Conversion of Alcohols to Alkyl Azides Using *O*-Nitrobenzenesulfonyl Azide

By

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Conversion of Alcohols to Alkyl Azides using *O*-Nitrobenzenesulfonyl Azide

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Thesis Abstract

In this thesis, primary alcohols, secondary alcohols as well as sugars were successfully converted to their corresponding alkyl azides using *o*-nitrobenzesulfonyl azide as the azide tranfering reagent. This method of azidation successfully converted various groups of alcohols to their corresponding azides with little or no by-products. The thesis also deals with the investigation of the reaction mechanism the process of azidation goes through.

Acknowledgements

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Introduction

Organic azides are organic compounds with an azide group (N_3^-) attached to an alkyl, aryl or acyl group. Since their discovery in 1864 by Peter Grieβ,[1] organic azides have become one of the most important and versatile classes of compounds in synthetic chemistry. They are useful organic compounds that can undergo a range of functional group inter-conversions.[2] They are classified as energy rich compounds and usually illustrated as shown below (Figure 1).[3]

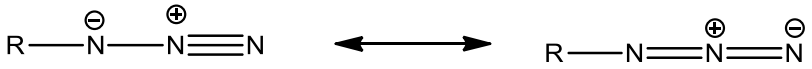
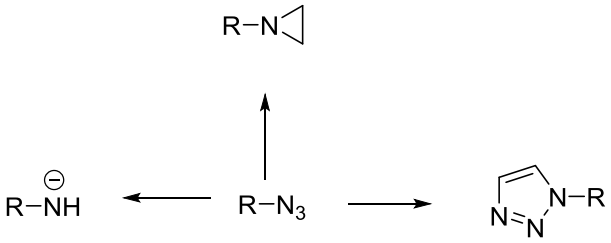


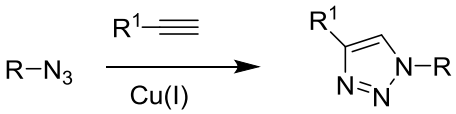
Figure 1: Illustration of the resonance structures of an organic azide

Due to their ready conversion into amines, isocyanates and their use as energetic polymers,[4] azides have received more attention in the pharmaceutical industry.[5] The easily polarization of the π-bond of the azide ion N_3^- results in a breakdown of the azide ion and leads to the release of molecular nitrogen and nitrene.[4] They are considered powerful precursors for reactive species such as nitrenes and nitrenium ions as well as nitrogen-rich compounds such as aziridines, azirines, triazoles, triazolines and triazenes (Scheme 1).[4]



Scheme 1: Conversion of organic azide to nitrogen-rich compounds

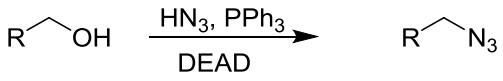
There has been rising interest in the synthesis of organic azides because they are valuable and versatile reagents within the concepts of 'Click Chemistry', [1] and therefore there is a need for efficient, safe and less expensive methods for their synthesis.



Scheme 2: Copper(I)-catalyzed addition of alkynes to organic azides.[6]

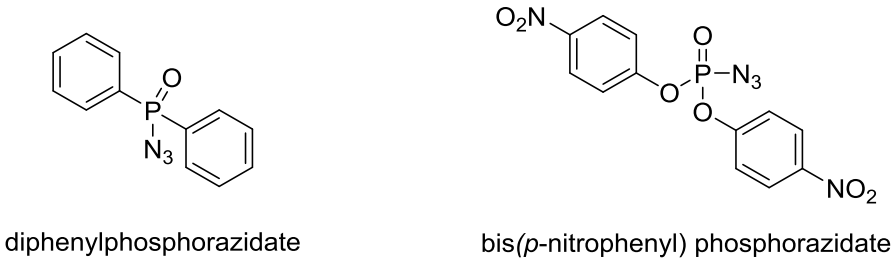
Due to the explosive nature of azides and their high sensitivity to heat, sodium azide is used in automobile airbags.[1] The syntheses of azides are very important in that they can be used to produce anti-retroviral drugs in the treatment of HIV/AIDS.[1,4] The major sources of organic azides that most researchers use are NaN_3, and substrates bearing leaving groups such as sulfonates and halides. There has been development of numerous synthetic pathways over the past years for the synthesis of organic azides, however, most of these routes are considered unsafe and can be expensive and time-consuming. Although there are a lot of indirect methods in the literature, few direct methods are known.[5]

One of the commonly known direct methods is the Mitsunobu displacement. In which hydrazoic acid (HN_3) is used as the source of azide in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) which serves as hydroxyl group activator (Equation 1).[5]



Equation 1: Conversion of alcohols to azides by Mistusnobu displacement

Hydrazoic acid is considered to be an explosive and toxic chemical with its toxicity compared to that of hydrogen cyanide. The use of hydrazoic acid is seen as a major drawback of the Mitsunobu displacement. Since hydrazoic acid is considered a health hazard, there have been several modifications to the Mitsunobu process. This includes the use of diphenyl phosphorazidate(DPPA)[4], zinc azide/*bis*-pyridine complex,[4,7] and bis(*p*-nitrophenyl)phosphorazidate (Figure 2).

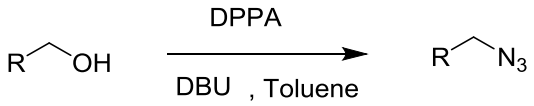


diphenylphosphorazidate

bis(*p*-nitrophenyl) phosphorazidate

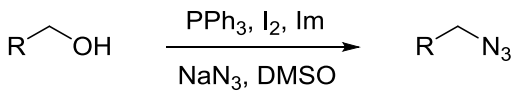
Figure 2: Structures of diphenyl phosphorazidate and bis(*p*-nitrophenyl) phosphorazidate

In a recent publication by Thompson *et al.,* the Mitsunobu displacement was modified by converting alcohols to azides by the use of diphenyl phosphorazidate (DPPA) in the presence of 1, 8-diazabicyclo [5.4.0] undec-7-ene (DBU),[8] where DPPA acts as the azide source and DBU as a base to help convert the alcohol to the corresponding phosphate intermediate, followed by the direct displacement of the phosphate by the highly nucleophilic azide ion.[9] Although their procedure was successful, very few alkanols were converted to their corresponding azides.[9]



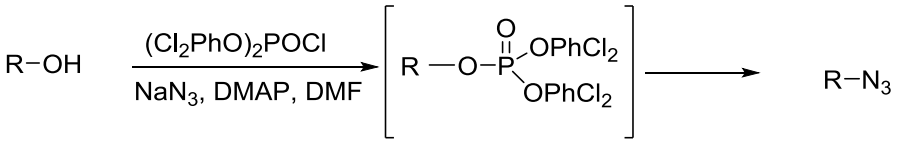
Equation 2: Conversion of alcohols to azides using (DPPA) as the source of azide

Rokhum and Ghanashyam reported a modification of the Mitsunobu reaction in which the organic azides were synthesized directly from their corresponding alcohols using a mixture containing equal amounts of triphenylphosphine, iodine, imidazole and sodium azide with dimethyl sulfoxide (DMSO) as solvent (equation 3).[5] The compounds were synthesized at room temperature. This modification was done to replace the very toxic hydrazoic acid and the very expensive DEAD.



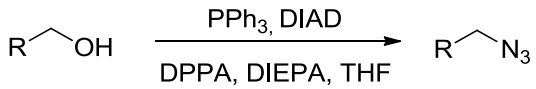
Equation 3: Conversion of alcohols to azides by modifying the Mitsunobu displacement

Researchers at Rutgers University used bis(2,4-dichlorophenyl)chlorophosphate to convert simple alkanols or less reactive benzyl alcohols to their corresponding azides.[9] They used 4-(dimethylamino)pyridine as a base. They developed their procedure due to the inability of the researchers at Merck Laboratory to convert alkanols and benzylic diols to their corresponding azides. They were able to convert the alkanols and benzylic diols in high yields between 76% and 92% to their corresponding azides (Equation 4).

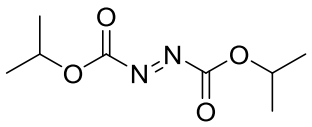


Equation 4: Conversion of alcohols to azides using NaN_3 as the azide source

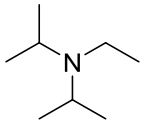
There has also been a successful conversion described by Scott and Co-workers in a more recent publication by using triphenylphosphine, diisopropylazodicarboxylate (DIAD), diphenyl-phosphoryl azide (DPPA)[10] and diissopropylethylamine in THF (Equation 5 and Figure 3).[11] However, triphenylphosphine oxide has always been difficult to separate from reaction mixture. There has also been the use of 2-azido-1,3-dimethylimidazolinium hexafluoro-phosphate in the synthesis of organic azides as reported by Kitamura *et al.*[12]



Equation 5: Conversion of alcohols to azides by modifying Mitsunobu displacement



diisopropylazodicarboxylate

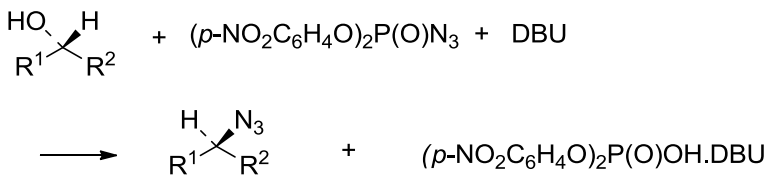


diisopropylethylamine

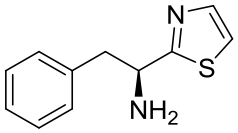
Figure 3: Structures of diisopropylazodicarboxylate and diissopropylethylamine

Mizuno and Shioiri described the total conversion of alcohols to azides by using bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA) and DBU (Equation 6).[13] For their

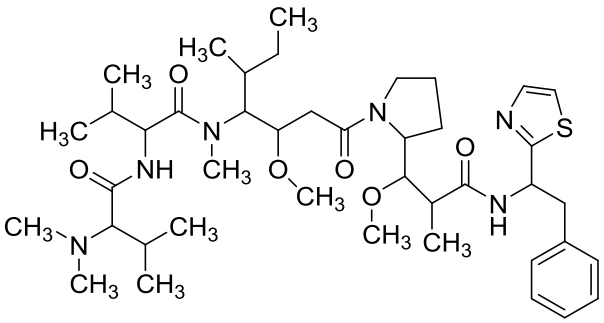
procedure, DPPA was replaced by *p*-NO_2DPPA which is easily prepared by the nitration of DPPA. They chose *p*-NO_2DPPA over DPPA because they believe the *p*-NO_2DPPA reaction rates were faster than using DPPA as the source of azide. This method was very efficient in the synthesis of azides however there is a disadvantage of not being able to convert cyclohexanol and (-)-menthol into their corresponding azides. They were however successful at converting (*R*)-(+)-2-phenyl-1-(thiazol-2-yl) ethanol to its corresponding azide which happens to be an intermediate for synthesizing dolaphenine [(*S*)-(-)-2-Phenyl-1-(thiazol-2-yl) ethylamine], the C-terminus of dolastin 10 which has a strong anticancer activity (Figure 4).



Equation 6: Conversion of alcohols to azides using bis(*p*-nitrophenyl) phosphorazidate as the source of azide



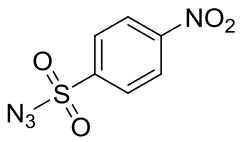
(S)-(-)-2-Phenyl-1-(thiazol-2-yl) ethylamine



Dolastin 10

Figure 4: Structures of dolaphenine and dolastin 10[14]

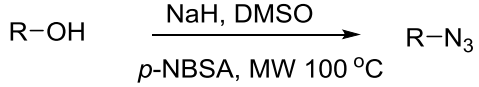
Brian A. Dobosh, a past student of YSU, successfully converted alcohols to azides using *para*-nitrobenzenesulfonyl azide (*p*-NBSA) as the source of azide and NaH as base in a microwave reactor.[15]



p-nitrobenzenesulfonylazide

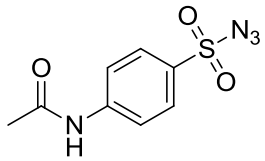
Figure 5: Structure of *p*-NBSA

The drawback of this procedure was the fact that the reaction (Equation 7) could not be run on a larger scale due to the small size of the tubes used in the CEM microwave reactor.



Equation 7: Conversion of alcohols to azides using *p*-NBSA as the source of azide

After several attempts made by Charles Alan Hartranft to develop a protocol, he succeeded in synthesizing azides from alcohols using a one-pot procedure. Hartranft used *p*-ABSA (Figure 6) as the azide transferring agent and DBU as a base for the primary alcohols. For the secondary alcohols, he used *p*-NBSA which happens to contain a much more electron- withdrawing group than the *p*-ABSA as the azide source.[3]

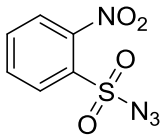


p-Acetamidobenzenesulfonyl Azide

Figure 6: Structure of *p*-ABSA

There has been increasing interest in the synthesis of organic azides and most of the procedures seen in the literature are indirect methods. Indirect methods result in the formation of intermediates which need work-up and isolation. This makes the procedure tedious and time consuming. In most direct methods which involve the use of triphenylphosphine, there is a likelihood of problems arising since the triphenylphosphine oxide is difficult to separate from the reaction mixture. There are instances where some of the researchers use toluene as solvent in the direct method. Toluene is a health hazard and the less expose one has to it, the better. The use of DMF and DMSO sometimes leads to difficulties in terms of isolation of the product and the use of diphenylphosphoryl azide happens to be expensive. The drawbacks of these procedures led to the development of our procedure. This thesis focuses on the use of *o*-nitrobenzenesulfonyl azide (*o*-NBSA) as the source of azide. *o*-NBSA was chosen because of its high solubility in THF unlike

p-NBSA. In the development of our protocol, tetrahydrofuran (THF) was chosen as solvent because it is inexpensive and readily available.



ortho-Nitrobenzenesulfonylazide

Figure 7: Structure of *o*-NBSA

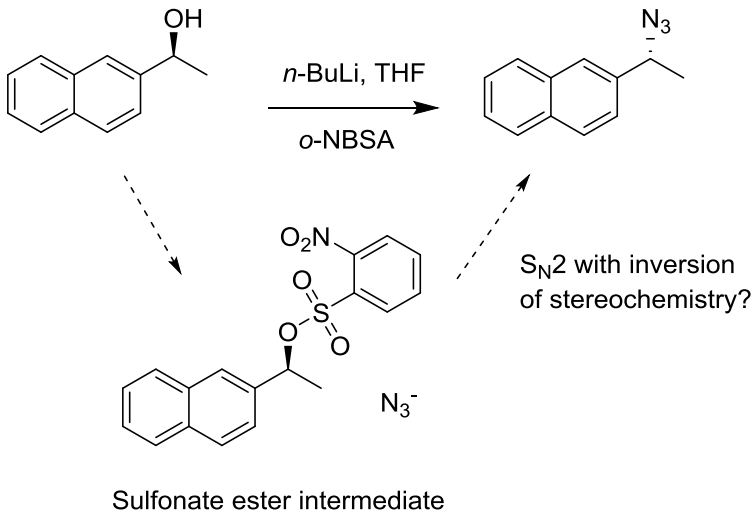
Verification of Reaction Mechanism

In most cases the synthesis of organic azides starts with the activation of the hydroxyl group by a base and electrophile followed by the displacement of the intermediate (eg. sulfonate ester intermediate) by the highly nucleophilic azide ion (N_3^-). Aliphatic azides are usually synthesized by the nucleophilic substitution of sulfonates or halides by the azide ion.[16] The current method of azidation is believed to be a bimolecular nucleophilic substitution (S_N2)[17] reaction due to the fact that two reacting species are involved in the rate determining step. The rate of an S_N2 reaction depends primarily on the nature of the substrates; less hindered substrates react faster than more hindered substrates. That is, in S_N2, primary substrates react faster, followed by secondary substrates. If the substrate involved in the reaction is optically active, there will be an inversion of stereochemistry at the end of the reaction.[18,19]

Thompson and co-workers reported in their work that they converted fourteen alcohols to their corresponding azides with inversion of stereochemistry. This indicated

that their synthesis was an S_N2 type of reaction.[8] Since their starting alcohols were optically active, the introduction of the azide ion proceeded with a clean inversion of stereochemistry. Mizuno *et al.*, reported the conversion of (*R*)-(-)-octan-2-ol to (*S*)-(+)-2-azidooctane.[13]

There are many literature examples stating that the method of azidation proceeds via S_N2 type of reaction, however not much work has been done on proving whether it actually goes through S_N2 mechanism. The few people who did work on this had limitations with their procedures. The syntheses of aliphatic azides are most commonly achieved through the use of nucleophilic substitution, to be specific an S_N2 type.[9] In the course of our search for an efficient method for the synthesis of azides, we decided to try to verify the type of reaction the azidation goes through. An optically pure alcohol was used in this part of the research and THF was chosen as the solvent since THF is a polar aprotic solvent and favors S_N2 (Scheme 3).



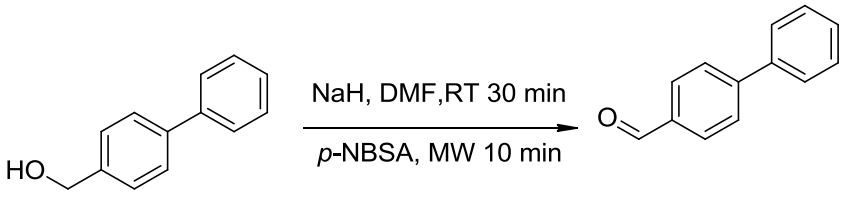
Scheme 3: Proposed mechanism of azidation

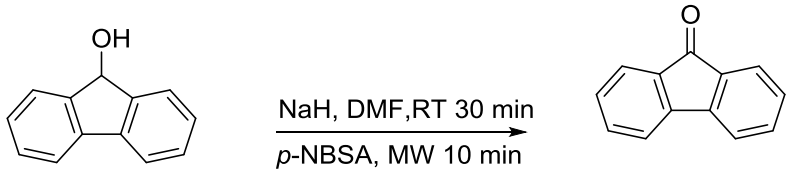
Statement of Problem

The syntheses of organic azides have drawn the attention of numerous researchers due to their convenient source of organic compounds such as amines which are very important in the pharmaceutical industry. The most common procedure for the synthesis of azide is indirect methods. This method involves two separate procedures which can be tedious, time consuming and expensive. This research is geared toward developing an efficient, safe and inexpensive protocol for azide synthesis with the aim of achieving higher yields, eliminating or minimizing byproducts as well as investigating the reaction type the method of azidation goes through.

Results and Discussion

The focus of this research project is based on initial studies by Brian J. Dobosh; a past student of Youngstown State University who synthesized organic azides using *p*-ABSA as the azide transferring reagent and NaH as the base. In his research, DMF was used as the solvent and the reaction was carried out in a microwave reactor at 100 ^{o}C. Though the method described in his thesis for the synthesis of azides worked, the reaction could not be carried out on a larger scale due to the size of the CEM tube in the microwave reactor. This was a major disadvantage of the procedure. There was also the problem of lower yields due to the fact that the reaction was run on a small scale and therefore aqueous work-up and purification led to loss of product. There were instances where some of the reactions led to different functional groups such as aldehyde and ketone instead of the expected azide product. The attempt to convert 9-hydroxyfluorene to its corresponding azide led to the formation of 9-hydroxyfluorenone and the conversion of 4-biphenylmethanol led to the formation of 4-biphenylcarbaldehyde. Due to the high temperature at which the reaction was carried out, there were formations of side products as well.



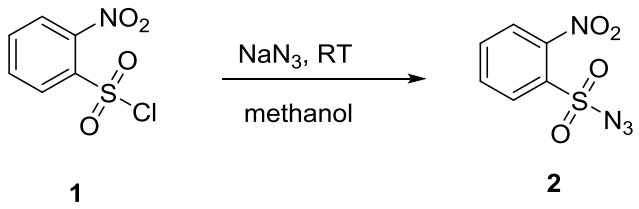


Scheme 4: Unexpected results in an attempt to synthesize azides from alcohols by Brian J. Dobosh

Charles Hartranft, also a past YSU student did similar research as that of Brian Dobosh. In his method, the reaction was carried out at a milder condition compared to that of Brian Dobosh. Hartranft used the same base and azide transferring reagent that Dobosh used but performed the reaction at room temperature. Although the procedure successfully converted alcohols to azides, there were formations of intermediates and by-products which reduced the overall yield.

Looking at the drawbacks of their procedures, we made changes to their general procedure to improve upon their results. At the beginning of this research, the question asked was: how can alkyl azides be synthesized on a larger scale by avoiding formations of intermediates and lowering, or if possible preventing, the formation of by-products? The main aim was to eliminate all the problems the previous researchers faced by altering some of the reaction conditions. The first thing that was changed was the azide source. We decided to use *ortho*-nitrobenzenesulfonyl azide (*o*-NBSA) as the azide transferring reagent. This was chosen because *o*-NBSA, unlike *p*-NBSA, is highly soluble in THF which happens to be the choice of solvent due to its readily availability, comparatively low boiling point and low cost.

We began the research by synthesizing *o*-NBSA (**2**, Equation 8). This was easily synthesized from *ortho*-nitrobenzensulfonyl chloride (**1**) and NaN_3 using methanol as solvent. The reaction was left to stir overnight at room temperature and thin layer chromatography (TLC) of the product showed a spot (R_f = 0.29) which appeared yellow upon heating when *p*-anisaldehyde was used as the TLC stain. Most azides in general burn yellow upon heating when stained with *p*-anisaldehyde. The infra-red (IR) spectrum of the recrystallized product showed a signal at 2150 cm^{-1} which corresponds to an azide functional group. ^{1}H NMR and ^{13}C NMR spectra of the product also showed that *o*-NBSA has been successfully synthesized.



1 **2**

Equation 8: Conversion of *ortho*-nitrobenzenesulfonyl chloride (**1**) to *ortho*-nitrobenzenesulfonyl azide **(2**)

The first alcohol that was used for the research was 4-methylbenzyl alcohol (**3**, Equation 9). This alcohol is a simple primary alcohol and since the reaction is believed to be an S_N2 type of reaction, this primary alcohol should give the azide product without any difficulty. In our first attempt to start converting alcohols to alkyl azides, sodium hydride (NaH) was used as the base and tetrahydrofuran (THF) as solvent. The reaction was carried out at room temperature and was left to stir overnight. TLC (2:1 hexane: ethyl acetate) of the reaction mixture showed two spots. One spot had an R_f closer to the

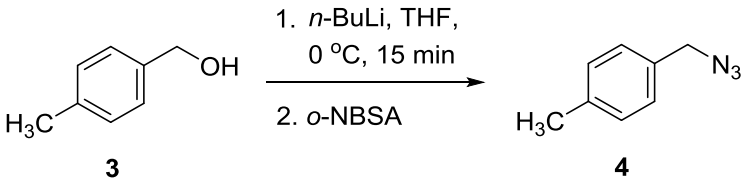
alcohol starting material and the other spot had an R_f which matched that of *o*-NBSA indicating that the starting materials stayed in solution without reacting.

Next we varied the amount of reacting species. Since the previous reaction was carried out on a 1 mmol scale, the amount of base (NaH) was increased to 3 mmol while keeping the alcohol and *o*-NBSA at 1 mmol. The reaction was once again left to stir overnight. TLC (2:1 hexane: ethyl acetate) of the reaction mixture showed that there was formation of product but very little amount of the product was being formed while leaving the majority of the starting material in solution. We then decided to use DMF instead of THF but had similar results even when the reaction was carried out with higher amount (5 mmol) of the base.

At this point, we decided to keep varying the reaction conditions and see which one worked best. We decided to choose *n*-butyllithium (*n*-BuLi) as the base and change the temperature. This base was chosen based on the fact that it is a stronger base (p*K*a of the conjugate acid is > 50) and can deprotonate a wide range of weak bronsted acids such as alcohols. Compared to NaH, *n*-BuLi was also considered easier to work with since it comes in readily-handled solution whereas NaH is mixed in a suspension of mineral oil.

The alcohol was first dissolved in THF and allowed to cool to 0 ^{o}C. The reaction was carried out at this temperature to prevent the deprotonation of THF by the *n*-BuLi. The base (*n*-BuLi) was added and then the reaction was allowed to stir for 15 minutes. This was done to ensure complete activation of the alcohol. A solution of *o*-NBSA in THF was then added in dropwise and the reaction was monitored via thin layer chromatography (TLC). TLC (2:1 hexane: ethyl acetate) showed a spot (R_f = 0.62) that was believed to be the product. The spot gave a yellow color when burned using *p*-

anisaldehyde as the TLC stain. There were also spots whose R_f (alcohol = 0.30, *o*-NBSA = 0.23) matched that of the starting materials. Aqueous work-up with saturated NH_4Cl and ethyl acetate gave the product (**4**) as yellow syrup. When an IR of the product was taken, it gave a signal at 2099 cm^{-1} which indicated the presence of an azide. ^1H NMR of the product showed an upfield shift of the CH_2 singlet from 4.54 ppm to 4.21 ppm indicating the attachment of a nucleophilic N_3^- ion. There was also a signal at 4.54 ppm which showed that the starting alcohol (**3**) was not completely consumed.



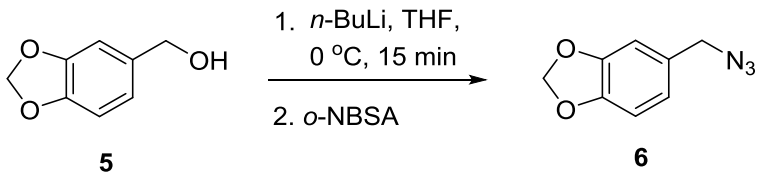
3 **4**

Equation 9: Conversion of 4-methylbenzyl alcohol (**3**) to 1-(azidomethyl)-4-methylbenzene(**4**)

These results gave some indication of progress and we decided to change the quantities of the starting materials that were initially used to see if all the starting materials would be consumed. The quantity of *o*-NBSA was increased to 2.22 mmol while the alcohol and the base were each increased to 2.0 mmol. Thin layer chromatography of the reaction mixture showed a single spot (R_f = 0.62) which happens to be the product indicating the complete consumption of the alcohol starting material. When the TLC plate was stained with *p*-anisaldehyde, the spot believed to be the product appeared yellow upon heating which indicated that an azide might have been synthesized.

Aqueous work-up on the product gave clear yellow syrup as the product with 72.8% yield. An IR spectrum of the product showed an azide peak at 2098 cm^{-1} and there was also a disappearance of the alcohol peak at around 3200-3600 cm^{-1}. At this point we knew we were closer to getting the results we wanted. ^1H NMR of the product showed a shift of the CH_2 group further upfield to 4.21 ppm indicating the attachment of the azide ion. This value matched the value of previously reported data on the product.

The next alcohol we tested with our procedure was piperonyl alcohol (**5**, Equation 10). Piperonyl alcohol is also a primary alcohol and working on it should be similar to the first alcohol that was used. Since the reaction mechanism of this protocol is believed to be an S_N2 reaction, it should be easier for the reaction to work on primary systems. The base (*n*-BuLi) was added to the alcohol at low temperature in dry THF, then after 15 minutes *o*-NBSA dissolved in dry THF was added. The reaction was stirred overnight after which TLC of the reaction mixture gave a spot (R_f = 0.47) which burned yellow upon heating when *p*-anisaldehyde was used as the TLC stain. There was also one other spot which had the same R_f as the starting alcohol indicating that there was no complete consumption of the piperonyl alcohol. An IR spectrum of the product (**6**) proved that there was an attachment of an azide (peak at 2100 cm^{-1}). ^1H NMR on the product showed peaks of both the starting alcohol and the azide product.

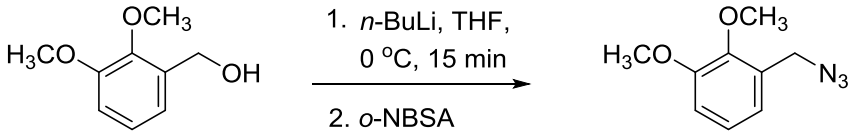


Equation 10: Conversion of piperonyl alcohol (**5**) to 5-(azidomethyl)benzo[*d*][1,3]dioxole (**6**)

This result made us think that not all the alcohol was activated or consumed. Next thing was to increase the amount of base that was used initially. When the amount of the base was increased to 2.2 mmol (initially used 2.0 mmol of *n*-BuLi), TLC showed complete consumption of the starting materials with a single spot which burned yellow upon heating when the TLC plate was stained with *p*-anisaldehyde solution. An IR spectrum of the product showed an azide peak at 2099 cm^{-1} and the disappearance of the alcohol peak at 3200-3600 cm^{-1}. ^{1}H NMR of the product showed a single peak at 4.14 ppm; the original alcohol peak was at 4.58 ppm. The movement of the peak further upfield indicated an attachment of the less electronegative azide group.

Another primary system that was tested was 2,3-dimethoxy benzyl alcohol (**7**, Equation 11). The formation of product was monitored by TLC, which showed the appearance of azide **8** (R_f = 0.49) and gradual disappearance of **7** with the spot burning yellow upon heating after the TLC plate was dipped in a solution of *p*-anisaldehyde. TLC revealed that not all the starting materials have been converted to **8**. Although the IR spectrum showed that azidation was successful, there was a peak at around

3600 cm^{-1} showing the presence of hydroxyl group. This was also seen when ^1H NMR of the product was taken. Subsequent purification by silica gel flash column chromatography (4:1 hexane: ethyl acetate) afforded **8** as a yellow syrup. The neat IR spectrum of the purified product showed a complete disappearance of the alcohol peak. It also showed the azide peak at 2104 cm^{-1}. There was a shift of the singlet CH_2 peak further upfield from 4.72 ppm to 4.37 ppm when ^1H NMR of the purified product was taken.

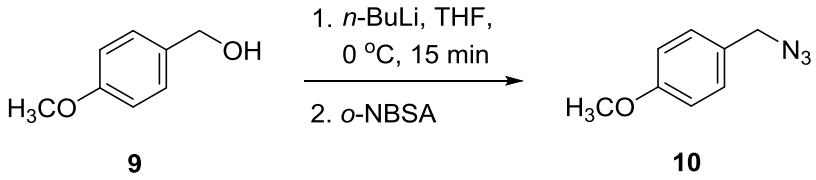


7 **8**

Equation 11: Conversion of 2,3-dimethoxybenzyl alcohol (**7**) to 1-(azidomethyl)-2,3-dimethoxybenzene (**8**)

The next alcohol we decided to try our procedure on was 4-methoxy benzyl alcohol (**9**, Equation 12), which is also a primary benzylic alcohol. The amount of reagents used were 2.01 mmol of the alcohol, 2.2 mmol of the base and 2.22 mmol of the azide transferring reagent (*o*-NBSA). At low temperature, the base was added to the alcohol dissolved in dry THF. The reaction was allowed to stir for about 15 minutes, which led to the deprotonation of the alcohol. After 15 minutes, the azide source, *o*-NBSA dissolved in dry THF, was added to the reaction mixture and left to stir overnight. The appearance of the product was seen with TLC (R_f = 0.59). When the TLC plate was stained with *p*-anisaldehyde it gave a bright yellow color upon burning. Isolation of the product by

aqueous work-up and purification by flash column chromatography afforded a yellow syrup. The disappearance of the hydroxyl group was seen when an IR spectrum of the product was taken since there was no IR absorption for the starting alcohol at 3200-3600 cm^{-1}. There was instead an azide peak at 2107 cm^{-1}. Further analysis by ^1H NMR showed a movement of the CH_2 singlet peak further upfield to 4.25 ppm.

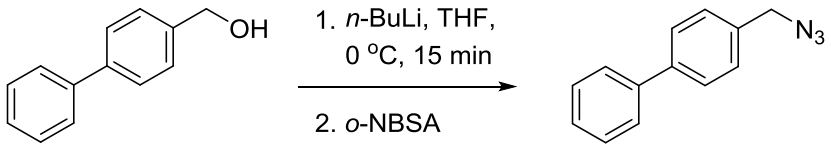


9 **10**

Equation 12: Conversion of 4-methoxybenzyl alcohol (**9**) to 1-(azidomethyl)-4-methoxybenzene (**10**)

We wanted to work on as many primary benzylic alcohols as we could so we decided to investigate this protocol on 4-biphenylmethanol (**11**, Equation 13). As well as ensuring safety in the produced azide, the benzene group in the primary alcohols helps with straightforward identification and analysis since it can be visualized with a UV lamp and allows the reaction to be monitored easily. The reaction of **11** with *o*-NBSA in the presence of *n*-BuLi at 0 ^oC (equation 14) was left to stir overnight. The formation of **12** was observed via TLC which gave a spot (R_f = 0.59) that burned yellow upon heating when TLC plate was stained with *p*-anisaldehyde. Aqueous work-up was performed with NH_4Cl and ethyl acetate to give yellow crystals of the product with 93.3% yield. Analysis of the product with IR spectroscopy showed an azide peak at 2097 cm^{-1} and ^1H NMR

showed a movement of the CH_2 group further upfield to 4.36 ppm which was initially at 4.73 ppm in the starting alcohol. This proved that azidation was successful.

