Heterocycle Synthesis via Rhodium (II)-Catalyzed Azido Carbenoid Cyclization.

by

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Thesis Abstract

Rhodium (II)-catalyzed reactions of diazocarbonyl compounds have been a very fertile field for the development of new synthetic methods. The resulting metal-carbenoid intermediates are capable of undergoing a range of unconventional reactions which can be utilized. This thesis presents a heterocycle synthesis via rhodium (II)-catalyzed cyclization of a diazo ester bearing a tethered azide unit representing a new and useful method for the construction of nitrogen-containing heterocycles.

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INTRODUCTION

Heterocycles

Heterocyclic compounds so far form the largest classical division of organic chemistry and are of great importance biologically and industrially. Most pharmaceuticals and biologically active agrochemicals are heterocyclic while a number of additives and modifiers used in industrial applications ranging from cosmetics, reprography and some plastics are heterocyclic in nature.[1] For many years, they have contributed to the development of society from a biological and industrial perspective as well as enhancing the understanding of life processes which is geared towards improving the quality of life. In more than twenty million chemical compounds identified by the end of the second millennium, more than two thirds are partially aromatic and approximately half are fully heterocyclic.

Many natural products like papaverine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are heterocycles. Almost all compounds we know of as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, are heterocyclic compounds (Figure 1), which are widely distributed in nature and are key intermediates in many biological processes. More specifically and important in this research are 1,4-diazepine motifs **(**Figure 2), a family of depressants used therapeutically to induce sleep, produce sedation, relieve anxiety and muscle spasms, and also to prevent seizures. Basically, 1,4-benzodiazepines derivatives normally act as hypnotics, anxiolytics and sedatives depending on the high, moderate and low dosage respectively.

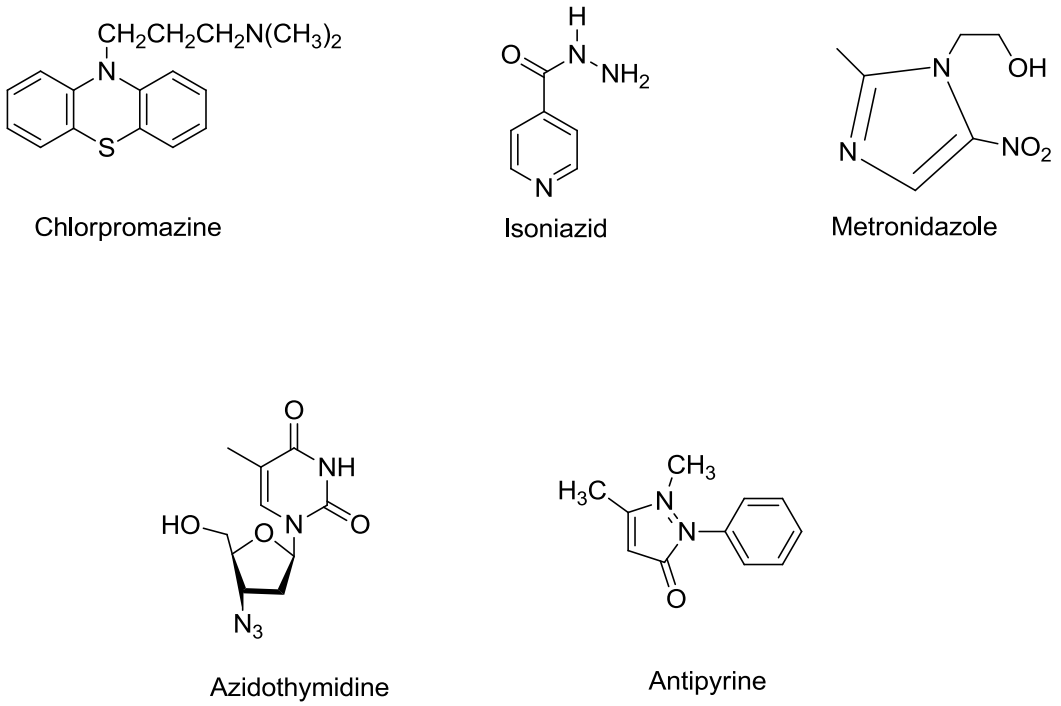


Figure 1: Some examples of heterocycles.

Generally, heterocyclic compounds isolated from natural sources act as main compounds for the construction of new biologically active molecules. Most of the heterocyclic compounds are not extracted from natural sources but are synthesized from readily available and cheap chemicals. Consequently, synthesis and characterization of new molecular entities integrating heterocyclic structures is very importance. It is in this regard that the crucial goal of synthetic organic chemistry is to construct complex and valuable molecules from simple starting materials with inexpensive and readily available reagents. Nitrogen-containing heterocycles (Figure 2) constitute one class of such medicinally important molecules, and therefore continuous efforts have been made to develop novel and efficient methods for their preparation.

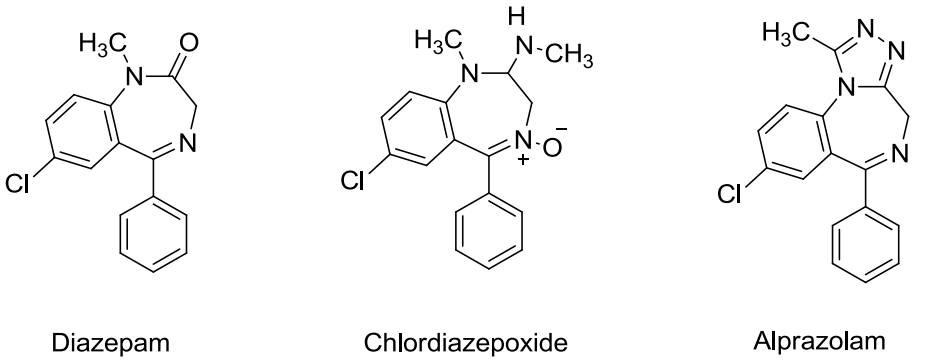
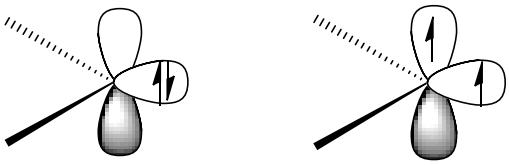


Figure 2: 1,4-Diazepine systems.

The synthetic possibility of diazo compounds, especially that of α-diazoesters and α-diazoketones, has been greatly improved by the ability of the derived carbene or metal-carbene intermediates to undergo inter- and intramolecular formation of C-*O*, *C-S*, *C-N* bonds.[2] The importance of these transformations, which are preferably performed with rhodium- or copper-based catalysts, are well established.[3] Therefore, carbenoid chemistry plays a major role and continues to spark interest of researchers.

Carbene Chemistry

Carbenes are described as neutral bivalent carbon intermediates in which two substituents are covalently bonded to carbon and the two remaining electrons are distributed between two non-bonding orbitals. A singlet carbene (**1**) is formed if the two electrons are spin-paired while a triplet carbene (**2**) forms if the spins of the electrons are parallel (Figure 3). The ground-state of methylene ($:CH_2$) is considered to be a triplet state whereas a molecule such as fluorocarbene (HFC:) and difluorocarbene (F_2C:) are considered to be ground-state singlet in nature. [4]



1 2

Figure 3: Electronic structure of carbene.

In a singlet state, a carbene possesses a *p*-orbital containing two non-bonding spin-paired electrons and an empty orthogonal *p*-orbital, where the fully occupied sp^2-orbital has anionic character and the empty *p*-orbital maintains cationic character.[5] Singlet (electrophilic) carbenes are generally associated with reactions such as cyclopropanation, insertion, and ylide generation. The electrophilic/nucleophilic character of the singlet carbene is strongly dependent on the electron-withdrawing/donating ability of the groups attached adjacent to the carbene carbon. Substituents which are electron-donating in nature (doubly bonded heteroatoms, such as oxygen and nitrogen) render the carbene carbon nucleophilic.

Reactive, unstable carbenes include those in which the divalent carbon is singly bound to a heteroatom or bonded to substituents which are less capable of maintaining resonance, such as alkyl groups. These "destabilizing" substituents render the divalent carbon more electrophilic in character and thus, reactive. The triplet state behaves as a diradical with unpaired electrons in each of the sp^3-orbitals. This type of carbene usually participates in hydrogen abstraction/recombination reactions. It is therefore very necessary to determine the multiplicity of the ground state carbene which exhibits nucleophilic reactivity as stable divalent carbon compounds.

In terms of reactivity, the word *carbenoid* is used to reflect the "carbene-like" structure of the reacting species, where a metal stabilizes the carbene carbon (Figure 4).

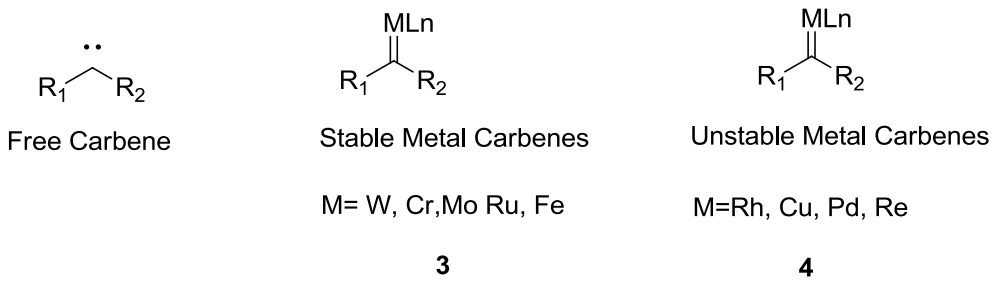


Figure 4: Carbene varieties

Carbenoids derived from early transition metals for instance tungsten, molybdenum, chromium, and iron, are often stable, isolable compounds (**3**) that are relatively unreactive in various synthetic methods.[6] Reactive carbenoids (**4**) exist mainly as transient species in catalytic processes and are usually derived from late transition metals such as rhodium, ruthenium, copper, and palladium. Reactive carbenoids have found greater utility in organic synthesis than their stable counterparts.[7] Interaction of the metal with the carbene drastically lowers reactivity and increases selectivity of the carbene. Furthermore, generation of these species occurs almost exclusively in the singlet state and they react similar to dipolar singlet states which are similar to dipolar intermediates.[8]

Rhodium catalysts have therefore been used for many years in the formation of a metal-carbenoid intermediate in the decomposition of diazo compounds.

Rhodium catalysts

The advent of rhodium (II) catalysts in the 1970s provided an alternative to copper catalysts and greatly expanded the field of diazocarbonyl chemistry. Based on the ligand type, there are two major classes of rhodium catalysts; dirhodium (II) carboxylates and rhodium (II) carboxamidates (Figure 5). Rhodium (II) tetraacetate was the first rhodium catalyst introduced for diazo decomposition by Teyssie and coworkers in 1973.[9] Rhodium (II) catalysts, in general, provide increased control over chemoselectivity than their copper- or palladium-based counterparts. The wide variety of ligands such as bridging carboxylate and carboxamidate ligands allows for electronic and steric fine-tuning and amplification of selectivity.

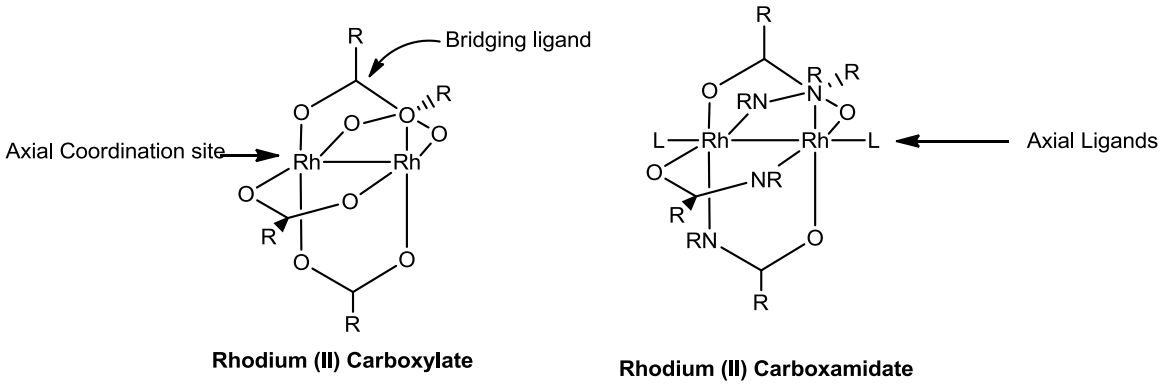


Figure 5: Dirhodium catalysts.

The dirhodium (II) acetate D_{4h} symmetrical complex consists of a dinuclear core surrounded by four bridging ligands and two axial ligands.[10] The core is held together by a rhodium-rhodium single bond and each rhodium is considered to have octahedral geometry. The axial ligands are labile and so they occupy the catalytically active sites of the paddlewheel complex. However, the overall lantern structure is considered to remain

intact during the catalysis. One interesting hypothesis concerning the dinuclear catalyst is that only one of the two rhodium centers serves as a carbene-binding site, while the second rhodium atom assists the diazo decomposition by serving as an "electron sink" to enhance the electrophilicity of the carbene. Another interesting suggestion is that the binding at one rhodium atom weakens the binding at the other site via the *trans* effect. Unfortunately, it is difficult to design a mechanistic experiment to support these suggestions.

The dirhodium (II) carboxylates such as the D_2 symmetrical dirhodium (II) tetraprolinates are kinetically more active than dirhodium (II) carboxamidates due to their electron-deficient character.[10] Rhodium carboxamidates, on the other hand, are very electron-rich due to the basicity of the carboxamide ligands and therefore catalytically less active than dirhodium carboxylates.[10] The dirhodium carboxamidates are limited to complexes with overall C_2-symmetry. This is because the preferred alignment of the carboxamidate ligands is *cis*-(2,2) configuration in which two nitrogen atoms are attached to each Rh in a *cis* fashion (Figure 5).[10]

The choice of catalyst (Figure 6) is highly dependent on the type of carbene transformation and conditions desired. Replacement of the acetate ligands with hexanoate or octanoate (**10**) increases the solubility of the Rh (II) complex in hydrocarbon solvents while displaying similar reactivity to the parent Rh (II) acetate (**5**). Pivalate (piv,**7**) and triphenylacetate (TPA, **6**) ligands are bulky ligands and could be utilized in situations where steric control is desired to promote selectivity. Increasing electron-withdrawing groups increases the reactivity (electrophilicity) of the carbenoid by placing a larger

charge density on the carbene carbon. Ligands of this nature include perfluorobutyl (pfb, **9**) and trifluoromethyl (-CF_3, **8**).

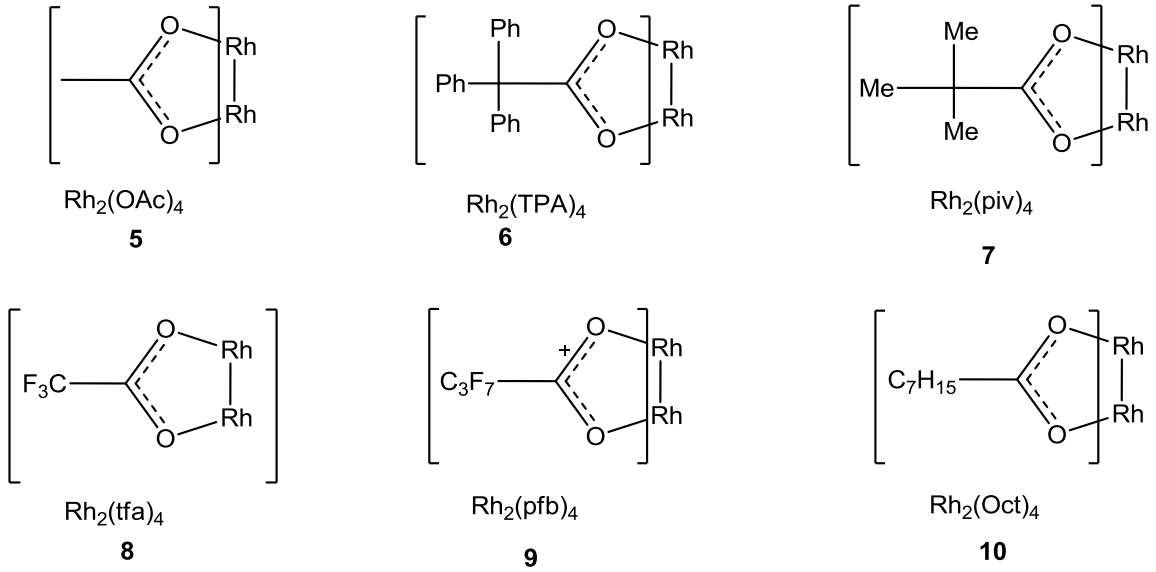


Figure 6: Examples of Rhodium Carboxylate Catalysts.

The application of a rhodium catalyst in organic synthesis especially in this research requires diazocarbonyls as starting materials for effective formation of carbenoid intermediates.

Diazocarbonyl Compounds and Carbenoids.

These are versatile reactive compounds capable of undergoing numerous carbon-carbon and carbon-X (X = N, S, O) bond-forming transformations. They are ambiphilic reagents since electrophiles can attack at the carbon atom and nucleophiles normally attack at the terminal nitrogen atom.[11] In organic syntheses, α-diazocarbonyl compounds serve as the source of high energy species referred to as carbenoid, a term used to describe a transition metal-bound carbene.[12] Based on their structure and reactivity

profile, carbenoid intermediates can be classified into three major groups: acceptor, acceptor/acceptor-and acceptor/donor-substituted α-diazocarbonyls.[13] The terms "acceptor" and "donor" refer, respectively, to the withdrawal and donation of the electron density by the functional groups flanking the carbenoid (Figure 7). Generally, an acceptor substituent makes the carbenoid species more electrophilic and more reactive, whereas a donor group makes the carbenoid more stable and thus more selective.[11]

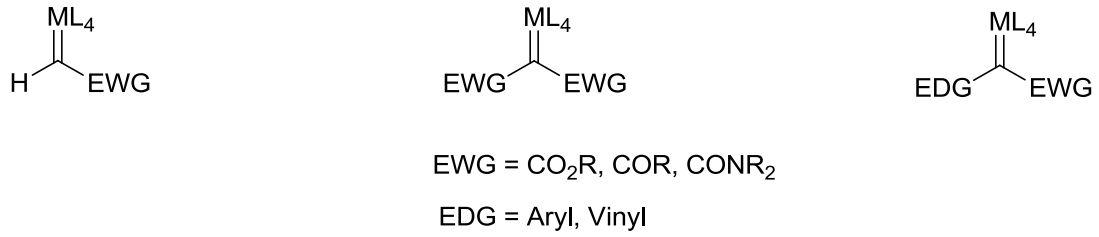


Figure 7: Classification of carbenoid intermediates.

The degree of electrophilicity bestowed upon the carbenoid species depends on the nature of their substituents (acceptor and donor group). For example, carbenoids derived from diazoketones are usually more reactive than the carbenoids derived from diazoacetates, whereas the carbenoids derived from diazoacetamides are the least reactive (Figure 8).[14] Diazocarbonyls with two electron-withdrawing groups tend to be indefinitely stable at room temperature, while most vinyldiazocarbonyls are stored at -20 ºC. Finally, depending on the stability of the diazocarbonyl, a different amount of energy is required for its decomposition, and usually higher temperature is required for the decomposition of an acceptor/acceptor than for acceptor/donor diazocarbonyl.

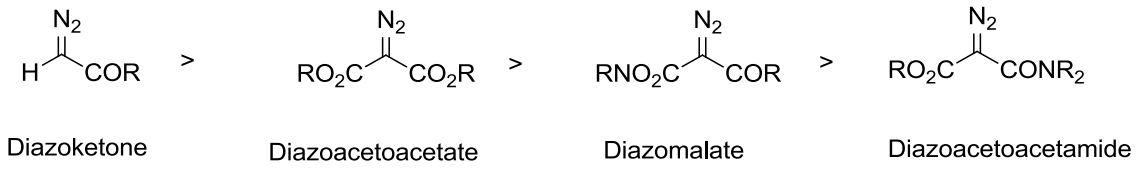


Figure 8: Reactivity of different diazocarbonyl substrates.

Synthesis of diazo carbonyls has been explored and is well established. Depending on its application in synthesis, diazo transfer therefore is the most popular in synthesis of α-diazocarbonyls.

Diazo transfer

The importance of diazo compounds as precursors to carbenoid formation has led to intensive research into their synthesis. Generally, most of the diazocarbonyl compounds are prepared via a diazo transfer procedure, which refers to the transfer of a complete diazo group from a donor (sulfonyl azide) to an acceptor (a carbonyl derivative).[15] Transfer of the diazo moiety to the α-methylene position of a carbonyl compound requires the presence of a base of sufficient strength to deprotonate the substrate. For acceptor/acceptor-substituted diazo precursors, triethylamine is strong enough to deprotonate the α-methylene prior to diazo transfer, and for acceptor/donor substituted precursors, the non-nucleophilic base 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) is normally used.[15]

Different diazo transfer donors are available to chemists, but all of them are invariably sulfonyl azides.[15] Methanesulfonyl azide (MsN_3, Figure 9) is the most hazardous diazo transfer reagent, because it exhibits the highest specific heat of decomposition and the highest shock sensitivity. However, it is also superior to *p*-

toluenesulfonyl (tosyl) azide for diazo transfer, its main advantage being the greater ease with which the sulfonamide by-product is removed from the reaction mixture by washing with 10% aqueous NaOH solution.[15] The sulfonamide by-product of *p*-dodecyl-benzenesulfonyl azide (*p*-DBSA) is an oil and this diazo transfer reagent is used when the diazocarbonyl product is a solid. Conversely, if the diazocarbonyl product is oil, then the crystalline *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) is employed in the diazo transfer since its sulfonamide by-product is a solid, which can easily be removed by column chromatography. Other diazo transfer reagents that have been used in the past include but are not limited to *p*-nitrobenzenesulfonyl azide (*p*-NBSA) and *p*-carboxybenzenesulfonyl azide.

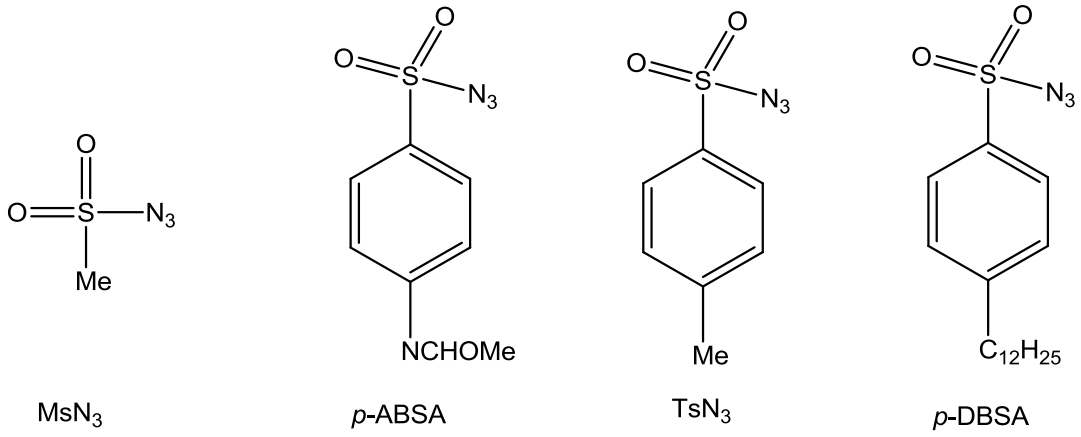
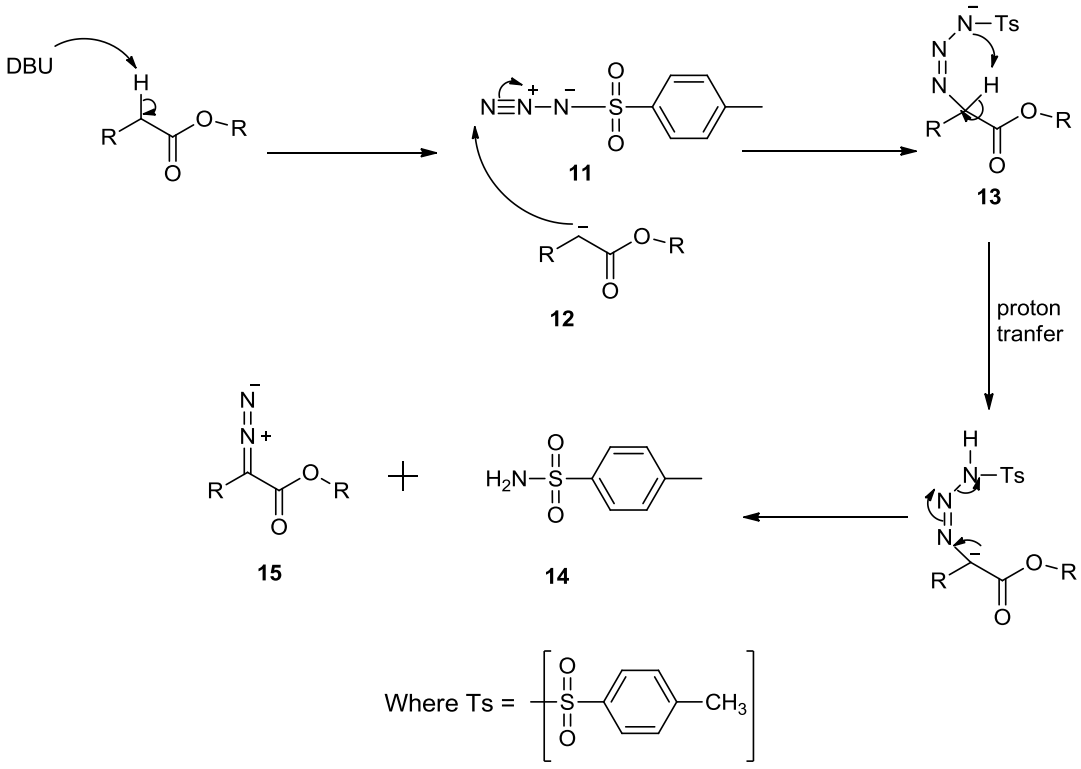


Figure 9: Diazo transfer agents.

The mechanism for the transfer of a diazo group onto activated methylene compounds (Scheme 1) from *p*-toluenesulfonyl azide (**11**) proceeds in most cases through an intermediate triazine (**13**). Deprotonation of the α-keto ester (**3**) with DBU leads to the formation of a carbanion (**12**) which attacks the electrophilic N of the sulfonyl azide (**11**)

producing the intermediate tosyl derivative (**13**). Proton transfer occurs within this intermediate which is then followed immediately by the elimination of *p*-toluene sulfonamide as the byproduct (**14**) and the formation of diazo compound (**15**).



Scheme 1: Mechanism for the diazo transfer**.**

Organic Azides

Organic azide chemistry began with the synthesis of phenyl azide in 1864 by Griess.[16] This was later enhanced by the discovery of rearrangement of acyl compounds with hydrogen azides by Curtius in 1890. [17] Intensive research has since been conducted and various synthetic organic reactions have been developed using alkyl, acyl, and aryl azides, which have been extensively used for the synthesis of nitrogen-containing aza-heterocycles as well as peptides.[18] This has always been achieved as a result of the diverse chemical reactivity of azide-containing compounds.

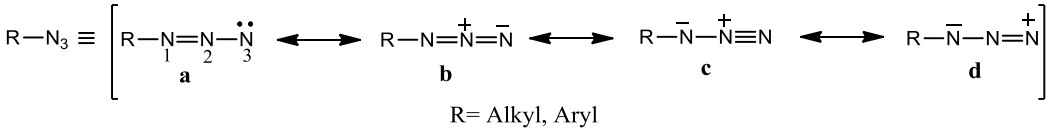


Figure 10: Polar mesomeric structures

The basis for the chemical diversity of azides comes from their physicochemical properties. A number of properties can be explained by a consideration of polar mesomeric structures (Figure 10). The dipolar structures of type **c** and **d** compellingly explain the facile decomposition into the corresponding nitrene and dinitrogen as well as the reactivity as a 1,3-dipole which allows for [3+2] cycloaddition with unsaturated bonds, such as those in alkynes and alkenes as well as carbonitriles to form triazolines, triazoles and tetrazoles respectively. The mesomeric structure **d** explains the regioselectivity of their reactions with electrophiles and nucleophiles which is simply expressed by attack on N^3 by nucleophiles as well as the attack by N^1 by the electrophiles. Finally, the generation of anions, cations, and radicals at the α-position to the azido moiety can result in rapid denitrogenation to deliver the corresponding iminyl species, which can be used in further synthetic transformations (e.g. carbon–nitrogen bond formation).[19]

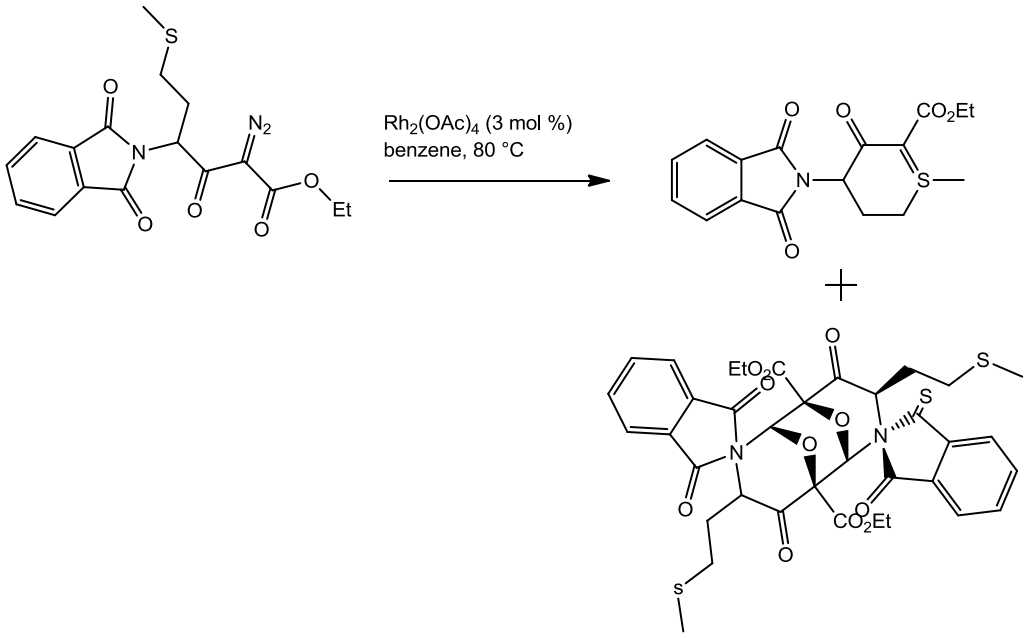
One of the methods used to synthesize azides is the classic nucleophilic substitution (S_N2). Aliphatic azides are compounds readily accessible with the highly nucleophilic azide ion and sodium azide is the most commonly used azide source. In most cases halides, carboxylates, and sulfonates, as well as mesylates, nosylates, and triflates, are chosen as leaving groups.[19]

As a potential nucleophile, the current research is based on the utilization of this property of azides to synthesize heterocyclic systems based on the azide being tethered on a donor/acceptor rhodium carbenoid.

