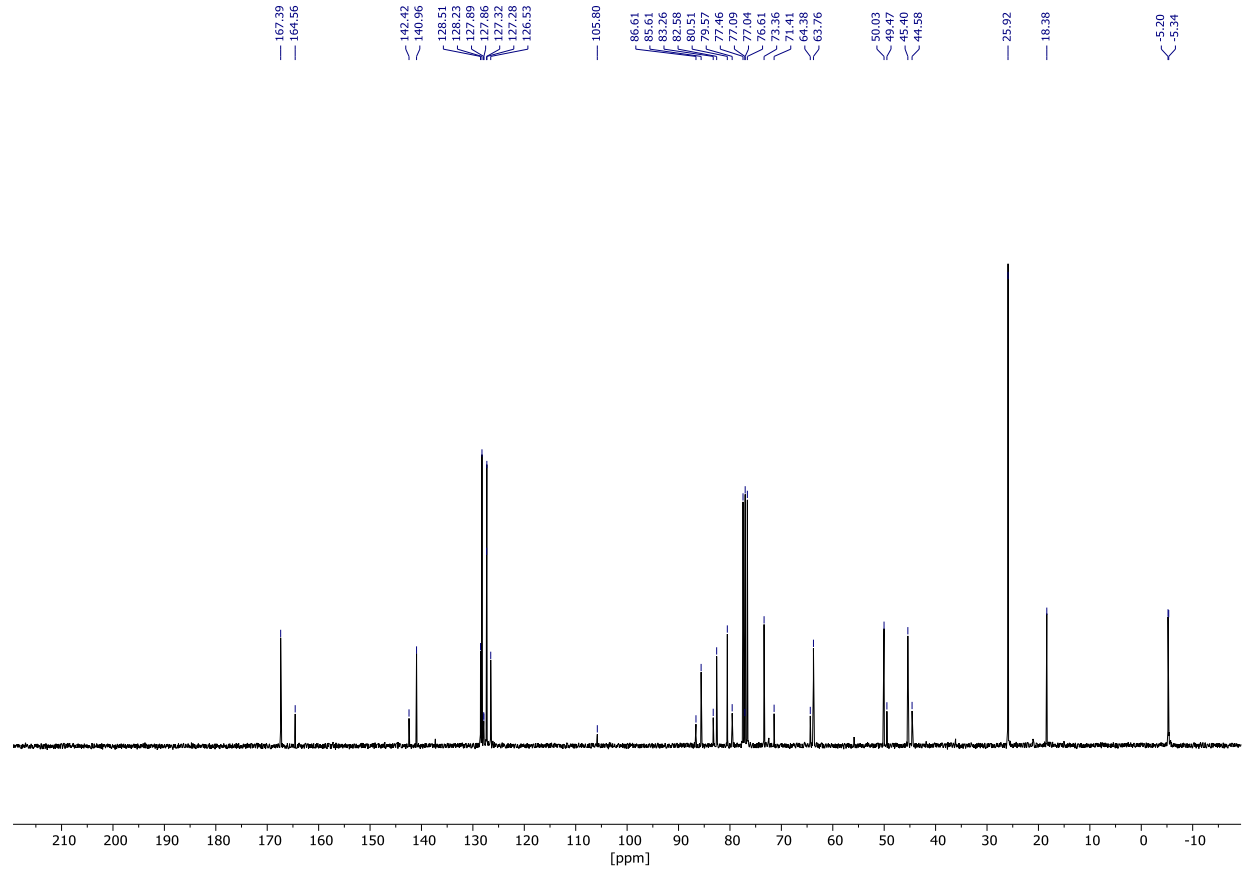
^{1}H NMR (300 MHz, $CDCl_3$) compound **120b**



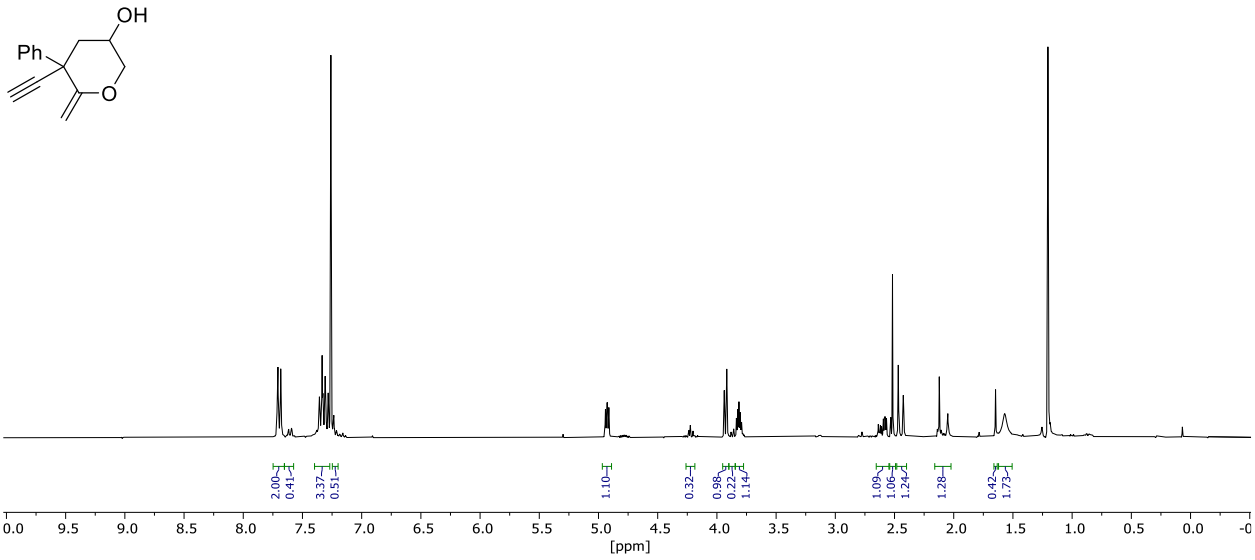
^{13}C NMR (75 MHz, $CDCl_3$) of compound **120b**



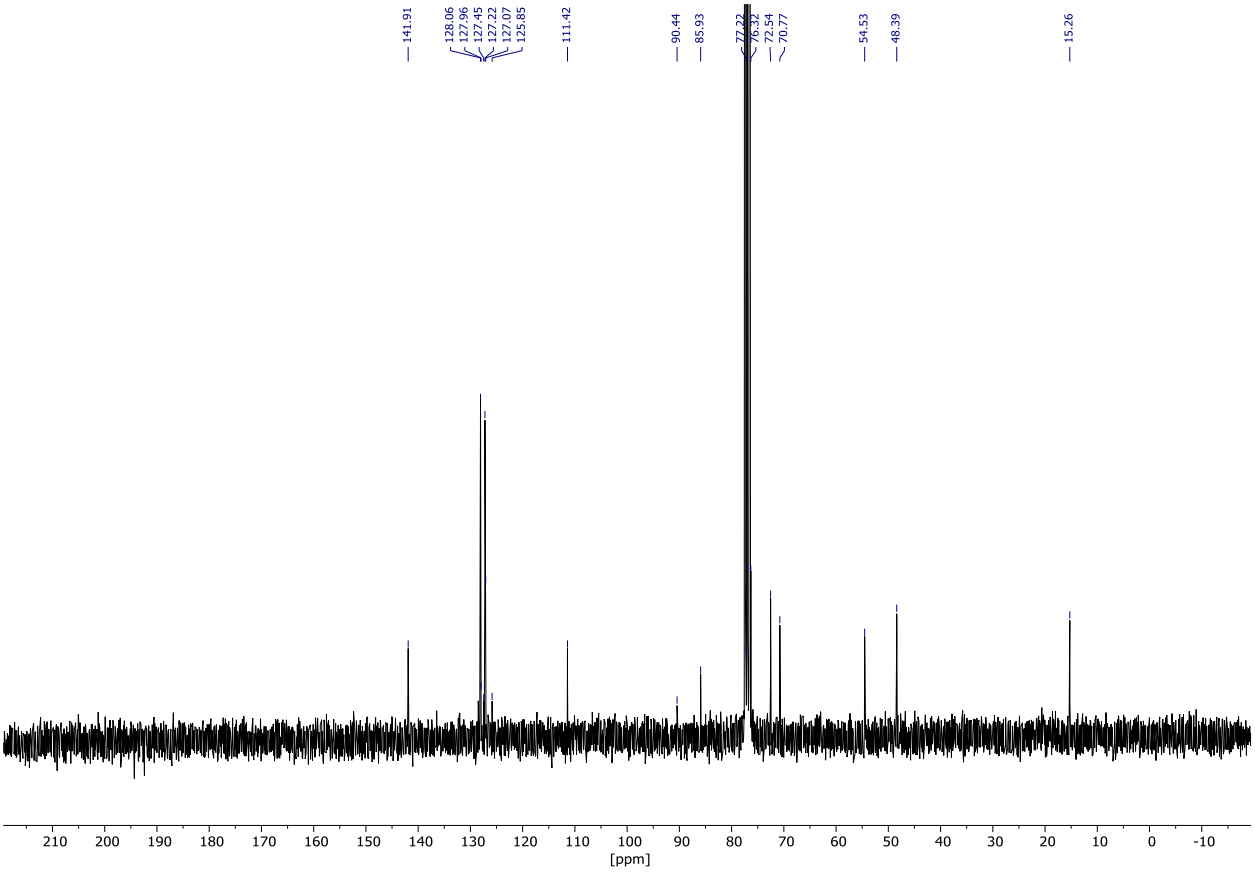
^{1}H NMR (300 MHz, $CDCl_3$) of compound **122b**