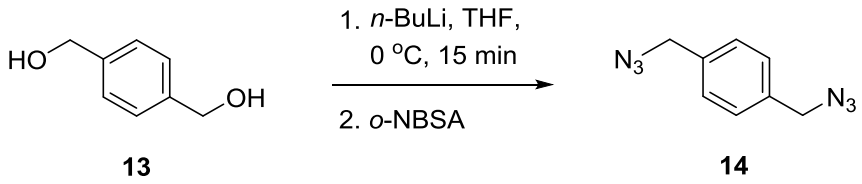


11 **12**

Equation 13: Conversion of 4-biphenylmethanol (**11)** to 4-(azidomethyl)-1,1[1]-biphenyl (**12**)

As the conversions of the simple primary benzylic systems were successful, more questions arose. Will this procedure work on other compounds different from the previously converted alcohols? This time around an alcohol bearing two hydroxyl groups (a diol) was chosen to test the new procedure. The diol used was 1,4-benzenedimethanol (**13**, Equation 14) which is also a primary alcohol. The reaction was set up the same way as previous alcohols but here the amounts of *o*-NBSA and *n*-BuLi were increased to 4.45 mmol and 4.4 mmol respectively. The amounts of base and the azide transferring reagent were doubled here because the alcohol **13** has two hydroxyl groups. The reaction was left to stir overnight and TLC of the reaction mixture showed the appearance of the azide product **14** (R_f = 0.85) which burned yellow upon heating when TLC plate was dipped in a solution of *p*-anisaldehyde indicating the presence of an azide group. Workup and subsequent purification by silica gel column chromatography afforded yellow syrup in

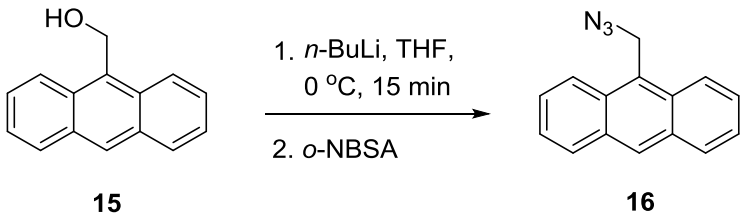
73.6% isolated yield. There was an azide peak at 2102 cm^{-1} when the IR spectrum of **14** was taken. The ^1H NMR spectrum of azide **14** showed a singlet peak at 4.34 ppm; in contrast the starting alcohol **13** showed that corresponding signal at 4.70 ppm. The movement of the CH_2 peak of **13** further upfield indicates the attachment of the less electronegative azide functional group in compound **14**. In this case the current procedure successfully converted not only primary systems with one hydroxyl group to their corresponding azides but also a diol.



13 **14**

Equation 14: Conversion of 1,4-benzenedimethanol (**13**) to 1,4-bis(azidomethyl)benzene (**14**)

The last primary benzylic alcohol that was worked on was 9-anthracene methanol (**15**, Equation 15). Unlike all the other alcohols, this gave a bright blue spot (R_f = 0.84) when TLC plate was viewed under UV lamp and burned yellow when the TLC plate was stained with *p*-anisaldehyde. Aqueous work-up and subsequent purification afforded **16** as dark brown syrup. The IR spectrum of **16** showed a strong absorption at 2097 cm^{-1} indicating the presence of an azide group. There was a shift of the CH_2 peak from 5.59 ppm to 5.25 ppm showing that there has been an attachment of an azide group and revealing the success of azidation.

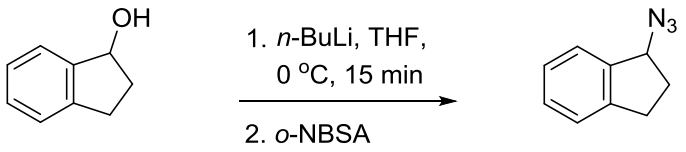


Equation 15: Conversion of 9-anthracene methanol (**15**) to 9-(azidomethyl)anthracene (**16**)

Since the mechanism of the reaction is believed to be an S_N2 process, we decided to test our procedure on secondary systems. Secondary alochols should react more slowly compared to primary alcohols. This is because the less hindered the alcohol is, the faster the rate of chemical reaction in an S_N2. We were anticipating potential side reactions and lower yields for the secondary alcohols but that was not the case. Some of the yields of the secondary alcohols were even higher than that for the primary alcohols. For all the secondary alcohols the reaction was carried out on a 1 mmol scale and then went higher to a 2 mmol scale.

The first secondary benzylic system that was worked on was (+/-)-1-indanol (**17**, Equation 16). The reaction was first run on a 1 mmol scale and monitored via TLC which showed a new spot (R_f = 0.68) under the UV lamp. The spot burned yellow when the TLC plate was stained with *p*-anisaldehyde indicating the presence of an azide. There was also a spot on the TLC plate which corresponded to the starting alcohol. Isolation and silica gel flash column chromatography led to loss of product, however. The amounts of reagents were then increased by using 2.0 mmol of the alcohol, 2.2 mmol of the base

and 2.22 mmol of the azide transferring reagent. When TLC of the reaction was taken, there was still some starting material even though there was a significant amount of product formed. The product spot, visualized under UV lamp, burned yellow upon heating after the TLC plate was immersed in a solution of *p*-anisaldehyde. Isolation of the product using saturated NH_4Cl and ethyl acetate extraction and subsequent purification by silica gel flash column chromatography afforded **18** as a yellow syrup. Analysis of **18** with IR spectroscopy showed an azide signal at 2089 cm^{-1} and the ^1H NMR spectrum showed the movement of the CH peak from 5.24 ppm to 4.86 ppm indicating the attachment of the azide group. The peak at 4.86 ppm showed up as a doublet of doublets.

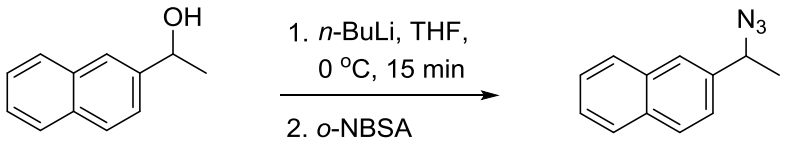


17 **18**

Equation 16: Conversion of (+/-)-1-indanol (**17**) to (+/-)-1-azido-2,3-dihydro-1*H*-indene (**18**)

The next secondary alcohol that was worked on was (+/-)-α-methyl-2-naphthalene methanol (**19**, Equation 17). At low temperature, 2.2 mmol of the base was added to 2.0 mmol of **19** in dry THF. The reaction was left to stir for 15 minutes to ensure complete activation of the alcohol and then 2.22 mmol of *o*-NBSA dissolved in dry THF was added dropwise. The reaction was left to stir overnight and then TLC showed the appearance of azide **20** and disappearance of alcohol **19**. The new spot (R_f = 0.59) was visualized under UV lamp and burned yellow upon heating after the TLC plate had been dipped in *p*-

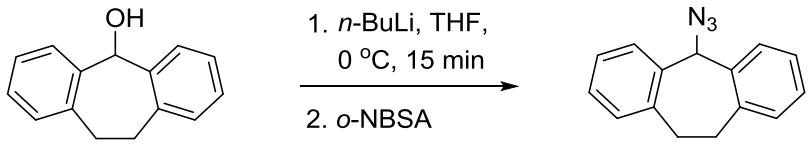
anisaldehyde solution. Aqueous work-up led to isolation of the product and purification gave yellow syrup in 89% yield. The IR spectrum showed the disappearance of **19** (no OH signal at 3200-3600 cm^{-1}) and formation of **20** (azide signal at 2101 cm^{-1}). The ^1H NMR spectrum of **20** showed a shift of the quartet peak which corresponded to the hydrogen of the CH group from 5.09 ppm to 4.68 ppm. The splitting was due to the 3H of the neighboring CH_3 group.



19 **20**

Equation 17: Conversion of (+/-)-α-methyl-2-naphthalene methanol (**19**) to (+/-)-2-(1-azidoethyl)naphthalene (**20**)

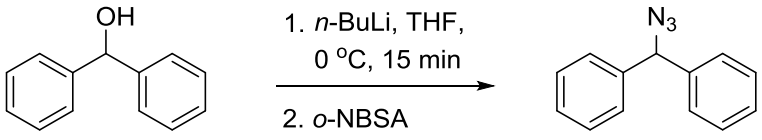
The next secondary benzylic alcohol to test the procedure on was dibenzosuberol (**21**, Equation 18). The formation of **22** when the reaction was left to stir overnight was confirmed by TLC which gave a spot (R_f = 0.57) visualized under UV lamp and burned yellow upon heating when stained with a solution of *p*-anisaldehyde. Aqueous work-up with NH_4Cl solution and ethyl acetate followed by purification via flash column chromatography afforded azide **22** as yellow syrup in 79% yield. The IR spectrum of **22** showed absorption at 2089 cm^{-1} indicating the presence of an azide group. There was also movement of the CH signal to 5.60 ppm when ^1H NMR spectrum of the product was taken proving a successful attachment of an azide group.



21 **22**

Equation 18: Conversion of dibenzosuberol (**21**) to 5-azido-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene (**22**)

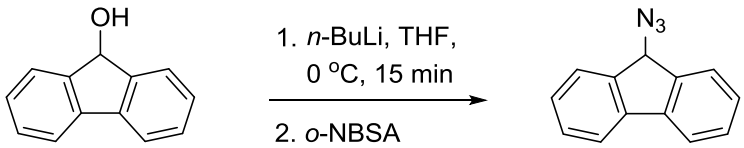
In equation 19 below, the newly designed procedure was tested on benzhydrol (**23**) which is also a secondary alcohol. The formation of the product was monitored via TLC and a spot (R_f = 0.70) of the product was seen under the UV lamp which burned yellow when *p*-anisaldehyde was used as a TLC stain. There was also IR absorption at 2099 cm^{-1} which indicated the presence of an azide group. The analysis was further backed-up with results taken from ^{1}H NMR and ^{13}C NMR spectra. Importantly, there was a shift of the CH signal further upfield from 5.81 ppm to 5.69 ppm.



23 **24**

Equation 19: Conversion of benzhydrol (**23**) to (azidomethylene)dibenzene (**24**)

The last simple secondary benzylic alcohol that the procedure was tested on was secondary alcohol 9-hydroxy-fluorene (**25**, Equation 20). The spot (R_f = 0.74) seen under the UV lamp which was believed to be the product did not burn yellow upon heating like the previous azides. This was unusual since most azides burn yellow upon heating when *p*-anisaldehyde is used as TLC stain. However, isolation of the product using saturated NH_4Cl and ethyl acetate and purification via flash column chromatography gave the azide product as dark brown syrup. When an IR spectrum was taken, there was absorption at 2100 cm^{-1} which indicated the attachment of N_3^-. ^1H NMR of the product proved the presence of azide in (**26**) due to the movement of the CH group further upfield to 5.19 ppm from 5.53 ppm.

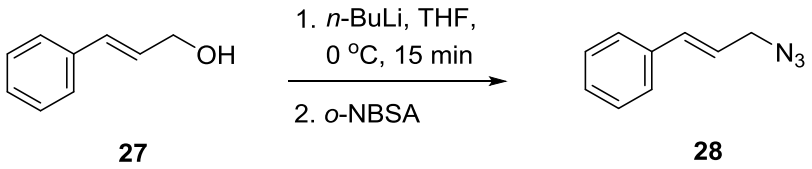


25 **26**

Equation 20: Conversion of 9-hydroxyfluorene (**25**) to 9-azido-9*H*-fluorene (**26**)

The next thing was to try the method on different systems. Cinnamyl alcohol (**27**, Equation 21) which has a double bond in its aliphatic domain was chosen for this part of the research. The reaction was left to stir overnight and TLC (R_f = 0.89) showed formation of **28** which burned bright yellow upon heating using a solution of *p*-anisaldehyde as the TLC stain. Thereafter an IR spectrum showed a peak at 2096 cm^{-1} which indicated the presence of an azide group. The CH_2 peak showed up as doublets of doublets splitting due to the double bond present in the compound. There was shift of the

doublets of doublets peak from 4.28 ppm to 3.91 ppm when **28** was analyzed with ^{1}H NMR proving that azidation has been successful.

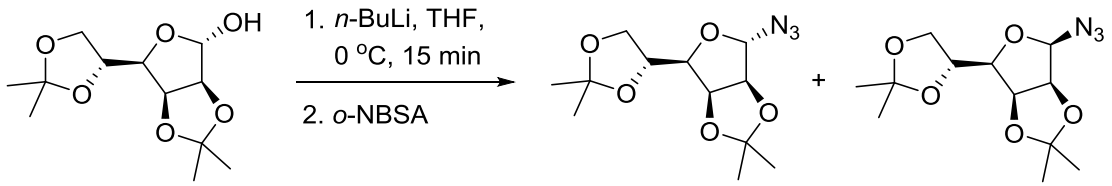


27 **28**

Equation 21: Conversion of cinnamyl alcohol (**27**) to cinnamyl azide (**28**)

At this point in the research we knew the procedure was successful at converting benzylic and allylic primary and secondary alcohols to their various azides. However, the procedure was not yet tested on sugars which also have hydroxyl groups in their chemical structure. After we decided to test this procedure on a carbohydrate, 2,3;5,6-Di-*O*-isopropylidene-α-D-mannofuranose (**29**, Equation 22) was chosen since it favors only the alpha anomer in solution. Because (**29**) is a secondary alcohol, and since the mechanism of the reaction is thought to be S_N2, the procedure should go without any difficulty. The reaction was carried out with 2 mmol of the sugar, 2.2 mmol of the base and 2.2 mmol of the azide transferring reagent. TLC of the reaction mixture showed spots (R_f = 0.17, 0.59) and all of them appeared green upon burning when the TLC plate was stained with *p*-anisaldehyde. Aqueous work-up with saturated ammonium chloride and ethyl acetate gave yellow crystals with 76% yield. The IR spectrum of the product showed a peak at 2119 cm^{-1} which represents the azide group. Analysis by ^{1}H NMR showed the formation of a mixture of products **30** and **31**. These results could be due to the carbohydrate ring opening up in solution leading to formation of the anomers. Because of this, the reaction

was repeated by adding the *o*-NBSA 10 minutes after adding the base but this gave similar results as before.

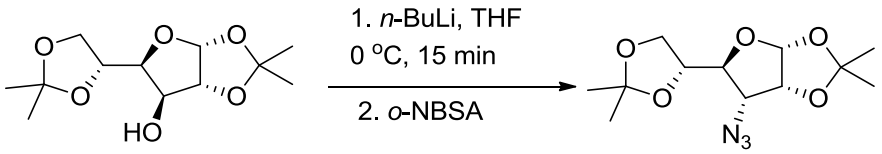


29 **30** **31**

Equation 22: Conversion of 2,3;5,6-Di-*O*-isopropylidene-α-D-mannofuranose (**29**) to glycosyl azides (**30**) and (**31**)

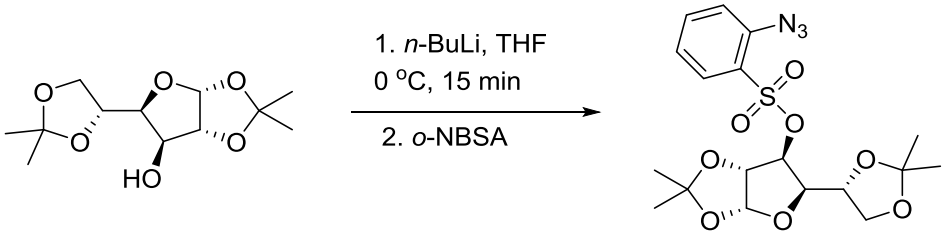
Following the successful azidation of 2,3:5,6-Di-*O*-α-D-mannofuranose, investigation of this procedure was also carried out using 1,2:5,6-Di-*O*-α-D-glucosfuranose as a model substrate. Treatment of 1,2:5,6-Di-*O*-α-D-glucofuranose with *n*-BuLi and *o*-NBSA did not give the expected results. TLC (2:1 hexane : ethyl acetate) of the reaction mixture gave a spot which burned black upon staining with a solution of *p*-anisaldehyde unlike the rest of the compounds synthesized earlier which gave bright yellow color upon staining with *p*-anisaldehyde. Aqueous work-up with saturated NH_4Cl and ethyl acetate gave yellow crystalline product. Although IR spectrum of the product showed absorption at 2140 cm^{-1}, there was no significant movement of the CH peak which is attached to the hydroxyl group as expected when the product was analyzed with ^1H NMR. Rather there was doublet of doublets peak (8.20 ppm) and multiplet peak (7.93-7.77 ppm) at the aromatic region which were not expected to be there. These peaks were seen when ^1H NMR of *o*-NBSA was taken. Further analysis of ^{13}C NMR of the product

showed that the product formed was the sulfonate ester intermediate of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**35**) instead of the expected 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**33**). Although the hydroxyl group of 1,2:5,6-Di-*O*-α-D-glucofuranose is at the secondary position and should give the azide product, it is much hindered making it difficult for the N_3^- ion to displace the sulfonate group.



32 **33**

Equation 23: Conversion of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**32**) to 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**33**)



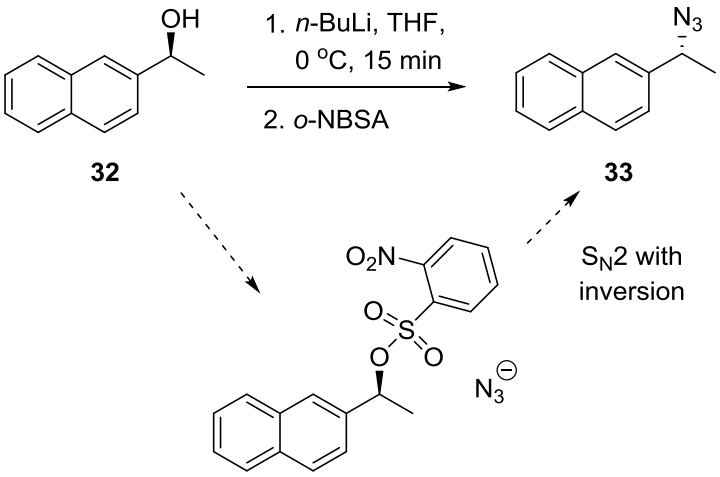
34 **35**

Equation 24: Sulfonate ester intermediate (**35**) of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucose(**34**)

Verification of Reaction Mechanism

The method of azidation is believed to be a nucleophilic bimolecular substitution (S_N2) reaction. During the search of this method of azidation, we decided to investigate if the reaction actually undergoes S_N2 mechanism. In this case the introduction of the azide group will proceed with inversion of stereochemistry if the starting alcohol is optically active. In this part of the research, (*S*)-(-)-α-methyl-2-naphthalene methanol (**32**, Equation 25), which is an optically pure secondary alcohol, was used. The reaction was set up as previously and TLC proved consumption of **32** and appearance of **33** (R_f = 0.64). Isolation and purification gave 75% yield and the IR spectrum showed absorption at 2103 cm^{-1} indicating attachment of the azide. ^1H NMR also indicated the movement of the CH peak further upfield. Optical rotation taken with a polarimeter indicated a change of sign in the right direction (from negative to positive) with a calculated value of 19.0. However, this value does not match that in literature.

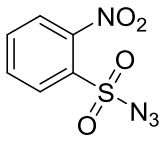
In conclusion, alkyl azides were successfully synthesized using our newly developed procedure which is efficient, safe and less time consuming. The alcohols were not only converted to their corresponding azides but also there were little or no by-products which increased the overall yields. In the future, more work should be done on non-UV active compounds and also complex compounds such as cholesterol. For the research on the optically active alcohol to prove the reaction mechanism, there was a change of sign in the right direction however the calculated optical rotation did not match that of literature. More work need to be done to prove that the process of the azidation is truly an S_N2 reaction.



Equation 25: Conversion of (*S*)-(-)-α-methyl-2-naphthalene methanol (**32**) to (*R*)-2-(1-azidoethyl)naphthalene(**33**)

Experimental

Conversion of *ortho*-Nitrobenzenesulfonyl chloride to *ortho*-Nitrobenzenesulfonyl azide



2

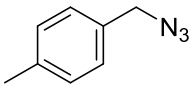
In a 250 mL oven-dried round bottom flask fitted with a septum and magnetic stir bar, *o*-nitrobenzenesulfonyl chloride (5.00g, 22.6 mmol) was dissolved in methanol (100 mL) and sodium azide (10.0 g, 154 mmol) was added. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.29 showed complete consumption of starting material. The excess NaN_3 was filtered off and the organic mixture was concentrated under vacuum. The crystals were dissolved in deionized water (50 mL) and then the organic material was extracted with ethyl acetate (3 x 50 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum. The product was recrystallized with hot ethyl alcohol to give *o*-nitrobenznesulfonyl azide as yellow crystals (3.25 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, J= 6.3, 1.5 Hz, 1H), 7.94-7.81 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 135.7, 133.1, 132.6, 131.7, 125.4.

IR absorption: 2150 cm^{-1}

Conversion of 4-methylbenzyl alcohol to 1-(azidomethyl)-4-methylbenzene



4

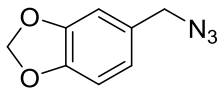
In a 50 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, 4-methylbenzyl alcohol (0.244 g, 2.00 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.00 mL, 2.0 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.62 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to give yellow syrup of 1-(azidomethyl)-4-methylbenzene (0.214 g, 72.8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.10 (m, 4H), 4.21 (s, 2H), 2.28 (s, 3H).[20]

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 132.3, 129.5 (double intensity), 128.2 (double intensity), 54.6, 21.2.

IR absorption: 2098 cm^{-1}

Conversion of piperonyl alcohol to 5-(azidomethyl)benzo[*d*][1,3]dioxole



6

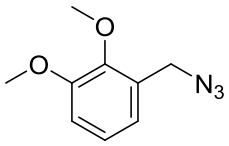
In a 50 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, piperonyl alcohol (0.304 g, 1.998 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.47 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and then the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to give yellow syrup of 5-(azidomethyl)benzo[*d*][1,3]dioxole (0.347 g, 98.1%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73-6.70 (m, 3H), 5.89 (s, 2H), 4.14 (s, 2H).[21]

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 147.7, 129.1, 122.0, 108.8, 108.4, 101.3, 54.7.

IR absorption: 2099 cm^{-1}

Conversion of 2, 3-dimethoxybenzyl alcohol to 1-(azidomethyl)-2,3-dimethoxybenzene



8

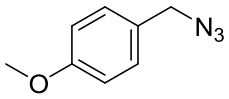
In a 50 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, 2,3-dimethoxybenzyl alcohol (0.336 g, 1.998 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.49 showed appearance of **8**. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the aqueous mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of 1-(azidomethyl)-2,3-dimethoxybenzene (0.363 g, 94.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07-7.04 (m, 1H), 6.93-6.88 (m, 2H), 4.37 (s, 2H), 3.89 (s, 3H), 3.87 ppm (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 147.5, 129.2, 124.1, 121.8, 113.0, 61.1, 55.8, 49.8.

IR absorption: 2104 cm^{-1}

Conversion of 4-methoxybenzyl alcohol to 1-(azidomethyl)-4-methoxybenzene



10

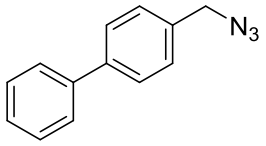
In a 50 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, 4-methoxylbenzyl alcohol (0.25 mL, 2.01 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.1 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.59 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic solution was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of 1-(azidomethyl)-4-methoxybenzene (0.26 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J= 8.7 Hz, 2H), 6.90 (d, J= 8.7 Hz, 2H), 4.25 (s, 2H), 3.80 (s, 3H).[22]

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 129.8 (double intensity), 127.4, 114.2(double intensity), 55.3, 54.4.

IR absorption: 2107 cm^{-1}

Conversion of 4-biphenylmethanol to 4-(azidomethyl)-1,1[1]-biphenyl



12

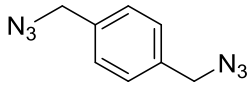
In a 50 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, 4-biphenylmethanol (0.368 g, 1.998 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^oC in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.59 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and this layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to give yellow crystals of 4-(azidomethyl)-1,1[1]-biphenyl (0.390 g, 93.3%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.60-7.57 (m, 4H), 7.46-7.33 (m, 5H), 4.36 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 140.5, 134.3, 128.8 (double intensity), 128.7 (double intensity), 127.6 (double intensity), 127.5, 127.1 (double intensity), 54.5.

IR absorption: 2097 cm^{-1}

Conversion of 1,4-benzenedimethanol to 1,4-bis(azidomethyl)benzene



14

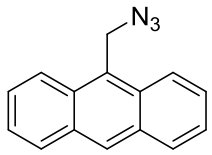
In a 50 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, 1,4-benzenedimethanol (0.276 g, 1.998 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (2.20 mL, 4.4 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (1.097 g, 4.448 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.85 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of 1,4-bis(azidomethyl)benzene (0.240 g, 73.6%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 4H), 4.34 (s, 4H).[22]

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 128.6 (double intensity), 54.4 (double intensity).

IR absorption: 2102 cm^{-1}

Conversion of 9-anthracene methanol to 9-(azidomethyl)anthracene



16

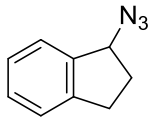
In a 50 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, 9-anthracene methanol (0.416 g, 1.997 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.84 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and then the solution was extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and then concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel 20 g, hexane: ethyl acetate 4:1) gave dark brown syrup of 9-(azidomethyl)anthracene (0.460 g, 98.7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.23 (dd, J = 8.1, 0.9 Hz, 2H), 7.99 (dt, J = 7.2, 0.6 Hz, 2H), 7.56-7.52 (m, 2H), 7.48-7.44 (m, 2H), 5.25 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.4, 130.7, 129.3 (double intensity), 129.0, 126.9 (double intensity), 125.8, 125.2 (double intensity), 123.5 (double intensity), 46.4.

IR absorption: 2097 cm^{-1}

Conversion of (+/-)-1-Indanol to (+/-)-1-azido-2,3-dihydro-1*H*-indene



18

In a 50 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, (0.268 g, 1.997 mmol) of (+/-)-1-indanol was dissolved in dry THF (10 mL). A nitrogen balloon was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.68 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and this layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification

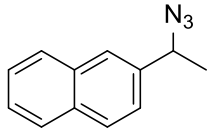
via silica gel column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of (+/-)-1-azido-2,3-dihydro-1*H*-indene (0.30 g, 94%).

^{1}H NMR (400 MHz, CDC_{l3}): δ 7.40-7.24 (m, 4H), 4.88-4.84 (dd, J = 4.6, 2.5 Hz, 1H), 3.11-3.04 (m, 1H), 2.91-2.83 (m, 1H), 2.48-2.40 (m, 1H), 2.16-2.08 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 140.7, 128.8, 126.8, 125.1, 124.5, 65.9, 32.5, 30.4.

IR absorption: 2089 cm^{-1}

Conversion of (+/-)-α-methyl-2-naphthalene methanol to (+/-)-2-(1-azidoethyl)naphthalene



20

In a 50 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, **(+/-)-**α-methyl-2-naphthalene methanol (0.344 g, 1.997 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.59

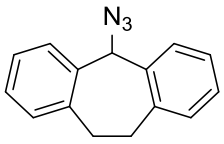
showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of (+/-)-2-(1-azidoethyl)-naphthalene (0.35 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.67 (m, 4H), 7.41-7.34 (m, 3H), 4.68 (q, J= 6.9, 6.8 Hz, 1H), 1.51 (d, J= 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2, 132.2, 132.1, 127.7, 126.9, 126.7, 125.4, 125.2, 124.3, 123.2, 60.3, 20.5.

IR absorption: 2101 cm^{-1}

Conversion of dibenzosuberol to 5-azido-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulene



22

In a 50 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, dibenzosuberol (0.420 g, 1.997 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^oC in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol)

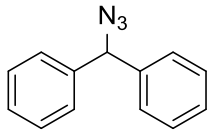
dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.57 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and this layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and then concentrated under vacuum. Purification by silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of 5-azido-10,11-dihydro-5*H*-dibenzo-[*a*,*d*][7]annulene (0.37 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.13 (m, 8H), 5.60 (s, 1H), 3.55-3.49 (m, 2H), 2.96-2.89 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 135.9, 130.6 (double intensity), 129.7 (double intensity), 128.8 (double intensity), 126.2 (double intensity), 71.6, 32.3 (double intensity).

IR absorption: 2089 cm^{-1}

Conversion of benzhydrol to (azidomethylene)dibenzene



24

In a 50 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, benzhydrol (0.368 g, 1.997 mmol) was dissolved in dry THF (10 mL). A balloon

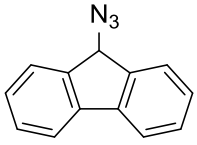
filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.70 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of (azidomethylene)dibenzene (0.26 g, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 10H), 5.69 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 128.7 (double intensity), 128.1 (double intensity), 127.4 (double intensity), 68.6.

IR absorption: 2099 cm^{-1}

Conversion of 9-hydroxyfluorene to 9-azido-9*H*-fluorene



26

In a 50 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, 9-hydroxyfluorene (0.364 g, 1.998 mmol) was dissolved in dry THF (10 mL). A

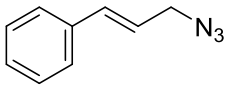
balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.74 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the organic layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave dark brown syrup of 9-azido-9*H*-fluorene (0.39 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.58 (m, 4H), 7.48-7.32 (m, 4H), 5.19 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 140.8, 129.4 (double intensity), 127.9 (double intensity), 125.2 (double intensity), 120.3 (double intensity), 64.3.

IR absorption: 2100 cm^{-1}

Conversion of cinnamyl alcohol to (*E*)-(3-azidoprop-1-en-1-yl)benzene



28

In a 50 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, cinnamyl alcohol (0.26 mL, 2.02 mmol) was dissolved in dry THF (10 mL). A

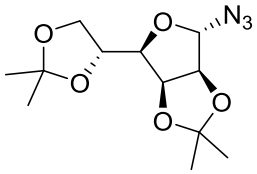
balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.548 g, 2.22 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.89 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the organic layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of (*E*)-(3-azidoprop-1-en-1-yl) benzene (0.26 g, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (m, 5H), 6.63 (d, J =15.8 Hz, 1H), 6.23 (dt, J = 15.8, 6.5, 2.6 Hz, 1H), 3.91 (dd, J = 5.8, 0.7 Hz, 2H).[23,24]

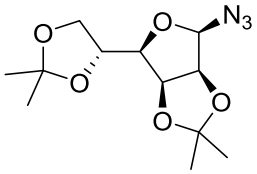
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 134.6, 128.7, 128.2, 126.7, 122.5, 53.0.

IR absorption: 2096 cm^{-1}

Conversion of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose to 1-azido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose and 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranose



30



31

In a 50 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (0.521 g, 2.00 mmol) was dissolved in dry THF (10 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (1.10 mL, 2.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.547 g, 2.20 mmol) dissolved in dry THF (6 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.17, 0.59 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and the organic layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to give yellow crystals of 1-azido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose and 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranose (0.43 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 1H), 4.78 (dd, J = 3.6, 2.4 Hz, 1H), 4.69 (dd, J = 3.6, 2.4 Hz, 1H), 4.49-4.46 (m, 1H), 4.47-4.40 (m, 2H), 4.16-4.03 (m, 7H), 3.61 (dd, J =

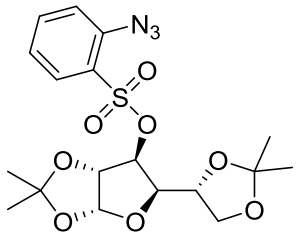
4.0, 3.6 Hz, 1H), 1.56 (s, 3H), 1.47 (s, 6H), 1.45 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 113.6, 109.3, 95.5, 89.1, 85.0, 81.9, 81.1, 79.5, 79.5, 78.5, 72.9, 72.8, 66.8, 66.7, 26.9, 26.9, 25.8, 25.2, 25.1, 25.1, 25.1, 22.5.

IR absorption: 2119 cm^{-1}

Conversion of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose to the

3-*O*-sulfonate ester intermediate



35

In a 25 mL oven-dried triple neck round bottom flask fitted with a septum and magnetic stir bar, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.260 g, 1.00 mmol) was dissolved in dry THF (5 mL). A balloon filled with nitrogen gas was attached to the set-up. The solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (0.60 mL, 1.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.274 g, 1.11 mmol) dissolved in dry THF (3 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.52 showed complete consumption of starting material. The reaction mixture was diluted

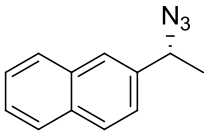
with saturated NH_4Cl (10 mL) and the organic layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to give the 3-*O*-sulfonate ester intermediate of 1, 2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.40 g, 90%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, J = 1.4, 1.1 Hz, 1H), 7.93-7.77 (m, 3H), 5.60 (d, J = 3.6 Hz, 1H), 4.98 (d, J = 2.9 Hz, 1H), 4.89 (d, J = 3.6 Hz, 1H), 4.30-4.26 (m, 1H), 4.06 (dd, J = 2.9, 2.8 Hz, 1H), 4.00 (dd, J = 6.1 Hz, 1H), 3.93 (dd, J = 4.1 Hz, 1H), 1.50 (s, 3H), 1.34 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 133.1, 132.3, 131.9, 129.4, 125.2, 112.7, 109.0, 105.2, 84.2, 83.5, 79.8, 71.8, 67.2, 26.7, 26.6, 26.2, 24.5.

