Towards a total synthesis of bazzanin K

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I hereby declare that this dissertation has been written independently and with no sources or aids other than those quoted. The parts performed by project collaborators have been clearly indicated.

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Abbreviations

Ac	Acetyl
Am	Amyl
[Au]	generic gold species
BHT	Butylated hydroxytoluene
Bpin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolanyl
°C	degrees celcius
2D	2-dimensional
Å	Ångstrom (10^{-10}m)
Bn	Benzyl
Bu	Butyl
c	concentration
calcd.	calculated
cat.	catalytic
Cy	Cyclohexyl
d	doublet (NMR)
Dba	Dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	Dichloromethane
DCB	1,2-dichlorobenzene
dd	doublet of doublets (NMR)
ddd	doublet of doublet of doublets (NMR)
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
ddt	doublet of doublet of triplets (NMR)
DFT	Density functional theory
DMF	*N*,*N*-dimethylformamide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-(diphenylphosphino)ferrocene
dt	doublet of triplets (NMR)
EI	Electron Ionisation
equiv.	equivalents
ESI-MS	Electrospray Ionisation Mass Spectrometry
et al.	et alia
eV	electron volt
Fig.	Figure
g	gram
GP	General procedure
h	hour
HMDS	Hexamethyldisilazide
HPLC	High Performance Liquid Chromotography
HRMS	High Resolution Mass Spectrometry

HWE	Horner-Wadsworth-Emmons
Hz	Hertz
*i*Pr	*iso*-propyl
IR	Infrared spectroscopy
J	Joule
J	Coupling constant
K	Kelvin
L	Ligand
M	Metal
M	Molar (mol/L)
m	multiplet (NMR)
m/z	mass to charge ratio
MBB	macrocyclic bis-bibenzyl
*m*CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
min	minute
mL	milliliter
MOM	Methoxymethyl
MS	Molecular sieves
MTBE	Methyl-*tert*-butyl ether
NCS	*N*-chlorosuccinimide
NBS	*N*-bromosuccinimide
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
p	*para*
Ph	Phenyl
Piv	Pivaloyl
PMB	*para*-methoxybenzyl
PG	Protecting group
ppm	parts per million
Pr	Propyl
[Pt]	Generic platinum species
*p*TsOH	*para*-toluenesulfonic acid
PPTS	pyridinium *p*-toluenesulfonate
py	pyridine
q	quartet (NMR)
quant.	quantitative
R	generic substituent
RCM	Ring-Closing Alkene Metathesis
R_f	Retardation factor
RT	room temperature
S	singlet (NMR)

SEM	[2-(Trimethylsilyl)ethoxy]methyl
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
T	Temperature
T_m	Melting Temperature
t	Time
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
TEA	Triethylamine
TEP	Tolman Electronic Parameter
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromotography
TMS	Trimethylsilyl
Ts	4-Methylbenzenesulfonyl
$\tilde{\nu}$	wavenumbers
WWII	World War 2
X	Generic substituent
δ	Chemical shift

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1. Introduction

1.1. The history of total synthesis

The humble beginnings of the art of total synthesis lie in the 19th century. For a long time, it was believed that for the synthesis of organic substances a metaphysical force called *vis vitalis* was needed that every living thing possessed. However, in 1828, F. WÖHLER showed for the first time, that it is indeed possible to synthesize urea – a well-known organic substance – from a strictly anorganic starting material.[1] This marks not only the beginning of organic chemistry but also the start of the goal-oriented total synthesis.

According to NICOLAOU, the historical development of the total synthesis can be divided into four eras with distinct breakthroughs in regards of molecular complexity: The pre-WWII era until 1939, the WOODWARD era until the 1980s, the COREY era, and the 1990s era.[2]

The first era before WWII is characterized by an increasing complexity of the target molecules. Starting at first with rather simple benzenoid substances, more intricate substances were prepared, such as camphor (**1**) by KOMPPA in 1903[3] or tropinone (**2**) in an elegant one-step synthesis by ROBINSON (1917).[4] Especially impressive is the total synthesis of the haemin (**3**) featuring elevated molecular complexity by FISCHER in 1929[5] (see Fig. 1).

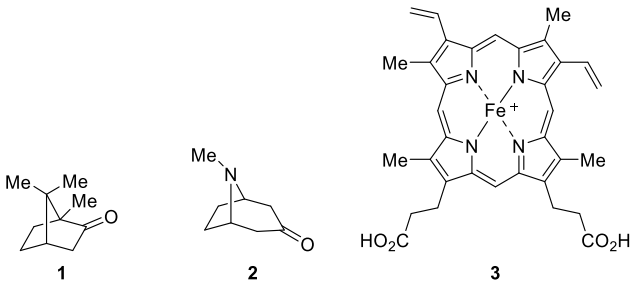


Figure 1: Selection of total synthetic highlights of the pre-WWII era.

With R. B. WOODWARD beginning his professorial career at Harvard university in 1937, a significant development in organic synthesis took place. His contribution to the field of total synthesis can be shown by countless syntheses of natural products of exceeding structural complexity. Some of WOODWARD'S accomplishments such as quinine (**4**) (1944)[6], cephalosporin C (**5**) (1966)[7] and vitamin B_{12} (**6**) (1973 with ESCHENMOSER)[8] in total synthesis are shown in Fig. 2.

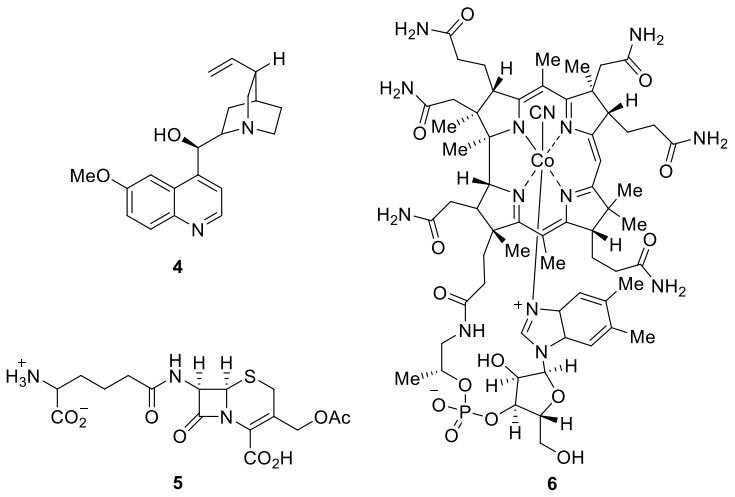


Figure 2: Selection of total synthetic highlights of the WOODWARD era.

Further progress in the organic synthesis was notably made by E. J. COREY when he started his professorship at Harvard university in 1959. He did not only introduce the concept of retrosynthetic analysis for increasingly complex target molecules, but also developed a plethora of new synthetic methods which were directly applied in his total synthetic strategies. To many modern organic chemists his invented methodologies are known today as name reactions like the COREY-BAKSHI-SHIBATA-reduction[9] or the COREY-FUCHS reaction.[10] Fig. 3 shows selected accomplishments in COREY'S advances towards total syntheses of longifolene (**7**) in 1961[11], erythronolide B (**8**) (1975)[12], leukotriene C_4 (**9**) (1980)[13] and glycinoeclepin A (**10**) in 1990.[14]

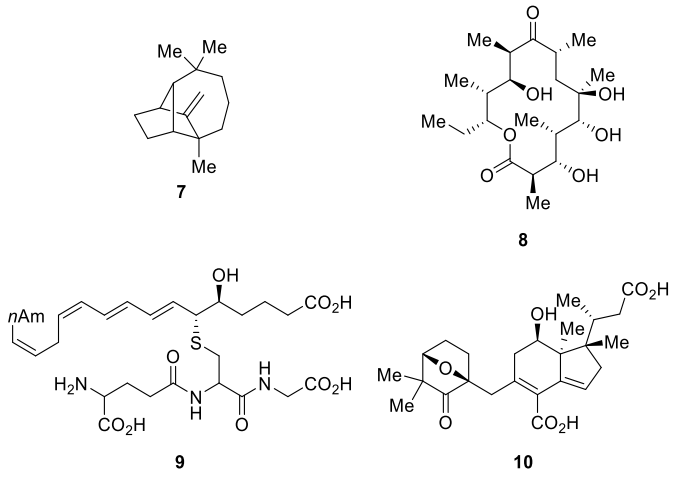


Figure 3: Selection of total synthetic highlights of the COREY era.

While previously the strive to find a total synthesis for natural products was mostly done to test the limits of chemistry and to validate structure assignments, the development in the 1990s showed motivations rooted in the fields of biology and medicine. Since chemists and biologists

realized the enormous potential that lies in the combination of both scientific fields, the total synthesis of a variety of biologically active substances with tremendous complexity was performed. A selection of the 1990s era's successfully synthesized target molecules with taxol (**11**) by NICOLAOU (1994)[15], aspidophytine (**12**) by COREY (1994)[16] and vancomycin aglycon (**13**) by BOGER (1999)[17] is shown in Fig. 4.

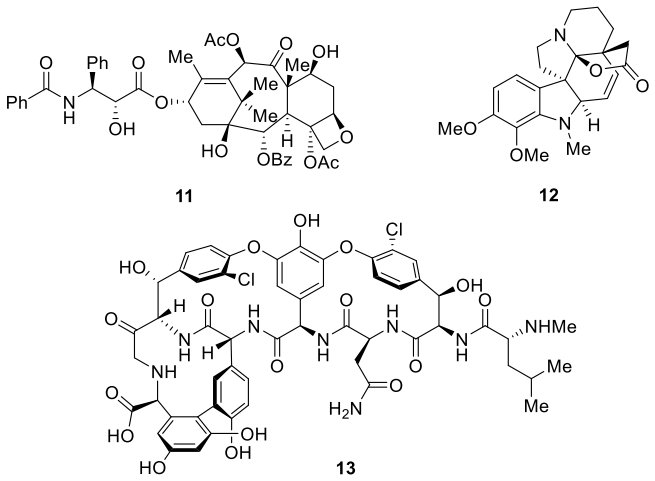


Figure 4: Selection of total synthetic highlights of the 1990s era.

Nonetheless, it might be appropriate to ask about the current state and the future development of total synthesis and its place in regards of usefulness, costs, and overall interest from chemists. In his 2018 article "Natural Product Total Synthesis: As Exciting as Ever and Here To Stay", P. S. BARAN gives a determined eulogy for organic synthesis in general.[18] While historically, the products from organic synthesis found widespread application in industry, total synthesis today is more important than just being the provision of chemicals as it provides much needed experience in many fields of organic synthesis enabling practical synthetic problem solving.[19] The true value of the pursuit of organic synthesis lies in the possibility of proving new concepts and methods. Furthermore, it can highlight neglected chemical insights which could lead to fundamentally new discoveries.[2] Moreover, the synthesis of natural products provides a huge supply for biologically active substances that are required in the discovery of new drugs.[20] Despite the improvement of analytical methods, having a synthetically prepared sample in hand can usually help in elucidating structural questions and clear up misassignments.[21] One could argue that increasing automatization could make the practicing chemist obsolete.[22] But in the end it is "boring old human ingenuity, creativity and curiosity"[23] that develops new strategies and methodologies for the synthesis of increasingly complex target molecules.[24]

In conclusion, the pursuit of total synthesis was and is still relevant and will be important in future days as well not only for the very act of producing needed chemicals but also more importantly for the stimulation of creative chemical thought.

1.2. Bazzanin K

This work deals with the total synthesis of the natural product bazzanin K (**14**). Fig. 5 shows that this substance has some distinct features which are interesting synthetic challenges, such as a macrocyclic carbon skeleton and a phenanthrene moiety. To understand bazzanin K's position in the context of nature products, the following chapters shall illuminate the field of related isolated substances and the state of the art in their total syntheses.

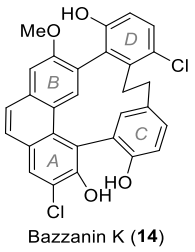


Figure 5: Structure of bazzanin K (**14**).

1.2.1. Macrocyclic bis-bibenzyls

Bazzanin K (**14**) is a distinguished member of the family of macrocyclic bis-bibenzyls (MBBs). Therefore, this group of natural products shall be introduced in this chapter in order to understand the origin and the diversity of these interesting substances. MBBs are a large family of secondary metabolites found and isolated from liverworts and other bryophytes.[25] Historically, bryophytes found widespread use as folk medicine all around the world for the treatment of a variety of conditions[26] and due to the high pharmacological potential of these plants, ASAKAWA and his coworkers systematically studied the isolation of secondary metabolites of liverwort species indigenous to Japan.[27] The bis-bibenzyls found in those plants show a variety of biological activities such as cytotoxic, antimicrobial, antiviral and antifungal effects.[28]

Structurally, MBBs are typically based on four different general structure motifs (**16**) containing two lunularin (**15)** subunits with varying connectivity between ring *A* and *C,* and *B* and *D*, as shown in Fig. 6.[29]

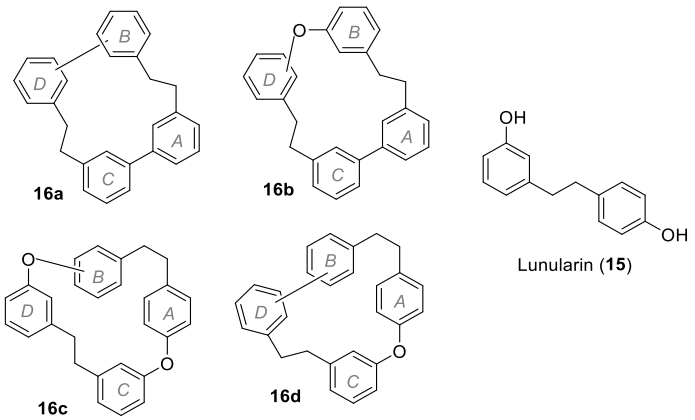


Figure 6: General structures of macrocyclic bis-bibenzyls (**16**) and lunuralin (**15**).

Henceforward, a method of ring enumeration devised by ASAKAWA will be used which assigns the labels *A*-*D* to each of the four aromatic rings in the bis-bibenzyls.[25] The lunularin subunits can either be connected *via* two diaryl ethers like in general structure **16c**, or with two direct C-C bonds in general structure **16a**. The structures **16b** and **16d** contain both connective motifs at different positions on the molecule. In the past 30 years many new and structurally interesting MBBs were identified and described in detail in a review by HARROWVEN and KOSTIUK in 2012[29] and in the following chapters some of these natural products shall be introduced.

1.2.2. Cavicularin

ASAKAWA *et al.* were able to isolate cavicularin (**17**) from the Japanese liverwort *Cavicularia densa* and elucidated its structure using 2D-NMR and X-ray crystallographic analysis (see Fig. 7).[30] Cavicularin (**17**) has the general structure **16d** with a C-C connection between rings *B* and *D* and a biaryl ether bridge between rings *A* and *C*. Interestingly, there is a dihydrophenanthrene moiety in the *CD*-part of cavicularin (**17**) resulting from an oxidative bond formation between rings *C* and *D*. Despite the lack of stereogenic carbon centers, the natural product showed optical rotation. The observed optical activity results from planar and axial chiral elements caused by the hindered rotation due to the significant strain of the macrocycle. Furthermore, it is appropriate to note, that ring *A* possesses a boat-like conformation, which further shows the high molecular strain.

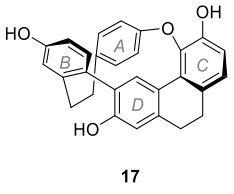


Figure 7: Structure of cavicularin (**17**).

1.2.3. Riccardins

A small structural branch of MBBs related to cavicularin (**17**) is represented by the riccardins (Fig 8). Riccardin A (**18**) and C (**19**) have been isolated by ASAKAWA *et al.* from the liverworts *Reboulia hemisphaerica* and *Riccardia multifida* in the early 1980s.[31] In general, these compounds feature one diaryl ether between rings *A* and *C*, one biaryl-connection and one *para*-disubstituted *A*-ring, which are a decorated variant of general structure **16b**.

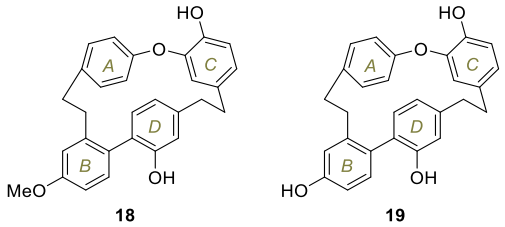
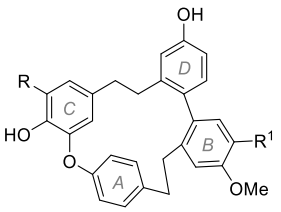


Figure 8: Riccardin A (**18**) and riccardin C (**19**) as examples for the structural family of the riccardins.

1.2.4. Plagiochins

The plagiochins contain the four molecules plagiochin A–D (**20**–**23**) which were isolated by the ASAKAWA group from *Plagiochila acantophyllya japonica* in 1987.[32] They exhibit the general structure **16d** of MBBs containing one biaryl connection rings *B* and *D* and one biaryl ether bridge between rings *A* and *C* which can be seen in Fig. 9. The difference between the riccardins and the plagiochins lies in the *ortho*-substitution at ring *D.* It is interesting to note, that another plagiochin was found and characterized. However, SPEICHER *et al*. could show in their total synthesis that the assigned structure was indeed wrong[33], further proving the previously mentioned necessity of organic synthesis of natural products for structure validation.



Plagiochin A (**20**) R = R^1 = OH
Plagiochin B (**21**) R = OH, R^1 = H
Plagiochin C (**22**) R = H, R^1 = OH
Plagiochin D (**23**) R = H, R^1 = H

Figure 9: The family of plagiochins.

1.2.5. Marchantins

The marchantins are a large class of MBBs with the general structure **16c** which is distinguished from other structures by the presence of two biaryl ether bridges connecting the two lunularin sub-units (see Fig. 10). They are named after the bryophyte *Marchantiales*, where they are

commonly found.[34] All in all, there are about two dozen marchantins and related natural products isolated from bryophytes.

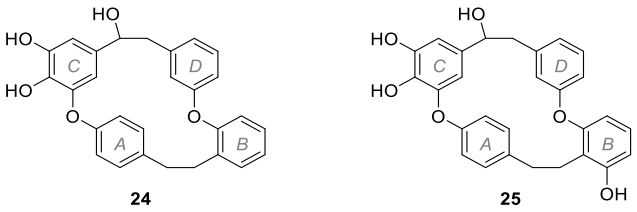
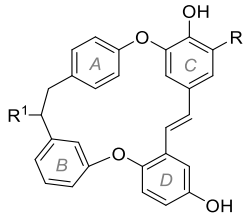


Figure 10: Marchantin A (**24**) and marchantin D (**25**) as examples for the structural family of the marchantins

1.2.6. Ptychantols

From the liverwort *Ptychanthus striatus*, ASAKAWA and co-workers isolated another class of MBBs, namely the ptychantols A–C (**26**–**28**).[35] Having two biaryl-ether connections, they belong to the general structure **16c** of MBBs. In contrast to the previously mentioned nature products, ptychantols prominently feature a *trans*-stilbene as a functional motif as shown in Fig 11. Interestingly, ptychantols show no optical rotation despite containing the rigid double bond in their core structure.



Ptychantol A (**26**) R = R^1 = H
Ptychantol B (**27**) R =OH R^1 = H
Ptychantol C (**28**) R = R^1 = OH

Figure 11: The family of ptychantols.

1.2.7. Bazzanins

The large group of the bazzanins contains more than a dozen chlorinated MBBs which have been isolated from the liverwort *Bazzania trilobata* by ASAKAWA.[36] Since chlorinated natural products are usually found in marine sources,[37] it was assumed, that the origin of the bazzanins lies in artefacts from chlorination of other naturally occurring secondary metabolites. However, SPEICHER *et al*. showed that the bazzanins are indeed a family of genuine natural products.[38] Structurally, they feature two direct C-C bonds between the lunularin units and have one unsaturated ethylene bridge (see Fig 12). Notably, bazzanin K (**14**) is an exception. It is even more oxidized and contains a phenanthrene motif. This natural product is the center of attention in this work and in the following chapters a discussion of the general synthetic possibilities will be made because no successful total synthetic approach has been made yet.

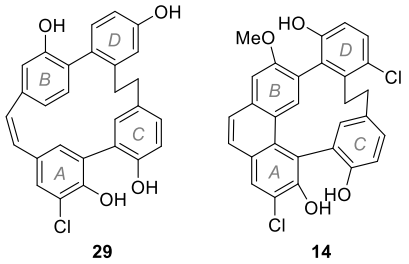


Figure 12: Bazzanin A (**29**) and bazzanin K (**14**) as examples for the structural family of the bazzanins.

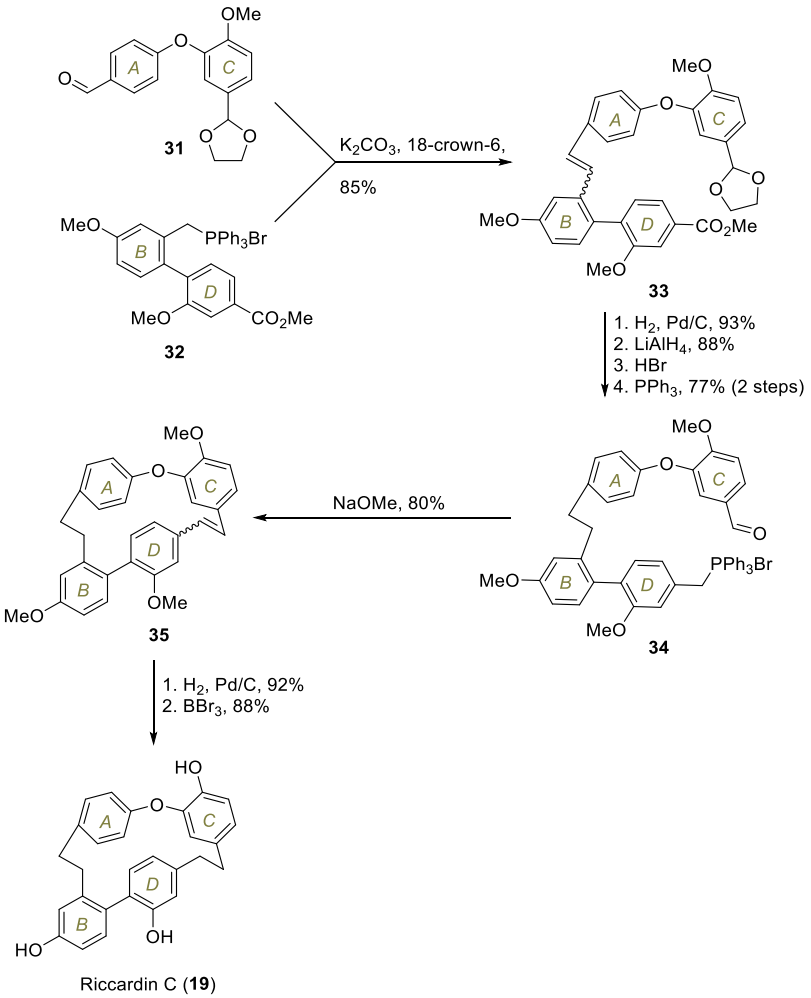
1.3. The synthesis of macrocyclic bis-bibenzyls

From the synthetic perspective of an organic chemist, it can easily be concluded that the most intricate and important step in the synthesis of MBBs is the macrocyclization. In most cases high dilution and long reaction times are needed and side reactions are extremely likely.[39] Not only the macrocyclization is of significance, but also the synthesis of the aromatic building blocks. The preparation of highly functionalized poly-substituted aromatics is far away from being a trivial task for ambitious scientists, let alone the connection between the building blocks. This chapter shall illuminate a plethora of literature known strategies and approaches in the total synthesis of MBBs especially in regards of the macrocyclization and shall give inspiration towards the synthesis of bazzanin K (**14**).

1.3.1. Macrocyclization by WITTIG reaction

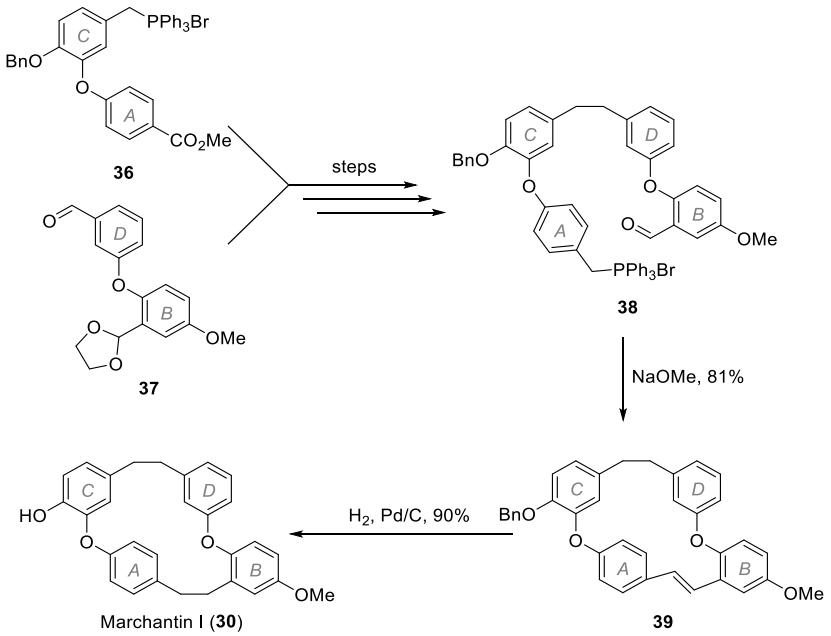
An intramolecular WITTIG reaction was used by EICHER *et al.* in 1998 to facilitate the total syntheses of a small variety of MBBs, such as riccardin C (**19**) and marchantin I (**30**).[40] For riccardin C, they prepared the *AC*-fragment **31** with a synthetic pathway including a copper-mediated ULLMANN coupling for the synthesis of the biaryl ether. This is a rather common way to prepare biaryl ether fragments in general and is found as a connective strategy in many synthetic approaches towards MBBs.[41–44] Another way of preparing biaryl ether fragments for MBBs is nucleophilic aromatic substitution. [40,45]

The *AC*-fragment **31** was used as a substrate in a WITTIG reaction with the *BD*-fragment **32**, to deliver the tetraarene **33** (shown in Scheme 1). Hydrogenation of the olefin to the respective alkane and successive conversion of the ester-function to a WITTIG salt yielded substrate **34**, required for the intramolecular WITTIG reaction. Macrozyclization to deliver **35** took place under basic conditions with NaOMe and high dilution (6.7 mM) with an astonishing yield of 80%. Final hydrogenation and removal of the protecting groups led to the formation of riccardin C (**19**).



Scheme 1: Synthesis of riccardin C (**19**) by EICHER using a WITTIG macrocyclization.

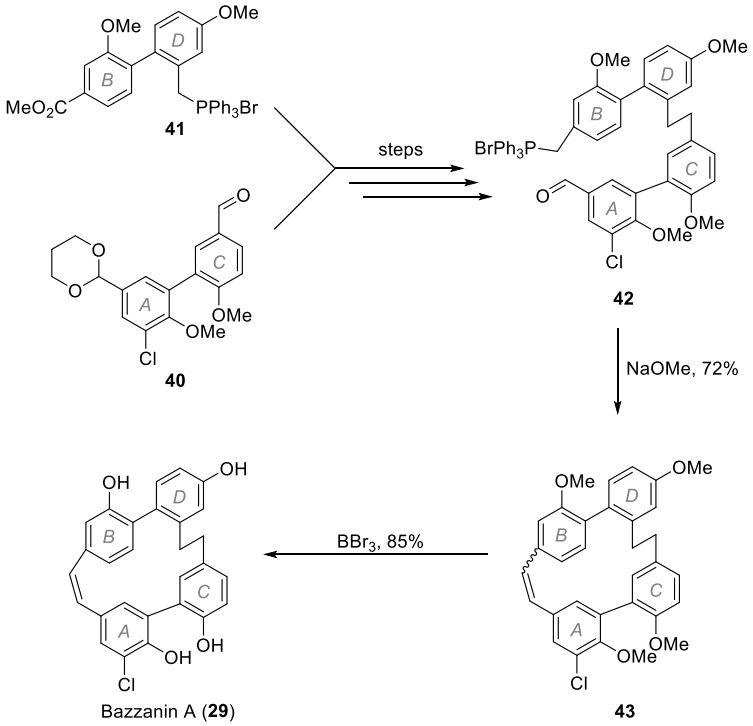
With the same strategy, EICHER and co-workers managed the synthesis of marchantin I (**30**) following the synthetic route shown in Scheme 2. They used the ULLMANN coupling and a nucleophilic aromatic substitution based methodology to prepare the *AC*- and the *BD*-fragments **36** and **37**. Again, after a series of functional group interconversions phosphonium salt **38** was prepared, which is a suitable substrate for the desired intramolecular WITTIG reaction. Interestingly, the macrocyclization afforded product **39** with similarly satisfactory yield (81%). Subsequently, treatment with H_2 and Pd/C as a catalyst finally yielded marchantin I (**30**).



Scheme 2: Schematic depiction of EICHER's strategy for the total synthesis of marchantin I (**30**).

In 2002, SPEICHER and co-workers used this methodology in their total syntheses of several chlorinated MBBs such as bazzanin A (**29**) in Scheme 3.[46] They started with the preparation of the *AC*-fragment **40** and the *BD*-fragment **41** which are the products of SUZUKI couplings of suitably substituted arenes. Coupling to tetraarene **42** was achieved *via* WITTIG reaction and further functional group transformations. The following WITTIG reaction with NaOMe as a base and *pseudo*-diluted conditions resulted in the formation of macrocycle **43** in 72% containing a mixture of conformers. Finally, direct cleaving of the methyl ethers gave bazzanin A (**29**). Despite the differences in structure, this approach could be an inspiration for the synthesis of other bazzanins, such as bazzanin K (**14**).

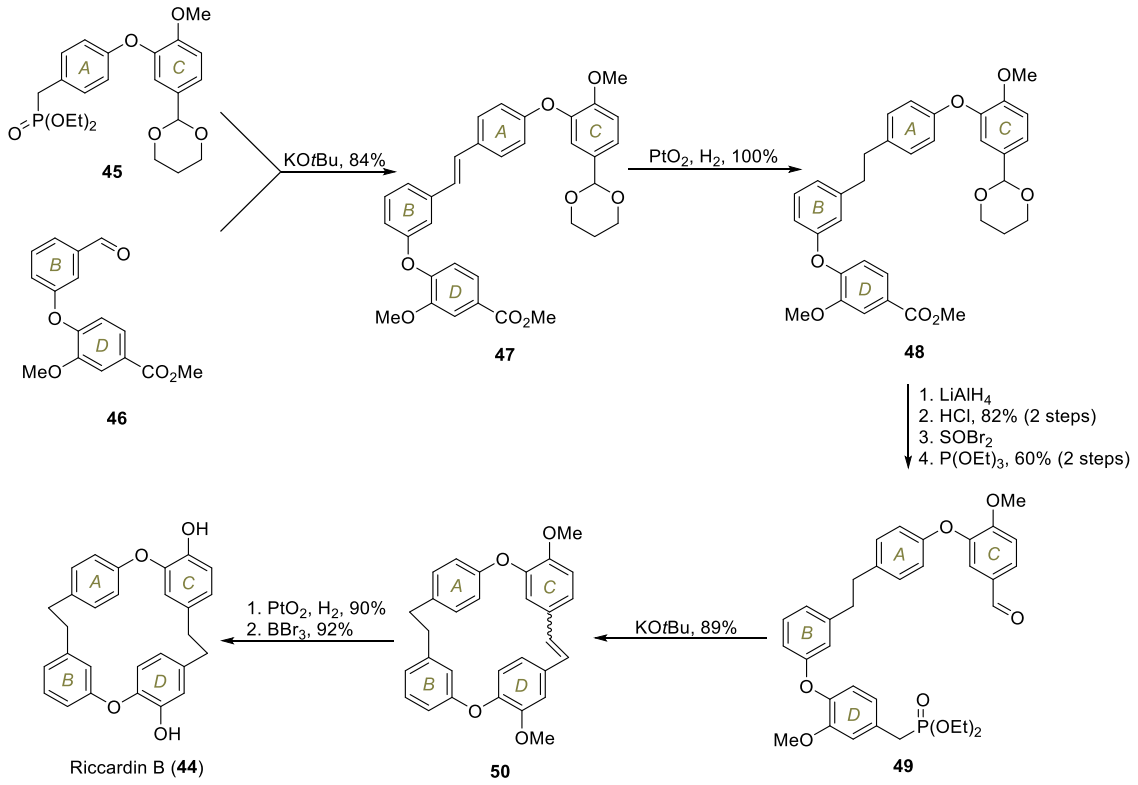
Besides these previously mentioned total syntheses, WITTIG macrocyclizations were used as a key step for the preparation of many other MBBs.[47a, 47b, 47c, 48] With these many examples, WITTIG reactions showed their potential in the preparation of strained macrocycles which could make their application in the synthesis of bazzanin K (**14**) rather promising.



Scheme 3: Schematic depiction of SPEICHER'S strategy for the total synthesis of bazzanin A (**29**).

1.3.2. Macrocyclization by HORNER-WADSWORTH-EMMONS olefination

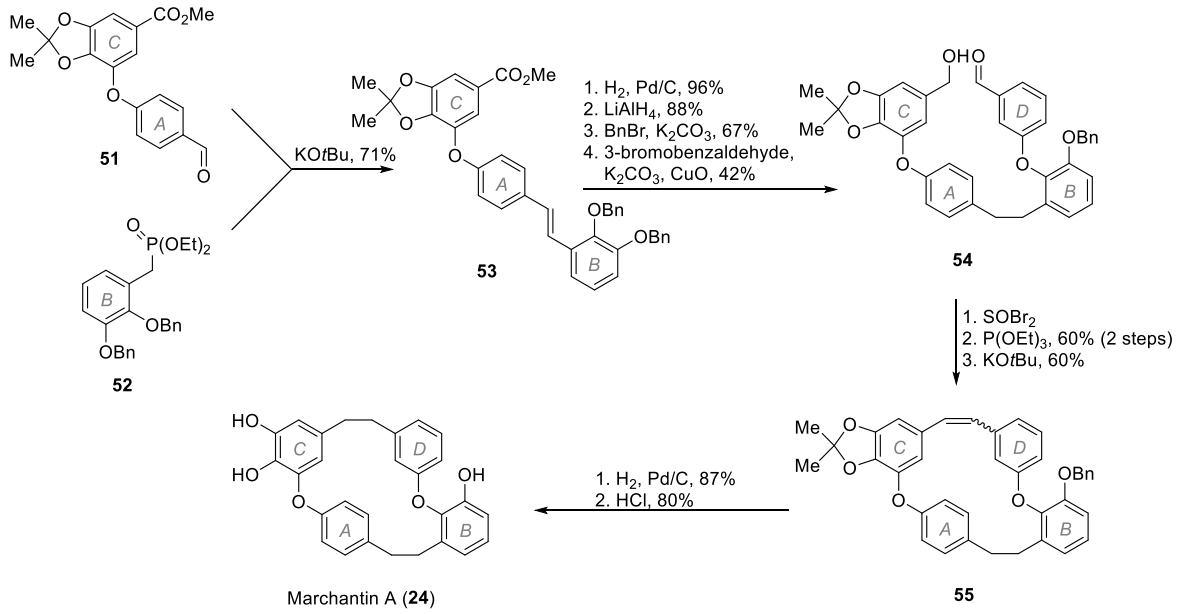
Relatively similar and closely related to the WITTIG methodology is the use of HORNER-WADSWORTH-EMMONS (HWE) olefination as a key step for the macrozyclization. The first literature known protocol which utilized an intramolecular HWE olefination for the total synthesis of MBBs was reported by the KODAMA group in 1988 (Scheme 4).[44] Since the analytical data of isolated riccardin B (**44**) could be in agreement with two possible structures, a total synthesis should bring clarity to that question. KODAMA *et al.* managed to prepare riccardin B (**44**) and marchantin A (**24**) using HWE methodology. Shown in Scheme 4, they started their synthetic approach of riccardin B (**44**) by preparing *AC*-fragment **45** *via* the previously mentioned ULLMANN methodology. Subsequent HWE olefination with the *BD*-fragment **46** also prepared by an ULLMANN coupling, afforded the tetraarene **47**. To facilitate the macrocyclization, the double bond was hydrogenated to tetraarene **48**, and the ester was reduced to the benzyl alcohol using $LiAlH_4$. Further conversion of functional groups led to the formation of phosphonate **49**. Finally, under basic conditions with KO*t*Bu and a low concentration of 1.4 mM, the cyclization took place with a formidable yield of 89% as a mixture of conformers. In the end of this total synthesis, the olefin **50** was hydrogenated, and the protecting groups were removed, which resulted in the isolation of riccardin B (**44**).



Scheme 4: KODAMA'S total synthesis of riccardin B (**44**) with a HWE reaction as the key step for the macrocyclization.

As mentioned before, in an additional synthesis, KODAMA *et al.* prepared marchantin A (**24**) by the same methodology (Scheme 5). First, they prepared the *ABC*-fragment **53** *via* HWE olefination from the aldehyde **51** and **52**. After a series of functional group transformations and another ULLMANN coupling, tetraarene **54** was obtained and the macrocyclization in the form of a ring closing HWE reaction was performed under highly diluted conditions (1.4 mM). The desired macrocycle **55** was obtained as a mixture of *Z* and *E* isomers in a respectable yield of 60%. Interestingly, the group reported, that a higher concentration (2.4 mM) of the phosphonate led to a significantly predominant formation of the dimer instead of the monomer, showing how crucial high dilution is in terms of selectivity towards the formation of the monomer. However, hydrogenation of the olefin **55** and subsequent cleavage of the protecting groups yielded marchantin A (**24**).

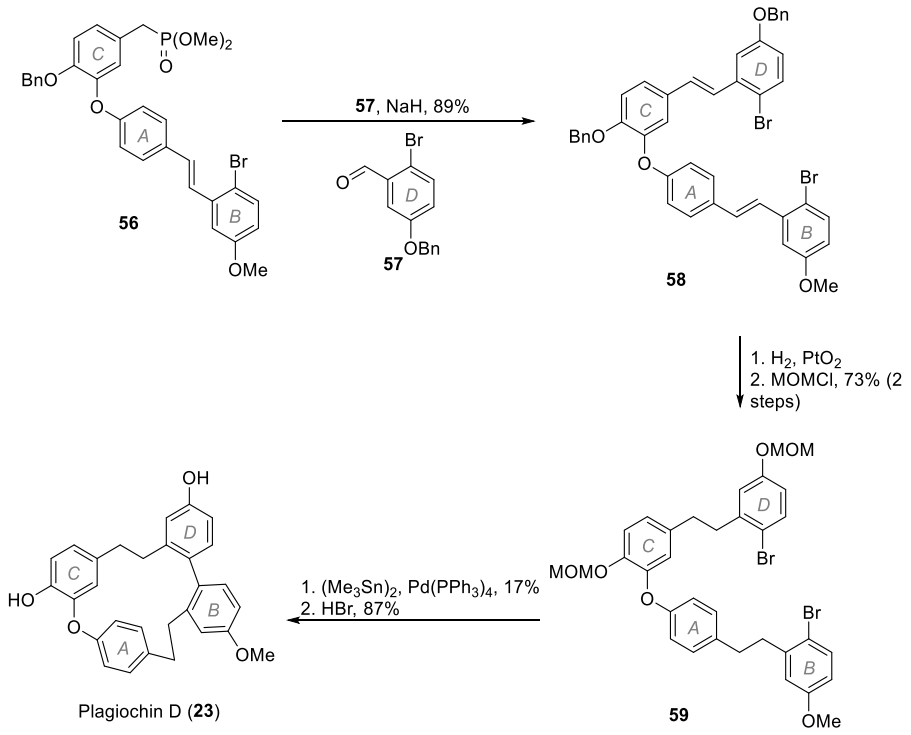
HWE reactions are indeed comparable to classic WITTIG reactions in regards of their potential as macrocyclization reactions.



Scheme 5: KODAMA'S total synthesis of marchantin A (**24**) with a HWE reaction as the key step for the macrocyclization.

1.3.3. Macrocyclization by transition metal-catalyzed aryl-aryl coupling

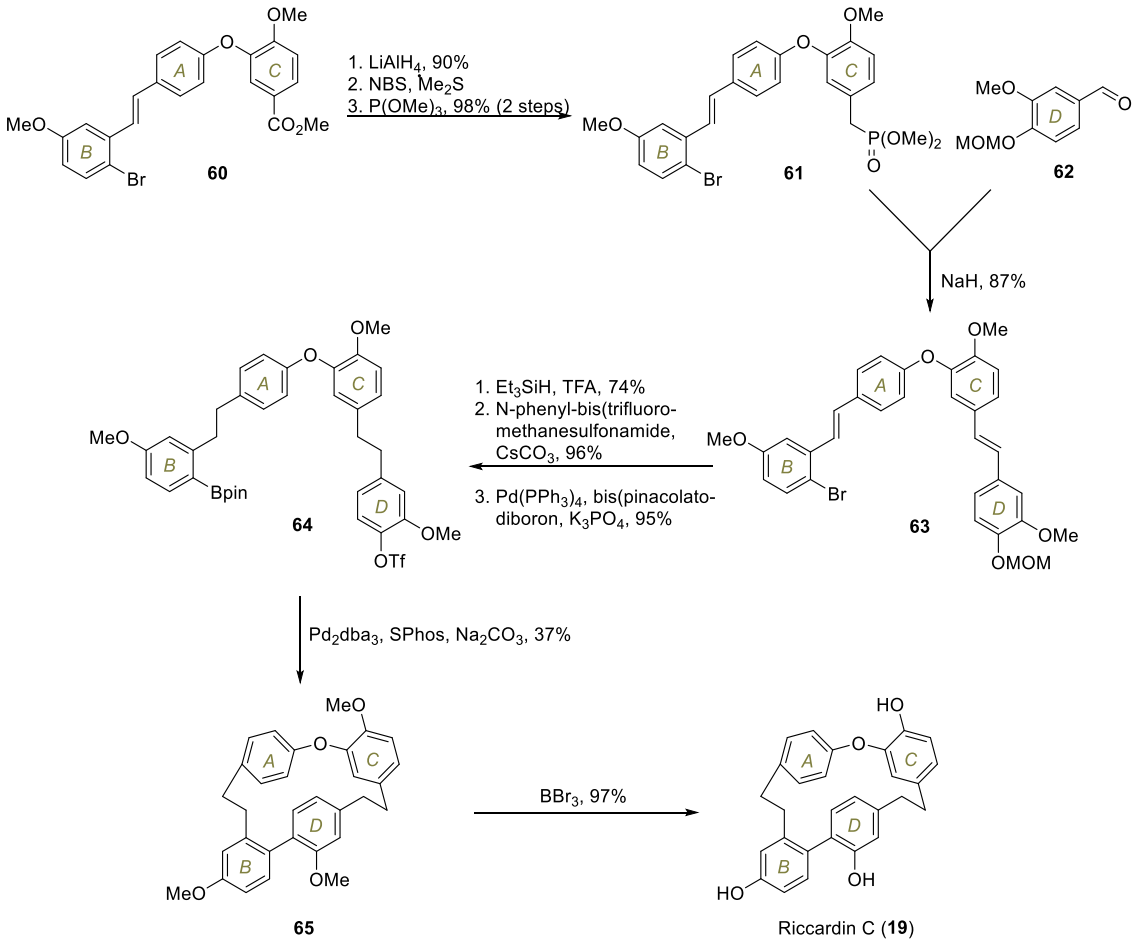
Another thinkable approach for macrocyclizations are cross-coupling reactions like SUZUKI-, or STILLE coupling reactions. The first successful attempt at utilizing this strategy was reported by FUKUYAMA *et al.* in 1999 with the total synthesis of plagiochin D (**23**) (see Scheme 6).[49] They started by preparing the *ACB*-fragment **56** *via* HWE reaction. Another HWE reaction with aldehyde **57** and successive hydrogenation of the olefin led to the formation of tetraarene **58**. Since the hydrogenolytic conditions led to the cleavage of the benzyl ethers, the free OH groups were protected with MOMCl to the precursor **59** for the macrocyclization. Finally, a STILLE-KELLY reaction was conducted with a relatively high concentration of 0.01 M to facilitate the macrocyclization in a poor yield of 17%. Subsequent deprotection gave access to plagiochin D (**23**).



Scheme 6: FUKUYAMA'S total synthesis of plagiochin D (**23**) with palladium-mediated aryl-aryl coupling as the key step for the macrocyclization.

An additional protocol utilizing a SUZUKI coupling as the macrocyclization step was published in 2009 by HIOKI *et al.* with the reported total synthesis of riccardin C (**19**) (Scheme 7).[50] After preparing triarene **60** *via* HWE reaction, the ester-function was transformed into phosphonate **61**, which in turn could perform another HWE reaction with aldehyde **62** to tetraarene **63**. To synthesize a substrate suitable for a SUZUKI coupling, HIOKI and co-workers used a few functional group transformations to arrive at key-substrate **64** with a triflate and a boronic ester, which was subjugated to palladium-catalysis under high dilution (5 mM) to facilitate the macrocyclization to macrocycle **65** in mediocre yield of 37%. Interestingly, a significant amount (27%) of the dimer was also formed.

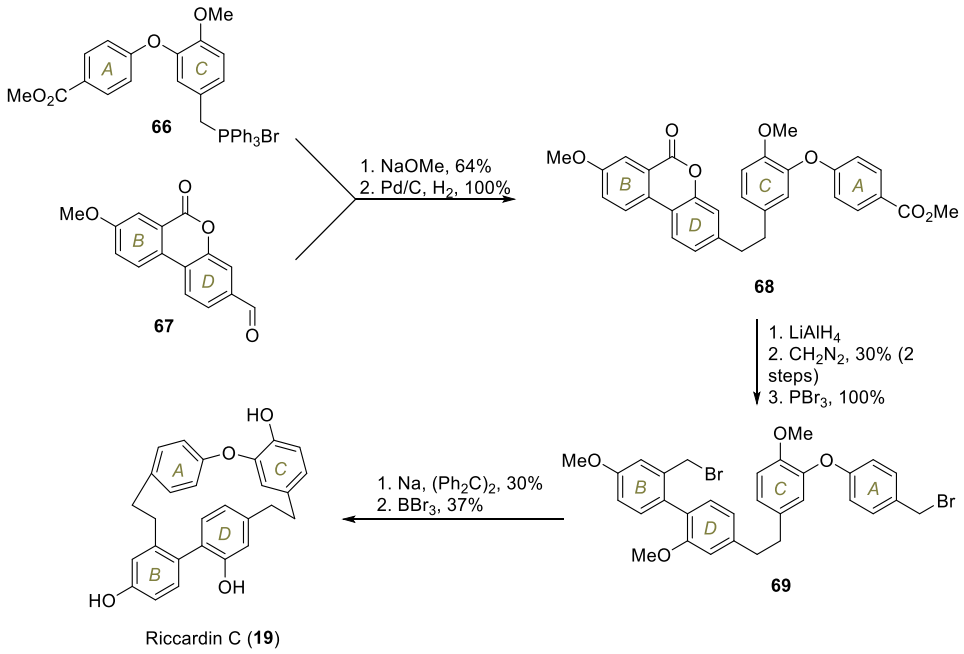
Concluding, even if transition metal mediated couplings of arenes found some application in the total synthesis of MBBs, the yield is usually lower, and the reaction needs at least some optimization.



Scheme 7: HIOKI's total synthesis of riccardin C (**19**) with a SUZUKI coupling as the key step for the macrocyclization.

1.3.4. Macrocyclization by WURTZ-type coupling reactions

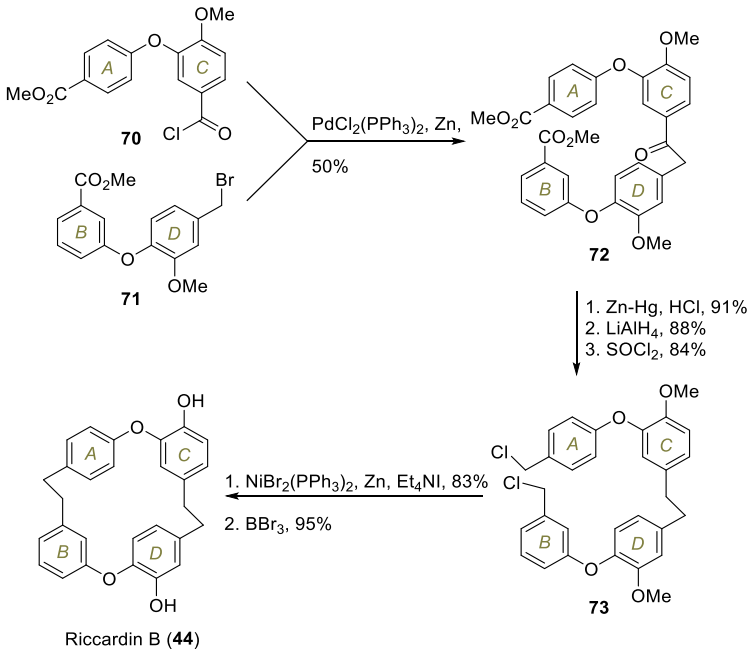
In hist first total synthesis of riccardin C (**19**) in 1988, NÓGRÁDI and co-workers approached the problem of macrocyclization with a WURTZ coupling.[51] Firstly, they started assembling the *AC*-fragment **66** *via* ULLMANN coupling as a connective methodology for biaryl ethers (Scheme 8). Secondly, lactone **67** was prepared as the *BD*-fragment. Using WITTIG methodology to connect both fragments and successive hydrogenation of the double bond yielded tetrarene **68** which was further converted to dibromide **69**. Finally, the macrocyclization of dibromide **69** using sodium metal and tetraphenylethylene and successive deprotection of the methyl ethers gave the desired riccardin C (**19**). In addition to that, NÓGRÁDI *et al.* were also able to utilize this methodology to prepare riccardin B (**44**) as the diacetate, riccardin A (**18**)[41] and more MBBs.[43] However, the yields for the macrocyclizations were rather poor with 30% being the best result.



Scheme 8: NÓGRÁDI's total synthesis of riccardin C (**19**).

In a related strategic approach for the synthesis of riccardin B (**44**), IYODA and co-workers used similar ULLMANN methodology and further functional group manipulation to facilitate the preparation of acid chloride **70** as an *AC*-fragment and benzylbromide **71** as the *BD*-fragment in Scheme 9.[42] Both substrates were then connected *via* a FUJISAWA-modified NEGISHI coupling, yielding the tetraarene **72** which in turn was reduced *via* CLEMMENSEN reduction and further converted into the dichloride **73**. IYODA *et al.* performed a macrocyclization using activated zinc as a reducing agent to activate $NiBr_2(PPh_3)_2$ in the present of Et_4NI under high dilution conditions (0.3 mM). Compared to the previously mentioned cyclizations performed by NÓGRÁDI, the yield of 83% is rather spectacular. In a final step, the protecting groups were removed and the desired riccardin B (**44**) was obtained.

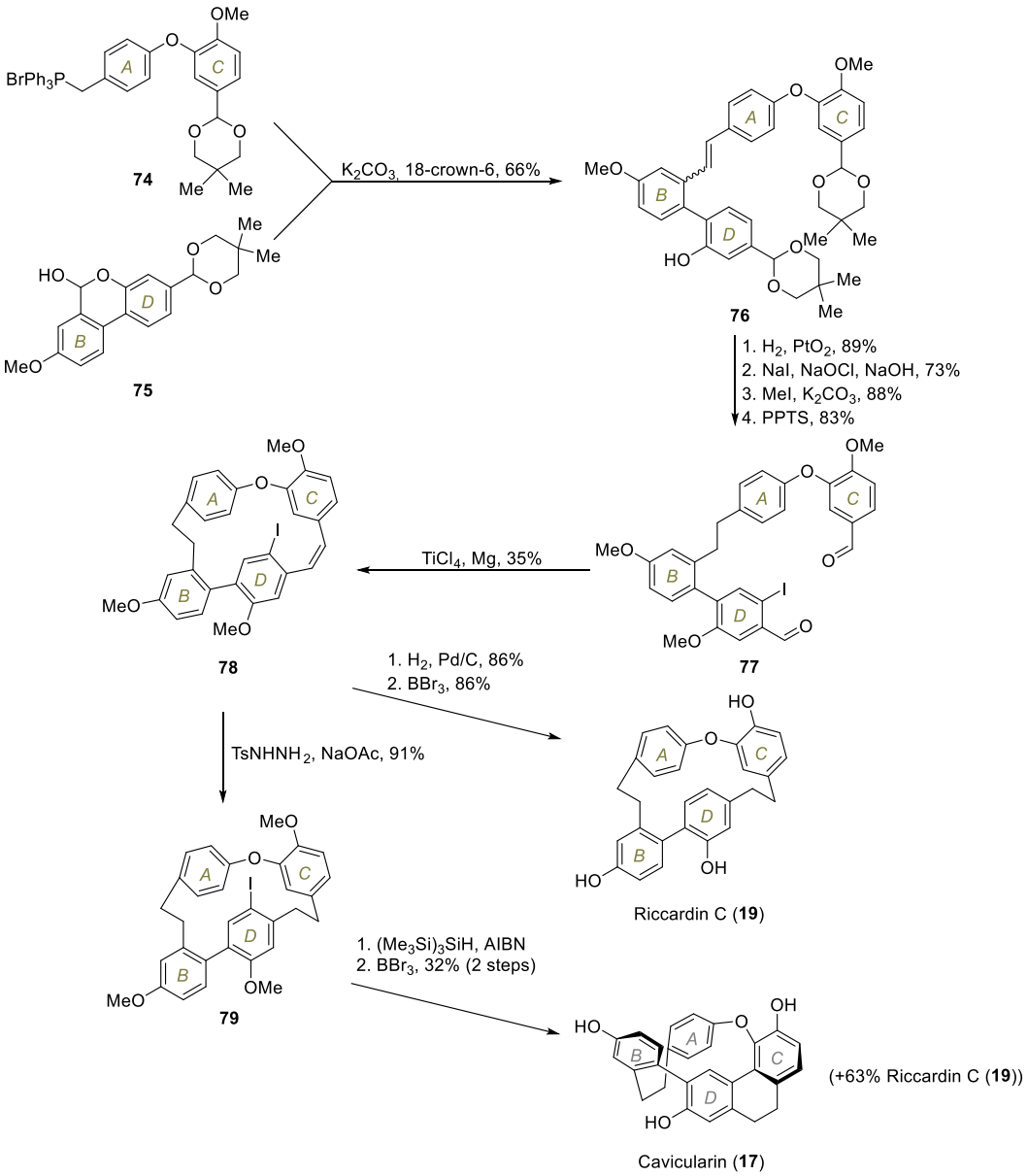
Noticeably, except for IYODA'S methodology, the WURTZ coupling had significantly poor yields.



Scheme 9: IYODA'S total synthesis of riccardin B (**44**).

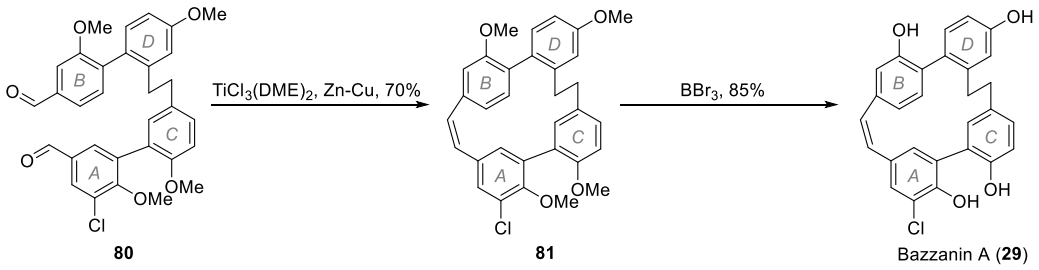
1.3.5. Macrocyclization by MCMURRY reactions

The MCMURRY reaction was used in a few total syntheses of MBBs. For example, it was used by HARROWVEN and co-workers in the unified syntheses of riccardin C (**19**) and cavicularin (**17**) as a method for macrocyclization (Scheme 10).[48] In a rather elegant way, they were able to use a long common synthetic pathway to furnish both natural products. Beginning with the preparation of the *AC*-fragment **74**, they used the hemi-acetal **75** to synthesize the tetraarene **76** in a WITTIG reaction, which was further converted to the iodinated di-aldehyde **77**. The reductive coupling of the two carbonyl groups using $TiCl_4$ and magnesium facilitated the *Z*-selective macrocyclization with a mediocre yield of 35%. With this last common intermediate **78** in hand, subsequent reduction *via* $TsNHNH_2$ and NaOAc to **79**, radical induced ring contraction and removal of the methyl-ethers led to the formation of cavicularin (**17**) in moderate yield of 32%. Interestingly, the side product of this synthetic pathway was riccardin C, which could be obtained in 63% yield from the last two reactions originating from hydrodehalogenation. However, for riccardin C (**19**), intermediate **78** was subjected to hydrogenative conditions with H_2 and Pd/C, which resulted in the hydrogenation of the double bond and dehalogenation. Finally, cleavage of the protecting groups gave the desired product **19**, as well.



Scheme 10: HARROWVEN'S total synthesis of riccardin C (**19**) and cavicularin (**17**) with a MCMURRY reaction as the key step for the macrocyclization.

Another inspiring application of a MCMURRY reaction was done by SPEICHER *et al.* with the synthesis of bazzanin A (**29**) shown in Scheme 11.[46] The macrocyclization of bazzanin A (**29**) was not only carried out as a WITTIG reaction as mentioned above, SPEICHER and co-workers also used MCMURRY methodology for the *Z*-selective macrocyclization of dialdehyde **80** to macrocycle **81** in surprisingly good yield of 70%. Finally, removal of the protecting groups resulted in the formation of the desired bazzanin A (**29**).

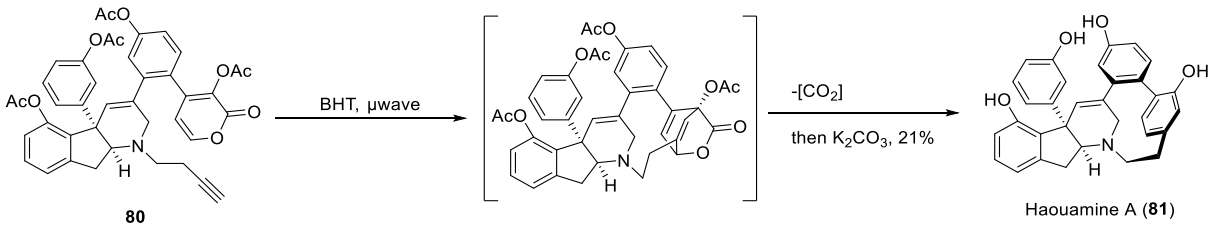


Scheme 11: SPEICHER'S final steps in the synthesis of bazzanin A (**29**) using a MCMURRY reaction for the macrocyclization.

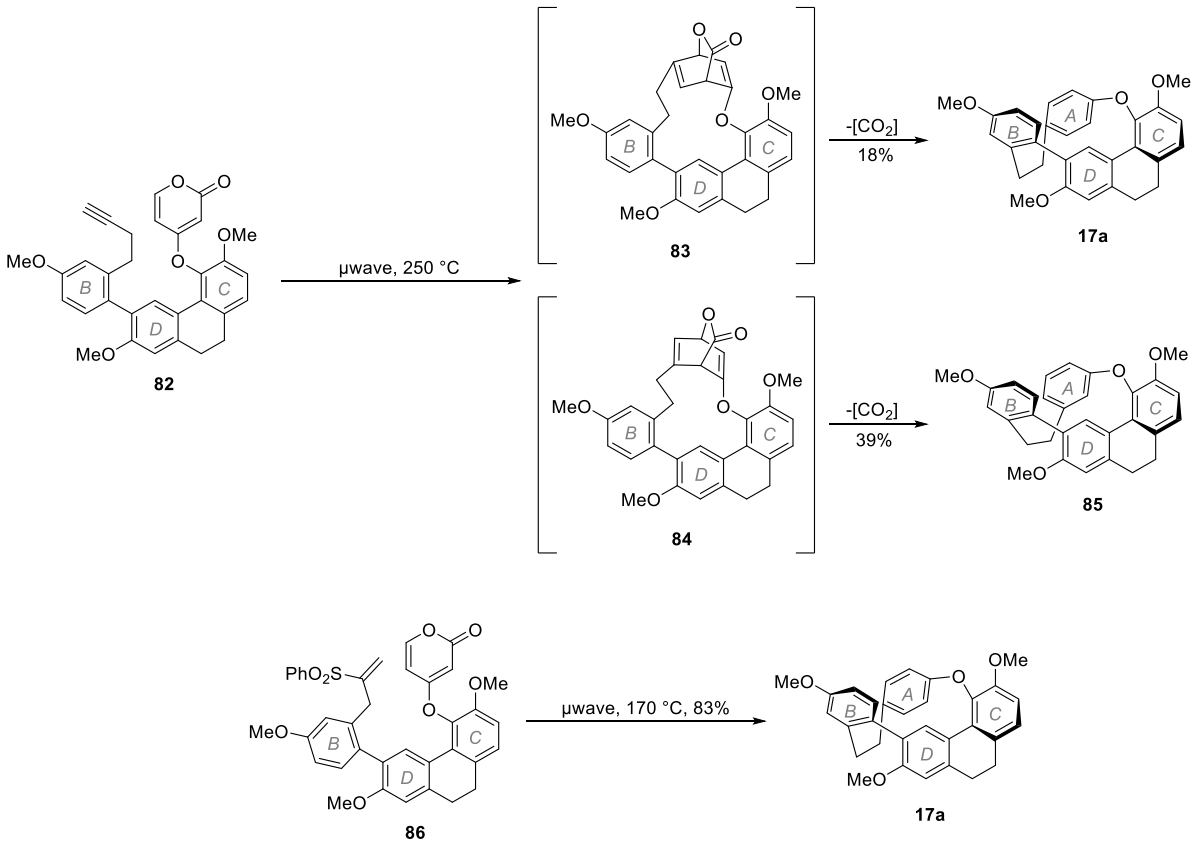
In comparison, the WITTIG methodology requires more steps for the proper functionalization than the MCMURRY-approach but in most cases gives better yields and is more reliable.

1.3.6. Macrocyclization by *de novo* construction of an arene

While previous attempts of macrocyclization focused purely on connectivity issues, BARAN and BURNS published a successful attempt of utilizing a *de novo* synthesis of an arene for the macrocyclization of precursor **80** to houamine A (**81**) in 2006 (see Scheme 12).[52] ZHAO and BEAUDRY utilized this methodology and even refined it in the synthesis of cavicularin (**17**) as shown in Scheme 13.[53] Under high temperatures alkyne **82** undergoes a [4+2] cycloaddition with two possible outcomes (**83** and **84**) leading to a mixture of products. Further retro-DIELS-ALDER reaction under liberation of CO_2 results in the formation of the desired *para*-substituted ring *A* in trimethyl cavicularin (**17a**) in 18% yield or the *meta*-substitution in regioisomer **85** in 39% yield. To lower the required temperatures and gain control over the regiochemistry, ZHAO and BEAUDRY used the polarized vinyl sulfone **86** for the DIELS-ALDER reaction instead. All in all, this methodology led to the formation of trimethyl cavicularin (**17a**) as the single product with 83% yield. Further studies even found a way of utilizing a chiral auxiliar, which was able to allow an enantioselective synthesis.



Scheme 12: [4+2]-cycloaddition as a key step in BARAN'S total synthesis of haouamine A (**81**).

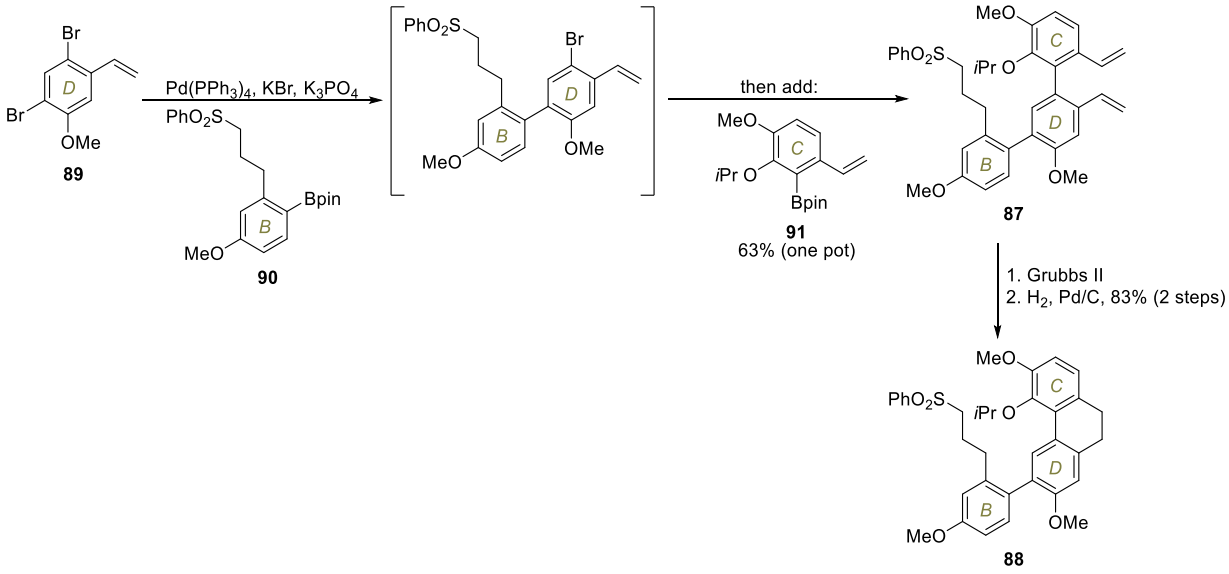


Scheme 13: ZHAO and BEAUDRY'S development of the *de novo* synthesis of an arene as the key macrozyclization in the total synthesis of cavicularin (**17**).

The *de novo* synthesis of arenes is a viable method for the macrocyclization step in the synthesis of MBBs but requires a lot of consideration in regards of regioselectivity.

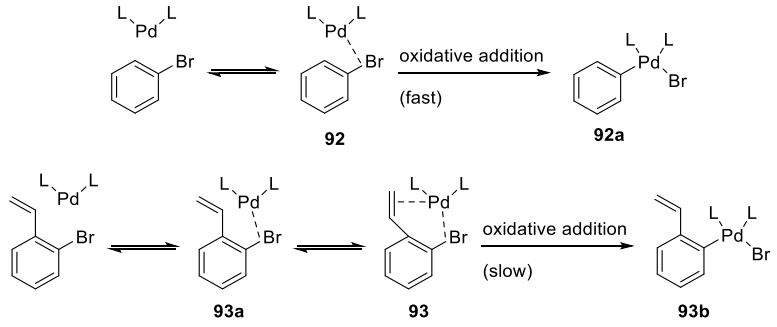
1.4. State of the art in regards of bazzanin K

There is a recent publication dealing with the total synthesis of bazzanin K (**14**). In 2019, BEAUDRY *et al.* published an attempt of the synthesis of this MBB.[54] In previous efforts to synthesize cavicularin (**17**), BEAUDRY and co-workers used a one-pot-SUZUKI-method to prepare the precursor **87** for the dihydrophenanthrene-motif (**88**) from dibromo arene **89** and the boronic esters **90** and **91** (see Scheme 14)[53] utilizing the ability of alkene-substituents to affect the regiochemical control of SUZUKI couplings on dibromo-arenes.[55]



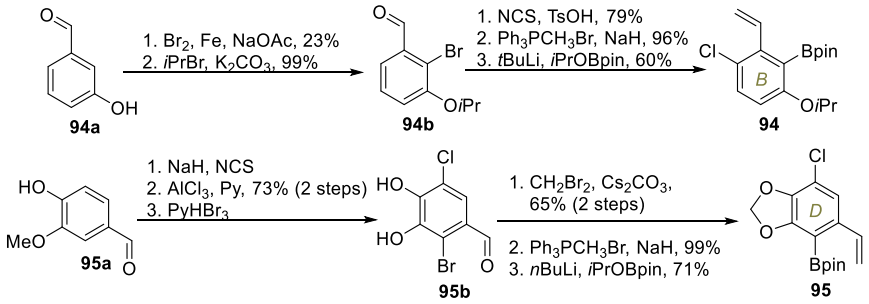
Scheme 14: BEAUDRY'S strategic key step in the synthesis of cavicularin (**17**).

The underlaying mechanistic reason for that selectivity is the reaction rate of the oxidative addition for the Pd-complexes **92** and **93** as depicted in Scheme 15. While complex **92** easily undergoes rapid oxidative addition and subsequent SUZUKI coupling with the respective boronic ester, complex **93** is already saturated in regards of coordination which is why the oxidative addition occurs considerably slower.



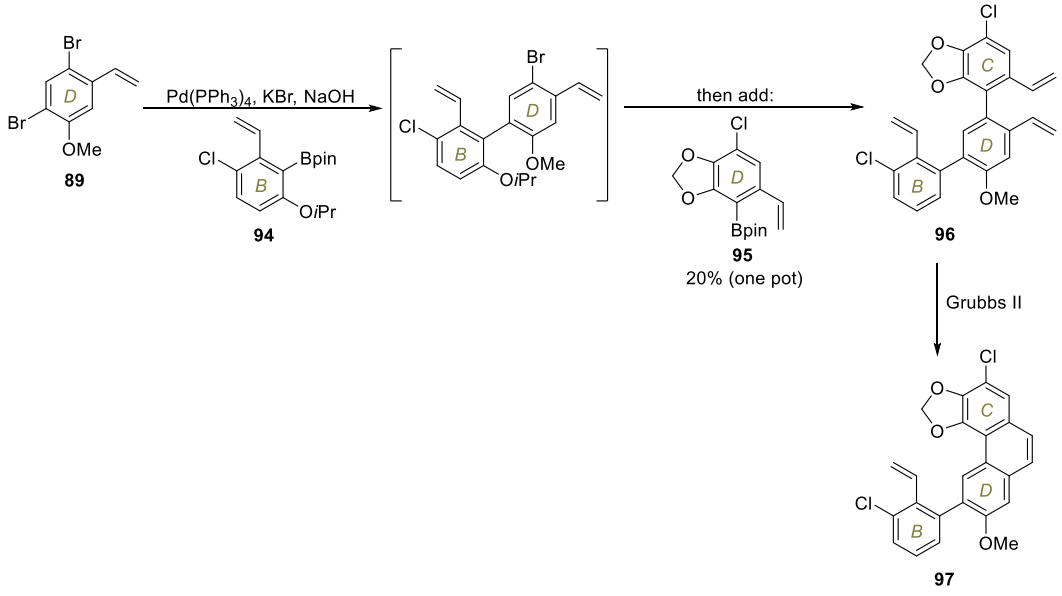
Scheme 15: Mechanistic considerations in regards of reaction rate.

Subsequently, the BEAUDRY group used this to their benefit in their synthetic approach towards bazzanin K (**14**). Starting with ring *B* and *D*, they devised two short synthetic routes to synthesize boronic esters **94** and **95** (see Scheme 16).



Scheme 16: Preparation of boronic esters **94** and **95** as substrates for the three component SUZUKI coupling.

Depicted in Scheme 17 is a three component one-pot SUZUKI coupling of these building blocks which led to the formation of terphenyl **96** in 20% yield. Despite giving two diastereomeric atropisomers, successive ring closing metathesis (RCM) of the product mixture using the GRUBBS II catalyst gave the desired *BCD*-fragment **97**. Even if BEAUDRY did not finish the total synthesis, the methodology is inspiring and shows new possibilities.

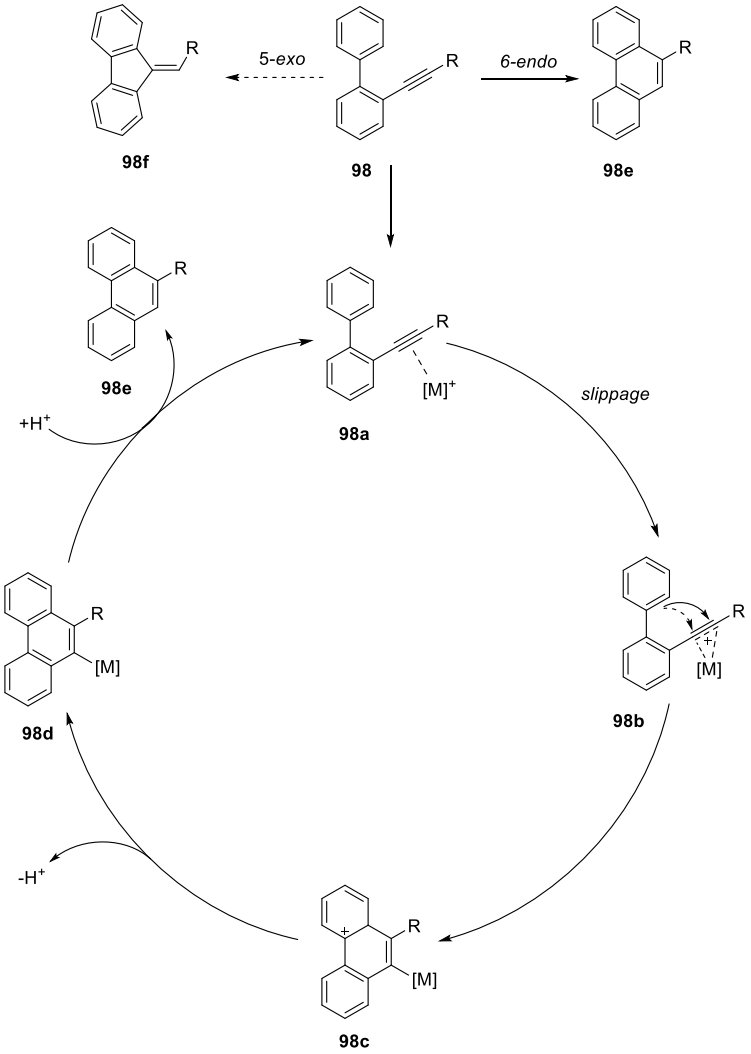


Scheme 17: BEAUDRY'S progress towards the total synthesis towards bazzanin K (**14**).

1.5. π-acid-catalysis in the synthesis of phenanthrenes

The most prominent structural motif featured in bazzanin K (**14**) is the phenanthrene moiety. There are multiple methods for the synthesis of phenanthrenes, one of which is the use of π-acid-catalysis with a substituted biphenyl **98**, that has an alkyne in *ortho*-position.[56,57] The mechanism for that reaction begins with an activation of the polarizable alkyne by coordination of the carbophilic metal M (see **98a** in Scheme 18). Slippage of the metal to one carbon of the alkyne allows the attack of an appropriate nucleophile in **98b**, which is the electron rich phenyl

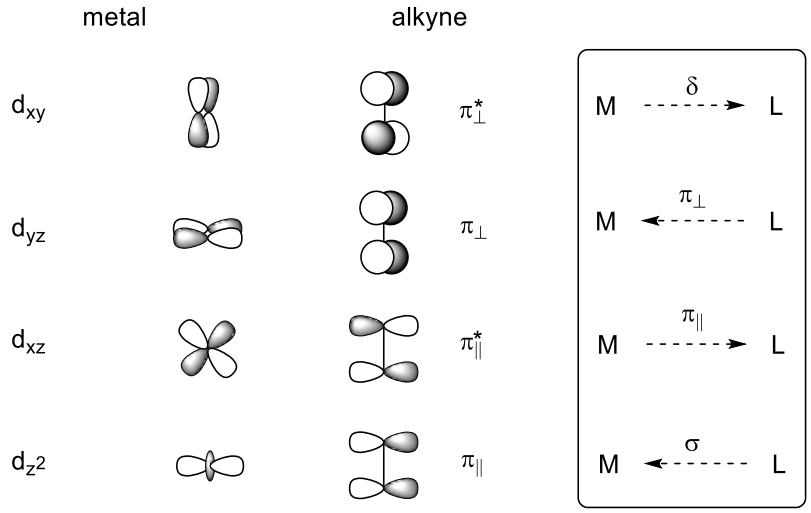
group in *ortho*-position of the alkyne in this example. This attack can take place as a 6-*endo-dig* or 5-*exo-dig* cyclisation. While the first furnishes the desired phenanthrene, the latter reaction leads to the dibenzofulven **98f**. The 5-*exo-dig* cyclisation is depicted with dashed arrows in Scheme 18. FÜRSTNER *et. al.* showed that the product distribution is highly dependent on the catalyst.[56] Nonetheless, the catalysts resulting in good overall yields like $PtCl_2$ or *in situ* formed catalytic systems containing cationic platinum halides and a halide abstractor like $AgSbF_6$ all have a highly π-accepting character in common. After the nucleophilic attack, rearomatization of **98c** under abstraction of a proton facilitates the formation of intermediate **98d**. Finally, proto-demetallation gives the phenanthrene **98e** as a product and the catalytic cycle is closed.



Scheme 18: Mechanism of the transition metal catalyzed cycloisomerization reaction to phenanthrenes.

The rate determining step of this reaction has been determined to be the nucleophilic attack of the aromatic ring to the activated alkyne. Removal of electron density at the metal should increase the reaction rate.[58] Hence, it is highly desirable to further increase the π-acceptor-

properties at the metal-center. In order to understand the overall mechanistic situation, a closer look at the orbital interactions between the alkyne and the respective transition metal shall elucidate the circumstances on a qualitative level. According to the DEWAR-CHATT-DUCANSON model, interactions of alkyne ligands with transition metals can be viewed as donor-acceptor interactions between two closed-shell fragments (see Scheme 19).[59,60] Thus, the bonding situation is described by four general contributions. The σ-symmetric donation of the ligand to the metal has its origin in the overlap of an empty metal orbital with suitable symmetry and the $\pi_{\parallel}$-system of the alkyne which is also responsible for the π-symmetric back-donation of the metal to the ligand. Additionally, the orthogonal, out-of-plane $\pi_{\perp}$ orbitals can furnish ligand to metal donation. Finally, the δ-symmetric back-donation of the metal to the ligand only contributes in a small quantity to the whole bonding situation due to the small orbital overlap.



Scheme 19: Qualitative orbital diagram of the interaction of a transition metal with an alkyne ligand.[60]

The research of the ALCARAZO group focuses next to other topics on the development of α-cationic phosphine-ligands and especially their application in π-acid-catalyzed reactions.[58] The positive charge in direct neighborhood to the phosphorous atom significantly increases the π-acceptor-properties of the ligand. To semi-quantitatively evaluate the donating/accepting character of a ligand, the TOLMANN electronic parameters (TEPs) can be measured experimentally by determining the CO-stretching frequency of $[Ni(CO)_3(L)]$ with the respective ligand L.[61] Due to the toxicity of the required $[Ni(CO)_4]$, it is also favorable to calculate these values with GUSEV'S method.[62] These TEPs together with the cone-angle θ of the ligand can be put into the TOLMAN stereoelectronic map for phosphines (see Fig. 13). Red dots correspond to experimental values, whereas blue dots stand for calculated values.

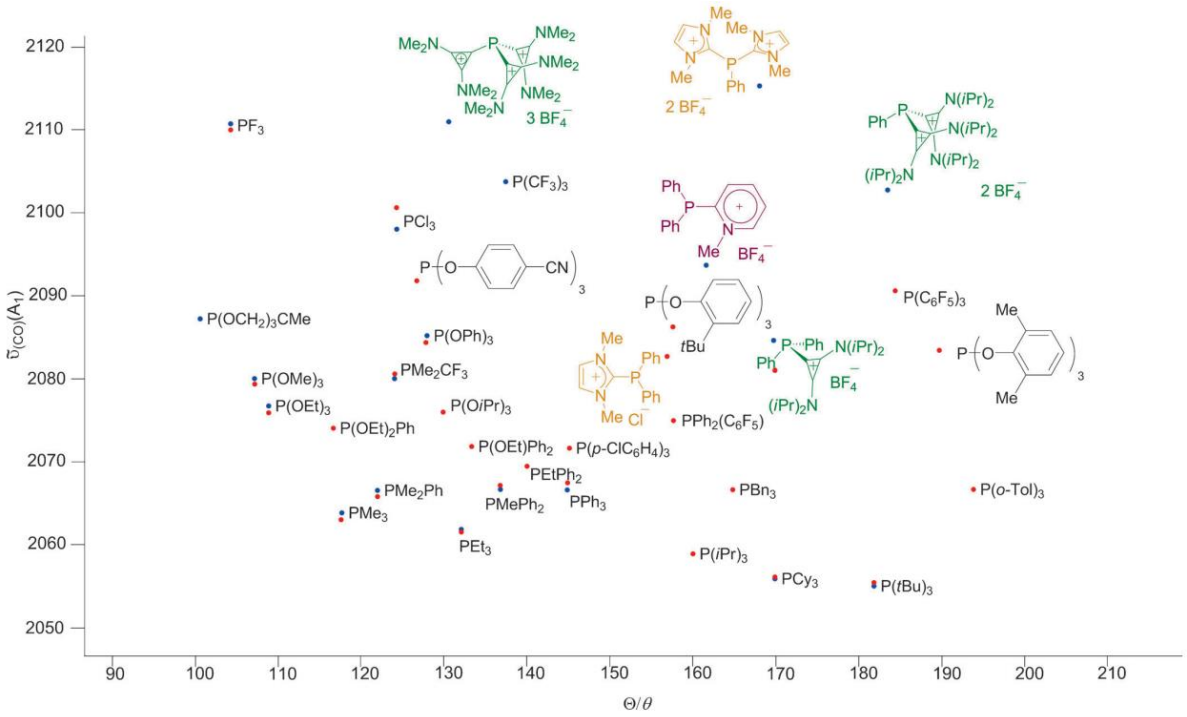


Figure 13: TOLMAN stereoelectronic map for selected phosphines.[58]

One can see that there is a plethora of ligands with low TEPs, which correspond to phosphines with high σ-donating character. However, ligands with higher stretching frequencies corresponding to a high π-accepting character are scarce. Focusing on the black colored ligands on the map, there exist only phosphines such as PF_3, $P(CF_3)_3$ or PCl_3 with CO-stretching frequencies above 2100 cm^{-1}. Despite these excellent π-accepting properties, these phosphines are highly reactive and prone to oxidation in air. Some of the α-cationic phosphine-ligands colored in yellow, green, and purple depict similarly high TEPs. Interestingly, they are bench stable and easy to handle solids making their use very convenient.[58]

The respective Pt(II) and Au(I) complexes of α-cationic phosphine-ligands show great results in cycloisomerization reactions and have been used to synthesize a variety of phenanthrene motifs in natural products (**99-101**)[58], enantiopure helicenes (**102** and **103**)[63], and other structures (**104**)[64] in excellent yield (see Fig. 14, the bond colored in red is the bond formed during the cycloisomerization step).

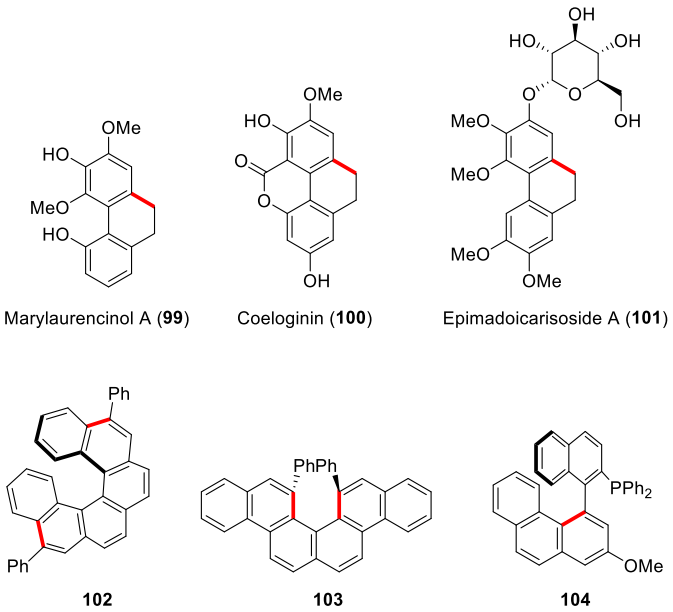


Figure 14: Examples for products with a gold or palladium catalyzed cycloisomerization reaction with α-cationic phosphine-ligands as a key step.

Since this methodology results in excellent yield and has an acceptable functional group tolerance, it shall be the key step for implementing the phenanthrene moiety into bazzanin K (**14**).

2. Aim of the project

The main goal of this project is to find a total synthetic approach towards bazzanin K (**14**). Inspired by the previously described strategies for similar target molecules, bazzanin K (**14**) shall be prepared using appropriately decorated aromatic building blocks, which are to be connected *via* palladium catalyzed cross-coupling reactions. Since the advanced substitution pattern of the building blocks requires high regioselectivity and optimal yields, elaborate strategies must be developed to tackle these issues. This includes, but is not limited to, reasonable protecting group strategies and careful consideration of functional group tolerances of a variety of reactions and transformations. Furthermore, the macrocyclization shall be conducted at some point in the synthetic approach. A plethora of methodologies was introduced in the previous chapters for that transformation and a reliable method must be found in order to facilitate the formation of the core structure of bazzanin K (**14**). Additionally, the phenanthrene moiety shall be implemented by the application of α-cationic phosphine-ligands. Pt(II) or Au(I) complexes with these ligands have the potential to show their great benefit, especially in late-stage functionalizations of intricate precursors of bazzanin K (**14**) Additionally, another significant obstacle in the pursuit of the total synthesis is the axial chirality of the target molecule. Since this issue has not been tackled in related chiral natural products of the MBB family, the problems of the connectivity shall be solved first (see Fig. 15).

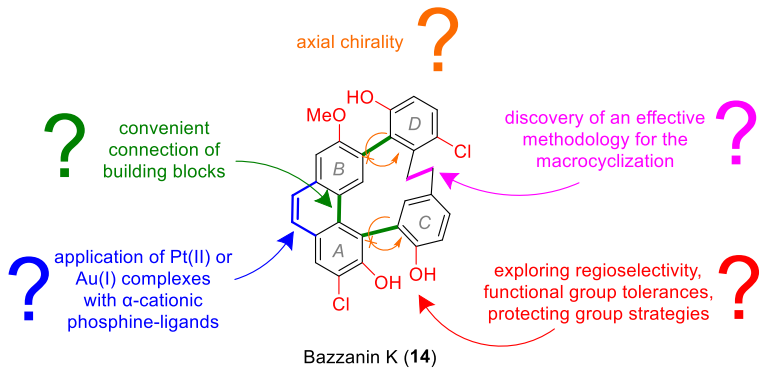


Figure 15: The challenges in the synthesis of bazzanin K (**14**) tackled in this work.

The startling complexity of bazzanin K (**14**) makes it imperative to deploy the key steps of the envisaged synthesis on a simplified model system. Following this preliminary approach towards the synthesis of the target molecule, the key steps of the total synthesis can be tested in regards of their feasibility and limitations without spending an exceeding amount of time producing highly substituted yet inexpedient aromatic compounds. For the sake of further simplification, the possible chiral nature of the model substrate shall be ignored. As mentioned before, the critical steps in the synthesis of bazzanin K (**14**) are primarily the macrocyclization and the introduction of the phenanthrene motif to prove the viability of cationic phosphines in gold or platinum catalysis regarding the synthesis of phenanthrenes in complex structures *via* hydroarylation (see Fig. 16). However, with this proof of concept in hand, the total synthesis of bazzanin (K) (**14**) can commence.

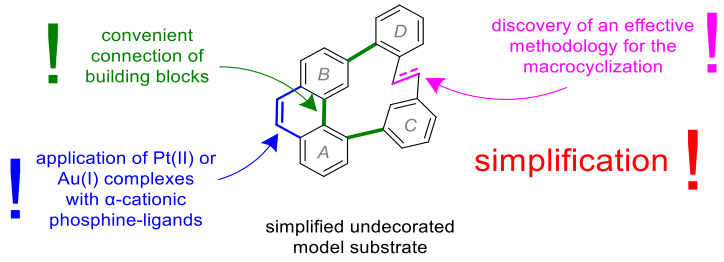
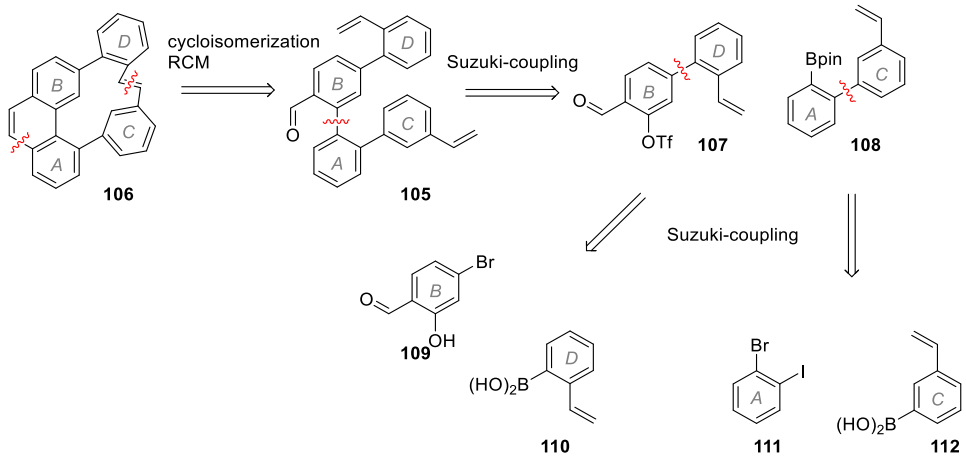


Figure 16: Less challenging hurdles in the synthesis of a simplified model substrate as proof of concept.

2.1. Synthesis of a model substance

2.1.1. RCM as a key step for the macrocyclization

The very first approach for the construction of a macrocycle will be the application of ring-closing metathesis (RCM) of a dialkene under high diluted conditions. Even though RCM did not prove useful in the synthesis of riccardin C (**19**)[48] it could produce better results for other related structures. Furthermore, the di-alkene **105** is accessible in a few steps. Retrosynthetic analysis (see Scheme 20) led to a straightforward synthesis of a suitable substrate **106** by separating the bond on the left side for the cycloisomerization and the right double bond for the RCM.

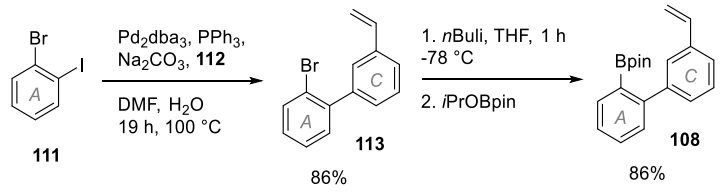


Scheme 20: Retrosynthetic analysis of the model substance **106**.

A sequence of palladium catalyzed SUZUKI cross-coupling reactions should lead to the desired intermediate **105**. The correct substitution pattern is crucial not only for the position of the functional groups of the natural product itself but also for a strategy of multiple cross-coupling reactions. A nucleophilic and a halogen- or pseudohalogen- substituted substrate are needed. Since the SUZUKI coupling is a reliable tool in connecting aromatic building blocks (see introduction), it was chosen as the C-C coupling for these reactions. Triflates are a reactive functional group for SUZUKI couplings,[65] which can easily be generated from a phenol.[66] Since phenols of many varieties are abundantly found in nature, they are cheap and readily available candidates for suitable starting substrates. That means the next step in the retrosynthesis is a division of the aldehyde **105** into the triflate **107** and the boronic ester **108** which should be suitable coupling partners following a SUZUKI coupling protocol. The triflate can be further divided into the bromide **109** which can be turned into a triflate and the boronic acid **110** which should facilitate the formation of the desired C-C-bond in accordance with a SUZUKI-protocol. At first, a SUZUKI coupling with 2-iodobromobenzene (**111**) and boronic

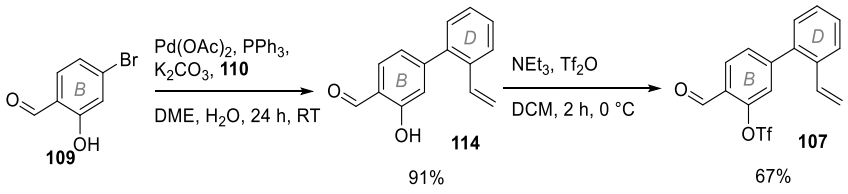
acid **112** should be highly regioselective as the iodide is more reactive than the adjacent bromide. After that, a lithium-halogen-exchange and borylation with *i*PrOBpin should yield the desired boronic ester **108**.

Beginning with commercially available boronic acid **112** and 2-iodobromobenzene (**111**), regioselective C-C bond formation yielded the corresponding biphenyl **113** in acceptable yield of 86%. In order to obtain a suitable substrate for the following SUZUKI coupling, a lithium-halogen-exchange was carried out and the reaction was quenched with a boronic ester. Simple esters like triethyl- or triisopropyl borates and successive acidic workup did not yield the respective boronic acid. A better solution was the addition of *i*PrOBpin instead. This way pinacolborane **108** was isolated in excellent yield as seen in Scheme 21.



Scheme 21: Synthesis of *AC*-fragment **108**.

Having the *AC*-fragment **108** of the molecule in hand, the next step was the preparation of the *BD*-fragment. Starting with commercially available boronic acid **110** and aldehyde **109**, a simple palladium mediated cross-coupling yielded the biphenyl **114** in excellent yield (Scheme 22). Again, it was necessary to implement a suitable substituent that allows for a cross-coupling reaction to occur. To introduce a triflate functionality into the molecule, an esterification of phenol **109** was carried out with triflic anhydride. Triflate **107** was obtained in acceptable yield as a colorless solid. Connectivity was confirmed by X-ray crystallography (Fig. 17).



Scheme 20: Synthesis of the *BD*-fragment **107**.

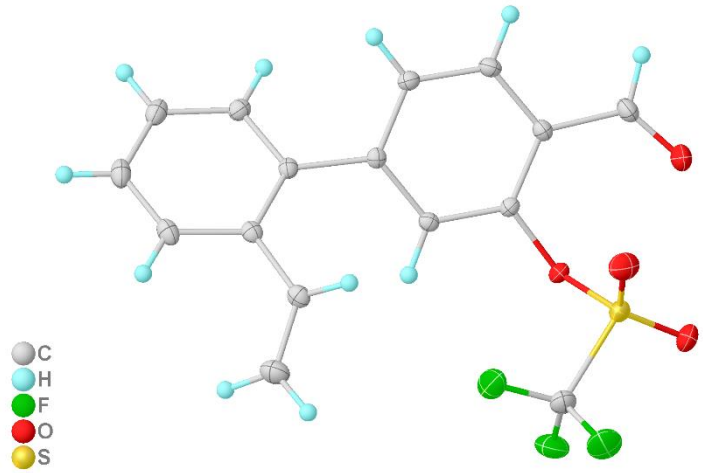
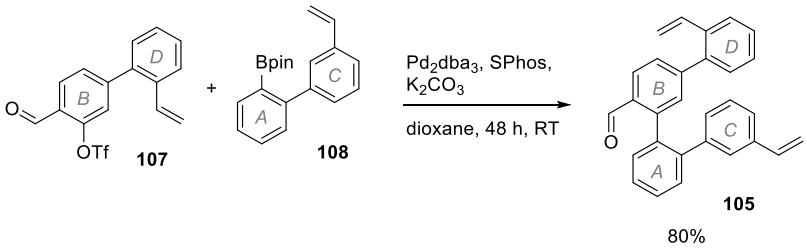


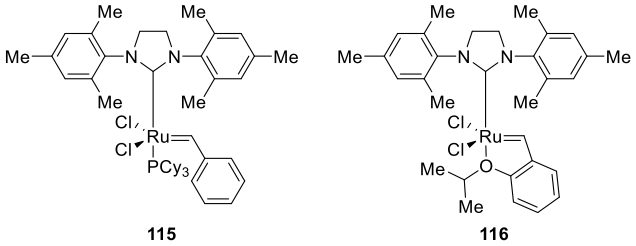
Figure 17: Molecular structure of **107** in the solid state. Displacement ellipsoids drawn at 50% probability level.

A final SUZUKI coupling of the previously prepared triflate **107** and the boronic ester **108** yielded the desired tetraarene **105**. A NEGISHI coupling could probably lead to the same result but since it requires a highly nucleophilic organo-zincate, the aldehyde of triflate **107** would have needed protection as an acetal. To minimize steps, in this specific case the SUZUKI coupling was the reaction of choice (Scheme 23).



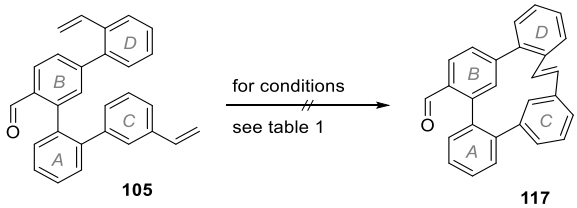
Scheme 21: Synthesis of tetraarene **105**.

With **105** in hand, multiple attempts at the macrocyclization were carried out using different catalysts such as GRUBBS II (GII, **115**) or HOVEYDA-GRUBBS II (HGII, **116**) (see Scheme 24 and Fig. 18), varying the concentrations and temperatures (see table 1) in the attempted RCMs. To avoid oligomerization, highly diluted conditions were chosen.[67] The second-generation GRUBBS catalyst **115** was chosen because of its availability and frequent use for a variety of transformations.[68] Because of the lack of conversion with this catalyst however, the second generation HOVEYDA-GRUBBS catalyst **116** was tested because of its higher stability.[69] Unfortunately, no conversion could be observed with either of these catalytic systems.



115 116

Figure 18: The catalysts GRUBBS II (**115**) and HOVEYDA-GRUBBS II (**116**) used in the attempted RCM.



105 117

Scheme 22: Attempts at RCM of aldehyde **105**.

Table 1: Reaction conditions for the macrocyclization *via* RCM.

Entry	Solvent	Catalyst	Concentration	Temperature	Time	Result
1	DCM	GII, 25 mol%	1.06 µmol/L	reflux	24 h	no conversion
2	DCM	GII, 10 mol% +10 mol% after 28 h	0.45 µmol/L	reflux	48 h	no conversion
3	toluene	GII, 10 mol% +10 mol% after 17 h	0.45 µmol/L	90 °C	72 h	no conversion
4	DCM	GII, 10 mol% +10 mol% after 4 h +10 mol% after 8 h +10 mol% after 24 h	0.25 µmol/L	RT	72 h	no conversion
5	DCM	HGII, 10 mol% +10 mol% after 2 d	0.25 µmol/L	RT	6 d	no conversion
6	DCE	HGII, 10 mol% +10 mol% after 1 d	0.25 µmol/L	80 °C	4 d	no conversion
7	DCE	HGII, 10 mol% +10 mol% after 2 d	0.25 µmol/L	40 °C	5 d	no conversion

It was assumed, that there is a free equilibrium between the two conformers, with the terminal alkenes turned away in the one and at relatively close proximity in the other. Quantum theoretical-calculations (B3LYP/6-31+G(d)) showed that the enthalpic energy difference between the two conformers is 12.7 kJ/mol (see Fig 19). Considering only the thermodynamic situation, apparently the for the reaction purposeful conformer is not favored, and thus

minimizing the probability of the two alkenes meeting, which is a fundamental problem with this reaction.

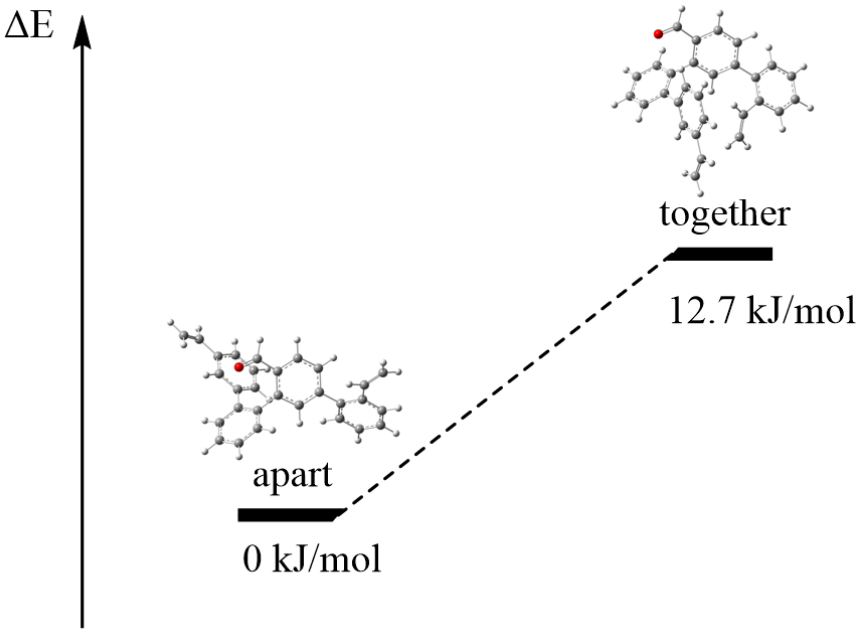


Figure 19: Schematic depiction of the energetic differences between the two conformers of compound **105**.

Since no conversion to macrocycle **117** could be observed, RCM should be tried with the phenanthrene motif already implemented into the molecule, to see if the changed angles in the molecule could help the macrocyclization step. In order to obtain the phenanthrene **118**, the tetraarene **105** had to be turned into the alkyne **119** using the OHIRA-BESTMANN reagent (**120**). The OHIRA-BESTMANN reagent (see Fig. 19) is able to perform a conversion of an aldehyde into an alkyne.[70] This is a variant of the SEYFERTH-GILBERT-homologation that requires K_2CO_3 as a base which is milder than the alcoholate that is usually used for the standard SEYFERTH-GILBERT-homologation.[71] According to literature,[72] the reaction to the phenanthrene **118** with KOZMAPhos[Pt] (**121**) (see Fig. 20) as the precatalyst was carried out in acceptable yield and in notably short reaction time (Scheme 25).

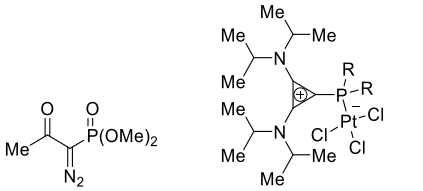
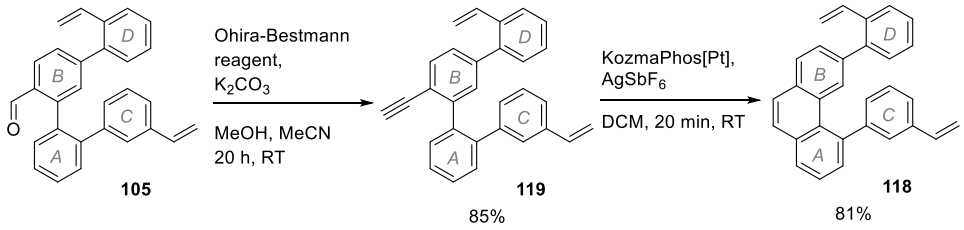


Figure 20: The OHIRA-BESTMANN reagent (**120**) for the homologation of an aldehyde to the alkyne and KOZMAPhos[Pt] (**121**) for the cycloisomerization.



Scheme 23: Synthesis of phenanthrene **118**.

The connectivity of terminal alkyne **119** could be confirmed by X-ray crystallography (Fig. 21).

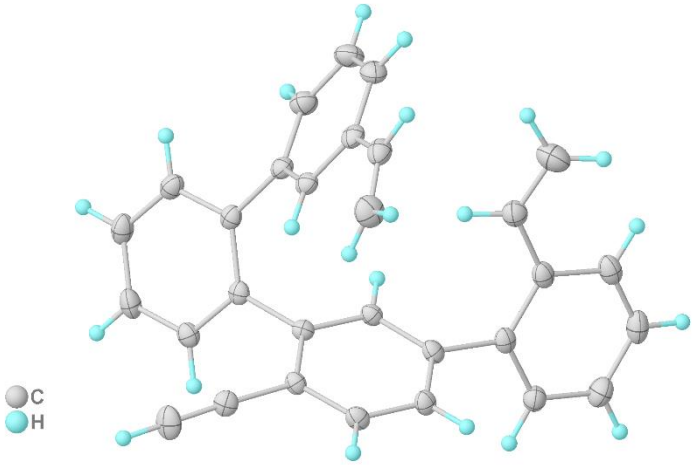
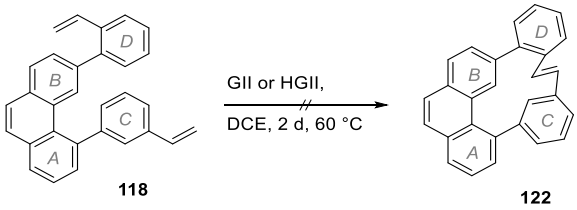


Figure 21: Molecular structure of **119** in the solid state. Displacement ellipsoids drawn at 50% probability level.

Unfortunately, the follow up reaction with both GRUBBS II- and HOVEYDA- GRUBBS II-catalyst to macrocycle **122** was not successful since only starting material could be reisolated (Scheme 26). The reactions were carried out using 20 mol% of the respective catalyst at a concentration of 0.25 µmol/L. The lack of conversion was expected due to the calculations carried out with the related substrate **105**.



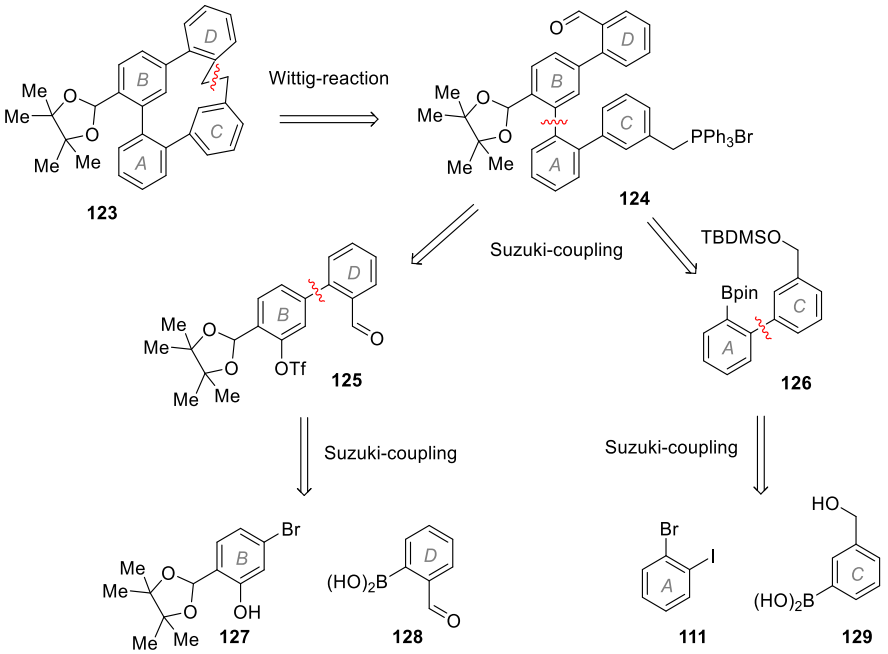
Scheme 24: Attempted macrocyclization of phenanthrene **118** by RCM.

These results led to the understanding that the formation of the phenanthrene is not likely to cause trouble in the synthesis of the natural product, but the macrocyclization using RCM is rather problematic. To overcome the shortcomings of the attempted RCM, a new strategy was devised. Because of the success in the total synthesis of a variety of other MBBs, a similar

retrosynthetic pathway was worked out based on an intramolecular WITTIG reaction as the key step.

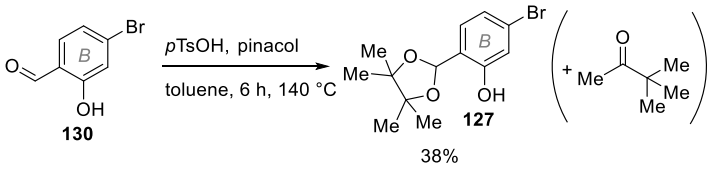
2.1.2. Intramolecular WITTIG reaction as a key step for the macrocyclization

Because of the difficulties in the RCM as a method for the ring closure, a strategy was developed revolving around a WITTIG reaction for the macrocyclization to model substrate **123** similar to literature known procedures for relates MBBs (see introduction for examples and references). For that, tetraarene **124** was required which contains an aldehyde and a P-ylide at the proper positions of the molecule (Scheme 27). To obtain the WITTIG salt, a benzyl bromide was needed as a substituent at the *C*-ring of the molecule, which could be generated from the free alcohol. This substrate **124** was further divided at the bond connecting the *BD*-fragment with the *AC*-fragment. The retrosynthetic separation resulted in triflate **125** which has a suitable, particularly reactive group for a SUZUKI coupling or any other cross-coupling reaction, and boronic ester **126** which is also substituted in a way that a SUZUKI coupling can occur at the correct position. Important is the presence of the protected benzyl alcohol which is the precursor for the P-ylide. The *BD*-fragment **125** was again divided into a pair of coupling partners along the bond connecting the two arenes, one of which is the bromide **127** and the other the boronic acid **128** with an aldehyde substituent. Similar to the retrosynthetic analysis described for substrate **108**, the molecule was separated into 2-iodobromobenzene (**111**) which can preferably react in a SUZUKI coupling at the more reactive iodo-substituent and the boronic ester **129** with a benzyl alcohol as a substituent. This alcohol should be protected after the coupling of the two substrates to enable the borylation to *AC*-fragment **126**.



Scheme 25: New retrosynthetic analysis for a WITTIG reaction as the ring closing reaction.

The first step in this new approach was the conversion of the aldehyde **130** into its protected relative, the pinacol **127** (see Scheme 28). This protecting group was chosen, because of its stability towards many conditions, especially basic and acidic environments.[73] Preceding experience with other protecting groups and their rather unsatisfactory stability in SUZUKI couplings deemed this necessary, since it was crucial for some intermediates to include a free aldehyde next to the protected aldehyde.



Scheme 26: Synthesis of the protected bromide **127** with pinacolone as a side product.

The yield of the reaction was poor due to the pinacol rearrangement occurring as a side reaction in this acidic environment. Using an excess of pinacol led to a small increase in the yield but the side product pinacolone was always present in big amounts after the reaction. However, this reaction could be performed on a multigram scale, and the starting material could easily be reisolated. Furthermore, a single crystal of the product **127** could be isolated, and X-ray crystallographic analysis confirmed the connectivity (Fig. 22).

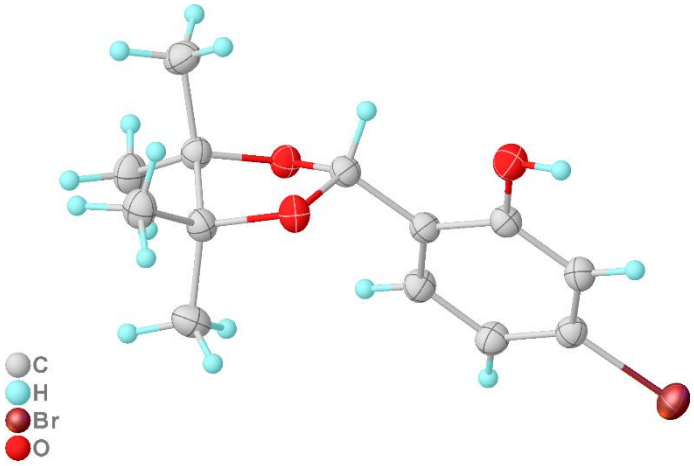
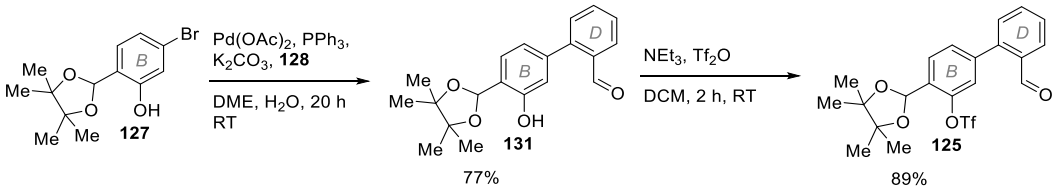


Figure 22: Molecular structure of **127** in the solid state. Displacement ellipsoids drawn at 50% probability level.

A SUZUKI coupling reaction with the commercially available boronic acid **128** led to the formation of the desired biphenyl **131** in good yields (Scheme 29). To obtain the triflate **125** as a suitable substrate for a successive cross-coupling in quantitative yield, phenol **131** was treated with triflic anhydride under basic conditions. X-ray analysis confirmed the connectivity of *BD*-fragment **131** (Fig. 23).



Scheme 29: Synthesis of triflate **125** *via* SUZUKI coupling of bromide **127** and boronic acid **128**, and successive triflylation.

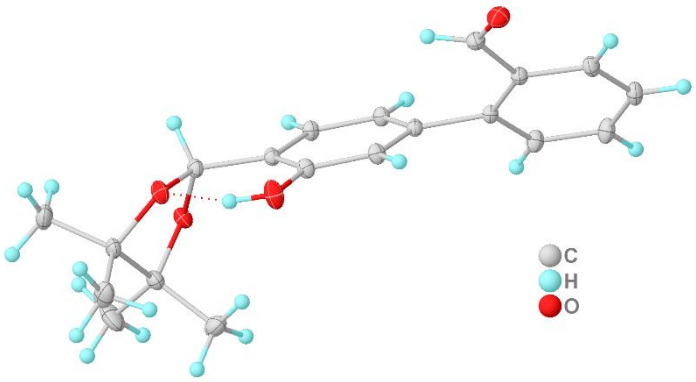
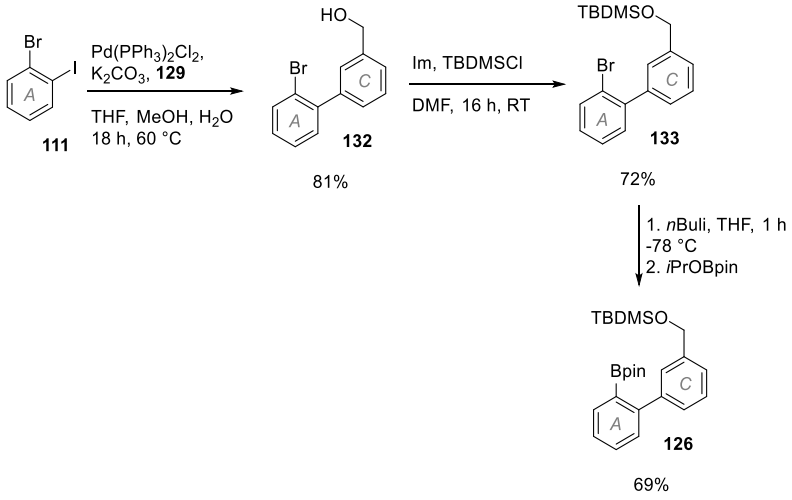


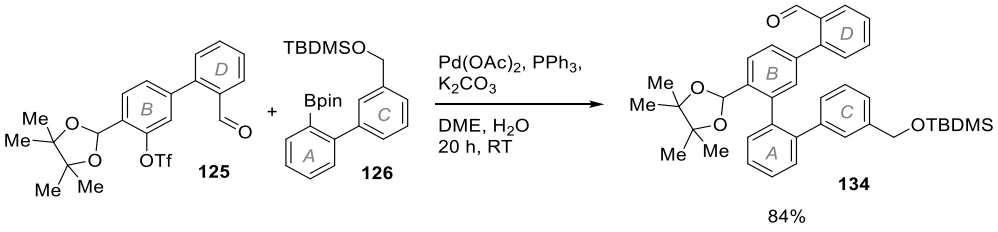
Figure 23: Molecular structure of **131** in the solid state. Displacement ellipsoids drawn at 50% probability level.

The preparation of the *AC*-fragment **126** of the molecule was started with a SUZUKI coupling between 2-iodobromobenzene (**111**) and the commercially available boronic ester **129** in satisfactory yield (see Scheme 30).



Scheme 27: Synthesis of the boronic ester **126**.

The benzyl alcohol **132** had to be converted into the respective boronic ester. To prevent side reactions, the alcohol was silylated beforehand with TBDMSCl to deliver silyl ether **133**. Now the borylation *via* lithium-halogen-exchange and successive quenching with *i*PrOBpin was executed. Other sources of boron were not considered, because of the satisfactory results with previous substrate **108** in termss of yield and stability. The connection between the *BD*-fragment **125** and the *AC*-fragment **126** in a SUZUKI coupling to tetraarene **134** was carried out in good yield (Scheme 31).



Scheme 28: Coupling of triflate **125** and pinacol borane **126** to tetraarene **134**.

The NMR-spectra (Fig. 24) of **134** showed the formation of two diastereomers in a ratio of ~1:1.7, especially noticeable due to the aldehyde- and the benzylic protons. Furthermore, the methyl groups of the protecting group show a complicated pattern of signals.

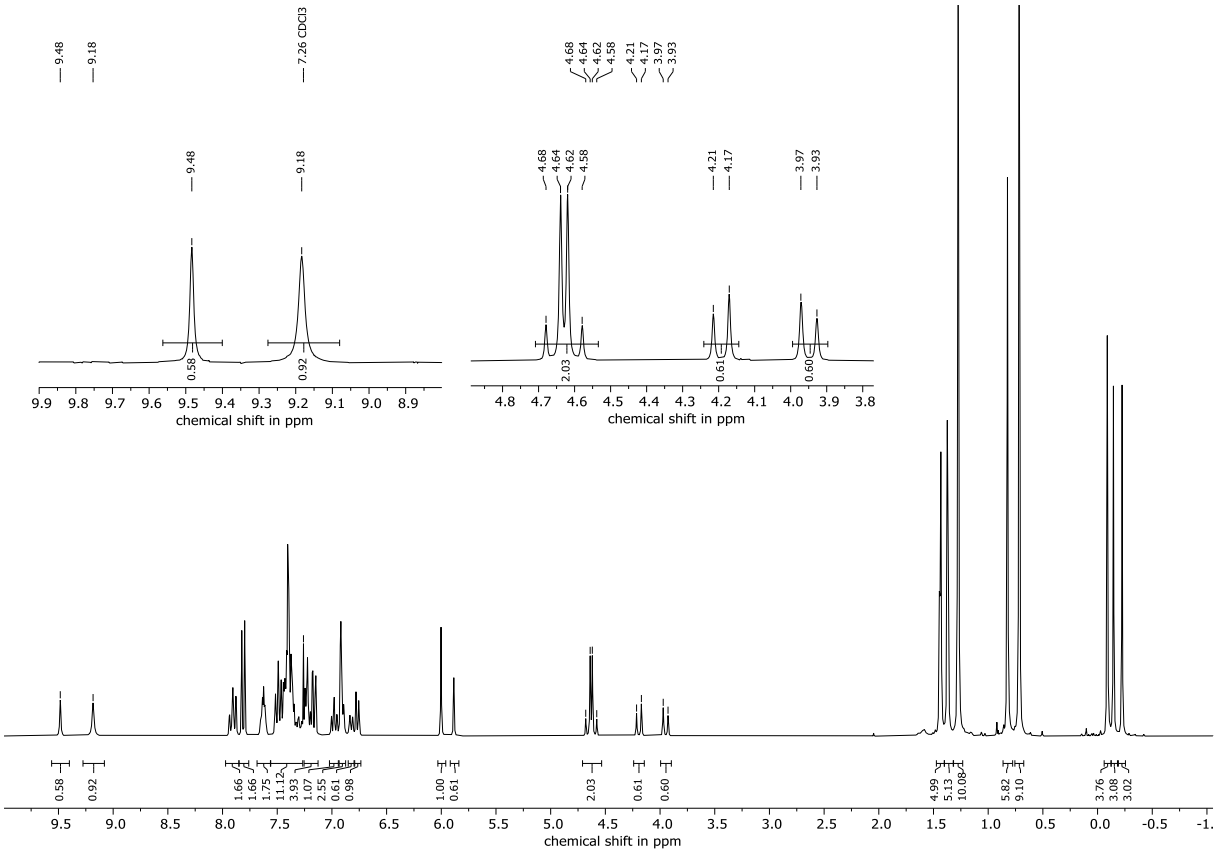
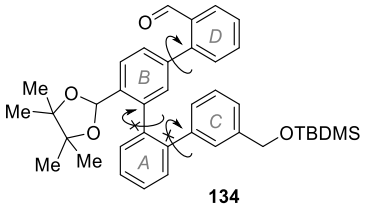


Figure 29: ^{1}H NMR-spectrum of the tetraarene **134**, showing two diastereomers.

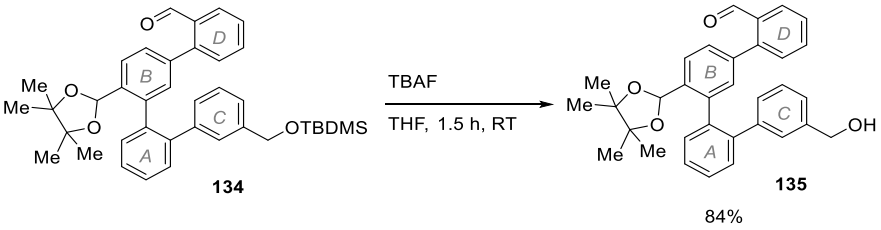
Most likely the rotation of *AB*- and the *AC*-axis in this molecule is blocked due to steric hindrance. The *D*-arene in Fig. 25 has the aldehyde as the only *ortho*-substituent, which is rather small, while the *B*-arene has the protected aldehyde as a bulky substituent in *ortho*-position. The pinacol-protected aldehyde occupies a rather large volume. Furthermore, arene *A* has arene *C* as another sterically demanding substituent in *ortho*-position. *AC*-axis only has one arene with an *ortho*-substituent, but it is a substituted arene that is characterized by a lot of steric demand. Arene *C* only has a meta-substituent, which is rather large, thus leading to the hindered rotation around the *AC*-axis (Fig. 25).



134

Figure 24: Hindered rotation of the bonds in molecule **134** due to bulky substituents.

As it was not possible to separate the diastereomers, the next synthetic steps were carried out nonetheless, to prove at least that the following steps are possible. For further functionalization the silyl group was cleaved with a fluoride (Scheme 32).



Scheme 30: Deprotection of the silyl ether **134** with TBAF as a fluoride source.

Interestingly, with the steric bulk of the TBDMS group gone, no different diastereomers were observed in the NMR-spectra of **135** (Fig. 26).

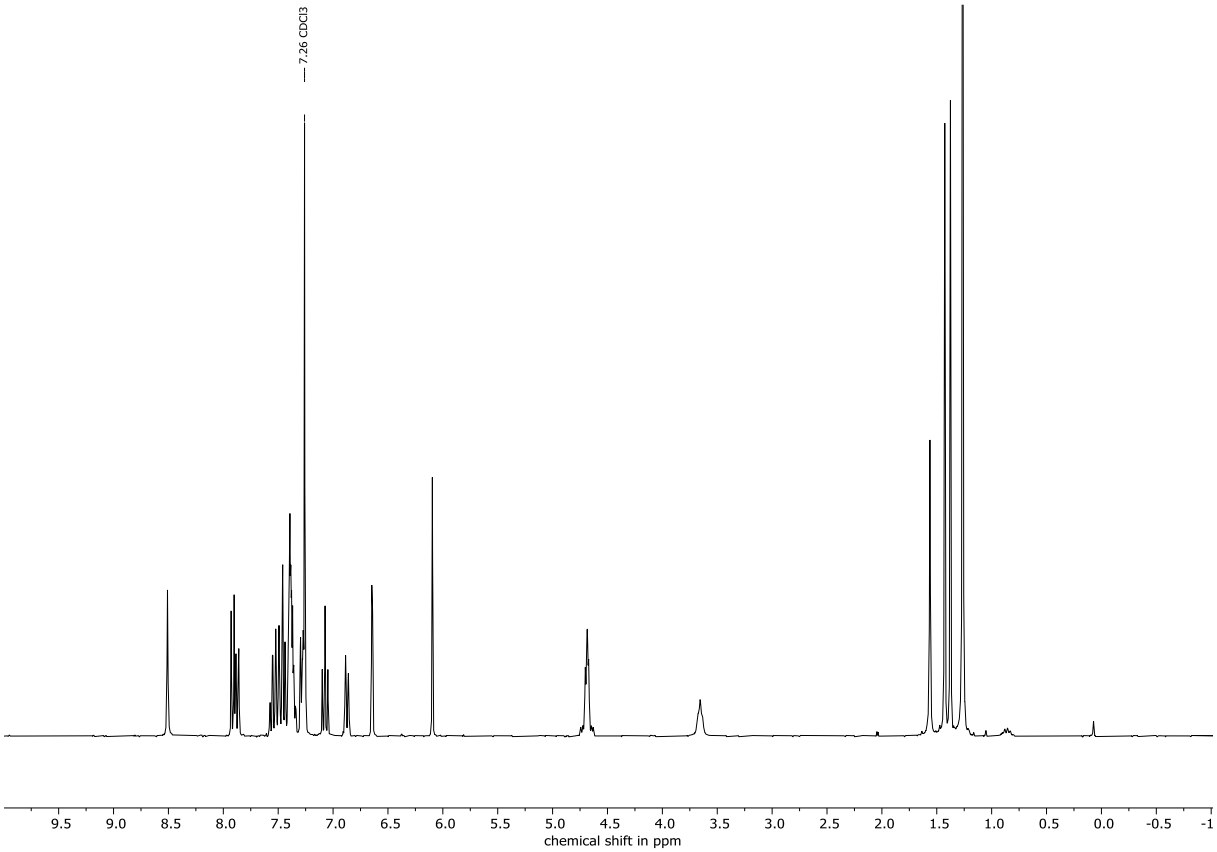


Figure 26: ^{1}H NMR-Spectrum of benzylalcohol **135** showing no different diastereomers.

This further indicates the previously mentioned origin of the two diastereomers due to steric hindrance. Moreover, single crystal diffractometry confirmed the connectivity and revealed an intramolecular hydrogen-bond between the benzyl alcohol and the aldehyde present in the molecule in the solid state (Fig. 27).

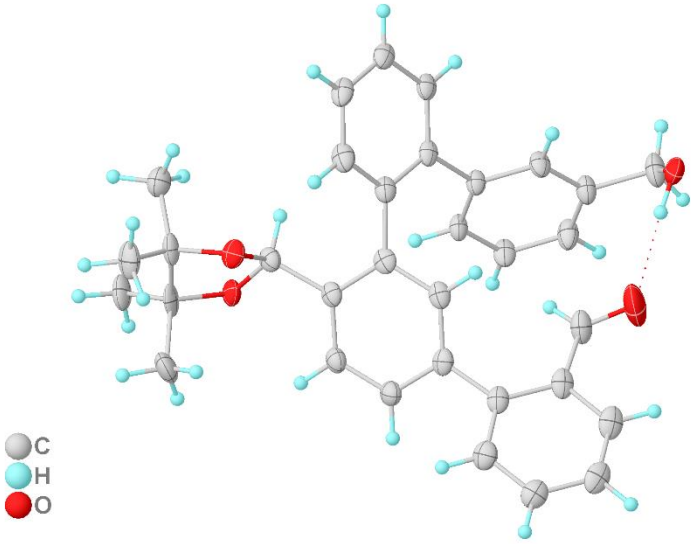
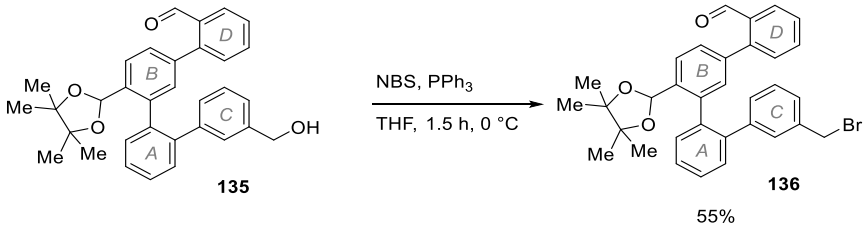


Figure 27: Molecular structure of **135** in the solid state. Displacement ellipsoids drawn at 50% probability level.

The free benzyl alcohol **135** was converted to the benzyl bromide **136** in mediocre yield using a variant of the APPEL reaction with NBS and PPh_3 (Scheme 33). Standard APPEL conditions[74] were avoided since they are very similar to the conditions in the first step of the COREY-FUCHS reaction. It could be possible that the aldehyde reacted to the respective 1,2-dibromoalkene with CBr_4 and PPh_3.[10] A reaction with the very reactive PBr_3 would probably lead to the formation of the desired product, but under these harsh conditions side reactions are more likely, so this milder version of the reaction was chosen instead.



Scheme 33: Synthesis of benzyl bromide **136** *via* a variety of the APPEL reaction.

Again, the NMR-spectra showed that the product was a mixture of two diastereomers in a ratio of ~1:2 (Fig. 28). This is easiest to recognize with the aldehyde protons and the benzylic protons. The bigger radius of bromide compared to the OH group could only partially explain why the bond between ring *A* and *C* is not able to rotate freely.

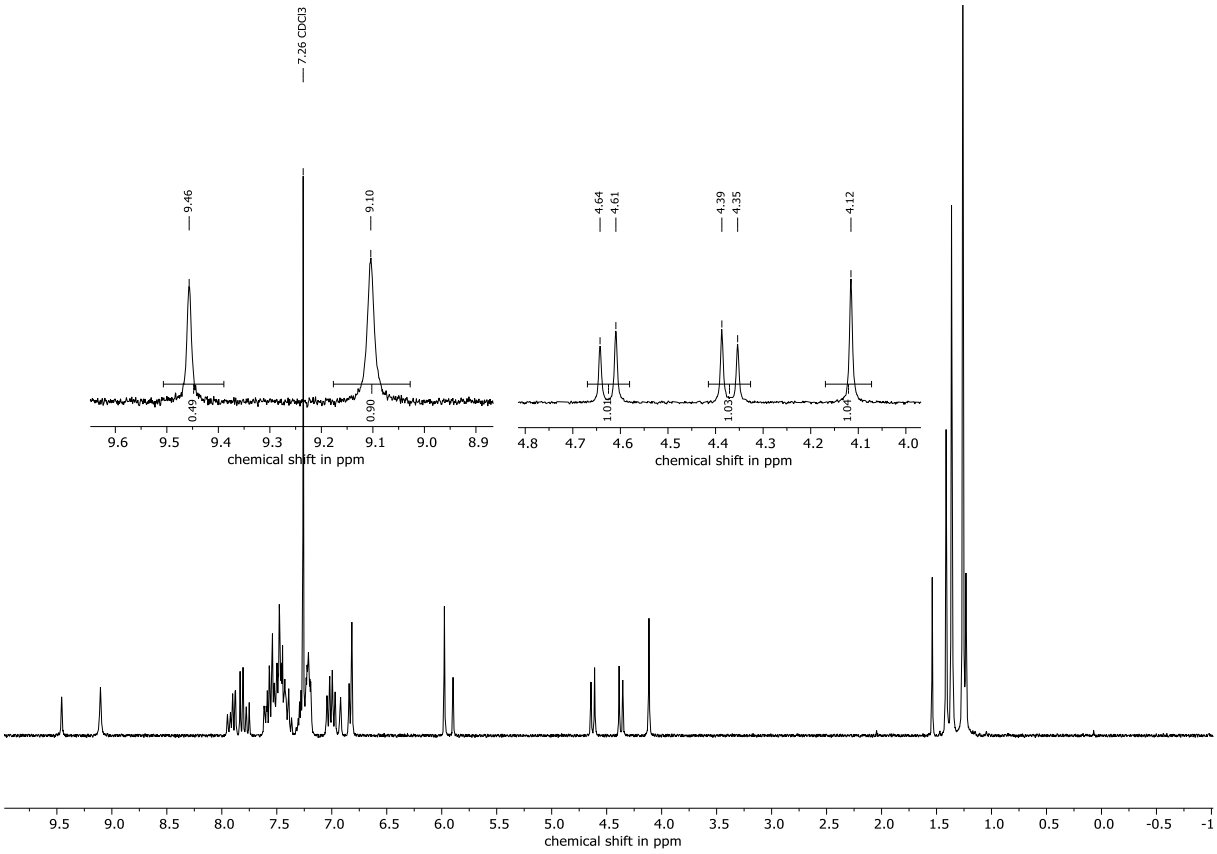
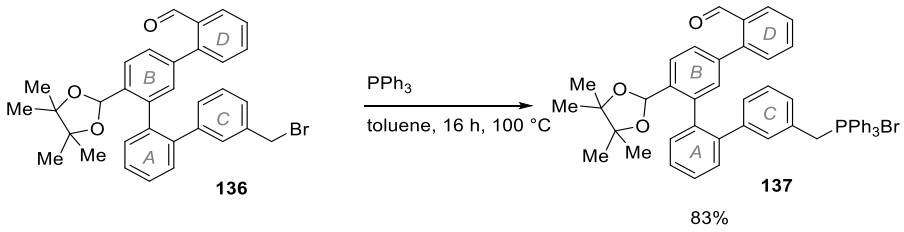


Figure 28: ^{1}H NMR-spectrum of bromide **136** showing again the presence of two different diastereomers.

Finally, reaction with PPh_3 under elevated temperatures afforded the WITTIG salt **137** as a key intermediate for the macrocyclization *via* WITTIG reaction in acceptable yield (Scheme 34).



Scheme 34: Synthesis of the WITTIG salt **137** by nucleophilic substitution.

According to the NMR-spectra, two diastereomers were obtained in this reaction in a ratio of ~4:5 (Fig. 29). Since the starting material was a mixture of diastereomers this result is to be expected. However, it is interesting to note the change of the ratio in the synthetic sequence.

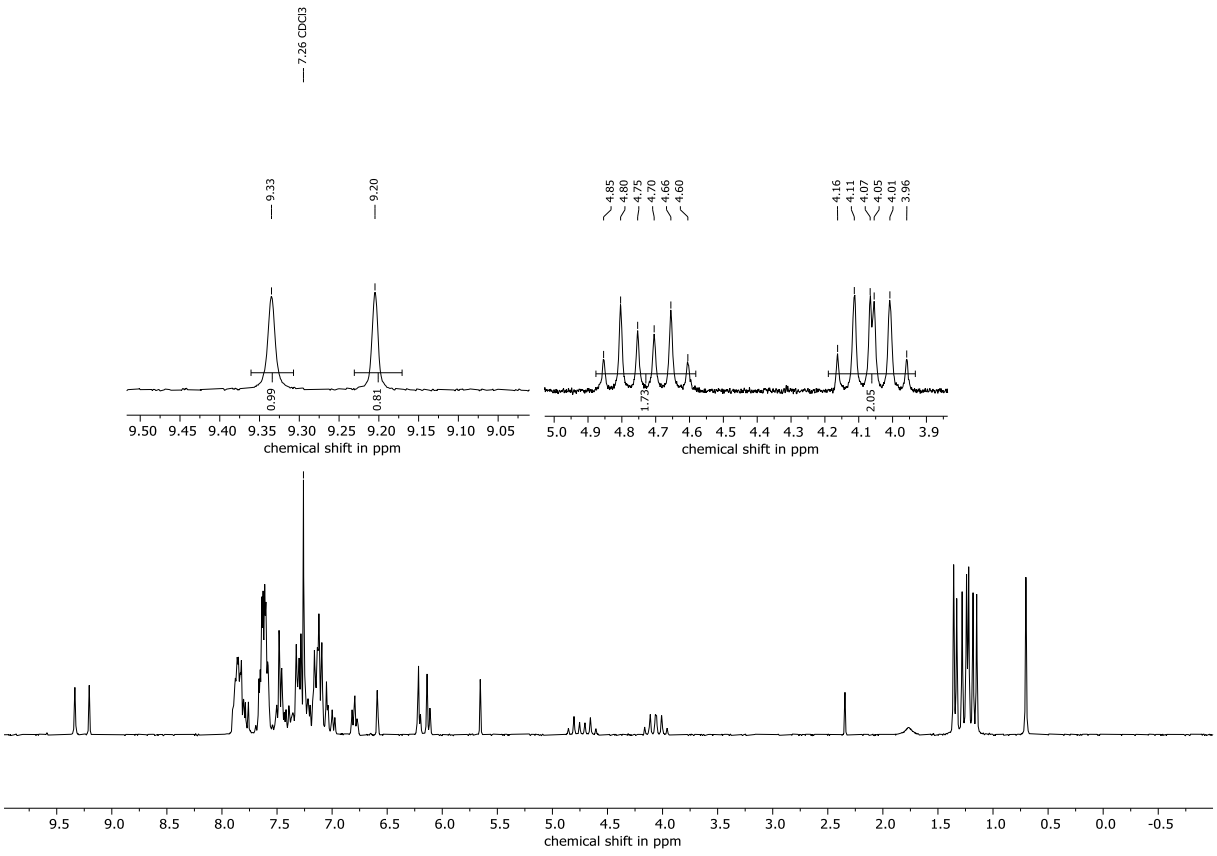
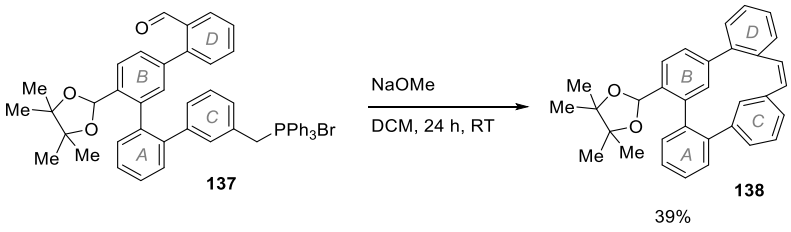


Figure 29: [1]H NMR-spectrum of WITTIG salt **137** showing two diastereomers.

The explanation for the presence of different diastereomers is most likely a rotation barrier in the range of 50 to 80 kJ/mol. Since the chromatographic separation of the isomers was not possible, higher energy barriers are not very likely. With this product-mixture in hand, the macrocyclization was attempted under pseudo-high dilution by slow addition of a solution of the salt **137** into a solution of a base. This way, the concentration of the substrate stayed low as the starting material had time to be consumed before further substrate was added. Higher concentrations of the substrate usually promote the formation of dimers or oligomers instead of the intramolecular ring closure.[67] Like EICHER in his synthesis of riccardin C (**19**), NaOMe was used to deprotonate the salt **137** to the ylide,[40] which facilitated the desired ring formation in mediocre but satisfying yield (Scheme 35).



Scheme 35: Synthesis of macrocycle **138** by intramolecular WITTIG reaction under pseudo-high dilution.

In contrast to the WITTIG salt, the product contained only one diastereomer in the *Z*-configuration. For steric reasons the *E*-configuration of the double bond is not very likely. This is further supported by the low coupling constant (see NMR) indicating the presence of a *Z*-substituted double bond.

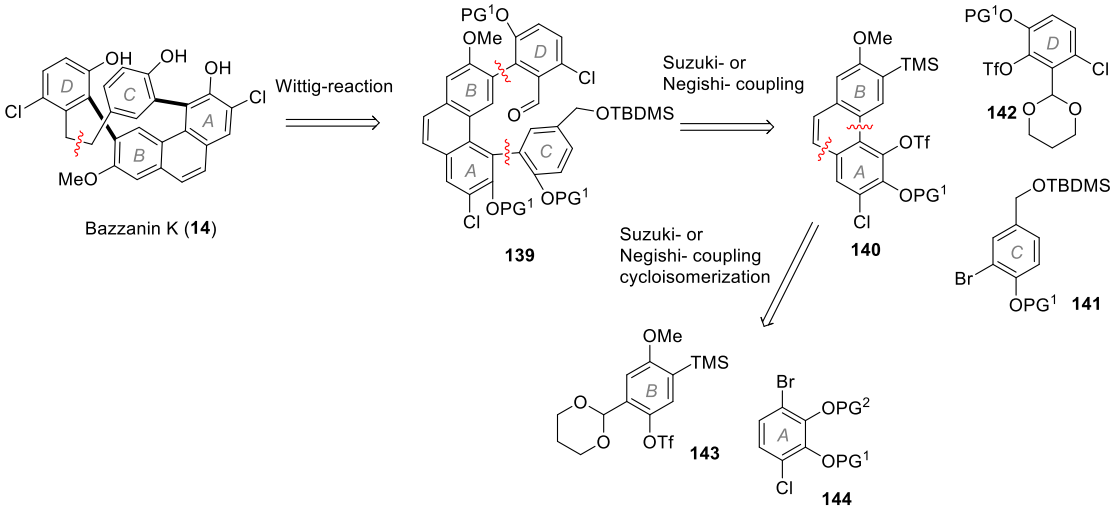
This could mean two different things; either only one of the diastereomers of the product reacted in the WITTIG reaction or both reacted and formed only one product. Comparing the ratio of the diastereomers in the starting material (~1:1.25 according to NMR) with the yield of the macrocyclization reaction suggests that the first statement could be true. This is only sensible under the assumption that the actual yield was nearly quantitative, which is not very likely for macrocyclizations (see introduction). No other side product could be isolated, which could be explained by slow interconversion of the two diastereomers during the reaction.