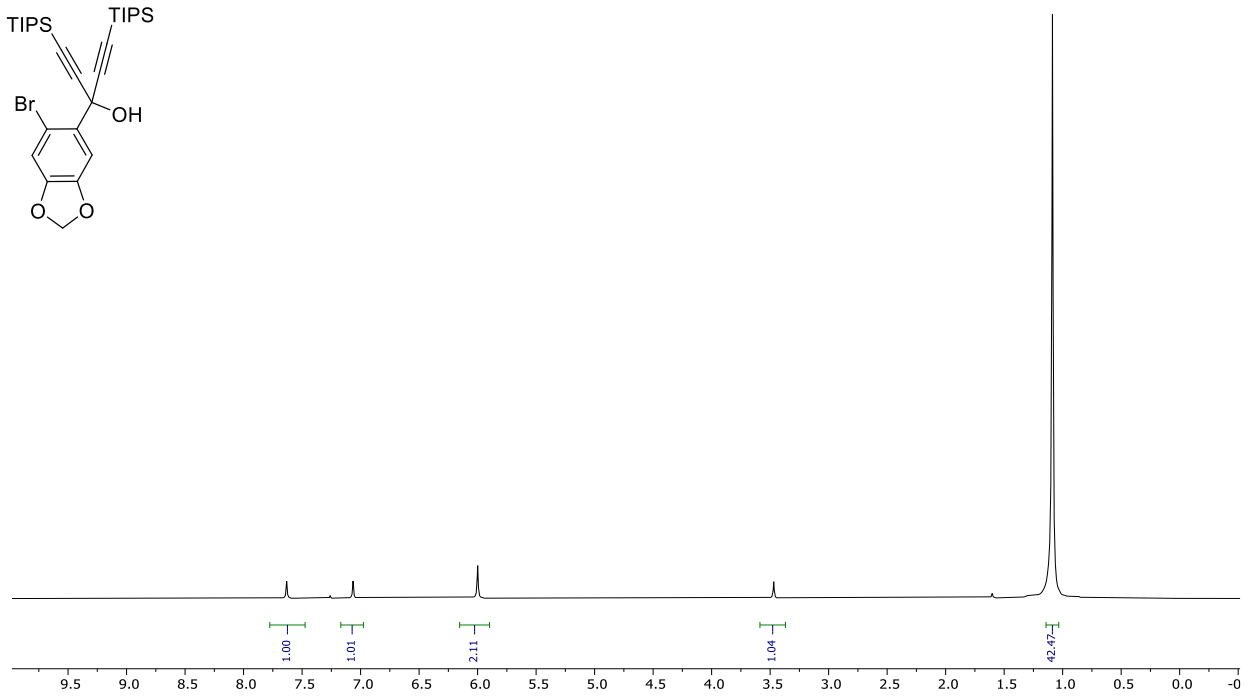
^{13}C NMR (75 MHz, $CDCl_3$) of compound **122b**



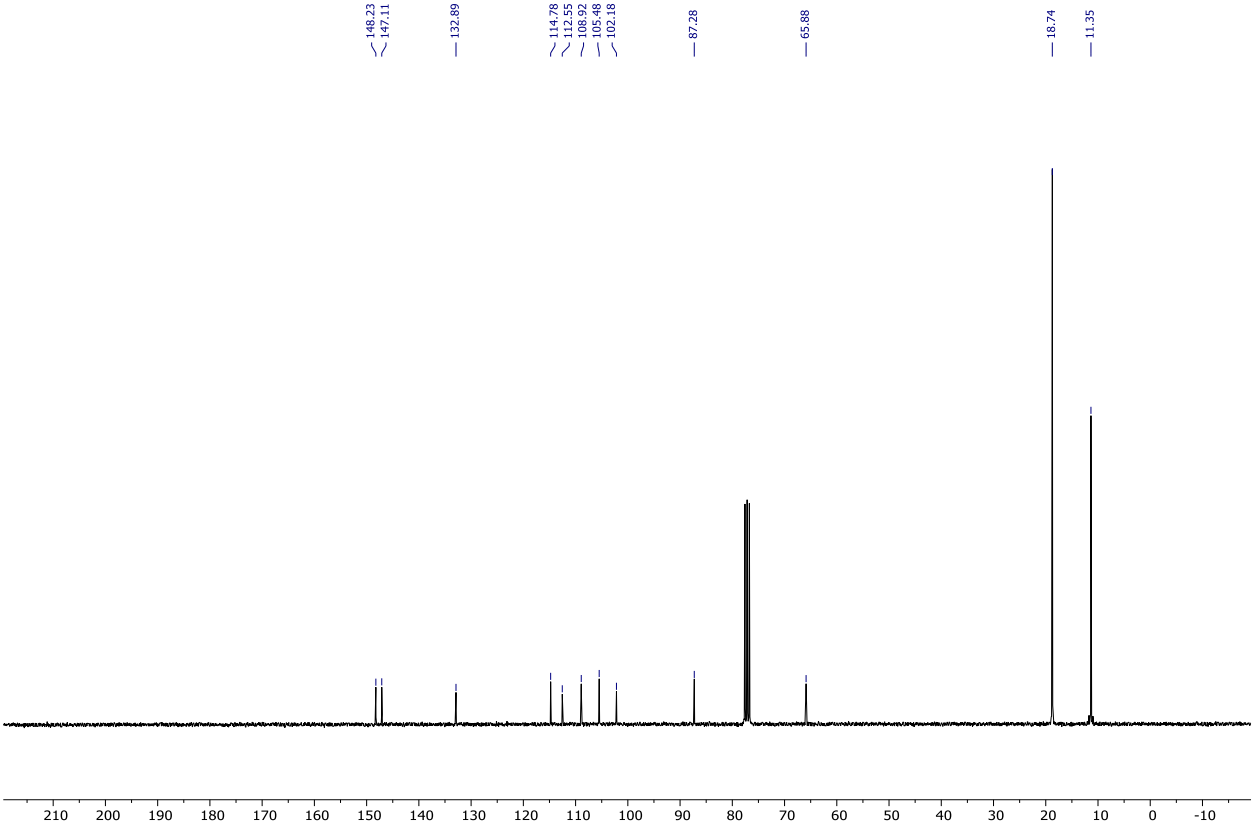
^{1}H NMR (300 MHz, $CDCl_3$) of compound **121a**



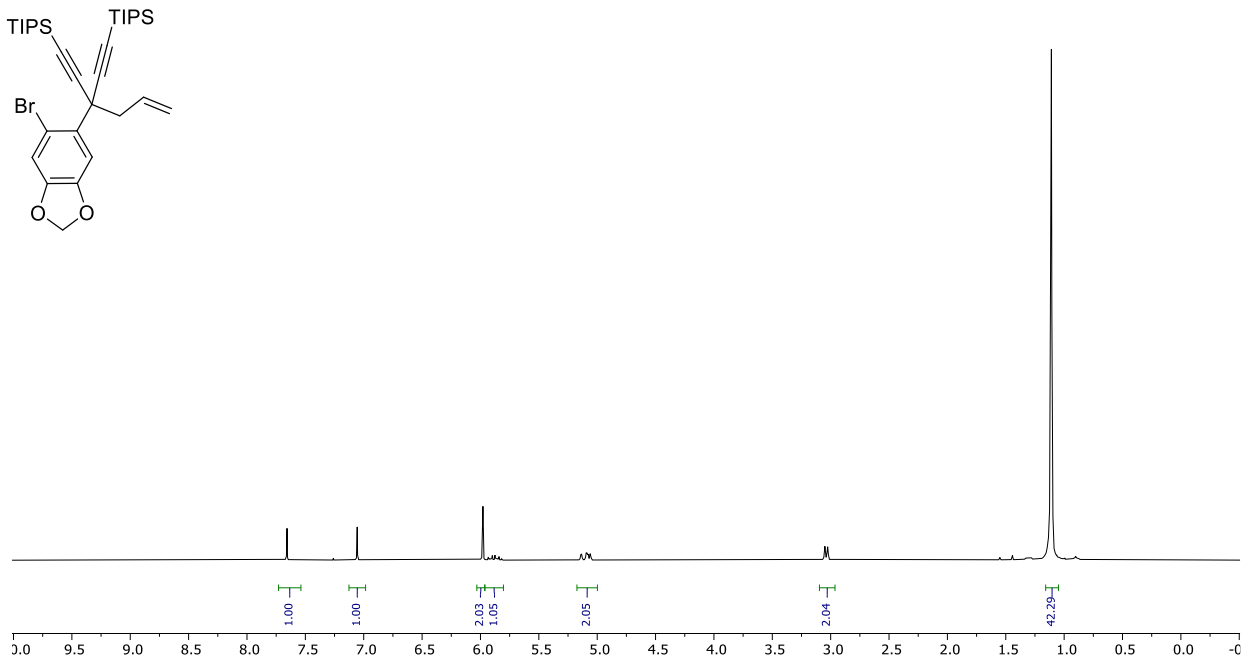
^{13}C NMR (75 MHz, $CDCl_3$) of compound **121a**