IR absorption: 2140 cm^{-1}

Conversion of (*S*)-(-)-α-methyl-2-naphthalene methanol to (*R*)-(+)-2-(1-azidoethyl)naphthalene



37

In a 25 mL oven-dried three neck round bottom flask fitted with a septum and magnetic stir bar, (*S*)-(-)-α-methyl-2-naphthalene methanol (0.175 g, 1.02 mmol) was dissolved in dry THF (5 mL). A balloon filled with nitrogen gas was attached to the set-up. The

solution was cooled to 0 ^{o}C in an ice-bath and then *n*-BuLi (0.60 mL, 1.2 mmol) was added dropwise. The reaction was allowed to stir for 15 minutes and then *o*-NBSA (0.273 g, 1.11 mmol) dissolved in dry THF (3 mL) was added dropwise to the reaction mixture. The reaction was left to stir overnight and TLC (2:1 hexane: ethyl acetate) R_f = 0.64 showed complete consumption of starting material. The reaction mixture was diluted with saturated NH_4Cl (10 mL) and then the organic layer was extracted with ethyl acetate (3 x 10 mL). The combined organic solution was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification via silica gel flash column chromatography (silica gel = 20 g, hexane: ethyl acetate 4:1) gave yellow syrup of (*R*)-(+)-2-(1-azidoethyl)naphthalene (0.15 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.74 (m, 4H), 7.49-7.42 (m, 3H), 4.76 (q, J = 6.8 Hz, 1H), 1.59 (d, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 133.2, 133.1, 128.8, 128.1, 127.8, 126.4, 126.3, 125.3, 124.3, 61.3, 21.7.

1R absorption: 2103 cm^{-1}

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Apendix A

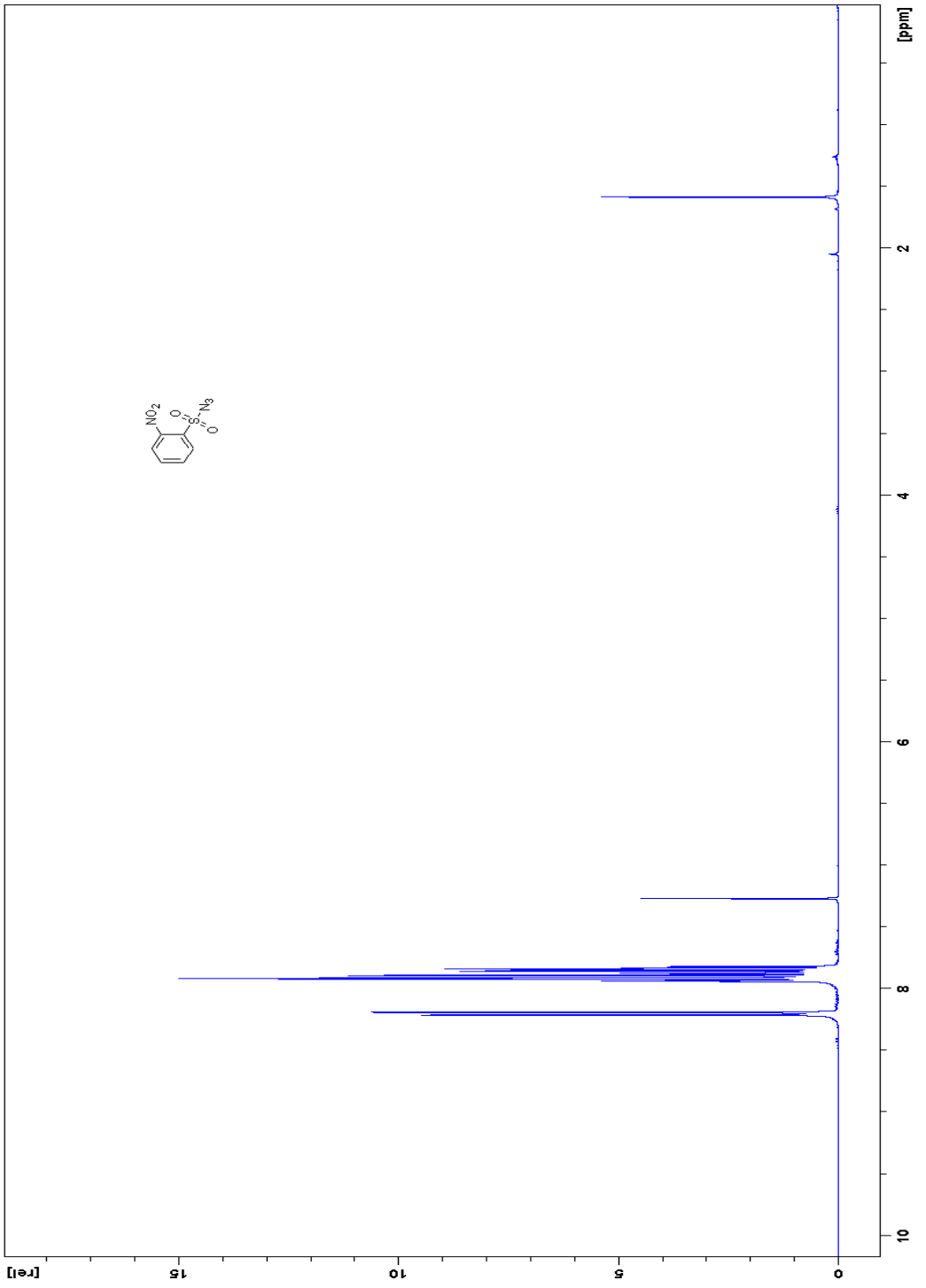

Figure 8: ^{1}H NMR of *ortho*-Nitrobenzenesulfonyl azide (**2**)

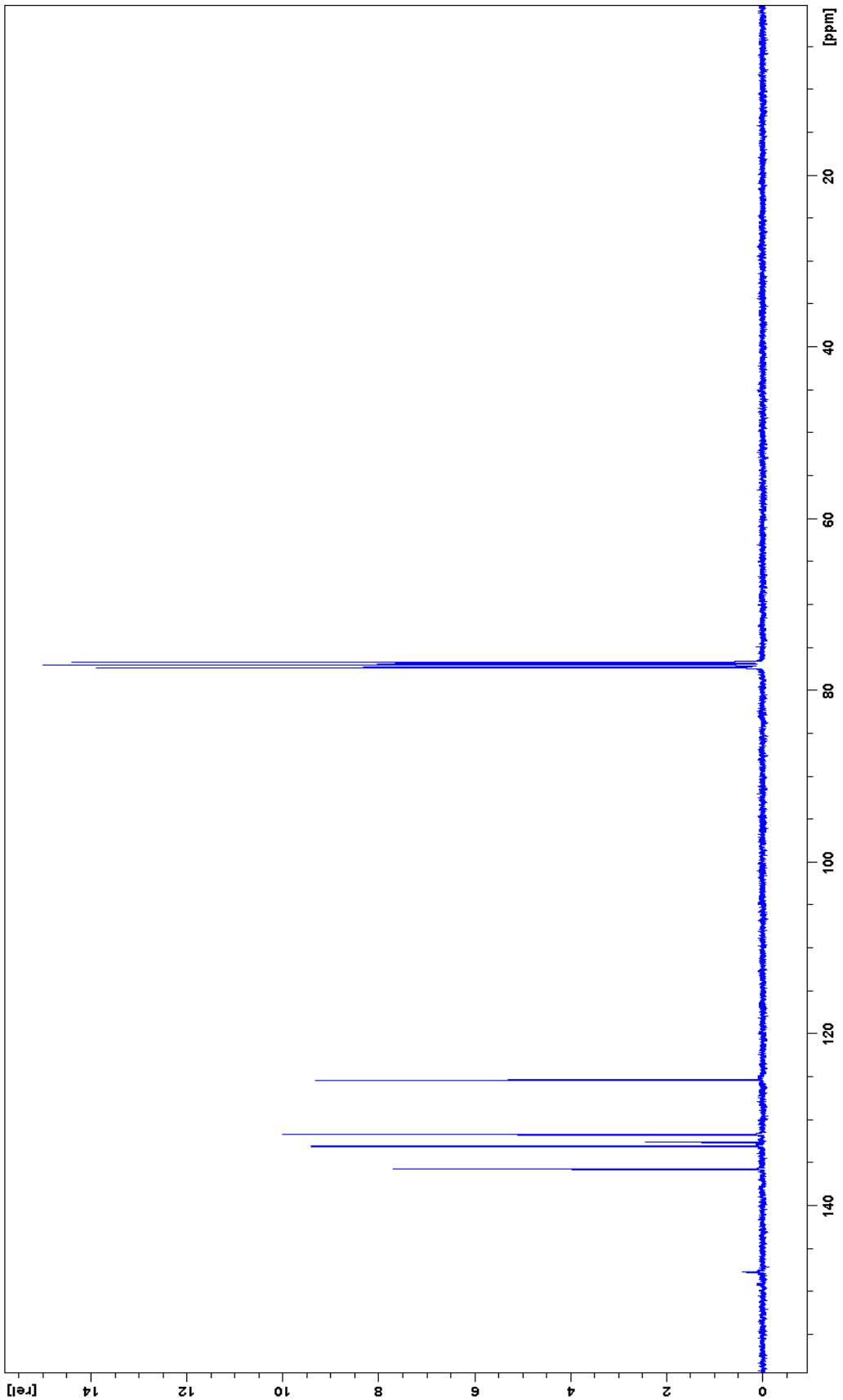

Figure 9: ^{13}C NMR of *ortho*-Nitrobenzenesulfonyl azide (**2**)

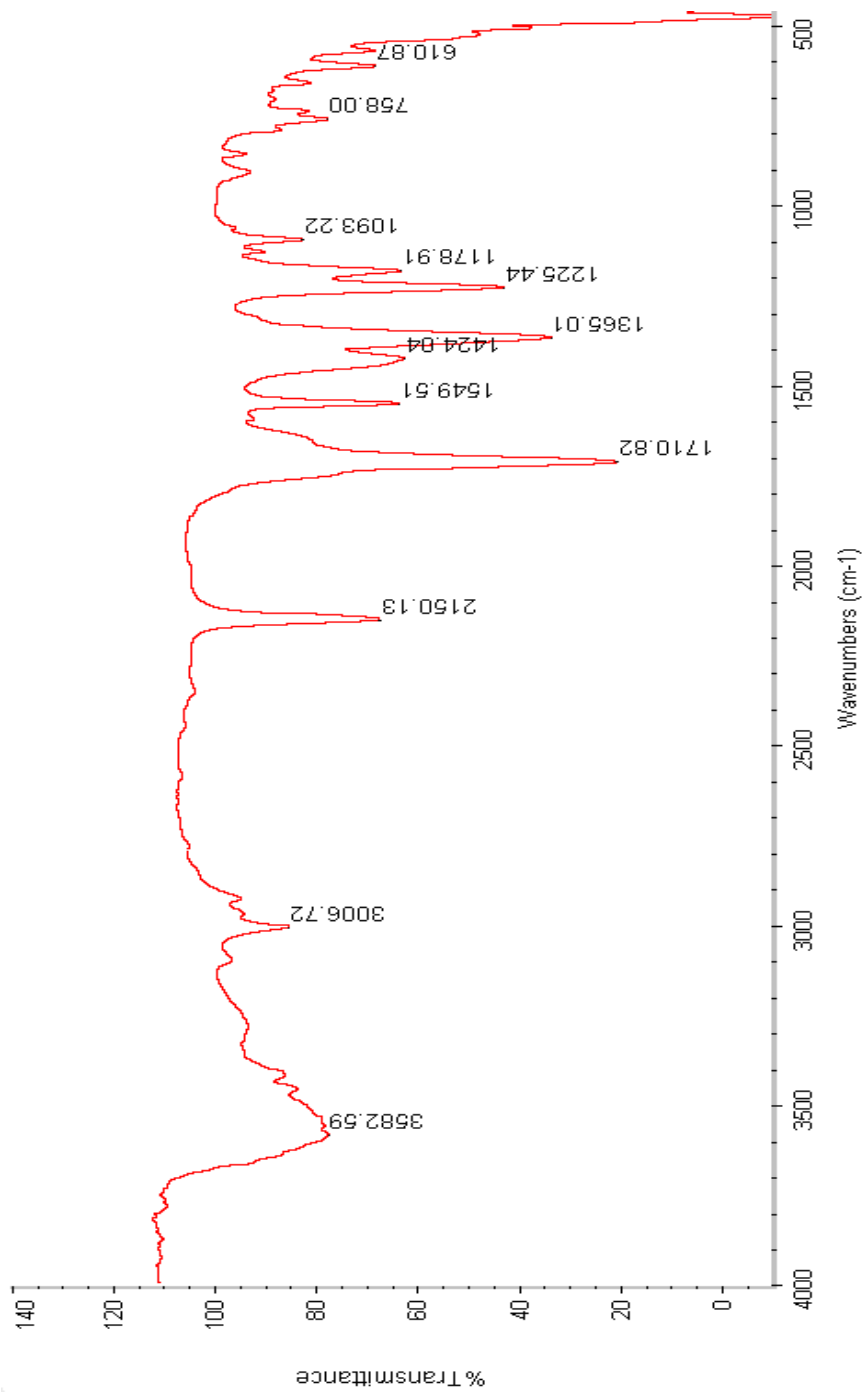

Figure 10: IR spectrum of *ortho*-Nitrobenzenesulfonyl azide (**2**)

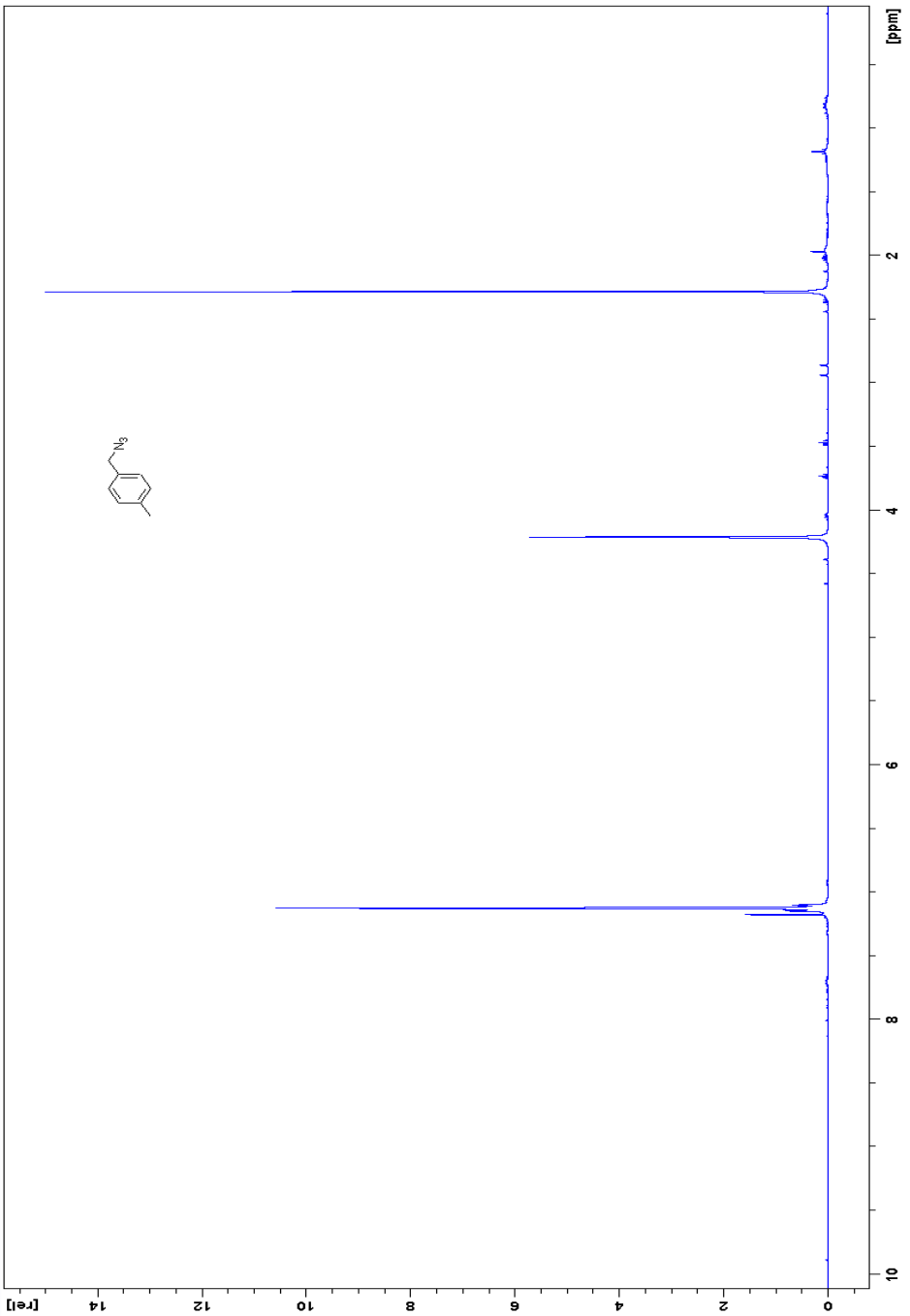

Figure 11: ^{1}H NMR of 1-(azidomethyl)-4-methylbenzene (**4**)

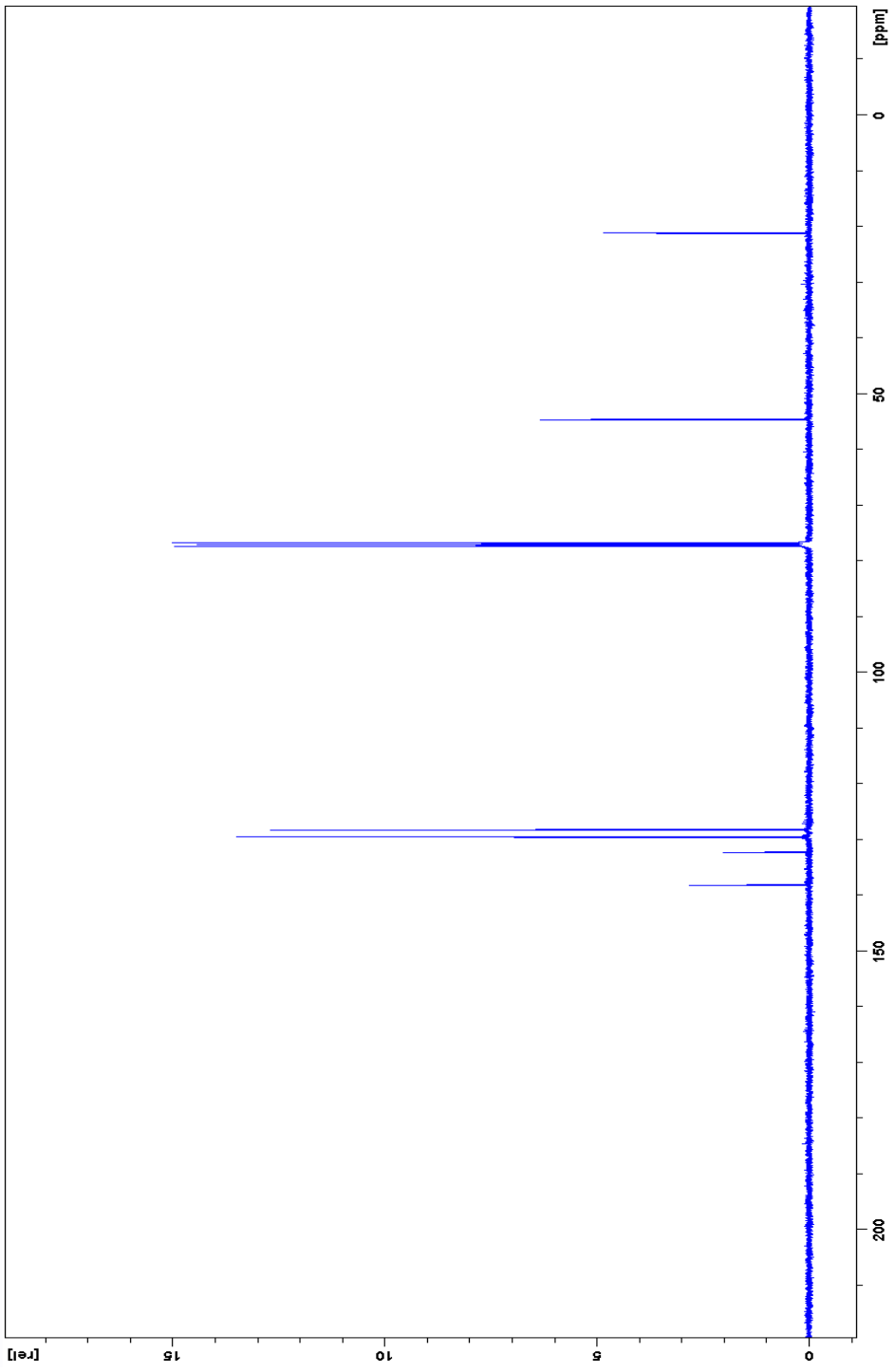

Figure 12: ^{13}C NMR of 1-(azidomethyl)-4-methylbenzene (**4**)

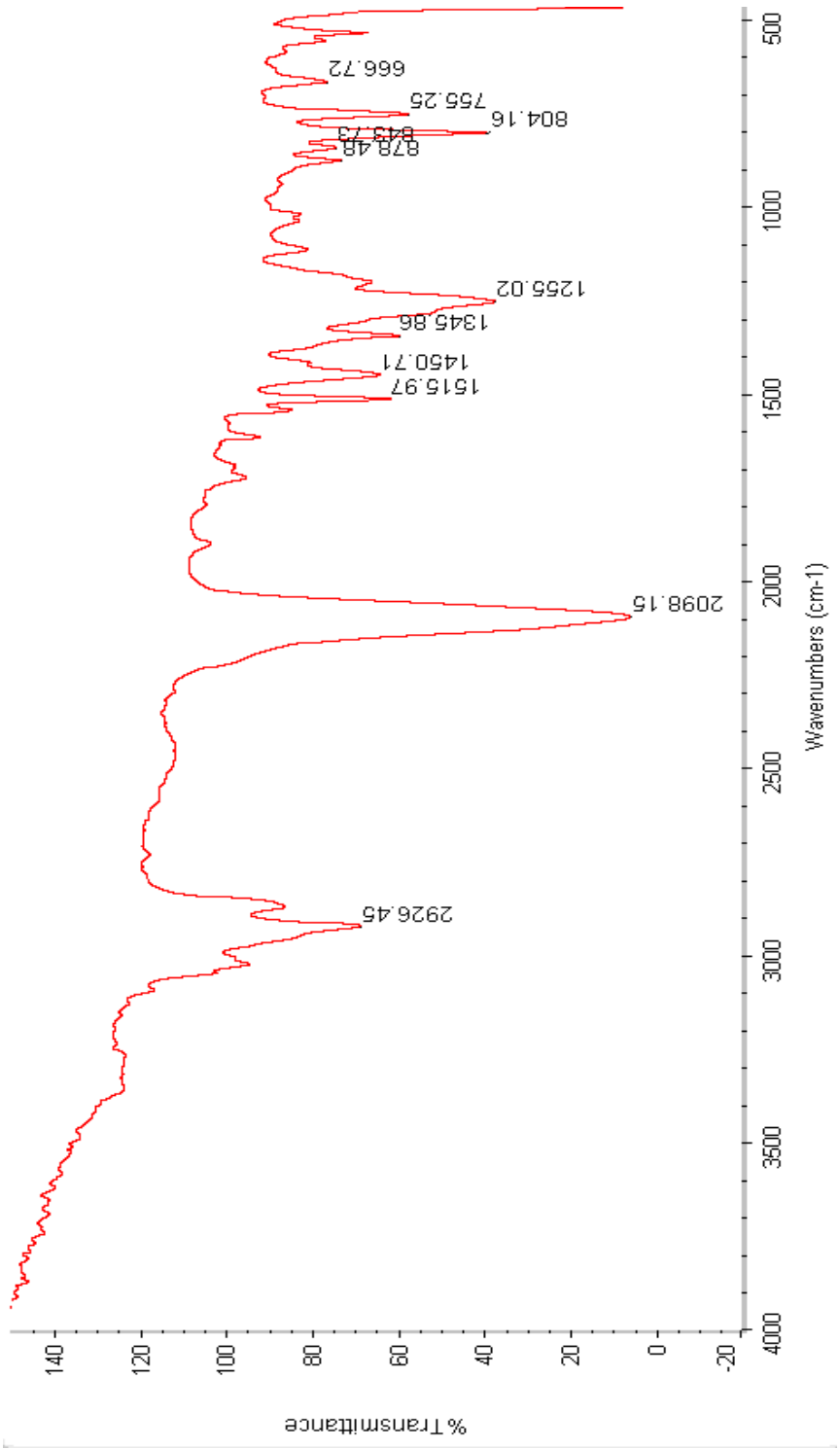

Figure 13: IR spectrum of 1-(azidomethyl)-4-methylbenzene (**4**)

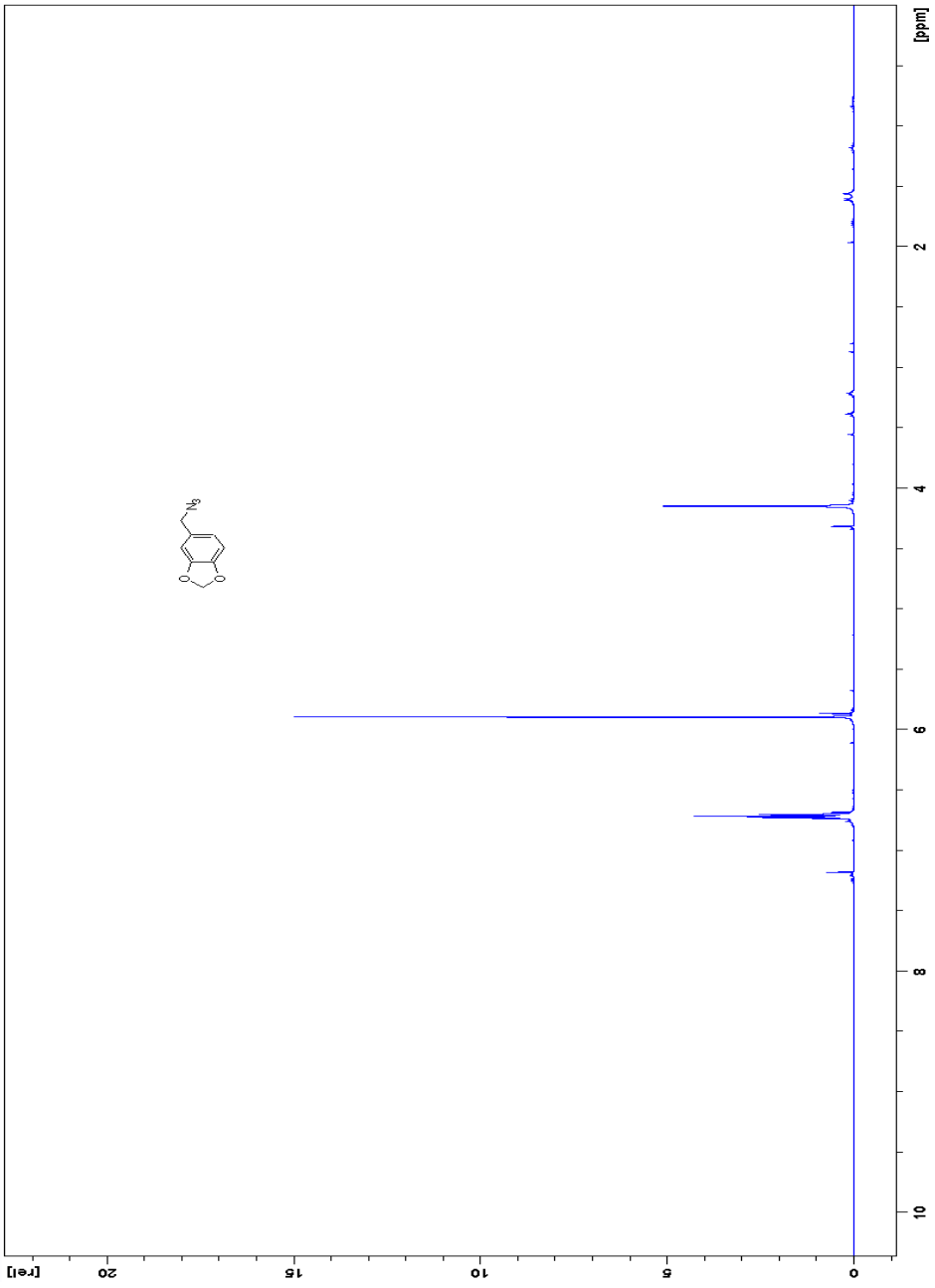

Figure 14: ^{1}H NMR of 5-(azidomethyl)benzo[*d*][1,3]dioxole (**6**)

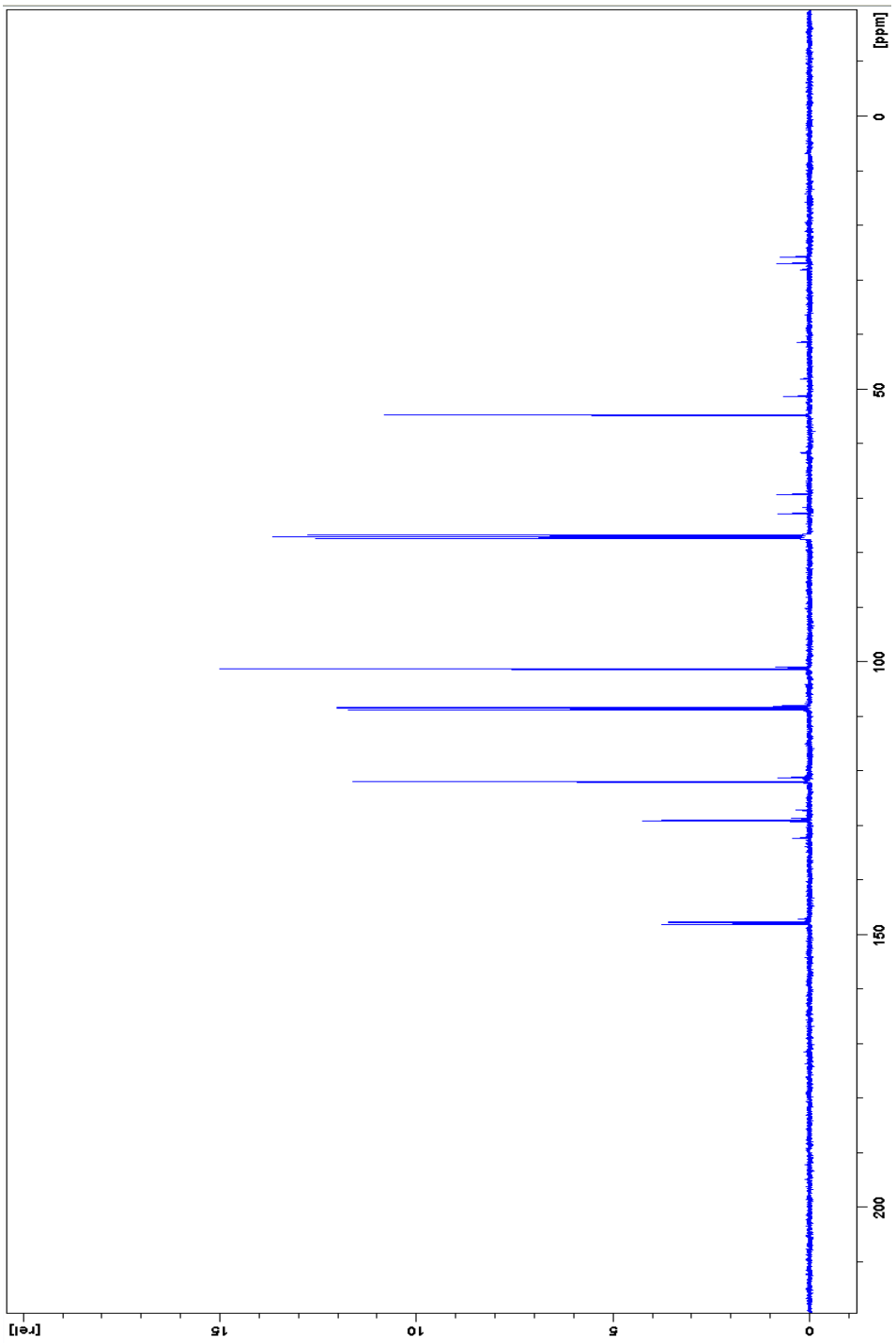

Figure 15: ^{13}C NMR of 5-(azidomethyl)benzo[*d*][1,3]dioxole (**6**)

