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Grau de Química

Treball Final de Grau

New organic ligands applicable to the design of nanotechnological devices

Nous lligands orgànics aplicables al disseny de dispositius nanotecnològics

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REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

This project is aimed at the synthesis of new molecules that could be key to the development of new nanoscale electronic devices with innovative functions in storage capacity and magnetic sensing. This ambitious goal could well fit into the "Industry, Innovation and Infrastructures" category.[1]

On the one hand, the development of molecular spintronic devices (MSDs) can be seen as an innovation and improvement in information storage capacity, which is essential for society's constant demand for high computational capacity. In addition, spintronic devices could operate faster and consume less energy. Thirdly, if such devices can be made at the nanoscale, it will be possible to reduce the amount of raw materials needed to manufacture them.

These aspects could mark an important point in technological progress and in the improvement of communication infrastructures.

CONTENTS

1. SUMMARY

Molecular spintronic devices (MSDs) not only work by controlling electrical charge (as conventional electronic devices do), but also by controlling spins, which is another intrinsic property of electrons. In this way, novel functions in magnetic sensing and information storage can be achieved.

The magnetic tunnel junction (MTJ) design is characteristic of the so-called multilayer edge molecular electronic devices (MEMEDs), which are a type of MSD. This design is based on passing electrons through two ferromagnetic electrodes separated by a thin insulating layer, closing the electronic circuit with a molecular ligand that is connected at each end to each electrode.

In this work, we study the synthesis of new candidate molecules to perform this function in MSDs. Our goal is a symmetric molecule with an imino-phenolic centre and a chain at each end with an electron donor group as a terminal functional group. It can be synthesized from simple commercially available reagents such as aliphatic and aromatic diols or bromoalcohols, following a variety of routes.

Although the final synthetic target has not been achieved in the present work, it has been possible to reach advanced intermediates in the synthetic pathway, and it is hoped to be able to complete it in the near future.

Keywords: Molecular spintronic device, magnetic tunnel junction, ligand, naphthol, *tert*-butyldimethylsilyl group, addition-elimination mechanism, nucleophilic substitution, pivaloyl group, Rieche formylation.

2. RESUM

Els dispositius espintrònics moleculars (MSDs) no només funcionen mitjançant el control de la càrrega elèctrica (com els dispositius electrònics convencionals), sinó que també ho fan mitjançant el control dels espins, que és l'altra propietat intrínseca dels electrons. D'aquesta manera, es poden assolir funcions novedoses en quant a la detecció magnètica i l'emmagatzematge d'informació.

El disseny d'unió túnel magnètica (MTJ) és característic dels anomenats dispositius electrònics moleculars de vora multicapa (MEMEDs), els quals són un tipus de MSD. Aquest disseny es basa en fer passar electrons a través de dos elèctrodes ferromagnètics separats per una fina capa aïllant, tancant el circuit electrònic amb un lligand molecular que es connecta per cada extrem a cada elèctrode.

En aquest treball s'estudia la síntesi de noves molècules candidates a realitzar aquesta funció en els MSDs. El nostre objectiu és una molècula simètrica amb un centre imino-fenòlic y una cadena a cada extrem amb un grup donador d'electrons com a grup funcional terminal. Pot sintetitzar-se a partir de reactius senzills disponibles al mercat, com diols alifàtics i aromàtics o bromoalcohols, seguint diverses rutes.

Tot i que en el present treball no s'ha aconseguit l'objectiu sintètic final, sí que s'ha pogut arribar a intermedis avançats en la ruta sintètica, i s'espera poder completar-la en un futur proper.

Paraules clau: Dispositiu espintrònic molecular, unió túnel magnètica, lligand, naftol, grup *tert*-butildimetilsilil, mecanisme d'addició-eliminació, substitució nucleòfila, grup pivaloil, formilació de Rieche.

3. INTRODUCTION

Two of the most valued aspects in the design of a new electronic device is the speed of processing the information and having a great capacity of storage.

Conventional electronic devices work by controlling the flow of electric charge. In contrast, in spintronic devices, in addition to the flow of electric charge, the flow of spins is also controlled thus increasing a degree of freedom.[2] Spins, associated with a magnetic moment, are other intrinsic property of electrons, along with charge. Thus, by applying spintronics to computing and computation, it is hoped that devices can be made faster and require less power than current electronic devices, making possible smaller computational devices down to a few nanometres.[3]

Spintronics (or magnetoelectronics) is an emergent branch of nanotechnology and one of the most active research areas of nanomagnetism, which was born in 1988 and has already led to innovative applications in hard disk information storage and magnetic sensing.[4]

Molecular spintronics is an interdisciplinary field that combines organic spintronics, molecular magnetism and quantum computing.[3] Its main objective is to control the spin of electrons and, consequently, to control spin-polarised information signals. In this field, it has been studied that organic molecules can be used as a mean to transport and control spin-polarised signals.[5]

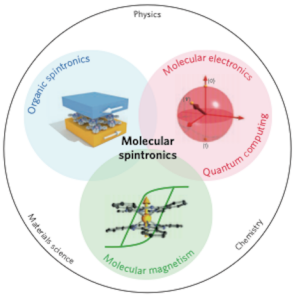


Figure 1. Molecular spintronics, an interdisciplinary field.[3]

Recent advances have shown that single-molecule magnets can be successfully transferred to surfaces with retention of their magnetic behaviour and potentially exploited as molecular

spintronic devices (MSDs).[4] MSDs can achieve miniaturisation of computational devices down to a few nanometres by offering versatile functions.[3]

A key aspect for the creation of these nanoscale molecular devices is the magnetism of the interface resulting from the interaction between a magnetic molecule, which must retain its structure, functionality and properties, and metal surface. The properties of the resulting nanomaterial (such as magnetism) can be affected by the coupling of the molecules to the surface, and it is therefore very important to consider how the molecules connect to the surface.[2,7]

The magnetic tunnel junction (MTJ) design is characteristic of so-called "multilayer edge molecular electronic devices" (MEMEDs). It consists of passing electrons through two ferromagnetic electrodes (such as Co, Ni, Au or Cr) separated by an ultra-thin insulator (usually Al_2O_3 or MgO) about 1-2 nm thick, which acts as a tunnel junction.[6–8] To close the electron circuit, a magnetic molecule is chemically bonded at each end to an electrode, while on the inside it is coordinated with a metal in solution, thus acting as a ligand between the two electrodes.

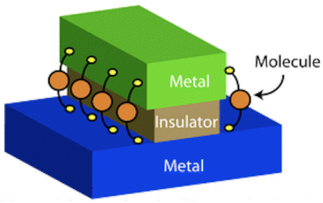
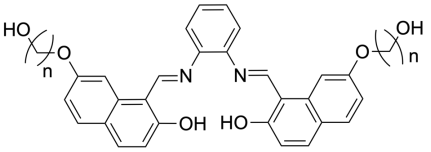


Figure 2. Scheme of a MEMED.[6]

Due to the academic importance of the study of these molecular spintronic devices and their technological potential, the SMBioCom group of the Organic Chemistry Section of the University of Barcelona (Spain) is collaborating with the GMMF group of the Inorganic Chemistry Section and the University of the District of Columbia (USA), in the development of molecular ligands that can be useful for bonding to both conductive surfaces at each of the two ends.

