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Synthesis of Water-Soluble Phosphite-Ligands for Pd-Catalyzed Tsuji-Trost-Allylations

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Institute of Organic Chemistry

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This master thesis was completed under the supervision of Univ.-Prof. Dipl.-Ing. Dr.rer.nat. Rolf Breinbauer at the Institute of Organic Chemistry at the Faculty of Technical Chemistry, Chemical & Process Engineering and Biotechnology at Graz University of Technology between August 2016 and January 2017.

Meiner Familie

KURZFASSUNG

Proteine sind biologische Makromoleküle von herausragender Bedeutung für das Leben. Deren Funktionstüchtigkeit hängt jedoch nicht ausschließlich von der fehlerlosen Translation von RNA und dem korrekten Falten der Polypeptidkette ab, sondern ist in manchen Fällen an spezielle post-translationale Modifikationen (PTM) geknüpft. Eine mögliche Form von PTM stellt die Prenylierung von Cystein-Resten dar, welche für die biologische Aktivität von bestimmten Proteinen, wie beispielsweise onkongene Ras-Proteine, unabdinglich ist.

Aus diesem Grund wäre eine chemische Methode zur selektiven Prenylierung von Cystein in Peptiden bzw. Proteinen von außerordentlichem Interesse. Obwohl bereits mehrere verschiedene Methoden zur Cystein-Modifizierung bekannt sind, sind diese durch diverse Nachteile in ihrer Anwendbarkeit beschränkt. Dieser Umstand hat zur Entwicklung einer Übergangsmetall-katalysierten Methode für die selektive Prenylierung von Cystein-haltigen Peptiden innerhalb unserer Arbeitsgruppe geführt. Hierbei konnte gezeigt werden, dass die Pd-katalysierte Tsuji-Trost Allylierung bei Verwendung des Bisphosphit-Liganden BIPHEPHOS sowohl eine hohe Selektivität gegenüber Cystein als auch ein hohes *n*/*i*-Verhältnis aufweist.

Ziel dieser Arbeit war die Entwicklung einer Synthese für wasserlösliche BIPHEPHOS-Derivate, welche die Übertragung der Pd-katalysierten, Thiol-selektiven Allylierung ins wässrige Medium erlauben, welches für die Stabilität der meisten Proteine erforderlich ist. Zu diesem Zweck wird eine Syntheseroute vorgestellt, welche die Herstellung von wasserlöslichen Phosphit-Liganden ermöglichen soll. Unter Verwendung dieser Route wurden bisher ein einzähniger, sowie die Vorstufe eines zweizähnigen Phosphit-Liganden hergestellt.

ABSTRACT

Proteins are highly important biomolecules indispensable for life. The proper function of proteins does not only depend on the correct translation of RNA and folding of the polypeptide chain but require special post-translational modifications (PTM) in some cases. Prenylation of cysteine residues is one type of PTM, which was found to be crucial for biological activity of certain proteins, such as oncogenic Ras proteins.

For this reason, a chemical methodology for the site-selective prenylation of cysteine within peptides and proteins would be highly attractive. Although many different protocols for cysteine modification have been reported, they all suffer from certain drawbacks and limitations. This has prompted the development of a transition-metal catalyzed protocol for the selective prenylation of Cys-containing peptides by our research group. It was found that the Pd-catalyzed Tsuji-Trost allylation using the bisphosphite ligand BIPHEPHOS exhibits both high selectivity as well as a high *n*/*i*-ratio of the product.

This thesis was aimed at the development of a synthesis of a water-soluble derivative of BIPHEPHOS that would allow the transfer of the Pd-catalyzed thiol-selective allylation protocol into aqueous medium, which is required for the stability of most proteins. For this purpose, a synthesis route that is anticipated to allow for the preparation of water-soluble phosphite ligands is presented. This is corroborated by the synthesis of a PEGylated monodentate phosphite ligand as well as a precursor of a bidentate phosphite ligand.

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1. INTRODUCTION

Proteins are biomolecules indispensable for life that are part of many biological activities of the cell. Beside their catalytic activities, proteins are also known to regulate gene expression and participate in signal transduction. This class of macromolecules is therefore regarded as the molecular and cellular machinery sustaining life.[1]

Moreover, proteins are the final products of the readout of the genetic code. The directed flow of information is commonly expressed by the central dogma of molecular biology.[2] This concept was first enunciated in 1958 and published in 1970 by Crick (Figure 1).[3] It states that in most organisms the genetic information encoded in the DNA can either be copied to reproduce DNA (DNA replication) or used to produce RNA (transcription), which in turn serves as a template for protein synthesis (translation).[2,3]

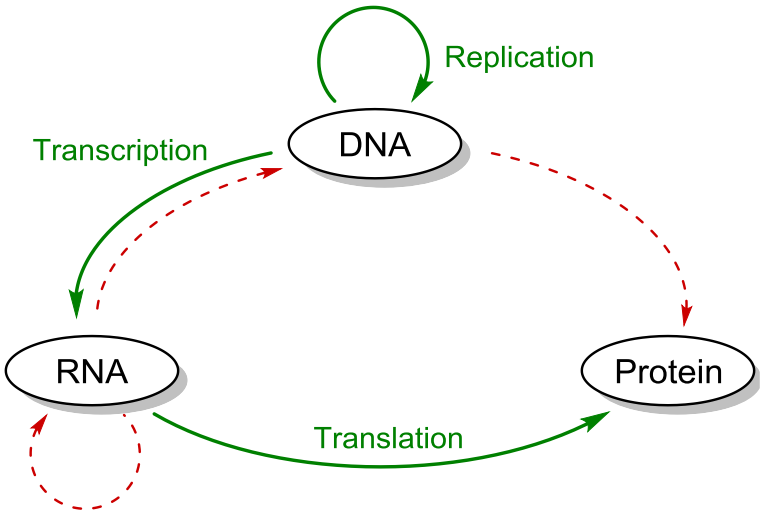


Figure 1. Central dogma of molecular biology. Plain arrows indicate general transfers occurring in nearly all cells, whereas dashed arrows indicate special transfers present in some cells (e.g. certain RNA viruses and plants). Direct transformation from DNA to proteins is unknown but not regarded as impossible.[2,3]

In contrast to the transcription, the translation process from RNA to proteins encompasses a change in 'language' from that of a nucleobase sequence in RNA to that of an amino acid sequence in proteins.[2] In the course of this process, the final product of the information pathway is generated by the covalent linkage of amino acids, generally based on an ubiquitous set of 20 different side chains, in a characteristic linear sequence. The diversity of polypeptidic proteins is thus primarily based on the type and sequence of amino acids

linked by peptide bonds.[4] These polypeptide chains then fold into highly ordered three-dimensional structures in order to minimize the conformational energies, maximize hydrogen-bonding interactions of polar groups and to bury hydrophobic residues in the core of the protein away from the aqueous environment.[1]

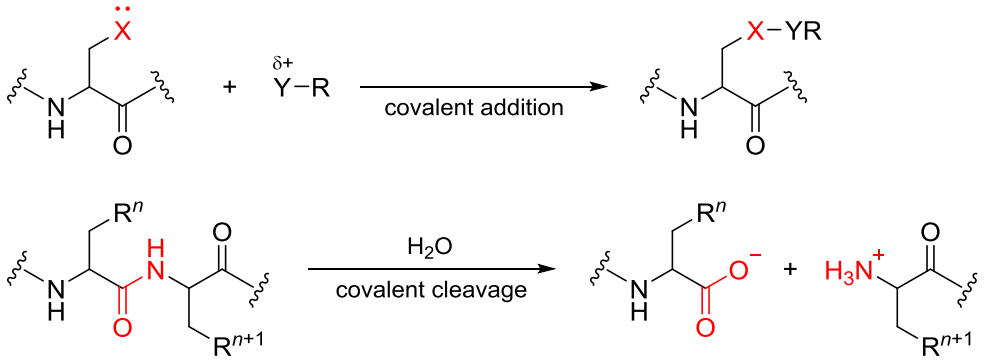
However, some bacterial, archaeal and eukaryotic proteins do not automatically attain their biological active form by folding. These proteins have to undergo further processing subsequent to translation. The corresponding transformations, which are usually omitted by the central dogma of molecular biology, are called post-translational modifications.[4]

2. THEORETICAL BACKGROUND

2.1. Post-Translational Modifications of Proteins

2.1.1. Expanding the Proteome

Post-translational modification (PTM) is the most important diversification strategy beside mRNA splicing to expand the proteome making it two to three orders of magnitude more complex than the encoding genome. PTM subsumes all covalent modifications of nascent or folded proteins that are carried out after DNA transcription and RNA translation. These enzyme-catalyzed transformations are classified, with regard to their site of action, into covalent addition to a side chain residue or covalent cleavage of the backbone.[5]

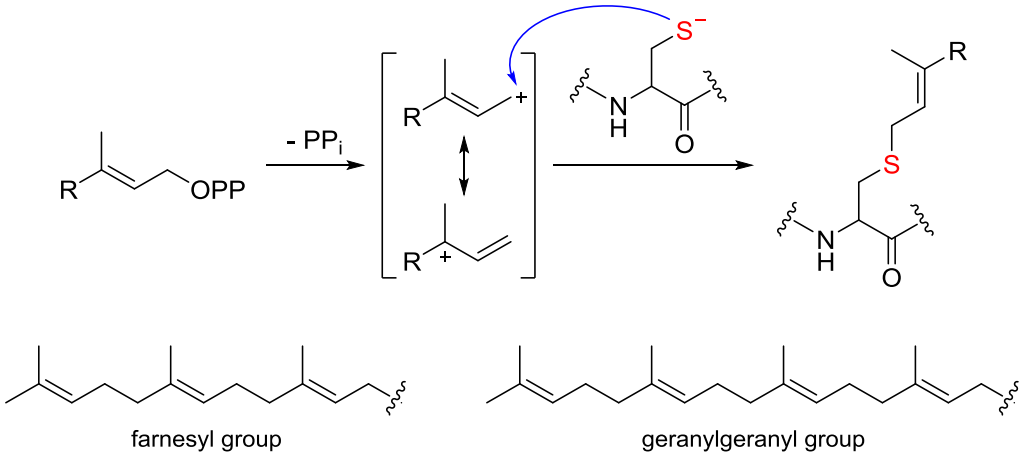


Scheme 1. Types of post-translational modifications with regard to the site of transformation. Covalent addition usually involves the reaction of a nucleophilic amino acid residue with an electrophile, whereas covalent cleavage describes the hydrolysis of a specific peptide bond.[5]

Covalent additions are known for all amino acids except for poorly functionalized residues (Leu, Ile, Val, Ala, Phe) and involve phosphorylation, acylation, alkylation, glycosylation, and oxidation.[5]

2.1.2. Cysteine Prenylation

Aside from methylations the transfer of farnesyl and geranylgeranyl groups to cysteine residues constitute the most relevant class of alkylation reactions among PTM.[5,6] Protein *S*-prenylation is catalyzed by farnesyl transferase (FTase) or geranylgeranyl transferase (GGTase-I/II) using the corresponding isoprenylpyrophosphates as electrophilic alkyl donors (Scheme 2).[5,7]



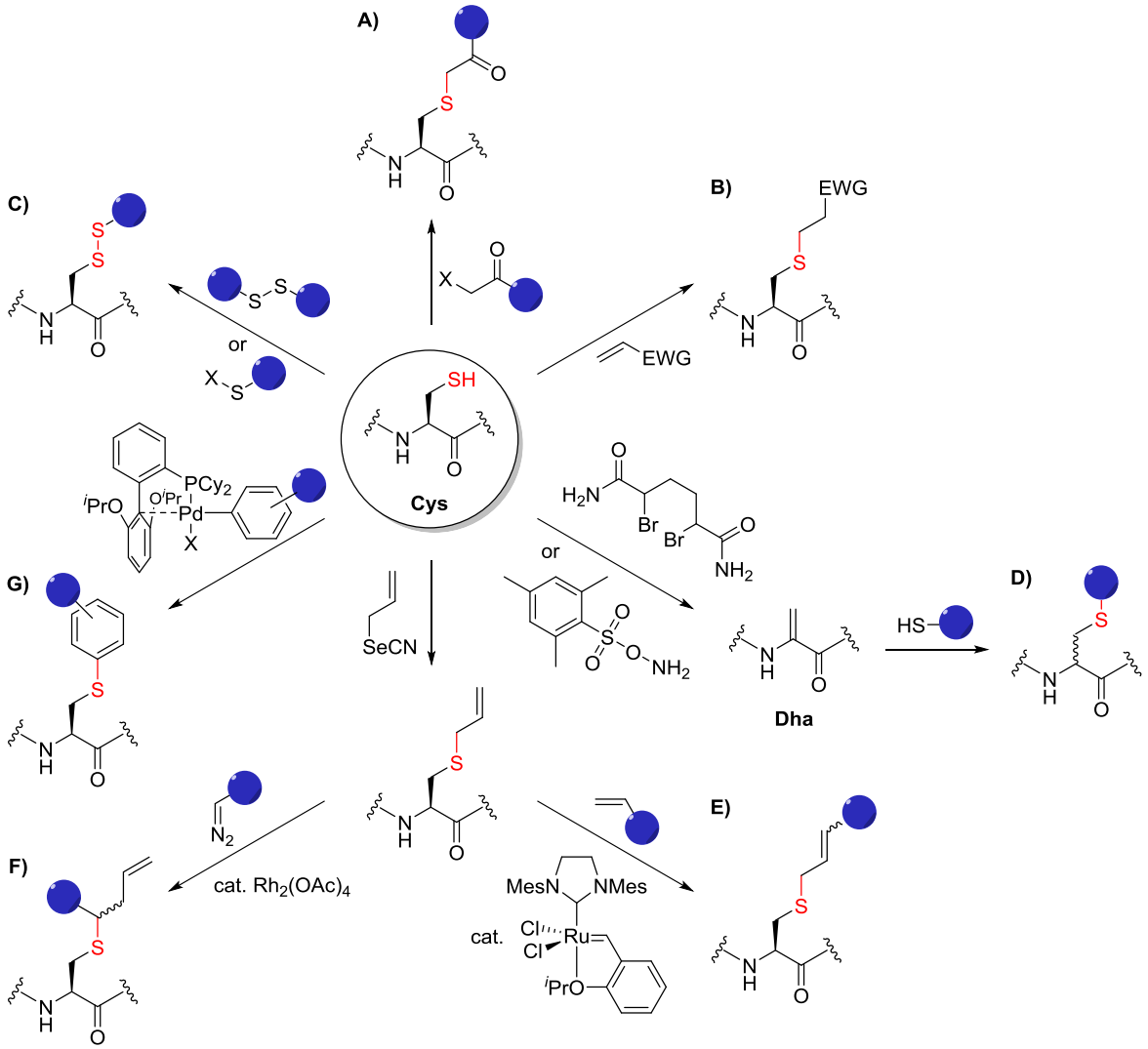
Scheme 2. Mechanism of protein *S*-prenylation.[5]

The site of prenylation is recognized by the transferase due to a characteristic amino acid motif at the *C*-terminus of the protein. FTase and GGTase-I act on proteins that exhibit a *C*-terminal CaaX motif (the so-called 'CaaX-box') consisting of the cysteine to be prenylated (C), two small aliphatic amino acids (aa) and another amino acid (X), which dictates whether a farnesyl or geranylgeranyl group is attached.[8] Afterwards, the aaX tripeptide is released from the prenylated protein and the α-carboxyl group of prenyl cysteine is methylated.[9] GGTase-II in contrast recognizes *C*-terminal CC, CXC or $CCX_{1\text{-}3}$ motifs in Rab proteins resulting in the geranylgeranylation of both cysteine residues.[7,10] Prenylation does not only provide the protein with hydrophobic anchors that allow binding to membranes[9] but is crucial for the proper function of the proteins Ras, Rho/Rac and Rab in cellular processes.[11] The biological significance of prenylation was first highlighted when oncogenic forms of the Ras proteins were shown to require prenylation in order to transform cells.[12,13] Since then extensive research on Ras prenylation has been conducted.[9]

2.2. Chemical Modification of Cysteine within Proteins

Exquisite chemoselectivity is of utmost importance for the successful implementation of a methodology to chemically modify a specific amino acid residue (e.g. cysteine). Among the vast number of competing side chains containing various different nucleophilic and electrophilic functional groups only the desired residue should react. Furthermore, the reaction has to work under mild conditions (in water near neutral pH, moderate temperatures, presence of protein-stabilizing salts and surfactants[14]) to avoid protein denaturation. Finally, a high reaction rate is necessary to ensure full conversion even at low protein concentration.[15]

The proteinogenic amino acid cysteine is an especially attractive target since both its strongly nucleophilic thiol group and the low natural abundance[16] in proteins allow for the introduction of a single or a few modifications. In case of a protein lacking Cys-residues, cysteine can be incorporated with standard site-directed mutagenesis.[15] Therefore, the derivatization of Cys-containing peptides and proteins has been intensively studied, leading to numerous reaction protocols, some of which are highlighted in Scheme 3. Due to the inherent nucleophilicity of cysteine it is not surprising that most methodologies take advantage of this property by treating the Cys-residue with different electrophiles.

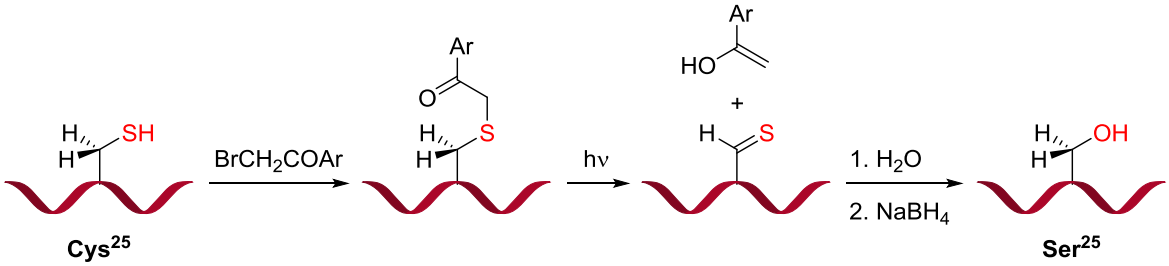


Scheme 3. Overview of methods for the modification of cysteine within peptides and proteins.

2.2.1. α-Halocarbonyl Compounds

α-Halocarbonyl compounds (Scheme 3A) and iodoacetamides in particular represent one of the oldest groups of alkylating agents for cysteine.[15] Iodoacetamide was already employed in 1935 to derivatize and study the Cys-rich protein keratin.[17] The electrophilicity of the reagent can be adapted by using chloroacetamide, which does not

alkylate lysine residues, a common side reaction observed with iodoacetamide.[18] Moreover, larger organic moieties (e.g. carbohydrates) were linked to iodoacetamide, enabling the synthesis of mimics of the natural asparagine-linked glycoproteins.[19] Structurally different α-bromoacetophenones were reported as reagents for the chemical mutation of papain. For this purpose, the formed α-carbonylthioether was photochemically cleaved to formyl glycine as intermediate, which in turn was further converted to either a serine or glycine to complete the mutation (Scheme 4).[20,21]



Scheme 4. Artificial point mutation of Gly^{25} to Ser^{25} of papain using an α-bromoacetophenone (Ar = 2,4-dimethoxyphenyl).[20,21]

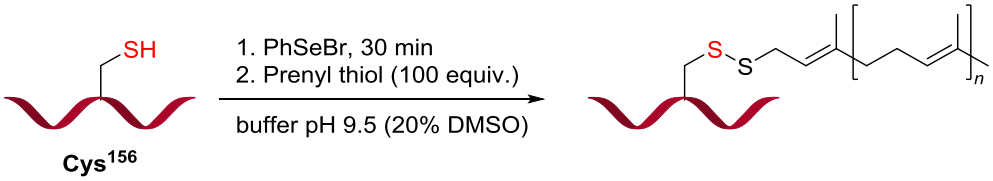
2.2.2. Michael Acceptors

Michael acceptors such as maleimides, vinyl sulfones and other α,β-unsaturated compounds have been proven to be fruitful electrophiles for Cys-residues (Scheme 3B).[15] As early as 1956, bis-maleimides were used to cross-link reactive thiol groups in bovine plasma albumin and wool keratin.[22] More recent examples based on maleimides include the site-selective glycosylation of bovine Hb[23] and the covalent conjugation of a carrier protein to a tumor-specific antibody via a thioether linkage.[24] Similarly, vinyl sulfone handles were used as linkers between proteins.[25] Another driving force in the development of Cys-modification techniques beside the selectivity was the demand for either reversible or irreversible derivatizations. Electron-deficient alkynes (alkynoic amides, esters and alkynones) for the reversible modification of unprotected proteins[26] nicely complement the irreversible attachment of allenamides.[27]

2.2.3. Thiols and Disulfides

In addition to its strong nucleophilicity, cysteine is unique due to its inherent oxidizability responsible for the most common natural Cys-modification – disulfide bridges. While air oxidation of a Cys-containing protein in presence of a thiol usually results in long and unspecific reactions,[15] the corresponding disulfide reagents such as 5,5-dithiobis(2-nitrobenzoate) (DTNB or Ellman's Reagent)[28] or thiopyridyl disulfide have proven

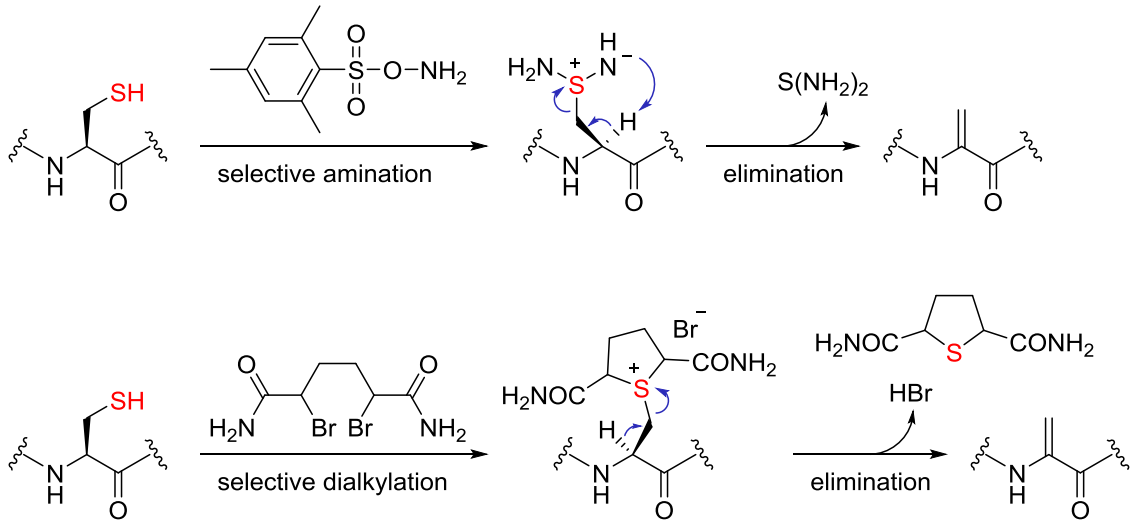
successful (Scheme 3C).[29] Activation of the thiol group by PhSeBr was demonstrated to allow for the prenylation of proteins, closely related to the topic of this thesis. However, drawbacks of this protocol were the poor water-solubility of the hydrophobic prenyl thiols used and the fact that the labile disulfide-linkage between prenyl-chain and protein installed can only mimic the natural post-translational modification involving a thioether-linkage (Scheme 5).[30]



Scheme 5. SeS-mediated prenylation (n = 1, 2) of a mutant (S156C) of subtilisin *Bacillus lentus* (SBL) by the formation of a disulfide linkage.[30]

2.2.4. Desulfurization

A completely different approach is the desulfurization of cysteine to the versatile intermediate dehydroalanine (Dha). This was realized by either oxidative elimination using *O*-mesitylenesulfonylhydroxylamine (MSH)[31] or by a sequential alkylation-elimination sequence using 2,5-dibromohexanediamide (Scheme 6).[32] Starting from the Michael acceptor Dha, various moieties can be attached to the protein by conjugate addition of the corresponding thiol (Scheme 3D). According to this protocol many modifications, including phosphorylation, glycosylation, peptide conjugation and farnesylation, are accessible.[31] A disadvantage of this methodology is that the stereogenic center at Cys is lost during desulfurization and the conjugate addition was found to proceed with low diastereoselectivity.[33,34]

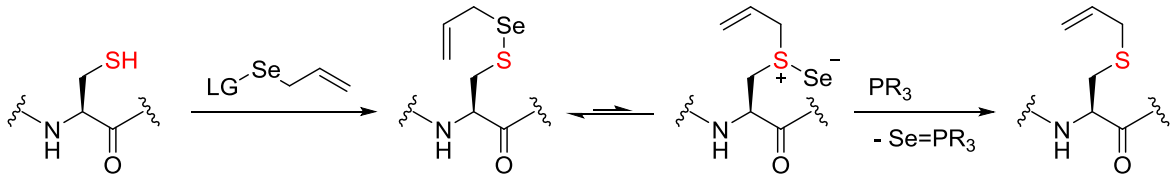


Scheme 6. Mechanisms for the elimination of cysteine to dehydroalanine by MSH (upper sequence) and 2,5-dibromohexanediamide (lower sequence).[32]

2.2.5. Transition Metal-Catalyzed Modifications

Transition metal-catalysts have proven their great utility in numerous examples for small molecule transformations offering excellent chemo-, regio- and stereoselectivity as well as reactivity.[35] It seems therefore consequential to apply these catalysts to the challenges posed by biomolecules.