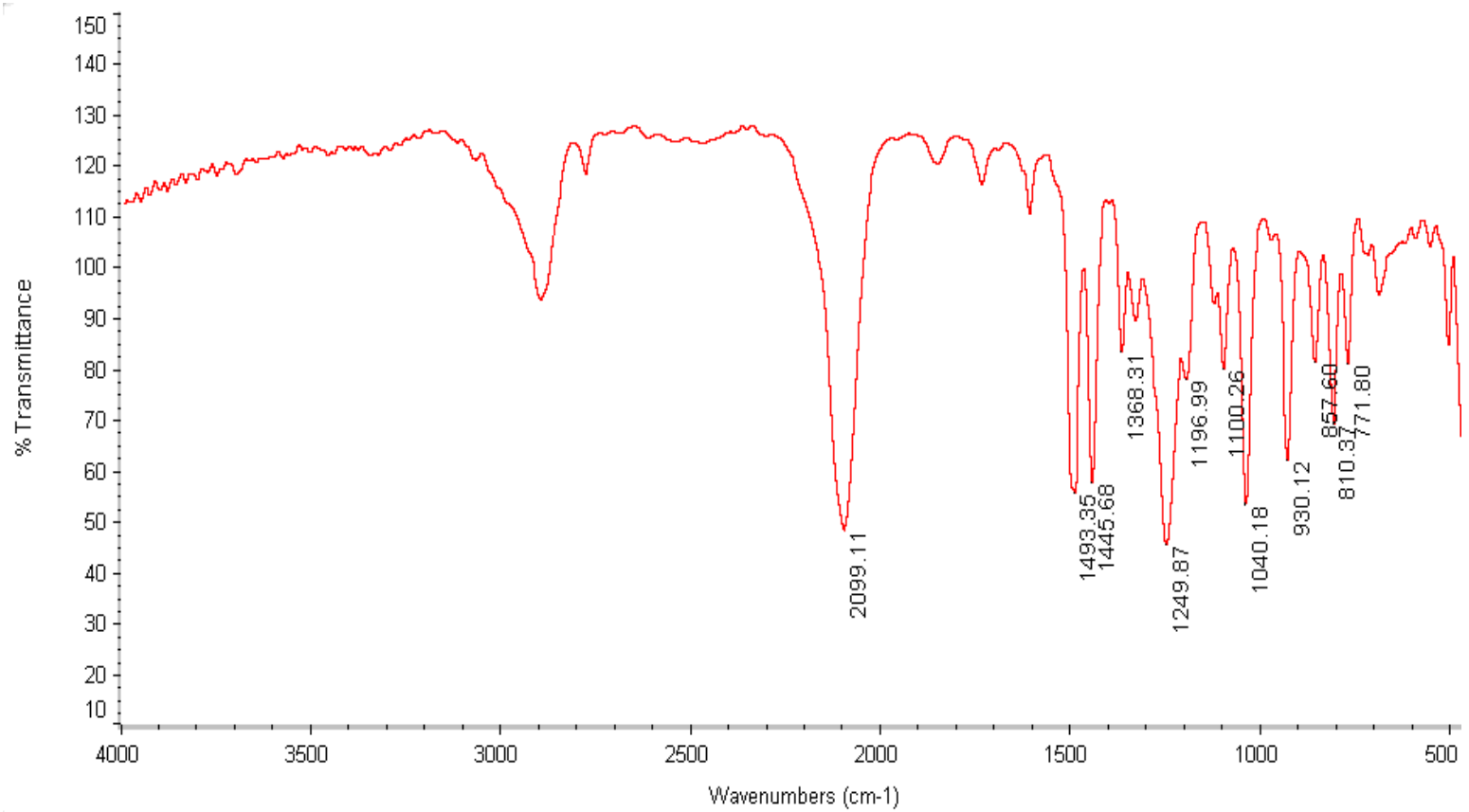

Figure 16: IR spectrum of 5-(azidomethyl)benzo[*d*][1,3]dioxole (**6**)

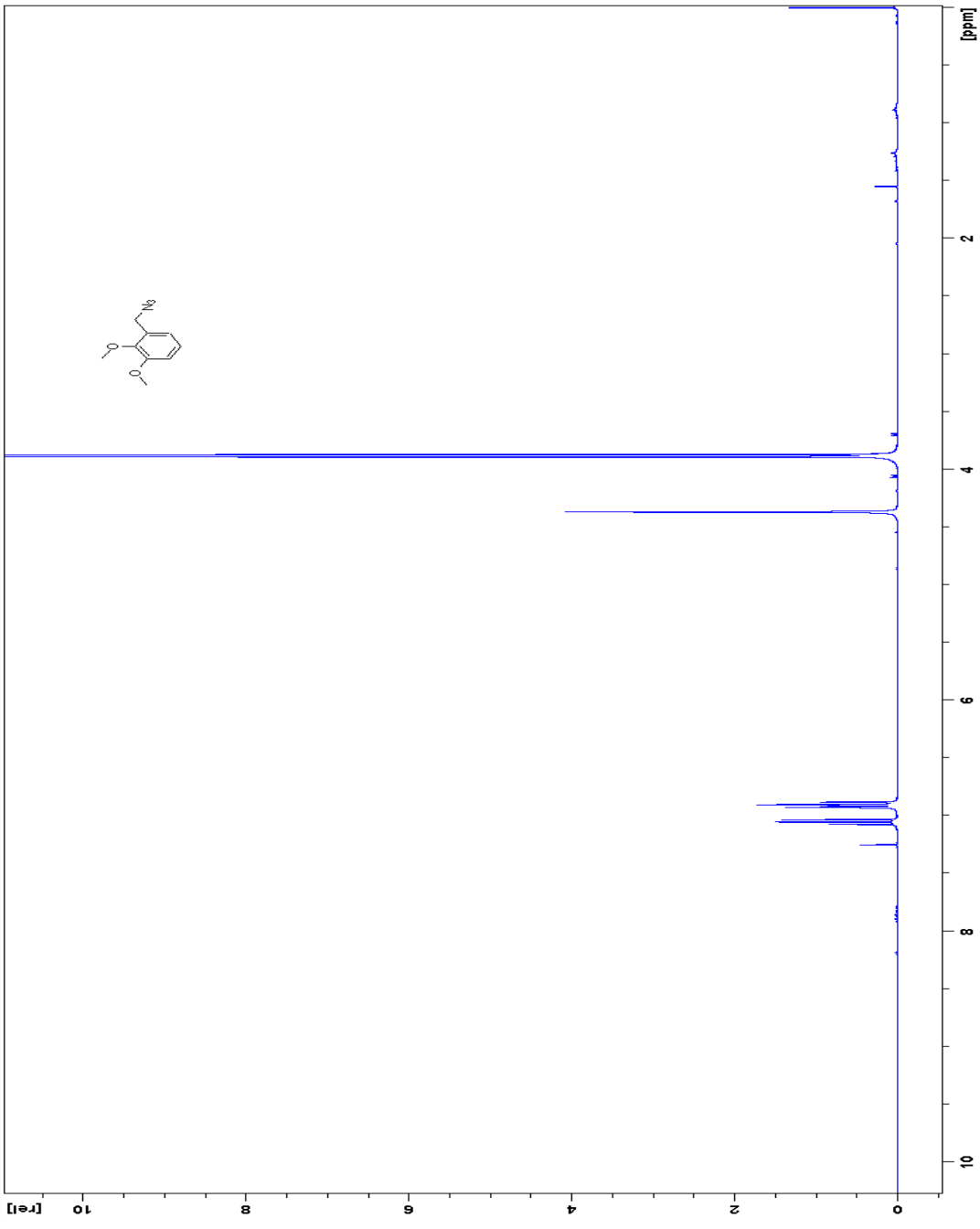

Figure 17: ^{1}H NMR of 1-(azidomethyl)-2,3-dimethoxybenzene (**8**)

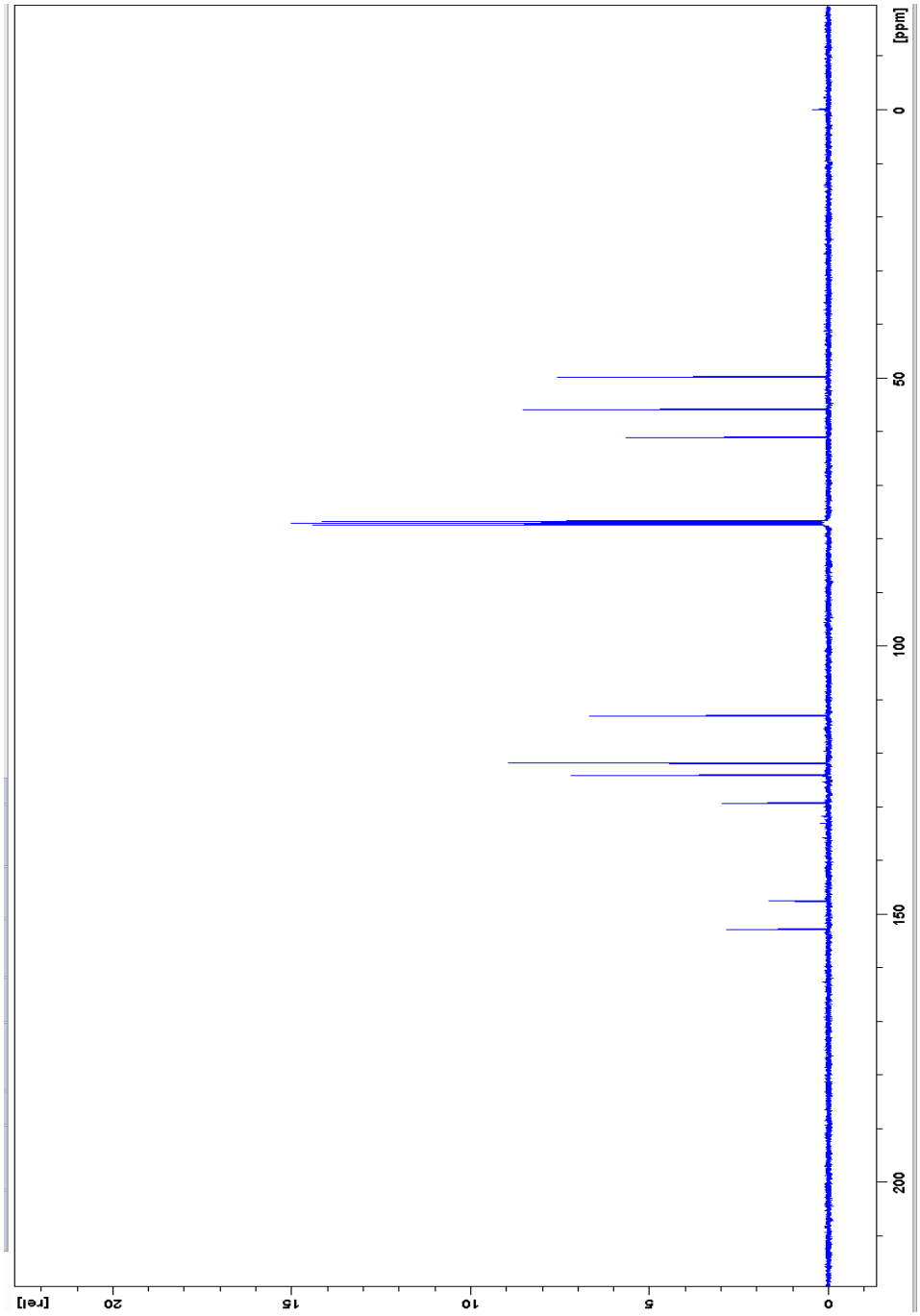

Figure 18: ^{13}C NMR of 1-(azidomethyl)-2,3-dimethoxybenzene (**8**)

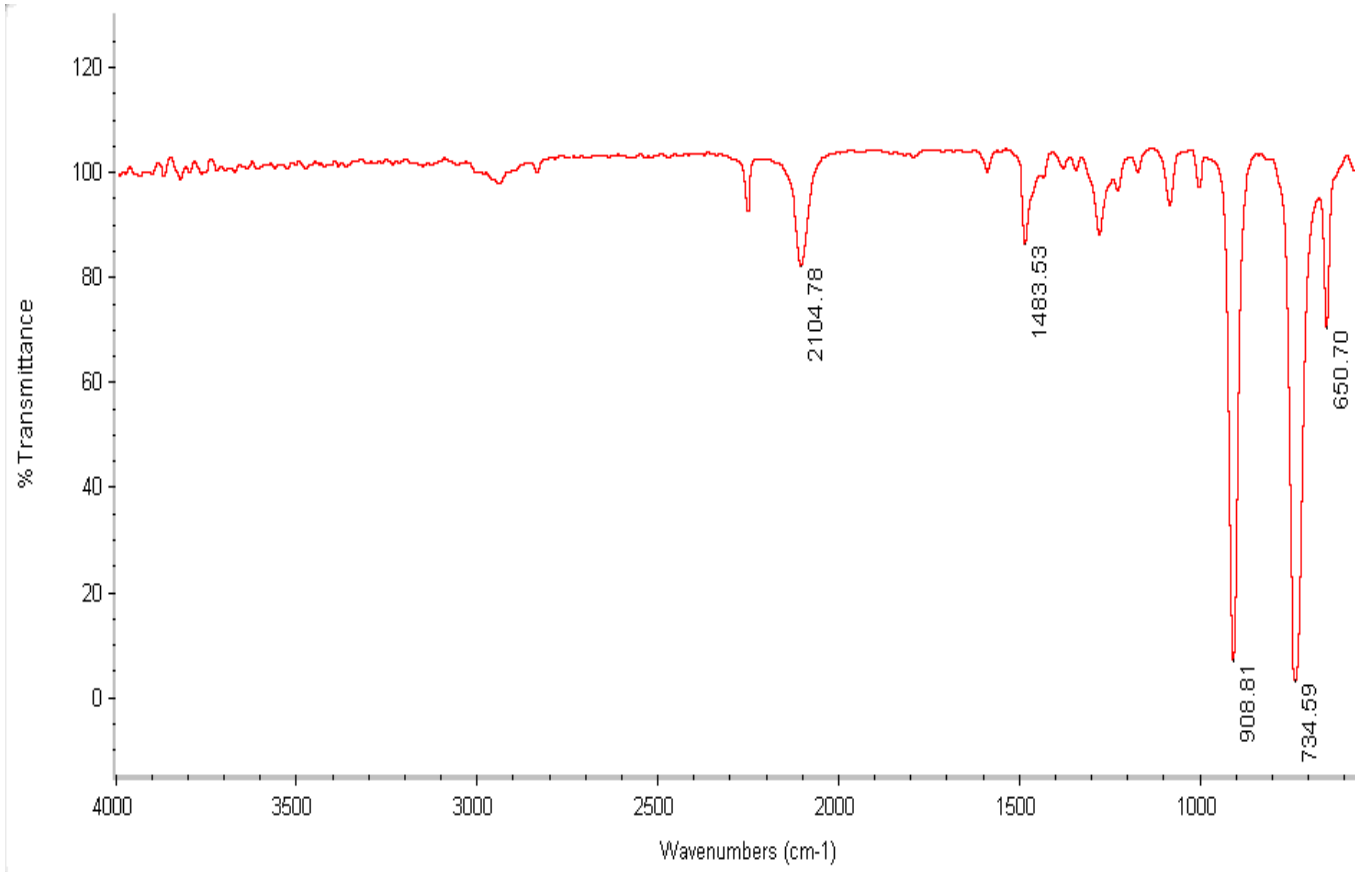

Figure 19: IR spectrum of 1-(azidomethyl)-2,3-dimethoxybenzene (**8**)

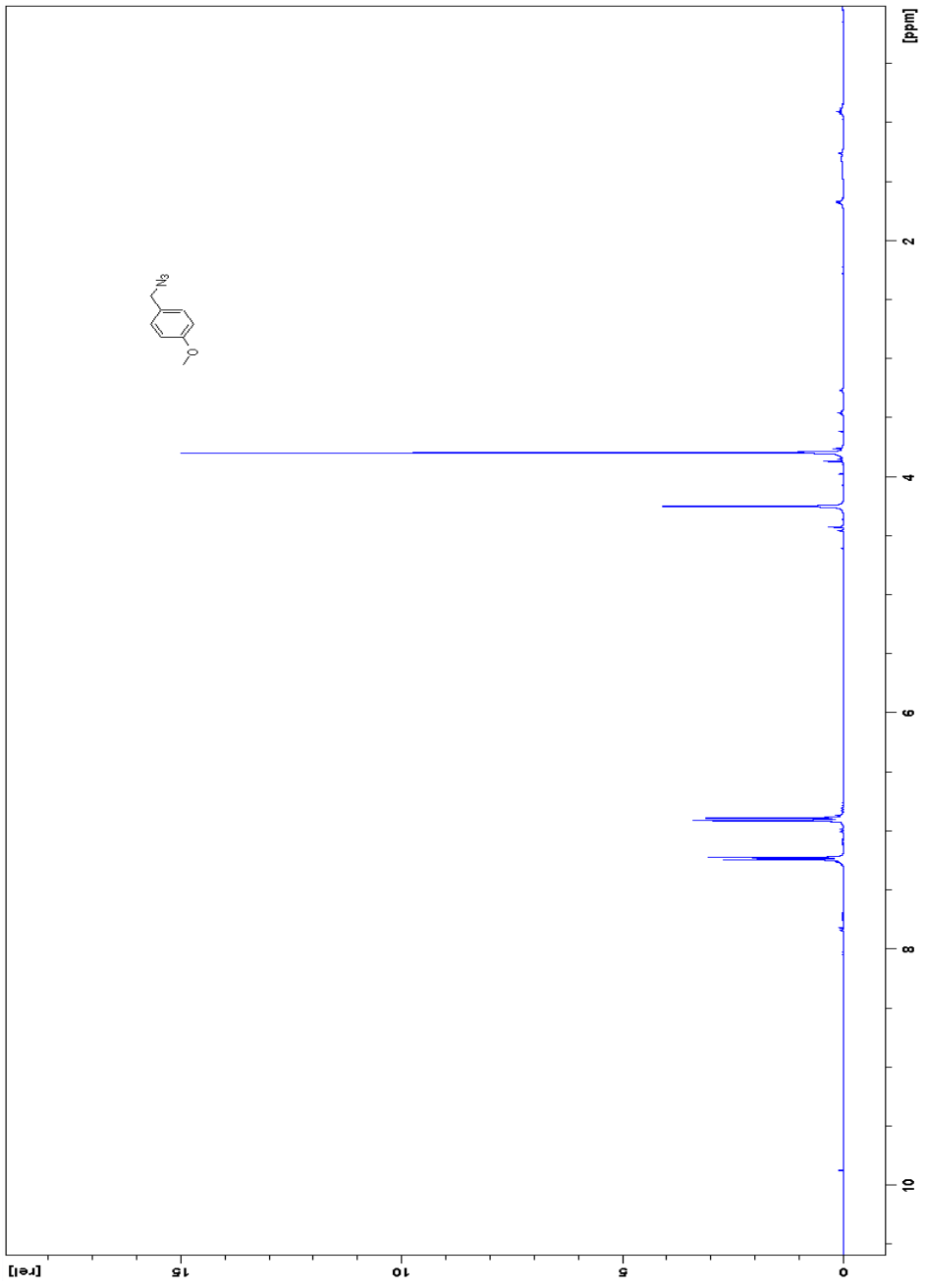

Figure 20: ^{1}H NMR of 1-(azidomethyl)-4-methoxybenzene (**10**)

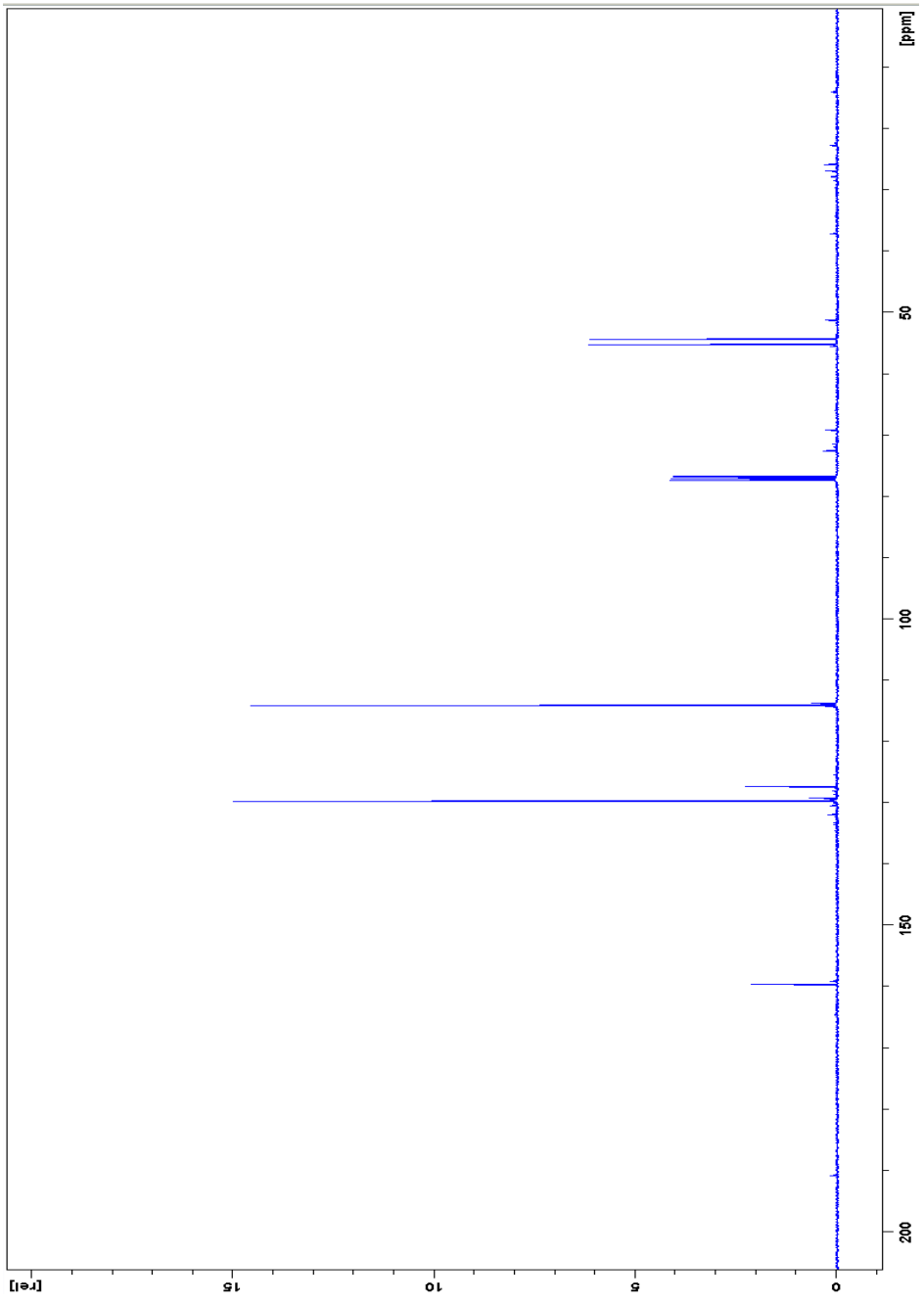

Figure 21: ^{13}C NMR of 1-(azidomethyl)-4-methoxybenzene (**10**)

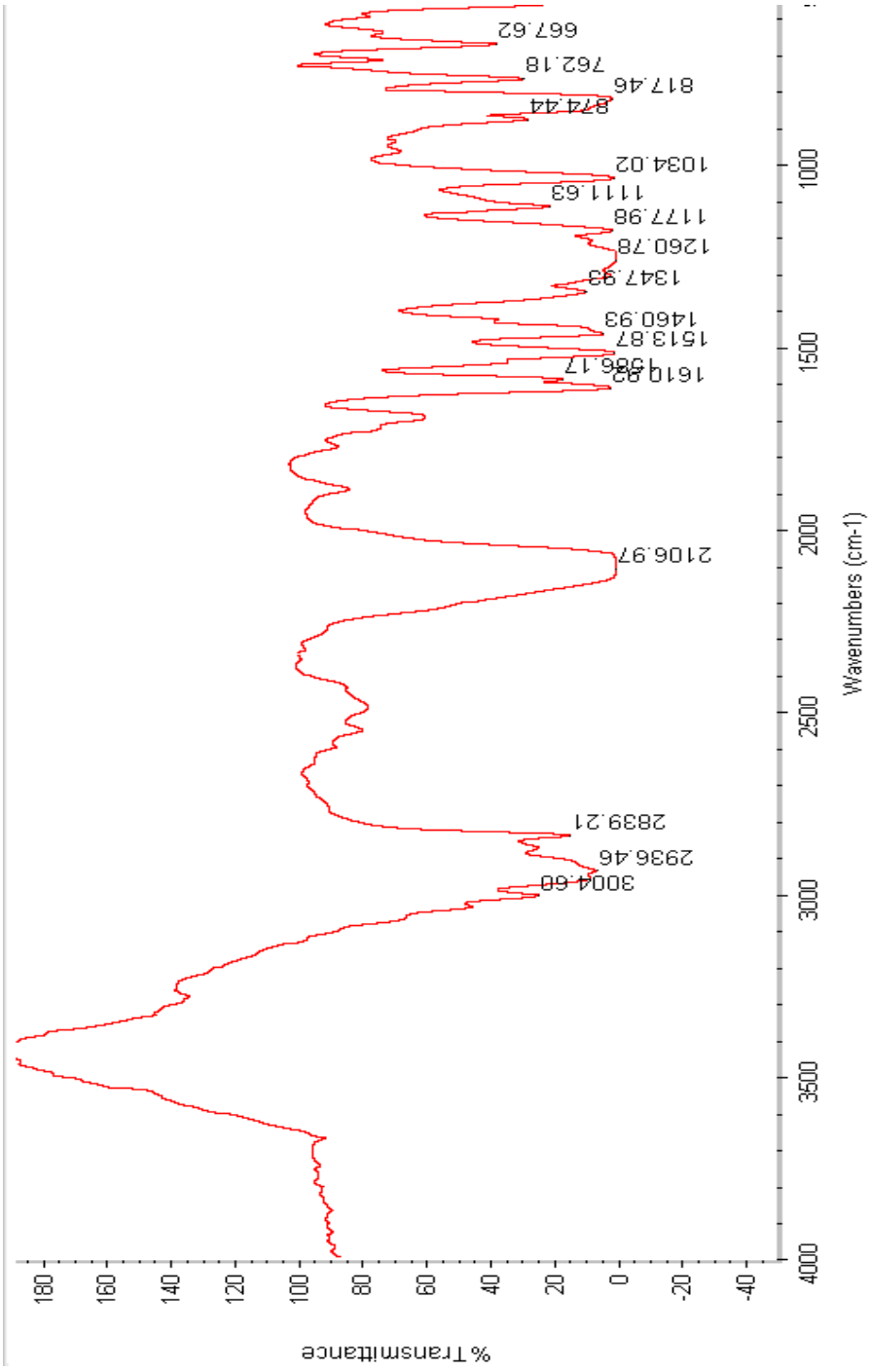

Figure 22: IR spectrum of 1-(azidomethyl)-4-methoxybenzene (**10**)

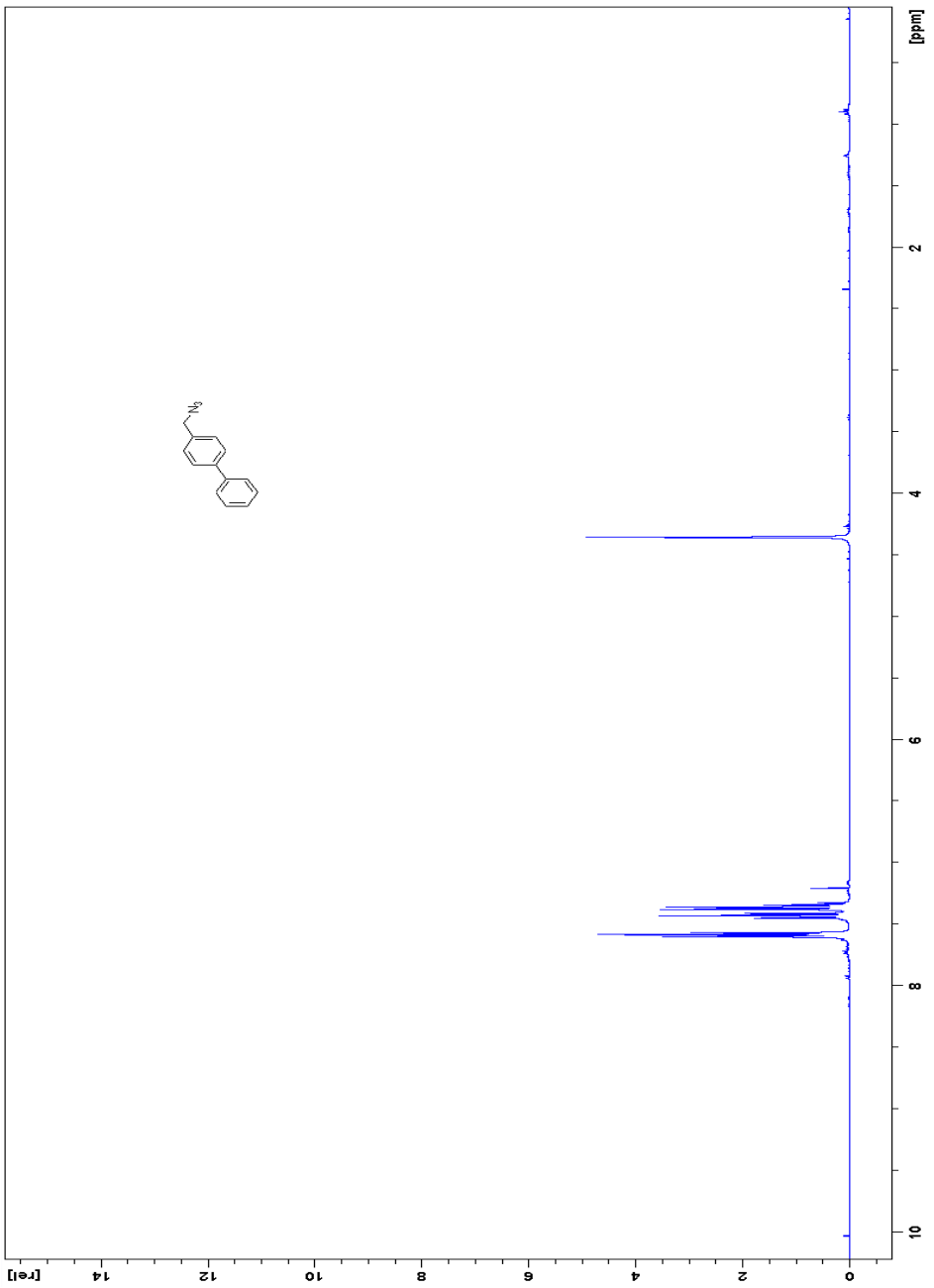

Figure 23: ^{1}H NMR of 4-(azidomethyl)-1,1^{1}-biphenyl (**12**)

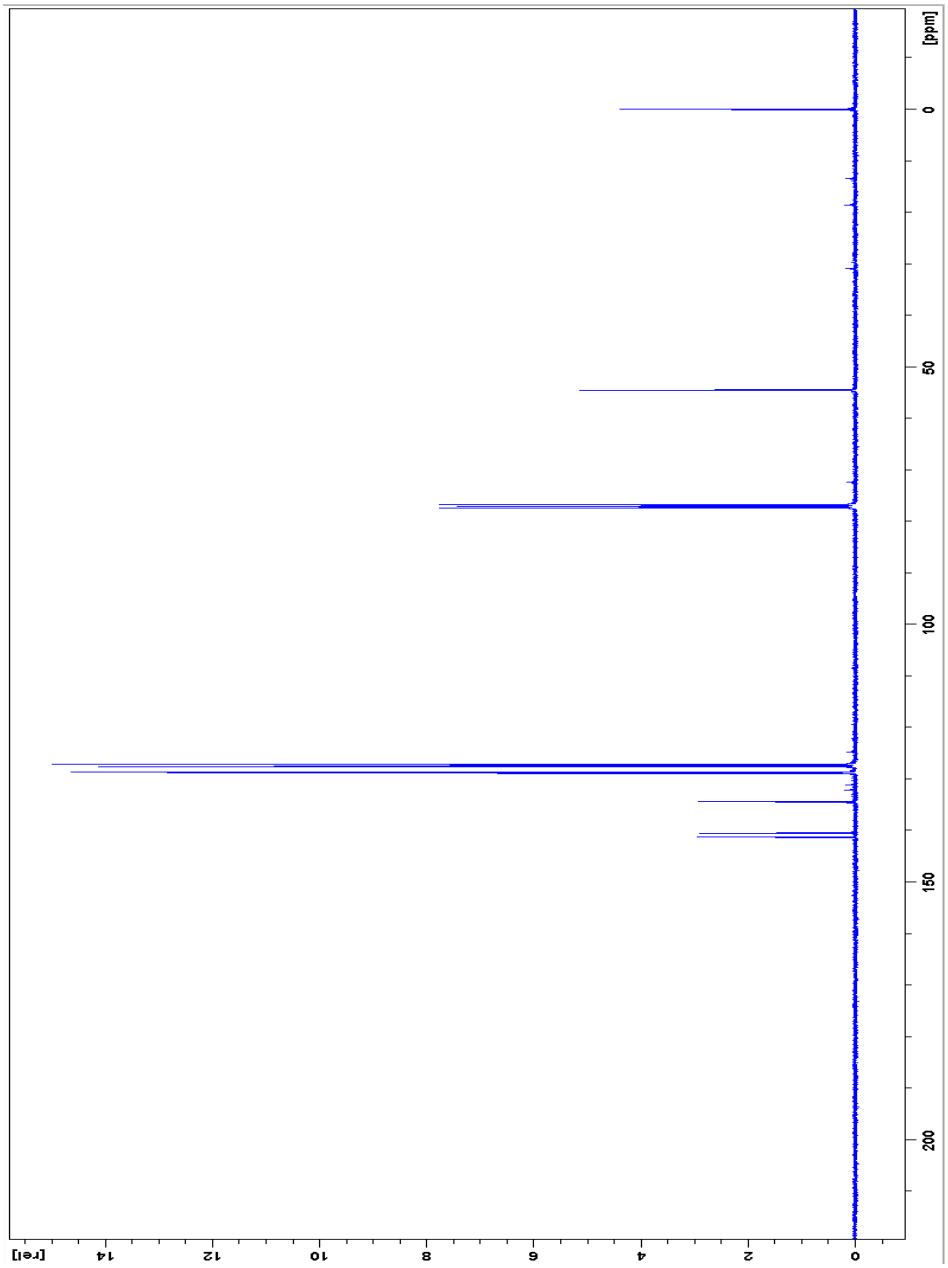

Figure 24: ^{13}C NMR of 4-(azidomethyl)-1,1^{1}-biphenyl (**12**)

