Charles University
Faculty of Science

Study programme: Medicinal Chemistry

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Synthesis of Tricyclic Hydrocarbon Derivatives
Příprava derivátů tricyklických uhlovodíků

Bachelor´s thesis

Supervisor: doc. Mgr. Radim Hrdina, Ph.D.

Prague, 2023

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložená k získání jiného nebo stejného akademického titulu.

V Praze:

Podpis

Abstract

This bachelor thesis deals with the preparation of enantiopure Binol-derived phosphoric acids with different substituents at the 3,3’-position, which are typically used as Brønsted acids in enantioselective non-covalent organocatalysis.

The prepared 3,3’-adamantane substituted Binol-derived phosphoric acids are planned to be used as organocatalysts. Bulky alkyl substituents at the 3,3' position have been introduced in order to compare their properties with those of phenyl substituents at the 3,3' position. The different dispersion forces between substrate and catalyst are expected when aryl and alkyl substituents are incorporated into the catalyst structure.

Keywords

Organocatalysis, asymmetric synthesis, Brønsted acids.

Abstrakt

Tato bakalářská práce se zabývá přípravou enantiomerně čistých fosforečných kyselin odvozených od Binolu s různými substituenty v poloze 3,3'-, které se obvykle používají jako Brønstedovy kyseliny v enantioselektivní nekovalentní organokatalýze.

Připravené 3,3'-adamantanem substituované fosforečné kyseliny odvozené od Binolu budou v budoucnu použity jako organokatalyzátory. Do polohy 3,3' byly zavedeny objemné alkylové substituenty, aby bylo možné porovnat jejich vlastnosti s vlastnostmi fenylových substituentů v těchto polohách. Očekávají se rozdílné disperzní síly mezi substrátem a katalyzátorem.

Klíčova slova

Organokatályza, asymmetrická sýnteza, Brønstedovy kyseliny.

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List of abbreviations

Binol	1,1'-binaftol
OTMS	Octadecyltrimethoxysilane
Me	Methyl
Et	Ethyl
Boc	*tert*-butyloxycarbonyl
Nu	Nucleophile
Ph	Phenyl
PMP	Polymethylpentene
DMSO	Dimethyl sulfoxide
Bn	Benzyl
DCM	Dichloromethane
DCE	1,2-Dichloroethane
ee	Enantiomeric excess
*i*Pr	*Iso*-propyl
NMR	Nuclear magnetic resonance
HRMS	High-resolution mass spectrometry
IR	Infrared spectroscopy
TLC	Thin-layer chromatography
t-Bu	*tert*-butyl
MOM	Methomexymethyl
Ar	Aryl
Anh.	Anhydrous

1. Introduction

1.1. Enantioselective Brønsted acid organocatalysis

Organocatalysis is nowadays frequently applied in the field of asymmetric synthesis. Chiral organic compounds, such as organic Brønsted acids, can serve as non-covalent organocatalysts to achieve enantioselectivity in various organic transformations.[1]

Currently, Binol-derived phosphoric acids are considered the main representatives in this field, a huge number of Binol-derived phosphoric acids have found their application in organic reactions (Figure 1). To achieve interaction of the catalyst with the substrates, Binol-derived phosphoric acids typically differ in the substitution pattern at the 3,3'-positions. Partially saturated H_8-Binol derived phosphoric acids are also applied in organocatalysis. The angle between aromatic units joined at 1,1' position is in such cases higher than for fully unsaturated naphthalene rings.[2]

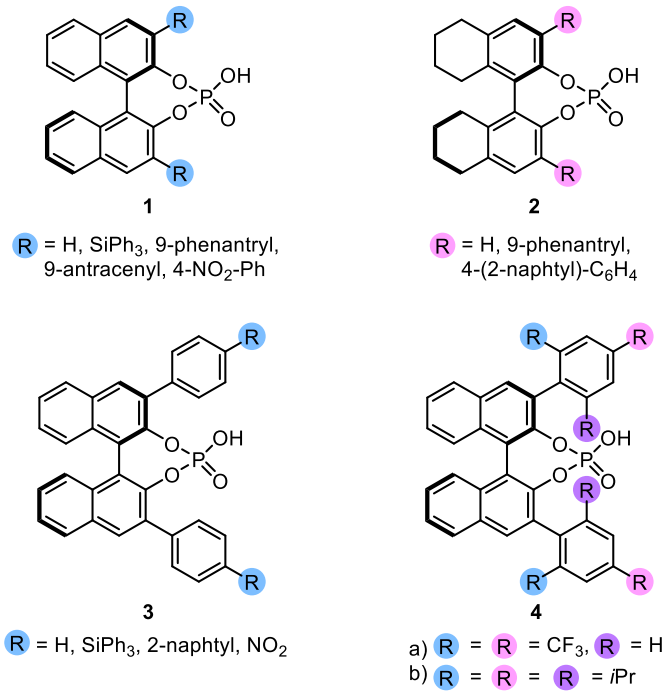
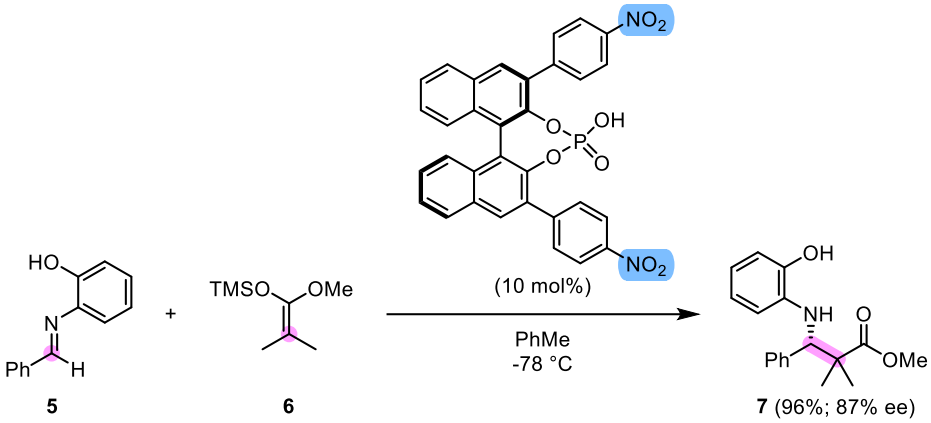


Figure 1. Selected Binol-derived phosphoric acids that were applied in catalysis.

Despite the fact that Binol-derived phosphoric acids have been known for a long time, they have started to be used only recently. Akiyama is considered one of the first to study this field and presented their use in Mannich reaction. In the reaction of 2-aminofenol derivative **5** and silyl ketene acetals **6** were tested various catalysts with different substituents at the 3,3'-positions to control a β–amino ester **7** formation with desired high enantioselectivity (Scheme 1).[3]



Scheme 1. First enantioselective Mannich reaction catalyzed by Binol-derived phosphoric acid.

Seven-membered ring containing the phosphorous atom and its optically active Binol part makes the Brønsted acid conformationally stable.[4] Phosphate with appropriate acidity (Brønsted acid) can activate substrate by protonation, which leads to an increase in their electrophilicity. Following nucleophilic attack can produce enantioenriched products due to the bond between a protonated substrate and a chiral phosphate anion. The oxygen of the P=O bond acts as a hydrogen bond acceptor and behaves as Lewis base. Because of the presence of both Lewis basic and Brønsted acid sites, Binol phosphoric acids can be viewed as bifunctional catalysts (Figure 2).[5]

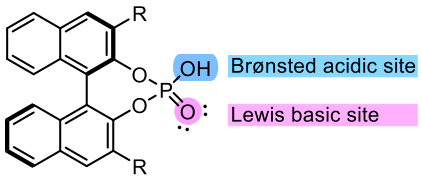
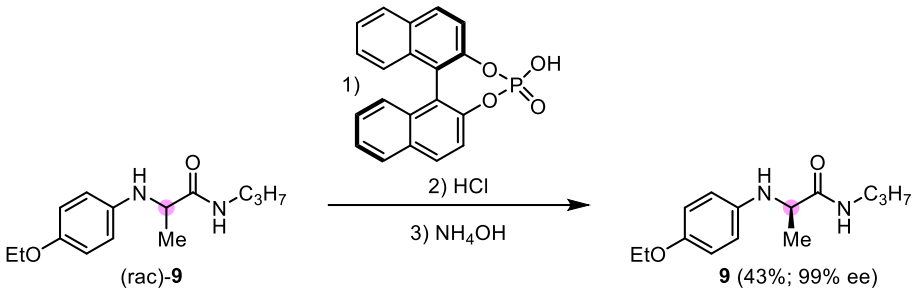


Figure 2. Properties of Binol-derived phosphoric acids.

1.2. Binol-phosphoric acids as resolving agents

Binol-phosphoric acids were previously used as resolving agents. One of their first application was in 1971, where Binol-derived phosphoric acid reacted with a racemic mixture of amine **9**

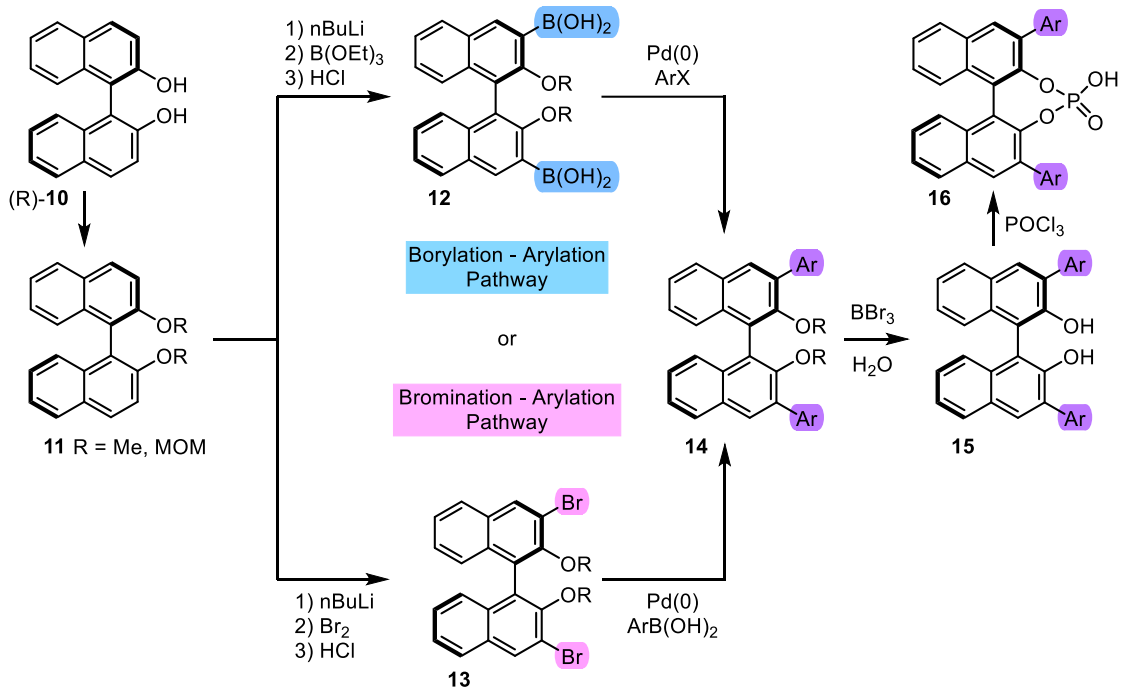
to form a diastereomeric salt. By following crystallization, the diastereomers were separated and after acid-base wash it was possible to obtain the enantiopure amine (Scheme 2).[6]



Scheme 2. Resolution of chiral amines using enantiopure Binol-phosphoric acid as resolution agent.

1.3. Synthesis of Binol-phosphoric acid derivatives

General synthesis starts with commercially available Binol in selected absolute configuration (*R*)- or (*S*)-**10**. The protection of the hydroxy groups to **11** is followed by *ortho*-lithiation, borylation and boronic ester hydrolysis to gain compound **12**. Another option to obtain a compound **12** is lithium-halogen exchange to obtain a compound **13**. Each of these two compounds can take place in metal catalyzed cross-coupling reactions. Using Pd(0) as a catalyst with a relevant coupling partner leads to formation of a compound **14**, which can be then converted (BBr_3 promoted ether cleavage) to compound **15.** Final step is the condensation reaction with $POCl_3$ and final hydrolysis to desired acid **16** (Scheme 3).[7]



Scheme 3. Typical synthesis of enantiopure Binol-derived phosphoric acid.

2. Modes of activation in catalysis

Binol-derived phosphoric acids can be applied in a wide variety of reactions not only because of their unique structure and Brønsted acidity, but also because of their functionality. Catalysts can activate the substrate through diverse interactions during the main stereoselective step. In general, they can be classified according to their activation modes into three groups: 1) mono activation, 2) dual activation, 3) bifunctional activation.

2.1. Mono activation

The term "Mono activation" includes ion-pairing and hydrogen bonding (Figure 3). Ion-pairing describes relations between ions with opposite charges, which lead to the formation of ion pairs. In case of hydrogen bonding, the hydrogen is shared between the substrate, which is hydrogen bond acceptor and the catalysts, which is called a hydrogen bond donor.[8]

The principle by which the reaction will take place is influenced by factors such as Brønsted acidity, substrate structure or solvents. Using imines as substrates in an explanation model, more electron-rich imines were predisposed to form ion pairs, whereas electron-deficient imines were predisposed to hydrogen bonding interactions.[9]

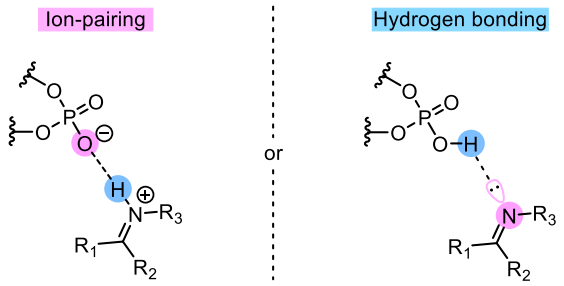
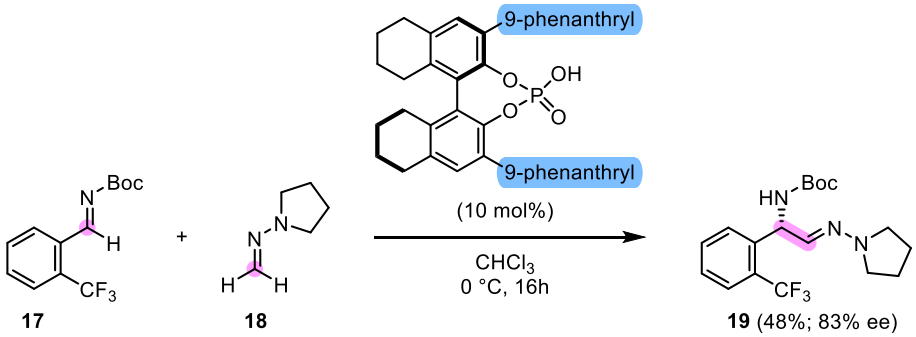


Figure 3. Mechanism of mono activation via ion-pairing and hydrogen-bonding using imines as a model substrate.

2.1.1. Reactions with iminium ions

Iminium ions are widely used as electrophiles for the addition of nucleophiles. In this selected case hydrazone derivative **18** was chosen as the effective formyl anion equivalent. The reaction with hydrazone **18** and *N*-Boc imine **17** in the presence of (*R*)-H_8-Binol-phosphoric acid catalyst was carried out in $CHCl_3$ at 0 ℃ to obtain final α-aminated hydrazone **19** with high enantioselectivity (Scheme 4).[10]



Scheme 4. Addition of hydrazones into imines catalysed by enantiopure H_8-Binol-derived phosphoric acid.

In this reaction, non-hydrogenated and hydrogenated Binol-derived catalysts with 9-phenanthryl at the 3,3'-position were tested. [H_8]-catalysts provided higher enantioselectivities because sterically demanding substituents at the 3,3' positions found optimal interaction with

substrate. The corresponding imine is supposed to be activated by Brønsted acid catalyst through mono activation (Figure 4).[10]

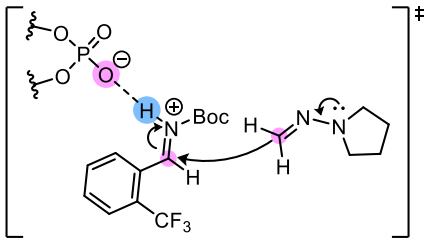
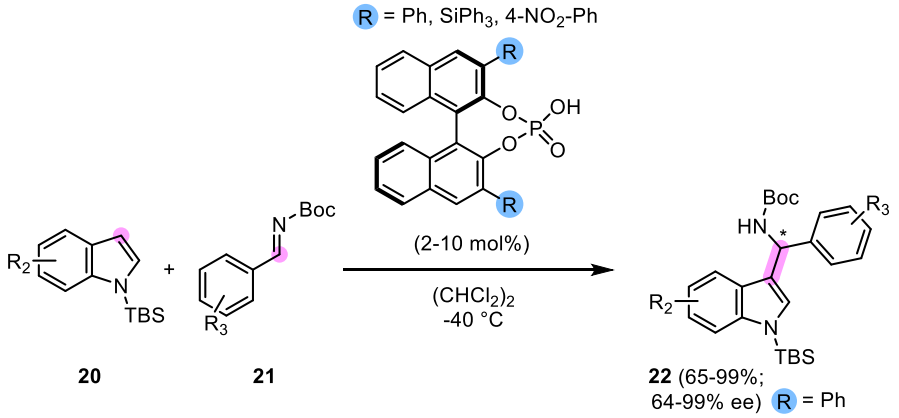


Figure 4. Proposed transition state in Brønsted acid catalysed addition of formaldehyde hydrazones to *N*-Boc protected imines.

2.1.2. Friedel-Crafts reaction

The Friedel-Crafts reaction is an electrophilic aromatic substitution in which the alkyl substituent replaces hydrogen on aromatic rings. This is one of the most powerful approaches to forming C-C bonds and modifying aromatic compounds.

Terada was the first, who introduced asymmetric Friedel-Crafts reaction and it became the subject of research. The most common reaction in which Binol-derived phosphoric acid catalyst can be applied is reaction with indoles **20** and imines **21** for obtaining 3-indolyl-methanamine **22** in good yield and enantioselectivity. In this reaction three catalysts with different substituents at the 3,3'-positions were tested. The selected Brønsted acid catalyst with triphenylsilyl **b** substituent at the 3,3'-position showed the best results. Using 10 mol % of catalyst led to obtain a final product with 98% of enantiomeric excess (Scheme 5).[11]



Scheme 5. Friedel-Crafts reaction of indoles with imines catalysed by Binol-derived phosphoric acid.

In this case, imine can be activated by Brønsted acid as a catalyst through ion-pairing. Activation of imine by the catalyst through mono activation controls and enhances the enantioselective course of the reaction (Figure 5).

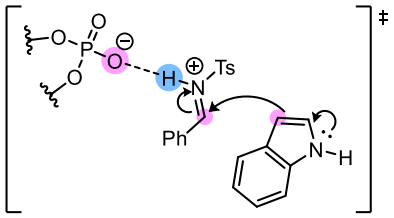
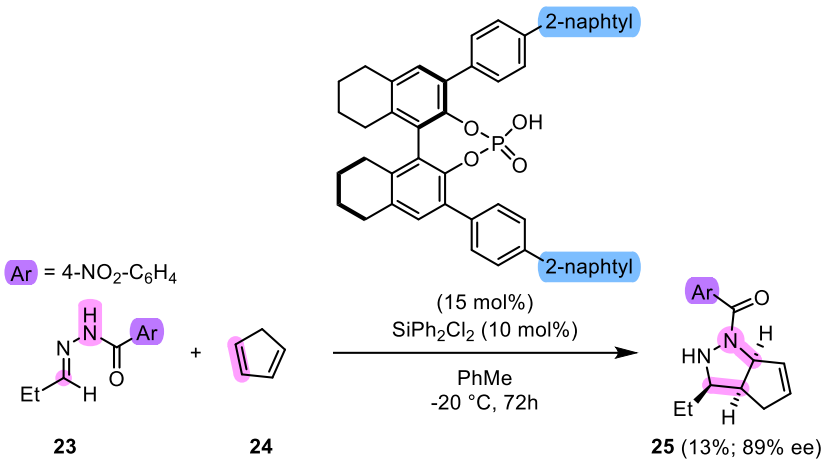


Figure 5. Proposed transition state in Brønsted acid catalysed Friedel-Crafts reaction of indoles and imines.

