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Taehee Kim Date

Copper catalyzed C-O cross-coupling synthesis of structurally complex vinylic ethers: Enabling technology for the non-traditional synthesis of various glycosides

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Taehee Kim

B.S., Chatham University, 2017

Advisor: Frank E. McDonald, Ph.D.

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Abstract

Copper catalyzed C-O cross-coupling synthesis of structurally complex vinylic ethers: Enabling technology for the non-traditional synthesis of various glycosides

By Taehee Kim

Carbohydrates are the most abundant macromolecules that participate in various biological activities and have shown therapeutic effect, such as antibacterial vaccines, tumor-associated carbohydrate antigens, and diabetes treatment. Accessing a large quantity of structurally defined glycosides is critical in a comprehensive understanding of this macromolecule. Due to hetereogeous nature of carbohydrates, it is often impractical to extract it from natural sources. The chemical synthesis of glycosides is an alternative to provide structurally defined glycosides. Although traditional glycosylation is well developed, the field of glycosylation still suffers a lack of uniform methodology to form a glycosidic bond due to its complicated mechanism that varies from S_N2 and S_N1 mechanism. An alternative approach is an electrophile-promoted intramolecular oxacyclization of carbohydrate-derived acyclic vinylic ethers. However, we discovered a gap in knowledge regarding an efficient synthetic method for vinylic ethers with structural complexity on both sides of the ether linkages.

Addressing the lack of efficient synthesis of structurally complex vinylic ethers, we developed an efficient synthesis of vinylic ethers via the C-O cross-coupling catalyzed by Cu(I) and cyclic (±)-*N,N'*-dimethylethylenediamine (CyDMEDA) as a ligand. The substrate scope of this cross-coupling included polyhydroxy alcohols, unsaturated alcohols, tertiary amine containing alcohol, and reducible anomeric alcohol,

Our C-O cross coupling method enabled the synthesis of acyclic vinylic ethers from monosaccharide building blocks, namely from D-lyxose, D-ribose, and D-arabinose. This was the first example of synthesizing 1,2-disubstituted vinylic ethers with structural and stereochemical complexity on both sides of the ether linkage via cross-coupling. The cross-coupling method provided stereospecific 1,2-disubstituted vinylic ethers, unlike previously used Horner-Wittig olefination or Julia-Kocienski olefination. Upon epoxidation / *in-situ* oxacyclization of each acyclic vinylic ether product, we have synthesized disaccharides with α-D-talo-, β-D-allo-, and α-D-altropyranoside stereochemistry.

Subsequently, we began expanding the electrophile-promoted oxacyclization of acyclic vinylic ether intermediates toward the synthesis of 6-deoxy- and 2,6-dideoxyglycosides. The preliminary investigation with D-ribo stereoisomer showed that the acid-catalyzed intramolecular oxacyclization can form 2,6-dideoxyglycosides directly from acyclic vinylic ether intermediates. Further investigation of this transformation is warranted, with other diastereomers and protective group patterns.

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Table of Contents

List of Schemes

List of Figures

List of Tables

Chapter 1 Introduction

1.1 Carbohydrates

1.1.1 Background

Carbohydrates are the most abundant and structurally diverse macromolecules. They are involved in various biological activities ranging from cell-cell interaction to antibacterial vaccines[1] to tumor-associated carbohydrate antigens [2]. For example, Globo H is an anti-tumor antigen [3]; Merremoside A is a treatment for diabetes and respiratory illness [4,5]; Saccharomicin A is an antibiotics against Gram-positive and Gram-negative pathogens [6,7] (Figure 1.1).

The increasing interest in carbohydrates requires the homogeneous form of carbohydrates in sufficient amount [8–10]. However, carbohydrates have diverse structures and stereochemical arrangements and often exist as a heterogeneous form in nature. These characteristics of carbohydrates prevent practical extraction of the pure samples from the nature source [8,9,11,12]. Chemical synthesis of carbohydrates can provide an alternative way to obtain the homogeneous forms of carbohydrates.

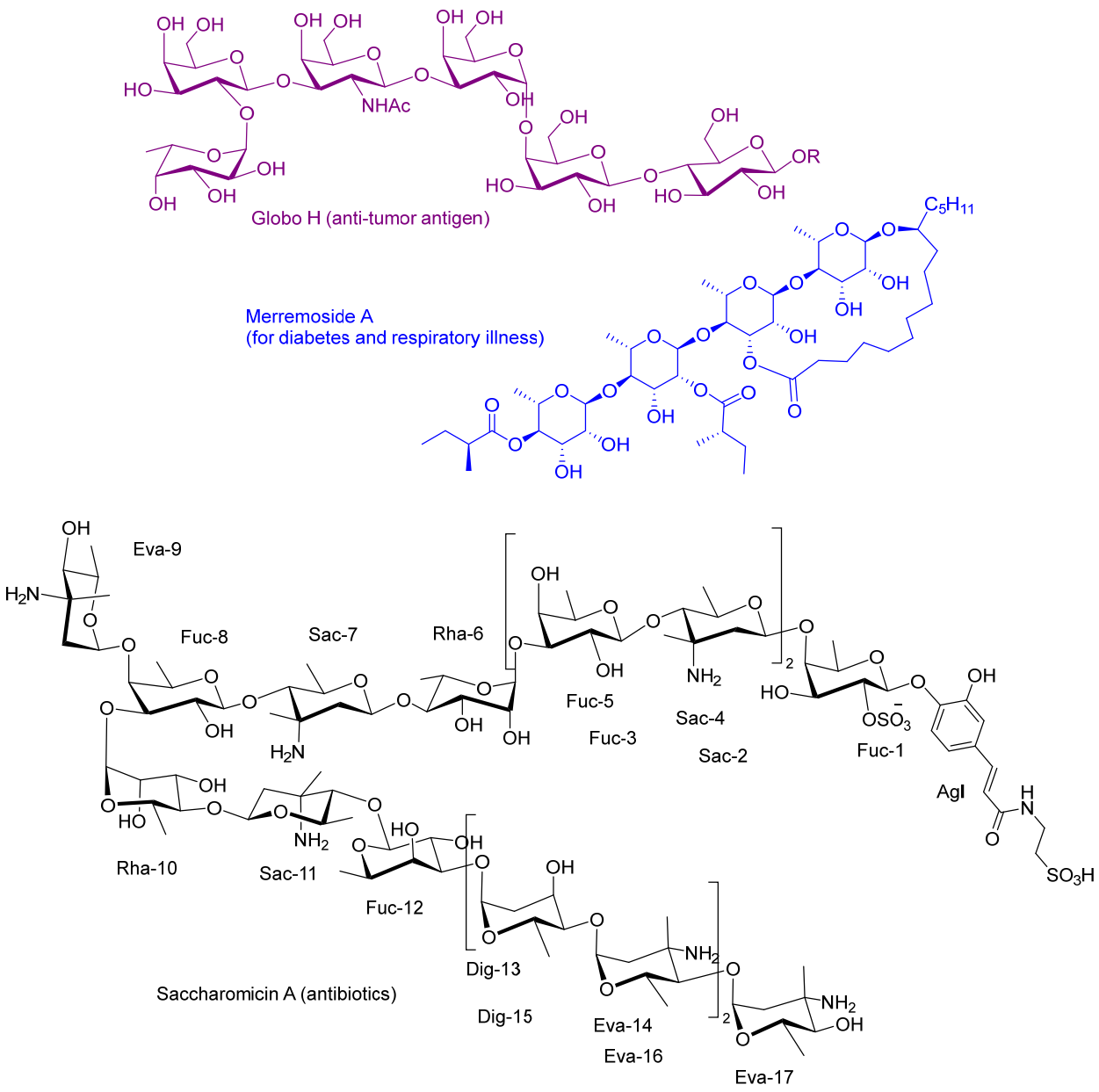


Figure 1.1 Pharmaceutically relevant carbohydrates

1.1.2 Traditional glycosylation

Traditional glycosylation is a formation of glycosidic bonds between a nucleophile, “glycosyl acceptor,” and a secondary electrophile with a substituent at the anomeric center, “glycosyl

donor", that is activated by a promoter (Figure 1.2). The common substituent at the anomeric center of glycosyl donor includes halides (Koenigs-Knorr glycosylation), acetimidates, glycosyl esters, and thioglycosides [13–16]. The promoter can be a stoichiometric or catalytic amount of Brønsted/Lewis acids [17], late transition metals [13], and organocatalysts [18].

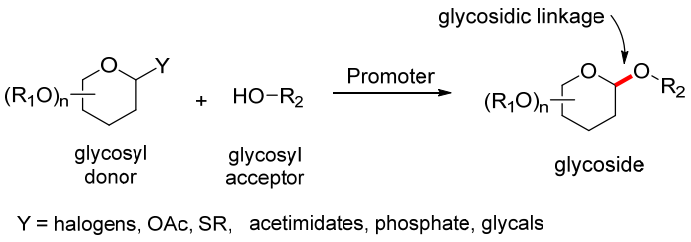


Figure 1.2. Generic scheme of traditional glycosylation

The mechanism of traditional glycosylation is a nucleophilic substitution that exhibits a continuum of S_N2 and S_N1 mechanisms[19] (Figure 1.3). In a general sense, when a promoter activates the glycosyl donor, a contact ion pair forms between the newly formed oxocarbenium ion and a counter anion.

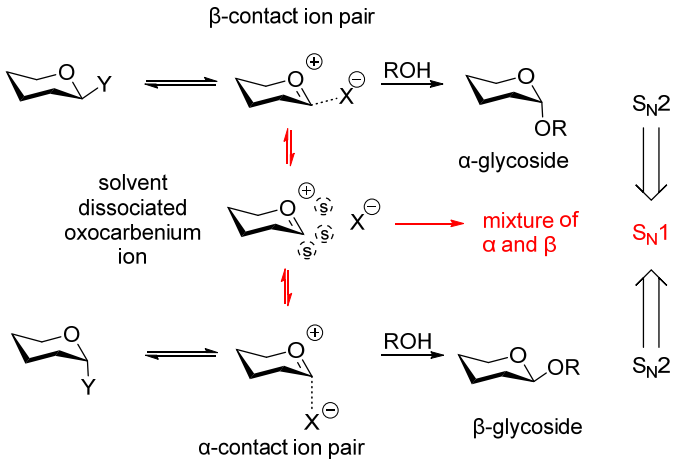


Figure 1.3. Proposed mechanism of glycosylation

Depending on the nature of the counter anion, these contact ion pairs can be tightly bound and direct the nucleophilic attack via S_N2-like mechanism, resulting in the stereoselective

formation of an anomer with inverted stereocenter. On the other hand, these ion pairs can be loosely bound or dissociated by solvent, resulting in an oxocarbenium cation. A nucleophile can attack either side of the oxocarbenium cation via S_N1 mechanism, resulting in the mixture of α and β anomers. The stereoselectivity of glycosylation is further complicated by the reversibility among the contact ion pairs and oxocarbenium cation.

1.1.3 Controlling stereoselectivity in traditional glycosylation

The stereoselectivity of glycosylation can be controlled through different protecting group strategies, such as anchimeric assistance (or neighboring group participation)[20]. Anchimeric assistance is achieved when a Lewis basic group of a protecting group on C2, such as ester, forms a stabilizing intermediate with oxocarbenium cation (Figure 1.4, eq. 1). The following nucleophilic attack on the opposite side of the protecting group results in a highly stereoselective formation of 1,2-*trans* glycoside. A protecting group on other positions of the ring, e.g. C3, can also provide stereochemical control that leads to stereoselective formation of 1,3-*trans* glycoside (Figure 1.4, eq. 2).

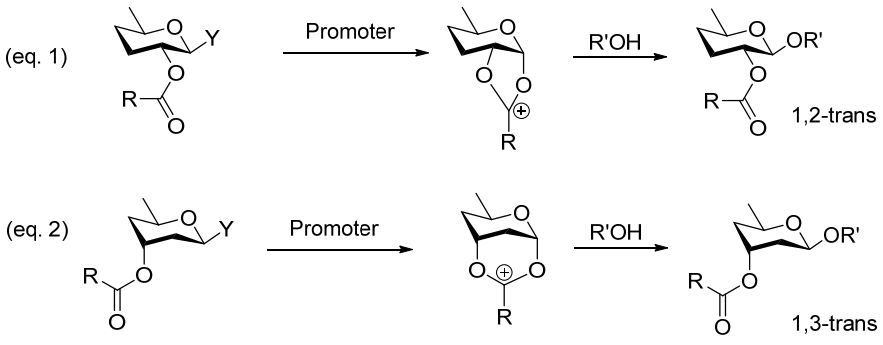
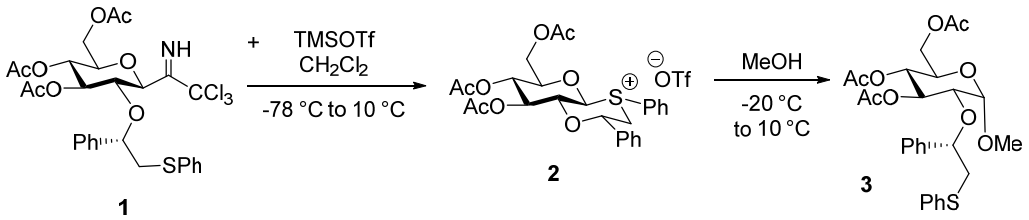


Figure 1.4. General representation of anchimeric assistance with an ester protecting group

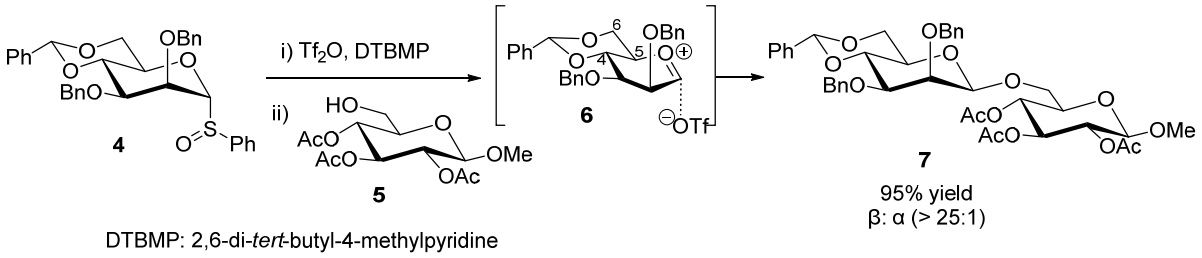
Anchimeric assistance often results in 1,2-*trans* glycosides. On the other hand, a chiral auxiliary on C2 can afford 1,2-*cis* glycosides. The Boons's group reported the synthesis of 1,2-*cis* glycoside with (1S)-phenyl2-(phenylsulfanyl)ethyl moiety as a chiral auxiliary at C2 of glycosyl donor **1** [21] (Scheme 1.1). When activated by TMSOTf, the chiral auxiliary formed an equatorially substituted anomeric sulfonium **2**, which directed a glycosyl acceptor on an axial side and stereoselectively formed an α-anomer **3**.

Scheme 1.1 Synthesis of 1,2-cis glycoside with chiral auxiliary on C2



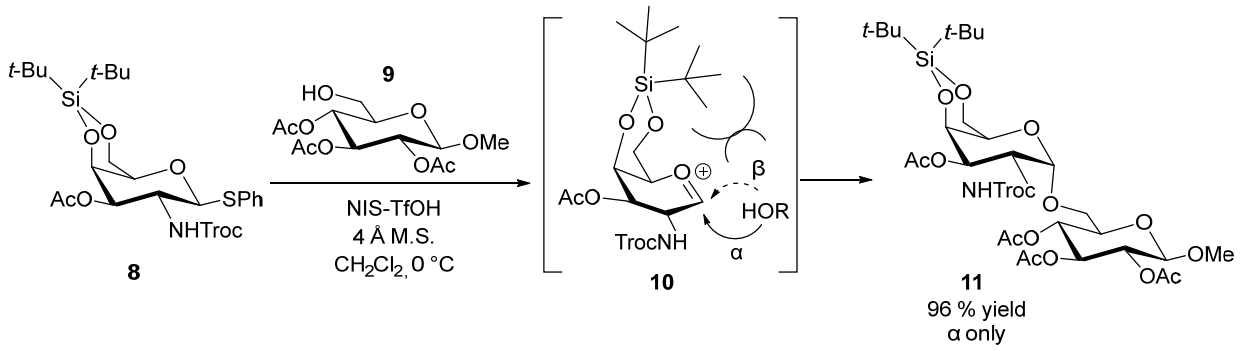
Additionally, a conformational constraint can control the stereoselectivity of traditional glycosylation. A conformational constraint is achieved through cyclic group protecting diols, including benzylidene, carbonate, oxazolidinone, and cyclic silyl groups [20]. For example, Crich demonstrated a highly β-stereoselective glycosylation with sulfoxide **4** bearing a 4,6-benzylidene protecting group (Scheme 1.2) [22]. The 4,6-benzylidene group constrained the C5-C6 bond in the *trans*-gauche conformation in which the C6-O6 bond is held antiperiplanar to the C5-O5 bond [23]. The electron-withdrawing effect of oxocarbenium ion is maximized in this conformation, which favors the conformation of the α-triflate intermediate **6**.

Scheme 1.2. Synthesis of β-Mannopyranosides from 4,6-benzylidene sulfoxide



Another example would be the cyclic di-tert-butylsilyl protecting group (DTBS) on O4-O6. The Kiso group reported a highly α-stereoselective galactosylation with DTBS protecting group on O4-O6 on glycosyl donor **8** (Scheme 1.3). The steric hindrance from the tert-butyl group in intermediate **10** prevented the nucleophile from attacking on the same side as the bulky protecting groups, resulting in a highly stereoselective synthesis of α-anomer **11**.

Scheme 1.3. DTBS-directed α-galactosylation



Comprehensive overview of traditional glycosylation can be found in several review articles, including one-pot protection, glycosylation and protection-glycosylation strategies [11,17,20,24,25]. Additionally, there are several reviews on the different types of promoters/catalysts [13,14,18], periodic reviews [8,15,26,27], and finally automation technology for glycosylation [28–30].

In fact, there is a special issue "Carbohydrate Chemistry" on *Chemical Reviews* published in 2018 that was dedicated to showing the advancements and limitations associated with the latest

developments of the intermolecular glycosylation. In the introductory remarks, the editor, Professor Nicola Pohl stated that “Chemistry is now often the bottleneck to the development of a sophisticated understanding and use of this class of biomolecules…” [10]. The general agreement is that there is no universal approach to glycosylation. Due to diverse structures of carbohydrates and the complicated mechanism ranged over S_N1-S_N2 continuum, strenuous optimization for each target glycosides are necessary. Professor Townsend shared the same statement as Professor Pohl and called for “those who can bring novel tools to address problems…” in a 2023 review article [9].

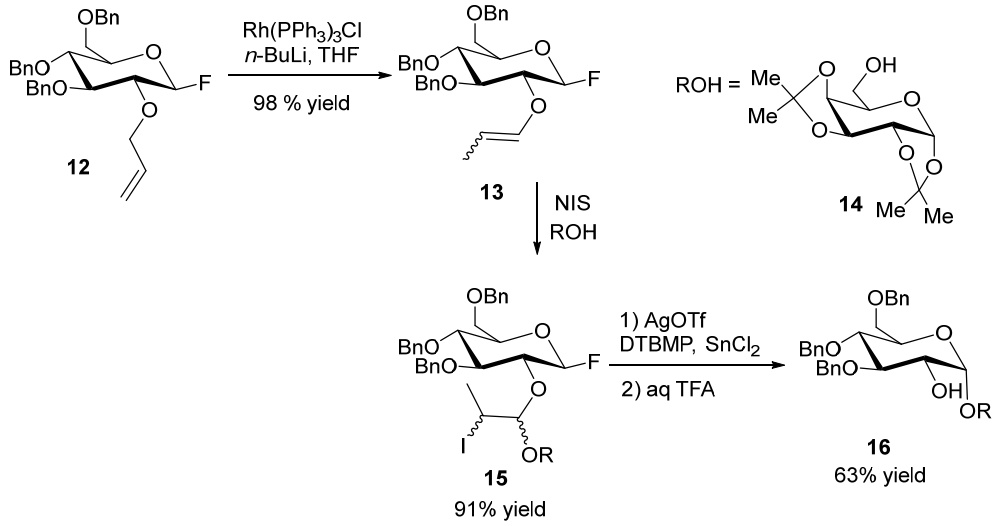
1.1.4 Intramolecular Glycosylation

An alternative approach to the traditional, intermolecular glycosylation is an intramolecular formation of glycosides, which gained considerably less attention than the intermolecular glycosylation [31–34]. The principle behind the intramolecular glycosylation is to increase the reactivity of glycosyl donor and acceptor by bringing the two reactants in proximity. This also limits the conformation of substrate, which may achieve higher stereoselectivity through facial selectivity when a nucleophile attacks the glycosyl donor counterpart [33].

The glycosyl donor and the acceptor can be joined by a tether group. One of the most common tethering methods is called intramolecular aglycon delivery (IAD) method, in which the reactive site on the glycosyl acceptor is joined with the glycosyl donor [32,33]. There are various types of tether group, including dimethyl ketal, dimethylsilaketal, alkylidene acetal, and methoxybenzylidene acetal [32]. An example of the IAD involved in isomerization of an allylic ether **12** to vinylic ether mixture **13**, followed by NIS-mediated tethering with glycosyl acceptor **14**

(Scheme 1.4) [35]. The resulting iodopropylidene acetal **15** was subjected to IAD to give **16** as a single diastereomer.

Scheme 1.4. Allylic ether as the tethering group in intramolecular aglycon delivery glycosylation



Despite a stereospecificity of this approach, IAD methods are often reserved for the substrates that are difficult to synthesize since the tethering approaches require additional steps of installing and removing the tethering groups [8,32,33].

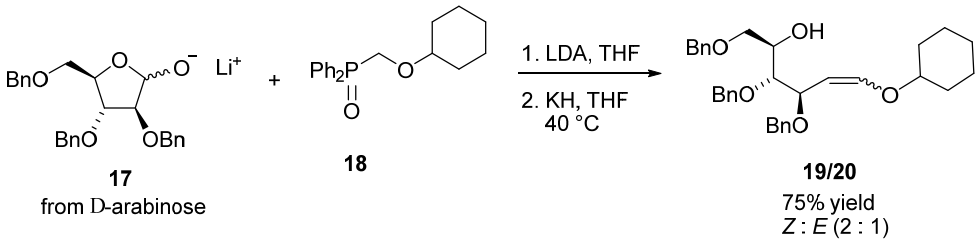
Another type of intramolecular glycosylation uses the vinylic ethers where both substituents of the ether linkages are derived from carbohydrates. The electron-rich vinylic ether is treated with an electrophile, which promotes oxacyclization of internal O6 to an α-carbon on the alkene moiety. Unlike most of the tethering group, the alkene moiety in the acyclic vinylic ether directly participates in the glycosylation, eliminating the need to remove the tethering group.

1.1.4.1 Electrophile-promoted oxacyclization and the synthesis of carbohydrate-derived acyclic vinyl ethers

In 1982, Suzuki and Mukaiyama pioneered a glycosylation via electrophile-promoted oxacyclization of acyclic vinylic ether [36,37]. They synthesized a mixture of *Z/E*-vinylic ethers **19**/**20**

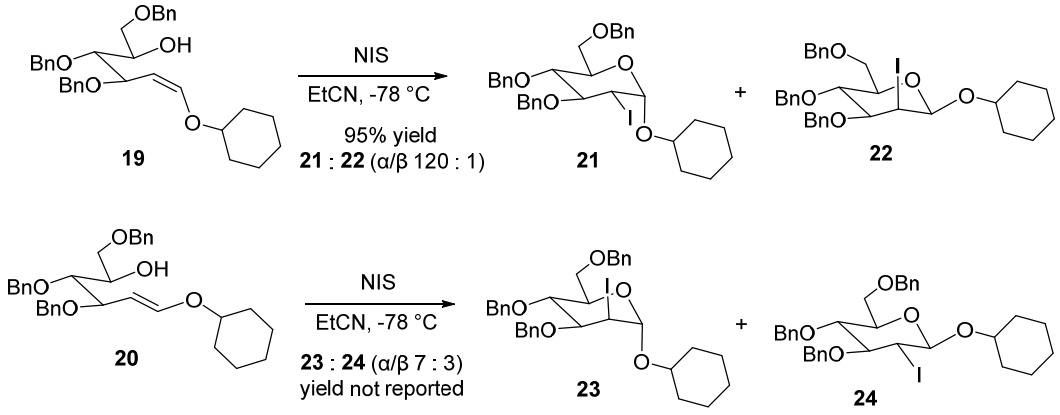
via Horner-Witting olefination (Scheme 1.5). Alkoxide generated from the glycosyl donor counterpart **17** reacted with phosphonate of aglycone moiety **18** under strongly basic conditions.

Scheme 1.5. Synthesis of carbohydrate-derived vinylic ethers via Horner-Wittig olefination



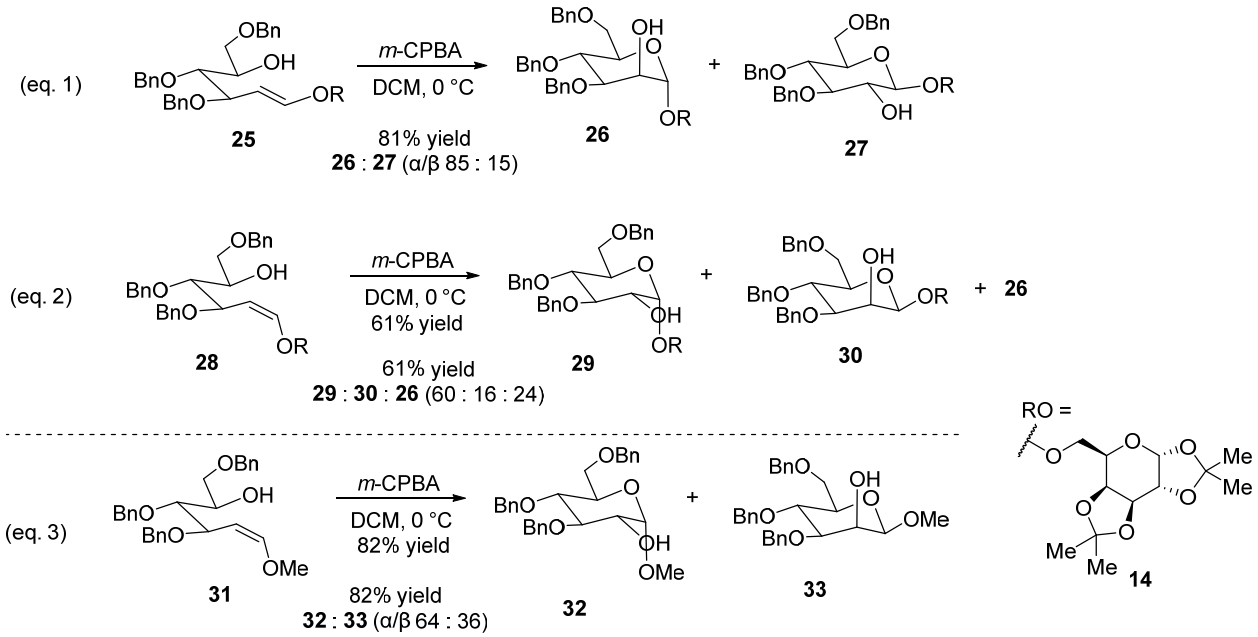
They demonstrated that electrophiles, such as mercury trifluoroacetate, phenylselenyl chloride, and N-iodosuccinimide, promoted the intramolecular oxacyclization of carbohydrate-derived acyclic vinylic ether, resulting in the stereoselective synthesis of glycosides [36,37]. For example, iodocyclization proceeded through the stereospecific *trans*-addition of iodide and internal hydroxy group as only 1,2-*cis* diastereomers **21** and **22** were formed from *Z*-vinylic ether **19** (Scheme 1.6). Although the diastereoselectivity from *E*-vinylic ether **20** was modest (α/β 7:3), only 1,2-trans diastereomers **23** and **24** were formed (Scheme 1.6).

Scheme 1.6. Synthesis of 2-deoxy-2-iodo-glycoside via NIS-promoted oxacyclization



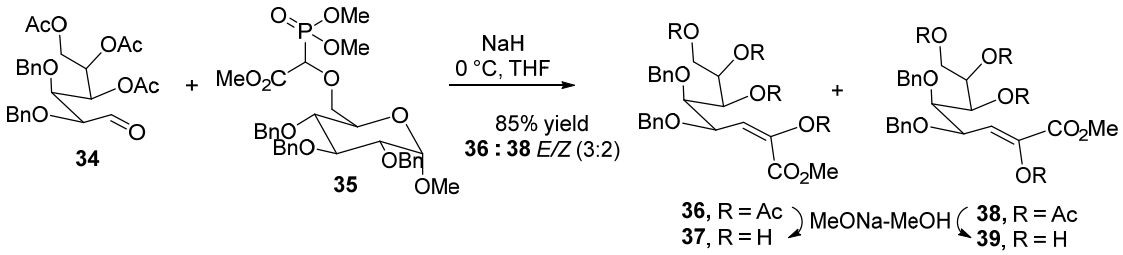
Subsequently, Nicotra reported that treating a vinylic ether with an epoxidating reagent, such as *m*-CPBA, generated an epoxide intermediate that can be stereoselectively opened with the internal O6 group [38,39]. He observed that only 1,2-*trans*-glycosides formed from the *E*-vinylic ethers, while stereoselectivity with *Z*-vinylic ethers were varying. For example, 1,2-*trans*-disaccharides **26** and **27** (α/β 85:15) formed when *E*-vinylic ether **25** was treated with *m*-CPBA while 1,2-*cis*-disaccharides **29** and **30** were formed along with **26** from *Z*-vinylic ether **26** (Scheme 1.7, eq. 1 vs. 2). When *Z*-vinylic ether **26** was synthesized from a sterically less bulky methanol, the 1,2-*trans*-disaccharide was not detected (Scheme 1.7, eq. 3). They hypothesized that steric interaction between the aglycone moiety and the axial hydrogen on C4 in the reactive conformation might have prevented a facile ring-closing of the epoxides when the aglycone moiety is sterically bulky.

Scheme 1.7. Synthesis of disaccharides via m-CPBA promoted oxacyclization of acyclic vinylic ether



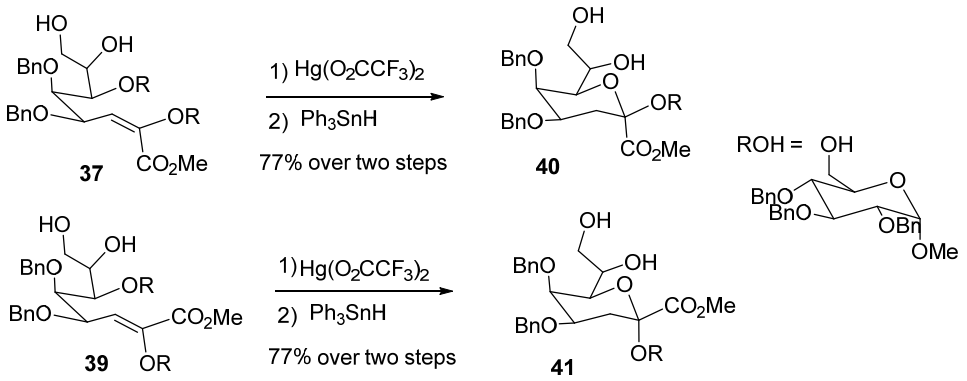
Paquet and Sinaÿ reported the oxymercuration-demercuration of trisubstituted vinylic ether to synthesize the sialic acid, such as 3-deoxy-D-manno-2-octulosonic acid and N-acetylneuraminic acid [40,41]. They synthesized a mixture of *E/Z* vinylic ethers **36** and **38** via Horner-Wittig olefination of aldehyde **34** and phosphonate **35** (Scheme 1.8).

Scheme 1.8. Synthesis of trisubstituted vinylic ether as a *E*/*Z* mixture



After the *E/Z* mixture was separated on a column chromatography and deacetylated, each vinylic ether was treated with mercuration-demercuration. The β-linked anomer **40** was synthesized as a single isomer from *E*-vinylic ether **37,** and the α-linked anomer **41** from *Z*-vinylic ether **39** (Scheme 1.9).

Scheme 1.9. Oxacyclization of trisubstituted vinylic ether via oxymercuration-demercuration



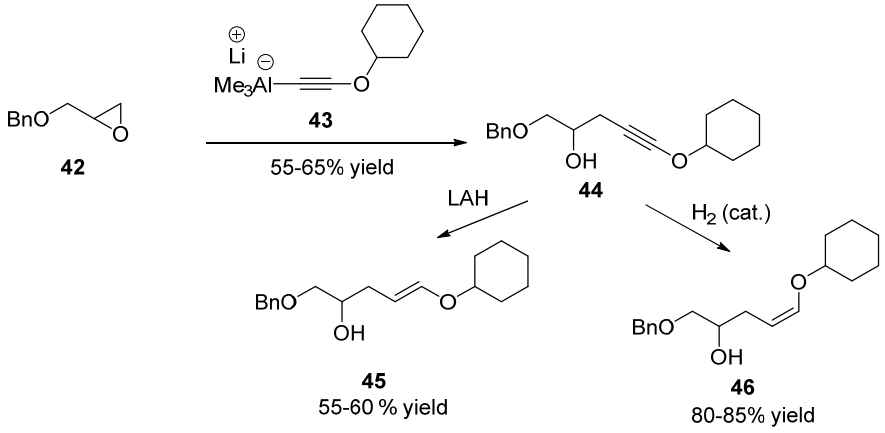
Despite the promising earlier studies, this approach toward glycosidic linkages had little development until we published our findings in 2024, which will be discussed in chapter 3 [42]. The

lack of efficient synthesis of vinylic ether with structural complexity might have prevented further development in the intramolecular glycosylation via oxacyclization of acyclic vinylic ethers.

As described above, the Horner-Wittig olefination resulted in a mixture of *Z/E*-vinylic ethers in ratio ranging from 2:1 to 2:3. Although each isomer synthesized in the 1980s reports was separated on a column chromatography, it often takes substantial efforts to separate a mixture of *Z/E* isomers, thus a stereoselective synthesis of vinylic ethers is attractive.

In 1994, Lipshutz demonstrated the stereospecific synthesis of *E*- and *Z*-vinylic ethers via partial hydrogenation of hydroxy alkynes [43]. Hydroalkoxylation of epoxide **42** yielded alkynyl ether **44** (Scheme 1.10). Treating **44** with lithium aluminum hydride (LAH) gave *E*-vinylic ether **45** as a single isomer while treating it with a catalytic amount of H_2 resulted in *Z*-vinylic ether **46**.

Scheme 1.10. Stereospecific partial hydrogenation of hydroxy alkyne **44**

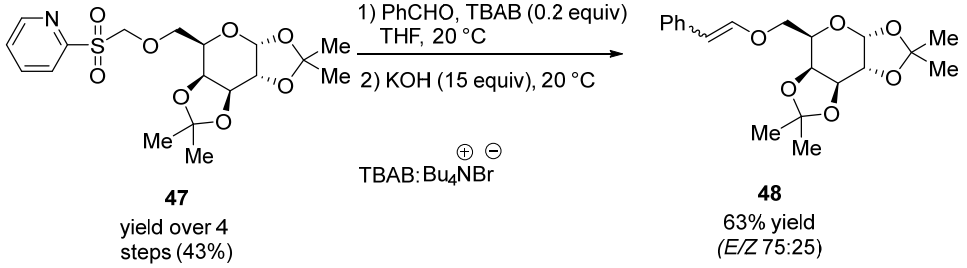


Although this classical synthesis of vinylic ether is stereospecific [44], the harsh conditions limit the substrate scope, and the major disadvantage of this method is the difficulty in the synthesis of starting alkynyl ether [45,46].

In 2000s, the carbohydrate-derived vinylic ethers were synthesized from aldehydes and sulfones via Julia-Lythgoe olefination [47,48]. The carbohydrate-derived sulfone **47** was reacted with

benzaldehyde with tetrabutylammonium bromide to give a mixture of *E/Z* 1,2-disubsituted vinylic ethers **48** (Scheme 1.11) [47].

Scheme 1.11. Julia-Lythgoe-Kocienski olefination of sulfone **47**



Over the past decades, there have been significant advancements in the synthesis of vinylic ethers. Some of the examples and their limitations will be explained in the next section.

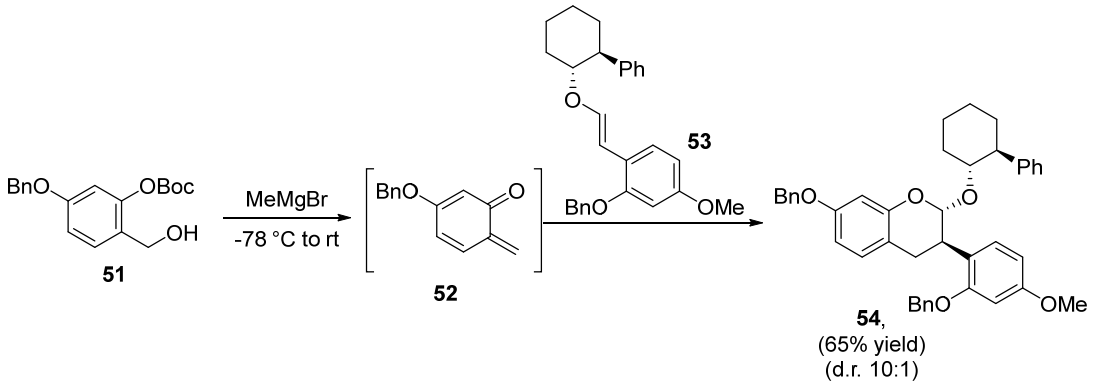
1.2 Vinylic Ethers

1.2.1 Background

Vinylic ethers are electron-rich alkenes that are versatile intermediates for various chemical transformations [45,46]. They are especially versatile in cyclization reactions since they often give high levels of regio- and stereo-selectivity. Pharmaceutically relevant scaffolds, such as chromanes, can be synthesized via inverse demand Diels-Alder reaction between vinylic ether as the dienophile and *o*-quinone methides (*o*-QMs) as the diene [49]. For example, the *in-situ* generated *o*-QM **52** was reacted with *E*-vinylic ether **53** to give chromane ketal **54** (d.r. 10:1), an intermediate in the total synthesis of potential antibacterial drug (-)-Medicarpin[50] (Scheme 1.12). The stereoselectivity of this Diels-Alder cycloaddition was dependent on the geometry of vinylic ether [51]. Compound **53** was synthesized as a mixture of *E/Z* via Wittig olefination of corresponding

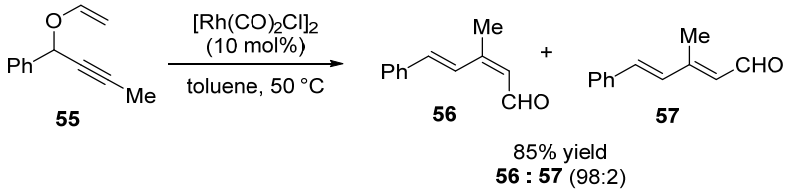
phosphonium ion and a benzaldehyde derivative. The Pettus group could not optimize the stereoselectivity of the Wittig olefination [50].

Scheme 1.12. Synthesis of chromane **54** via Diels-Alder Cycloaddition of **53**



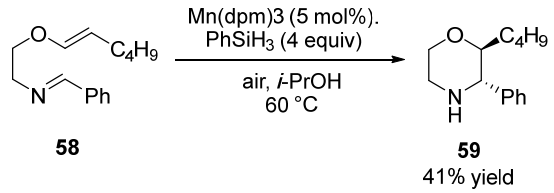
Allyl vinylic ethers also serve as a precursor to the [3+3] Claisen rearrangement, which provides γ,δ-unsaturated carbonyl compounds [52,53]. Additionally, propargylic vinylic ether can undergo Claisen rearrangement to afford a dienal. Vidhani et.al reported a highly stereoselective synthesis of *Z,E*-dienal **56** (98:2) via Rh-catalyzed Claisen rearrangement of propargylic vinylic ether **55** (Scheme 1.13) [54].

Scheme 1.13. Catalytic asymmetric Claisen rearrangement of allyl vinylic ether **55**



The amino vinylic ethers were condensed with various aldehydes to synthesize imine containing vinylic ethers that were treated in a radical HAT cyclization to afford bridged bicyclic and spirocyclic saturated N-heterocycles, and 1,2-substituted morpholines. For example, 1,2-disubstituted morpholine **59** was synthesized as a single diastereomer from 1,2-disubstituted vinylic ether **58** (Scheme 1.14) [55].

