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Synthesis of 5-substituted 3-pyridineboronic esters as building-blocks for the modular assembly of teraryl-based α-helix mimetics

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Meiner Familie

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1 Introduction

Interactions between molecules are nearly as old as time itself. Right after the formation of the first atoms in the early universe they started to interact with each other forming molecules and consequently all matter we know today. Indeed interactions between these particles have given rise to the world as we know it today. Especially nature brought this concept of interaction to a whole new level of complexity. Both small molecules and biopolymers engage with each other like gear wheels in a perfect process creating and maintaining life itself. Among the many molecules essential for life on earth proteins play an important role as they are crucial for virtually every process of the cell. Naturally, interactions between these kinds of molecules frequently occur and are an essential mechanism for the regulation of biological processes. These so-called protein-protein interactions (PPIs) are highly interesting targets for drug discovery as they coordinate and control numerous cellular processes like signal transduction, transcription, differentiation and apoptosis. Errors within these regulations can induce numerous diseases such as HIV, cancer, diabetes and neurodegenerative diseases.[1,2] However, while a considerable amount of effort was put into the targeting of enzyme active sites only small progress was made in the field of PPIs.[1]

Hamilton *et al.* could show that teraryl structures are able to inhibit PPIs as they act as α-helix mimetics.[3] These molecules are able to interact with α-helices on the protein surface containing essential amino acid residues for PPIs (“hot spots”).[4] This interaction renders the protein surface less attractive for PPIs. However, the linear synthesis of these teraryls would be inefficient and time consuming. Therefore our group developed a highly convergent strategy for the assembly of teraryls based on Suzuki cross-coupling reactions of ready-made building blocks containing aryl rings with all natural amino acid residues. For this strategy a library consisting of these building-blocks has to be generated.[5,6]

This work contributed to our project by synthesising more of these building blocks to complete the library of the desired building blocks in the near future and finally prove the advantages of this promising concept.

2 Theoretical Background

2.1 Protein-Protein Interactions (PPIs)

Proteins often fulfil their functions in cells as part of groups with other proteins forming so-called protein-complexes.[4] Interactions between proteins are of utmost importance for living organisms. These protein-protein interactions (PPIs) coordinate and control numerous cellular processes like signal transduction, transcription, differentiation and apoptosis. Therefore it is obvious that disruption of PPIs can lead to disease states such as HIV, cancer, diabetes and neurodegenerative diseases.[1,2] As a result a better understanding of the formation of these protein complexes has many practical applications such as the design of new therapeutic agents and the analysis of metabolic and signal transduction networks.[4]

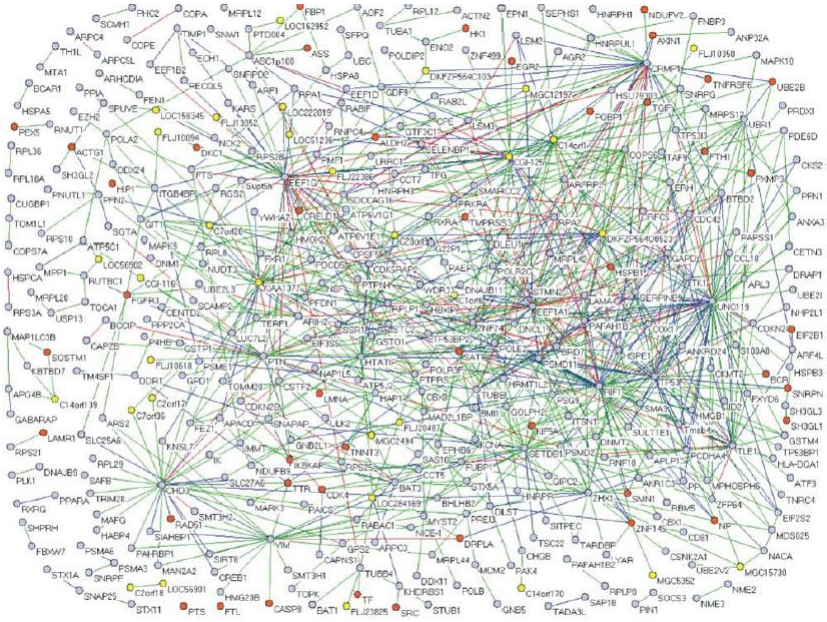


Figure 1: Protein-protein interaction map of 401 proteins and 911 interactions (picture taken from Stelzl *et al.*[7]).

In Figure 1 the results of the investigation of Stelzl *et al.* on PPIs are displayed in form of an interaction map. This map displays the interactions of disease proteins (45), uncharacterized proteins (49) and known proteins (307) of the human proteome. It was found that the 45 disease proteins participate in 163 PPIs. The majority of the proteins are linked and form a large interaction network. This picture gives a good impression of the fundamental meaning of PPIs for biological processes.[7]

As PPIs pose a way for nature to achieve control and function within a living cell, strategies to selectively modulate these interactions are of great importance. However, in comparison to the research efforts performed on targeting enzyme active sites with the effort to target PPIs have been considerably smaller.[1,8]

The reason for this development was the assumption that it would be too difficult to modulate PPIs with small molecules as the interactions with proteins occur over large surfaces. While enzymes only have small pockets that can be targeted by small molecules the interfaces of PPIs can cover areas up to 2000-4660 $Å^2$ with many amino acid residues involved.[4,9] However, according to the discoveries of Clackson and Wells[10] only a small number of amino acid residues on the protein surface contribute most to the free binding energy of PPIs.[9] These so-called "hot spots" are often located on secondary structures on the protein surface and its dimensions are often comparable to the size of small molecules.[9,11]

Arora *et al.* investigated the proteins of the PDB (version August 2009) for these secondary structures. The results of this study showed that 15 % of the entries in the database consisted of multiprotein complexes and of these, 62 % have an α-helix at the interface.[11] This illustrates the importance of this secondary structure, which is the most common among the secondary structural elements in Proteins.[2] It could be shown that synthetic small molecules mimicking these structural key elements are able to inhibit PPIs with high affinity and specificity.[8,11]

Molecules that interfere with PPIs via mimicking α-helices, called α-helix mimetics are a diverse group of structures, which were developed using different approaches.[11]

2.2 α-Helix Mimetics

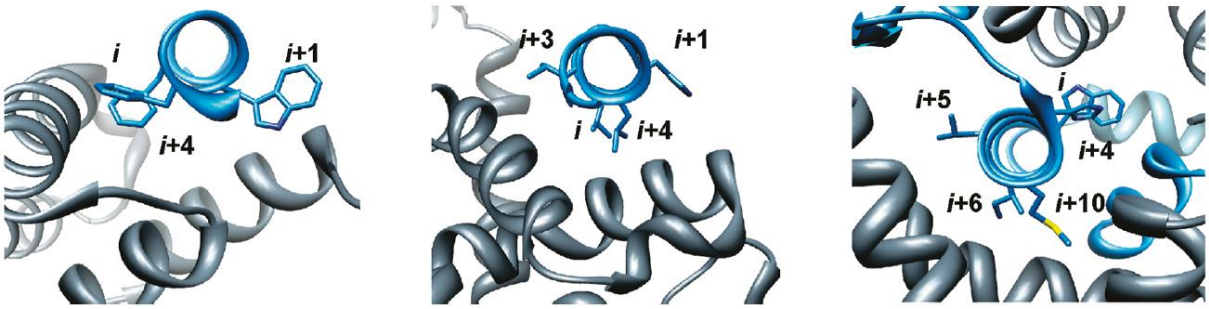


Figure 2: PPIs with hot spot residues on one, two or three faces of an α-helix (picture taken from Arora *et al.*[11]).

As in Figure 2 illustrated the "hot spot" residues, which are crucial for many PPIs as mentioned before can be located on one face, two faces or all three faces of an α-helix. The letter "*i*" in this picture marks the first amino acid moiety where an interaction with the other protein chains occurs starting at the *N*-terminus of the α-helix. The other labels "*i* + n" designate the positions of the follwoing "hot spot" amino acid residues relative to the first amino acid residue on the α-helix. Knowing these different types of interactions several strategies for the design of α-helix mimetics have been developed:[11]

- Helix stabilization
- Helical foldamers
- Helical surface mimetics

2.2.1 Helix Stabilization

One of the methods for helix stabilization is based on side-chain cross-links. In this strategy peptides are synthetically modified in order to force the desired α-helix structure on peptides making them suitable to act as functional probes or therapeutic agents. The introduction of cross-links into the amino acid side-chains stabilizes the helical form of peptides when these are free in solution and preorganize their amino acid residues to favour binding to a protein. The helical form also helps the peptide to reduce the exposure of the polar amide backbone making it easier for the molecule to pass through biological membranes and to raise the resistance to cleavage by proteases.[12,13] There are different methods to achieve cross-linking like disulfide bond formation,[14] lactam bridges[15] and cysteine alkylation[16]. One method that was used by Verdine *et al.*[12,13] was the application of ruthenium-catalyzed ring-closing metathesis (RCM). This reaction requires synthetic peptides containing non-natural amino acid residues such as amino acids with olefinic side chains.[12]

Another method to stabilize short peptides which act as α-helix mimetics is the application of hydrogen-bond surrogates (HBSs). For this method the peptide is stabilized in its helical form by replacing one of the intramolecular hydrogen bonds between the *i* and *i* + 4 residues of the peptide chain with a C-C bond. This covalent bond in place of an intrastrand hydrogen bond in α-helices can be introduced via a ruthenium-catalyzed ring-closing metathesis reaction (RCM). In contrast to the previously mentioned method the placement of the cross-link on the inside of the helix does not block solvent-exposed molecular recognition surfaces of the molecule. In addition this short helical peptides which are stabilized by this method maintain their conformation also well in buffers and under elevated temperatures.[17,18]

2.2.2 Helical Foldamers

The term "foldamers" refers to oligomers that adopt well-defined structures and conformations. These chemical substances consist of unique, non-biological backbones and are capable of forming helical structures with the potential to inhibit PPIs mediated by α-helices.[19,20] These molecules have many advantages. For example the synthesis can be carried out on solid phase and allows access to chemical diverse side-chains. These molecules exhibit stability of their conformation, resistance to degradation *in vivo* and water solubility, which makes them favourable for pharmacological applications.[21]

There are different classes of amino acid analogues that can be used to generate helical foldamers.

One group consists of so-called β-peptides. These molecules are typically composed of β-amino acids which are linked by amide bonds. These amide bonds are capable of forming intramolecular hydrogen bonds, which can stabilize secondary structures of the molecule. As the structures of β-amino acids are closely related to those of α-amino acids it is possible for peptides made from β-amino acids or mixtures of α- and β-amino acids to mimic α-helical structures and inhibit PPIs.[19,22]

Another group of foldamers are called peptoides. They are oligomers of *N*-substituted glycine which are connected via amide bonds. It is also possible to generate extensive compound libraries of these structures. They display similar characteristics as β-peptides which also have been used as α-helix mimetics.[20,21]

2.2.3 Helical Surface Mimetics

In contrast to the previously mentioned strategies for designing α-helix mimetics this concept is entirely based on mimicking elements of protein secondary structure with completely non-peptidic constructs, which makes it possible to avoid the complex expression, purification and chemical synthesis of peptidic elements. Furthermore these peptidomimetics are metabolically stable, can permeate membranes and are readily absorbed. [2]

In addition peptides have many disadvantages when used as therapeutic agent like low resistance towards degrading enzymes, poor absorption in the gastro-intestinal tract and may cause allergies.[23] As a result non-peptidic α-helix mimetics as they are also synthesized for our project are more favourable for pharmaceutical application.

One of the most prominent representatives of this group is the teraryl scaffold. In 2001 Hamilton *et al.* could show that these molecules project their side chain functionality in similar distance and angular relationships to those found in α-helices (Figure 3). Teraryls can be synthesized in a modular fashion by cross-coupling reactions making them easily accessible. Furthermore by selecting suitable substituents they can mimic the arrangement of "hot spot" amino acid residues in an α-helix scaffold, which makes them powerful tools for inhibition of PPIs. [3,8] However, these molecules with substituents which resemble the *i*, *i* + 3 (or *i* + 4) and *i* + 7 amino acid postions[8] of α-helices are only able to mimic the functionality of one face of α-helices, whereas the previously mentioned proteomimetics are capable of interacting with two or all three faces. Nonetheless Arora *et al.* could show that roughly 60 % of the helical interfaces of PPIs in the PDB have "hot spot" residues on one face of the helix.[11]

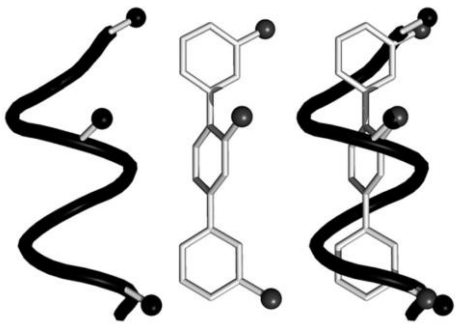


Figure 3: Teraryls show similar spatial arrangement of its moieties as the "hot spot" residues of α-helices (picture taken from Breinbauer *et al.*[5])

Hamilton *et al.* could show in many cases the effectiveness of the application of terphenyl scaffolds for PPI inhibition.[8] One example would be the disruption of the N36/C34 complexation which is a crucial PPI for the formation of the membrane transporter Gp41 involved in HIV1 entry into host cells.[24] Another example is the inhibition of the interaction between the proteins calmodulin (CaM) and smooth muscle myosin light chain kinase (smMLCK), which are involved in muscle contraction by a terphenyl.[3] These examples are only a small aspect of many potential targets of PPIs that can be inhibited using teraryls.[8]

To improve the poor water solubility of teraryls Hamilton and co-workers also introduced heterocyclic compounds such as pyridine into the teraryl scaffold.[8,25]

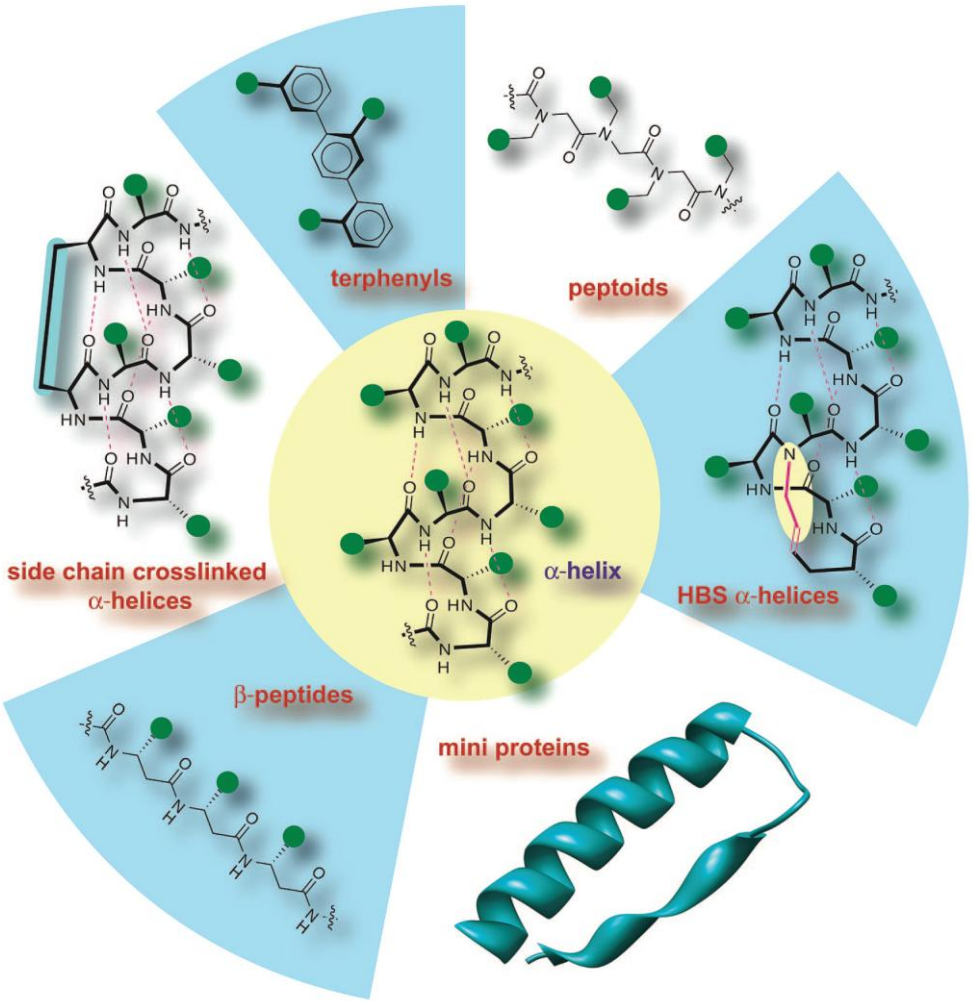


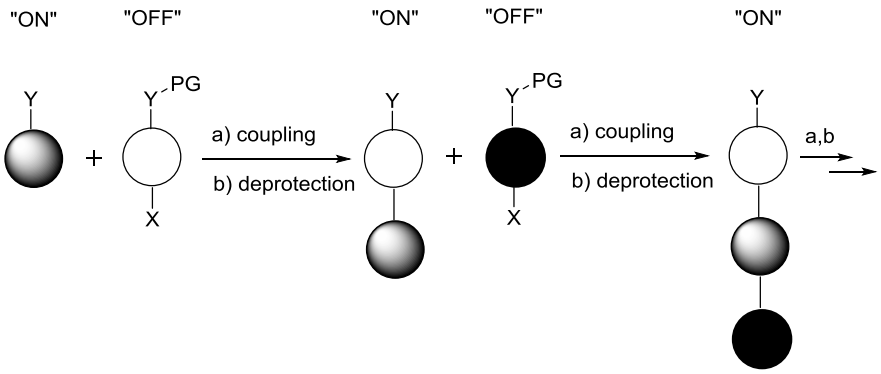
Figure 4: Summary of possible designs for α-helix mimetics (picture taken from Arora *et al.*[17]).

In Figure 4 common strategies to design α-helix mimetics are summarized. As it can be seen not just the previously mentioned strategies but also miniature proteins can be deployed to inhibit PPIs. In this concept a small protein is crafted on one face of the α-helix in order to stabilize the helical folding of the peptide. This protein grafting involves the identification of the "hot spot" residues which are necessary for PPIs and substituting them onto the helical region of a protein scaffold. One protein that can be used for this purpose is the avian pancreatic polypeptide (aPP) which consists only of 35 amino acid residues.[19]

All in all teraryls, especially those with good solubility such as terpyridines, are interesting compounds which have many benefits compared to peptidic structures used to inhibit PPIs (see above). Therefore the great potential as candidates for future therapeutic agents should be further explored.

2.3 Iterative Palladium-catalyzed Cross-Coupling

The word iteration is derived from the Latin term “iterare”, which means to repeat. Indeed, this powerful strategy enables chemists to synthesize complex oligomers from readily available building blocks by repeated coupling sequences. In iterative reactions bi- or multifunctional building blocks are employed that contain only one reactive functional group. As displayed in Scheme 1 if the reactivity of certain groups is switched “ON” (X, Y) it allows selective coupling of these building blocks, while all other functional groups are unreactive and therefore switched “OFF” (Y-PG). In this way uncontrolled polymerisation can be suppressed. After the coupling step another previously unreactive functional group is deprotected (“ON”) and the coupling can be repeated.[26]



Scheme 1: General iterative coupling sequence of building blocks bearing activated (Y, X, “ON”) and protected (Y-PG, “OFF”) functional groups (picture taken from Glorius *et al.*[26]).

This concept is excessively used by nature for the biosynthesis of major classes of biopolymers. Most of the molecules necessary for life are made via assembly of a limited number of bi-functional building blocks. Examples for these biopolymers are proteins which are derived from 20 amino acids and DNA and RNA which are biosynthesized from a set of 4 different nucleotides. Also 75 % of all mammalian oligosaccharides comprise only 36 monosaccharide units.[27] In recent years chemists have made use of this inherent modularity and established iterative and automated synthesis for these biopolymers.[28]

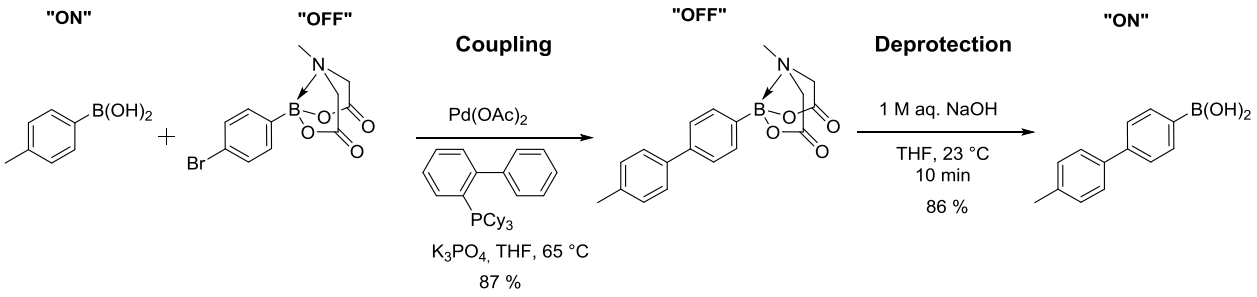
In contrast to these accomplishments an automated synthesis of small-molecule natural products could not be accomplished in the same fashion as for other biopolymers. The laboratory synthesis of such small molecules has traditionally involved the development of a unique pathway and collection of building blocks to access each target. However, the biosynthesis of natural products like polyterpenes also requires building blocks such as isopentenyl and dimethylallyl pyrophosphate, which are assembled in a modular fashion. This suggests that a systematic approach based on building blocks could make an iterative strategy possible, which would allow the efficient and flexible production of many small molecules analogously.[27]

In order to design such a strategy the criteria of an ideal iterative strategy must be defined:[26]

- Coupling and deprotection steps should be high yielding, tolerant of many functional groups and not require or produce any toxic substances.
- Many diverse building blocks which are inexpensive and readily available.
- Handling, separation and purification are facile.
- The iterative coupling sequence is reliable and predictable.
- The sequence is suitable for solid phase synthesis and automation.

In order to fulfil the first point of this list of requirements for the development of an iterative synthesis, it was necessary to find a suitable way for coupling and deprotection of the building blocks. Syntheses based on palladium-mediated cross-coupling are especially attractive due to the mild, nonacidic and stereospecific nature of these methods.[29] Therefore research groups of Hiyama,[30] Suginome[31] and Burke[27] developed iterative concepts based on palladium-catalyzed cross-coupling reactions. However, among these probably the most outstanding accomplishments in this field were made by Burke *et al.*[27]

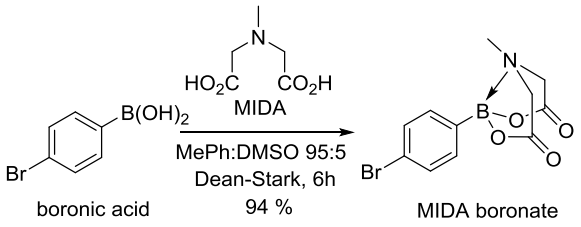
In 2007 Burke and co-workers published the first results of their strategy, which involves the use of Suzuki-Miyaura reaction for C-C coupling and a protection of the boronic acid function as *N*-methyliminodiacetic acid (MIDA) adduct (Scheme 2).[32]



Scheme 2: First attempts of Burke *et al.* for an iterative palladium-catalyzed cross coupling.[32]

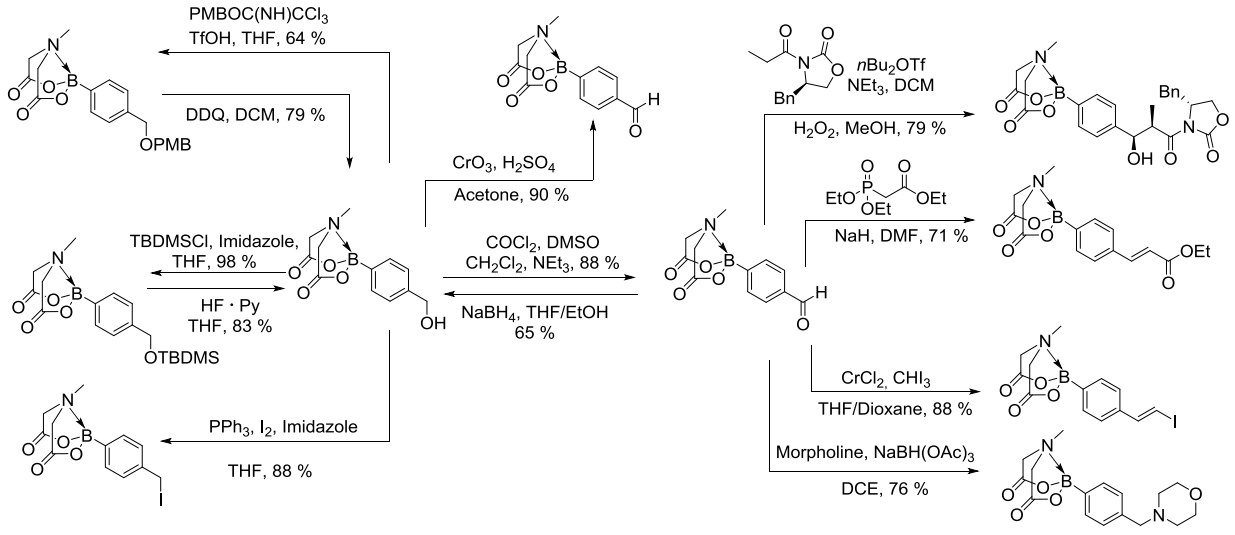
As it can be seen in Scheme 2 Burke *et al.* chose the Suzuki-Miyaura reaction[33] for the coupling step. Among the palladium-catalyzed cross-couplings this reaction is especially important due to its use of nontoxic boronic acid reagents and wide functional group compatibility. As the MIDA-protective group is not stable under aqueous basic conditions Buchwald's anhydrous Suzuki-Miyaura conditions[34] were applied for this reaction.[29]

The most outstanding feature of this concept is the introduction of MIDA-boronates as protective groups for boronic acids. This protecting group makes it possible to switch the reactivity of the boronic acid function "ON" or "OFF", which allows the selective coupling of building blocks (Scheme 2). The reason for this selectivity in Suzuki-Miyaura ractions is the sp^3-hybridization of the boron atom within MIDA boronates. As this reaction needs a vacant and Lewis acidic p-orbital only sp^2-hybridized boron compounds are able to participate in the palladium-catalyzed cross-coupling.[32]



Scheme 3: Example for the synthesis of a MIDA boronate.[35]

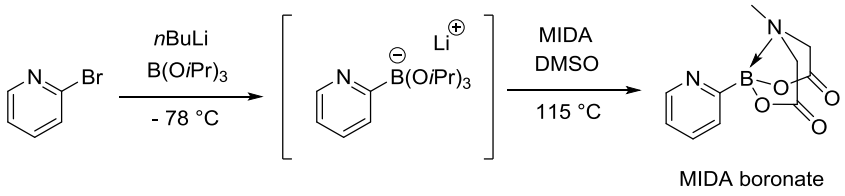
MIDA boronates are compounds with remarkable properties for iterative cross-coupling reactions. Many MIDA boronates can be synthesized easily and in good yields from boronic acids (Scheme 3).[32] Moreover MIDA boronates are surprisingly inert to a host of reaction conditions including treatment with nucleophiles, electrophiles, oxidants, reductants, acids, and several bases (Scheme 4). However, the most important characteristics of this class of substances is their exceptional stability to benchtop storage and their general compatibility with column chromatography.[36]



Scheme 4: MIDA boronates are compatible with a wide range of common synthetic reagents.[36]

The efficient deprotection can be accomplished using a standard set of mild aqueous basic conditions (1 M NaOH/THF, RT, 10 min or MeOH/aq $NaHCO_3$, 3.5 h). MIDA boronates are generally incompatible with $LiAlH_4$, DIBAL, TBAF and a variety of metalloxides.[32,36] A further advantage of MIDA is its simple preparation from iminodiacetic acid, which is produced on an industrial scale, making it cheap and readily available.[37]

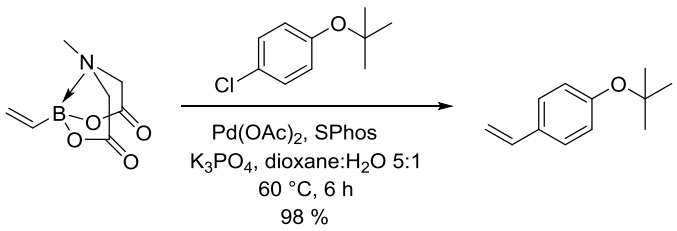
Although polyenyl and 2-pyridyl MIDA boronates are stable their corresponding boronic acids are rather unstable. Therefore Burke *et al.* developed syntheses of these MIDA borates using other intermediates than boronic acids (Scheme 5).[29,38]



Scheme 5: Synthesis of 2-pyridyl MIDA boronate according to Burke *et al.*[38]

In 2009 Burke and co-workers published a more refined cross-coupling reaction which allows direct use of MIDA boronates as starting-material without any previous deprotection of the boronic acid function. This so-called slow-release cross-coupling uses the fact that the MIDA boronate adducts are unstable in aqueous bases. With this knowledge Burke *et al.* used a Suzuki-Miyaura coupling with the weak base K_3PO_4 in a dioxane/H_2O mixture (5:1).