Nonetheless, while being unsuccessful with the RCM methodology, the formation of this twelve-membered cycle was shown to be possible with an intramolecular WITTIG reaction. With this proof of concept, the total synthesis of bazzanin K (**14**) could be started containing this macrocyclization *via* WITTIG reaction as a key step.

2.2. Towards the total synthesis of bazzanin K

Compared to the analogue molecules presented previously. bazzanin K (**14**) shows a more complex substitution pattern. Thus, a synthetic strategy must consider the relative stabilities of different functional groups as well as orthogonality of a variety of protecting groups. Additionally, the aromatic building blocks of the molecule must be prepared on a large scale with high regioselectivities. Like the strategy used for the model substances, the key step will be the macrocyclization as one of the last steps in the total synthesis. Thus, the first retrosynthetic cut for the bazzanin K (**14**) is the intramolecular WITTIG reaction cutting the ethylene bridge (Scheme 36). A closer look at the molecule **139** reveals a structure containing four aromatic building blocks which could be connected *via* cross-coupling reactions. The reactions could be SUZUKI-, NEGISHI-, or other palladium-catalyzed reactions which were the synthetic tool in previous total synthetic approaches for the preparation of biphenyls (see introduction). Another challenging obstacle will be the presence of two chiral axes present in the molecule, so the final couplings had to be done in an enantioselective way. However, in this work just the connectivity issues were tackled, as enantioselective couplings of phenols are everything but trivial on their own and can be investigated once a clear synthetic path will be found. Unfortunately, the complex substitution pattern of the phenols requires well defined and thought out prefunctionalization before connecting, thus leading to lengthy synthetic pathways. The prior, rather convergent synthesis of the model substance with the connection of an *AC*- and a *BD*-fragment will not be easily possible with the bazzanin K (**14**) due to the complex substitution patterns of the intermediates. Thus, another strategy was developed with an *AB*-fragment **140** as a key building block, which contains a triflate substituent to facilitate a cross-coupling reaction with building block **141**. Building block **141** needs a bromide in order to be converted into a suitable substrate for a SUZUKI- or NEGISHI coupling, which could be either a boronic ester or a zincate. Most parts of the preparation of building block **141** are already known in literature.[75] The TMS group of the phenanthrene **140** should be easily transformed into a iodide substituent without much trouble using ICl[76], which can be utilized as a boronic ester or a zincate in a coupling with building block **142** containing a triflate group. Fragment *D* (**142**) on the other hand, could be obtained by further derivatization of 2,3-dihydroxybenzaldehydes. The phenanthrene **140** itself will be the product of a cross-coupling of the two building blocks **143** and **144**. After the coupling, the acetal has to be deprotected and the aldehyde will be converted into the respective terminal alkyne. With this triple bond present in the molecule, a cycloisomerization *via* π-acid-catalysis could be performed to yield the phenanthrene. Building block **143** can be synthesized in a few functionalizations starting from 4-methoxyphenol (**145**)

and the preparation of fragment *A* (**144**) is in parts known in literature[75] and only requires a few more steps.

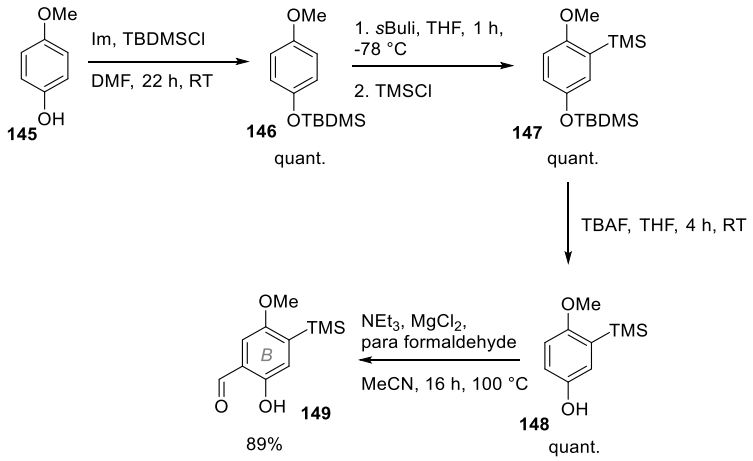


Scheme 36: Retrosynthetic analysis of bazzanin K (**14**) using a cascade of palladium catalyzed C-C-bond bond formations and an intramolecular WITTIG-cyclization.

Hence, the very first milestone in the total synthesis of bazzanin K (**14**) is the preparation of the four substituted benzenes fragments. Crucial to this endeavor was the choice of adequate protecting groups PG^1 and PG^2 to ensure proper synthetic feasibility. One of the last steps in the synthesis is the hydrogenation of the double bond coming from the WITTIG reaction. To provide maximal efficiency and orthogonality, a protecting group needs to be chosen for PG^1 that can be cleaved by hydrogenolysis but is otherwise stable under a multitude of conditions. The benzyl group meets these requirements perfectly and was thus the protecting group chosen for PG^1. For PG^2 a group was chosen that could be installed easily and removed effortlessly. Furthermore, this group should play a major role in the synthesis, besides the protection of the phenol, as an *ortho*-directing group, which was crucial in the functionalization in the correct position. MOM was the only protecting group fulfilling those conditions and was chosen for PG^2.[77,78]

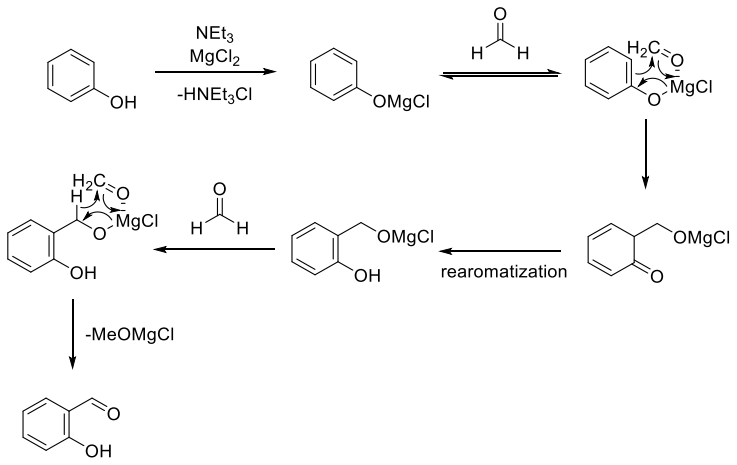
2.2.1. Synthesis of fragment *B*

Beginning with the commercially available 4-methoxyphenol (**145**), the OH-function was protected as a bulky TBDMS ether according to a known procedure[79] to enable selective *ortho*-directed lithiation next to the methoxy group in the next step in quantitative yield adapted from a similar literature known procedure (Scheme 37).[80]



Scheme 37: Synthesis of aldehyde **149** as the precursor for building block **143**.

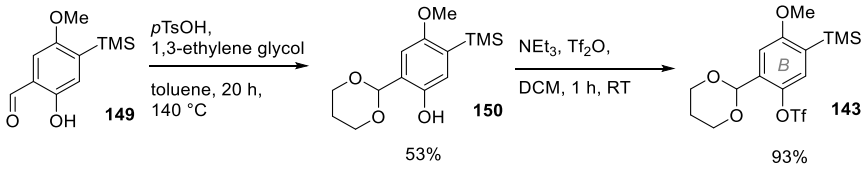
After adding *s*Buli to perform the afore mentioned lithiation, TMSCl was used as an electrophile to quench the lithiated species. The previously installed protecting group was cleaved effortlessly using TBAF as a source of fluoride ions. In order to put an aldehyde functionality into the position next to the phenol a variant of the CANNIZARRO reaction was conducted which was adapted from literature.[81] Para formaldehyde reacts with the substrate to the desired aldehyde **149** and methanol as a side product according to the mechanism shown in Scheme 38.[82]



Scheme 38: Mechanism of the formylation in *ortho*-position of a phenol.

The NEGISHI coupling appeared to be a promising method of connecting the building blocks **143** and **144** efficiently. The employed organozinc compounds may react with the aldehyde instead, thus protection of **149** as an acetal was required. In general, aldehydes protected as 1,3 dioxanes are more stable towards hydrolysis than 1,3 dioxolanes.[78] For this reason 1,3-propanediol was chosen for the protection. The acid-catalyzed reaction to the dioxane **150** was

carried out using a DEAN-STARK-apparatus to remove *in situ* formed water from the mixture and push the equilibrium of this reaction to the side of the product (Scheme 39).



Scheme 39: Synthesis of triflate **143** by acetal protection of aldehyde **149** and further triflylation.

The mediocre yield of this reaction might be explained with the formation of a six membered cycle with the alcohol and the aldehyde by hydrogen bonds. Scheme 40 shows how the proton is stabilized by the aldehyde, which in turn is diminished in its reactivity. This situation can be described by a resonance structure with an enol which has no electrophilic character. Finally, the phenol **151** was treated with triflic anhydride under basic conditions and building block **143** could be obtained in excellent yield. All in all, fragment *B* (**143**) was prepared in an overall yield of 43%. The connectivity of triflate **143** could be validated *via* X-ray analysis (Fig. 30).

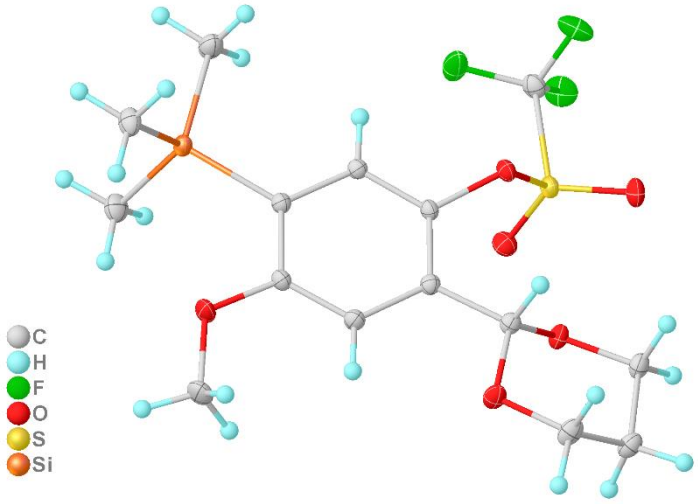
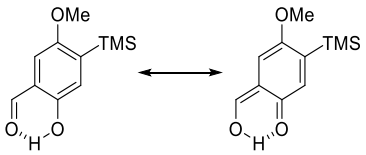


Figure 30: Molecular structure of **143** in the solid state. Displacement ellipsoids drawn at 50% probability level.

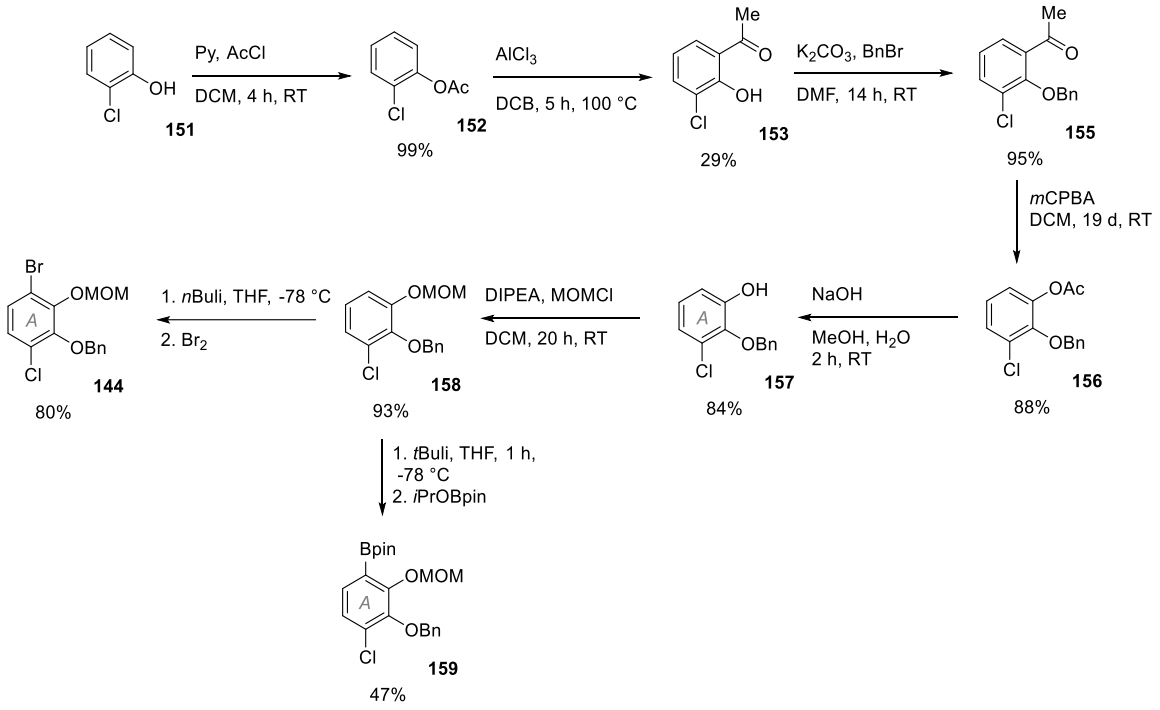
With the triflate group a functionalization was introduced which can facilitate a connection with building block **144** in a SUZUKI- or NEGISHI coupling.



Scheme 40: Possible deactivation of aldehyde **149** by a hydrogen bond forming a six-membered cycle that can be described by two resonance structures.

2.2.2. Synthesis of fragment *A*

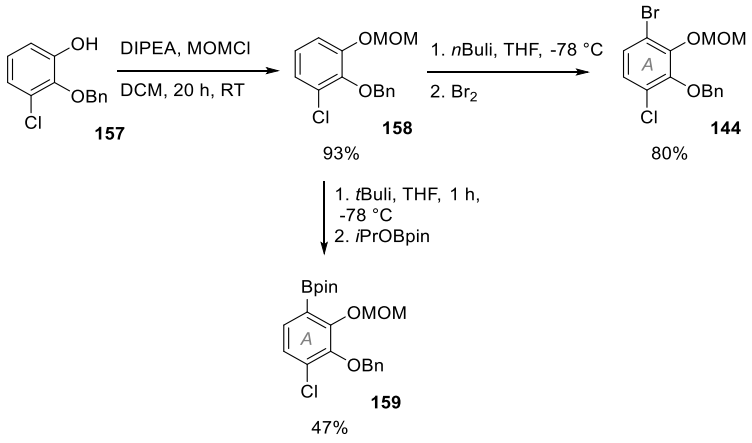
Following a few steps of a literature known procedure[75] in Scheme 41, the preparation of the second building block **144** was envisioned starting with the acetylation of commercially available 2-chlorophenol (**151**).



Scheme 41: Literature known synthesis of phenol **157** starting from 2-chlorophenol (**151**).

In a FRIES-rearrangement of the acetate-protected phenol **152** two possible products could be conceived. The *para*-substituted product **154** and the *ortho*-substituted product **153**. Unfortunately, the desired *ortho*-substituted substrate **153** is the minor component in the product mixture, which results in a poor yield of 29%. This is in agreement with reported results[75] and is most likely the case because of the higher electron density in *para*-position to the OH group. Furthermore, this position is also preferred due to steric reasons. Nonetheless, the reaction could be carried out on a multigram scale, and the starting materials are rather cheap, making this bottleneck reaction tolerable. With this substrate **153** in hand, a benzylation of the phenyl was performed using BnBr to protect the alcohol. In the pursuit of synthesizing the building block **144** the ketone **155** had to be transformed into the respective protected alcohol. A BAEYER-VILLIGER-oxidation was conducted with *m*CPBA in DCM. While the FRIES-rearrangement was a limitation in regards of yield, this reaction was a limitation in terms of reaction time with 19 days of stirring. Monitoring the reaction with TLC showed a very slow progress which could have been accelerated by heating the reaction. Nonetheless, no further effort was put into optimizing the conditions, as the yield was satisfactory. Saponification of

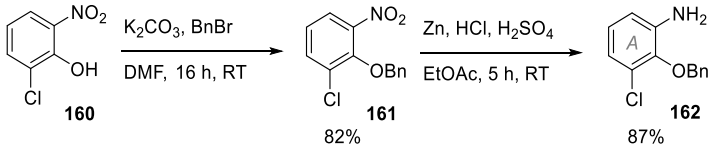
the ester **156** with NaOH finally yielded the alcohol **157**. With the intermediate **157** in hand, the previously mentioned question of a suitable protecting group arises. Since bromination with elemental bromine yielded a complex mixture of inseparable products, a regioselective method needed to be established. To install bromine at the desired position on the ring, a workaround in the form of an *ortho*-directed lithiation and quenching with bromine was used. For that strategy MOM appeared to be the ideal protecting group as it has excellent properties as an *ortho*-directing group for lithiations. Treatment of phenol **157** with MOMCl under basic conditions yielded the desired MOM-protected alcohol **158** (Scheme 42).



Scheme 42: Synthesis of bromide **144** by *ortho*-directed bromination for further use in NEGISHI- and SUZUKI couplings and reaction to boronic ester **159**.

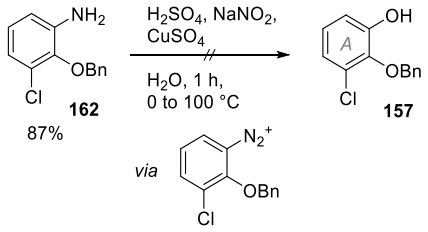
Attempting the *ortho*-directed lithiation with *n*Buli and successive addition of bromine as an electrophile was successful and the bromide **144** was obtained in good yield. In conclusion fragment *A* was prepared in an overall yield of 15%. Since the reaction worked well, it was also used to prepare the boronic ester **159** in the same fashion. This reaction however resulted only in a mediocre yield of 47%. While not useful in this synthetic route, boronic ester **159** found application in later stages of the total synthesis.

Since the previous method was rather long with seven steps for the bromide **144**, another more concise approach towards fragment *A* was envisioned. Starting from the commercially available nitroarene **160**, benzylation with BnBr and successive reduction of the nitro group with zinc under acidic environment gave the amine **162** (see Scheme 43).



Scheme 31: Synthesis of amine **162** as an intermediate for fragment *A*.

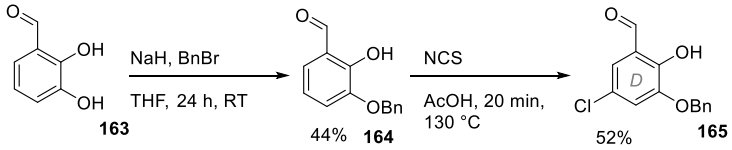
Unfortunately, the following transformation of the amine **162** to the desired phenol **157** with the respective diazonium salt as a key-intermediate was unsuccessful (Scheme 44).



Scheme 44: Attempt at the conversion of amine **162** to phenol **157**.

2.2.3. Synthesis of fragment *D*

For the fragment *D* the substitution pattern is not trivial as it was crucial to install the chlorine in the correct position next to the aldehyde. For that, three strategies are possible; the use of an already chlorinated starting material, the SANDMEYER reaction with an amine or the direct chlorination. In a first attempt, a literature known benzylation[83] of one of the OH groups of commercially available **163** was conducted (Scheme 45). However, the successive reaction with NCS exclusively facilitated the chlorination in *para*-position of the OH group, yielding the wrong regioisomer **165**, which is clearly indicated by the small coupling-constant (J = 2.4 Hz) of the two proton signals of the phenol in the ^{1}H-NMR-spectrum (Fig. 31).



Scheme 45: First attempt at preparing fragment *D* with the chlorination as the second step.

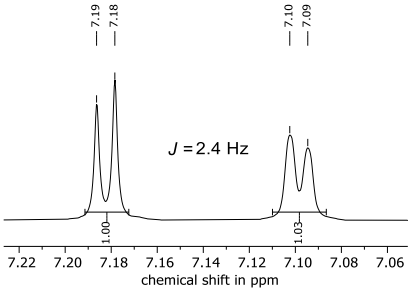
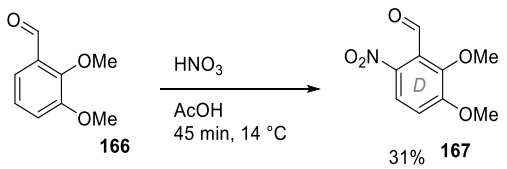


Figure 31: Aromatic protons of phenol **165** showing a meta coupling.

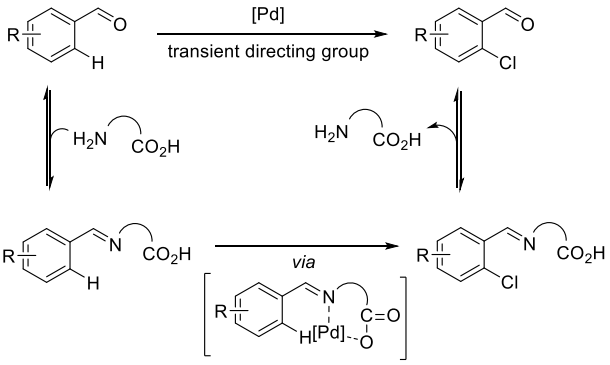
Furthermore, for the building block **142** a synthetic route with a SANDMEYER reaction for the introduction of a chloride was envisioned. However, the nitration according to literature[84] in Scheme 46 of the commercially available 2,3-dimethoxybenzaldehyde (**166**) was not

promising. The yield was poor, and the isolation was rather complicated due to low solubility of the product. Additionally, there were many side products with similar R_f-values.



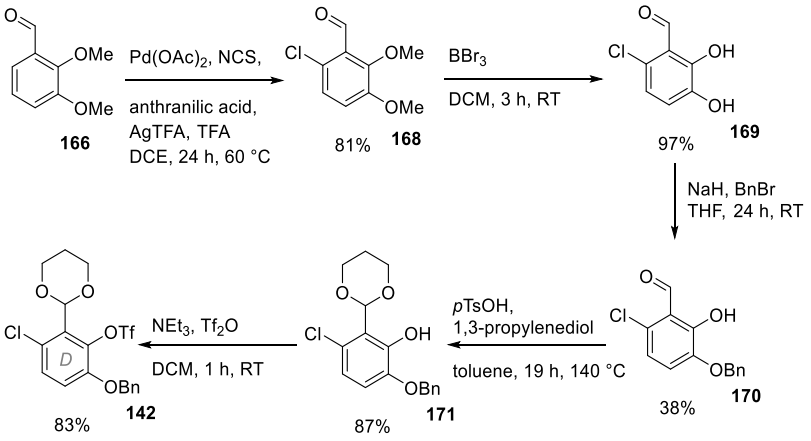
Scheme 46: Synthesis of nitro benzaldehyde **167** by direct nitration with nitric acid.

Reduction of the nitro group and subsequent SANDMEYER reaction with CuCl should yield the correctly substituted building block. However, this synthetic strategy was very inconvenient as the amine could react with the aldehyde and side reactions were to be expected. Recently, JIN-QUAN YU *et al.*[85] published a convenient method to perform a palladium catalyzed functionalization in *ortho*-position of an aldehyde with transient directing groups which we believed could be applied to our problem.



Scheme 47: Mechanism of the chlorination using a transient *ortho*-directing group.

According to JIN-QUAN YU the *ortho*-directed chlorination should work with NCS as the chlorination agent and anthranilic acid as the transient directing group (Scheme 47). The reaction was indeed successful, and the chloride **168** was obtained in satisfactory yield of 81% as seen in Scheme 48. Unfortunately however, 10 mol% of catalyst loading is necessary for this reaction to proceed, which is a serious drawback.



Scheme 48: Synthesis of triflate **142** by *ortho*-directed chlorination and regioselective benzylation as key steps.

In order to achieve selective benzylation at the 3-position, both methoxy groups needed to be cleaved with BBr_3. The success of this reaction can be seen in the X-ray structure of intermediate **169** (Fig. 32).

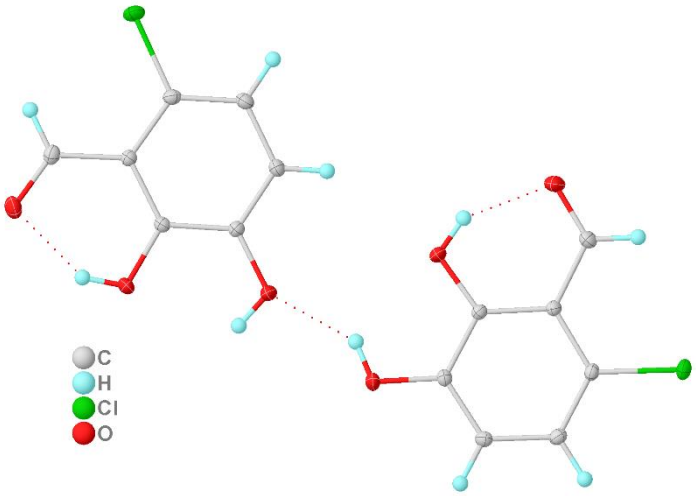
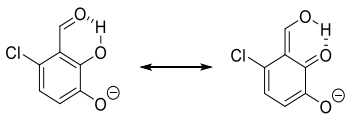


Figure 32: Molecular structure of **169** in the solid state. Displacement ellipsoids drawn at 50% probability level.

The reaction required no further purification steps, since the catechol **169** was very pure and column chromatography resulted in partial decomposition of the product, only diminishing purity and yield. According to literature,[83] benzylation of the OH group in 3-position resulted in rather poor yields of 38%. The assumed selectivity of this reaction stems again from the formation of a six-membered ring that stabilizes the proton of the OH group in *ortho*-position to the aldehyde *via* a hydrogen bond which can be seen in Scheme 49. The right resonance structure shows the reduced nucleophilic character of the OH group in *ortho*-position to the

aldehyde. This stabilizing effect theoretically allows only for the other alcohol to be deprotonated by the base, which in turn can act as a nucleophile towards the benzyl bromide.



Scheme 49: Key intermediate in the selective benzylation of catechol **169** with a hydrogen bond stabilized by a six membered cycle described by two resonance structures.

Similar to molecule **150**, the aldehyde was protected as an acetal to enable reactions with nucleophiles such as zincates in possible NEGISHI couplings. Interestingly, in this case the stabilization *via* hydrogen bond does not diminish the yield which is more than acceptable with 87% Finally, treatment with triflic anhydride under basic conditions led to the formation of triflate **142**, which is able to react in palladium catalyzed cross-coupling reactions. The *D*-fragment **142** for bazzanin K (**14**) could be obtained in an overall yield of 18% and the connectivity is confirmed by X-ray analysis of a single crystal (Fig. 33).

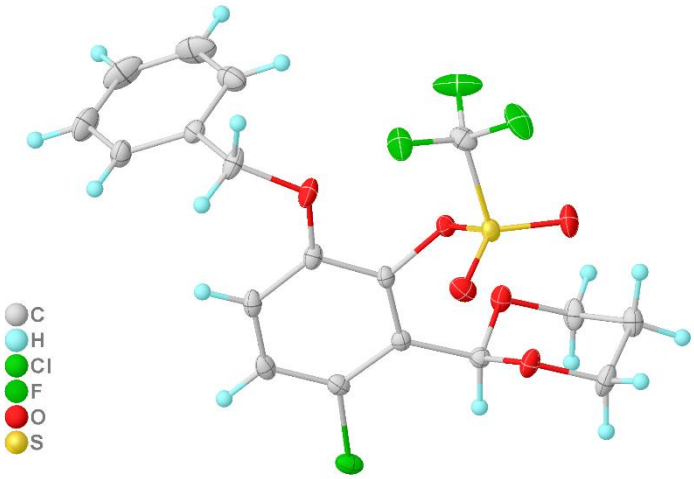
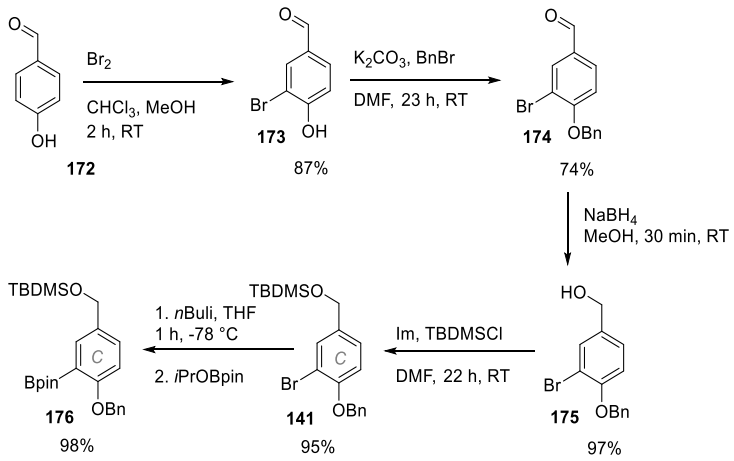


Figure 33: Molecular structure of **142** in the solid state. Displacement ellipsoids drawn at 50% probability level.

2.2.4. Synthesis of fragment *C*

The last building block was the easiest to prepare. Beginning from 4-methoxybenzaldehyde (**172**) as a cheap and commercially available starting material, the very first step was a literature known bromination.[86] The electron density in *ortho*-position to the OH group and *meta* to the aldehyde is the highest on the benzene ring, resulting in the selective electrophilic aromatic substitution in this position (Scheme 50).

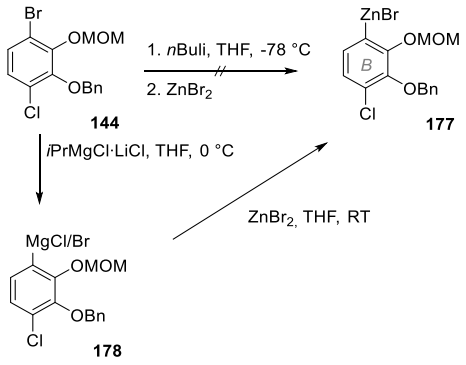


Scheme 50: Concise synthesis of boronic ester **176** in five steps.

Benzylation of the alcohol afforded the desired product in mediocre yield of 74%. The low yield is a result of the purification step being a crystallization in which a compromise between high yield and high purity had to be made. Since a benzyl alcohol is required in the total synthesis which will later be turned into a benzyl bromide and then into a P-ylide, a reduction of the aldehyde with $NaBH_4$ was conducted resulting in nearly quantitative yield of the benzyl alcohol **175**. In a protecting step the benzyl alcohol was protected using TBDMSCl. This step was necessary for the treatment with *n*Buli to prevent possible side reactions. In the final borylation the boronic ester **176** was obtained in excellent yield. The overall yield for fragment *C* was 46%.

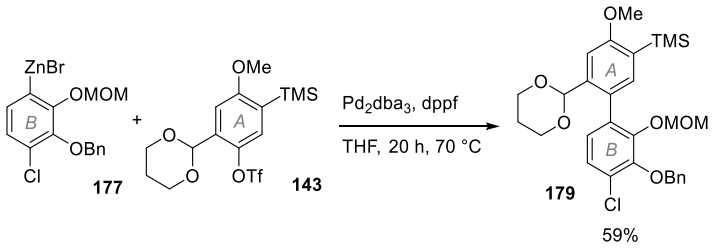
2.2.5. Connection of two building blocks and synthesis of the *AB*-fragment

With all building blocks in hand, the synthesis of the first biphenyl could start. A NEGISHI coupling of building block **143** with **144** was attempted by preparing the zincate **177** of bromide **144** with *n*Buli and addition of $ZnBr_2$ *in situ* (Scheme 51). According to literature,[87] this is a common way to obtain the desired organozinc compounds. While the synthesis of the respective boronic ester **159** for a SUZUKI coupling was possible as shown in Scheme 42, the yield was rather poor, and the generation of the zincate saved a step in the synthesis. However, the reaction with triflate **143** did not yield the desired biphenyl but only the reprotonated zincate and reisolated triflate **143**.



Scheme 51: Preparing metalorganic reagents for cross-coupling reactions.

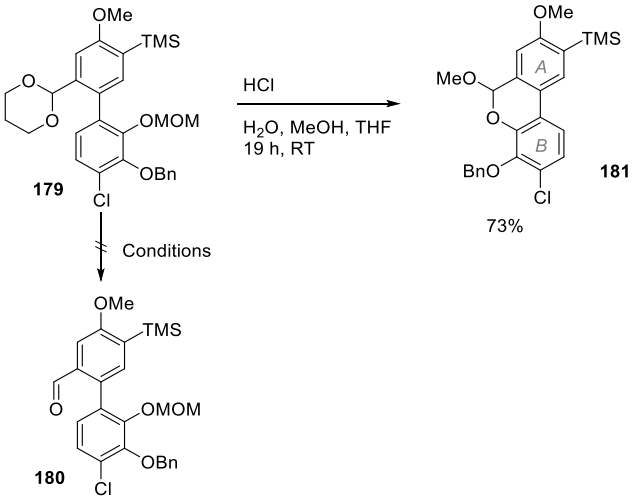
Another attempt in form of a KUMADA coupling with $NiCl_2$(dppe) was made by using the magnesium-organyl **178**, which was prepared according to a KNOCHEL protocol[88] with *i*PrMgCl·LiCl, which is also known as "turbo GRIGNARD". Again, only the reprotonated compound **142** and unconsumed triflate **143** could be isolated. Since the KNOCHEL protocol also gave a method to prepare zincates from GRIGNARD reagents, a NEGISHI coupling was attempted again using the "turbo-GRIGNARD" to prepare the GRIGNARD reagent **178** which was treated with $ZnBr_2$ to form the zincate **177** *in situ*.



Scheme 32: Successful NEGISHI coupling with the zincate **177** prepared *via* the GRIGNARD reagent **178**.

Fortunately, the reaction with the triflate **143** gave the desired biphenyl **179** in moderate yield of 53% (Scheme 52).

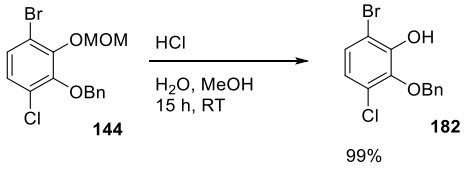
Originally, the plan was to carry out a deprotection of the acetal and the MOM group under acidic conditions, perform a triflylation of the alcohol and a subsequent SEYFERT-GILBERT homologation of the aldehyde to obtain the terminal alkyne on the upper ring and the triflate on the lower. However, as shown in Scheme 53, the attempts at HCl catalyzed hydrolysis in THF and water as the solvents only led to complete degradation of the substrate. With methanol and THF another product was observed. A six-membered cycle with an intramolecular acetal **181** was obtained. A variety of different temperatures, reaction times and concentrations were tested to selectively cleave only the acetal but the desired mono deprotected biphenyl **180** could not be obtained.



Scheme 53: Attempted deprotection of the protected aldehyde **179** and synthesis of the side product **181**.

In order to prevent these selectivity issues, at least one of the building blocks used in this coupling reaction had to be modified to fit the new requirements. On one hand, it should be possible to exchange the MOM group with a group that can be cleaved under conditions that are orthogonal to the other protecting groups in the molecule, namely the benzyl group and the acetal group. On the other hand, since a terminal alkyne is needed for a key intermediate anyway, it could also be installed in the upper building block before the coupling to the respective biphenyl.

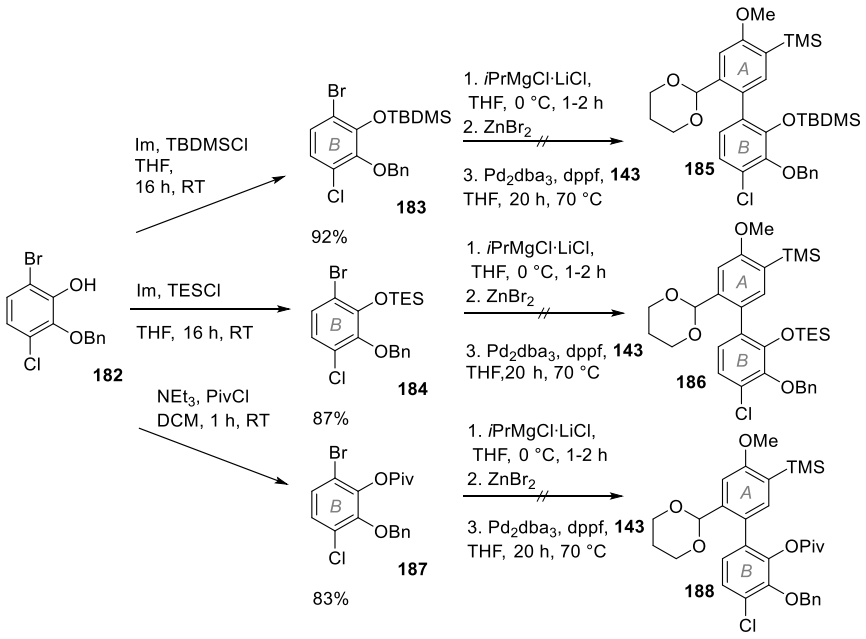
Following this idea, the MOM group of building block **144** was cleaved under acidic conditions to obtain the free alcohol **182** in nearly quantitative yield, which can be further functionalized (Scheme 54).



Scheme 54: Synthesis of the free alcohol **182** under acidic conditions.

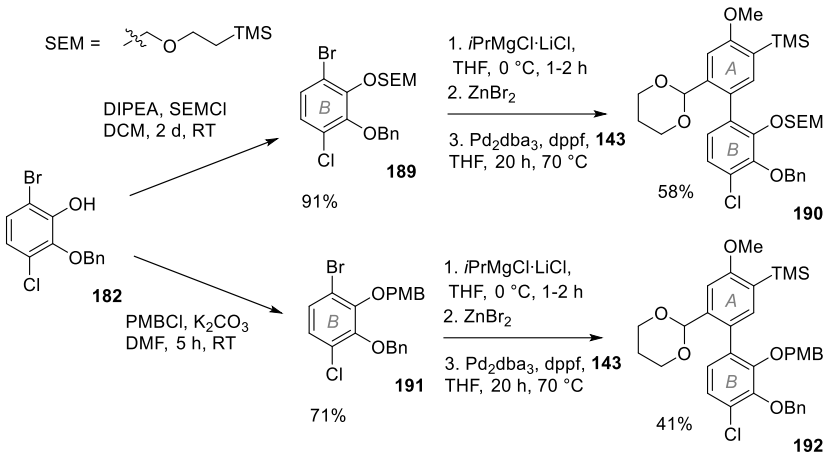
Thus, the synthetic focus was switched to finding a suitable protecting group for the OH group which is shown in scheme 55. At first TBDMS and TES were tested as protecting groups for the OH group, since they are easy to introduce and remove. In both cases the reaction yielded the desired silyl ether **183** and **184** in high yield. The substrate **183** with the TBDMS group did not participate in the attempted NEGISHI coupling to **185**, presumably because of the large steric hindrance in *ortho*-position to the bromine. While TES has less steric hindrance as the TBDMS group,[89] the substrate **184** is also prone to decomposition during the reaction, and the desired

biphenyl **186** could not be obtained. KNOCHEL and coworkers published an alternative protocol regarding the use of zincates for NEGISHI couplings in the presence of (sterically hindered) esters.[88] This report led to the attempt of using a pivaloic ester **187**. Unfortunately, the GRIGNARD reagent of the ester which is a key intermediate in the preparation of the zincate for the NEGISHI coupling most likely reacted in agreement with the expectation as a nucleophile with the electrophilic ester and did not participate in the desired cross-coupling reaction to biphenyl **188**.



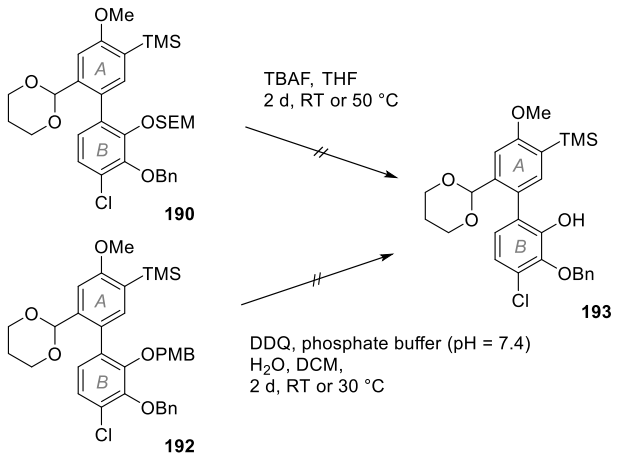
Scheme 55: Attempts at using TBDMS, TES and Piv as protecting groups for the OH group in the synthesis of biphenyls.

According to literature, the SEM group could be cleaved under similar conditions as silyl ethers with TBAF[90] and it fulfills the need for a protecting group which is orthogonal to an acetal and has less steric influence at the neighboring position. Installation of the group was successful and formation of **189** took place in high yield as shown in Scheme 56. The NEGISHI coupling of the zincate with the triflate **144** to the respective biphenyl **190** was performed in mediocre yield without any further optimization. Another protecting group, the PMB group, was used to mask the phenol in reasonable yield. PMB could be removed under oxidative conditions with DDQ in the presence of an acetal.[91] Cleavage of the Bn group could also happen under these conditions, but due to the higher electron density at the PMB group it was rational to expect a faster reaction with the PMB protected OH-functionality. The nucleophilic substitution at the phenol occurred and the NEGISHI coupling with this new substrate **191** proceeded with poor but satisfactory yield of biphenyl **192**.



Scheme 56: Using SEM and PMB as suitable protecting groups for the OH group in the synthesis of biphenyls.

As mentioned before, the SEM group is supposed to be cleaved with fluoride ions from TBAF. Unfortunately, it was not possible to remove the protecting group.



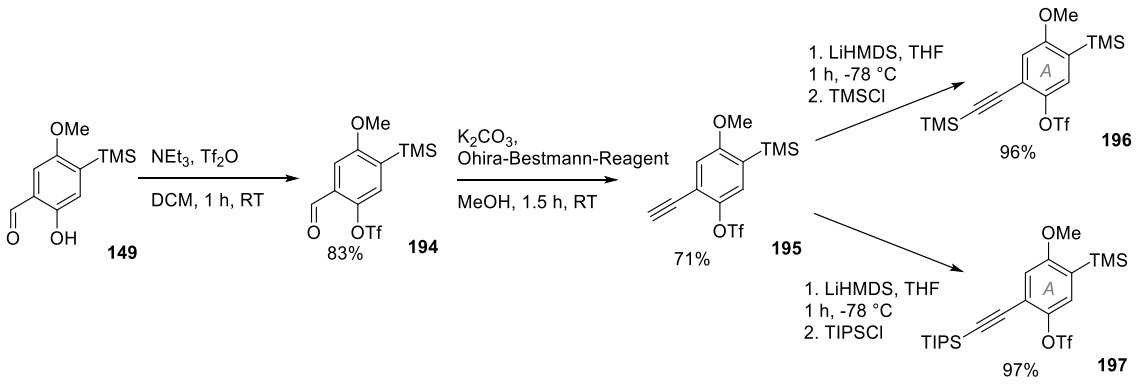
Scheme 57: Attempts at cleaving the protecting groups to obtain biphenyl **193**.

As seen in Scheme 57, at room temperature no conversion could be observed, while elevated temperatures led to complete decomposition of the biphenyl **190**. The cleavage of PMB with DDQ was also unsuccessful. Like previous experiences, the result was either no conversion at room temperature or decomposition at elevated temperatures. Since all these attempts failed, the synthetic approach needed to be changed.

2.2.6. New synthetic strategy for the *AB*-fragment

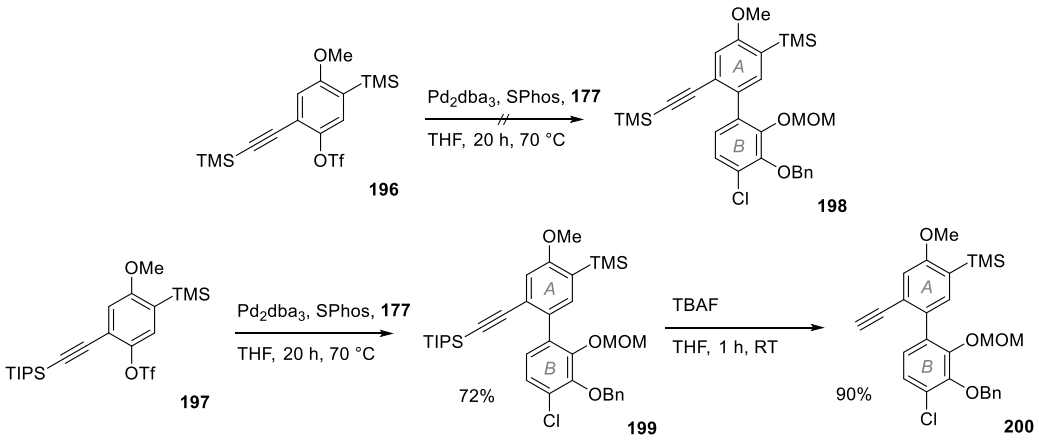
As the acetal **193** needed to be transformed into a terminal alkyne in the respective biphenyl anyway, the new idea was to install a terminal alkyne into the building block to prevent difficulties with deprotection of the MOM group. Additionally, protection of the alkyne was necessary to prevent side reaction like SONOGASHIRA couplings. Thus, starting from the

previously described aldehyde **149**, a triflylation and a SEYFERT-GILBERT-homologation in the OHIRA-BESTMANN-variant were performed as seen in Scheme 58.



Scheme 58: Conversion of aldehyde **149** to a protected alkyne by SEYFERT-GILBERT-homologation and silylation of the terminal alkyne.

In a first attempt, TMS was installed as a protecting group by deprotonation of the terminal alkyne and addition of TMSCl as an electrophile. Since the following NEGISHI coupling of this product **196** with the zincate **177** only led to decomposition, a bulkier protecting group was chosen for the alkyne. With the TIPS group installed in **197** the same way as the smaller silyl group, the NEGISHI coupling proceeded smoothly, and the desired *AB*-fragment **199** was obtained in acceptable yield (Scheme 59).



Scheme 59: Unsuccessful NEGISHI coupling with a TMS-protected alkyne **196** and successful coupling with a TIPS-protected alkyne **197** to biphenyl **199**.

Interestingly, a single crystal of a side product **201** was isolated and subjected to X-ray analysis, which showed that the desired product **199** reacted at the chlorine with another equivalent of **177** to form a chain of three connected aromatic rings as a side reaction (Fig. 34).

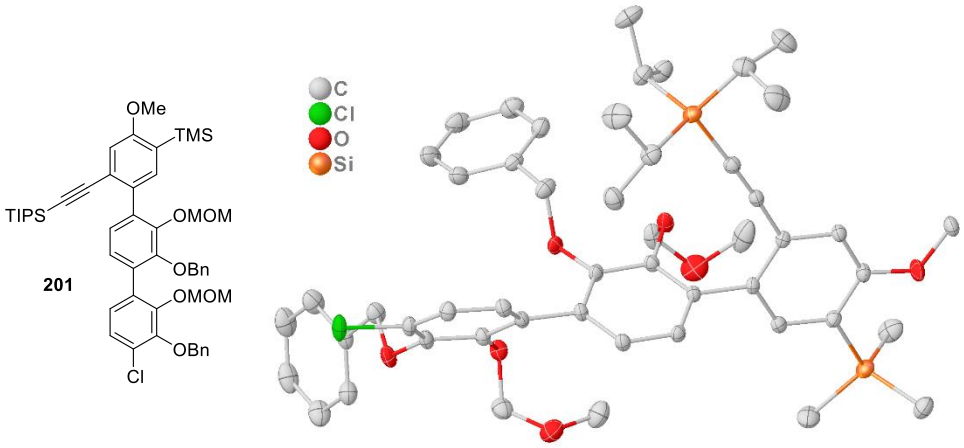
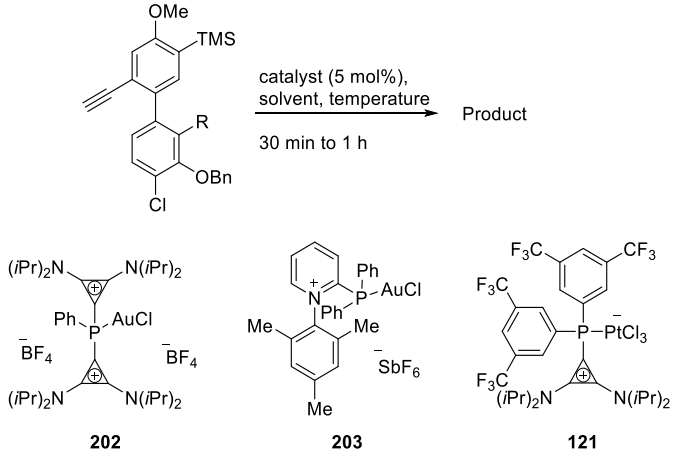


Figure 34: Molecular structure of **201** in the solid state. Hydrogen atoms and minor disorder parts omitted for clarity. Displacement ellipsoids drawn at 50% probability level.

With intermediate **199** in hand, the TIPS group was cleaved with TBAF and finally, the formation of the phenanthrene with π acid catalysis could be attempted. The attempts of the formation of the phenanthrene are shown in Scheme 60 and 62. It is important to note that a 5 mol% solution of $AgSbF_6$ in the respective solvent was added to the precatalysts **121**, **202** and **203** as a halide abstractor to activate the catalyst. The respective metal center needs to have a vacant coordination site in order to interact with the alkyne. The Ag^+ ions form the insoluble AgCl with the chloride of the precatalyst and thus enables the aforementioned coordination of the alkyne.

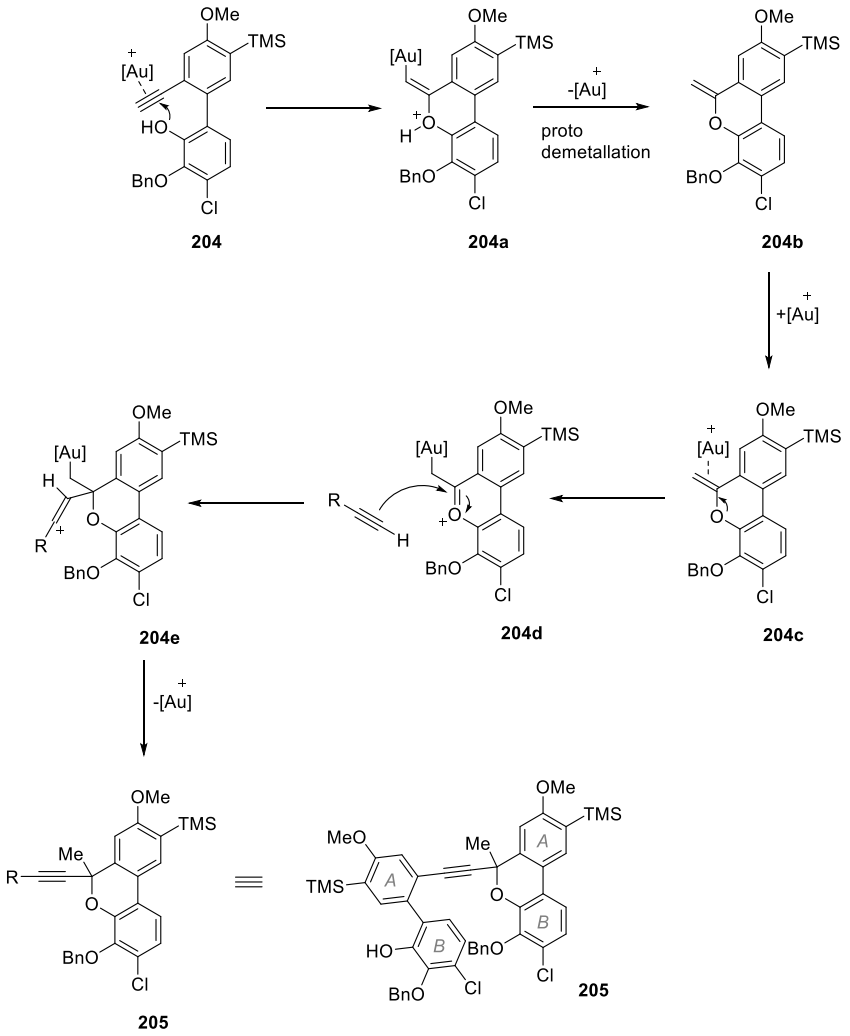


Scheme 60: Schematic depiction of the screening of different substrates and conditions for the synthesis of a phenanthrene and the precatalysts used for the transformations.

Table 2: Screening of different substrates and conditions for the synthesis of a phenanthrene.

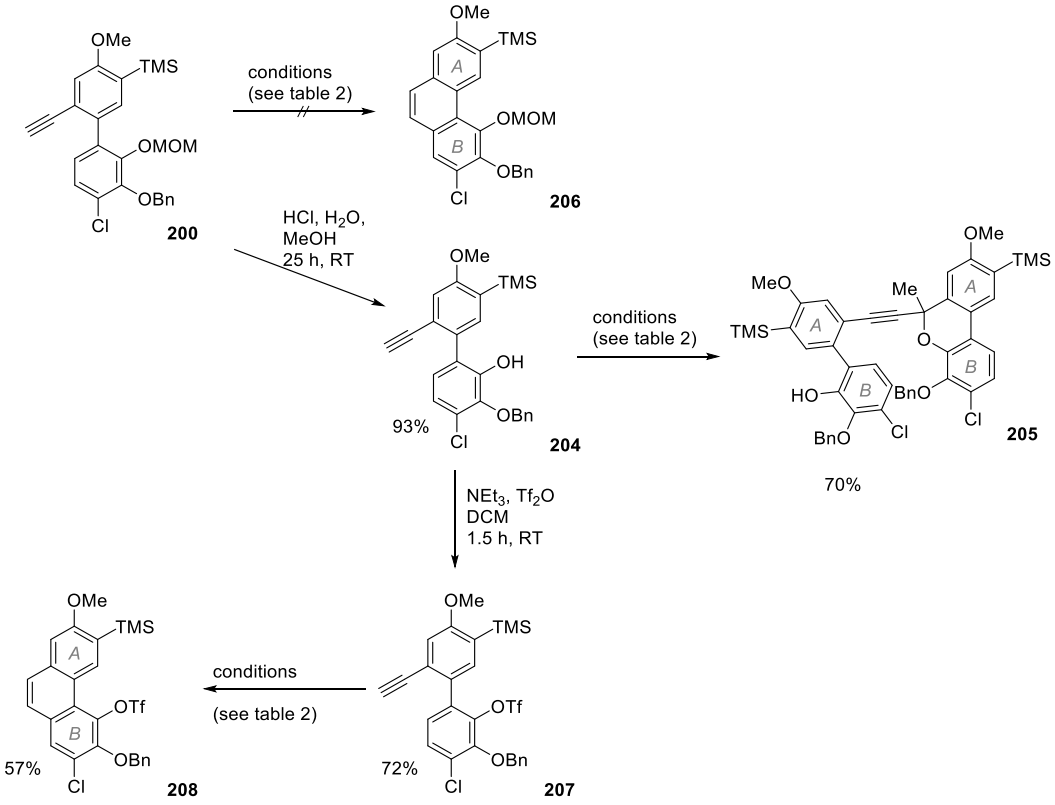
Entry	R	Catalyst	Solvent and Temperature	Yield	Comment
1	OMOM	$PtCl_2$	toluene, 80°C	-	complete degradation
2	OMOM	**202**	toluene, RT	-	no reaction
3	OMOM	**203**	toluene, 0°C	-	complete degradation
4	OMOM	**121**	toluene, 80°C	-	complete degradation
5	OMOM	**121**	DCM, RT	-	complete degradation
6	OMOM	**121**	DCM, -40°C	-	no reaction
7	OMOM	**121**	DCM, -20°C	-	complete degradation
8	OH	**121**	DCM, -20°C	-	partial degradation
9	OH	**203**	DCM, RT	70%	dimer **205**
10	OH	**121**	DCE, 80°C	-	complete degradation
11	OTf	**203**	DCM, RT	-	no reaction
12	OTf	**121**	DCE, 80°C	57%	phenanthrene **208**

However, subjecting biphenyl **200** to a variety of catalytic systems (see table 2), led only to complete decomposition. The high π-acidity of the catalysts most likely cleaved the MOM group which is usually cleaved under acidic conditions and further side reactions took place. Nonetheless, the MOM group was cleaved on purpose to verify, if the OH group is responsible for the formation of by-products in the catalysis. Interestingly, a main product **205** could be isolated in high yields which appeared to be a dimer of the substrate **204**. The structure was determined using 2D-NMR-spectra. Apparently, the OH group acted as a nucleophile towards the activated alkyne of the same molecule resulting in the formation of enolether **204b (**Scheme 61). Another activation of the highly polarized alkene allows the nucleophilic attack of another alkyne and after regeneration of the catalyst, the catalytic cycle is closed, and the dimer **205** is released.



Scheme 61: Possible mechanism for the formation of side product **205**.

In a last attempt, the OH group was transformed into the respective triflate **206**. On one hand, this protection inhibits the oxygen atom to act as a nucleophile. Since another C-C cross-coupling reaction needed to be conducted in this position anyway, the triflate was a convenient choice as it minimizes the number of steps in the synthesis. On the other hand, the electron withdrawing triflate greatly reduces electron density in the aromatic ring. This leads to a lower nucleophilicity of the phenyl which negatively affects the reaction. To enable the nucleophilic attack towards the activated alkyne, a higher reaction temperature was needed. With these new conditions (see table 2 entry 12), the phenanthrene **207** could finally be obtained in acceptable yield. Furthermore, the connectivity could be confirmed by X-ray analysis of a single crystal (Fig. 35).



Scheme 62: Synthetic attempts at obtaining a phenanthrene from various substrates and the final viable preparation of phenanthrene **208**.

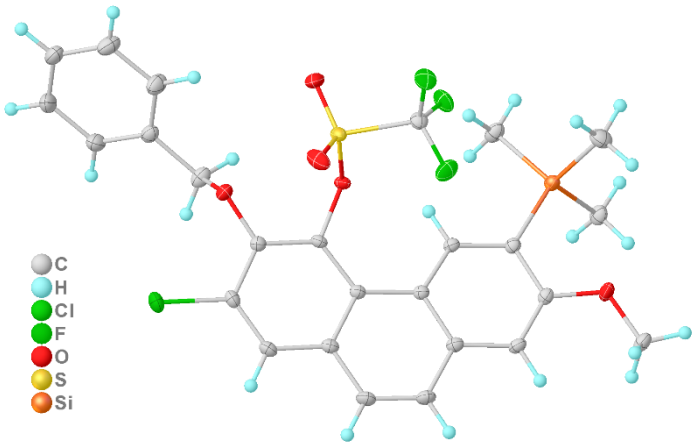


Figure 25: Molecular structure of **208** in the solid state. Displacement ellipsoids drawn at 50% probability level.

The following step was the cross-coupling of the phenanthrene **208** with ring *C*. Different coupling partners were tested in multiple attempts to facilitate the bond formation. Since the NEGISHI coupling showed promising results in previous C-C couplings, it was the first choice for this reaction. However, it was not successful. Only the proto detriflylation product (**208a**) could be observed and characterized via single crystal diffractometry (X-ray structure in Fig. 36).

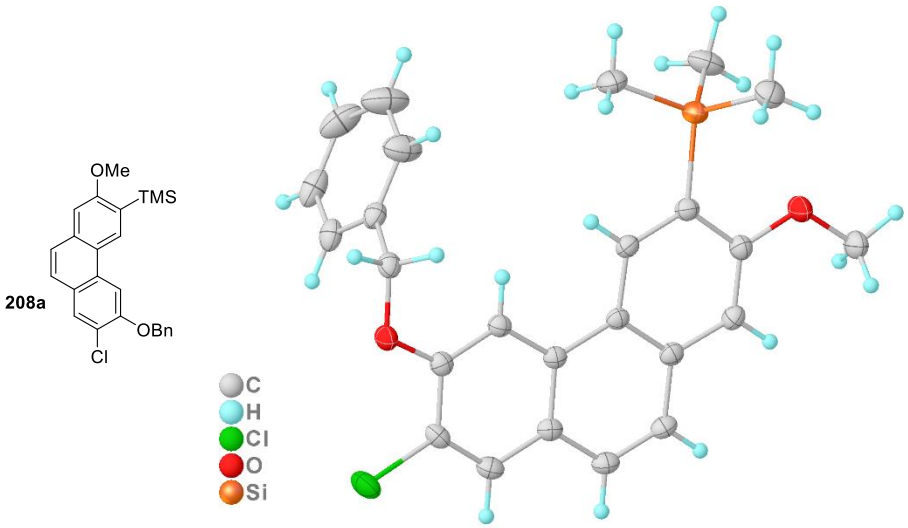
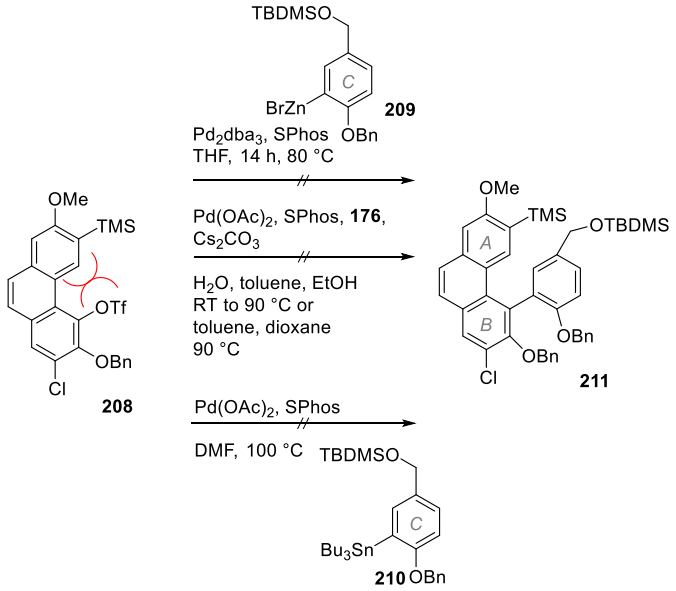


Figure 26: Molecular structure of **208a** in the solid state. Displacement ellipsoids drawn at 50% probability level.

As shown in Scheme 63, this is most likely due to the steric hindrance of the planar phenanthrene which inhibits the proper coupling to form the desired compound **211**.

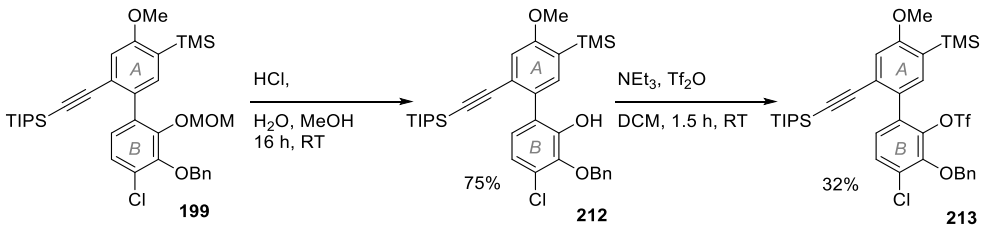


Scheme 63: Attempted NEGISHI- SUZUKI- and STILLE coupling reactions with the phenanthrene **208**.

With the NEGISHI coupling not giving the desired results, SUZUKI couplings were attempted with the boronic ester **176** but did not show any conversion with the phenanthrene **208** at room temperature nor at elevated temperatures under the chosen conditions. As a last attempt, bromide **141** was converted to the respective organo-stannane **210** which was generated *in situ* by treatment of bromide **141** with *n*Buli and *n*Bu_3SnCl. In the STILLE-cross-coupling reaction however, stannanes are very stable and selective substrates with a broad functional group

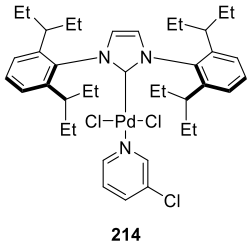
tolerance.[92] Unfortunately, even this attempt resulted only in the isolation of the unconverted phenanthrene **208**.

To prepare a slightly less sterically hindered substrate for a cross-coupling reaction, a concise synthesis was envisioned to obtain the TIPS protected biphenyl **213** from **199**, which is shown in Scheme 64.



Scheme 64: Shorter synthetic pathway for triflate **213**.

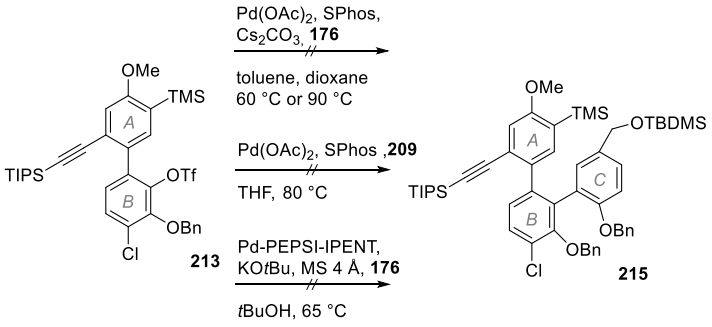
Since the bond between the two arenes is still able to rotate in biphenyl **213**, it was believed that the steric hindrance is significantly reduced in this molecule compared to the phenanthrene **208**. Nonetheless, the attempted SUZUKI- and NEGISHI couplings as shown in Scheme 65 were not successful and only starting material could be reisolated. A protocol published by ORGAN *et al.* used Pd-PEPPSI-IPENT (**214**) (Fig. 37) as a catalytic system and *t*BuOH as a solvent which was supposed to be especially useful in the coupling of sterically hindered triple or even quadruple *ortho*-substituted phenols.[93]



214

Figure 27: Pd-PEPPSI-IPENT (**214**) for the coupling of sterically demanding arenes.

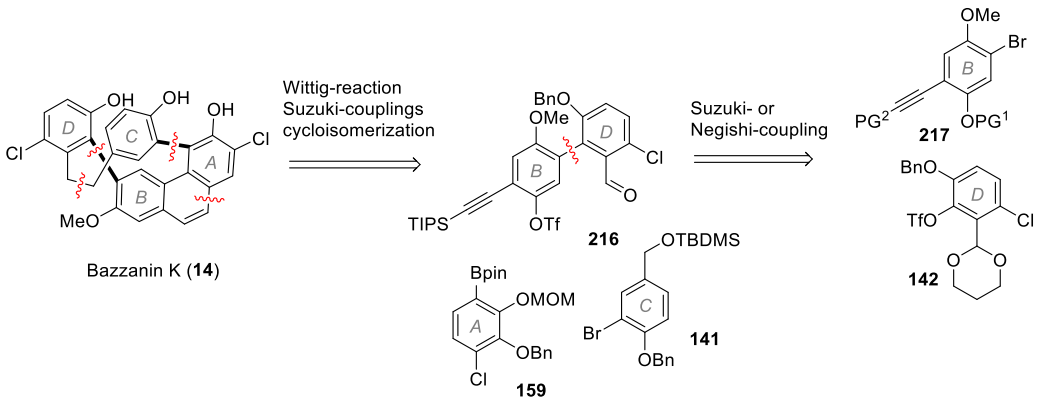
However, following this procedure, the attempts did not result in the formation of the desired product and no conversion could be observed.



Scheme 65: Attempted coupling reaction with the TIPS protected triflate **213**.

As many synthetic possibilities with this substrate were tested and the limitations of this synthetic pathway became obvious, a new strategy was needed to overcome these barriers.

2.3. New retrosynthetic strategy towards bazzanin K



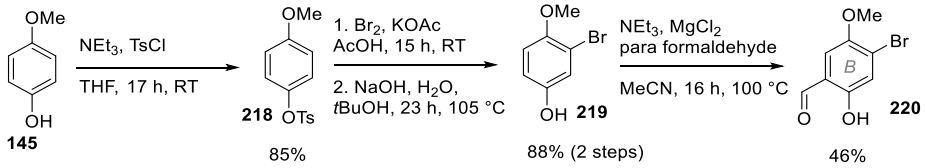
Scheme 66: Division into a *BD*-fragment **216** and two southern building blocks as the new retrosynthetic approach to bazzanin K (**14**).

Because of the lack of success with the previous pathway of using the *AB*-fragment **208** or **213** as a key intermediate, a different strategic approach was envisioned, which is shown in Scheme 66. Since the coupling of ring *A* and *B* caused no problems with different substrates, the new strategy aimed at connecting the fragments *B* and *D* first, and then attach the rings *A* and *C* in a later step. Due to functional group tolerance, SUZUKI couplings were chosen to connect the third building block **159** to the *BD*-fragment **216** and subsequently in later steps the fourth building block **141** to the rest of the molecule. Due to the presence of an aldehyde as an electrophile, a NEGISHI coupling is avoided, because of the nucleophilicity of the respective zincate. Since building blocks **141**, and **159** had been successfully prepared in previous attempts, no further effort had to be put into new synthetic strategies concerning these molecules. The *BD*-fragment **216** was supposed to derive from the connection of building block **217** and **142** *via* a suitable cross-coupling reaction. This could be a either a SUZUKI coupling with the respective boronic ester or a NEGISHI coupling with a zincate derived from the bromide **217**. In theory, a few protecting groups qualified for PG^1, which will be discussed later in detail. This molecule could be prepared in a concise sequence from an aldehyde by SEYFERT-GILBERT-homologation and subsequent protection of the terminal alkyne with a suitable silyl group PG^2. The choice of this group will also be discussed later.

2.3.1. Synthetic approach of the new fragment *B*

To facilitate the synthesis of the *BD*-fragment **216** of the molecule, commercially available substrate **145** was chosen as a starting material in a literature known sequence[94]. As shown in Scheme 67, in a first step, a tosylation was performed to establish the proper electronic properties at the aromatic ring and be able to mono brominate the ring selectively. It diminishes

the electron density at the *ortho*-positions and thus determines the regioselectivity towards the desired product **219**.



Scheme 67: Synthesis of aldehyde **220** in a short and concise pathway containing four steps.

After that, the tosyl group was cleaved as it was only needed to solve the regioselectivity issues of the previous reaction. The CANNIZARRO-type reaction with para formaldehyde yielded the aldehyde **220** according to literature[94] and single crystal diffractometry confirmed the connectivity (Fig. 38).

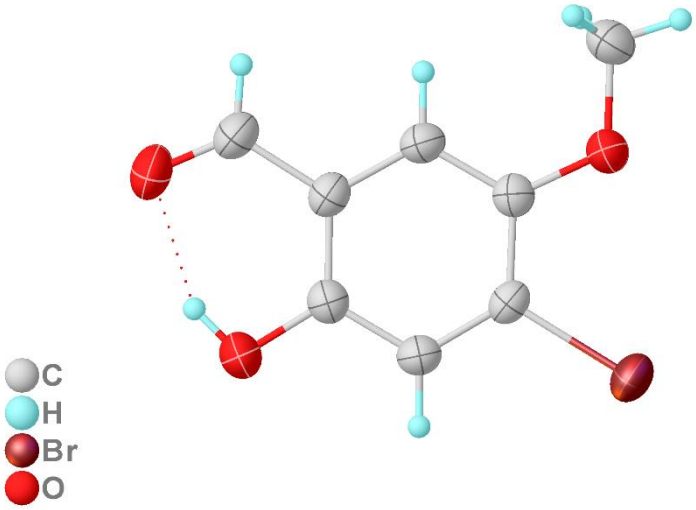
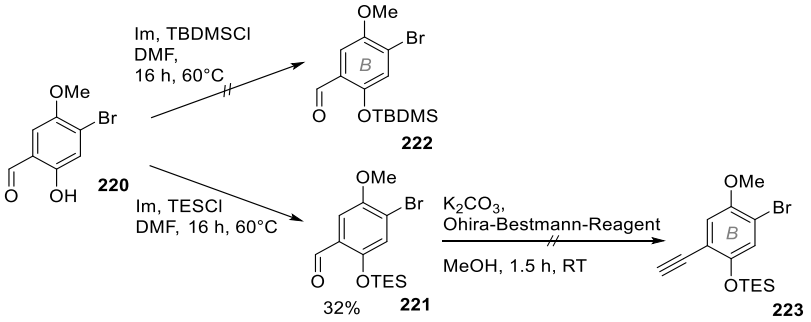


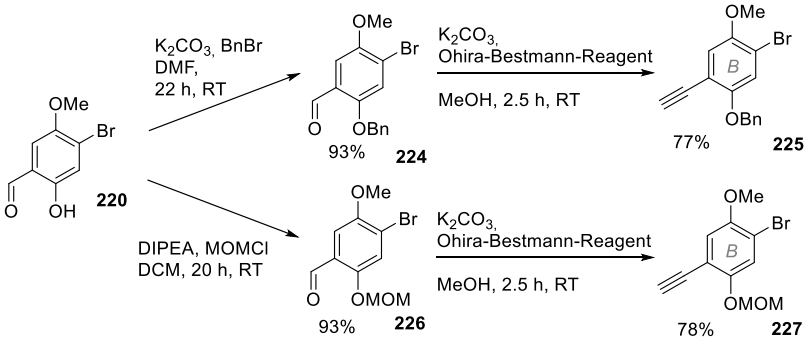
Figure 28: Molecular structure of **220** in the solid state. Displacement ellipsoids drawn at 50% probability level.

Since a free alcohol could lead to side products in the next reactions, the OH group needed to be protected with a suitable protecting group. A few previously used protective groups were tested in regards of their stability and easy removal. Silyl ethers are usually easy to cleave and tolerate most conditions and the attempts of using them as protecting groups are shown in Scheme 68. Protection with TESCl gave poor yields of the respective silyl ether **221**. However, the same attempt with TBDMSCl did not result in the desired product **222** which in theory should have been more stable than the former group. Perhaps the slightly larger steric bulk of the *t*Bu group prevented the proper nucleophilic attack of the deprotonated alcohol.



Scheme 68: Attempted testing of the silyl groups TBDMS and TES as protecting groups.

In a next step, a SEYFERT-GILBERT-homologation was carried out in the OHIRA-BESTMANN variant. However, only decomposition products could be observed with the TES group. In a next series of attempts, benzyl- and MOM-protection were conducted (see Scheme 69). Protection with BnBr and MOMCl gave the respective protected products **224** and **226** in excellent yields. This could be confirmed in the case of intermediate **224** by single crystal diffractometry (Fig. 39).



Scheme 69: Successful testing of MOM and Bn as protecting groups and further homologation to the terminal alkynes **225** and **227**.

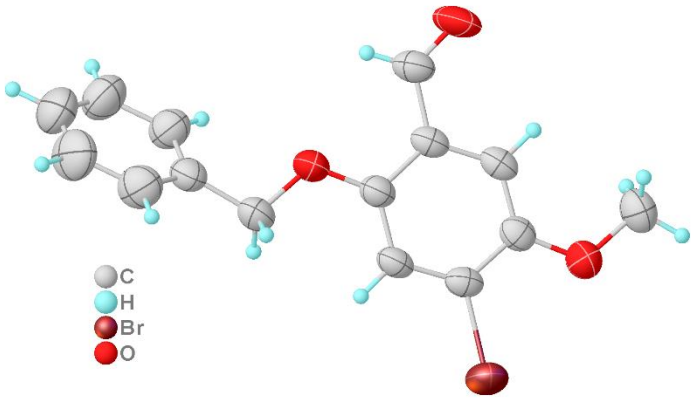


Figure 29: Molecular structure of **224** in the solid state. Displacement ellipsoids drawn at 50% probability level.

While the benzyl group could be cleaved under hydrogenolysis, MOM just needs acidic conditions as mentioned before. The silyl protected substrate **221** was not stable under the

conditions for the homologation reaction, but the MOM and benzyl protected substrates **224** and **226** underwent the desired transformation to the protected terminal alkynes **225** and **227** in high yield. For the MOM-protected alkyne **227**, a single crystal was isolated and subjugated to X-ray analysis which confirmed the aspired connectivity (Fig. 40).

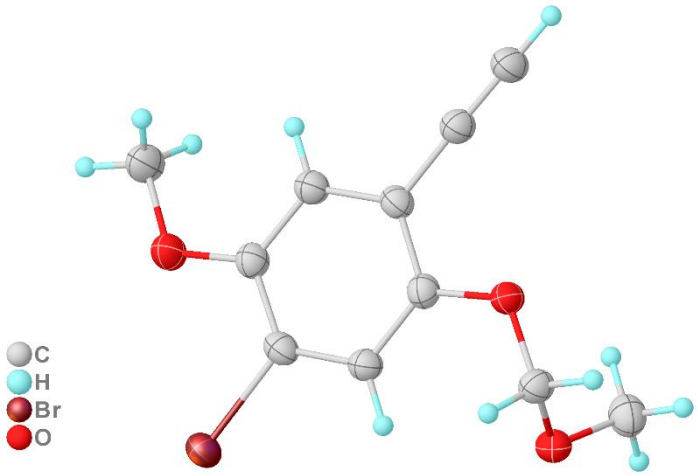
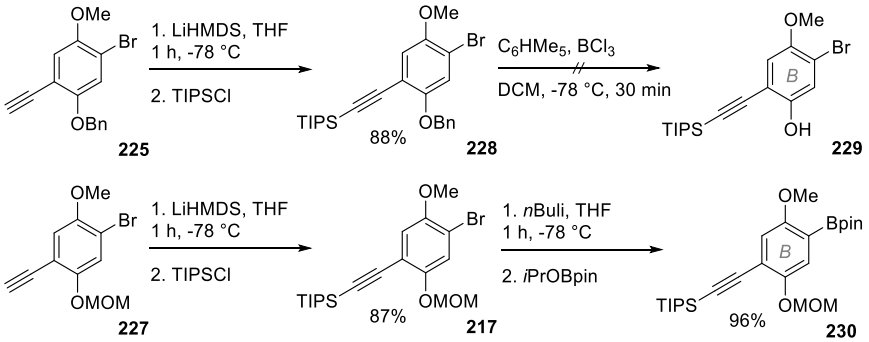


Figure 40: Molecular structure of **227** in the solid state. Displacement ellipsoids drawn at 50% probability level.

To prevent SONOGASHIRA-type reactions with the terminal alkyne, both substrates were treated with LiHMDS as a base to deprotonate the alkyne and TIPSCl as an electrophile which resulted in the desired protected alkyne in both cases (see Scheme 70). Since the building block **141**, which should be connected with the aforementioned building block **217** carries a necessary benzyl group that is planned to be removed at the very end of the total synthesis, the benzyl group of the protected alkyne **228** needed to be cleaved in the following step. The usual procedure for that is the hydrogenolysis with Pd/C. This method not only cleaves the benzyl ester but is also known to reduce the alkyne, an alternative procedure was used. According to TOKUYAMA, cleavage of this group is also possible with BCl_3 and pentamethylbenzene as a non-LEWIS-basic cation scavenger.[95] This should be orthogonal to the methoxy- and the TIPS group also present in the molecule. As shown in Scheme 71 however, in practice the desired substrate **229** could not be isolated since only decomposition products were observed. Thus, the benzyl group was rejected as a protecting group and only the substrate **217** with MOM was suitable for further derivatization.

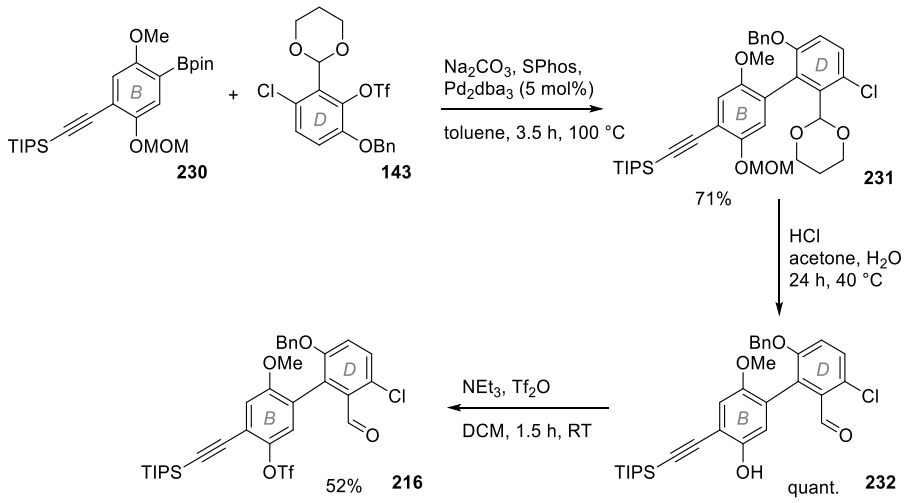


Scheme 71: Further derivatization of the MOM-protected substrate **227** to boronic ester **230**, and unsuccessful deprotection of the benzyl group.

The MOM protected substrate **217** could be directly borylated using *n*Buli and *i*PrOBpin as an electrophile to furnish the desired coupling partner **230** for a SUZUKI coupling.

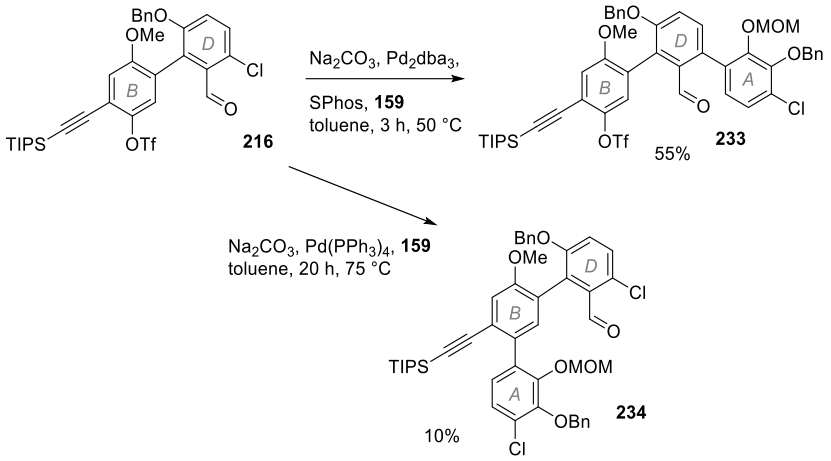
2.3.2. Preparation of the *BD*-fragment

The coupling reaction with triflate **143** succeeded and yielded the biphenyl **231** in high yield as shown in Scheme 72. In the next step, the deprotection of the MOM group could not be performed without also cleaving the acetal protected aldehyde under acidic conditions. After a little optimization however, the desired product **232** could be isolated in quantitative yield. For a SUZUKI coupling, the OH-functionality was transformed into the triflate **216** in mediocre yield.



Scheme 72: Successful SUZUKI coupling of **230** and **143**, and synthesis of *BD*-fragment **216** for the next coupling.

Using a catalytic system containing Pd^0 and SPhos at 50 °C with the substrate **159** only yielded the wrong regioisomer **233** with the C-C bond formation taking place at the chlorine-substituted position (see Scheme 73).



Scheme 73: Coupling with the third building block **159**.

According to FU and co-workers, a catalytic system with Pd_2dba_3 and P(*t*Bu)$_3$ facilitates a SUZUKI coupling selectively at a chlorinated position rather than a triflate in a direct competition with both functional groups present in a substrate.[65] The chosen catalyst in the attempt at preparing the triarene **234** was rather similar and maybe has the same selectivity towards the chlorinated position. Furthermore, this position is most likely activated due to the aldehyde in *ortho*-position. Most likely, the aldehyde is able to coordinate to the palladium as it has a free coordination site with one SPhos being the only other ligand.[96] That means the reaction mechanism is defined by the kinetics of an intramolecular coupling and therefore happens preferably in comparison to the intermolecular reaction. To change the reactivity towards the coupling at the triflate position, a different catalytic system was chosen with $Pd(PPh_3)_4$. This catalyst is fully saturated with ligands and does not possess a free coordination site. This way, the aldehyde present in the substrate **216** could be hindered in the coordination to the palladium center. Another advantage of this catalyst is a diminished reactivity in SUZUKI couplings compared to SPhos.[96] Usually, this is a disadvantage, but in this very case, the triflate substituent holds an intrinsic reactivity. In general, chlorine by itself is usually not a good substituent for a SUZUKI coupling.[97] By using a less reactive catalytic system, the reactivity at the triflate could be high enough to furnish the coupling at the desired position. In a first attempt, this idea led to the formation of desired product **234** with the correct regioselectivity in poor yield. Accidentally, at this attempt the solvent evaporated during the reaction, probably due to a leak in the reaction vessel. Due to the small amount of the product only a ^{1}H-NMR-spectrum and a mass-spectrum could be obtained (shown in Fig. 41 and Fig. 42). Both confirm the formation of the triarene **234**.

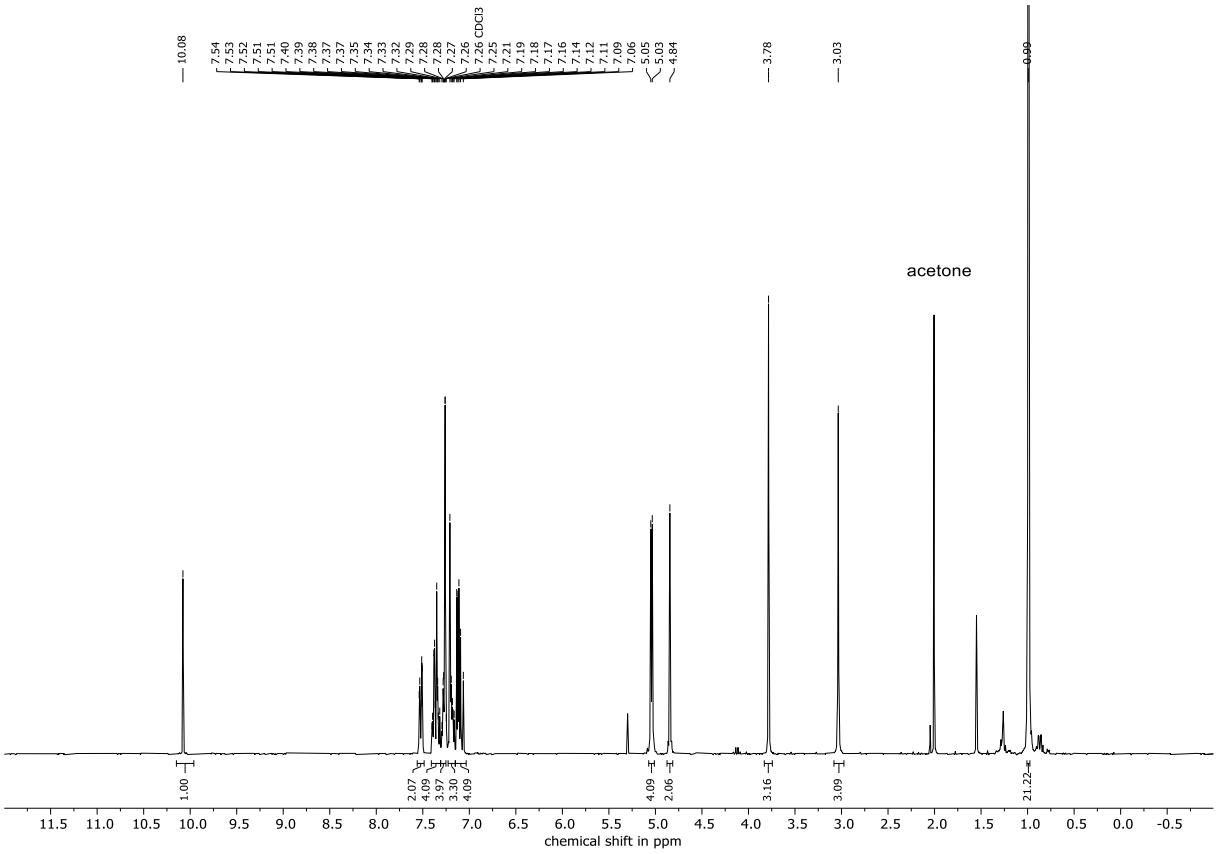


Figure 41: [1]H NMR-spectrum of the desired triarene **234**.

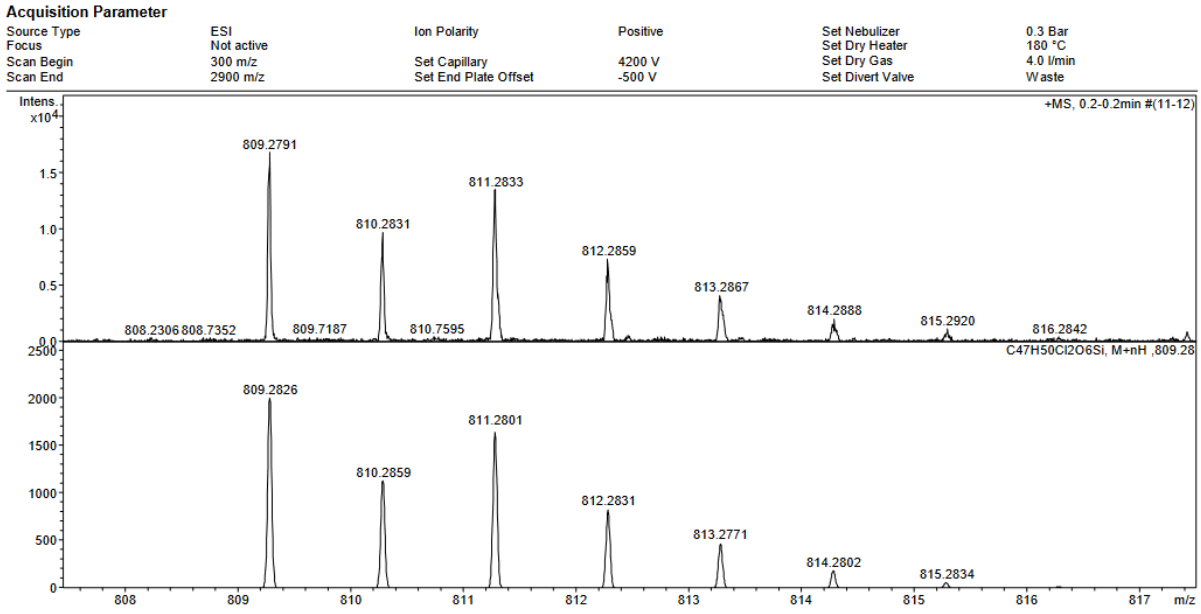


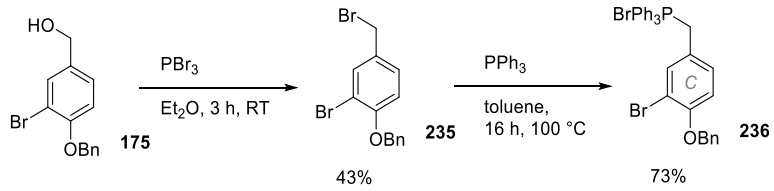
Figure 42: Mass-spectrum of the desired triarene **234**.

Further attempts were unsuccessful as only unreacted starting materials could be isolated. Elevation of the reaction temperature to 100 °C resulted in decomposition of the starting material. Even trying to simulate slow evaporation of the solvent by flushing the reaction mixture with nitrogen during the reaction with a canula in the septum failed repeatedly. A

STILLE coupling was also attempted with an *in situ* generated organo-stannane but this attempt failed as well. Despite great effort, the successful result of the reaction could not be reproduced.

In theory from this point on two different pathways were possible. On one hand, the MOM group could be transformed into a triflate and another coupling could be attempted. And on the other hand, contrary to the synthesis of the model substance **106**, a WITTIG reaction could be carried out at the aldehyde. Since previous tries at performing a C-C coupling in the *ortho*-position of biphenyl **213** showed massive difficulties due to steric hindrance, the first proposal was not particularly promising. Instead, after the WITTIG reaction took place the triflate could be installed and after a borylation, an intramolecular SUZUKI coupling could be attempted to overcome the problems mentioned as the direct special proximity of the two coupling partners might promote the desired reaction under suitable conditions like high dilution reminiscent to the total synthesis of HIOKI.[50]

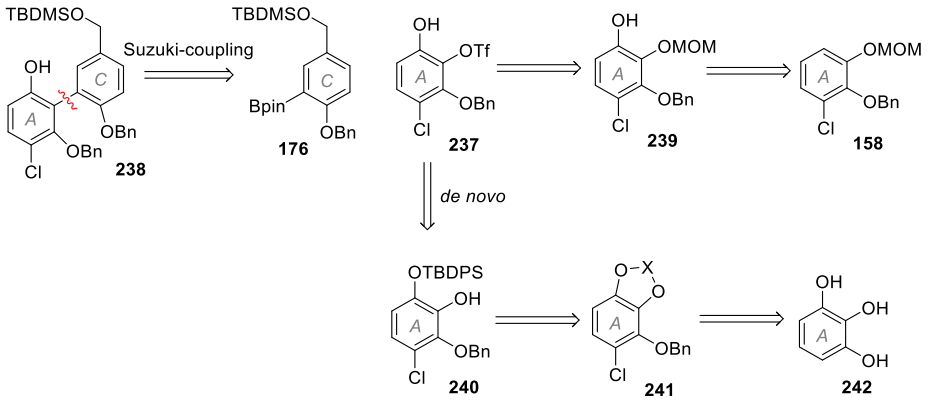
Despite the irreproducibility of the synthesis of substrate **233**, the WITTIG salt **236**, required for further reactions, was prepared by using benzyl alcohol **175** and reacting it with PBr_3 to furnish benzyl bromide **235**. Further reaction with PPh_3 finally yielded the desired salt **236** as seen in Scheme 74.



Scheme 74: Synthesis of WITTIG salt **236**.

2.3.3. Connecting both southern fragments to the *AC*-fragment before the connection with the *BD*-fragment

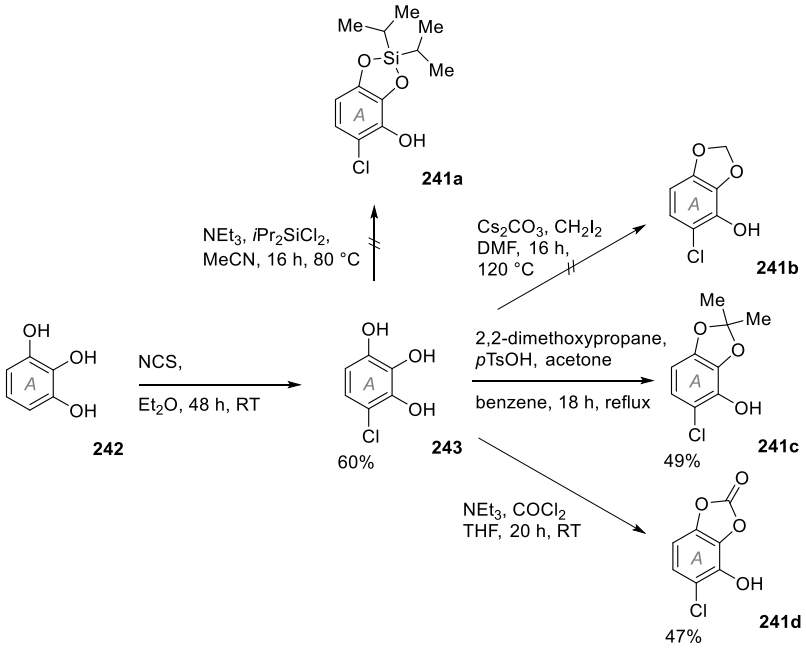
As a new and final strategic idea, the building blocks **176** and **237** could be connected to the *AC*-fragment prior to the connection with the *BD*-fragment **216** which should lead to either the intermolecular WITTIG reaction or an intermolecular SUZUKI coupling as the reaction of choice for the macrocyclization (see Scheme 75), depending on the choice of order, in which the two fragments will be connected. The major drawback of this strategy is the number of steps involved in the synthesis of the *AC*-fragment **238**. The key idea is to put a protected phenol in *ortho*-position to the MOM group present in the molecule **239**, and then exchange MOM for a triflate. In another step, the protecting group must be removed to diminish the steric hindrance for the SUZUKI coupling.



Scheme 75: Retrosynthetic analysis of the *AC*-fragment **238** by using either the already prepared building block **158** or a *de novo* preparation starting with pyrogallol (**242**).

In order to make the synthesis more convenient, a theoretically more concise pathway was also envisioned starting from pyrogallol (**242**). This strategy is based upon a 1,2-protection of two OH groups which enables regioselective benzylation of the third OH group. And after cleaving this protection group X, a sterically very demanding protecting group should block the more exposed OH group in *para*-position to the chlorine-atom with higher selectivity. However, the viability of this much shorter synthesis has to be investigated, because most steps were not yet tested in literature.

At this point the alternative and much shorter synthetic pathway should be introduced. Starting from the commercially available pyrogallol (**242**), a literature known chlorination with NCS was conducted[98] and yielded the chlorobenzene **243** in mediocre, yet acceptable yield because this was the first reaction and it could be done on a multigram scale. With this substrate **243** in hand, it was crucial to perform a selective bridging protection of the two OH groups opposite to the chlorine. Four different functionalities were considered in the protection as shown in Scheme 76: A silyl group, a methylene group, an acetonide and a carbonate.



Scheme 76: Search for a suitable protecting group for the 1,2-protection of chloro-pyrogallol (**243**).

The protection with dichlorodiisopropylsilylsilane[99] and methyleneiodide[100] analogous to literature did not result in the formation of the desired silyl-protected **241a** nor the methylene-bridged **241b**, as no conversion could be observed. However, the acetonide protection with 2,2-dimethoxypropane under acidic conditions worked out with an acceptable yield of 48 % and the correct regioselectivity of the reaction to substrate **241c** could be verified *via* X-ray diffractometry of a single crystal (Fig. 43). Moreover, the protection with phosgene had similarly satisfying results. Again, crystallography verified the desired regioselectivity of the reaction to product **241d**. (Fig. 44).

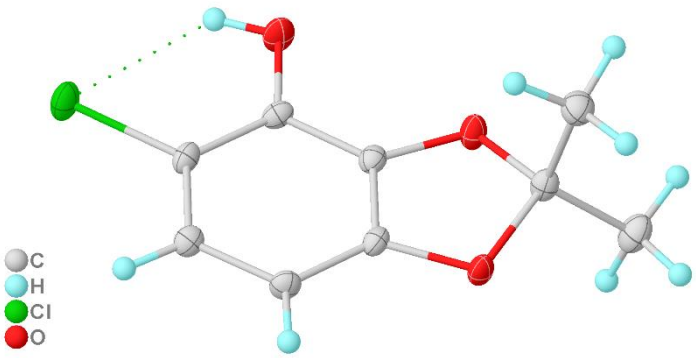


Figure 43: Molecular structure of **241c** in the solid state. Displacement ellipsoids drawn at 50% probability level.

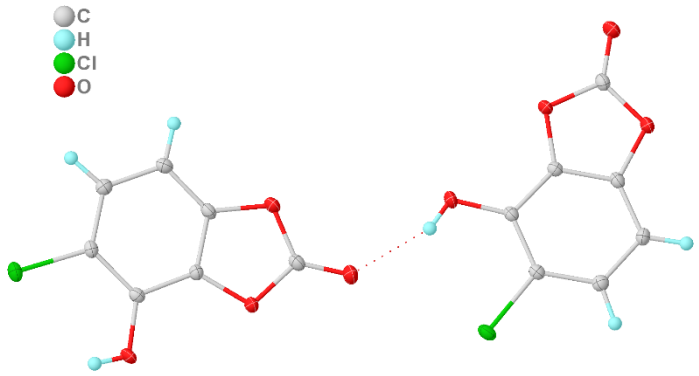
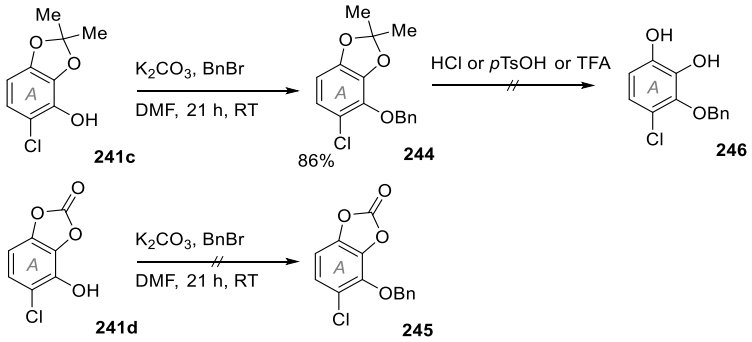


Figure 44: Molecular structure of **241d** in the solid state. Displacement ellipsoids drawn at 50% probability level.

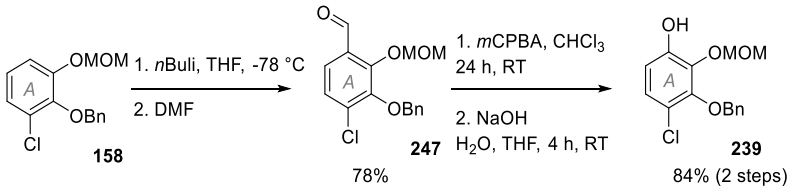
As shown in Scheme 77, in a next step, a benzyl group had to be installed at the remaining OH group. While treatment with BnBr under basic conditions yielded the benzylated acetonide **244** in good yield, the carbonate **241d** decomposed in the basic environment and the product **245** could not be obtained.



Scheme 77: Attempted benzylation and cleaving of the protecting group to test the viability of an acetonide and a carbonate as suitable protecting groups.

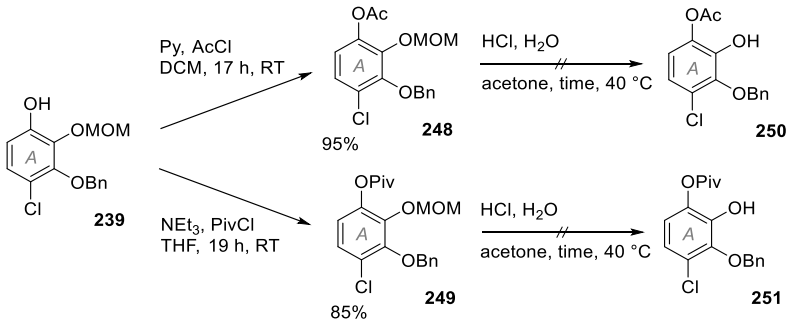
According to literature,[78] deprotection of an aliphatic acetonide derived from 1,3-diols and 1,2-diols can easily be performed under slightly acidic conditions. Unfortunately, deprotection of substrate **244** did not occur under these conditions, nor did it work under other conditions for similar substrates with TFA.[101] This shorter synthetic route was not followed any further, since it failed to prepare the required substrate **240**.

As shown in Scheme 78, starting with the former mentioned pathway the first reaction is an *ortho*-directed lithiation and subsequent quenching with DMF as an electrophile yielded aldehyde **247**. A BAEYER-VILLIGER oxidation with *m*CPBA and a saponification of the crude reaction mixture with NaOH led to the formation of the desired phenol **239** in satisfactory yield of 84% after two steps. Since the deprotection of MOM requires acidic conditions, a protecting group is needed, which is stable at low pH-values.



Scheme 78: Concise synthesis of phenol **239** by *ortho*-directed functionalization and BAEYER-VILLIGER reaction as key steps.

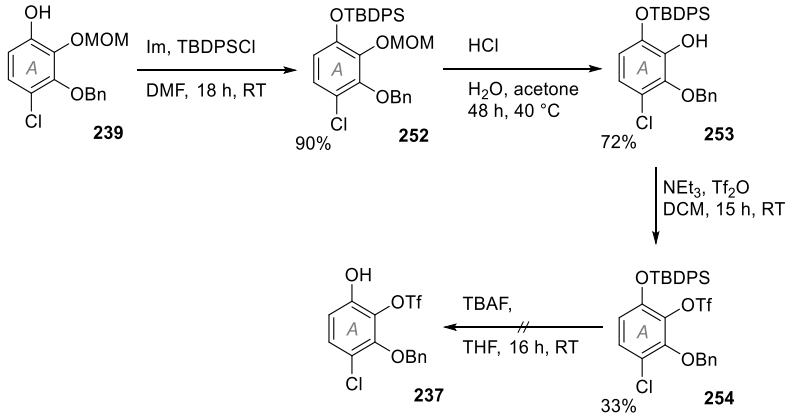
Esters like acetyl- or the sterically more demanding pivaloic esters are usually somewhat stable under mild acidic conditions[78] and their feasibility as protection groups was tested (see Scheme 79). Reaction of the free phenol **239** with the corresponding acid chloride under basic conditions yielded the desired protected substrates **248** and **249** in excellent yield of 85% and 95% respectively. However, cleavage of the MOM group resulted in decomposition in the case of both acyl-protected substrates. Since separation of the two compounds was not possible, another solution was needed.



Scheme 79: Attempting the use of esters as protecting groups for the phenol **239**.

With esters being eliminated as good protecting groups, silyl groups were considered. In general, smaller silyl groups tend to be rather delicate towards acidic conditions. While TMS gets hydrolyzed very fast in the presence of an acid, TBDPS shows much more resistance.[102] Therefore, the latter group was chosen as a protecting group in further procedures.

As seen in Scheme 80, protection of the OH group as the silyl ether **252** was conducted successfully and acidic cleavage of the MOM group finally yielded the desired substrate **253** with acceptable yield. To install a group into the substrate that can react in a C-C coupling reaction, a triflylation was conducted, which gave substrate **254** in poor yield which might be due to the steric hindrance of the big silyl group.



Scheme 80: Attempting the synthesis of triflate **237** by deprotection of the MOM group, triflylation and final deprotection of the TBDPS group.

Unfortunately, cleaving of the silyl group with fluoride-ions only led to decomposition and the desired deprotected triflate **237** could not be isolated. One could imagine that the coupling with substrate **254** is also feasible with the protected OH group, but the TBDPS group poses an exceptionally big steric bulk, which most likely will prevent the C-C coupling in *ortho*-position from happening.

2.4. Conclusion

As seen in Fig. 45, it could be shown through the synthesis of model substance **118** that there are viable reactions and methods for the introduction of a phenanthrene into a similar molecular scaffold as bazzanin K (**14**). Furthermore, with the successful preparation of model substrate **138** by an intramolecular WITTIG reaction, a reaction was found that was able to facilitate the macrocyclization of a rather strained 12-membered MBB containing four rigid phenol moieties. These results gave reason to devise different synthetic strategies and pathways for an attempt at synthesizing bazzanin K.

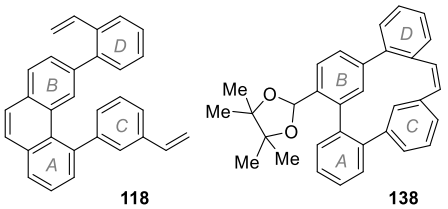


Figure 45: Successfully prepared model substances **118** and **138**.

However, the total synthesis of bazzanin K (**14**) was an exceedingly difficult task, since the executed strategies and pathways were mostly unknown to literature and partly even the synthetic concept of some ideas was not yet explored. Furthermore, the chiral character of the target molecule posed a problem which could only be tackled after the connectivity issues had been solved. Unfortunately, the total synthesis did not come to a satisfactory conclusion since the goal of complete preparation of bazzanin K (**14**) could not be reached. Nonetheless, the limitations of many known reactions could be tested and overcome in a variety of substrates and a big plethora of arenes with interesting and potentially useful substitution patterns was synthesized and their effective use in the synthesis of complex biphenyls with numerous substituents and functional groups could be shown (see Fig. 46). Additionally, the benefit of α-cationic phosphine-ligands in cycloisomerization reactions and the limitations in regards of functional group tolerance were investigated.

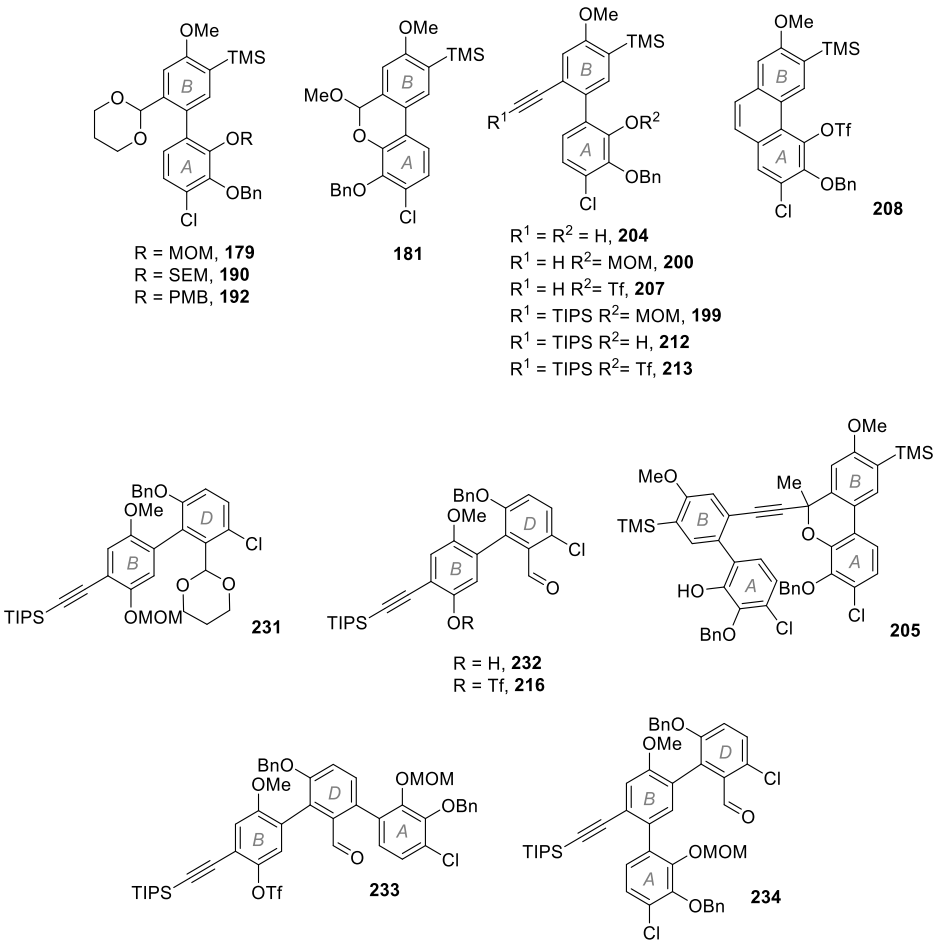
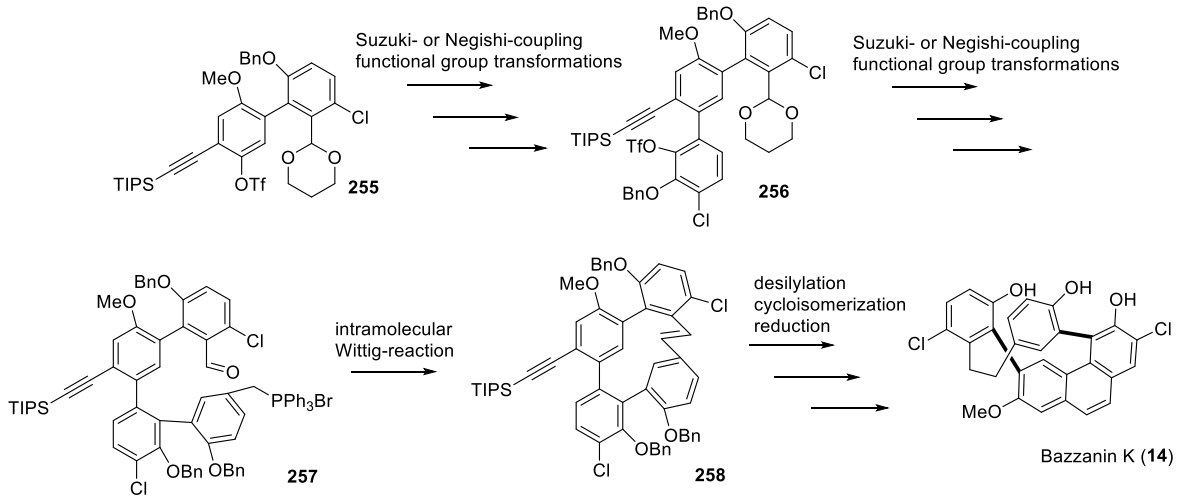


Figure 30: Successfully prepared biphenyls and other derivatives of interest.

In the end, many strategies could be found that did not lead to the desired outcome but added to the pool of experience and knowledge in regards of protecting groups, the chemistry of aromatics and palladium-catalyzed cross-coupling reactions with sterically hindered substrates with a multitude of substituents.

2.5. Outlook

Even if the total synthesis of bazzanin K (**14**) was not yet finished, the prepared building blocks might still be useful for different strategies in future attempts. For example, it might be possible to perform a protection of the aldehyde of substrate **216** to the respective acetal **255**. With this functionalization, the coordination to the aldehyde in the SUZUKI coupling could be prevented and eventually, the reaction can take place at the triflate to facilitate the coupling to the desired product. After a few derivatization steps of turning the MOM group into the respective triflate in substrate **256**, another coupling could be performed to install the final building block **176** into the molecule. This intermediate could be turned into the WITTIG salt **257** and can perform the macrocyclization to ring **258**. After desilylation and performing the hydroarylation under π-acid-catalysis, the phenanthrene only needs cleaving of the benzyl groups and finally bazzanin K (**14**) could be obtained. It should be noted that while cleaving the benzyl groups under hydrogenolytic conditions, the double bond derived from the WITTIG reaction can also be reduced to the desired ethylene-bridge. In case the same reduction happens at the phenanthrene successive oxidation with DDQ could be used to reestablish the phenanthrene moiety (Scheme 81).



Scheme 81: Potential synthetic pathway to bazzanin K (**14**) in future attempts.

3. Experimental Part

3.1. General information

All reactions were carried out under nitrogen atmosphere and in dried glassware using standard SCHLENK-technique unless otherwise stated. All anhydrous solvents were obtained from the solvent purification system MB-SPS-7 from MBRAUN or from drying over molecular sieves 3 Å. Air- and moisture sensitive reagents were stored in a glovebox (MBRAUN UNILAB plus).

3.1.1. Starting materials/chemicals

All commercially available compounds (ABCR, ACROS ORGANICS, ALFA AESAR, SIGMA ALDRICH, CHEMPUR GMBH FLUOROCHEM, TCI, THERMO FISHER SCIENTIFIC) were used as received. Compounds, **146**[79], **157**[75], **167**[84], **174**[86], **220**[94], **243**[98] were prepared according to literature.

3.1.2. Analytical methods

IR: JASCO FT-4600 or JASCO FT-4100 spectrometer, wavelengths in cm^{-1}.

MS(EI): ACCUTOF (JEOL) (70 eV). ESI MS: ESI-HRMS: MICROTOF (BRUKER) and MAXIS (BRUKER).

Melting points: BÜCHI MELTING POINT M-560.

GC-MS: Reactions were monitored by GC-MS on AGILENT TECHNOLOGIES 7820A gaschromatography system coupled with an AGILENT TECHNOLOGIES 5977 E MSD EI-MS detector. NMR: Spectra were recorded on BRUKER AV 500, 400 or 300 spectrometers; ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale.

Flash column chromatography was performed using SiOH 40-63 µm from MACHEREY-NAGEL or the BIOTAGE ONE ISOLERA automated column chromatography system on CHROMABOND® Flash BT, 15 g (or 25 g) SiOH 40-63 µm from MACHEREY-NAGEL.

Thin-layer chromatography (TLC) analysis was performed using POLYGRAM® SIL G/UV254 TLC plates from MACHEREY-NAGEL and visualized by UV irradiation and/or phosphomolybdic acid staining.

Crystals suitable for X-Ray diffraction were obtained by crystallization from ethyl acetate/ hexane. Data collection was done on two dual source equipped BRUKER D8 VENTURE four-circle-diffractometer from BRUKER AXS GMBH; used X-ray sources: microfocus *IµS 2.0* Cu/Mo and microfocus *IµS 3.0* Ag/Mo from INCOATEC GMBH with mirror optics HELIOS and single-hole collimator from BRUKER AXS GMBH*;* used detector: PHOTON III CE14 (Cu/Mo)

and PHOTON III HE (Ag/Mo) from BRUKER AXS GMBH; for data collection with internal number below 0800 PHOTON II from BRUKER AXS GMBH.

Used programs: APEX3 SUITE (early v2017.3-0; late v2019.11-0) for data collection and therein integrated programs SAINT V8.40A (Integration) und SADABS 2016/2 (Absorption correction) from BRUKER AXS GMBH; structure solution was done with SHELXT, refinement with SHELXL-2018/3[1]; OLEX[2] and FINALCIF were used for data finalization[2].

Special Utilities: SMZ1270 stereomicroscope from NIKON METROLOGY GMBH was used for sample preparation; crystals were mounted on MICROMOUNTS or MICROLOOPS from MITEGEN in NVH oil; crystals were cooled to given temperature with CRYOSTREAM 800 from OXFORD CRYOSYSTEMS.

[1] Both: G.M. Sheldrick, *Acta Cryst*. **2008,** *A64*, 112-122.

[2] O.V. Dolomanov, L.J. Bourhis, R.J Gildea, J.A.K. Howard, H. Puschmann, *J. Appl. Cryst*. **2009,** *42*, 339-341; D. Kratzert, *FinalCif*, *V96*, https://dkratzert.de/finalcif.html.

3.2. Syntheses of new compounds

3.2.1. General procedure A (GP A) for the triflylation of phenols

Triflic acid anhydride (1.5 equiv.) and TEA (2.0 equiv.) were added to a solution of the desired phenol (1.0 equiv.) in dry DCM (0.4 M) at 0 °C under nitrogen. After the addition, the cooling bath was removed, and subsequently the obtained solution was stirred at room temperature for two additional hours. After that, the reaction mixture was diluted with DCM (20 mL) and water was added (20 mL). The phases were separated, and the aqueous phase was extracted three times with DCM (20 mL). Finally, the combined organic phases were washed with brine and dried over magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil/solid, which was further purified *via* flash chromatography to afford the desired product.

3.2.2. General procedure B (GP B) for the silyl-protection of alcohols or phenols

TESCl, TBDMSCl or TBDPSCl (1.1 equiv.) was added to a solution of an alcohol or phenol (1.0 equiv.) and imidazole (1.1 equiv.) in DMF (2 M). The solution was stirred at room temperature for 16 h. Water (20 mL) was added, and the phases were separated. The aqueous phase was extracted three times with ethyl acetate (20 mL). Finally, the combined organic phases were washed with brine. After drying over Na_2SO_4, removal of the solvent under reduced pressure afforded an oil/solid, which was further purified *via* flash chromatography to afford the desired product.

3.2.3. General procedure C (GP C) for the SEYFERTH-GILBERT-homologation using the OHIRA-BESTMANN reagent

K_2CO_3 (2.4 equiv.) was added to a solution of an aldehyde (1.0 equiv.) in dry MeOH (0.3 M) The OHIRA-BESTMANN reagent (**120**) (2.0 equiv.) was added, and the suspension was stirred at room temperature for 3 h. Water (50 mL) was added, and the solution was extracted three times with ethyl acetate (20 mL). The phases were separated, and the combined organic phases were washed with brine. The solvent was removed under reduced pressure. Purification of the residue *via* flash chromatography afforded the desired product.

3.2.4. General procedure D (GP D) for the deprotection of silyl ethers and silyl-protected alkynes using TBAF

TBAF (1.1 equiv., 1 M in THF) was added to a solution of a silyl ether or silyl-protected alkyne (1.0 equiv.) in dry THF (0.15 M) at 0 °C. After the addition, the cooling bath was removed and stirring was continued for 1 h at room temperature. To quench the reaction mixture, water (50 mL) was added, and the mixture was extracted three times with ethyl acetate (20 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced

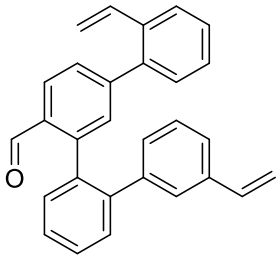
pressure. Purification of the residue *via* flash chromatography afforded the desired product.

3.2.5. General Procedure E (GP E) for the NEGISHI coupling of a bromide and a triflate

*i*PrMgCl·LiCl (1.3 M in THF, 1.3 equiv.) was added to a solution of a bromide (1.1-1.4 equiv.) in dry THF (0.4-0.5 M) at 0 °C. The solution was allowed to warm to room temperature and was stirred for 2 h. A solution of $ZnBr_2$ (1.2 equiv.) in dry THF (1.65 M) was added to the reaction mixture and stirring was continued for 30 min. Another solution was prepared by dissolving a triflate (1.0 equiv.), $Pd_2(dba)_3$ (5 mol%) and dppf (10 mol%) in dry THF (0.9 M). The solution of the zincate was transferred into the solution and the reaction mixture was stirred at 70 °C for 20 h. After cooling to room temperature, the reaction mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. Purification of the residue *via* flash chromatography afforded the desired product.

3.2.6. Procedures

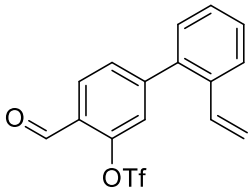
Synthesis of 2''',3-divinyl-[1,1':2',1'':3'',1'''-quaterphenyl]-6''-carbaldehyde (105)



A SCHLENK flask was charged with **107** (83 mg, 0.233 mmol, 1 equiv.), **108** (72 mg, 0.236 mmol, 1.0 equiv.), K_2CO_3 (93 mg, 0.673 mmol, 3.0 equiv.), Pd_2dba_3 (13 mg, 1.42 µmol, 0.6 mol%), SPhos (41 mg, 10.0 mmol, 4.2 mol%) and degassed dioxane (2 mL). The reaction mixture was stirred for 48 h and the solvent was removed under reduced pressure. Column chromatography of the residue (ethyl acetate/hexane, 1/15) yielded 2''',3-divinyl-[1,1':2',1'':3'',1'''-quaterphenyl]-6''-carbaldehyde (**105**) (72 mg, 0.186 mmol, 80%) as a colorless oil.

R_f = 0.57 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 9.88 (d, J = 0.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.60 (dd, J = 7.8, 1.4 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.46 (dt, J = 7.5, 4.3 Hz, 1H), 7.43 – 7.41 (m, 1H), 7.37 – 7.33 (m, 2H), 7.29 (td, J = 7.5, 1.4 Hz, 1H), 7.24 (tt, J = 3.4, 1.4 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.13 (ddd, J = 4.2, 2.8, 1.5 Hz, 2H), 7.02 (dt, J = 7.6, 1.5 Hz, 1H), 6.57 (dd, J = 17.6, 10.9 Hz, 1H), 6.40 (dd, J = 17.4, 10.9 Hz, 1H), 5.64 (dd, J = 17.4, 1.3 Hz, 1H), 5.54 (dd, J = 17.6, 0.9 Hz, 1H), 5.14 (ddd, J = 22.5, 10.9, 1.1 Hz, 2H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ =191.6, 146.2, 145.2, 141.8, 140.7, 139.3, 137.6, 136.6, 136.4, 135.9, 135.2, 133.2, 132.6, 131.5, 130.3, 130.0, 129.4, 129.3, 128.9, 128.5, 128.4, 128.0, 127.9, 127.5, 127.3, 126.1, 125.0, 115.9, 114.4 ppm. **IR** (neat): 3085, 3059, 3023, 2982, 2844, 2749, 1685, 907, 757, 731, 713 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{29}H_{22}NaO^+$: 409.1563 $[M+Na]^+$; found: 409.1556.

Synthesis of 4-formyl-2'-vinyl-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (107)

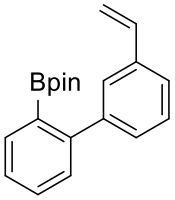


Triflate **107** was prepared according to **GP A** using phenol **114** (200 mg, 0.90 mmol). After purification *via* flash chromatography (ethyl acetate/hexane, 1/15), 4-formyl-2'-vinyl-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (**107**) (214 mg, 0.60 mmol, 67%) was obtained as colorless crystals.

T_m: 85-86°C. R_f = 0.49 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.31 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 7.6, 1.6 Hz, 1H), 7.56 (dd, J = 8.0, 1.5 Hz, 1H), 7.50 – 7.36 (m, 3H), 7.29 (dd, J = 7.5, 1.7 Hz, 1H), 6.61 (dd, J = 17.4, 11.0 Hz, 1H), 5.75 (dd, J = 17.4, 1.1 Hz, 1H), 5.31 (dd, J = 11.0, 1.1 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =186.4, 149.6, 149.5, 137.3, 136.2, 134.9, 130.6, 130.3, 129.8, 129.4, 128.3, 127.0, 126.8, 123.9, 118.8 (q, J = 320.6 Hz), 117.1 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -72.8 ppm. **IR** (neat): 3089, 3063, 3026, 2860, 2760, 1702, 1608, 1425, 1196, 1136, 1093, 929, 905, 826, 598.

cm^{-1} **HRMS** (ESI) *m/z* calcd for $C_{16}H_{12}F_3O_4S^+$: 357.0402 $[M+H]^+$; found: 357.0403.

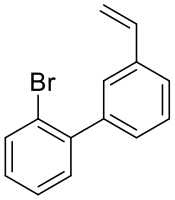
Synthesis of 4,4,5,5-tetramethyl-2-(3'-vinyl-[1,1'-biphenyl]-2-yl)-1,3,2-dioxaborolane (108)



*n*Buli (1.01 mL, 1.62 mmol, 1.6 M in hexane, 1.05 equiv.) was added dropwise to a solution of **113** (400 mg, 1.54 mmol, 1.0 equiv.) in dry THF (6.2 mL) at -78 °C. After stirring at this temperature for 1 h, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.31 mL, 1.54 mmol, 1.0 equiv) was added and the solution was allowed to warm to room temperature overnight. Water (10 mL) was added, and the mixture was extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 1/10) yielded 4,4,5,5-tetramethyl-2-(3'-vinyl-[1,1'-biphenyl]-2-yl)-1,3,2-dioxaborolane (**108**) (406 mg, 1.33 mmol, 86%) as a colorless oil.

R_f = 0.66 (1/4, ethyl acetate/hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.76 – 7.68 (m, 1H), 7.50 – 7.27 (m, 7H), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.78 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.25 (dd, *J* = 10.9, 1.0 Hz, 1H), 1.19 (s, 12H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.5, 143.6, 137.1, 137.0, 134.6, 130.2, 129.1, 128.7, 128.2, 127.3, 126.5, 125.0, 113.8, 83.9, 24.77. ppm. **IR** (neat): 3056, 2977, 2929, 1594, 1379, 1342, 1309, 1144, 764, 661 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{24}{}^{10}BO_2^+$: 306.1900 $[M+H]^+$; found: 306.1890.

Synthesis of 2-bromo-3'-vinyl-1,1'-biphenyl (113)

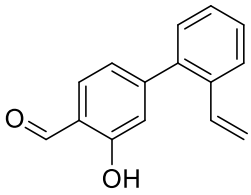


1-bromo-2-iodobenzene (0.26 mL, 2.03 mmol, 1.0 equiv.) was added to a degassed solution of Pd_2dba_3 (66 mg, 72.1 µmol, 6 mol%) and PPh_3 (314 mg, 1.20 mmol, 0.6 equiv.) in DMF (33 mL) at room temperature and the solution was stirred for 15 min at room temperature. A degassed suspension of (3-vinylphenyl)boronic acid (300 mg, 2.03 mmol, 1.0 equiv.) in Na_2CO_3 (aq.) (33 mL, 2 M) was added and the reaction mixture was stirred for 19 h at 100 °C. After cooling to room temperature, DCM (10 mL) was added, and the phases were separated. The aqueous phase was extracted with DCM (2 x 50 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Column chromatography of the residue (hexane) yielded 2-bromo-3'-vinyl-1,1'-biphenyl (**113**) (451 mg, 1.74 mmol, 86%) as a colorless oil.

R_f = 0.72 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.4 Hz, 1H), 7.49 – 7.28 (m, 6H), 7.21 (ddd, *J* = 8.0, 6.3, 2.8 Hz, 1H), 6.77 (dd, *J* = 17.6, 10.9 Hz, 1H),

5.80 (d, J = 17.5 Hz, 1H), 5.29 (d, J = 10.9 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =142.6, 141.5, 137.5, 136.8, 133.3, 131.4, 128.99, 128.95, 128.3, 127.5, 127.1, 125.6, 122.8, 114.4 ppm. **IR** (neat): 3086, 3053, 2979, 1466, 1022, 988, 906, 800, 753, 711 cm^{-1}. **HRMS** (EI) *m/z* calcd for $C_{14}H_{11}{}^{79}Br^{+\cdot}$: 258.0039 $[M]^{+\cdot}$; found: 258.0038.

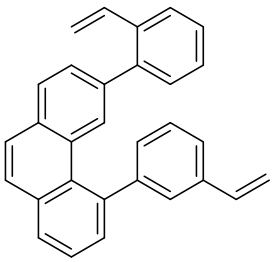
Synthesis of 3-hydroxy-2'-vinyl-[1,1'-biphenyl]-4-carbaldehyde (114)



A SCHLENK flask was charged with 4-bromo-2-hydroxybenzaldehyde (371 mg, 1.84 mmol, 1.0 equiv.), (2-vinylphenyl)boronic acid (300 mg, 2.03 mmol, 1.1 equiv.), K_2CO_3 (770 mg, 5.50 mmol, 3 equiv.), $Pd(OAc)_2$ (6.0 mg, 26.7 µmol, 15 mol%), PPh_3 (11 mg, 41.9 µmol, 23 mol%), DME (2.5 mL) and water (2.5 mL). The reaction mixture was stirred at room temperature for 24 h and DCM (10 mL) was added. The phases were separated and the aqueous phase was extracted with DCM (2 x 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography of the residue (hexane) yielded 3-hydroxy-2'-vinyl-[1,1'-biphenyl]-4-carbaldehyde (**114**) (374 mg, 1.67 mmol, 91%) as a colorless oil.

R_f = 0.58 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.68 (d, J = 7.4 Hz, 1H), 7.49 – 7.28 (m, 6H), 7.21 (ddd, J = 8.0, 6.3, 2.8 Hz, 1H), 6.77 (dd, J = 17.6, 10.9 Hz, 1H), 5.80 (d, J = 17.5 Hz, 1H), 5.29 (d, J = 10.9 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.3, 161.5, 150.3, 139.3, 135.9, 135.4, 133.4, 129.7, 128.7, 128.0, 126.2, 122.0, 119.6, 119.0, 115.9 ppm. **IR** (neat): 3085, 3059, 3026, 2988, 2940, 2743, 1650, 1190, 922, 753, 712 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{11}O_2^-$: 223.0765 $[M-H]^-$; found: 223.0760.

Synthesis of 3-(2-vinylphenyl)-5-(3-vinylphenyl)phenanthrene (118)

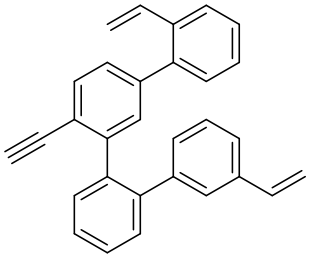


A SCHLENK flask was charged with **119** (133 mg, 0.348 mmol, 1.0 equiv.), precatalyst **121** (16.6 mg, 16.8 µmol, 5 mol%) and dry DCM (6.7 mL). A solution of $AgSbF_6$ in dry DCM (0.42 mL, 0.04 mM, 5 mol%) was added to the reaction mixture at room temperature, and the solution turned black in a few seconds. After stirring for 20 min, the mixture was filtered through a pad of silica and rinsed with DCM and the solvent was removed under reduced pressure. Column chromatography of the residue (ethyl acetate/hexane, 1/10) yielded 3-(2-vinylphenyl)-5-(3-vinylphenyl)phenanthrene (**118**) (108 mg, 0.283 mmol, 81%) as a colorless solid.

R_f = 0.65 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.92 (dd, J = 7.9, 1.4

Hz, 1H), 7.86 – 7.83 (m, 2H), 7.82 – 7.77 (m, 2H), 7.61 (dd, *J* = 7.9, 7.1 Hz, 1H), 7.53 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.50 – 7.45 (m, 3H), 7.43 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.34 (dt, *J* = 7.3, 1.5 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H), 6.83 (ddd, *J* = 7.6, 1.4, 0.5 Hz, 1H), 6.73 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.55 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.74 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.61 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.25 (dd, *J* = 10.9, 0.9 Hz, H), 5.11 (dd, *J* = 11.0, 1.3 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 145.7, 140.9, 140.5, 138.6, 137.5, 136.9, 136.2, 135.6, 133.9, 132.3, 130.8, 130.7, 130.4, 129.6, 128.8, 128.7, 128.6, 127.7, 127.6, 127.40, 127.38, 127.3, 127.1, 125.9, 125.7, 124.9, 114.7, 114.4 ppm. **IR** (neat): 3084, 3052, 3019, 2982, 1625, 1593, 1575, 1479, 1442, 1414, 991, 907, 846, 763, 729 cm^{-1}. **HRMS** (EI) *m/z* calcd for $C_{30}H_{22}^{\cdot+}$: 382.1716 $[M]^{\cdot+}$; found: 382.1711.

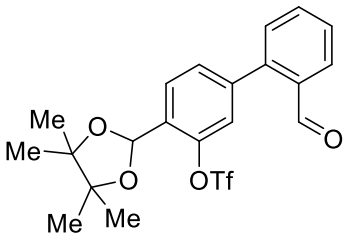
Synthesis of 6''-ethynyl-2''',3-divinyl-1,1':2',1'':3'',1'''-quaterphenyl (119)



Alkyne **119** was prepared according to **GP C** using aldehyde **105** (273 mg, 0.706 mmol). Deviating from **GP C**, dry MeCN/MeOH (1/11) was used as a solvent. After recrystallization from hexane, 6''-ethynyl-2''',3-divinyl-1,1':2',1'':3'',1'''-quaterphenyl (**119**) (230 mg, 0.602 mmol, 85%) was obtained as colorless crystals.

T_m: 132-133°C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 7.9, 0.5 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.50 (dddd, *J* = 7.7, 3.5, 1.5, 0.6 Hz, 2H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 (td, *J* = 7.4, 1.6 Hz, 1H), 7.28 (ddd, *J* = 7.3, 1.5, 0.6 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.20 – 7.17 (m, 1H), 7.17 – 7.15 (m, 1H), 7.09 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.62 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.23 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.62 – 5.53 (m, 2H), 5.17 (dd, *J* = 10.9, 0.9 Hz, 1H), 5.02 (dd, *J* = 10.9, 1.4 Hz, 1H), 3.02 (s, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 144.4, 141.6, 141.13, 141.0, 139.7, 139.1, 137.3, 136.9, 135.8, 135.3, 132.8, 132.3, 131.1, 130.0 (2 C), 129.4, 128.4, 128.2 (2 C), 127.9, 127.8, 127.7, 127.0, 125.8, 124.7, 120.8, 115.4, 114.0, 83.0, 80.8 ppm. **IR** (neat): 3285, 3057, 3023, 991, 910, 837, 803, 761, 714, 650 cm^{-1}. **HRMS** (EI) *m/z* calcd for $C_{30}H_{22}^{\cdot+}$: 382.1716 $[M]^{\cdot+}$; found: 382.1719.

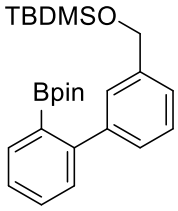
Synthesis of 2'-formyl-4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (125)



Triflate **125** was prepared according to **GP A** using phenol **131** (700 mg, 2.15 mmol, 1.0 equiv.). After purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 4%→10%), 2'-formyl-4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (**125**) (875 mg, 1.91 mmol, 89%) was obtained as a colorless solid.

R_f = 0.47 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 9.97 (s, 1H), 8.05 (dd, J = 7.8, 1.5 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.68 (td, J = 7.5, 1.5 Hz, 1H), 7.56 (tt, J = 7.6, 1.1 Hz, 1H), 7.41 (td, J = 7.9, 7.4, 1.4 Hz, 2H), 7.34 (d, J = 1.6 Hz, 1H), 6.25 (s, 1H), 1.36 (s, 6H), 1.29 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 191.5, 147.7, 143.3, 140.4, 134.0, 133.8, 132.8, 130.8, 130.0, 128.9, 128.3, 128.2, 122.8, 118.7 (q, J = 320.3 Hz), 95.0, 83.4, 24.3, 22.2 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ =-73.73 ppm. **IR** (neat): 2980, 2933, 2871, 1695, 1422, 1390, 1204, 1138, 1111, 1060, 917, 766, 602 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{21}H_{22}F_3O_6S^+$: 459.1084 $[M+H]^+$; found: 459.1085.

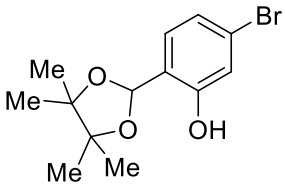
Synthesis of *tert*-butyldimethyl((2'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-3-yl)methoxy)silane (126)



*n*Buli (0.43 mL, 0.69 mmol, 1.6 M in hexane, 1.05 equiv.) was added to a solution of **133** (200 mg, 0.661 mmol, 1.0 equiv.) in dry THF (3 mL) at -78 °C. After stirring at this temperature for 1 h, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.31mL, 1.54 mmol, 2.3 equiv.) was added at -100 °C and the solution was allowed to warm to room temperature overnight. Water (0.05 mL) was added, and the solvent was removed under reduced pressure. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→5%) yielded *tert*-butyldimethyl((2'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-3-yl)methoxy)silane (**126**) (194 mg, 0.457 mmol, 69%) as a colorless oil.

R_f = 0.71 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.75 – 7.68 (m, 1H), 7.49 – 7.41 (m, 1H), 7.40 – 7.23 (m, 6H), 4.79 (s, 2H), 1.21 (s, 12H), 0.95 (s, 9H), 0.11 (s, 6H). ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.8, 143.2, 140.9, 134.6, 130.2, 129.2, 128.0, 127.9, 126.2, 126.4, 124.7, 83.8, 65.2, 26.1, 24.7, 18.6, -5.1 ppm. **IR** (neat): 2977, 2954, 2928, 2856, 1596, 1348, 1310, 1254, 1145, 1077, 758 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{25}H_{37}{}^{10}B^{79}BrNaO_3Si^+$: 446.3534 $[M+Na]^+$; found: 446.3538.

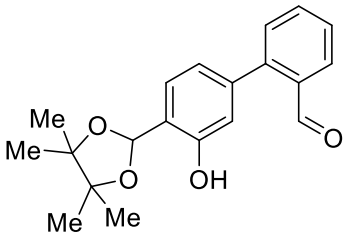
Synthesis of 5-bromo-2-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenol (127)



A solution of 4-bromo-2-hydroxybenzaldehyde (1.98 g, 9.85 mmol, 1.0 equiv.), *p*TsOH·H_2O (55 mg, 0.289 mmol, 3 mol%) and pinacol (1.54 g, 13.0 mmol, 1.3 equiv.) in toluene (16 mL) was stirred at reflux for 6 h. After cooling to room temperature, aq. sat. $NaHCO_3$ (10 mL) was added, and the phases were separated. The organic phase was washed with water (10 mL) and brine (10 mL) and the solvent was removed under reduced pressure. Recrystallisation from ethyl acetate yielded 5-bromo-2-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenol (**127**) (1.11 g, 3.69 mmol, 38%) as colorless crystals.