In our group, we envisaged that a molecule like the ones shown in **Figure 3** could be a suitable candidate to connect the two ferromagnetic electrodes. These compounds have a tetradentate imino-phenolic central part suitable for making a metal complex on the MEMEDs and two chains functionalised at the ends with a donor electron group (-OH, -SH, $-NH_2$…) to bond to the upper and lower electrodes. The total length of the molecule is determined by the exact thickness of the insulator; thus, the carbon chain at each end of the molecule can be variable, between 3 and 6

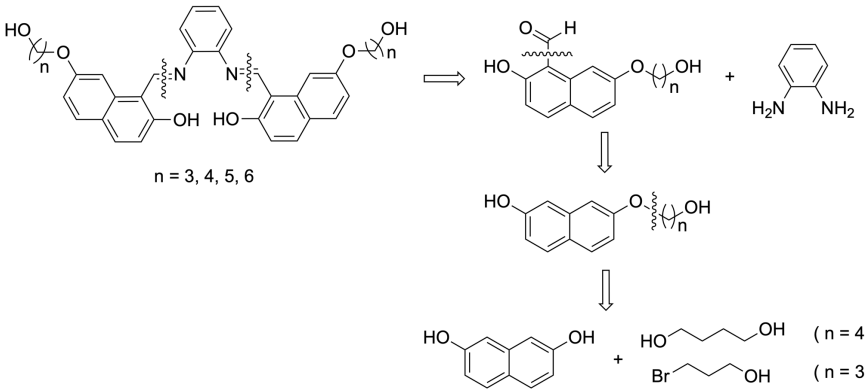
atoms (n).[8] This ligand should be complexed with metals such as Fe or Ni before testing the resulting nanodevice performance.



n = 3, 4, 5, 6

Figure 3. Candidate molecules for connecting the two electrodes.

In the present work, the strategy proposed to obtain the desired molecule is based on the formation of imine in the last step, by reaction of an aromatic aldehyde and an aromatic diamine. The retrosynthesis of the required molecule is shown in **Scheme 1**.



Scheme 1. Retrosynthetic analysis of the synthetic target.

The disconnection of the formyl group is justified, since in a synthetic way a selective formylation at this position of the molecule can be thought of due to the presence of a free hydroxyl group, which is a strong activator of electrophilic substitutions in aromatic systems at the *ortho* and *para* positions.

The side chain attached to the phenol is then disconnected. The incorporation of the functionalised carbon chain into the aromatic system may be carried out synthetically by a bimolecular nucleophilic substitution (S_N2). It should be noted that in the proposed molecule in **Figure 3**, the presence of the phenol facilitates the disconnection, which would be more difficult to carry out if it were an aromatic electrophilic substitution (S_EAr) to form a C-C bond in the position

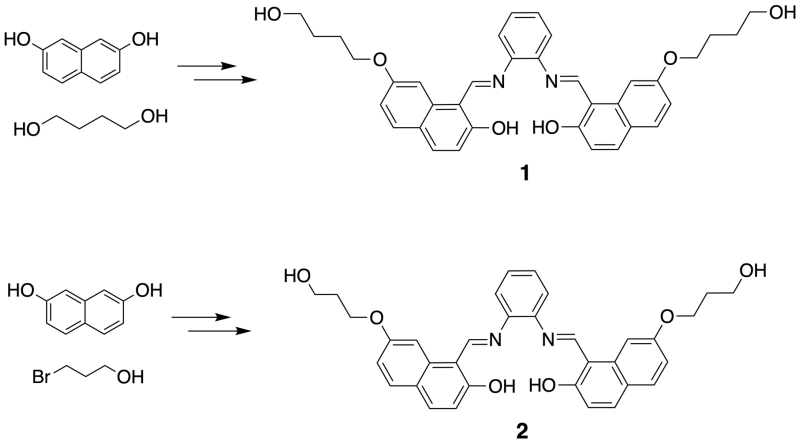
of interest. Finally, by disconnecting the molecule by the O-carbon chain bond, it is observed that the synthesis can be initiated with commercially available aromatic and aliphatic alcohols.

In a preliminary work carried out by Neus Santiago in the final part of her Master's thesis, the link of the side chain to the phenolic system by a Mitsunobu reaction was tested.[9] Although some precedents in the literature supported this reaction, Santiago's results were poor, and it was discarded.

4. OBJECTIVES

The aim of this work has been the search for a suitable route to obtain the desired synthetic target (either compounds **1** or **2**, indifferently) from simple commercial reagents, such as aliphatic and aromatic alcohols. To this end, we have taken into account the previous results of our research group (Neus Santiago's Master's thesis), which had not been sufficiently satisfactory.[9]

It should be pointed out that not significant quantities of the final ligand are required to validate the ligand model that we propose. Thus, we have not prioritised the optimisation of the reactions, but rather sought to advance as fast as possible towards the final objective in the limited time available.

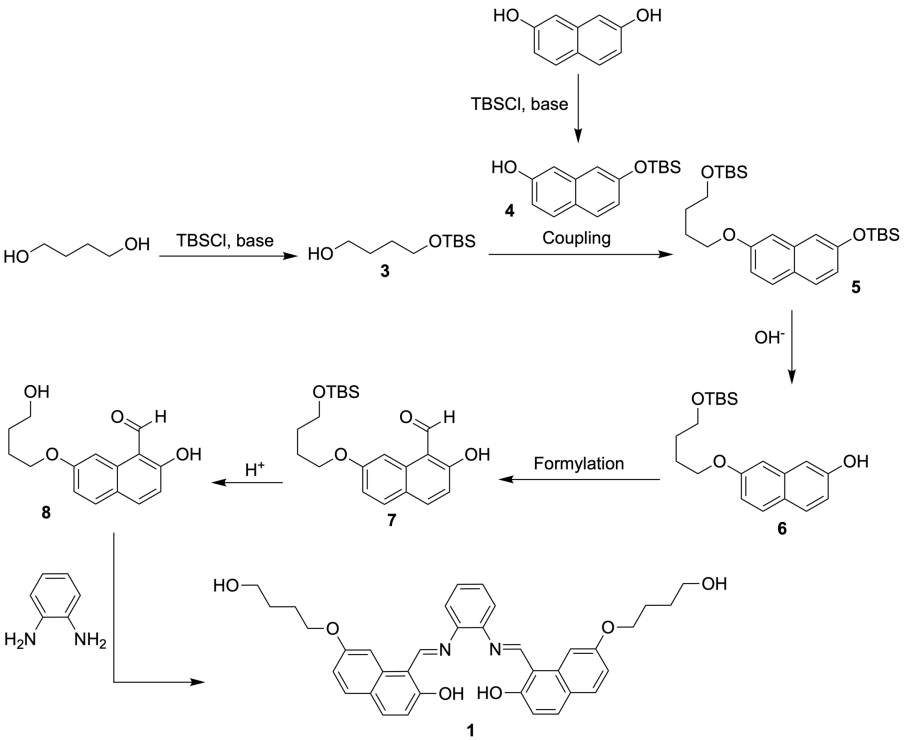


Scheme 2. Synthetic objectives **1** and **2** from different commercial reagents.

