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Synthesis of multiply charged components suitable for electrostatic self-assembly

Syntéza vícenásobne nabitých komponent vhodných pro elektrostatickou
samoskladbu

Bachelor's thesis

Supervisor: doc. RNDr. Jindřich Jindřich, CSc.

Prague, 2025

PROHLÁŠENÍ

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V Praze dne 17. 5. 2025

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I declare that I have worked on this thesis independently under the supervision of doc. RNDr. Jindřich Jindřich, CSc., and I have cited all used information sources and literature. I declare that this work or its important section has not been presented to obtain other or the same academic degree.

In Prague, 17. 5. 2025

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Marek Olos

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ABSTRACT

Synthesis of multiply charged components suitable for electrostatic self-assembly

This bachelor's thesis aims to synthesize triply negatively charged neopentyl (Np) skeleton-based compounds, bearing sulfonic acid functional groups, and develop a deprotection method for the propargyl (Prg) functional group. This work aims to reproduce, improve, and further explore the derivatization of compounds prepared by previously described protocols. These compounds have the potential to prepare materials that are suitable for electrostatic self-assembly (SA), specifically crystalline porous organic salts (CPOSs), which, as a new emerging class of porous materials (PMs), find application, e.g., in gas storage, proton conduction, and catalysis.

Keywords: multiply charged compounds, neopentyl skeleton, sulfonic acid, propargyl, electrostatic self-assembly, CPOSs

ABSTRAKT

Syntéza vícenásobně nabitých komponent vhodných pro elektrostatickou samoskladbu

Cílem této bakalářské práce je syntéza trojnásobně negativně nabitých látek, založených na neopentylovém skeletu, obsahujících sulfonovou kyselinu jako funkční skupinu a vývoj metody na odchránění propargylové funkční skupiny. Tato práce si klade za cíl reprodukovat, vylepšit, a dále prozkoumat derivatizaci látek připravených podle dříve popsanych protokolů. Tyto látky mají potenciál na přípravu materiálů, které jsou vhodné k elektrostatické samoskladbě, konkrétně krystalické porézní organické soli (CPOS), které, jako skupina nových, vyvíjejících se porézních materiálů (PM), nacházejí využití např. při uskladňování plynů, vodivosti protonů a katalýze.

Klíčová slova: vícenásobně nabitě sloučeniny, neopentylový skelet, sulfonová kyselina, propargyl, elektrostatická samoskladba, CPOS

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LIST OF ABBREVIATIONS

Ac	acetyl
Bu	butyl
COF	covalent organic framework
CPOS	crystalline porous organic salt
CR	click reaction
CuAAC	copper-catalyzed azide-alkyne cycloaddition
DMA	dimethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
Et	ethyl
HOF	hydrogen-bonded organic framework
HRMS	high-resolution mass spectrometry
MCCs	multiply charged compounds
Me	methyl
MIM	1-methylimidazole
MOF	metal-organic framework
MS	mass spectrometry
NMNO	<i>N</i> -methylnmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
Np	neopentyl
PCC	permanently charged compound
Pe	pentaerythritol
PEMEDA- β -CD	6 ¹ -pentamethylethylenediammonio- β -cyclodextrin
PEMPDA- β -CD	6 ¹ -pentamethylpropylenediammonio- β -cyclodextrin
PM	porous material
POF	porous organic framework
Prg	propargyl
PYR	pyridine
RT	room temperature

SA	self-assembly
S _N	nucleophilic substitution
<i>t</i> Bu	<i>tert</i> -butyl
Tf	trifluoromethanesulfonyl (triflyl)
TLC	thin layer chromatography
TMA	trimethylamine
Ts	tosyl

1 INTRODUCTION

The introduction of synthetic zeolites in the 1940s marked the beginning of the rapid development of porous materials (PMs). At the start of the 21st century, another breakthrough came in the form of porous organic framework (POF), specifically metal-organic framework (MOF) and covalent organic framework (COF), for their properties like high surface area, permanent porosity, and thermal and chemical stability. Hydrogen-bonded organic framework (HOF) expanded on the previous discoveries and brought new properties in terms of flexibility of structure formation and ease of regeneration; however, they lack overall stability when compared to POFs.

CPOSSs are stabilized by ionic bonding between organic acids and bases. The CPOSSs are prepared simply by dissolving the corresponding building blocks in an appropriate solvent and mixing them together. The precipitated salt is then easily purified. The main challenge when preparing CPOSSs is the collapse of the framework after removing the guest molecule. The strength of the ionic bonds in the framework is crucial for its stability. The charge density can be increased three times by using charge multipliers like neopentyl (Np) skeleton-based multiply charged compounds (MCCs). When attaching these compounds to structures like tetraphenylmethane (TPM) or cyclodextrin (CD), the charge density can be increased to 12 or up to 21 (on β -CD) charged groups, respectively, which have the potential to stabilize the formed CPOSSs.

The Np skeleton bears up to 3 charges, with one remaining methylene group bearing a functional group for attachment to a charge multiplier. Different ways of bonding to the multiplier can be achieved by modifying this functional group.

2 AIMS OF THE WORK

- 1) Reproduce and improve the propargylation of pentaerythritol (Pe) on a multigram scale.
- 2) Reproduce and improve the preparation of the triply negatively charged Np “anchor” bearing Prg functional group.
- 3) Develop a method to deprotect the Prg group to prepare derivatives of the triply negatively charged anchor.

3 STATE OF THE ART

3.1 Permanently charged compounds

Permanently charged compounds (PCCs) exist in ionic form at environmental pH.¹ Negatively charged PCCs are most commonly anions of strong acids, e.g., sulfonate, and positively charged PCCs are, e.g., quaternary ammonium or phosphonium groups. They differ from partially charged compounds, which exist in different ratios of charged and neutral forms, depending on the pH. These usually include weakly acidic compounds, such as carboxylic acids, or basic compounds, such as amines. PCCs find application as binding groups in ion exchange resins, such as strong cation exchange resins (Figure 1), to treat wastewater contaminated with heavy metals.²⁻⁴ Quaternary ammonium salts have been extensively used as antimicrobials, surfactants, or in cosmetics like shampoo or hair conditioners.⁵⁻⁷ Another application is permanent charge derivatization, which increases ionization efficiency in mass spectrometry (MS) analysis.⁸ Nafion is a negatively charged sulfonated tetrafluoroethylene copolymer⁹ solid support with well-established usage in fuel cells¹⁰ or chlor-alkali process¹¹. Our group managed to electrostatically bind permanently positively charged CD¹² derivatives onto the surface of Nafion[®] 117 membrane and test the stability of the inclusion complex with guest molecules.¹³ In another publication Nafion[®] 117 membrane with electrostatically bonded positively charged CD derivative was successfully tested for chiral resolution of tryptophan enantiomers.¹⁴

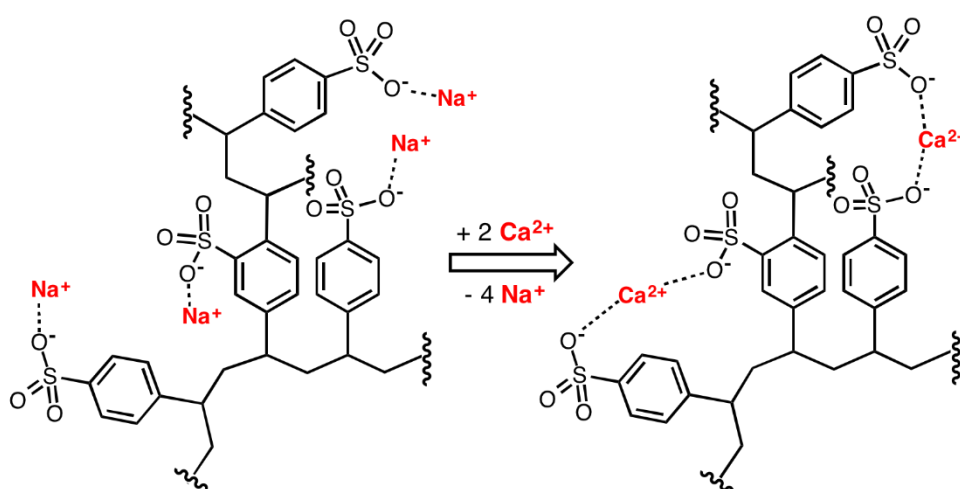
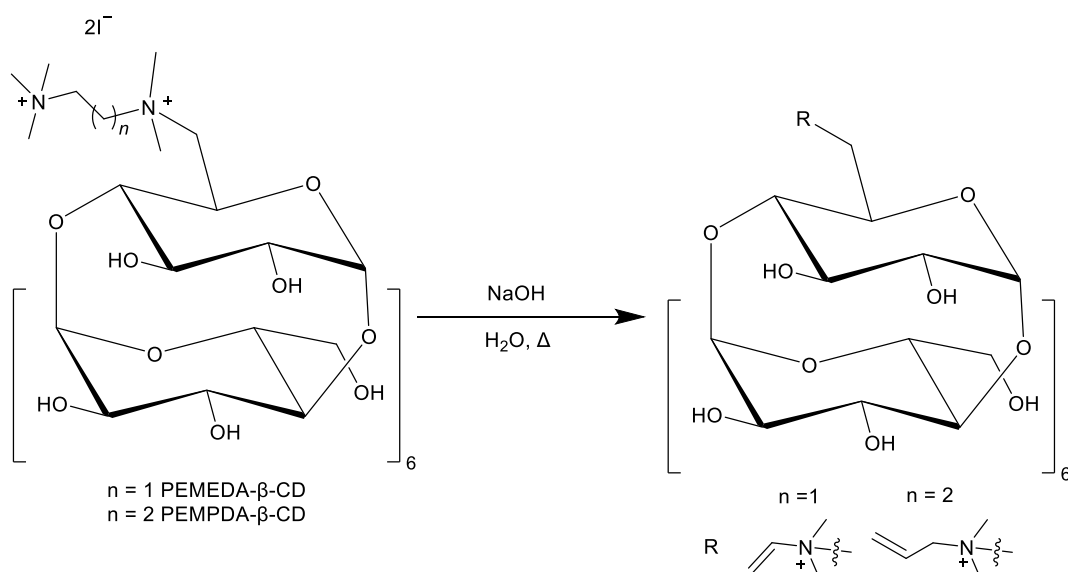