2.1.3. 1,3- Dipolar cycloadditions

1,3-Dipolar cycloadditions include reactions, where the substrate contains a dipole in a 1,3-relationship to undergo reaction. Cycloadditions can be classified based on the number of newly formed σ −bonds. The [3+2]-cycloaddition leads to the formation of five-membered rings.[12]

In 2011, Tsogoeva introduced the [3+2] cycloaddition reaction of hydrazone, which can be used to give pyrazolines and pyrazolidines. The reaction of hydrazone **23** with cyclopentadiene **24** catalysed by selected Brønsted acid catalyst for obtaining the desired product **25** with high enantioselectivity (Scheme 6).[13] This catalyst turned out to be the most suitable for the reaction. Despite the fact that the reaction yield is rather low, the enantioselectivity is very high. Using other catalysts, the same high level of enantioselectivity could not be obtained.



Scheme 6. [3+2]-cycloaddition reaction of hydrazone with cyclopentadiene catalysed by Binol-derived phosphoric acid.

The mechanism proposed provides interactions between the Brønsted acid catalyst and the silylated hydrazone. The weak silicon Lewis acid is activated by binding to an electron-withdrawing group, which is defined by the phosphoric acid in the corresponding catalyst (Figure 6).[13] Due to the interaction between the corresponding substrate and the catalyst it became possible to achieve high enantioselectivity.

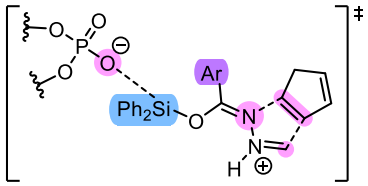
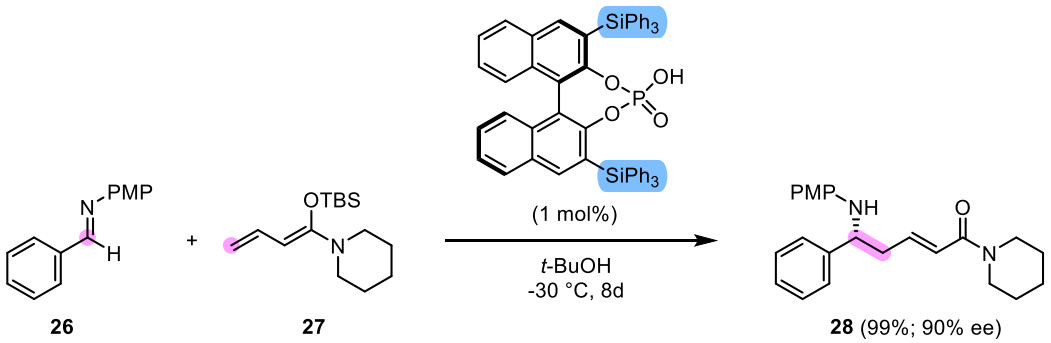


Figure 6: Proposed transition state in [3+2]-cycloaddition reaction of hydrazone with cyclopentadiene catalysed by Binol-derived phosphoric acid.

2.1.4. Mannich reaction

The Mannich reaction is a very powerful reaction that started the development of Brønsted acid catalysis. Using imines as electrophiles leads to the formation of β-amino carbonyl compounds[14] Although the substrate in the Mannich reaction can be activated through all known activation modes, the example of mono activation will be shown.

The vinylogous Mannich reaction in the presence of imines **26** and silyl *N,O*- acetals **27** was catalyzed by Binol-derived phosphoric acid and gave unsaturated amide product **28**. In this case, only one catalyst was tested. Using 1 mol % of the corresponding Binol-derived phosphoric acid catalyst with triphenylsilyl substituents made it possible to get the product in high yield and 90% of enantiomeric excess (Scheme 7).[15]



Scheme 7. Vinylogous Mukaiyama-Mannich reaction of imines and silyl *N,O*-acetals catalysed by Binol-derived phosphoric acid.

Brønsted acid as a catalyst interacts with the imine by ion-pairing. Activation of the substrate, which is imine by Binol-derived phosphoric acid by mono activation leads to obtain a desired compound with good enantioselectivity (Figure 7).

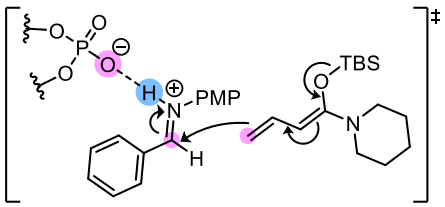


Figure 7. Proposed transition state in Brønsted acid catalysed Mannich reaction.

3.1. Dual activation

Dual activation occurs when the substrate makes two contacts to the catalyst. In the first case, the substrate makes two contacts to the acidic proton and this method is considered the most common. This typically occurs when the activated group contains a basic Lewis site close to the substrate. The second case affects the substrate by making two contacts to the catalyst, where oxygen in the P=O bond is an H-bond acceptor, which forms another hydrogen bond with the substrate (Figure 8).[8]

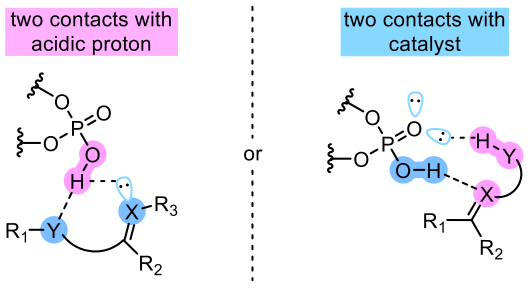
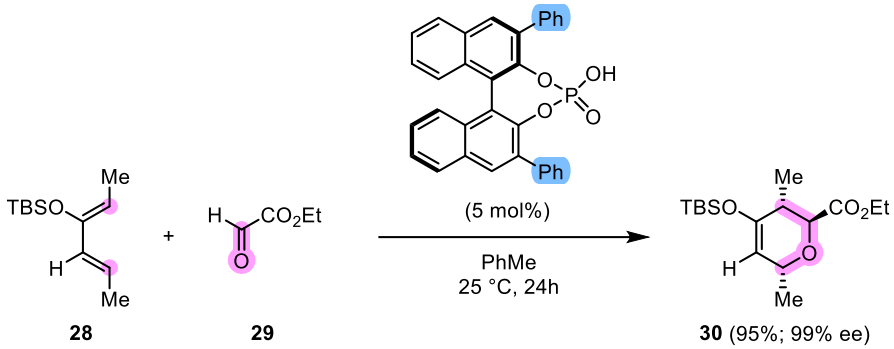


Figure 8. Examples of different modes related to dual activation.

3.1.1. Diels-Alder reaction

The Diels-Alder reaction is one of the most prominent reactions in organic chemistry. It involves the [4 + 2] cycloaddition reaction between the conjugated diene and the dienophile to give a substituted cyclohexene.

In 2009, Terada showed the reaction between dienes **28** and glyoxylate **29**, which leads to obtain dihydropurans **30** by activation of the carbonyl group by Brønsted acid catalyst. Although imines are generally substrates that can be activated by Binol-derived phosphoric acid catalyst, this case shows that carbonyl groups also have this ability. Using 5 mol % of the catalyst with phenyl group at the 3,3'- position leads to obtain the final product in high yield and enantioselectivity (Scheme 8).[16]



Scheme 8. Hetero-Diels−Alder reaction of dienes and glyoxylates catalysed by Binol-derived phosphoric acid.

The highest enantioselectivity was achieved, when the dienophile was activated through the carbonyl group by Binol-derived phosphoric acid catalyst. Two hydrogen bonds are formed between the catalyst and the glyoxylate (Figure 9). The aldehyde proton must be acidic enough to be able to participate in the interaction with the basic Lewis site of the catalyst together with the interaction between the aldehyde oxygen atom and the acidic proton of the catalyst.[2]

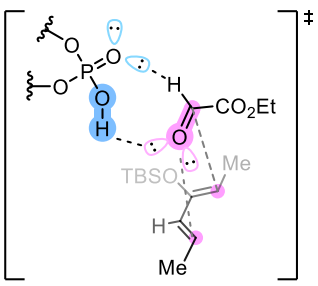
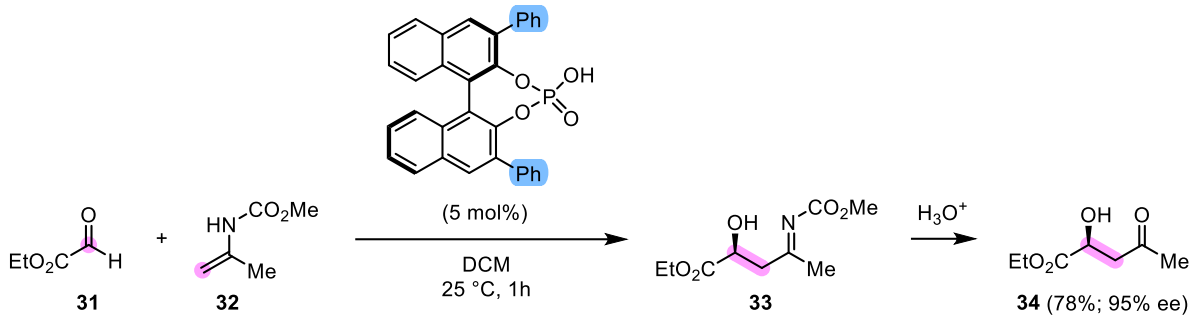


Figure 9. Proposed transition state in Brønsted acid catalysed Hetero-Diels−Alder reaction.

3.1.2. Aza-ene type reaction

Another example of activation of carbonyl compounds by Brønsted acid catalysts is the aza-ene type reaction.

In 2008, Terada showed the first example of the activation of aldehydes by Brønsted acid catalysts. The reaction with enecarbamate **32** and glyoxylate **31** leads to the synthesis of $\beta-$ hydroxy ketone **34**.[17] The use of 5 mol % of Binol-derived phosphoric acid catalyst with phenyl group at the 3,3'- position followed by hydrolysis leads to the high degree of enantioselectivity (Scheme 9).[17]



Scheme 9. Aza-ene type reaction of enecarbamates and glyoxylates catalysed by Binol-derived phosphoric acid.

The corresponding aldehyde is activated by the catalyst, resulting in the formation of two hydrogen bonds between them (Figure 10). In this case, dual activation by hydrogen-bonding is the key to achieving high level of enantioselectivity.

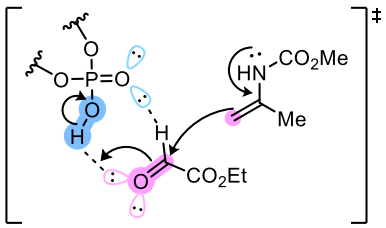


Figure 10. Proposed transition state in Brønsted acid catalysed aza-ene type reaction.

4.1. Bifunctional activation

As shown in the previous cases, the interaction takes place between two molecules, the substrate and the catalyst, where ion pairs or hydrogen bonds are formed. In addition, interactions in Brønsted acids can take place between three molecules: the catalyst and two reactants. In this case, they can be called bifunctional catalysts.[8] It can be concluded, that the oxygen in the P=O bond also has activating features. Bifunctional catalysis is considered to be one of the most powerful methods of activation and covers most the of reactions catalysed by Binol-derived phosphoric acids.

Godman studied bifunctional mode of activation for the Binol-derived phosphoric acids and concluded, that bifunctional activation can be divided into Type I and Type II models based on how they reflect the transition state (Figure 11).[18] The oxygen atoms of the phosphoric acid are in the plane and the bulky substituents are on opposite sides.

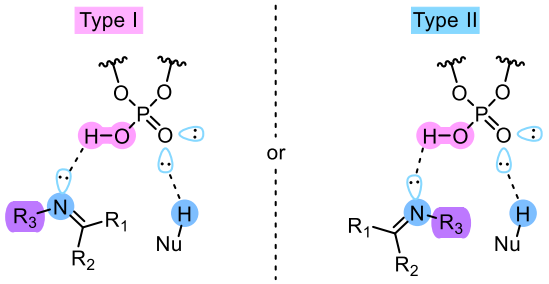


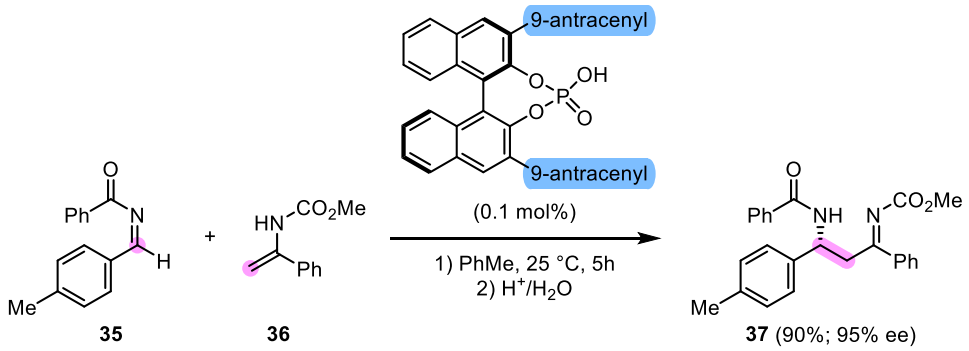
Figure 11. Type I and type II models for bifunctional activation.

Both models explain, that if the nucleophile has an acidic proton, the H-bond to the catalyst will form. In the case of the Type I, the transition state has the lowest energy and R^3 is located in an empty space. The energy of Type II transition state is higher, due to the position of the imine toward the substituent of the catalyst and steric interaction will be involved.[18,2]

4.1.1. Addition of nucleophiles to iminium ions

In 2006, Terada and co-workers presented another example of the aza-ene type reaction of enecarbamates acting as nucleophiles. The reaction of enecarbamates **36** derived from acetophenone and *N*-benzoylated imines **35** leads to obtain β −amino-imine derivatives **37** with high enantioselectivity and good yields (Scheme 10).[19] Only one catalyst was tested in

this reaction and, thanks to its use, it was possible to obtain the desired product with 95 % of enantiomeric excess.



Scheme 10. Aza-ene reaction of enecarbamates and *N*-benzoylated imines catalysed by Binol-derived phosphoric acid.

The transition state involves the electrophilic activation of the imine by the Brønsted acid catalyst via protonation, while receiving the NH proton from the enecarbamate via the Lewis site of the catalyst (Figure 12).[2] Due to the proposed transition state, where the catalyst activates the substrate via bifunctional activation, the enantioselectivity increases.

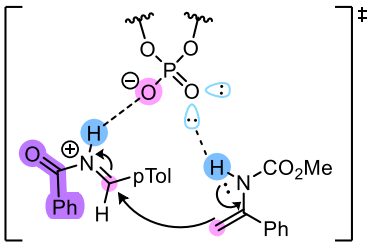
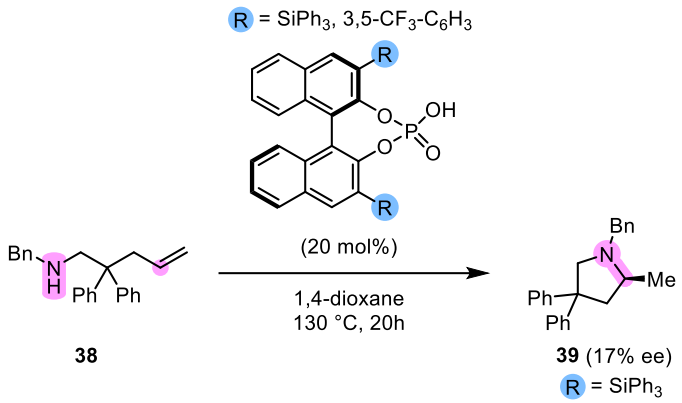


Figure 12. Proposed transition state in Brønsted acid catalysed addition of enecarbamates to *N*-benzoylated imines.

4.1.2. Addition of nucleophiles to alkenes

This type of reaction includes the intramolecular addition of a nucleophile to the alkene double bond without activation. Despite the complexity of activating a group with no natural binding sites, in 2008, Ackerman reported the first example of the reaction of unsaturated amines **38** in the presence of a catalyst leading to obtain the pyrrolidine **39**. Two catalysts with different substituents were tested. The use of the catalyst with triphenylsilyl substituents **a** at the 3,3'-position gave better results than with the catalyst with substituents **b** (Scheme 11). [20]



Scheme 11. Hydroamination of an unactivated alkene catalysed by Binol-derived phosphoric acid.

The corresponding Binol-derived phosphoric acid catalyst demonstrates its bifunctionality in the transition state, where the amine coordinates with the Lewis basic site of the catalyst, while proton of the catalyst interacts with the alkene (Figure 13). By activating the corresponding alkene with a catalyst, enantioselectivity was achieved.

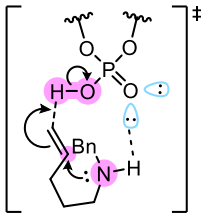
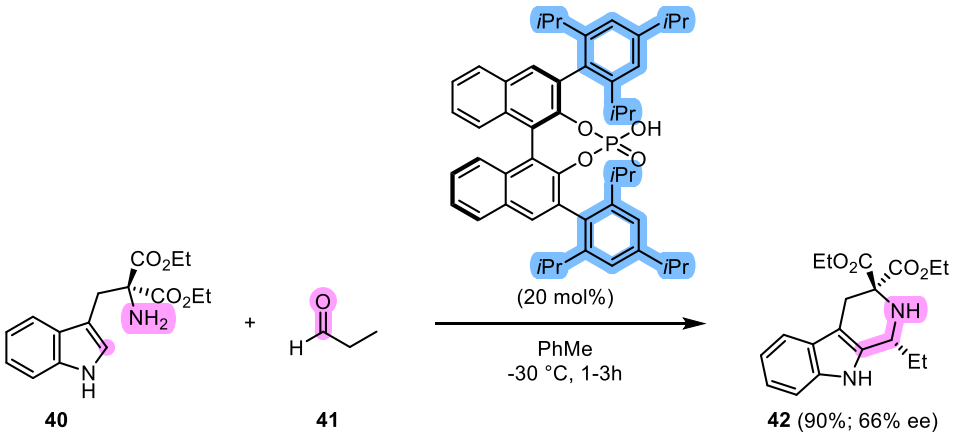


Figure 13. Proposed transition state in Brønsted acid catalysed addition of nucleophiles to alkenes.

4.1.3. Pictet–Spengler reaction

The Pictet-Spengler reaction is the condensation reaction of β- arylethylamine with aldehydes or ketones leading to the ring closure. This is a powerful strategy for the synthesis of alkaloid products with strong biological activity, such as tetrahydroisoquinolines and tetrahydro-β-carbolines and for the preparation of pharmaceuticals.[20]

In 2007, List published a procedure for the asymmetric Pictet-Spengler reaction. The reaction of tryptamines **40** with aldehydes **41** is catalysed by Brønsted acid catalyst to obtain a final product tetrahydro-β-carboline **42** in high yield and enantioselectivity.[22] Using the corresponding catalyst with isopropyl groups increases the enantiomeric excess of tetrahydro-β-carboline **42** to 66 % (Scheme 12).



40 **41** **42** (90%; 66% ee)

Scheme 12. Asymmetric Pictet-Spengler reaction of tryptamine and aldehyde catalysed by Binol-derived phosphoric acid.

Activation occurs via bifunctional mechanism, where the basic Lewis site of catalyst is coordinated to the N-H indole and the protonated imine is coordinated to the Bronsted site of catalyst, giving the highest enantioselectivity (Figure 13).

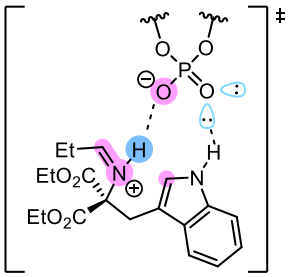
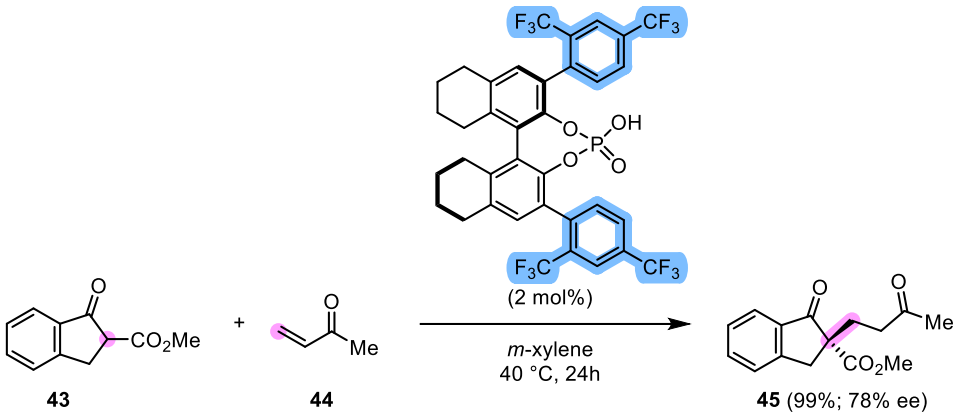


Figure 13. Proposed transition state in Brønsted acid catalysed Pictet-Spengler reaction.