5. RESULTS AND DISCUSSION

5.1. INITIAL SYNTHETIC PROPOSAL

The structure of our synthetic target is adaptable to the use of different starting materials and reactions in its construction, as there are several synthetic alternatives to obtain the same (or a similar equally valid) product.



Scheme 3. Initial synthetic proposal.

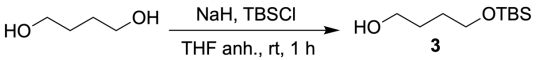
Our initial proposal for compound **1**, shown in **Scheme 3**, starts from commercial 1,4-butanediol and 2,7-dihydroxynaphthalene. Once these two starting materials were monoprotected

with *tert*-butyldimethylsilyl (TBS) group, a coupling step of the two fragments would be necessary. Reasonable options are the use of a Mitsunobu reaction or by activating the hydroxyl of compound **3** in the form of a sulphonate or a bromine derivate that would make possible the attack of the phenol by a S_N2 reaction. In this work, the monoprotected products **3** and **4** have been obtained. From there, the important steps would be the selective formylation of the naphthol derivate and the final condensation with *ortho*-benzenediamine.

5.1.1. Preparation of compound 3

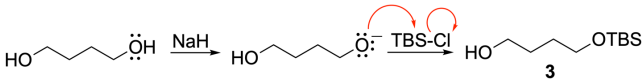
tert-Butyldimethylsilyl (TBS) is the most widely used protecting group of the silyl ether family for the protection of alcohols. Silyl protecting groups are often readily deprotected by basic hydrolysis or by fluoride ions.[10–12]

For the monoprotection of 1,4-butanediol with TBS, the diol was treated with a limited amount of TBSCl in the presence of base (NaH) at 0 ºC and using an anh. solvent (THF), following a procedure reported in the literature.[13] An addition-elimination mechanism can be assumed for this process.



Scheme 4. Reaction of formation of compound **3**.

The monoprotection of a symmetrical diol can be difficult, since besides the desired monoprotection product, deprotection and non-protection (starting material) products can be also present in the crude.[14] In this respect, THF plays an important role for the selective monoprotection: when a proton of the diol is kinetically deprotonated, the resulting monoanion can become insoluble in THF, so that when TBSCl is added, there will be a small amount of monoanion dissolved and the rest in suspension; TBSCl reacts with this small amount of monoanion in solution, so that the equilibrium is altered and more monoanion passes into the solvent, thus favouring the monoprotection product. In addition, to favour the monoprotected product, an excess of 1,4-butanediol is added with respect to the silylating agent. The mechanism of this reaction is shown in **Scheme 5**.



Scheme 5. Mechanism of formation of compound **3**.

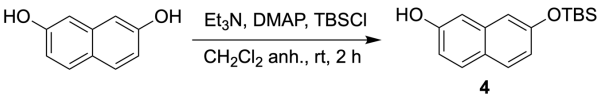
After the quench of the reaction, the organic compounds were extracted in ethyl acetate. The reaction crude contained several compounds and traces of starting material; therefore, a flash column chromatography was performed to separate them.

Finally, from 2.579 g of TBSCl, compound **3** (1.041 g, 30 %) was isolated as a colorless oil.

From the TLC and ^{1}H-NMR performed, it is known that there are two reaction by-products more apolar than **3**: one of them (the more abundant by-product) was the diprotected product and the other one could not be identified.

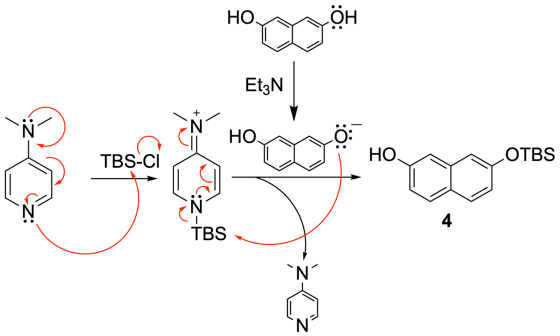
5.1.2. Preparation of compound 4

For the TBS monoprotection of 2,7-dihydroxynaphthalene, TBSCl was used in the presence of amine as a base (Et_3N) and 4-dimethylaminopyridine (DMAP) as a catalyst to increase the kinetics of the reaction at rt, following the procedure reported in the literature.[15]



Scheme 6. Reaction of formation of compound **4**.

On the one hand, since triethylamine can deprotonate 2,7-dihydroxynaphthalene to a good extent (pKa (Et_3NH^+) = 10.8; pKa (2,7-dihydroxynaphthalene) = 9.1), the first step reaction would be the deprotonation of the phenol. On the other hand, DMAP is known to react with TBSCl to generate a more reactive silylating agent that can react with the phenoxide generated by the action of the triethylamine. The oxygen of the phenoxide attacks nucleophilically the new silylating agent and DMAP is displaced as a leaving group, thus regenerating into its initial catalyst structure. This possible reaction mechanism is shown in **Scheme 7**.



Scheme 7. Mechanism of formation of compound **4**.

The reaction was quenched by the addition of water and the organic compounds were extracted in an organic phase of DCM. The crude contained two main compounds and traces of starting 2,7-dihydroxynaphthalene. A flash column chromatography was performed to separate them.

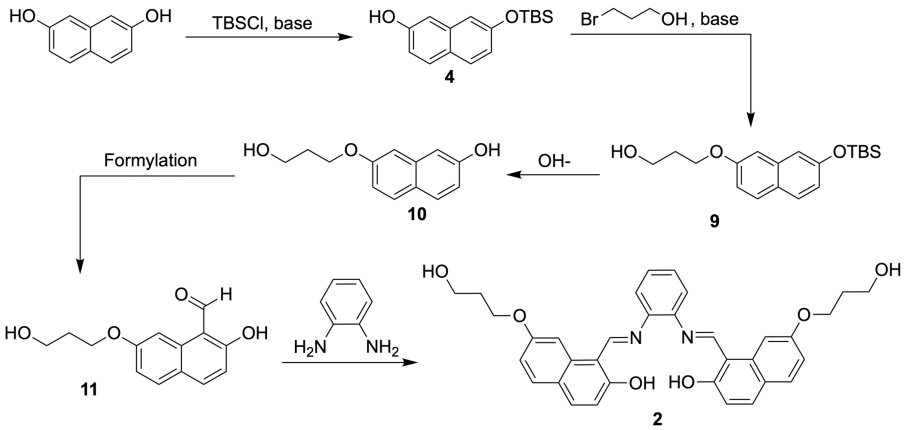
Finally, from 2.014 g of 2,7-dihydroxynaphthalene, product **4** (1.358 g, 39 %) was obtained as a brown solid.

The other by-product was analysed by TLC and ^{1}H-NMR and was found to be the diprotected product. The ratio of the monoprotected to the diprotected product was approximately 2:1.