Two successful examples require the prefunctionalized *S*-allyl cysteine (Sac), which is accessible either by reaction of Dha with allylthiol[36] or directly from cysteine using allyl selenocyanate in order to avoid epimerization (Scheme 7).[37]



Scheme 7. Cys-specific allylation by dechalcogenative rearrangement of allyl selenenylsulfides (LG = CN, SO_3^-, SO_2R).[37,38]

Having installed this handle, protein modifications can be accomplished by means of Ru-catalyzed cross metathesis (Scheme 3E)[36] or Rh-catalyzed Kirmse-Doyle reaction (Scheme 3F).[39] Impressively, Hoveyda-Grubbs second generation catalyst was not only found to withstand the challenging reaction conditions (aqueous medium, potential catalyst-poisoning sulfur(II) donor sites) but exhibited even increased reactivity towards allyl sulfides. Solubility-issues concerning the hydrophobic catalyst as well as the competing self-metathesis of the sterically less demanding alkene might pose some limitations to this method.[36,40] The Kirmse-Doyle strategy employs a rhodium carbenoid derived sulfur ylide, which undergoes a subsequent 2,3-sigmatropic rearrangement to give the peptide conjugate. This reaction, however, is not compatible with tyrosine residues.[39] A recent methodology developed by Buchwald et al. does not require prefunctionalization of the Cys-residue. In this study, benchtop Pd(II)-complexes were identified as valuable reagents for the efficient and highly selective conjugation of cysteine to fluorescent tags, affinity tags, bioconjugation handles and drug molecules (Scheme 3G). The protocol was reported to be also applicable to peptide stapling and antibody-drug conjugation.[41]

2.3. Water-Soluble *P*-Donor Ligands

2.3.1. Phosphine Ligands

The development of water-soluble (phosphine) ligands was mainly driven by the idea to have separate phases for both catalyst/ligand (aqueous) and substrate/product (organic). This allows reactivity across the phase boundaries as long as the biphasic mixture is stirred but upon completion of the reaction when stirring is stopped the two phases separate. Thereby the desired product can be isolated by simple decantation, while the catalyst/ligand remains in the aqueous phase available for immediate re-use (Figure 2).[42,43]

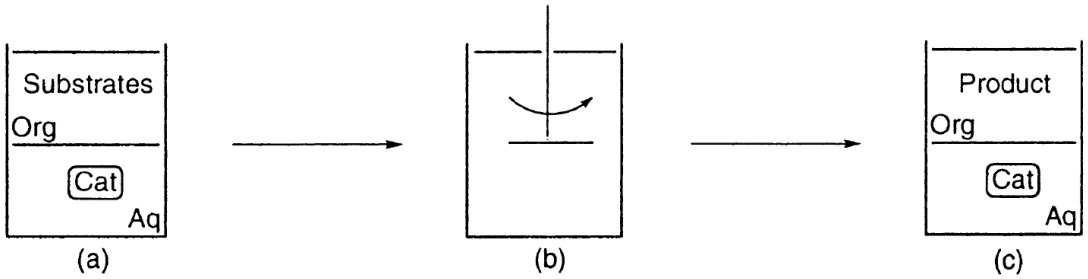


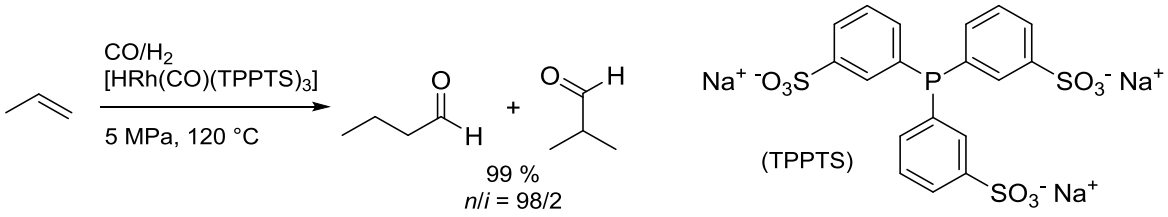
Figure 2. Schematic representation of a biphasic catalytic reaction (Org = organic phase, Aq = aqueous phase, Cat = catalyst) before the reaction (a), during the reaction (b) and after the reaction (c). (Figure taken from Pinault et al.[43])

A great number of water-soluble phosphine ligands bearing various hydrophilic groups and applicable to many different reactions is known today. Therefore, a classification of these ligands according to the hydrophilic groups seems reasonable (Figure 3).[42,43]

anionic groups	cationic groups	neutral groups
$\sim\!\!-SO_3^-$	$\sim\!\!-NR_3^+$	$\sim\!\!-OH$
$\sim\!\!-COO^-$	$\sim\!\!-PR_3^+$	$\sim\!\!-O(CH_2CH_2O)_nR$
$\sim\!\!-PO_3^{2-}$		$\sim\!\!-$carbohydrate

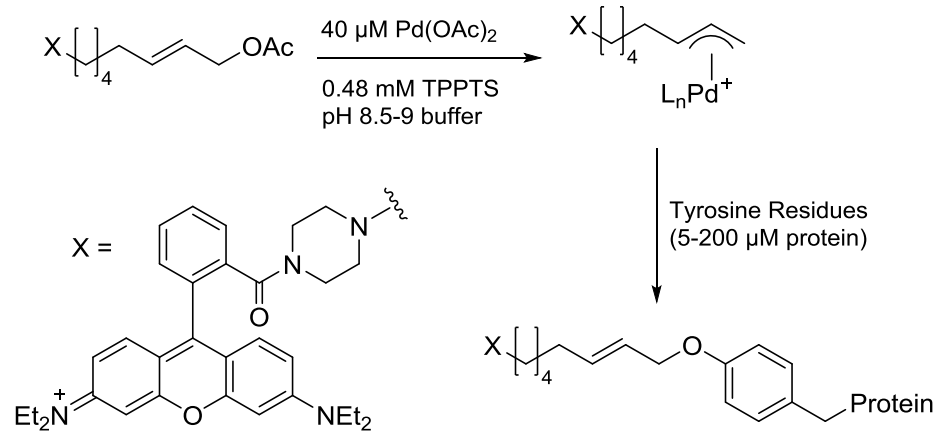
Figure 3. Common hydrophilic groups to increase the water-solubility of phosphine ligands.[42,43]

The most widely used sulfonated phosphine ligands are (3-sulfonatophenyl)-diphenylphosphine (TPPMS) and tris(3-sulfonatophenyl)phosphine (TPPTS).[43] For instance, the highly water-soluble TPPTS is applied in the Ruhrchemie/Rhône-Poulenc process, in which propene is hydroformylated in high yield and *n*/*i*-selectivity (Scheme 8).[44]



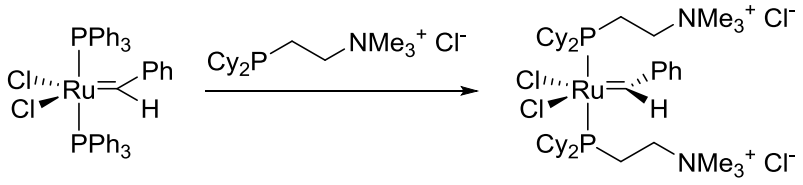
Scheme 8. Hydroformylation of propene (Ruhrchemie/Rhône-Poulenc process).[44]

Another application of TPPTS that is especially inspiring for this work is the site-selective modification of tyrosine residues in proteins using π-allylpalladium complexes (Scheme 9). It was demonstrated that under the selected reaction conditions only tyrosine was alkylated while lysine or cysteine were not.[45]



Scheme 9. Site-selective tyrosine modification with π-allylpalladium complexes.[45]

Grubbs et al. developed water-soluble ruthenium alkylidenes bearing cationically functionalized phosphine ligands (Scheme 10). These catalysts were found to initiate a rapid and quantitative ROMP of various norbornenes and 7-oxanorbornenes in presence of a Brønsted acid in water.[46,47]



Scheme 10. Preparation of a water-soluble ruthenium alkylidene that is able to initiate ROMP of norbornenes and 7-oxanorbornenes in methanol and water.[46,47]

Although only a few ligands are highlighted above, these examples clearly indicate the great potential of water-soluble ligands for a wide variety of catalytic systems.

2.3.2. Phosphite Ligands

Compared to the class of phosphine ligands discussed above, the number of known water-soluble phosphite ligands is much smaller reflecting the insufficient research on this type of compounds. Although phosphite ligands are known to have properties superior to weaker π-accepting phosphines for certain applications,[35] the possible instability of P–OR bonds to hydrolysis might have precluded broader scientific efforts towards water-soluble derivatives, which are still scarce (Figure 4).

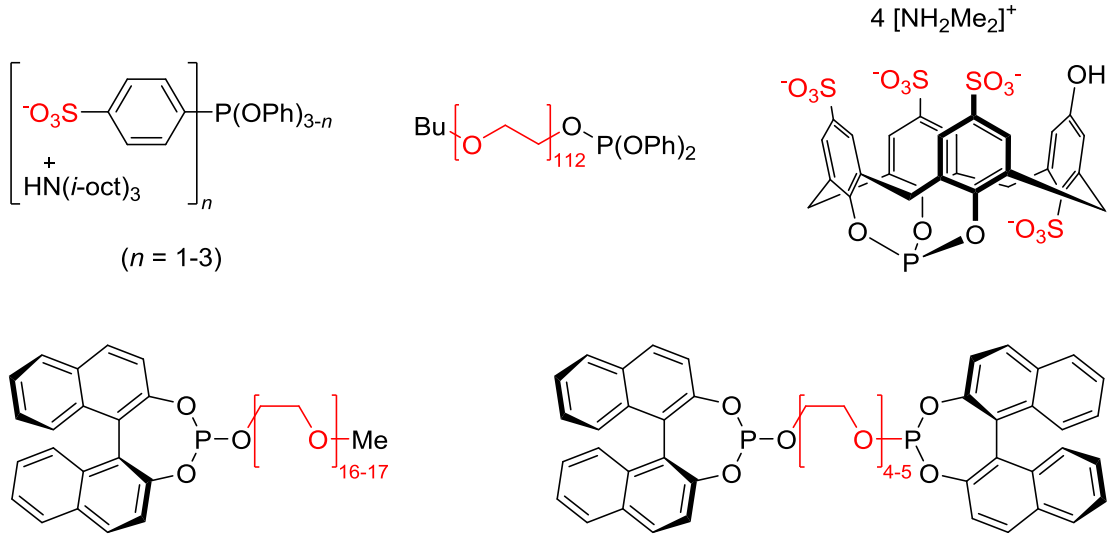


Figure 4. Water-soluble phosphite ligands bearing sulfonate or polyethylene glycol groups.

In an early work by Fell et al. the phenoxy-groups of $P(OPh)_3$ could be substituted by *p*-sulfonated phenols to give a mixture of mono-, di- and trisulfonated triphenylphosphite. The hydrolytic stability of these ligands compared to $P(OPh)_3$ could be significantly enhanced by the use of triisooctylammonium as counterion. Moreover, the *n*/*i*-ratio could be increased compared to $P(OPh)_3$ and PPh_3.[48] Another approach took advantage of a polar but uncharged polyethylene glycol moiety on the phosphite to improve the water-solubility. The resulting ligand $Bu(OCH_2CH_2)_{112}OP(OPh)_2$, however, seemed to be hydrolyzed too fast in order to allow catalysis.[49] Similar ligands accessible from (*S*)-binaphtol and shorter polyether chains, suffering from moderate water-solubility, were reported by Breuzard et al.[50] More recently a water-soluble phosphite containing a sulfonated calix[4]arene-scaffold was developed. Remarkably, the hydrolysis of the free ligand ($t_{1/2}$ = 5 h) could be efficiently suppressed upon coordination to Rh(I) ($t_{1/2} \approx$ 4 months).[51]

Despite their possible hydrolytic lability, the P–OR bonds can also be regarded as strategic advantage since they allow easy ligand synthesis from readily available alcohols and

render the P-atom less sensitive towards oxidation.[52] It is therefore not surprising that many phosphite-based but not water-soluble ligands emerged over the years.[53,54] A popular ligand of particular interest for this work is the bidentate phosphite BIPHEPHOS. In case of the hydroformylation of 1-alkenes this ligand was not only demonstrated to have a good functional group tolerance (ketones, esters, acids, amides, alcohols, nitriles and halides) but to produce the *n*-aldehyde regioselectively over the *i*-aldehyde.[55] Beside the commercial hydroformylation of simple alkenes,[56] this ligand was also employed in the synthesis of natural products.[57]

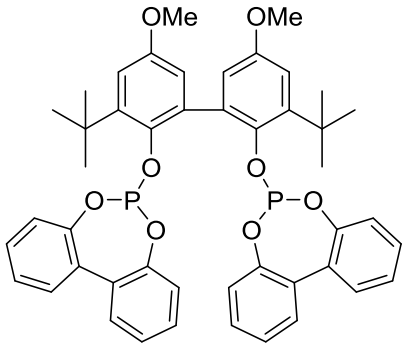
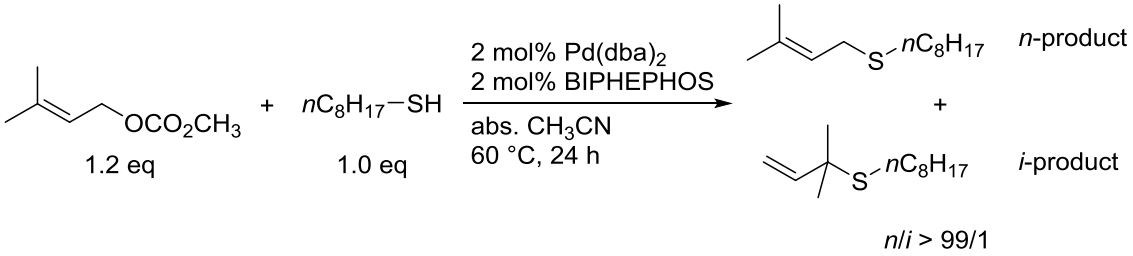


Figure 5. Structure of the bidentate phosphite ligand BIPHEPHOS.

The excellent *n*/*i*-selectivity of BIPHEPHOS, however, is not restricted to hydroformylation of alkenes, but was also observed in the Pd-catalyzed Tsuji-Trost allylation of thiols, which has been established by H. Schröder in our lab (Scheme 11).[58]



Scheme 11. Pd-catalyzed Tsuji-Trost allylation of octane-1-thiol using BIPHEPHOS as ligand.[58]

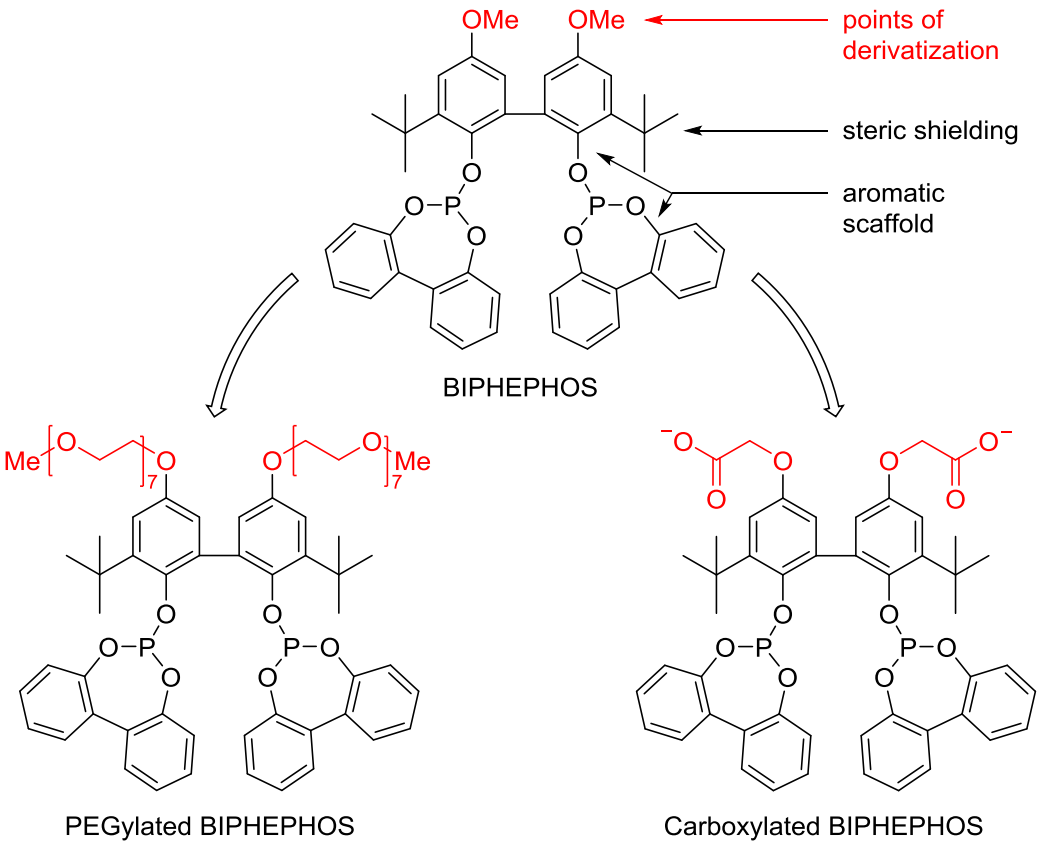
In addition, this catalyst system was shown to be selective for thiol groups in the allylation of peptides demonstrated by the farnesylation of a 32 aa peptide exclusively at the position of cysteine.[58,59]

3. AIMS OF THE THESIS

The ultimate goal of this research was the synthesis of a water-soluble derivative of the bidentate phosphite ligand BIPHEPHOS, which is expected to allow for the transfer of a Pd-catalyzed thiol-selective allylation protocol developed in our research group[58,59] into aqueous medium. If successful, this would enable the implementation of a new methodology to modify peptides and proteins selectively at cysteine. Although numerous different methods have been reported so far,[15,60–63] many of these suffer from drawbacks limiting their applicability. Therefore, a new protocol based on *S*-allylation would not only expand the tool box for cysteine modifications but is anticipated to be the first method for the site-selective prenylation of peptides and proteins at cysteine as an artificial post-translational modification.

In addition, with regard to the few examples of water-soluble phosphite ligands reported in literature,[48–51] a new compound of this type might be applicable also to other reactions such as hydroformylation, for which the utility of BIPHEPHOS has already been recognized.[55,57]

The challenge in designing a water-soluble phosphite ligand for the Pd-catalyzed Tsuji-Trost-allylation of cystein-containing peptides is not only to increase the solubility of the lead compound BIPHEPHOS but also to preserve its inherent activity and selectivity. For this purpose, the structural modifications related to the introduction of polar functional groups should be as minor as possible, which implicated that the preservation of the aromatic scaffold including the rigid bridging part and the two dibenzo[*d*,*f*][1,3,2]-dioxaphosphepin moieties in its entirety seemed expedient with regard to the denticity and bite angle of the ligand. Furthermore, *tert*-butyl groups, although hydrophobic, might be crucial for the steric demand of the ligand, which could be the reason for high *n*/*i*-ratios. Therefore, the methoxy substituents were regarded as the ideal points for the formal derivatization of BIPHEPHOS. Eventually, the polar groups should be attached to the aromatic ring via an ether bond to prevent any changes in the electronic properties of the ligand (Scheme 12).



Scheme 12. Strategies pursued in this work to enhance the water-solubility of BIPHEPHOS.

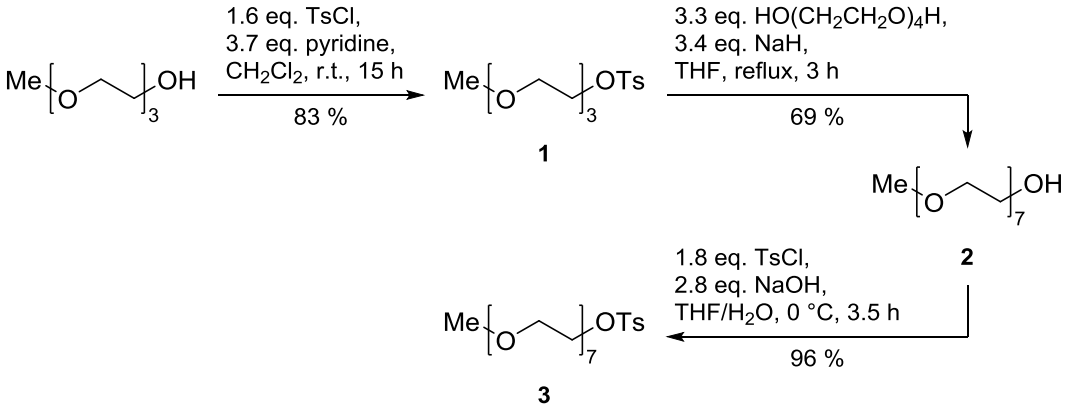
The first approach of this work involves the attachment of heptaethylene glycol side chains to the core fragment since this type of neutral yet polar polyether groups are reported to enhance the water-solubility of metal complexes.[47] On the other hand, the introduction of ionic carboxylate groups was considered as an alternative strategy.

4. RESULTS AND DISCUSSION

4.1. PEGylated BIPHEPHOS

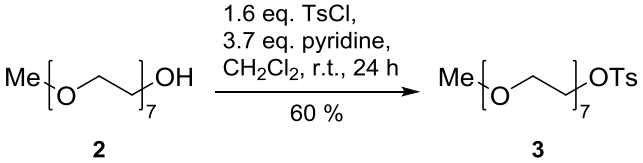
4.1.1. Synthesis of the Heptaethylene Glycol Side Chain

Since oligoethylene glycol monomethyl ethers of the type $Me(OCH_2CH_2)_nOH$ are not commercially available with discrete chain lengths for $n > 4$, the desired side chain precursor (**3**) had to be prepared starting from triethylene glycol monomethyl ether. Fortunately, the ethylene glycol chain could be readily extended via a successive tosylation and etherification protocol (Scheme 13) according to Dong et al.[64]



Scheme 13. Synthesis of heptaethylene glycol monomethyl ether (**3**) via successive tosylation and etherification steps.

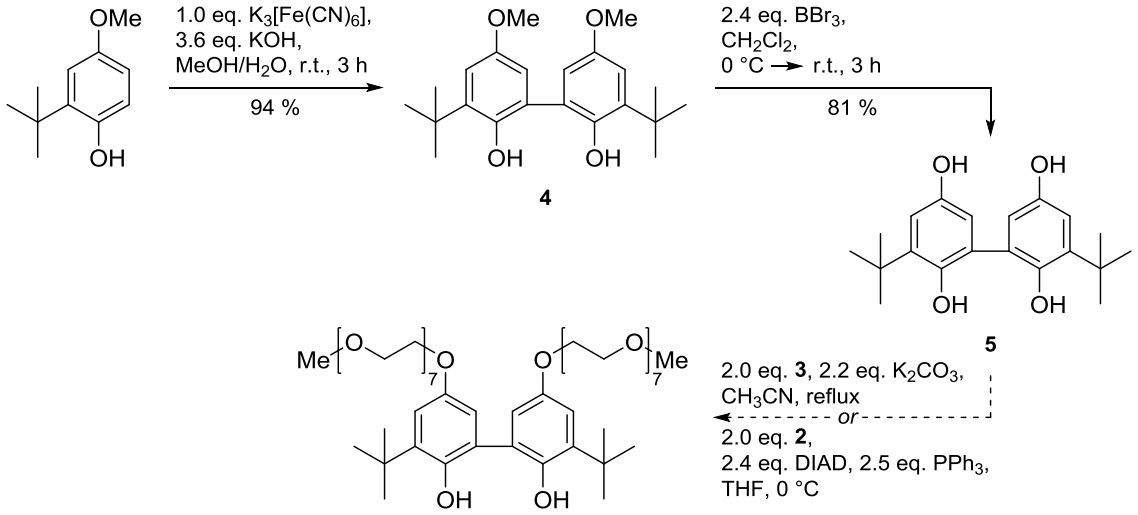
Starting from commercially available triethylene glycol monomethyl ether, tosylation using TsCl and pyridine in CH_2Cl_2 afforded **1** in 83 % yield. Treatment of tosylate **1** with an excess of tetraethylene glycol and NaH[64] provided the elongated compound **2** in 69 % yield. Subsequent tosylation by an aqueous protocol[65,66] gave the desired side chain precursor **3** in excellent 96 % yield. It is noteworthy that this protocol did not require chromatographic purification and exhibited improved yields compared to the classic procedure involving pyridine (Scheme 14).



Scheme 14. Tosylation of **2** following the classic TsCl/pyridine-protocol.

4.1.2. Etherification

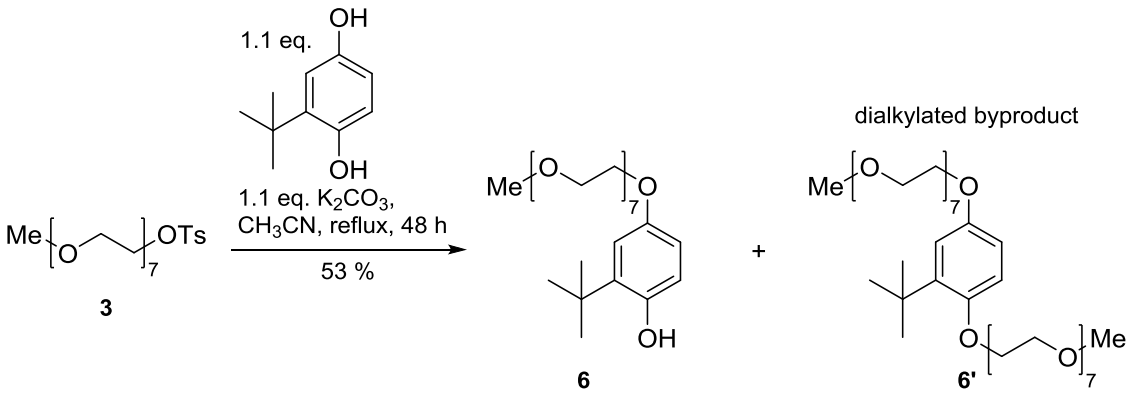
Having the tosylated heptaethylene glycol monomethyl ether (**3**) in hand, the focus shifted towards the attachment of the polar side chains to the aromatic core structure. First attempts were aimed at the dialkylation of tetraol **5**, which is accessible in two steps from 3-*tert*-butyl-4-hydroxyanisole (Scheme 15).



Scheme 15. Synthesis of tetraol **5** and unsuccessful etherification attempts thereof.

Following literature procedures,[67,68] 3-*tert*-butyl-4-hydroxyanisole could be oxidatively dimerized using $K_3[Fe(CN)_6]$ to biphenol **4** in excellent yield, which was then subjected to aryl ether cleavage by BBr_3. The tetraol **5** prepared in this manner was intended to be dialkylated at positions 5 and 5', which should be sterically less shielded by the *tert*-butyl groups and hence more reactive. For this purpose, **5** was treated with tosylate **3** in presence of K_2CO_3 (Williamson ether synthesis), but this led to a complex mixture as indicated by TLC and HPLC-MS. In the case of Mitsunobu conditions using heptaethylene glycol monomethyl ether (**2**) no product could be detected by HPLC-MS.

Therefore, it was decided to introduce the polyether side chain before the oxidative dimerization step. After a short reaction screening in which different bases (K_2CO_3, Cs_2CO_3, KO*t*Bu) and solvents (CH_3CN, DMF, THF) were tested, the best reaction conditions were found to be heating tosylate **3** and *tert*-butylhydroquinone under reflux in presence of K_2CO_3 in CH_3CN affording the desired monoalkylated product **6** in satisfying 53 % yield (Scheme 16). The relatively low yield was attributed to selectivity issues giving rise to the formation of the dialkylated byproduct **6'**, which was isolated and characterized in 33 % yield (corresponding to a molar ratio of **6**:**6'** ≈ 3:1). Nevertheless, **6** could be readily purified and was subjected to subsequent reaction steps.



Scheme 16. PEGylation of *tert*-butylhydroquinone via Williamson ether synthesis.

Although alkylation adjacent to the bulky *tert*-butyl group appeared highly unlikely, the formation of the desired isomer was confirmed by NOE-experiments (Figure 6). Upon irradiation of the terminal CH_2-group (4.07 ppm), a NOE was observed for two separate aromatic protons, one of which in turn exhibits a NOE to the *tert*-butyl group. Therefore, the isomeric structure can be excluded since NOEs from the terminal CH_2-group to one aromatic proton and the *tert*-butyl group should be recorded in this case.

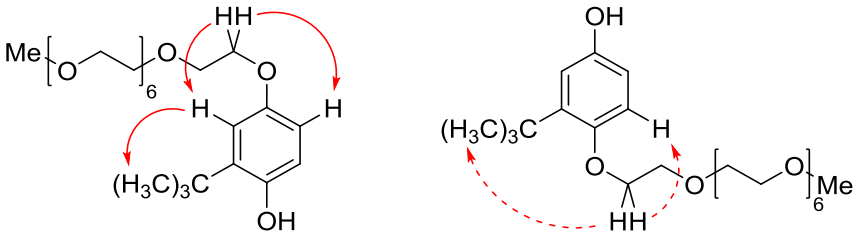
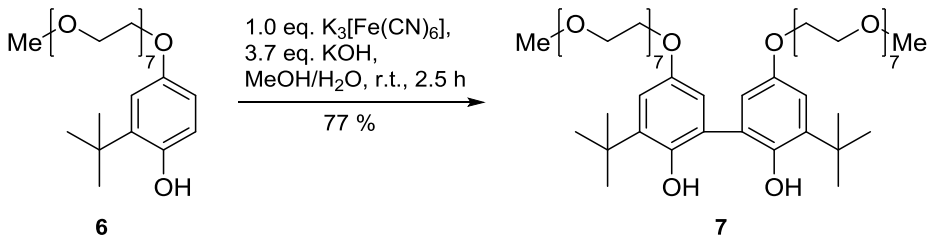


Figure 6. Confirmation of the position of alkylation by NOE-experiments (plain arrows indicate observed NOEs, dashed arrows indicate expected NOEs for the isomeric compound).

4.1.3. Oxidative Dimerization

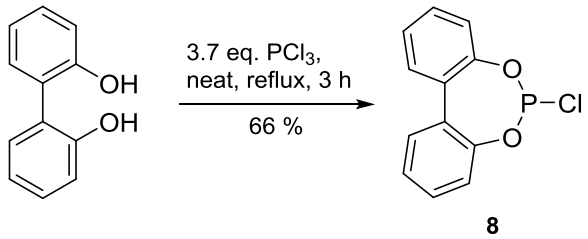
The next step in the synthesis of the PEGylated BIPHEPHOS is the oxidative dimerization to give the characteristic biphenol-bridging unit. This oxidation using $K_3[Fe(CN)_6]$ was reported for 3-*tert*-butyl-4-hydroxyanisole by van der Vlugt et al.[67] and could be also applied to the PEGylated compound **6** to afford biphenol **7** in 77 % yield (Scheme 17).



Scheme 17. Oxidative dimerization of PEGylated *tert*-butylhydroquinone **6**.