Scheme 1.14. 1,2-substituted morpholine synthesis via HAT cyclization of imine vinylic ether

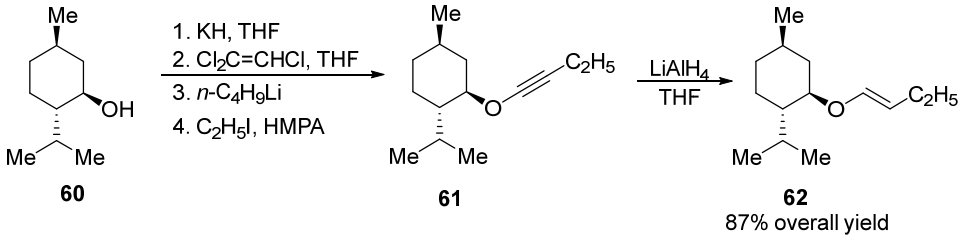


However, these chemical transformations have been restricted to simple vinylic ethers due to difficulty in synthesizing structurally complex vinylic ethers. Some of the representative methods in the vinylic ether synthesis and their limitations are discussed in the next section.

1.2.2 Previous methods to synthesize vinylic ethers

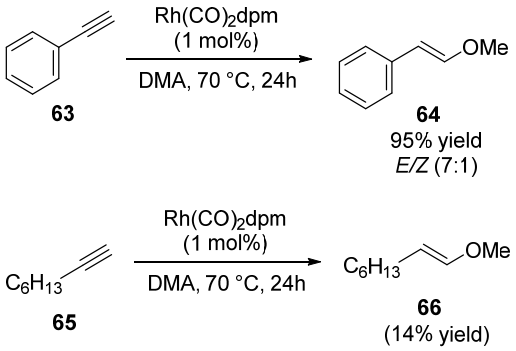
One of the classical methods to synthesize vinylic ethers is hydroalkoxylation of alkynyl ethers (Scheme 1.15) [44]. This process is an indirect synthesis of vinylic ethers from alcohol, involving three major steps: ethynylation, alkylation, and partial hydrogenation. Although this method is stereospecific, it is not suitable for the synthesis of structurally complex vinylic ethers due to its harsh conditions. Additionally, the synthesis of the starting alkynyl ether is limitation itself [45,46].

Scheme 1.15. Partial hydrogenation of alkynol ether **61**



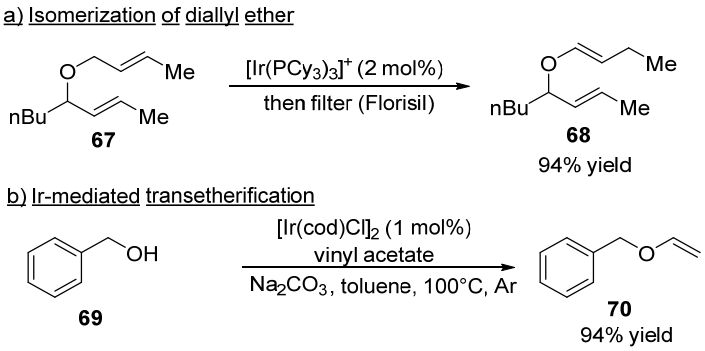
Hydroalkoxylation of aryl acetylenes via Rh catalyst resulted in stereoselective synthesis of vinylic ethers, but alcohol was used as the solvent (Scheme 1.16). The substrate scope included only few alcohols, and the yield diminished for alkyl vinylic ether, such as **66** [56,57].

Scheme 1.16. Rh-catalyzed hydroalkoxylation of alkynes



Iridium-catalyzed isomerization of allyl ether provided 1,2-disubstituted vinylic ether in a stereoselective manner (Scheme 1.17a) [58]. However, this method is limited to easily prepared allylic ether. Transetherification of vinyl acetate to alcohol is mediated by iridium, which were limited to monosubsittued vinylic ethers and 1,1-disubstituted vinylic ethers (Scheme 1.17b) [59].

Scheme 1.17. Ir-catalyzed syntheses of vinylic ethers



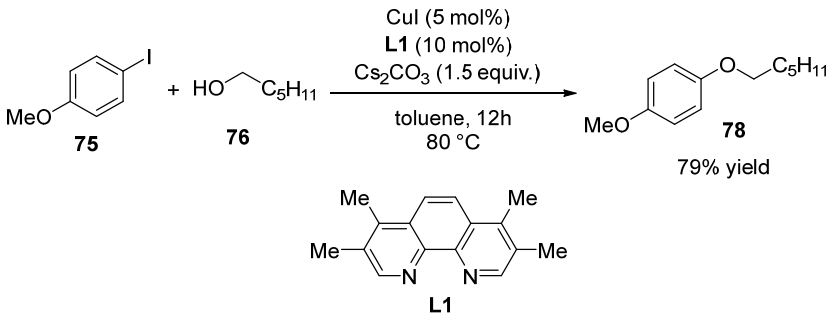
1.2.3 Copper-catalyzed C(sp^2)-O cross coupling

Synthesizing 1,2-disubstituted vinylic ethers via cross-coupling reactions are attractive because they are often stereoselective, and the alcohols can be directly used. Inexpensive copper salts combined with ligands have been shown to catalyze C(sp^2)-O bond formation. The Cu(I)-catalyzed C-O cross-coupling is well developed for aromatic ethers, but the corresponding

synthesis of vinylic ethers from less acidic aliphatic alcohols and substituted vinylic synthons are underdeveloped. Nonetheless, these developments provide a lead in selecting ligand and other reaction parameters. The ligands can be bidentate ligands, including phenanthrolines (N,N-type), diamines (N,N-type), amino acids (N,O-type), and diketonates (O,O-type) [60].

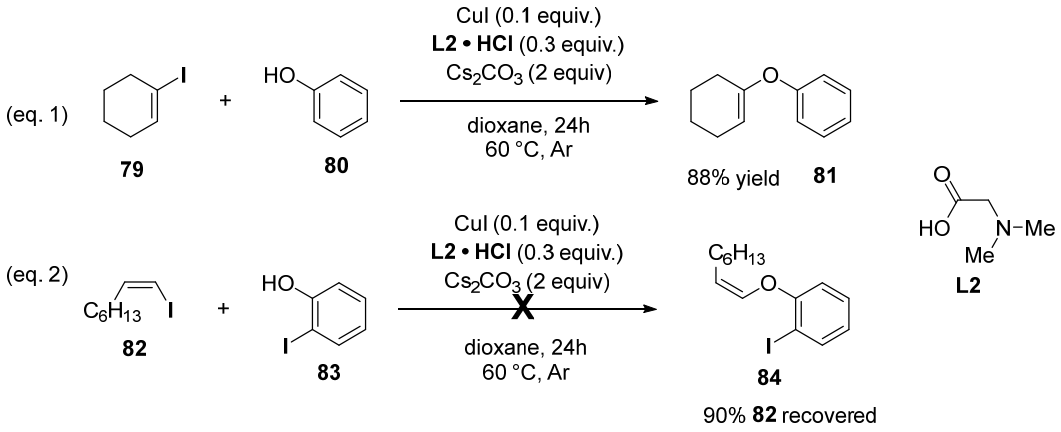
Tetramethyl-phenanthroline **L1** with Cu(I) catalyzed both arylation [61] and vinylation [62] of aliphatic alcohols. The arylation of alcohols included primary and secondary alcohols (an example in Scheme 1.18). The vinylation of aliphatic alcohols with Cu(I)/**L1** will be discussed at the end of this section.

Scheme 1.18. Cu(I)/**L1**-catalyzed cross coupling of aryl halides and aliphatic alcohols



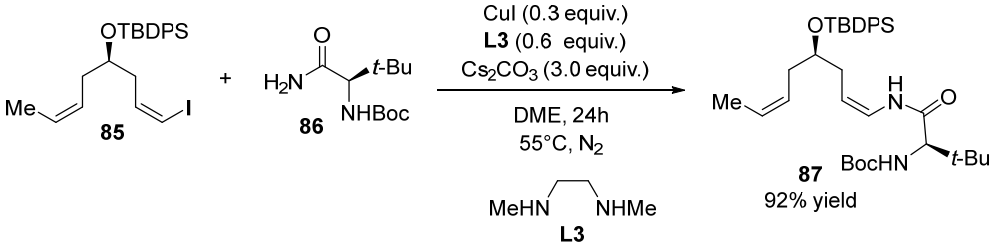
The Ma's group extensively worked with the amino acids and other N,O-type ligands [63] in the Cu(I)-catalyzed cross-coupling of diaryl ethers and aryl vinylic ethers [64,65]. In his earlier work, *N,N*-dimethylglycine HCl salt facilitated the cross-coupling between cyclic vinylic iodide and phenols (Scheme 1.19, eq. 1) [66]. However, extending these conditions to acyclic vinylic iodide was not successful (Scheme 1.19, eq. 2).

Scheme 1.19. Cu(I)/**L2** catalyzed cross coupling of aryl vinylic ether



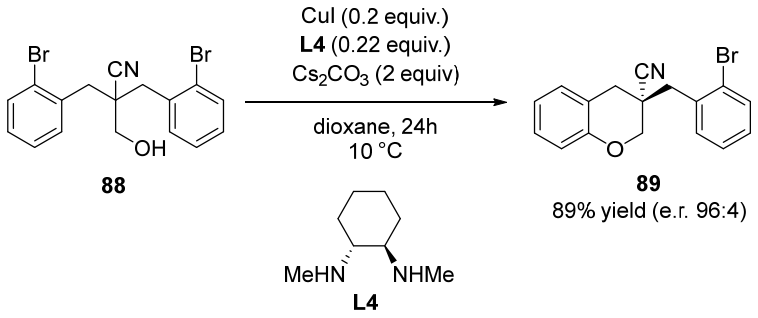
The diamine ligands have been mostly used in the Cu(I)-catalyzed C-N cross-coupling [67]. Li demonstrated the Cu(I)-catalyzed cross-coupling between amino-acid derivatives and vinylic iodides with *N,N*-dimethylethylamine **L3** and observed a positive solvent effect with dimethylethane (DME). They applied the methodology to synthesize enamide **87**, an intermediate in the total synthesis of a potent tubulin-binding agent, plocabulin[68] (Scheme 1.20).

Scheme 1.20. Cu(I)/**L3**-catalyzed cross-coupling



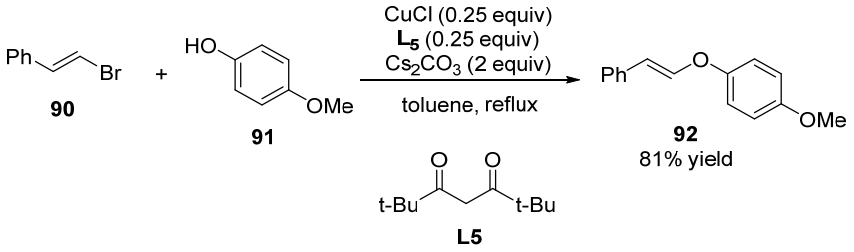
A few studies of C(sp^2)-O cross-coupling catalyzed by the diamine ligands were available[69,70]. As an example, the Cu(I) with *trans-N,N*-dimethylcyclohexane-1,2-diamine **L4** catalyzed an intramolecular cross-coupling between aryl bromide and internal primary alcohol (Scheme 1.21).

Scheme 1.21. Intramolecular cross-coupling between aryl bromide and internal alcohol



The O,O-type ligand such as di-*tert*-buty-diketone **L5** facilitated the cross-coupling between styryl bromide and phenols with CuCl salt (example in Scheme 1.22) [71].

Scheme 1.22. Cu(I)/**L5**-catalyzed cross-coupling of styryl bromide and phenols

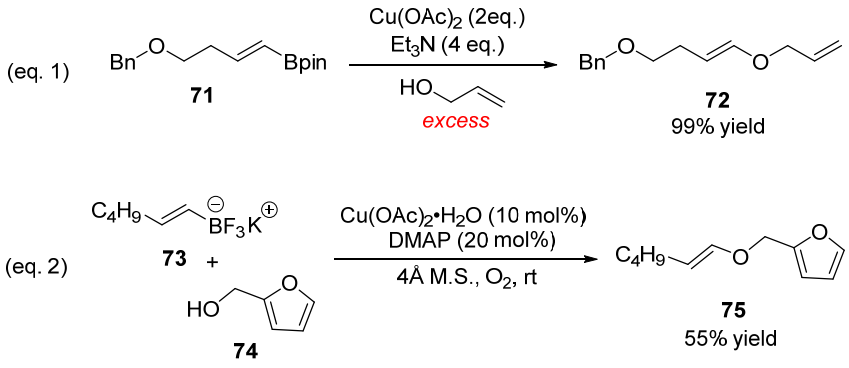


A relatively fewer number of alkyl vinylic ether synthesis via copper catalyzed cross-coupling methods were reported in the literature. They demonstrated a rather limited substrate scope, and other limitations prevented a facile synthesis of vinylic ethers with structural complexity on both sides of ether linkage.

Chan-Lam-Evans coupling is a Cu(II)-catalyzed cross coupling of vinylic boronates and allylic alcohols. An excess amount of allylic alcohol was used as the solvent (Scheme 1.23, eq. 1)[72]. This is not viable with an alcohol that is expensive and highly viscous, such as carbohydrate alcohols. Quach and Batey reported a Cu(II)-catalyzed cross-coupling from organotrifluoroborate salt and alcohols [73]. The substrate scope included both phenols and aliphatic alcohols as well as phenyl and vinylic trifluoroborate salts, albeit with a fewer number of the alkyl vinylic ethers, e.g.

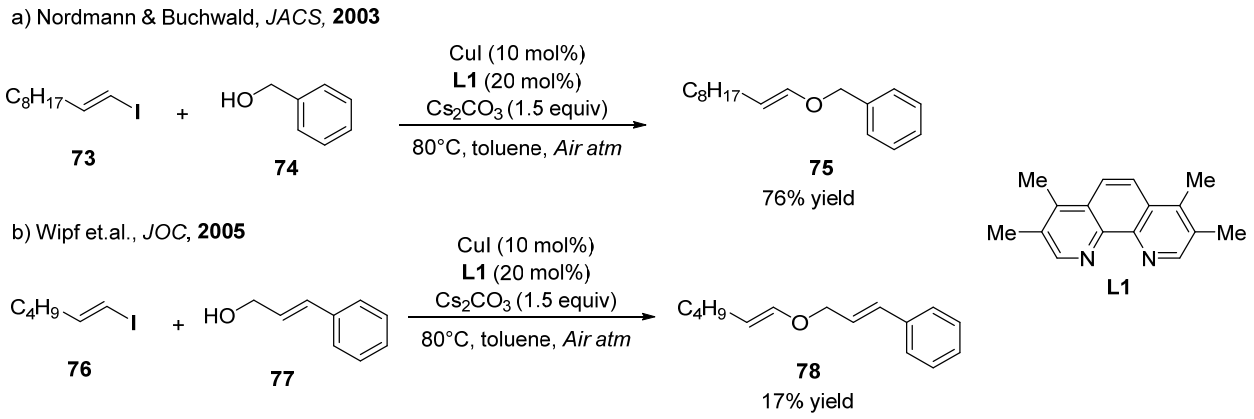
75 (Scheme 1.23, eq. 2). However, our lab could not apply this method with more challenging carbohydrate substrates (Paul Beasley, 2021-2023)[74] (San Pham, 2023-2025, *manuscript in progress*).

Scheme 1.23. Cu(II)-catalyzed cross-coupling



In 2003, the Buchwald's lab reported that Cu(I)-tetramethyl phenanthroline **L1** catalyzed the cross coupling of *E*-vinylic halides and alcohols[62]. They reported two different sets of conditions. The first set of conditions were at 120 °C that reacted allylic alcohol with tri- and tetra-substituted vinylic iodides to afford the corresponding aldehydes via a "domino C-O coupling-Claisen rearrangement". The second set of conditions were at a lower temperature of 80 °C in an *air atmosphere*. Under the second set of conditions, they demonstrated the synthesis of three 1,2-disubstituted vinylic ethers, including **75** (Scheme 1.24a). Although the reaction was stereospecific and high yielding in the original paper, it was not reproducible as the Wipf lab obtained only 17% yield of allylic vinylic ether **78** (Scheme 1.24b).

Scheme 1.24. Cu(I)/**L1**-catalyzed cross-coupling of vinylic iodides and aliphatic alcohols

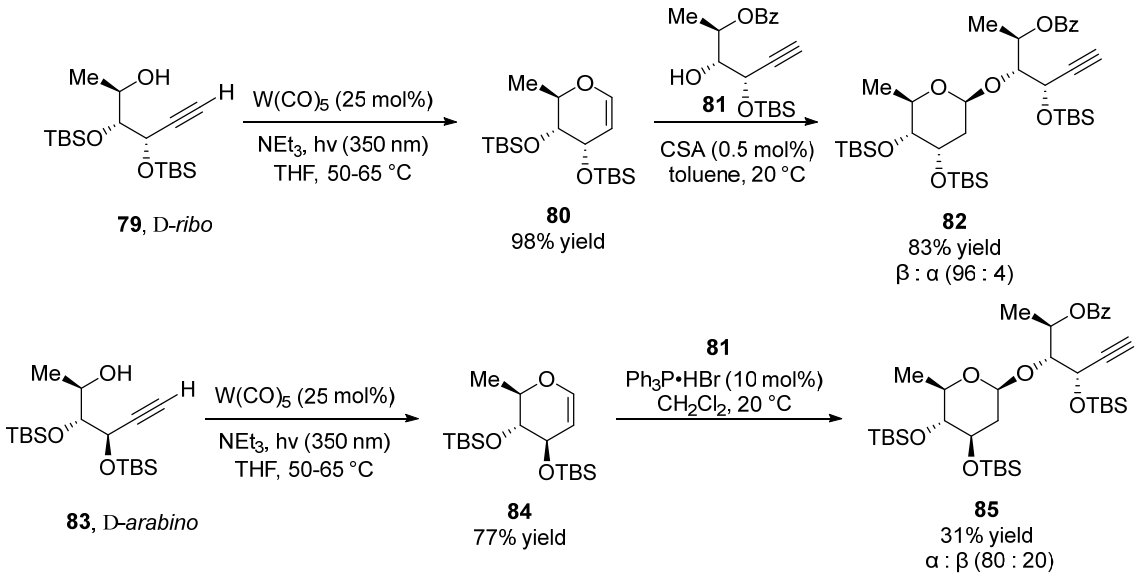


1.3 Motivation

1.3.1 Previous studies on oxacyclization from the McDonald's lab

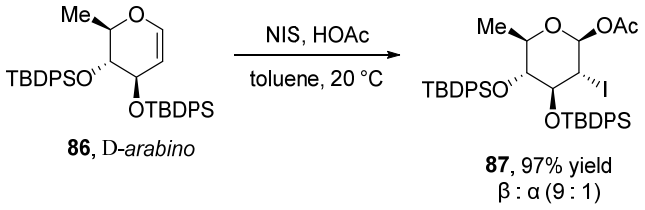
The McDonald's group has been long interested in oxacyclization of acyclic alkynols to form pyranosyl 1,2-glycals[75–77]. In 2000, our group reported the tungsten catalyzed cycloisomerization of alkynols to synthesize 6-deoxy-1,2-glycals, a class of cyclic vinylic ethers (Scheme 1.25). The resulting 1,2-glycals were subjected to acid-catalyzed intermolecular glycosylation with alkynol glycosyl acceptor to directly make 2,6-dideoxyglycosides with a varying degree of diastereoselectivity [77]. When D-ribo-glycal **80** was treated with CSA, β-diastereomer **82** as a major product with the d.r. of 96 : 4. However, acid-catalyzed glycosylation of D-arabino-glycal **84** proceeded with a much slower rate with CSA. When triphenylphosphonium hydrogen bromide was used with **84**, the reaction rate improved, but the stereoselectivity and yield were lower than the reaction with **80**.

Scheme 1.25. Cycloisomerization of alkynol followed by acid-catalyzed glycosylation



They circumvented this problem by treating TBDPS protected D-arabino glycal **86** in NIS-promoted glycosylation. When glycal **86** was treated with NIS and acetic acid, 2-iodo-6-deoxyglycoside **87** was synthesized in d.r. β : α of 9 : 1 (Scheme 1.26). Dehalogenation of compound **87** would afford a corresponding 2,6-dideoxyglycoside.

Scheme 1.26. Iodoacetate formation from *arabino* diastereomer **86**



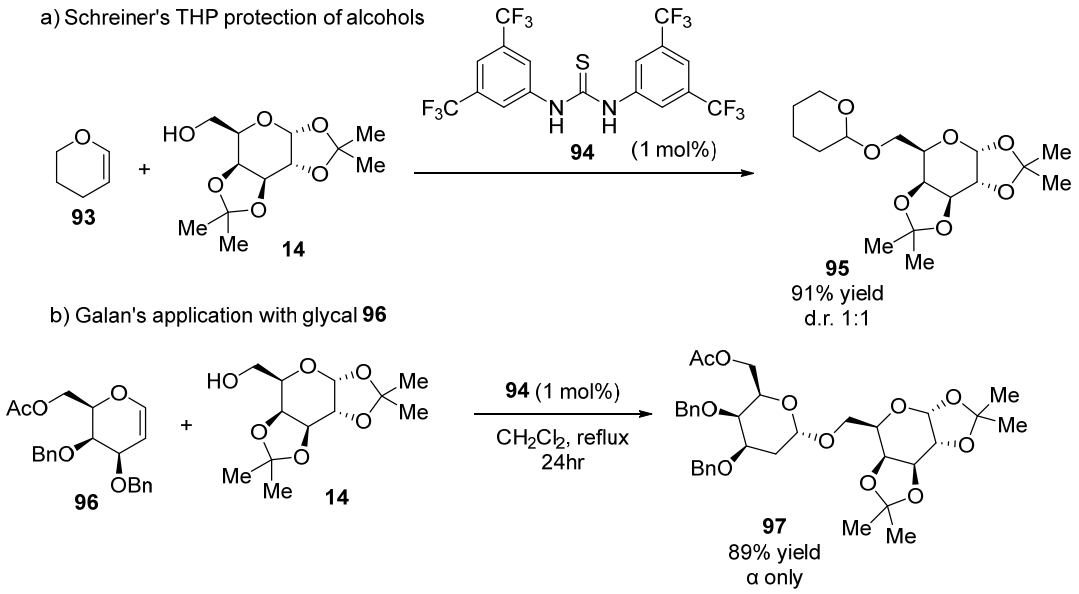
Our group demonstrated the versatility of this approach involving the tungsten catalyzed cycloaddition in combination with the acid-catalyzed glycosylation in the synthesis of various carbohydrates, including digoxin trisaccharide glycal [78], L-oliose trisaccharide [79], C-glycoside substructure of Altromycin B [80], and disaccharide glycal substructure of Saccharomicin [81].

1.3.2 Acid-catalyzed glycosylation

Several achiral acids have demonstrated the acid-catalyzed glycosylation [17]. Our group used the catalytic amount of triphenylphosphnium hydrogen bromide (PPh_3 • HBr) in the intermolecular reaction between 1,2-glycals and the glycosyl acceptor (Scheme 1.25 in section 1.3.1) [77].

Schreiner pioneered the use of thiourea **94** in the protection of alcohol with a tetrahydropyran (THP). The resulting THP-protected ether contains cyclic acetal moiety resembling the glycosidic linkages. In fact, he showed the formation of a glycosidic linkage between bis-acetonide galactose **14** and glycal **93** (Scheme 1.27a). Galan group applied the thiourea-catalyzed THP protection method to synthesize 2-deoxyglycoside **97**. The reaction was highly α-stereoselective (Scheme 1.27b) [82].

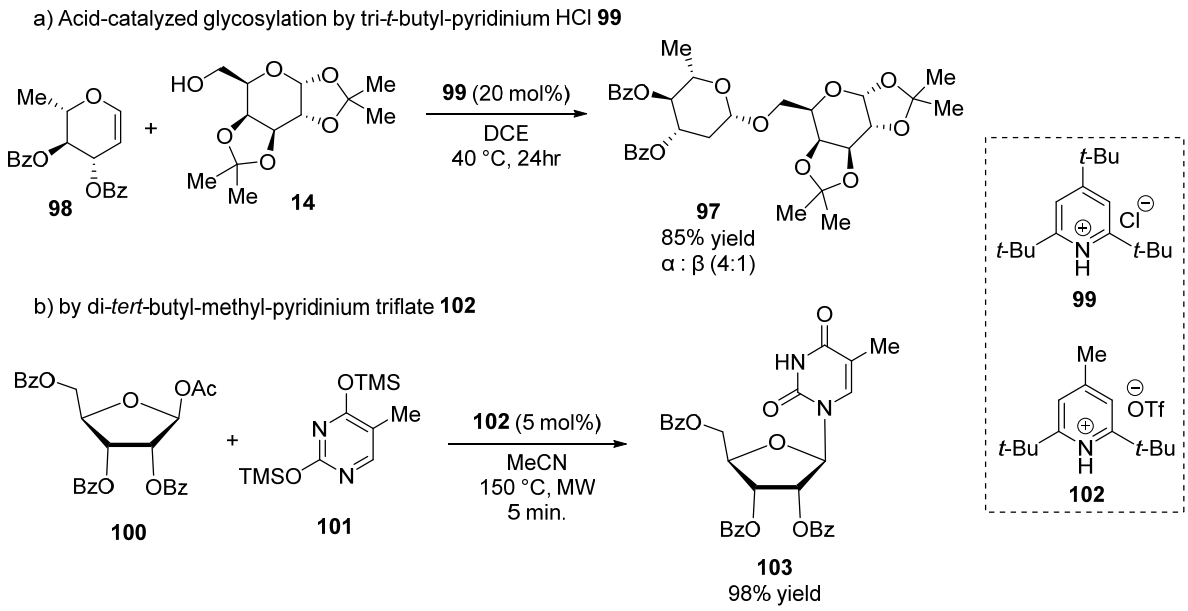
Scheme 1.27. Thiourea **94** acid-catalyzed reaction between cyclic vinylic ethers and alcohols



Tri-*tert*-butyl-pyridinium HCl **99** has shown to catalyze glycosylation between 1,2-glycals and various glycosyl acceptors (Scheme 1.28a) [83]. The more affordable pyridinium salt from di-

tert-butyl-pyridinium **102** catalyzed glycosylation of nucleoside in a one-flow multi-step synthesis (Scheme 1.28b) [84].

Scheme 1.28. Acid-catalyzed glycosylation with substituted pyridinium salts



1.3.3 This project

The overall objective of this project was to demonstrate the electrophile-promoted intramolecular oxacyclization of acyclic hydroxy vinylic ethers. The working hypothesis was that the intramolecular reaction provides high effective concentrations of alcohol and vinylic ether, so the resulting stereoinduction in the reactive conformation would lead to stereoselective formation of glycosides. Mechanistic proposals from intermolecular reactions with 1,2-glycals suggest that acid catalyst may first hydrogen bond with alcohol nucleophiles [83]. In case with vinylic ether substrate **104**, the hydrogen bonding between the acid and internal hydroxy group may promote the formation of ion pair **105** to form C-O bond of glycoside **106** (Figure 1.5).

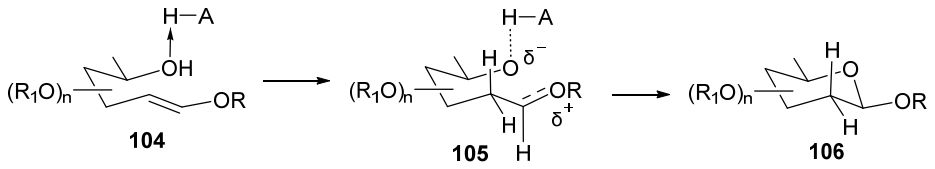


Figure 1.5. Proposed highly stereoselective oxacyclization via hydrogen bonding

The different protecting groups on O3-O4 may lead to different stereoselectivity. For example, a conformation of vinylic ether **107** with synclinal substituents exposes the *re* face of vinylic ether to activated alcohol, resulting in the formation of β-glycoside **108** (Figure 1.6). A protecting group such as an acetal moiety enforces this conformation at O3-O4. Meanwhile, sterically bulky silyl protecting group may force antiperiplanar conformation of O3-O4, exposing the *si* face of vinylic ether to the activated alcohol, giving α-glycoside **111**.

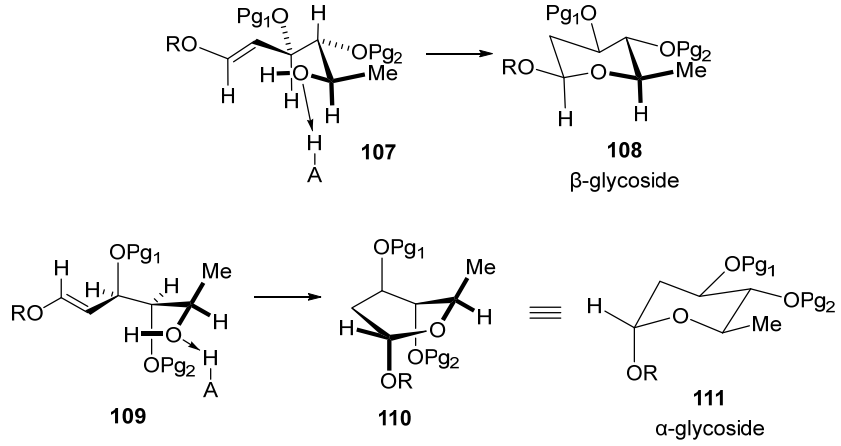
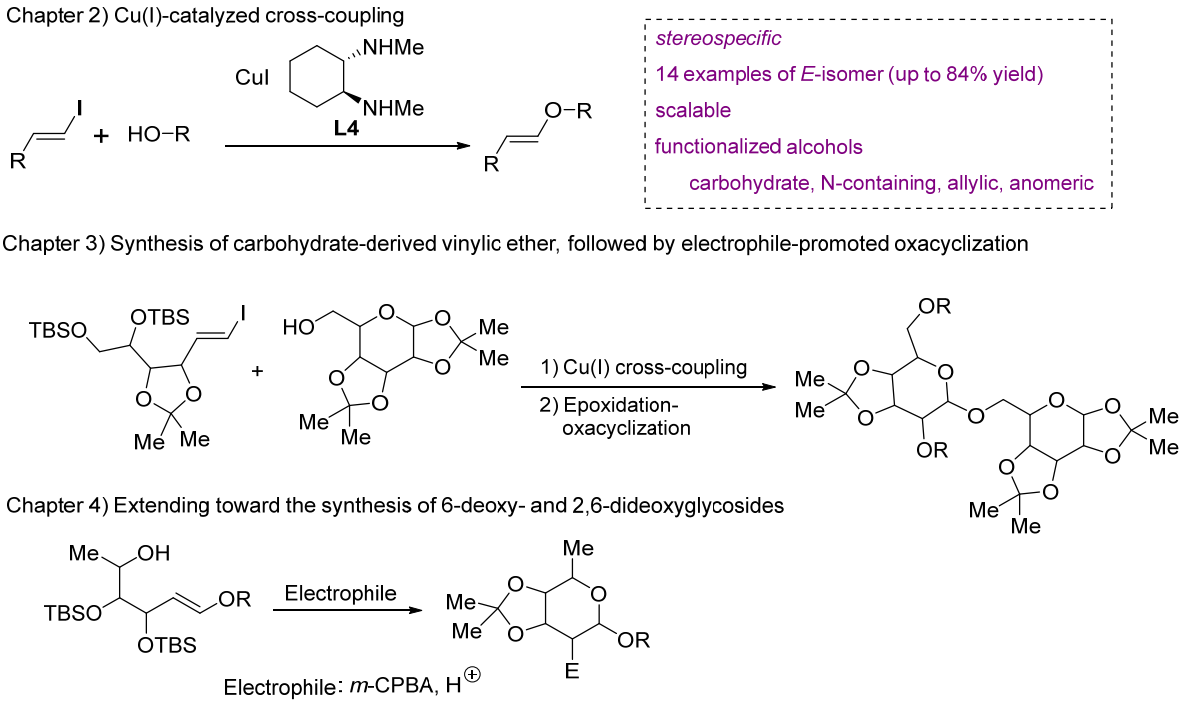


Figure 1.6. Possible conformations for oxacyclizations

The overall objective of this project was to demonstrate the electrophile-promoted intramolecular oxacyclization of acyclic hydroxy vinylic ethers. However, a gap had been presented in the efficient synthetic methods of vinylic ether that can serve as an intermediate in intramolecular oxacyclization (section 1.2).

To address this gap, we developed an efficient Cu(I)-catalyzed cross-coupling vinylic ethers from vinylic halides and aliphatic alcohols (Chapter 2) (Scheme 1.29). We successfully applied the cross-coupling methodology in the synthesis of carbohydrate-derived acyclic vinylic ethers, followed by an electrophile-promoted oxacyclization to synthesize disaccharides (Chapter 3). Finally, we strived to extend this approach toward the synthesis of 6-deoxy and 2,6-dideoxyglycosides (Chapter 4).

Scheme 1.29. Overview of this dissertation



Chapter 2 Cu(I)-catalyzed cross-coupling synthesis of vinylic ethers

2.1 Introduction

Vinylic ethers are electron-rich alkenes that are versatile intermediates for various chemical transformations, including the inverse-demand Diels-Alder cycloaddition, Claisen rearrangement, HAT cyclization, and electrophile-promoted oxacyclization of carbohydrate-derived vinylic ethers (discussed in Chapter 1) [45,46]. However, these chemical transformations have been restricted to simple vinylic ethers due to difficulty in synthesizing vinylic ethers with complex structures on both sides of the ether linkage.

In this chapter, I will discuss our efforts in developing an efficient Cu(I)-catalyzed cross-coupling method in the synthesis of vinylic ethers with structural complexity.

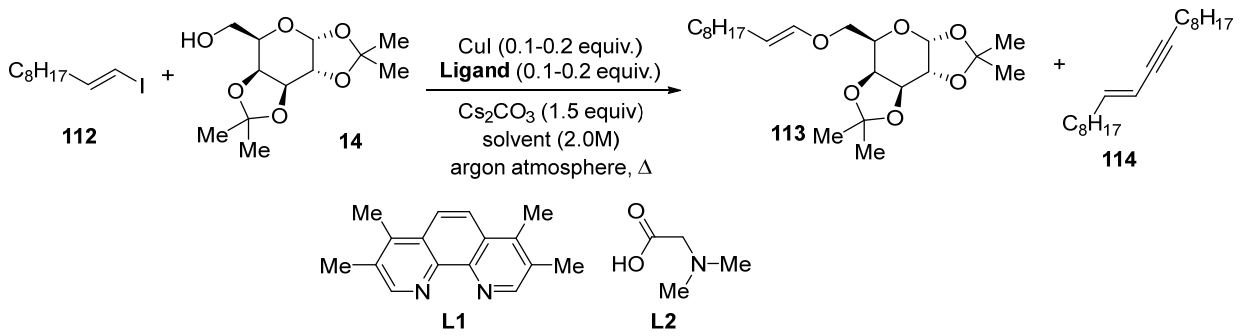
2.2 Results and discussion

2.2.1 Optimization

The substrates for the model study were simple vinylic iodide *E*-iododecene **112** and structurally complex galactose alcohol **14**. Initially, I obtained the desired *E*-vinylic ether **113** in 16% yield via Cu(I) catalyst with tetramethyl-phenanthroline ligand **L1** under air. The major side product, enyne **114** was formed. When I replaced the air with the argon, the yield of vinylic ether **113** increased only slightly (34% yield) with the formation of **114** in 18% conversion.

The initial solvent screening demonstrated that tetraglyme was the superior solvent, and the vinylic iodide consumption was faster (Table 2.1, entry 1-3). However, the overall yield did not change. The anionic ligand *N,N*-dimethylglycine **L2** resulted in a higher yield at lower temperature than **L1** (entry 4 vs. 5). However, the overall recovery of vinylic components (vinylic ether + recovered vinyl iodide) was not improved. After adjusting the reagent amounts, an almost equimolar mixture of **112** and **14** gave a higher percentage of vinylic component when stirred for a longer period (45 hrs) (entry 6).

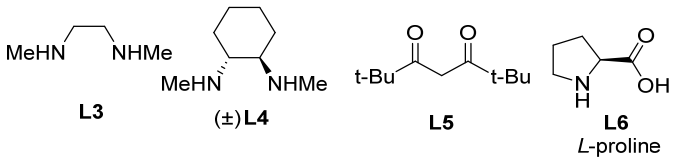
Table 2.1. Initial optimization with a model system



Entry	**112** : **14** (eq.)	Solvent	CuI/**L** (mol%)	T (°C)	t (hr)	% Yield **113**	% **112** to **114**	% **112** Rec.
1	1 : 2	*o*-xylene	10/20 **L1**	120	39	31	18	None
2	1 : 2	DMF	10/20 **L1**	120	40	30	18	None
3	1 : 2	Tetraglyme	10/20 **L1**	120	21	35	20	None
4	1 : 2	Tetraglyme	10/20 **L1**	80	21	20	11	18
5	1 : 2	Tetraglyme	10/20 **L2**	80	17	46	5	None
6	1.2 :1	Tetraglyme	10/10 **L2**	80	45	62	<5	29

I screened additional ligands, including the ligands used in the Cu(I)-catalyzed C(sp^2)-O cross-coupling (**L3-L6**) (section 1.2.3). However, the reaction rates were slower, and none of them showed improvements in yield or conversion (Table 2.2).

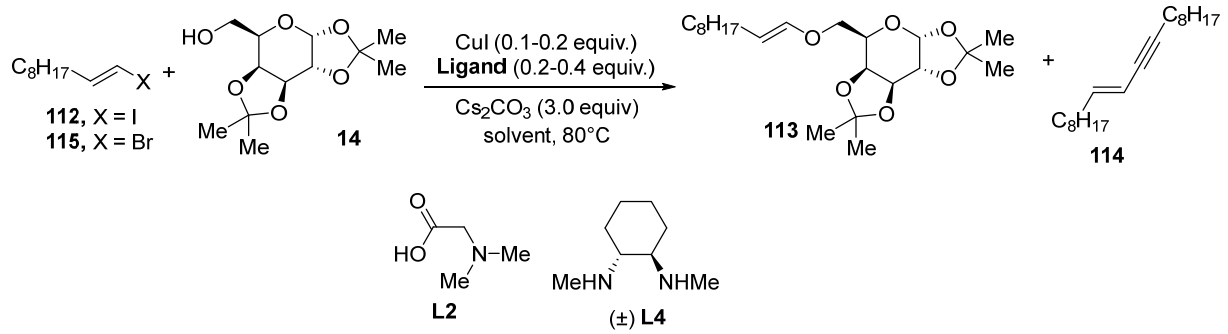
Table 2.2. Ligand screening



Entry	**112** : **14** (eq.)	Solvent	CuI/**L** (mol%)	t (hr)	% Yield **113**	% **112** to **114**	% **112** Rec.
1	1.2 : 1	Tetraglyme	10/20 **L3**	41	51	< 1	24
2	1.2 : 1	Tetraglyme	10/20 **L4**	41	54	ND	23
3	1.2 : 1	Tetraglyme	10/10 **L5**	40	26	< 5	49
4	1.2 : 1	Tetraglyme	10/10 **L6**	41	39	< 5	36

Although I was able to increase the yield of vinylic ether **113** to 78% when I increased the amount of Cs_2CO_3 and the catalyst loading (Table 2.3, entry 1), we did not proceed with **L2** for screening the substrate scope. San Pham (Emory, 2021-2023) discovered that only the corresponding *Z*-enyne byproduct was formed under **L2**-catalyzed conditions while (±)-N,N,-dimethyl-diamino-cyclohexane **L4** in DME resulted in the desired *Z*-vinylic ethers as the major compound. The ligand (±)-**L4** was also compatible with the *E*-isomer, resulting in 75% yield of *E*-vinylic ether with no detectable amount of enyne **114** (Table 2.3, entry 2) [85]. Decreasing the catalyst loading and the amount of base resulted in a lower yield with a recovery of some vinylic iodide (entry 3). Using *E*-bromodecene instead of iododecene resulted in the desired vinylic ether **113** in a lower yield, 57% yield (entry 4). The two control experiments confirmed that CuI and **L2** are necessary to ensure an optimal result (entry 5 and 6).

