SYNTHESIS AND CHEMISTRY OF NEW SUGAR-DERIVED DIAZOESTERS AND ACYL AZIDES

by

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Abstract

This thesis deals with the synthesis of new diazo- and azidosugars, the chemistry of which can lead to several types of novel compounds. Through the use of metal catalysts or heat, intramolecular insertions can occur which may or may not occur at C-1 of the sugar ring possibly creating a glycoside. Additionally, the formation of a sugar-heterocycle hybrid, *via* a [3+2] cycloaddition, may be optimized towards the production of compounds, which might mimic a specific oligosaccharide.

Acknowledgements

First, I am grateful towards the graduate school for the opportunity and funding for the past two years that allowed me to study here. A large thank you is also extended to Dr.'s Mike and Mincey who's assistance was helpful in placing me in this program.

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Introduction

For many years, carbohydrate chemistry was a division of organic chemistry that received little attention. As time has passed, the chemistry of the carbohydrates has broadened. Both the areas of chemistry and biology have built up the study of carbohydrates to the point of it becoming not only one of the largest classes of organic molecules but also a most varied area. Carbohydrates have found their way into every part of modern society ranging from flocculating agents in mining processes,[1] biomaterials in the medical arena,[2] additives in the food industry,[3] agents for chiral syntheses in chemistry,[4] to the numerous conjugates found in biochemistry and the life sciences.

The three elements found in simple carbohydrates are often present in the ratio of 1:1:2 carbon:oxygen:hydrogen respectively providing the basic chemical equation of $(CH_2O)_n$ where n is a minimum of three. Carbohydrates in the open chain form consist of a polyhydroxylated carbon chain consisting of three or more carbons, one of which forms a carbonyl with an oxygen, while the other oxygens form hydroxyl groups attached to each of the remaining carbons. The structure of the molecules may be either cyclic or linear depending on the parent sugar. When cyclized, carbohydrates are also described as polyhydroxylated cyclic ethers wherein one of the nucleophilic hydroxyl groups on one end of the chain attacks the carbonyl located at least four carbons away. Carbohydrates with more than three carbons usually contain numerous chiral centers, the arrangement of which differentiates the sugars into different isomers.

Every reducing carbohydrate contains a carbonyl group within its carbon chain. The location of the double bonded oxygen divides the family of carbohydrates into two

distinct subfamilies. If the carbonyl is located on the first carbon of the chain creating an aldehyde then the sugar is classified as an *aldose* (***Figure 1***) whereas, if said functional group is located on a secondary carbon forming a ketone then the carbohydrate belongs to the *ketose* subfamily (***Figure 1***).

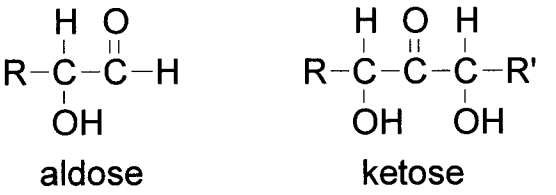


Figure 1. Structural representation of an aldose and a ketose

As a sugar's chain length increases from that of a three-carbon sugar, the number of stereoisomers increases exponentially each time a CH_2O group is added. The majority of carbohydrates demonstrate multiple chiral centers that necessitate the need to accurately and easily make a distinction between the different structures or isomers. The molecular structure of a carbohydrate can be represented several ways, including by Fischer projection or Haworth projection. The Fischer convention of representing carbohydrate structure consists of the molecule shown as an upright straight carbon chain with the aldehyde or ketone positioned near the top and the top most carbon numbered 1. The backbone is constantly bending out of the plane of illustration with the hydrogen and hydroxyl of a perspective carbon in the chain pointing out of the plane (***Figure 2***). Fischer projections may be drawn with bonds connecting the nucleophilic hydroxyl and the carbonyl (***Figure 2***). This allows for the anomeric designation α or β, which will be discussed later.

Haworth projections are a representation of a carbohydrate structure that uses wedges to simulate the three dimensional cyclic nature of the molecules. The sugar is

drawn starting with the oxygen at the top right position, and proceeding in a clockwise fashion beginning with carbon 1 and using wedges and lines to work back around to the ring oxygen. Straight lines leading straight up or straight down are drawn off the ring carbons depicting the bonds to hydrogen and the hydroxyl groups. In the Haworth projection, the anomeric designations are depicted by a bond leading up for β and a bond pointing down for α. In a Fischer projection of the cyclic molecule it is depicted by the position of the hydroxyl, if inside the ring then it is a β anomer, if said hydroxyl is outside the ring then it is an α anomer.

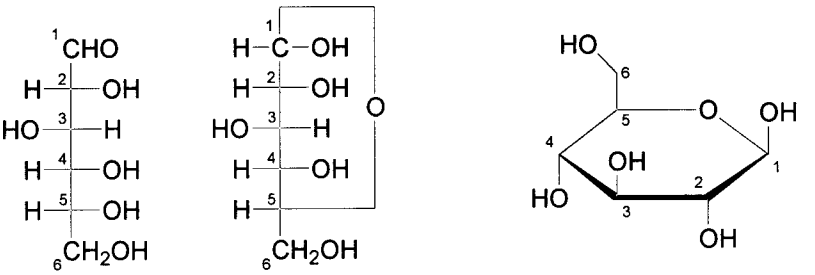


Figure 2. Examples of Fischer and Haworth projections

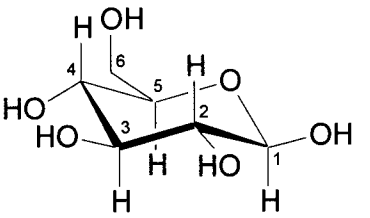


Figure 3. Chair structure of β-D-Glucose

Carbohydrates can be drawn using a combination of the Haworth projection and traditional stereochemical representations such as the chair conformation (***Figure 3***). In this depiction, the axial and equatorial nature of the hydrogen and hydroxyl substituents

is seen with a more accurate representation of the true ring structure rather than the flat ring examples given by a Fischer or Haworth projection.

Both Haworth and Fischer projections allow the depiction of a sugar as being *D* or *L*. These designations are concerned with the configuration of the chiral carbon furthest away from the carbonyl. For instance if, the chiral center farthest away from the carbonyl has the hydroxyl to the right in the Fischer projection then the sugar is termed D, if that said chiral center has the hydroxyl to the left in the Fischer projection then the sugar is L. In both D and L enantiomers of the same sugar the configuration of the last chiral center dictates the position of the previous hydroxyls, therefore, for anomerically equivalent carbohydrates, this one chiral center dictates the absolute stereochemistry of the molecule in question. This concept discovered by Emil Fischer but molded into principle by Rosanoff who started with both enantiomers of the simplest *aldose* glyceraldehyde and, using the cyanohydrin synthesis of monosaccharides, correlated the configurations in the starting sugars with their higher order relatives. Rosanoff later applied this principle to ketoses.[5]

Most carbohydrates that are of sufficient chain length prefer to be cyclized in five or six member rings by the formation of a hemiacetal or hemiketal group. Stated earlier, sugars cyclize *via* nucleophilic attack of the carbonyl group by a hydroxyl at least four carbons down the chain. For aldoses, a five-member ring resembling tetrahydrofuran forms after attack of the aldehyde by the hydroxyl at C-4 (***Figure 4, path 2***). The sugar is then in the *furanose* form. For the *pyranose* form of a cyclized sugar attack of the carbonyl occurs by a hydroxyl attached five carbons away. This six-membered heterocycle now resembles tetrahydropyran and hence its designation (***Figure 4 path 1***).

Different sugars prefer different ring conformations; D-mannose for example, forms little if any furanose rings and likewise *erythro-* and *threo-* pentulose refuse to form any six member pyranose rings.[6]

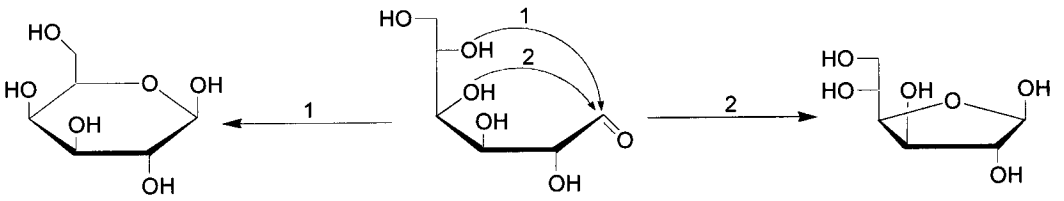


Figure 4. Formation of furanose ring versus pyranose ring

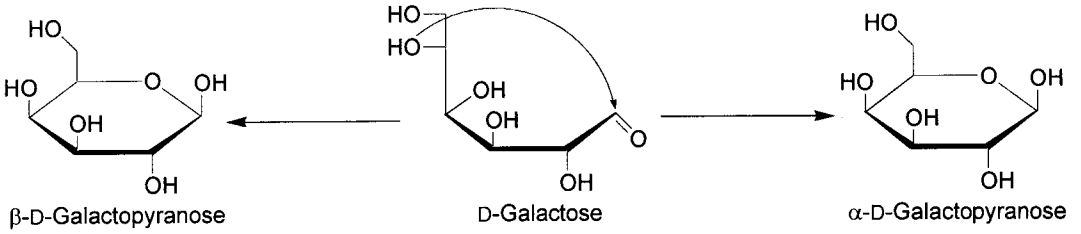


Figure 5. Mutarotation of D-galactopyranose

When stereoisomers of the same sugar form cycles another division in the total genus occurs known as anomers. The formation of a specific anomer, α or β, depends upon the direction the attacking hydroxyl comes from and the position of the hydroxyl resulting form the carbonyl being attacked. For instance, in D-glucopyranose, if the resultant hydroxyl is in the equatorial form then the anomer is β. Similarly, if the hydroxyl is axial then the anomeric designation is α. Like the cyclic forms, sugars will assume a favored anomeric position, which for reducible sugars in solution can change due to *mutarotation* or the reversion of a sugar back to its linear form and then nucleophilic attack from a direction opposite to the previous one while it is in solution (***Figure 5***). It should be noted that, because they are both chiral centers, the anomeric position and the last chiral center effect the optical rotation of a molecule, however,

although a carbohydrate can change from one anomer to another it never changes its D or L designation during mutarotation.[7]

Monosaccharides have the ability to polymerize into di-, tri-, and polysaccharides by means of an oxygen bridge between the anomeric carbon and one of the ring hydroxyl groups at usually C-4 or C-6. The linkages are either α or β and are specifically represented in the nomenclature. For instance, the disaccharide maltose (***Figure 6***) consists of two glucoses linked left to right from the anomeric carbon of the first glucose to C-4 of the second glucose ring in α position pertaining to the bond from the anomeric carbon. Hence, maltose is symbolized by the nomenclature as the following: glucose-α-1,4-glucose.[8] Higher order oligosaccharides are likewise textually represented by the same formula [sugar-anomeric designation-linkage-sugar-anomeric designation-linkage-sugar-anomeric designation-linkage-etc].

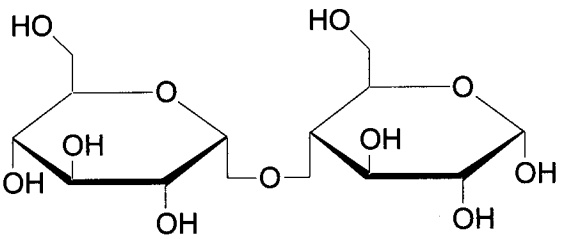


Figure 6. The disaccharide maltose

Biology has been the foil to chemistry in the study of carbohydrates due to their prevalence throughout living systems. Living organisms have been performing chemistry with carbohydrates and using these moieties for millions of years for either cell surface recognition, structure, or cell signaling and identification. One example includes the blood-group substances such as Rh factor and the ABO system whereby specific oligosaccharides are found on the surfaces of red blood cells.[9] Another example is the glycosaminoglycan heparin,[10] a repeating disaccharide unit, found in blood serum that

acts as a powerful anticoagulant (***Figure 7***). Heparin shares the glycosaminoglycan family with several disaccharides that are used mainly in structural roles such as cartilage, ligaments and synovial fluid. The functional groups found on this family of sugars make them perfect for trapping water molecules on the surface of joints providing lubrication.

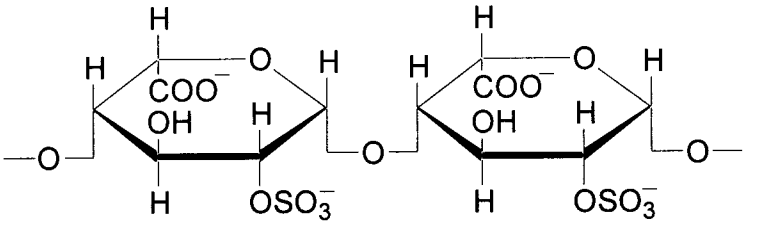


Figure 7. The anticoagulant heparin

The most prevalent form of biological oligosaccharides is in the form of cellulose, which is comprised mainly of β-1,4 linked glucose, and which serves as the main structural component of plants. Chitin, which is similar to cellulose except for the *N*-acetyl group at C-2 is found in the exoskeletons of insects. Starch, α-1,4 linked glucose, is the main form of energy storage in plants it is also the main source of energy in animals. In humans, oligosaccharides not only play an important structural and physiological role but also play a large role in metabolism. The glycolytic pathway found in humans acts to retrieve the energy stored in the chemical bonds of carbohydrates while any of the starch consumed but not immediately used is stored in the form of glycogen. Glycogen differs from the structure of starch in that it is a highly branched polysaccharide consisting of not only α-1,4 linkages but also α-1,6 allowing for a larger amount of individual glucose molecules in a smaller amount of space. For humans, approximately 180 g of glycogen is available at any one time. Finally, all organisms

utilize a phosphodiester linked oligosaccharide backbone as the storage scaffold for the genetic materials DNA and RNA.

In order to manipulate carbohydrates efficiently, living systems use enzymes. These enzymes are conveniently thought of as miniature machines and display unrivaled efficiency and accuracy in execution of their specific task. Yet, while proteomics and gene manipulation are providing desirable results in the pursuit to design enzymes tailor made to do our bidding they are still many years away from success. For the time being, the easier route is to introduce inhibitors, whose structures match those of the transition states of the reactions catalyzed catalyzed by the respective enzyme. These enzyme inhibitors are naturally found in nature or can be synthesized to suit the specific enzyme.

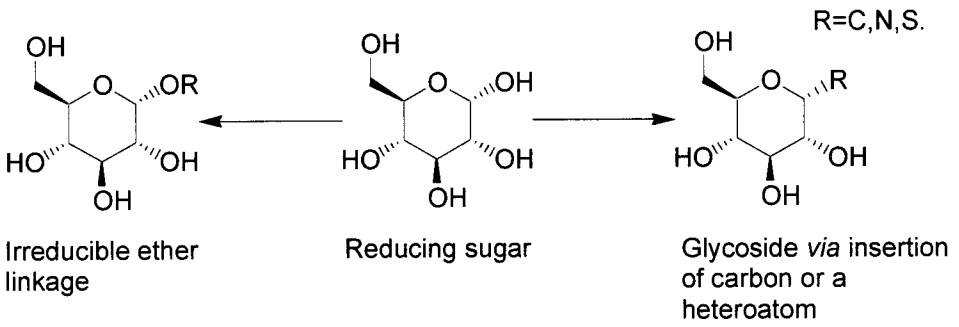


Figure 8. General example of glycosides

Various glycosides are enzyme inhibitors specific for carbohydrate processing enzymes and may also be called *glycomimetics*. Glycomimetics act to inhibit the chemistry that takes place at the anomeric carbon essentially inhibiting the creation of the acetal linkage created by glycosylation enzymes.[11] There are two methods for creating glycomimetics. First, the insertion of an atom such as carbon, nitrogen, or even sulfur at C-1 and reduction to remove the hydroxyl is sufficient to render the sugar non-reduceable. Insertion of the prospective atom and reduction will give its corresponding glycoside *i.e.* *C*-glycoside, *N*-glycoside, *S*-glycoside. A second approach is the formation

of an *O*-glycoside by creation of an irreducible ether bond (***Figure 8***). Many important therapeutic agents are glycosides. Several examples that are naturally found are potent antibiotic streptothricin F,[12] the cancer chemotherapeutic amygdalin[13] and vineomycinone a natural *C*-glycoside discovered by Inamura et. al.[14], have found use as a dual role antimicrobial/antitumor agent (***Figure 9***).

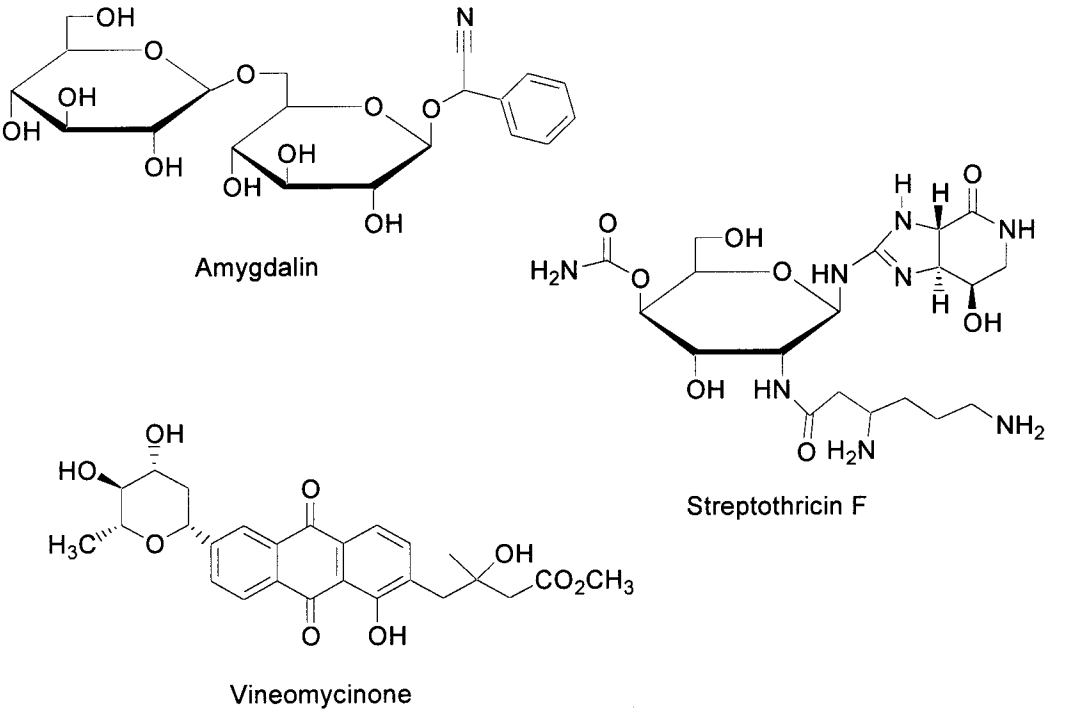


Figure 9. The glycoside therapeutics amygdalin, streptothricin F, and vineomycinone

Past synthetic approaches to *C*-glycosides have centered around nucleophilic attack on the anomeric hemiacetal carbon. There are several examples including the use of Grignard[15] reagents (***Figure 10A***) or a cyanate ion[16] (***Figure 10B***) to make a carbon-to-carbon bond with the anomeric carbon. Wittig conditions can be employed with either hemiacetal or lactone forms of the sugar.[17] The lactone can be synthesized *via* oxidation with dimethylsulfoxide and acetic anhydride as demonstrated by Kuzuhara and Fletcher.[18] Aside from Wittig conditions, lactones can also be reacted with titanium

alkylidene (Tebbe reagent)[19] to create a *C*-glycoside or with hexamethylphosphorotriamide and chloroform that allows the formation of a dichloromethylene species[20] (***Figure 10C***) Although there exists substantial literature concerning carbon-carbon bond formation utilizing metal-catalyzed carbenoid insertions there are none that have been applied towards the direct synthesis of a *C*-glycoside.

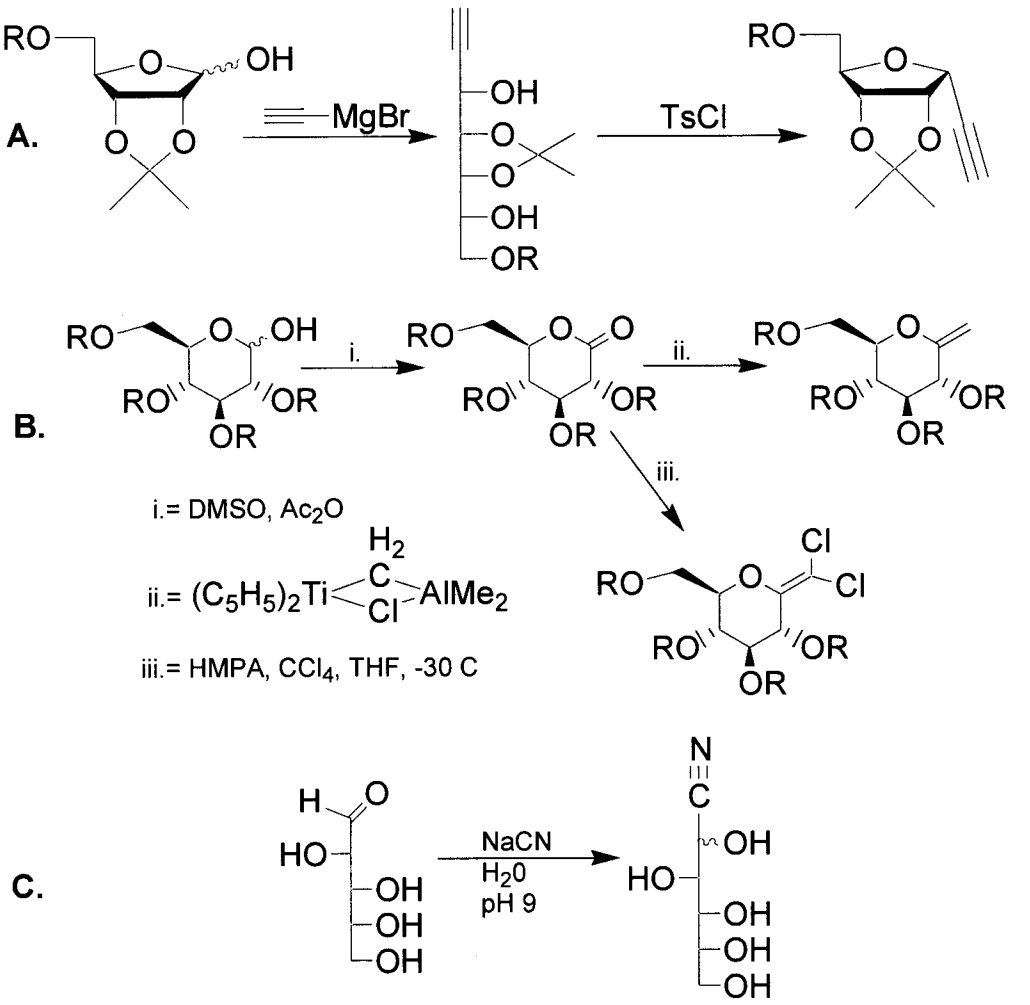


Figure 10. *C*-glycosides from: A-Grignard reagents, B-*via* lactones, and C- cyanohydrin

Project 1-Survey of the chemistry of diazoesters.

As discussed above, the formation of the majority of glycosides occurs by nucleophilic attack of the anomeric carbon. Project 1 deals with the synthesis and use of

phenacyldiazoesters in the presence of a metal catalyst, liberating nitrogen gas, to create a *carbenoid* intermediate which behaves as the nucleophilic species to effect a C-H insertion on the sugar ring and the potential for formation of an intramolecular *C*-glycoside.

The diazo functional group consists of two nitrogens double bonded to each other with one of the nitrogens double bonded to a carbon chain (***Figure 11***). The result of a diazo decomposition is the formation of a carbene and the loss of nitrogen gas, which is the driving force for the reaction. Lower molecular weight diazo compounds, such as diazomethane, are toxic and extremely unstable species. Due to its extreme reactivity, diazomethane does not behave selectively, which hinders its usefulness. The reactivity of a diazo compound can be tuned with the addition of carbonyl groups α to the diazo moiety,[21] and α-diazoketones and diazoesters can be formed two ways: by reacting diazomethane with the appropriate acid chloride or by employing a diazo transfer agent (which are different arenesulfonyl azide species or alkylsulfonyl azides) that adds a diazo group.

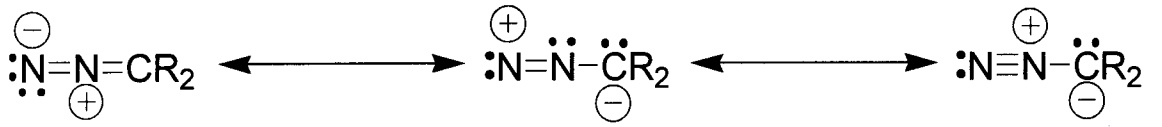


Figure 11. Resonance forms of the diazo group

There are several approaches to forming carbon-to-carbon bonds with diazo esters. α-Diazoketones can be induced to cyclize with adjacent unsaturated bonds when boron trifluoride is allowed to coordinate with the oxygen on the carbonyl group adjacent to the diazo group (***Figure 12A***).[22] In another scheme, the reaction of the diazoketone or diazoester with an alkyl borane will give a species with a C-C bond (***Figure 12B***).[23,24] A

third method involves the decomposition of the diazoketone to yield a carbene using UV light, heat, or metal catalysts.[25,26] Carbenes are similar to a radical except that there are two electrons, instead of one, that are able to form a bond. Carbenes will form another bond with the closest saturated carbon, which can act to limit their effectiveness.

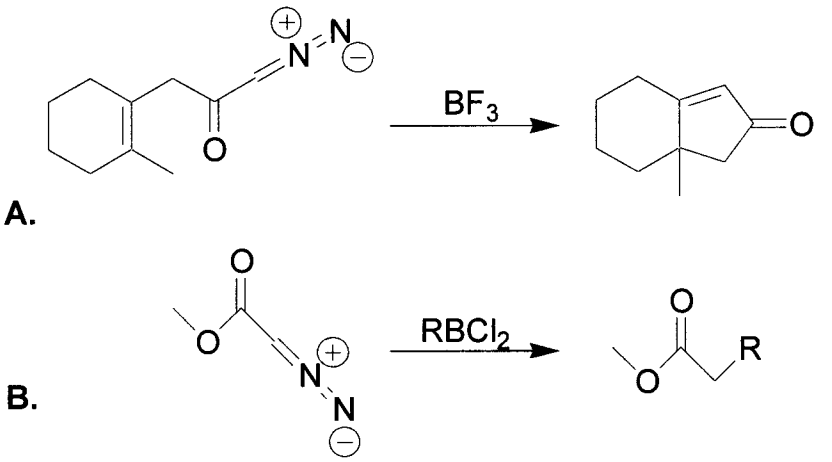


Figure 12. Carbon-to-carbon bond formation with diazo compounds

When conducting metal-catalyzed insertions several issues are taken into account. Two considerations concern the reactivity of the diazocompound being decomposed and the degree of reactivity of the metal chosen to stabilize the resultant carbenoid structure. For instance, as the reactivity of the diazocompound increases so does the threat of explosion. Additionally, the degree of reactivity of the carbenoid may be so high that selectivity diminishes. In general, simple alkyl substituted diazo compounds are most reactive with diketone species being the least reactive (***Figure 13***).

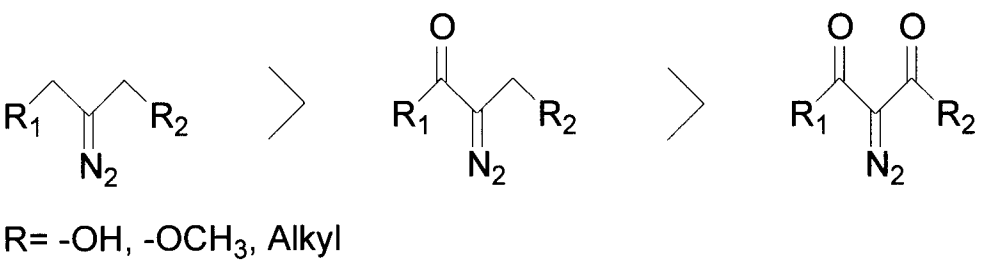


Figure 13. Degree of reactivity of diazo compounds

The selection of a properly reactive metal catalyst is essential. The catalysts are essentially Lewis acids with varying acidities, dictated by the extent that they accept electron pairs. For example, rhodium(II) has been found more suitable than copper(II) when dealing with the decompositions of diazo compounds, however there are several other metals that have yet to be considered such as ruthenium, palladium, and platinum. Both of these aspects have been thoroughly assessed by Doyle et. al.[28] In addition, when considering metal-catalyzed reactions there exist stereochemical issues concerning the steric interaction between the ligands attached to the organometallic complex, the diazo compound, and the molecule upon which the insertion occurs. To exemplify this, the basic rhodium diacetate dimer allows the carbenoid species to be trapped from either side. In contrast, a rhodium dimer with a ligand that protrudes out into one side of the metal face that coordinates with the carbene will favor reaction opposite of the ligand thereby favoring one stereochemistry over the other. These ideas have been reviewed by Doyle et. al. and several other primary sources.[28-34]

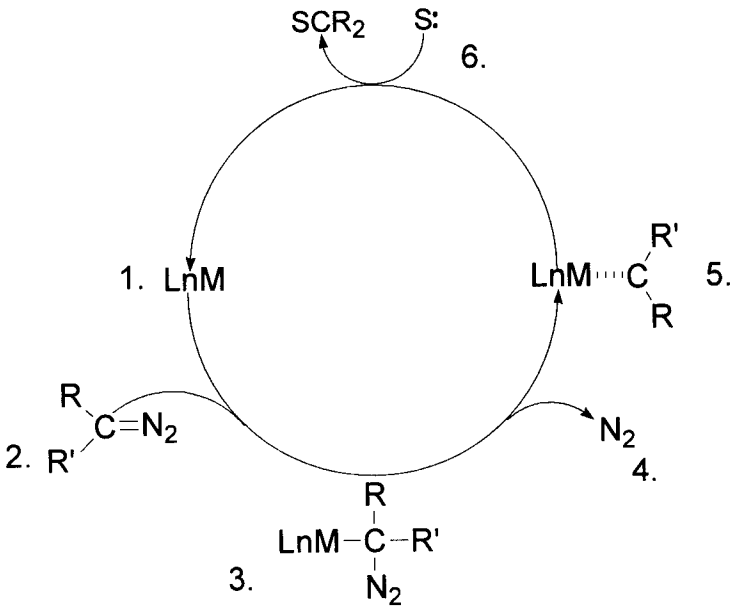


Figure 14. Rhodium catalytic cycle

Metal catalysts proceed through a regeneration cycle that may or may not be specific to a particular metal. For instance, the rhodium cycle (***Figure 14***) is as follows. While the metal catalyst is stirring in the appropriate solvent, (1) the diazo compound is added dropwise (2). The catalyst complexes with a lone pair on the diazo group weakening the carbon to nitrogen bond (3). Once sufficiently weakened, the nitrogen leaves as a gas allowing the carbon to assume carbenoid character (4). This allows full coordination between the carbene and catalyst (5) until an electron donor or similar species picks up the carbene (6).[35]

There are several examples in the literature of rhodium catalysts being used to decompose diazo compounds. The most common occurrences are cyclopropanation with an unsaturated group on another substrate[36] or intramolecular cyclopropanation (***Figure 15***).[26]

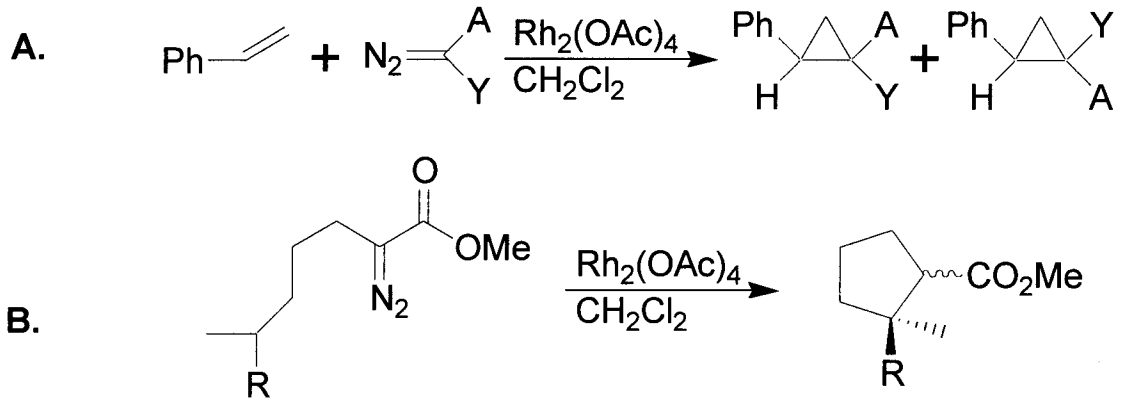


Figure 15. Rhodium catalyzed diazo decompositions A.-intermolecular cyclopropanation B.-intramolecular cyclopropanation

There are very few references concerning the decomposition of diazo compounds in the presence of a carbohydrate. Due to their unsaturation, glycals have been found to give cyclopropanated products when the appropriate diazo structure is catalytically reacted in their presence (***Figure 16***).[37] Carbenes could possibly react in the presence of

saturated sugars to cause intramolecular insertion along any of the carbons in the chain. The main difficulty would be in controlling the regio- and stereochemistry of the reaction. This is accomplished using several techniques. First, using a diazo compound that was already attached to the sugar would restrict the area of reactivity. Second, using a class of diazo compounds that was less reactive would help by limiting unwanted insertions. Third, as stated previously the ligands attached to the rhodium catalyst would allow tailoring of the carbenes reactivity. Carbene insertion into ring carbons C-2 through C-6 would create a branched chain sugar with itself giving a bicyclic system. Insertion at the anomeric carbon would not only give a branched chain sugar but a *C*-glycoside, a potential enzyme inhibitor.

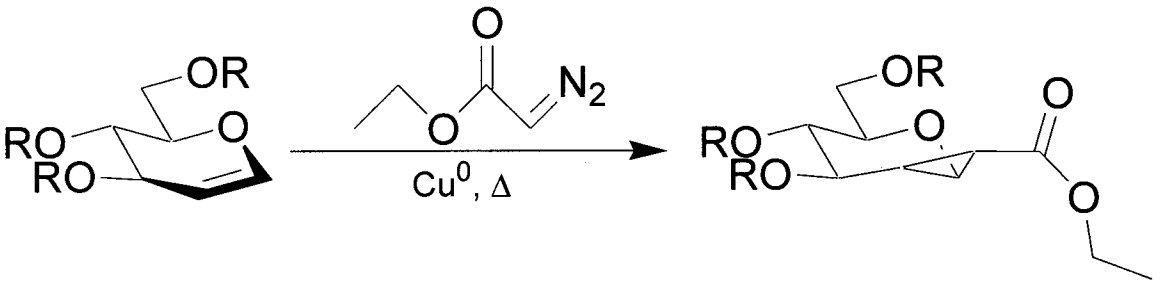


Figure 16. Decomposition of a diazoester in the presence of a glycal

Project 2-Survey of the chemistry of azides.

Project 2 deals with the varied chemistry of azides as applied to carbohydrates. Similar to Project 1, the decomposition of an azide results in the departure of diatomic nitrogen and the creation of a *nitrene* intermediate that can effect an insertion on the ring of the sugar creating potential for the creation of an intramolecular *N*-glycoside. Additionally, the azide group also possesses properties which make it a versatile reactant for the introduction of a nitrogen in a structure.

Azides are a functional group where three nitrogen atoms are linked by multiple bonds with several resonance forms possible (***Figure 17***). Azide species share similar levels of toxicity and instability as diazo compounds. The main synthesis of an alkyl azide involves the nucleophilic substitution of an alkyl halide, or other appropriate leaving group, with sodium azide.[38] The synthesis of acyl azides is also accomplished by substitution chemistry, however the use of a catalyst such as tetra-*N*-butyl ammonium bromide activates the carbonyl group during the reaction giving improved yields.

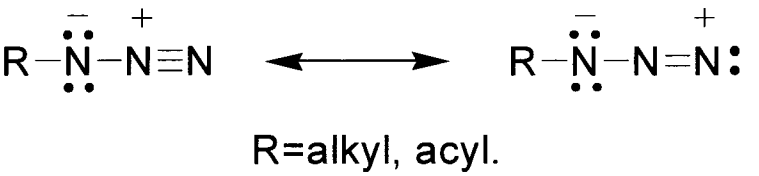


Figure 17. Resonance forms of azides

Once synthesized an azide is extremely useful when the presence of nitrogen containing species is desired. For instance, azides may be reduced to give an amine or amide depending upon whether the azide was alkyl or acyl (***Figure 18 A***).[39] Azides may be subjected to heat or UV light to produce a nitrene, a reactive intermediate similar to a carbene (***Figure 18 B***).[40] Finally, an azide group is an excellent 1,3-dienophile and reacts with dipolarophilic species such as alkenes and alkynes to give a [3+2] cycloaddition product (***Figure 18 C***).

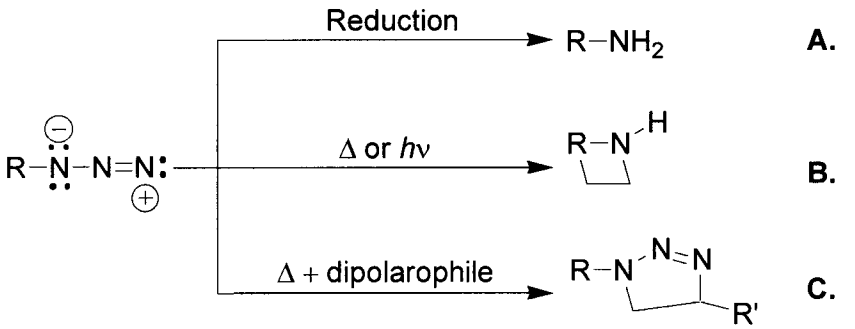


Figure 18. Utility of azide derivatives in synthesis

Application of azide chemistry to carbohydrates allows for the generation of important and interesting products. Amino sugars are created after reduction of an azido sugar, and the possibility of *N*-branched sugar or *N*-glycosides is apparent when a nitrene species is produced from conditions, discussed earlier, such as limiting reactivity of the intermediate species and length of the carbon chain linking the azide to its sugar. Although similar to the stipulations placed on the creation of the carbenoid sugar, it should be noted that nitrenes do not require a metal catalyst.

The prospect of performing cycloadditions is exciting in that this opens the possibility of creating a heterocycle between two sugars, one a dipolar group and the other sugar a dipolarophile. This is enticing in that the product may be sterically similar to that of a trisaccharide containing the same two sugars with the heterocycle being formed from suitable sugar precursors, one containing a 1,3-dipole the other a dipolarophile (***Figure 19***). The potential for this chemistry is important because the formation of oligosaccharides becomes increasingly complex as the number of sugar units increases. For example, as the number of sugars being linked by the traditional O-linkage increases the potential reactive sites increases by at least 5 hydroxyls. Indeed, even protected sugars are a hindrance due to steric interactions or chemical incompatibility of the protecting groups. Numerous compounds can be easily synthesized by combining specific azidosugars and sugars with dipolarophiles attached. Purchasing oligosaccharides that are commercially available, and attaching functional groups needed for the cycloaddition, could allow larger sugar-heterocycle hybrids not to mention the application of combinatorial synthetic methods.

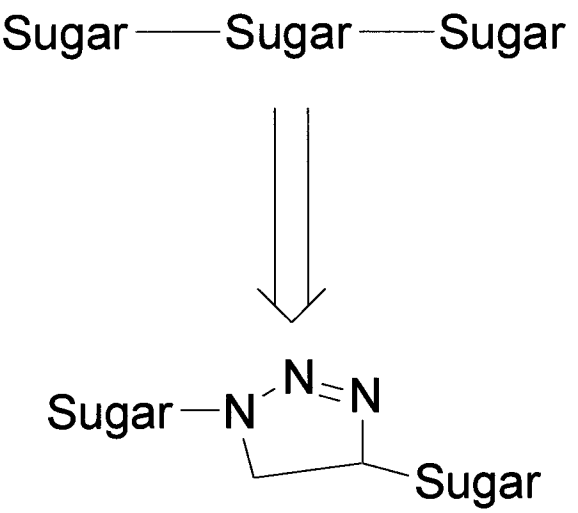


Figure 19. Proposed similarity of sugar-heterocycle hybrid to target oligosaccharides

Combinatorial synthesis involves the creation of several starting libraries that consist of similar classes of molecules. A molecule from one class would be reacted with an appropriate molecule from another class to form an entirely different molecule. For example, six azidosugars are combined with two different classes of dipolarophile sugars with six members apiece to give seventy-two different molecules (regioisomeric potential not demonstrated) (***Figure 20***). The difference between combinatorial synthesis and conventional synthesis is that conventional synthesis has a specific target molecule whereas using combinatorial methods thousands of molecules can be synthesized and, using high-throughput screening, molecules with the desired properties can be discovered.

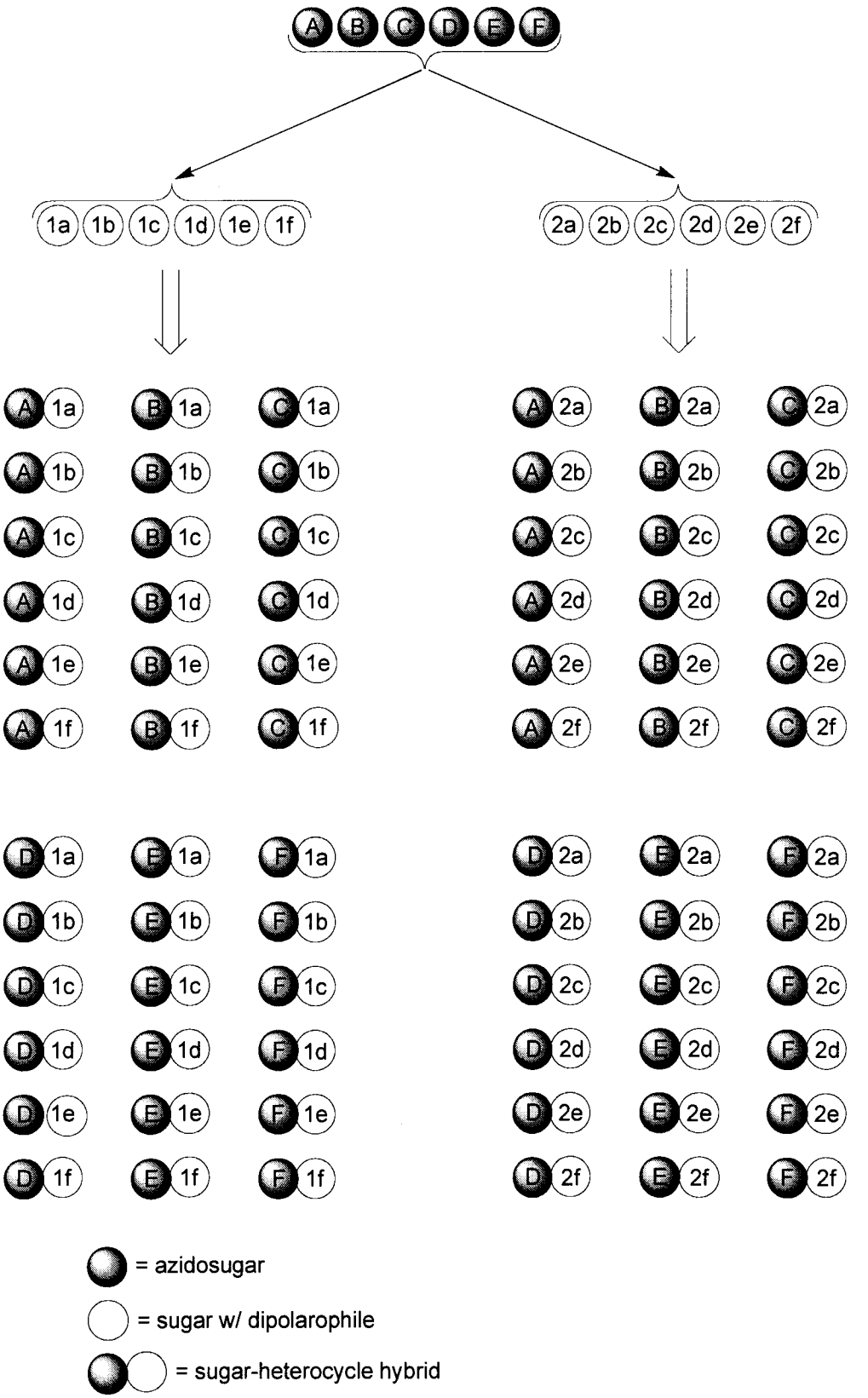


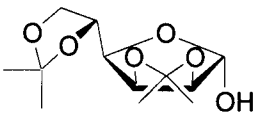
Figure 20. Potential of combinatorial synthetic method

Statement of Problem

Sugar derivatives and oligosaccharides are prevalent throughout chemistry and the application of the functionality of diazocompounds and azides has demonstrated effective in several areas of synthesis. The combination of the two shows promise, although little in the way of previous work has been pereformed in this area.

Results and Discussion

The chemistry of carbohydrates often deals with the hydroxyl groups located on the ring, therefore measures must be taken to restrict chemistry to the desired hydroxyl group. This is accomplished by protecting the nondesired hydroxyl groups by reaction with an acetylating reagent such as acetic anhydride and pyridine, the addition of isopropylidene groups or the use of silyl chloride derivatives. A good example of a protected sugar is 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **1** where the sugar is protected at C-2 and C-3 of the furanose with an isopropylidene group and at C-5 and C-6 with an isopropylidene group permitting only the hydroxyl group at C-1 to react.



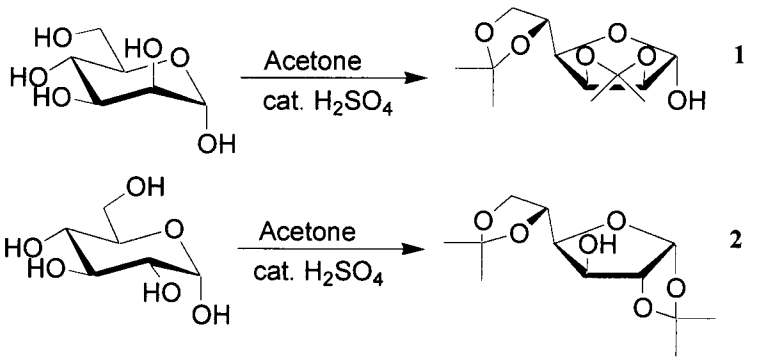
1

Figure 21. 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **1**

2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **1** and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **2** were both synthesized using acetone and sulfuric acid (Scheme 1). Three other protected sugars were purchased from suppliers; 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose from Aldrich while 1-bromo-1-deoxy-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose and 1-bromo-1-deoxy-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose were obtained from Fluka.

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose **1** was made by reacting D-mannose with dry acetone and sulfuric acid while stirring. TLC (1:1 hexane:ethyl acetate) was used to monitor the progression of the reaction and showed the consumption of starting material, which remained on the baseline in addition to the appearance of two,

less polar spots. After neutralizing the solution with sodium carbonate and evaporating, a white solid was produced that was pure by TLC.

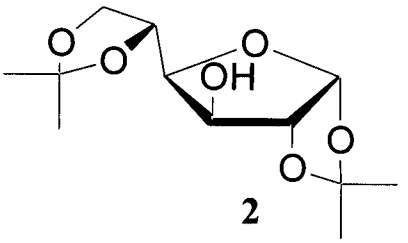


Scheme 1

Clean ^{13}C and proton nuclear magnetic resonance spectra of the protected sugar provide proof that the solid produced was indeed **1**. ^{13}C spectrum shows four peaks at 24.5, 25.2, 25.9, and 26.9 ppm for the methyl groups on the isopropylidene protecting groups, peaks at 66.5, 73.2, 79.5, 80.1, 85.4, and 101.1 ppm correlating to the carbons C-1 through C-6 on the sugar chain with the peak at 101.1 ppm for the anomeric carbon or C-1 The two remaining peaks at 109.0 and 112.5 ppm relate to the quaternary carbons of the protecting groups.

Interpreting the proton NMR of **1** is a simple task in that it is possible to assign the peaks a position on the sugar by calculating and matching up the coupling constants, splitting patterns and position of the different peaks with each other. In the ^{1}H NMR of **1** four peaks at 1.31, 1.37, 1.44, and 1.45 ppm are for methyl protons of the protecting groups, moving downfield a doublet at 3.35 ppm is most likely from the hydroxyl at C-1. Next on the proton spectrum at 4.06 ppm is a multiplet of two hydrogens, most likely the geminal protons found at C-6. At 4.17 ppm a doublet of doublets is the peak for H-3 on the ring while at 4.40 ppm a doublet of doublets of doublets exists for H-5 on the ring. H-

5 assumes this splitting pattern due to the presence of the two geminal protons on C-6 and the proton on C-4. At 4.60 ppm a doublet for the proton at H-2 is present while at 4.80 ppm a doublet of doublet signal the proton at C-4. Finally, farthest downfield, due to its place on the anomeric carbon, at 5.36 ppm is a doublet for H-1. Because H-1 has a dihedral angle of ~90 degrees with H-2 this peak splits into a doublet with a very small coupling constant.



2

Figure 22. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose

Analogous to the synthesis of **1**, D-glucose was dissolved in dry acetone and stirred in an icebath while 48 mL of sulfuric acid was added dropwise. After neutralizing with sodium hydroxide the compound was purified by recrystallization with hexane to produce **2**.

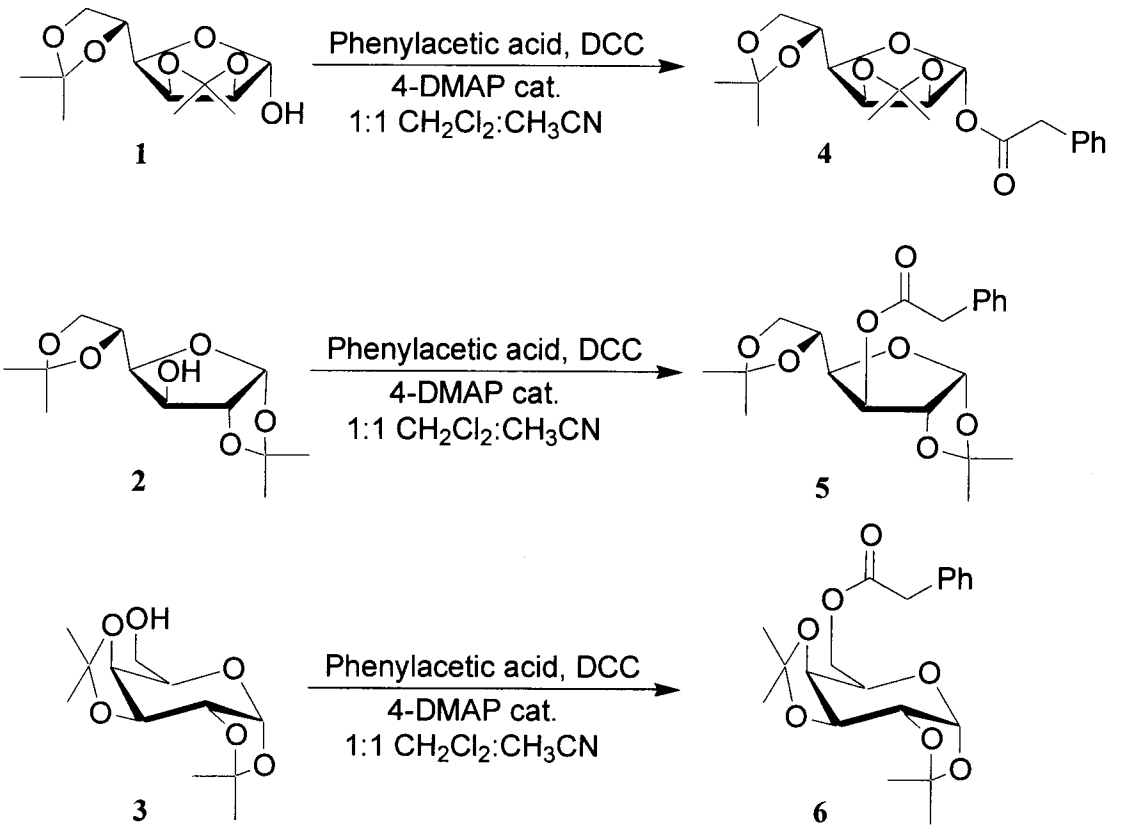
The ^{1}H and ^{13}C spectra of **2** and **1** are similar to the each other in many ways. The ^{13}C spectrum shows four peaks at 25.2, 26.2, 26.8, and 26.9 ppm for the isopropylidene methyl groups while five of the six carbons of the furanose ring found from 67.5, 73.1, 74.8, 81.0, and 85.0 ppm and the peak at 105.0 ppm for the anomeric carbon. Similarly to diacetone mannose, the peaks at 109.4, 111.6 ppm are for the quaternary carbons in the protecting groups.

Using the proton spectrum of **2** the assignment of the peaks to their respective protons on the furanose can be determined. Starting with the primary alkyl peaks, from the isopropylidene protecting groups, at 1.32, 1.36, 1.44, and 1.50 ppm the next peak

encountered moving downfield is a doublet at 3.0 for the free hydroxyl at C-3. Moving downfield, the next signal is a doublet of doublets at 4.01 ppm for one of the geminal protons at C-6. The other geminal proton appears as a doublet of doublets at 4.06 ppm. At 4.2 ppm is the doublet of doublets for H-4. Next to that peak is a multiplet at 4.3 ppm for two protons that are most likely a combination of a doublet for H-3 and a doublet of doublets of doublets for H-5. A doublet, at 4.5 ppm, for H-2 can be found in addition to a doublet at 5.9 ppm, both sharing the same *J* value for their coupling constant, representing H-1 on the anomeric carbon.

Project 1-Synthesis and chemistry of phenacyldiazoester sugars

Synthesis of phenacylester derivatives.



Scheme 2

The synthesis of 2,3:5,6-di-*O*-isopropylidene-1-*O*-phenacyl-α-D-mannofuranose (**4**) occurred by the reaction of **1,** as shown above in Scheme 2. A catalytic amount of 4-dimethylaminopyridine (4-DMAP), and phenylacetic acid were dissolved in CH_2Cl_2 and CH_3CN while a 1.0 M solution of the coupling reagent 1,3-dicyclohexylcarbodiimide (DCC) was added dropwise to the stirring reaction mixture causing the formation of a white precipitate. After stirring overnight thin layer chromatography (2:1 hexane:ethyl acetate) indicated the complete consumption of starting material and a spot for the less polar product.

^{1}H NMR of the product showed the appearance of two new signals in addition to those of compound 1; a singlet at 3.62 ppm for the alkyl group α to the phenyl ring and a multiplet corresponding to the aforementioned phenyl ring at 7.3 ppm. Furthermore, The singlet for the proton on the anomeric carbon shifts downfield, from 5.36 ppm to 6.13 ppm, when compared to starting material due to the presence of the phenacyl ester.

^{13}C NMR spectra indicated the presence of a peak at 169.7 ppm corresponding to the carbonyl of the ester and four peaks between 127.1 to 133.2 ppm (two with double intensity) corresponding to the aromatic ring carbons. Additionally, a slight upfield shift from 85.4 to 79.2 ppm occurs on the signal for the anomeric carbon and the appearance of a signal for the secondary carbon α to the phenyl ring at 41.4 ppm. ElectroSpray Ionization-Mass Spectrometry (ESI-MS) verified the molecular weight of the molecule (378.42) with two positive ions; the first (379.22) is the molecule with H^+ and a second ion (396.29), which is the molecule plus water.

The synthesis of the glucose derivative of a phenacylester sugar was approached similarly to that of the mannose derivative. As illustrated in Scheme 2, 1,2:5,6-di-*O*-

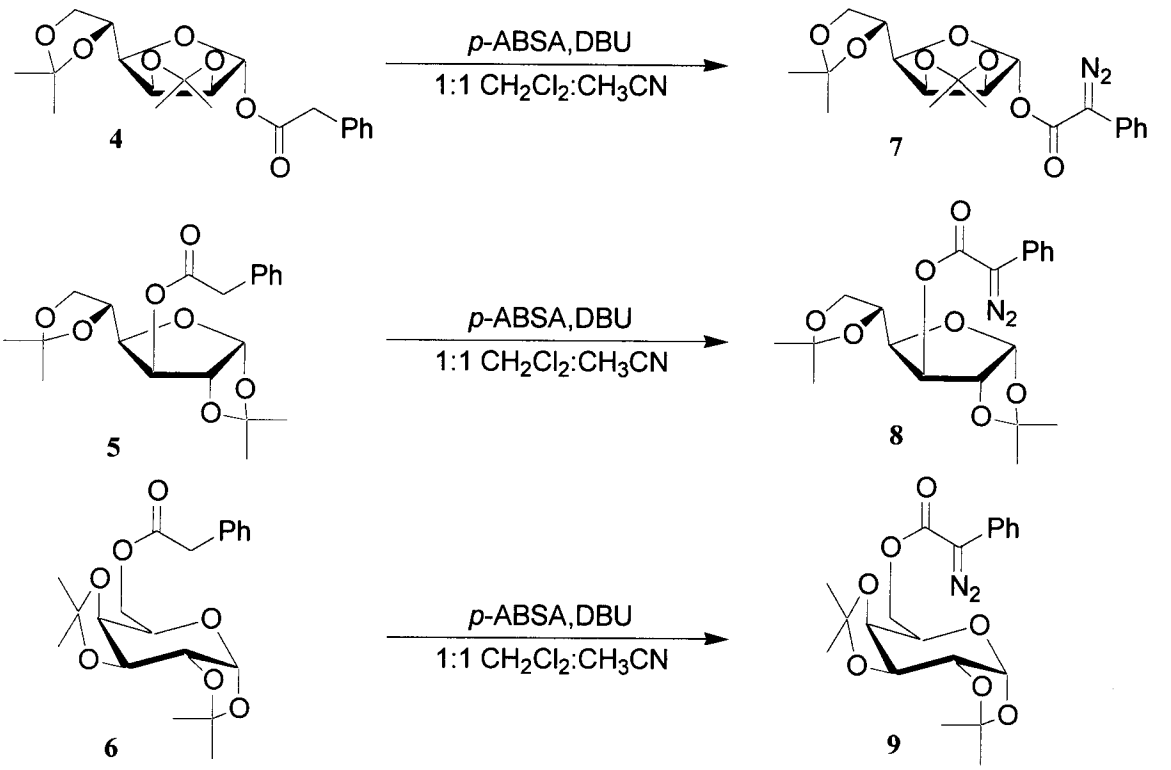
isopropylidene-α-D-glucofuranose **2** was treated with phenylacetic acid in the presence of 1.0 molar DCC and 4-DMAP producing a white precipitate that was filtered off after determining by TLC (3:1 hexane:ethyl acetate) the complete consumption of the starting sugar and appearance of a less polar spot that was UV active.