4.1.4. Phosphite Synthesis

The preparation of the phosphite, the final step in the synthesis, turned out to be the most challenging of all steps. The standard procedure for phosphite synthesis, which has also been used in the synthesis of BIPHEPHOS,[69,70] involves the reaction of a chlorophosphite with an alcohol in the presence of a base (typically triethylamine). For this purpose, the chlorophosphite **8** was prepared from 2,2'-biphenol and phosphorus trichloride (Scheme 18).[69,70]



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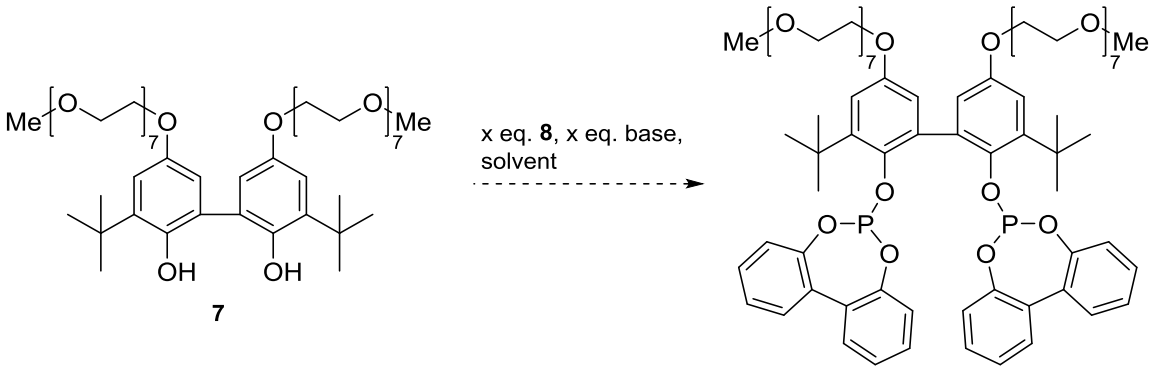
Scheme 18. Preparation of 6-chlorodibenzo[*d*,*f*][1,3,2]dioxaphosphepin (**8**).

Although 6-chlorodibenzo[*d*,*f*][1,3,2]dioxaphosphepin (**8**) is highly moisture sensitive, it can be purified by vacuum distillation and conveniently stored in the glove box at room temperature for months.

Having this reagent in hand, the desired PEGylated BIPHEPHOS was anticipated to be readily available by the reaction of biphenol **7** with chlorophosphite **8**. Unfortunately, this reaction was unsuccessful, which made a screening of several reaction parameters necessary (Table 1). Standard conditions starting from -30 °C or -40 °C followed by slow warming to room temperature did not give any conversion (entries 1 and 2). Further heating to reflux, however, led to decomposition of the starting material as indicated by ^{1}H-NMR spectroscopy (entry 2). It was then considered to use stronger bases (NaH or DBU) in order to deprotonate **7** efficiently, but again no conversion was detected (entries 3 and 4). The application of triethylamine in presence of DMAP in THF starting at 0 °C was also not able to enhance the conversion (entry 5). Eventually, to exclude any water from the reaction mixture, the reaction was performed in toluene in presence of pre-activated 4 Å molecular sieves (entries 6 and 7). In case of an initial temperature of -40 °C a complex mixture according to HPLC-MS was obtained.

Table 1. Screening of reaction conditions for the synthesis of PEGylated BIPHEPHOS.



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Entry	8	Base[b]	Solvent[c]	Temp.	Reaction monitoring
1	2.1 eq.	8.2 eq. NEt_3	toluene	-30 °C → r.t.	no conv. (TLC)
2	2.0 eq.	8.2 eq. NEt_3	toluene	-40 °C → r.t. → reflux	no conv. (TLC) decomp. (^{1}H-NMR)
3	2.2 eq.	2.2 eq. NaH	toluene	-40 °C → r.t.	no conv. (TLC)
4	2.2 eq.	4.0 eq. DBU	toluene	-40 °C → r.t.	no conv. (TLC)
5	2.1 eq.	8.5 eq. NEt_3 + 0.2 eq. DMAP	THF	0 °C → r.t → reflux	no conv. (TLC) no conv. (HPLC)
6[a]	2.0 eq.	8.0 eq. NEt_3	toluene	-40 °C → r.t	complex mixture (HPLC)
7[a]	2.4 eq.	8.1 eq. NEt_3	toluene	0 °C → r.t	full conv. (HPLC)

[a] Addition of freshly-activated 4 Å molecular sieves. [b] Anhydrous NEt_3 was used. [c] Anhydrous solvents were used.

If the reaction was carried out starting from 0 °C full conversion accompanied by the formation of three major peaks according to HPLC-MS was achieved. Since no product mass could be detected by HPLC-MS, the reaction mixture was subjected to aqueous work up and a ^{31}P-NMR spectrum of the crude product was recorded (Figure 7).

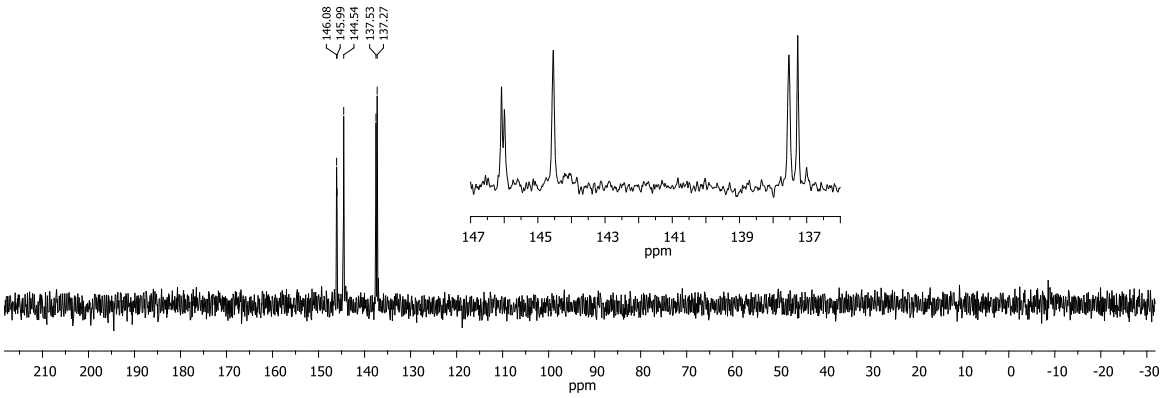
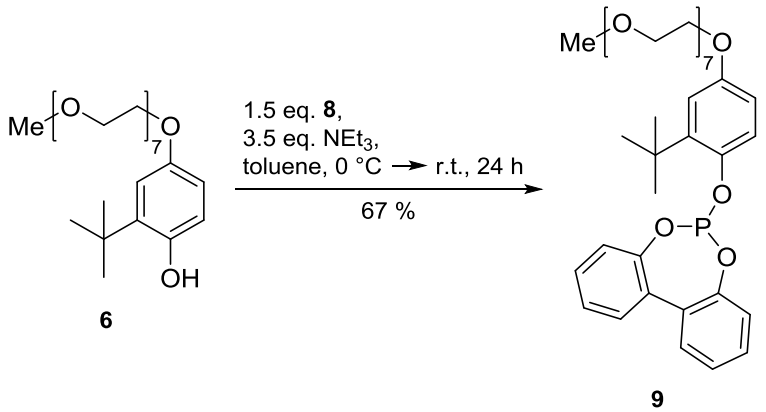


Figure 7. ^{31}P-NMR spectrum (121.42 MHz, CD_3CN) of the crude phosphite-product.

Although no pure product was obtained, the ^{31}P-NMR spectrum clearly indicates the formation of a phosphite giving rise to the signals between + 137 ppm and + 146 ppm.[71] Importantly, no hydrolysis products, which would cause ^{31}P-NMR signals around 0 ppm,[71] were formed. The partial success of the phosphite synthesis is corroborated by the ^{1}H-NMR spectrum showing signals of both the polyether side chains as well as the biphenyl-groups from **8**. Nevertheless, further efforts to find proper reaction conditions favoring a single product have to be made.

4.2. Monodentate PEGylated Phosphite Ligand

In order to demonstrate that the chosen reaction conditions are in principle suitable for the synthesis of a PEGylated phosphite, the undimerized phenol **6** was reacted with chlorophosphite **8** in toluene in presence of triethylamine at an initial temperature of 0 °C without the application of molecular sieves (Scheme 19).



Scheme 19. Synthesis of monodentate PEGylated phosphite **9**.

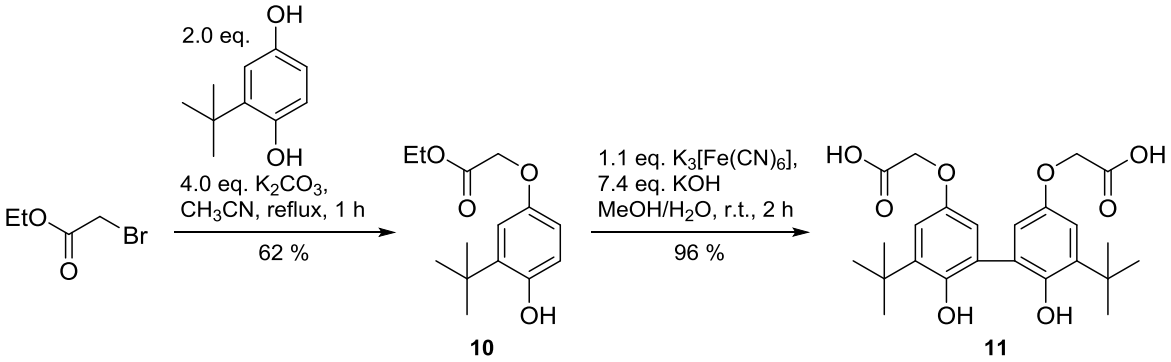
Interestingly, this reaction smoothly afforded the expected PEGylated phosphite **9** in rather good yield of 67 %, indicating that appropriate reaction conditions, even in the presence of

polyether side chains, were applied. Moreover, the monodentate ligand **9** was easily purified by flash column chromatography demonstrating its stability on silica gel.

4.3. Carboxylated BIPHEPHOS

4.3.1. Carboxylated Biphenol Precursor

Due to unexpected problems in the synthesis of the PEGylated phosphite (Chapter 4.1.4.), a second approach independent of polyether groups was pursued. For this purpose, ionic carboxylate groups were considered to enhance the water-solubility. Minor adaptions of the synthetic route used in the synthesis of PEGylated biphenol **7**, allowed the preparation of its derivative **11** bearing glycolate group instead of the PEG-chain (Scheme 20).



Scheme 20. Synthesis of the carboxylated biphenol **11**.

Starting from ethyl bromoacetate the monoalkylated *tert*-butyl hydroquinone **10** was prepared in 62 % yield. The moderate yield might be again attributed to the formation of dialkylated side product as suggested by GC-MS. The formation of the desired isomer was confirmed by HMBC, exhibiting couplings from the phenolic proton to a tertiary, aromatic carbon atom and two quaternary, aromatic carbon atoms, one of which is in turn clearly assigned to be adjacent to the *tert*-butyl group. The isomeric compound, however, should show couplings from the phenolic proton to two tertiary and one quaternary, aromatic carbon atoms (Figure 8).

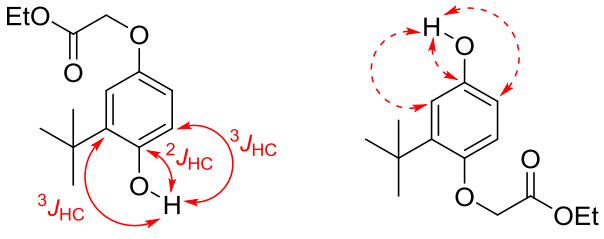


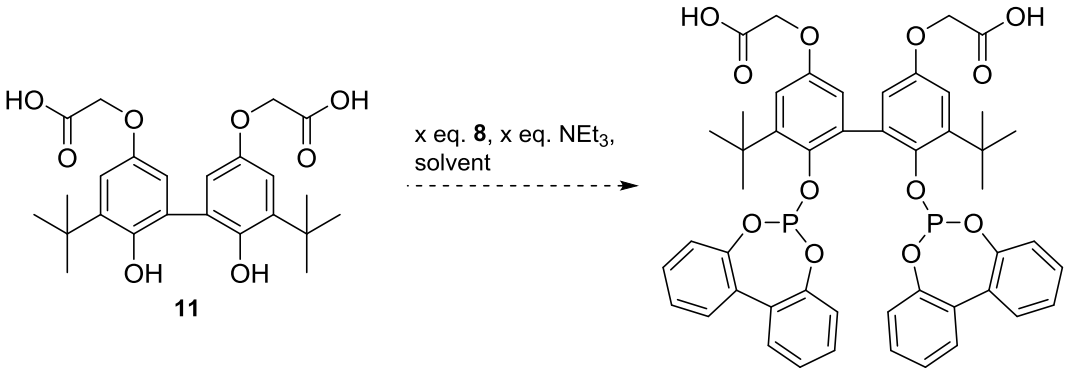
Figure 8. Confirmation of the position of alkylation by HMBC-experiments (plain arrows indicate observed HMBC-couplings, dashed arrows indicate expected HMBC-couplings for the isomeric compound).

Subsequently, compound **10** was oxidatively dimerized with $K_3[Fe(CN)_6]$ in alkaline solution, similar to a procedure from van der Vlugt et al.,[67] affording the saponified product **11** in excellent 96 % yield. Together with compounds **4** and **7**, this reaction demonstrates the high tolerance of ether substituents at positions 5 and 5' of this oxidation protocol, inviting for the introduction of other functional groups.

4.3.2. Phosphite Synthesis

The focus of synthetic efforts then shifted towards the conversion of **11** to the corresponding bisphosphite ligand. Having the troublesome synthesis of PEGylated BIPHEPHOS in mind, different reaction conditions were tested (Table 2).

Table 2. Screening of reaction conditions for the synthesis of carboxylated BIPHEPHOS.

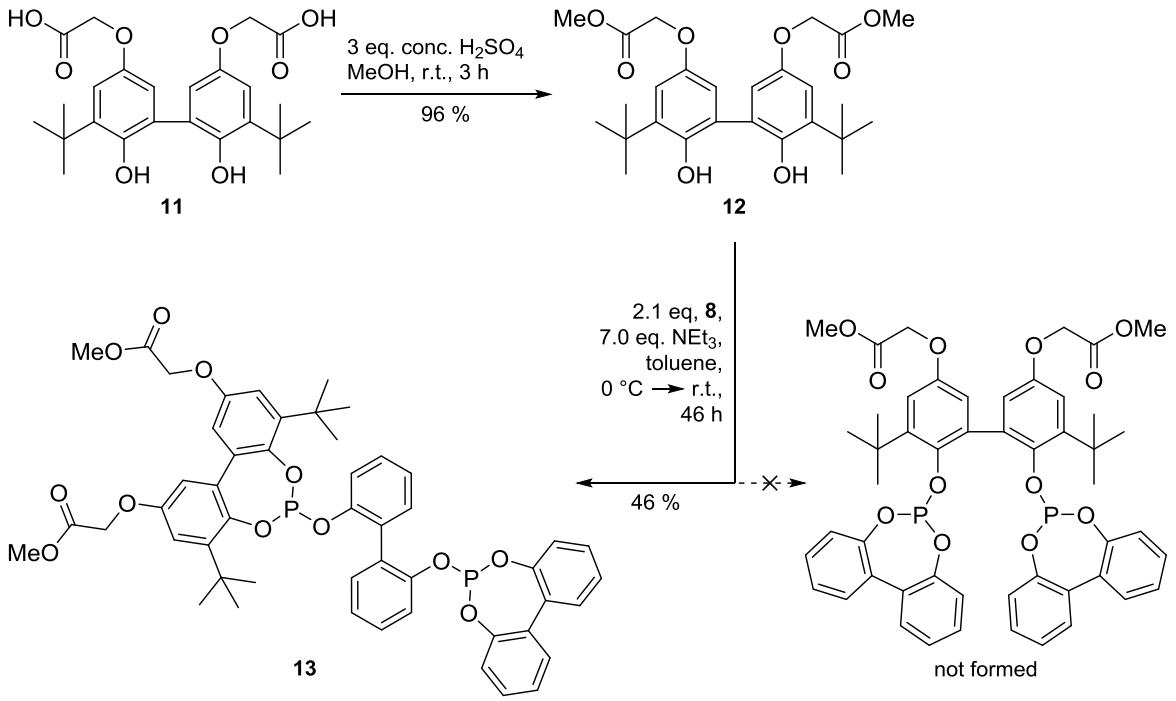


Entry	8	NEt_3[b]	Solvent[c]	Temp.	Reaction monitoring
1	2.1 eq.	6.2 eq.	THF	0 °C → r.t.	no conv. (HPLC)
2	3.2 eq.	7.9 eq.	toluene/THF (2/1)	-40 °C → r.t.	mixture (HPLC)
3	3.4 eq.	8.1 eq.	toluene	-40 °C → r.t.	no conv. (TLC)
4[a]	2.5 eq.	6.6 eq.	THF	0 °C → r.t.	mixture (HPLC)

[a] Addition of freshly-activated 4 Å molecular sieves. [b] Anhydrous NEt_3 was used. [c] Anhydrous solvents were used.

Depending on the solvent and reaction temperature either no conversion at all (entries 1 and 3) or a mixture of various products (entries 2 and 4) was obtained, but no product mass could be observed via HPLC-MS. Although the formation of a phosphite in presence of a carboxylic acid group is reported in the literature,[72] it was then considered to protect these in form of their methyl ester. This was accomplished by stirring diacid **11** in methanol in

presence of conc. H_2SO_4 at room temperature in almost quantitative yield (Scheme 21). The methyl ester protected compound **12** was then subjected to phosphorylation using classic conditions (treatment with chlorophosphite **8** and triethylamine in toluene). Reaction monitoring by HPLC-MS indicated the formation of a single product, which was isolated by aqueous work up and purified via flash column chromatography.



Scheme 21. Esterification of diacid **11** and subsequent phosphite synthesis with unexpected ring interconversion.

Surprisingly, the NMR spectra of the isolated product were contradictory to the structure of the intended BIPHEPHOS-like product. This discrepancy was especially pronounced in the ^{31}P-NMR spectrum (Figure 9) exhibiting two doublets instead of a single singlet usually observed in this kind of products.

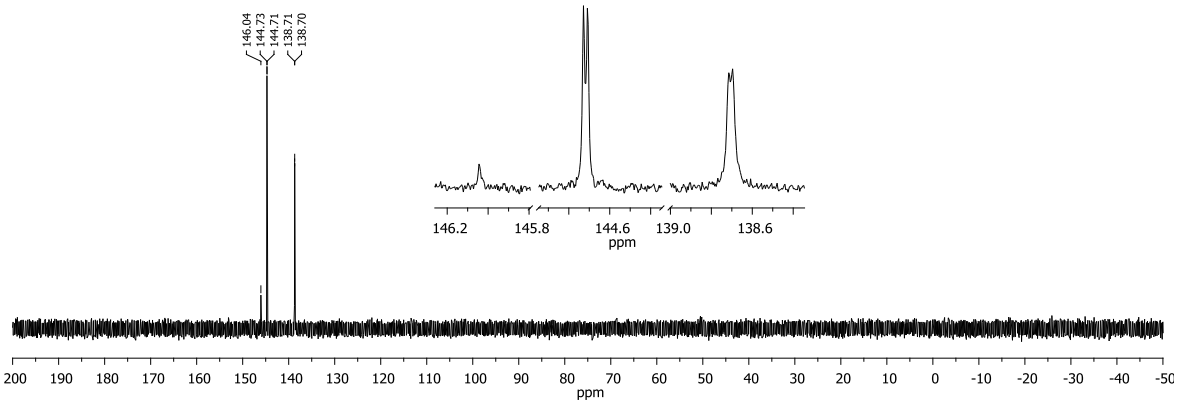


Figure 9. ^{31}P-NMR spectrum (202.35 MHz, C_6D_6) of compound **13**.

The two major signals at +138.7 ppm and +144.7 ppm have an integral ratio of 1.0:1.0 and furthermore, couple with each other (J_{PP} = 4.0 Hz) as confirmed by $^{31}P,^{31}P$-COSY. Further analysis by $^{1}H,^{1}H$-COSY and HSQC revealed three independent aromatic spin-systems of the type d–t–t–d in a ratio of 4H:4H:8H for the two biphenol moieties (Figure 10). This is in disagreement with the expectation of two d–t–t–d biphenol-spin-systems in a ratio of 8H:8H for a BIPHEPHOS-like product.

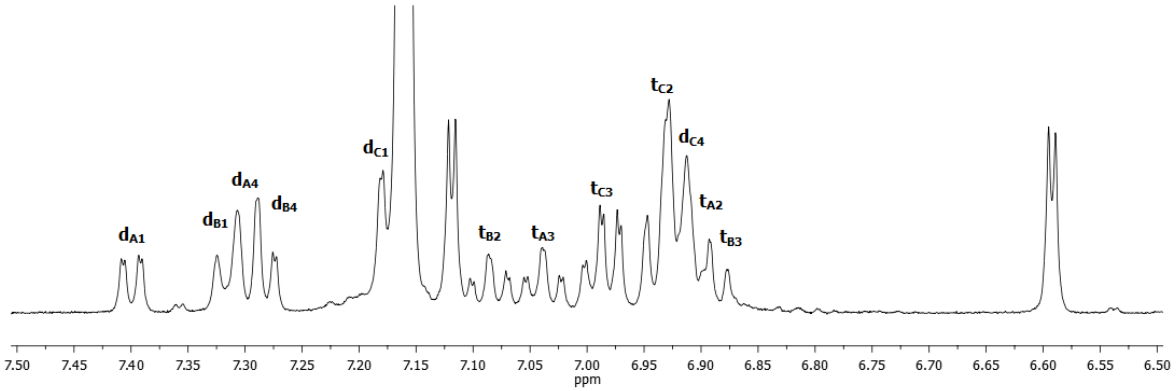
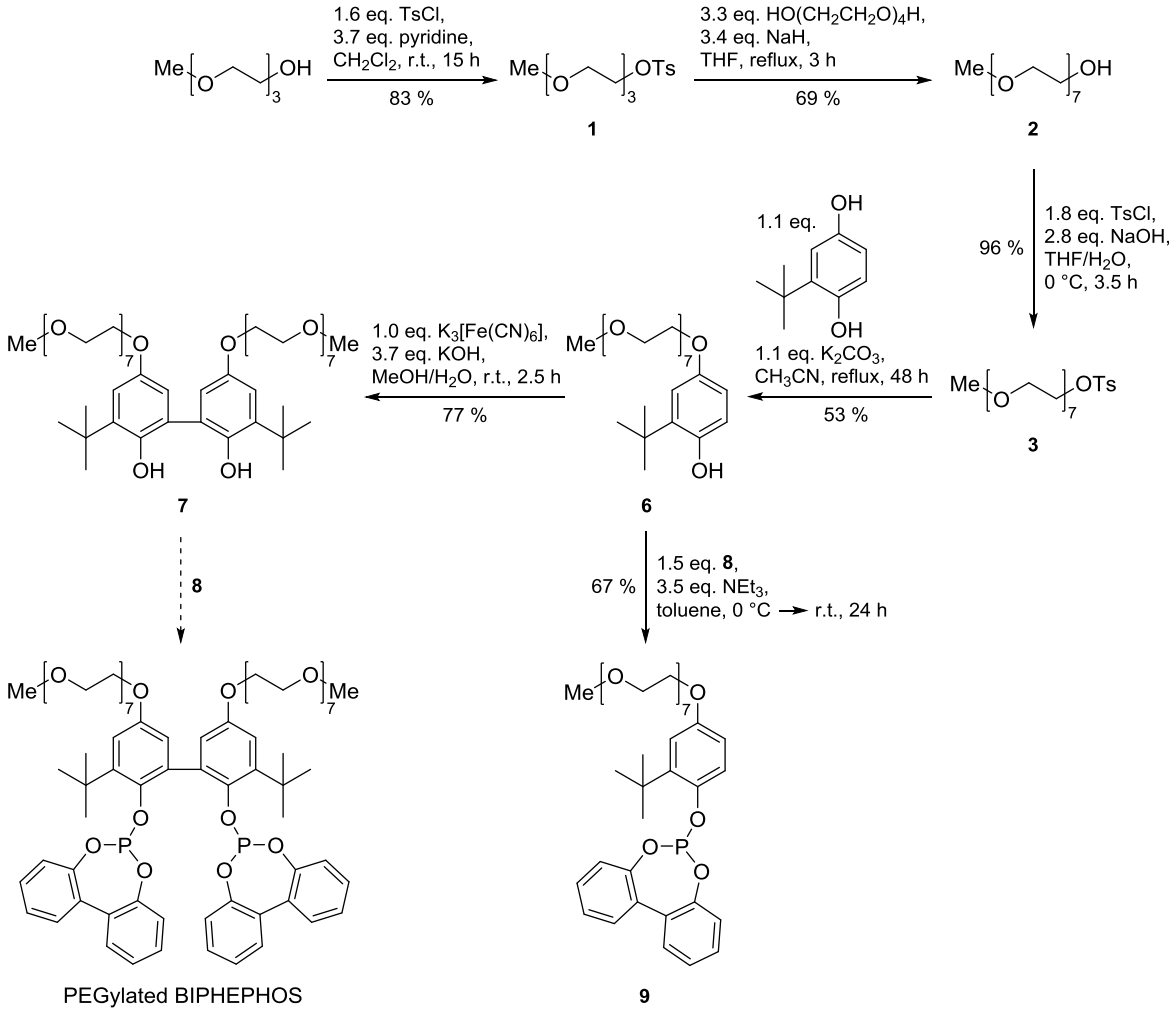


Figure 10. Aromatic region of the ^{1}H-NMR spectrum (499.87 MHz, C_6D_6) of compound **13**, exhibiting the three spin-systems d_{A1}–t_{A2}–t_{A3}–d_{A4} (4x1H), d_{B1}–t_{B2}–t_{B3}–d_{B4} (4x1H) and d_{C1}–t_{C2}–t_{C3}–d_{C4} (4x2H) as assigned by $^{1}H,^{1}H$-COSY and HSQC.

For this reason, a revised structure **13** was postulated, which with its asymmetry is in full accordance with all spectroscopic data. The ring interconversion, inevitable for the formation of the rearranged structure **13**, involves the opening of a cyclic phosphite and has been rarely reported in literature so far.[73–75] However, the rearrangement observed in the course of this work is especially remarkable since the reactants of this phosphite synthesis are highly similar to the BIPHEPHOS synthesis where no ring interconversion is observed. Moreover, the only structural differences are located *para* to the reacting phenol groups and should therefore not interfere with the phosphorylation due to sterics.

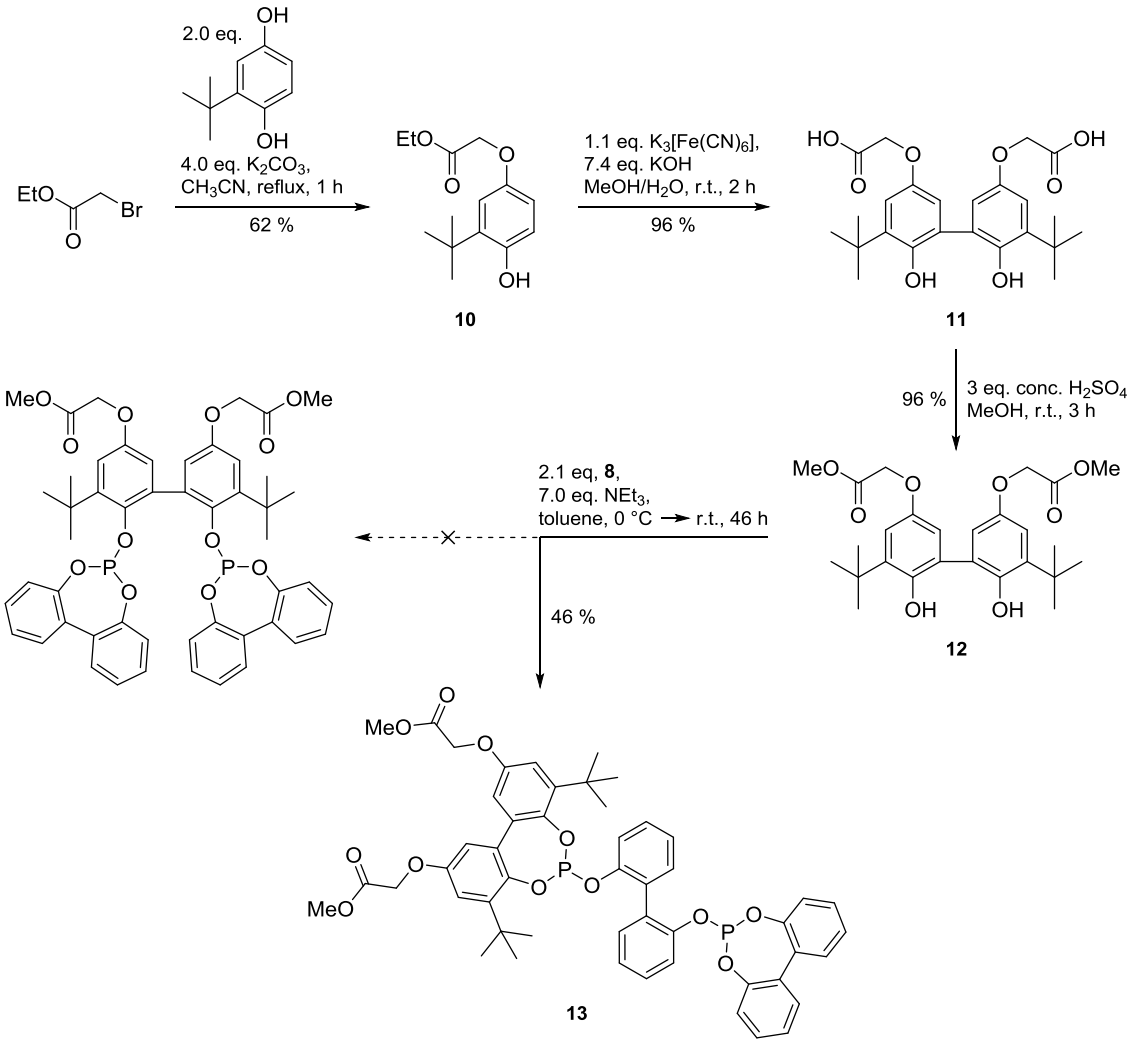
5. SUMMARY AND OUTLOOK

The first part of this thesis was aimed at the development of the synthesis of a PEGylated BIPHEPHOS ligand in order to enhance its water-solubility (Scheme 22). For this purpose, the PEGylated biphenol **7** was prepared over 5 steps from triethylene glycol monomethyl ether. Phosphorylation using 6-chlorodibenzo[*d*,*f*][1,3,2]dioxaphosphepin (**8**), however, resulted only in a mixture of unknown phosphites so far. Nevertheless, the undimerized PEGylated phenol **6** could be successfully phosphorylated to give the monodentate ligand **9**, demonstrating that appropriate reaction conditions were applied.