4.1.4. Michael reaction

Michael addition is the reaction between the Michael donor (nucleophile) and Michael acceptor (α, β − unsaturated carbonyl compounds), resulting in the formation of C-C bonds. In 2009, Akiyama demonstrated the Michael reaction catalysed by a Brønsted acid catalyst.

The addition reaction with β −ketoester **43** and methyl vinyl ketone **44** in the presence of catalyst leads to get a product **45** in good yield and enantioselectivity (Scheme 13). [23] The use of the corresponding catalyst leads the desired Michael adduct in 78% of enantiomeric excess.



Scheme 13. Enantioselective Michael addition of β −ketoesters to methyl vinyl ketones catalysed by Binol-derived phosphoric acid.

The highest enantioselectivity was achieved with bifunctional activation by protonation of the carbonyl and interactions of the enol tautomer of the β −ketoester **43** with the catalyst (Figure 14).

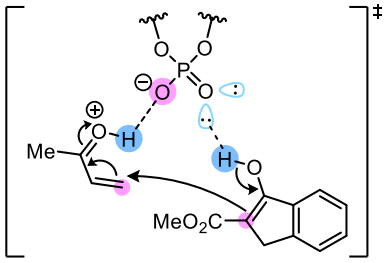
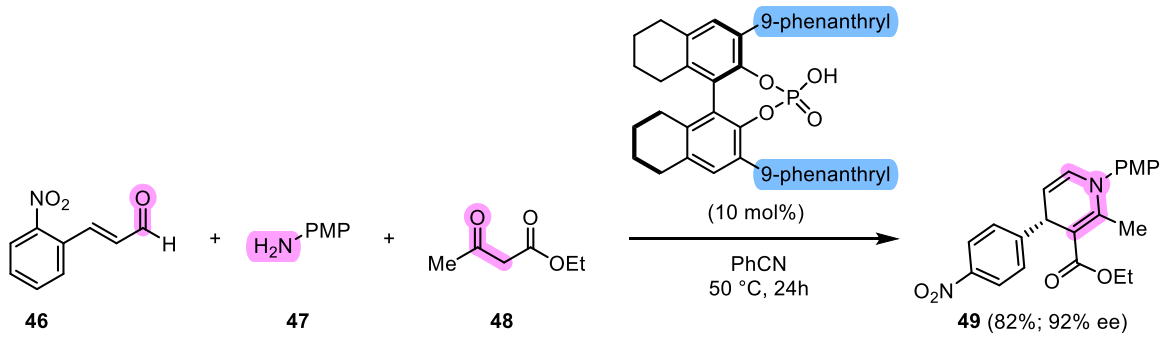


Figure 14. Proposed transition state in Brønsted acid catalysed Michael reaction.

4.1.5. Biginelli reaction

The Biginelli reaction refers to multi-component reactions and is commonly used in the synthesis of dihydropyrimidinones. The formation of an iminium intermediate leads to the nucleophilic addition of keto ester in its enol form. [5]

Although the classic Biginneli reaction was described a long time ago, in 2008, Gong group showed the application of H_8-Binol-derived phosphoric acid catalyst in this reaction. Reaction with unsaturated aldehydes **46**, primary amines **47** and β–ketoesters **48** in the presence of catalyst leads to obtain dihydropyridine **49**.[24] In this case, the highest level of enantioselectivity was obtained by using the H_8-Binol-derived phosphoric acid instead of unsaturated catalyst (Scheme 14).



Scheme 14. Three-component cyclization of aldehydes, primary amines and *β*–ketoesters catalysed by Binol-derived phosphoric acid.

The proposed mechanism is bifunctional activation, where the incoming enol interacts with the Lewis basic site of the catalyst through the hydrogen bonding, leading to high enantioselectivity (Figure 15).

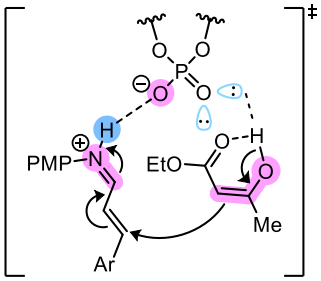
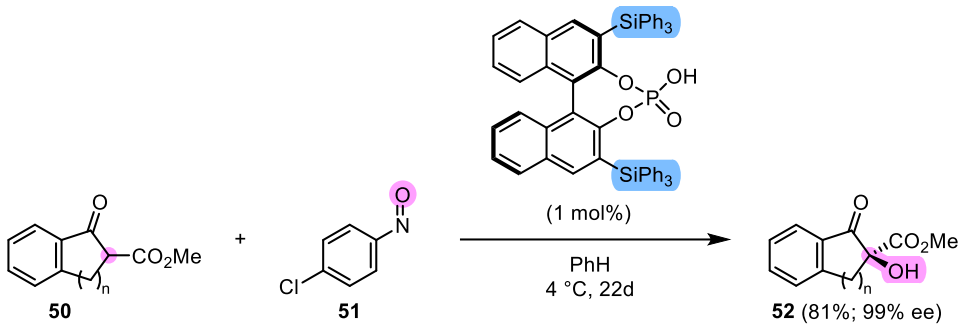


Figure 15. Proposed transition state in Brønsted acid catalysed Biginelli reaction.

4.1.6. Oxidation of *β* −dicarbonyls

A good example of an asymmetric oxidation reaction is hydroxylation, in which a C-H bond is converted to C-OH bond.

In 2009, Zhong announced the first hydroxylation reaction of β − dicarbonyls. The starting β −dicarbonyl **50** in the presence of 4-nitrochlorobenzene **51** can be modified to the corresponding α – hydroxy product **52** in high yield and enantioselectivity.[25] Selected Brønsted catalyst with triphenylsilyl substituents at the 3,3'-positions provided the highest enantioselectivity in this reaction (Scheme 15).



Scheme 15. Hydroxylation of β −dicarbonyl catalysed by Binol-derived phosphoric acid.

Phosphoric acid is suggested to act as bifunctional catalyst, activating the enol form of β − dicarbonyl **50** and the nitroso compound **51**. In addition, it is argued that Brønsted acid inhibits the attack of **50** on the nitrogen atom by forming a hydrogen bond with the nitrogen atom of the nitroso compound (Figure 16).[2] The use of Brønsted acid catalyst results in a 99 % of enantiomeric excess.

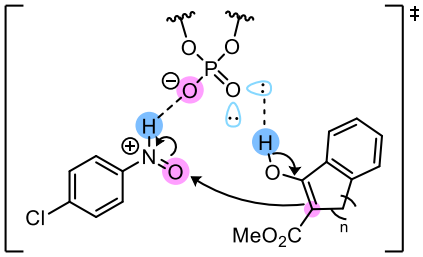
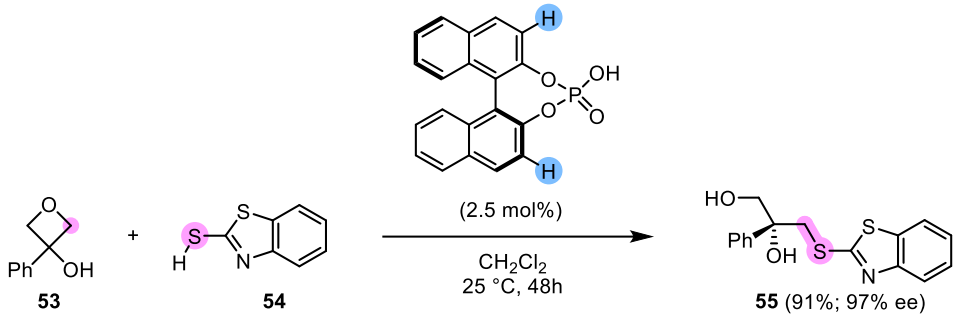


Figure 16. Proposed transition state in Brønsted acid catalysed hydroxylation reaction of β −dicarbonyl.

4.1.7. Desymmetrization of oxetanes

Enantioselective desymmetrization is a powerful approach to accessing chiral building blocks. In general, this type of reaction can be used to introduce chirality. The use of oxetanes, homologues of epoxides, leads to the synthesis of chiral building blocks by enantioselective ring opening with nucleophiles. In this case, chiral phosphoric acid is a suitable catalyst for activation of the oxetane its good chiral environment leading to subsequent nucleophilic attack.

Reaction with 3-substituted oxetane **53** and aromatic thiol **54**, which are present here to open the oxetane ring and give the three-carbon unit product **55** with good enantioselectivity (Scheme 16).[26]



Scheme 16. Enantioselective desymmetrization of oxetanes with thiols catalysed by Binol-derived phosphoric acid.

The use of classical Binol-derived phosphoric acid proved to be the best way to achieve high enantioselectivity in the reaction. The mechanism is offered to be bifunctional where the oxetanes and the thiols are coordinated to the Brønsted acid catalyst, which helps to achieve the highest enantioselectivity (Figure 17).

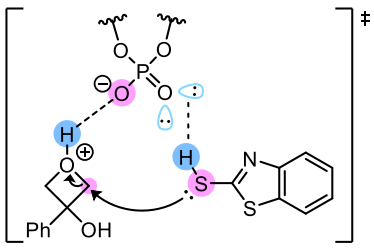


Figure 17. Proposed transition state in Brønsted acid catalysed desymmetrization reaction.

5. Goals

The goal of this work was to synthesize 3,3'-adamantane substituted Binol-derived phosphoric acids (Figure 5.1). The products obtained will then be applied to reactions and tested as catalysts. Obtained 3,3'-adamantane substituted Binol-derived phosphoric acids will be compared with 3,3'-phenyl substituted Binol-derived phosphoric acids.

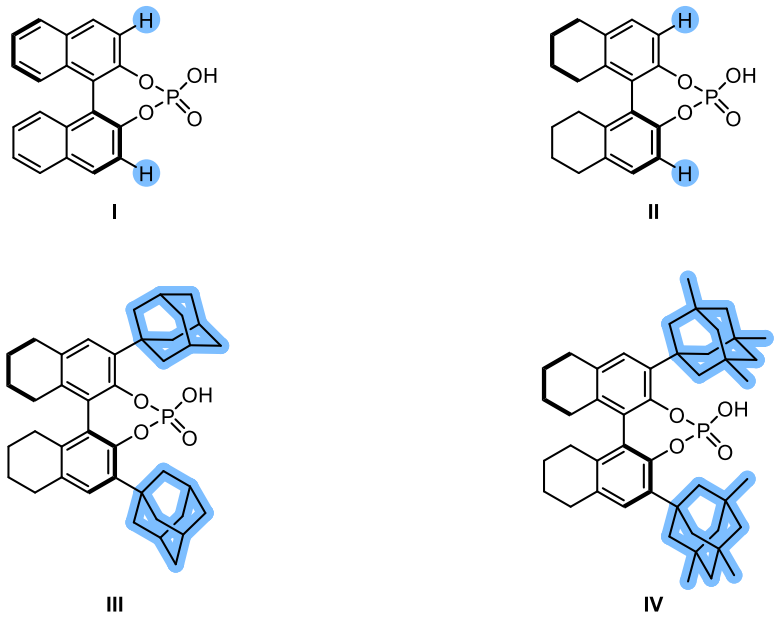


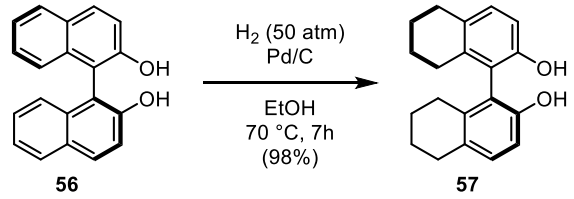
Figure 5.1. Overview of prepared compounds.

6. Results and discussion

6.1. Preparation of starting materials

6.1.1. Preparation of (*S*)-H_8-Binol

The synthesis of the desired products **II, III, IV** began with the preparation of (*S*)-H_8-Binol, which was prepared according to a published procedure [27](Scheme 6.1).

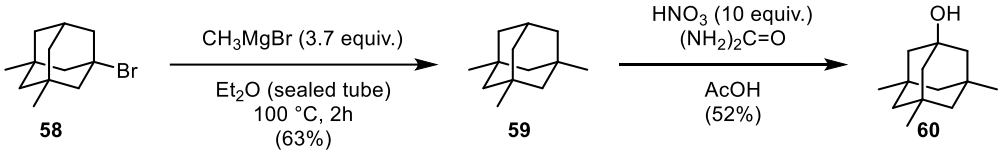


Scheme 6.1. Synthesis of (*S*)-H_8-binol.

The reduction of commercially available (*S*)-Binol **56** in the presence of metal catalyst Pd/C was carried out at 70 ℃ for 7 h under 50 barr of H_2 pressure. The desired product **57** was obtained in a high yield.

6.1.2. Preparation of 3,5,7-trimethyladamantan-1-ol

For the catalysts **IV** it was necessary to prepare 3,5,7-trimethyladamantan-1-ol **60** which was prepared in two steps using commercially available adamantane derivative [28,29] (Scheme 6.2).



Scheme 6.2. Two-step synthesis of 3,5,7-trimethyladamantan-1-ol **60.**

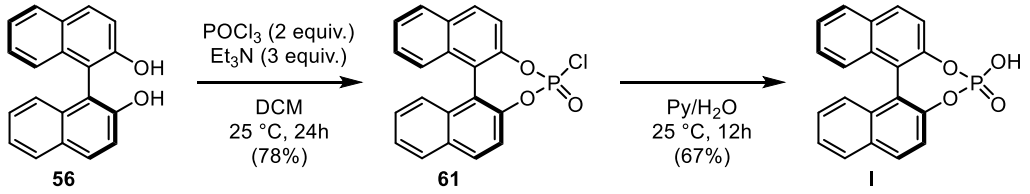
The synthesis was started with 1-bromo-3,5-dimethyladamantane **58** using Grignard reagent to convert the bromide to the methyl group. The reaction was carried out at 90 ℃ for 2 h according to a published procedure and the final product was obtained.

The next step encompassed production of alcohol by nitroxylation with fuming nitric acid. The reaction of 1,3,5-trimethyladamantane **59** in the presence of fuming nitric acid and glacial acid was carried out at 20℃ for 1 h, then solution of urea in aqueous acetic acid was added and

the reaction mixture was stirred at 100 ℃ for 1 h. Compound **60** was purified by silica gel chromatography to give the desired 3,5,7-trimethyladamantan-1-ol **60** in a good yield.

6.2. Preparation of Binol-derived phosphoric acid I

Compound **I** was prepared in two steps: The condensation reaction with $POCl_3$ leads to obtain the chloride of (*S*)-binaphthyl-phosphoric acid **61**, which is then converted by hydrolysis in the presence of pyridine as solvent into resulting (S)-binapthyl-phosphoric acid. [30] (Scheme 6.3).

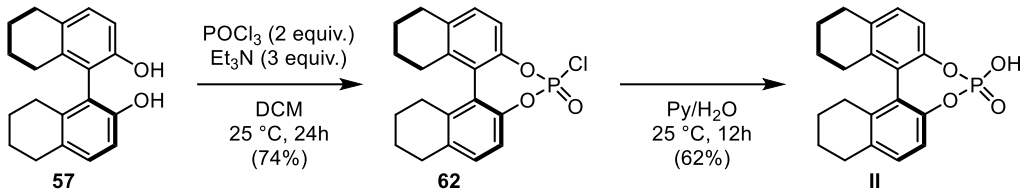


Scheme 6.3. Synthesis of Binol-derived phosphoric acid **I**.

The synthesis of Binol phosphoric acid **I** was started from commercially available (*S*)-Binol **56** and carried out according to a published procedure. The reaction in DCM with $POCl_3$ and Et_3N was carried out at 25 ℃ for 24 h, then pyridine and water were added for hydrolysis and chloride of (*S*)-binaphthyl-phosphoric acid **61** was converted to the resulting (*S*)-binapthyl-phosphoric acid **I**. For purification was decided to convert acid into salt with Na_2CO_3 and dilute it with EtOAc to get rid of the starting material. Using this method, the product was obtained in a good yield.

6.3. Preparation of Binol-derived phosphoric acid II

Compound **II** was prepared in the same was as compound **I** according to a published procedure**,** using (*S*)-H_8-Binol **57** as a starting material [30] (Scheme 6.4). Condensation reaction with $POCl_3$ followed by hydrolysis in the presence of pyridine afforded the desired product **II**.

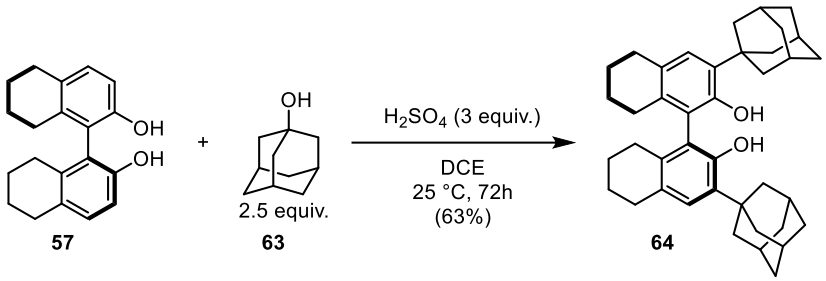


Scheme 6.4. Synthesis of Binol-derived phosphoric acid **II**.

The reaction in DCM using $POCl_3$ and Et_3N was stirred at 25 ℃ for 24 h. The corresponding chloride **62** was dissolved in pyridine and water was added for hydrolysis. The reaction mixture was stirred for 12 h to give the resulting (*S*)- binapthyl-phosphoric acid **II**. For the purification product was converted into salt and washed with EtOAc to remove starting material **57**.

6.4. Preparation of Binol-derived phosphoric acid III

The first step in the synthesis of compound **III** was Friedel-Crafts reaction, where in the presence of H_2SO_4 a carbocation forms and then participates in electrophilic aromatic substitution[31] (Scheme 6.5).



Scheme 6.5. Friedel-Crafts reaction of (*S*)-H_8-Binol **57** and 1-adamantanol **63**.

Commercially available 1-adamantanol **63** and (*S*)-H_8-Binol **57** were dissolved in DCE and H_2SO_4 was added. The reaction was carried out at room temperature for 3 days. For purification it was decided to do a silica gel column using hexane/EtOAc 10:1 as solvents.

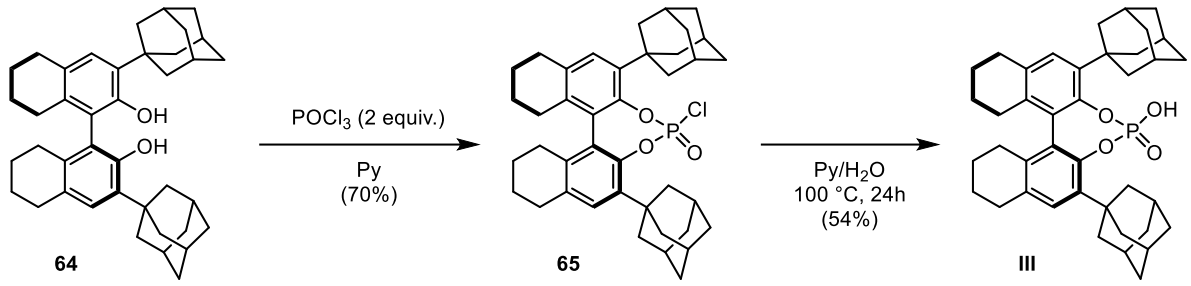
The second step was the reaction with $POCl_3$. First, the method used for the catalysts **I** and **II** was pursued [30], but according to the NMR spectra of the crude mixture showed that only

the starting material was present and the conversion was about 3 %. The reaction was then carried out under different conditions, varying temperature and time. Different solvents were also used as the compound was not soluble in DCM. In general, three different conditions were tested (Table 6.1).

Solvent	Conditions	Conversion (%)
DCM	rt, 24 h	≈ 3
DCE	50 ℃, 24 h	≈ 5
Benzene	rt, 24 h	≈ 1

Table 6.1. Optimization of the reaction conditions.

None of the reactions above achieved the isolation of the final product as the conversion was still low. Despite the failure to obtain the desired product, it was decided to try another procedure, where pyridine was to be used as a solvent [32] (Scheme 6.6).