Table 2.3. Final optimization



Entry	**112** : **14** (eq.)	Solvent	CuI/L (mol%)	t (hr)	% Yield **113**	% **112** to **114**	% **1112** Rec.
1	1:1	Tetraglyme (2 M)	20/20 **L2**	48	78	2	ND
2[a]	**1:1**	DME (0.7M)	20/40 (±)-**L4**	48	75	ND	ND
3[b]	**1:1**	DME (0.7M)	10/20 (±)-**L4**	41	62	ND	10
4	**(115) 1:1**	DME (0.7M)	10/20 (±)-**L4**	41	57	ND	ND
5	**1:1**	DME (0.7M)	0/40 (±)-**L4**	48	ND	ND	Rec.
6	**1:1**	DME (0.7M)	10/0 (±)-**L4**	48	17	ND	57

ND = not detected. [a] 1.0 g of **3** formed. [b] Cs_2CO_3 (2 equiv)

2.2.1.1 Proposed mechanism

The proposed mechanism of Cu(I)-catalyzed cross-coupling between aryl synthons involves the coordination of alcohol to the copper, oxidative addition of aryl halide to Cu(I), and reductive elimination of Cu(III) complex to form C(sp^2)-O bond and regenerate Cu(I) catalyst[86–88]. Due to low acidity of aliphatic alcohols relative to phenols, we hypothesized that oxidative addition of vinylic iodide may occur prior to alcohol coordination (Figure 2.1). The reductive elimination from the Cu(III) complex forms the C-O bond in the vinylic ether and regenerates Cu(I) catalyst.

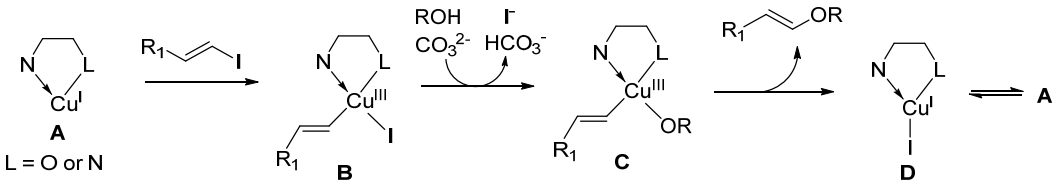


Figure 2.1 Proposed mechanism of Cu(I)-catalyzed cross-coupling

The enyne formation would most likely occur via Cu(I)-catalyzed Sonogashira cross-coupling [89,90] (Figure 2.2). The alkyne could be generated via β-hydride elimination of the complex **E.** The alkyne coordinates with the ligated Cu(I) complex. The oxidative addition of vinylic iodide gives a penta-coordinated Cu(III) complex **G**. The reductive elimination from complex **G** forms enyne and regenerates Cu(I) catalyst.

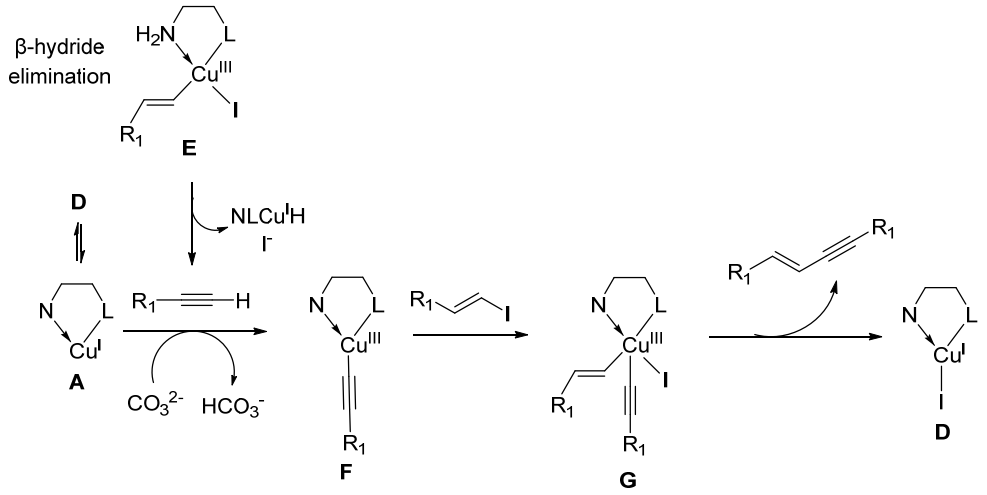


Figure 2.2 Proposed mechanism of enyne formation via Sonogashira cross-coupling

2.2.2 Substrate scope

Fourteen *E*-vinylic ethers have been reported in our publication. Vinylic ethers from primary alcohols were synthesized by using equimolar mixture of vinylic iodide and the alcohols (Figure 2.3) [85]. The corresponding *E*-vinylic ethers were synthesized in good–

high yields with primary alcohols, including hydroxylated alcohols (**116** and **117**), oxetane (**118**), and weak nucleophilic trifluoroethanol (**119**). The Cu(I)/**L4** cross-coupling of propargylic alcohol and allylic alcohol afforded the vinylic ethers (**120** and **121**) in higher yields than previously reported cases [62,91]. The N-containing alcohols were also compatible with the cross-coupling reaction with their respective N-protecting groups (Boc group in **122**) and (imine in **123**, synthesized after publishing ref. **85**) intact.

The cross-coupling with the secondary alcohols required 2 equiv of the alcohols and generally resulted in lower yields than the primary alcohols (Figure 2.1B). The cross-coupling of secondary alcohols with sterically bulky substituents afforded vinylic ethers (**125** and **126**). The tertiary amine-containing cyclohexanol gave a higher yield than cyclohexanol (**124** vs. **127**). Homoallylic alcohols were compatible as well (**128** and **129**). The reducible anomeric alcohols were also suitable with this cross-coupling reaction, albeit with lower yields (**130** and **131**), synthesized after publishing ref. **85**).

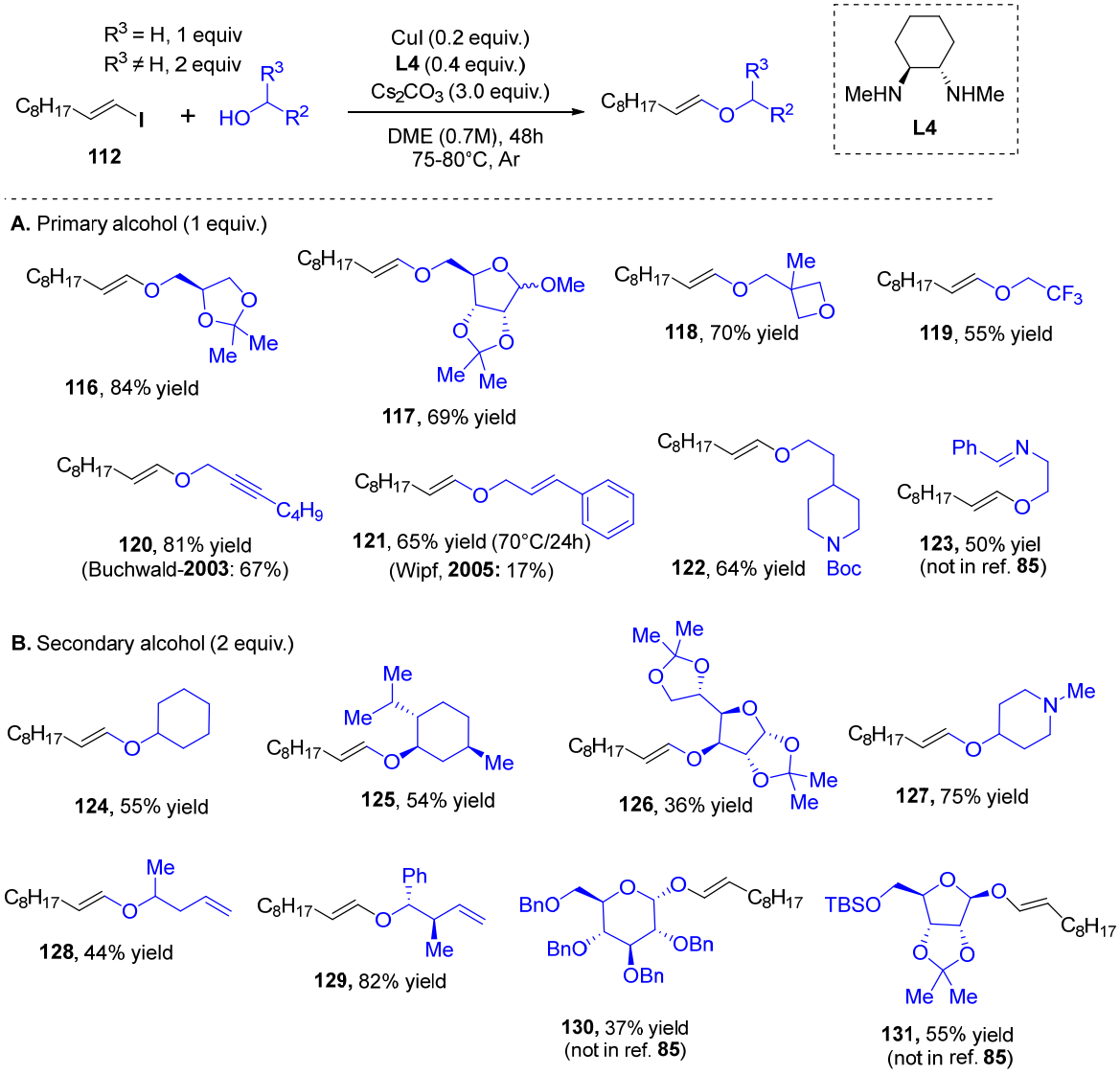


Figure 2.3. Substrate scope of vinylic ethers via Cu(I)/**L4**-catalyzed cross-coupling

Structurally complex vinylic iodides were also successfully coupled with the galactose alcohol, although the yield of cyclohexyl vinyl ether **133** was low (Figure 2.4).

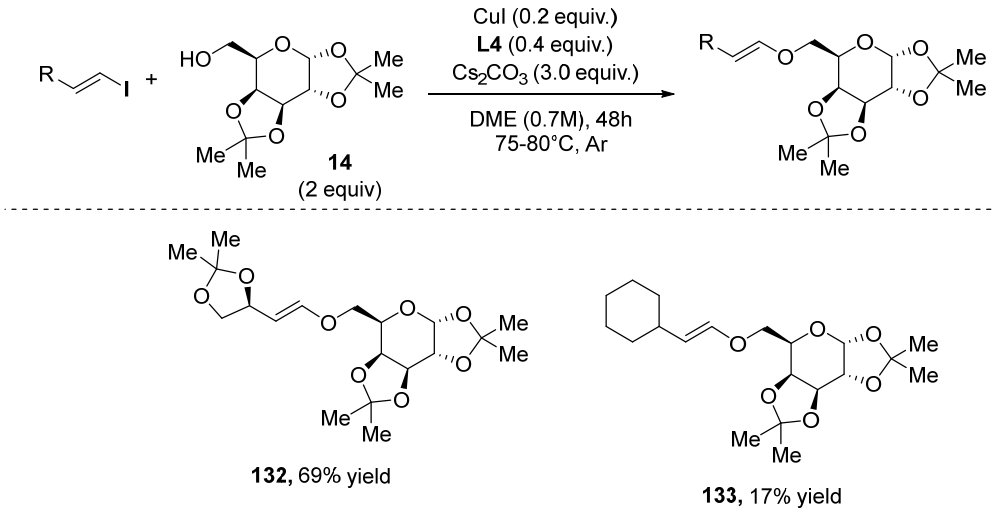
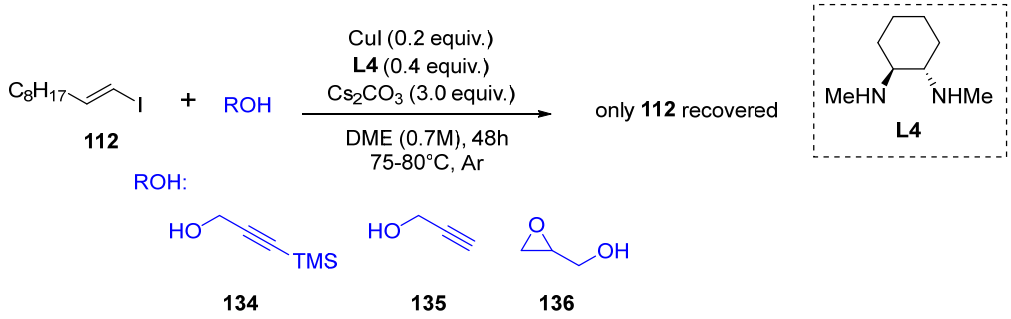


Figure 2.4. Substrate scope of vinylic iodides

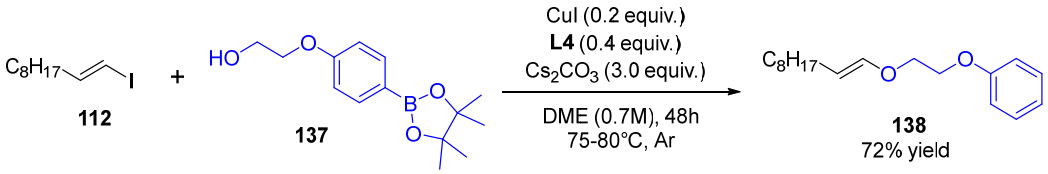
Some of the alcohols we examined gave subpar results. For these substrates, only 1 equiv. of alcohols was used since they were primary alcohols, and the coupling partner was *E*-iododecene. Terminal propargylic alcohols **134** and **135** were degraded under the basic conditions (Scheme 2.1). Oxirane methanol **136** was polymerized under the basic conditions. Only iododecene **112** was recovered from these reactions.

Scheme 2.1. Base-reactive alcohol substrates



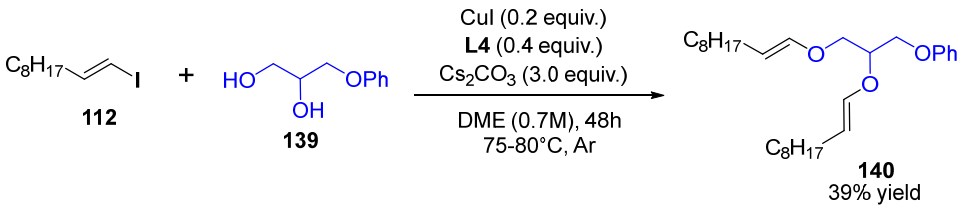
In case of alcohol with aryl boronate **137**, the cross-coupling was successful, but the Bpin moiety was removed via protodeboronation, resulting in the vinylic ether **138** in 72% yield (Scheme 2.2).

Scheme 2.2. Synthesis of **138** resulting from protodeboronation



When 1,2-hydroxy-propyl-phenoxide **139** was reacted under the standard conditions, divinylation occurred, resulting in **140** in 39% yield. When the reaction was repeated at a lower temperature for a shorter period (60 °C/ 19hr), a mixture of monovinylated regioisomers formed in 25% yield (Scheme 2.3).

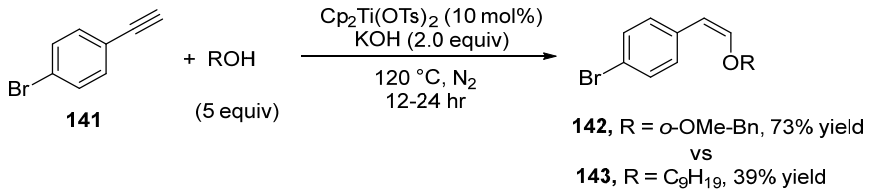
Scheme 2.3. Cross-coupling of diol **139**



2.3 Concurrent methods of vinylic ether synthesis

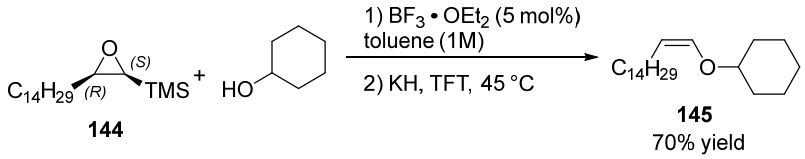
Different groups published their vinylic ether synthesis after we published our findings in 2023. Li group reported titanium-catalyzed anti-Markovnikov hydroalkoxylation of alkyne to afford Z-vinylic ethers [92]. It was notable that the reaction was highly stereoselective, but the scope of this reaction used an excess of alcohols. The substrate scopes of alkynes included only phenylacetylenes. The yields were higher for alcohols with the electron-donating aryl substituents than the alcohol with a longer alkyl chain (**142** vs. **143**) (Scheme 2.4).

Scheme 2.4. *Z*-vinylic ether synthesis via titanium-catalyzed anti-Markovnikov hydroalkoxylation of alkyne



Golding group reported a synthesis of *Z*-vinylic ethers via Peterson elimination of 1-alkoxy-2-hydroxyalkylsilane, which was formed by opening the TMS-substituted epoxide **144** under Lewis acidic conditions [93]. Although it was noteworthy that the substrate scope included a few secondary alcohols, this indirect approach used a harsh condition for the elimination step, which restricted the substrate scope.

Scheme 2.5 Indirect synthesis of *Z*-vinylic ethers



2.4 Conclusion

In conclusion, we developed a stereoselective synthesis of structurally complex vinylic ethers via Cu(I)-catalyzed cross-coupling reaction under mild conditions. This methodology is efficient and applicable to various aliphatic alcohols, including hydroxylated alcohols, N-containing alcohols, allylic, homoallylic, internal propargylic alcohols, secondary alcohols with bulky substituents, and anomeric alcohols. It will be a useful tool for synthetic chemists to diversify the vinylic ether intermediates in various chemical transformation, such as the synthesis of chromanes via inverse-demand Diels-Alder cycloaddition, γ,δ-unsaturated carbonyl

compounds via Claisen rearrangement, and substituted morpholines via reductive HAT cyclization (discussed in Chapter 1).

Next, we demonstrated that this methodology enabled the synthesis of carbohydrate-derived vinylic ethers directly from commercially available bis-acetonide galactose alcohol **14**. The carbohydrate-derived vinylic ethers served as intermediates in the electrophile-promoted intramolecular oxacyclization to afford disaccharides. The details of this research will be discussed in Chapter 3.

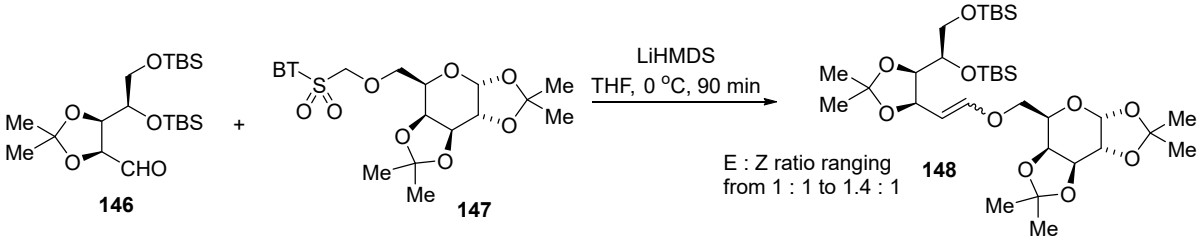
Chapter 3 Non-traditional approach toward disaccharides via acyclic vinylic ether intermediates

3.1 Background

The overall goal of this research was to synthesize glycosides via oxacyclization of carbohydrate-derived acyclic vinylic ethers. This approach was first pioneered by Suzuki and Mukaiyama in 1982 and further explored by Nicotra and Sinaÿ [36,37,39–41]. However, this approach has been underdeveloped due to a lack of efficient method to synthesize acyclic vinylic ethers with structural complexity on both sides of ether linkage (discussed in Chapter 1).

In 2021, Eric Meindl of our group utilized Julia-Lythgoe-Kocienski olefination to obtain a vinylic ether from the carbohydrate-derived synthons **146** and **147** (Scheme 3.1). However, Julia olefination resulted in poor *E/Z* stereoselectivity, and the mixture of diastereomers were difficult to separate [42]. Additionally, the synthesis of sulfone **147** from galactose alcohol **14** was challenging and required 4 steps, including temperature-sensitive oxidation step to form sulfone. Although synthesizing **146** was straightforward, it still required 3 steps from D-lyxose.

Scheme 3.1 Synthesis of vinylic ether **148** via Julia-Lythgoe-Kocienski olefination



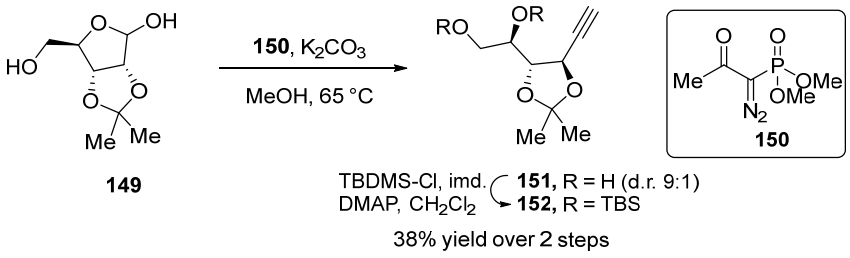
Addressing the gap in the efficient synthesis of vinylic ethers, we sought a stereospecific synthesis of *E* and *Z*-vinylic ethers via Cu(I) catalyzed C-O cross coupling [85]. Our development of this methodology is detailed in Chapter 2. We had envisioned this cross-coupling methodology to enable the synthesis of carbohydrate-derived vinylic ethers, which would undergo substrate-controlled diastereoselective epoxidation and stereospecific *anti*-oxacyclization to form disaccharides. This chapter discusses our efforts to extend the scope of Cu(I) cross-coupling to carbohydrate-derived synthons and subsequent synthesis of disaccharide via *m*-CPBA promoted oxacyclization.

3.2 Results and Discussion

3.2.1. Synthesis of vinylic iodides from monosaccharide building blocks

Commercially available furanose, such as acetonide protected D-ribofuranoside **149**, can be homologated to give the corresponding alkyne (Scheme 3.2). I initially used the Bestmann-Ohira reagent **150**, which epimerized and resulted in D-arabino-diastereomer **151** (d.r. 9:1) [94,95].

Scheme 3.2 Seyferth-Gilbert Homologation of **149**



Epimerization occurs due to the basic reaction conditions required for *in-situ* generation of diazophosphonate from **150**. The base deprotonates the α proton and forms an enolate and destroys the chiral center adjacent to the aldehyde (Figure 3.1).

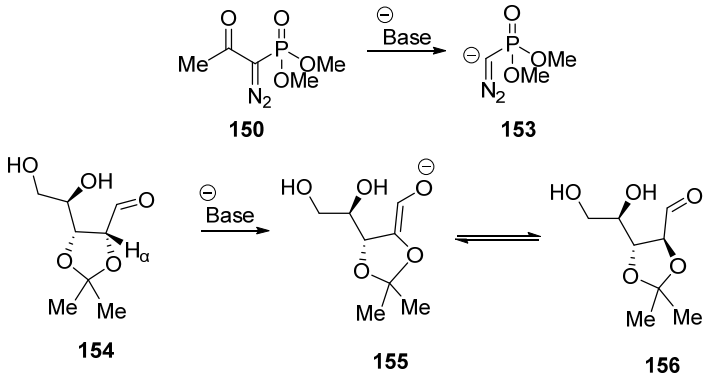
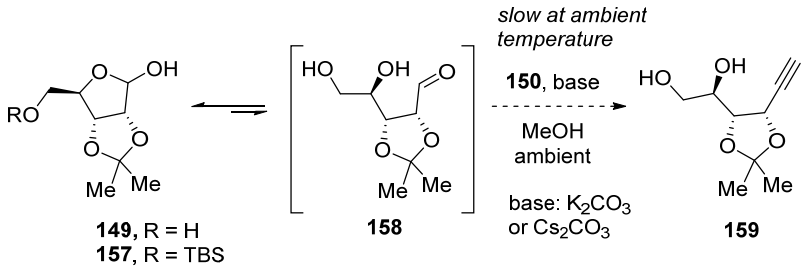


Figure 3.1 Enolate formation in the basic conditions

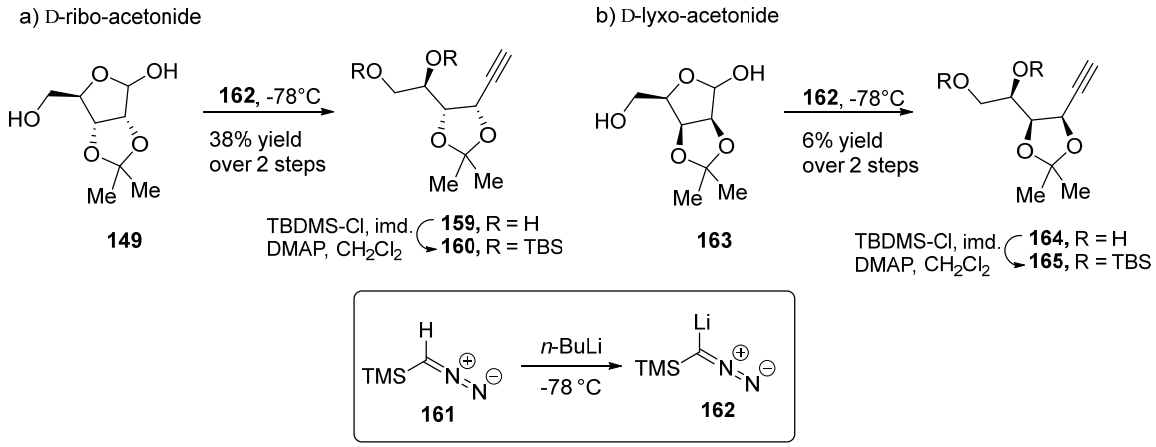
In the pursuit of synthesizing ribo-alkyne **159**, several attempts were made to facilitate the reaction at room temperature (Scheme 3.3). Only a trace amount of alkynes formed when the reaction was conducted at room temperature even after adding extra equivalents of **150** and K_2CO_3 sequentially for 3 days. Changing the base from K_2CO_3 to more basic Cs_2CO_3 or reacting TBS protected lactol **157** did not improve the result. This lack of reactivity is likely due to lactol-aldehyde equilibrium that disfavors the aldehyde **158** [96–98], which is the reactive species in the homologation.

Scheme 3.3. Attempts to homologate D-ribo-alkyne without epimerization



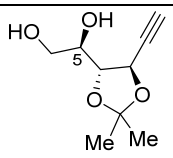
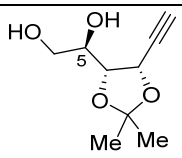
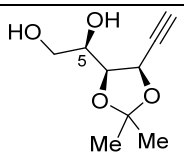
As an alternative for alkyne synthesis, Colvin homologation uses trimethylsilyl diazomethyllithium **162** as the one-carbon source and avoids using basic solution of methanol[96,99]. We treated ribo-lactol **149** with **162** at -78 °C, which produced ribo-alkyne **159** as a single isomer without epimerization (Scheme 3.4a). The alkynylation of D-lyxo-lactol **163** with trimethylsilyl diazomethyllithium **162** was slow and low-yielding, but it provided enough materials to proceed, so it was not optimized (Scheme 3.4b). The unreacted lactol **163** was recovered from the crude mixture by column chromatography.

Scheme 3.4 Colvin homologation of lactol **149** and **163**



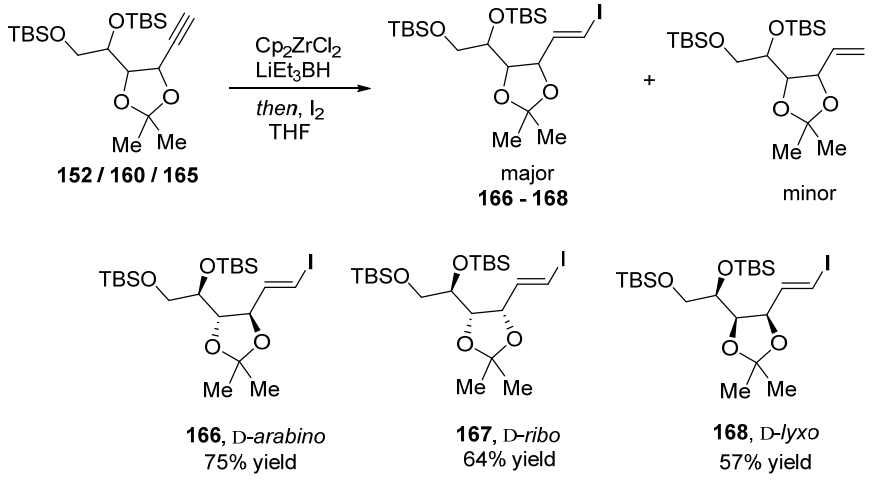
The alkynyl diol diastereomers **151**, **159**, and **164** followed a trend previously established for the relative chemical shifts for H5 [95] (Table 3.1). The chemical shifts for H5 of ribo- and lyxo-diastereomers **159** and **164** were deshielded (higher than 4.00 ppm) relative to the arabino-diastereomer **151** (lower than 4.00 ppm). Additionally, acetonide methyl chemical shifts exhibited greater separation for alkynes **159** and **164**, relative to **151**.

Table 3.1 Trends in δ_H (ppm) for alkynyl diol diastereomers in $CDCl_3$

	 **151,** D-arabino	 **159,** D-ribo	 **164**, D-lyxo
H5	3.92 (dt, *J* = 6.0, 4.5 Hz)	4.05 (ddd, *J* = 8.7, 5.3, 3.3 Hz)	4.06 (ddd, *J* = 6.8, 5.2, 3.6 Hz)
Me/Me	1.51 / 1.44 ($\Delta\delta_H$ = 0.07)	1.57 / 1.38 ($\Delta\delta_H$ = 0.19)	1.52 / 1.35 ($\Delta\delta_H$ = 0.17)

After protecting the diols with TBS group, each alkyne was treated with hydrozirconation-iodination to synthesize the corresponding *E*-vinylic iodides **166 - 168** in moderate to high yields. About 10-15% of corresponding terminal alkenes formed, which were carried onto the cross-coupling reactions. The *in-situ* formation of Cp_2ZrHCl by treating Cp_2ZrCl_2 with a hydride can generate Cp_2ZrH_2 from over-reduction, which can react with the vinylic zirconium intermediate to form terminal alkenes.

Scheme 3.5 Hydrozirconation-iodination of alkynes



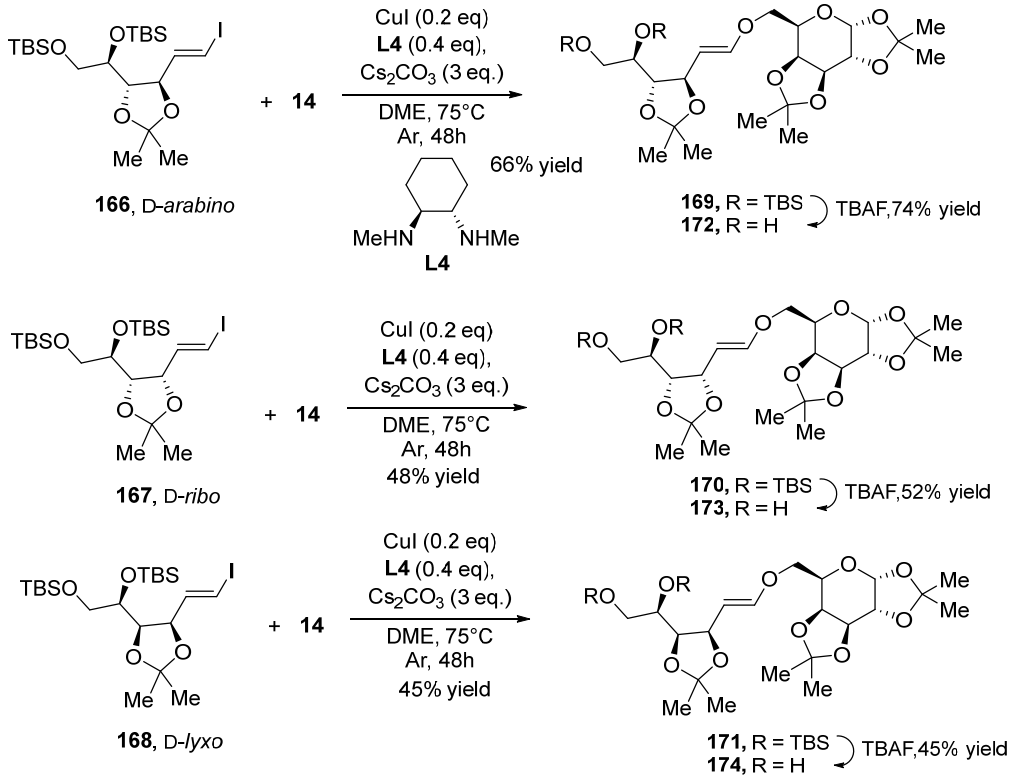
3.2.2 Vinylic ethers via Cu(I) catalyzed cross-coupling

The C-O cross coupling between each of the three *E*-vinylic iodides **166-168** and galactose alcohol **14** (2 equiv) were successful under our conditions: CuI (0.2 equiv), CyDMEDA (**L4**, 0.4 equiv), Cs_2CO_3 (3 equiv) in DME at 80 °C, affording the desired *E*-vinylic ethers **169-171** in moderate yields. The moderate yields might be due to the formation of enyne by-products. Although the enyne by-product was not formed with arabino-vinylic ether **169**, approximately 20% of enyne by-product formed with ribo-vinylic ether **170**, which accounted for 40% of vinylic iodide **167.** The exact yield of enyne by-product was not quantified for the lyxo-diastereomer, but it was presented in the crude mixture of lyxo-vinylic ether **171**. The diagnostic alkene peaks of enyne **175** and **176** had coupling constants of 15.8-15.9 Hz, which were comparable to that of previously synthesized simple enyne **114** (Figure 3.2).

Despite the moderate yields, this is the first example of stereoselective C-O cross coupling synthesis of vinylic ethers with structural complexity on both sides of the ether linkage. This direct synthesis from the alcohol was operationally simple, and the purifications of crude mixtures were straightforward with triethylamine treated silica gel.

The deprotection of TBS groups was straightforward with tetrabutyl ammonium fluoride (TBAF) and afforded the dihydroxy vinylic ether intermediates for the subsequent electrophile-promoted oxacyclization step.

Scheme 3.6 The synthesis of acyclic vinylic ethers via Cu(I)/**L4** catalyzed C-O cross-coupling



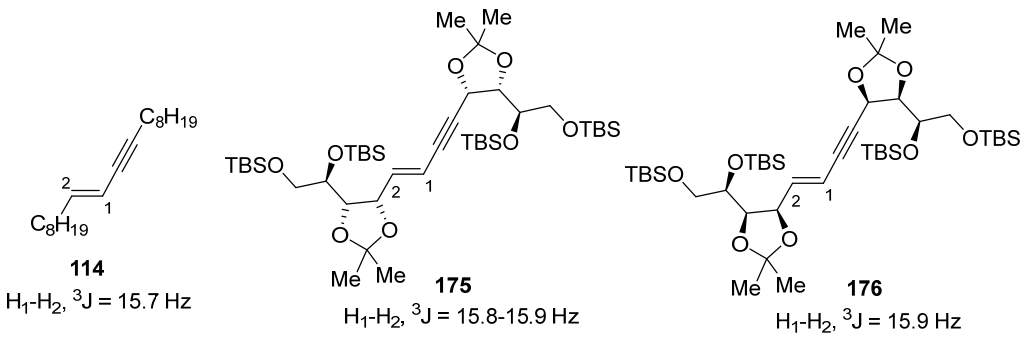


Figure 3.2 Comparison of ^{3}J of H1-H2 in enyne by-products

3.2.3. Electrophile promoted oxacyclization of carbohydrate-derived vinylic ethers

3.2.3.1. Proposed mechanism

We hypothesized that epoxide **A** would form *in-situ* when we treated a dihydroxy vinylic ether with *m*-CPBA. The subsequent intramolecular oxacyclization would undergo a stable 6-membered transition state, which would promote a nucleophilic attack of O5 to C1 and form pyranoside **B** (Figure 3.3a). C2 is less likely to react since C1 is more reactive acetal carbon with electron-withdrawing substituents. The possible products of C2 are degradation products from **C** and **D** (Figure 3.3b). Although a 7-membered transition state is less stable than the 6-membered transition state, the septanoside **F** can form when O6 bonds with C1 (Figure 3.3c).

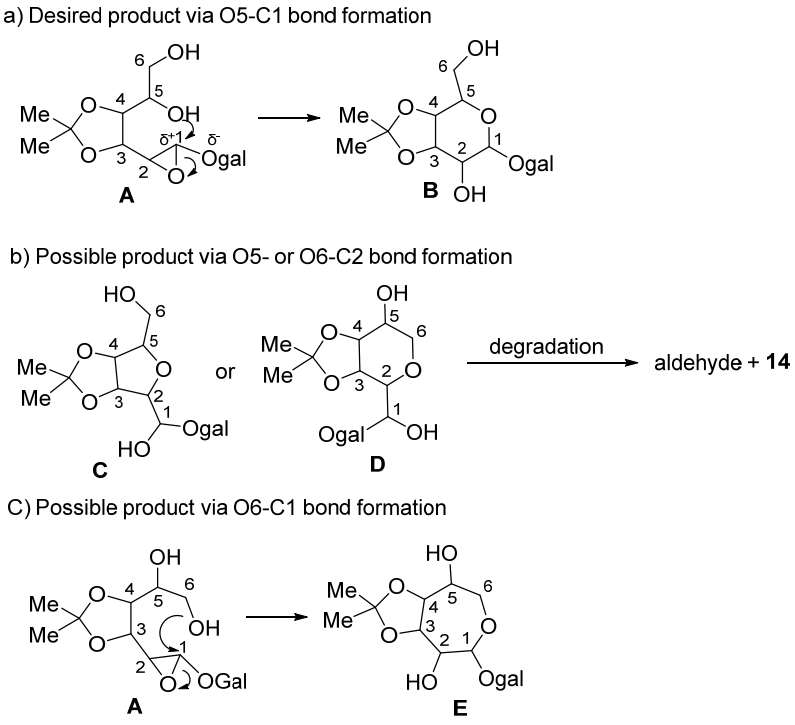


Figure 3.3 Expected products

These possible cyclic products have two hydroxy groups on the different positions of the ring. Pyranoside **B** has a primary alcohol on C6 and a secondary alcohol on C2 while septanoside **E** has two secondary alcohols on C2 and C5. Product **C** and **D** would be an aldehyde with one hydroxy group.

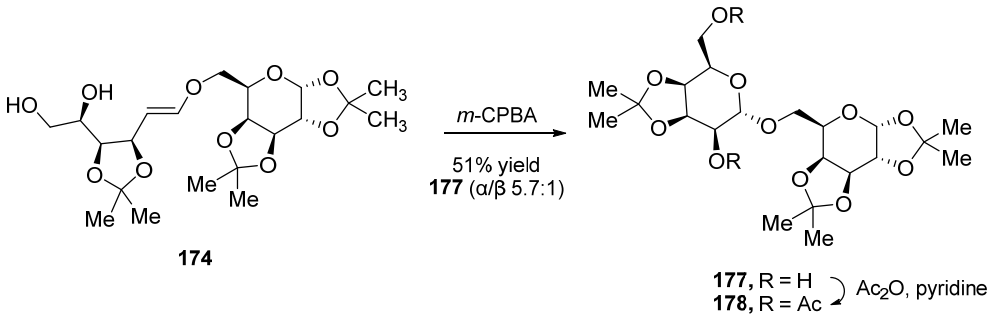
The acetylation of free hydroxy group often changes the chemical shifts of hydrogens alpha to the resulting ester groups. Given that the hydroxy groups are in different positions on the possible cyclic products, we will be able to determine the ring size of the product by analyzing the diacetate derivatives.

3.2.3.2 Results

After deprotection of TBS group, each of the resulting dihydroxy vinylic ether was treated with *m*-CPBA. We analyzed the 1D and 2D NMR spectra of the resulting dihydroxy cyclic compounds and their diacetate derivatives to characterize the structure and determine the relative stereochemistry of the product. Details of the analysis will be discussed in section 3.2.4.

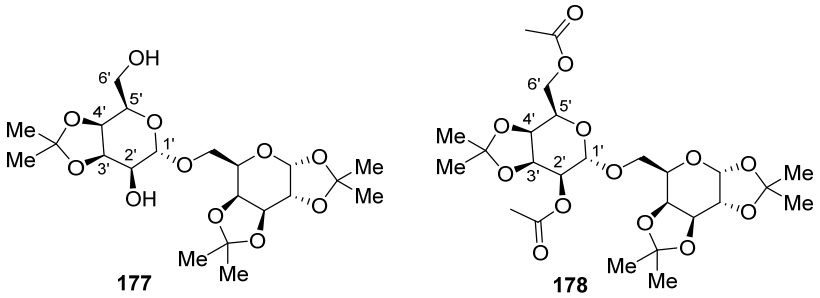
The lyxo-vinylic ether **174** was treated with *m*-CPBA to give α-talopyranoside **177** as the major diastereomer in 51% yield (d.r. 5.7:1) (Scheme 3.7).