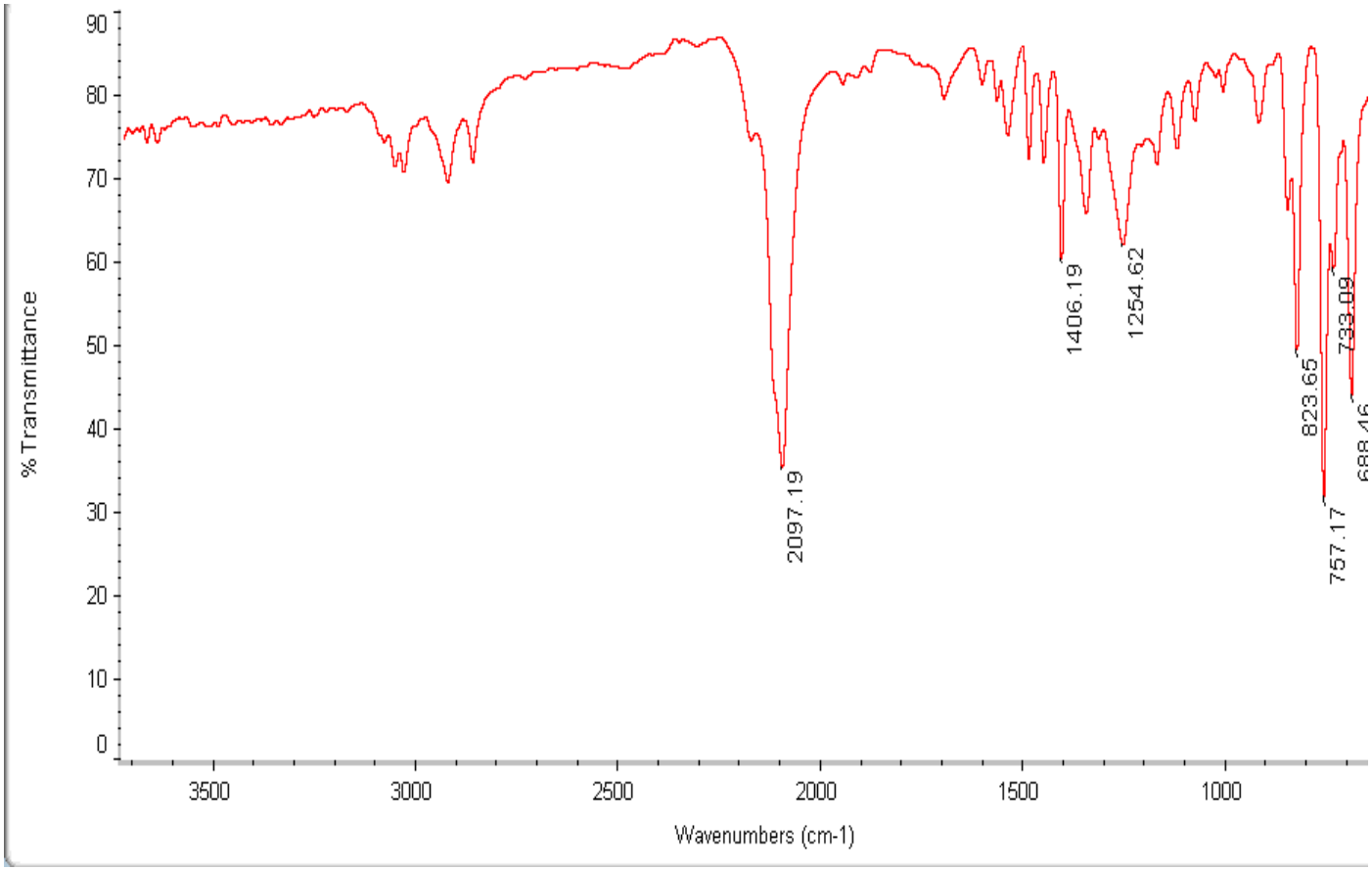

Figure 25: IR spectrum of 4-(azidomethyl)-1,1[1]-biphenyl (**12**)

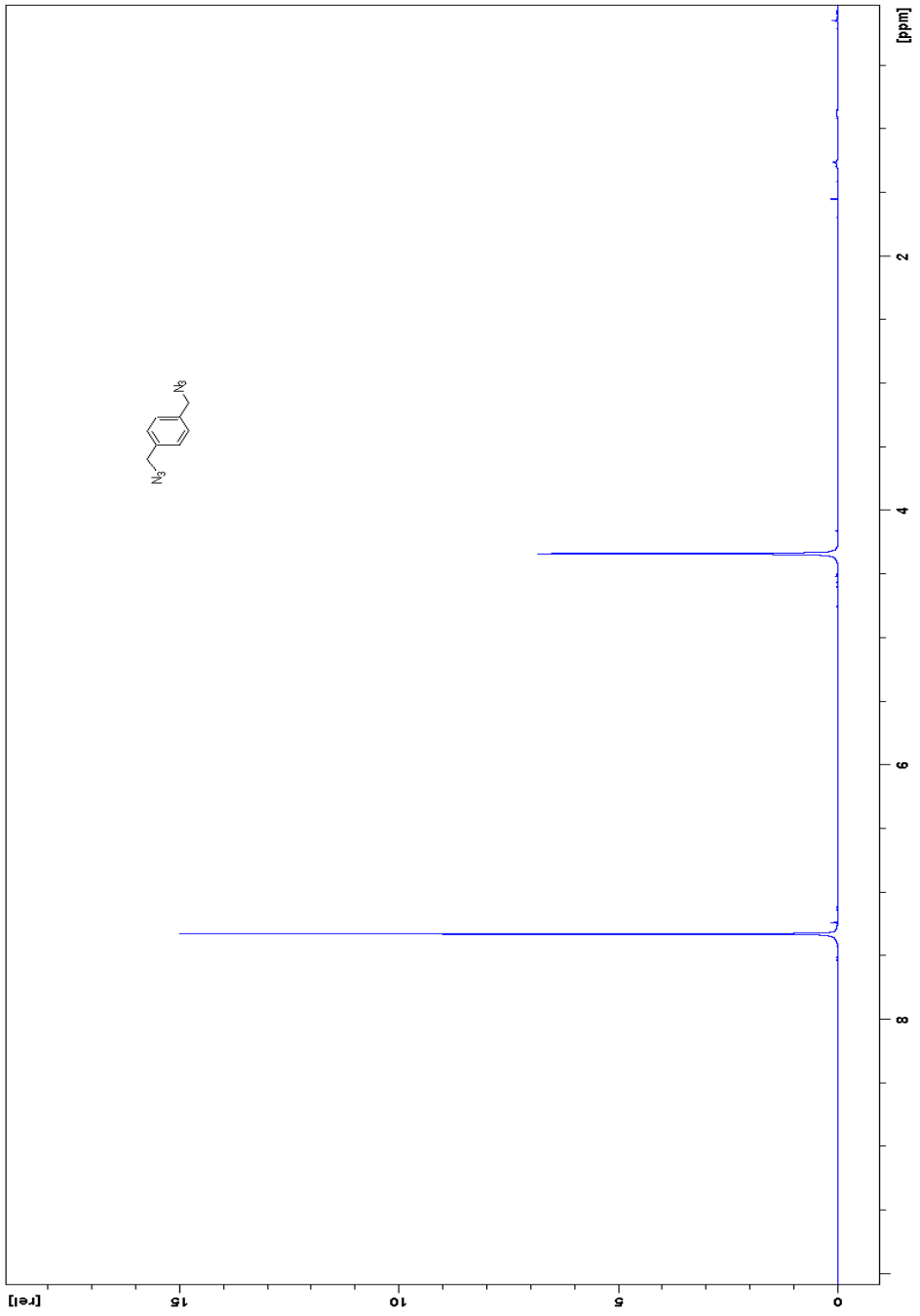

Figure 26: ^{1}H NMR of 1,4-bis(azidomethyl)benzene (**14**)

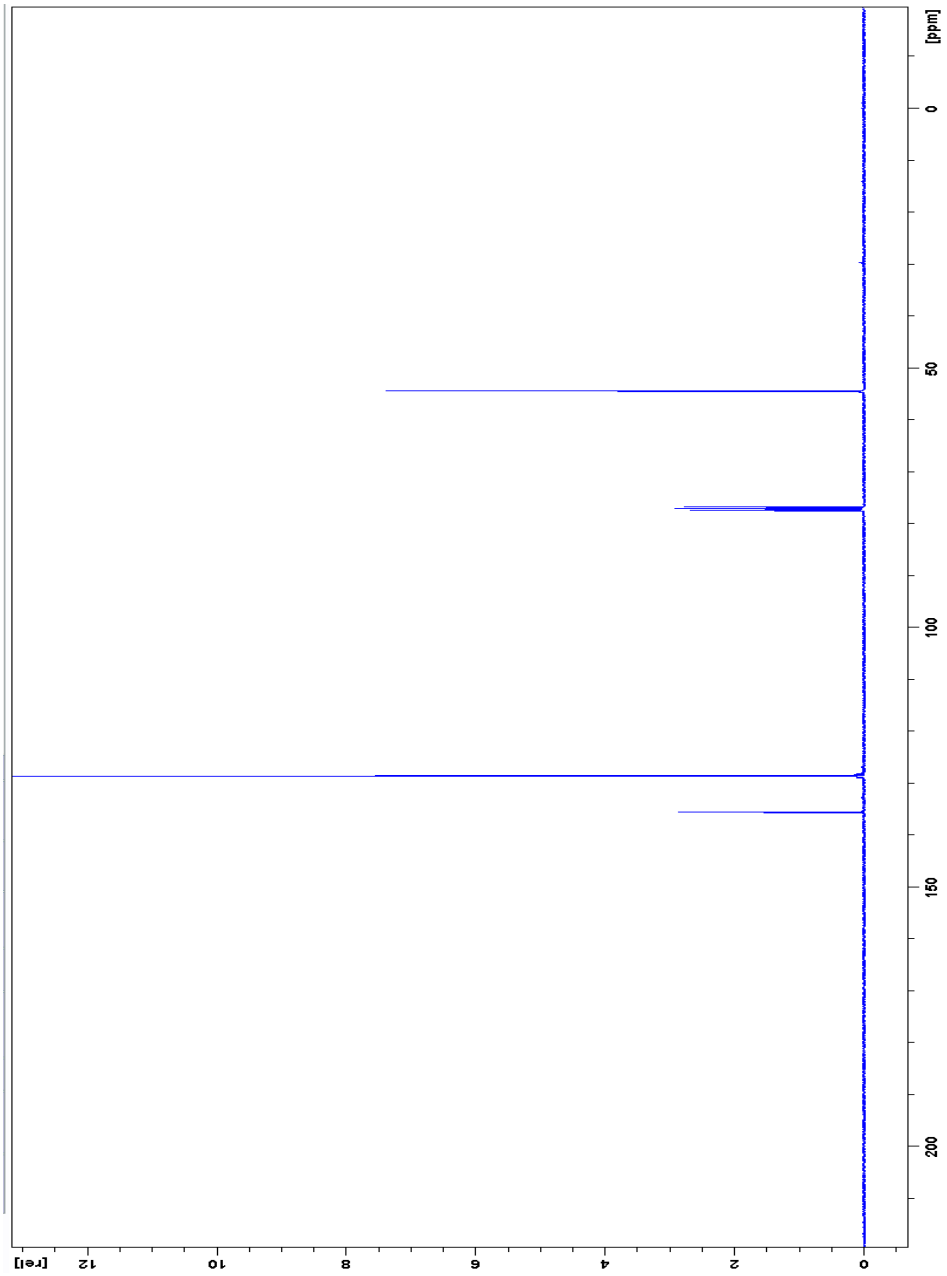

Figure 27: ^{13}C NMR of 1,4-bis(azidomethyl)benzene (**14**)

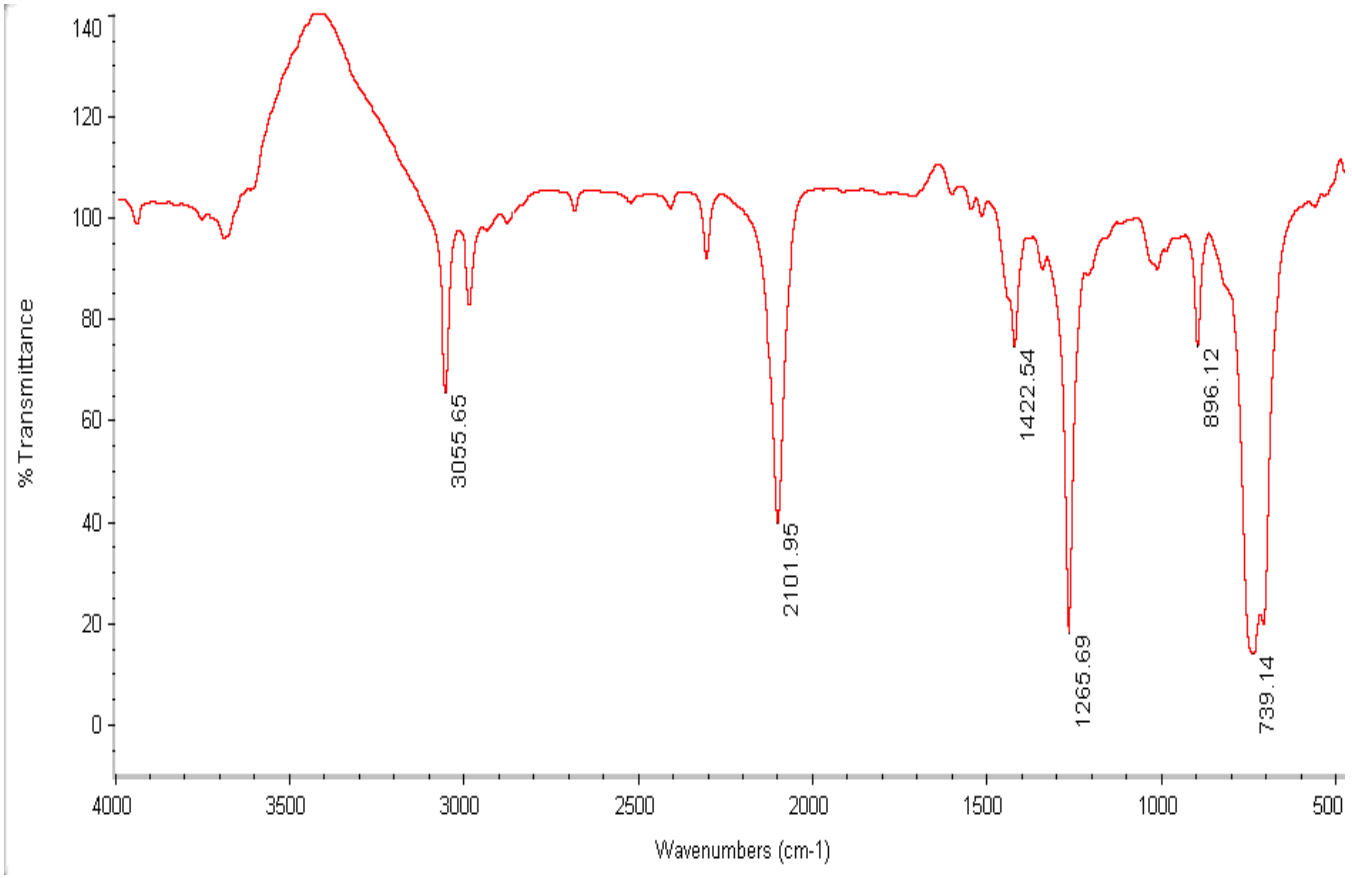

Figure 28: IR spectrum of 1,4-bis(azidomethyl)benzene (**14**)

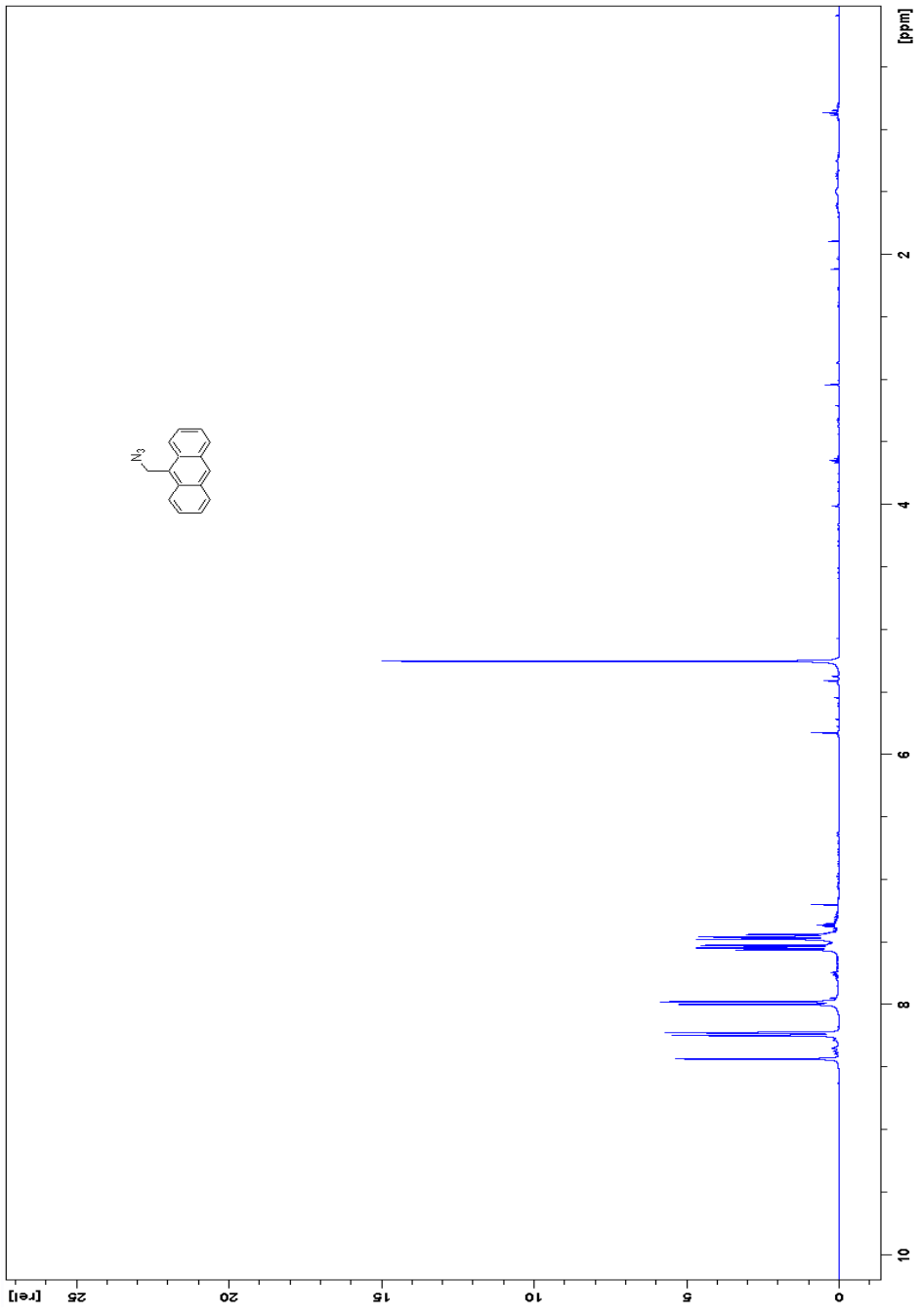

Figure 29: ^{1}H NMR of 9-(azidomethyl)anthracene (**16**)

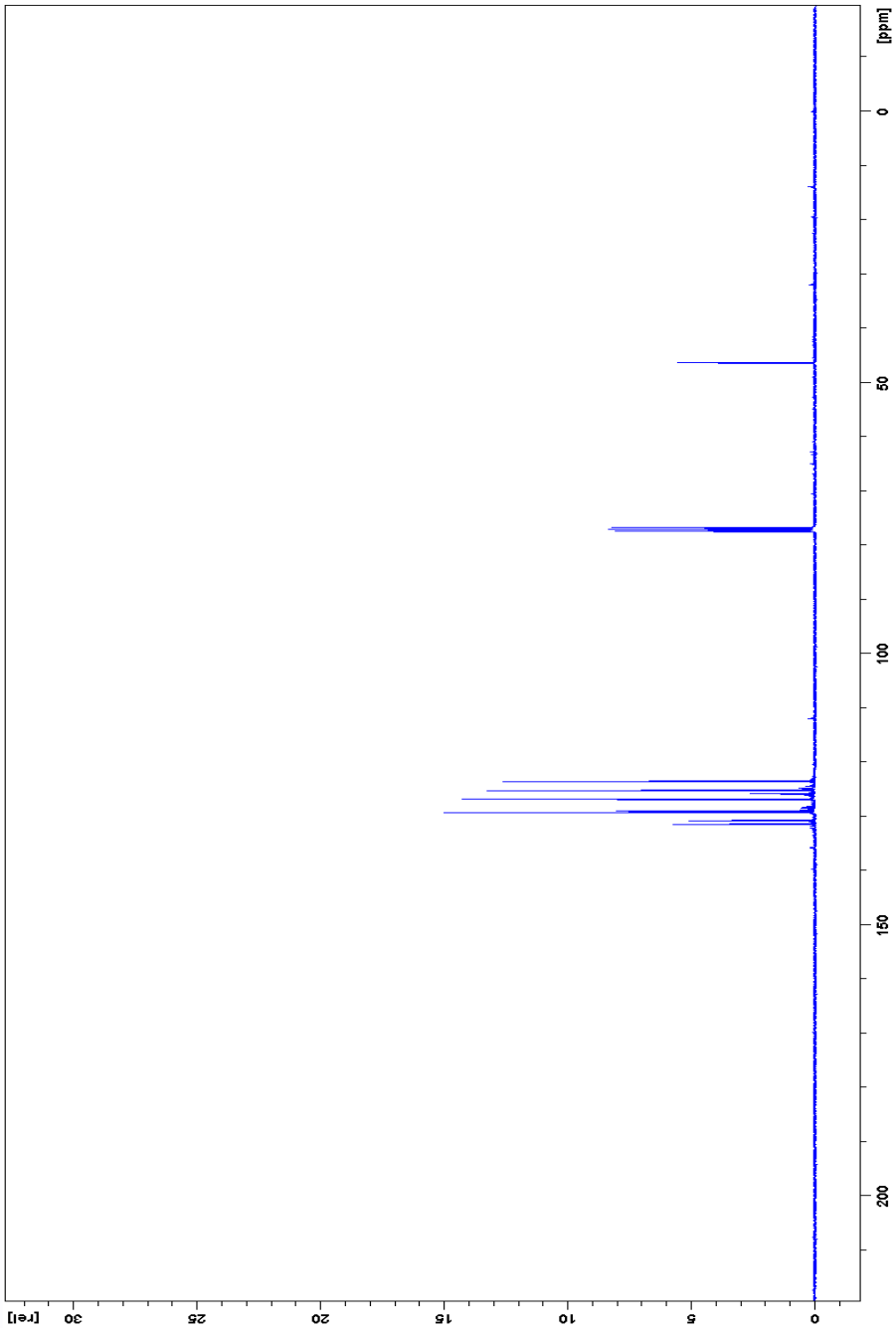

Figure 30: ^{13}C NMR of 9-(azidomethyl)anthracene (**16**)

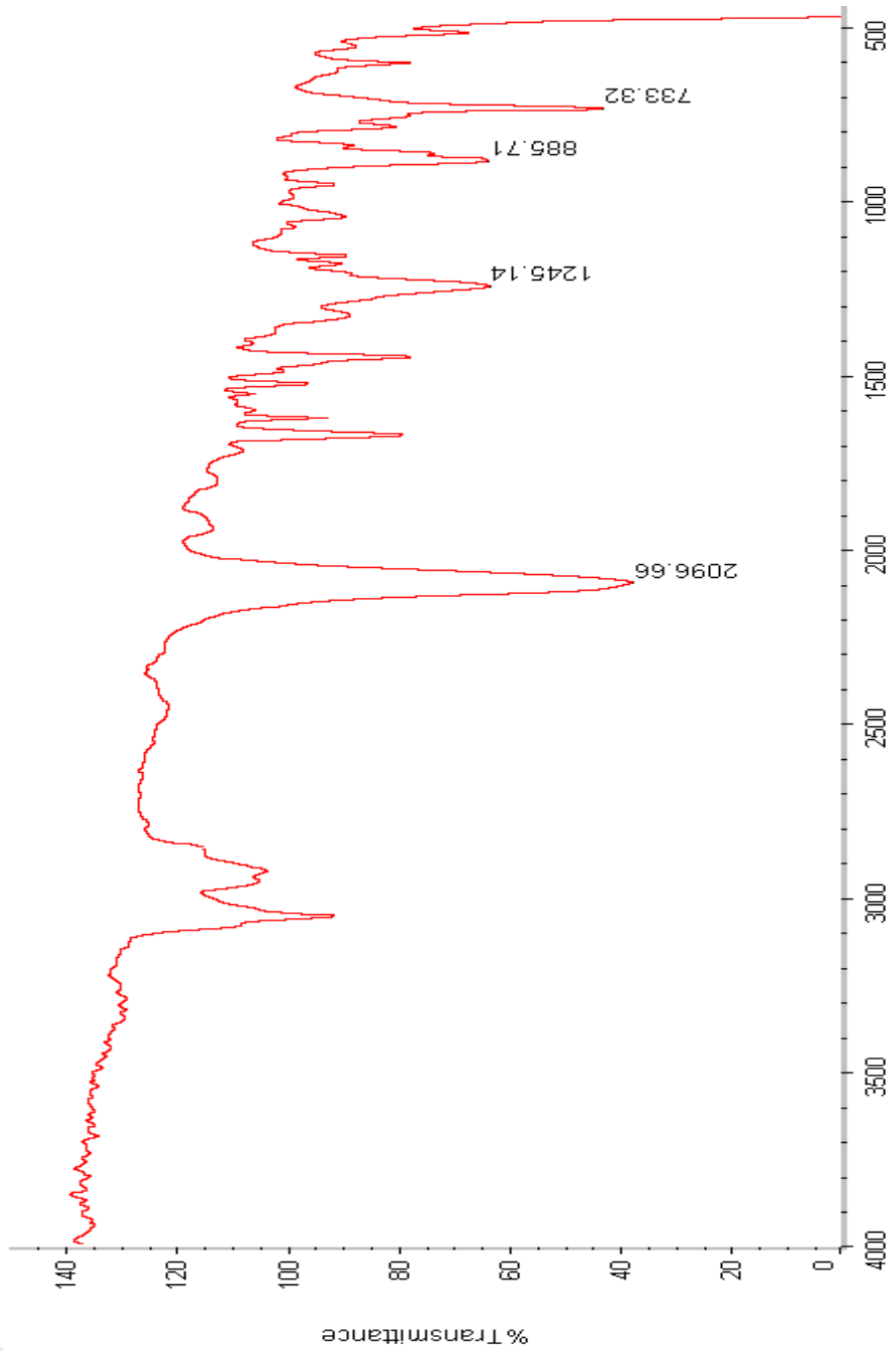

Figure 31: IR spectrum of 9-(azidomethyl)anthracene (**16**)

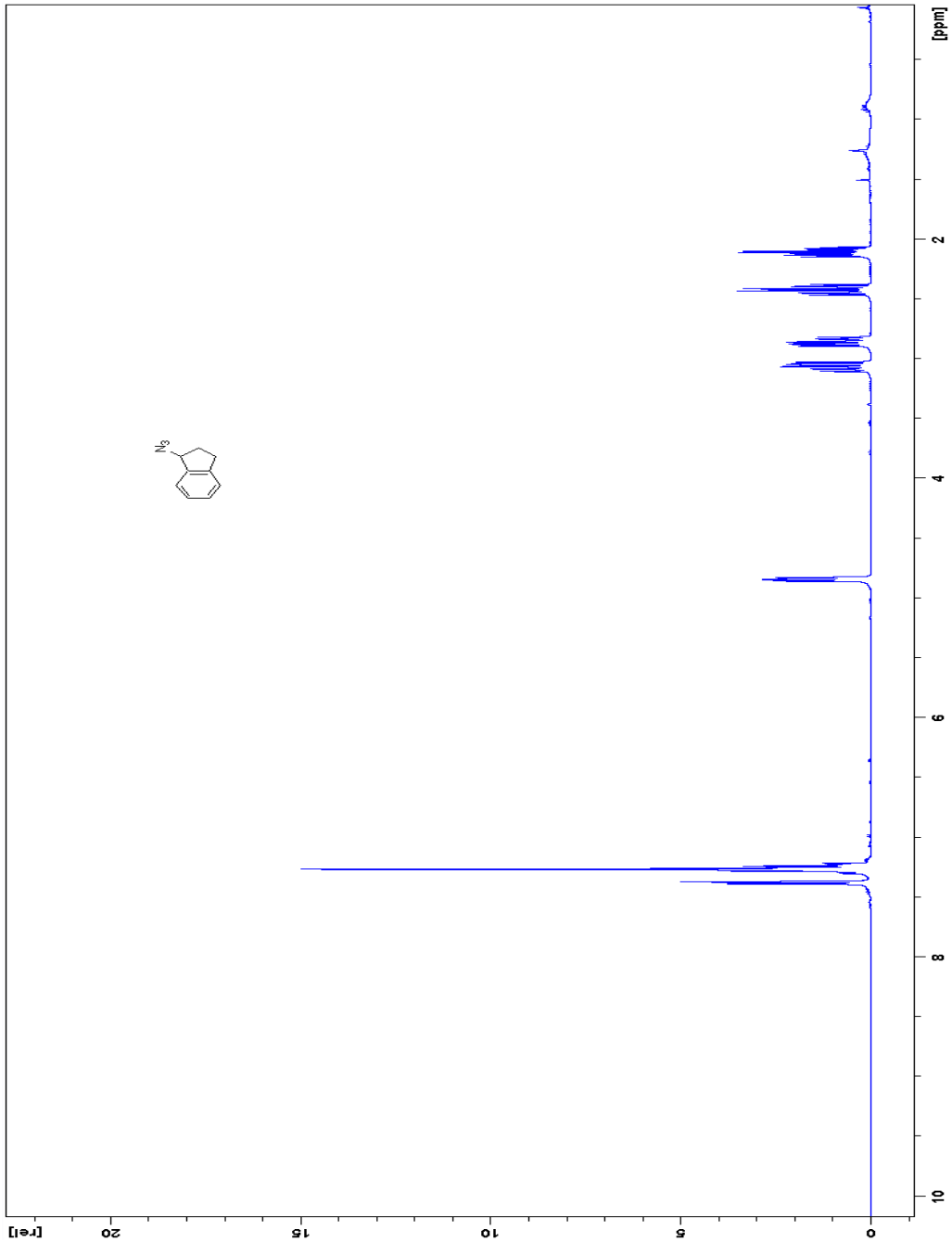

Figure 32: ^{1}H NMR of 1-azido-2,3-dihydro-1*H*-indene (**18**)