Rhodium-catalyzed azido-carbenoid cyclization

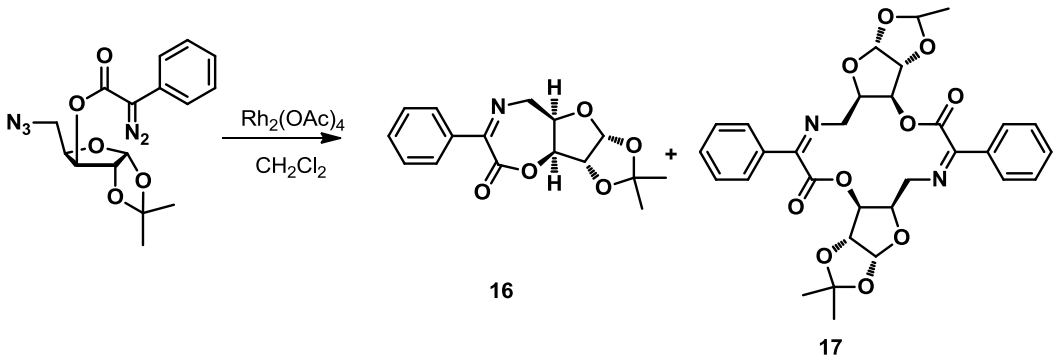
Rhodium carbenoid intermediates are capable of a range of unusual reactions that can lead to novel strategies for synthesis. They are conveniently prepared by metal-catalyzed extrusion of nitrogen from diazo compounds. Their reactivity is highly dependent on the carbenoid structure, and consequently, they have been classified into three major groups, acceptor, acceptor/ acceptor and donor/acceptor (Figure 7). Typical acceptor groups are keto, nitro, cyano, phosphonyl and sulfonyl, while typical donor groups are vinyl, aryl and heteroaryl. The metal carbenoids generally display electrophilic character; thus, acceptor groups will tend to make the carbenoids more reactive and less selective, and the reverse would be the case for donor groups.

The cyclization of cationic species containing internal nitrogen nucleophiles represents a very useful method for obtaining a wide range of substituted aza heterocycles. Beilstein and his co-workers have successfully synthesized numerous heterocycles containing internal amino groups (Equation **1**) which are based on acceptor/acceptor carbenoids.[20]



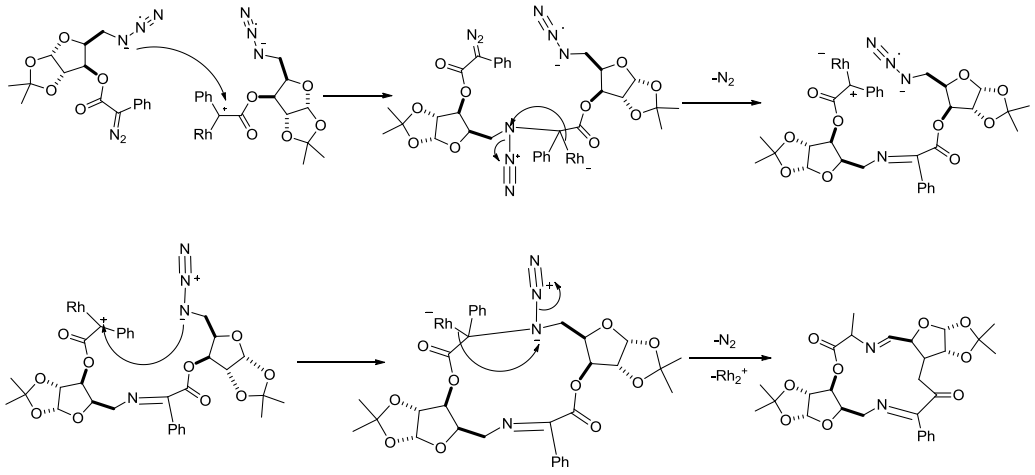
Equation 1: Rhodium (II)-catalyzed carbenoid reaction.

However, an emerging area of heterocyclic synthesis is the use of donor/acceptor-carbenoid cyclizations. This has greatly spurred interest because they display much greater selectivity than other carbenoid substrates. In the bid to synthesize oxazepine moieties, Norris and his group investigated the azido-diazo carbenoid cyclization and successfully synthesized compounds **16** and **17**.



Equation 2: Diazo decomposition of diazo-azido sugar.

In this work, the C-N bond formation proceeded through the proposed mechanism (Scheme 2). This work facilitated further investigations on the development of heterocyclic systems via carbenoid heterocycle cyclization in which azides are used as internal nucleophiles.



Scheme 2: proposed mechanism for the decomposition and subsequent cyclization.

STATEMENT OF PROBLEM

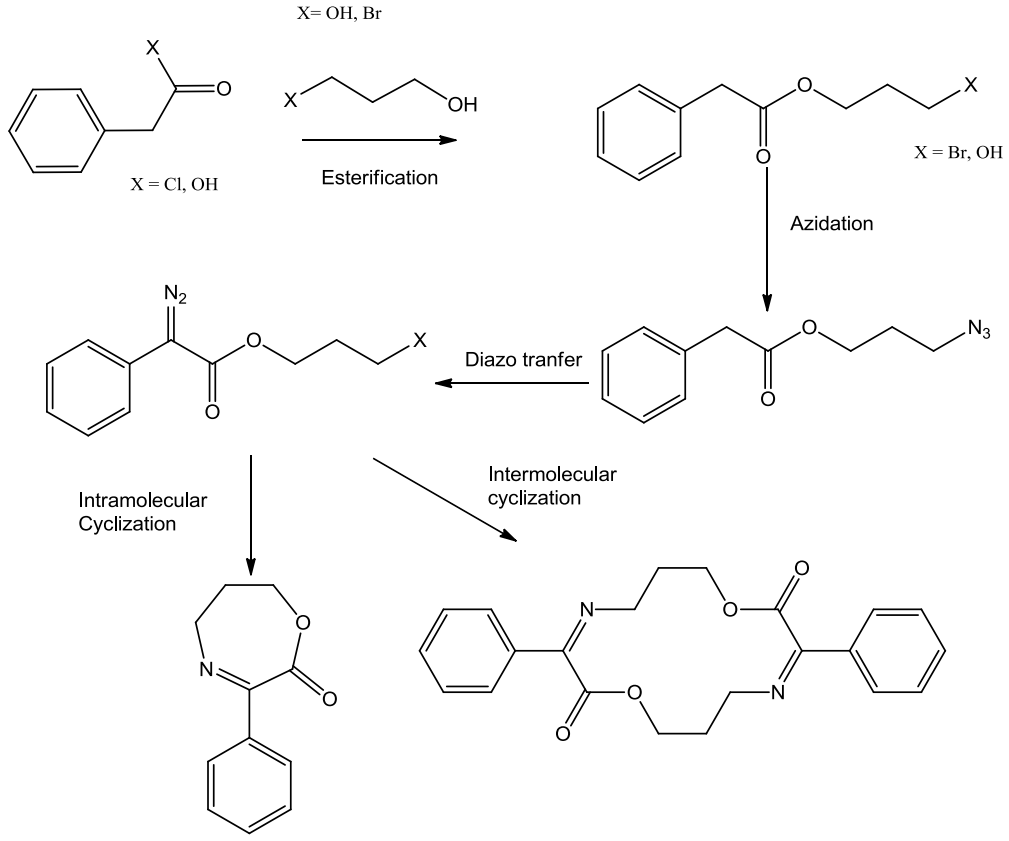
Heterocycle synthesis plays a key role in organic chemistry. Metal-catalyzed decomposition of azido carbenoids offers a potentially useful route for intramolecular and intermolecular heterocycle synthesis. Phenylacetylesters will be used as starting material to synthesize diazo compounds, which will then serve as precursors to the heterocyclic compound. The decomposition reaction will be studied to determine the fate of the carbenoid intermediate formed in the presence of a rhodium (II) catalyst, including any effects on selectivity that the azide group might have on intramolecular reaction. This reaction will be monitored by TLC and infrared spectroscopy and further characterization will be done by nuclear magnetic resonance spectroscopy, X-ray crystallography and mass spectrometry.

RESULTS AND DISCUSSION

Synthetic strategy

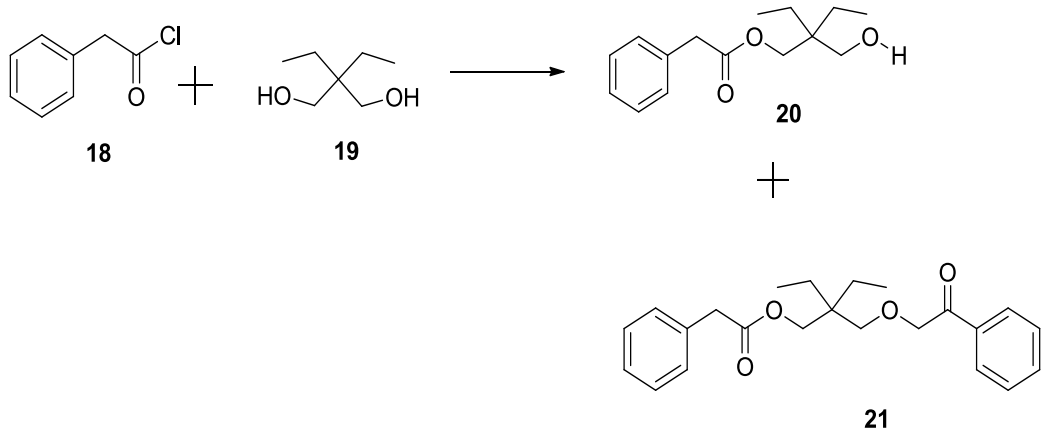
The main goal of this research was to synthesize heterocyclic systems via rhodium-catalyzed cyclization reactions which have proven to be one of the most efficient and straightforward methods to construct such systems and even more complex polycyclic systems.[21] The strategy for the cyclization was to design a donor/ acceptor diazocarbonyl substrate precursors that have an azide attached to the acceptor side. The careful choice of the starting material was envisioned in the strategy (Scheme 2) below. The donor side (stabilizing group) had a phenyl group therefore making it possible to either use phenyl acetic acid or phenyl acetyl chloride as starting materials which are cheap and easily available. The acceptor side had azido propane which was carefully selected since the target heterocycle should either be seven membered (intramolecular cyclization) or 14-membered ring (intermolecular cyclization).

In the view of this strategy, the research continued in two synthetic pathways. The main reason for the alternative pathways was to allow for the fictionalization of the synthesized heterocycle.



Scheme 3: Synthetic strategy for rhodium (II) catalyzed azido carbenoid cyclization.

Synthesis of 2-ethyl-2-(hydroxymethyl) butyl 2-phenylacetate *via* phenylacetyl chloride



Equation 3.

The initial step in the heterocyclic synthesis was the preparation of 2-ethyl-2-(hydroxymethyl) butyl 2-phenylacetate (**20**) as the starting material in this pathway. The selection of the reagents for this reaction was done in such a manner that allows for the interconversion of the functional groups which will be used to attach the azide at a later stage. For this reason, 2,2-diethylpropane-1,3-diol and phenylacetayl chloride were reacted under Steglich conditions.[23] Pyridine was used to deprotonate the possible HCl produced during this reaction which was maintained at -10 °C due to its exothermic nature. The reaction was monitored by TLC, which showed two new spots at a higher R_f value higher than the starting materials. Once the reaction was deemed complete, it was quenched with cold deionized water which was followed by the aqueous work up as shown in the procedure[3] and purification on a silica gel column (10:1 hexanes : EtOAc) to give 2.26 g (60% yield) of monoester **20** as colorless syrup and 2.02 g (40% yield) diester **21**. The high yield of the diester was as a result of the symmetrical diol **19** which necessitated equal chances of esterification on either side of the OH groups. To optimize the synthesis of the monoester **20**, the diol reacted in excess and the introduction of phenylacetyl **18** was dropwise.

The evidence of monoester **20** synthesis was shown by ^{1}H NMR in which a triplet signal at 0.77 ppm representing 6H for CH_3 groups and a coupling constant of 7.56 Hz. A 4H multiplet at 1.11-1.27 ppm for the CH_2 groups was present and, most significantly, a 1H singlet at 2.00 ppm representing the OH group. The proton NMR also showed 2H singlets at 3.21, 3.64, and 3.97 ppm which confirmed the CH_2-OH, CH_2-Ar and OCH_2

signals respectively. The analysis for the formation of the monoester was finalized by the 5H multiplet at 7.25-7.32 ppm for the aromatic ring.

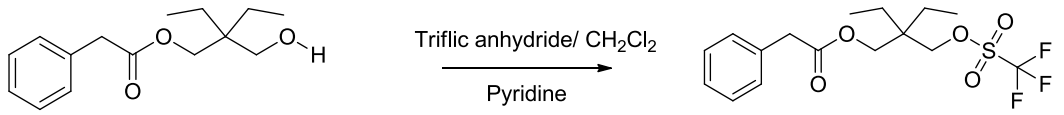
^{13}C NMR spectrum of **20** showed 2 x C signals at 6.97 and 22.09 ppm for -CH_3 and CH_2 groups respectively. The quaternary carbon showed at 41.28 ppm whereas the benzylic carbon showed at 64.31 ppm. One carbon signals appeared at 64.31 ppm and 66.64 ppm for CH_2OH and OCH_2 respectively. The phenyl ring was represented by the 4 signals at 127.23, 128.65, 129.22 and 133.97 ppm for 1C, 2C, 2C and 1C respectively. Finally the signal for the ester carbonyl appeared at 172.33 ppm.

The diester **21** was equally characterized and the ^{1}H NMR spectrum substantiated the diesterication. First, there was disappearance of the 1H singlet at 2.00 ppm for the OH group. The other important indication was the indication of symmetry and chemical environment similarity by a 4H singlet at 3.84 ppm that correlated to the OCH_2 groups. Similarly the appearance of a 4H singlet for the benzylic protons at 3.56 ppm and a neat 10H multiplet at 7.21-7.26 accurately indicated the two phenyl rings with same chemical shifts. The -CH_3 and -CH_2 groups fairly remained at the same positions as those in the monoester but shifted slightly upfield due to the presence of electron donating groups in the new compound.

^{13}C NMR further supported product **21** formation with signals representing the 2 phenyl rings showing at 127.11, 128.57, 129.26 and 134.07 ppm. The number of carbons in these 4 signals totaled 12 which suggested the symmetry of the phenyl rings. There were two additional signals representing the carbons in the diester; the first of these appeared at 41.53 ppm and corresponded to the carbon alpha to the carbonyl and the second at 171.37 ppm representing the carbonyl carbon. The quaternary carbon was also

shown at 39.56 ppm. ESI mass spectrometric analysis provided an M^+ of 391.4, which corresponded to the calculated molecular mass of 368.20 with the addition of a sodium atom.

Synthesis of 3-(((trifluoromethyl)sulfonyl)oxy)propyl-2-phenylacetate (22)



20 **22**

Equation 4.

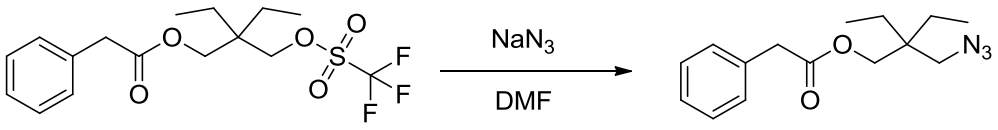
Since the hydroxyl group is not a very good leaving group, there was need to activate it so as to pave way for the S_N2 (azidation) reaction. This allowed for the synthesis of the triflate as an intermediate in the azidation reaction. Trifluoromethyl sulfonate ion ($CF_3SO_3^-$, commonly referred to as triflate ion) is one of the best leaving groups ever known to chemists.[22] It is basically the ion of CF_3SO_3H which is an exceedingly strong acid even much more than sulfuric acid. Therefore triflation was prepared from the reaction of an alcohol with triflic anhydride in the presence of a base (Equation **5**). The reaction was done carefully under inert conditions at low temperatures. A solution of 2-ethyl-2-(hydroxymethyl)butyl-2-phenylacetate (**20**) in CH_2Cl_2 was added to a flame-dried round bottom flask. Anhydrous pyridine was then slowly added and the flask content cooled to –10 °C. Triflic anhydride dissolved in CH_2Cl_2 was added dropwise to the solution. Pyridine was used in excess to abstract protons and therefore

reduces the possible formation the acid. The workup was done and dried and solvents removed under vacuum to afford 70% yield of a crude product as orange syrup. Further purification of the triflate was not done due to the instability of the triflate. However, the spectroscopic analysis also proved the purity of the product.

Triflates (OSO_2CF_3) is one of the most inductively strong electron-withdrawing groups which is comparable with $N(CH_3)_3^+$. ^1H NMR spectrum showed the downfield chemical shift of the CH_2O singlet signal from 3.21 ppm to 3.64 ppm, the signal clearly indicated the attachment of triflate. A 2H singlet at 4.24 and 3.94 ppm for the OCH_2 and benzylic protons respectively were also affected by the presence of the functional group. However it was expected that its presence may not change the chemical environment of the ring which indeed was retained as a 5H multiplet at 7.24-7.32 ppm. A 6H triplet for the CH_3 and 4H showed up at 0.79 ppm and multiplet for CH_2 was also seen in thr range og 1.25-1.31 ppm.

The synthesis of trifate **22** was confirmed by the ^{13}C NMR spectrum which showed an additional carbon at 120.22 ppm that belongs to the CF_3SO_2, the appearance at the downfield region was because of the electron-withdrawing groups within the trifuoromethane sulfonate functionality. The other carbons in the structure also shifted as expected but the most indisputable one was the carbon attached to the triflate at 117.05 ppm that moved downfield from 64.31 ppm of the alcohol.

2-(Azidomethyl)-2-ethylbutyl 2-phenylacetate (23).



22 **23**

Equation 5.

After the activation of the OH group in the monoester by the triflate functionality, the structure **22** was further reacted in DMF at 60 °C with sodium azide. After several attempts, this reaction, resulted in an overall yield of 60%, is seen in Equation 6.[23] Azidation of triflates usually give products at a very high yield however this was not the case in this reaction. Due to several reasons; one of such is the steric hindrance due to the presence of diethyl groups in the structure **22** that largely affected the accessibility for the nucloephilic attack, leading to the possible formation of other byproducts like reported by Zhu.[24]

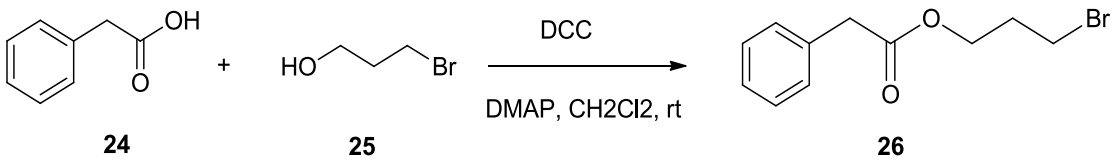
The characterization of synthesized desired product **23** was done by nuclear magnetic resonance. The ^{1}H NMR signals for methyl and ethyl groups were neatly integrated to 6H and 4H respectively at the upfield region of 0.75 and 1.16-1.23 ppm as triplet and multiplet in that order. A 2H singlet at 3.09, 3.64 and 3.97 accurately represented the CH_2N, CH_2Ph and OCH_2 respectively. The appearance of a multiplet that integrated to 5H at the aromatics region should also be taken into account as a strong

indication of the benzene ring. The carbon NMR also showed both the aliphatic carbons and the aromatic as expected in the upfield and downfield regions respectvely.

Due to steric hindrance in the azidation and possible side reactions, there was going to be problem in diazo transfer and also in the eventual decomposition of this molecule. A shorter synthetic rout was suggested with a good living group already attached.

Synthesis of 3-bromopropyl 2-phenylacetate

The reaction was the beginning point in the second synthetic pathway in which simple and easily available starting reagents, phenyl acetic acid and 3-bromo-1-propanol were used. The reaction was carried out undergo a Steglich esterification (Equation **7**).[25] Generally a Steglich esterification involves reaction of an alcohol with a carboxylic acid in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC).[25] In order to construct the desired ester, compound **26** was reacted with 1.3 equivalents of phenylacetic acid while slowly adding a 1.0 M DCC solution. The completion of reaction was determined by TLC which indicated a less polar product. Filtration was used to remove the DCU as a byproduct. Despite these efforts, not all of the byproduct was removed so further purification was required. Flash column chromatography (10:1, hexane : ethyl acetate) resulted in a pure colorless syrup that was shown to be 3-bromopropyl 2-phenylacetate.



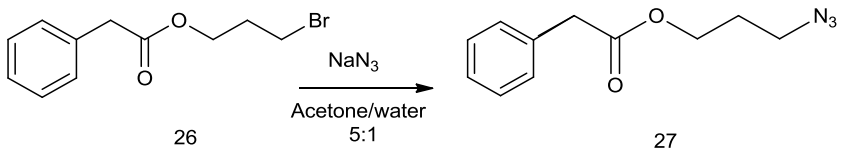
Equation 6.

The attempts to crystallize this product were unsuccessful, however, the ^{1}H NMR spectrum substantiated this method for esterification of the acid **24** in presence of alcohol **25** by showing the characteristic singlet at 3.61 ppm that corresponds to the two protons of the -CH_2 *alpha* to the carbonyl of the newly formed ester. Esterification was also confirmed by the disappearance of the broad singlet belonging to the hydroxyl group. A 5H multiplet at 7.25–7.34 ppm was observed for the protons on the phenyl ring. It was also interesting to note the appearance of 2H triplet at 4.21 with a coupling constant of 6.08 Hz that corresponded to the OCH_2. The triplet signal for CH_2Br was observed further downfield at 3.35 ppm compared to the CH_2 protons *alpha* to protons which appeared as 2H quintet at 2.13 ppm representing CH_2 group sandwiched by other two CH_2 groups.

The carbon-13 NMR spectrum of 3-bromo 2-phenylacetate (**26**) supported the evidence gained from the ^{1}H NMR spectrum. Four signals in the aromatic region, 127-134 ppm, worth a total of 6 carbons agrees with a symmetrical benzene ring. At 41.16 ppm, a single carbon signal appears belonging to the carbon *alpha* to the ester attached at the bromopropyl group. The benzylic carbon was shown at 62.52 ppm due to the effect of the electron-withdrawing group. Similarly, further downfield at 171.34 ppm, a signal of

significantly less intensity is seen for the ester carbonyl clearly completed the proof for the synthesized bromo ester **26**.

Synthesis of 3-azidopropyl 2-phenylacetate (27)



26 27

Equation 7.

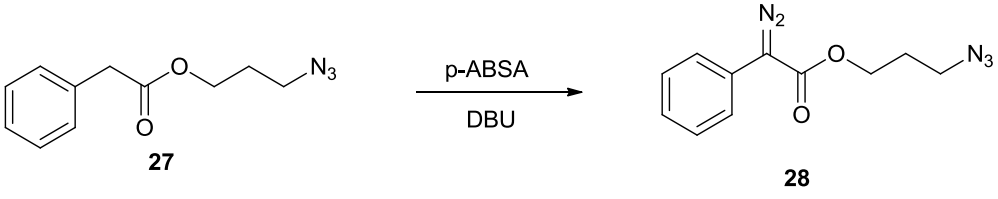
The presence of bromine tethered to the compound **27** provides a good basis for the azidation using classical nucleophilic substitution (S_N2). In this case, the source of nucleophile was sodium azide and bromide group was a good leaving goup. The reaction continued after 3-bromo 2-phenylacetate was dissolved in 5 : 1 acetone and water mixture. Sodium azide was added and the solution was stirred 18 hours at 40 ^{0}C until starting materials were consumed. The TLC confirmed the appearance of the spot at an R_f value of 0.47 (4:1, hexanes: ethyl acetate). The purification of the product was simple since it only required aqueous work up and extraction with ethyl acetate gave 88 % yield of **28.**

A proton nuclear magnetic resonance spectrum was taken of the azide **27**, to prove that it was surely produced. The appearance of signal at 1.86 ppm (quintet) represents the secondary methylene protons of the azido propane side of the compound whereas the signals at 3.30 ppm (triplet) and 4.16 ppm are indicative of the methyl

protons adjacent to nitrogen and oxygen respectively. These signals have generally shifted slightly upfield due to the presence of less electronegative azide hence facilitating the shielding effect. The signals representing two benzylic protons (singlet) and multiplet of the phenyl group maintained their positions.

The ^{13}C NMR spectrum of **28** showed two signals at 28.09, 41.37, and 48.09 ppm for the methylene groups on 3-azidopropyl 2-phenylacetate, and the peak at 61.5 ppm correlates to the benzylic carbon. The four signals belonging to the six carbons of the benzene ring maintained the positions at a range between 127 and 134. Similarly, there was no significant chemical shift of the carbonyl signal at 171.40 ppm. The confirmation of the synthesis of azide **28** was further shown by the infrared signal for azide at 2102 cm^{-1}. Mass spectrometry showed a peak with an M^+ of 242.20, which was indicative of the addition of a sodium atom to the calculated molecular mass of 219.10.

Synthesis of 3-azidopropyl 2-diazo-2-phenylacetate (28)



Equation 8.

The synthetic process continued with the diazo transfer reaction of **28**. In this case, A mixture of 3-azidopropyl 2-phenylacetate and *p*-acetamidobenzene sulfonyl

azide, which acted as the diazo group donor) was added to a flame-dried round bottom flask equipped with a magnetic stir bar, purged with nitrogen and dissolved in dry CH_2Cl_2 under nitrogen. The inert conditions sought to avoid the possible formation of the carbonyl byproducts. 1, 8-diazabicyclo [5, 4, 0] undec-7-ene was used as a base and added dropwise over 3 hours to facilitate the sequential deprotonation process of the benzylic proton that was followed by electrophilic attack on the N of the sulfonyl azide necessitating the internal diazo transfer hence producing an orange solution. TLC showed the formation of a new product at an R_f = 0.51 (4:1 hexanes : EtOAc). The workup followed the laid down procedure,[23] and final purification of **29** on a silica gel column (8:1 hexanes : EtOAc) afforded 1.91 g (68%) as orange syrup. The characterization of the product was done and the following information obtained.

The ^{1}H NMR spectrum of **29** proved the expected disappearance of a 2H singlet at 3.70 ppm for the α-hydrogens of the phenylacetyl group. A 5H multiplet at 7.25–7.34 ppm for the protons on the phenyl ring split into three distinct multiplets: 1H multiplet at 7.17-7.21 ppm representing the proton at the *para* position, 2H multiplet at 7.37-7.41 ppm corresponding to the protons at the *meta* position and 2H multiplet at 7.46-7.49 ppm further downfield was due to resonance effects caused by diazo group. The other major significant change is the chemical shift of the 2H triplet signal at 4.38 ppm corresponding to OCH_2 that shifted downfield from 4.16 ppm. This was attributed to the introduction of diazo group which is more electron-withdrawing hence causing the deshielding effect. Both the 2H triplet at 3.43 ppm and 2H quintet signal at 1.99 ppm also experience slight downfield shift.

The analysis of the ^{13}C NMR spectrum of (**29**) showed the signal for the carbon the disappearance of the one carbon that was initially at 41.38 ppm, this could probably be as a result of C=N bond formation which sometimes don't show up in the carbon NMR. The C=O signal appeared at 164.94 ppm as expected. The other aliphatic carbons; OCH_2, CH_2 and CH_2N retained their chemical shift.

Rhodium (II)-catalized azido carbenoid cyclization

The synthetic possibility of diazo compounds, particularly stabilized α-diazoesters, is greatly extended by the ability of the derived carbene or metal-carbene intermediates to undergo intramolecular and intermolecular formation of C-N bonds. Having synthesized and characterized successfully the starting materials required with the two important functionalities (diazo and the azido groups) and after considerations of the physical properties of the sensitive nature of diazo compounds in presence of light and heat, as well as the sensitivity of the Rhodium catalyst to water, the experiment was then carried out with all of these aspects taken into account and allowed for the first cyclization to be attempted.

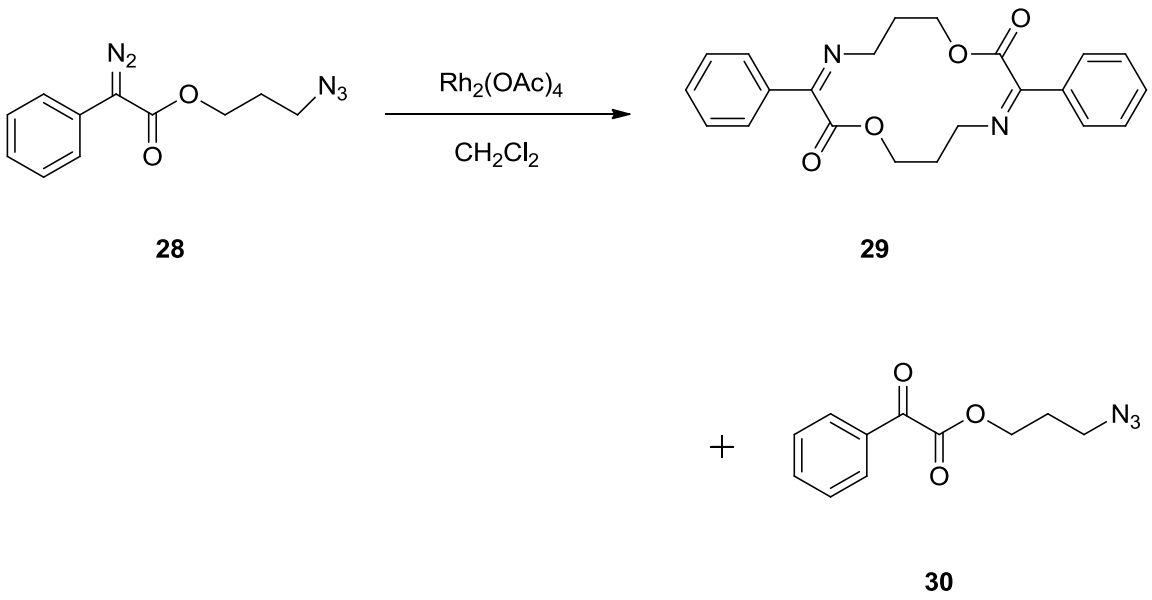
In the first attempt, $Rh_2(OAc)_4$ (3 mol % of the diazoester) was suspended in de-gassed anhydrous CH_2Cl_2 under N_2 atmosphere, a solution of diazoester (**29**) was dissolved in anhydrous CH_2Cl_2 and degassed for 30 minutes. Then the solution was added dropwise at the rate of 7 mL/hour using a syringe pump at room temperature in the hood. The reaction was allowed to continue for 24 hours after the completion of the addition. Upon testing *via* TLC, numerous spots appeared meaning the sample was a mixture of products. Thus flash chromatography was used to further analyze the sample,

but unfortunately even after this step of purification the product(s) still contained impurites. ^{1}H NMR analysis of products did not show any good resolution; the spectrum was difficult to analyze due to the signal overlap. The second attempt of cyclization was done within a controlled environment known as the glove bag and using the same procedure as previously stated. However there is discrepancy due the size of the bag, the syringe pump could not be used in the dropwise introduction of the diazo compound. At this point the TLC showed five products with a streak still indicating impurities within the sample. When separated via flash chromatography with gradient elution (5:1, hexane: ethyl acetate; 2:1, ethyl acetate: hexane), the compounds did not separate well and the analysis via NMR spectroscopy showed that there were some new peaks though they were not well resolved. The infrared spectrum showed that there was azido group in the first fraction but still there were two peaks at the carbonyl region of carbon-13 NMR which probably indicated a possibility of diazo oxidation.