Figure 1. Strong cation exchange resin with sulfonate groups. Picture taken from¹⁵.

3.1.1 Multiply charged Np anchors

A former member of our group, Martin Popr, synthesized permanently charged monosubstituted CD derivatives containing 1 to 3 positive charges.¹⁶ Due to the presence of β -hydrogen next to the alkylammonium group in Popr's CDs, the compounds tended to undergo Hofmann elimination in basic conditions (Scheme 1). Firstly, 6^l-pentamethylethylenediammonio- β -cyclodextrin (PEMEDA- β -CD) was prepared. Partial decomposition of the PEMEDA- β -CD was observed already at 60 °C when dried.¹³ For this reason, 6^l-pentamethylpropylenediammonio- β -cyclodextrin (PEMPDA- β -CD) was synthesized. Thermal stability measurement of PEMEDA- β -CD and PEMPDA- β -CD was carried out by heating the corresponding compound to 80 °C with 1 equivalent of NaOH, and monitoring the decomposition with TLC. After complete decomposition of PEMEDA- β -CD, PEMPDA- β -CD spot was still detected on TLC. The increased stability of PEMPDA- β -CD is most likely due to the longer chain separation of positive charges, which makes the elimination to olefins less probable. Even with increased stability of PEMPDA- β -CD compared to PEMEDA- β -CD, instability in basic environment was still a problem.



*Scheme 1. – Hofmann elimination of PEMEDA- β -CD and PEMPDA- β -CD.
Redrawn from Popr et al.¹³*

That is why another former group member, Petr Kasal, developed a procedure that led to the preparation of Np-based multiply charged derivatives.¹⁷ The reactivity of Np alcohol with several nucleophile sources in nucleophilic substitution (S_N) was investigated long ago.¹⁸ Most reactions failed to proceed even at elevated temperatures, and rearrangement products were observed from the oxonium salt of Np alcohol with

HBr. The reactivity of NpBr in S_N2 was found to be much lower than that of other primary alkyl bromides.^{19,20} The decreased reactivity of the Np skeleton is attributed to the steric environment of the *tert*-butyl part of the skeleton, making S_N2 reaction more difficult even on the primary carbon atom.²⁰ The starting material for synthesizing charged Np anchors was different Np polyols, depending on the number of charges the final product would bear (Figure 2)

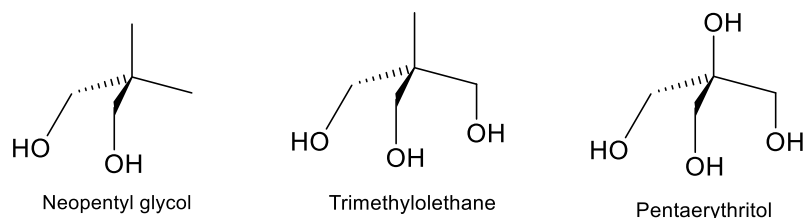
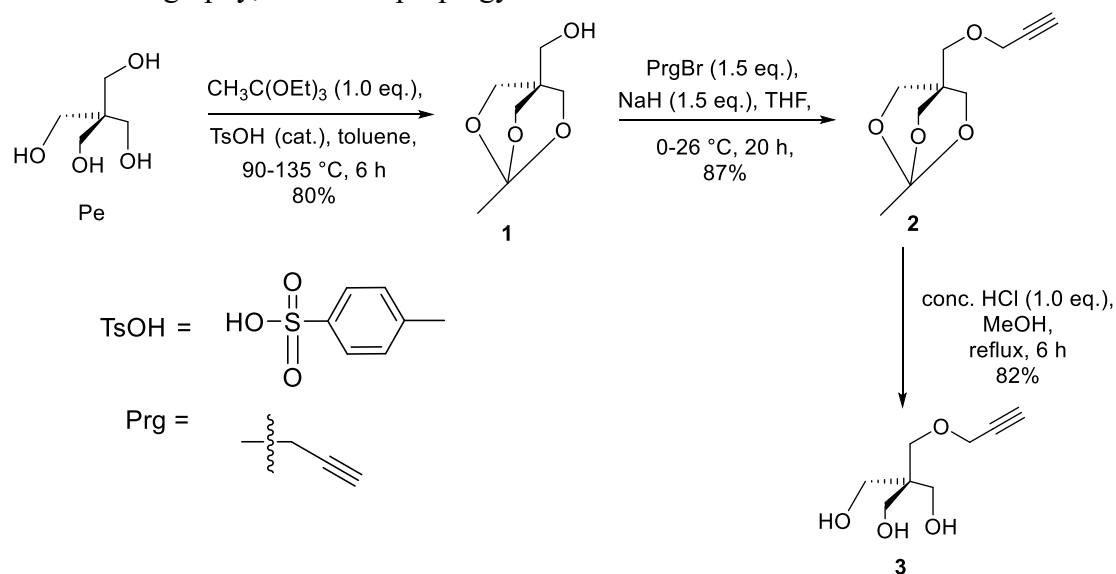


Figure 2. – Different Np polyol structures.

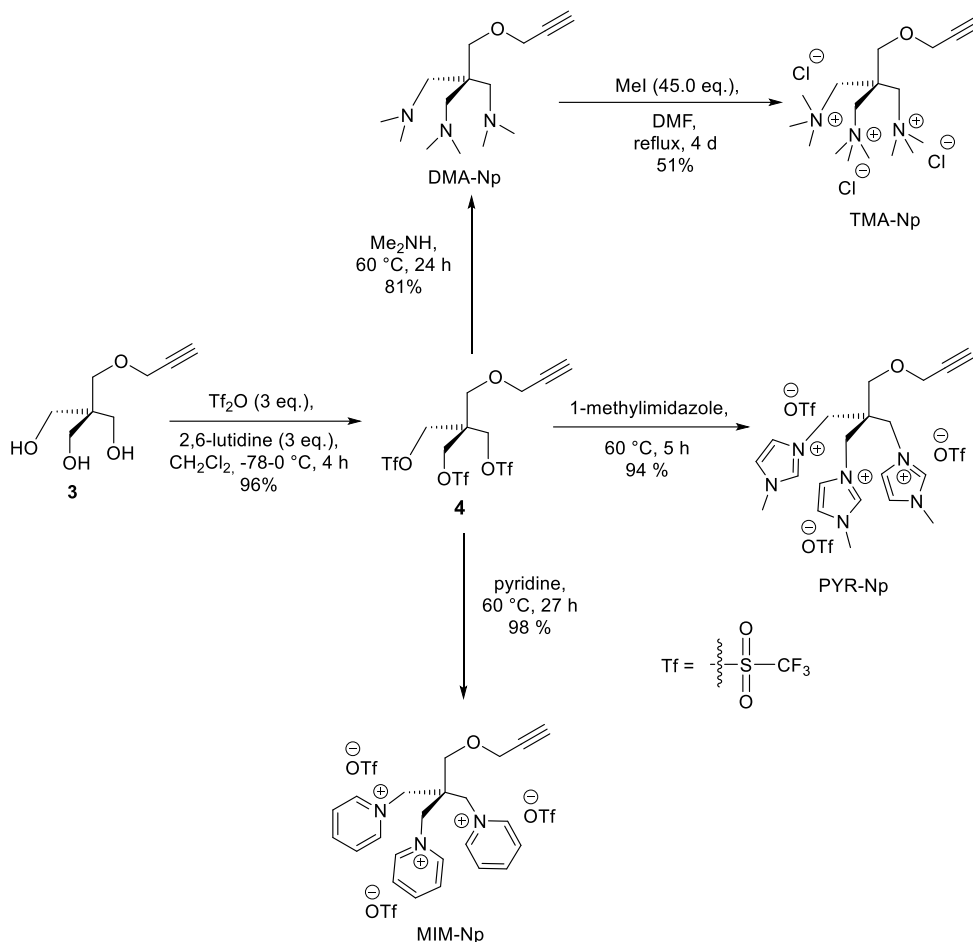
The complete procedure for the preparation of multiply positively charged anchors bearing 1 to 3 charges was described by Kasal¹⁷; however, this thesis focuses on the preparation of derivatives that possess three charges, therefore, the attention will be shifted mainly to those. The starting tetraol for the synthesis of triply charged anchors is pentaerythritol (Pe) (Scheme 2). Following the literature, by protecting three hydroxyl groups with triethyl orthoacetate, compound **1** was prepared.²¹ The Prg group was attached to compound **1** to prepare compound **2**.²² Prg was chosen as the functional group to utilize these MCCs as anchors to connect in copper-catalyzed azide-alkyne cycloaddition (CuAAC) with charge multipliers such as CD or TPM possessing azide functional groups. The original deprotection procedure²³ was modified by Kasal to omit column chromatography, and monopropargylated Pe **3** was obtained.¹⁷