Scheme 6.6. Synthesis of Binol-derived phosphoric acid **III**.

The reaction was carried out in compliance to a published procedure.[32] Compound **64** was dissolved in pyridine and $POCl_3$ was added. The reaction mixture was heated to 50 ℃ and stirred for 12 h, then water was added for subsequent hydrolysis and the reaction mixture was kept stirring for 24 h at the same temperature. According to the NMR spectra, the conversion was about 15% as the starting material was rather prominent. Therefore, in the first step, the temperature and time were increased and the reaction was tested again. In total, three different conditions were tested (Table 6.2).

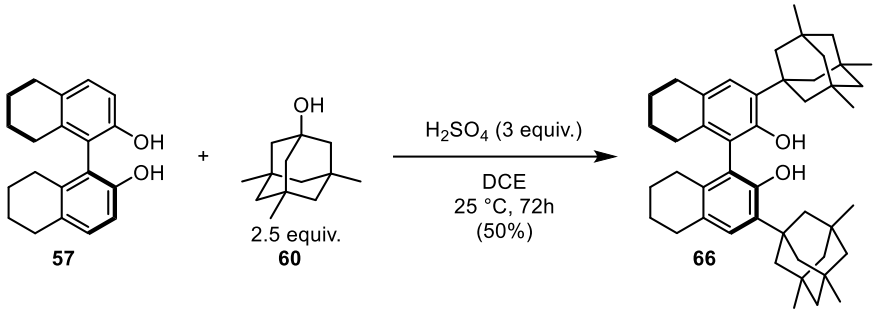
Entry	Conditions	Conversion (%)
1	12 h, 70℃	≈ 15
2	24 h, 100℃	≈ 35
3	72 h, 100℃	≈ 75

Table 6.2. Optimization of the reaction conditions.

The third reaction, where the reaction mixture was stirred for 72 h at 100 ℃ was the most successful. Having analysed NMR spectra of crude mixture, it was evident that the conversion was high with the final product prevailing. For the purification of the final product was decided to do a silica gel column using DCM/MeOH 5%. The first attempt was carried out using a small amount of the final product and a clean product was achieved successfully. When the same method of purification was applied on a larger scale, much of the product was lost and we weren't able to get the product we wanted at a high yield. A new purification method was found, where the compound was converted into salt using NH_4OH. Due to the fact that the final product and starting material have different solubility, the corresponding salt was washed with EtOAc and Et_2O to get rid of the compound **64**. Then salt was converted into the acid by extraction with 6N HCl. Using this method, we were able to effectively isolate final Binol-derived phosphoric acid **III** in a good yield.

6.5. Preparation of Binol-derived phosphoric acid IV

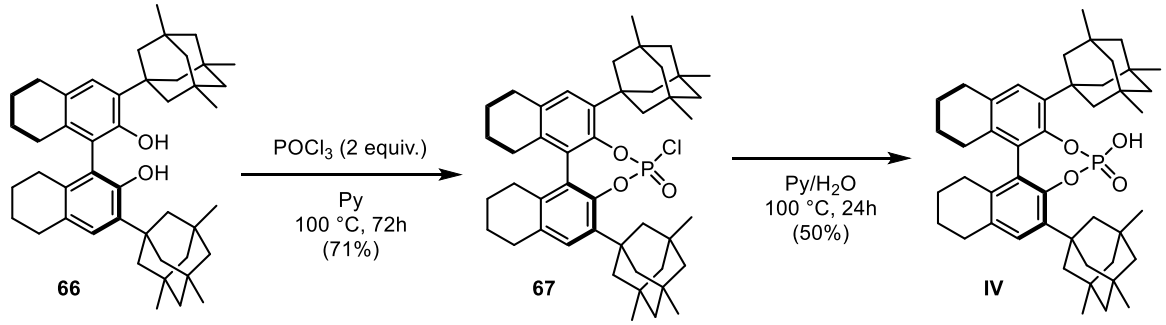
For the synthesis of the catalyst **IV** the first step was an electrophilic aromatic substitution, where 3,5,7-trimethyladamantan-1-ol **60** can be restructured to carbocation in the presence of sulfuric acid. The reaction was carried out according to a published procedure.[31] The procedure used was the same as for the compound **III (**Scheme 6.7).



Scheme 6.7. Friedel-Crafts reaction of (*S*)-H_8-Binol **57** and 3,5,7-trimethyladamantan-1-ol **60**.

The mixture of starting materials **57** and **60** in DCE in the presence of H_2SO_4 was kept at room temperature for 72 h. The crude mixture was separated by silica gel column chromatography using combination of solvents hexane/Et_2O (10:1). Using this method resulted in obtaining the product **66** in the yield of 50 %.

For the synthesis of the corresponding phosphoric acid the same procedure as for Binol-derived phosphoric acid **III** was tested [32] (Scheme 6.8).



Scheme 6.8. Synthesis of Binol-derived phosphoric acid **IV** and its X-ray crystal structure.

The condensation reaction of compound **66** in the presence of $POCl_3$ is followed by hydrolysis to give the desired Binol-derived phosphoric acid **IV**. Analyzing the NMR spectra, it was shown, that reaction was successful due to the fact, that the starting material was practically not present and the conversion was about 70 %. It was clear, that conditions were

chosen correctly and there was no need to optimize the reaction. For purification final product was converted into salt with the aid of NH_4OH and washed with EtOAc and Et_2O. Desired product **IV** was obtained in the yield of 50 %.

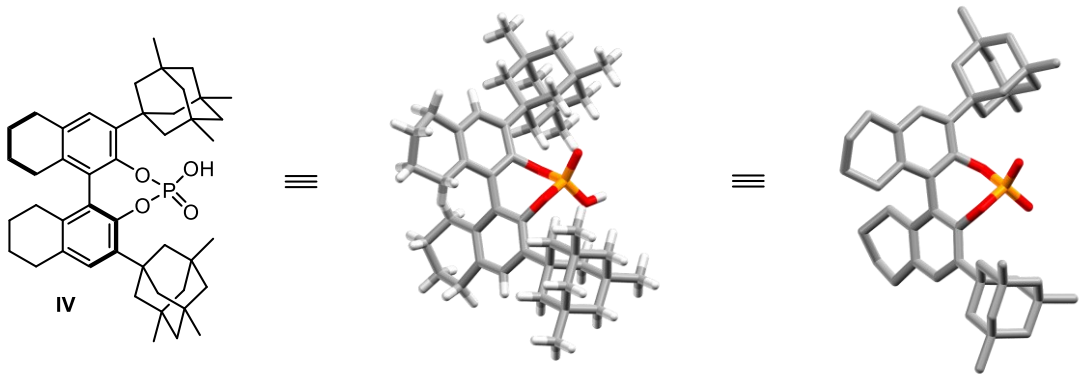


Figure 6.1. X-ray structure of Binol-derived phosphoric acid **IV**

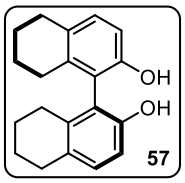
7. Experimental section

7.1. Materials and methods

Reactions with air and moisture sensitive compounds were carried out under inert atmosphere using argon and anhydrous solvents. Reactions under air were done in distilled solvents. Work-up and purification of compounds was carried out on air with reagent-grade solvents. Used abbreviation "r.t" stands for 'room temperature'. Silica gel used for column chromatography was SiliaFlash® P60 (4063 μm; 230-400 mesh) silica gel. Thinlayer chromatography (TLC) was done using Macherey-Nagel POLYGRAM® SIL G/UV_{254} precoated plates (0.2 mm). High- resolution mass spectra were measured by Brucker compact Q-TOF (ESI). Infrared (IR) spectra were measured by Thermo Nicolet-Avatar 370 5T-IR. Melting points were measured in open capillary tubes. X-Ray data were measured by Bruker D8 Venture Kappa Duo PHOTON III. Nuclear magnetic resonance (NMR) spectra were measured by Brucker 400 MHz spectrometer at room temperature. ^{1}H NMR chemical shifts were referenced to $\delta_H(CDCl_3)$ = 7.26 ppm, δ_H(*d*-DMSO) = 2.50 ppm and ^{13}C to $\delta_C(CDCl_3)$ = 77.00 ppm, δ_C(*d*-DMSO) =40.00 ppm. Chemical shifts δ are given in ppm and values of interaction constants *J* in Hz. Specific optical rotations were measured by AUTOMATIC POLARIMETR, Autopol III at room temperature.

7.2. Experimental procedures and spectral data

(*S*)-H$_8$-Binol (57)

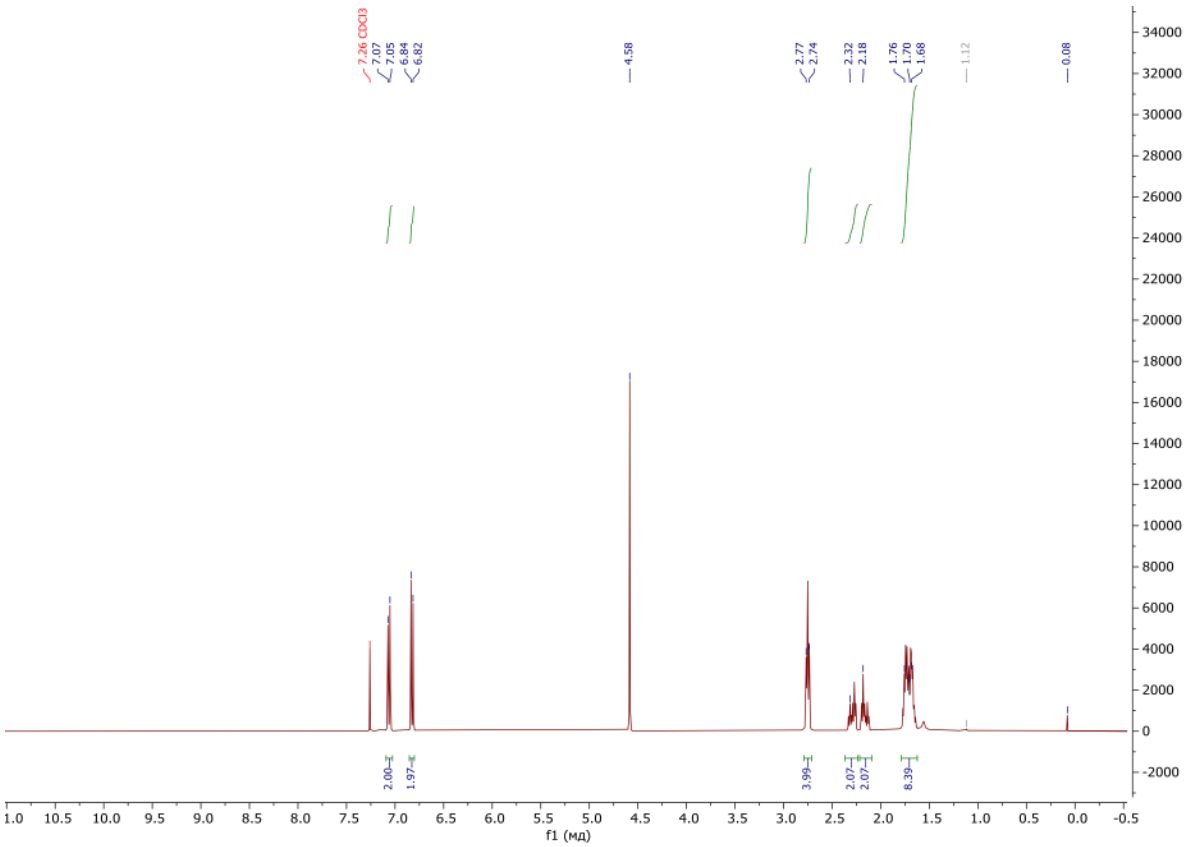


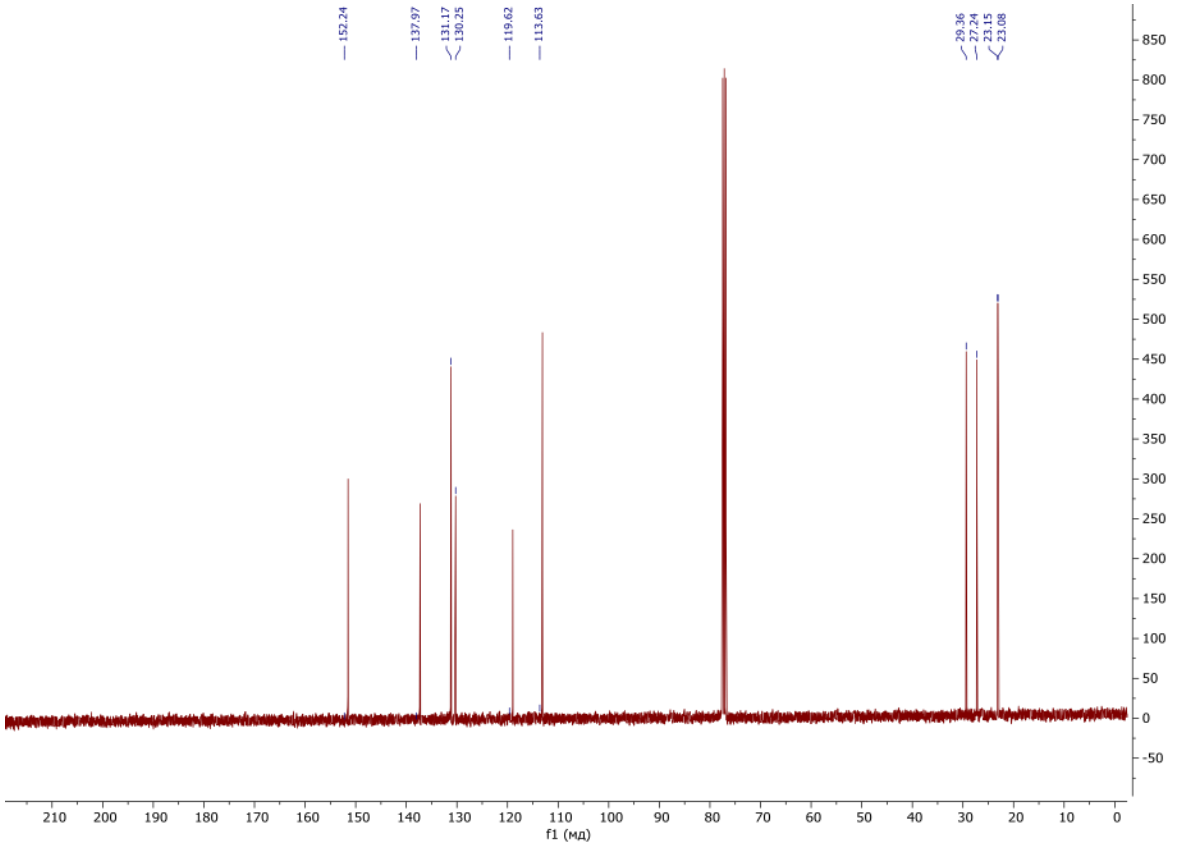
(*S*)-Binol **56** (1 g, 3.5 mmol), 0.3 g of 10 % Pd/C and ethanol (20 mL) were placed into autoclave and stirred at 70 ℃ for 7 h. After this time, the reaction mixture was cooled to room temperature. The metal catalyst was filtered off trough Celite and washed 3x with DCM. The combined filtrates were evaporated to give 1 g (98% yield) of white solid **57**.

R$_f$: 0.4 (DCM)

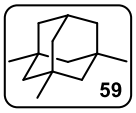
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 2.77 – 2.74 (m, 4H), 2.32 – 2.26 (m, 2H), 2.20 – 2.12 (m, 2H), 1.76 – 1.68 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.24 (2C), 137.97 (2C), 131.17 (2C), 130.25 (2CH), 119.62 (2C), 113.63 (2CH), 29.36 ($2CH_2$), 27.24 ($2CH_2$), 23.15 ($2CH_2$), 23.08 ($2CH_2$).


7.26 CDCl3
7.07
7.05
6.84
6.82
4.58
2.77
2.74
2.32
2.18
1.76
1.70
1.68
1.12
0.08
2.00
1.97
3.99
2.07
2.07
8.39
f1 (мд)


152.24
137.97
131.17
130.25
119.62
113.63
29.36
27.24
23.15
23.08
f1 (мд)

1,3,5-trimethyladamantane (59)

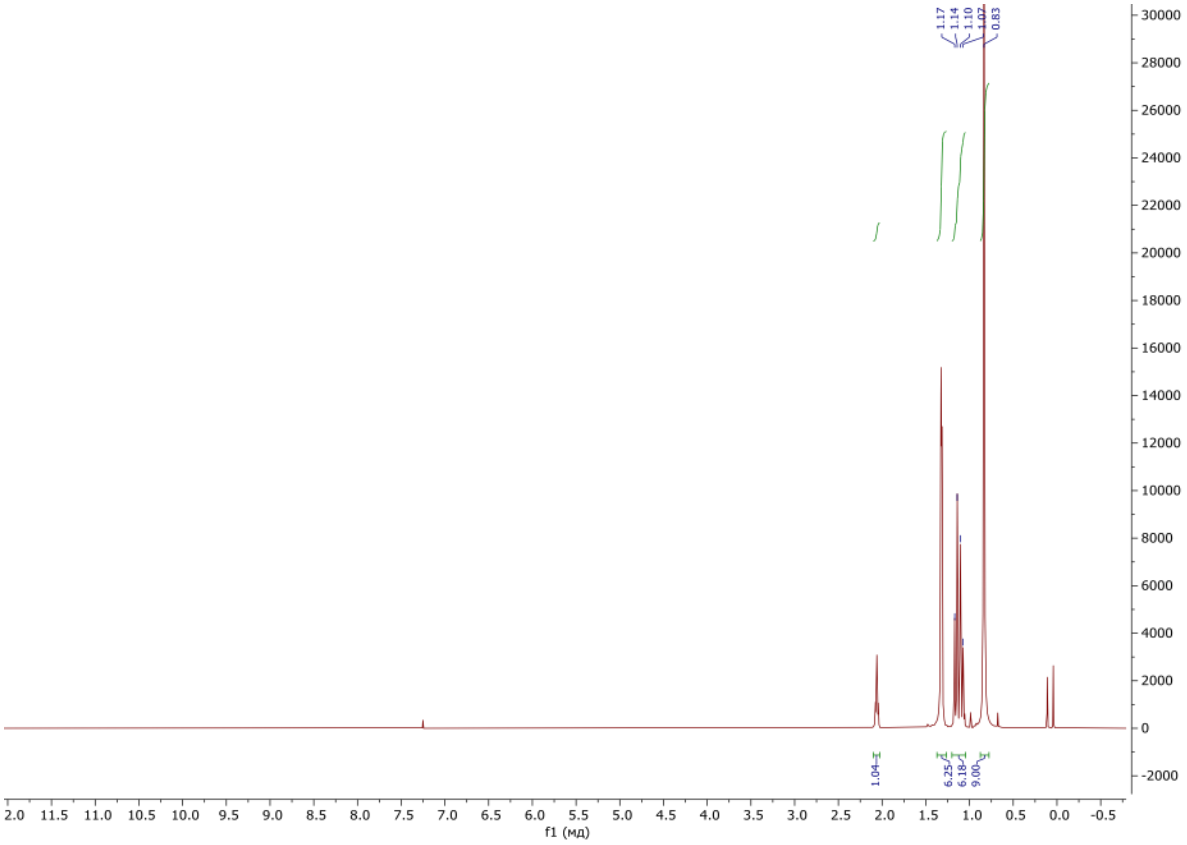


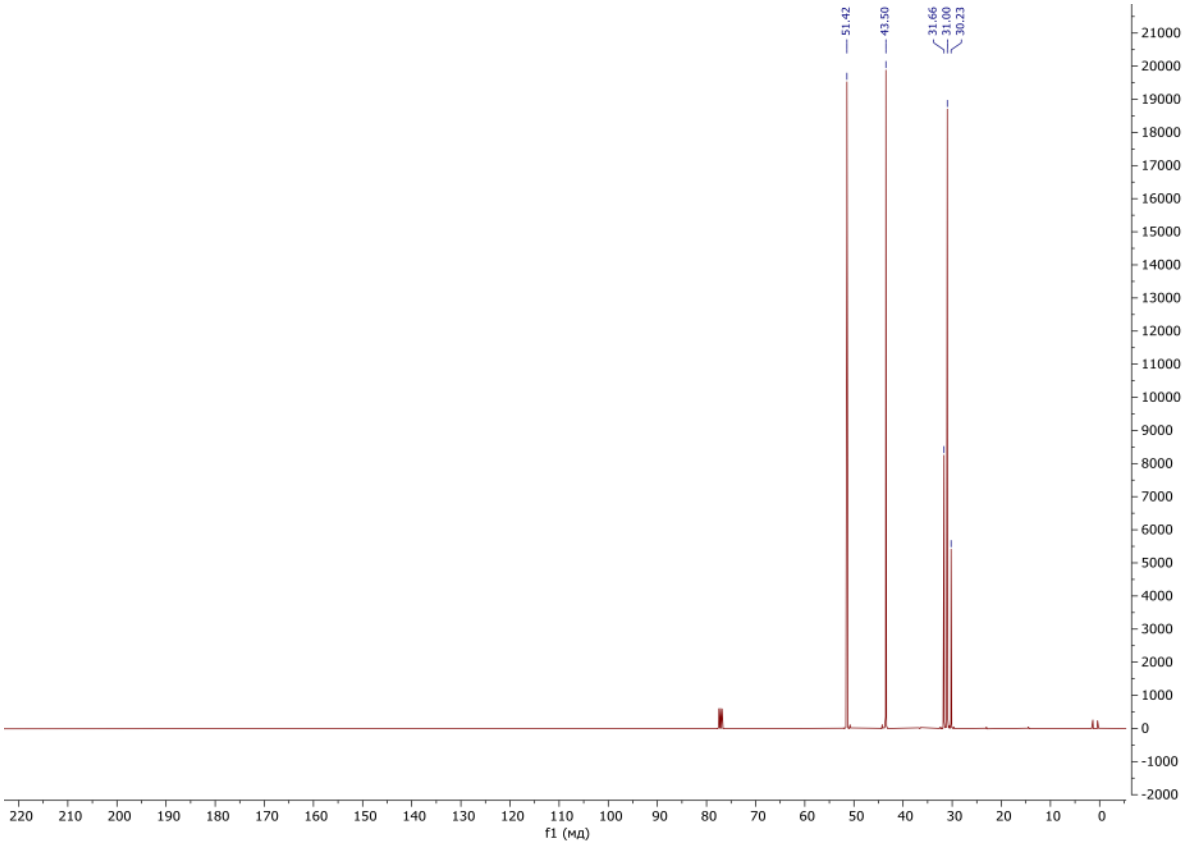
The mixture of 1-bromo-3,5-dimethyladamantane **58** (5 g, 20.5 mmol) and 25 mL of CH_3MgBr was stirred at 90℃ for 2 h. After cooling to r.t., 40 mL of pentane was added. For destruction of Grignard reagents was used 20 mL of HCl (2 %). The aqueous layer was extracted 3x with 20 mL of pentane. The organic layers were washed with water and dried over anh. Na_2SO_4. The solvent was evaporated under the reduced pressure. The product **59** was obtained as an oil in a yield of 63% (2.3 g).