This weak base causes under elevated temperatures a slow degradation of the MIDA boronate releasing the reactive boronic acid *in situ* (Scheme 6). In later attempts with automated syntheses this slow-release strategy was chosen as the final step of an iterative synthesis due to the generally higher yields of this procedure.[27,39]



Scheme 6: Example of a slow-release cross-coupling reaction from Burke *et al.*[39]

All these accomplishments show the great potential of MIDA boronates as platform to design building blocks for iterative cross-coupling reactions. In an idealized form of this approach a collection of building blocks with the right stereochemistry and having all functional groups pre-installed in the correct oxidation state serves as a basic library for the synthesis of a respectable number of natural products using only cross-coupling reactions for assembly.[40]

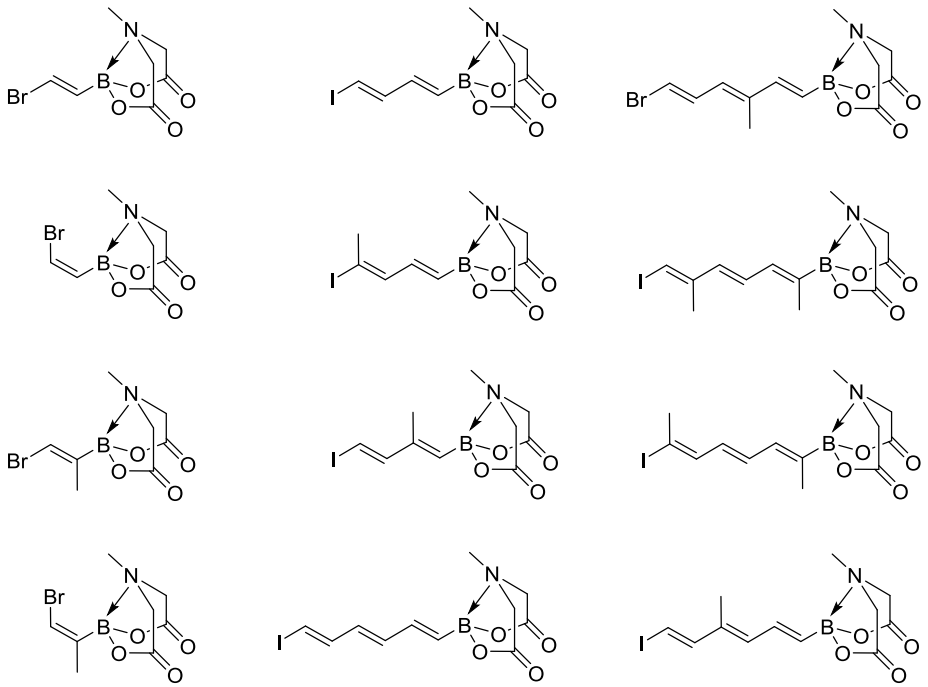
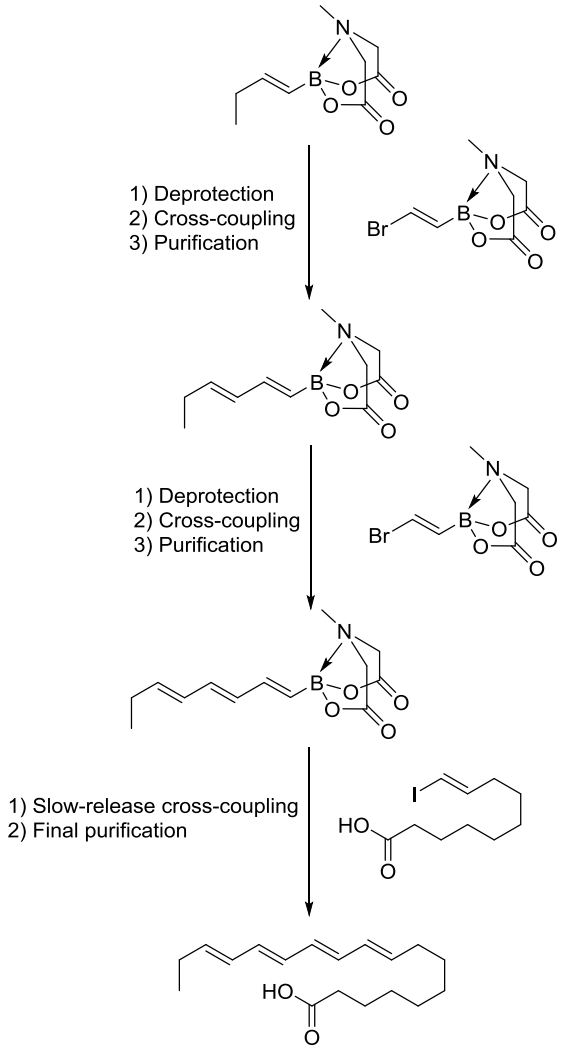


Figure 5: Most polyene motifs can be synthesized with a collection of only 12 bifunctional building blocks.[27]

With the powerful tools of MIDA boronates and their optimized coupling conditions it was possible for Burke and co-workers to advance to the next step and develop an automated iterative synthesis of polyene natural products. Even though, these polyenes are interesting molecules with a many applications, the synthesis is challenging due to their sensitivities to light, oxygen and many common reagents, as well as difficulties in controlling the stereochemistry of each double bond. After thorough investigations Burke *et al.* proposed the hypothesis that more than 75 % of all known polyene natural products can be synthesized using just 12 building blocks which are illustrated in Figure 5.[27]

One of the last problems that had to be overcome for an automation approach of an iterative polyene synthesis was the optimization of the purification of MIDA boronates. This was accomplished by a "catch and release" strategy, in which the reaction mixture after the cross-coupling step was adsorbed onto silica gel and eluted with a mixture of Et_2O and 1.5 % MeOH (v/v). As MIDA boronates cannot be eluted with such a solvent mixture all other reaction reagents as well as unreacted boronic acids can be removed. The pure MIDA boronate is later recovered from the silica gel by elution with THF or other solvents such as MeCN and acetone. Another purification method developed by Burke *et al.* is the precipitation of MIDA boronates in hexanes/THF (3:1 v/v) as virtually all molecules containing a MIDA protected boronic acid group are insoluble in this mixture. Also cyclohexane or any other isomer of hexanes can be used.[41]

All those accomplished tasks finally enabled Burke *et al.* to design an automated synthesis using the above displayed building blocks to generate polyene natural products via iterative palladium-catalyzed cross-coupling (Scheme 7).



Scheme 7: Automated iterative synthesis of β-parinaric acid.[41]

Scheme 7 shows the general steps of the automated synthesis of β-parinaric acid as described in one of the patents of Burke *et al.*[41] The first step of this scheme is always the deprotection of the MIDA boronate by addition of base. To make this step more convenient for automation the base is a basic ion exchange resin. After the reaction mixture has been acidified to liberate the boronic acid the resin is removed via filtration. Then the mixture is dried and used for the second step of the iterative circle which was the palladium-catalyzed cross-coupling under anhydrous conditions. The last action of one iterative step is the purification which can be performed according to the earlier described "catch and release" strategy.[41]

In 2014 Burke *et al.* described an alternative deprotection method using a basic pinacol solution (pinacol and $NaHCO_3$ in MeOH) to convert the MIDA boronate into a pinacol boronic ester, which is more stable than polyenyl boronic acids providing higher yields for the following steps. As a consequence of this synthetic protocol the following cross-coupling step under anhydrous conditions requires DMSO as solvent.[27]

All in all Burke and co-workers accomplished tremendous advances in the field of automated iterative cross-coupling. His synthetic strategy comes very close to the ideal criteria for an ideal iterative synthesis mentioned at the beginning of this chapter. One of the milestones of his concept was without a doubt the introduction of MIDA boronates as protective groups for the boronic acid function as these molecules show enormous potential for organic syntheses. As many building blocks are already commercially available the advantages of this new concept can also be experienced now by a large number of research groups. A disadvantage of this concept might be the excessive use of DMSO for MIDA chemistry, as this solvent can be troublesome to remove. Another problem of this automation concept is the fact that unlike the previously mentioned biopolymers, small molecules do not inherently possess a common-functional group which can be used for attachment to a solid support, which could make the synthesis much better applicable for automation.[27]

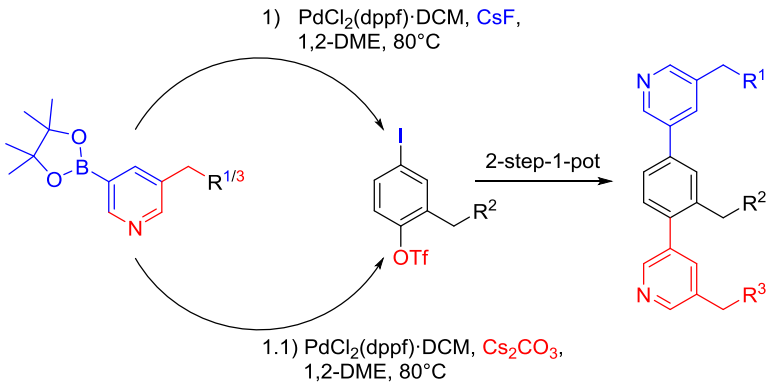
All in all Burke's concept makes it possible to synthesize 1 % of all isolated natural products to date. To also access the other 99 % of the natural products many new such strategies and breakthroughs are necessary, so that maybe one day all substances found in nature can be produced by machines.[27]

3 Aim of this Work

Based on the work by Hamilton *et al.* it was discovered that teraryl structures are able to inhibit protein-protein interactions (PPIs) as they act as α-helix mimetics.[3] These small molecules are able to interact with α-helices on the protein surface containing essential amino acid residues for PPIs ("hot spots"). This interaction is indeed the main factor for the inhibition of PPIs.[4]

As the linear synthesis of these teraryls would be inefficient and time consuming, our group was developed a highly convergent strategy for the assembly of teraryls based on Suzuki cross-coupling reactions of ready-made building blocks containing aryl rings with amino acid residues R^1 to R^2 (Scheme 8). This strategy consists of a retrosynthetic division of the teraryls into a core subunit consisting of a phenyl ring and two peripheral pyridine subunits. The general idea was to generate a library of building blocks containing all 20 natural amino acid residues, except proline. As the two peripheral pyridine subunits only differ in their substituted amino acid moiety, they can be provided from the same library of pyridine building blocks.[5,6]

It was also possible to perform the palladium-catalyzed cross-coupling as an *in situ* two-step synthesis (Scheme 8). For this method after the first cross-coupling step the reaction mixture was filtered through silica, concentrated in vacuum and then the second base was added together with the second building block and fresh Pd-catalyst. The switch of base ensured a high regioselectivity.[5,6]



Scheme 8: General procedure of teraryl assembly via Suzuki cross-coupling reactions.[5,6]

In Figure 6 the target molecules of this work can be seen. In order to fill the library of the outer pyridine subunits the synthesis of the displayed structures remained as scientific task. These pyridine building blocks contain unpolar (valine), polar (cysteine) and aromatic (tyrosine, tryptophane) amino acid moieties.

Both Sebastian Grimm and Martin Peters have already established a set of standard reactions for substitutions and functional group transformations that would conveniently allow to solve many problems of this work.[6,42]

Another difficulty of this work was the purification of the final products since pinacol boronic esters cannot be purified via column chromatography other purification methods like Kugelrohr-distillation had to be investigated.

The last task was to introduce suitable protecting groups which should be stable under most reaction conditions and allow easy purification.

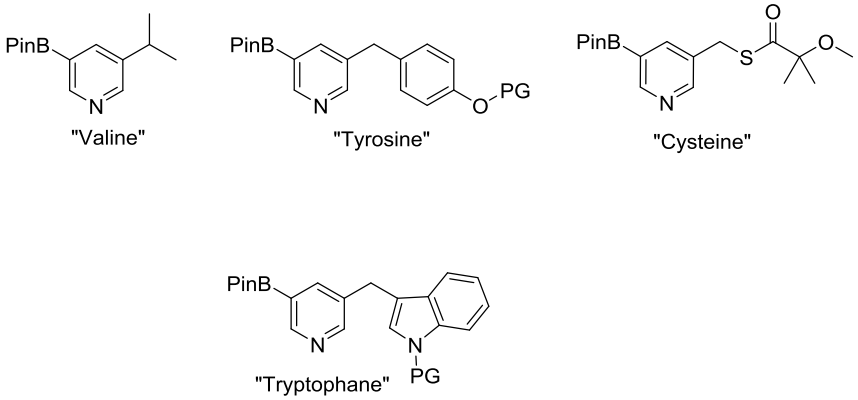
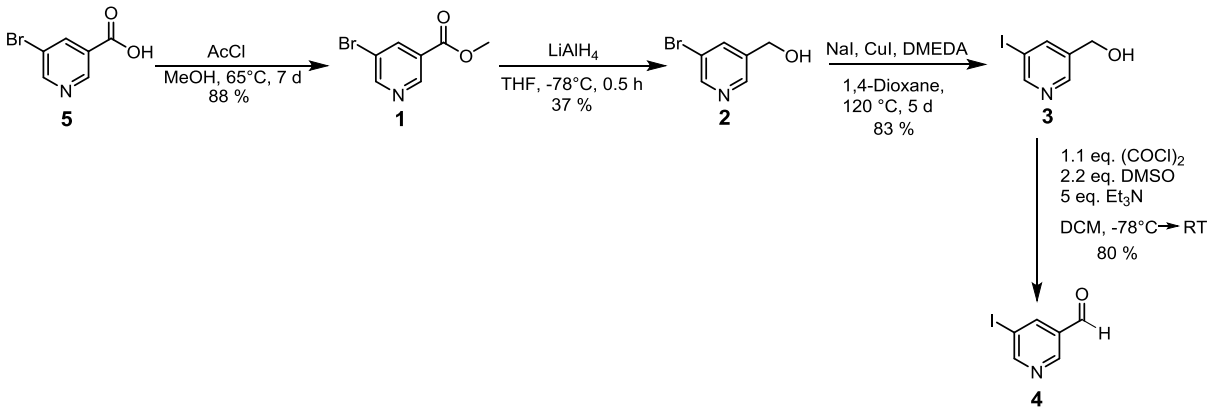


Figure 6: Target molecules of this work.

4 Results and Discussion

4.1 General Synthetic Pathway



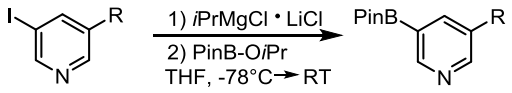
Scheme 9: General strategy for the synthesis of 5-iodonicotinaldehyde (**4**).

The synthetic route that played a major role for this work is displayed in Scheme 9. The molecules, which are produced during this reaction sequence, are important intermediates for the synthesis of the desired building blocks. This synthetic strategy was mainly developed and optimized by Sebastian Grimm,[42] who previously worked on this project. One of its main advantages was the introduction of 5-bromonicotinic acid (**5**) as starting material, which is readily available and inexpensive. Therefore it is a suitable substrate for the synthesis of 3,5-substituted pyridines. Through esterification, followed by reduction and oxidation reactions it could be easily converted into the corresponding alcohol **3** and aldehyde **4**. The fact that aldehydes show high reactivity towards nucleophiles such as Grignard reagents made the 5-iodonicotinaldehyde (**4**) an especially attractive intermediate as it was used for the synthesis of the tyrosine derivative and opened also a possible synthetic pathway for the tryptophane derivative.

The first reaction step, which was a Fischer-type esterification[43] produced the methyl 5-bromonicotinate (**1**) in high yield and purity, allowed the use of the product for the following reactions without further purification.

Afterwards a reduction was performed by using lithium aluminium hydride in order to generate (5-bromopyridin-3-yl)methanol (**2**).[43] Unfortunately, the desired product could only be obtained in a yield of 37 %, unlike when it was performed by Sebastian Grimm, who was able to produce the crude product (**2**) in a yield of 94 %.[42] The reason for this behaviour might be an operator error or problems that occurred due to the upscaling, since the reaction was performed on a 18.00 g (83.32 mmol) scale, like inefficient stirring. Nevertheless, the produced amount of the purified product **2** was sufficient to perform the following reaction steps and to synthesize the desired building blocks.

The third reaction of the synthetic route was a substitution of the bromine in 5-position of the pyridine ring with an iodine by performing a Buchwald-variation of the Finkelstein reaction.[6,44] According to Sebastian Grimm the reaction was performed with dry chemicals under inert conditions to achieve full conversion with a yield of 83 %.[42] Furthermore the product could be used without any purification for the following oxidation to the aldehyde **4**. Even though the substitution worked well, the reaction was heated for 5 d to reach full conversion to the (5-iodopyridin-3-yl)methanol (**3**). Moreover repeated addition of 0.1 eq of the catalysts CuI and DMEDA were necessary in order to complete the reaction. The reason for this behaviour might be due to the oxidative sensitivity of the Cu(I)-compound or a general sensitivity of the reaction towards air and water.



Scheme 10: Introduction of a pinacol boronic ester function by using iPrMgCl·LiCl.

The substitution of the bromine with iodine at the pyridine ring **2** was an important reaction. As in later synthetic steps the final introduction of the pinacol boronic ester function at the pyridine ring was facilitated via an iodine-magnesium exchange using the reagent iPrMgCl·LiCl, which was developed by Knochel *et al*. (Scheme 10).[45] Knochel and his co-workers performed such reactions also with bromo-substituted pyridines.[46] However, during this work it was observed that the reaction with iodopyridines worked faster and could be performed at lower temperatures as iodine is a more potent leaving group. The procedure for these particular reactions was developed by Martin Peters.[6]

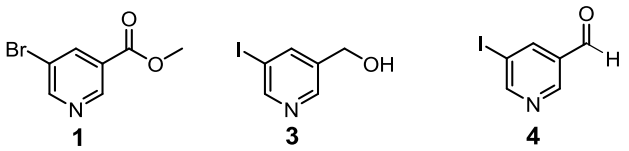
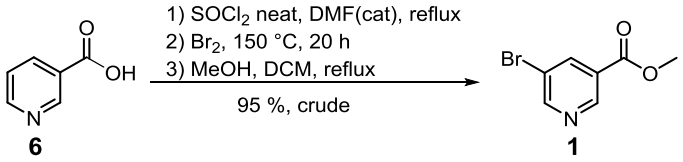


Figure 7: Main intermediates for the synthesis of the desired building blocks.

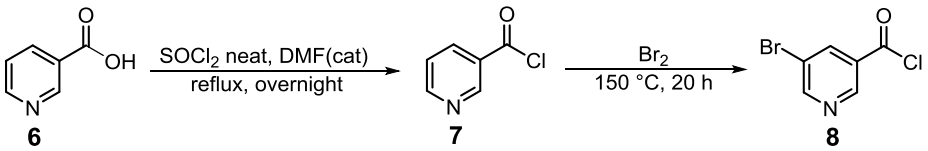
The Swern oxidation[43,47] was the final reaction of the reactions described in Scheme 9. This reaction gave the 5-iodonicotinaldehyde (**4**) in high yield of 80 % and could be easily purified via flash column chromatography. Not only the aldehyde **4** but also the methyl 5-bromonicotinate (**1**) and the (5-iodopyridin-3-yl)methanol (**3**) acted as a starting material for the synthesis of the desired building blocks as it is described in the following sections (Figure 7).

4.1.1 Alternative synthetic strategies



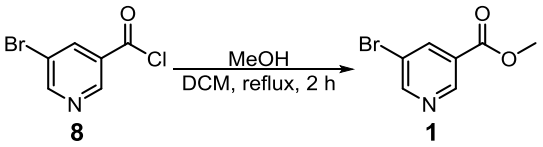
Scheme 11: Alternative synthetic route for the synthesis of methyl 5-bromonicotinate (**1**).

An interesting alternative for the already existing synthetic strategy was the introduction of nicotinic acid as a starting material (Scheme 11). Nicotinic acid (**6**) is also known as niacin or vitamin B_3 and widely used in food industry, in agriculture, in medicine and cosmetics. It is produced on a scale of several thousand tons per year.[48,49] Therefore it is an ideal starting material in terms of cost efficiency and availability. Moreover the reagents which were used for the chemical reactions displayed in Scheme 11 are also inexpensive. The reactions were performed following the work of Gaudino and co-workers.[50]



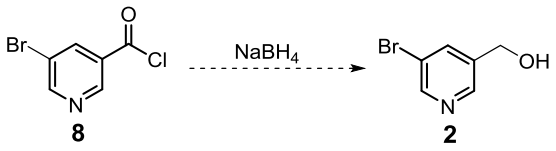
Scheme 12: Synthesis of 5-bromonicotinoyl chloride (**2**) from nicotinic acid (**6**).

At first the nicotinic acid (**6**) was converted into the corresponding acid chloride by using thionyl chloride and a catalytic amount of DMF (Scheme 12). Afterwards the resulting crude product **7** was treated with bromine for a period of 20 h at 150 °C.



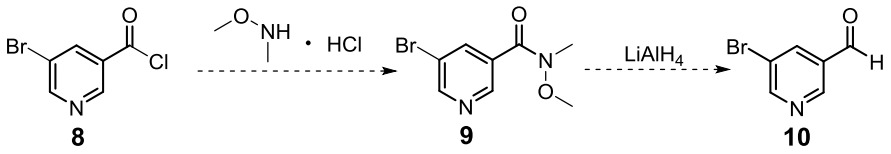
Scheme 13: Conversion of 5-bromonicotinoyl chloride (**8**) with methanol to methyl 5-bromonicotinate (**1**).

After quenching of the 5-bromonicotinoyl chloride (**8**) with methanol and DCM as solvent the desired methyl ester **1** was obtained in 95 % yield and a purity of 94 % purity (HPLC) over 3 steps (Scheme 13).



Scheme 14: Reduction of 5-bromonicotinoyl chloride (**8**) by $NaBH_4$ as reducing agent.

As a result it could be shown that the methyl 5-bromonicotinate (**1**) could be also generated by using this alternative synthetic route in good yield and purity. Moreover the acid chloride **8** seems to be an interesting reactive intermediate, which could be used to generate directly the alcohol **2** through an appropriate reducing agent such as $NaBH_4$ (Scheme 14).[51]

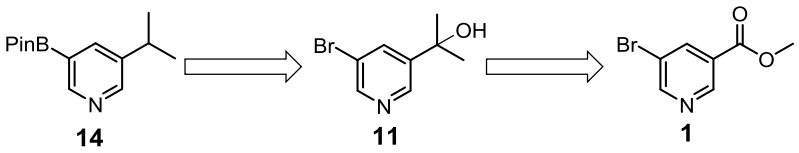


Scheme 15: Formation of 5-bromonicotinaldehyde (**10**) via Weinreb amide **9**.

Another shortcut for the general synthetic route of Scheme 9 would be the conversion of the acid chloride **8** into a Weinreb amide **9** which can be reduced into an aldehyde **10** by $LiAlH_4$ (Scheme 15).[52,53]

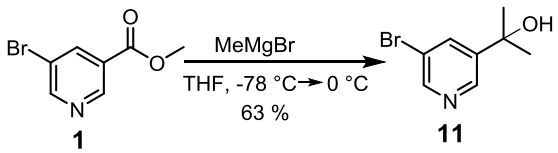
Although these two alternative synthetic strategies were not tested during this work they seem to be a promising approach for future studies on this project.

4.2 Valine Derivative



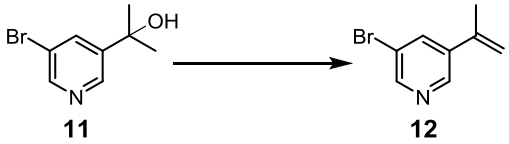
Scheme 16: Retrosynthetic analysis of the valine derivative **14** starting from methyl 5-bromonicotinate (**1**).

According to the retrosynthetic analysis (Scheme 16) it was decided to produce the valine derivative **14** from methyl 5-bromonicotinate (**1**) via 2-(5-bromopyridin-3-yl)propan-2-ol (**11**). In the following reactions the synthesized compound **11** would then be transformed into the desired product **14** by elimination, hydration and substitution reactions.



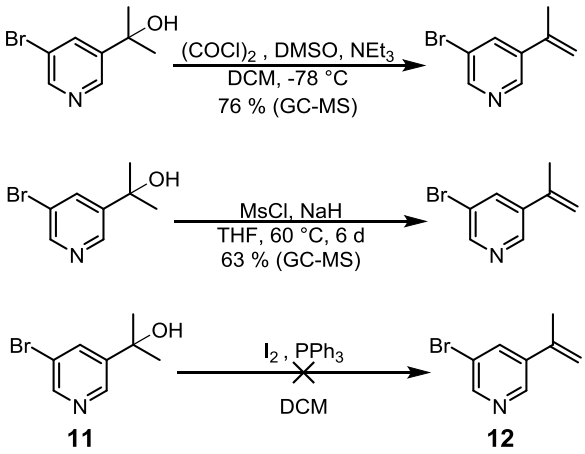
Scheme 17: Synthesis of 2-(5-bromopyridin-3-yl)propan-2-ol (**11**) by methylmagnesium bromide.

The first synthetic step for the preparation of the valine derivative **14** was the Grignard reaction of methyl 5-bromonicotinate (**1**) with a 3.0 M solution of methylmagnesium bromide (Grignard reagent) in diethyl ether to yield 2-(5-bromopyridin-3-yl)propan-2-ol (**11**) (Scheme 17). The temperature was kept at -78 °C in order to prevent any bromine-magnesium exchange. The Grignard reagent was purchased and freshly opened before it was applied to the reaction mixture. The product was obtained in good yield and could be easily purified via flash column chromatography. The synthesis was performed according to the work of Sebastian Grimm.[42]



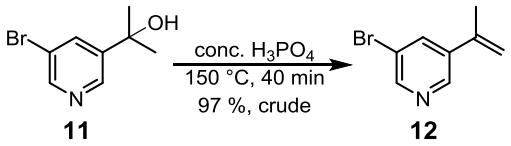
Scheme 18: Synthesis of 3-bromo-5-(prop-1-en-2-yl)pyridine (**12**) via an elimination reaction.

The next reaction step was the elimination of 2-(5-bromopyridin-3-yl)propan-2-ol (**11**) which was the most challenging reaction of this synthetic route (Scheme 18). Many different attempts in order to obtain the desired 3-bromo-5-(prop-1-en-2-yl)pyridine (**12**) were carried out.



Scheme 19: Tested methods for the elimination of the tertiary alcohol **11**.

In Scheme 19 the attempted elimination methods are displayed. Despite being widely practiced for other substrates,[54,55] none of these methods could lead to satisfying conversions of the tertiary alcohol **11**. In fact for the reaction of the starting material **11** with iodine and PPh_3[56] no product could be observed. Therefore the search for an appropriate method that could produce the product in good yields continued.



Scheme 20: Elimination reaction of 2-(5-bromopyridin-3-yl)propan-2-ol (**11**) under acidic conditions.

It was finally decided to apply a very common method[57] using concentrated H_3PO_4 (85 % w/w) at 150 °C for the elimination of the 2-(5-bromopyridin-3-yl)propan-2-ol (**11**) (Scheme 20). As the reaction was carried out under rather harsh conditions it was necessary to optimize these conditions (reaction time) in order to maintain a good overall yield for the synthetic route as a whole.

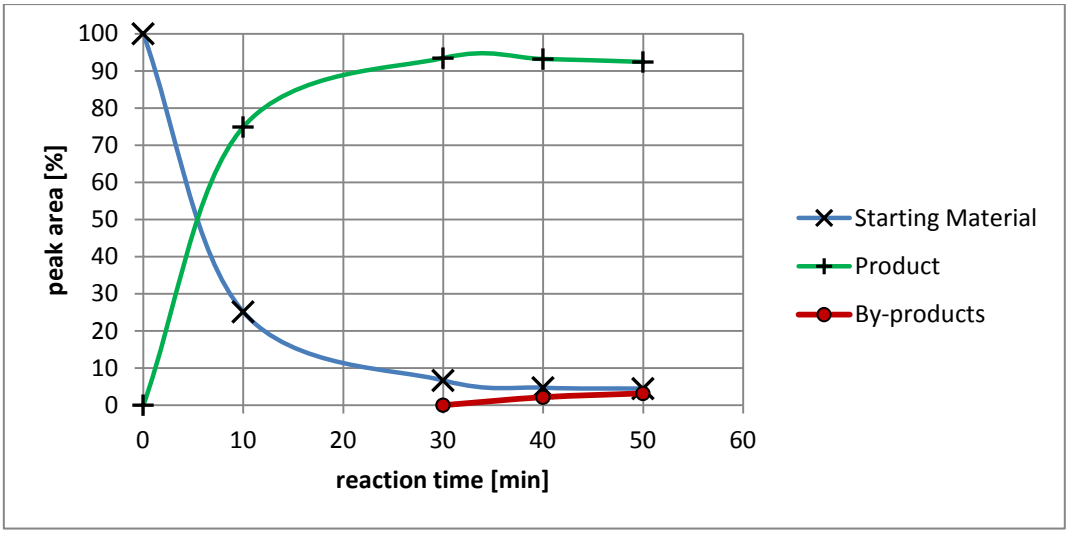
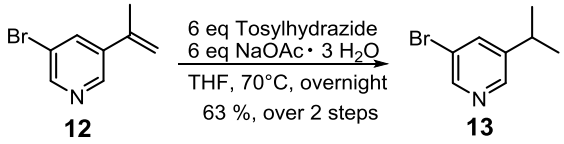


Figure 8: Measurement of the conversion of starting material **11** and formation of products by HPLC as a function of the reaction time.

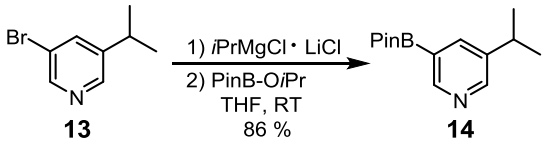
The results of the kinetic investigations of the elimination of 2-(5-bromopyridin-3-yl)propan-2-ol by concentrated H_3PO_4 are shown in Figure 8. The measurements were performed by HPLC. As it is shown in the graph between 30 min and 40 min the amounts of product **12** and starting material **11** (conversion > 90 %) did not undergo significant changes anymore. Also the formation of by-products started within this time interval. Therefore it was decided to perform the elimination at 150 °C and a reaction time of 40 min so that the conversion of the starting material was at a maximum while the amount of by-products was kept at a minimum.



Scheme 21: Reduction of the C-C double bond via diimide reaction.

The next reaction was the reduction of the C-C double bond by a diimide reduction (Scheme 21). Another possibility would have been the catalytic reduction of 3-bromo-5-(prop-1-en-2-yl)pyridine (**12**) using Pd/C as catalyst. However, the main problem of this reaction was the complete removal of the bromine from the pyridine ring under these conditions. Therefore the reduction with diimide was a more adequate solution to this synthetic problem, since diimide is highly selective for carbon-carbon double bonds. The hydrogen atoms are transferred in *syn* fashion on both carbon atoms of the double bond in a concerted mechanism.[58] As diimide is highly reactive and prone to disproportion and oxidation it has to be *in situ* generated and often the required reagents are applied in excess.[59,60] There are several known methods for the *in situ* production of diimide.[61,62] For this work the diimide was generated by treating *p*-toluenesulfonyl hydrazide with sodium acetate as shown in Scheme 21.[63]

Both the elimination reaction of 2-(5-bromopyridin-3-yl)propan-2-ol (**11**) after the optimization and the following reduction of 3-bromo-5-(prop-1-en-2-yl)pyridine (**12**) could be carried out without any further problems. The formed 3-bromo-5-isopropylpyridine (**13**) was the final intermediate for the synthesis of the valine derivative. After purification the product **13** could be obtained in 63 % over two steps.



Scheme 22: Final step of the synthetic route for the valine derivative **14**.

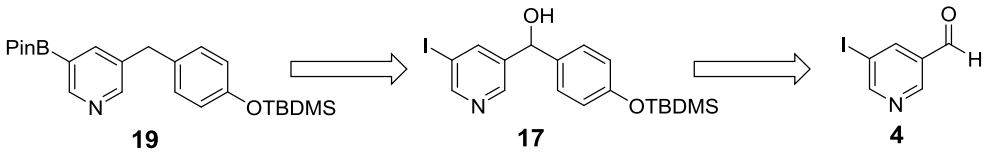
The final step for the synthesis of the valine derivative **14** from 3-bromo-5-isopropylpyridine (**13**) (Scheme 22) was carried out by a bromine-magnesium exchange as it was described by Knochel *et al.*[45, 46] However, the reaction had to be performed at RT, otherwise the bromine-metal exchange could not be accomplished. Since the molecule had no functional groups that would be sensitive towards Grignard reagents the reaction conditions were acceptable. As other building blocks do contain such groups it was necessary to use pyridine rings containing iodine instead of bromine. Since iodine is a better leaving group which allows the halogen-metal exchange proceeds even at -78°C.[6]

Another problem that had to be overcome was the purification of the crude product **14** of this Grignard reaction (Scheme 22). As column chromatography does not lead to useful results due to instability of boronic esters on silica gel[6] and no suitable conditions for recrystallisation were found, the only option left was to purify the product through distillation or sublimation. Since only small amounts of product was produced and high vacuum was needed the best choice was to use Kugelrohr-distillation or Kugelrohr-sublimation. The vacuum was generated by using an oil pump.
Although this method works quite well several conditions must be met in order to perform a successful purification:

- High vacuum should be applied (< 0.1 mbar).
- The product must be stable at high temperature.
- The molecular mass should not exceed 490 g/mol. The ability of the molecule to be sublimated under these conditions is not just defined by the molecular mass, though.