Scheme 2. – Synthesis of monopropargylated pentaerythritol. Redrawn from Kasal¹⁷.

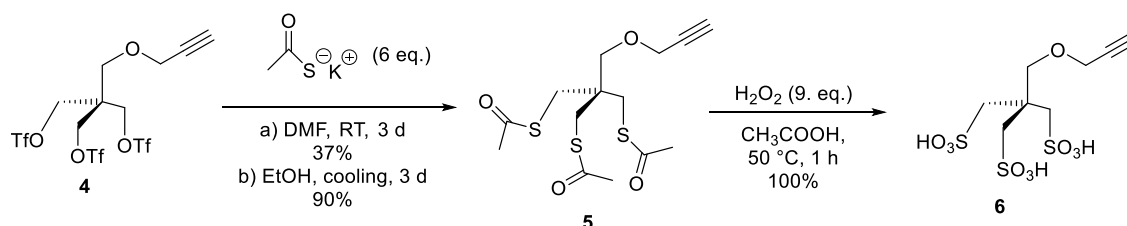
A proper leaving group had to be chosen to functionalize the Np skeleton with charged groups. Based on the kinetic studies conducted by Kasal, the triflate (TfO) functional group proved to be the best by far compared to other tested groups.²⁴ The triflation reaction inspired by the literature²⁵ was carried out using Tf₂O, but according to Kasal¹⁷, when Et₃N is used as a base, the reaction does not proceed as expected. With a change to a less nucleophilic base, 2,6-lutidine, the yields are almost quantitative and do not need column chromatography purification. With compound **4** prepared, charged functional groups could be substituted.

Pyridine (PYR), 1-methylimidazole (MIM), and trimethylamine (TMA) were utilized as PCCs in the synthesis of triply positively charged anchors (Scheme 3).¹⁷ PYR and MIM Np derivatives were prepared directly from compound **4**. MIM substitution was the most efficient, achieving high yield in the shortest time out of the three. PYR substitution took longer, but had an almost quantitative yield. The TMA substitution proved to be the most difficult of the three. The anchor did not react directly with TMA, because of the bulkiness of the three methyls. Instead, dimethylamine was used to prepare DMA-Np. The yield was exceptional, considering that dimethylamine is still a bulky group, thus increasing the difficulty of fully substituting the Np skeleton. DMA-Np was subsequently quaternized using methyl iodide.



Scheme 3. – Synthesis of triply positively charged anchors. Redrawn from Kasal¹⁷.

Former colleague Adéla Tomanová developed a procedure for preparing 1 to 3 triply negatively charged compounds, with the charge-bearing group being sulfonic acid.²⁶ The synthesis is the same as preparing positively charged anchors up to compound **4**. Then the compound **4** is reacted with potassium thioacetate²⁷ (AcSK) to obtain compound **5**, which is oxidized in the next step to trisulfonic acid using hydrogen peroxide in acidic conditions²⁸ (Scheme 4).



Scheme 4. – Synthesis of triply negatively charged anchors. Partially redrawn from Tomanová²⁶.

3.2 Electrostatic self-assembly

Self-assembly (SA) is the spontaneous establishment utilizing pre-existing units to form organized higher-order structures.²⁹ Different types of SA structures are classified according to interactions, which drive their formation. These include weak non-covalent intermolecular interactions like electrostatic³⁰, hydrophobic³¹, π - π interactions³², or hydrogen bonds³³. Listed

interactions are fundamental in biological systems such as DNA double helix formation, protein tertiary and quaternary structures, or the lipid bilayer. Another example from everyday life is micelle formation utilizing detergents.³⁴ The “bottom-up” concept is building up macroscopic frameworks from simple atom or molecule building blocks utilizing SA.³⁵ This approach can be used to synthesize PMs. PMs are usually solid structures with voids that can adsorb liquid or gas molecules (Figure 3). Many different PMs have been developed throughout the last 80 years.³⁶ One of the most used PMs is zeolites.³⁷ They mainly gained attention due to their invaluable application in the petrochemical industry as catalysts.³⁸ Another class of PMs is MOFs³⁹ and COFs⁴⁰; together, they are classified as POFs. POFs demonstrate high porosity, while MOFs have an exceptionally high active surface area, which can be applied in gas storage⁴¹. COFs exhibit good thermal and chemical stabilities because of linkage through covalent bonds and reversible formation of the crystalline structure. They have found application, for example, in catalysis.⁴²