R_f : = 0.2 (CH_2Cl_2)

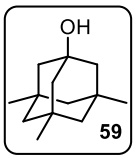
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 – 1.31 (s, 1H), 1.17-1.14 (m, 6H), 1.10 – 1.07 (m, 6H), 0.83 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 51.42 ($3CH_2$), 43.50 ($3CH_2$), 31.66 (3C), 31.00 ($3CH_3$), 30.23 (CH).


1.17
1.14
1.10
1.02
0.83
1.04
6.25
6.18
9.00
f1 (мд)


51.42
43.50
31.66
31.00
30.23
f1 (мд)

3,5,7-trimethyladamantan-1-ol (60)

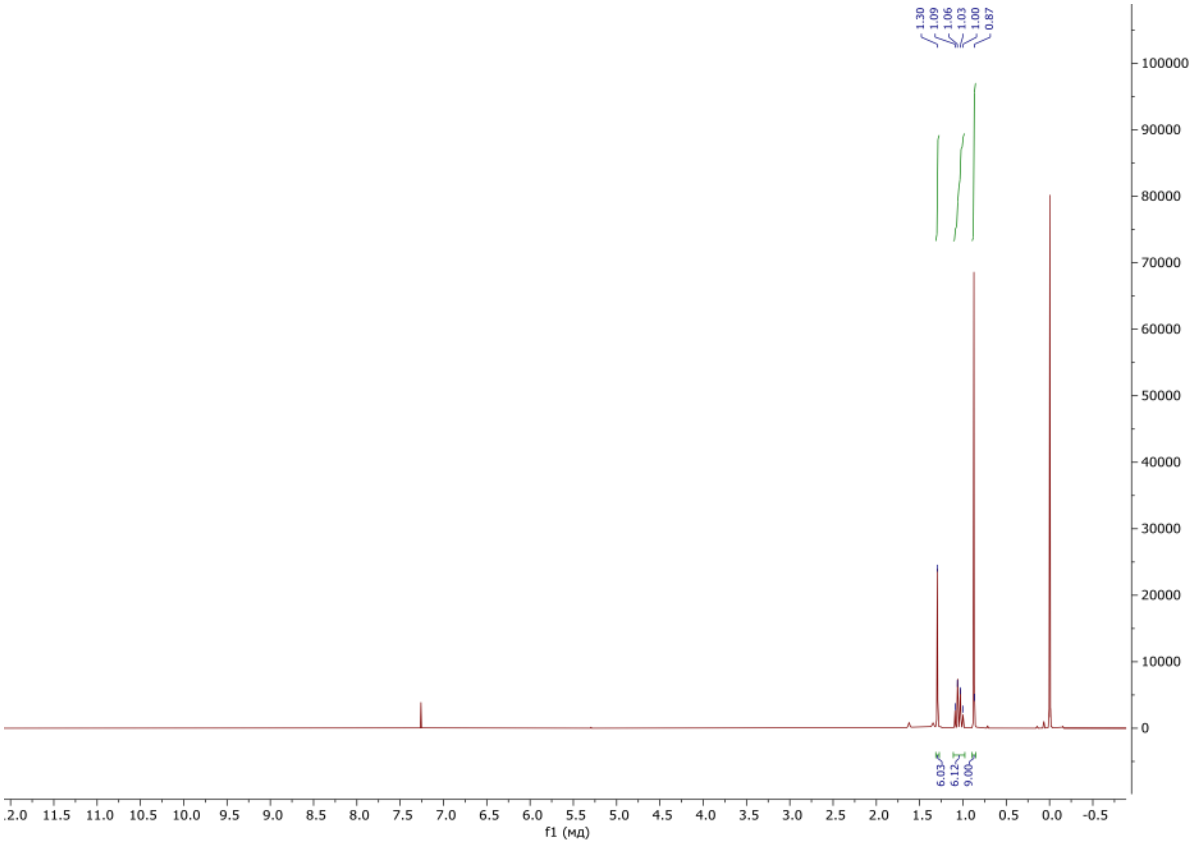


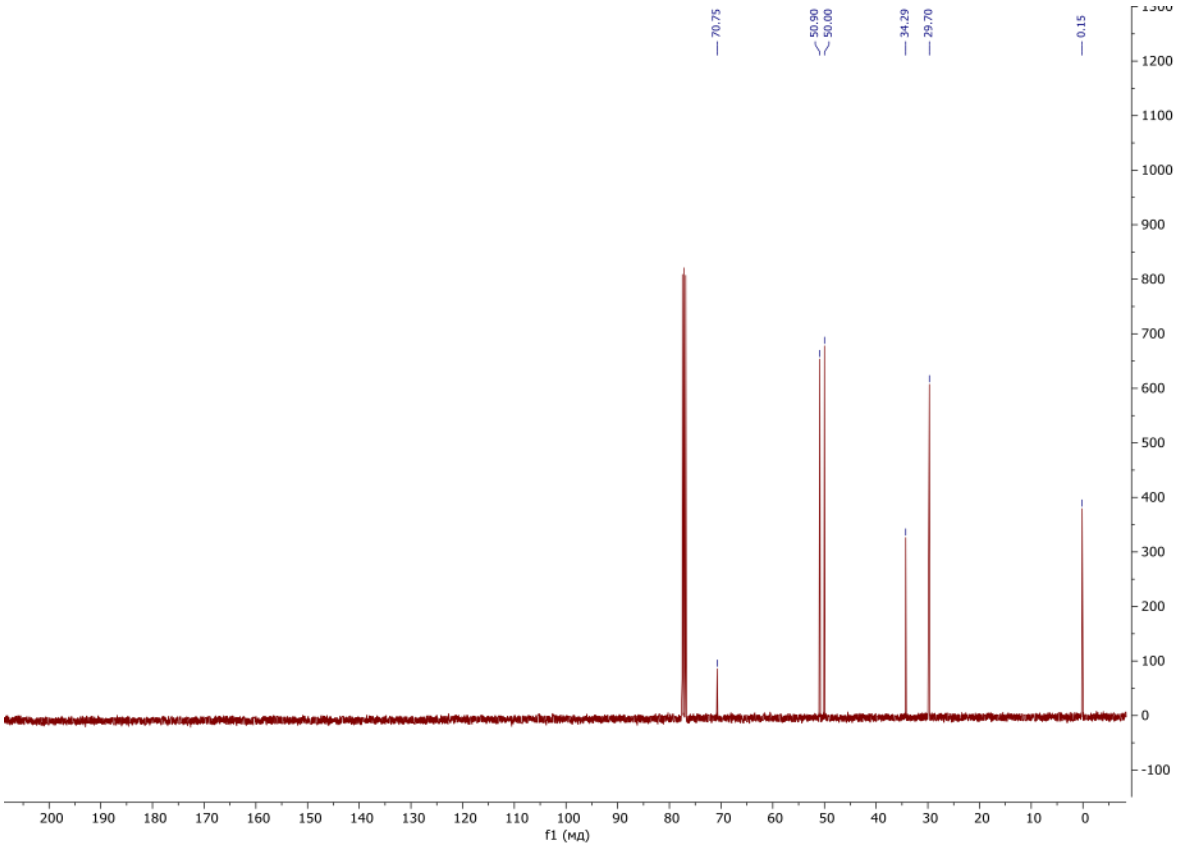
1,3,5-trimethyladamantane **59** (2 g, 11.2 mmol) was dispersed in 4 mL of glacial acetic acid and HNO_3 (4.7 mL, 112 mmol, 10 eq.) was added dropwise. The reaction mixture was stirred at 20℃ for 1 hour. 0.6 g of urea was dissolved in 16 mL of 15% aqueous acetic acid and the solution was added dropwise to the reaction. The mixture was heated to 100℃ and stirred for 1 hour, then cooled to 50 ℃. After cooling, 40% NaOH was added to pH 10 and the reaction mixture was filtered and evaporated. The final product was purified by a column chromatography on a silica gel using hexane/EtOAc 1:1. 1.1 g (52 % yield) of white solid **60** was obtained.

R_f : 0.3 (CH_2Cl_2)

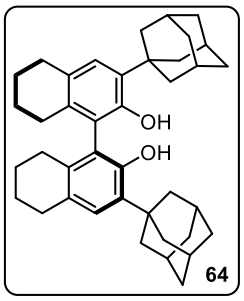
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 6H), 1.04 (q, $2J$ = 12 Hz, 6H), 0.87 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 70.75 (2C), 50.90 ($3CH_2$), 50.00 ($3CH_2$), 34.29 (2C), 29.70 ($2CH_3$), 0.15 (CH_3).


1.30
1.09
1.06
1.03
1.00
0.87
6.03
6.12
9.00
f1 (мд)


70.75
50.90
50.00
34.29
29.70
0.15
f1 (мд)

(*S*)-1,1'-(5,5',6,6',7,7',8,8'-Octahydro-3,3'-di(1-adamanyl)-binaphtalene)-2,2'-diol (64)



The previously prepared H_8-Binol **57** (1g, 3.4 mmol) and 1-adamantanol **63** (1.29 g, 8.5 mmol, 2.5 eq.) were dissolved in DCE (23 mL). The reaction mixture was cooled to 0 ℃ and H_2SO_4 (546 µL, 10.2 mmol, 3 eq.) was added dropwise. The reaction mixture was warmed to the room temperature and was stirred for 72 h. The reaction mixture was neutralised with $NaHCO_3$. The mixture was extracted with DCM. The organic layers were collected, dried with anhydrous sodium sulphate and evaporated under reduced pressure. The final product was purified by a column chromatography on a silica gel using hexane/EtOAc 10:1. 1.2 g of product **64** was obtained as a white solid (63% yield).

R_f: 0.8 (hexane/EtOAc 10:1)

m.p. = 286,9 ℃ (recrystallized from CH_2Cl_2)

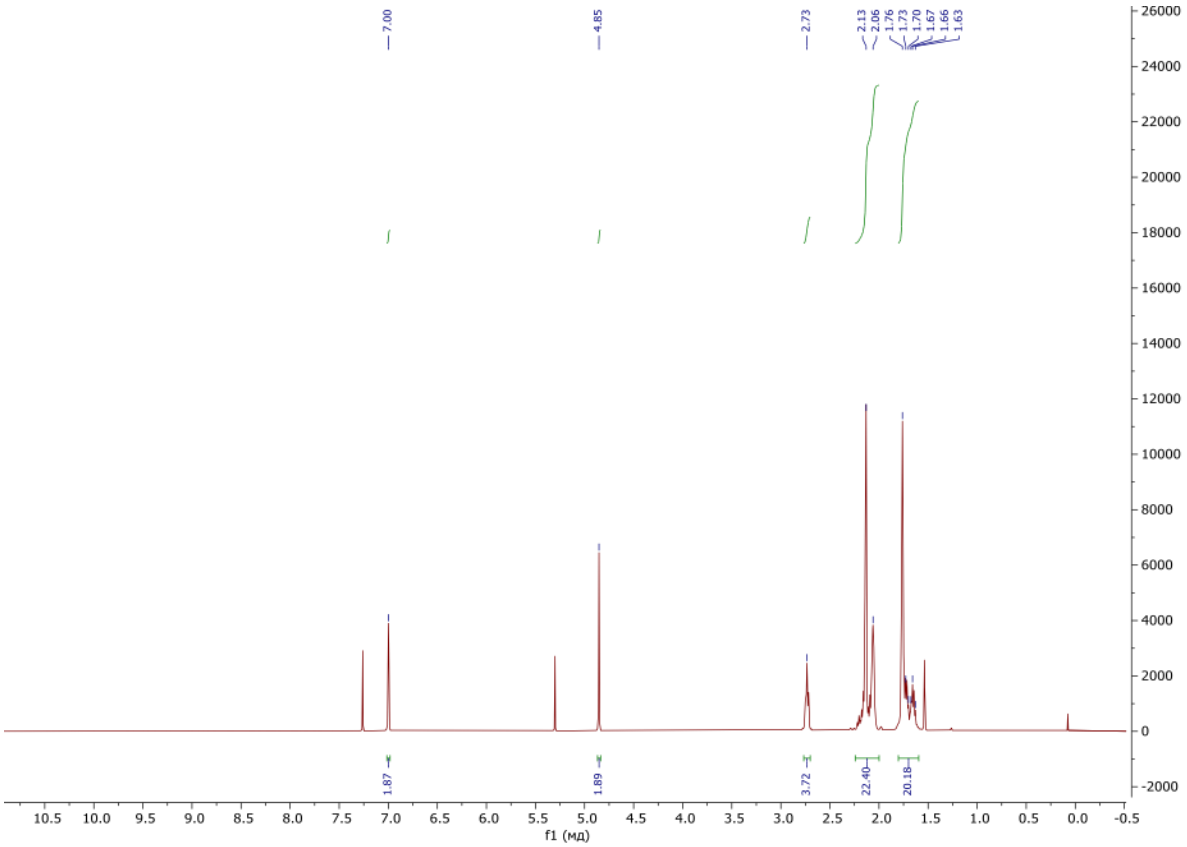
$[\alpha]_D = -28{,}3°$ (c 1.0, CH_2Cl_2)

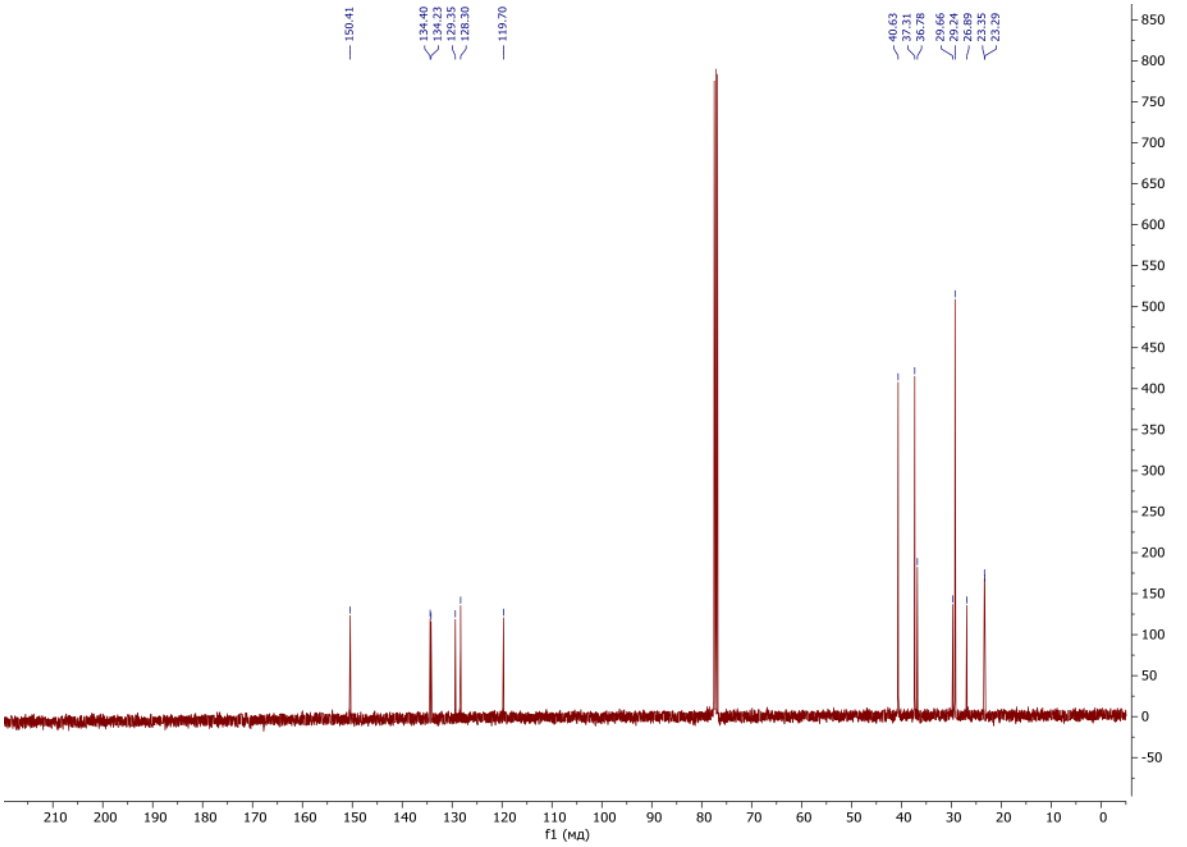
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H), 4.85 (s, 2H), 2.75 - 2.73 (m, 4H), 2.13 – 2.06 (m, 22H), 1.76-1.63 (m, 20H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.41 (2C), 134.40 (2C), 134.23 (2C), 129.35 (2C), 128.30 (2CH), 119.70 (2C), 40.63 (2C), 37.31 ($3CH_2$), 36.78 ($3CH_2$), 29.66 (CH_2), 29.24 (6CH), 26.89 (CH_2), 23.35 ($4CH_2$), 23.29 (CH_2).

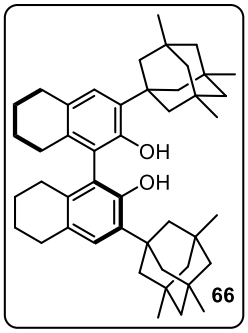
IR (neat): /cm^{-1} = 3500, 2900, 2844, 1448, 1425, 1406, 1367, 1342, 1327, 1315, 1217, 1180, 1163, 1117, 1099, 1072, 1053, 1020, 906, 876, 845, 818, 791, 731, 690, 661, 648, 600, 557, 465.

HRMS(m/z): Calcd for $C_{40}H_{50}NaO_2$: 585.3703 $[M + Na]^+$; Measured: 585.3708.