Scheme 22. Reaction sequence for the synthesis of PEGylated BIPHEPHOS precursor **7** and the monodentate PEGylated ligand **9**.

The second, PEG-independent strategy pursued in this work was the use of carboxylate groups to increase the ligands water-solubility. The corresponding methyl ester protected biphenol **12** was readily accessible via a slightly modified synthesis route (Scheme 23). The phosphorylation of **12** resulted in the formation of a single product, which exhibited two different phosphorus atoms as indicated by ^{31}P-NMR spectroscopy. Therefore, not the expected symmetric bisphosphite formed but an unusual ring-interconversion[73–75] occurred, yielding the asymmetric bidentate ligand **13**.



Scheme 23. Reaction sequence for the synthesis of bisphosphite **13** exhibiting an unexpected ring interconverted structure.

In summary, the synthetic route established in this work proved to be flexible in terms of the *para*-position of the sterically demanding biphenol unit, which should allow the introduction of a variety of polar function groups beside –O(CH_2CH_2O)$_7$Me (**7**), –OCH_2COOH (**11**) and –OCH_2COOMe (**12**).

The PEGylated monodentate phosphite **9** as well as the unexpectedly rearranged bisphosphite **13** were successfully prepared according to this route so far. These ligands

may serve as model compounds to study the influence of the ligand denticity or asymmetry on the catalytic performance compared to BIPHEPHOS. Furthermore, the PEGylated ligand **9** might provide first insight towards its water-solubility as well as hydrolytic stability.

Future efforts will be aimed at the mild hydrolysis of the ester groups of ligand **13** to liberate the carboxylic acids, which are anticipated to enhance the water-solubility. As an alternative, the application of another protecting group that can be cleaved under non-hydrolytic conditions (e.g. TMSE[76]) could be beneficial.

6. EXPERIMENTAL SECTION

6.1. General Aspects

If reactions were performed under inert conditions, e.g. exclusion of water, oxygen or both, all experiments were carried out using established Schenk techniques. Herein solvents were dried and/or degassed with common methods and afterwards stored under inert gas atmosphere (argon or nitrogen) over molecular sieves. In some cases, when explicitly mentioned, dry solvents were received from the mentioned suppliers. In general, when high vacuum (*in vacuo*) was stated in experimental procedures, typically a vacuum of 10^{-2}-10^{-3} mbar was applied. Degassing of solvents or reaction mixtures was performed by bubbling argon from a balloon via cannula through the solvent or the reaction mixture during ultrasonification for about 20 min. All reagents were added in a counterstream of inert gas to keep the inert atmosphere. All reactions were stirred with Teflon-coated magnetic stirring bars.

Molecular sieves (Sigma-Aldrich, beads with 8-12 mesh) were activated in a round-bottom flask with a gas inlet adapter by heating them carefully in a heating mantle at level 1 at least for 24 h under high vacuum until complete dryness was obtained. These activated molecular sieves were stored at r.t. under argon atmosphere.

In general, temperatures were measured externally if not otherwise stated. When working at a temperature of 0 °C, an ice-water bath served as the cooling medium. Lower temperatures were achieved by using an acetone/dry ice cooling bath. Reactions, which were carried out at higher temperatures than r.t., were heated in a silicon oil bath on a heating plate (RCT basic IKAMAG® safety control, 0-1500 rpm) equipped with an external temperature controller.

6.2. Solvents

Acetonitrile: Anhydrous acetonitrile was purchased from Alfa Aesar. It was transferred into an amber 1 L Schenk bottle and stored over activated 3 Å MS under argon atmosphere.

Dichloromethane: Anhydrous dichloromethane was produced by pre-drying EtOH stabilized dichloromethane over P_4O_{10} and afterwards heating it under reflux over CaH_2 for 24 h under argon atmosphere. It was distilled into an amber 1 L Schlenk bottle over activated 4 Å MS and under argon atmosphere.

***N*,*N*-Dimethylformamide:** *N*,*N*-Dimethylformamide was purchased in extra dry quality from Alfa Aesar. It was transferred into an amber 1 L Schlenk bottle and stored over activated 3 Å MS under argon atmosphere.

Tetrahydrofuran: Anhydrous tetrahydrofuran was produced by heating it over Na under reflux for 48 h under argon atmosphere until benzophenone indicated its dryness by turning into deep blue color. It was distilled into an amber 1 L Schlenk bottle and stored over activated 4 Å MS and under argon atmosphere.

Toluene: Dry toluene was prepared by filtering through an alox-column (Pure Solv by Innovative Technology) and stored in an amber 1 L Schlenk bottle over activated 4 Å MS under argon atmosphere.

The following solvents were used in reactions as well as workup processes, which were directly performed under atmospheric conditions: cyclohexane, dichloromethane, ethyl acetate, methanol and toluene were purchased from Fisher Scientific. Diethylether, *n*-pentane and tetrahydrofuran were purchased from VWR. All solvents were used without further purification except for diethylether, *n*-pentane and tetrahydrofuran. These were distilled before use and in case of diethylether and tetrahydrofuran stored over solid KOH in amber glass bottles.

6.3. Reagents

All commercially available chemicals and reagents were obtained from Acros Organics, Alfa Aesar, Fluka, Riedel-de Haën, Roth, Sigma-Aldrich, TCI Chemicals or VWR and were used without further purification, unless otherwise stated.

Pyridine: Anhydrous pyridine was purchased from Merck. It was transferred into an amber 1 L Schenk bottle and stored over activated 4 Å MS under argon atmosphere.

Triethylamine: Triethylamine was first distilled over KOH and then distilled over CaH_2 under argon atmosphere and stored in an amber 1 L Schlenk bottle over activated 4 Å MS under argon atmosphere.

6.4. Analytical Methods

6.4.1. Thin Layer Chromatography

Analytical thin layer chromatography (TLC) was carried out on Merck TLC silica gel aluminium sheets (silica gel 60, F_{254}, 20 x 20 cm). All separated compounds were visualized by UV light (λ = 254 nm and/or λ = 366 nm) and by the listed staining reagents followed by the development in the heat.

$KMnO_4$: 0.3 g $KMnO_4$ as well as 20 g K_2CO_3 were dissolved in 300 mL H_2O and afterwards 5.0 mL 5 % aq. NaOH were added.

CAM: 50 g $(NH_4)_6Mo_7O_{24}$, 2.0 g $Ce(SO_4)_2$ and 50 mL conc. H_2SO_4 were dissolved in 400 mL water.

6.4.2. Flash Column Chromatography

Flash column chromatography was performed on silica gel 60 from Acros Organics with particle sizes between 35 µm and 70 µm. Depending on the problem of separation, a 30 to 100 fold excess of silica gel was used with respect to the dry amount of crude material. The dimension of the column was adjusted to the required amount of silica gel and formed a pad between 10 cm and 30 cm. In general, the silica gel was mixed with the eluent and the column was equilibrated. Subsequently, the crude material was dissolved in the eluent and loaded onto the top of the silica gel and the mobile phase was forced through the column using a rubber bulb pump. The volume of each collected fraction was adjusted between 20 % and 40 % of the silica gel volume.

6.4.3. Gas Chromatography

GC-MS analyses were performed on an Agilent Technologies 7890A GC system equipped with a 5975C mass selective detector (inert MSD with Triple Axis Detector system) by electron-impact ionization (EI) with a potential of E = 70 eV. Herein, the samples were separated depending on their boiling point and polarity. The desired crude materials or pure compounds were dissolved either in CH_2Cl_2 or EtOAc and the solutions were injected by employing the autosampler 7683B in a split mode 1/20 (inlet temperature: 280 °C; injection volume: 0.2 µL). Separations were carried out on an Agilent Technologies J&W GC HP-5MS capillary column ((5 %-phenyl)methylpolysiloxane, 30 m x 0.2 mm x

0.25 µm) with a constant helium flow rate (He 5.0 (Air Liquide), 1.085 $mL \cdot min^{-1}$, average velocity: 41.6 $cm \cdot s^{-1}$). A general gradient temperature method was used:

50_S: initial temperature: 50 °C for 1 min; linear increase to 300 °C (40 $°C \cdot min^{-1}$); hold for 5 min; 1 min post-run at 300 °C; detecting range: 50.0-550.0 amu; solvent delay: 2.60 min.

6.4.4. High Performance Liquid Chromatography

Analytical HPLC-MS analyses were performed on an Agilent Technologies 1200 Series system (G1379 Degasser, G1312 Binary Pump, G1367C HiP ALS SL Autosampler, G1330B FC/ALS Thermostat, G1316B TCC SL column compartment, G1365C MWD SL multiple wavelength detector (deuterium lamp, 190-400 nm)) equipped with a single quadrupole LCMS detector "6120 LC/MS" using electrospray ionization source (ESI in positive and negative mode). The analyses were carried out on an Agilent Poroshell 120 SB-C18 (100 x 3.0 mm, 2.7 µm) column equipped with a Merck LiChroCART® 4-4 pre-column. The following methods were used:

2_100_MEOH: 0.0 min: 98 % H_2O + 0.01 % HCOOH and 2 % MeOH; 0.0-6.0 min: linear gradient to 100 % MeOH; 6.0-8.0 min: 100 % MeOH; 8.0-8.5 min: linear gradient to 98 % H_2O + 0.01 % HCOOH and 2 % MeOH; 8.5-9.5 min: 98 % H_2O + 0.01 % HCOOH and 2 % MeOH; 0.700 $mL \cdot min^{-1}$; 30 °C.

2_100_MECN: 0.0 min: 98 % H_2O + 0.01 % HCOOH and 2 % CH_3CN; 0.0-6.0 min: linear gradient to 100 % CH_3CN; 6.0-8.0 min: 100 % CH_3CN; 8.0-8.5 min: linear gradient to 98 % H_2O + 0.01 % HCOOH and 2 % CH_3CN; 8.5-9.5 min: 98 % H_2O + 0.01 % HCOOH and 2 % CH_3CN; 0.700 $mL \cdot min^{-1}$; 30 °C.

6.4.5. Nuclear Magnetic Resonance Spectroscopy

NMR spectra were recorded on a Bruker AVANCE III 300 spectrometer (^1H: 300.36 MHz; ^{13}C: 75.53 MHz) with autosampler, a Varian Unity Inova 500 spectrometer (^1H: 499.87 MHz; ^{13}C: 125.69 MHz, ^{31}P: 202.35 MHz) or a Varian Inova 300 spectrometer (^{31}P: 121.42 MHz).

Chemical shifts δ are referenced to the residual proton and carbon signal of the deuterated solvent ($CDCl_3$: δ = 7.26 ppm (^1H), 77.16 ppm (^{13}C); DMSO-d_6: δ = 2.50 ppm (^1H), 39.52 ppm (^{13}C); CD_3CN: δ = 1.94 ppm (^1H), 118.26 ppm (^{13}C); C_6D_6: δ = 7.16 ppm (^1H), 128.06 ppm (^{13}C)[77,78]). Chemical shifts δ are given in ppm (parts per million) and coupling constants *J* in Hz (Hertz). If necessary, 1D spectra (APT and NOESY) as well as 2D spectra (H,H-COSY, HSQC, HMBC and ^{31}P,^{31}P-COSY) were recorded for the identification and confirmation of the structure. Signal multiplicities are abbreviated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet), q (quadruplet) and m (multiplet). Additionally, carbon atoms are designated as C_q, CH, CH_2 and CH_3 based on APT spectra. Deuterated solvents for nuclear resonance spectroscopy were purchased from euriso-top®.

6.4.6. High Resolution Mass Spectrometry

High-resolution mass spectra were recorded on a Waters Micromass GCT Premier system. Ionization was realized by an electron impact source (EI ionization) at a constant potential of 70 eV. Herein, individual samples were either inserted directly (direct inlet electron impact ionization; DI-EI) or prior to this gas chromatographically separated on an Agilent 7890A system equipped with an Agilent Technologies J&W GC-column DB-5MS (length: 30 m; inner-diameter: 0.250 mm; film: 0.25 µm) at a constant helium flow. Molecule ions were analyzed by a time-of-flight (TOF) mass analyzer in the positive mode (TOF MS EI+). Besides molecular formulas, calculated as well as determined *m/z* ratios of each molecule peak are denoted.

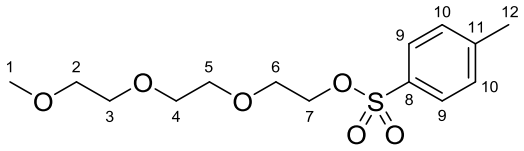
Further high-resolution mass spectra were recorded using MALDI TOF on a Waters Micromass® MALDI micro MX Mass spectrometer. Dithranol (1,8-dihydroxy-9,10-dihydroanthracen-9-one) served as matrix and PEG as internal standard. The stated values are *m/z*.

6.4.7. Determination of Melting Points

Melting points were determined on a Mel-Temp® melting point apparatus from Electrothermal with an integrated microscopical support. They were measured in open capillary tubes with a mercury-in-glass thermometer and were not corrected.

6.5. Experimental Procedures and Analytical Data

6.5.1. 2,5,8-Trioxadecan-10-yl 4-methylbenzenesulfonate (1)



In a flame-dried, evacuated and nitrogen purged 500 mL two-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar and drying tube ($CaCl_2$), 16.3 g (99.5 mmol, 1 eq.) triethylene glycol monomethyl ether and 30 mL (0.37 mol, 3.7 eq.) abs. pyridine were dissolved in 150 mL abs. CH_2Cl_2. Subsequently, 30.6 g (160 mmol, 1.6 eq.) *p*-toluenesulfonyl chloride were added over a period of 5 min and the reaction mixture was stirred at r.t. for 15 h (reaction monitoring via GC-MS). The resulting yellow suspension was diluted with 150 mL CH_2Cl_2, 20 mL H_2O were added and the mixture was stirred vigorously for 30 min. The organic layer was separated, washed with 5 wt% aq. HCl (2 x 150 mL) and the combined aq. HCl phases were back-extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ solution (2 x 150 mL) and the combined aq. $NaHCO_3$ phases were back-extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash column chromatography (400 g SiO_2, 17.0 x 7.5 cm, cyclohexane:EtOAc = 2:1 to 1:3 (v/v)) provided the title compound as a light yellow oil.

Yield: 26.2 g (82.2 mmol, 83 %), light yellow oil

$C_{14}H_{22}O_6S$ [318.38 g·mol^{-1}]

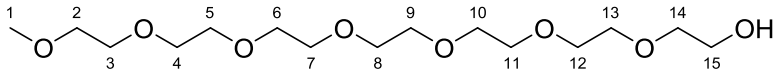
R_f = 0.18 (cyclohexane:EtOAc = 2:1 (v/v), UV)

GC-MS (50_S): t_R = 7.75 min; *m/z* (%) = 273 (3), 243 (6), 199 (100), 155 (57), 91 (77), 59 (49).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.78 (d, $^3J_{HH}$ = 8.2 Hz, 2H, H9), 7.33 (d, $^3J_{HH}$ = 8.0 Hz, 2H, H10), 4.15 (t, $^3J_{HH}$ = 4.8 Hz, 2H, H7), 3.67 (t, $^3J_{HH}$ = 4.8 Hz, 2H, H6), 3.62-3.55 (m, 6H, H3-5), 3.55-3.49 (m, 2H, H2), 3.36 (s, 3H, H1), 2.43 (s, 3H, H12).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 144.9 (C_q, C11), 133.2 (C_q, C8), 129.9 (CH, C10), 128.1 (CH, C9), 72.0 (CH_2, C2), 70.9 (CH_2), 70.7 (2 x CH_2), 69.3 (CH_2, C7), 68.8 (CH_2, C6), 59.1 (CH_3, C1), 21.7 (CH_3, C12).

6.5.2. 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol (2)



This compound was prepared similar to the literature.[64]

In a flame-dried, evacuated and nitrogen purged 100 mL three-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, air condenser, dropping funnel and bubbler, 0.417 g (10.4 mmol, 3.4 eq., 60 % dispersion in mineral oil) NaH were suspended in 22 mL abs. THF and cooled to 0 °C (ice bath). Subsequently, 1.99 g (10.3 mmol, 3.3 eq.) tetraethylene glycol dissolved in 2.5 mL abs. THF were added dropwise over a period of 5 min. The light yellow solution was heated under reflux in an oil bath. A solution of 0.986 g (3.10 mmol, 1 eq.) **1** in 2.5 mL abs. THF was added dropwise over a period of 5 min and the reaction mixture was heated under reflux for 3 h (reaction monitoring via GC-MS). The beige suspension was allowed to cool to r.t., MeOH (5 mL) and 5 wt% aq. HCl (1.5 mL) were added. After evaporation of THF the residue was extracted using 5 wt% aq. HCl (25 mL) and CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash column chromatography (50 g SiO_2, 33.5 x 2.0 cm, CH_2Cl_2:MeOH = 20:1 (v/v)) provided the title compound as a light yellow oil.

Yield: 0.722 g (2.12 mmol, 69 %), light yellow oil

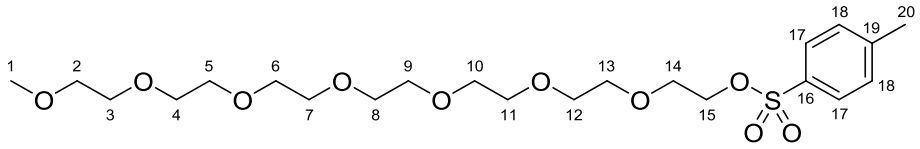
$C_{15}H_{32}O_8$ [340.41 g·mol^{-1}]

GC-MS (50_S): t_R = 7.70 min; *m/z* (%) = 177 (5), 147 (9), 133 (24), 103 (46), 89 (60), 59 (100).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 3.71-3.45 (m, 28H, H2-15), 3.32 (s, 3H, H1), 2.73 (t, $^3J_{HH}$ = 5.9 Hz, 1H, OH).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 72.5 (CH_2), 71.9 (CH_2), 70.6 (9 x CH_2), 70.5 (CH_2), 70.4 (CH_2), 61.7 (CH_2, C15), 59.0 (CH_3, C1).

6.5.3. 2,5,8,11,14,17,20-Heptaoxadocosan-22-yl 4-methylbenzene-sulfonate (3)



This compound was prepared according to the literature.[66]

In a 50 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar and dropping funnel, 5.76 g (16.9 mmol, 1 eq.) **2** were dissolved in 9 mL THF, cooled to 0 °C (ice bath) and an ice-cold solution of 1.89 g (47.4 mmol, 2.8 eq.) NaOH in 9 mL H_2O was added. Subsequently, 5.90 g (31.0 mmol, 1.8 eq.) *p*-toluenesulfonyl chloride dissolved in 9 mL THF were added over a period of 1 h. The reaction mixture was stirred for an additional 2.5 h at 0 °C (reaction monitoring via GC-MS), poured into ice-cold H_2O (25 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with H_2O (2 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the pure title compound as a colorless oil, which was used without further purification.

Yield: 8.04 g (16.3 mmol, 96 %), colorless oil

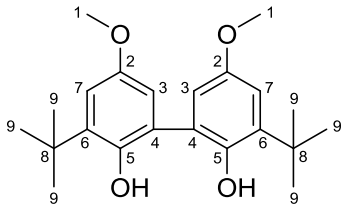
$C_{22}H_{38}O_{10}S$ [494.60 g·mol^{-1}]

R_f = 0.35 (EtOAc:MeOH = 10:1 (v/v), $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.79 (d, $^3J_{HH}$ = 8.2 Hz, 2H, H17), 7.34 (d, $^3J_{HH}$ = 8.0 Hz, 2H, H18), 4.15 (t, $^3J_{HH}$ = 4.8 Hz, 2H, H15), 3.71-3.51 (m, 26H, H2-H14), 3.37 (s, 3H, H1), 2.44 (s, 3H, H20).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 144.9 (C_q, C19), 133.2 (C_q, C16), 130.0 (CH, C18), 128.1 (CH, C17), 72.1 (CH_2, C2), 70.9 (CH_2), 70.8 (CH_2), 70.7 (8 x CH_2), 70.7 (CH_2), 69.4 (CH_2, C15), 68.8 (CH_2, C14), 59.2 (CH_3, C1), 21.8 (CH_3, C20).

6.5.4. 3,3'-Di-*tert*-butyl-5,5'-dimethoxy-[1,1'-biphenyl]-2,2'-diol (4)



This compound was prepared according to the literature.[67]

In a 500 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar and dropping funnel, 3.33 g (18.5 mmol, 1 eq.) 2-*tert*-butyl-4-methoxyphenol were dissolved in 100 mL MeOH. Subsequently, a solution of 6.12 g (18.6 mmol, 1.0 eq.) $K_3[Fe(CN)_6]$ and 3.71 g (66.1 mmol, 3.6 eq.) KOH in 100 mL H_2O was added over a period of 1 h at r.t. The resulting reddish suspension was stirred for an additional 2 h at r.t. (reaction monitoring via GC-MS). After addition of 70 mL H_2O, the suspension was extracted with EtOAc (2 x 170 mL) and Et_2O (50 mL). The combined organic layers were washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude brownish red product was washed with *n*-pentane (4 x 10 mL) to give the pure title compound as a reddish powder, which was used without further purification.

Yield: 3.11 g (8.67 mmol, 94 %), reddish powder

$C_{22}H_{30}O_4$ [358.48 g·mol^{-1}]

R_f = 0.72 (cyclohexane:EtOAc = 3:1 (v/v), CAM)

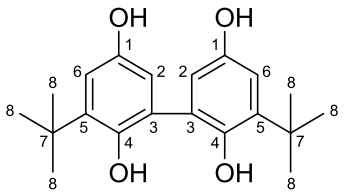
GC-MS (50_S): t_R = 8.12 min; *m/z* (%) = 358 (100), 302 (37), 287 (65), 272 (14), 246 (20).

mp = 230-232 °C

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 6.96 (d, $^4J_{HH}$ = 2.9 Hz, 2H, H7), 6.63 (d, $^4J_{HH}$ = 3.0 Hz, 2H, H3), 5.03 (s, 2H, OH), 3.78 (s, 6H, H1), 1.43 (s, 18H, H9).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 153.4 (C_q, C2), 146.1 (C_q, C5), 139.1 (C_q, C6), 123.3 (C_q, C4), 115.4 (CH, C7), 111.9 (CH, C3), 55.9 (CH_3, C1), 35.3 (C_q, C8), 29.7 (CH_3, C9).

6.5.5. 3,3'-Di-*tert*-butyl-[1,1'-biphenyl]-2,2',5,5'-tetraol (5)



This compound was prepared according to the literature.[68]

In a flame-dried, evacuated and nitrogen purged 250 mL three-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar and dropping funnel, 1.18 g (3.30 mmol, 1 eq.) **4** were dissolved in 50 mL abs. CH_2Cl_2 and cooled to 0 °C (ice bath). Subsequently, 8.0 mL (8.0 mmol, 2.4 eq.) BBr_3 (1 M soln. in CH_2Cl_2) were added over a period of 10 min. The reaction mixture was stirred for an additional 10 min at 0 °C and was then allowed to warm to r.t. Upon completion of the reaction (GC-MS, 2.5 h), the brown solution was quenched by the addition of ice and the colorless precipitate was dissolved by the addition of Et_2O (100 mL). The organic layer was separated, washed with 1 M aq. HCl (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was recrystallized from Et_2O/*n*-pentane, filtered and washed with *n*-pentane to give the pure title compound as an off-white powder.

Yield: 0.885 g (2.68 mmol, 81 %), off-white powder

$C_{20}H_{26}O_4$ [330.42 g·mol^{-1}]

R_f = 0.41 (cyclohexane:EtOAc = 2:1 (v/v), $KMnO_4$)

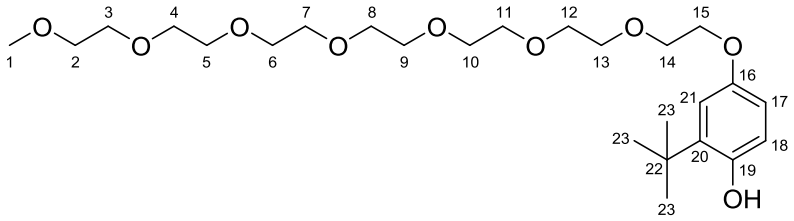
GC-MS (50_S): t_R = 8.94 min; *m/z* (%) = 330 (95), 315 (9), 274 (30), 259 (100), 241 (13).

mp = 228-229 °C

^{1}H-NMR (300.36 MHz, DMSO-d_6): δ = 8.86 (br s, 2H, 1-OH), 8.39 (s, 2H, 4-OH), 6.68 (s, 2H, H6), 6.49 (s, 2H, H2), 1.36 (s, 18H, H8).

^{13}C-NMR (75.53 MHz, DMSO-d_6): δ = 151.0 (C_q, C1), 143.7 (C_q, C4), 140.3 (C_q, C5), 131.1 (C_q, C3), 114.9 (CH, C2), 113.2 (CH, C6), 34.6 (C_q, C7), 29.9 (CH_3, C8).

6.5.6. 4-((2,5,8,11,14,17,20-Heptaoxadocosan-22-yl)oxy)-2-(*tert*-butyl)phenol (6)



In a flame-dried, evacuated and nitrogen purged 50 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, air condenser and bubbler, 0.898 g (1.82 mmol, 1 eq.) **3**, 0.332 g (2.00 mmol, 1.1 eq.) *tert*-butylhydroquinone and 0.279 g (2.02 mmol, 1.1 eq.) K_2CO_3 were suspended in 15 mL abs. CH_3CN. The reaction mixture was degassed and heated under reflux in an oil bath for 48 h (reaction monitoring via TLC and ^{1}H-NMR). The dark red suspension was allowed to cool to r.t. and after evaporation of CH_3CN the residue was extracted using CH_2Cl_2 (30 mL) and sat. NH_4Cl solution (15 mL). The aqueous phase was then back-extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash column chromatography (125 g SiO_2, 13.5 x 5.0 cm, EtOAc:MeOH = 10:1 (v/v)) provided the title compound as a orange-brown oil.

Yield: 0.471 g (0.964 mmol, 53 %), orange-brown oil

$C_{25}H_{44}O_9$ [488.62 g·mol^{-1}]

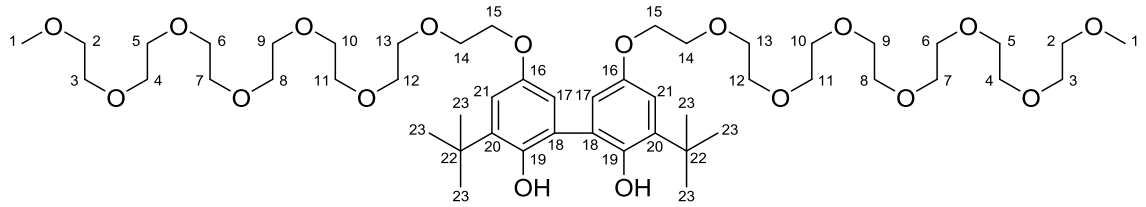
R_f = 0.37 (EtOAc:MeOH = 10:1 (v/v), $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 6.86 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H21), 6.62 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H18), 6.58 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.6 Hz, 1H, H17), 5.49 (br s, 1H, OH), 4.05 (t, $^3J_{HH}$ = 4.8 Hz, 2H, H15), 3.81 (t, $^3J_{HH}$ = 4.8 Hz, 2H, H14), 3.75-3.49 (m, 24H, H2-13), 3.37 (s, 3H, H1), 1.37 (s, 9H, H23).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 152.5 (C_q, C16), 149.0 (C_q, C19), 137.5 (C_q, C20), 116.9 (CH, C18), 115.1 (CH, C21), 111.7 (CH, C17), 72.1 (CH_2), 70.9 (CH_2), 70.8 (2 x CH_2), 70.7-70.6 (8 x CH_2), 70.1 (CH_2, C14), 68.2 (CH_2, C15), 59.1 (CH_3, C1), 34.8 (C_q, C22), 29.6 (CH_3, C23).