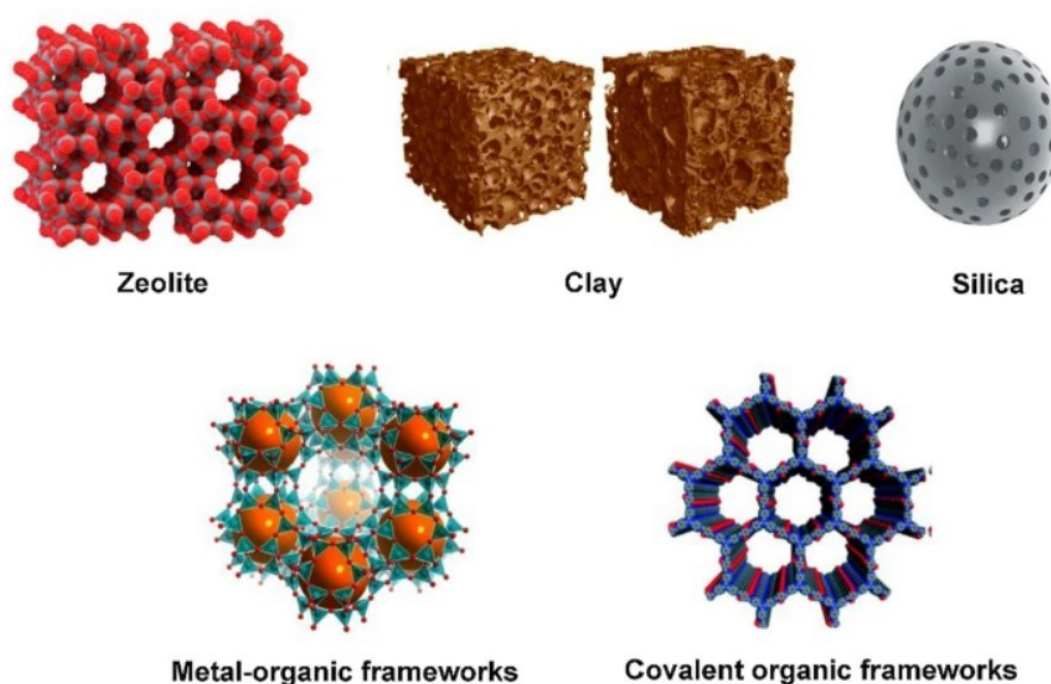


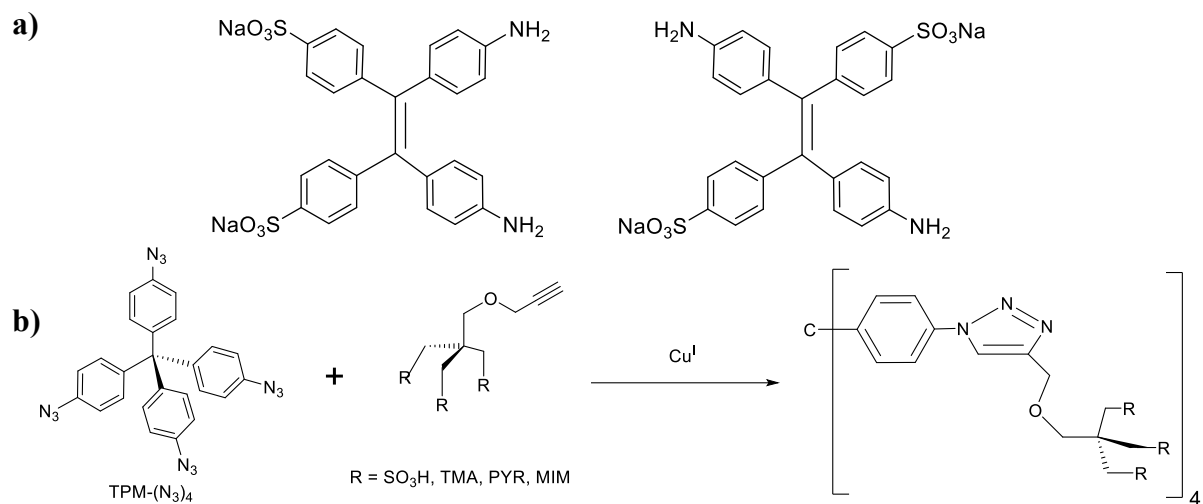
Figure 3. – Porous materials. Picture taken from⁴³.

HOFs are PMs assembled through weak intermolecular hydrogen-bonding interactions, unlike COFs and MOFs. That is why the stability of HOFs tends to be lower when compared to COFs and MOFs. Still, at the same time, they are more flexible when it comes to bonding energies and angles, which allows the preparation of different isomeric structures.^{44,45} Following the development of HOFs, new PMs and CPOSSs have emerged in recent years. CPOSSs framework is held together by ionic interactions provided by building units (tectons) that are usually organic acids and bases. An essential feature of CPOSSs is the simplicity of

preparation by crystallization from polar solvents and permanent porosity. The latter also seems to be the most challenging part, because in many attempts to prepare the CPOs, the framework collapses after removing the guest molecule.⁴⁶ Xing et al. managed to synthesize CPOs with permanent porosity applicable for proton conduction by using tectons with multiple strong acids and bases, strengthening the framework's stability.⁴⁷

3.3 Tectons

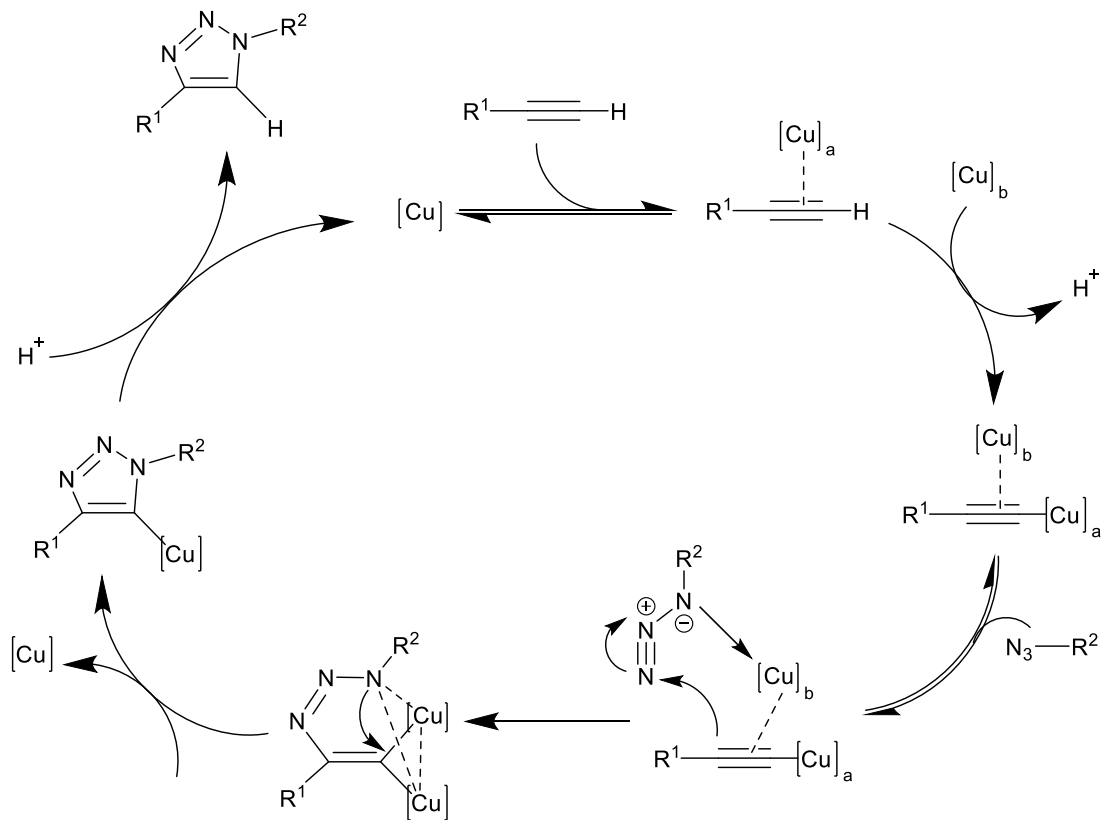
Tectons, from Greek τέκτων, meaning carpenter or builder, are molecules serving as a subunit for the SA of higher-order structures, by interacting with each other through intermolecular forces.⁴⁸ Focusing on CPOs, the choice of tectons allows for different types of structures to be assembled with adjustable pore sizes and varying potential applications.⁴⁶ TPM derivatives are the structural units that gained attention in CPOs synthesis due to their rigid tetrahedral structure. Through attachment of four charged groups, e.g., ammonium, amidino, carboxylate, or sulfonate, a rigid structure can be formed through connection with oppositely charged TPM, which was applied in atmospheric water adsorption by Zhang et al..⁴⁹ Different topologies can be achieved by altering the oppositely charged tectons.⁵⁰ The standard approach in CPOs synthesis is the use of two oppositely charged tectons, however recently Wang et al. investigated formation of CPOs using single tecton with alternating positive and negative charge (Scheme 5) and showed the ability of the formed CPOs to control release of polar molecules such as DMSO.⁵¹ The advantage of using the zwitterionic approach is the requirement of only one tecton, which provides more straightforward modification of the final structure, and far easier study of the aggregation of the crystal structure formed from only one building block. Utilizing the rigidity of TPM and the benefits of the zwitterionic strategy, zwitterionic TPM derivatives may be prepared, which have not been reported yet. Furthermore, by attaching multiply charged Np derivatives onto functionalized TPM, up to 12 charged groups can be obtained, possibly improving the stability of a CPO framework. To our knowledge, these structures have not been described yet. Our group has preliminarily confirmed the applicability of this approach (Scheme 5). While this represents an application of the MCCs with the propargyl group, this thesis aims to modify this group to allow connections with different tectons, directly through the central carbon atom of the anchor.



Scheme 5. – a) Zwitterionic structures prepared by Wang et al.⁵¹ b) Synthesis of multiply charged TPM derivatives from tetrakis(4-azidophenyl)methane and multiply charged Np anchors utilizing click reaction.

3.4 Click reaction

CuAAC is a type of click reaction (CR) utilizing Cu^I for catalysis of [3+2] cycloaddition reaction involving azide and alkyne, resulting in a 1,4-disubstituted triazole ring, thus connecting the two moieties via carbon-nitrogen bonds. The CR has gained renown due to the work of Sharpless⁵² and, at the same time, Meldal⁵³ independently. CR's criteria and main advantages are high yields, mild conditions, scale-up potential, stereospecificity, and purification without chromatography. There is a variety of copper sources available for CuAAC.⁵⁴ The most efficient catalyst employed has been CuSO₄ in aqueous conditions with sodium ascorbate as a reducing agent. From Cu(I) sources, copper halides, most frequently CuI, are used alongside a base that promotes copper-acetylide complex formation. As a Cu(0) source, copper tunings or powder can be used, which allows easy separation of solid copper from the reaction mixture. The proposed mechanism⁵⁵ involves reversible coordination of σ -bound copper acetylide along with π -bound copper to the azide. In the next step, the azide nitrogen is nucleophilically attacked by acetylide carbon. Then ring closure takes place, and by protonation, the final triazole ring is formed (Scheme 6).