7.00
4.85
2.73
2.13
2.06
1.76
1.73
1.70
1.67
1.66
1.63
1.87
1.89
3.72
22.40
20.18
f1 (мд)


150.41
134.40
134.23
129.35
128.30
119.70
40.63
37.31
36.78
29.66
29.24
26.89
23.35
23.29
f1 (мд)

(*S*)-1,1'-(5,5',6,6',7,7',8,8'-Octahydro-3,3'-di(3,5,7-trimethyladamanyl)-binaphtalene)-2,2'-diol (66)



(*S*)-H_8-Binol **57** (1g, 3.4 mmol) and 3,5,7-trimethyladamantan-1-ol **60** (1.6 g, 8.5 mmol, 2.5 eq.) were diluted in 29.5 mL of DCE. The reaction mixture was cooled to 0 ℃ and H_2SO_4 (550 µL, 10.2 mmol, 3 eq.) was added dropwise. The reaction was allowed to react at the room temperature and neutralised with $NaHCO_3$ after 72 hours. The aqueous layer was then extracted with DCM. The organic layers were combined, dried over Na_2SO_4 and evaporated. Final product was purified by silica gel column chromatography using hexane/Et_2O (10:1). 1.1 g of white solid **66** were obtained (50 % yield).

R_f: 0.8 (hexane/Et_2O 10:1)

m.p. = 205,3 ℃ (recrystallized from CH_2Cl_2)

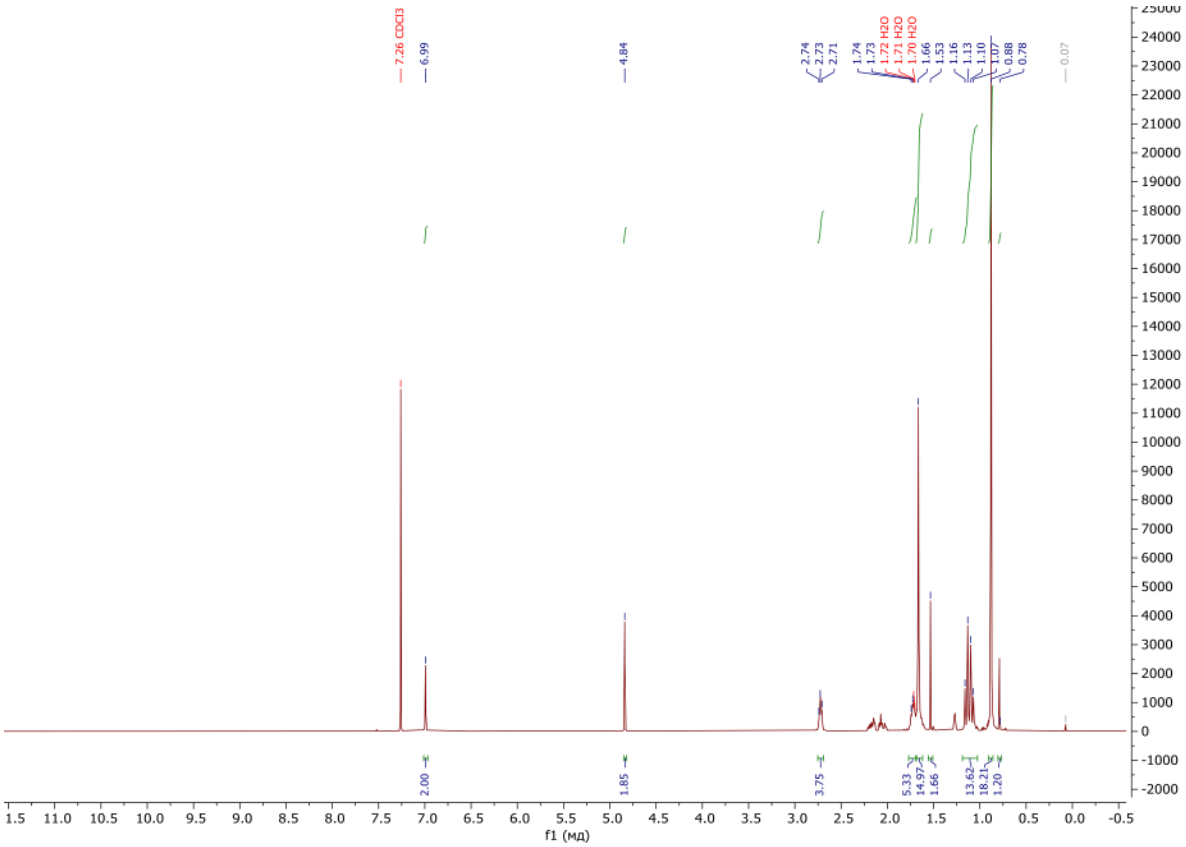
$[\alpha]_D = -23{,}6°$ (c 1.0, CH_2Cl_2)

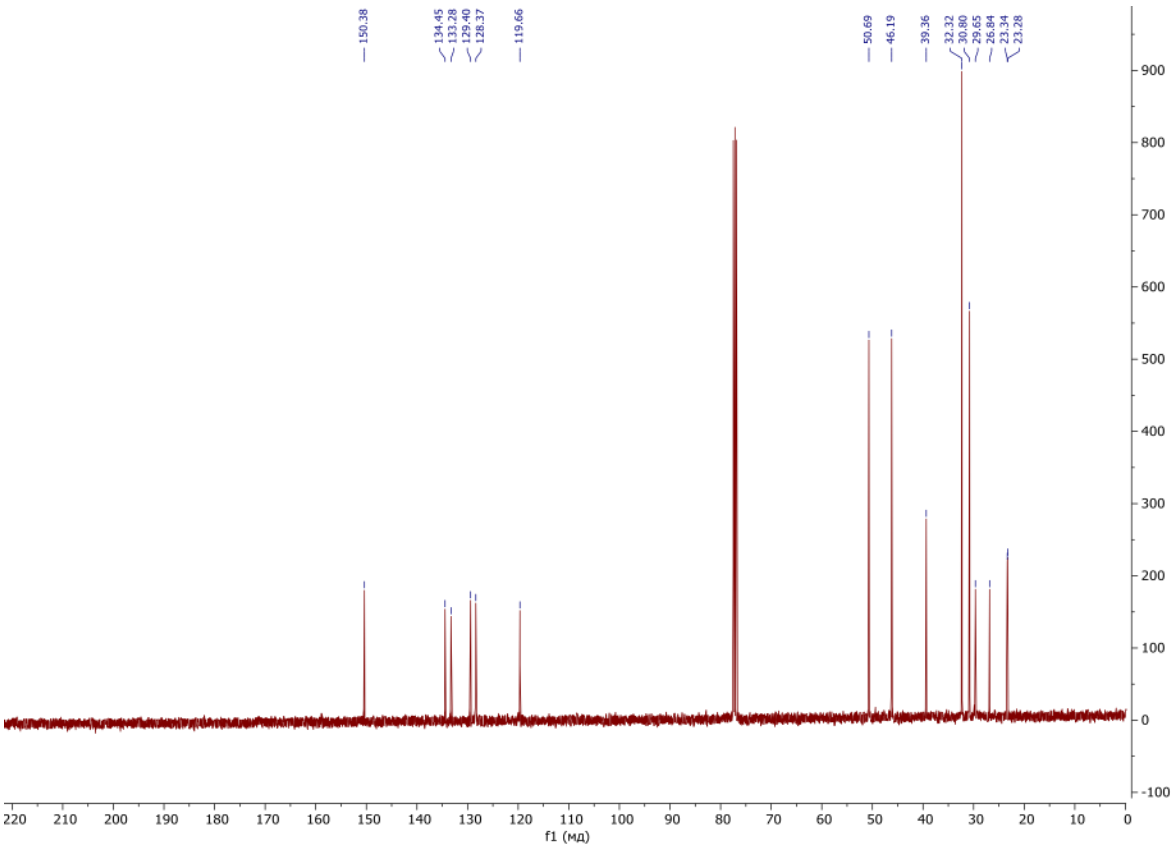
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 2H), 4.64 (s, 2H), 2.74 – 2.71 (m, 4H), 1.74 – 1.71 (m, 5H), 1.66 (s, 15H), 1.53 (s, 2H), 1.16 – 1.07 (m, 14H), 0.88 (s, 18H), 0.78 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.38 (2C), 134.45 (2C), 133.28 (2C), 129.40 (3C), 128.37 (2CH), 119.66 (3C), 50.69 ($6CH_2$), 46.19 ($6CH_2$), 39.36 ($2CH_2$), 32.32 ($6CH_3$), 30.80 ($2CH_2$), 29.65 (6C), 26.84 (CH_2), 23.34 (CH_2), 23.28 ($2CH_2$).

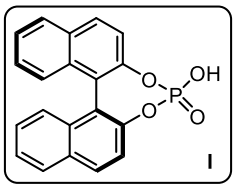
IR (neat): /cm^{-1} = 3504, 2941, 2920, 2889, 2860, 2833, 1603, 1454, 1433, 1406, 1373, 1352, 1325, 1304, 1279, 1248, 1219, 1190, 1178, 1161, 1093, 947, 910, 895, 874, 839, 823, 754, 721, 667, 656, 604, 571, 436.

HRMS(m/z): Calcd for $C_{46}H_{62}NaO_2$: 669.4642 $[M + Na]^+$; Measured: 669.4652.


7.26 CDCl3
6.99
4.84
2.74
2.73
2.71
1.74
1.73
1.72 H2O
1.71 H2O
1.70 H2O
1.66
1.53
1.16
1.13
1.10
1.07
0.88
0.78
0.07
2.00
1.85
3.75
5.33
14.97
1.66
13.62
18.21
1.20
f1 (мд)


150.38
134.45
133.28
129.40
128.37
119.66
50.69
46.19
39.36
32.32
30.80
29.65
26.84
23.34
23.28
f1 (мд)

(*S*)-1,1'-Binaphtalene-2,2'-diyl phosphoric acid (I)



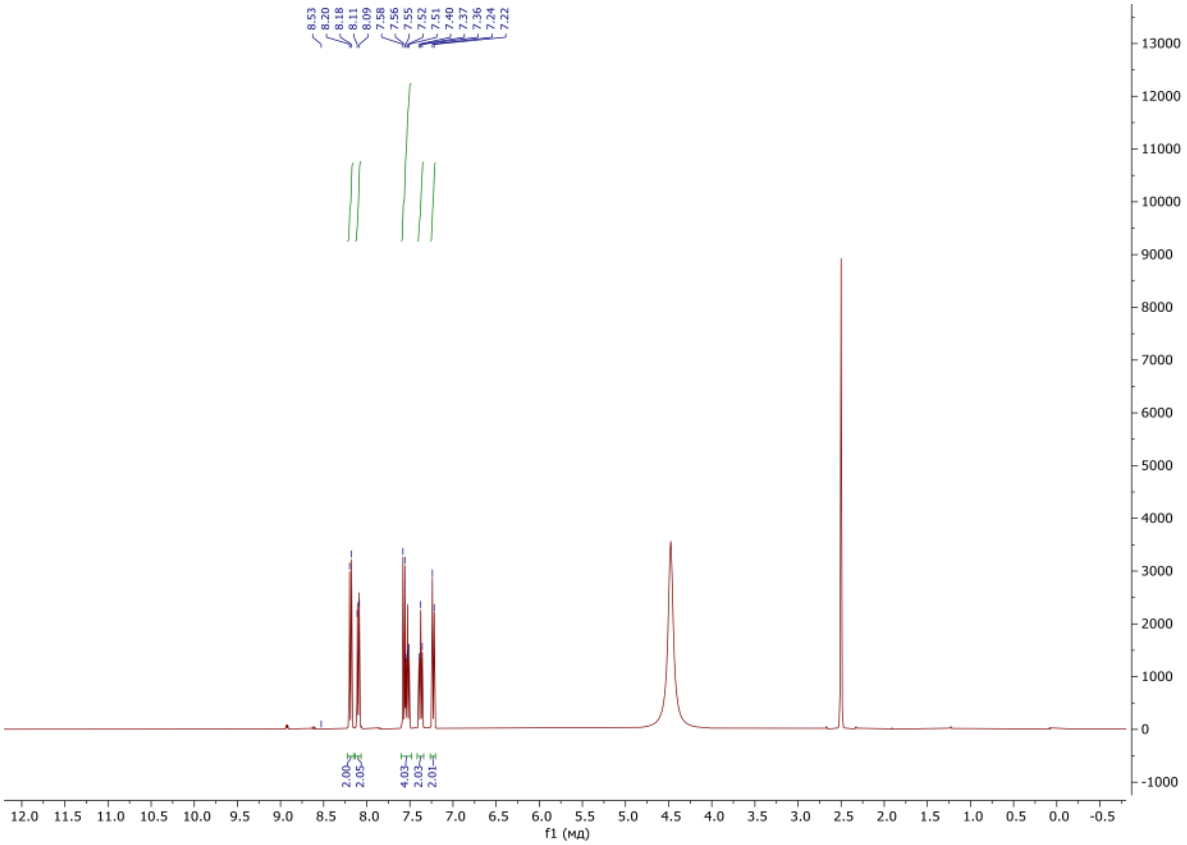
Commercially available *(S)*-Binol **56** (1 g, 3.5 mmol) was dissolved in DCM (7.5 mL). The reaction mixture was cooled to 0℃ and Et_3N (1.6 mL, 10.5 mmol, 3 eq.) and $POCl_3$ (0.63 mL, 7 mmol, 2 eq.) were added dropwise ℃. The reaction mixture was warmed to 25 ℃ and stirred for 24 h. After this time, the reaction was quenched with 4 mL of H_2O. The reaction mixture was extracted 3x with DCM. The organic layers were combined, concentrated under *vacuo* and filtered through a short pad of silica gel using DCM as a solvent. The compound was then dissolved in pyridine (5 mL) and water (0.6 mL) was added for the hydrolysis. The reaction was stirred for 12 h at 25 ℃. Pyridine was evaporated under the reduced pressure. The final product was washed with 1M HCl to get rid of pyridine residues and filtered. For purification, Na_2CO_3 solution was added to form a salt, washed with EtOAc and extracted with 1M HCl. The product **I** was obtained as white solid in a yield of 67 % (811 mg).

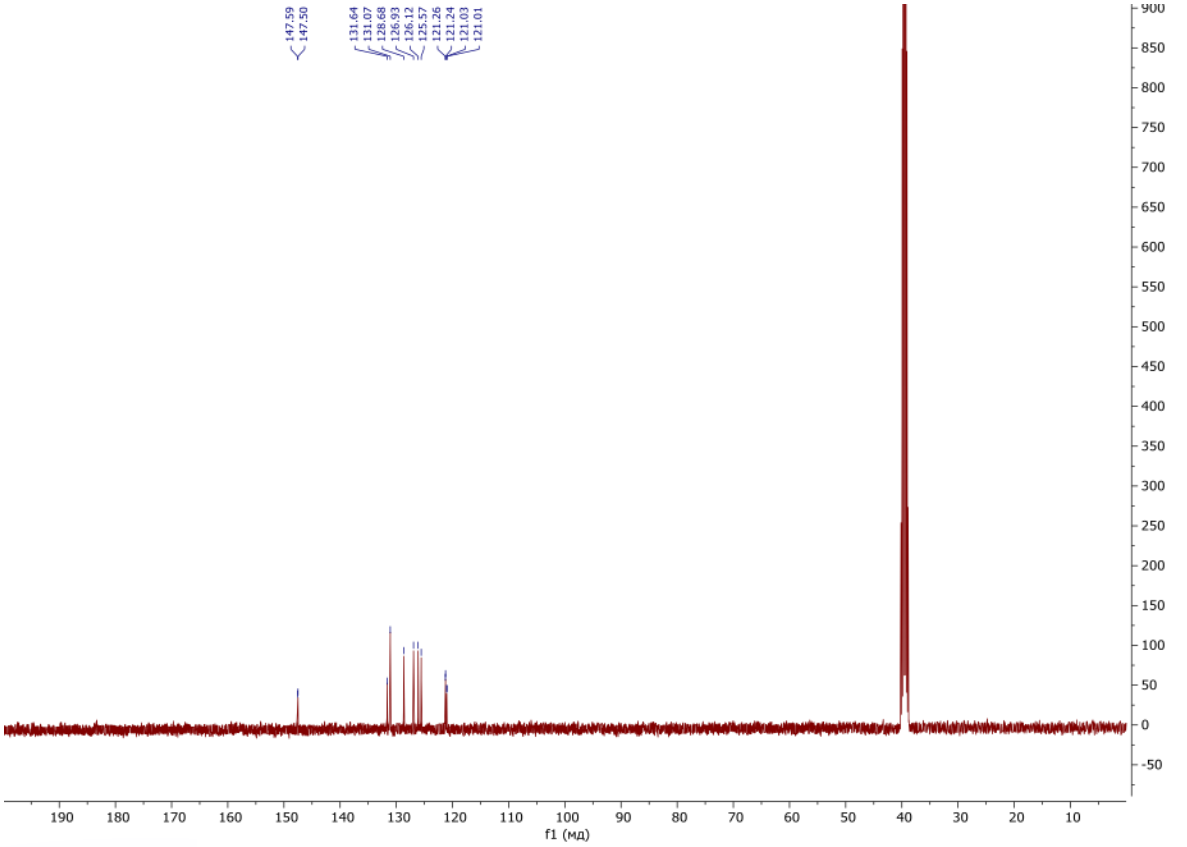
R_f : 0,2 (DCM/MeOH 5%)

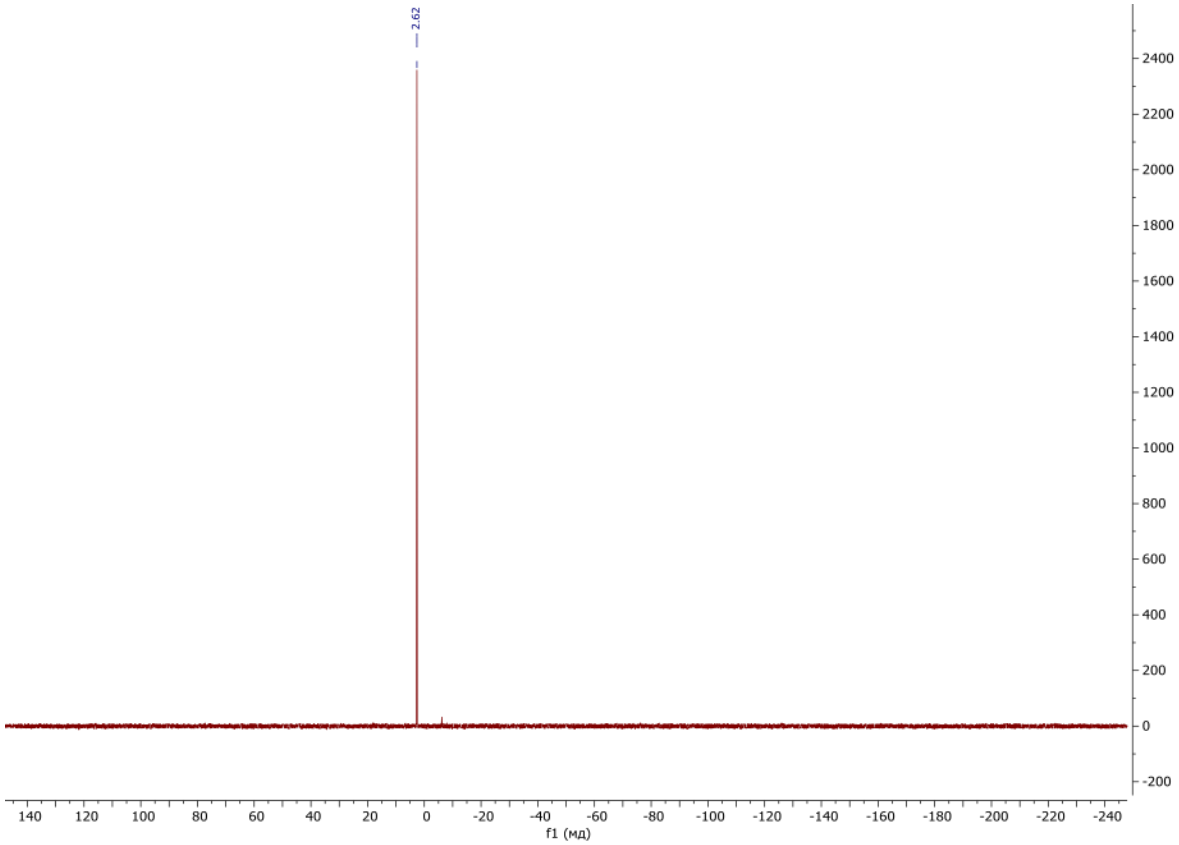
^{1}H NMR (400 MHz, *d*-DMSO): δ 8.19 (d, J = 8.0 Hz, 2H), 8.10 (d, J = 8.0 Hz, 2H), 7.58-7.51 (m, 4H), 7.40-7.36 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H).