5.2. SECOND SYNTHETIC PROPOSAL: COUPLING STEP ALTERNATIVE

A Mitsunobu reaction between substrates similars to **3** and **4** (but protected as acetates instead of silyl ethers) was attempted in the Master's thesis of Neus Santiago, but without success.[9] Because of this precedent, we considered alternative substrates to introduce the side chains of the aromatic system. One option is based on the use of 3-bromopropan-1-ol for the formation of the ether via S_N2 by the action of compound **4** in basic medium (see **Scheme 8**). This variant would not lead to aldehyde **8** (precursor of ligand **1**) but to the aldehyde **11** (precursor of a ligand with one carbon shorter side chain, **2**). This second proposal has the advantage that

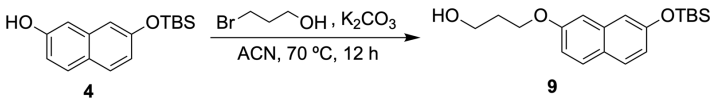
the 3-bromopropan-1-ol is commercially available and the step of protecting one of the two starting materials is spared.



Scheme 8. Second synthetic proposal.

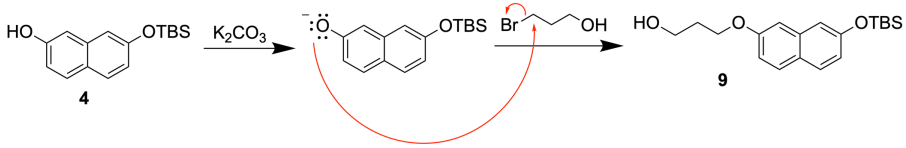
5.2.1. Preparation of compound 9

The preparation of compound **9** by bimolecular nucleophilic substitution in basic medium was performed following an experimental process found in the literature[16] for the synthesis of a similar compound.



Scheme 9. Reaction of formation of compound **9**.

As mentioned above, phenols have a pKa ~ 10 while that of primary aliphatic alcohol is ~ 16. Therefore, it is possible deprotonate the phenol in the presence of the aliphatic alcohol, and the phenoxide formed can attack the 3-bromopropan-1-ol, with the bromide being the leaving group (see **Scheme 10**).



Scheme 10. Mechanism of formation of compound **9**.

To favour the kinetics of the reaction, we heated the reaction mixture in a reflux system using acetonitrile (ACN) as solvent. During the heating, it was observed that the potassium carbonate was partially dissolved in the solvent, although most of it remained in suspension. However, the medium would be basic enough to deprotonate compound **4**.

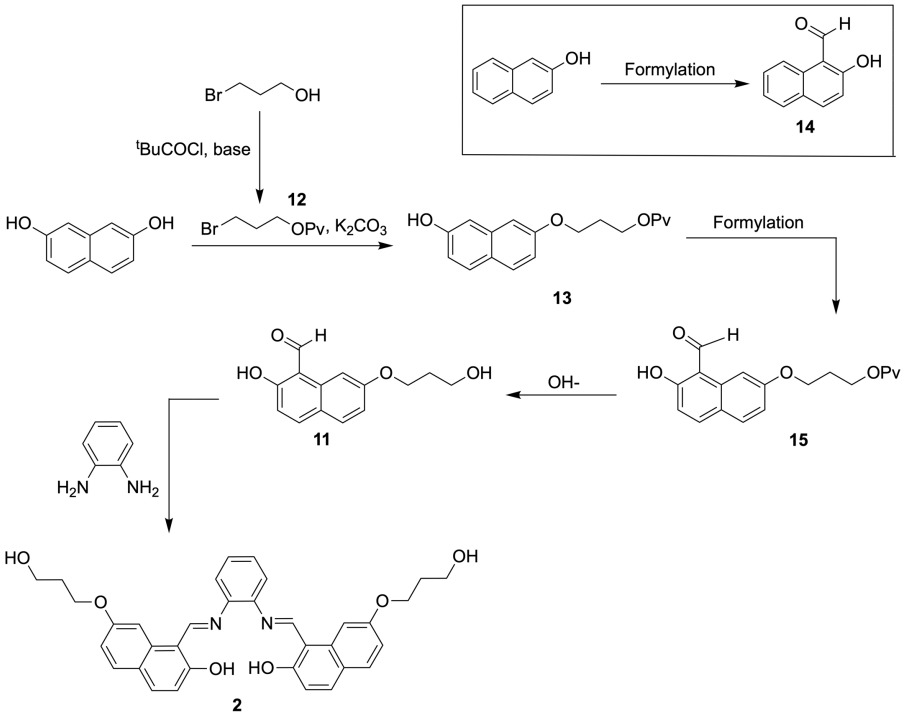
After 12 h of reaction, the TLC of the final crude showed a mixture of products that we tried to separate by flash column chromatography. Unfortunately, a second chromatography was necessary to isolate **9** from impurities with similar polarity.

Finally, from 0.536 g of starting material **4**, we were able to get quite pure product **9** as a brown solid in very small quantities (0.034 g, 5 %).

The nature of all by-products generated in this reaction could not be identified with certainty. However, due to the presence in the TLC of compounds more polar than starting material **9**, we assumed that TBS may be thought to be unstable in the reaction medium and some of the reaction by-products would be 2,7-dihydroxynaphthalene and compound **10**.

5.3. THIRD SYNTHETIC PROPOSAL: PROTECTIVE GROUP ALTERNATIVE

In view of the low yield and reaction by-products, TBS is probably not the best protecting group for this synthesis. Therefore, we tested the behaviour of an alternative protecting group. We resumed the preparation of **2** from the same starting materials as in **Section 5.2.** but using 3-bromopropan-1-ol monoprotected as pivaloyl ester (see **Scheme 11**). Ether formation was also planned via S_N2 and a subsequent formylation would be carry out to obtain compound **15**.

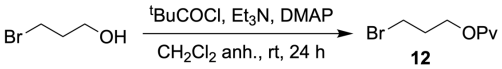


Scheme 11. Third synthetic proposal.

5.3.1. Preparation of compound 12

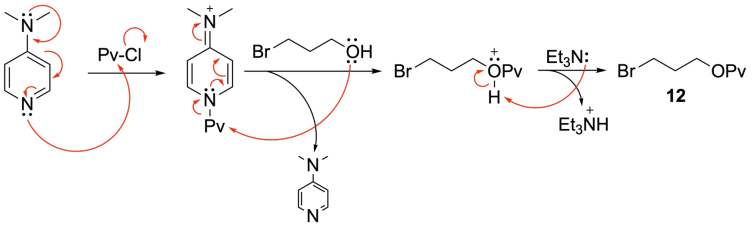
The pivaloyl group is a relatively bulky protecting group, more stable than acetate, and it can be used in primary alcohols. Acyl protecting groups are usually deprotected under basic or reductive conditions.[12]

In a typical protocol for the introduction of pivaloyl group, the alcohol is treated with pivaloyl chloride in the presence of base (Et_3N) and DMAP (which acts as catalyst) in anh. DCM as solvent. Somehow, the experimental protocol resembles that of the protection of aromatic alcohol with TBS.



Scheme 12. Reaction of formation of compound **12**.

It is accepted that DMAP reacts with pivaloyl chloride to generate a more reactive electrophilic agent. Triethylamine is not basic enough to deprotonate the aliphatic alcohol. The action of triethylamine, therefore, takes place in the last step of the reaction, capturing the proton from the resulting cation. The reaction mechanism is shown in **Scheme 13**.