Since more side reactions occurred due to the presence of water and oxygen, a more controlled, inert atmosphere was desired. This controlled inert atmosphere was achieved by conducting reactions in using the glove box. The solvent used in this reaction was CH_2Cl_2 which was dried with molecular sieves for duration of one week and then degassed before being transferred to an appropriate sealed round bottom flask. Rhodium (II) tetraacetate was introduced to this environment and dried on a vacuum pump for at least one week. Oxygen and water levels were recorded at the start of each new reaction to ensure that the reaction occurred efficiently. Reaction setup was the same as stated above, and still included the dropwise addition of the diazoester **28** solution. The diazoester solution was added *via* syringe pump to the solution of rhodium (II) catalyst.

The use of TLC to monitor the reaction's progress was used only when the reaction vessel was removed from this contained environment after adequate reaction time.

The initial reaction performed in the inert atmosphere of the glove box was the decomposition of 3-azidopropyl 2-diazo-2-phenylacetate (**28**) in the presence of rhodium (II) tetraacetate catalyst (Equation 9). The whole procedure was repeated with same chemical equivalents. The glove box conditions were recorded: (T 28 °C; H_2O = 204 ppm; O_2 = 262 ppm). TLC was taken after the reaction and showed that there was formation of two major products. These products were separated via a careful flash column and resulted in the formation of 14-membered ring **29** (52% yield) as a white syrup and a trace of a second product which was resolved and identified as azido ketoester **30** as a yellow oil (6%, yield). The production of the macrocycle **29** in relatively high yield which was attributed to the high rate of addition of the diazo compound.



Equation 9.

The analysis of the ^{1}H NMR of 14-membered ring **29** showed a 4H multiplet at 2.17-2.25 ppm for the -CH_2 groups sandwiched by -CH_2N and OCH_2-. There were two triplet signals at 3.70, and 4.33 ppm that integrated neatly to 4 protons each and corresponded to -CH_2N, and OCH_2 respectively due to the electronegativity difference between oxygen and nitrogen enhancing the deshielding effect. The formation of the dimer was demonstrated by the presence of two phenyl rings indicated by 4H and 6H multiplets at 7.40-7.50 and 7.69-7.72 ppm for the *ortho* and (*meta* and *para*) positions respectively. The further structural confirmations were done by the ^{13}C NMR which clearly showed three aliphatic carbons shielded upfield and four signals for the aromatic rings as expected indicating the equivalent chemical shift. More importantly was the presence of only two signals at 161.55 ppm for C=O and 165.47 ppm for C=N). The

analysis was consequently done by mass spectrometry using ESI and found out that the compound **29** had a mass of 379.30 which confirmed its calculated mass of 378.16.

Further characterization of the heterocyclic compound was done by X-ray crystallographic analysis which finally confirmed that it was a 14-membered dimeric heterocyclic compound. The crystal structure was obtained from a colorless plate that belonged to the monoclinic crystal system (Figure **4**). Unit cell dimensions were as follows: a = 12.151 (2) Å, a = 90°; b = 14.099 (2) Å, b = 106(2)°; c = 5.5321(9) Å, g = 90°. Regardless of the packing pattern (Figure 5), this 14-membered macrocycle is actually observed to be a centrosymmetric molecule and belongs to space group P21/c.

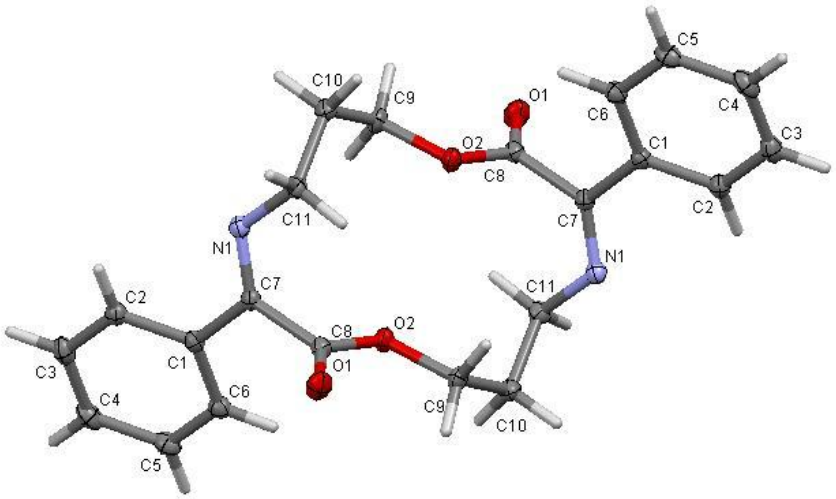


Figure 11: X-ray crystal structure for the 14-membered heterocycle **29**.

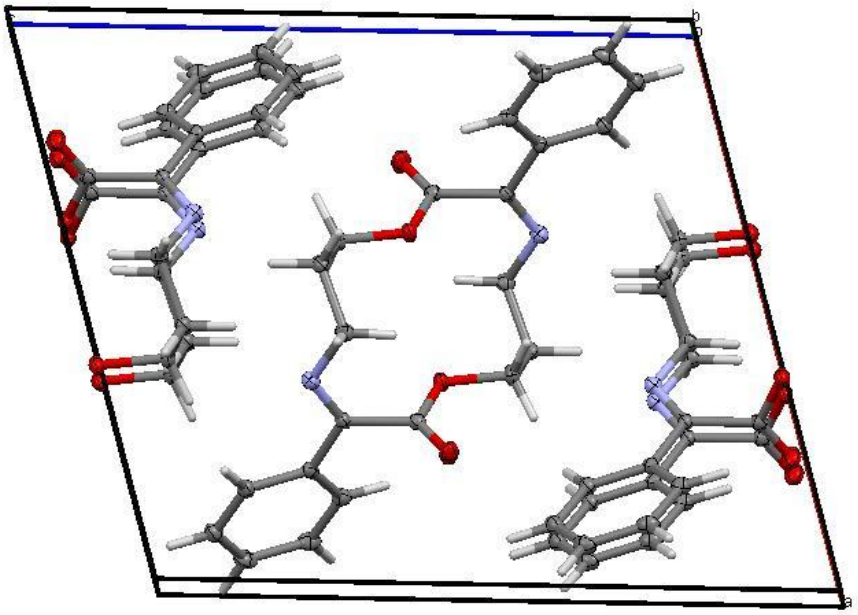
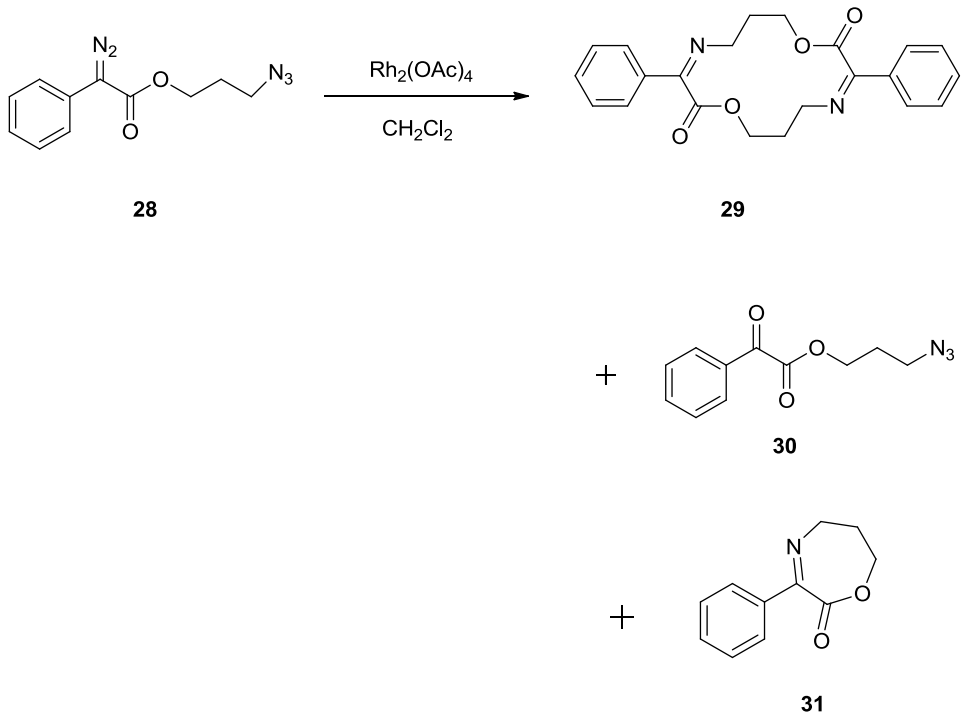


Figure 12: Unit cell packing showing the symmetry of heterocycle **29**.

The second structure **30**, which was the side reaction was also conclusively characterized. Proton analysis showed a downfield shift of the 2H triplet signal of OCH_2 from 4.38 ppm in diazoester **29** to 4.48 ppm, this was a clear indication that a carbonyl group has been added at the *alpha* position to the ester group. There were distinctive shifts in phenyl ring signals represented by three multiplets of 2H, 1H and 2H at 7.51-7.55, 7.66-7.70 and 8.00-8.02 ppm respectively that shifted downfield further proving the attachment of C=O at the benzylic position. The ^{13}C NMR cemented the argument by presenting two signals at 163.62 ppm for O-C=O and 186.02 for PhC=O. the aliphatic carbons and phenyl carbons for this compound were also present in the structure. Further characterization continued with infrared showing the retention of the azide stretch at 2102 cm^{-1} and also the appearance of two carbonyl signals at 1739 and 1691 cm^{-1}. The mass

spectrum, obtained by ESI, confirmed that the compound had molecular mass of 256 which included the calculated mass (233) of the compound **30** and that of sodium.

The production of **29** at relatively high yield was attributed to the high rate of addition of the diazo compound while the production of the azido ketoester could be as a result of the trace amount of oxygen in the glove box. The research on the intramolecular cyclization possibility continued with an attempt to reduce the rate of introduction of the diazo compound into the reaction round bottom flask. Therefore, the procedure was maintained except the rate of introduction was reduced to 4 mL/hour. This reduction of the rate was not easily controlled due to high rate of decomposition which was accompanied by extrusion of molecular nitrogen. This lead to imbalanced pressure inside the bottle and the various attempts to vent it without introduction of oxygen into reaction were futile. However, at this rate the TLC showed three products (**29**, **30**, and **31**) which were purified via flash column chromatography with the eluting solvent system (4:1 hexanes : ethyl acetate, 2:1 ethyl acetate : hexanes). The loading of the crude product was done as a dry silica mixture.



Equation 10.

The first attempt to characterize the seven-membered ring (**31**) was done via ^{1}H NMR and was not very conclusive even though it showed the three aliphatic protons signal which integrated neatly into 2H at 1.79, 3.52 and 3.69 ppm, correlating to $–CH_{2,}$ $-CH_2N$ and CH_2O respectively. The aromatic ring signals were recorded as expected and was split into three multiplets of 2H, IH and 2H at the aromatic region. A more convincing result was achieved by the carbon-13 NMR with the appearance of two signals at 162.96 ppm for an imine carbon and, and 187.93 ppm for the ester carbon. The analysis of infrared data showed the absence of absorption band at 2100 cm^{-1} for the azide which suggested a successful decomposition of the azide. The conclusive result was finally found by the mass spectrometry that showed a peak with an M^{+} of 190.20,

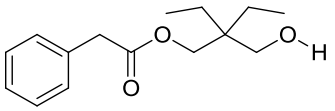
which was indicative of the corresponded to the calculated molecular mass of 189.08.

EXPERIMENTAL SECTION

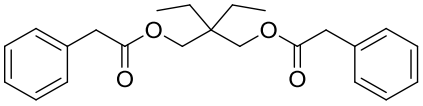
General Procedures

Reaction progress was monitored by thin layer chromatography (TLC) with UV light detection on Whatman 250 μm layer, aluminum-backed plates. The TLC plates were then treated with phosphomolybdic acid/ethanol solution to burn the reaction material to provide indication of the product(s). Purification of products was achieved either by recrystallization or flash column chromatography, which was performed with 32-60 μm, 60-Å silica gel. Bruker Avance II and III 400 MHz NMR spectrometers were used to obtain 400 MHz ^{1}H and ^{13}C spectra using $CDCl_3$ (0.1% w/v TMS) as the solvent. Chemical shifts (δ) are recorded in parts per million (ppm). Multiplicities for NMR spectra are listed as follows: s (singlet), t (triplet), qu (quintet) and m (multiplet), and all coupling constants (*J*) are labeled in Hertz (Hz). A Bruker Esquire-HP 1100 LC/MS was used to obtain mass spectra. A Thermo Electron Corporation IR 200 infrared spectrometer was used to obtain the infrared data. X-Ray diffraction was used to determine the solid-state crystal structure of the compounds produced herein. For the samples, data was collected using a Bruker SMART APEX 4K CCD single crystal diffractometer at 100 K with Mo (K_α) radiation.

Synthesis of 2-ethyl-2-(hydroxymethyl)butyl 2-phenylacetate from phenylacetyl chloride (20).



20



21

In an oven-dried 250 mL, round bottom flask containing a magnetic stirrer with an addition funnel, a mixture of 2,2-diethyl-1,3-propanol (2.6 g, 19.7 mmol) and DMAP (0.19 g, 1.50 mmol) were added and dissolved in 35 mL of anhydrous pyridine. The flask and its contents were cooled in an ice/acetone mixture at -10 °C and stirred under an argon atmosphere over a 10 minute period. To the resulting colorless clear solution, a solution of phenylacetyl chloride (2 mL, 15.5 mmol) in 25 mL of dry dichloromethane was added dropwise over a 2 hr period. After the addition was complete, the resulting orange, cloudy reaction mixture was stirred for 5 hours at 0 °C, then for an additional 10 hours at room temperature while monitoring via TLC. The reaction mixture was diluted with 20 mL of dichloromethane, and then poured into 50 g/mL of water containing crushed ice. The organic phase was separated and the aqueous layer extracted twice with 20 mL portions of dichloromethane. The organic phase and the extracts were combined, washed twice with 25 mL portions of 5% sulfuric acid and 25 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The filtrate was evaporated to give the crude product, which was then purified on a silica gel column (10:1 hexanes : EtOAc) to give 2.26 g (60% yield) of monoester **20** as colorless syrup and 1.31 g (35% yield) of diester **21**.

2-Ethyl-2-(hydroxymethyl)-butyl 2-phenylacetate (20).

^{1}H NMR (400 MHz): δ 0.77 (t, 6H, -CH_3, J = 7.56 Hz), 1.11-1.27 (m, 4H, -CH_2), 2.00 (s, 1H, OH), 3.21 (s, 2H, CH_2-OH), 3.64 (s, 2H, CH_2-Ar), 3.97 (s, 2H, OCH_2), 7.25-7.32 (m, 5H, Ar).

^{13}C NMR (100 MHz): δ 6.97 (2 × C, -CH_3), 22.09 (2 × C, -CH_2), 41.28 (1 × C, C-*quaternary*), 41.58 (1 × C, CH_2Ph), 64.31 (1 × C, CH_2OH,), 66.64 (1 × C, OCH_2). 127.23 (1 × C, Ar), 128.65 (2 × C, Ar), 129.22 (2 × C, Ar), 133.97 (1 × C, Ar), 172.33 (1 × C, C=O).

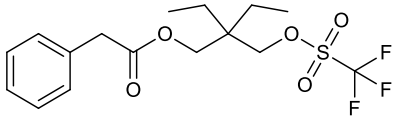
2, 2-Diethylpropane-1,3-diyl-bis(2-phenylacetate) (21)

^{1}H NMR (400 MHz): δ 0.69, (t, 6H, -CH_3, J = 7.56 Hz), 1.14-1.21 (m, 4H, -CH_2), 3.56 (s, 4H, CH_2-Ar), 3.84 (s, 4H, OCH_2), 7.21-7.26 (m, 10H, Ar).

^{13}C NMR (100 MHz): δ 6.98 (1 × C, -CH_3), 22.99 (1 × C, -CH_2), 39.56 (1 × C, C-*quaternary*.), 41.53 (2 × C, CH_2Ph) 65.87 (2 × C, CH_2OH), 127.11 (2 × C, Ar), 128.57 (4 × C, Ar), 129.26 (4 × C, Ar), 134.07 (2 × C, Ar), 171.37 (2 × C, C=O).

m/z calculated 368.20 *m/z* found (ESI): 391.4 (+Na)

Synthesis of 3-(((trifluoromethyl)sulfonyl)oxy)propyl-2-phenylacetate (22).



22

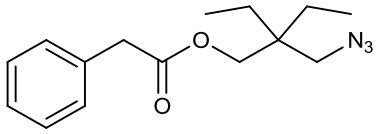
Into a round bottom flask equipped with magnetic stir bar, a solution of 2-ethyl-2-(hydroxymethyl)butyl-2-phenylacetate (**20**) (1.82 g, 7.28 mmol) in 20 mL of CH_2Cl_2 was added. Anhydrous pyridine (25 mL) was slowly added and the flask content cooled to –10 °C. Triflic anhydride (2.45 mL, 14.56 mmol) dissolved in 30 mL of CH_2Cl_2 was added dropwise to maintain a reaction temperature of 0-2 ^oC. The mixture was stirred at 0 ^oC for 30 min and then room temperature until the reaction was deemed complete. The reaction mixture was quenched with 50 mL of cold water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with cold aqueous 5% sulfuric acid (3 × 50 mL), cold water (1 × 50 mL), brine (2 × 50 mL) and then dried over anhydrous magnesium sulfate. After filtration, the solvent was removed under vacuum to give 1.95 g (70% yield) of the crude product as orange syrup.

^1H NMR (400 MHz): δ 0.79, (t, 6H, -CH_3, J = 7.56 Hz), 1.25-1.31 (m, 4H, -CH_2), 3.64 (s, 2H, CH_2-OH), 3.94 (s, 2H, CH_2-Ar), 4.24 (s, 2H, OCH_2), 7.24-7.32 (m, 5H, Ar-H).

^{13}C NMR (100 MHz): δ 6.63 (2 × C, -CH_3), 22.11 (2 × C, -CH_2), 40.52 (1 × C, C-*quaternary*), 41.34 (1 × C, CH_2Ph), 64.71 (1 × C, CH_2OH,), 66.64 (1 × C, OCH_2),

117.04 (1 × C, CH_2OTf), 120.22 (q, 1 × C, OTf), 127.20 (1 × C, Ar), 128.62 (2 × C, Ar), 129.20 (2 × C, Ar), 133.82 (1 × C, Ar), 171.02 (1 × C, C=O).

2-(azidomethyl)-2-ethylbutyl 2-phenylacetate (23).



23

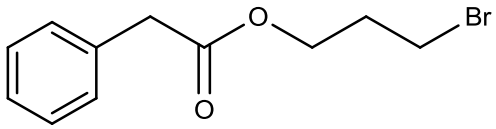
Into an oven-dried 100 mL round bottom flask equipped with a stir bar, a mixture of 3-((trifluoromethyl)sulfonyl)oxy)-propyl 2-phenylacetate (1.95 g, 5.01 mmol) and NaN_3 (1.63 g, 25 mmol) were dissolved in 50 mL of DMF. The reaction was stirred overnight at 60 ^oC, and then the reaction mixture was diluted with 50 mL of cold deionized water and was separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with cold aqueous 5% sulfuric acid (3 × 50 mL), cold water (1 × 50 mL), brine (1 × 50 mL) and then dried over magnesium sulfate. After filtration, the solvent was removed under vacuum to give 0.8 g (60% yield) of the azide as a white syrup.

IR (thin film): 2104 cm^{-1}.

^{1}H NMR (400 MHz): δ 0.75, (t, 6H, -CH_3, J = 7.56 Hz), 1.16-1.23 (m, 4H, -CH_2), 3.09 (s, 2H, CH_2N), 3.64 (s, 2H, CH_2-Ar), 3.97 (s, 2H, OCH_2), 7.25-7.32 (m, 5H, Ar).

^{13}C NMR (100 MHz): δ 7.01 (2 × C, -CH_3), 23.51 (2 × C, -CH_2), 40.52 (1 × C, C-*quaternary*), 41.59 (1 × C, CH_2Ph), 54.92 (1 × C, CH_2OH,), 65.19 (1 × C, OCH_2). 127.13 (1 × C, Ar), 128.58 (2 × C, Ar), 129.27 (2 × C, Ar), 134.07 (1 × C, Ar), 171.27 (1 × C, C=O).

Synthesis of 3-bromo 2-phenylacetate (26)



26

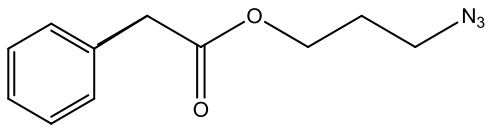
In an oven-dried 100 mL round bottom flask containing a magnetic stir bar, a mixture of phenylacetic acid (2 g, 14.7 mmol), and 4-dimethylaminopyridine (0.18 g, 1.47 mmol) were added and dissolved in anhydrous CH_2Cl_2 (40.0 mL). It was then cooled to 0 °C and 3-bromo-1-propanol (1.7 mL, 19.1 mmol) was slowly added dropwise. While stirring under nitrogen atmosphere, 1,3-dicyclohexylcarbodiimide solution (14 mL, 1.0 M in CH_2Cl_2) was added dropwise at the rate of 7 mL/hr *via* syringe pump resulting in a white precipitate. The reaction mixture was stirred for 6 hours at

room temperature. Thin layer chromatography showed the formation of a new product at an R_f value higher than phenyl acetic acid. After the completion of the reaction, the mixture was gravity filtered, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) and the solution washed with 5% H_2SO_4 (3 × 25 mL) and H_2O (2 × 25 mL). After drying with $MgSO_4$, the filtrate was evaporated to give the crude product, which was then purified on a silica gel column (10:1 hexanes : EtOAc) to give 3.02 g (80% yield) of **27** as colorless syrup:

^{1}H NMR (400 MHz): δ 2.13 (qu, 2H, -CH_2, J = 6.36 Hz), 3.35 (t, 2H, -CH_2Br, J = 6.56 Hz), 3.61 (s, 2H, -CH_2Ph), 4.21 (t, 2H, O-CH_2-, J = 6.08 Hz), 7.23-7.33 (m, 5H, Ar-H).

^{13}C NMR (100 MHz): δ 29.33, 31.57, 41.35, 62.52, 127.20 (1 × C, Ar), 128.64 (2 × C, Ar), 129.22 (2 × C, Ar), 133.87 (1 × C, Ar), 171.34 (1 × C, C=O).

Synthesis of 3-azidopropyl 2-phenylacetate (27)



27

In an oven-dried 250 mL round bottom flask equipped with a stirrer, 3-bromo-2-phenylacetate (3.0 g, 11.6 mmol) was dissolved in a 5 : 1 acetone and water mixture (80 mL). Sodium azide (3.77 g, 58 mmol) was added and the solution was stirred for 18

hours at 40 °C until starting materials were consumed. The reaction was monitored *via* TLC (4:1, hexanes: ethyl acetate) which showed the product at R_f = 0.47. The acetone was removed under vacuum and the remaining slurry was partitioned between water and ethyl acetate (50 mL each). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic extracts was dried with anhydrous magnesium sulfate, filtered and reduced under vacuum to leave colorless syrup (2.23 g, 88% yield).

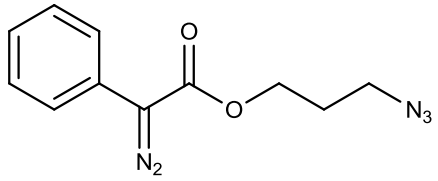
IR (thin film): 2102 cm^{-1};

^{1}H NMR (400 MHz): δ 1.86 (qu, 2H, -CH_2, J = 6.43 Hz), 3.30 (t, 2H, -CH_2N_3, J = 6.72 Hz), 3.63 (s, 2H, -CH_2Ph), 4.16 (t, 2H, O-CH_2, J = 6.16 Hz), 7.23-7.34 (m, 5H, Ar-H).

^{13}C NMR (100 MHz): δ 28.10, 41.37, 48.09, 61.68, 127.19 (1 × C, Ar), 128.64 (2 × C, Ar), 129.24 (2 × C, Ar), 133.94 (1 × C, Ar), 171.41 (1 × C, C=O).

m/z calculated 219.10 *m/z* found (ESI): 242.2 (+Na)

Synthesis of 3-azidopropyl 2-diazo-2-phenylacetate (28).



28

A mixture of 3-azidopropyl-2-phenylacetate (2.0 g, 7.77 mmol) and *p*-acetamidobenzene sulfonyl azide (4.38 g. 18.20 mmol) was added to a flame-dried 250 mL round bottom flask equipped with a magnetic stir bar, purged with nitrogen and dissolved in dry CH_2Cl_2 (40.0 mL) under nitrogen. While stirring at room temperature, 1,8-diazabicyclo[5,4,0]undec-7-ene (2.80 mL, 8.20 mmol) was added dropwise over 3 hours producing an orange solution. TLC showed the formation of new product with an R_f = 0.51 (4:1 hexanes : EtOAc) and, after stirring for 16 hours, ^{1}H NMR was used to monitor the disappearance of the singlets representing benzylic protons and therefore a sure confirmation that reaction by was complete. The reaction mixture was then concentrated under reduced pressure, after which it was diluted with 50.00 mL of CH_2Cl_2 and transferred to a 250 mL separatory funnel to perform an aqueous workup; the organic phase was washed with 5% H_2SO_4 (3 x 50mL), deionized water (3 x 50mL), and then dried over anhydrous magnesium sulfate. The filtered solution was concentrated and the orange syrup was purified on a silica gel column (8:1 hexanes : EtOAc) to afford 1.91 g (68%) of **28** as orange syrup.

IR (thin film): 2093 cm^{-1};

^{1}H NMR (400 MHz): δ 2.00 (qu, 2H, –CH_2, J = 6.42 Hz), 3.43 (t, 2H, -CH_2N_3, J = 6.61 Hz), 4.37 (t, 2H, O-CH_2, J = 5.26 Hz), 7.17-7.21 (m, 1H, Ar), 7.37-7.41 (m, 2H, Ar), 7.46-7.49 (m, 2H, Ar).

^{13}C NMR (100 MHz): δ 28.10, 41.37, 48. 21, 61.84, 124.19 (1 × C, Ar) 125.32 (2 × C, Ar), 126.00 (2 × C, Ar), 129.01 (1 × C, Ar), 164.95 (2 × C, C=O).

General procedure for diazo transfer

2-Phenylacetyl derivative **23** or **27** (1.0 equivalent) and *p*-acetamidobenzene sulfonyl azide (1.5 equivalents) were added to a flame-dried flask and dissolved in dry CH_2Cl_2. While stirring at room temperature, 1,8-diazabicyclo [5,4,0] undec-7-ene (1.5 equivalents) was added dropwise producing an orange solution. TLC showed the product at an R_f of 0.44 (4:1 hexanes : EtOAc) and, after stirring for 16 h, the reaction solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with 5% H_2SO_4, deionized water and brine. After drying with $MgSO_4$ the solvent was evaporated to give the crude product which was then purified on silica gel (6:1 hexanes : EtOAc) to afford the diazoester as orange syrup in good yields:

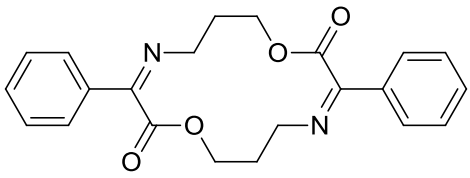
Rhodium (II)-Catalyzed Cyclizations

General procedure

$Rh_2(OAc)_4$ (3 mol % of the diazoester) was suspended in degassed anhydrous CH_2Cl_2 (10 mL) under N_2 atmosphere and a solution of diazoester (**29**), dissolved in anhydrous CH_2Cl_2 and degassed for 30 minutes, was then added dropwise at the rate of 7 mL/hour using a syringe pump at room temperature. The reaction was allowed to continue for 24 hours after the completion of the addition. TLC showed a major product

forming with an R_f value of 0.25 (4:1 hexanes: Ethyl acetate), identified as the heterocyclic dimer by X-ray crystallography. The solvent was removed under reduced pressure and the residue was purified using a flash column with gradient elution, (hexanes: ethyl acetate 5:1 to ethyl acetate : hexane 2:1). The products were isolated, recrystallized in ethanol as white crystals and yields calculated.

Intermolecular cyclization under inert conditions (glove box).



29

3-Azidopropyl 2-diazo-2-phenylacetate (1.5 g, 6.12 mmol) was dried for 5 days on a high vacuum pump before being transferred to the glove box. Once the dry orange syrup was placed inside the glove box, it was dissolved in 30 mL of dichloromethane then transferred to a 20 mL syringe and the rest placed in a dry scintillation vial. Into a 250 mL round bottom flask, 50 mL of methylene chloride was added and then 0.052 g of rhodium (II) tetraacetate was added. The diazoester was added dropwise over two hours to the catalyst solution *via* syringe pump. After the completion of the addition, the mixture was allowed to stir overnight before being removed from the glove box (T 26 °C; H_2O = 215 ppm; O_2 = 262 ppm). TLC verified that there was formation of two major products. The mixture was filtered through celite to remove the suspended rhodium

catalyst. The further purification of the product was done by flash column chromatography with a gradient eluting solvent system (4:1 hexanes : ethyl acetate, 2:1 ethyl acetate : hexanes). The loading of the crude product was done as a dry silica mixture. The cyclization resulted in the formation of 14-membered ring **30** (0.97 g, 2.57 mmol, 41%) as white crystals. and a ketoester **31** (0.52 g, 2.40 mmol, 36%) as a yellow oil.

(3*Z*,10*Z*)-3,10-diphenyl-1,8-dioxa-4,11-diazacyclotetradeca-3,10-diene-2,9-dione (29)

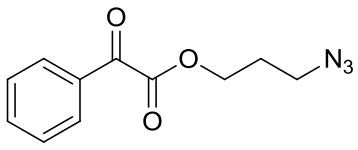
^{1}H NMR (400 MHz): δ 2.17-2.25 (m, 4H, -CH_2), 3.70 (t, 4H, -CH_2N, J = 6.14 Hz), 4.33 (t, 4H, O-CH_2, J = 5.26 Hz), 7.40-7.50 (m, 6H, Ar), 7.69-7.72 (m, 4H, Ar).

^{13}C NMR (400 MHz): δ 29.21 (2 × C), 51.37 (2 × C), 62.08 (2 × C), 127.21(2 × C, Ar), 128.69 (4 × C, Ar), 131.24 (4 × C, Ar), 133.86 (2 × C, Ar), 161.55 (2 × C, C=N), 165.47(2 × C, C=O).

m/z calculated 378.16 *m/z* found (ESI): 379.3(+Na)

R_f = 0.25 (4:1 hexanes : ethyl acetate*).*

Azido Ketoester (30)



30

IR (thin film): 2102 cm^{-1};

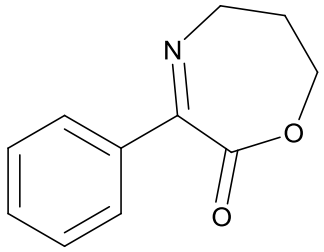
^{1}H NMR (400 MHz): δ 2.05 (qu, 2H, $–CH_2$, J = 6.42 Hz), 3.47 (t, 2H, $-CH_2N_3$, J = 6.56 Hz), 4.48 (t, 2H, $O-CH_2$, J = 6.20 Hz), 7.51-7.55 (m, 1H, Ar), 7.66-7.70 (m, 2H, Ar), 8.00-8.02 (m, 2H, Ar).