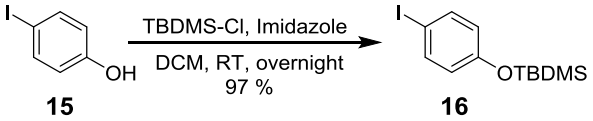
These requirements posed no problem to the synthesis of the valine derivative **14**. However, the synthetic strategy for the other building blocks such as the tyrosine and cysteine derivative needed some additional considerations. Nevertheless, after the reaction (Scheme 22) was done the crude product **14** could be easily purified by Kugelrohr-distillation. All in all the desired 3-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**14**) could be obtained in 30 % yield over 5 steps.

4.3 Tyrosine Derivative



Scheme 23: Retrosynthetic analysis of the tyrosine derivative **19** starting from 5-iodonicotinaldehyde (**4**).

From a retrosynthetic point of view the 5-iodonicotinaldehyde (**4**) seemed to be an ideal starting material to generate the desired tyrosine derivative **19**. The aryl side-chain could be introduced via Grignard reaction to yield the benzyl alcohol **17**, which was converted into the target molecule **19** by removing the hydroxyl group followed by a substitution of the iodine with pinacol boronic ester (Scheme 23).

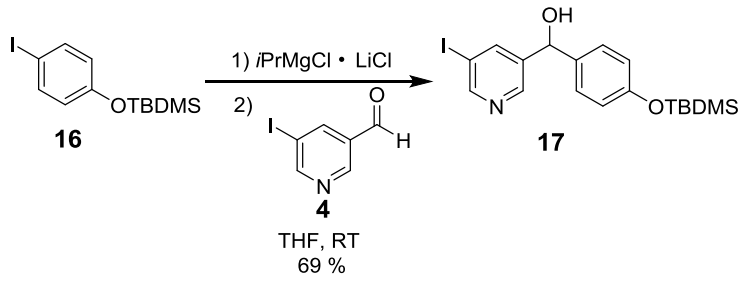


Scheme 24: Protection of the OH-group of *p*-iodophenol (**15**) with TBDMS.

Previously to the reactions of the synthetic approach (Scheme 23) TBDMS-protected *p*-iodophenol **16** was prepared by treating a solution of *p*-iodophenol (**15**) in DCM with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) in presence of a base (Scheme 24).[64] The 3-*tert*-butyl(4-iodophenoxy) dimethylsilane (**16**) could be isolated as pure product in 97 % yield and was used without any further purification.

The protection of the OH-group of the *p*-iodophenol (**15**) was necessary in order to prevent a protonation of the Grignard reagents which were used in the following synthetic steps. There were several reasons why this particular protective group was chosen. Firstly, in the synthetic concepts for the already synthesized building blocks TBDPS-protecting groups play an important role. Secondly, these silyl ethers can be easily introduced and cleaved selectively with TBAF under mild conditions. Moreover they are stable under a wide range of different reaction conditions.[65] So it was perfectly reasonable to choose this class of protective groups also for the synthetic routes of this work.

However, the already mentioned TBDPS-protective group would be disadvantageous for the final step of the synthetic route for the tyrosine derivative as the purification via Kugelrohr-distillation cannot be performed with molecules possessing a high molecular mass. Therefore it was decided to use the lighter and less sterically hindered TBDMS-protective group, which would be more suitable for Kugelrohr-distillation. Although in contrast to the TBDPS-group this protective group is more susceptible to strong acids and bases, which could have become a problem for the later performed dehydroxylation reaction by TFA and triethylsilane (Scheme 26).[65]

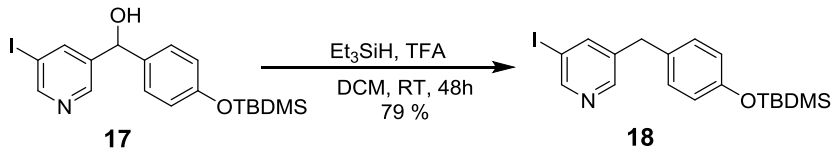


Scheme 25: Synthesis of (4-((*tert*-butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (**16**) via Grignard reaction.

The first step of the synthesis of the tyrosine derivative **19** consisted of a Knochel-Grignard reaction[66] (Scheme 25). The iodine-magnesium exchange at the 3-*tert*-butyl(4-iodophenoxy) dimethylsilane (**16**) was performed at room temperature since the molecule did not contain any functional groups that would be affected by Grignard reagents. This high temperature was necessary as aromatic iodides containing electron-donating groups do not undergo an iodine-magnesium exchange at low temperatures.[66]

Other attempts to perform a halogen-metal exchange via *t*BuLi or ethylmagnesium bromide instead of iPrMgCl·LiCl did not lead to satisfying results. The use of *t*BuLi produced a mixture of many different compounds with only traces of product. The reaction with ethylmagnesium bromide in diethyl ether without LiCl proved to be rather interesting as no product could be observed, even though it was also a Grignard reagent. This showed the great efficiency of Knochel *et al.*'s approach.[66]

After the addition of the 5-iodonicotinaldehyde (**4**) the reaction mixture was worked-up and pure (4-((*tert*-butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (**17**) was obtained after column chromatography in 69 % yield.

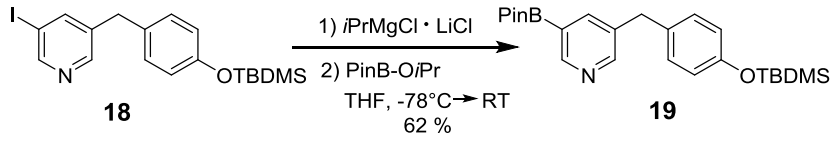


Scheme 26: Removal of the OH-group of compound **17** by triethylsilane and TFA.

As mentioned before the TBDMS-group is less stable under strong acidic or basic conditions,[65] which could have become a problem for the synthesis of the tyrosine derivative. As a consequence a preliminary experiment was carried out with TBDMS-protected phenol, which was treated in a similar fashion as the (4-((*tert*-butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (**17**) in Scheme 26 with dry solvent under inert conditions. As a result even after 3 d no phenol could be observed via GC-MS, which leads to the conclusion that this protective group strategy may prove to be useful.

For the actual dehydroxylation reaction or hydrogenation reaction using triethylsilane and TFA under inert conditions was used, because it is a well known and very useful method for the removal of benzylic OH-groups. It seems the mechanism of this reaction proceeds over a carbonium ion which is generated in a strong acid, followed by a hydride-transfer from the triethylsilane.[67,68]

All in all the removal of the OH-group[69] at the actual starting material **17** (Scheme 26) worked quite well and gave 3-(4-((*tert*-butyldimethylsilyl)oxy)benzyl)-5-iodopyridine (**18**) in 79 % yield.



Scheme 27: Preparation of the tyrosine derivative **19** via Knochel Grignard reaction.

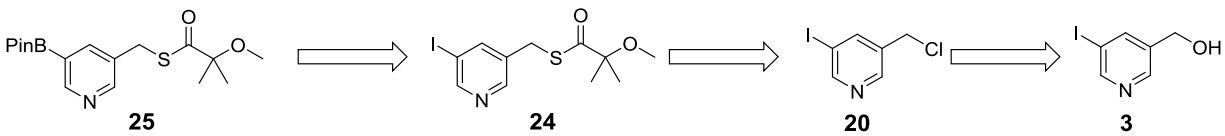
In the final step of the synthesis of the tyrosine derivative **19** the pinacol boronic ester was introduced into the molecule via a Knochel-Grignard reaction according to the procedure of Sebastian Grimm and Martin Peters (Scheme 27).[6,42]

Unlike the previous bromine-magnesium exchange the reaction of the Grignard reagent with the iodinated compound **18** went smoothly at low temperatures. The desired 3-(4-((*tert*-butyldimethylsilyl)oxy)benzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridine (**19**) could be successfully purified by Kugelrohr-sublimation and obtained in an overall yield of 7.3 % over 7 steps.

4.4 Cysteine Derivative

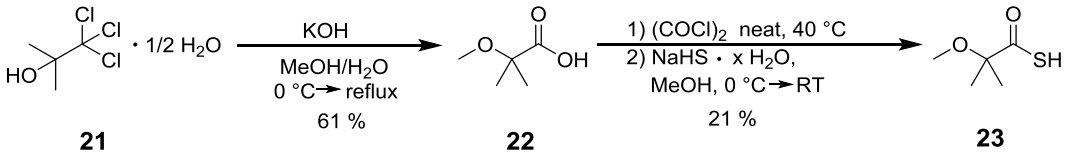
The third building block, which was synthesized for this work, was the cysteine derivative **25**. A challenge for the later application of this building block in Suzuki-coupling reactions[6] was the thiol group which the molecule conatins. Even though palladium-catalyzed cross-coupling reactions possess a wide tolerance against functional groups thiol groups exhibit a strong affinity for palladium and other late transition metals, which would cause a poisoning of the Pd-catalyst. Different protective groups for thiols, such as thioethers or thioesters can be used for Suzuki-couplings. As thioethers afford rather harsh cleaving conditions a more suitable approach would be thioesters since they can be both easily introduced into the molecule and cleaved by treating with aqueous base.[70]

Terfort *et al.*[70] tested a number of different acyl groups for the protection of thiols under Suzuki conditions and came to the conclusion that a 2-methoxyisobutyryl group led to the highest yields for the tested reactions. Terfort and co-workers also reported that not hydrolysis under basic conditions but a side-reaction of the thioester with the palladium might cause low yields.[70] As a result the cysteine derivative **25** was designed to contain this protective group forming a thioester.



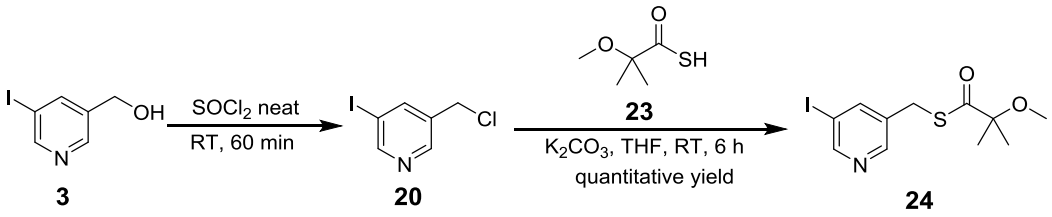
Scheme 28: Retrosynthetic considerations for the synthesis of the cysteine derivative **25**.

In Scheme 28 the results of the retrosynthetic analysis of the cysteine derivative **25** can be seen. The starting point of this synthetic concept was the (5-iodopyridin-3-yl)methanol (**3**), which was converted into 3-(chloromethyl)-5-iodopyridine (**20**) by thionyl chloride. After this chlorination the chlorine at the side chain was substituted with a thiocarboxylic acid in order to form the thioester **24**. It was then planned to exchange the iodine with the pinacol boronic ester function via a Knochel-Grignard reaction to obtain the cysteine derivative **25**. However, as it is later explained due to purification problems of the final product **25** the strategy was directed into an interesting new direction, which made it possible to explore the recently developed field of MIDA boronates.[36]



Scheme 29: Synthesis of 2-methoxy-2-methylpropanethioic *S*-acid (**23**) as protective group for the cysteine derivative **25**.

Previous to the synthetic steps described in Scheme 28 the production of 2-methoxy-2-methylpropanethioic *S*-acid (**23**) was necessary in order to attach the 2-methoxyisobutyryl-protective group to the cysteine derivative **25**. The synthesis of the thiocarboxylic acid **23** was carried out in three steps. In the first step the 1,1,1-trichloro-2-methyl-2-propanol hemihydrates (**21**), which is inexpensive and readily available, was converted into 2-methoxy-2-methylpropanoic acid (**22**) by treating with KOH in aqueous methanol. The synthesis was well described in literature and gave acceptable yields.[79,80] Afterwards the 2-methoxy-2-methylpropanoic acid (**22**) was treated with neat oxalyl chloride[71,79] to obtain the corresponding acid chloride, which was immediately used to generate the desired thiocarboxylic acid **23** (Scheme 29). The poor yield of only 21 % was probably due to the fact that the acid chloride was added to a solution of NaHS in methanol during the reaction. This might have caused excessive formation of the methyl ester of the 2-methoxy-2-methylpropanoic acid (**22**) as by-product.

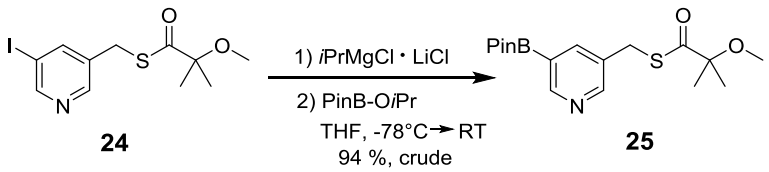


Scheme 30: Production of the precursor **24** of the cysteine derivative **25**.

According to the retrosynthetic analysis in Scheme 28 the *S*-((5-iodopyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**24**) was synthesized by using 3-(chloromethyl)-5-iodopyridine (**20**) as starting material. Before this work started compound **20** has already been produced in large quantity with 84 % yield by Sebastian Grimm[42] following the procedure of Martin Peters,[6] so that it was not necessary to make a new batch of this substance.

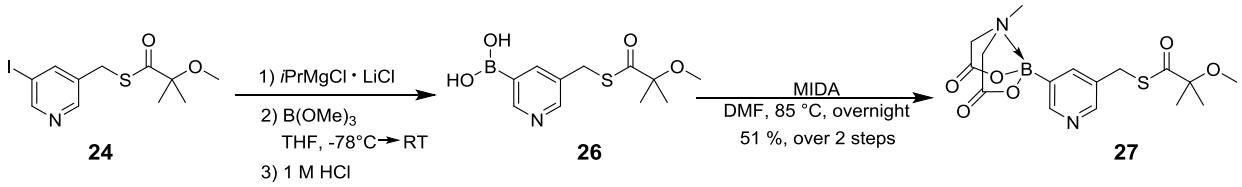
In the following reaction the 3-(chloromethyl)-5-iodopyridine (**20**) was treated with the previously synthesized 2-methoxy-2-methylpropanethioic *S*-acid (**23**) in the presence of K_2CO_3 in THF (Scheme 30). This reaction worked well and gave *S*-((5-iodopyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**24**) in quantitative yield.

In an later attempt the stability of the thioester function of compound **24** under weak basic conditions was tested by treating *S*-((5-iodopyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**24**) with a mixture of methanol and saturated $NaHCO_3$ solution for 4.5 h.[36] Analysis via HPLC showed that 10 % of the substance **24** lost their attached 2-methoxyisobutyryl-protective group by hydrolysis, while the other 90 % remained untouched. The results of this experiment were important for the later application of MIDA boronates as the MIDA group can be removed under these conditions.



Scheme 31: Synthesis of the cysteine derivative **25** via Knochel-Grignard reaction.

With the already synthesized precursor **24** of the cysteine derivative the final reaction step could be carried out. In this step the pinacol boronic ester was introduced into the molecule via a Knochel-Grignard reaction according to the procedure of Sebastian Grimm and Martin Peters (Scheme 31).[6,42] Although the crude product could be isolated in good yield and 90 % purity (HPLC), the product **25** could not be purified via Kugelrohr-distillation. Unfortunately, the molecule becomes unstable at high temperatures, which caused decomposition of the substance during distillation. Given the difficulties of other purification methods for pinacol boronic esters it was decided to use an alternative method to generate a different building block design.



Scheme 32: Synthesis of a MIDA boronate as final cysteine derivative **27**.

The turning point of the synthetic route for the cysteine derivative was the decision to change design of the building block structure into a MIDA boronate as these compounds are interesting new molecules, which have been intensively studied by Burke *et al.*[36]

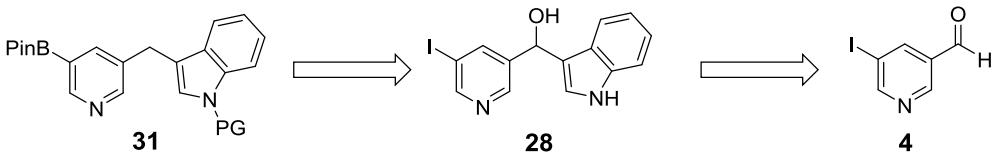
The synthesis of the altered cysteine derivative **27** proceeded in 2 steps (Scheme 32). The first step started with an iodine-magnesium exchange with iPrMgCl·LiCl at -78 °C. After the exchange was completed trimethyl borate was added and the reaction mixture was quenched with aqueous HCl, which caused the rapid hydrolysis of the just formed methyl boronic acid ester into the corresponding boronic acid **26**.[72]

The product was isolated by extraction and immediately treated with MIDA (methyliminodiacetic acid) in a DMF solution following the procedures of Grob *et al.*[73] In contrast to the synthetic protocols of Burke *et al.*,[35] which use DMSO as a reaction cosolvent and required azeotropic removal of water by Dean-Stark distillation, this reaction procedure led to a more convenient access to the desired cysteine derivative **27**.[73] For the reaction only dry DMF was required, which could be easier removed than DMSO. Another advantage of MIDA boronates is their high stability, which allows them to be purified via column chromatography.

As a result the desired *S*-((5-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)pyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**27**) could be obtained in 51 % yield and an overall yield of 12 % over 6 steps. However, even after purification via column chromatography traces of DMF remained within the product. For following repetitions of this synthesis further purification via recrystallisation from acetonitrile as it was described by Burke *et al.*[37] is recommended.

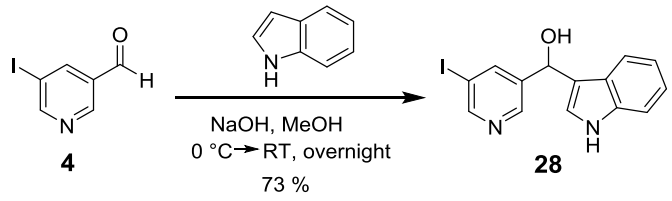
Last but not least it was necessary to consider the strategy for the removal of the MIDA boronates as our synthetic approach for teraryls is based on boronic acids or pinacol boronic esters.[6] The main problem was that both the MIDA group and the thioester protective group can be removed under basic conditions. However, MIDA can be removed even in solvents with low basicity like mixtures from methanol and saturated $NaHCO_3$ solution.[36] Whereas it could be shown that the 2-methoxyisobutyryl-protective group displayed good stability under these conditions (see above). These results confirmed the general applicability of the MIDA boronate for this building block.

4.5 Tryptophane Derivative



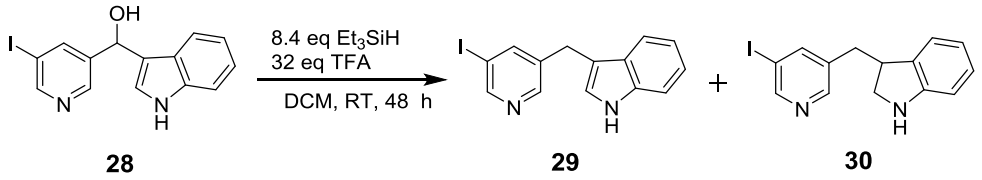
Scheme 33: Retrosynthetic analysis of the tryptophane derivative (**31**).

In Scheme 33 the results of the retrosynthetic analysis of the tryptophane derivative **30** are displayed. It was decided to use 5-iodonicotinaldehyde (**4**) as a starting material since its aldehyde function can be readily attacked by suitable nucleophiles such as indole under basic conditions.[74] After the removal of the OH-group from the formed benzylic alcohol **28** it was planned to attach a suitable protective group (PG). In the final step of this synthetic route the pinacol boronic ester would be introduced into the molecule via Knochel-Grignard reaction to obtain the desired tryptophane derivative **31**.



Scheme 34: Synthesis of (1*H*-indol-3-yl)(5-iodopyridin-3-yl)methanol (**28**) via nucleophilic addition of indole.

In the first step of the synthetic route for the tryptophane derivative (**31**) the 5-iodonicotinaldehyde (**4**) was treated with indole in a basic solution of NaOH and methanol (Scheme 34).[74,75] The reaction went well and the pure product **28** could be easily isolated by filtration of the reaction mixture in 73 % yield.



Scheme 35: Removal of the OH-group of the benzyl alcohol **28**.

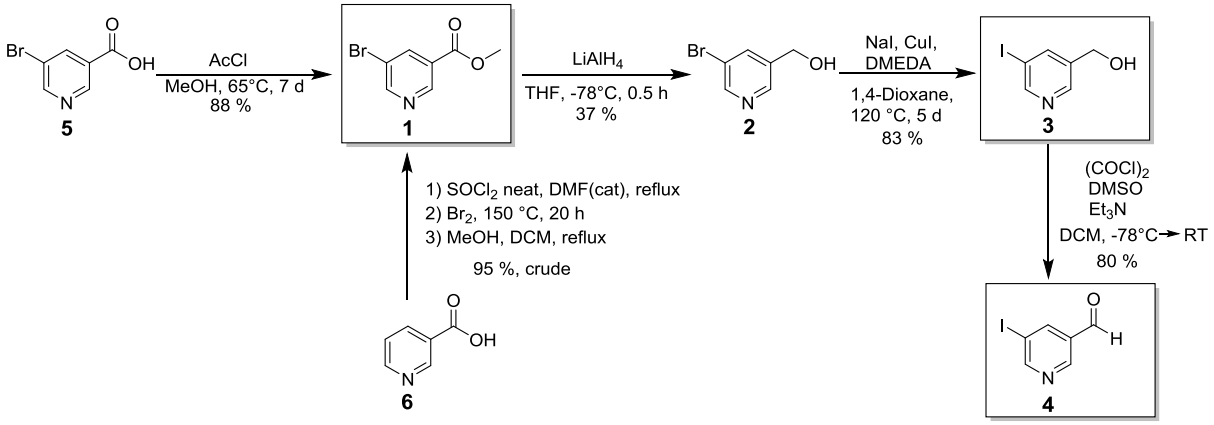
In the following step of the synthesis it was attempted to remove the OH-group by triethylsilane and TFA (Scheme 35). This reaction was performed in the same way as it has already been carried out successfully at the synthesis of the tyrosine derivative.[69] Unfortunately, a mixture of the desired product **29** (14 %, HPLC) and an indoline derivative **30** (86 %, HPLC) was obtained. The reason for the reduction of not only the benzylic C-Atom but also of the C-C double bond of the indole might be due to the prolonged reaction time. As literature suggests the removal of the OH-group of similar structures only takes a few hours.[74,76,77] Therefore this reaction (Scheme 35) should be repeated with a shorter period of reaction time and only a slight excess of triethylsilane (1.1 eq) in order to optimize the yield of the desired product **29** and minimize the formation of by-products.

Another possibility would be the re-oxidation of the indoline derivative **30** in order to give the desired compound **29**. This re-oxidation reaction can be easily carried out with many different reagents like MnO_2, DDQ or trichloroisocyanuric acid with DBU.[78]

Unfortunately, due to time limitation this optimization and the other synthetic steps in order to obtain the desired tryptophane derivative **31** could not be performed during this work anymore. It will be a task of future works on this project to complete the synthesis of the tryptophane derivative **31** and the remaining building blocks.

5 Summary and Outlook

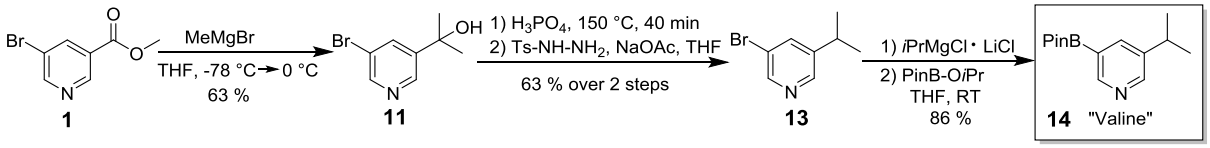
The aim of this work was the synthesis of the pyridine building blocks containing the amino acid residues of valine, tyrosine, cysteine and tryptophane in order to fill the library for the production of teraryls. Once useful synthetic routes for all teraryl building blocks are established it will be possible to generate all 5670 theoretical permutations of teraryls containing all 20 amino acid moieties and test their biological function as α-helix mimetics.



Scheme 36: General reaction scheme for the synthesis of precursors for the desired pyridine building blocks.

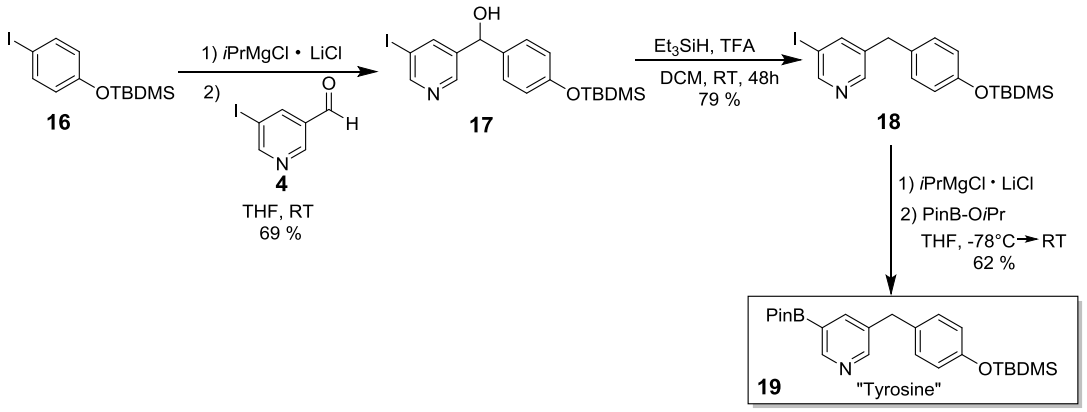
In Scheme 36 the general synthetic pathway for the synthesis of important intermediates for the following formation of the pyridine building blocks is displayed. This synthetic strategy was based on the accomplishments of Sebastian Grimm who previously worked on this project.[42] In this route 5-bromonicotinic acid (**5**) acted as starting material from which all other important compounds like methyl-5-bromonicotinate (**1**), (5-iodopyridin-3-yl)methanol (**3**) and 5-iodonicotinaldehyde (**4**) are derived. The synthetic steps of this scheme worked well and the products could be obtained in good yield. The only exception was the reduction of methyl-5-bromonicotinaldehyde (**1**) into the corresponding alcohol **2**, which gave probably due to operative errors only 37 % in opposition to the yield Sebastian Grimm obtained for this reaction (94 %, crude).[42]

For this work the use of nicotinic acid as a possible starting material was investigated since it is cheap and readily available. As a result it could be shown that nicotinic acid can be utilized for the synthesis of methyl-5-bromonicotinate (**1**) and consequently acts as a starting point for the synthesis of all building blocks.



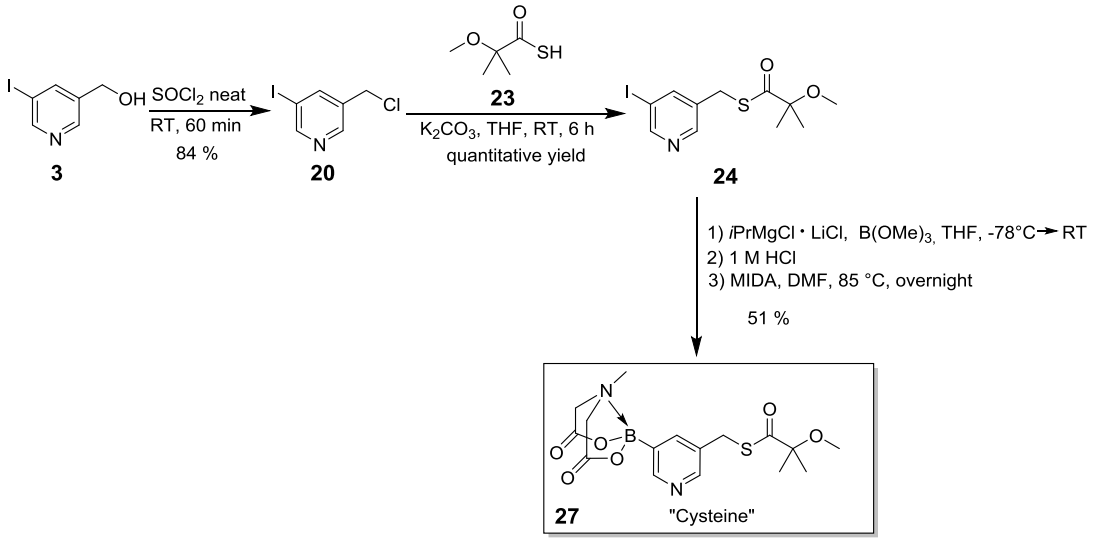
Scheme 37: Synthesis of the valine derivative **14**.

The first building block that was successfully synthesized was the valine derivative **14**. The problem of this reaction sequence was to find the optimal conditions for the elimination of the tertiary alcohol **11**. After these conditions were determined the synthesis of the valine derivative could be carried out in good yields (Scheme 37).



Scheme 38: Summary of the reactions to obtain the tyrosine derivative **19**.

At the synthesis of the tyrosine derivative **19** it could be observed that once TBDMS was used as a protective group for the OH-function the desired product **19** could be obtained without any problems (Scheme 38). It seems that TBDMS was the right choice for this synthetic strategy as it was stable under the given conditions and light enough to allow purification via Kugelrohr-distillation.



Scheme 39: The cysteine derivative **27** was obtained as a MIDA boronate.

The third and last building block that could be finished during this work was the cysteine derivative **27** (Scheme 39). The most challenging task of this synthesis was to obtain a building block, which would be stable for under purification conditions. The cysteine derivative containing the pinacole boronic ester **25** was unstable under high temperatures as they would occur during Kugelrohr-distillation. Therefore it was decided to change the current concept for the design of the desired building blocks. Instead of a pinacol boronic ester the pyridine ring of the final product **27** had a MIDA boronate as a substituent. This new approach allowed the purification or the cysteine derivative **27** via column chromatography and opened the way for new strategies for the yet to be synthesized building blocks (Figure 10).

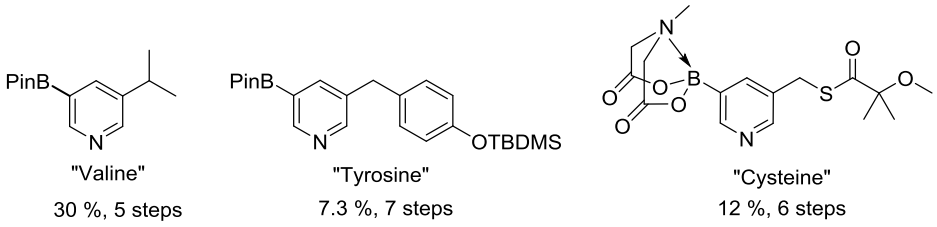
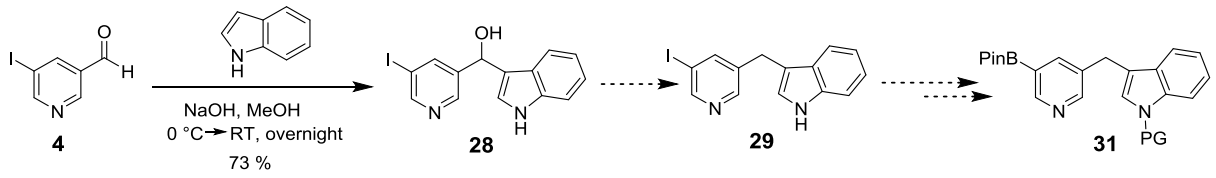


Figure 9: Overall yields and required steps of the synthesized pyridine building blocks.