^{13}C NMR (101 MHz, *d*-DMSO) δ 147.59 (C), 147.50 (C), 131.64 (2C), 131.07 (2CH), 128.68 (2C), 126.93 (2CH), 126.12 (2CH), 125.57 (2CH), 121.26 (CH), 121.24 (CH), 121.03 (2C), 121.01 (2CH).

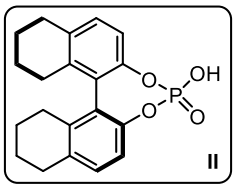
^{31}P **NMR** (122 MHz, *d*-DMSO): δ 2.62.


8.53
8.20
8.18
8.11
8.09
7.58
7.56
7.55
7.52
7.51
7.40
7.37
7.36
7.24
7.22
2.00
2.05
4.03
2.03
2.01
f1 (мд)


147.59
147.50
131.64
131.07
128.68
126.93
126.12
125.57
121.26
121.24
121.03
121.01
f1 (мд)


2.62
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (мд)

(*S*)-1,1'-(5,5',6,6',7,7',8,8'-Octahydro-binaphtalene)-2,2'-diyl phosphoric acid (II)



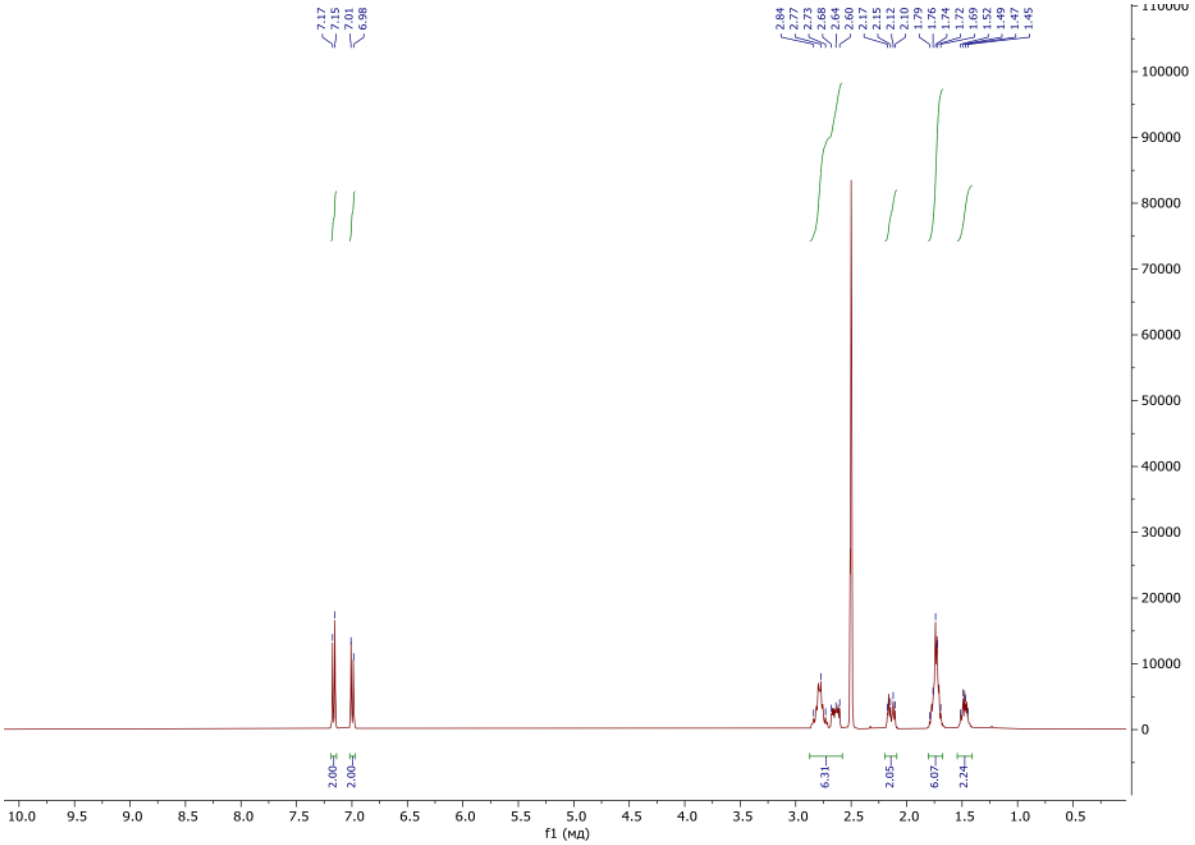
Compound **7** was prepared using the same procedure as compound **6**. *(S)*-H_8-Binol (1 g, 3.4 mmol) was dissolved in DCM (8 mL). The reaction mixture was cooled to 0℃ and Et_3N (1.6 mL, 10.5 mmol, 3 eq.) and $POCl_3$ (0.63 mL, 7 mmol, 2 eq.) were added dropwise. The reaction mixture was warmed to 25 ℃ and stirred for 24 h. After this time, the reaction was quenched with 4 mL of H_2O. The reaction mixture was extracted 3x with 20 mL of DCM. The organic layers were combined, concentrated under *vacuo* and filtered through a short pad of silica gel using DCM as a solvent. The compound was then dissolved in pyridine (6 mL) and water (0.5 mL) was added for the hydrolysis. The reaction was stirred for 12 h at 25 ℃. Pyridine was evaporated under the reduced pressure. The final product was washed with 1M HCl to get rid of pyridine residues and filtered. For purification, solution of Na_2CO_3 was added to form a salt, washed with EtOAc and Et_2O and extracted with 1M HCl. Final product **II** was converted into acid with 1M HCl and obtained as a white solid in a yield of 62 % (750 mg).

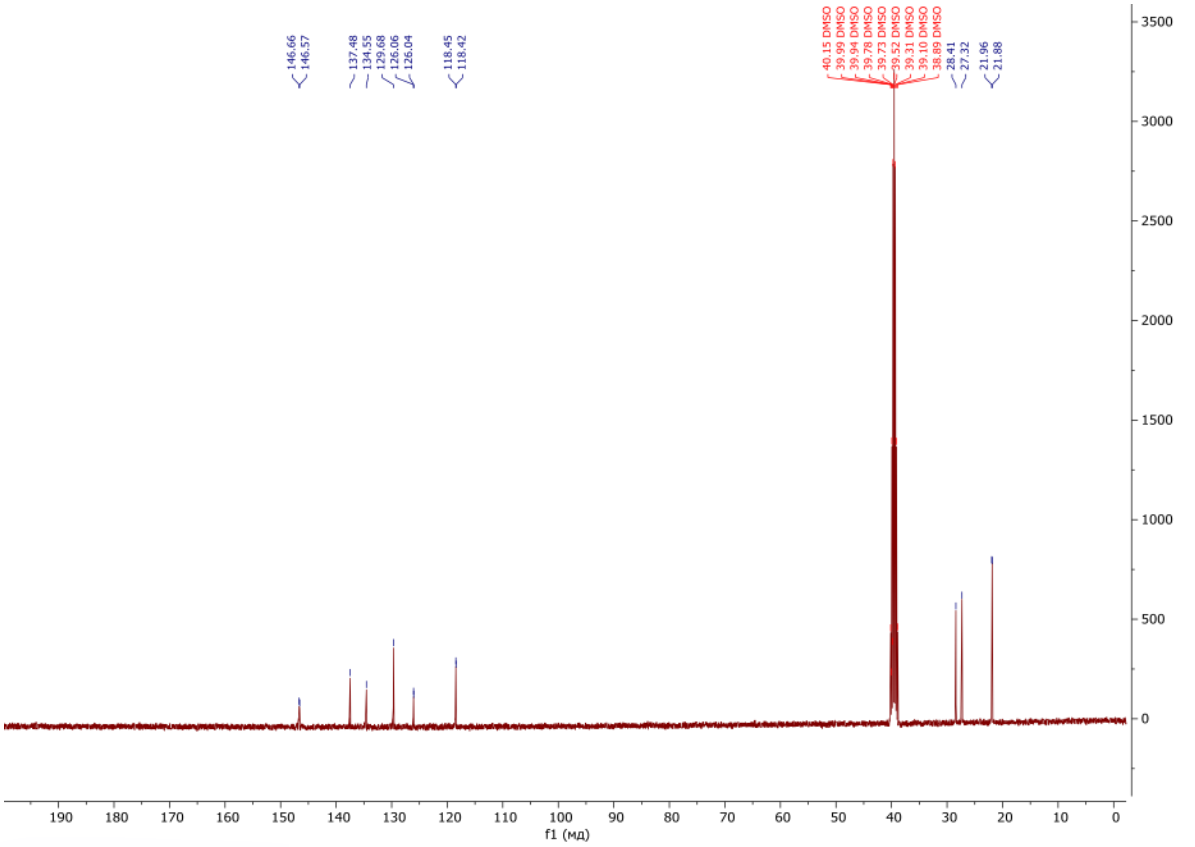
R_f : 0.2 (DCM/MeOH 5%)

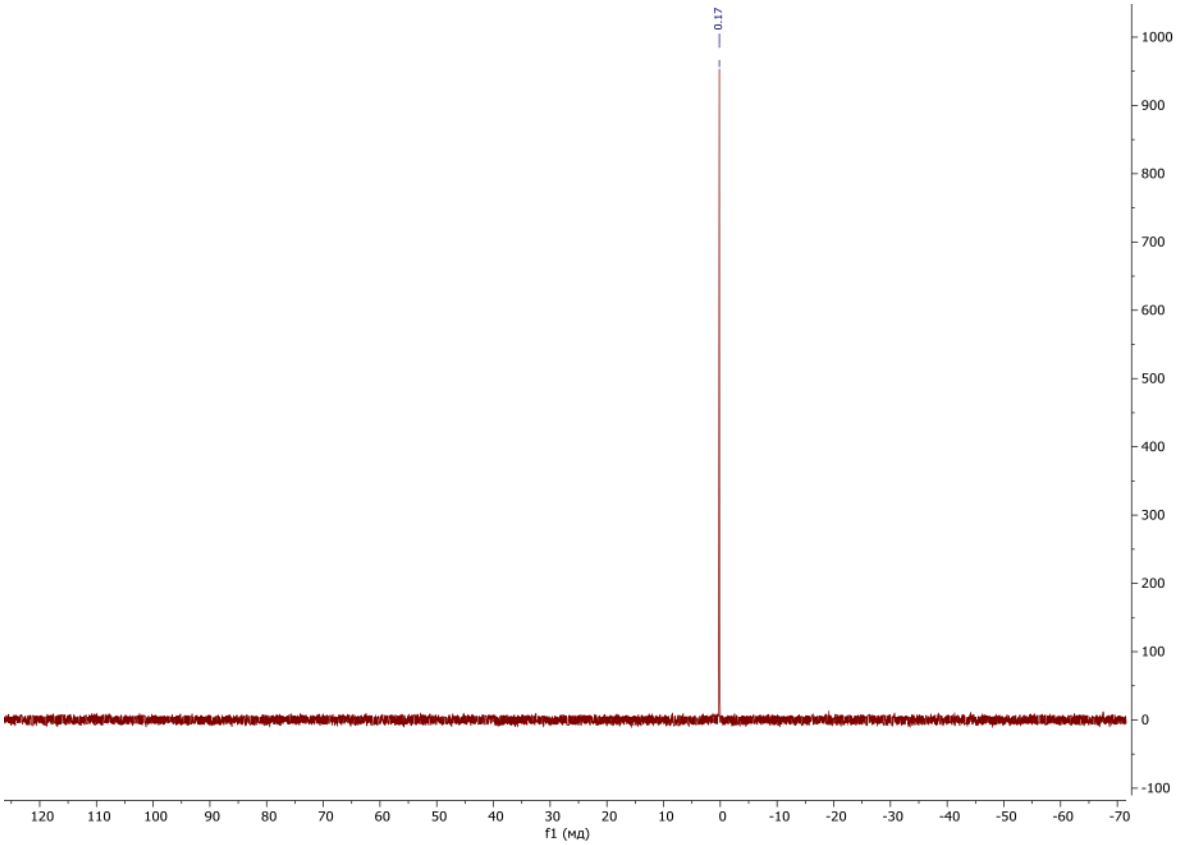
^{1}H NMR (400 MHz, *d*-DMSO): δ 7.09 (dd, J = 66.0, 8.0 Hz, 4H), 2.84 - 2.60 (m, 6H), 2.17 – 2.10 (m, 2H), 1.79 – 1.69 (m, 6H), 1.52 – 1.45 (m, 2H).

^{13}C NMR (101 MHz, *d*-DMSO) δ 146.66 (C), 146.57 (C), 137.48 (2CH), 134.56 (2C),129.68 (2C), 126.06 (C), 126.04 (C), 118.45 (CH), 118.42 (CH), 28.41 ($2CH_2$), 27.31 ($2CH_2$), 21.96 ($2CH_2$), 21.88 ($2CH_2$).

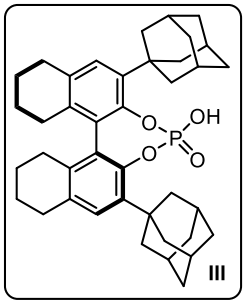
^{31}P NMR (122 MHz, *d*-DMSO): δ 0.17


7.17
7.15
7.01
6.98
2.84
2.77
2.73
2.68
2.64
2.60
2.17
2.15
2.12
2.10
1.79
1.76
1.74
1.72
1.69
1.52
1.49
1.47
1.45
2.00
2.00
6.31
2.05
6.07
2.24
f1 (мд)


146.66
146.57
137.48
134.55
129.68
126.06
126.04
118.45
118.42
40.15 DMSO
39.99 DMSO
39.94 DMSO
39.78 DMSO
39.73 DMSO
39.52 DMSO
39.31 DMSO
39.10 DMSO
38.89 DMSO
28.41
27.32
21.96
21.88
f1 (мд)


0.17
1000
900
800
700
600
500
400
300
200
100
0
-100
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
f1 (мд)

(*S*)-1,1'-(5,5',6,6',7,7',8,8'-Octahydro-3,3'- di(1-adamanyl)-binaphtalene)-2,2'-diyl phosphoric acid (III)



Compound **64** (700 mg, 1.24 mmol) was dissolved in pyridine (12 mL) and $POCl_3$ (0.23 mL, 2.5 mmol, 2.0 eq.) was added dropwise. The mixture was heated to 100℃ and stirred for 72 h. Then 12 mL of water was added and the mixture was stirred for 24 h at the same temperature. The aqueous layer was extracted 3x with DCM. The pyridine was evaporated under reduced pressure. To remove pyridine residues, the mixture was washed 2x with 6N HCl and the organic layer was evaporated. For purification product was dissolved in DCM. Then NH_4OH was added to form a salt and the mixture was washed with EtOAc and Et_2O and filtered. The salt was converted into the acid by 3x extraction with 6N HCl. The product **III** was obtained as a pale yellow solid in a yield of 51 % (390 mg).

R_f : 0.3 (DCM/MeOH 5%)

m.p. = 291,4 ℃ (recrystallized from $CHCl_3$)

$[\alpha]_D = +93°$ (c 1.0, $CHCl_3$)

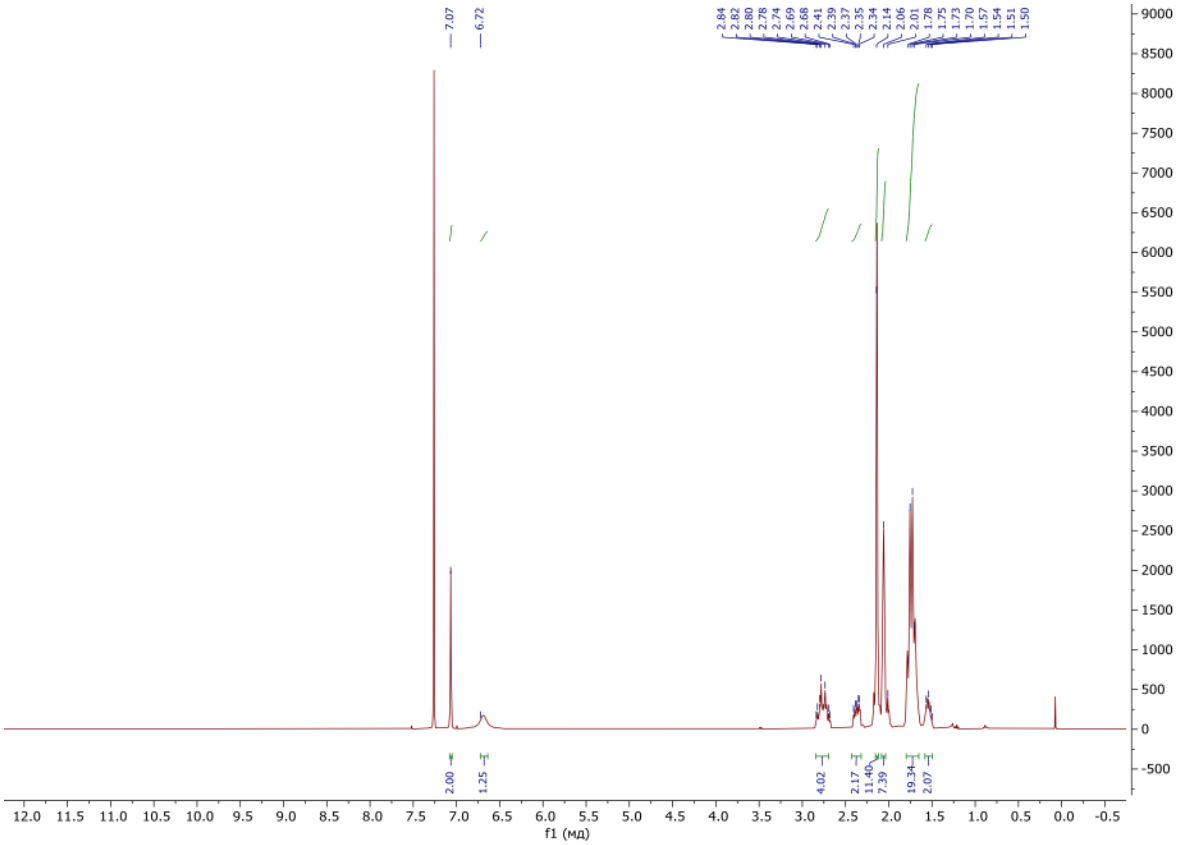
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 2H), 6.72 (s, 1H), 2.84 - 2.68 (m, 4H), 2.41 - 2.34 (m, 2H), 2.17 – 2.10 (m, 11H), 2.06 – 2.01 (m, 7H), 1.78 – 1.70 (m, 19H), 1.57 – 1.50 (m, 2H).