Scheme 6. – Proposed mechanism of CuAAC. Redrawn from⁵⁵.

3.5 Prg ether cleavage

Most of the multiply charged Np anchors prepared in our group so far have been prepared for subsequent click reaction; therefore, they contain the propargyl group. This thesis focuses on a different approach to connect multiply charged Np anchors, which will be discussed more closely in the following chapter. The initial reaction involves the depropargylation of compound 7. Cleavage of Prg ethers is not very common; therefore, the literature regarding this specific procedure is far more underdeveloped when compared to, for example, deprotection of the benzyl or allyl group. Rambabu et al. managed to cleave aryl Prg ethers with H₂O as the solvent, and using Pd/C with 2-ethanolamine as a base⁵⁶. Low valent titanium compounds TiCl₃/Mg⁵⁷, and Ti(O-*i*-Pr)₄/MX_{*n*}(halogen source)/Mg⁵⁸ have been reported to cleave allyl and Prg ethers. Deprotection of saccharides^{59,60} was carried out by isomerization of Prg to allenyl in basic conditions using K⁺OtBu, and subsequent oxidative cleavage with OsO₄ and N-methyl morpholine N-oxide (NMNO). Another examples of Prg deprotection include palladium complexes combined with hydride donors such as Bu₃SnH⁶¹, benzyltriethylammonium tetrathiomolybdate^{62,63}, or SmI₂ in basic conditions. SmI₂ achieves high yields in a short time; however, it is too expensive to use in large-scale synthesis. Hydrogen halides⁶⁴, such as hydroiodic acid, are used to cleave various alkyl and aryl ethers due to their versatility. The harsh reagent cannot be employed with compounds containing acid-sensitive functional groups; however, when no such groups are present, as in the case of the triply negatively charged Np anchor (7), HI can cleave the propargyl ether.

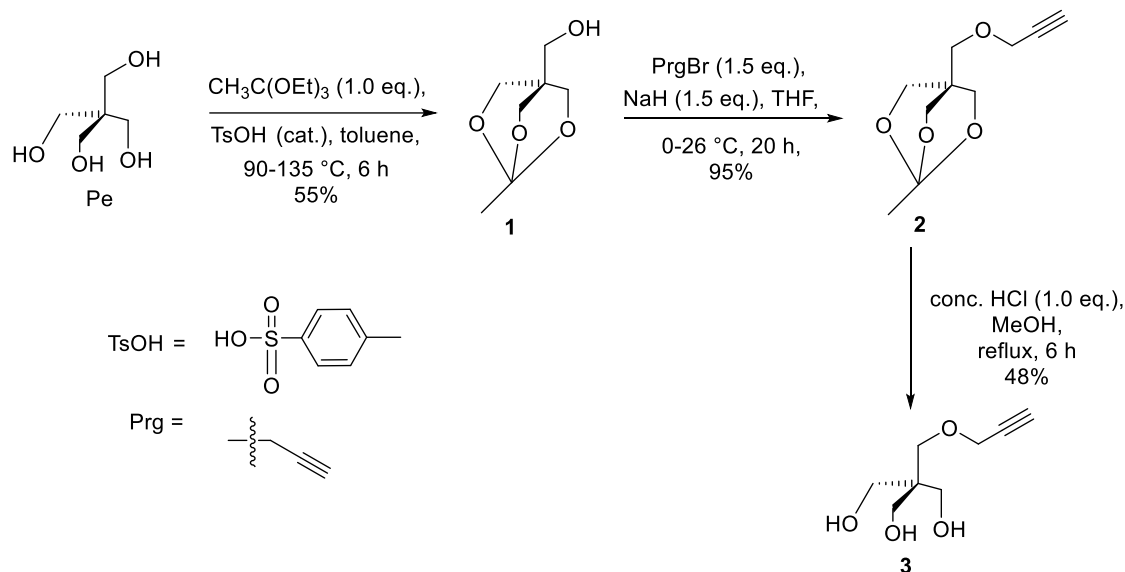
4 RESULTS AND DISCUSSION

The previous chapter introduced the synthesis of multiply charged anchors and the potential to use the Prg functional group as a bonding unit combined with an azide. This thesis focused on preparing materials for the future synthesis of negatively charged Np anchors utilizing carbocation species as the bonding unit through electrophilic aromatic substitution with TPM. That is why the depropargylation method of the negatively charged anchor was developed. Propargylation of Pe and triflation was done according to procedures described by Kasal¹⁷, AcS substitution, and its oxidation was done according to Tomanová²⁶. Protocols were reproduced on a multigram scale.

4.1 Synthesis of propargyloxy-neopentane-trisulfonic acid

4.1.1 Synthesis of propargyloxy-neopentane-triol

The following reactions were introduced in the State of the Art chapter, along with original procedure references. The procedures (Scheme 7) were reproduced according to the doctoral thesis of Petr Kasal.¹⁷ The first three reactions focused on attaching the Prg group to Pe.



Scheme 7. – Monopropargylated Pe synthesis reproduction. Redrawn from¹⁷.

The orthoacetate-protected Pe (**1**) was synthesized using *p*-toluenesulfonic acid (TsOH) monohydrate as a catalyst. The resulting ethanol and toluene, used as a solvent, were distilled from the reaction mixture. The final product was obtained after Kugelrohr distillation. Reaction, using 1 g of Pe, yielded similar results to those of Kasal; however, when the reaction was scaled up to 20 g, the consistency of the product after Kugelrohr distillation changed from solid to a very sticky gel. The resulting yield of 55% Pe was 13 g, enough for further synthesis. The propargylation to obtain compound **2**

was carried out using PrgBr and NaH as the base. In this case, Kugelrohr distillation was not problematic. Almost quantitative yield was achieved at a multigram scale. Finally, orthoester was cleaved with concentrated HCl under reflux while using MeOH as the solvent. The modest yield of compound **3**, 48%, was due to my mistake of disposing of the filter cake before checking the yield of the reaction, because some of the product probably did not dissolve in acetone in the final purification step. Nevertheless, monopropargylated Pe was obtained on a multigram scale.

4.1.2 Triflation

The triflation reaction was carried out using triflic anhydride (Tf₂O) in DCM and 2,6-lutidine as the base. (Scheme 8) Initial attempts at triflation afforded unsatisfactory yields and required column purification. After drying the 2,6-lutidine with 3 Å molecular sieves, the reaction afforded compound **4** in expected yields without the need for column chromatography.

4.1.3 AcS substitution

This and the following reaction were done according to bachelor's thesis of Adéla Tomanová²⁶. The substitution of TfO for AcS was done using an excess of AcSK, firstly in EtOH and at room temperature (RT). Different reaction times were investigated from 2 to 4 days, but yields achieved ranged from 36% to 63%, which were not optimal. In THF, the yield was higher, 76% after 4 days (Scheme 8). Afterwards, the reaction was set up with ice/water cooling bath, in which case, after 3 days of reaction, the yield was 89% for a small-scale reaction. On a multigram scale, the yield was 76% after 4 days. The attention then shifted to optimizing this reaction by pushing to full conversion and avoiding column chromatography purification. A series of parallel reactions was run to test different conditions (Table 1).

Table 1. – Optimization of AcS substitution reaction.

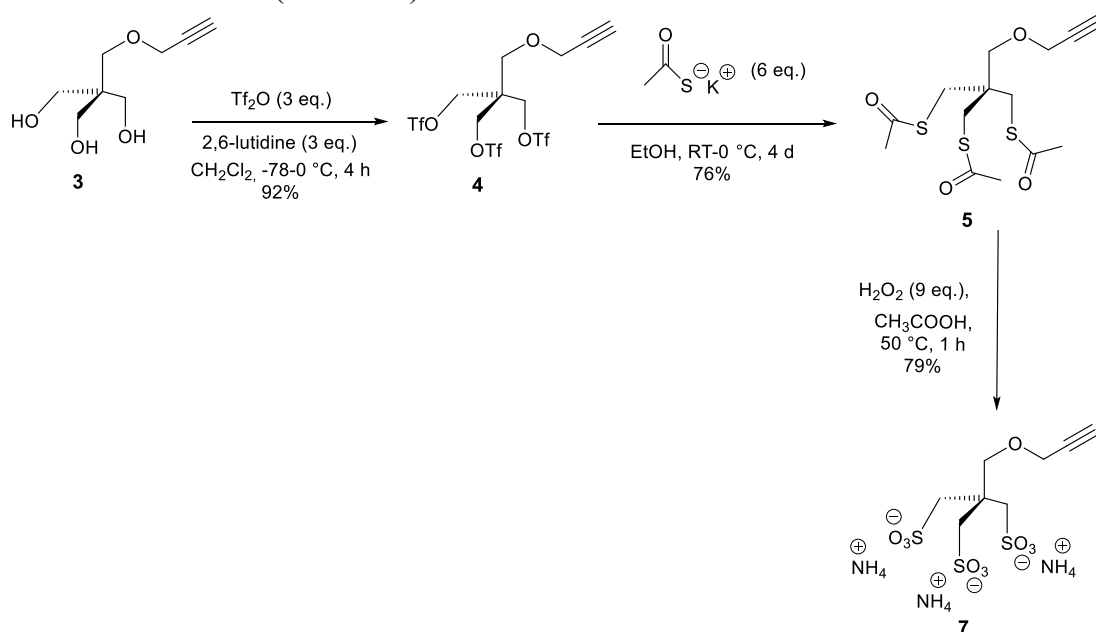
Reaction	AcSK eq.	Workup	Cooling
1.	6	Acid/base, NaCl (aq.)	Dry ice
2. (35% yield)	6	NaCl (aq.)	Ice
3.	6	NaCl (aq.)	Dry ice
4.	3.3	Acid/base, NaCl (aq.)	Ice
5.	3.3	Acid/base, NaCl (aq.)	Dry ice
6. (35% yield)	3.3	NaCl (aq.)	Ice
7.	3.3	NaCl (aq.)	Dry ice