Scheme 3.7 Epoxidation *in-situ* oxacyclization of acyclic vinylic ether **174**



Subsequent *O*-acylation resulted in diacetate **178**. The chemical shifts (ppm, C_6D_6) of H2' and H6a/b' of diacetate **178** were higher than those of diol **177** due to an electron-withdrawing effect from the ester (Table 3.2). The differences in the chemical shifts of diol **177** and diacetate **178** are corresponding with the differences observed in carbohydrate diols and diacetates [100,101].

Table 3.2 Changes in δ_H (ppm) from diol **177** to diacetate **178**



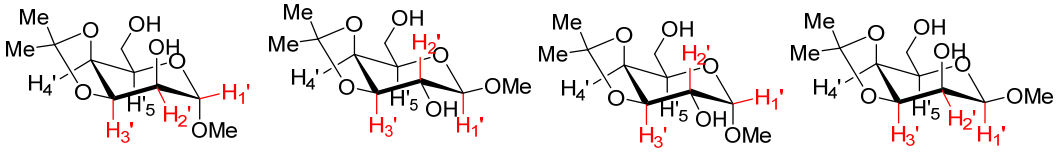
^{1}H	**177**	**178**	$\Delta\delta_H$
2'	3.56	5.13	1.57
6a'	3.93	4.43	0.50
6b'	3.73	4.31	0.58

We validated the proton assignments for diacetate **178** by analyzing the 2D NMR spectra (COSY, HSQC, and HMBC). Additionally, we observed the 3-bond correlations between the carbonyl carbons and the alpha hydrogens (H2' and H6a'/b') on HMBC spectrum of diacetate (details are

given in section 3.2.4). This confirmed the presence of free hydroxy groups on C2' and C6', indicating the formation of pyranoside.

Relative stereochemistry of the major compound was determined by comparing $^{3}J_{H1'-H2'}$ and $^{3}J_{H2'-H3'}$ of four possible diastereomers. Specifically, α-talo-pyranoside **179** [102] and β-galacto-pyranoside **180** [103] are the possible 1,2-*trans*-disaccharides while α-galacto-pyranoside **181** [104] and β-talo-pyranoside **182** [102] are the possible 1,2-*cis*-disaccharides (Table 3.3). We compared the $^{3}J_{H1'-H2'}$ and $^{3}J_{H2'-H3'}$ of **179-182** with that of the major compound from the oxacyclization of vinylic ether **174**. The $^{3}J_{H1'-H2'}$ of **177** closely corresponds to diequatorial H1'-H2' in **179** (^{3}J = 5.4 - 5.9 Hz) while the larger $^{3}J_{H1'-H2'}$ of 8.3 Hz corresponds to the diaxial H1'-H2' in **180**. The 1,2-*cis*-disaccharides **181** and **182** exhibited the smaller $^{3}J_{H1'-H2'}$ for the pair of equatorial and axial hydrogens on H1'/H2'. Additionally, the $^{3}J_{H2'-H3'}$ of **177** closely corresponds to H2'(eq)-H3'(ax) in **179** (^{3}J = 3.1-3.4 Hz).

Table 3.3 Comparison of δ_H (ppm) and $^{3}J_{H1'-H2'}$ and $^{3}J_{H2'-H3'}$ (Hz) of **179-182** with **177**



179 methyl α-talo-pyranoside

180 methyl β-galacto-pyranoside

181 methyl α-galacto-pyranoside

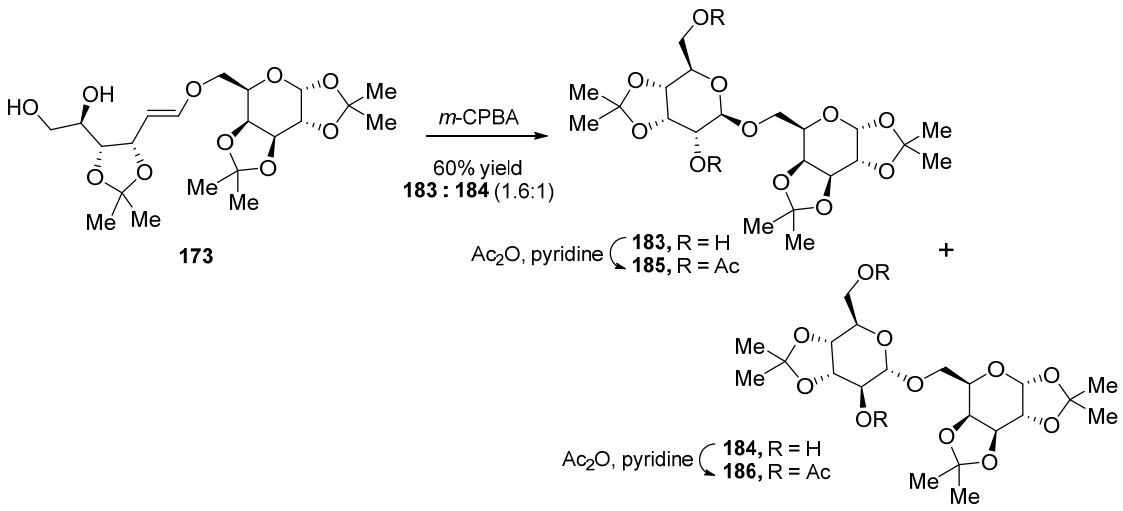
182 methyl β-talo-pyranoside

	177 (C_6D_6)	**179** ($CDCl_3$)	**180** ($CDCl_3$ + D_2O)	**181** (MeOD)	**182** ($CDCl_3$)
H1'	4.99 (d, $J_{1,2}$ = 6.0)	4.75 (d, $J_{1,2}$ = 5.4)	4.12 (d, $J_{1,2}$ = 8.3)	4.64 (d, $J_{1,2}$ = 3.6)	4.46 (d, $J_{1,2}$ = 1.9)
H2'	3.62 ($J_{2,3}$ = 3.1-3.4)	3.81-3.66 ($J_{2,3}$ = 3.4)	3.53 (dd, $J_{2,3}$ = 7.2)	3.53 (dd, $J_{2,3}$ = 7.7)	3.90-3.73 ($J_{2,3}$ = 4.7)

Despite that the NMR samples were in different solvents, the similar chemical shifts for H1' and H2' of **179** and of the major compound **177** also indicate that **177** is α-talopyranoside. Out of the four possible diastereomers, only one two major doublets (4.99 ppm for H1' and 5.52 ppm for H1) were present in the anomeric region 4.4-5.5 ppm [98,105]. A small amount of a minor diastereomer was isolated as a mixture. Further purification was not possible with such a small amount. Although full characterization was not possible due to peak overlapping, there was a doublet in the anomeric region (4.69 d, ^3J = 6.7 Hz) that may represent another diastereomer.

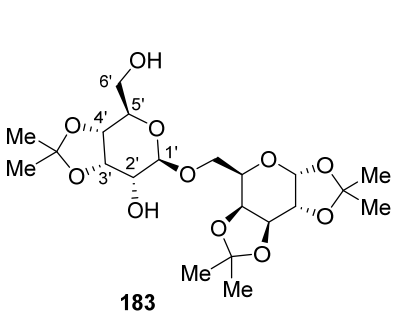
The epoxidation and *in-situ* oxacyclization of the ribo-diastereomer **173** afforded a 1.6 :1 mixture of two diastereomers **183** and **184** (Scheme 3.8). The diastereomers were partially separated by the column chromatography. The pure materials were subjected to *O*-acylation.

Scheme 3.8 Epoxidation followed by *in-situ* oxacyclization of acyclic vinylic ether **173**

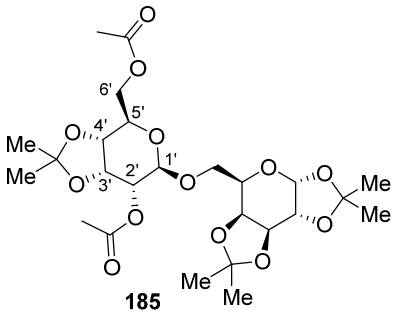


Subsequent *O*-acylation resulted in diacetates **185** and **186**. The chemical shifts (ppm, C_6D_6) of H6a', H6b', and H2' of the diacetates were higher than those of the corresponding diols, confirming that the hydroxy groups on C6' and C2' in the pyranoside were acylated (Table 3.4).

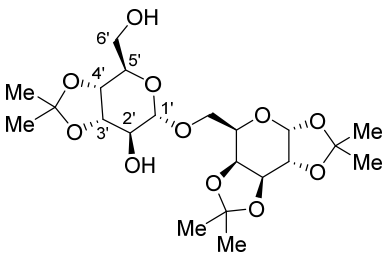
Table 3.4 δ_H (ppm) in diol **183** and **184** and diacetate **185** and **186**



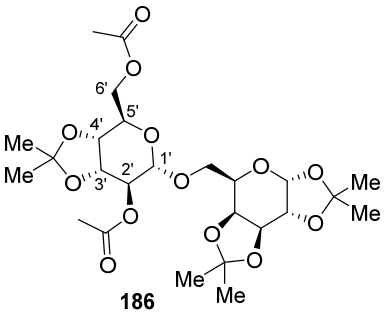
183



185



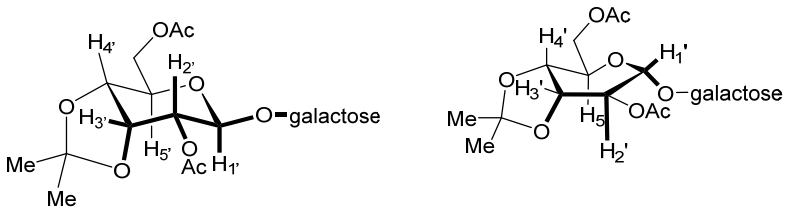
184



186

^{1}H	Diol **183**	Diacetate **185**	$\Delta\delta_H$	Diol **184**	Diacetate **186**	$\Delta\delta_H$
2’	3.77	5.32	1.55	3.91	5.51	1.6
6a’	3.82	4.35	0.53	3.81	4.44	0.63
6b’	3.61	4.20	0.59	3.60	4.25	0.65

Relative stereochemistry was determined for each diastereomer by analyzing the diacetate derivatives **185** and **186**. We assigned relative stereochemistry with larger H1’ - H2’ coupling constants (^3J > 7 Hz) for diaxial hydrogens in diacetate of β-allopyranoside (Figure 3.4)**.** The coupling constant of H1’ - H2’ in the minor compound was 3.5 Hz, which we assigned as vicinal hydrogens in a twisted boat-like conformer of α-altropyranoside acetate (Figure 3.4).



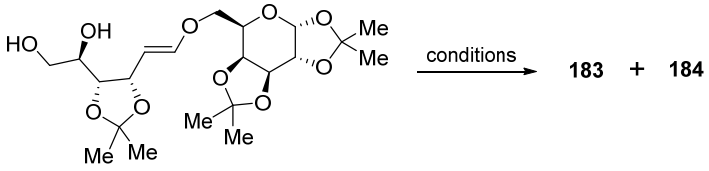
185
$H_{1'}$ - $H_{2'}$, ^3J = 7.7 Hz
$H_{2'}$ - $H_{3'}$, ^3J = 4.3 Hz
$H_{3'}$ - $H_{4'}$, ^3J = 4.9 Hz
$H_{4'}$ - $H_{5'}$, ^3J = 9.1 Hz

186
$H_{1'}$ - $H_{2'}$, ^3J = 3.5 Hz
$H_{2'}$ - $H_{3'}$, ^3J = 5.6 Hz
$H_{3'}$ - $H_{4'}$, ^3J = 6.0 Hz
$H_{4'}$ - $H_{5'}$, ^3J = 9.1 Hz

Figure 3.4 Diagnostic ^{3}J in diastereomer β-allo-**185** and α-altro-**186**

Different oxidants were screened with ribo-vinylic ether **173** to improve stereoselectivity (Table 3.5). TFAA (trifluoroacetic anhydride) and UHP (urea hydrogen peroxide) were used to generate trifluoroacetic acid (TFA) *in-situ*. The preliminary results showed that TFAA/UHP gave a lower stereoselectivity than *m*-CPBA (1.2:1 vs 1.6:1). While $VO(acac)_2$ and TBHP resulted in a slower conversion, it resulted in higher selectivity toward β-allo-**183** (4:1). A longer reaction at ambient temperature to increase the conversion of vinylic ether **173** resulted in the degradation of products.

Table 3.5 Different conditions for epoxidation



173

Entry	Conditions	**173**[a]	**183**[a]	**184**[a]
1	$VO(acac)_2$, TBHP at 0 °C, 5hr	0.55	0.36	0.09
2	TFAA and UHP at 20 °C, 4hr	0	0.54	0.46

[a]Ratio was determined from the ^{1}H NMR spectrum of the crude

These results suggested that stereoinduction effects from the adjacent acetonide substituent and hydrogen-bonding from the internal hydroxy group controlled the stereoselectivity of oxacyclization differently for each vinylic ether [106,107].

Hydrogen-bonding of O5' with the peracid directs the formation of epoxide on the back side of the alkene moiety, which results in the formation of α-anomer (Figure 3.5). The stereoinduction from the O3'-O4' acetonide protecting group allows the peracid to attack on the back side of the alkene moiety. The matched effects of stereoinduction from O3' and hydrogen-bonding from O5' afforded a higher α-stereoselectivity with lyxo-vinylic ether **174**.

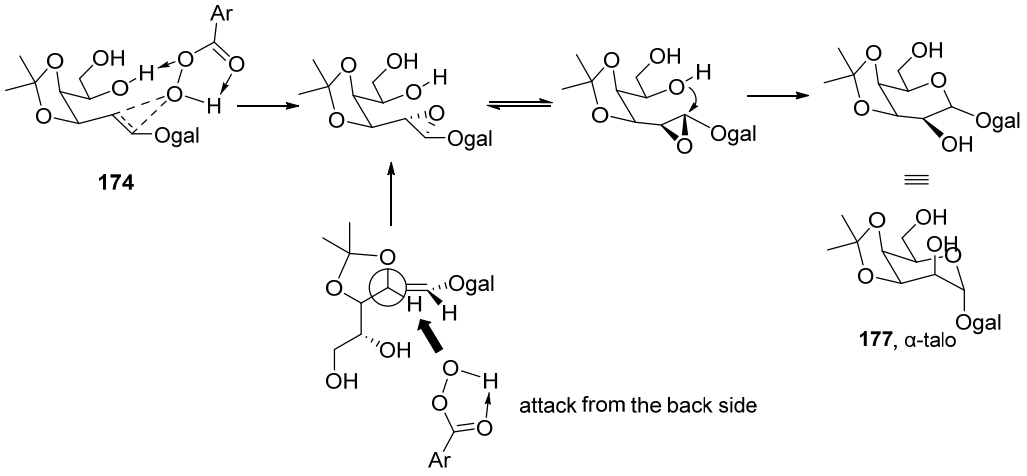


Figure 3.5 Matched effects of stereoinduction and hydrogen bonding in the electrophile-promoted oxacyclization of vinylic ether **174**

Similar to lyxo-diastereomer **174**, hydrogen-bonding with O5' in ribo-vinylic ether **173** promotes the peracid to attack from the back side of the alkene moiety, resulting in the formation of α-altro-pyranoside **184** (Figure 3.6). However, the stereoinduction of O3'-O4' acetonide group in ribo-vinylic ether **173** directs the peracid to attack from the front side of the alkene moiety,

resulting in β-allopyranoside **183**. The mismatched effects of stereoinduction and hydrogen-bonding in ribo-vinylic ether afforded a mixture of diastereomers.

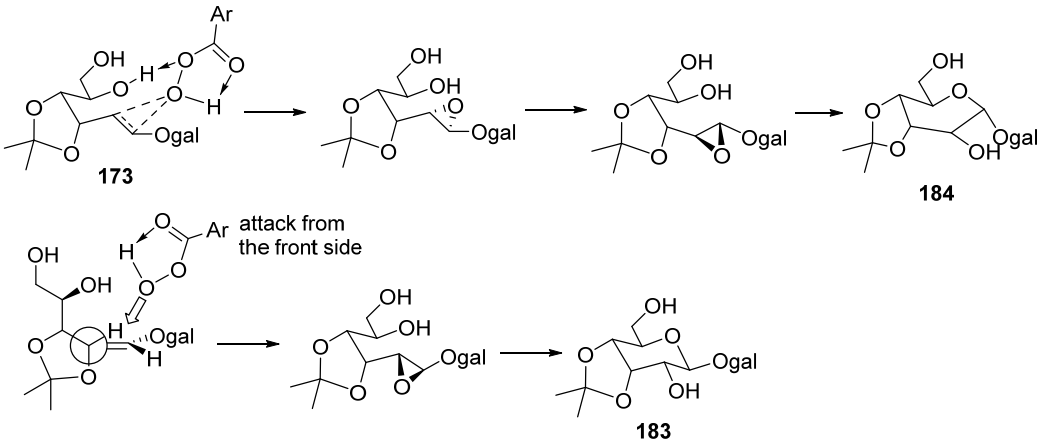
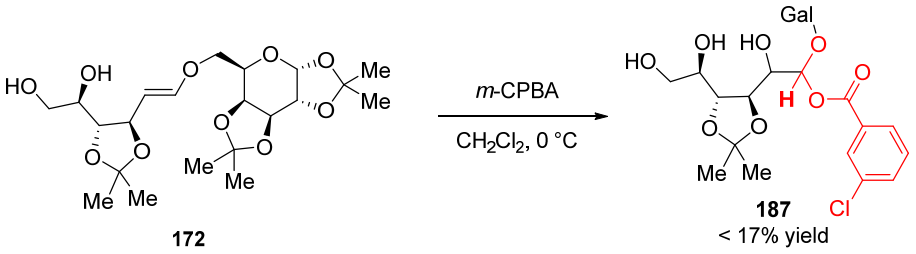


Figure 3.6 Mismatched effects of stereoinduction and hydrogen bonding in the electrophile-promoted oxacyclization of vinylic ether **173**

When D-arabino vinylic ether **172** was treated with *m*-CPBA, the desired disaccharide was not formed and resulted in a mixture of compounds (Scheme 3.9). We reasoned that the *trans* configuration of O3'-O4' constrained in the acetonide would prevent a facile *in-situ* oxacyclization. It is possible that *m*-chlorobenzoate opened the epoxide ring to form hemiacetal **187** [108].

Scheme 3.9 Treatment of vinylic ether **172** with *m*-CPBA



The compound **187** was isolated as a mixture of unidentifiable compounds on a column chromatography, and the insufficient amount of the mixture could not be purified again. I could

determine the diagnostic δ_H corresponding to those of simpler hemiacetal **188** [109] (Figure 3.7). Four hydrogens on m-chlorobenzoate were present as well as a doublet at 6.01 ppm for H1' at the acetal carbon.

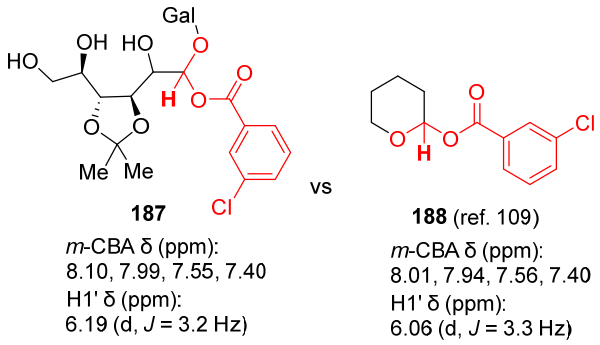


Figure 3.7 Comparing the δ_H of **187** and a known acetal **188**

3.2.4 Structural determination of disaccharides

Relative stereochemistry of each disaccharide was determined by analysis of 2D NMR spectra, which included HSQC (1 bond ^{13}C-^{1}H coupling), HMBC (2-3 bond ^{13}C-^{1}H coupling), and COSY (^{1}H-^{1}H coupling) analyses. The samples of disaccharides were prepared in benzene-D6. The assignments for the newly generated hexose of disaccharides are described in this section. Full assignment of each disaccharide is available in section 6.3.3.

The relative stereochemistry of α-talopyranoside was determined by analyzing the 2D NMR spectra of diacetate derivative **178**. We first assigned **Ha** at 5.49 ppm as H1 since H1 usually appears around 5.5 ppm in the bis-acetonide protected galactose **14**. We assigned the next deshielded δ_H **F/Hb** as C1'/H1'. HMBC spectrum showed a 3-bond ^{13}C-^{1}H correlation between carbonyl carbon **A** and a set of methylene peaks **Hf/Hg** (H6a'/H6b') (Figure 3.8). HMBC spectrum

showed a 2-bond correlation between **N** and **Hf/Hg** (H6a'/H6b') and a 3-bond correlation with **Hb** (H1'), so we assigned **N/Hm** as C5'/H5'. HMBC also showed a 2-bond correlation between **Hn** and **N** (C5'), so we assigned **Hn** as H4'. Based on the COSY, **Hc** correlates with **Hb** (H1') and **He**, which correlates with **Hn** (H4'), so we assigned **Hc** and **He** as H2' and H3' respectively (blue lines in Figure 3.8).

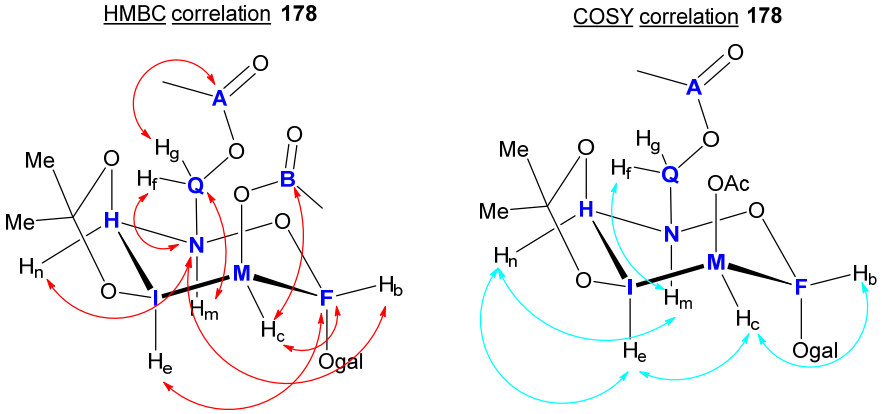


Figure 3.8 HMBC and COSY correlation compound **178**

The relative stereochemistry of β-allo-pyranoside **183** was determined by analyzing the 2D NMR spectra of diacetate derivative **185**. After assigning **Ha** as H1, we assigned the next deshielded δ_H **F/Hb** as C1'/H1'. HMBC spectrum showed a 3-bond ^{13}C-^{1}H correlation between carbonyl carbon **A** and a set of methylene peaks **Hf/Hn** (H6a'/H6b') (Figure 3.9). HMBC spectrum showed a 2-bond correlation between **I** and **Hf/Hn** (H6a'/H6b') and a 3-bond correlation with **Hc** (H1'), so we assigned **I/Hn** as C5'/H5'. HMBC also showed a 2-bond correlation between **Hm** and **I** (C5'), so we assigned **Hm** as H4'. Based on the COSY spectrum, **Hb** correlates with **Hc** (H1') and **Hd**, which correlates with **Hm** (H4'), so we assigned **Hb** and **Hd** as H2' and H3' respectively (blue lines in Figure 3.9).

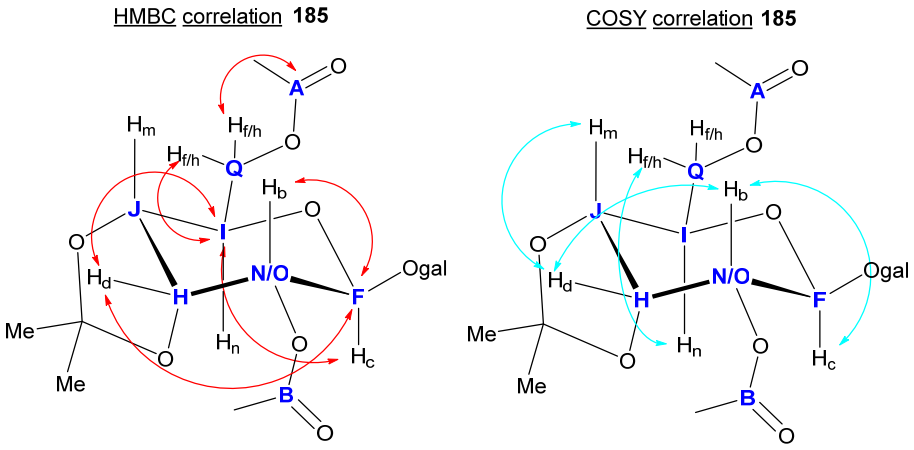


Figure 3.9 HMBC and COSY correlation compound **185**

The relative stereochemistry of α-altro-pyranoside **184** was determined by analyzing the 2D NMR spectra of diacetate derivative **186**. HMBC spectrum showed a 3-bond correlation between **Ha** and carbonyl carbon **B**, so we assigned **J/Ha** as C2'/H2' (Figure 3.10). We assigned the next deshielded δ_H **Hb** as C1/H1 (not shown). There was a 2-bond ^{13}C-^{1}H correlation between **J** (C2') and **Hc** and a 3-bond ^{1}H-^{1}H correlation between **Ha** and **Hc**, so we assigned **F/Hc** as C1'/H1'. HMBC spectrum showed a 3-bond ^{13}C-^{1}H correlation between carbonyl carbon **A** and a set of methylene peaks **He/Hf** (H6a'/H6b'). HMBC showed a 3-bond correlation between **Hc** (H1') and **I** that also had a 2-bond correlation with **He/Hf** (H6a'/H6b'), so we assigned **I/Hm** as C5'/H5'. There was a ^{1}H-^{1}H correlation between **Hm** (H5') and **Hg** and between **Ha** (H2') and **Hl**, so we assigned **N/Hg** and **H/Hl** as C4'/H4' and C3'/H3', respectively.

HMBC spectrum showed a 2-bond correlation between **H** and **Hm/Hn** (H6a'/H6b') and a 3-bond correlation with **Hb** (H1'), so we assigned **H/Hk** as C5'/H5'. The correlation between **G** and H3' and H4' are tentative due to overlapping peaks, but **G** has either a 2-bond correlation with **Hj** or a 3-bond with **Hi**. Since **Hl** has a ^{1}H-^{1}H correlation with **Hb**, we assigned **G/Hl** as C2'/H2' (blue line in equation 3.10). Due to overlapping peaks, **Hk** and **Hm/Hn** are tentatively assigned.

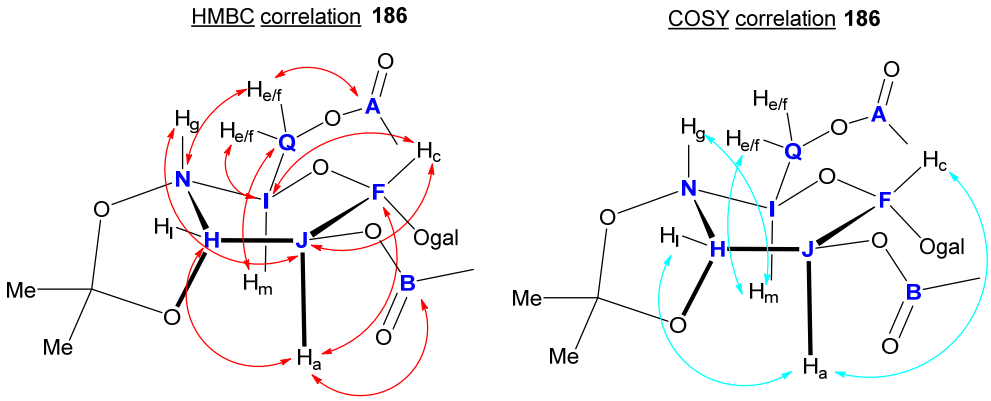


Figure 3.10 HMBC and COSY correlation compound **186**

3.3 Conclusion

We have established that catalytic C-O cross-coupling enables stereoselective synthesis of vinylic ethers with structural and stereochemical complexity on both sides of the ether linkage. The resulting vinylic ethers from carbohydrate synthons served as the intermediates in the electrophile-promoted intramolecular oxacyclization that afforded disaccharides.

Although the oxacyclization occured for epoxide intermediates from the *cis*-substituted acetonide substrates **173** and **174**, *trans*-substituted acetonide substrate **172** disfavored oxacyclization of a diol-epoxide intermediate. We did not sought for a different protecting group for *trans*-substituted acetonide substrates since we synthesized arabino-alkyne **151** as an epimerized product arising from acetonide-protected ribo-lactol **149** in the Seyferth-Gilbert homologation at reflux temperature. The Colvin homologation of acetonide-protected lactol was rather low-yielding, and the Seyferth-Gilbert homologation with the Bestmann-Ohira reagent was only efficient at high temperature, which resulted in epimerization.

For these reasons, further optimization of electrophile-promoted intramolecular oxacyclization of acyclic vinylic ether will be conducted with 6-deoxy-alkyne substrates synthesized *de novo*. Our efforts to extend this strategy to 6-deoxy and 2,6-dideoxyglycosides will be discussed in Chapter 4.

Chapter 4 Synthesis of 6-deoxy and 2,6-dideoxy glycosides via acyclic vinylic ether intermediates

4.1 Background

The McDonald's group has been long interested in oxacyclization of acyclic alkynols to form pyranosyl 1,2-glycals[75–77]. In 2000, our group reported a tungsten catalyzed cyclo-isomerization of alkynols to synthesize 6-deoxy-1,2-glycals that were subjected to acid-catalyzed glycosylation with glycosyl acceptor to directly synthesize 2,6-dideoxyglycosides[77] (section 1.3.1). Four alkynes with different relative stereochemistry were examined (Figure 4.1). The acid-cataylzed glycosylation was high yielding and highly diastereoselective for O3-O4-*cis*-glycals, but it resulted in diminished yields and diastereoselectivity for O3-O4-*trans*-glycals. Although they circumvented this problem with iodocyclization, the deiodonation was required to synthesize 2,6-dideoxyglycosides from the resulting 2-iodo-pyranoside.

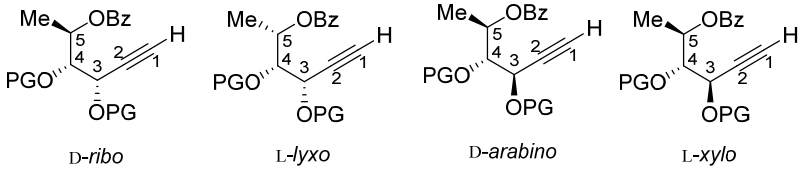


Figure 4.1 Alkyne substrates with different relative stereochemistry

We have demonstrated that the catalytic C-O cross-coupling enables stereoselective synthesis of vinylic ethers with structural and stereochemical complexity on both sides of the ether linkage (Chapter 2), and the subsequent epoxidation *in-situ* intramolecular oxacyclization

of the hydroxy vinylic ethers affords pyranosides (Chapter 3). We will discuss our initial efforts to extend this strategy toward the synthesis of 6-deoxy and 2,6-deoxyglycosides in this chapter.

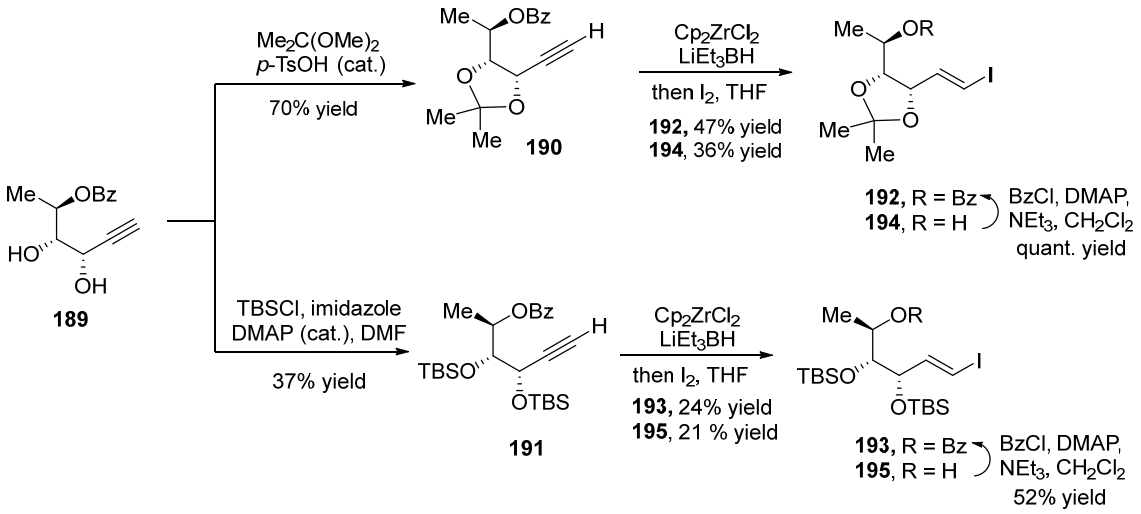
4.2 Results and Discussion

4.2.1 Synthesis of *E*-vinylic iodides from D-ribo-alkynes

Initially, alkynyl diol **189** with D-ribo stereochemistry was synthesized in *de novo* synthesis previously reported by our group [77,80,81]. After protecting diol **189**, hydrozirconation-iodination of alkynes **190** and **191** afforded the desired *E*-vinylic iodide **192** and **193**, respectively (Scheme 4.1). The secondary alcohol **194** and **195** were formed as by-products from debenzoylation. Debenzoylation might have occurred from unreacted $LiEt_3BH$ during *in-situ* generation of Cp_2ZrHCl and not by Cp_2ZrHCl or Cp_2ZrH_2 (a possible over-reduced by-product) [110].

However, debenzoylation still occurred when I used a commercial bottle of Cp_2ZrHCl. The oxo-bridged dimer of zirconocene can be formed from Cp_2ZrCl_2 and Cp_2ZrHCl when exposed to air and moisture. The possible presence of oxo-bridged dimer of zirconocene in the bottles of Cp_2ZrCl_2 and Cp_2ZrHCl might have promoted debenzoylation[111]. A subsequent acylation of alcohol **194** and **195** with benzoyl chloride resulted in the desired benzoate **192** and **193**.

Scheme 4.1 Synthesis of vinylic iodides from known D-ribo alkyne **189**



4.2.2. Synthesis of hydroxy vinylic ether intermediates via Cu-catayzed cross-coupling followed by debenzoylation

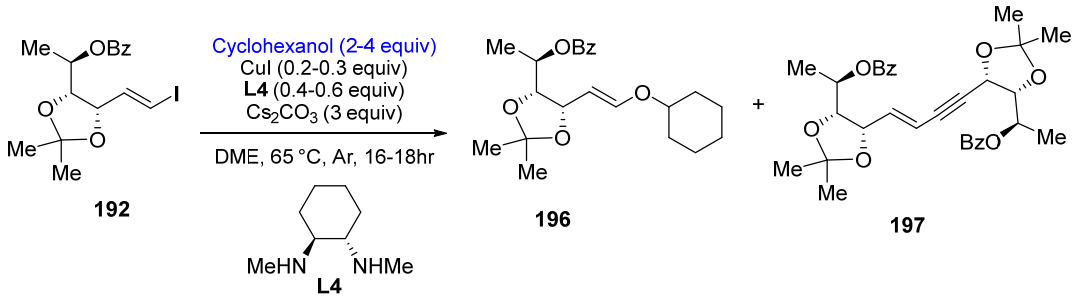
4.2.2.1. Synthesis of vinylic ethers via Cu(I)-catalyzed cross-coupling

Prior to executing the Cu(I)-catalyzed cross-coupling reaction, we were concerned about the stability of benzoate group under the basic condition of cross-coupling reaction and the possibility of removing the benzoate group from the resulting vinylic ether. We chose cyclohexanol as the coupling partner because it is a simple secondary alcohol that would be less likely to react with the benzoate under the basic reaction condition, and it might simplify the NMR analysis. The reaction was stirred at a lower temperature for a shorter period (80 °C/40 hrs to 65 °C/16hrs) to prevent debenzoylation from occurring during the cross-coupling reaction.

When vinylic iodide **192** was treated under our reported conditions with the above modifications, vinylic ether **196** was synthesized in 42% yield (Table 4.1, entry 1). Enyne **197** was

isolated (6% yield) in this attempt. A trace amount of benzoylated cyclohexanol was detected in the crude ^{1}H NMR spectrum. Increasing only the catalyst loading resulted in a slight improvement (entry 2). After increasing the catalyst loading and the amount of alcohol, the vinylic ether **196** was synthesized in 74% yield (entry 3).

Table 4.1 Optimization of Cu(I) cross-coupling with **192** and cyclohexanol



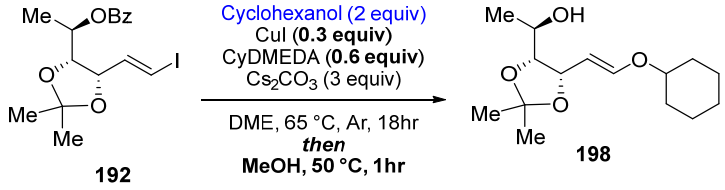
Entry	Modifications from the reported conditions	**196** (% yield)	**197** (% yield)
1	65 °C, 16 hr	42	6
2	65 °C, 16 hr , CuI/CyDMEDA (0.3/0.6 equiv)	47	9
3	65 °C, 16 hr, CuI/CyDMEDA (0.3/0.6 equiv) Cyclohexanol (4 equiv)	74	3

A few reagents were examined to remove the benzoate group. DIBAL-H destroyed the vinylic ether and resulted in a mixture of compounds. Treating **196** with methanolic ammonia only resulted in the recovery of starting material. When benzoate **196** was treated with K_2CO_3 in MeOH and stirred overnight, debenzoylation afforded the alcohol **198** in 39% yield.

After confirming that hydroxy vinylic ether **198** was separable from cyclohexanol on TLC, the debenzoylation was telescoped with the cross-coupling step. I used only 2 equivalents of cyclohexanol in this reaction to ensure a facile separation of hydroxy vinylic ether **198** and excess cyclohexanol. After stirring the reaction mixture of Cu(I)-catalyzed cross-coupling at 65 °C for

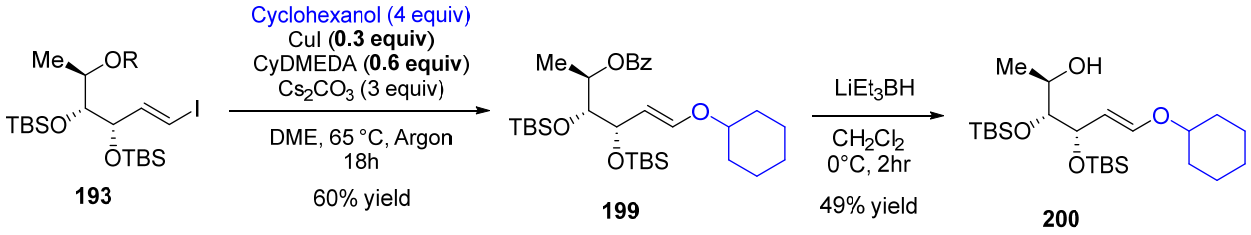
18hrs, the reaction was cooled to room temperature. Since Cs_2CO_3 was already present in the reaction mixture, only MeOH was added at room temperature. The reaction was stirred for 1hr at 50 °C, resulting in the desired hydroxy vinylic ether **198** in 43% yield from vinylic iodide **192** (Scheme 4.2).

Scheme 4.2 Synthesis of hydroxy vinylic ether **198**



The TBS-protected vinylic iodide **193** was successfully coupled with cyclohexanol to give vinylic ether **199** in 60% yield (Scheme 4.3). Our group previously observed a silyl migration during debenzoylation with inorganic carbonate bases. Therefore, vinylic ether **199** was isolated and then treated with $LiEt_3BH$ in a subsequent step to synthesize alcohol **200** in 49% yield.

Scheme 4.3 Synthesis of vinylic ether **200** via Cu(I)-catalyzed cross-coupling followed by hydride reduction of benzoate



4.2.2.2 Attempt at the synthesis of vinylic boronate and Cu(II)-catalyzed cross-coupling

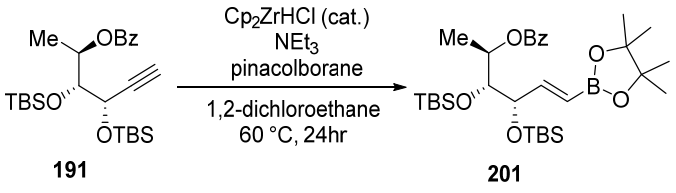
The Cu(II)-catalyzed cross-coupling is an alternative synthesis of vinylic ethers (developed by San Pham, *manuscript in progress*, 2023-2025). This method uses N-isopropyl imidazole (NPI)

as a ligand, and dicumyl peroxide (DCP) instead of O_2 as the stoichiometric oxidant and requires 1-2 equiv of alcohol rather than as the solvent.