Clean ^{1}H and ^{13}C NMR provide several clues indicative of a successful reaction. On the proton spectra the appearance of multiplets at 7.35 ppm and a singlet at 3.6 ppm are indicative respectively of the phenyl group and the methylene group between the aromatic ring and ester. The proton at C-3 shifts downfield from 4.3 ppm in the spectra for the protected sugar to 5.27 ppm indicative of the reaction of the phenacyl ester with the hydroxyl at C-3 on the furanose ring. The ^{13}C NMR shows the appearance of new peaks at 169.8 ppm for a carbonyl, 133.2, 129.0, 128.5, and 127.1 ppm for aromatic carbons, and 41.4 ppm for the secondary alkyl next to the phenyl ring. In addition, there is also a rearrangement in the peaks falling between 65 to 95 ppm relating to a change in the environment of the glucose ring due to addition of the phenacylester at C-3. Mass Spectrometry, using the atmospheric pressure chemical ionization (APCI) method, verified the molecular weight of the compound (378.42) by producing two positive molecular ions one with an H^{+}(379.27) and a second ion complexed with water (396.33).

A third phenacylester sugar synthesis, depicted in Scheme 2, was carried out by the reaction of phenylacetic acid, a catalytic amount of 4-DMAP, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **3** and dropwise addition of 1.0 molar solution of DCC. As with the previous phenacylester sugars, TLC (1:1 hexane:ethyl acetate) revealed the creation of a less polar product accompanied with consumption of the starting material.

The ^{13}C NMR showed the expected signals for the methylene group, phenyl ring, and carbonyl at 41.1, 126.7, 128.2, 129.0, 133.6, and 171.1 ppm respectively, in addition to the shift of C-6 due to the addition of the phenacyl ester. Complementing the carbon spectra, the proton spectrum shows the expected geminal protons next to the phenyl ring at 3.66 ppm and the multiplet for the phenyl ring at 7.30 ppm along with the expected downfield shift of the geminal protons H-6 and H-6'.

Synthesis of diazoester sugars.



Scheme 3

Following Scheme 3, compound **4** was reacted with 1.0 equivalent of the diazo transfer reagent *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) in the presence of 1.1 equivalents of the large organic amine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)

turning the solution yellow. TLC of the reaction mixture (5:2 hexane:ethyl acetate) demonstrated consumption of starting material and the appearance of multiple spots, in addition to the desired product, some of which were UV active.

After flash column chromatography the proton NMR spectra of **7** (while cleaner in appearance than the crude reaction still appeared to contain a contaminant) appeared similar to that of **4** except for the disappearance of the singlet at 3.62 ppm on the proton NMR spectrum for the alkyl protons α to the phenyl ring. Although the carbon spectrum shows the presence of a contaminant, it also displays two changes. First, the carbonyl peak shifted upfield from 169.7 to 163.0. Second, the signal corresponding to the alkyl carbon previously at 41.4 ppm has disappeared. This information corresponds to the replacement of the geminal protons found on the phenacyl ester with a group such as a diazo and is consistent with the results of other researchers such as Davies et. al.[41]

The addition of the diazo group onto the *gluco* phenacyl ester **5** was achieved using *p*-ABSA and DBU. The resultant yellow solution was stirred for 2 days whereupon the TLC (3:1 hexane:ethyl acetate) of the reaction mixture demonstrated the complete consumption of the starting phenacyl ester and the production of several spots consisting of molecules with varying polarities. After an acidic work up of the reaction, purification was achieved by flash chromatography (9:2 hexane:ethyl acetate) to produce the *gluco* diazoester **8** in 87% yield.

An Infrared spectrum was obtained that showed, among the expected peaks for a protected carbohydrate, no peaks in the 3600-3200 cm^{-1} region for O-H bond stretching and peaks appearing at 2088 cm^{-1} and 1716 cm^{-1} relating to the diazo group and the carbonyl of the ester respectively.

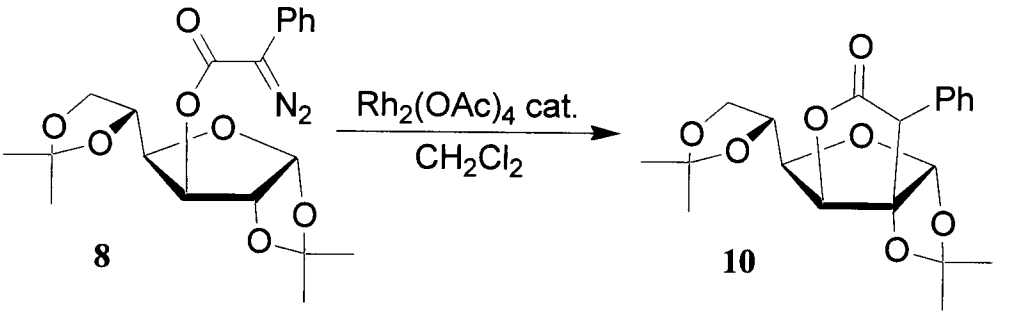
Proton NMR of the product demonstrated the loss of the methylene peak at 3.6 ppm due to replacement by the diazo group. The disappearance of the methylene peak originally at 41.4 and shift of the carbonyl from 169.8 to 163.55 ppm is evidence of the presence of the electron withdrawing diazo group in their vicinity. While the results from positive mode ESI-MS (405.34) showed the addition of H^+ to the molecule (404.16) those from negative mode APCI-MS are puzzling at first glance, however it is likely that during the process the molecule (404.16) loses N_2 creating a carbene that immediately reacts with a molecule of water forming the major negative ion (393.22).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(phenacyldiazo)-α-D-galactopyranose **9** was also synthesized using DBU and the diazo transfer reagent *p*-ABSA, and **6**. The formation of the UV active less polar product as well as several other spots was noted in addition to the consumption of starting material on the TLC (1:1 hexane:ethyl acetate). After flash column chromatography of **9** proton NMR revealed the disappearance of the doublet at 3.66 ppm relating to the geminal protons on the phenacyl ester. The ^{13}C spectrum displayed the expected shift of the carbonyl from 171.1 to 164.4 ppm relating to the addition of the diazo group. Infrared spectroscopy confirmed the presence of the ester carbonyl at 1743 cm^{-1} and of the diazo group at 2120 cm^{-1}. The ESI method of mass spectrometry confirmed the molecular weight of the compound (404.41) with a positive ion of the molecule complexed with a proton (405.22).

Rhodium decomposition of a diazoester sugar.

Following Scheme 4, the rhodium-catalyzed decomposition of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(phenacyldiazo)-α-D-glucofuranose occurred by the reaction of **8** with dirhodium diacetate [$Rh_2(OAc)_4$] to produce an intramolecular insertion at C-2.

There are several measures that must be taken to limit undesirable reactions such as the creation of a dicarbonyl species due to reaction with oxygen, the formation of a hydroxylated compound through reaction with water, and dimerization or intermolecular insertion, with another sugar derivative or suitable organic molecule. Therefore, to make certain that the carbene has enough of a chance to form the desired intramolecular insertion, care must be taken to assure that the reaction is as clean and dry as possible in addition to being free from dissolved oxygen in solution. This is achieved by thoroughly flame drying all glassware under nitrogen and purging all the components of the reaction with nitrogen gas. The metal catalyst is also dried using an Abderhalden drying pistol. To limit the degree of dimerization, two steps are taken, only 0.05 equivalents of the metal catalyst are available for reaction, also the sugar is dissolved in dry dichloromethane and added dropwise *via* syringe pump over four hours into a rapidly stirring solution of dry dichloromethane and dried dirhodium diacetate.



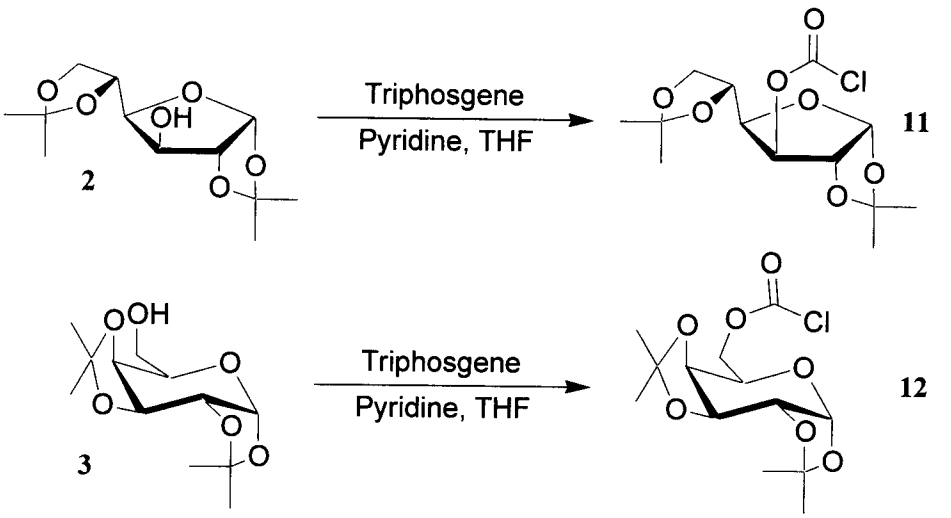
Scheme 4

There were several clues in the fairly clean NMR spectra that point to the conclusion that the main product of the reaction was indeed an intramolecular insertion at C-2 (**10**). The proton spectrum provides evidence in several ways. First, the collapse of the doublet at 5.83 ppm, for the proton attached to the anomeric carbon, down to a singlet indicates either a change in the dihedral angle between the H-1 and H-2 to 90° or the

complete lack of a proton at C-2. However, because there is no peak corresponding to H-2 the latter possibility is most likely the case. The ^{13}C NMR reveals the upfield shift of one of the furanose carbons from 77.2 ppm to 54.0 ppm and the emergence of a peak at 131 ppm for the carbon α to the phenyl ring. ESI-MS provided further proof that product **10** was produced with the visualization of a positive molecular ion complexed with water (393.16), which compares well with the molecular weight of the product (376.15).

Project 2-Synthesis and chemistry of azidosugars

Synthesis of chloroacyl sugars.



Scheme 5

The reactive intermediate 3-*O*-(chloroacyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **11** was the result of combining 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **2** with triphosgene while pyridine was added dropwise to the icebath cooled reaction solution of dry THF. TLC confirmed the progression of the reaction by the consumption of the protected sugar and appearance of a less polar spot.

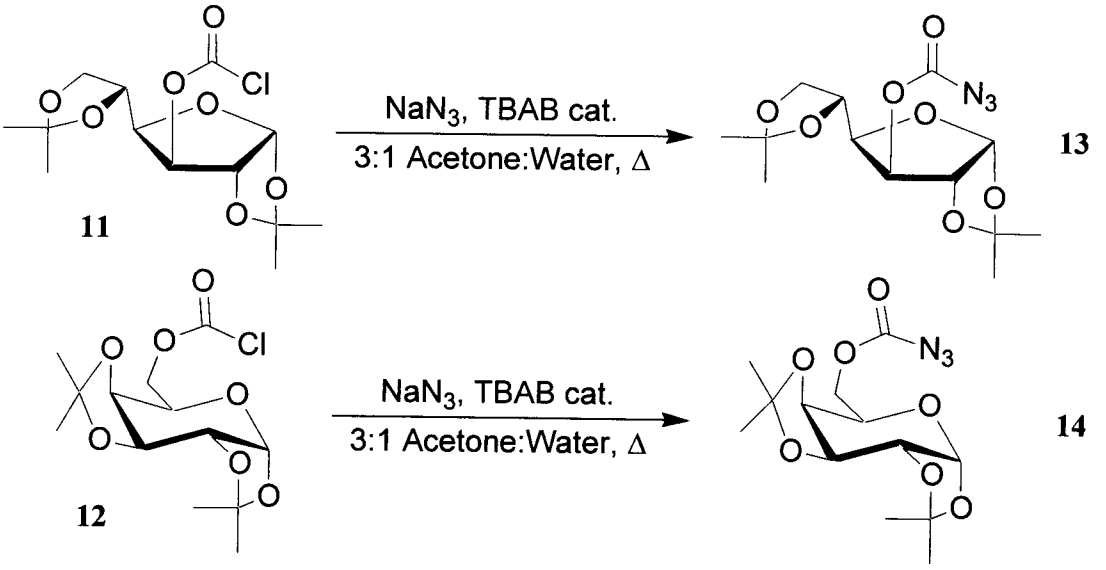
The fairly clean ^{13}C spectrum indicates the addition of the expected carbonyl peak at 149.7 ppm in addition to the downfield shift of C-1 of the furan ring from 74.8 to 82.5 ppm. ^{1}H NMR displays the downfield shift of H-3 from 3.0 ppm to 5.31 ppm while the rest of the spectrum remains similar to that of **2**.

6-*O*-(Chloroacyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**12**) was synthesized by way of reacting 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**), which was purchased from Aldrich, with triphosgene and anhydrous pyridine while being stirred in an icebath. The TLC plates (2:1 hexane:ethyl acetate) demonstrated the consumption of starting material while producing a less polar spot with little evidence of other spots. After filtering the off-white pyridinium hydrochloride salt from the solution the translucent gray syrup was prepared for analysis. ESI mass spectrometry of the chloroacyl derivative **12** (322.74) proved its identity. In addition to an ion of the compound combined with water (340.36), several other ions appear; two resulting from the presence of the two different isotopes of chlorine (342.14 and 347.08) bound to water and a molecular ion created with sodium (345.13). The appearance of a carbonyl signal in the ^{13}C NMR spectrum at 151.8 ppm is also sufficient evidence for the creation of compound **12**.

Synthesis of azidoacyl sugars.

As demonstrated in Scheme 6, creating an ester-linked azide **13** with the chloroacyl sugar **11** was done by reacting the sugar with sodium azide and a catalytic amount of tetra-*N*-butyl ammonium bromide (TBAB), which activates the carbonyl for nucleophilic acyl substitution with the azide. The reaction was monitored for completion by TLC (2:1 hexane:ethyl acetate). The complete consumption of the chloroacyl sugar

accompanied the appearance of a less polar spot and the resultant pink solution was quickly purified by flash column before characterization.



Scheme 6

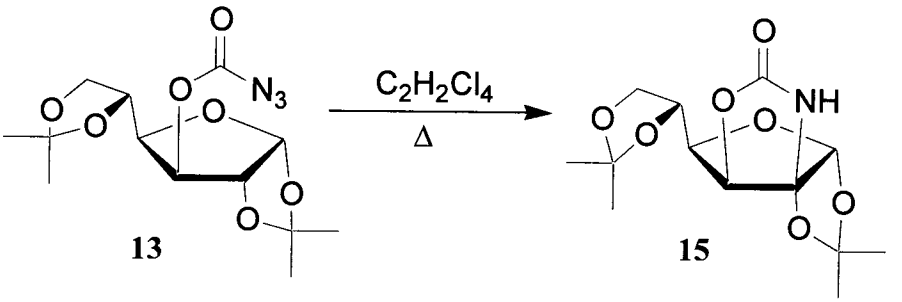
IR spectroscopy of compound **13** revealed the presence of an azide with signals at 2188 cm^{-1} and 2142 cm^{-1} and the presence of the ester carbonyl at 1743 cm^{-1}. Mass spectrometry confirmed the molecular weight of the product (329.31) with the production of a positive ion (330.37) resulting from the addition of H^+ using ESI. The NMR spectra displayed subtle changes such as the slight upfield shift of the H-3 doublet from 5.31 to 5.23 ppm in the ^1H spectrum and the downfield shift of the carbonyl peak from 149.7 to 156.5 ppm in the carbon spectrum all of which is indicative of the substitution of the chloride with the azide on the ester.

The azidation of 6-*O*-(chloroacyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-pyranose **12**, shown above in Scheme 6, is nearly identical to that of the *gluco* analog **13**. The carbonyl activating catalyst tetra-*N*-butyl ammonium bromide used in conjunction with sodium azide acts to alter the chloroacyl species into an acyl azide derivative. TLC

(1:1 hexane:ethyl acetate) of the pink solution showed the production of a slightly more polar compound as well as the expected consumption of the starting sugar.

After purification *via* flash column chromatography, the ^{1}H NMR spectrum and ^{13}C spectrum showed little change in their appearance, however through the use of ESI mass spectrometry and IR spectroscopy the presence of the azide was able to be confirmed. Infra Red confirmed the presence of the azide with the peaks at 2219, 2196, and 2147 cm^{-1} in the appropriate region in addition to the carbonyl peak at 1716 cm^{-1}. The mass spectrometry results indicated the creation of two positive ions, one that was the molecular weight (329.29) plus H^{+} (330.30) and a positive ion of the molecule complexed with water (347.26).

Thermal decomposition of an acyl azide sugar.



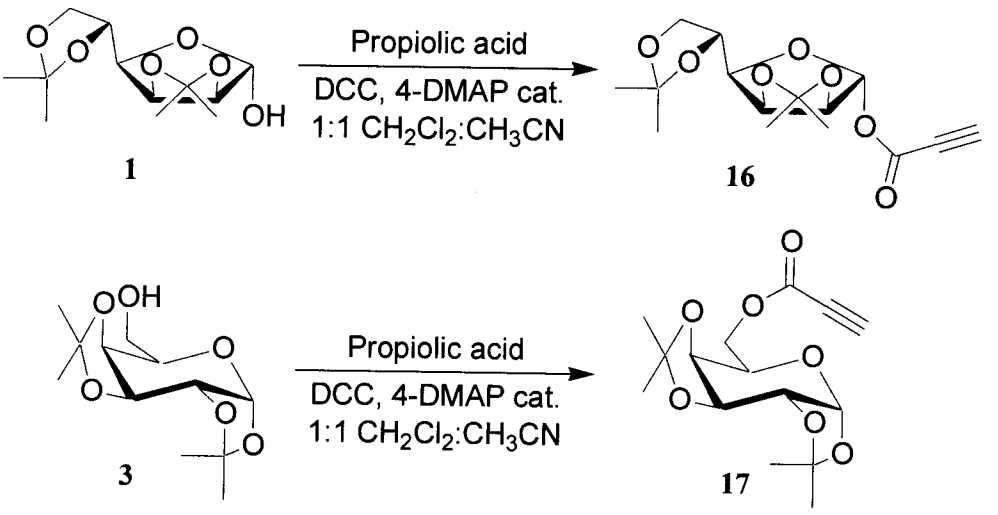
Scheme 7

The *gluco* acyl azide **13** was converted to a nitrene species by thermally decomposing the compound in a high boiling solvent. Chlorobenzene was first utilized as the solvent, however better results were later achieved with 1,1:2,2-tetrachloroethane. Similar to carbene chemistry, dimerization is one of the possible reactions in Scheme 7. Two ways of limiting dimerization and unwanted side reactions is the addition of the compound to the main reaction mixture after the solvent begins to reflux and refluxing in

a sufficient amount of solvent to avoid intermolecular reactions. After three hours, TLC (3:1 hexane:ethyl acetate) showed the complete conversion of starting material into several more polar spots with the least polar spot in the reaction mixture as the largest. After isolation of the largest spot the light yellow syrup was analyzed.

After reviewing the data, it is most likely that an intramolecular nitrene insertion occurred at C-2 on the glucofuranose resulting in compound **15**. Convincing proof presented first in the ^{1}H NMR spectrum, where the doublet corresponding to H-2, previously at 4.59 ppm, has disappeared and the doublet for H-1 at 5.63 ppm has collapsed to a singlet. ^{13}C spectrum shows a shift in the position of C-2 downfield from 79.5 to 101.6 ppm. The infrared spectrum showed the disappearance of the azide peak while the peak remained for the carbonyl at 1716 cm^{-1}. Two weak signals in the IR at 3448 cm^{-1} and 3362 cm^{-1} could possibly correspond to N-H bonds. Positive mode APCI-MS verified the molecular weight (301.12) of compound **15** by the formation of a positive ion with H^{+} (302.16).

Synthesis of propionyl sugars.



Scheme 8

Propiolic acid was reacted with **1** resulting in 2,3:5,6-di-*O*-isopropylidene-1-*O*-propionyl-α-D-mannofuranose **16** by use of the coupling reagent DCC. While the carbodiimide was being added dropwise to the reaction flask cooled in an icebath the reaction mixture slowly turned clear to yellow to dark brown. TLC (1:1 hexane:ethyl acetate) demonstrated the production of two less polar spots, when compared to the starting material, one of which was UV active. After purification by flash column chromatography the product was characterized by nuclear magnetic resonance spectroscopy.

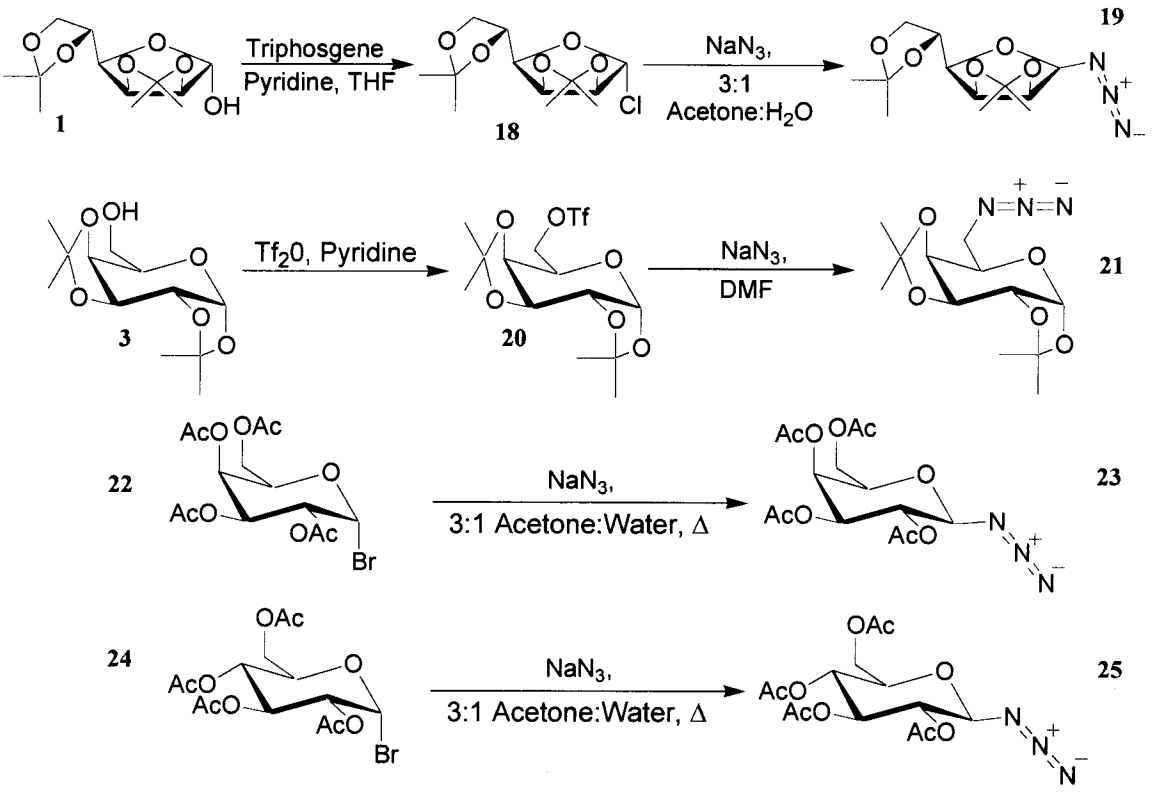
The clean proton NMR spectrum provided evidence of a downfield shift of H-1 from 5.36 to 6.19 ppm and the appearance of a singlet at 3.07 ppm for the proton on the end of the propiolate group. ^{13}C NMR revealed the presence of three additional peaks at 150.7, 76.0, and 74.0 ppm for the carbonyl of the added ester and the two alkyne carbons respectively.

The synthesis of the propionyl sugar, 1,2:3,4-di-*O*-isopropylidene-6-*O*-propionyl-α-D-galactopyranose **17** was begun by adding DCC dropwise to a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**), propiolic acid and 4-DMAP dissolved in dry CH_2Cl_2 and CH_3CN while stirring in an icebath. After one and a half hours total consumption of the starting material and appearance of several spots, one of which was major and less polar than the starting material, were visualized by TLC (3:1 hexane:ethyl acetate). The reaction mixture was then purified by flash column chromatography.

The NMR spectra demonstrated several notable peaks. ^{13}C NMR verified the presence of a carbonyl group at 152.3 ppm in addition to the presence of two peaks for the two alkyne carbons of the propionyl group at 75.2 and 75.3 ppm. Proton NMR

supports these claims by the appearance of a singlet at 2.94 in addition to the shift of the H-6 and H-6' protons downfield due to the presence of the ester attached to C-6. APCI mass spectrometry confirmed the molecular weight (312.32) of compound **17** with two different positive ions. The first ionized molecule (313.28) resulted from the attachment of H^+ to **17** while the second molecular ion (330.27) resulted from the addition of a molecule of water to **17**.

Synthesis of deoxy azide sugars.



Scheme 9

The synthesis of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride **18** began by dissolving triphosgene with the starting sugar **1**, in anhydrous tetrahydrofuran (THF), and adding pyridine dropwise to the reaction flask while being stirred.[42] The appearance of a whitish yellow precipitate and generation of gas accompanied the

addition of the pyridine. The reaction progress was monitored using TLC (1:1 hexane:ethyl acetate) and was marked by the appearance of two major spots along with consumption of the starting material. These two spots are most likely the α and β anomers of the glycosyl chloride as witnessed by the proton NMR which shows not only major peaks with complementary coupling constants for the α anomer, but a number of smaller signals possibly corresponding to the β anomer of **18**. ^{1}H NMR indicates a shift of the peak for H-1, from 5.36 to 6.08 ppm, due to the electronegativity of the chloride. Due to the unstable nature of the mannosyl chloride it was quickly reacted with sodium azide in a 3:1 mixture of acetone and deionized water. This mixture is necessary due to the different solubilities of the compounds utilized. Although acetone and water are miscible in each other salts do not dissolve easily in acetone while the same principle applies for water and organic molecules

The azidation of the mannosyl chloride, Scheme 9 compound **18**, was followed using TLC (1:1 hexane:ethyl acetate), which showed two spots; one similar to the chloride intermediate and a less polar spot. After purification of the top spot, the clean proton NMR spectrum displayed a large upfield shift for H-1 from 6.08 to 4.40 ppm indicating the displacement of the electronegative chloride with the azide species. The appearance of a coupling constant (3.5 Hz) for H-1 similar to that of H-2 is indicative that the anomeric configuration of the azidosugar **19** is β. IR spectroscopy confirmed the presence of an azide 2121 cm^{-1} while mass spectrometry provided additional support in the form of two positive ions; one *via* ESI (303.2), which is the weight of the molecule (285.13) plus water and another ion by APCI (258.38) whereby diatomic nitrogen is lost.

The synthesis of a deoxy azidosugar **21**, similar to **19** produced from diacetone mannose, with the protected sugar 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**) began by first transforming the hydroxyl group at C-6 into a triflate **20**. The formation of the intermediate was verified by both proton and ^{13}C NMR spectroscopy. The proton spectrum provided evidence for formation **20** by the downfield shift of the peaks of the geminal protons from 3.86 ppm in the protected starting sugar to 4.6 ppm. The ^{13}C spectrum displayed a quartet at 118.4 ppm due to the splitting caused by the fluorines bound to the sole carbon in the triflate group bound at C-6. The rearrangement of the peaks for C-2 thru C-6 is also indicative of the presence of the triflate on **3**.

Before decomposition of the *galacto* triflate **20** could occur it was dissolved in anhydrous dimethylformamide (DMF) and sodium azide in a classic S_N2 reaction whereby the azide ion attacks C-6 to displace the triflate, an excellent leaving group. The reaction was followed by thin layer chromatography (2:1 hexane:ethyl acetate) where the production of a spot slightly less polar than that for the triflate was witnessed. After purification, the molecule was analyzed using several methods.

Positive mode ESI mass spectrometry gave two molecular ions, the first (286.13) complexed with H^+ and the second (303.2) with H_2O compared well with the molecular weight (285.30). The ^{13}C NMR spectrum provided evidence for the displacement of the triflate group by disappearance of the aforementioned quartet and normal arrangement of peaks for the carbons in the pyranose ring. The best evidence for the addition of the azide is from IR spectroscopy wherein the peak for the azide appears at 2121 cm^{-1}.

In addition to the *manno* (**19**) and *galacto* (**21**) deoxyazidosugars already produced, two other azido sugars were synthesized employing two acetylated sugar

species which were brominated at C-1 and readily available for purchase from Fluka. Identical syntheses were used to make the azides from both 1-bromo-1-deoxy-2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**22**) and 1-bromo-1-deoxy-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**24**).

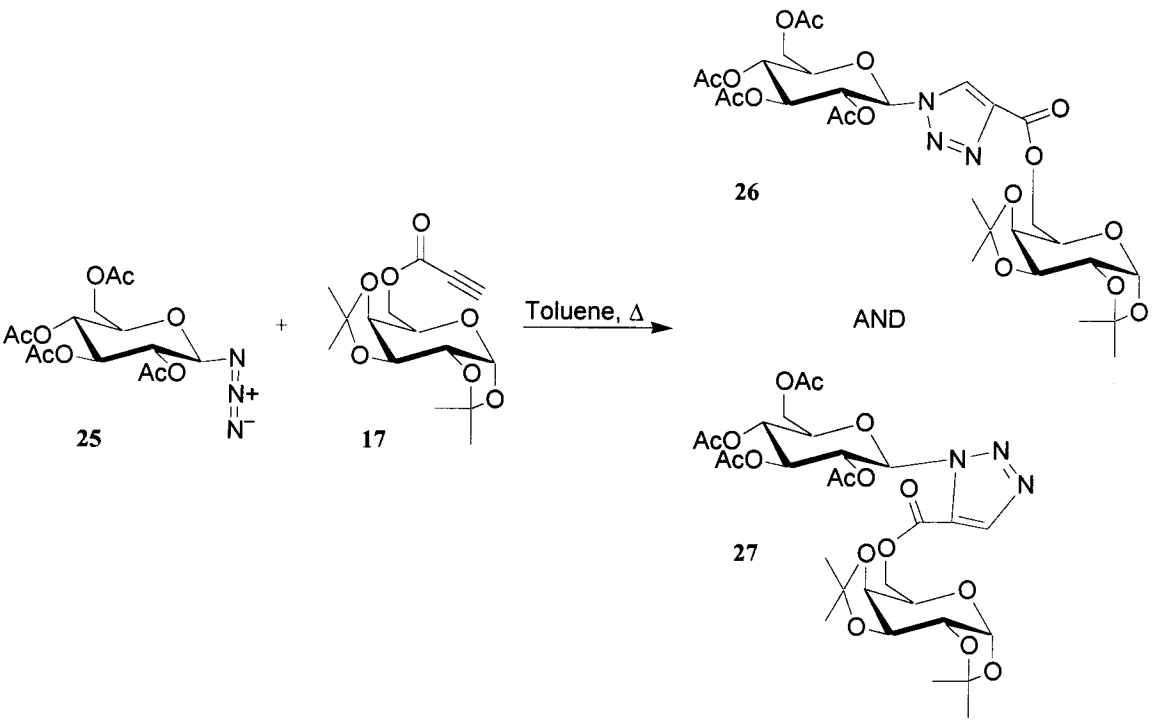
The synthesis of azido sugars **23** and **25** by displacement of the bromine at C-1 was identical to the reaction of the protected mannosyl chloride **19** with the azide anion. The sugars were dissolved in a mixture of acetone and water and, while refluxing, sodium azide was added. After 2 hours, TLC (2:1 hexane:ethyl acetate) confirmed the presence of a slightly less polar spot and the lack of starting material in the reaction mixture. Despite the fact that the reaction of the *gluco* derivative **25** consumed all of the starting material **24**, it contained a small amount of impurities and necessitated purification by flash column chromatography. The *galacto* derivative **23** did not show any presence of the starting sugar **22** and was pure by TLC after washing with deionized water and evaporating to a light yellow solid.

The mass (373.32) of both of the compounds, 1-azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**25**) and 1-azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-galacto-pyranose (**24**) was verified by positive mode ESI mass spectrometry. Both molecules formed positive ions with a water molecule (391.28) for the galactose version **24** and (391.27) for the glucose derivative **25**.

Formation of sugar-heterocycle hybrids.

In the Introduction, the prospect of performing [3+2] cycloadditions between azidosugars and appropriate sugar dipolarophiles, such as the propionyl derivatives **16** and **17**, was suggested. In these syntheses, the general scheme of reaction consisted of

the presence of two isomers in the ratio of 1:1. Unfortunately, only the topmost spot of the two was able to be cleanly isolated in appreciable amounts and subsequently analyzed.

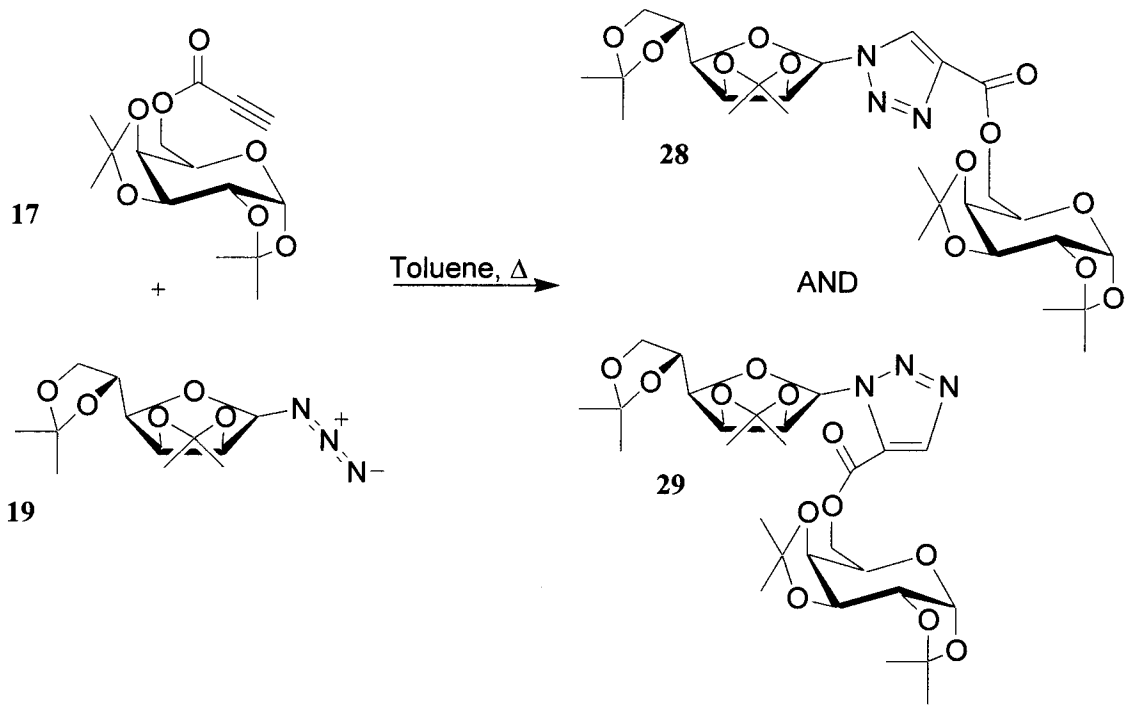


Scheme 10

The ^{1}H spectrum of the topmost spot consisted of four peaks from 1.36 to 1.61 ppm for the isopropylidene methyl groups and four peaks for the methyl groups on the acetates ranging from 1.85 to 2.08 ppm. From 4.13 to 6.43 ppm is a collection of multiplets some of which correspond to, and subsequently matched with, signals found in the parent sugars. Further downfield at 8.25 ppm is a singlet of one proton, which is attached to one of the carbons in the heterocycle. ^{13}C NMR provides verification of the presence of the four acetate methyls and four protecting group methyls between 20.5 and 20.9 ppm and 24.4 ppm to 26.0 ppm respectively. Five peaks from 156.9 to 170.4 ppm appear for carbonyls found on the acetate protecting groups and the ester linkage between

the heterocycle and the protected galactose. While there are also 12 peaks from 61.5 to 96.2 ppm for the pyranose carbons, of importance is the presence of two peaks at 129.2 and 139.1 ppm which are for the two carbons that were previously only part of the propionyl group attached to **17** but have now become part of the heterocycle and assumed aromatic character.

The next heterocycle combination illustrated in Scheme 11 resulted from the combination of **19** and **17** in the same manner explained above. After several hours TLC (3:1 Hexane:ethyl acetate) indicated the utilization of both starting materials and the appearance of two spots both of which were amenable to isolation and purification by flash column chromatography.



Scheme 11

Both spots were characterized using positive mode ESI mass spectrometry and produced similar molecular ions with H^+ that relate well to the molecular mass of the

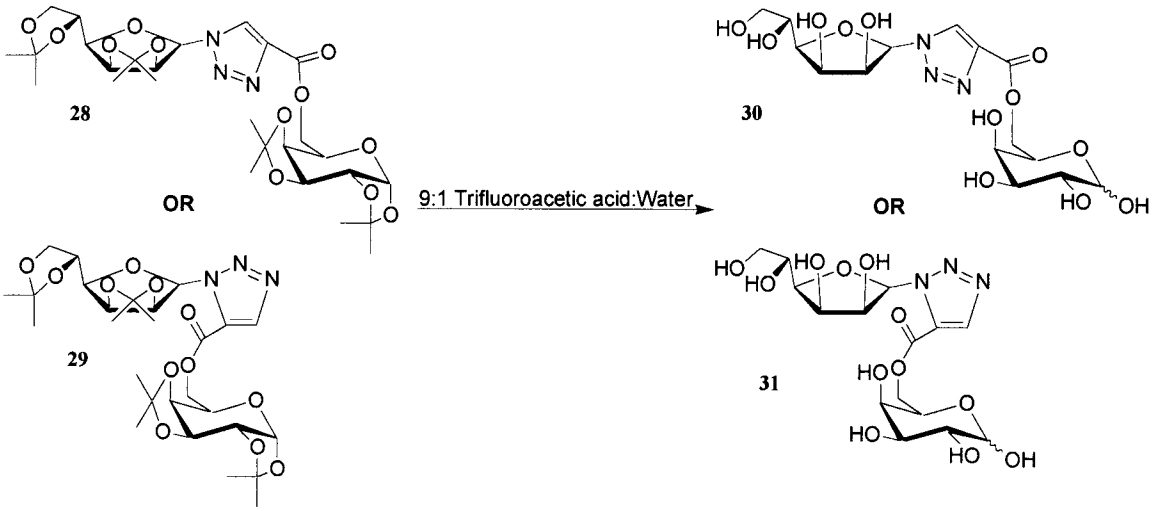
proposed structure (597.61). The less polar spot of the two produced an ion with the molecular weight of 598.33 while the lower spot produced an ion with the molecular weight of 598.40. This demonstrates that while possessing different polarities the two compounds share an identical molecular weight.

^{1}H NMR spectra of both compounds were similar in that eight peaks could be found between 1.32 ppm and 1.56 ppm for the upper spot and 1.18 ppm to 1.51 ppm for the lower spot which correspond to the methyl groups found on the two isopropylidene groups. The expected assortment of multiplets ranging from 3.81 ppm to 6.17 ppm for the upper spot, or 4.0 ppm to 6.55 ppm for the lower spot, were identified and assigned using the chemical shifts and coupling constants of their respective starting materials. Of specific interest is the noticeable difference in the chemical shifts, 8.2 (lower spot) and 8.36 (upper spot), of the peak for the proton found on the heterocycle. Integrating these peaks on the proton spectrum of the crude reaction mixture indicated an isomeric ratio of 3:1.

As with the ^{1}H spectra, the ^{13}C spectra of both compounds were nearly identical in that eight peaks were found from 24.0 to 27.2 ppm signaling the alkyl groups from the isopropylidenes. Next, as expected, a collection of 12 peaks for the sugar ring carbons were found from 63.9 ppm to 96.2 ppm and four peaks from 108.7 to 114.6 ppm for the quaternary carbons of the isopropylidene protecting groups in addition to the carbonyl of the ester linkage at 160.1 (upper spot) and 157.8 (lower spot). On both spectra, peaks for the two aromatic carbons on the heterocycle were found at 128.4, 139.1 (upper spot) and 127.6, 138.1 (lower spot). The combination of evidence from TLC, ESI-MS, and NMR spectra indicate the presence of two isomers of similar structure however, without

thorough multi-dimensional NMR experiments or X-ray diffraction it cannot be concluded which compound is which isomer.

The deprotection of one of the isomers, **28** or **29**, shown in Scheme 12, was accomplished by stirring the compound, which was in greater isomeric excess, in a 9:1 mixture of trifluoroacetic acid and deionized water. The resultant residue was then analyzed using ^{13}C NMR and ESI-MS. The proton NMR proved to be of little use due to the presence of the numerous hydroxyl groups confusing matters.

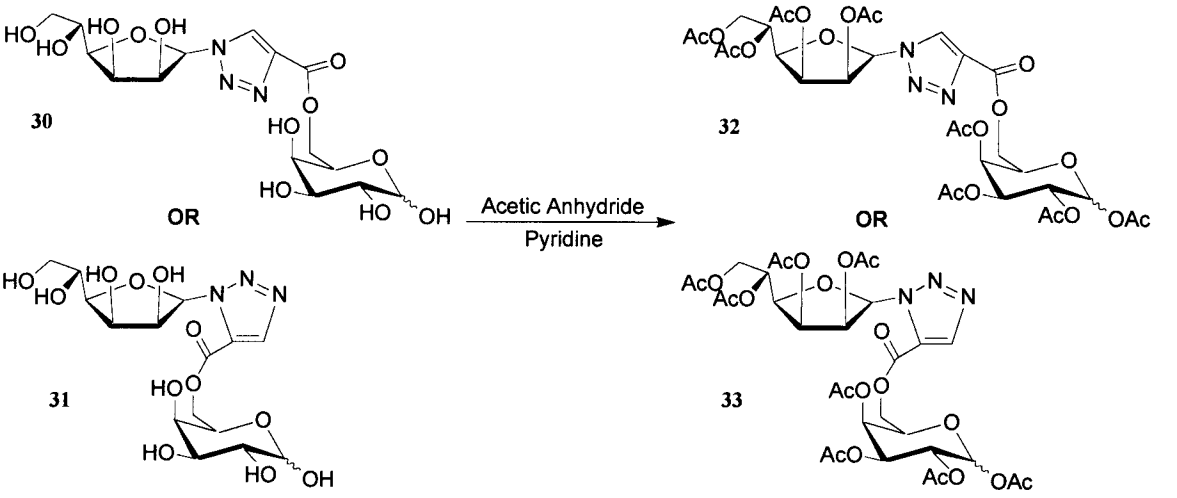


Scheme 12

The mass spectrometry results of the reaction in Scheme 12 compared nicely with the expected molecular weight (437.36) and produced a positive ion (438.20) with H^+ and a negative ion from the loss of H^+ (436.20). The ^{13}C NMR spectrum showed the absence of eight alkyl peaks between 24 ppm and 30 ppm and four peaks between 108 and 115 ppm for the quaternary carbons indicating loss of the isopropylidene groups. In addition to the expected peaks for the two heterocycle carbons at 129.5 ppm and 138.4 ppm the carbonyl peak appeared at 160.1 ppm. Although from 56.0 to 97.2 ppm, the range for ring

carbon on the sugars, 18 peaks were found where there should have been only 12 this is probably due to the anomerization of galactose in the molecule to a mixture of α and β isomers after deprotection.

To prove the deprotection of compound **28** or **29** was successful, acetylation was performed on the crude residue, consisting of either **30** or **31**, as presented in Scheme 13. After 24 hours, TLC confirmed the complete transformation of the starting material and appearance of a less polar spot. In the discussion of the proton and ^{13}C spectrum of this reaction it should be remembered that the compound being acetylated now consists of a galactose that has assumed two anomeric configurations.



Scheme 13

^{1}H NMR revealed the presence of twelve methyl groups attached to acetates in the form of ten signals from 1.86 to 2.05 two of which, shown by integration, possess twice the expected amount of protons. Moving further downfield in the spectrum finds a collection of different multiplets spanning from 4.17 to 6.59 ppm and signifies the protons attached to the pyranose and furanose rings as well. At 8.25 a singlet for one hydrogen is present and accounts for the proton bound to the carbon on the heterocycle

ring. Likewise, the carbon spectrum demonstrated a similar increase in the amount of expected signals. Ten signals were discovered from 20.0 ppm to 20.9 ppm, one of which was of triple intensity that represented the methyl groups of the acetates attached. Additionally, twelve different peaks for the carbonyls of the acetates were found from 168.6 to 170.2 ppm along with the peak for the ester carbonyl at 159.3 ppm. Finally, the presence of the 18 peaks, from 61.4 to 92.0 ppm, for the ring carbons and the two aromatic peaks at 127.1 ppm and 138.5 ppm are proof that **28** or **29** remained intact during deprotection and was acetylated producing compound **32** or **33**.

General Procedures

Reactions were analyzed by TLC on Whatman aluminum-backed plates. Nuclear Magnetic Resonance Spectra were recorded on samples dissolved in either $CDCl_3$ or d_6-DMSO, using an Oxford magnet attached to a Varian Gemini 2000 system, at a frequency of 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra. All chemical shifts were recorded in parts per million (ppm). Multiplicities of the signals[43] are labeled as follows: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), q (quartet), m (multiplet) and coupling constants (*J*) measured in Hertz. Infrared spectra were recorded on a Jasco FT/IR-410 spectrophotometer. Purifications *via* flash column chromatography used 70-270 mesh 60-Å silica gel. All mass spectra were obtained through the use of a Bruker Esquire LC-MS instrument.

Project 1

Synthesis of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (1).

In a flame dried 2 L Erlenmeyer flask 20.0 g of D-mannose was combined with 750 mL of dry acetone and the flask was capped with a drying tube. While stirring, 14.0 mL of conc. H_2SO_4 was added portionwise (2 mL every 5 min). After stirring for 4 hours the straw colored solution was neutralized with excess sodium carbonate and allowed to stir for 1 hour, whereupon the solution was filtered and refluxed for 1 hour with several grams of sodium carbonate and charcoal. After cooling, the solution was filtered and evaporated under reduced pressure to leave 21.1 g of a white powder (**1**) in 73% yield that was homogenous by TLC (1:1 hexane:ethyl acetate).

^{1}H NMR: δ 1.31 (s, 3H, -CH_3), 1.37 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3), 3.35 (d, 1H, -OH, J = 2.6 Hz), 4.06 (m, 2H, H-6, H-6'), 4.17 (dd, 1H, H-3, J = 3.7, 7.1 Hz), 4.4 (ddd, 1H, H-5, J = 3.9, 5.9, 6.0 Hz,), 4.6 (d, 1H, H-2, J = 6.0 Hz), 4.8 (dd, 1H, H-4, J = 3.7, 5.9 Hz), 5.36 (d, 1H, H-1, J = 2.4 Hz).

^{13}C NMR: δ 24.5, 25.2, 25.9, 26.9, 66.5, 73.2, 79.5, 80.1, 85.4, 101.1, 109.0, 112.5.

Synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2).

In a flame dried 2 L Erlenmeyer flask 60.0 g of D-glucose was combined with 1200 mL of dry acetone and capped with a drying tube. While stirring in an icebath 48.0 mL of conc. H_2SO_4 was added portionwise (5 mL every 10 min.). After stirring for 4 hours the straw colored solution was neutralized with sodium hydroxide solution (73.5 g in 90 mL deionized water) and allowed to stir for 1 hour whereupon, after checking for slight basicity, the solution was placed in the refrigerator overnight. The resultant fibrous precipitate was then filtered using vacuum and washed with ice-cold hexane. The filtrate was partially evaporated and returned to the freezer where additional product formed. After filtering and washing the additional product from the second recrystallization both batches were combined and dried with vacuum yielding 86.04 g (99%) of white fibrous solid (**2**) which was pure by TLC (2:1 hexane:ethyl acetate).

^{1}H NMR: δ 1.32 (s, 3H, -CH_3), 1.36 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3), 1.5 (s, 3H, -CH_3), 3.0 (d, 1H, -OH J = 4.0 Hz), 4.01 (dd, 1H, H-6, J = 5.1, 8.8 Hz), 4.06 (dd,

1H, H-6', J = 2.8, 8.1 Hz), 4.2 (dd, 1H, H-4, J = 6.0, 8.6 Hz), 4.3 (m, 2H, H-3, H-5), 4.5 (d, 1H, H-2, J = 3.7 Hz), 5.9 (d, 1H, H-1, J = 3.7 Hz).

^{13}C NMR: δ 25.2, 26.2, 26.8, 26.9, 67.5, 73.1, 74.8, 81.0, 85.0, 105.0, 109.4, 111.6.

MS: Calculated: 260.28, Found: (ESI pos) 261.27 ($M+H^+$), (ESI neg) 259.34 ($M-H^+$).

Synthesis of 2,3:5,6-di-*O*-isopropylidene-1-*O*-phenacyl-α-D-mannofuranose (4) from 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (1).

1.0 Equivalent of **1** (5.0 g, 19.6 mmol), 1.0 equivalent of phenylacetic acid (2.61 g, 19.6 mmol), and 4-dimethylaminopyridine (422 mg, 3.45 mmol) were added to a 500 mL round bottom flask, that was previously flame dried under nitrogen, and dissolved in 80 mL of dry CH_2Cl_2 and 100 mL of dry CH_3CN. While stirring, 1.1 equivalents of 1.0 M 1,3-dicyclohexylcarbodiimide solution (21.1 mL, 21.1 mmol) were added dropwise *via* syringe pump (30 mL per hour) resulting in a white precipitate. The reaction mixture was monitored by TLC (2:1 hexane:ethyl acetate), which, after stirring for 12 hours at room temperature, confirmed the complete consumption of starting material and formation of a less polar product. After gravity filtering the mixture, the solvents were removed using the rotary evaporator and the resultant off-white residue was dissolved in 50 mL CH_2Cl_2. The solution was then washed with 5% H_2SO_4 (3 x 25 mL) and finally deionized water (2 x 25 mL). After drying with $MgSO_4$ the filtrate was evaporated to give 7.14 g (98%) of **4** as a pale yellow solid.

^{1}H NMR: δ 1.31 (s, 3H, -CH_3), 1.36 (s, 3H, -CH_3), 1.43 (s, 3H, -CH_3), 1.46 (s, 3H, -CH_3), 3.62 (s, 2H, -CH_2-), 3.89 (dd, 1H, H-4, J = 3.5, 8.1 Hz), 3.94 (dd, 1H, H-6, J = 4.2, 9.0 Hz), 4.06 (dd, 1H, H-6', J = 6.0, 9.0 Hz), 4.36 (ddd, 1H, H-5, J = 4.2, 6.0, 8.0 Hz), 4.65 (d, 1H, H-2, J = 5.9 Hz), 4.8 (dd, 1H, H-3 J = 3.5, 5.9 Hz), 6.13 (s, 1H, H-1), 7.2-7.5 (m, 5H, Ar-H).

^{13}C NMR: δ24.7, 25.2, 25.9, 27.0, 41.4, 66.8, 72.7, 79.2, 82.2, 84.8, 100.7, 109.2, 113.1, 127.1, 128.5 (*2*), 128.9 (*2*), 133.2, 169.7.

MS: Calculated: 378.42, Found (ESI pos): 379.22 ($M+H^+$), 396.32 ($M+H_2O$).

Synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-phenacyl-α-D-glucofuranose (5) from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2).

To a flame dried 100 mL round bottom flask 1.0 equivalent of **2** (2.6 g, 10.0 mmol), 1.1 equivalents of phenylacetic acid (1.5 g, 11.0 mmol), and 4-dimethylaminopyridine (200 mg, 1.6 mmol) were dissolved in 25 mL of dry CH_2Cl_2, and 25 mL of dry CH_3CN. Next, 1.1 equivalents of 1 M 1,3-dicyclohexylcarbodiimide (11.0 mL, 11.0 mmol) was added dropwise through an addition funnel resulting in the formation of a white precipitate. The reaction was monitored by TLC (3:1 hexane:ethyl acetate) for the absence of starting material and the appearance of a less polar product. After stirring at room temperature for 4 hours, the precipitate was removed from the reaction by gravity filtration and rinsed with CH_2Cl_2 (2 x 15 mL). The organic rinse was recombined with the reaction solution, which was then evaporated on a rotary evaporator to leave a yellow-white solid. The solid was then dissolved in 30 mL of CH_2Cl_2 and

washed with 5% H_2SO_4 (3 x 20 mL) and deionized water (3 x 30 mL) before drying with $MgSO_4$. After filtering the solution into a tared round bottom flask the solution was evaporated to yield 3.4 g (90%) of yellow solid (**5**).

^{1}H NMR: δ 1.25 (s, 3H, -CH_3), 1.28 (s, 3H, -CH_3), 1.38 (s, 3H, -CH_3), 1.5 (s, 3H, -CH_3), 3.6 (s, 2H, -CH_2), 3.95 (dd, 1H, H-6, J = 5.3, 8.6 Hz), 3.99 (dd, 1H, H-6', J = 5.9, 8.6 Hz), 4.08 (ddd, 1H, H-5, J = 5.3, 5.9, 8.1 Hz), 4.18 (dd, 1H, H-4, J = 2.9, 8.1 Hz), 4.42 (d, 1H, H-2, J = 3.8 Hz), 5.27 (d, 1H, H-3, J = 2.9 Hz), 5.81 (d, 1H, H-1, J = 3.7 Hz), 7.25-7.55 (m, 5H, Ar-H).

^{13}C NMR: δ 25.2, 26.2, 26.8, 26.9, 41.4, 67.2, 72.2, 76.3, 79.8, 83.1, 104.9, 109.2, 112.2, 127.1, 128.5 (*2*), 129.0 (*2*), 133.2, 169.8.

MS: Calculated: 378.42, Found: (APCI pos) 379.27 ($M+H^+$), 396.33 ($M+H_2O$).

Synthesis of 1,2:3,4-di-*O*-isopropylidene-6-*O*-phenacyl-α-D-galactopyranose (6) from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (3).

In a flame dried 100 mL round bottom flask, 1.0 equivalent of **3** (2.34 g, 8.98 mmol), 1.1 equivalents of phenylacetic acid (1.35 g, 9.89 mmol), and 200 mg of 4-dimethylaminopyridine (1.6 mmol) were dissolved in 25 mL of dry CH_2Cl_2 and 25 mL of dry CH_3CN. To this solution 1.1 equivalents of 1.0 M 1,3-dicyclohexylcarbodiimide (9.9 mL, 9.9 mmol) was added dropwise over 1 hour to the solution while stirring at room temperature. Monitoring of the reaction was performed using TLC (1:1 hexane:ethyl acetate). The appearance of a less polar product and no starting material remaining indicated that the reaction had proceeded to completion. The solution was then

evaporated to dryness, dissolved in 30 mL of CH_2Cl_2, and washed with 5% H_2SO_4 (3 x 15 mL) and deionized H_2O (3 x 15 mL). After drying over $MgSO_4$ the filtrate was evaporated at reduced pressure to give 3.25 g (96%) of pale yellow solid (**6**).

^{1}H NMR: δ 1.34 (s, 3H, -CH_3), 1.35 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3), 1.46 (s, 3H, -CH_3), 3.66 (d, 2H, -CH_2-, J = 2.6 Hz), 4.0 (ddd, 1H, H-5, J = 1.8, 4.6, 7.7 Hz), 4.17 (dd, 1H, H-6, J = 1.8, 7.7), 4.22 (d, 1H, H-4, J = 7.9 Hz), 4.32 (d, 1H, H-2, J = 4.6 Hz), 4.34 (dd, 1H, H-6', J = 4.6, 8.4 Hz), 4.6 (dd, 1H, H-3, J = 2.6, 7.9), 5.54 (d, 1H, H-1, J = 4.9 Hz), 7.20-7.5 (m, 5H, Ar-H).

^{13}C NMR: δ 24.4, 24.9, 25.9, 25.92, 41.1, 63.7, 65.8, 70.2, 70.5, 70.8, 96.0, 108.5, 109.4, 126.7, 128.2 (*2*), 129.0 (*2*), 133.6, 171.1.

Synthesis of 2,3:5,6-di-*O*-isopropylidene-1-*O*-(phenacyldiazo)-α-D-mannofuranose (7) from 2,3:5,6-di-*O*-isopropylidene-1-*O*-phenacyl-α-D-mannofuranose (4).

1.0 Equivalent of **4** (3.94 g, 10.4 mmol) and 1.0 equivalent of *p*-acetamidobenzenesulfonyl azide (2.5 g, 10.4 mmol) in a flame dried 100 mL round bottom flask were dissolved in 20 mL of dry CH_2Cl_2 and 20 mL of dry CH_3CN. While stirring at room temperature, 1.1 equivalents 1,8-diazabicyclo[5.4.0]undec-7-ene (1.71 mL, 11.44 mmol) was added dropwise over 3 hours with a syringe pump producing a bright yellow solution. TLC (5:2 hexane:ethyl acetate) was used to assess the progress of the reaction. After stirring 48 hours, the reaction was evaporated to remove solvents and the residue was dissolved in 50 mL CH_2Cl_2 and washed with 5% H_2SO_4 (1 x 20 mL) and deionized water (2 x 30 mL). Drying of the organic layer was accomplished using

$MgSO_4$, which was then removed by filtration. The organic layer was evaporated onto silica gel (11 g) and the mixture was purified by flash column chromatography on 110 g of silica gel using 4:1 hexane:ethyl acetate to give 3.44 g (81%) of **7** as a yellow syrup.

^{1}H NMR: δ 1.36 (s, 3H, -CH_3), 1.39 (s, 3H, -CH_3), 1.47 (s, 3H, -CH_3), 1.51 (s, 3H, -CH_3), 4.1 (m, 3H, H-4, H-6, H-6'), 4.43 (ddd, 1H, H-5, J = 4.2, 5.8, 7.8 Hz), 4.8 (d, 1H, H-2, J = 5.9 Hz), 4.9 (dd, 1H, H-3, J = 3.7, 5.9 Hz), 6.32 (s, 1H, H-1), 7.3-7.6 (m, 5H, Ar-H).

^{13}C NMR: δ24.8, 25.2, 26.1, 27.1, 66.8, 72.8, 72.9, 79.3, 82.3, 85.0, 101.1, 109.3, 113.3, 124.0 (*2*), 126.1, 128.9 (*3*), 163.0.

Synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(phenacyldiazo)-α-D-glucofuranose (8) from 1,2:5,6-di-*O*-isopropylidene-3-*O*-phenacyl-α-D-glucofuranose (5).