T_m: 114-115°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.28 (s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 1.9 Hz, 1H), 7.00 (dd, J = 8.1, 1.9 Hz, 1H), 6.08 (s, 1H), 1.32 (s, 6H), 1.23 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.4, 128.6, 123.2, 123.1, 123.0, 120.3, 99.5, 83.6, 23.8, 22.3 ppm. **IR** (neat): 3275, 2979, 2904, 1593, 1417, 1389, 1143, 1070, 940, 801 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{13}H_{17}{}^{79}BrNaO_3^+$: 323.0253 $[M+Na]^+$; found: 323.0246.

Synthesis of 3'-hydroxy-4'-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1'-biphenyl]-2-carbaldehyde (131)

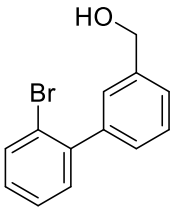


A SCHLENK flask was charged with **127** (1.00 g, 3.32 mmol, 1.0 equiv.), **128** (553 mg, 3.69 mmol, 1.1 equiv.), K_2CO_3 (1.40 g, 10.1 mmol, 3.0 equiv.), $Pd(OAc)_2$ (10 mg, 0.044 mmol, 13 mol%), PPh_3 (23 mg, 0.088 mmol, 26 mol%) water (4.3 mL) and DME (4.3 mL). After degassing for 5 min, the reaction mixture was stirred for 20 h. Water (5 mL) and ethyl acetate (5 mL) were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 5 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was removed and column chromatography of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 7%→15%) yielded 3'-hydroxy-4'-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1'-biphenyl]-2-carbaldehyde (**131**) (833 mg, 2.55 mmol, 77%) as a colorless crystalline solid.

T_m: 115-116°C. ***R*$_f$** = 0.29 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.01 (d, J = 0.8 Hz, 1H), 8.35 (s, 1H), 8.01 (dd, J = 7.7, 1.5 Hz, 1H), 7.62 (td, J = 7.5, 1.5 Hz, 1H), 7.47 (ddd, J = 16.4, 7.6, 1.2 Hz, 2H), 7.32 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 1.7 Hz, 1H), 6.87 (dd, J = 7.8, 1.8 Hz, 1H), 6.21 (s, 1H), 1.36 (s, 6H), 1.30 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 192.6, 154.6, 145.6, 139.5, 133.9, 133.7, 130.7, 128.0, 127.6, 127.5, 123.7, 122.1, 118.7, 99.8, 83.7, 23.9, 22.3 ppm. **IR** (neat): 3292, 2990, 2978, 2889, 2855, 1686, 1562, 1375,

1212, 1068, 780, 676, 654 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{23}O_4^+$: 327.1591 $[M+H]^+$; found: 327.1595.

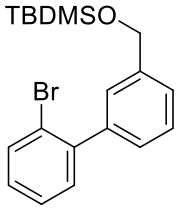
Synthesis of (2'-bromo-[1,1'-biphenyl]-3-yl)methanol (132)



A SCHLENK flask was charged with (3-(hydroxymethyl)phenyl)boronic acid (668 mg, 4.42 mmol, 1.0 equiv.), K_2CO_3 (1.82 g, 13.2 mmol, 3.0 equiv.), $Pd(PPh_3)_2Cl_2$ (63 mg, 89.8 µmol, 5 mol%), THF (16 mL), MeOH (4 mL) and 4 drops of water. The suspension was degassed with nitrogen for 5 min and 1-bromo-2-iodobenzene (1.1 mL, 8.55 mmol, 1.9 equiv.) was added. The reaction mixture was stirred at 60 °C for 18 h. HCl (1 M, 10 mL) and ethyl acetate (10 mL) was added, and the phases were separated. The aqueous solution was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 10%→50%) yielded (2'-bromo-[1,1'-biphenyl]-3-yl)methanol (**132**) (935 mg, 3.55 mmol, 81%) as a colorless solid.

R_f = 0.29 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.67 (dd, J = 7.9, 1.4 Hz, 1H), 7.59 (dd, J = 7.6, 1.4 Hz, 1H), 7.45 (td, J = 7.5, 1.5 Hz, 1H), 7.37 (td, J = 6.9, 1.3 Hz, 2H), 7.28 (d, J = 1.0 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.16 (dd, J = 7.5, 1.5 Hz, 1H), 4.51 (dd, J = 12.9, 5.5 Hz, 1H), 4.41 (dd, J = 12.9, 6.7 Hz, 1H), 1.57 – 1.52 (t, J = 6.7 Hz 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.5, 140.1, 138.6, 132.8, 131.2, 129.8, 129.3, 128.6, 128.0, 127.6, 127.4, 123.8, 63.3 ppm. **IR** (neat): 3227, 3053, 2952, 2890, 1464, 1003, 993, 726, 694 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{13}H_{11}{}^{79}BrNaO^+$: 284.9885 $[M+Na]^+$; found: 284.9888.

Synthesis of ((2'-bromo-[1,1'-biphenyl]-3-yl)methoxy)(*tert*-butyl)dimethylsilane (133)

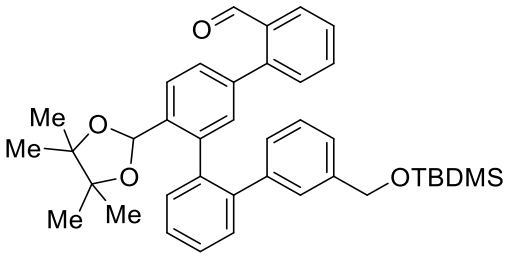


Silyl ether **133** was prepared according to **GP B** using alcohol **132** (860 mg, 3.27 mmol) and TBDMSCl. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane 0%→10%) yielded ((2'-bromo-[1,1'-biphenyl]-3-yl)methoxy)(*tert*-butyl)dimethylsilane (**133**) (894 mg, 2.37 mmol, 72%) as a colorless oil.

R_f = 0.80 (1:4, ethyl acetate:hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.67 (dd, J = 8.0, 1.2 Hz, 1H), 7.43 – 7.27 (m, 6H), 7.20 (ddd, J = 8.0, 6.6, 2.5 Hz, 1H), 4.80 (s, 2H), 0.95 (s, 9H), 0.12 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.8, 141.3, 141.1, 133.3, 131.4, 128.8, 128.1, 128.0, 127.5, 127.3, 125.5, 122.8, 65.1, 26.1, 18.6, -5.1 ppm. **IR** (neat): 3056, 2952, 2927, 2854, 1469, 1462, 1253, 1106, 1079, 952, 775 cm^{-1}. **HRMS** (ESI) *m/z* calcd for

$C_{19}H_{25}{}^{79}BrNaOSi^+$: 399.0750 $[M+Na]^+$; found: 399.0753.

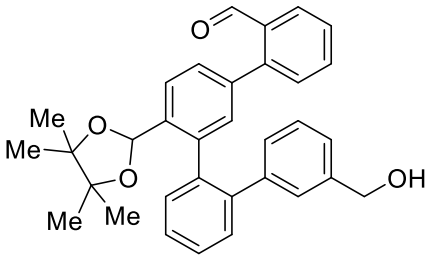
Synthesis of 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-2'''-carbaldehyde (134)



A SCHLENK flask was charged with **125** (400 mg, 0.870 mmol, 1.0 equiv.), **126** (369 mg, 0.870 mmol, 1.0 equiv.), K_2CO_3 (368 mg, 2.65 mmol, 3.0 equiv), $Pd(OAc)_2$ (10 mg, 0.079 mmol, 9 mol%), PPh_3 (52 mg, 0.199 mmol, 23 mol%), water (3 mL) and DME (3 mL). After degassing for 5 min, the reaction mixture was stirred for 20 h. Water (5 mL) and ethyl acetate (5 mL) were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 5 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was removed and purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 4%→7%) yielded 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-2'''-carbaldehyde (**134**) (443 mg, 0.730 mmol, 84%) as a colorless oil.

R_f = 0.60 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): mixture of diastereomers δ = 9.48 (s), 9.18 (s), 7.95 – 7.78 (m), 7.63 (td, J = 5.2, 3.1 Hz), 7.54 – 7.29 (m), 7.25 – 7.13 (m), 6.98 (td, J = 7.5, 1.4 Hz), 6.94 – 6.88 (m), 6.82 (d, J = 7.5 Hz), 6.77 (dd, J = 7.7, 1.4 Hz, 2H), 6.00 (s), 5.89 (s), 4.71 – 4.55 (m), 4.19 (d, J = 13.2 Hz), 3.95 (d, J = 13.2 Hz), 1.47 – 1.25 (m), 0.82 (s), 0.72 (s), -0.08 – -0.25 (m) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): mixture of diastereomers δ = 192.2, 192.1, 145.6, 145.5, 141.0, 140.40, 140.38, 139.8, 139.7, 139.1, 139.0, 138.6, 137.8, 137.7, 137.5, 137.1, 136.4, 136.1, 133.6, 133.4, 133.3, 133.2, 132.4, 131.9, 131.6, 131.1, 131.0, 130.90, 130.86, 130.7, 130.39, 129.37, 129.1, 128.6, 127.9, 127.8, 127.7, 127.6, 127.24, 127.21, 127.19, 127.1, 126.8, 126.7, 126.6, 126.5, 126.4, 97.3, 97.1, 83.1, 83.0, 82.94, 82.85, 63.7, 62.4, 26.0, 25.9, 25.7, 25.4, 24.6, 24.4, 22.8, 22.7, 22.3, 22.1, 18.4, -5.3, -5.4, -5.55, -5.57 ppm. **IR** (neat): 2953, 2927, 2854, 1693, 1597, 1469, 1389, 1253, 1068, 834, 752. **HRMS** (ESI) *m/z* calcd for $C_{39}H_{47}O_4Si^+$: 607.3238 $[M+H]^+$; found: 607.3229.

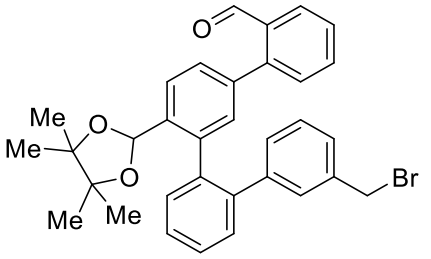
Synthesis of 3-(hydroxymethyl)-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-2'''-carbaldehyde (135)



Alcohol **135** was prepared according to **GP D** using silyl ether **134** (540 mg, 0.980 mmol). Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 20%→50%), 3-(hydroxymethyl)-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-2'''-carbaldehyde (**135**) (406 mg, 0.824 mmol, 84%) was obtained as a colorless solid.

T_m: 159-160°C. ***R*f** = 0.18 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.51 (s, 1H), 7.94 – 7.84 (m, 2H), 7.49 (m, 4H), 7.42 – 7.27 (m, 6H), 7.07 (t, J = 7.6 Hz, 1H), 6.90 – 6.84 (m, 1H), 6.64 (d, J = 1.9 Hz, 1H), 6.10 (s, 1H), 4.77 – 4.60 (m, 2H), 3.66 (s, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.26 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 193.2, 145.4, 142.4, 141.5, 141.4, 141.2, 137.6, 137.2, 137.1, 134.2, 134.0, 133.2, 131.4, 131.1, 130.2, 129.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.3, 126.6, 125.8, 97.4, 83.1, 83.0, 65.7, 25.3, 24.6, 22.6, 22.3 ppm. **IR** (neat): 3454, 2977, 2929, 2867, 1690, 1596, 1389, 1150, 1069, 753 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{33}H_{33}O_4^+$: 493.2373 $[M+H]^+$; found: 493.2378.

Synthesis of 3-(bromomethyl)-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-2'''-carbaldehyde (136)

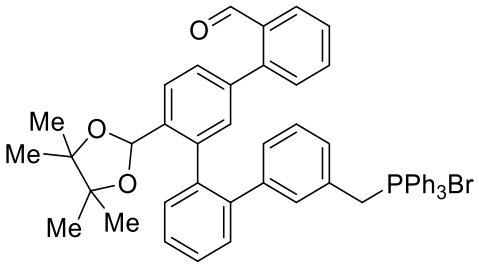


Freshly recrystallized NBS (218 mg, 1.22 mmol, 1.0 equiv.) and PPh_3 (318 mg, 1.21 mmol 1.0 equiv.) was added to a solution of **135** (600 mg, 1.22 mmol, 1.0 equiv.) in dry THF (11 mL) at 0 °C. The solution was stirred for 1.5 h at this temperature. Water (20 mL) and ethyl acetate (20 mL) were added, and the phases were separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 5%→10%) yielded 3-(bromomethyl)-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-2'''-carbaldehyde (**136**) (371 mg, 0.668 mmol, 55%) as a colorless solid.

***R*f** = 0.47 (ethyl acetate/hexane, 1/4).**^{1}H NMR** (300 MHz, $CDCl_3$): mixture of diastereomers δ = 9.46 (s), 9.10 (s), 7.96 – 7.86 (m), 7.79 (m), 7.65 – 7.34 (m), 7.32 – 7.17 (m), 7.05 – 6.96 (m), 6.92 (m), 6.85 – 6.80 (m), 5.98 (s), 5.90 (s), 4.63 (d), 4.37 (d), 4.12 (s), 1.43 – 1.34 (m), 1.25 (m) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): mixture of diastereomers δ = 192.1, 145.4, 145.3,

140.7, 140.6, 140.4, 139.5, 138.9, 138.3, 137.8, 137.5, 137.4, 136.7, 136.1, 135.5, 133.62, 133.58, 133.5, 133.4, 133.2, 132.4, 131.9, 131.7, 131.4, 131.3, 131.2, 131.03, 130.95, 130.9, 130.7, 130.4, 129.4, 129.0, 128.2, 128.1, 128.04, 127.96, 127.9, 127.8, 127.6, 127.4, 127.32, 127.26, 127.0, 126.8, 97.3, 96.7, 83.1, 82.94, 82.91, 32.3, 32.1, 25.3, 25.2, 25.1, 24.6, 22.7, 22.6, 22.5, 22.3 ppm. **IR** (neat): 3059, 2977, 2928, 2852, 2750, 1691, 1596, 1389, 1151, 1133, 1069, 762 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{33}H_{31}{}^{79}BrO_3^+$: 577.1349 $[M+H]^+$; found: 577.1330.

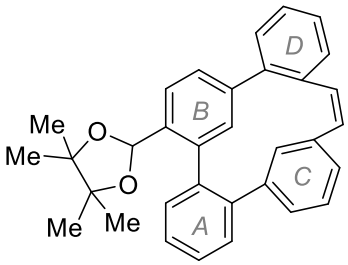
Synthesis of ((2'''-formyl-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-3-yl)methyl)triphenylphosphonium bromide (137)



A solution of **136** (107 mg, 0.192 mmol 1.0 equiv.) and PPh_3 (76 mg, 0.290 mmol, 1.5 equiv.) in toluene (1 mL) was heated to 100 °C for 16 h. After cooling to room temperature, diethyl ether (1 mL) was added, and the solvent was filtered of. The precipitate was washed with ether (2 x 1 mL). ((2'''-formyl-6''-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-[1,1':2',1'':3'',1'''-quaterphenyl]-3-yl)methyl)triphenylphosphonium bromide (**137**) (130 mg, 0.159 mmol, 83%) was obtained as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): mixture of diastereomers δ = 9.33 (s), 9.20 (s), 7.93 – 7.73 (m), 7.62 (m), 7.54 – 7.38 (m), 7.29 (m), 7.19 – 6.93 (m), 6.59 (d, J = 1.8 Hz), 6.21 (d, J = 5.4 Hz), 6.12 (d, J = 7.9 Hz), 5.66 (s), 4.73 (m), 4.19 – 3.93 (m), 1.49 – 1.08 (m), 0.70 (s) ppm.**^{13}C NMR** (101 MHz, $CDCl_3$): mixture of diastereomers δ = 192.9, 191.8, 145.0, 144.9, 142.61, 142.55, 141.7, 139.9, 139.0, 138.6, 138.0, 137.9, 137.42, 137.35, 137.3, 135.88, 135.87, 135.85, 135.30, 134.25, 134.1, 134.04, 134.01, 133.9, 133.7, 133.6, 133.5, 133.3, 132.7, 132.5, 132.3, 132.2, 131.7, 131.2, 131.1, 131.0, 130.8, 130.7, 130.6, 129.9, 129.7, 129.34, 129.30, 129.2, 128.9, 128.8, 128.7, 128.57, 128.56, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 125.0, 117.6, 117.2, 116.8, 116.4, 96.9, 96.7, 83.4, 83.3, 83.0, 82.9, 29.7, 29.2, 28.5, 28.0, 25.8, 25.1, 24.6, 24.2, 22.50, 22.46, 22.22, 22.17 ppm. **IR** (neat): 3362, 3054, 2977, 2926, 2852, 2753, 1687, 1437, 1110, 1069, 751, 688, 507 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{51}H_{46}O_3P^+$: 737.3179 $[M-Br]^+$; found: 737.3169.

Synthesis of (*E*)-2-(5,9:16,20-di(metheno)dibenzo[*a*,*h*][16]annulen-6-yl)-4,4,5,5-tetramethyl-1,3-dioxolane (138)



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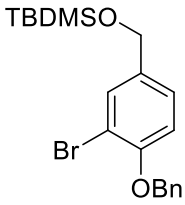
A solution of **137** (100 mg, 123 µmol, 1.0 equiv.) in dry DCM (20 mL) was added to a solution of NaOMe (16 mg, 296 µmol, 2.4 equiv.) in dry DCM (60 mL) *via* syringe pump over 3 h. The reaction mixture was stirred for 24 h and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 2%→ 18%) yielded (*E*)-2-(5,9:16,20-di(metheno)dibenzo[*a*,*h*][16]annulen-6-yl)-4,4,5,5-tetramethyl-1,3-dioxolane (**138**) (22 mg, 48 µmol, 39%) as a colorless solid.

R_f = 0.62 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 1H), 7.44 – 7.41 (m, 2H), 7.41 – 7.36 (m, 2H), 7.34 – 7.29 (m, 2H), 7.25 – 7.22 (m, 3H), 7.20 – 7.16 (m, 2H), 7.15 – 7.12 (m, 1H), 7.07 – 7.04 (m, 1H), 7.02 (ddd, *J* = 7.8, 1.7, 0.6 Hz, 1H), 6.41 (d, *J* = 16.6 Hz, 1H), 5.89 (dd, *J* = 16.6, 0.9 Hz, 1H), 5.54 (s, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H).ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* = 193.2, 145.4, 142.4, 141.5, 141.4, 141.2, 137.6, 137.2, 137.1, 134.2, 134.0, 133.2, 131.4, 131.1, 130.2, 129.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.3, 126.6, 125.8, 97.4, 83.1, 83.0, 65.7, 25.3, 24.6, 22.6, 22.3 ppm. **IR** (neat): 3056, 2978, 2028, 1475, 1437, 1388, 1155, 1073, 753, 733 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{33}H_{31}O_2^+$: 459.2319 $[M+H]^+$; found: 459.2311.

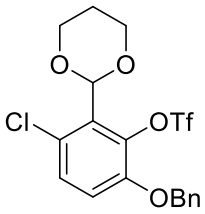
Synthesis of ((4-(benzyloxy)-3-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (141)



Silyl ether **141** was prepared according to **GP B** using alcohol **175** (3.80 g, 13.0 mmol) and TBDMSCl. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded the product ((4-(benzyloxy)-3-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (**141**) (5.06 g, 12.4 mmol, 95%) as a colorless oil.

R_f = 0.72 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* = 7.52 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.43 – 7.28 (m, 3H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.15 (s, 2H), 4.64 (s, 2H), 0.94 (s, 9H), 0.09 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* = 154.1, 136.8, 135.7, 131.5, 128.7, 128.0, 127.2, 126.3, 113.9, 112.5, 71.1, 64.1, 26.1, 18.6, -5.1 ppm. **IR** (neat): 2952, 2927, 2855. 1494, 1251, 1080, 1048, 834, 774, 734, 694 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{28}O_2{}^{79}BrSi^+$: 405.0880 $[M+H]^+$; found: 405.0864.

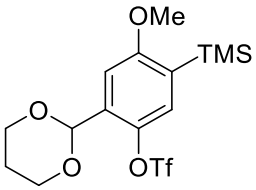
Synthesis of 6-(benzyloxy)-3-chloro-2-(1,3-dioxan-2-yl)phenyl trifluoromethanesulfonate (142)



Triflate **142** was prepared according to **GP A** using phenol **171** (356 mg, 1.11 mmol). After purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→20%), 6-(benzyloxy)-3-chloro-2-(1,3-dioxan-2-yl)phenyl trifluoromethanesulfonate (**142**) (419 mg, 0.925 mmol, 83%) was obtained as a colorless solid.

R_f = 0.39 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.41 – 7.30 (m, 5H), 7.23 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.06 (s, 1H), 5.17 (s, 2H), 4.29 (ddd, J = 12.1, 5.0, 1.4 Hz, 2H), 3.95 (td, J = 12.3, 2.3 Hz, 2H), 2.44 (qt, J = 12.7, 4.9 Hz, 1H), 1.46 – 1.33 (m, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =149.8, 138.1, 135.3, 130.5, 129.9, 128.9, 128.5, 127.4, 125.3, 118.9 (q, J = 321.7 Hz), 115.4, 98.5, 71.3, 67.8, 25.0 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -70.94 ppm. **IR** (neat): 2985, 2964, 2934, 2855, 1404, 1201, 914, 806 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{18}H_{17}O_6{}^{35}ClF_3S^+$: 453.0381 $[M+H]^+$; found: 453.0370.

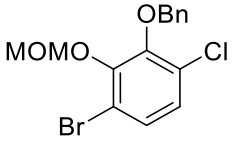
Synthesis of 2-(1,3-dioxan-2-yl)-4-methoxy-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (143)



Triflate **143** was prepared according to **GP A** using phenol **150** (1.62 g, 5.74 mmol). After purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) 2-(1,3-dioxan-2-yl)-4-methoxy-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (**143**) (2.21 g, 5.33 mmol, 93%) was obtained as a colorless solid.

T_m: 62-63°C. R_f = 0.53 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.17 (s, 1H), 7.13 (s, 1H), 5.70 (s, 1H), 4.27 (ddd, J = 12.1, 5.1, 1.4 Hz, 2H), 4.07 – 3.95 (m, 2H), 3.85 (s, 3H), 2.35 – 2.16 (m, 1H), 1.46 (ddd, J = 13.5, 2.6, 1.3 Hz, 1H), 0.25 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.5, 140.6, 133.5, 131.8, 127.4, 118.7 (q, J = 319.9 Hz), 108.4, 97.0, 67.6, 55.8, 25.7, -1.3 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -74.4 ppm. **IR** (neat): 3003, 2977, 2865, 2816, 1419, 1377, 1214, 1189, 1120, 948, 838, 595 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{22}F_3O_6SSi^+$: 415.0853 $[M+H]^+$; found: 415.0846.

Synthesis of 2-(benzyloxy)-4-bromo-1-chloro-3-(methoxymethoxy)benzene (144)

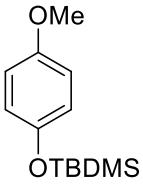


*n*Buli (4.4 mL, 11.0 mmol, 2.5 M, 1.05 equiv.) was added to a solution of **158** (2.44 g, 10.4 mmol, 1.0 equiv.) in dry THF (30 mL) at -78°C. After stirring at this temperature for 1 h, bromine (0.54 mL, 10.5 mmol,

1.0 equiv.) was added, and the solution was allowed to warm to room temperature. A sat. aq. solution of Na_2SO_3 (10 mL) was added, and phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography of the residue (ethyl acetate/hexane, 1/10) yielded 2-(benzyloxy)-4-bromo-1-chloro-3-(methoxymethoxy)benzene (**144**) (2.96 g, 8.28 mmol, 80%) as a colorless oil.

R_f = 0.62 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 – 7.46 (m, 2H), 7.43 – 7.32 (m, 3H), 7.28 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 5.21 (s, 2H), 5.03 (s, 2H), 3.61 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.5, 149.4, 136.4, 128.8, 128.72, 128.67, 128.65, 128.6, 126.3, 116.4, 99.7, 75.6, 58.4 ppm. **IR** (neat): 3032, 2930, 2828, 1736, 1428, 1367, 1237, 1160, 940, 696 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{15}{}^{35}Cl^{79}BrO_3^+$: 378.9707 $[M+H]^+$; found: 378.9710.

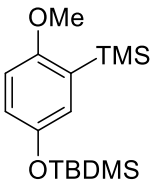
Synthesis of *tert*-butyl(4-methoxyphenoxy)dimethylsilane (146)



Silyl ether **146** was prepared according to **GP B** using phenol **145** (20.0 g, 161 mmol) and TBDMSCl. Evaporation of the solvent yielded *tert*-butyl(4-methoxyphenoxy)dimethylsilane (**146**) (38.7 g, 161 mmol, quant.) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (s, 4H), 3.76 (s, 3H), 0.98 (s, 9H), 0.17 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.2, 149.5, 120.8, 114.6, 55.8, 25.9, 18.3, -4.4 ppm.

Synthesis of *tert*-butyl(4-methoxy-3-(trimethylsilyl)phenoxy)dimethylsilane (147)

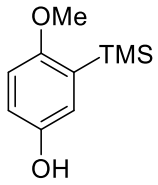


*s*Buli (100 mL, 1.3 M in hexane, 130 mmol, 1.2 equiv.) was added dropwise to a solution of **146** (26.0 g, 109 mmol, 1.0 equiv.) in dry THF (80 mL) at -78 °C. After stirring for 30 min at this temperature, TMSCl (23.4 mL, 185 mmol, 1.7 equiv.) was added, and the reaction mixture was stirred at -78 °C for 1 h. Once the reaction mixture reached room temperature, water (180 mL) and hexane (180 mL) were added. The phases were separated, the organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. *tert*-butyl(4-methoxy-3-(trimethylsilyl)phenoxy)dimethylsilane (**147**) (33.8 g, 109 mmol, quant.) was obtained as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84 (d, J = 2.9 Hz, 1H), 6.77 (dd, J = 8.7, 2.9 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 3.75 (s, 3H), 0.98 (s, 9H), 0.24 (s, 9H), 0.17 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 158.9, 149.2, 129.2, 126.3, 121.2, 110.6, 55.7, 25.9, 18.4, -0.9, -4.3 ppm. **IR** (neat): 3033, 3013, 2951, 1504, 1441, 1368, 1177, 1101, 1030, 821 cm^{-1}. **HRMS** (ESI) *m/z*

calcd for $C_{16}H_{31}O_2Si_2^+$: 311.1857 $[M+H]^+$; found: 311.1859.

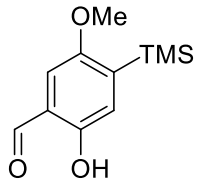
Synthesis of 4-methoxy-3-(trimethylsilyl)phenol (148)



Phenol **148** was prepared according to **GP D** using silyl ether **147** (33.8 g, 109 mmol). After evaporation of the solvent, 4-methoxy-3-(trimethylsilyl)phenol (**148**) (21.4 g, 109 mmol, quant.) was obtained as a colorless oil.

R_f = 0.44 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.85 (d, J = 3.0 Hz, 1H), 6.79 (dd, J = 8.7, 3.0 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 4.58 (s, 1H), 3.75 (s, 3H), 0.25 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 158.7, 149.3, 129.8, 121.8, 116.7, 111.0, 55.9, -0.9 ppm. **IR** (neat): 3313, 2952, 2898, 2857, 1479, 1424, 1217, 1031, 832, 735 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{10}H_{17}O_2Si^+$: 197.0992 $[M+H]^+$; found: 197.0991.

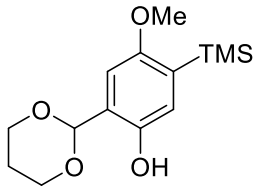
Synthesis of 2-hydroxy-5-methoxy-4-(trimethylsilyl)benzaldehyde (149)



$MgCl_2$ (15.7 g, 165 mmol, 1.5 equiv.), TEA (115 mL, 824 mmol, 7.6 equiv.) and para formaldehyde (23.3 g, 775 mmol, 7.1 equiv.) were added to a solution of **148** (21.4 g, 109 mmol, 1.0 equiv.) in dry MeCN (400 mL). The suspension was refluxed for 16 h. After cooling to room temperature, the reaction mixture was poured into HCl (800 mL, 1 M) and after stirring for 30 min, DCM (400 mL) was added. The phases were separated, and the organic phase was washed with water (2 x 400 mL), brine (400 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. After column chromatography of the residue (ethyl acetate/hexane, 1/10), 2-hydroxy-5-methoxy-4-(trimethylsilyl)benzaldehyde (**149**) (21.8 g, 96.6 mmol, 89%) was obtained as a yellow solid.

R_f = 0.60 (ethyl acetate:hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.61 (s, 1H), 9.87 (s, 1H), 7.04 (s, 1H), 6.87 (s, 1H), 3.82 (s, 3H), 0.28 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.2, 157.4, 155.5, 142.0, 124.5, 120.4, 111.1, 55.8, -1.1 ppm. **IR** (neat): 2952, 2839, 1656, 1464, 1305, 1245, 1153, 1060, 1000, 837 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{11}H_{17}O_3Si^+$: 225.0941 $[M+H]^+$; found: 225.0940.

Synthesis of 2-(1,3-dioxan-2-yl)-4-methoxy-5-(trimethylsilyl)phenol (150)

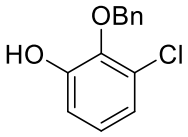


A solution of **149** (296 mg, 1.32 mmol), *p*TsOH·H_2O (2 mg, 11 µmol, 0.8 mol%) and 1,3-ethylene glycole (0.16 mL, 2.14 mmol, 1.6 equiv.) in toluene (25 mL) with a DEAN-STARK apparatus was stirred at reflux for 20 h. After cooling to room temperature, aq. sat. $NaHCO_3$ solution

(10 mL) was added, and the phases were separated. The organic phase was washed with water (10 mL) and brine (10 mL), and the solvent was removed under reduced pressure. Column chromatographic purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded 2-(1,3-dioxan-2-yl)-4-methoxy-5-(trimethylsilyl)phenol (**150**) (202 mg, 0.715 mmol, 54%) as a colorless crystalline solid.

$\mathbf{T_m}$: 127-128°C. $\boldsymbol{R_f}$ = 0.28 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.35 (s, 1H), 6.91 (s, 1H), 6.66 (s, 1H), 5.63 (s, 1H), 4.31 (ddd, J = 12.2, 5.0, 1.5 Hz, 2H), 4.01 (td, J = 12.3, 2.4 Hz, 2H), 3.74 (s, 3H), 2.36 – 2.18 (m, 1H), 1.51 (d, J = 13.7 Hz, 1H), 0.23 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.8, 148.5, 131.0, 123.8, 123.0, 108.6, 102.8, 67.6, 55.8, 25.8, -0.9 ppm. **IR** (neat): 3316, 2952, 2857, 1486, 1393, 1242, 1146, 1092, 946, 828 $cm^{-1.}$ **HRMS** (ESI) *m/z* calcd for $C_{14}H_{23}O_4Si^+$: 183.1360 $[M+H]^+$; found: 183.1359.

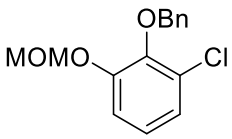
Synthesis of 2-(benzyloxy)-3-chlorophenol (157)



An aqueous solution of NaOH (5.1 mL, 12.8 mmol, 2.5 M, 1.1 equiv.) was added to a solution of 2-(benzyloxy)-3-chlorophenyl acetate (3.17 g, 11.5 mmol, 1.0 equiv.) in MeOH (32 mL). After stirring for 2 h at room temperature, the solution was acidified with 4 M HCl and extracted with DCM (3 x 30 mL). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. After removing the solvent under reduced pressure, 2-(benzyloxy)-3-chlorophenol (**157**) (2.28 g, 9.71 mmol, 84%) was obtained as a brownish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 – 7.36 (m, 5H), 7.01 – 6.89 (m, 2H), 6.83 (dd, J = 6.1, 3.6 Hz, 1H), 5.52 (s, 1H), 5.09 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.5, 142.3, 136.5, 129.08, 129.06, 128.7, 127.3, 125.5, 121.8, 114.4, 76.0 ppm.

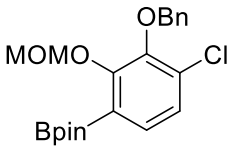
Synthesis of 2-(benzyloxy)-1-chloro-3-(methoxymethoxy)benzene (158)



MOMCl (2.56 mL, 23.6 mmol, 2.0 equiv.) was added to a solution of **157** (2.78 g, 11.8 mmol, 1.0 equiv.) and DIPEA (5.7 mL, 23.6 mmol, 2.0 equiv.) in dry DCM (45 mL). The solution was stirred at room temperature for 20 h. Water (80 mL) and DCM (100 mL) were added, and the phases were separated. The aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases were washed with brine (50 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography (ethyl acetate/hexane, 1/10) yielded 2-(benzyloxy)-1-chloro-3-(methoxymethoxy)benzene (**158**) (3.07 g, 11.0 mmol, 93%) as a colorless oil.

***R*f** = 0.50 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.56 – 7.50 (m, 2H), 7.42 – 7.30 (m, 3H), 7.10 – 7.03 (m, 2H), 7.01 – 6.94 (m, 1H), 5.19 (s, 2H), 5.06 (s, 2H), 3.50 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.0, 145.4, 137.3, 129.1, 128.6, 128.5, 128.3, 124.7, 123.7, 115.6, 95.7, 75.2, 56.5 ppm. **IR** (neat): 3032, 2953, 2825, 1473, 1453, 1260, 1157, 1146, 1080, 990, 922, 734, 696 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{16}{}^{35}ClO_3^+$: 279.0782 $[M+H]^+$; found: 279.0780.

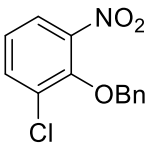
Synthesis of 2-(3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (159)



*t*Buli (1.4 mL, 2.40 mmol, 1.7 M, 2.2 equiv.) was added to a solution of **158** (302 mg, 1.08 mmol, 1.0 equiv.) in dry THF (9.4 mL) at -78 °C. After stirring at this temperature for 1 h, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.33 mL, 1.62 mmol, 1.5 equiv.) was added and the solution was stirred at -78 °C for 30 min. The solution was allowed to warm to room temperature overnight. Water (0.05 mL) was added, and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 2-(3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**159**) (207 mg, 0.512 mmol, 47%) as a colorless oil.

***R*f** = 0.5 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.58 – 7.49 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.30 (m, 3H), 7.17 (d, *J* = 8.1 Hz, 1H), 5.19 (s, 2H), 5.04 (s, 2H), 3.55 (s, 1H).1.36 (s, 12H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.9, 148.3, 137.1, 132.6, 132.2, 128.6, 128.5, 128.3, 125.6, 100.7, 84.1, 75.3, 57.9, 25.0 ppm. **IR** (neat): 2978, 1738, 1581, 1422, 1347, 1229, 1139, 958, 853, 697, 688 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{21}H_{27}{}^{10}B^{35}ClO_5^+$: 404.1671 $[M+H]^+$; found: 404.1657.

Synthesis of 2-(benzyloxy)-1-chloro-3-nitrobenzene (161)

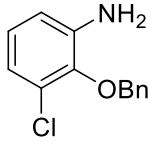


K_2CO_3 (10.0 g, 72.0 mmol, 2.5 equiv.) was added to a solution of 2-chloro-6-nitrophenol (5.00 g, 28.8 mmol, 1.0 equiv.) in DMF (90 mL). BnBr (3.4 mL, 31.9 mmol, 1.1 equiv.) was added to the suspension, and it was stirred for 16 h at room temperature. Water (100 mL) was added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organic phases were washed with water (2 x 50 mL) and brine (50 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography of the residue (ethyl acetate/hexane, 1/10) yielded 2-(benzyloxy)-1-chloro-3-nitrobenzene (**161**) (6.20 g, 23.5 mmol, 82%) as an off-white

solid.

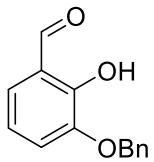
***R*f** = 0.45 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.73 (dd, J = 8.2, 1.7 Hz, 1H), 7.66 (dd, J = 8.1, 1.7 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.48 – 7.31 (m, 3H), 7.20 (t, J = 8.1 Hz, 1H), 5.21 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =148.5, 146.1, 135.7, 134.9, 131.1, 128.89, 128.86, 128.7, 124.8, 123.8, 76.7 ppm. **IR** (neat): 3077, 3033, 2953, 2895, 1592, 1525, 1453, 1360, 939, 748, 695 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{13}H_{10}{}^{35}ClNNaO_3^+$: 286.0241 $[M+Na]^+$; found: 286.0237.

Synthesis of 2-(benzyloxy)-3-chloroaniline (162)



Zinc powder (120 g, 1.80 mol, 77 equiv.) was added to a solution of **161** (6.20 g, 23.5 mmol, 1 equiv.) in ethyl acetate (150 mL), conc. HCl (225 mL) and sulfuric acid (225 mL) at room temperature. The reaction mixture was stirred for 5 h and filtered through a pad of celite. The phases were separated, the organic phase was washed with NaOH (100 mL, 1 M in water) and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded 2-(benzyloxy)-3-chloroaniline (**162**) (4.78 g, 20.5 mmol, 87%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.55 – 7.48 (m, 2H), 7.45 – 7.32 (m, 3H), 6.86 (t, J = 7.9 Hz, 1H), 6.78 (dd, J = 8.0, 1.6 Hz, 1H), 6.64 (dd, J = 7.9, 1.6 Hz, 1H), 5.00 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =142.3, 141.8, 137.2, 128.8, 128.5 (2 C), 128.2, 125.4, 119.7, 114.5, 74.3 ppm. **IR** (neat): 3460, 3372, 3202, 3031, 2877, 1608, 1479, 1455, 1220, 749, 696. **HRMS** (ESI) *m/z* calcd for $C_{13}H_{12}{}^{35}ClNNaO^+$: 256.0500 $[M+Na]^+$; found: 256.0497.

Synthesis of 3-(benzyloxy)-2-hydroxybenzaldehyde (164)

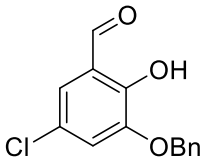


NaH (7.23 g, 181 mmol, 60% in paraffin, 2.5 equiv.) was added to a solution of 2,3-dihydroxybenzaldehyde (10.0 g, 72.4 mmol, 1.0 equiv.) in dry THF (100 mL) in small portions at 0 °C. The reaction mixture was stirred at room temperature for 1 h. BnBr (8.61 mL, 72.4 mmol, 1.0 equiv.) was added dropwise, and the suspension was stirred for additional 21 h. The reaction mixture was poured into water (400 mL) and conc. HCl was added until pH = 1. The mixture was extracted with DCM (2 x 400 mL) and the organic phase was dried over $MgSO_4$. After removing the solvent under reduced pressure, the residue was purified by column chromatography (ethyl acetate/hexane, 1/19). 3-(benzyloxy)-2-hydroxybenzaldehyde (**163**) (7.36 g, 32.2 mmol, 44%) was obtained as a slightly yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.11 (s, 1H), 9.92 (s, 1H), 7.48 – 7.43 (m, 2H), 7.42 – 7.31 (m, 3H), 7.19 (dd, J = 7.8, 1.5 Hz, 1H), 7.13 (dd, J = 8.0, 1.5 Hz, 1H), 6.90 (t, J = 7.9 Hz, 1H),

5.20 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.6, 152.4, 147.3, 136.6, 128.8, 128.2, 127.7, 127.5, 125.4, 121.1, 119.6, 71.5 ppm.

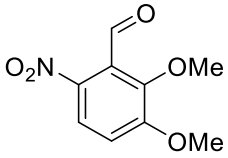
Synthesis of 3-(benzyloxy)-5-chloro-2-hydroxybenzaldehyde (165)



NCS (2.21 g, 16.6 mmol, 1.0 equiv.) was added to a solution of **164** (4.00 g, 17.5 mmol, 1.05 equiv.) in glacial acetic acid (20 mL). The reaction mixture was stirred at 130 °C for 20 min. After cooling to room temperature, water (50 mL) was added slowly, and a yellow precipitate was formed. Recrystallization of the crude product from DCM/hexane yielded 3-(benzyloxy)-5-chloro-2-hydroxybenzaldehyde (**165**) (2.40 g, 9.14 mmol, 52%) as yellow to orange crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.93 (s, 1H), 9.87 (s, 1H), 7.47 – 7.33 (m, 5H), 7.18 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 5.17 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.4, 151.1, 148.2, 135.8, 128.9, 128.5, 127.6, 124.4, 123.7, 121.1, 120.7, 77.5, 76.8, 71.7 ppm. **IR** (neat): 3108, 3068, 3034, 2933, 1682, 1455, 1248, 751, 738 cm^{-1}. **HRMS** (EI) *m/z* calcd for $C_{14}H_{11}{}^{35}ClO_3{}^{\cdot+}$: 262.0391 $[M]^{\cdot+}$; found: 262.0392.

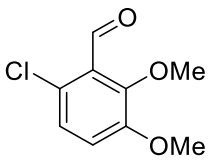
Synthesis of 2,3-dimethoxy-6-nitrobenzaldehyde (167)



Fuming HNO_3 (19 mL) was added to a solution of 2,3-dimethoxybenzaldehyde (4.00 g, 24.1 mmol, 1.0 equiv.) in AcOH (80 mL) at 14°C. The reaction mixture was stirred at this temperature for 45 min. Ice water (100 mL) was added and the precipitate was filtered off. Column chromatography of the residue (ethyl acetate/hexane, 1/2) yielded 2,3-dimethoxy-6-nitrobenzaldehyde (**167**) (1.58 g, 7.48 mmol, 31%) as a greenish solid.

***R*$_f$** = 0.12 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.36 (s, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.05 (d, J = 9.1 Hz, 1H), 4.00 (s, 3H), 3.89 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 188.5, 158.7, 147.3, 139.7, 130.6, 121.7, 112.6, 62.9, 56.7 ppm. **IR** (neat): 3103, 2982, 2948, 2846, 1695, 1510, 1475, 1326, 1276, 1242, 1073, 1028, 948, 824, 735 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_9H_{10}NO_5{}^+$: 212.0553 $[M+H]^+$; found: 212.0555.

Synthesis of 6-chloro-2,3-dimethoxybenzaldehyde (168)

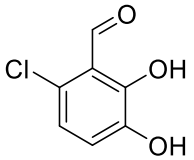


TFA (9.2 ml, 120 mmol, 10 equiv.) was added to a solution of 2,3-dimethoxybenzaldehyde (2.00 g, 12.0 mmol, 1.0 equiv.), NCS (2.42 g, 18.0 mmol, 1.5 equiv.), $Pd(OAc)_2$ (270 mg, 1.20 mmol, 10 mol%), anthranilic acid (494 mg, 3.60 mmol, 30 mol%) and AgTFA (264 mg, 1.20 mmol, 10 mol%) in

dry DCE. The solution was heated to 60 °C and stirred for 24 h. After cooling to room temperature, aq. sat. $NaHCO_3$ solution (50 mL) was added, and the mixture was filtered through celite and rinsed with DCM. The phases were separated, and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic phases were dried over Na_2CO_3 and the solvent was removed under reduced pressure. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 6-chloro-2,3-dimethoxybenzaldehyde (**168**) (1.95 g, 9.72 mmol, 81%) as a colorless solid.

R_f = 0.27 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.43 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.9 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ =189.6, 152.3, 152.2, 127.6, 126.2, 125.9, 117.4, 62.4, 56.4 ppm. **IR** (neat): 3087, 3011, 2991, 2953, 2887, 1688, 1574, 1471, 1267, 1236, 930, 816 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_9H_{10}{}^{35}ClO_3^+$: 223.0132 $[M+H]^+$; found: 223.0135.

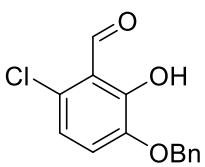
Synthesis of 6-chloro-2,3-dihydroxybenzaldehyde (169)



BBr_3 (10 mL, 10 mmol, 1 M in DCM, 4.0 equiv.) was added to a solution of **168** (500 mg, 2.49 mmol, 1.0 equiv.) in dry DCM (22 mL) at 0 °C. The solution was stirred for 4 h at room temperature and water (10 mL) was added. The phases were separated, and the aqueous phase was extracted with DCM (2 x 10 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL). Removal of the solvent under reduced pressure yielded 6-chloro-2,3-dihydroxybenzaldehyde (**169**) (415 mg, 2.41 mmol, 97%) as a yellow-brown solid.

T_m: 129-130°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 12.05 (s, 1H), 10.36 (s, 1H), 7.08 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 5.64 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.1, 150.8, 144.2, 127.8, 121.7, 121.0, 116.7 ppm. **IR** (neat): 3376, 2988, 2902, 1633, 1437, 1381, 1272, 1196, 914, 817, 710 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_7H_4O_3{}^{35}Cl^-$: 170.9854 $[M-H]^-$; found: 170.9858.

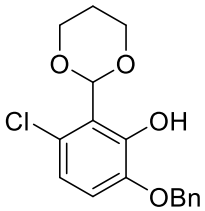
Synthesis of 3-(benzyloxy)-6-chloro-2-hydroxybenzaldehyde (170)



NaH (180 mg, 4.50 mmol, 2.5 equiv.) was added to a solution of **169** (310 mg, 1.80 mmol, 1.0 equiv.) in dry THF (1.5 mL). After stirring at room temperature for 1 h, a solution of BnBr (0.21 mL, 1.80 mmol, 1.0 equiv.) in dry THF (0.5 mL) was added. After stirring for 24 h, water (10 mL) was added, the reaction mixture was acidified with conc. HCl and extracted with chloroform (3 x 20 mL). The combined organic phases were dried over Na_2SO_4. Purification of the residue *via*

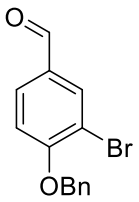
ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 3-(benzyloxy)-6-chloro-2-hydroxybenzaldehyde (**170**) (182 mg, 0.693 mmol, 38%) as a yellow solid.
***R*f** = 0.48 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 12.21 (s, 1H), 10.38 (s, 1H), 7.46 – 7.28 (m, 5H), 6.99 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 5.17 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =196.2, 155.1, 146.7, 136.3, 129.1, 128.9, 128.4, 127.5, 121.3, 120.1, 117.1, 71.7 ppm. **IR** (neat): 3088, 3065, 3027, 2891, 2862, 1647, 1445, 1377, 1253, 726, 690 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{14}H_{12}{}^{35}ClO_3^+$: 263.0469 $[M+H]^+$; found: 263.0467.

Synthesis of 6-(benzyloxy)-3-chloro-2-(1,3-dioxan-2-yl)phenol (171)



A solution of **170** (357 mg, 1.36 mmol, 1.0 equiv.), *p*TsOH·H_2O (3 mg, 15.8 µmol, 1 mol%) and 1,3-propylene glycol (0.17 mL, 2.37 mmol, 1.7 equiv.) in toluene (20 mL) was stirred at reflux for 19 h with a DEAN-STARK apparatus attached. After cooling to room temperature, aq. sat. $NaHCO_3$ solution (10 mL) was added, and the phases were separated. The organic phase was washed with water (10 mL) and brine (10 mL), and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 5%→25%) yielded 6-(benzyloxy)-3-chloro-2-(1,3-dioxan-2-yl)phenol (**171**) (380 mg, 1.18 mmol, 87%) as a colorless solid.
***R*f** = 0.20 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.67 (s, 1H), 7.48 – 7.23 (m, 5H), 6.77 (d, J = 1.6 Hz, 2H), 6.05 (s, 1H), 5.11 (s, 2H), 4.32 (dd, J = 11.7, 4.9 Hz, 2H), 4.03 (td, J = 12.4, 2.5 Hz, 2H), 2.29 (qt, J = 12.6, 5.0 Hz, 1H), 1.52 (d, J = 13.8 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.1, 146.7, 137.0, 128.6, 128.0, 127.4, 125.0, 120.12, 120.08, 116.4, 101.8, 71.6, 68.0, 25.8 ppm. **IR** (neat): 3239, 3063, 3033, 2975, 2901, 2855, 1817, 1446, 1230, 1100, 985, 666 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{18}{}^{35}ClO_4^+$: 321.0888 $[M+H]^+$; found: 321.0871.

Synthesis of 4-(benzyloxy)-3-bromobenzaldehyde (174)

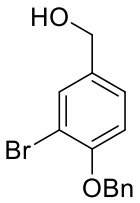


K_2CO_3 (6.90 g, 48.8 mmol, 2.5 equiv.) was added to a solution of **173** (4.00 g, 19.9 mmol, 1.0 equiv.) in DMF (60 mL). BnBr (2.6 mL, 21.9 mmol, 1.1 equiv.) was added to the suspension, and it was stirred for 23 h at room temperature. Water (100 mL) was added, and the solution was extracted with DCM (3x 75 mL). The combined organic phases were washed with water (2 x 50 mL) and brine (50 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to obtain 4-(benzyloxy)-3-bromobenzaldehyde (**174**) (4.32 g,

14.8 mmol, 74%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.84 (s, 1H), 8.11 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.5, 2.0 Hz, 1H), 7.53 – 7.30 (m, 5H), 7.05 (d, J = 8.5 Hz, 1H), 5.26 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 189.7, 159.9, 135.6, 134.9, 131.1, 131.0, 128.9, 128.5, 127.1, 113.4, 113.2, 71.2 ppm.

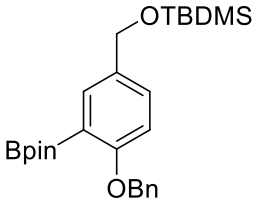
Synthesis of (4-(benzyloxy)-3-bromophenyl)methanol (175)



$NaBH_4$ (0.780 g, 20.6 mmol, 1.5 equiv.) was added to a solution of **174** (4.00 g, 13.8 mmol, 1.0 equiv.) in MeOH (30 mL) in small portions at 0 °C. After allowing the solution to warm to room temperature, it was stirred for additional 30 min. Water (50 mL) was added and the mixture was extracted with DCM (2 x 50 mL). The combined organic phases were washed with brine (30 mL) and dried over Na_2SO_4. After removing the solvent under reduced pressure, (4-(benzyloxy)-3-bromophenyl)methanol (**175**) (3.92 g, 13.4 mmol, 97%) was obtained as a colorless solid and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, J = 2.1 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.43 – 7.29 (m, 3H), 7.22 (dd, J = 8.4, 2.1 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.17 (s, 2H), 4.60 (s, 2H), 1.68 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.6, 136.6, 135.0, 132.5, 128.7, 128.0, 127.3, 127.1, 114.0, 112.7, 71.0, 64.4 ppm. **IR** (neat): 3315, 3230, 2900, 2855, 1602, 1499, 1445, 1403 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{14}H_{14}{}^{79}BrNaO_2^+$: 314.9991 $[M+Na]^+$; found: 314.9987.

Synthesis of ((4-(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)(*tert*-butyl)dimethylsilane (176)

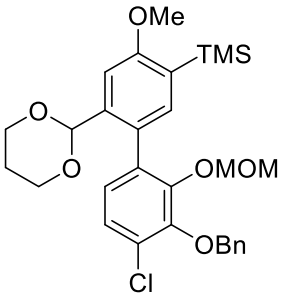


*n*Buli (0.21 mL, 0.525 mmol, 2.5 M in THF, 1.07 equiv.) was added dropwise to a solution of **141** (200 mg, 0.491 mmol, 1.0 equiv.), in dry THF (10 mL) at -78°C. After stirring at this temperature for 1 h, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolan (0.20 mL, 0.980 mmol, 2.0 equiv.), was added and the reaction mixture was allowed to warm up to room temperature overnight. Water (20 mL) was added, and the solution was extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine (40 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded ((4-(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)(*tert*-butyl)dimethylsilane (**176**) (218 mg, 0.480 mmol, 98%). The product could be used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 – 7.56 (m, 3H), 7.44 – 7.27 (m, 4H), 6.92 (d, J = 8.4 Hz,

1H), 5.12 (s, 2H), 4.69 (s, 2H), 1.36 (s, 12H), 0.93 (s, 9H), 0.08 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.6, 137.9, 134.8, 133.5, 130.8, 128.3, 127.4, 126.9, 112.3, 83.6, 70.3, 64.8, 26.1, 25.1, 18.6, -5.0 ppm. **IR** (neat): 2954, 2928, 1607, 1494, 1343, 1250, 1143, 1067, 835 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{39}{}^{10}BNaO_4Si^+$: 477.2608 $[M+Na]^+$; found: 477.2612.

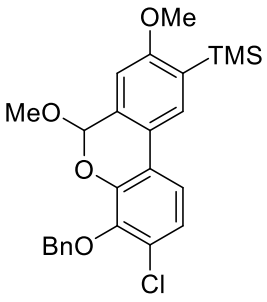
Synthesis of (3'-(benzyloxy)-4'-chloro-6-(1,3-dioxan-2-yl)-4-methoxy-2'-(methoxymethoxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (179)



Biphenyl **179** was prepared according to **GP E** using bromide **144** (500 mg, 1.40 mmol, 1.1 equiv.) and triflate **143** (522 mg, 1.26 mmol, 1.0 equiv.). After purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%), (3'-(benzyloxy)-4'-chloro-6-(1,3-dioxan-2-yl)-4-methoxy-2'-(methoxymethoxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (**179**) (401 mg, 0.738 mmol, 59%) was obtained as a colorless oil.

R_f = 0.33 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.59 – 7.53 (m, 2H), 7.43 – 7.32 (m, 3H), 7.22 – 7.20 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.28 (s, 1H), 5.15 (d, *J* = 1.9 Hz, 2H), 4.86 (d, *J* = 5.8 Hz, 1H), 4.78 (d, *J* = 5.8 Hz, 1H), 4.15 (m, 2H), 3.88 (s, 3H), 3.72 (m, 2H), 2.92 (s, 3H), 2.20 (qt, *J* = 12.7, 5.0 Hz, 1H), 1.39 – 1.29 (m, 1H), 0.24 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.3, 149.3, 148.4, 139.3, 137.3, 137.0, 134.8, 128.7, 128.64, 128.58, 128.4, 127.9, 127.9, 127.7, 124.9, 106.7, 100.3, 99.0, 75.3, 67.6, 67.4, 57.0, 55.3, 25.8, -0.9 ppm. **IR** (neat): 2962, 2861, 1597, 1458, 1426, 1364, 1216, 1153, 1101, 942, 835, 819, 696 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{29}H_{35}{}^{35}ClNaO_6Si^+$: 565.1784 $[M+Na]^+$; found: 565.1798.

Synthesis of (4-(benzyloxy)-3-chloro-6,8-dimethoxy-6*H*-benzo[*c*]chromen-9-yl)trimethylsilane (181)

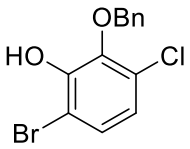


6 M HCl (0.12 mL) was added to a solution of **179** (100 mg, 0.184 mmol, 1.0 equiv.) in MeOH (2 mL) and THF (1 mL) and the solution was stirred for 19 h. Water (5 mL) and ethyl acetate (10 mL) were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane,

0%→10%) yielded (4-(benzyloxy)-3-chloro-6,8-dimethoxy-6*H*-benzo[*c*]chromen-9-yl)trimethylsilane (**181**) (60 mg, 0.132 mmol, 72%) as a colorless oil.

R_f = 0.48 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.81 (s, 1H), 7.66 – 7.58 (m, 2H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.33 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.81 (s, 1H), 6.03 (s, 1H), 5.25 (d, *J* = 10.7 Hz, 1H), 5.13 (d, *J* = 10.7 Hz, 1H), 3.89 (s, 3H), 3.63 (s, 3H), 0.34 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =164.6, 145.0, 144.3, 137.5, 132.1, 130.6, 129.3, 128.5, 128.4, 128.2, 127.2, 123.0, 122.4, 120.4, 118.0, 106.8, 99.7, 75.4, 56.3, 55.4, -0.9 ppm. **IR** (neat): 2952, 2844, 1605, 1458, 1438, 1382, 1240, 1010, 841 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{25}H_{27}{}^{35}ClNaO_4Si^+$: 477.1259 $[M+Na]^+$; found: 477.1257.

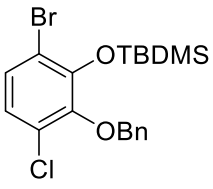
Synthesis of 2-(benzyloxy)-6-bromo-3-chlorophenol (182)



HCl (8.4 mL, 6 M) was added dropwise to a solution of **144** (6.00 g, 16.8 mmol, 1.0 equiv.) in MeOH (85 mL). After stirring at room temperature for 15 h, conc. HCl (10 mL) was added, and the solution was stirred for another 30 min. Water (100 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. 2-(benzyloxy)-6-bromo-3-chlorophenol (**182**) (5.22 g, 16.6 mmol, 99%) was obtained as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 – 7.36 (m, 5H), 7.19 (d, *J* = 8.8, Hz, 1H), 6.86 (d, *J* = 8.8, Hz, 1H), 5.85 (s, 1H), 5.11 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.0, 143.1, 136.2, 129.1, 129.0, 128.7, 128.3, 127.0, 122.1, 107.8, 76.1 ppm. **IR** (neat): 3345, 3022, 1445, 1316, 1219, 963, 909, 787, 738, 697 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{13}H_{11}{}^{79}Br^{35}ClO_2^+$: 312.9625 $[M+H]^+$; found: 312.9602.

Synthesis of (2-(benzyloxy)-6-bromo-3-chlorophenoxy)(*tert*-butyl)dimethylsilane (183)

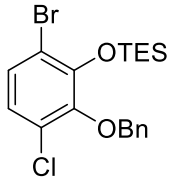


Silyl ether **183** was prepared according to **GP B** using phenol **182** (100 mg, 0.319 mmol) and TBDMSCl. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded (2-(benzyloxy)-6-bromo-3-chlorophenoxy)(*tert*-butyl)dimethylsilane (**183**) (125 mg, 0.292 mmol, 92%) as a colorless oil.

R_f = 0.80 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.57 – 7.47 (m, 2H), 7.46 – 7.32 (m, 3H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 4.99 (s, 2H), 1.08 (s, 9H), 0.21 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.4, 147.9, 136.8, 128.6, 128.49, 128.47, 128.46, 128.34, 128.29, 128.24, 123.6, 115.0, 74.9, 26.2, 18.8, -3.5 ppm. **IR** (neat):

2928, 2857, 1447, 1432, 1372, 1252, 950, 826, 784 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{19}H_{25}{}^{79}Br^{35}ClO_2Si^+$: 427.0490 $[M+H]^+$; found: 427.0482.

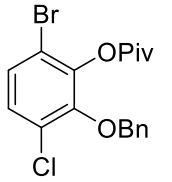
Synthesis of (2-(benzyloxy)-6-bromo-3-chlorophenoxy)triethylsilane (184)



Silyl ether **184** was prepared according to **GP B** using phenol **182** (100 mg, 0.319 mmol) and TESCl. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded (2-(benzyloxy)-6-bromo-3-chlorophenoxy)triethylsilane (**184**) (119 mg, 0.278 mmol, 87%) as a colorless oil.

***R*f** = 0.85 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 – 7.44 (m, 2H), 7.44 – 7.30 (m, 3H), 7.22 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 4.96 (s, 2H), 0.93 (t, *J* = 7.6 Hz, 9H), 0.85 – 0.70 (m, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.0, 147.9, 136.8, 128.5 (2 Cs), 128.4, 128.32, 128.28, 123.5, 115.0, 75.0, 6.8, 5.5 ppm. **IR** (neat): 2954, 2875, 1447, 1435, 1372, 1234, 950, 731 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{19}H_{24}{}^{79}Br^{35}ClNaO_2{}^+$: 449.0310 $[M+Na]^+$; found: 449.0300.

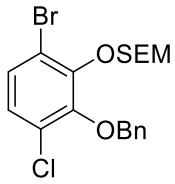
Synthesis of 2-(benzyloxy)-6-bromo-3-chlorophenyl pivalate (187)



Pivoyl chloride (0.07 mL, 0.382 mmol, 1.2 equiv.) was added to a solution of **182** (100 mg, 0.319 mmol, 1.0 equiv.) and TEA (0.05 mL, 0.350 mmol, 1.1 equiv.) in dry DCM (1.0 mL). The solution was stirred at room temperature for 1 h. Water (10 mL) was added, and the phases were separated. The aqueous phase was extracted with DCM (2 x 10 mL). The combined organic phases were washed with water (2 x 10) and brine (10 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded 2-(benzyloxy)-6-bromo-3-chlorophenyl pivalate (**187**) (105 mg, 0.264 mmol, 83%) as a colorless oil.

***R*f** = 0.67 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.48 – 7.42 (m, 2H), 7.41 – 7.34 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 5.01 (s, 2H), 1.32 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 175.3, 149.1, 144.1, 136.5, 128.58, 128.46, 128.44, 128.38, 128.33, 128.2, 116.0, 75.6, 39.4, 27.3 ppm. **IR** (neat): 2974, 2933, 2872, 1759, 1449, 1431, 1369, 1089 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{18}H_{18}{}^{79}Br^{35}ClKO_3{}^+$: 434.9759 $[M+K]^+$; found: 434.9764.

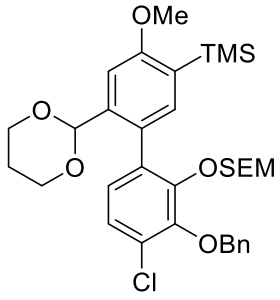
Synthesis of (2-((2-(benzyloxy)-6-bromo-3-chlorophenoxy)methoxy)ethyl)trimethylsilane (189)



SEMCl (0.15 mL, 0.858 mmol, 1.2 equiv.) was added to a solution of **182** (220 mg, 0.702 mmol, 1.0 equiv) and DIPEA (0.39 mL, 2.29 mmol, 3.3 equiv) in dry DCM (2.5 mL) at 0 °C. The solution was stirred for 2 d at room temperature. Water (10 mL) and ethyl acetate (20 mL) were added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with brine (20 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→7%) yielded (2-((2-(benzyloxy)-6-bromo-3-chlorophenoxy)methoxy)ethyl)trimethylsilane (**189**) (283 mg, 0.638 mmol, 91%) as a colorless oil.

R_f = 0.68 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.54 – 7.47 (m, 2H), 7.39 (dd, J = 9.6, 3.9 Hz, 3H), 7.27 (d, J = 8.6 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 5.26 (s, 2H), 5.03 (s, 2H), 3.97 – 3.86 (m, 2H), 0.99 – 0.92 (m, 2H), -0.01 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =149.44, 149.41, 136.5, 128.73, 128.66, 128.59, 128.56, 126.1, 116.4, 97.8, 75.5, 68.2, 18.2, -1.3 ppm. **IR** (neat): 3033, 2952, 2894,1433, 1368, 1247, 947, 833, 695 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{19}H_{24}{}^{79}Br^{35}ClNaO_3Si^+$: 465.0259 $[M+Na]^+$; found: 465.0250.

Synthesis of (3'-(benzyloxy)-4'-chloro-6-(1,3-dioxan-2-yl)-4-methoxy-2'-((2-(trimethylsilyl)ethoxy)methoxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (190)

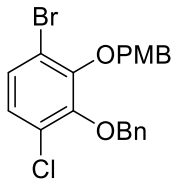


Biphenyl **190** was prepared according to **GP E** using bromide **189** (100 mg, 0.225 mmol, 1.25 equiv.) and triflate **143** (75.0 mg, 0.181 mmol, 1.0 equiv.). After purification *via* flash chromatography (ethyl acetate/hexane, 0%→15%) (3'-(benzyloxy)-4'-chloro-6-(1,3-dioxan-2-yl)-4-methoxy-2'-((2-(trimethylsilyl)ethoxy)methoxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (**190**) (66.0 mg, 0.105 mmol, 58%) was obtained as a colorless oil.

R_f = 0.53 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.63 – 7.53 (m, 2H), 7.45 – 7.32 (m, 3H), 7.21 (s, 2H), 7.17 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.33 (s, 1H), 5.17 (d, J = 1.7 Hz, 2H), 4.88 (s, 2H), 4.14 (m, 2H), 3.88 (s, 3H), 3.74 (m, 2H), 3.19 (ddt, J = 10.5, 6.8, 3.2 Hz, 2H), 2.20 (qt, J = 12.6, 5.0 Hz, 1H), 1.34 (d, J = 13.4 Hz, 1H), 0.76 – 0.58 (m, 2H), 0.26 (s, 9H), -0.12 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =164.1, 149.2, 148.5, 139.1, 137.3, 137.1, 134.8, 128.6, 128.54, 128.50, 128.3, 128.0, 127.8, 127.7, 124.8, 106.7,

100.2, 97.0, 75.2, 67.5, 67.4, 66.9, 55.1, 25.8, 17.7, -0.8, -1.4 ppm. **IR** (neat): 2952, 2851, 1459, 1363, 1246, 1218, 1103, 835, 731 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{33}H_{45}{}^{35}ClNaO_6Si_2^+$: 651.2335 $[M+Na]^+$; found: 651.2312.

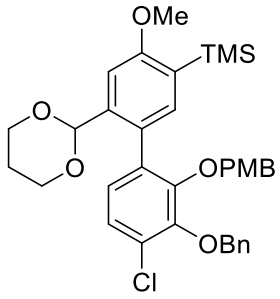
Synthesis of 2-(benzyloxy)-4-bromo-1-chloro-3-((4-methoxybenzyl)oxy)benzene (191)



K_2CO_3 (88.2 mg, 0.638 mmol, 2.0 equiv.) was added to a solution of **182** (100 mg, 0.319 mmol, 1.0 equiv.) in DMF (1 mL). PMBCl (0.05 mL, 0.371 mmol, 1.16 equiv.) was added to the suspension, and it was stirred for 5 h at room temperature. Water (5 mL) was added, and the solution was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine (5 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded 2-(benzyloxy)-4-bromo-1-chloro-3-((4-methoxybenzyl)oxy)benzene (**191**) (98 mg, 0.226 mmol, 71%) as a colorless solid.

R_f = 0.70 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.52 – 7.46 (m, 2H), 7.43 – 7.34 (m, 5H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.94 – 6.83 (m, 2H), 5.06 (s, 2H), 5.00 (s, 2H), 3.83 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.0, 151.0, 150.0, 136.6, 130.8, 128.9, 128.68, 128.63, 128.57, 128.46, 126.2, 116.9, 114.0, 75.8, 75.5, 55.5 ppm. **IR** (neat): 3031, 2996, 2936, 2888, 2838, 1613, 1516, 1434, 1367, 1254, 950, 697 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{21}H_{18}{}^{79}Br^{35}ClNaO_3^+$: 455.0020 $[M+Na]^+$; found: 455.0027.

Synthesis of (3'-(benzyloxy)-4'-chloro-6-(1,3-dioxan-2-yl)-4-methoxy-2'-((4-methoxybenzyl)oxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (192)

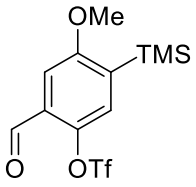


Biphenyl **192** was prepared according to **GP E** using bromide **191** (94.0 mg, 0.217 mmol, 1.1 equiv.) and triflate **143** (81.0 mg, 0.195 mmol, 1.0 equiv.). After purification *via* flash chromatography (ethyl acetate/hexane, 0%→25%) (3'-(benzyloxy)-4'-chloro-6-(1,3-dioxan-2-yl)-4-methoxy-2'-((4-methoxybenzyl)oxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (**192**) (50.0 mg, 80.7 µmol, 41%) was obtained as a colorless oil.

R_f = 0.31 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.56 – 7.46 (m, 2H), 7.41 – 7.31 (m, 3H), 7.25 (m, 2H), 7.18 (d, *J* = 8.4, 1H), 7.01 (d, *J* = 8.4, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.28 (s, 1H), 5.22 – 5.06 (m, 2H), 4.71 – 4.53 (m, 2H), 4.14 (dt, *J* = 10.7, 4.8 Hz, 2H), 3.93 (s, 3H), 3.77 (s, 3H), 3.71 (td, *J* = 9.2, 4.5 Hz, 2H), 2.30 – 2.11 (m, 1H), 1.33 (d, *J* = 13.5 Hz, 1H), 0.24 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.4,

159.4, 151.3, 148.9, 139.1, 137.4, 137.1, 134.6, 130.1, 129.4, 128.9, 128.6, 128.5, 128.3, 127.69, 127.67, 127.5, 124.5, 113.6, 106.8, 100.2, 75.4, 74.7, 67.5, 67.4, 55.4, 55.3, 25.8, -0.9 ppm. **IR** (neat): 2954, 2850, 1514, 1458, 1247, 1219, 1104, 839 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{35}H_{39}{}^{35}ClKO_6Si^+$: 657.1836 $[M+K]^+$; found: 657.1835.

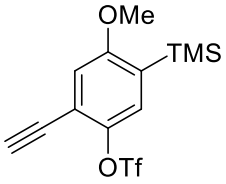
Synthesis of 2-formyl-4-methoxy-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (194)



Triflate **194** was prepared according to **GP A** using phenol **149** (1.59 g, 6.69 mmol). After purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%), 2-formyl-4-methoxy-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (**194**) (2.13 g, 5.98 mmol, 83%) was obtained as a yellow oil.

R_f = 0.62 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.25 (s, 1H), 7.32 (s, 2H), 3.89 (s, 3H), 0.30 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =186.6, 163.6, 144.1, 139.8, 129.8, 128.6, 118.8 (q, J = 320.7 Hz), 108.7, 56.0, -1.5 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -72.81 ppm. **IR** (neat): 2958, 2902, 1697, 1425, 1375, 1205, 1137, 839 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{12}H_{16}F_3O_5SSi^+$: 357.0434 $[M+H]^+$; found: 357.0428.

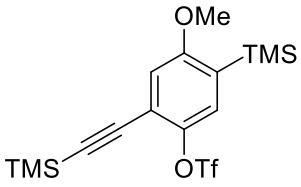
Synthesis of 2-ethynyl-4-methoxy-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (195)



Alkyne **195** was prepared according to **GP C** using aldehyde **194** (2.70 g, 7.58 mmol). After column chromatography (ethyl acetate/hexane, 1/13), 2-ethynyl-4-methoxy-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (**195**) (1.90 g, 5.39 mmol, 71%) was obtained as slightly red crystals.

R_f = 0.54 (ethyl acetate/hexane, 1/9). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.19 (s, 1H), 6.94 (s, 1H), 3.82 (s, 3H), 3.40 (s, 1H), 0.27 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9, 144.3, 132.9, 127.7, 118.9 (q, J = 320.4), 118.4 114.2, 84.4, 56.6, -1.3 ppm. **^{19}F NMR** (377 MHz, $CDCl_3$): δ = -73.39 ppm. **IR** (neat): 3309, 2962, 1600, 1543, 1477, 1463, 1409 cm^{-1}. **HRMS** (EI) *m/z* calcd for $C_{13}H_{16}F_3O_4SSi^+$: 353.0485 $[M+H]^+$; found: 353.0487.

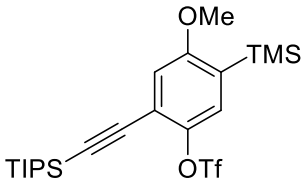
Synthesis of 4-methoxy-5-(trimethylsilyl)-2-((trimethylsilyl)ethynyl)phenyl trifluoromethanesulfonate (196)



LiHMDS (180 mg, 1.08 mmol, 1.3 equiv.) was added to a solution of **195** (295 mg, 0.837 mmol, 1.0 equiv.) in dry THF (6 mL) at -78°C. The mixture was stirred for 1 h at this temperature. After that, TMSCl (0.35 mL, 2.76 mmol, 3.3 equiv.) was added and the solution was allowed to warm to room temperature. Water (20 mL) and hexane (20 mL) were added. The phases were separated, and the aqueous phase was extracted with hexane (2 x 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded 4-methoxy-5-(trimethylsilyl)-2-((trimethylsilyl)ethynyl)phenyl trifluoromethanesulfonate (**196**) (340 mg, 0.801 mmol, 96%) as a colorless oil.

R_f = 0.74 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.16 (s, 1H), 6.90 (s, 1H), 3.81 (s, 3H), 0.28 (s, 9H), 0.26 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =162.8, 144.2, 132.3, 127.5, 119.5, 118.9 (q, J = 320.5 Hz), 113.9, 102.9, 98.0, 55.9, -0.3, -1.3 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -73.63 ppm. **IR** (neat): 2958, 2901, 2163, 1599, 1424, 1373, 1247, 1202, 837, 760 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{16}H_{24}F_3O_4SSi^+$: 425.0880 $[M+H]^+$; found: 425.0875.

Synthesis of 4-methoxy-2-((triisopropylsilyl)ethynyl)-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (197)

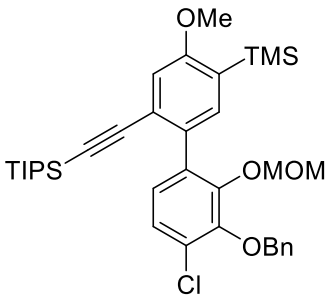


LiHMDS (6.30 mL, 6.30 mmol, 1 M in THF, 1.2 equiv.) was added to a solution of **195** (1.80 g. 5.10 mmol, 1.0 equiv.) in dry THF (33.7 mL) at -78°C. The mixture was stirred for 1 h at this temperature and TIPSCl (1.41 mL, 6.64 mmol, 1.3 equiv.) was added. After allowing the solution to warm to room temperature, water (75 mL) and ethyl acetate (50 mL) were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography of the residue (ethyl acetate/hexane, 1/99), 4-methoxy-2-((triisopropylsilyl)ethynyl)-5-(trimethylsilyl)phenyl trifluoromethanesulfonate (**197**) (2.52 g, 4.95 mmol, 97%) was obtained as a colorless oil.

R_f = 0.82 (ethyl acetate/hexane, 1/9). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.16 (s, 1H), 6.89 (s, 1H), 3.83 (s, 3H), 1.15 (s, 21H), 0.25 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.8,

144.0, 132.1, 127.33, 127.32, 118.9 (q, J = 320.8 Hz), 112.0, 114.4, 99.9, 99.7, 55.9, 18.7, 11.4, -1.3 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.38 ppm. **IR** (neat): 945, 2865, 1598, 1463, 1426 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{22}H_{36}F_3O_4SSi_2^{\cdot+}$: 509.1819 $[M+H]^+$; found: 509.1814.

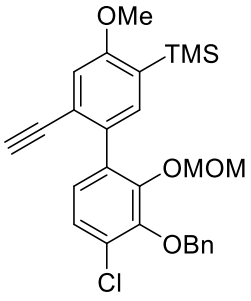
Synthesis of ((3'-(benzyloxy)-4'-chloro-4-methoxy-2'-(methoxymethoxy)-5-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)ethynyl)triisopropylsilane (199)



Biphenyl **199** was prepared according to **GP E** using bromide **144** (680 mg, 1.90 mmol, 1.4 equiv.) and triflate **197** (690 mg, 1.36 mmol, 1.0 equiv.). After purification *via* flash chromatography (ethyl acetate/hexane, 0%→15%), ((3'-(benzyloxy)-4'-chloro-4-methoxy-2'-(methoxymethoxy)-5-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)ethynyl)triisopropylsilane (**199**) (622 mg, 0.976 mmol, 72%) was obtained as a colorless oil.

***R*$_f$** = 0.35 (ethyl acetate/hexane, 1/49). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.58 – 7.52 (m, 2H), 7.43 – 7.33 (m, 3H), 7.29 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.96 (s, 1H), 5.09 (s, 2H), 4.85 (s, 2H), 3.85 (s, 3H), 3.01 (s, 3H), 0.96 (s, 21H), 0.26 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.4, 149.5, 148.4, 137.1, 135.3, 132.7, 129.1, 128.61 (2 C), 128.59, 128.3, 127.9, 127.7, 125.2, 124.8, 112.9, 106.2, 99.3, 94.6, 75.3, 57.0, 55.4, 18.7, 11.3, -0.9 ppm. **IR** (neat): 2941, 2862, 2155, 1581, 1454, 1424 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{36}H_{50}{}^{35}ClO_4Si_2^+$: 637.2931 $[M+H]^+$; found: 637.2924.

Synthesis of (3'-(benzyloxy)-4'-chloro-6-ethynyl-4-methoxy-2'-(methoxymethoxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (200)

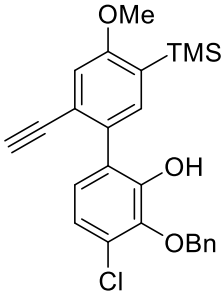


Terminal alkyne **200** was prepared according to **GP D** using silyl-protected alkyne **199** (1.60 g, 2.51 mmol). After purification *via* ISOLERA (ethyl acetate/hexane, 0%→9%), (3'-(benzyloxy)-4'-chloro-6-ethynyl-4-methoxy-2'-(methoxymethoxy)-[1,1'-biphenyl]-3-yl)trimethylsilane (**200**) (1.09 g, 2.27 mmol, 90%) was obtained as a colorless solid.

***R*$_f$** = 0.59 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.57 – 7.51 (m, 2H), 7.42 – 7.34 (m, 3H), 7.31 (s, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 7.01 (s, 1H), 5.12 (s, 2H), 4.88 (s, 2H), 3.84 (s, 3H), 3.01 (s, 1H), 2.94 (s, 3H), 0.27 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 163.4, 149.6, 148.4, 137.1, 137.0, 135.1, 133.0, 129.8, 128.7, 128.6, 128.4, 128.2, 127.0, 125.0, 123.9, 113.1, 99.3, 83.2, 80.2, 75.3, 56.9, 55.4, -0.9 ppm. **IR** (neat): 3270, 2949, 2838, 1362, 1220, 1158, 948, 838, 749 cm^{-1}. **HRMS** (ESI) *m/z* calcd for

$C_{27}H_{30}{}^{35}ClO_4Si^+$: 481.1596 $[M+H]^+$; found: 481.1588.

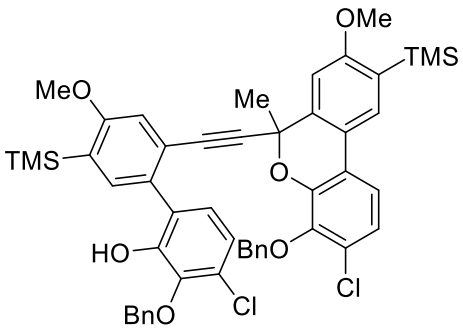
Synthesis of 3-(benzyloxy)-4-chloro-2'-ethynyl-4'-methoxy-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-ol (204)



Conc. HCl (7.5 mL) was added to a solution of **200** (1.08 g, 2.24 mmol, 1.0 equiv.) in MeOH (30 mL) and THF (15 mL), and the solution was stirred for 1 h. Water (50 mL) was added, and the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→12%) yielded 3-(benzyloxy)-4-chloro-2'-ethynyl-4'-methoxy-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-ol (**204**) (915 mg, 2.09 mmol, 93%) as a colorless solid.

***R*f** = 0.57 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.54 – 7.44 (m, 2H), 7.43 – 7.35 (m, 3H), 7.26 (m, 1H), 7.00 (m, 3H), 5.65 (s, 1H), 5.13 (s, 2H), 3.83 (s, 3H), 2.99 (s, 1H), 0.25 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.5, 148.0, 142.4, 136.9, 136.6, 131.6, 130.2, 128.96, 128.95, 128.8, 127.3, 126.8, 126.4, 123.6, 120.8, 113.6, 83.0, 80.2, 75.9, 55.4, -0.9 ppm. **IR** (neat): 3506, 3286, 2952, 2897, 2840, 1586, 1432, 1359, 1214, 835 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{25}H_{25}{}^{35}ClKO_3Si^+$: 475.0893 $[M+K]^+$; found: 475.0907.

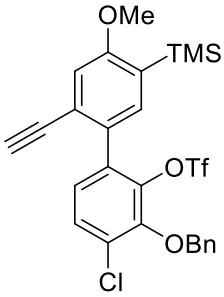
Synthesis of 3-(benzyloxy)-2'-((4-(benzyloxy)-3-chloro-8-methoxy-6-methyl-9-(trimethylsilyl)-6*H*-benzo[*c*]chromen-6-yl)ethynyl)-4-chloro-4'-methoxy-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-ol (205)



$AgSbF_6$ (46 µL, 0.05 M in DCM, 2.3 µmol, 5 mol%) was added to a solution of **204** (20.0 mg, 45.8 µmol, 1.0 equiv.) and precatalyst **203** (2.0 mg, 2.3 µmol, 5 mol%) in dry DCM (0.85 mL) at room temperature. The reaction mixture was stirred for 1 h and filtered through a pad of silica. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 3-(benzyloxy)-2'-((4-(benzyloxy)-3-chloro-8-methoxy-6-methyl-9-(trimethylsilyl)-6*H*-benzo[*c*]chromen-6-yl)ethynyl)-4-chloro-4'-methoxy-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-ol (**205**) (14 mg, 16.0 µmol, 70%) as a white solid.

***R*f** = 0.52 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.62 (s, 1H), 7.58 – 7.53 (m, 2H), 7.40 – 7.29 (m, 10H), 7.20 (s, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.82 (s, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.68 (s, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.50 (s, 1H), 5.14 (d, *J* = 10.9 Hz, 1H), 5.03 (d, *J* = 10.9 Hz, 1H), 4.98 – 4.91 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 1.94 (s, 3H), 0.31 (s, 9H), 0.21 (s, 9H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 164.9, 163.4, 147.8, 145.5, 145.1, 142.3, 138.2, 137.6, 136.9, 136.6, 131.2, 130.0, 129.7, 128.9 (2 C), 128.8, 128.73, 128.66, 128.5, 128.2, 127.1, 127.0, 126.5, 126.0, 123.6, 123.5, 122.9, 120.5, 120.3, 117.7, 113.1, 104.8, 92.3, 85.7, 75.8, 75.6, 74.6, 55.41, 55.38, 27.6, -0.8, -1.0 ppm. **IR** (neat): 3509, 2953, 2898, 2843, 1461, 1435, 1364, 1215, 840 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{50}H_{51}{}^{35}Cl_2O_3Si_2^+$: 873.2596 $[M+K]^+$; found: 873.2588.

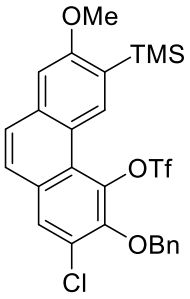
Synthesis of 3-(benzyloxy)-4-chloro-2'-ethynyl-4'-methoxy-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (207)



Triflate **207** was prepared according to **GP A** using phenol **204** (854 mg, 1.95 mmol, 1.0 equiv.). After purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→20%), 3-(benzyloxy)-4-chloro-2'-ethynyl-4'-methoxy-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (**207**) (804 mg, 1.41 mmol, 72%) was obtained as an off-white solid.

***R*f** = 0.54 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 – 7.49 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 7.01 (s, 1H), 5.19 (d, *J* = 1.9 Hz, 2H), 3.85 (s, 3H), 2.99 (s, 1H), 0.25 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.2, 147.6, 142.1, 136.8, 135.6, 134.2, 130.4, 129.49, 129.46, 129.3, 128.9, 128.64, 128.55, 127.8, 123.9, 118.2 (q, *J* = 320.8 Hz), 113.4, 82.3, 80.8, 75.9, 55.5, -1.1 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -74.78 ppm. **IR** (neat): 3281, 2963, 2899, 1587, 1423, 1247, 1200, 912, 800 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{25}{}^{35}ClF_3O_3SSi^{\cdot+}$: 569.0827 $[M+H]^+$; found: 569.0815.

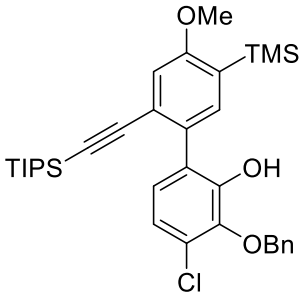
Synthesis of 3-(benzyloxy)-2-chloro-7-methoxy-6-(trimethylsilyl)phenanthren-4-yl trifluoromethanesulfonate (208)



$AgSbF_6$ (127 µL, 0.05 M in DCM, 6.4 µmol, 5 mol%) was added to a solution of **207** (75 mg, 0.129 mmol, 1.0 equiv.) and precatalyst **121** (7.0 mg, 6.4 µmol, 5 mol%) in dry DCE (2.7 mL) at 80 °C. The reaction mixture was stirred for 20 h at this temperature. After cooling to room temperature, the reaction mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. Washing the residue with hexane yielded 3-(benzyloxy)-2-chloro-7-methoxy-6-(trimethylsilyl)phenanthren-4-yl trifluoromethanesulfonate (**208**) (43 mg, 74.0 mmol, 57%) as an off-white solid.

R_f = 0.48 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.80 (s, 1H), 7.89 (s, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.55 – 7.51 (m, 3H), 7.41 – 7.33 (m, 3H), 7.14 (s, 1H), 5.27 (s, 2H), 3.96 (s, 3H), 0.37 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =163.5, 146.5, 140.5, 136.0, 135.5, 134.6, 130.3, 129.6, 129.5, 129.2, 128.9, 128.5, 128.4, 126.2, 125.7, 123.9, 121.2, 118.5 (q, J = 321.2 Hz), 106.2, 55.2, -0.9 ppm. **^{19}F NMR** (565 MHz, $CDCl_3$): δ = -73.08 ppm. **IR** (neat): 3030, 2938, 1605, 1592, 1421, 1257, 1245, 1205, 1140, 841 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{25}{}^{35}ClF_3O_3SSi^+$: 569.0827 $[M+H]^+$; found: 569.0827.

Synthesis of 3-(benzyloxy)-4-chloro-4'-methoxy-2'-((triisopropylsilyl)ethynyl)-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-ol (212)

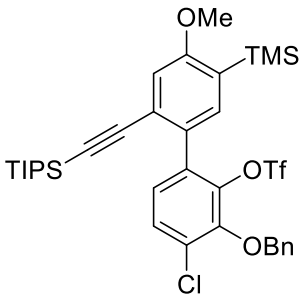


Conc. HCl (0.43 mL) was added to a solution of **199** (330 mg, 0.518 mmol, 1.0 equiv.) in MeOH (10 mL) and THF (18 mL), and the solution was stirred at room temperature for 16 h. Water (50 mL) was added, and the reaction mixture was extracted with DCM (20 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography of the residue(ethyl acetate/hexane, 1/49) yielded 3-(benzyloxy)-4-chloro-4'-methoxy-2'-((triisopropylsilyl)ethynyl)-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-ol (**212**) (230 mg, 0.388 mmol, 75%) as a colorless oil.

R_f = 0.33 (ethyl acetate/hexane, 1/9). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.53 – 7.43 (m, 2H), 7.46 – 7.32 (m, 3H), 7.24 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 5.56 (s, 1H), 5.10 (s, 2H), 3.84 (s, 3H), 0.98 (s, 21H), 0.25 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.6, 148.0, 142.5, 136.8, 136.7, 131.5, 129.5, 128.9, 128.8, 128.5, 127.6, 127.3, 126.3, 125.2, 120.7, 113.2, 106.0, 94.4, 90.3, 75.8, 55.4, 18.6, 11.3, -0.9 ppm. **IR** (neat): 3516, 2945, 2863, 1587, 1463, 1432 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{34}H_{46}O_3{}^{35}ClSi_2^+$:

593.2669 $[M+H]^+$; found: 593.2651.

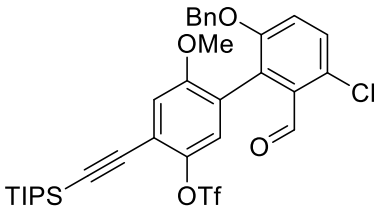
Synthesis of 3-(benzyloxy)-4-chloro-4'-methoxy-2'-((triisopropylsilyl)ethynyl)-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (213)



Triflate **213** was prepared according to **GP A** using phenol **212** (230 mg, 0.388 mmol). Column chromatography (ethyl acetate/hexane, 1/49) yielded 3-(benzyloxy)-4-chloro-4'-methoxy-2'-((triisopropylsilyl)ethynyl)-5'-(trimethylsilyl)-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (**213**) (90.0 mg, 0.124 mmol, 32%) as a colorless oil.

R_f = 0.58 (ethyl acetate/hexane, 1/49). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.62 – 7.53 (m, 2H), 7.41 (m, 4H), 7.25 (d, J = 8.3 Hz, 1H), 7.15 (s, 1H), 7.00 (s, 1H), 5.19 (s, 2H), 3.88 (s, 3H), 1.00 (s, 21H), 0.28 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 164.1, 147.6, 142.0, 136.6, 135.7, 134.5, 129.6, 129.2, 129.2, 129.1, 128.8, 128.5, 128.4, 128.3, 125.4, 118.2 (q, J = 320.7 Hz), 113.2, 105.3, 95.2, 75.8, 60.6, 55.5, 18.6, 11.3, -1.1 ppm. **^{19}F NMR** (471 MHz, $CDCl_3$): δ =-74.79 ppm. **IR** (neat): 2943, 2865, 2153, 1586, 1461, 1422 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{35}H_{45}{}^{35}ClF_3O_5SSi_2^+$: 725.2161 $[M+H]^+$; found: 725.2141.

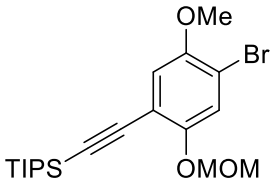
Synthesis of 6'-(benzyloxy)-3'-chloro-2'-formyl-6-methoxy-4-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (216)



Triflate **216** was prepared according to **GP A** using phenol **232** (393 mg, 0.716 mmol). After purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%), 6'-(benzyloxy)-3'-chloro-2'-formyl-6-methoxy-4-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-3-yl trifluoromethanesulfonate (**216**) (252 mg, 0.370 mmol, 52%) was obtained as a yellow oil.

R_f = 0.44 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.15 (s, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.34 – 7.23 (m, 3H), 7.18 – 7.08 (m, 4H), 7.03 (s, 1H), 5.11 – 4.95 (m, 2H), 3.73 (s, 3H), 1.18 (s, 21H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 190.3, 155.5, 155.0, 143.6, 136.0, 132.8, 131.5, 128.7, 128.13, 128.07, 127.9, 126.8, 125.7, 124.4, 118.9, 118.8 (q, J = 320.9 Hz), 118.5, 115.6, 99.8, 71.0, 56.2, 18.7, 11.4 ppm. **^{19}F NMR** (162 MHz, $CDCl_3$): δ = -73.28 ppm. **IR** (neat): 2944, 2866, 1695, 1429, 1203, 1138, 879, 668, 602 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{33}H_{37}{}^{35}ClF_3O_6SSi^+$: 681.1725 $[M+H]^+$; found: 681.1730.

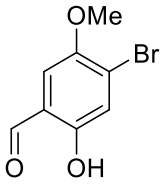
Synthesis of ((4-bromo-5-methoxy-2-(methoxymethoxy)phenyl)ethynyl)triisopropylsilane (217)



LiHMDS (2.9 mL, 2.9 mmol, 1 M in THF, 1.05 equiv.) was added to a solution of **227** (747 mg, 2.76 mmol, 1.0 equiv.) in dry THF (17 mL) at -78°C. The mixture was stirred for 1 h at this temperature. After that, TIPSCl (0.66 mL, 2.9 mmol, 1.05 equiv.) was added and the solution was allowed to warm to room temperature. Water (50 mL) and ethyl acetate (50 mL) were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→20%) yielded ((4-bromo-5-methoxy-2-(methoxymethoxy)phenyl)ethynyl)triisopropylsilane (**217**) (1.03 g, 2.41 mmol, 87%) as a colorless oil.

R_f = 0.74 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.29 (s, 1H), 6.93 (s, 1H), 5.15 (s, 2H), 3.86 (s, 3H), 3.50 (s, 3H), 1.14 (s, 21H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.7, 151.1, 121.8, 116.2, 114.4, 112.6, 102.3, 96.4, 95.9, 56.9, 56.4, 18.8, 11.5 ppm. **IR** (neat): 2941, 2864, 2152, 1486, 1372, 1151, 992, 802, 675 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{32}{}^{79}BrO_3Si^+$: 427.1299 $[M+H]^+$; found: 427.1292.

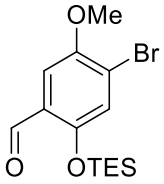
Synthesis of 4-bromo-2-hydroxy-5-methoxybenzaldehyde (220)



$MgCl_2$ (7.24 g, 76.1 mmol, 1.5 equiv.), TEA (27 mL, 193 mmol, 3.8 equiv.) and para formaldehyde (10.6 g, 355 mmol, 7.0 equiv.) was added to a solution of 3-bromo-4-methoxyphenol (10.3 g, 50.3 mmol, 1.0 equiv.) in dry MeCN (150 mL). The white suspension was refluxed for 16 h. After cooling to room temperature, the reaction mixture was poured into DCM (500 mL) and stirred for 10 min. The solution was washed with water (2 x 100 mL) and brine (1000 mL). The solvent was removed under reduced pressure. After column chromatography of the residue (ethyl acetate/hexane, 1/20), 4-bromo-2-hydroxy-5-methoxybenzaldehyde (**220**) (5.35 g, 23.2 mmol, 46%) was obtained as a yellow crystalline solid.

T_m: 138-139°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.71 (s, 1H), 9.84 (s, 1H), 7.26 (s, 1H), 6.97 (s, 1H), 3.90 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.5, 156.0, 149.8, 123.1, 123.0, 119.5, 114.0, 57.0 ppm.

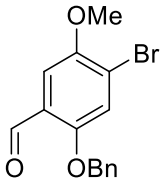
Synthesis of 4-bromo-5-methoxy-2-((triethylsilyl)oxy)benzaldehyde (221)



Silyl ether **221** was prepared according to **GP B** using phenol **220** (1.00 g, 4.33 mmol) and TESCl. Deviating from **GP B**, the reaction mixture was stirred at 60 °C. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 5%→25%) yielded 4-bromo-5-methoxy-2-((triethylsilyl)oxy)benzaldehyde (**221**) (472 mg, 1.37 mmol, 32%) as a colorless oil.

***R*f** = 0.68 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.36 (s, 1H), 7.27 (s, 1H), 7.13 (s, 1H), 3.89 (s, 3H), 1.01 (t, J = 7.8 Hz, 9H), 0.80 (qd, J = 7.5, 7.1, 1.5 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =189.4, 153.2, 151.0, 126.4, 125.4, 120.3, 109.0, 56.8, 6.7, 5.2 ppm. **IR** (neat): 2956, 2876, 1683, 1596, 1473, 1390, 1208, 981, 764 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{14}H_{22}{}^{79}BrO_3Si^+$: 345.0516 $[M+H]^+$; found: 345.0520.

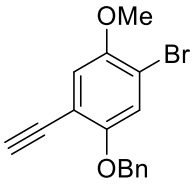
Synthesis of 2-(benzyloxy)-4-bromo-5-methoxybenzaldehyde (224)



BnBr (0.60 mL, 4.76 mmol, 1.1 equiv.) was added to a suspension of **220** (1.00 g, 4.32 mmol, 1.0 equiv.) and K_2CO_3 (1.50 g, 10.9 mmol, 2.5 equiv.) in DMF (14 mL). After stirring at room temperature for 22 h, water (50 mL) and ethyl acetate (50 mL) were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic phases were dried over $MgSO_4$ und the solvent was removed under reduced pressure. The resulting solid was washed with hexane and ether. 2-(benzyloxy)-4-bromo-5-methoxybenzaldehyde (**224**) (1.28 g, 3.99 mmol, 92%) was obtained as a yellow crystalline solid.

***R*f** = 0.48 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 10.44 (s, 1H), 7.44 – 7.32 (m, 7H), 5.13 (s, 2H), 3.90 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ =188.8, 155.5, 150.9, 135.8, 128.9, 128.6, 127.6, 124.9, 120.4, 119.4, 109.6, 71.7, 56.9 ppm. **IR** (neat): 3077, 3005, 2930, 2861, 1672, 1600, 1485, 1393, 1203, 1017, 723 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{13}{}^{79}BrNaO_3^+$: 342.9940 $[M+Na]^+$; found: 342.9947.

Synthesis of 1-(benzyloxy)-5-bromo-2-ethynyl-4-methoxybenzene (225)

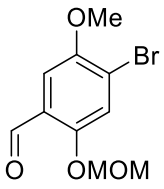


Alkyne **225** was prepared according to **GP C** using aldehyde **224** (1.20 g, 3.74 mmol). After washing with MeOH, 1-(benzyloxy)-5-bromo-2-ethynyl-4-methoxybenzene (**225**) (909 mg, 2.87 mmol, 77%) was obtained as a brownish solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (dd, J = 7.7, 1.6 Hz, 2H), 7.42 – 7.31 (m, 3H), 7.15 (s, 1H), 7.00 (s, 1H), 5.11 (s, 2H), 3.84 (s, 3H), 3.36 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.4, 150.3, 136.5, 128.7, 128.1, 127.3, 119.1, 116.8, 113.2, 112.0, 82.3, 79.5, 71.7, 56.9

ppm. **IR** (neat): 3288, 3062, 3030, 2982, 2947, 2108, 1681, 1495, 1374, 1208, 1011 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{16}H_{14}{}^{79}BrO_2^+$: 317.0172 $[M+H]^+$; found: 317.0168.

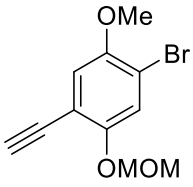
Synthesis of 4-bromo-5-methoxy-2-(methoxymethoxy)benzaldehyde (226)



MOMCl (0.94 mL, 12.4 mmol, 2.9 equiv.) was added to a solution of **220** (1.00 g, 4.32 mmol, 1.0 equiv.) and DIPEA (2.1 mL, 12.1 mmol, 2.8 equiv.) in dry DCM (15 mL). The solution was stirred at room temperature for 20 h. Water (50 mL) and DCM (20 mL) were added, and the phases were separated. The aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine (50 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded 4-bromo-5-methoxy-2-(methoxymethoxy)benzaldehyde (**226**) (1.10 g, 4.00 mmol, 93%) as a colorless oil.

R_f = 0.36 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.40 (s, 1H), 7.50 (s, 1H), 7.31 (s, 1H), 5.22 (s, 2H), 3.88 (s, 3H), 3.51 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 188.8, 154.0, 151.4, 125.2, 121.4, 120.4, 109.2, 95.6, 56.8, 56.7 ppm. **IR** (neat): 3105, 3020, 2968, 2894, 2841, 1676, 1474, 1382, 1152, 963, 871 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{10}H_{12}{}^{79}BrO_4^+$: 274.9913 $[M+H]^+$; found: 274.9910.

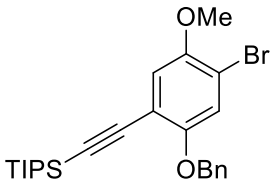
Synthesis of 1-bromo-4-ethynyl-2-methoxy-5-(methoxymethoxy)benzene (227)



Alkyne **227** was prepared according to **GP C** using aldehyde **226** (500 mg, 1.82 mmol). Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded 1-bromo-4-ethynyl-2-methoxy-5-(methoxymethoxy)benzene (**227**) (387 mg, 1.43 mmol, 78%) as a slightly orange oil.

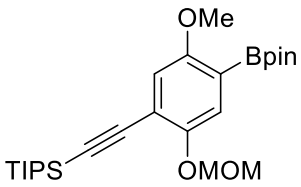
R_f = 0.43 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 6.97 (s, 1H), 5.18 (s, 2H), 3.85 (s, 3H), 3.52 (s, 3H), 3.33 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.9, 151.1, 121.5, 116.5, 113.4, 112.5, 96.0, 81.9, 79.56, 56.9, 56.5 ppm. **IR** (neat): 3307, 3238, 2942, 2830, 1480, 1371, 1197, 1149, 1080, 984, 861 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{11}H_{12}{}^{79}BrO_3^+$: 270.9964 $[M+H]^+$; found: 270.9961.

Synthesis of ((2-(benzyloxy)-4-bromo-5-methoxyphenyl)ethynyl)triisopropylsilane (228)



LiHMDS (2.60 mL, 2.60 mmol, 1 M in THF, 1.1 equiv.) was added to a solution of **225** (749 mg, 2.36 mmol, 1.0 equiv.) in dry THF (15 mL) was added at -78°C. The mixture was stirred for 1 h at this temperature. After that, TIPSCl (0.56 mL, 2.60 mmol, 1.1 equiv.) was added and the solution was allowed to warm to room temperature. water (50 mL) and ethyl acetate (50 mL) were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded ((2-(benzyloxy)-4-bromo-5-methoxyphenyl)ethynyl)triisopropylsilane (**228**) (986 mg, 2.08 mmol, 88%) as a colorless oil. R_f = 0.71 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.51 – 7.42 (m, 2H), 7.39 – 7.28 (m, 3H), 7.14 (s, 1H), 6.97 (s, 1H), 5.06 (s, 2H), 3.86 (s, 3H), 1.10 (s, 21H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.5, 150.2, 136.6, 128.5, 128.0, 127.6, 118.6, 116.8, 113.5, 112.6, 102.4, 96.5, 71.5, 57.0, 18.8, 11.5 ppm. **IR** (neat): 2940, 2863, 2149, 1485, 1457, 1220, 1206, 853, 671 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{25}H_{34}{}^{79}BrO_2Si^+$: 473.1506 $[M+H]^+$; found: 473.1504.

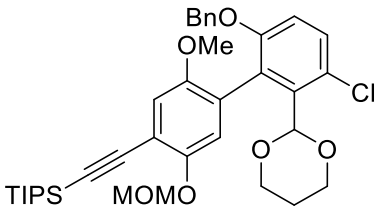
Synthesis of triisopropyl((5-methoxy-2-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethynyl)silane (230)



*n*Buli (0.4 mL, 1.00 mmol, 2.5 M in THF, 1.15 equiv.) was added dropwise to a solution of **217** (370 mg, 0.866 mmol, 1.0 equiv.) in dry THF (4.1 mL) at -78 °C. After stirring at this temperature for 1 h, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolan (0.42 mL, 2.06 mmol, 2.4 equiv.), was added and the reaction mixture was allowed to warm up to room temperature overnight. Water (10 mL) was added, and the solution was extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (25 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded triisopropyl((5-methoxy-2-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethynyl)silane (**230**) (393 mg, 0.828 mmol, 96%). The product was used without further purification.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 (s, 1H), 6.89 (s, 1H), 5.19 (s, 2H), 3.79 (s, 3H), 3.52 (s, 3H), 1.34 (s, 12H), 1.14 (s, 21H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 159.1, 152.0, 124.3, 118.2, 115.7, 103.4, 96.3, 95.9, 83.8, 56.8, 56.5, 25.0, 18.8, 11.5 ppm. **IR** (neat): 2945, 2865, 2147, 1604, 1386, 1197, 1143, 1011, 999 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{44}{}^{10}BO_5Si^+$:

474.3082 $[M+H]^+$; found: 474.3071.

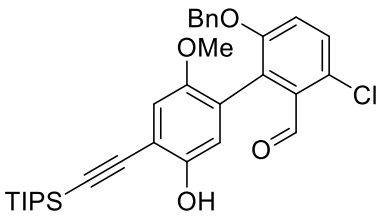
Synthesis of ((6'-(benzyloxy)-3'-chloro-2'-(1,3-dioxan-2-yl)-2-methoxy-5-(methoxymethoxy)-[1,1'-biphenyl]-4-yl)ethynyl)triisopropylsilane (231)



A SCHLENK flask was charged with **230** (310 mg, 0.653 mmol, 1.0 equiv.), **143** (280 mg, 0.676 mmol, 1.04 equiv.), Pd_2dba_3 (60 mg, 65.5 µmol, 10 mol%), SPhos (108 mg, 0.263 mmol, 40 mol%), Na_2CO_3 (1.2 mL, 2 M in water), and toluene (3.6 mL). After degassing with nitrogen for 5 min, the reaction mixture was stirred at 100 °C for 3.5 h. The cooled solution was filtered through a pad of celite, and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded ((6'-(benzyloxy)-3'-chloro-2'-(1,3-dioxan-2-yl)-2-methoxy-5-(methoxymethoxy)-[1,1'-biphenyl]-4-yl)ethynyl)triisopropylsilane (**231**) (302 mg, 0.464 mmol, 71%) as a colorless oil.

R_f = 0.40 (ethyl acetate/hexane, 1/4). **^{1}H -MR** (400 MHz, $CDCl_3$): δ = 7.28 – 7.18 (m, 4H), 7.15 – 7.08 (m, 2H), 6.96 (s, 1H), 6.93 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.58 (s, 1H), 5.15 (s, 2H), 4.97 (s, 2H), 4.16 – 4.07 (m, 2H), 3.74 – 3.60 (m, 5H), 3.48 (s, 3H), 1.94 (qt, J = 12.6, 4.8 Hz, 1H), 1.18 – 1.14 (s, 22H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.0, 152.7, 151.8, 137.1, 134.5, 130.8, 129.6, 128.5, 127.6, 127.5, 126.6, 125.5, 121.6, 115.0, 114.5, 114.3, 103.2, 100.4, 96.2, 94.9, 70.6, 67.5, 67.3, 56.4, 56.3, 25.5, 18.9, 11.6 ppm. **IR** (neat): 2943, 2864, 1502, 1460, 1380, 1152, 1001, 677 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{37}H_{48}{}^{35}ClO_6Si^+$: 651.2903 $[M+H]^+$; found: 651.2884.

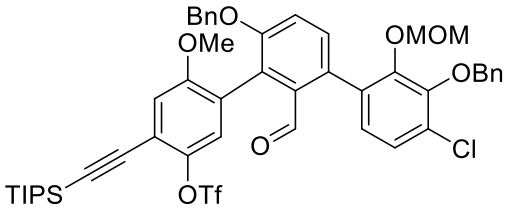
Synthesis of 6-(benzyloxy)-3-chloro-5'-hydroxy-2'-methoxy-4'-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-2-carbaldehyde (232)



HCl (10 mL, 4 M) was added to a solution of **231** (523 mg, 0.803 mmol, 1.0 equiv.) in acetone (20 mL) and the reaction mixture was stirred at 40 °C for 24 h. After cooling to room temperature, sat. aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with DCM (3 x 20 mL) and the combined organic phases were washed with brine (25 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 6-(benzyloxy)-3-chloro-5'-hydroxy-2'-methoxy-4'-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-2-carbaldehyde (**232**) (439 mg, 0.800 mmol, quant.) as a yellow oil.

R_f = 0.35 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.00 (s, 1H), 7.38 – 7.27 (m, 4H), 7.22 – 7.16 (m, 2H), 7.05 (d, J = 8.8 Hz, 1H), 6.89 (s, 1H), 6.81 (s, 1H), 5.58 (s, 1H), 5.05 (s, 2H), 3.67 (s, 3H), 1.17 (s, 21H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 190.8, 155.0, 152.5, 151.4, 136.5, 133.1, 131.0, 130.9, 128.7, 128.0, 126.9, 126.2, 124.2, 120.2, 118.2, 115.4, 115.2, 103.1, 95.94, 95.88, 70.9, 56.3, 56.1, 18.8, 11.5 ppm. **IR** (neat): 3231, 2975, 2855, 1445, 1372, 1230, 986, 738, 701, 665 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{32}H_{38}{}^{35}ClO_4^+$: 549.2222 $[M+H]^+$; found: 549.2219.

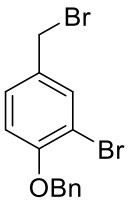
Synthesis of 3'',6'-bis(benzyloxy)-4''-chloro-2'-formyl-6-methoxy-2''-(methoxymethoxy)-4-((triisopropylsilyl)ethynyl)-[1,1':3',1''-terphenyl]-3-yl trifluoromethanesulfonate (233)



A SCHLENK flask was charged with **216** (43.0 mg, 63 µmol, 1.0 equiv.), **159** (28.0 mg, 69 µmol, 1.1 equiv.), Pd_2dba_3 (6.5 mg, 7.1 µmol, 11 mol%), SPhos (12.0 mg, 29 µmol, 4.0 equiv.), toluene (0.5 mL) and Na_2CO_3 (0.18 mL, 2 M in water). The reaction mixture was stirred for 3 h and filtered through silica and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→10%) yielded 3'',6'-bis(benzyloxy)-4''-chloro-2'-formyl-6-methoxy-2''-(methoxymethoxy)-4-((triisopropylsilyl)ethynyl)-[1,1':3',1''-terphenyl]-3-yl trifluoromethanesulfonate (**233**) (32.0 mg, 34.7 µmol, 55%) as a colorless oil.

R_f = 0.57 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 9.69 (s, 1H), 7.52 – 7.47 (m, 2H), 7.42 – 7.27 (m, 7H), 7.20 (m, 4H), 7.12 (s, 1H), 7.06 (s, 1H), 6.99 (s, 1H), 5.13 – 5.03 (m, 4H), 4.89 (m, 2H), 3.73 (s, 3H), 2.85 (s, 3H), 1.19 (s, 21H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 191.5, 156.1, 155.9, 149.1, 148.5, 143.7, 136.9, 136.6, 135.1, 133.7, 132.7, 132.2, 129.1, 128.8, 128.70, 128.6, 128.5, 128.1, 127.0, 126.6, 126.4, 125.8, 124.6, 119.0. (q, J = 321.0 Hz), 118.6, 117.2, 115.9, 100.0, 99.7, 99.5, 75.5, 71.1, 56.8, 56.2, 18.8, 11.6 ppm. **HRMS** (ESI) *m/z* calcd for $C_{48}H_{50}{}^{35}ClF_3NaO_9SSi^+$: 945.2478 $[M+Na]^+$; found: 945.2478.

Synthesis of 1-(benzyloxy)-2-bromo-4-(bromomethyl)benzene (235)

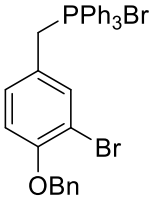


PBr_3 (0.1 mL, 1.02 mmol, 1.0 equiv.) was added dropwise to a solution of **175** (299 mg, 1.02 mmol, 1.0 equiv.) in dry diethyl ether (10 mL) at 0 °C. After warming up to room temperature, the solution was stirred for 3 h. Water (10 mL) was added, and the phases were separated. The aqueous phase was extracted with ether (2 x 10 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash

chromatography (ethyl acetate/hexane, 0%→15%) yielded 1-(benzyloxy)-2-bromo-4-(bromomethyl)benzene (**235**) (156 mg, 0.438 mmol, 43%) as a colorless oil that solidified overnight.

R_f = 0.58 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.61 (d, J = 2.2 Hz, 1H), 7.49 – 7.31 (m, 5H), 7.26 (dd, J = 8.4, 2.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.16 (s, 2H), 4.43 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.2, 136.3, 134.2, 131.8, 129.4, 128.8, 128.2, 127.1, 113.8, 112.6, 71.0, 32.6 ppm. **IR** (neat): 3063, 3026, 2898, 2857, 1602, 1498, 1263, 1054, 733 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{14}H_{12}{}^{79}Br_2NaO^+$: 376.9147 $[M+Na]^+$; found: 376.9163.

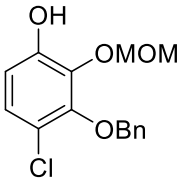
Synthesis of (4-(benzyloxy)-3-bromobenzyl)triphenylphosphonium bromide (236)



A SCHLENK flask was charged with **235** (150 mg, 0.421 mmol, 1.0 equiv.), PPh_3 (165 mg, 0.632 mmol, 1.5 equiv.) and toluene (2.2 mL). The reaction mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the precipitate was filtered off and washed with cold toluene. The product (4-(benzyloxy)-3-bromobenzyl)triphenylphosphonium bromide (**236**) (189 mg, 0.306 mmol, 73%) was obtained as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 – 7.67 (m, 9H), 7.67 – 7.53 (m, 6H), 7.42 – 7.21 (m, 6H), 6.91 (t, J = 2.4 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 5.47 (d, J = 14.1 Hz, 2H), 5.02 (s, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.9 (d, J = 3.9 Hz), 136.2, 135.6 (d, J = 5.0 Hz), 135.0 (d, J = 3.1 Hz), 134.6 (d, J = 9.8 Hz), 132.6 (d, J = 5.8 Hz), 130.2 (d, J = 12.6 Hz), 128.6, 120.7 (d, J = 8.7 Hz), 118.2, 117.4, 113.7 (d, J = 3.2 Hz), 112.00 (d, J = 3.8 Hz), 70.7, 29.6 (d, J = 46.8 Hz) ppm. **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 23.05 ppm. **IR** (neat): 3043, 3004, 2840, 2765, 1488, 1435, 1258, 1111, 1048, 718, 498 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{32}H_{27}{}^{79}BrOP^+$: 537.0977 $[M-Br]^+$; found: 537.0976.

Synthesis of 3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenol (239)

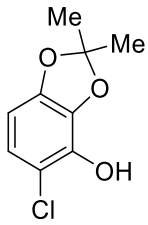


*m*CPBA (1.27 g, ~5.6 mmol, ≤77%, 2.1 equiv.) was added to a solution of **247** (810 mg, 2.64 mmol, 1.0 equiv.) in chloroform (5 mL) and the reaction mixture was stirred at room temperature for 24 h. Water (10 mL) was added, and the phases were separated. The aqueous phase was extracted with chloroform (2 x 10 mL). The combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. To the residue was added THF (12 mL) and NaOH (5 mL, 25%, aq.) and the solution was stirred at room temperature for 4 h. The solution

was acidified with hydrochloric acid (4 M) and ethyl acetate (25 mL) was added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 2%→25%) yielded 3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenol (**239**) (651 mg, 2.21 mmol, 84%) as a colorless solid.

R_f = 0.15 (ethyl acetate:hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.53 – 7.46 (m, 2H), 7.43 – 7.33 (m, 3H), 7.05 (d, J = 8.9 Hz, 1H), 6.77 – 6.68 (m, 2H), 5.04 (s, 2H), 5.03 (s, 2H), 3.55 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.2, 148.0, 140.2, 136.9, 128.63, 128.58, 128.5, 125.7, 119.4, 112.5, 100.2, 75.6, 57.8 ppm. **IR** (neat): 3349, 2913, 2833, 1450, 1208, 1040, 955, 907, 695 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{16}{}^{35}ClO_4^+$: 295.0732 $[M+H]^+$; found: 295.0733.

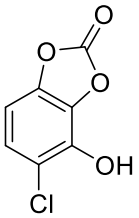
Synthesis of 5-chloro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (241c)



A flask was charged with **243** (3.12 g, 19.4 mmol, 1.0 equiv.), *p*TsOH·H_2O (100 mg, 0.526 mmol, 3 mol%), 2,2-dimethoxy propane (9.4 mL 76.7 mmol, 4.0 equiv.), acetone (94 mL) and benzene (312 mL). A SOXHLET extractor filled with molecular sieves (82 g, 4 Å) and a reflux condenser were attached and the reaction mixture was refluxed for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and aq. sat. $NaHCO_3$ (100 mL) and ethyl acetate (100 mL) were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→40%) yielded 5-chloro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-ol (**141c**) (1.89 g, 9.42 mmol, 49%) as a colorless solid.

R_f = 0.34 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.76 (d, J = 8.4 Hz, 1H), 6.34 (d, J = 8.5 Hz, 1H), 5.27 (s, 1H), 1.71 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.9, 136.0, 134.9, 120.6, 120.2, 113.7, 101.8, 25.9 ppm. **IR** (neat): 3442, 2998, 1636, 1460, 1297, 1206, 1110, 976, 772, 510 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_9H_{10}{}^{35}ClO_3^+$: 201.0313 $[M+H]^+$; found: 201.0318.

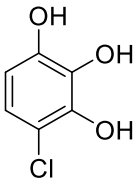
Synthesis of 5-chloro-4-hydroxybenzo[*d*][1,3]dioxol-2-one (241d)



TEA (0.86 mL, 6.22 mmol, 2.0 equiv.) was added to a solution of **243** (500 mg, 3.11 mmol, 1.0 equiv.) in dry THF (10 mL). Phosgene (2.2 mL, 3.11 mmol, 15% in toluene, 1.0 equiv.) was added dropwise to the reaction mixture, and stirring was continued for 22 h at room temperature. Water (25 mL) was added, and the solution was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→30%) yielded 5-chloro-4-hydroxybenzo[*d*][1,3]dioxol-2-one (**241d**) (270 mg, 1.45 mmol, 47%) as a crystalline solid.

R_f = 0.26 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 5.79 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.7, 143.3, 136.7, 131.2, 124.6, 117.5, 103.1 ppm. **IR** (neat): 3377, 3075, 1804, 1651, 1463, 1262, 1217, 1107, 795, 539 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_7H_2{}^{35}ClO_4^+$: 184.9647 $[M-H]^-$; found: 184.9649.

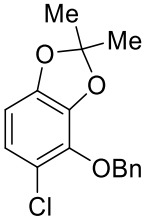
Synthesis of 4-chlorobenzene-1,2,3-triol (243)



A flask was charged with benzene-1,2,3-triol (5.00 g, 39.6 mmol, 1.07 equiv.), NCS (4.95 g, 37.1 mmol, 1.0 equiv.) and diethyl ether (1.5 L). The reaction mixture was stirred for 48 h at room temperature and the solvent was removed under reduced pressure. Column chromatography of the residue (ethyl acetate/hexane, 2/5) yielded 4-chlorobenzene-1,2,3-triol (**243**) (3.60 g, 22.4 mmol, 60%) as a colorless solid.

^{1}H NMR (300 MHz, Acetone): δ = 7.91 (s, 3H), 6.67 (d, J = 8.8 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, Acetone): δ =145.6, 143.1, 135.1, 120.0, 112.3, 108.3 ppm.

Synthesis of 4-(benzyloxy)-5-chloro-2,2-dimethylbenzo[*d*][1,3]dioxole (244)

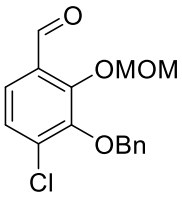


K_2CO_3 (1.10 g, 7.80 mmol, 2.8 equiv.) was added to a solution of **241c** (550 mg, 2.74 mmol, 1.0 equiv.) in DMF (9.5 mL). BnBr (0.42 mL, 3.53 mmol, 1.3 equiv.) was added to the suspension, and it was stirred for 20 h at room temperature. Water (25 mL) was added, and the solution was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed with water (2 x 25 mL) and brine (25 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane,

0%→15%) yielded 4-(benzyloxy)-5-chloro-2,2-dimethylbenzo[*d*][1,3]dioxole (**244**) (690 mg, 2.37 mmol, 86%) as a slightly yellow oil.

***R*f** = 0.60 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, Acetone): δ = 7.51 – 7.42 (m, 2H), 7.39 – 7.30 (m, 3H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 5.25 (s, 2H), 1.65 (s, 6H) ppm. **^{13}C NMR** (101 MHz, Acetone): δ = 147.9, 138.8, 138.4, 137.1, 128.5, 128.3, 128.2, 121.6, 119.4, 119.0, 103.6, 74.0, 25.9 ppm. **IR** (neat): 3032, 2990, 2937, 1473, 1455, 1270, 1208, 1049, 980, 695 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{16}H_{16}{}^{35}ClO_3^+$: 291.0782 $[M+H]^+$; found: 291.0790.

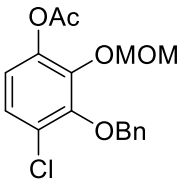
Synthesis of 3-(benzyloxy)-4-chloro-2-(methoxymethoxy)benzaldehyde (247)



*n*Buli (1.45 mL, 3.63 mmol, 2.5 M in hexane, 1.01 equiv.) was added dropwise to a solution of **158** (1.00 g, 3.59 mmol, 1.0 equiv.) in dry THF (9 mL) at -78°C. After stirring at this temperature for 1 h, dry DMF (0.5 mL) was added, and the solution was allowed to warm to room temperature overnight. Water (10 mL) was added, and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue*via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 3-(benzyloxy)-4-chloro-2-(methoxymethoxy)benzaldehyde (**247**) (860 mg, 2.80 mmol, 78%) as a colorless oil.

***R*f** = 0.44 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 10.39 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.44 – 7.37 (m, 3H), 7.27 (dd, *J* = 8.5, 0.8 Hz, 1H), 5.26 (s, 2H), 5.06 (s, 2H), 3.53 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 189.3, 154.7, 148.6, 136.3, 129.8, 128.7, 128.6, 126.2, 123.8, 100.5, 75.6, 58.3 ppm. **IR** (neat): 2951, 2880, 1688, 1579, 1434, 1254, 953, 698 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{16}H_{16}{}^{35}ClO_4^+$: 307.0732 $[M+H]^+$; found: 307.0724.

Synthesis of 3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenyl acetate (248)

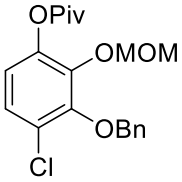


AcCl (0.17 mL, 2.43 mmol, 1.1 equiv.) was added to a solution of **239** (651 mg, 2.21 mmol, 1.0 equiv.) and pyridine (0.21 mL, 2.65 mmol, 1.2 equiv.) in dry DCM (9 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. Water (10 mL) was added, and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→30%) yielded 3-(benzyloxy)-4-chloro-2-

(methoxymethoxy)phenyl acetate (**248**) (705 mg, 2.09 mmol, 95%) as a colorless oil.

***R*f** = 0.30 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 – 7.46 (m, 2H), 7.45 – 7.29 (m, 3H), 7.15 (d, *J* = 8.9 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 1H), 5.13 (s, 2H), 5.05 (s, 2H), 3.53 (s, 3H), 2.34 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.8, 149.2, 144.0, 143.5, 136.6, 128.6, 128.5, 126.7, 124.9, 119.2, 99.4, 75.6, 57.6, 20.9 ppm. **IR** (neat): 3032, 2936, 2828, 1769, 1368, 1179, 1038, 946 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{18}{}^{35}ClO_5^+$: 337.0837 $[M+H]^+$; found: 337.0828.

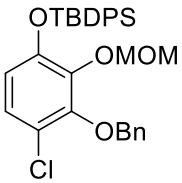
Synthesis of 3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenyl pivalate (249)



TEA (0.05 mL, 0.361 mmol, 2.1 equiv.) was added to a solution of **239** (50.0 mg, 0.170 mmol, 1.0 equiv.) in dry THF (0.5 mL). PivCl (25 µL, 0.203 mmol, 1.2 equiv.) was added to the reaction mixture, and it was stirred for 18 h at room temperature. Water (5 mL) was added, and the solution was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenyl pivalate (**249**) (55.1 mg, 0.145 mmol, 85%) as colorless oil.

***R*f** = 0.37 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.56 – 7.47 (m, 2H), 7.45 – 7.31 (m, 3H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 5.13 (s, 2H), 5.05 (s, 2H), 3.49 (s, 3H), 1.39 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 176.5, 149.2, 144.1, 143.7, 136.7, 128.6, 128.5, 126.4, 124.7, 119.2, 99.5, 75.6, 57.9, 39.2, 27.3 ppm. **IR** (neat): 2972, 1755, 1466, 1445, 1269, 1102, 946, 697 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{24}{}^{35}ClO_5^+$: 379.1307 $[M+H]^+$; found: 379.1302.

Synthesis of (3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenoxy)(*tert*-butyl)diphenylsilane (252)

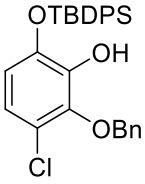


Silyl ether **252** was prepared according to **GP B** using phenol **239** (95.1 mg, 0.322 mmol) and TBDPSCl. Purification *via* ISOLERA flash chromatography (ethyl acetate/hexane 0%→10%) yielded (3-(benzyloxy)-4-chloro-2-(methoxymethoxy)phenoxy)(*tert*-butyl)diphenylsilane (**252**) (155 mg, 0.291 mmol, 90%) as a colorless oil.

***R*f** = 0.62 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.72 (dt, *J* = 6.6, 1.6 Hz, 4H), 7.58 – 7.50 (m, 2H), 7.46 – 7.28 (m, 9H), 6.67 (d, *J* = 9.0 Hz, 1H), 6.23 (d, *J* = 9.0 Hz, 1H), 5.28 (s, 2H), 5.06 (s, 2H), 3.56 (s, 3H), 1.12 (s, 9H) ppm. **^{13}C NMR** (101 MHz,

$CDCl_3$): δ = 149.4, 148.4, 142.7, 137.2, 135.6, 132.3, 130.3, 128.6, 128.5, 128.3, 128.0, 124.0, 121.0, 116.5, 99.1, 75.5, 57.8, 26.7, 19.6 ppm. **IR** (neat): 3070, 2930, 2857, 1469, 1428, 1058, 957, 822, 697 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{31}H_{34}{}^{35}ClO_4Si^+$: 533.1909 $[M+H]^+$; found: 533.1894.

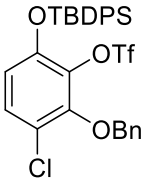
Synthesis of 2-(benzyloxy)-6-((*tert*-butyldiphenylsilyl)oxy)-3-chlorophenol (253)



HCl (2.4 mL, 4 M) was added to a solution of **252** (100 mg, 0.188 mmol, 1.0 equiv.) in acetone (5 mL) and the reaction mixture was stirred at 40 °C for 48 h. After cooling to room temperature, sat. aq. $NaHCO_3$ (10 mL) was added. The mixture was extracted with DCM (3 x 10 mL) and the combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue *via* ISOLERA flash chromatography (ethyl acetate/hexane, 0%→15%) yielded 2-(benzyloxy)-6-((*tert*-butyldiphenylsilyl)oxy)-3-chlorophenol (**253**) (66 mg, 0.135 mmol, 72%) as a colorless solid.

R_f = 0.61 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.76 – 7.65 (m, 4H), 7.59 – 7.50 (m, 2H), 7.49 – 7.30 (m, 9H), 6.50 (dd, *J* = 8.9, 0.7 Hz, 1H), 6.21 (d, *J* = 8.9 Hz, 1H), 5.69 (s, 1H), 5.12 (s, 2H), 1.13 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.7, 142.4, 141.7, 137.1, 135.5, 132.0, 130.4, 128.64, 128.60, 128.5, 128.1, 120.7, 119.4, 114.9, 75.2, 26.8, 19.7 ppm. **IR** (neat): 3522, 3070, 2930, 2857, 1470, 1208, 1046, 697 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{29}H_{30}{}^{35}ClO_3Si^+$: 489.1647 $[M+H]^+$; found: 489.1643.

Synthesis of 2-(benzyloxy)-6-((*tert*-butyldiphenylsilyl)oxy)-3-chlorophenyl trifluoromethanesulfonate (254)



Triflate **254** was prepared according to **GP A** using phenol **253** (106 mg, 0.217 mmol). After purificationa *via* ISOLERA flash chromatography (ethyl acetate/hexane 0%→20%), 2-(benzyloxy)-6-((*tert*-butyldiphenylsilyl)oxy)-3-chlorophenyl trifluoromethanesulfonate (**254**) (44 mg, 70.8 µmol, 33%) was obtained as a colorless solid.

R_f = 0.64 (ethyl acetate/hexane, 1/4). **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.75 – 7.69 (m, 4H), 7.50 – 7.44 (m, 4H), 7.44 – 7.34 (m, 7H), 6.83 (d, *J* = 9.2 Hz, 1H), 6.17 (d, *J* = 9.2 Hz, 1H), 5.08 (s, 2H), 1.10 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 148.1, 147.9, 135.7, 135.5, 135.5, 131.2, 130.5, 129.0, 128.8, 128.54, 128.45, 128.3, 120.8, 118.7 (q, *J* = 320.8 Hz), 116.5, 76.3, 26.1, 19.4 ppm. **^{19}F NMR** (565 MHz, $CDCl_3$): δ = -73.33 ppm. **IR** (neat): 3036, 2959, 2858, 1476, 1424, 1063, 795, 696, 597 cm^{-1}. **HRMS** (ESI) *m/z* calcd for $C_{30}H_{28}{}^{35}ClF_3O_5SSi^+$:

643.0960 $[M+H]^+$; found: 643.0956.

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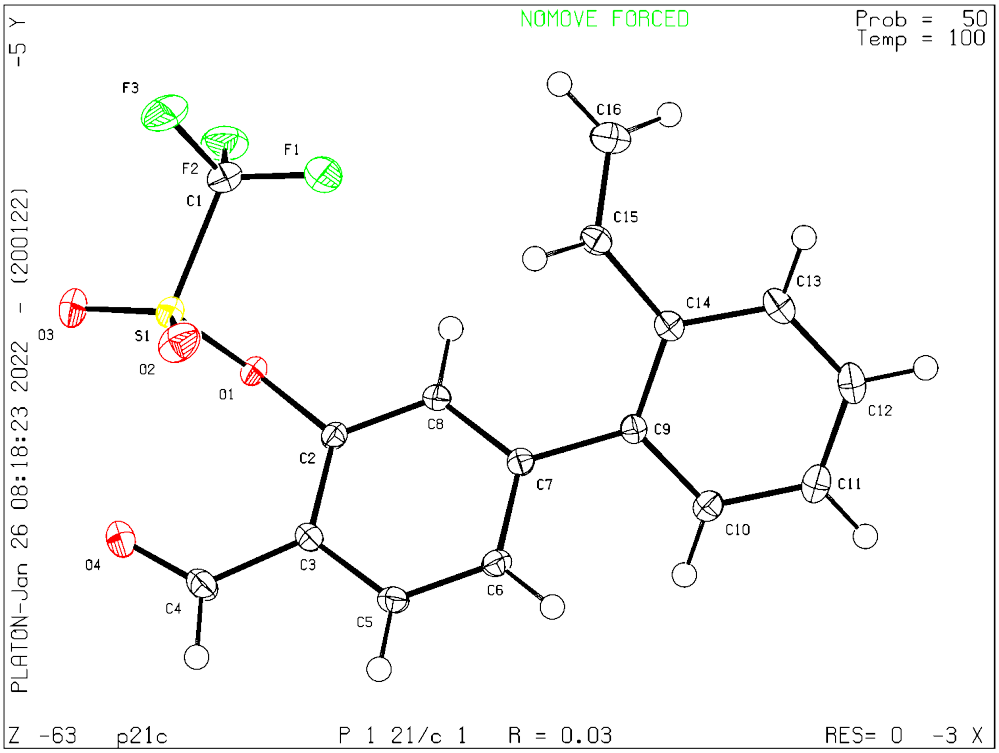
5. Appendix

5.1. Single crystal X-ray diffraction analysis

Refinement table and ORTEP plot for **107**



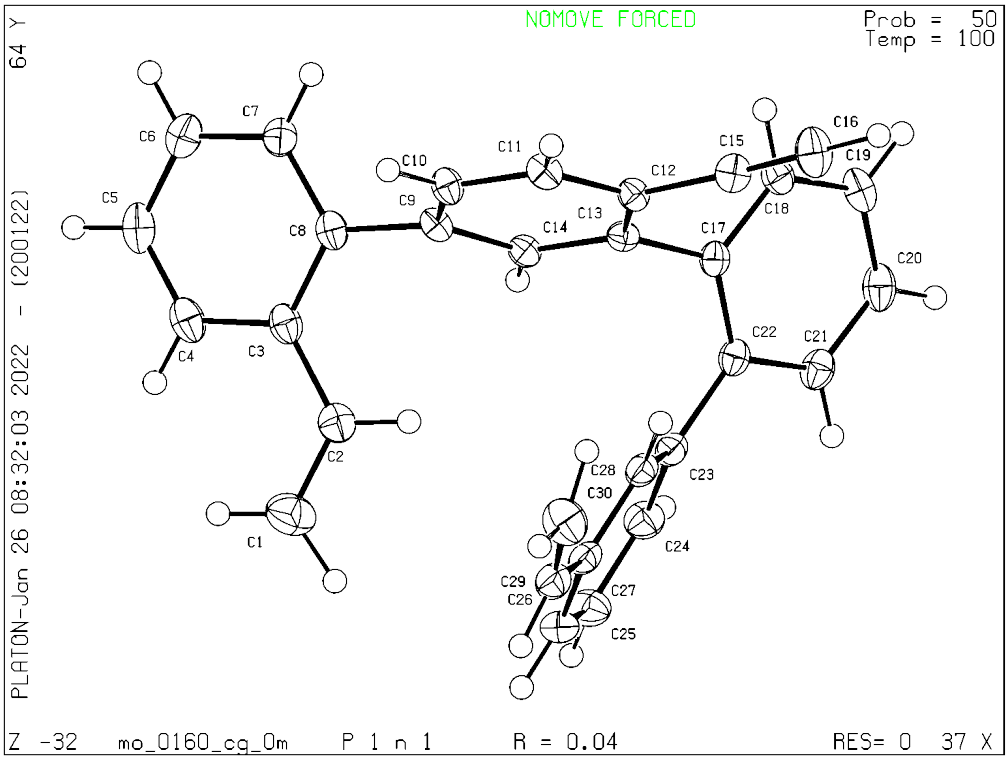
Internal number	0091
Empirical formula	$C_{16}H_{11}F_3O_4S$
Formula weight	356.31
Temperature [K]	99.98
Crystal system	monoclinic
Space group (number)	$P2_1/c$ (14)
a [Å]	14.5671(7)
b [Å]	14.4076(7)
c [Å]	7.2298(4)
α [°]	90
β [°]	94.217(2)
γ [°]	90
Volume [Å^3]	1513.26(13)
Z	4
ρ_{calc} [gcm^{-3}]	1.564
μ [mm^{-1}]	0.266
F(000)	728
Crystal size [mm^3]	0.244×0.138×0.116
Crystal colour	colourless

Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)
2Θ range [°]	5.66 to 59.15 (0.72 Å)
Index ranges	-20 ≤ h ≤ 20 -19 ≤ k ≤ 19 -10 ≤ l ≤ 10
Reflections collected	23578
Independent reflections	4234 R_{int} = 0.0239 R_{sigma} = 0.0169
Completeness to Θ = 25.242°	99.7 %
Data / Restraints / Parameters	4234/0/225
Goodness-of-fit on F^2	1.026
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0325 wR_2 = 0.0865

Final *R* indexes [all data]	R_1 = 0.0356 wR_2 = 0.0889

Largest peak/hole [eÅ^{-3}]	0.44/-0.44

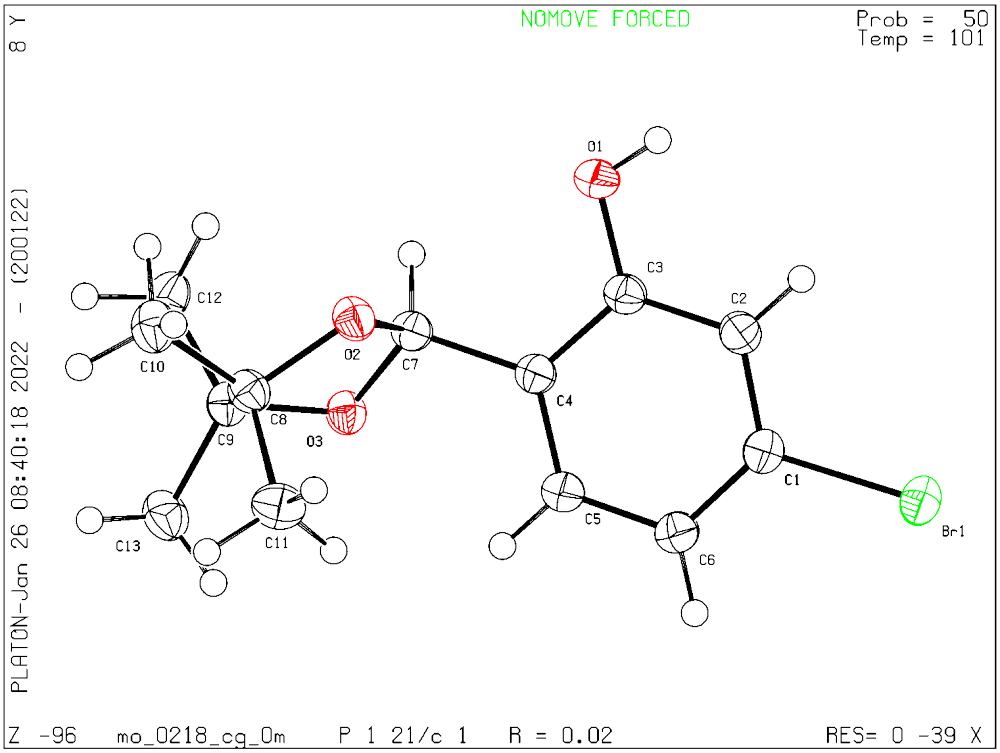
Refinement table and ORTEP plot for **119**



Internal number	0160
Empirical formula	$C_{30}H_{22}$
Formula weight	382.47
Temperature [K]	100.0
Crystal system	monoclinic
Space group (number)	*Pn* (7)
a [Å]	7.2509(4)
b [Å]	8.3860(4)
c [Å]	17.8288(10)
α [°]	90
β [°]	101.422(2)
γ [°]	90
Volume [Å^3]	1062.63(10)
Z	2
ρ_{calc} [gcm^{-3}]	1.195
μ [mm^{-1}]	0.068
F(000)	404
Crystal size [mm^3]	0.234×0.136×0.036
Crystal colour	colourless
Crystal shape	plate
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	4.66 to 57.42 (0.74 Å)
Index ranges	$-9 \le h \le 9$ $-11 \le k \le 11$ $-24 \le l \le 24$
Reflections collected	23007
Independent reflections	5445 R_{int} = 0.0294 R_{sigma} = 0.0273
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	5445/2/287
Goodness-of-fit on F^2	1.053
Final *R* indexes [$I \ge 2\sigma(I)$]	R_1 = 0.0363 wR_2 = 0.0894
Final *R* indexes [all data]	R_1 = 0.0393 wR_2 = 0.0914
Largest peak/hole [eÅ^{-3}]	0.25/-0.19
Flack X parameter	0.2(10)

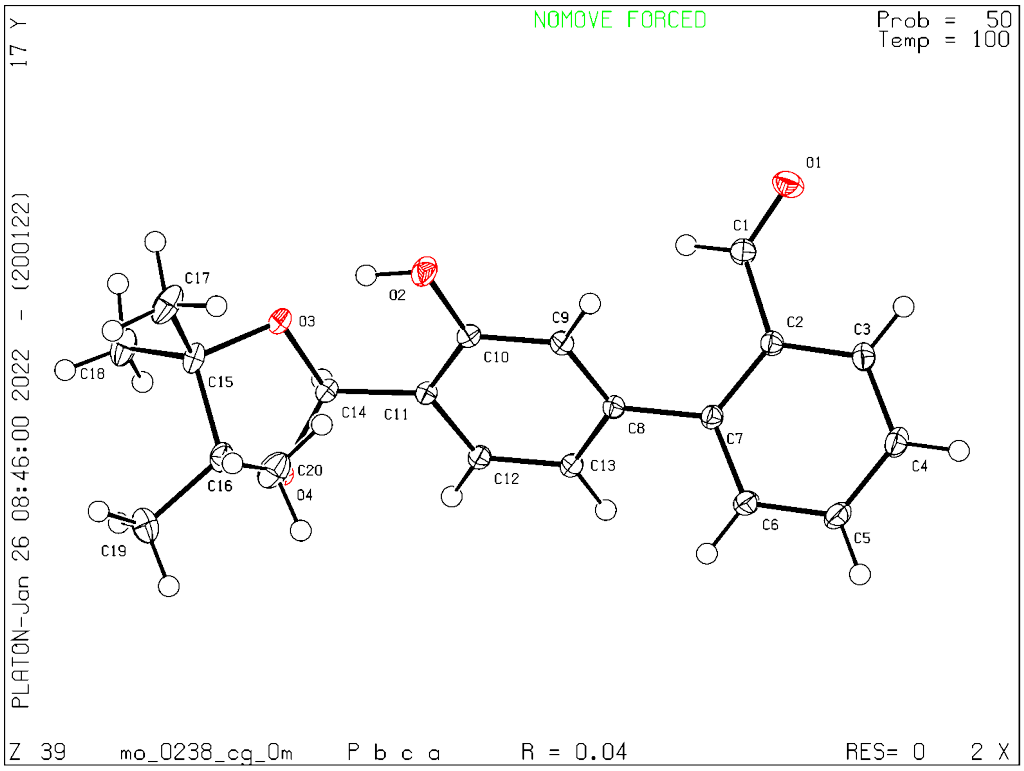
Refinement table and ORTEP plot for **127**



Internal number	0218
Empirical formula	$C_{13}H_{17}BrO_3$
Formula weight	301.17
Temperature [K]	100.88
Crystal system	monoclinic
Space group (number)	$P2_1/c$ (14)
a [Å]	11.1293(8)
b [Å]	8.1459(7)
c [Å]	14.9603(9)
α [°]	90
β [°]	101.276(3)
γ [°]	90
Volume [Å^3]	1330.09(17)
Z	4
ρ_{calc} [gcm^{-3}]	1.504
μ [mm^{-1}]	3.085
F(000)	616
Crystal size [mm^3]	0.261×0.197×0.051
Crystal colour	colourless
Crystal shape	plate
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	5.55 to 65.22 (0.66 Å)
Index ranges	-16 ≤ h ≤ 16 -12 ≤ k ≤ 12 -22 ≤ l ≤ 22
Reflections collected	50893
Independent reflections	4847 R_{int} = 0.0257 R_{sigma} = 0.0150
Completeness to Θ = 25.242°	99.8 %
Data / Restraints / Parameters	4847/1/161
Goodness-of-fit on F^2	1.086
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0226 wR_2 = 0.0650
Final *R* indexes [all data]	R_1 = 0.0244 wR_2 = 0.0657
Largest peak/hole [eÅ^{-3}]	0.65/-0.28

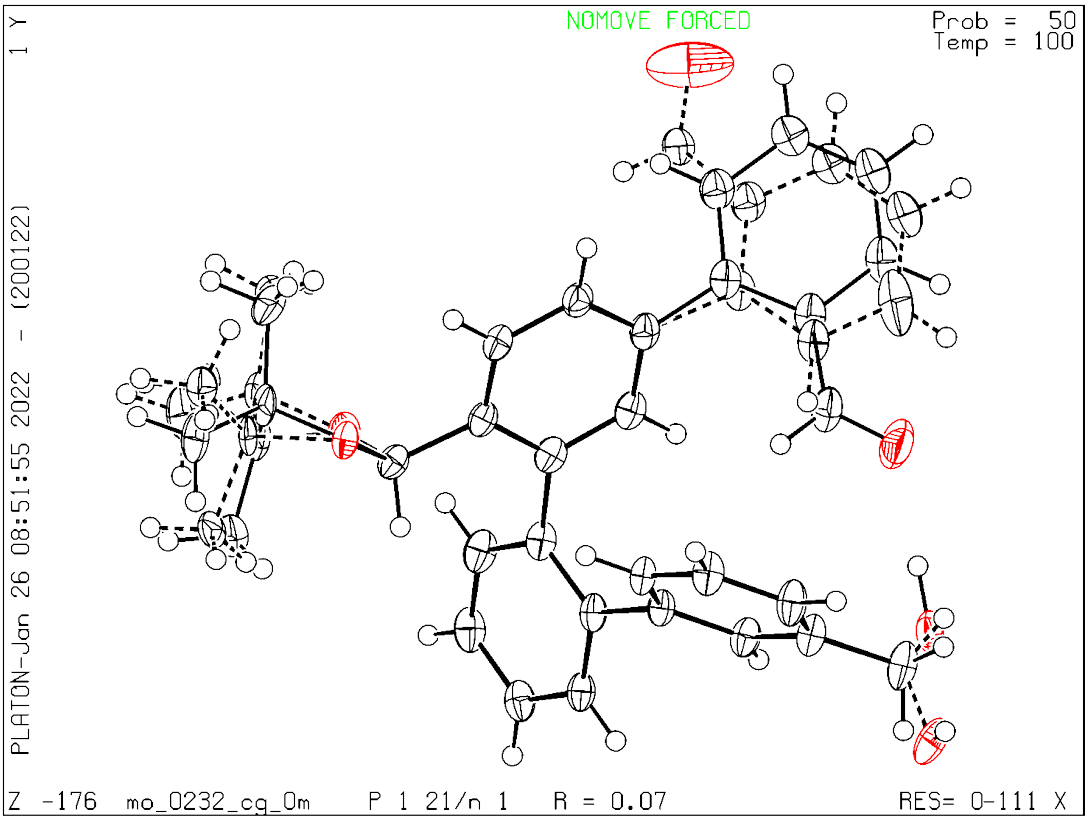
Refinement table and ORTEP plot for **131**



Internal number	0238
Empirical formula	$C_{20}H_{22}O_4$
Formula weight	326.37
Temperature [K]	100.01
Crystal system	orthorhombic
Space group (number)	*Pbca* (61)
a [Å]	13.2011(10)
b [Å]	15.0975(9)
c [Å]	17.1446(11)
α [°]	90
β [°]	90
γ [°]	90
Volume [Å^3]	3417.0(4)
Z	8
ρ_{calc} [gcm^{-3}]	1.269
μ [mm^{-1}]	0.087
F(000)	1392
Crystal size [mm^3]	0.363×0.322×0.23
Crystal colour	colourless
Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	4.74 to 63.05 (0.68 Å)
Index ranges	-19 ≤ h ≤ 19 -22 ≤ k ≤ 22 -25 ≤ l ≤ 25
Reflections collected	85316
Independent reflections	5689 R_{int} = 0.0190 R_{sigma} = 0.0104
Completeness to Θ = 25.242°	99.8 %
Data / Restraints / Parameters	5689/0/224
Goodness-of-fit on F^2	1.055
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0360 wR_2 = 0.1034
Final *R* indexes [all data]	R_1 = 0.0376 wR_2 = 0.1048
Largest peak/hole [eÅ^{-3}]	0.47/-0.22

Refinement table and ORTEP plot for **135**



Structural Comment: Two separate positional disorder were found. The lactone rotates by 180 degree and the occupancy factor was refined to 0.578(5). The second disorder contains mainly the phenyl aldehyde fragment which changes between intramolecular and intermolecular hydrogen bond to the benzylic alcohol, the occupancy factor was refined to a value of 0.911(4) in favor of the former.