The desired pyridine building blocks that have successfully been synthesized during this work are displayed in Figure 9. As it can be seen the valine derivative could be acquired in only 5 steps and with an overall yield of 30 %. The obtained yield of the other two building blocks was considerably lower. There were two reasons for this situation. On one hand the synthetic route consisted of more steps in order to obtain the product. On the other hand the synthesis of the tyrosine-derivative and cysteine-derivative involved the reduction of the methyl 5-bromonicotinate (**1**) to (5-bromopyridin-3-yl)methanol (**2**) which provided only a low amount of product.



Scheme 40: Already accomplished and intended steps for the synthesis of the tyrosine-derivative (**31**).

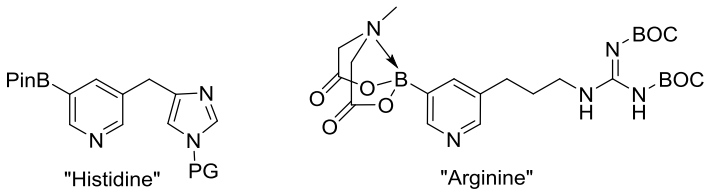


Figure 10: Yet to be synthesized building blocks for this project.

Scheme 40 and Figure 10 display the pyridine building blocks with amino acid moieties that could not be synthesized during this work. While the first steps for the production of the tryptophane derivative **31** have already been explored, both the final stages of its synthesis and the other two remaining building blocks with the histidine and arginine residue still remain as a task for future synthetic attempts. It is also important to find suitable protecting groups (PG) which are stable under Grignard conditions. These protecting groups should be also at low molecular weight and stable at high temperature so that purification via Kugelrohr-distillation can be performed.

The arginine derivative will be especially challenging for the establishment of a feasible synthetic concept. As the guanidine group of this building block will be difficult to synthesize from the existing set of intermediates. Therefore it should be considered to use the approach of Burke *et al.*[36] and create the desired arginine derivative as a MIDA boronate (Figure 10). These MIDA boronates display a high compatibility with functional group transformations and are easy to isolate,[36,73] which makes them ideal candidates for the development of new building blocks.

Another possibility would be to introduce the guanidine group after the assembling of the teraryls. However, this procedure would conflict with our highly modular approach of the teraryl generation from a library of building blocks.

Besides the just mentioned synthetic tasks the main goal for the future of this project will be the production of teraryl structures. Once the library of building blocks is completed the most promising structures for the inhibition of certain PPIs will be designed, synthesized and tested on their inhibition capability in screenings. The results of these screenings will indicate the benefits of this project for the production of potential new drug candidates.

6 Experimental Section

6.1 General Experimental Aspects

All chemicals were purchased from Sigma Aldrich, Acros Organics, Alfa Aesar, Fluka or Fisher Scientific. If not stated otherwise all chemicals were used as purchased. All solvents were bought and/or prepared as described in the following solvent section. When it was necessary to perform a reaction under inert atmosphere, a Schlenk flask or a suitable round-bottom flask with a Schlenk adapter was heated in vacuum with a heat gun. After they cooled back down to room temperature they were flushed with nitrogen. This procedure was repeated for three times. All subsequent transferring of reagents and solvents was performed by using standard Schlenk techniques.

When working at a temperature of 0°C an ice/water bath was used as a cooling agent. A temperature of -78°C was achieved by using a dry ice/acetone cooling bath.

Degassing was carried out by passing a stream of argon via a syringe through the solvent or reaction mixture while the reaction flask was immersed in an ultrasonic bath.

Molecular sieves were activated by heating (~150°C) in a round bottom flask under vacuum for several hours until a constant pressure was reached.

6.2 Solvents

Acetonitrile: Dry acetonitrile was purchased from ACROS Organics in 99.9% purity without stabilizer stored over 3 Å molecular sieves and was transferred into a brown 1 L Schlenk bottle with activated 3 Å molecular sieves and was stored under an argon atmosphere.

Cyclohexane: Cyclohexane was used as purchased and stored in 5 L aluminium canisters.

DCM: Dichloromethane was used as purchased. Dry DCM was pre-dried over phosphoric pentoxide, refluxed over calcium hydride and subsequently distilled to be stored over 4 Å molecular sieves under argon in brown glass bottles with a Schlenk adapter.

***N*,*N*-Dimethylformamide:** *N*,*N*-Dimethylformamide was purchased from ACROS Organics as extra dry solvent (<50 ppm water, over 3 Å molecular sieves, AcroSeal®) and was transferred to a dry brown 1 L Schlenk bottle with activated 3 Å molecular sieves and stored under argon atmosphere.

1,4-Dioxane: 1,4-Dioxane was used as purchased. Dry 1,4-dioxane was used as purchased, but transferred to be stored over 4 Å molecular sieves under argon in brown glass bottles with a Schlenk adapter.

Ethyl acetate: Ethyl acetate was used as purchased and stored in brown 2.5 L glass bottles.

Methanol: Methanol was used as purchased. Dry methanol was obtained by refluxing the solvent over iodine activated magnesium for 2 d and subsequent distillation. It was stored over 3 Å molecular sieves under argon in brown glass bottles with a Schlenk adapter.

THF: To remove the present stabilizer, commercial tetrahydrofuran was distilled on a rotary evaporator. To safely bind the during light and oxygen exposure generated peroxides, the stabilizer free THF was stored over KOH in brown glass bottles. Dry THF was produced by refluxing the stabilizer free solvent under inert atmosphere over sodium using benzophenone as an indicator. The solvent is considered dry and ready to be distilled if the colour turns to purple. The so generated THF was stored over 4 Å molecular sieves under argon in brown glass bottles with a Schlenk adapter.

Triethylamine: Triethylamine was used as purchased and stored in brown glass bottles. Dry triethylamine was produced by inert distillation over CaH_2. It was stored over 4 Å molecular sieves under argon in brown glass bottles with a Schlenk adapter.

6.3 Separation Techniques

6.3.1 Thin Layer Chromatography

Silica on aluminium plates were used for reaction control by thin layer chromatography (TLC). TLC plates from Merck (Merck silica gel 60-F_{254}) were used. Spots were visualized by UV-light (λ = 254 or 366 nm), CAM- or $KMnO_4$-stain.

CAM: 5.0 g phosphomolybdic acid were dissolved in 16 mL concentrated sulphuric acid and 200 mL H_2O. After slowly adding 2.0 g cerium(IV)sulphate the suspension was stirred until all solid parts were dissolved to form a yellow solution.

$KMnO_4$: 3.0 g potassium permanganate and 20.0 g potassium carbonate were dissolved in 1.5% NaOH solution to form a purple solution.

6.3.2 Flash Chromatography

Flash column chromatography was performed for purification purposes. Silica gel 60 Å (35-70 µm particle size) from Acros Organics was used. Depending on the separation problem 10 to 100 times the amount of the weight of the crude product was used. The column diameter was chosen depending on the amount of silica used to achieve a column height between 15 and 30 cm. The separation was usually performed under increased pressure applied by a hand pump. Substances with low solubility in the mobile phase were usually adsorbed onto Celite® or silica gel before they were applied on the column.

6.3.3 Kugelrohr-Distillation and Sublimation

Kugelrohr distillation was performed by using a Büchi GKR-51. The flask where the product was supposed to be collected was cooled with a mixture of ice/water dropping onto the flask.

Sublimation was performed with a sublimation finger in a Büchi GKR-51 Kugelrohr-distillation-oven.

6.3.4 Gas Chromatography

Analytical gas chromatography was performed with an "Agilent Technologies 7890A GC-System" with a polar HP-5MS capillary column (length: 30 m, inner diameter: 0.25 mm, film thickness: 0.25 µm). The "Agilent Technologies 7683 Series Auto sampler" and the "Agilent technologies 7683B Series Injector" were used to select and inject the correct samples. Helium 5.0 was used as a carrier gas. After ionisation with an electron impact ion source, operated with a potential difference of 70 V the ions were detected with an "Agilent Technologies 5975C inert MSD with Triple-Axis detector". The following method was used:

SG_50_S:

Split 1:20; 50°C 1 min, linear temperature increase 40°C/min until 300°C, 300°C 5 min

To estimate the conversion of a reaction, the area under a peak in the total ion count chromatogram (TIC) was used and compared to other peaks in the same chromatogram. All values are only relative values. No standards were measured. Samples were dissolved in a suitable solvent with a concentration of ~1 mg/L. If the GC-MS was used for reaction control, a small aliquot of the reaction mixture was quenched with an aqueous solution, extracted with a suitable organic solvent, dried with $MgSO_4$ and filtrated.

6.3.5 High Performance Liquid Chromatography

Analytical HPLC measurements were performed on a "Shimadzu Nexera Liquid Chromatograph" with thermostatically controlled column oven. The separation of the analytes was carried out using a "C-18 reversed-phase" column of the type „Poroshell® 120 SB-C18, 3.0 x 100 mm, 2.7 µm" by Agilent Technologies. Detection of the substances was accomplished with a „Shimadzu SPD-M20A Prominence Diode Array Detector" at a wavelength of $\lambda = 210$ nm and with the mass selective detector „Shimadzu LCMS-2020 Liquid Chromatograph Mass Spectrometer" in the modes "ESI positive" and "ESI negative". The mobile phase consisted of acetonitrile and water with 0.01% HCOOH as an additive. The following method was used:

Poroshell 120_001HCOOH_MeCN_10 auf 95:

0 min 90 % water/HCOOH and 10 % CH_3CN, 0 - 4.50 min linear to 95 % CH_3CN,
4.50 – 6.50 min 95 % CH_3CN, 6.50 – 6.60 min linear to 10 % CH_3CN,
6.60 - 8.50 min 10 % CH_3CN; 0.7 mL/min, 40°C

6.4 High Resolution Mass Spectrometry

The measurement of high resolution mass spectrometry spectra was performed on a "Waters GCT Premier" system after ionisation with an EI ionisation source of a potential of 70 V. All measurements were performed by Prof. Robert Saf and his working group. Depicted are the corresponding calculated and measured masses.

6.5 Nuclear Magnetic Resonance

All enclosed NMR spectra were recorded on a Bruker Avance III 300 MHz FT NMR spectrometer (300.36 MHz (^{1}H), 75.53 MHz (^{13}C)) at 27°C. Chemical shifts are listed as δ [ppm]. All spectra were referenced to the residual protonated solvent signals as internal standards ($CDCl_3$ = 7.260 (^{1}H), 77.160 (^{13}C); d-DMSO = 2.500 (^{1}H), 39.520 (^{13}C)). Signals multiplicities are written as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet) or m (multiplet). Signals are assigned parts of the molecule by stating how many atoms correspond to the signal followed by the binding situation (C_q for quaternary carbons, CH, CH_2, CH_3). They are further described by superscripts, describing the part of the molecule they are attached to, or the molecule itself if mixtures of molecules are observed.

They are used as follows: H^{Py}, C^{Py} for atoms part of a pyridine ring; H^{Ar}, C^{Ar} for atoms part of phenyl ring; H^{TBDMS}, C^{TBDMS} for atoms part of a *tert*-butyl dimethyl silyl protecting group; H^{Pin}, C^{Pin} for atoms part of a pincaol boronic acid ester; H^{MIDA}, C^{MIDA} for atoms part of a MIDA boronate; H^{Ind}, C^{Ind} for atoms part of an indole ring.

All ^{13}C and APT spectra were ^{1}H broadband decoupled to produce clear and easy to read spectra. If boronic acid esters were measured, then the signal corresponding to the quaternary *ipso*-pyridine carbon (C_q; C^{Py}) at the boronic acid ester was not observed.

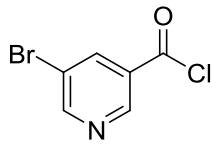
6.6 Melting Point

All depicted melting points were measured with the "Mel-Temp®" from Electrothermal. For easier determination of the melting point a built in microscope was used. The measured values were not corrected with a standard and used as determined.

6.7 Synthetic Procedures

The syntheses of the compounds **1B, 2-4, 11** and **32** were carried out according to the procedures from the master thesis of Sebastian Grimm, who previously worked on this project.[42]

6.7.1 5-Bromonicotinoyl chloride (8)[50]



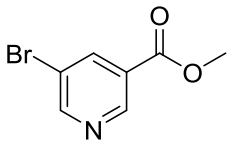
8

A 50 mL round-bottom flask equipped with a reflux condenser was charged with 10.00 g nicotinic acid (81.23 mmol, 1 eq) (**6**). Upon the addition of 25 mL of thionyl chloride (343 mmol, 4.2 eq) and 1 mL DMF via the reflux condenser gas was formed immediately. This gas was directed into two gas-washing bottles consecutively. The first gas-washing bottle was empty and served as a safety bottle. The second gas-washing bottle was filled with 200 mL saturated $NaHCO_3$ solution. After the yellow suspension had been stirred under reflux overnight the excess thionyl chloride was removed in vacuum by using a cold trap.

The resulting yellow crystals were treated with 5.8 mL bromine (113 mmol, 1.4 eq) in the same apparatus as used before. For the second gas-washing bottle a solution of 200 mL of $Na_2S_2O_3$ (50 % w/v) and 40 mL 5 M NaOH was used. The dark brown suspension was heated to 150 °C under stirring for 20 h. Excess thionyl chloride was removed in vacuum to give a dark brown highly viscous oil that was used for the next step without further purification.

Yield: 29.22 g (163 %, crude product), dark brown highly viscous oil, $C_6H_3BrClNO$ [220.45 g/mol].

6.7.2 Methyl 5-bromonicotinate (1)



1

6.7.2.1 Method A[50]

A 50 mL round-bottom flask equipped with a reflux condenser was charged with 24.00 g 5-bromonicotinoyl chloride (**8**) (66.7 mmol, 1 eq). While cooling the flask in an ice bath a mixture of 20 mL methanol and 15 mL DCM was added slowly under stirring. Afterwards the flask was put in an ultrasonic bath until the starting-material was dissolved. The mixture was then heated to reflux temperature for 2 h. After cooling to room temperature the dark brown solution was rinsed into an Erlenmeyer flask with 40 mL methanol and carefully treated with 40 mL 5 M NaOH under ice cooling. Then the mixture was transferred into a separation funnel and 20 mL 50 % (w/v) $Na_2S_2O_3$ solution were added. The aqueous phase was extracted with DCM (5x40 mL). The combined organic phases were washed with a solution of 20 mL 5 M NaOH and 20 mL 50 % (w/v) $Na_2S_2O_3$, dried over Na_2SO_4 and concentrated in vacuum. The resulting brown solid was sufficiently pure (94 %, HPLC-MS) to be directly used for the following steps.

Yield: 13.68 g (95%, crude product), brown solid, $C_7H_6BrNO_2$ [216.03 g/mol].

m.p.$^{exp.}$ = 91-94 °C.

6.7.2.2 Method B[42]

In a 1000 mL round-bottom flask equipped with an air condenser and drying tube 25.00 g 5-bromonicotinic acid (123.8 mmol, 1 eq) were suspended in 360 mL methanol. Upon the addition of 12.8 mL acetyl chloride (14.1 g, 180 mmol, 1.45 eq) the reaction mixture became a colourless solution. After heating under reflux for 7 d the flask was put into the fridge overnight. The precipitate (colourless crystals) was collected by filtration with a fritted funnel and washed with cold methanol (3x100 mL).

The filtrate was concentrated in vacuum to give a white solid, which was dissolved in 300 mL DCM and 250 mL saturated $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with DCM (3x300 mL). The combined organic layers were washed with brine (1x500 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give an orange solid. Both the orange solid and the colourless crystals were pure enough to be used for further reactions.

Yield: 11.06 g (88 %), orange solid or colourless crystals, $C_7H_6BrNO_2$ [216.03 g/mol].

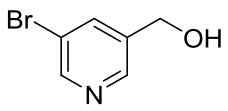
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.11 (d, ^4J(H,H) = 1.5 Hz, 1H,CH, H^{Py}), 8.83 (d, ^4J(H,H) = 2.2 Hz, 1H, CH, H^{Py}), 8.4 (m, 1H, CH, H^{Py}), 3.96 (s, 3H, CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 164.6 (C_q, $C^{Carbonyl}$), 154.7 (CH, C^{Py}), 149.0 (CH, C^{Py}), 139.6 (CH, C^{Py}), 127.5 (C_q, C^{Py}), 120.7 (C_q, C^{Py}), 52.9 (CH_3) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 5.268 min; *m/z* (%): 217 (67), 215 (68), 186 (97), 184 (100), 158 (76), 156 (77), 130 (17), 76 (46).

m.p.$^{exp.}$ = 98-99 °C (**m.p.**$^{lit.}$ = 98-99 C).[50]

6.7.3 (5-Bromopyridin-3-yl)methanol (2)[42]



2

In a flame dried and nitrogen flushed 1000 mL two-neck round-bottom flask, equipped with an addition funnel and nitrogen inlet 6.32 g lithium aluminium hydride (167 mmol, 2 eq) were suspended in 200 mL dry THF and cooled to -78°C in a dry ice/acetone bath. Through the addition funnel a solution of 18.00 g methyl 5-bromonicotinate (**1**) (83.32 mmol, 1 eq) dissolved in 200 mL dry THF was added dropwise to the reaction mixture over a period of 1 h. Then the addition funnel was rinsed with dry THF (3x20 mL). After stirring the suspension at -78°C for 2.5 h the reaction was quenched by adding 22.4 mL ethyl acetate. After the addition of 6.4 mL H_2O, 6.4 mL 10 % NaOH and 19 mL H_2O the mixture was allowed to warm up to RT and was stirred vigorously overnight. The reaction was dried over anhydrous $MgSO_4$ and filtered through a glass frit. The solvent was removed under reduced pressure to give a brown oil. The crude was purified via flash column chromatography (400 g SiO_2, 17x8 cm, Cyclohexane/EtOAc = 1/1).

Yield: 5.80 g (37 %), yellow oil, C_6H_6BrNO [188.02 g/mol].

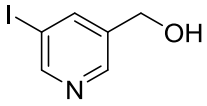
R_f = 0.18 (Cyclohexane/EtOAc = 1/1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, ^4J(H,H) = 1.9 Hz, 1H, CH, H^{Py}), 8.45 (bs, 1H, CH, H^{Py}), 7.89 (bs, 1H, CH, H^{Py}), 4.72 (s, 2H, CH_2), 2.88 (bs, 1H, OH) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 150.0 (CH, C^{Py}), 146.4 (CH, C^{Py}), 138.3 (C_q, C^{Py}), 137.5 (CH, C^{Py}), 121.1 (C_q, C^{Py}), 61.9 (CH_2) ppm.

GC-MS (EI, 70 eV; MT_50_S): t_R = 5.436 min; *m/z* (%): 189 (80), 187 (82), 160 (90), 158 (100), 108 (42), 90 (23), 78 (49).

6.7.4 (5-Iodopyridin-3-yl)methanol (3)[42]



3

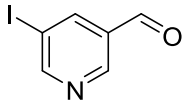
A flame dried and nitrogen flushed Schlenk flask was charged with 8.94 g NaI (59.7 mmol, 2 eq) and 0.568 g CuI (2.98 mmol, 0.1 eq). The salts were dried by heating in vacuum with a heat gun for 20 min. 5.61 g (5-bromopyridin-3-yl)methanol (**2**) (29.8 mmol, 1 eq) were dissolved in 40 mL dry 1,4-dioxane in a flame dried round-bottom flask with nitrogen inlet. After addition of 320 µL *N,N′*-dimethylethylenediamine (2.98 mmol, 0.1 eq) the solution was degassed by bubbling nitrogen through the liquid in an ultrasonic bath. The degassed solution was transferred to the flask with the iodine salts and was heated to 120°C for 5 d until full conversion was detected by GC-MS. The GC-samples were prepared by quenching a small aliquot of the reaction mixture with saturated NH_4Cl solution, extraction with DCM and drying with $MgSO_4$. Each day an incomplete conversion was detected 0.1 eq of CuI and *N,N′*-dimethylethylenediamine were added (3x). The brown suspension was quenched with 50 mL saturated NH_4Cl solution. The aqueous phase was extracted with DCM (6x50 mL). The combined brown organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to dryness. The crude product was used for subsequent reactions without further purification.

Yield: 5.85 g (83 %, crude product), brown solid, C_6H_6INO [235.02 g/mol].

GC-MS (EI, 70 eV; SG_50_S): t_R = 5.858 min; *m/z* (%):235 (100), 217 (8), 206 (42), 127 (27), 108 (16), 90 (21), 79 (17).

m.p.$^{exp.}$ = 58-61 °C.

6.7.5 5-Iodonicotinaldehyde (4)[42]



4

A flame dried and nitrogen flushed 250 mL three-neck round-bottom flask equipped with an addition funnel and a nitrogen inlet was charged with 1.30 mL oxalyl chloride (15.4 mmol, 1.1 eq) in 32 mL dry DCM. After cooling the reaction mixture to -78 °C 2.20 mL dry DMSO (31.0 mmol, 2.2 eq) in 23 mL dry DCM were added dropwise over a period of 40 min. The reaction was stirred for 20 min followed by the addition of a solution of 3.24 g (5-iodopyridin-3-yl)methanol (**3**) (13.8 mmol, 1 eq) in 20 mL dry DCM over a period of 30 min. After the reaction mixture was stirred for 30 min 9.60 mL of dry triethylamine (68.9 mmol, 5 eq) were added over a period of 10 min. Afterwards the reaction was allowed to warm up to RT. After addition of 80 mL saturated $NaHCO_3$ solution, the phases were separated and the aqueous phase extracted with DCM (3x80 mL). The combined organic phases were washed with brine (1x180 mL), dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified via flash column chromatography (70 g SiO_2, 22x3 cm, Cyclohexane/EtOAc = 4/1).

Yield: 2.55 g (80 %), slightly yellow solid, C_6H_4INO [233.01 g/mol].

R_f = 0.30 (Cyclohexane/EtOAc = 4/1, UV).

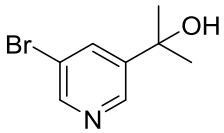
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.03 (s, 1H, H^{Ald}), 9.05 (d, ^4J(H,H) = 1.9 Hz, 1H, CH, H^{Py}), 9.00 (d, ^4J(H,H) = 1.5 Hz, 1H, CH, H^{Py}), 8.49-8.48 (m, 1H, CH, H^{Py}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 189.3 (C^{Ald}), 160.6 (CH, C^{Py}), 150.2 (CH, C^{Py}), 144.1 (CH, C^{Py}), 132.9 (C_q; C^{Py}), 94.0 (C_q; C^{Py}) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 5.278 min; *m/z* (%): 233 (100), 204 (16), 177 (5), 127 (15), 78 (12).

m.p.$^{exp.}$ = 142-144°C.

6.7.6 2-(5-Bromopyridin-3-yl)propan-2-ol (11)[42]



11

A flame dried and nitrogen flushed 250 mL two-neck round-bottom flask equipped with an addition funnel and a nitrogen inlet was charged with 4.77 g methyl 5-bromonicotinate (**1**) (22.08 mmol, 1 eq) dissolved in 48 mL dry THF. After cooling the reaction mixture to -78°C 15.5 mL MeMgBr in diethyl ether (46.37 mmol, 3.00 M, 2.1 eq) were added dropwise to the reaction mixture over a period of 10 min. After stirring the reaction for 80 min it was quenched by addition of 7 mL ethyl acetate and allowed to warm up to 0°C. 1 M HCl solution was added dropwise until the dark oily residue in the mixture was dissolved. The reaction mixture was made basic by the addition of 100 mL saturated $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted with ethyl acetate (3x100 mL). The combined organic phases were washed with saturated NaCl solution (1x200 mL), dried over Na_2SO_4 and concentrated in vacuum to yield a yellow solid. The crude product was purified via flash column chromatography (150 g SiO_2, 25x4 cm, Cyclohexane/EtOAc = 2/1).

Yield: 3.02 g (63 %), yellow oil, $C_8H_{10}BrNO$ [216.08 g/mol].

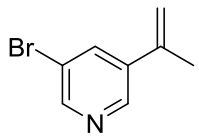
R_f = 0.23 (Cyclohexane/EtOAc = 2/1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (d, ^4J(H,H) = 1.7 Hz, 1H, CH, H^{Py}), 8.49 (d, ^4J = 2.0 Hz, 1H, CH, H^{Py}), 7.99 (m, 1H, CH, H^{Py}), 2.88 (bs, 1H, OH), 1.85 (s, 6H, CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 148.9 (CH, C^{Py}), 146.6 (C_q, C^{Py}), 144.7 (CH, C^{Py}), 135.5 (CH, C^{Py}), 120.8 (C_q, C^{Py}), 71.0 (CH), 31.8 (CH_3).

GC-MS (EI, 70 eV; SG_50_S): t_R = 5.917 min; *m/z* (%): 217 (5), 215 (5), 202 (98), 200 (100), 158 (10), 91 (1), 78 (10).

6.7.7 3-Bromo-5-(prop-1-en-2-yl)pyridine (12)



12

In a 50 mL round bottom flask 2.84 g 2-(5-bromopyridin-3-yl)propan-2-ol (**11**) (13.1 mmol, 1 eq) were dissolved in 14.0 mL 85 % (w/w) phosphoric acid (204 mmol, 15.6 eq). The yellow solution was then heated to 150 °C for 40 min. Afterwards the reaction mixture was diluted with 20 mL water and treated with 100 mL 5 M NaOH under ice cooling. After transferring the mixture into a separation funnel 100 mL water and 100 mL DCM were added. The aqueous phase was extracted with DCM (5x40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuum to yield a yellow oil. The product was used for the following step without further purification.

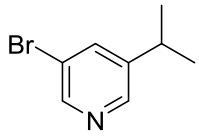
Yield: 2.53 g (97 %, crude product), yellow oil, C_8H_8BrN [198.06 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$, purified sample): δ = 8.61 (d, ^4J(H,H) = 1.8 Hz, 1H, CH, H^{Py}), 8.55 (d, ^4J = 2.0 Hz, 1H, CH, H^{Py}), 7.85 (m, 1H, CH, H^{Py}), 5.43 (s, 1H, CH_2), 5.22 (s, 1H, CH_2), 2.13 (s, 3H, CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, purified sample): δ = 149.5 (CH, C^{Py}), 145.3 (CH, C^{Py}), 139.4 (C_q, C=CH_2), 138.4 (C_q, C^{Py}), 135.5 (CH, C^{Py}), 120.7 (C_q, C^{Py}), 115.7 (CH_2), 21.5 (CH_3).

GC-MS (EI, 70 eV; SG_50_S): t_R = 5.036 min; *m/z* (%): 199 (99), 197 (100), 184 (15), 182 (17), 117 (79), 103 (23), 91 (56).

6.7.8 3-Bromo-5-isopropylpyridine (13)



13

A round bottom flask equipped with a reflux condenser was charged with 2.60 g 3-bromo-5-(prop-1-en-2-yl)pyridine (**12**) (13.1 mmol, 1 eq), 14.67 g *p*-tosylhydrazide (78.78 mmol, 6 eq) and 10.72 g $NaOAc \cdot 3H_2O$ (78.78 mmol, 6 eq) suspended in 100 mL THF. The reaction mixture was heated under reflux temperature overnight. Then 200 mL saturated $NaHCO_3$ and 300 mL DCM were added carefully to the reaction mixture after it had been cooled to RT. The phases were separated and the aqueous layer was extracted with DCM (2x300 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed in vacuum. The crude product was purified via flash column chromatography (125 g SiO_2, 20x4 cm, Cyclohexane/EtOAc = 10/1, R_f = 0.30, UV).

Yield: 1.65 g (63 %, over 2 steps), yellow oil, $C_8H_{10}BrN$ [200.08 g/mol].

R_f = 0.30 (Cyclohexane/EtOAc = 10/1, UV).

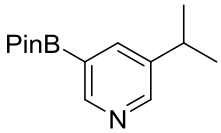
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, ^4J(H,H) = 2.0 Hz, 1H, CH, H^{Py}), 8.39 (d, ^4J = 1.5 Hz, 1H, CH, H^{Py}), 7.66 (bs, 1H, CH, H^{Py}), 2.98-2.85 (m, 1H, CH), 1.26 (d, ^3J(H,H) = 6.9 Hz, 6H, CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 148.5 (CH, C^{Py}), 147.0 (CH, C^{Py}), 145.7 (C_q, C^{Py}), 136.5 (CH, C^{Py}), 120.8 (C_q, C^{Py}), 31.7 (CH), 23.6 (CH_3).

GC-MS (EI, 70 eV; SG_50_S): t_R = 4.918 min; *m/z* (%): 201 (47), 199 (49), 186 (100), 184 (99), 120 (11), 104 (45), 91 (13).

HRMS (EI): calcd for [M^+]: 198.9997; found: 199.0001.

6.7.9 3-Isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (14)



14

A flame dried and nitrogen flushed 50 mL two-neck round-bottom flask equipped with a nitrogen inlet was charged with 1.37 g 3-bromo-5-isopropylpyridine (**13**) (6.86 mmol, 1 eq) dissolved in 20 mL dry THF. After cooling the solution to 0 °C 4.2 mL *i*PrMgCl·LiCl solution (**32**) (7.5 mmol, 1.8 M, 1.1 eq) were added dropwise. The orange solution was stirred for a period of 90 min at 0 °C before it was allowed to warm to RT. After 4.5 h at RT complete metal-halogen exchange was detected by GC-MS. The GC-samples were prepared by quenching a small aliquot of the reaction mixture with saturated $NaHCO_3$ solution, extraction with DCM and drying with $MgSO_4$. Then the reaction mixture was again cooled in an ice bath and 1.60 mL PinBO*i*Pr (7.89 mmol, 1.15 eq) were added and the solution was stirred overnight. After full conversion was detected via GC-MS the reaction mixture was quenched by adding 66 mL saturated NH_4Cl solution. The phases were separated and the aqueous layer extracted with DCM (4x80 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to yield a yellow solid. The crude product was purified via Kugelrohr-distillation (190 °C, $70 \cdot 10^{-3}$ mbar) to yield a colourless solid.

Yield: 1.45 g (86 %), colourless solid, $C_{14}H_{22}BNO_2$ [247.14 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, ^4J(H,H) = 1.3 Hz, 1H, CH, H^{Py}), 8.53 (d, ^4J(H,H) = 2.3 Hz, 1H, CH, H^{Py}), 7.89 (bs, 1H, CH, H^{Py}), 2.97-2.87 (m, 1H, CH), 1.35 (s, 12H, CH_3, H^{Pin}), 2.12 (d, ^3J(H,H) = 7.0 Hz, 6H, CH_3) ppm.

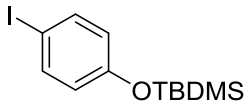
^{13}C NMR (76 MHz, $CDCl_3$): 153.3 (CH, C^{Py}), 151.1 (CH, C^{Py}), 142.9 (C_q, C^{Py}), 140.0 (CH, C^{Py}), 84.3 (C_q, C^{Pin}), 32.0 (CH), 25.0 (CH_3, C^{Pin}), 23.8 (CH_3) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 6.324 min; *m/z* (%): 247 (49), 232 (100), 204 (6), 190 (35), 148 (68), 132 (35).