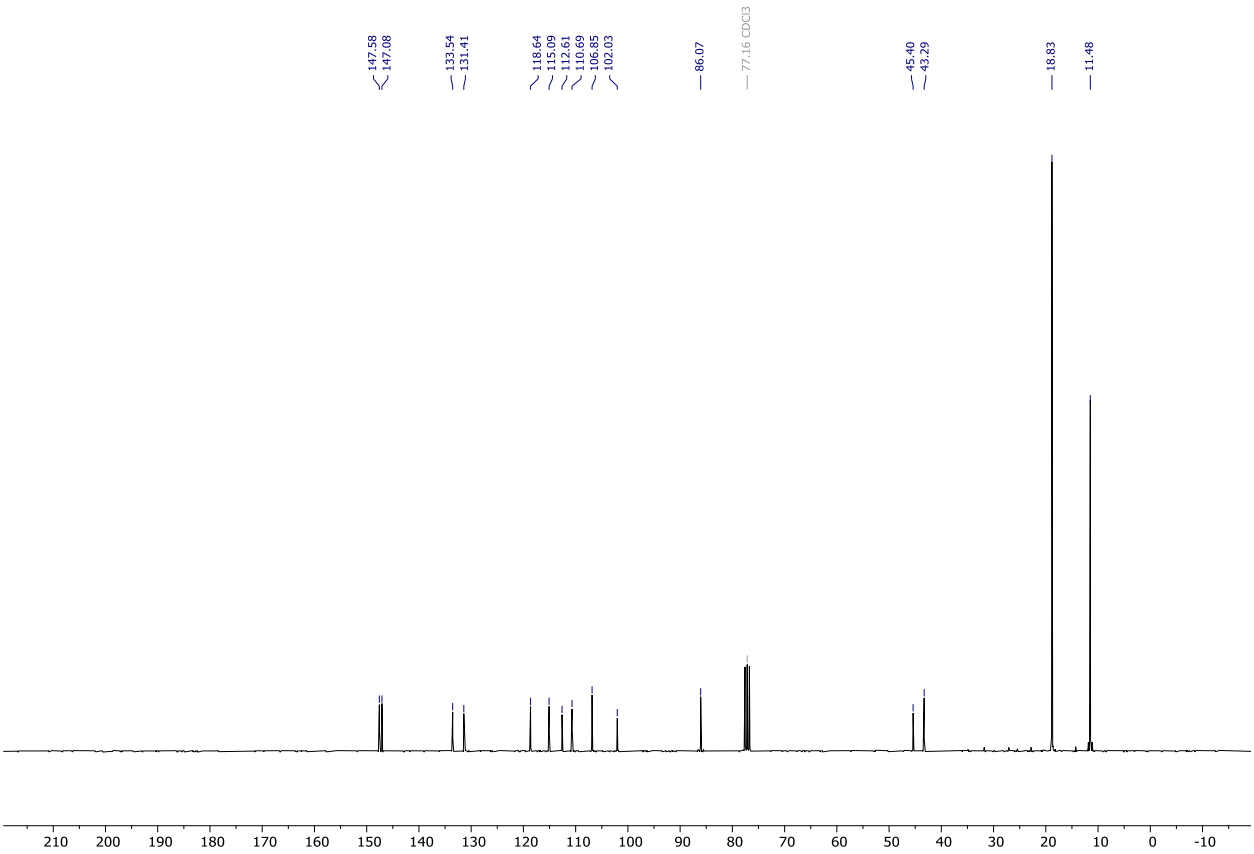
^{1}H NMR (300 MHz, $CDCl_3$) of compound **74d**



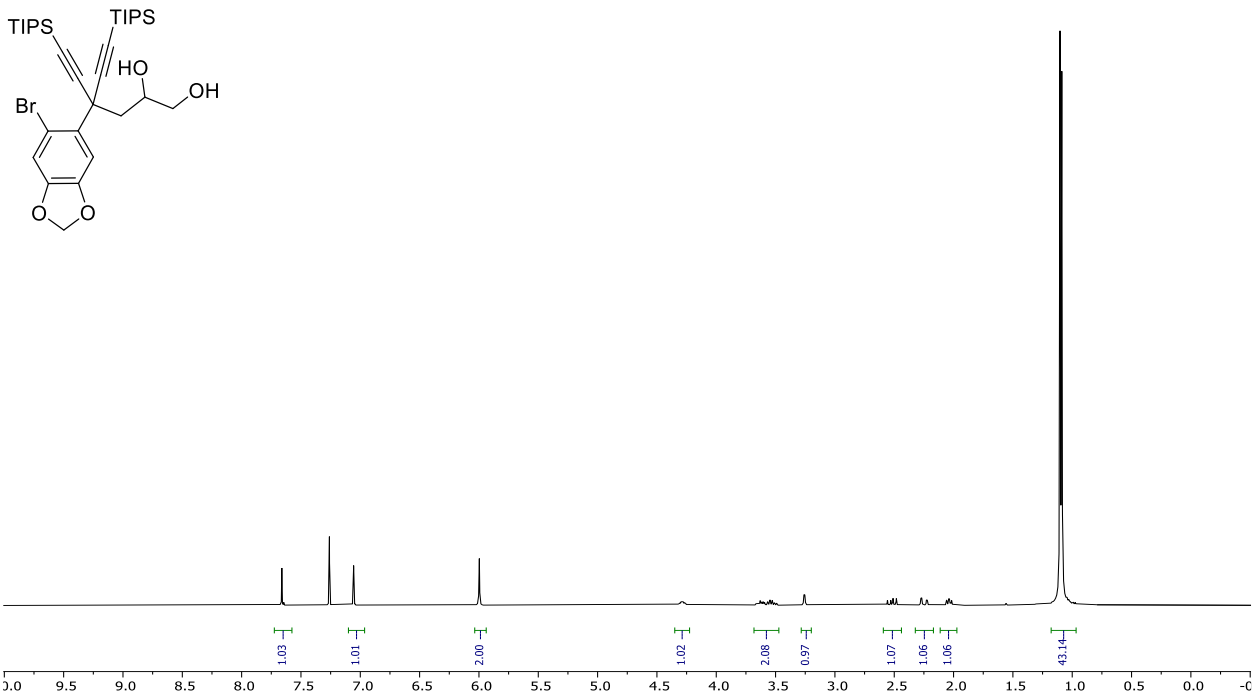
^{13}C NMR (75 MHz, $CDCl_3$) of compound **74d**



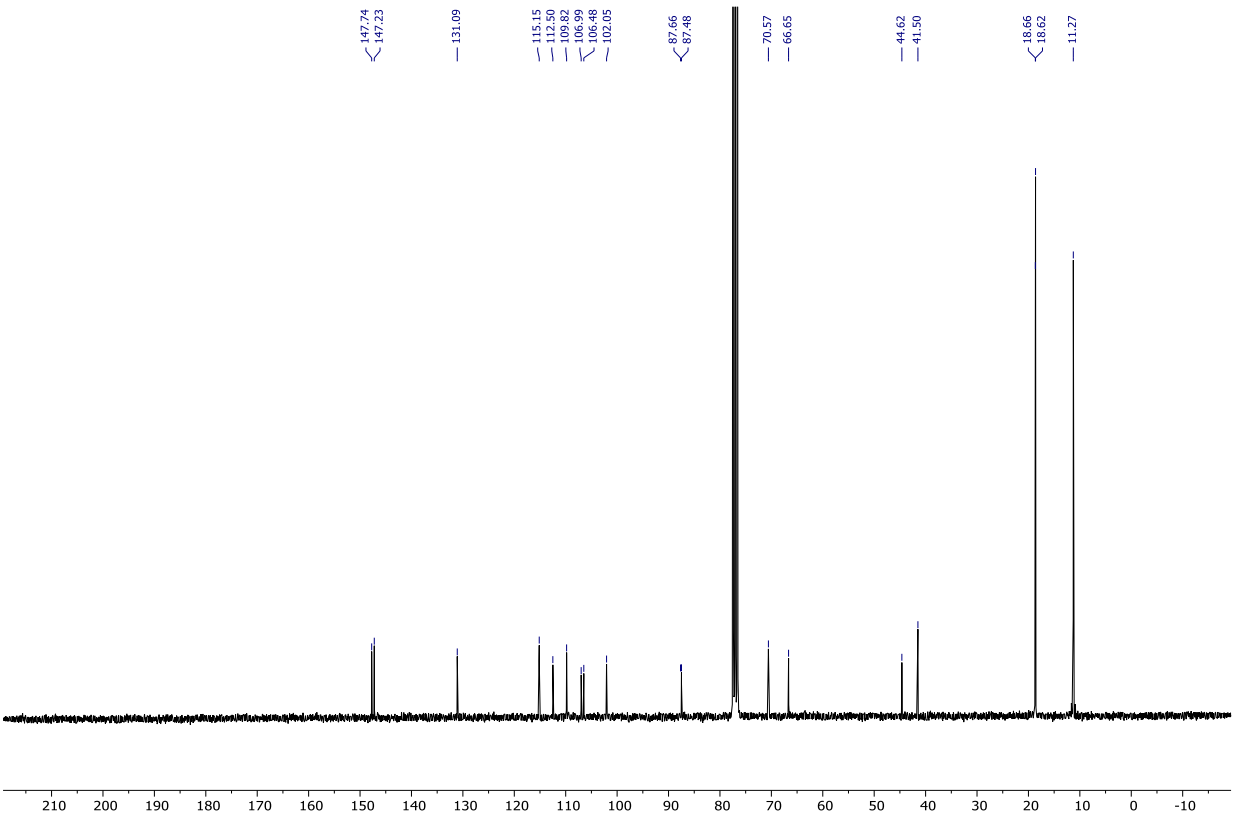
^{1}H NMR (300 MHz, $CDCl_3$) of compound **96d**