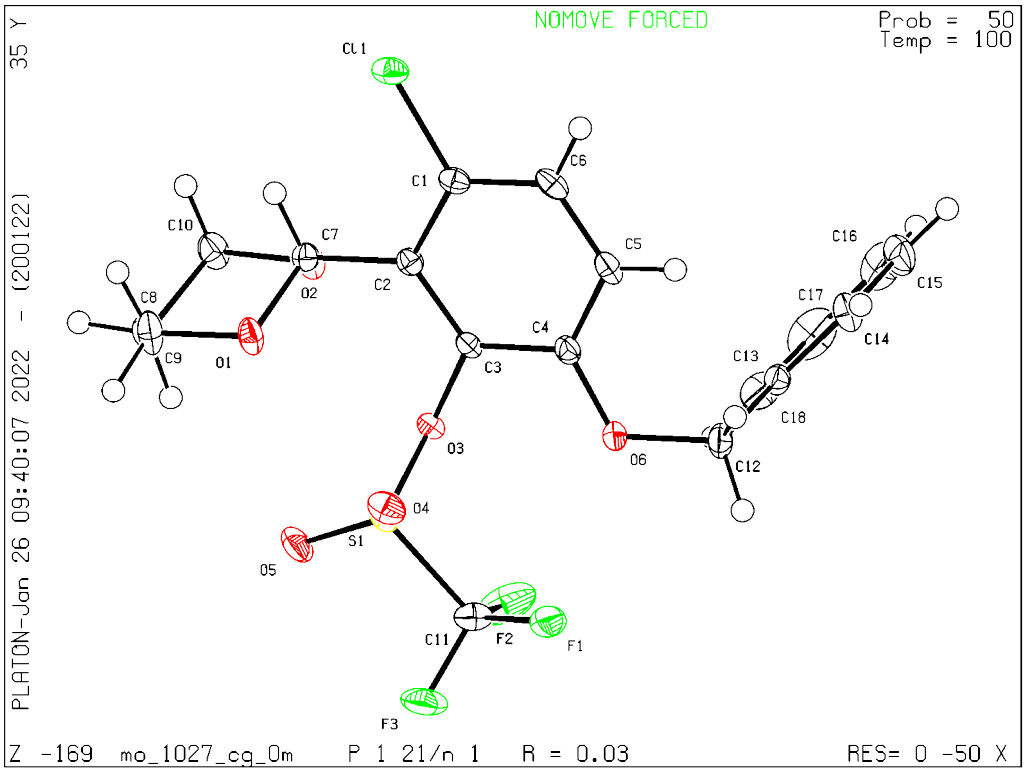
Internal number	0232
Empirical formula	$C_{33}H_{32}O_4$
Formula weight	492.58
Temperature [K]	99.98
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	14.095(3)
b [Å]	7.7155(19)
c [Å]	24.055(6)
α [°]	90
β [°]	99.600(6)
γ [°]	90
Volume [Å^3]	2579.4(10)
Z	4
ρ_{calc} [gcm^{-3}]	1.268
μ [mm^{-1}]	0.082
F(000)	1048

Crystal size [mm^3]	0.25×0.223×0.061
Crystal colour	colourless
Crystal shape	plate
Radiation	MoK_α (λ=0.71073 Å)
2Θ range [°]	5.49 to 57.65 (0.74 Å)
Index ranges	-19 ≤ h ≤ 16 -8 ≤ k ≤ 10 -29 ≤ l ≤ 32
Reflections collected	20429
Independent reflections	6681 R_{int} = 0.0573 R_{sigma} = 0.0676
Completeness to Θ = 25.242°	99.8 %
Data / Restraints / Parameters	6681/1/445

Goodness-of-fit on F^2	1.034
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0699 wR_2 = 0.1649

Final R indexes [all data]	R_1 = 0.0984 wR_2 = 0.1786
Largest peak/hole [eÅ^{-3}]	0.37/-0.35

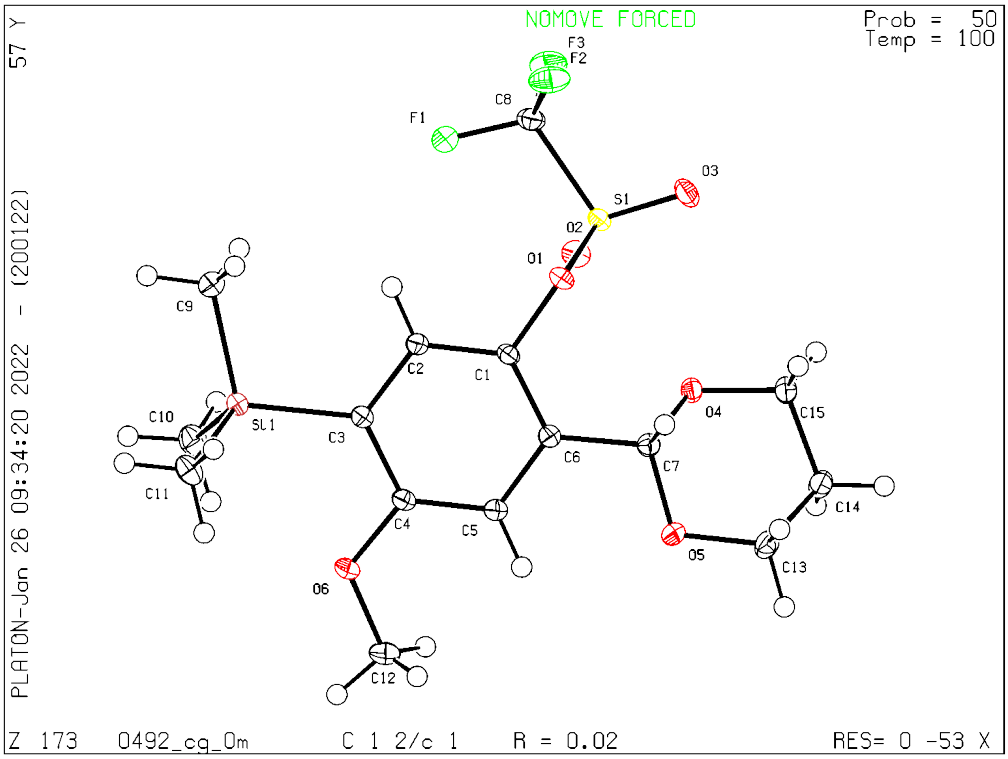
Refinement table and ORTEP plot for 142



Internal number	1027
Empirical formula	$C_{18}H_{16}ClF_3O_6S$
Formula weight	452.82
Temperature [K]	100.0
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	10.9041(12)
b [Å]	9.1374(8)
c [Å]	19.2956(17)
α [°]	90
β [°]	103.451(3)
γ [°]	90
Volume [Å^3]	1869.8(3)
Z	4
ρ_{calc} [gcm^{-3}]	1.609
μ [mm^{-1}]	0.380
F(000)	928
Crystal size [mm^3]	0.454×0.118×0.084
Crystal colour	colourless
Crystal shape	needle
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	4.34 to 63.11 (0.68 Å)
Index ranges	-16 ≤ h ≤ 14 -13 ≤ k ≤ 12 -28 ≤ l ≤ 28
Reflections collected	88027
Independent reflections	6140 R_{int} = 0.0314 R_{sigma} = 0.0153
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	6140/0/262
Goodness-of-fit on F^2	1.045
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0290 wR_2 = 0.0702
Final *R* indexes [all data]	R_1 = 0.0336 wR_2 = 0.0733
Largest peak/hole [eÅ^{-3}]	0.42/-0.41

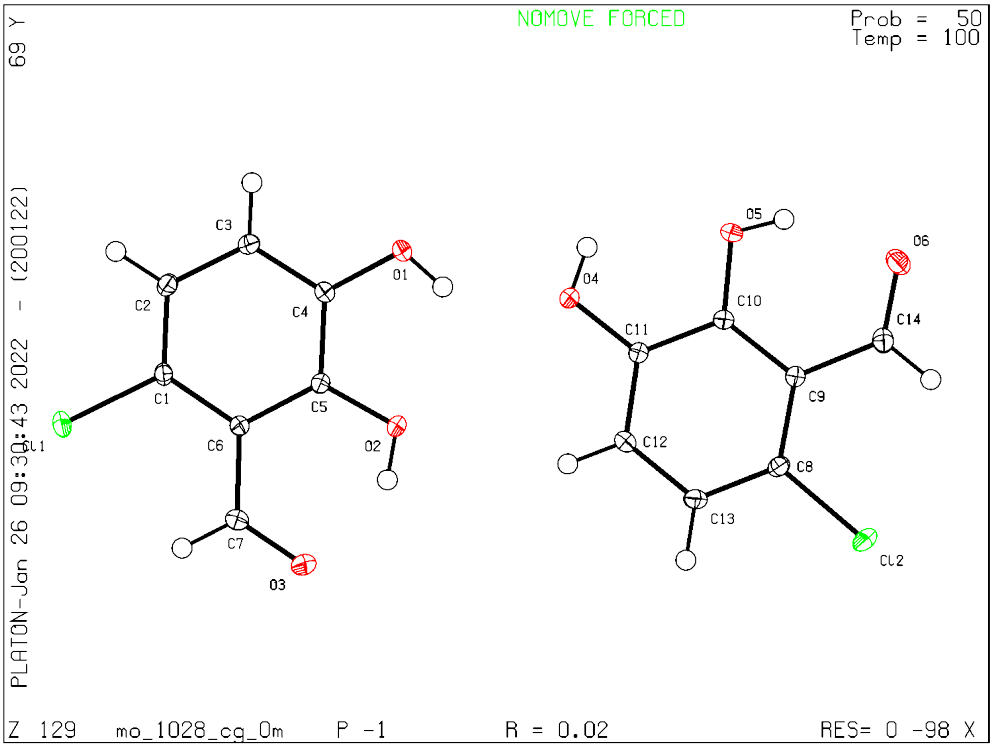
Refinement table and ORTEP plot for 143



Internal number	0492
Empirical formula	$C_{15}H_{21}F_3O_6SSi$
Formula weight	414.47
Temperature [K]	100.03
Crystal system	monoclinic
Space group (number)	$C2/c$ (15)
a [Å]	22.5592(10)
b [Å]	8.3945(3)
c [Å]	22.0471(10)
α [°]	90
β [°]	114.5590(10)
γ [°]	90
Volume [Å^3]	3797.4(3)
Z	8
ρ_{calc} [gcm^{-3}]	1.450
μ [mm^{-1}]	0.290
F(000)	1728
Crystal size [mm^3]	0.489×0.32×0.31
Crystal colour	colourless
Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	5.24 to 65.18 (0.66 Å)
Index ranges	-34 ≤ h ≤ 34 -12 ≤ k ≤ 12 -33 ≤ l ≤ 33
Reflections collected	59138
Independent reflections	6918 R_{int} = 0.0245 R_{sigma} = 0.0140
Completeness to Θ = 25.242°	99.5 %
Data / Restraints / Parameters	6918/0/239
Goodness-of-fit on F^2	1.057
Final R indexes [I≥2σ(I)]	R_1 = 0.0249 wR_2 = 0.0704
Final R indexes [all data]	R_1 = 0.0267 wR_2 = 0.0717
Largest peak/hole [eÅ^{-3}]	0.50/-0.36

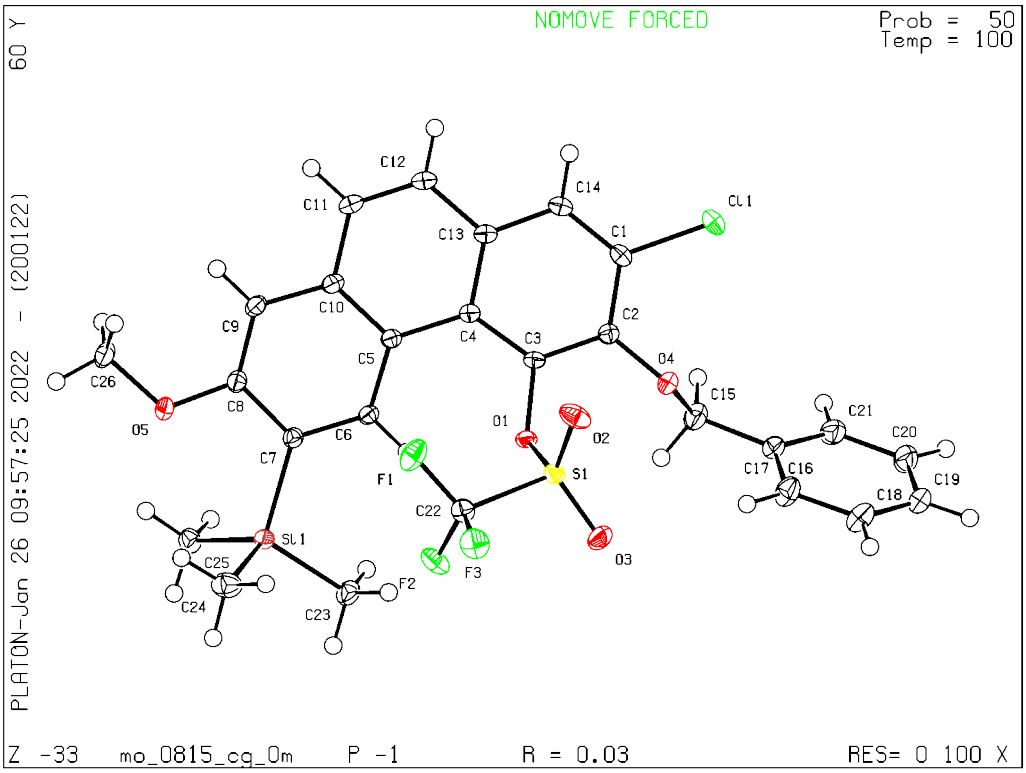
Refinement table and ORTEP plot for **169**



Internal number	1028
Empirical formula	$C_7H_5ClO_3$
Formula weight	172.56
Temperature [K]	100.0
Crystal system	triclinic
Space group (number)	$P\overline{1}$ (2)
a [Å]	6.9861(7)
b [Å]	7.8898(6)
c [Å]	13.6893(16)
α [°]	85.525(4)
β [°]	86.903(4)
γ [°]	64.863(4)
Volume [Å^3]	680.82(12)
Z	4
ρ_{calc} [gcm^{-3}]	1.684
μ [mm^{-1}]	0.505
F(000)	352
Crystal size [mm^3]	0.449×0.156×0.072
Crystal colour	yellow
Crystal shape	plank
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	5.71 to 63.08 (0.68 Å)
Index ranges	-10 ≤ h ≤ 10 -11 ≤ k ≤ 11 -20 ≤ l ≤ 20
Reflections collected	72255
Independent reflections	4534 R_{int} = 0.0173 R_{sigma} = 0.0084
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	4534/0/203
Goodness-of-fit on F^2	1.079
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0220 wR_2 = 0.0664
Final *R* indexes [all data]	R_1 = 0.0227 wR_2 = 0.0670
Largest peak/hole [eÅ^{-3}]	0.54/-0.26

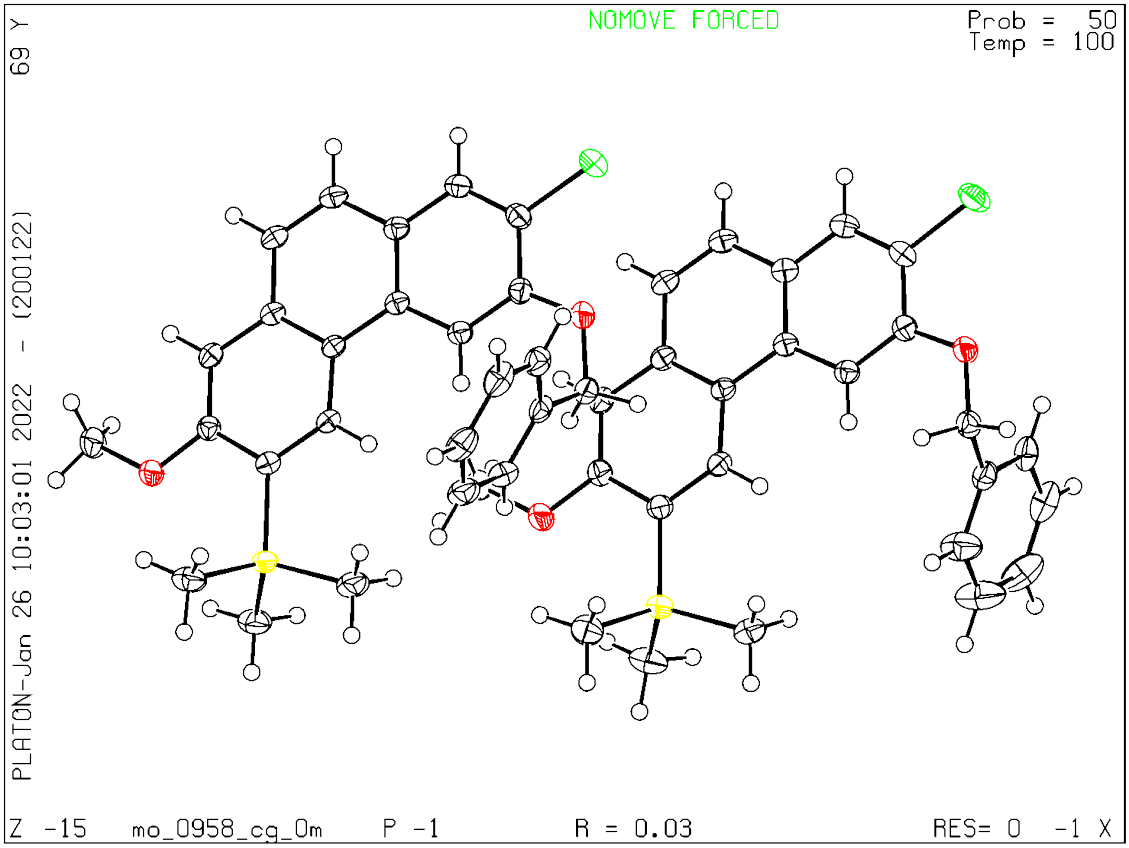
Refinement table and ORTEP plot for **208**



Internal number	0815
Empirical formula	$C_{26}H_{24}ClF_3O_5SSi$
Formula weight	569.05
Temperature [K]	100.0
Crystal system	triclinic
Space group (number)	$P\bar{1}$ (2)
a [Å]	8.7187(8)
b [Å]	11.9157(10)
c [Å]	14.0456(11)
α [°]	112.864(3)
β [°]	100.412(2)
γ [°]	97.769(2)
Volume [Å^3]	1287.99(19)
Z	2
ρ_{calc} [gcm^{-3}]	1.467
μ [mm^{-1}]	0.334
F(000)	588
Crystal size [mm^3]	0.32×0.32×0.285
Crystal colour	colourless
Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	3.81 to 61.06 (0.70 Å)
Index ranges	-12 ≤ h ≤ 12 -17 ≤ k ≤ 16 -20 ≤ l ≤ 20
Reflections collected	54584
Independent reflections	7865 R_{int} = 0.0259 R_{sigma} = 0.0166
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	7865/0/338
Goodness-of-fit on F^2	1.041
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0270 wR_2 = 0.0720
Final *R* indexes [all data]	R_1 = 0.0301 wR_2 = 0.0741
Largest peak/hole [eÅ^{-3}]	0.43/-0.38

Refinement table and ORTEP plot for **208a**



Crystal structure has one void that contains one molecule of severely disordered hexane. Solvent mask with standard settings was used to remove it.

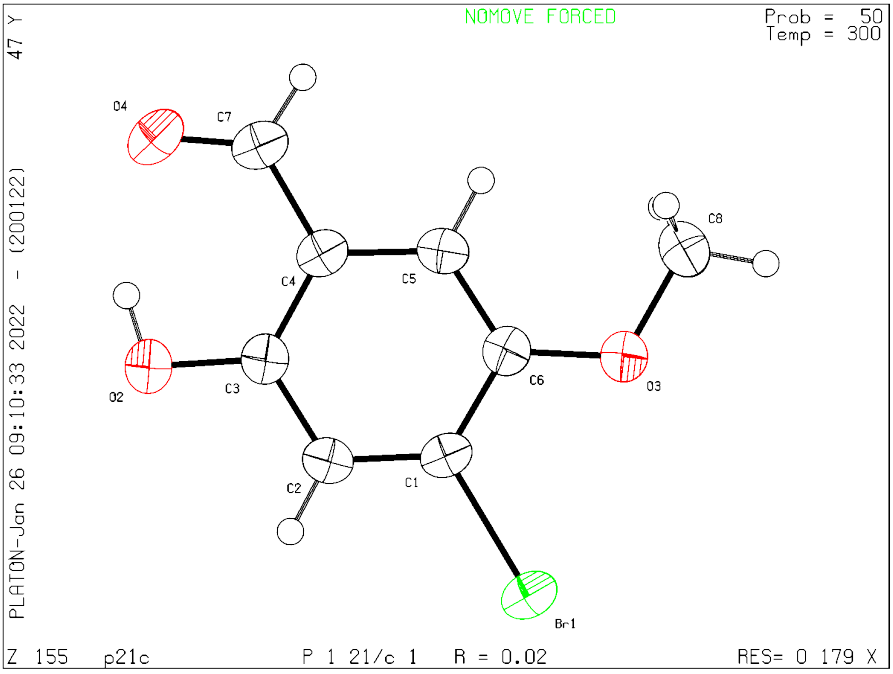
Internal number	0958
Empirical formula	$C_{26.50}H_{28.50}ClO_2Si$
Formula weight	442.53
Temperature [K]	100.0
Crystal system	triclinic
Space group (number)	$P\bar{1}$ (2)
a [Å]	9.9055(12)
b [Å]	14.4673(16)
c [Å]	18.768(2)
α [°]	104.278(5)
β [°]	103.672(4)
γ [°]	106.701(3)
Volume [Å^3]	2355.8(5)
Z	4
ρ_{calc} [gcm^{-3}]	1.248
μ [mm^{-1}]	0.234
F(000)	938
Crystal size [mm^3]	0.179×0.119×0.038
Crystal colour	colourless

Crystal shape	plate
Radiation	MoK_α (λ=0.71073 Å)
2Θ range [°]	4.38 to 55.76 (0.76 Å)
Index ranges	-13 ≤ h ≤ 13 -19 ≤ k ≤ 19 -24 ≤ l ≤ 24
Reflections collected	170407
Independent reflections	11202 R_{int} = 0.0322 R_{sigma} = 0.0135
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	11202/0/531
Goodness-of-fit on F^2	1.040
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0343 wR_2 = 0.0947

Final *R* indexes [all data]	R_1 = 0.0419 wR_2 = 0.1011

Largest peak/hole [eÅ^{-3}]	0.37/-0.48

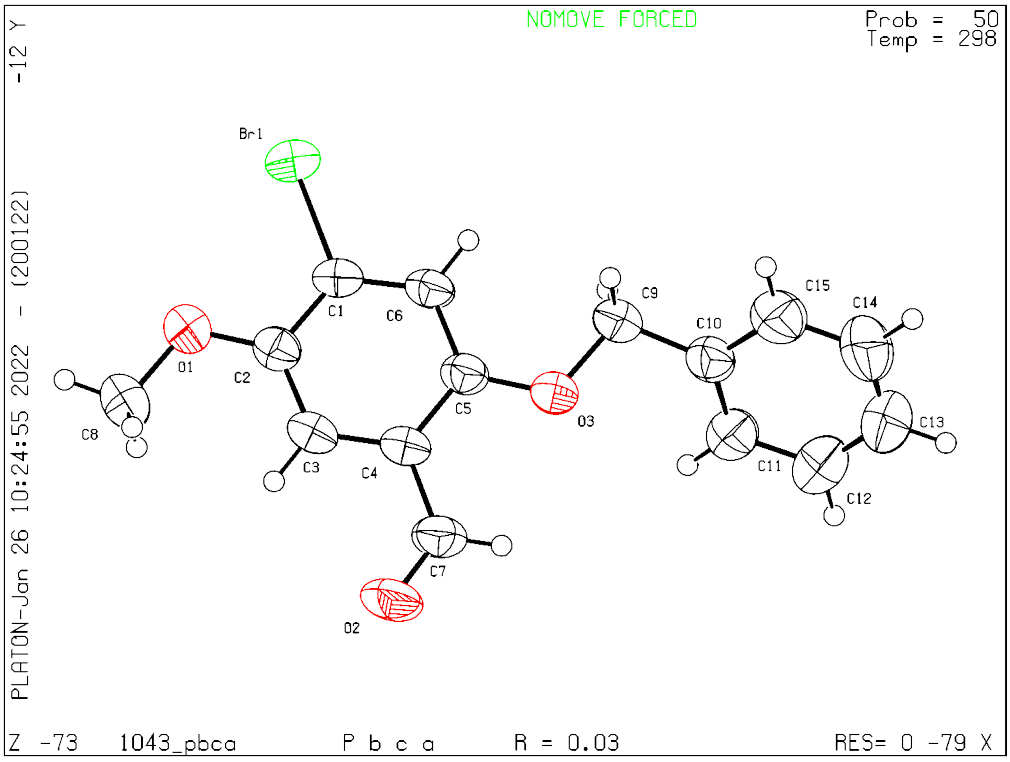
Refinement table and ORTEP plot for **220**



Internal number	0356
Empirical formula	$C_8H_7BrO_3$
Formula weight	231.05
Temperature [K]	300
Crystal system	monoclinic
Space group (number)	$P2_1/c$ (14)
a [Å]	8.574(2)
b [Å]	13.521(4)
c [Å]	7.692(2)
α [°]	90
β [°]	112.966(9)
γ [°]	90
Volume [Å^3]	821.1(4)
Z	4
ρ_{calc} [gcm^{-3}]	1.869
μ [mm^{-1}]	4.966
F(000)	456
Crystal size [mm^3]	0.342×0.216×0.2
Crystal colour	colourless
Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	5.16 to 59.45 (0.72 Å)
Index ranges	-11 ≤ h ≤ 11 -18 ≤ k ≤ 18 -10 ≤ l ≤ 10
Reflections collected	31428
Independent reflections	2326 R_{int} = 0.0338 R_{sigma} = 0.0163
Completeness to Θ = 25.242°	99.8 %
Data / Restraints / Parameters	2326/1/113
Goodness-of-fit on F^2	1.086
Final *R* indexes [I≥2σ(I)]	R_1 = 0.0228 wR_2 = 0.0547
Final *R* indexes [all data]	R_1 = 0.0265 wR_2 = 0.0562
Largest peak/hole [eÅ^{-3}]	0.34/-0.30

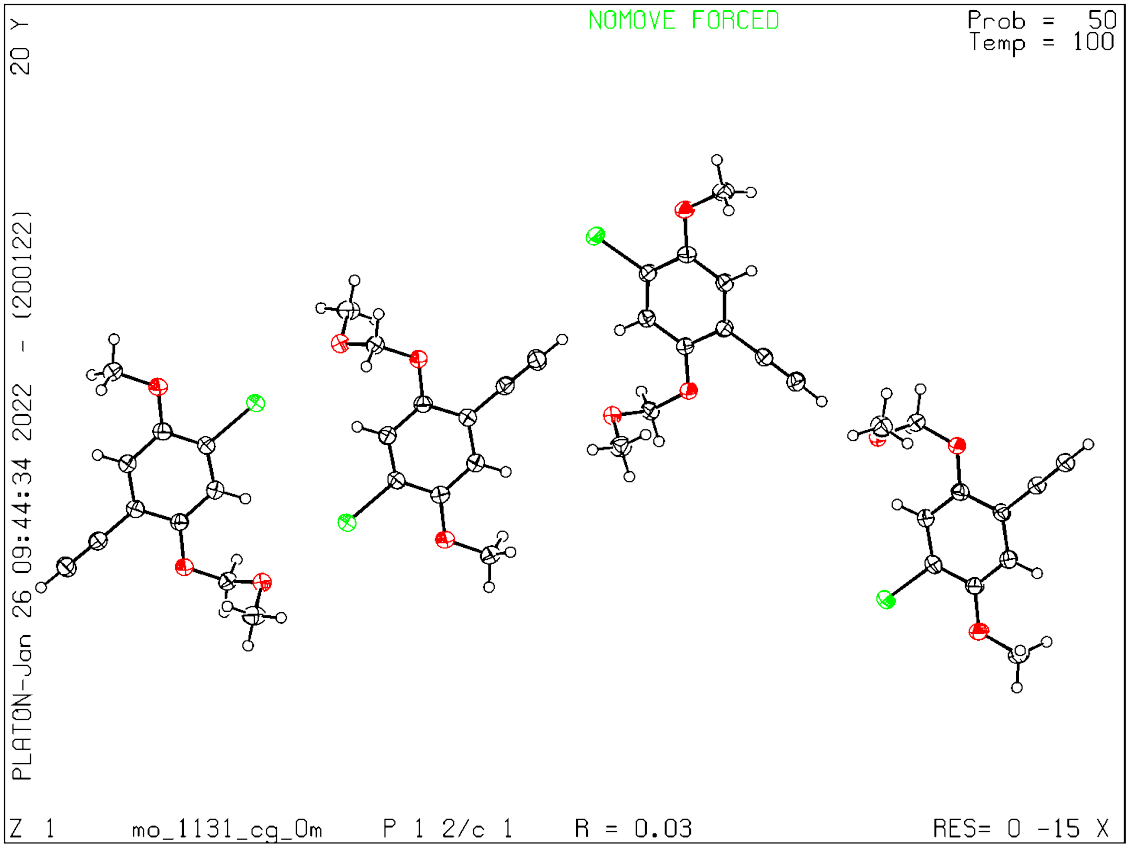
Refinement table and ORTEP plot for **225**



Internal number	1043
Empirical formula	$C_{15}H_{13}BrO_3$
Formula weight	321.16
Temperature [K]	298.0
Crystal system	orthorhombic
Space group (number)	*Pbca* (61)
a [Å]	15.5462(12)
b [Å]	6.8351(4)
c [Å]	26.468(2)
α [°]	90
β [°]	90
γ [°]	90
Volume [Å^3]	2812.4(4)
Z	8
ρ_{calc} [gcm^{-3}]	1.517
μ [mm^{-1}]	2.924
F(000)	1296
Crystal size [mm^3]	0.249×0.213×0.1
Crystal colour	colourless
Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)

2Θ range [°]	5.24 to 54.22 (0.78 Å)
Index ranges	-19 ≤ h ≤ 19 -8 ≤ k ≤ 8 -33 ≤ l ≤ 33
Reflections collected	33108
Independent reflections	3100 R_{int} = 0.0248 R_{sigma} = 0.0133
Completeness to Θ = 25.242°	99.8 %
Data / Restraints / Parameters	3100/0/173
Goodness-of-fit on F^2	1.042
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0299 wR_2 = 0.0780
Final *R* indexes [all data]	R_1 = 0.0369 wR_2 = 0.0824
Largest peak/hole [eÅ^{-3}]	0.18/-0.49

Refinement table and ORTEP plot for **228**



CheckCIF/Addsym detects additional symmetry plane and suggests space group P2/c instead, with half sized unit cell. However, the model in the smaller unit cell has slightly worse R value and rather unhealthy-looking ellipsoids. Apparently, the thermal motion is breaking the symmetry here, so the bigger unit cell was favored in this case.

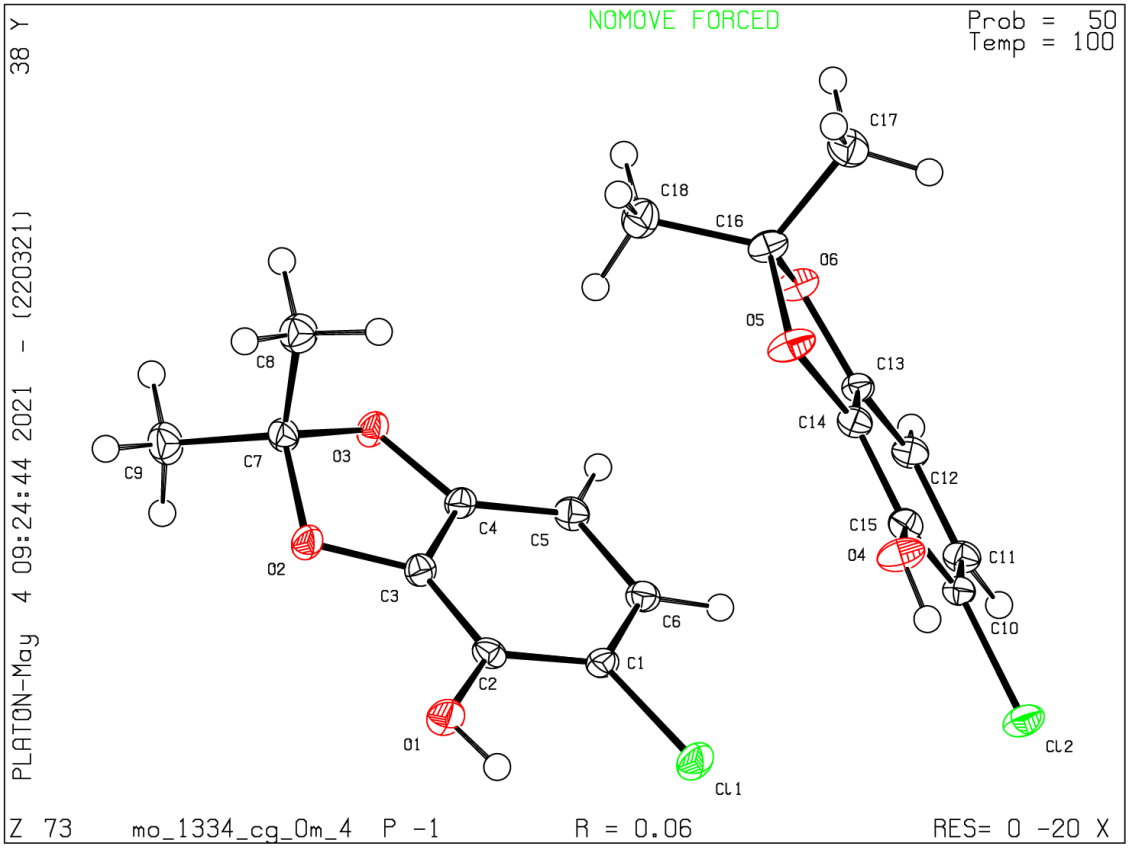
Internal number	1131
Empirical formula	$C_{11}H_{11}BrO_3$
Formula weight	271.11
Temperature [K]	100.0
Crystal system	monoclinic
Space group (number)	$P2/c$ (13)
a [Å]	16.3447(18)
b [Å]	9.0997(12)
c [Å]	31.002(4)
α [°]	90
β [°]	101.170(4)
γ [°]	90
Volume [Å^3]	4523.7(10)
Z	16
ρ_{calc} [gcm^{-3}]	1.592
μ [mm^{-1}]	3.619

F(000)	2176
Crystal size [mm^3]	0.35×0.242×0.064
Crystal colour	colourless
Crystal shape	plate
Radiation	MoK_α (λ=0.71073 Å)
2Θ range [°]	4.03 to 59.27 (0.72 Å)
Index ranges	-22 ≤ h ≤ 22 -12 ≤ k ≤ 12 -43 ≤ l ≤ 42
Reflections collected	145964
Independent reflections	12730 R_{int} = 0.0430 R_{sigma} = 0.0246
Completeness to Θ = 25.242°	100.0 %

Data / Restraints / Parameters	12730/0/549
Goodness-of-fit on F^2	1.068
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0298$ w$R_2 = 0.0724$

Final R indexes [all data]	$R_1 = 0.0439$ w$R_2 = 0.0798$
Largest peak/hole [eÅ^{-3}]	0.88/-0.38

Refinement table and ORTEP plot for **141c**



Non-merohedral twinning was detected for the crystal. The twin transformation matrix was found to be (-0.007 0.055 0.983 / 0.996 0.017 0.013 / 0.013 1.013 -0.148). Final refinement against hklf5 data with refined batch scale factor of 0.583(2).

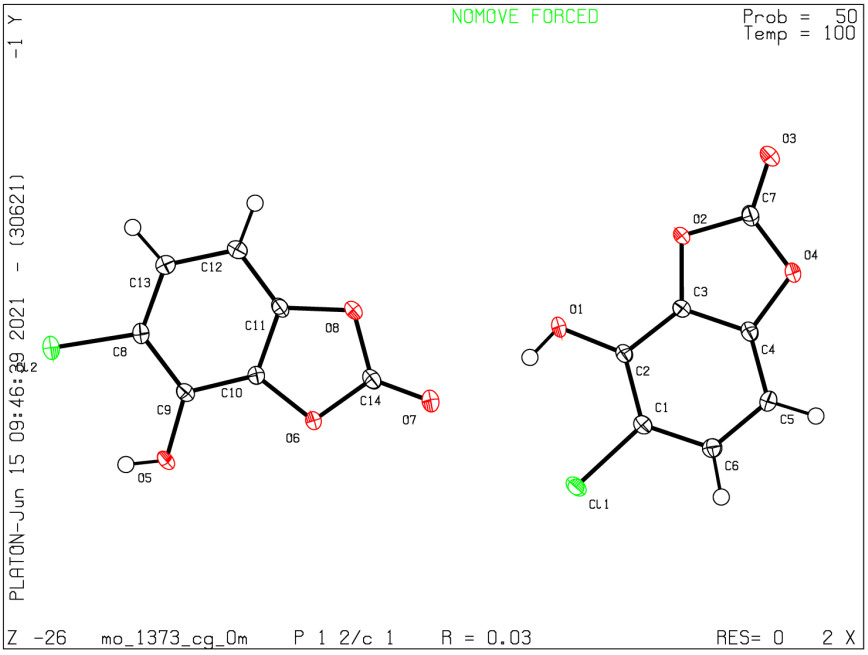
Internal number	1334
Empirical formula	$C_9H_9ClO_3$
Formula weight	200.61
Temperature [K]	100.0
Crystal system	triclinic
Space group (number)	$P\bar{1}$ (2)
a [Å]	7.4586(17)
b [Å]	10.778(3)
c [Å]	11.912(2)
α [°]	88.201(5)
β [°]	79.527(5)
γ [°]	70.220(6)
Volume [Å^3]	885.7(3)
Z	4
ρ_{calc} [gcm^{-3}]	1.505
μ [mm^{-1}]	0.400
F(000)	416

Crystal size [mm^3]	0.149×0.096×0.086
Crystal colour	colourless
Crystal shape	plate
Radiation	MoK_α (λ=0.71073 Å)
2Θ range [°]	5.23 to 61.31 (0.70 Å)
Index ranges	-10 ≤ h ≤ 10 -15 ≤ k ≤ 15 -17 ≤ l ≤ 17
Reflections collected	10433
Independent reflections	10433 R_{int} = 0.0495 R_{sigma} = 0.0528
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	10433/0/247

Goodness-of-fit on F^2	1.097
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0554$ w$R_2 = 0.1385$
Final R indexes [all data]	$R_1 = 0.0806$ w$R_2 = 0.1520$

Largest peak/hole [eÅ^{-3}]	0.56/-0.47
Extinction coefficient	0.028(4)

Refinement table and ORTEP plot for **241d**

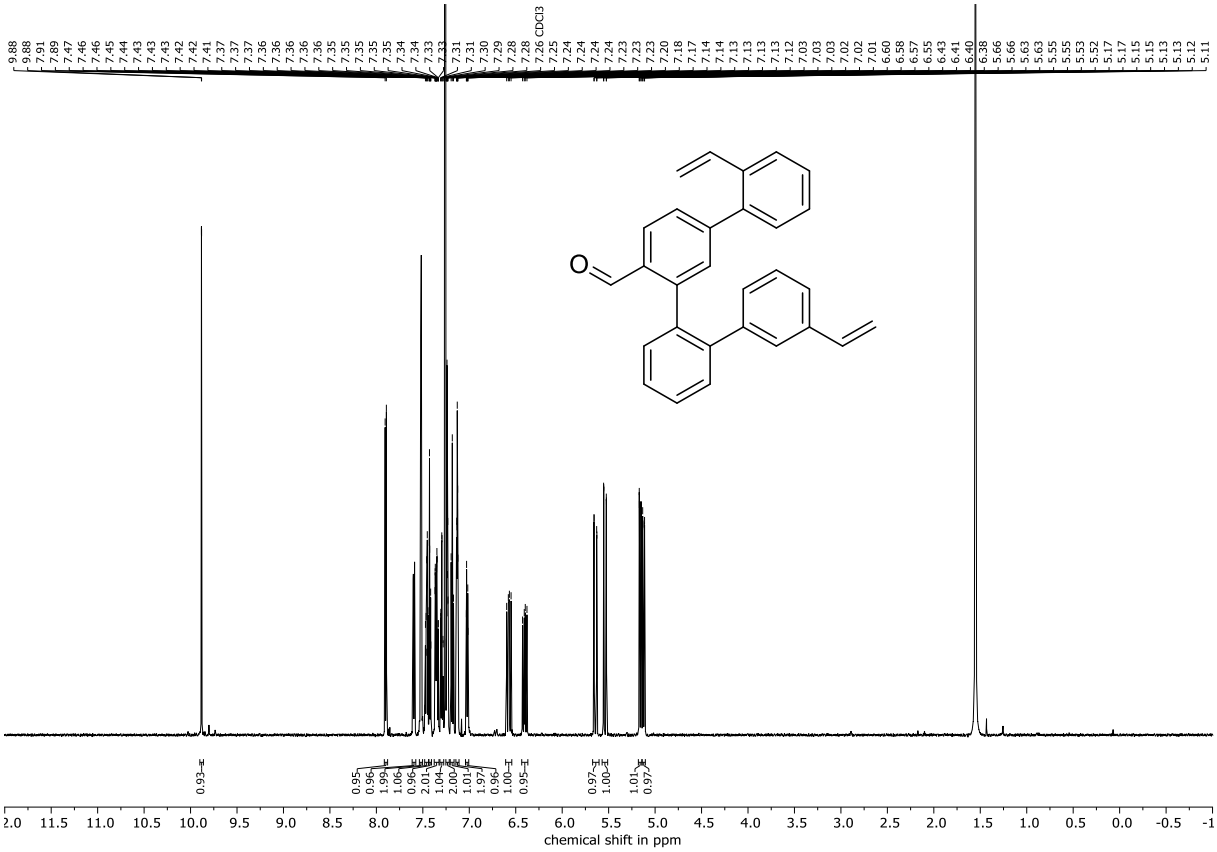


Internal number	1373
Empirical formula	$C_7H_3ClO_4$
Formula weight	186.54
Temperature [K]	100.0
Crystal system	monoclinic
Space group (number)	$P2/c$ (13)
a [Å]	15.6802(5)
b [Å]	6.9344(3)
c [Å]	12.9858(5)
α [°]	90
β [°]	104.6900(10)
γ [°]	90
Volume [Å^3]	1365.83(9)
Z	8
ρ_{calc} [gcm^{-3}]	1.814
μ [mm^{-1}]	0.522
F(000)	752
Crystal size [mm^3]	0.318×0.11×0.048
Crystal colour	colourless
Crystal shape	plank
Radiation	MoK_α (λ=0.71073 Å)
2Θ range [°]	5.37 to 63.10 (0.68 Å)
Index ranges	-23 ≤ h ≤ 22 -10 ≤ k ≤ 10 -19 ≤ l ≤ 19

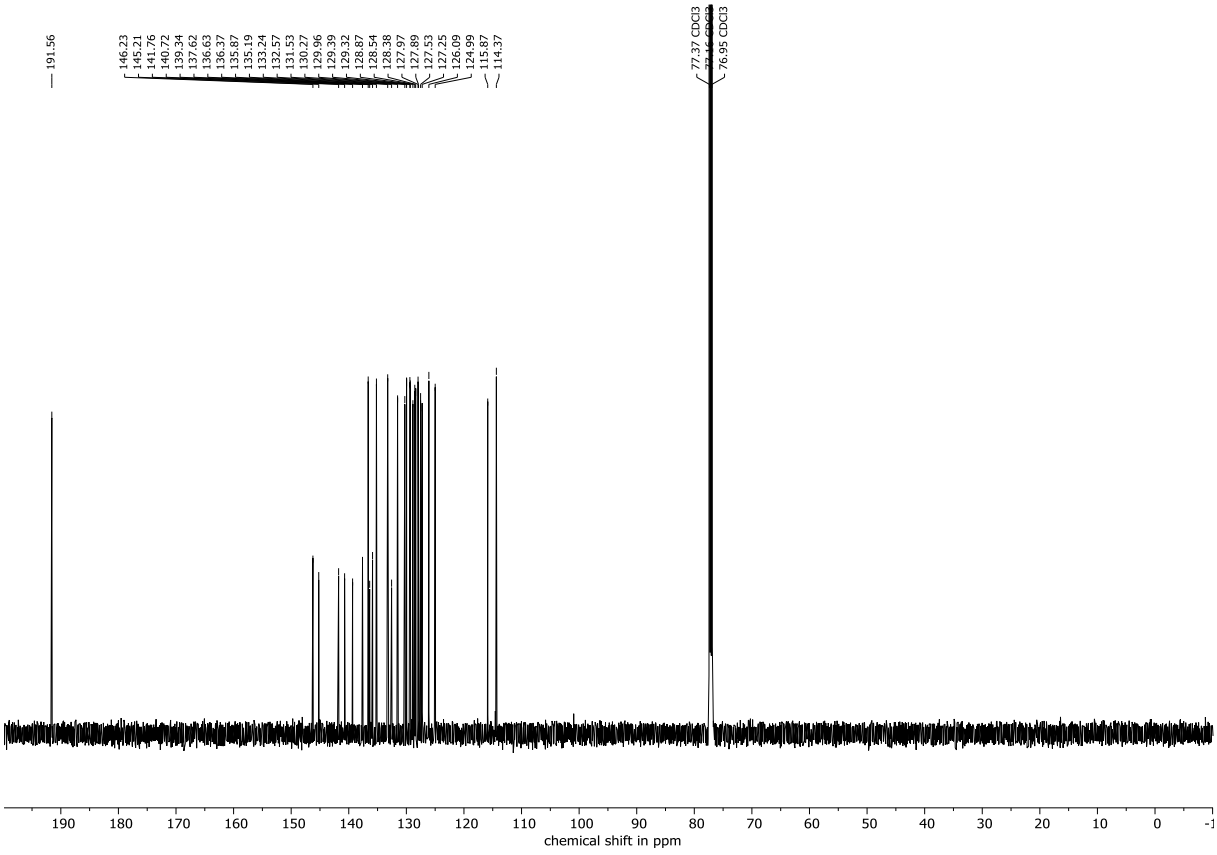
Reflections collected	42075
Independent reflections	4549 R_{int} = 0.0389 R_{sigma} = 0.0212
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	4549/0/223
Goodness-of-fit on F^2	1.031
Final R indexes [I≥2σ(I)]	R_1 = 0.0346 wR_2 = 0.0870
Final R indexes [all data]	R_1 = 0.0468 wR_2 = 0.0948
Largest peak/hole [eÅ^{-3}]	0.74/-0.28

5.2. NMR-Spectra

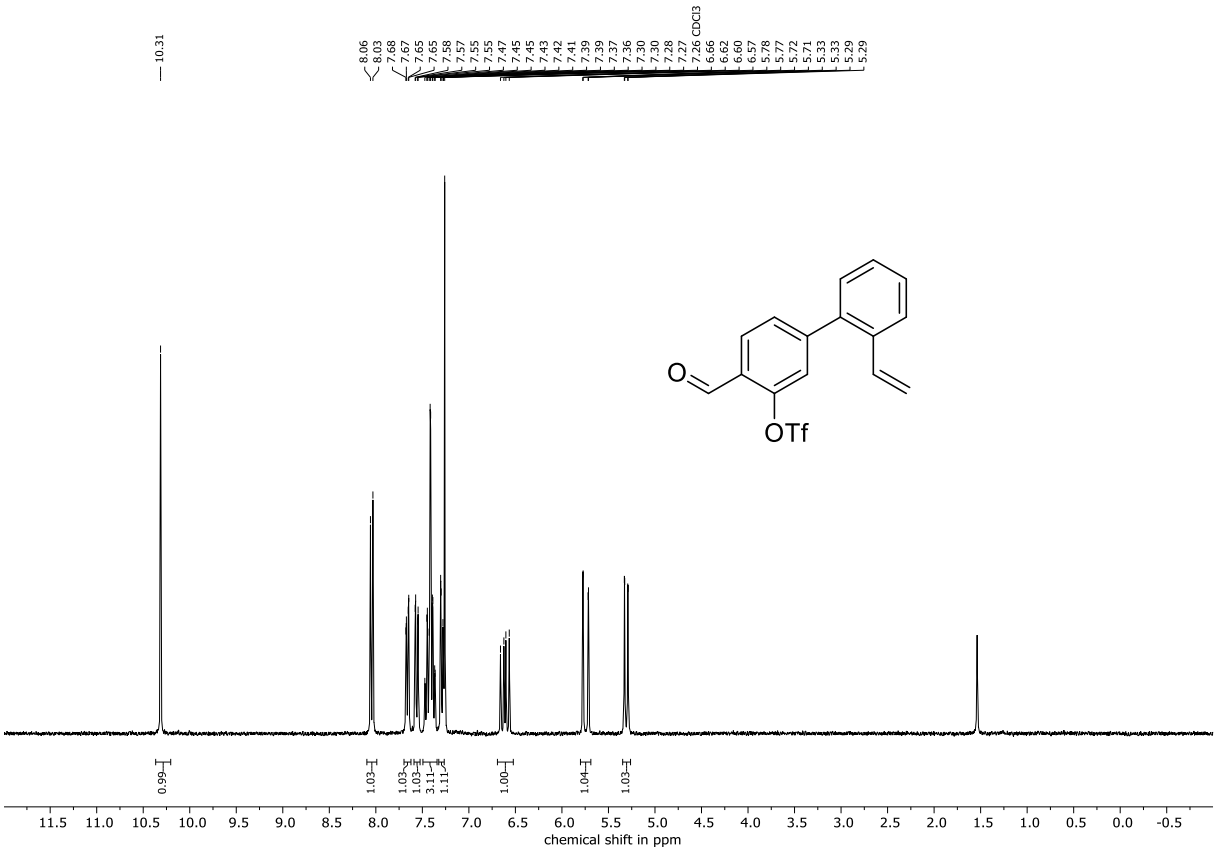
^{1}H NMR (600 MHz, $CDCl_3$) of **105**



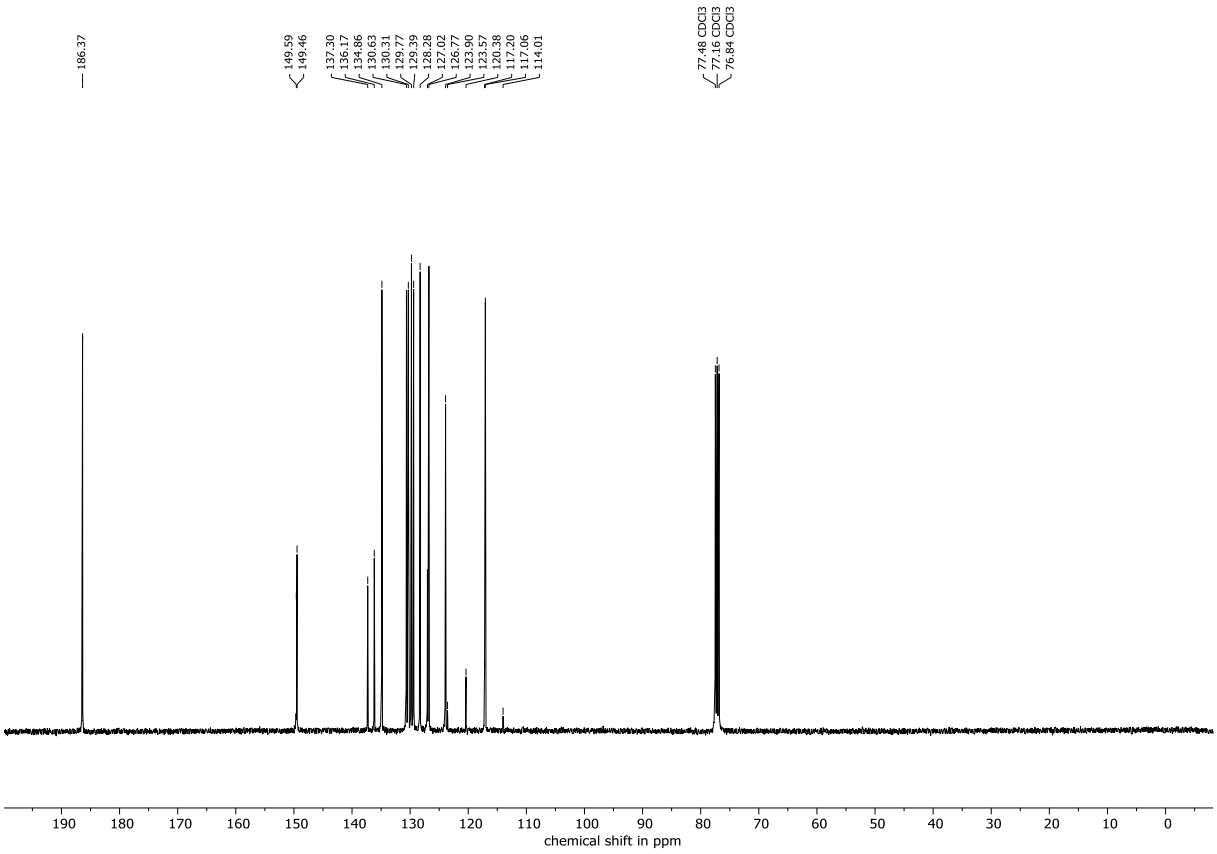
^{13}C NMR (151 MHz, $CDCl_3$) of **105**



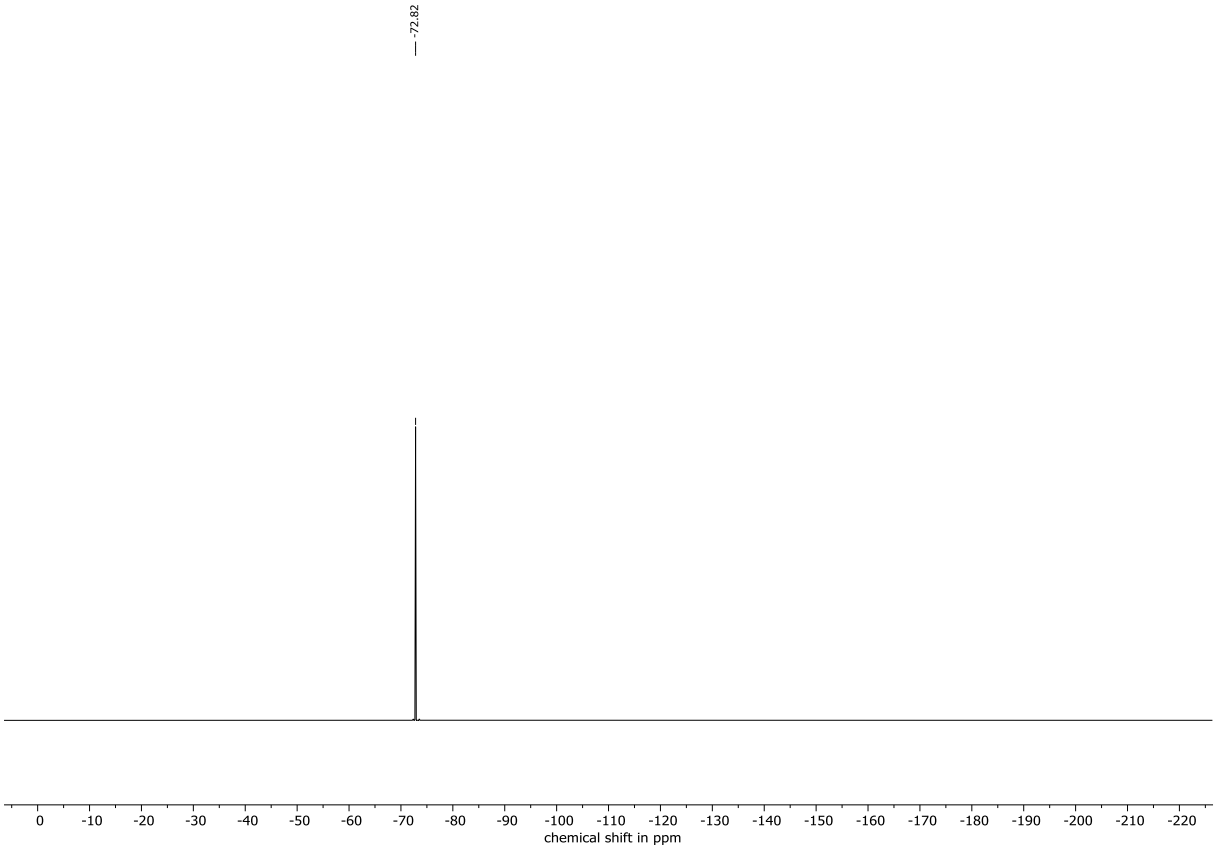
^{1}H NMR (300 MHz, $CDCl_3$) of **107**



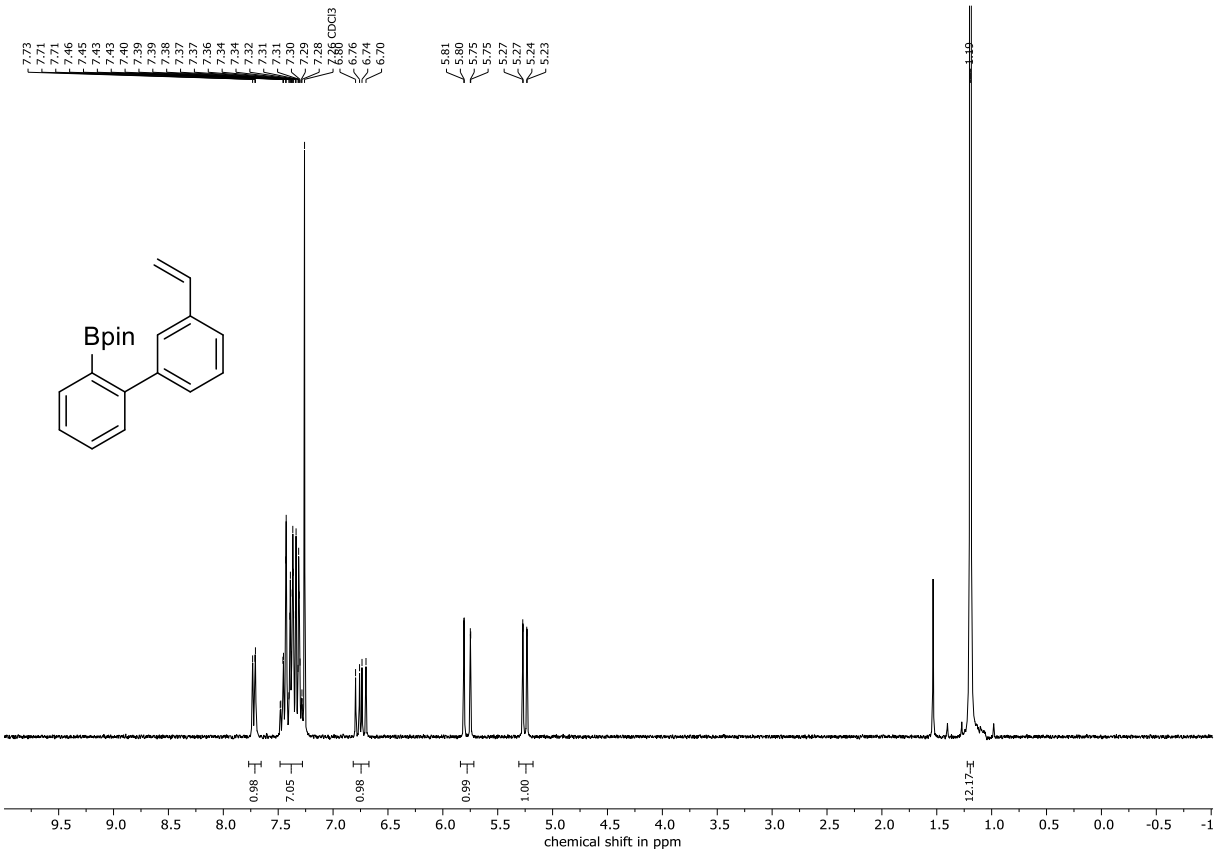
^{13}C NMR (101 MHz, $CDCl_3$) of **107**



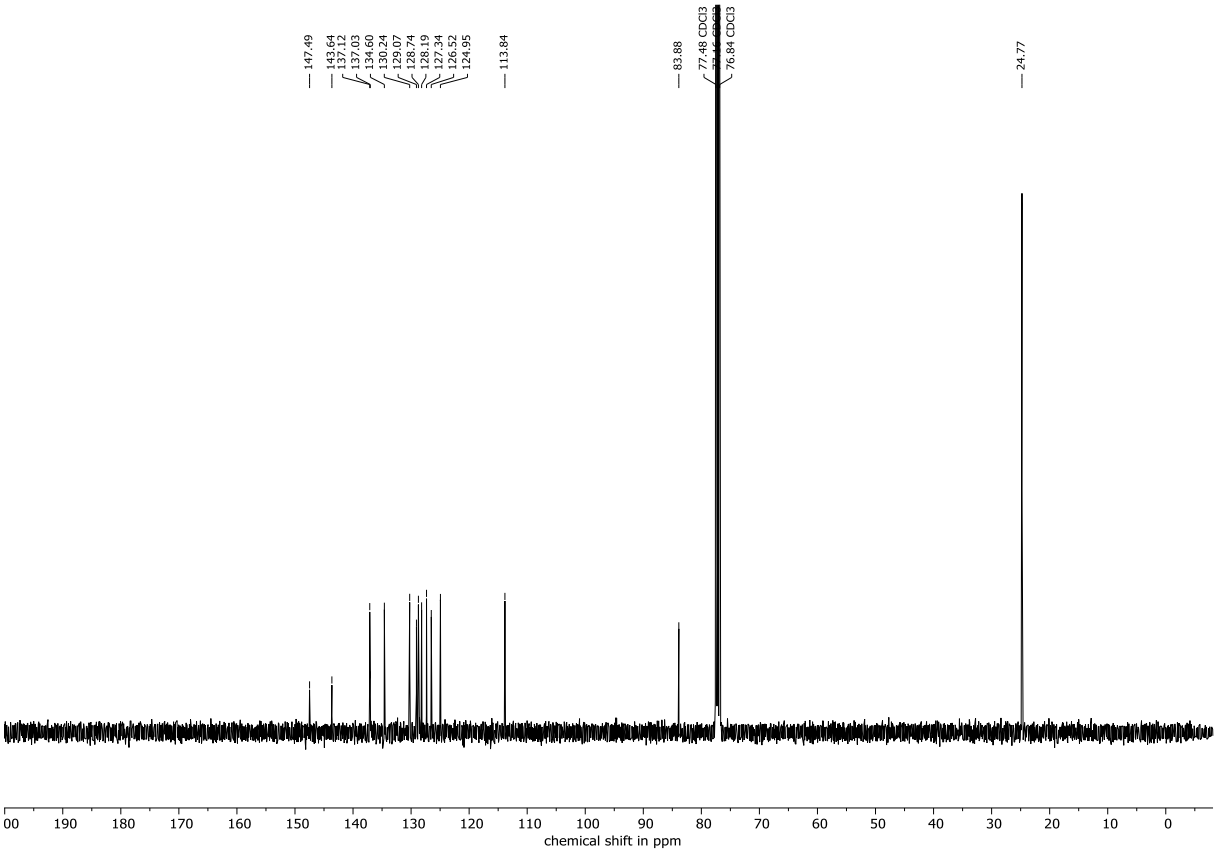
^{19}F NMR (282 MHz, $CDCl_3$) of **107**



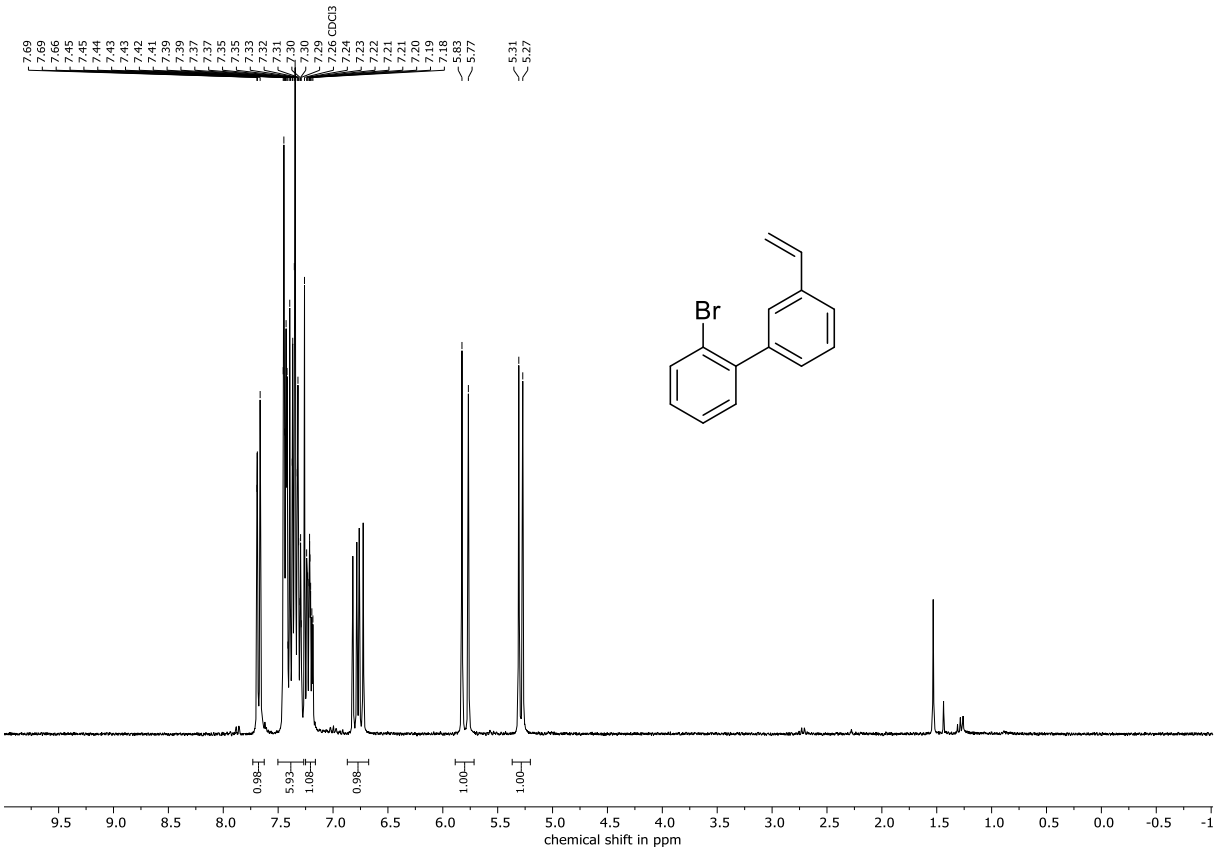
^{1}H NMR (300 MHz, $CDCl_3$) of **108**



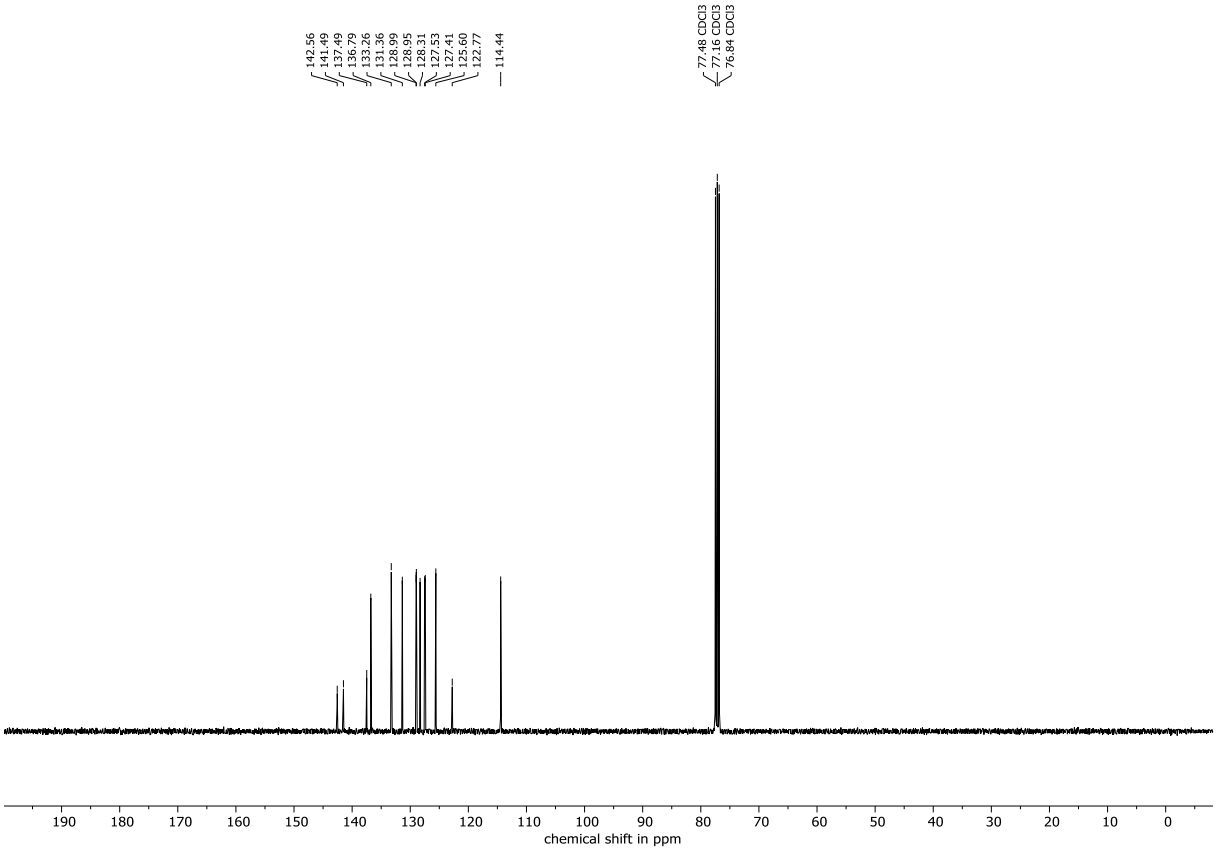
^{13}C NMR (101 MHz, $CDCl_3$) of **108**



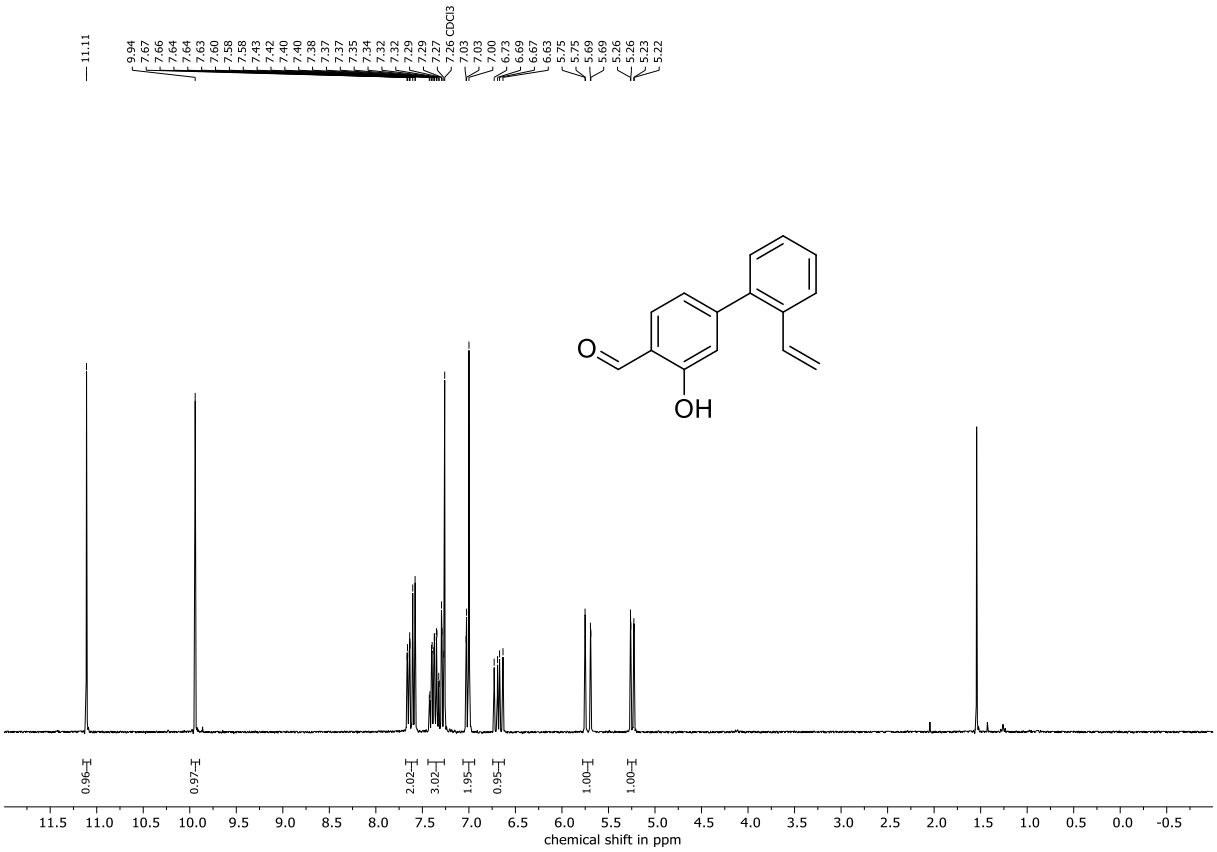
^{1}H NMR (300 MHz, $CDCl_3$) of **113**



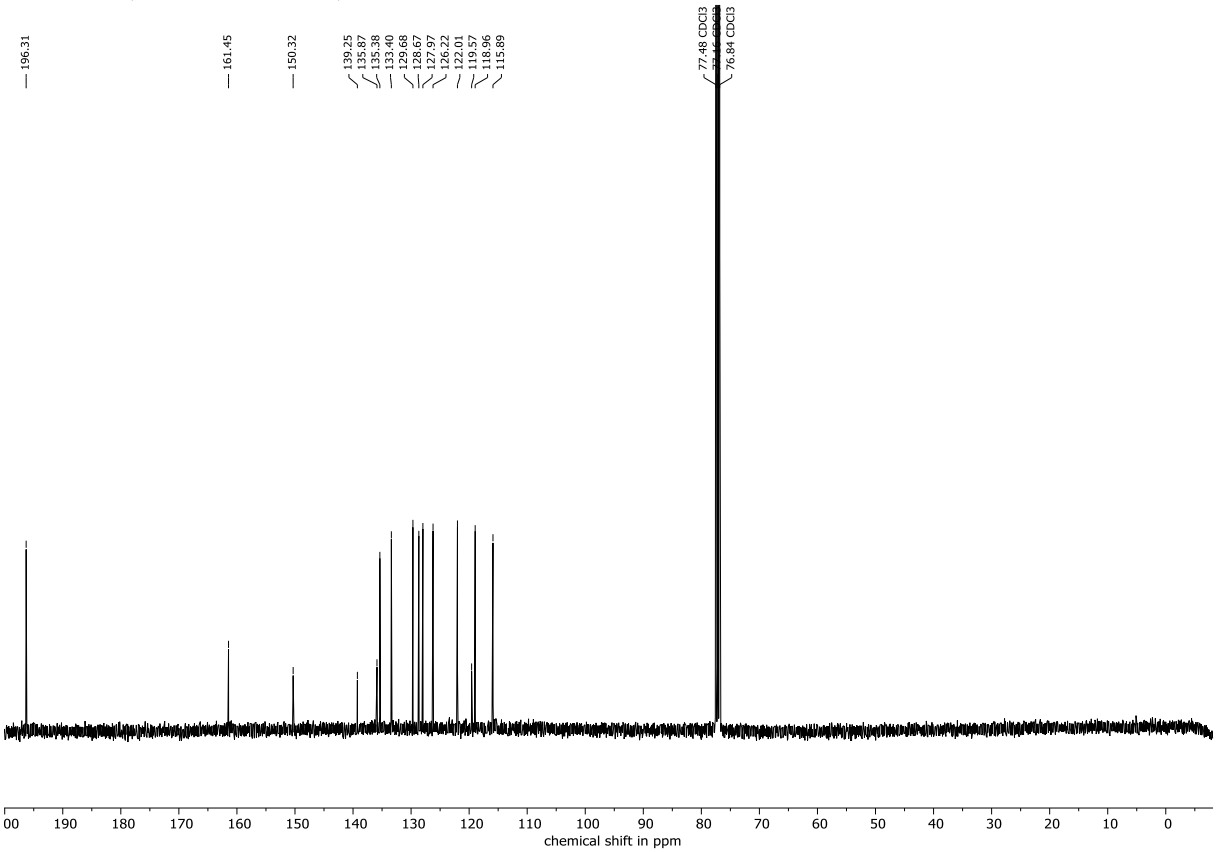
^{13}C NMR (101 MHz, $CDCl_3$) of **113**



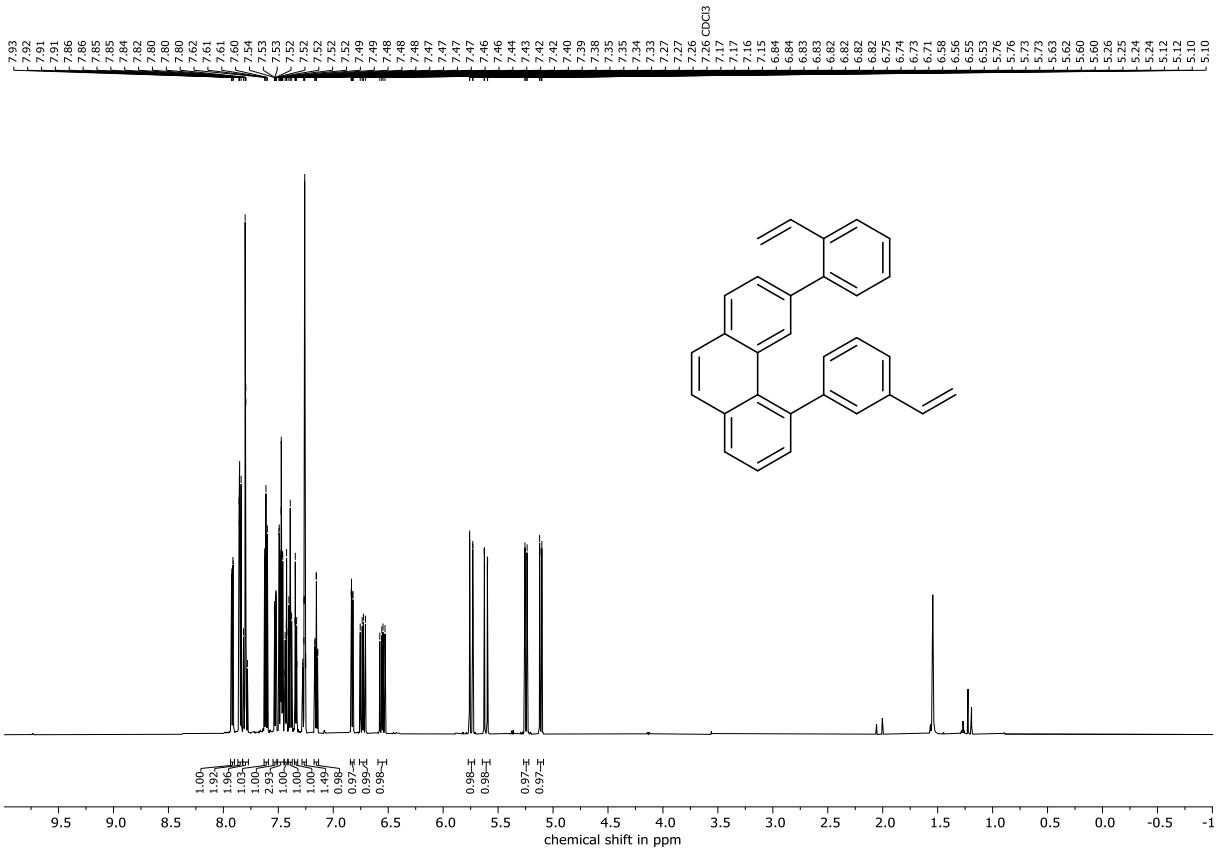
^{1}H NMR (300 MHz, $CDCl_3$) of **114**



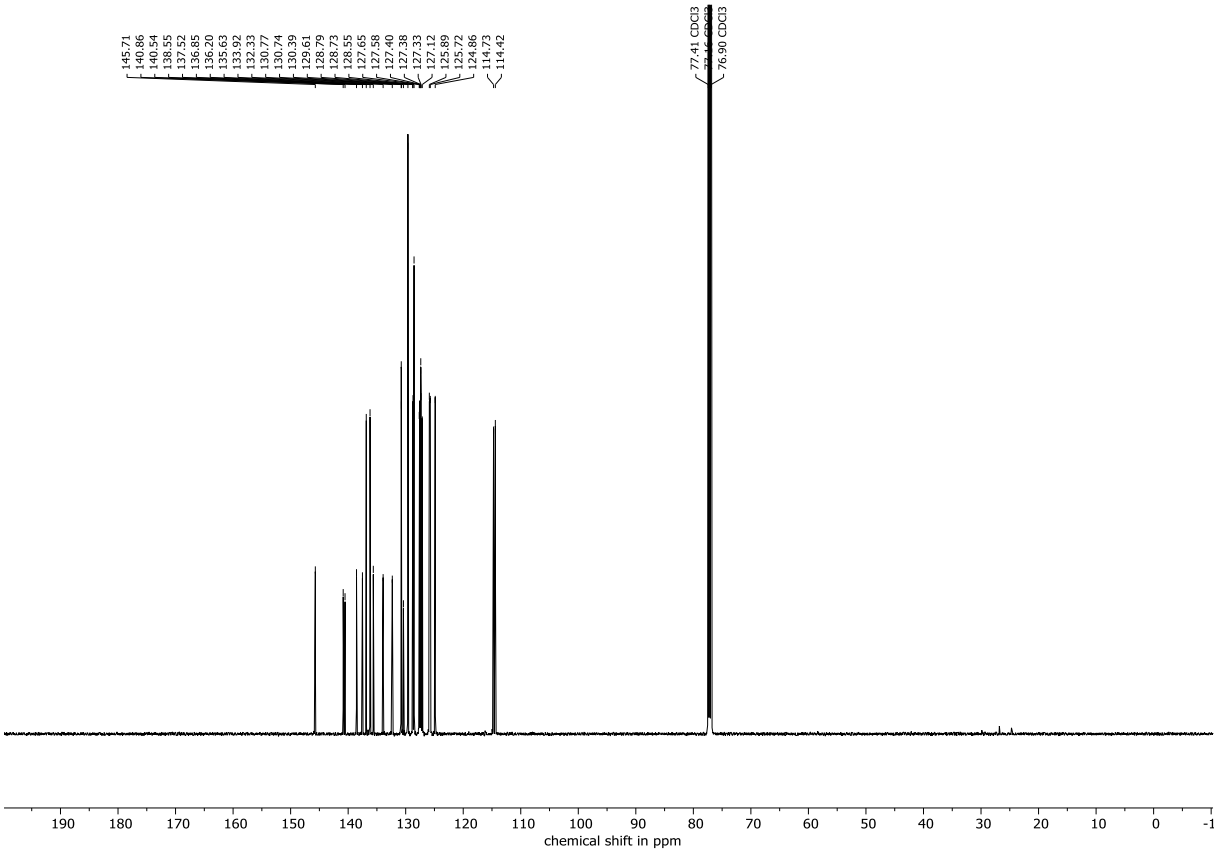
^{13}C NMR (101 MHz, $CDCl_3$) of **114**



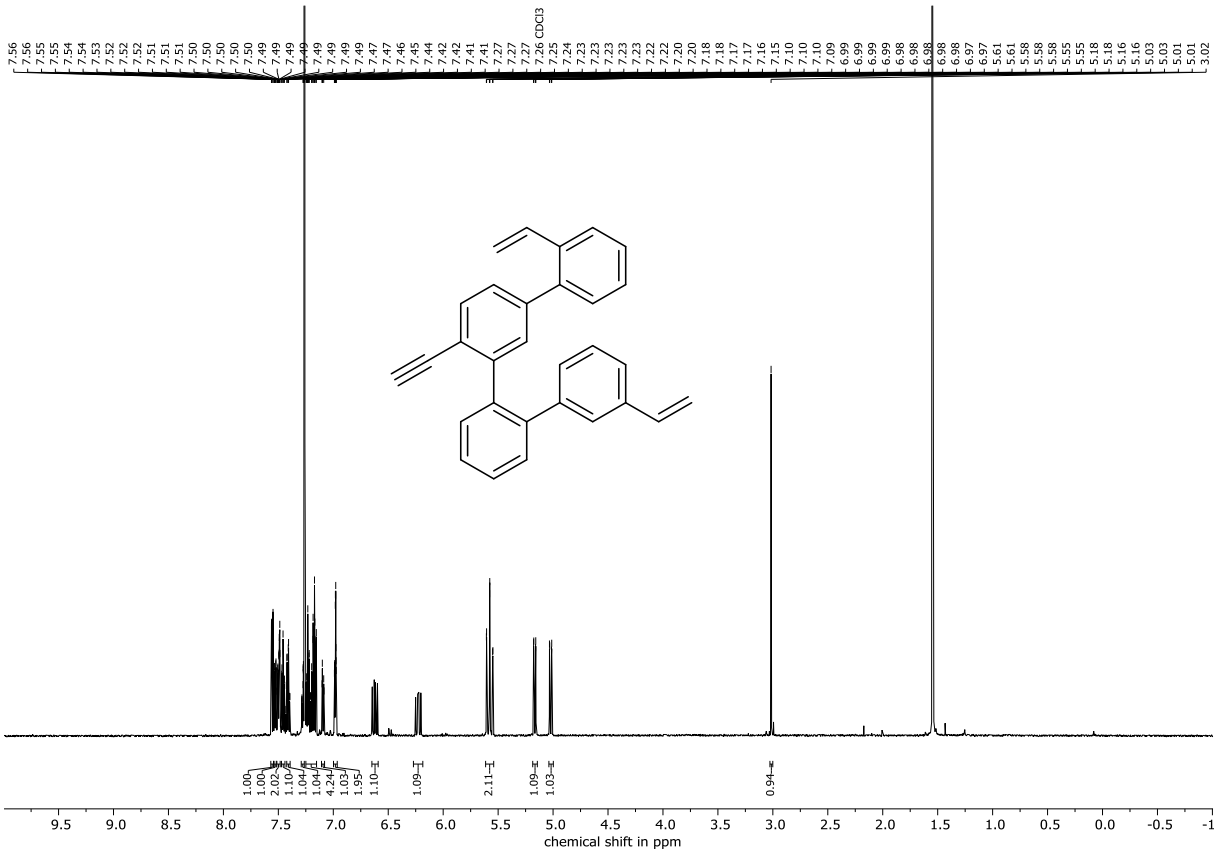
^{1}H NMR (600 MHz, $CDCl_3$) of **118**



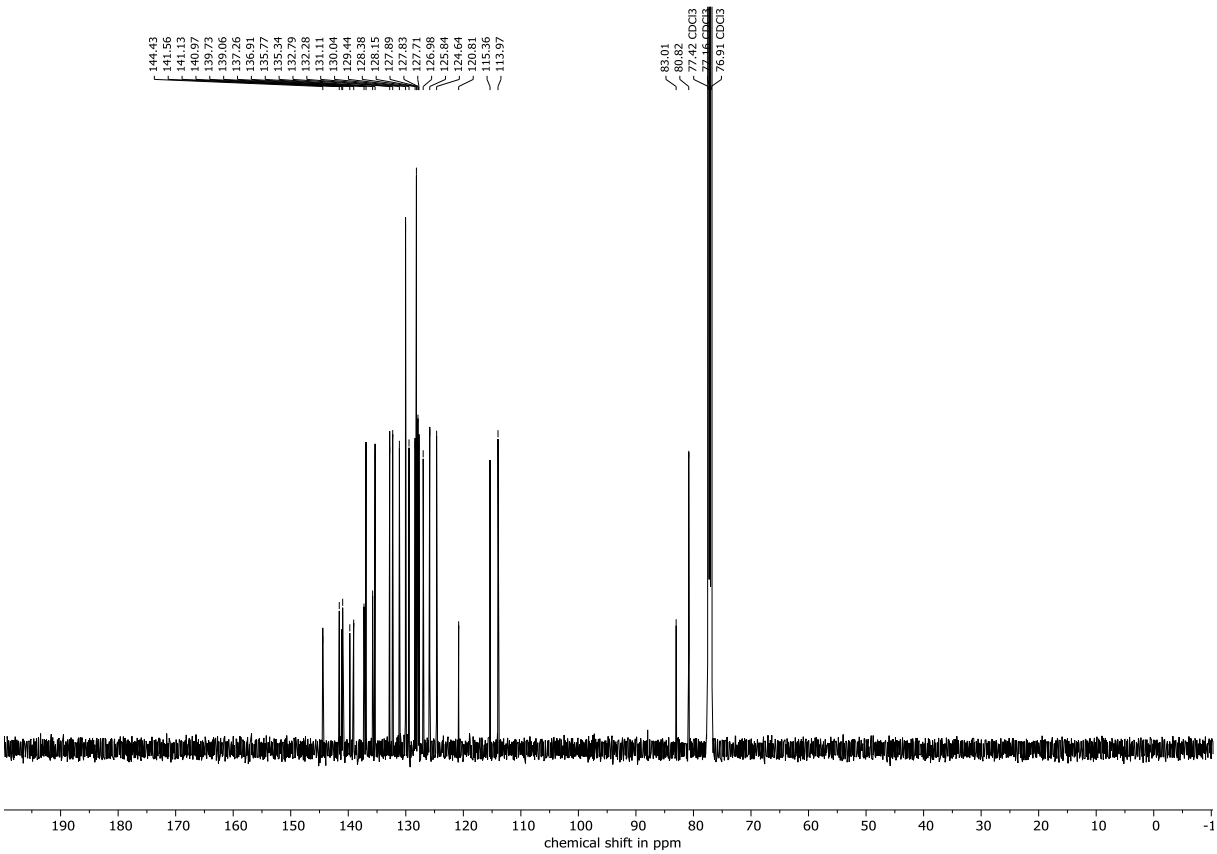
^{13}C NMR (126 MHz, $CDCl_3$) of **118**



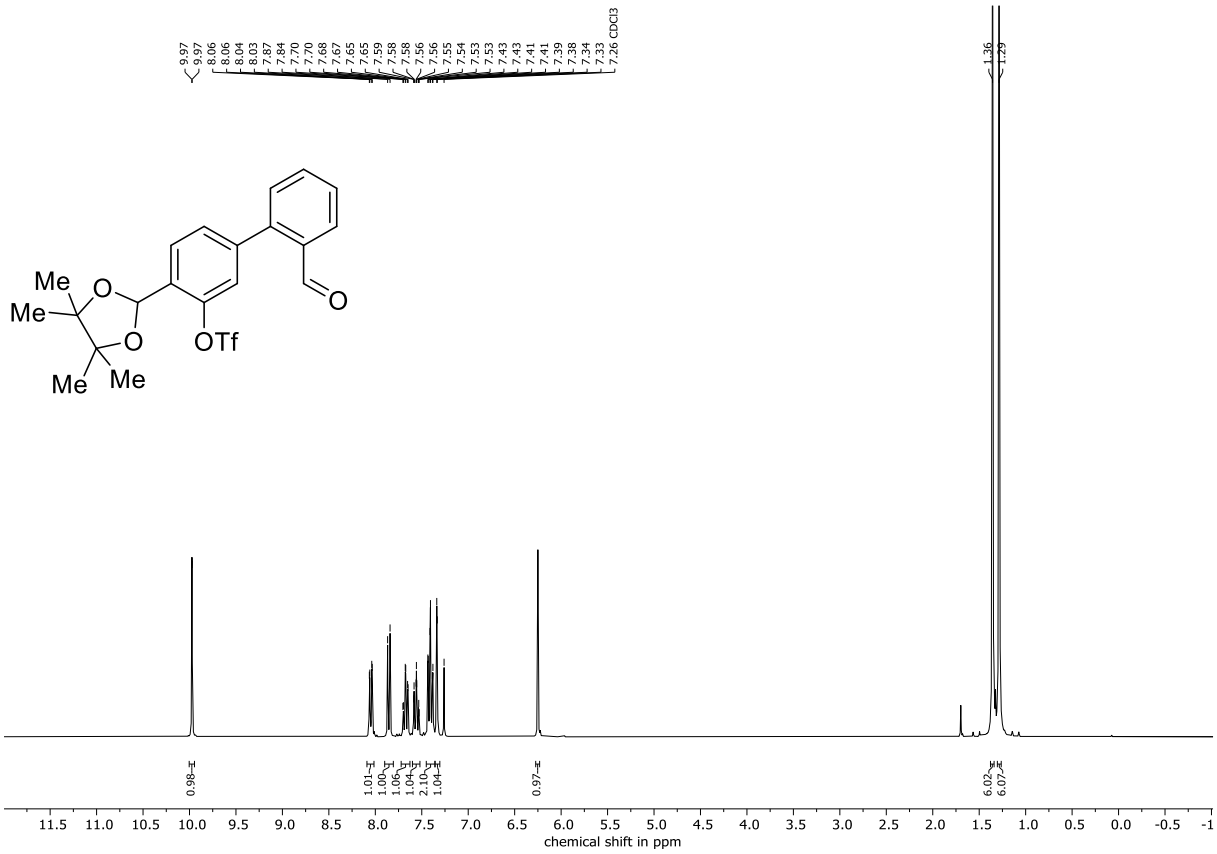
^{1}H NMR (600 MHz, $CDCl_3$) of **119**



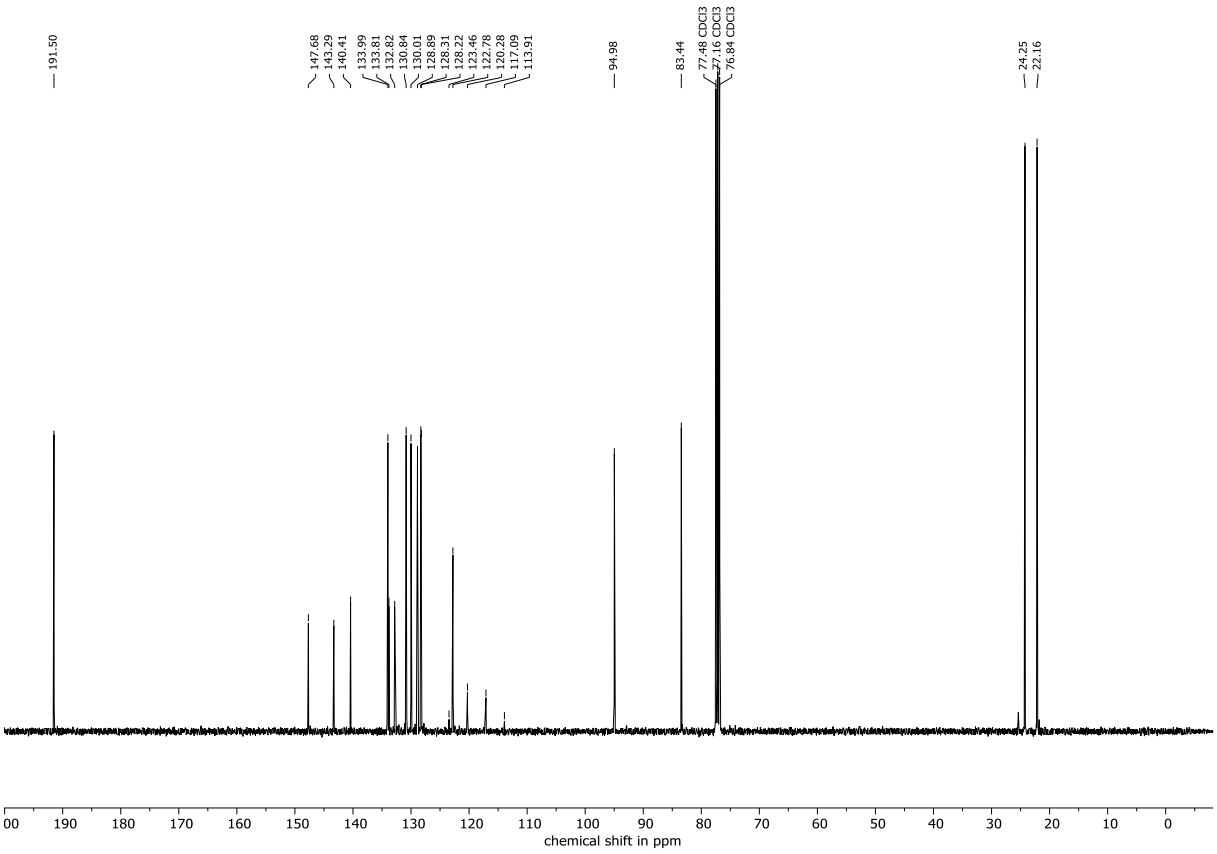
^{13}C NMR (126 MHz, $CDCl_3$) of **119**



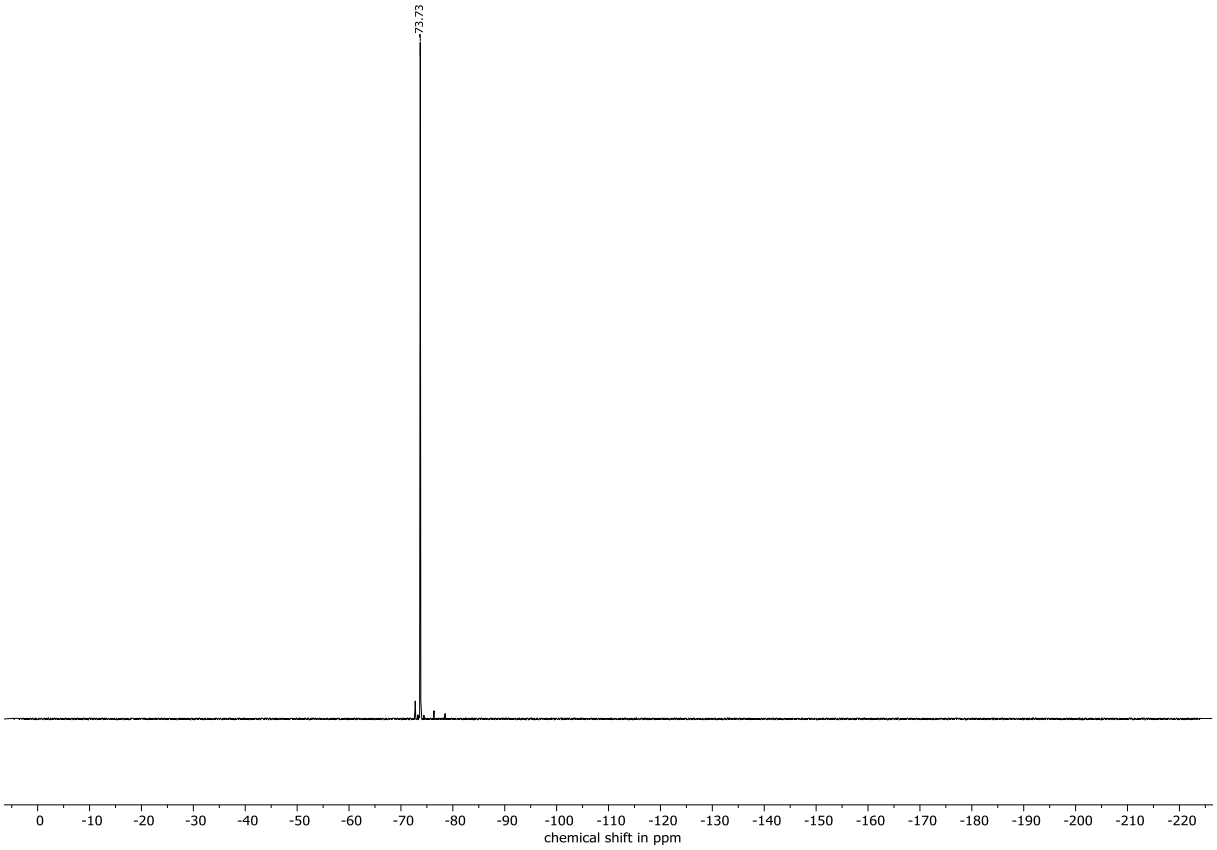
^{1}H NMR (300 MHz, $CDCl_3$) of **125**



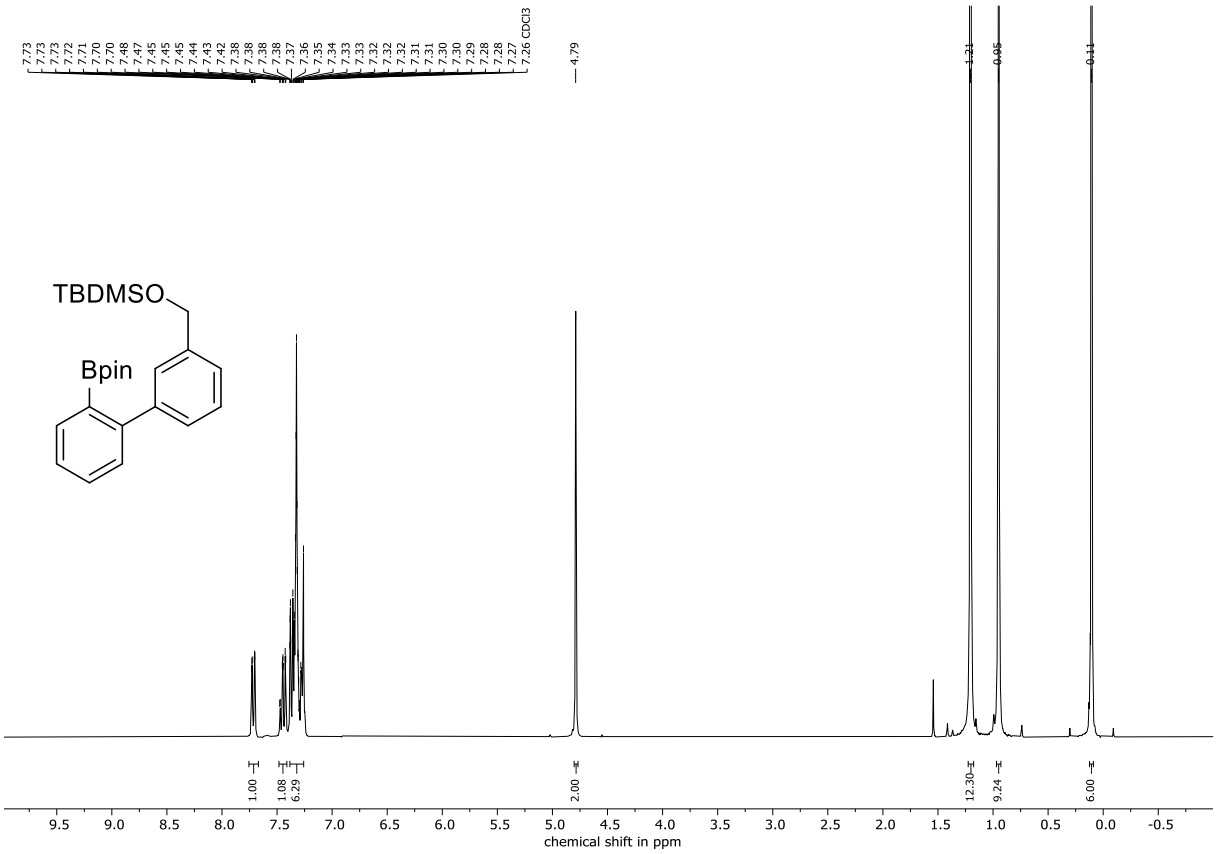
^{13}C NMR (101 MHz, $CDCl_3$) of **125**



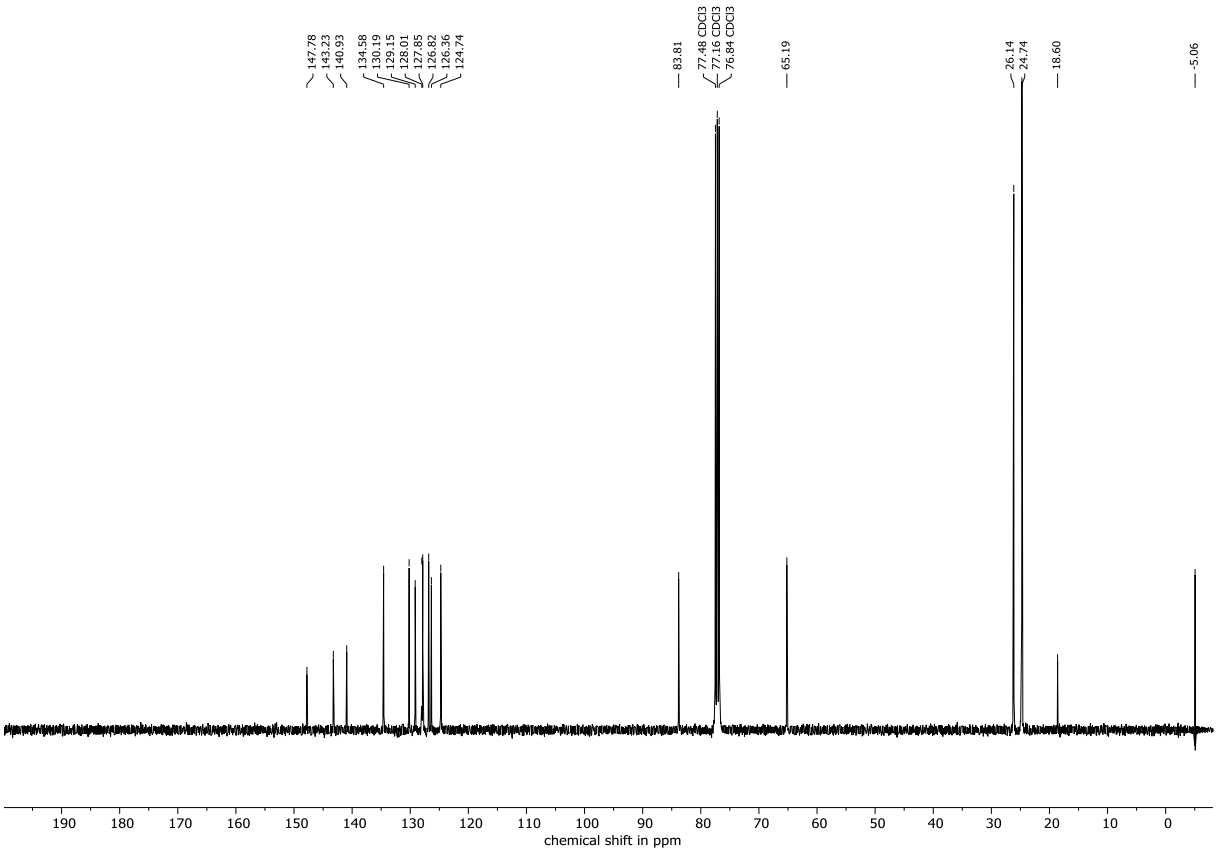
^{19}F NMR (282 MHz, $CDCl_3$) of **125**



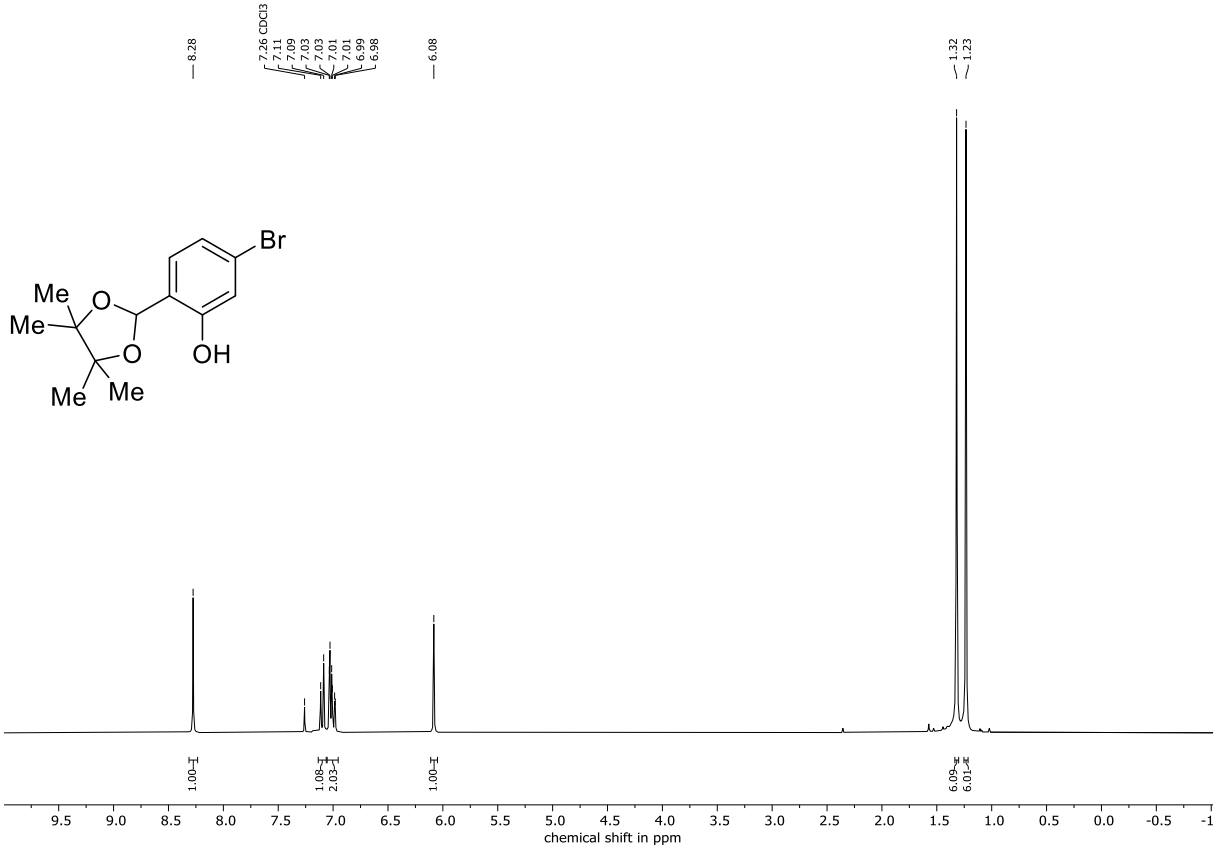
^{1}H NMR (300 MHz, $CDCl_3$) of **126**



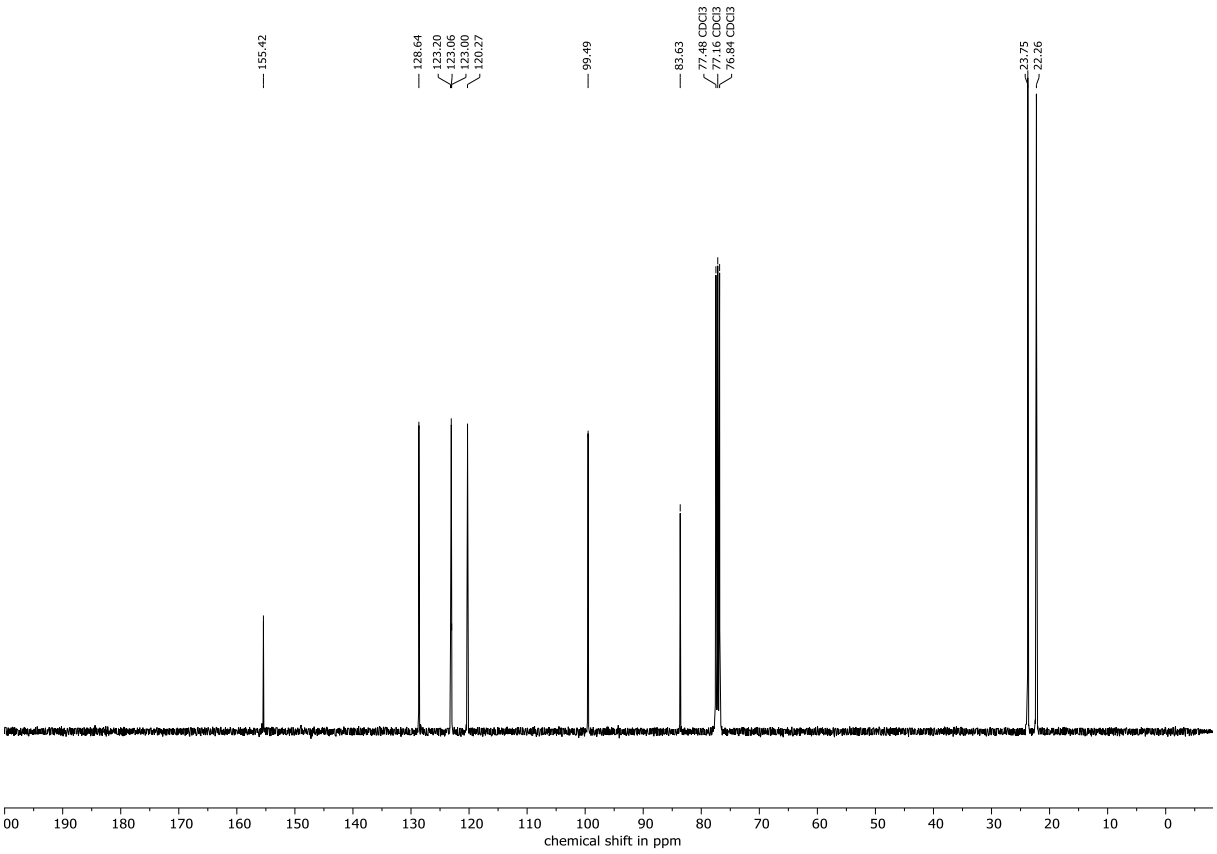
^{13}C NMR (101 MHz, $CDCl_3$) of **126**



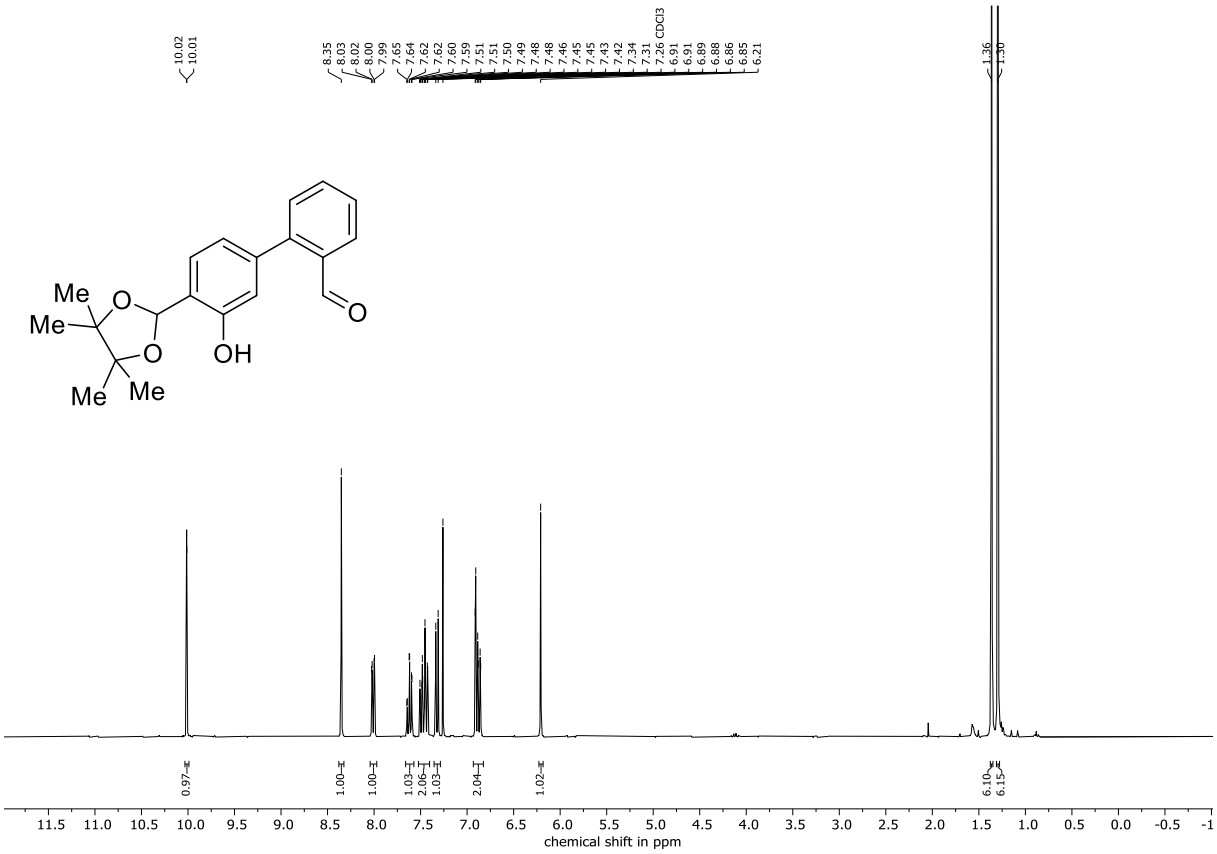
^{1}H NMR (300 MHz, $CDCl_3$) of **127**



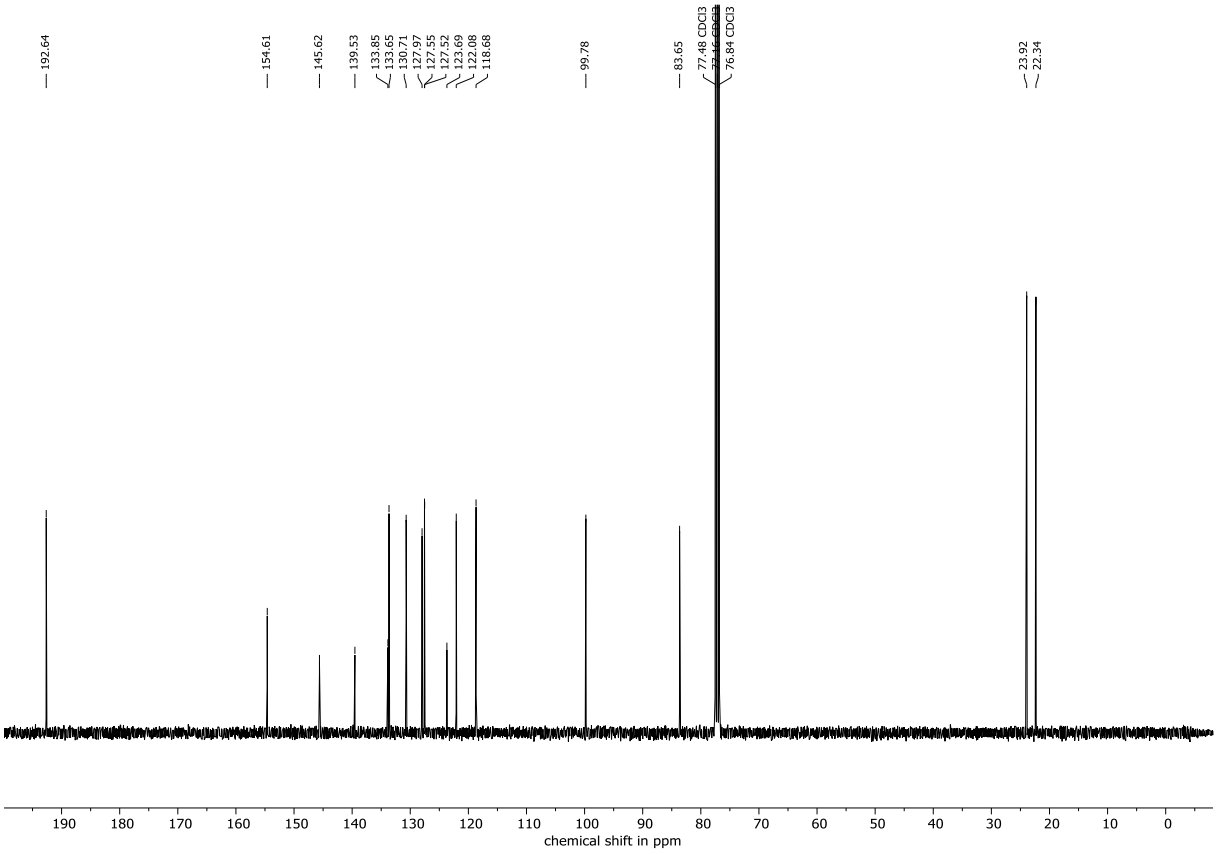
^{13}C NMR (101 MHz, $CDCl_3$) of **127**



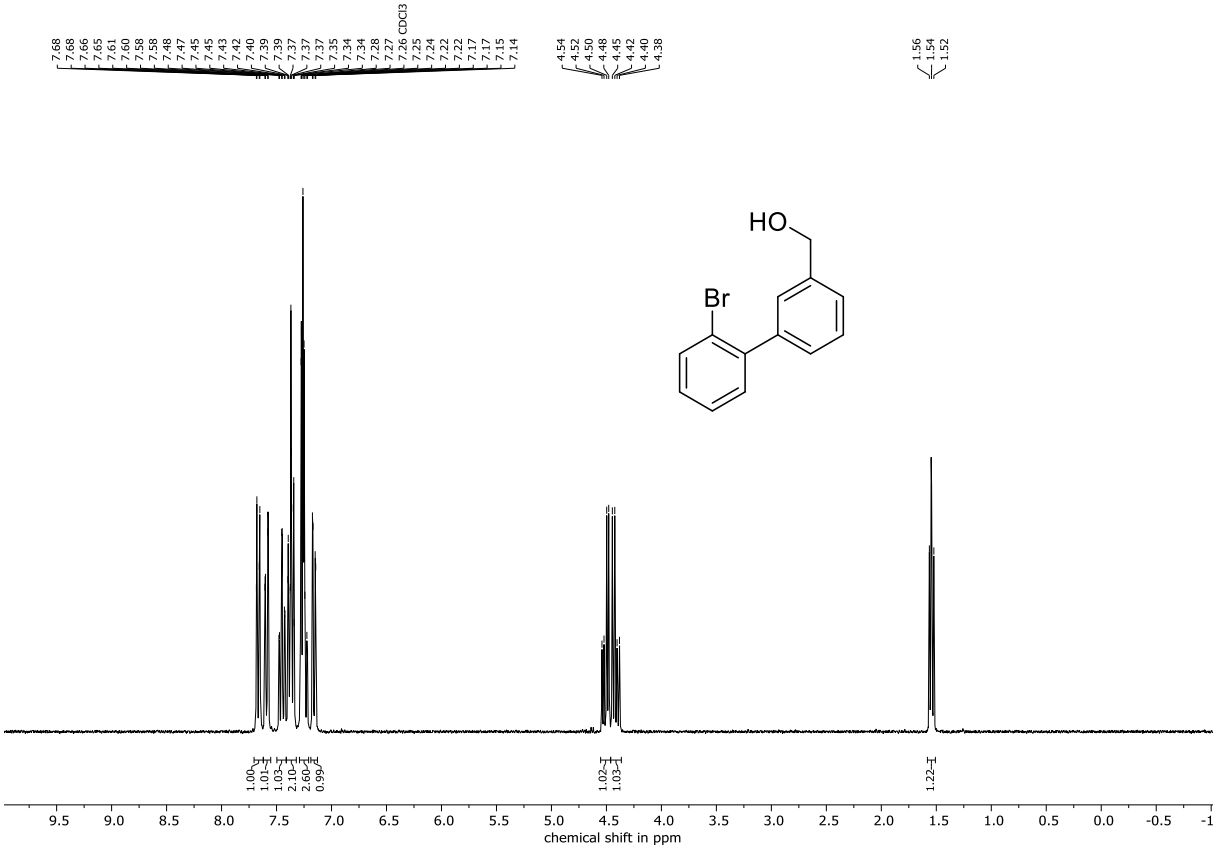
^{1}H NMR (300 MHz, $CDCl_3$) of **131**



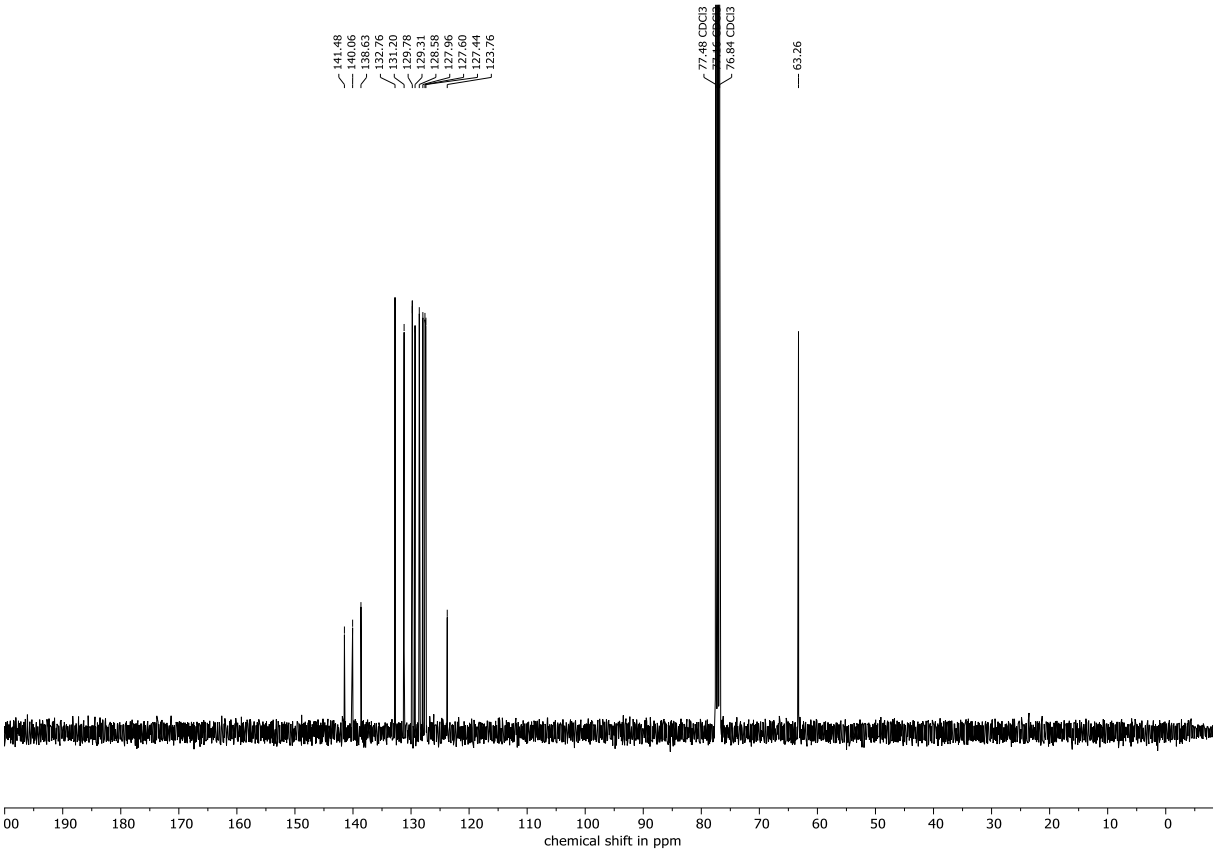
^{13}C NMR (101 MHz, $CDCl_3$) of **131**



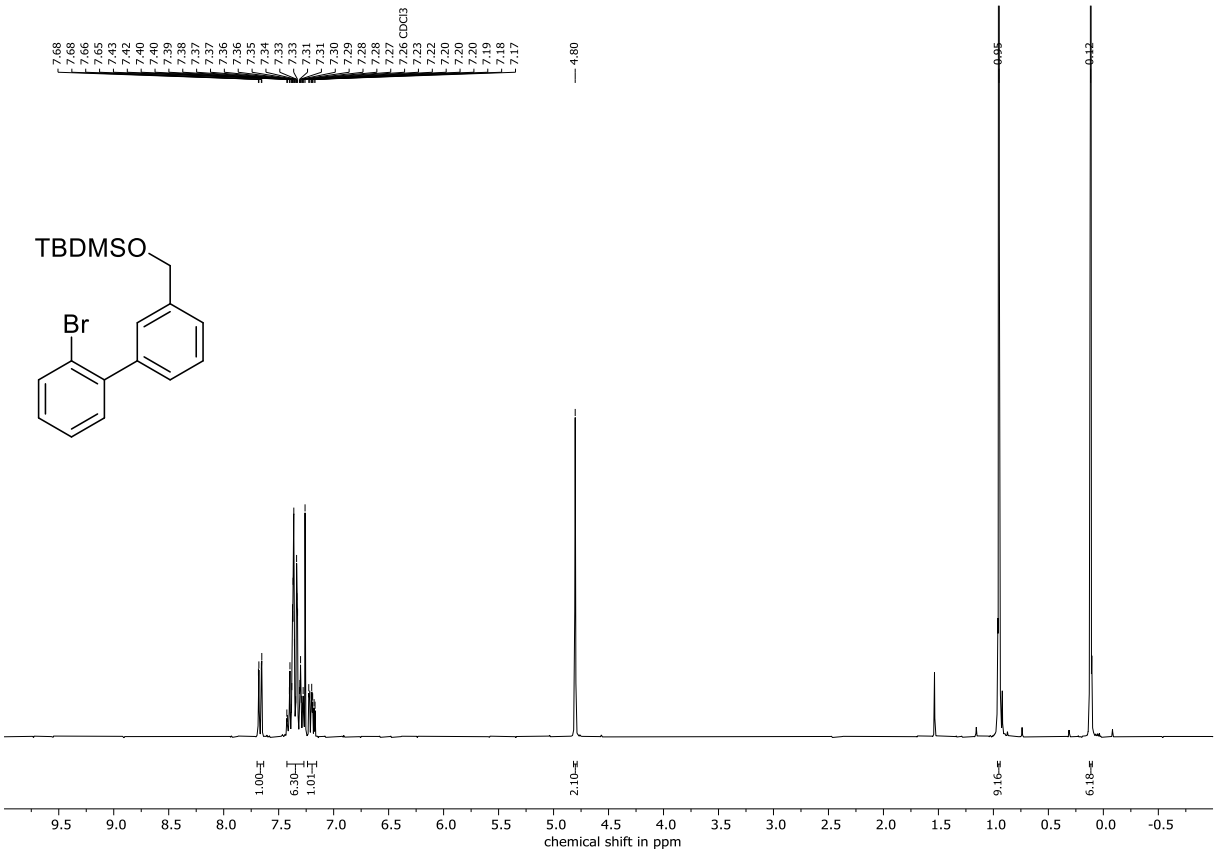
^{1}H NMR (300 MHz, $CDCl_3$) of **132**



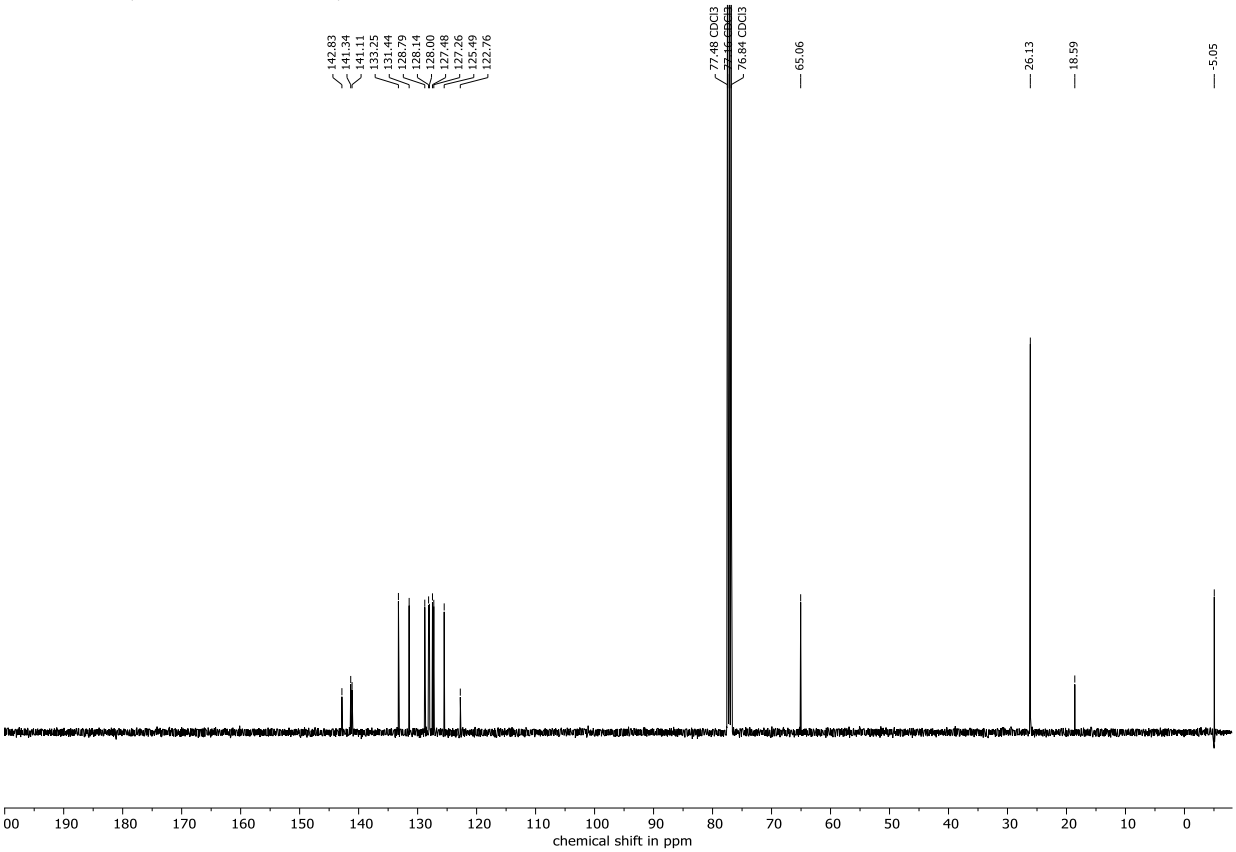
^{13}C NMR (101 MHz, $CDCl_3$) of **132**