In a 100 mL round bottom flask flame dried under N_2, 1.0 equivalent of **5** (3.78 g, 10.0 mmol) and 1.1 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.67 mL, 11.0 mmol) were dissolved in 40 mL of a 50/50 mixture of dry CH_2Cl_2 and dry CH_3CN. After degassing the reaction vessel with N_2, 1.0 equivalent of *p*-acetamidobenzenesulfonyl azide (2.4 g, 10.0 mmol) dissolved in 5 mL of dry CH_2Cl_2 was added dropwise with a syringe pump (1 mL/hr) resulting in a clear yellow solution. Using TLC (3:1 hexane:ethyl acetate) the reaction was monitored for completion. After stirring 48 hours at room temperature, the reaction was evaporated under reduced pressure and dissolved in 35 mL of CH_2Cl_2. The solution was subsequently washed with 5% H_2SO_4 (1 x 25 mL) and deionized water (2 x 25 mL) and dried with $MgSO_4$. The solution was then evaporated

onto silica gel (12 g) and purified by flash column chromatography using 90 g of silica gel and 9:2 hexane:ethyl acetate as eluent yielding 3.54 g (87%) of **8** as a bright yellow syrup.

^{1}H NMR: δ 1.33 (s, 3H, -CH_3), 1.43 (s, 3H, -CH_3), 1.55 (s, 3H, -CH_3), 1.61 (s, 3H, -CH_3), 4.03 (dd, 1H, H-6, J = 4.8, 8.6 Hz), 4.11 (dd, 1H, H-6', J = 5.9, 8.6 Hz), 4.19 (ddd, 1H, H-5, J = 4.8, 5.9, 8.1 Hz), 4.27 (dd, 1H, H-4, J = 2.9, 8.1 Hz), 4.68 (d, 1H, H-2, J = 3.7 Hz), 5.38 (dd, 1H, H-3, J = 0.6, 2.9 Hz), 5.92 (d, 1H, H-1, J = 3.7 Hz), 7.3-7.6 (m, 5H, Ar-H).

^{13}C NMR: δ 25.3, 26.3, 26.8, 26.9, 67.4, 72.5, 77.2, 79.9, 83.4, 105.0, 109.4, 112.3, 123.9, 124.7, 127.4 (*2*), 130.1 (*2*), 163.6.

IR: 2088 cm^{-1} (N_2), 1716 cm^{-1} (C=O).

MS: Calculated: 404.16, Found: (ESI pos) 405.34 ($M+H^+$), (APCI neg) 393.22 ($M-N_2+^-OH$).

Synthesis of 1,2:3,4-di-*O*-isopropylidene-6-*O*-(phenacyldiazo)-α-D-galactopyranose (9) from 1,2:3,4-di-*O*-isopropylidene-6-*O*-phenacyl-α-D-galactopyranose (6).

To a flame dried 50 mL round bottom flask 1.0 equivalent of compound **6** (1.05 g, 2.77 mmol) and 2.0 equivalents of *p*-acetamidobenzenesulfonyl azide (1.33 g, 5.55 mmol) in 25 mL of CH_2Cl_2 and 25 mL of CH_3CN. Next, 2.5 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.04 mL, 6.94 mmol) were added dropwise over 45 minutes changing the solution from straw colored to deep yellow. After confirming the

consumption of starting material and the formation of a slightly less polar product using TLC (1:1 hexane:ethyl acetate), the reaction was evaporated after stirring for 18 hours at room temperature and dissolved in 40 mL CH_2Cl_2. The solution was then washed with 5% H_2SO_4 (1 x 25 mL) and deionized water (2 x 25 mL) before drying with $MgSO_4$ and filtering. The solution was then evaporated onto silica gel (3 g) and purified by eluting with 7:1 hexane:ethyl acetate on a flash column giving 1.05 g (93%) of product in the form of a yellow syrup (**9**).

^{1}H NMR: δ 1.34 (s, 3H, -CH_3), 1.35 (s, 3H, -CH_3), 1.47 (s, 3H, -CH_3), 1.52 (s, 3H, -CH_3), 4.12 (ddd, 1H, H-5, J = 1.8, 5.1, 7.0 Hz), 4.27 (dd, 1H, H-4, J = 1.8, 7.9 Hz), 4.35 (dd, 1H, H-2, J = 2.6, 4.9 Hz), 4.4 (dd, 1H, H-6, J = 1.8, 6.5 Hz), 4.45 (dd, 1H, H-6', J = 3.9, 11.5 Hz), 4.65 (dd, 1H, H-3, J = 2.6, 7.9 Hz), 5.56 (d, 1H, H-1, J = 4.9 Hz), 7.2-7.5 (m, 5H, Ar-H).

^{13}C NMR: δ 24.4, 24.9, 25.9, 26.0, 63.8, 66.0, 70.3, 70.5, 70.8, 96.0, 108.6, 109.5, 123.7, 125.1, 125.5, 128.6 (*2*), 128.7, 164.6.

IR: 2120 cm^{-1} (N_2), 1743 cm^{-1} (C=O).

MS: Calculated: 404.41, Found: (ESI pos) 405.22 ($M+H^+$).

Rhodium catalyzed decomposition of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(phenacyl-diazo)-α-D-glucofuranose (8) to form compound 10.

In a flame dried 100 mL round bottom flask 91 mg (0.2 mmol) of dirhodium acetate was stirred in 15 mL of dry CH_2Cl_2 while 1.67 g (4.13 mmol) of **8** was dissolved

in 15 mL of dry CH_2Cl_2. After degassing both solutions with N_2, the diazosugar solution was added dropwise to the dirhodium acetate solution over 4 hours using a syringe pump. After stirring 18 hours the TLC (4:1 hexane:ethyl acetate) revealed complete consumption of the starting material. The solution was then filtered with celite and evaporated to light yellow syrup. The reaction was then purified using a MPLC column and 9:2 hexane:ethyl acetate to give 0.74 g (47%) of **10** as a clear syrup.

^{1}H NMR: δ 1.29 (s, 3H, -CH_3), 1.41 (s, 3H, -CH_3), 1.46 (s, 3H, -CH_3), 1.49 (s, 3H, -CH_3), 4.07 (dd, 1H, H-6, J = 4.4, 8.8 Hz), 4.17 (dd, 1H, H-6', J = 6.0, 8.7 Hz), 4.28 (dd, 1H, H-4, J = 2.7, 8.4 Hz), 4.42 (ddd, 1H, H-5, J = 4.6, 6.0, 10.1 Hz), 4.91 (d, 1H, H-3, J = 2.7 Hz), 5.83 (s, 1H, H-1), 7.2-7.6 (m, 5H, Ar-H).

^{13}C NMR: δ 25.1, 26.7, 27.0, 27.7, 52.9, 67.1, 72.4, 81.1, 85.1, 109.7, 110.9, 113.3, 128.1, 128.6 (2), 128.9 (2), 129.9, 132.2, 173.2.

MS: Calculated: 376.15 , Found: (ESI pos) 393.16 (M+H_2O).

Project 2

Synthesis of 3-*O*-(chloroacyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (11) from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2).

1.0 Equivalent of **2** (1.0 g, 3.8 mmol) and 2.0 equivalents of triphosgene (2.3 g, 7.68 mmol) were added to a flame dried 100 mL round bottom flask and dissolved in 50 mL of dry tetrahydrofuran. While stirring in an icebath and under inert atmosphere, 3.0 equivalents of pyridine (0.93 mL, 11.52 mmol) were added, using a syringe pump, dropwise over 30 minutes creating a white precipitate. TLC (2:1 hexane:ethyl acetate)

revealed consumption of the starting sugar and the presence of a less polar spot. After stirring for 2 hours the reaction was filtered and evaporated to 0.98 g (79%) of translucent gray syrup (**11**).

^{1}H NMR: δ 1.32 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3), 1.42 (s, 3H, -CH_3), 1.51 (s, 3H, -CH_3), 4.02 (dd, 1H, H-6, J = 4.4, 8.8 Hz), 4.12 (dd, 1H, H-6', J = 5.7, 8.8 Hz), 4.19 (dd, 1H, H-4, J = 2.7, 8.4 Hz), 4.21-4.23 (m, 1H, H-5), 4.64 (d, 1H, H-2, J = 3.7 Hz), 5.31 (d, 1H, H-3, J = 2.7 Hz), 5.94 (d, 1H, H-1, J = 3.7 Hz).

^{13}C NMR: δ 25.2, 26.3, 26.7, 27.0, 67.3, 72.1, 79.6, 82.6, 82.9, 104.9, 109.5, 112.6, 149.7.

Synthesis of 6-*O*-(chloroacyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (12) from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (3).

1.0 Equivalent of diacetone galactose (**3**) (3.25 g, 12.5 mmol) and 1.5 equivalents of triphosgene (5.56 g, 18.75 mmol) were dissolved in a 250 mL round bottom flask with 125 mL of anhydrous tetrahydrofuran. Next, 3.8 equivalents of pyridine (3.83 mL, 47.5mmol) were added dropwise over 30 minutes causing the formation of a white precipitate. Monitoring of the reaction was performed by TLC (2:1 hexane:ethyl acetate) for the disappearance of starting material and the appearance of a less polar spot. After stirring for 4 hours, the reaction was filtered with celite and evaporated to give 3.26 g (81%) of **12** as a crude gray syrup.

^{1}H NMR: δ 1.33 (s, 6H, -CH_3), 1.44 (s, 3H, -CH_3), 1.53 (s, 3H, -CH_3), 4.09 (ddd, 1H, H-5, J = 1.8, 6.0, 8.1 Hz), 4.24 (dd, 1H, H-6, J = 2.0, 7.9 Hz), 4.25-4.29 (m,

1H, H-6'), 4.35 (dd, 1H, H-2, J = 2.6, 4.9 Hz), 4.44-4.46 (m, 1H, H-4), 4.64 (dd, 1H, H-3, J = 2.6, 7.9 Hz), 5.54 (d, 1H, H-1, J = 4.9 Hz).

^{13}C NMR: δ24.5, 25.0, 26.0, 26.1, 65.4, 70.2, 70.3, 70.6, 70.7, 96.1, 108.9, 109.9, 150.6.

MS: Calculated: 322.74, Found: (ESI pos) 340.36 (M^1+H_2O), 342.14 (M^2+H_2O), 345.13 (M+Na^+), 347.08 (M^3+H_2O).

Synthesis of 3-*O*-(azidoacyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (13) from 3-*O*-(chloroacyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (11).

In a flame dried 100 mL round bottom flask 1.0 equivalent of **11** (2.47 g, 7.7 mmol), and 200 mg of tetra-*N*-butyl ammonium bromide were dissolved in 50 mL of CH_2Cl_2. While refluxing and stirring 1.5 equivalents of sodium azide (0.75 g, 11.5 mmol) were added causing a color change from pale yellow to deep yellow. After stirring for 18 hours TLC (2:1 hexane:ethyl acetate) verified a change in the reaction mixture. The reaction was then filtered with celite and washed with deionized water (1 x 40 mL) before drying with $MgSO_4$. After removing the drying agent, the filtrate was purified with a flash column using 20 g of silica gel and 8:1 hexane:ethyl acetate as eluent. The fractions were then evaporated yielding 1.94 g (78%) of thick yellow syrup identified as **13**.

^{1}H NMR: δ 1.32 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3), 1.42 (s, 3H, -CH_3), 1.53 (s, 3H, -CH_3), 4.0 (dd, 1H, H-6, J = 4.4, 9.0 Hz), 4.1 (dd, 1H, H-6', J = 5.9, 9.0 Hz),

4.17-4.24 (m, 1H, H-5), 4.2 (d, 1H, H-3, J = 2.4 Hz), 4.59 (d, 1H, H-2, J = 3.7 Hz), 5.23 (dd, 1H, H-4, J = 0.55, 2.4 Hz) 5.9 (d, 1H, H-1, J = 3.7 Hz).

^{13}C NMR: δ 25.3, 26.3, 26.7, 27.0, 67.3, 72.1, 79.6, 79.9, 82.9, 104.9, 109.4, 112.4, 156.5.

IR : 2189 cm^{-1} (N_3), 2142 cm^{-1} (N_3), 1743 cm^{-1} (C=O).

MS: Calculated: 329.31, Found (ESI pos) 330.37 ($M+H^+$).

Synthesis of 6-*O*-(azidoacyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (14) from 6-*O*-(chloroacyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (12).

In a 100 mL flame dried round bottom flask 1.0 equivalent of **12** (1.64 g, 5.07 mmol) and 100 mg of tetra-*N*-butyl ammonium bromide were dissolved in 50 mL of CH_2Cl_2. While stirring the reaction, 2.0 equivalents of sodium azide (0.659 g, 10.14 mmol) were added causing the solution to begin turning pink. TLC (2:1 hexane:ethyl acetate) confirmed a change in the reaction mixture and after stirring for 18 hours the reaction was filtered with celite and washed with deionized water (1 x 40 mL). After drying with $MgSO_4$, the solution was filtered and evaporated onto silica gel (4 g) and then purified by a flash column (30 g of silica gel) and eluted with 7:1 hexane:ethyl acetate producing 1.1 g (66%) of light yellow syrup (**14**).

^{1}H NMR: δ 1.30 (s, 3H, -CH_3), 1.31 (s, 3H, -CH_3), 1.42 (s, 3H, -CH_3), 1.50 (s, 3H, -CH_3), 4.04 (ddd, 1H, H-5, J = 1.8, 5.3, 7.1 Hz), 4.21 (dd, 1H, H-4, J = 2.0,

7.9 Hz), 4.30-4.34 (m, 3H, H-2, H-6, H-6'), 4.6 (dd, 1H, H-3, 2.6, 7.9 Hz), 5.5 (d, 1H, H-1, J = 5.0 Hz).

^{13}C NMR: δ 24.5, 25.0, 26.0, 26.1, 65.6, 67.0, 70.3, 70.6, 70.7, 96.1, 108.7, 109.6, 157.2.

IR: 2219 cm^{-1} (N_3), 2196 cm^{-1} (N_3), 2147 cm^{-1} (N_3), 1716 cm^{-1} (C=O).

MS: Calculated: 329.29, Found: (ESI pos) 330.30 ($M+H^+$), 347.26 ($M+H_2O$).

Thermal decomposition of 3-*O*-(azidoacyl)-1,2:5,6-di-*O*-isopropylidene-α-D-gluco-furanose (13) in 1,1:2,2-tetrachloroethane producing compound 15.

0.28 g Of **13** was placed in a 50 mL round bottom flask and dissolved in 15 mL of 1,1:2,2-tetrachloroethane. The reaction was refluxed for 3 hours until TLC (3:1 hexane:ethyl acetate) confirmed the disappearance of the starting sugar. The reaction was then evaporated under reduced pressure onto silica gel (1 g) and purified by flash chromatography using 15 g of silica gel and 9:2 hexane:ethyl acetate to provide 0.13 g (44%) of **15** as a clear syrup.

^{1}H NMR: δ 1.36 (s, 3H, -CH_3), 1.45 (s, 6H, 2 x -CH_3), 1.52 (s, 3H, -CH_3), 4.02 (dd, 1H, H-6, J = 4.21, 8.79 Hz), 4.13 (dd, 1H, H-6', J = 5.49, 8.60 Hz), 4.31-4.39 (m, 1H, H-5), 4.36 (d, 1H, H-4, J = 3.3 Hz), 4.75 (d, 1H, H-3, J = 3.5 Hz), 5.63 (s, 1H, H-1), 7.73 (s, 1H, N-H).

^{13}C NMR: δ 25.1, 26.9, 27.0, 27.1, 66.7, 72.0, 81.1, 84.7, 101.6, 106.9, 109.7, 112.3, 156.9.

IR: 3448 cm^{-1} (N-H), 3362 cm^{-1} (N-H), 1716 cm^{-1} (C=O).

MS: Calculated: 301.12, Found (APCI pos) 302.16 ($M+H^+$).

Synthesis of 2,3:5,6-di-*O*-isopropylidene-1-*O*-propionyl-α-D-mannofuranose (16) from 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (1).

In a flame dried 250 mL round bottom flask were dissolved 1.0 equivalent of diacetone mannose (**1**) (2.0 g, 7.68 mmol), 2.0 equivalents of propiolic acid (0.95 mL, 15.36 mmol), and 4-dimethylaminopyridine (154 mg) in 20 mL dry CH_3CN and 5 mL dry CH_2Cl_2. While stirring in an ice bath, 2.1 equivalents of a 1.0 M solution of 1,3-dicyclohexylcarbodiimide in CH_2Cl_2 (16.14 mL, 16.14 mmol) were added dropwise over 45 minutes. Monitoring of the reaction was accomplished by observing TLC plates (1:1 hexane:ethyl acetate) for the appearance of a less polar spot and disappearance of starting material in the reaction mixture. After stirring at room temperature for 2 hours the solvent in the dark brown reaction mixture was removed *via* rotary evaporation and the residue dissolved in 25 mL ethyl acetate. The organic layer was then washed with: 5% H_2SO_4 (2 x 20 mL); saturated NaCl solution (2 x 20 mL); and deionized water (1 x 20 mL). The solution was then dried using $MgSO_4$, gravity filtered with celite to remove small particles, and prepared for flash column purification by evaporating onto silica gel (5 g). Purification was carried out on a flash column (30 g of silica) eluting with 3:1 hexane:ethyl acetate, which yielded 1.49 g of **16** (62%) as a light yellow syrup.

^1H NMR: δ 1.35 (s, 3H, $-CH_3$), 1.38 (s, 3H, $-CH_3$), 1.46 (s, 3H, $-CH_3$), 1.48 (s, 3H, $-CH_3$), 3.06 (s, 1H, -CH), 4.04 (dd, 1H, H-6, J = 4.2, 9.0 Hz), 4.08, (s, 1H, H-

2), 4.1 (dd, 1H, H-6', J = 6.2, 9.0 Hz), 4.40 (ddd, 1H, H-5, J = 4.2, 6.0, 7.9 Hz), 4.77 (d, 1H, H-3, J = 5.9 Hz), 4.89 (dd, 1H, H-4, J = 3.7, 5.9 Hz), 6.19 (s, 1H, H-1).

^{13}C NMR: δ 24.7, 25.2, 26.0, 27.1, 66.7, 72.7, 74.0, 76.0, 79.1, 82.6, 84.8, 102.0, 109.4, 113.4, 150.7.

Synthesis of 1,2:3,4-di-*O*-isopropylidene-6-*O*-propionyl-α-D-galactopyranose (17) from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (3).

To a flame dried 100 mL round bottom flask 1.0 equivalent of compound **3** (1.67 g, 6.4 mmol), 2.0 equivalents of propiolic acid (0.788 mL, 12.8 mmol), and 268 mg of 4-dimethylaminopyridine were dissolved in 10 mL of dry CH_2Cl_2, and 20 mL dry CH_3CN. While immersed in an ice bath and stirring, 2.1 equivalents of a 1.0 M solution of 1,3-dicyclohexylcarbodiimide (13.4 mL, 13.4 mmol) were added dropwise over 1 hour using a syringe pump creating a solution that gradually turned from cloudy yellow to dark brown. Using TLC (3:1 hexane:ethyl acetate) the consumption of the starting sugar was noted after 1.5 hours. After stirring, the reaction mixture was evaporated, dissolved in 40 mL of ethyl acetate, and then washed with: 5% H_2SO_4 (2 x 20 mL); saturated NaCl solution (2 x 40 mL); and deionized water (1 x 30 mL). After drying with $MgSO_4$ and filtering with celite the dark brown solution was evaporated onto silica gel (3.0 g) and purified using a flash column with 20 g of silica gel and 7:1 hexane:ethyl acetate as the eluent to give 0.88 g (44%) of a light yellow syrup (**17**).

^{1}H NMR: δ 1.34 (s, 3H, -CH_3), 1.35 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3), 1.53 (s, 3H, -CH_3), 2.94 (s, 1H, ≡CH), 4.06 (ddd, 1H, H-5, J = 1.8, 5.3, 7.1 Hz), 4.26 (dd, 1H, H-3, J = 2.0, 7.9 Hz), 4.32 (dd, 1H, H-6, J = 7.3, 11.5 Hz), 4.34 (d, 1H, H-2, J = 4.9 Hz), 4.37 (dd, 1H, H-6', J = 5.1, 11.5 Hz), 4.64 (dd, 1H, H-3, J = 2.6, 7.9 Hz), 5.54 (d, 1H, H-1, J = 4.9 Hz).

^{13}C NMR: δ 24.5, 25.0, 26.0, 26.1, 64.8, 65.5, 70.3, 70.6, 70.7, 74.4, 75.3, 96.1, 108.7, 109.6, 152.3.

MS: Calculated: 312.32, Found: (APCI pos) 313.28 ($M+H^+$), 330.27 ($M+H_2O$).

Synthesis of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride (18) from 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (1).

To a flame dried 100 mL round bottom flask, 1.0 equivalent of **1** (1.0 g, 3.85 mmol) and 0.4 equivalents of triphosgene (0.46 g, 1.54 mmol) were dissolved in 20 mL of dry tetrahydrofuran. While stirring at room temperature, 1.0 equivalent of anhydrous pyridine (0.39 mL, 3.85 mmol) was added dropwise by syringe over 30 minutes produced a white precipitate and noxious gas. The progress of the reaction was monitored by TLC (1:1 hexane:ethyl acetate) for the disappearance of starting material. After 8 hours, the white precipitate was filtered off and the reaction mixture was evaporated to give a crude yield of 0.67 g (63%) of **18** as a translucent syrup.

^{1}H NMR: δ 1.35 (s, 3H, -CH_3), 1.41 (s, 3H, -CH_3), 1.48 (s, 3H, -CH_3), 1.49 (s, 3H, -CH_3), 4.03 (dd, 1H, H-6, J = 4.2, 9.2 Hz), 4.10 (dd, 1H, H-6', J = 6.2, 9.2 Hz), 4.21 (dd, 1H, H-4, J = 3.5, 7.8 Hz), 4.40 (ddd, 1H, H-5, J = 4.4, 6.2, 7.9 Hz),

4.89 (dd, 1H, H-3, J = 3.7, 5.7 Hz), 4.96 (d, 1H, H-2, J = 5.9 Hz), 6.08 (s, 1H, H-1).

Synthesis of 1-azido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranose (19) from 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride (18).

In a 100 mL round bottom flask, mannosyl chloride **18** (1.0 g, 3.6 mmol) was dissolved in 24 mL of acetone and 8 mL of deionized water. Upon refluxing, 5 equivalents of sodium azide (1.17 g, 18.0 mmol) were added, and the subsequent solution was stirred while refluxing for 6 hours. The reaction was monitored by TLC (1:1 hexane:ethyl acetate), which showed disappearance of starting material in the reaction solution, along with the appearance of the desired product and several polar side products in smaller amounts. Upon completion of the reaction, the acetone was removed using the rotary evaporator and the remaining light yellow syrup was transferred to a separatory funnel after partitioning between 30 mL of CH_2Cl_2 and 30 mL of deionized water. The organic layer was washed with deionized water (2 x 30 mL) after which the organic layer was dried over $MgSO_4$ and filtered. The organic solution was then evaporated onto silica gel (~3 g) and purified on a flash column using 3:1 hexane:ethyl acetate as the eluent and 20 g of silica gel, which allowed for the recovery of 0.8 g of pure product (**19**) (77%).

^{1}H NMR: δ 1.35 (s, 3H, -CH_3), 1.38 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3), 1.55 (s, 3H, -CH_3), 3.6 (dd, 1H, H-4, J = 3.5, 7.5 Hz), 4.06-4.14 (m, 2H, H-6, H-6'), 4.4 (d, 1H, H-1, J = 3.5 Hz), 4.5 (ddd, 1H, H-5, J = 4.8, 6.0, 7.5 Hz), 4.67 (dd, 1H, H-2, J = 3.5, 6.0 Hz), 4.76 (dd, 1H, H-3, J = 3.5, 6.0 Hz).

^{13}C NMR: δ 24.4, 25.18, 25.24, 27.0, 66.7, 72.8, 78.5, 79.4, 81.0, 88.9, 109.1, 113.4.

IR: 2121 cm^{-1} (N_3).

MS: Calculated: 285.13, Found: (APCI pos) 258.38 ($M-N_2$), (ESI pos) 303.2 ($M+H_2O$).

Synthesis of 1,2:3,4-di-*O*-isopropylidene-6-*O*-(trifluoromethylsulfonyl)-α-D-galacto-pyranose (20) from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (3).

In a flame dried 100 mL three neck round bottom flask 30 mL of dry CH_2Cl_2 and 0.63 mL of anhydrous pyridine (7.69 mmol) were cooled in a dry ice/acetone bath under inert atmosphere. A flame dried addition funnel was charged with a mixture of 1.29 mL of triflic anhydride (7.69 mmol) in 10 mL of dry CH_2Cl_2, which was added dropwise to the round bottom flask over 30 minutes forming a pink slurry. From a separate dry addition funnel 1.0 g of **3** (3.84 mmol) dissolved in 10 mL of dry CH_2Cl_2 was added dropwise to the pink slurry over 30 minutes. TLC (3:1 hexane:ethyl acetate) was utilized to monitor reaction progress. After stirring in the dry ice/acetone bath for 3 hours the reaction was poured over 25 mL of ice water and was then extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were then combined and dried over $MgSO_4$. After filtering, the CH_2Cl_2 was removed under vacuum and the residue was extracted with warm hexanes (3 x 40 mL), which was then evaporated to give 0.98 g (75%) of clear syrup (**20**).

^1H NMR: δ 1.33 (s, 3H, $-CH_3$), 1.34 (s, 3H, $-CH_3$), 1.45 (s, 3H, $-CH_3$), 1.53 (s, 3H, $-CH_3$), 4.12 (ddd, 1H, H-5, J = 2.0, 4.6, 7.1 Hz), 4.25 (dd, 1H, H-4, J = 2.0,

7.9 Hz), 4.37 (dd, 1H, H-2, J = 2.6, 4.9 Hz), 4.6 (m, 2H, H-6, H-6'),4.66 (dd, 1H, H-3, J = 2.5, 7.9 Hz) 5.54 (d, 1H, H-1, J = 4.6 Hz).

^{13}C NMR: δ 24.4, 24.9, 25.9, 26.0, 66.0, 70.2, 70.3, 70.6, 74.7, 96.0, 109.0, 110.0, 118.4 (q, J = 270 Hz).

Synthesis of 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (21) from 1,2:3,4-di-*O*-isopropylidene-6-*O*-(trifluoromethylsulfonyl)-α-D-galactopyranose (20).

1.0 Equivalent of **20** (1.0 g, 2.6 mmol) was dissolved in a flame dried 100 mL round bottom flask with 30 mL of DMF. While stirring, 2.5 equivalents of sodium azide (0.43 g, 6.6 mmol) were added and the mixture stirred for 12 hours. After verifying the completion of the reaction using TLC (3:1 hexane:ethyl acetate), the DMF was removed using the rotary evaporator. The residue was then dissolved in 20 mL CH_2Cl_2 and washed with 20 mL of deionized water. The reaction was dried with $MgSO_4$, filtered, and evaporated onto silica gel (2 g) for addition onto a flash column. The mixture was then purified using 20 g of silica gel with 3:1 hexane:ethyl acetate. After evaporating, 0.47 g (63%) of thick clear syrup (**21**) resulted.

^{1}H NMR: δ 1.32 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3), 1.54 (s, 3H, -CH_3), 3.35 (dd, 1H, H-6, J = 5.3, 12.8 Hz), 3.51 (dd, 1H, H-6', J = 7.9, 12.6 Hz), 3.9 (ddd, 1H, H-5, J = 1.7, 5.5, 7.5 Hz), 4.19 (dd, 1H, H-4, J = 1.8, 7.9 Hz), 4.33 (dd, 1H, H-2, J = 2.6, 4.9 Hz), 4.62 (dd, 1H, H-3, J = 2.6, 7.9 Hz), 5.54 (d, 1H, H-1, J = 4.9 Hz).

^{13}C NMR: δ24.5, 25.0, 26.0, 26.1, 50.7, 67.0, 70.3, 70.7, 71.1, 96.2, 108.7, 109.5.

IR: 2121 cm^{-1} (N_3).

MS: Calculated: 285.30, Found: (ESI pos) 286.13 ($M+H^+$), 303.2 ($M+H_2O$).

Synthesis of 1-azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose (23) from 1-bromo-1-deoxy-2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (22).

1.0 Equivalent of compound **22** (1.0 g, 2.4 mmol) was dissolved in 24 mL of acetone and 8 mL of deionized water in a 100 mL round bottom flask. After the solution began refluxing 5.0 equivalents of sodium azide (0.79 g, 12.2 mmol) were added. TLC (2:1 hexane:ethyl acetate) provided confirmation of reaction. After refluxing for 2 hours the reaction was filtered and evaporated before dissolving in 30 mL of CH_2Cl_2. After washing with 30 mL of deionized water the organic layer was dried with $MgSO_4$, which was then removed by filtration before evaporating to 0.90 g (100%) of light yellow solid (**23**) which was pure by TLC (2:1 hexane:ethyl acetate).

^{1}H NMR: δ2.0 (s, 3H, -CH_3), 2.07 (s, 3H, -CH_3), 2.10 (s, 3H, -CH_3), 2.18 (s, 3H, -CH_3), 4.04 (ddd, 1H, H-5, J = 1.1, 6.2, 6.2 Hz), 4.16 (dd, 1H, H-6', J = 6.04, 11.53 Hz), 4.19 (dd, 1H, H-6, J = 6.96, 11.35 Hz), 4.63 (d, 1H, H-1, J = 8.6 Hz), 5.05 (dd, 1H, H-3, J = 3.3, 10.4 Hz), 5.17 (dd, 1H, H-2, J = 8.61, 10.4 Hz), 5.43 (dd, 1H, H-4, J = 1.1, 3.3 Hz).

^{13}C NMR: δ 20.6 (*2*), 20.7 (*2*), 61.1, 66.8, 67.9, 70.6, 72.7, 88.1, 169.1, 169.7, 169.8, 170.1.

MS: Calculated: 373.32, Found: (ESI pos) 391.28 ($M+H_2O$).

Synthesis of 1-azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (25) from 1-bromo-1-deoxy-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (24).

In a 100 mL round bottom flask 1.0 equivalent of **24** (1.0 g, 2.4 mmol) was dissolved in 32 mL of a 3:1 acetone:deionized water mixture. While the mixture was refluxing, 5.0 equivalents of sodium azide (0.79 g, 12.2 mmol) were added. The reaction was then refluxed for 2 hours whereupon TLC (2:1 hexane:ethyl acetate) confirmed the appearance of a slightly more polar spot. The reaction was filtered, evaporated, dissolved in 30 mL CH_2Cl_2 and washed with 30 mL of deionized water. After drying with $MgSO_4$ the filtrate was evaporated onto silica gel (3 g) and purified using a flash column (20 g of silica gel), which was eluted with 3:1 hexane:ethyl acetate to give 0.85 g (93%) of pale yellow syrup (**25**).

^{1}H NMR: δ 2.02 (s, 3H, -CH_3), 2.04 (s, 3H, -CH_3), 2.07 (s, 3H, -CH_3), 2.09 (s, 3H, -CH_3), 3.79 (ddd, 1H, H-5, J = 2.4, 4.8, 7.1Hz), 4.16 (dd, 1H, H-6, J = 2.2, 10.3 Hz), 4.27 (dd, 1H, H-6', J = 4.8, 12.5 Hz), 4.64 (d, 1H, H-1, J = 9.0 Hz), 4.95 (dd, 1H, H-2, J = 8.8, 9.5 Hz), 5.1 (dd, 1H, H-4, J = 9.9 Hz), 5.21 (dd, 1H, H-3, J = 0.0, 9.5 Hz).

^{13}C NMR: δ 20.7 (*2*), 21.9, 22.0, 62.8, 68.9, 71.7, 73.7, 75.1, 89.0, 170.1, 170.2, 171.0, 171.5.

MS: Calculated: 373.32, Found: (ESI pos) 391.27 ($M+H_2O$).

Synthesis of sugar-heterocycle hybrids (26 and 27) using 1,2:3,4-di-*O*-isopropylidene-6-*O*-propionyl-α-D-galactopyranose (18) and 1-azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (25).

In a flame dried 50 mL round bottom flask 1.0 equivalent of **18** (0.43 g, 1.38 mmol) was dissolved in 5 mL of toluene. Once the propionyl sugar mixture began refluxing, the acetoglucoazide **25**, which was previously dissolved in 5 mL of toluene, was added to the refluxing mixture. The reaction was followed by TLC (1:1 hexane:ethyl acetate) for 48 hours when the solution was evaporated onto silica gel (3 g) in preparation for flash column chromatography. The crude mixture was separated on 30 g of silica gel using 3:2 hexane:ethyl acetate as eluent to provide 0.3 g (32%) of light syrup (**26** and **27**).

^{1}H NMR: δ 1.36 (s, 3H, -CH_3), 1.40 (s, 3H, -CH_3), 1.48 (s, 3H, -CH_3), 1.61 (s, 3H, -CH_3), δ 1.85 (s, 3H, -CH_3), 2.05 (s, 3H, -CH_3), 2.07 (s, 3H, -CH_3), 2.08 (s, 3H, -CH_3), 4.08-4.17 (m, 3H), 4.19-4.25 (m, 1H) 4.28 (dd, 1H, J = 1.83, 7.9 Hz) 4.62 (dd, 1H, gluH-6, J = 2.9, 11.7 Hz), 4.68 (dd, 1H, gal, J = 2.4, 7.9 Hz), 5.26 (dd, 1H, gluH-4, J = 0.0, 9.7 Hz), 5.56 (dd, 1H, gluH-3, J = 0.0, 9.5 Hz), 5.61 (d, 1H, galH, J = 4.9 Hz), 6.18 (dd, 1H, gluH-2, J = 0.0, 9.5 Hz), 6.43 (dd, 1H, gluH-1, J = 0.0, 9.5 Hz), 8.25 (s, 1H, N-H).

^{13}C NMR: δ 20.5, 20.7, 20.8, 20.9, 24.4, 24.7, 25.9, 26.0, 61.5, 65.5, 66.2, 67.6, 69.3, 70.1, 70.7, 70.8, 73.5, 74.5, 83.8, 96.2, 109.1, 109.8, 129.2, 139.1, 156.9, 168.1, 169.1, 170.2, 170.4.

Synthesis of sugar-heterocycle derived hybrids (28 and 29) from 1,2:3,4-di-*O*-isopropylidene-6-*O*-propionyl-α-D-galactopyranose (18) and 1-azido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranose (19).

In a flame dried 50 mL round bottom flask 1.0 equivalent of **18** (0.3 g, 0.94 mmol) was dissolved in 10 mL of toluene. While refluxing the mixture, 1.0 equivalent of **19** (0.27 g, 0.94 mmol) was added. TLC (3:1 hexane:ethyl acetate) indicated consumption of the starting sugars. After 24 hours at reflux the reaction was evaporated onto silica gel (2 g) and purified using 3:2 hexane:ethyl acetate and 10 g of silica gel packed in a flash column yielding 0.32 g (56%) of clear syrup (**28** and **29**).

Upper spot-

^{1}H NMR: δ 1.32 (s, 3H, -CH_3), 1.35 (s, 6H, -CH_3), 1.41 (s, 3H, -CH_3), 1.47 (s, 6H, -CH_3), 1.50 (s, 3H, -CH_3), 1.56 (s, 3H, -CH_3), 3.81 (dd, 1H, manH-4, J = 3.7, 7.9 Hz), 4.07 (dd, 1H, manH-6, J = 4.0, 9.0 Hz), 4.14 (dd, 1H, manH-6', J = 6.2, 9.0 Hz), 4.21 (ddd, 1H, galH-5, J = 1.6, 5.3, 7.1 Hz), 4.33-4.36 (m, 2H), 4.44-4.53 (m, 3H), 4.57 (dd, 1H, galH-6, J = 5.3, 11.5 Hz), 4.65 (dd, 1H, galH-4, J = 2.6, 7.9 Hz), 4.91 (dd, 1H, manH-2, J = 3.7, 5.9 Hz), 4.98 (dd, 1H, manH-3, J = 3.7, 5.9 Hz), 5.55 (d, 1H, galH-3, J = 4.9 Hz), 6.17 (d, 1H, galH-1, J =3.5 Hz), 8.36 (s, 1H, N-H).

^{13}C NMR: δ 24.0, 24.5, 25.0, 25.2, 25.5, 26.0, 26.1, 27.1, 63.9, 65.8, 66.7, 70.4, 70.6, 70.8, 72.5, 79.0, 79.4, 79.6, 88.7, 96.1, 108.7, 109.5, 109.5, 113.9, 128.4, 139.1, 160.1.

Lower spot-

^{1}H NMR: δ 1.18 (s, 3H, -CH_3), 1.26 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3), 1.40 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3), 1.47 (s, 3H, -CH_3), 1.51 (s, 3H, -CH_3), 4.0 (dd, 1H, manH-4, J = 3.8, 8.2 Hz), 4.13 (ddd, 1H, galH-5, J = 1.6, 4.0, 7.9 Hz), 4.19-4.25 (m, 2H), 4.26-4.29 (m, 2H), 4.36 (dd, 1H, galH-2, J = 2.6, 4.9 Hz), 4.42 (dd, 1H, manH-6, J = 8.1, 11.5 Hz), 4.50 (dd, 1H, manH-6', J = 4.2, 11.5 Hz), 4.64 (dd, 1H, galH-6', J = 2.6, 7.9 Hz), 4.78 (ddd, 1H, manH-5, J =4.0, 5.8, 8.2 Hz), 4.92 (dd, 1H, manH-3, J = 3.7, 5.9 Hz), 5.13 (dd, 1H, manH-2, J = 4.8, 6.0 Hz), 5.55 (d, 1H, galH-3, J = 5.1 Hz), 6.55 (d, 1H, galH-1, J = 4.8 Hz), 8.2 (s, 1H, N-H).

^{13}C NMR: δ 24.5, 25.0, 25.1, 25.2, 25.3, 26.0, 26.1, 27.2, 64.9, 65.7, 67.0, 70.2, 70.6, 70.8, 72.8, 79.7, 80.2, 80.5, 90.2, 96.2, 108.7, 109.3, 109.7, 114.6, 127.6, 138.1, 157.8.

MS: Calculated: 597.61, Found: (Upper spot ESI pos) 598.33 (Lower spot ESI pos) 598.40.

Deprotection of compound 28 or 29 to compound 30 or 31.

In a clean and dry scintillation vial 0.3 g of **28** or **29** was dissolved in 3 mL of a 9:1 mixture of trifluoroacetic acid and deionized water. TLC (ethyl acetate) was used to monitor progression of the reaction. After stirring 10 minutes, the reaction was evaporated to dryness. In order to remove any excess trifluoroacetic acid, the residue was then dissolved in warm absolute ethanol, which was evaporated a second time. The

residue was again dissolved in warm absolute ethanol and evaporated to finally yield 0.2 g of thick white residue of **30** or **31**. ^{13}C NMR was then performed in d_6-DMSO.

^{13}C NMR: δ 56.0, 63.1, 64.8, 64.9, 68.4, 68.8, 68.9, 69.0, 69.2, 69.3, 71.3, 71.6, 71.9, 72.9, 80.8, 88.5, 92.6, 97.2, 129.5, 138.4, 160.1.

MS: Calculated: 437.36, Found: (ESI pos) 438.2 ($M+H^+$), 436.2 ($M-H^+$).

Acetylation of 30 or 31 to 32 or 33.

0.1 g Of compound **30** or **31** was dissolved in 5 ml of acetic anhydride to this stirring reaction mixture 0.25 mL of anhydrous pyridine was added dropwise. The reaction was monitored *via* TLC (1:1 hexane:ethyl acetate) for the formation of a less polar spot. After stirring 24 hours, visualization of conversion to a single spot was witnessed by TLC. The reaction mixture was evaporated to give 0.120 g of crude product (**32** or **33**). Proton and ^{13}C NMR spectra of the crude product were obtained.

^1H NMR: δ 1.86 (s, 3H, $-CH_3$), 1.87 (s, 3H, $-CH_3$), 1.96 (s, 3H, $-CH_3$), 1.97 (s, 3H, $-CH_3$), 2.01 (s, 3H, $-CH_3$), 2.02 (s, 6H, $-CH_3$), 2.03 (s, 6H, $-CH_3$), 2.03 (s, 3H, $-CH_3$), 2.05 (s, 3H, $-CH_3$), 2.05 (s, 3H, $-CH_3$), 4.17 (dd, 1H, J = 4.4, 12.4 Hz), 4.29 (m, 1H), 4.41 (m, 2H), 4.49 (m, 2H), 4.61 (dd, J = 2.4, 12.6 Hz), 5.09 (dd, 1H, J = 3.3, 10.3 Hz), 5.34 (m, 1H), 5.51 (m, 2H), 5.70 (m, 2H), 6.59 (d, 1H, J = 6.4 Hz), 8.25 (s, 1H, N-H).

^{13}C NMR: δ 20.0, 20.3, 20.4, 20.5, 20.6, 20.7 (*3*), 20.8, 20.8, 20.8, 20.9, 61.4, 62.2, 66.6, 67.1, 67.3, 67.7, 68.3, 68.6, 70.5, 70.8, 71.3, 77.4, 86.7, 92.0, 127.1,

138.5, 159.3, 168.6, 168.6, 168.6, 168.7, 168.7, 169.0, 169.1, 169.5, 169.6, 169.8, 169.8, 170.2.