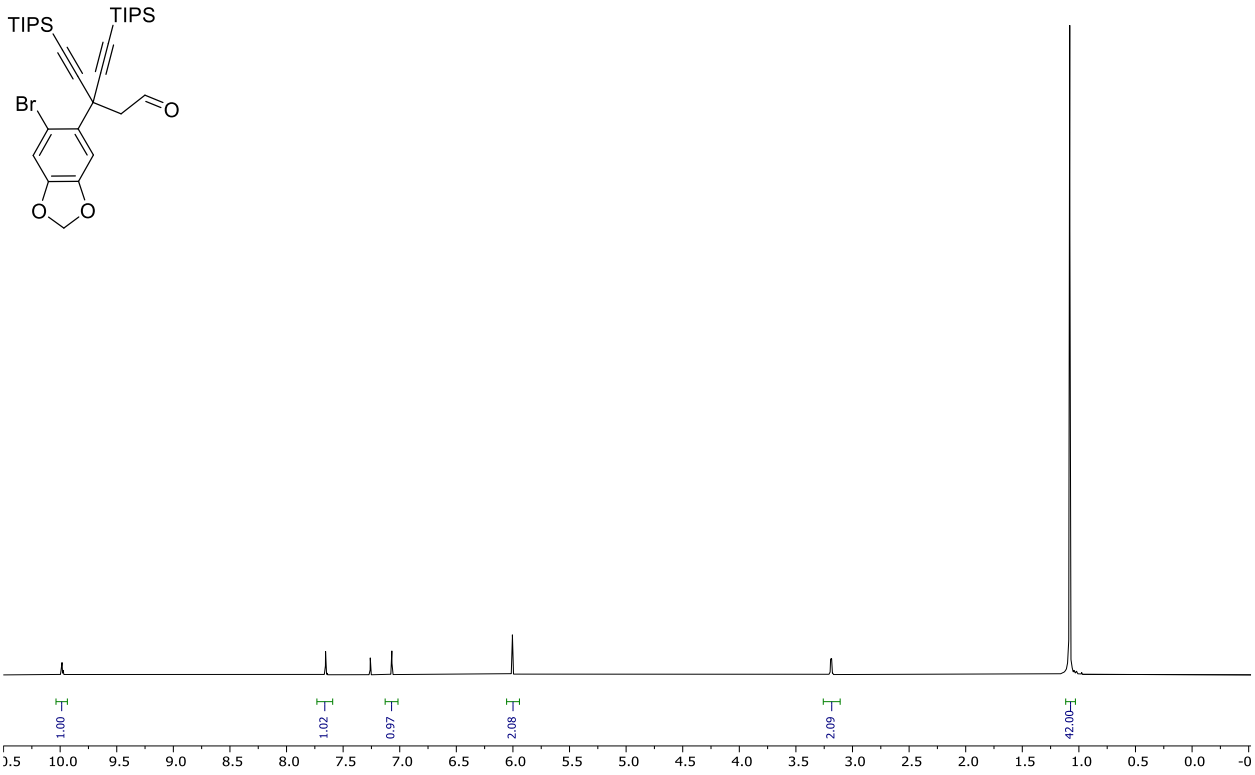
^{13}C NMR (75 MHz, $CDCl_3$) of compound **96d**



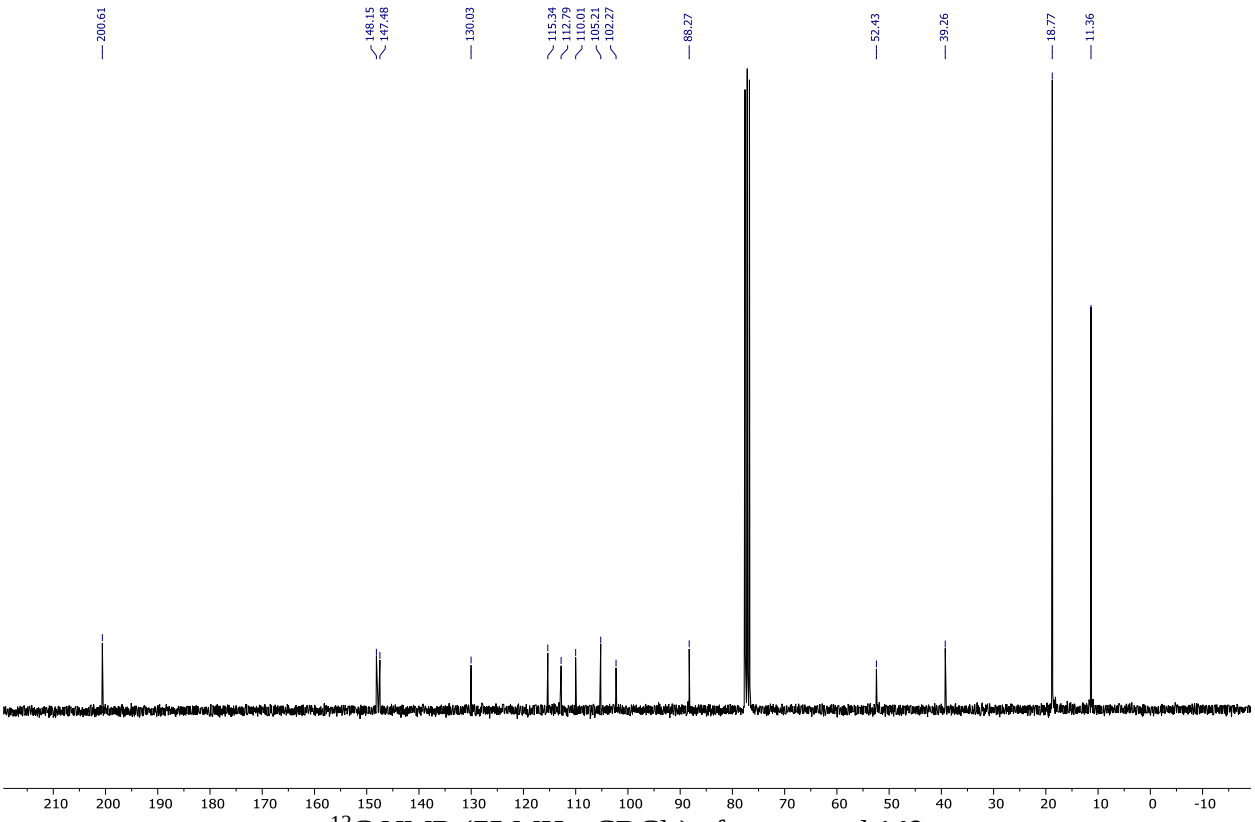
^{1}H NMR (300 MHz, $CDCl_3$) of **4-(6-bromobenzo[d][1,3]dioxol-5-yl)-6-(triisopropylsilyl)-4-((triisopropylsilyl)ethynyl)hex-5-yne-1,2-diol**



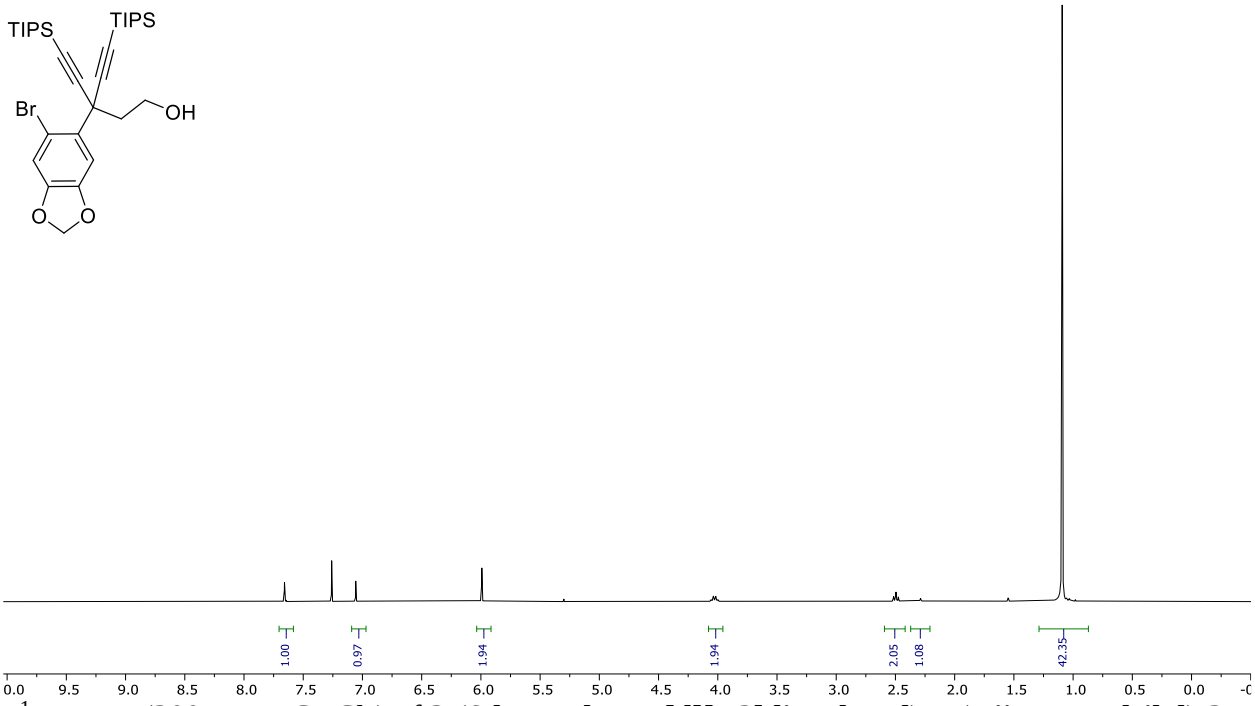
^{13}C NMR (75 MHz, $CDCl_3$) of **4-(6-bromobenzo[d][1,3]dioxol-5-yl)-6-(triisopropylsilyl)-4-((triisopropylsilyl)ethynyl)hex-5-yne-1,2-diol**