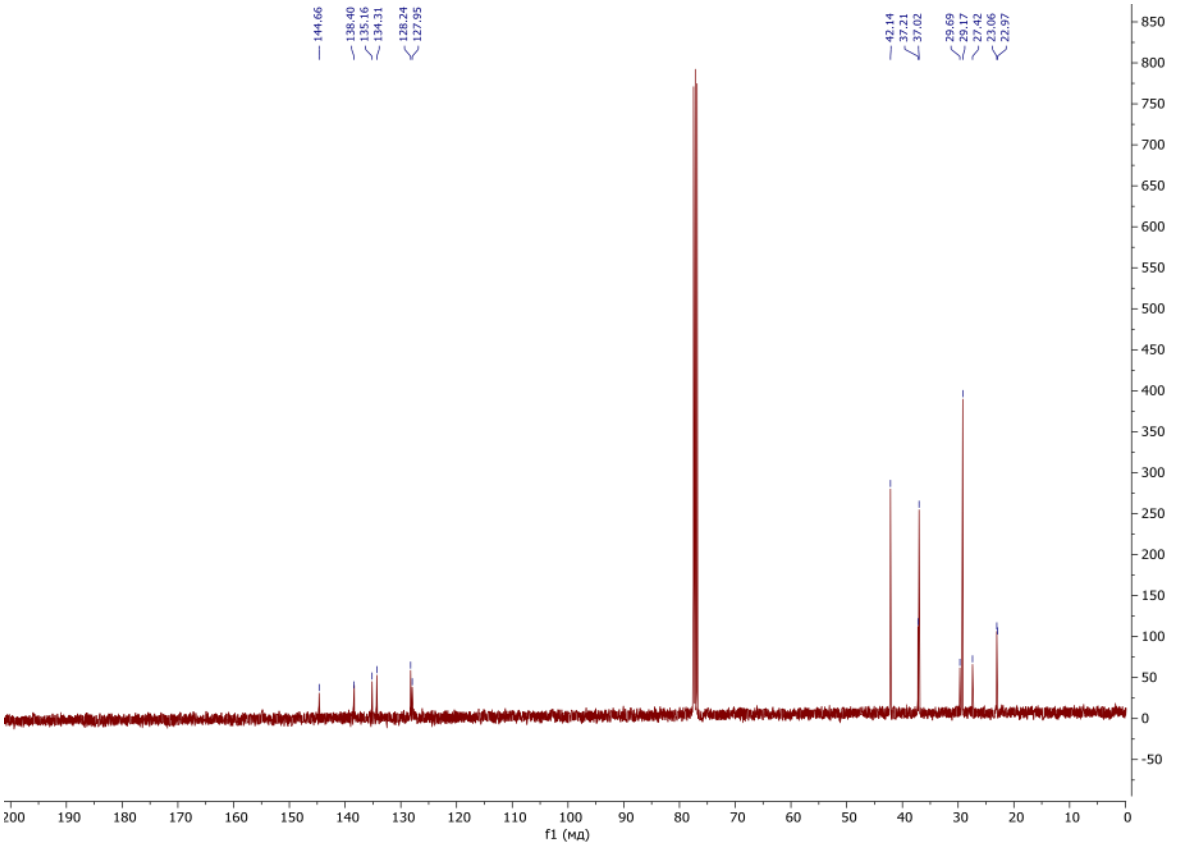
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.66 (2C), 138.40 (2C), 135.16 (2C), 134.31 (2C), 128.24 (2CH), 127.95 (2C), 42.14 ($6CH_2$), 37.21 ($6CH_2$), 37.02 ($2CH_2$), 29.69 (2C), 29.17 (6CH), 27.42 ($2CH_2$), 23.06 ($2CH_2$), 22.97 ($2CH_2$).

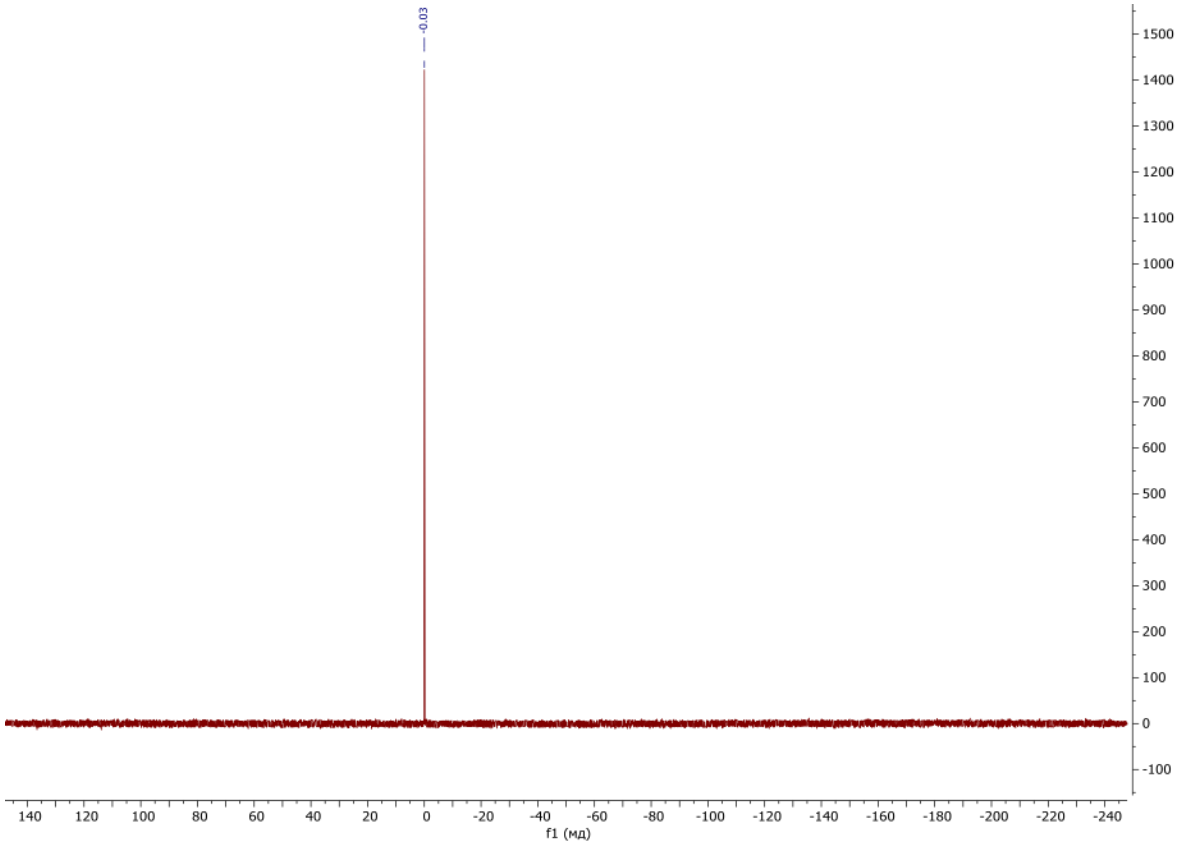
^{31}P NMR (122 MHz, $CDCl_3$) δ 0.03

IR (neat): /cm^{-1} = 3502, 2902, 2848, 2679, 2657, 1633, 1558, 1448, 1435, 1417, 1369, 1344, 1315, 1250, 1209, 1186, 1165, 1119, 1099, 1014, 968, 908, 885, 816, 791, 766, 719, 683, 604, 565, 528, 459.

HRMS(m/z): Calcd for $C_{40}H_{49}NaO_4P$: 647.3261 $[M + Na]^+$; Measured: 647.3253.


7.07
6.72
2.84
2.82
2.80
2.78
2.74
2.69
2.68
2.41
2.39
2.37
2.35
2.34
2.14
2.06
2.01
1.78
1.75
1.73
1.70
1.57
1.54
1.51
1.50
2.00
1.25
4.02
2.17
11.40
7.39
19.34
2.07
f1 (мд)


144.66
138.40
135.16
134.31
128.24
127.95
42.14
37.21
37.02
29.69
29.17
27.42
23.06
22.97
f1 (мд)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1400
1300
1200
1100
1000
900
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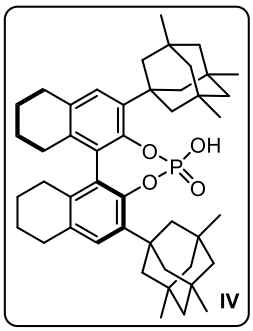
700
600
500
400
300
200
100
0
-100
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (мд)

(*S*)-1,1'-(5,5',6,6',7,7',8,8'-Octahydro-3,3'—di(3,5,7-trimethyladamanyl)-binaphtalene)-2,2'-diyl phosphoric acid (IV)



Compound **IV** was prepared by the same procedure as compound **III.** Compound **67** (600 mg, 0.93 mmol) was dissolved in pyridine (9.6 ml) and $POCl_3$ (0.17 mL, 1.9 mmol, 2.0 eq.) was added dropwise. The reaction mixture was heated to 100℃ and stirred for 72 h. After this time, H_2O (9.6 mL) was added and the mixture was stirred for 24 h at the same temperature. After cooling to r.t., the aqueous layer was extracted 3x with DCM. Pyridine was evaporated under reduced pressure. To get rid of pyridine residues the mixture was washed 2x with 6N HCl and the organic layer was evaporated. For purification, the product was dissolved in DCM, then NH_4OH was added to form a salt and the mixture was washed with EtOAc and Et_2O and filtered. The salt was converted to the acid by 3x extraction with 6N HCl. The product **IV** was obtained as a pale yellow solid in a yield of 50 % (330 mg).

R_f : 0.3 (DCM/MeOH 5%)

m.p. = 253,7℃ (recrystallized from $CHCl_3$)

$[\alpha]_D = +189°$ (c 1.0, $CHCl_3$)

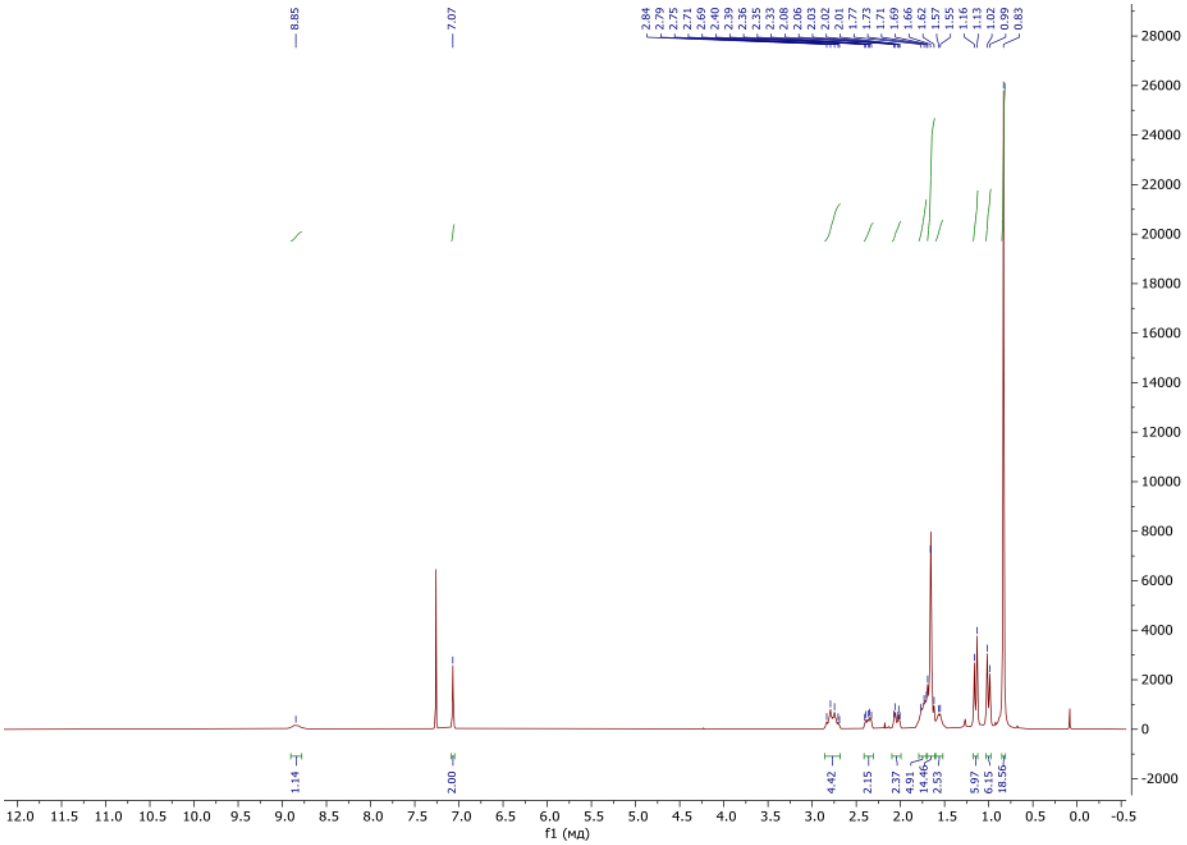
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.07 (s, 2H), 2.84 – 2.69 (m, 4H), 2.40 – 2.33 (m, 2H), 2.08 – 2.01 (m, 2H), 1.74 – 1.71 (m, 5H), 1.69 – 1.62 (14H), 1.57 – 1.54 (m, 2H), 1.16 – 1.13 (m, 6H), 1.02 – 0.99 (m, 6H), 0.83 (s, 18H).

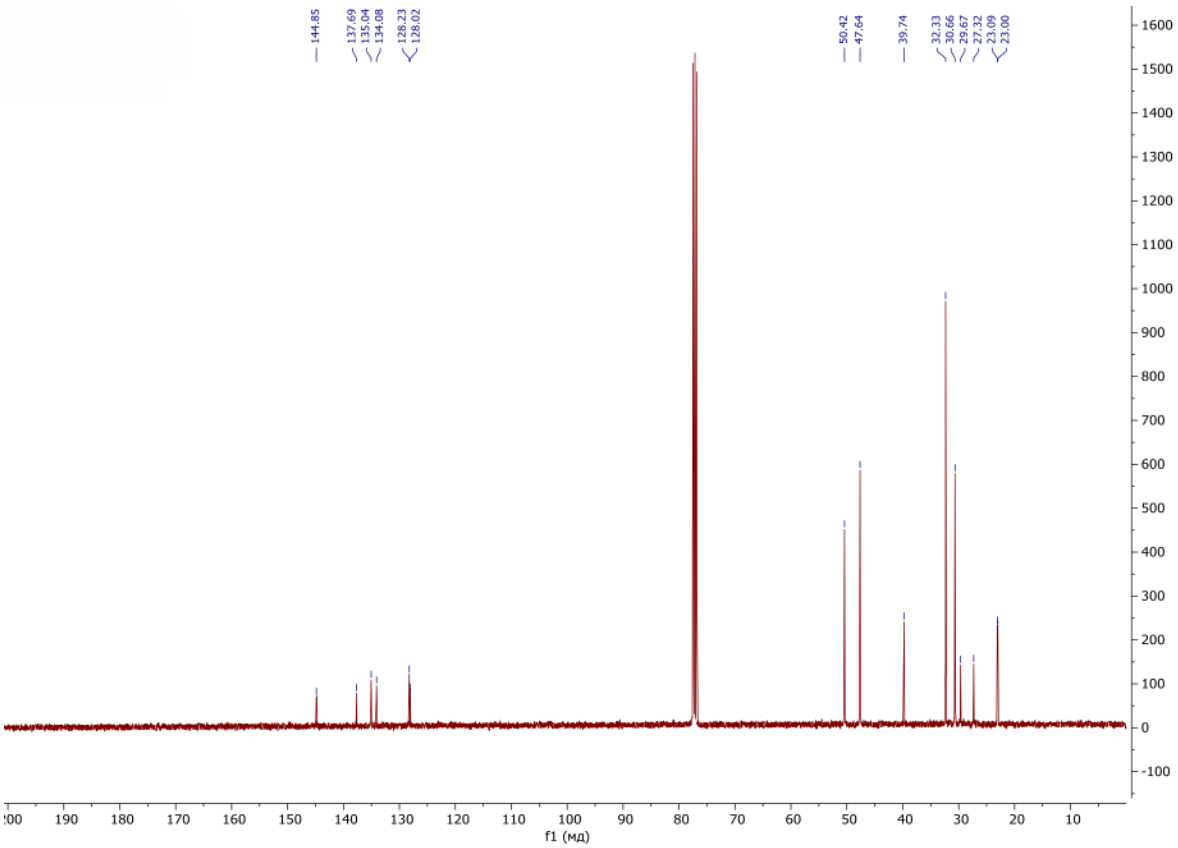
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.85 (4C), 137.69 (4C), 135.04 (3C), 134.08 (2C), 128.19 (2C), 128.23 (2CH), 128.02 ($6CH_2$), 50.42 ($6CH_2$), 47.64 (C), 39.74 (2C), 32.33 ($6CH_3$), 30.66 ($2CH_2$), 29.67 ($2CH_2$), 23.09 ($2CH_2$), 23.00 ($2CH_2$).

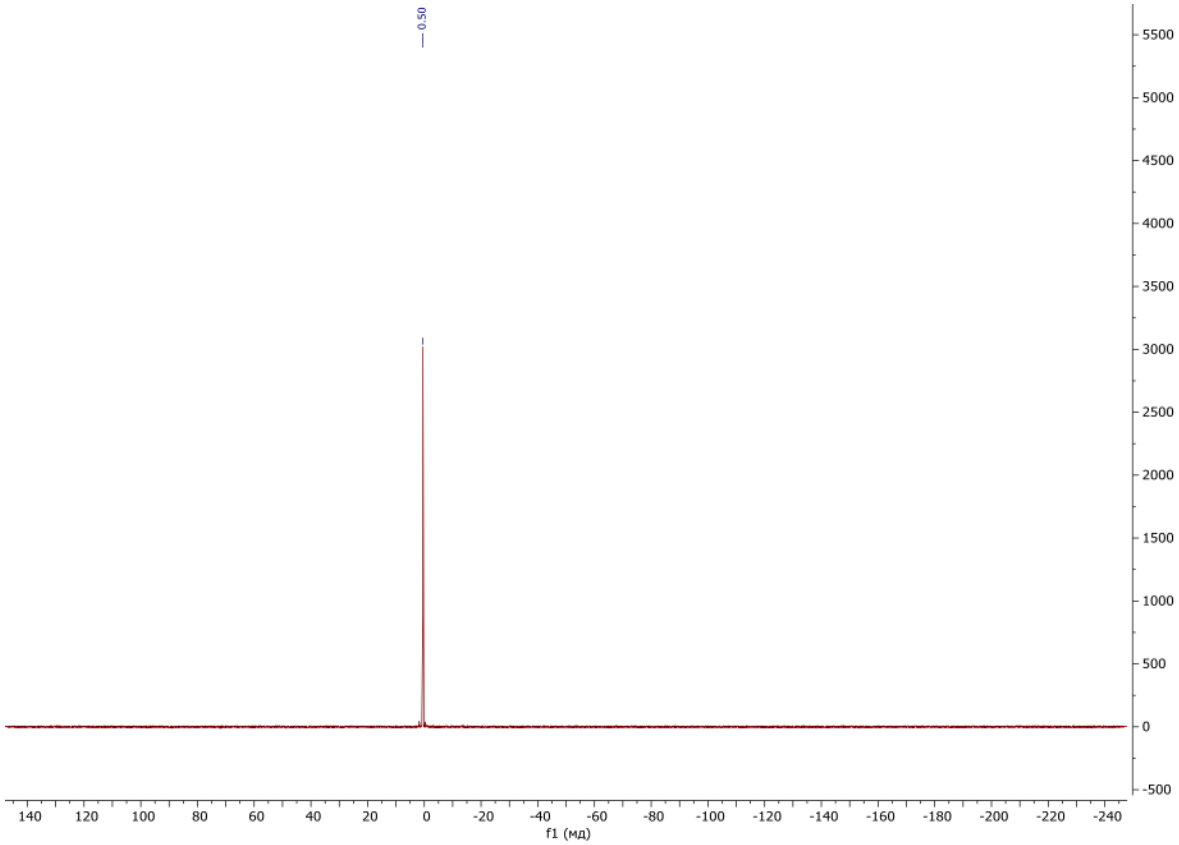
^{31}P **NMR** (122 MHz, $CDCl_3$) δ 0.50.

IR (neat): /cm^{-1} = 2900, 2846, 1452, 1417, 1371, 1352, 1248, 1201, 1174, 1119, 1095, 1012, 968, 953, 908, 885, 870, 816, 754, 714, 604, 567, 528, 496, 461.

HRMS(m/z): Calcd for $C_{46}H_{61}NaO_4P$: 731.4200 $[M + Na]^+$; Measured: 731.4185.



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500
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40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (мд)

8. Conclusion

This bachelor work deals with the preparation of chiral Binol-derived phosphoric acids. In general, four compounds were prepared.

Compounds **I** and **II** were prepared in two steps: Condensation reaction with $POCl_3$ followed by hydrolysis. The synthesis of compound **I** started from Binol **56**. The desired Binol-derived phosphoric acid was obtained in yield of 67%. The synthesis of compound **II** started from H_8-Binol **57** and the final product was obtained in a yield of 62%.

For the synthesis of compounds **III** and **IV** the reaction was optimised. The preparation of compound **III** was started with Friedel-Crafts reaction of H_8-Binol **57** with 1-adamantanol **63** to give compound **64**, which was then condensed in the presence of $POCl_3$. The desired Binol-derived phosphoric acid **III** was obtained in the yield of 51 %. The synthesis of compound **IV** started with preparation of starting material **60**, which was then subjected in the Friedel-Crafts reaction with H_8-Binol **57**.

The condensation reaction with $POCl_3$ and subsequent hydrolysis led to the desired Binol-derived phosphoric acid **IV** in the yield of 50 %.

The prepared compounds will be tested as catalysts and their activity will be studied. The obtained 3,3'-adamantane substituted Binol-derived phosphoric acids **III** and **IV** will be compared with 3,3'-phenyl substituted Binol-derived phosphoric acids.

9. Literature

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