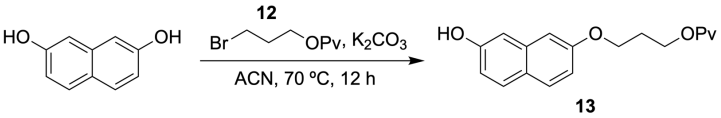
Scheme 13. Mechanism of formation of compound **12**.

The progress of the reaction was monitored via TLC until no changes (disappearance of reagents or formation of more products) were observed. After a work-up, and basic and acid washes, ^{1}H-NMR spectrum of the reaction crude showed the product **12** slightly impurified with a reaction by-product (3-hydroxypropyl pivalate). The crude was used in the next step without further purification.

Finally, from 2.001 g of 3-bromopropan-1-ol, product **12** (2.780 g, 86 %) was obtained as an orange oil.

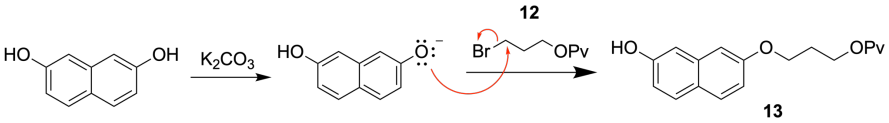
5.3.2. Preparation of compound 13

The formation of compound **13** was achieved via bimolecular nucleophilic substitution between 2,7-dihydroxynaphthalene and compound **12** in basic medium.



Scheme 14. Reaction of formation of compound **13**.

The aromatic alcohol was deprotonated in the basic medium and the resulting phenoxide attacked the electrophile, displacing the bromide as leaving group as shown in **Scheme 15.**



Scheme 15. Mechanism of formation of compound **13**.

After completion of the reaction, the mixture was poured over water and DCM. The solvent (acetonitrile) soluble in both water and DCM was partially distributed between the two phases and the extraction became a little hard, as both phases were of the same colour and could not be easily differentiated.

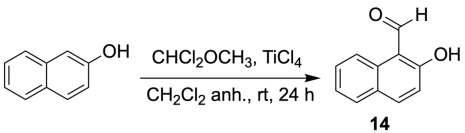
Once organic phase was collected and the volatiles eliminated, the crude was purified. The chromatography was not very successful due to the presence of three compounds of very close polarity that could not be well separated.

Finally, from 2.011 g of starting material **12**, compound **13** (0.344 g, 13 %) was obtained as a brown solid.

Among the by-products generated, 7-hydroxynaphthalen-2-yl pivalate (the aromatic monoacylation product) could be identified.

5.3.3. Preparation of compound 14

We performed the formylation of 2-naphthol using dichloromethyl methyl ether and 1 M titanium (IV) chloride in DCM (Rieche reaction) as reagents, following the procedure reported in the literature.[9] The objective was to check that the procedure worked in our hands before using it with compound **12**.

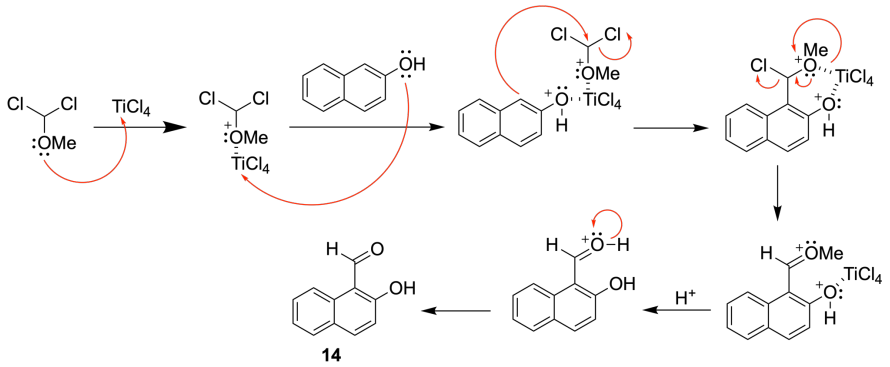


Scheme 16. Reaction of formation of compound **14**.

The Rieche reaction is useful for the formylation of aromatic rings activated with electron donor groups, such as the hydroxyl group, since they selectively direct the formyl group towards the *ortho* position with respect to the directing group.[17,18]

The hydroxyl group is a strong activator of aromatic rings, which means that its presence increases the reactivity of the aromatic ring towards electrophilic reagents.

Titanium (IV) chloride acts as activating agent: on the one hand, it coordinates with the oxygen of the dichloromethyl methyl ether and, on the other hand, it coordinates with the oxygen of the leading hydroxyl group of the aromatic system. Then, via an aromatic electrophilic substitution, the next activated carbon of the aromatic ring attacks the electrophilic reagent, thereby eliminating a chloride as a leaving group. Finally, upon treatment with aq. HCl, titanium (IV) chloride is hydrolysed, as well as the new group linked to the aromatic ring is hydrolysed to aldehyde. The suggested reaction mechanism is shown in **Scheme 17**.



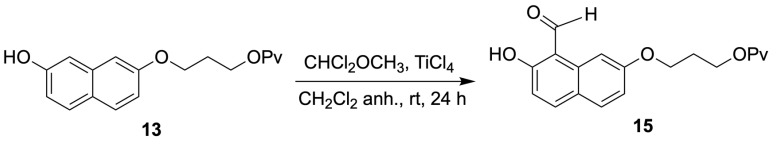
Scheme 17. Mechanism of formation of compound **14**.

After the work-up, the crude was sufficiently pure by TLC. Then, the ^{1}H-NMR performed corroborates that the sample contains negligible impurities.

Thus, from 1.300 g of 2-naphthol, compound **14** (1.475 g, 95 %) was obtained as a violet solid.

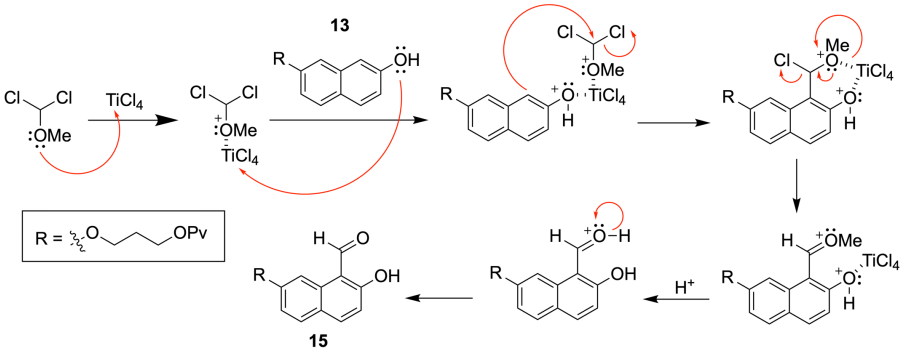
5.3.4. Preparation of compound 15

Due to the success of the 2-naphthol formylation, the same approach was used for formylating compound **13**.



Scheme 18. Reaction of formation of compound **15**.

The possible reaction mechanism is shown in **Scheme 19**.



Scheme19. Mechanism of formation of compound **15**.

After the work-up, the organic phase was extracted and the TLC analysis showed that the crude contained several compounds of very similar polarity. Thus, a flash column chromatography was required. A small amount of completely pure compound **15** was isolated. However, traces of our desired product remained in other column fractions. An attempt to purify these fractions by a second flash column chromatography with other eluents was unsuccessful.