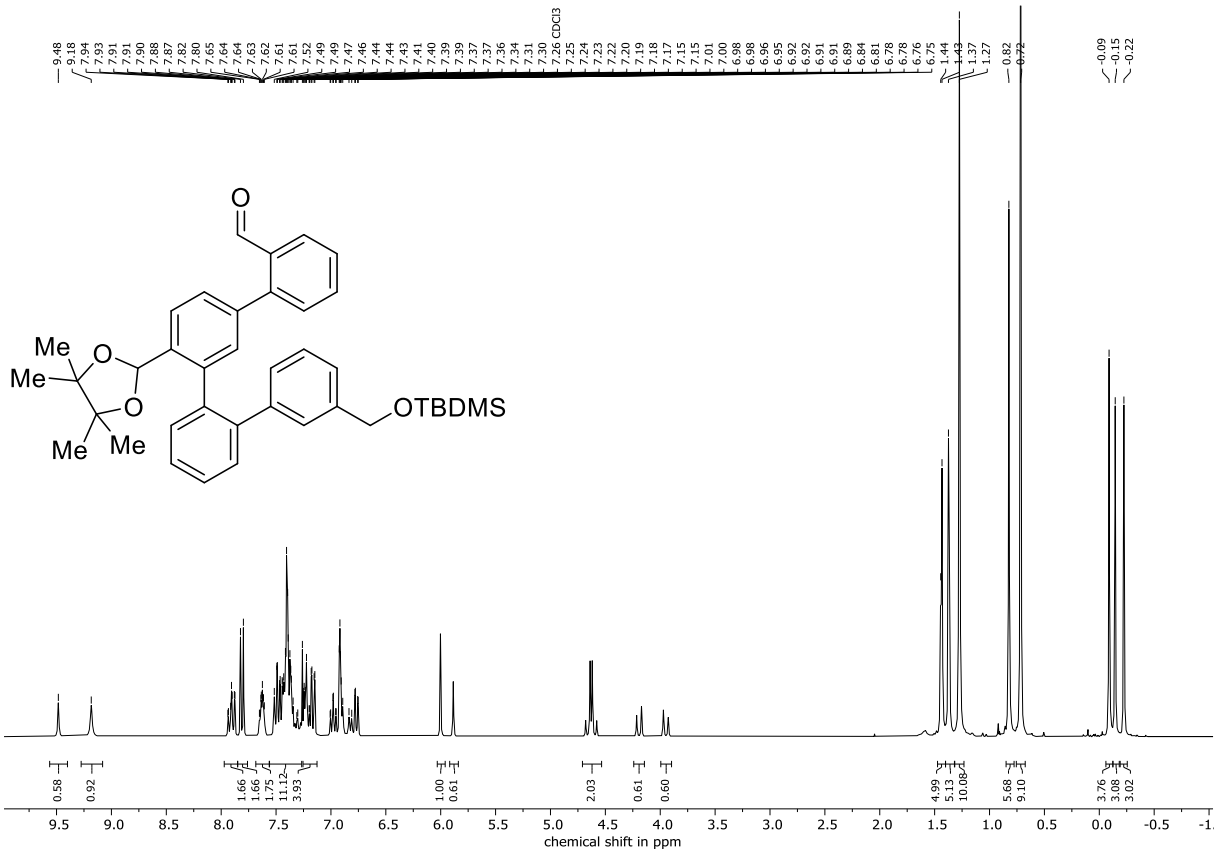
^{1}H NMR (300 MHz, $CDCl_3$) of **133**



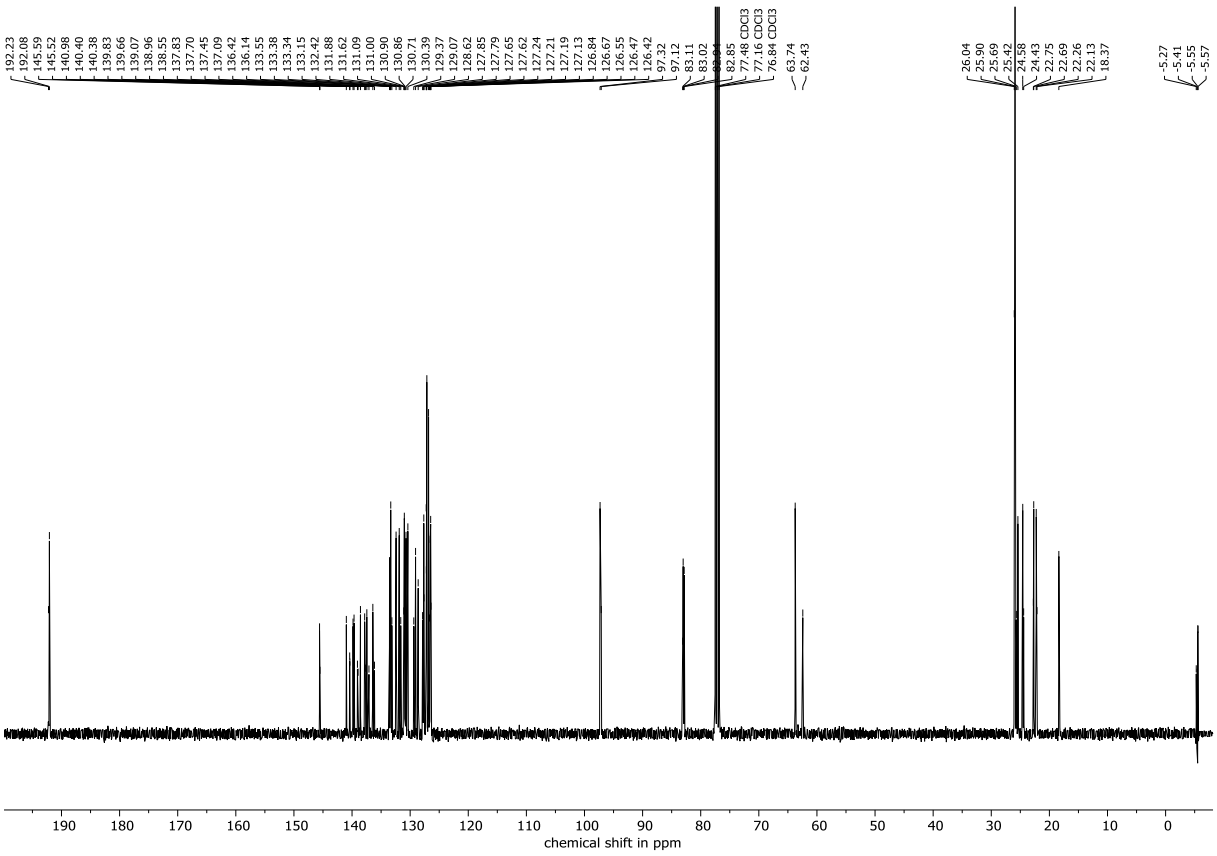
^{13}C NMR (101 MHz, $CDCl_3$) of **133**



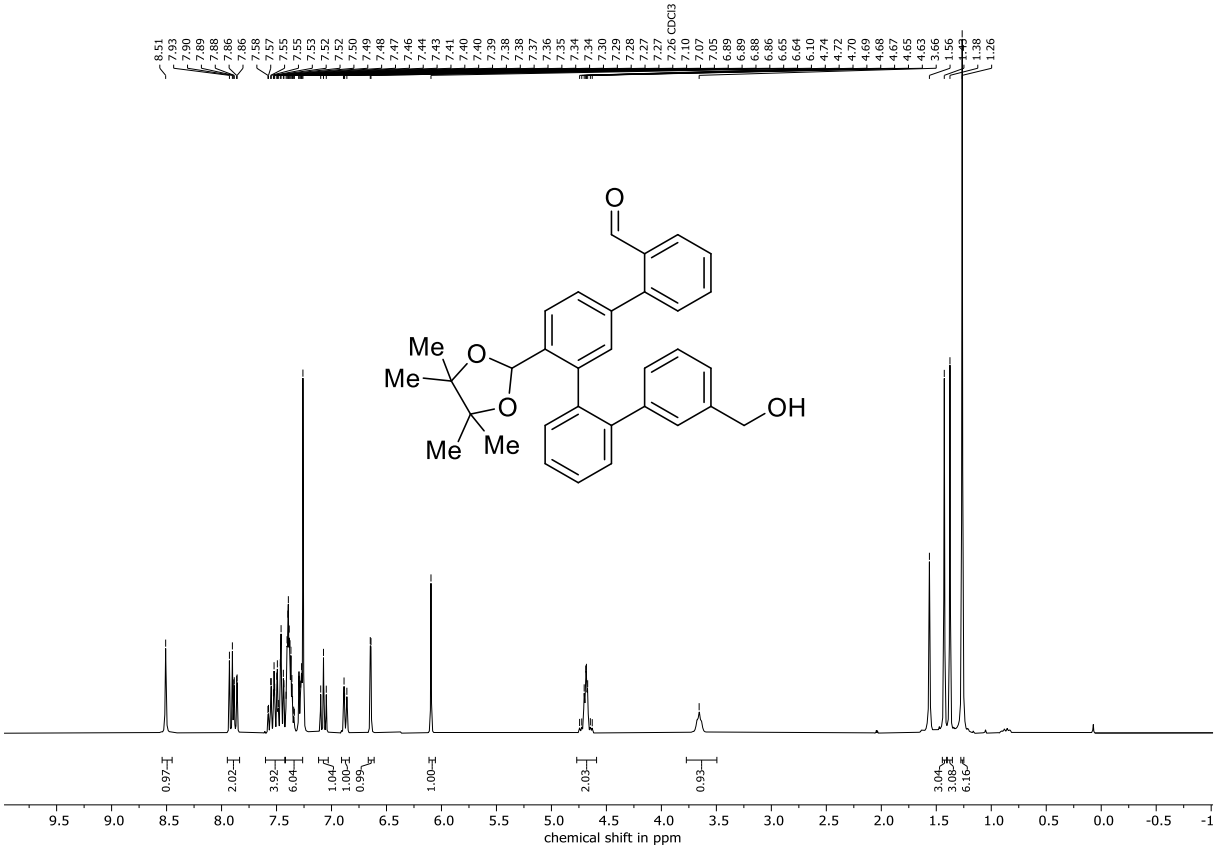
^{1}H NMR (300 MHz, $CDCl_3$) of **134**



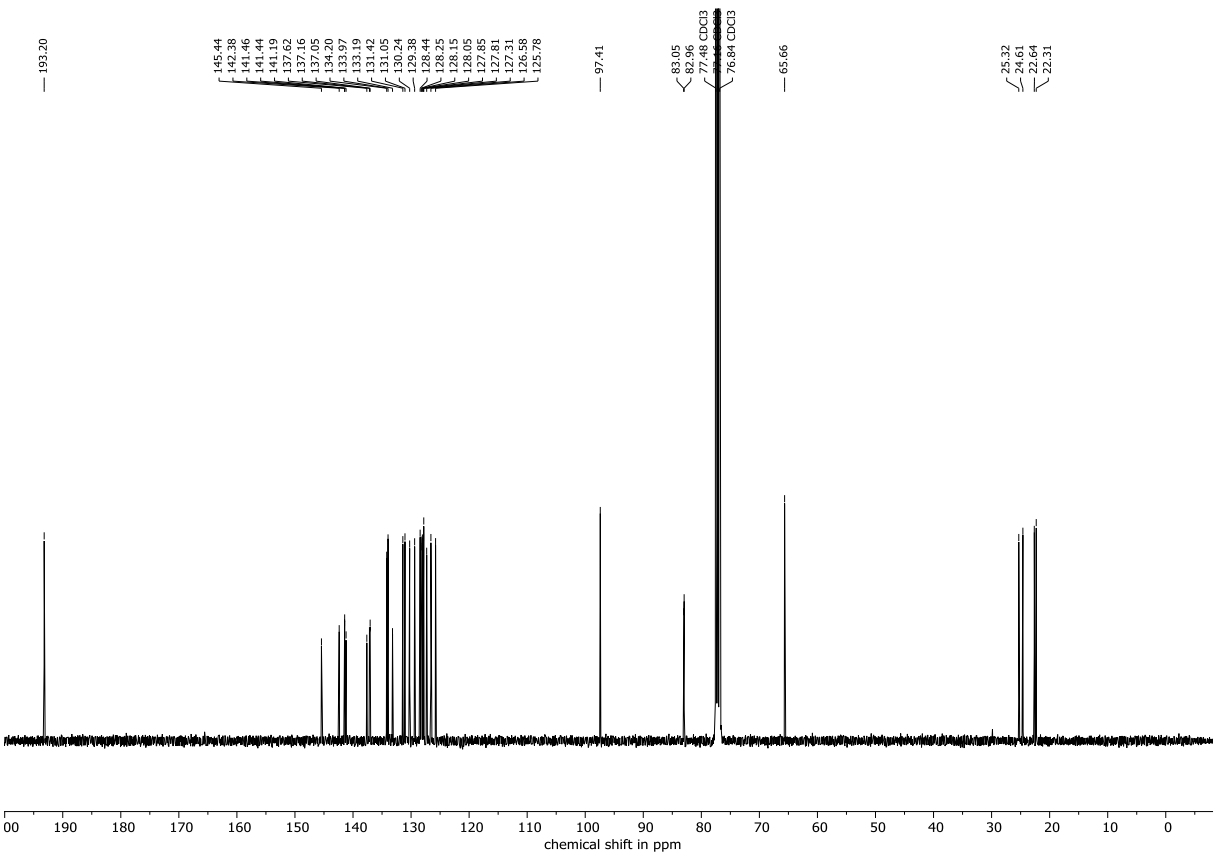
^{13}C NMR (101 MHz, $CDCl_3$) of **134**



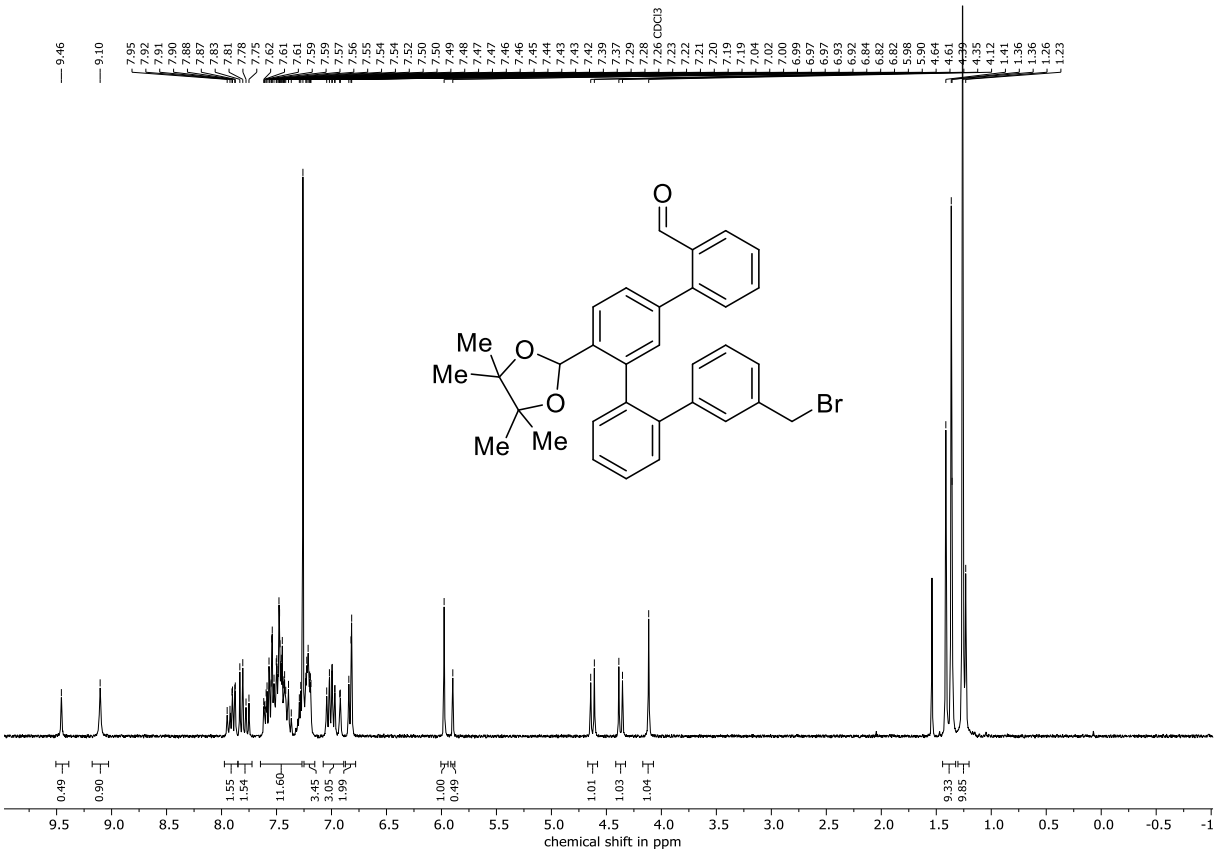
^{1}H NMR (300 MHz, $CDCl_3$) of **135**



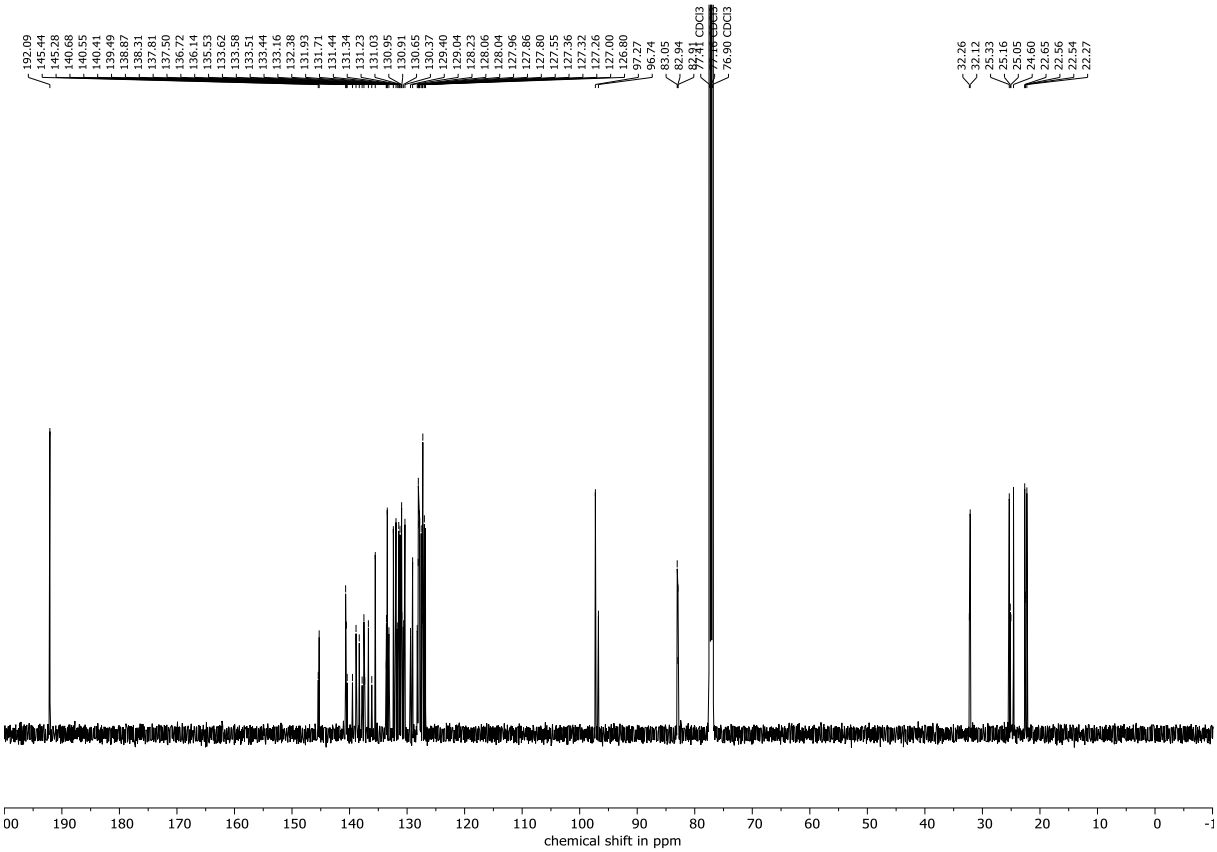
^{13}C NMR (101 MHz, $CDCl_3$) of **135**



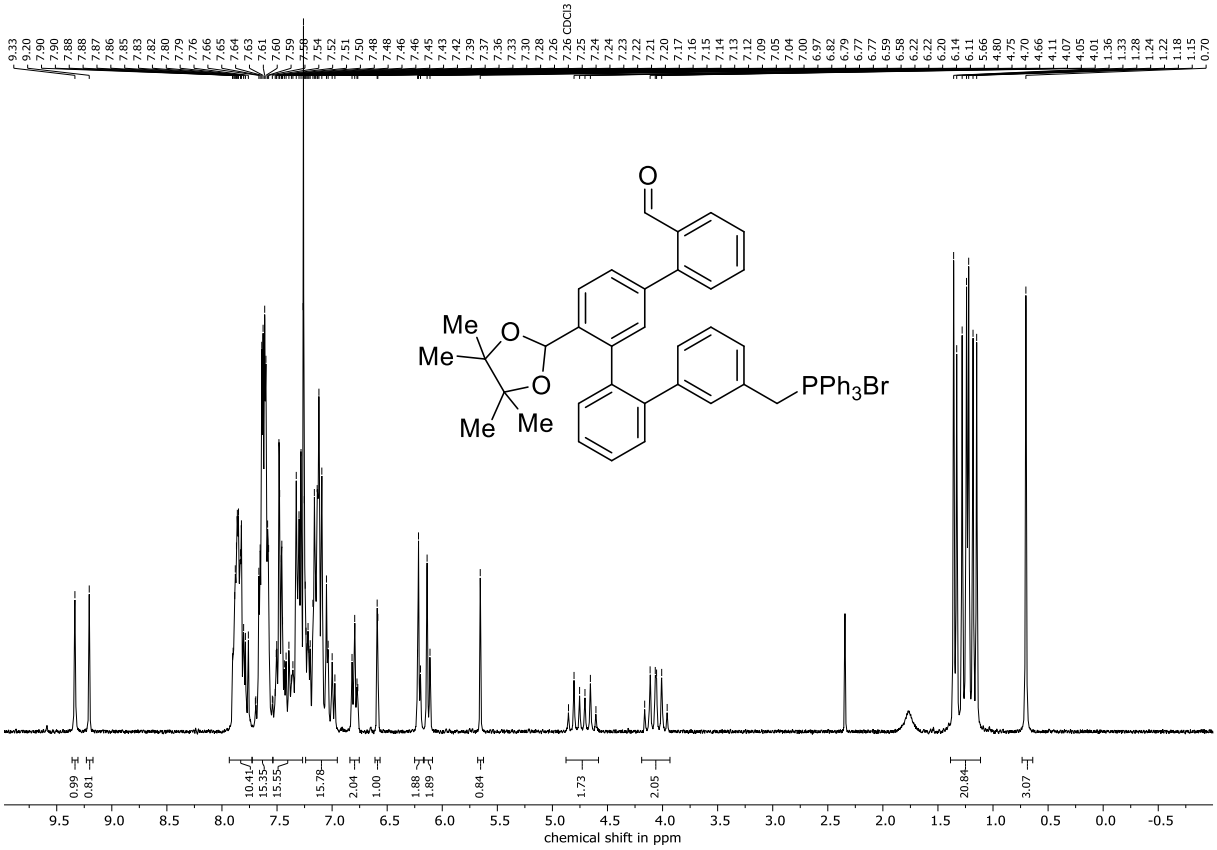
^{1}H NMR (300 MHz, $CDCl_3$) of **136**



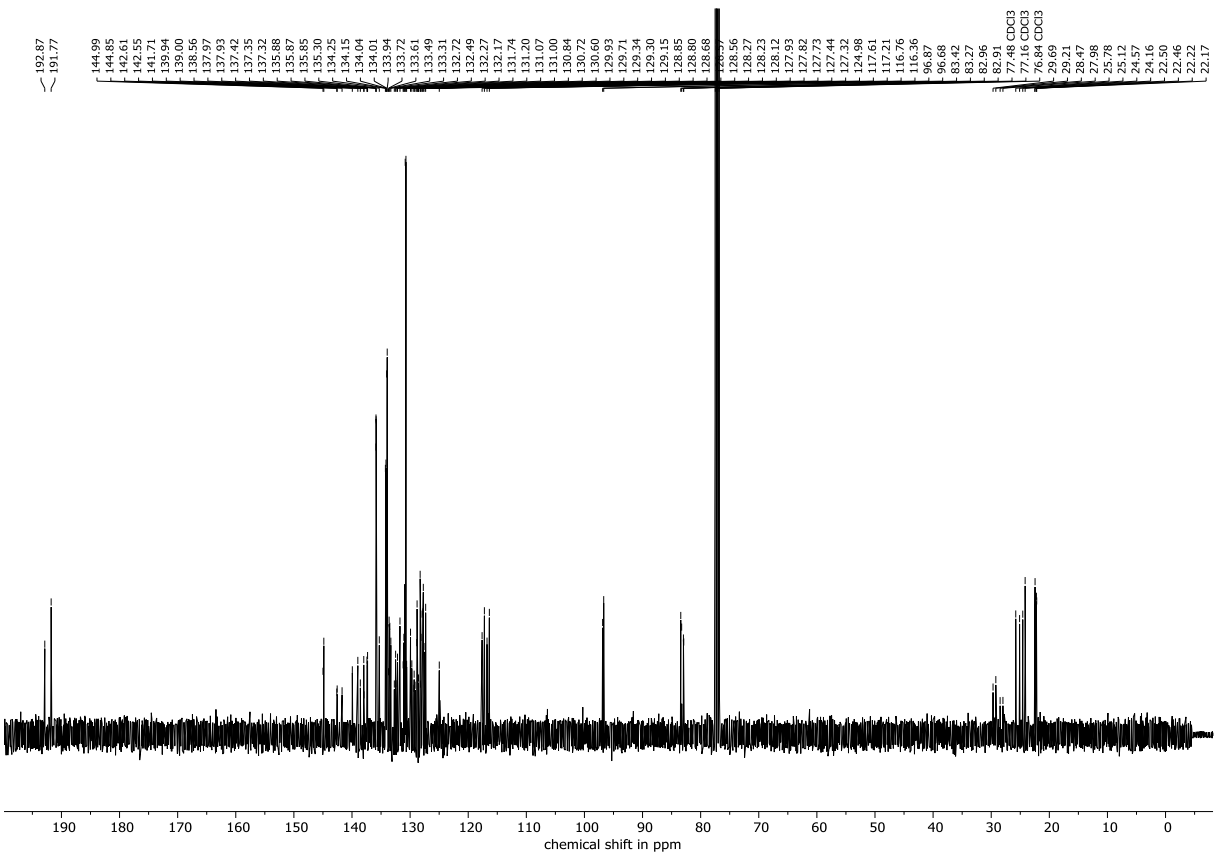
^{13}C NMR (126 MHz, $CDCl_3$) of **136**



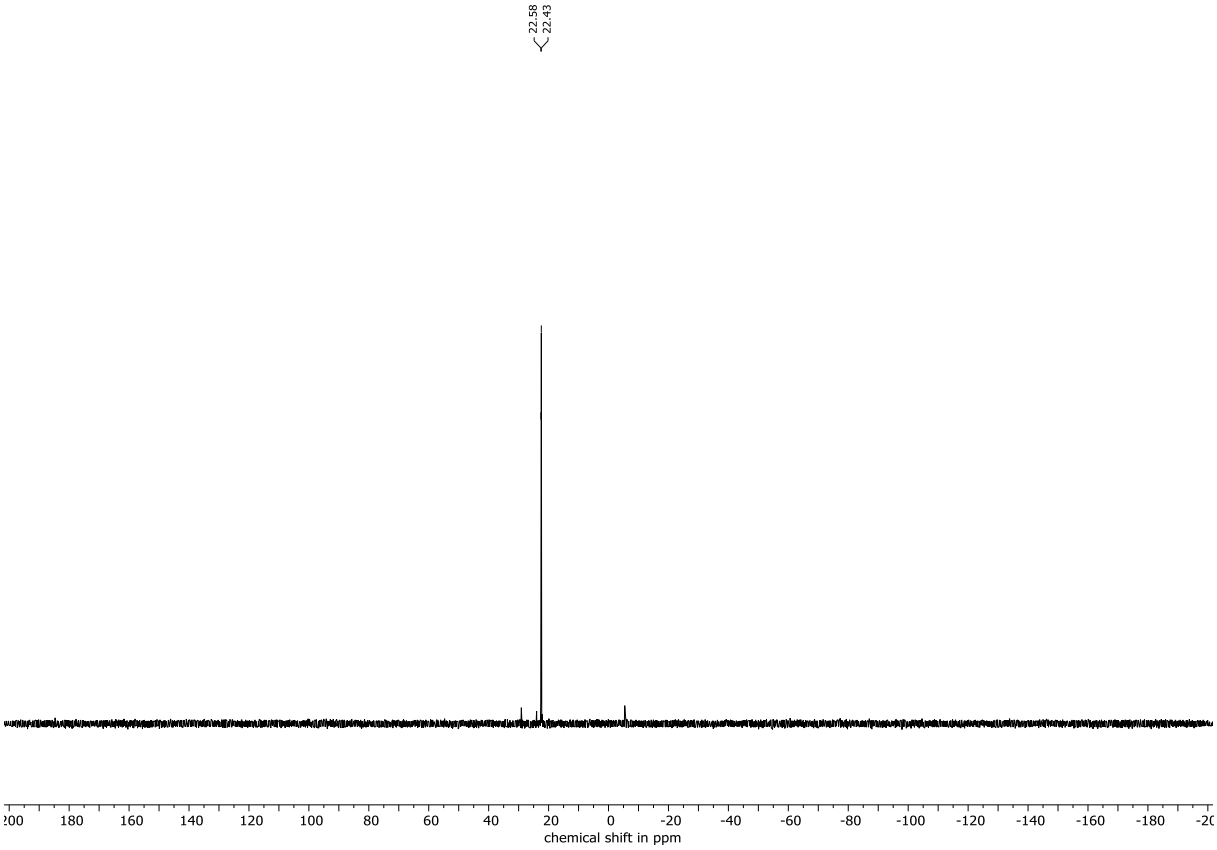
^{1}H NMR (300 MHz, $CDCl_3$) of **137**



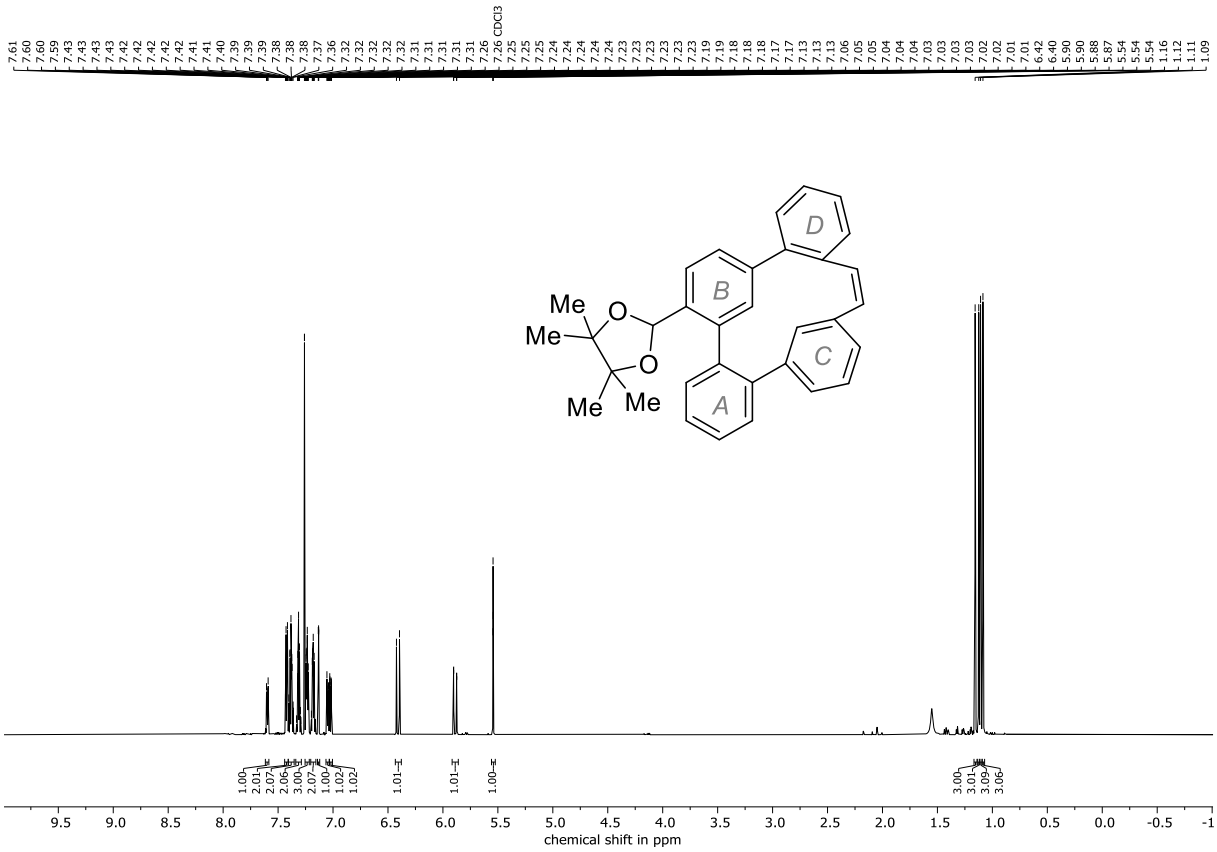
^{13}C NMR (101 MHz, $CDCl_3$) of **137**



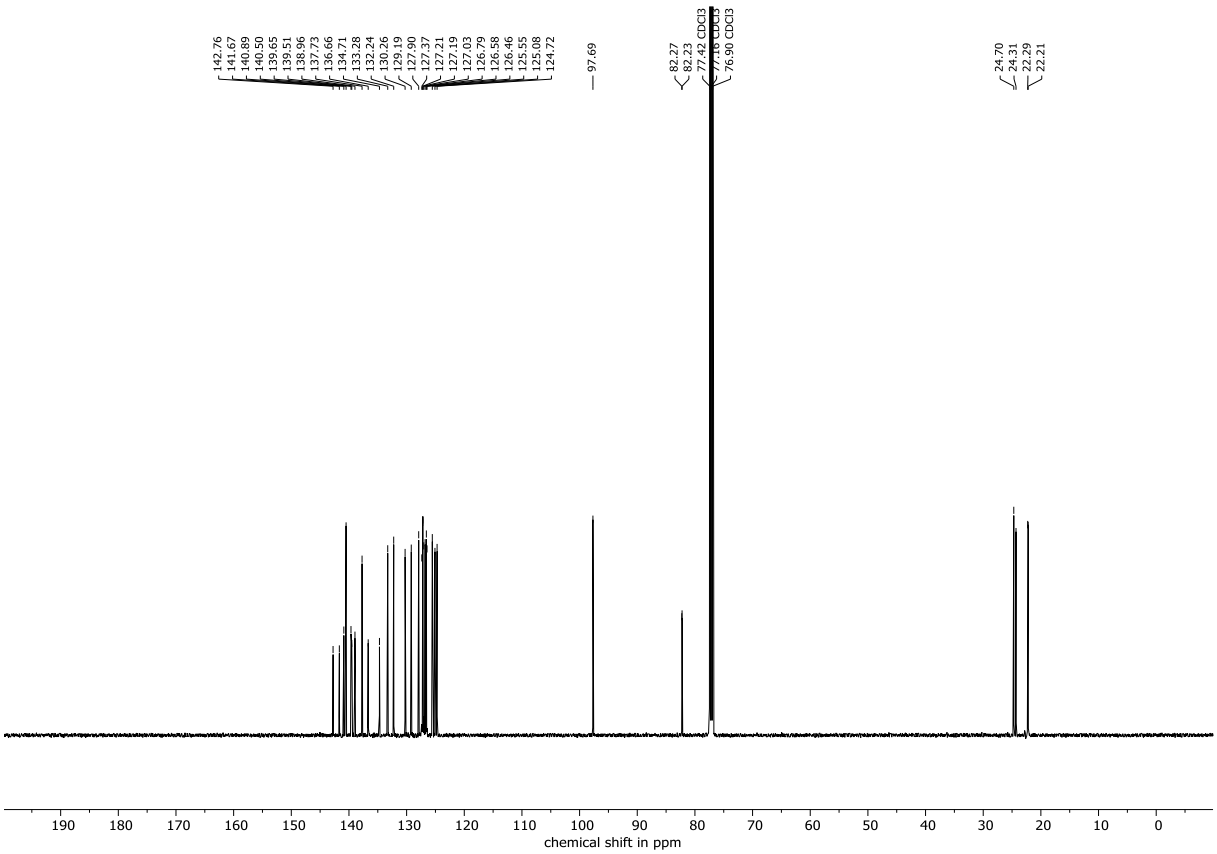
^{31}P NMR (121 MHz, $CDCl_3$) of **137**



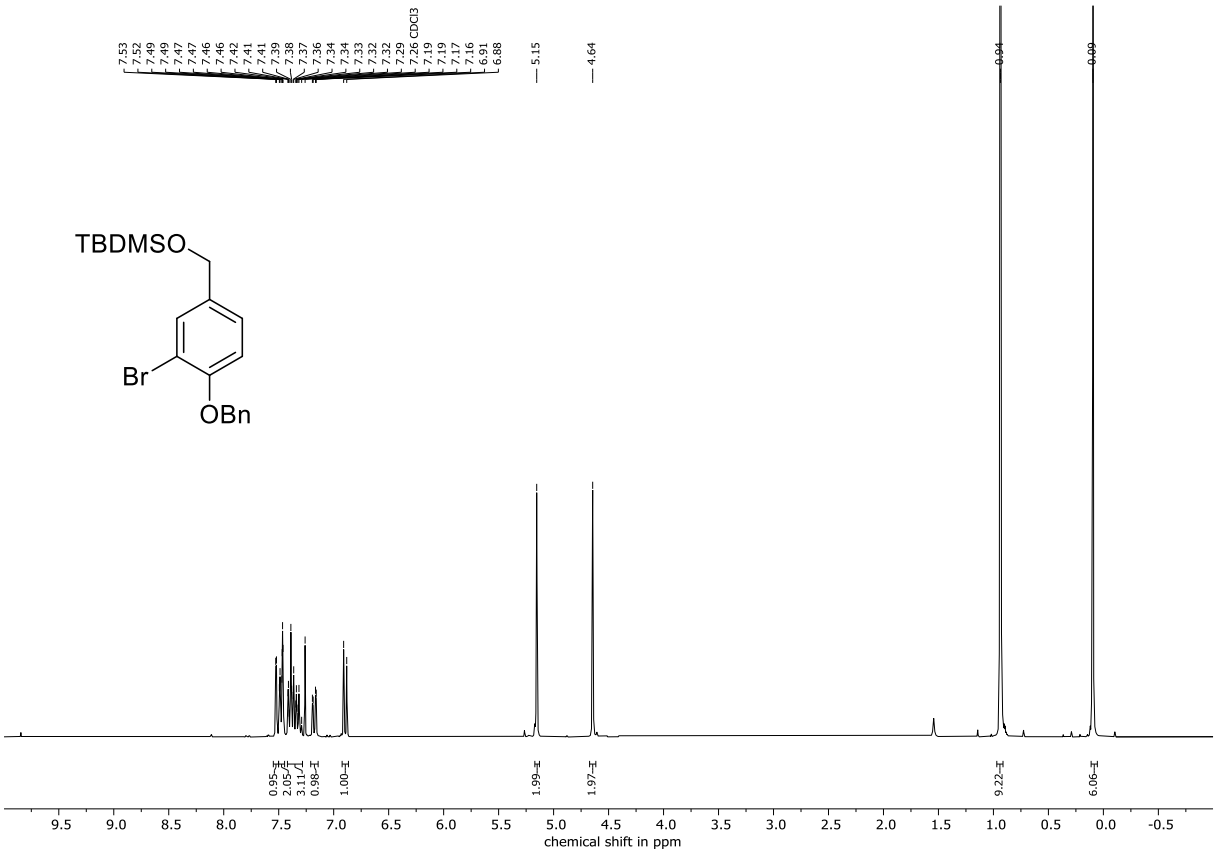
^{1}H NMR (600 MHz, $CDCl_3$) of **138**



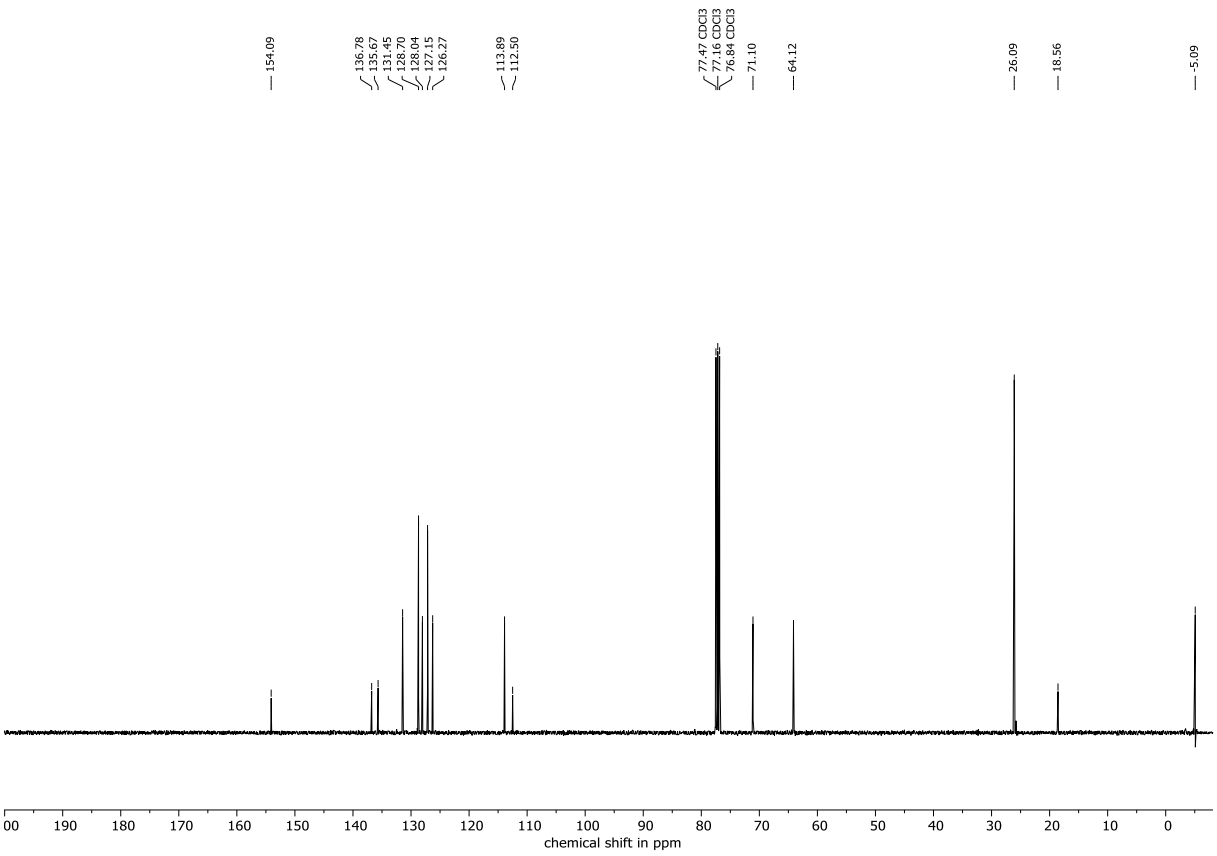
^{13}C NMR (126 MHz, $CDCl_3$) of **138**



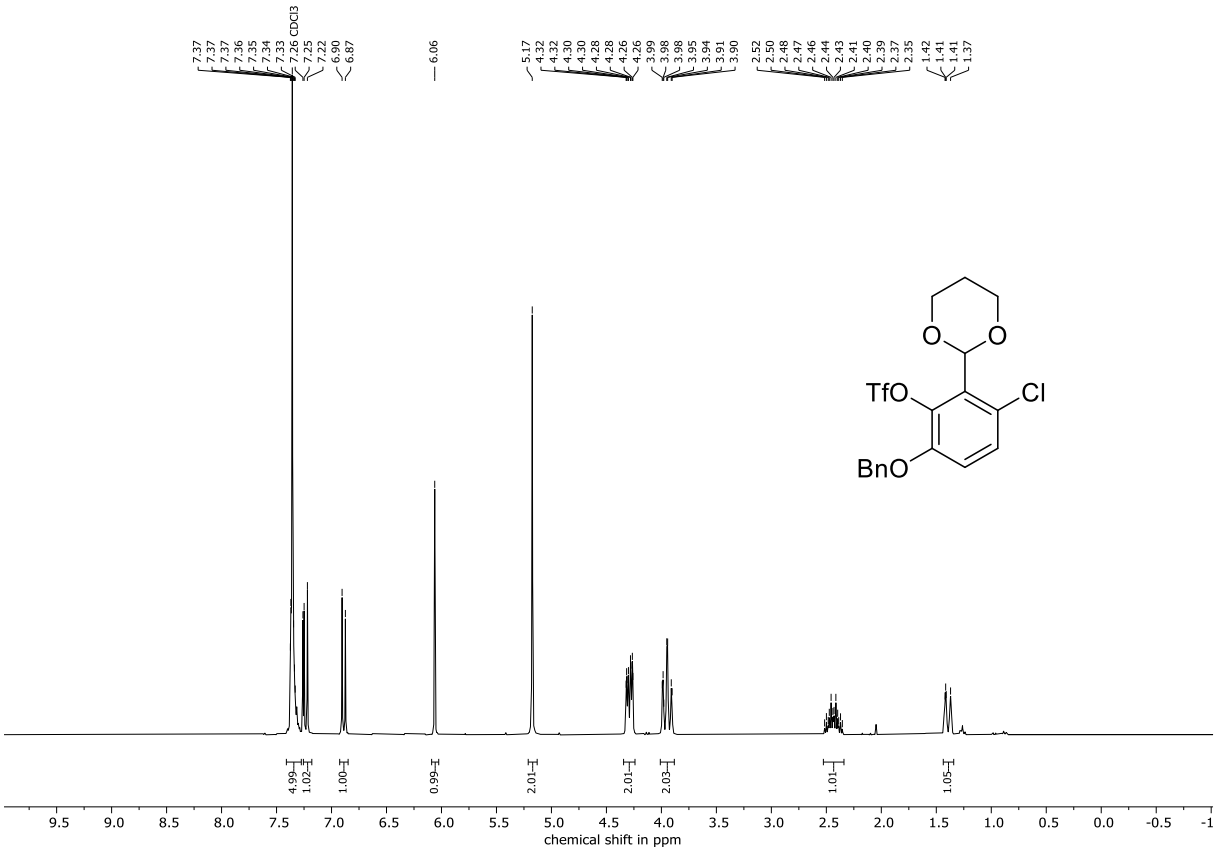
^{1}H NMR (300 MHz, $CDCl_3$) of **141**



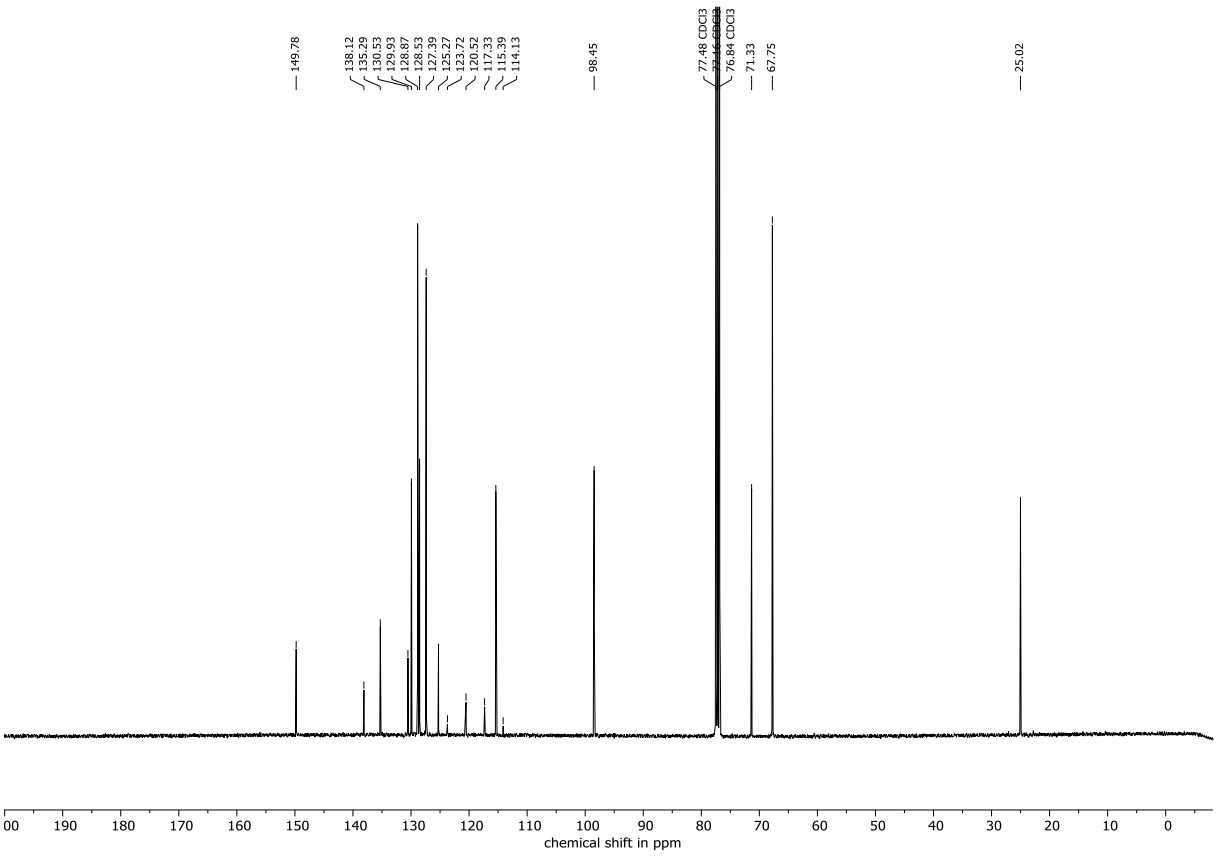
^{13}C NMR (101 MHz, $CDCl_3$) of **141**



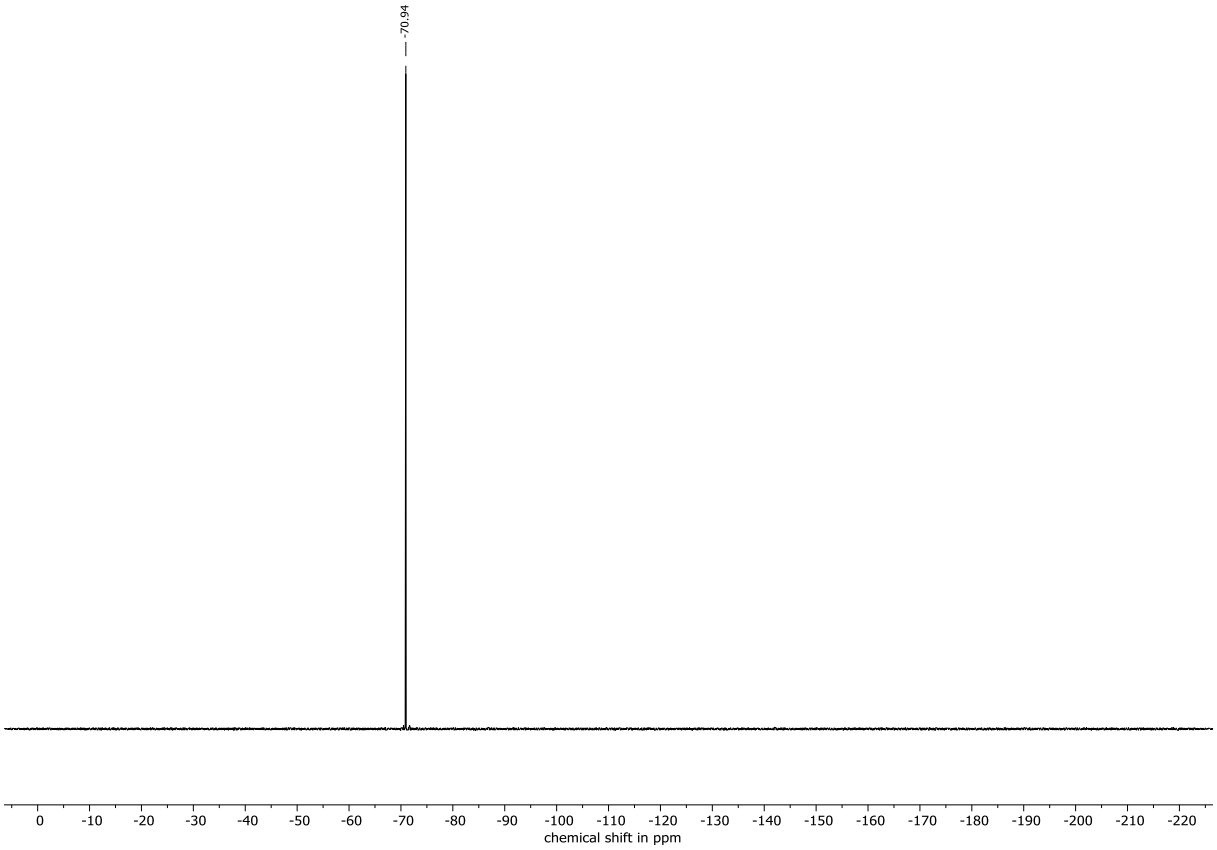
^{1}H NMR (300 MHz, $CDCl_3$) of **142**



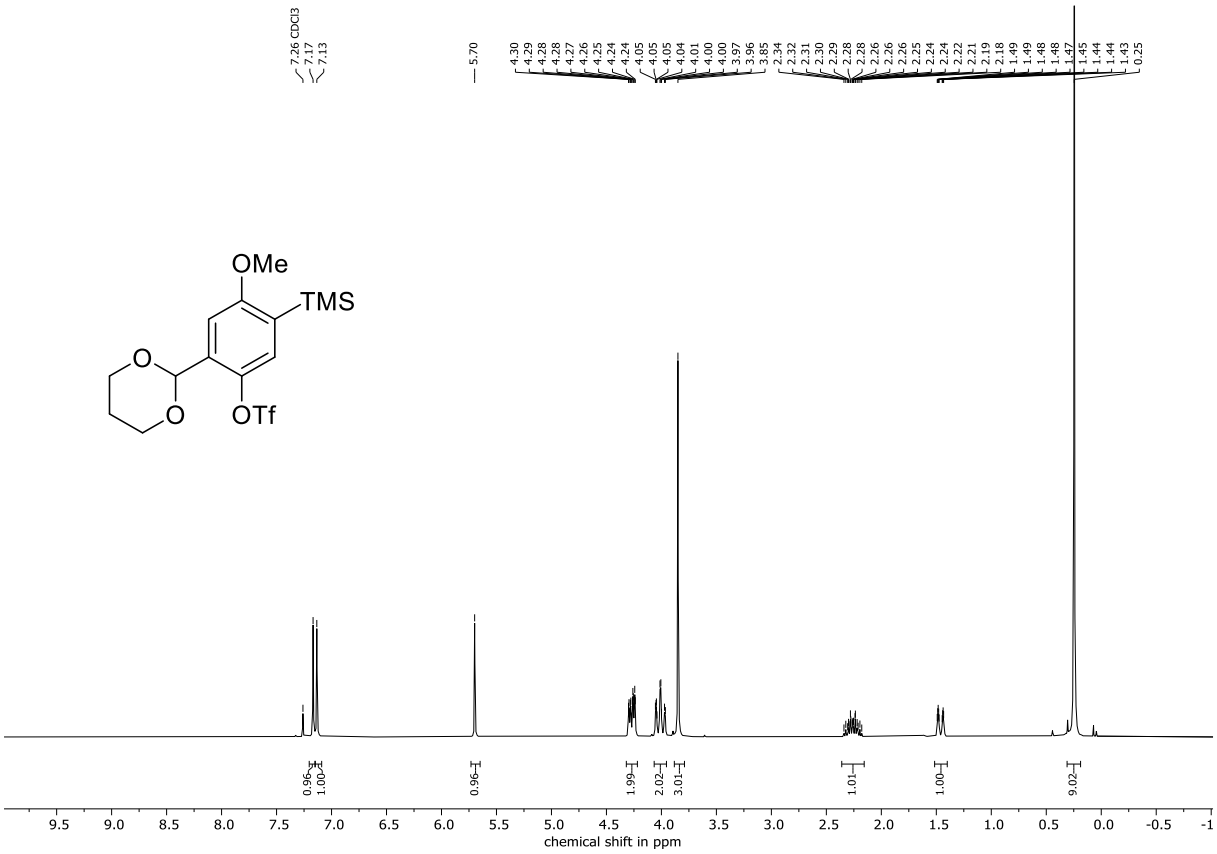
^{13}C NMR (101 MHz, $CDCl_3$) of **142**



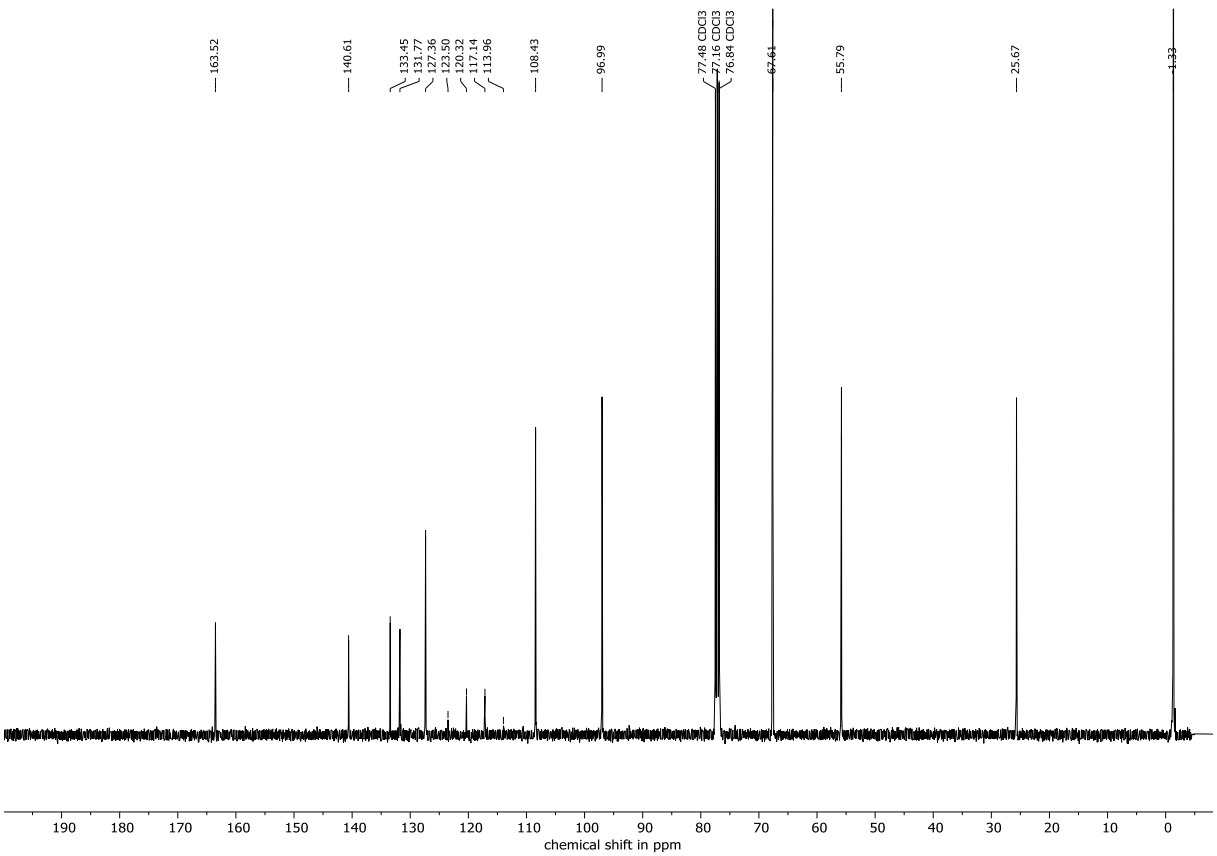
^{19}F NMR (282 MHz, $CDCl_3$) of **142**



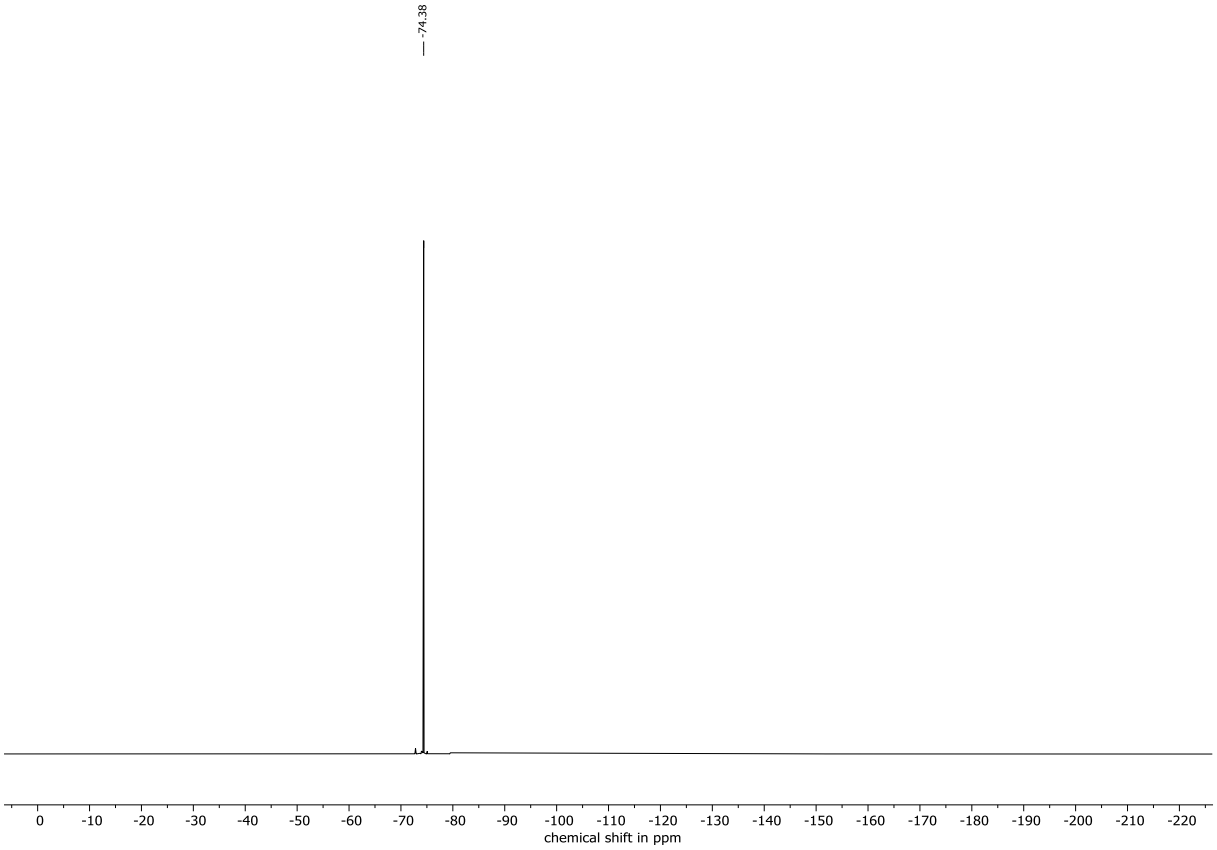
^{1}H NMR (300 MHz, $CDCl_3$) of **143**



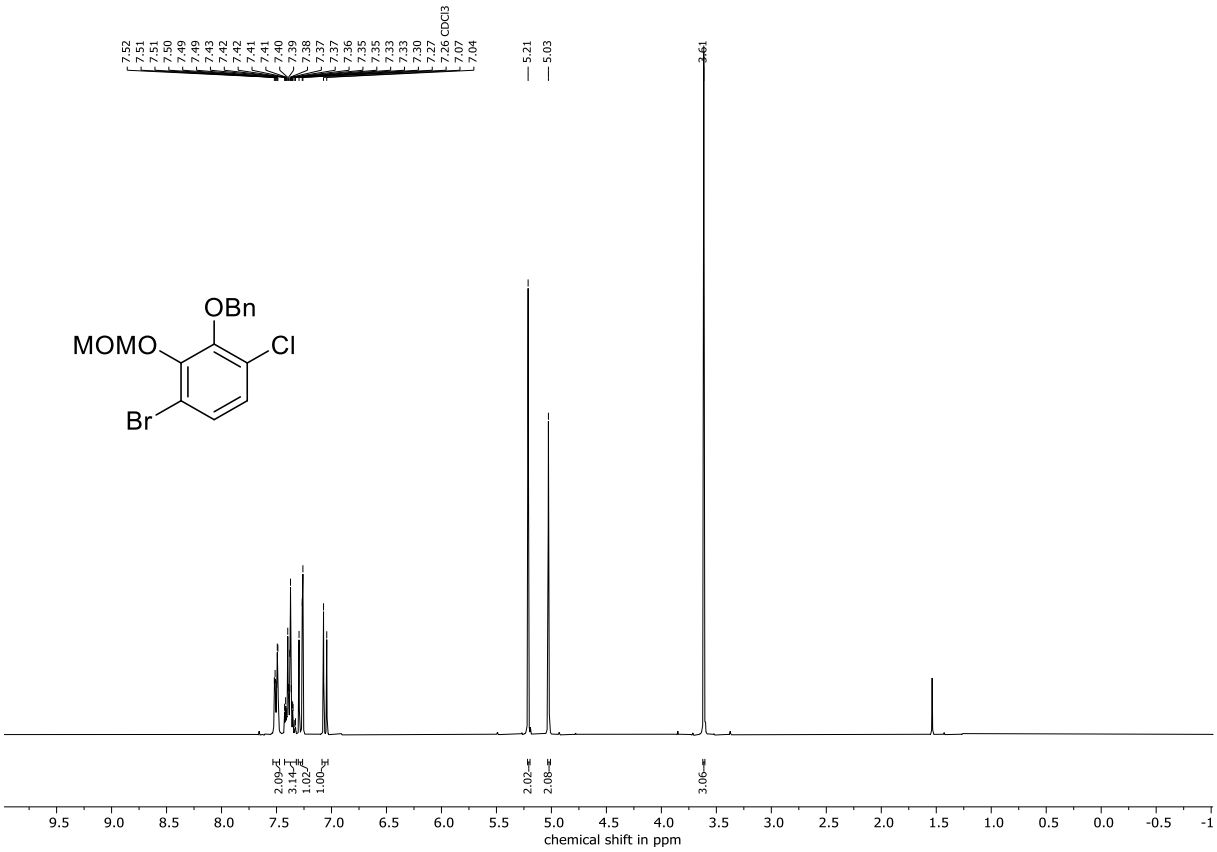
^{13}C NMR (101 MHz, $CDCl_3$) of **143**



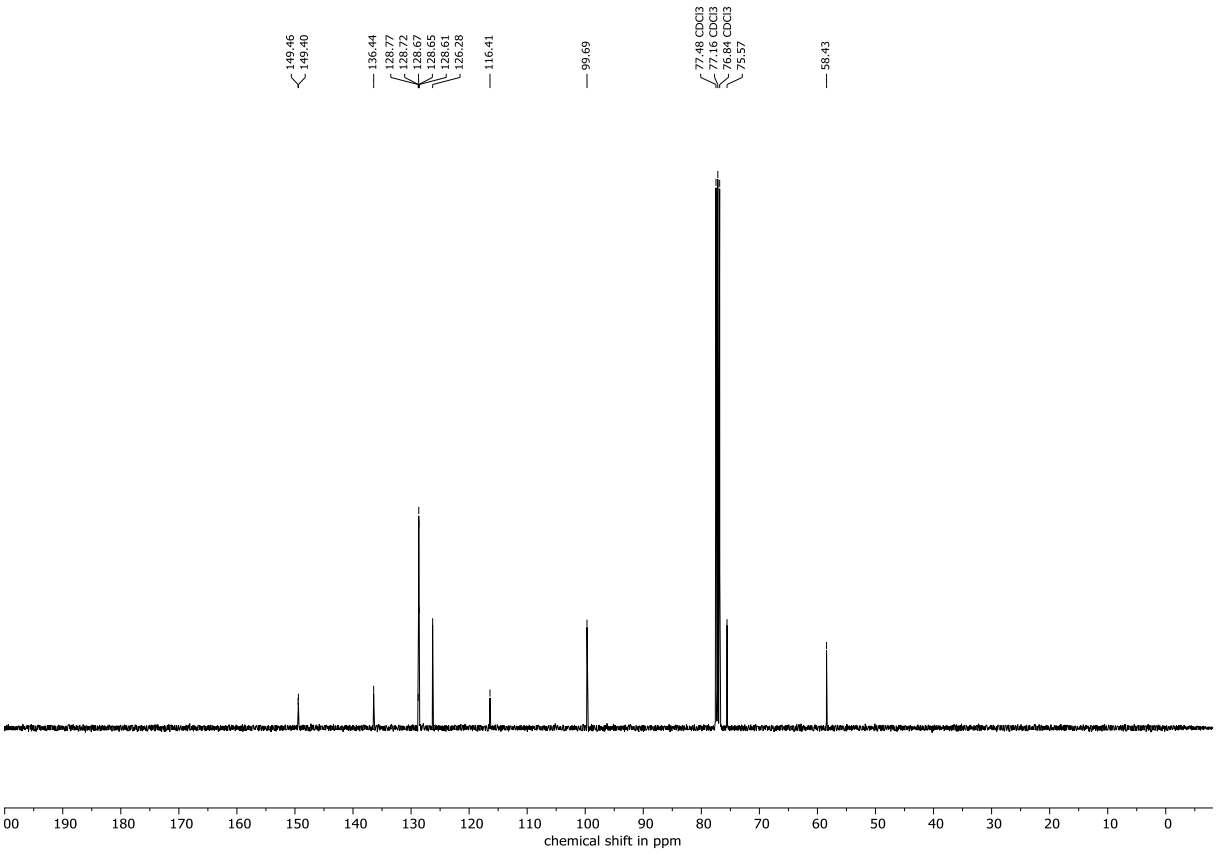
^{19}F NMR (282 MHz, $CDCl_3$) of **143**



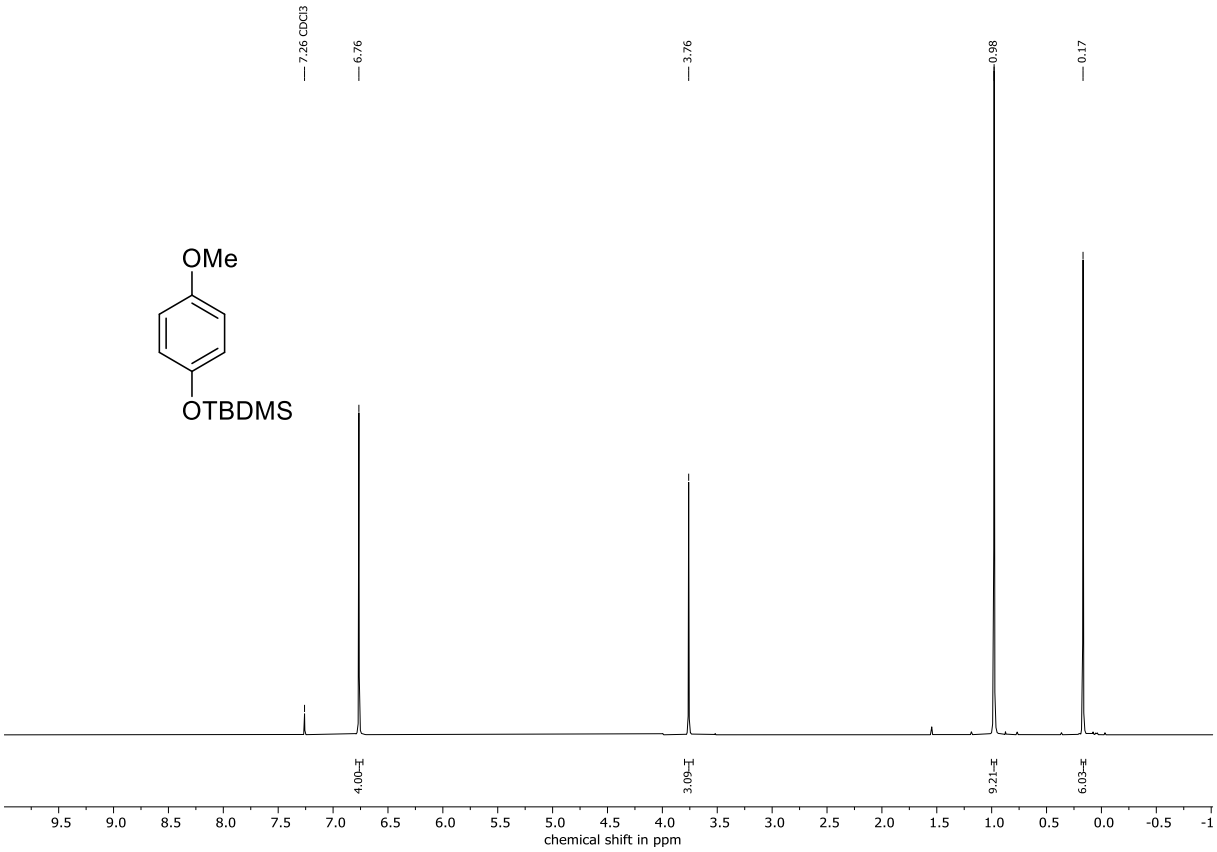
^{1}H NMR (300 MHz, $CDCl_3$) of **144**



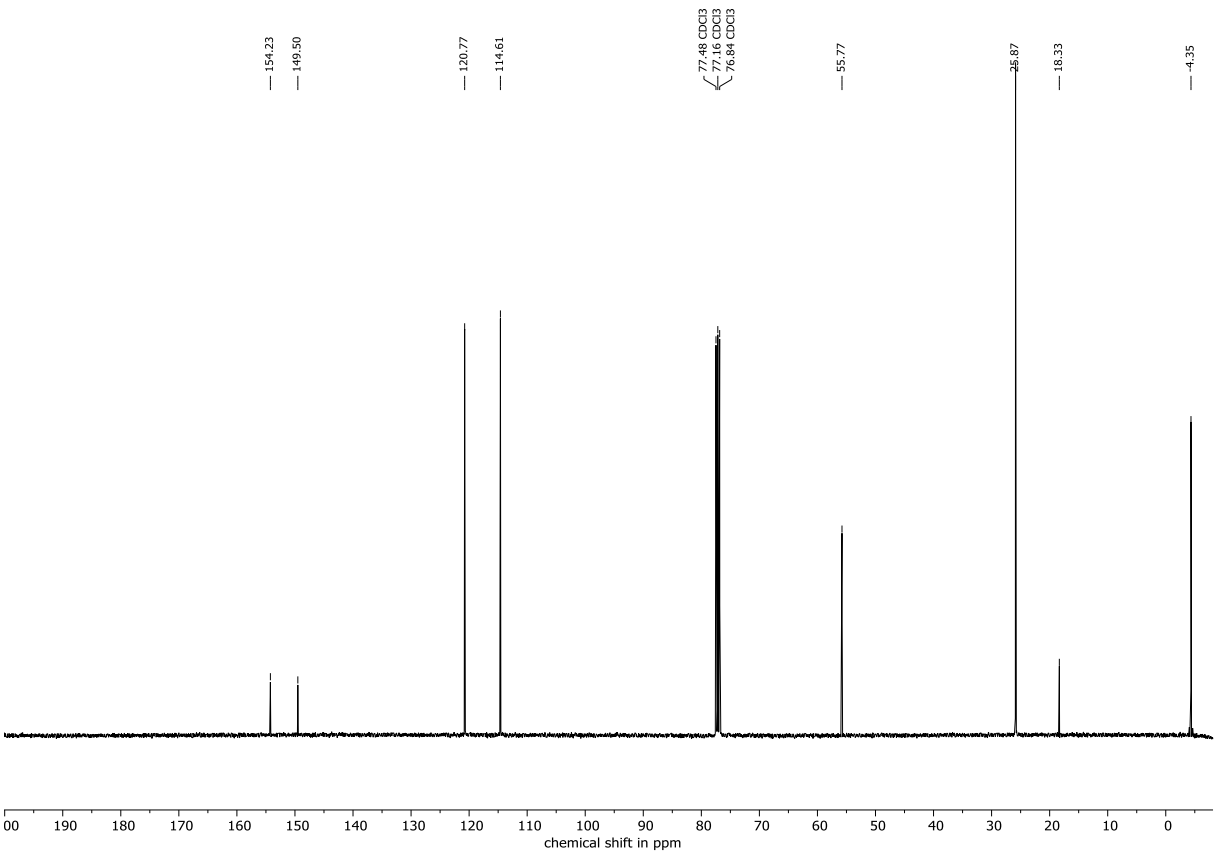
^{13}C NMR (101 MHz, $CDCl_3$) of **144**



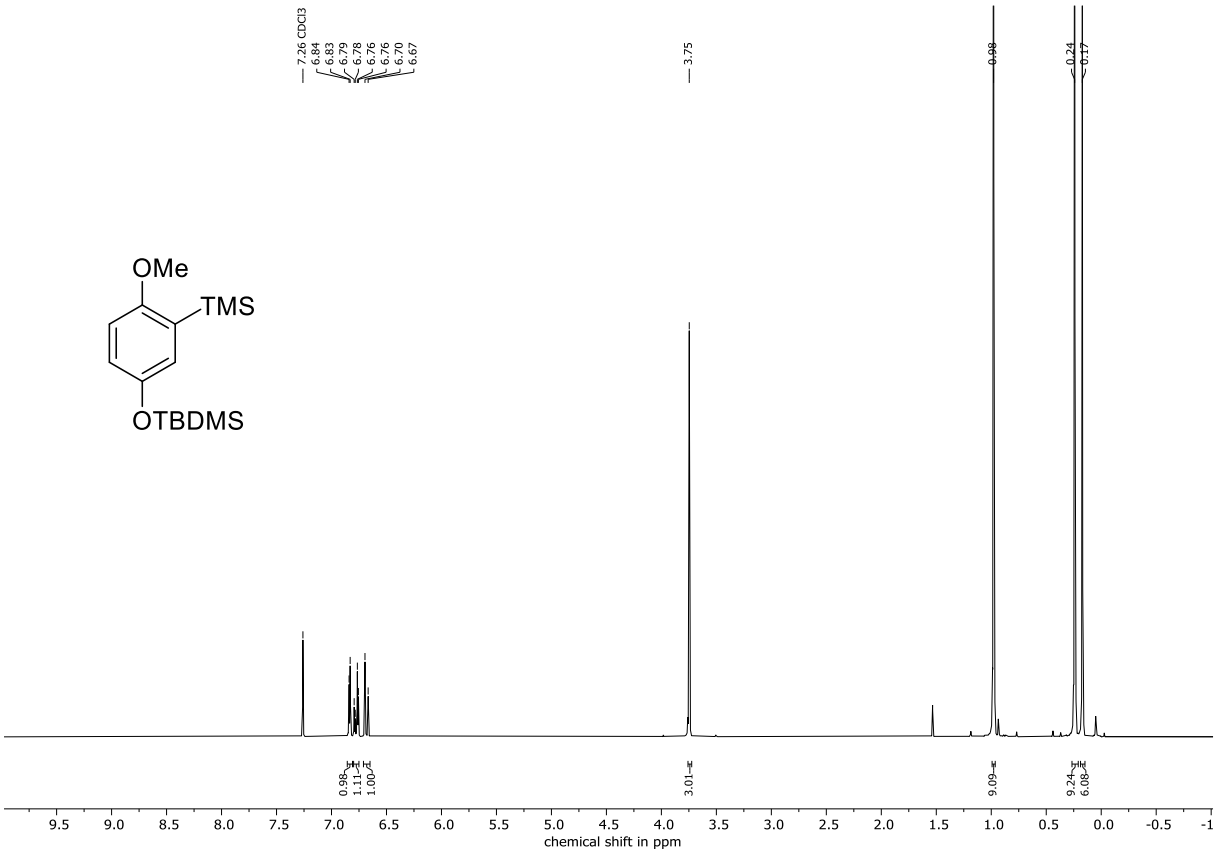
^{1}H NMR (300 MHz, $CDCl_3$) of **146**



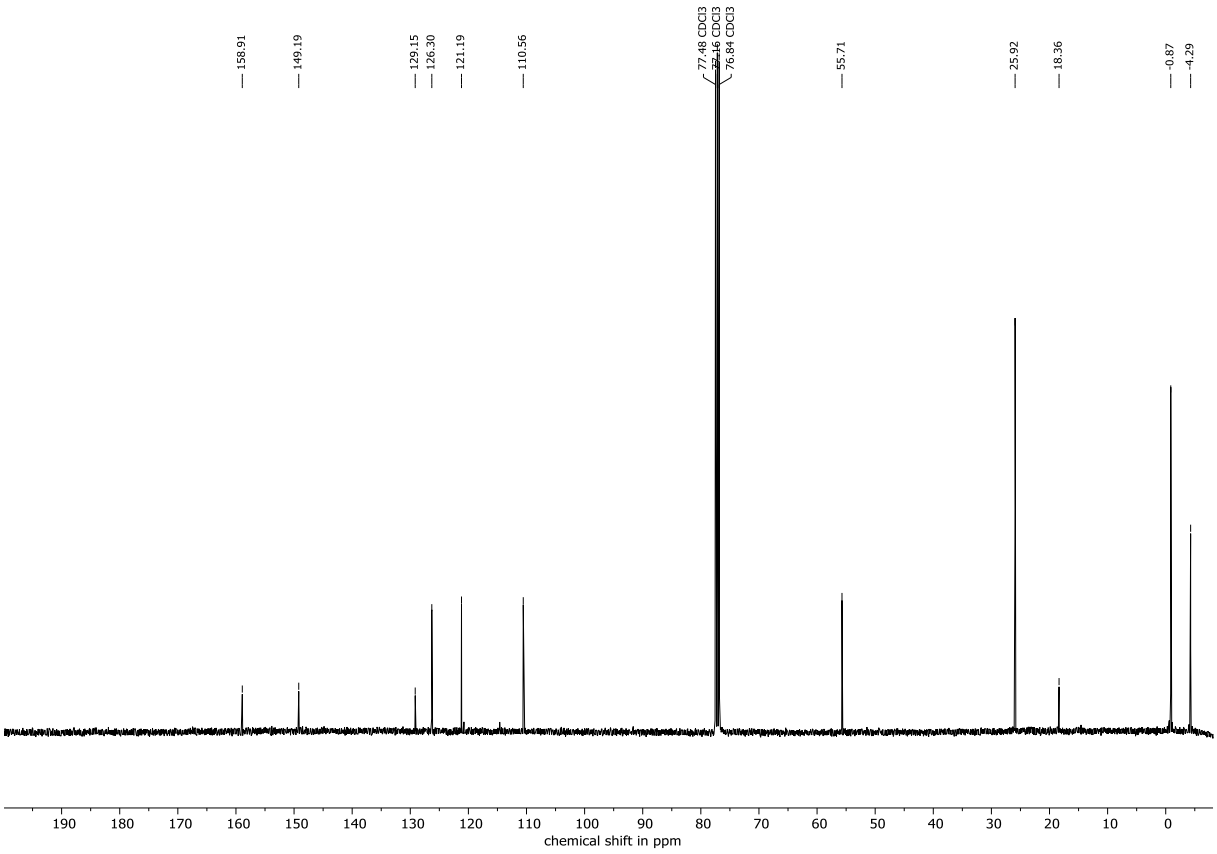
^{13}C NMR (101 MHz, $CDCl_3$) of **146**



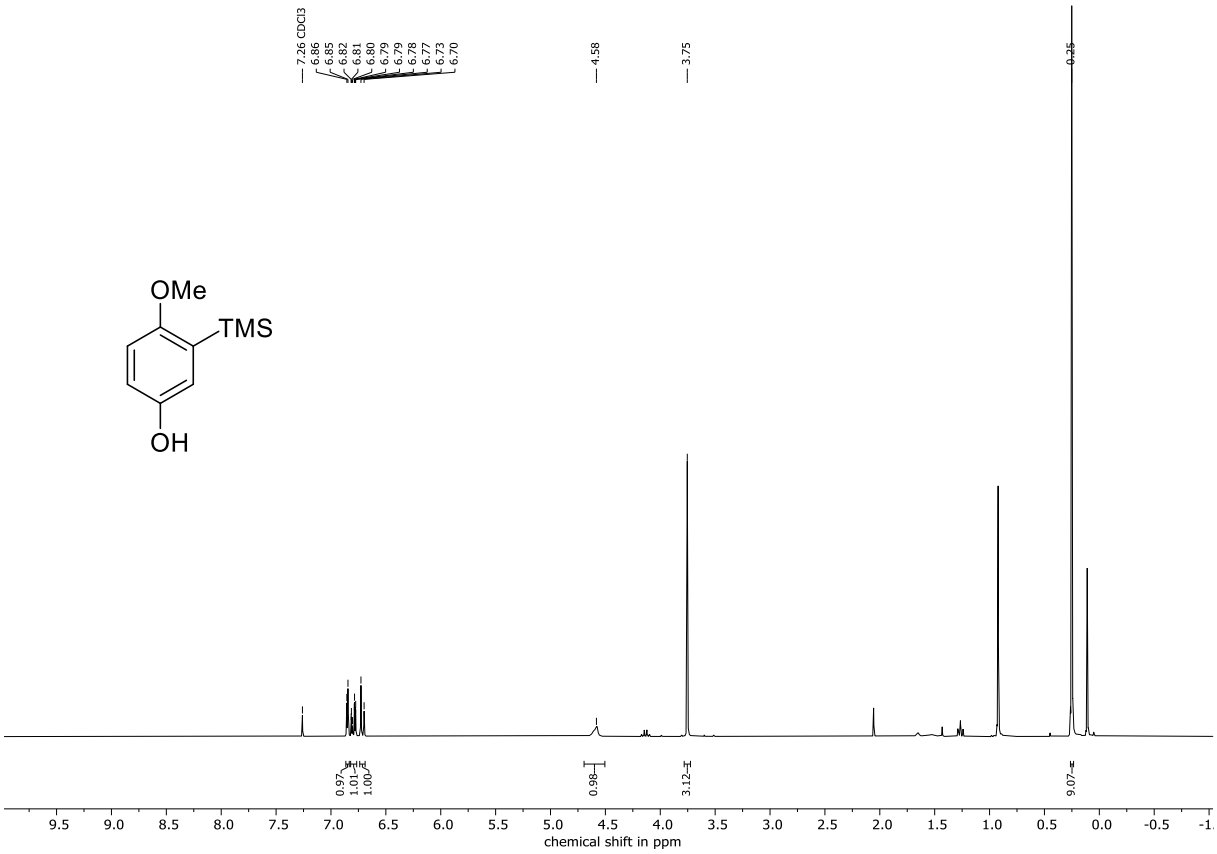
^{1}H NMR (300 MHz, $CDCl_3$) of **147**



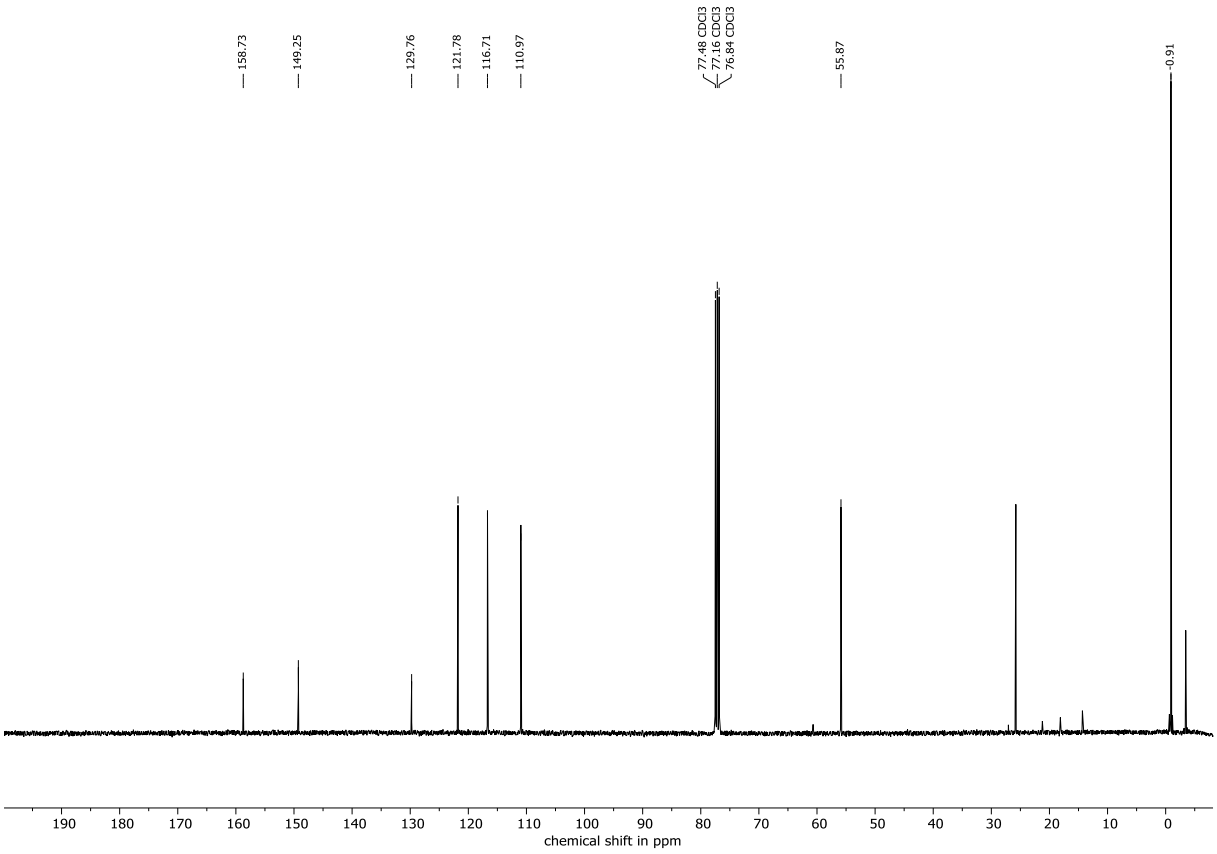
^{13}C NMR (101 MHz, $CDCl_3$) of **147**



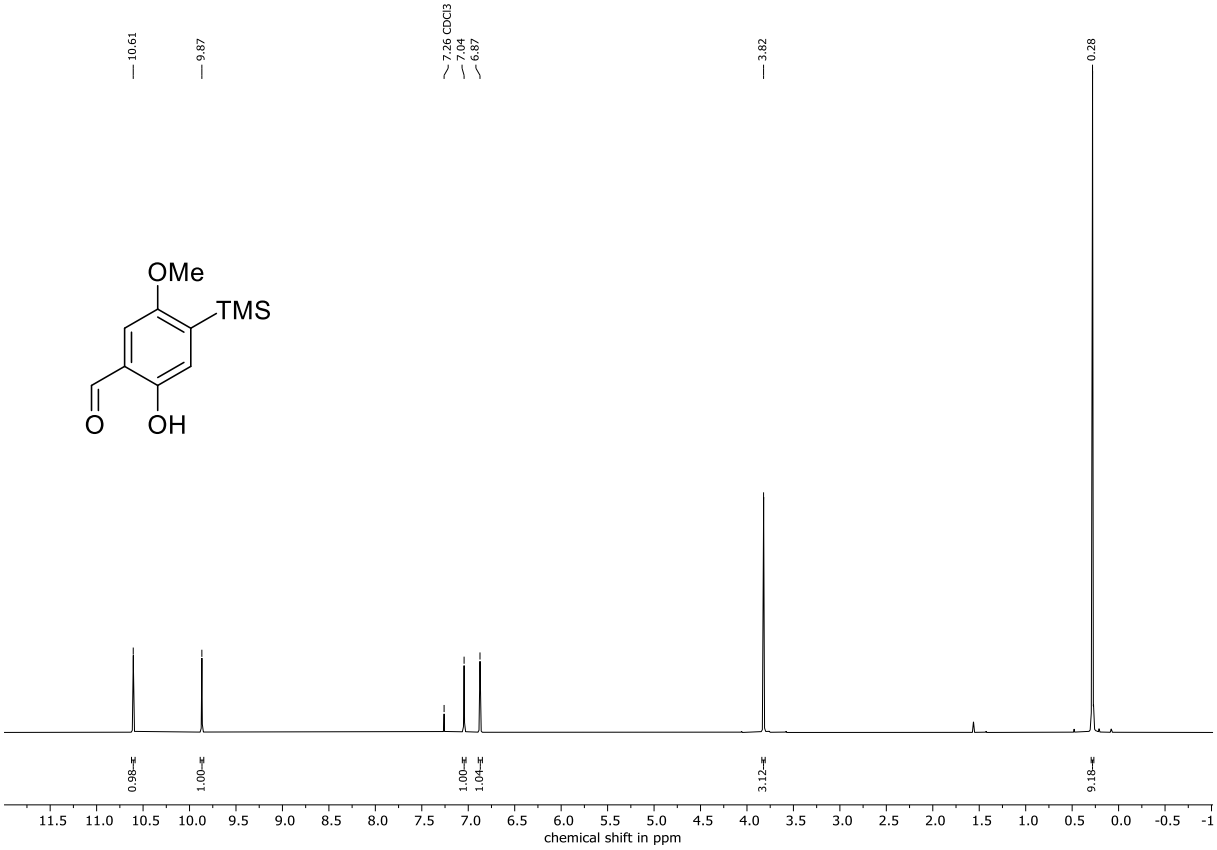
^{1}H NMR (300 MHz, $CDCl_3$) of **148**



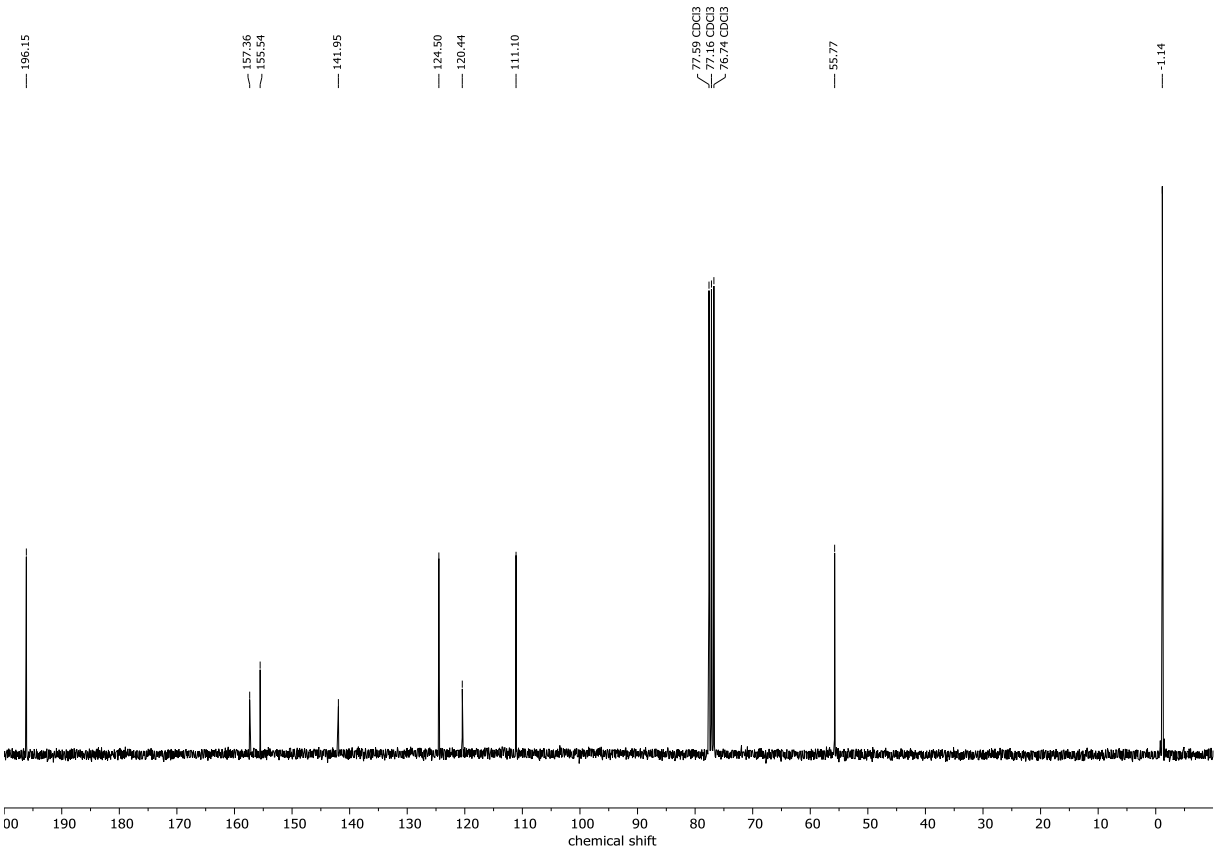
^{13}C NMR (101 MHz, $CDCl_3$) of **148**



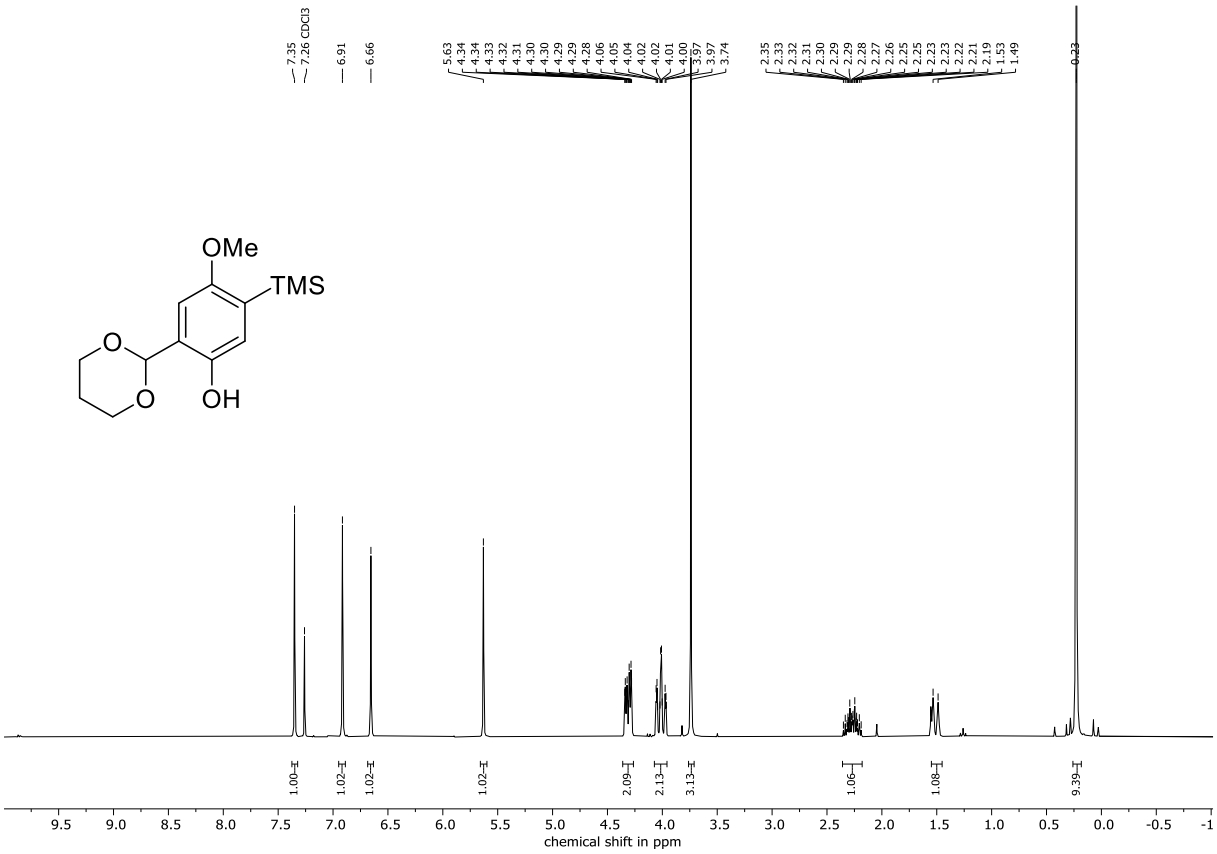
^{1}H NMR (300 MHz, $CDCl_3$) of **149**



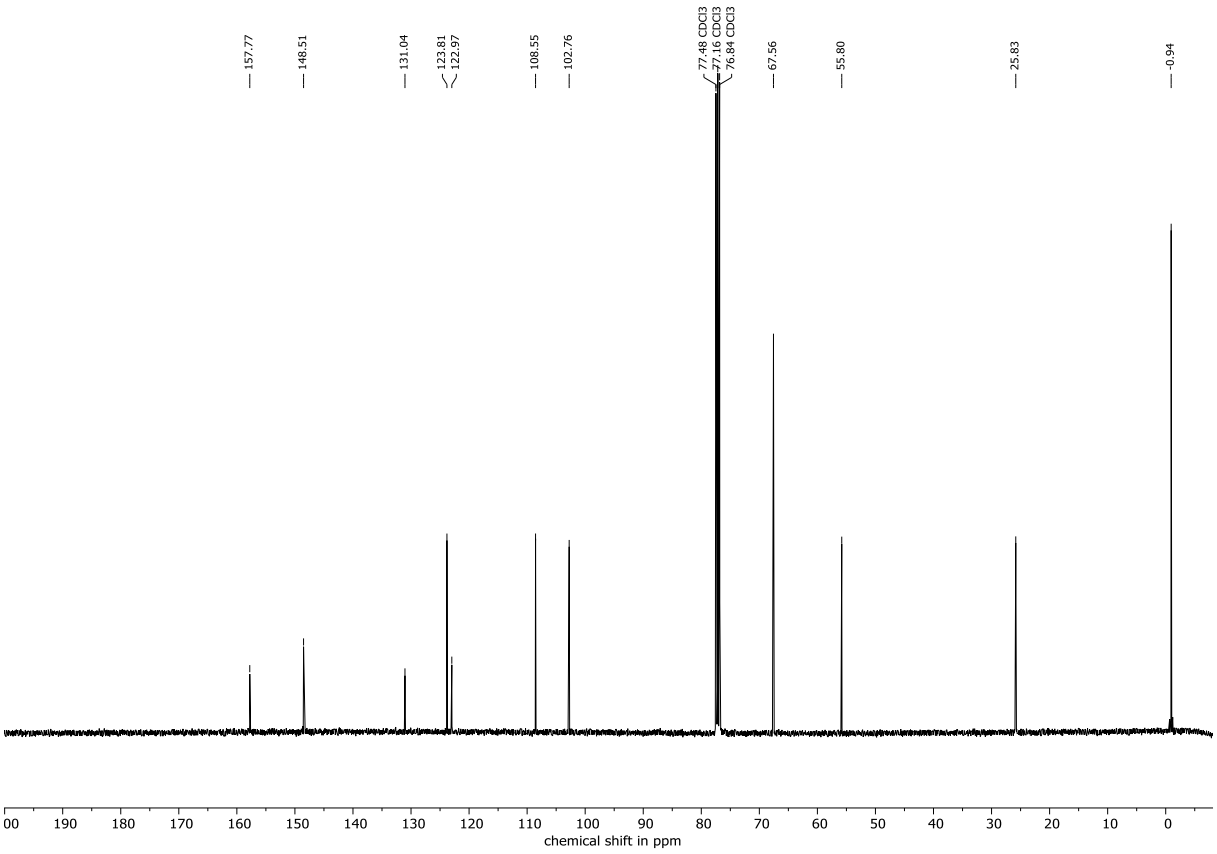
^{13}C NMR (75 MHz, $CDCl_3$) of **149**



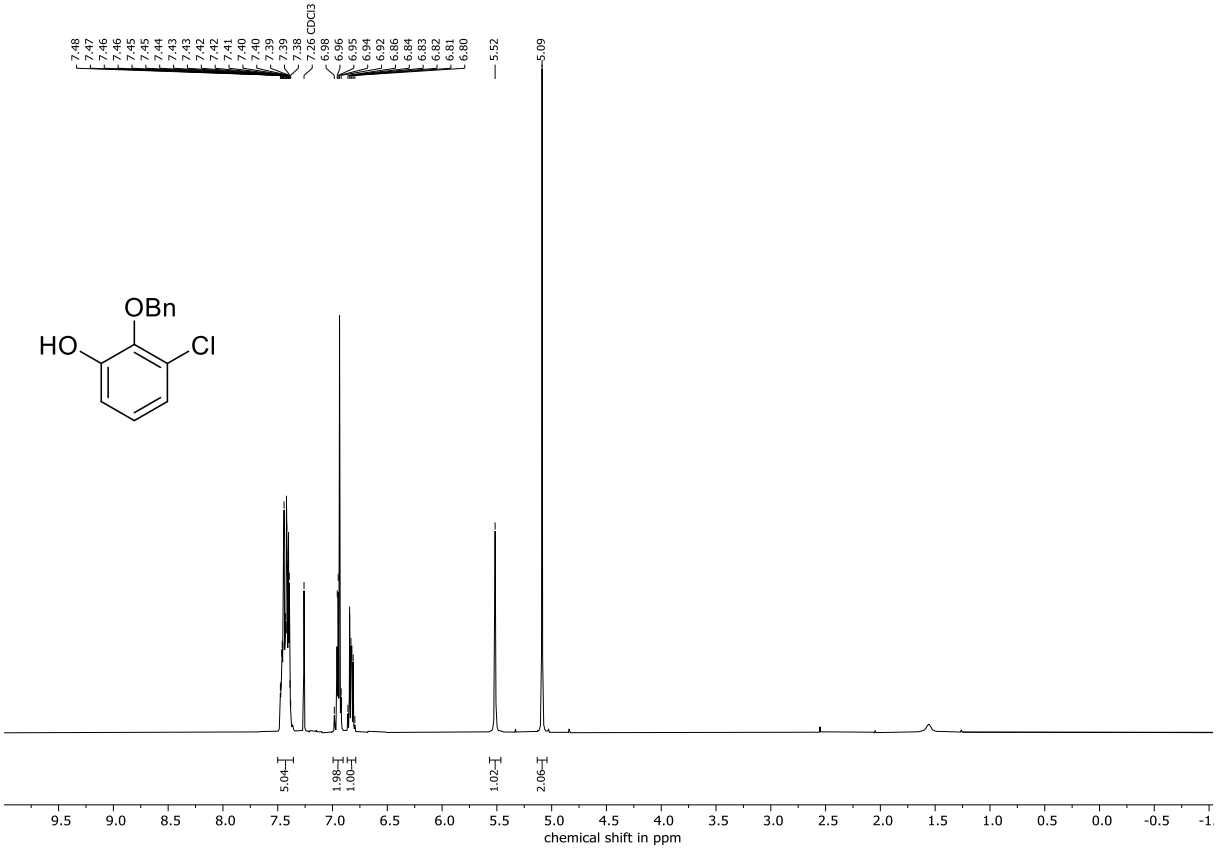
^{1}H NMR (300 MHz, $CDCl_3$) of **150**



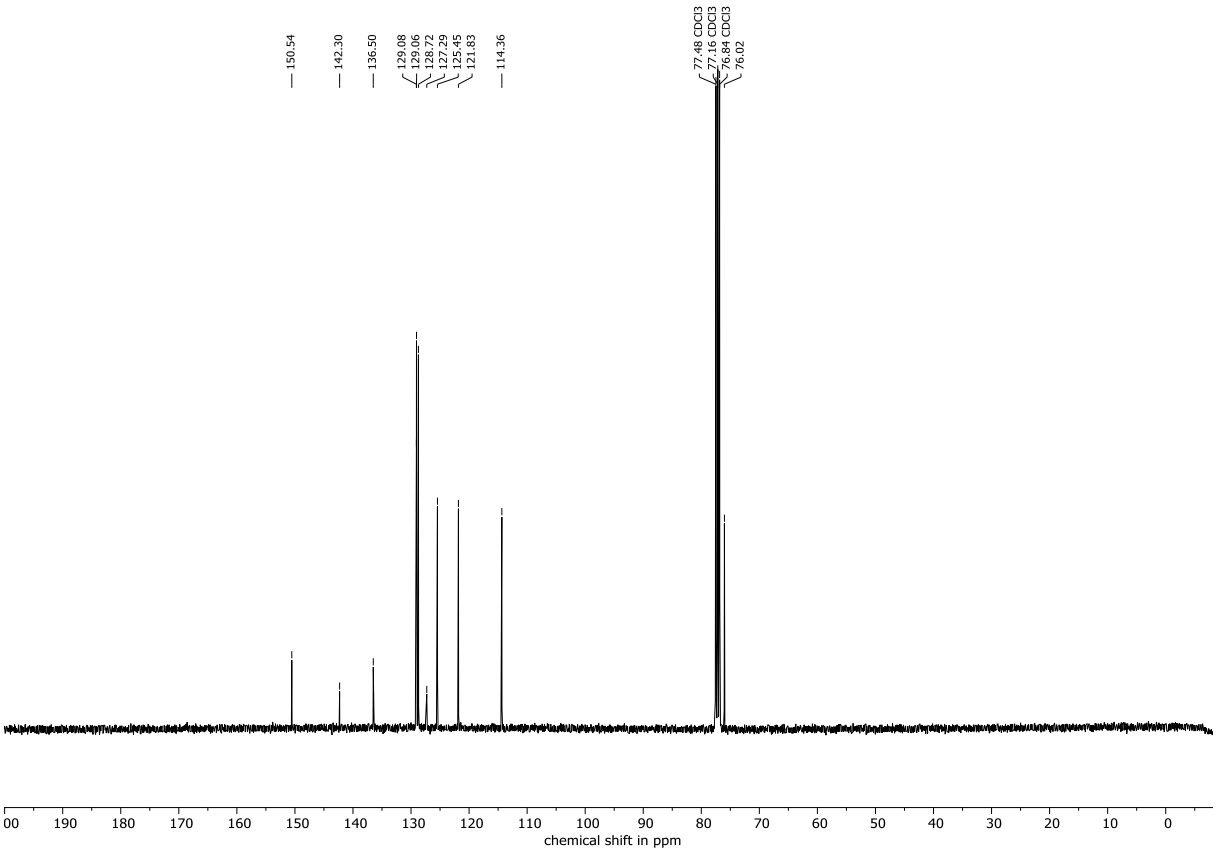
^{13}C NMR (101 MHz, $CDCl_3$) of **150**



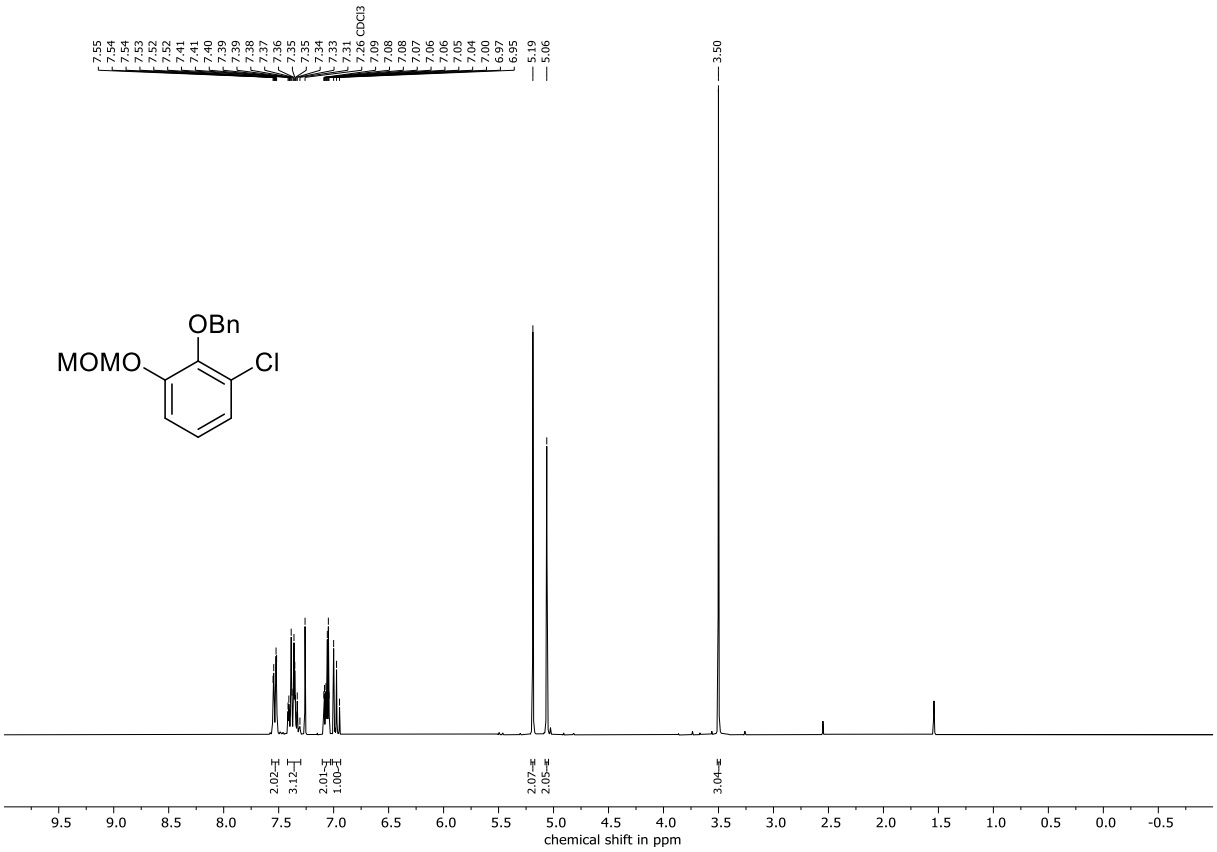
^{1}H NMR (300 MHz, $CDCl_3$) of **157**



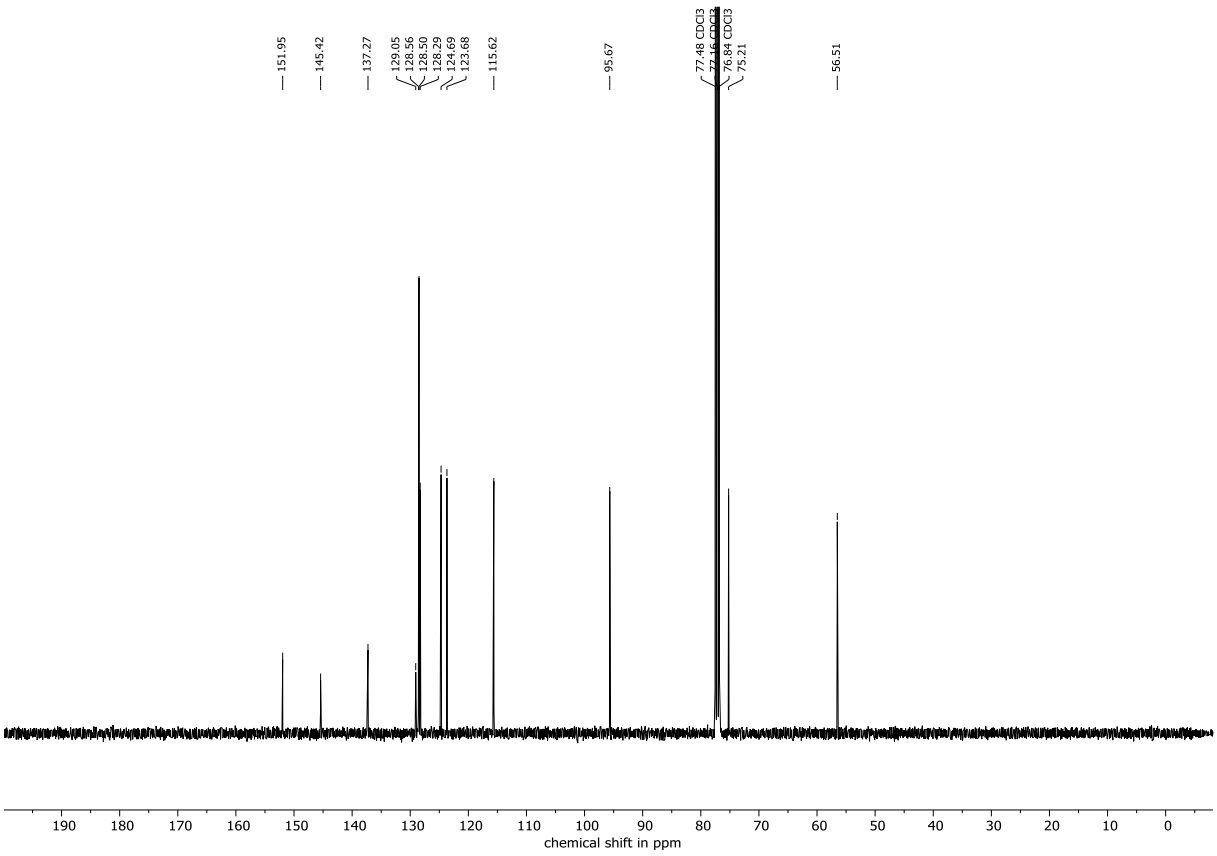
^{13}C NMR (101 MHz, $CDCl_3$) of **157**



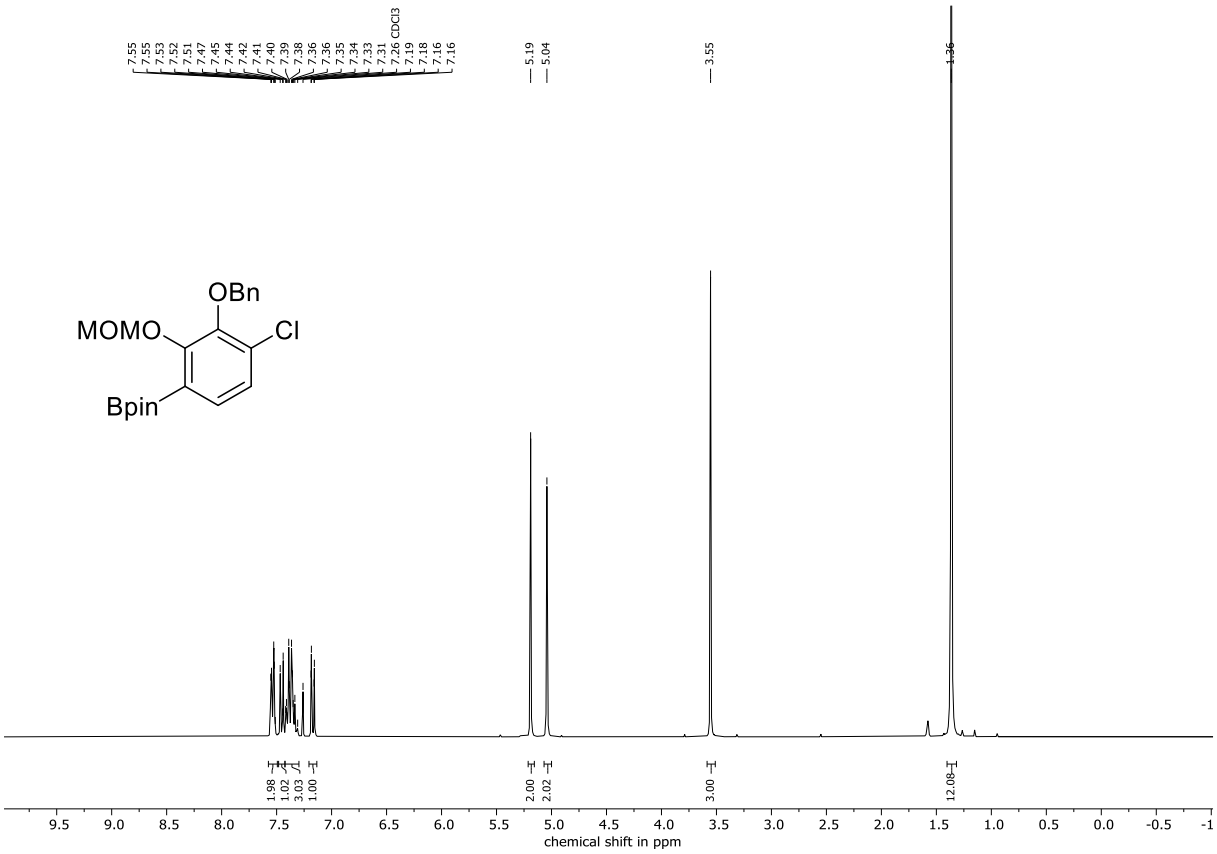
^{1}H NMR (300 MHz, $CDCl_3$) of **158**



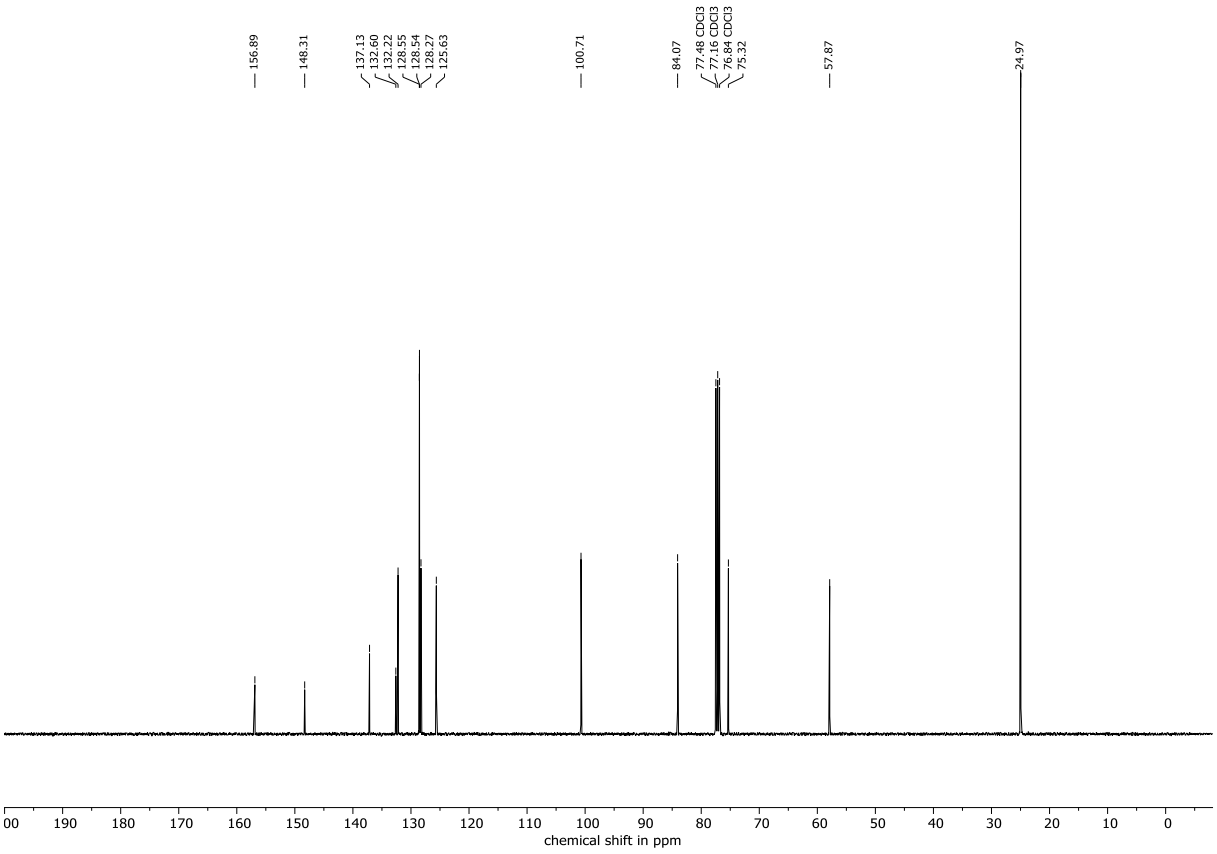
^{13}C NMR (101 MHz, $CDCl_3$) of **158**



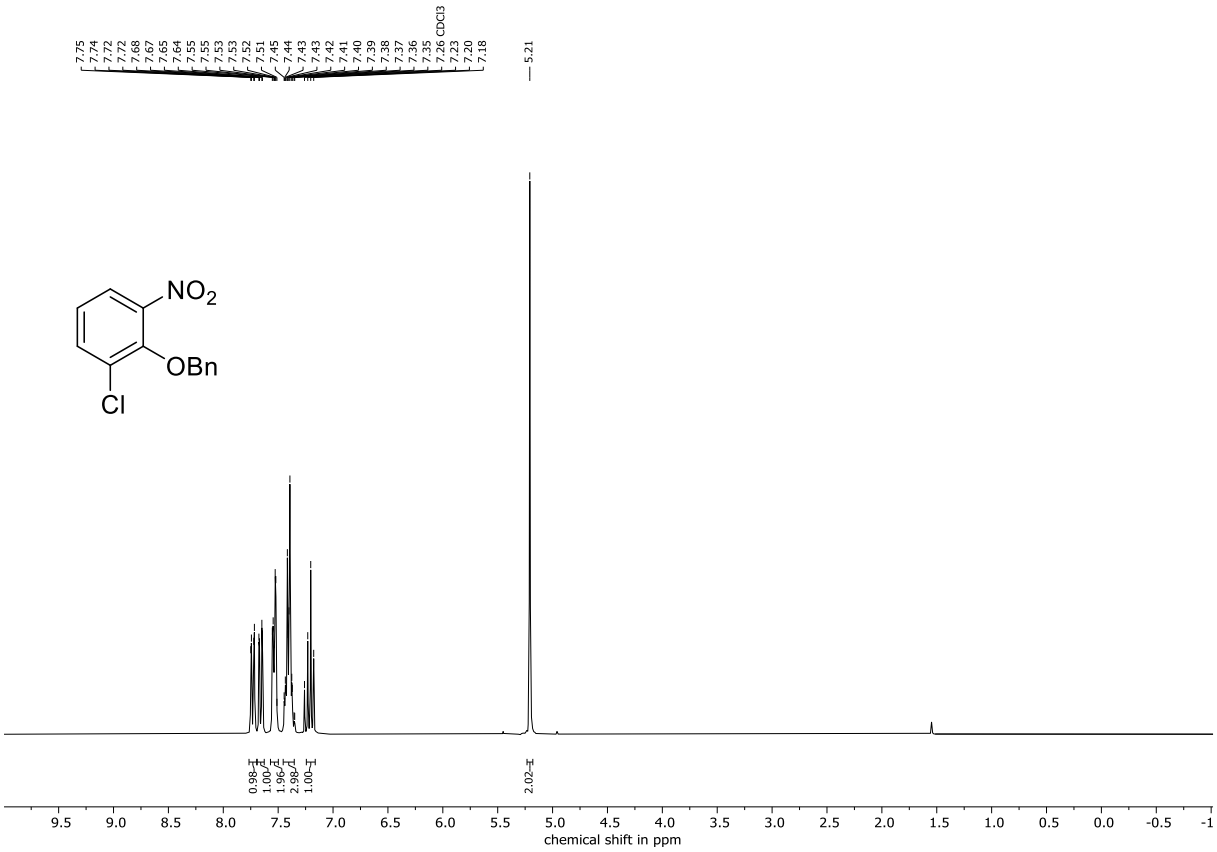
^{1}H NMR (300 MHz, $CDCl_3$) of **159**



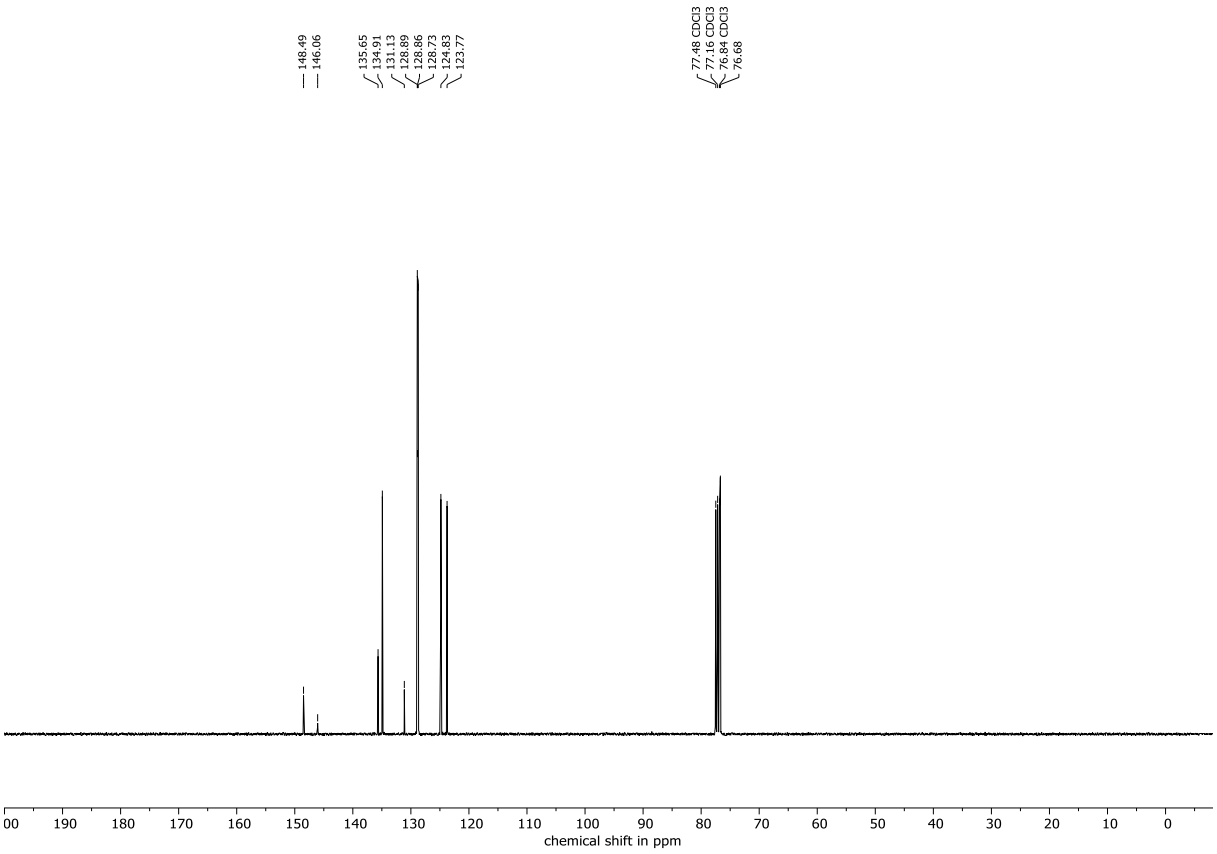
^{13}C NMR (101 MHz, $CDCl_3$) of **159**



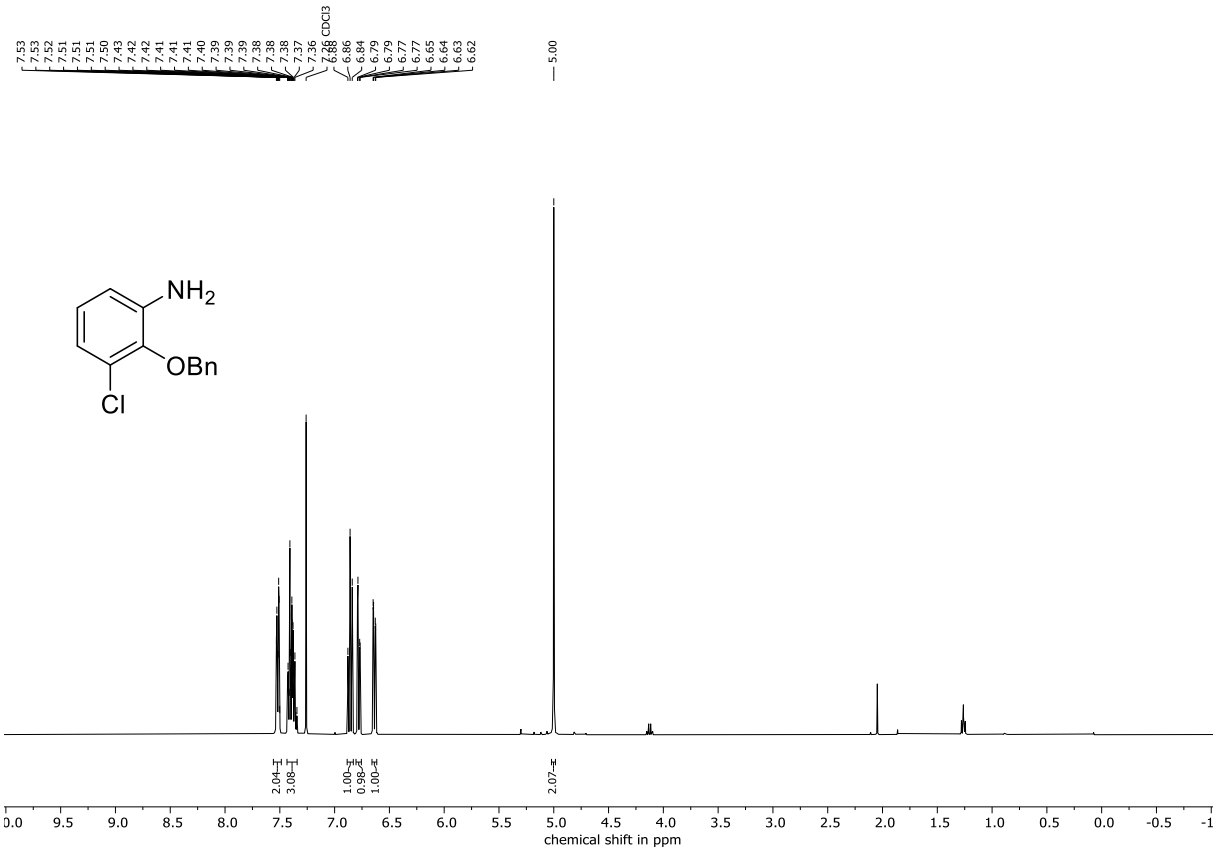
^{1}H NMR (300 MHz, $CDCl_3$) of **161**



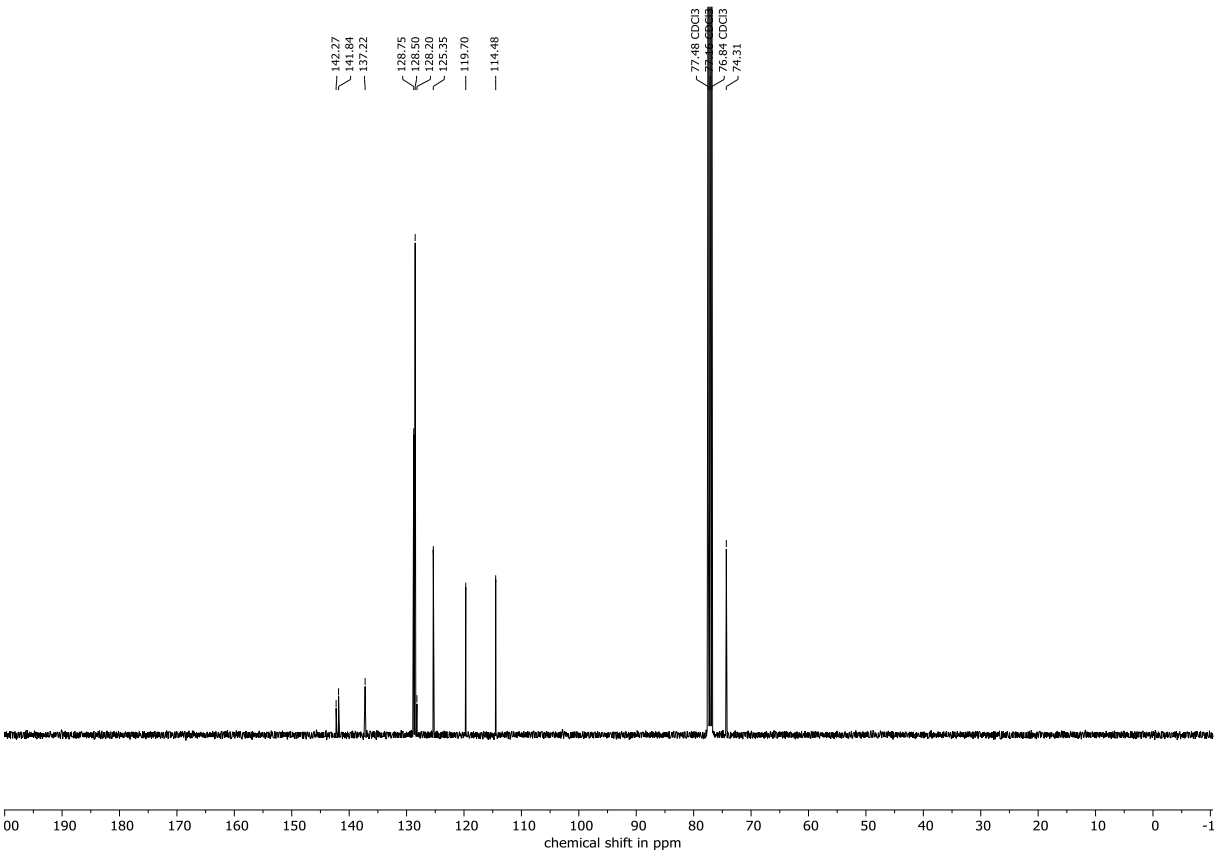
^{13}C NMR (101 MHz, $CDCl_3$) of **161**