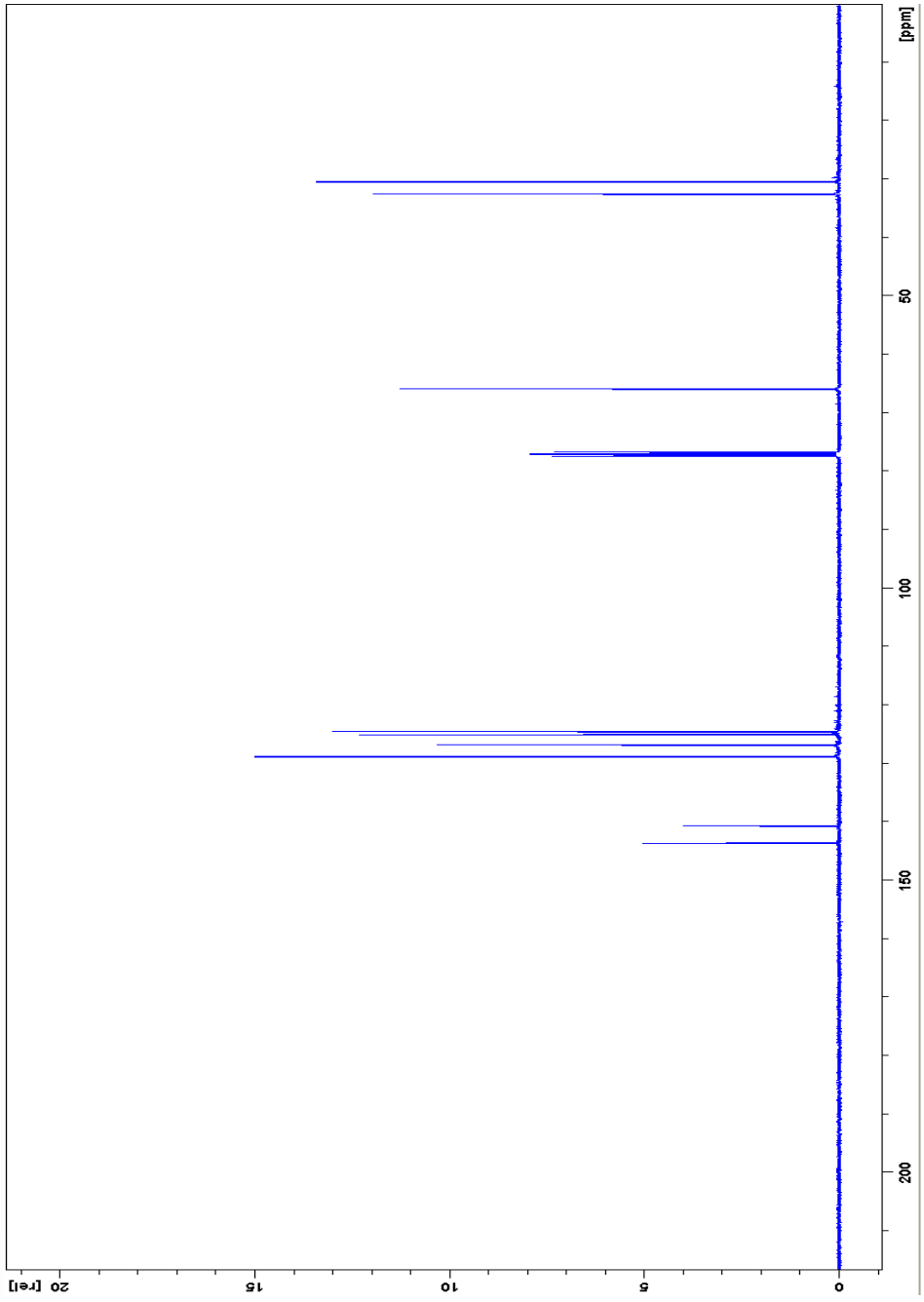

Figure 33: ^{13}C NMR of 1-azido-2,3-dihydro-1*H*-indene (**18**)

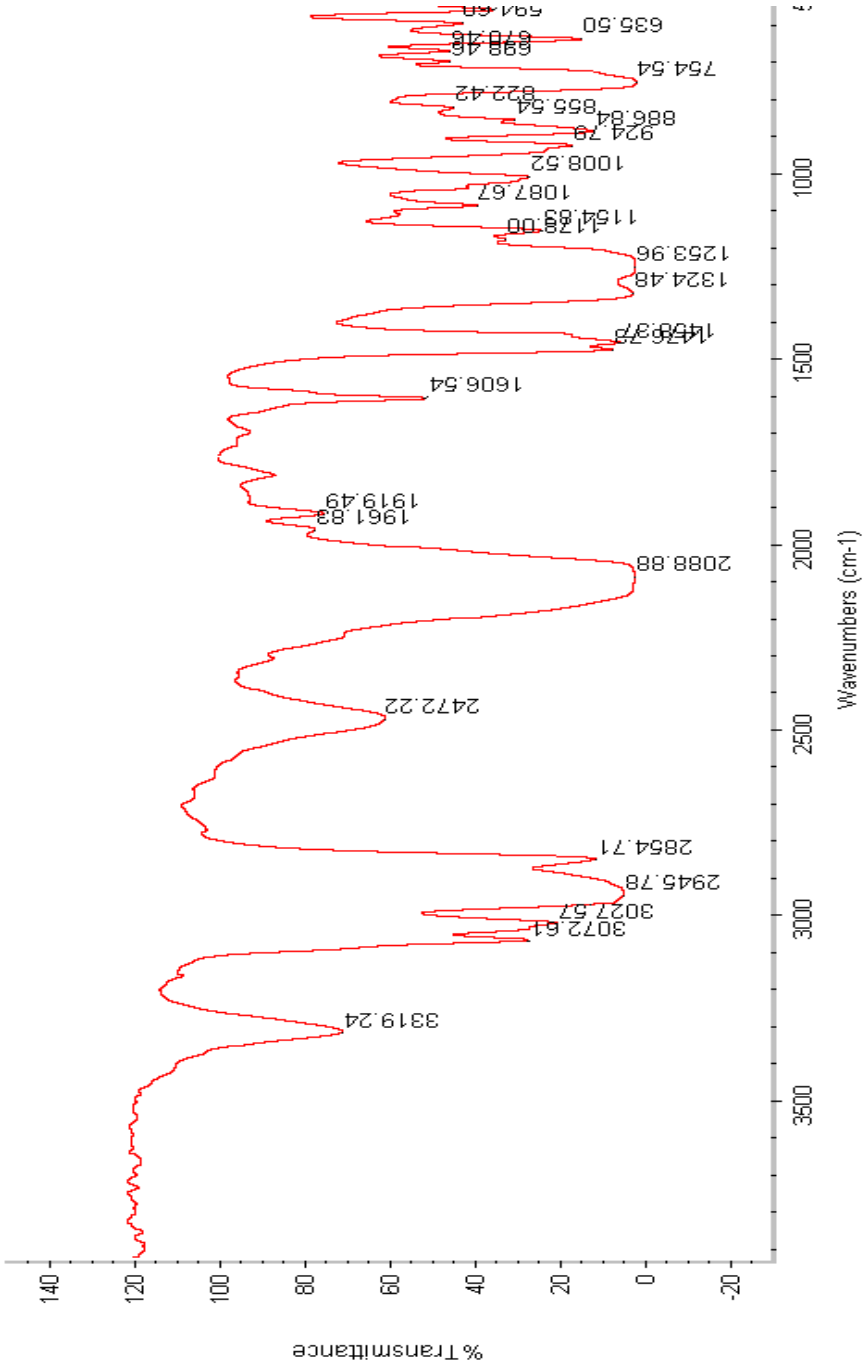

Figure 34: IR spectrum of 1-azido-2,3-dihydro-1*H*-indene (**18**)

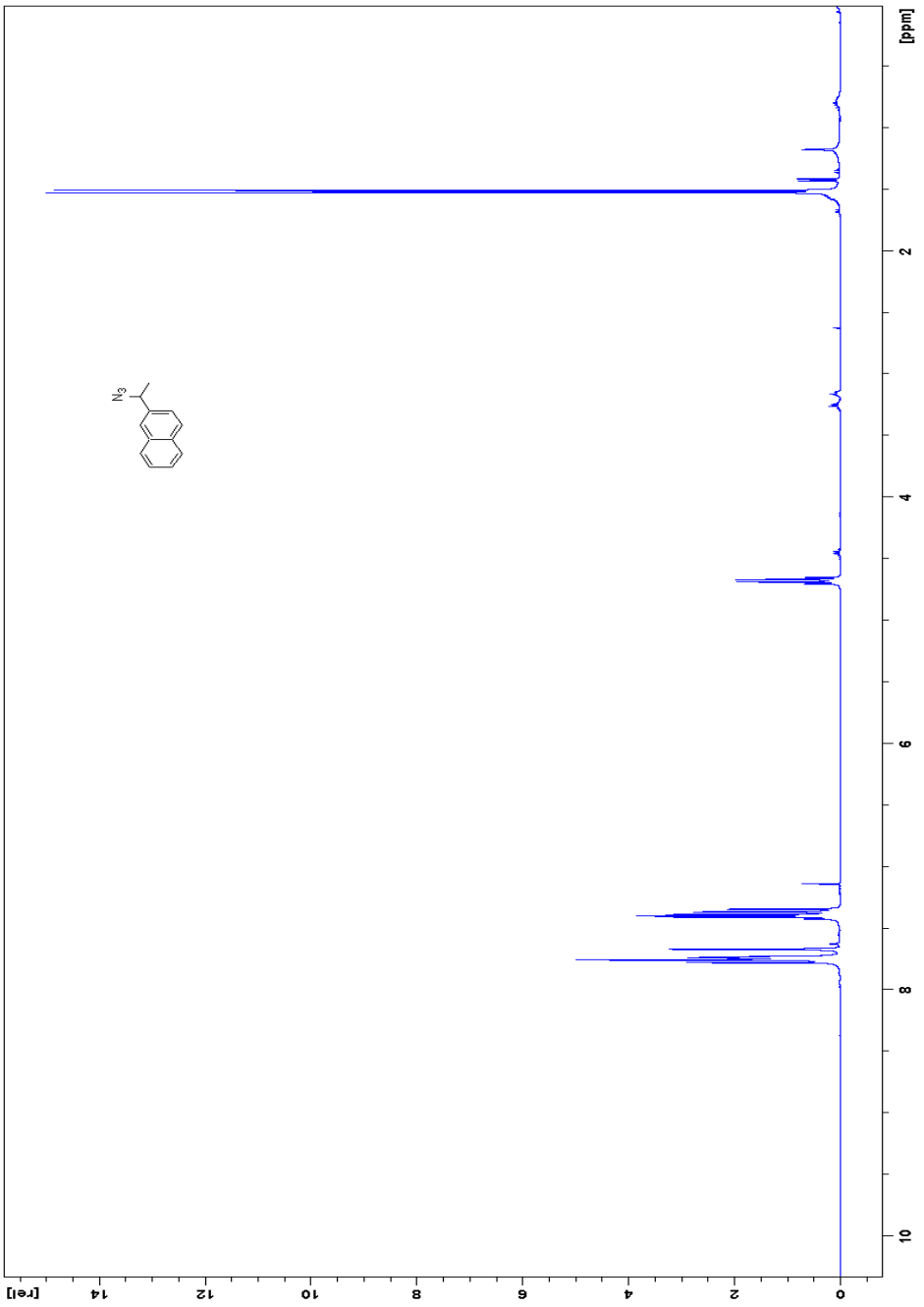

Figure 35: ^{1}H NMR of 2-(1-azidoethyl)naphthalene(**20**)

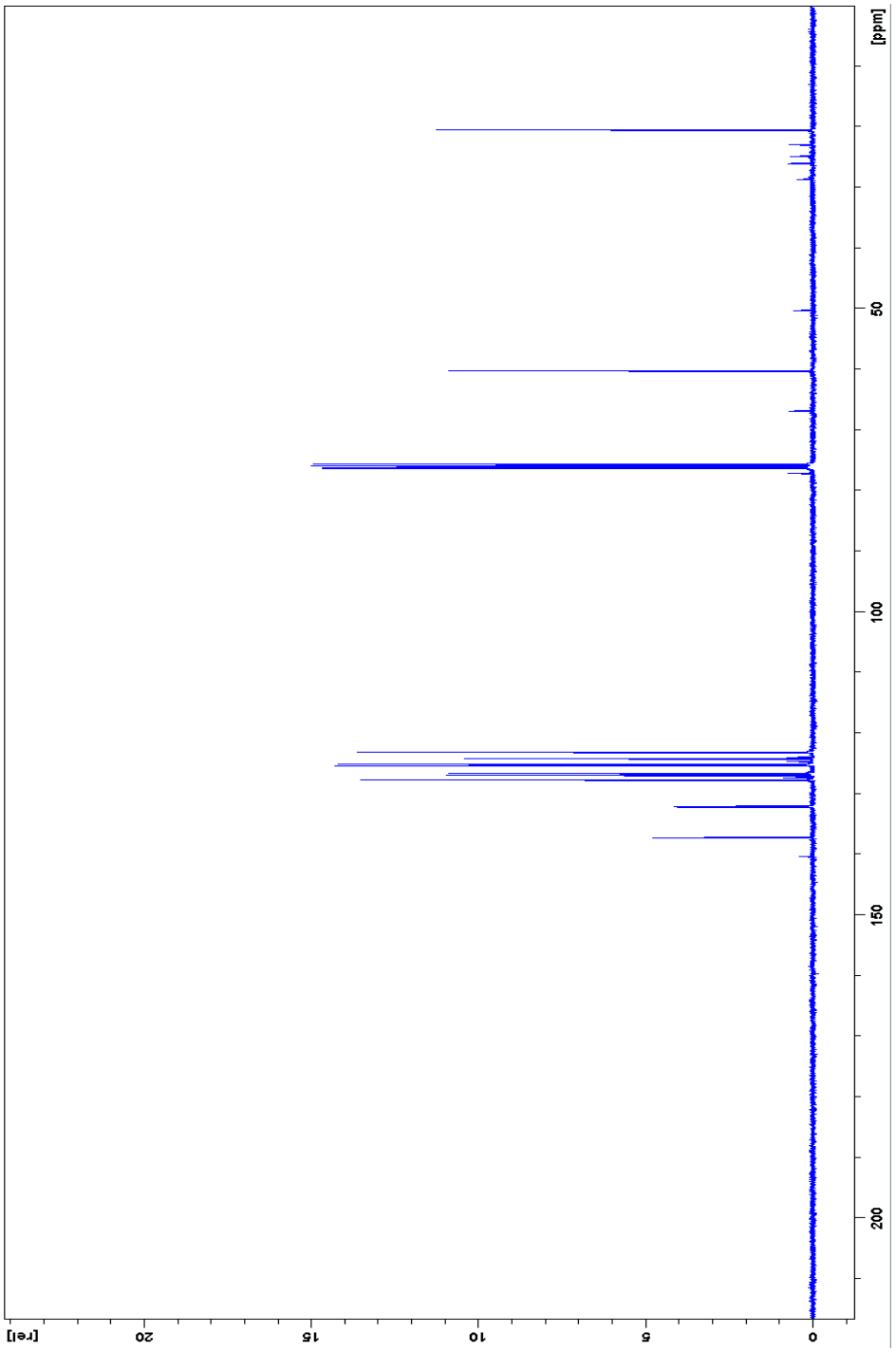

Figure 36: ^{13}C NMR of 2-(1-azidoethyl)naphthalene (**20**)

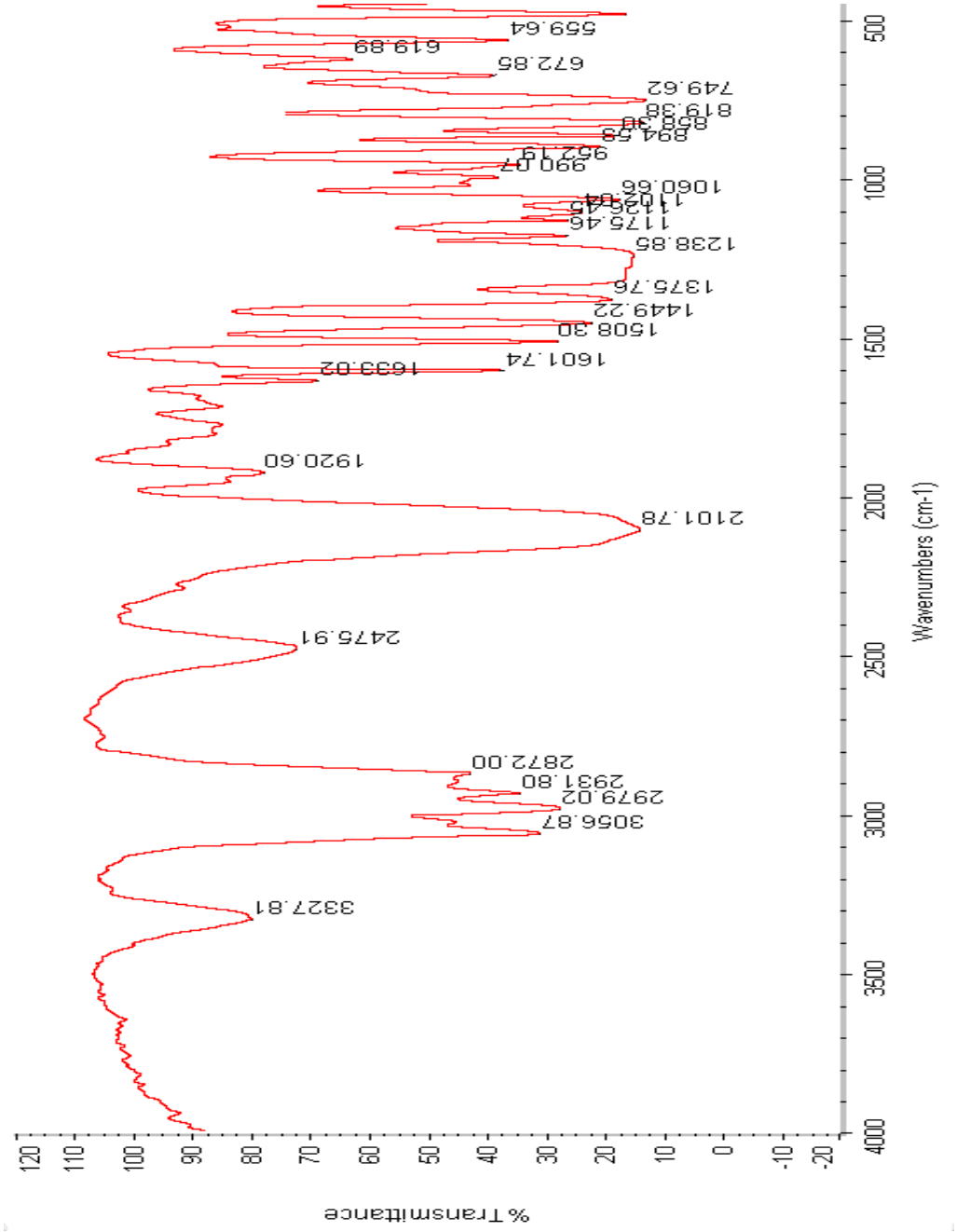

Figure 37: IR spectrum of 2-(1-azidoethyl)naphthalene (**20**)

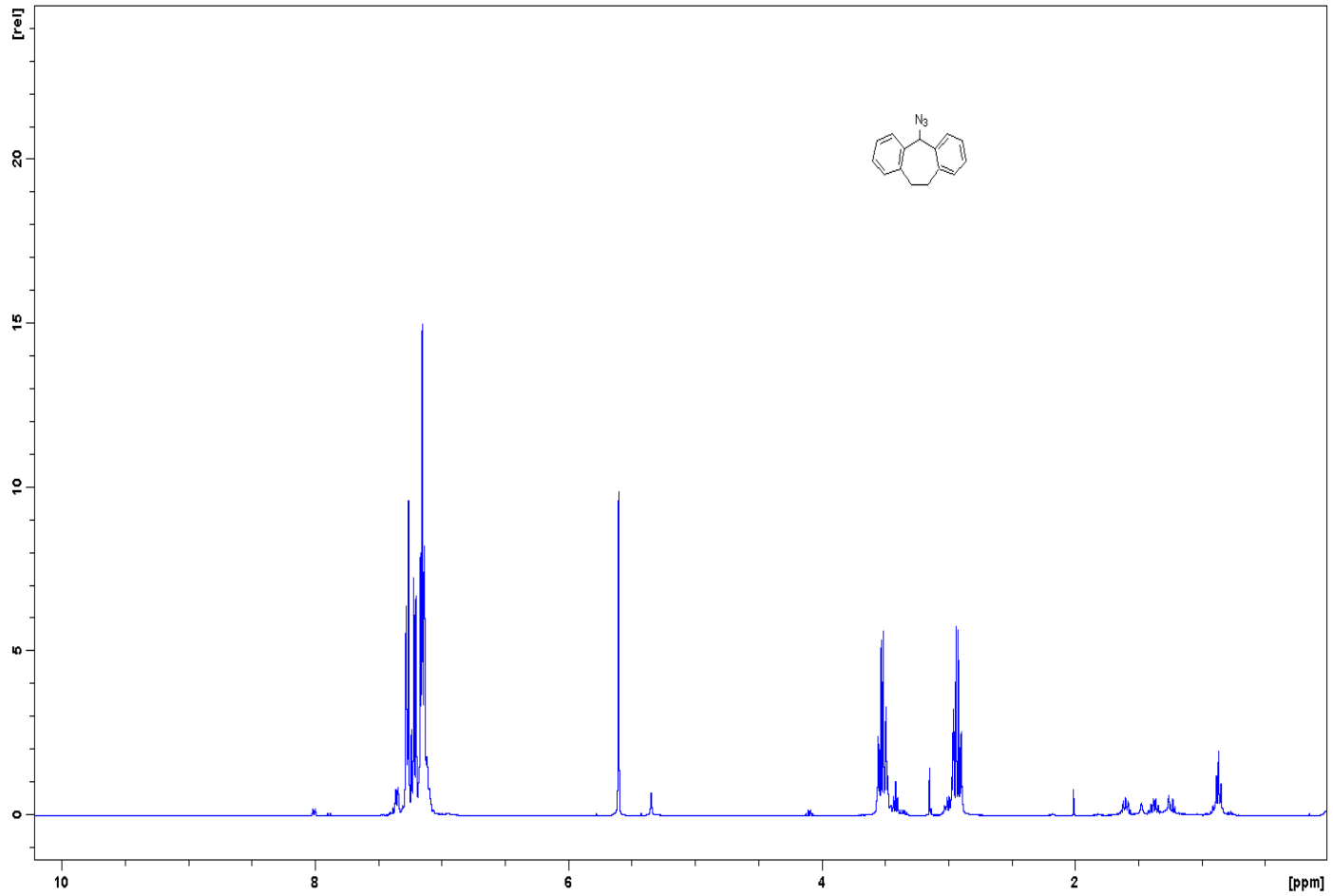

Figure 38: ^{1}H NMR of 5-azido-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene (**22**)

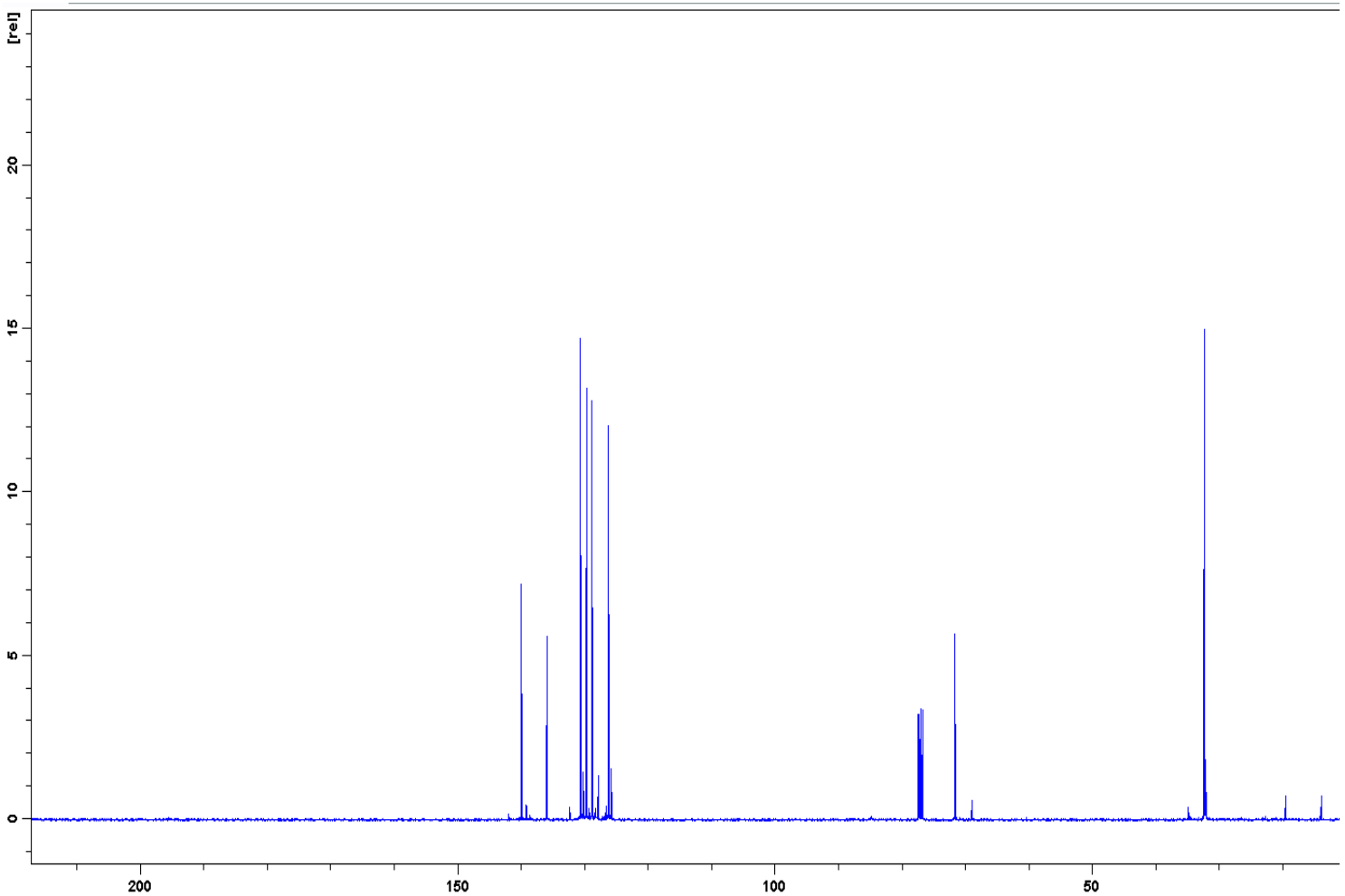

Figure 39: ^{13}C NMR of 5-azido-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene (**22**)

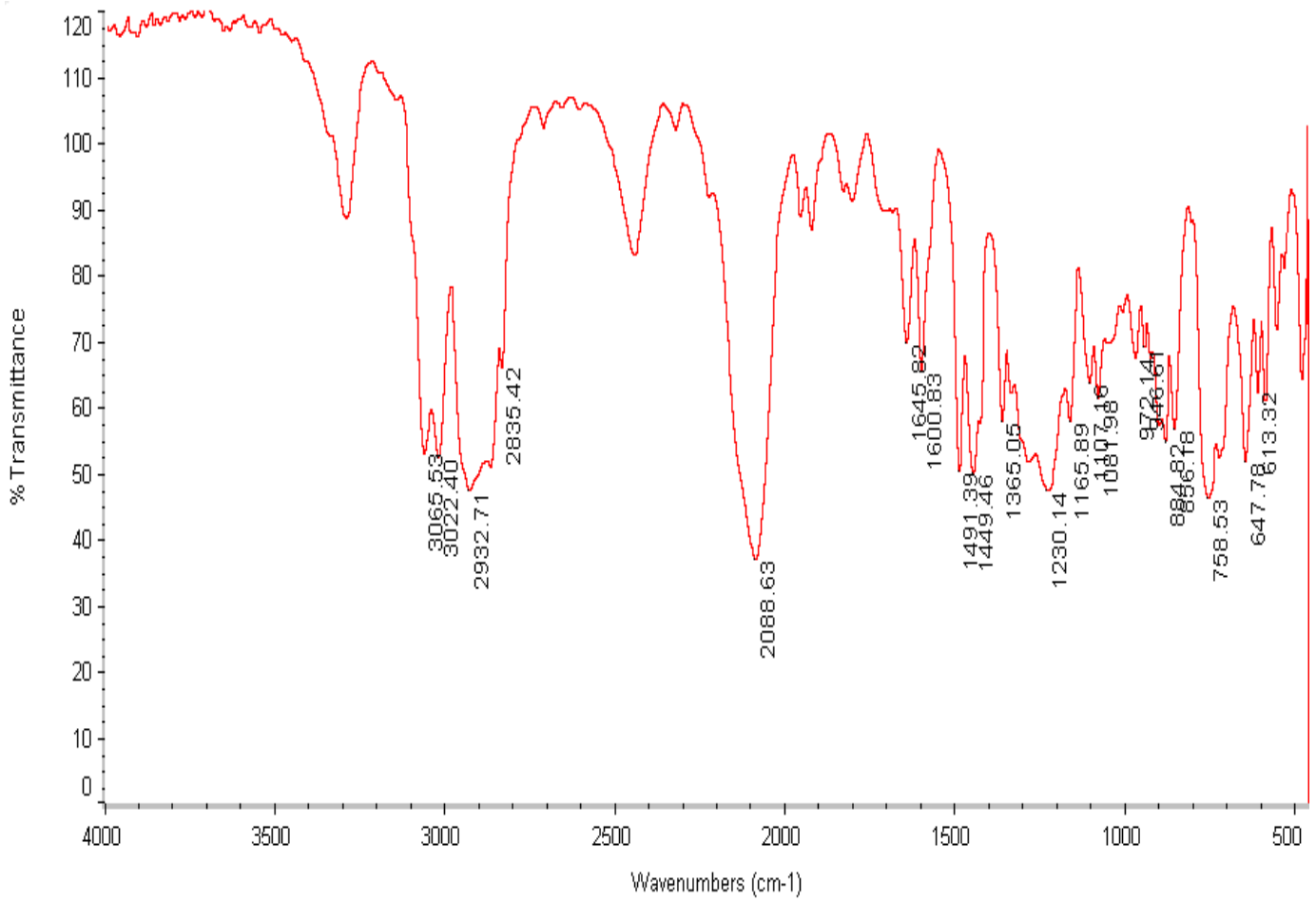

Figure 40: IR spectrum of 5-azido-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene (**22**)

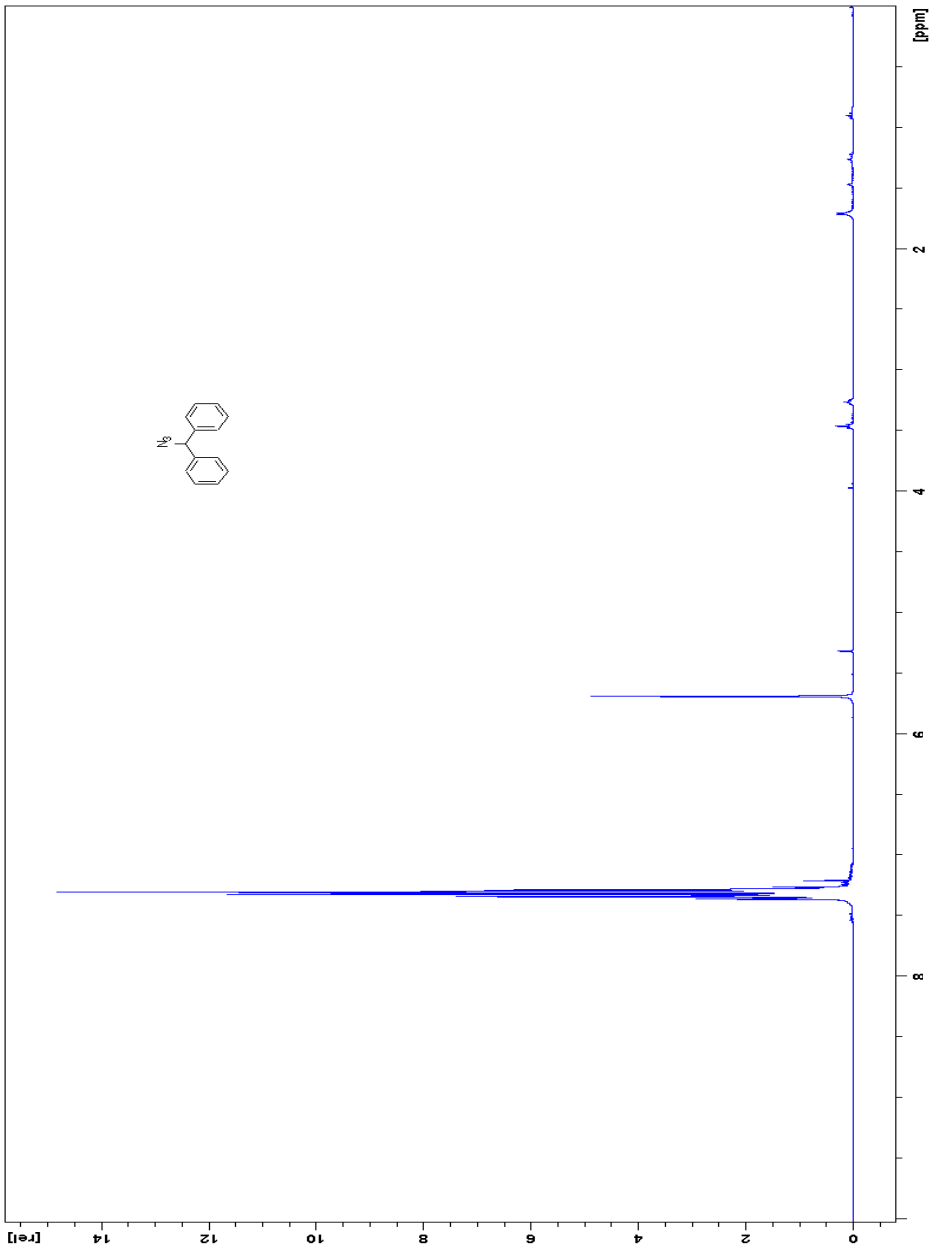

Figure 41: ^{1}H NMR of (azidomethylene)dibenzene (**24**)