Thus, from 0.344 g of starting material **13**, compound **15** (0.048 g, 13 %) was obtained as a yellow solid.

The small amount of compound **15** available and the lack of additional time decided us to terminate this TFG at this point and temporarily stop the studies to obtain the desired ligands.

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

6.1.1. Nuclear Magnetic Resonance Spectroscopy (NMR)

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Brucker 400 MHz and Brucker 500 MHz instruments, indicated in each case. The multiplicity of the singlets is described as a singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m) and doublet of doublets (dd). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are given in Hz, using as a reference tetramethylsilane (TMS) or the residual solvent signal ($CDCl_3$, ^{1}H at 7.26 and ^{13}C at 77.16 ppm; $(CD_3)_2SO$ ^{1}H at 2.50 and ^{13}C at 39.52 ppm) as internal standards. To prepare the samples, 10 mg (in the case of ^{1}H-NMR) or 30 mg (in the case of ^{13}C-NMR) of the compound were dissolved in 0.7 mL of the deuterated solvent. NMR spectra were analysed using MestReNova software.

6.1.2. Thin Layer Chromatography (TLC)

TLC was carried out on aluminium-backed sheets of a layer of silica (60 F_{254}). Plates were visualised under UV light and/or, it fit is necessary, treatment with staining agents, which are potassium permanganate (1.5 g of $KMnO_4$, 10 g of K_2CO_3 and 1.25 mL of 10 % NaOH in 200 mL of water) and phosphomolybdic acid (10 g of phosphomolybdic acid in 100 mL of absolute EtOH).

6.1.3. Column Chromatography

Purification of products was performed by flash column chromatography using as stationary phase VWR BDH Chemicals silica gel (technical grade, 40-63 μm particle size) on regular columns. The eluents and the conditions of elution are indicated in each case. Samples with low solubility in the eluent were dissolved in DCM, evaporated onto silica, and added onto a silica column.

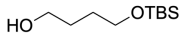
6.1.4. Infrared Spectroscopy (IR)

IR spectra were recorded on a Thermo Nicolet 6700 FT-IR instrument at rt. The signals are reported in cm^{-1}. IR spectra were analysed using Omnic software.

6.2. INITIAL SYNTHETIC PROPOSAL

6.2.1. Preparation of 4-((*tert*-butyldimethylsilyl)oxy)butan-1-ol (3)[13]

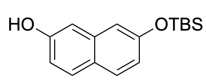
Sodium hydride (60 % dispersion in mineral oil, 0.74 g, 30.8 mmol) was added to a solution of 1,4-butanediol (2.27 g, 25.2 mmol) in anh. THF (25 mL) at 0 ºC. After stirring for 30 min at 0 ºC, TBSCl (2.58 g, 17.1 mmol) was added. After stirring for an additional 1 h at rt, the mixture was quenched by addition of sat. ammonium chloride (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried over anh. Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc 75:25) to afford 1.041 g (30 %) of compound **3** as a colorless oil.



Colorless oil. **TLC** (hexane/EtOAc 75:25): R_f = 0.48. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 3.67 (m, 4 H), 2.52 (s, 1 H), 1.64 (m, 4 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

6.2.2. Preparation of 7-((*tert*-butyldimethylsilyl)oxy)naphthalen-2-ol (4)[15]

DMAP (0.02 g, 0.18 mmol) and triethylamine (1.74 mL, 12.26 mmol) was added to a solution of 2,7-dihydroxynaphthalene (2.01 g, 12.57 mmol) in anh. DCM (50 mL) at 0 ºC. The reaction mixture was further treated with TBSCl (2.08 g, 17.02 mmol) and it was stirred at rt for 2 h. The reaction mixture was poured into water, and then extracted with DCM (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over anh. $MgSO_4$ and concentrated in vacuo to give a residue, which was purified by flash column chromatography (silica gel, hexane/EtOAc 75:25) to afford 1.358 g (39 %) of compound **4** as a brown solid.

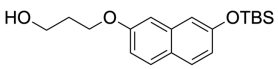


Brown solid. **TLC** (hexane/EtOAc 75:25): R_f = 0.50. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 9.0, 1 H), 7.64 (d, *J* = 9.0, 1 H), 7.03 (d, *J* = 2.3, 1 H), 7.00 (d, *J* = 2.5, 1 H), 6.94 (dd, *J* = 9.0, 2.3, 1 H), 6.92 (dd, *J* = 9.0, 2.5, 1 H), 1.01 (s, 9 H), 0.24 (s, 6 H).

6.3. SECOND SYNTHETIC PROPOSAL: COUPLING STEP ALTERNATIVE

6.3.1. Preparation of 3-((7-((*tert*-butyldimethylsilyl)oxy)naphthalen-2-yl)oxy)propan-1-ol (9)[16]

To a stirred mixture of **4** (0.536 g, 1.95 mmol) and 3-bromopropan-1-ol (0.347 g, 2.50 mmol) in ACN (15 mL), potassium carbonate (1.355, 9.80 mmol) was added, and the reaction mixture was heated at 70 ºC for 12 h under nitrogen environment. Then, the solid was removed from the solution and the volatiles of the solution were removed to obtain a residue, which was purified by flash chromatography (silica gel, hexane/EtOAc 75:25, 60:40, 50:50 and 0:100) to afford the product. A second flash column chromatography (silica gel, CH_2Cl_2/MeOH 97:3) was required to separate the impurities with similar polarity to that of the product **9** (0.034 g, 5 %), as an orange oil.

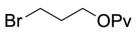


Orange oil. **TLC** (CH_2Cl_2/MeOH 97:3): R_f = 0.63. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 9.1, 1 H), 7.57 (d, *J* = 9.0, 1 H), 7.03 (d, *J* = 2.3, 1 H), 6.96 (d, *J* = 2.5, 1 H), 6.93 (dd, *J* = 9.1, 2.3, 1 H), 6.86 (dd, *J* = 9.0, 2.5, 1 H), 4.17 (t, *J* = 6.0, 2 H), 3.85 (t, *J* = 6.0, 2 H), 2.05 (m, 2 H), 0.96 (s, 9 H), 0.19 (s, 6 H). **^{13}C-NMR** (500 MHz, $CDCl_3$): δ = 157.1, 154.2, 135.9, 129.2, 129.1, 124.8, 119.7, 116.6, 114.2, 105.8, 65.7, 60.6, 32.0, 25.8, 18.3, -4.3.

6.4. THIRD SYNTHETIC PROPOSAL: PROTECTIVE GROUP ALTERNATIVE

6.4.1. Preparation of 3-bromopropyl pivalate (12)

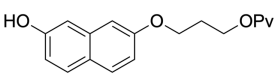
To a mixture of 3-bromopropan-1-ol (2.001 g, 14.40 mmol), anh. triethylamine (2.934 g, 28.99 mmol) and DMAP (0.879 g, 7.19 mmol) in anh. DCM (20 mL), a solution of pivaloyl chloride (3.128 g, 25.94 mmol) in anh. DCM (10 mL) was added dropwise at 0 ºC. The reaction mixture was stirred overnight at rt. Next day, the aqueous layer was extracted by addition of 1 M aq. HCl (3 x 25 mL), sat. $NaHCO_3$ (3 x 25 mL) and brine (25 mL). The organic layer was dried over anh. $MgSO_4$ and concentrated in vacuo to give 2.780 g (87 %) of compound **12** as an orange oil.