HRMS (EI): calcd for [M^+]: 247.1746; found: 247.1751.

m.p.$^{exp.}$ = 106-108 °C.

6.7.10 3-*tert*-Butyl(4-iodophenoxy)dimethylsilane (16)



16

In a 100 mL round bottom flask 1.76 g 4-iodophenol (**15**) (8.00 mmol, 1 eq) and 1.36 g imidazole (20.0 mmol, 2.5 eq) were dissolved in 37 mL dry DCM. After the addition of 1.33 g TBDMSCl (8.80 mmol, 1.1 eq) to the yellow solution a colourless precipitate was formed. The suspension was stirred overnight and then transferred into a separation funnel. The organic layer was washed with saturated $NaHCO_3$ solution (3x40 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuum. The resulting brown oil was pure enough to be used for subsequent reactions.

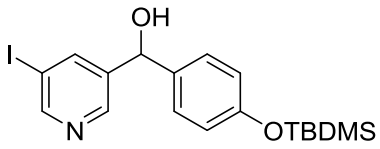
Yield: 2.58 g (97 %), brown oil, $C_{12}H_{19}IOSi$ [334.27 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, ^3J(H,H) = 8.7 Hz, 2H, CH, H^{Ar}), 6.61 (d, ^3J(H,H) = 8.7 Hz, 2H, CH, H^{Ar}), 0.97 (s, 9H, $C(CH_3)_3$, H^{TBDMS}), 0.18 (s, 6H, CH_3, H^{TBDMS}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): 155.8 (C_q, C^{Ar}), 138.5 (CH, C^{Ar}), 122.7 (CH, C^{Ar}), 83.8 (C_q, C^{Ar}), 25.8 (CH_3, C^{TBDMS}), 18.3 (C_q, C^{TBDMS}), -4.3 (CH_3, C^{TBDMS}) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 6.287 min; *m/z* (%): 334 (35), 277 (100), 150 (85), 135 (59), 91 (13).

6.7.11 (4-((*tert*-Butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (17)



17

A flame dried and nitrogen flushed 100 mL two-neck-round bottom flask equipped with a nitrogen inlet was charged with 1.45 g 3-*tert*-butyl(4-iodophenoxy)dimethylsilane (**16**) (4.34 mmol, 1 eq) dissolved in 20 mL dry THF. Upon cooling the solution to -78 °C 2.94 mL *i*PrMgCl·LiCl solution (**32**) (5.0 mmol, 1.7 M, 1.15 eq) were added dropwise. While stirring the metal-halogen exchange was monitored by GC-MS. The GC-samples were prepared by quenching a small aliquot of the reaction mixture with saturated $NaHCO_3$ solution, extraction with DCM and drying with $MgSO_4$. After 7 h the solution was allowed to warm to RT overnight until the metal-halogen exchange was >95 %.

Meanwhile in a second flame dried and nitrogen flushed 100 mL two-neck round-bottom flask equipped with a nitrogen inlet 1.01 g 5-iodonicotinaldehyde (**4**) (4.34 mmol, 1 eq) were mixed with 20 mL dry THF and cooled to 0 °C. The previously prepared reaction mixture was added to this suspension via a syringe dropwise over a period of 15 min, causing the formation of a yellow solution. After the addition the flask of the previous metal-halogen exchange was rinsed with 5 mL dry THF and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was allowed to warm to RT and continued to stir until full conversion of the starting material could be detected by GC-MS. After 2.5 h the reaction mixture was quenched by adding 40 mL saturated NH_4Cl solution and subsequently 40 mL saturated $NaHCO_3$ solution. The phases were separated and the aqueous layer extracted with DCM (4x40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to yield an orange oil. The crude product was purified via flash column chromatography (60 g SiO_2, 20x3 cm, Cyclohexane/EtOAc = 3/1).

Yield: 1.32 g (69 %), yellow oil, $C_{18}H_{24}INO_2Si$ [441.38 g/mol].

R_f = 0.33 (Cyclohexane/EtOAc = 3/1, UV and CAM).

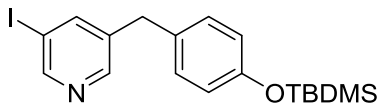
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, ^4J(H,H) = 1.7 Hz, 1H, CH, H^{Py}), 8.45 (d, ^4J = 1.3 Hz, 1H, CH, H^{Py}), 8.06 (bs, 1H, CH, H^{Py}), 7.17 (d, ^3J = 8.5 Hz, 2H, CH, H^{Ar}), 6.82 (d, ^3J = 8.5 Hz, 2H, CH, H^{Ar}), 5.73 (s, 1H, CH), 2.96 (bs, 1H, OH), 0.97 (s, 9H, $C(CH_3)_3$, H^{TBDMS}), 0.19 (s, 6H, CH_3, H^{TBDMS}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 155.9 (C_q, C^{Ar}), 154.5 (CH, C^{Py}), 146.7 (CH, C^{Py}), 142.3 (CH, C^{Py}), 141.7 (C_q, C^{Py}), 135.4 (C_q, C^{Ar}), 128.1 (CH, C^{Ar}), 120.6 (CH, C^{Ar}), 93.5 (C_q, C^{Py}), 73.3 (CH), 25.8 (CH_3, C^{TBDMS}), 18.3 (C_q, C^{TBDMS}), -4.3 (CH_3, C^{TBDMS}) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 9.365 min; *m/z* (%): 441 (32), 384 (100), 234 (27), 151 (56), 91 (3).

HRMS (EI): calcd for [M^+]: 441.0621; found: 441.0633.

6.7.12 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-iodopyridine (18)



18

A 25 mL round-bottom-flask equipped with a Schlenk adapter was flushed with nitrogen and charged with 626 mg (4-((*tert*-butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (**17**) (1.42 mmol, 1 eq) dissolved in 13 mL dry DCM. After the dropwise addition of 1.9 mL triethylsilane (12 mmol, 8.4 eq) and 3.5 mL trifluoroacetic acid (46 mmol, 32 eq) the yellow solution was stirred at RT overnight. Afterwards the mixture was poured on 150 mL saturated $NaHCO_3$ solution, stirred vigorously for 1 h and transferred into a separation funnel. The phases were separated and the aqueous layer extracted with DCM (5x50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to yield a yellow oil. The crude product was purified via flash column chromatography (15 g SiO_2, 4x3.5 cm, Cyclohexane/EtOAc = 10/1).

Yield: 476 mg (79 %), yellow oil, $C_{18}H_{24}INOSi$ [425.39 g/mol].

$\mathbf{R_f}$ = 0.34 (Cyclohexane/EtOAc = 10/1, UV).

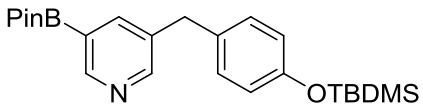
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (bs, 1H, CH, H^{Py}), 8.40 (bs, 1H, CH, H^{Py}), 7.78 (bs, 1H, CH, H^{Py}), 7.01 (d, ^3J = 8.4 Hz, 2H, CH, H^{Ar}), 6.78 (d, ^3J = 8.4 Hz, 2H, CH, H^{Ar}), 3.85 (s, 2H, CH_2), 0.98 (s, 9H, $C(CH_3)_3$, H^{TBDMS}), 0.19 (s, 6H, CH_3, H^{TBDMS}) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 154.6 (C_q, C^{Ar}), 153.6 (CH, C^{Py}), 148.7 (CH, C^{Py}), 144.6 (CH, C^{Py}), 139.3 (C_q, C^{Py}), 131.6 (C_q, C^{Ar}), 130.0 (CH, C^{Ar}), 120.5 (CH, C^{Ar}), 93.7 (C_q, C^{Py}), 38.0 (CH_2), 25.8 (CH_3, C^{TBDMS}), 18.3 (C_q, C^{TBDMS}), -4.3 (CH_3, C^{TBDMS}) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 8.575 min; *m/z* (%): 425 (24), 368 (100), 241 (11), 207 (20), 91 (7).

HRMS (EI): calcd for [M^+]: 425.0672; found: 425.0680.

6.7.13 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (19)



19

A flame dried and nitrogen flushed Schlenk flask was charged with 150 mg 3-(4-((*tert*-butyldimethylsilyl)oxy)benzyl)-5-iodopyridine (**18**) (0.353 mmol, 1 eq) dissolved in 1 mL dry THF. After cooling the solution to -78 °C 230 µL *i*PrMgCl·LiCl solution (**32**) (0.391 mmol, 1.7 M, 1.1 eq) were added dropwise. After 1 h complete metal-halogen exchange was detected by GC-MS. The GC-samples were prepared by quenching a small aliquot of the reaction mixture with saturated $NaHCO_3$ solution and extraction with DCM. After adding 100 µL PinBO*i*Pr (0.490 mmol, 1.4 eq) the reaction mixture was allowed to warm up in the cooling bath overnight and full conversion was detected by GC-MS. The reaction mixture was quenched by adding 5 mL saturated NH_4Cl solution. The phases were separated and the aqueous layer extracted with DCM (4x10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to yield a yellow oil. The crude product was purified by Kugelrohr-sublimation (185 °C, $26 \cdot 10^{-3}$mbar) to yield a colourless solid.

Yield: 93 mg (62 %), colourless solid, $C_{24}H_{36}BNO_3Si$ [425.45 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (bs, 1H, CH, H^{Py}), 8.51 (d, ^4J = 2.0 Hz, 1H, CH, H^{Py}), 7.86 (bs, 1H, CH, H^{Py}), 7.01 (d, ^3J = 8.4 Hz, 2H, CH, H^{Ar}), 6.76 (d, ^3J = 8.4 Hz, 2H, CH, H^{Ar}), 3.89 (s, 2H, CH_2), 1.34 (s, 12H, CH_3, H^{Pin}) 0.97 (s, 9H, $C(CH_3)_3$, H^{TBDMS}), 0.17 (s, 6H, CH_3, H^{TBDMS}) ppm.

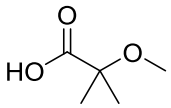
^{13}C NMR (76 MHz, $CDCl_3$): δ = 154.3 (C_q, C^{Ar}), 153.3 (CH, C^{Py}), 152.5 (CH, C^{Py}), 142.7 (CH, C^{Py}), 136.2 (C_q, C^{Py}), 132.7 (C_q, C^{Ar}), 129.9 (CH, C^{Ar}), 120.3 (CH, C^{Ar}), 84.3 (C_q, C^{Py}), 38.4 (CH_2), 25.8 (CH_3, C^{TBDMS}), 25.0 (CH_3, C^{Pin}), 18.3 (C_q, C^{TBDMS}), -4.3 (CH_3, C^{TBDMS}) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 9.594 min; *m/z* (%): 425 (28), 368 (49), 268 (100), 207 (18), 91 (6).

HRMS (EI): calcd for [M^+]: 425.2562; found: 425.2570.

m.p.$^{exp.}$ = 98-99 °C.

6.7.14 2-Methoxy-2-methylpropanoic acid (22)[79,80]



22

A flame dried and nitrogen flushed 500 mL three-neck round-bottom flask equipped with an addition funnel, a reflux condenser and a mechanical stirrer was charged with 24.08 g KOH (428.6 mmol, 4 eq) dissolved in a mixture of 54 mL methanol and 12.4 mL H_2O. After cooling the reaction mixture to 0 °C a solution of 20.00 g 1,1,1-trichloro-2-methyl-2-propanol hemihydrates (**21**) (107.3 mmol, 1 eq) in 38 mL methanol was added dropwise within 30 min. Then the ice bath was removed and the suspension was stirred for 1 h under RT. Afterwards the reaction mixture was heated to reflux for 2 h and filtered after cooling to RT. The filtrate was concentrated in vacuum, the resulting residue was cooled to 0 °C and 42 mL 1 M H_2SO_4 were added. The colourless precipitate was removed via filtration and washed with DCM (5x30 mL). The phases were separated and the aqueous layer extracted with DCM (4x50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by fractionated distillation (114-116 °C, 57 mbar) to yield a colourless liquid.

Yield: 7.76 g (61 %), colourless liquid, $C_5H_{10}O_3$ [118.13 g/mol].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.33 (s, 3H, OCH_3), 1.46 (s, 6H, CH_3) ppm.*

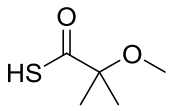
^{13}C NMR (76 MHz, $CDCl_3$): δ = 179.4 (C_q, COOH), 128.1 (C_q, $C(CH_3)_3$), 52.0 (OCH_3), 23.7 (CH_3) ppm.

HPLC-MS (Poroshell 120_001HCOOH_MeCN_10 auf 95): t_R = 1.912 min.

b.p.$^{exp.}$ = 114-116 °C, 57 mbar, (**b.p.**$^{lit.}$ = 98-99 °C, 20 torr).[80]

* Signal of the proton at the carboxylic acid function was not observed.

6.7.15 2-Methoxy-2-methylpropanethioic *S*-acid (23)



23

A 25 mL round-bottom flask equipped with a reflux condenser was charged with 3.00 g 2-methoxy-2-methylpropanoic acid (**22**) (25.4 mmol, 1 eq). Upon the addition of 5.2 mL of oxalyl chloride (60 mmol, 2.4 eq) the reaction mixture was heated to reflux for 5 min, which caused rapid development of gas. This gas was directed into two gas-washing bottles consecutively. The first gas-washing bottle was empty and served as a safety bottle. The second gas-washing bottle was filled with 200 mL saturated $NaHCO_3$ solution. After the yellow suspension had been stirred at RT for 1 the excess oxalyl chloride was removed in vacuum by using a cold trap.[79]

Meanwhile in a second round-bottom flask 4.74 g sodium hydrosulfide hydrate (50.82 mmol, 2 eq) were mixed with 16 mL methanol and cooled to 0 °C. The previously prepared acid chloride was added to this suspension via a syringe dropwise over a period of 1.5 h. After the addition was completed the orange suspension was stirred for 1 h at 0 °C and 1 h at RT consecutively. Then the reaction mixture was poured onto 100 mL H_2O and extracted with DCM (4x50 mL). The organic layer was discarded while the aqueous layer was transferred into a 500 mL three-neck round-bottom flask with nitrogen inlet and acidified by addition of 25 mL of 20 % HCl causing a rapid generation of gas, which was directed into two gas-washing bottles consecutively. The first gas-washing bottle was empty and served as a safety bottle. The second gas-washing bottle was filled with 100 mL 15 % NaOCl solution. The reaction mixture was stirred overnight and flushed with a gentle stream of nitrogen. Afterwards the yellow solution was transferred into a separation funnel and extracted with DCM (4x50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by fractionated distillation (62 °C, 49 mbar) to yield a colourless liquid.

Yield: 704 mg (21 %), colourless liquid, $C_5H_{10}O_2S$ [134.19 g/mol].

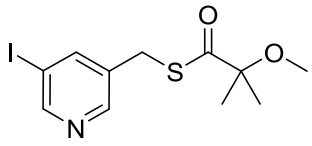
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.63 (s, 1H, COSH), 3.32 (s, 3H, OCH_3), 1.36 (s, 6H, CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 205.9 (C_q, COSH), 83.7 (C_q, $C(CH_3)_2$), 52.4 (OCH_3), 23.5 (CH_3) ppm.

HPLC-MS (Poroshell 120_001HCOOH_MeCN_10 auf 95): t_R = 2.864 min.

b.p.$^{exp.}$ = 62 °C, 49 mbar, (**b.p.**$^{lit.}$ = 40-55 °C, 5-10 torr).[81]

6.7.16 *S*-((5-Iodopyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (24)



24

A 5 mL one-neck-round-bottom-flask was charged with 127 mg 3-(chloromethyl)-5-iodopyridine (**20**) (0.501 mmol, 1 eq) and a solution of 81 mg 2-methoxy-2-methylpropanethioic *S*-acid (**23**) (0.60 mmol, 1.2 eq) in 1.5 mL THF. After the addition of 151 mg potassium carbonate (1.09 mmol, 2.2 eq) the yellow suspension was stirred for 5 h at RT. The reaction mixture was quenched by addition of 10 mL saturated $NaHCO_3$ solution and extracted with DCM (4x20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to yield a yellow oil. The crude product was used for the following reaction without further purification.*

Yield: 176 mg (quantitative yield), yellow oil, $C_{11}H_{14}INO_2S$ [351.20 g/mol].

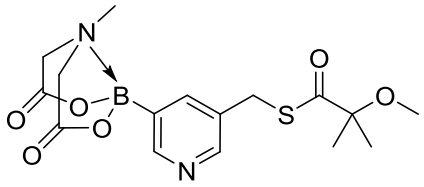
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, ^4J(H,H) = 1.7 Hz, 1H, CH, H^{Py}), 8.49 (d, ^4J = 1.5 Hz, 1H, CH, H^{Py}), 7.95 (bs, 1H, CH, H^{Py}), 3.95 (s, 2H, CH_2), 3.29 (s, 3H, OCH_3), 1.38 (s, 6H, CH_3) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 205.1 (C_q, COSH), 154.6 (CH, C^{Py}), 148.6 (CH, C^{Py}), 144.6 (CH, C^{Py}), 136.2 (C_q, C^{Py}), 93.4 (C_q, C^{Py}), 83.4 (C_q, $C(CH_3)_2$), 52.3 (OCH_3), 29.3 (CH_2), 23.9 (CH_3) ppm.

GC-MS (EI, 70 eV; SG_50_S): t_R = 7.336 min; *m/z* (%): 251 (18), 219 (8), 91 (3), 73 (100).

* No molecular peak was found by HRMS (EI) due to thermal decomposition.

6.7.17 *S*-((5-(6-Methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)pyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (27)



27

A flame dried and nitrogen flushed Schlenk flask was charged with 200 mg *S*-((5-iodopyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**24**) (0.570 mmol, 1 eq) and dissolved in 1.8 mL dry THF. After cooling the solution to -78 °C 370 µL *i*PrMgCl·LiCl solution (**32**) (0.627 mmol, 1.7 M, 1.1 eq) were added dropwise. After 1 h complete metal-halogen exchange was detected by GC-MS. The GC-samples were prepared by quenching a small aliquot of the reaction mixture with saturated $NaHCO_3$ solution and extraction with DCM. After adding 108 µL trimethyl borate (0.969 mmol, 1.7 eq) the reaction mixture was allowed to warm up in the cooling bath overnight. Afterwards the colourless suspension was cooled to -20 °C and 1.14 mL 1 M HCl were added, causing the formation of a biphasic mixture, which was stirred for 1 h. Then the cooling bath was removed and the phases were separated. The aqueous phase was neutralized by addition of 5 M NaOH, saturated with NaCl and extracted with THF (5x2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to yield a yellow solid, which was transferred into a nitrogen flushed 25 mL round-bottom-flask equipped with a Schlenk adapter. After the addition of 126 mg methyliminodiacetic acid (0.856 mmol, 1.5 eq) and 2 mL dry DMF the reaction mixture was heated to 85 °C overnight. Then the solvent was removed in vacuum by using a cold trap to yield a yellow oil. The crude product was purified via flash column chromatography (25 g SiO_2, 8x3 cm, EtOAc/MeCN = 100/0 → 0/100).[*]

Yield: 110 mg (51 %), colourless gum-like solid, $C_{16}H_{21}BN_2O_6S$ [380.22 g/mol].

R_f = 0.58 (MeCN), UV and CAM.

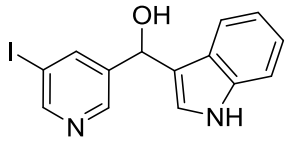
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (bs, 1H, CH, H^{Py}), 8.46 (bs, 1H, CH, H^{Py}), 7.74 (bs, 1H, CH, H^{Py}), 4.37 (d, ^2J = 17.2 Hz, 2H, CH_2, H^{MIDA}), 4.15 (d, ^2J = 17.2 Hz, 2H, CH_2, H^{MIDA}), 4.07 (s, 2H, CH_2), 3.19 (s, 3H, OCH_3), 2,54 (s, 3H, NCH_3, H^{MIDA}), 1.28 (s, 6H, CH_3) ppm.

[*] No molecular peak was found by HRMS (EI) due to thermal decomposition.

^{13}C NMR (76 MHz, $CDCl_3$, APT): δ = 204.9 (C_q, COSH), 169.2 (C_q, CO^{MIDA}), 151.8 (CH, C^{Py}), 150.1 (CH, C^{Py}), 140.5 (CH, C^{Py}), 132.9 (C_q, C^{Py}), 82.7 (C_q, $C(CH_3)_2$), 61.9 (CH_2^{MIDA}), 51.7 (OCH_3), 47.7 (CH_3N^{MIDA}), 29.0 (CH_2), 23.5 (CH_3) ppm.

HPLC-MS (Poroshell 120_001HCOOH_MeCN_10 auf 95): t_R = 2.464 min.

6.7.18 (1*H*-Indol-3-yl)(5-iodopyridin-3-yl)methanol (28)



28

A 5 mL one-neck-round-bottom-flask was charged with 65 mg indole (0.56 mmol, 1.3 eq) dissolved in 0.5 mL methanol and 12 µL 5 M NaOH. After the solution was cooled to 0 °C 100 mg 5-iodonicotinaldehyde (**4**) (0.429 mmol, 1 eq) were added. Afterwards the ice bath was removed and the reaction mixture became a yellow solution, which was stirred overnight. The formed precipitate was collected by filtration with a fritted funnel and washed twice with 2.5 mL of an acetone / cyclohexane mixture (3:7) to yield a colourless solid.

Yield: 109 mg (73 %), colourless solid, $C_{14}H_{11}IN_2O$ [350.16 g/mol].

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.00 (bs, NH), 8.66-8.64 (m, 2H, CH, H^{Py}), 8.18 (bs, 1H, CH, H^{Py}), 7.48 (d, ^3J = 7.8 Hz, 1H, CH, H^{Ind}), 7.35 (d, ^3J = 8.1 Hz, 1H, CH, H^{Ind}), 7.20 (s, ^{1}H, CH, H^{Ind}), 7.06 (t, ^3J = 7.4 Hz, 1H, CH, H^{Ind}), 6.93 (t, ^3J = 7.3 Hz, 1H, CH, H^{Ind}), 6.01 (s, 1H, CH), 5.89 (bs, 1H, OH) ppm.

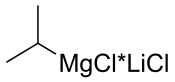
^{13}C NMR (76 MHz, DMSO-d_6): δ = 153.3 (CH, C^{Py}), 146.6 (CH, C^{Py}), 143.4 (C_q, C^{Ind}), 141.7 (CH, C^{Py}), 136.5 (C_q, C^{Py}), 125.2 (C_q, C^{Ind}), 123.0 (CH, C^{Ind}), 121.2 (CH, C^{Ind}), 119.2 (CH, C^{Ind}), 118.6 (CH, C^{Ind}), 118.2 (C_q, C^{Ind}), 111.6 (CH, C^{Ind}), 93.9 (C_q, C^{Py}), 66.3 (CH) ppm.

HPLC-MS (Poroshell 120_001HCOOH_MeCN_10 auf 95): t_R = 3.222 min.

HRMS (EI): calcd for [M^+]: 349.9916; found: 349.9923.

m.p.$^{exp.}$ = 200-205 °C (spontaneous decomposition).

6.7.19 Isopropylmagnesium chloride lithium chloride solution (*i*PrMgCl•LiCl) (32)[6,42]



32

A flame dried 100 mL three-neck round-bottom flask equipped with a reflux condenser and a nitrogen inlet was charged with 3.29 g magnesium turnings (135 mmol, 1.1 eq). The flask was evacuated and heated with a heat gun for 10 min. After letting the flask cool down to RT ~4 mg of iodine were added and it was stirred for 60 min. The magnesium was suspended in 20 mL dry THF and "activated" in an ultrasound bath for 10 min. After cooling the mixture down to 0 °C 11.2 mL isopropyl chloride (122 mmol, 1 eq) were added at once. Removal of the cooling bath and subsequent slight heating with the heat gun started the formation of the Grignard reagent. After 45 min the violent reaction had finished. The reaction mixture was diluted with 30 mL dry THF, stirred under reflux over a period of 3 h and then stirred overnight at RT. The grey solution was separated from the residual magnesium by transfer it into a Schlenk flask via a Teflon cannula with an attached filter. The concentration of the Grignard reagent was determined by titration according to procedure 6.7.19.1. According to the concentration and estimation of the volume, 1 eq of dried and pulverized lithium chloride was added. The grey mixture was stirred for 4 d at RT. The solution was stored under nitrogen in a Schlenk flask at -28°C and the concentration determined via titration according to procedure 6.7.19.1 before each use. The solution was both stable for the whole time period of this work and the concentration of the Grignard reagent only slightly decrased (0.3 mol/L in 6 months).

6.7.19.1 Titration of Isopropylmagnesium chloride lithium chloride solution (*i*PrMgCl•LiCl) (32)

The concentration was determined in triplicates. A flame dried and nitrogen flushed Schlenk flask was charged with 150 mg menthol (0.960 mmol) and ~1 mg *N*-phenyl-4-phenylazoaniline. After the solids were dissolved in 2 mL dry THF the Grignard solution was added dropwise via a syringe to the Schlenk flask while stirring under an inert atmosphere until a colour change from yellow to dark red was observed. The concentration could be obtained by dividing the amount of menthol through the consumed volume of the Grignard solution.

7 References

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8 Abbreviations

Analytical methods:

ATP	attached proton test
bs	broad singlet
C_q	quaternary carbon
d	doublet
EI	electron impact ionization
eV	electron Volt
FT	Fourier transform
GC-MS	Gas chromatography-mass spectrometry
HPLC-MS	High performance liquid chromatography-mass spectrometry
HRMS	high resolution mass spectrometry
J	coupling constant
m	multiplet
m.p.	melting point
m/z	mass-charge ratio
MSD	mass sensitive detector
NMR	nuclear magnetic resonance
ppm	parts per million
q	quadruplet
R_f	retardation factor
s	singlet
t	triplet
TIC	total ion count
TLC	thin layer chromatography
t_R	retention time
UV	ultraviolet
δ	chemical shift

Chemical abbreviations:

AcCl	acetyl chloride
Ar	aryl
Boc	*tert*-butyloxycarbonyl
bpy	2,2′-bipyridine

*n*Bu	*n*-butyl
brine	saturated sodium chloride solution in water
Bz	benzyl
CAM	cerium-ammonium-molybdate
COD	1,5-cyclooctadiene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO-d_6	D_6-dimethyl sulfoxide
DIBAL-H	diisobutylaluminium hydride
DMEDA	*N*,*N'*-dimethylethylenediamine
DMSO	dimethyl sulfoxide
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
HBS	hydrogen bond surrogate
Ind	indole
*i*Pr	isopropyl
LAH	lithium aluminum hydride
Me	methyl
MIDA	*N*-methyliminodiacetic acid
OAc	acetate
p	para
PMB	p-methoxybenzyl
PDB	protein data base
PG	protective group
Ph	phenyl
Pin	2,3-dimethyl-2,3-butanediol
PPI	protein-protein interaction
Py	pyridine
RF	reflux
TBDPS	*tert*-butyldiphenylsilyl
TBDMS	*tert*-butyldimethylsilyl
*t*Bu	1,1-dimethylethyl
Tf	triflate
THF	tetrahydrofuran

Others:

%	percent
°C	degree Celsius
µm	micrometer
Å	angstrom
cm	centimeter
d	day
eq	equivalents
g	gramm
h	hour
Hz	Hertz
m	meter
M	molar (mol/L)
mbar	millibar
mg	milligram
MHz	megaHertz
min	minute
mL	milliliter
mmol	millimole
Mol%	mole percent
nm	nanometer
ON	over night
RT	room temperature
T	temperature
tert	tertiary
V	Volt
v/v	volume/volume
w/w	weight/weight

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EIDESSTATTLICHE ERKLÄRUNG

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10 Appendix

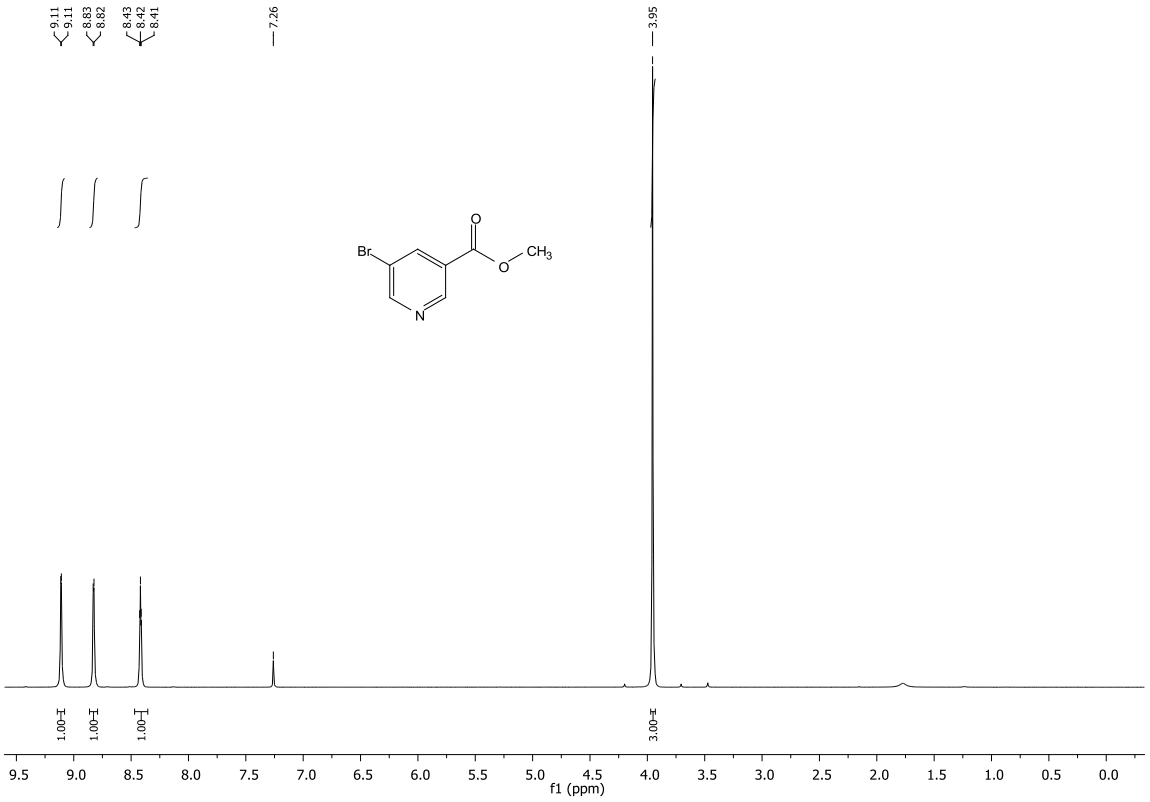

Figure 11: ^{1}H NMR; Methyl 5-bromonicotinate (**1**).