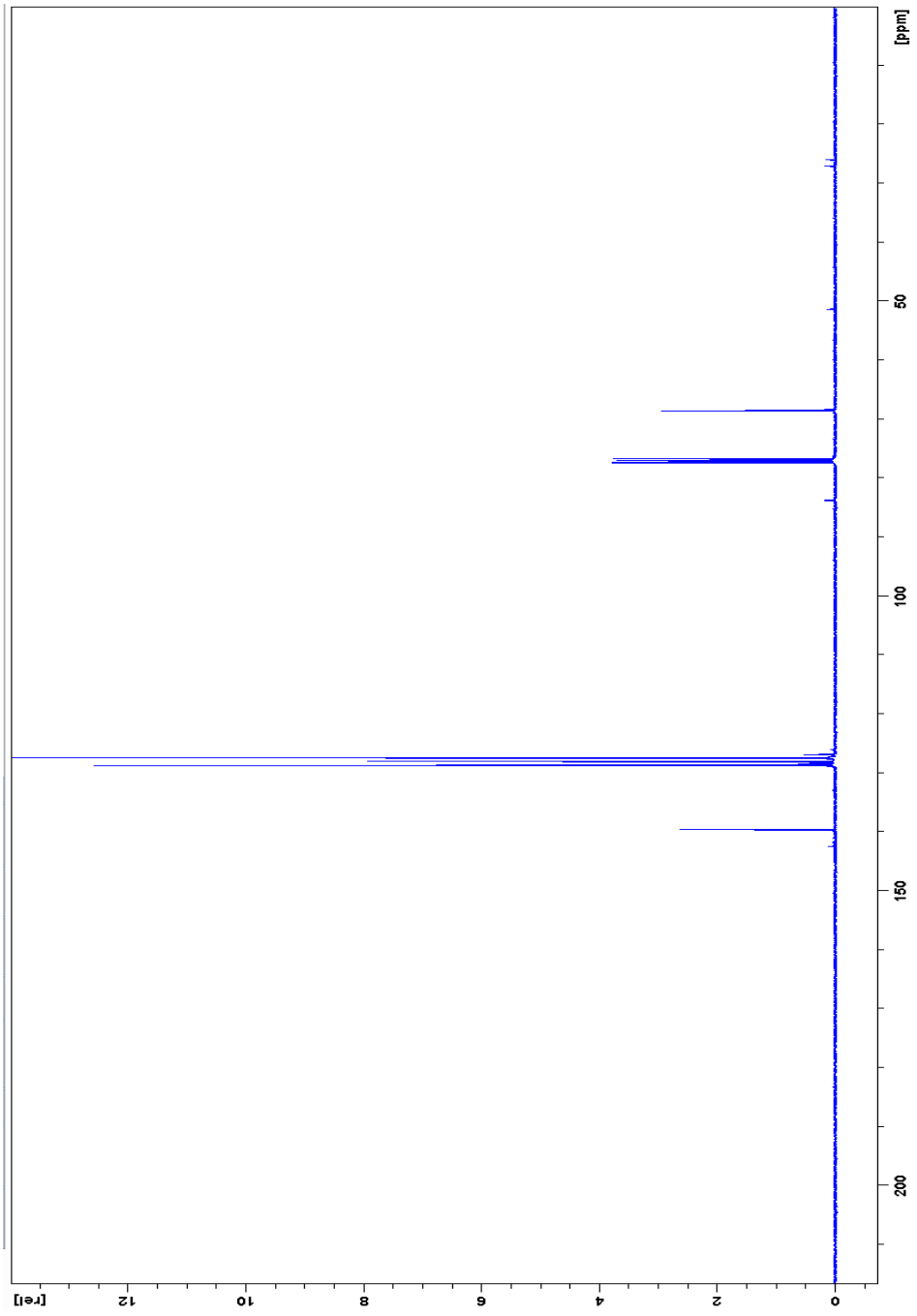

Figure 42: ^{13}C NMR of (azidomethylene)dibenzene (**24**)

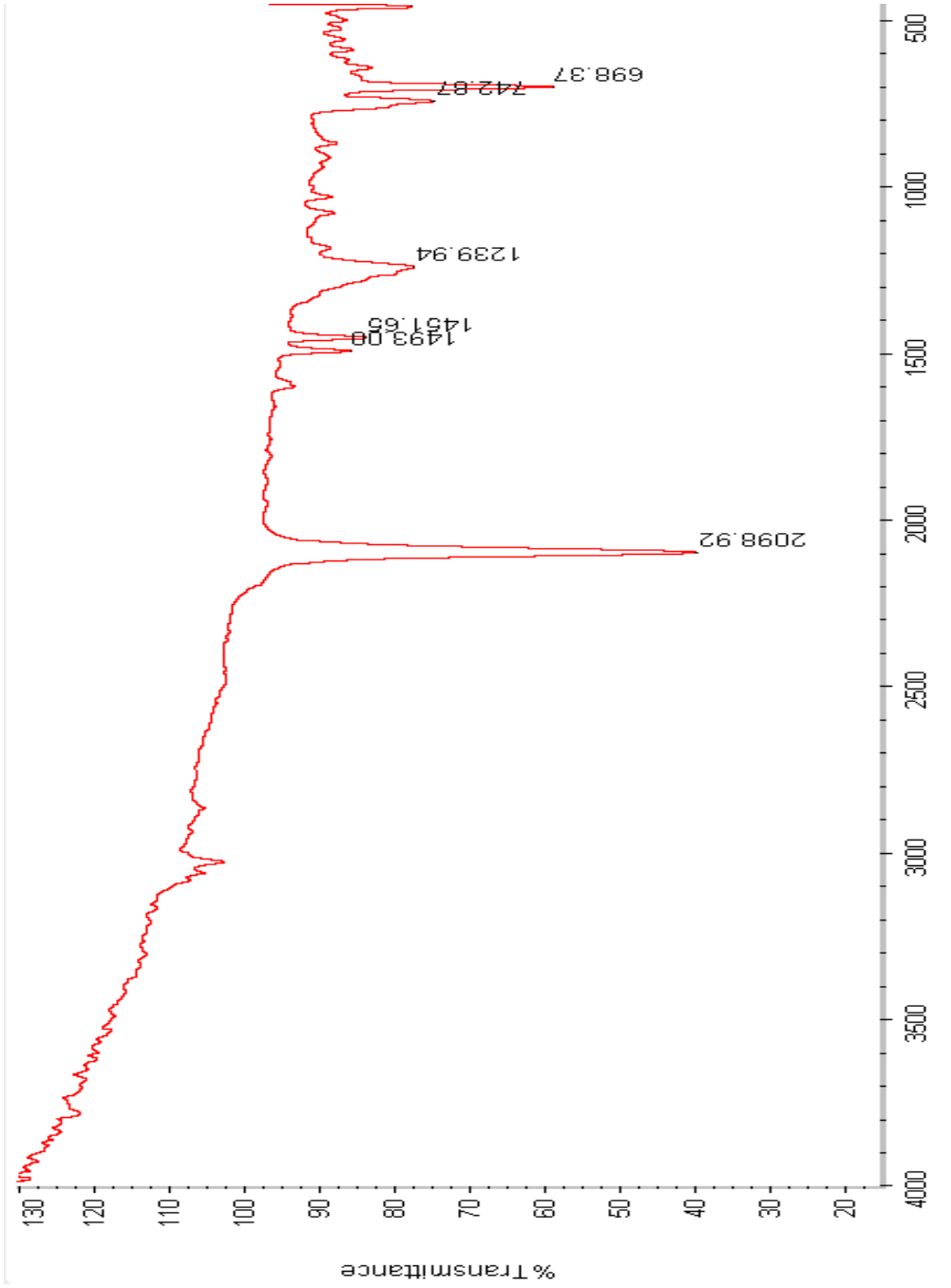

Figure 43: IR spectrum of (azidomethylene)dibenzene (**24**)

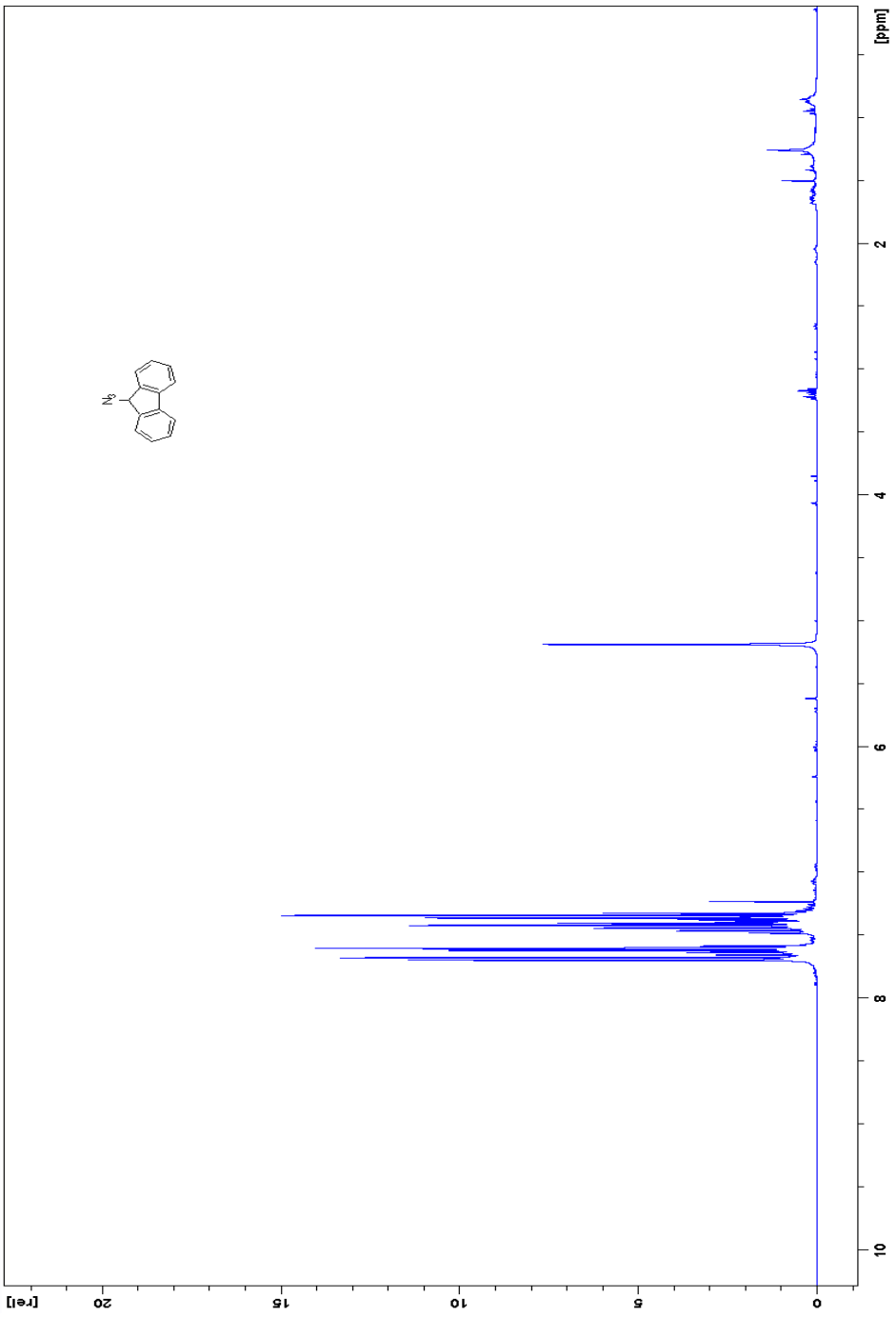

Figure 44: ^{1}H NMR of 9-azido-9*H*-fluorene (**26**)

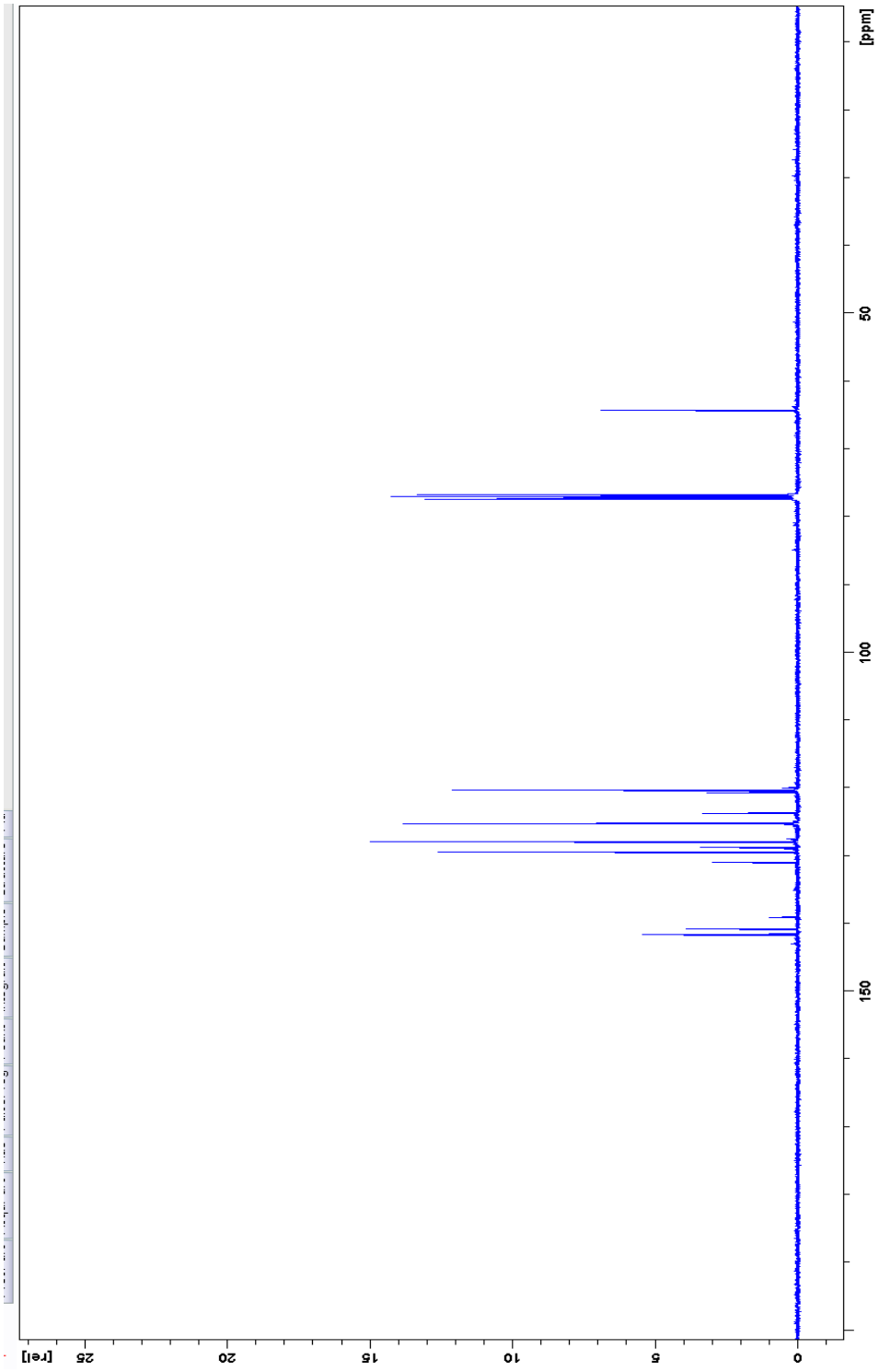

Figure 45: ^{13}C NMR of 9-azido-9*H*-fluorene (**26**)

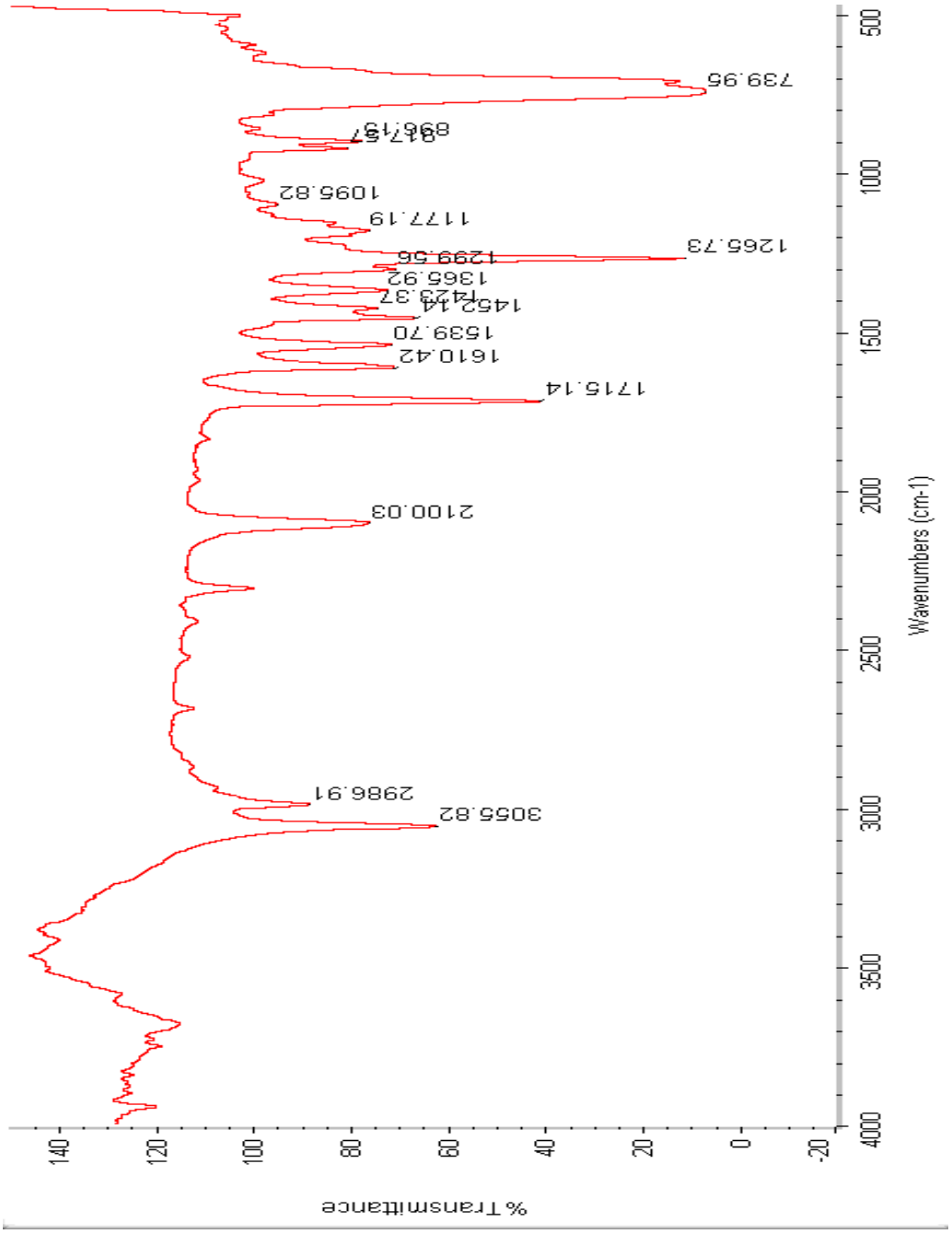

Figure 46: IR spectrum of 9-azido-9*H*-fluorene (**26**)

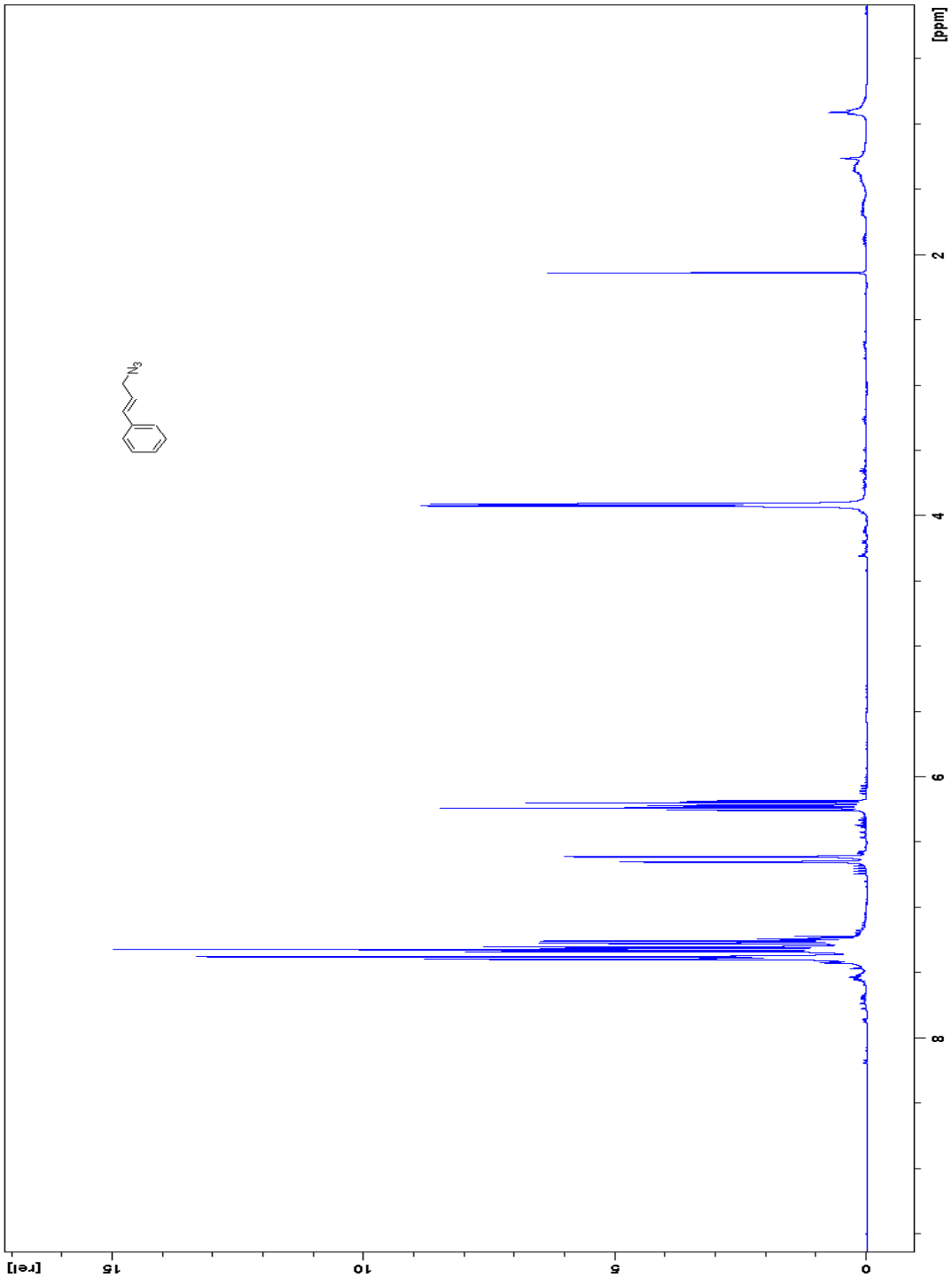

Figure 47: ^{1}H NMR of (*E*)-(3-azidoprop-1-en-1-yl)benzene (**28**)

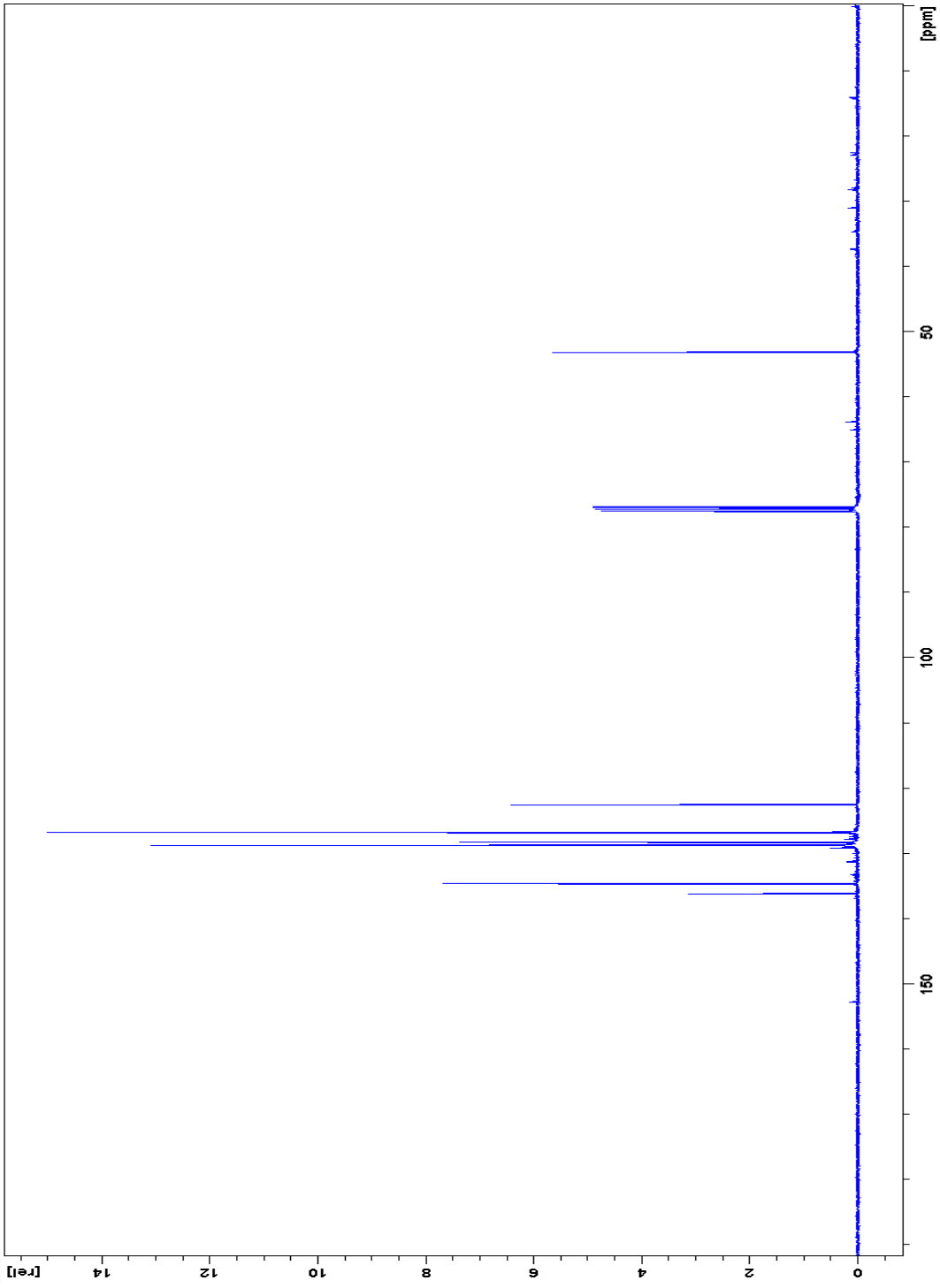

Figure 48: ^{13}C NMR of (*E*)-(3-azidoprop-1-en-1-yl)benzene (**28**)

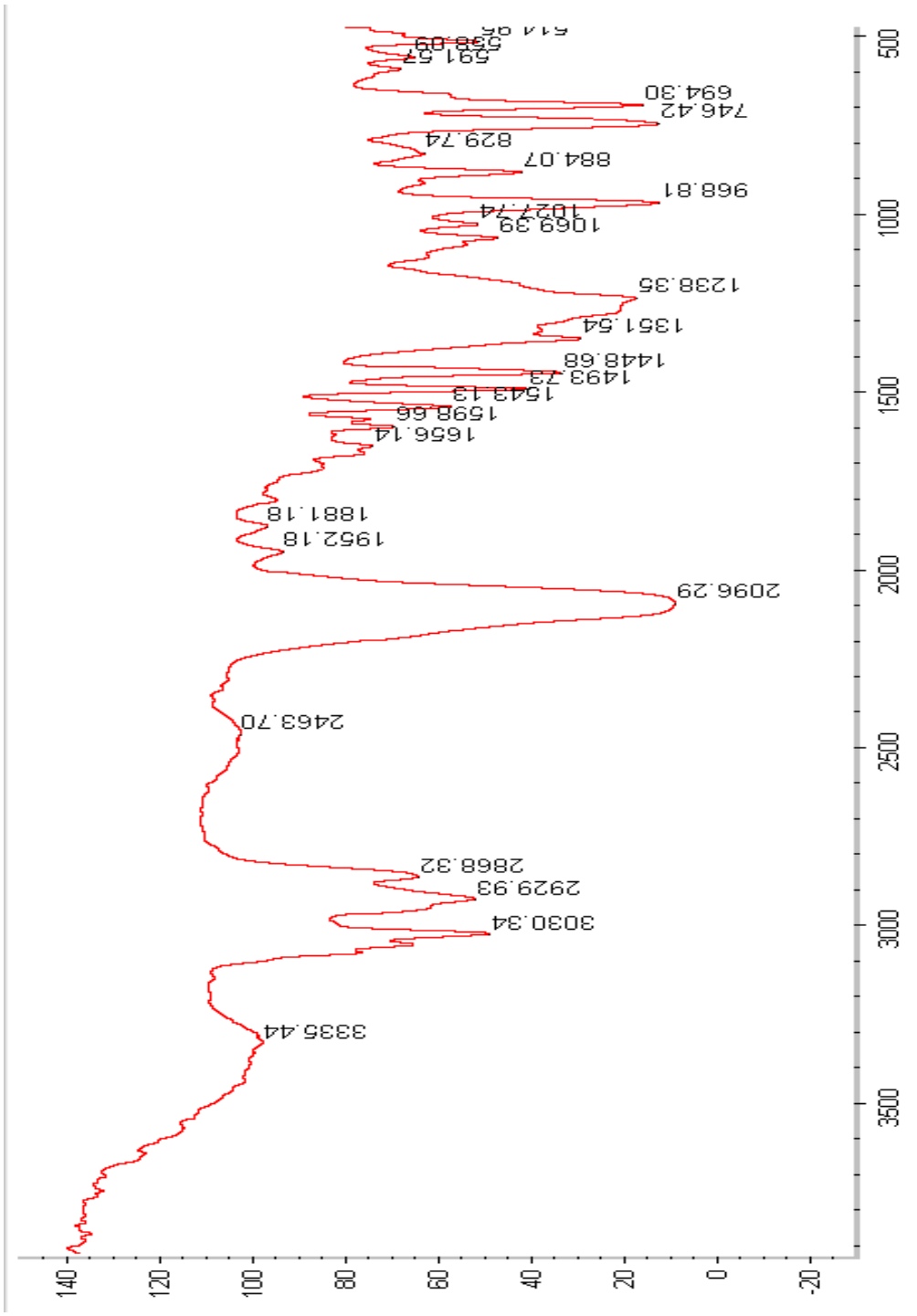

Figure 49: IR spectrum of (*E*)-(3-azidoprop-1-en-1-yl)benzene (**28**)