Orange oil. **TLC** (hexane/EtOAc 90:10): R_f = 0.68. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.21 (t, *J* = 6.3, 2 H), 3.61 (t, *J* = 6.3, 2 H), 2.10 (m, 2 H), 1.21 (s, 9 H). **^{13}C-NMR** (400 MHz, $CDCl_3$): δ = 178.4, 77.1, 61.1, 41.2, 31.7, 27.2.

6.4.2. Preparation of 3-((7-hydroxynaphthalen-2-yl)oxy)propyl pivalate (13)

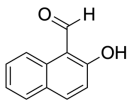
To a mixture of potassium carbonate (3.737 g, 27.04 mmol) and 2,7-dihydroxynaphthalene (2.887 g, 18.02 mmol) in ACN (15 mL), a solution of **12** (2.011 g, 9.01 mmol) in ACN (5 mL) was added and the reaction mixture was heated for 12 h at 70 ºC under nitrogen environment. After that, the reaction was poured by addition of DCM (100 mL) and water (25 mL) and the aqueous layer was extracted with more water (4 x 25 mL). The combined organic layers were dried with anh. $MgSO_4$ and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc 75:25) to afford compound **13** (0.344 g, 13 %) as a brown solid.



Brown solid. **TLC** (hexane/EtOAc 75:25): R_f = 0.34. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.8, 2 H), 7.03 (d, *J* = 2.5, 1 H), 6.95 (m, 3 H), 4.30 (t, *J* = 6.3, 2 H), 4.13 (t, *J* = 6.3, 2 H), 2.17 (m, 2 H), 1.21 (s, 9 H). **^{13}C-NMR** (500 MHz, $CDCl_3$): δ = 179.1, 157.4, 154.3, 136.0, 129.5, 129.3, 124.3, 116.3, 115.4, 108.8, 105.5, 64.3, 61.5, 38.9, 28.6, 27.2.

6.4.3. Preparation of 2-hydroxy-1-naphthaldehyde (14)[9]

A mixture of dichloromethyl methyl ether (0.82 mL, 9.06 mmol) and 1 M titanium (IV) chloride (18.03 mL, 18.03 mmol) in anh. DCM (10 mL) was stirred for 15 min at 0 ºC. A solution of 2-naphthol (1.298 g, 9.00 mmol) in anh. DCM (10 mL) was added dropwise, and the reaction mixture was stirred overnight at rt. The mixture was quenched by addition of 1 M aq. HCl (10 mL). The aqueous layer was extracted by addition of DCM (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried with anh. $MgSO_4$ and concentrated in vacuo to obtain 1.475 g (95 %) of compound **14** as a violet solid.

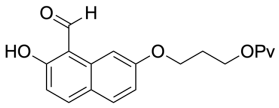


Violet solid. **TLC** (hexane/EtOAc 75:25): R_f = 0.75. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 13.16 (s, 1 H), 10.81 (s, 1 H), 8.35 (d, *J* = 8.2, 1 H), 7.98 (d, *J* = 9.1, 1 H), 7.80 (d, *J* = 8.2, 1 H), 7.62 (m, 1 H), 7.44 (m, 1 H), 7.14 (d, *J* = 9.1, 1 H).

6.4.4. Preparation of 3-((8-formyl-7-hydroxynaphthalen-2-yl)oxy)propyl pivalate (15)

A mixture of dichloromethyl methyl ether (0.131 g, 1.14 mmol) and 1 M titanium (IV) chloride (1.14 mL, 1.14 mmol) in anh. DCM (10 mL) was stirred for 15 min at 0 ºC. A solution of **13** (0.334 g, 1.14 mmol) in anh. DCM (15 mL) was added dropwise and the reaction mixture was stirred

overnight at rt. Then, the mixture was quenched by addition of 1 M aq. HCl (15 mL). The aqueous layer was extracted by addition of DCM (3 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried with anh. $MgSO_4$ and concentrated in vacuo to obtain a residue, which was purified by flash column chromatography (silica gel, hexane/EtOAc 75:25) to afford an impure product. A further flash column chromatography (silica gel, CH_2Cl_2/MeOH 98:2 and 97:3) was required to separate the impurities with similar polarity to that of the product **15** (0.048 g, 13 %), as a yellow solid.



Yellow solid. **TLC** (hexane/EtOAc 75:25): R_f = 0.38. **^{1}H-NMR** (400 MHz, $(CH_3)_2SO$): δ = 10.76 (s, 1 H), 10.08 (s, 1 H), 8.59 (d, *J* = 2.4, 1 H), 8.12 (d, *J* = 9.0, 1 H), 7.77 (d, *J* = 8.8, 1 H), 7.28 (d, *J* = 8.8, 1 H), 6.99 (dd, *J* = 8.8, 2.4, 1 H), 4.33 (t, *J* = 6.2, 2 H), 4.23 (t, *J* = 6.2, 2 H), 2.14 (m, 2 H), 1.13 (s, 9 H). **^{13}C-NMR** (400 MHz, $(CH_3)_2SO$): δ = 191.3, 177.9, 164.6, 159.9, 138.5, 133.3, 130.9, 123.5, 117.2, 114.9, 110.8, 106.7, 66.4, 61.3, 38.7, 28.6, 27.3. **IR**: 3171, 2959, 2923, 1715.

7. CONCLUSIONS AND FUTURE PERSPECTIVES

Although the synthetic target of this work (either compounds **1** or **2**, indifferently) has not been achieved, it has been possible to explore different synthetic alternatives to find a suitable one.

1) It has been possible to monoprotect 1,4-butanediol and 2,7-dihydroxynaphthalene with *tert*-butyildimethylsilyl group, isolating the resulting compounds (**3** and **4**, respectively). Monoprotection of each of these starting materials was not too complex, but yields were lower than expected. It was considered to carry out the coupling step by a Mitsunobu reaction or by activation of the other hydroxyl of the 1,4-butanediol as a tosylate. However, we changed our mind and preferred first to try another starting material: 3-bromopropan-1-ol instead of 1,4-butanediol.
2) The substitution reaction between monoprotected 2,7-dihydroxynaphthalene with TBS (**4**) and 3-bromopropan-1-ol was tested. The expected ether (**9**) was isolated in very low yield with the suspicion that TBS was not a good protecting group for the synthesis of our synthetic target, due to the by-products generated. So, we preferred to change to another protective group: Pv group instead of TBS group.
3) 3-Bromopropan-1-ol was protected with a pivaloyl group and the resulting monoprotected compound (**12**) reacted with 2,7-dihydroxynaphthalene to afford compound **13**, although in low yield. The presence of the monoacylation compound (7-hydroxynaphthalen-2-yl pivalate) as one of the reaction by-products suggests that this protecting group is not sufficiently robust in the reaction medium.
4) As a previous check, a sample of 2-naphthol was formylated according to a protocol described in the literature with good results. Based on this positive result, the formylation of compound **13** was carried out, obtaining a very small amount of pure compound **15**, confirming the feasibility of the process.