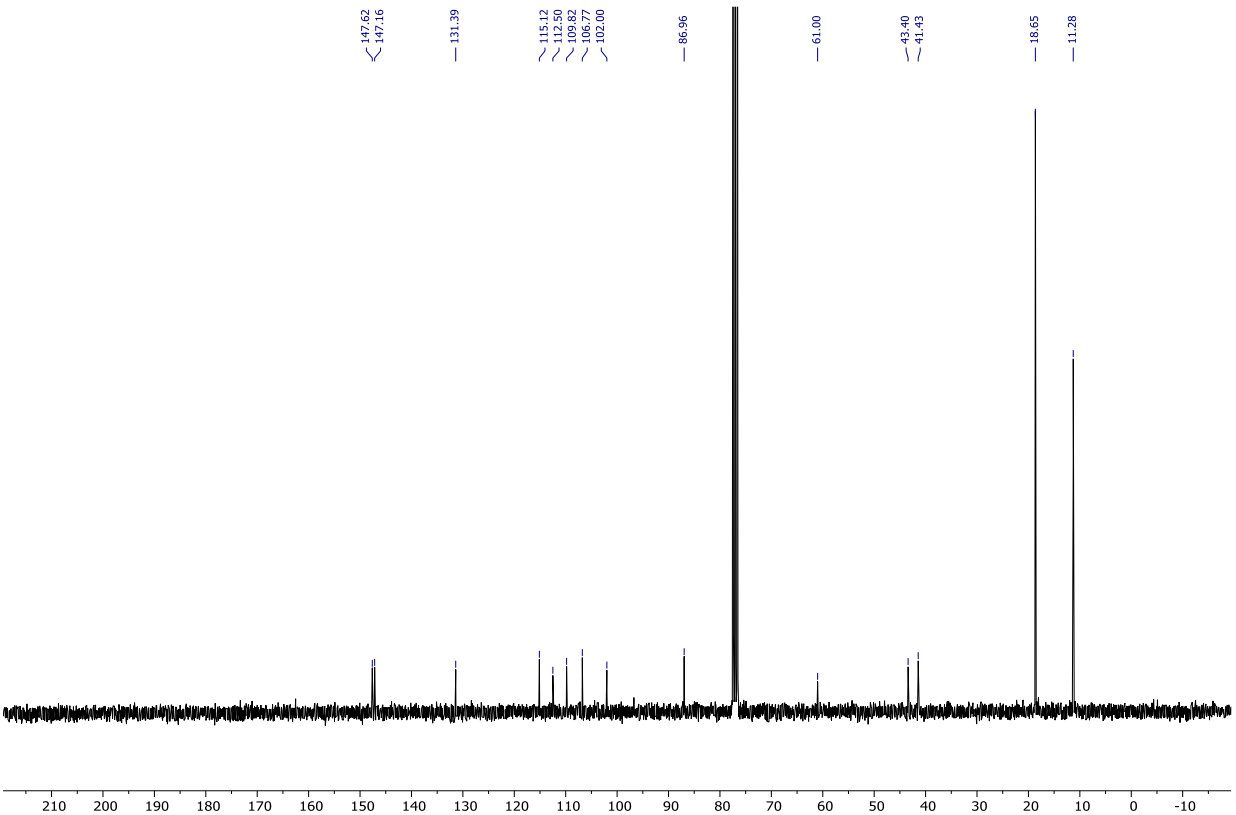
^{1}H NMR (300 MHz, $CDCl_3$) of compound **149**



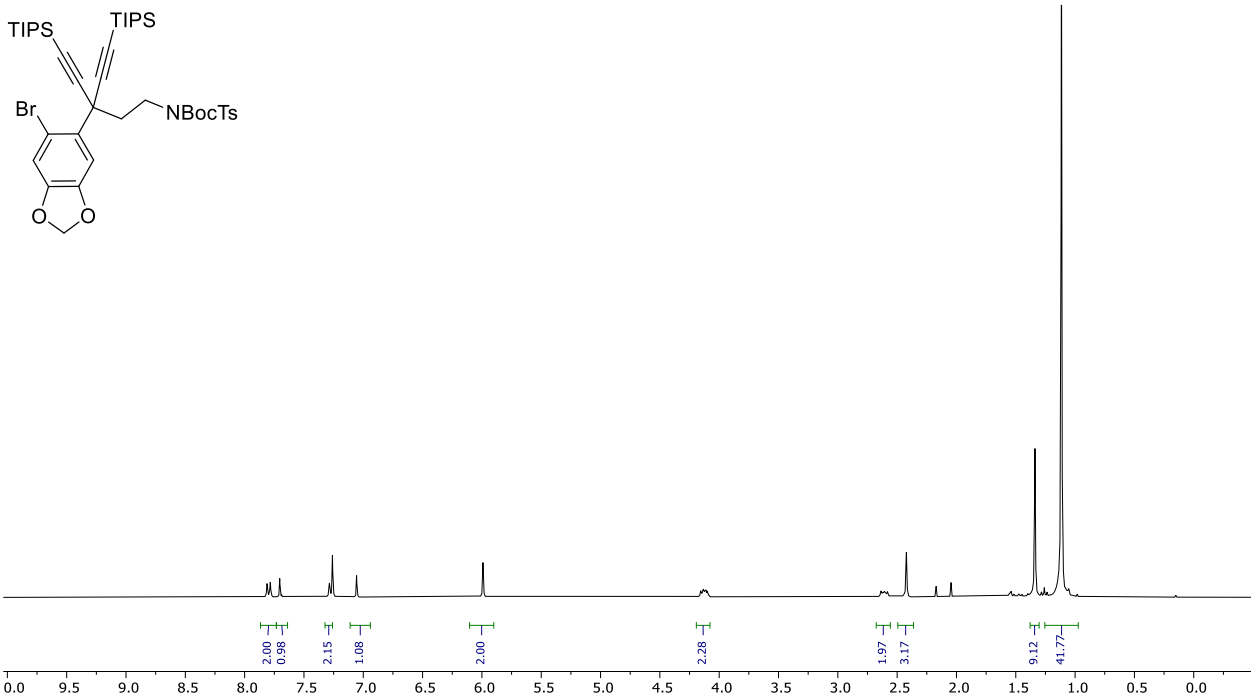
^{13}C NMR (75 MHz, $CDCl_3$) of compound **149**