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Appendix

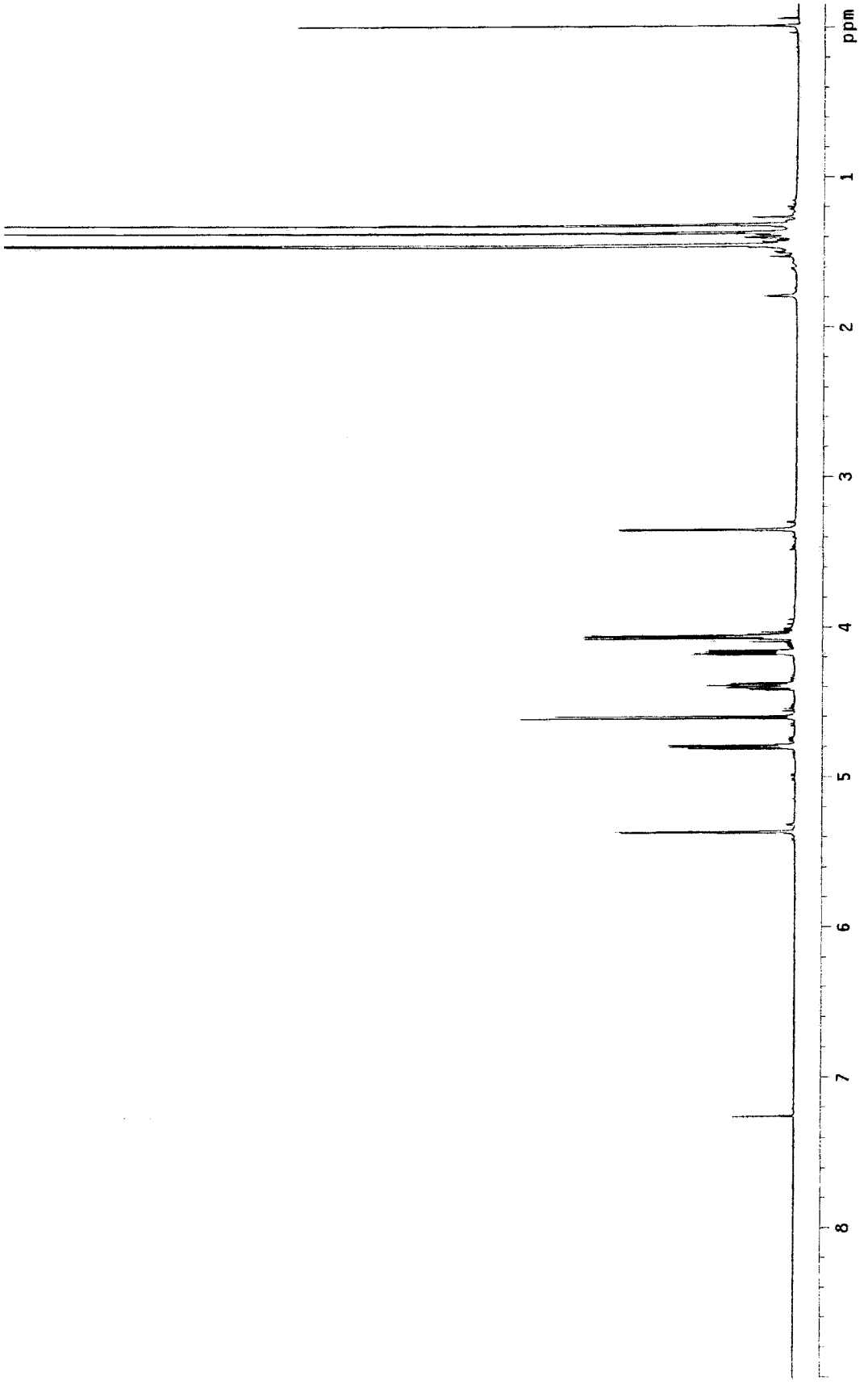

Figure 24. ^{1}H NMR of **1**

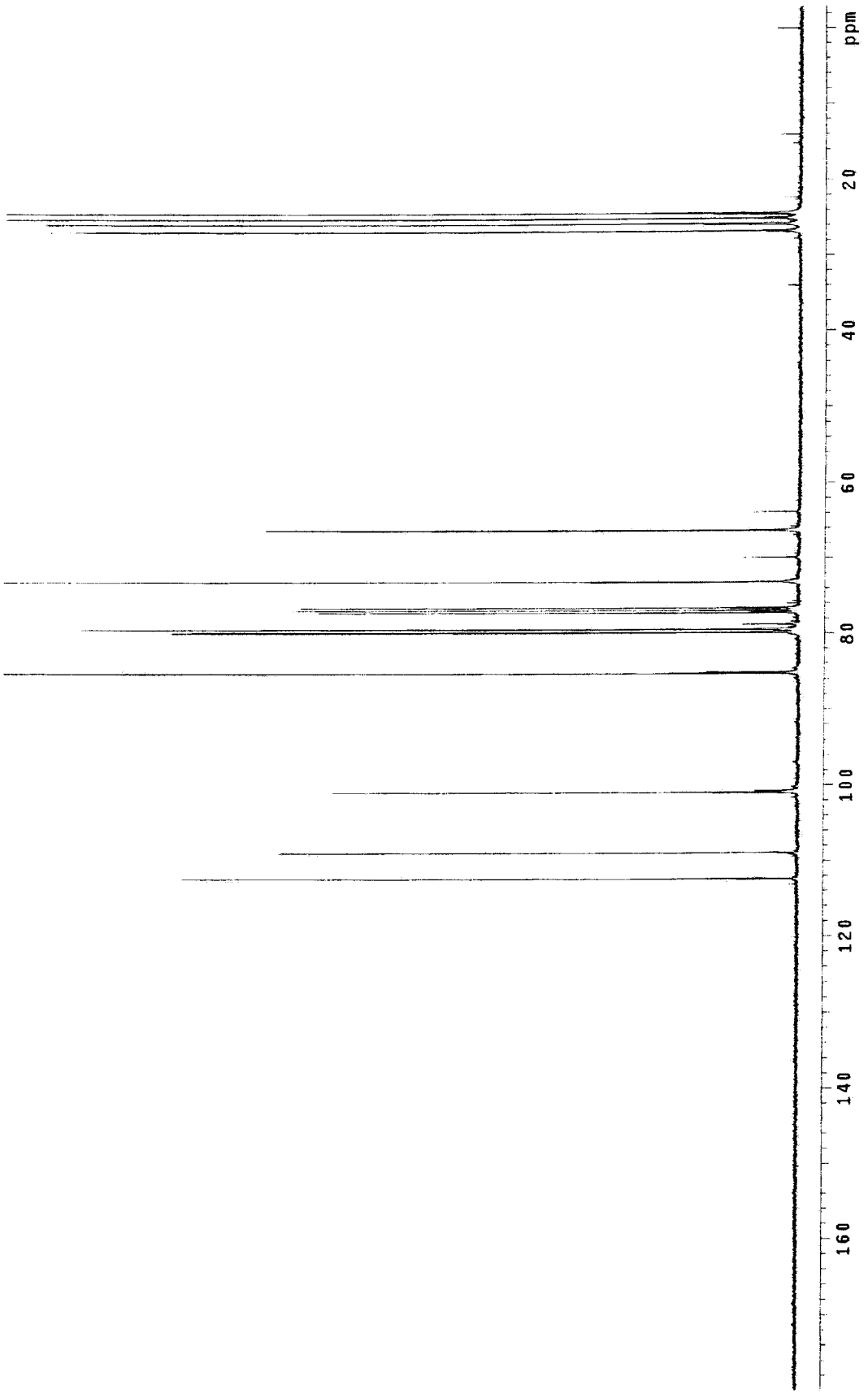

Figure 25. ^{13}C NMR of **1**

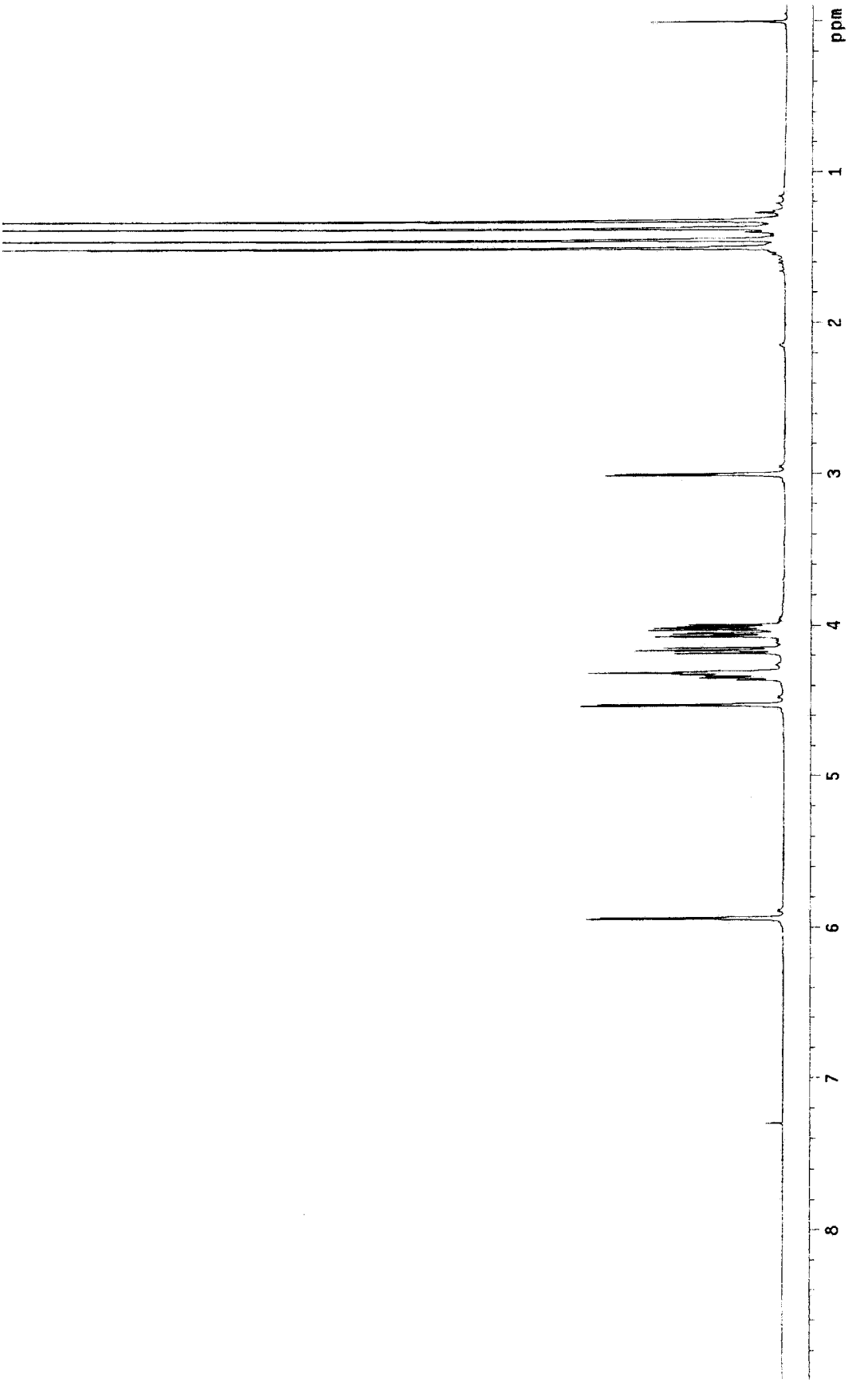

Figure 26. ^{1}H NMR of **2**

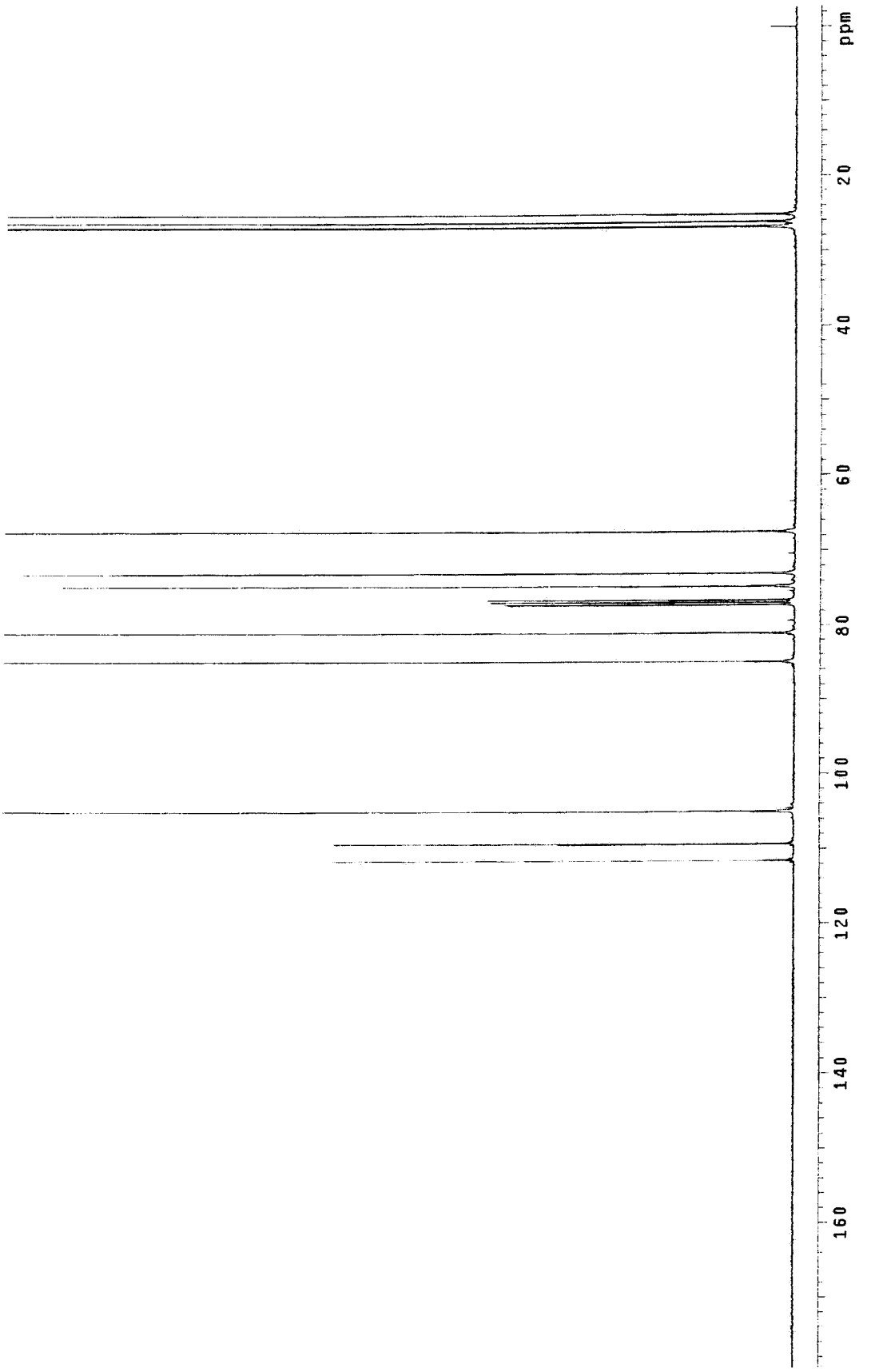

Figure 27. ^{13}C NMR of **2**

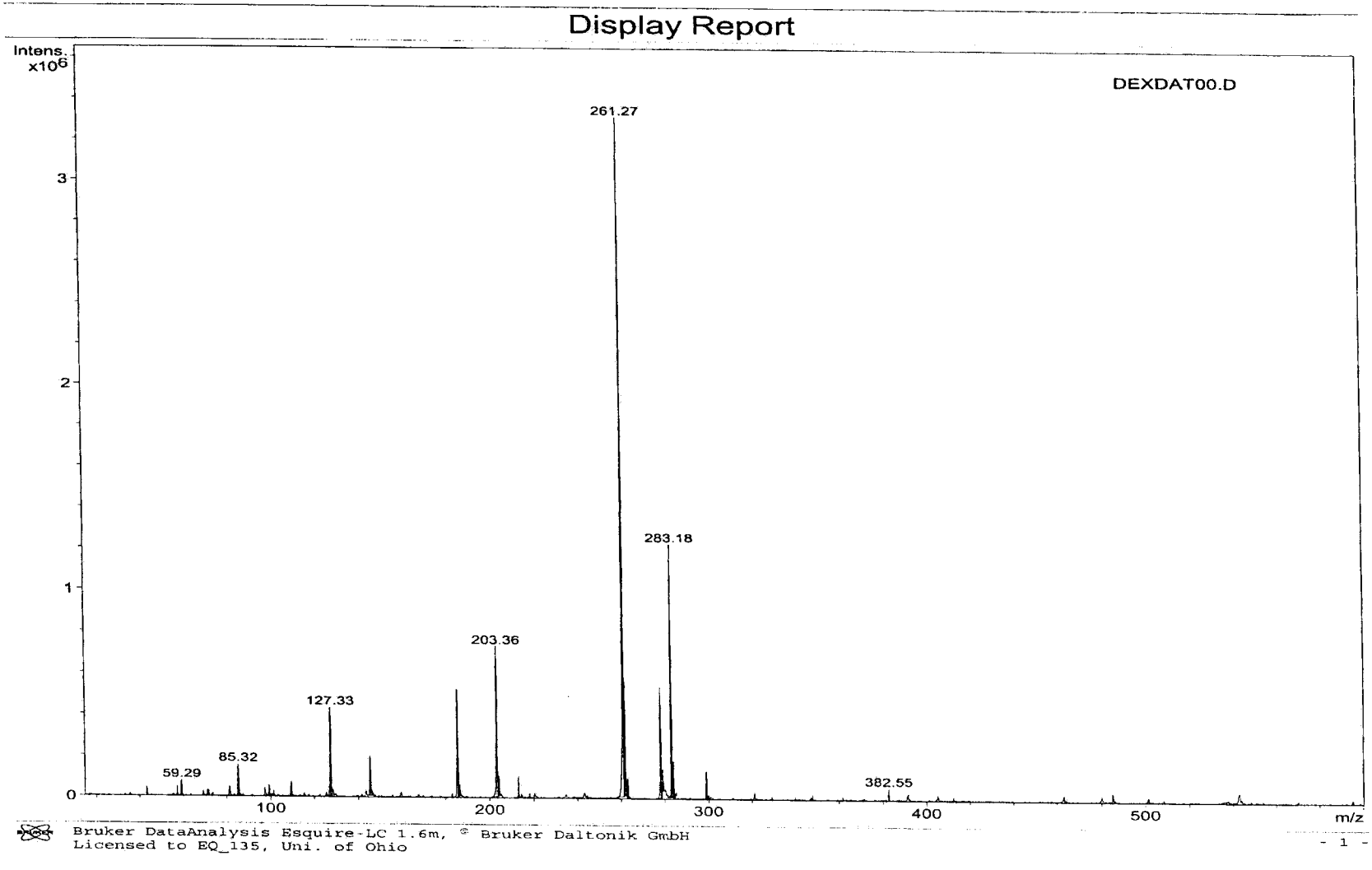

Figure 28. Positive mode ESI-MS of **2**

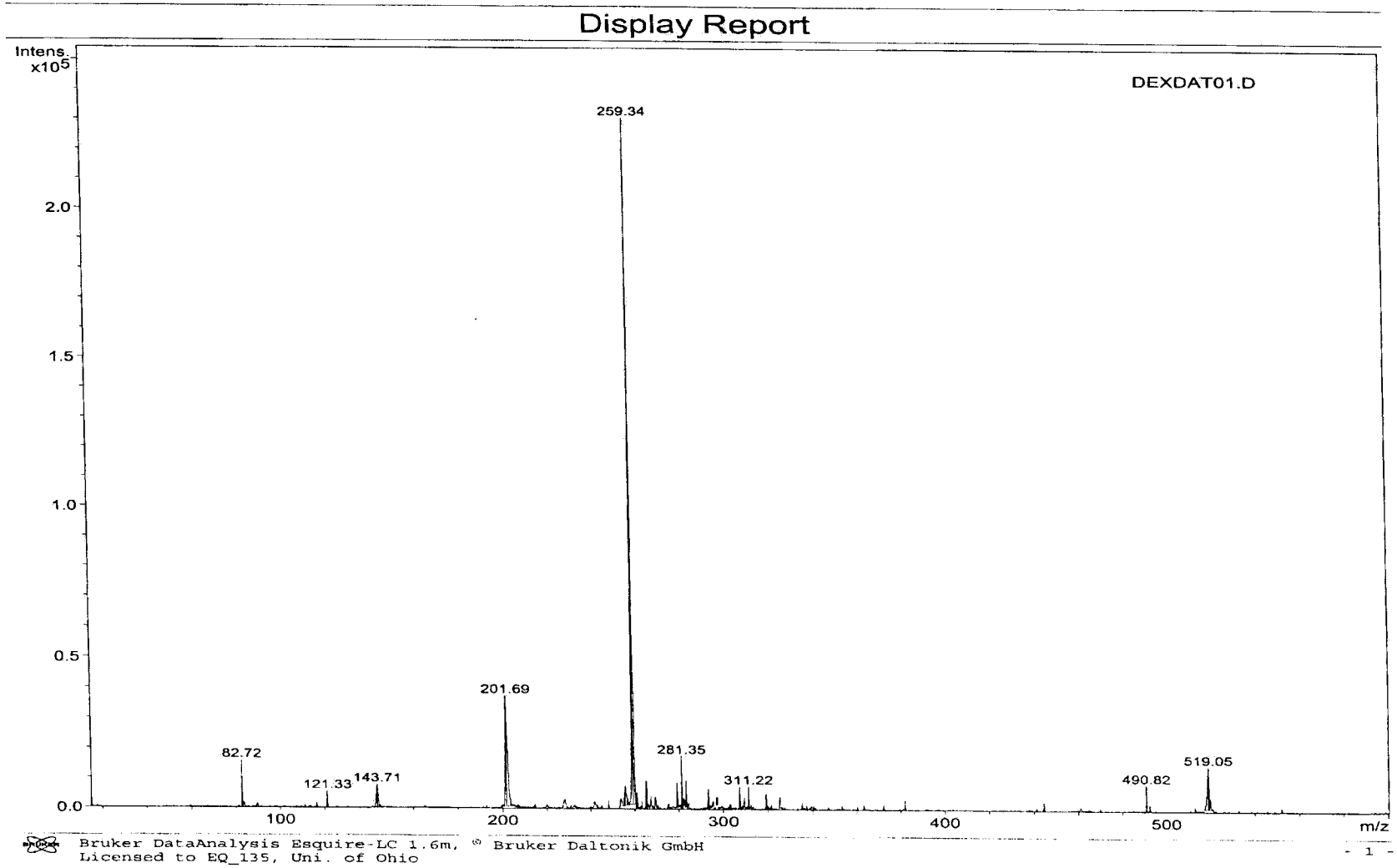

Figure 29. Negative mode ESI-MS of **2**

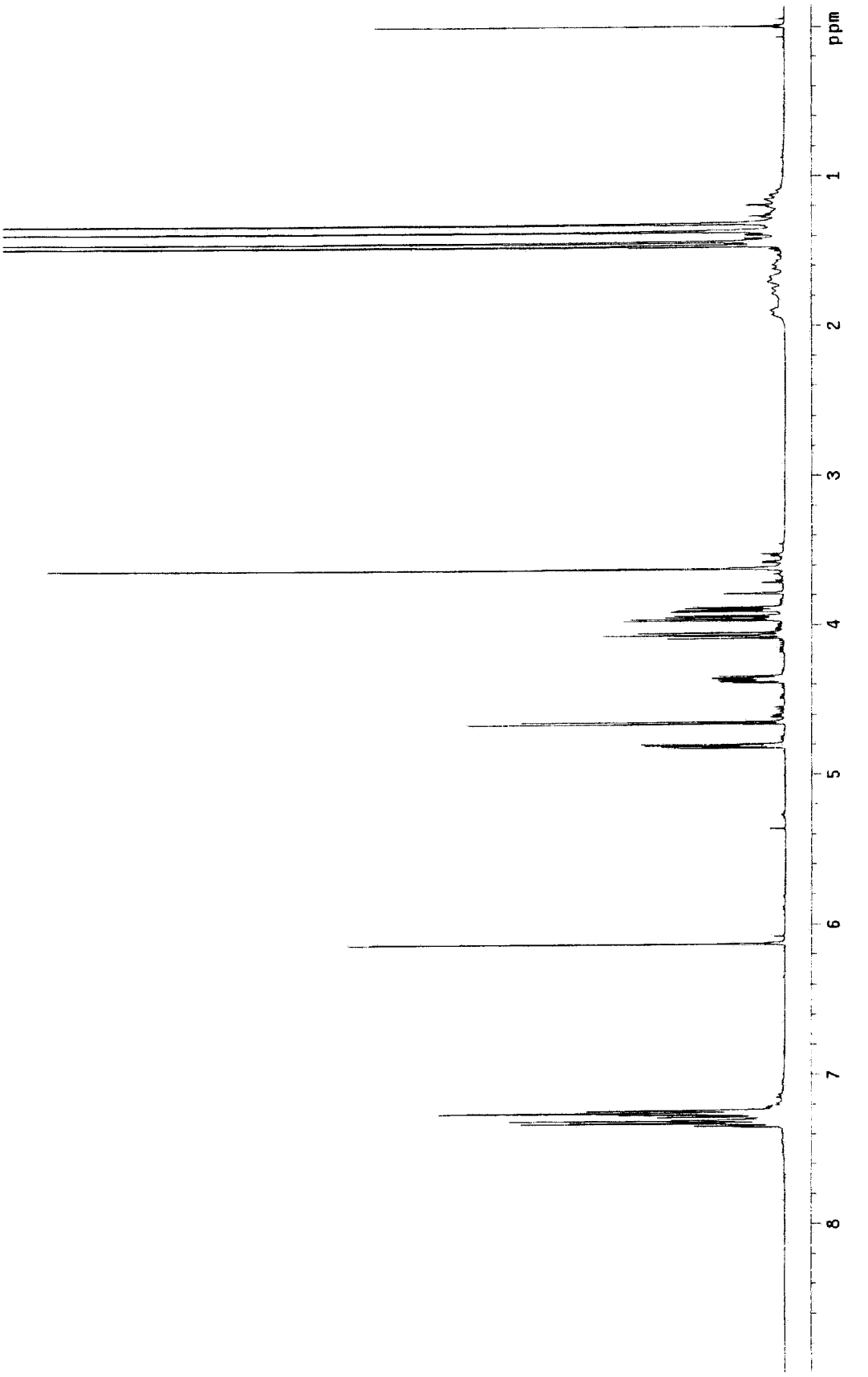

Figure 30. ^{1}H NMR of **4**

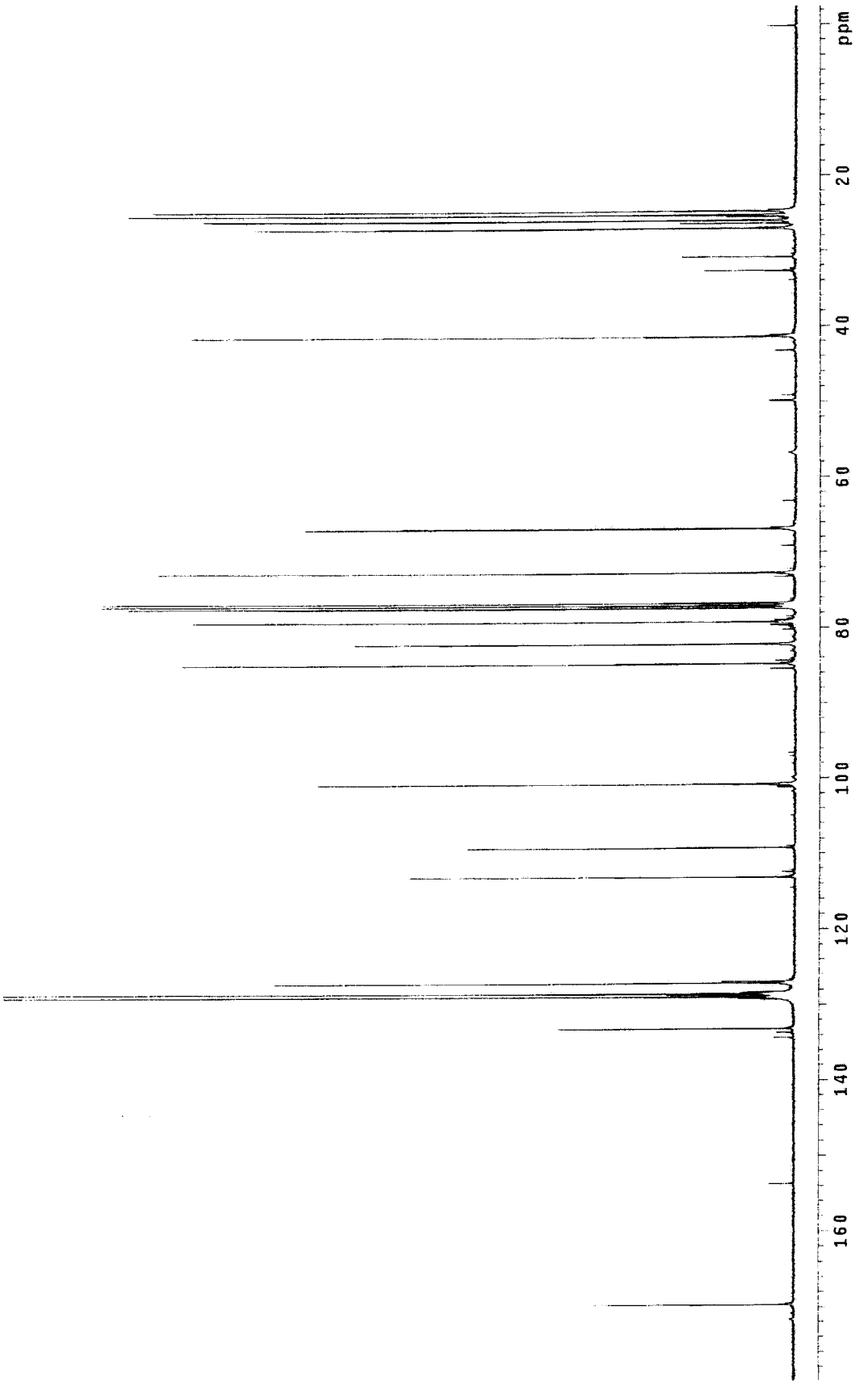

Figure 31. ^{13}C NMR of **4**

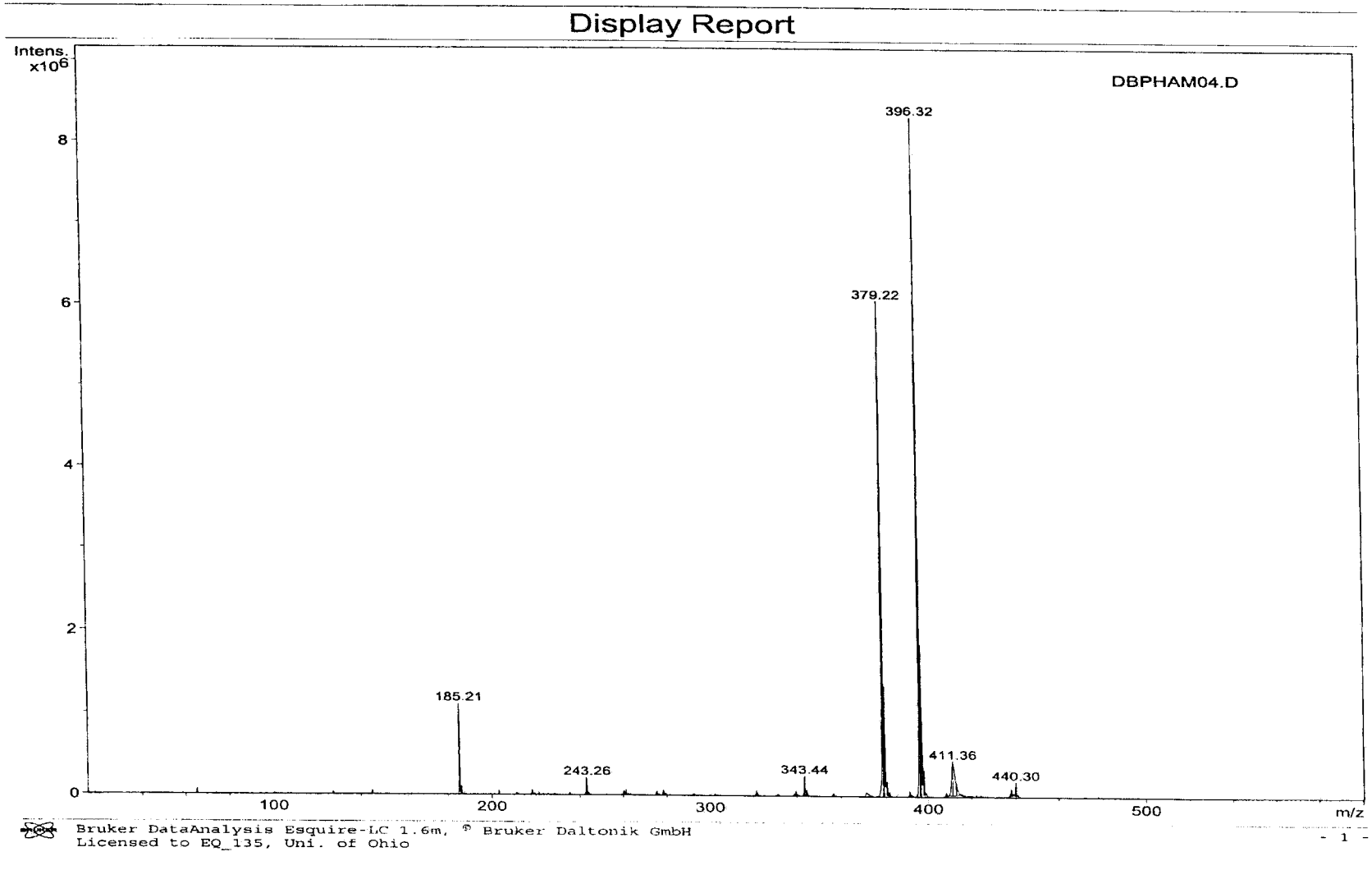

Figure 32. Positive mode ESI-MS of **4**

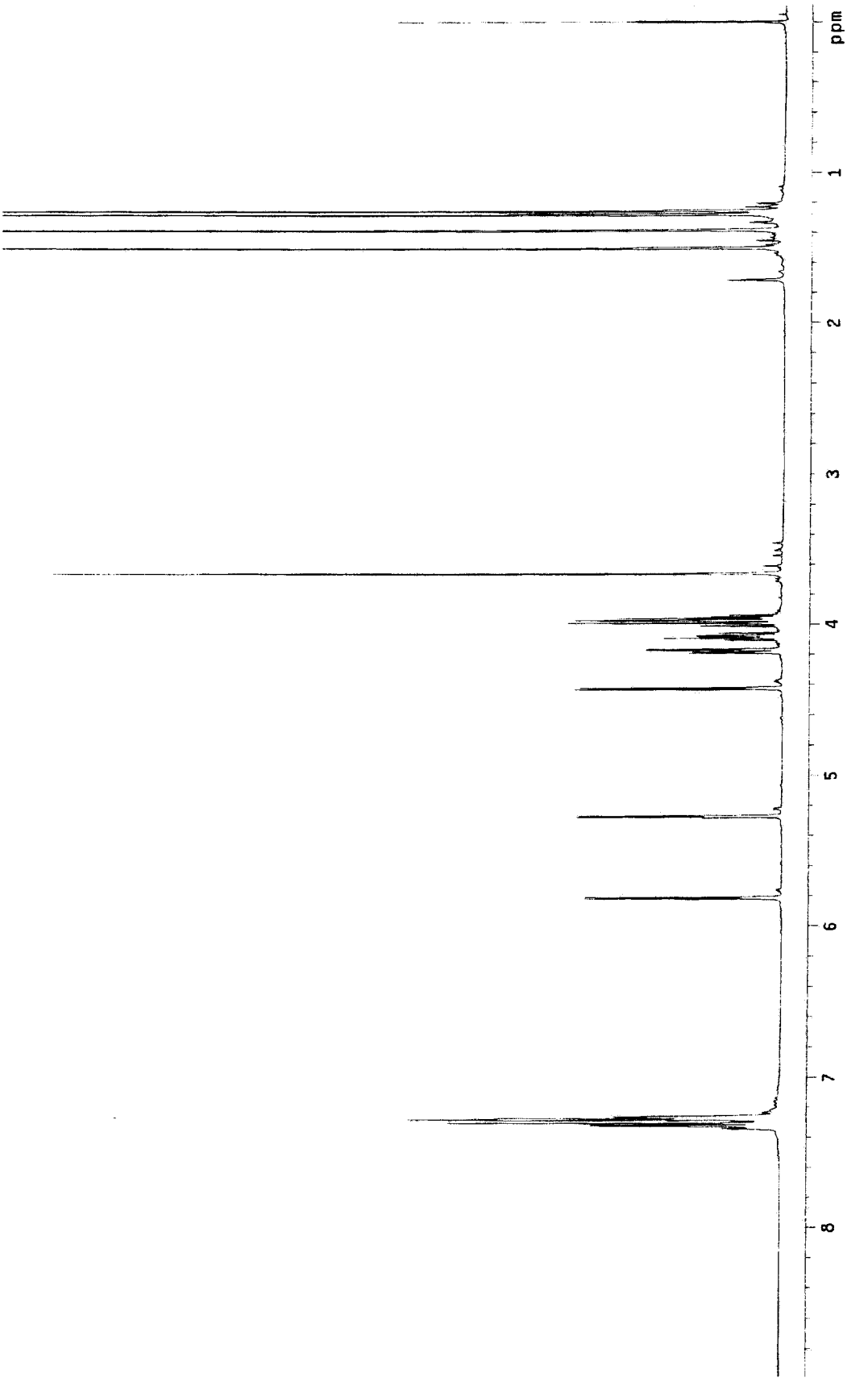

Figure 33. ^{1}H NMR of **5**

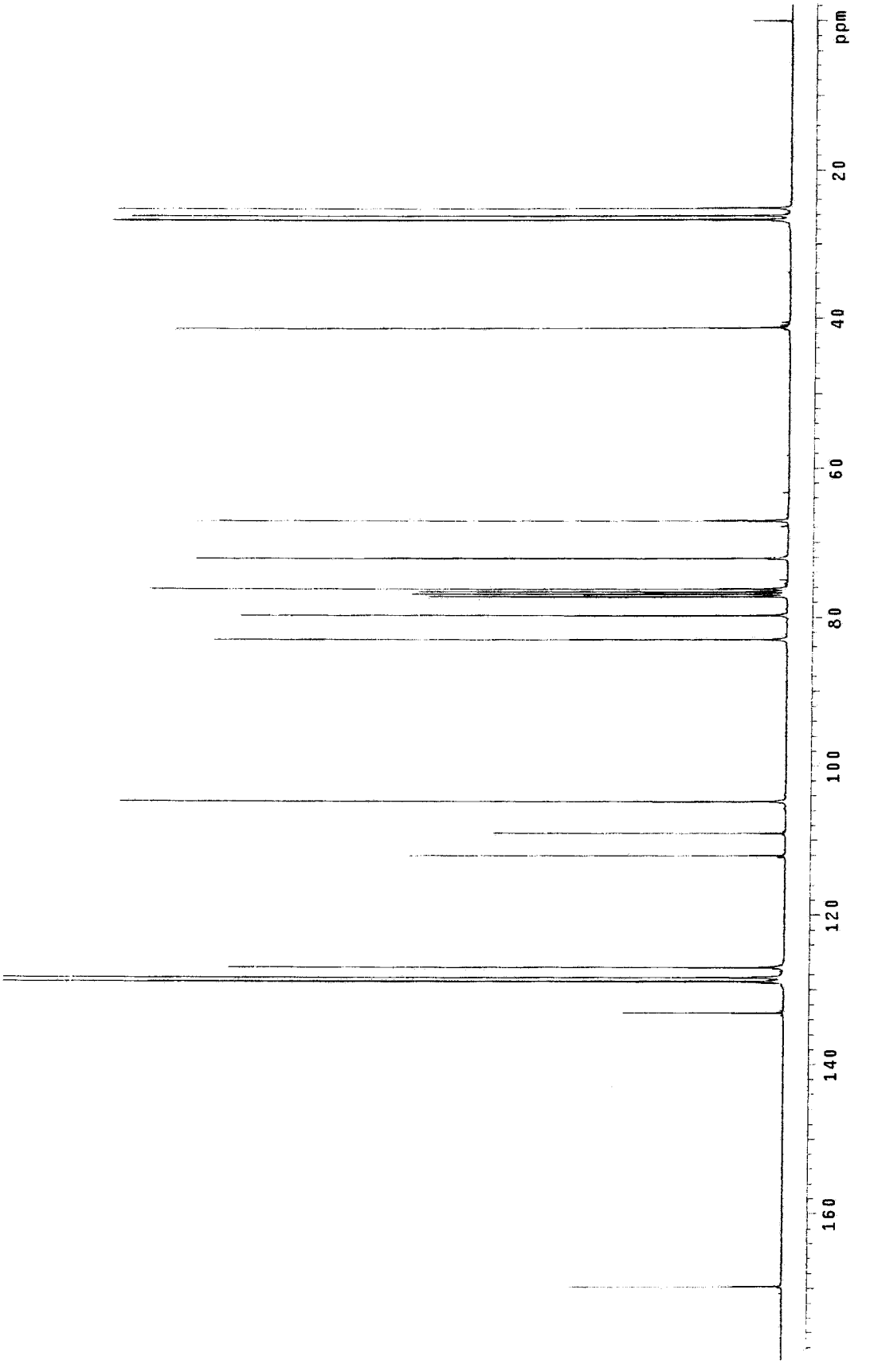

Figure 34. ^{13}C NMR of **5**

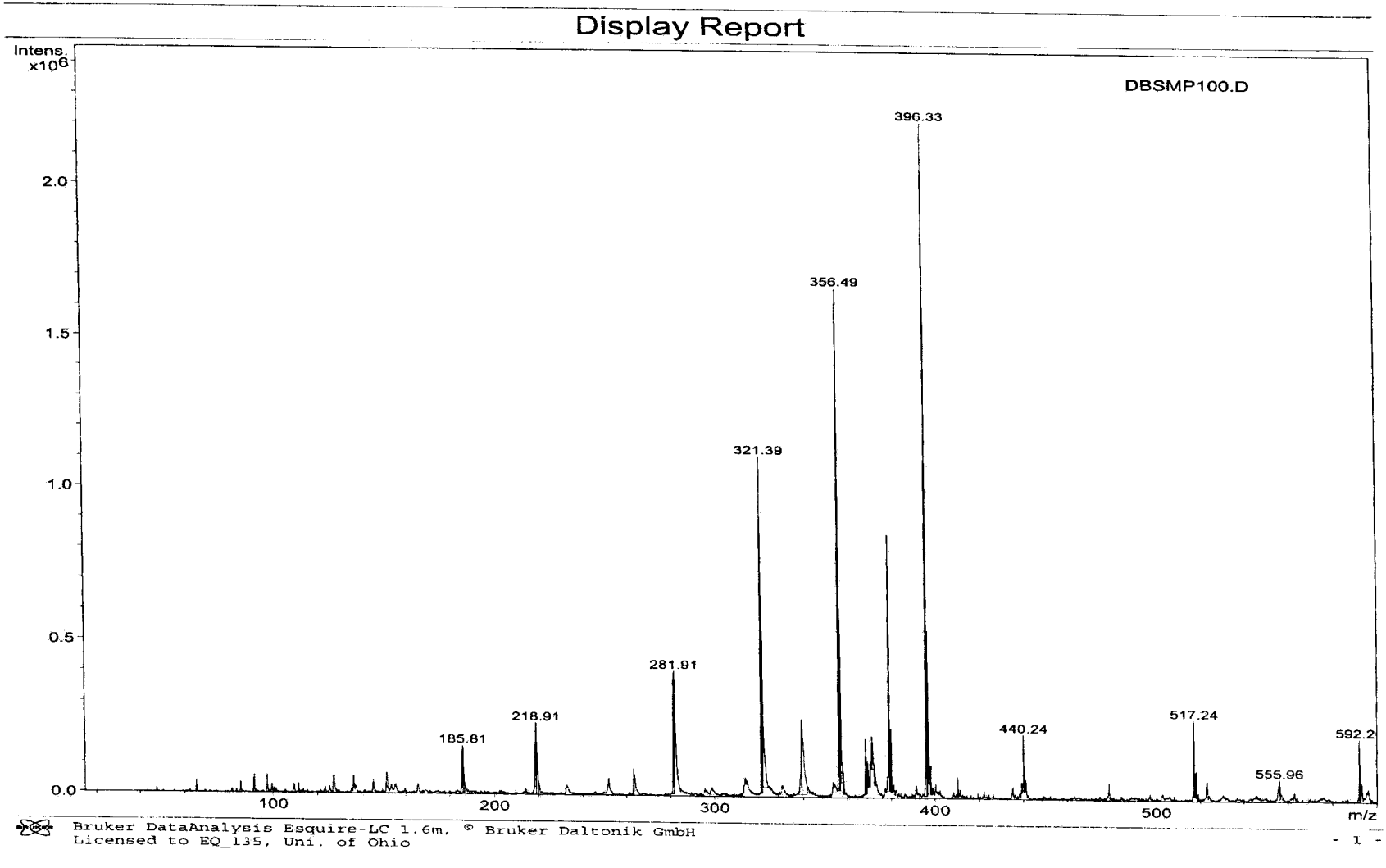

Figure 35. Positive mode APCI-MS of **5**

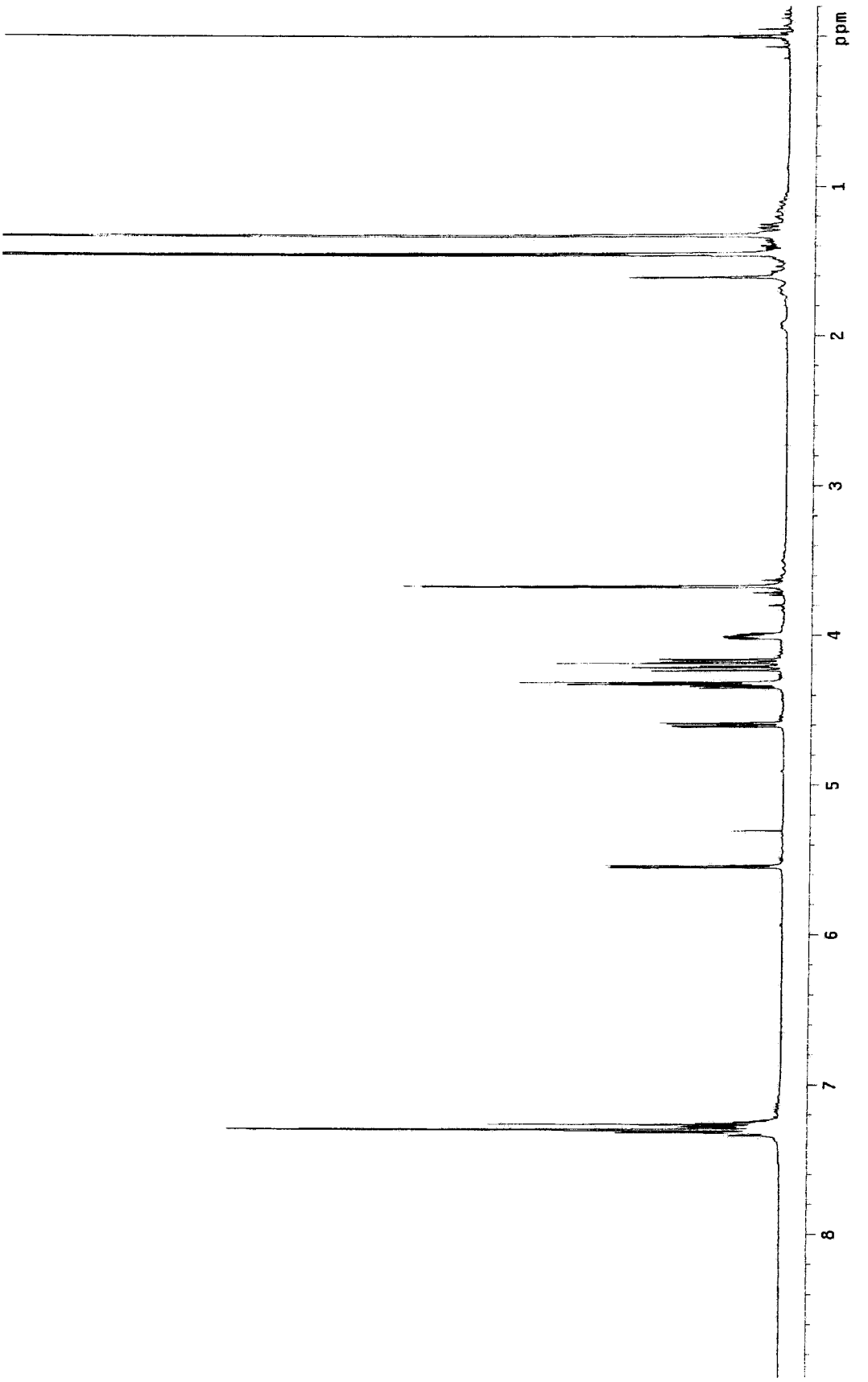

Figure 36. ^{1}H NMR of **6**

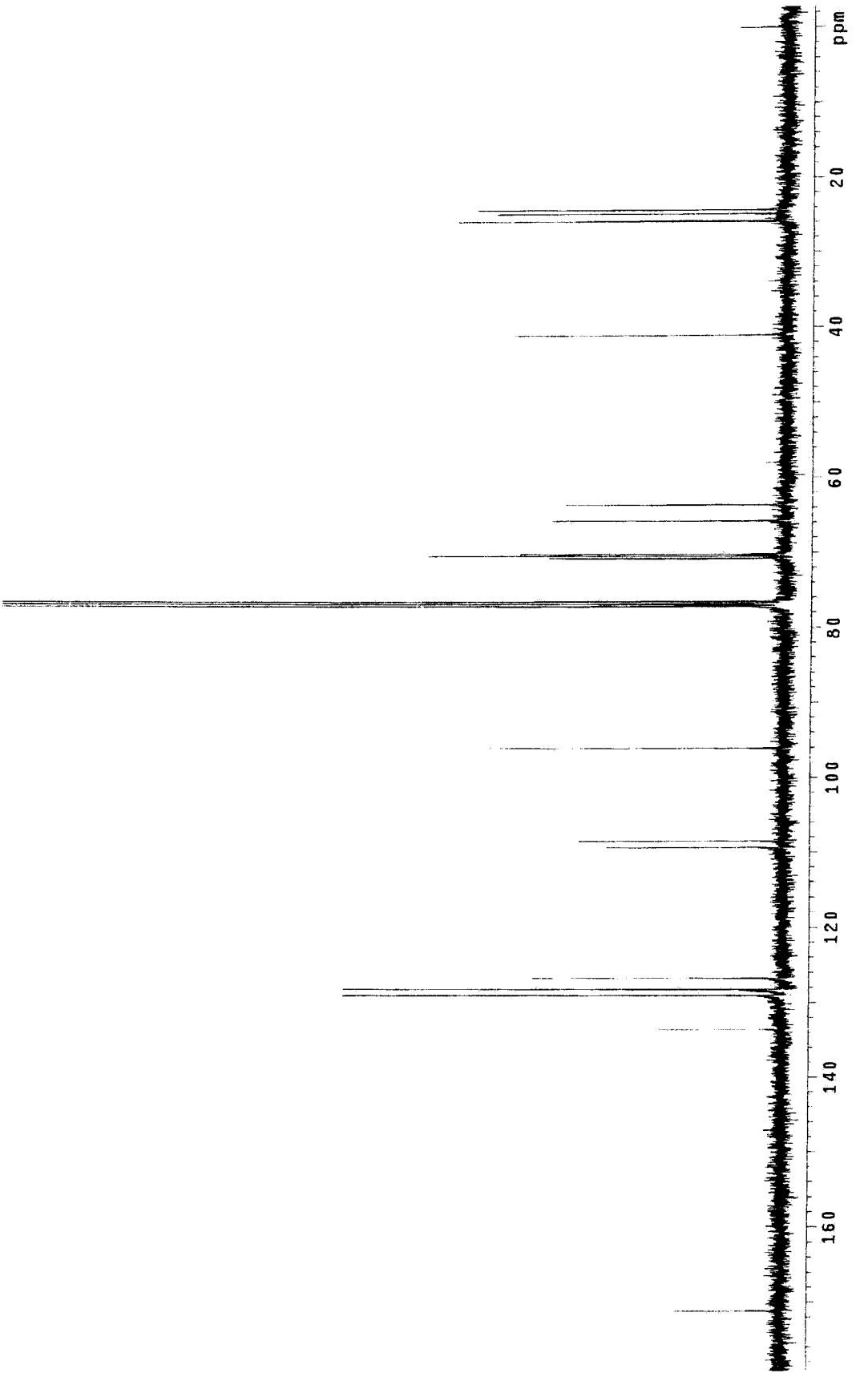

Figure 37. ^{13}C NMR of **6**

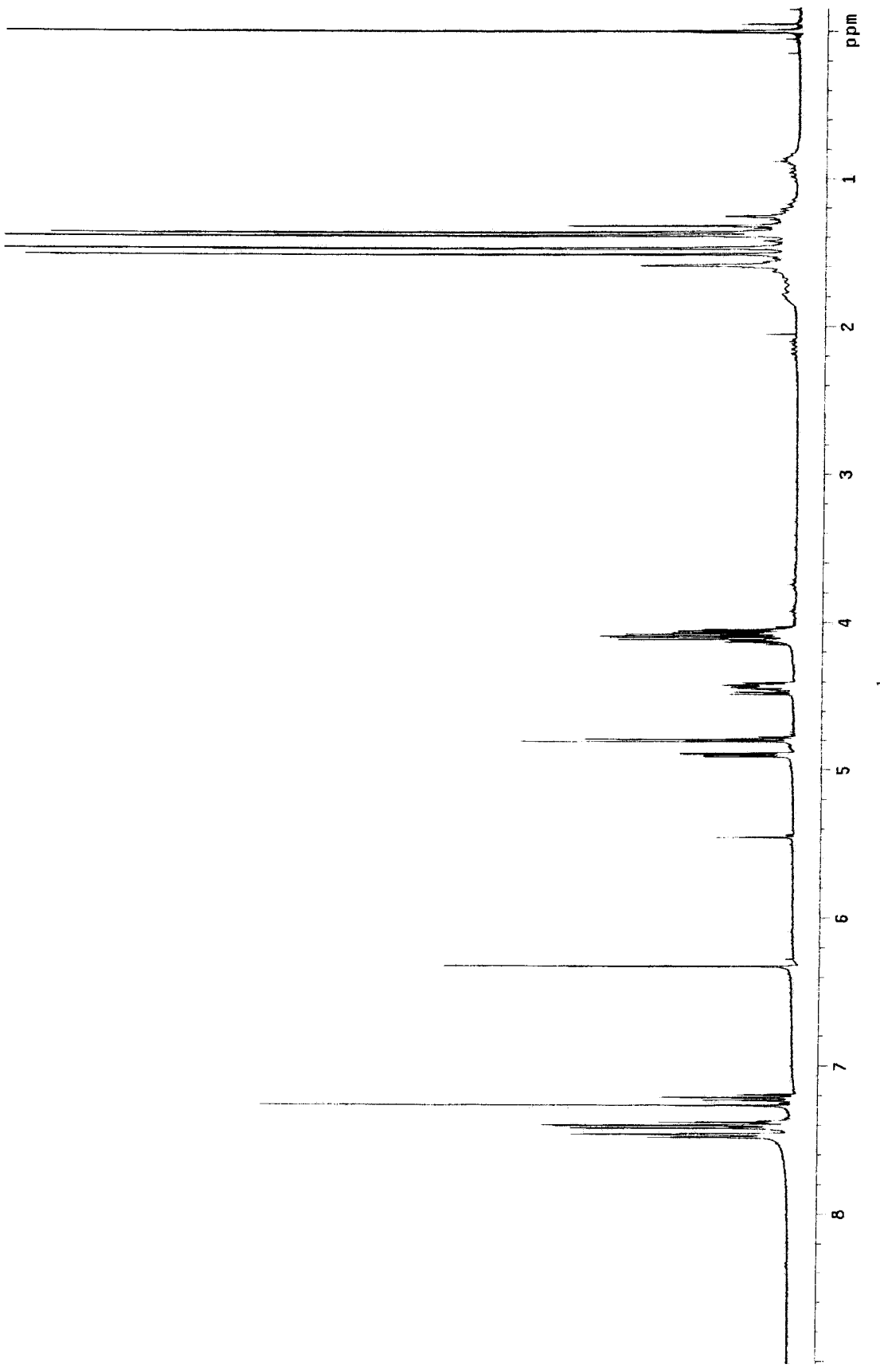

Figure 38. ^{1}H NMR of **7**

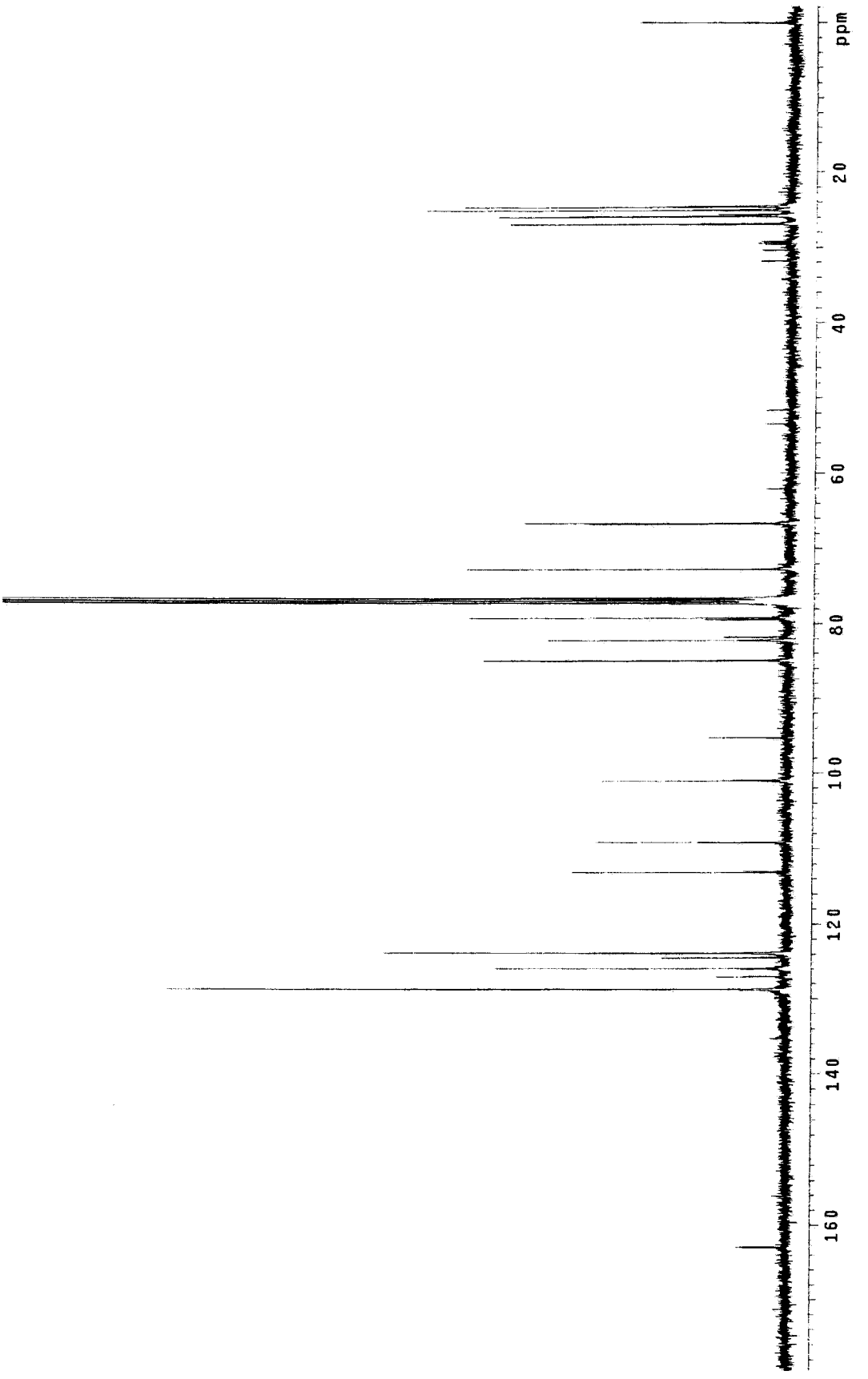

Figure 39. ^{13}C NMR of **7**