Since the hydrozirconation-iodination was low-yielding for TBS-protected vinylic iodide **193**, we intended to synthesize vinylic ether via Cu(II)-catalyzed cross-coupling of vinylic boronate, which can be synthesized by catalytic Zr-mediated hydroboration [112]. Debonzoylation should be minimized with catalytic amount of Schwartz's reagent.

I treated TBS-protected alkyne **191** with a catalytic amount of Cp_2ZrHCl, triethylamine, and pinacolborane in 1,2-dichloroethane (3 M). The reaction solution was stirred for 24 hr at 60 °C. Although the ^1H NMR spectrum of crude mixture showed vinylic boronate **201** as the major product, the purification of vinylic boronate was difficult. Only a small amount of **201** (10% yield) was isolated. It was shown that pinacol boronic esters can adsorb to silica gel too strongly[113]. While purification can be facilitated by impregnating silica gel with boric acid[113], this was not further investigated due to a presence of acid-sensitive TBS protecting group. Although this was not attempted, the crude mixture of vinylic boronate may be subjected to the Cu(II)-catalyzed cross-coupling in the future.

Scheme 4.4 Synthesis of E-vinylic boronate **201**

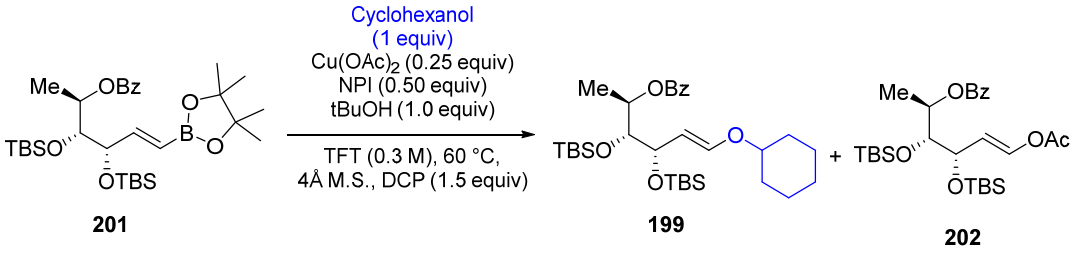


191 201

I was still able to conduct Cu(II)-catalyzed cross-coupling at a small-scale (0.03 mmol). Due to its small scale, I needed to increase the amount of solvent from the optimized concentration

(0.6M) to (0.3 M) to facilitate the stirring. The reaction was stirred at 60 °C for 18 hrs to give a partial conversion to vinylic ether **199** and vinylic acetate **202** (Scheme 4.5). The ratio of **201** : **199** : **202** was determined from the crude ^{1}H NMR spectrum, which was 0.54 : 0.30 : 0.16. This was a promising preliminary result, and it may be optimized in the future.

Scheme 4.5 Cu(II)-catalyzed cross-coupling of vinylic boronate **201** and cyclohexanol

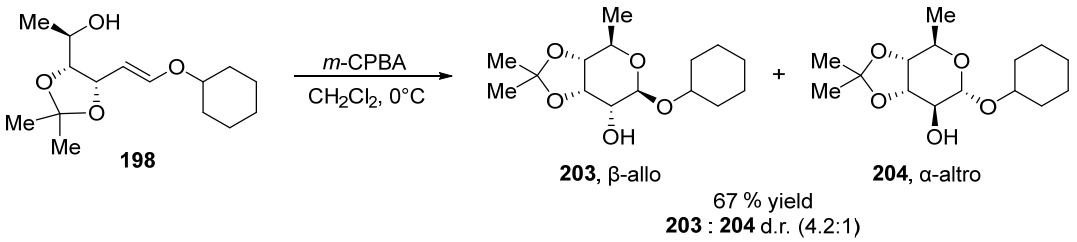


4.2.3. Electrophile-promoted oxacyclization of acyclic vinylic ether intermediates

4.2.3.1 Synthesis of 6-deoxyglycosides via m-CPBA promoted oxacyclization

The first experiment was to treat acetonide bearing vinylic ether **198** with *m*-CPBA, which resulted in the diastereomeric mixture of 6-deoxyglycosides **203** and **204** in 67% yield (d.r. 4.2:1).

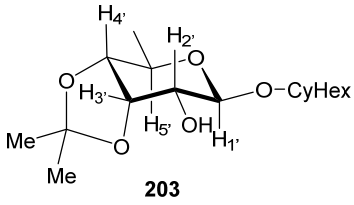
Scheme 4.6 *m*-CPBA promoted oxacyclization of vinylic ether **198**

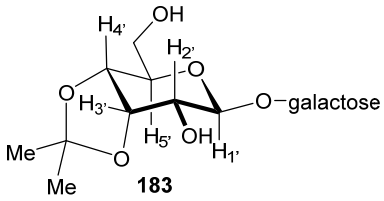


The relative stereochemistry of major compound **203** was determined by comparing its δ_H and ^{3}J coupling constants with β-allo-pyranoside **183** we previously synthesized (described in Chapter 3). Their δ_H and ^{3}J coupling constants are mostly comparable except for H4'. The δ_H of

axial H4’ in 6-deoxy-β-allo-pyranoside **203** is more shielded than the corresponding H4’ in **183** that has an electron-withdrawing O6’ (Table 4.2).

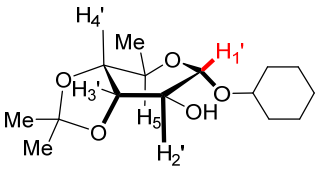
Table 4.2 Comparison of δ_H (ppm, C6D6) and ^3J of **203** and **183**





Hydrogen	δ_H (^3J, Hz) **203**	δ_H (^3J, Hz) **183**
H1’	4.83, d (7.1)	4.87, d (6.7)
H2’	3.74, dd (7.2, 4.5)	3.77, dt (6.6, 4.4)
H3’	4.22, apparent t (4.8)	4.23, dd (5.5, 4.4)
H4’	3.48, dd (9.0, 5.0)	3.92, dd (9.1, 5.6)
H5’	3.62, dd (9.2, 6.4)	3.66, ddd (9.1, 5.5, 2.7)
H6’	1.27, d (6.2) (3H, Me)	3.82, ddd (11.8, 6.0, 2.7) 3.61, dt (11.8, 5.9)

Although the ^{1}H NMR spectrum of minor isomer **204** was of poor quality due to low concentration, I determined that it is a 6-deoxy-α-altropyranoside based on a doublet at 4.76 ppm (^3J = 5.8 Hz), which is comparable with H1’ of α- altropyranoside **184** we previously synthesized (Figure 4.2).



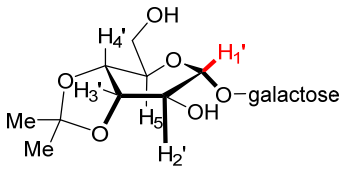
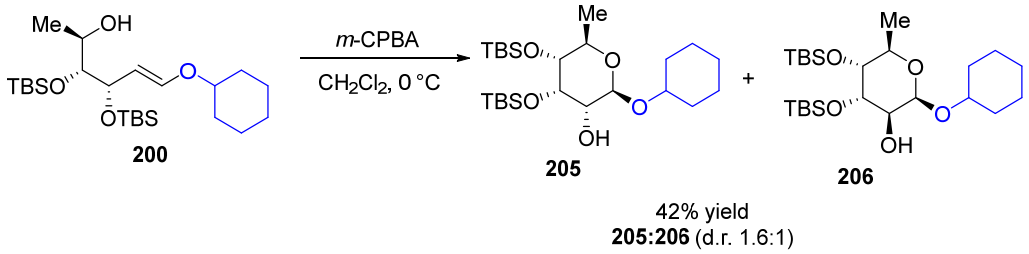


Figure 4.2 Diagnostic δH (ppm, C6D6) and ^3J of of **204** and **184**

Subsequently, TBS-protected hydroxy vinylic ether **200** was treated with *m*-CPBA and resulted in a diastereomeric mixture of **205** and **206** (42% yield d.r. 1.6 : 1) (Scheme 4.7).

Scheme 4.7 *m*-CPBA promoted oxacyclization of TBS-protected vinylic ether **200**

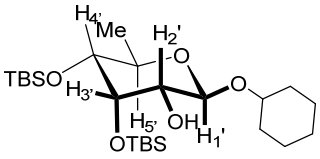


The relative stereochemistry of the products were determined by comparing their ^{3}J with the ^{3}J of four diastereomers with *cis*-O3-O4 benzyl protecting group synthesized (**207-210**) by Nicotra in 1987 [39]. The ^{1}H NMR spectral data for compound **209** does not provide all the necessary ^{3}J coupling constants. The spectral data for unprotected 6-deoxy-alpha-altropyranoside **211** are available [114].

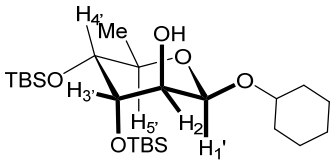
The ^{3}J coupling constants for the major diastereomer **205** closely correspond to β-allopyranoside **210** (Table 4.3). The major diastereomers from acetonide protected vinylic ethers **173** and **198** were β-allopyranoside for the synthesis of disaccharide and 6-deoxyglycoside. All three compounds of β-allopyranoside that I synthesized (**183**, **203**, and **205**) have a larger coupling constant (6.7-8 Hz) for the diaxial H1'-H2' of β-allopyranoside **210** (Table 4.2 and 4.3).

The ^{3}J coupling constants for the minor diastereomer **206** closely correspond to β-altropyranoside **208**. This was unexpected as compound **208** is 1,2-*cis*-glycoside.

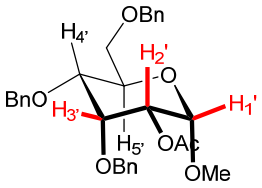
Table 4.3 Comparison of ^{3}J constants of four possible diastereomers



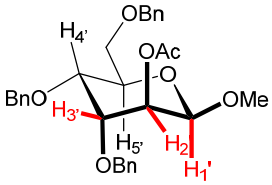
205
β-allopyranoside



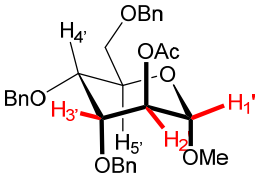
206
β-altropyranoside



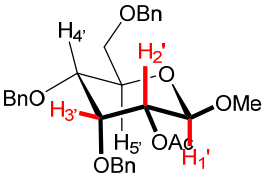
207
α-allopyranoside



208
β-altropyranoside

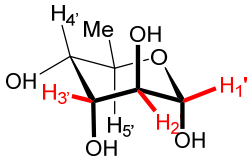


209
α-altropyranoside



210
β-allopyranoside

≈



211

	Previously reported				From TBS-vinylic ether **200**	
	207	**208**	**209/211**	**210**	**205**	**206**
H1'-H2'	4.5	1.5	4.1	8	7.6	1.1
H2'-H3'	3	4.5	6.2	2.5	2.3	4.2-4.3
H3'-H4'	3	3	3.2	2.1	2.3	2.7-2.9
H4'-H5'	10	9.5	6.2	9.5	8.8-8.9	8.0-8.1
H5'-H6a'	3.5	3	6.2	2	6.4 (3H)	6.5-6.6 (3H)
H5'-H6b'	2.5	5	N/A	4.5	N/A	N/A
H6a'-H6b'	N/A	10.5	N/A	11	N/A	N/A

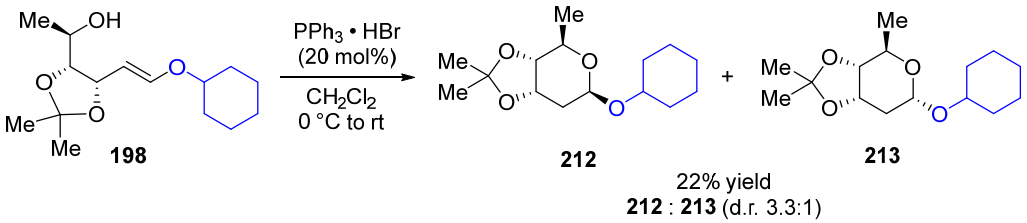
4.2.3.2 Synthesis of 2,6-dideoxyglycosides via acid-catalyzed oxacyclization

The acid-catalyzed oxacyclization directly synthesizes 2,6-deoxyglycosides via oxacyclization of acyclic vinylic ether, unlike other electrophiles such as selenium, mercury, or iodine that needs to be removed in a subsequent step. There is a challenge associated with the

acid-catalyzed oxacyclization using achiral acid since the addition of acid to the alkene moiety may proceed via oxocarbenium cation that can diminish the stereoselectivity.

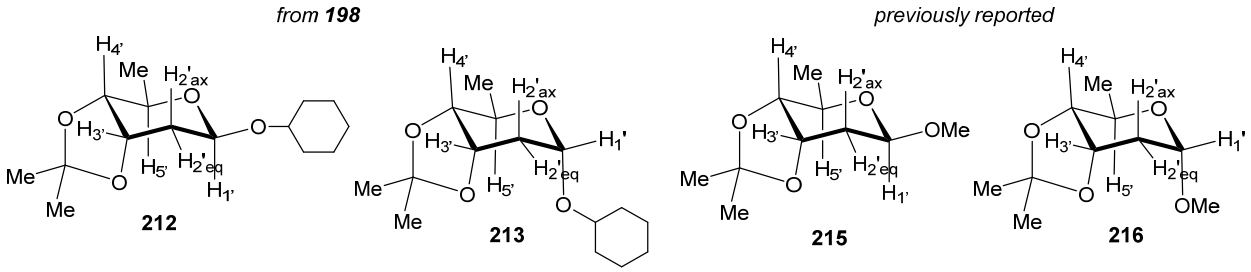
The acetonide-protected acyclic vinylic ether **198** was treated with an acid to synthesize 2,6-dideoxyglycoside. We first used triphenyl phosphonium hydrogen bromide (PPh_3 • HBr), resulting in a diastereomeric mixture of 2,6-dideoxyglycosides **212** and **213** (Scheme 4.8) along with a small amount of hydrolysis by-product **214** (Table 4.5, entry 1). The d.r. of **212** : **213** was 3.3 : 1, which was comparable to *m*-CPBA promoted oxacyclization.

Scheme 4.8 Acid-catalyzed oxacyclization of vinylic ether **198**



The relative stereochemistry of **212** was determined by comparing its ^3J with those of methoxy derivative **215** and **216** [115]. The ^3J values of **212** closely correspond to those of β-**215** and not correspond to the α-anomer **216** (Table 4.4) The two diastereomers were not separable on the column chromatograph, and I could not get an accurate spectral data for the minor diastereomer **213**. However, the δ_H and ^3J value for H1' of **213** was 4.80 ppm (t, ^3J = 5.8 Hz), which corresponds to H1' of α-anomer **216**.

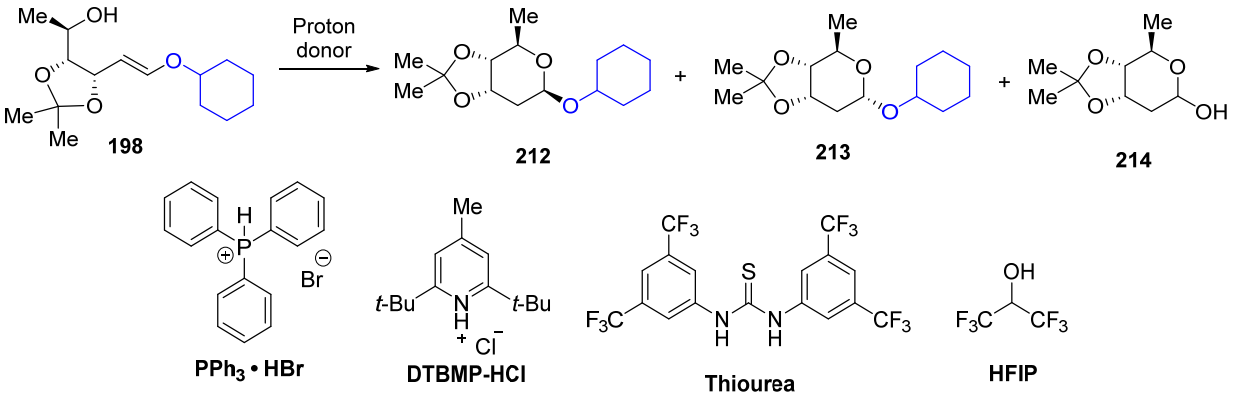
Table 4.4 Comparison of ^{3}J (Hz) of compound **212** (C_6D_6) with **215** and **216** ($CDCl_3$)



	212	β-**215**	α-**216**
H1'-H2a'	8.7	8.8	5.5
H1'-H2b'	2.5-2.6	2.6	5.5
H2a'-H2b'	14.6	14.7	N/A
H2a'-H3'	2.6-2.7	4.8	6.3
H2b'-H3'	4.9-5.0	2.6	6.3
H3'-H4'	5.0	4.8	6.3
H4'-H5'	9.1	9.5	N/A
H5'-H6'	6.1	6.9	5.9

Different achiral acids were examined (Table 4.5). Di-*tert*-butylmethyl-pyridine HCl salt (DTBMP-HCl) resulted in a lower stereoselectivity (d.r. 2.5 : 1) (entry 2). Thiourea did not promote oxacyclization even at high temperature in non-hydrogen bonding solvent like trifluorotoluene (TFT) (entry 3). When the reaction with thiourea was conducted in hydrogen-bonding solvent HFIP, vinylic ether **198** was partially converted into **212** and **213** with lower diastereoselectivity. Given the hydrogen-bonding capability of HFIP and its mild acidity (aqueous pKa = 9.3) [116,117], a control experiment without thiourea was conducted in HFIP (entry 5). The 2,6-dideoxyglycosides **212** and **213** formed in comparable ratio as with DTBMP-HCl with an improved yield (56% yield). Attempts to lower the temperature in other co-solvents (trifluorotoluene, CCl_4, and TCE) only decreased the reaction rate.

Table 4.5 Screening acids for acid-catalyzed oxacyclization of vinylic ether **198**

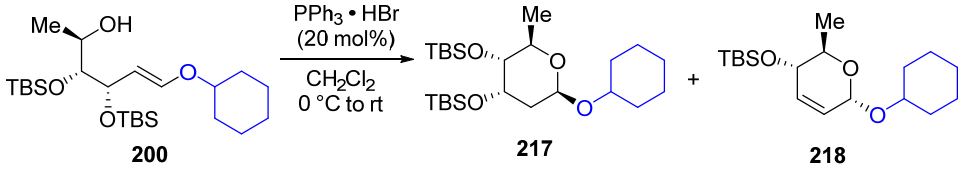


Entry	Proton donor (mol %)	Reaction conditions	Ratio[a] of **198** : **212** : **213** : **214**	**212** + **213** (% yield)
1	PPh_3 • HBr (20)	0 °C, 4.5 h, DCM	0.02 : 0.67 : 0.16 : 0.15	22
2	DTBMP-HCl (10)	20 °C, 5 hr, DCM	0 : 0.62 : 0.25 : 0.14	17
3	Thiourea (10)	95°C, overnight, TFT	Only **198**	N/A
4	Thiourea (20)	50 °C overnight, HFIP	0.13 : 0.55 : 0.25 : 0.08	N/A
5	HFIP (0.2 M = 5 equiv)	50 °C overnight	0.08 : 0.65 : 0.25 : 0.03	56

[a] Ratio was determined from the ^{1}H NMR spectrum of crude mixture

The TBS-protected acyclic vinylic ether **200** was treated with PPh_3 • HBr (20 mol%). The reaction was not completed at 5hr, and only the vinylic ether **200** was recovered. When the reaction was stirred overnight, a 1:1 mixture of **217** and **218** formed. Cyclic allylic ether **218** was formed by the Ferrier rearrangement.

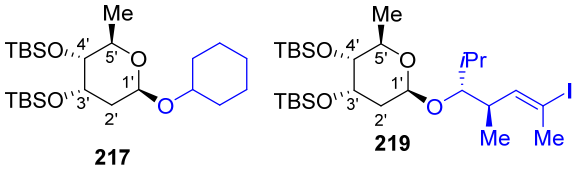
Scheme 4.9 Acid-catalyzed oxacyclization of vinylic ether **200**



The structures of **217** and **218** were characterized by comparing their δ_H and ^3J with those of the similar compounds reported in the literature. Hofferberth and Brückner reported compound **219** as a building block of β-lipomycin [118]. The δ_H and ^3J values of **217** closely

correspond to those of **219** (Table 4.6). The ^{1}H NMR spectrum obtained from the $CDCl_3$ solution of compound **217** gave a poor resolution for the two H2'. Fortunately, the ^{3}J obtained from the C_6D_6 solution gave the comparable ^{3}J values as those of **219.**

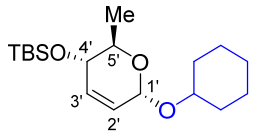
Table 4.6 Comparison of δ_H (ppm, $CDCl_3$) and ^{3}J of compound **217** and **219**



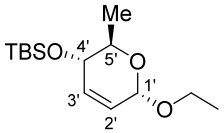
Hydrogens	δ_H (^{3}J, Hz) **217** ($CDCl_3$) (C_6D_6)	δ_H (^{3}J, Hz) **219** ($CDCl_3$)
H1'	4.98, dd (9.5, 2.1)	4.79, dd (9.4, 2.1)
H2'	1.87, d (3.3) 1.69 dd (13.0, 3.4) 2.06, ddd (13.4, 4.1, 2.2) 1.87, ddd (13.4, 9.3, 2.2)	1.98, ddd (13.4, 4.0, 2.1) 1.64, ddd (13.4, 9.5, 2.1)
H3'	3.99, m	3.99, ddd (4.1, 2.1)
H4'	3.29, dd (9.0, 2.4)	3.26, dd (9.0, 2.4)
H5'	3.87, dq (9.0, 6.3)	3.83, dq (9.0, 6.3)
(Me) H6'	1.19, d (6.4, 3H)	1.15, d(6.3, 3H)

The δ_H and ^{3}J values of compound **218** were comparable with those of similar compound **220**[119] (Table 4.6). H4' and H5' were tentatively assigned to multiplets in 3.89 – 3.75 due to peak overlapping. A poor resolution of peaks in 3.91-3.75 ppm for compound **220** integrates to 3H. They correspond to H5' (1H) and methylene hydrogens on ethoxy substituent (2H).

Table 4.7 Comparison of δ_H (ppm, $CDCl_3$) and ^3J of compound **218** and **220**



218



220

Hydrogens	δ_H (*J*, Hz) **218** ($CDCl_3$)	δ_H (*J*, Hz) **220** ($CDCl_3$)
H1’	5.06, s	4.94, brs
H2’	5.81, d (10.2)	5.83, d (10.2)
H3’	5.64, dt (10.3, 2.3)	5.68, dt (10.2, 2.2)
H4’	3.89 – 3.75 (m, 2H)	3.60-3.50, m
H5’	3.89 – 3.75 (m, 2H)	3.91-3.75, m (3H)
Me-H6’	1.23 (d, *J* = 6.0 Hz, 3H)	1.25, d (6.60) (6H)

Different acids that were examined with the acetonide-vinylic ether **198** were also experimented with vinylic ether **200**, but they didn’t improve the results.

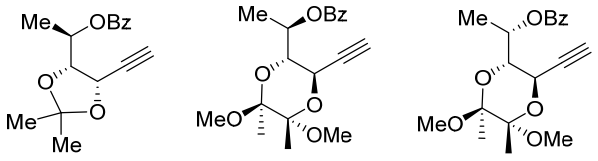
4.3 Conclusion and future works

The preliminary investigation of the electrophile-promoted oxacyclization of acyclic vinylic ether from a *de novo* synthesis established that the Cu(I)-catalyzed cross-coupling methodology synthesized acyclic vinylic ether intermediates for the electrophile-promoted intramolecular oxacyclization. The cross-coupling reaction conditions were compatible with the base-labile benzoate protecting group. The Cu(II)-catalyzed cross-coupling was also promising as it afforded the desired vinylic ether, albeit with a partial conversion at a small-scale reaction. Additionally, debenzoylation was telescoped with acetonide-bearing substrate **196**.

The results from the *m*-CPBA-promoted oxacyclization were interesting. Although the stereoselectivity with acetonide-bearing vinylic ether **198** was as expected with the formation of a diastereomeric mixture of 1,2-*trans*-pyranosides, the electrophile-promoted oxacyclization of TBS-bearing vinylic ether **200** resulted in 1,2-*tran*-β-pyranoside as well as 1,2-*cis*-β-pyranoside. Further investigation will be conducted to optimize stereoselectivity.

The acid-catalyzed oxacyclization can be improved. A mild acid with a higher pKa may increase the stereoselectivity via hydrogen bonding with the alkene moiety and may disfavor the formation of oxocarbenium cation. Although perfluoro-*tert*-butanol (PFTB) has a lower pKa than HFIP (pKa= 5.4 < 9.3), PFTB is an interesting candidate since it may promote oxacyclization at a lower temperature than HFIP. As an alternative to acid-catalyzed oxacyclization, NIS-promoted iodocyclization can synthesize 2,6-dideoxyglycosides from acyclic vinylic ether intermediates, albeit with additional dehalogenation step with tin hydride.

Further investigation of this transformation is warranted, with other diastereomers, namely L-lyxo **221**, D-arabino **222**, and L-xylo **223** (Figure 4.3). The *trans*-O3-O4 diastereomers will be protected with diketal group (**222** and **223**) as an alternative and more flexible protecting group for the O3-O4 diol moiety.



221 L-lyxo **222** D-arabino **223** L-xylo

Figure 4.3 Stereoisomers with different relative stereochemistry

References

(1) Seeberger, P. H. Discovery of Semi- and Fully-Synthetic Carbohydrate Vaccines Against Bacterial Infections Using a Medicinal Chemistry Approach. *Chem. Rev.* **2021**, *121* (7), 3598–3626.

(2) Feng, D.; Shaikh, A. S.; Wang, F. Recent Advance in Tumor-Associated Carbohydrate Antigens (TACAs)-Based Antitumor Vaccines. *ACS Chem. Biol.* **2016**, *11* (4), 850–863.

(3) Eller, C. H.; Chao, T.-Y.; Singarapu, K. K.; Ouerfelli, O.; Yang, G.; Markley, J. L.; Danishefsky, S. J.; Raines, R. T. Human Cancer Antigen Globo H Is a Cell-Surface Ligand for Human Ribonuclease 1. *ACS Cent. Sci.* **2015**, *1* (4), 181–190.

(4) Fan, B.; Jiang, X.; Li, Y.; Wang, W.; Yang, M.; Li, J.; Wang, A.; Chen, G. Chemistry and Biological Activity of Resin Glycosides from Convolvulaceae Species. *Med. Res. Rev.* **2022**, *42* (6), 2025–2066.

(5) Lee, S.; Rhee, Y. H. Total Synthesis of the Purported Structure of Branched Resin Glycosides Merremoside G and H $_2$. *Org. Lett.* **2024**, *26* (3), 602–606.

(6) Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Kong, F.; Greenstein, M. Saccharomicins, Novel Heptadecaglycoside Antibiotics Produced by *Saccharothrix Espanaensis* : Antibacterial and Mechanistic Activities. *Antimicrob. Agents Chemother.* **2000**, *44* (8), 2154–2159.

(7) Garreffi, B. P.; Maney, A. P.; Bennett, C. S. Synthesis of the Branched Tetrasaccharide Fragment of Saccharomicin A. *Org. Lett.* **2023**, *25* (2), 369–372.

(8) Das, R.; Mukhopadhyay, B. Chemical O-Glycosylations: An Overview. *ChemistryOpen* **2016**, *5* (5), 401–433.

(9) Streety, X. S.; Obike, J. C.; Townsend, S. D. A Hitchhiker's Guide to Problem Selection in Carbohydrate Synthesis. *ACS Cent. Sci.* **2023**, *9* (7), 1285–1296.

(10) Pohl, N. L. B. Introduction: Carbohydrate Chemistry. *Chem. Rev.* **2018**, *118* (17), 7865–7866.

(11) Kulkarni, S. S.; Wang, C.-C.; Sabbavarapu, N. M.; Podilapu, A. R.; Liao, P.-H.; Hung, S.-C. "One-Pot" Protection, Glycosylation, and Protection–Glycosylation Strategies of Carbohydrates. *Chem. Rev.* **2018**, *118* (17), 8025–8104.

(12) Bertozzi, C. R.; Kiessling, and L. L. Chemical Glycobiology. *Science* **2001**, *291* (5512), 2357–2364.

(13) Bauer, E. B. Transition Metal Catalyzed Glycosylation Reactions – an Overview. *Org. Biomol. Chem.* **2020,** *18*, 9160–9180

(14) Morelli, L.; Compostella, F.; Panza, L.; Imperio, D. Unusual Promoters and Leaving Groups in Glycosylation Reactions: The Evolution of Carbohydrate Synthesis. *Carbohydr. Res.* **2022**, *519*, 108625.

(15) Zhu, X.; Schmidt, R. R. New Principles for Glycoside-Bond Formation. *Angew. Chem. Int. Ed.* **2009**, *48* (11), 1900–1934.

(16) Nielsen, M. M.; Pedersen, C. M. Catalytic Glycosylations in Oligosaccharide Synthesis. *Chem. Rev.* **2018**, *118* (17), 8285–8358.

(17) Benito-Alifonso, D.; Galan, M. C. B Rønsted- and L ewis-Acid-Catalyzed Glycosylation. In *Selective Glycosylations: Synthetic Methods and Catalysts*; Bennett, C. S., Ed.; Wiley, 2017; pp 155–172.

(18) Gallier, F.; Miranda, L. S. de M. e. Organocatalysis Applied to Carbohydrates: From Roots to Current Developments. *Org. Biomol. Chem.* **2022**, *20* (5), 919–933.

(19) Bennett, C. S.; Nguyen, T.-A. V. *Carbohydrate Synthesis*; ACS In Focus; American Chemical Society, **2023**.

(20) Guo, J.; Ye, X.-S. Protecting Groups in Carbohydrate Chemistry: Influence on Stereoselectivity of Glycosylations. *Molecules* **2010**, *15* (10), 7235–7265.

(21) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. A General Strategy for Stereoselective Glycosylations. *J. Am. Chem. Soc.* **2005**, *127* (34), 12090–12097.

(22) Crich, D.; Sun, S. Direct Synthesis of β-Mannopyranosides by the Sulfoxide Method. *J. Org. Chem.* **1997**, *62* (5), 1198–1199.

(23) Crich, D.; Vinogradova, O. On the Influence of the C2−O2 and C3−O3 Bonds in 4,6- *O* -Benzylidene-Directed β-Mannopyranosylation and α-Glucopyranosylation. *J. Org. Chem.* **2006**, *71* (22), 8473–8480.

(24) Codée, J. D. C.; Ali, A.; Overkleeft, H. S.; Van Der Marel, G. A. Novel Protecting Groups in Carbohydrate Chemistry. *Comptes Rendus Chim.* **2010**, *14* (2–3), 178–193.

(25) Wang, T.; Demchenko, A. V. Synthesis of Carbohydrate Building Blocks *via* Regioselective Uniform Protection/Deprotection Strategies. *Org. Biomol. Chem.* **2019**, *17* (20), 4934–4950.

(26) *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 1989; Vol. 386.

(27) Mukherjee, M. M.; Ghosh, R.; Hanover, J. A. Recent Advances in Stereoselective Chemical O-Glycosylation Reactions. *Front. Mol. Biosci.* **2022**, *9*, 896187.

(28) Panza, M.; Pistorio, S. G.; Stine, K. J.; Demchenko, A. V. Automated Chemical Oligosaccharide Synthesis: Novel Approach to Traditional Challenges. *Chem. Rev.* **2018**, *118* (17), 8105–8150.

(29) Guberman, M.; Seeberger, P. H. Automated Glycan Assembly: A Perspective. *J. Am. Chem. Soc.* **2019**, *141* (14), 5581–5592.

(30) Lin, M.; Wolf, J. B.; Sletten, E. T.; Cambié, D.; Danglad-Flores, J.; Seeberger, P. H. Enabling Technologies in Carbohydrate Chemistry: Automated Glycan Assembly, Flow Chemistry and Data Science. *ChemBioChem* **2023**, *24* (4), e202200607.

(31) Cumpstey, I. Intramolecular Aglycon Delivery. *Carbohydr. Res.* **2008**, *343* (10–11), 1553–1573.

(32) Ishiwata, A.; Lee, Y. J.; Ito, Y. Recent Advances in Stereoselective Glycosylation through Intramolecular Aglycon Delivery. *Org. Biomol. Chem.* **2010**, *8* (16), 3596.

(33) Jia, X. G.; Demchenko, A. V. Intramolecular Glycosylation. *Beilstein J. Org. Chem.* **2017**, *13*, 2028–2048.

(34) Jung, K.-H.; Müller, M.; Schmidt, R. R. Intramolecular *O* -Glycoside Bond Formation. *Chem. Rev.* **2000**, *100* (12), 4423–4442.

(35) Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J. Stereospecific Synthesis of 1,2- *Cis* Glycosides by Allyl-Mediated Intramolecular Aglycon Delivery. 2. The Use of Glycosyl Fluorides. *Org. Lett.* **2001**, *3* (15), 2371–2374.

(36) Suzuki, K.; Mukaiyama, T. A Novel Method for the Synthesis of 2-Deoxydisaccharide by Stereoselective Cyclization of the Acyclic Precursor. *Chem. Lett.* **1982**, *11* (5), 683–686.

(37) Suzuki, K.; Mukaiyama, T. Highly stereoselective synthesis of α-D-Glucopyranosides by the N-Iodosuccinimide-promoted internal cyclization. *Chem. Lett.* **1982**, *11* (10), 1525–1528.

(38) Nicotra, F.; Panzal, L.; Ronchetti, F.; Russo, G.; Toma, L. A Novel Approach to the Synthesis of 1,2-Cis-Glycopyranosides. *Tetrahedron Lett.* **1985**, *26* (6), 807–808.

(39) Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. Formation of Glycosides by Epoxidation-Ring Closure of Open-Chain Hydroxyenol Ethers Obtained from Sugars. *J. Chem. Soc. Perkin 1* **1987**, 1319.

(40) Paquet, F.; Sinay, P. A New Stereocontrolled Approach to KDO Containing Disaccharides. *J. Am. Chem. Soc.* **1984**, *106* (26), 8313–8315.

(41) Paquet, F.; Sinaÿ, P. Intramolecular Oximercuration-Demercuration Reaction: A New Stereocontrolled Approach to Sialic Acid Containing Disaccharides. *Tetrahedron Lett.* **1984**, *25* (29), 3071–3074.

(42) Kim, T.; Meindl, E. J.; McDonald, F. E. Nontraditional Synthesis of Disaccharides via Acyclic Vinylic Ether Intermediates: Catalytic C–O Cross-Coupling as the Enabling Link. *J. Org. Chem.* **2024,** *89* (24), 18684-18688.

(43) Lipshutz, B. H.; Tirado, R. De Novo Approach to Dideoxyribosides. 5-Endo-Trig-like Cyclizations of .Delta.-Hydroxy Enol Ethers. *J. Org. Chem.* **1994**, *59* (26), 8307–8311.

(44) Acetylenic ethers from alcohols and their reduction to Z-and E-enol ethers: preparation of 1-menthoxy-1-butyne from menthol and conversion to (Z)- and (E)-1-menthoxy-1-butene. *Org. Synth.* **1997**, *74*, 13.

(45) Winternheimer, D.; Shade, R.; Merlic, C. Methods for Vinyl Ether Synthesis. *Synthesis* **2010**, *2010* (15), 2497–2511.

(46) Evano, G.; Gaumont, A.-C.; Alayrac, C.; Wrona, I. E.; Giguere, J. R.; Delacroix, O.; Bayle, A.; Jouvin, K.; Theunissen, C.; Gatignol, J.; Silvanus, A. C. Metal-Catalyzed Synthesis of Hetero-Substituted Alkenes and Alkynes. *Tetrahedron* **2014**, *70* (8), 1529–1616.

(47) Sánchez, I. P.; Turos, E. Glycosylated Vinyl Ethers by the Julia–Lythgoe–Kocienski Olefination: Application to the Synthesis of 2′,5′-Dideoxydisaccharides and Carbohydrated β-Lactams. *Tetrahedron Asymmetry* **2009**, *20* (14), 1646–1660.

(48) Corbet, M.; Bourdon, B.; Gueyrard, D.; Goekjian, P. G. A Julia Olefination Approach to the Synthesis of Functionalized Enol Ethers and Their Transformation into Carbohydrate-Derived Spiroketals. *Tetrahedron Lett.* **2008**, *49* (5), 750–754.

(49) Selenski, C.; Pettus, T. R. R. Enantioselective [4 + 2] Cycloadditions of *o* -Quinone Methides: Total Synthesis of (+)-Mimosifoliol and Formal Synthesis of (+)-Tolterodine. *J. Org. Chem.* **2004**, *69* (26), 9196–9203.

(50) Feng, Z.; Bai, W.; Pettus, T. R. R. Unified Total Syntheses of (−)-Medicarpin, (−)-Sophoracarpan A, and (±)-Kushecarpin A with Some Structural Revisions. *Angew. Chem. Int. Ed.* **2015**, *54* (6), 1864–1867.

(51) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. The Domestication of *Ortho* -Quinone Methides. *Acc. Chem. Res.* **2014**, *47* (12), 3655–3664.

(52) Geherty, M. E.; Dura, R. D.; Nelson, S. G. Catalytic Asymmetric Claisen Rearrangement of Unactivated Allyl Vinyl Ethers. *J. Am. Chem. Soc.* **2010**, *132* (34), 11875–11877.

(53) Rehbein, J. Claisen Rearrangement of Aliphatic Allyl Vinyl Ethers from 1912 to 2012: 100 Years of Electrophilic Catalysis. *N. Y.* **2013**.

(54) Vidhani, D. V.; Krafft, M. E.; Alabugin, I. V. Stereocontrolled Synthesis of (*E,Z*)-Dienals *via* Tandem Rh(I)-Catalyzed Rearrangement of Propargyl Vinyl Ethers. *Org. Lett.* **2013**, *15* (17), 4462–4465.

(55) Wang, Y.-Y.; Bode, J. W. Olefin Amine (OLA) Reagents for the Synthesis of Bridged Bicyclic and Spirocyclic Saturated N-Heterocycles by Catalytic Hydrogen Atom Transfer (HAT) Reactions. *J. Am. Chem. Soc.* **2019**, *141* (24), 9739–9745.

(56) Kondo, M.; Kochi, T.; Kakiuchi, F. Rhodium-Catalyzed Anti-Markovnikov Intermolecular Hydroalkoxylation of Terminal Acetylenes. *J. Am. Chem. Soc.* **2011**, *133* (1), 32–34.

(57) Lam, R. H.; Walker, D. B.; Tucker, M. H.; Gatus, M. R. D.; Bhadbhade, M.; Messerle, B. A. Intermolecular Hydroalkoxylation of Terminal Alkynes Catalyzed by a Dipyrrinato Rhodium(I) Complex with Unusual Selectivity. *Organometallics* **2015**, *34* (17), 4312–4317.

(58) Kerrigan, N. J.; Bungard, C. J.; Nelson, S. G. Pd(II)-Catalyzed Aliphatic Claisen Rearrangements of Acyclic Allyl Vinyl Ethers. *Tetrahedron* **2008**, *64* (29), 6863–6869.

(59) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. Development of a Highly Efficient Catalytic Method for Synthesis of Vinyl Ethers. *J. Am. Chem. Soc.* **2002**, *124* (8), 1590–1591.

(60) Wu, F.; Xie, J.; Zhu, Z. 1,10-Phenanthroline: A Versatile Ligand to Promote Copper-catalyzed Cascade Reactions. *Appl. Organomet. Chem.* **2020**, *34* (11), e5926.

(61) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. An Improved Cu-Based Catalyst System for the Reactions of Alcohols with Aryl Halides. *J. Org. Chem.* **2008**, *73* (1), 284–286.

(62) Nordmann, G.; Buchwald, S. L. A Domino Copper-Catalyzed C−O Coupling−Claisen Rearrangement Process. *J. Am. Chem. Soc.* **2003**, *125* (17), 4978–4979.