HRMS (DI-EI TOF): calcd. for $C_{25}H_{44}O_9^+$ $[M]^+$: 488.2985; found: 488.2993.

6.5.7. 5,5'-Bis((2,5,8,11,14,17,20-heptaoxadocosan-22-yl)oxy)-3,3'-di-*tert*-butyl-[1,1'-biphenyl]-2,2'-diol (7)



This compound was prepared similar to the literature.[67]

In a 50 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar and dropping funnel, 0.994 g (2.03 mmol, 1 eq.) **6** were dissolved in 10 mL MeOH. Subsequently, a solution of 0.679 g (2.06 mmol, 1.0 eq.) $K_3[Fe(CN)_6]$ and 0.418 g (7.46 mmol, 3.7 eq.) KOH in 10 mL H_2O was added at r.t. over a period of 1 h. The resulting reddish brown suspension was stirred for an additional 1.5 h at r.t. (reaction monitoring via TLC). After the addition of 20 mL H_2O, the organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 20 mL) and Et_2O (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash column chromatography (100 g SiO_2, 17.0 x 4.0 cm, EtOAc:MeOH = 10:1 (v/v)) provided the title compound as a brownish oil.

Yield: 0.759 g (0.778 mmol, 77 %), brownish oil

$C_{50}H_{86}O_{18}$ [975.22 g·mol^{-1}]

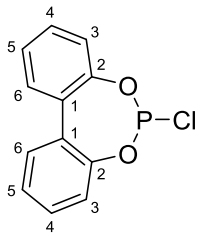
R_f = 0.10 (EtOAc:MeOH = 10:1 (v/v), $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 6.96 (d, $^4J_{HH}$ = 2.8 Hz, 2H, H21), 6.61 (d, $^4J_{HH}$ = 2.8 Hz, 2H, H17), 5.24 (s, 2H, OH), 4.06 (t, $^3J_{HH}$ = 4.5 Hz, 4H, H15), 3.82 (t, $^3J_{HH}$ = 4.5 Hz, 4H, H14), 3.73-3.47 (m, 48H, H2-13), 3.34 (s, 6H, H1), 1.40 (s, 18H, H23).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 152.6 (C_q, C16), 146.2 (C_q, C19), 139.2 (C_q, C20), 123.7 (C_q, C18), 116.0 (CH, C21), 112.9 (CH, C17), 72.1 (CH_2), 70.9 (CH_2), 70.8-70.6 (10 x CH_2), 70.1 (CH_2, C14), 68.1 (CH_2, C15), 59.2 (CH_3, C1), 35.3 (C_q, C22), 29.7 (CH_3, C23).

HRMS (MALDI TOF): calcd. for $C_{50}H_{86}O_{18}Na^+$ $[M+Na]^+$: 997.5712; found: 997.5718.

6.5.8. 6-Chlorodibenzo[*d,f*][1,3,2]dioxaphosphepin (8)



This compound was prepared according to the literature.[69,70]

In a flame-dried, evacuated and nitrogen purged 25 mL two-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, air condenser and bubbler, 4.59 g (24.7 mmol, 1 eq.) 2,2′-biphenol and 8.0 mL (92 mmol, 3.7 eq.) PCl_3 were heated under reflux in an oil bath for 3 h. The resulting yellowish solution was allowed to cool to r.t., before the excess of unreacted PCl_3 was removed *in vacuo* (0.6-1.0 mbar, 40-50 °C). The remaining residue was purified via vacuum distillation (0.68 mbar, 140-142 °C) to give the pure title compound as a colorless, highly viscous oil, which crystallizes readily upon standing in an inert atmosphere.

Yield: 4.09 g (16.3 mmol, 66 %), colorless solid

$C_{12}H_8ClO_2P$ [250.62 $g \cdot mol^{-1}$]

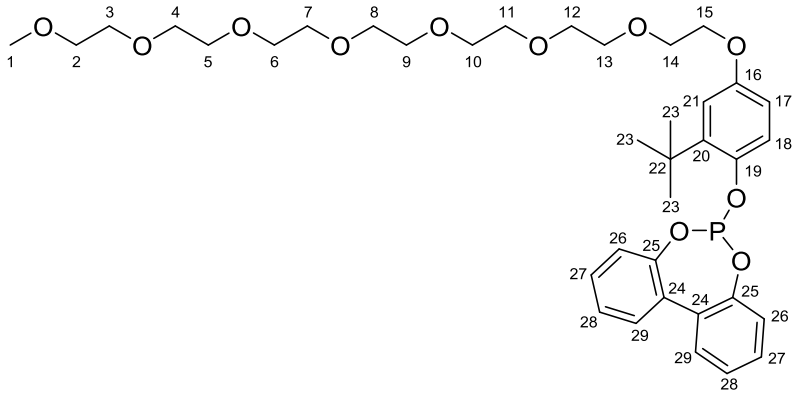
bp = 140-142 °C (0.68 mbar)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 7.3, 1.6 Hz, 2H), 7.39-7.25 (m, 4H), 7.16 (d, *J* = 7.8 Hz, 2H).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 149.4 (d, *J* = 5.8 Hz, C_q), 131.1 (d, *J* = 3.3 Hz, C_q), 130.4 (d, *J* = 1.2 Hz, CH), 129.6 (CH), 126.4 (CH), 122.4 (d, *J* = 2.1 Hz, CH).

^{31}P-NMR (121.42 MHz, $CDCl_3$): δ = 179.5.

6.5.9. 6-(4-((2,5,8,11,14,17,20-Heptaoxadocosan-22-yl)oxy)-2-(*tert*-butyl)phenoxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin (9)



In a flame-dried, evacuated and argon purged 5 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, 31.5 mg (126 µmol, 1.5 eq.) **8** were cooled to 0 °C (ice bath). Then a solution of 40.0 mg (81.9 µmol, 1 eq.) **6** and 0.04 mL (0.3 mmol, 3.5 eq.) abs. NEt_3 in 0.5 mL abs. toluene was added dropwise over a period of 10 min. The resulting reaction mixture was stirred for 10 min at 0 °C and for an additional 24 h at r.t. (reaction monitoring via TLC). Subsequently, 1 mL H_2O was added to the yellow-brownish solution, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash column chromatography (5 g SiO_2, 8.5 x 1.3 cm, EtOAc:MeOH = 30:1 (v/v)) provided the title compound as a yellow oil.

Yield: 38.5 mg (54.8 µmol, 67 %), yellow oil

$C_{37}H_{51}O_{11}P$ [702.78 g·mol^{-1}]

R_f = 0.46 (EtOAc:MeOH = 10:1 (v/v), $KMnO_4$)

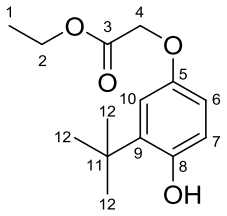
^{1}H-NMR (300.36 MHz, CD_3CN): δ = 7.59 (dd, *J* = 7.4 Hz, 1.3 Hz, 2H), 7.46 (td, *J* = 7.6 Hz, 1.6 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.23 (d, $^3J_{HH}$ = 8.7 Hz, 1H, H18), 6.96 (d, $^4J_{HH}$ = 2.9 Hz, 1H, H21), 6.79 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 3.0 Hz, 1H, H17), 4.09 (t, $^3J_{HH}$ = 4.5 Hz, 2H, H15), 3.77 (t, $^3J_{HH}$ = 4.5 Hz, 2H, H14), 3.66-3.40 (m, 24H, H2-13), 3.28 (s, 3H, H1), 1.38 (s, 9H, H23).

^{13}C-NMR (75.53 MHz, CD_3CN): δ = 156.4 (C_q, C16), 149.8 (d, $^2J_{CP}$ = 5.2 Hz, C_q, C25), 145.2 (d, $^2J_{CP}$ = 9.2 Hz, C_q, C19), 142.9 (d, $^3J_{CP}$ = 2.8 Hz, C_q, C20), 131.9 (d, $^3J_{CP}$ = 3.2 Hz, C_q, C24), 131.1 (d, J_{CP} = 1.0 Hz, CH), 130.6 (CH), 126.8 (CH), 123.0 (CH), 121.9 (d, $^3J_{CP}$ = 14.1 Hz, CH, C18), 116.1 (CH, C21), 112.4 (CH, C17), 72.6 (CH_2), 71.4 (CH_2),

71.3-71.1 (9 x CH_2), 71.0 (CH_2), 70.4 (CH_2, C14), 68.8 (CH_2, C15), 58.9 (CH_3, C1), 35.6 (C_q, C22), 30.2 (CH_3, C23).

^{31}P-NMR (202.35 MHz, CD_3CN): δ = 144.9, small resonance at 143.2 (6 %).

6.5.10. Ethyl 2-(3-(*tert*-butyl)-4-hydroxyphenoxy)acetate (10)



In a flame-dried, evacuated and nitrogen purged 500 mL three-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, dropping funnel, air condenser and bubbler, 4.99 g (30.0 mmol, 2.0 eq.) *tert*-butylhydroquinone and 8.28 g (59.9 mmol, 4.0 eq.) K_2CO_3 were suspended in 100 mL abs. CH_3CN and heated under reflux in an oil bath. Subsequently, a solution of 2.52 g (15.1 mmol, 1 eq.) ethyl bromoacetate in 10 mL abs. CH_3CN was added over a period of 30 min and the reaction mixture was heated under reflux for an additional 30 min (reaction monitoring via GC-MS). The red suspension was allowed to cool to r.t. and after evaporation of CH_3CN the residue was extracted using CH_2Cl_2 (250 mL) and sat. NH_4Cl solution (125 mL). The aqueous phase was then acidified with 1 M aq. HCl to pH 5-6 and back-extracted with CH_2Cl_2 (2 x 125 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash column chromatography (500 g SiO_2, 20.5 x 8.0 cm, toluene:EtOAc = 20:1 (v/v)) provided the title compound as a off-white solid.

Yield: 2.35 g (9.30 mmol, 62 %), off-white solid

$C_{14}H_{20}O_4$ [252.31 g·mol^{-1}]

R_f = 0.36 (toluene:EtOAc = 10:1 (v/v), CAM)

GC-MS (50_S): t_R = 6.62 min; *m/z* (%) = 252 (59), 237 (100), 209 (15), 179 (8), 163 (26).

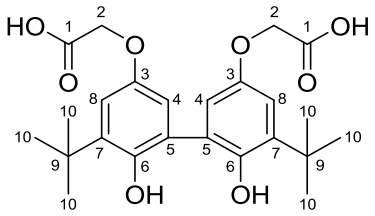
mp = 64 °C

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 6.92 (s, 1H, H10), 6.57 (m, 2H, H6, H7), 4.81 (s, 1H, OH), 4.55 (s, 2H, H4), 4.28 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H2), 1.38 (s, 9H, H12), 1.30 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H1).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 169.7 (C_q, C3), 151.8 (C_q, C5), 149.3 (C_q, C8), 137.8 (C_q, C9), 116.9 (CH, C7), 115.4 (CH, C10), 111.9 (CH, C6), 66.6 (CH_2, C4), 61.5 (CH_2, C2), 34.8 (C_q, C11), 29.6 (CH_3, C12), 14.3 (CH_3, C1).

HRMS (GC-EI TOF): calcd. for $C_{14}H_{20}O_4^+$ $[M]^+$: 252.1362; found: 252.1364.

6.5.11. 2,2'-((5,5'-Di-*tert*-butyl-6,6'-dihydroxy-[1,1'-biphenyl]-3,3'-diyl)bis(oxy))diacetic acid (11)



This compound was prepared similar to the literature.[67]

In a 500 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar and dropping funnel, 2.00 g (7.93 mmol, 1 eq.) **10** were dissolved in 40 mL MeOH. Subsequently, a solution of 2.87 g (8.72 mmol, 1.1 eq.) $K_3[Fe(CN)_6]$ and 3.30 g (58.8 mmol, 7.4 eq.) KOH in 40 mL H_2O was added at r.t. over a period of 30 min. The resulting red suspension was stirred for an additional 1.5 h at r.t. (reaction monitoring via HPLC-MS). After the addition of 40 mL H_2O, the solution was carefully acidified with 1 M aq. HCl to pH 3.0 (pH meter). In order to check for HCN exposure a HCN sensor was placed next to the reaction vessel. The yellow suspension was then extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the pure title compound as an off-white solid, which was used without further purification.

Yield: 1.70 g (3.81 mmol, 96 %), off-white solid

$C_{24}H_{30}O_8$ [446.50 g·mol^{-1}]

HPLC-MS (2_100_MEOH): t_R = 6.95 min; *m/z* (ESI-) = 445.2 $[M - H]^-$.

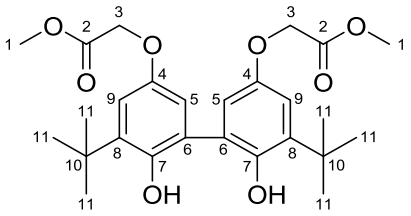
mp = 102-104 °C

^{1}H-NMR (300.36 MHz, DMSO-d_6): δz = 12.93 (br s, 2H, COOH), 8.69 (s, 2H, OH), 6.82 (d, $^4J_{HH}$ = 2.5 Hz, 2H, H8), 6.66 (d, $^4J_{HH}$ = 2.6 Hz, 2H, H4), 4.65 (s, 4H, H2), 1.38 (s, 18H, H10).

^{13}C-NMR (75.53 MHz, DMSO-d_6): δ = 170.6 (C_q, C1), 151.6 (C_q, C3), 145.5 (C_q, C6), 140.7 (C_q, C7), 130.6 (C_q, C5), 113.9 (CH, C4), 113.6 (CH, C8), 65.0 (CH_2, C2), 34.8 (C_q, C9), 29.7 (CH_3, C10).

HRMS (DI-EI TOF): calcd. for $C_{24}H_{30}O_8^+$ $[M]^+$: 446.1941; found: 446.1944.

6.5.12. Dimethyl 2,2'-((5,5'-di-*tert*-butyl-6,6'-dihydroxy-[1,1'-biphenyl]-3,3'-diyl)bis(oxy))diacetate (12)



In a 5 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, 40.0 mg (89.6 µmol, 1 eq.) **11** were dissolved in 1 mL MeOH and treated with one drop (~0.3 mmol, 3 eq.) conc. H_2SO_4. The resulting orange solution was stirred for 3 h at r.t. (reaction monitoring via HPLC-MS), quenched by the addition of 2 mL sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the pure title compound as an off-white solid, which was used without further purification.

Yield: 41.0 mg (86.4 µmol, 96 %), off-white solid

$C_{26}H_{34}O_8$ [474.55 g·mol^{-1}]

R_f = 0.41 (cyclohexane:EtOAc = 3:1 (v/v), $KMnO_4$)

HPLC-MS (2_100_MEOH): t_R = 7.08 min; *m/z* (ESI-) = 473.2 $[M - H]^-$.

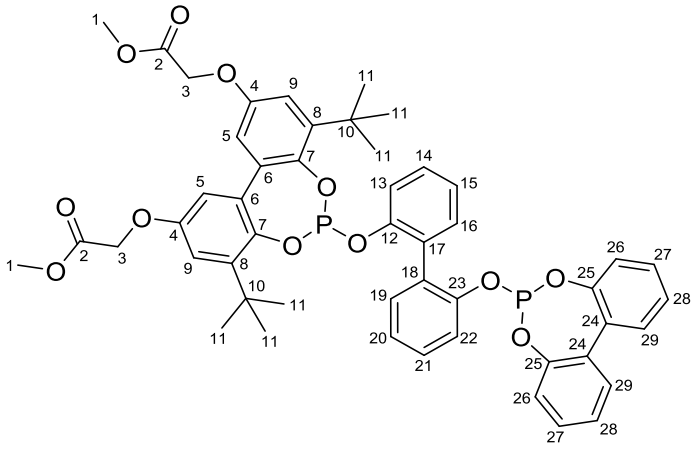
mp = 139-140 °C

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.02 (d, $^4J_{HH}$ = 2.8 Hz, 2H, H9), 6.56 (d, $^4J_{HH}$ = 2.9 Hz, 2H, H5), 5.07 (s, 2H, OH), 4.58 (s, 4H, H3), 3.80 (s, 6H, H1), 1.41 (s, 18H, H11).

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 169.7 (C_q, C2), 151.6 (C_q, C4), 146.9 (C_q, C7), 139.5 (C_q, C8), 123.0 (C_q, C6), 116.5 (CH, C9), 113.00 (CH, C5), 66.2 (CH_2, C3), 52.4 (CH_3, C1), 35.4 (C_q, C10), 29.6 (CH_3, C11).

HRMS (EI-DI TOF): calcd. for $C_{26}H_{34}O_8^+$ $[M]^+$: 474.2254; found: 474.2258.

6.5.13. Dimethyl 2,2'-((4,8-di-*tert*-butyl-6-((2'-(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yloxy)-[1,1'-biphenyl]-2-yl)oxy)dibenzo[*d*,*f*][1,3,2]-dioxaphosphepin-2,10-diyl)bis(oxy))diacetate (13)



In a flame-dried, evacuated and argon purged 10 mL one-neck round-bottom flask, equipped with a Teflon-coated magnetic stirring bar, 16.0 mg (63.8 µmol, 2.1 eq.) **8** were cooled to 0 °C (ice bath). Then a solution of 14.6 mg (30.8 µmol, 1 eq.) **12** and 0.03 mL (0.2 mmol, 7.0 eq.) abs. NEt_3 in 0.5 mL abs. toluene was added dropwise over a period of 5 min and the flask containing the former solution was rinsed with 0.25 mL abs. toluene. The resulting reaction mixture was stirred for 10 min at 0 °C and for an additional 46 h at r.t. (reaction monitoring via HPLC-MS). Subsequently, 1 mL H_2O was added to the yellow-brownish suspension, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash column chromatography (5 g SiO_2, 8.5 x 1.3 cm, cyclohexane:EtOAc = 3:1 (v/v)) provided the title compound as a colorless solid.

Yield: 12.8 mg (14.2 µmol, 46 %), colorless solid

$C_{50}H_{48}O_{12}P_2$ [902.87 g·mol^{-1}]

R_f = 0.30 (cyclohexane:EtOAc = 3:1 (v/v), CAM)

HPLC-MS (2_100_MECN): t_R = 8.13 min; no mass could be detected.

^{1}H-NMR (499.87 MHz, C_6D_6): δ = 7.40 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.34-7.27 (m, 3H), 7.19-7.16 (m, 2H), 7.12 (d, $^4J_{HH}$ = 3.1 Hz, 2H, H9), 7.09 (td, *J* = 8.1, 1.6 Hz, 1H), 7.04 (td, *J* = 8.0, 1.6 Hz, 1H), 6.99 (td, *J* = 7.6, 1.6 Hz, 2H), 6.96-6.86 (m, 6H), 6.59 (d, $^4J_{HH}$ = 3.0 Hz, 2H, H5), 4.18 (s, 4H, H3), 3.29 (s, 6H, H1), 1.32 (s, 18H, H11).

^{13}C-NMR (125.69 MHz, C_6D_6): δ = 169.0 (C_q, C2), 154.9 (C_q, C4), 150.0 (C_q), 149.9 (C_q), 149.9 (d, J_{CP} = 5.2 Hz, C_q), 143.4 (C_q, C8), 142.9 (d, J_{CP} = 5.8 Hz, C_q, C7), 134.2 (d, J_{CP} = 3.2 Hz, C_q, C6), 133.2 (CH), 132.8 (CH), 131.8 (d, J_{CP} = 2.5 Hz, C_q), 130.8 (d, J_{CP} = 2.6 Hz, C_q), 130.6 (C_q), 130.1 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 125.4 (CH), 124.3 (CH), 124.0 (CH), 122.6 (CH), 121.5 (d, J_{CP} = 11.4 Hz, CH), 121.2 (d, J_{CP} = 10.2 Hz, CH), 116.1 (CH, C9), 114.1 (CH, C5), 65.9 (CH_2, C3), 51.5 (CH_3, C1), 35.5 (C_q, C10), 31.0 (CH_3, C11).

^{31}P-NMR (202.35 MHz, C_6D_6): δ = 144.7 (d, J_{PP} = 4.0 Hz), 138.7 (d, J_{PP} = 3.8 Hz), small resonance at 146.0 (9 %).

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8. ABBREVIATIONS

%	percent
(*S*)	sinister (lat.: left)
(v/v)	volume per volume
°C	degree Celsius
µL	microliter
µm	micrometer
µM	micromolar
µmol	micromol
1D	one-dimensional
2D	two-dimensional
Å	ångström
aa	amino acid
abs.	absolute (dry solvent)
Ac	acetyl
amu	atomic mass unit
APT	attached proton test
aq.	aqueous (phase)
Ar	aryl
BIPHEPHOS	6,6'-((3,3'-di-*tert*-butyl-5,5'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(oxy))bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin)
bp	boiling point
br s	broad singlet
Bu	butyl
calcd.	calculated
CAM	cerium ammonium molybdate
Cat	catalyst
cat.	catalytic
cm	centimeter
conc.	concentrated
conv.	conversion

COSY	correlated spectroscopy
C_q	quaternary carbon
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublet
Dha	dehydroalanine
DIAD	diisopropyl azodicarboxylate
DI-EI	direct inlet electron impact ionization
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DTNB	5,5-dithiobis(2-nitrobenzoate)
E	energy
e.g.	exempli gratia (lat.: for example)
EI	electron-impact ionization
eq.	equivalent
equiv.	equivalent
ESI	electrospray ionization
et al.	et alii (lat.: and others)
Et	ethyl
EtOAc	ethyl acetate
eV	electronvolt
EWG	electron withdrawing group
FTase	farnesyl transferase
g	gram
GC-MS	gas chromatography mass spectrometry
GGTase	geranylgeranyl transferase
h	hour(s)
Hb	hemoglobin
HMBC	heteronuclear multiple-bond correlation
HPLC	high performance liquid chromatography

HPLC-MS	high performance liquid chromatography mass spectrometry
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
Hz	Hertz
i	iso
i-oct	isooctyl
*i*Pr	isopropyl
J	coupling constant
L	ligand
L	liter
LG	leaving group
m	meter
M	molar
m	multiplet
m/z	mass to charge ratio
MALDI	matrix-assisted laser desorption/ionization
mbar	millibar
Me	methyl
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mm	millimeter
mmol	millimol
mol%	mol percent
mp	melting point
MPa	megapascal
mRNA	messenger RNA
MS	mass spectrometry
MS	molecular sieve
MSH	*O*-mesitylenesulfonylhydroxylamine
n	normal (linear, unbranched)
nm	nanometer

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OAc	acetate
org.	organic (phase)
p	para
PEG	polyethylene glycol
pH	negative of the logarithm to base 10 of the activity of H_3O^+
Ph	phenyl
PP	pyrophosphate
ppm	parts per million
PTM	post-translational modification
q	quadruplet
r.t.	room temperature
R_f	retardation factor or ratio of fronts
RNA	ribonucleic acid
ROMP	ring-opening metathesis polymerization
rpm	revolutions per minute
s	second
s	singlet
Sac	*S*-allyl cysteine
sat.	saturated
SBL	subtilisin *Bacillus lentus*
soln.	solution
t	tertiary
t	triplet
$t_{1/2}$	half-life
td	triplet of doublet
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSE	(trimethylsilyl)ethyl
TOF	time-of-flight
TPPMS	(3-sulfonatophenyl)diphenylphosphine

TPPTS	tris(3-sulfonatophenyl)phosphine
t_R	retention time
Ts	tosyl
UV	ultraviolet
wt%	weight percent
δ	chemical shift
λ	wavelength

Amino Acid Abbreviations

Amino Acid	**Three Letter Code**	**One Letter Code**
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamic acid	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

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habt dieses auch um einiges unterhaltsamer gemacht und abseits davon für willkommenen Ausgleich gesorgt.

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10. APPENDIX

NMR-Spectra

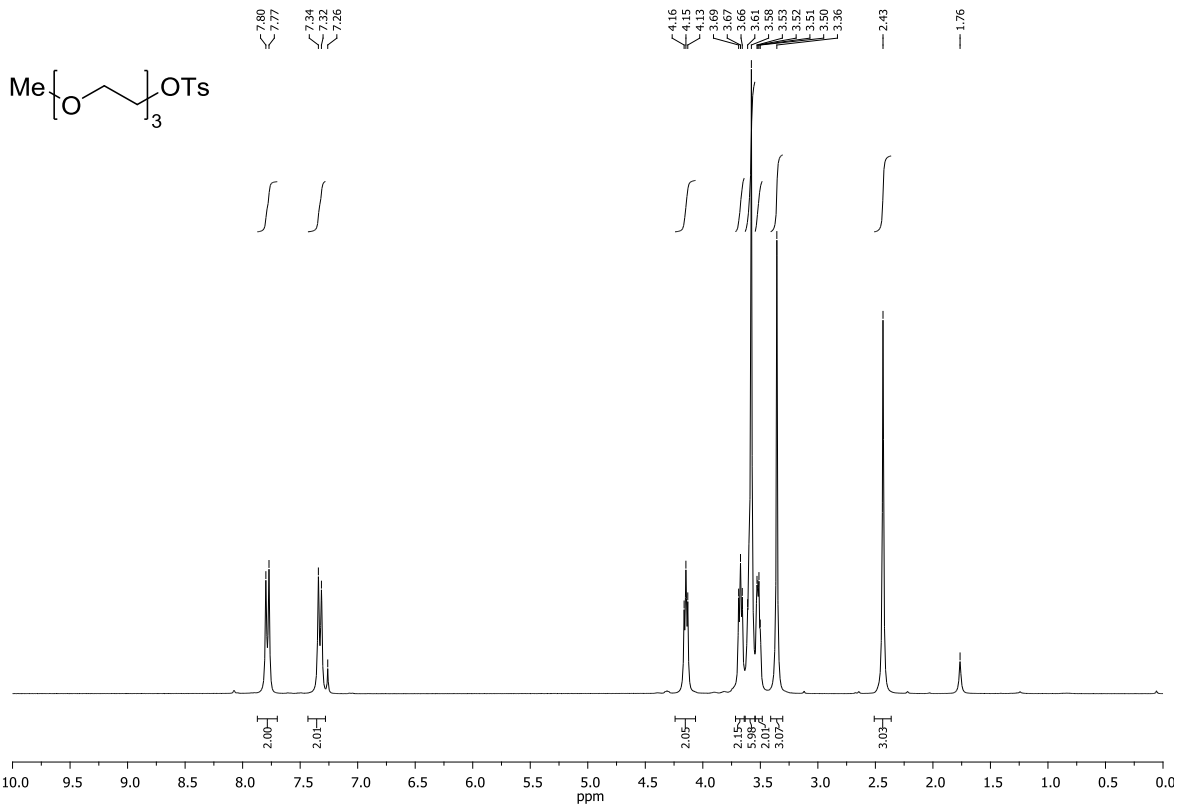

Figure 11. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **1**.