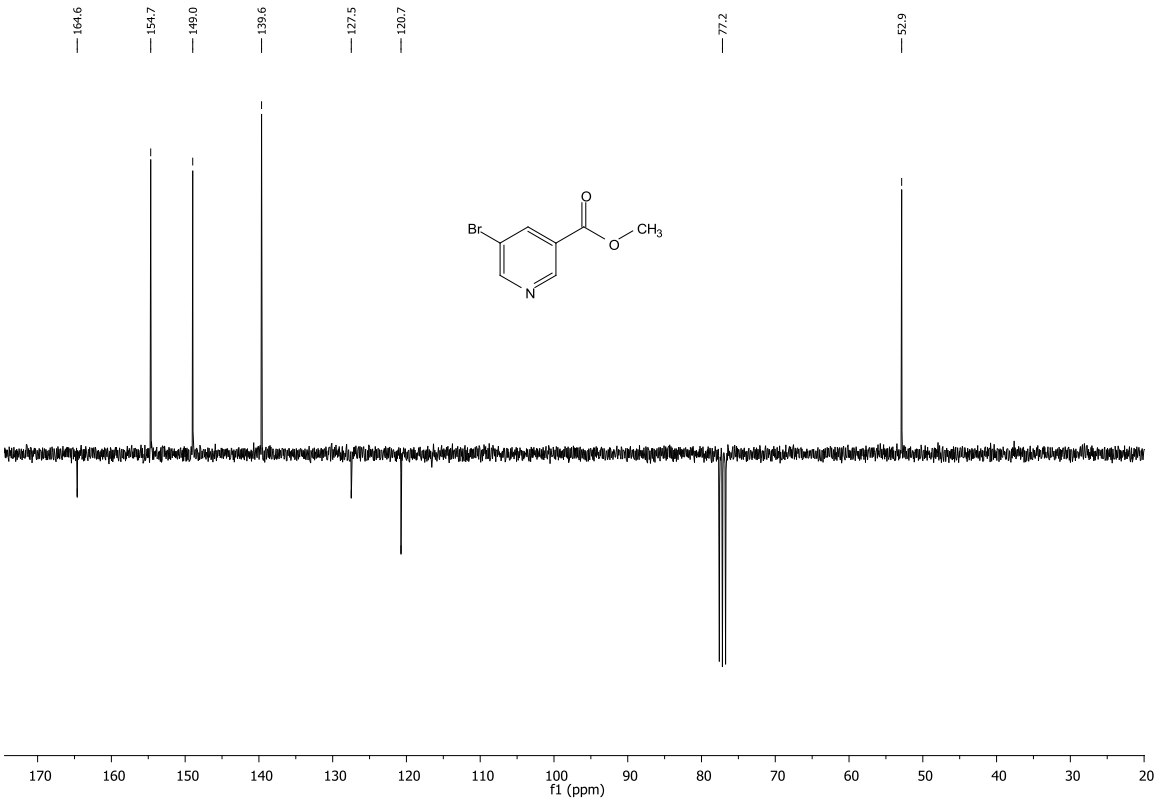

Figure 12: ^{13}C NMR, APT; Methyl 5-bromonicotinate (**1**).

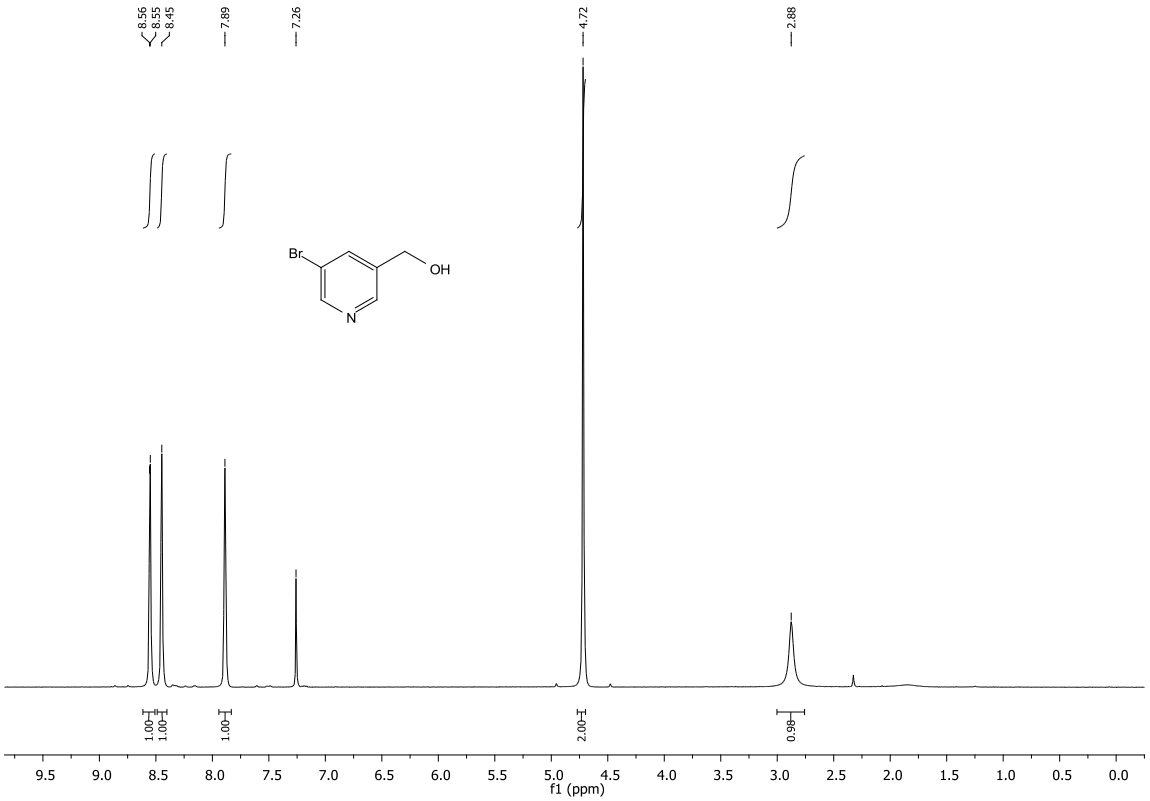

Figure 13: ^{1}H NMR; (5-Bromopyridin-3-yl)methanol (**2**).

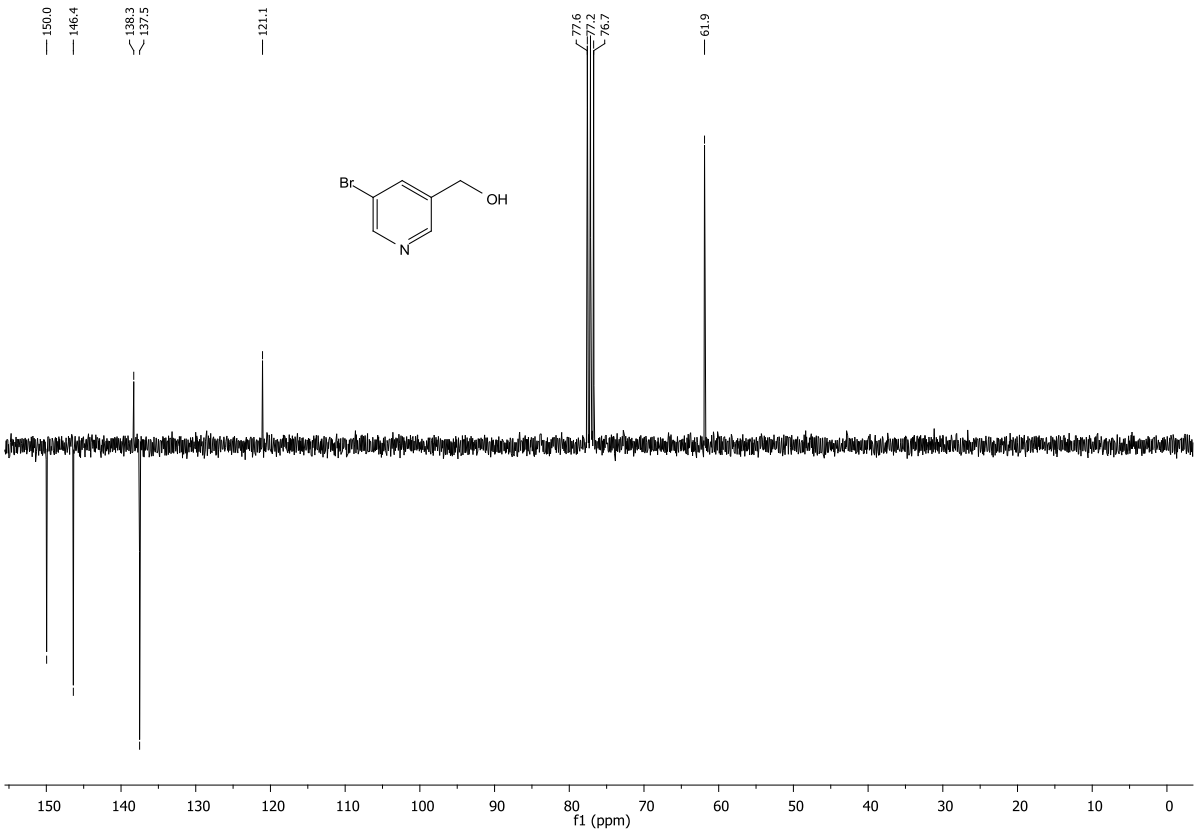

Figure 14: ^{13}C NMR, APT; (5-Bromopyridin-3-yl)methanol (**2**).

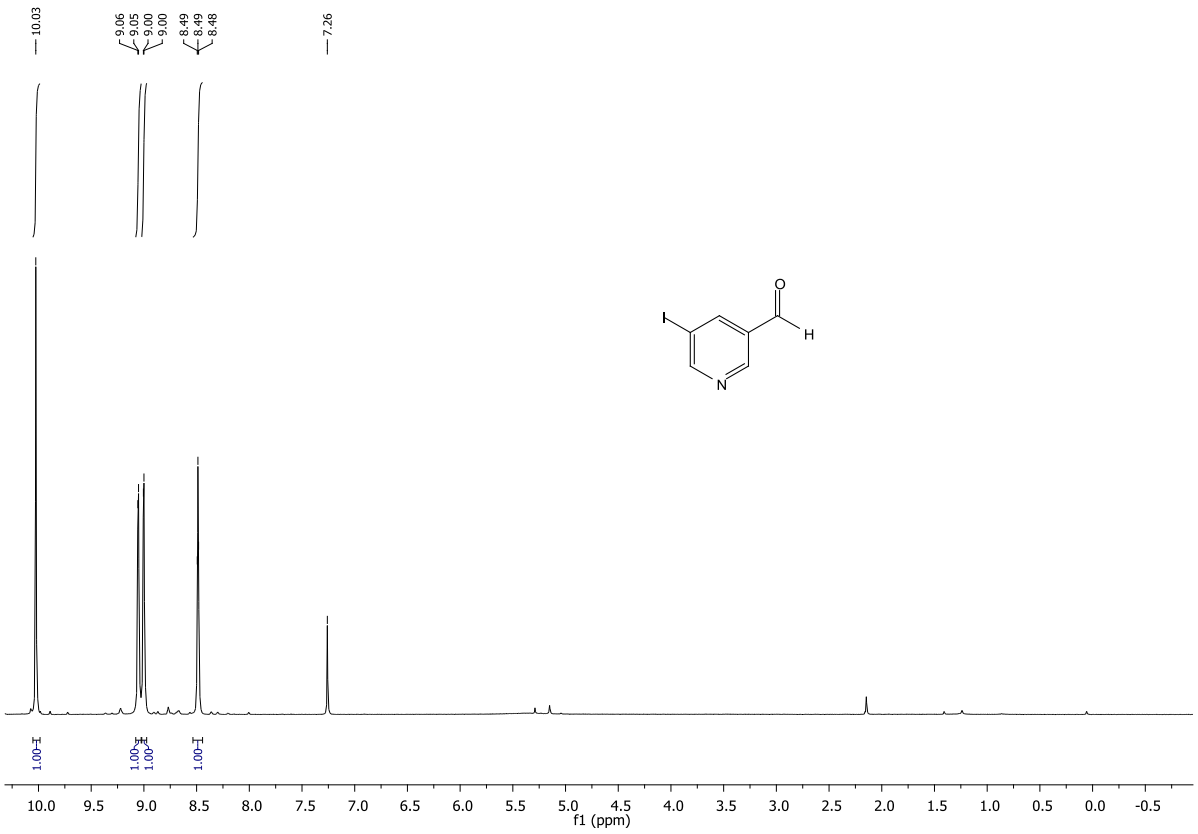

Figure 15: ^{1}H NMR; 5-Iodonicotinaldehyde (**4**).

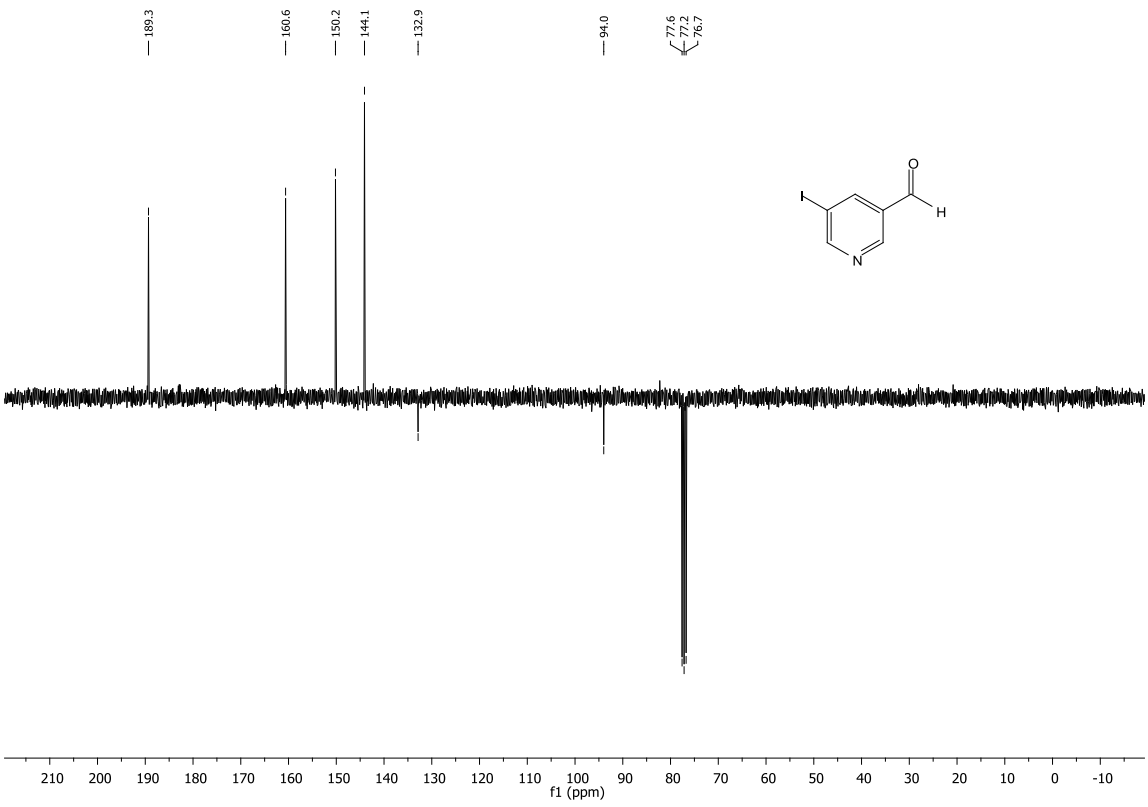

Figure 16: ^{13}C NMR, APT; 5-Iodonicotinaldehyde (**4**).

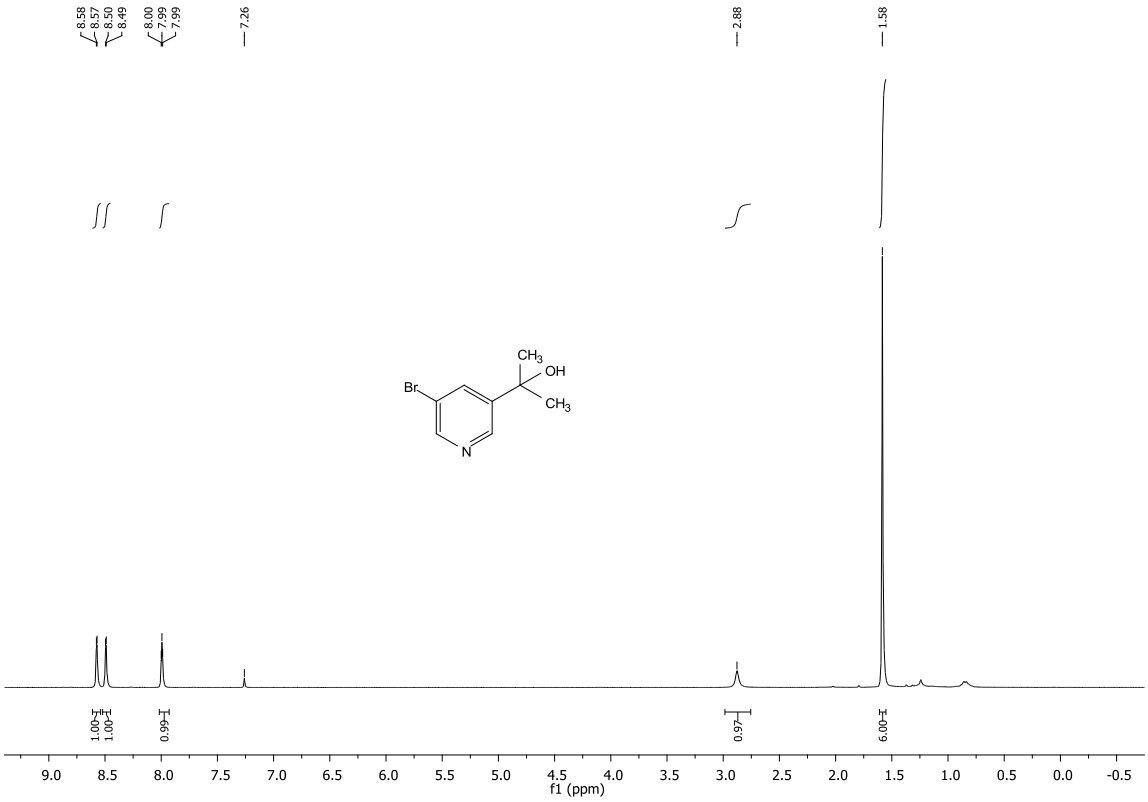

Figure 17: ^{1}H NMR; 2-(5-Bromopyridin-3-yl)propan-2-ol (**11**).

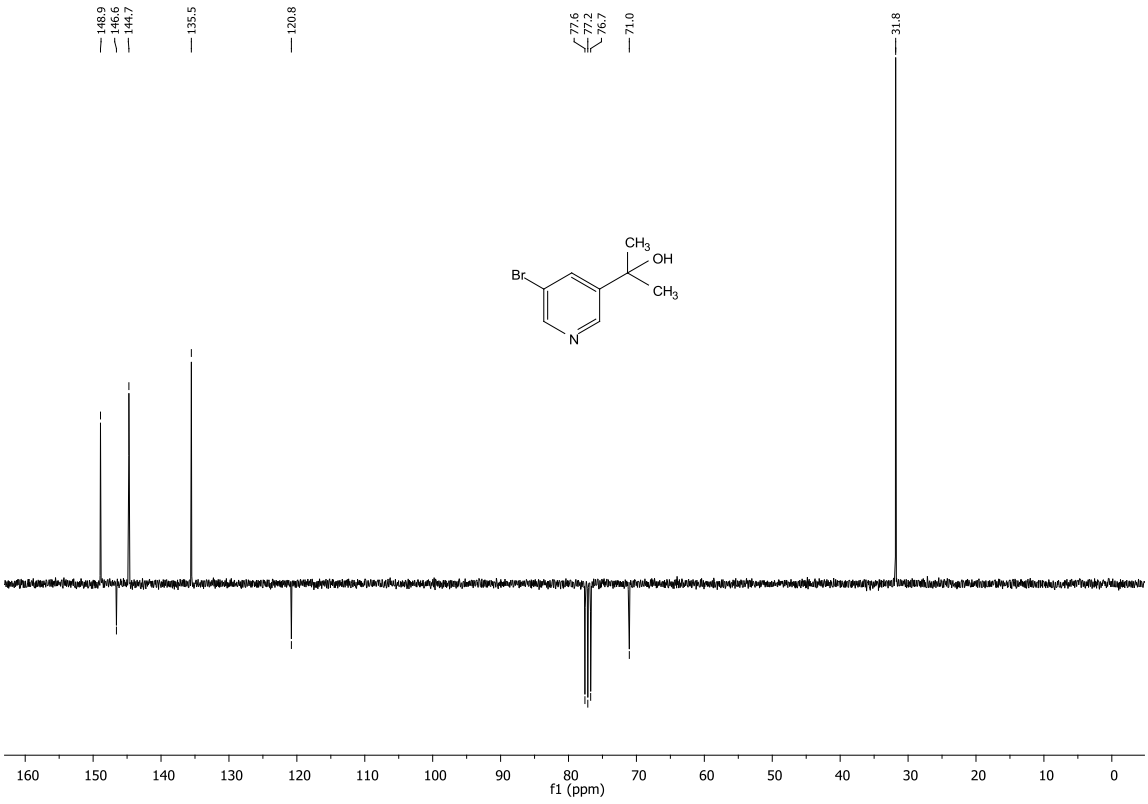

Figure 18: ^{13}C NMR, APT; 2-(5-Bromopyridin-3-yl)propan-2-ol (**11**).

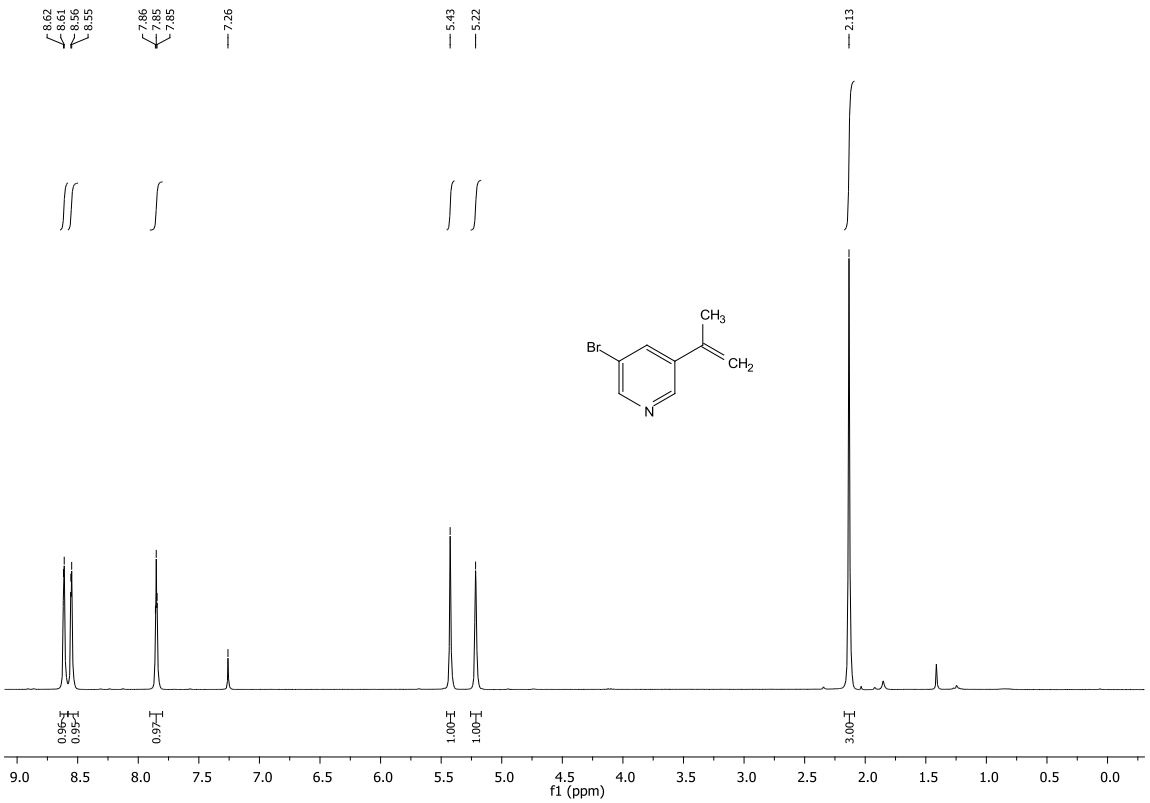

Figure 19: ^{1}H NMR; 3-Bromo-5-(prop-1-en-2-yl)pyridine (**12**).

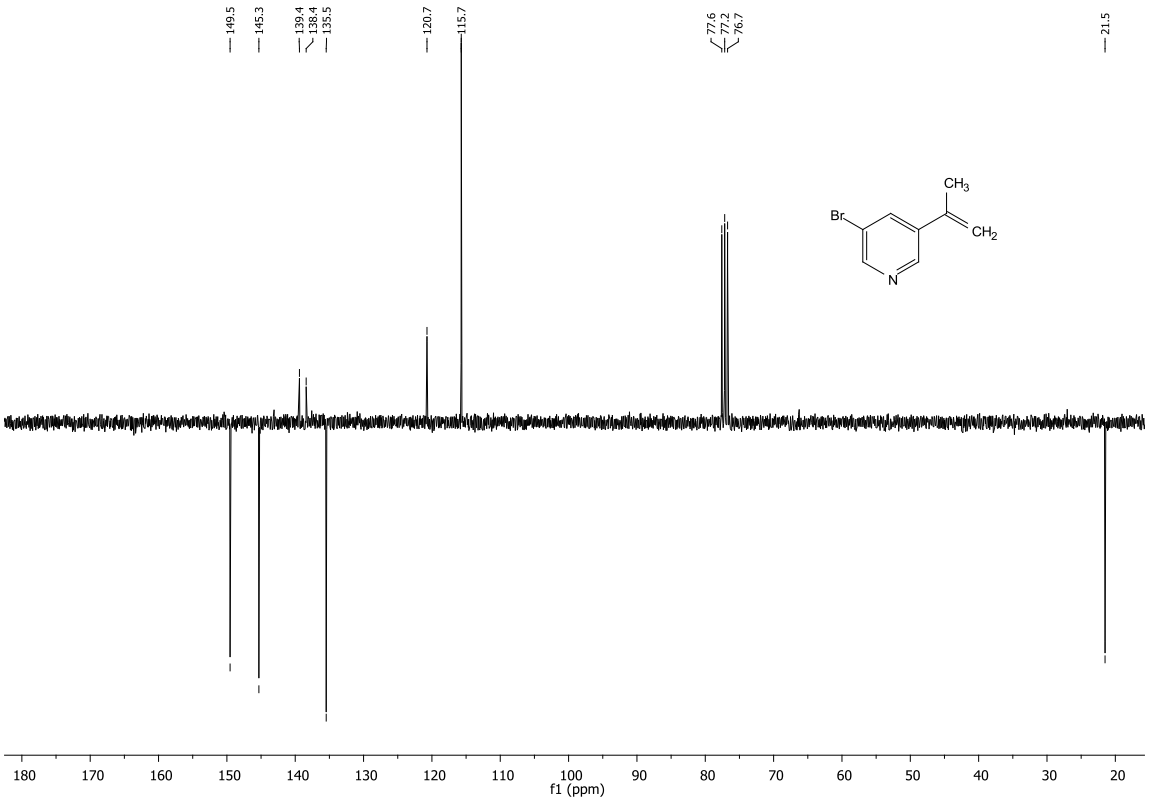

Figure 20: ^{13}C NMR, APT; 3-Bromo-5-(prop-1-en-2-yl)pyridine (**12**).

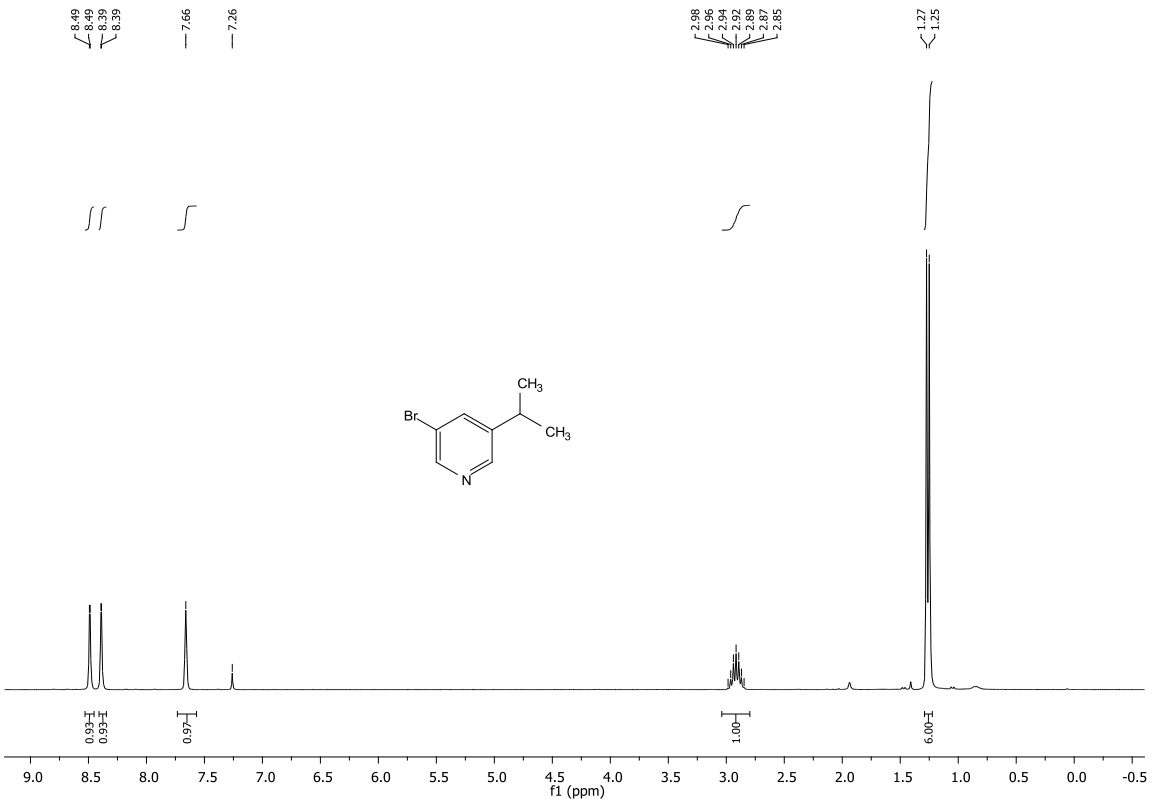

Figure 21: ^{1}H NMR; 3-Bromo-5-isopropylpyridine (**13**).