(63) Chen, Z.; Jiang, Y.; Zhang, L.; Guo, Y.; Ma, D. Oxalic Diamides and *Tert* -Butoxide: Two Types of Ligands Enabling Practical Access to Alkyl Aryl Ethers via Cu-Catalyzed Coupling Reaction. *J. Am. Chem. Soc.* **2019**, *141* (8), 3541–3549.

(64) Ma, D.; Cai, Q. Copper/Amino Acid Catalyzed Cross-Couplings of Aryl and Vinyl Halides with Nucleophiles. *Acc. Chem. Res.* **2008**, *41* (11), 1450–1460.

(65) Cai, Q.; Zhou, W. Ullmann-Ma Reaction: Development, Scope and Applications in Organic Synthesis. *Chin. J. Chem.* **2020**, *38* (8), 879–893.

(66) Ma, D.; Cai, Q.; Xie, X. CuI/ *N* , *N* -Dimethylglycine-Catalyzed Cross-Coupling Reaction of Vinyl Halides with Phenols and Its Application to the Assembly of Substituted Benzofurans. *Synlett* **2005**, No. 11, 1767–1770.

(67) Surry, D. S.; Buchwald, S. L. Diamine Ligands in Copper-Catalyzed Reactions. *Chem. Sci.* **2010**, *1* (1), 13.

(68) Wang, L.; Lei, X.; Wang, Q.; Li, Y. Copper-Catalyzed Cross-Coupling of Amino Acid-Derived Amides with (*Z*)-Vinyl Iodides: Unexpected Solvent Effect and Preparation of Plocabulin. *Tetrahedron* **2021**, *83*, 131953.

(69) Fang, Y.; Li, C. O-Arylation versus C-Arylation: Copper-Catalyzed Intramolecular Coupling of Aryl Bromides with 1,3-Dicarbonyls. *J. Org. Chem.* **2006**, *71* (17), 6427–6431.

(70) Cai, J.; Wang, Z.-K.; Usman, M.; Lu, Z.-W.; Hu, X.-D.; Liu, W.-B. Enantioselective Synthesis of β-Quaternary Carbon-Containing Chromanes and 3,4-Dihydropyrans via Cu-Catalyzed Intramolecular C–O Bond Formation. *Org. Lett.* **2019**, *21* (21), 8852–8856.

(71) Wan, Z.; Jones, C. D.; Koenig, T. M.; Pu, Y. J.; Mitchell, D. Vinyl Aryl Ethers from Copper-Catalyzed Coupling of Vinyl Halides and Phenols. *Tetrahedron Lett.* **2003**, *44* (45), 8257–8259.

(72) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. Copper-Promoted Coupling of Vinyl Boronates and Alcohols: A Mild Synthesis of Allyl Vinyl Ethers. *J. Am. Chem. Soc.* **2010**, *132* (4), 1202–1203.

(73) Quach, T. D.; Batey, R. A. Copper(II)-Catalyzed Ether Synthesis from Aliphatic Alcohols and Potassium Organotrifluoroborate Salts. *Org. Lett.* **2003**, *5* (8), 1381–1384.

(74) Beasley, P. *Metal Catalyst Methodology Development towards Carbon-Oxygen Bond Formation: Synthesis of Vinyl Ethers and Vinyl Esters*. Ph.D. Dissertation. Emory University, Atlanta, GA. **2023**.

(75) McDonald, F. E.; Zhu, H. Y. H. Synthesis of Pyranose Glycals via Tungsten and Molybdenum Pentacarbonyl-Induced Alkynol Cyclizations. *Tetrahedron* **1997**, *53* (32), 11061–11068.

(76) McDonald, F. E.; Zhu, H. Y. H. Novel Strategy for Oligosaccharide Synthesis Featuring Reiterative Alkynol Cycloisomerization. *J. Am. Chem. Soc.* **1998**, *120* (17), 4246–4247.

(77) McDonald, F. E.; Reddy, K. S.; Díaz, Y. Stereoselective Glycosylations of a Family of 6-Deoxy-1,2-Glycals Generated by Catalytic Alkynol Cycloisomerization. *J. Am. Chem. Soc.* **2000**, *122* (18), 4304–4309.

(78) McDonald, F. E.; Reddy, K. S. Convergent Synthesis of Digitoxin: Stereoselective Synthesis and Glycosylation of the Digoxin Trisaccharide Glycal. *Angew. Chem. Int. Ed.* **2001**, *40* (19), 3653.

(79) McDonald, F. E.; Wu, M. Stereoselective Synthesis of L -Oliose Trisaccharide via Iterative Alkynol Cycloisomerization and Acid-Catalyzed Glycosylation. *Org. Lett.* **2002**, *4* (22), 3979–3981.

(80) Koo, B.; McDonald, F. E. Synthesis of the Branched *C* -Glycoside Substructure of Altromycin B. *Org. Lett.* **2005**, *7* (17), 3621–3624.

(81) Balthaser, B. R.; McDonald, F. E. Brønsted Acid-Promoted Glycosylations of Disaccharide Glycal Substructures of the Saccharomicins. *Org. Lett.* **2009**, *11* (21), 4850–4853.

(82) Balmond, E. I.; Coe, D. M.; Galan, M. C.; McGarrigle, E. M. α-Selective Organocatalytic Synthesis of 2-Deoxygalactosides. *Angew. Chem. Int. Ed.* **2012**, *51* (36), 9152–9155.

(83) Ghosh, T.; Mukherji, A.; Kancharla, P. K. Sterically Hindered 2,4,6-Tri- *Tert* -Butylpyridinium Salts as Single Hydrogen Bond Donors for Highly Stereoselective Glycosylation Reactions of Glycals. *Org. Lett.* **2019**, *21* (10), 3490–3495.

(84) Sniady, A.; Bedore, M. W.; Jamison, T. F. One-Flow, Multistep Synthesis of Nucleosides by Brønsted Acid-Catalyzed Glycosylation. *Angew. Chem. Int. Ed.* **2011**, *50* (9), 2155–2158.

(85) Pham, S. L.; Kim, T.; McDonald, F. E. Stereospecific Cu(I)-Catalyzed C–O Cross-Coupling Synthesis of Acyclic 1,2-Di- and Trisubstituted Vinylic Ethers from Alcohols and Vinylic Halides. *Org. Lett.* **2023**, *25* (28), 5297–5301.

(86) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. Direct Observation of CuI/CuIII Redox Steps Relevant to Ullmann-Type Coupling Reactions. *Chem. Sci.* **2010**, *1* (3), 326.

(87) Lefèvre, G.; Franc, G.; Tlili, A.; Adamo, C.; Taillefer, M.; Ciofini, I.; Jutand, A. Contribution to the Mechanism of Copper-Catalyzed C–N and C–O Bond Formation. *Organometallics* **2012**, *31* (22), 7694–7707.

(88) Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. Theoretical Study on Copper(I)-Catalyzed Cross-Coupling between Aryl Halides and Amides. *Organometallics* **2007**, *26* (18), 4546–4554.

(89) Bates, C. G.; Saejueng, P.; Venkataraman, D. Copper-Catalyzed Synthesis of 1,3-Enynes. *Org. Lett.* **2004**, *6* (9), 1441–1444.

(90) Rajalakshmi, C.; Jibin, S. S.; Sulay, R.; Asha, S.; Ipe Thomas, V.; Anilkumar, G. Theoretical Investigation into the Mechanism of Copper-Catalyzed Sonogashira Coupling Using Trans-1,2-Diamino Cyclohexane Ligand. *Polyhedron* **2021**, *193*, 114869

(91) Wipf, P.; Waller, D. L.; Reeves, J. T. Transition-Metal-Mediated Cascade Reactions: The Water-Accelerated Carboalumination−Claisen Rearrangement−Carbonyl Addition Reaction. *J. Org. Chem.* **2005**, *70* (20), 8096–8102.

(92) Wang, Y.; Ma, B.; Mao, Y.; Wang, Z.; Peng, J.; Chen, C.; Li, Z. Titanium-Catalyzed Highly Stereoselective Anti-Markovnikov Intermolecular Hydroalkoxylation of Alkynes to Prepare Z-Enol Ethers. *Org. Biomol. Chem.* **2023**, *21* (47), 9422–9427.

(93) Tromans, J.; Zhang, B.; Golding, B. T. Harnessing the Peterson Reaction for the Stereospecific Synthesis of Z-Vinyl Ethers. *Chem. – Eur. J.* **2024**, *30* (2), e202302708.

(94) Mahankali, B.; Srihari, P. A Carbohydrate Approach for the First Total Synthesis of Cochliomycin C: Stereoselective Total Synthesis of Paecilomycin E, Paecilomycin F and 6'-*Epi* -Cochliomycin C: Total Synthesis of Cochliomycin C. *Eur. J. Org. Chem.* **2015**, *2015* (18), 3983–3993.

(95) McDonald, F. E.; Ding, D.; Ephron, A. J.; Bacsa, J. Alkynylation of Pentose Derivatives with Stereochemical Fidelity: Implications for the Regioselectivity of Alkynyl Diol Cycloisomerizations to Cyclic Enol Ethers. *Org. Lett.* **2019**, *21* (9), 3295–3298.

(96) Habrant, D.; Rauhala, V.; Koskinen, A. M. P. Conversion of Carbonyl Compounds to Alkynes: General Overview and Recent Developments. *Chem. Soc. Rev.* **2010**, *39* (6), 2007.

(97) Mahrwald, R. The Long Underestimated Carbonyl Function of Carbohydrates – an Organocatalyzed Shot into Carbohydrate Chemistry. *Chem. Commun.* **2015**, *51* (73), 13868–13877.

(98) Bubb, W. A. NMR Spectroscopy in the Study of Carbohydrates: Characterizing the Structural Complexity. *Concepts Magn. Reson. Part A* **2003**, *19A* (1), 1–19.

(99) Colvin, E. W.; Hamill, B. J. A Simple Procedure for the Elaboration of Carbonyl Compounds into Homologous Alkynes. *J. Chem. Soc. Perkin 1* **1977**, No. 8, 869.

(100) Sundell, R.; Kanerva, L. T. Lipases in the Regioselective Preparation of Glyceric Acid Esters of Methyl Glycosides. *Eur. J. Org. Chem.* **2013**, *2013* (22), 4971–4978.

(101) Kono, H.; Hashimoto, H.; Shimizu, Y. NMR Characterization of Cellulose Acetate: Chemical Shift Assignments, Substituent Effects, and Chemical Shift Additivity. *Carbohydr. Polym.* **2015**, *118*, 91–100.

(102) Attolino, E.; Catelani, G.; D'Andrea, F. Regiospecific Synthesis of 4-Deoxy-D-Threo-Hex-3-Enopyranosides by Simultaneous Activation–Elimination of the Talopyranoside Axial 4-OH with the NaH/Im2SO2 System: Manifestation of the Stereoelectronic Effect. *Eur. J. Org. Chem.* **2006**, *2006* (23), 5279–5292.

(103) Betaneli, V. I.; Ott, A. Ya.; Brukhanova, O. V.; Kochetkov, N. K. Synthesis of 1,2-O-Cyanoethylidene Derivatives of Alkyl Glycopyranuronates by Oxidation of the 6-Trityl Ethers of Their Hexose Analogues. *Carbohydr. Res.* **1988**, *179*, 37–50.

(104) Matwiejuk, M.; Thiem, J. Hydroxy Group Acidities of Partially Protected Glycopyranosides. *Eur. J. Org. Chem.* **2012**, *2012* (11), 2180–2187.

(105) Speciale, I.; Notaro, A.; Garcia-Vello, P.; Di Lorenzo, F.; Armiento, S.; Molinaro, A.; Marchetti, R.; Silipo, A.; De Castro, C. Liquid-State NMR Spectroscopy for Complex Carbohydrate Structural Analysis: A Hitchhiker's Guide. *Carbohydr. Polym.* **2022**, *277*, 118885.

(106) Fehr, C. Diastereoface-Selective Epoxidations: Dependency on the Reagent Electrophilicity. *Angew. Chem. Int. Ed.* **1998**, *37* (17), 2407–2409.

(107) McKittrick, B. A.; Ganem, B. Syn-Stereoselective Epoxidation of Allylic Ethers Using CF3CO3H. *Tetrahedron Lett.* **1985**, *26* (40), 4895–4898.

(108) Chiu, C. K.-F.; Govindan, S. V.; Fuchs, P. L. Synthesis of 15-Deoxy-16.Beta.-Ethoxybruceantin and Synthetic Efforts toward Bruceantin. *J. Org. Chem.* **1994**, *59* (2), 311–323.

(109) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. Lewis Acid-Catalyzed Ring-Opening Reactions of Semicyclic *N* , *O* -Acetals Possessing an Exocyclic Nitrogen Atom: Mechanistic Aspect and Application to Piperidine Alkaloid Synthesis. *J. Am. Chem. Soc.* **2001**, *123* (50), 12510–12517.

(110) Courant, T.; Gavel, M.; Renard, R. M. Q.; Gandon, V.; Joosten, A. Y. P.; Lecourt, T. Zirconium-Catalyzed Hydroalumination of C═O Bonds: Site-Selective De- *O* -Acetylation

of Peracetylated Compounds and Mechanistic Insights. *J. Org. Chem.* **2021**, *86* (14), 9280–9288.

(111) Kehner, R. A.; Hewitt, M. C.; Bayeh-Romero, L. Expanding Zirconocene Hydride Catalysis: *In Situ* Generation and Turnover of ZrH Catalysts Enabling Catalytic Carbonyl Reductions. *ACS Catal.* **2022**, *12* (3), 1758–1763.

(112) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. Zr-Mediated Hydroboration: Stereoselective Synthesis of Vinyl Boronic Esters. *Tetrahedron Lett.* **2005**, *46* (50), 8777–8780.

(113) Hitosugi, S.; Tanimoto, D.; Nakanishi, W.; Isobe, H. A Facile Chromatographic Method for Purification of Pinacol Boronic Esters. *Chem. Lett.* **2012**, *41* (9), 972–973.

(114) Tako, M.; Shimabukuro, J.; Jiang, W.; Yamada, M.; Ishida, H.; Kiso, M. Rare 6-Deoxy-D-Altrose from the Folk Medicinal Mushroom Lactarius Akahatsu. *Biochem. Compd.* **2013**, *1* (1), 5.

(115) Tsukamoto, S.; Hayashi, K.; Kaneko, K. Identification of the Absolute Stereochemistry of D- and L-Digitoxose Using a Chiral High-Pressure Liquid Chromatography Column. *J. Chem. Soc. Perkin 1* **1988**, No. 9, 2621.

(116) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M.; Aubé, J. HFIP in Organic Synthesis. *Chem. Rev.* **2022**, *122* (15), 12544–12747.

(117) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a Highly Versatile Solvent. *Nat. Rev. Chem.* **2017**, *1* (11), 0088.

(118) Hofferberth, M. L.; Brückner, R. A- and β-Lipomycin: Total Syntheses by Sequential Stille Couplings and Assignment of the Absolute Configuration of All Stereogenic Centers. *Angew. Chem. Int. Ed.* **2014**, *53* (28), 7328–7334.

(119) Kotammagari, T. K.; Gonnade, R. G.; Bhattacharya, A. K. Synthesis of Naturally Occurring (+)-Osmundalactone and 4-Epi-(+)-Osmundalactone from Triacetyl-O-d-Glucal. *Tetrahedron Lett.* **2015**, *56* (21), 2783–2786.

Experimental Sections

General considerations

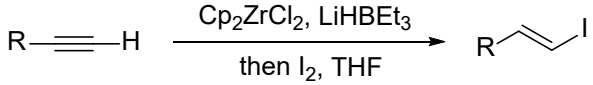
^{1}H and ^{13}C NMR spectra were recorded with Varian AVIII 400, INOVA 500, Bruker NEO 400, AVANCE 600 equipped with a cryogen probe, and ASCEND 800 spectrometers. NMR spectra were measured from solutions in deuterated chloroform ($CDCl_3$) and benzene (C_6D_6), using the residual chloroform resonances (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR) and benzene resonances (7.16 ppm ^{1}H NMR and 128.06 ppm for ^{13}C NMR) as internal standards, and were reported in parts per million (ppm). As vinylic ethers are susceptible to acid-catalyzed hydrolysis, deuterated chloroform was stored over anhydrous K_2CO_3 to neutralize traces of DCl and kept dry with anhydrous Na_2SO_4. Abbreviations for NMR signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet; br, broad.

Mass spectra (high resolution ESI and APCI) were recorded on a Thermo LTQ FTMS Mass spectrometer. IR spectra were collected on a Thermo Scientific Nicolet iS10 FT-IR spectrometer as neat films on a plate with diamond screw-down tip. Optical rotations were measured using a Perkin-Elmer 341 polarimeter (concentration in g/100mL). Thin layer chromatography (TLC) was performed on a precoated glass backed plates purchased from Silicycle (silica gel 60F254; 0.25 mm thickness), or on precoated aluminum-backed plates purchased from Whatman (silica gel 60F254). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle, or with neutral alumina (activated, Brockman activity I, 60 Å mean pore size) from Sigma Aldrich and Supelco.

All reactions were conducted with anhydrous solvents in oven-dried and argon-charged glassware. Reactants were used as received from commercial suppliers without prior purification, as were solvents used for extractions and chromatographic separations. All chemicals were purchased from Sigma Aldrich, Oakwood Chemical, TCI Chemicals, Ambeed, Synthonix, and Combi-blocks. Cs_2CO_3 (99.9% trace metal basis or 99% Reagent Plus) was purchased in 5-25 g quantities from Sigma Aldrich. CuI was purchased from Ambeed or Sigma Aldrich. Zn-Cu couple was purchased from Oakwood Chemicals. Anhydrous THF and DMF were obtained from the Pure Process Purification solvent system. Methanol, isopropanol, acetone, and tetraglyme were used as received from commercial suppliers. Anhydrous DME (with 100 ppm of BHT inhibitor, extra dry (≥99.0%, ≤0.005% H_2O), containing 4Å molecular sieves) was purchased from Acros Organic. Vinylic ethers are highly susceptible to hydrolysis, due to the mildly acidic nature of silica gel used for flash column chromatography. Most vinylic ethers were purified using silica gel pre-treated with at least 2% triethylamine.

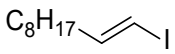
Experimental for Chapter 2

General protocol for (*E*)-vinylic iodides:



The following procedure has been modified from the published synthesis of (*E*)-vinyl iodide via hydrozirconation – iodination [1]:

An oven-dried reaction vessel (250-mL round bottom flask for the 20 mmol scale of decyne or 5-mL conical vial for 1-2 mmol of other alkynes) was charged with zirconocene dichloride (Cp_2ZrCl_2, 1.7 equiv) and corresponding alkyne in tetrahydrofuran (THF, 0.35 M). To this solution at room temperature was added a 1.0 M THF solution of lithium triethylborohydride ($LiHBEt_3$, 1.3 equiv). The cloudy solution turned clear orange or yellow. After 10 min of stirring, approximately 1 M solution of iodine (1.2 equiv) in THF was added dropwise until the brown color persisted. After additional stirring at rt for 10 min, the reaction mixture was quenched with a 1N HCl solution and then extracted with diethyl ether (× 3). The organic layer was washed with an aqueous solution of saturated $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered the solution through a filter paper and concentrated on rotary evaporator. The details of column chromatography and yields are listed below. The characterization data for various vinyl iodides **112**[2]**, S1**[3], and **S5**[4] matched the published data.

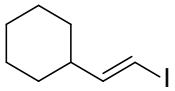


112

Synthesis of (*E*)-1-iodo-1-decene (112): Prepared 3.915 g (74% yield) from 1-decyne; eluent = pure hexanes

Characterization data for (*E*)-1-iodo-1-decene (**112**)[2]:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 14.3, 7.2 Hz, 1H), 5.97 (dt, *J* = 14.4, 1.4 Hz, 1H), 2.04 (qd, *J* = 7.2, 1.5 Hz, 2H), 1.43 – 1.21 (m, 12H), 0.94 – 0.81 (t, 3H).



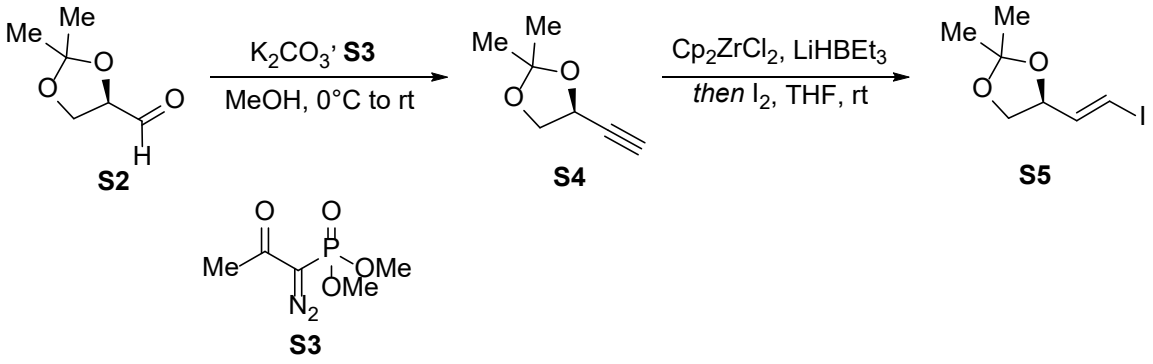
S1

Synthesis of (*E*)-(2-iodovinyl)cyclohexane (S1): Prepared 248.2 mg (76% yield) from cyclohexyl-acetylene, eluent = pure pentane; solvent was evaporated using rotary evaporator with bath temperature 5-10 °C.

Characterization data for (*E*)-(2-iodovinyl)cyclohexane (**S1**)[3]:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 14.5, 7.1 Hz, 1H), 5.95 (dd, *J* = 14.5, 1.3 Hz, 1H), 2.00 (dddd, *J* = 11.2, 5.5, 4.6, 2.8 Hz, 1H), 1.77 – 1.68 (m, 4H), 1.64 (ddq, *J* = 12.6, 3.6, 1.8 Hz, 1H), 1.37 – 1.03 (m, 5H).

Synthesis of (*S*,*E*)-4-(2-iodovinyl)-2,2-dimethyl-1,3-dioxolane (S5): Prepared in two steps via (*S*)-4-ethynyl-2,2-dimethyl-1,3-dioxolane (**S4**).



A solution of D-glyceraldehyde acetonide **S2** (50 w/w % in CH_2Cl_2, 0.956 g, 3.67 mmol) and the Bestmann–Ohira reagent **S3**[5] (1.41 g, 7.35 mmol; synthesized according to the published literature)[5] in methanol (18 mL) was cooled to 0 °C. Anhydrous K_2CO_3 (1.02 g, 7.35 mmol) was added in four portions over 30 min. The mixture was stirred for 15 h, while slowly warming to room temperature. Saturated aqueous ammonium chloride (50 mL) was added, and the aqueous solution was extracted with pentane (50 mL × 3). The organic layer was separated, dried over $MgSO_4$, and then filtered with filter paper. The solvent was carefully evaporated on rotary evaporator (bath 5-10 ºC). Due to its volatility, the crude alkyne **S4** was filtered through a short pad of Celite®/silica gel, then the short plug was washed with pentane/diethyl ether 10:1 (50 mL). Terminal alkyne **S4** (0.410 g, 88% yield) was isolated as a colorless oil. The ^{1}H NMR spectrum matched the published data[6].

Characterization data for (*S*)-4-ethynyl-2,2-dimethyl-1,3-dioxolane (**S4**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (td, *J* = 6.3, 2.1 Hz, 1H), 4.18 (dd, *J* = 8.1, 6.3 Hz, 1H), 3.95 (dd, *J* = 8.1, 6.2 Hz, 1H), 2.50 (d, *J* = 2.1 Hz, 1H), 1.50 (d, *J* = 0.8 Hz, 3H), 1.39 (d, *J* = 0.7 Hz, 3H).

Alkyne **S4** (50 mg, 0.39 mmol) was converted into the (*E*)-vinylic iodide **S5** following the general hydrozirconation - iodination procedure, giving 69.4 mg (69% yield), eluent = 10:1 pentane / diethyl ether; solvents were removed using rotary evaporator with bath temperature 5-10 °C.

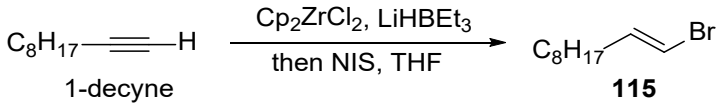
* Subsequent C-O cross-coupling with 1,2:3,4-di-*O*-isopropylidene-a-D-galactopyranose **14** revealed that vinylic iodide **S5** was produced as an 89 : 11 mixture of enantiomers. Stereochemical erosion is attributed to this step, preparing the alkyne **S4** from the epimerizable aldehyde **S2**.

Characterization data for (*S*,*E*)-4-(2-iodovinyl)-2,2-dimethyl-1,3-dioxolane (**S5**)[4]:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 14.5, 6.1 Hz, 1H), 6.50 (d, *J* = 14.5 Hz, 1H), 4.48 (dt, *J* = 7.1, 6.1 Hz, 1H), 4.11 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.65 (dd, *J* = 8.4, 7.1 Hz, 1H), 1.43 (d, *J* = 0.8 Hz, 3H), 1.38 (q, *J* = 0.7 Hz, 3H).

$[\alpha]^{22}_D$ +3.8 (c = 0.1, $CHCl_3$)

Synthesis of (*E*)-1-bromo-1-decene (115):



1-decyne **115**

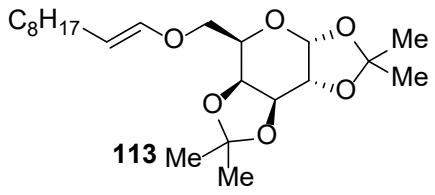
In an oven-dried 25mL round bottom flask was charged with Cp_2ZrCl_2 (987 mg, 1.7 equiv.) and 1-decyne (0.36 mL, 1.0 equiv) in THF (5.5 mL, 0.35 M). To this solution at room temperature was added a 1.0 M THF solution of $LiHBEt_3$ (2.6 mL, 1.3 equiv). After 10 min of stirring, *N*-bromosuccinimide (NBS, 471 mg, 1.2 equiv) was added. After additional stirring for 30 min, the reaction mixture was quenched with a 1N HCl solution (50 mL) and then extracted with diethyl ether (50 mL× 3). The organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL) and

brine (50 mL), dried over $MgSO_4$, and then filtered on filter paper. The solvent was concentrated on rotary evaporator. The crude was dissolved in hexanes, and white solids crashed out. The solution was filtered through a short pad of Celite®/silica gel and washed with hexanes to yield (*E*)-1-bromo-1-decene as a colorless oil (0.391 g, 89% yield). The ^{1}H NMR spectrum data matched the published data[7].

Characterization data for (*E*)-1-bromo-1-decene **(115):**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (dt, *J* = 13.4, 7.2 Hz, 1H), 6.00 (dt, *J* = 13.5, 1.4 Hz, 1H), 2.03 (qd, *J* = 7.2, 1.4 Hz, 2H), 1.45 – 1.21 (m, 12H), 0.92 – 0.81 (m, 3H).

Representative procedure for the synthesis of 1,2-disubstituted (*E*)-vinylic ethers (conditions A): An oven-dried 4 mL vial charged with a stir bar was added alcohol (1 equiv), Cs_2CO_3 (3 equiv), **L4** (0.4 equiv), and *E*-vinylic iodide (1 equiv) under argon. The reaction vial was purged continuously with argon for 5 min before CuI (0.2 equiv) was added. Anhydrous DME (0.5 mL, 0.7 M based on vinylic iodide) was added, and the reaction mixture was bubbled with argon for 5 minutes. The reaction vial was quickly closed with a solid cap, sealed with Teflon tape and electrical tape, and placed on the heat with internal temperature at 75 °C. The reaction was stirred over 40 - 48 hours, cooled to room temperature, and diluted with diethyl ether. The mixture was filtered through a Celite® pad and rinsed with diethyl ether (100 mL). The filtrate was concentrated by rotary evaporator, and the crude mixture was subjected to flash column chromatography with 2% Et_3N-treated silica gel using hexanes/EtOAc as eluent to purify vinylic ethers.



Using conditions A, with 1,2:3,4-di-*O*-isopropylidene-a-D-galactopyranose (**14**, 127 mg, 0.49 mmol, 1 equiv), vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1 inch diameter, up to 6-inch height), eluting with 92 : 8 hexanes/EtOAc (visualized with *p*-anisaldehyde stain) to afford vinylic ether **113** as a clear pale-yellow oil (152 mg, 78% yield).

Characterization data for (*E*)-vinylic ether **113**:

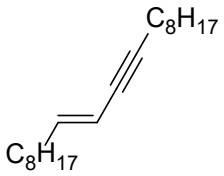
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (dt, *J* = 12.6, 1.3 Hz, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 4.80 (dt, *J* = 12.6, 7.3 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.32 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.26 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.02 (ddd, *J* = 7.3, 5.5, 1.9 Hz, 1H), 3.81 (qd, *J* = 10.3, 6.3 Hz, 2H), 1.89 (qd, *J* = 7.2, 1.3 Hz, 2H), 1.53 (s, 3H), 1.45 (s, 3H), 1.40 – 1.17 (m, 18H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.9, 109.5, 108.8, 104.8, 96.5, 71.2, 70.8, 70.7, 67.5, 66.4, 32.0, 30.8, 29.6, 29.4, 29.2, 27.8, 26.2, 26.1, 25.1, 24.6, 22.8, 14.3.

HRMS (APCI): *m/z* calcd for $C_{22}H_{39}O_6^+$ $[M+H]^+$ 399.2741, found 399.2739.

$[\alpha]^{22}_D$ -50.4 (c = 0.1, $CHCl_3$)

(*E*)-Enyne **114** was isolated from early experiments using ligand **L1**.

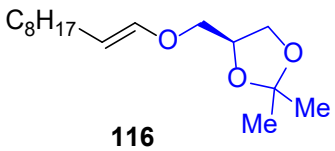


114

Characterization of (*E*)-enyne **114**[8]**:**

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.04 (dtd, J = 15.7, 7.0, 1.4 Hz, 1H), 5.44 (dp, J = 15.8, 1.9 Hz, 1H), 2.27 (tt, J = 7.3, 1.8 Hz, 2H), 2.06 (qd, J = 7.1, 1.6 Hz, 2H), 1.35 – 1.16 (m, 24H), 0.88 (tt, J = 7.2, 1.6 Hz, 6H).

HRMS (APCI): *m/z* calcd for $C_{20}H_{37}^+$, 277.2890, found 277.2891.



116

Using conditions A, with (*S*)-1,2-*O*-Isopropylideneglycerol (99.7 mg, 0.49 mmol, 1 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 98:2 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **116** as a clear pale-yellow oil (98.9 mg, 84%).

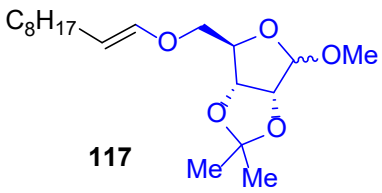
Characterization data for (*E*)-vinylic ether **116**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 12.7, 1.3 Hz, 1H), 4.77 (dt, *J* = 12.6, 7.4 Hz, 1H), 4.32 (apparent quintet, *J* = 6.0 Hz, 1H), 4.08 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.77 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.71 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.63 (dd, *J* = 10.1, 5.6 Hz, 1H), 1.89 (qd, *J* = 7.3, 1.4 Hz, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.32 – 1.22 (m, 12H), 0.87 (t, *J* = 6.6 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.9, 109.8, 104.9, 74.2, 69.7, 66.8, 32.0, 30.8, 29.6, 29.4, 29.2, 27.8, 26.9, 25.5, 22.8, 14.3.

HRMS (APCI): *m/z* calcd for $C_{16}H_{31}O_3^+$ $[M+H]^+$ 271.2268, found 271.2261.

$[\alpha]^{23}_D$ 5.80 (c = 0.1, $CHCl_3$).



117

Using conditions A, with methyl 2,3-*O*-(1-methylethylidene)-b-D-ribofuranoside (99.7 mg, 0.49 mmol, 1 equiv; synthesized according to literature from D-ribose)[34] and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 99:1 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **117** as a clear pale-yellow oil (129.5 mg, 77%).

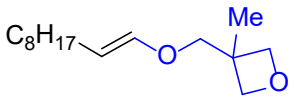
Characterization data for (*E*)-vinylic ether **117**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 12.5, 1.2 Hz, 1H), 4.97 (s, 1H), 4.77 (dt, *J* = 12.6, 7.3 Hz, 1H), 4.67 (dd, *J* = 5.9, 1.0 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 1H), 4.37 (ddd, *J* = 7.7, 6.4, 1.0 Hz, 1H), 3.71 – 3.56 (m, 2H), 3.32 (s, 3H), 1.89 (qd, *J* = 7.1, 1.3 Hz, 2H), 1.48 (s, 3H), 1.31 (s, 3H), 1.30 – 1.20 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.6, 112.6, 109.4, 105.0, 85.2, 84.7, 82.1, 69.5, 55.0, 32.0, 30.8, 29.6, 29.5, 29.2, 27.8, 26.6, 25.1, 22.8, 14.3.

HRMS (APCI): *m/z* calcd for $C_{19}H_{35}O_5^+$ $[M+H]^+$ 343.2479, found 343.2473.

$[\alpha]^{23}_D$ -31.4 (c = 0.1, $CHCl_3$).



118

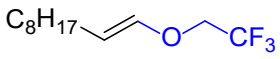
Using conditions A, with 3-methyl-3-oxetanemethanol (49.9 mg, 0.49 mmol, 1 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 95:5 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **118** as a clear pale-yellow oil (81.6 mg, 70%).

Characterization data for (*E*)-vinylic ether **118**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (dt, *J* = 12.8, 1.3 Hz, 1H), 4.79 (dt, *J* = 12.7, 7.3 Hz, 1H), 4.53 (d, *J* = 5.8 Hz, 2H), 4.38 (d, *J* = 5.8 Hz, 2H), 3.69 (s, 2H), 1.91 (qd, *J* = 7.2, 1.3 Hz, 2H), 1.33 (s, 3H), 1.32 – 1.22 (m, 12H), 0.88 (t, *J* = 6.5 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.3, 104.5, 80.0 (2C), 73.8, 39.7, 32.0, 30.9, 29.6, 29.5, 29.2, 27.9, 22.8, 21.4, 14.3.

HRMS (APCI): *m/z* calcd for $C_{15}H_{29}O_2^+$ $[M+H]^+$ 241.2162, found 241.2156.



119

Using conditions A, with 2,2,2-trifluoroethanol (48.9 mg, 0.49 mmol, 1 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 98:2 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **119** as a clear pale-yellow oil (64.0 mg, 55% yield).

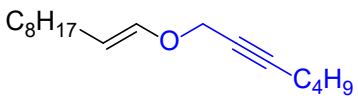
Characterization data for (*E*)-vinylic ether **119**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 – 6.18 (m, 1H), 4.90 (dt, *J* = 12.5, 7.4 Hz, 1H), 3.99 (q, $^{3}J_{HF}$ = 8.3 Hz, 2H), 1.91 (qd, *J* = 7.3, 1.3 Hz, 2H), 1.39 – 1.19 (m, 12H), 0.92 – 0.84 (m, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.8, 123.6 (q, $^{i}J_{CF}$ 278 Hz), 107.5, 66.6 (q, $^{2}J_{CF}$ = 35 Hz), 32.0, 30.4, 29.5, 29.4, 29.1, 27.4, 22.8, 14.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.22 (t, J = 8.3 Hz).

HRMS (APCI): *m/z* calcd for $C_{12}H_{21}F_3O^+$ $[M+H]^+$ 239.1617, found 239.1614.



120

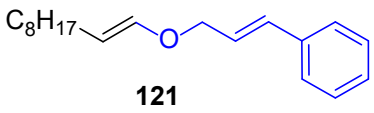
Using conditions A, with 2-heptyn-1-ol (46.4 mg, 0.41 mmol, 1 equiv) and **112** (110 mg, 0.41 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6.7-inch height), eluting with 100% hexanes (visualized with *p*-anisaldehyde) to afford vinylic ether **120** as a clear pale-yellow oil (84.0 mg, 81% yield).

Characterization data for (*E*)-vinylic ether **120**[9]**:**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dt, *J* = 12.5, 1.3 Hz, 1H), 4.87 (dt, *J* = 12.6, 7.4 Hz, 1H), 4.30 (t, *J* = 2.1 Hz, 2H), 2.22 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.91 (qd, *J* = 7.2, 1.3 Hz, 2H), 1.54 – 1.37 (m, 4H), 1.37 – 1.19 (m, 12H), 0.95 – 0.83 (m, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.7, 106.2, 87.9, 75.2, 57.5, 32.0, 30.70, 30.66, 29.6, 29.5, 29.2, 27.8, 22.8, 22.0, 18.6, 14.3, 13.7.

HRMS (APCI): *m/z* calcd for $C_{17}H_{31}O^+$ 251.2369, found 251.2370



121

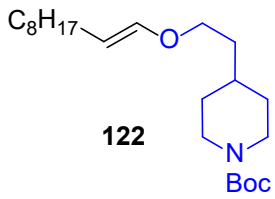
Using conditions A, with cinnamyl alcohol (65.5 mg, 0.49 mmol, 1 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The reaction mixture was stirred at 70 °C for 18 h. The crude ^{1}H NMR spectrum showed about 9% of two aldehyde diastereomers, in a 5 : 4 ratio, with doublets at 9.58 ppm and 9.44 ppm, respectively. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 100% hexanes (visualized with *p*-anisaldehyde) to afford vinylic ether **121** as a clear pale-yellow oil (85.9 mg, 65% yield).

Characterization data for (*E*)-vinylic ether **121**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.22 (m, 5H), 6.64 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.31 (dt, *J* = 15.9, 5.9 Hz, 1H), 6.27 (dt, *J* = 12.4, 1.1 Hz, 1H), 4.87 (dt, *J* = 12.5, 7.4 Hz, 1H), 4.35 (dd, *J* = 5.9, 1.5 Hz, 2H), 1.92 (qd, *J* = 7.2, 1.3 Hz, 2H), 1.40 – 1.23 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.6, 136. 7, 132.8, 128.7 (2C), 127.9, 126.7 (2C), 125.1, 105.5, 69.9, 32.0, 30.8, 29.6, 29.5, 29.2, 27.9, 22.8, 14.3.

HRMS (APCI): *m/z* calcd for $C_{19}H_{29}O^+$ $[M+H]^+$ 273.2213, found 273.2212.



122

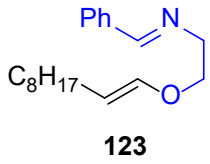
Using conditions A, with *N*-Boc-4-piperidineethanol (94.8 mg, 0.41 mmol, 1 equiv) and vinylic iodide **112** (110 mg, 0.41 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 9:1 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **122** as a clear pale-yellow oil (97.1 mg, 64%).

Characterization data for (*E*)-vinylic ether **122**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 12.6, 1.3 Hz, 1H), 4.75 (dt, *J* = 12.6, 7.3 Hz, 1H), 4.19 – 3.95 (br s, 2H), 3.67 (t, *J* = 6.1 Hz, 2H), 2.68 (br t, *J* = 12.8 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.64 (d, *J* = 3.6 Hz, 2H), 1.60 – 1.54 (m, 2H), 1.45 (s, 9H), 1.34 – 1.20 (m, 12H), 1.11 (qd, *J* = 12.5, 4.4 Hz, 2H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.0, 146.0, 104.5, 79.4, 66.5, 44.1, 36.0, 32.9, 32.2, 32.0, 30.9, 29.6, 29.5, 29.2, 28.6, 27.9, 22.8, 14.3.

HRMS (ESI): *m/z* calcd for $C_{22}H_{42}NO_3^+$ $[M+H]^+$ 368.3159, found 368.3156.



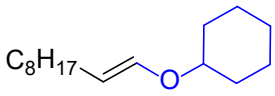
123

Using conditions A, with *(E)*-2-(benzylideneamino)ethan-1-ol[9] (72.9 mg, 0.5 mmol, 1 equiv) and vinylic iodide **112** (130 mg, 0.5 mmol, 1 equiv) as substrates. The dark brown crude oil was

subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 20:1 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **123** as a clear pale-yellow oil (70.0 mg, 50 %).