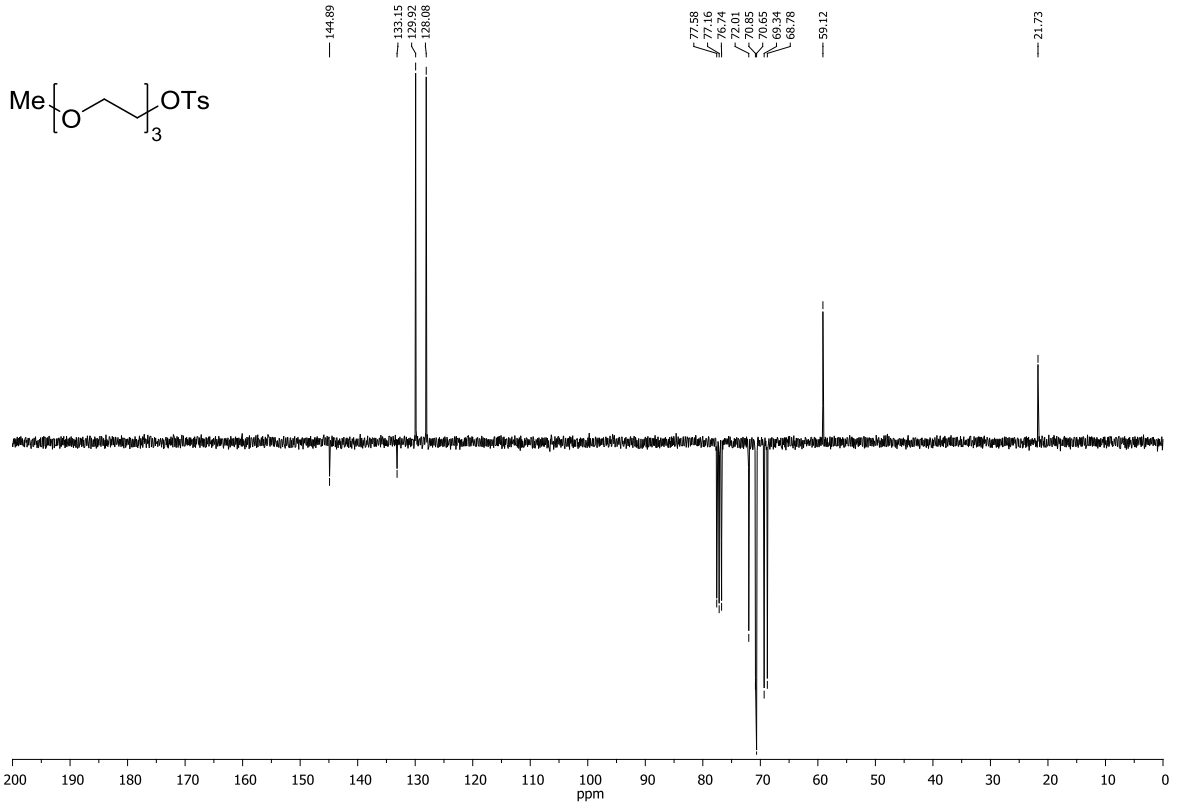

Figure 12. ^{13}C-NMR,APT (75.53 MHz, $CDCl_3$) of compound **1**.

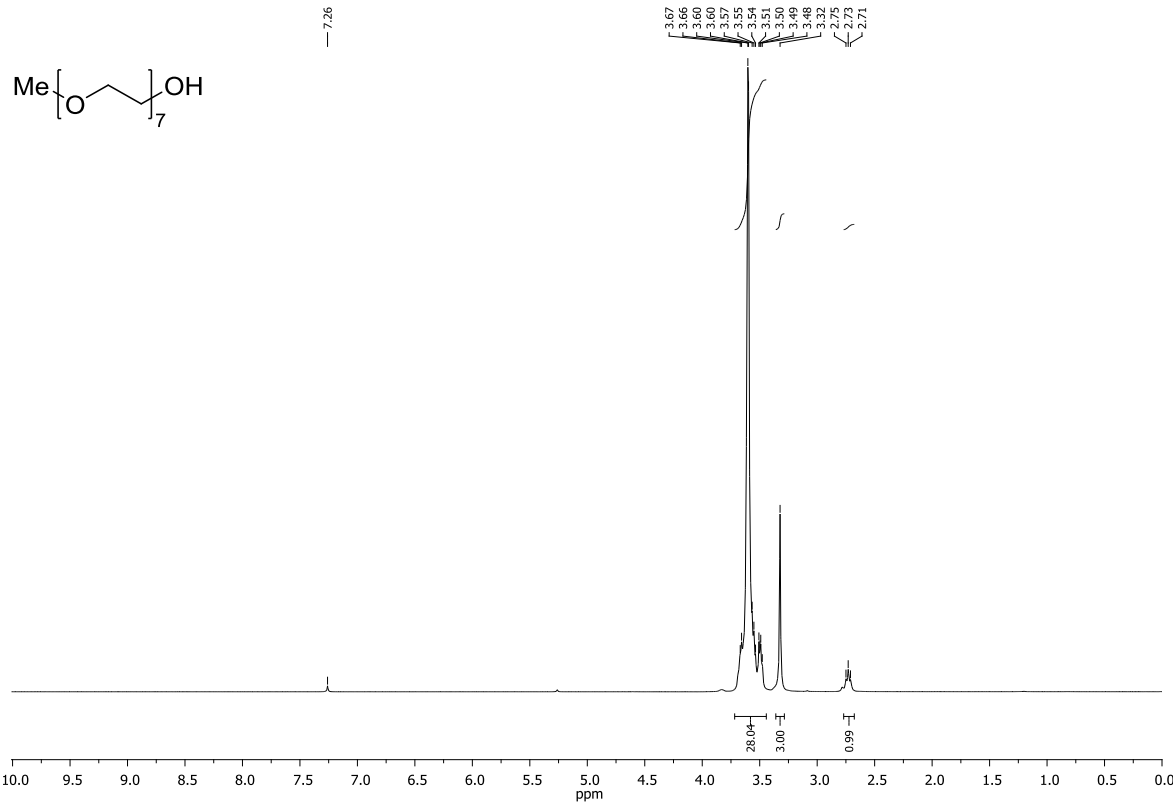

Figure 13. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **2**.

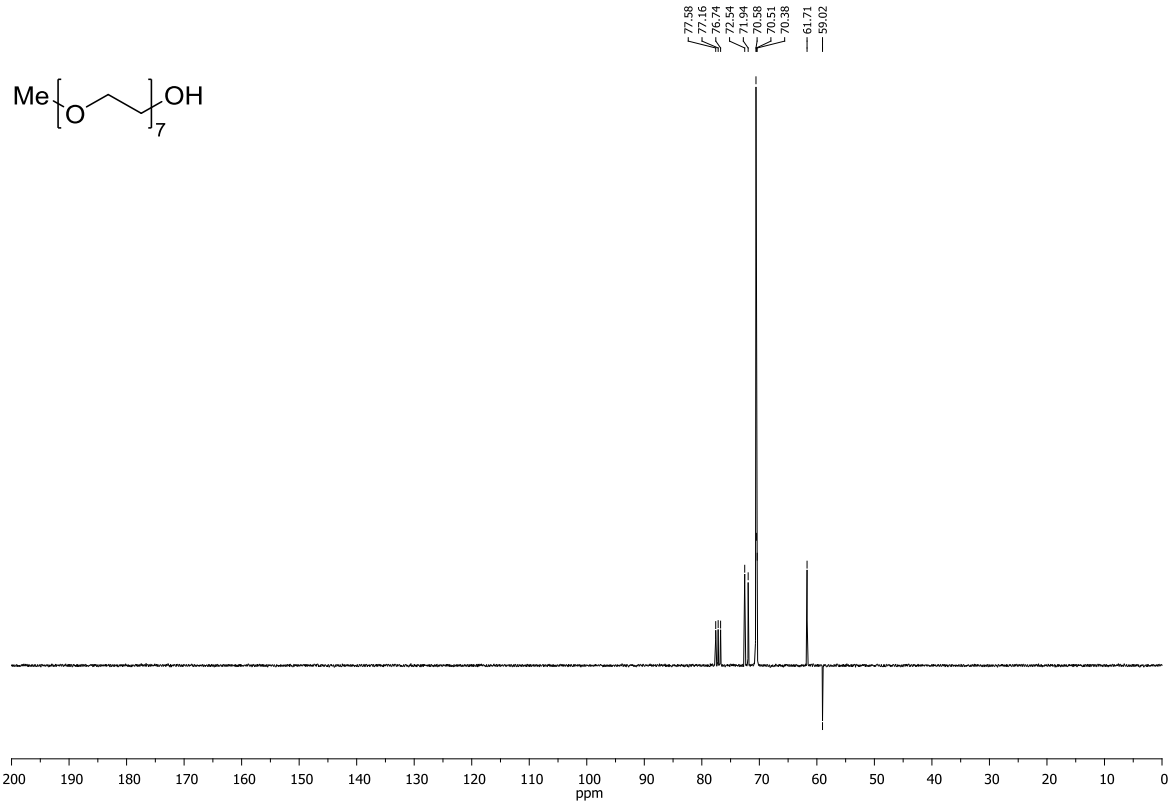

Figure 14. ^{13}C-NMR,APT (75.53 MHz, $CDCl_3$) of compound **2**.

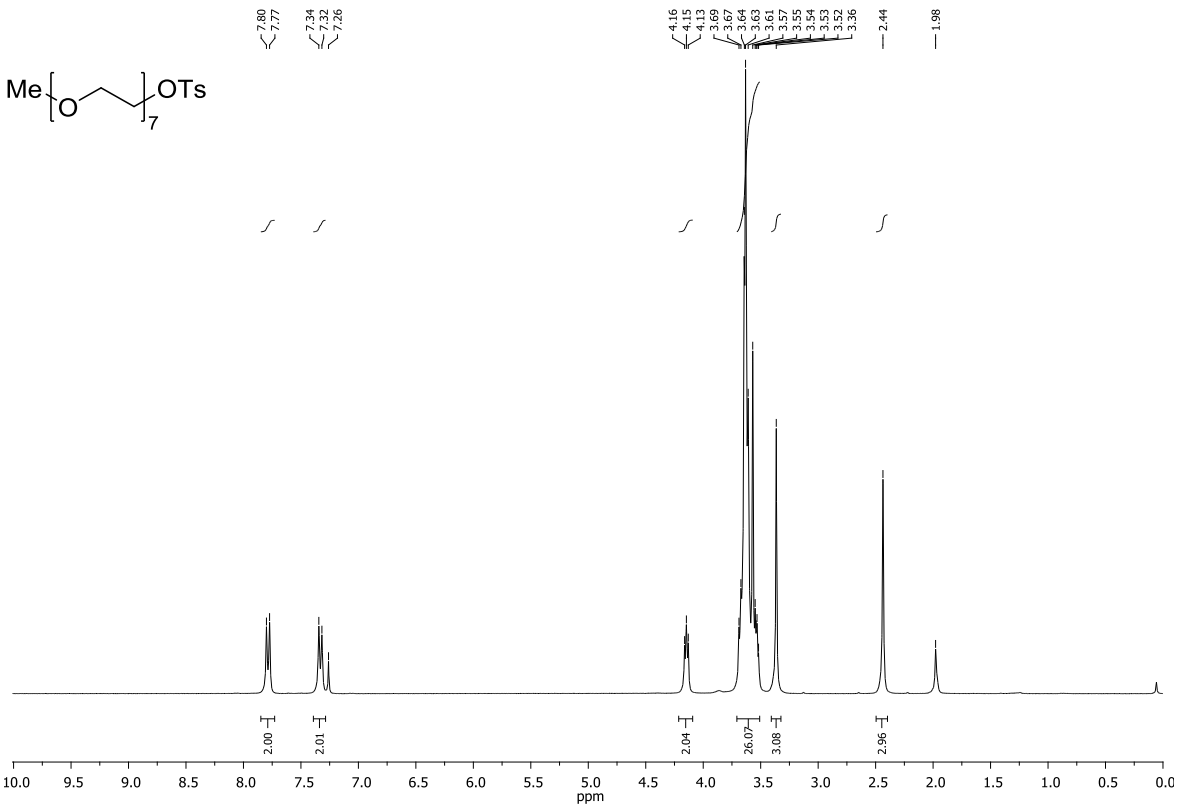

Figure 15. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **3**.

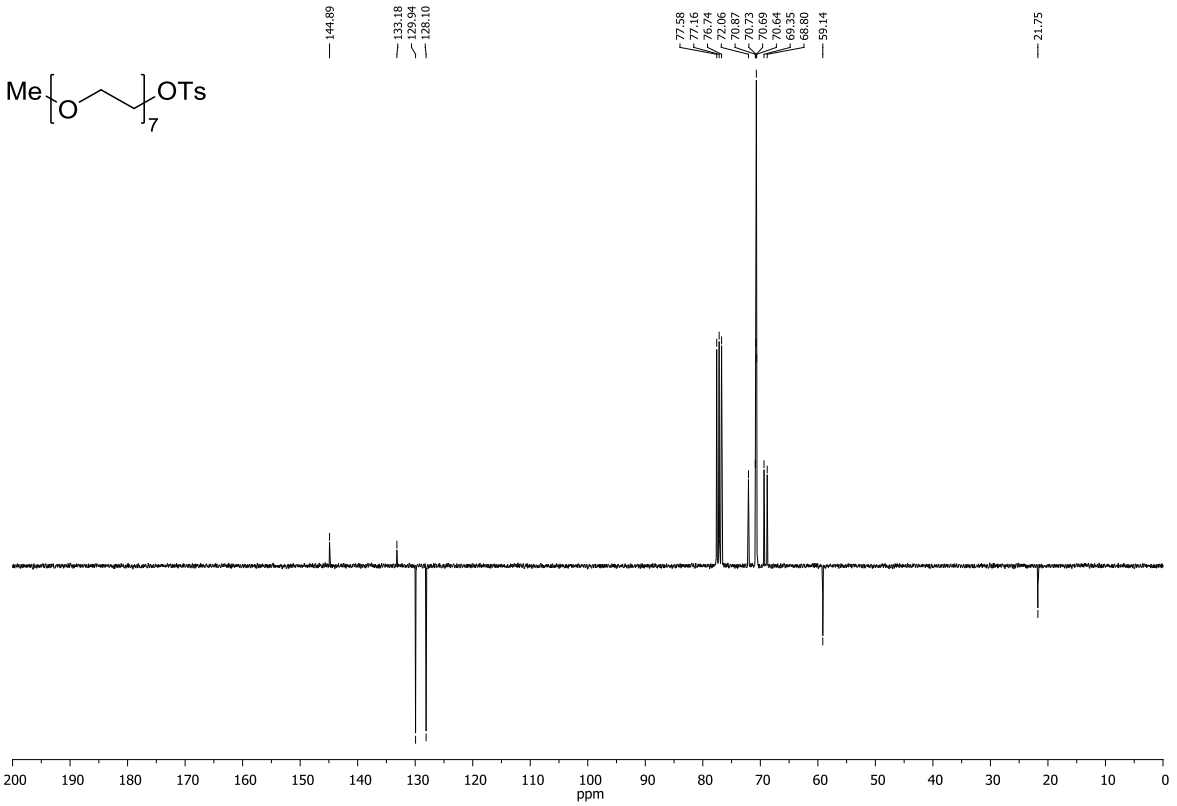

Figure 16. ^{13}C-NMR,APT (75.53 MHz, $CDCl_3$) of compound **3**.

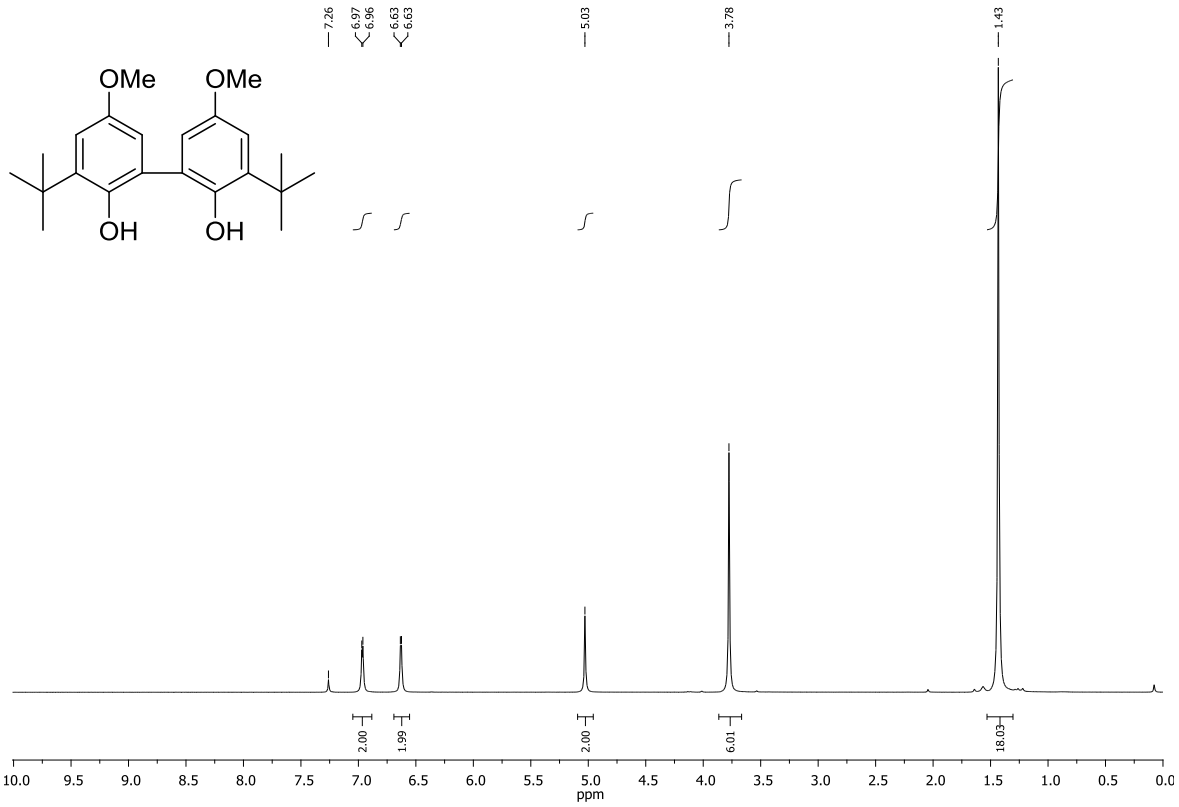

Figure 17. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **4**.

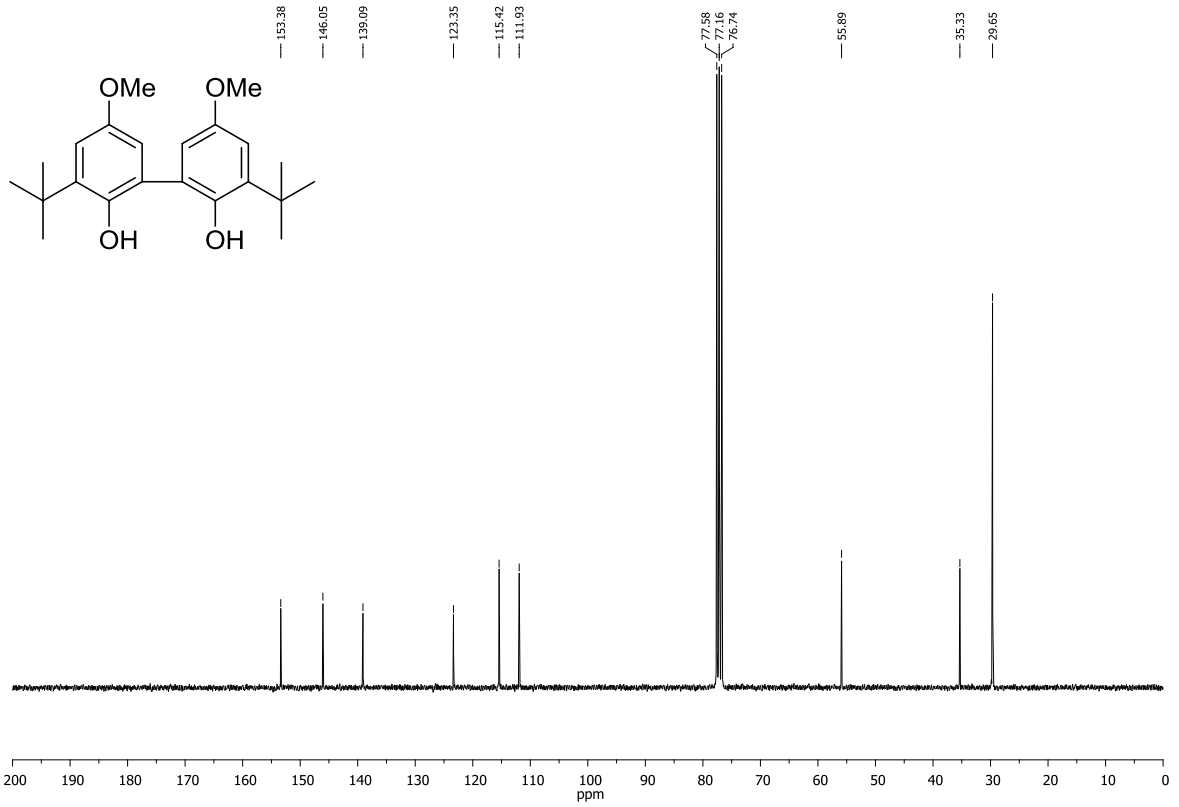

Figure 18. ^{13}C-NMR (75.53 MHz, $CDCl_3$) of compound **4**.

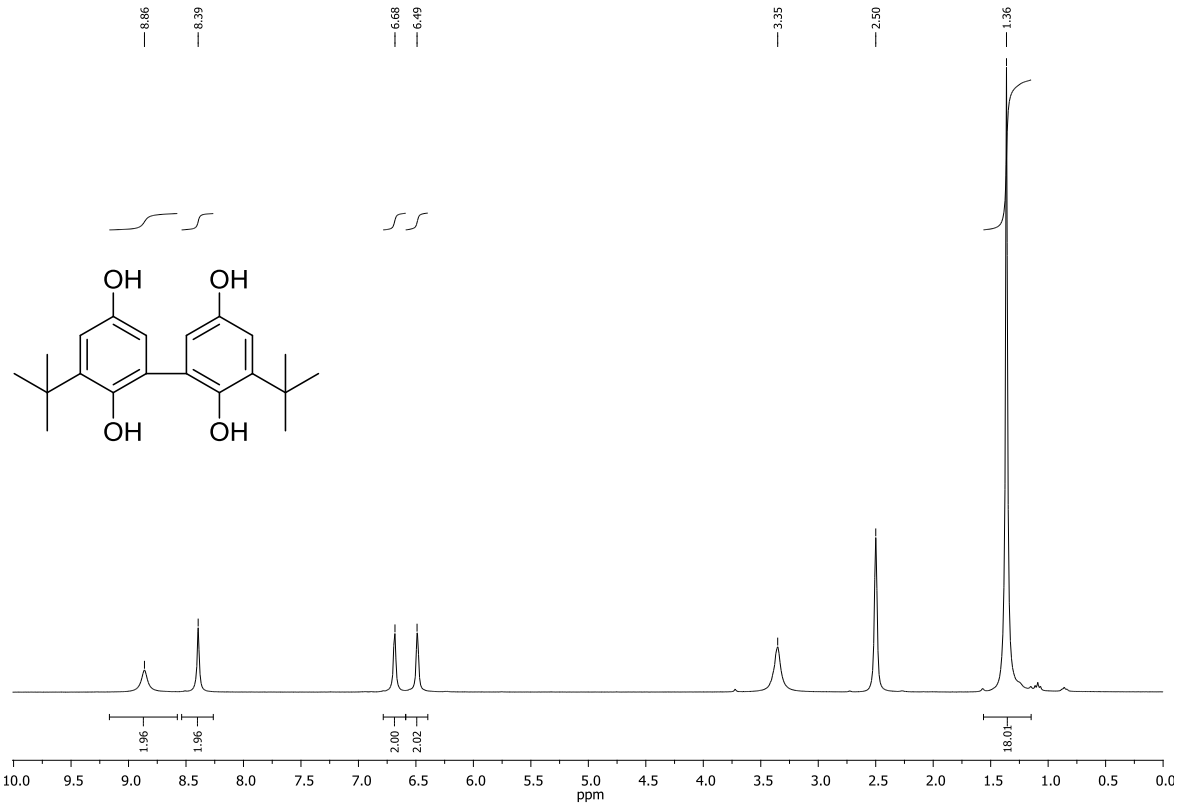

Figure 19. ^{1}H-NMR (300.36 MHz, DMSO-d_6) of compound **5**.

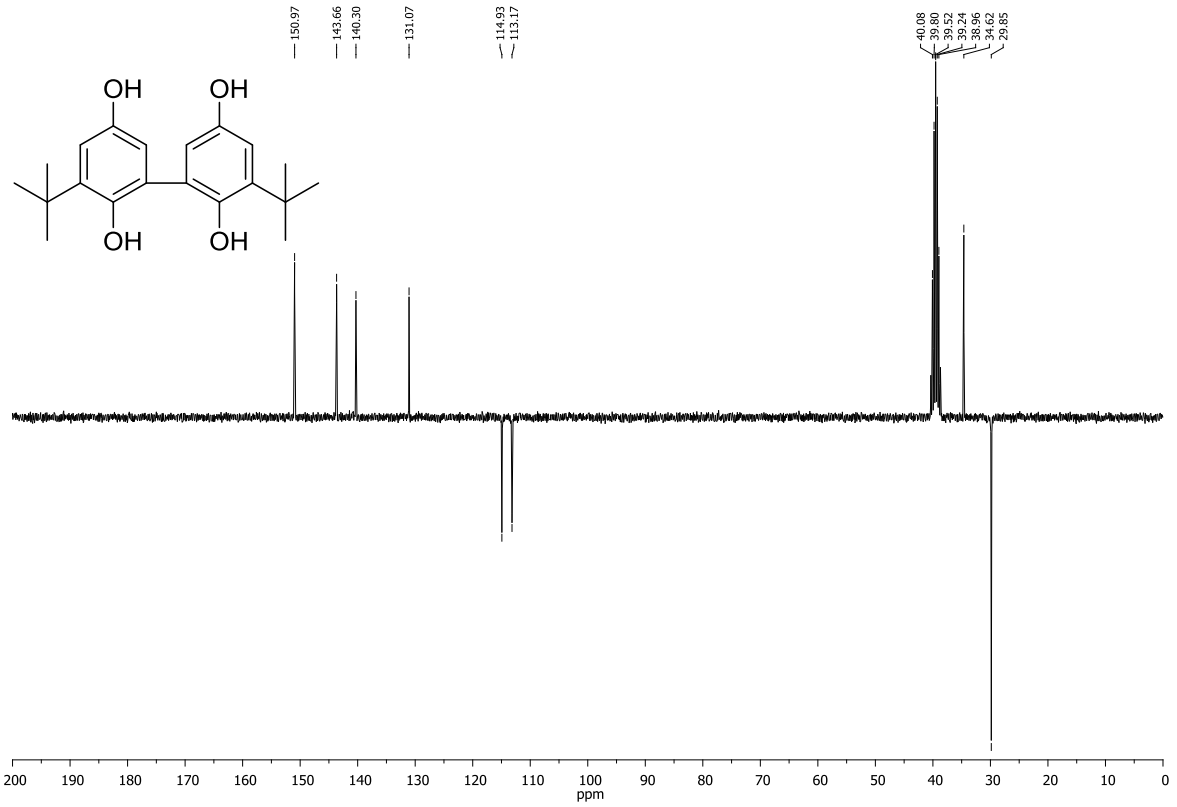

Figure 20. ^{13}C-NMR,APT (75.53 MHz, DMSO-d_6) of compound **5**.

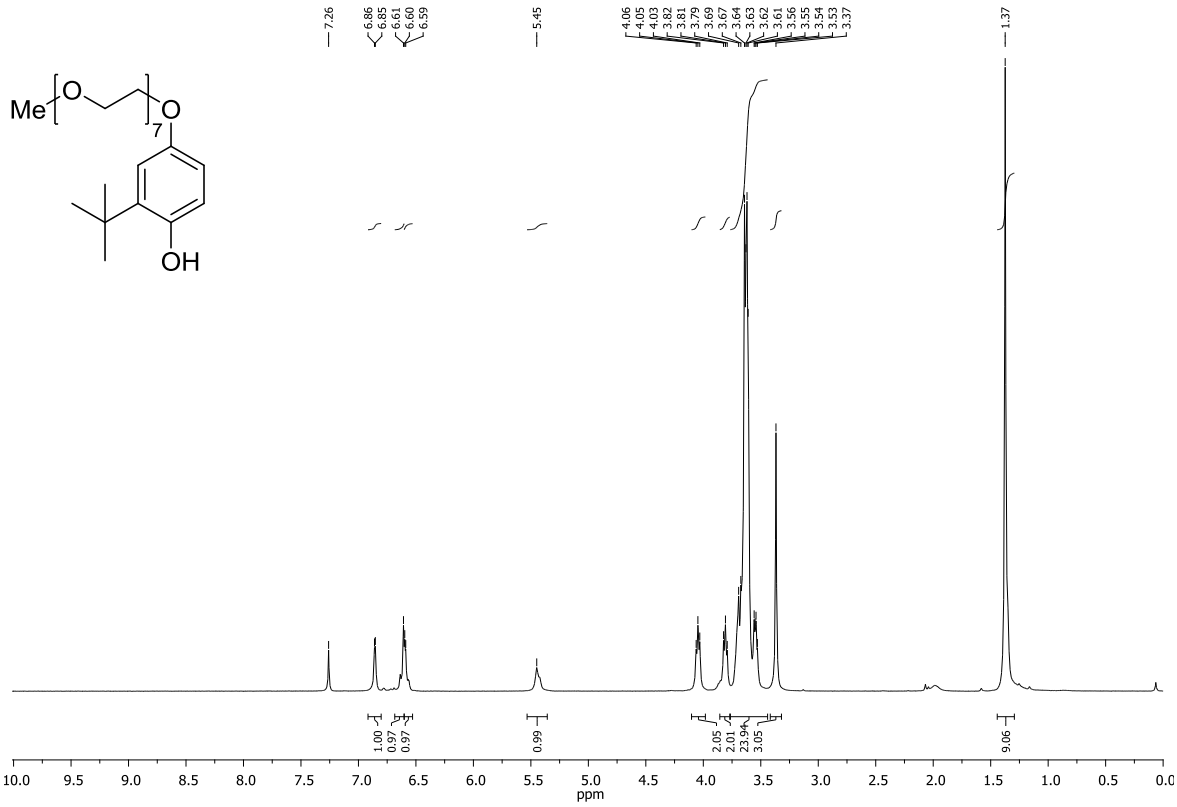

Figure 21. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **6**.