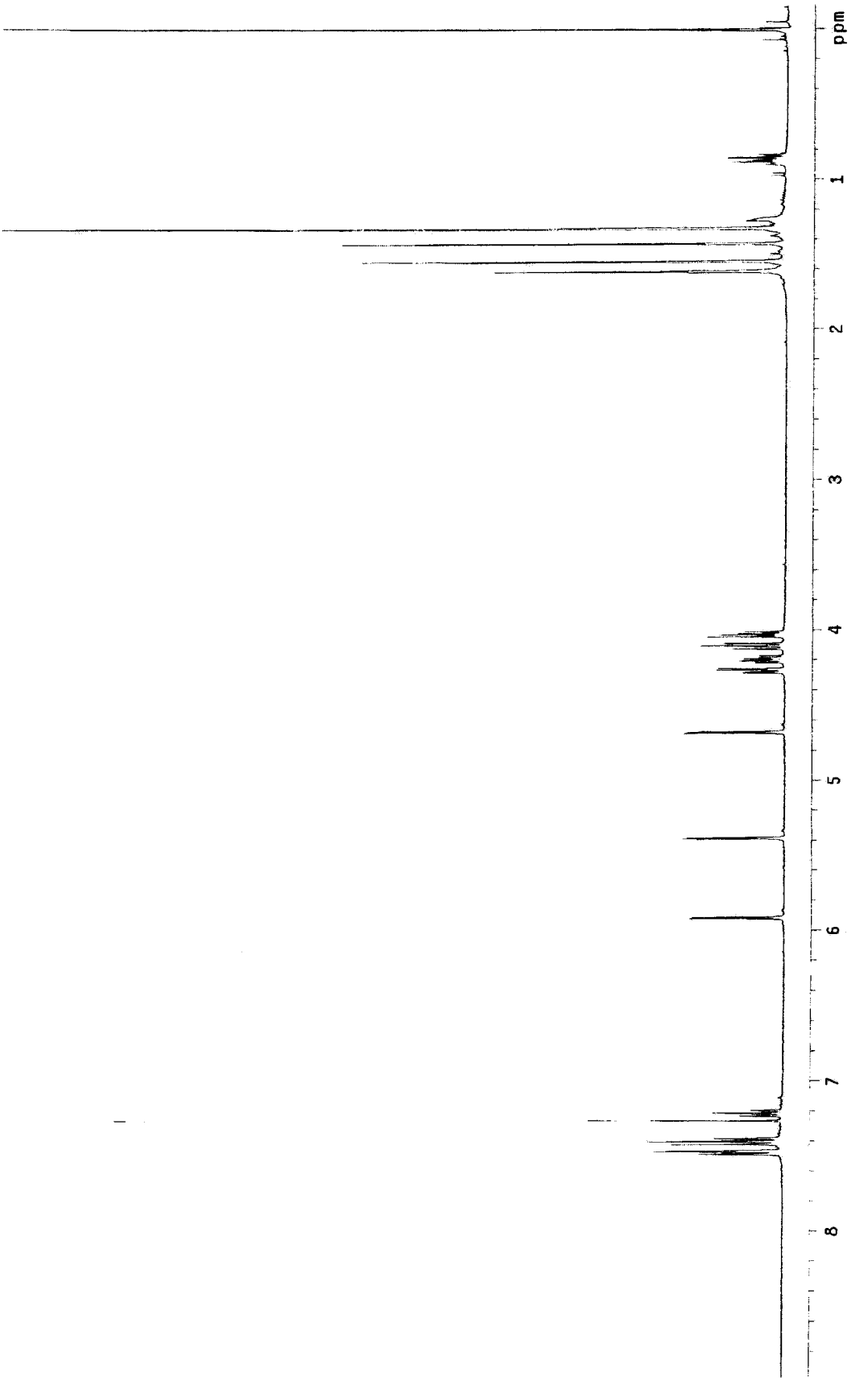

Figure 40. ^{1}H NMR of **8**

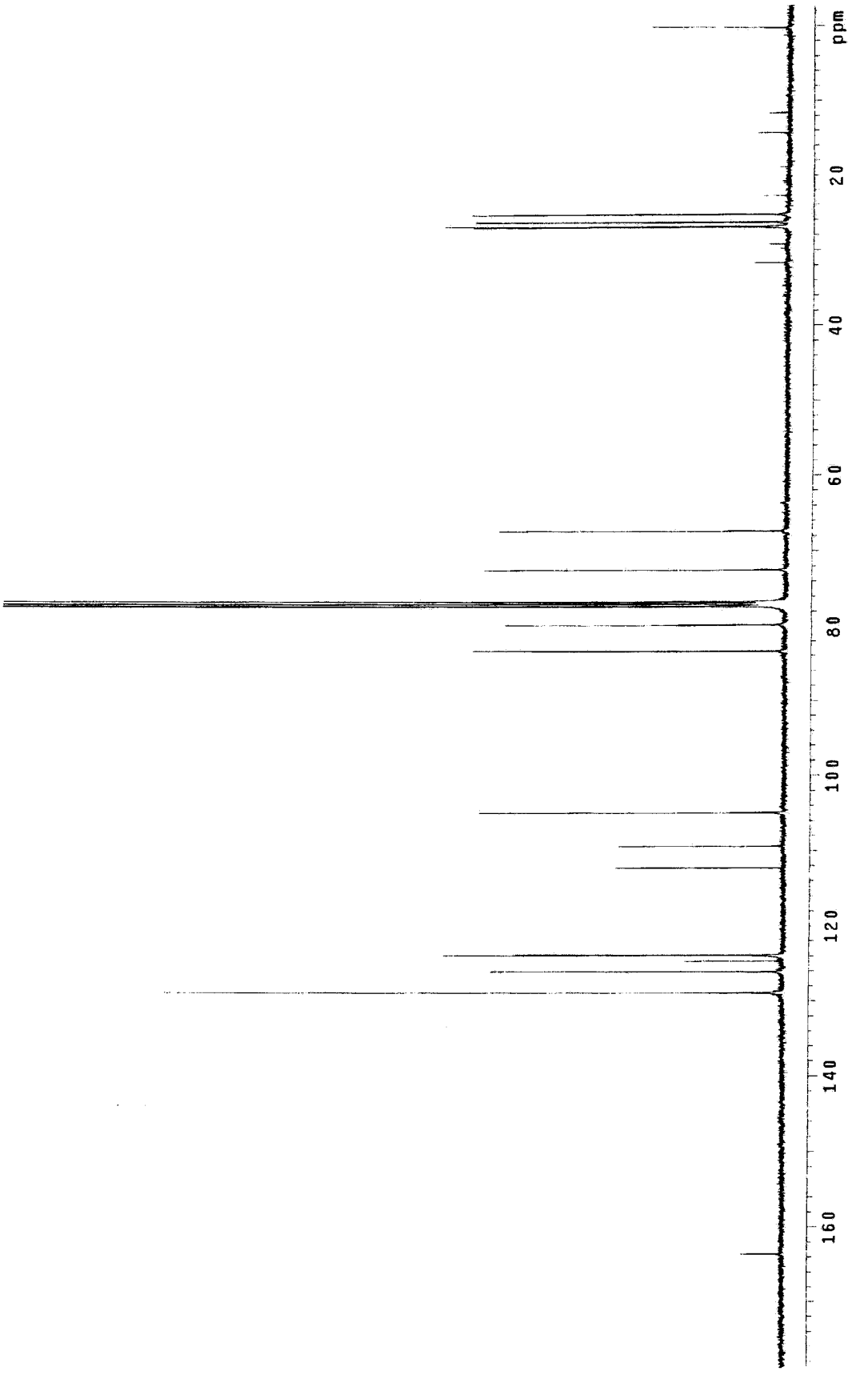

Figure 41. ^{13}C NMR of **8**

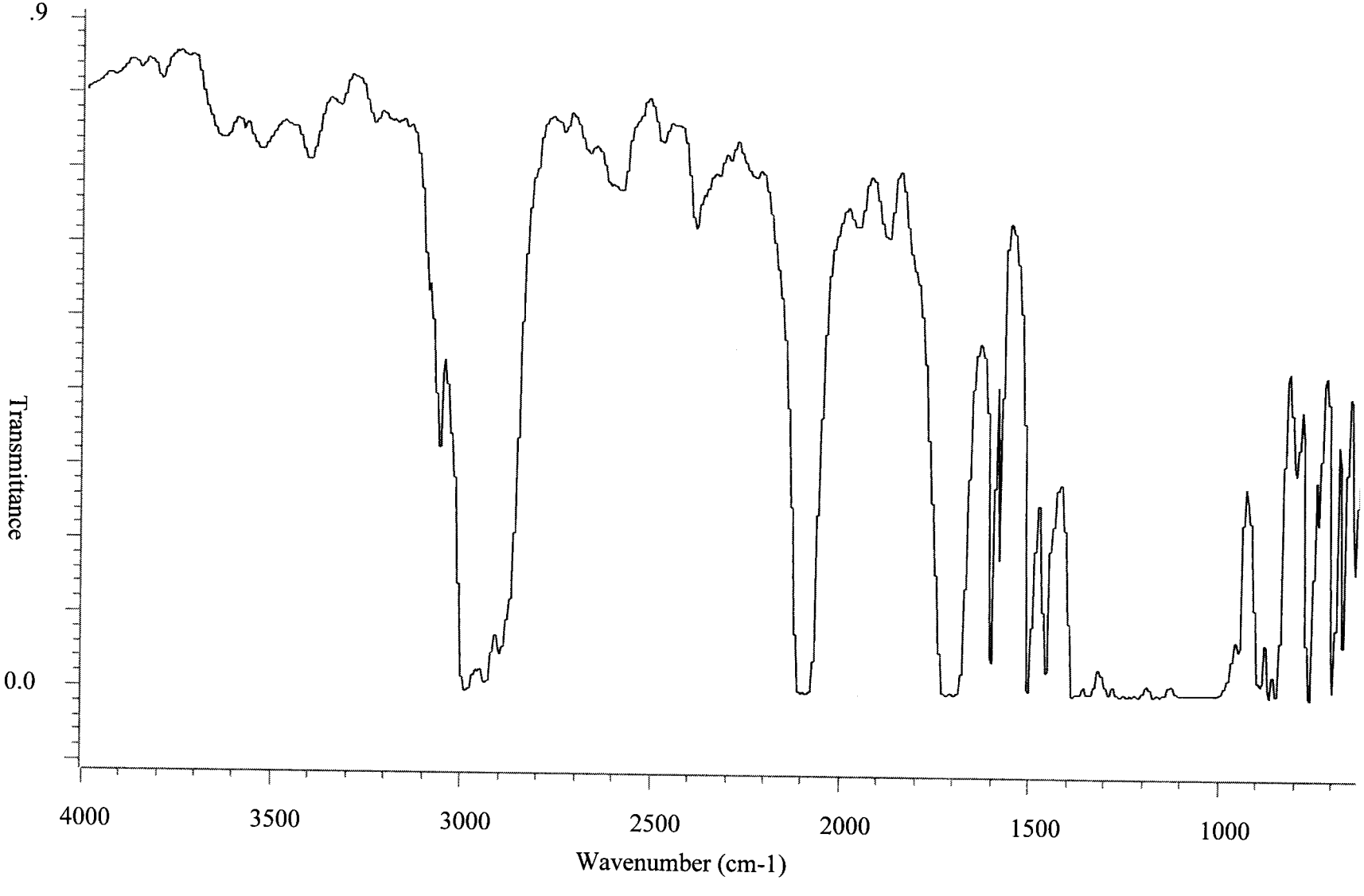

Figure 42. FT-IR of **8**

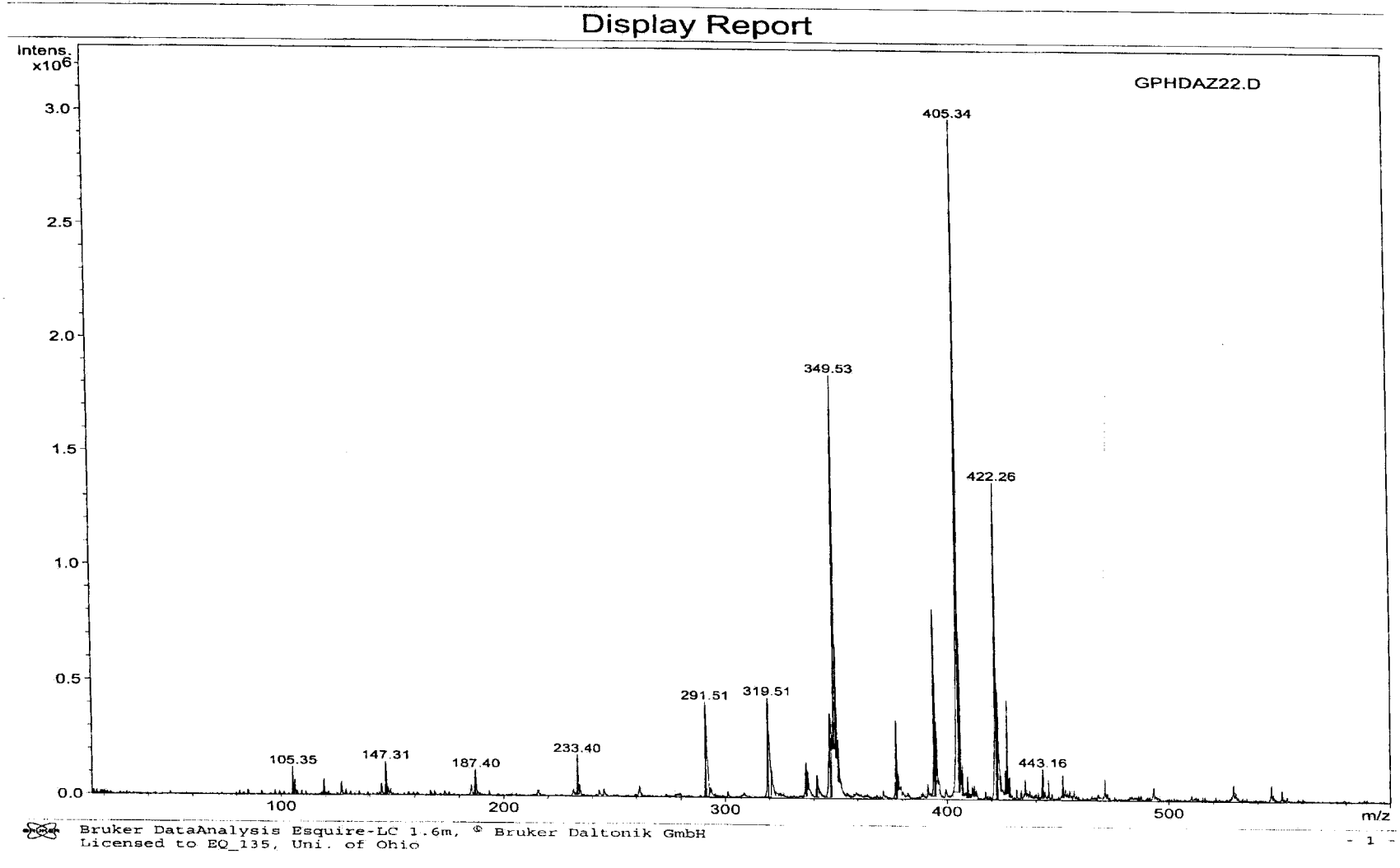

Figure 43. Positive mode ESI-MS of **8**

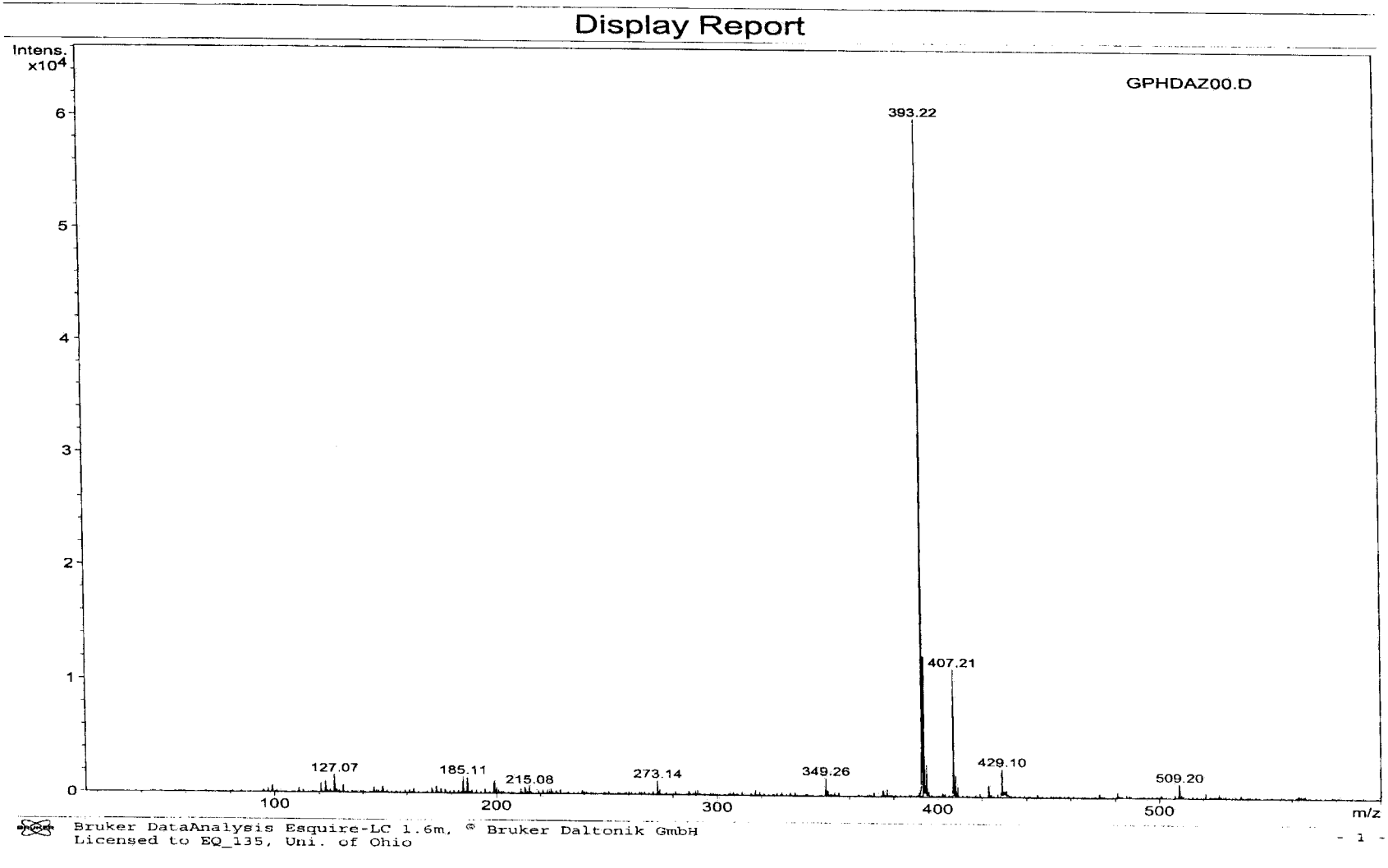

Figure 44. Negative mode APCI-MS of **8**

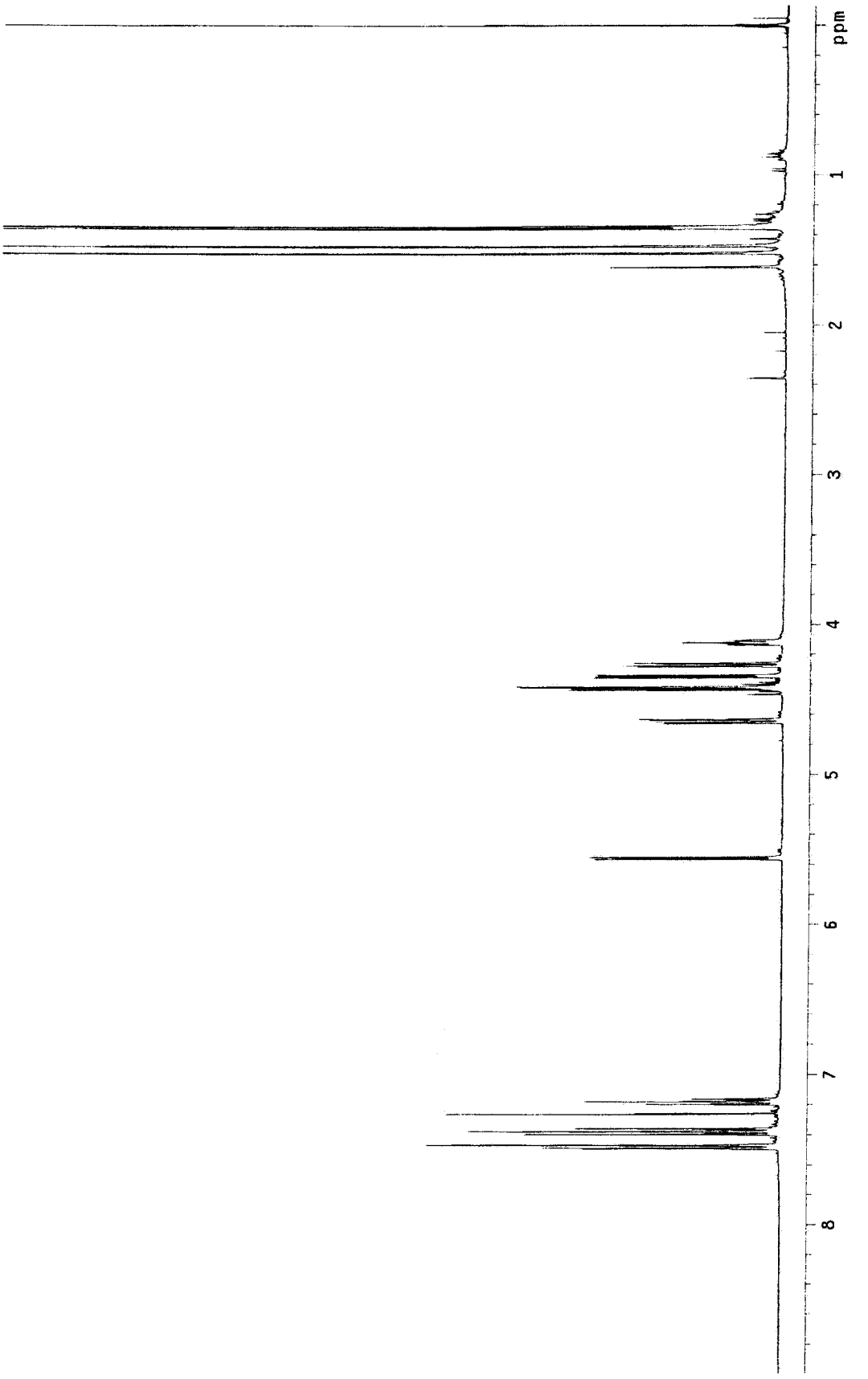

Figure 45. ^{1}H NMR of **9**

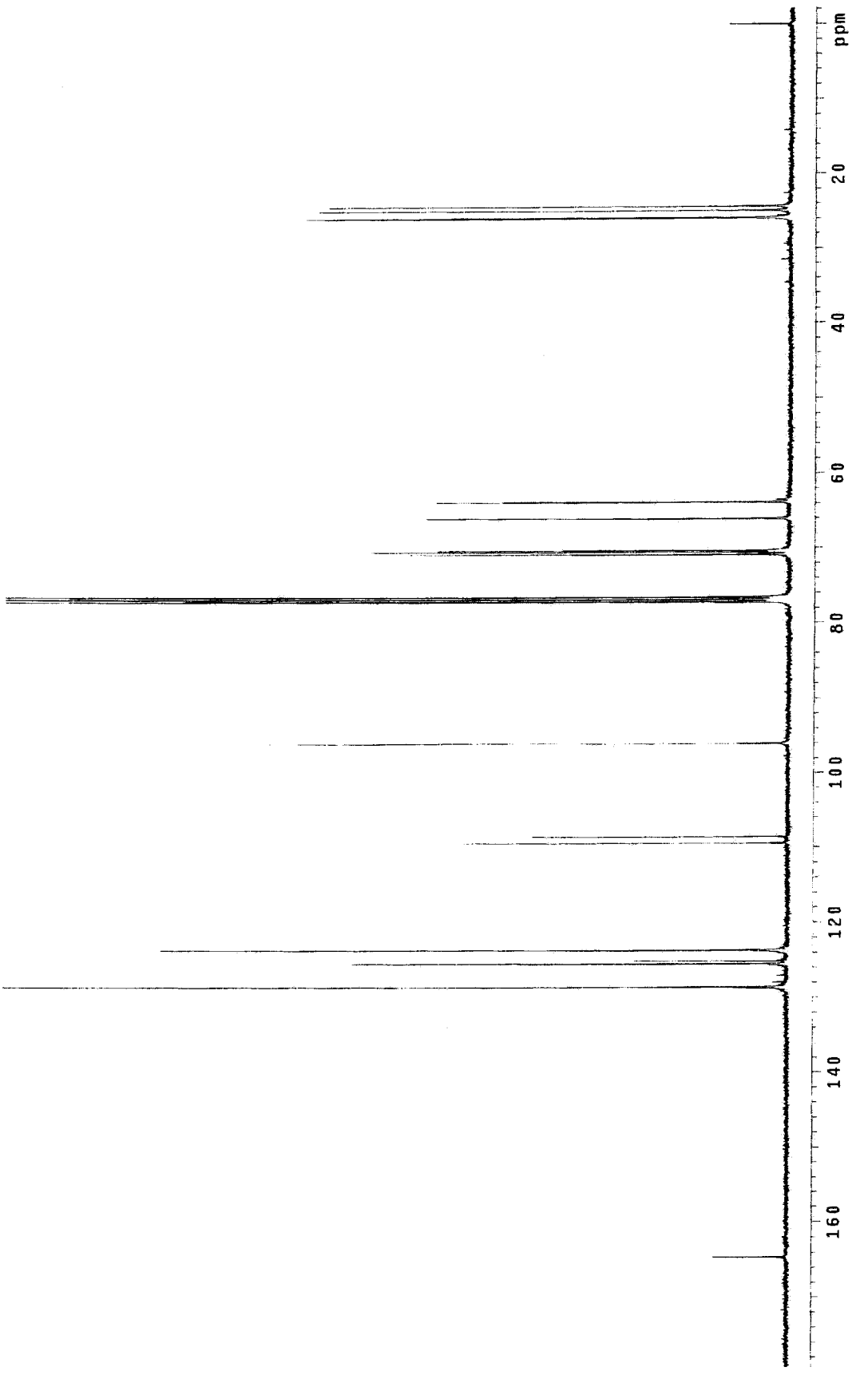

Figure 46. ^{13}C NMR of **9**

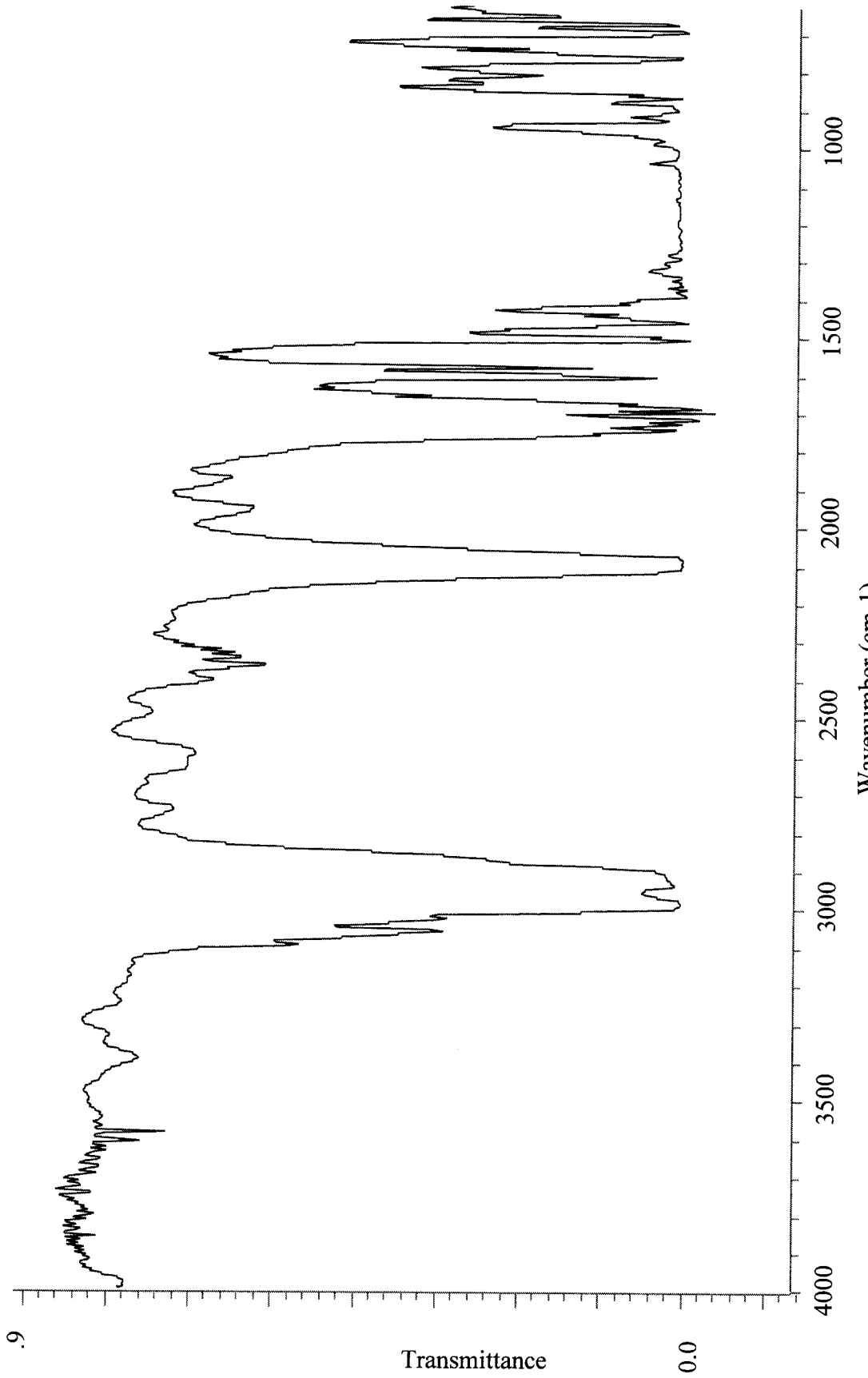

Figure 47. FT-IR of **9**

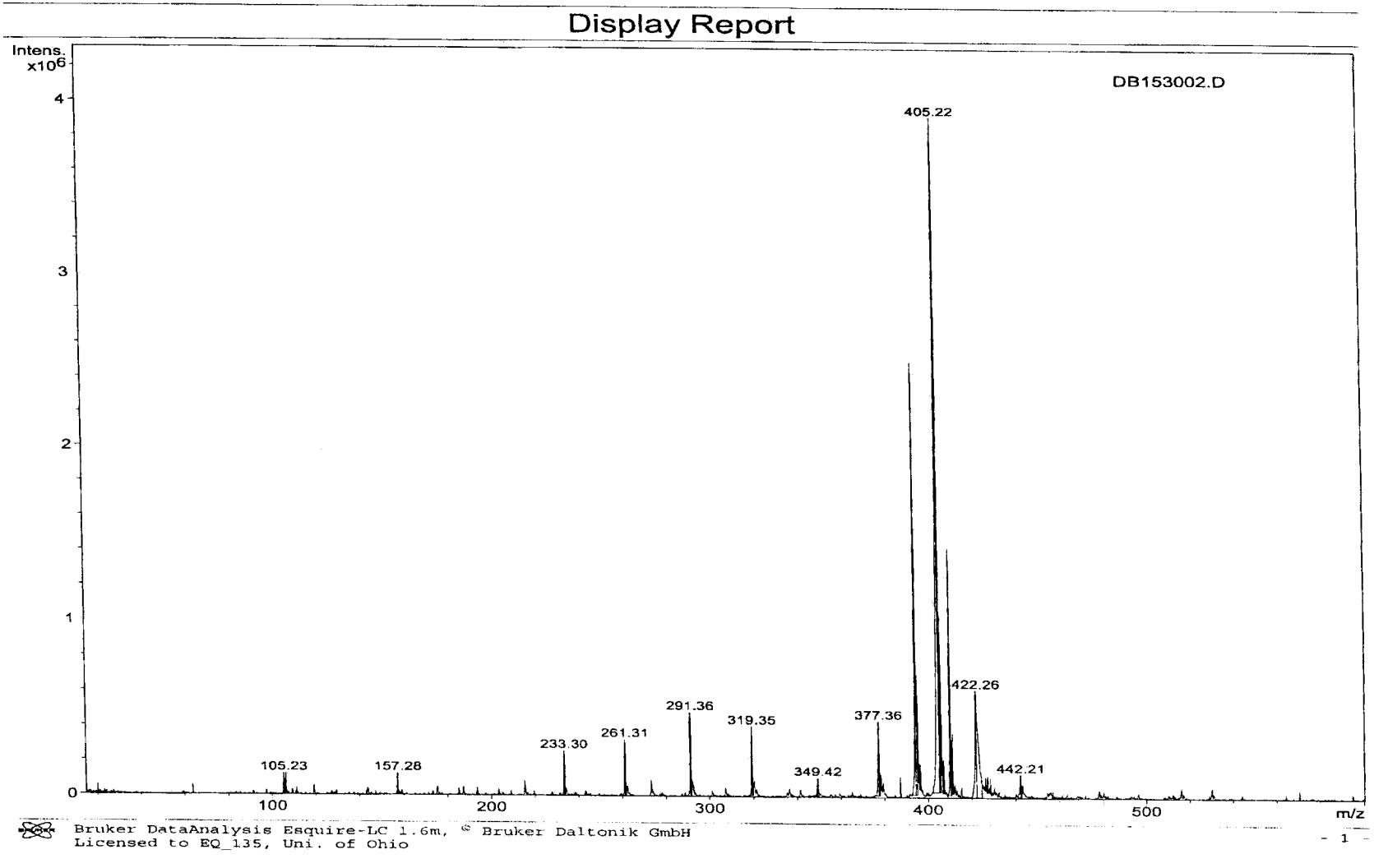

Figure 48. Positive mode ESI-MS of **9**

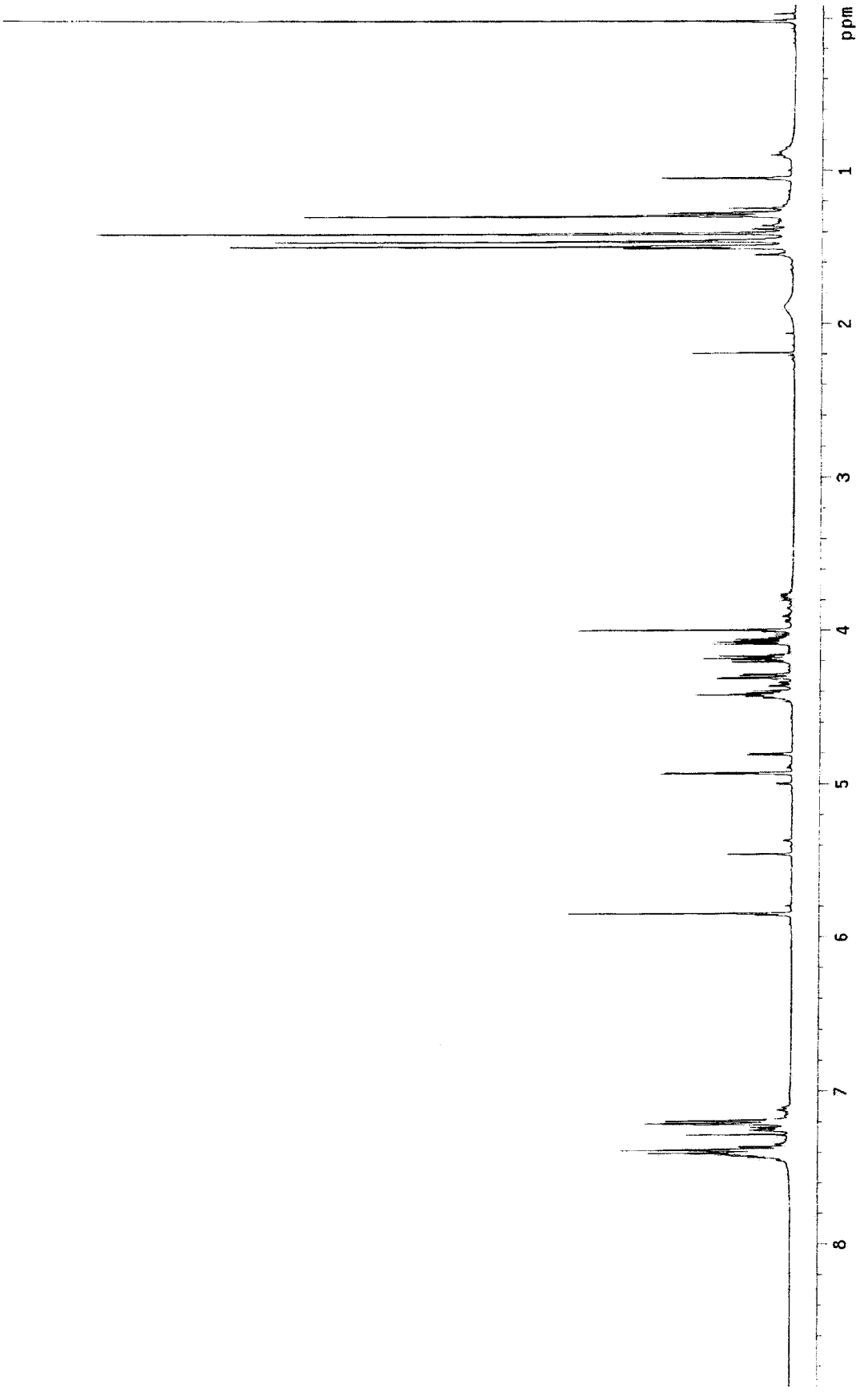

Figure 49. ^{1}H NMR of **10**

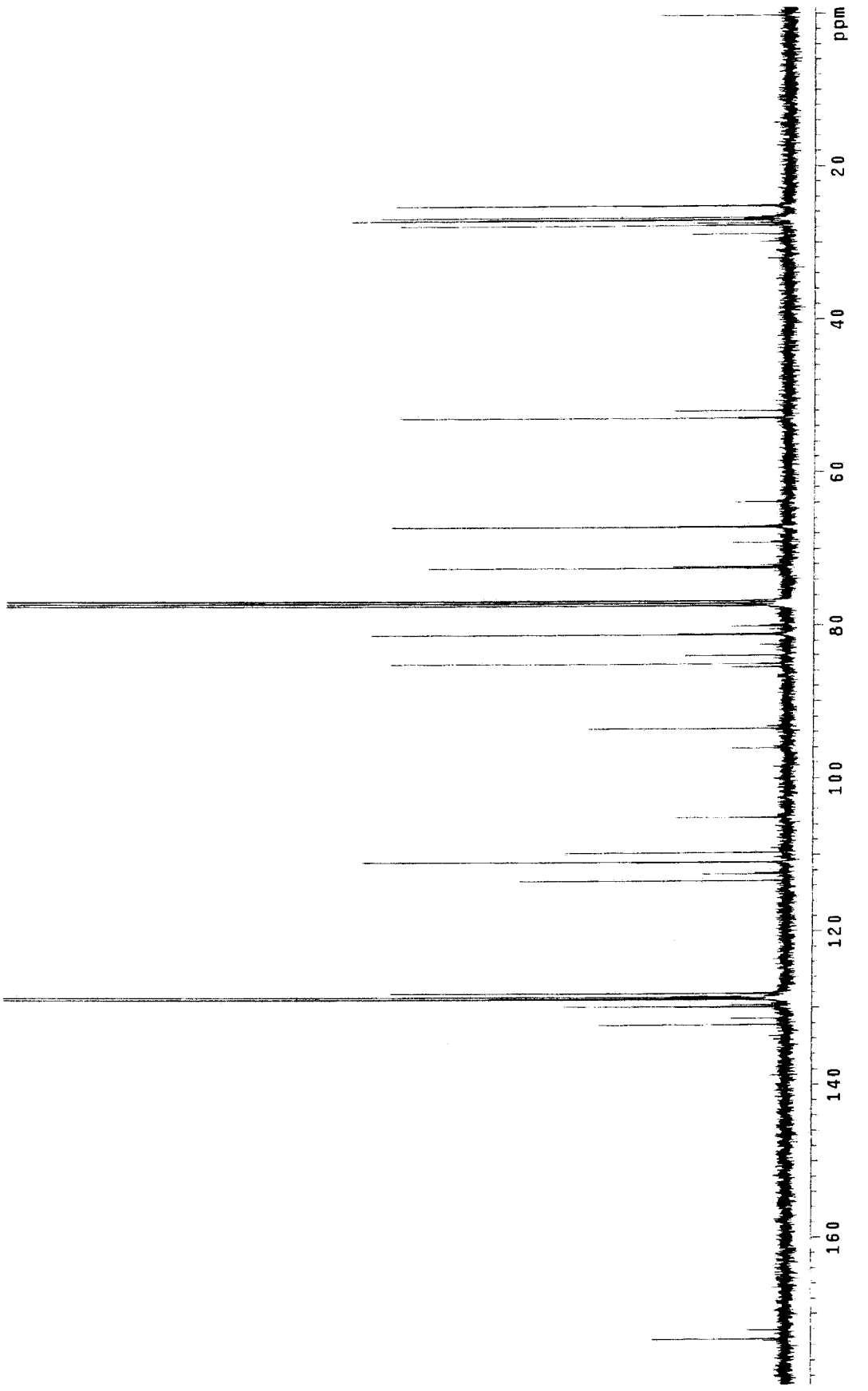

Figure 50. ^{13}C NMR of **10**

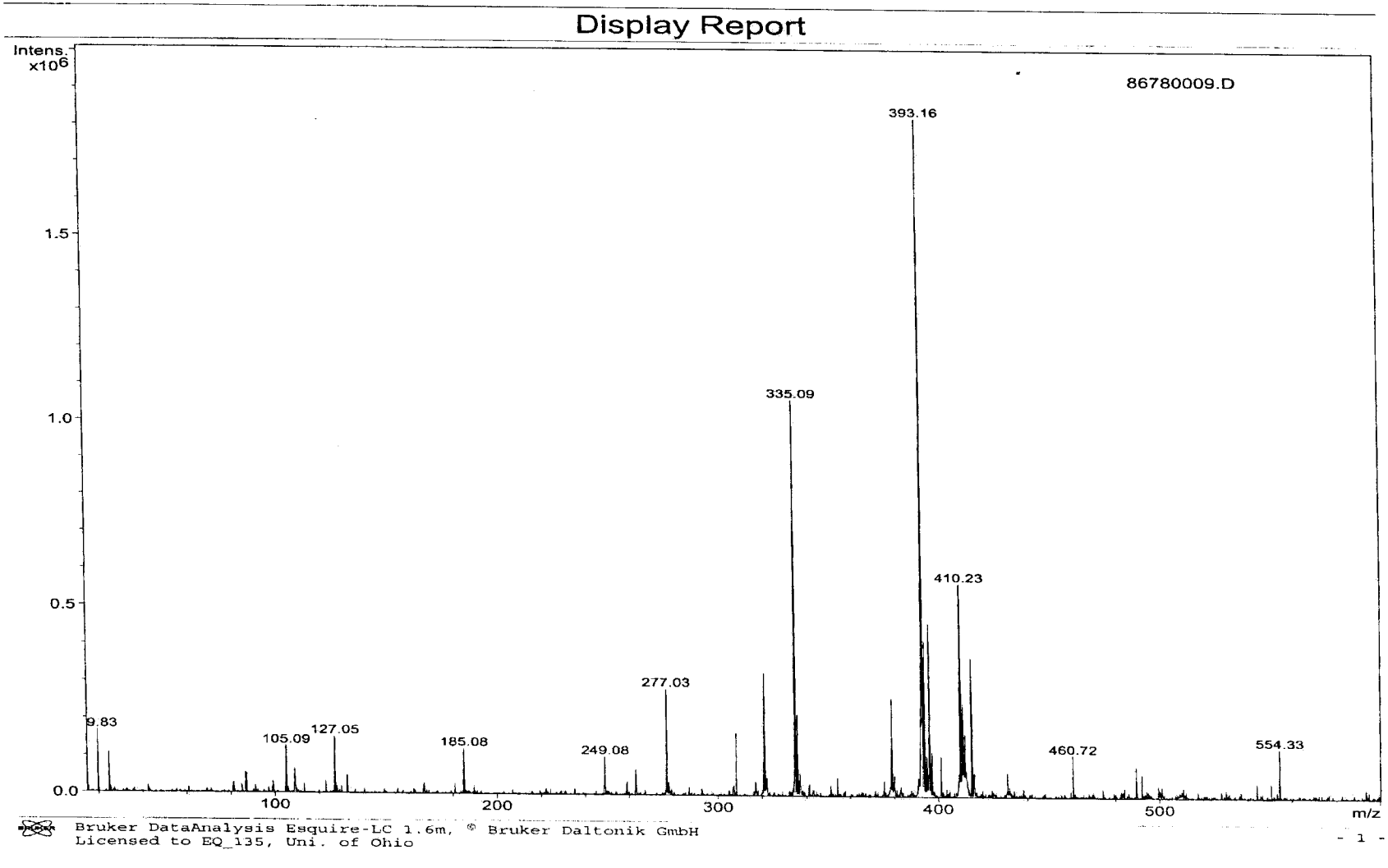

Figure 51. Positive mode ESI-MS of **10**

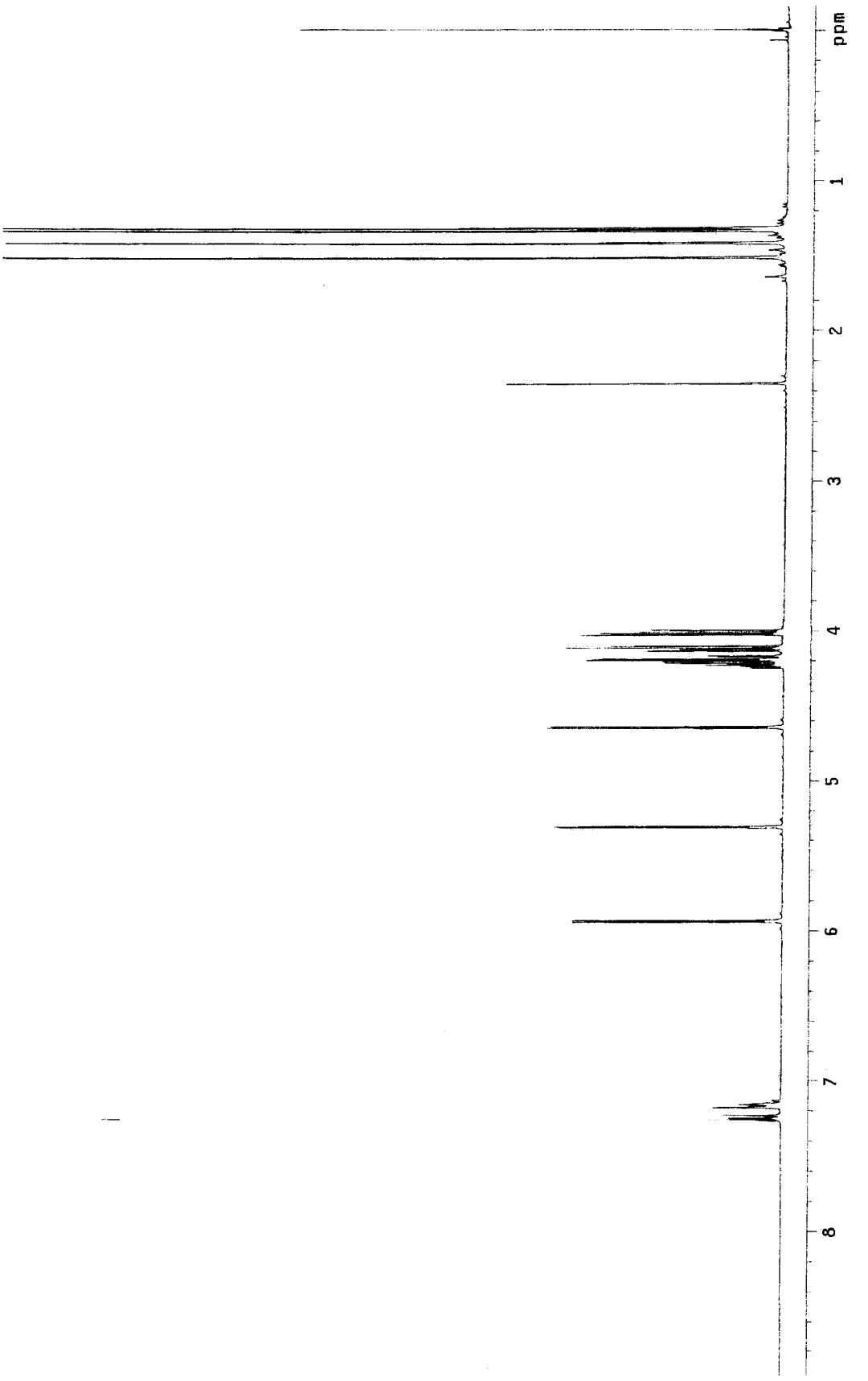

Figure52. ^{1}H NMR of **11**

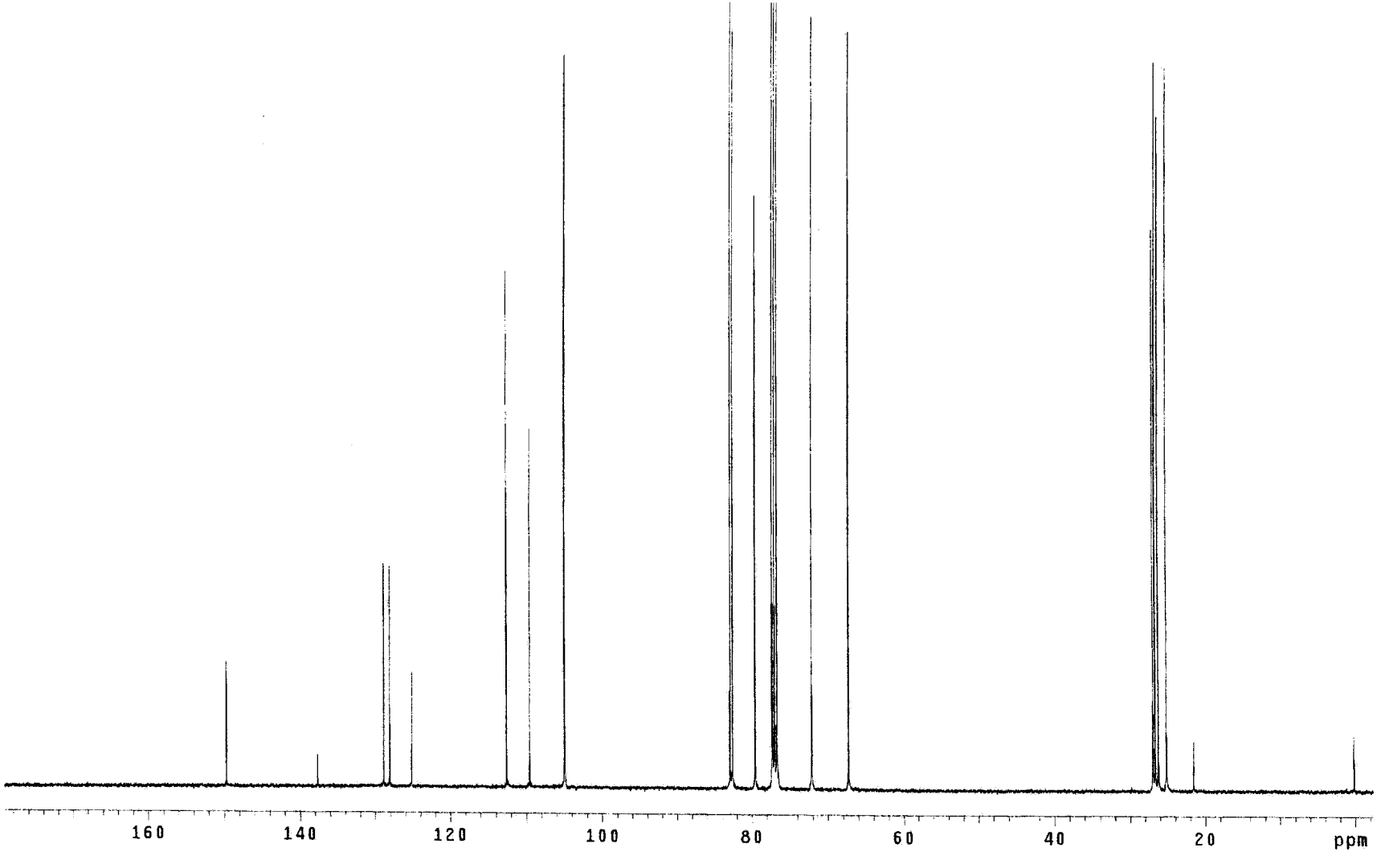

Figure 53. ^{13}C NMR of **11**

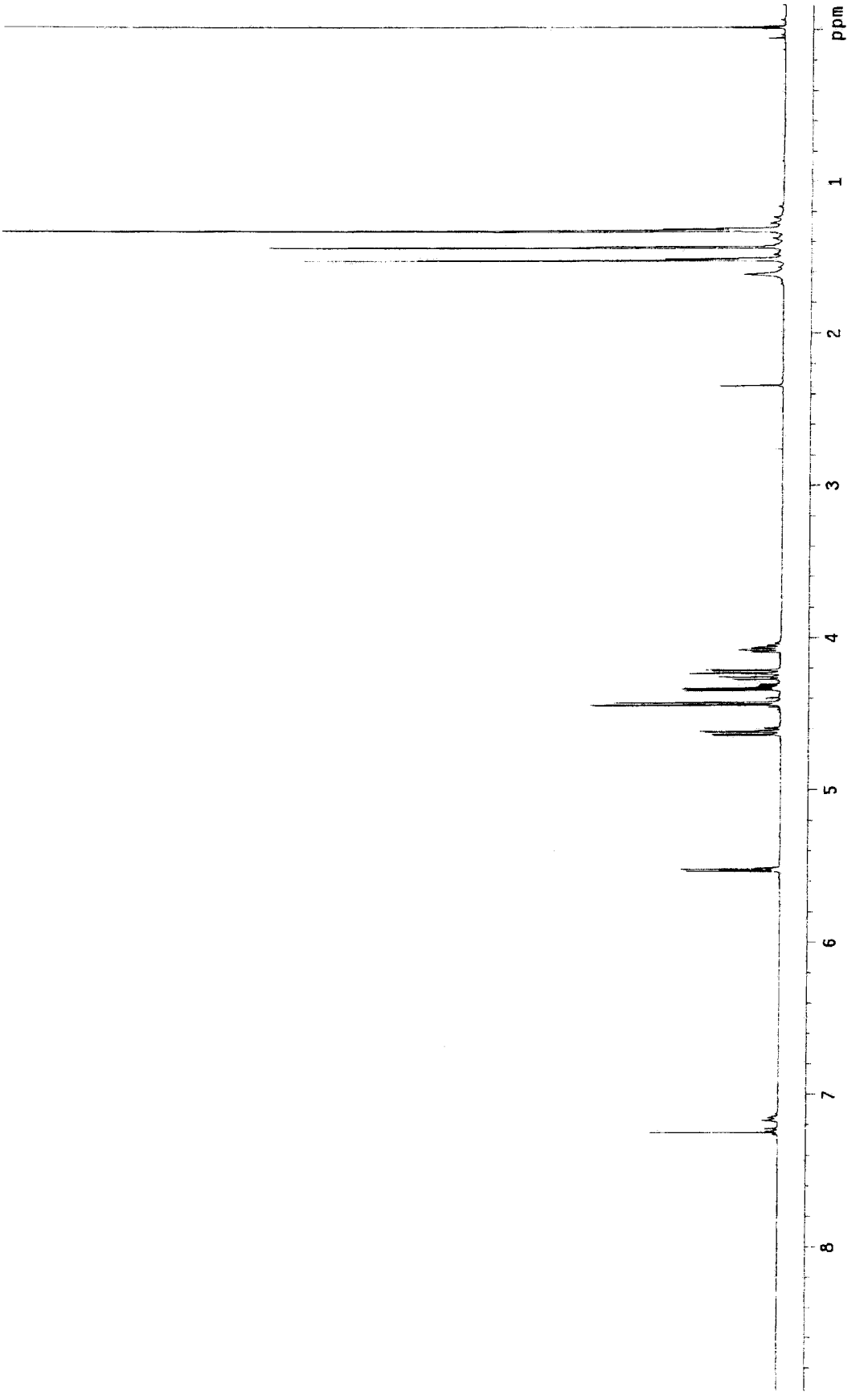

Figure 54. ^{1}H NMR of **12**

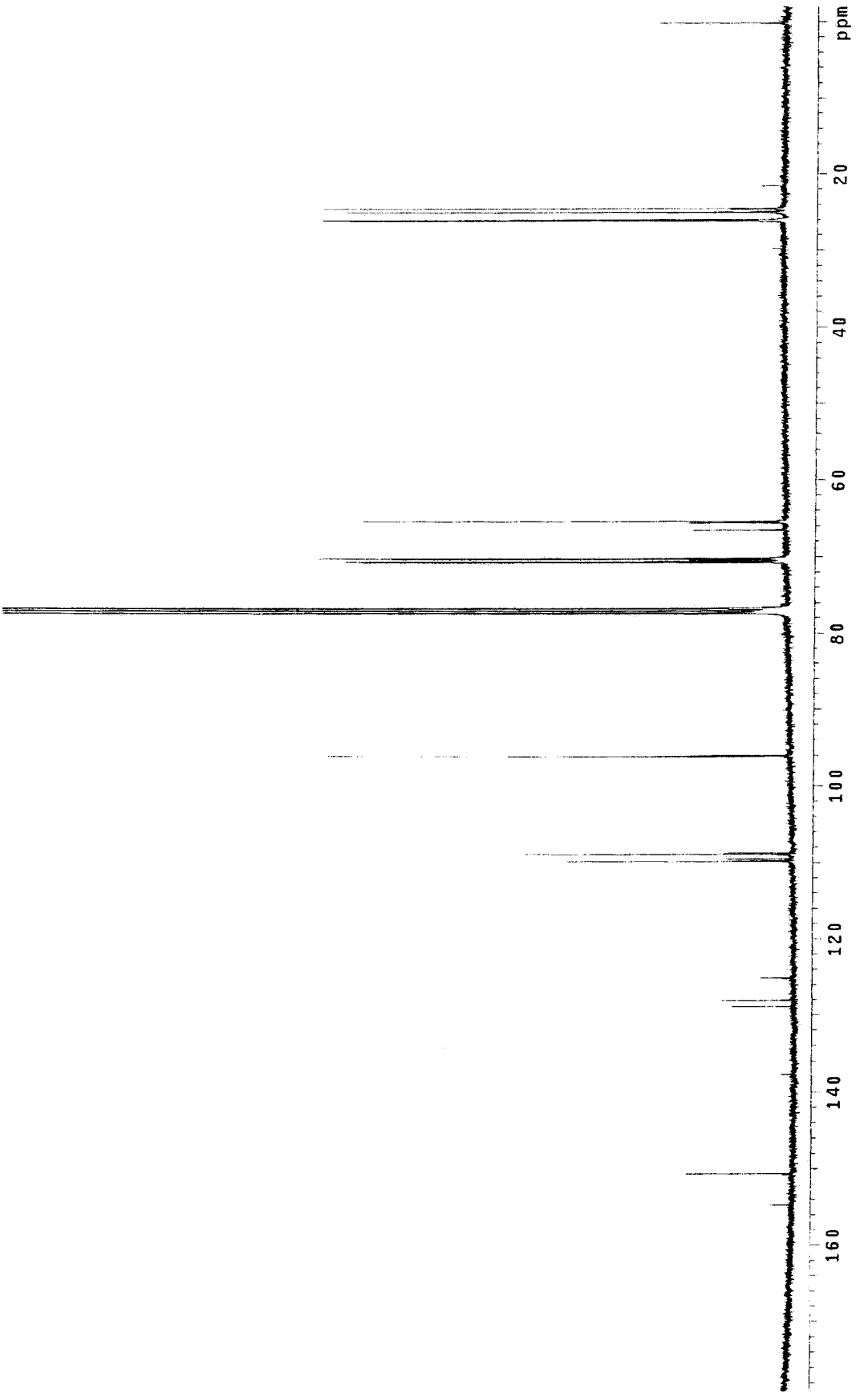

Figure 55. ^{13}C NMR of **12**

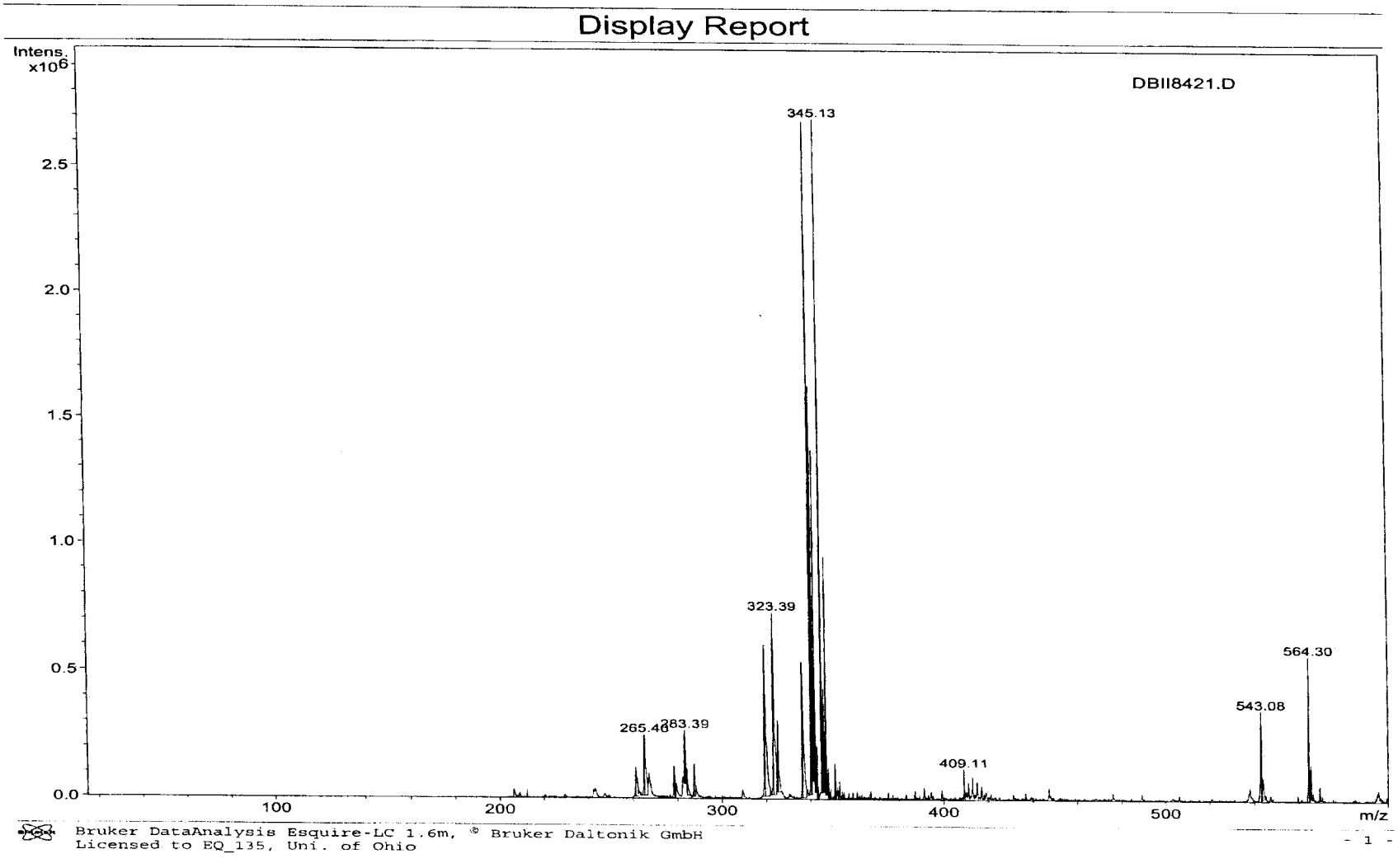

Figure 56. Positive mode ESI-MS of **12**