None of the conditions achieved an improvement in the reaction. THF was used as the solvent in all seven reactions, and fewer equivalents of AcSK were used to check if excess causes unwanted side products. Cooling with dry ice was tried based on the fact that ice cooling improved the reaction in EtOH. Lastly, acid/base workup was avoided to see if cleavage of the thioester occurred during workup. Reactions 1, 2, 4, and 6 were worked up. The cooling and omission of the acid/base workup did not improve the reaction. After column chromatography of reactions 2 and 6, the yields using 6 and 3.3 equivalents of AcSK were the same, 35%. Furthermore, the reaction in THF proved to be more efficient when not cooled.

4.1.4 Oxidation of propargyloxy-neopentane-trithiol-tristhioacetate

The final step was the oxidation of compound **5** with H₂O₂ in acetic acid. When attempting to repeat the procedure described by Tomanová²⁶, the decomposition of the product was observed while drying it at 80 °C on the vacuum pump. According to NMR, the Prg group was cleaved off. It was found out that after the oxidation, using a stoichiometric amount of H₂O₂, there is still some of it left after the oxidation. It could potentially be the reason for the cleavage of Prg during drying. When using fewer equivalents, a mixture of products was obtained. The side products were most probably an incompletely oxidized compound **5**. Several methods were tried afterwards to decompose or remove excess H₂O₂ after the reaction. Firstly, the co-distillation of H₂O₂ and acetic acid with H₂O did not succeed. Decomposition of H₂O₂ was successful, utilizing MnO₂; however, after celite filtration, broadening of the NMR peaks indicated that MnO₂ was still present in the product. An attempt was made to purify the compound through reverse-phase column chromatography, but the product and acetic

acid were too polar; therefore, no separation occurred. Although MnO_2 was effective at decomposing H_2O_2 , it became a new impurity, which had to be removed from the product. Furthermore, the acetic acid also needed to be removed; therefore, attention was shifted to finding a method to deal with both problems at the same time. Silica gel column chromatography was investigated as the first option. The second option was purification through a weak anion exchanger. Both methods were successful in separating the acetic acid from the product; however, on the silica gel column, half of the product fractions also contained H_2O_2 . A weak anion exchanger separated both the H_2O_2 and acetic acid, and after elution with 1 M NH_4HCO_3 , afforded the compound **7** in ammonium salt form (Scheme 8).

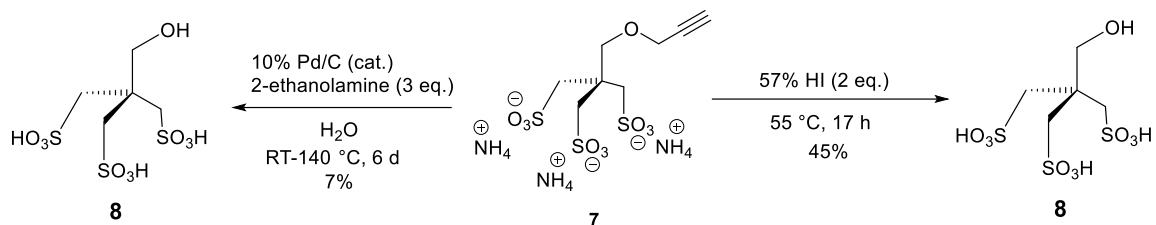


Scheme 8. Synthesis of propargyloxy-neopentanetrissulfonic acid. Ammonium salt obtained after elution from anion exchanger with 1 M NH_4HCO_3 . Redrawn from²⁶.

4.2 Depropargylation of propargyloxy-neopentanetriammonium-trissulfonate

As stated at the beginning of this chapter, the materials in this thesis were prepared for the synthesis of a carbocationic species. For this purpose, the depropargylation of compound **7** was explored. The alternative to synthesize the derivative of compound **7** with a benzyl group instead of a Prg is an applicable choice; however, since compound **7** can be used for the CuAAC reaction, it would be convenient to have uniform synthesis for the alternative intermediates based on deprotected compound **7**. The first attempt was based on literature⁶⁴, utilizing an excess of 57% HI aq. solution at 130 °C. Even in these harsh conditions, the Np skeleton with sulfonate groups survived; however, based on LC-MS and NMR, a compound that is

not the desired product was formed and was not further specified. Instead, the conditions were refined. Only 1-2 eq. of HI were used, temperatures ranging from RT to 55 °C, and the compound was successfully prepared (Scheme 9). Another alternative was tried using Pd/C with 2-ethanolamine in water⁵⁶; however, this reaction had to run at 140 °C for the starting material to react, and the yield obtained was only 7%. Therefore, this pathway was not further optimized.



Scheme 9. Depropargylation of propargyloxy-neopentanetriammonium-trisulfonate.

5 CONCLUSION

The goals of this thesis were:

1. The synthesis of triply negatively charged neopentyl anchor bearing the sulfonic acid and propargyl functional groups.
2. The development of a method to deprotect the propargyl group of the anchor.
3. The improvement of previously described protocols for the preparation of the anchor.

Apart from the final deprotection of propargylated Pe, which provided a lower yield, the first three compounds were still achieved on a multigram scale, with compound **2** prepared in an almost quantitative yield.

The synthesis of the triply charged propargylated anchor was challenging, but was finally achieved. While triflation afforded high yields without column purification, in substitution for AcS, the column could not be avoided with the tested methods. The last oxidation step required many attempts until an anion exchanger separation finally afforded the desired product.

The depropargylation was achieved using concentrated HI solution.

With the compounds prepared, further derivatization will be explored in the diploma thesis.

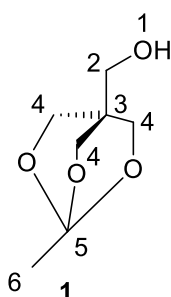
6 EXPERIMENTAL SECTION

6.1 General information

Barrel organic solvents were distilled before use. Solvents were dried using 3 Å molecular sieves, when dry conditions were required, according to the reference⁶⁵. Deionized water was used for reactions and column chromatography purifications. Reagents and solvents were purchased from Penta, Fluorochem, Sigma Aldrich, Lach-ner and P-lab, and used without further purification. Argon or nitrogen was used as an inert gas. Flash column chromatography was performed on SiliaFlash P60 (40-63 μm) or SiliaBond C18 (40-63 μm) both purchased from SiliCycle. TLCs were performed on aluminum sheets coated with a silica gel layer 60 F254 purchased from Merck. TLC spots were visualized under a UV-lamp ($\lambda = 254$ nm) or by dipping the TLC plate either in basic KMnO₄ aq. solution (S1) (1.5 g KMnO₄, 10 g K₂CO₃, 1.25 mL 10% w/w NaOH aq. solution, 200 mL H₂O) or bromocresol green ethanol solution (S2) (100 mL distilled ethanol, 0.04 g bromocresol green, 0.1 M NaOH dropwise addition until color changes from orange to green), and afterwards heating the plate to 200–250 °C with a heat gun. Solvents were evaporated on rotary vacuum evaporators from Büchi at RT-50 °C, and products were dried on an oil pump from LAVAT at RT-80 °C. ¹H NMR and ¹³C NMR spectra were measured on Bruker AVANCE III 400 MHz spectrometer at 400 MHz and 101 MHz, respectively. Samples were dissolved in CDCl₃ or D₂O. Deuterated solvents were purchased from ARMAR, Sigma Aldrich, and Deutero. MS low-resolution spectra were measured with Shimadzu LCMS-2020 spectrometer. HRMS spectra were measured on Agilent 6530 Q-TOF LC/MS.