^{13}C NMR (100 MHz): δ 27.97, 47.83, 62.96, 128.99 (1 × C, Ar), 130.04 (2 × C, Ar), 132.31 (2 × C, Ar), 135.10 (1 × C, Ar), 163.62 (1 × C, O-C=O), 186.02 (1 × C, PhC=O).

R_f = 0.31 (4:1 hexanes : ethyl acetate).

m/z calculated 233.08 *m/z* found (ESI): 256.2 (+Na)

Heterocyclic cyclization under inert conditions (glove box) at reduced rate of addition of diazo compound.



31

3-Azidopropyl 2-diazo-2-phenylacetate (1.5 g, 6.12mmol) was dried for one week on a high vacuum pump before being transferred to the glove box. Once the dry orange syrup was placed inside the glove box, it was dissolved in 30 mL of degassed

dichloromethane then transferred to a 20 mL syringe and the rest placed into a dry scintillation vial. Into a 250 mL round bottom flask, 50 mL of methylene chloride was added and then 0.049 g of rhodium (II) tetraacetate was added and diluted further with 48 mL of methylene chloride. The diazoester was added at the rate of 4 mL/ hour to the catalyst solution *via* syringe pump. After the completion of the addition, the mixture was allowed to stir for 26 hours before being removed from the glove box (T 27 °C; H_2O = 64 ppm; O_2 = 120.9 ppm. TLC showed three products which were purified *via* careful flash column chromatography with the eluting solvent system of 4:1 hexanes: ethyl acetate to 2:1 ethyl acetate : hexanes to afford compound **29** (1.25 g, 3.46 mmol, 54%) as a white crystal, ketoester **30** (0.12 g, 0.94 mmol, 10%) as a yellow syrup and oxazepine **31** (0.45 g, 1.93 mmol 31%) as a white syrup.

Seven membered ring (31)

^{1}H NMR (400 MHz): δ 1.79 (qu, 2H, –CH_2, 6.15 Hz), 3.52 (q, 2H, -CH_2N=C, J = 6.14 Hz), 3.69 (t, 4H, O-CH_2, J = 5.74 Hz), 7.43-7.47 (m, 2H, Ar), 7.58-7. 60 (m, 1H, Ar-H), 8.24-8.26 (m, 2H, Ar).

^{13}C NMR (100 MHz): δ 31.62 (1 × C), 36.60 (2 × C), 59.72 (1 × C), 128.52 (1 × C, Ar), 131.03 (2 × C, Ar), 133.19 (2 × C, Ar), 134.48 (1 × C, Ar), 162.96 (1 × C, C=N), 187. 93 (1 × C, C=O).

R_f = 0.08 ((4:1 hexanes : ethyl acetate).

m.p = N/A (syrup)

m/z Calculated 189.08 *m/z* found (ESI): 190.2

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APPENDIX A

NMR, IR and Mass spectra.

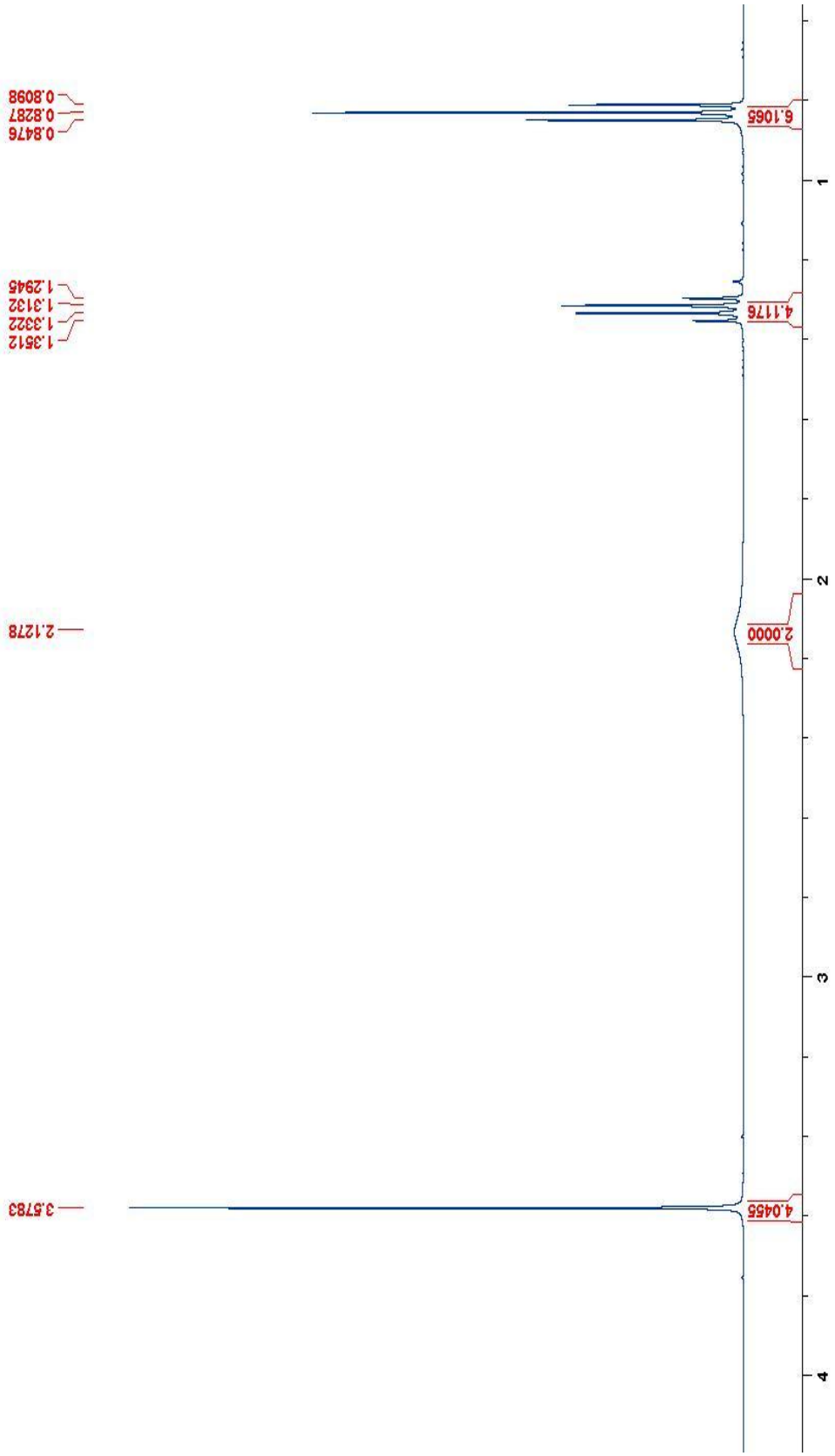

Figure 13: ^{1}H NMR spectrum of 2,2-diethylpropane-1,3-diol (**19**).

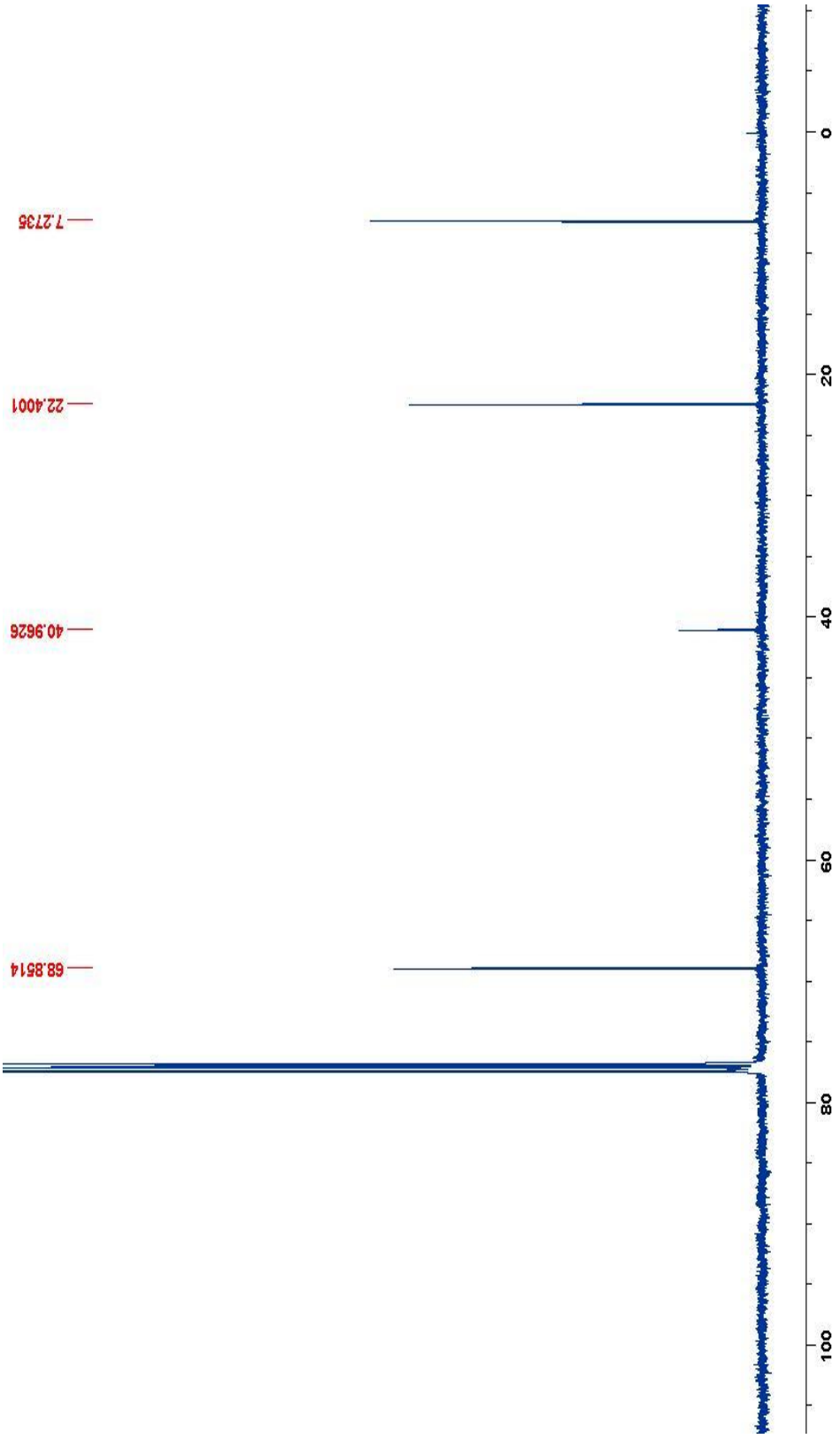

Figure 14: ^{13}C NMR spectrum of 2,2-diethylpropane-1,3-diol (**19**)

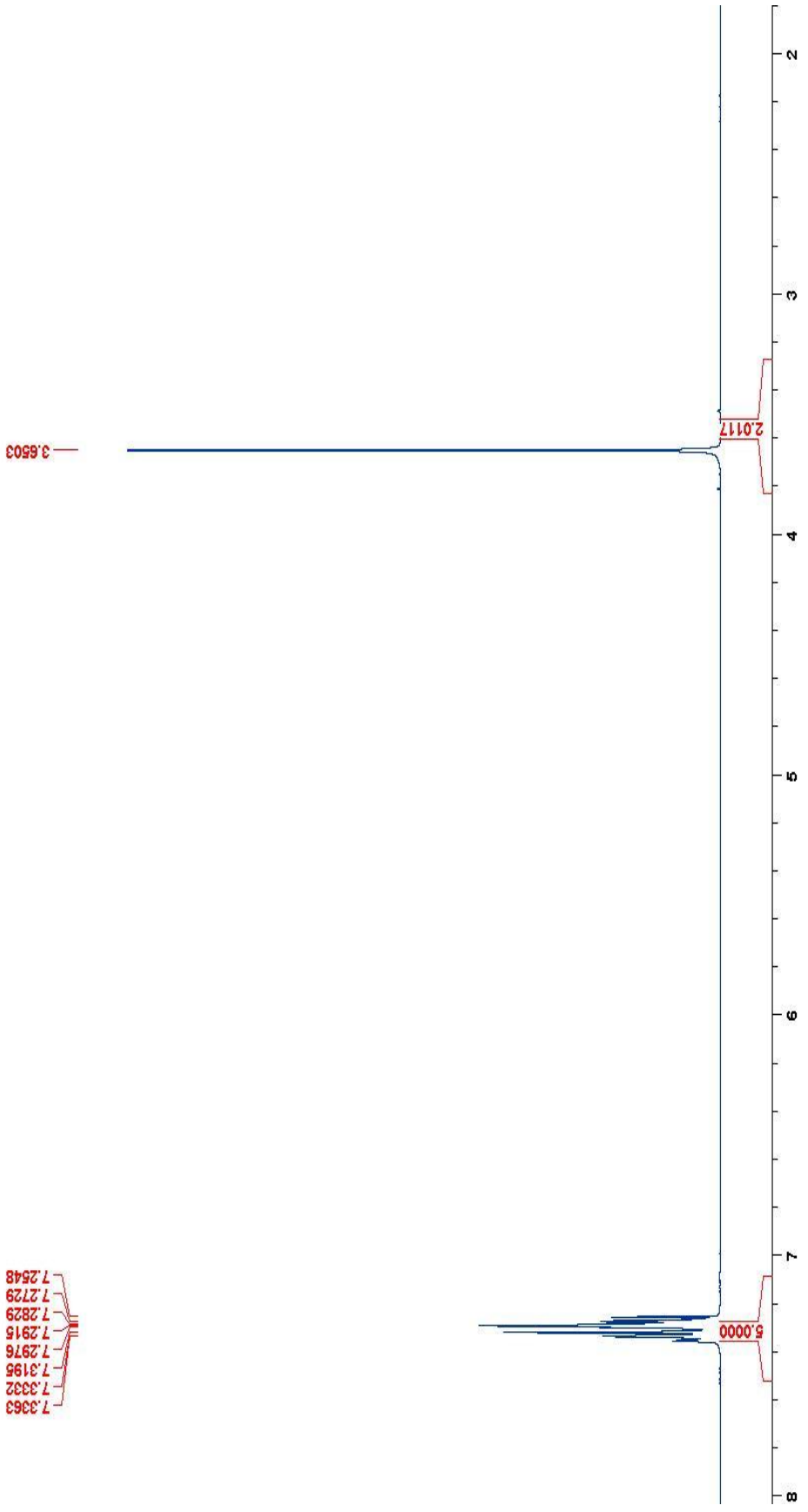

Figure 15: ^{1}H NMR spectrum of phenyl acetic acid (**18**).

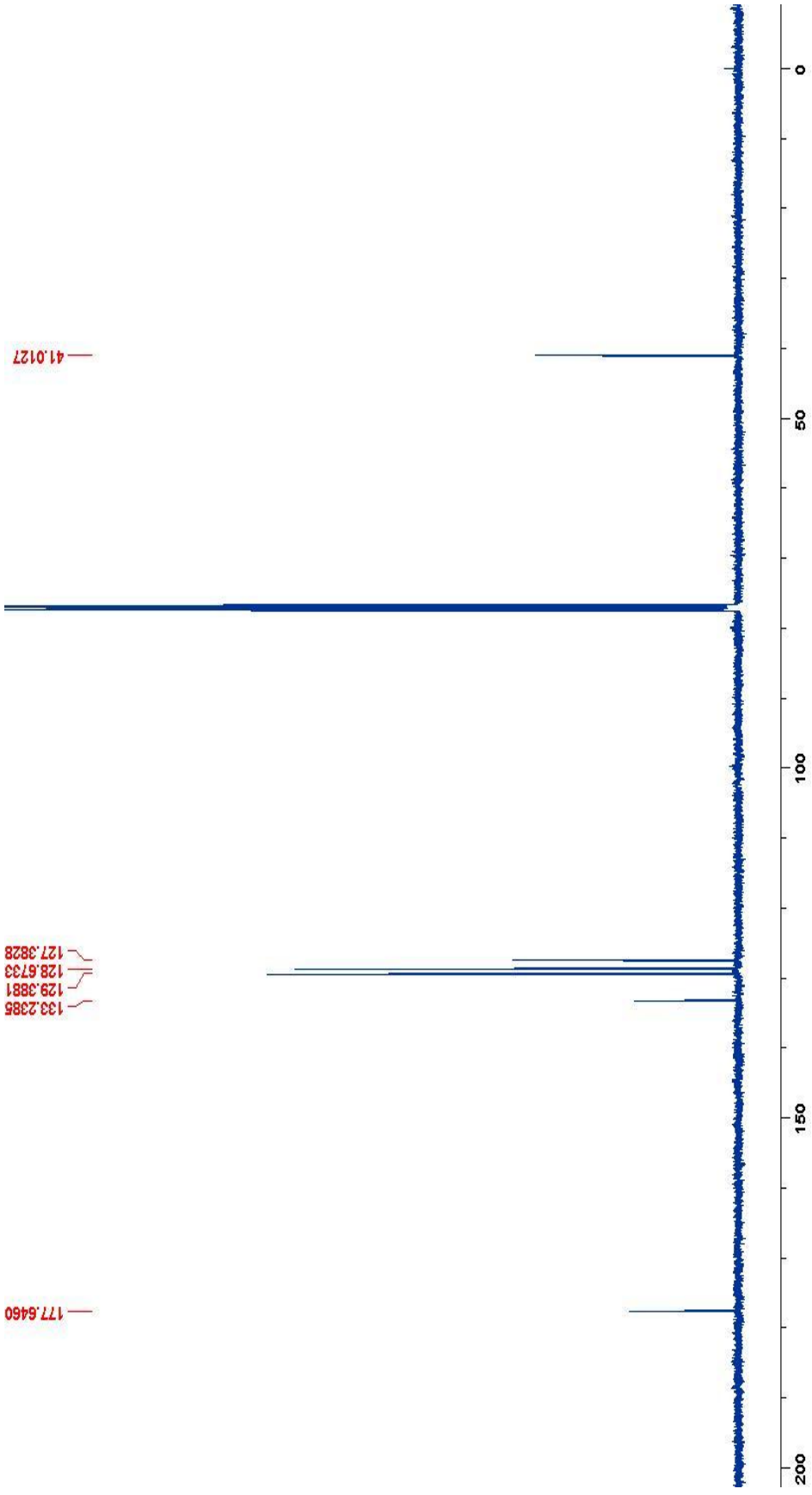

Figure 16: ^{13}C NMR spectrum Phenyl acetic acid (**18**).

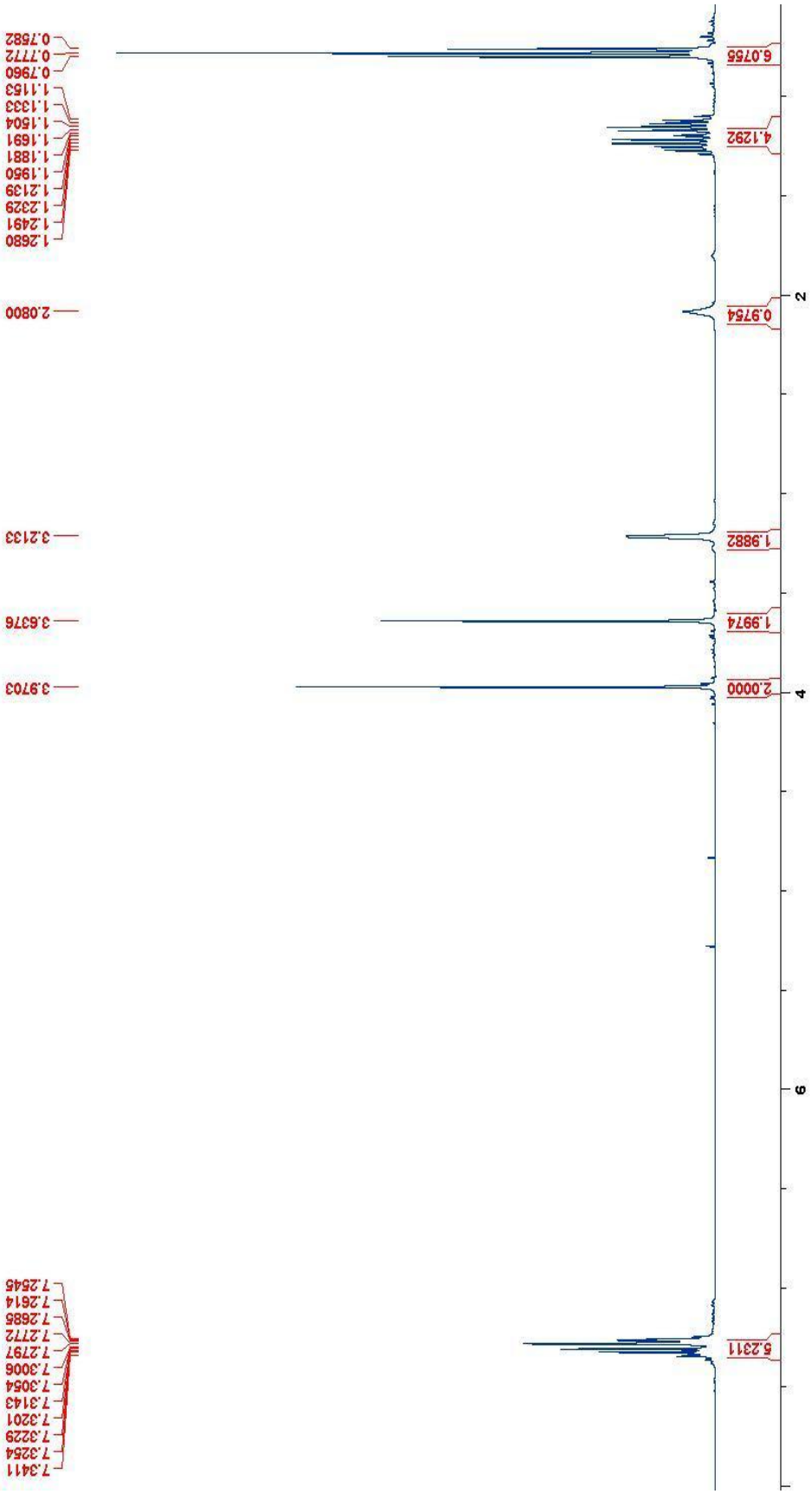

Figure 17: ^{1}H NMR spectrum of 2-ethyl-2-(hydroxymethyl)butyl 2-phenylacetate (**20**).

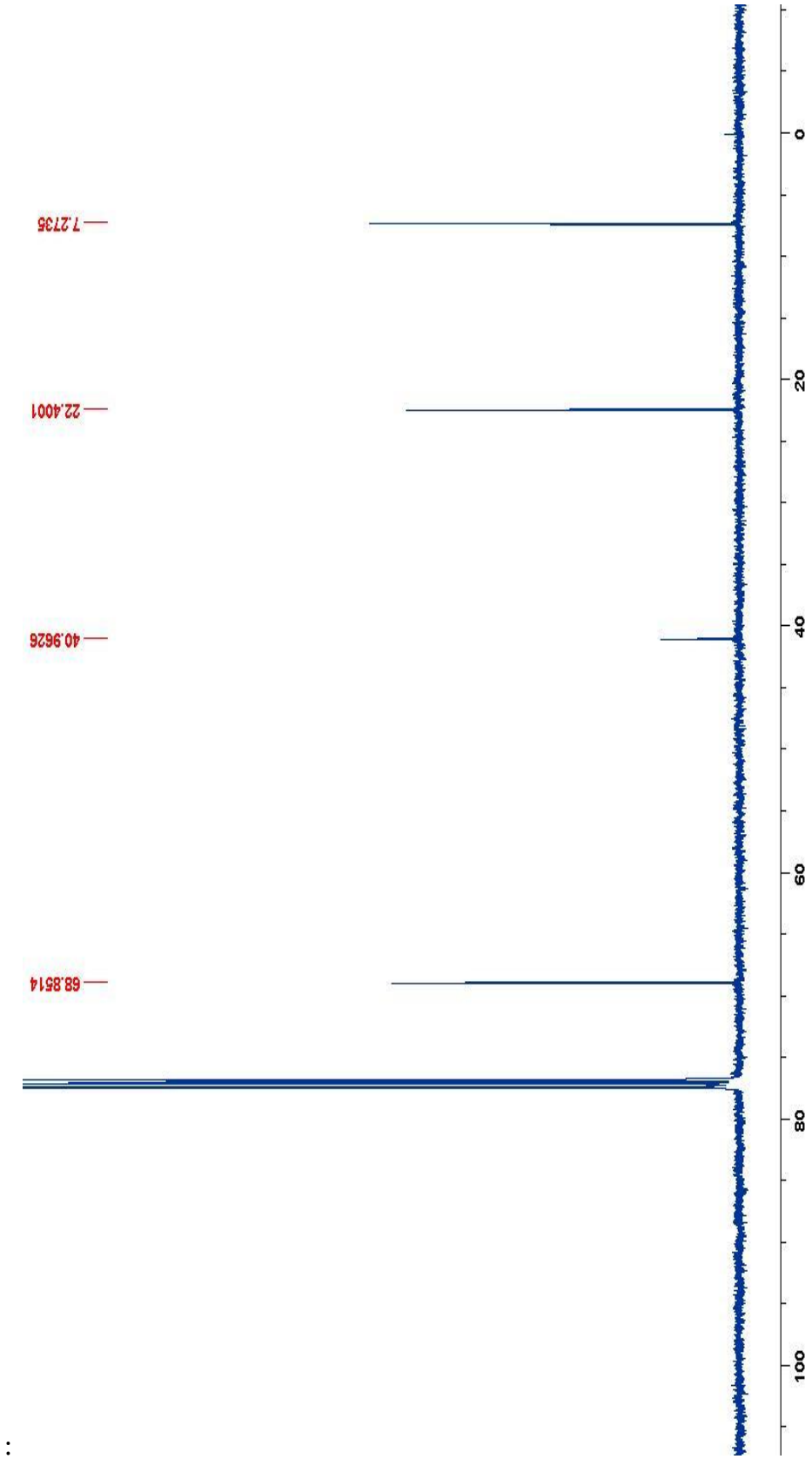

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Figure 18: ^{13}C NMR spectrum of 2-ethyl-2-(hydroxymethyl)butyl 2-phenylacetate(**20**).

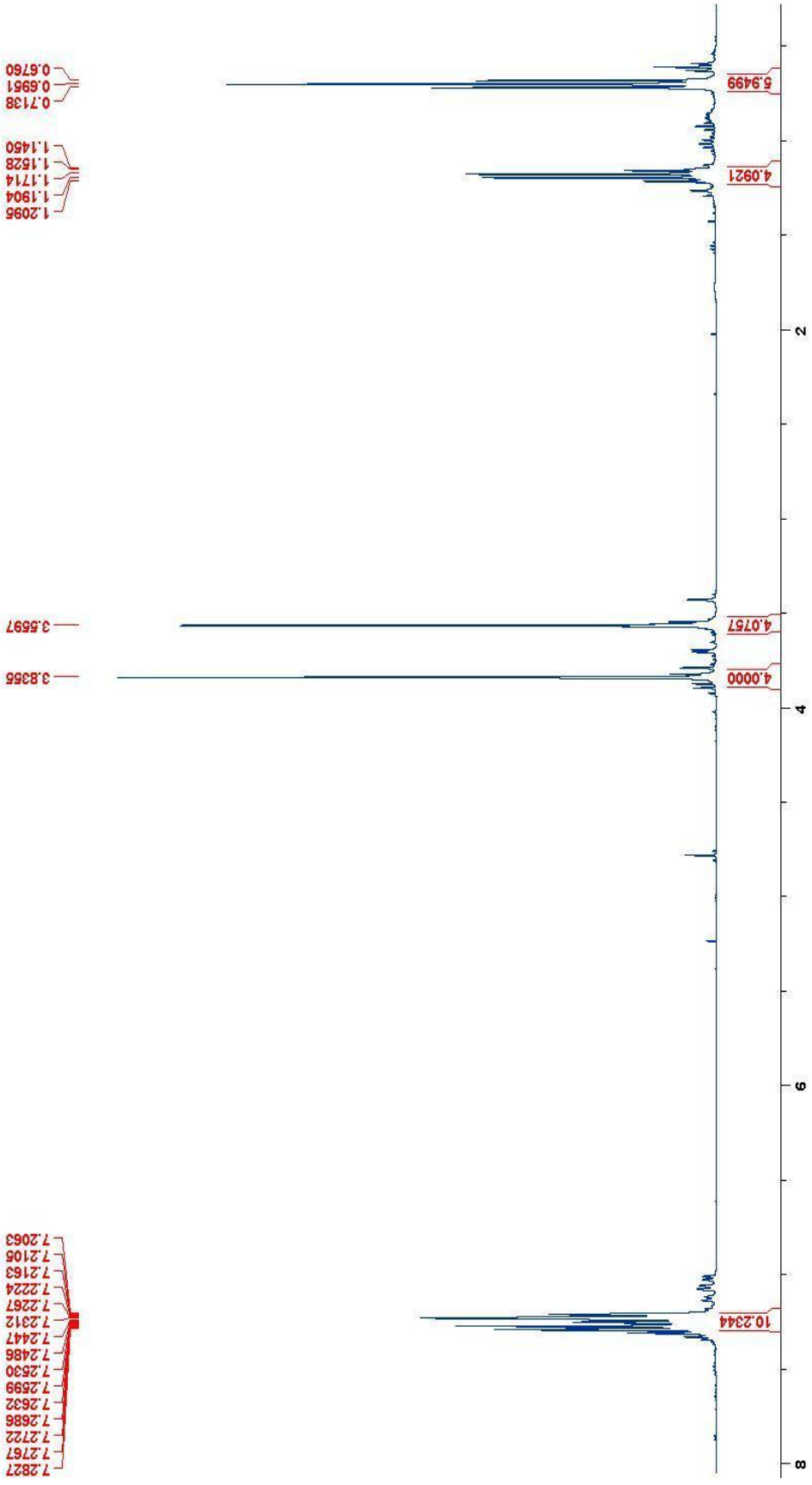

Figure 19: ^{1}H NMR spectrum of 2,2-Diethylpropane-1,3-diethyl-bis(2-phenylacetate) (**21**).