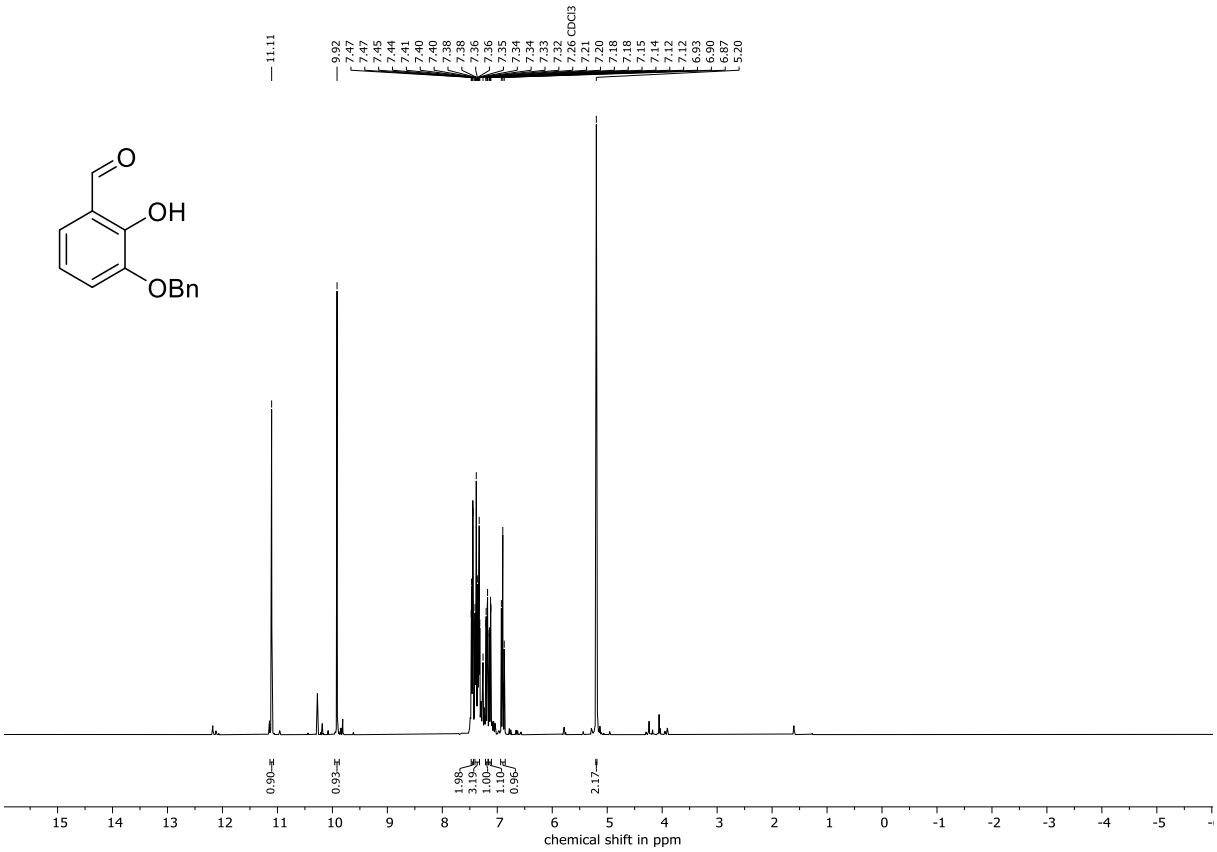
^{1}H NMR (400 MHz, $CDCl_3$) of **162**



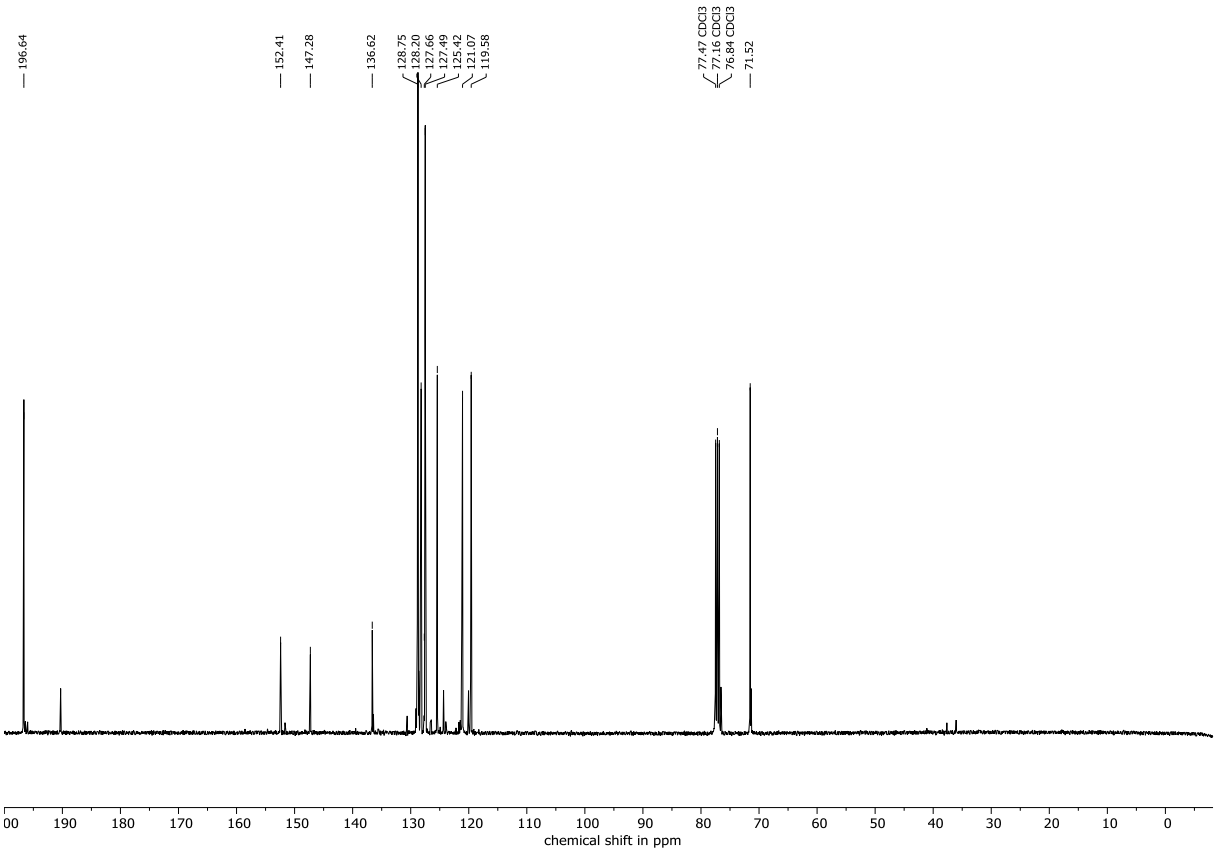
^{13}C NMR (101 MHz, $CDCl_3$) of **162**



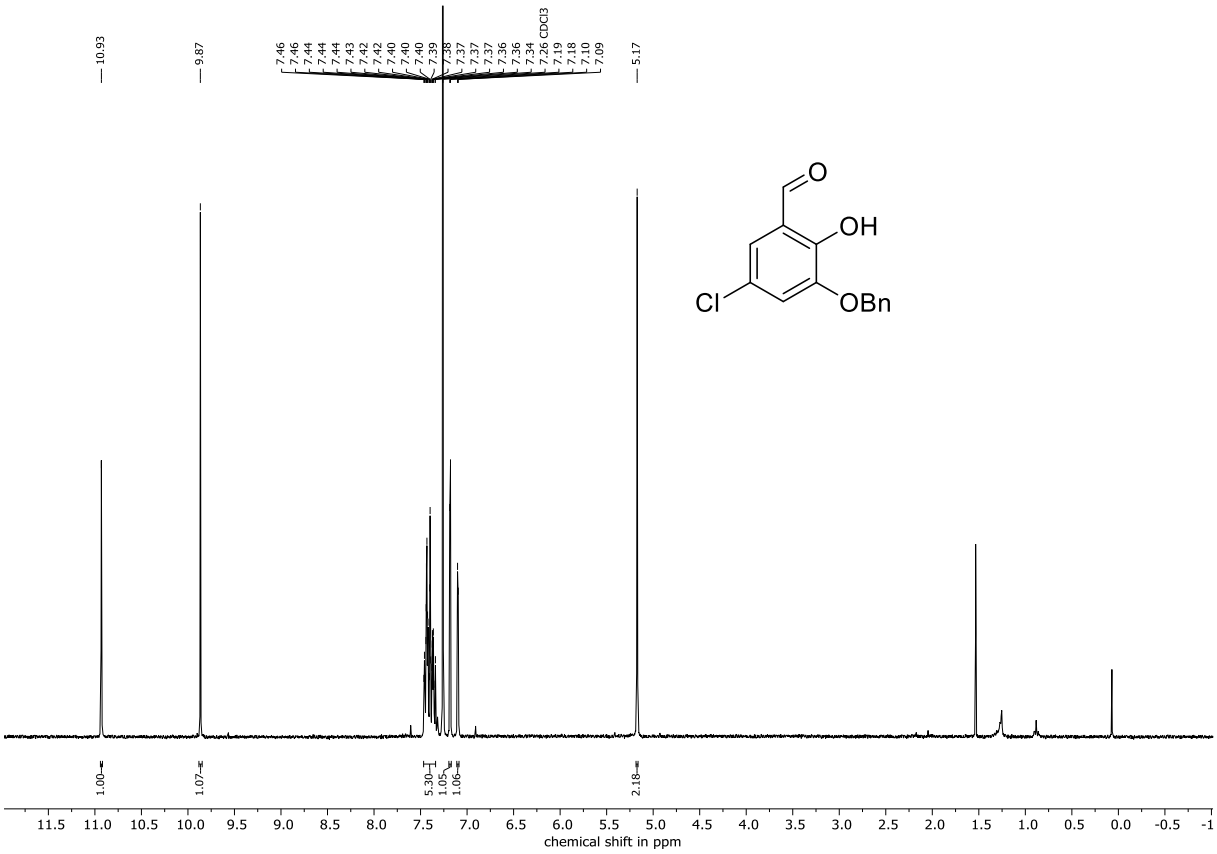
^{1}H NMR (300 MHz, $CDCl_3$) of **164**



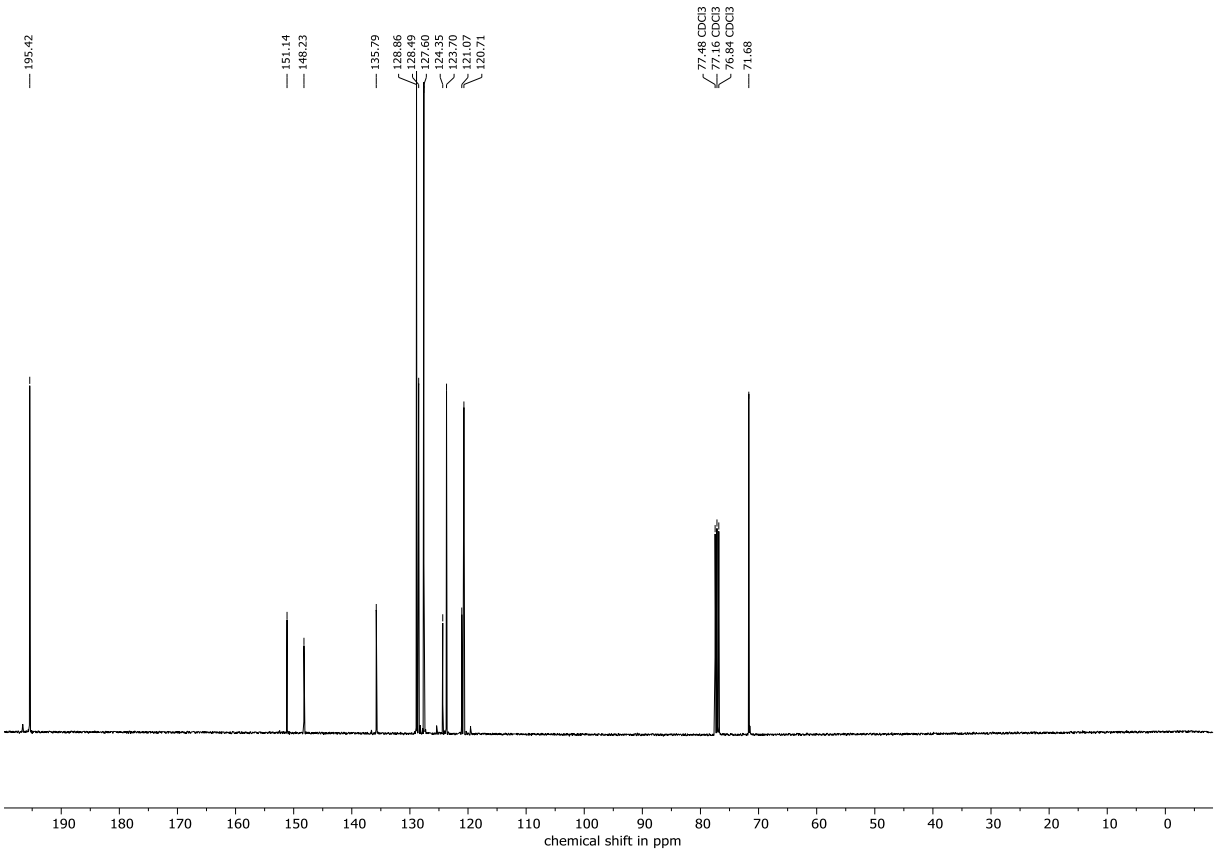
^{13}C NMR (75 MHz, $CDCl_3$) of **164**



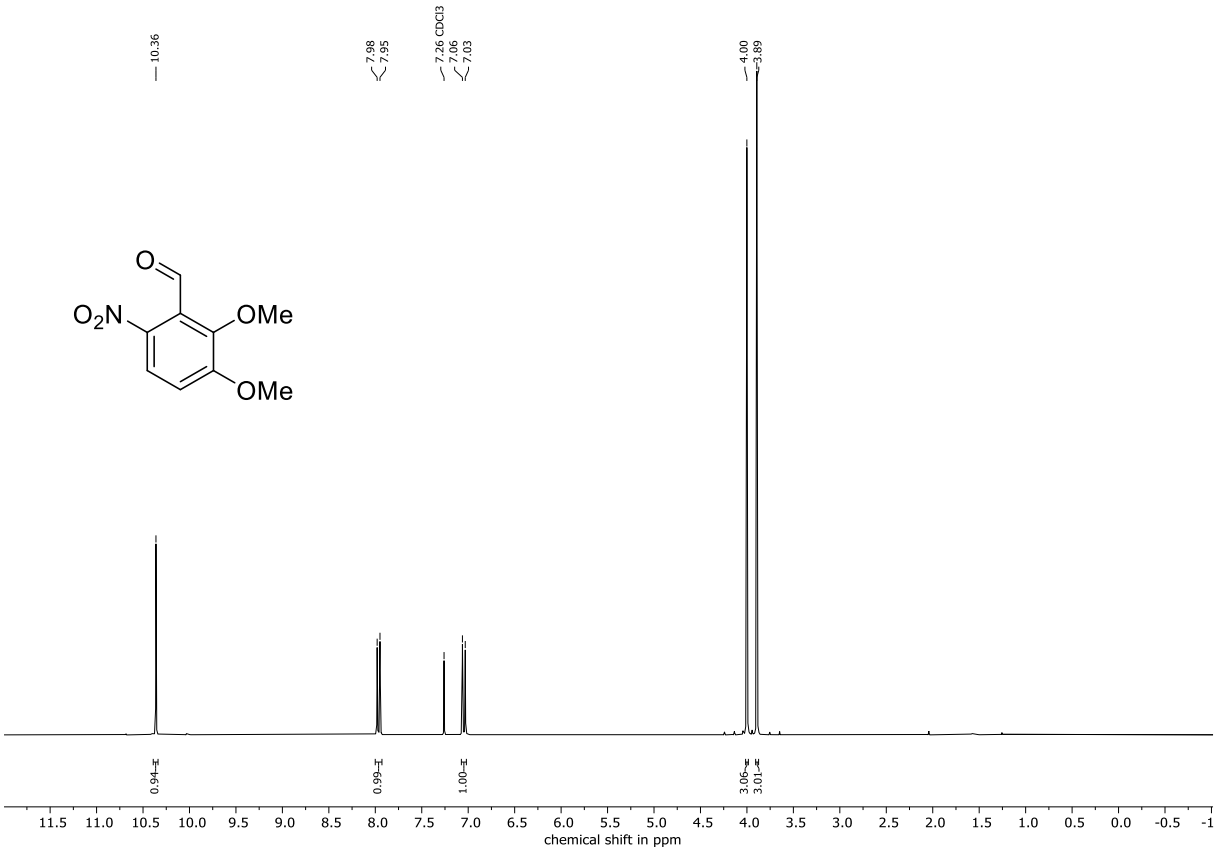
^{1}H NMR (300 MHz, $CDCl_3$) of **165**



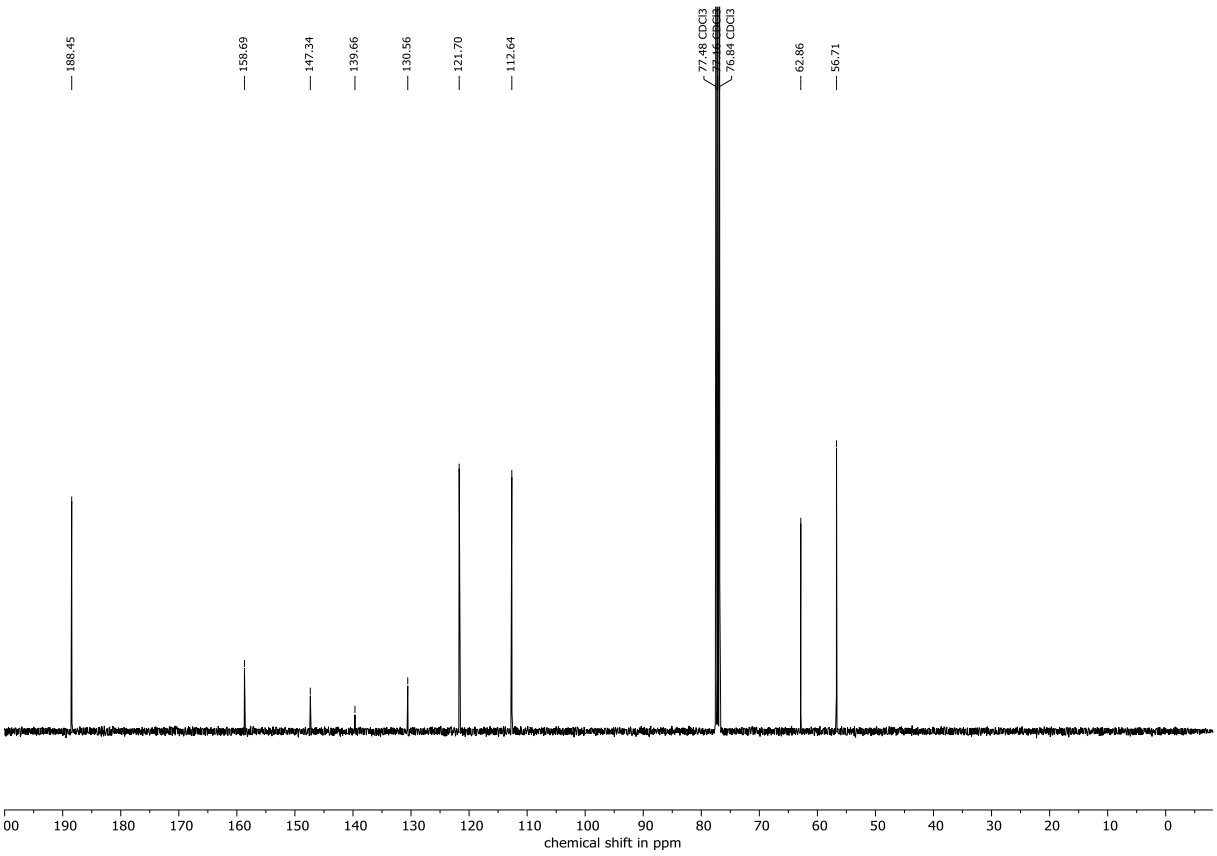
^{13}C NMR (101 MHz, $CDCl_3$) of **165**



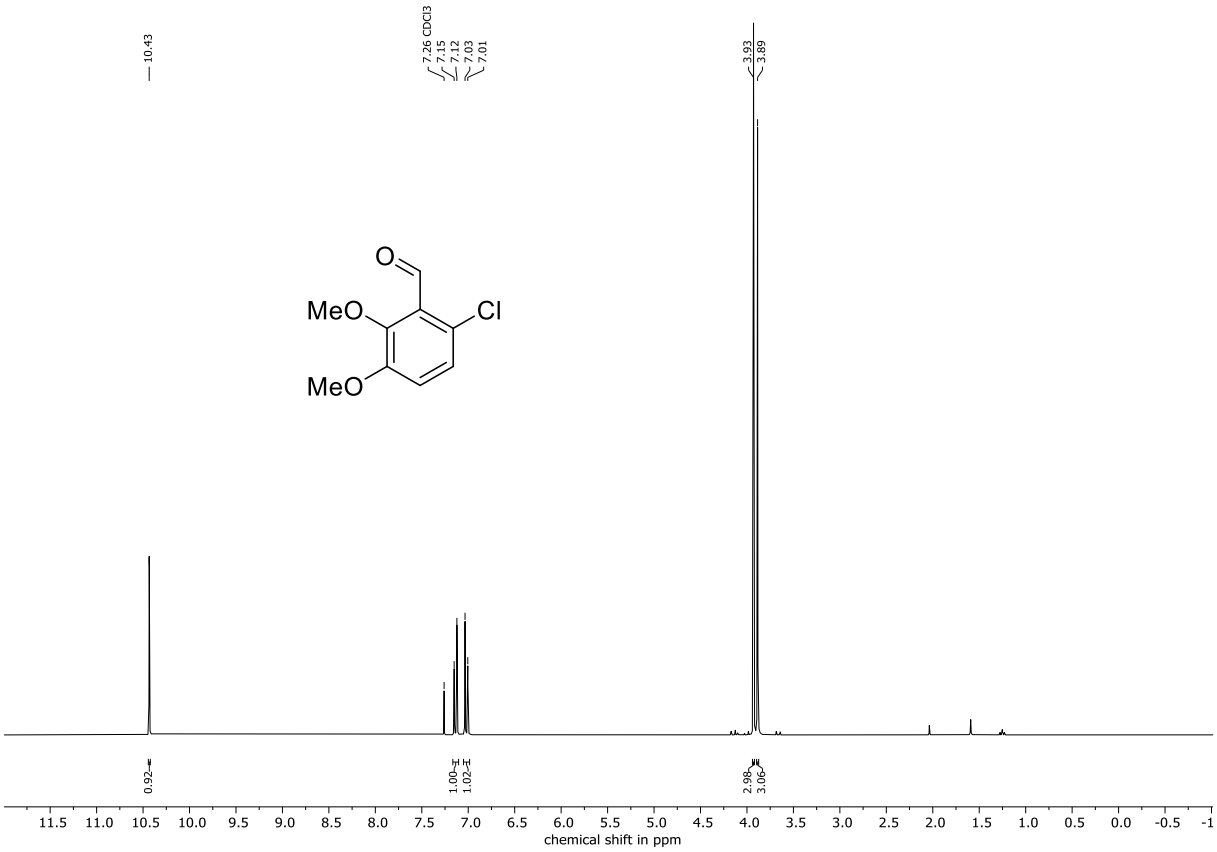
^{1}H NMR (300 MHz, $CDCl_3$) of **167**



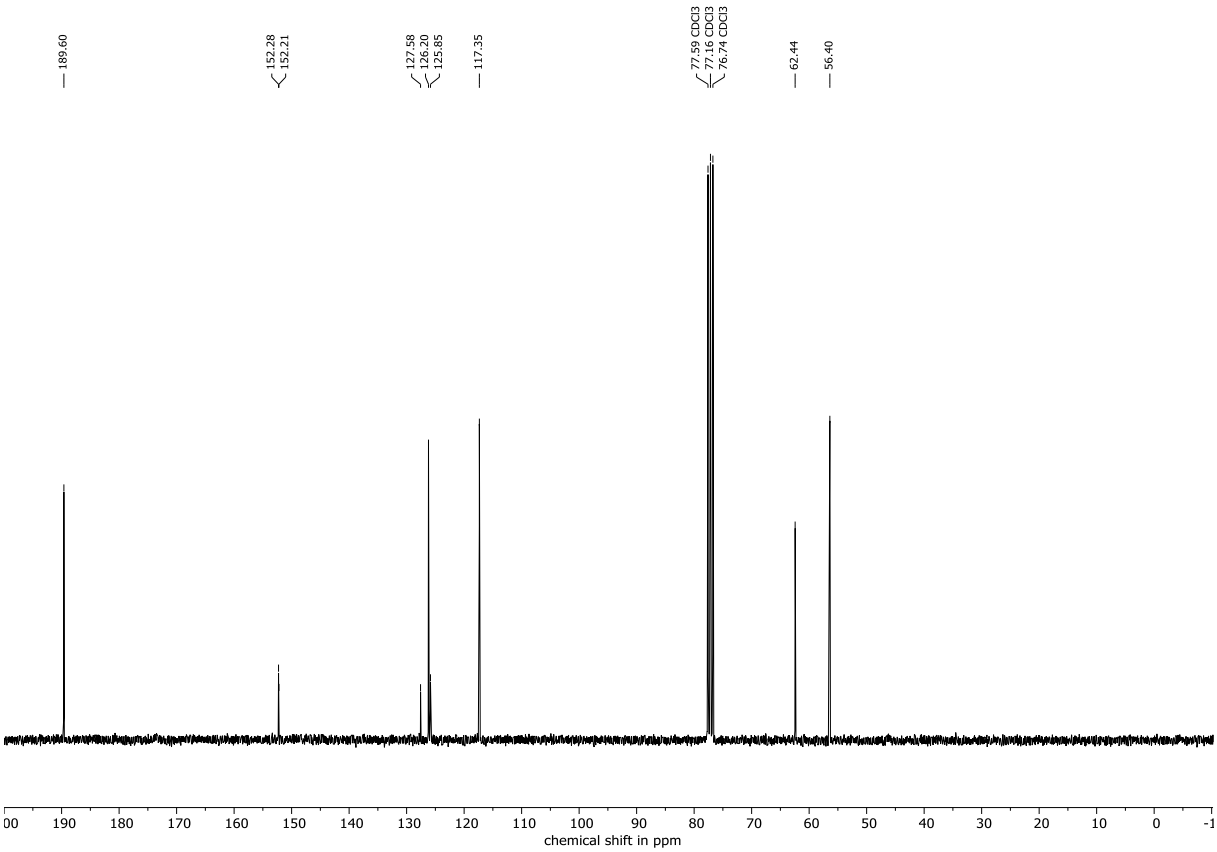
^{13}C NMR (101 MHz, $CDCl_3$) of **167**



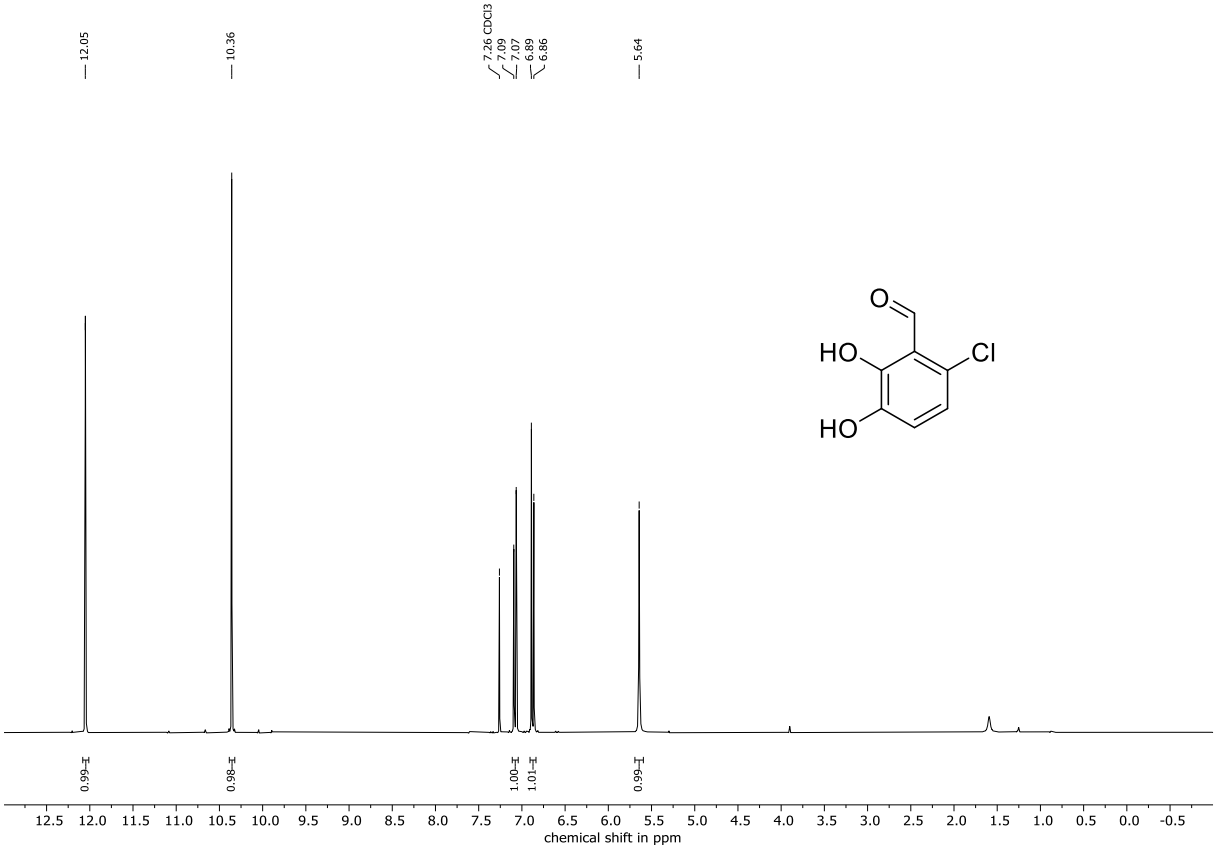
^{1}H NMR (300 MHz, $CDCl_3$) of **168**



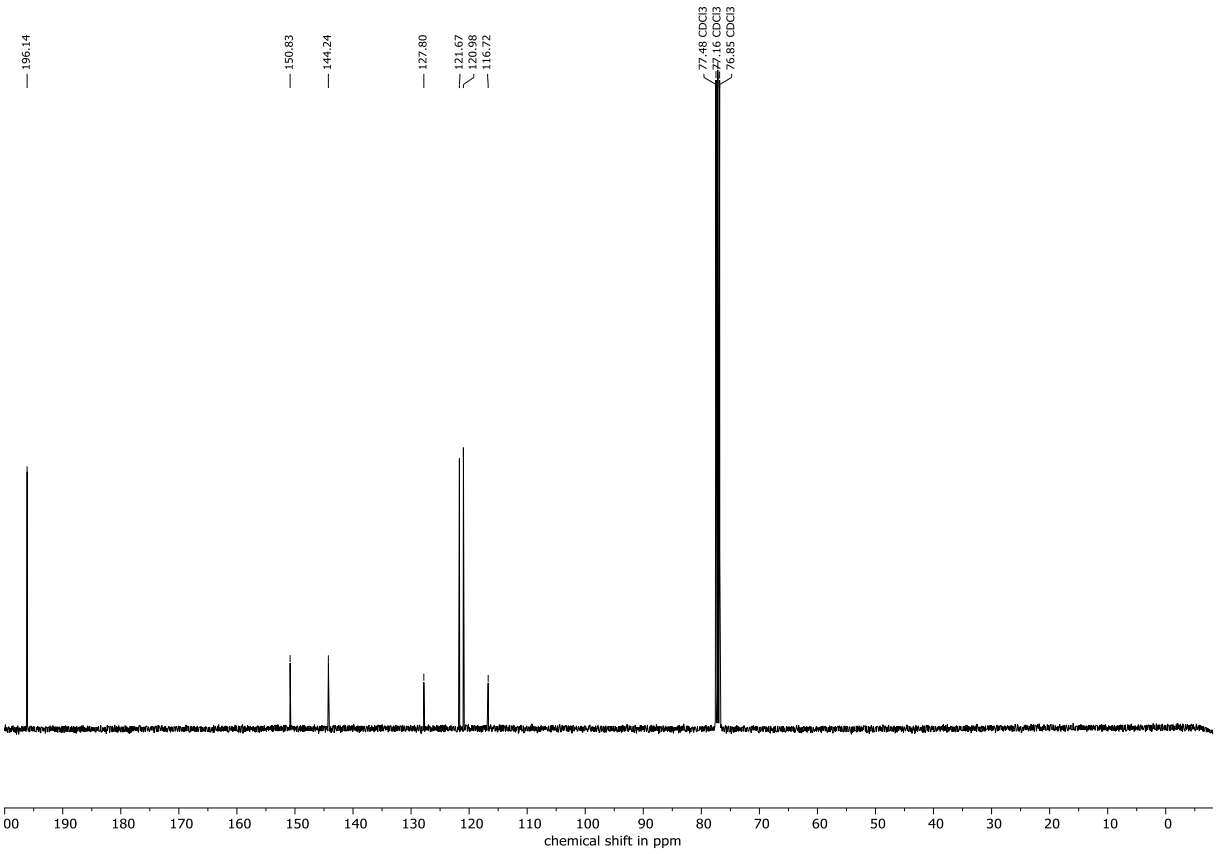
^{13}C NMR (75 MHz, $CDCl_3$) of **168**



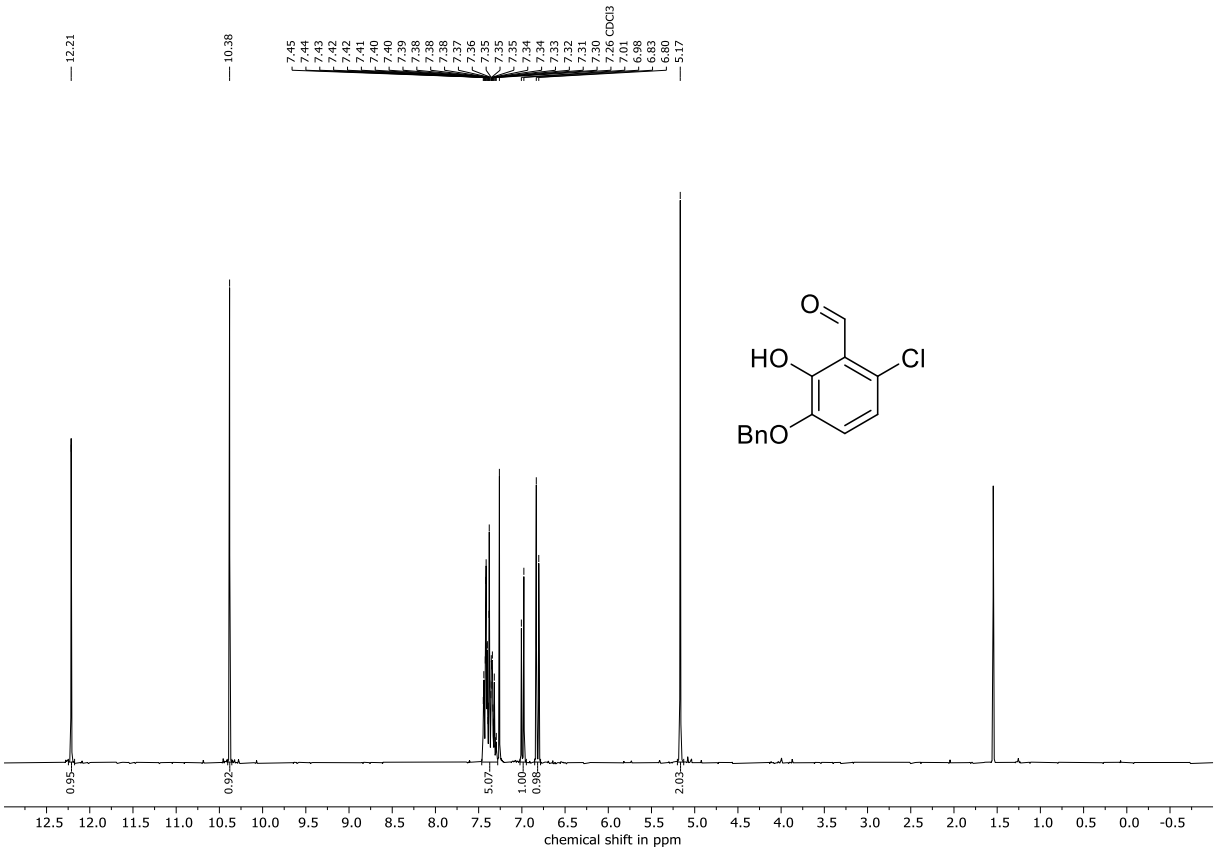
^{1}H NMR (300 MHz, $CDCl_3$) of **169**



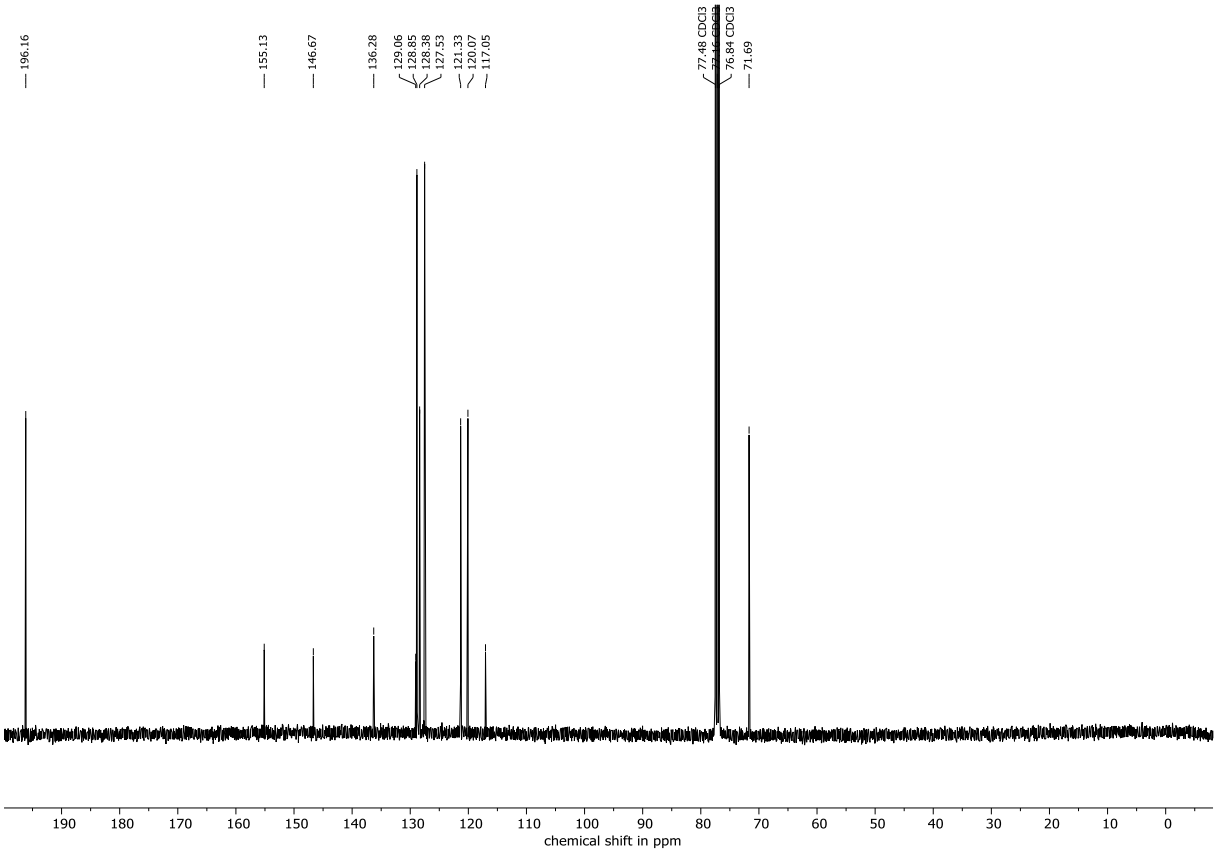
^{13}C NMR (101 MHz, $CDCl_3$) of **169**



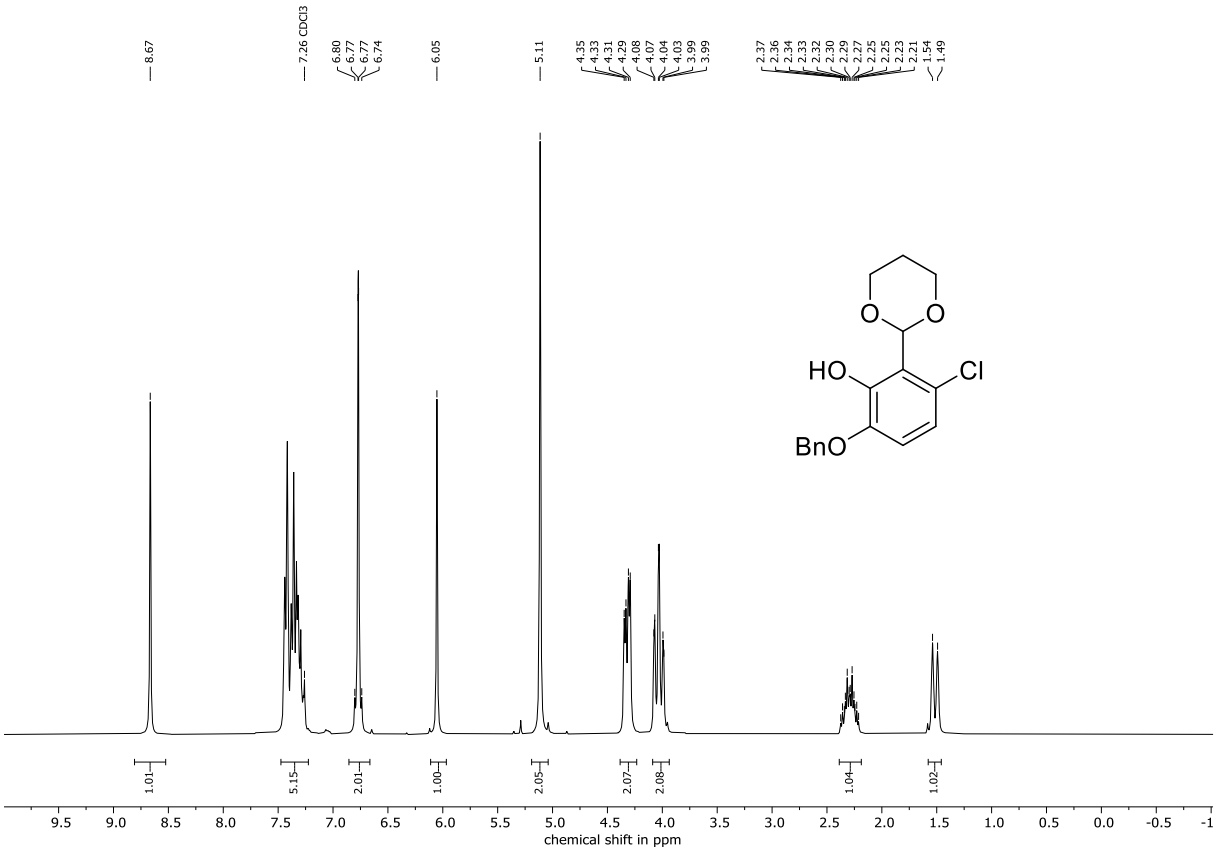
^{1}H NMR (300 MHz, $CDCl_3$) of **170**



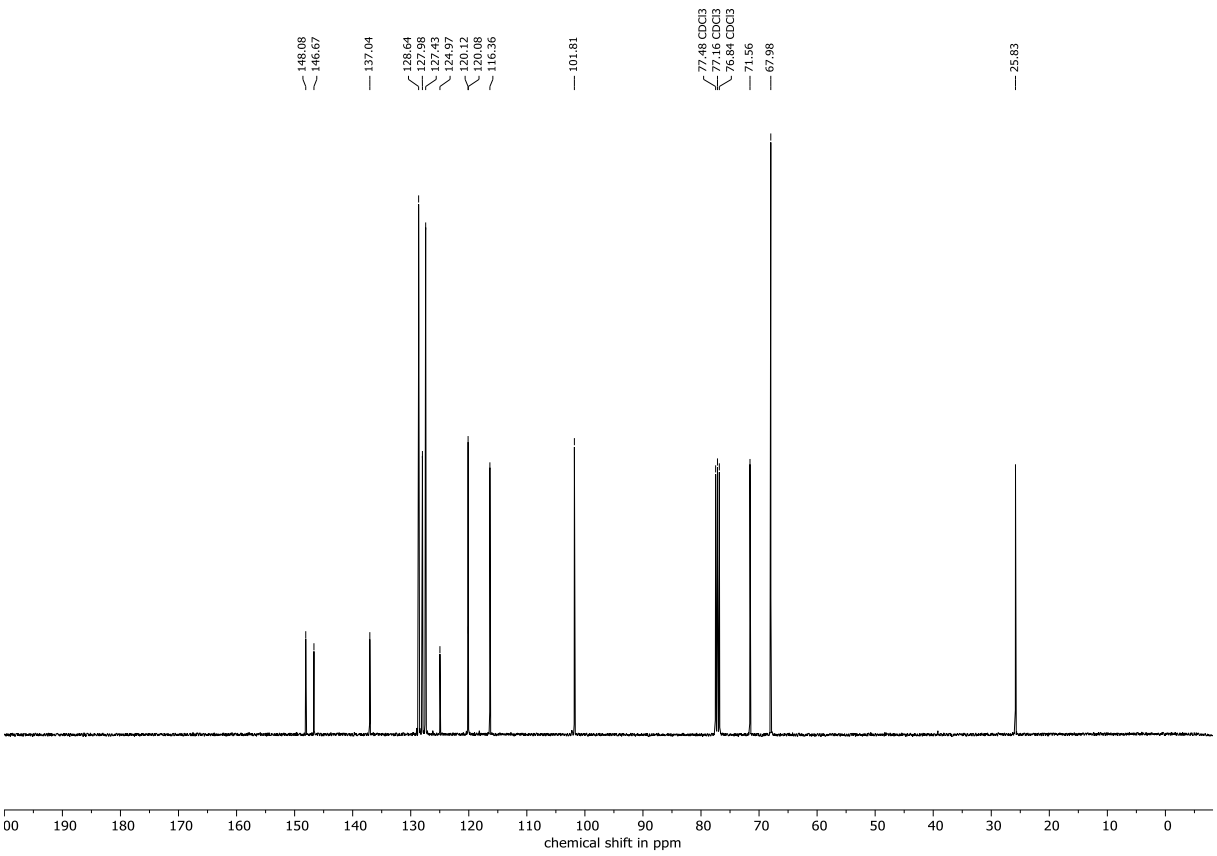
^{13}C NMR (101 MHz, $CDCl_3$) of **170**



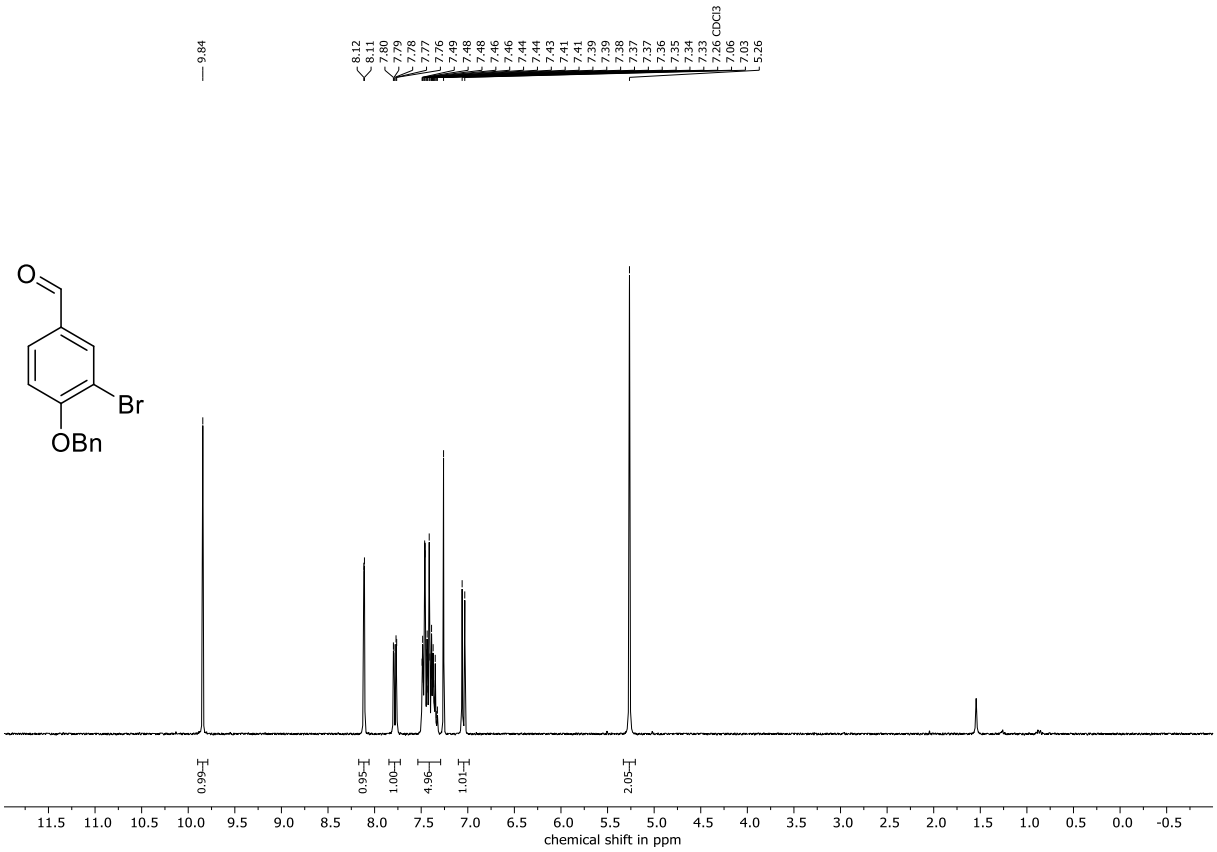
^{1}H NMR (300 MHz, $CDCl_3$) of **171**



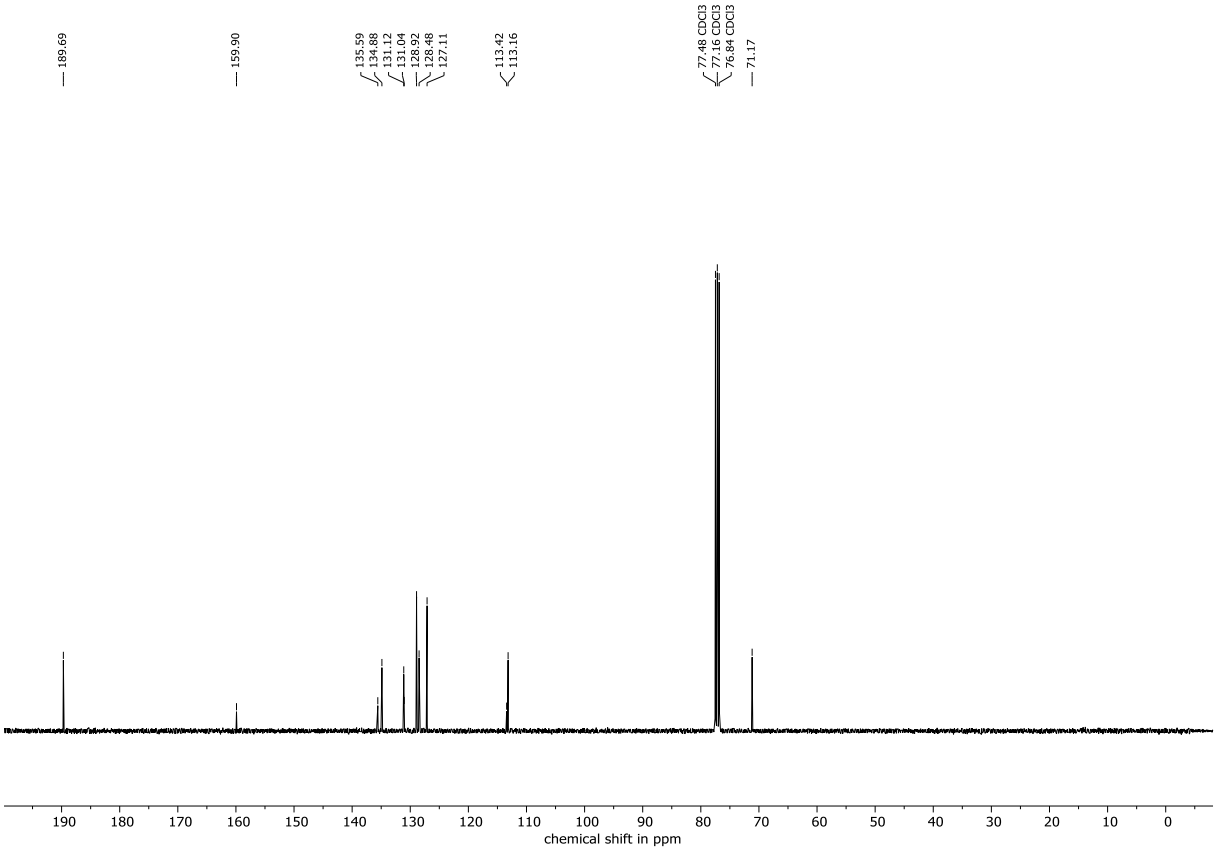
^{13}C NMR (101 MHz, $CDCl_3$) of **171**



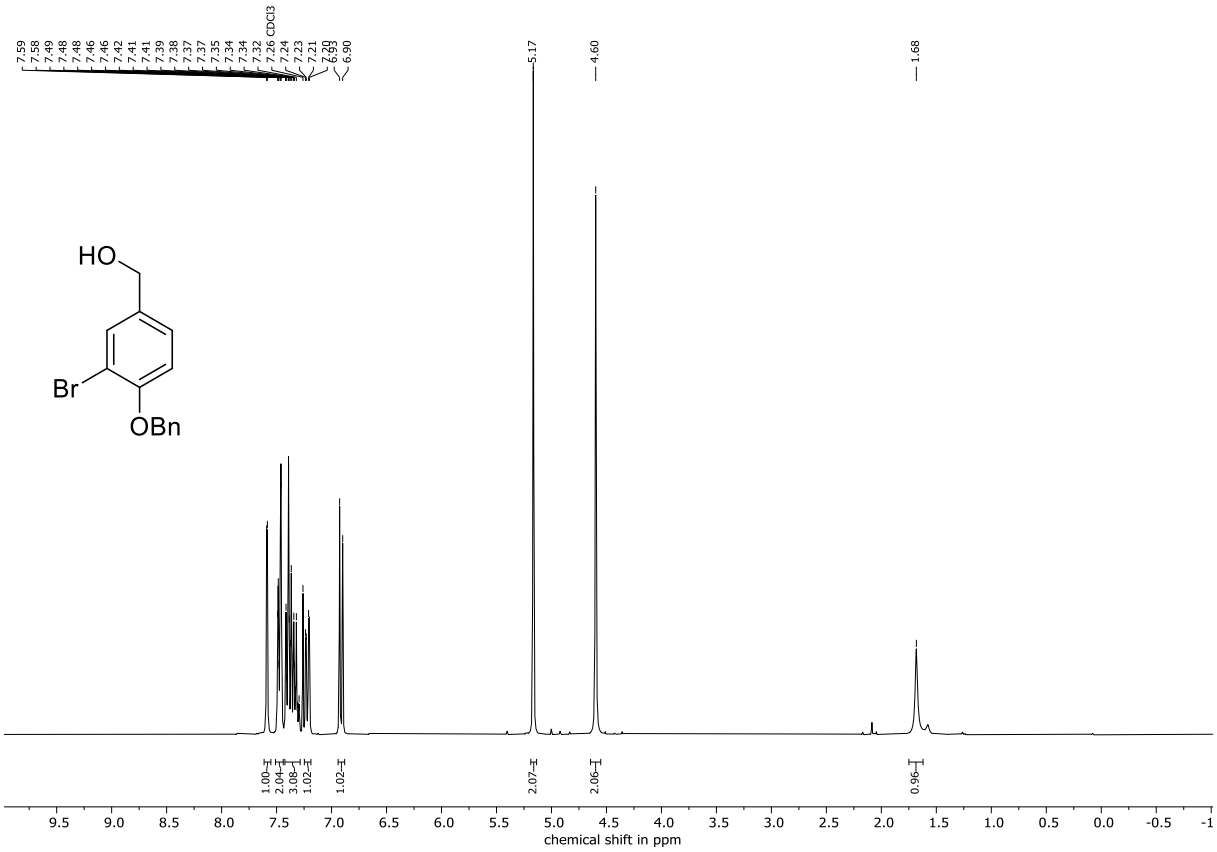
^{1}H NMR (300 MHz, $CDCl_3$) of **174**



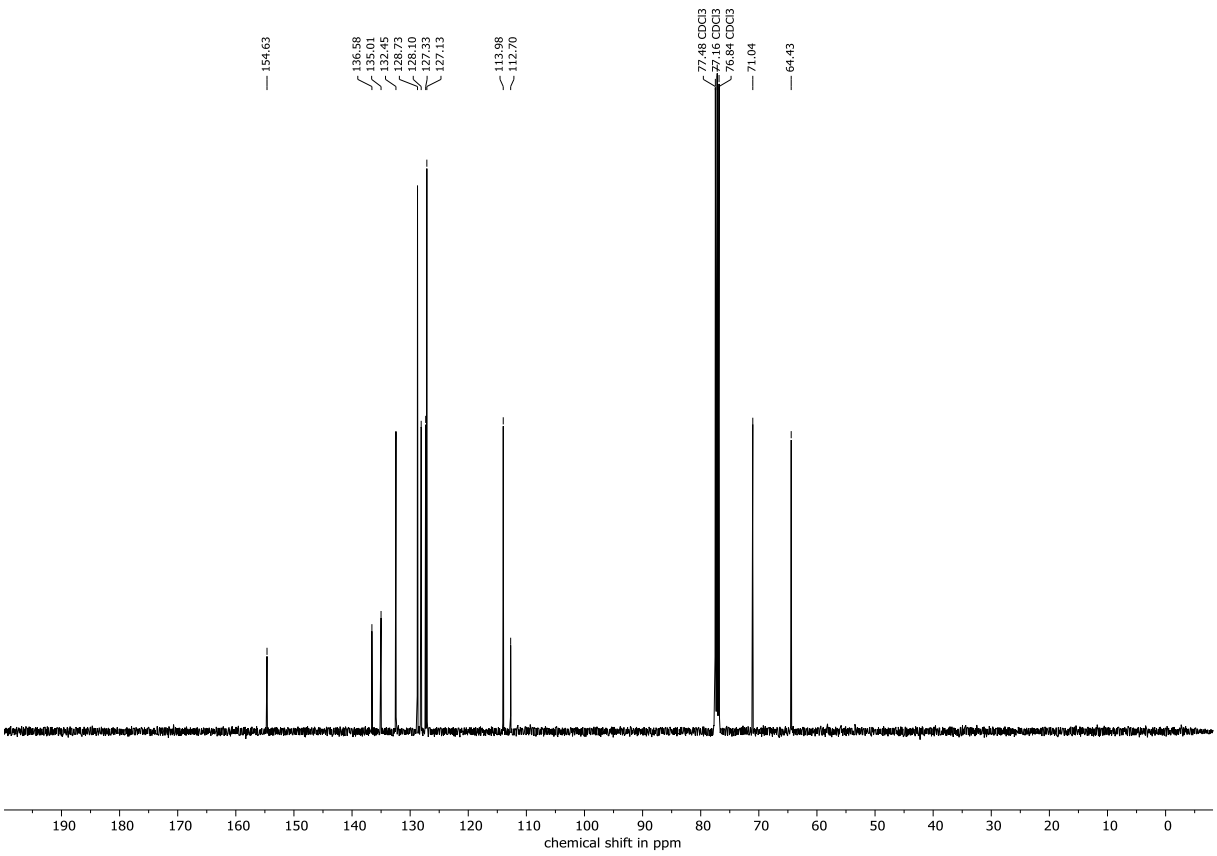
^{13}C NMR (101 MHz, $CDCl_3$) of **174**



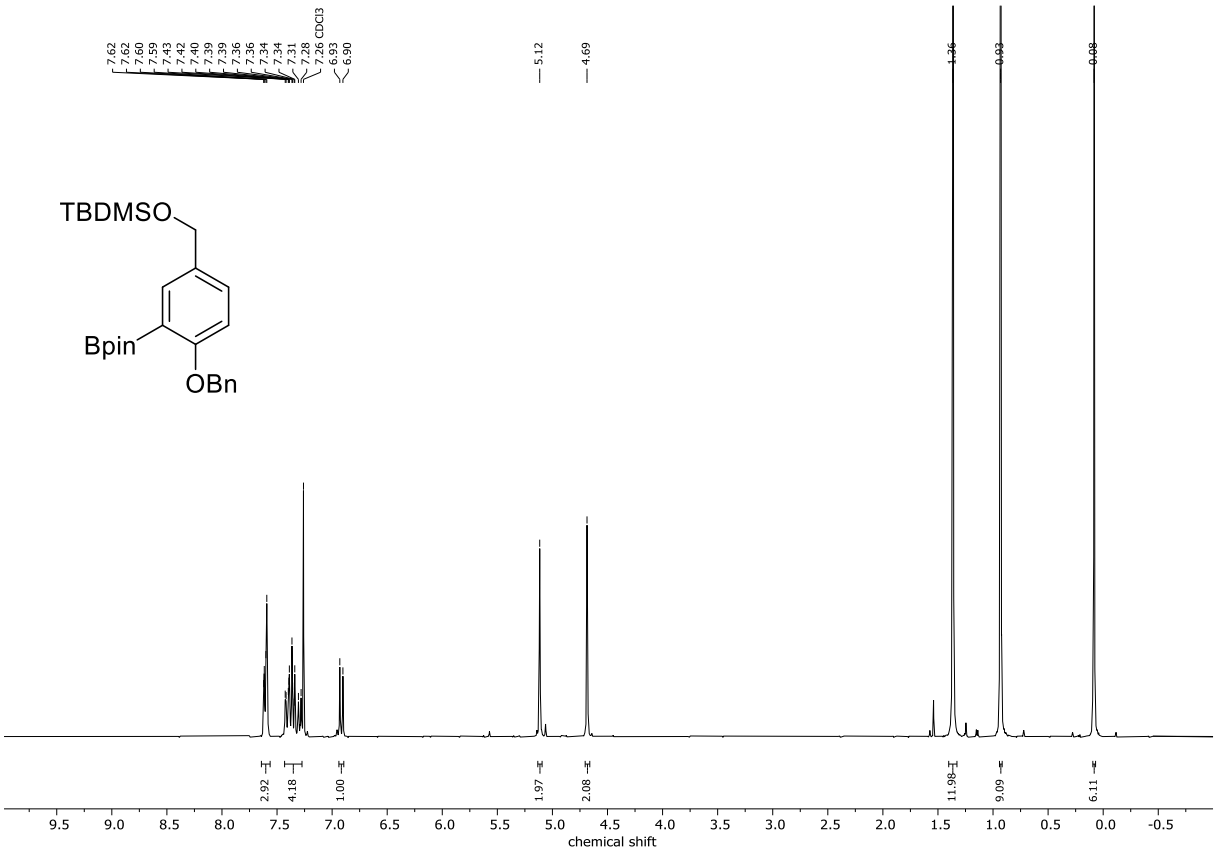
^{1}H NMR (300 MHz, $CDCl_3$) of **175**



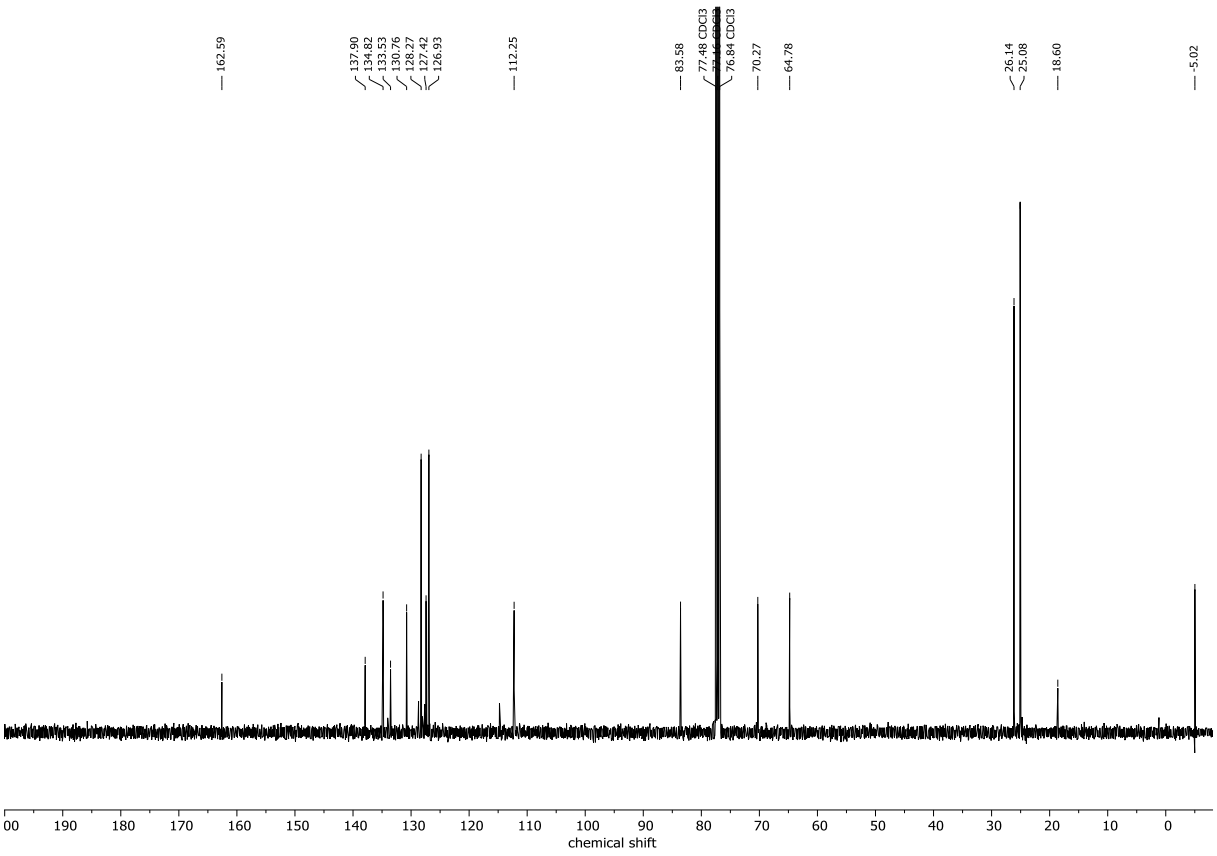
^{13}C NMR (101 MHz, $CDCl_3$) of **175**



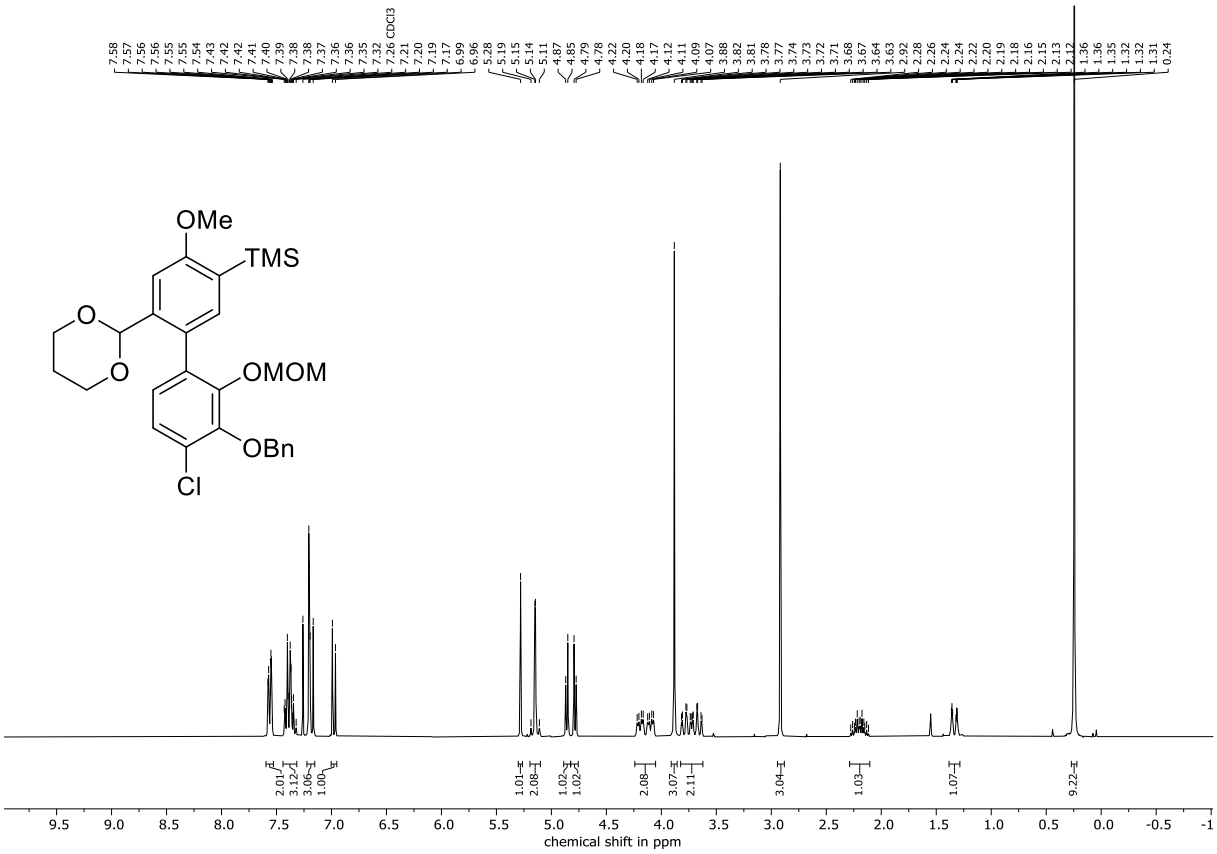
^{1}H NMR (300 MHz, $CDCl_3$) of **176**



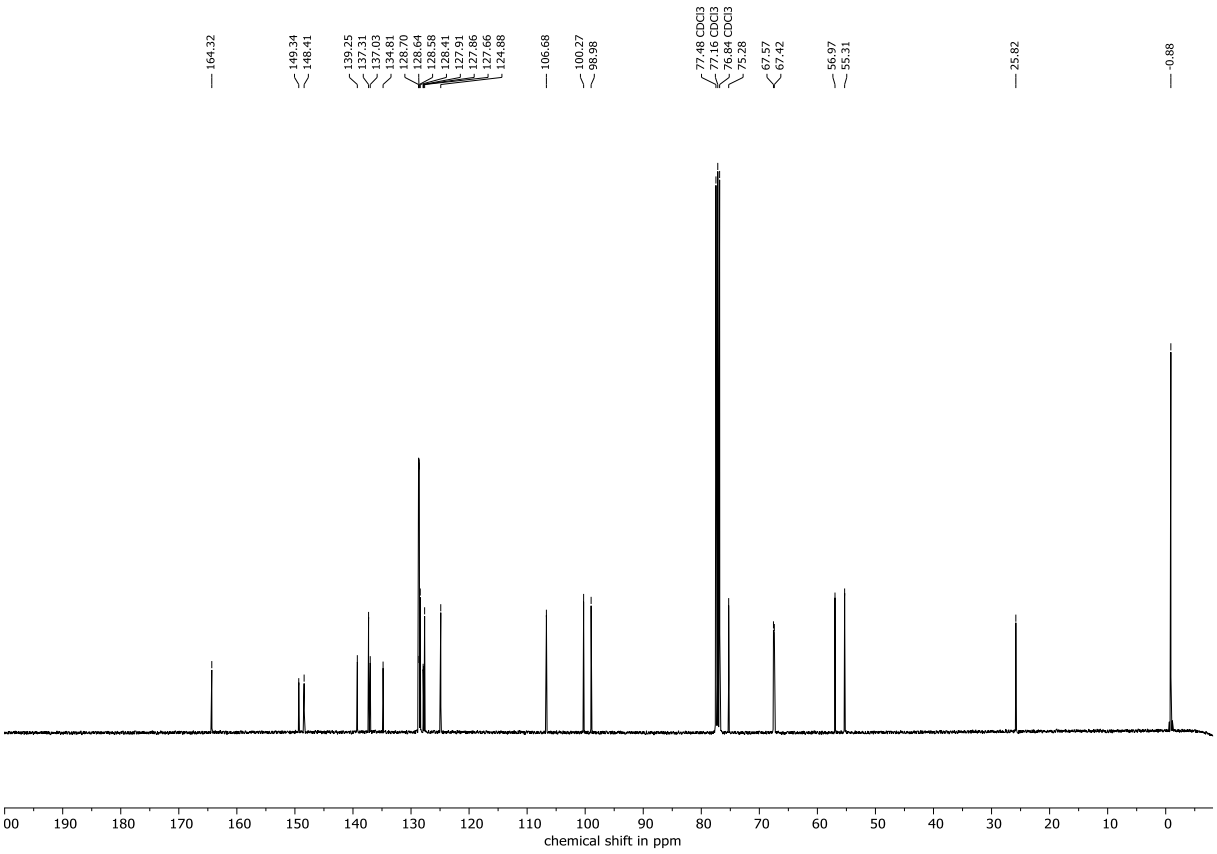
^{13}C NMR (75 MHz, $CDCl_3$) of **176**



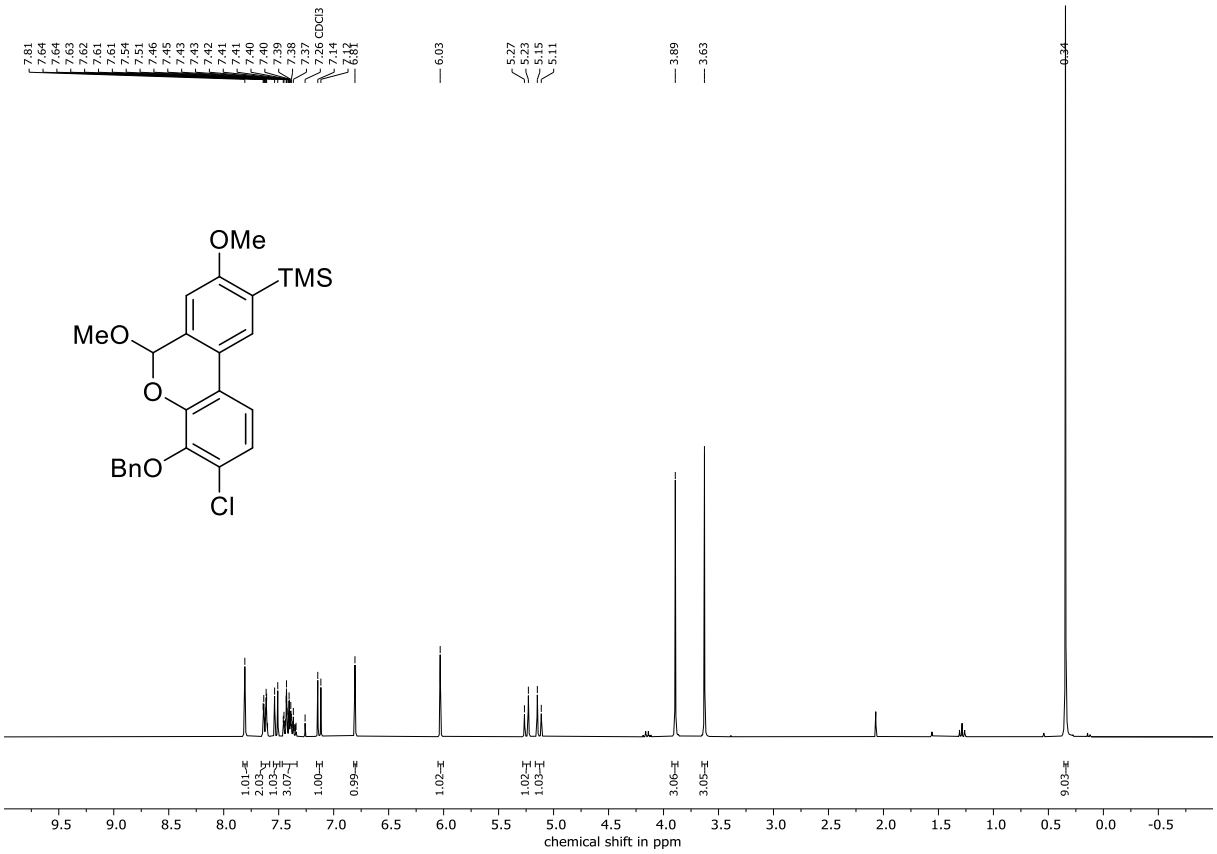
^{1}H NMR (300 MHz, $CDCl_3$) of **179**



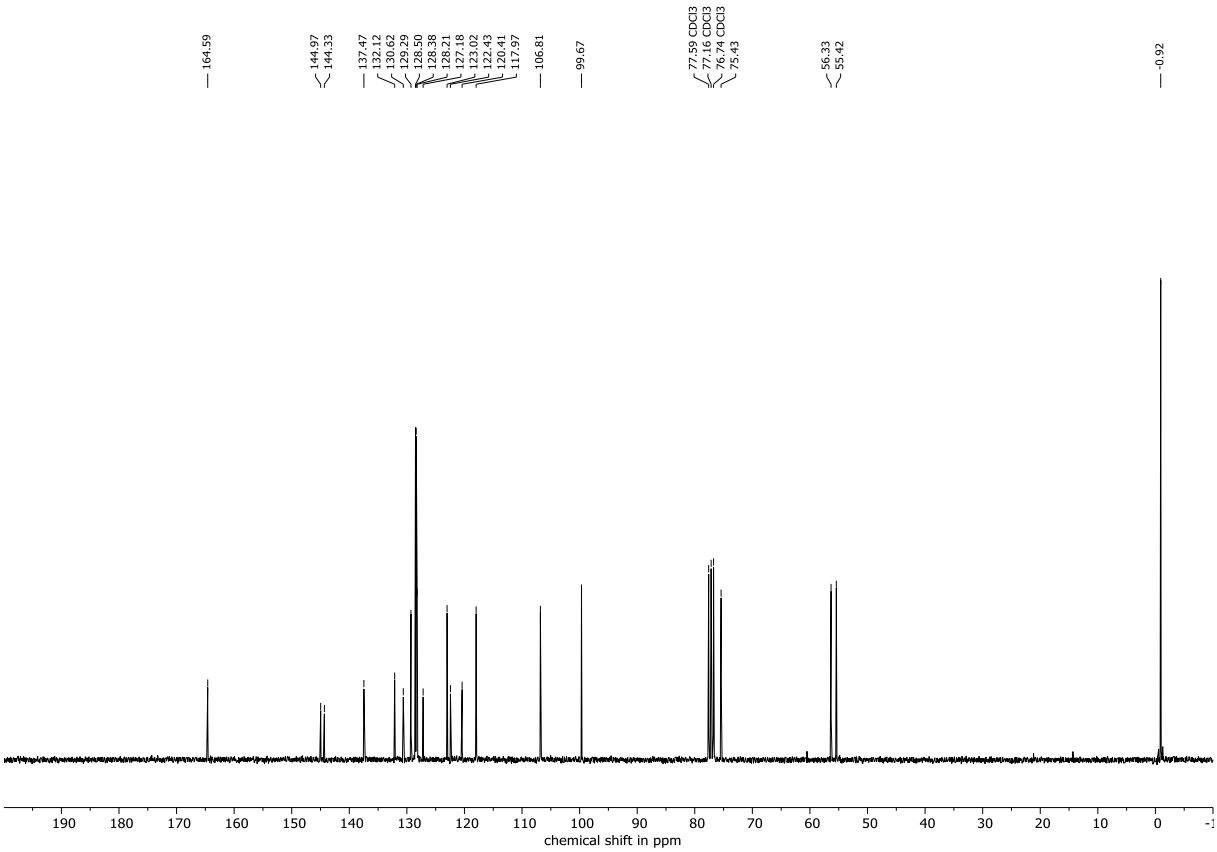
^{13}C NMR (101 MHz, $CDCl_3$) of **179**



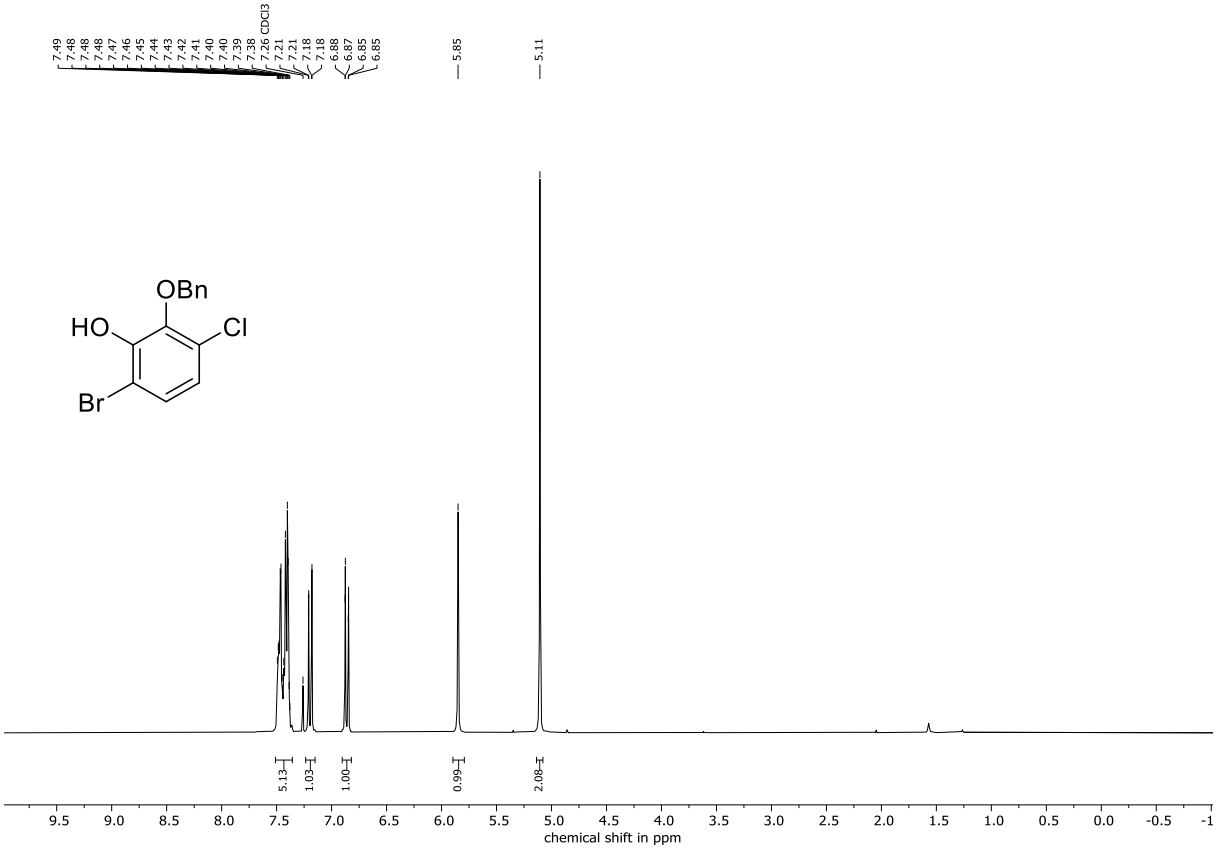
^{1}H NMR (300 MHz, $CDCl_3$) of **181**



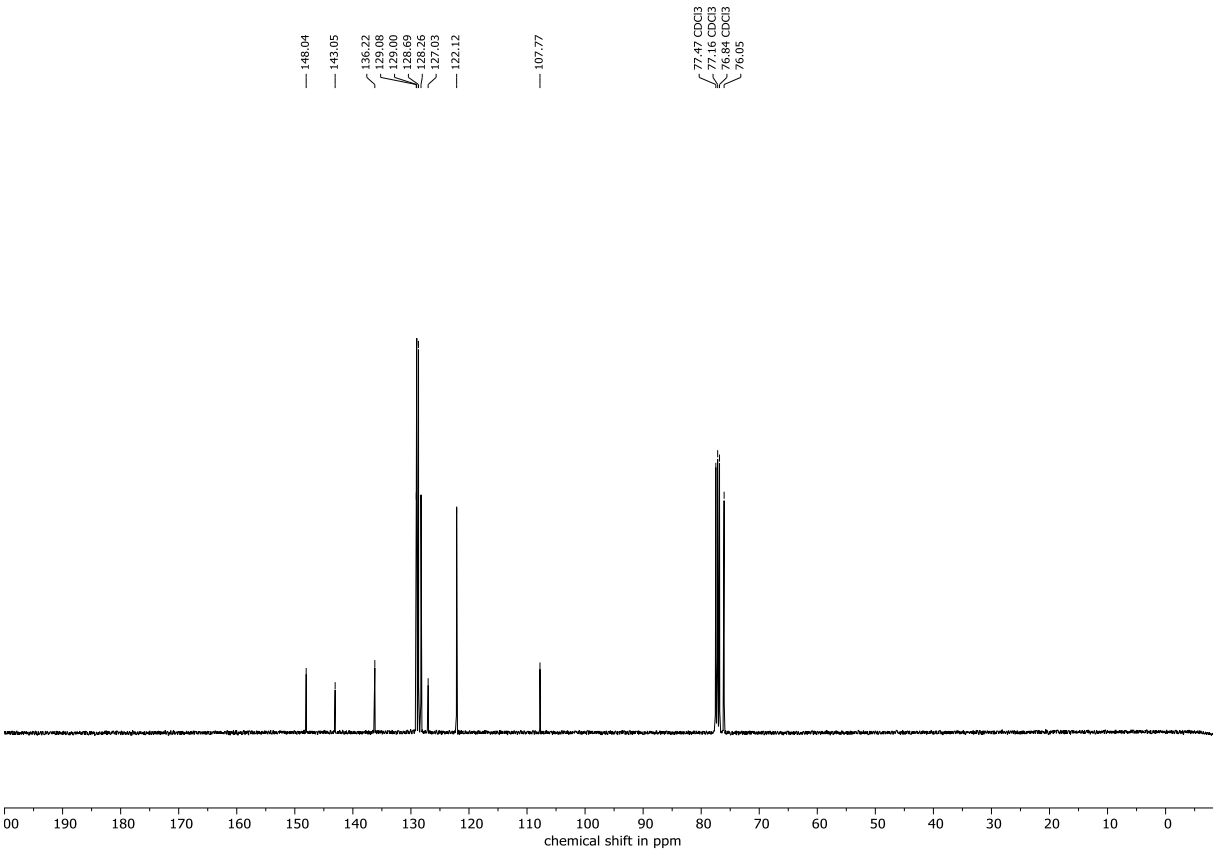
^{13}C NMR (101 MHz, $CDCl_3$) of **181**



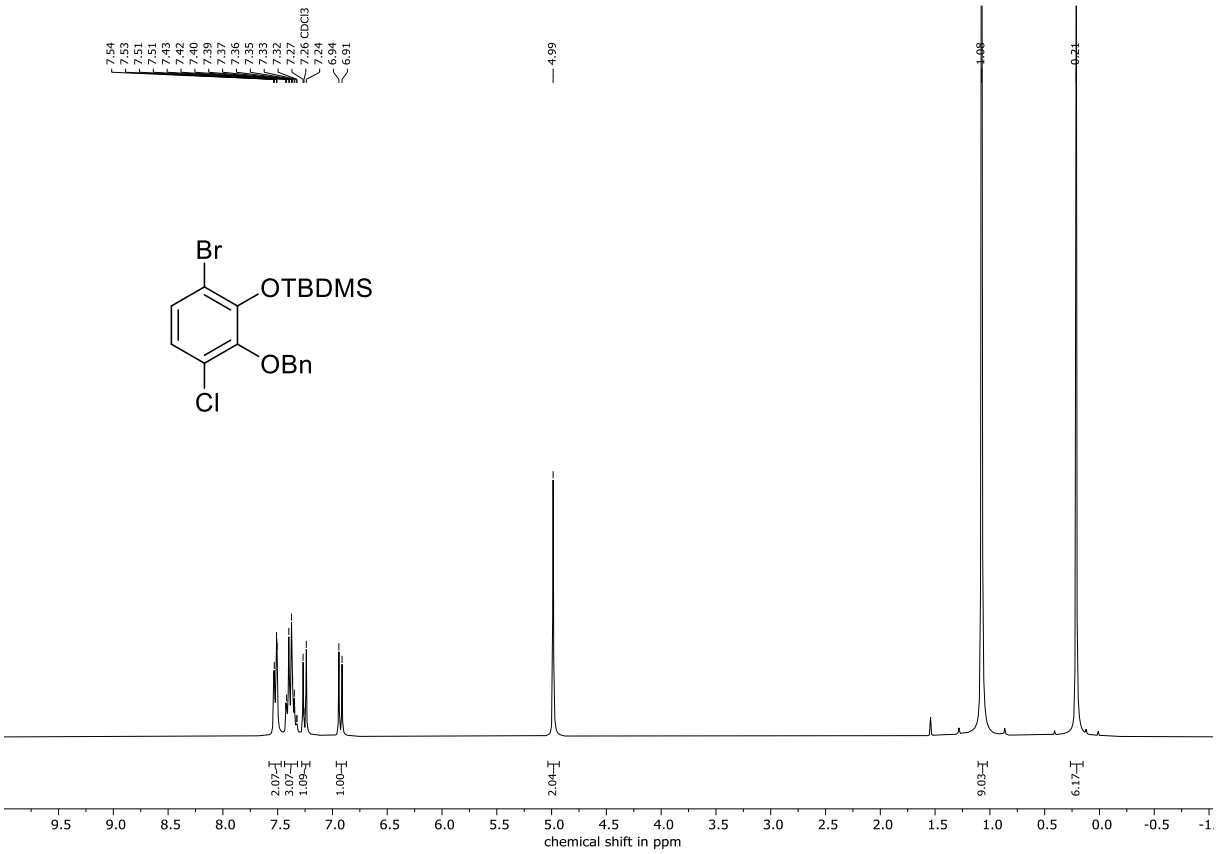
^{1}H NMR (300 MHz, $CDCl_3$) of **182**



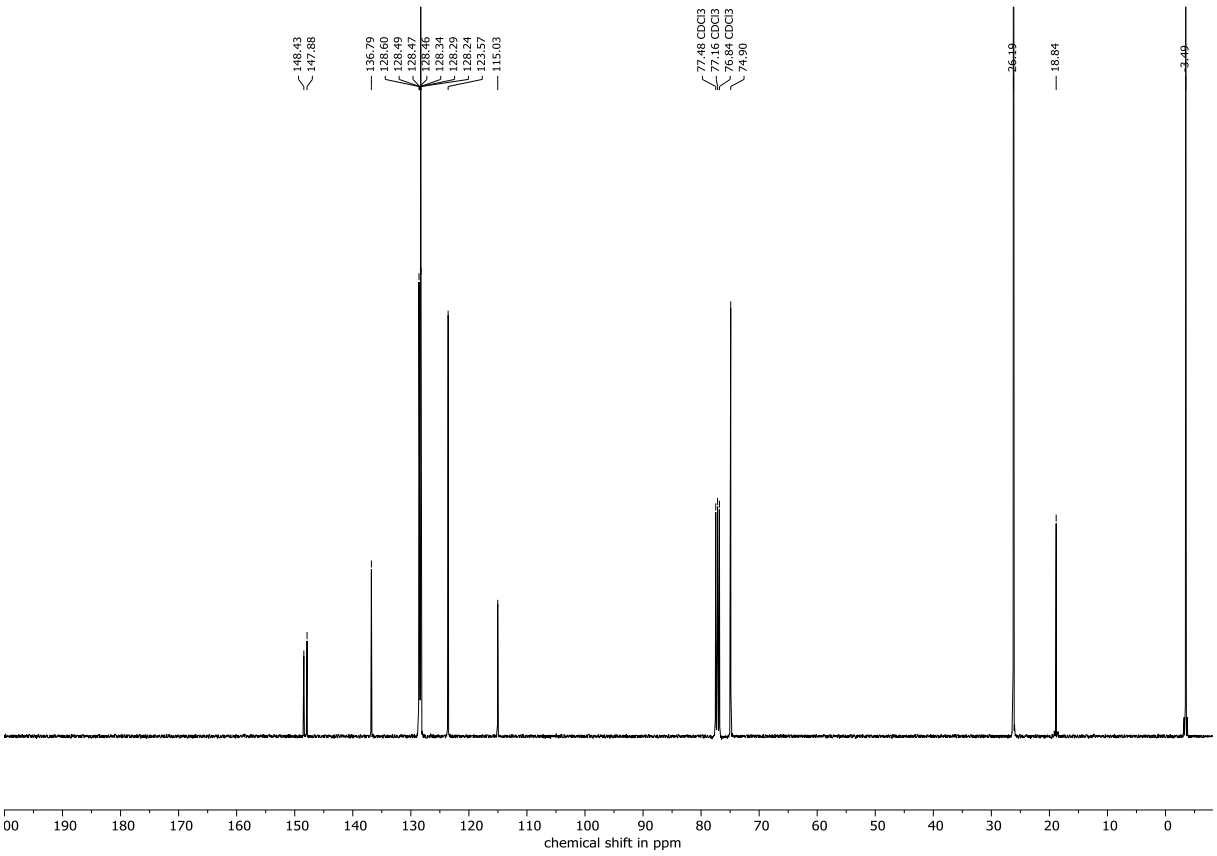
^{13}C NMR (101 MHz, $CDCl_3$) of **182**



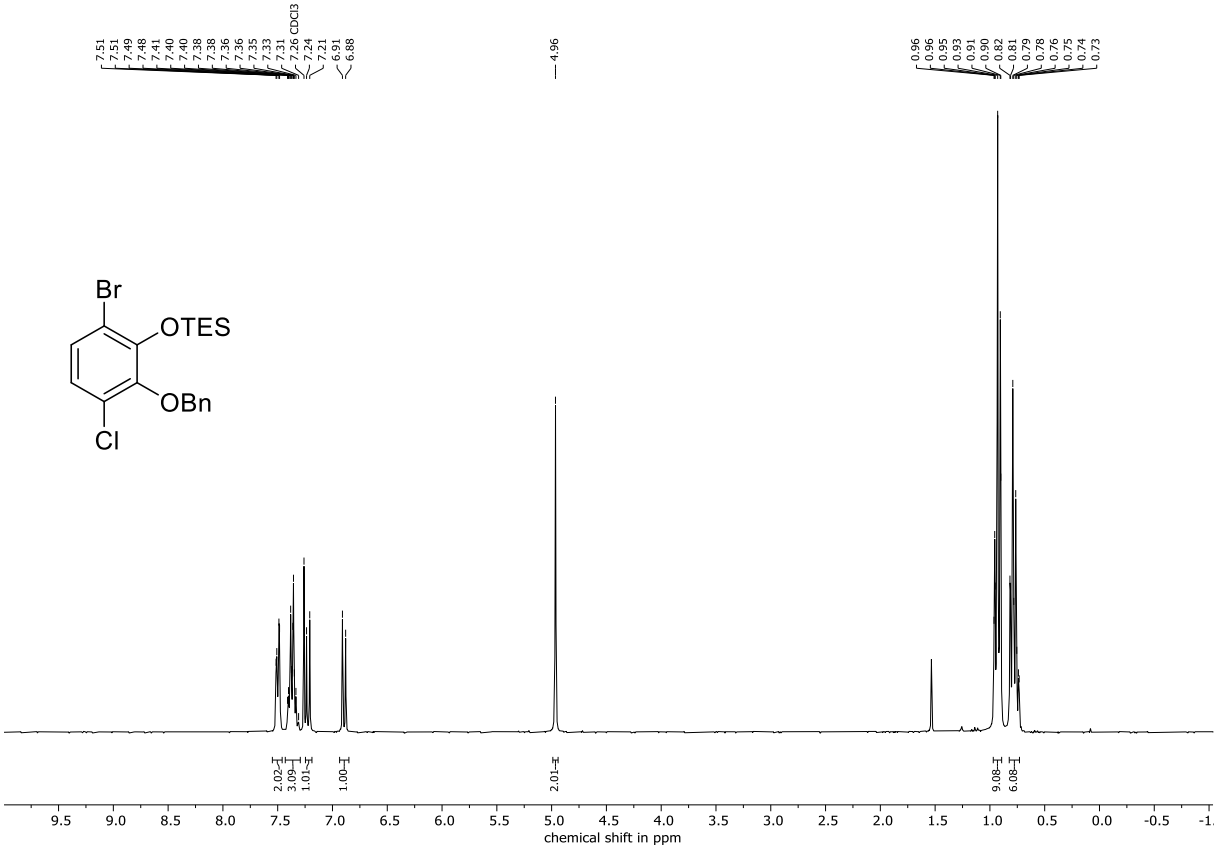
^{1}H NMR (300 MHz, $CDCl_3$) of **183**



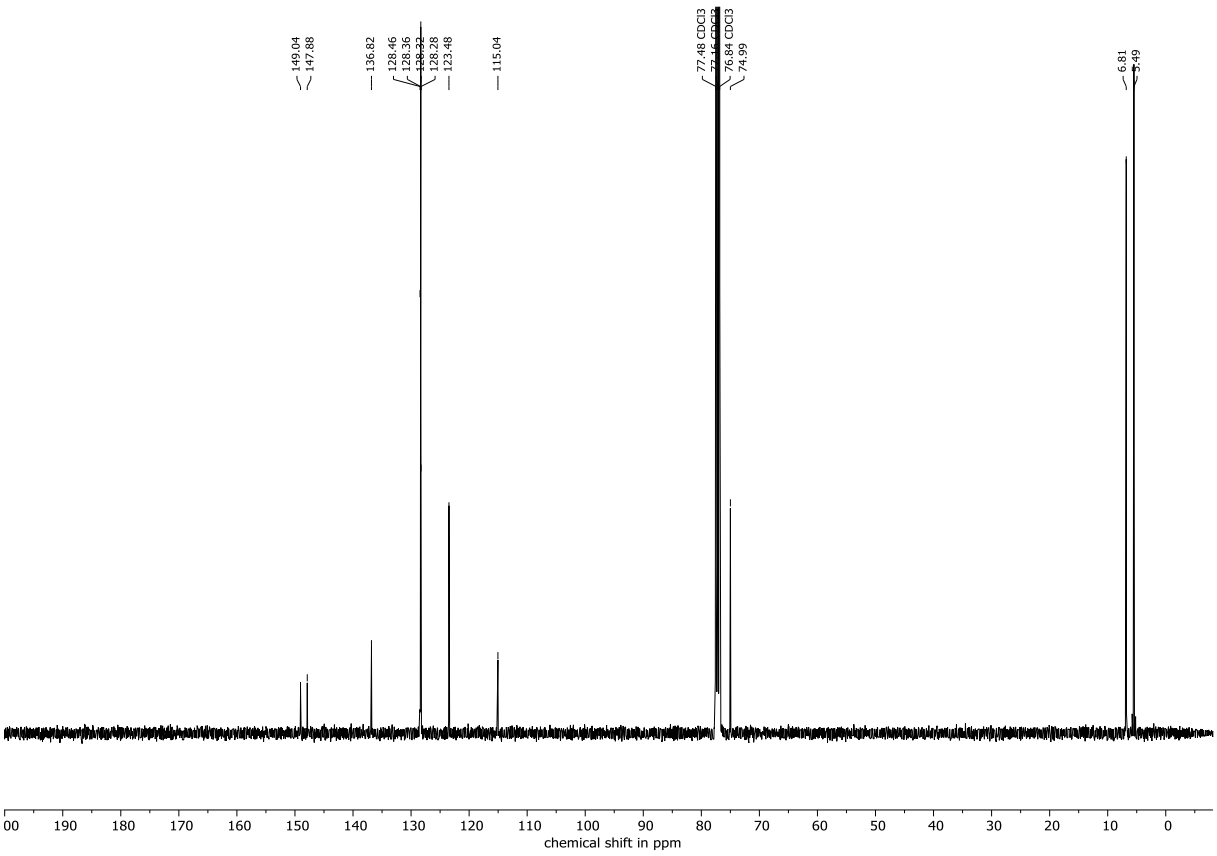
^{13}C NMR (101 MHz, $CDCl_3$) of **183**



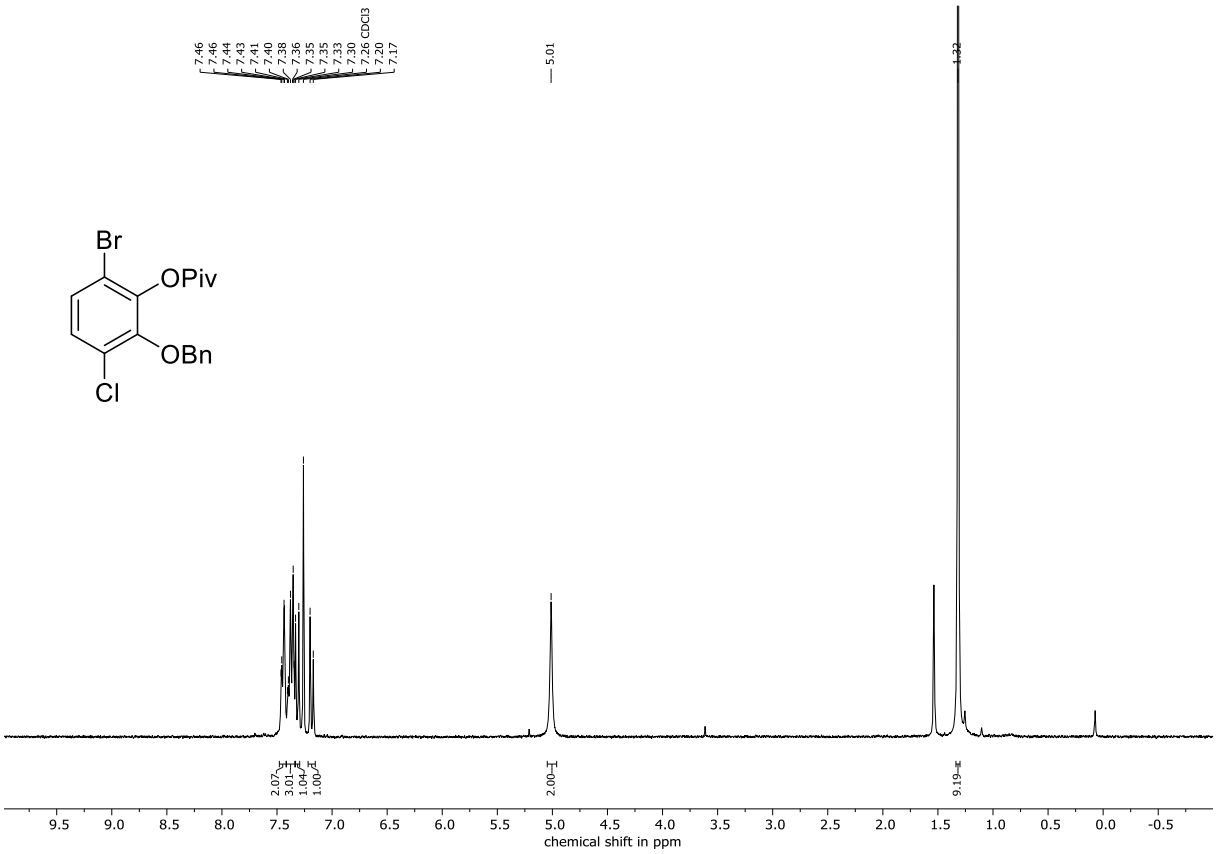
^{1}H NMR (300 MHz, $CDCl_3$) of **184**



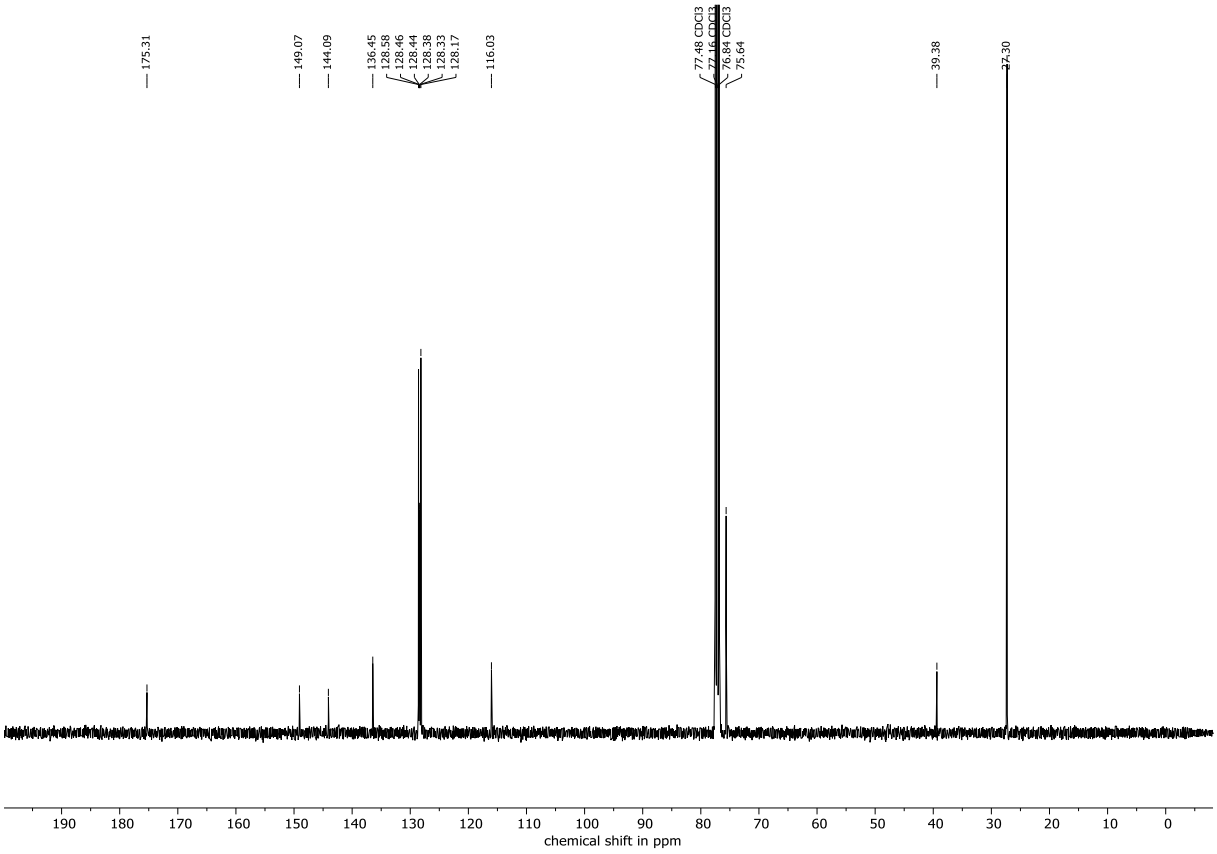
^{13}C NMR (101 MHz, $CDCl_3$) of **184**



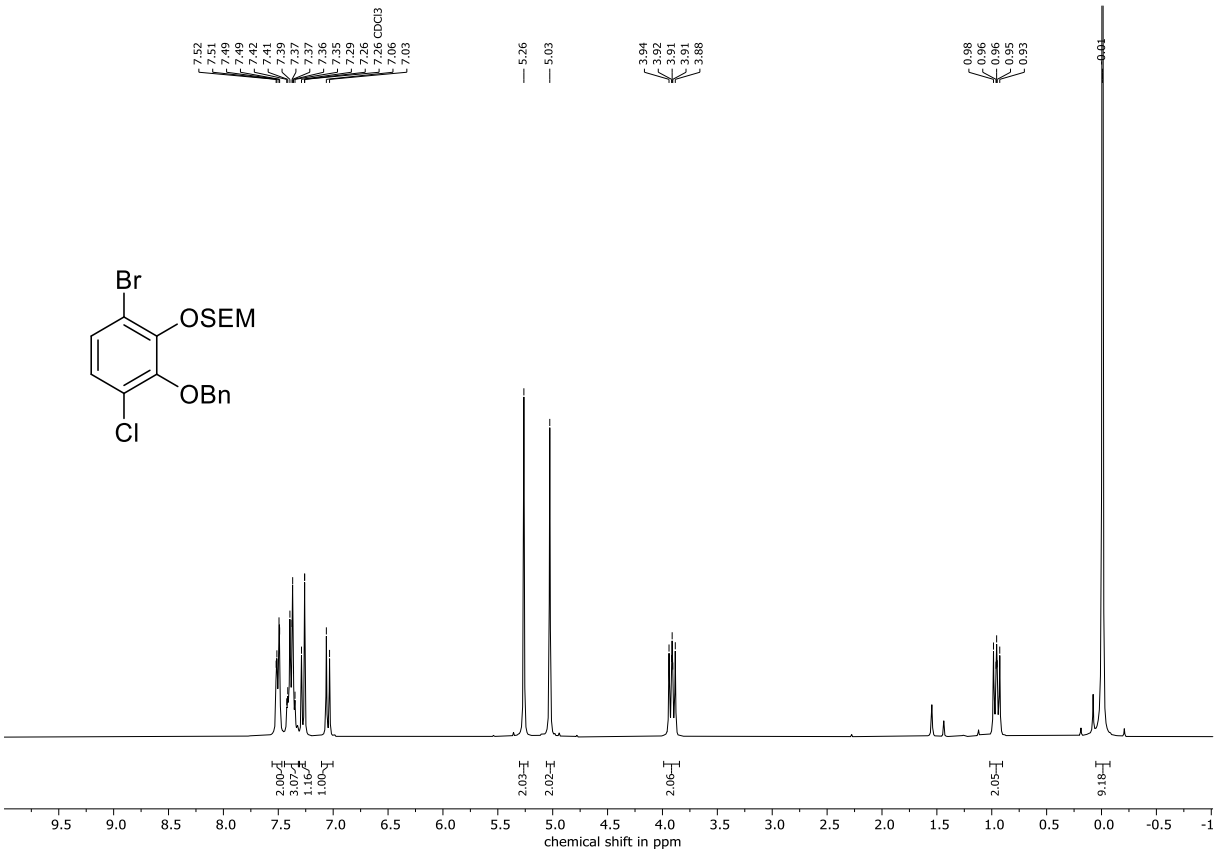
^{1}H NMR (300 MHz, $CDCl_3$) of **187**



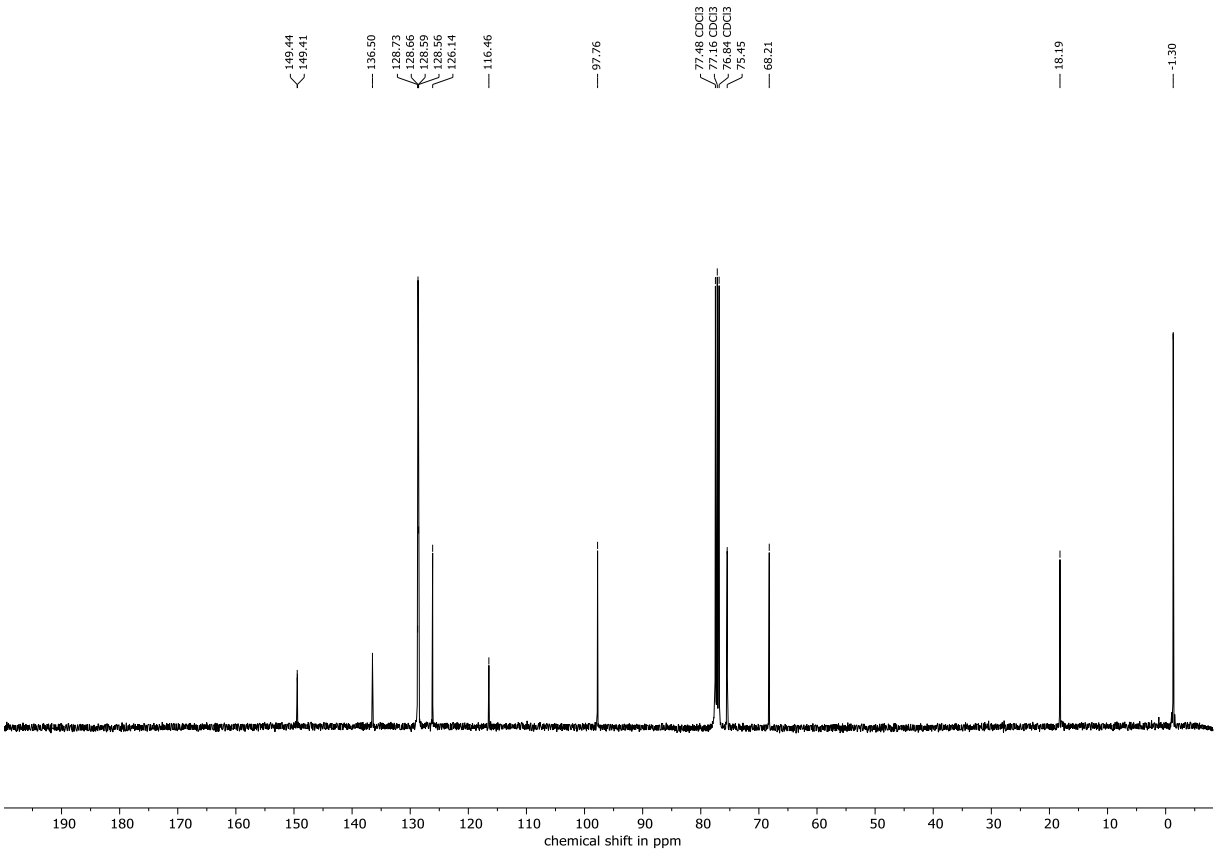
^{13}C NMR (101 MHz, $CDCl_3$) of **187**



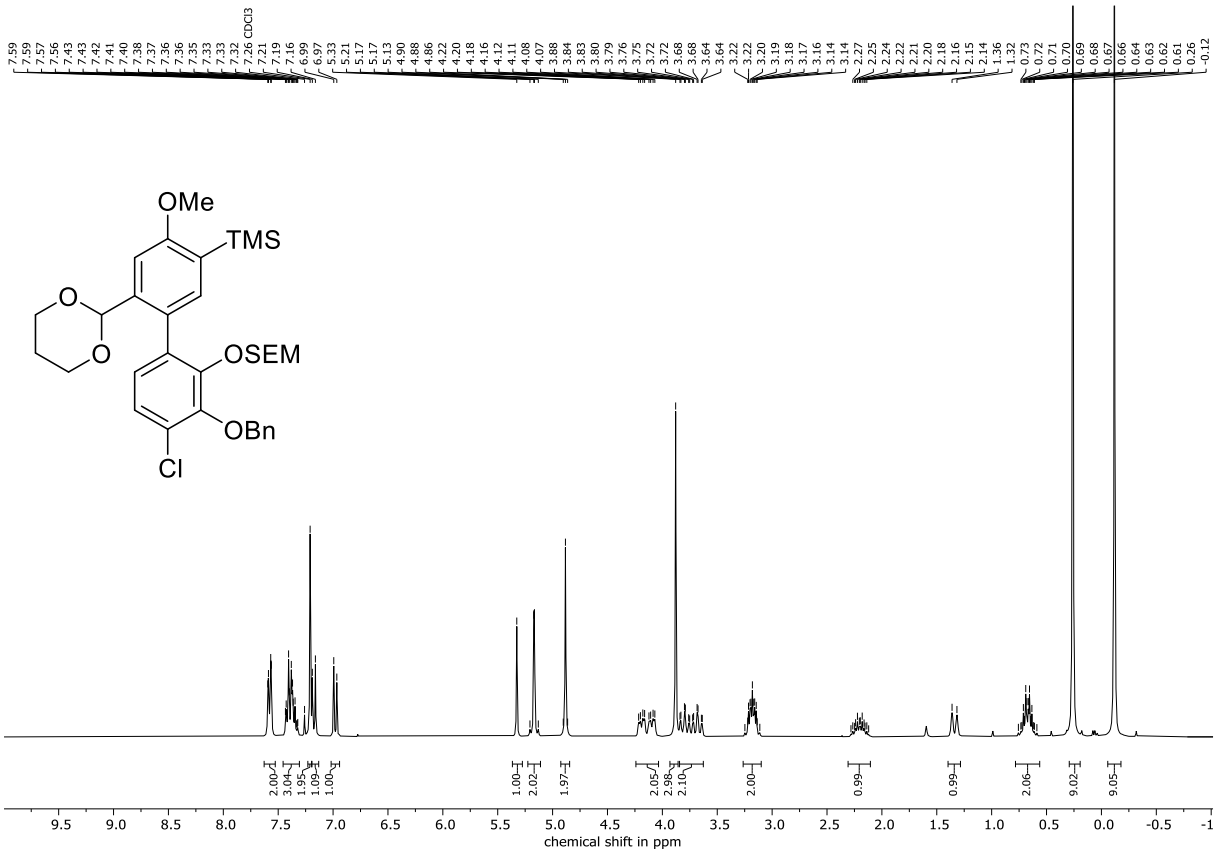
^{1}H NMR (300 MHz, $CDCl_3$) of **189**



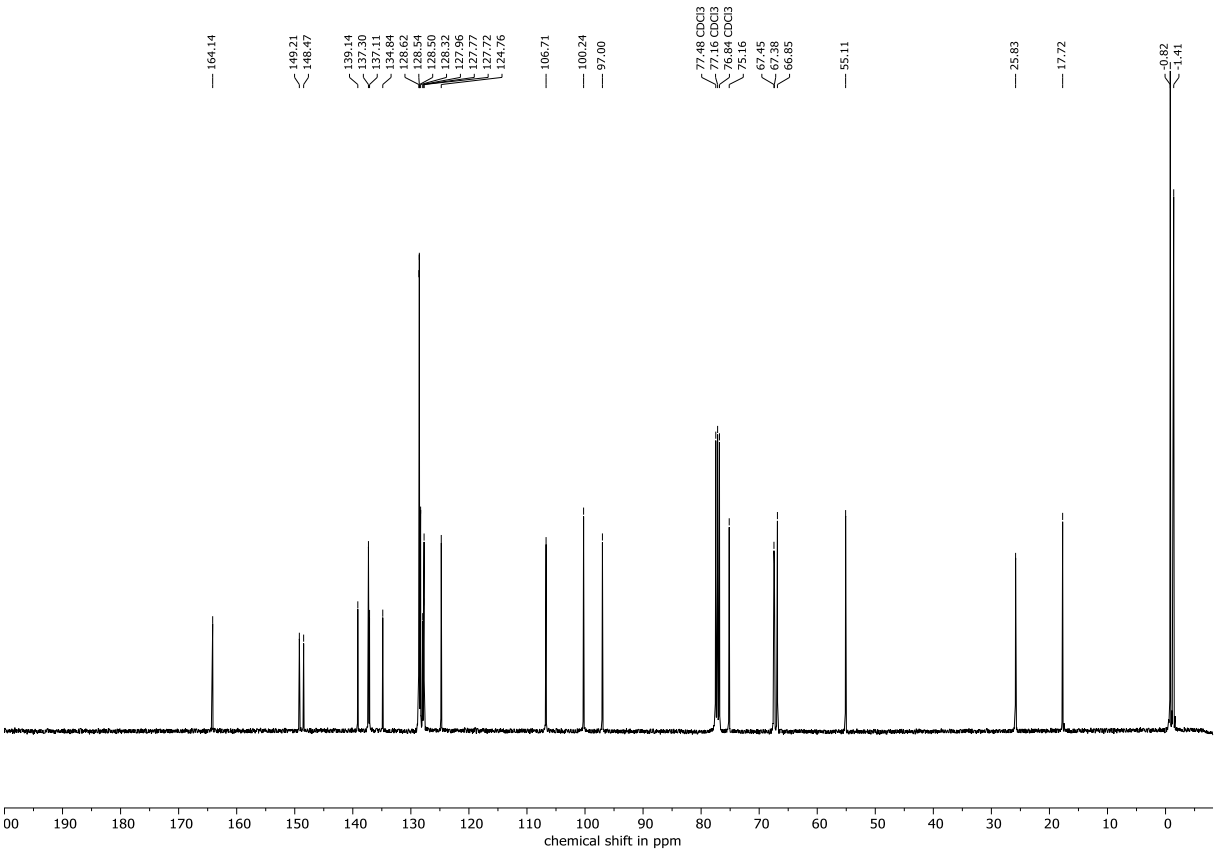
^{13}C NMR (101 MHz, $CDCl_3$) of **189**



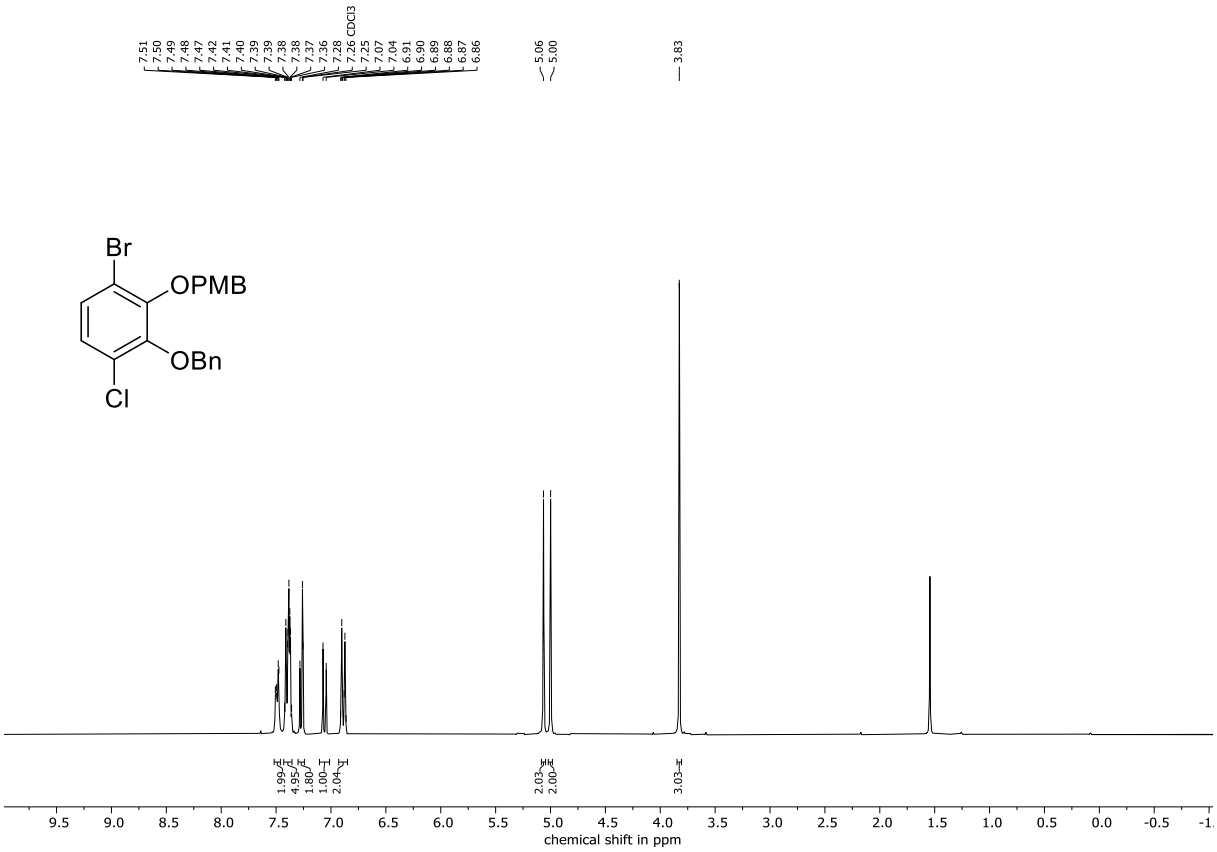
^{1}H NMR (300 MHz, $CDCl_3$) of **190**



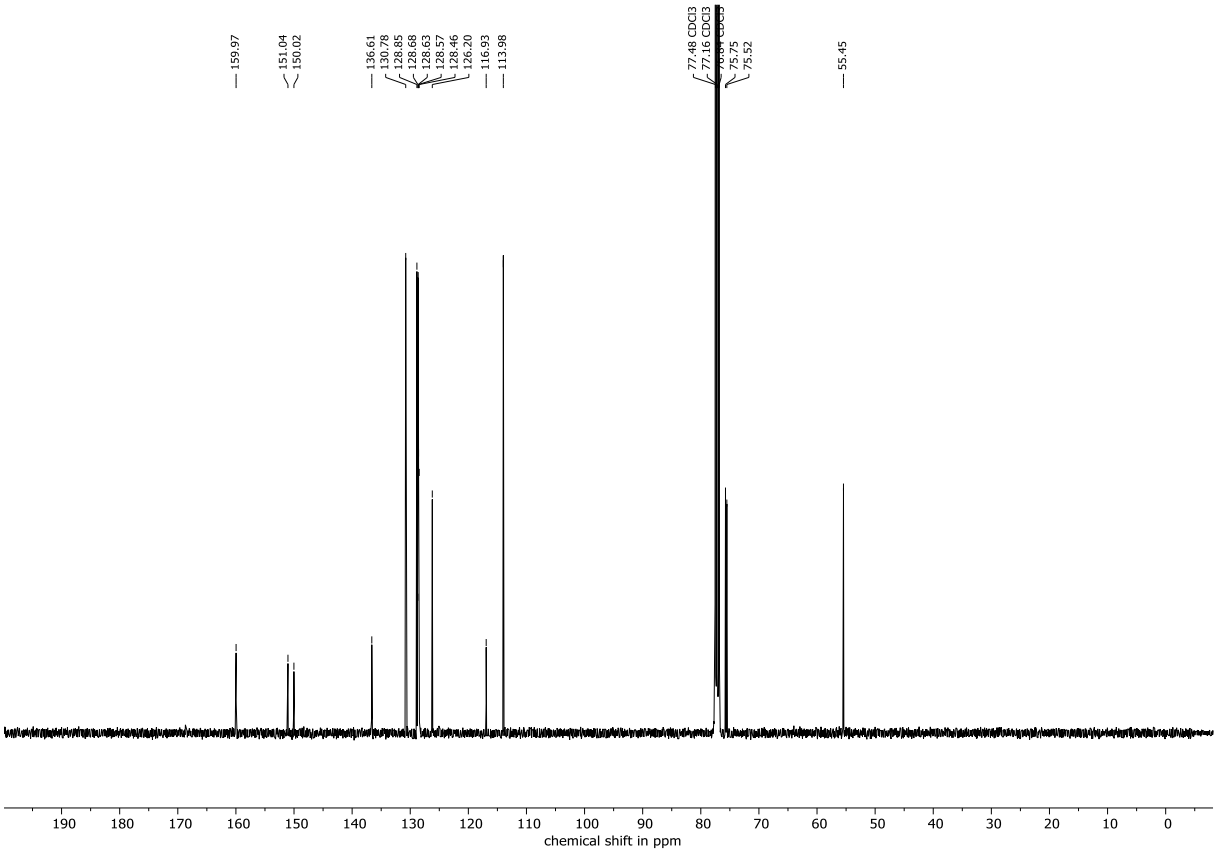
^{13}C NMR (101 MHz, $CDCl_3$) of **190**



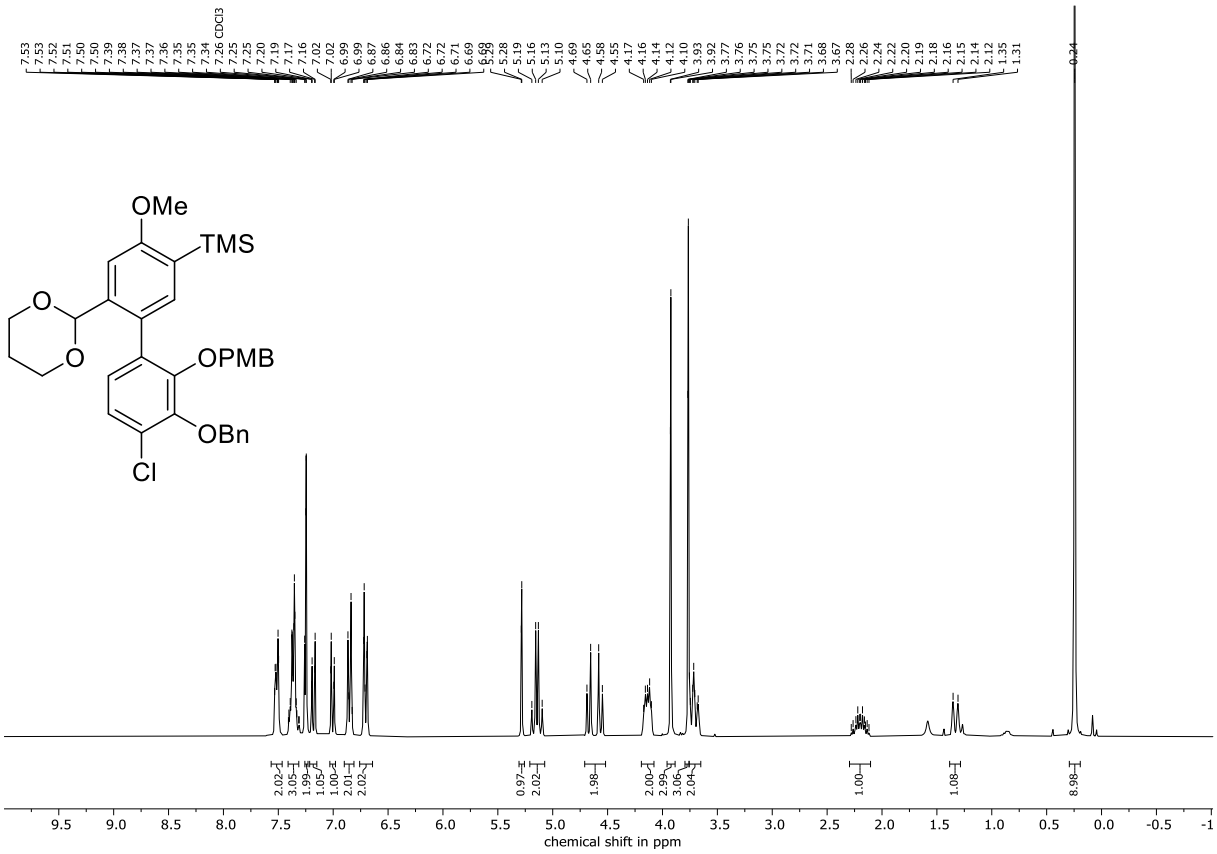
^{1}H NMR (300 MHz, $CDCl_3$) of **191**



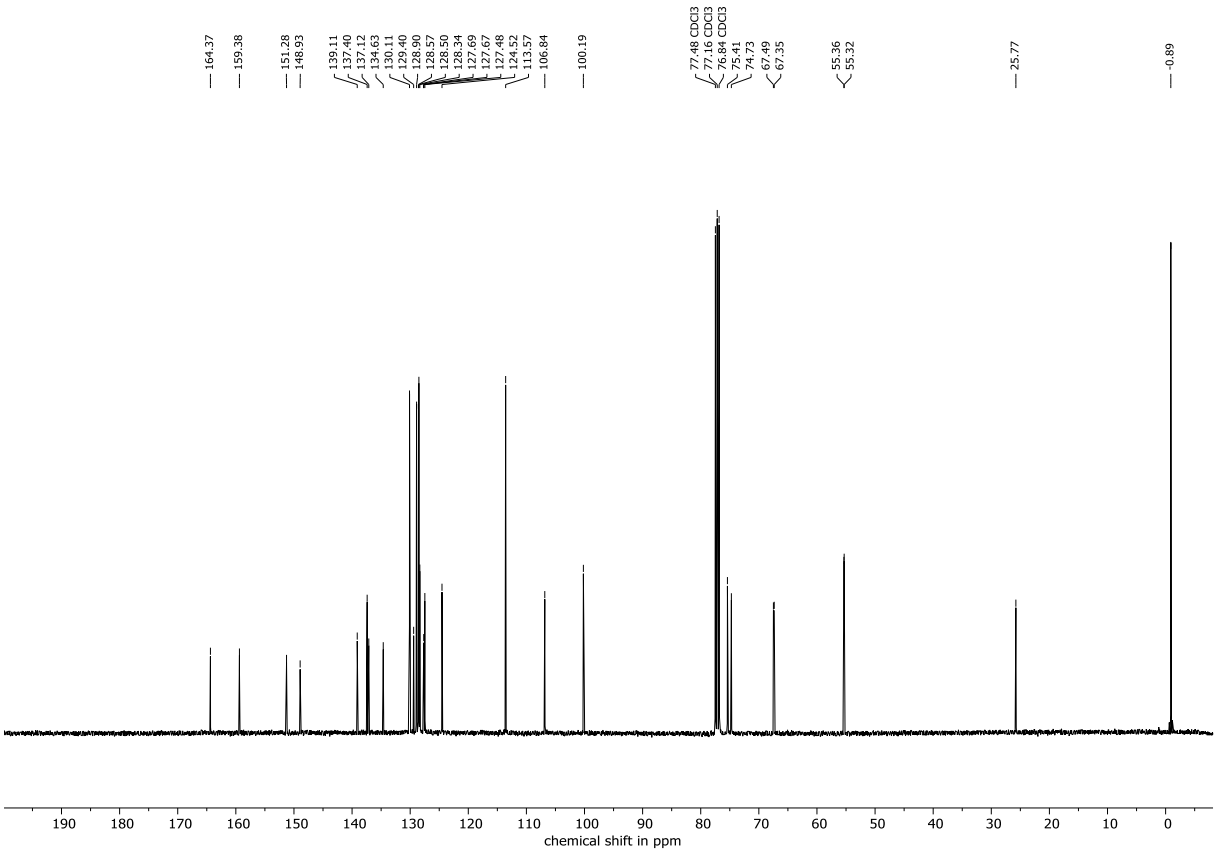
^{13}C NMR (101 MHz, $CDCl_3$) of **191**



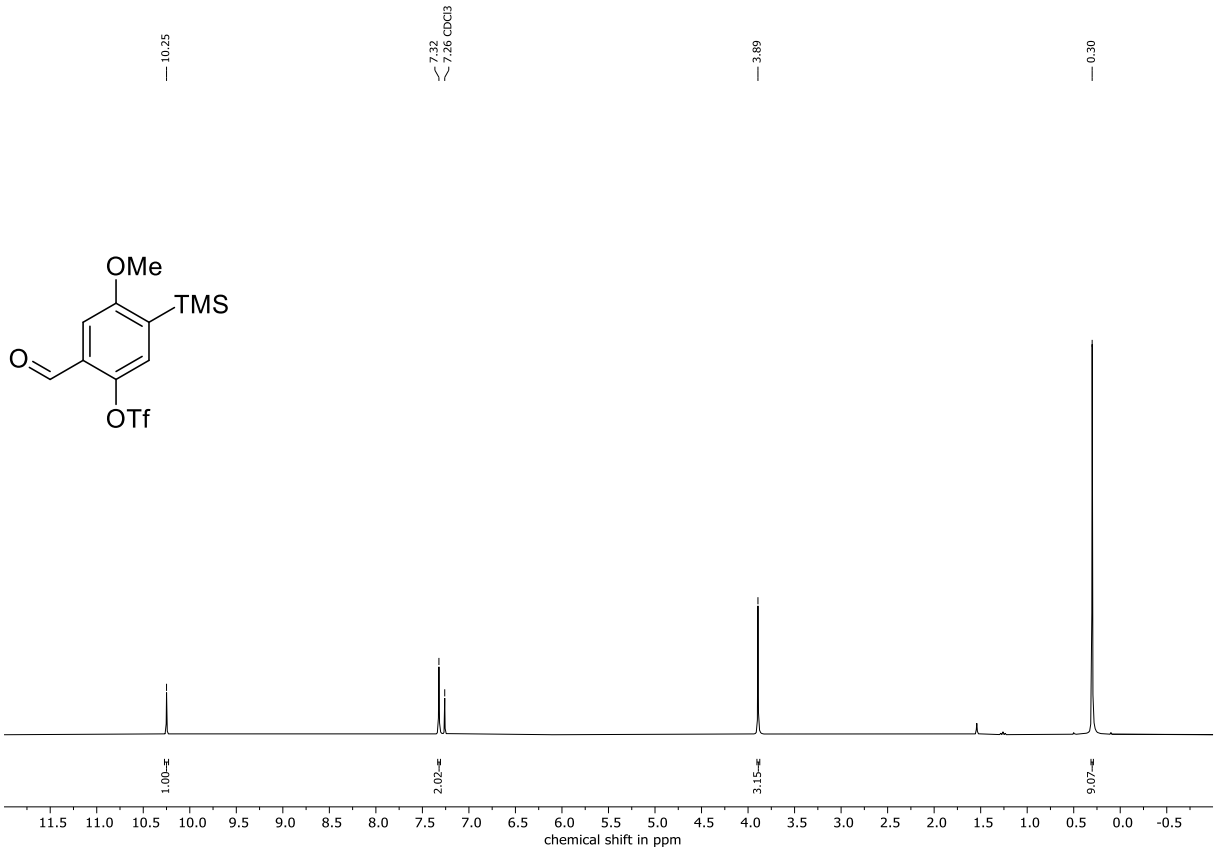
^{1}H NMR (300 MHz, $CDCl_3$) of **192**



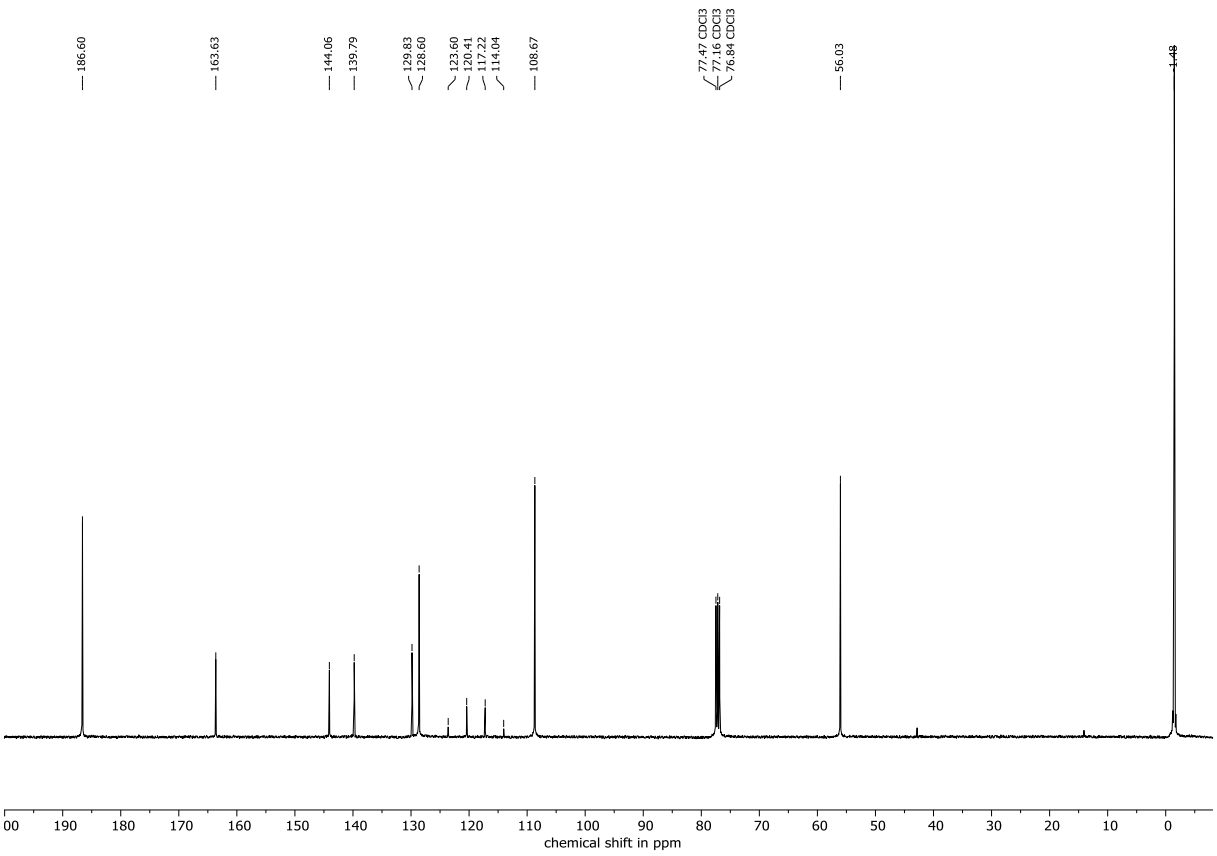
^{13}C NMR (101 MHz, $CDCl_3$) of **192**