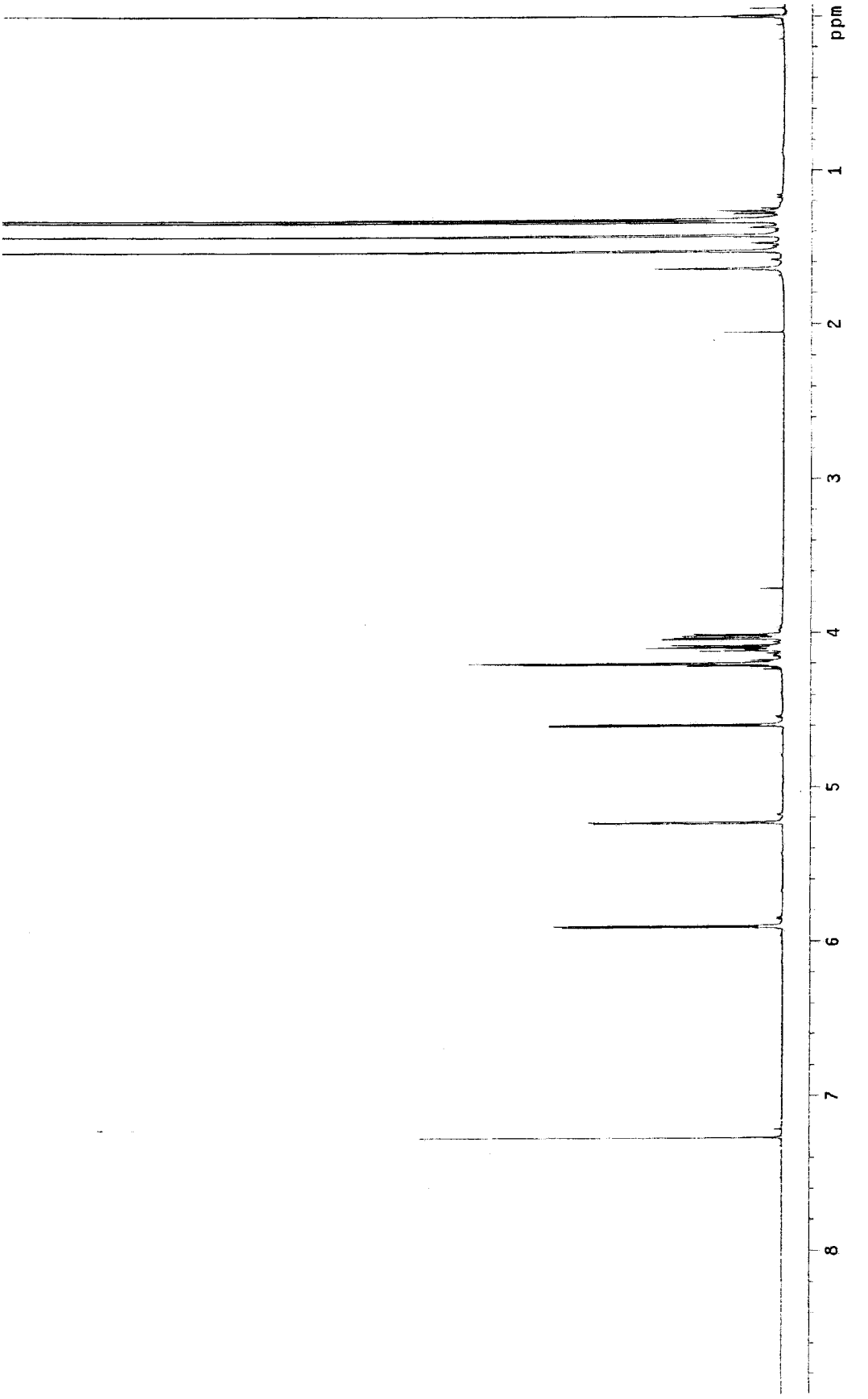

Figure 57. ^{1}H NMR of **13**

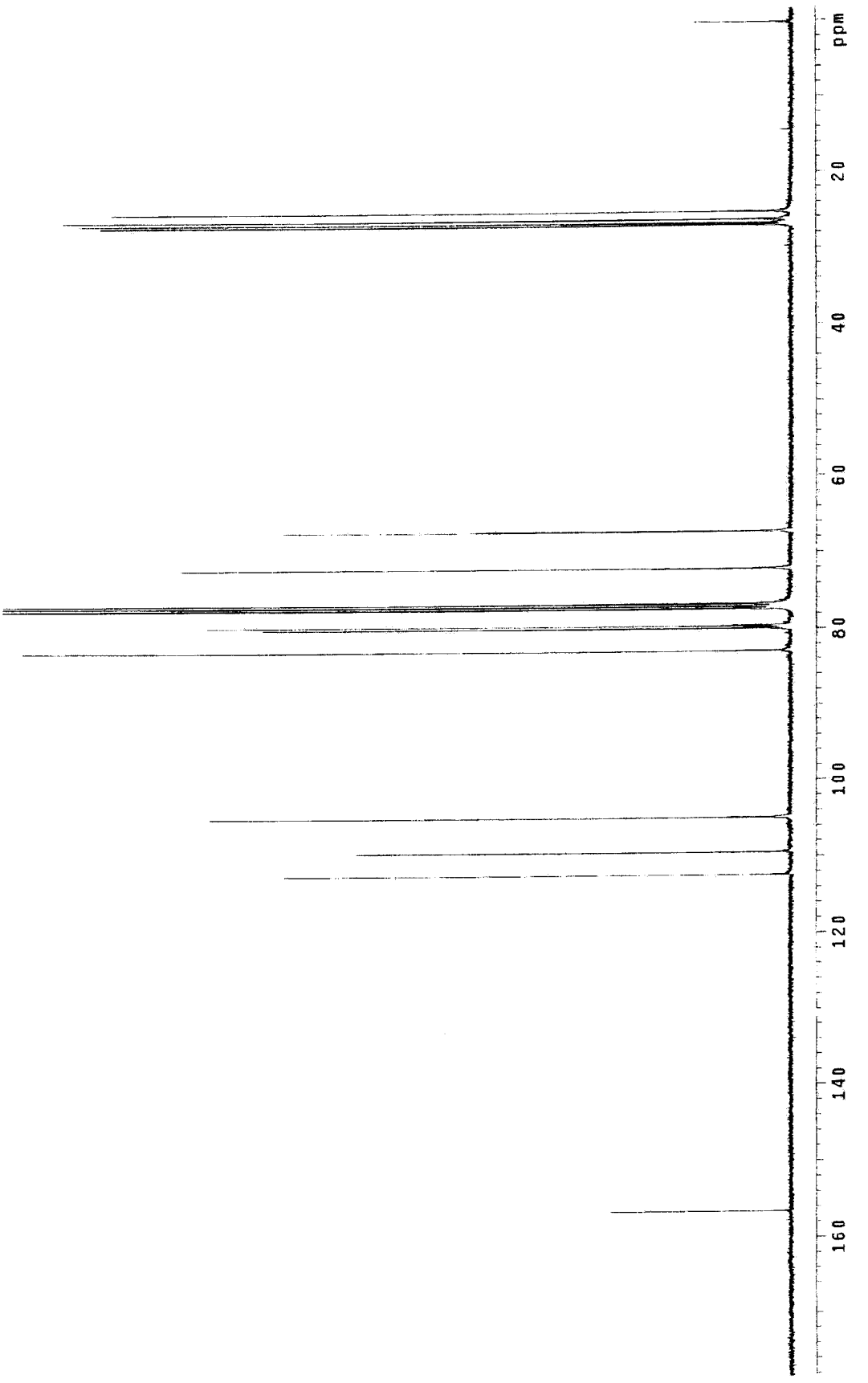

Figure 58. ^{13}C NMR of **13**

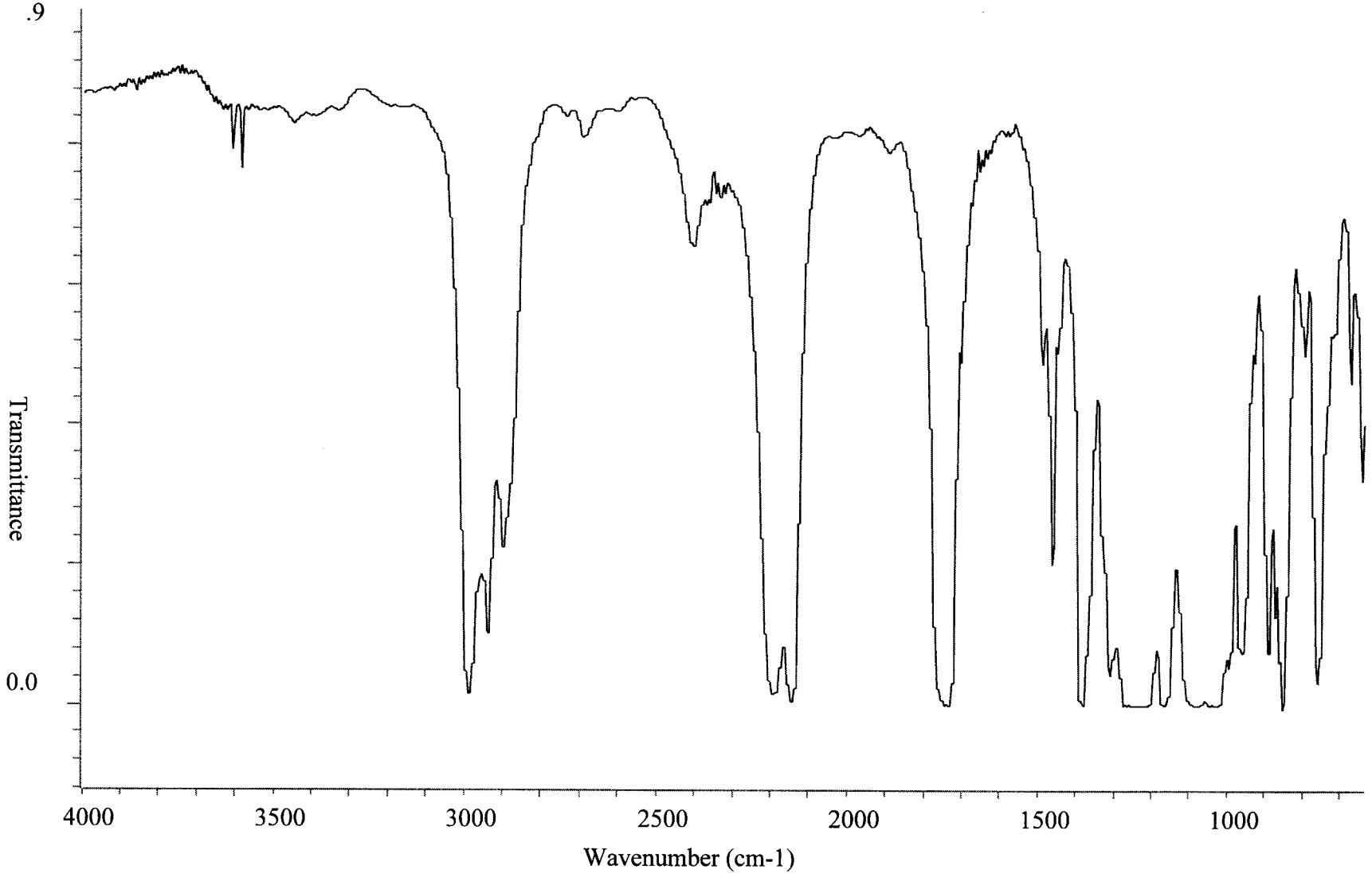

Figure 59. FT-IR of **13**

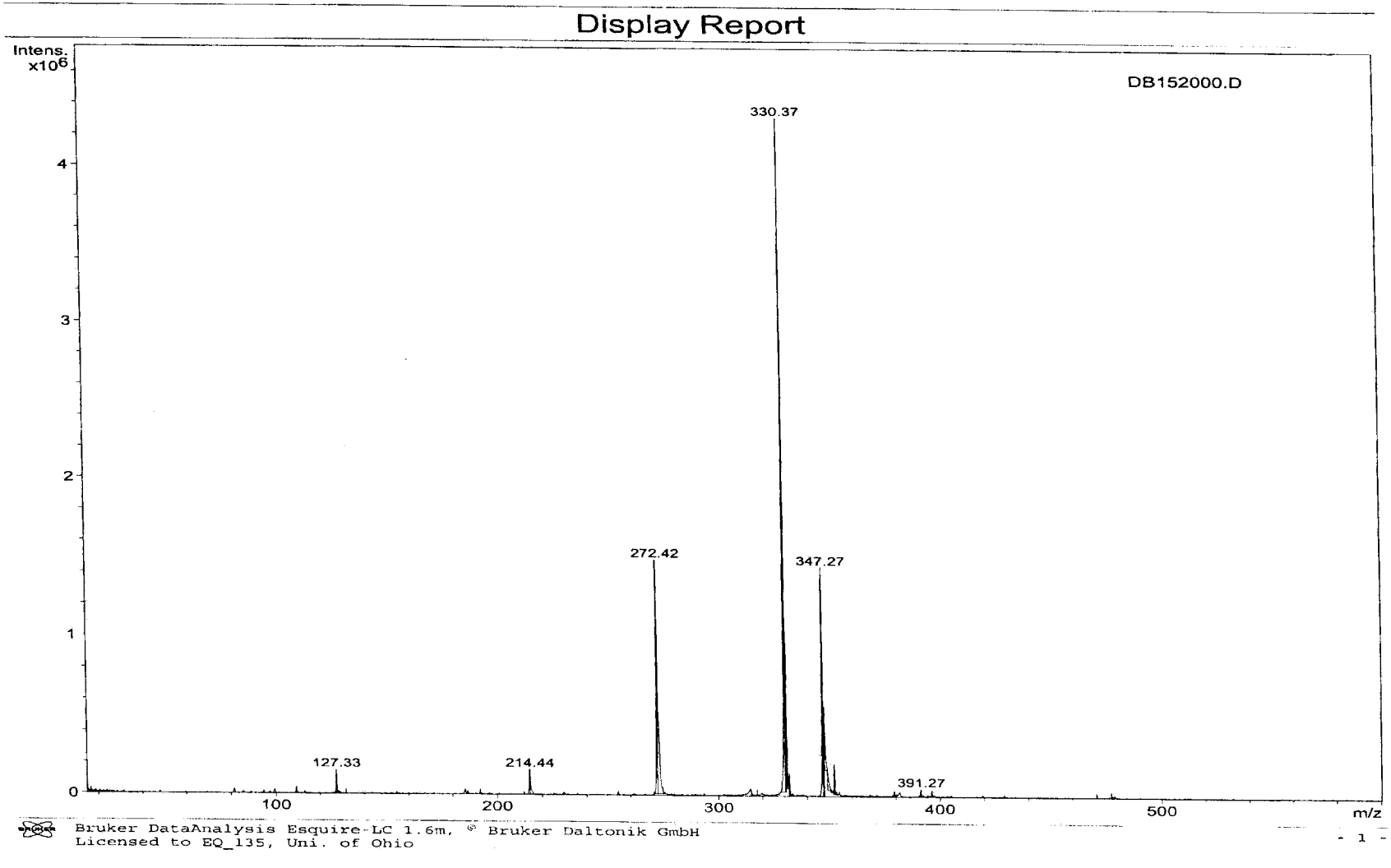

Figure 60. Positive mode ESI-MS of **13**

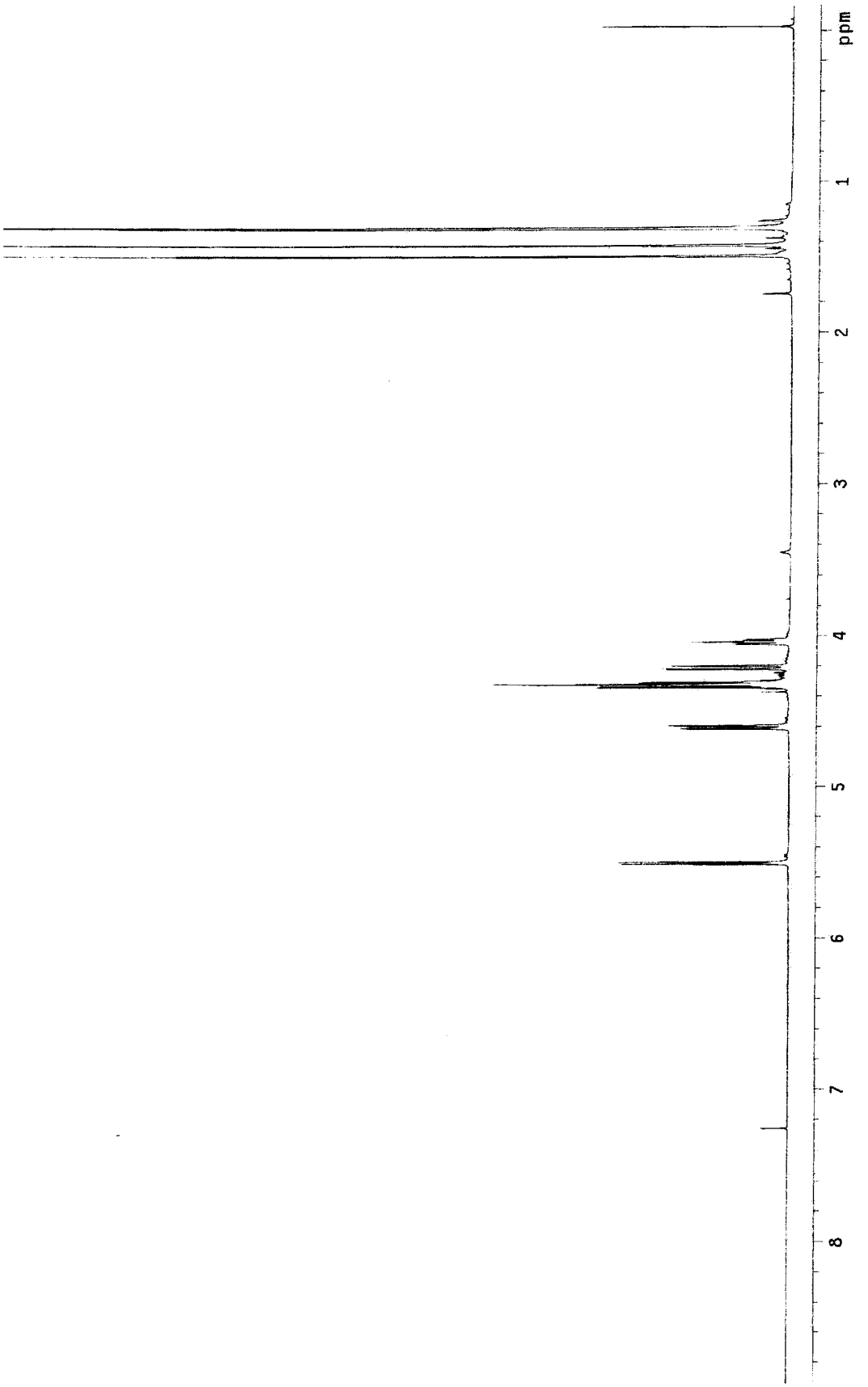

Figure 61. ^{1}H NMR of **14**

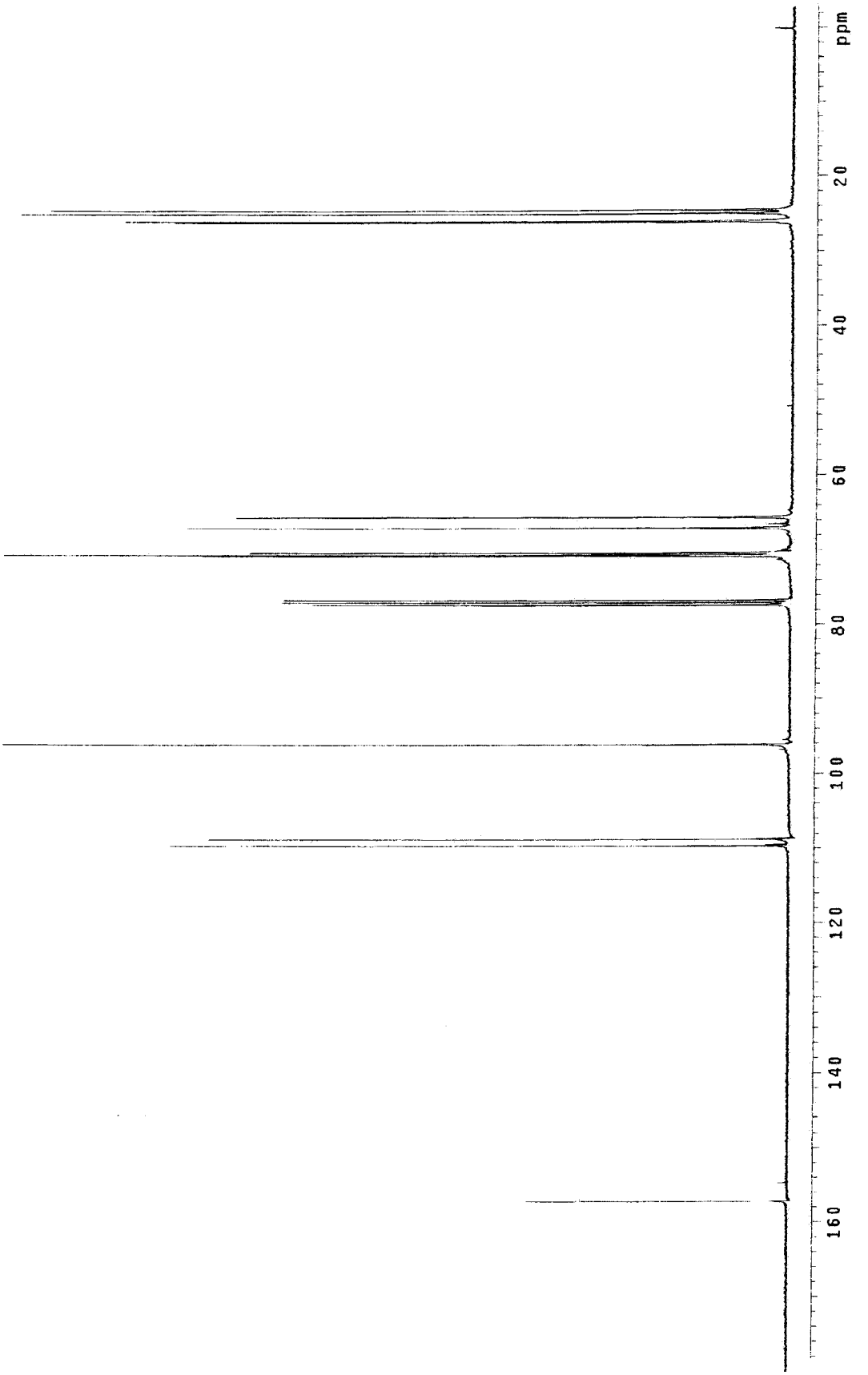

Figure 62. ^{13}C NMR of **14**

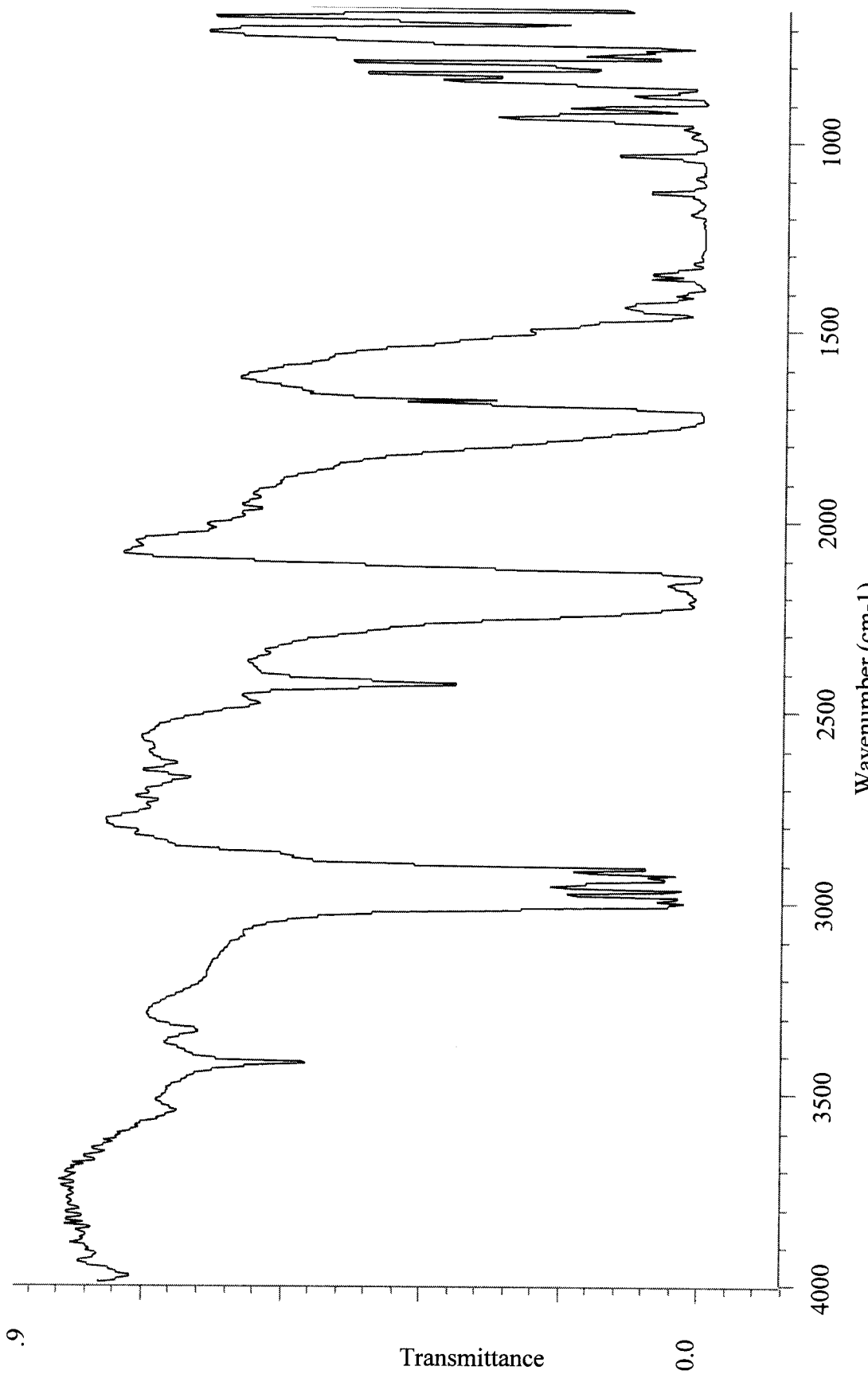

Figure 63. FT-IR of **14**

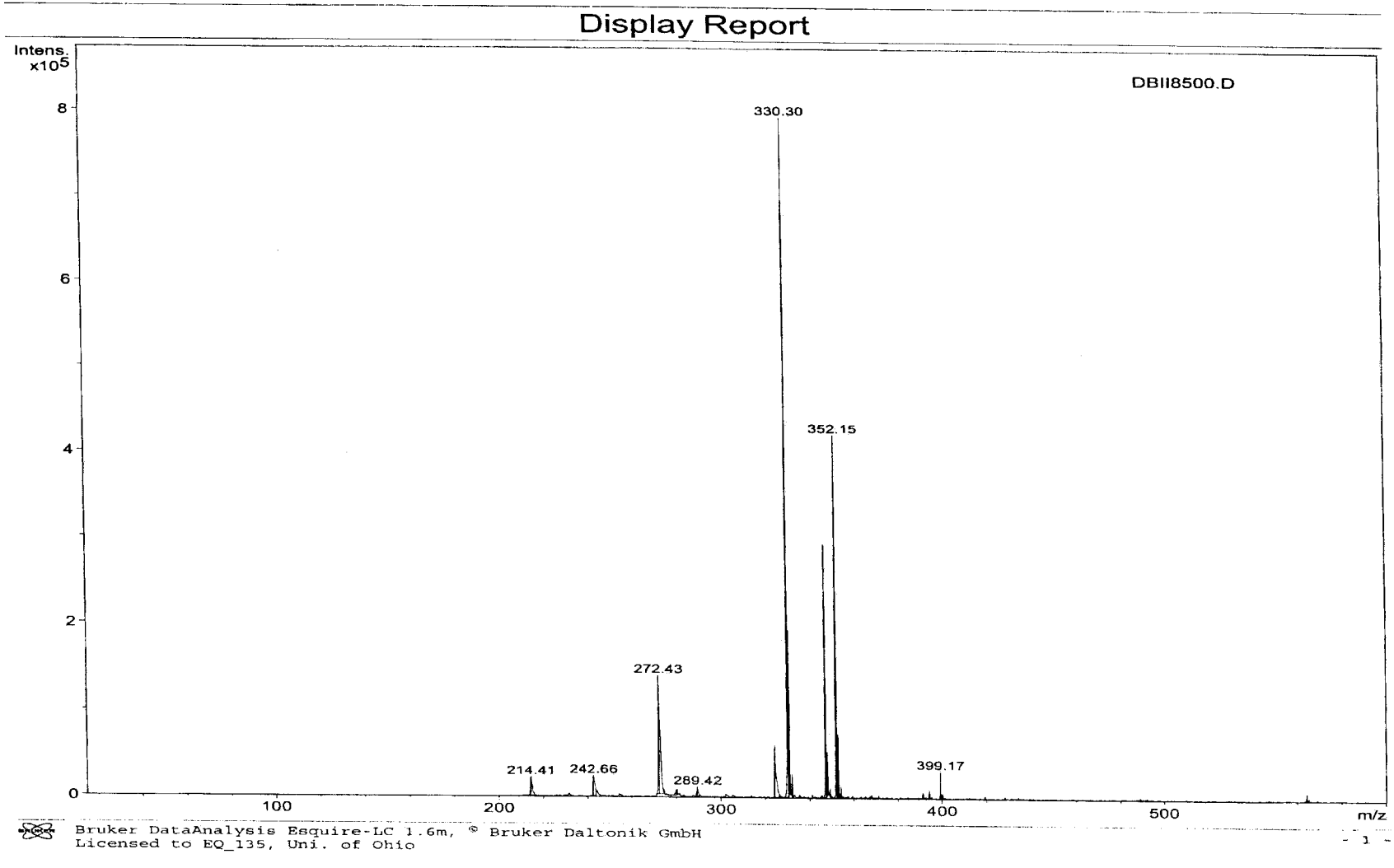

Figure 64. Positive mode ESI-MS of **14**

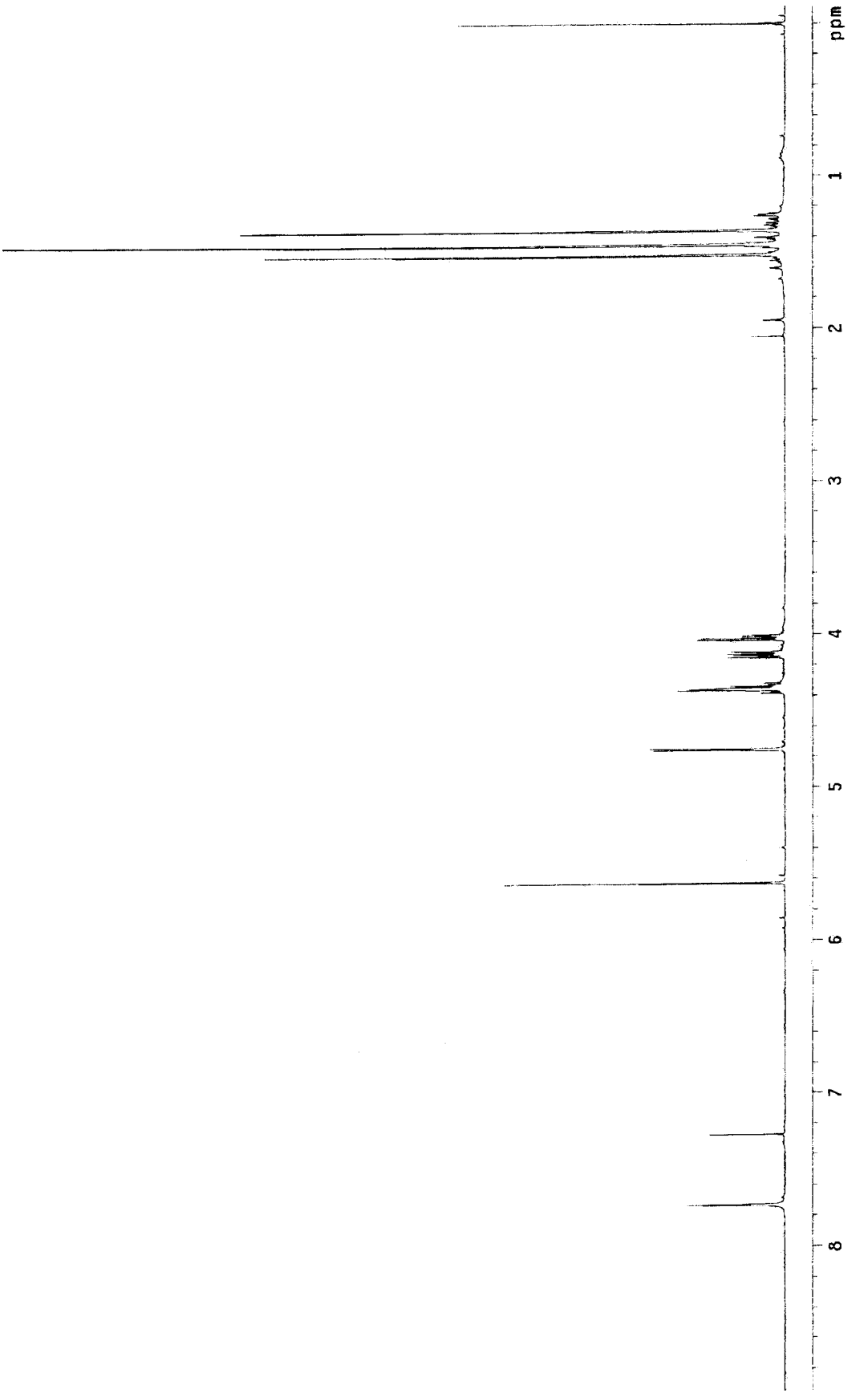

Figure 65. ^{1}H NMR of **15**

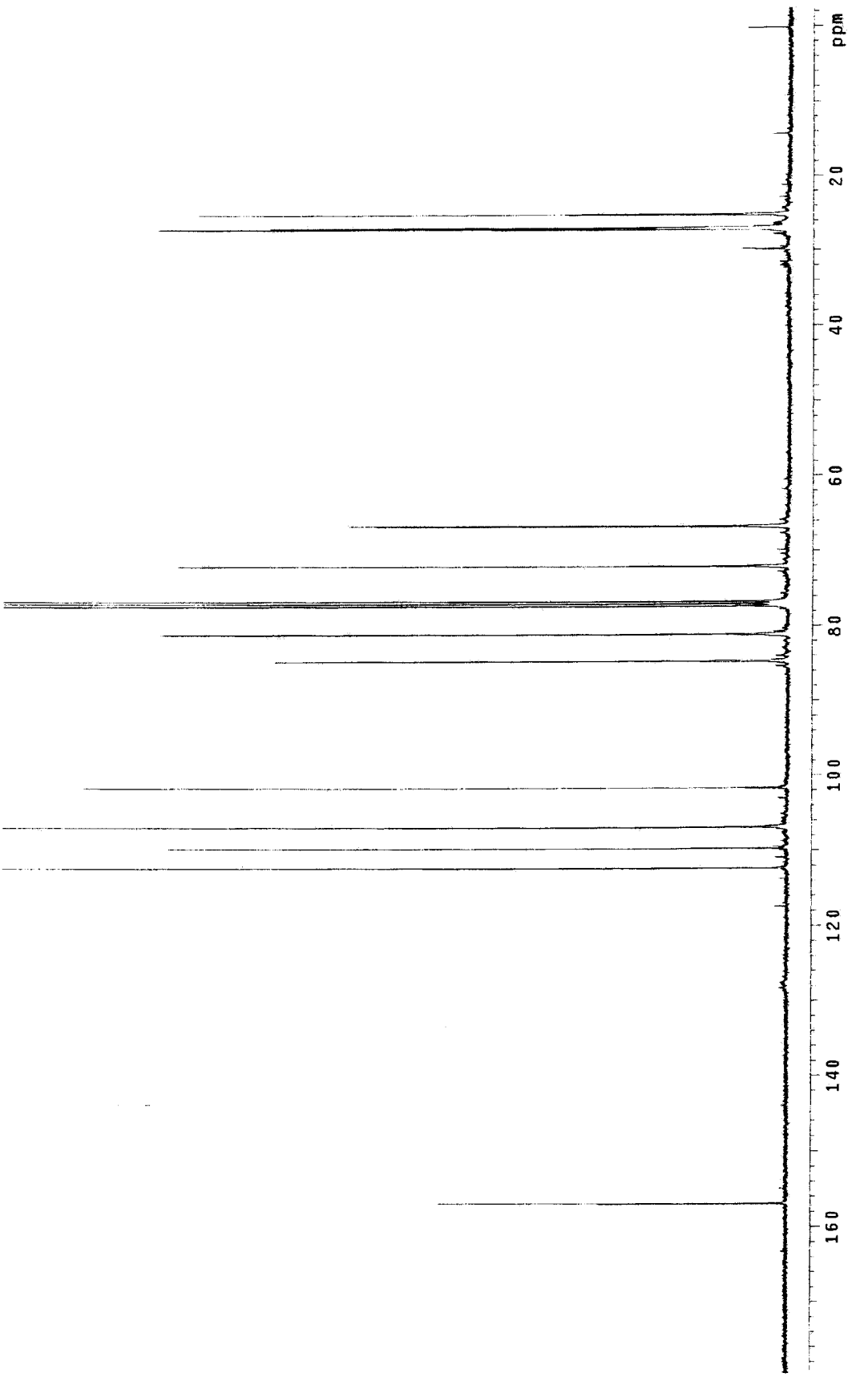

Figure 66. ^{13}C NMR of **15**

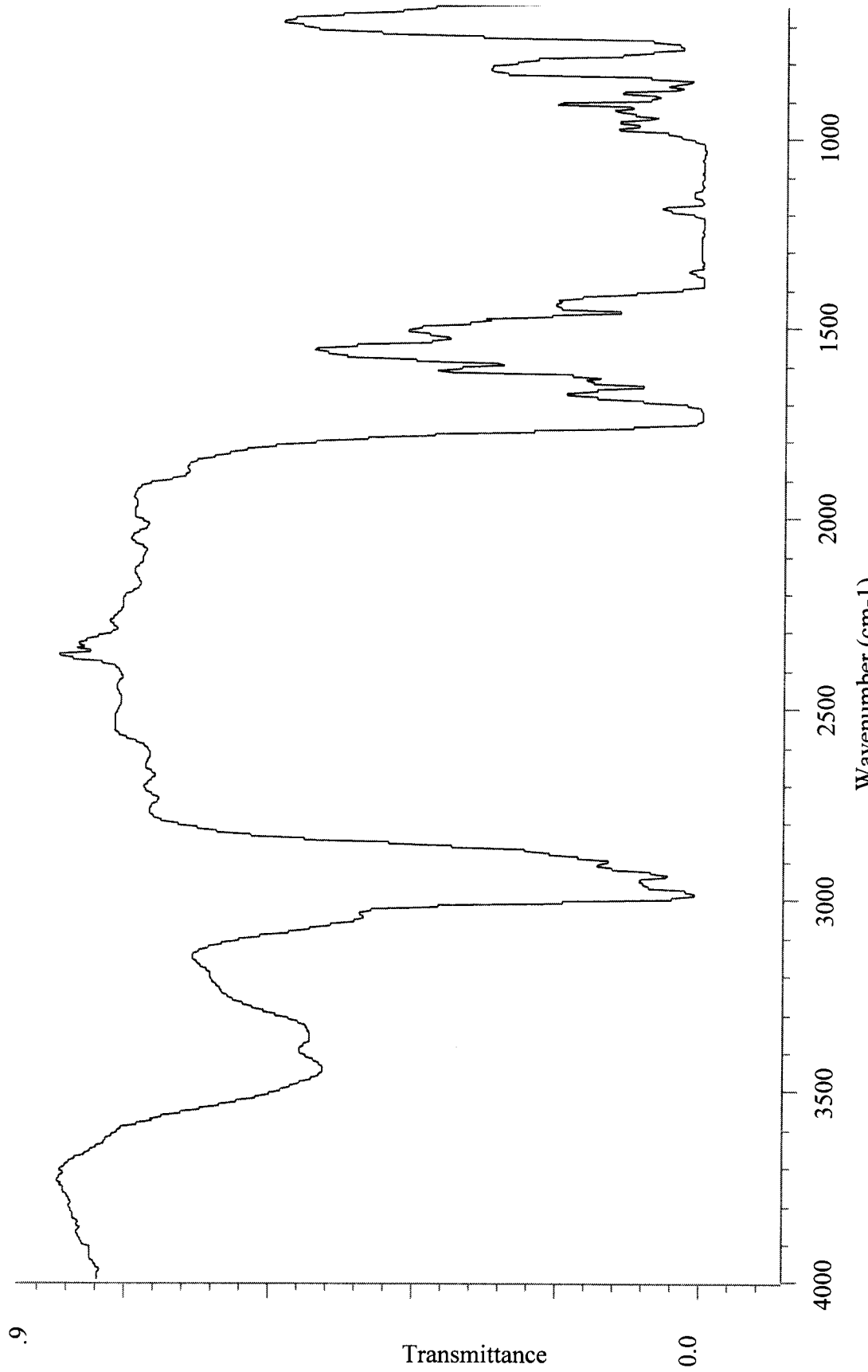

Figure 67. FT-IR of **15**

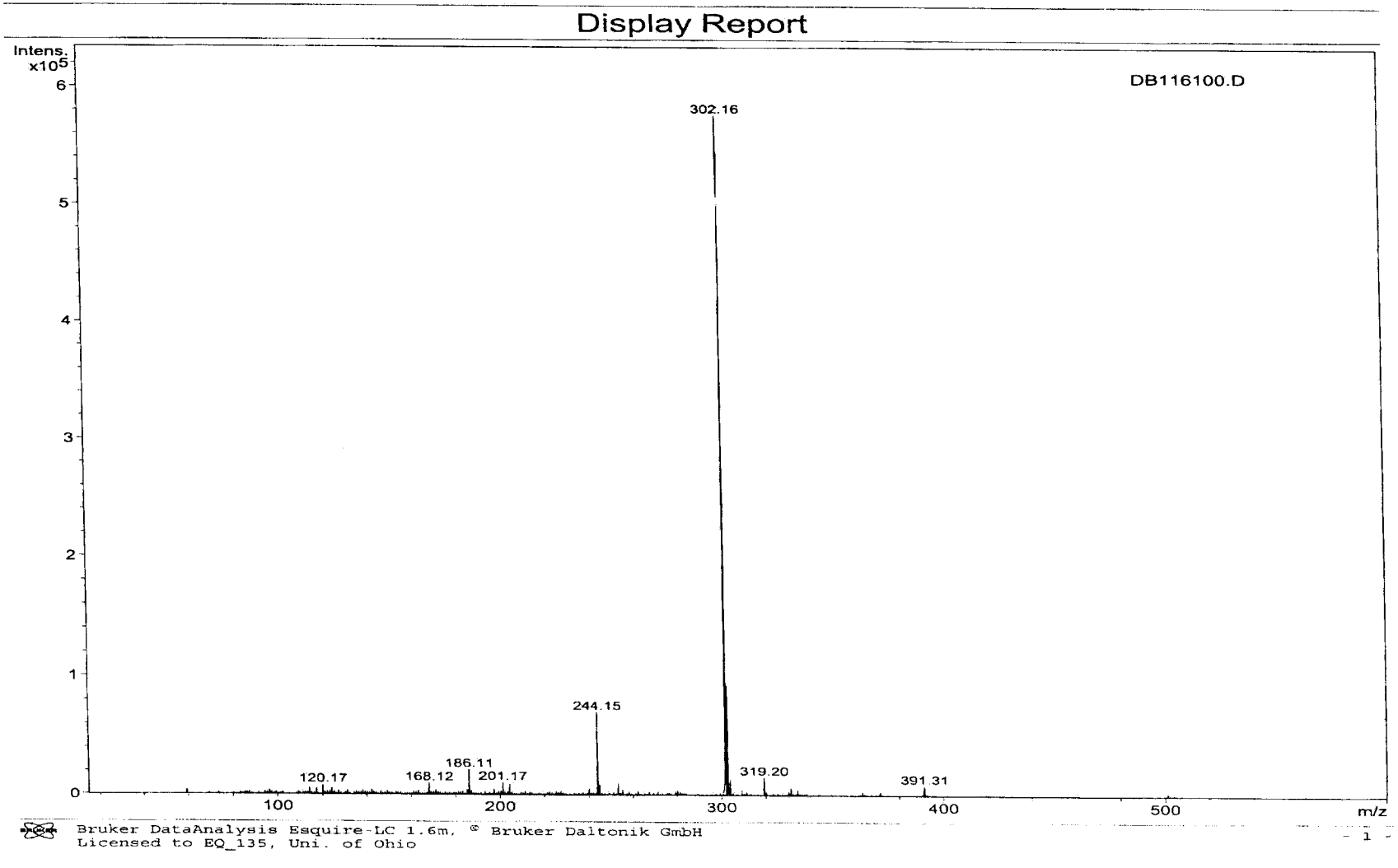

Figure 68. Positive mode APCI-MS of **15**

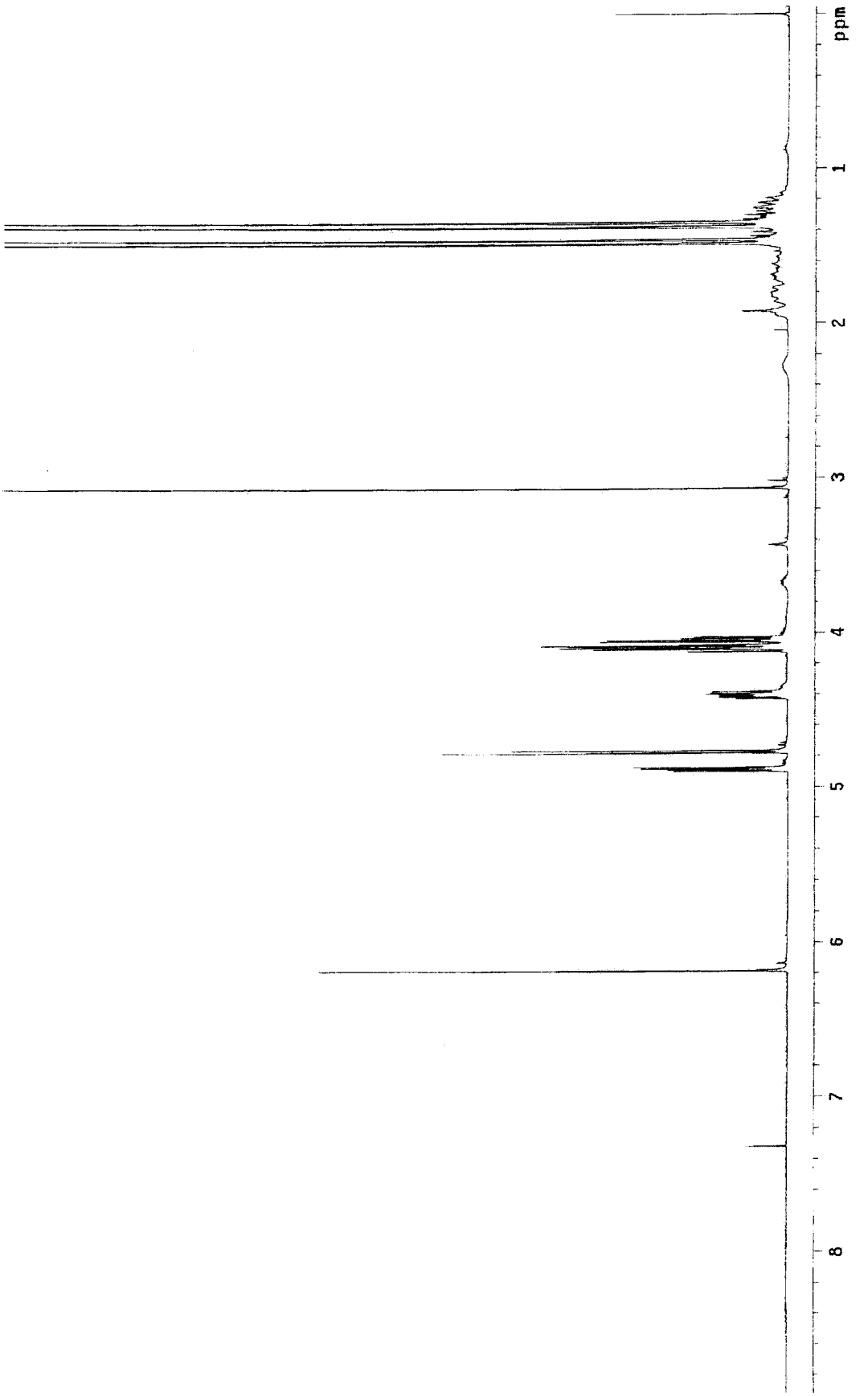

Figure 69. ^{1}H NMR of **16**

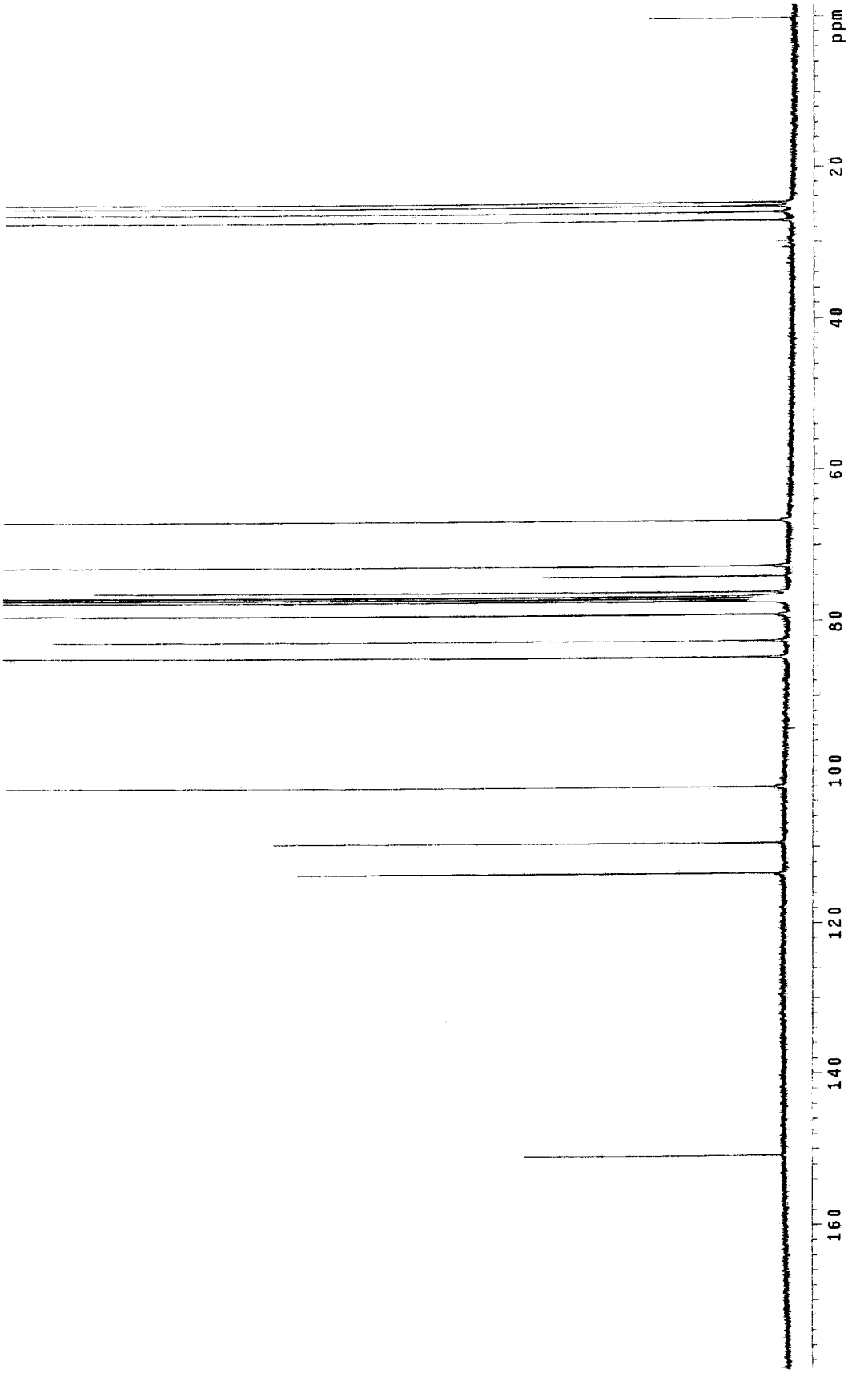

Figure 70. ^{13}C NMR of **16**

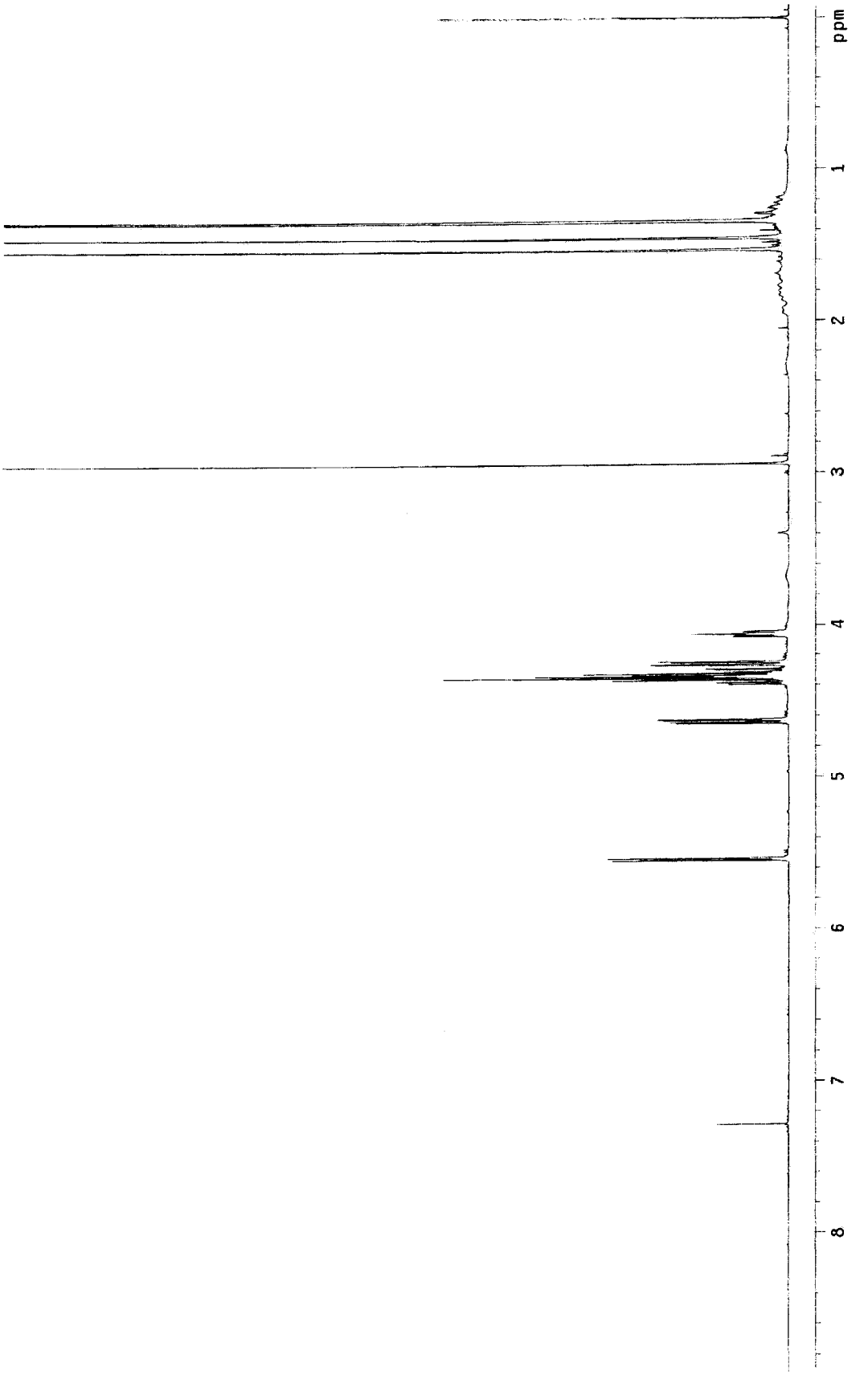

Figure 71. ^{1}H NMR of **17**

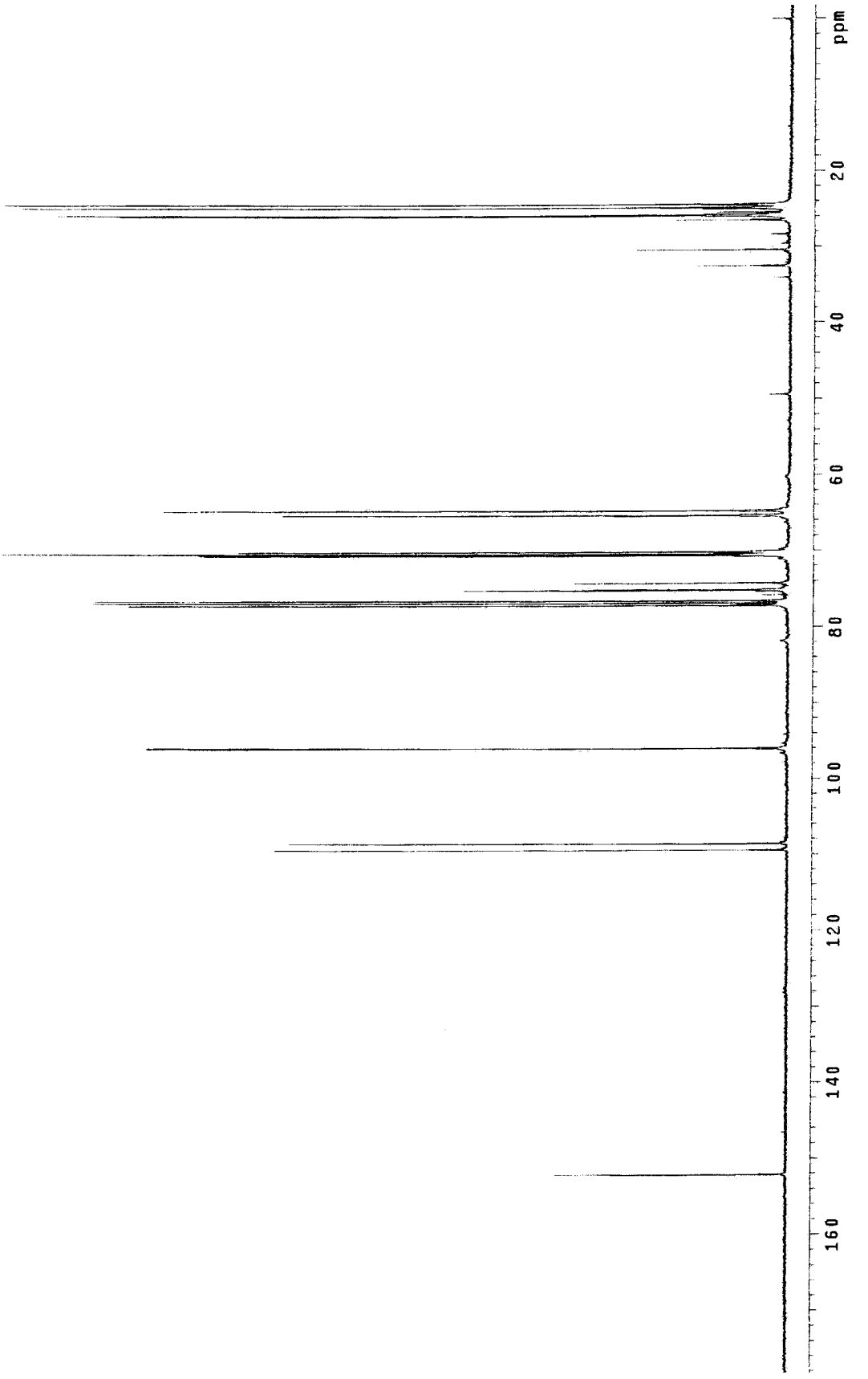

Figure 72. ^{13}C NMR of 17

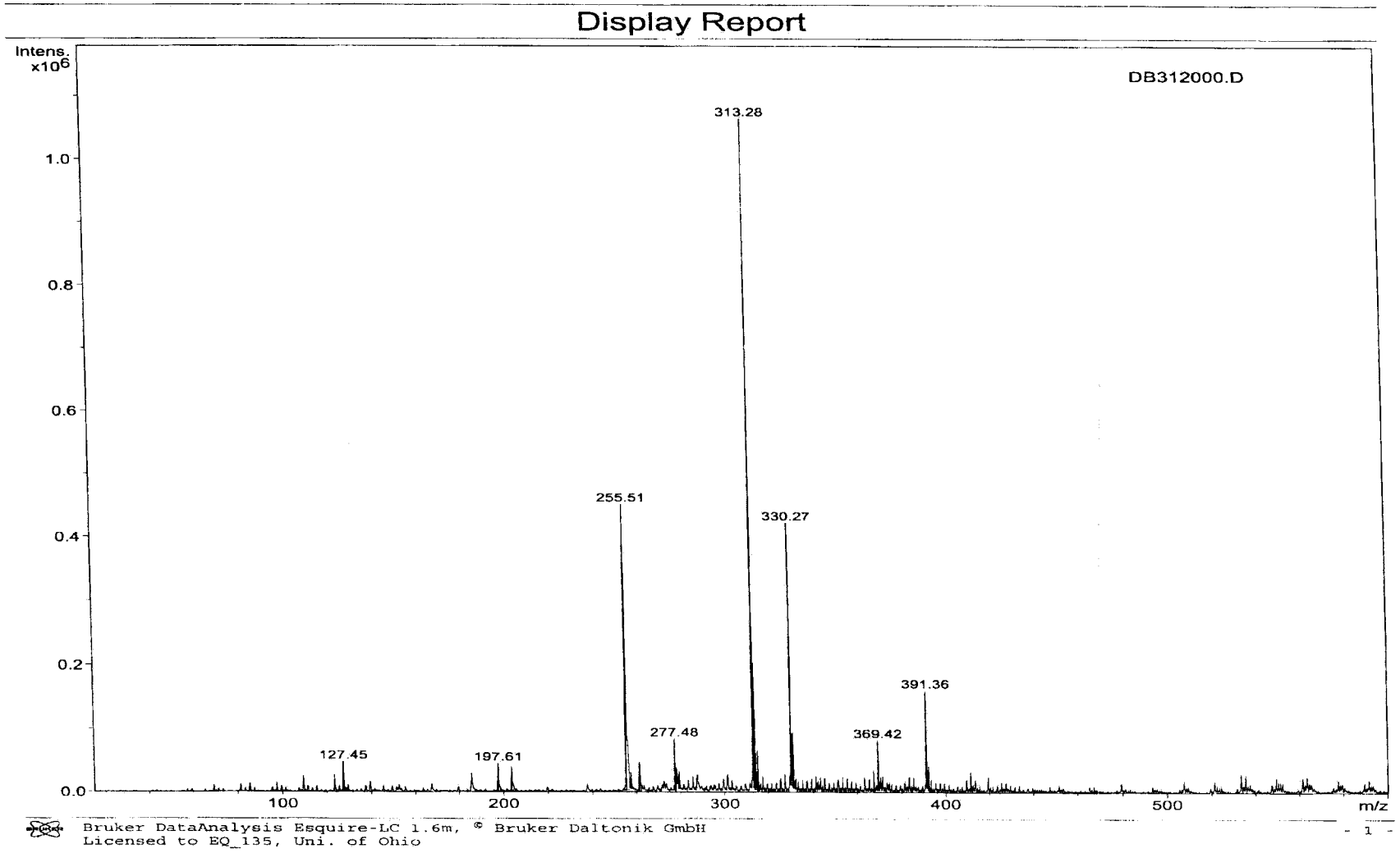

Figure 73. Positive mode APCI-MS of **17**