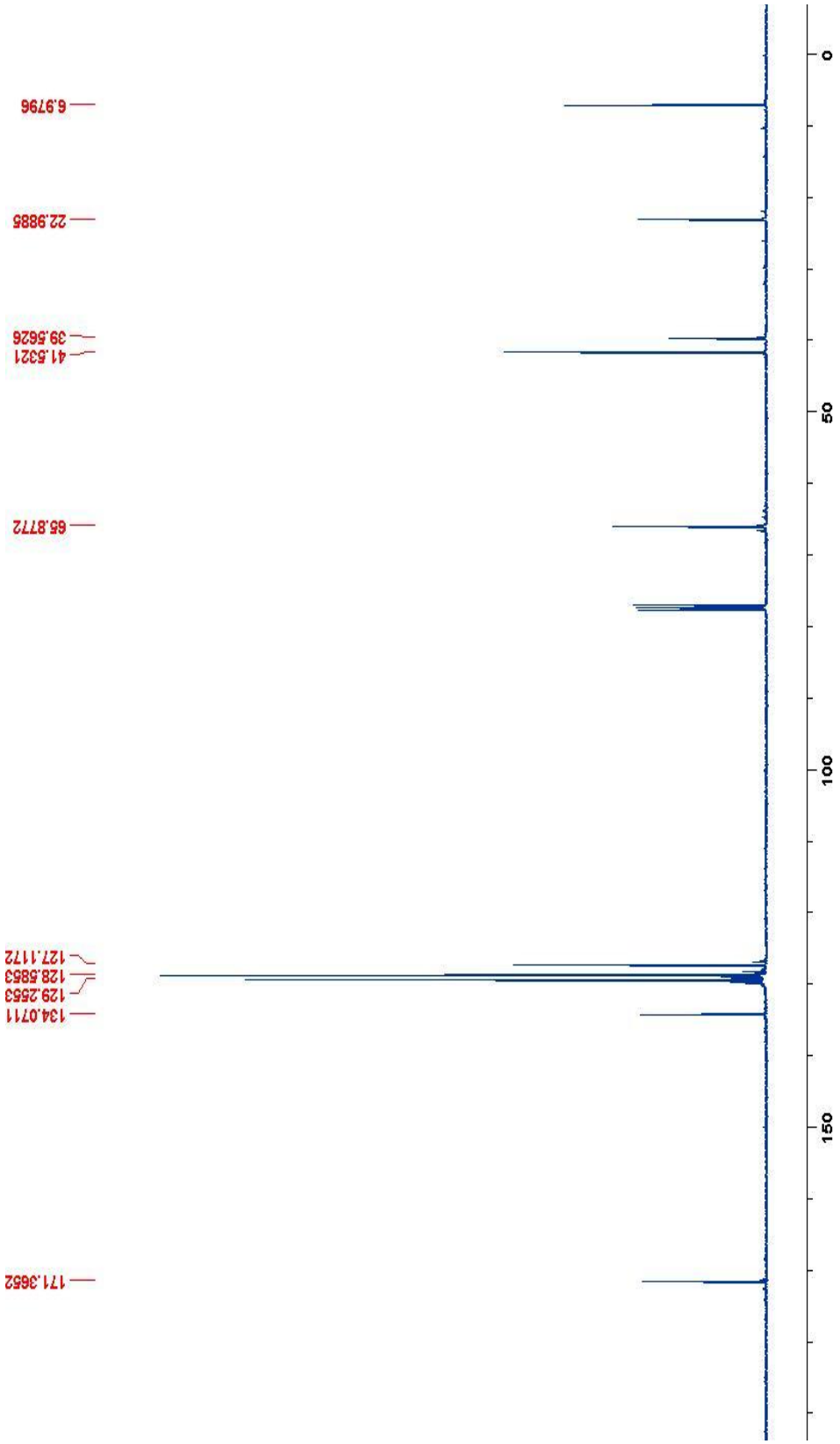

Figure 20: ^{13}C NMR spectrum of 2,2-Diethylpropane-1,3-diethyl-bis(2-phenylacetate) (**21**).

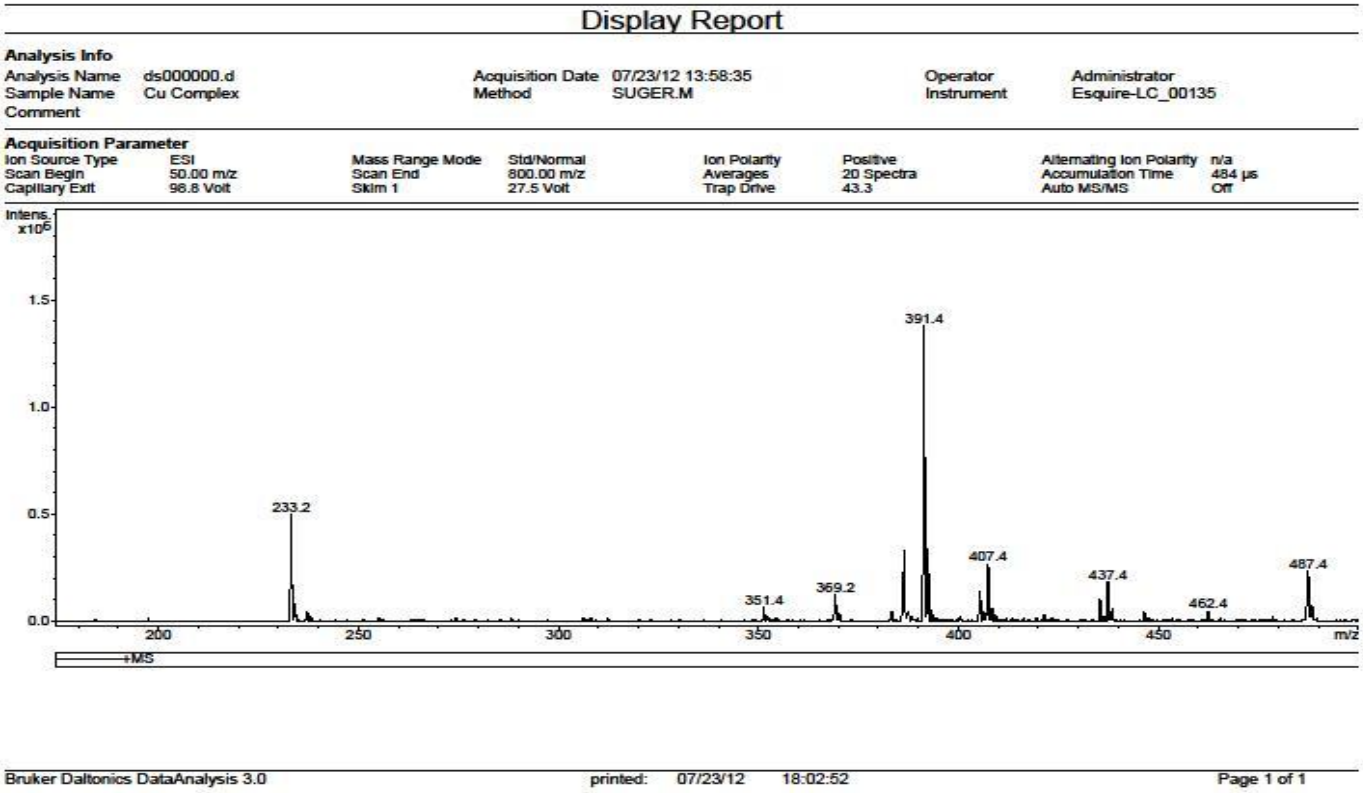

Figure 21: Mass spectrum of 2,2-Diethylpropane-1,3-diethyl-bis(2-phenylacetate) (**21**).

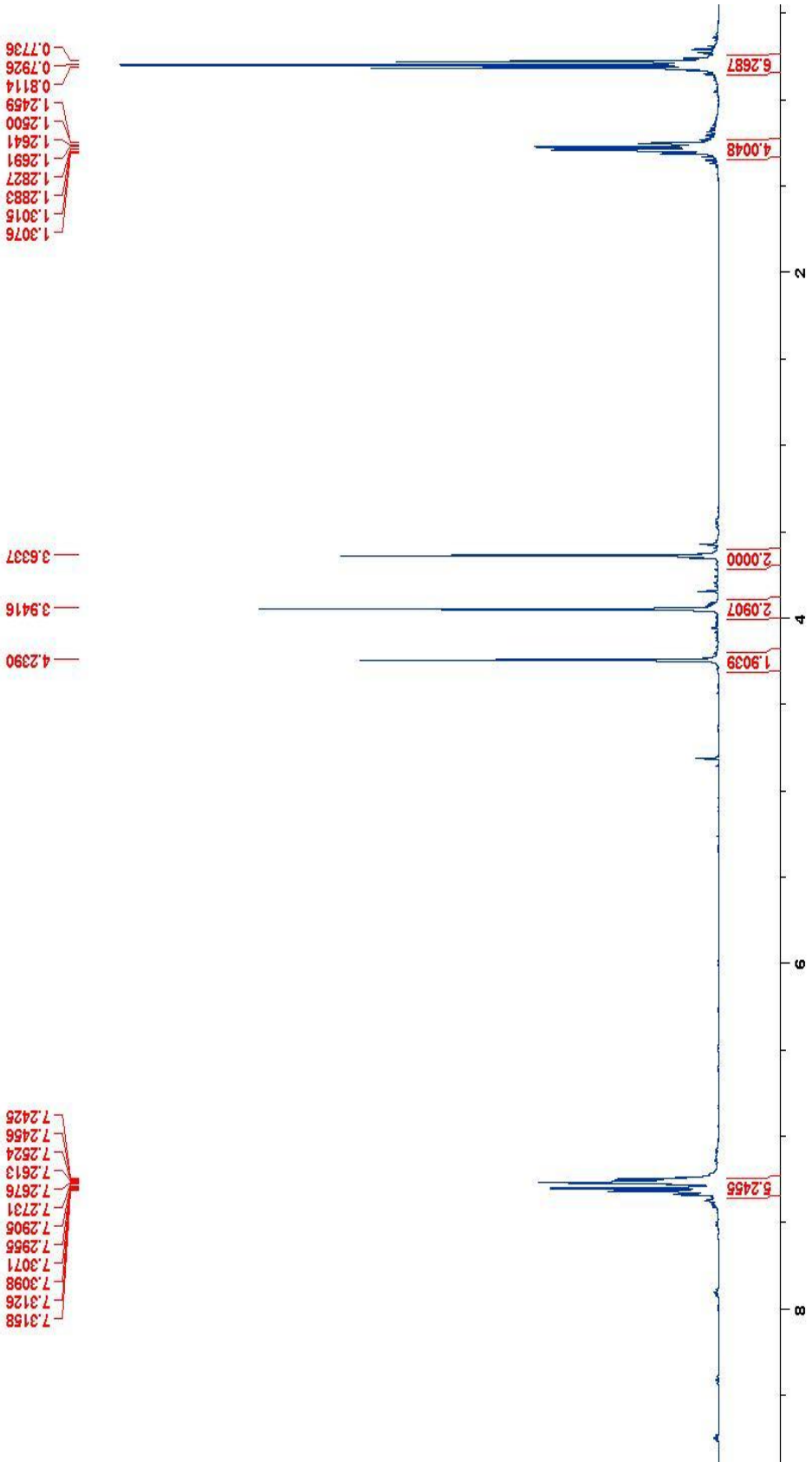

Figure 22: ^{1}H NMR spectrum of 3-(((trifluoromethyl)sulfonyl)oxy)propyl-2-phenylacetate (**22**).

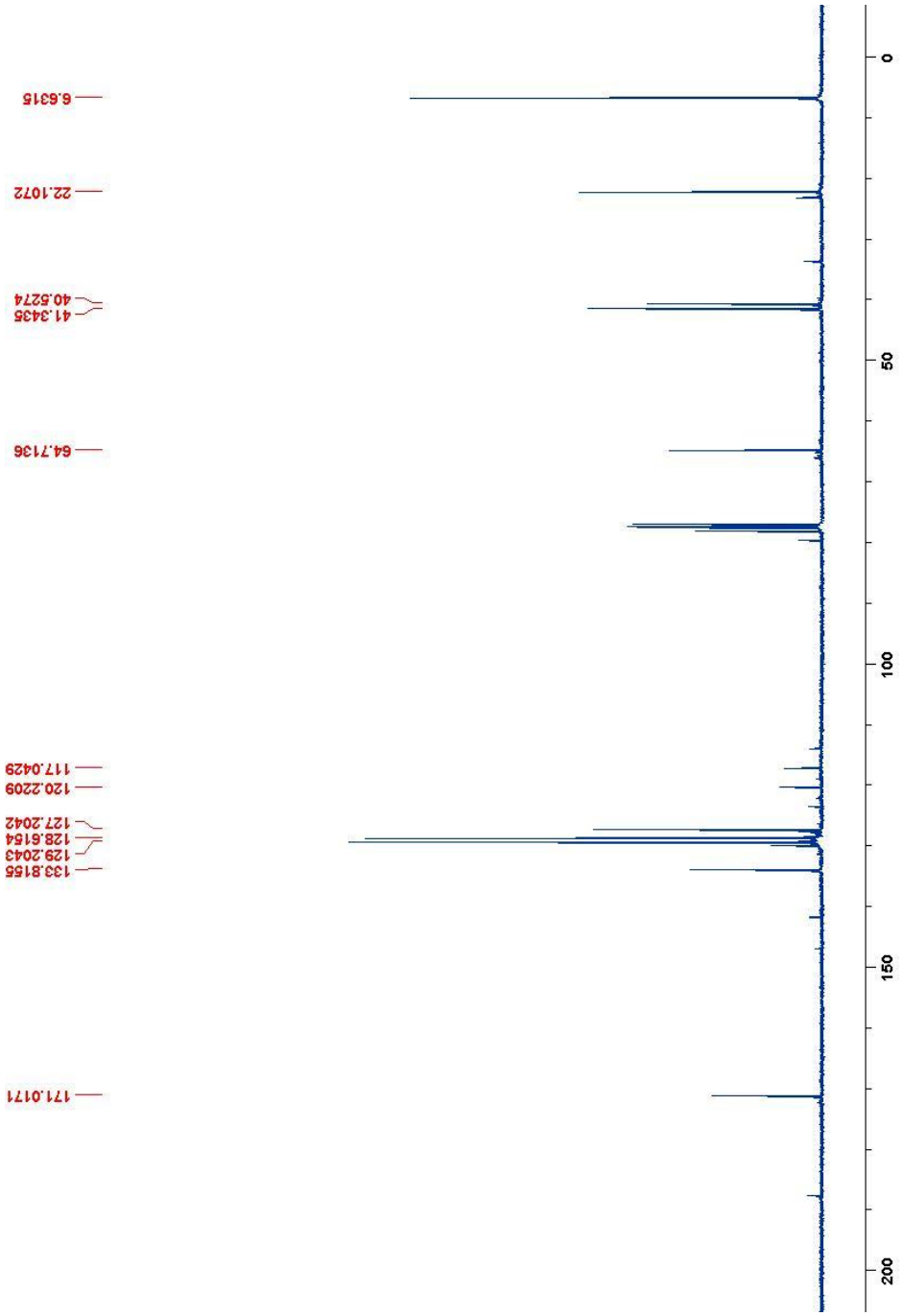

Figure 23: ^{13}C NMR spectrum of 3-(((trifluoromethyl)sulfonyl)oxy)propyl-2-phenylacetate (**22**).

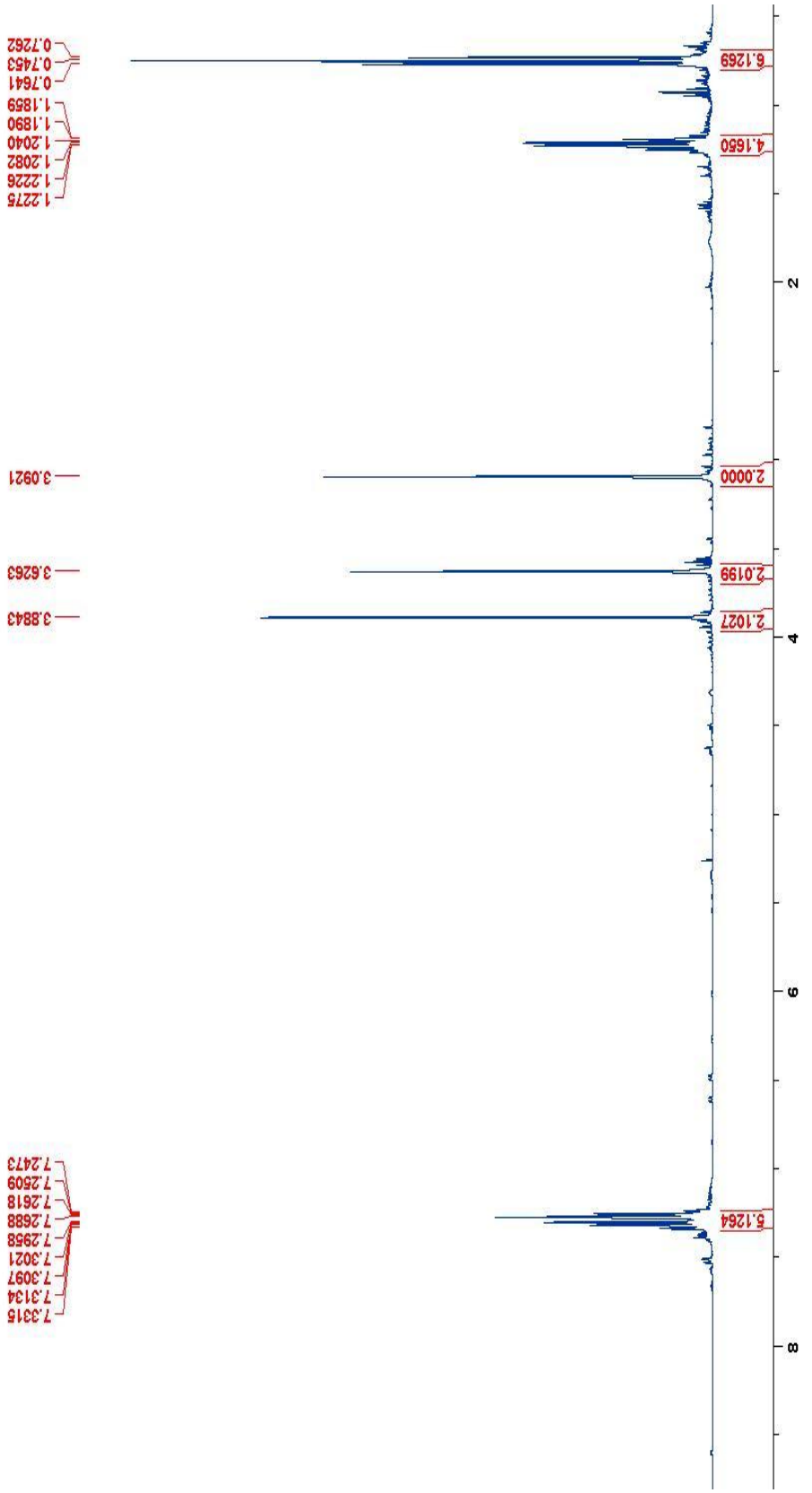

Figure 24: ^{1}H NMR spectrum of 2-(azidomethyl)-2-ethylbutyl 2-phenylacetate (**23**).

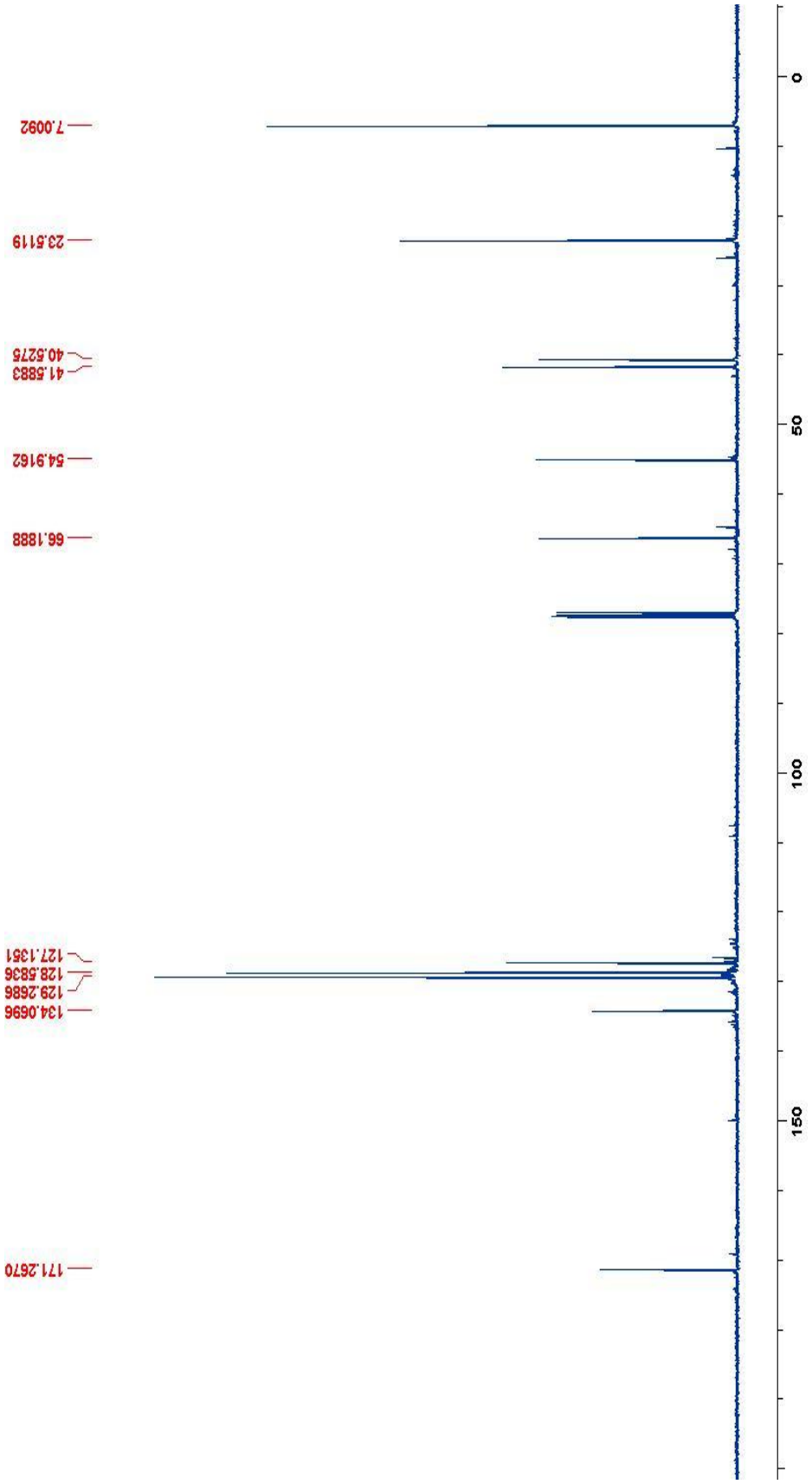

Figure 25: ^{13}C NMR spectrum of 2-(azidomethyl)-2-ethylbutyl 2-phenylacetate (**23**).

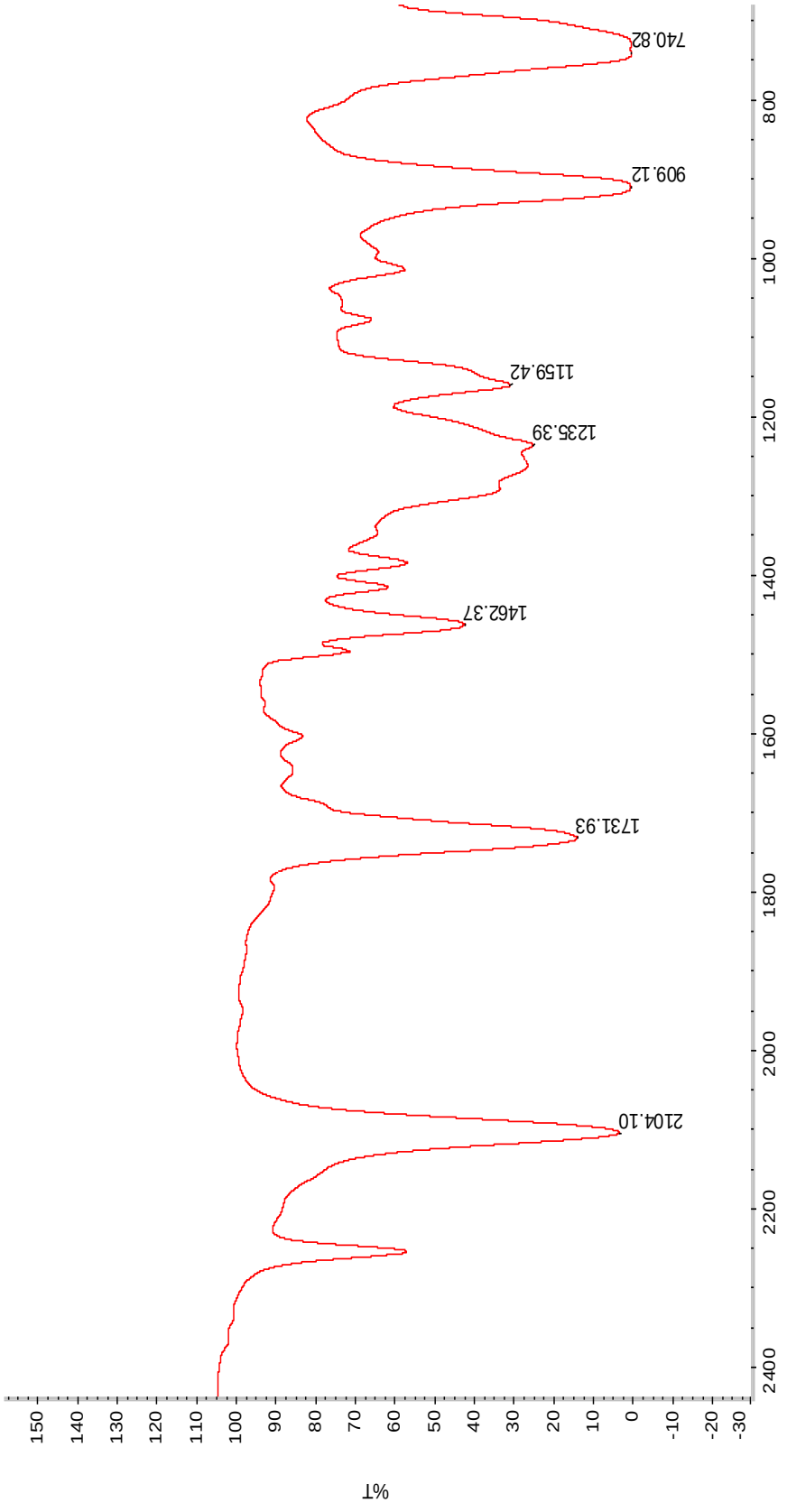

Figure 26: Infrared spectrum of 2-(azidomethyl)-2-ethylbutyl 2-phenylacetate (**23**).

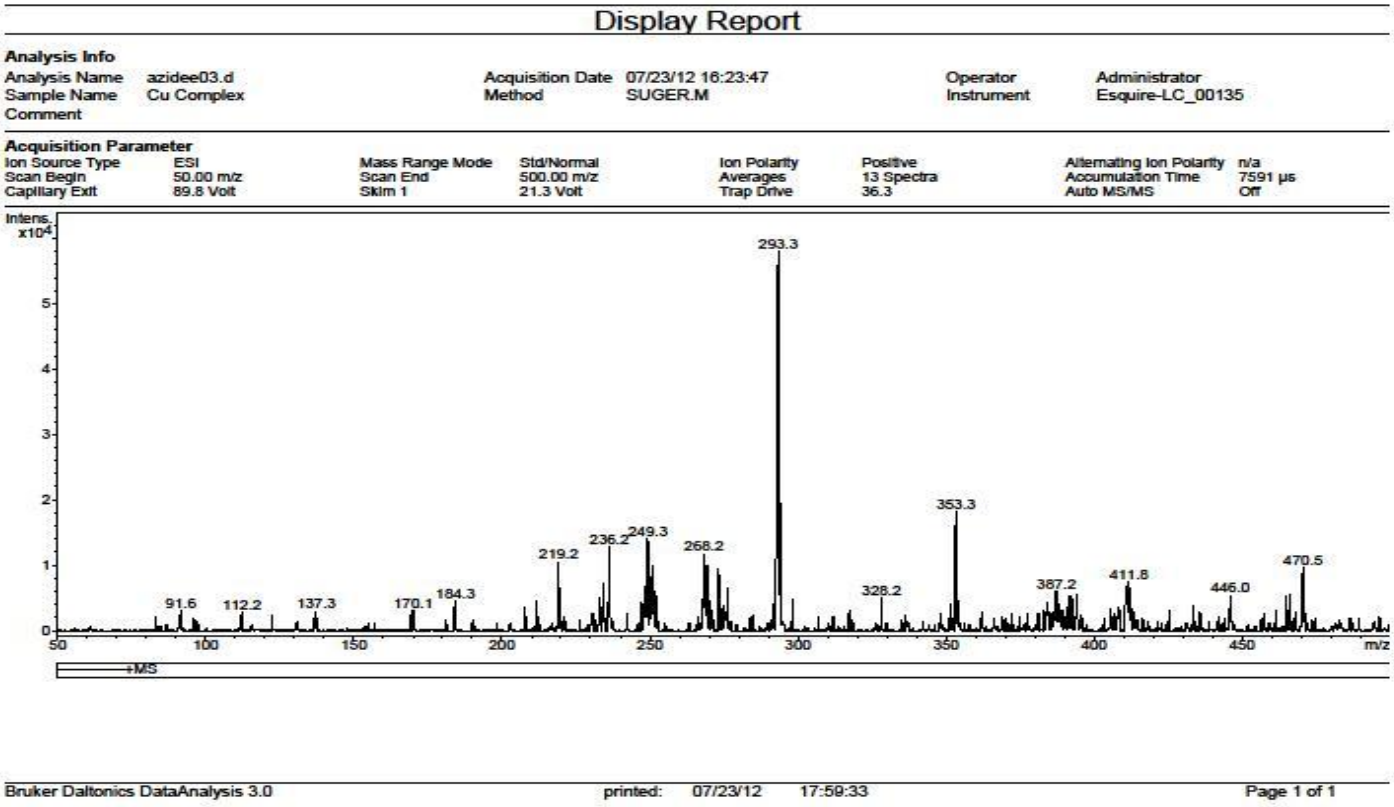

Figure 27: Mass spectrum of 2-(azidomethyl)-2-ethylbutyl 2-phenylacetate (**23**).