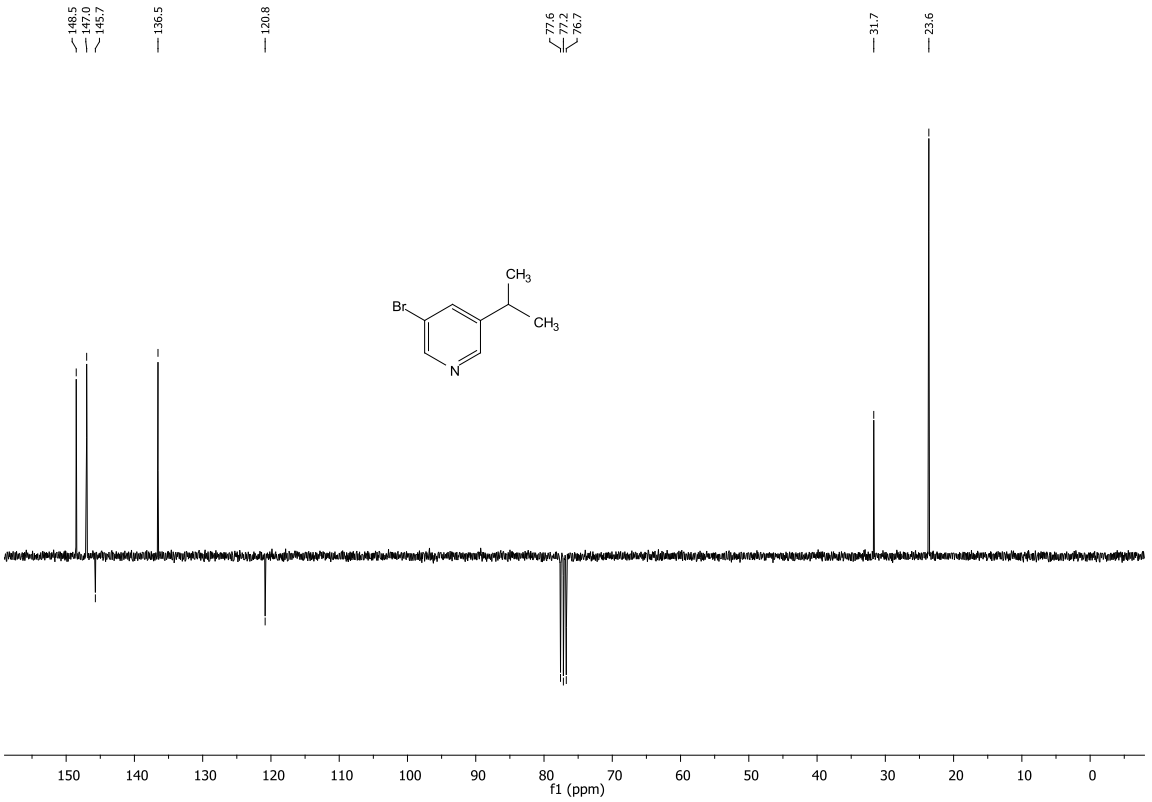

Figure 22: ^{13}C NMR, APT; 3-Bromo-5-isopropylpyridine (**13**).

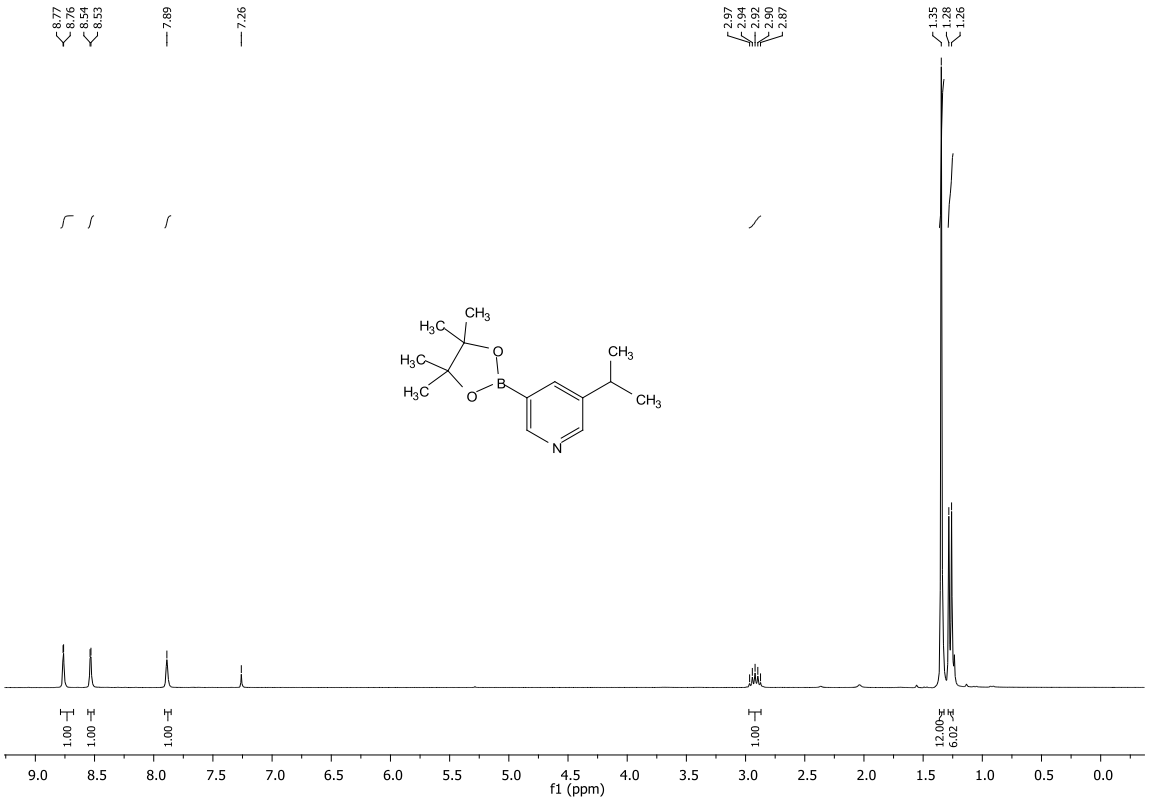

Figure 23: ^{1}H NMR; 3-Isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**14**).

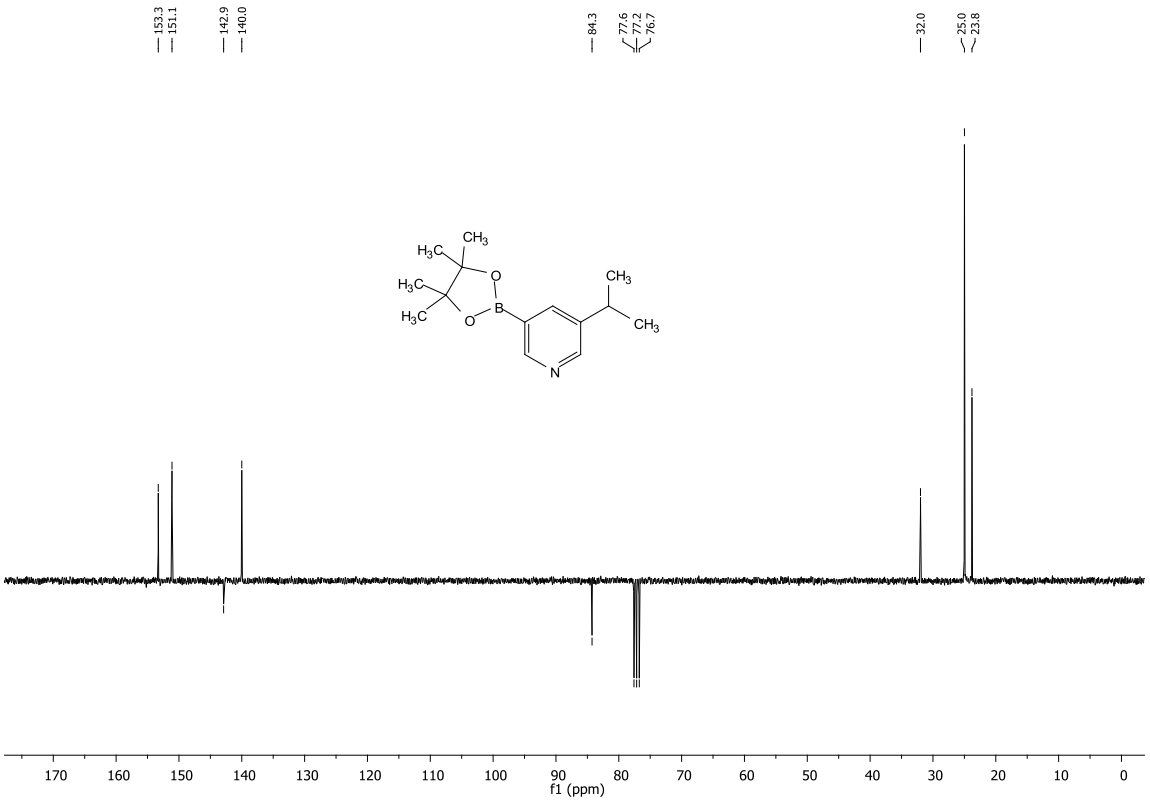

Figure 24: ^{13}C NMR, APT; 3-Isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**14**).

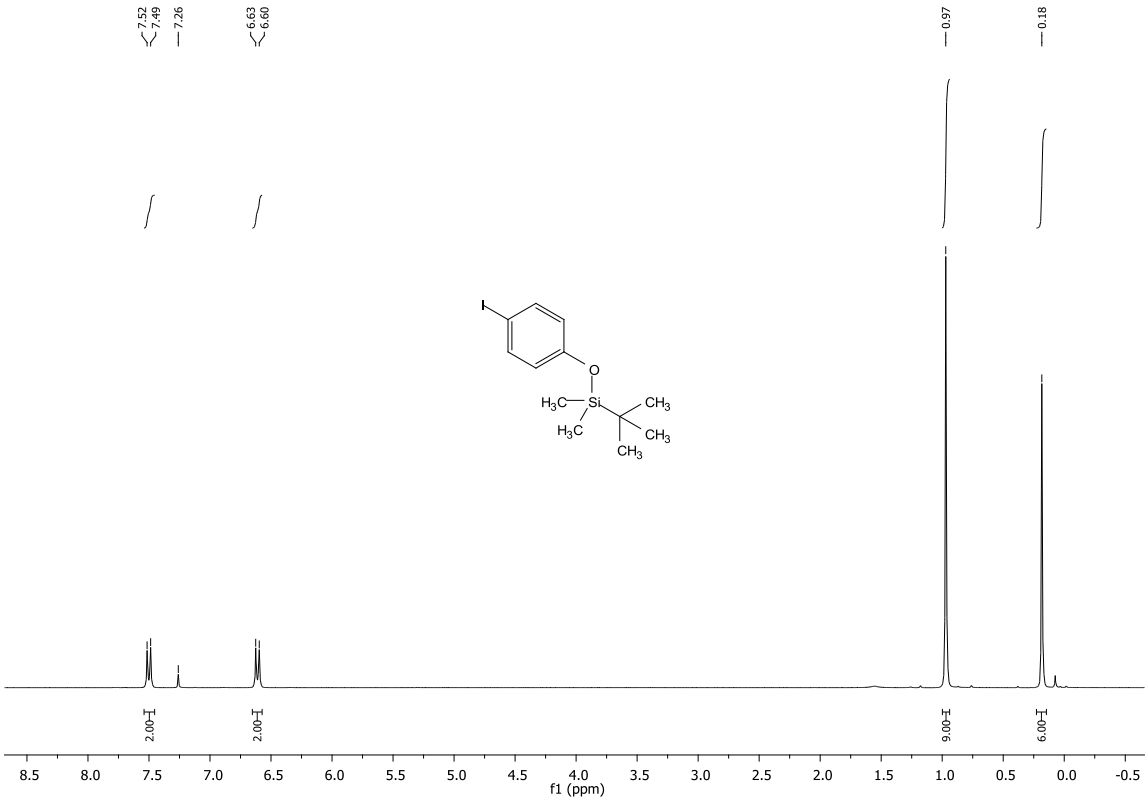

Figure 25: ^{1}H NMR; 3-*tert*-Butyl(4-iodophenoxy)dimethylsilane (**16**).

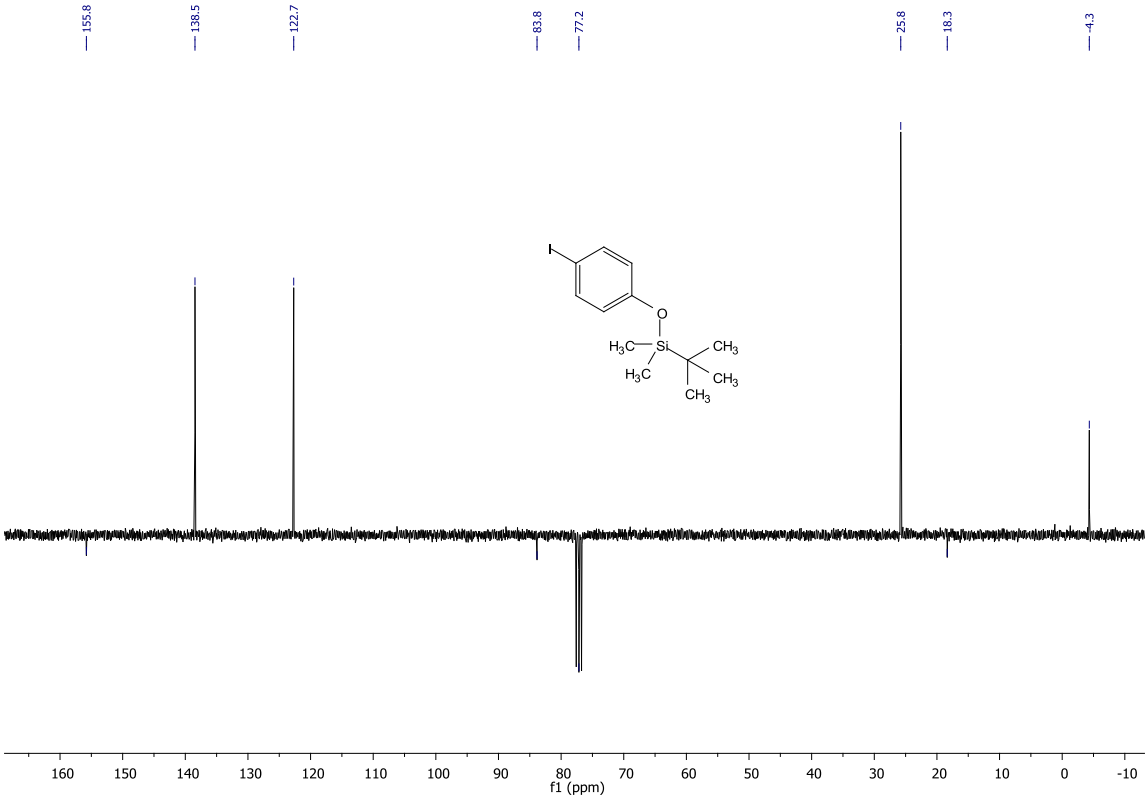

Figure 26: ^{13}C NMR, APT; 3-*tert*-Butyl(4-iodophenoxy)dimethylsilane (**16**).

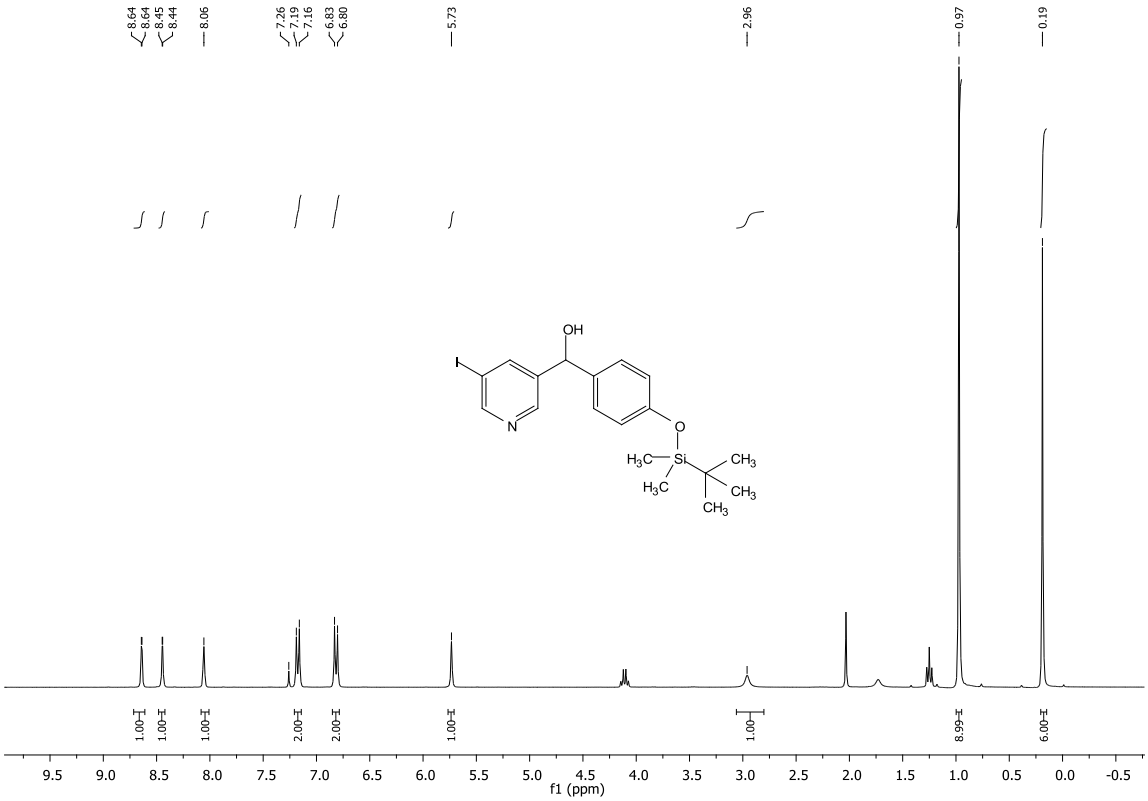

Figure 27: ^{1}H NMR; (4-((*tert*-Butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (**17**).

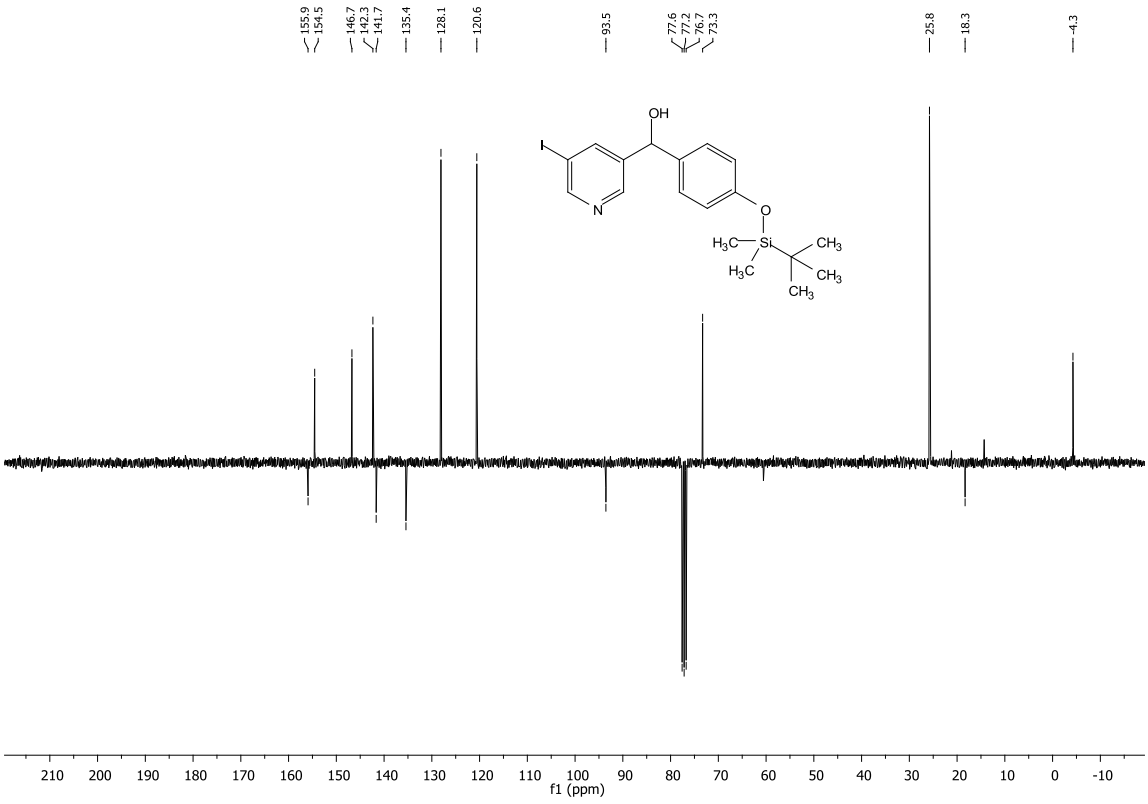

Figure 28: ^{13}C NMR, APT; (4-((*tert*-Butyldimethylsilyl)oxy)phenyl)(5-iodopyridin-3-yl)methanol (**17**).

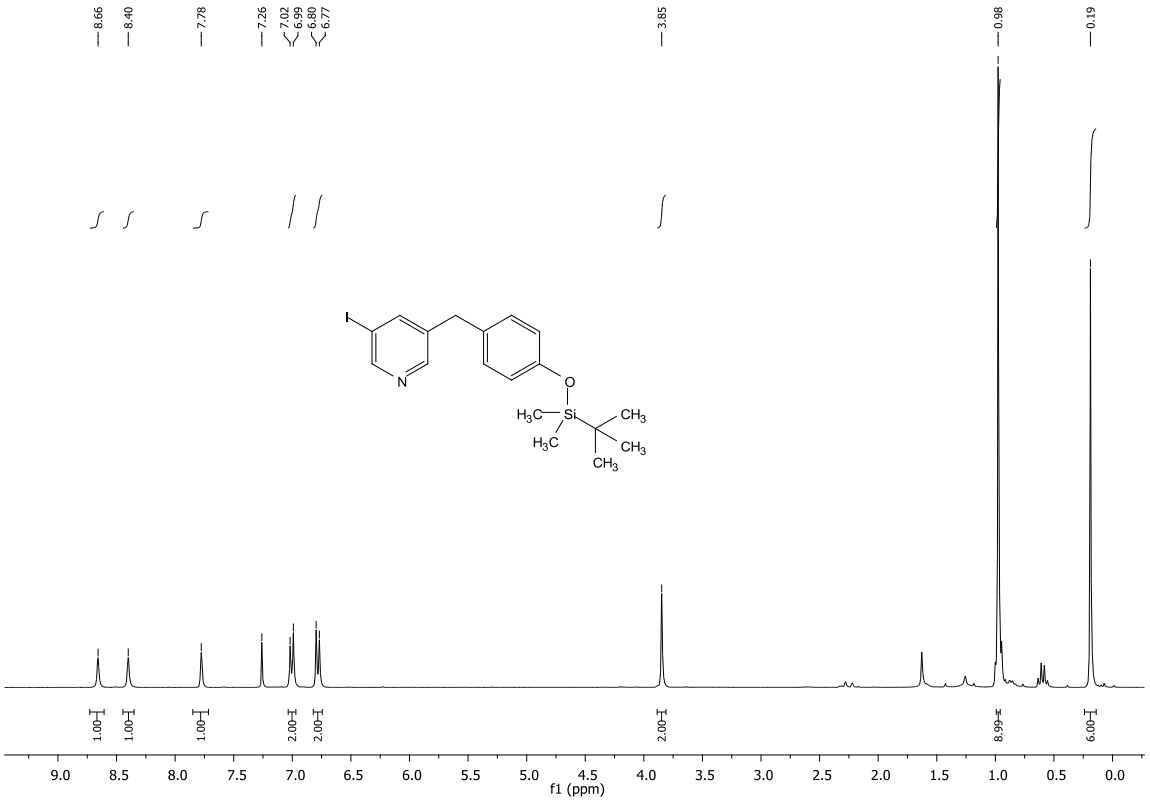

Figure 29: ^{1}H NMR; 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-iodopyridine (**18**).

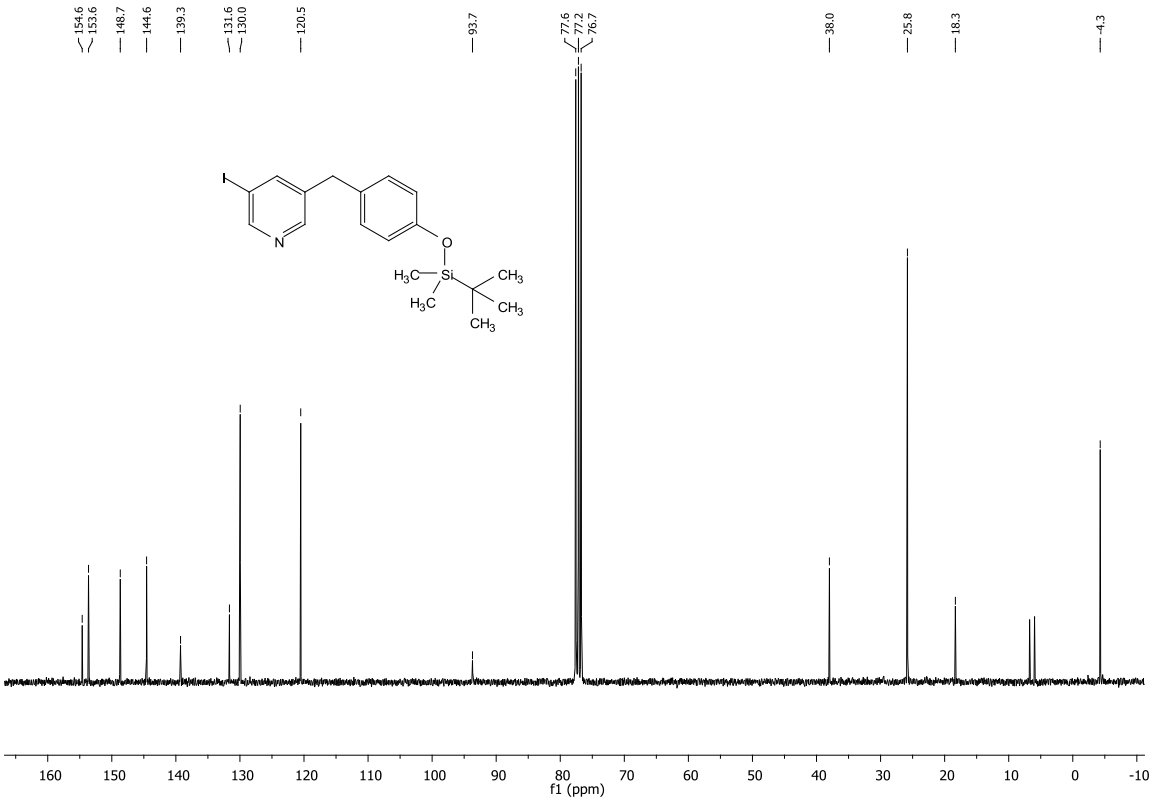

Figure 30: ^{13}C NMR; 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-iodopyridine (**18**).

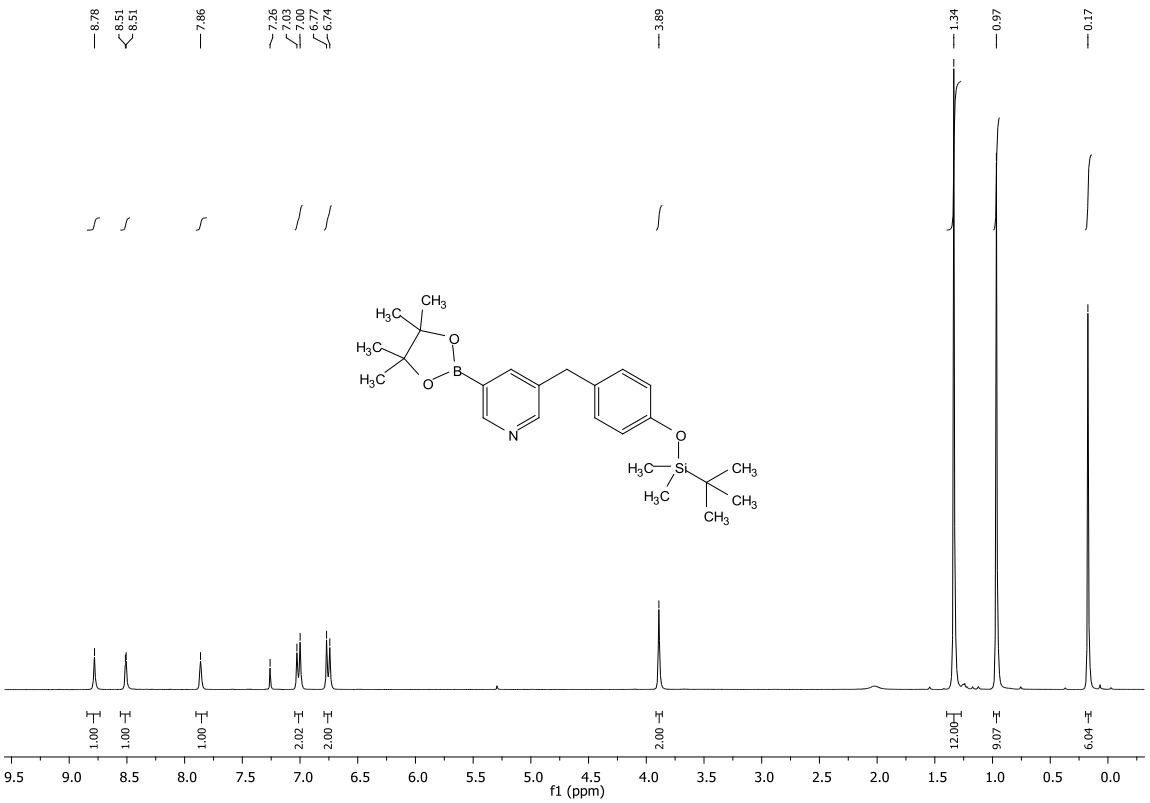

Figure 31: ^{1}H NMR; 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**19**).

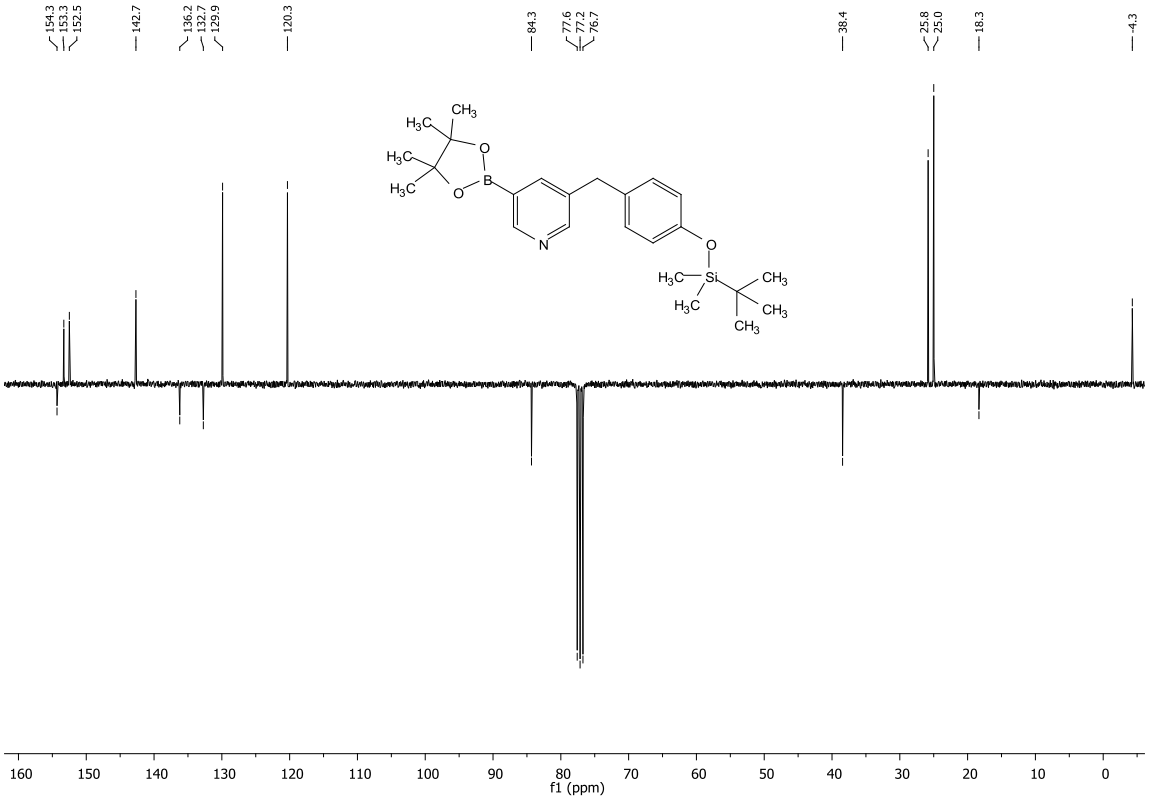

Figure 32: ^{13}C NMR, APT; 3-(4-((*tert*-Butyldimethylsilyl)oxy)benzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**19**).