At this point, the synthetic study had to be stopped. However, our group expect to continue the study in the near future. The reactions tested in the last synthetic approach can be considered positive, since in fact the expected products of each reaction has been obtained. However, an

optimisation of each reaction seems necessary to improve the yields and/or selectivities. The use of a more robust protective group, such as benzyl, can also be considered for the monoprotection of the starting materials.

8. REFERENCES AND NOTES

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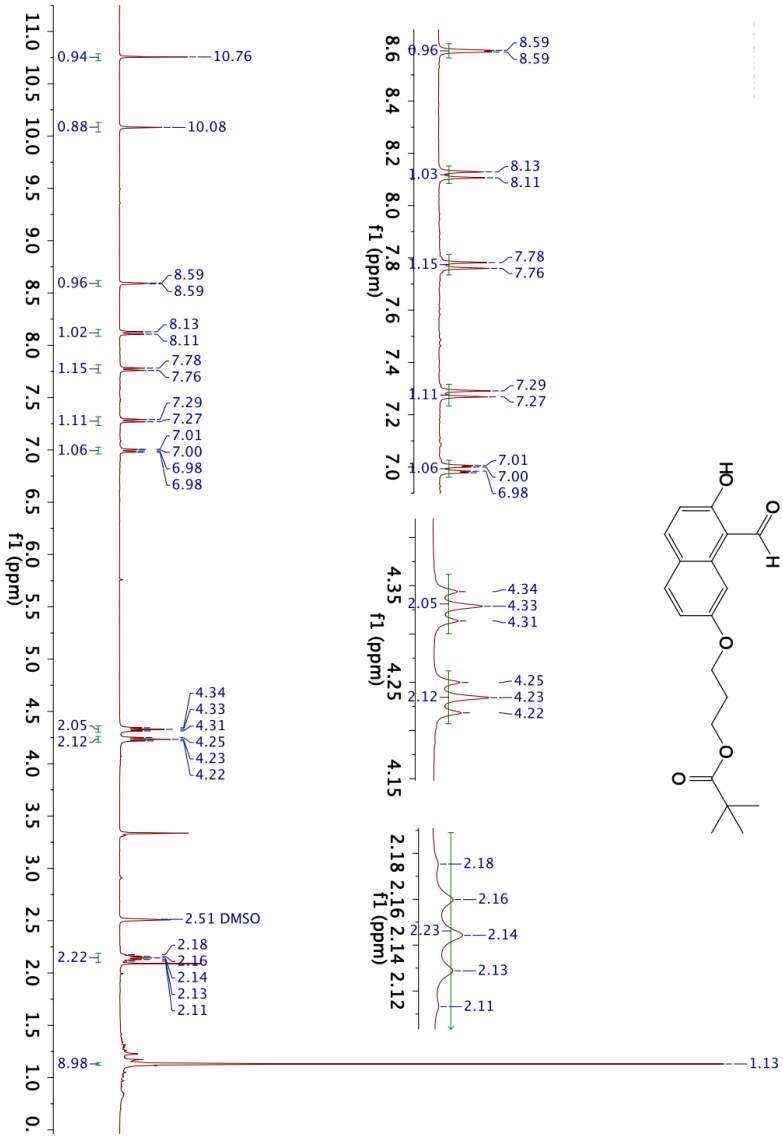
9. ABBREVIATIONS AND ACRONYMS

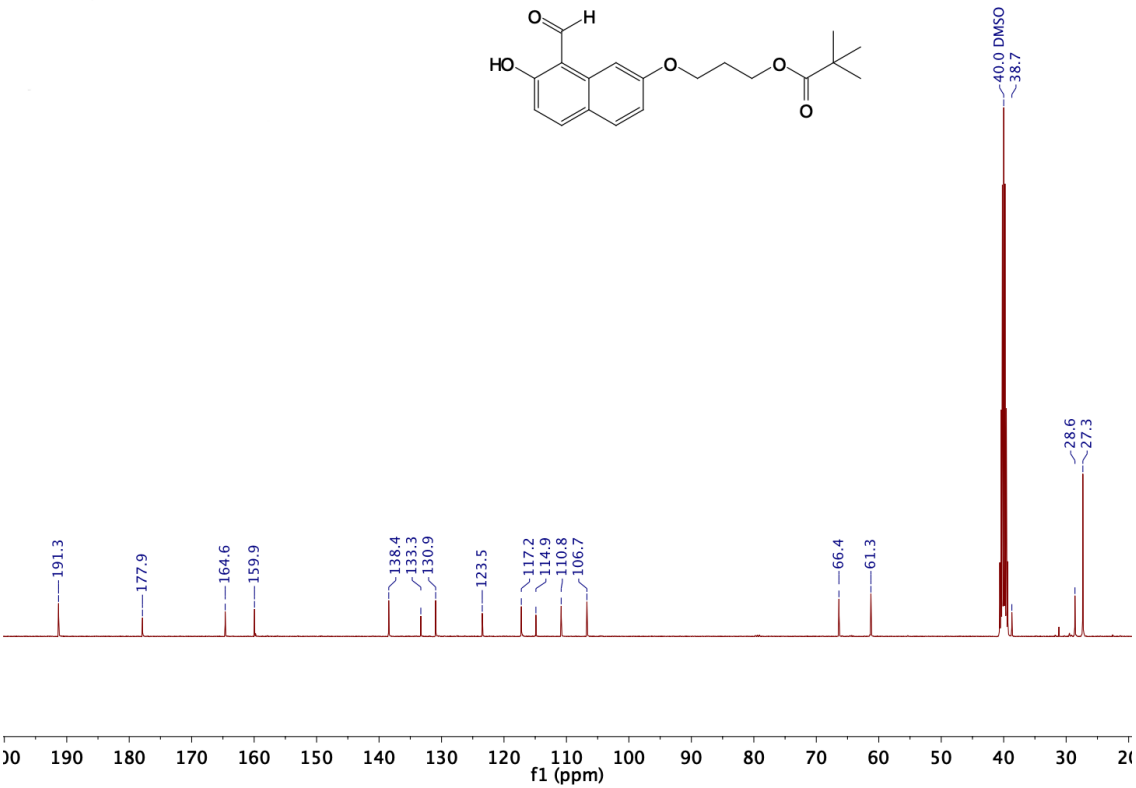
ACN	Acetonitrile
Anh.	Anhydrous
Aq.	Aqueous
d	Doublet
dd	Doublet of doublets
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
IR	Infrared
MTJ	Magnetic Tunnel Junction
MSD	Molecular Spintronic Device
MEMED	Multilayer Edge Molecular Electronic Device
m	Multiplet
NMR	Nuclear Magnetic Resonance
Pv	Pivaloyl group
q	Quadruplet
R_f	Retention factor
rt	Room temperature
Sat.	Saturated
s	Singlet
SDG	Sustainable Development Goals
TBS	*tert*-Butyldimethylsilyl group
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
t	Triplet
UV	Ultraviolet-Visible

APPENDICES

APPENDIX 1: ^{1}H-NMR AND ^{13}C-NMR OF COMPOUND 15

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164.6
159.9
138.4
133.3
130.9
123.5
117.2
114.9
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61.3
40.0 DMSO
38.7
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f1 (ppm)