Characterization data for (*E*)-vinylic ether **123**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 1.4 Hz, 1H), 7.78 – 7.64 (m, 2H), 7.47 – 7.34 (m, 3H), 6.23 (dt, *J* = 12.6, 1.3 Hz, 1H), 4.79 (dt, *J* = 12.6, 7.3 Hz, 1H), 4.50 – 4.42 (m, 0H), 3.96 (t, *J* = 5.8 Hz, 2H), 3.89 – 3.80 (m, 2H), 1.93 – 1.83 (m, 2H), 1.26 (d, *J* = 7.5 Hz, 12H), 0.93 – 0.81 (m, 3H).



124

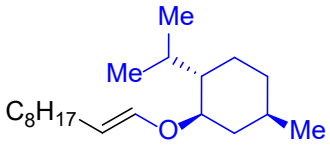
Using conditions A, with cyclohexanol (97.8 mg, 0.98 mmol, 2 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with gradient 98:2 to 97:3 hexanes/EtOAc (visualized with phosphomolybdic acid) to afford vinylic ether **124** as a clear pale-yellow oil (64.0 mg, 55%).

Characterization data for (*E*)-vinylic ether **124**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, *J* = 12.3, 1.3 Hz, 1H), 4.88 (dt, *J* = 12.3, 7.4 Hz, 1H), 3.59 (tt, *J* = 9.2, 3.8 Hz, 1H), 1.88 (tdd, *J* = 8.7, 4.6, 2.4 Hz, 4H), 1.80 – 1.67 (m, 2H), 1.57 – 1.47 (m, 1H), 1.46 – 1.15 (m, 17H), 0.86 (t, *J* = 6.8 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.6, 106.5, 78.1, 32.3, 32.0, 30.8, 29.6, 29.5, 29.2, 27.8, 25.7, 24.0, 22.8, 14.3.

HRMS (APCI): *m/z* calcd for $C_{16}H_{31}O^+$ $[M+H]^+$ 239.2369, found 239.2365



125

Using conditions A, with (-)-menthol (153 mg, 0.98 mmol, 2 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 100% hexanes (visualized with *p*-anisaldehyde) to afford vinylic ether **125** as a clear pale-yellow oil (59.0 mg, 41% yield).

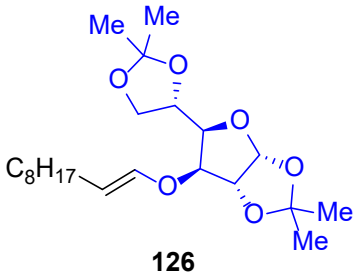
Characterization data for (*E*)-vinylic ether **125**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, *J* = 12.3, 1.3 Hz, 1H), 4.86 (dt, *J* = 12.3, 7.4 Hz, 1H), 3.38 (td, *J* = 10.7, 4.3 Hz, 1H), 2.13 (pd, *J* = 7.0, 2.8 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.88 (qd, *J* = 7.3, 1.4 Hz, 2H), 1.64 (ddq, *J* = 12.6, 6.3, 3.2 Hz, 2H), 1.42 – 1.29 (m, 1H), 1.31 – 1.20 (m, 15H), 1.08 – 0.80 (m, 4H), 0.90 (d, *J* = 2.2 Hz, 3H), 0.88 (d, *J* = 2.1 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 145.4, 106.0, 80.2, 48.0, 41.2, 34.6, 32.0, 31.7, 30.8, 29.6, 29.5, 29.2, 27.8, 25.8, 23.5, 22.8, 22.3, 20.9, 16.4, 14.3.

HRMS (APCI): *m/z* calcd for $C_{20}H_{39}O^+$ $[M+H]^+$ 295.2995, found 295.2993.

$[\alpha]^{23}_D$ -25.2 (c = 0.1, $CHCl_3$)



126

Using conditions A, with 1,2:5,6-di-*O*-isopropylidene-a-D-glucofuranose (254.3 mg, 0.98 mmol, 2 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 92:8 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **126** as a clear pale-yellow oil (70.0 mg, 36% yield).

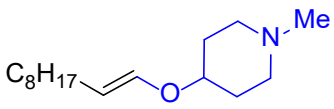
Characterization data for (*E*)-vinylic ether **126**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dt, *J* = 12.6, 1.3 Hz, 1H), 5.87 (d, *J* = 3.8 Hz, 1H), 4.94 (dt, *J* = 12.5, 7.4 Hz, 1H), 4.57 (d, *J* = 3.8 Hz, 1H), 4.31 (dt, *J* = 7.7, 5.8 Hz, 1H), 4.23 (d, *J* = 3.0 Hz, 1H), 4.16 (dd, *J* = 7.6, 3.0 Hz, 1H), 4.12 – 3.95 (m, 2H), 1.90 (qd, *J* = 7.1, 1.3 Hz, 2H), 1.51 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.30 – 1.16 (m, 12H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.2, 112.0, 109.3, 107.7, 105.3, 82.3, 81.2, 80.7, 72.3, 67.2, 32.0, 30.5, 29.6, 29.4, 29.3, 27.7, 27.0, 26.9, 26.4, 25.5, 22.8, 14.3.

HRMS (APCI): *m/z* calcd for $C_{22}H_{39}O_6^+$ $[M+H]^+$ 399.2741, found 399.2729.

$[\alpha]^{22}_D$ -12.0 (c = 0.1, $CHCl_3$).



127

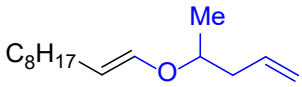
Using conditions A, with *N*-methyl-4-piperidinol (119 mg, 0.98 mmol, 2 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 3% Et_3N in EtOAc (column: 1-inch diameter, up to 6-inch height), eluting with 100:3 EtOAc/Et_3N (visualized with phosphomolybdic acid) to afford vinylic ether **127** as a clear pale-yellow oil (92.3 mg, 75%).

Characterization data for (*E*)-vinylic ether **127**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, *J* = 12.4, 1.3 Hz, 1H), 4.90 (dt, *J* = 12.3, 7.4 Hz, 1H), 3.67 (br tt, *J* = 8.2, 3.9 Hz, 1H), 2.63 (br t, *J* = 9.9 Hz, 2H), 2.17 (br t, *J* = 9.4 Hz, 2H), 1.88 (dtd, *J* = 10.3, 5.6, 2.0 Hz, 4H), 1.70 (dtd, *J* = 12.6, 8.4, 3.6 Hz, 2H), 1.39 – 1.17 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.2, 107.2, 74.7, 52.9, 46.3, 32.0, 31.3, 30.7, 29.6, 29.4, 29.2, 27.8, 22.8, 14.2.

HRMS (APCI): *m/z* calcd for $C_{16}H_{32}NO^+$ $[M+H]^+$ 254.2478, found 254.2476.



128

Using conditions A, with 4-penten-2-ol (84.1 mg, 0.98 mmol, 2 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch

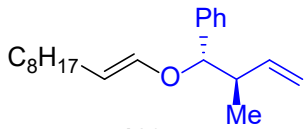
diameter, up to 6-inch height), eluting with 100% hexanes (visualized with *p*-anisaldehyde) to afford vinylic ether **128** as a clear pale-yellow oil (48.6 mg, 44% yield).

Characterization data for (*E*)-vinylic ether **128**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (dt, *J* = 12.3, 1.3 Hz, 1H), 5.80 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.12 – 5.07 (m, 1H), 5.06 (dtd, *J* = 3.2, 2.1, 1.3 Hz, 1H), 4.88 (dt, *J* = 12.4, 7.4 Hz, 1H), 3.81 (sextet, *J* = 6.2 Hz, 1H), 2.37 (dddt, *J* = 14.0, 7.0, 5.7, 1.4 Hz, 1H), 2.29 – 2.16 (m, 1H), 1.89 (qd, *J* = 7.3, 1.3 Hz, 2H), 1.36 – 1.21 (m, 12H), 1.19 (d, *J* = 6.2 Hz, 3H), 0.88 (t, *J* = 6.6 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.8, 134.5, 117.4, 106.9, 75.7, 40.8, 32.0, 30.7, 29.6, 29.5, 29.2, 27.8, 22.8, 19.7, 14.3.

HRMS (APCI): *m/z* calcd for $C_{15}H_{29}O^+$ $[M+H]^+$ 225.2212, found 225.2210.



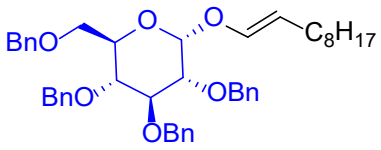
129

Using conditions A, with (1S,2R)-2-methyl-1-phenylbut-3-en-1-ol[10] (158.5 mg, 0.98 mmol, 2 equiv) and vinylic iodide **112** (130 mg, 0.49 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 100% hexanes (visualized with *p*-anisaldehyde) to afford vinylic ether **129** as a clear pale-yellow oil (89.6 mg, 82% yield).

Characterization data for (*E*)-vinylic ether **129**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.30 – 7.19 (m, 3H), 6.02 (dt, *J* = 12.4, 1.3 Hz, 1H), 5.85 (ddd, *J* = 17.2, 10.5, 7.3 Hz, 1H), 5.06 – 4.97 (m, 2H), 4.81 (dt, *J* = 14.9, 7.4 Hz, 1H), 4.44

(d, *J* = 6.6 Hz, 1H), 2.60 (h, *J* = 7.0 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.20 (s, 12H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H).

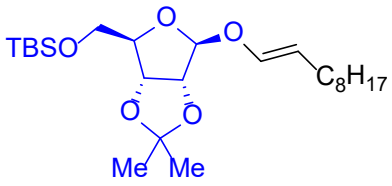


130

Using conditions A, with 2,3,4,6-Tetrakis-O-(phenylmethyl)-α-D-glucopyranose (324 mg, 0.6 mmol, 2 equiv) and vinylic iodide **112** (80 mg, 0.30 mmol, 1 equiv) as substrates. The crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 10:1 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **130** as a clear pale-yellow oil (75 mg, 37% yield).

Characterization data for (*E*)-vinylic ether **130**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 18H), 7.22 – 7.11 (m, 2H), 6.31 (dt, *J* = 12.2, 1.3 Hz, 1H), 5.19 (dt, *J* = 12.3, 7.5 Hz, 1H), 4.93 (dd, *J* = 10.9, 2.7 Hz, 2H), 4.82 (dd, *J* = 10.8, 9.2 Hz, 2H), 4.72 (d, *J* = 10.8 Hz, 1H), 4.65 – 4.59 (m, 2H), 4.59 – 4.50 (m, 2H), 3.77 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.70 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.66 (d, *J* = 8.9 Hz, 1H), 3.61 (t, *J* = 9.1 Hz, 1H), 3.57 – 3.53 (m, 1H), 3.53 – 3.48 (m, 1H), 2.01 – 1.87 (m, 2H), 1.33 – 1.20 (m, 12H), 0.89 (t, *J* = 6.7 Hz, 3H).

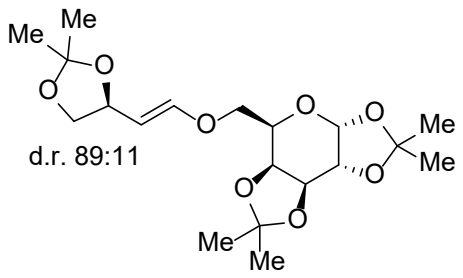


131

Using conditions A, with 5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-D-ribose[11] (183 mg, 0.6 mmol, 2 equiv) and vinylic iodide **112** (80 mg, 0.30 mmol, 1 equiv) as substrates. The crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 10:1 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford vinylic ether **131** as a clear pale-yellow oil (68 mg, 55% yield).

Characterization data for (*E*)-vinylic ether **131**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dt, *J* = 12.4, 1.3 Hz, 1H), 5.26 (s, 1H), 4.97 (dt, *J* = 12.4, 7.4 Hz, 1H), 4.76 – 4.72 (m, 1H), 4.65 (d, *J* = 6.0 Hz, 1H), 4.25 – 4.19 (m, 1H), 3.61 (dd, *J* = 10.4, 5.3 Hz, 1H), 3.52 (dd, *J* = 10.4, 9.3 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H), 1.26 (s, 12H), 0.89 (s, 9H), 0.88 (s, 3H), 0.06 (s, 6H).



132

Using conditions A, with alcohol **14** (188 mg, 0.71 mmol, 2 equiv) and vinylic iodide **S5** (90 mg, 0.35 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 9:1 hexanes/EtOAc (visualized with *p*-anisaldehyde) to afford the title compound **132** as a viscous residue (92.4 mg, 67% yield, 89:11 dr arising from vinylic iodide **S5**).

Characterization data for (*E*)-vinylic ether **132** (89:11 dr):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (d, *J* = 12.6 Hz, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 4.78 (dd, *J* = 12.7, 9.0 Hz, 1H), 4.62 (dd, *J* = 7.9, 2.5 Hz, 1H), 4.43 (td, *J* = 8.4, 5.9 Hz, 1H), 4.32 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.24 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.07 – 3.98 (m, 2H), 3.91 – 3.85 (m, 2H), 3.53 (t, *J* = 8.1 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H).

The diastereomers are distinguished in the ^{1}H NMR spectrum by two sets of doublets at 6.59 that partially overlap. The dr is determined from integrating the resonances at δ 6.62 (s, 1H) and 6.60 (s, 9H).

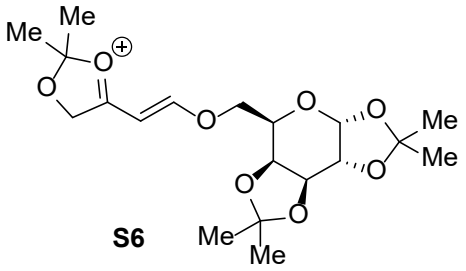
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.9, 109.7, 108.93, 108.88, 101.4, 96.4, 75.1, 71.1, 70.7, 70.6, 70.1, 68.0, 66.2, 27.0, 26.18, 26.17, 26.1, 25.1, 24.6.

All observed ^{13}C resonances are for the major diastereomer.

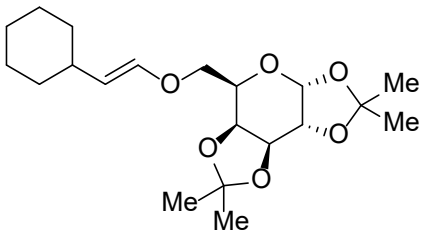
$[\alpha]^{23}_D$ -63.8 (c = 0.1, $CHCl_3$)

HRMS (ESI): *m/z* calcd for $C_{19}H_{31}O_8^+$ $[M+H]^+$ 387.2013, molecular ion not observed.

However, we observed a peak at *m/z* 385.1857 corresponding to formula $C_{19}H_{29}O_8^+$, calcd 385.1861. This corresponds to loss of hydride in the mass spectrometer, with proposed structure **S6**.



S6



133

Using conditions A, with alcohol **14** (220.3 mg, 0.85 mmol, 2 equiv) and vinylic iodide **S1** (100 mg, 0.42 mmol, 1 equiv) as substrates. The dark brown crude oil was subjected directly to flash column chromatography with silica gel pre-treated with 2% Et_3N in hexanes (column: 1-inch diameter, up to 6-inch height), eluting with 92:8 hexanes/EtOAc (visualized with phosphomolybdic acid stain) to afford the title compound **133** as a clear pale-yellow oil (27.0 mg, 17% yield). 47% of vinylic iodide **S1** was recovered.

Characterization data for (*E*)-vinylic ether **133**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (dd, *J* = 12.8, 1.0 Hz, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 4.76 (dd, *J* = 12.7, 7.7 Hz, 1H), 4.62 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.32 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.26 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.02 (ddd, *J* = 7.6, 5.6, 2.1 Hz, 1H), 3.80 (qt, *J* = 7.1, 5.4 Hz, 2H), 1.87 (tdd, *J* = 11.2, 8.9, 6.9 Hz, 1H), 1.74 – 1.60 (m, 5H), 1.53 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.29 – 0.97 (m, 5H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.7, 111.2, 109.6, 108.8, 96.5, 71.2, 70.8, 70.7, 67.5, 66.4, 37.1, 34.4, 26.3, 26.24, 26.22, 26.1, 25.1, 24.6.

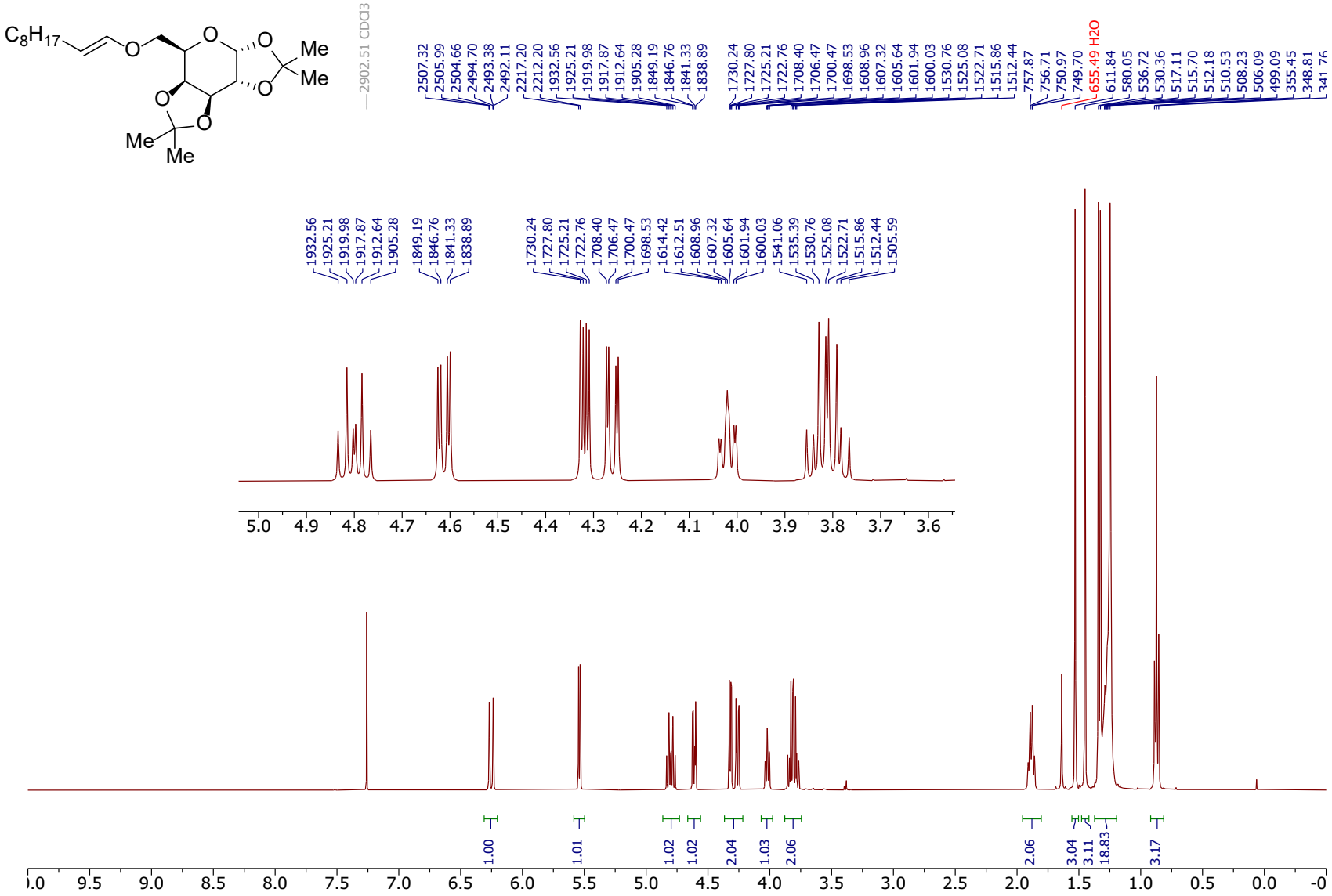
HRMS (APCI): *m/z* calcd for $C_{20}H_{33}O_6^+$ $[M+H]^+$ 369.2272, found 369.2268.

$[\alpha]^{22}_D$ -34.6 (c = 0.1, $CHCl_3$).

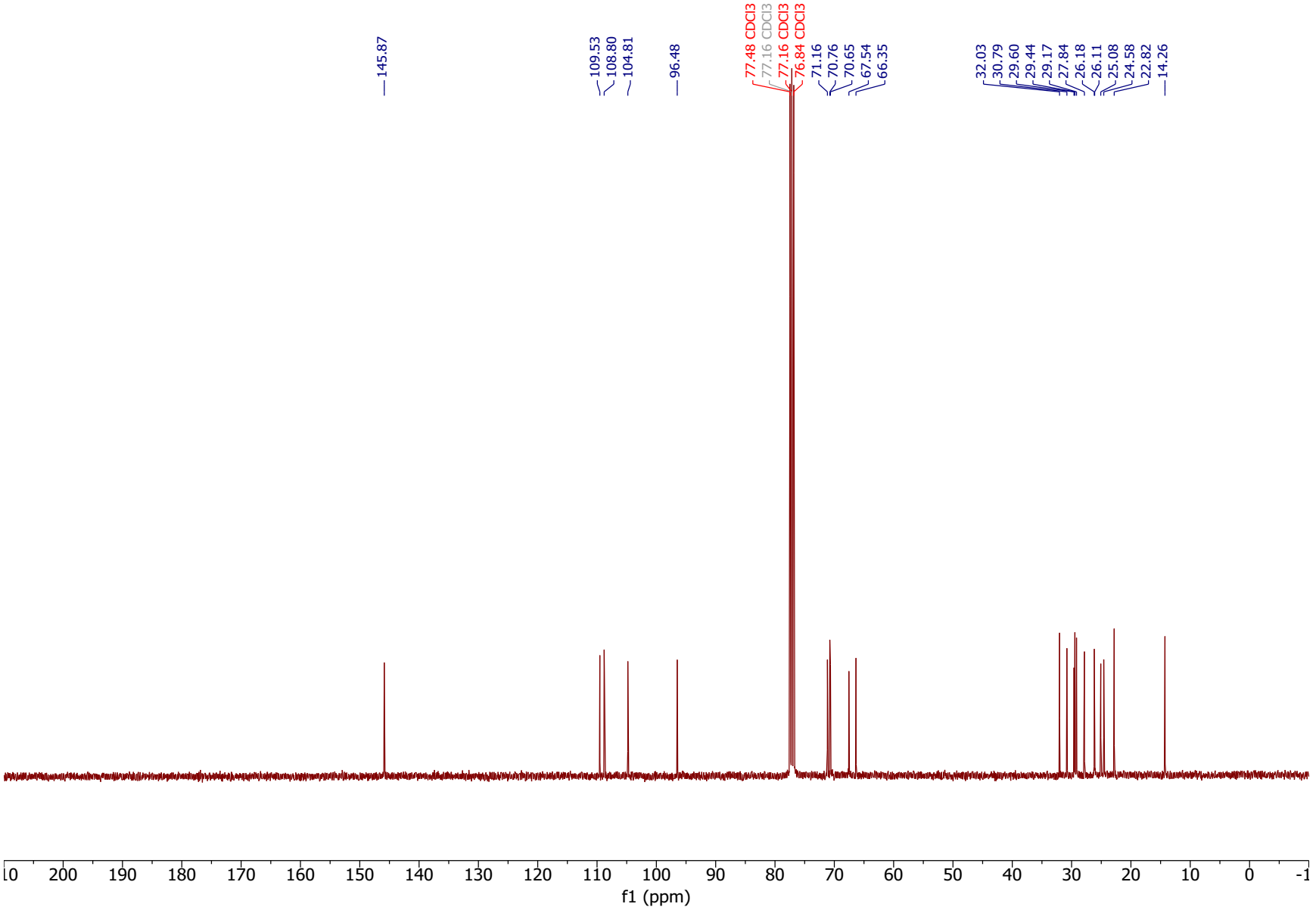
NMR Spectra of E-vinylic ethers

Next page

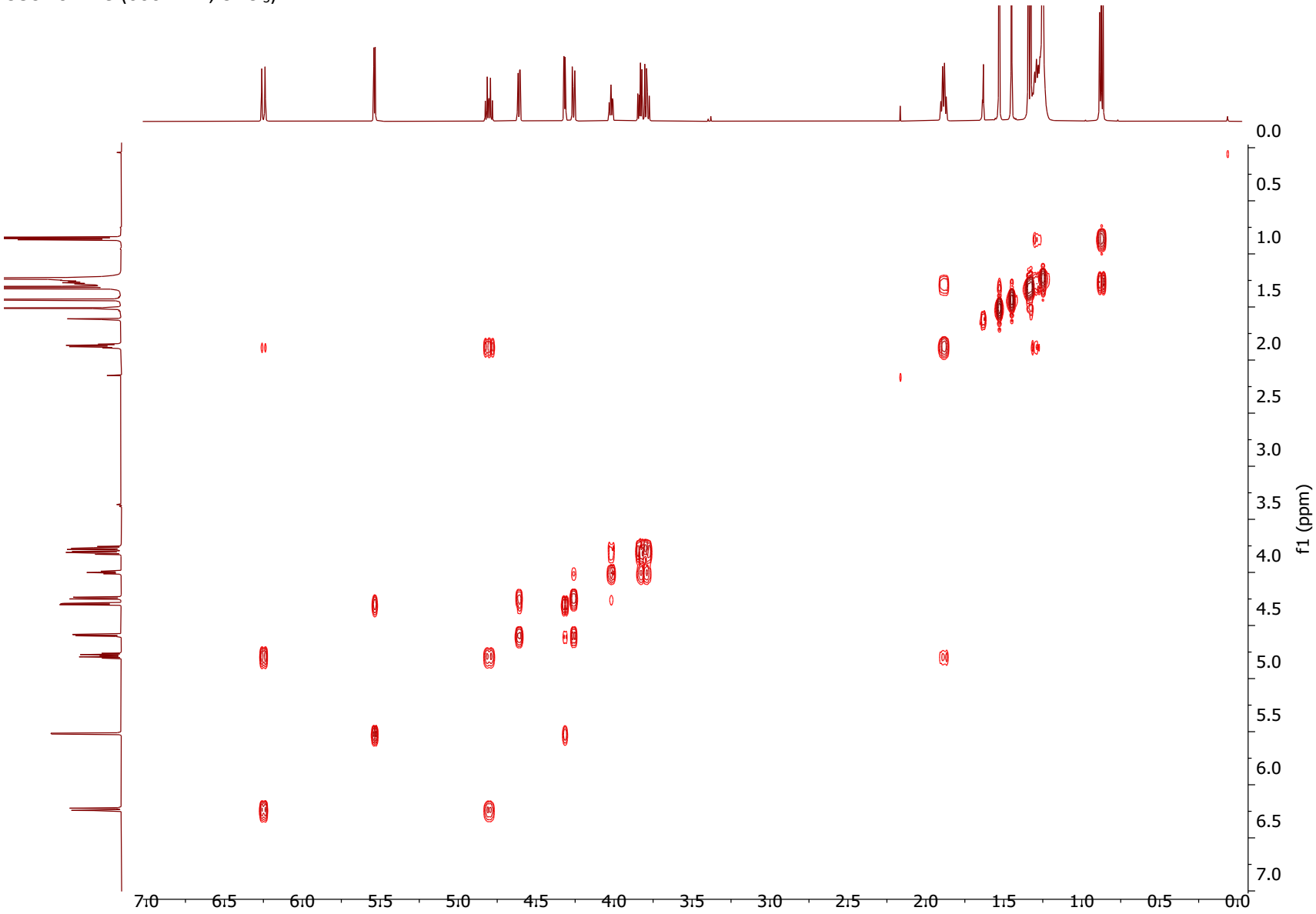
^{1}H NMR Spectrum of **113** (400 MHz, $CDCl_3$)



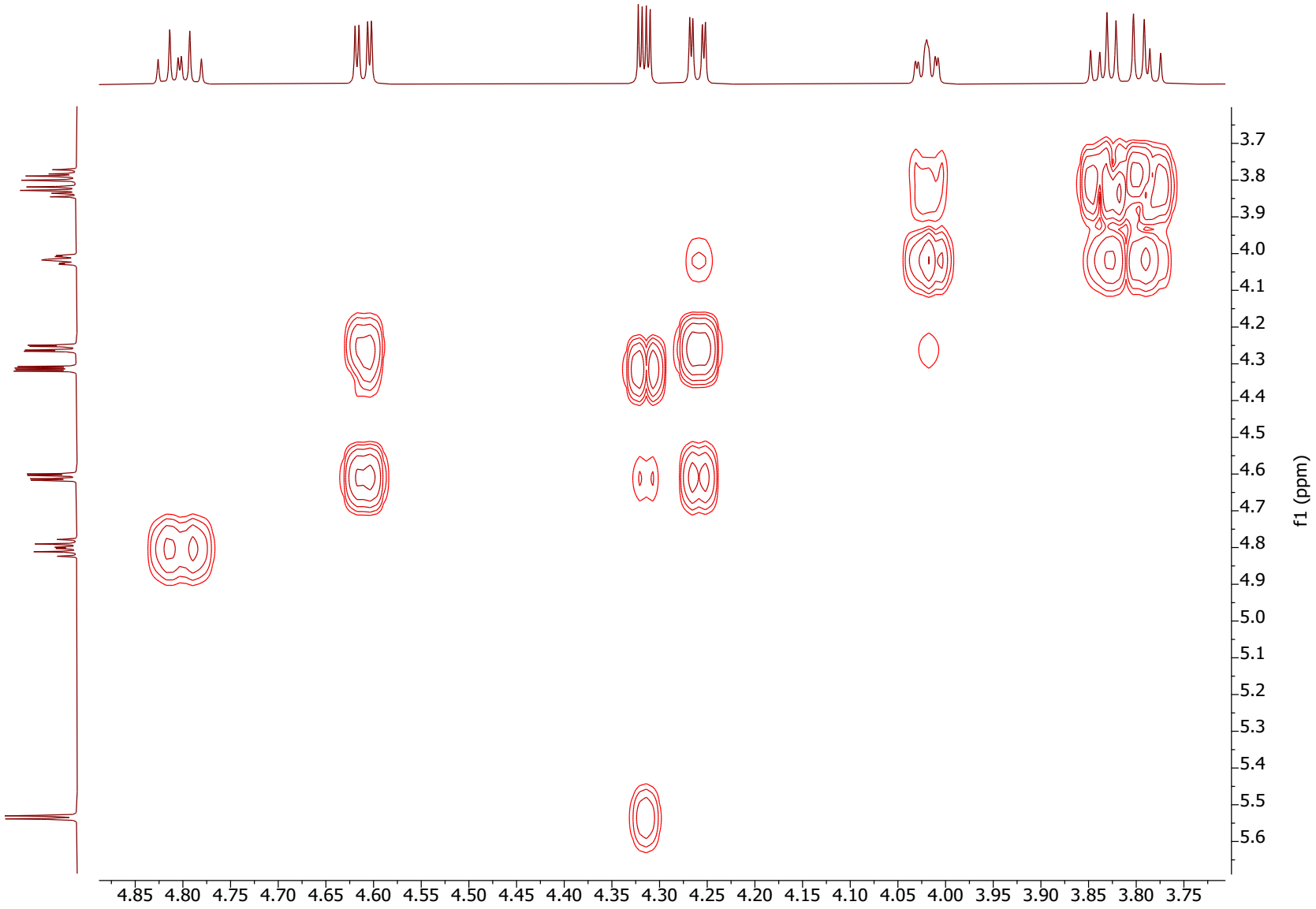
$^{13}C\{^{1}H\}$ NMR Spectrum of **113** (101 MHz, $CDCl_3$)



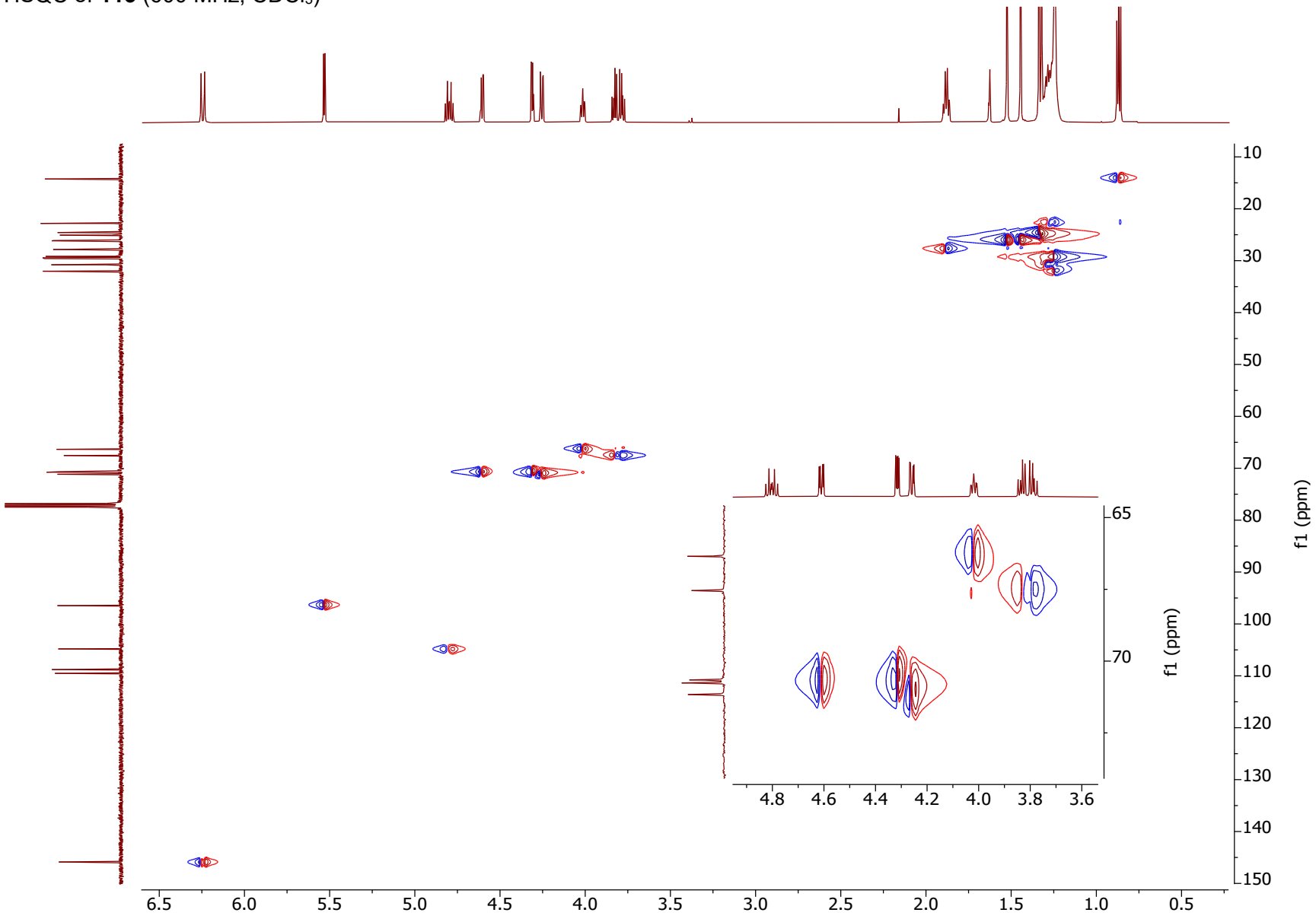
COSY of **113** (600 MHz, $CDCl_3$)



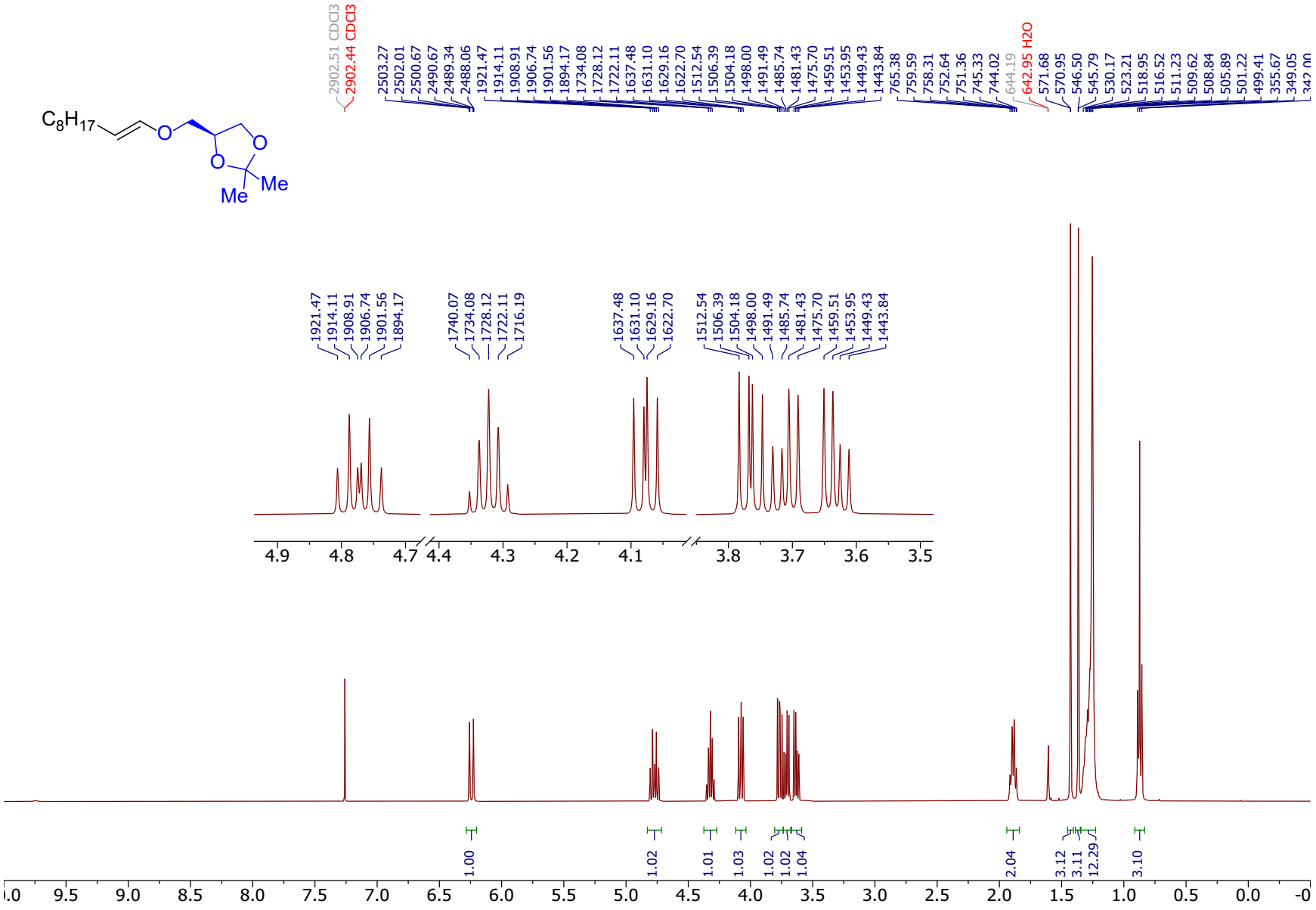
COSY of **113** (600 MHz, $CDCl_3$) Zoom-in