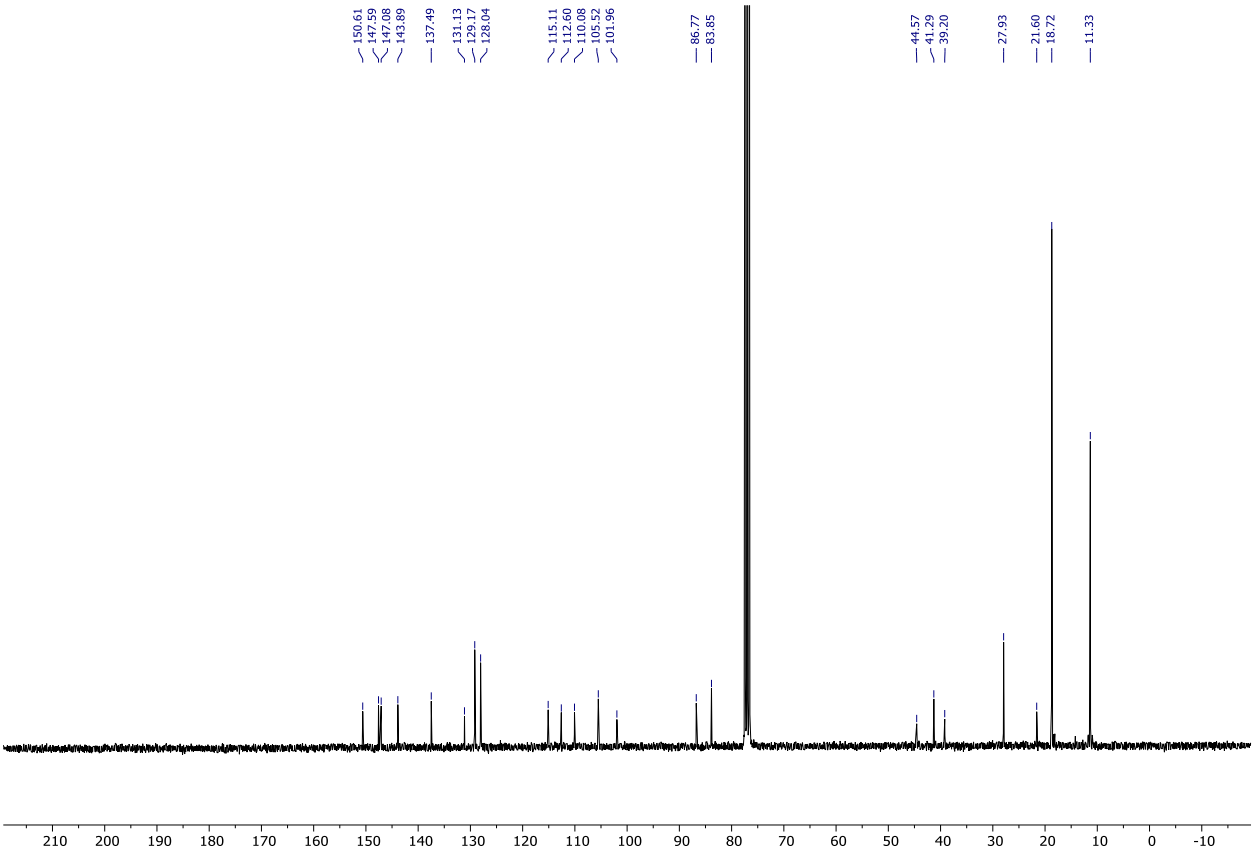
^{1}H NMR (300 MHz, $CDCl_3$) of **3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol**



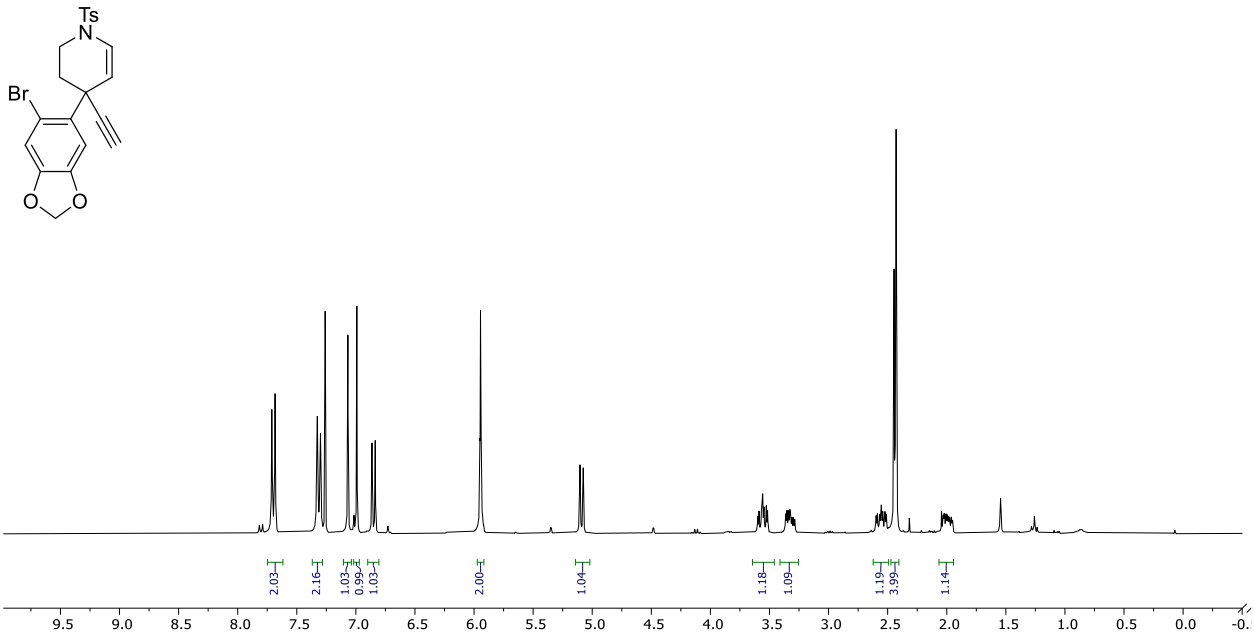
^{13}C NMR (75 MHz, $CDCl_3$) of **3-(6-bromobenzo[d][1,3]dioxol-5-yl)-5-(triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)pent-4-yn-1-ol**



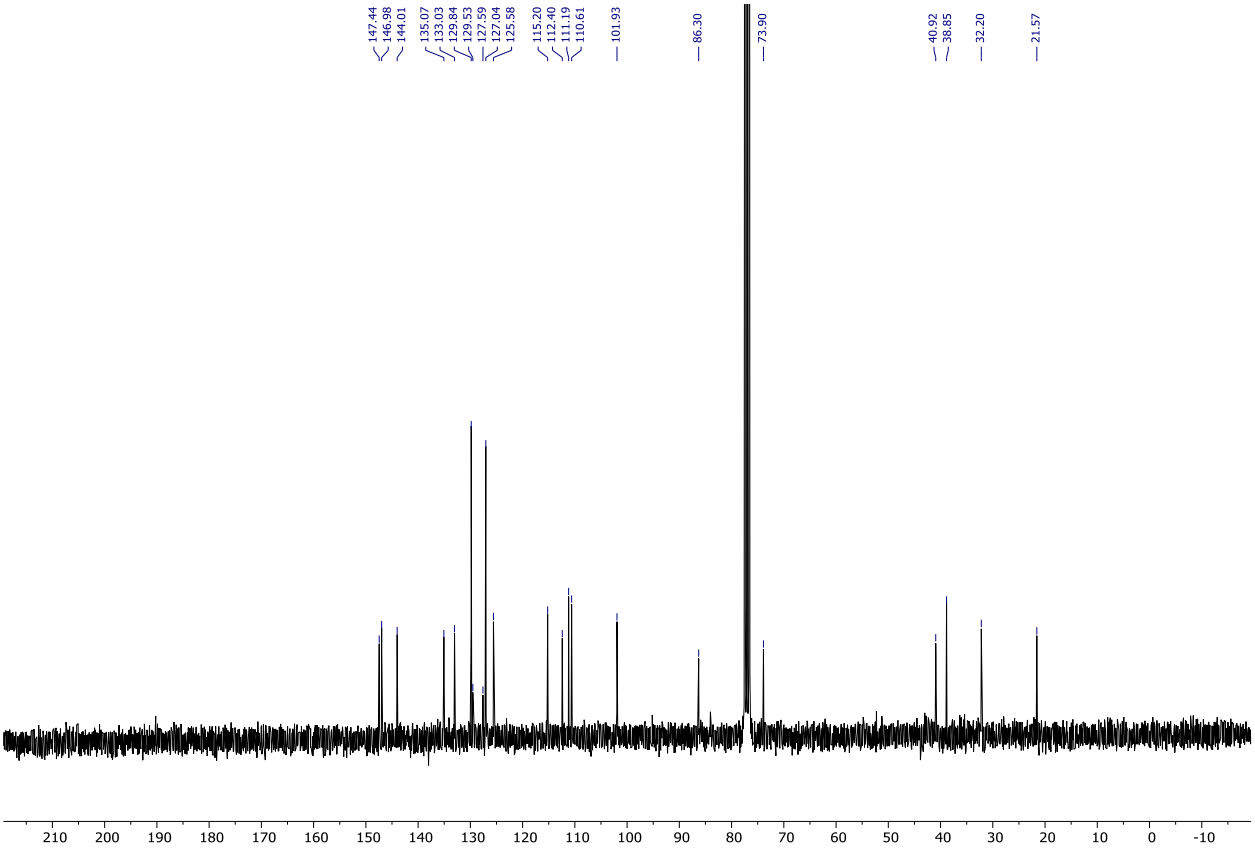
^{1}H NMR (300 MHz, $CDCl_3$) of compound **150**