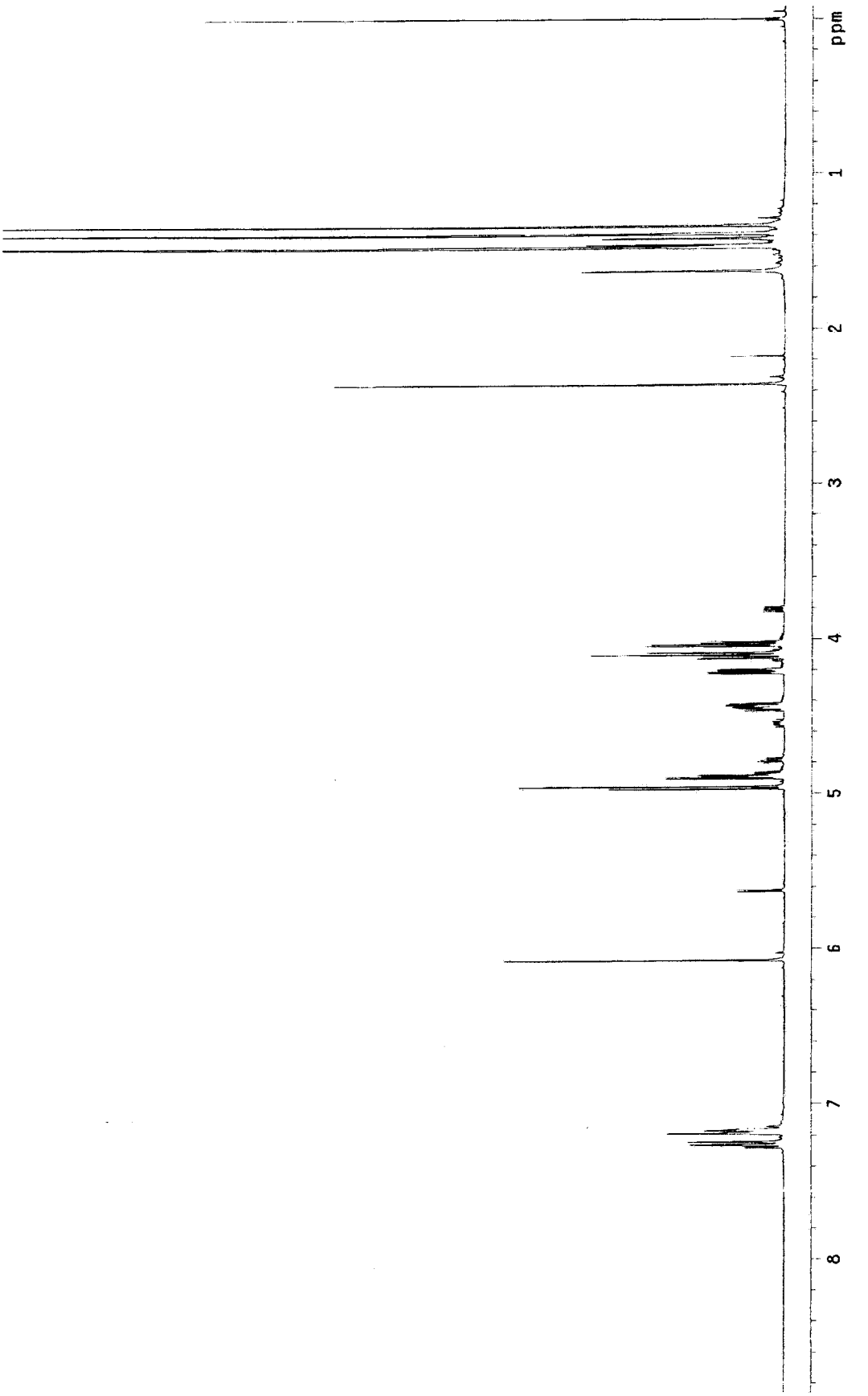

Figure 74. 1H NMR of **18**

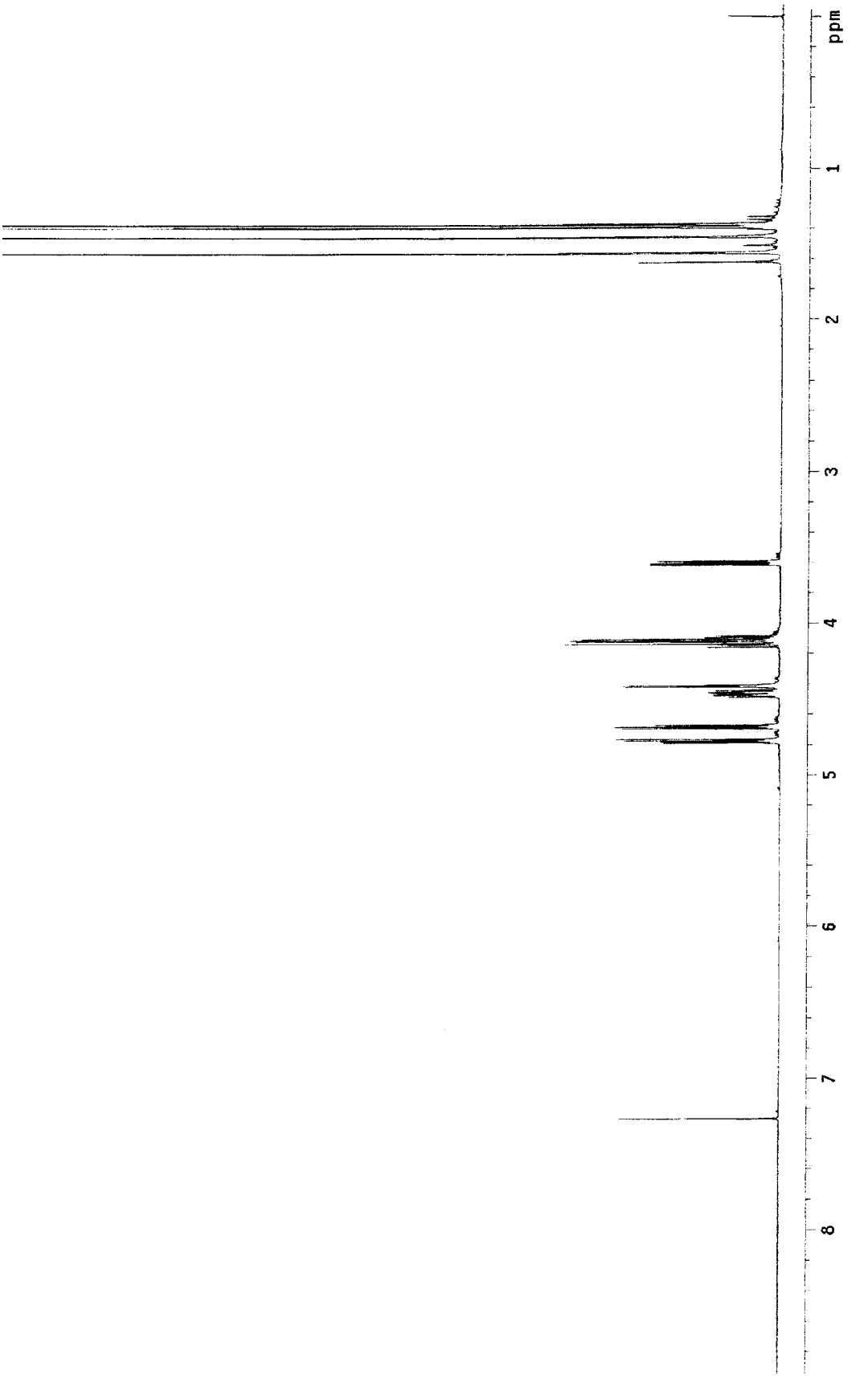

Figure 75. ^{1}H NMR of **19**

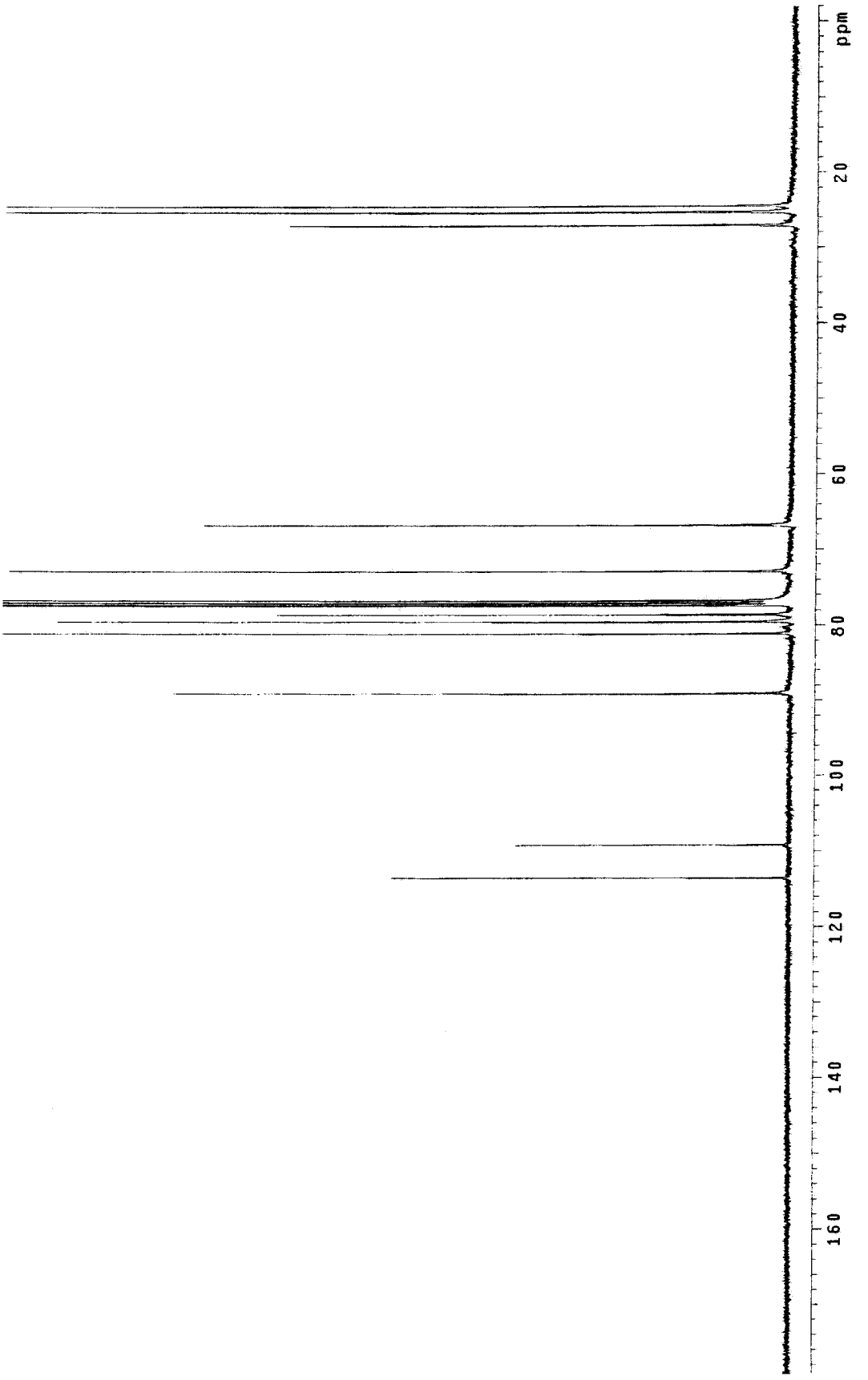

Figure 76. ^{13}C NMR of **19**

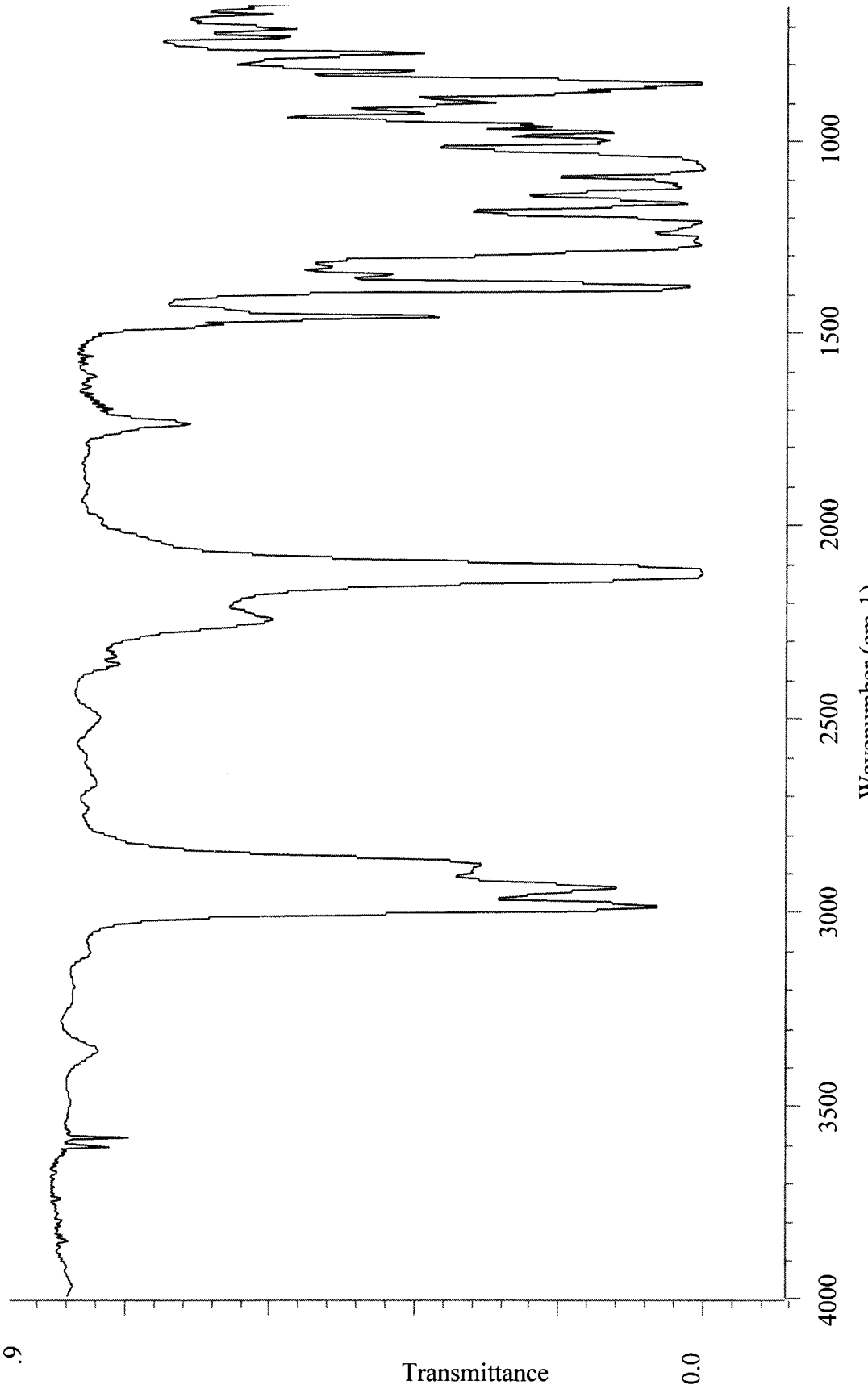

Figure 77. FT-IR of **19**

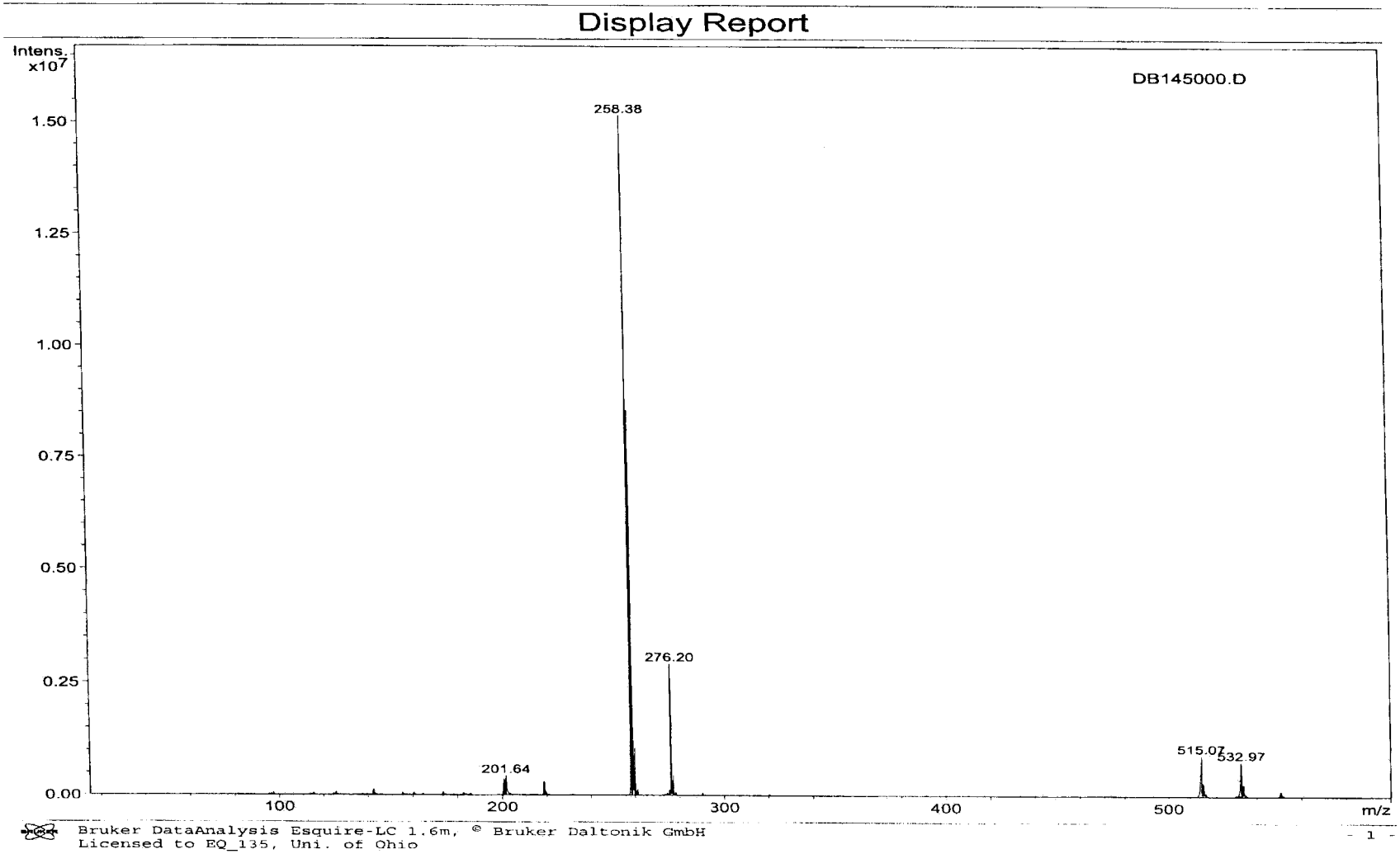

Figure 78. Positive mode APCI-MS of **19**

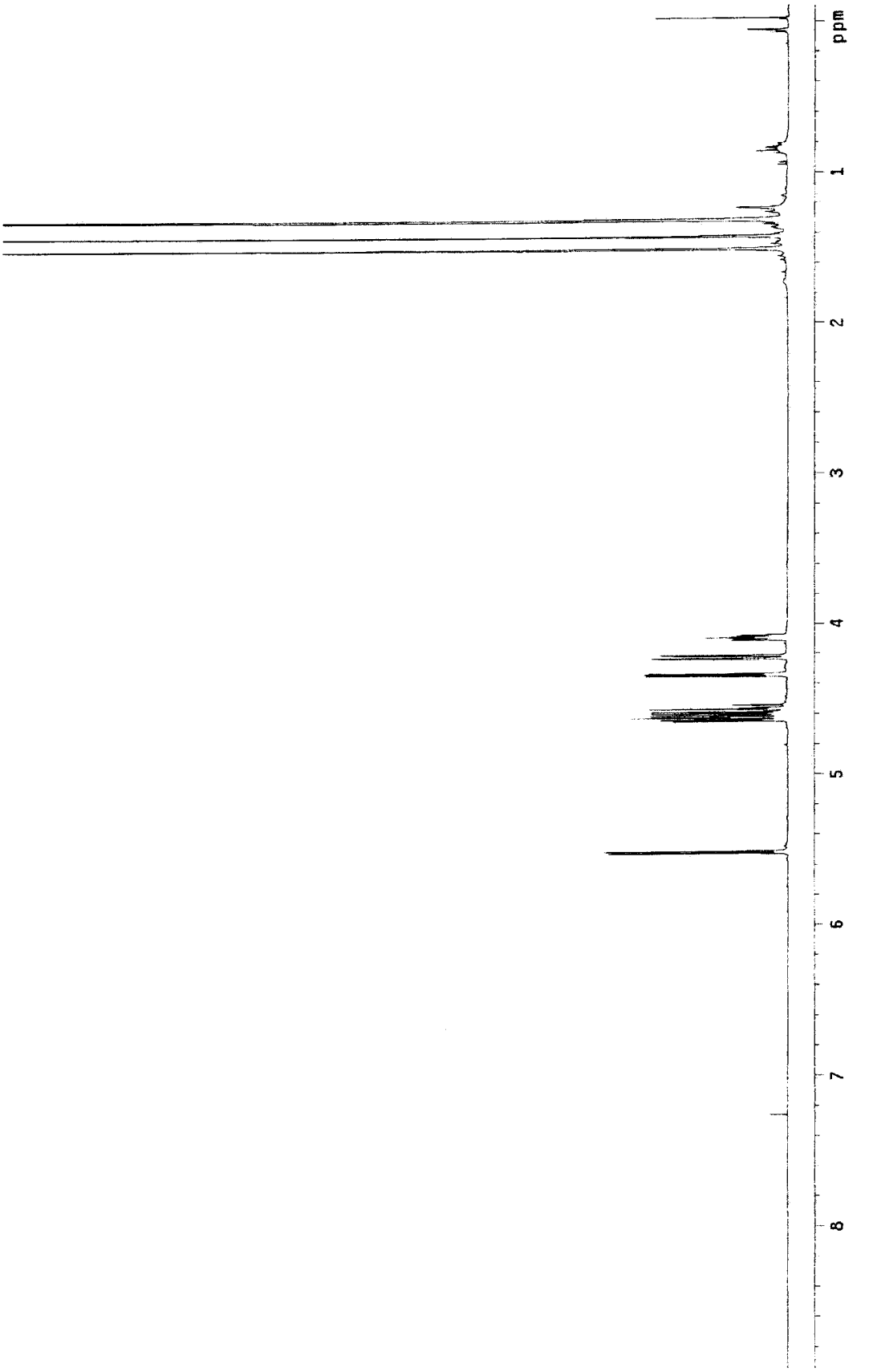

Figure 80. ^{1}H NMR of **20**

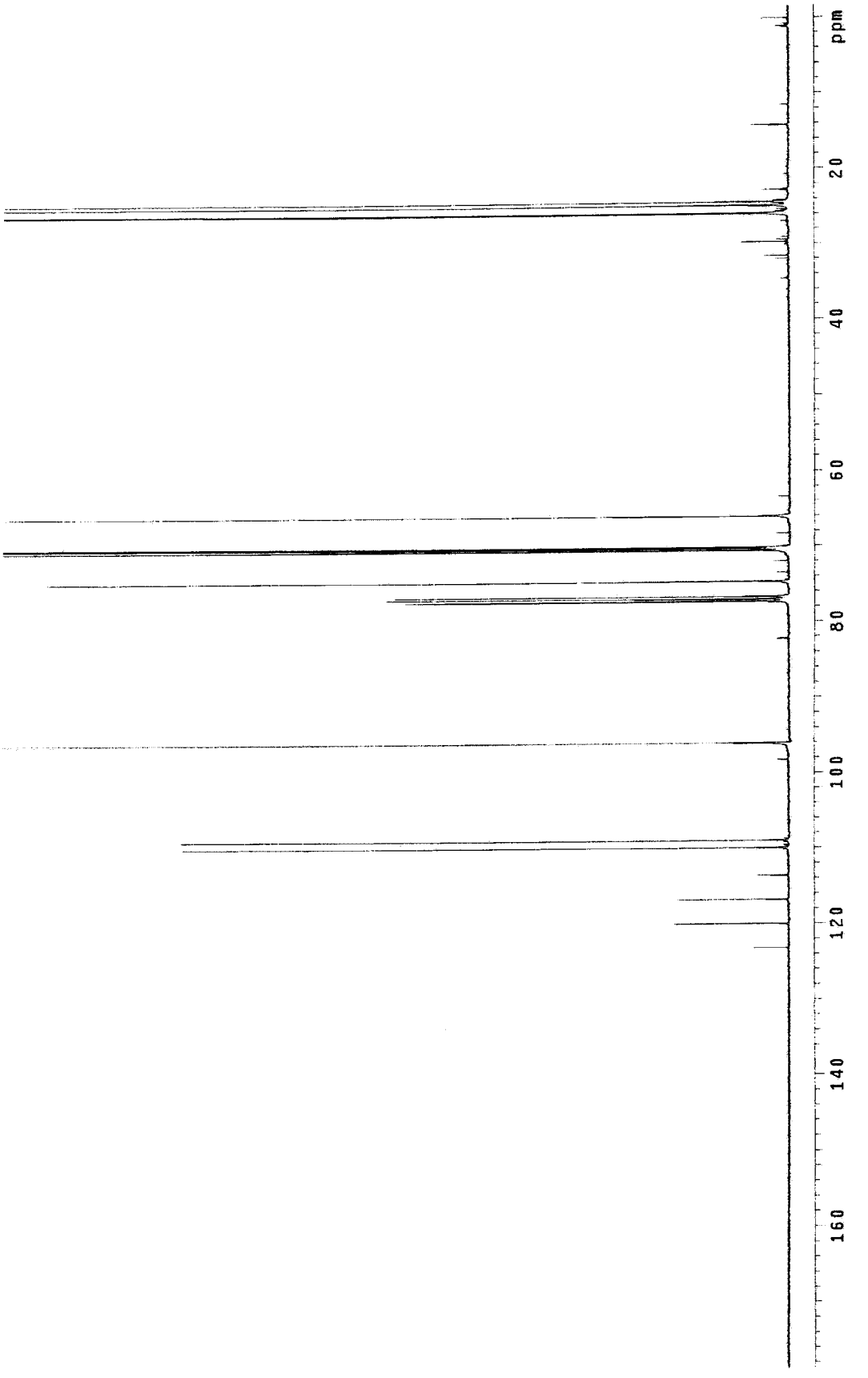

Figure 81. ^{13}C NMR of **20**

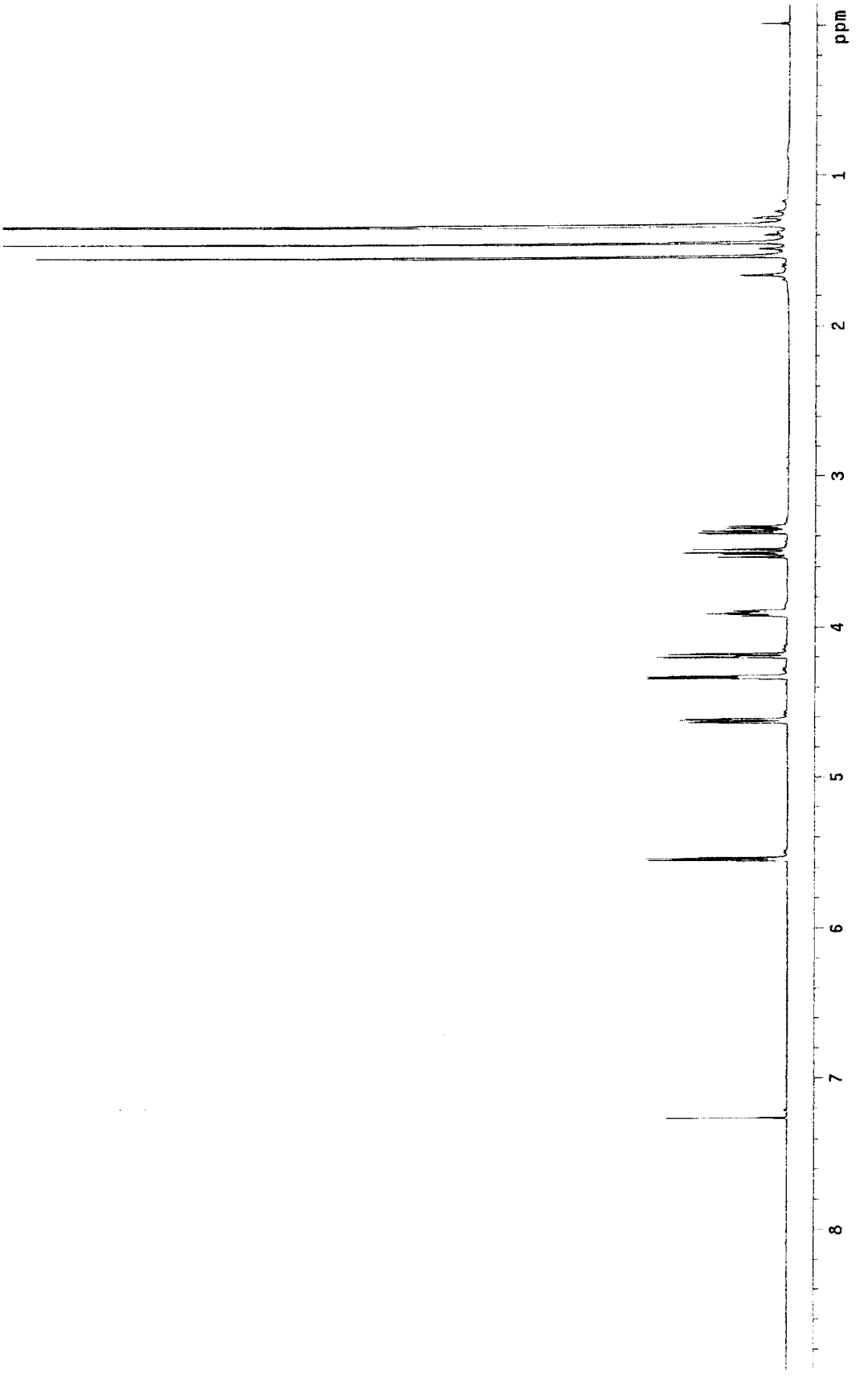

Figure 82. ^{1}H NMR of **21**

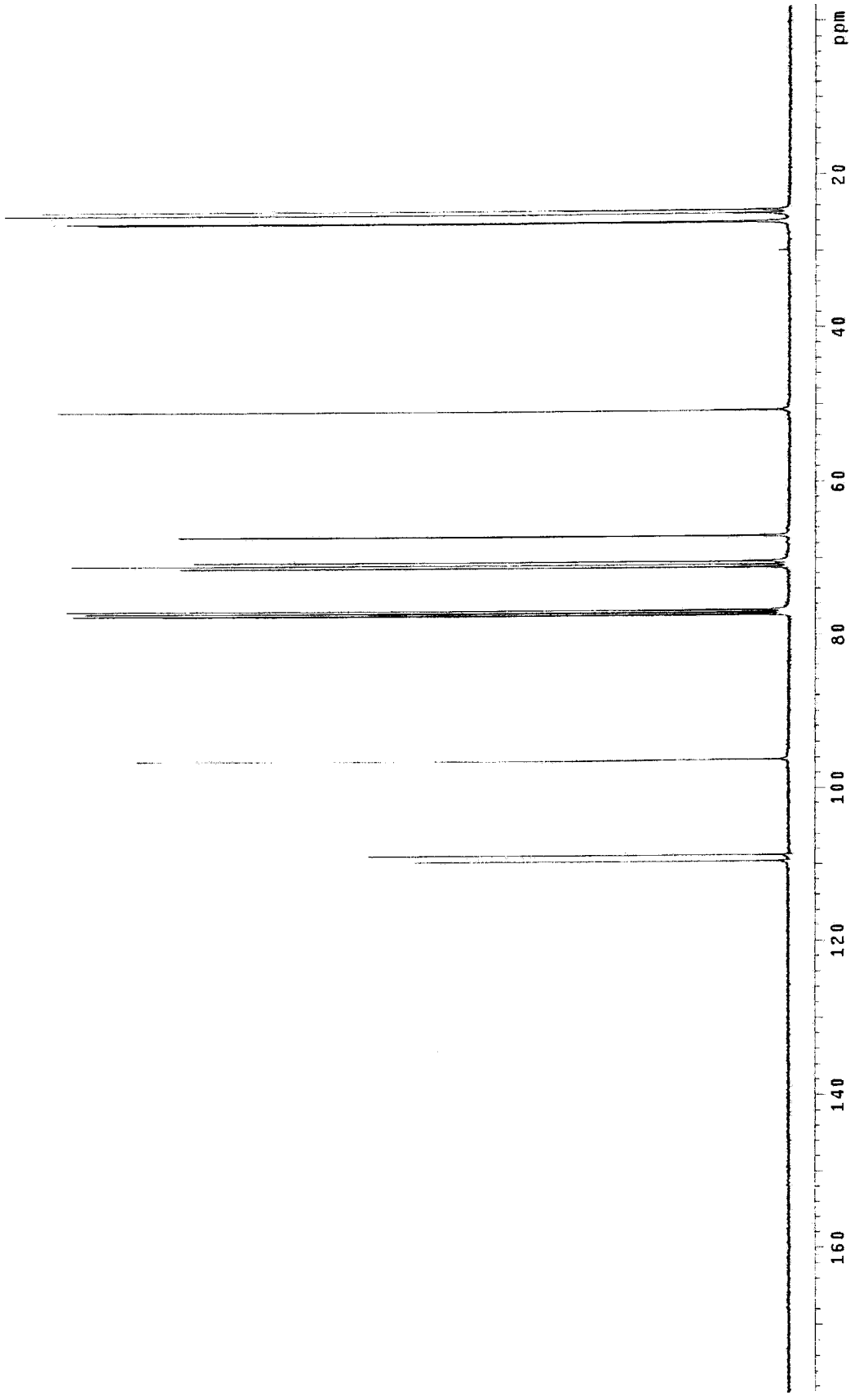

Figure 83. ^{13}C NMR of **21**

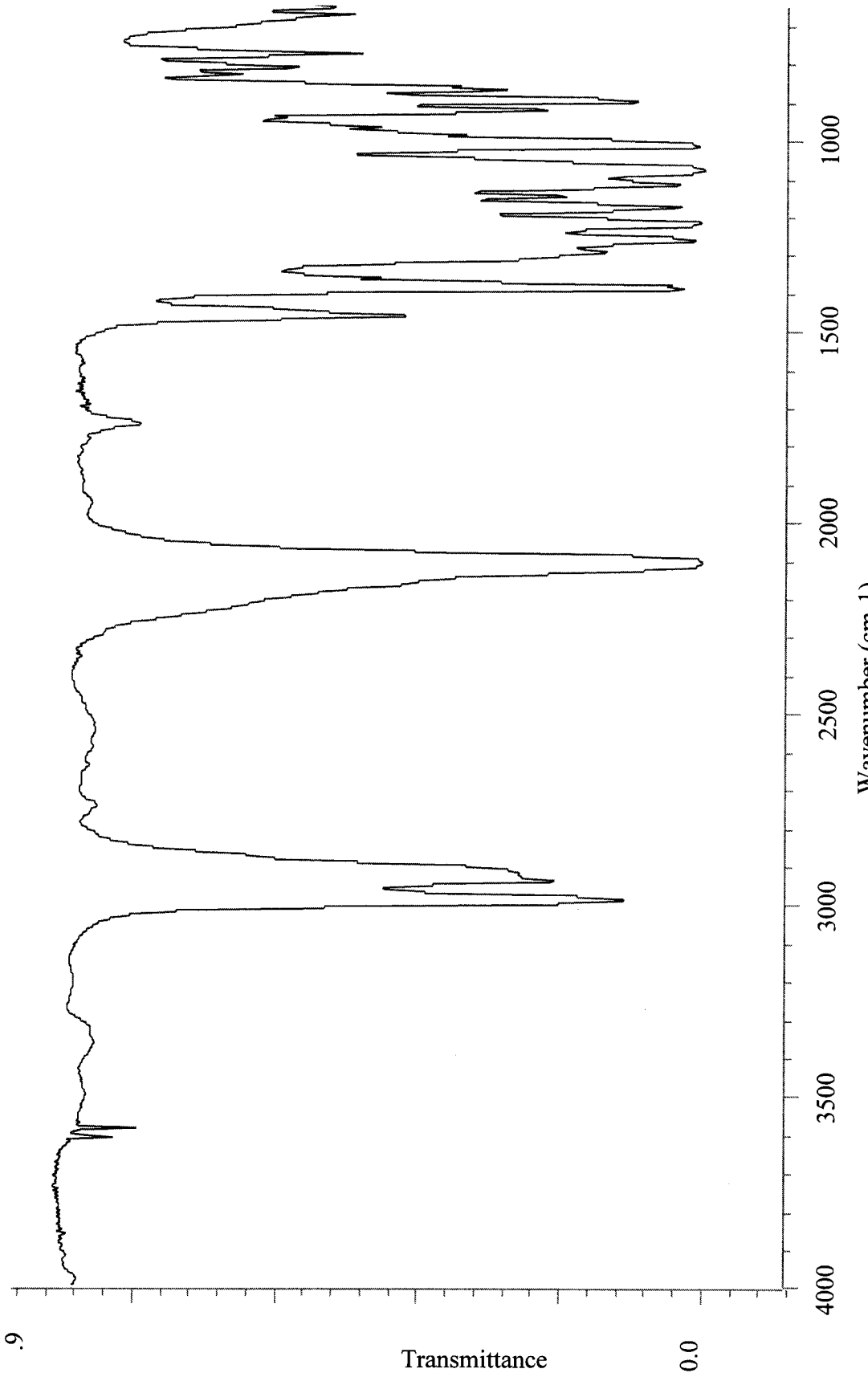

Figure 84. FT-IR of **21**

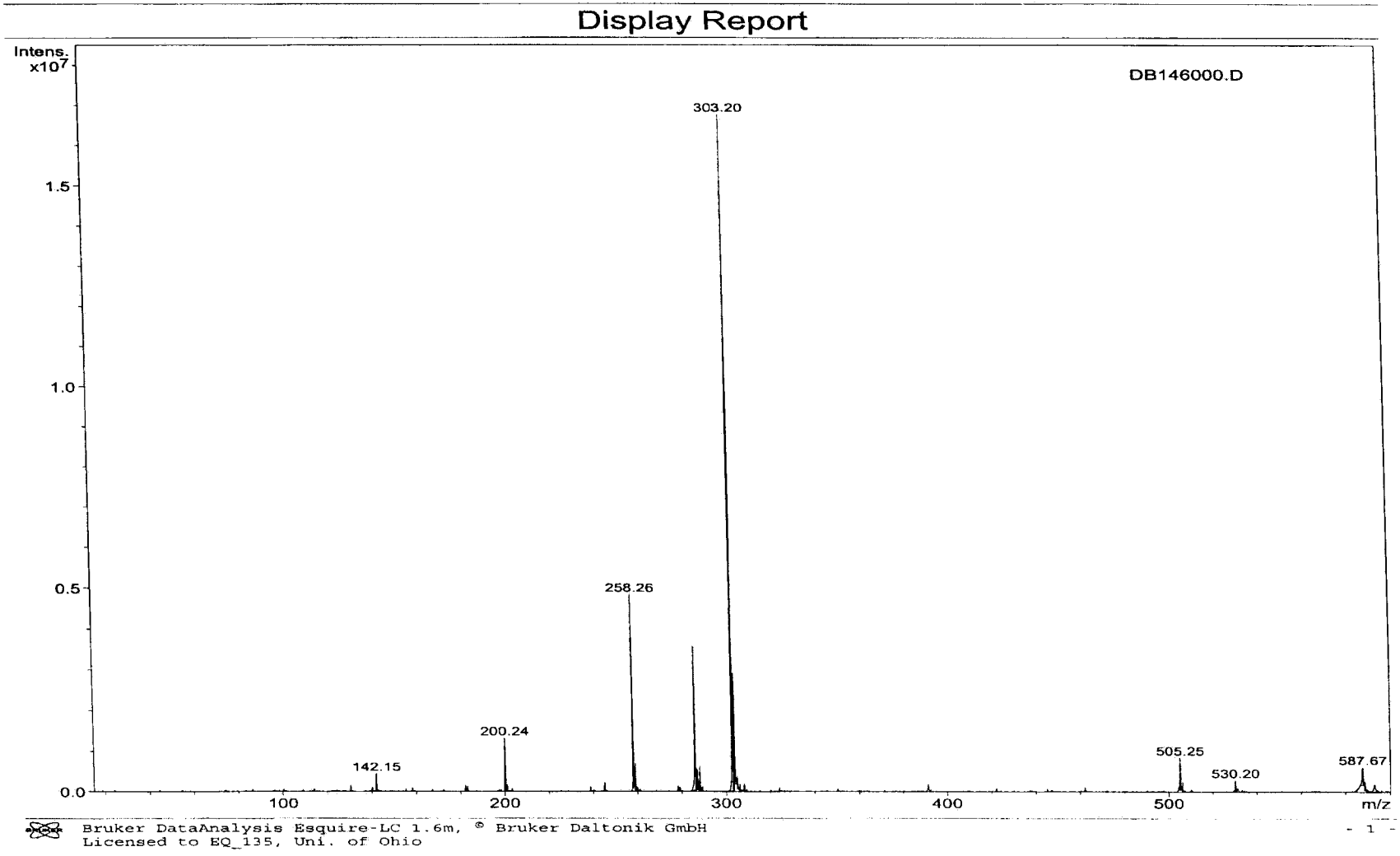

Figure 85. Positive mode ESI-MS of **21**

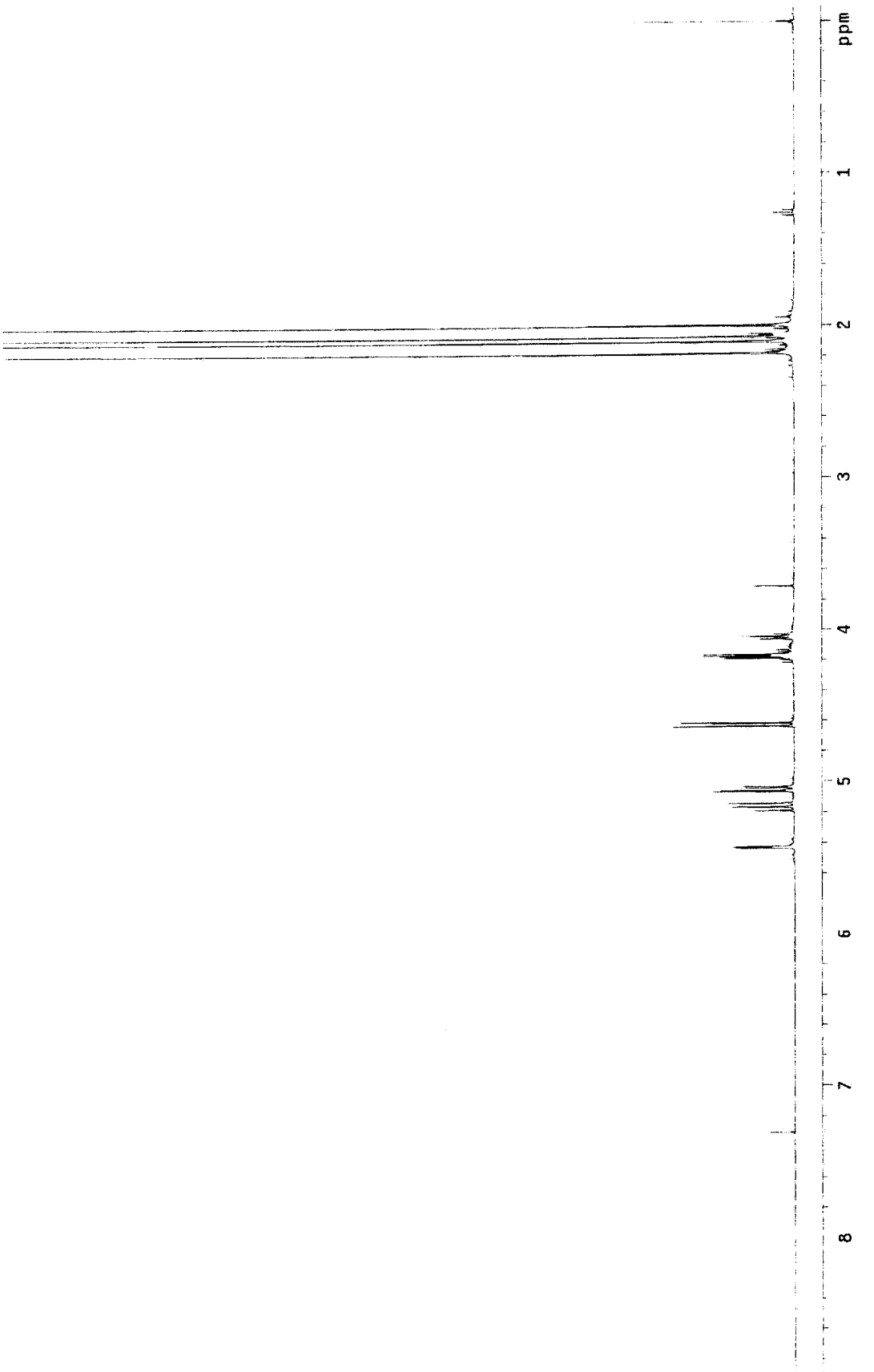

Figure 86. ^{1}H NMR of **23**

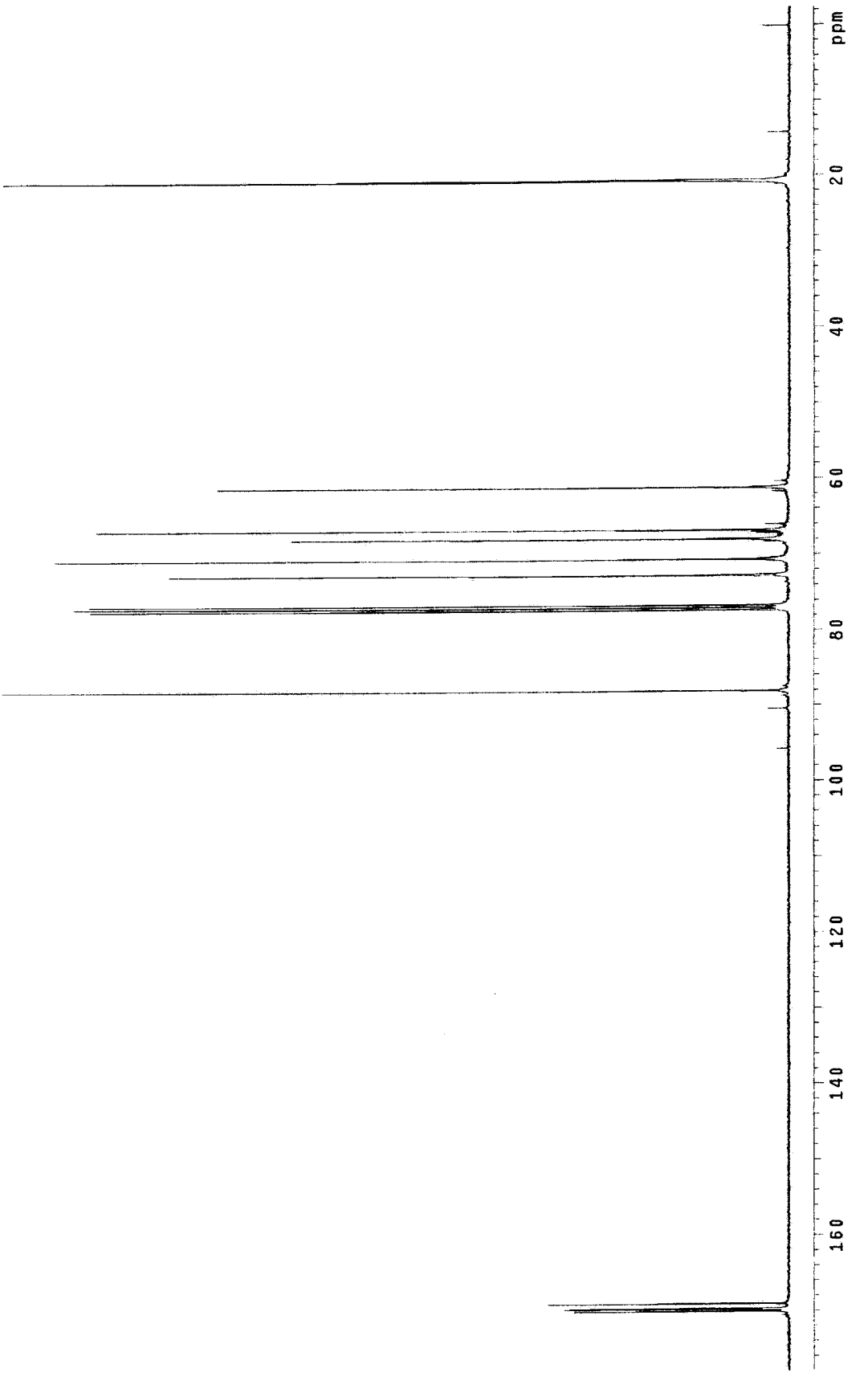

Figure 87. ^{13}C NMR of **23**

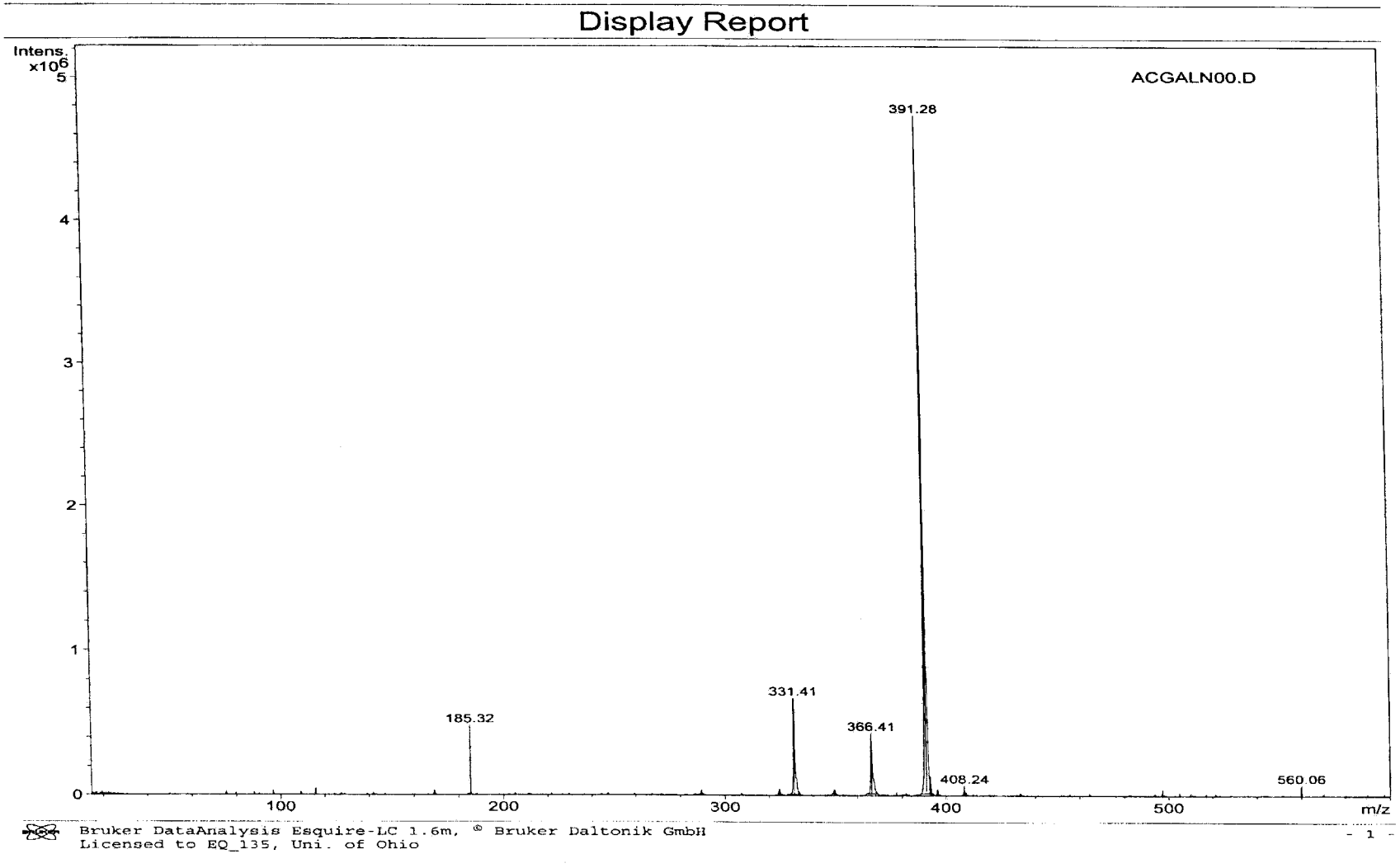

Figure 88. Positive mode ESI-MS of **23**

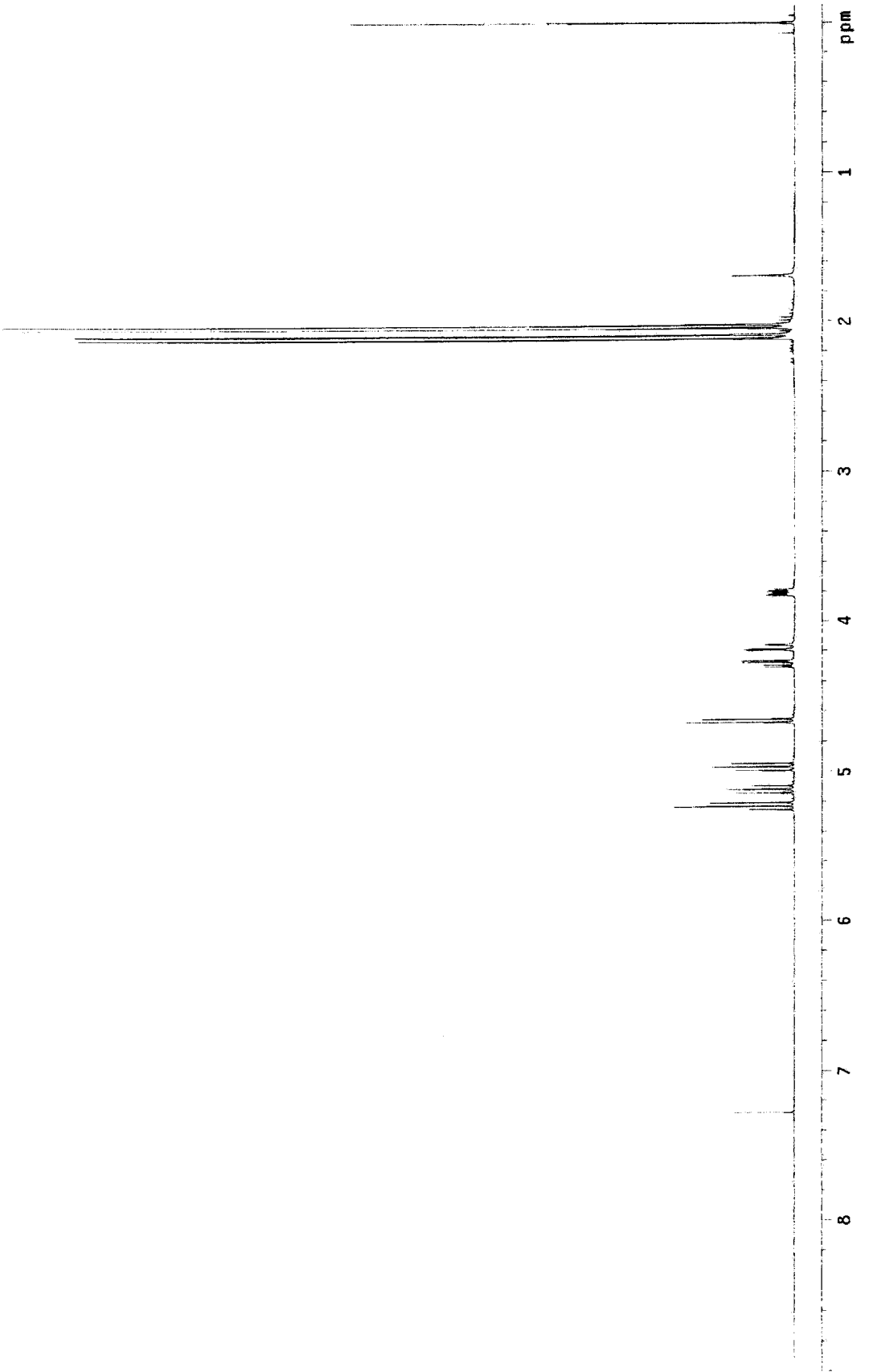

Figure 89. ^{1}H NMR of **25**

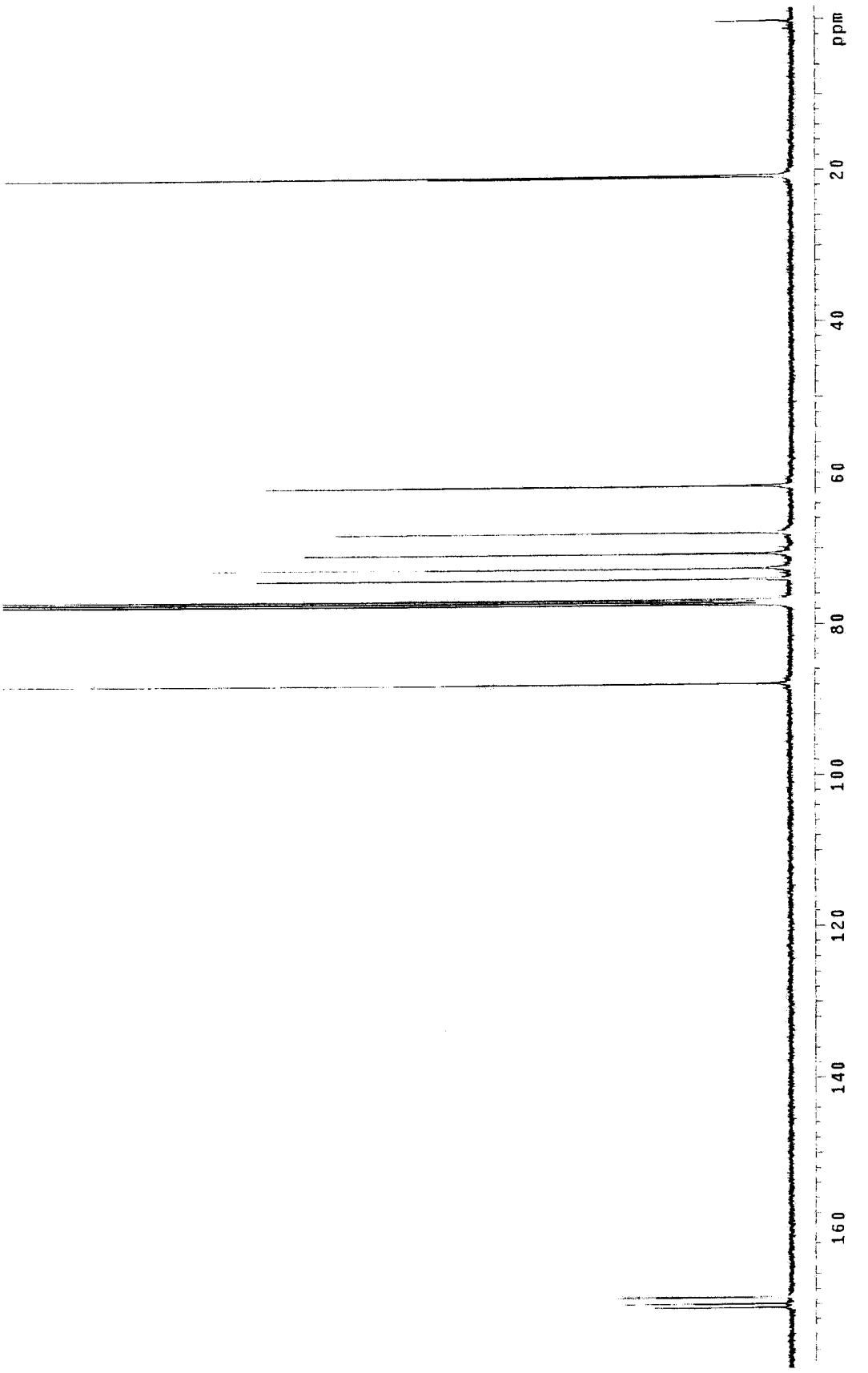

Figure 90. ^{13}C NMR of **25**

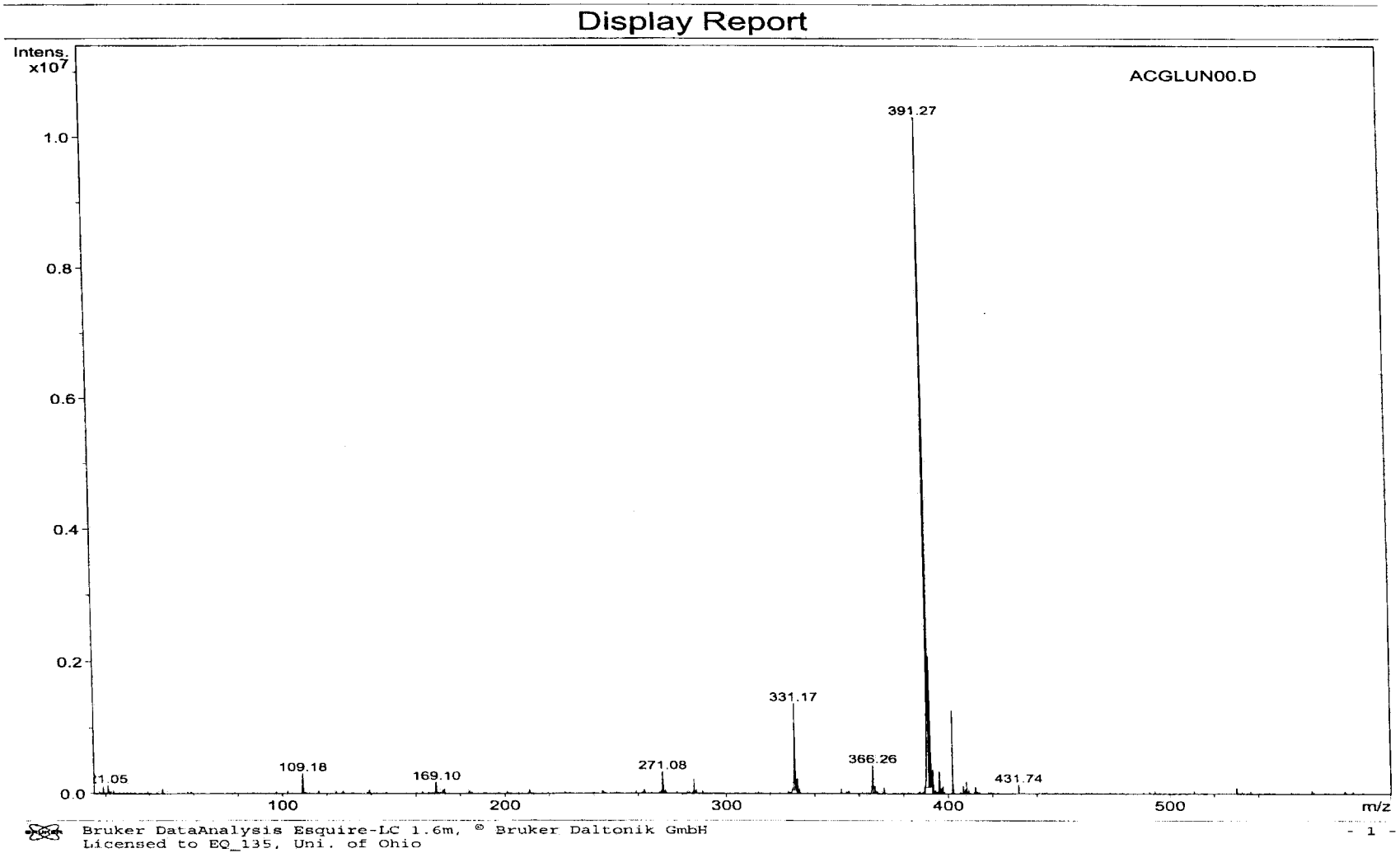

Figure 91. Positive mode ESI-MS of **25**

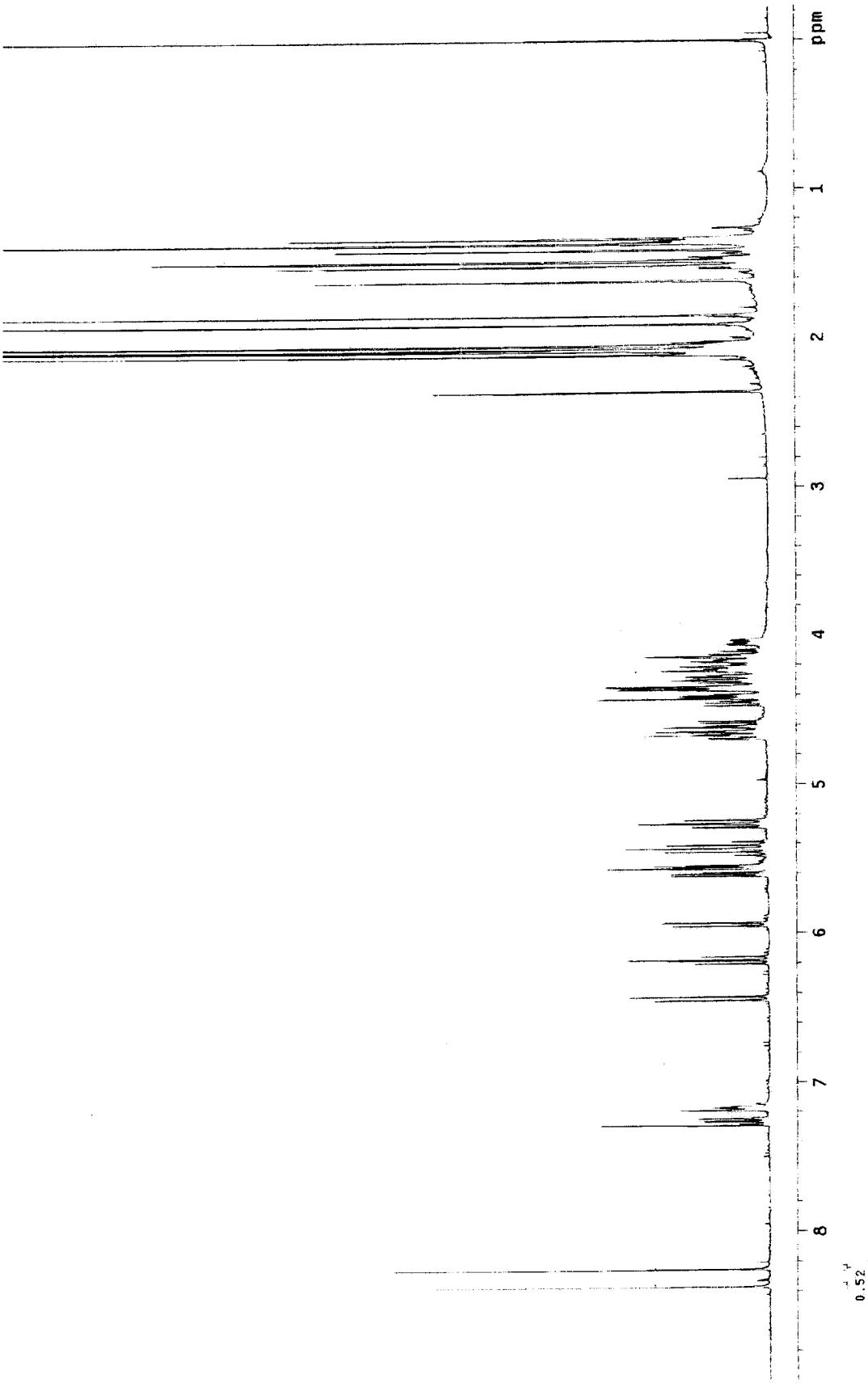