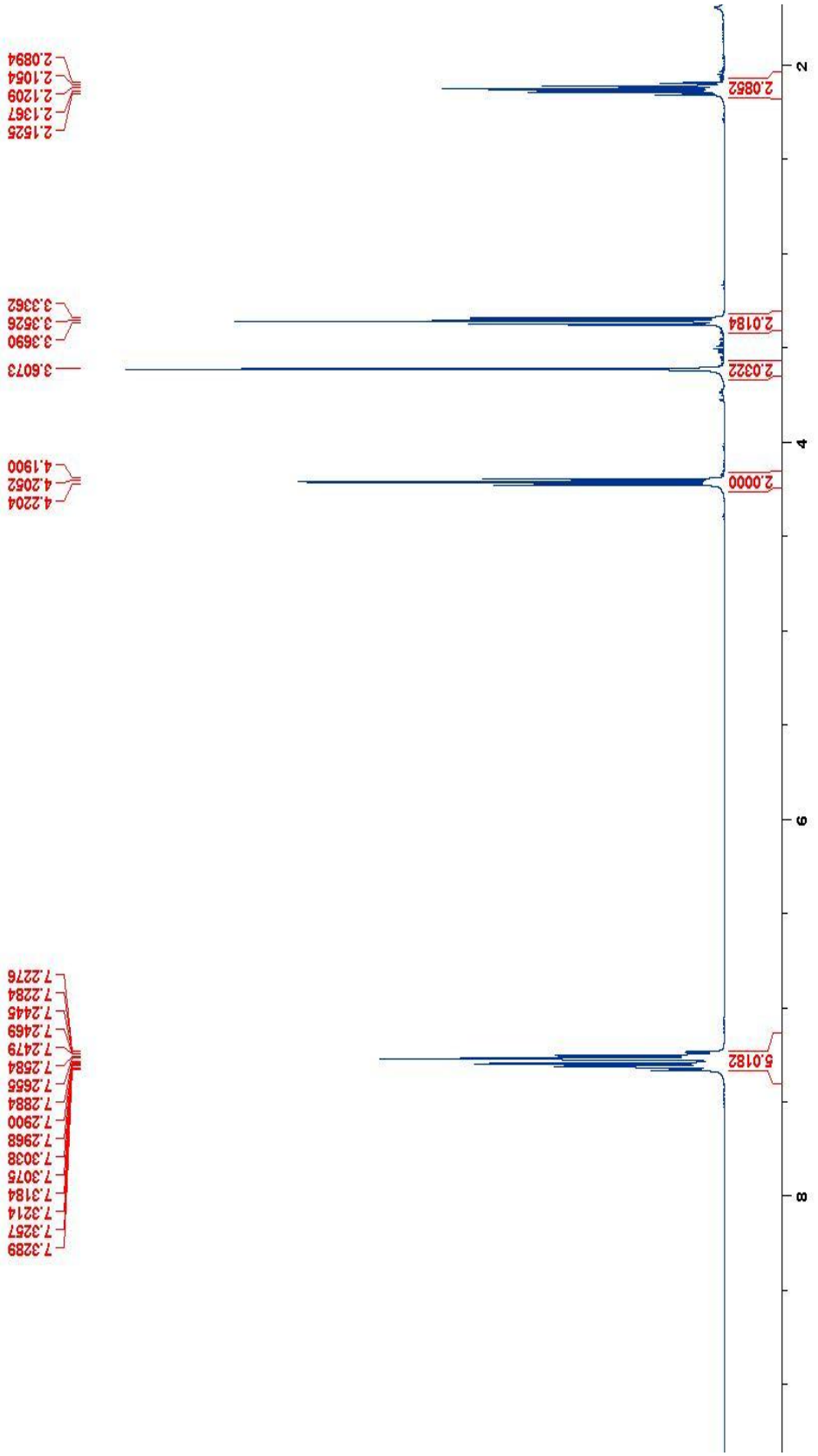

Figure 28: ^{1}H NMR spectrum of 3-bromo 2-phenylacetate (**26**).

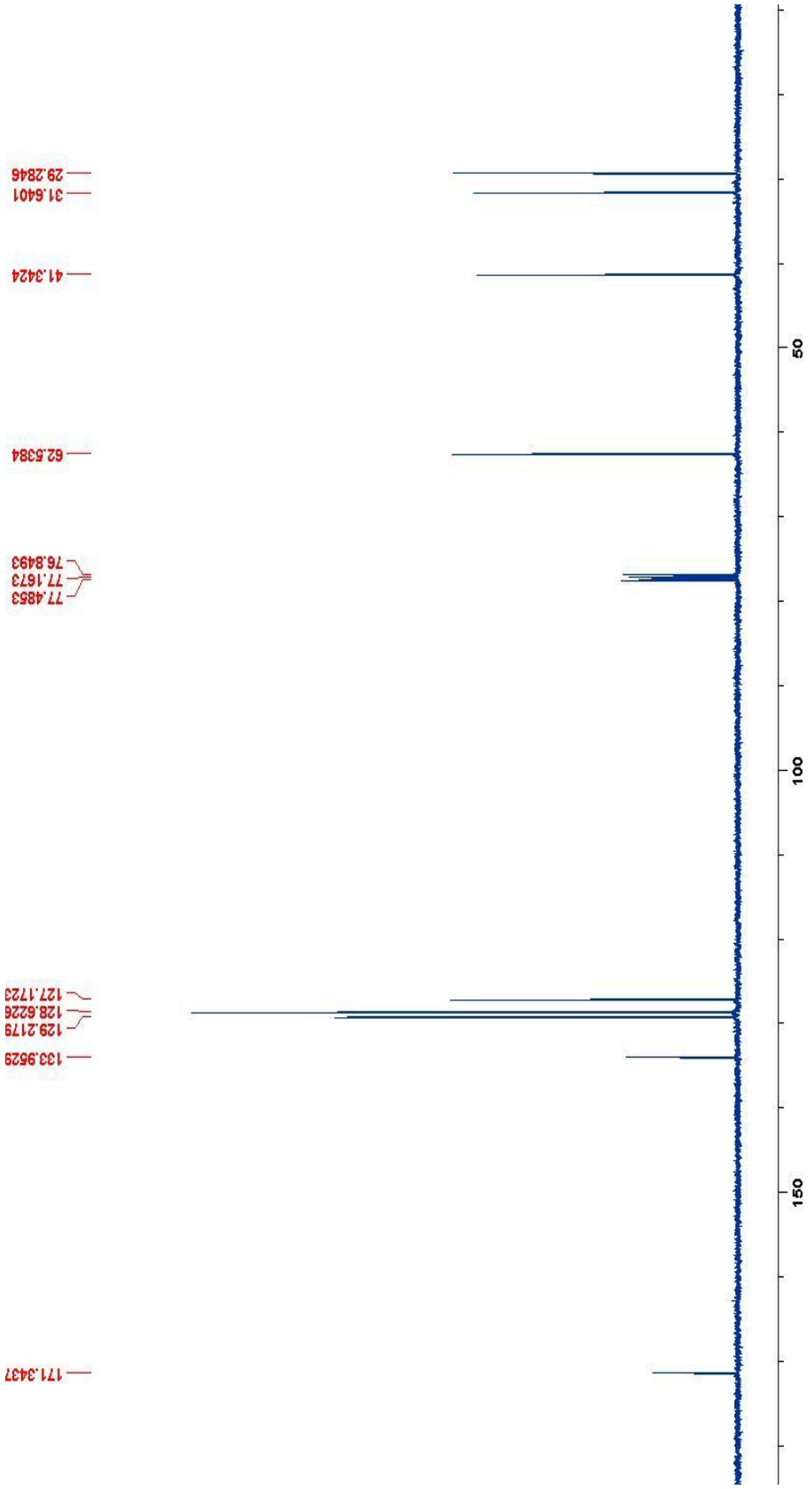

Figure 29: ^{13}C NMR spectrum of 3-bromo 2-phenylacetate (**26**).

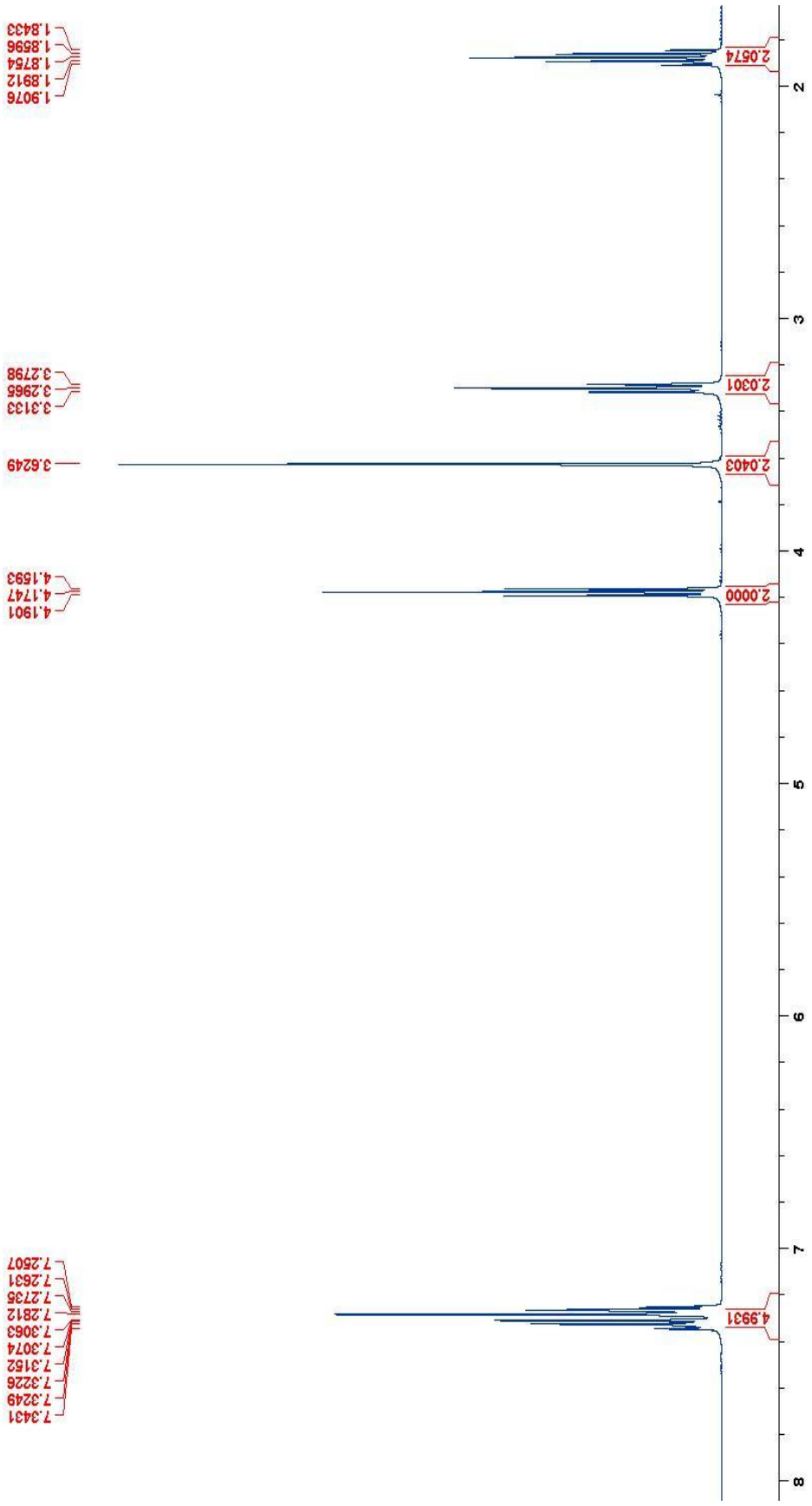

Figure 30: ^{1}H NMR spectrum of 3-azidopropyl 2-phenylacetate (**27**).

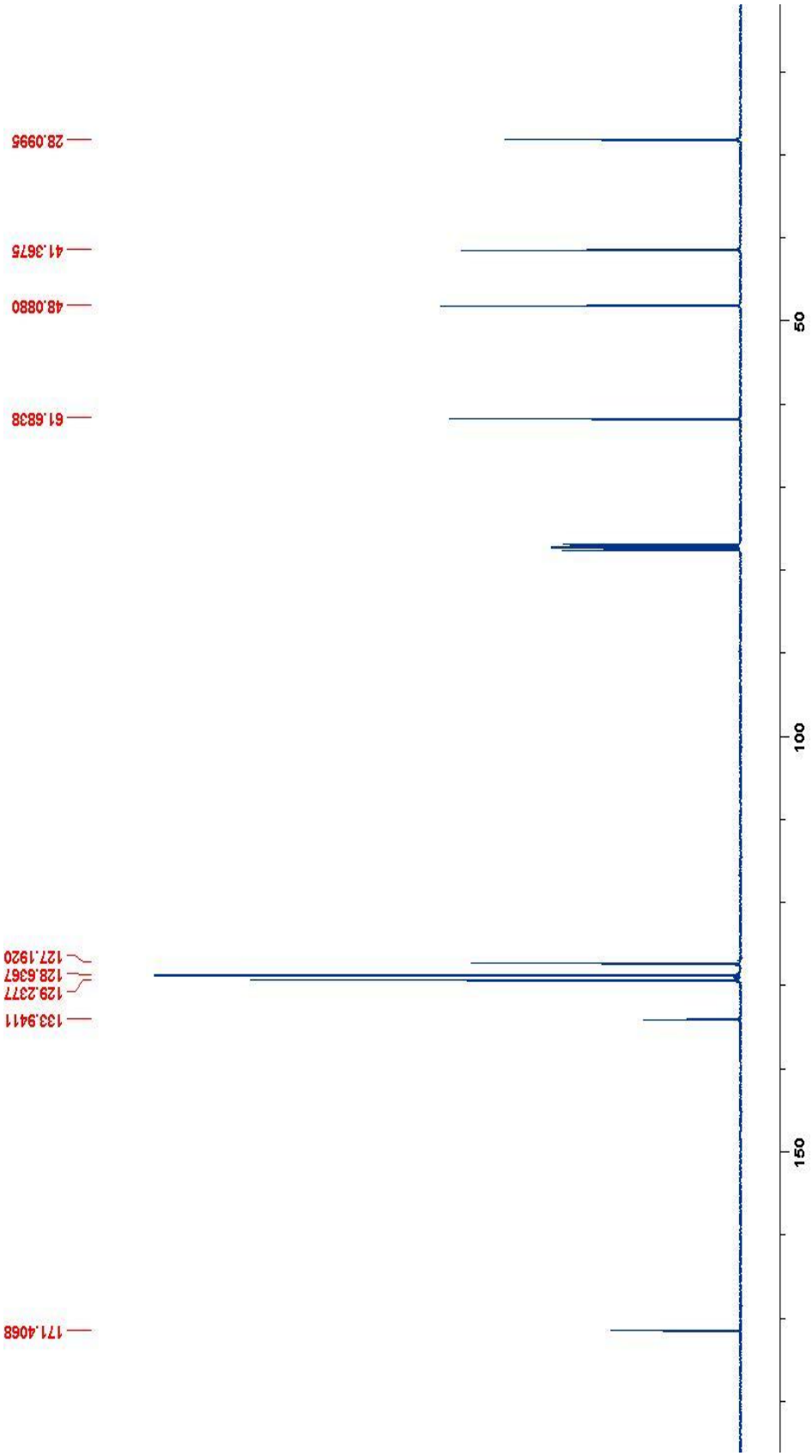

Figure 31: ^{13}C NMR spectrum of 3-azidopropyl 2-phenylacetate (**27**).

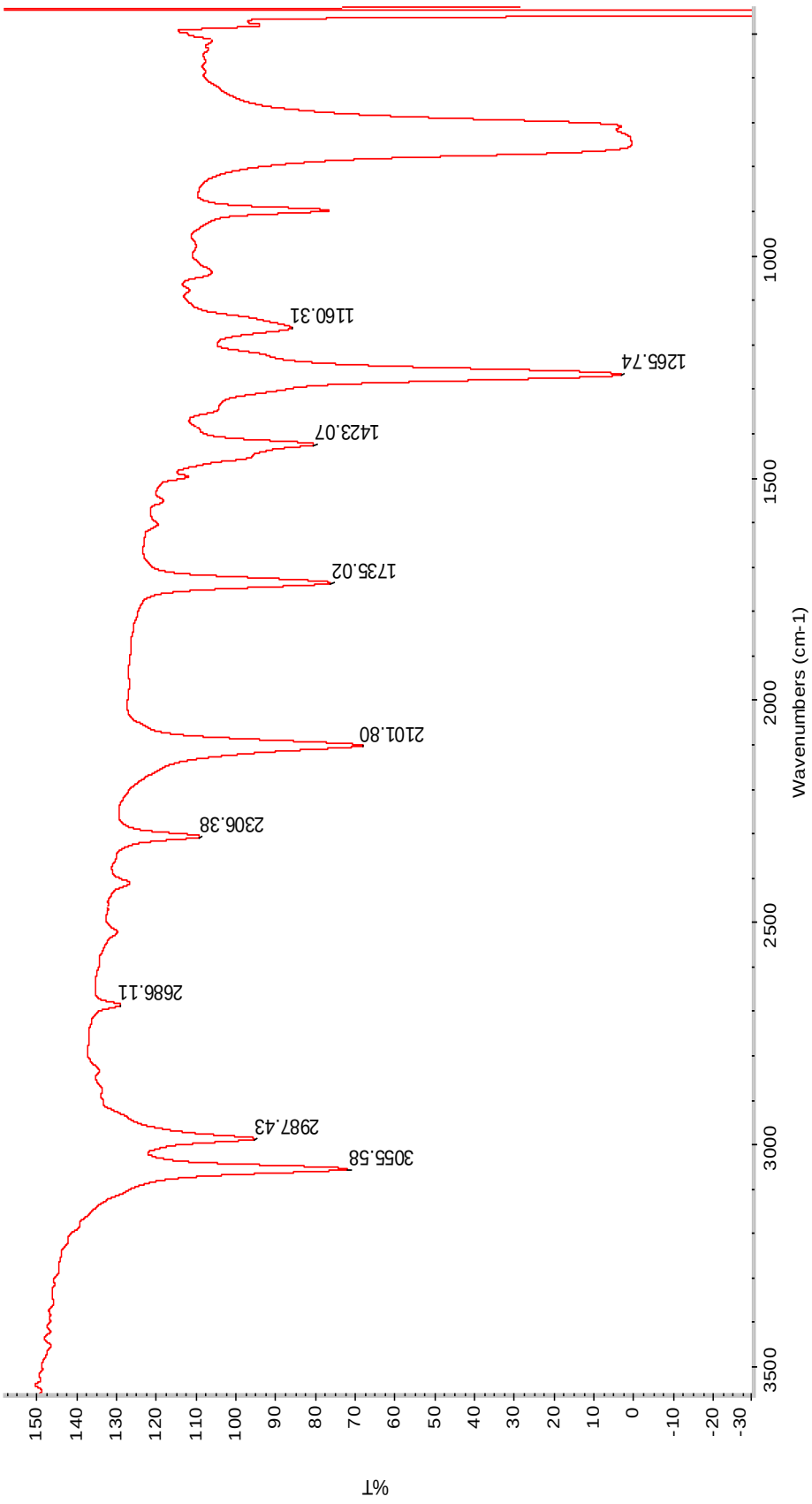

Figure 32: Infrared spectrum of 3-azidopropyl 2-phenylacetate (**27**).

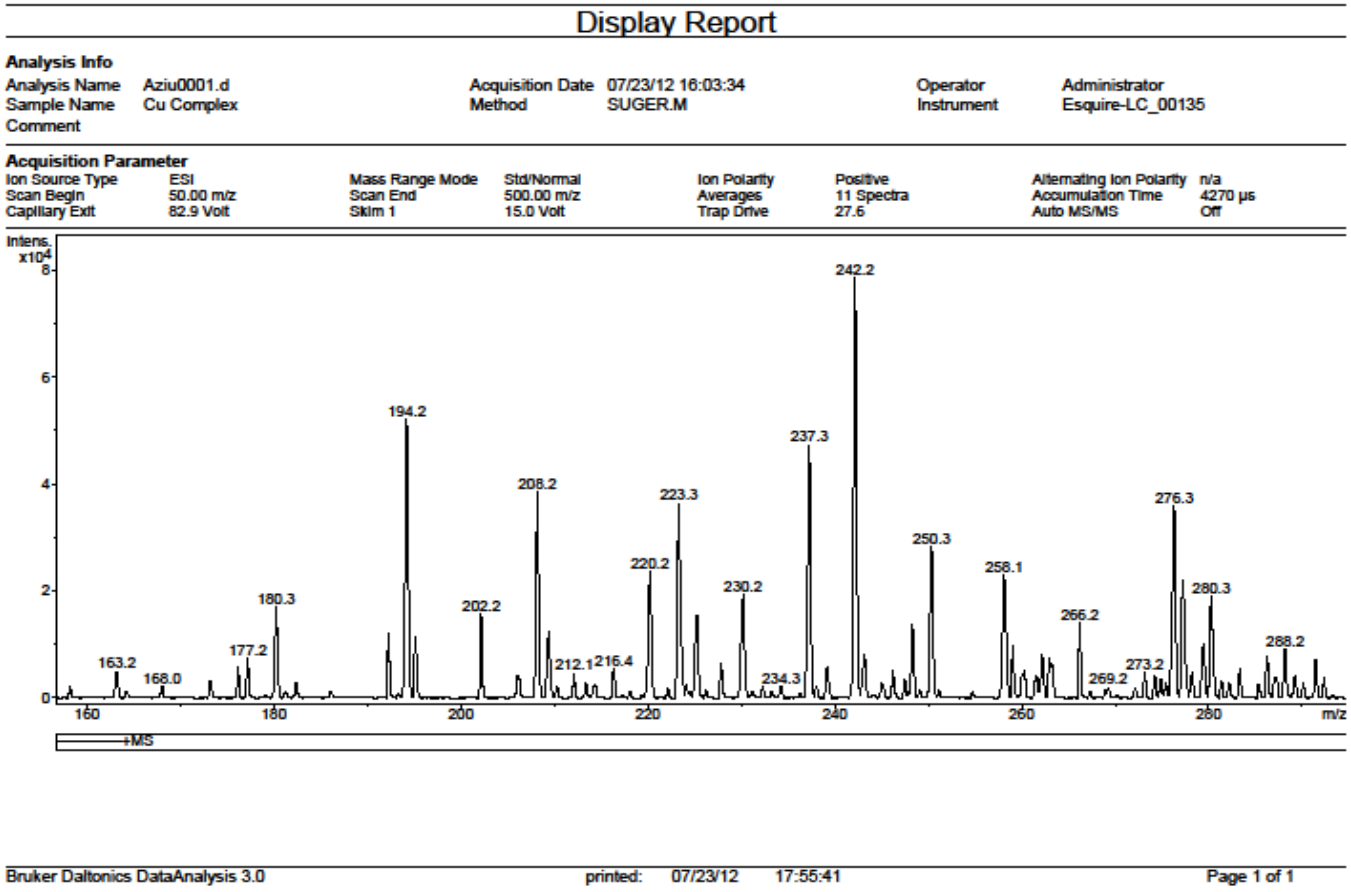

Figure 33: Mass spectrum of 3-azidopropyl 2-phenylacetate (**27**).

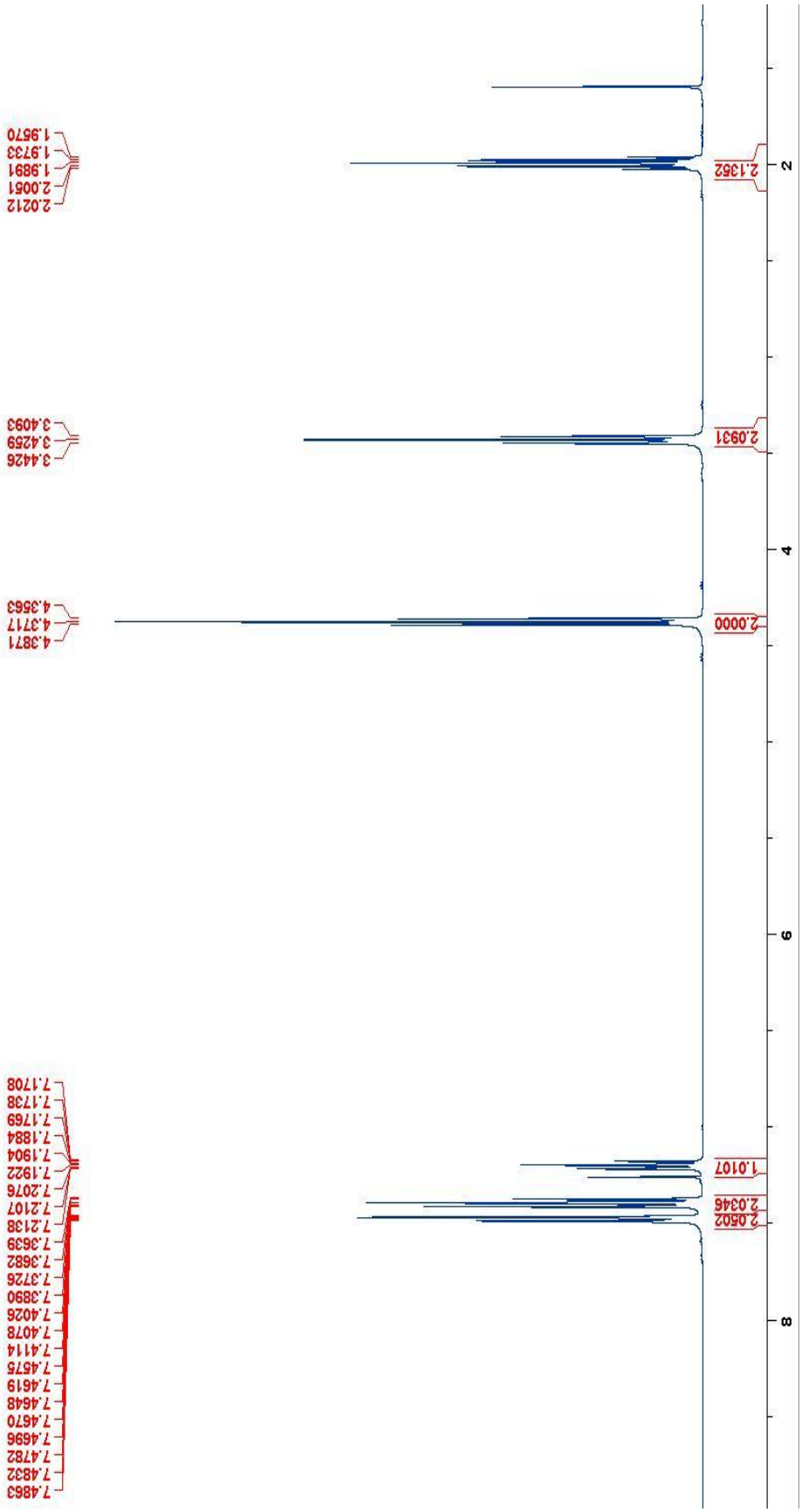

Figure 34: ^{1}H NMR spectrum 3-azidopropyl 2-diazo-2-phenylacetate (**28**).

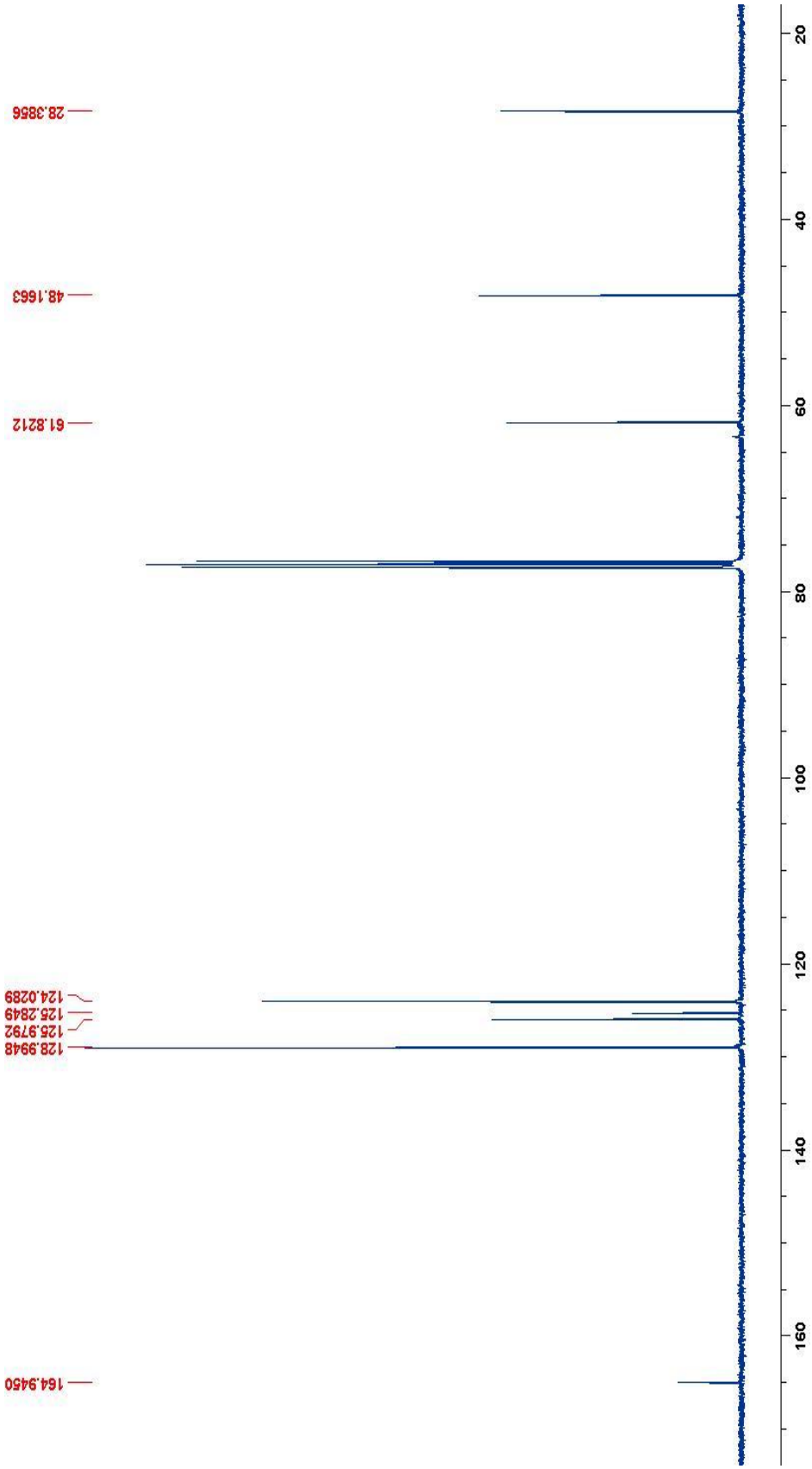

Figure 35: ^{13}C NMR spectrum 3-azidopropyl 2-diazo-2-phenylacetate (**28**).