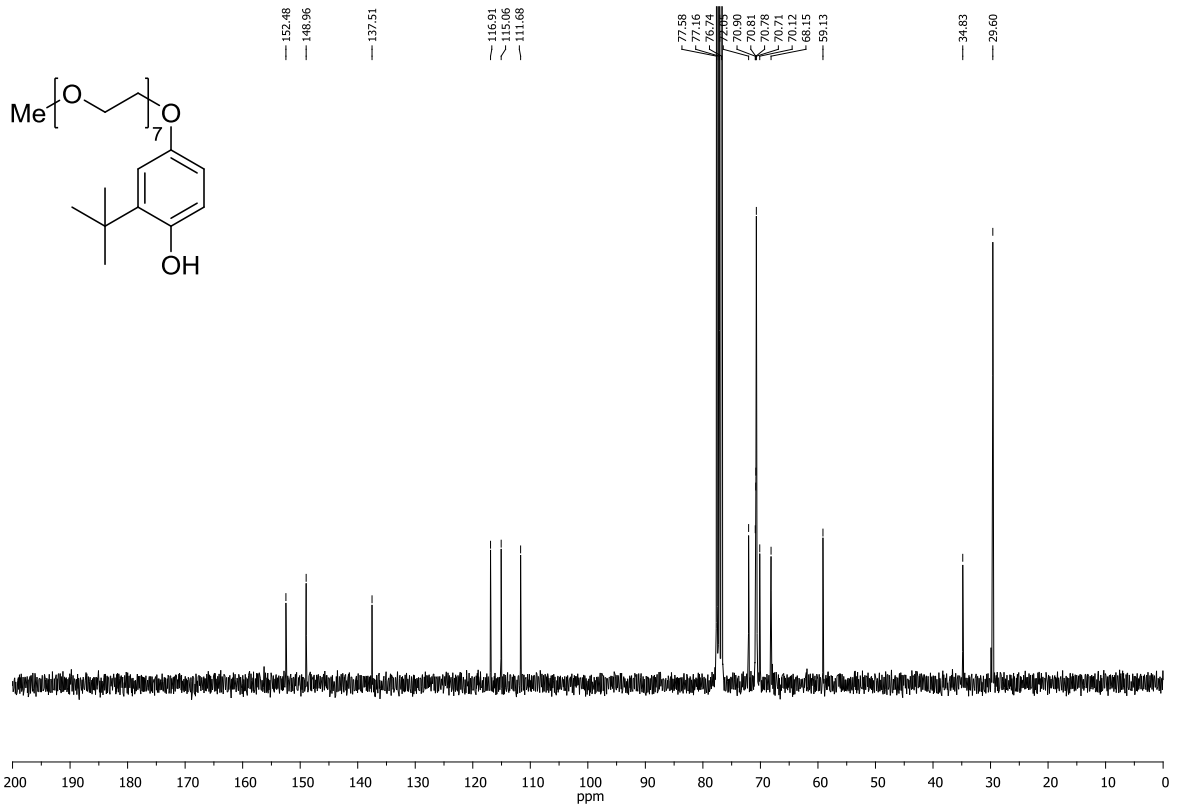

Figure 22. ^{13}C-NMR (75.53 MHz, $CDCl_3$) of compound **6**.

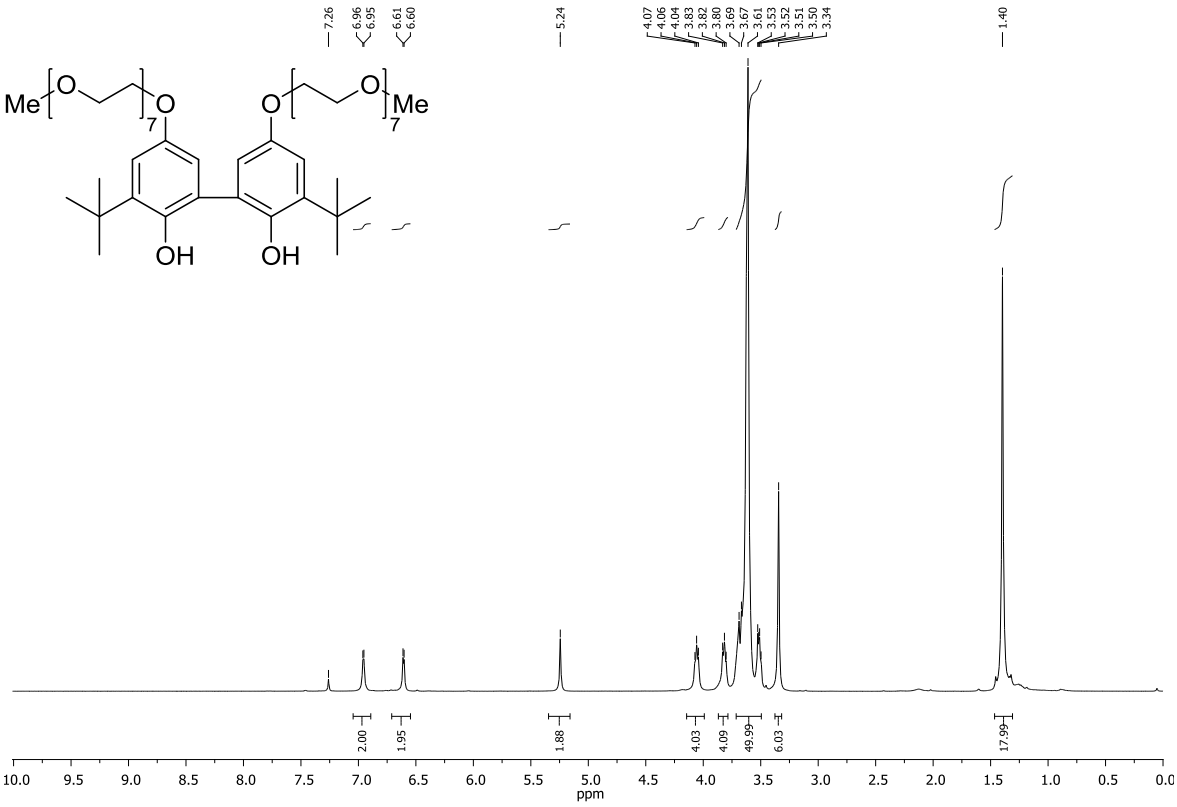

Figure 23. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **7**.

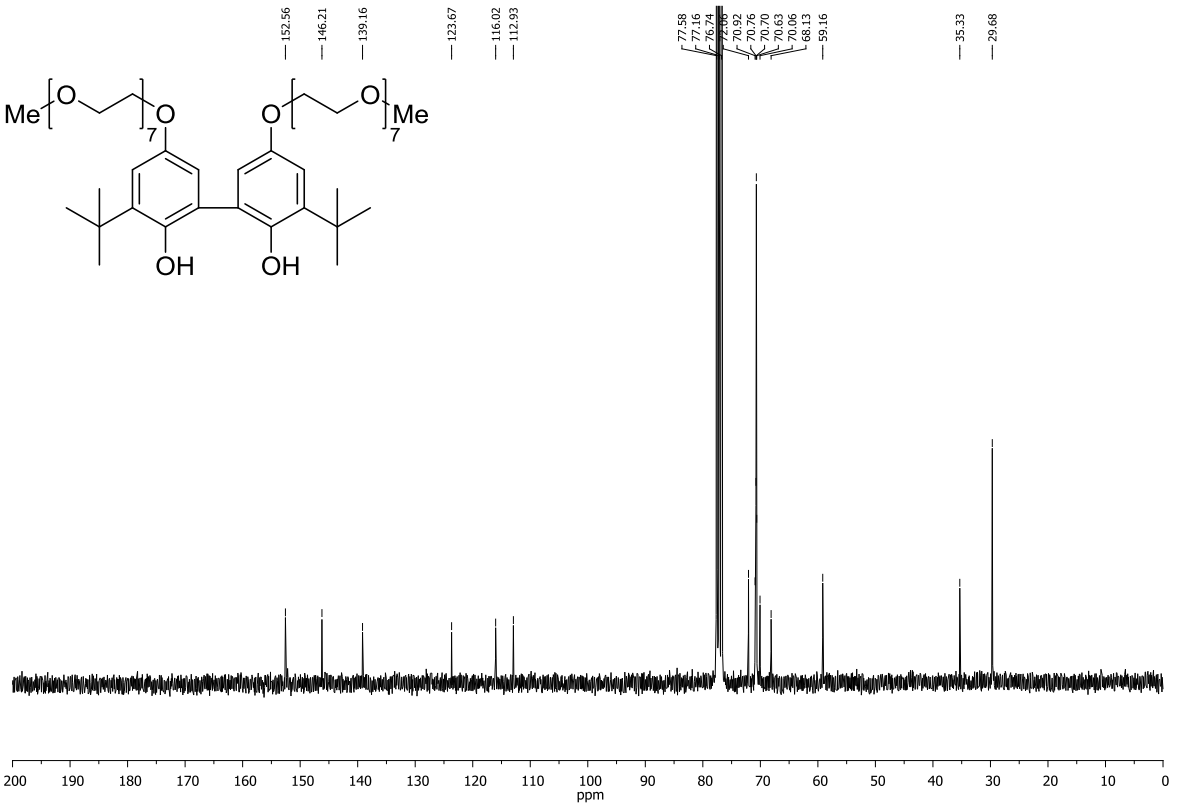

Figure 24. ^{13}C-NMR (75.53 MHz, $CDCl_3$) of compound **7**.

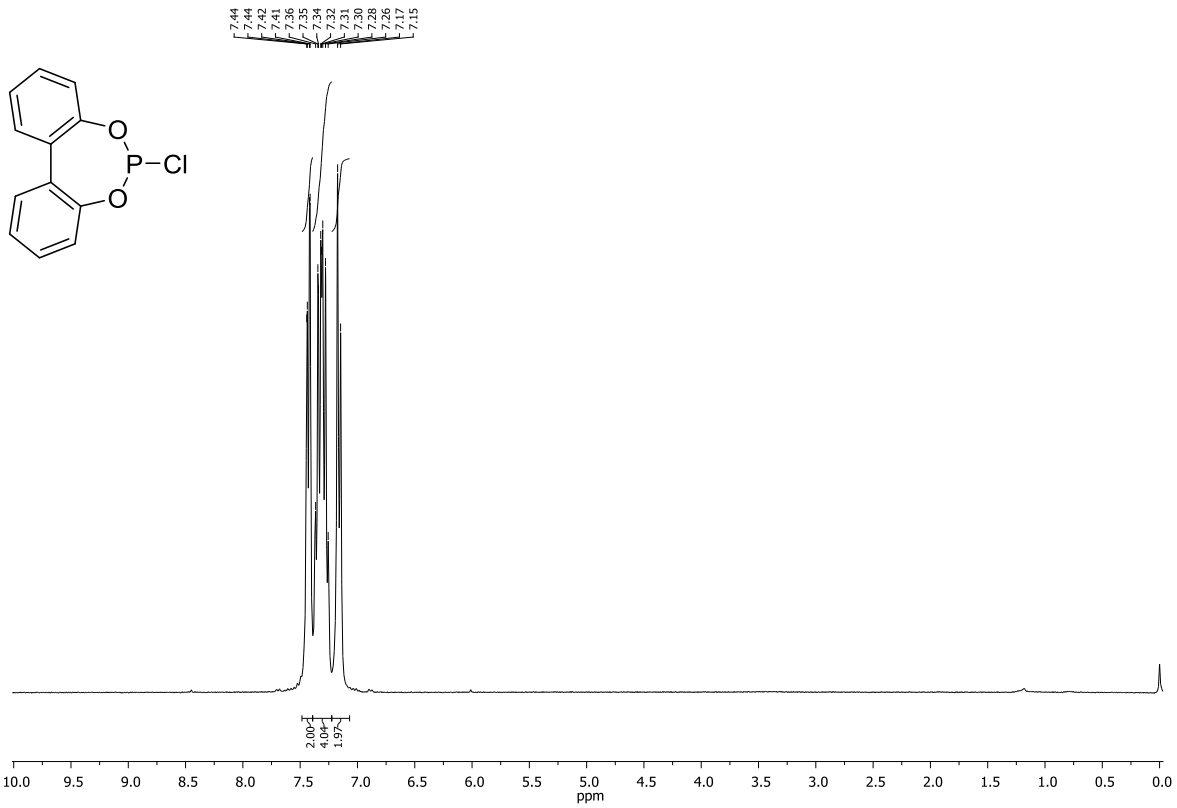

Figure 25. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **8**.

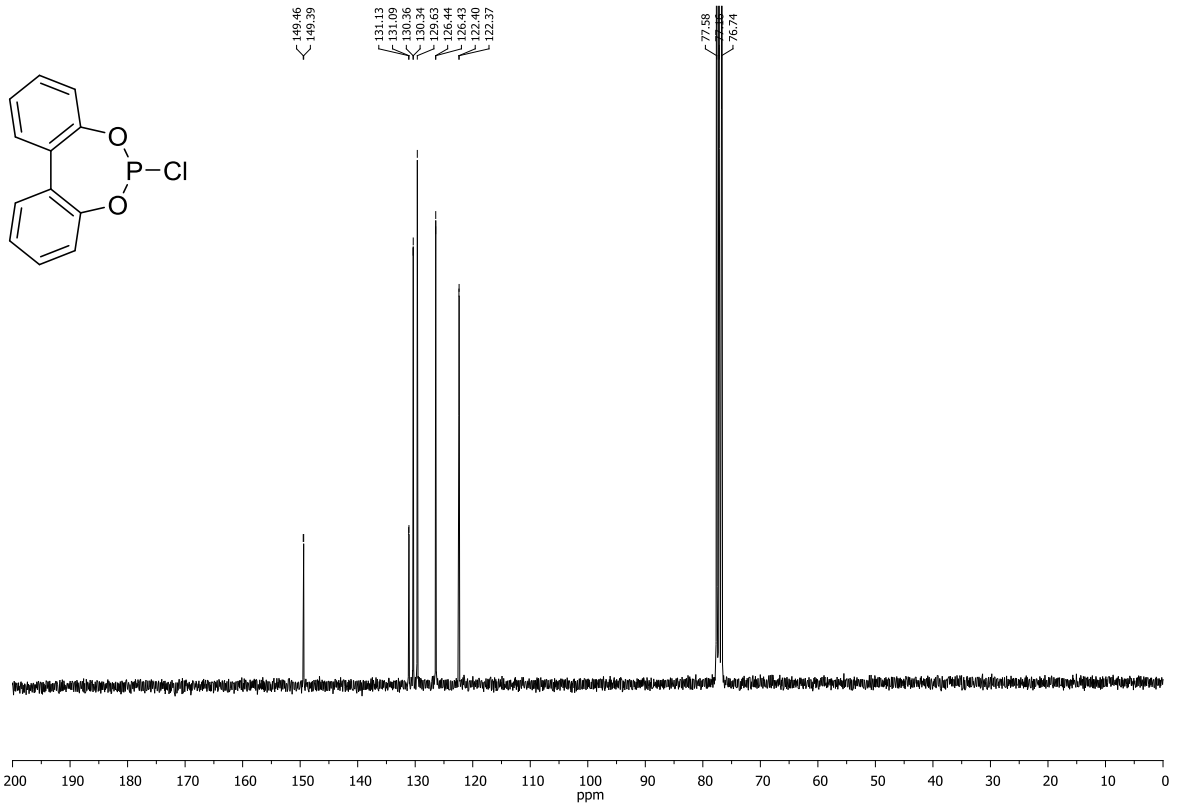

Figure 26. ^{13}C-NMR (75.53 MHz, $CDCl_3$) of compound **8**.

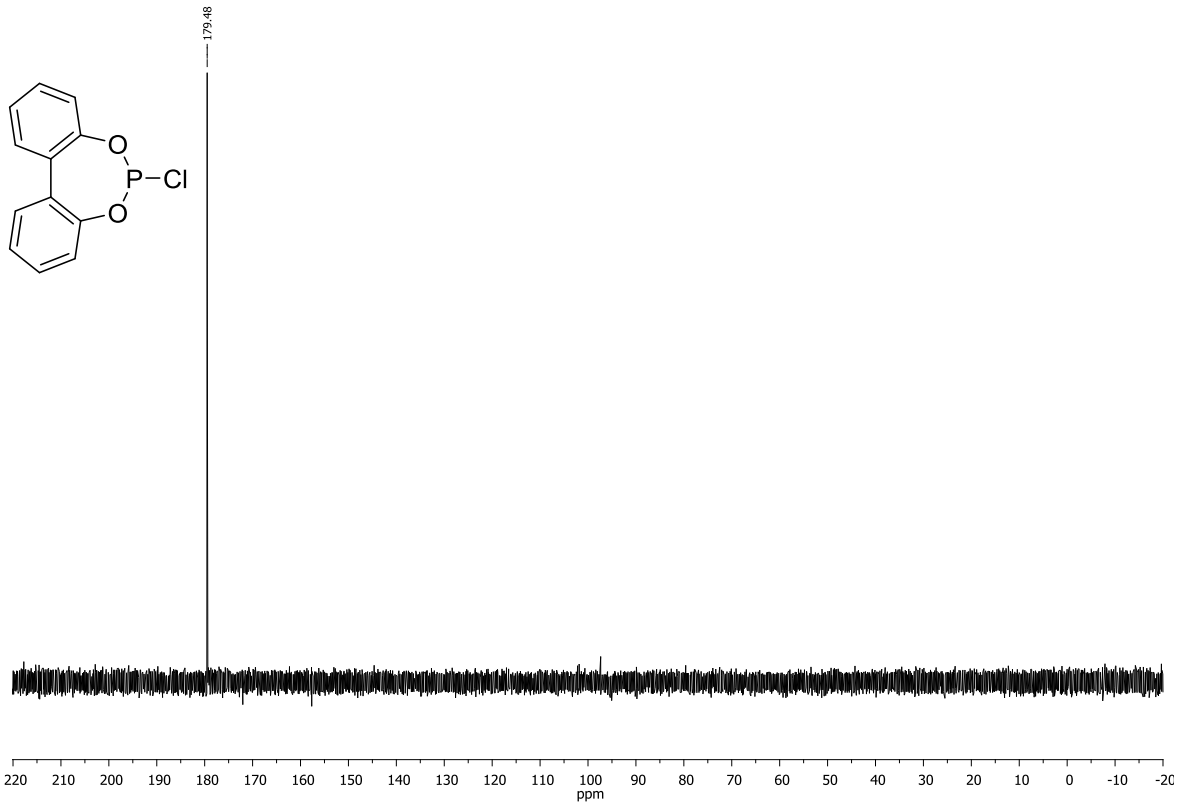

Figure 27. ^{31}P-NMR (121.42 MHz, $CDCl_3$) of compound **8**.

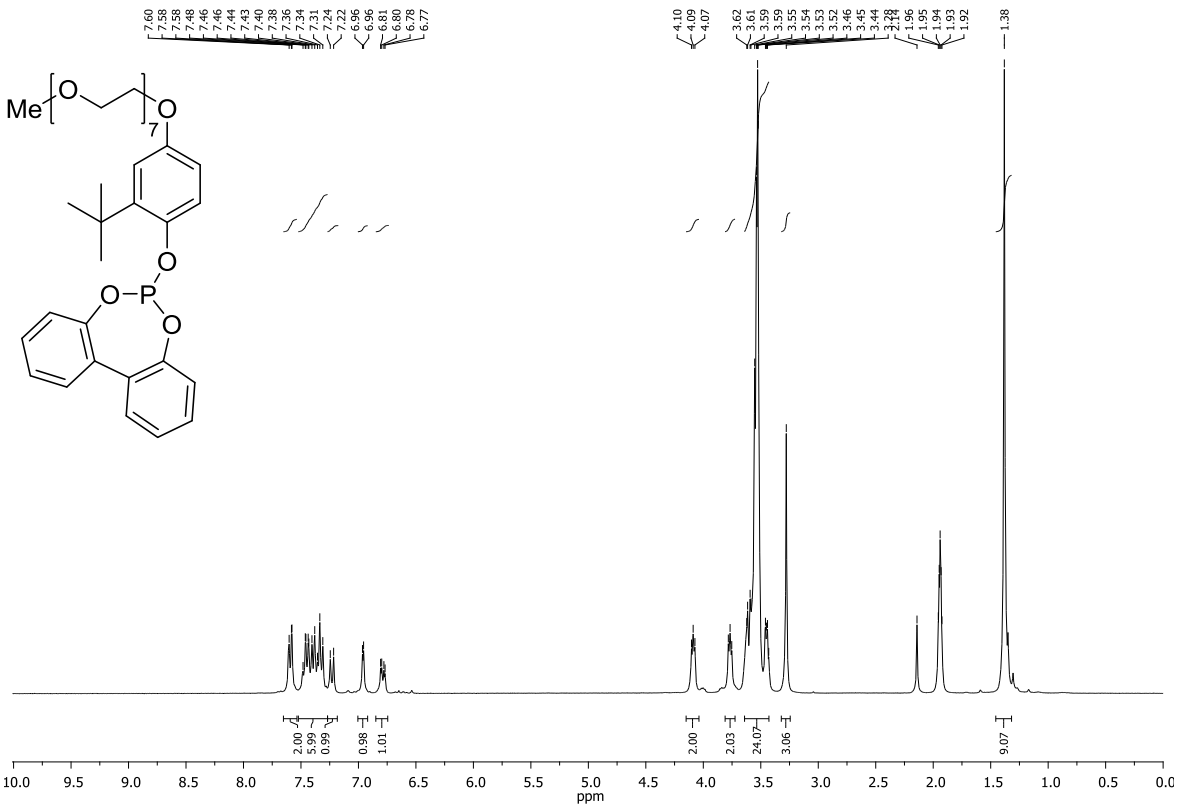

Figure 28. ^{1}H-NMR (300.36 MHz, CD_3CN) of compound **9**.

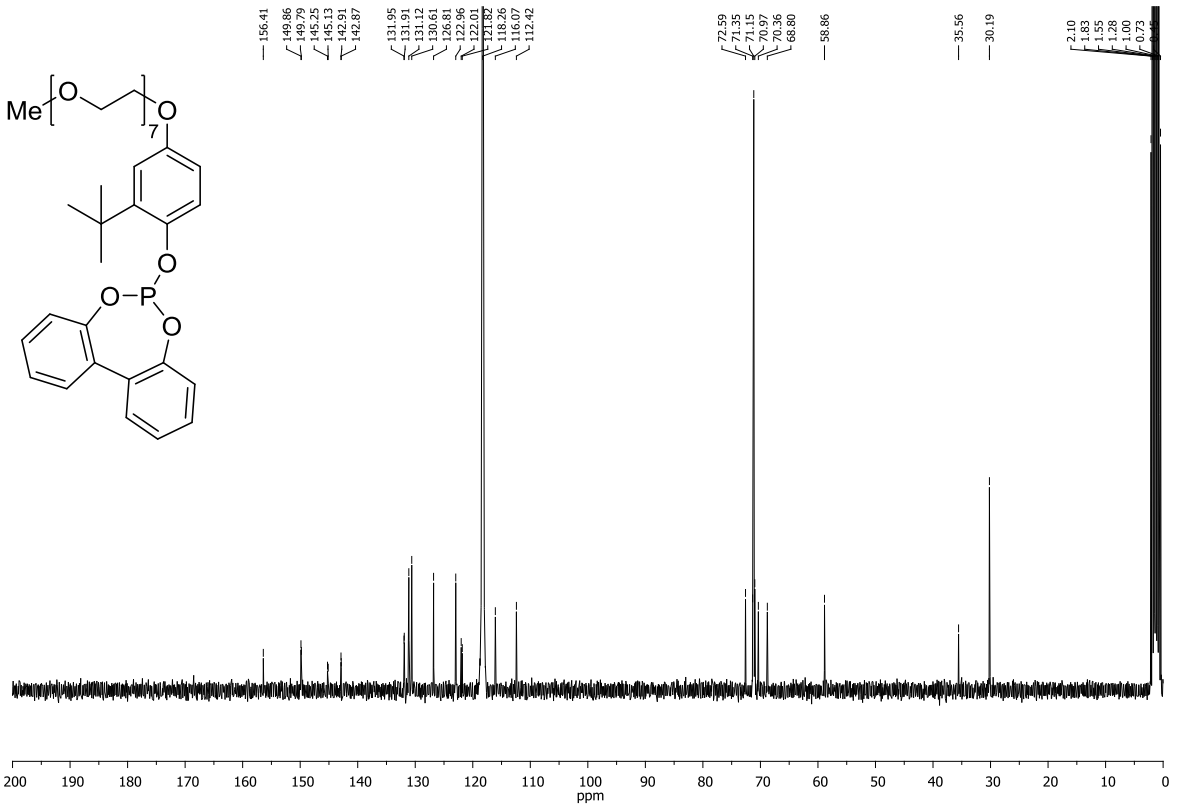

Figure 29. ^{13}C-NMR (75.53 MHz, CD_3CN) of compound **9**.

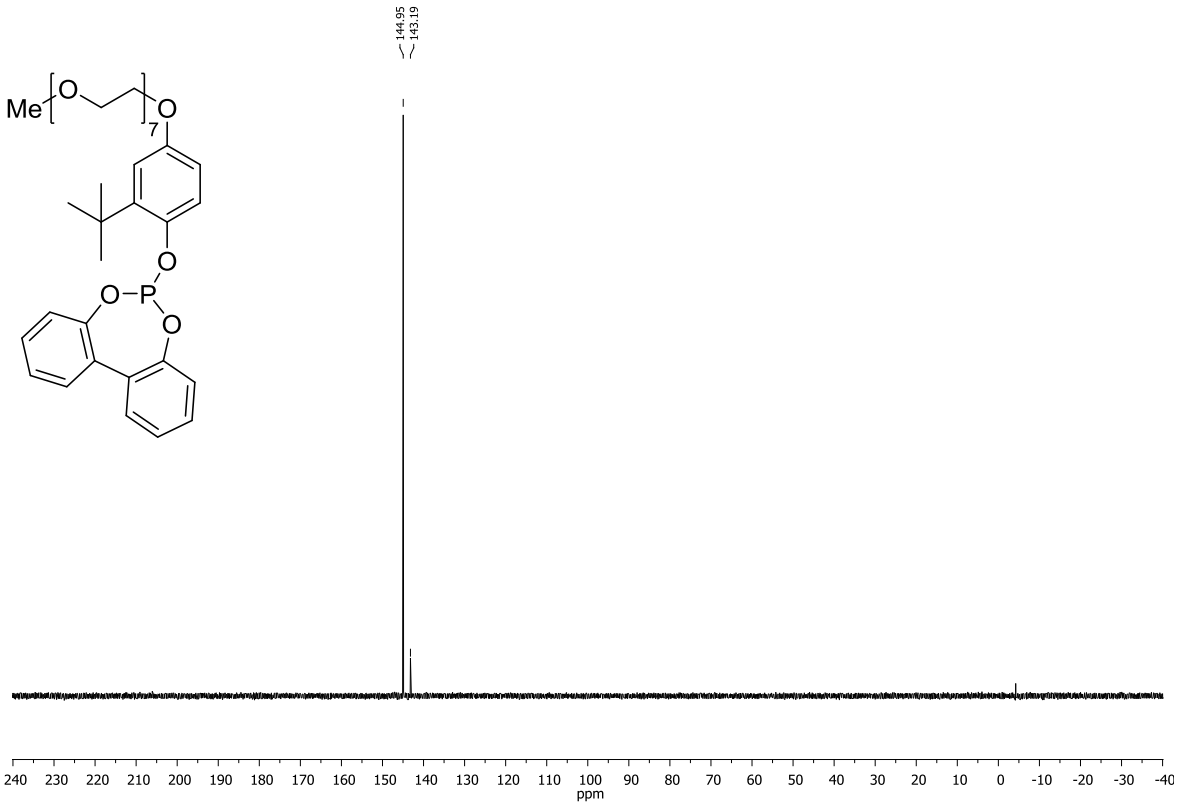

Figure 30. ^{31}P-NMR (202.35 MHz, CD_3CN) of compound **9**.