Figure 92. ^{1}H NMR of **26/27**-crude

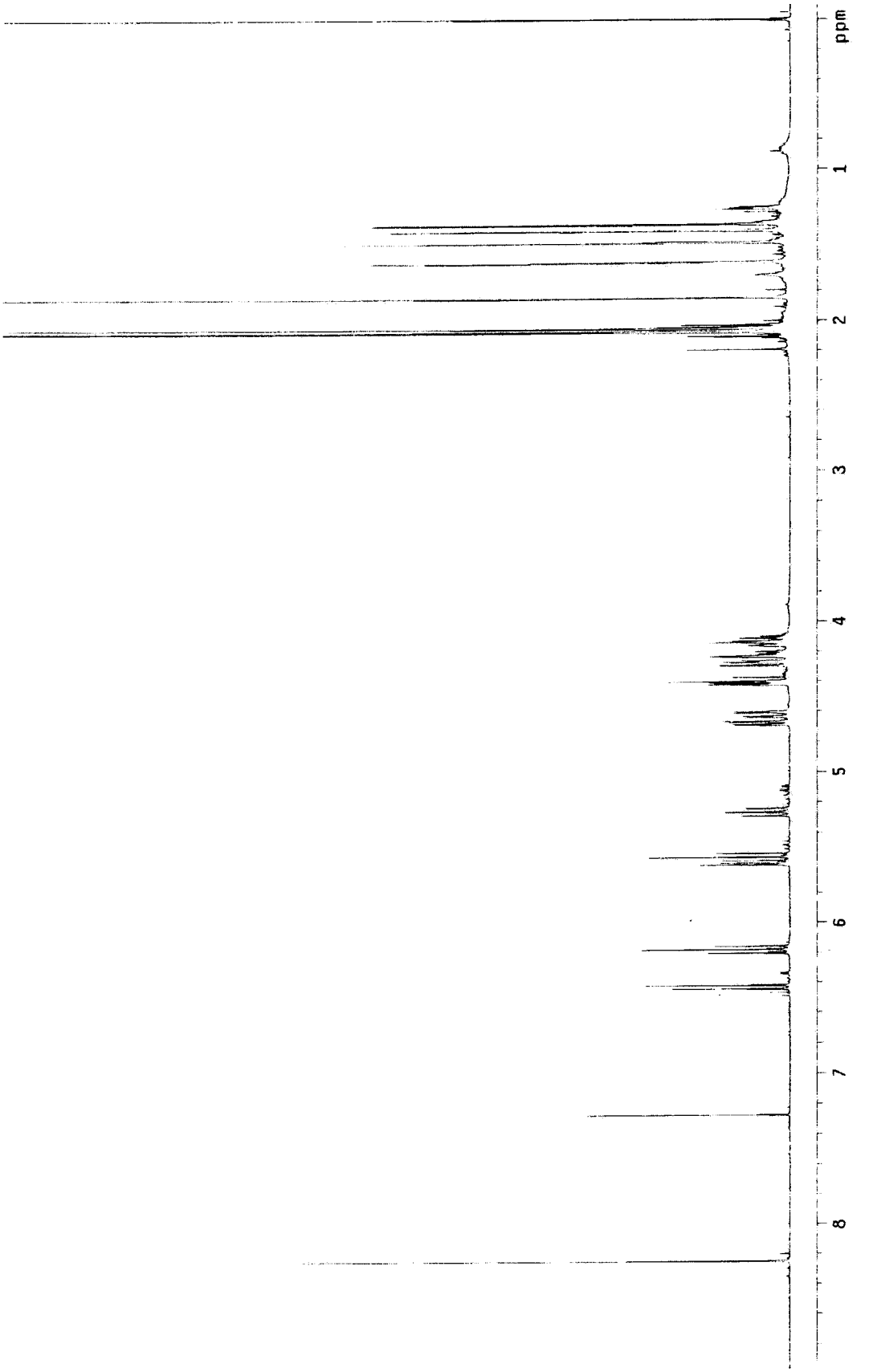

Figure 93. ^{1}H NMR of **26/27**-upper spot

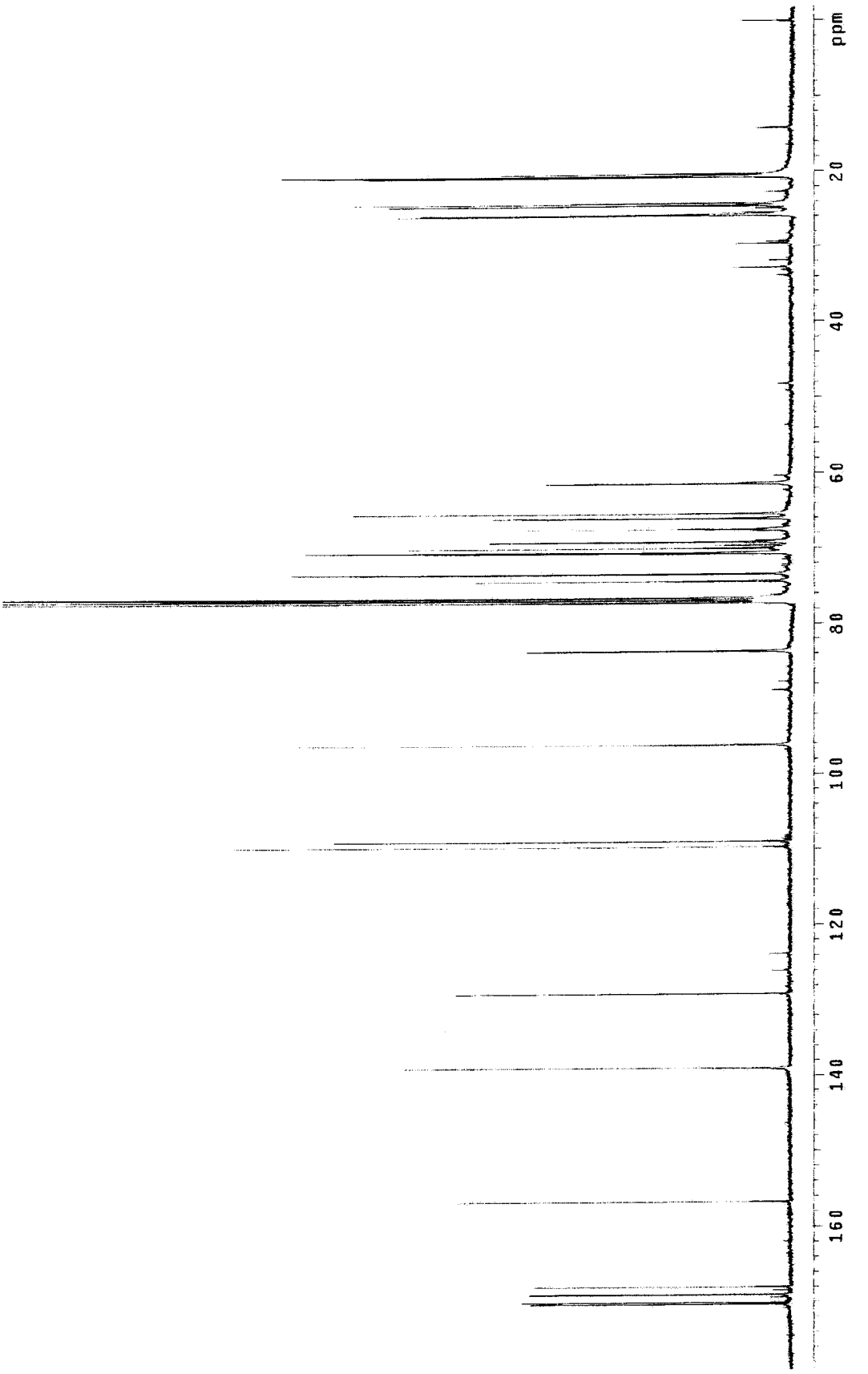

Figure 94. ^{13}C NMR of **26/27**-upper spot

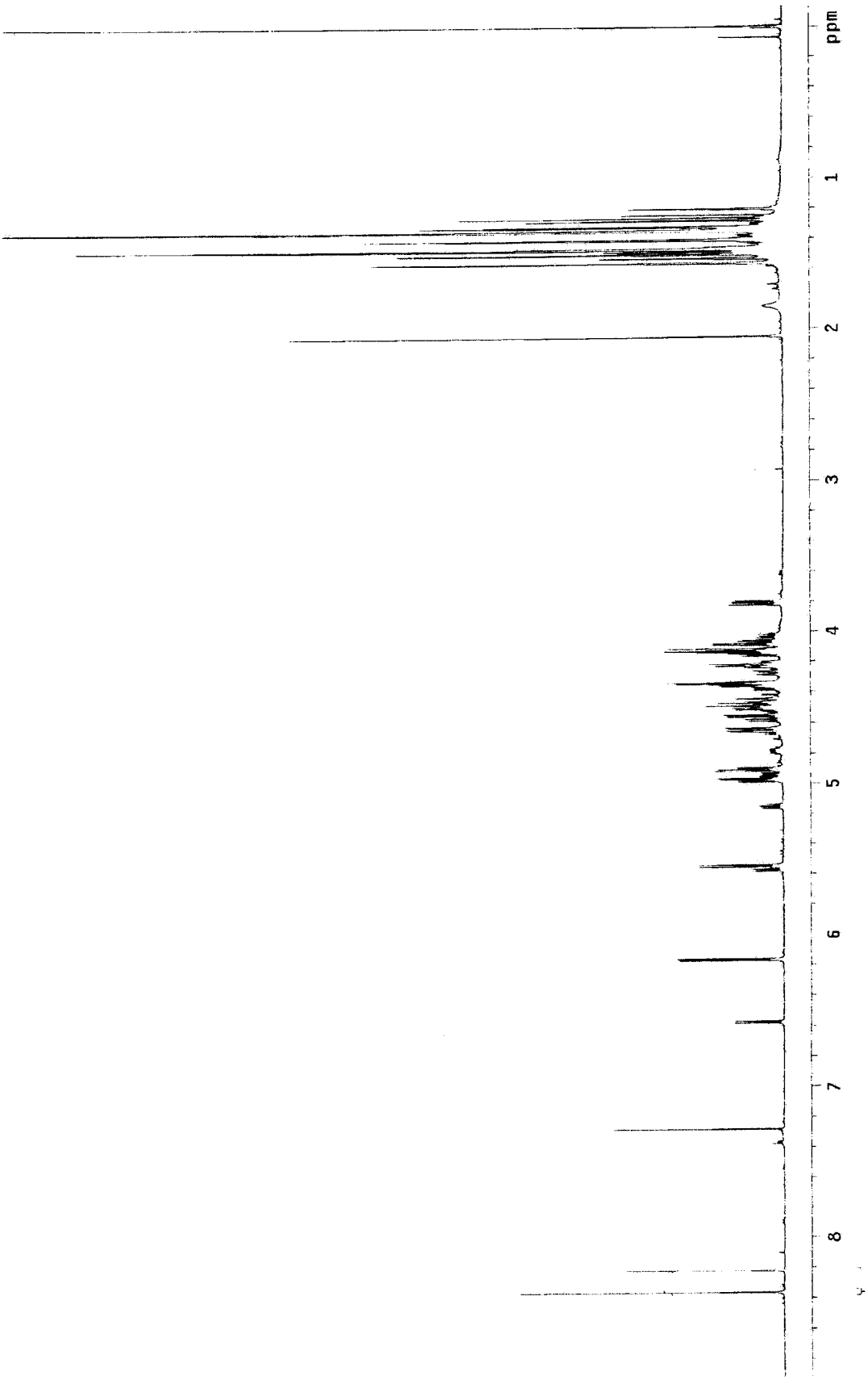

Figure 95. ^{1}H NMR of **28/29**-crude

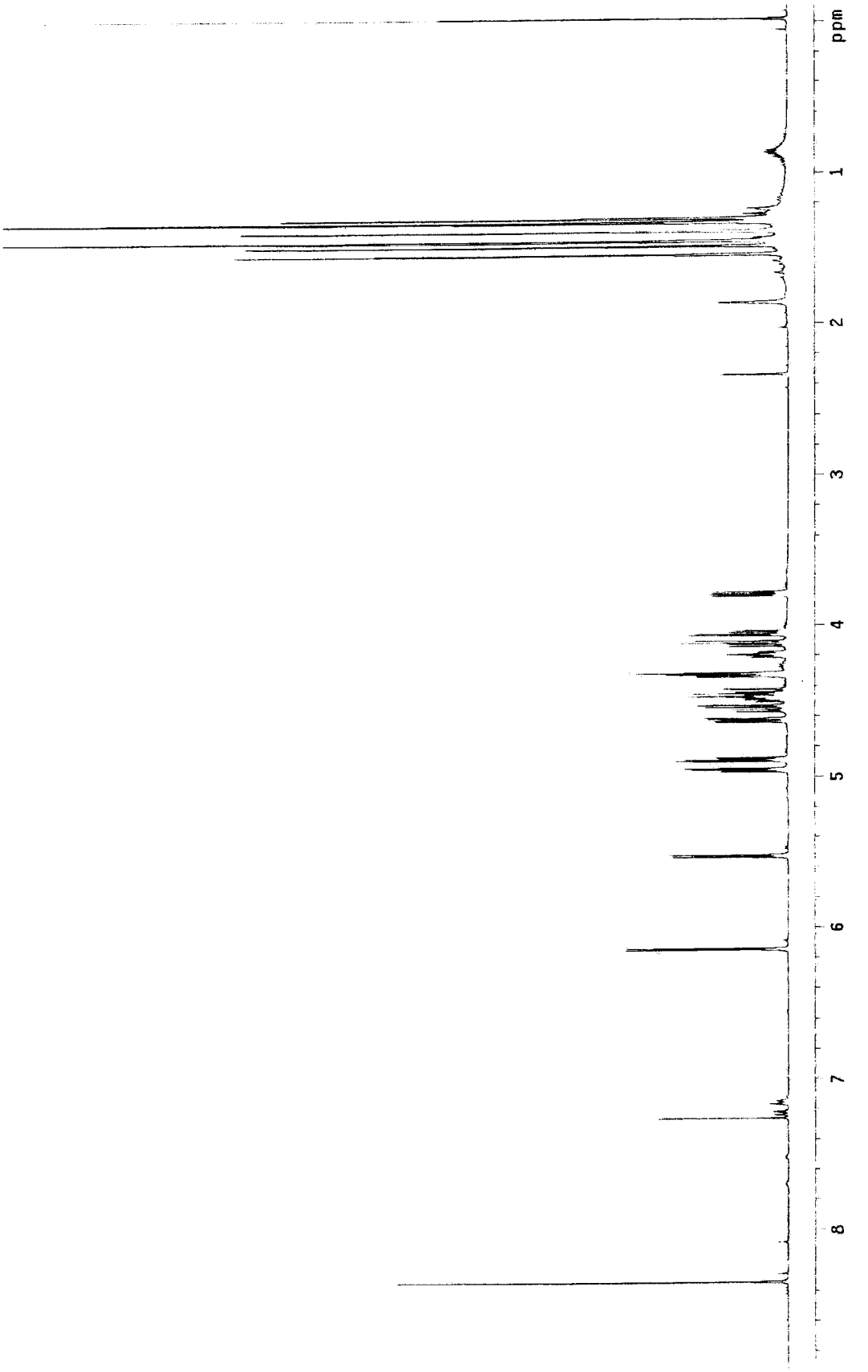

Figure 96. ^{1}H NMR of **28/29**-upper spot

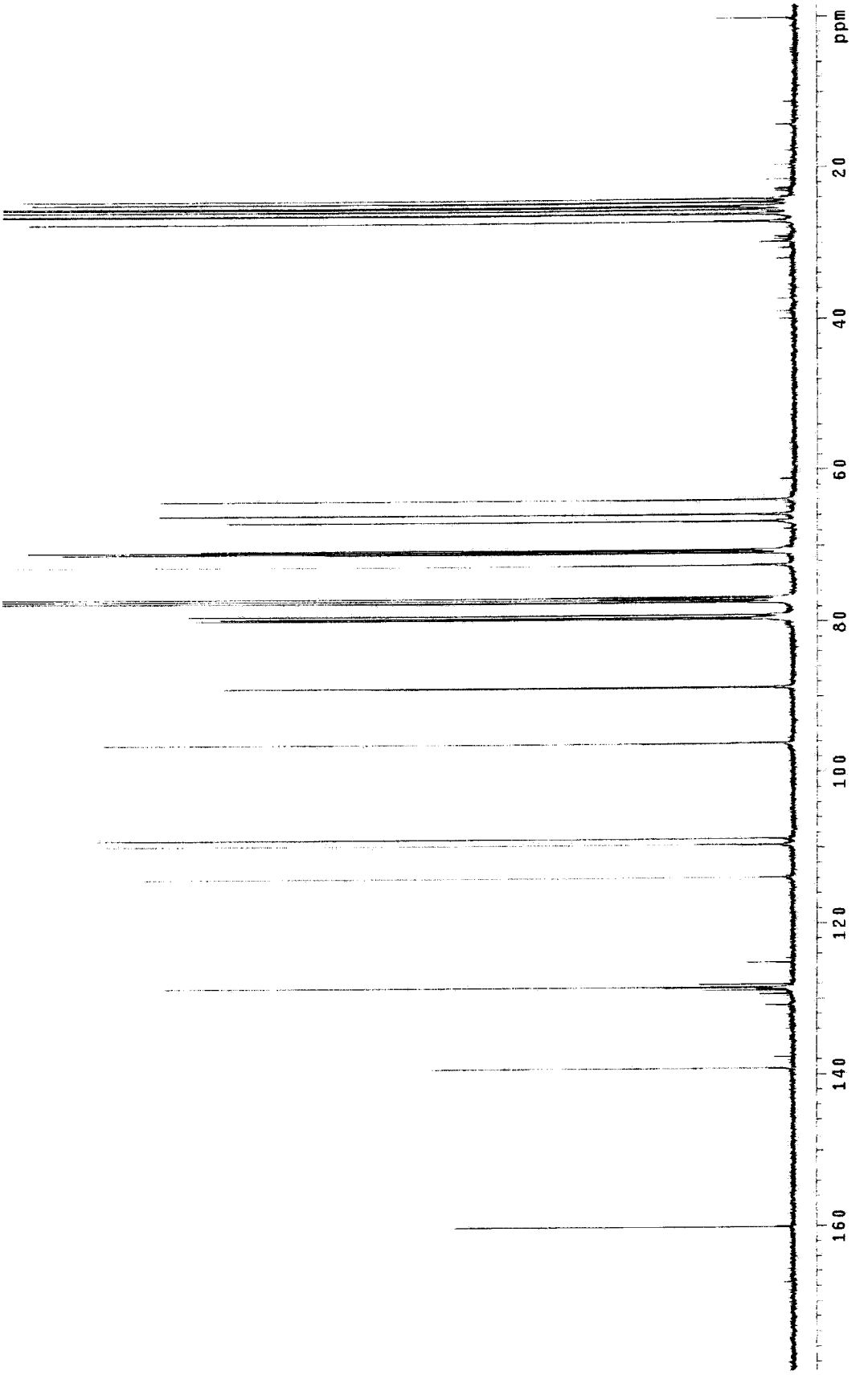

Figure 97. ^{13}C NMR of **28/29**-upper spot

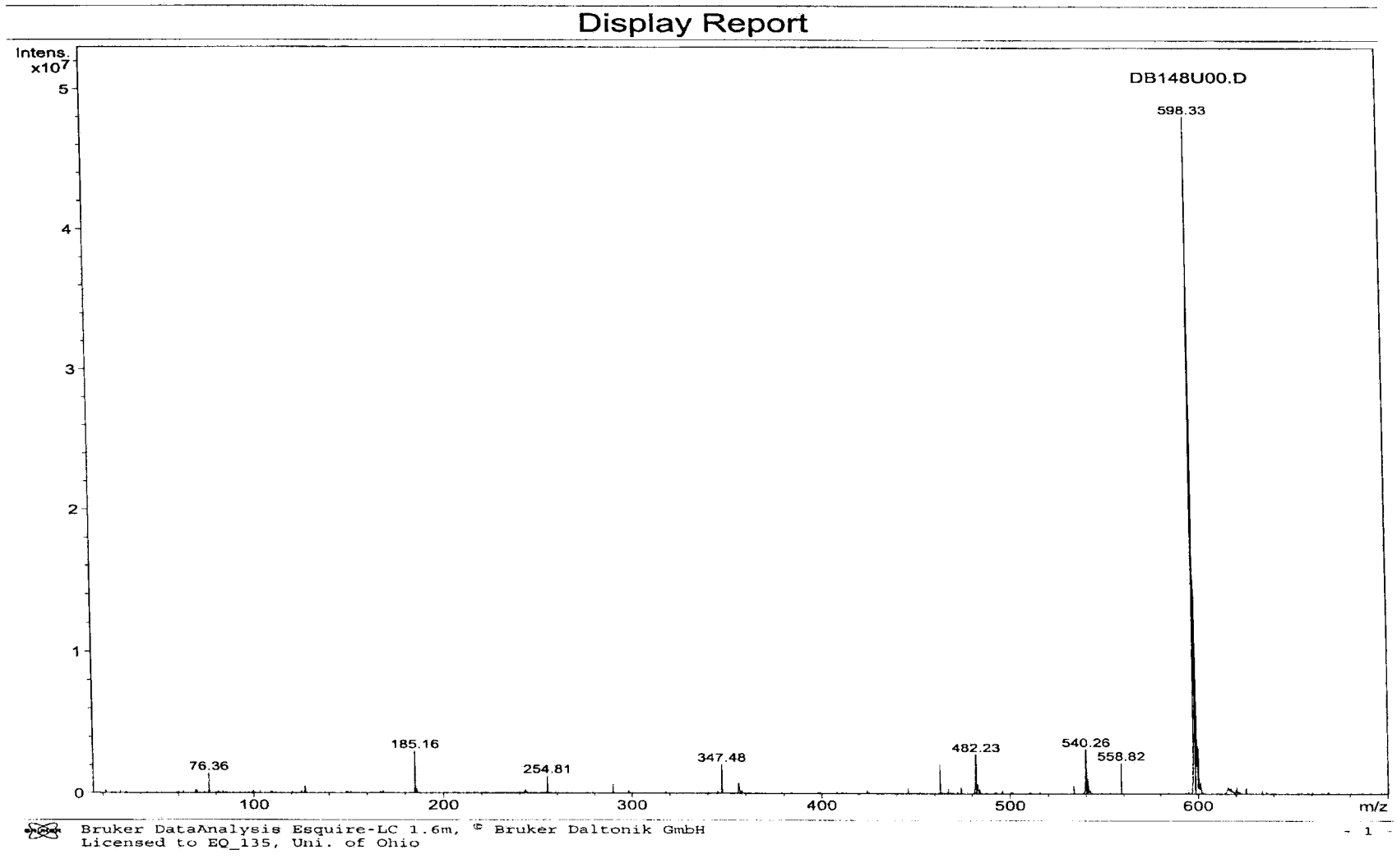

Figure 98. Positive mode ESI-MS of **28/29**-upper spot

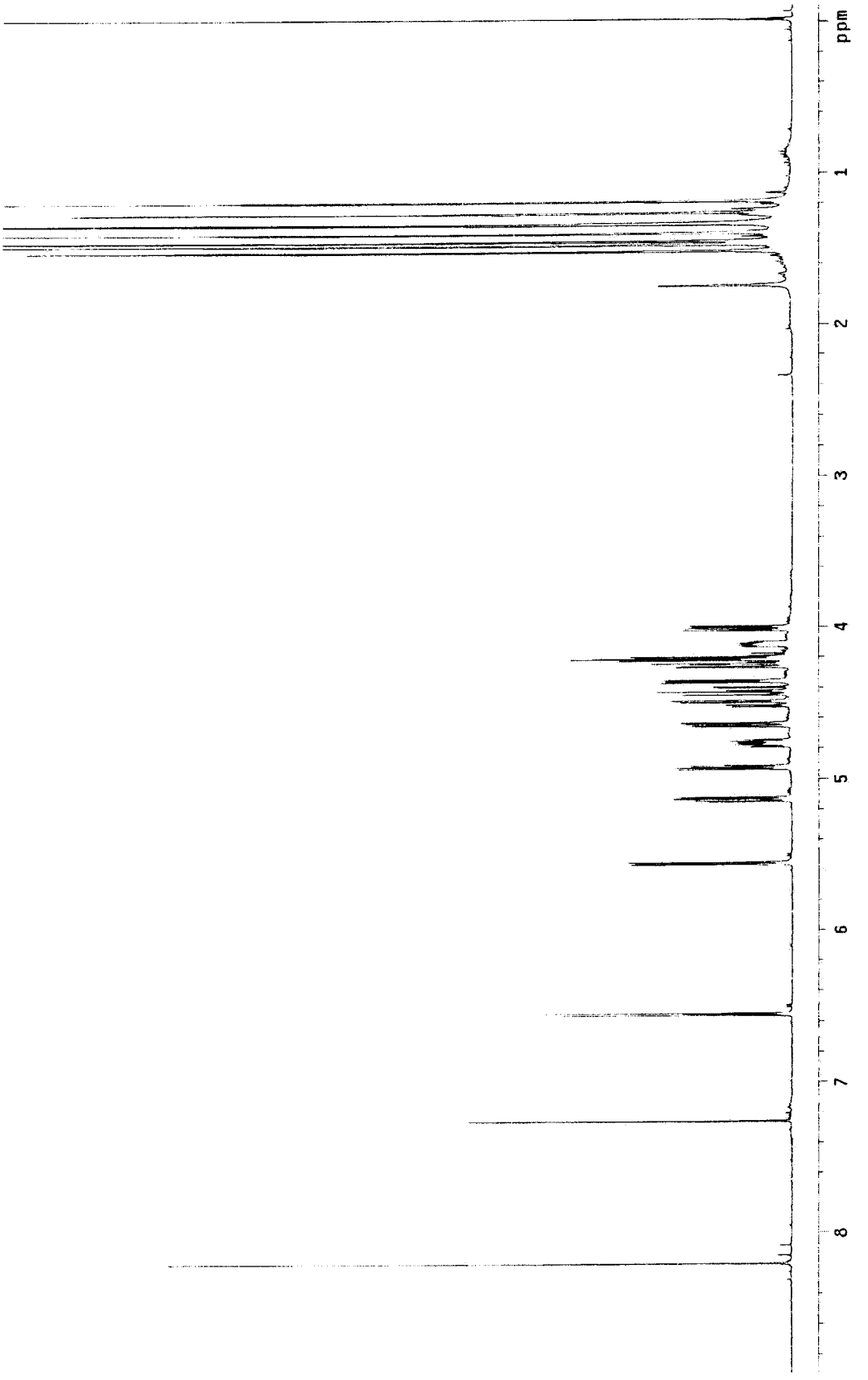

Figure 99. ^{1}H NMR of **28/29**-lower spot

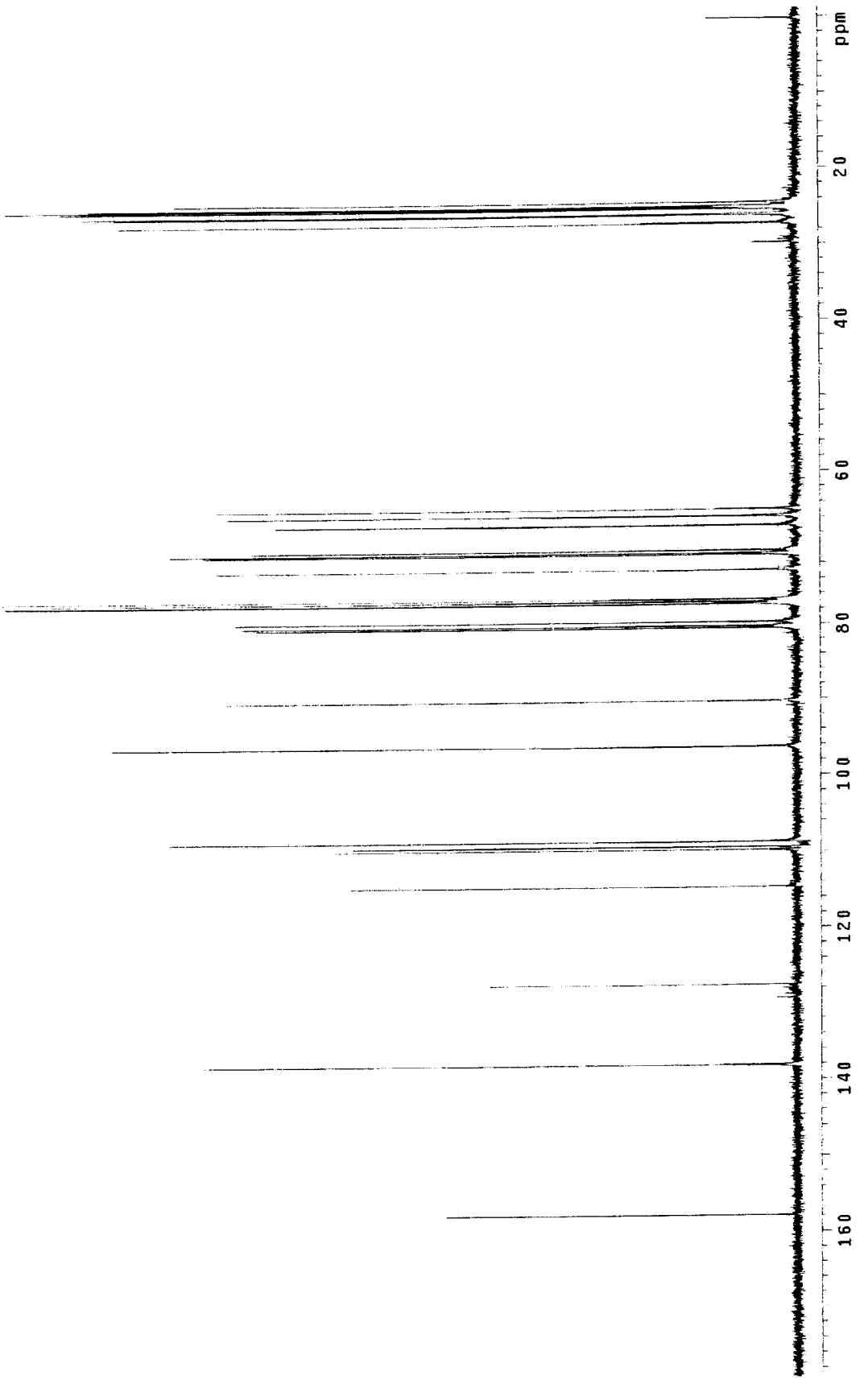

Figure 100. ^{13}C NMR of **28/29**-lower spot

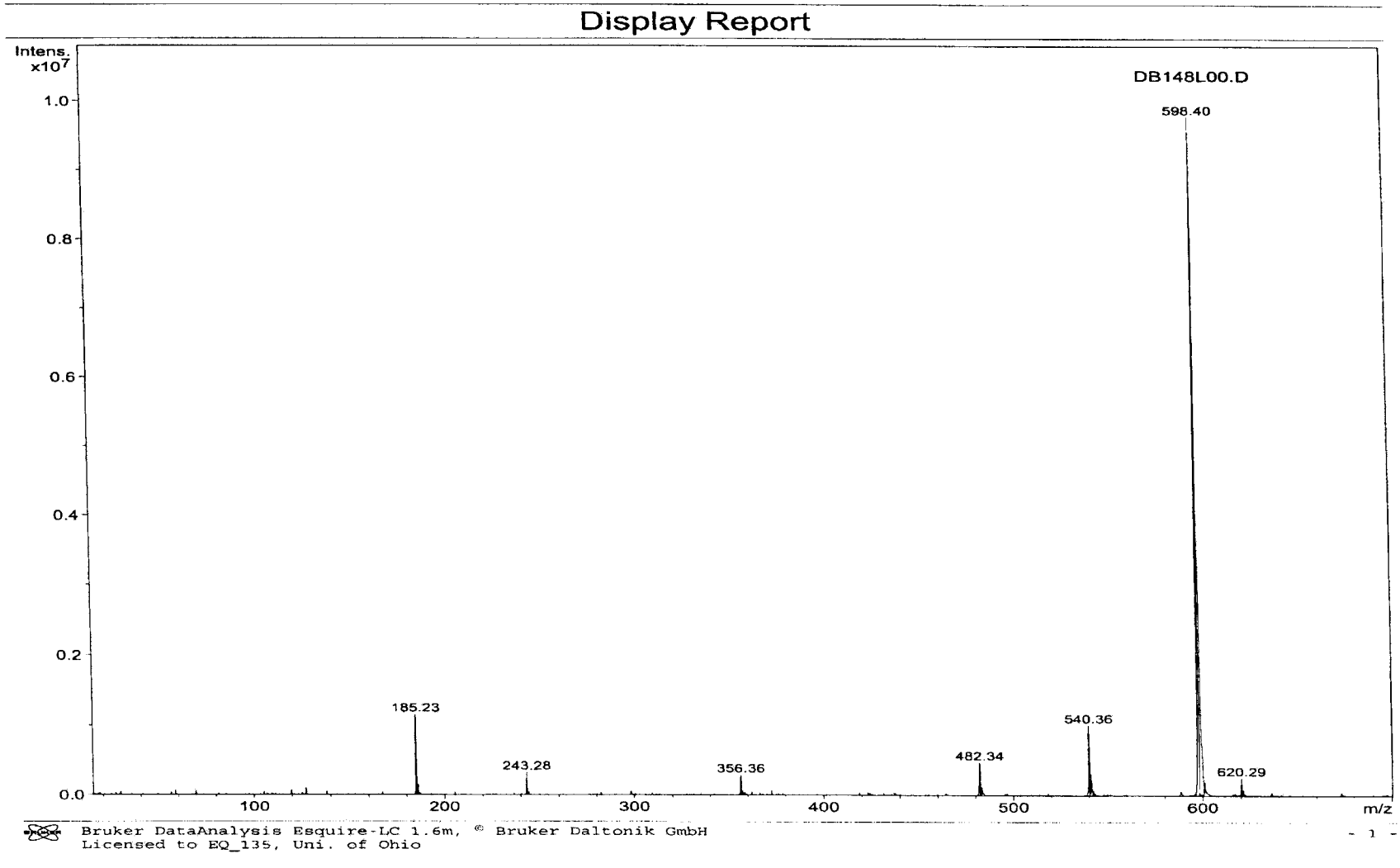

Figure 101. Positive mode ESI-MS of **28/29** lower spot

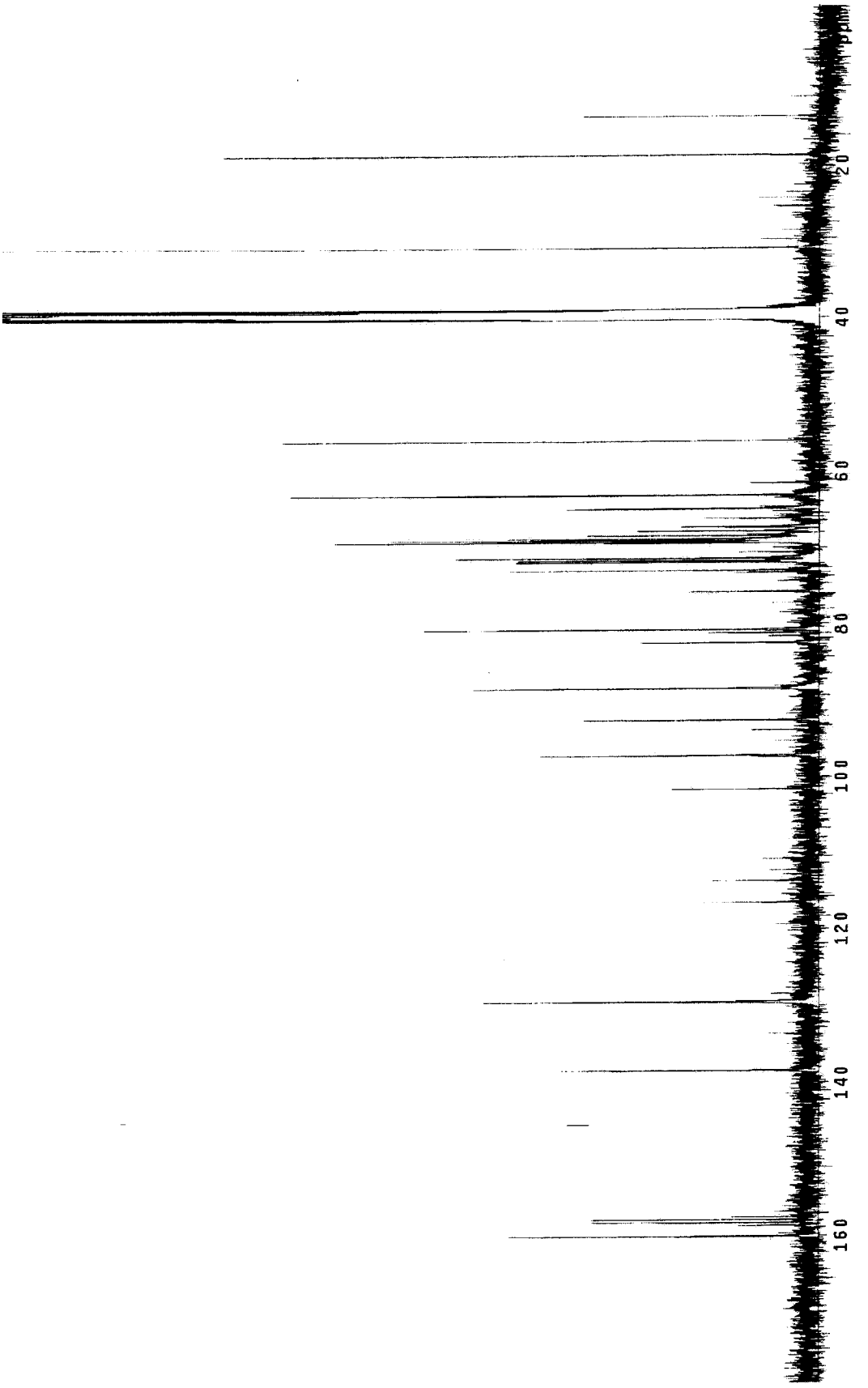

Figure 102. ^{13}C NMR of **30/31**-in d_6-DMSO

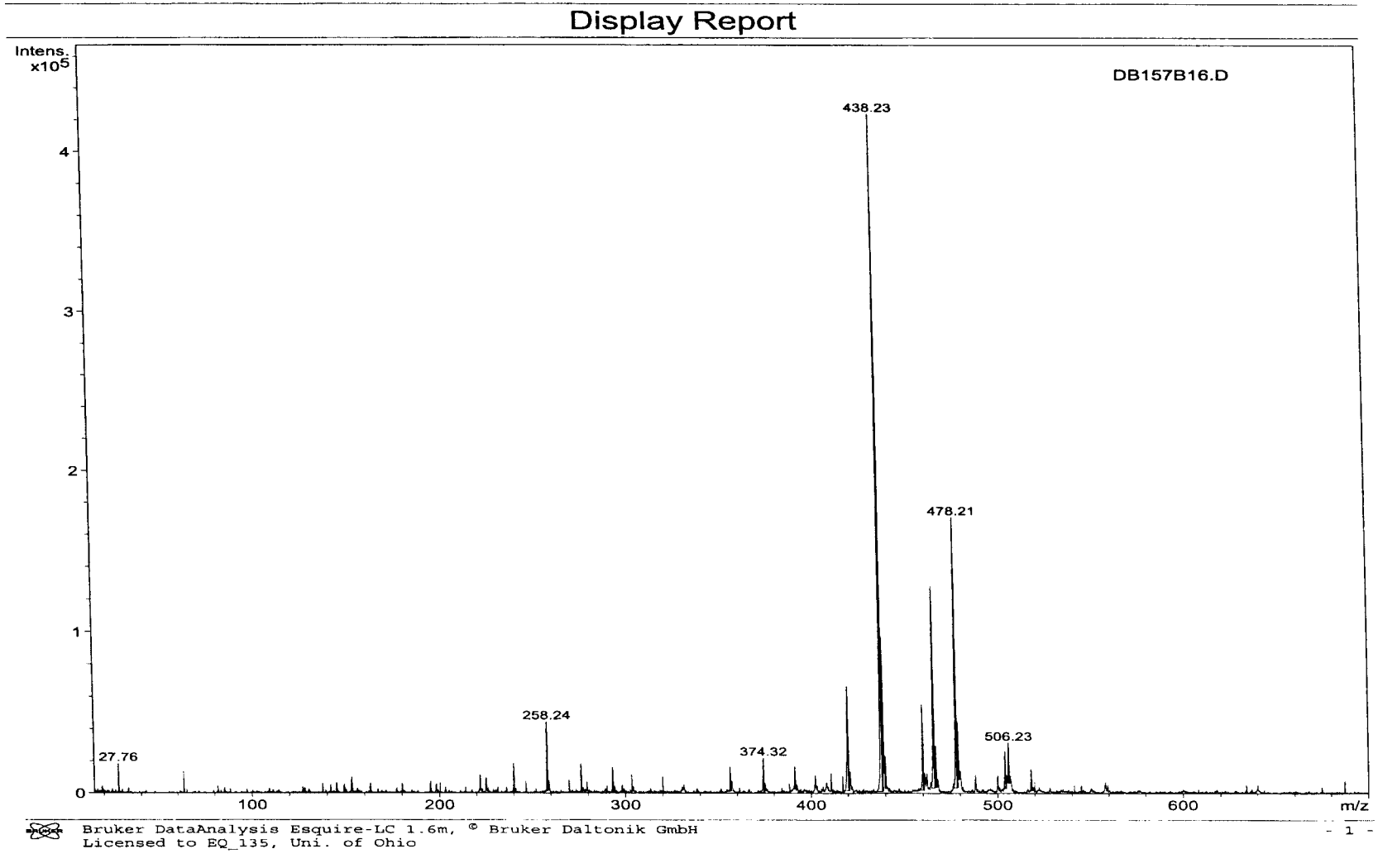

Figure 103. Positive mode ESI-MS of **30/31**

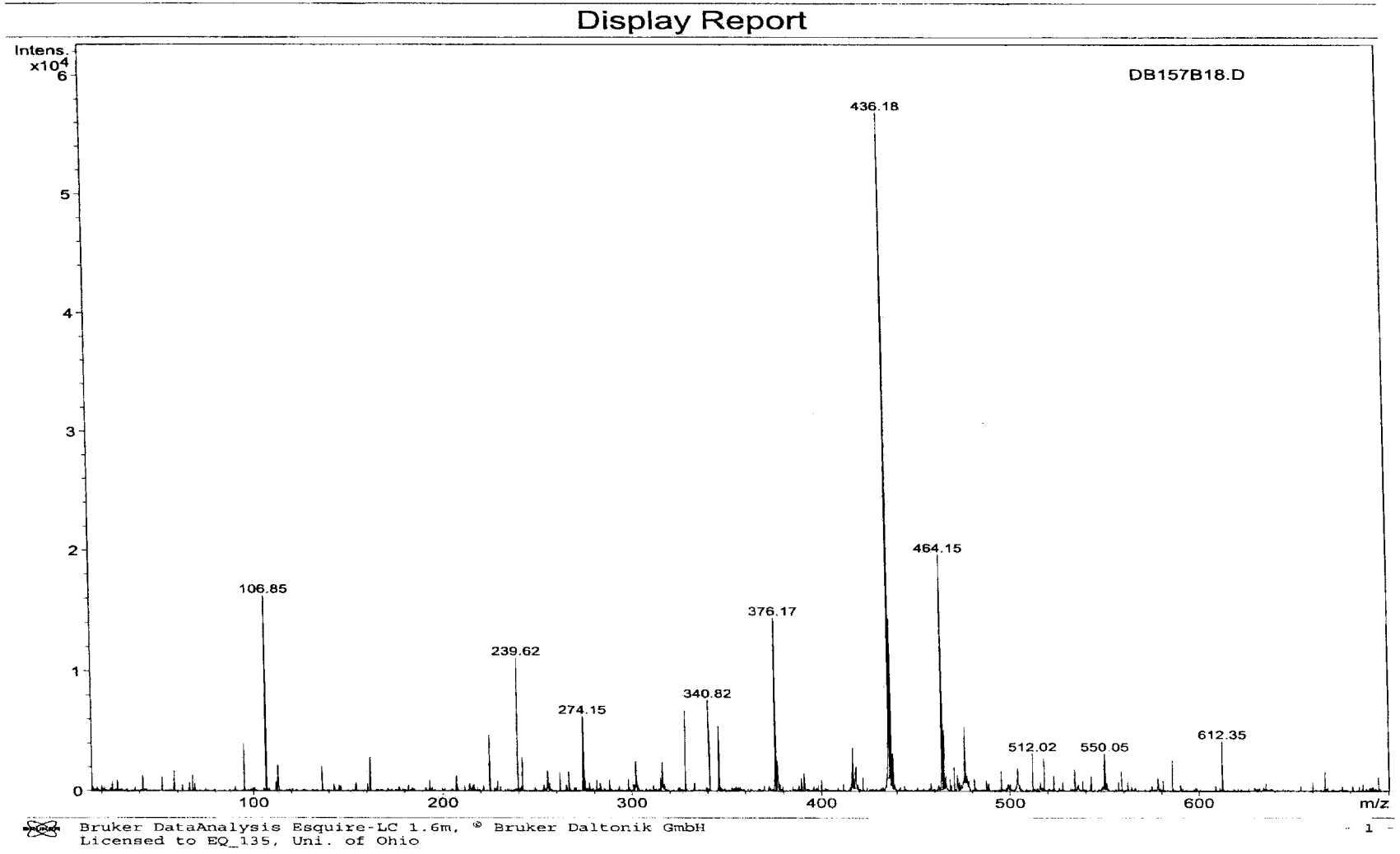

Figure 104. Negative mode ESI-MS of **30/31**

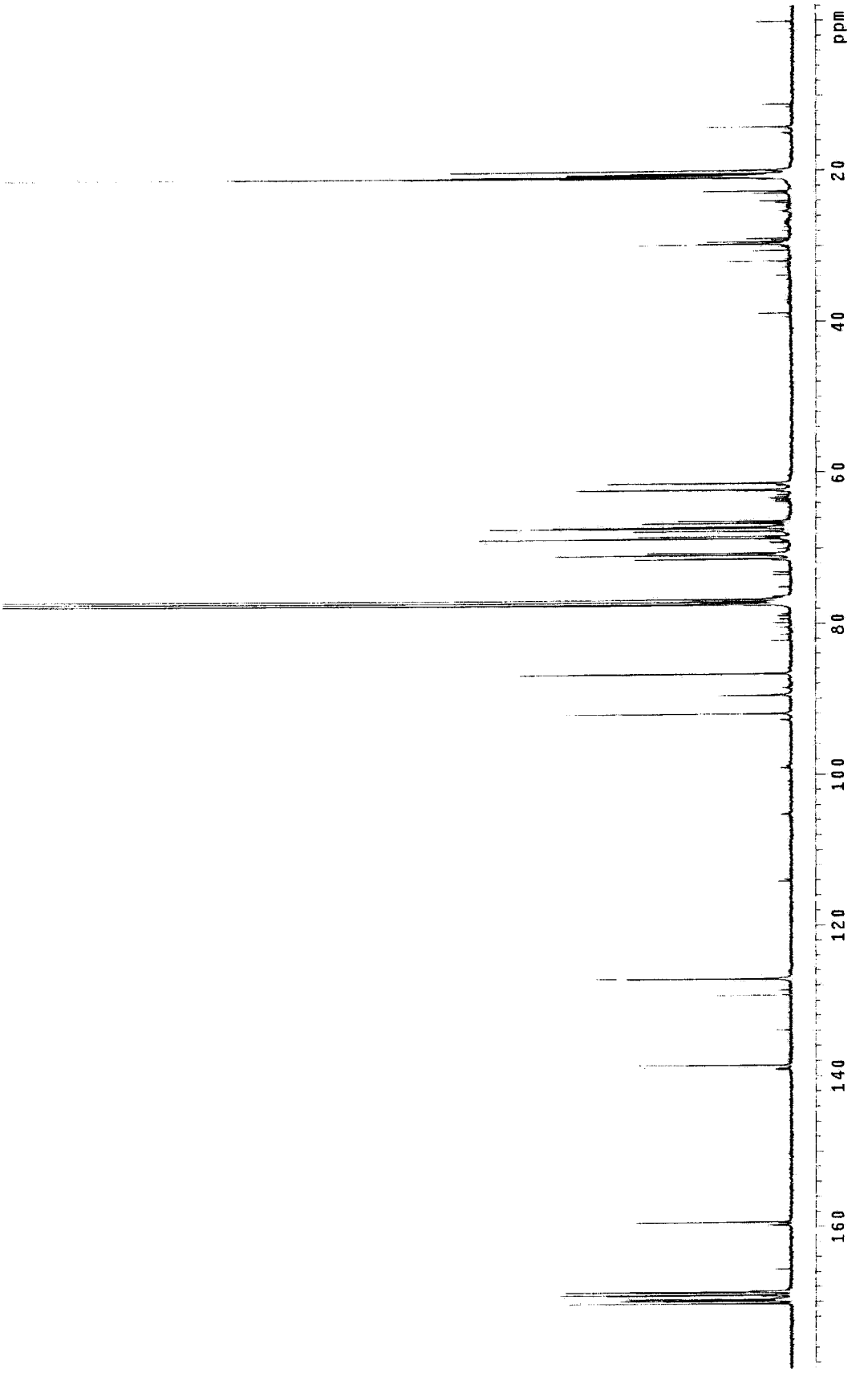

Figure 105. ^{1}H NMR of **32/33**

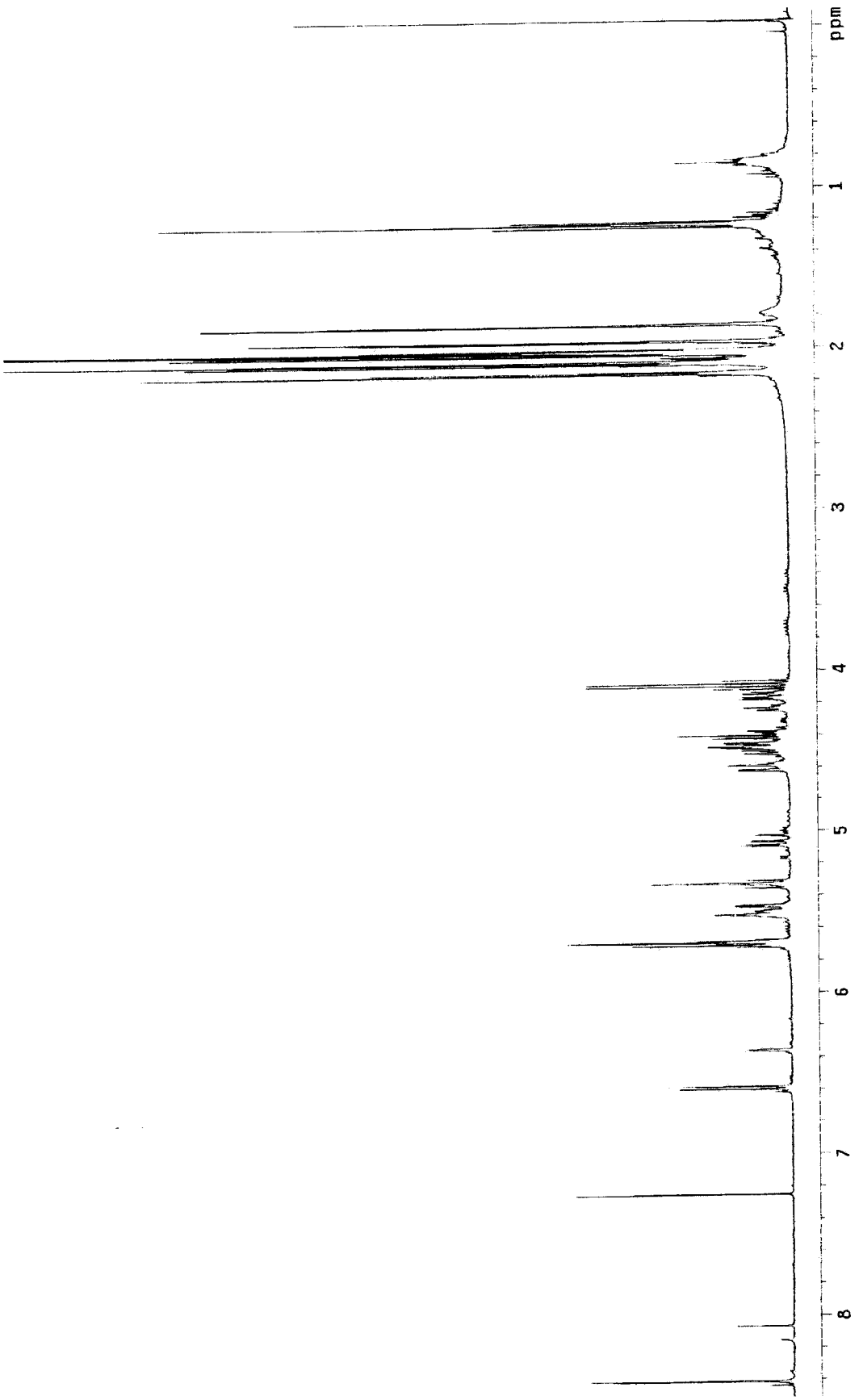

Figure 106. ^{13}C NMR of **32/33**