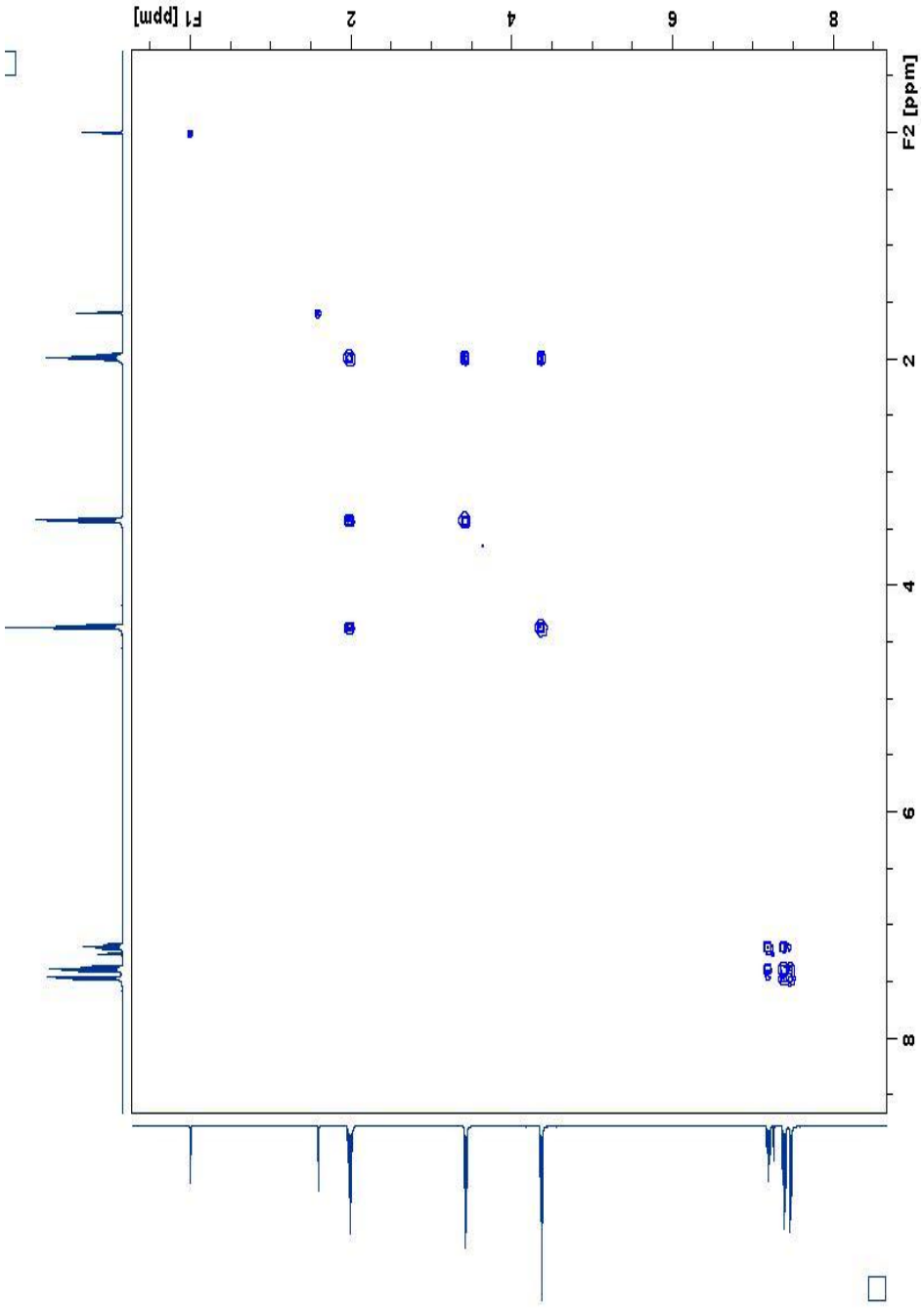

Figure 36: Cosy NMR spectrum 3-azidopropyl 2-diazo-2-phenylacetate (**28**).

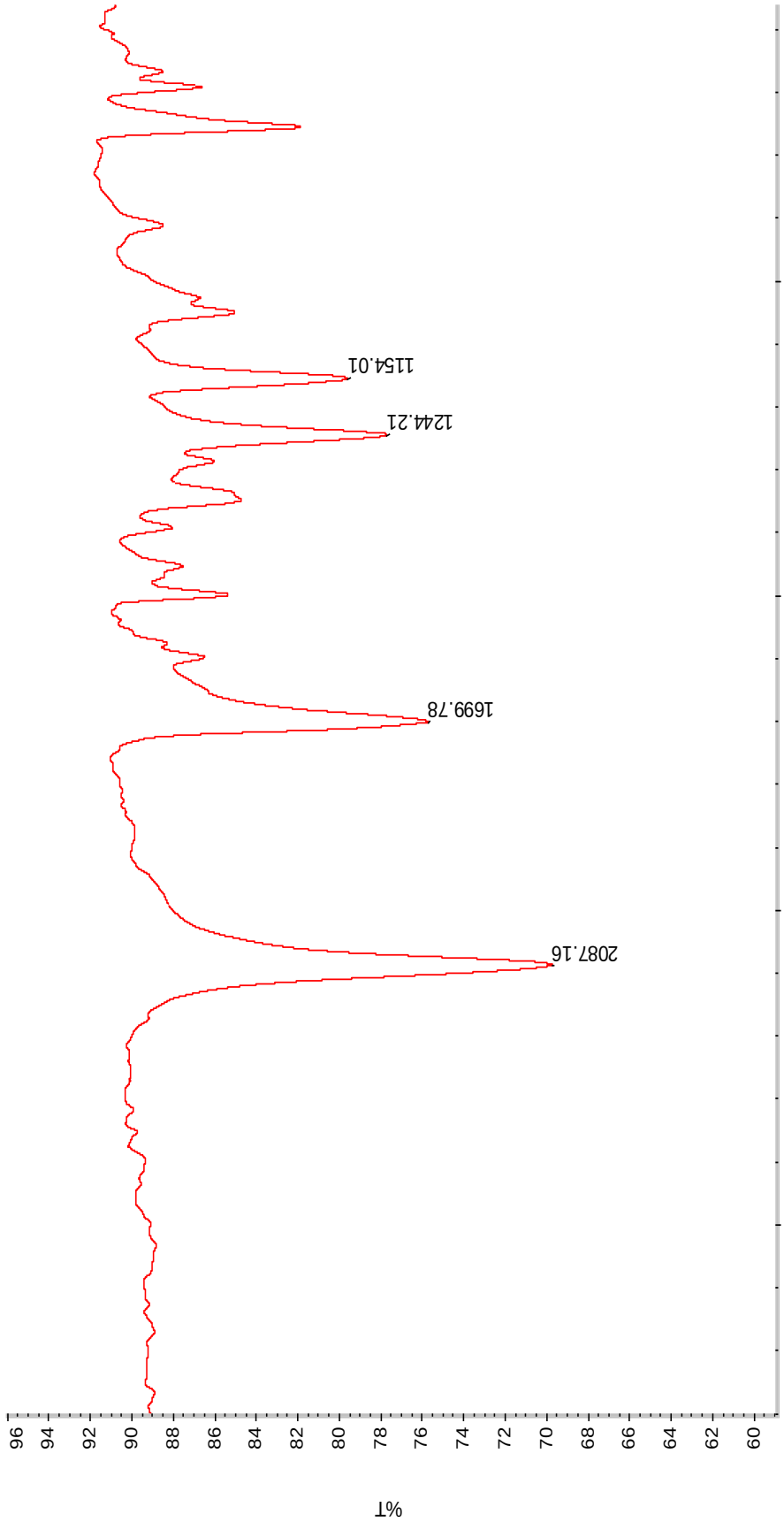

Figure 37: Infrared spectrum of 3-azidopropyl 2-diazo-2-phenylacetate (**28**).

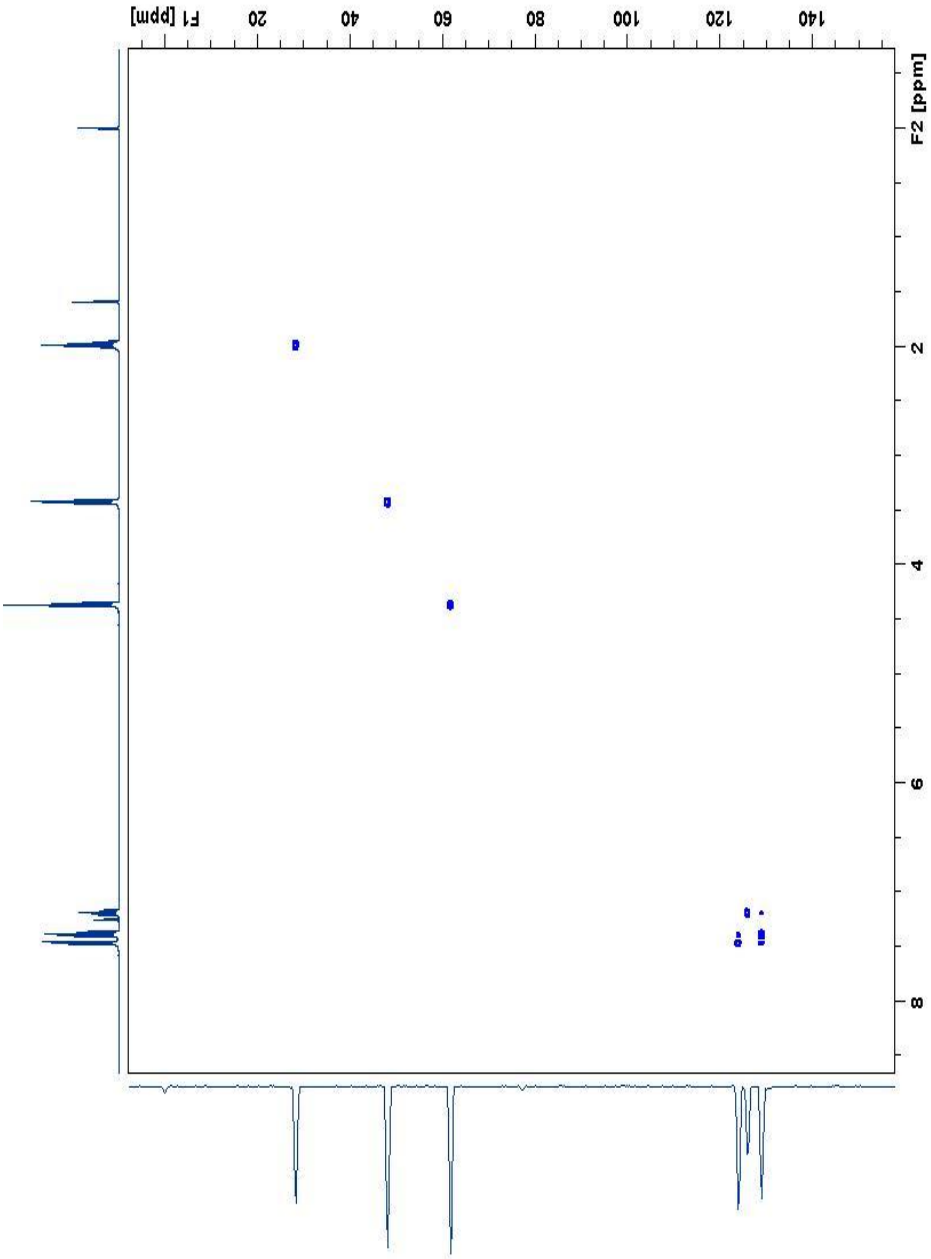

Figure 38: HSQC NMR of 3-azidopropyl 2-diazo-2-phenylacetate (**28**).

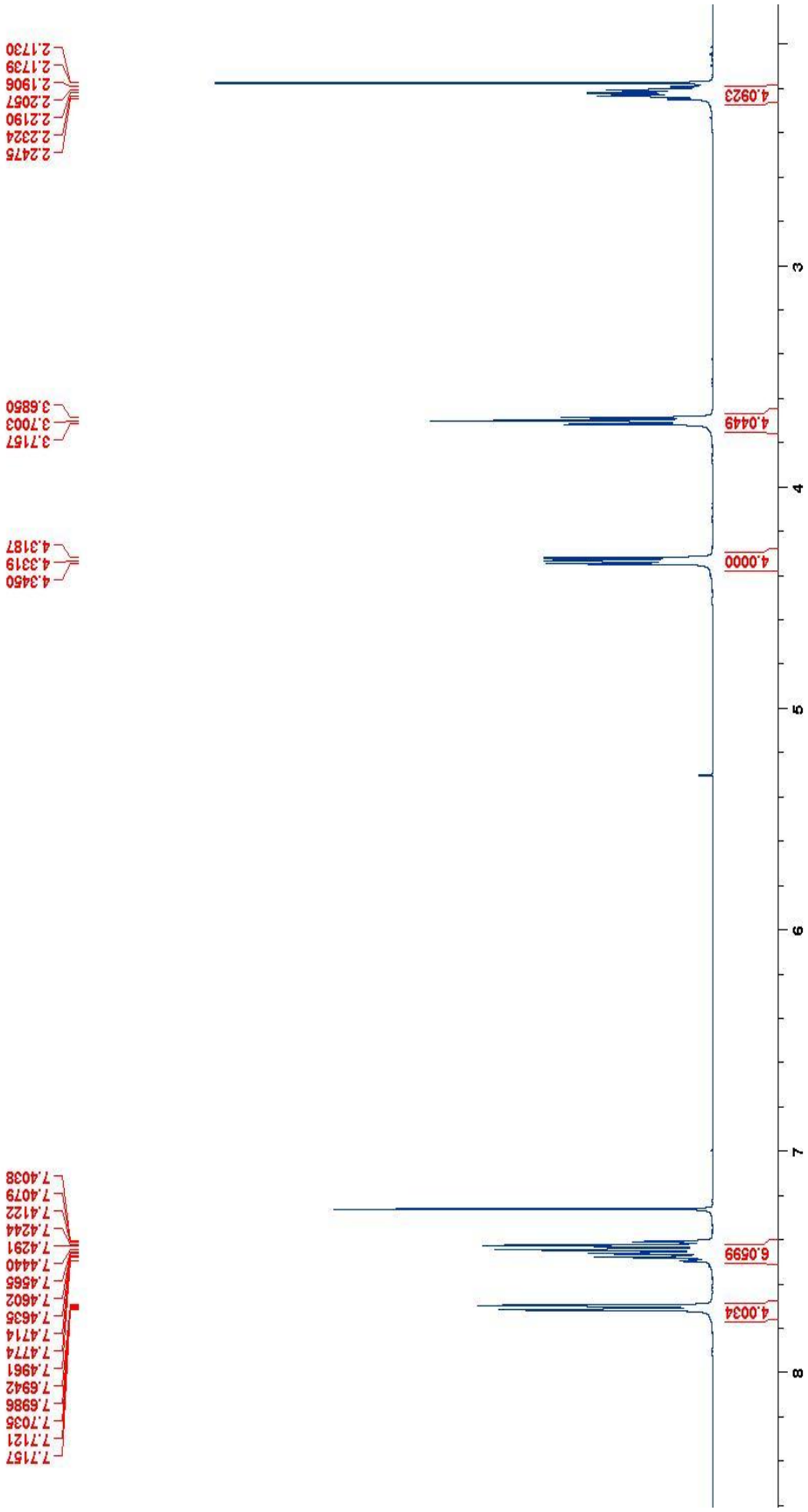

Figure 39: ^{1}H NMR spectrum of (3Z,10Z)-3,10-diphenyl-1,8-dioxa-4,11-diazacyclotetradeca-3,10-diene-2,9-dione (**29**).

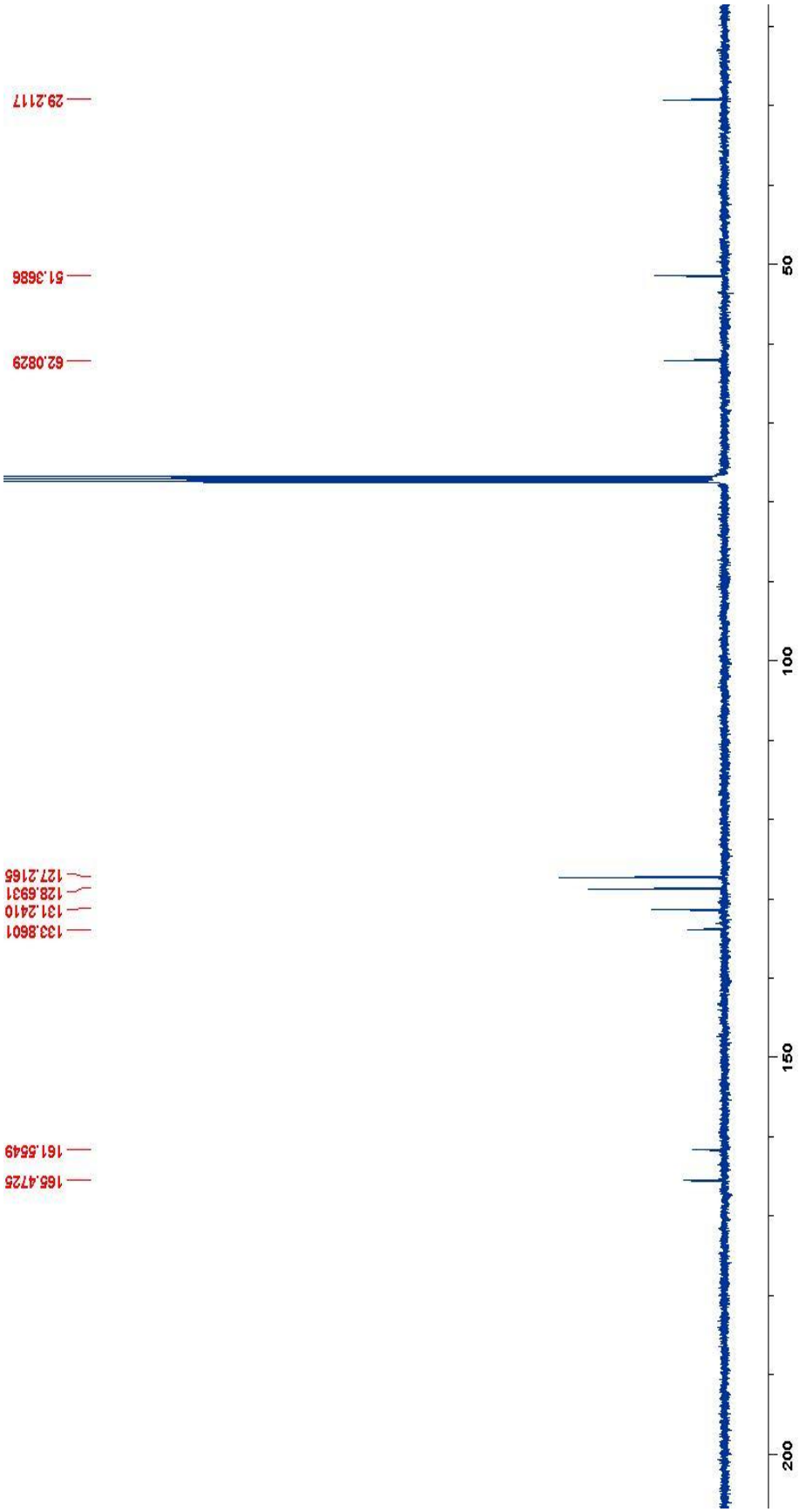

Figure 40: ^{13}C NMR spectrum of (3Z,10Z)-3,10-diphenyl-1,8-dioxa-4,11-diazacyclotetradeca-3,10-diene-2,9-dione (**29**).

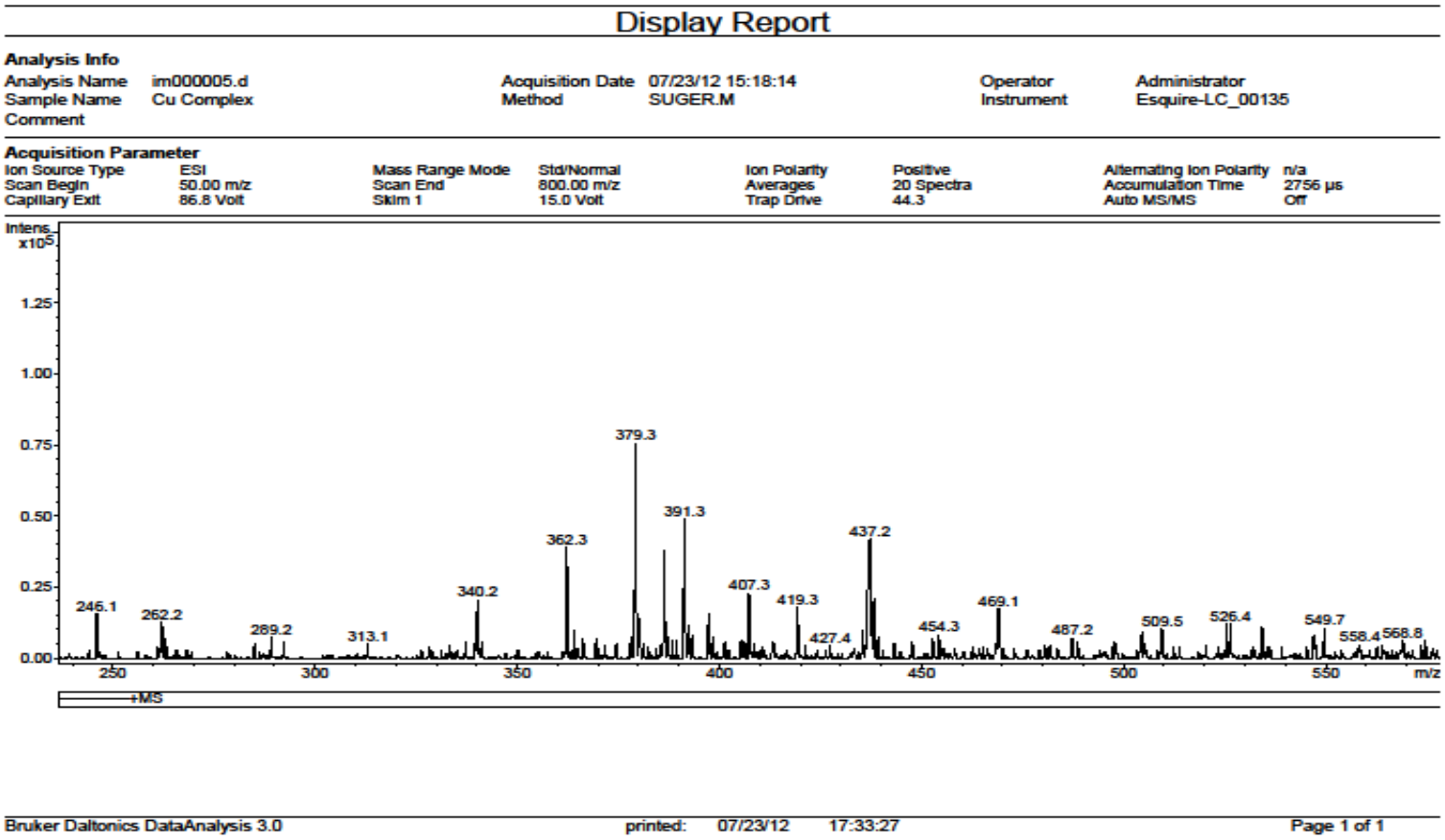

Figure 41: Mass spectrum spectrum of(3Z,10Z)-3,10-diphenyl-1,8-dioxa-4,11-diazacyclotetradeca-3,10-diene-2,9-dione (**29**).

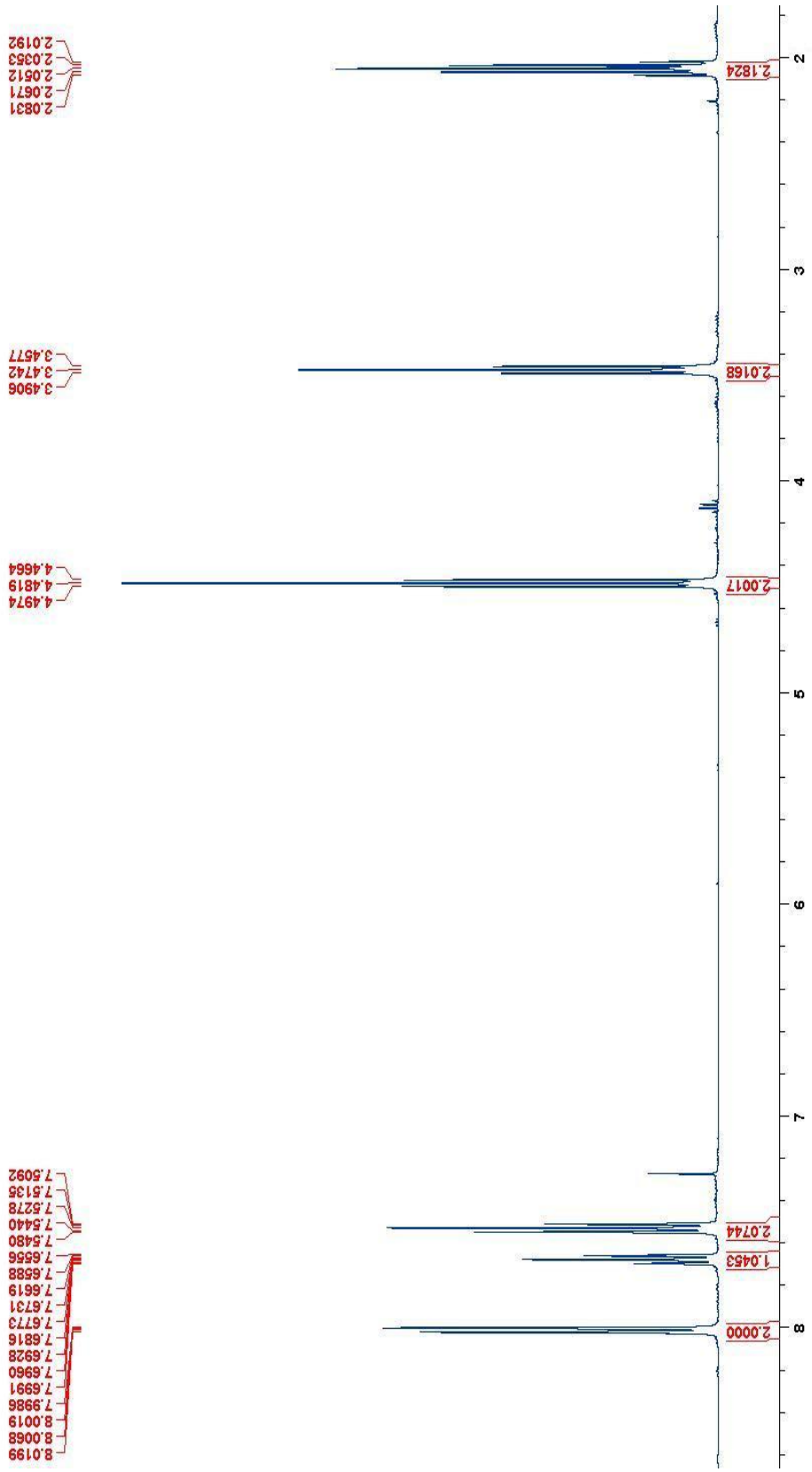

Figure 42: ^{1}H NMR spectrum of azido Ketoester (**30**).

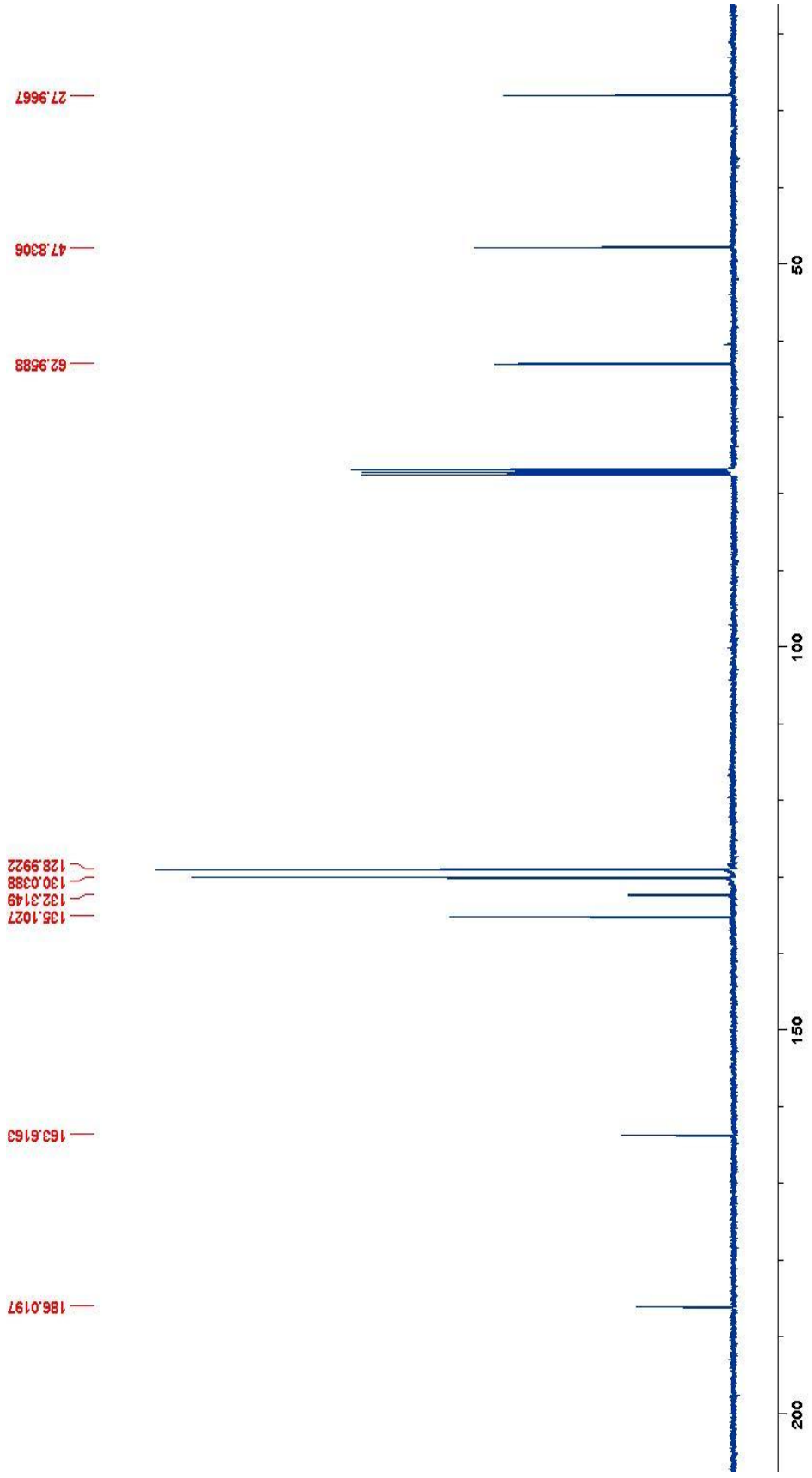

Figure 43: ^{13}C NMR spectrum of azido Ketoester (**30**).

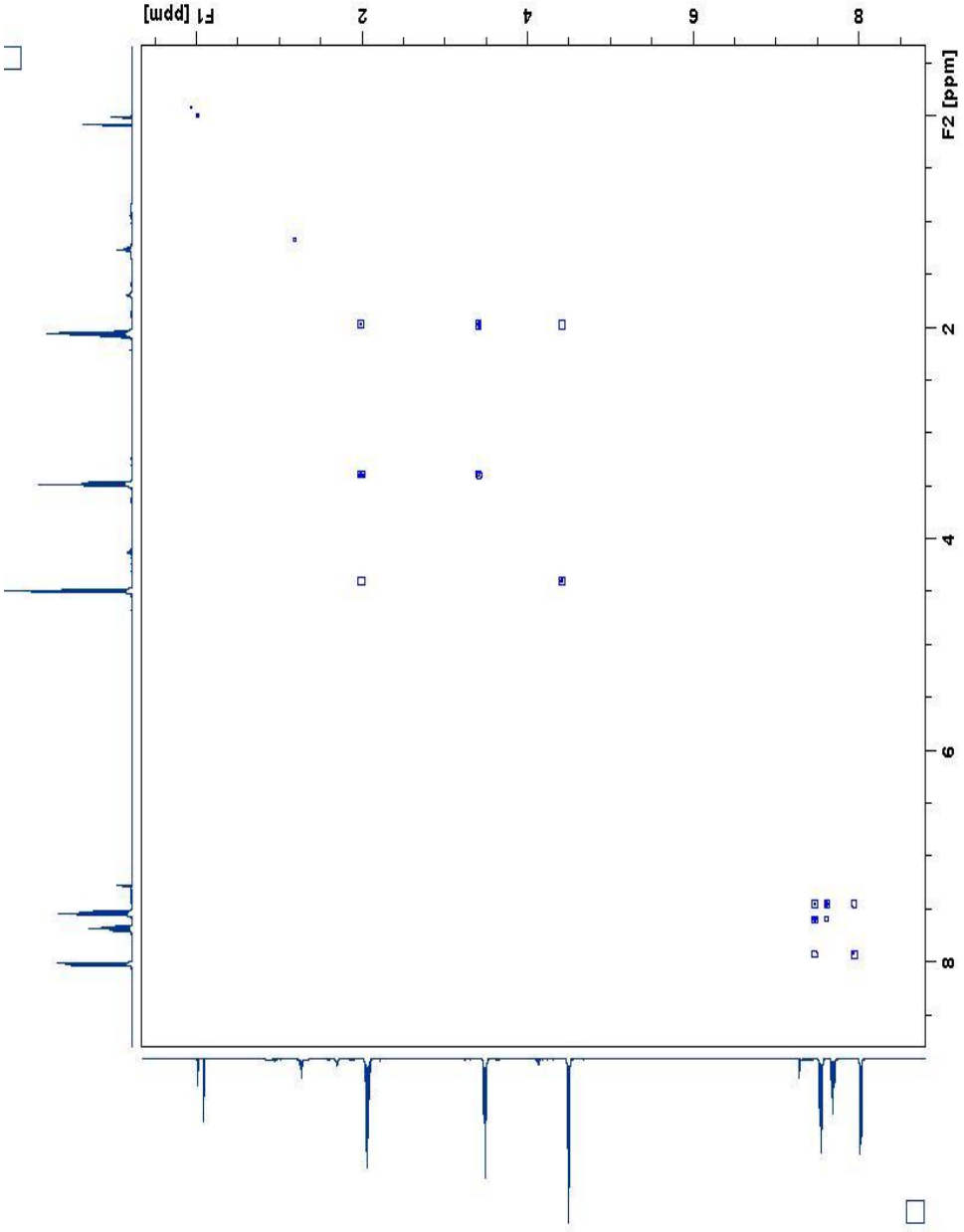

Figure 44: Cosy NMR spectrum of azido Ketoester (**30**).