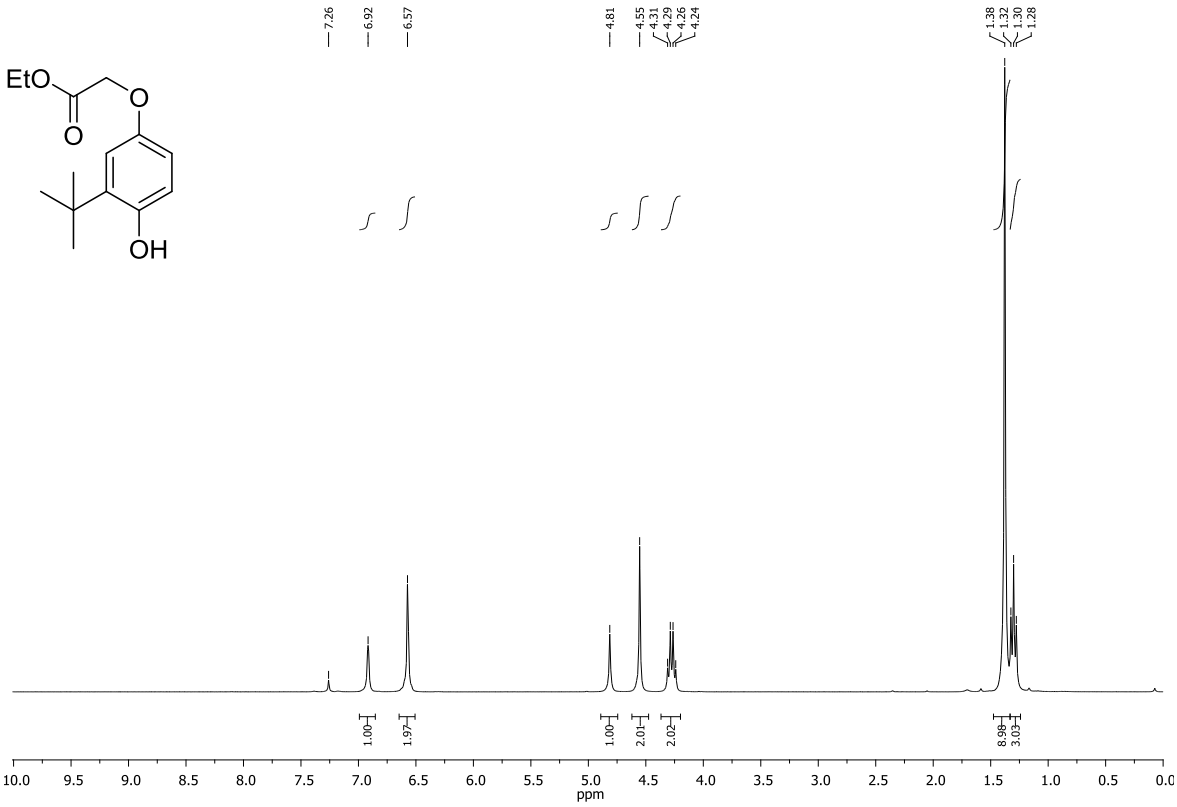

Figure 31. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **10**.

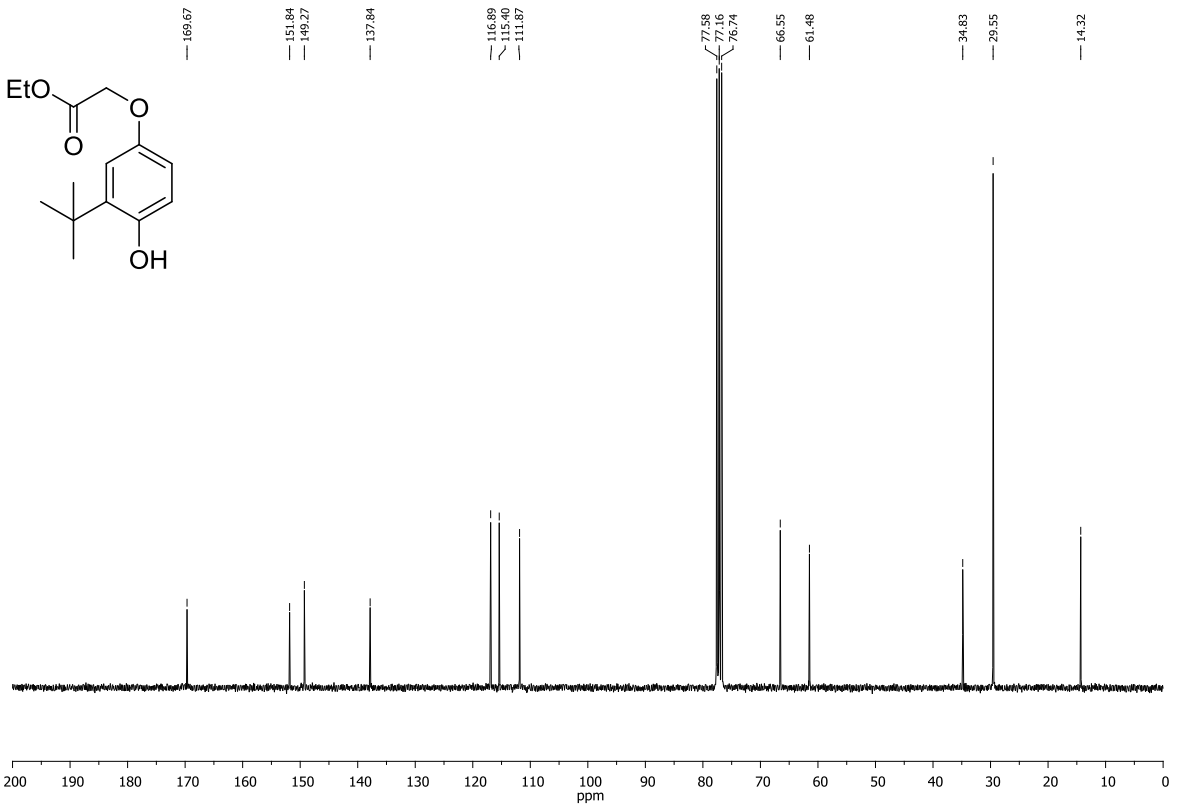

Figure 32. ^{13}C-NMR (75.53 MHz, $CDCl_3$) of compound **10**.

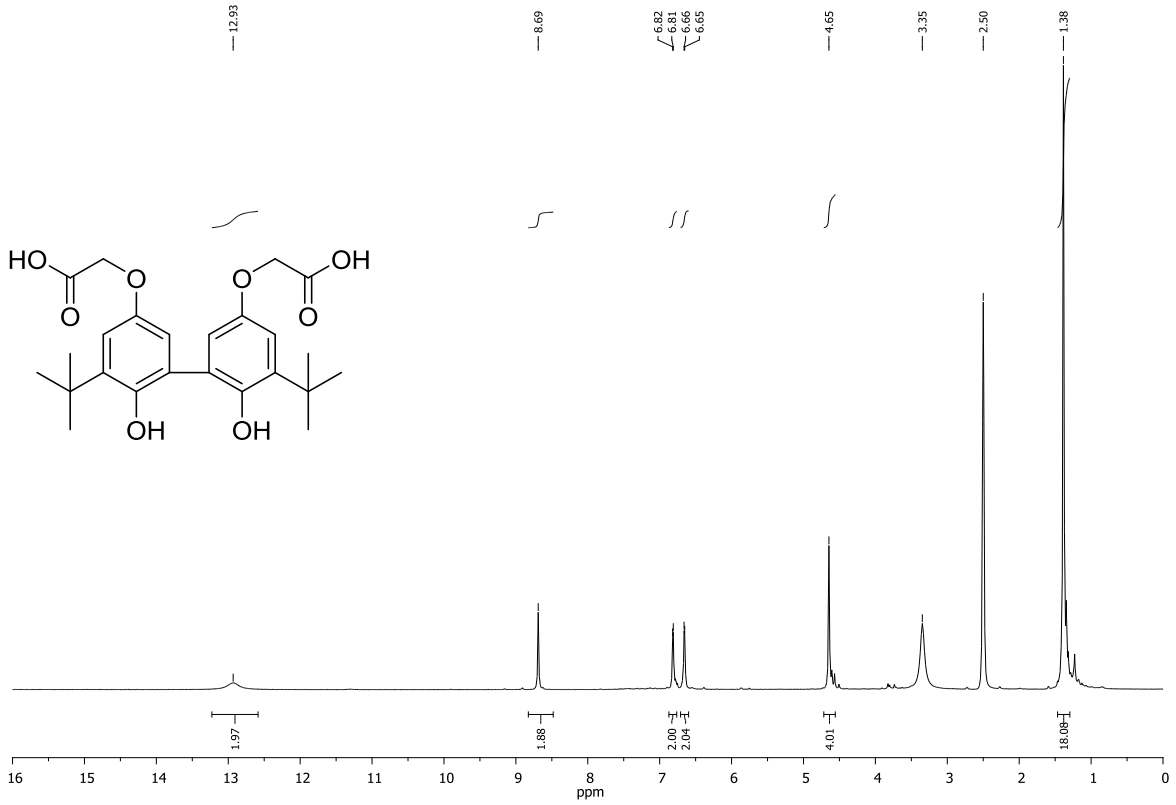

Figure 33. ^{1}H-NMR (300.36 MHz, DMSO-d_6) of compound **11**.

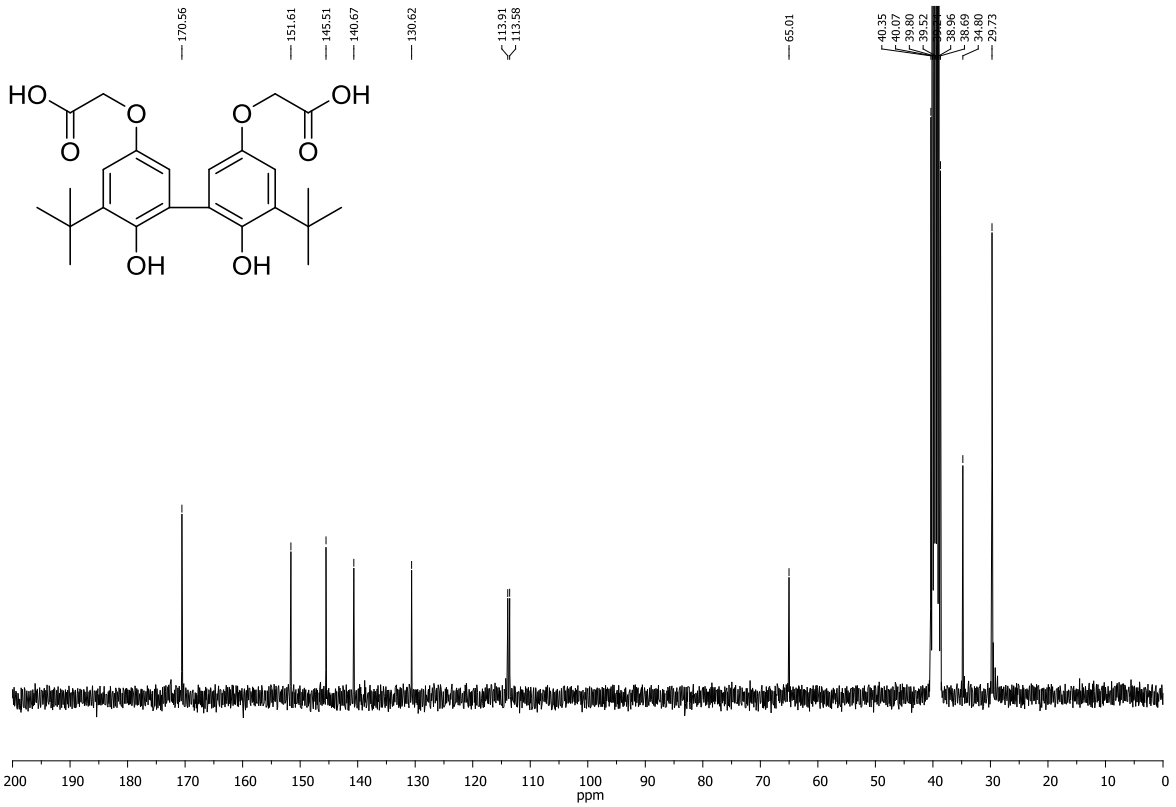

Figure 34. ^{13}C-NMR (75.53 MHz, DMSO-d_6) of compound **11**.

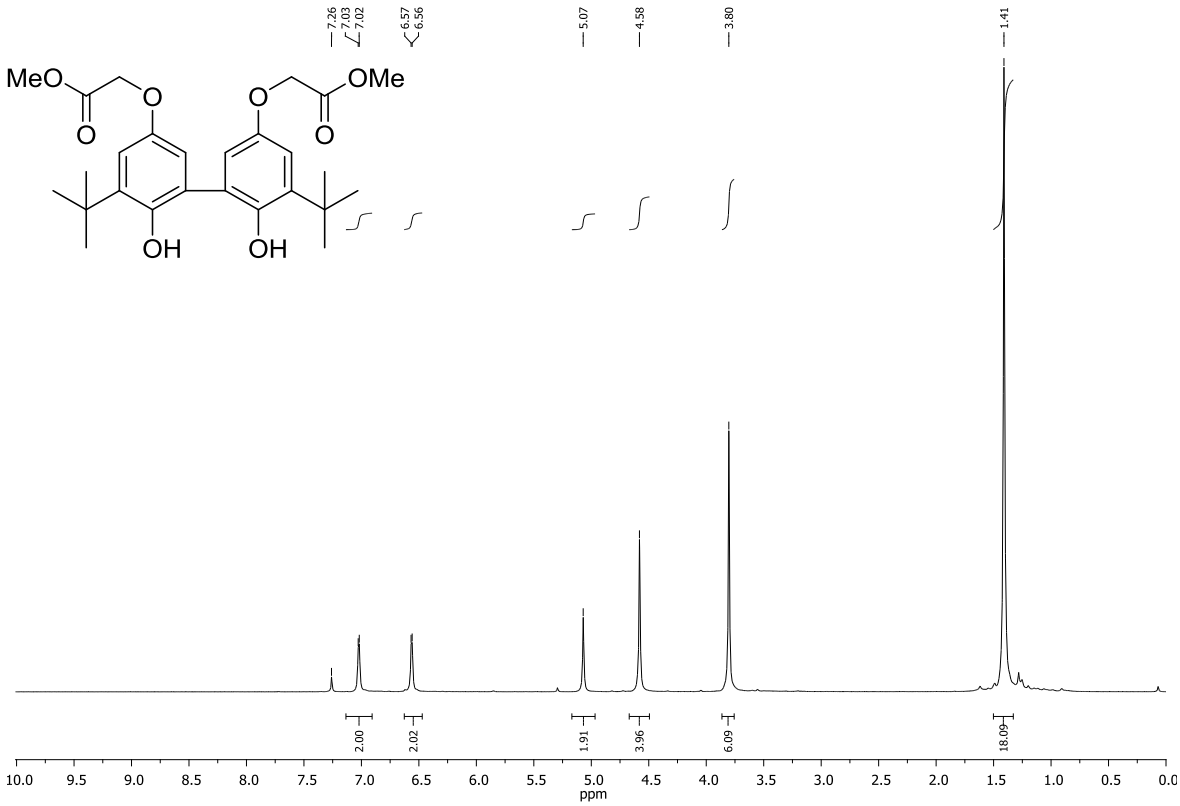

Figure 35. ^{1}H-NMR (300.36 MHz, $CDCl_3$) of compound **12**.

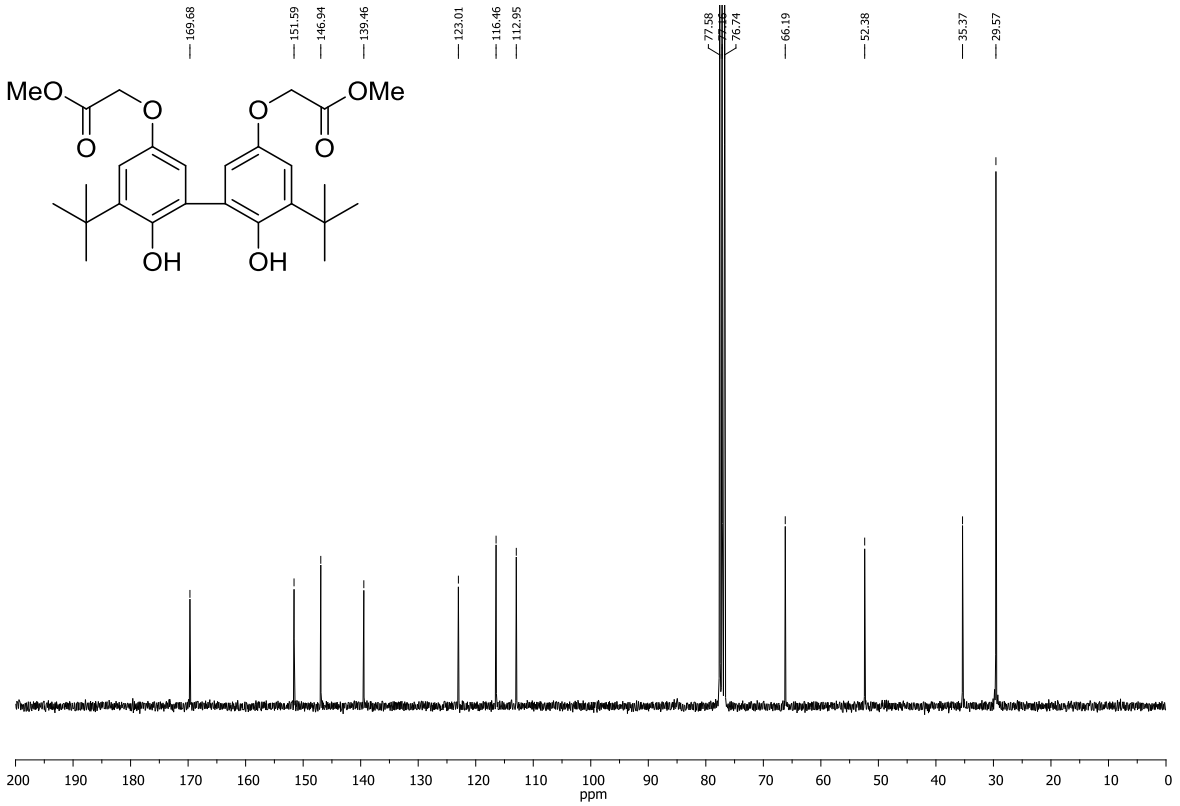

Figure 36. ^{13}C-NMR (75.53 MHz, $CDCl_3$) of compound **12**.

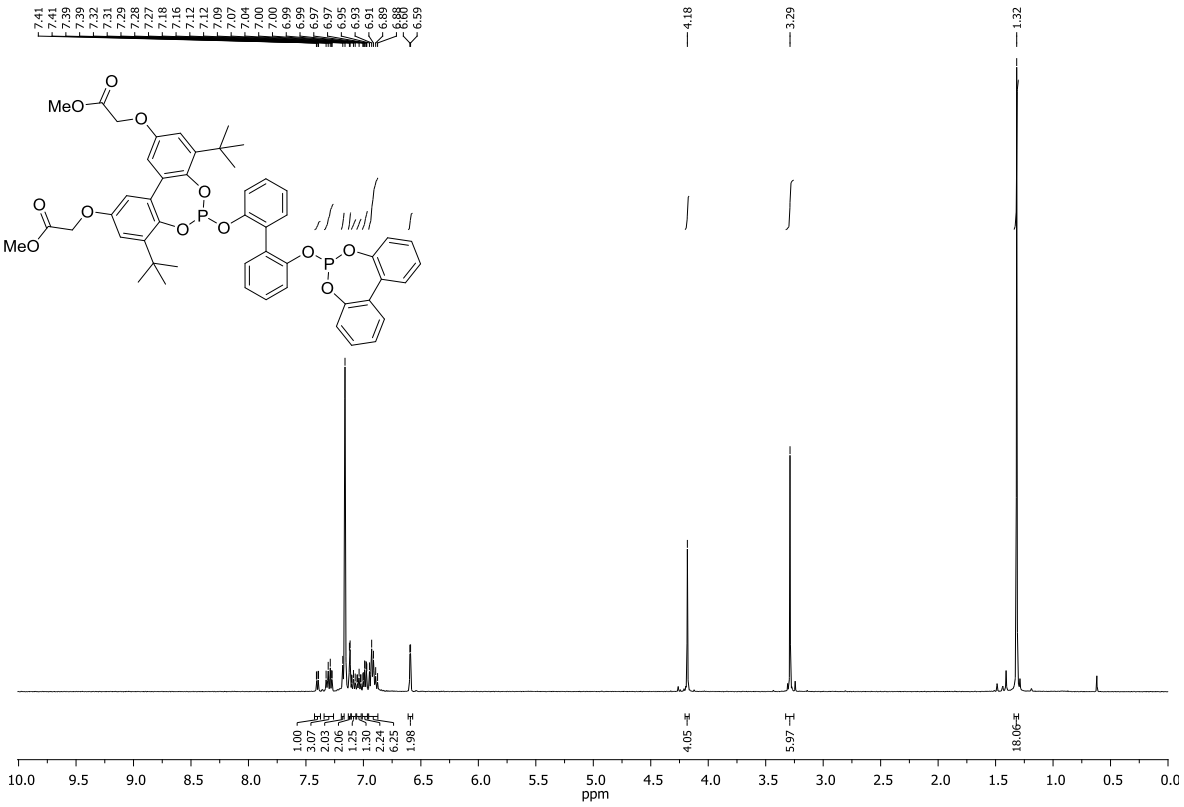

Figure 37. ^{1}H-NMR (499.87 MHz, C_6D_6) of compound **13**.

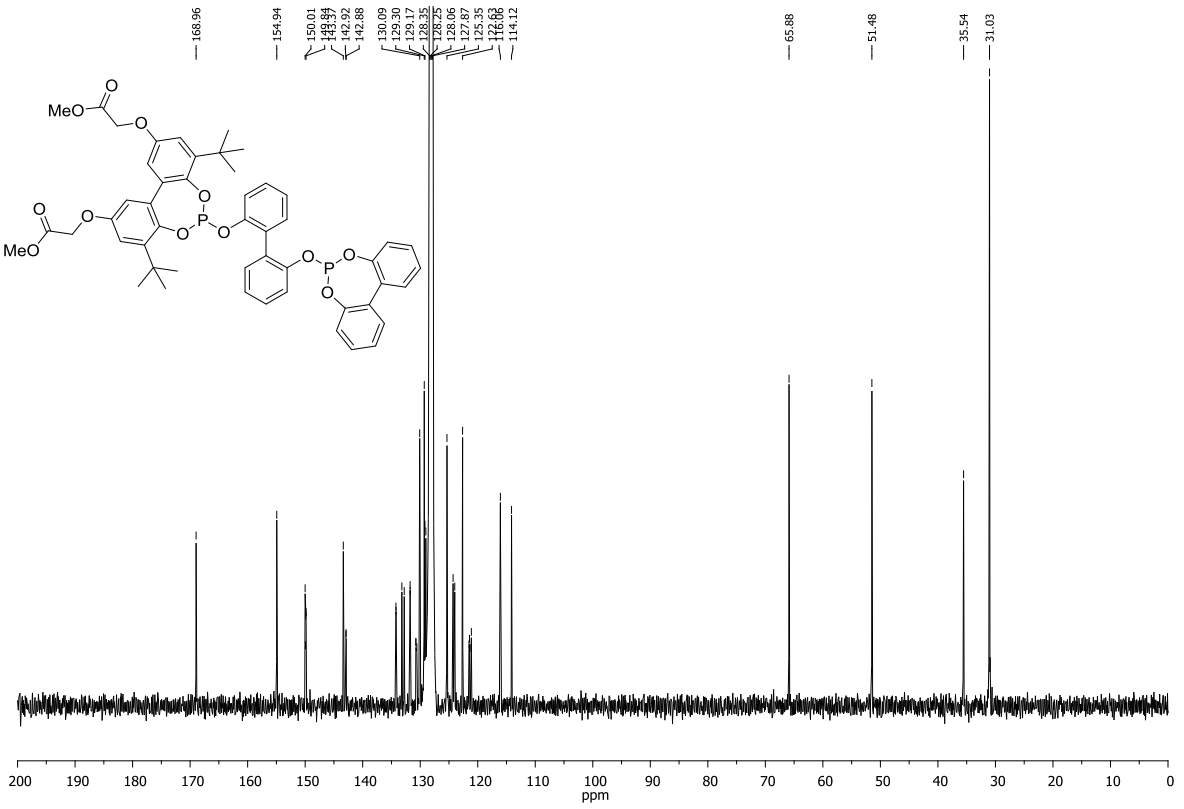

Figure 38. ^{13}C-NMR (125.69 MHz, C_6D_6) of compound **13**.

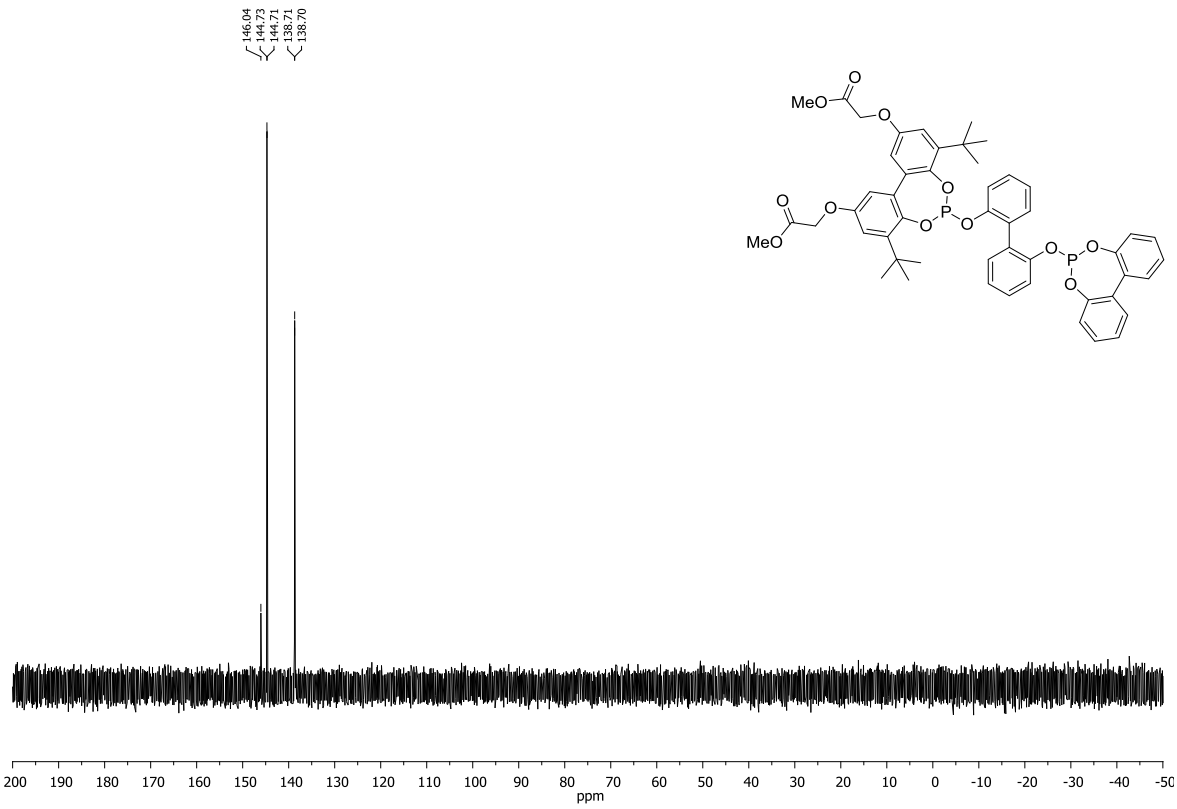

Figure 39. ^{31}P-NMR (202.35 MHz, C_6D_6) of compound **13**.