6.2 Synthesis

(1-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-4-yl)methanol (1)

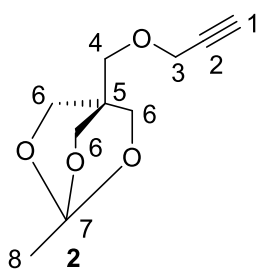


The compound was synthesized according to reference.¹⁷ Pentaerythritol (20 g, 0.147 mol) was suspended in dry toluene (15 mL). Triethyl orthoacetate (26.9 mL, 0.147 mol) and TsOH (72 mg, 0.374 mmol) were added to the reaction mixture. The reaction mixture was heated to 95 °C, and the produced EtOH was distilled from the reaction mixture by gradually increasing the temperature to 100 °C. The reaction mixture was monitored by TLC using a CHCl₃/MeOH

10:1 mixture, and spots were visualized with stain S1. After all EtOH was distilled from the reaction mixture, the temperature was gradually increased to 135 °C to distill off toluene. The gelatinous residue was sublimed in a Kugelrohr (180 °C, 5 mbar). The product was acquired partially in the form of a white solid and partially in the form of a white sticky gelatinous solid in a 55% yield (13.0 g). $R_F = 0.50$. ¹H NMR (400 MHz, CDCl₃): $\delta = 4.04$ (s, 6H, H-4), 3.48 (d, $J =$

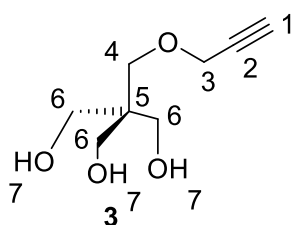
4.7 Hz, 2H, H-2), 1.57 (t, $J = 4.7$ Hz, 1H, H-1), 1.47 (s, 3H, H-6) ppm. **¹³C NMR** (101 MHz, CDCl₃): $\delta = 108.55$ (C-5), 69.28 (C-4), 61.38 (C-2), 35.59 (C-3), 23.40 (C-6) ppm. **HRMS**: for C₇H₁₂O₄ calcd: m/z 160.0736 (for [M+H]⁺ calcd: m/z 161.0808), found 161.0801 [M+H]⁺. ¹H and ¹³C NMR agree with the reference.¹⁷

1-Methyl-4-((prop-2-yn-1-yloxy)methyl)-2,6,7-trioxabicyclo[2.2.2]octane (2)



The compound was synthesized according to reference.¹⁷ Compound **1** (8 g, 0.05 mol) was dissolved in dry THF (75 mL). The reaction mixture was cooled down to 0 °C, and NaH (3 g, 0.075 mol, 60% dispersion in mineral oil) was slowly added. The reaction mixture was left to stir at 0 °C for 2 hours. Reaction mixture was bubbled with argon for 15 minutes before dropwise addition of Pr₃Br (8.35 mL, 0.075 mol, 80% solution in toluene). The reaction mixture was left to warm to RT and stirred for 20 hours. The reaction was monitored with TLC using a mobile phase hexane/EtOAc 1:1. Spots were visualized with stain S1. The mixture was filtered through a celite pad, and the filtrate was evaporated at 50 °C on a rotary evaporator. The product was sublimed in a Kugelrohr (170 °C, 5 mbar) to obtain white crystals, which partially dissolve upon manipulation, in a 95% yield (9.4 g). $R_F = 0.83$. **¹H NMR** (400 MHz, CDCl₃): $\delta = 4.11$ (d, $J = 2.4$ Hz, 2H, H-3), 4.03 (s, 6H, H-6), 3.31 (s, 2H, H-4), 2.47 (t, $J = 2.4$ Hz, 1H, H-1), 1.48 (s, 3H, H-8) ppm. **¹³C NMR** (101 MHz, CDCl₃) $\delta = 108.58$ (C-7), 78.83 (C-2), 75.21 (C-1), 69.41 (C-6), 67.99 (C-4), 58.74 (C-3), 34.71 (C-5), 23.42 (C-8) ppm. **HRMS**: for C₁₀H₁₄O₄ calcd: m/z 198.0892 (for [M+H]⁺ calcd: m/z 199.0965), found 199.0960 [M+H]⁺. ¹H and ¹³C NMR agree with the reference.¹⁷

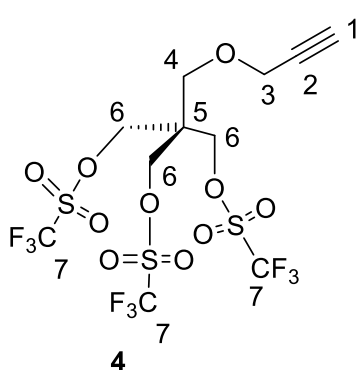
2-(Hydroxymethyl)-2-((prop-2-yn-1-yloxy)methyl)propane-1,3-diol (Propargyloxy-neopentanetriol) (3)



The compound was synthesized according to reference.¹⁷ Compound **2** (9 g, 0.045 mol) was dissolved in MeOH (180 mL), and concentrated HCl (4.0 mL, 0.045 mol) was added. The reaction mixture was stirred under reflux for 6 hours. The reaction was monitored with TLC using a mobile phase CHCl₃/MeOH 15:1. The spots were visualized with stain S1. The reaction mixture was cooled to RT and neutralized with 5% w/w NaOH aq. solution (50.4 mL), and the solvent was evaporated at 50 °C on a rotary evaporator. The residue was dissolved in H₂O (300 mL) and washed with CHCl₃ (3 × 300 mL). The water phase was evaporated at 50 °C. The residue was dissolved in acetone (150 mL), the mixture was filtered,

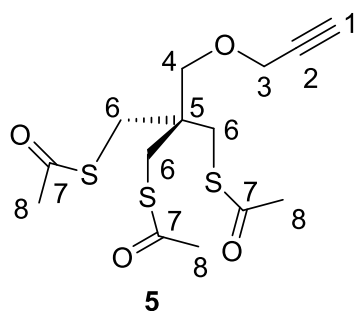
and the filtrate was evaporated at 40 °C. The product was dried on the oil pump at 80 °C. The product was obtained as yellow oil in a 48% yield (3.5 g). $R_F = 0.26$. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 4.17$ (d, $J = 2.3$ Hz, 2H, H-3), 3.73 (s, 6H, H-6), 3.58 (s, 2H, H-4), 2.49 (t, $J = 2.4$ Hz, 1H, H-1) ppm. $^{13}\text{C NMR}$ (101 MHz, CDCl_3) $\delta = 79.30$ (C-2), 75.03 (C-1), 71.43 (C-4), 64.32 (C-6), 58.88 (C-3), 45.04 (C-5) ppm. **ESI MS**: for $\text{C}_8\text{H}_{14}\text{O}_4$ calcd: m/z 174.1 (for $[\text{M}+\text{H}]^+$ calcd: m/z 175.1), found 175 $[\text{M}+\text{H}]^+$. **HRMS**: for $\text{C}_8\text{H}_{14}\text{O}_4$ calcd: m/z 174.0892 (for $[\text{M}+\text{Na}]^+$ calcd: m/z 197.0784), found 197.0782 $[\text{M}+\text{Na}]^+$. ^1H and ^{13}C NMR agree with the reference.¹⁷

2-((Prop-2-yn-1-yloxy)methyl)-2-(((trifluoromethyl)sulfonyl)oxy)methyl)propane-1,3-diyl-bis(trifluoromethanesulfonate) (Propargyloxy-neopentanetriol-tristriflate) (4)