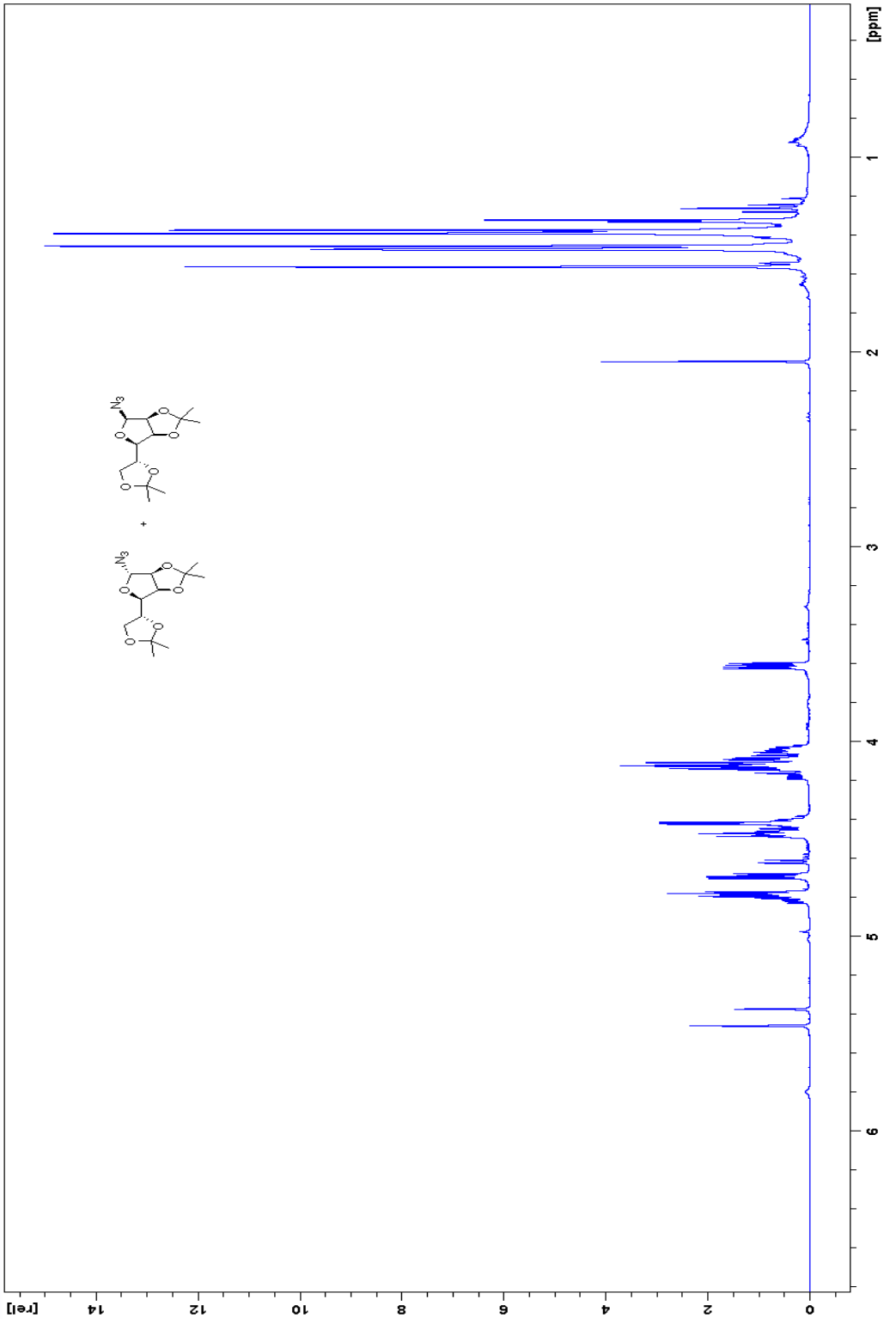

Figure 50: ^{1}H NMR of 1-azido-1-deoxy-2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose and 2,3:5,6-Di-*O*-isopropylidene-β-D- mannofuranose (**30**, **31**)

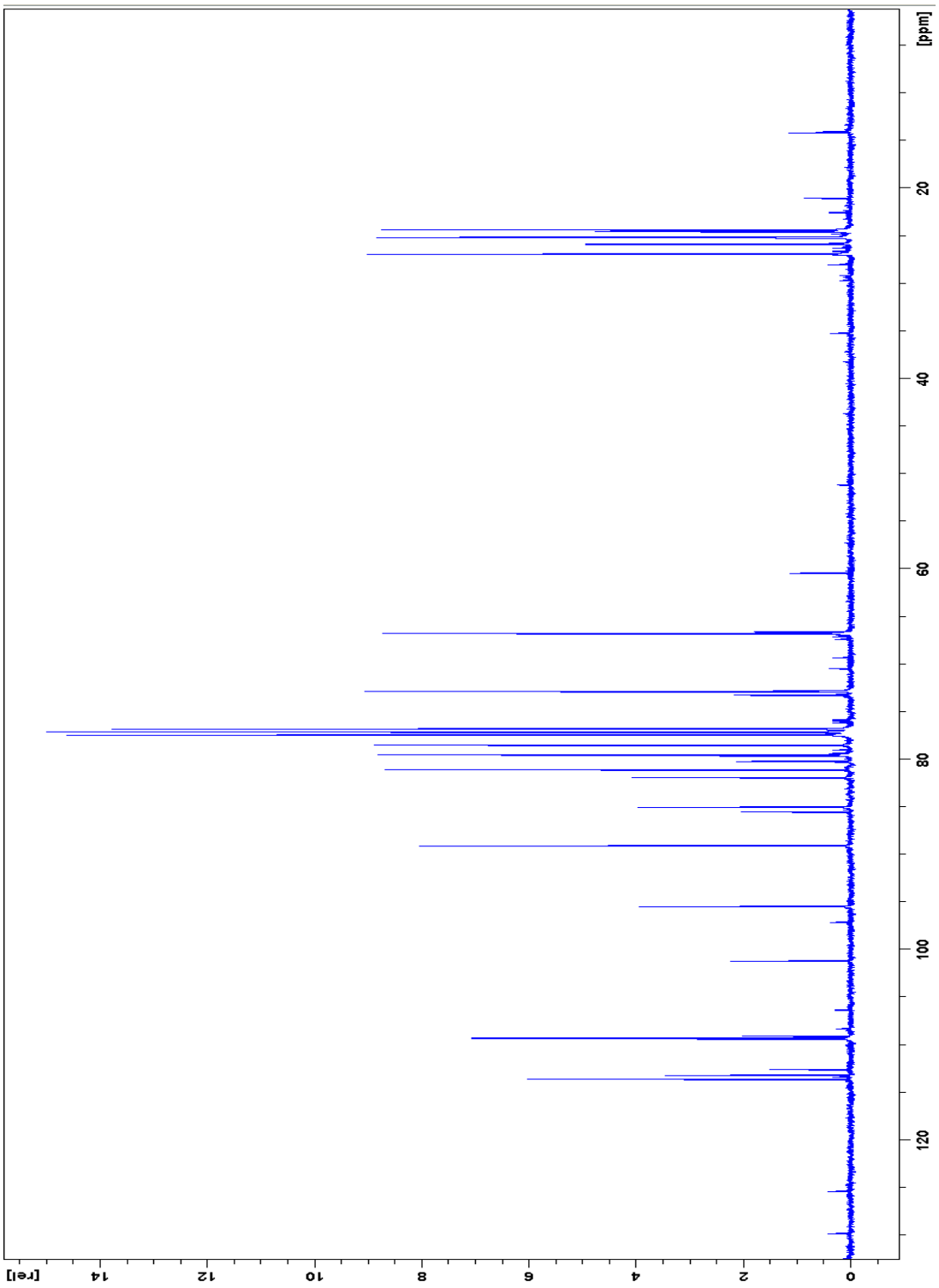

Figure 51: ^{13}C NMR of 1-azido-1-deoxy-2,3:5,6-Di-*O*-isopropylidene-*α*-D-mannofuranose and 2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranose (**30**, **31**)

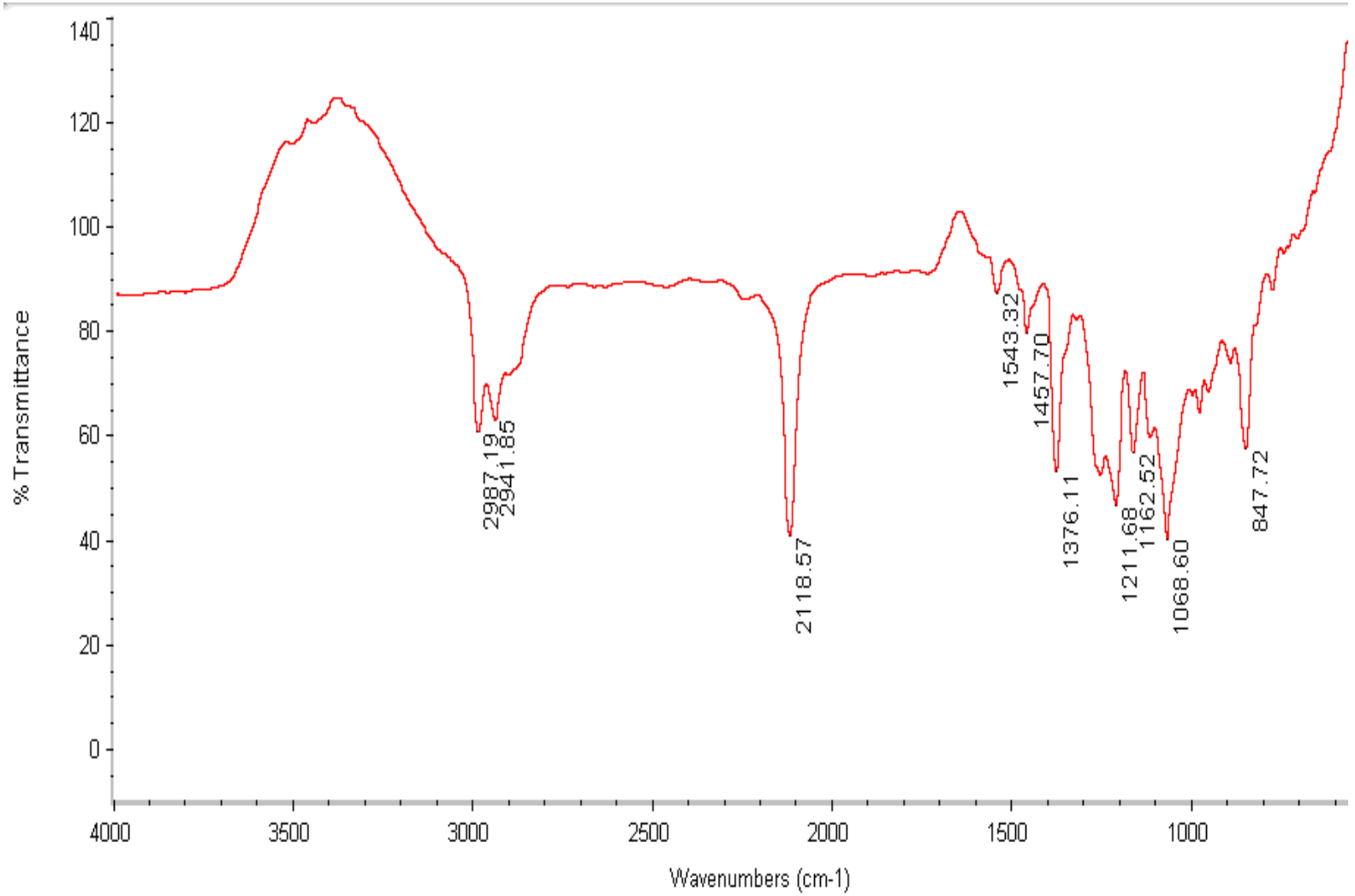

Figure 52: IR spectrum1-azido-1-deoxy-2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose and 2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranose (**30**, **31**)

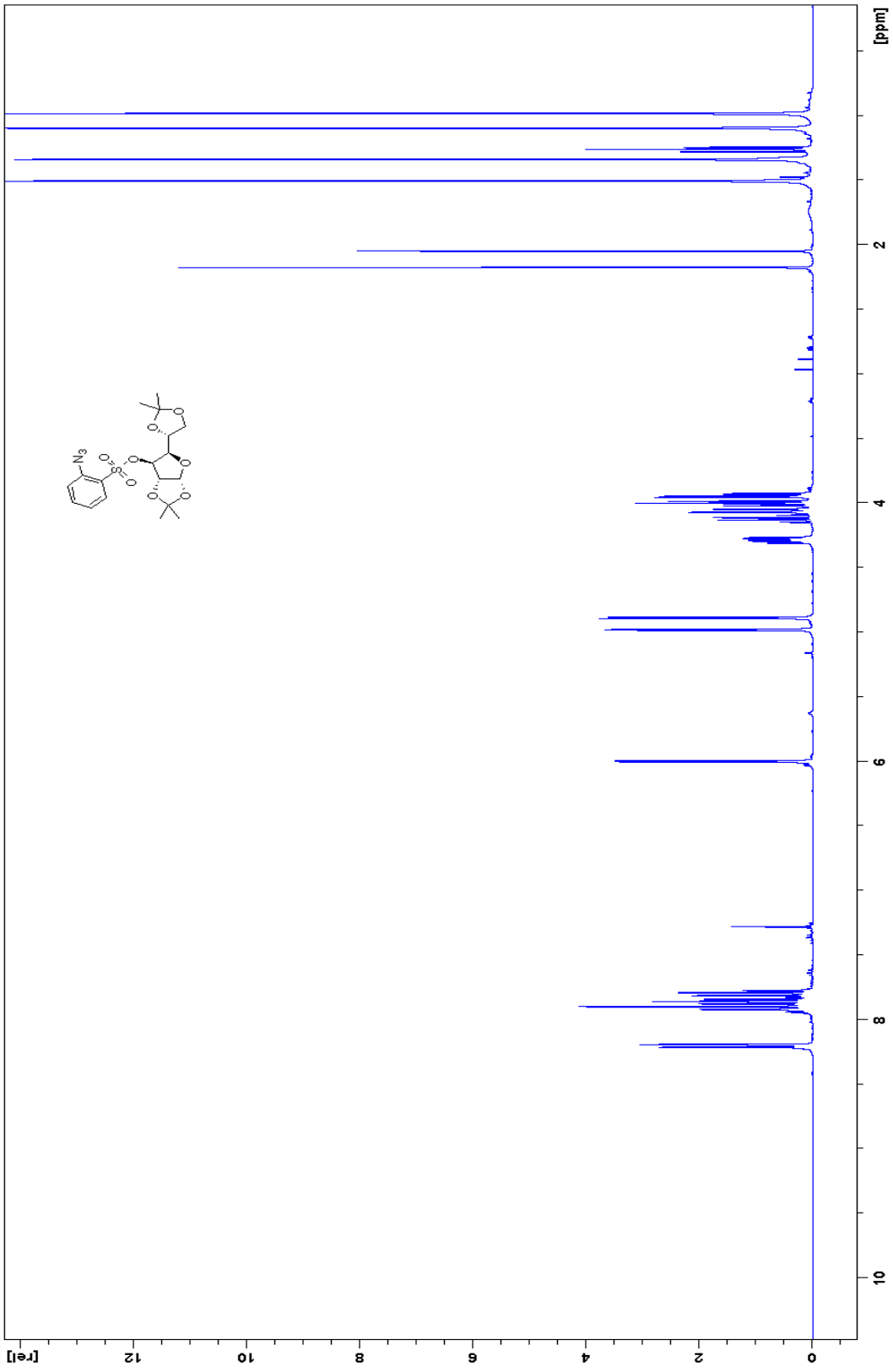

Figure 53: ^{1}H NMR of sulfonate ester intermediate of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**35**)

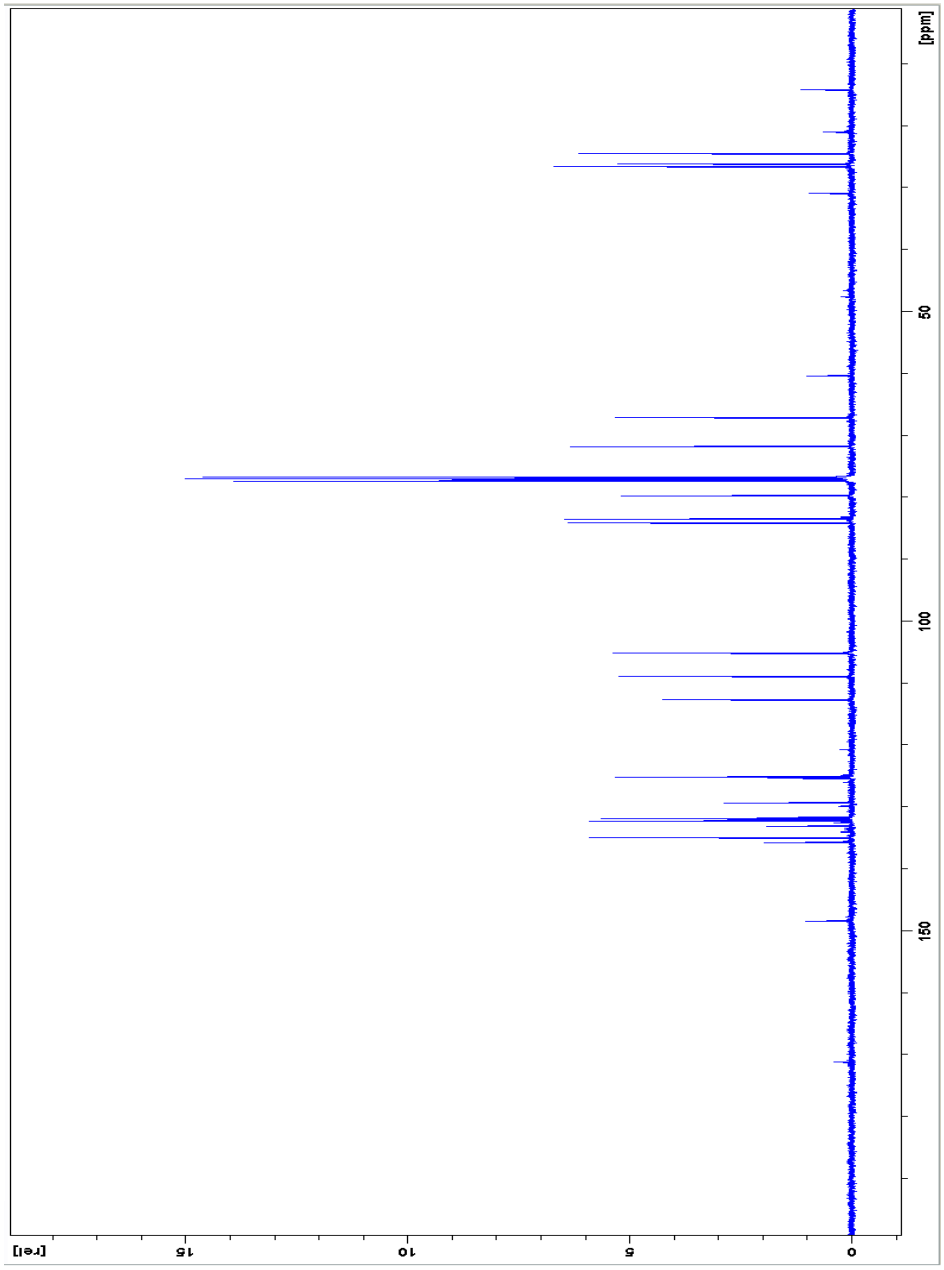

Figure 54: ^{13}C NMR of sulfonate ester intermediate of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**35**)

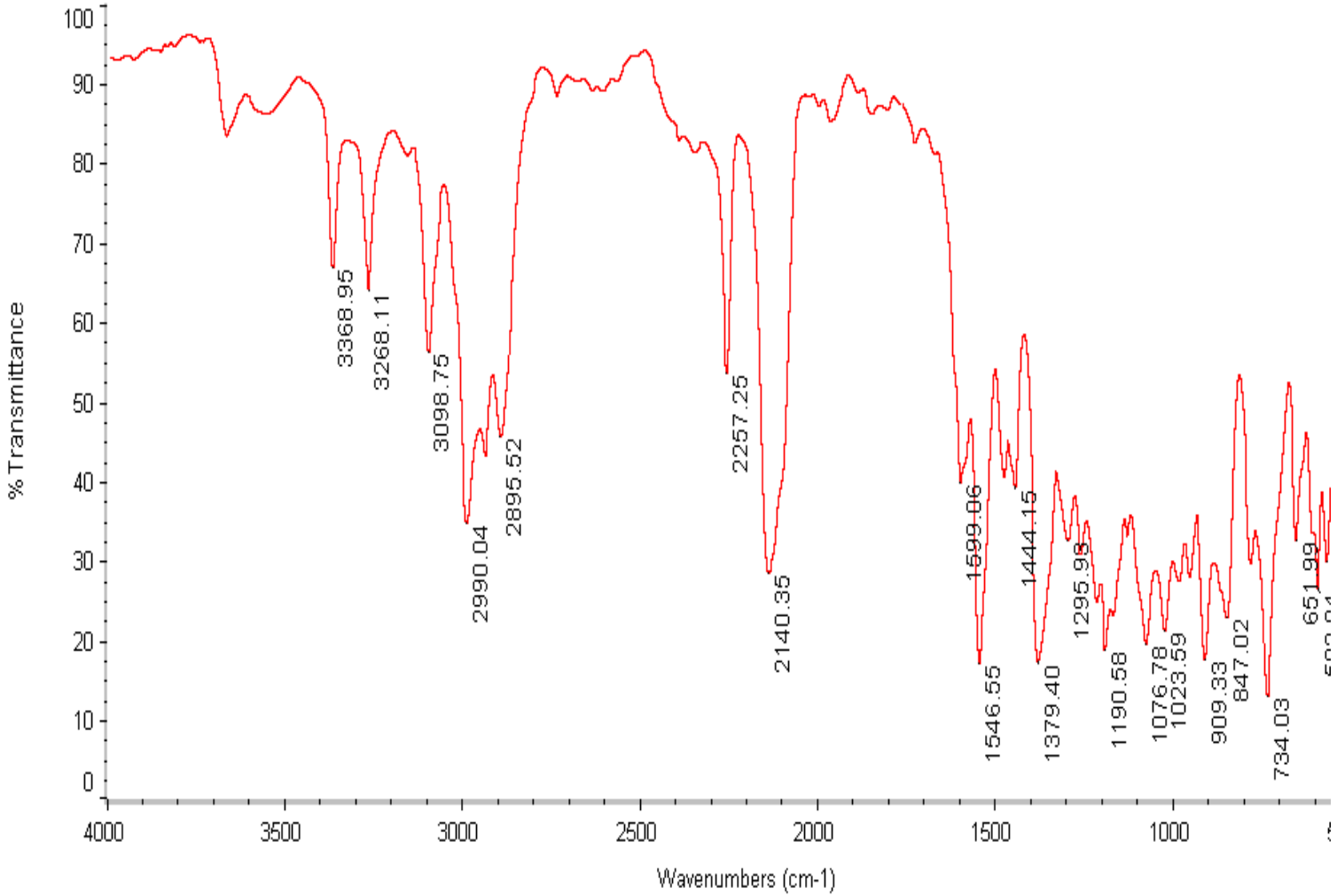

Figure 55: IR spectrum of sulfonate ester intermediate of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**35**)

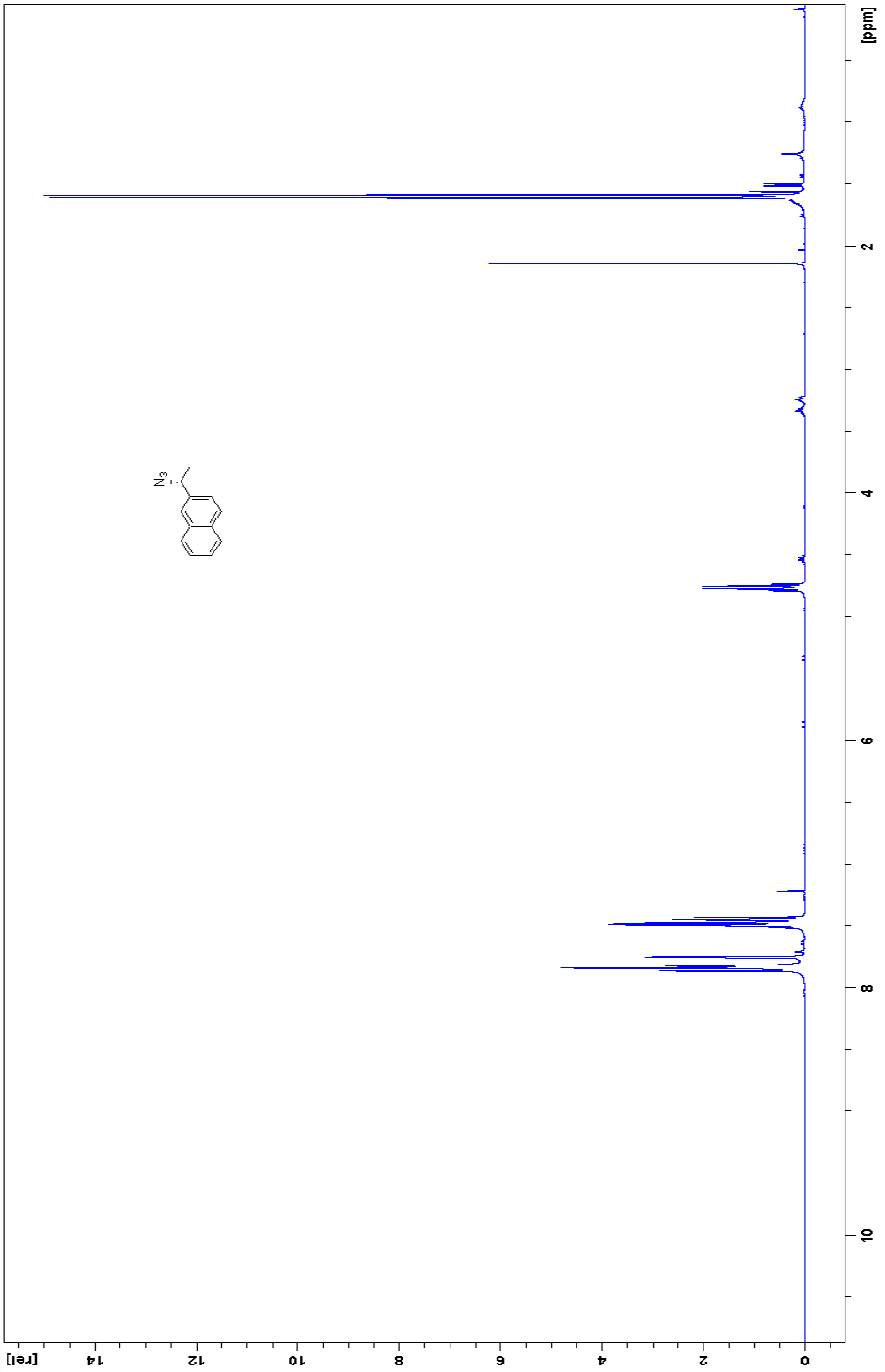

Figure 56: ^{1}H NMR of (R)-(+)-2-(1-azidoethyl)naphthalene (**37**)

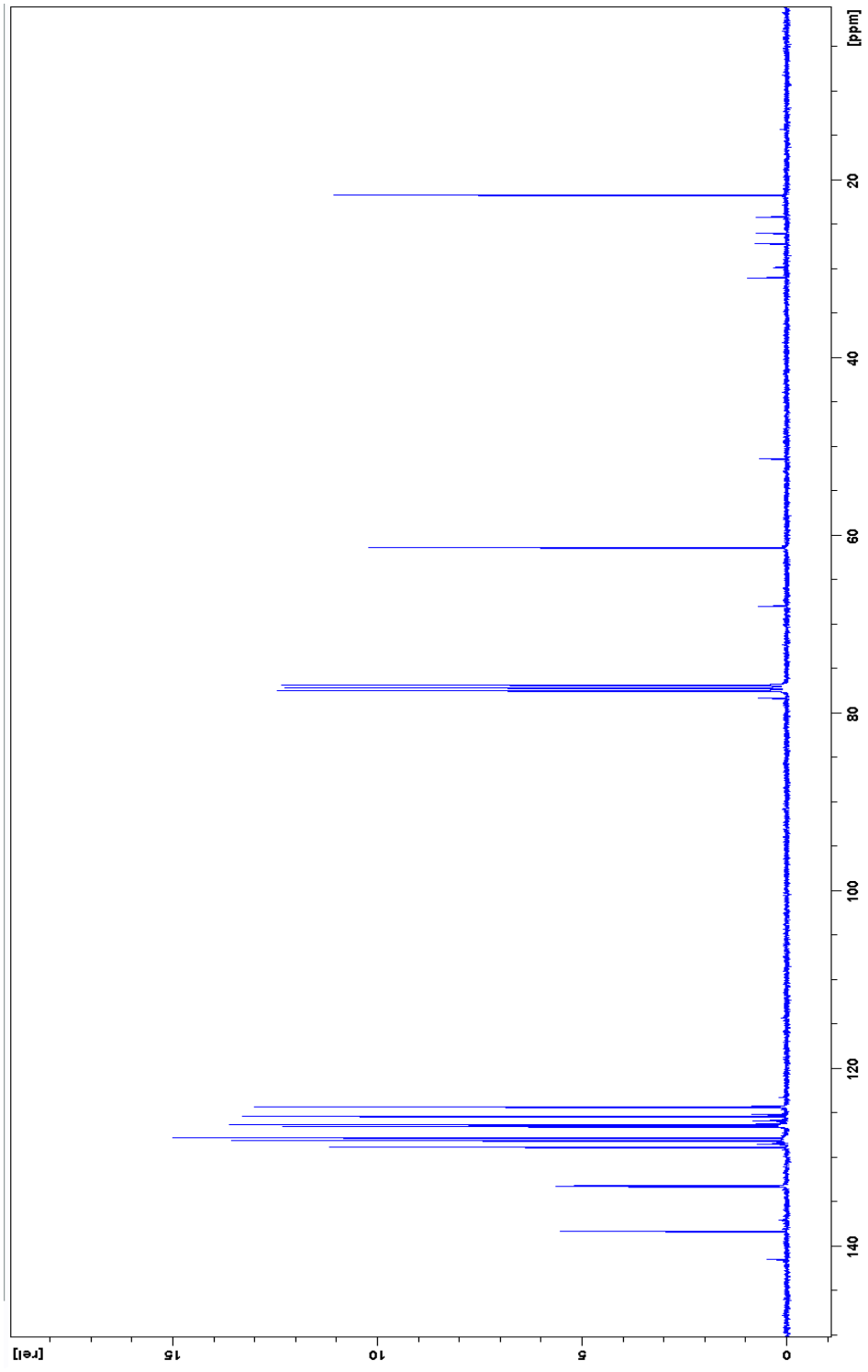

Figure 57: ^{13}C NMR of (R)-(+)-2-(1-azidoethyl)naphthalene (**37**)

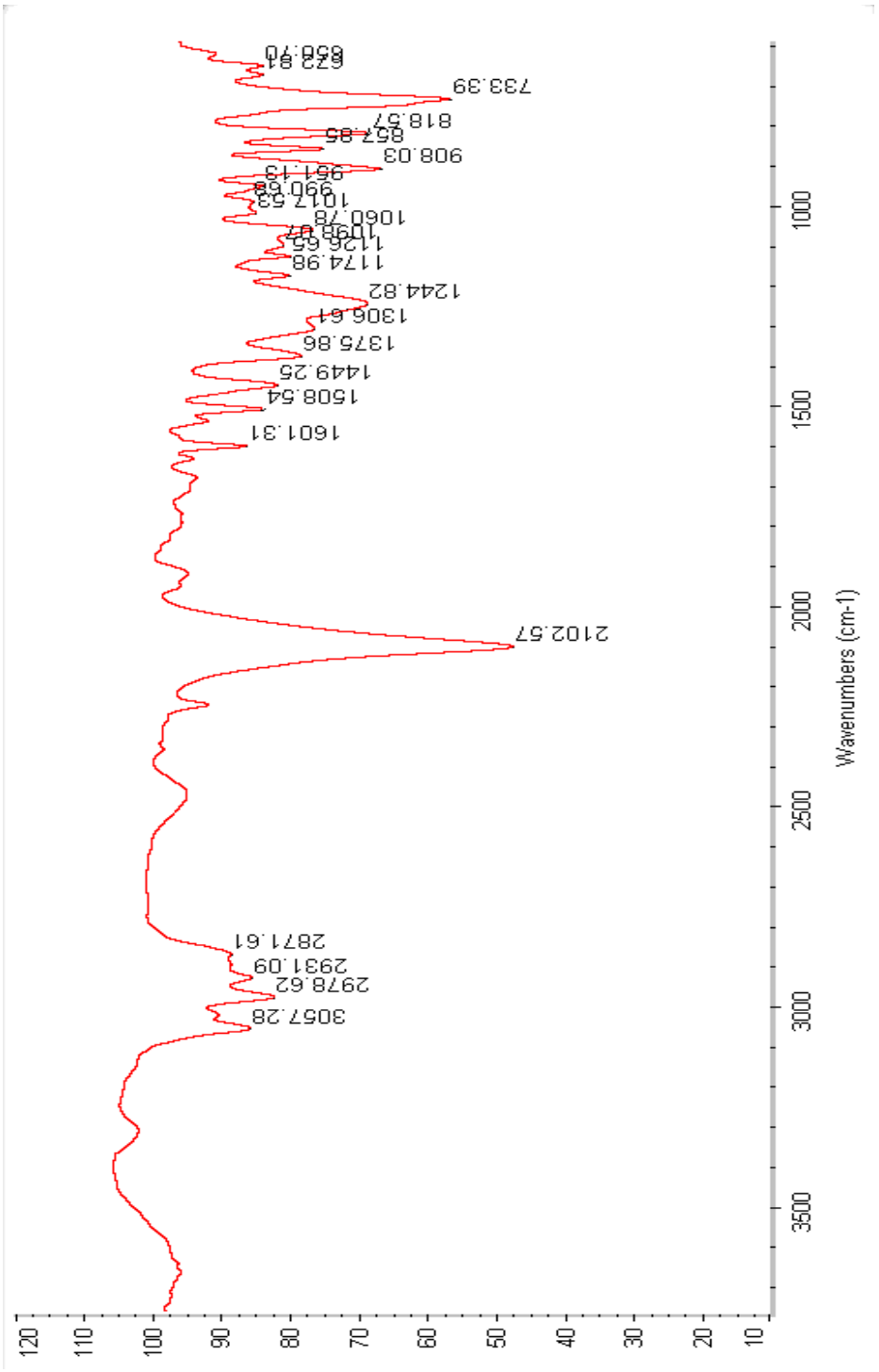

Figure 58: IR spectrum of (R)-(+)-2-(1-azidoethyl)naphthalene (**37**)