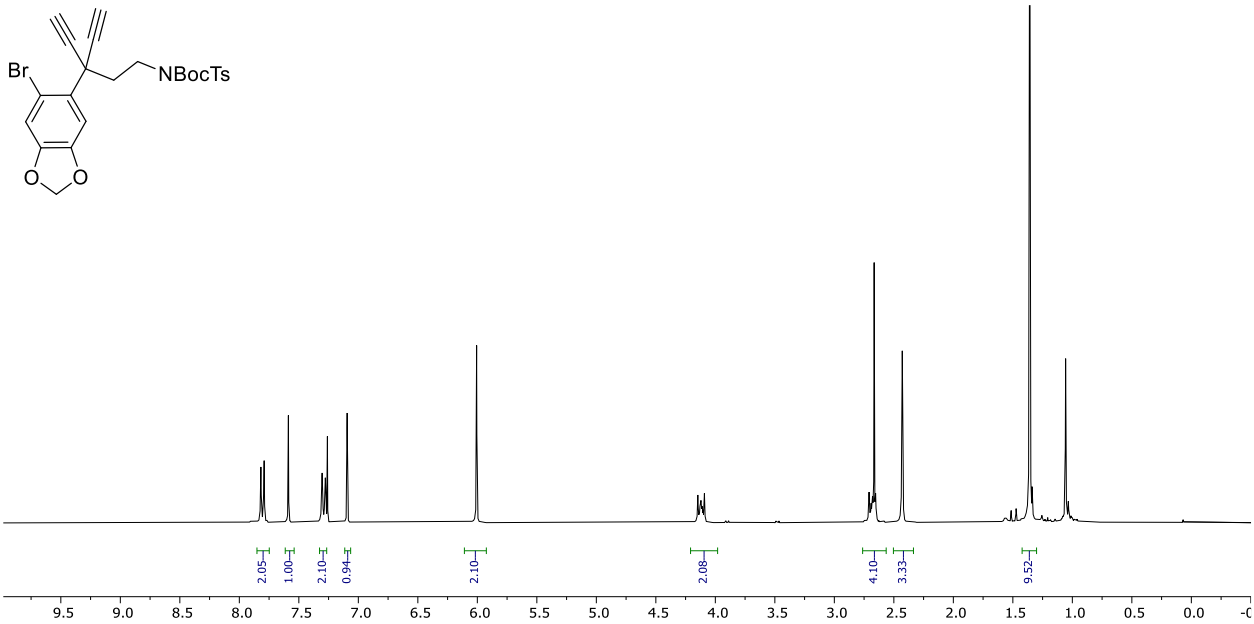
^{13}C NMR (75 MHz, $CDCl_3$) of compound **150**



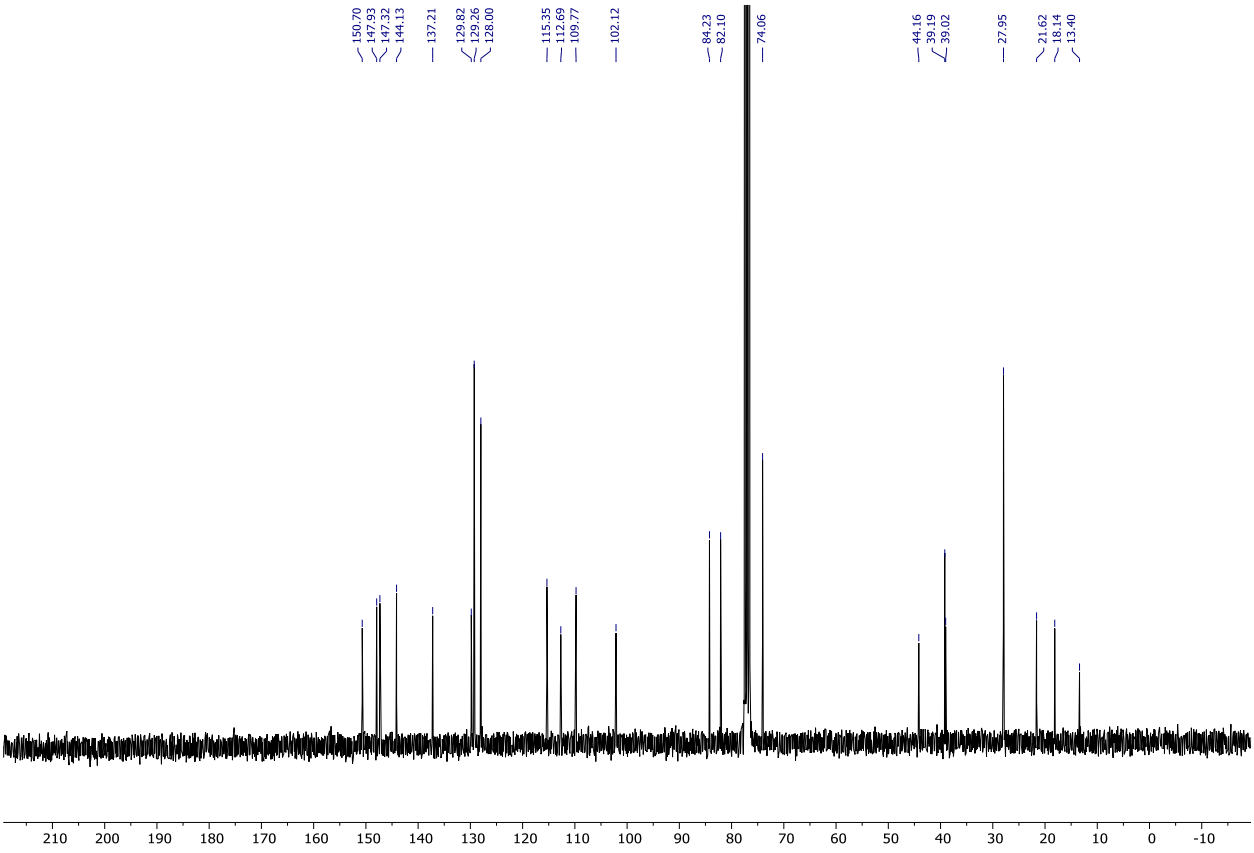
^{1}H NMR (300 MHz, $CDCl_3$) of compound **151**



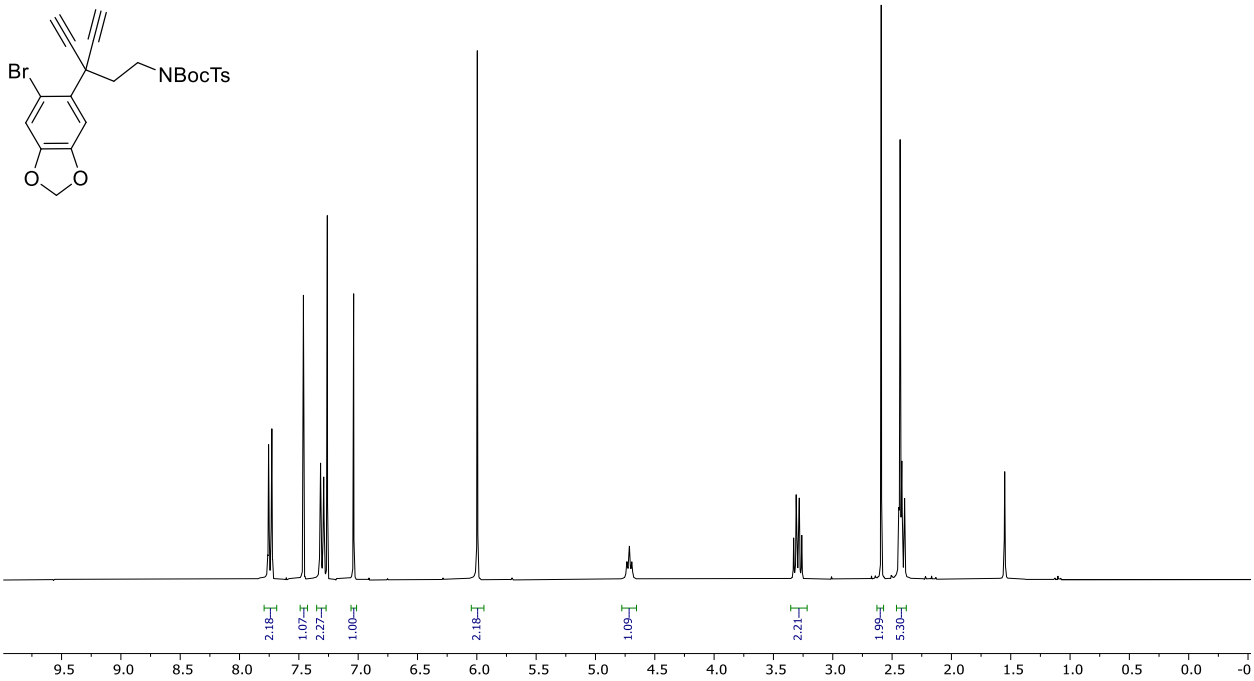
^{13}C NMR (75 MHz, $CDCl_3$) of compound **151**