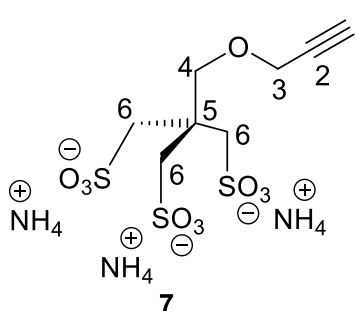
The compound was synthesized according to reference.¹⁷ Propargyloxy-neopentanetriol **3** (2.8 g, 16.1 mmol) was dissolved in dry DCM (90 mL) and the mixture was bubbled with argon for 10 minutes. Dry 2,6-lutidine (5.6 mL, 48.2 mmol) was added, and the reaction mixture was cooled to -76 °C. F_2O (8.1 mL, 48.2 mmol) was added dropwise, and the reaction mixture was stirred at -76 °C for 4 hours. The reaction was monitored with TLC using $\text{CHCl}_3/\text{MeOH}$ 15:1 mobile phase for the starting material and hexane/ EtOAc 10:1 for the product. The spots were visualized with stain S1. The reaction mixture was diluted with Et_2O (180 mL) and washed with 1 M HCl (170 mL). The organic phase was washed with saturated NaHCO_3 aq. solution (170 mL) and brine (170 mL). The product was dried with anhydrous MgSO_4 (3 g), filtered, and the solvent was evaporated at 30 °C on a rotary evaporator. The product was dried on the oil pump at RT. The product was obtained as a brown solid in a 92% yield (8.5 g). $R_F = 0.35$. $^1\text{H NMR}$: (400 MHz, CDCl_3): $\delta = 4.59$ (s, 6H, H-6), 4.25 (d, $J = 2.4$ Hz, 2H, H-3), 3.67 (s, 2H, H-4), 2.57 (t, $J = 2.4$ Hz, 1H, H-1) ppm. $^{13}\text{C NMR}$: (101 MHz, CDCl_3) $\delta = 118.50$ (q, $J = 319.9$ Hz, C-7), 77.02 (C-2) 76.60 (C-1), 71.29 (C-6), 64.47 (C-4), 58.90 (C-3), 44.70 (C-5) ppm. $^{19}\text{F NMR}$: (376 MHz, CDCl_3) $\delta = -73.81$ (- CF_3) ppm. **HRMS**: for $\text{C}_{11}\text{H}_{11}\text{F}_9\text{O}_{10}\text{S}_3$ calcd: m/z 569.9371 (for $[\text{M}+\text{Na}]^+$ calcd: m/z 592.9263), found 592.9259 $[\text{M}+\text{Na}]^+$. ^1H and ^{13}C NMR agree with the reference.¹⁷

S,S'-2-((Acetylthio)methyl)-2-((prop-2-yn-1-yloxy)methyl)propane-1,3-diyl)diethanethioate (Propargyloxy-neopentane-trithiol-triacetate) (5)



The compound was synthesized according to reference.²⁶ Potassium thioacetate (5.8 g, 50.8 mmol) was dissolved in dry EtOH (90 mL), and the reaction mixture was bubbled with argon for 15 minutes. Propargyloxy-neopentane-trithiol-trisulfate **4** (4.83 g, 8.46 mmol) was dissolved in dry EtOH (45 mL) and added to the reaction mixture via syringe through a septum. The reaction was cooled down to 0 °C and stirred at this temperature during the day and at RT at night for 4 days. The reaction was monitored with TLC using hexane/EtOAc 10:1 mobile phase. The spots were visualized with stain S1. The solvent was evaporated at 40 °C on a rotary evaporator, the residue was dissolved in 1 M HCl (152 mL), and the product was extracted with toluene (155 mL). The organic phase was washed with 1 M HCl (152 mL), saturated NaHCO₃ aq. solution (152 mL), and brine (152 mL). The organic phase was dried with anhydrous MgSO₄ (4.5 g), filtered, and the filtrate was evaporated at 40 °C. The residue was sorbed onto a silica gel column (80 g), and fractions were eluted with hexane/EtOAc 9:1 elution mixture to obtain the product as an orange oil in 76% yield (2.25 g). *R_F* = 0.18. ¹H NMR: (400 MHz, CDCl₃) δ = 4.11 (d, *J* = 2.4 Hz, 2H, H-3), 3.36 (s, 2H, H-4), 3.08 (s, 6H, H-6), 2.46 (t, *J* = 2.4 Hz, 1H, H-1), 2.36 (s, 9H, H-8) ppm. ¹³C NMR: (101 MHz, CDCl₃) δ = 194.67 (C-7), 79.24 (C-2), 74.84 (C-1), 72.45 (C-4), 58.50 (C-3), 42.74 (C-5), 33.10 (C-6), 30.60 (C-8) ppm. ESI MS: for C₁₄H₂₀O₄S₃ calcd: *m/z* 348.0 (for [M+NH₄]⁺ calcd: *m/z* 366.1), found 366 [M+NH₄]⁺. HRMS: for C₁₄H₂₀O₄S₃ calcd: *m/z* 348.0524 (for [M+Na]⁺ calcd: *m/z* 371.0421), found 371.0420 [M+Na]⁺. ¹H and ¹³C NMR agree with the reference.²⁶

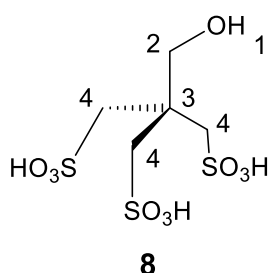
Triammonium 2-((Prop-2-yn-1-yloxy)methyl)-2-((trioxidanythio)methyl)propane-1,3-disulfonate (Triammoniumpropargyloxy-neopentane-trisulfonate) (7)



The compound was synthesized according to reference.²⁶ Propargyloxy-neopentane-trithiol-triacetate **5** (200 mg, 0.57 mmol) was dissolved in glacial acetic acid (4 mL), and H₂O₂ (0.53 mL, 5.17 mmol, 30% water solution) was added dropwise to the stirred solution. The reaction mixture was heated to 50 °C and left to stir for 1 hour. Reaction was monitored by TLC using hexane/EtOAc 10:1 mixture for the starting compound and MeOH/CHCl₃ 2:1 mixture for the product. Spots were visualized with stain S1. The reaction mixture was partially neutralized with

1 M NaOH (1.8 mL) to pH = 3–4. The reaction mixture was loaded onto 2 g of DEAE Sephadex A-25 weak anion exchanger. The product was eluted using 1 M NH₄HCO₃ solution. Solvent was evaporated on a rotary evaporator at 50 °C, and the product was dried on a vacuum pump at 60 °C. The product was obtained as a yellow glassy solid in a 79% yield (190 mg). $R_F = 0.77$. **¹H NMR** (400 MHz, D₂O): $\delta = 4.15$ (d, $J = 2.4$ Hz, 2H, H-3), 3.89 (s, 2H, H-4), 3.53 (s, 6H, H-6), 2.78 (t, $J = 2.3$ Hz, 1H, H-1) ppm. **¹³C NMR** (101 MHz, D₂O, *t*-BuOH) $\delta = 79.84$ (C-1), 75.66 (C-2), 71.37 (C-4), 69.75 (*t*-BuOH, -C-OH), 58.29 (C-3), 52.80 (C-2), 39.41 (C-5), 29.61 (*t*-BuOH, -CH₃) ppm. **ESI MS**: for C₈H₁₄O₁₀S₃ calcd: m/z 366.0 (for [M-H]⁻ calcd: m/z 365.0), found 365 [M-H]⁻, (for [M-2H]²⁻ calcd: m/z 182.0), found 182 [M-2H]²⁻. **HRMS**: for C₁₄H₂₀O₄S₃ calcd: m/z 365.9749 (for [M-H]⁻ calcd: m/z 364.9749), found 364.9663 [M-H]⁻, (for [M-2H]²⁻ calcd: m/z 181.9838), found 181.9798 [M-2H]²⁻. ¹H and ¹³C NMR agree with the reference.²⁶

2-(Hydroxymethyl)-2-((trioxidanyltio)methyl)propane-1,3-disulfonic acid (Hydroxy-neopentantrisulfonic acid) (8)



Triammoniumpropargyloxy-neopentanetrisulfonate **7** (21.4 mg, 0.051 mmol) was dissolved in 57% aq. HI (13.5 μ L, 0.103 mmol). The reaction mixture was heated to 55 °C and left to stir at this temperature for 17 hours. The reaction was monitored by LC-MS and TLC using MeOH/AcOH 1:5 mixture. Spots were visualized with stain S1. The product was sorbed on a DEAE Sephadex A-25 weak anion exchanger

and eluted with 0.25-0.5 M NH₄HCO₃. The fractions with product were evaporated at 40 °C on a rotary evaporator. The product was dried on a vacuum pump at 50 °C. The product was obtained as a transparent glassy solid in a 45% yield (7.6 mg). $R_F = 0-0.11$. **¹H NMR** (400 MHz, D₂O): $\delta = 3.86$ (s, 2H, H-2), 3.43 (s, 6H, H-4) ppm. **¹³C NMR** (101 MHz, D₂O) $\delta = 64.25$ (C-2), 53.06 (C-4), 40.55 (C-3) ppm. **ESI MS**: for C₅H₁₂O₁₀S₃ calcd: m/z 328.0 (for [M-H]⁻ calcd: m/z 327.0), found 326.9 [M-H]⁻, (for [M-2H]²⁻ calcd: m/z 163.0), found 163.0 [M-2H]²⁻. **HRMS**: for C₅H₁₂O₁₀S₃ calcd: 327.9593 (for [M-2H]²⁻ calcd: m/z 162.9797), found 162.9721 [M-2H]²⁻. ¹H and ¹³C NMR agree with the reference.²⁶

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