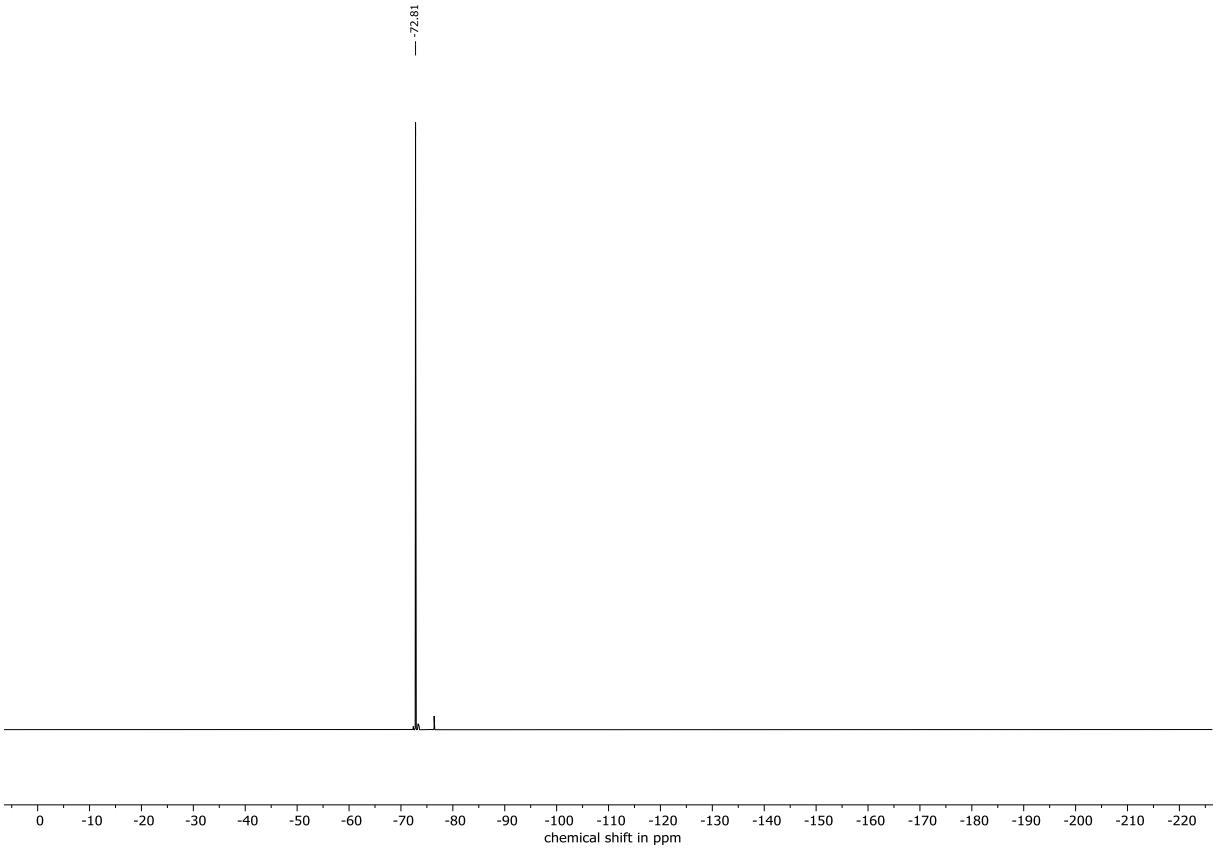
^{1}H NMR (300 MHz, $CDCl_3$) of **194**



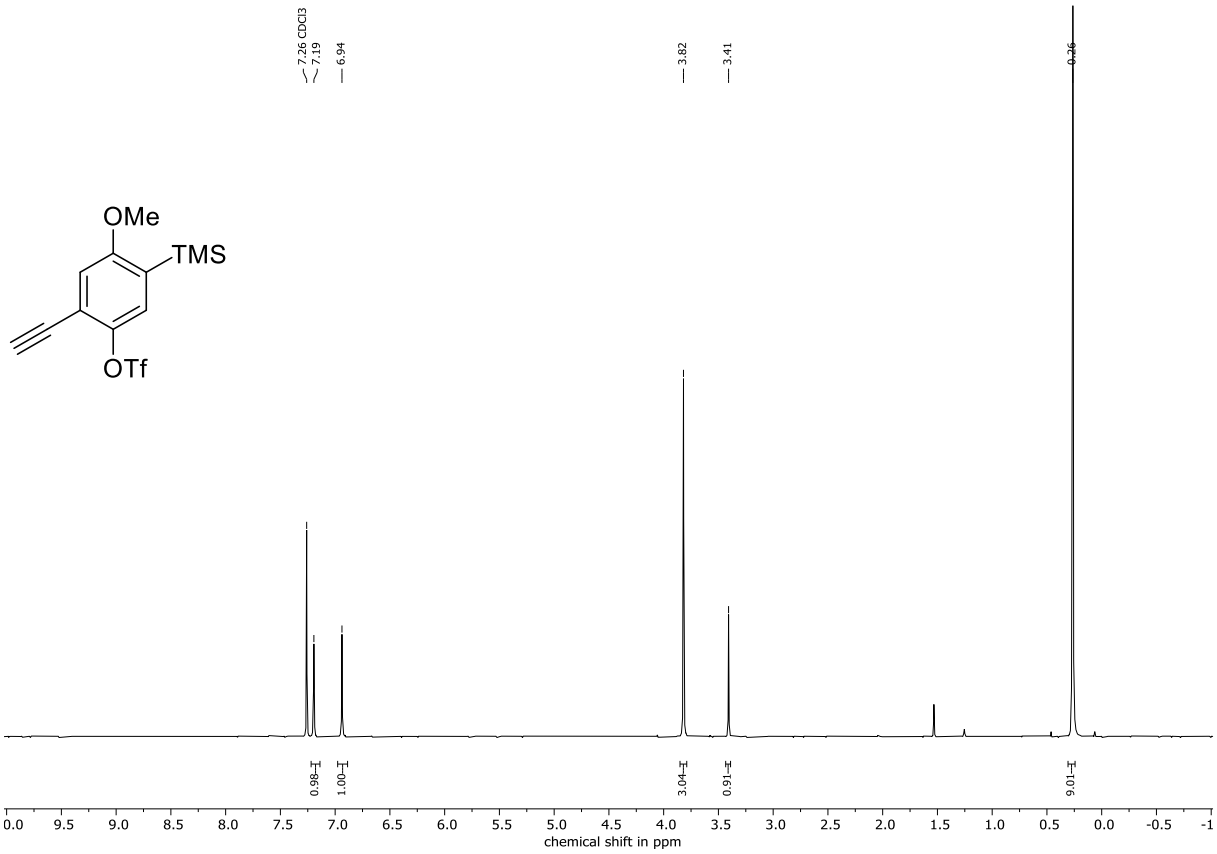
^{13}C NMR (101 MHz, $CDCl_3$) of **194**



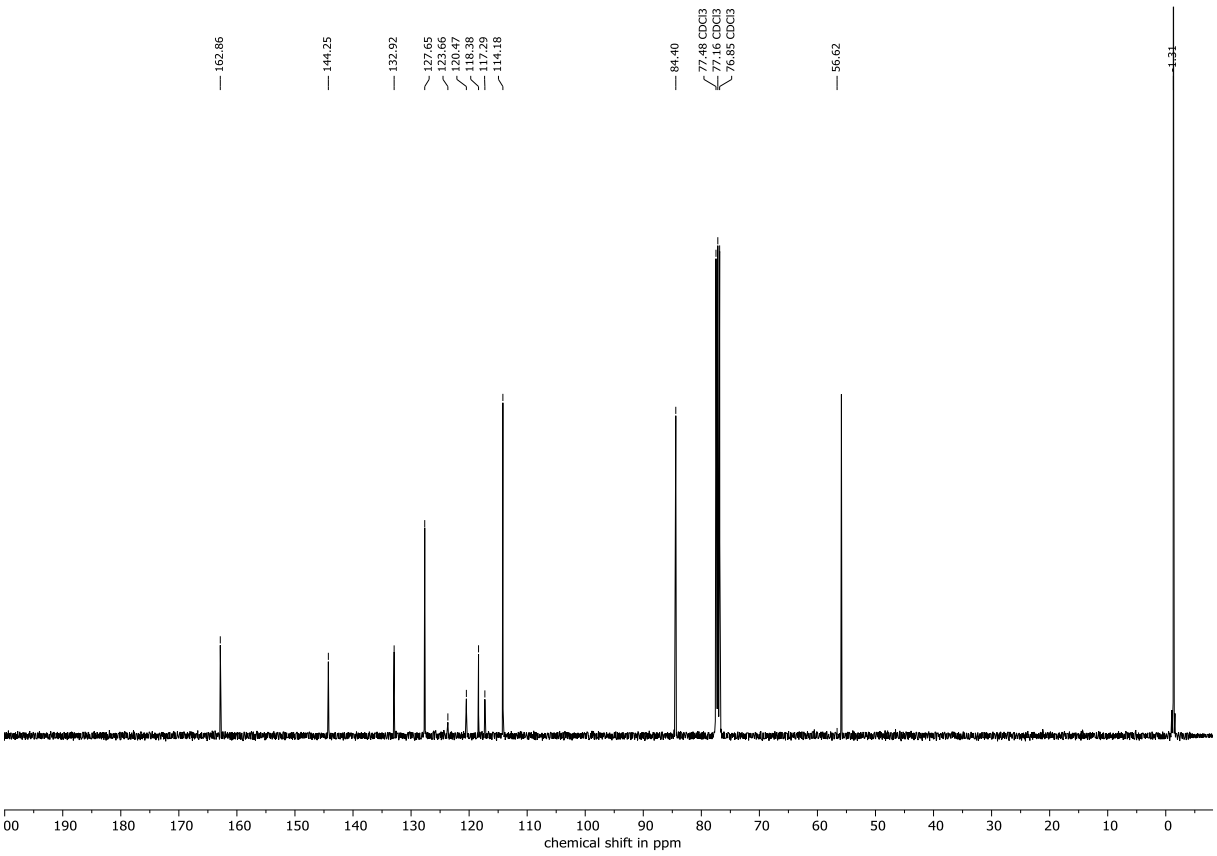
^{19}F NMR (282 MHz, $CDCl_3$) of **194**



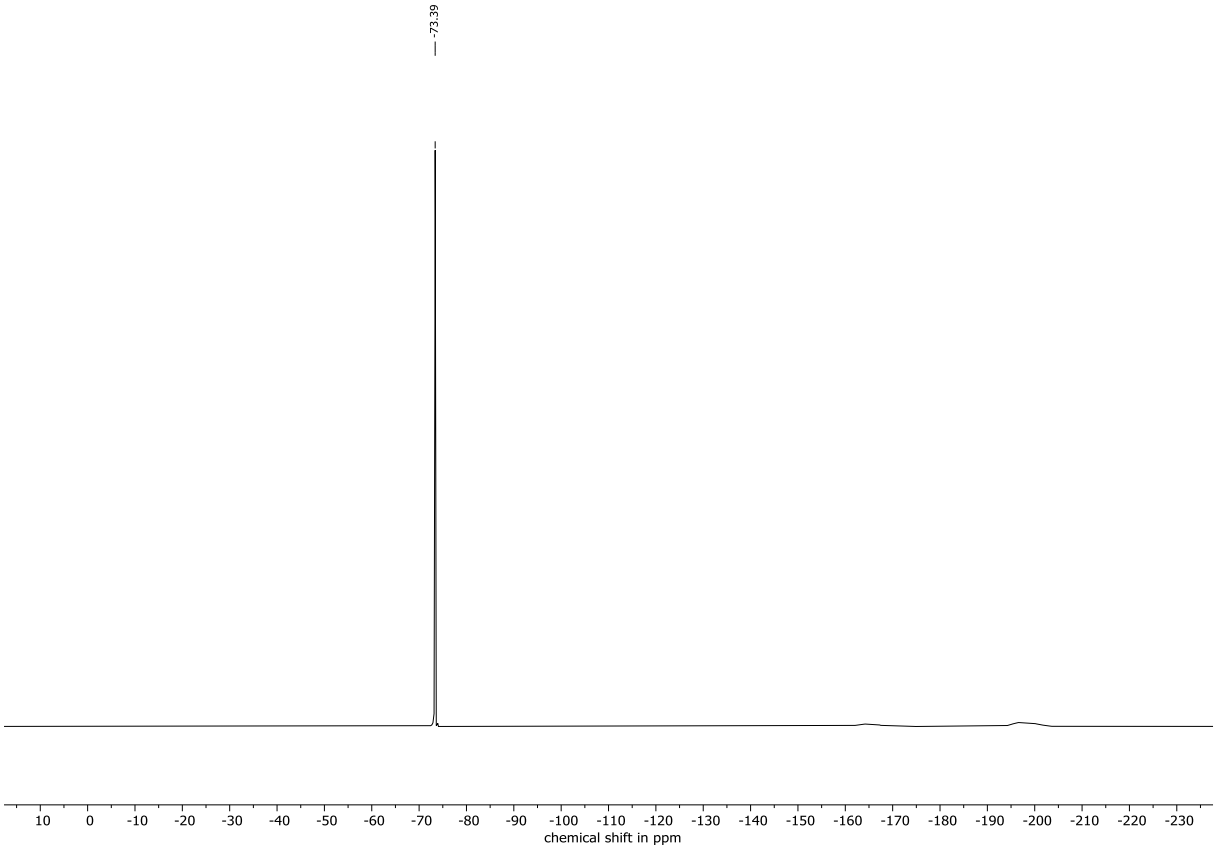
^{1}H NMR (300 MHz, $CDCl_3$) of **195**



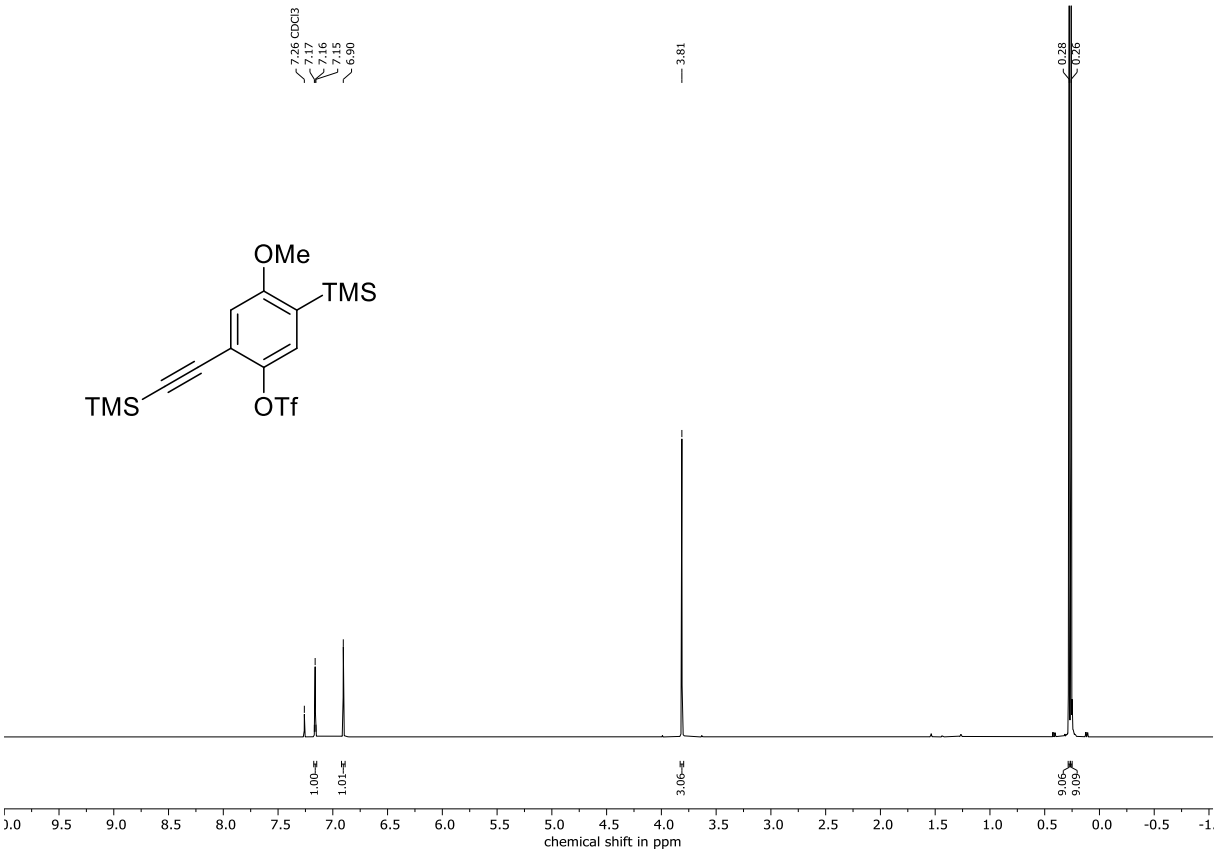
^{13}C NMR (101 MHz, $CDCl_3$) of **195**



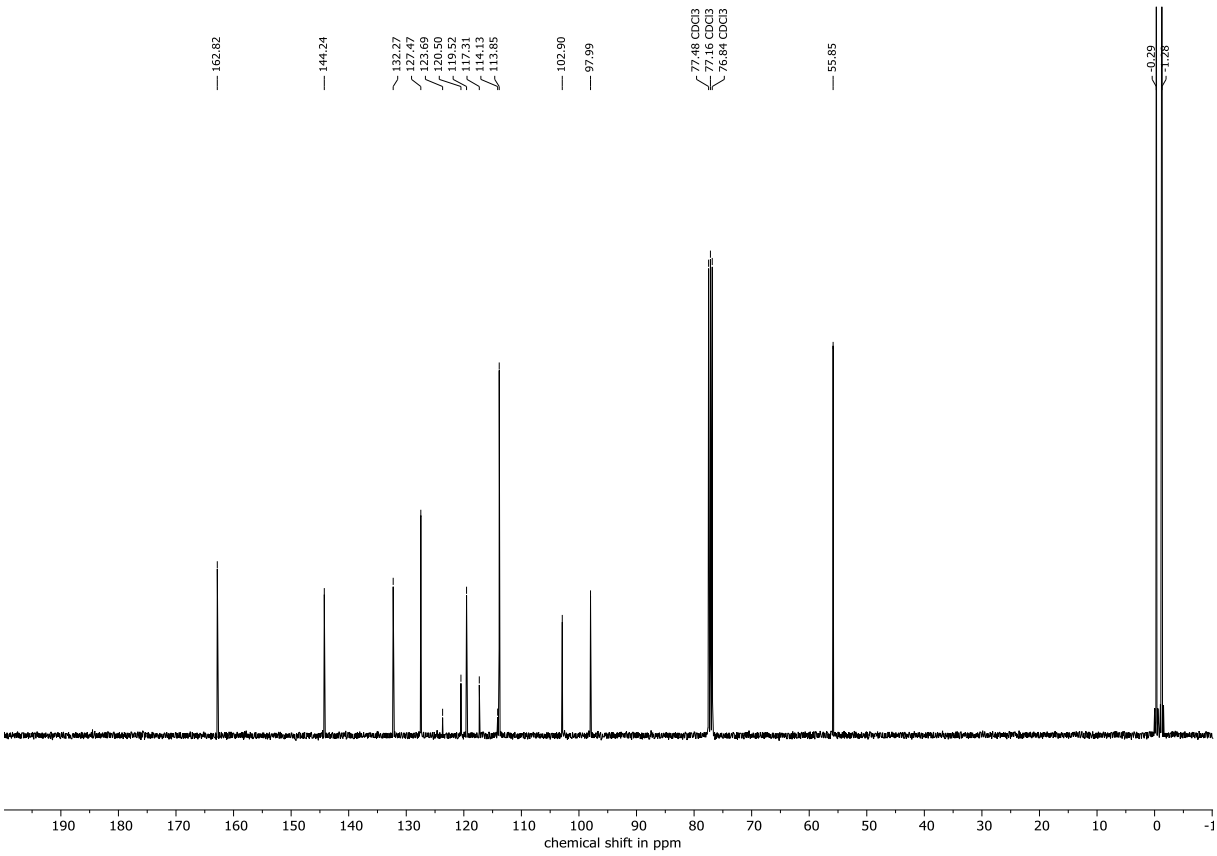
^{19}F NMR (377 MHz, $CDCl_3$) of **195**



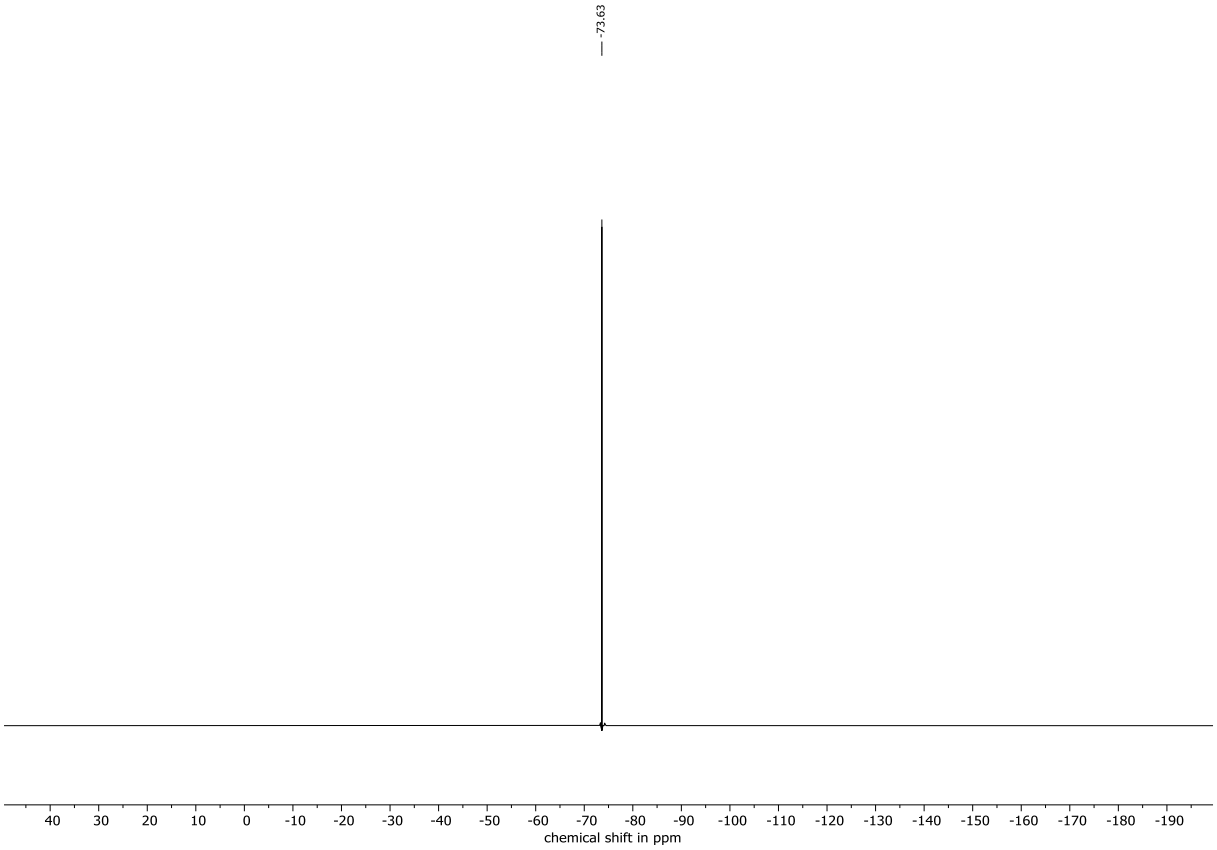
^{1}H NMR (400 MHz, $CDCl_3$) of **196**



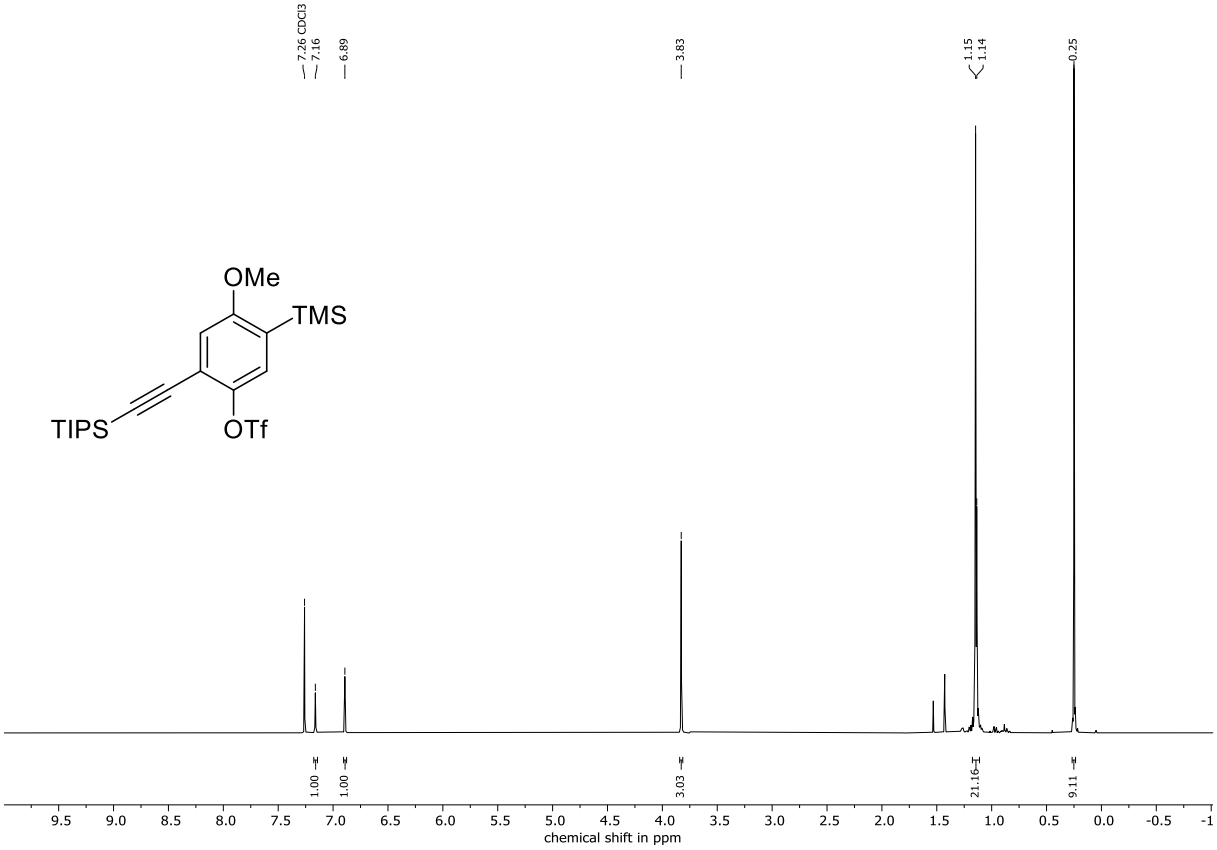
^{13}C NMR (101 MHz, $CDCl_3$) of **196**



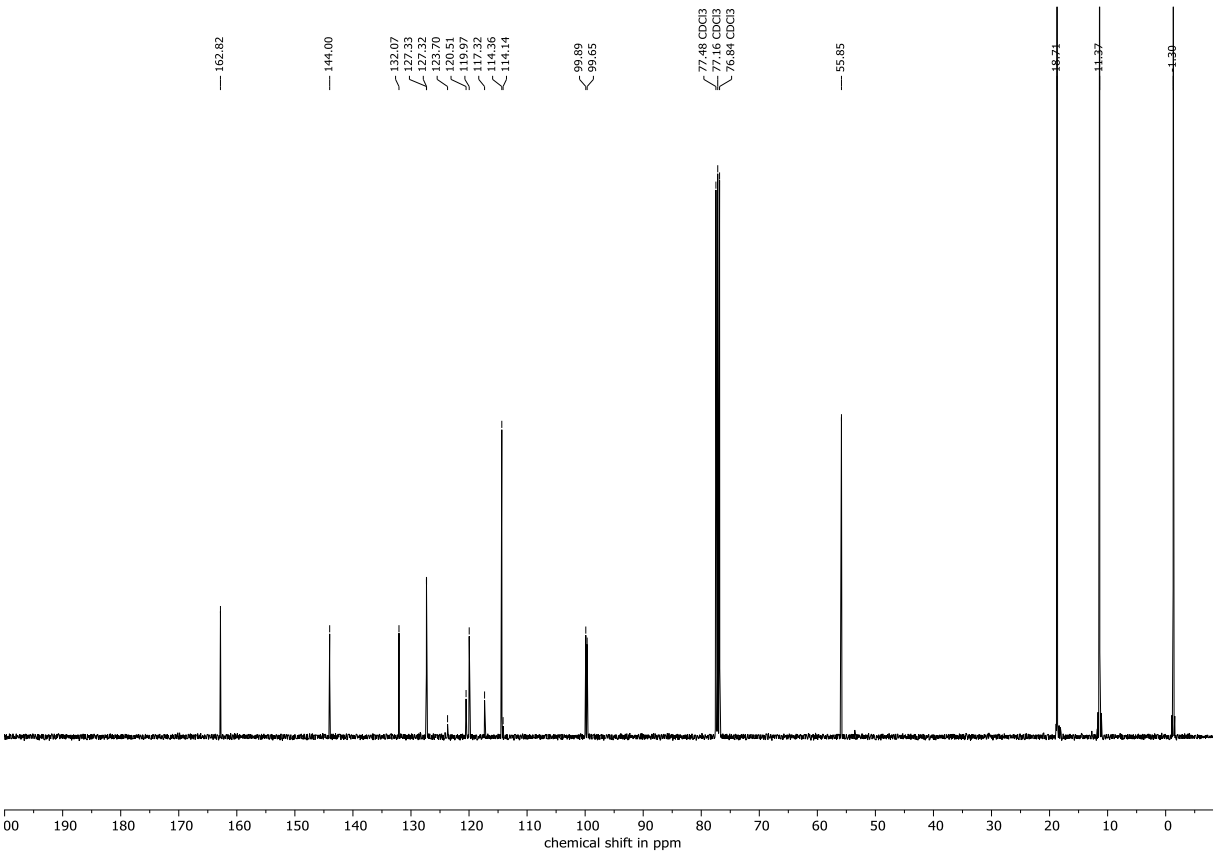
^{19}F NMR (376 MHz, $CDCl_3$) of **196**



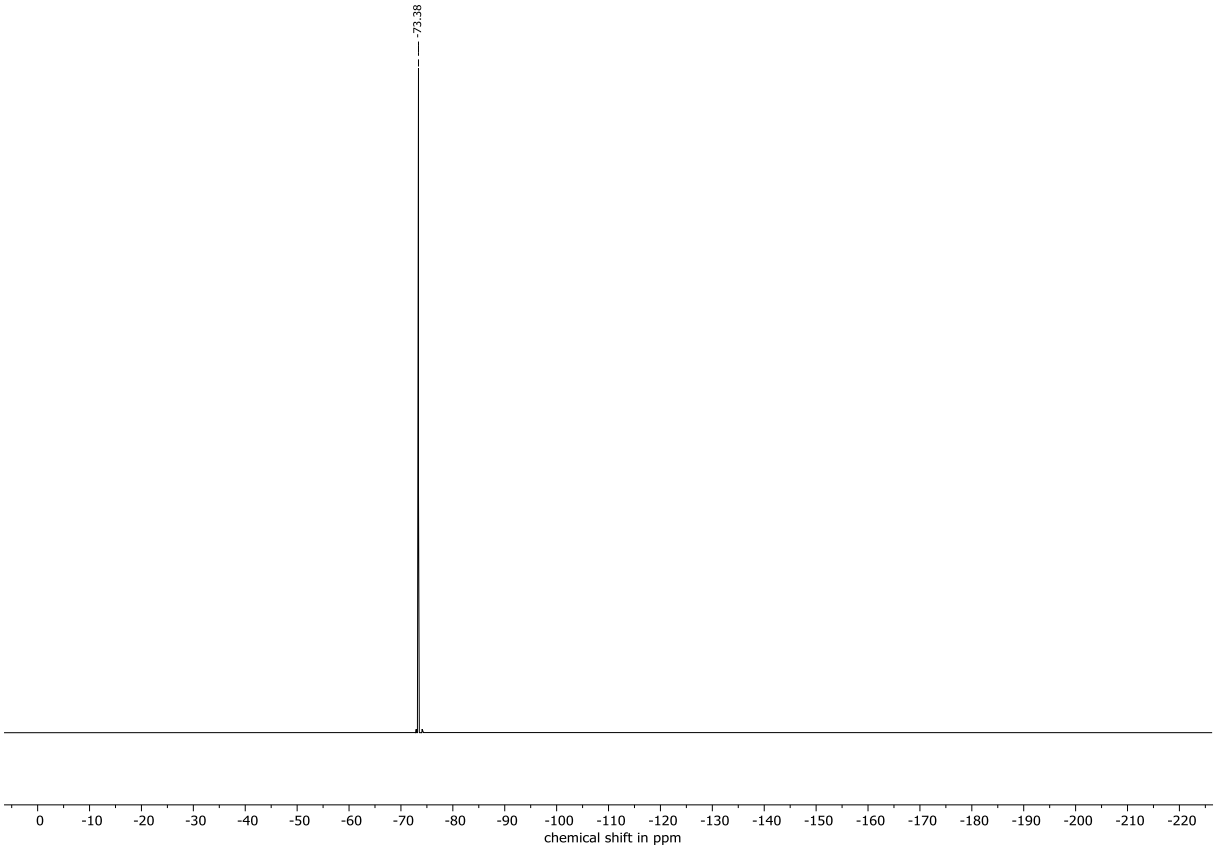
^{1}H NMR (300 MHz, $CDCl_3$) of **197**



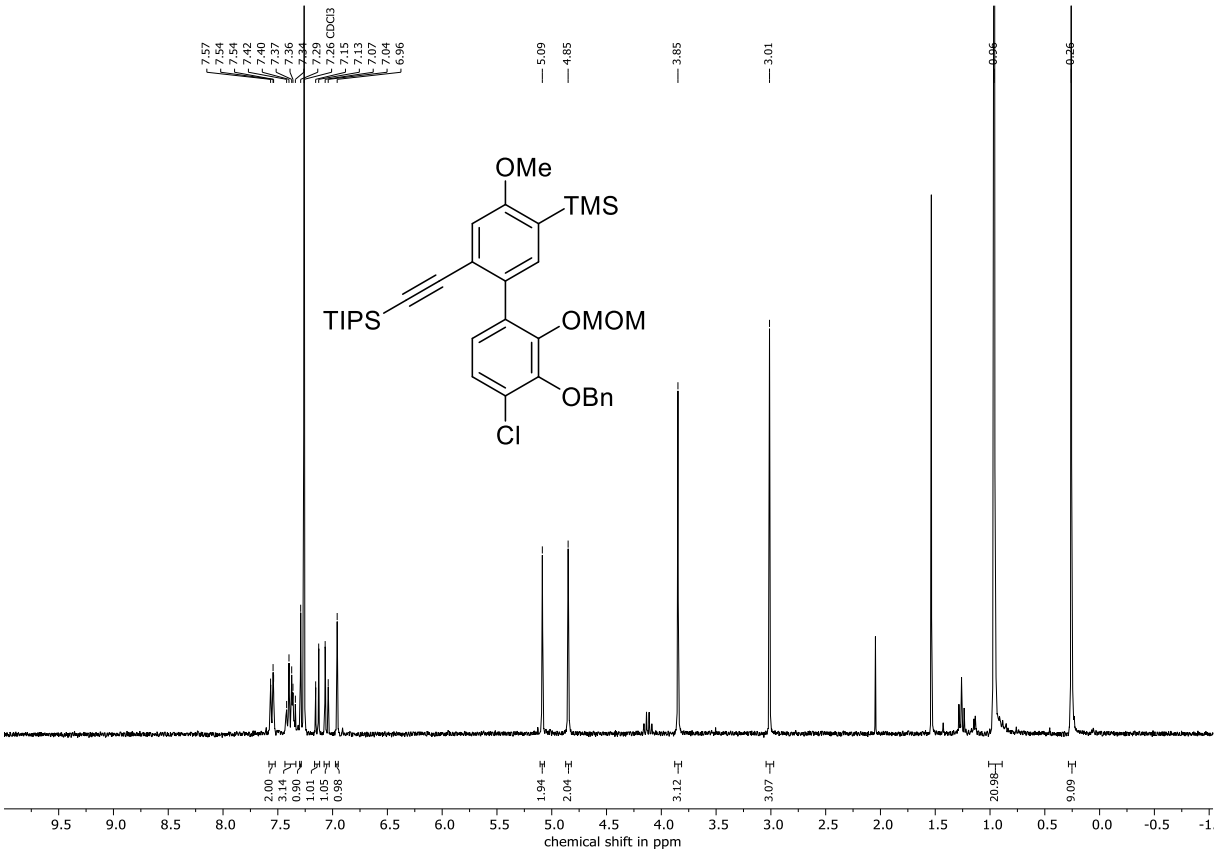
^{13}C NMR (101 MHz, $CDCl_3$) of **197**



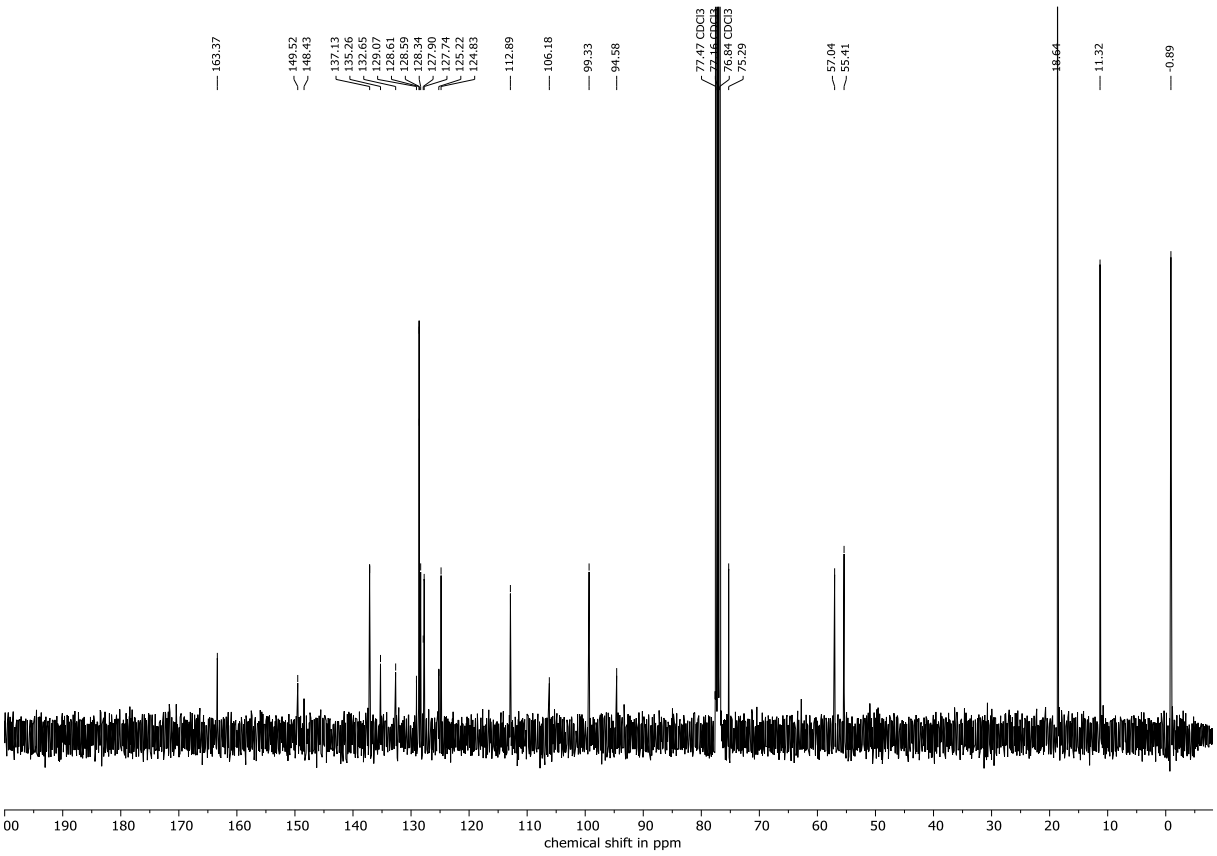
^{19}F NMR (282 MHz, $CDCl_3$) of **197**



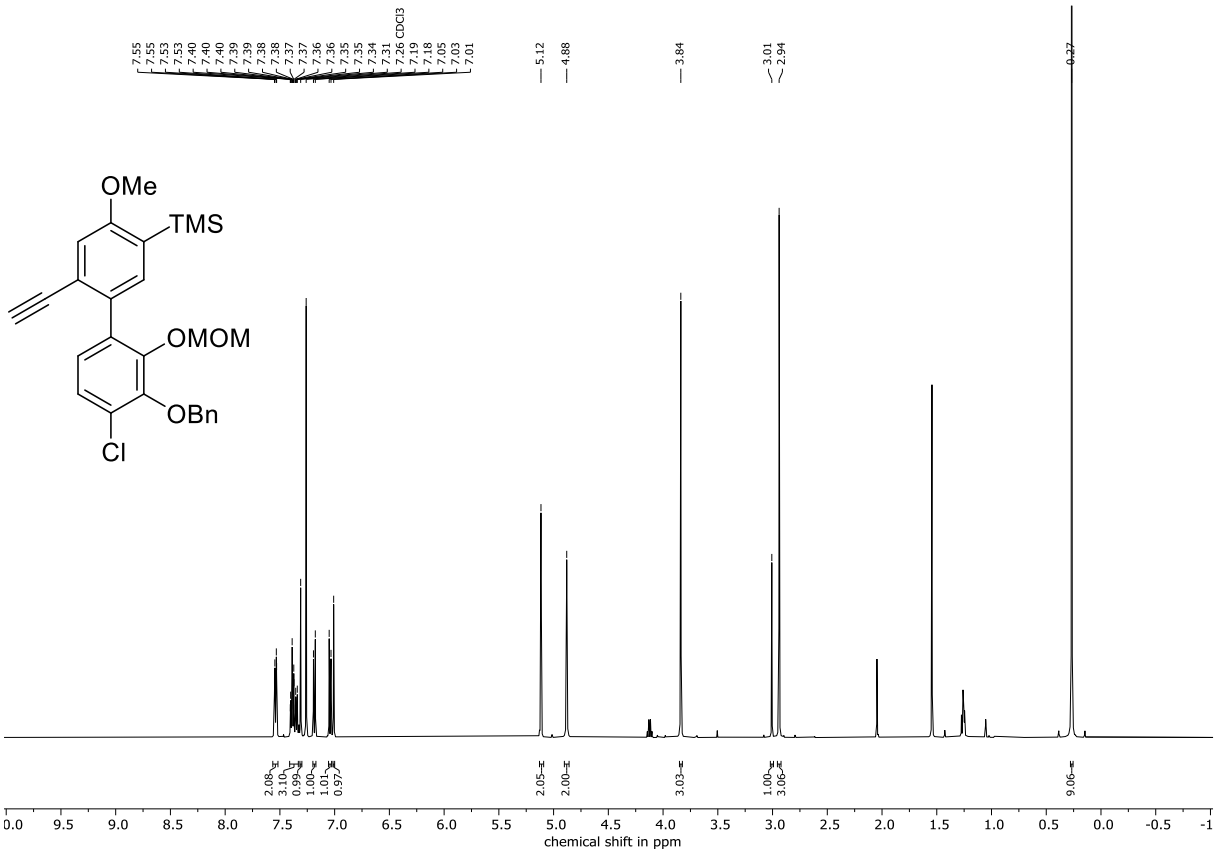
^{1}H NMR (300 MHz, $CDCl_3$) of **199**



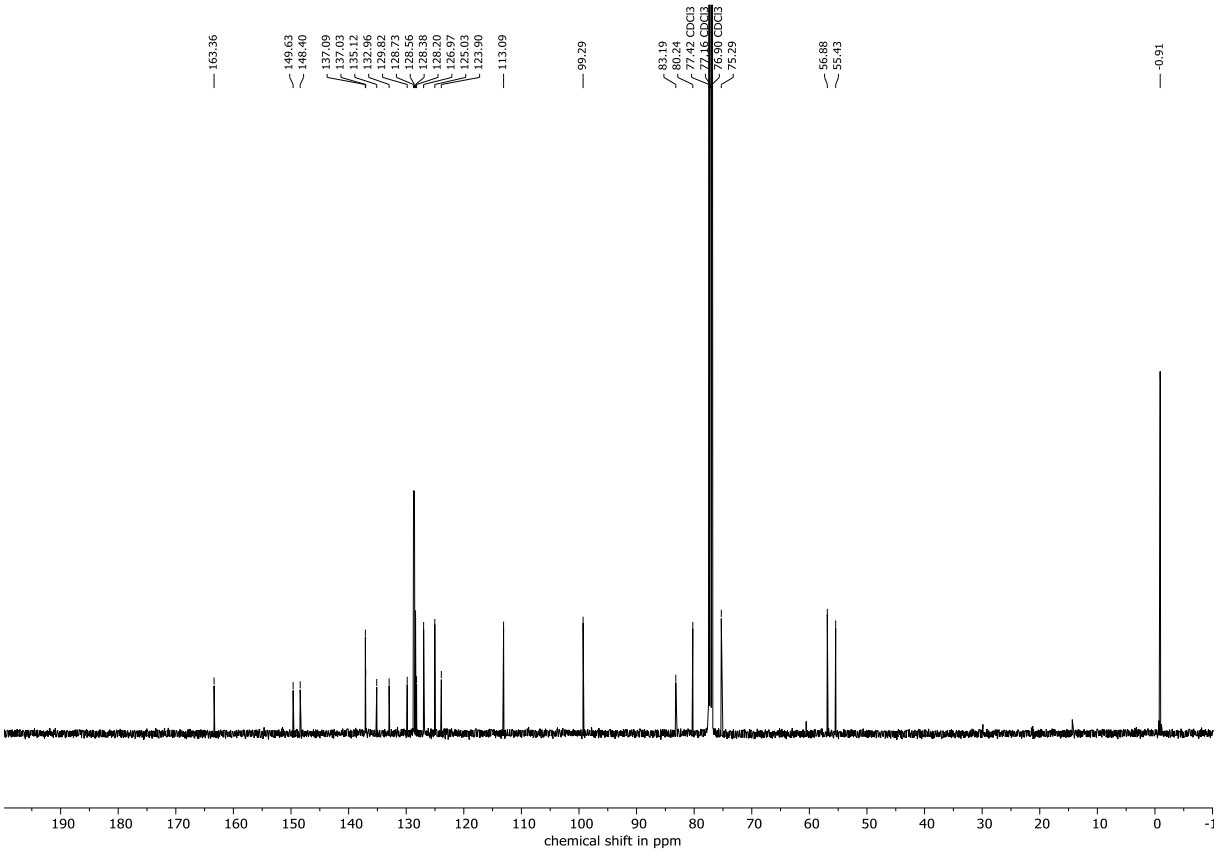
^{13}C NMR (101 MHz, $CDCl_3$) of **199**



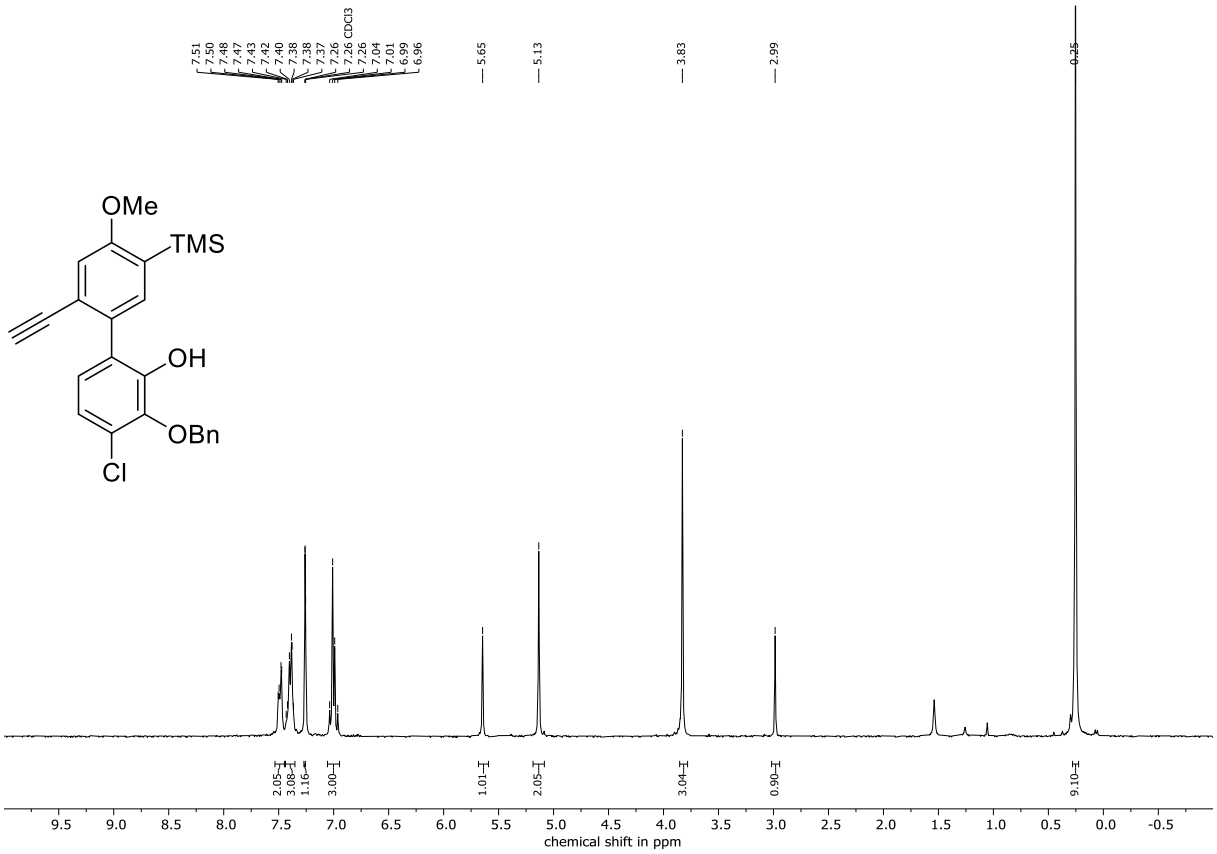
^{1}H NMR (500 MHz, $CDCl_3$) of **200**



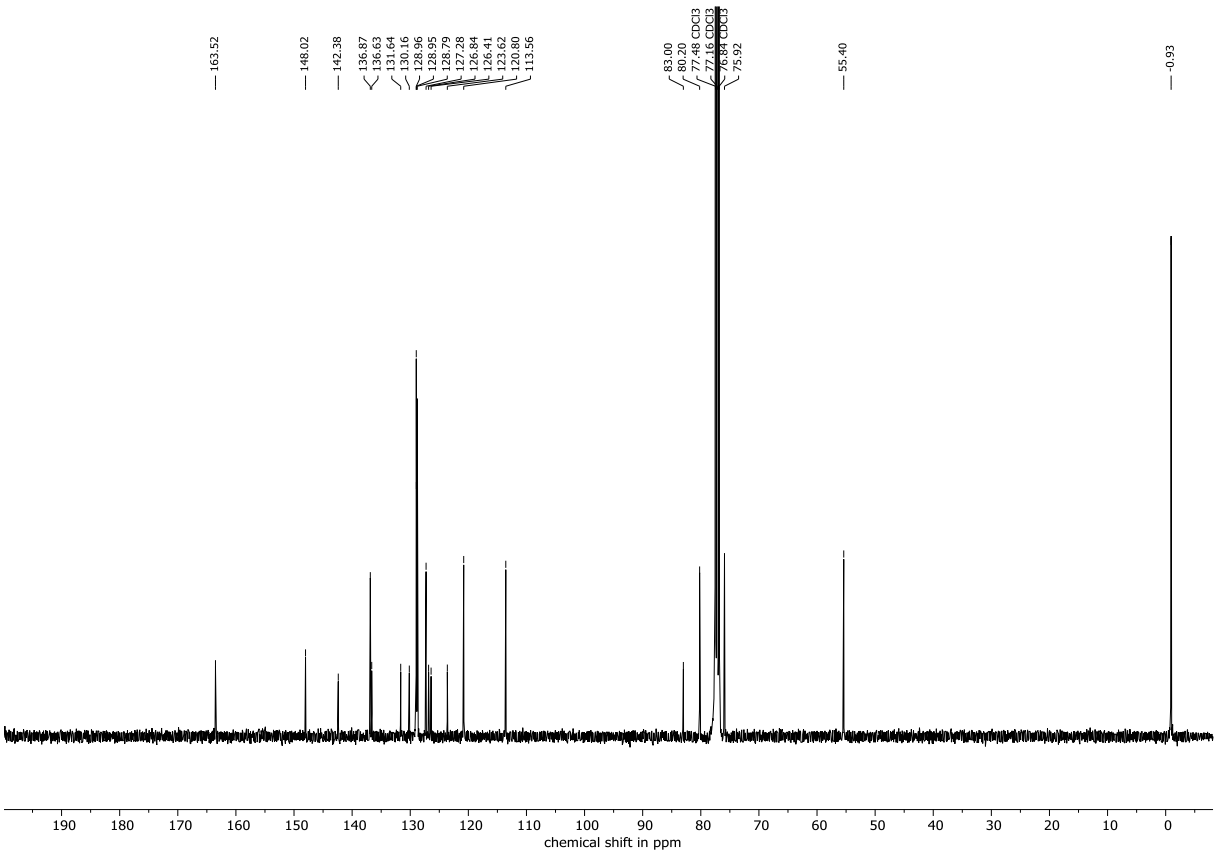
^{13}C NMR (126 MHz, $CDCl_3$) of **200**



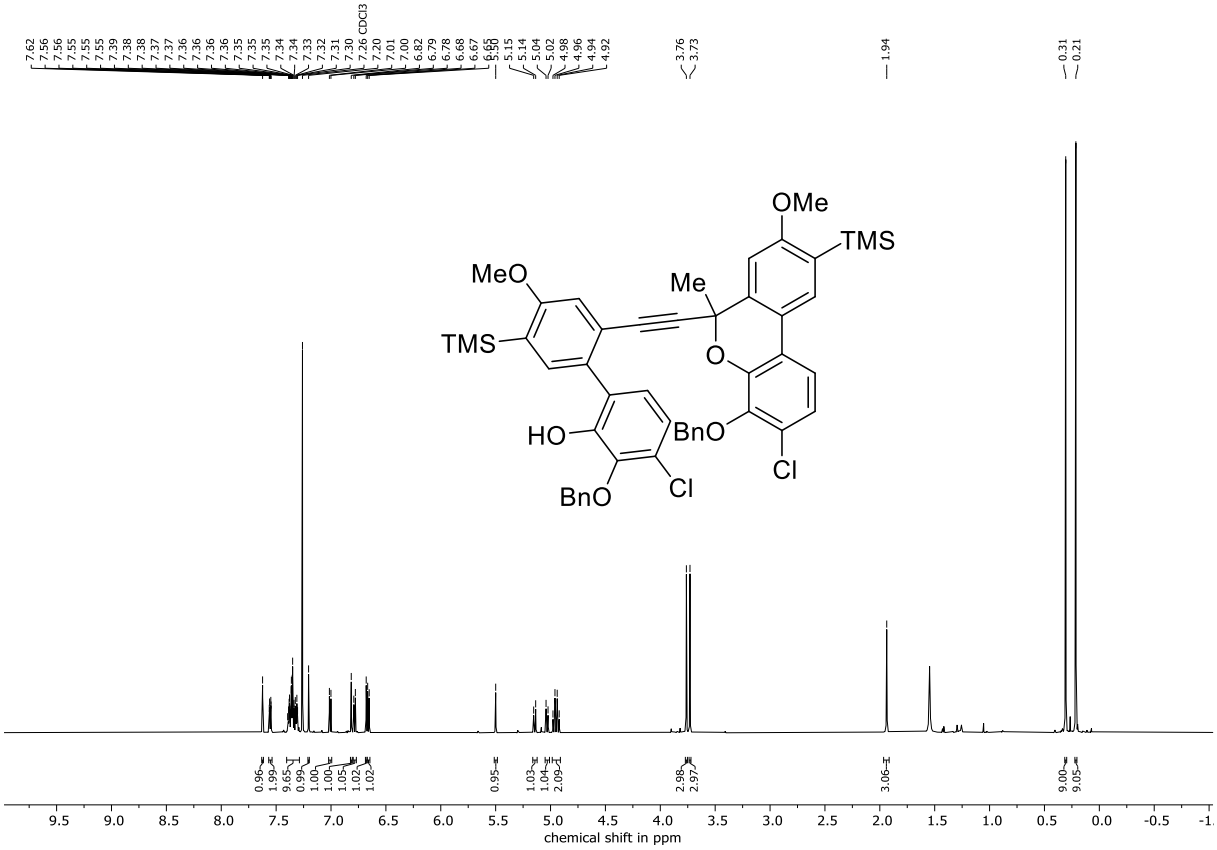
^{1}H NMR (300 MHz, $CDCl_3$) of **204**



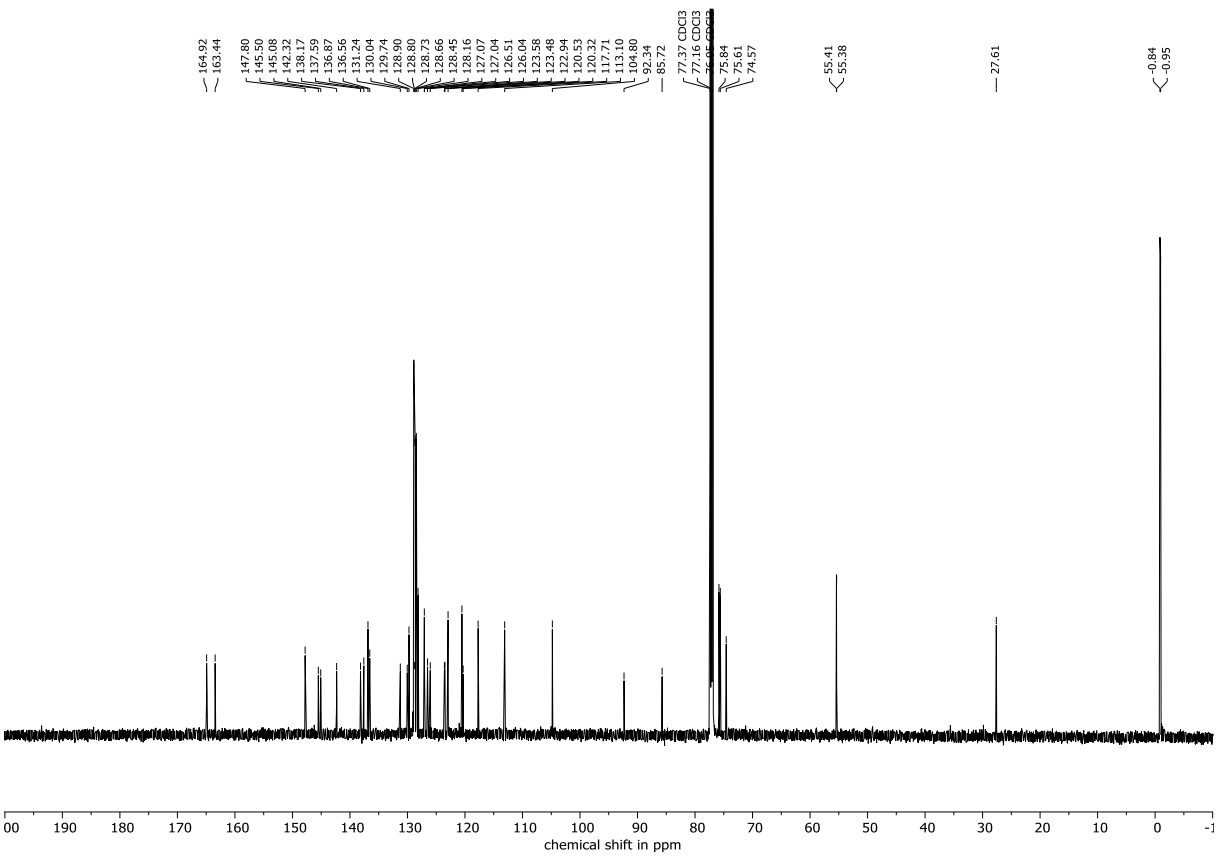
^{13}C NMR (101 MHz, $CDCl_3$) of **204**



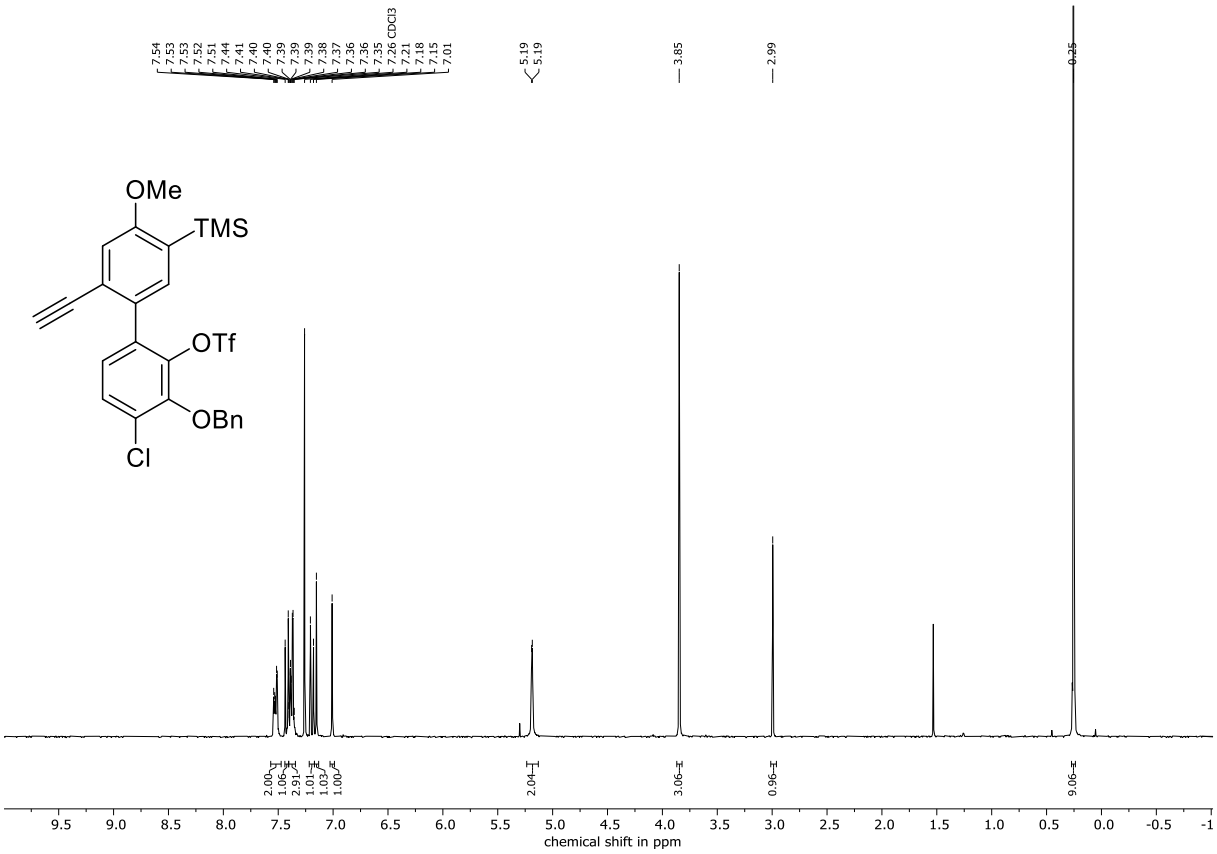
^{1}H NMR (600 MHz, $CDCl_3$) of **205**



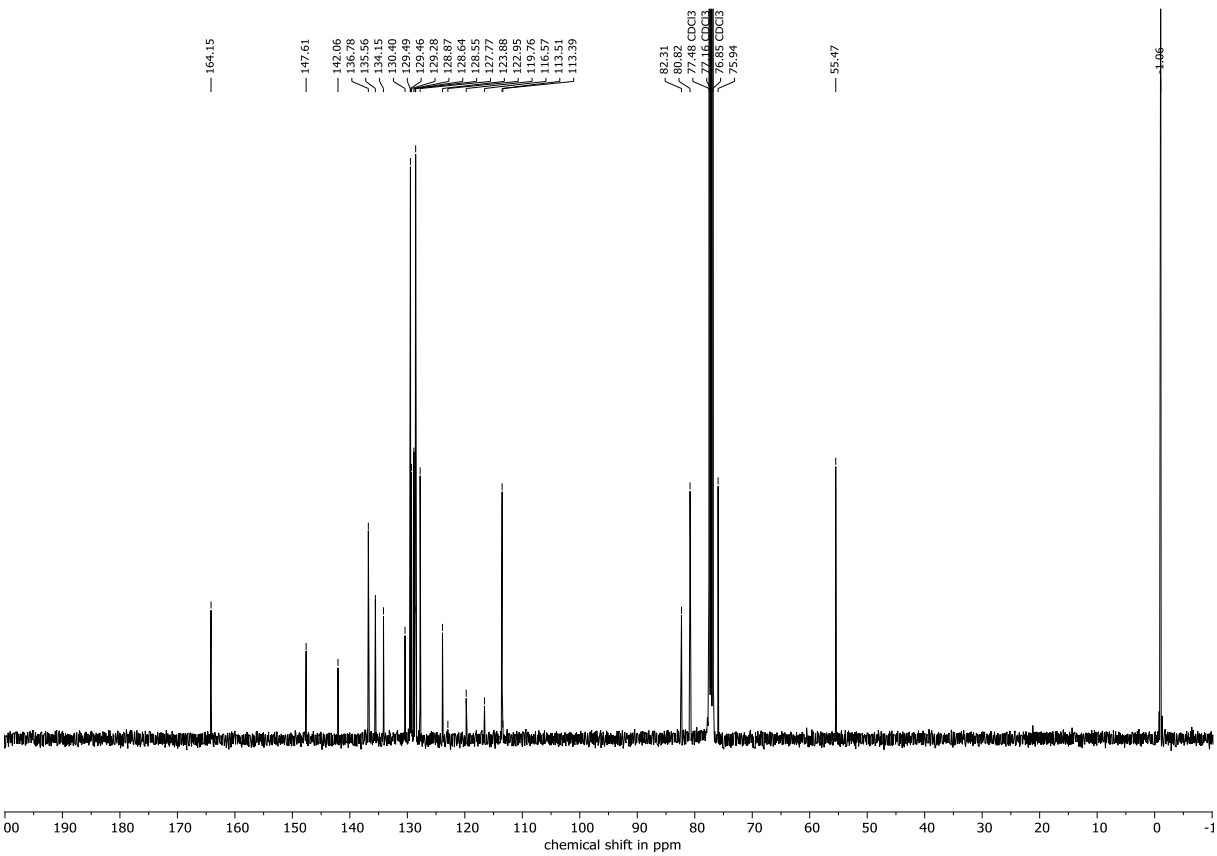
^{13}C NMR (151 MHz, $CDCl_3$) of **205**



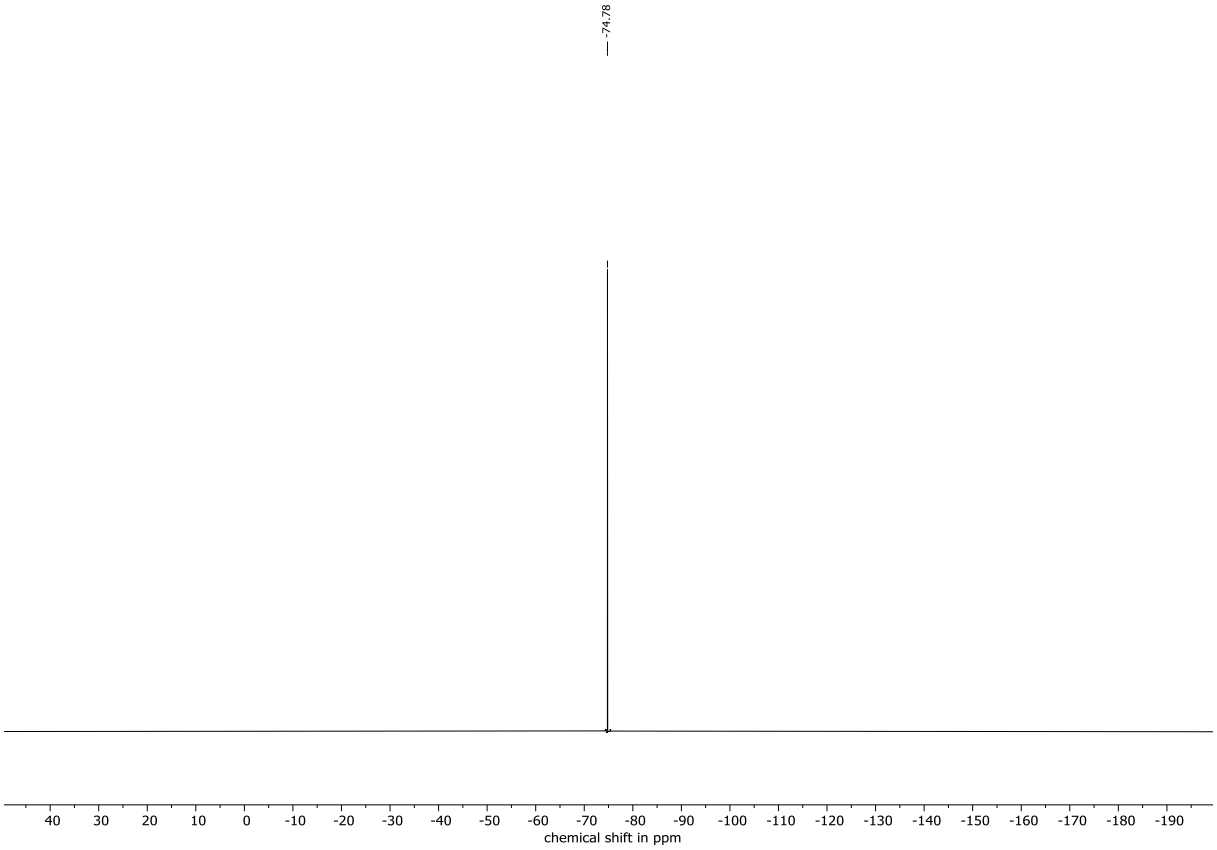
^{1}H NMR (300 MHz, $CDCl_3$) of **207**



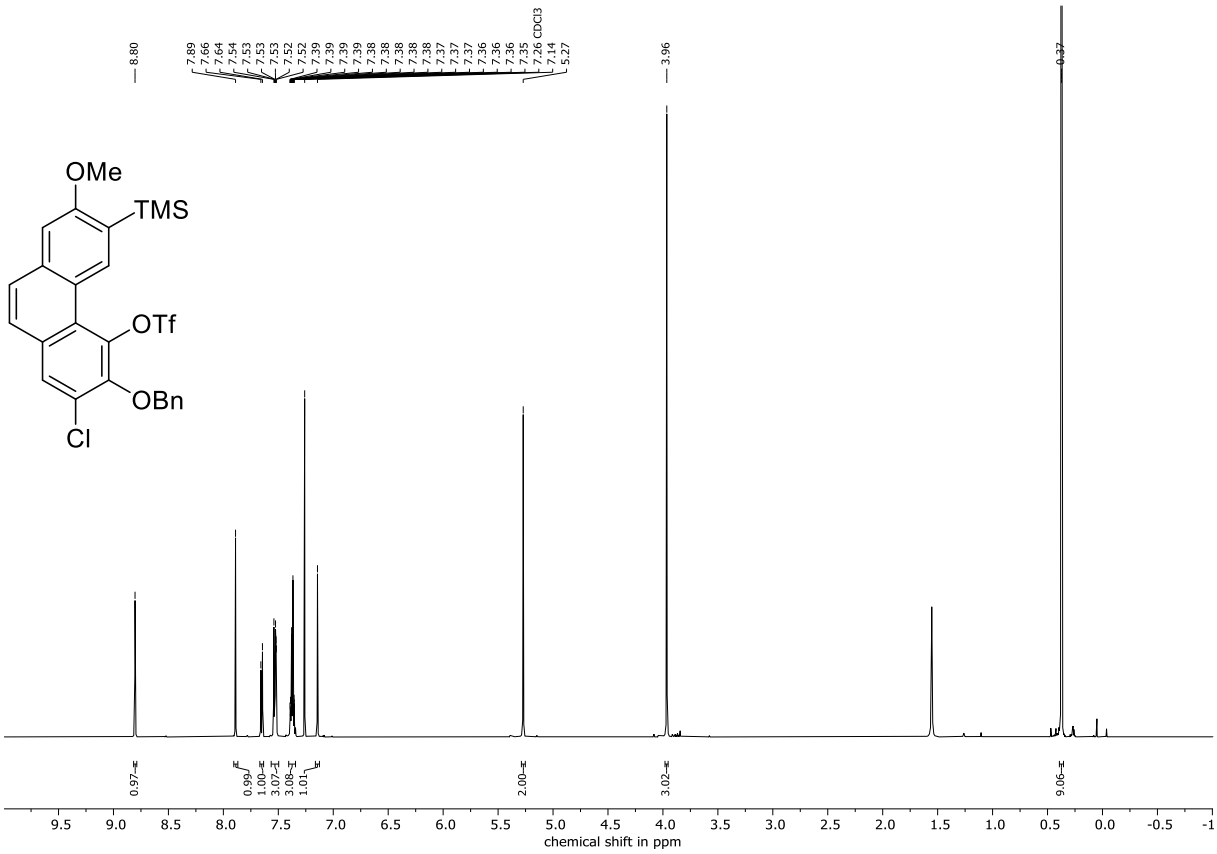
^{13}C NMR (101 MHz, $CDCl_3$) of **207**



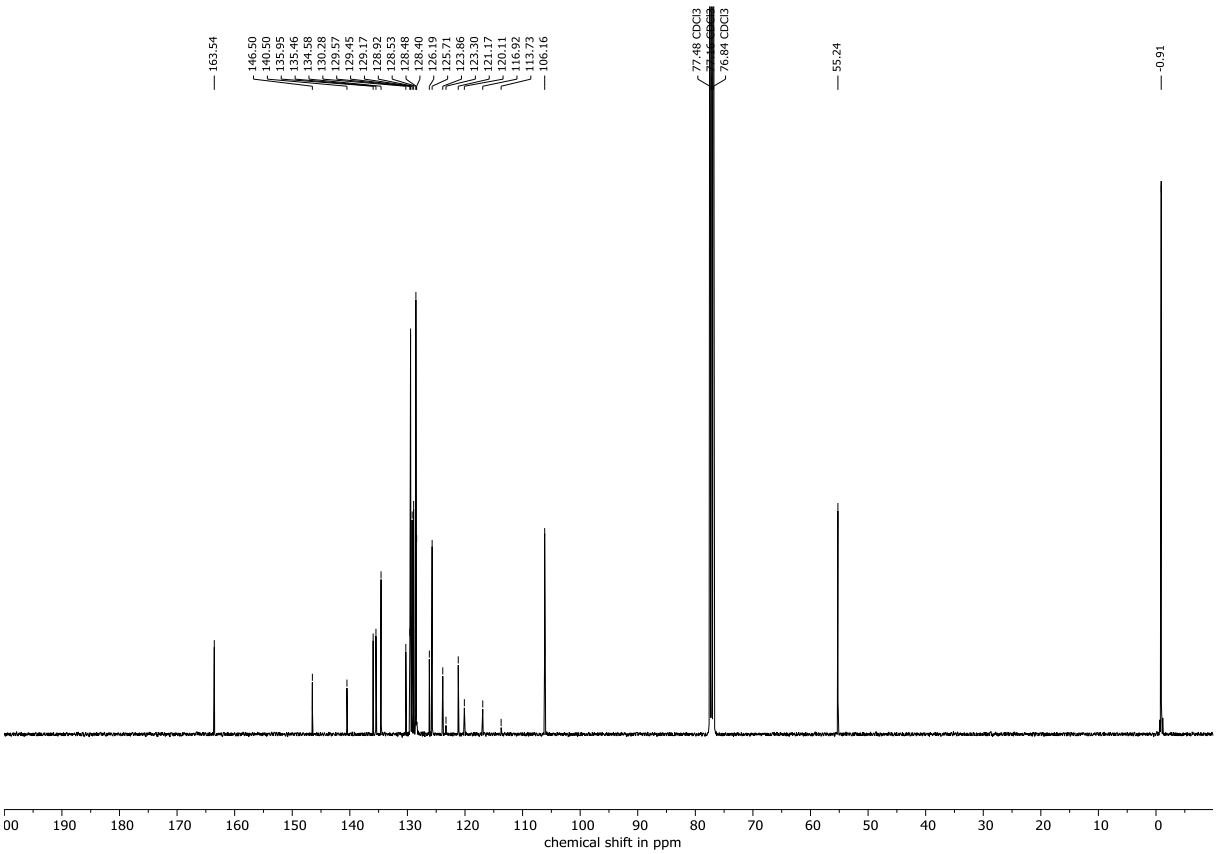
^{19}F NMR (376 MHz, $CDCl_3$) of **207**



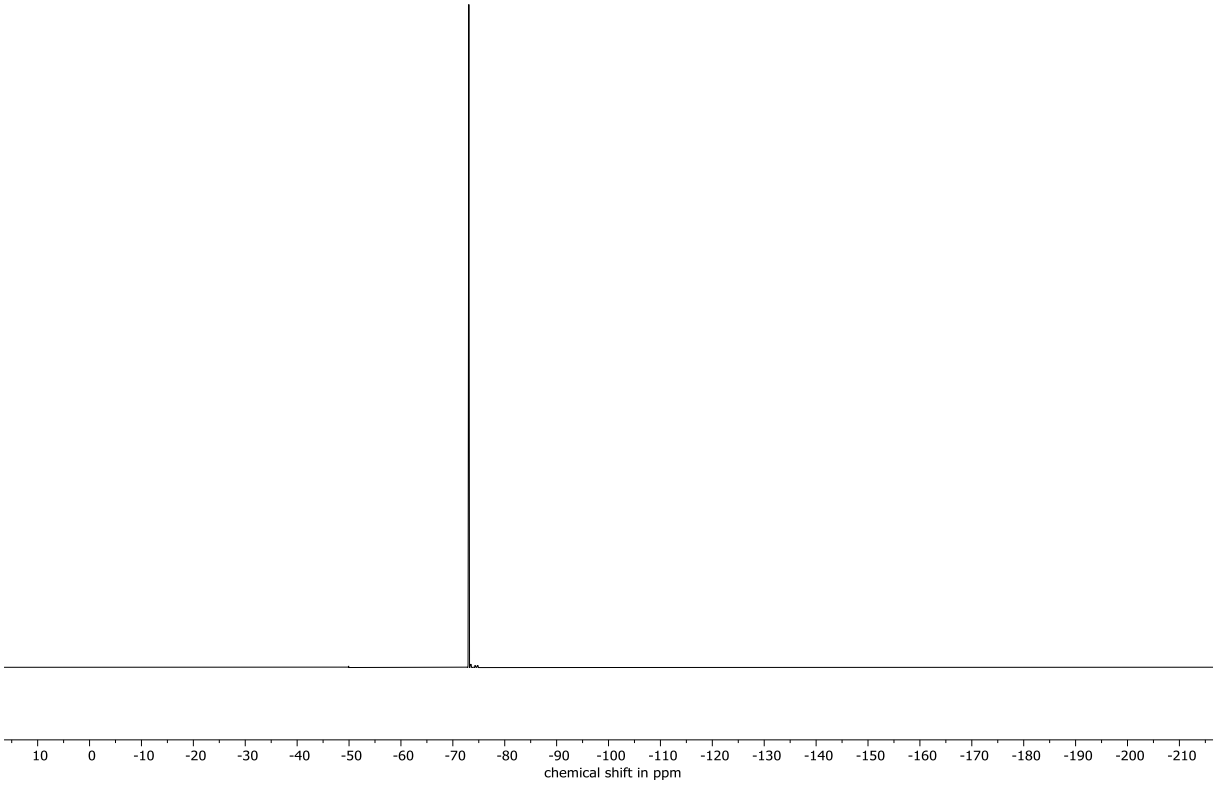
^{1}H NMR (600 MHz, $CDCl_3$) of **208**



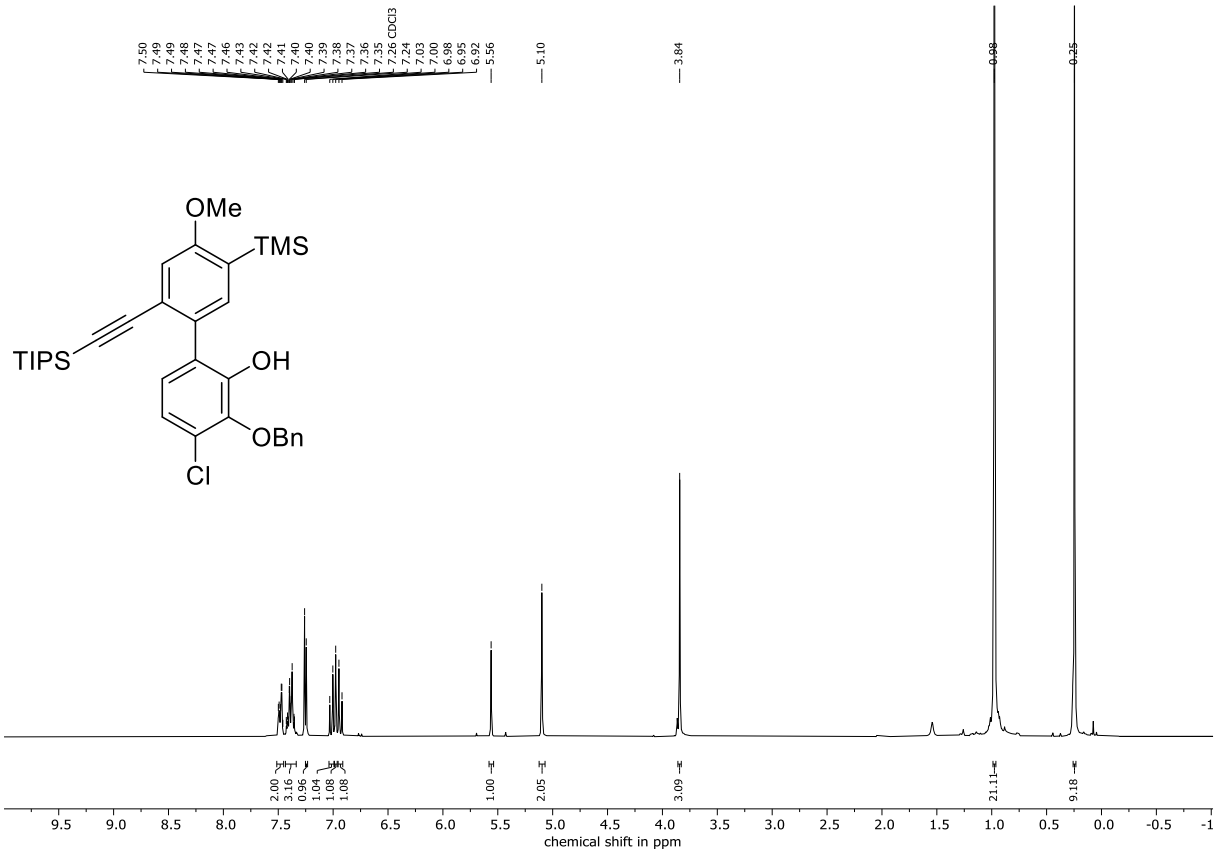
^{13}C NMR (151 MHz, $CDCl_3$) of **208**



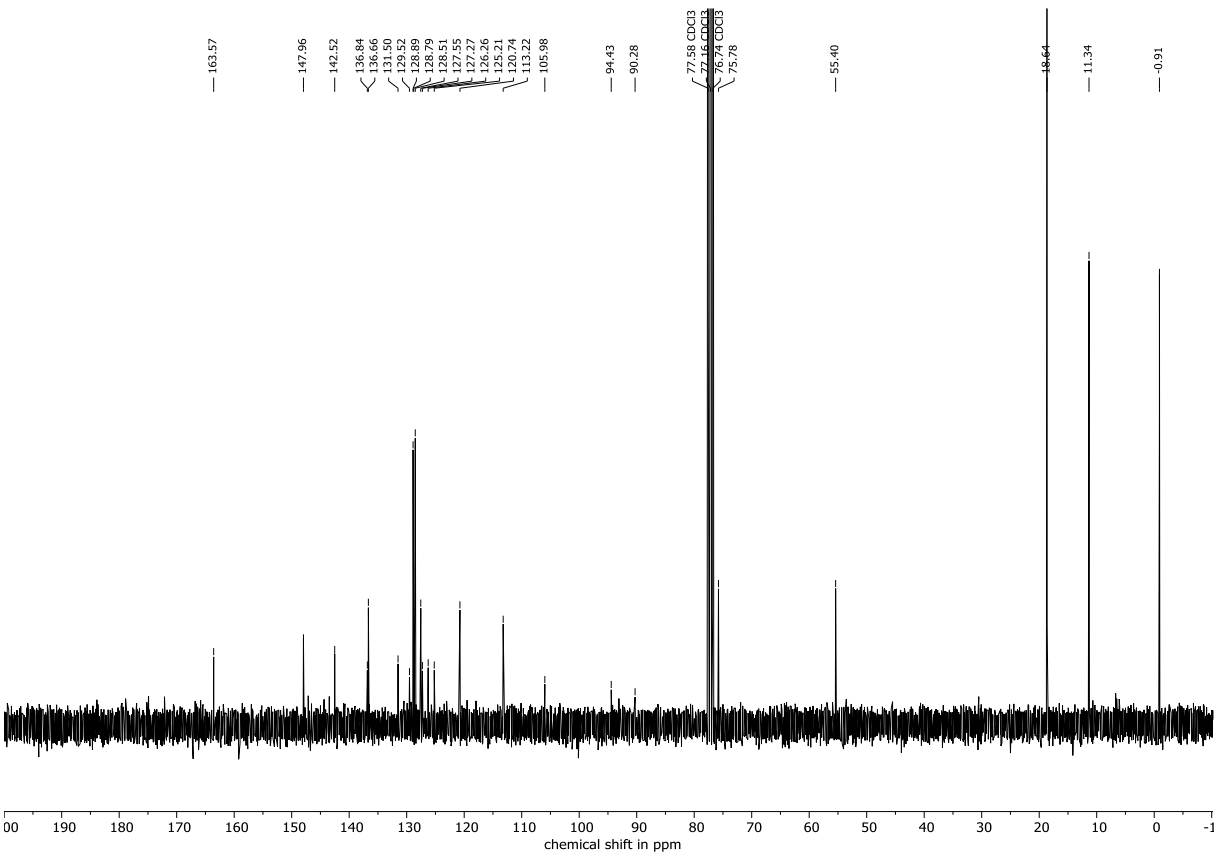
^{19}F NMR (565 MHz, $CDCl_3$) of **208**



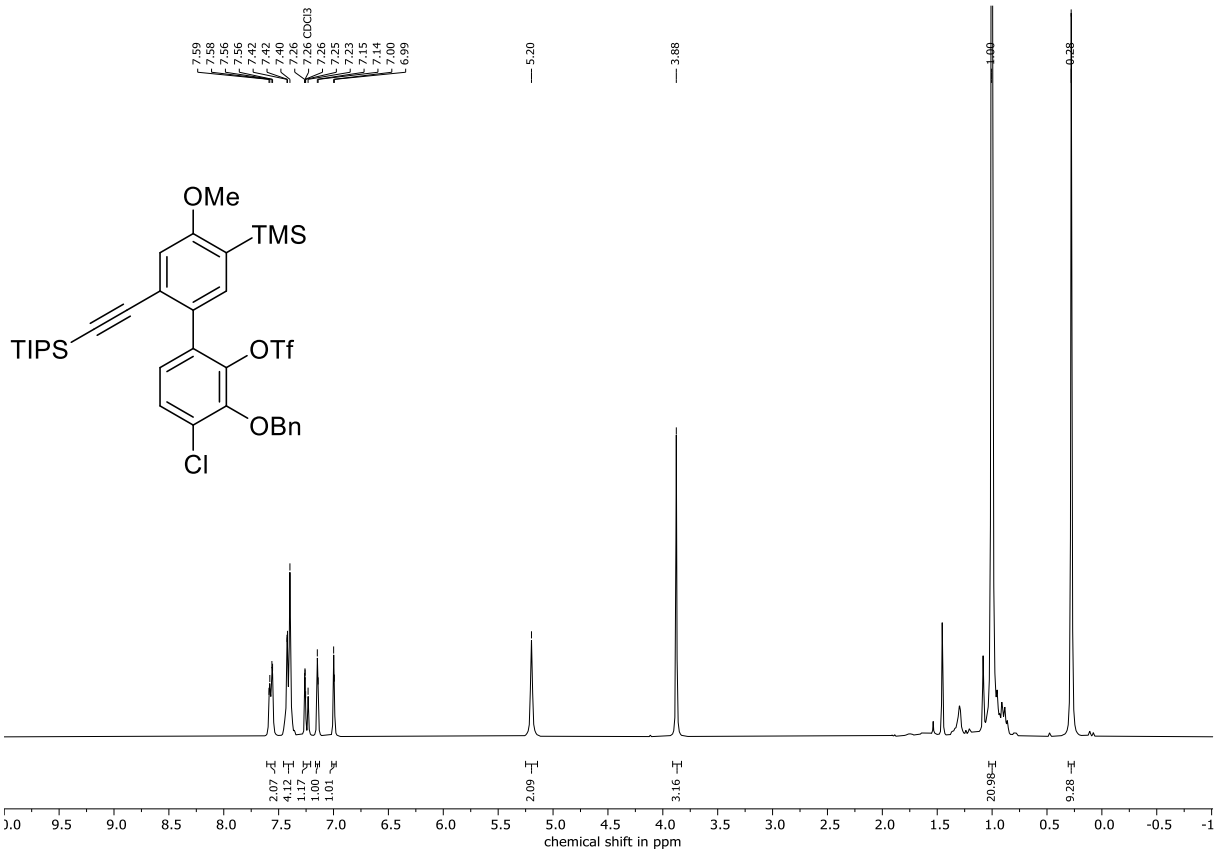
^{1}H NMR (300 MHz, $CDCl_3$) of **212**



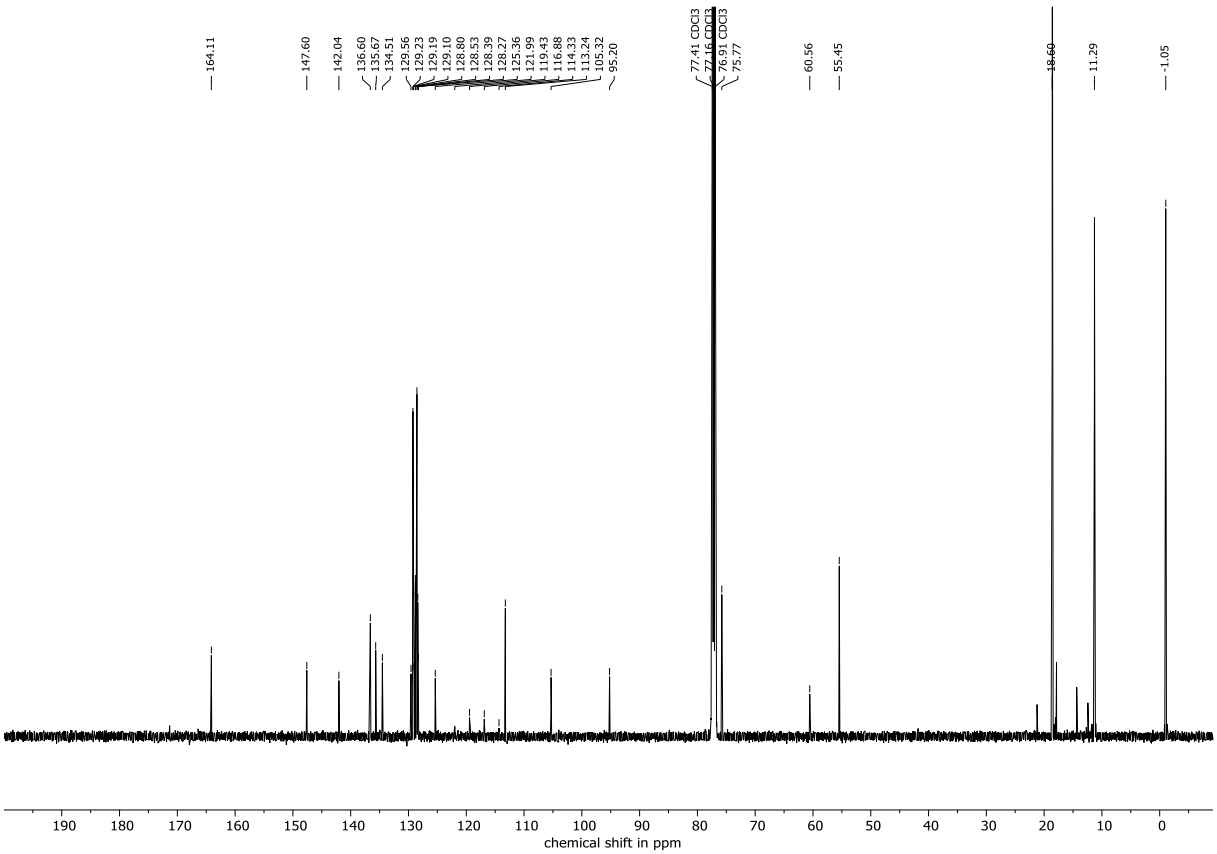
^{13}C NMR (75 MHz, $CDCl_3$) of **212**



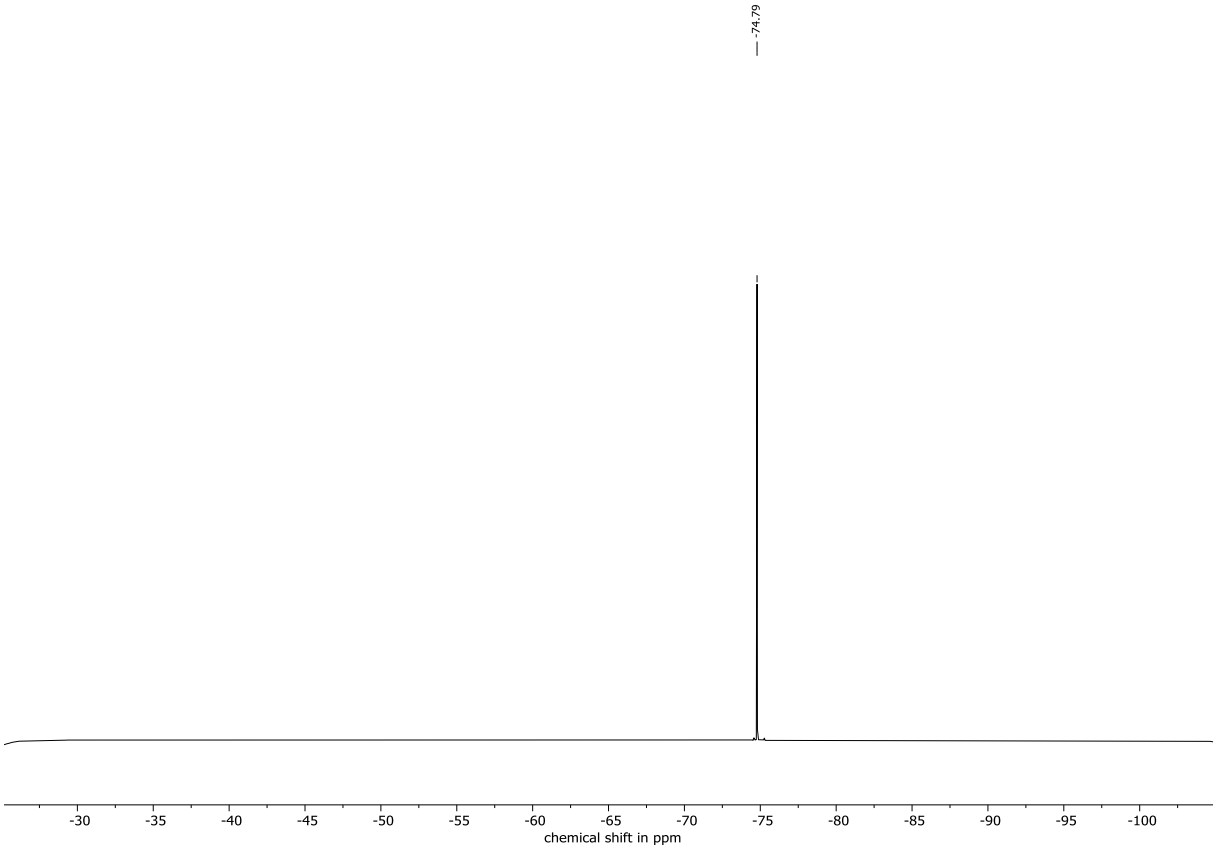
^{1}H NMR (300 MHz, $CDCl_3$) of **213**



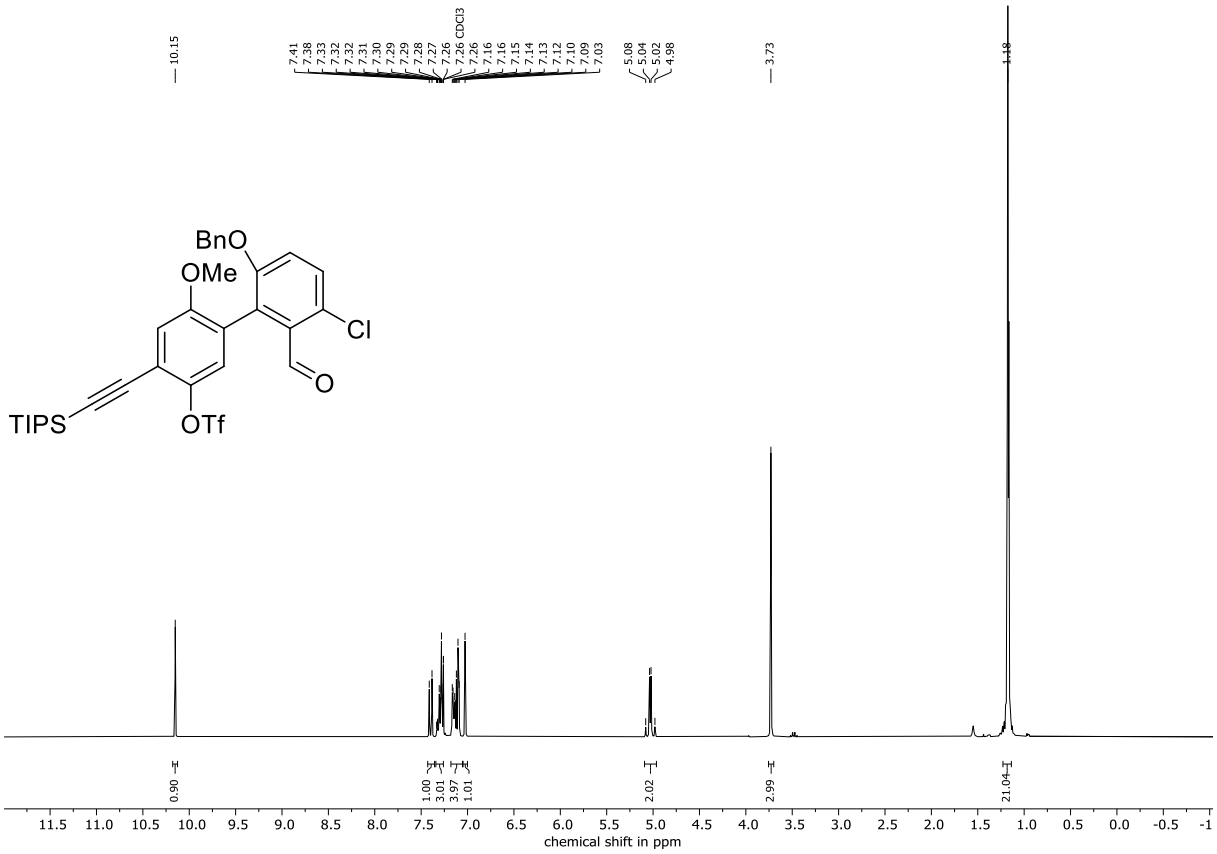
^{13}C NMR (101 MHz, $CDCl_3$) of **213**



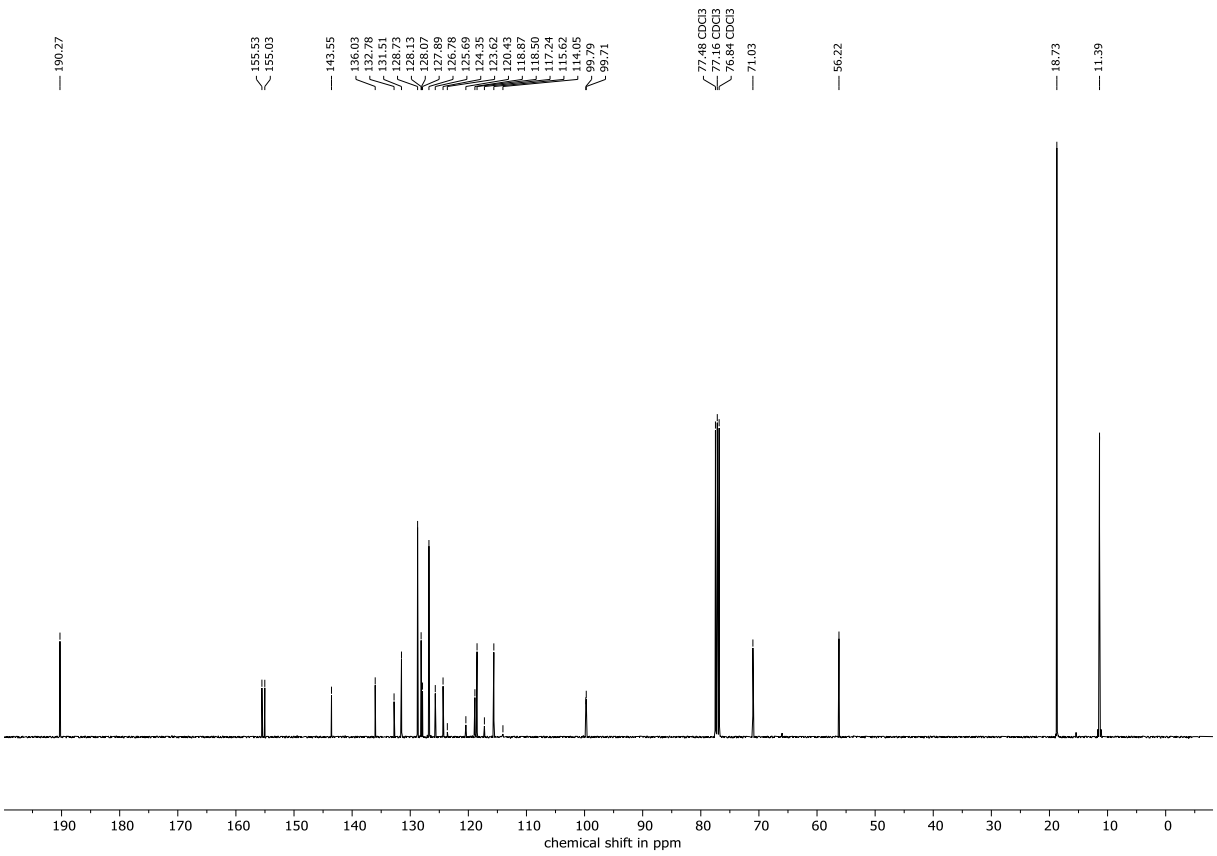
^{19}F NMR (471 MHz, $CDCl_3$) of **213**



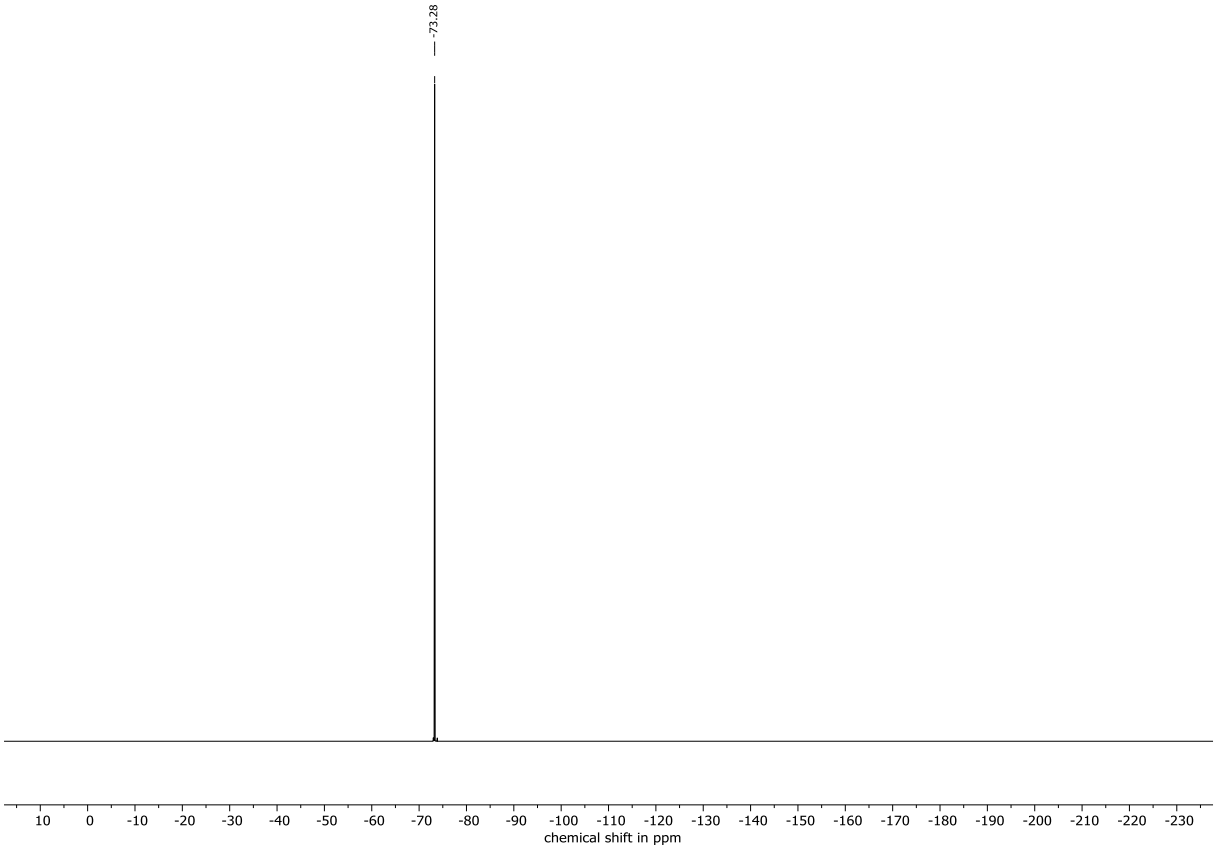
^{1}H NMR (300 MHz, $CDCl_3$) of **216**



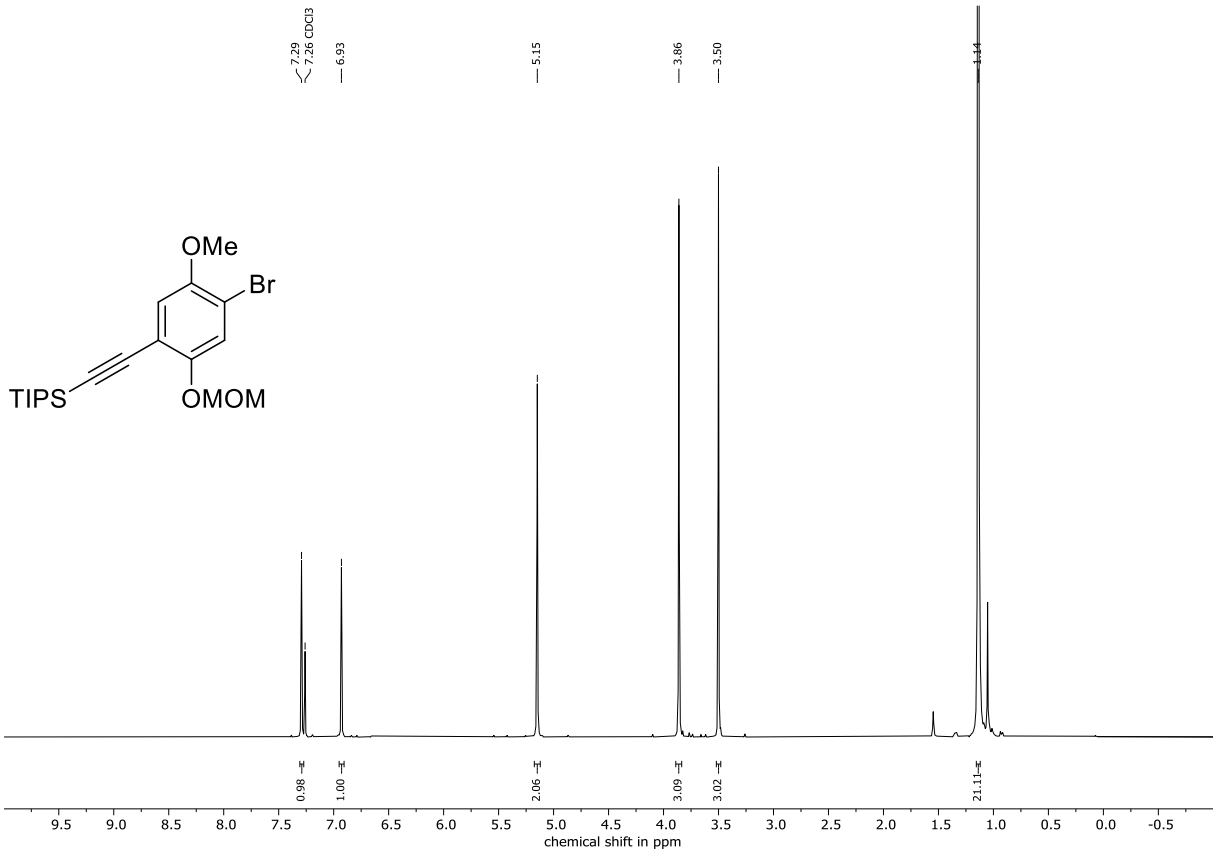
^{13}C NMR (101 MHz, $CDCl_3$) of **216**



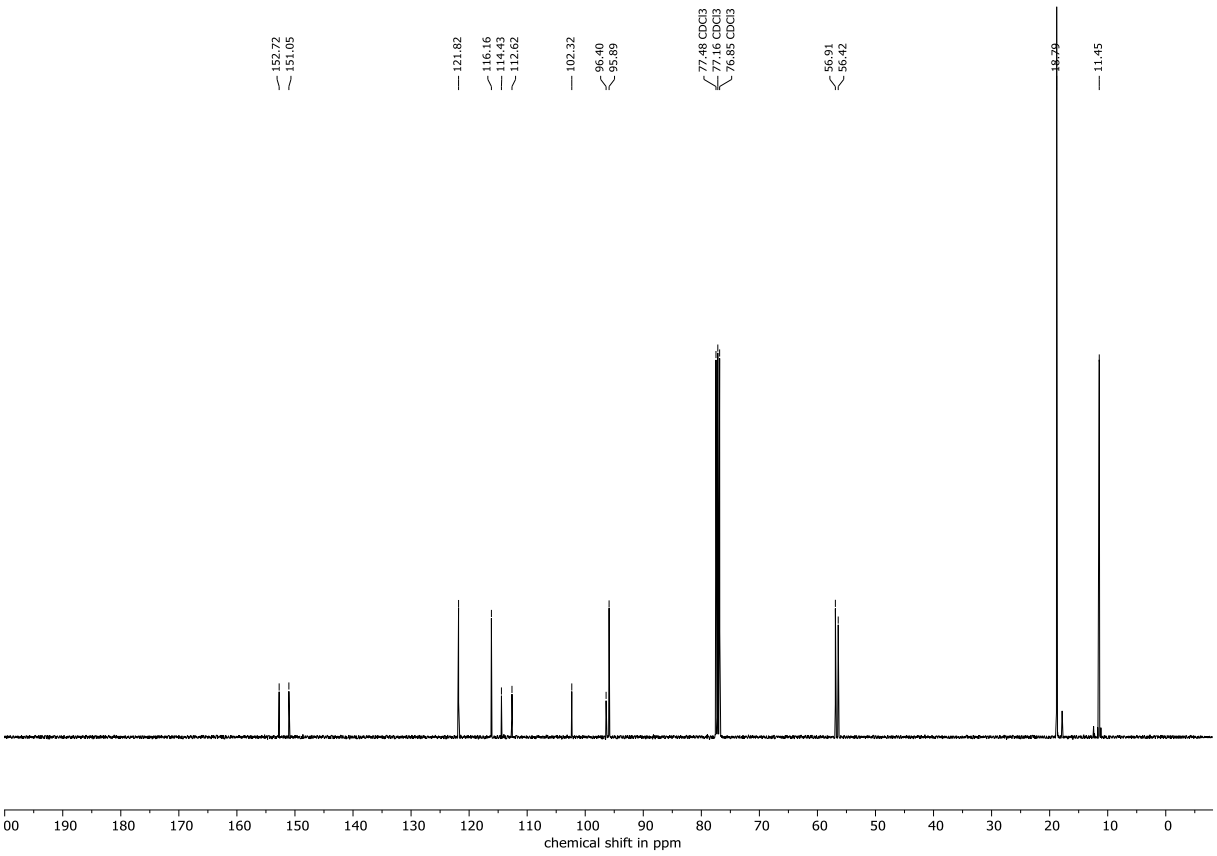
^{19}F NMR (377 MHz, $CDCl_3$) of **216**



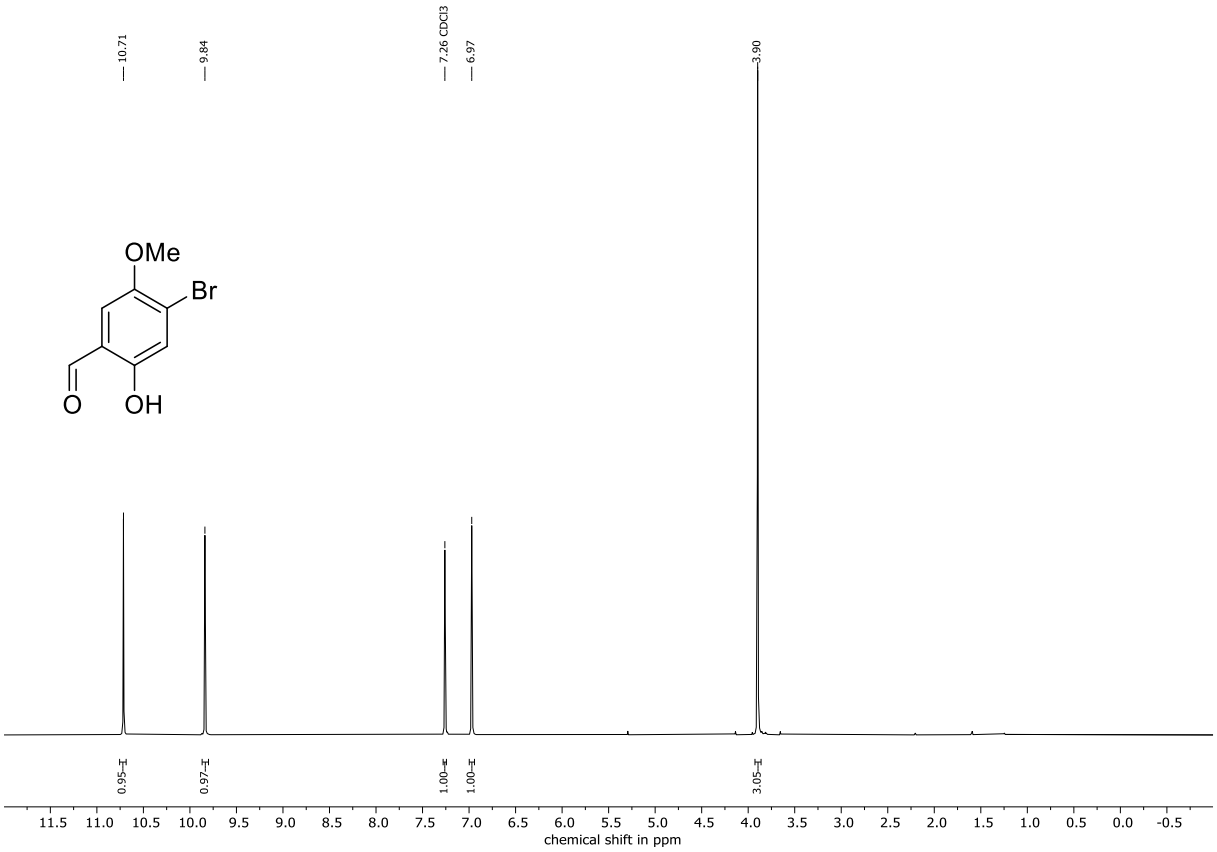
^{1}H NMR (300 MHz, $CDCl_3$) of **217**



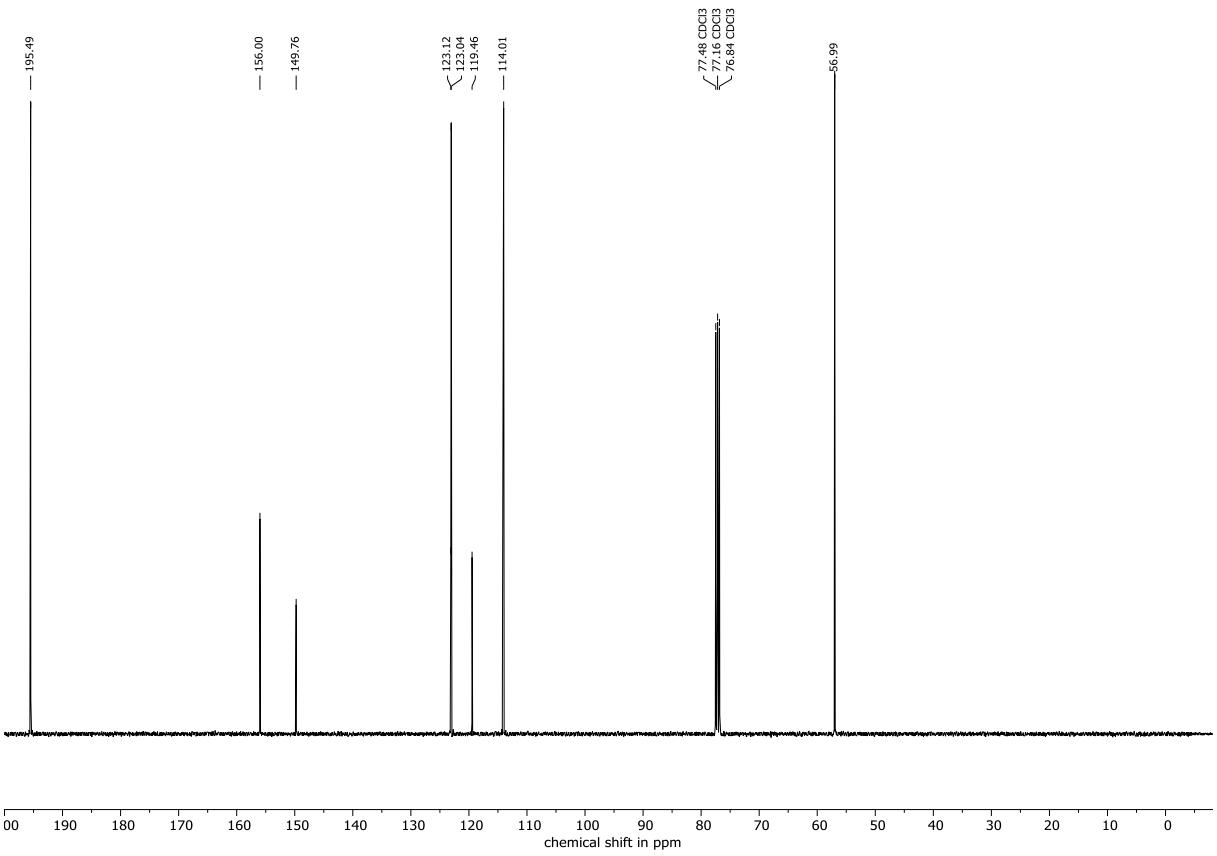
^{13}C NMR (101 MHz, $CDCl_3$) of **217**



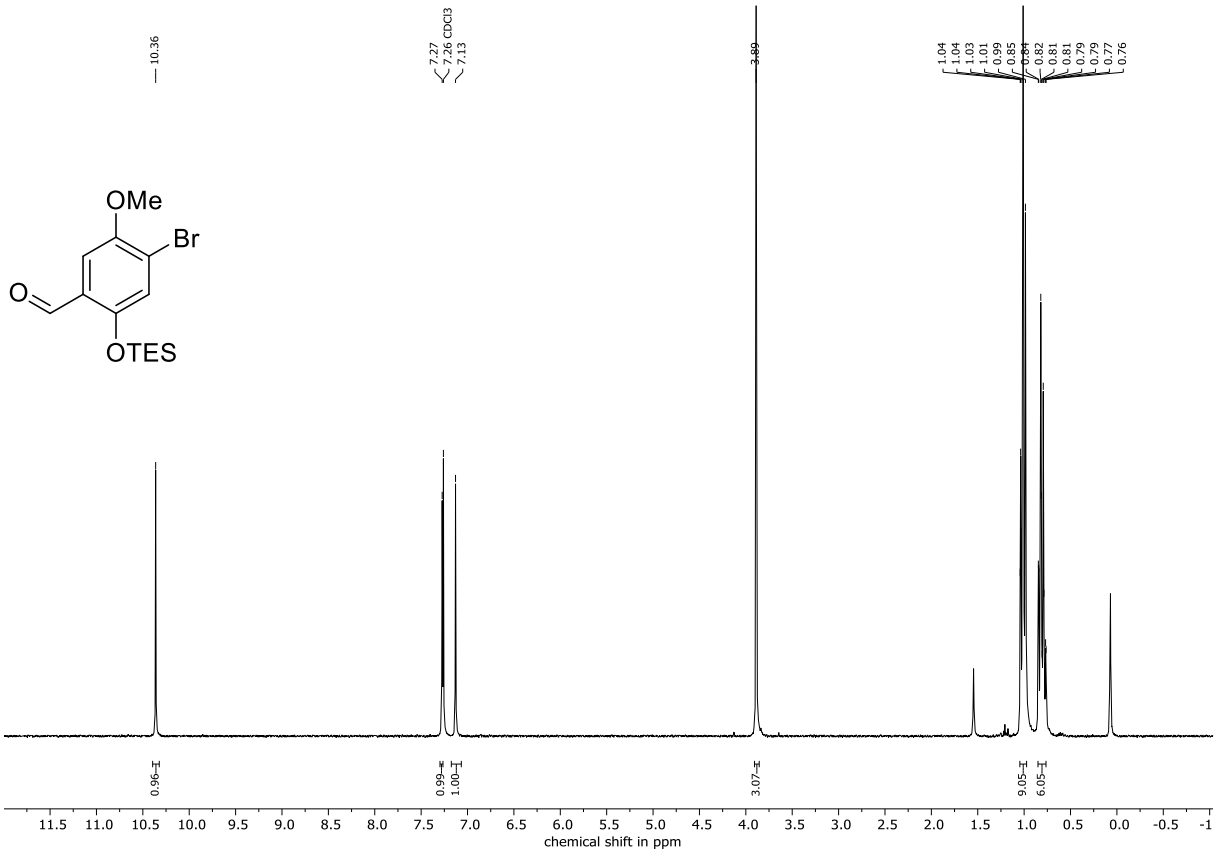
^{1}H NMR (300 MHz, $CDCl_3$) of **220**



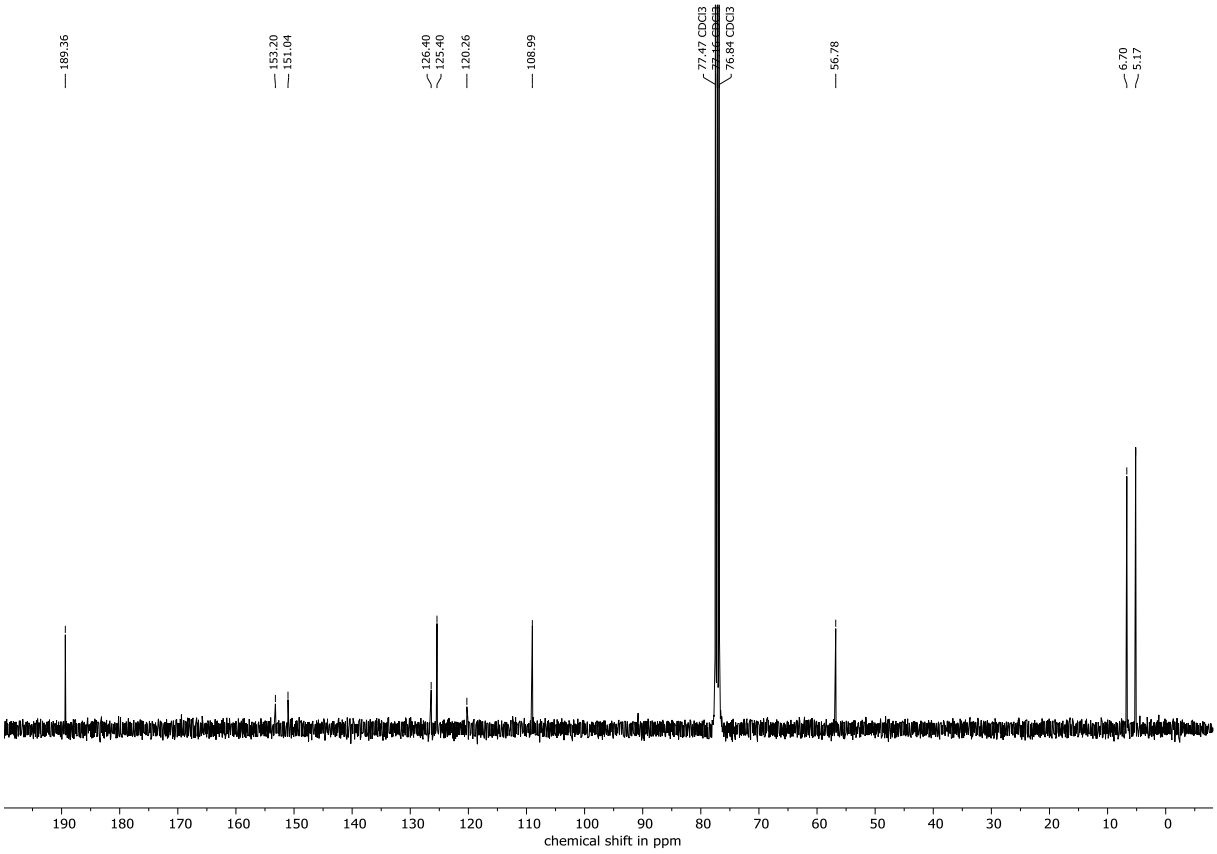
^{13}C NMR (101 MHz, $CDCl_3$) of **220**



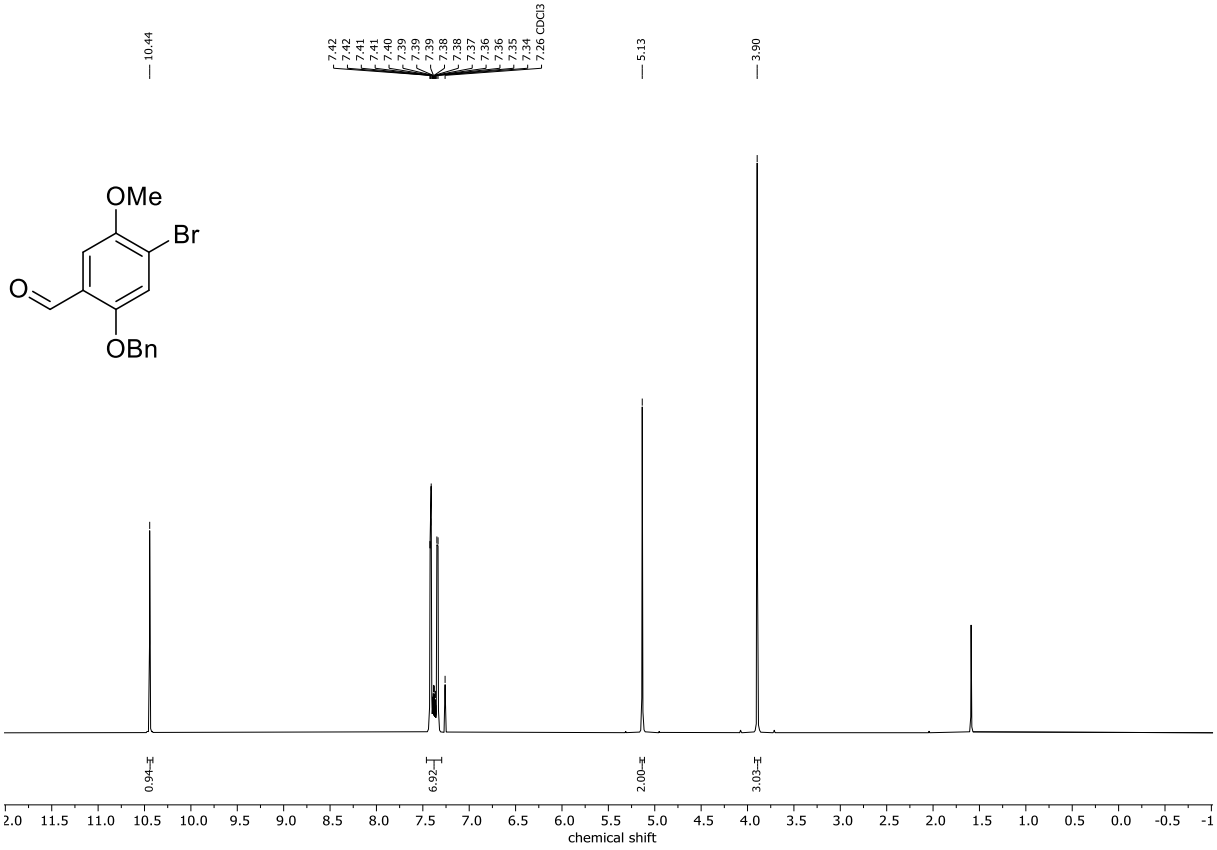
^{1}H NMR (300 MHz, $CDCl_3$) of **221**



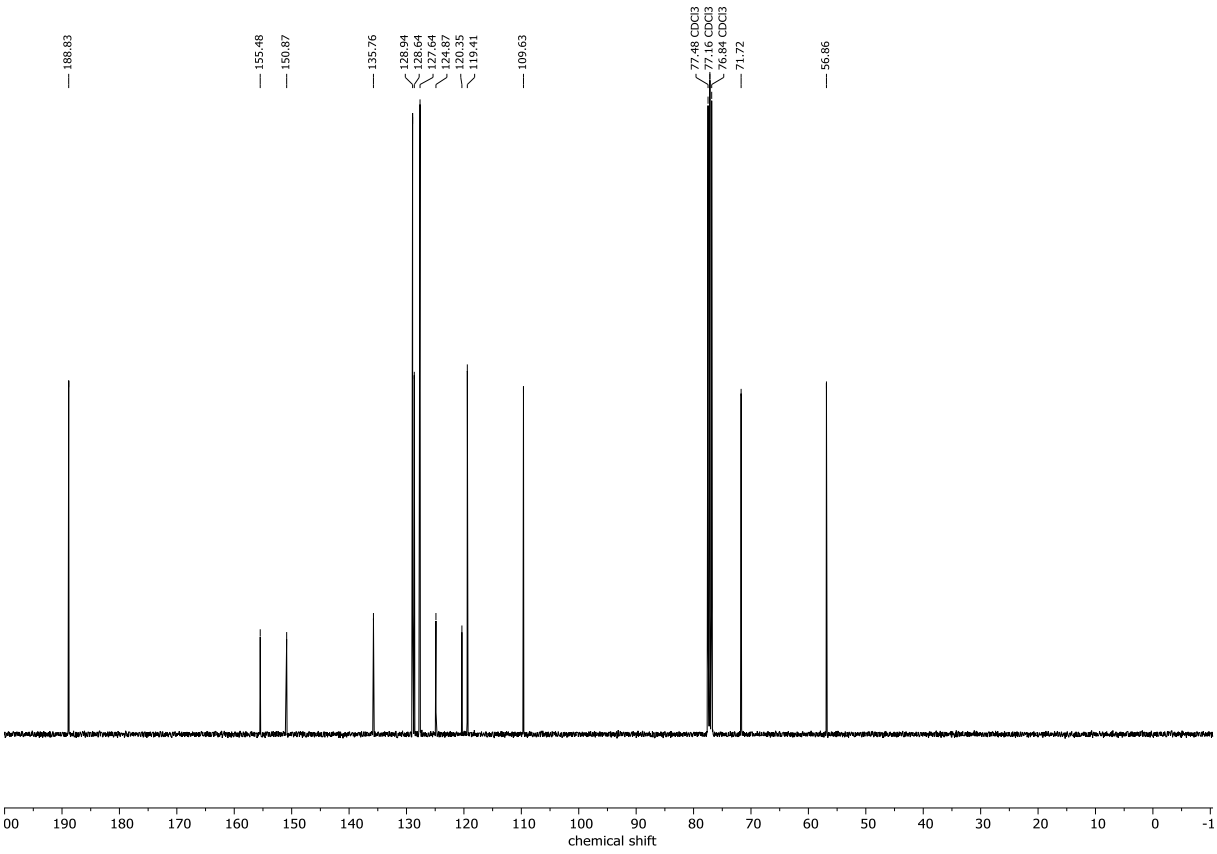
^{13}C NMR (101 MHz, $CDCl_3$) of **221**



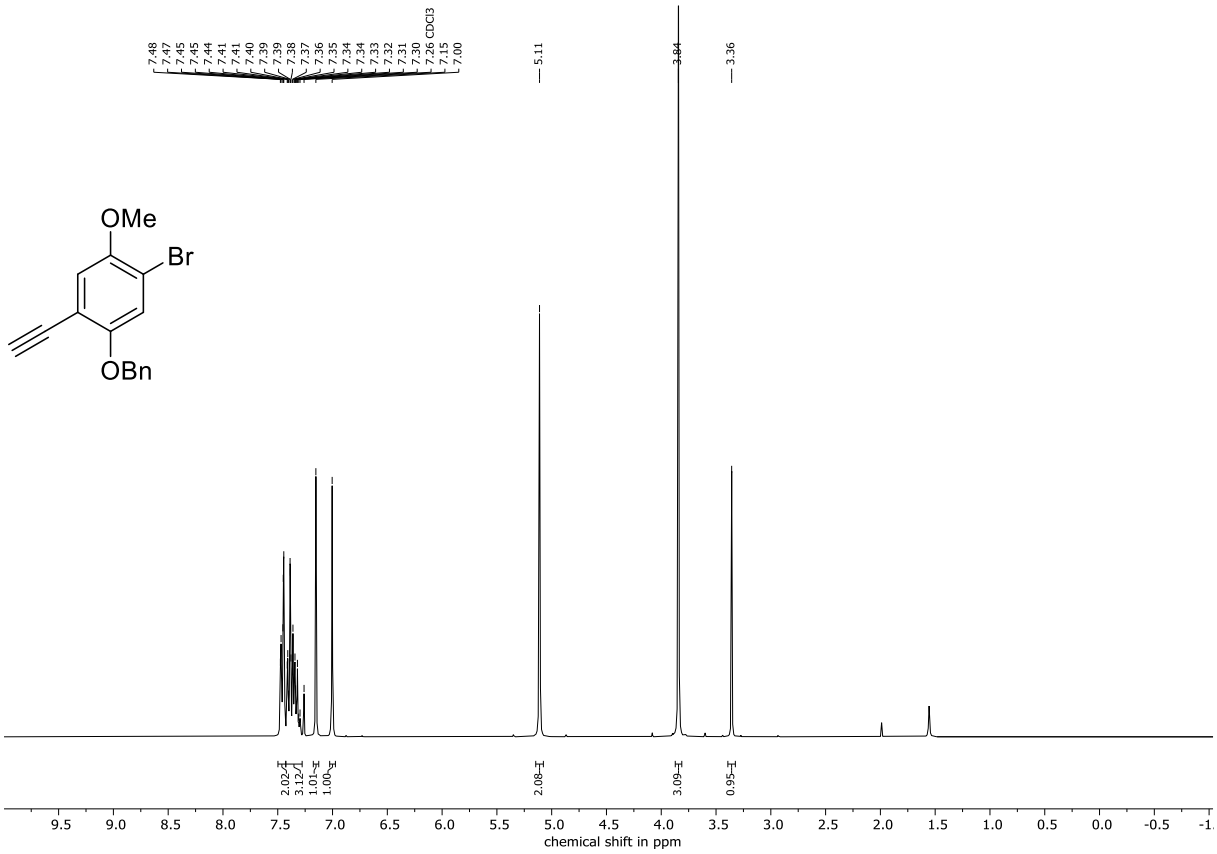
^{1}H NMR (300 MHz, $CDCl_3$) of **224**