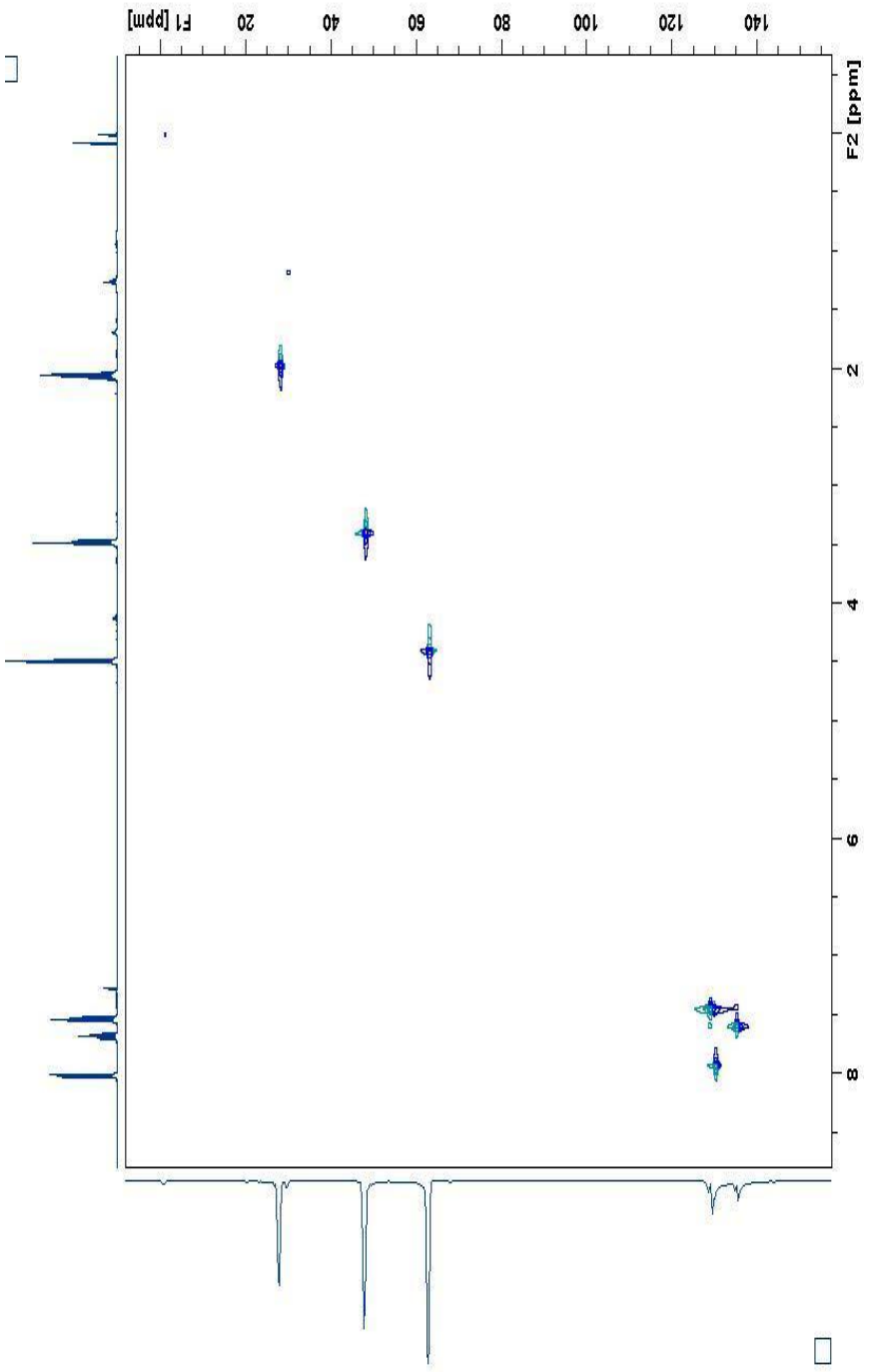

Figure 45: HSQC NMR spectrum of azido Ketoester (**30**).

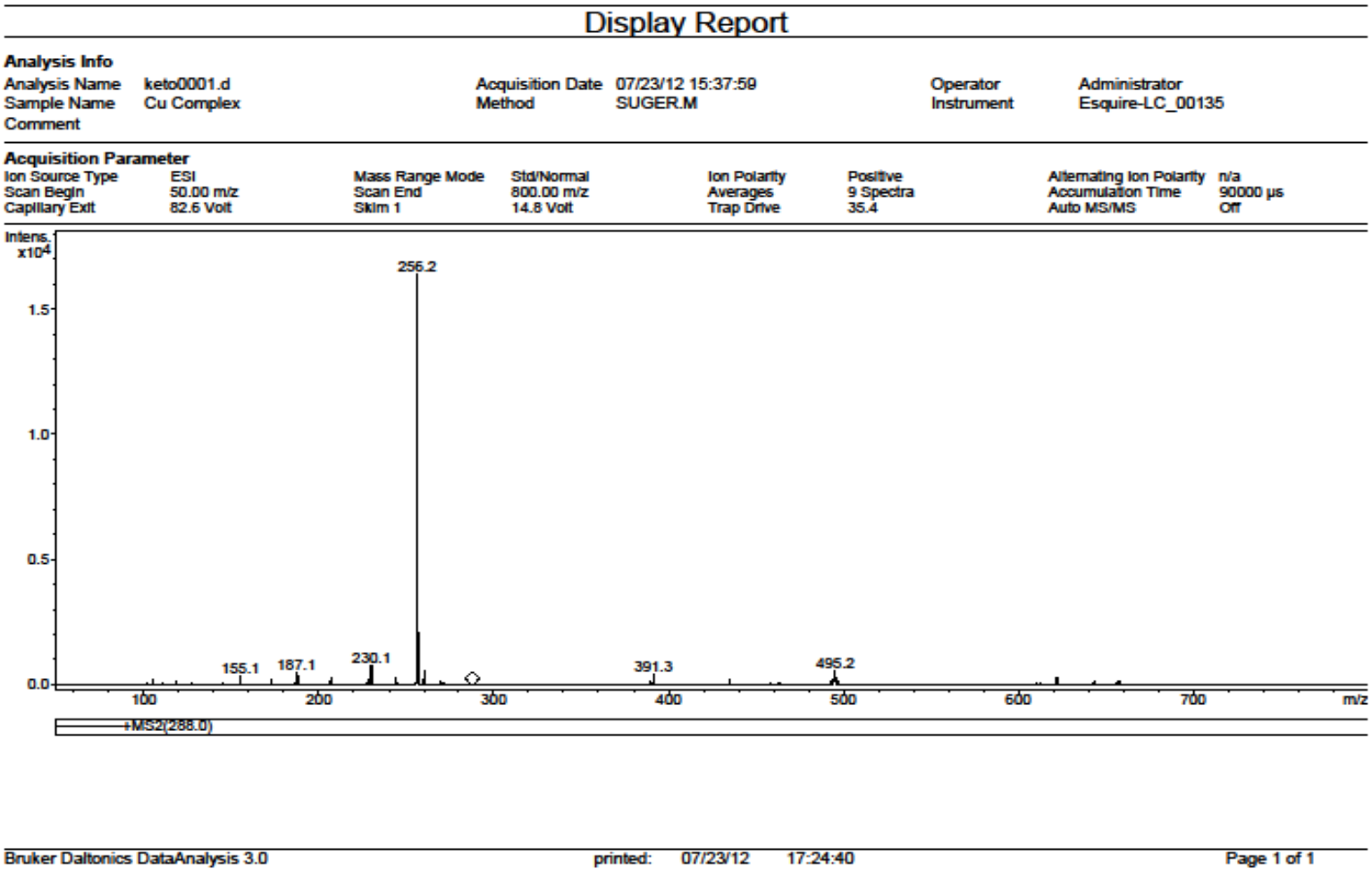

Figure 46: Mass spectrum of azido ketoester (**30**).

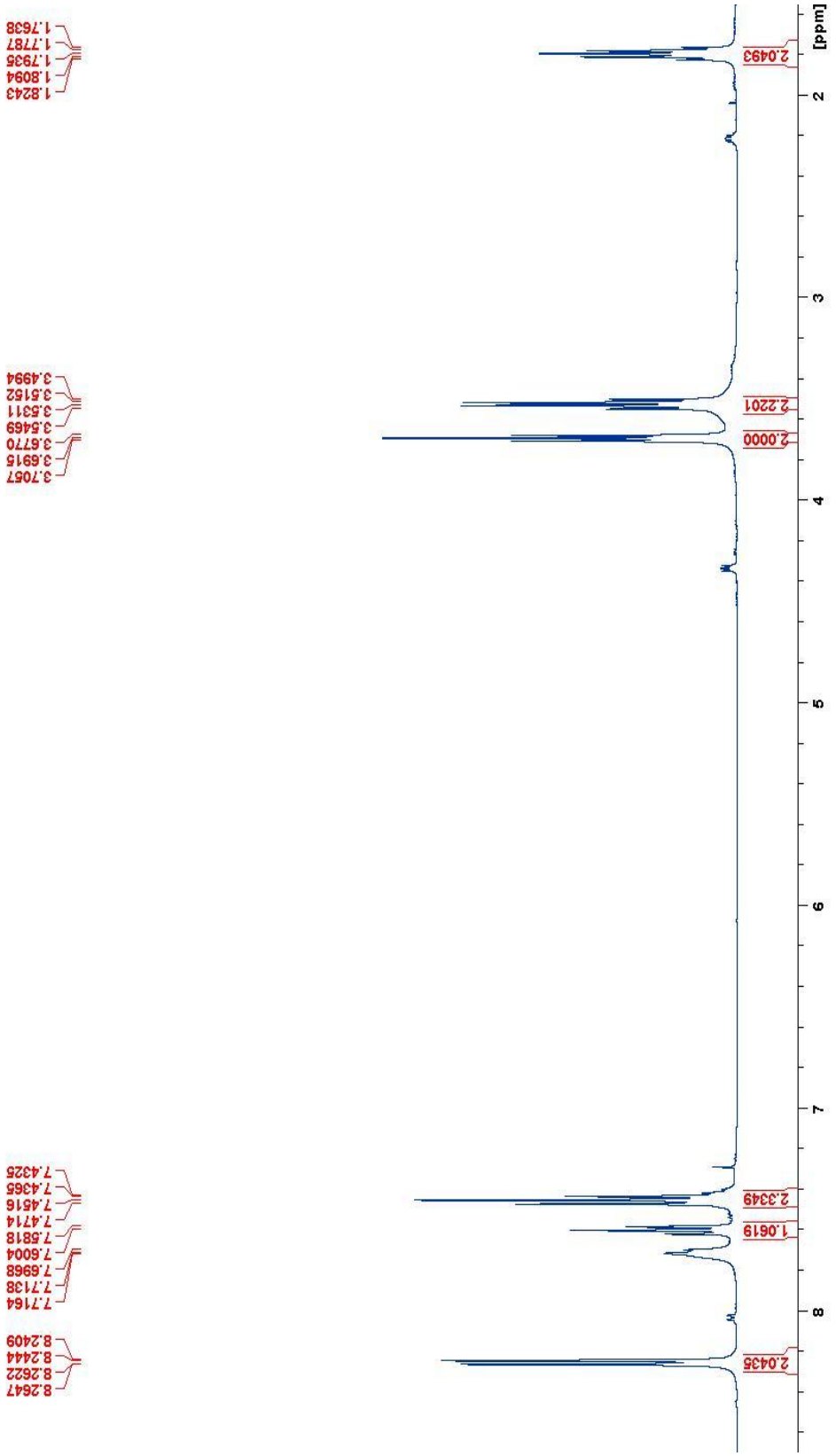

Figure 47: ^{1}H NMR of the Oxazepine (**31**).

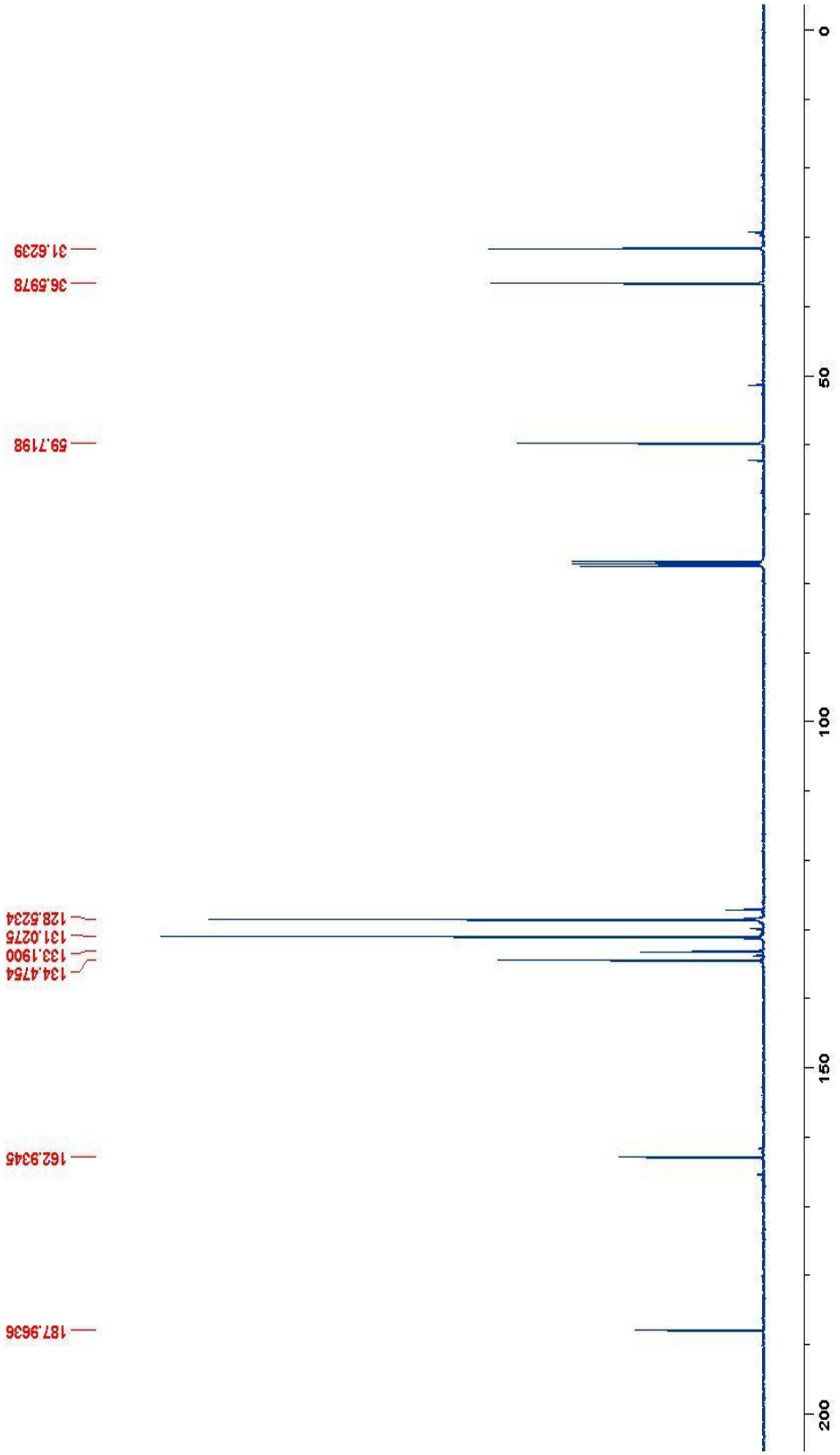

Figure 48: ^{13}C NMR spectrum of oxazepine (**31**).

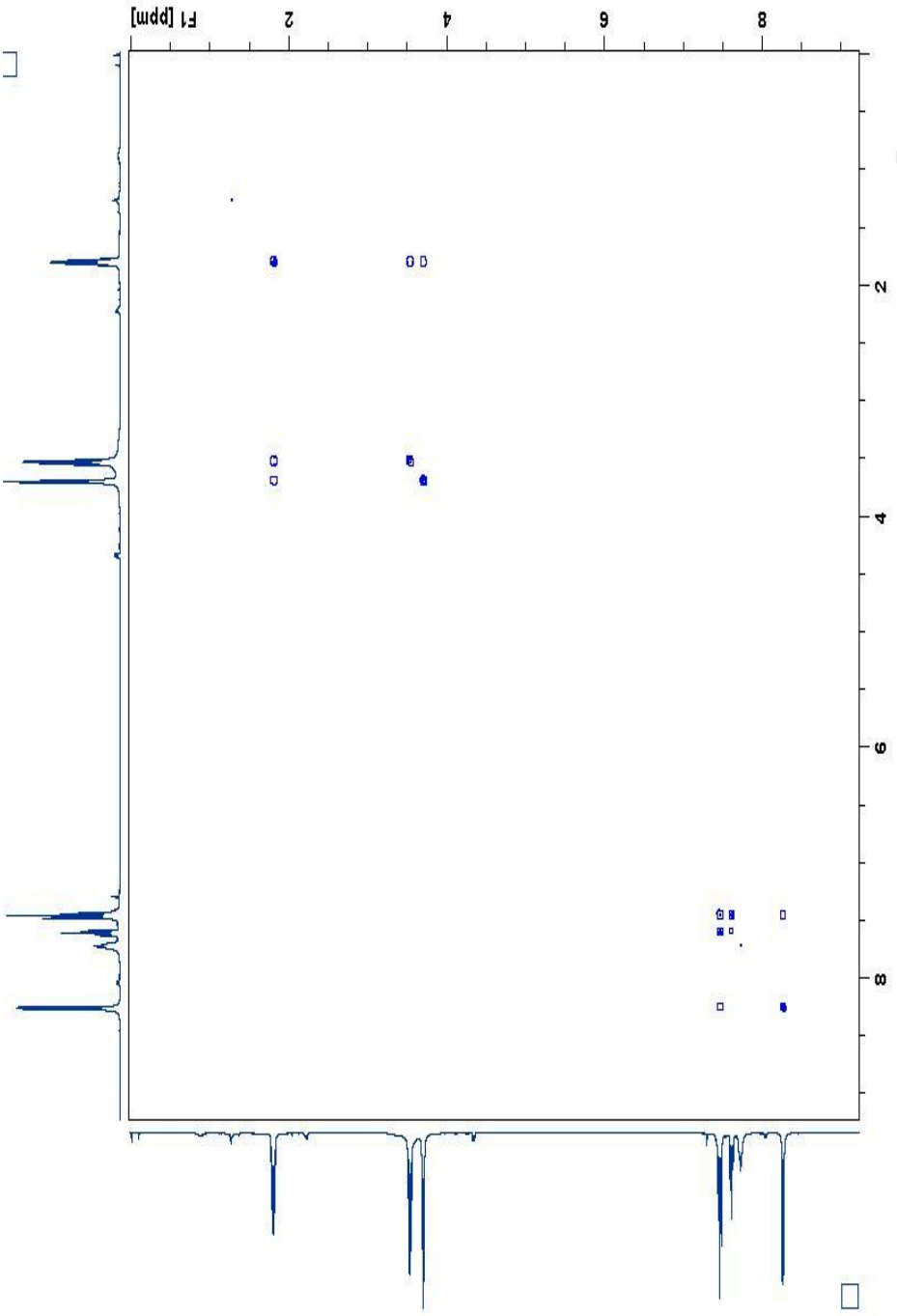

Figure 49: COSY NMR spectrum of oxazepine (**31**).

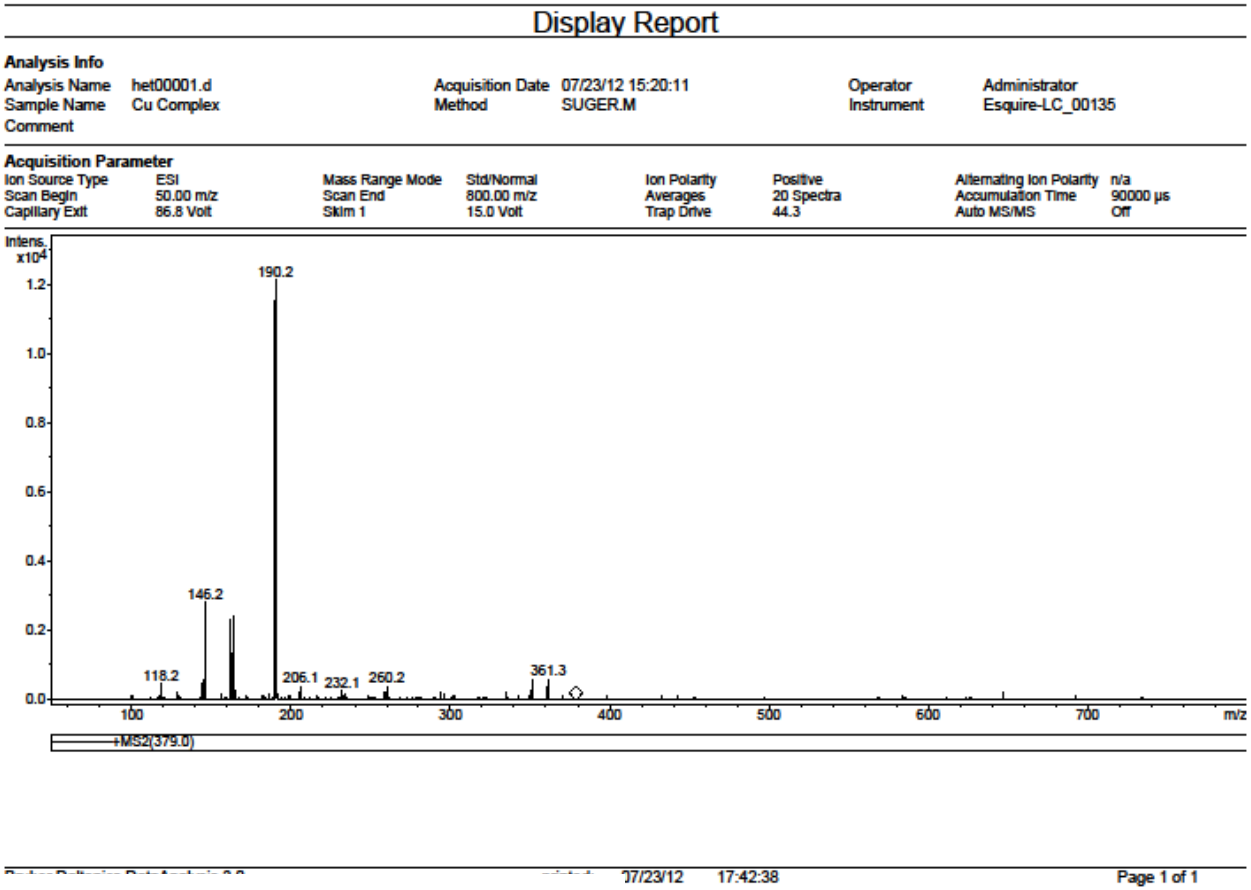

Figure 50: Mass spectrum of oxazepine (**31**).

APPENDIX B

X-Ray Crystallography

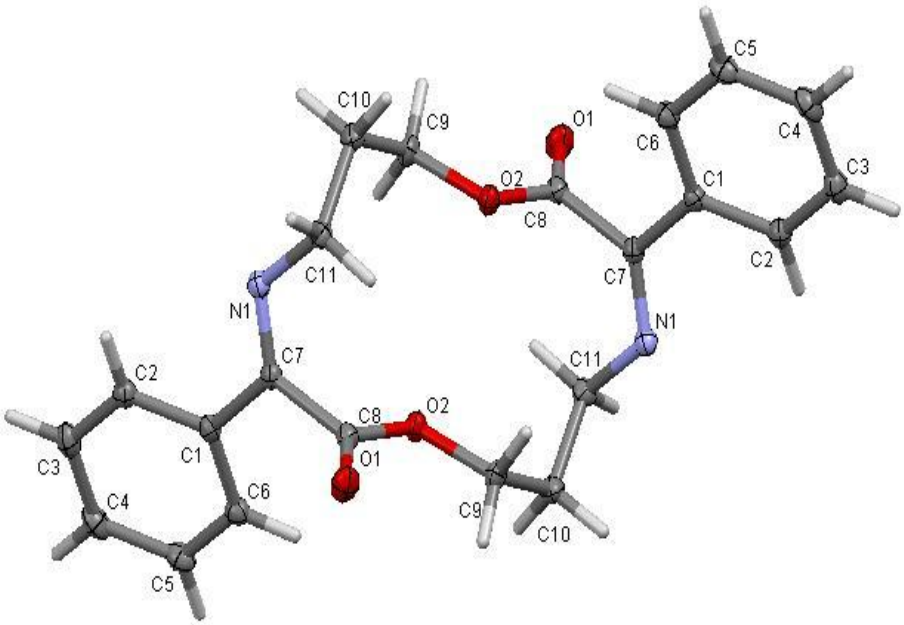

Figure 51: Unit cell with thermal ellipsoids at 50% probability.

Table 1. Experimental details

Chemical formula	$C_{22}H_{22}N_2O_4$
M_r	378.42
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	100
a, *b*, *c* (Å)	12.151 (2), 5.5321 (9), 14.099 (2)
b (°)	105.683 (2)
V (Å^3)	912.5 (3)
Z	2
Radiation type	Mo $K\alpha$
m (mm^{-1})	0.10
Crystal size (mm)	0.55 × 0.22 × 0.14
Diffractometer	Bruker AXS *SMART APEX* CCD diffractometer
Absorption correction	Multi-scan Apex2 v2011.2-0 (Bruker, 2011)
T_{min}, T_{max}	0.693, 0.746
No. of measured, independent and observed [$I > 2s(I)$] reflections	17720, 2922, 2631
R_{int}	0.022
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.037, 0.107, 1.05
No. of reflections	2922

No. of parameters	127
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.48, -0.19

Table 2. Selected geometric parameters (Å, º)

C1—C6	1.3988 (11)	C8—O1	1.2076 (10)
C1—C2	1.4033 (11)	C8—O2	1.3359 (10)
C1—C7	1.4835 (11)	C9—O2	1.4663 (10)
C2—C3	1.3907 (12)	C9—C10	1.5124 (12)
C2—H2	0.9500	C9—H9A	0.9900
C3—C4	1.3961 (14)	C9—H9B	0.9900
C3—H3	0.9500	C10—C11	1.5302 (12)
C4—C5	1.3928 (13)	C10—H10A	0.9900
C4—H4	0.9500	C10—H10B	0.9900
C5—C6	1.3930 (12)	C11—N1^{i}	1.4617 (11)
C5—H5	0.9500	C11—H11A	0.9900
C6—H6	0.9500	C11—H11B	0.9900
C7—N1	1.2770 (11)	N1—C11^{i}	1.4617 (11)
C7—C8	1.5221 (11)		
C6—C1—C2	119.60 (7)	O1—C8—C7	123.34 (7)
C6—C1—C7	120.67 (7)	O2—C8—C7	110.91 (7)
C2—C1—C7	119.70 (7)	O2—C9—C10	107.22 (6)
C3—C2—C1	119.88 (8)	O2—C9—H9A	110.3
C3—C2—H2	120.1	C10—C9—H9A	110.3
C1—C2—H2	120.1	O2—C9—H9B	110.3
C2—C3—C4	120.32 (8)	C10—C9—H9B	110.3

C2—C3—H3	119.8	H9A—C9—H9B	108.5
C4—C3—H3	119.8	C9—C10—C11	114.68 (7)
C5—C4—C3	119.91 (8)	C9—C10—H10A	108.6
C5—C4—H4	120.0	C11—C10—H10A	108.6
C3—C4—H4	120.0	C9—C10—H10B	108.6
C4—C5—C6	120.08 (8)	C11—C10—H10B	108.6
C4—C5—H5	120.0	H10A—C10—H10B	107.6
C6—C5—H5	120.0	N1^{i}—C11—C10	110.24 (7)
C5—C6—C1	120.20 (8)	N1^{i}—C11—H11A	109.6
C5—C6—H6	119.9	C10—C11—H11A	109.6
C1—C6—H6	119.9	N1^{i}—C11—H11B	109.6
N1—C7—C1	121.20 (7)	C10—C11—H11B	109.6
N1—C7—C8	121.84 (7)	H11A—C11—H11B	108.1
C1—C7—C8	116.94 (7)	C7—N1—C11^{i}	119.88 (7)
O1—C8—O2	125.73 (8)	C8—O2—C9	116.53 (6)
C6—C1—C2—C3	0.74 (12)	N1—C7—C8—O1	-88.56 (11)
C7—C1—C2—C3	-177.50 (7)	C1—C7—C8—O1	89.95 (10)
C1—C2—C3—C4	-0.14 (13)	N1—C7—C8—O2	89.87 (9)
C2—C3—C4—C5	-0.19 (13)	C1—C7—C8—O2	-91.62 (9)
C3—C4—C5—C6	-0.08 (13)	O2—C9—C10—C11	-66.25 (9)
C4—C5—C6—C1	0.68 (13)	C9—C10—C11—N1^{i}	-67.87 (9)
C2—C1—C6—C5	-1.01 (12)	C1—C7—N1—C11^{i}	180.00 (7)

C7—C1—C6—C5	177.21 (7)	C8—C7—N1—C11^{i}	-1.55 (12)
C6—C1—C7—N1	-156.13 (8)	O1—C8—O2—C9	2.54 (12)
C2—C1—C7—N1	22.09 (12)	C7—C8—O2—C9	-175.84 (6)
C6—C1—C7—C8	25.35 (11)	C10—C9—O2—C8	-158.99 (7)
C2—C1—C7—C8	-156.43 (7)		

Symmetry code(s): (i) -*x*+1, -*y*, -*z*.