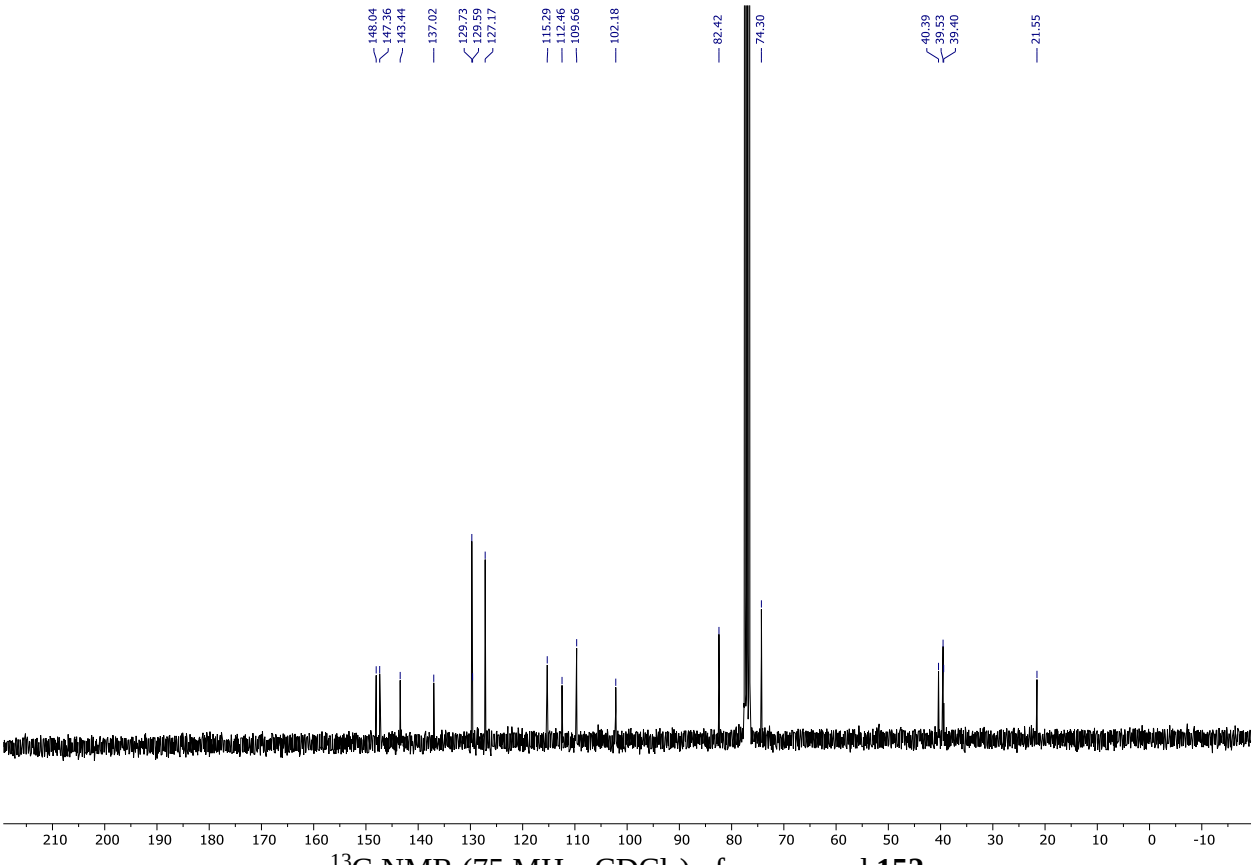
^{1}H NMR (300 MHz, $CDCl_3$) of ***tert*-butyl (3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)(toluenesulfonyl)carbamate**



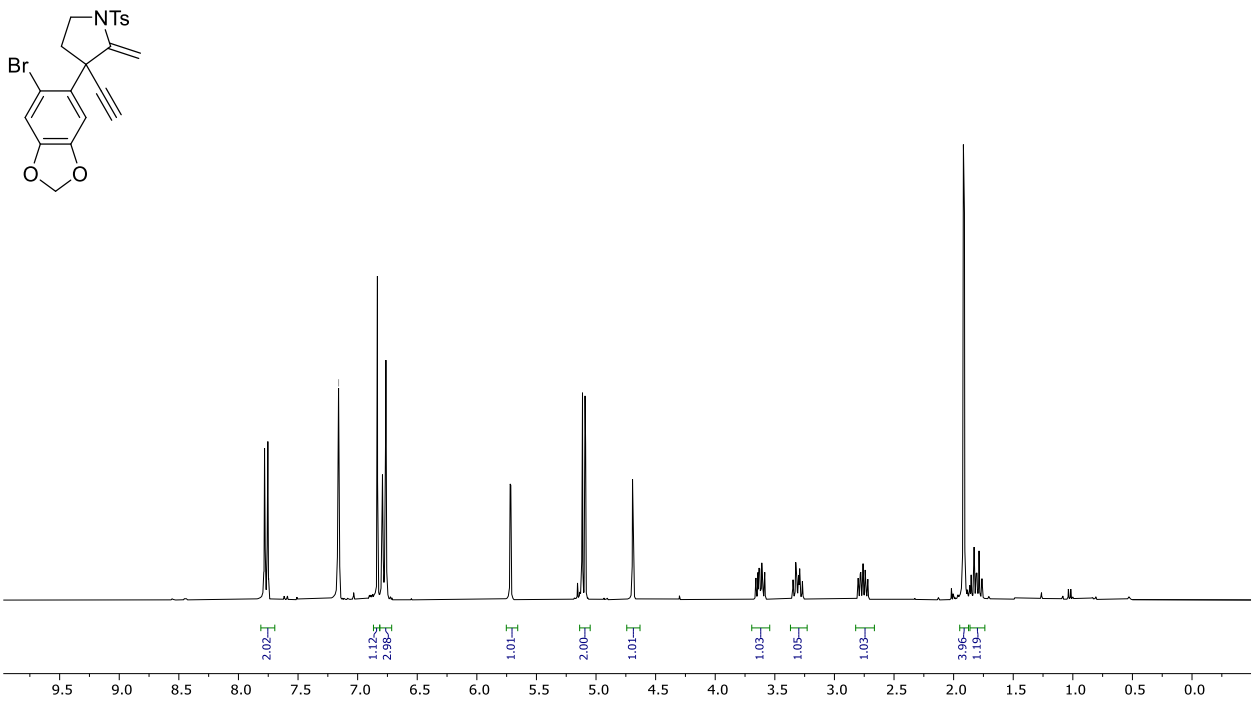
^{13}C NMR (75 MHz, $CDCl_3$) of ***tert*-butyl (3-(6-bromobenzo[d][1,3]dioxol-5-yl)-3-ethynylpent-4-yn-1-yl)(toluenesulfonyl)carbamate**



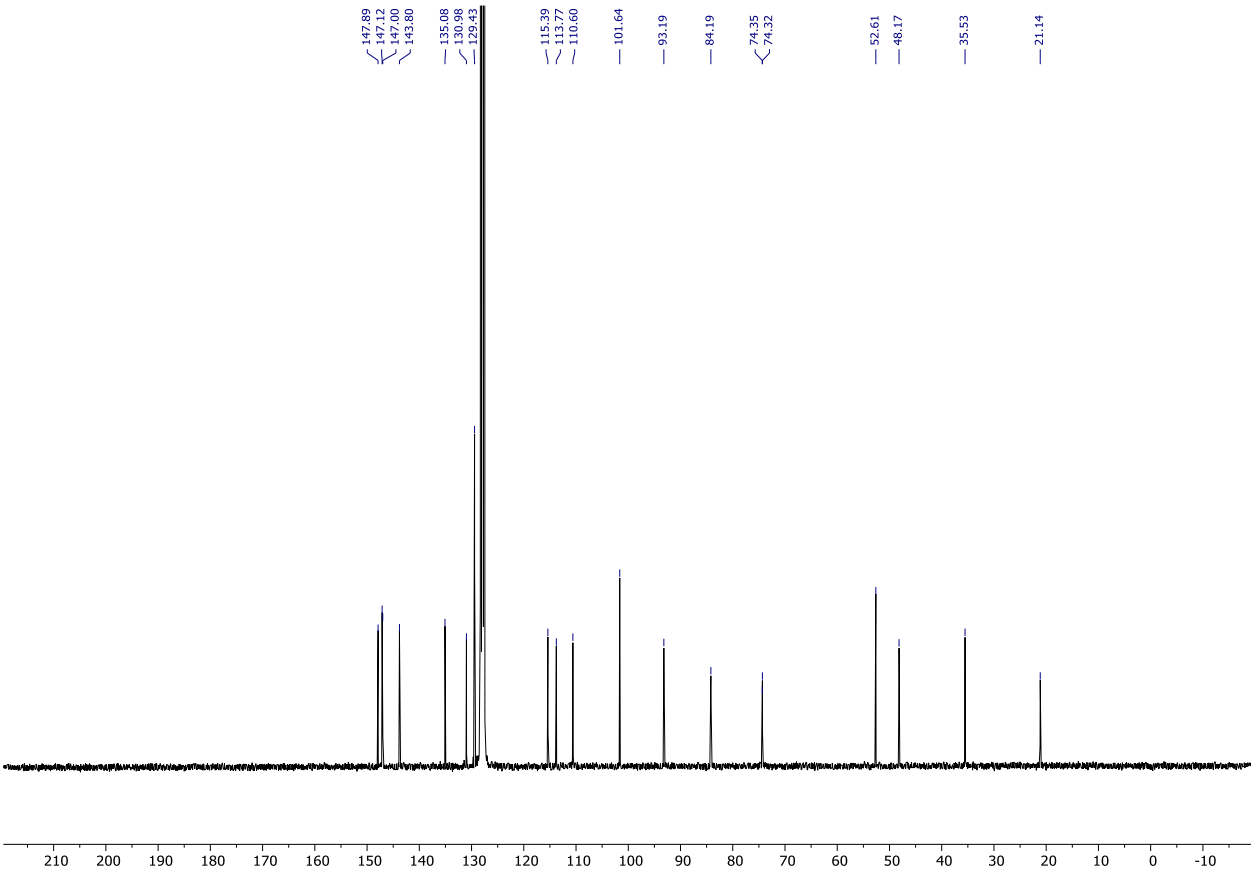
^{1}H NMR (300 MHz, $CDCl_3$) of compound **152**



^{13}C NMR (75 MHz, $CDCl_3$) of compound **152**



^{1}H NMR (300 MHz, $CDCl_3$) of compound **153**



^{13}C NMR (75 MHz, $CDCl_3$) of compound **153**

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