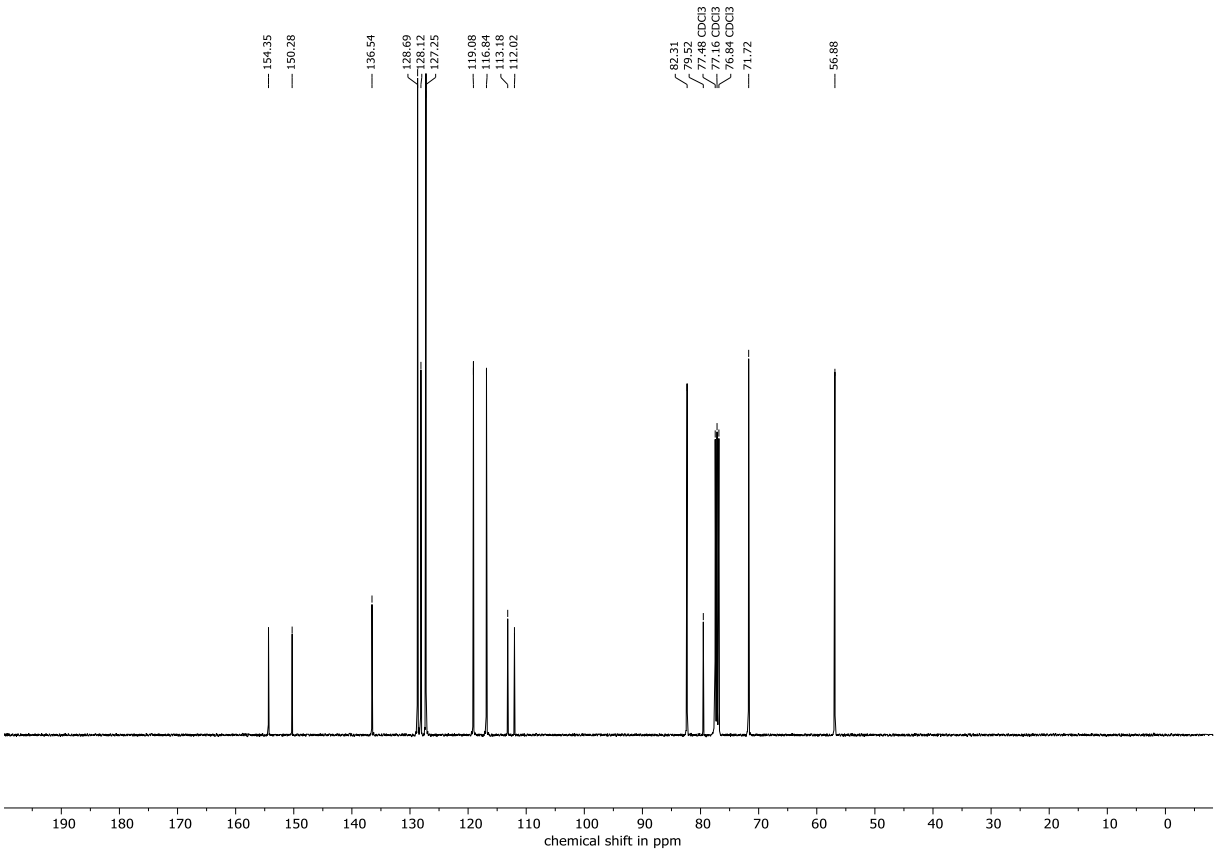
^{13}C NMR (101 MHz, $CDCl_3$) of **224**



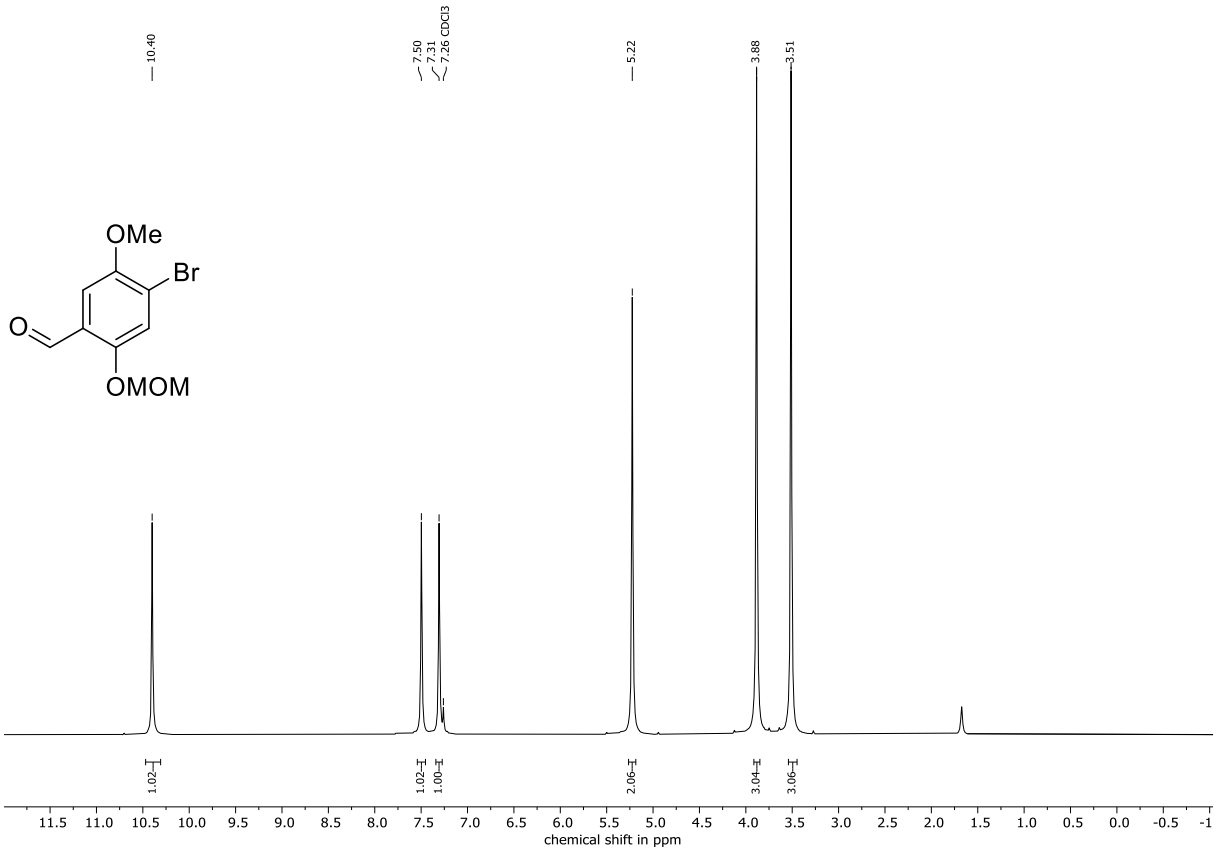
^{1}H NMR (300 MHz, $CDCl_3$) of **225**



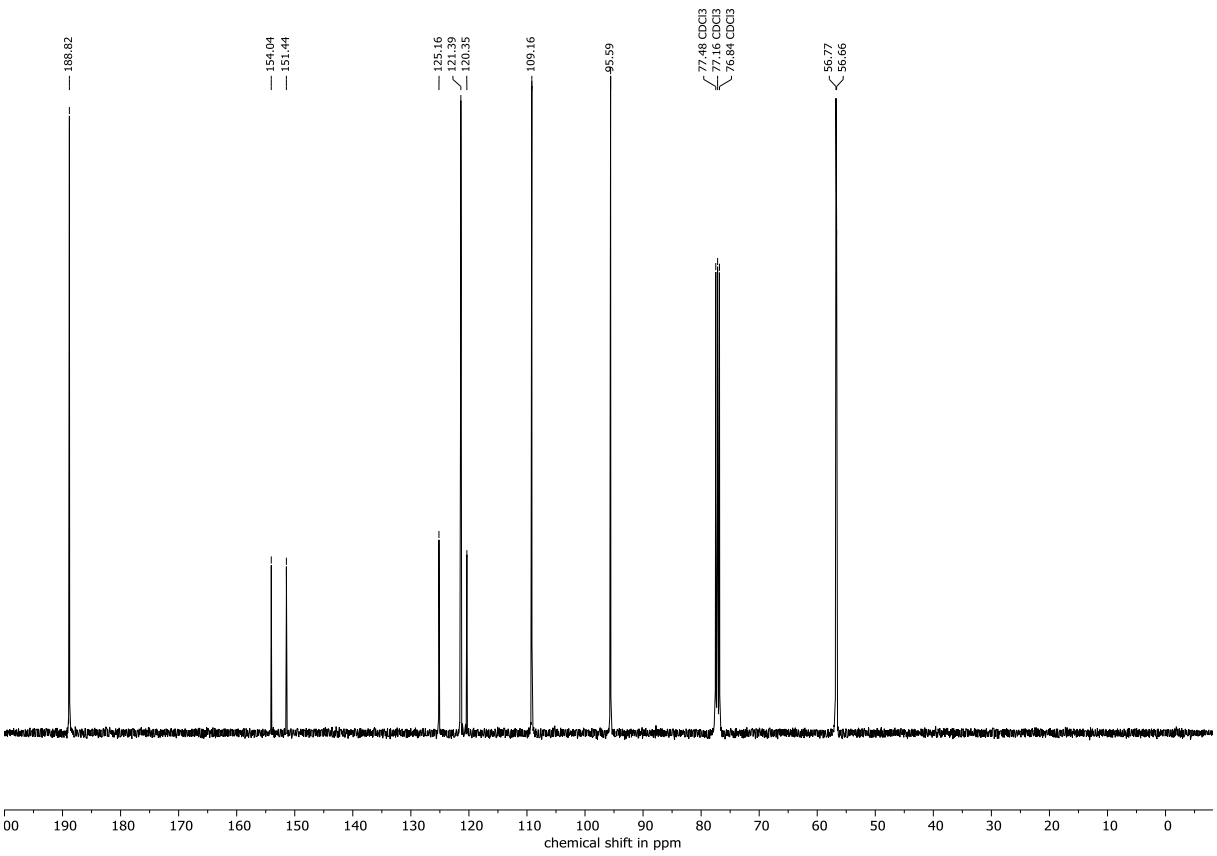
^{13}C NMR (101 MHz, $CDCl_3$) of **225**



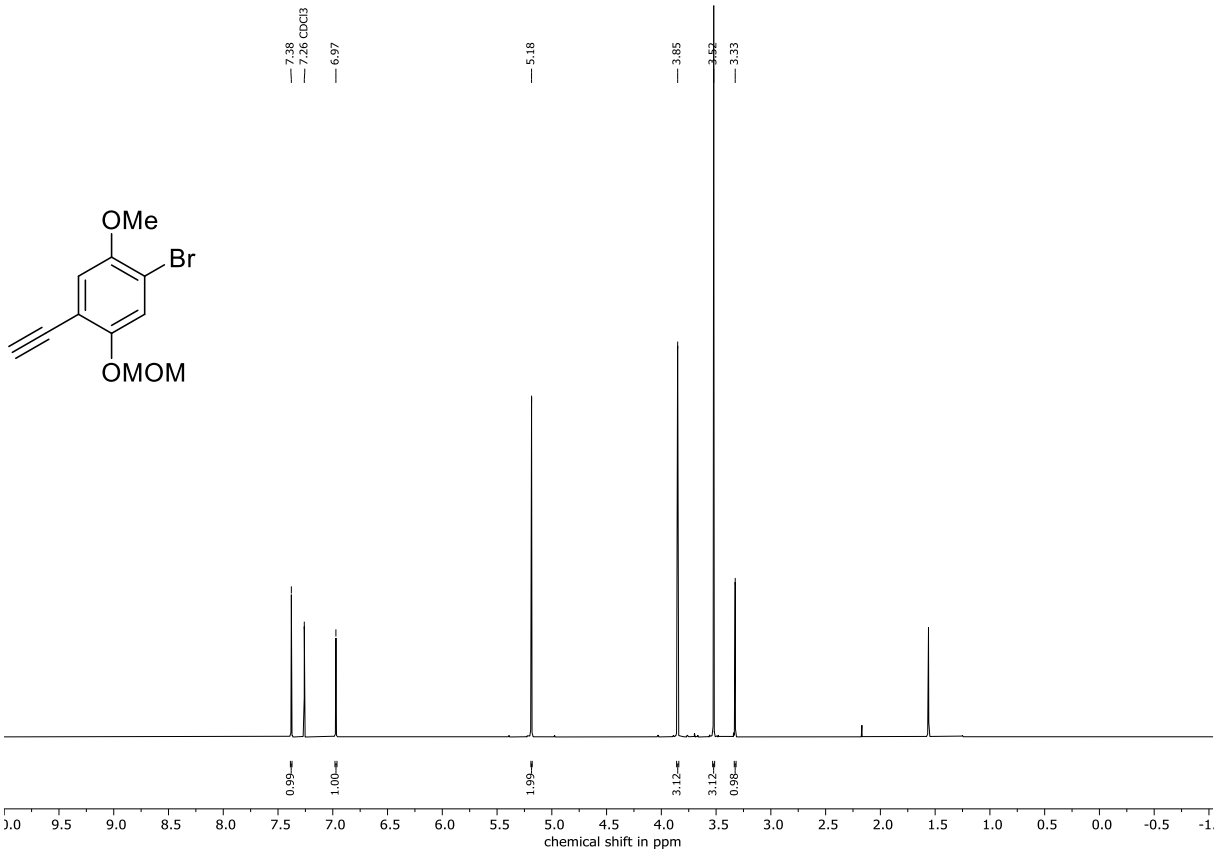
^{1}H NMR (300 MHz, $CDCl_3$) of **226**



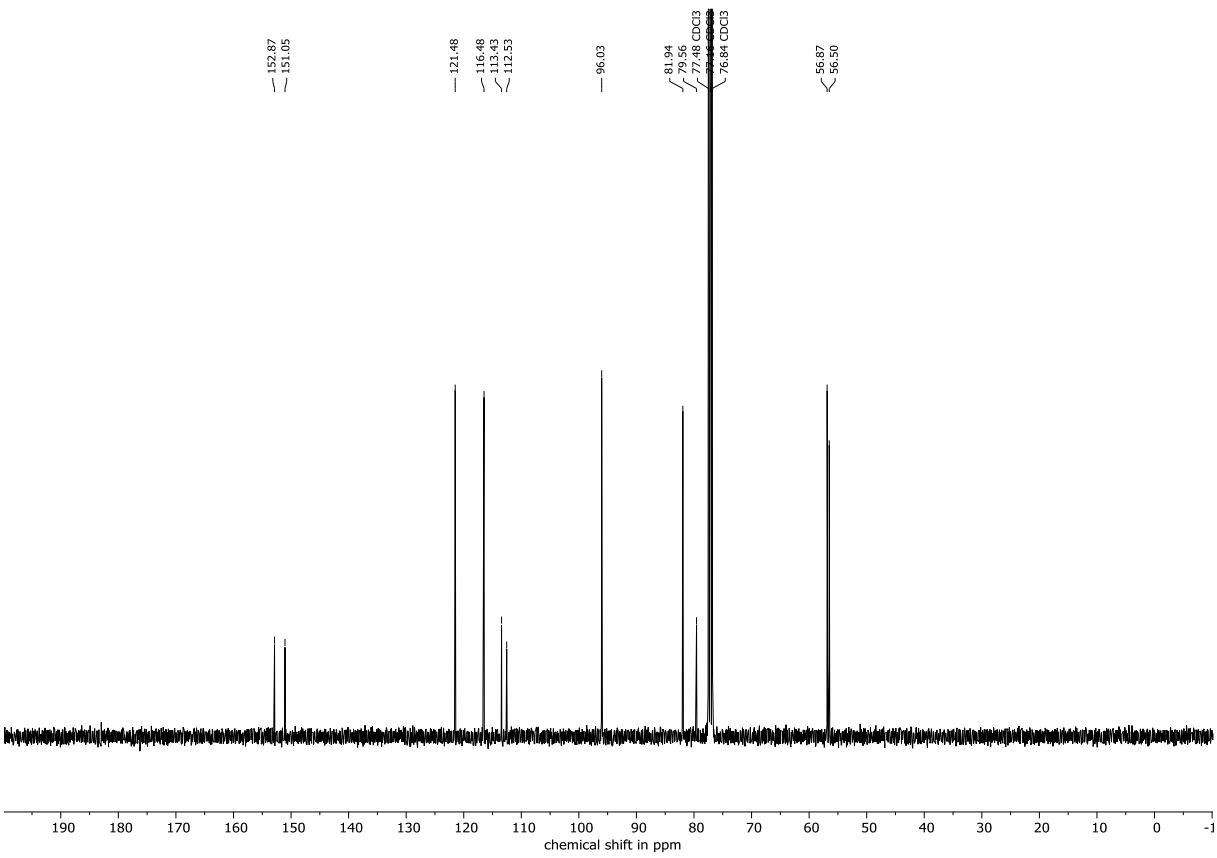
^{13}C NMR (101 MHz, $CDCl_3$) of **226**



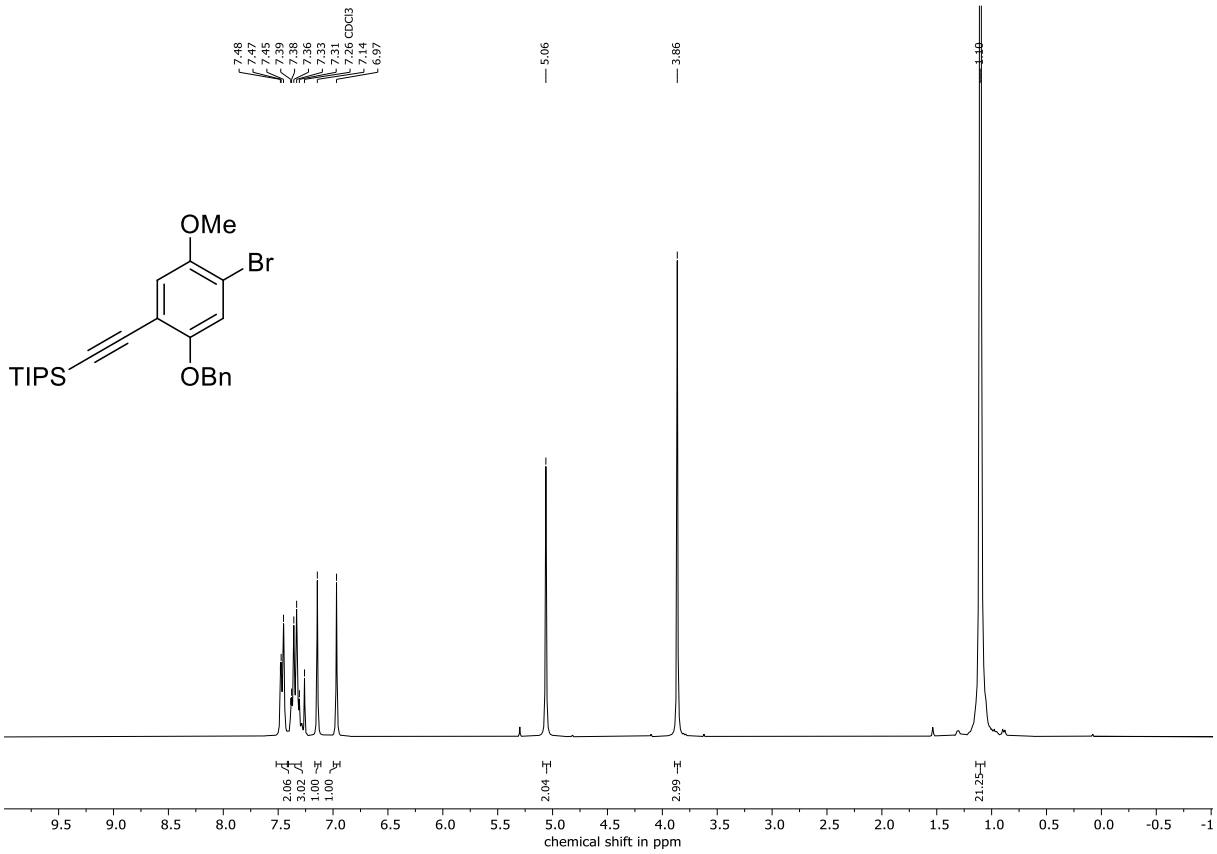
^{1}H NMR (400 MHz, $CDCl_3$) of **227**



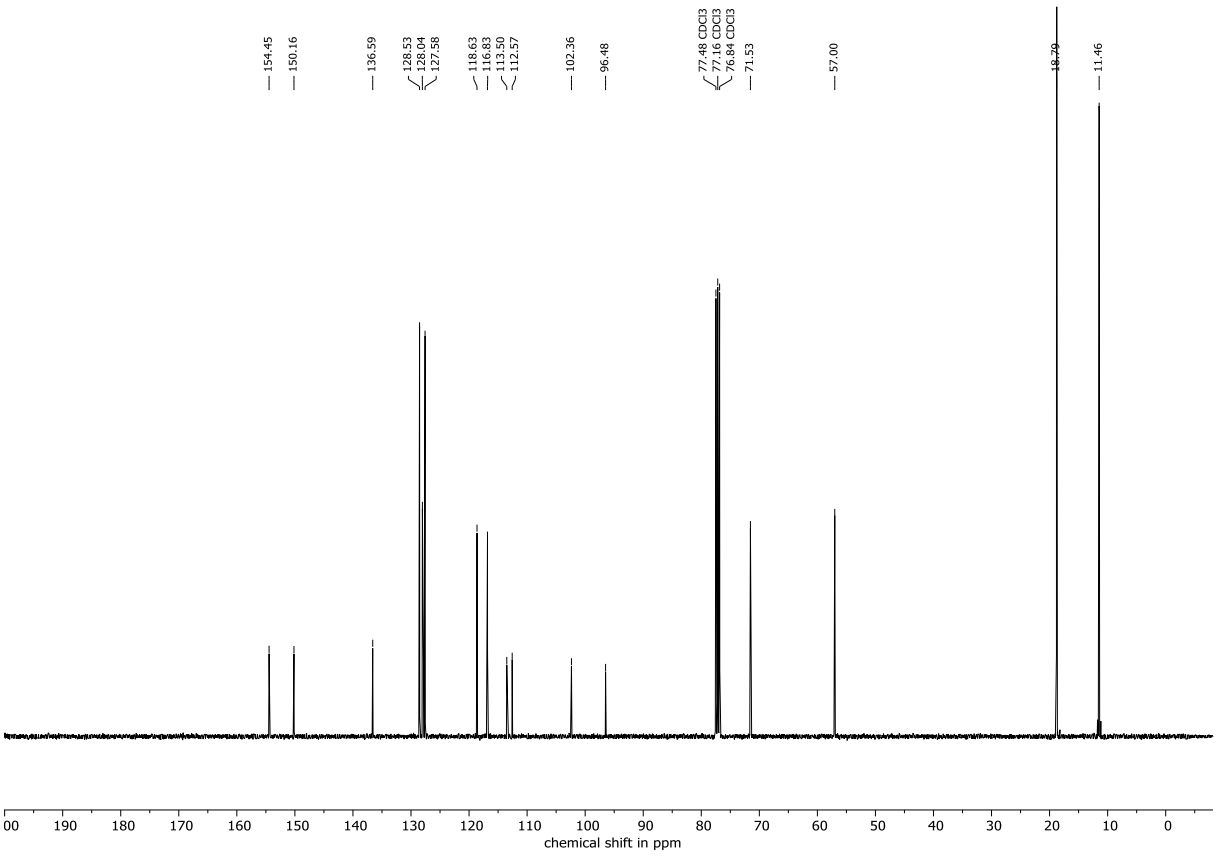
^{13}C NMR (101 MHz, $CDCl_3$) of **227**



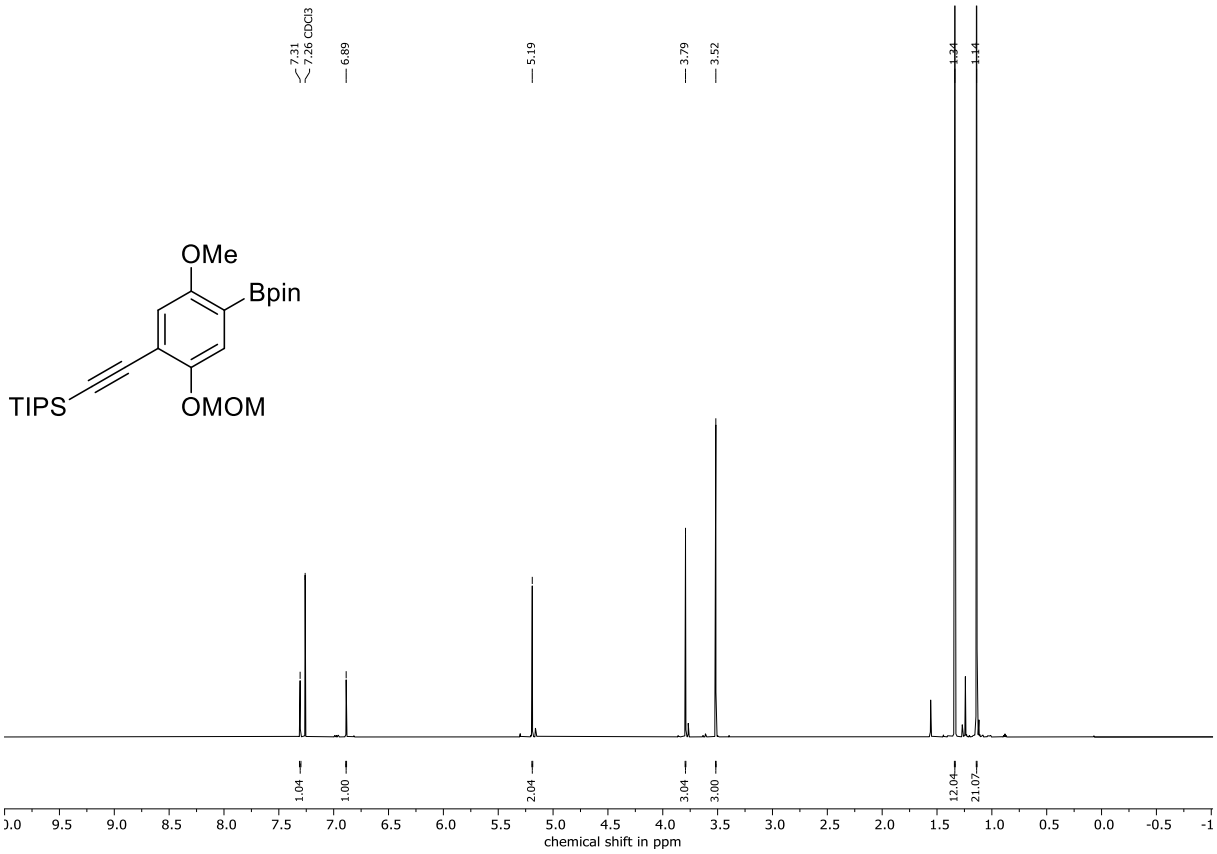
^{1}H NMR (300 MHz, $CDCl_3$) of **228**



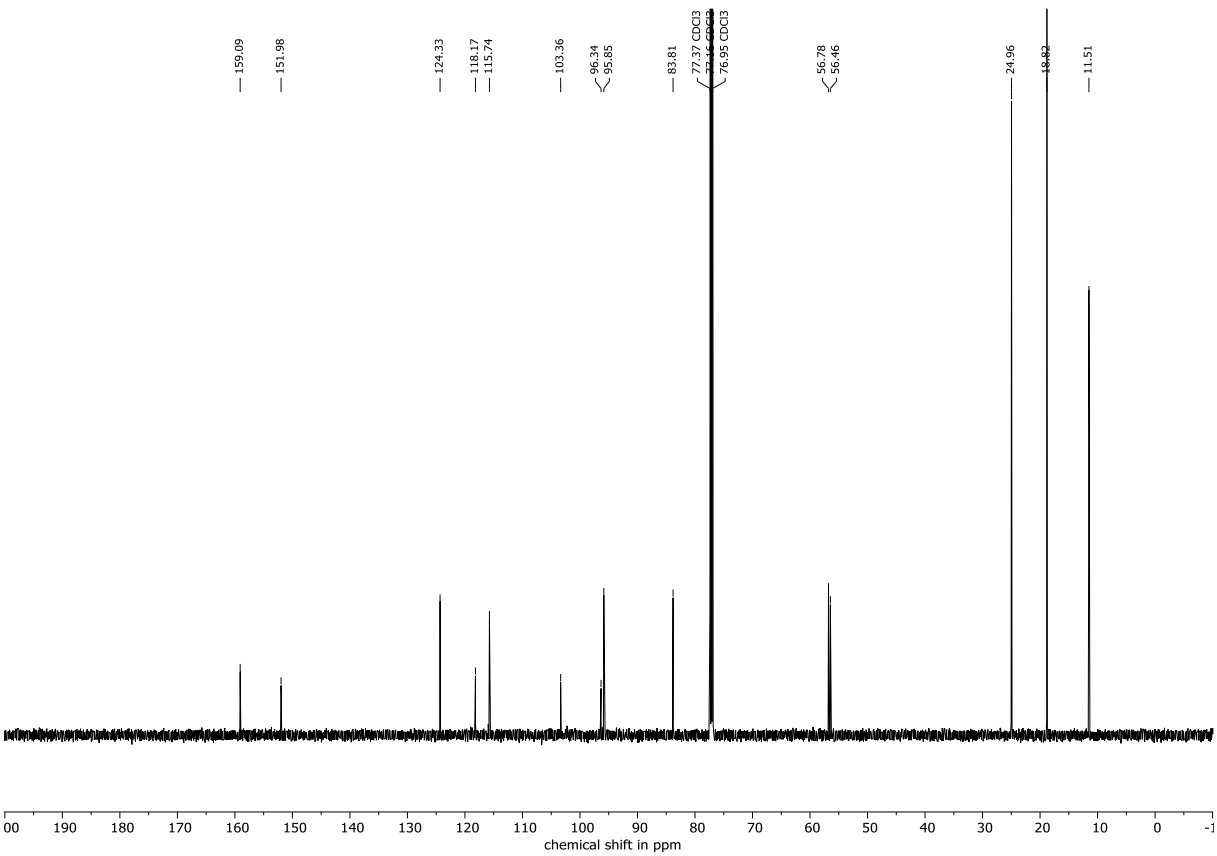
^{13}C NMR (101 MHz, $CDCl_3$) of **228**



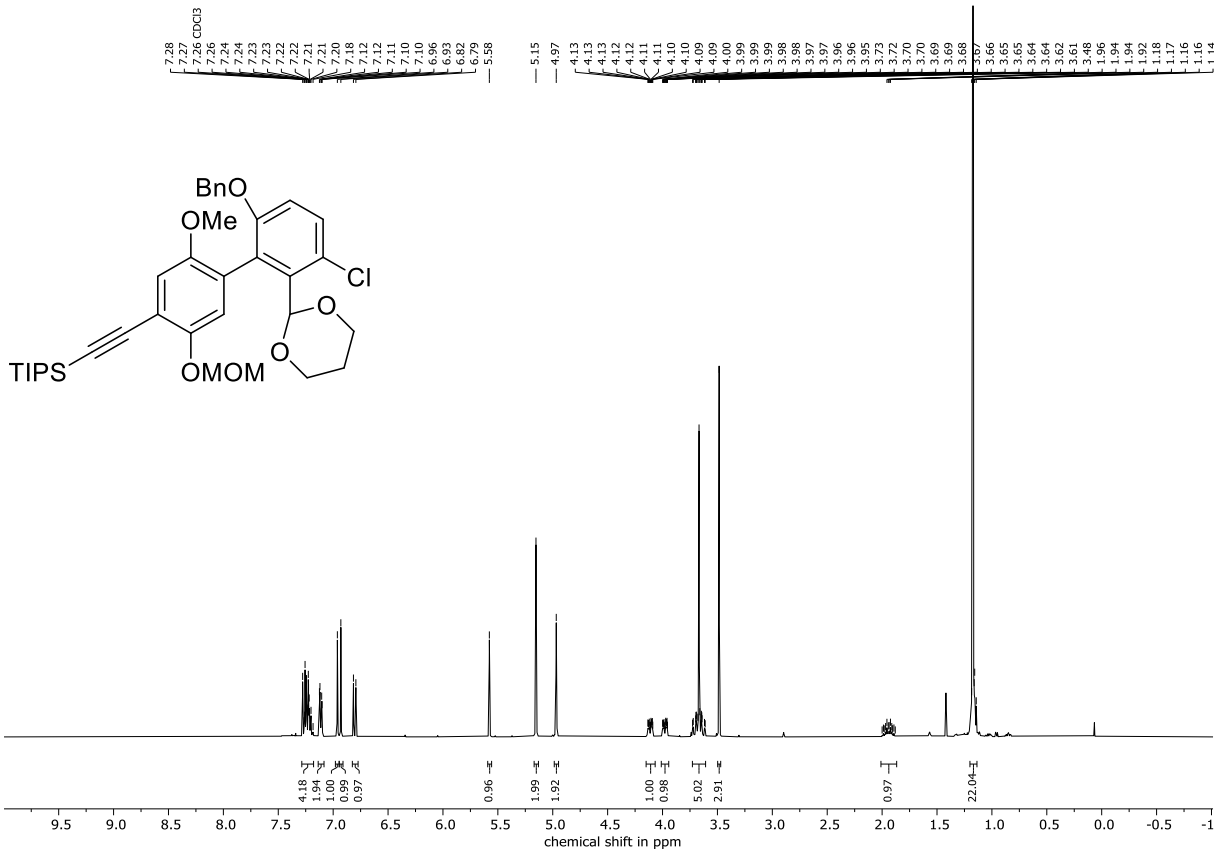
^{1}H NMR (600 MHz, $CDCl_3$) of **230**



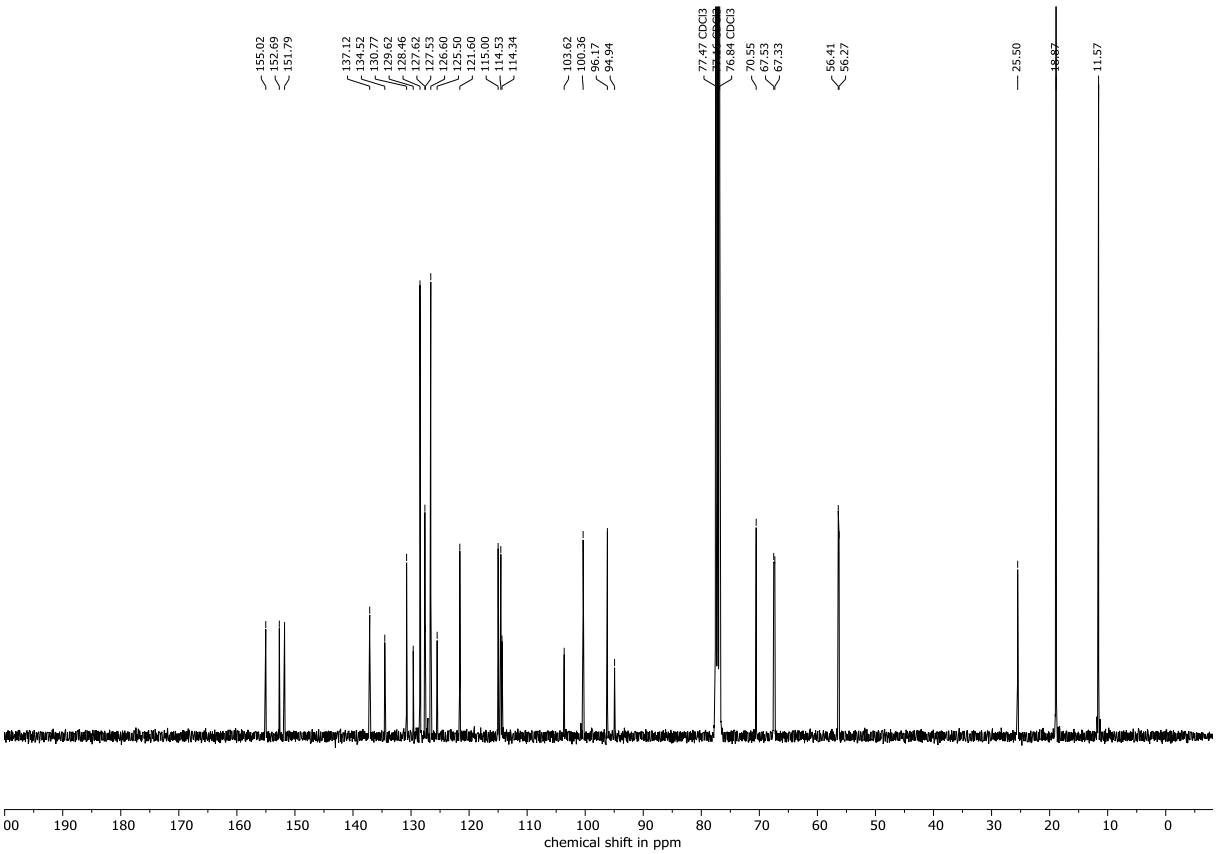
^{13}C NMR (151 MHz, $CDCl_3$) of **230**



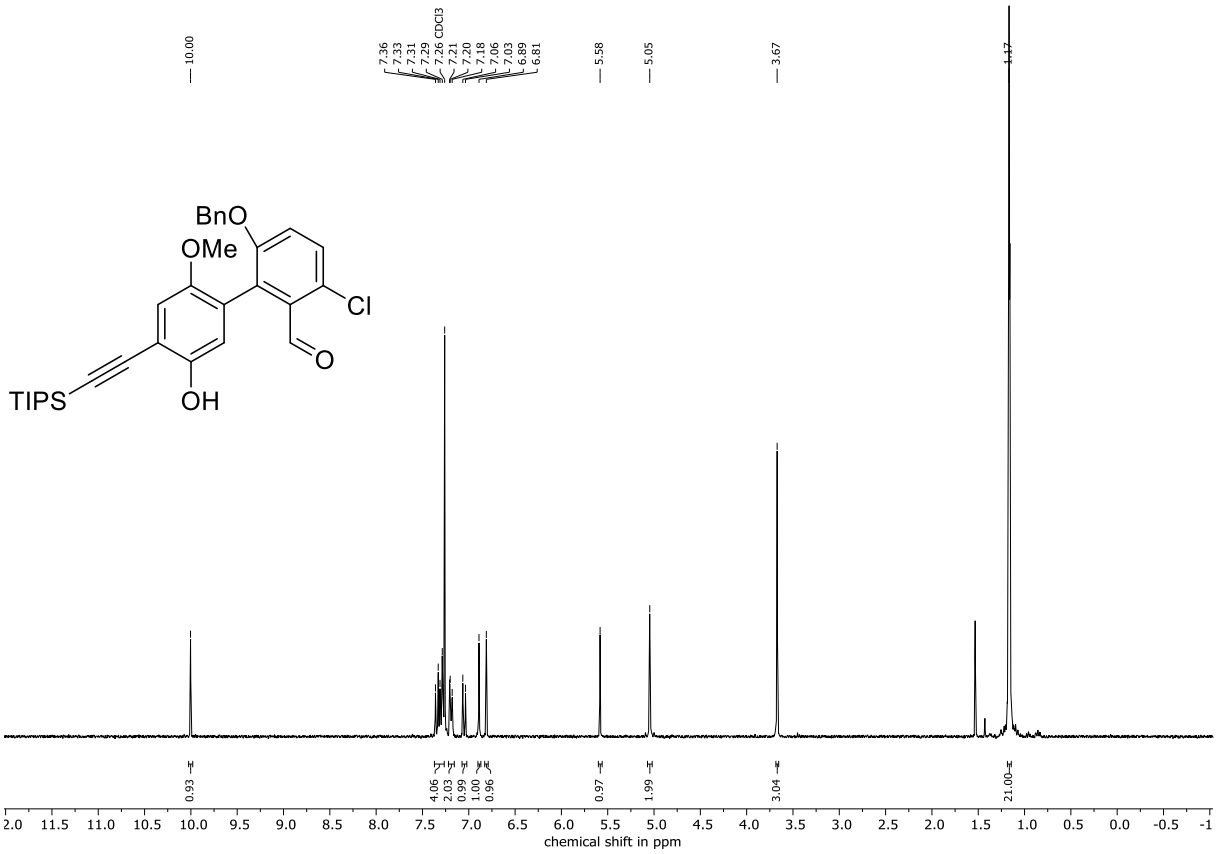
^{1}H NMR (400 MHz, $CDCl_3$) of **231**



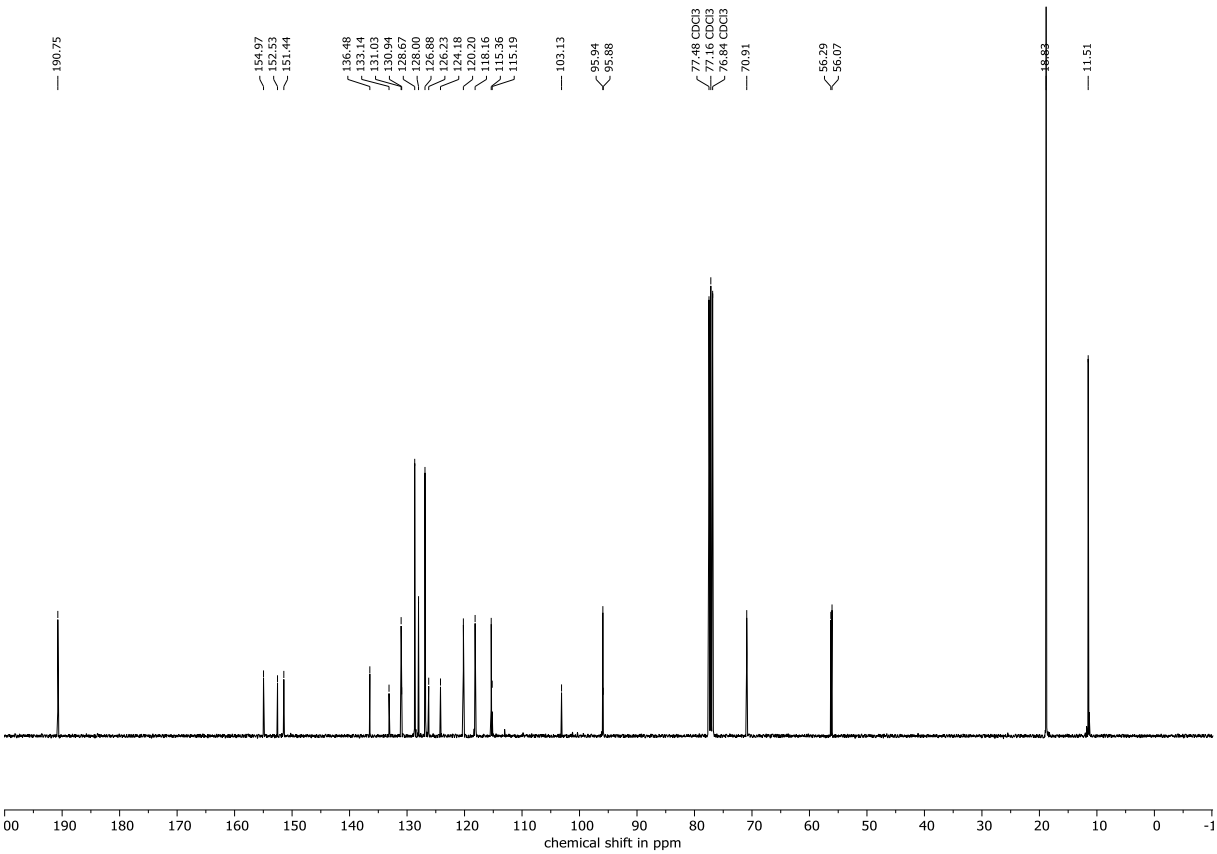
^{13}C NMR (101 MHz, $CDCl_3$) of **231**



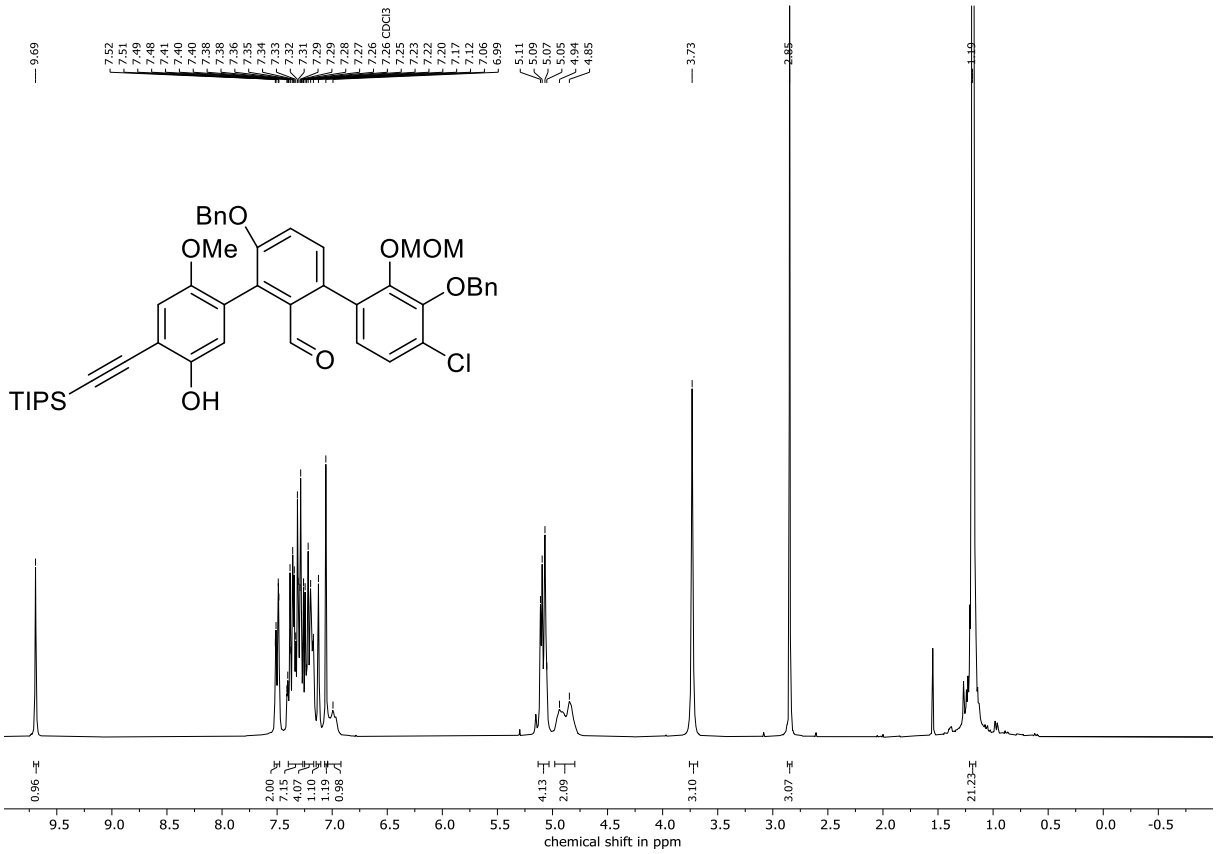
^{1}H NMR (300 MHz, $CDCl_3$) of **232**



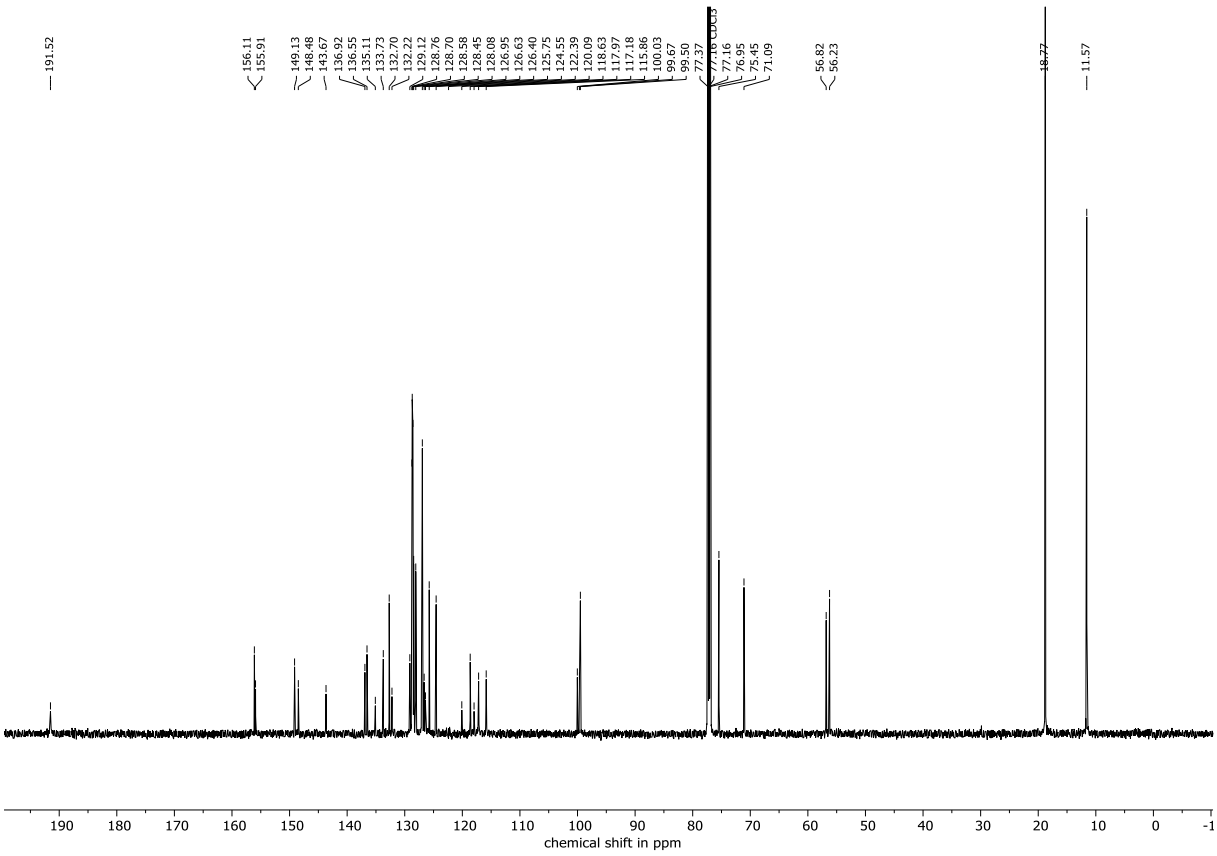
^{13}C NMR (101 MHz, $CDCl_3$) of **232**



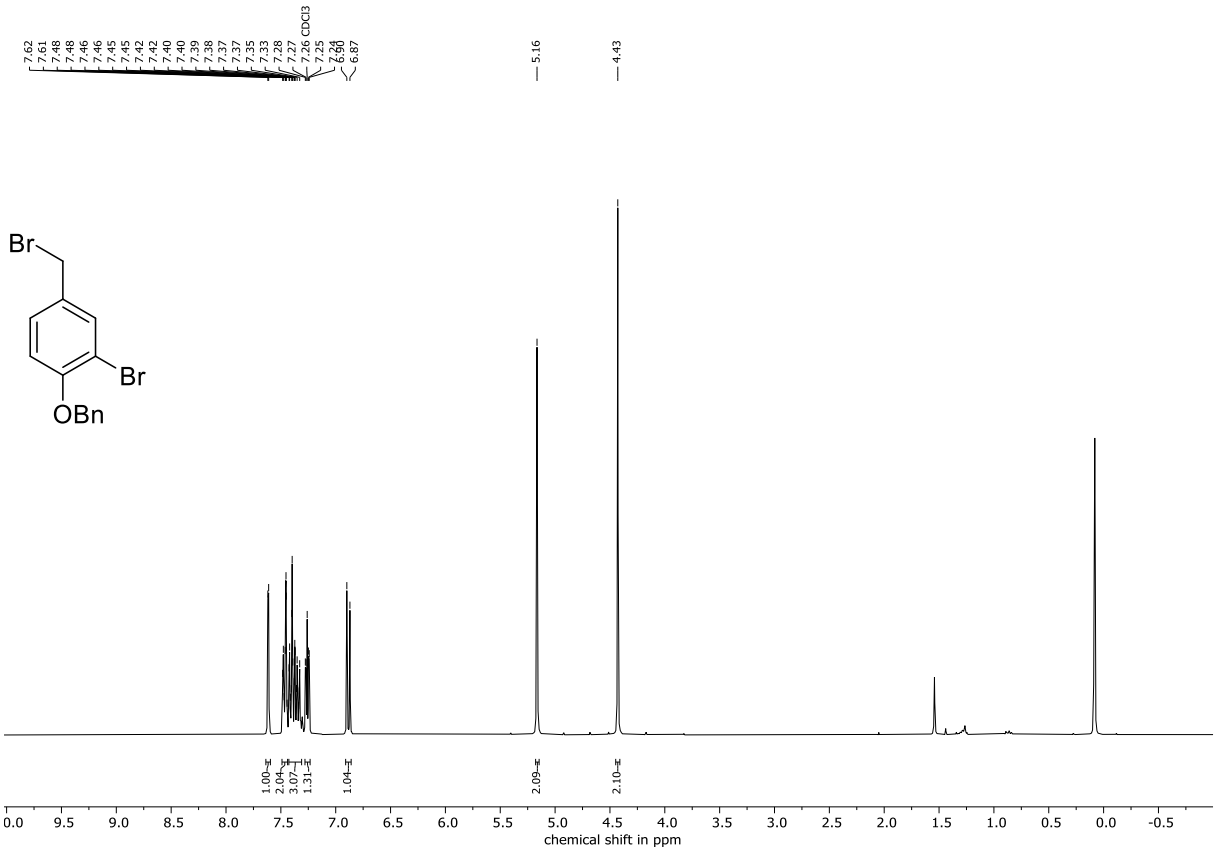
^{1}H NMR (300 MHz, $CDCl_3$) of **233**



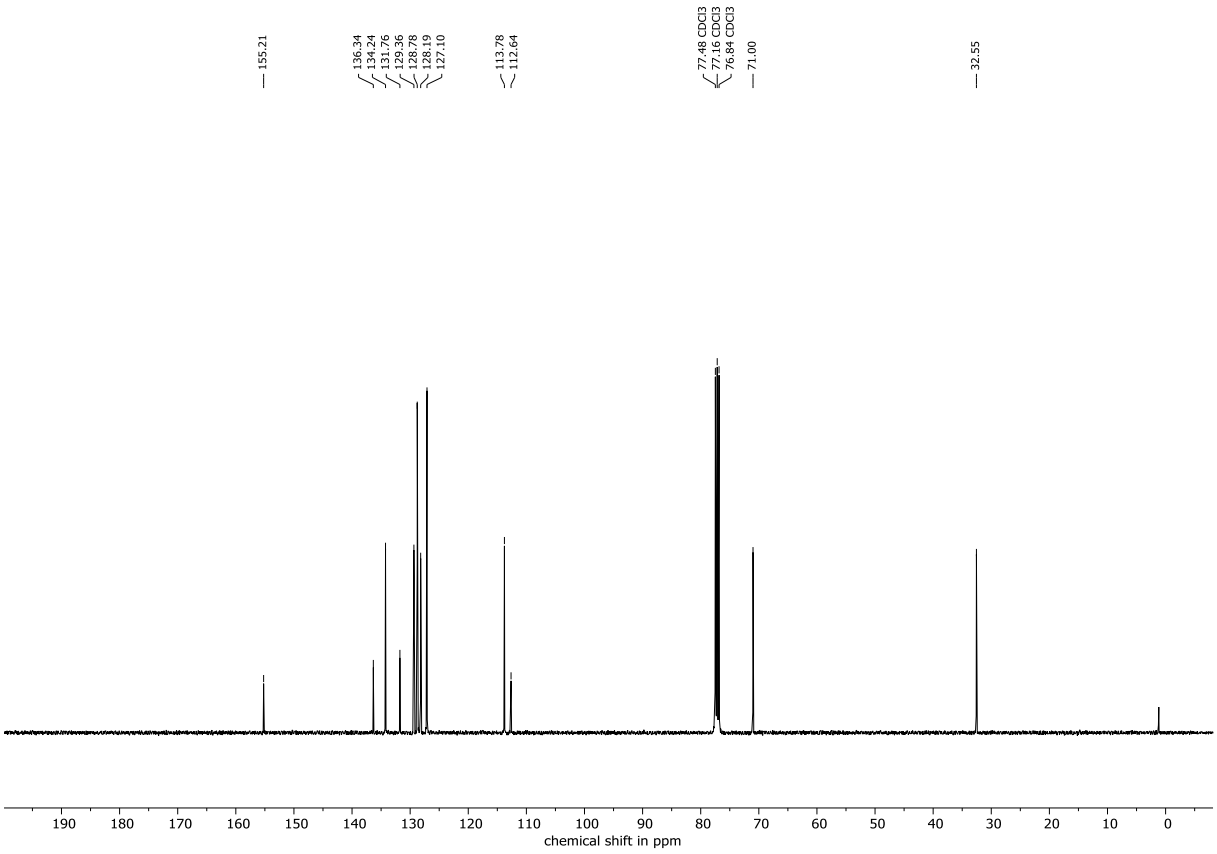
^{13}C NMR (101 MHz, $CDCl_3$) of **233**



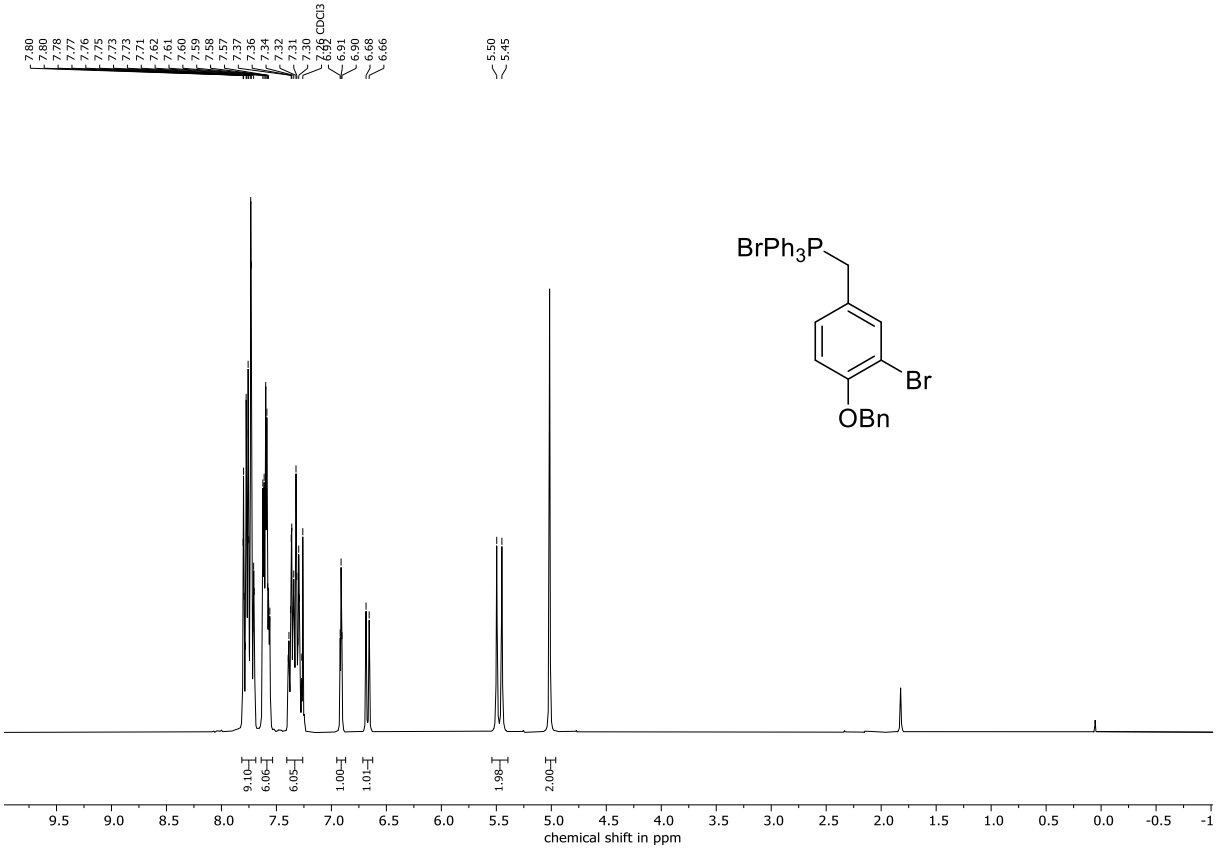
^{1}H NMR (300 MHz, $CDCl_3$) of **235**



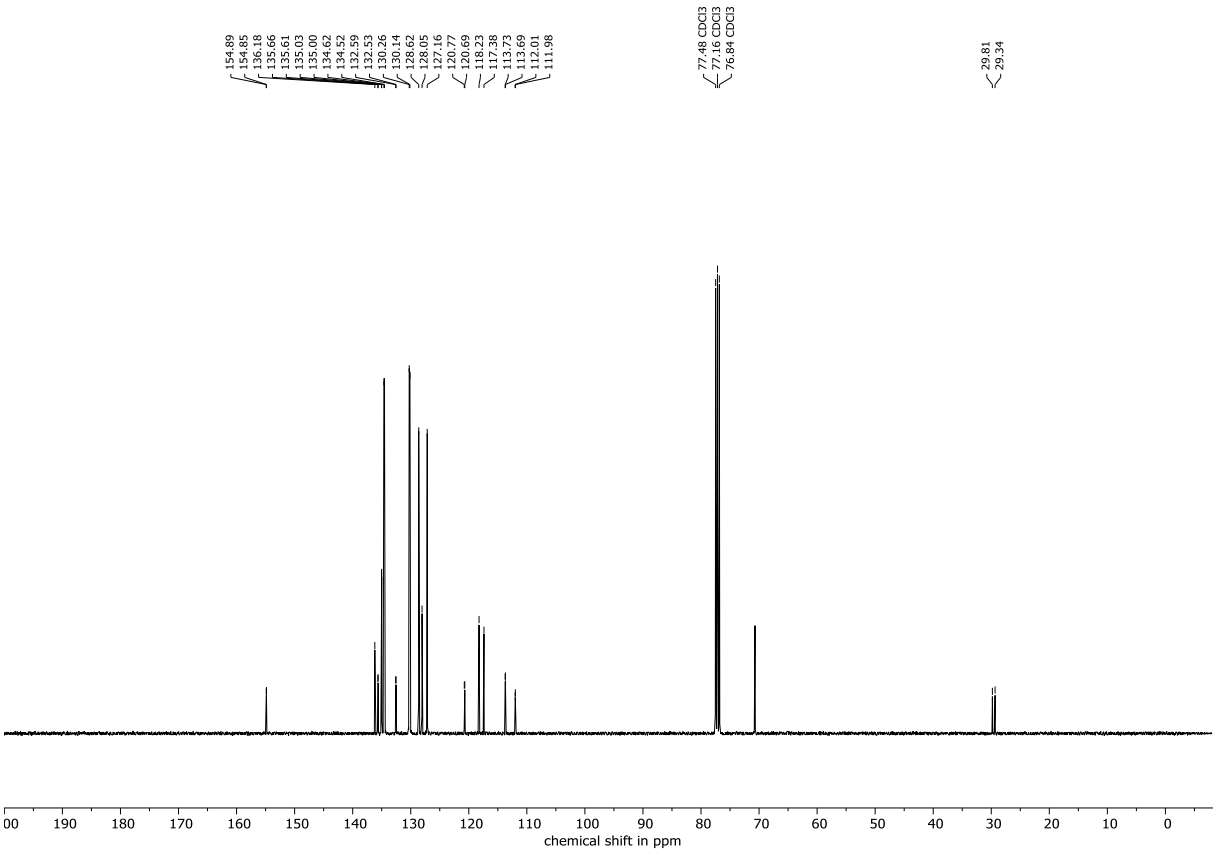
^{13}C NMR (101 MHz, $CDCl_3$) of **235**



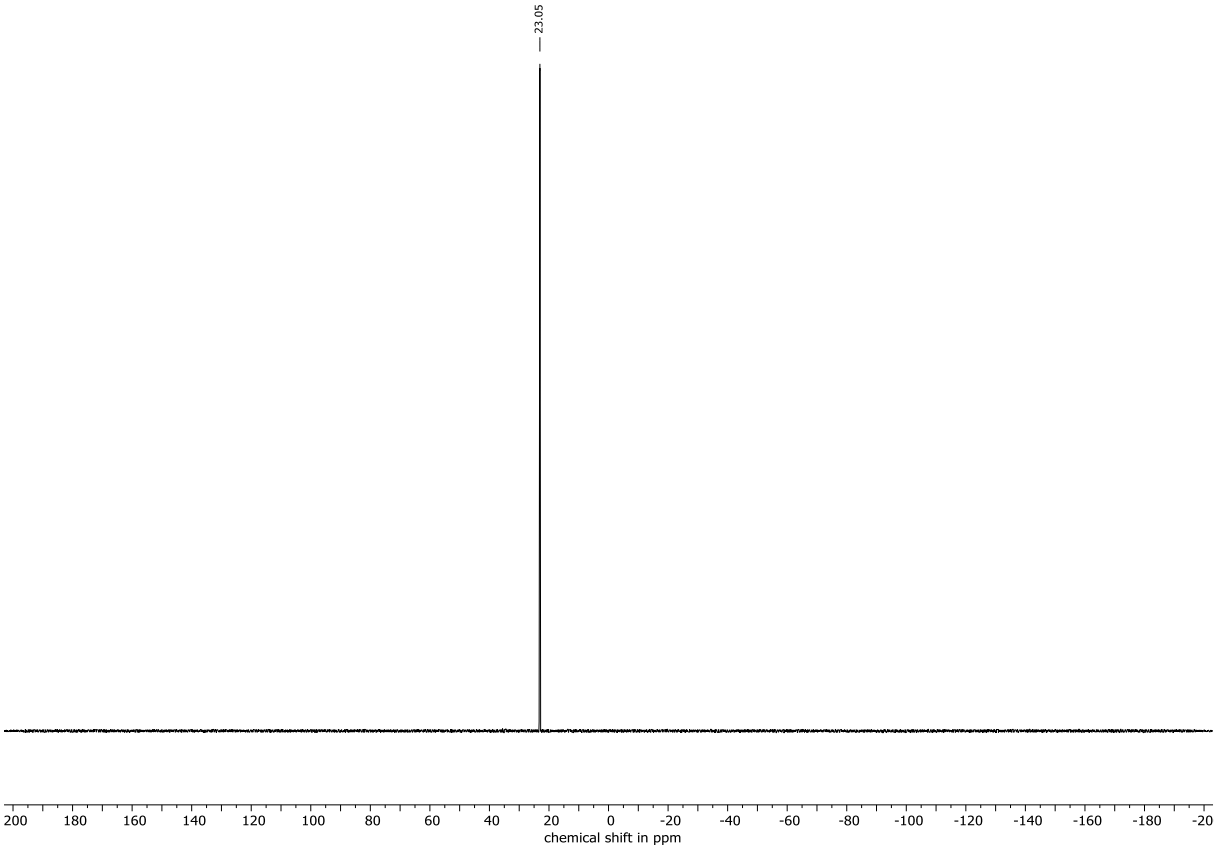
^{1}H NMR (300 MHz, $CDCl_3$) of **236**



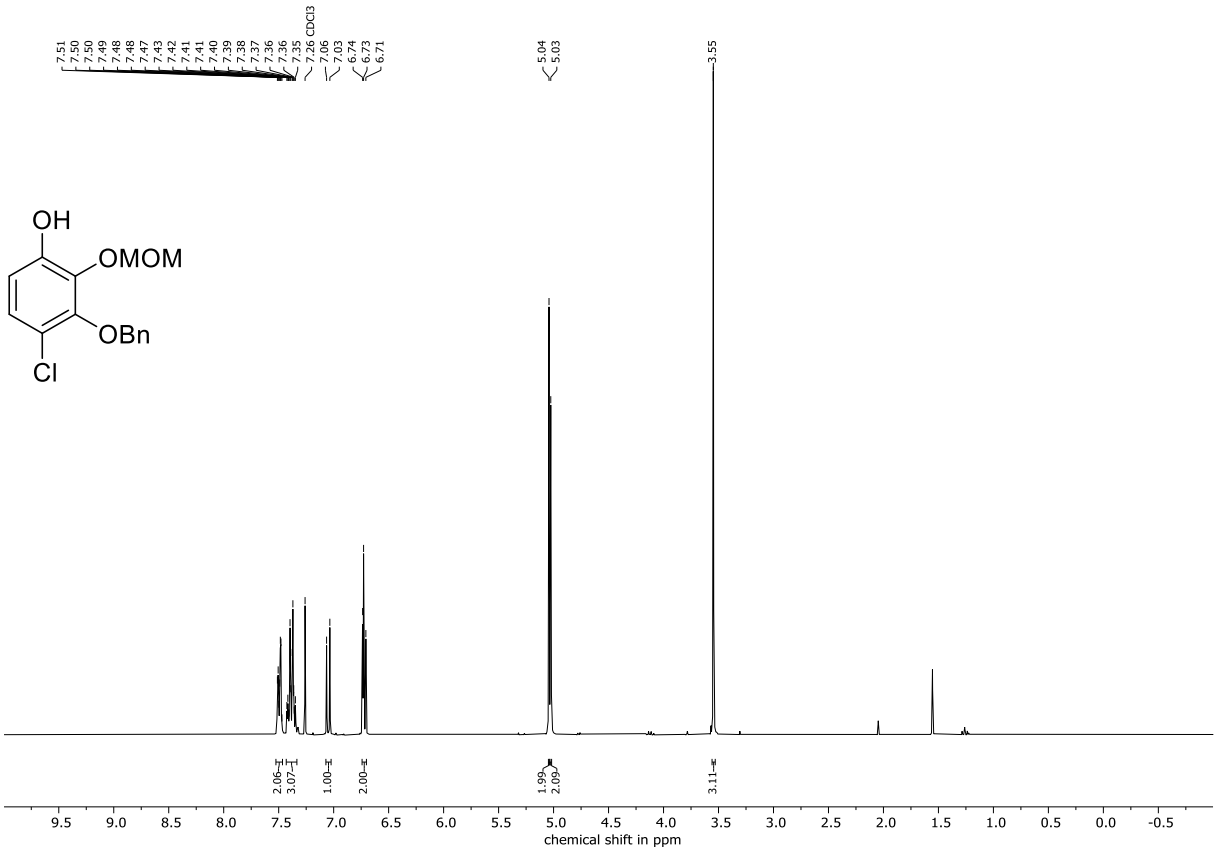
^{13}C NMR (101 MHz, $CDCl_3$) of **236**



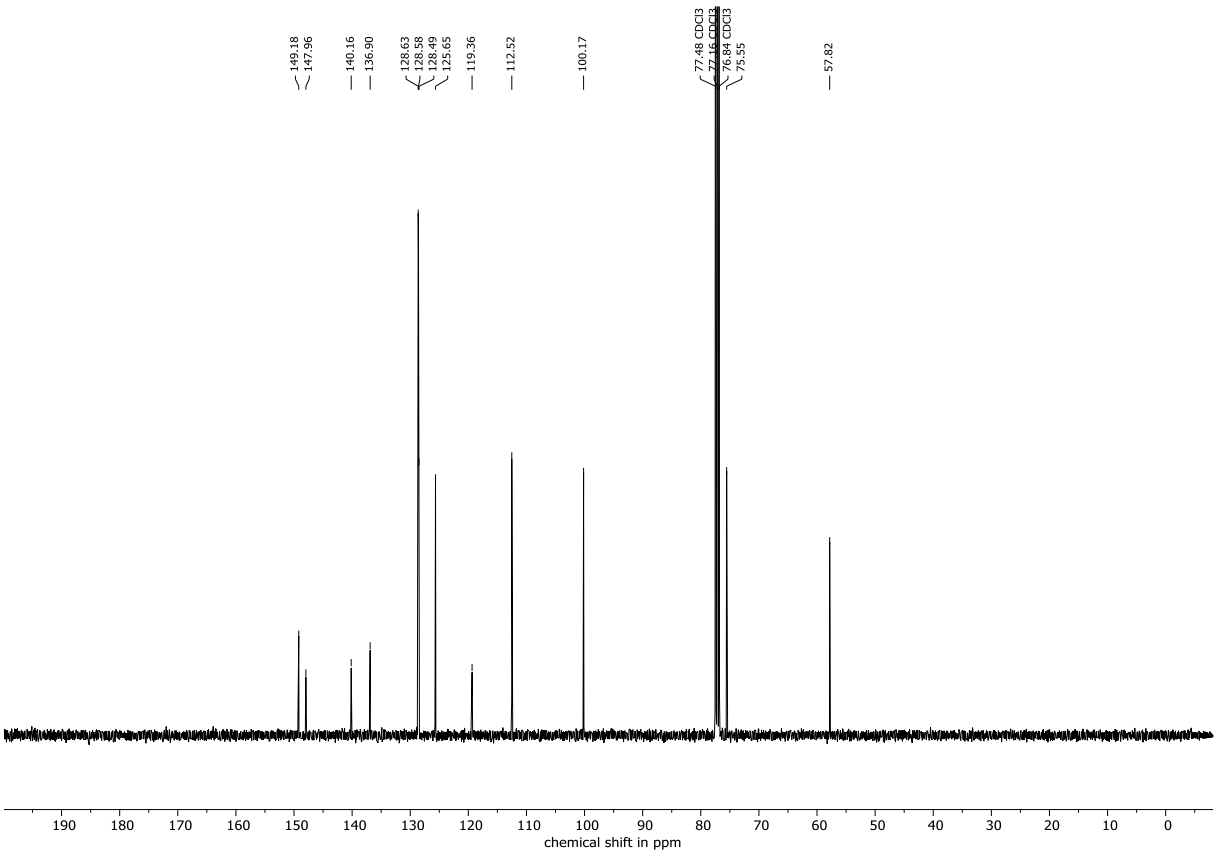
^{31}P NMR (162 MHz, $CDCl_3$) of **236**



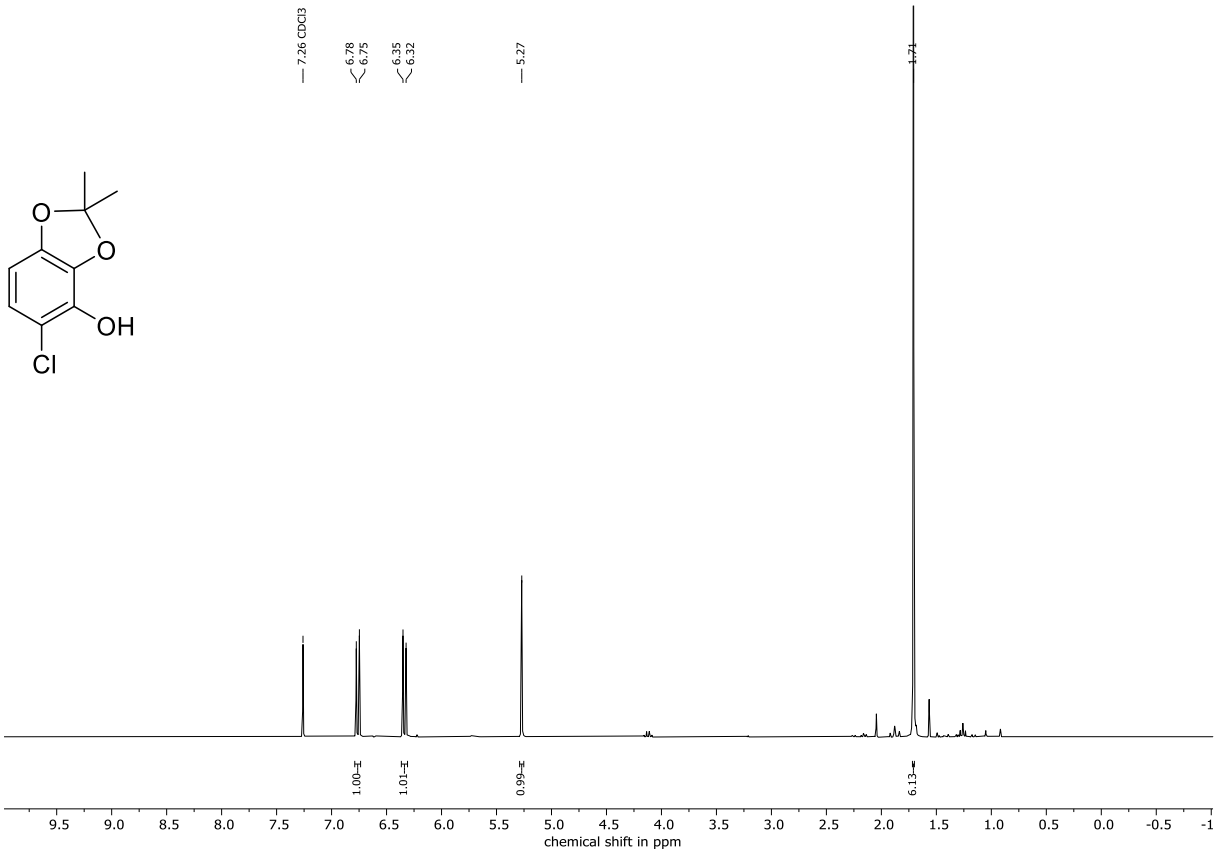
^{1}H NMR (300 MHz, $CDCl_3$) of **239**



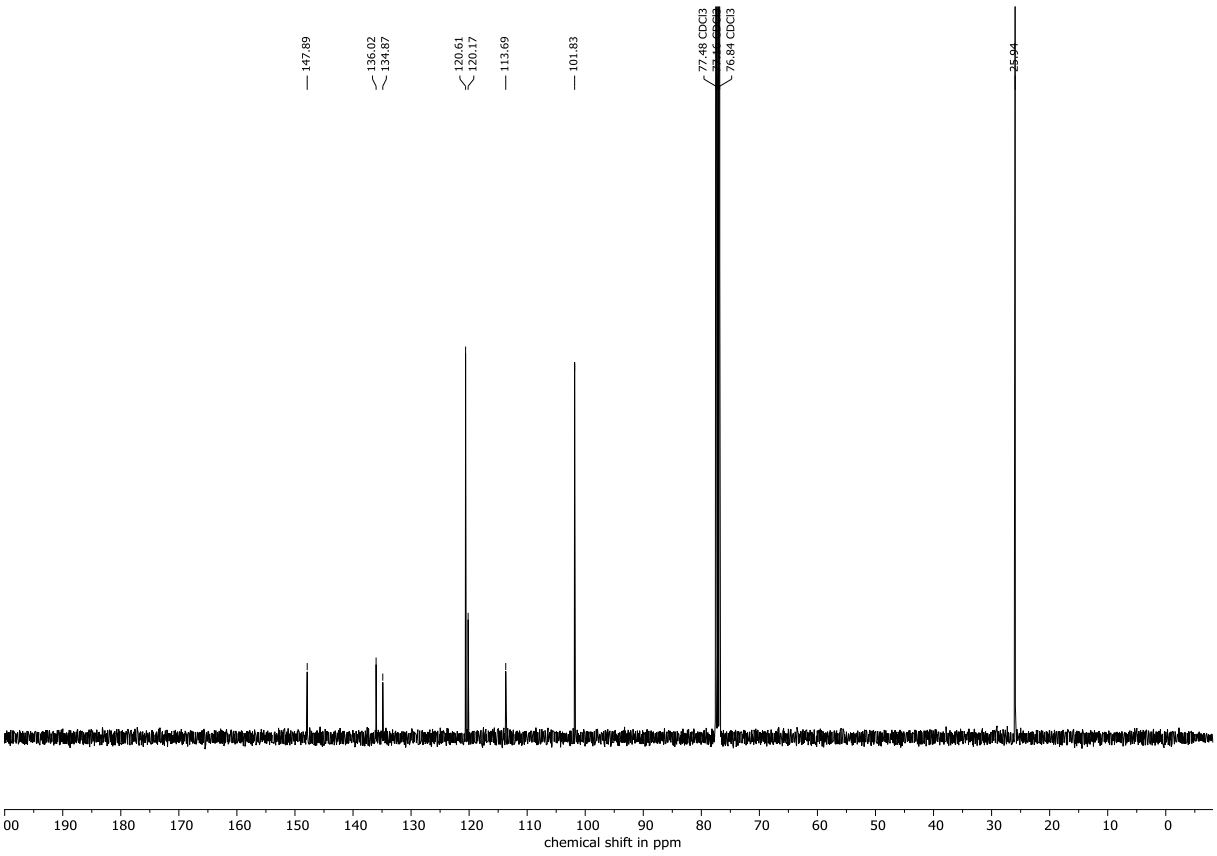
^{13}C NMR (101 MHz, $CDCl_3$) of **239**



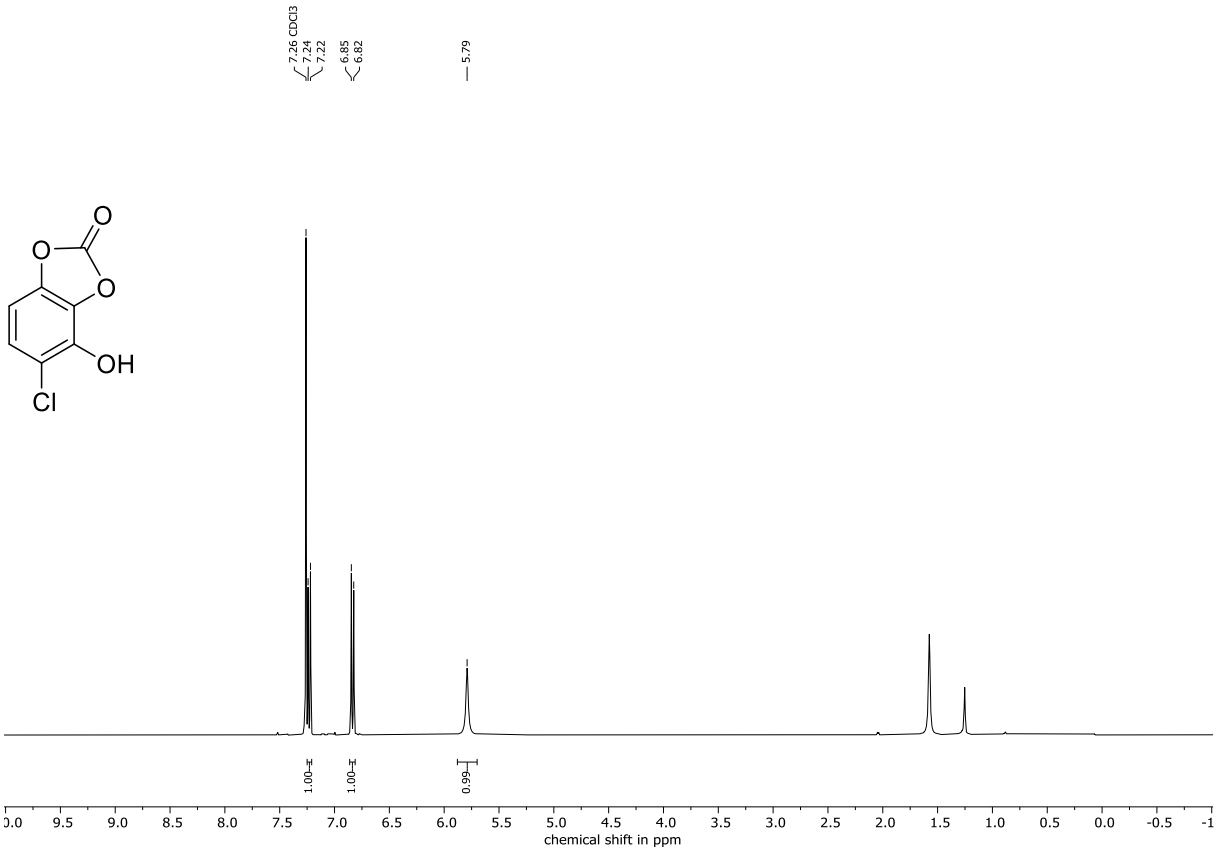
^{1}H NMR (300 MHz, $CDCl_3$) of **241c**



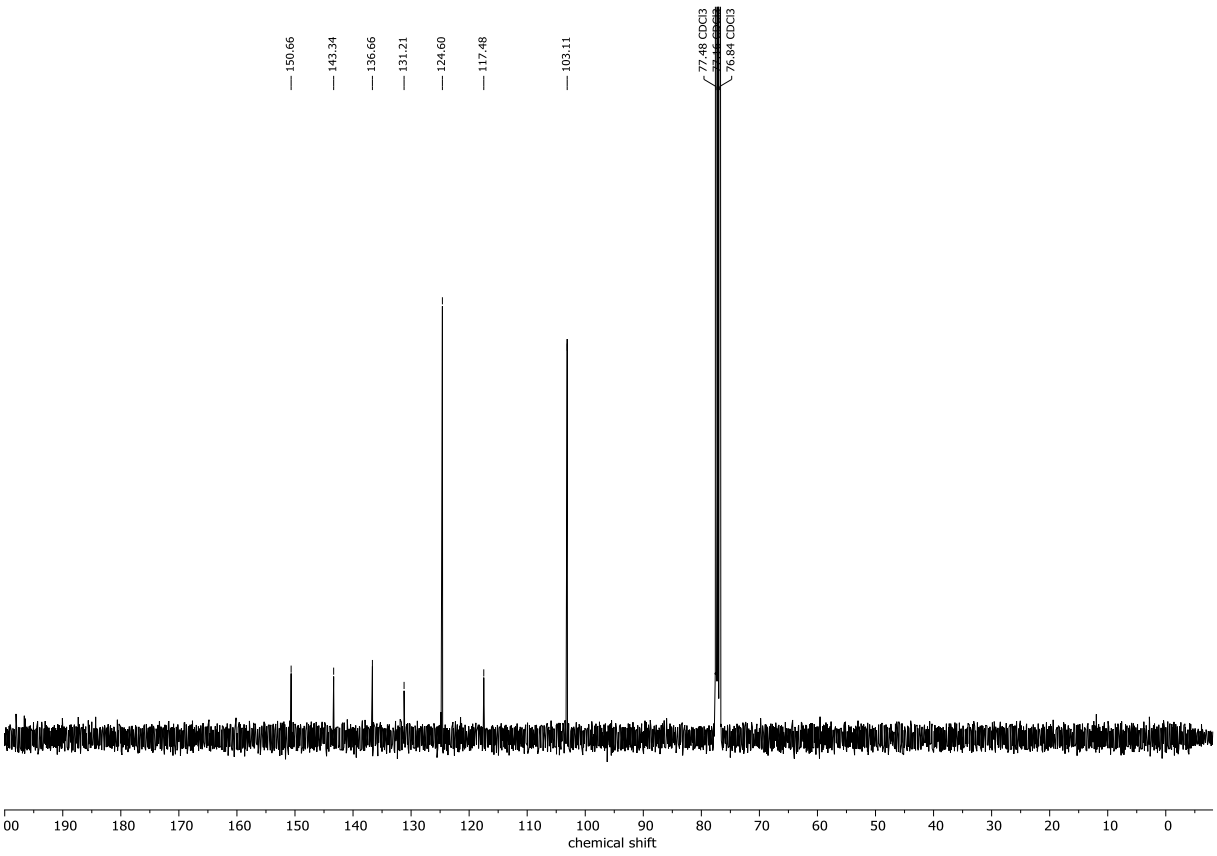
^{13}C NMR (101 MHz, $CDCl_3$) of **241c**



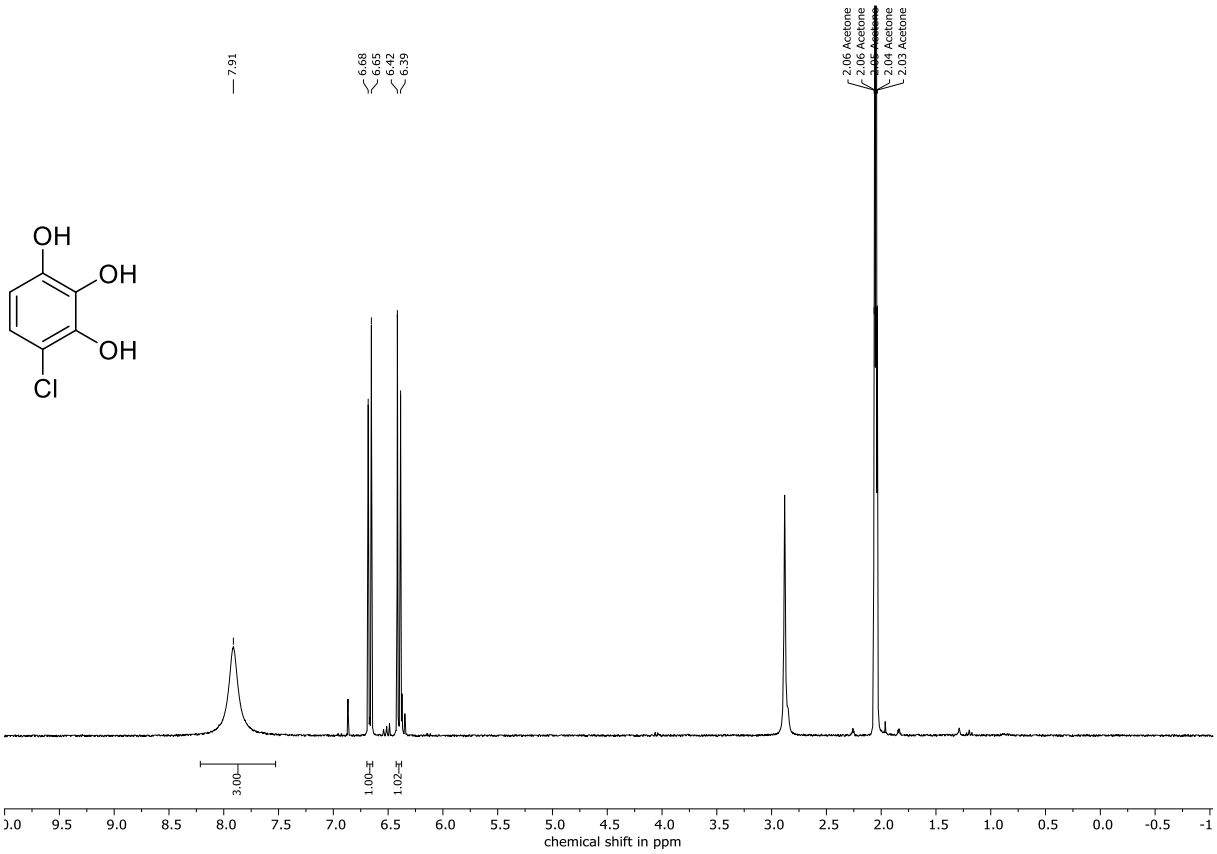
^{1}H NMR (400 MHz, $CDCl_3$) of **241d**



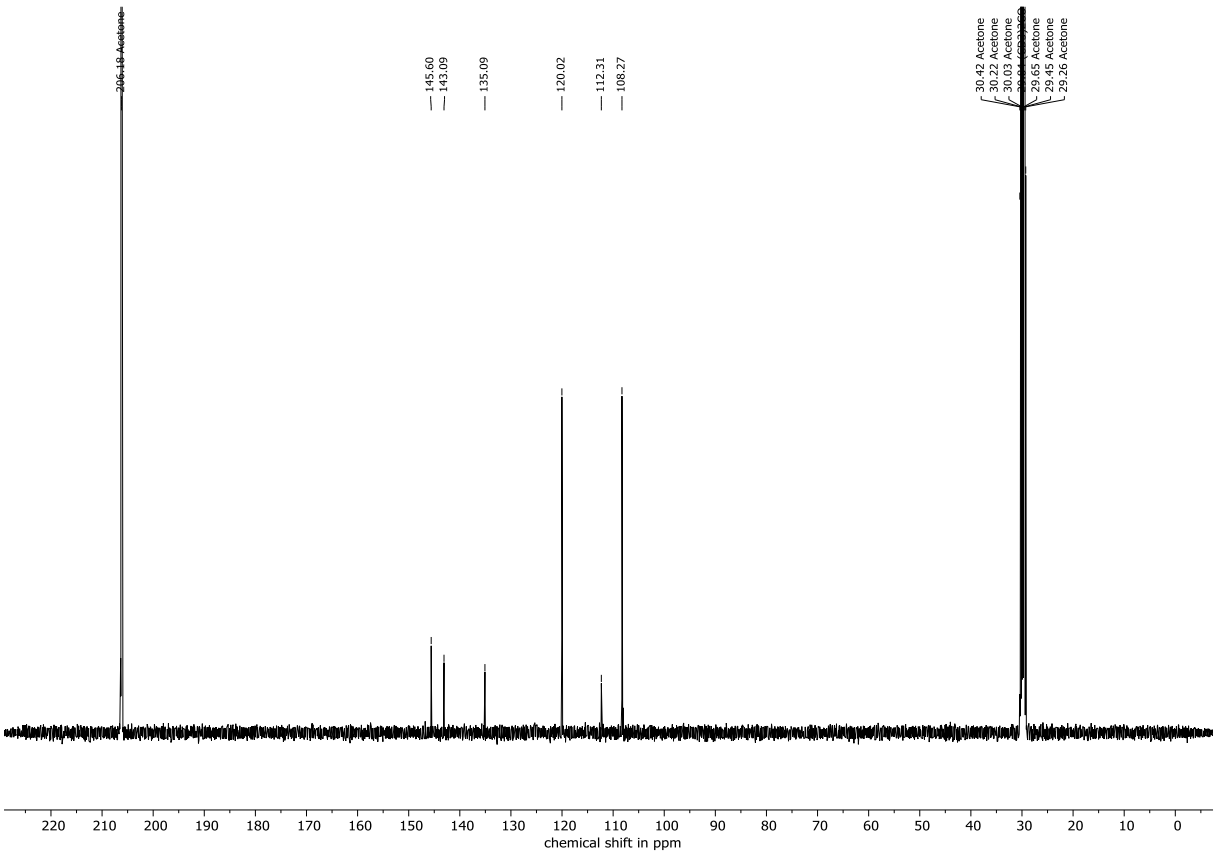
^{13}C NMR (101 MHz, $CDCl_3$) of **241d**



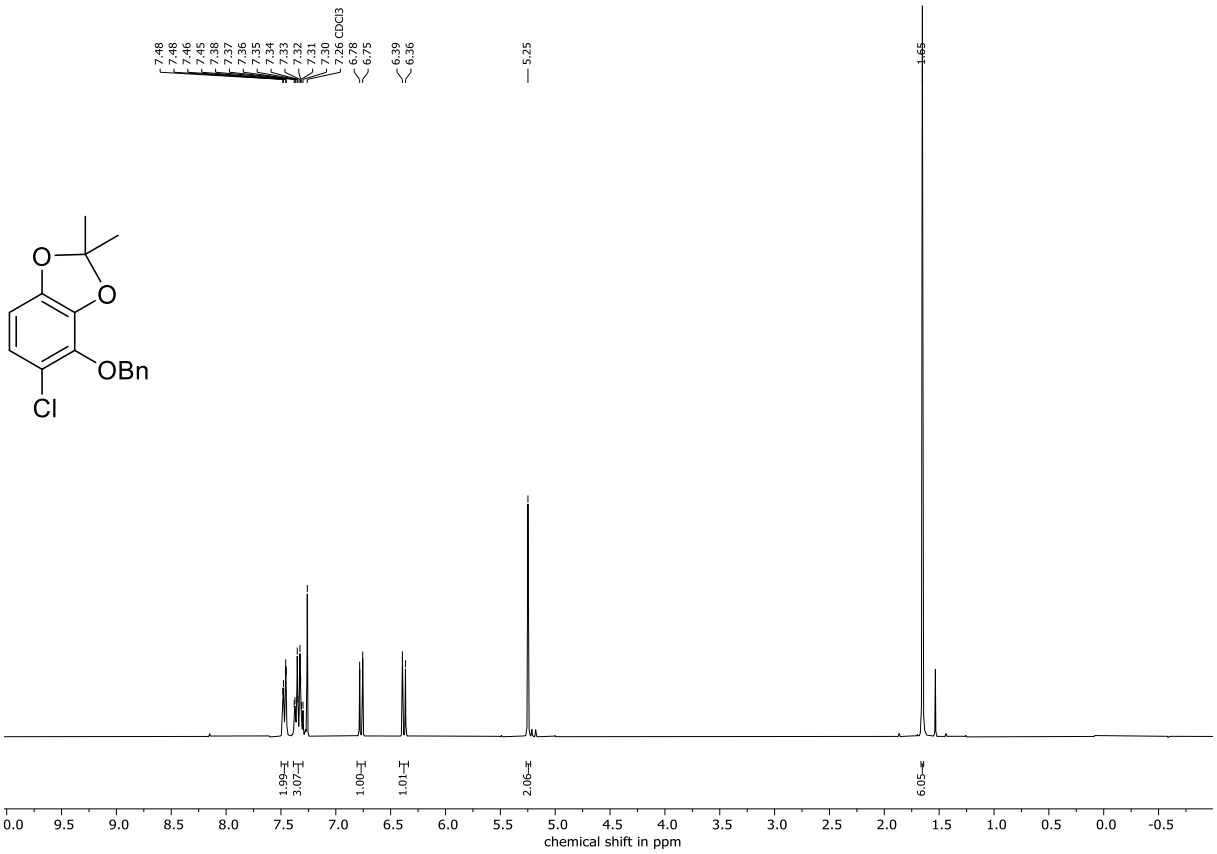
^{1}H NMR (300 MHz, Acetone) of **243**



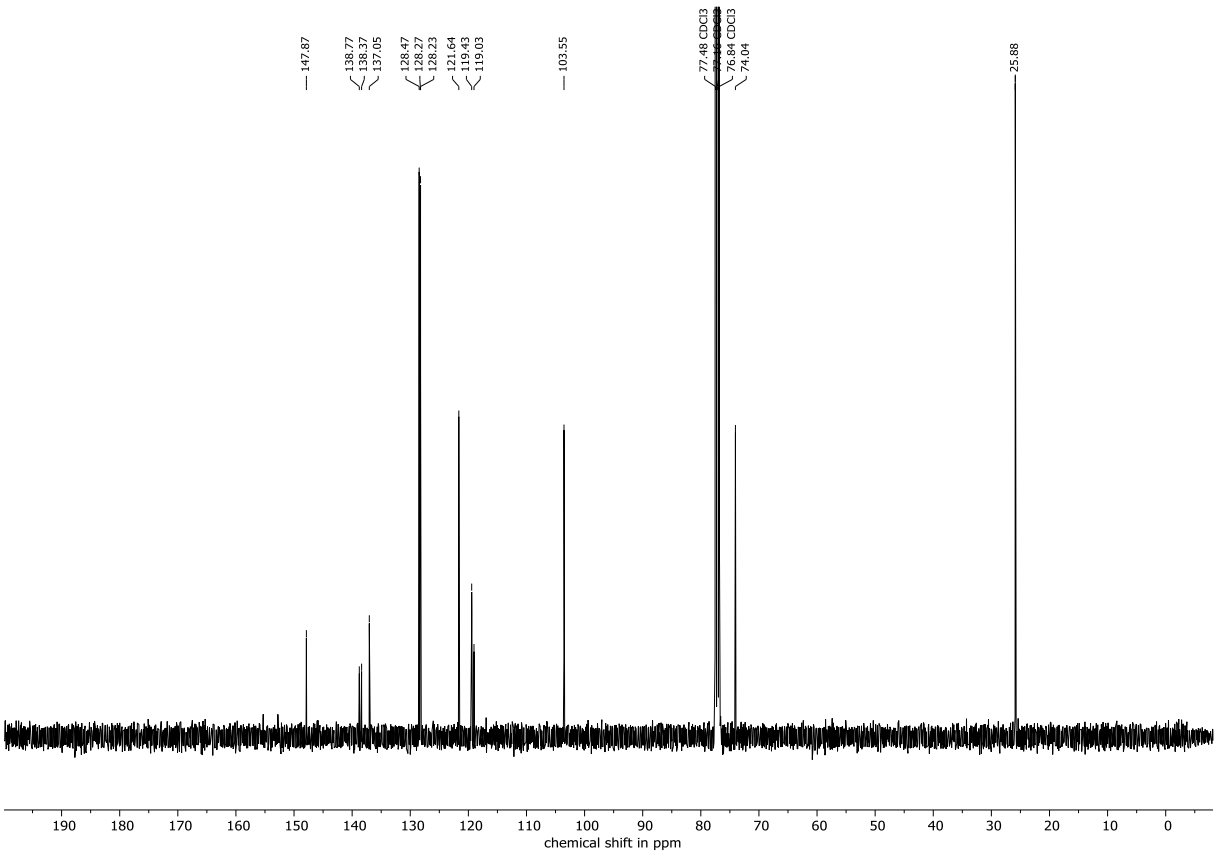
^{13}C NMR (101 MHz, Acetone) of **243**



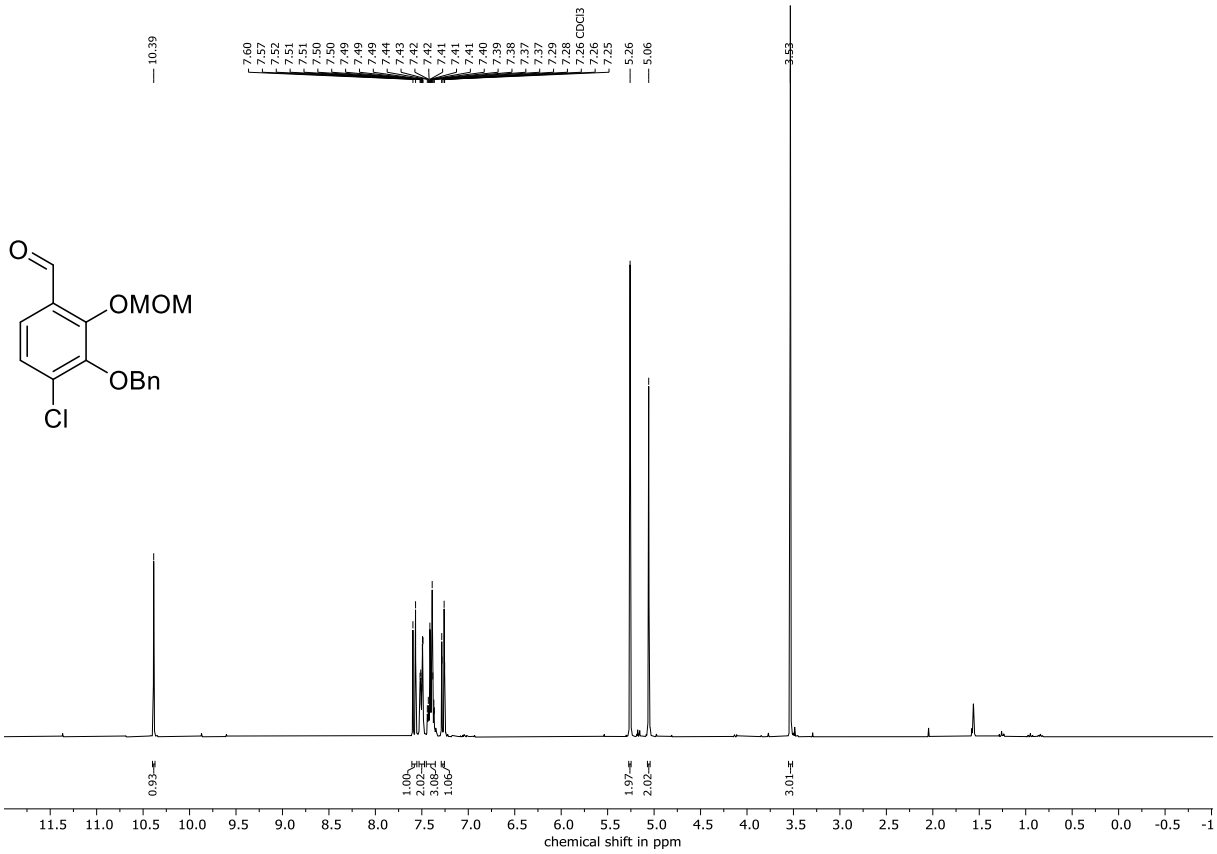
^{1}H NMR (300 MHz, $CDCl_3$) of **244**



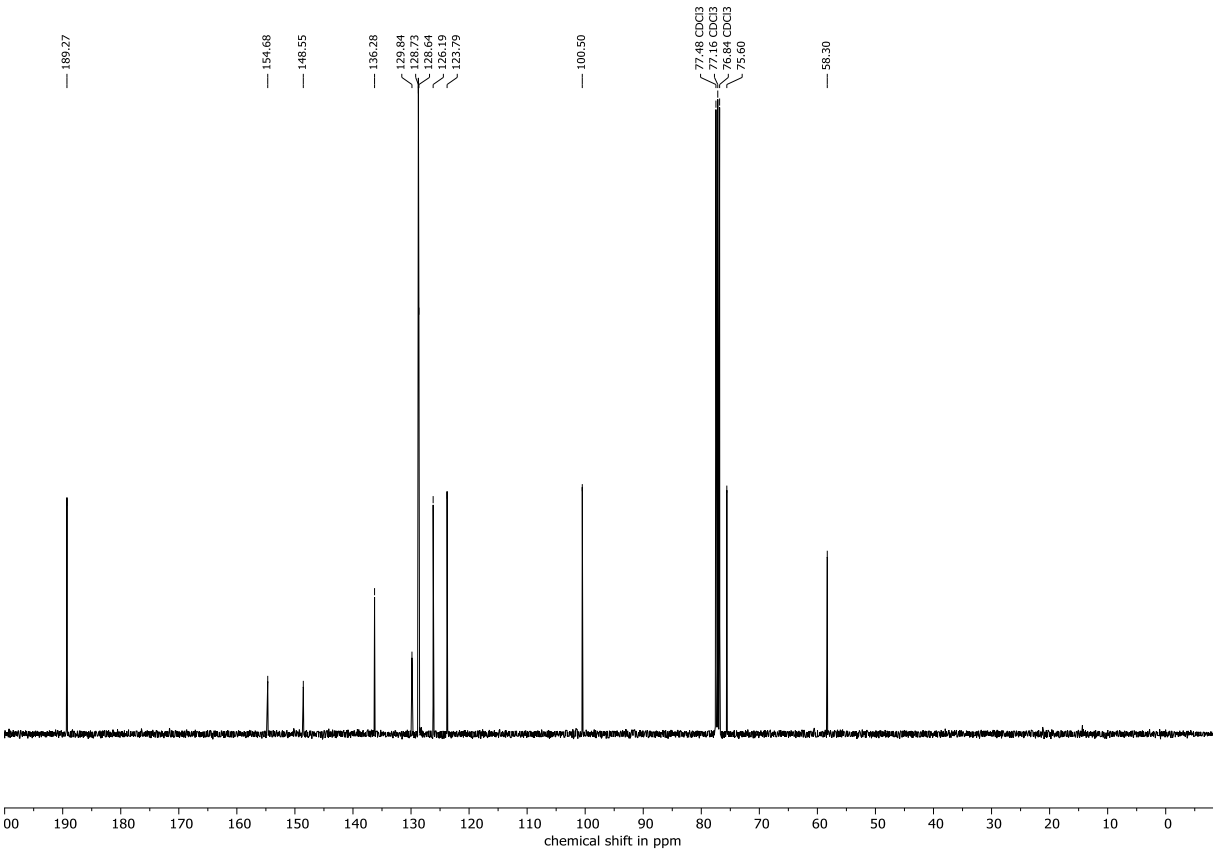
^{13}C NMR (101 MHz, $CDCl_3$) of **244**



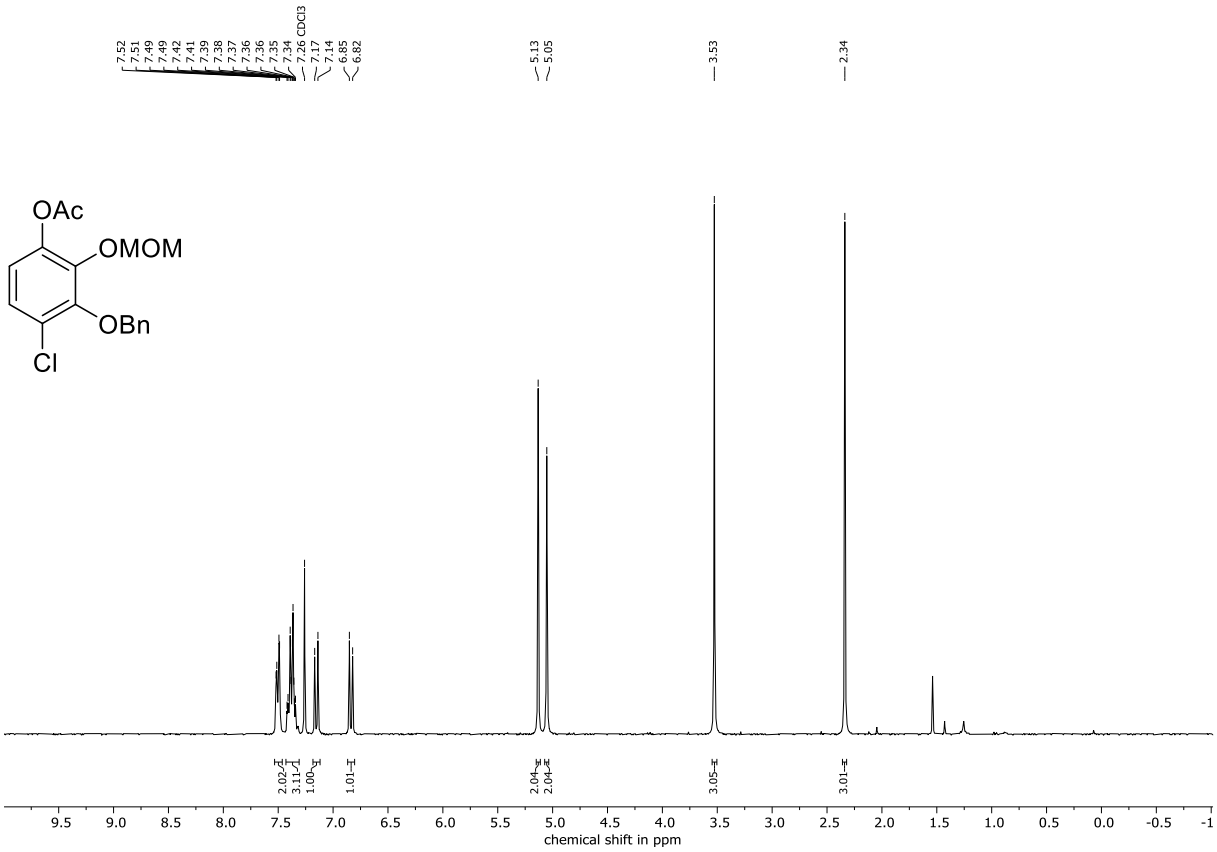
^{1}H NMR (300 MHz, $CDCl_3$) of **247**



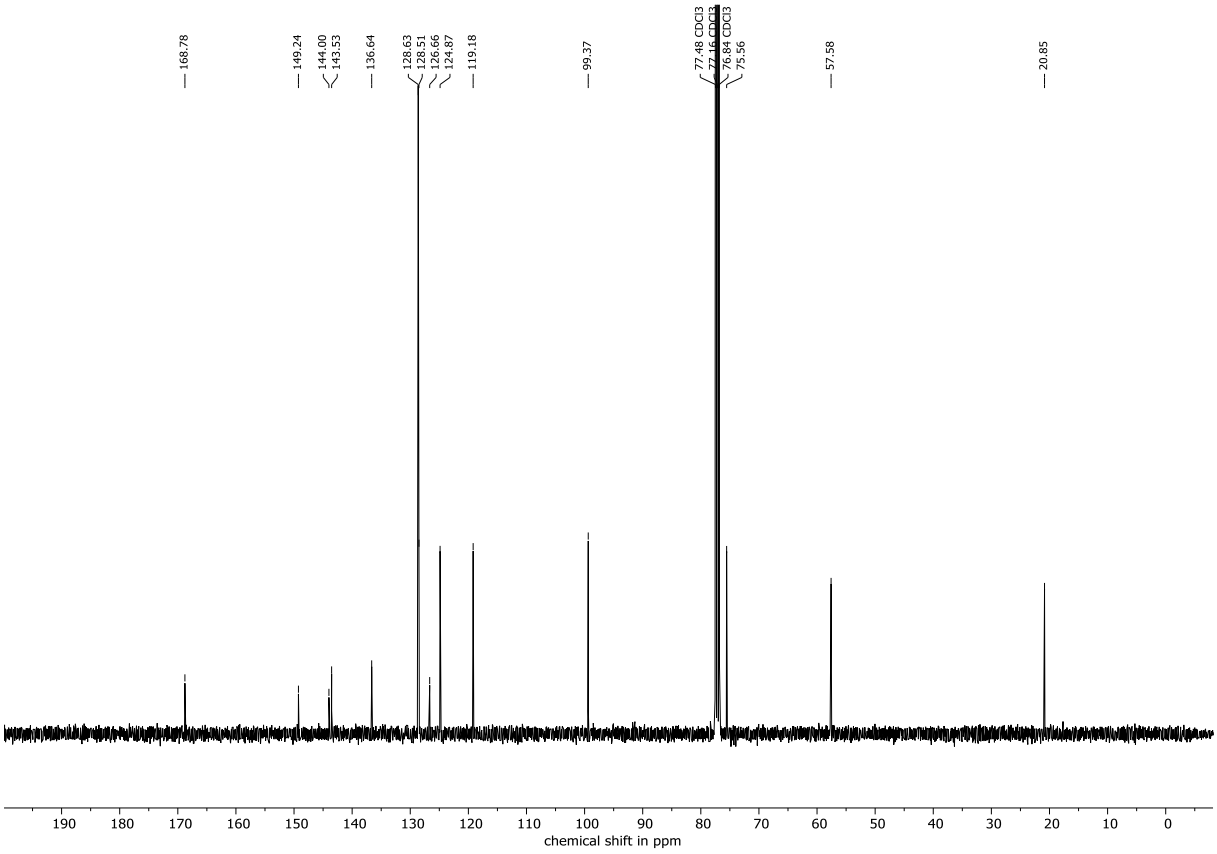
^{13}C NMR (101 MHz, $CDCl_3$) of **247**



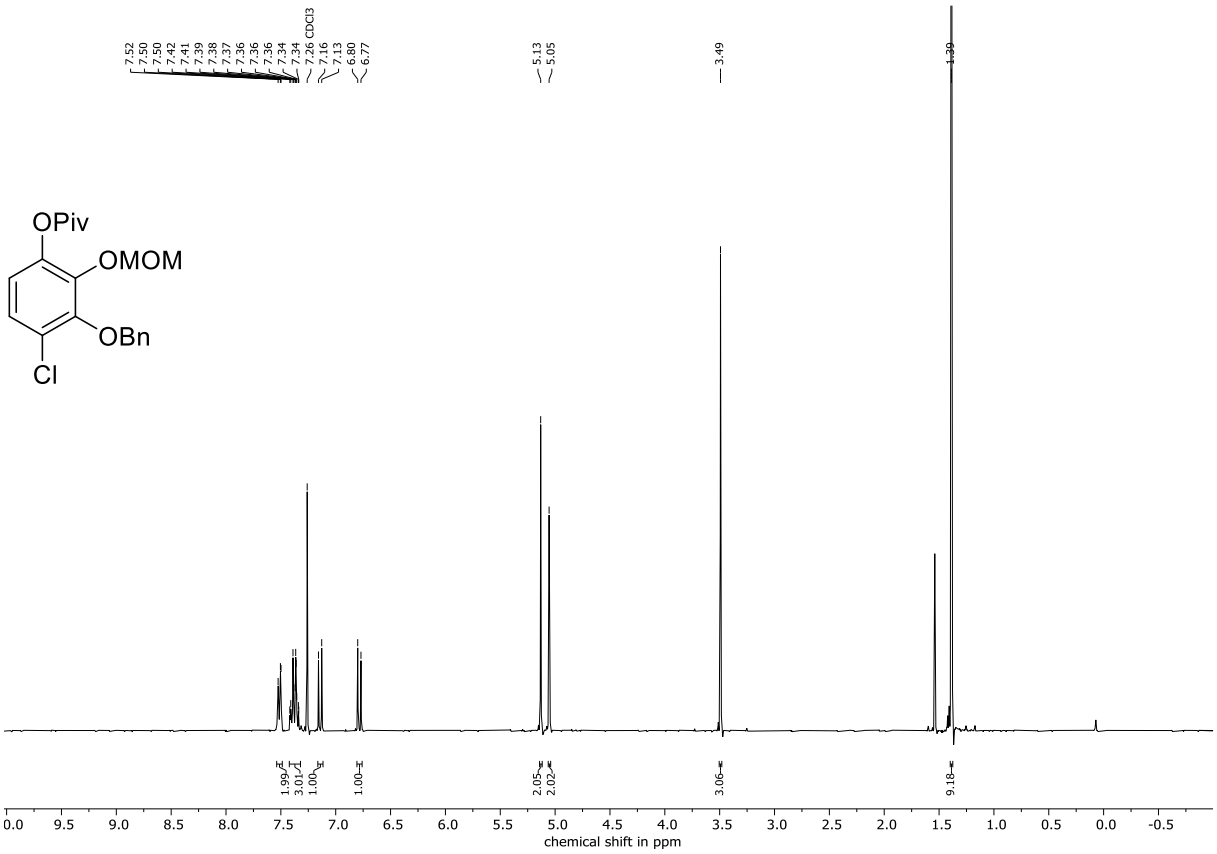
^{1}H NMR (300 MHz, $CDCl_3$) of **248**



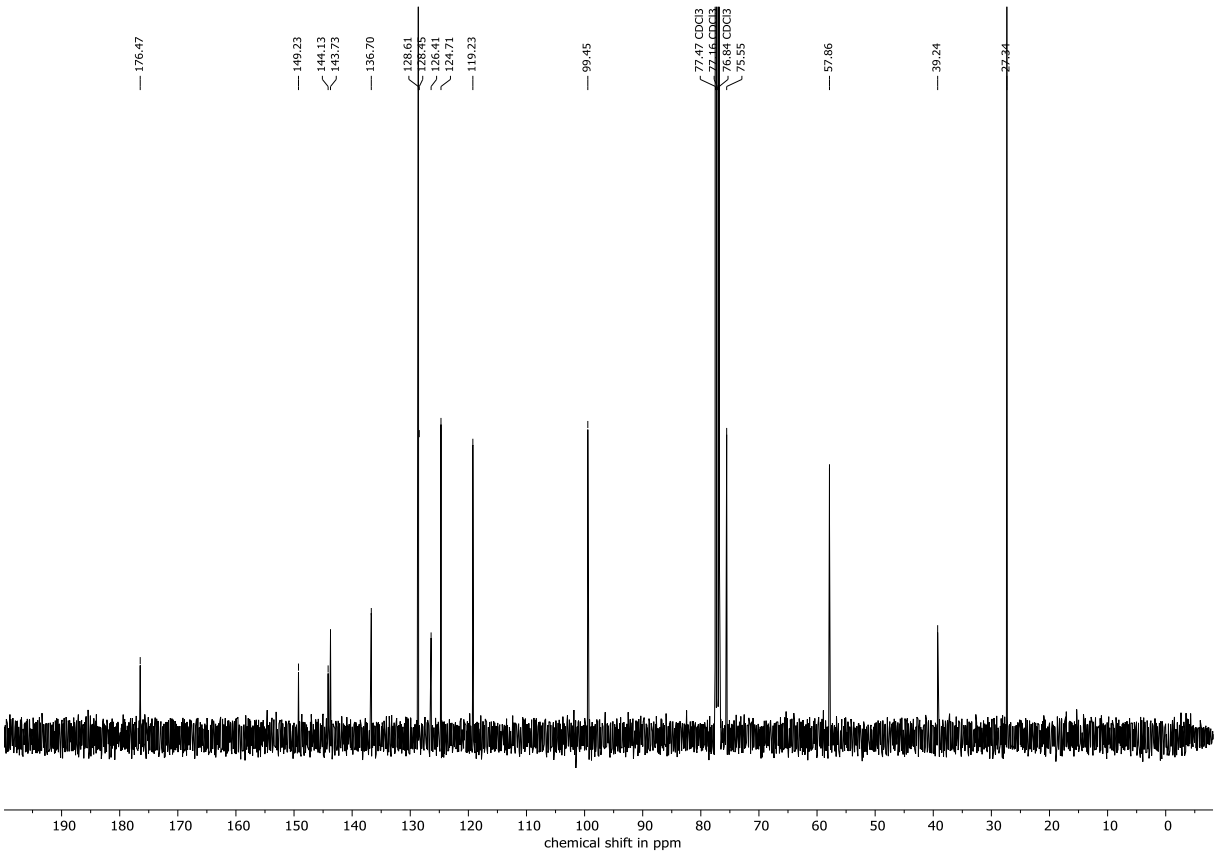
^{13}C NMR (101 MHz, $CDCl_3$) of **248**



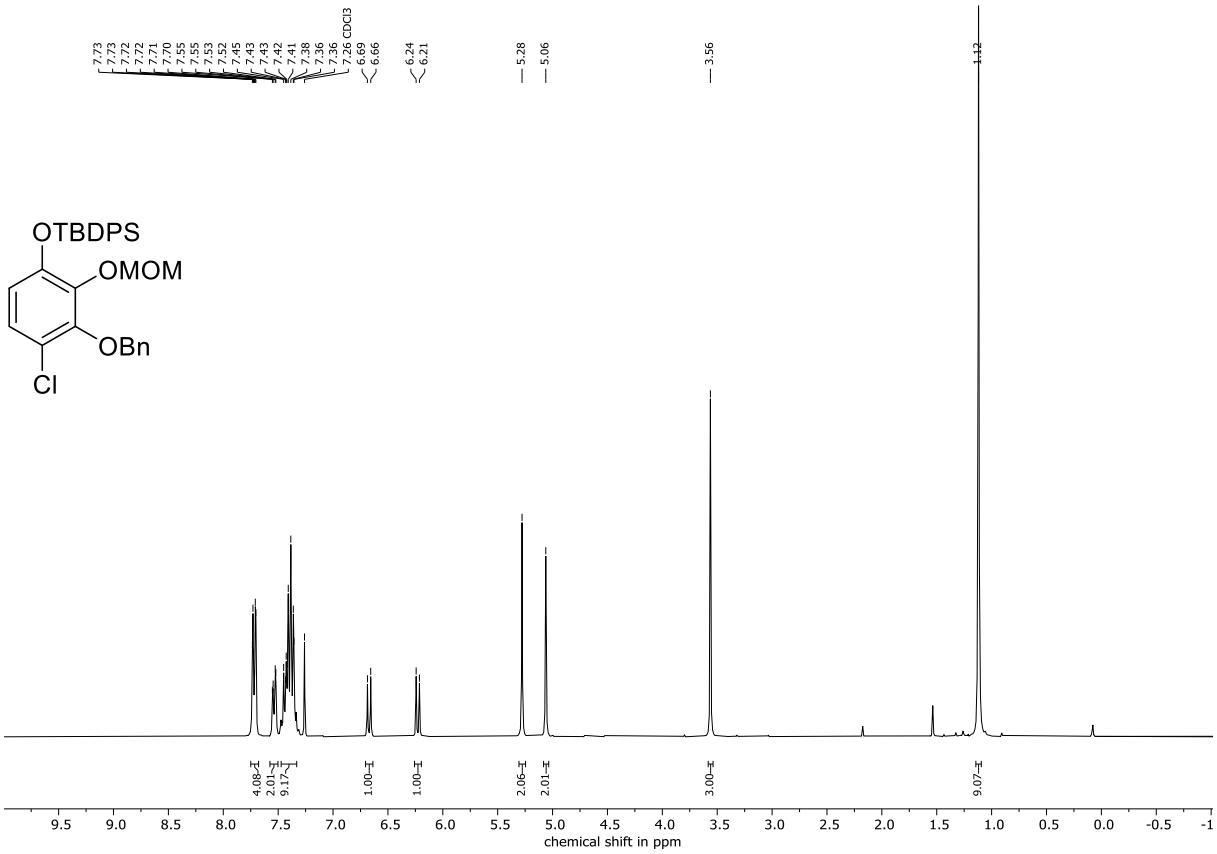
^{1}H NMR (300 MHz, $CDCl_3$) of **249**



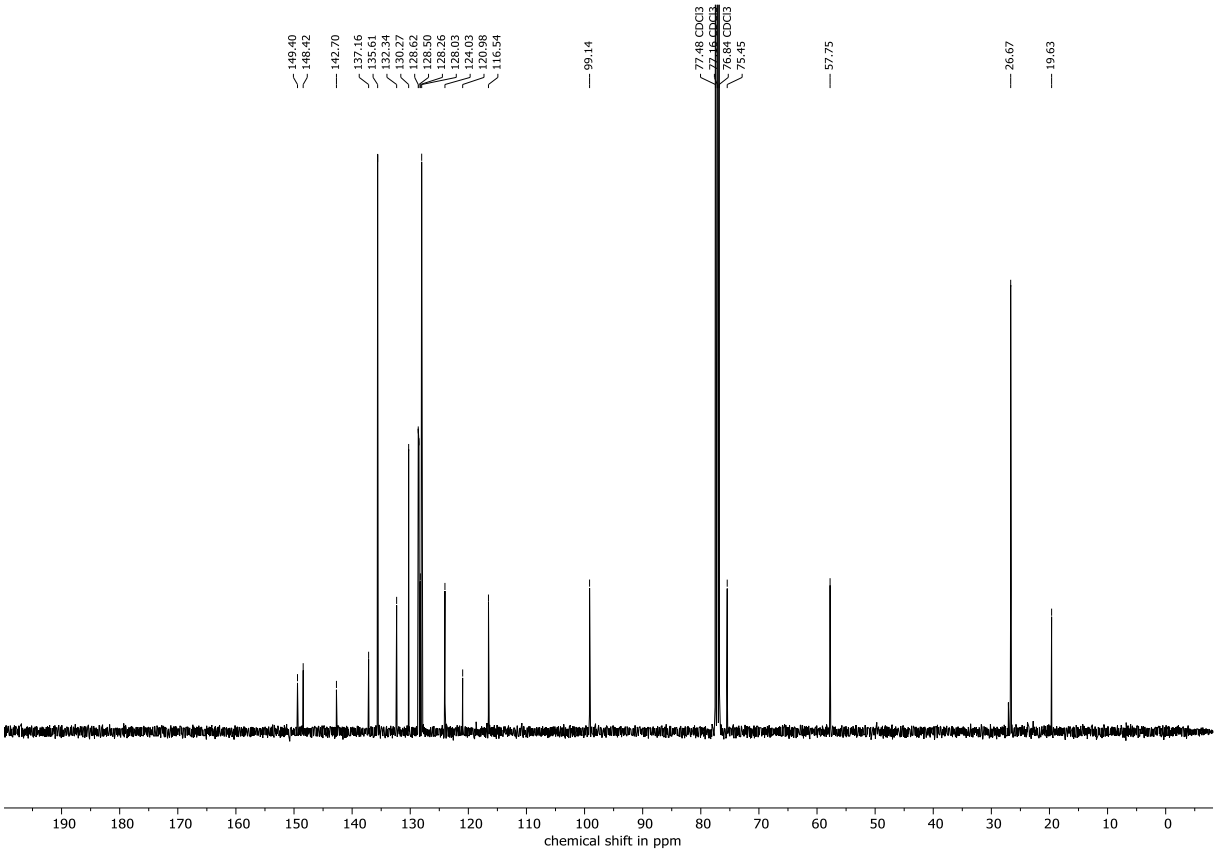
^{13}C NMR (101 MHz, $CDCl_3$) of **249**



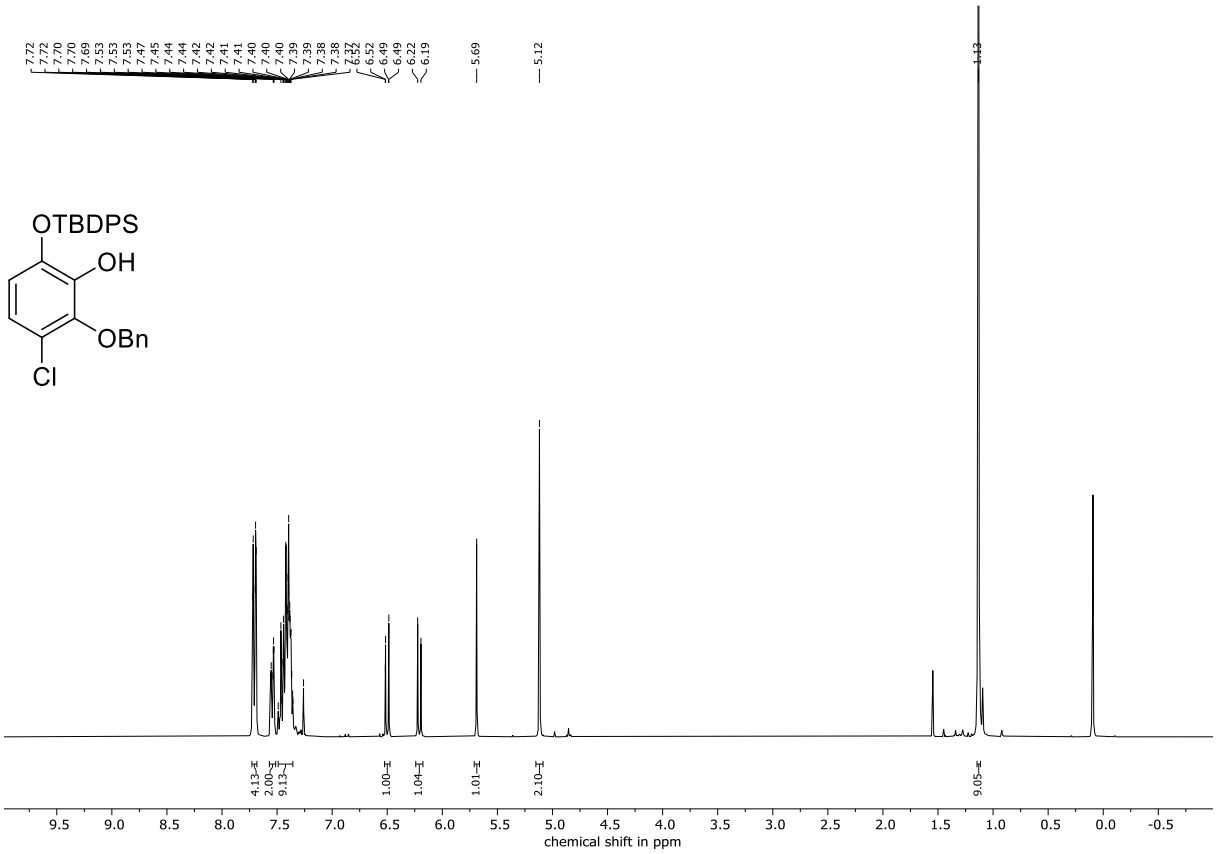
^{1}H NMR (300 MHz, $CDCl_3$) of **252**



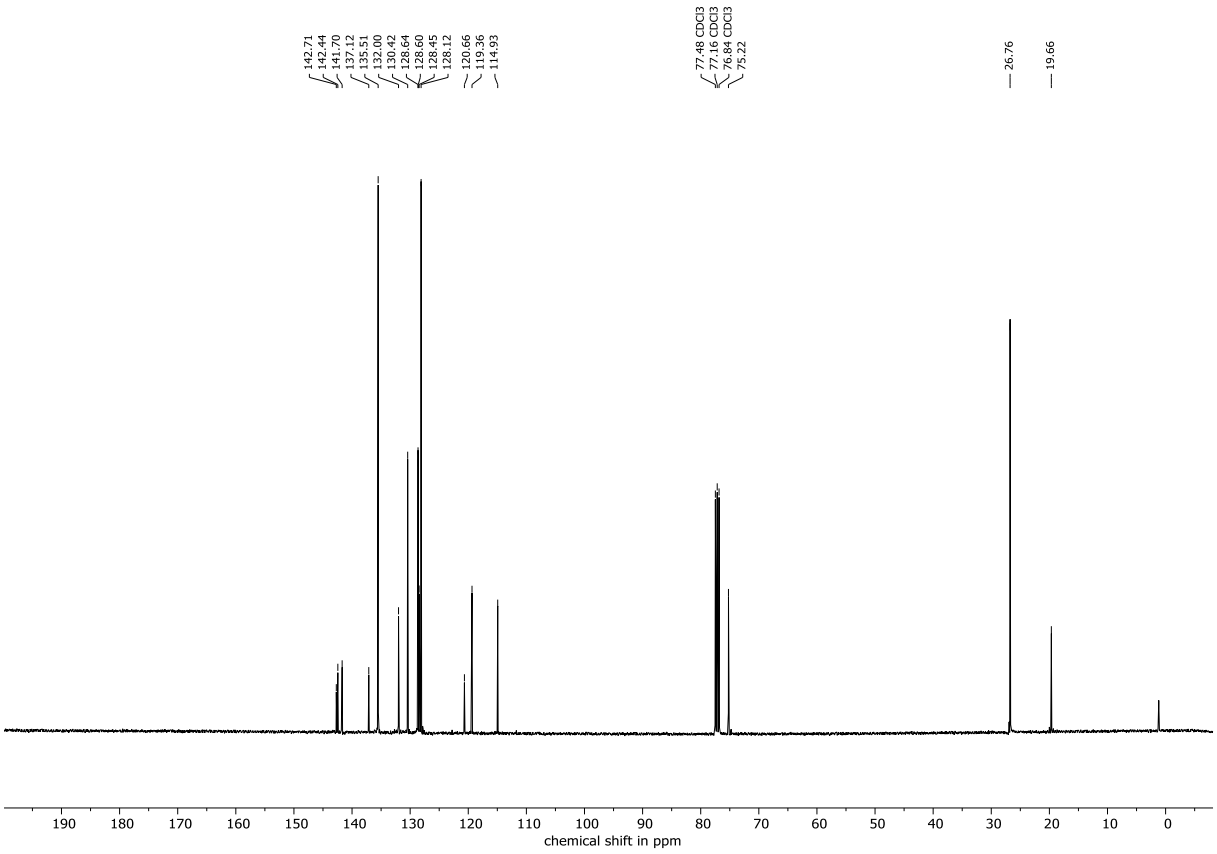
^{13}C NMR (101 MHz, $CDCl_3$) of **252**



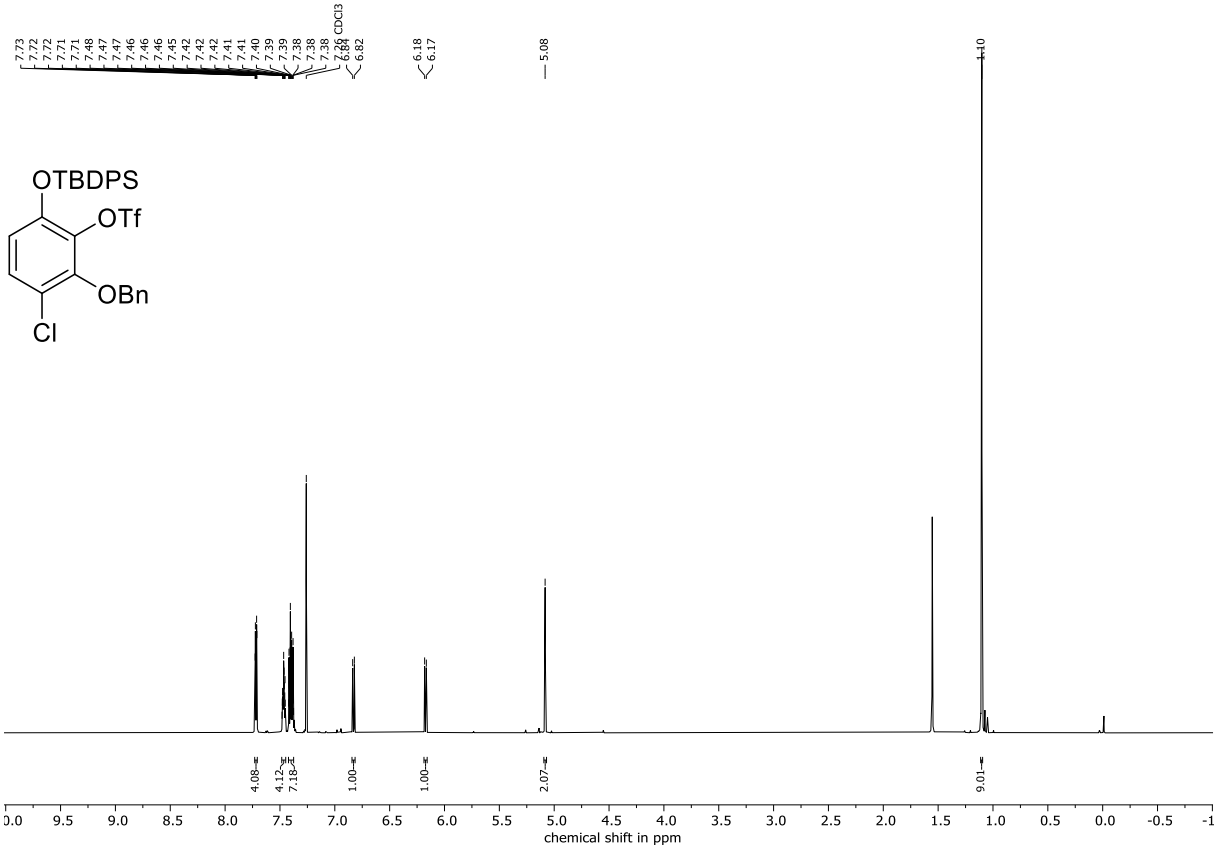
^{1}H NMR (300 MHz, $CDCl_3$) of **253**



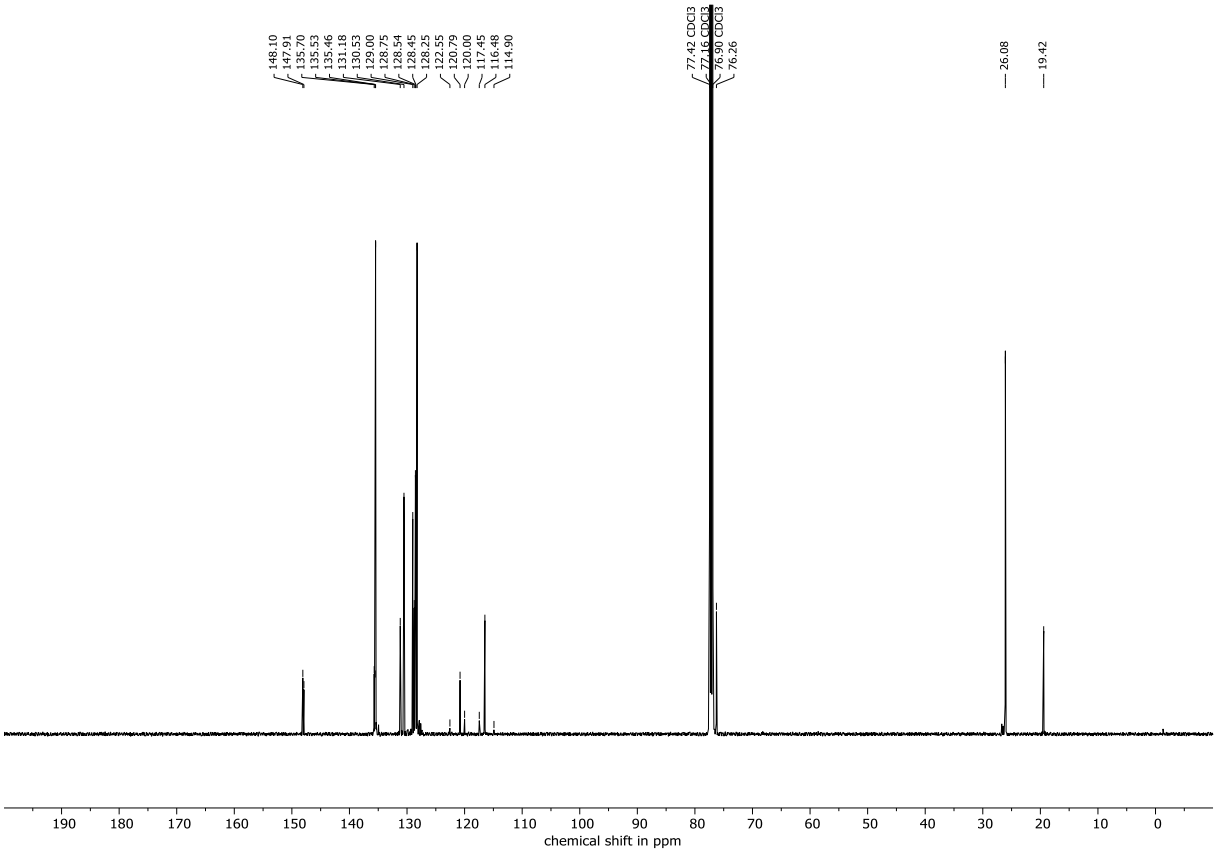
^{13}C NMR (101 MHz, $CDCl_3$) of **253**



^{1}H NMR (600 MHz, $CDCl_3$) of **254**



^{13}C NMR (126 MHz, $CDCl_3$) of **254**



^{19}F NMR (565 MHz, $CDCl_3$) of **254**