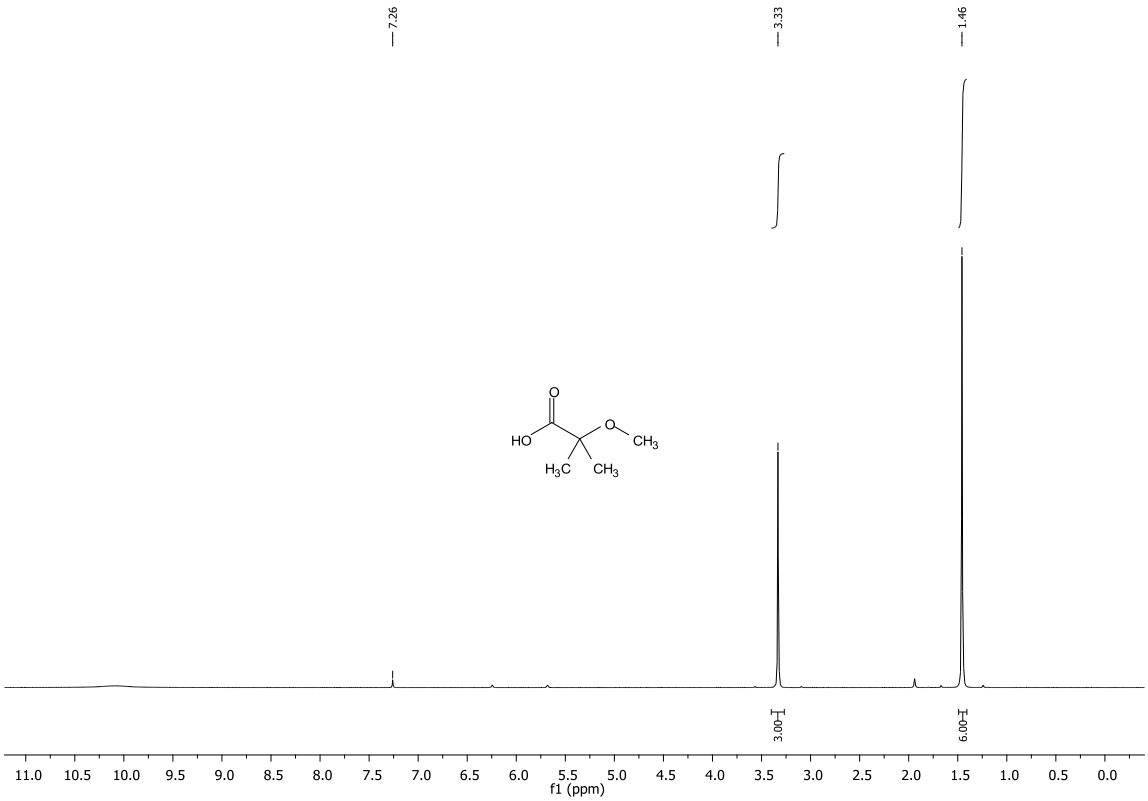

Figure 33: ^{1}H NMR; 2-Methoxy-2-methylpropanoic acid (**22**).

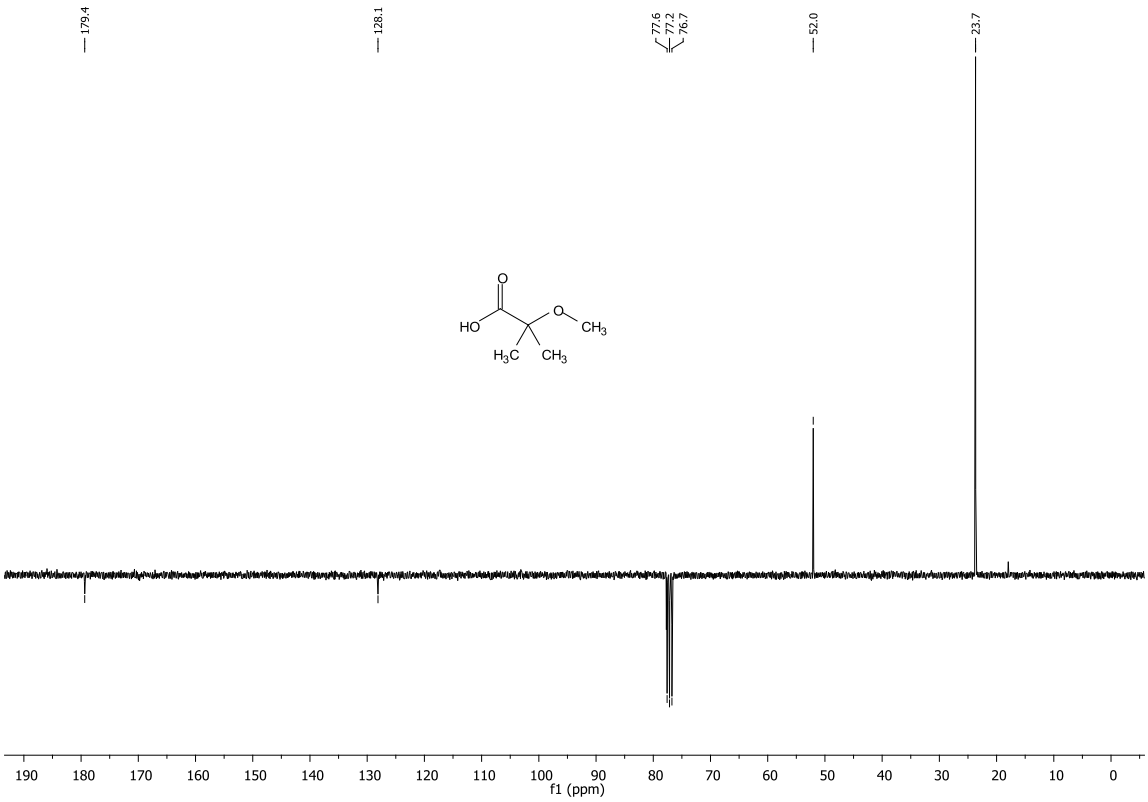

Figure 34: ^{13}C NMR, APT; 2-Methoxy-2-methylpropanoic acid (**22**).

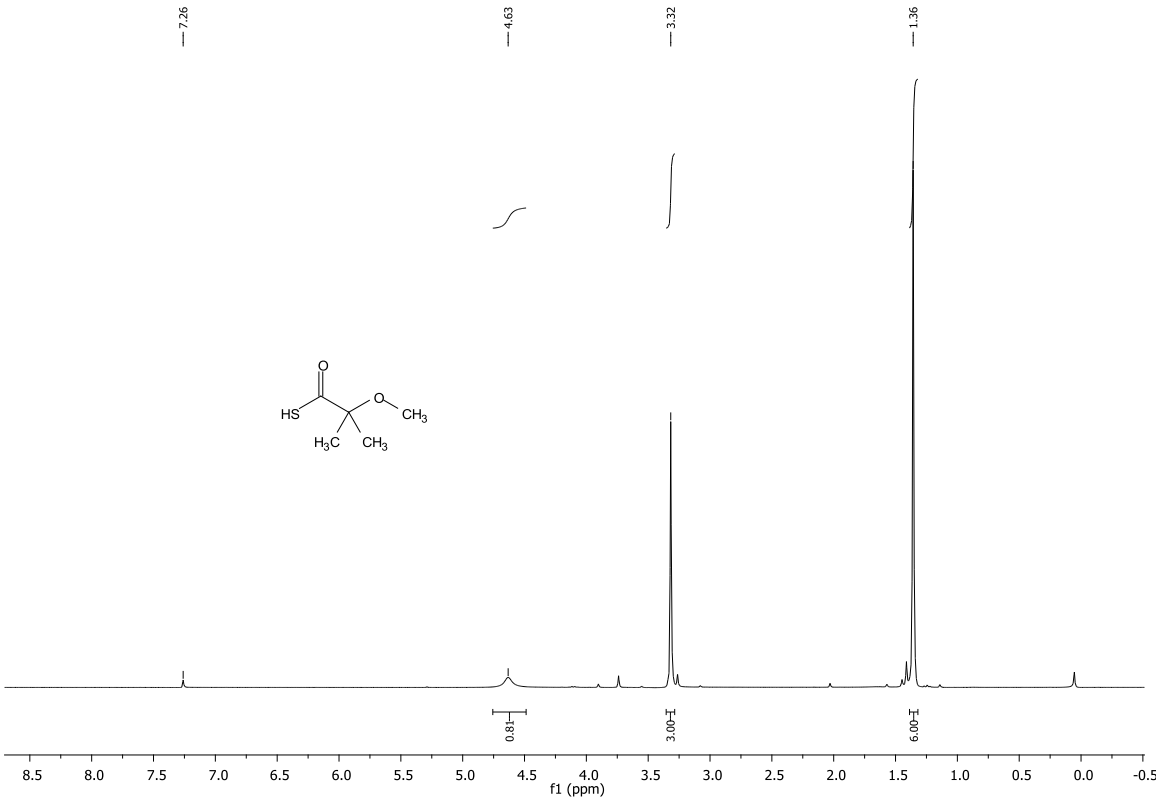

Figure 35: ^{1}H NMR; 2-Methoxy-2-methylpropanethioic *S*-acid (**23**).

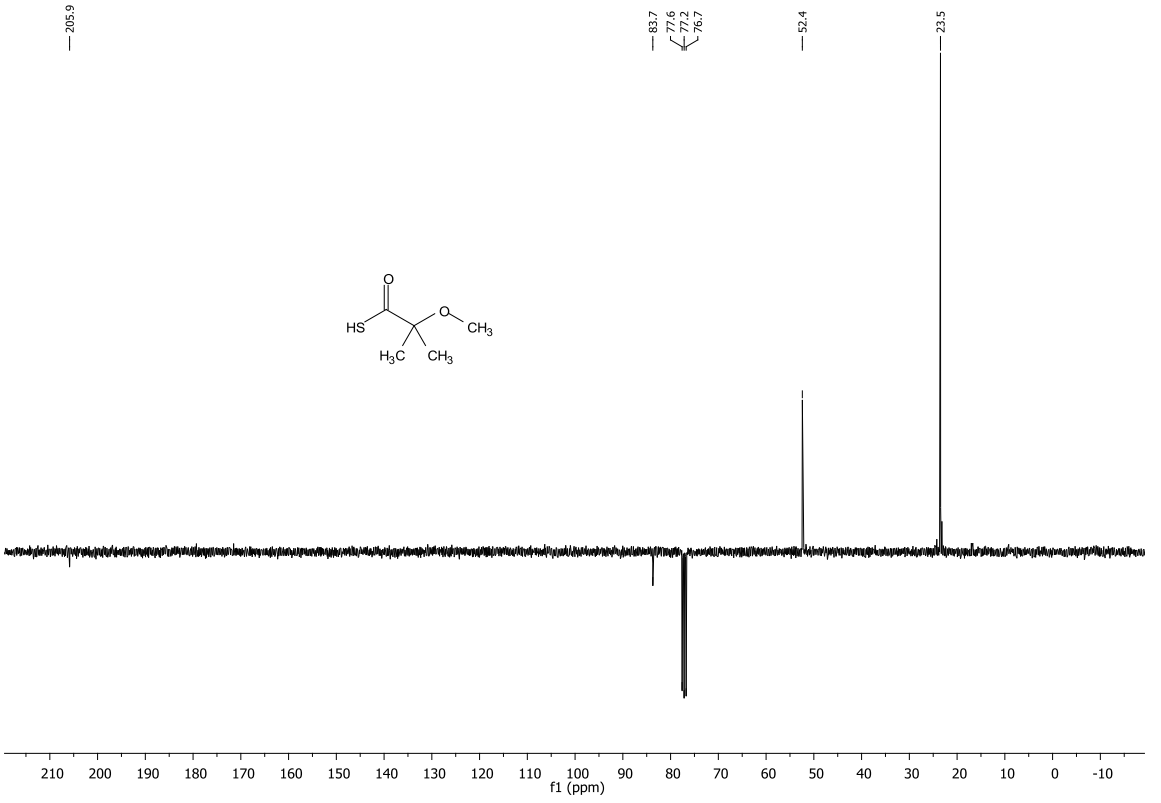

Figure 36: ^{13}C NMR, APT; 2-Methoxy-2-methylpropanethioic *S*-acid (**23**).

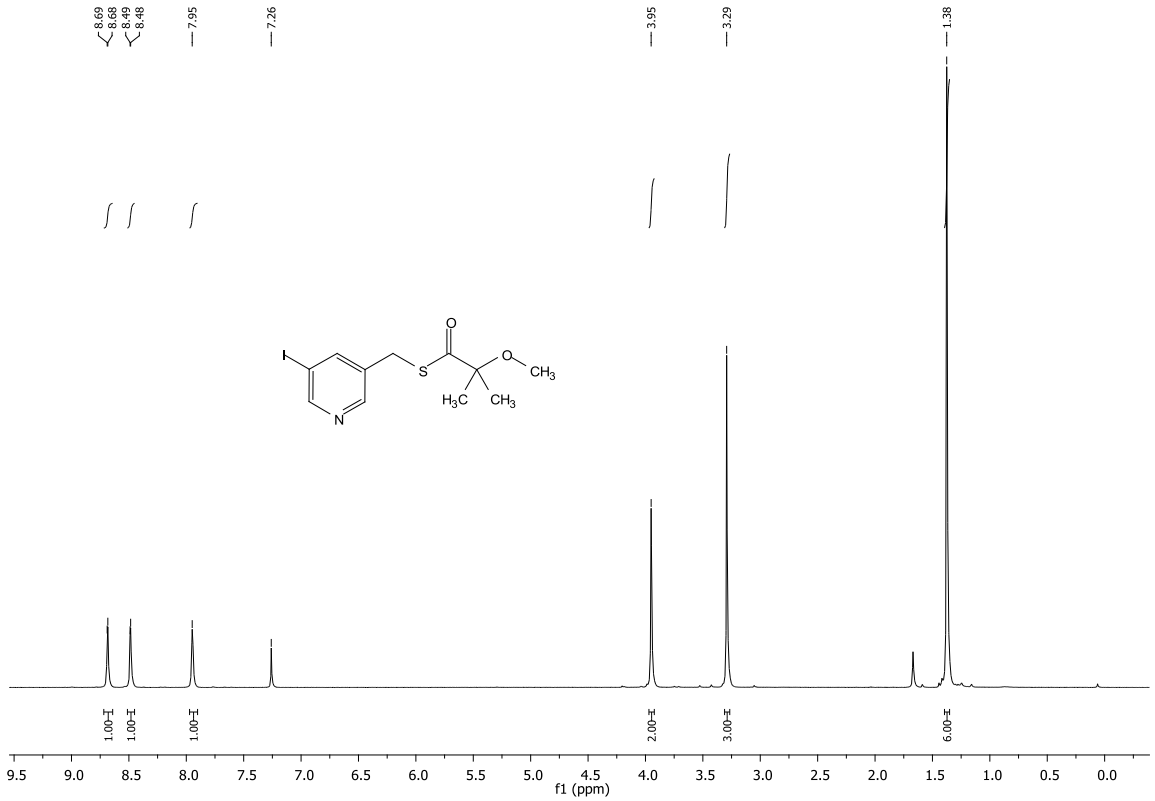

Figure 37: ^{1}H NMR; *S*-((5-Iodopyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**24**).

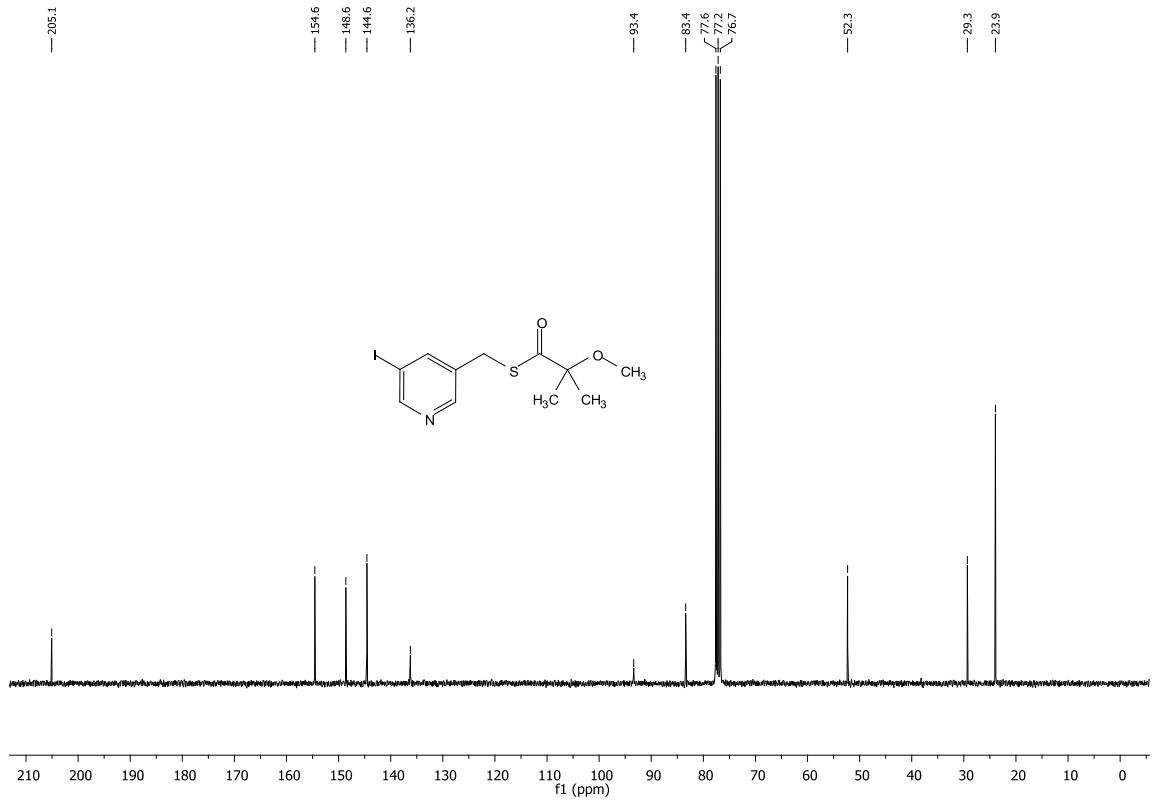

Figure 38: ^{13}C NMR; *S*-((5-Iodopyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**24**).

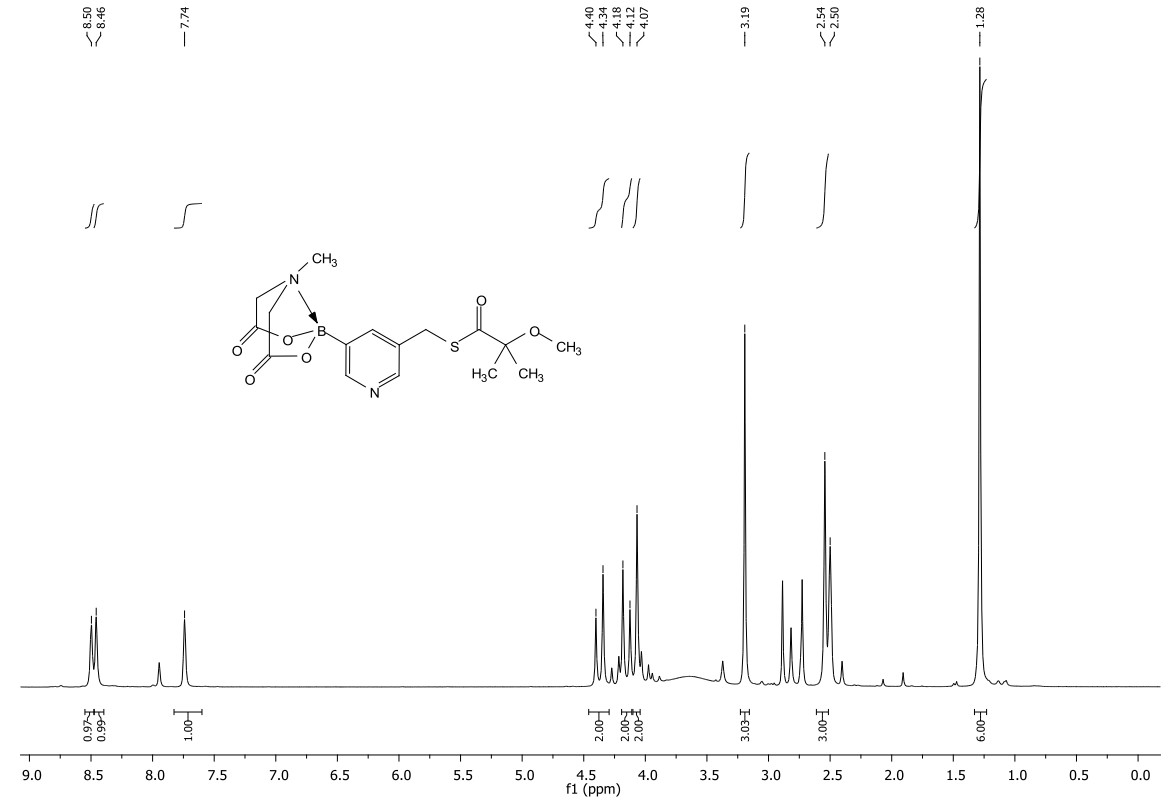

Figure 39: ^{1}H NMR; *S*-((5-(6-Methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)pyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**27**).

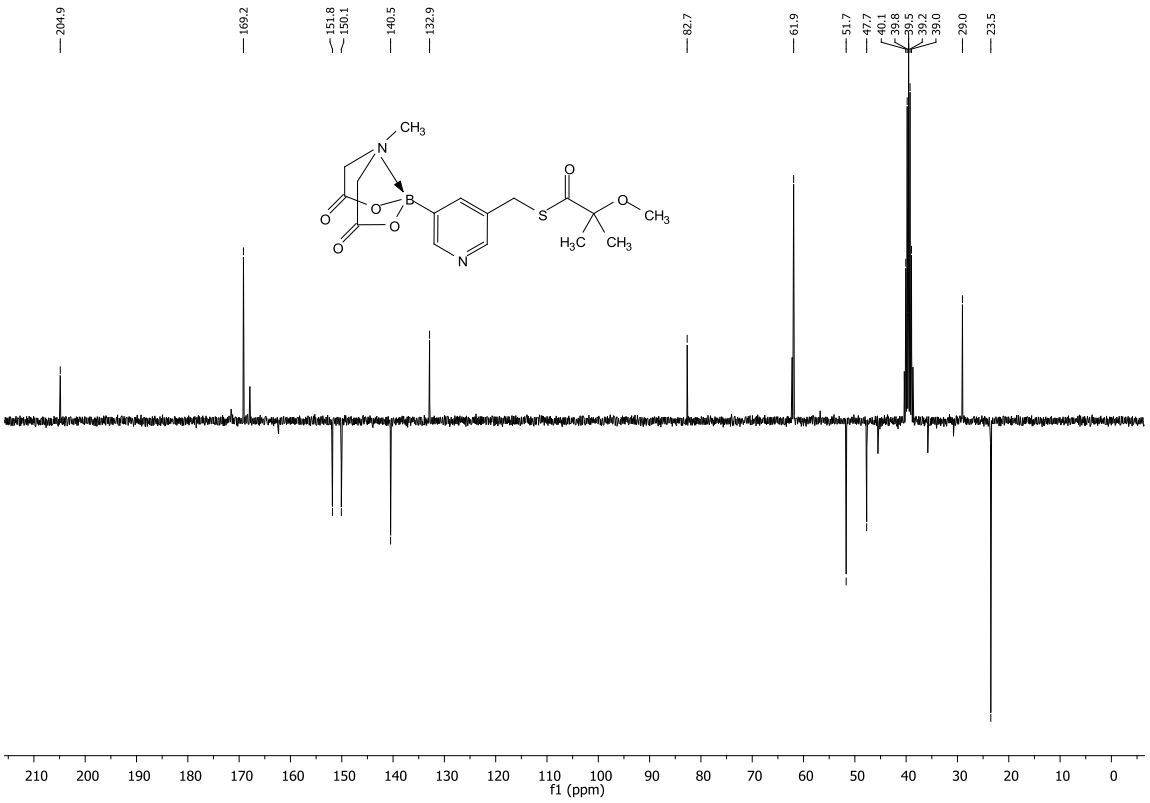

Figure 40: ^{13}C NMR, APT; *S*-((5-(6-Methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)pyridin-3-yl)methyl) 2-methoxy-2-methylpropanethioate (**27**).

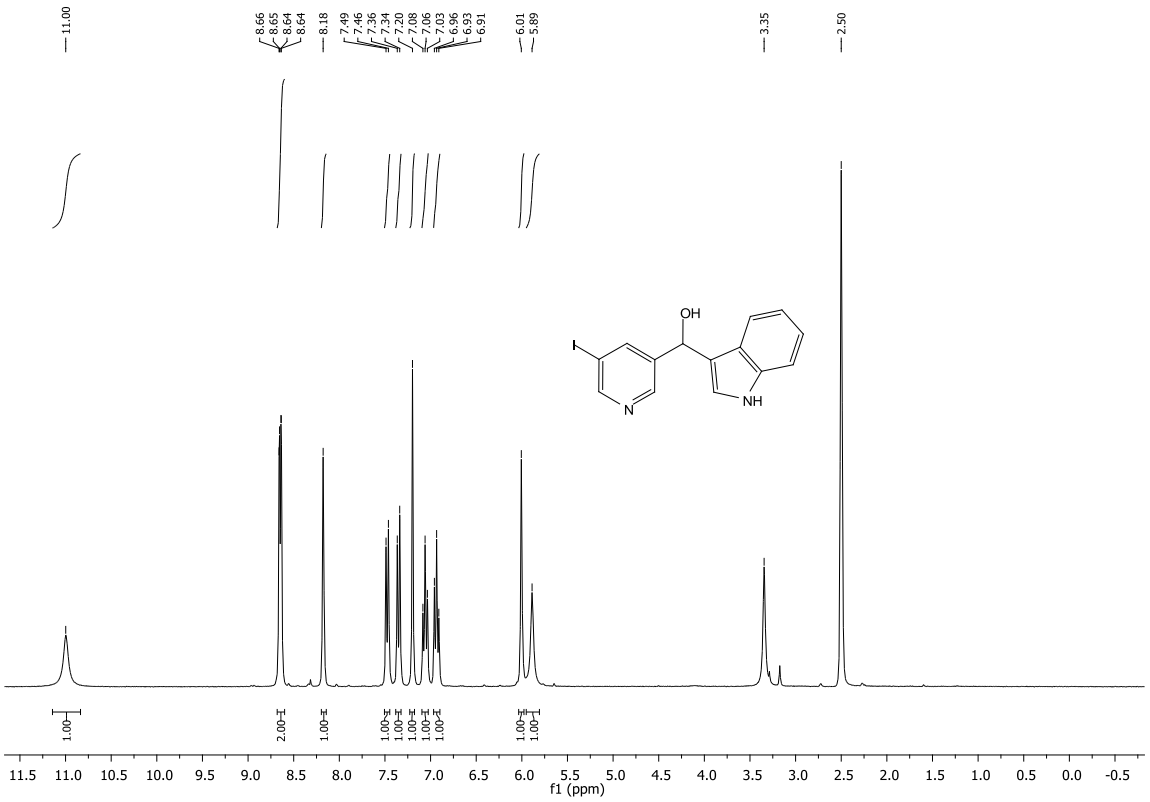

Figure 41: ^{1}H NMR; (1*H*-Indol-3-yl)(5-iodopyridin-3-yl)methanol (**28**).

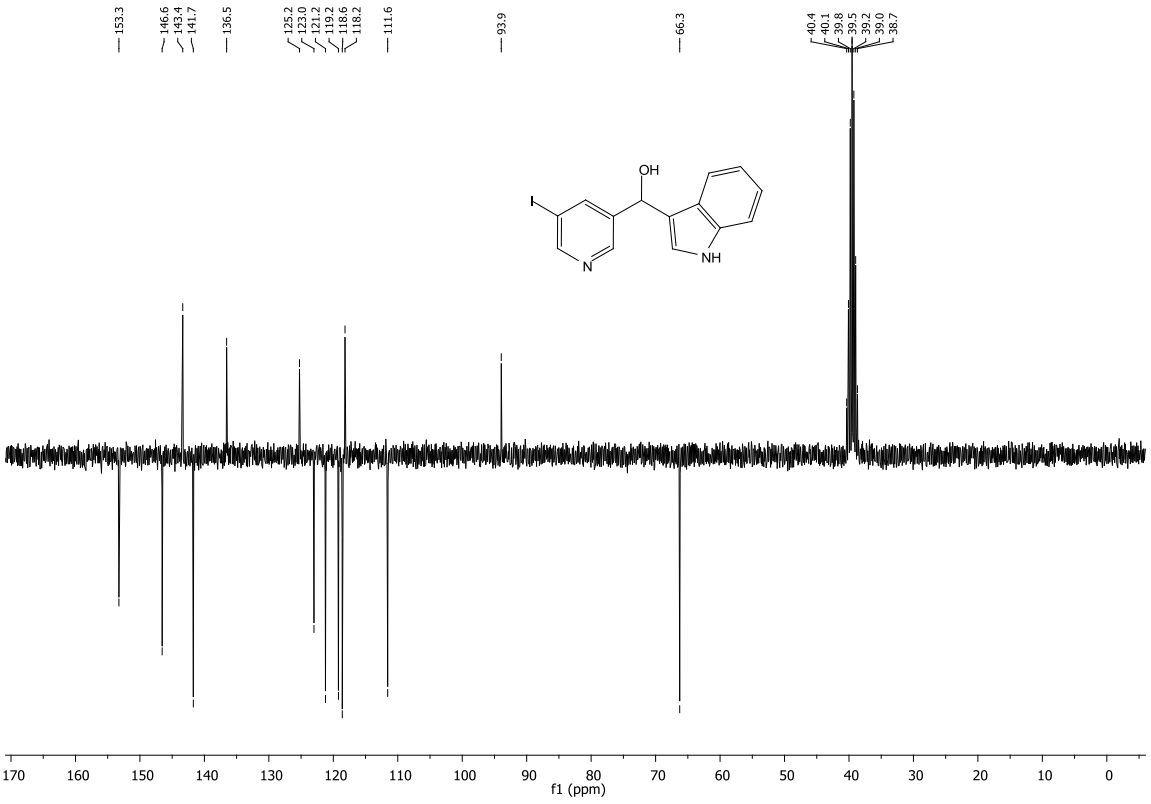

Figure 42: ^{13}C NMR; (1*H*-Indol-3-yl)(5-iodopyridin-3-yl)methanol (**28**).