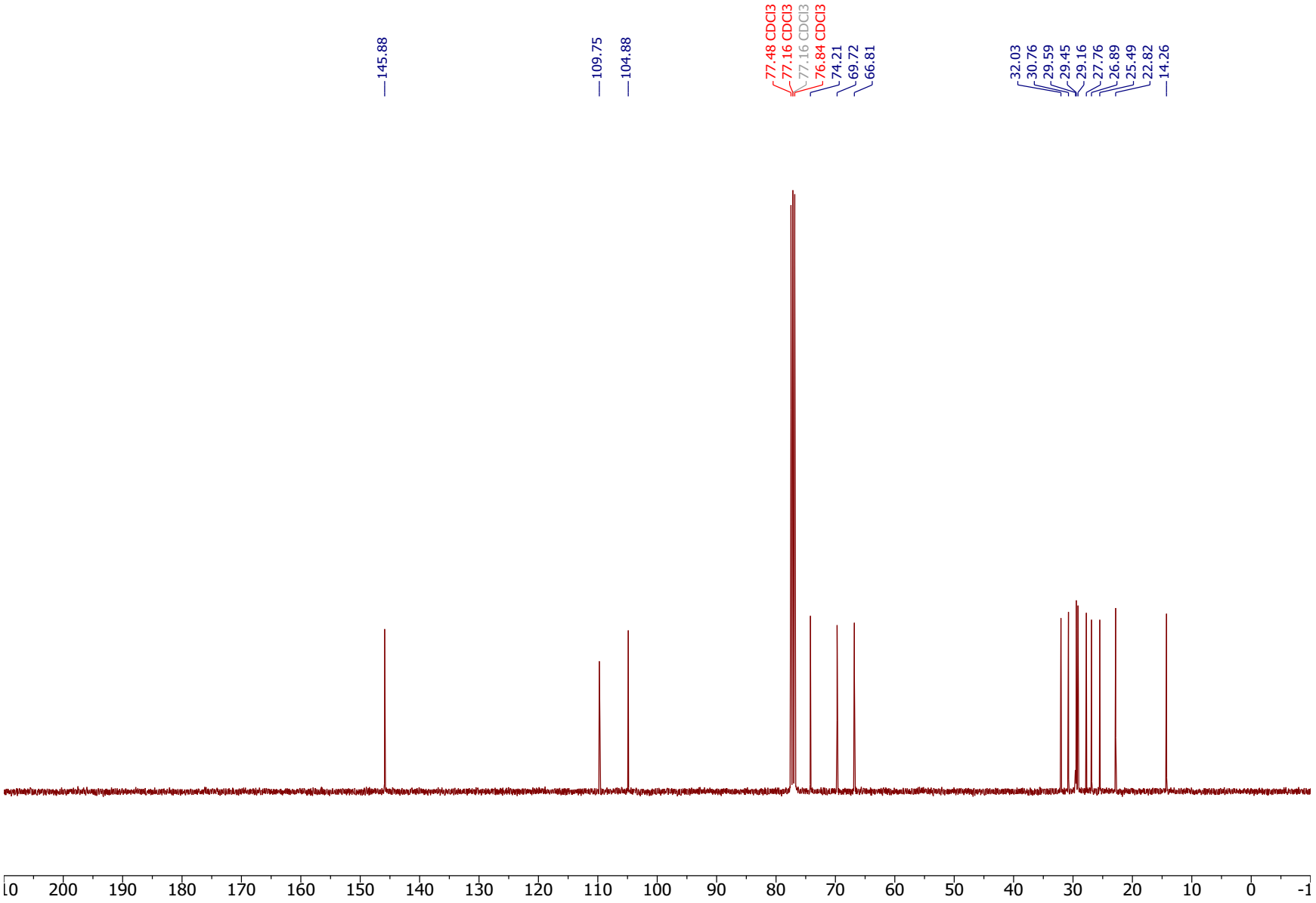
HSQC of **113** (600 MHz, $CDCl_3$)



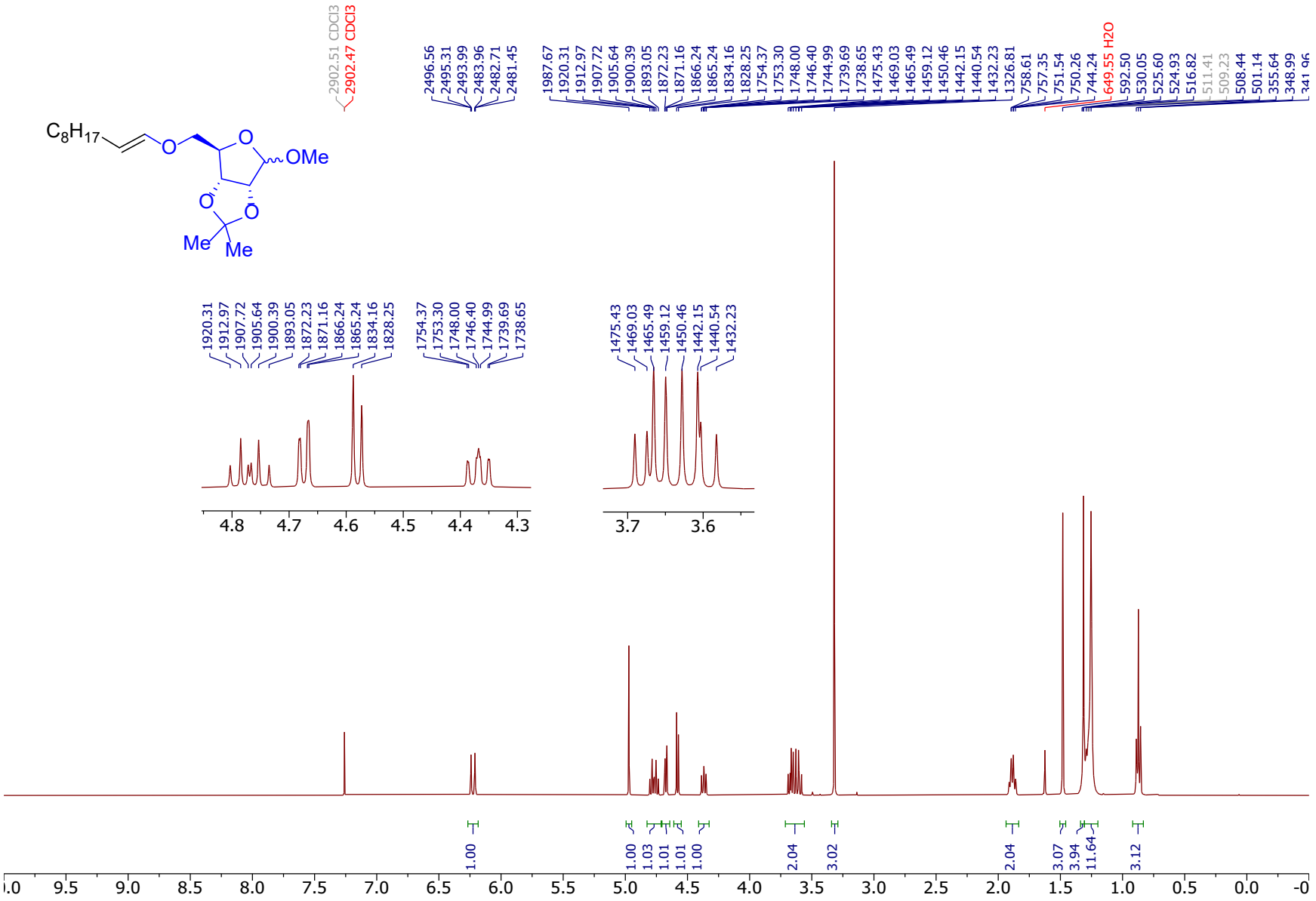
^{1}H NMR Spectrum of **116** (400 MHz, $CDCl_3$)



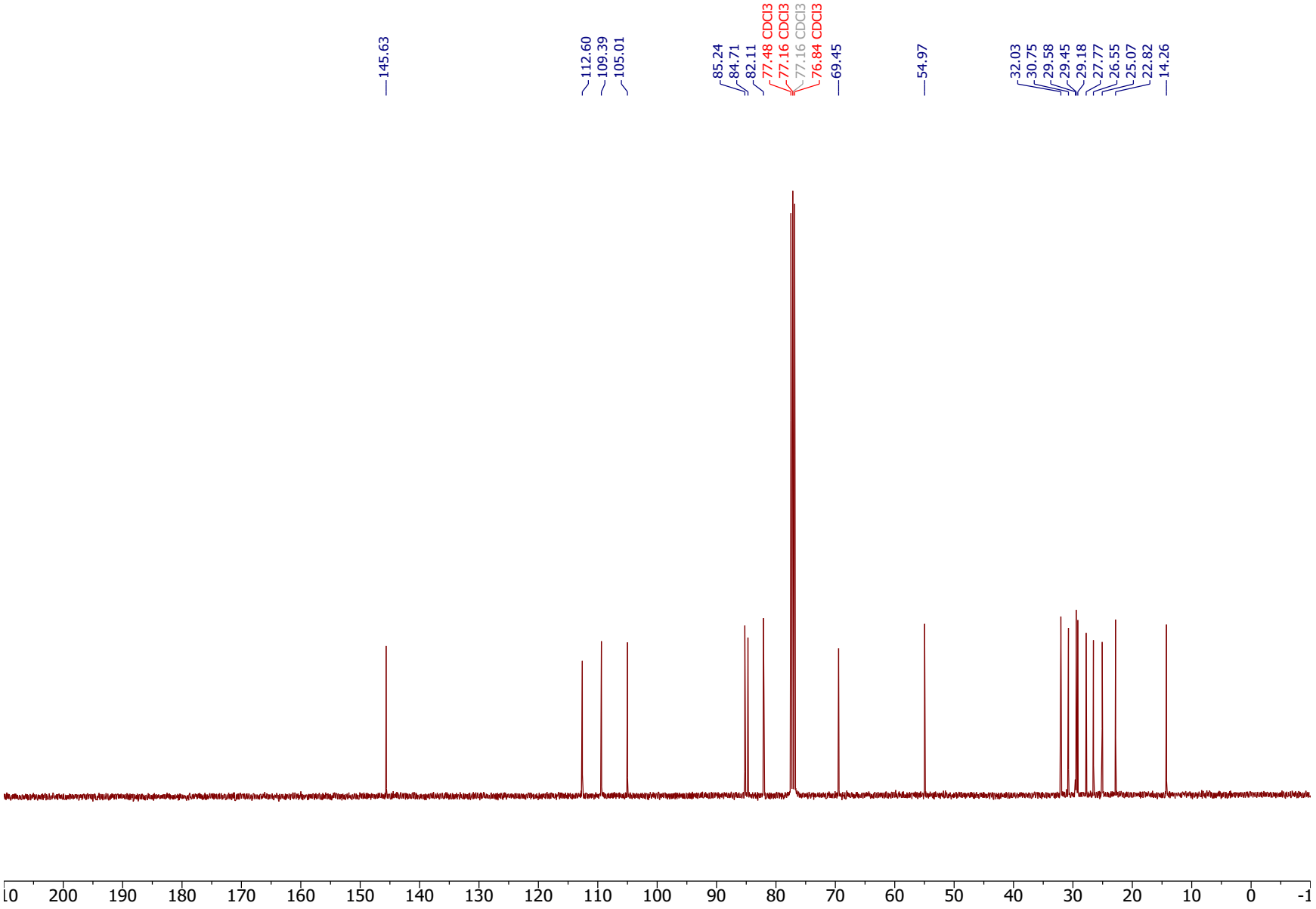
$^{13}C\{^{1}H\}$ NMR Spectrum of **116** (101 MHz, $CDCl_3$)



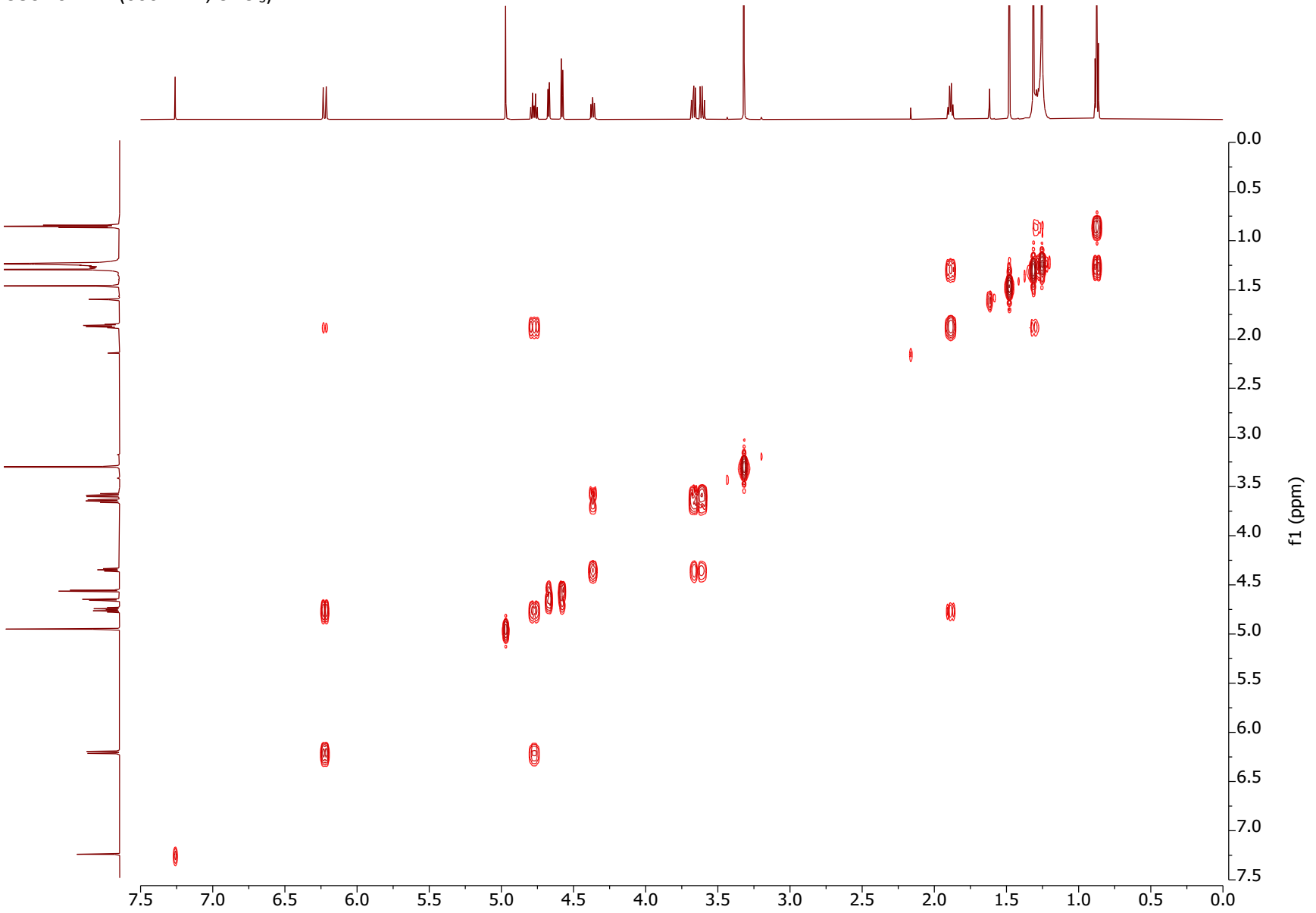
^{1}H NMR Spectrum of **117** (400 MHz, $CDCl_3$)



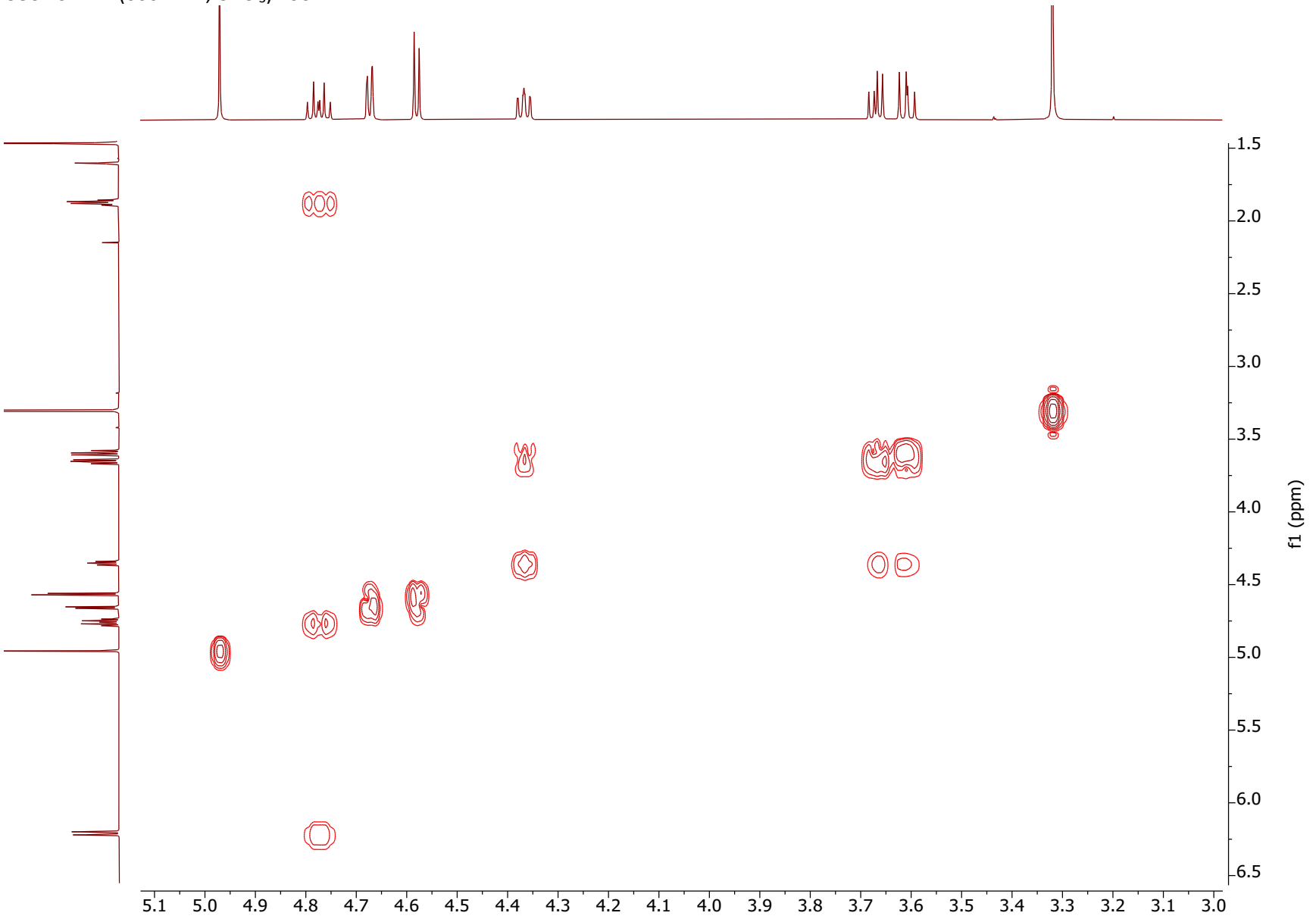
$^{13}C\{^{1}H\}$ NMR Spectrum of **117** (101 MHz, $CDCl_3$)



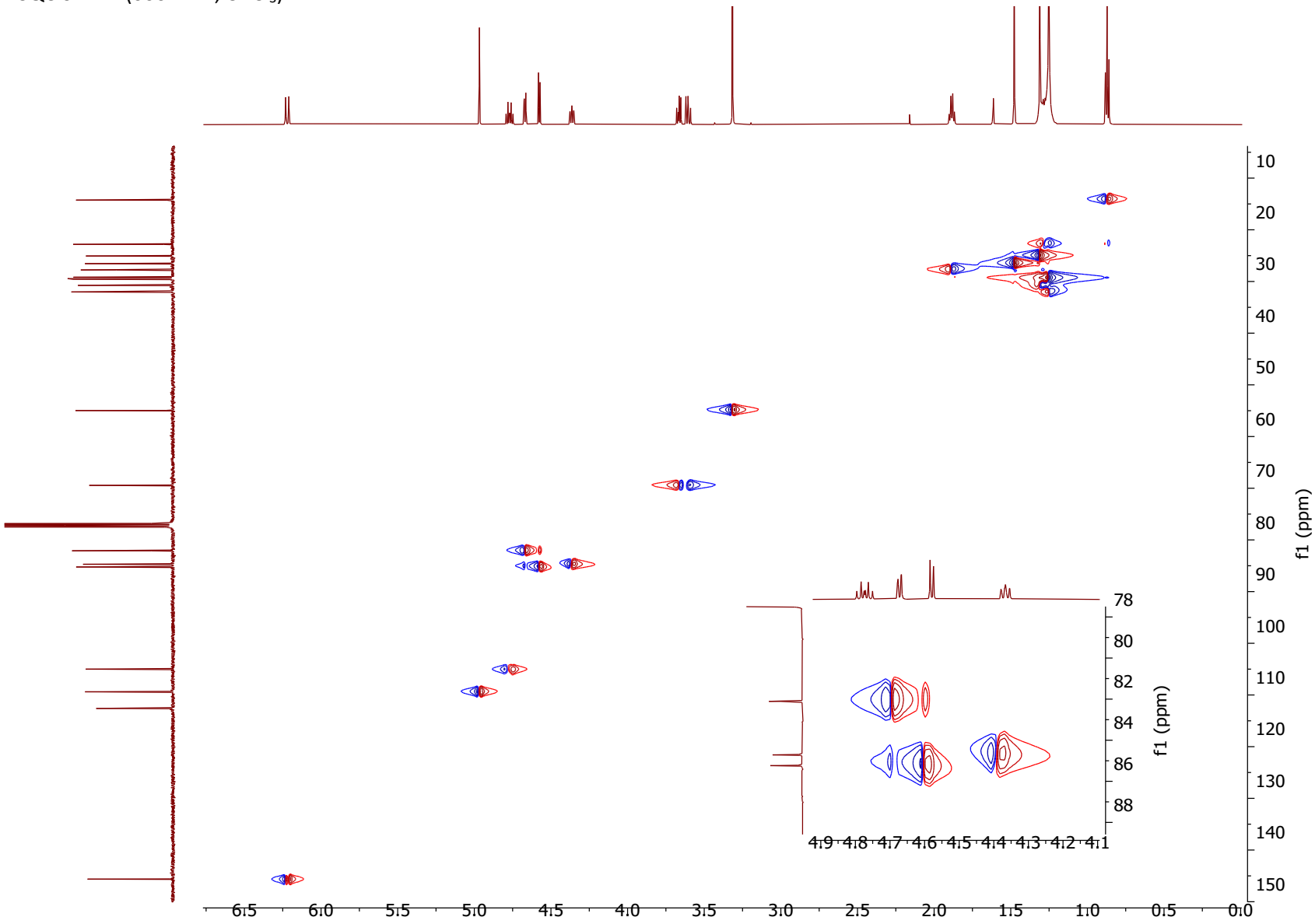
COSY of **117** (600 MHz, $CDCl_3$)



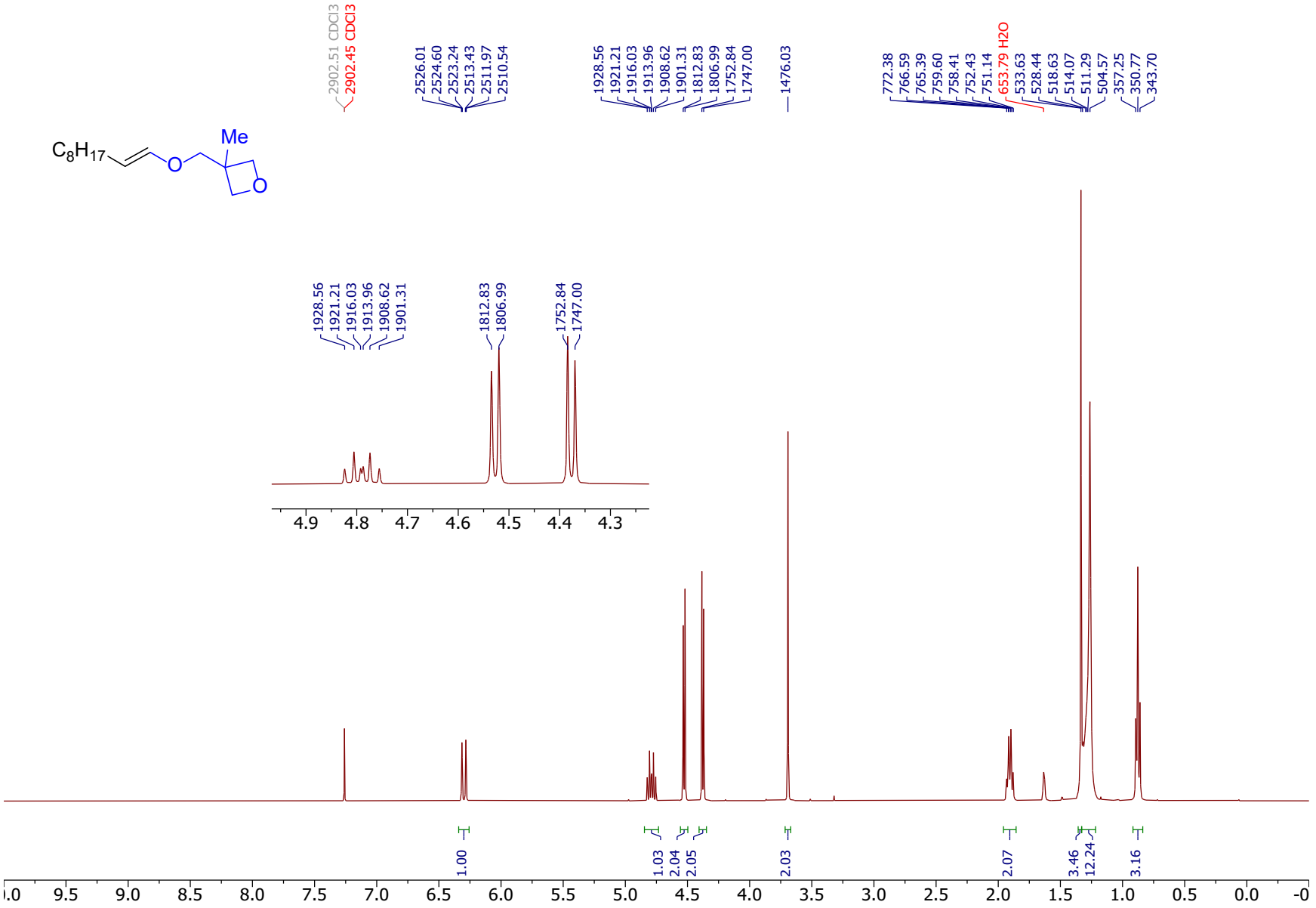
COSY of **117** (600 MHz, $CDCl_3$) Zoom-in



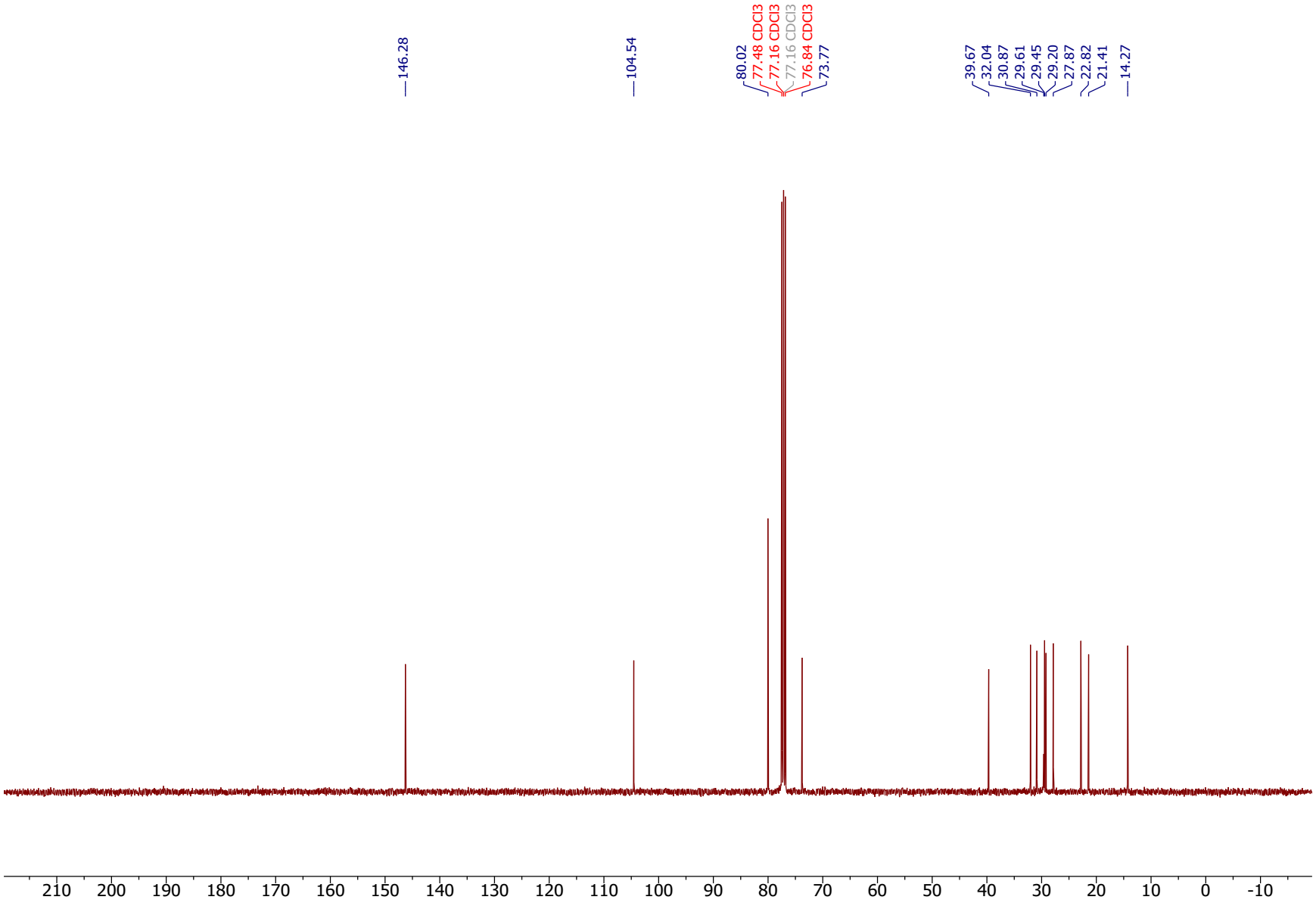
HSQC of **117** (600 MHz, $CDCl_3$)



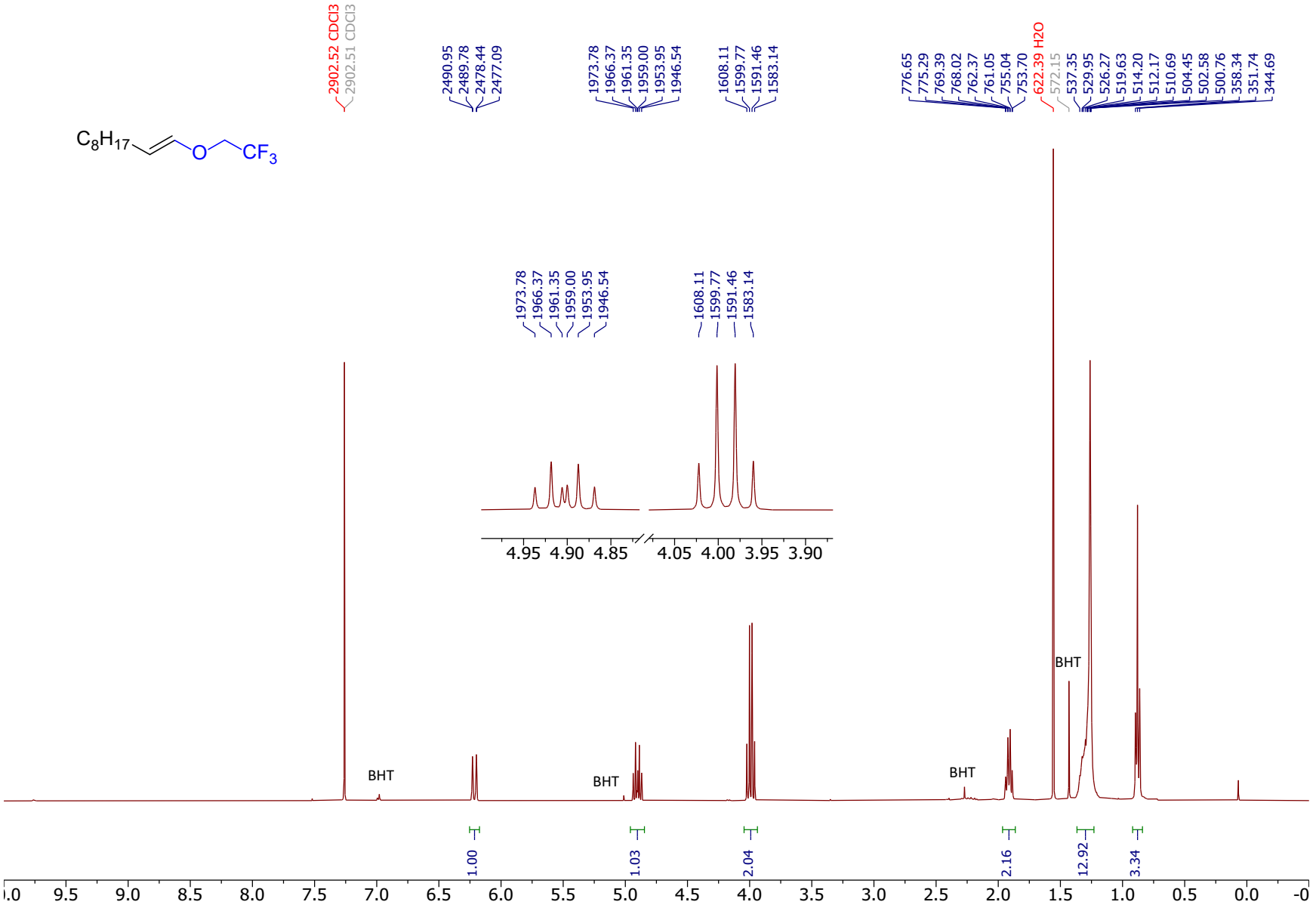
^{1}H NMR Spectrum of **118** (400 MHz, $CDCl_3$)



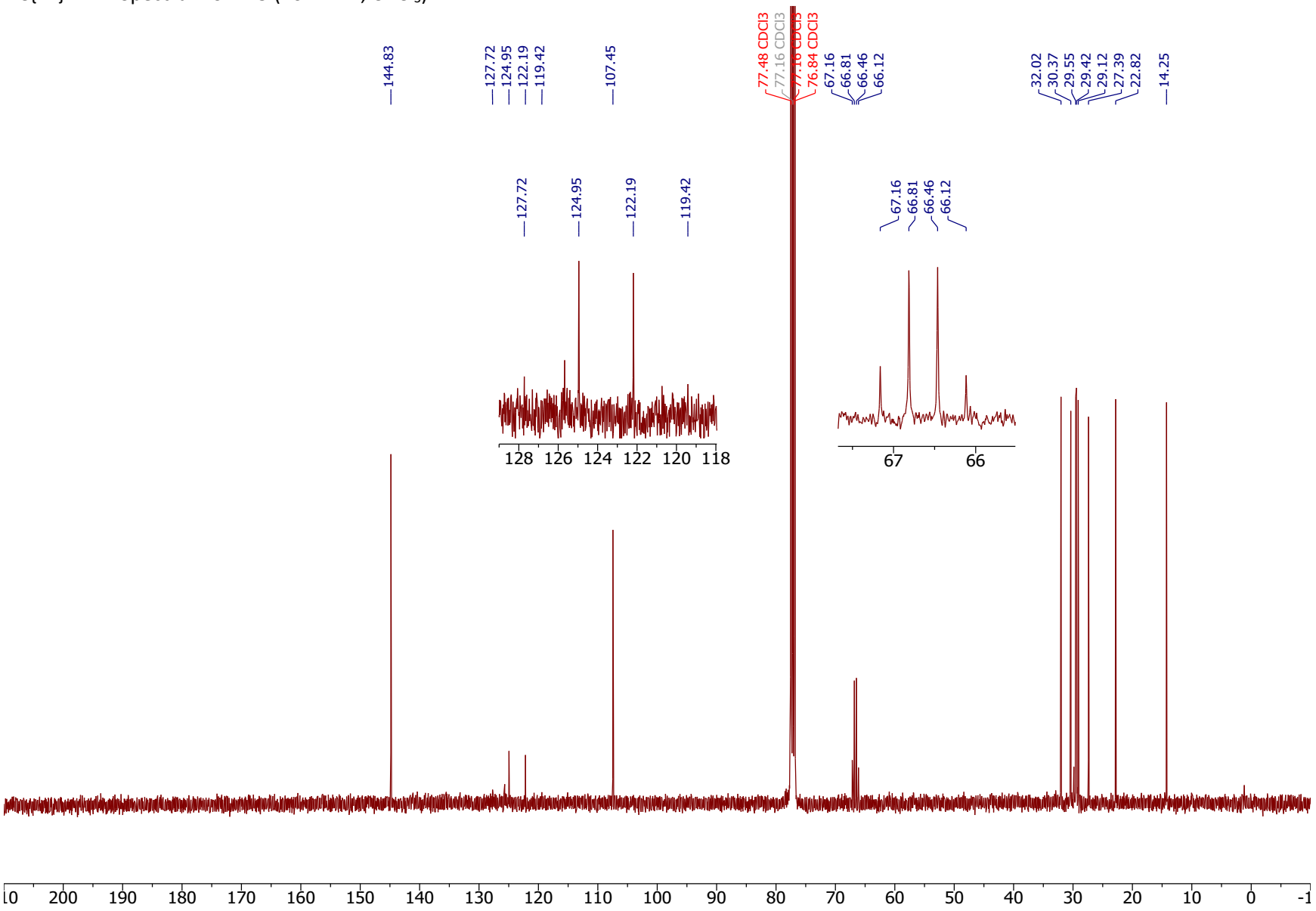
$^{13}C\{^{1}H\}$ NMR Spectrum of **118** (101 MHz, $CDCl_3$)



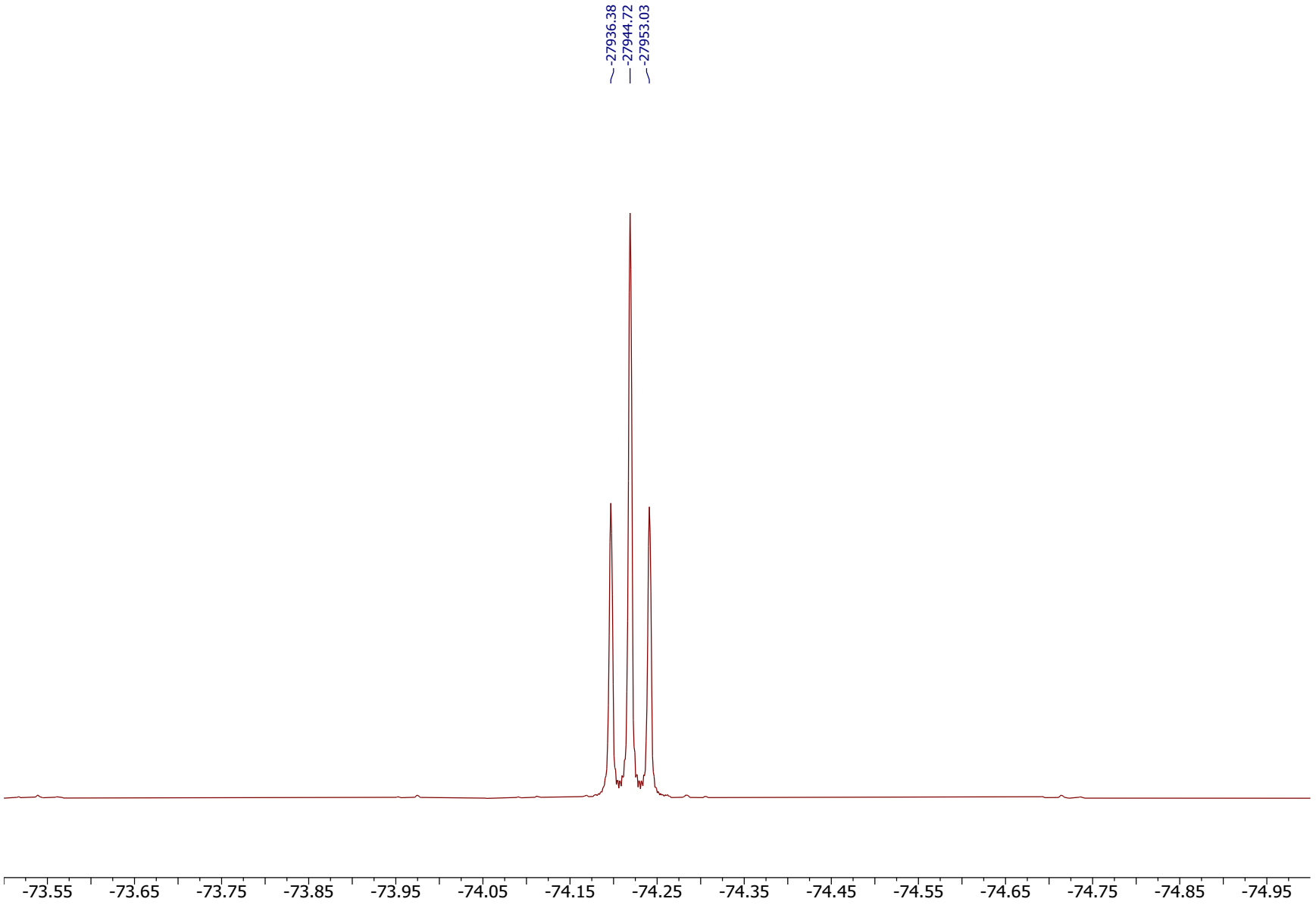
^{1}H NMR Spectrum of **119** (400 MHz, $CDCl_3$)



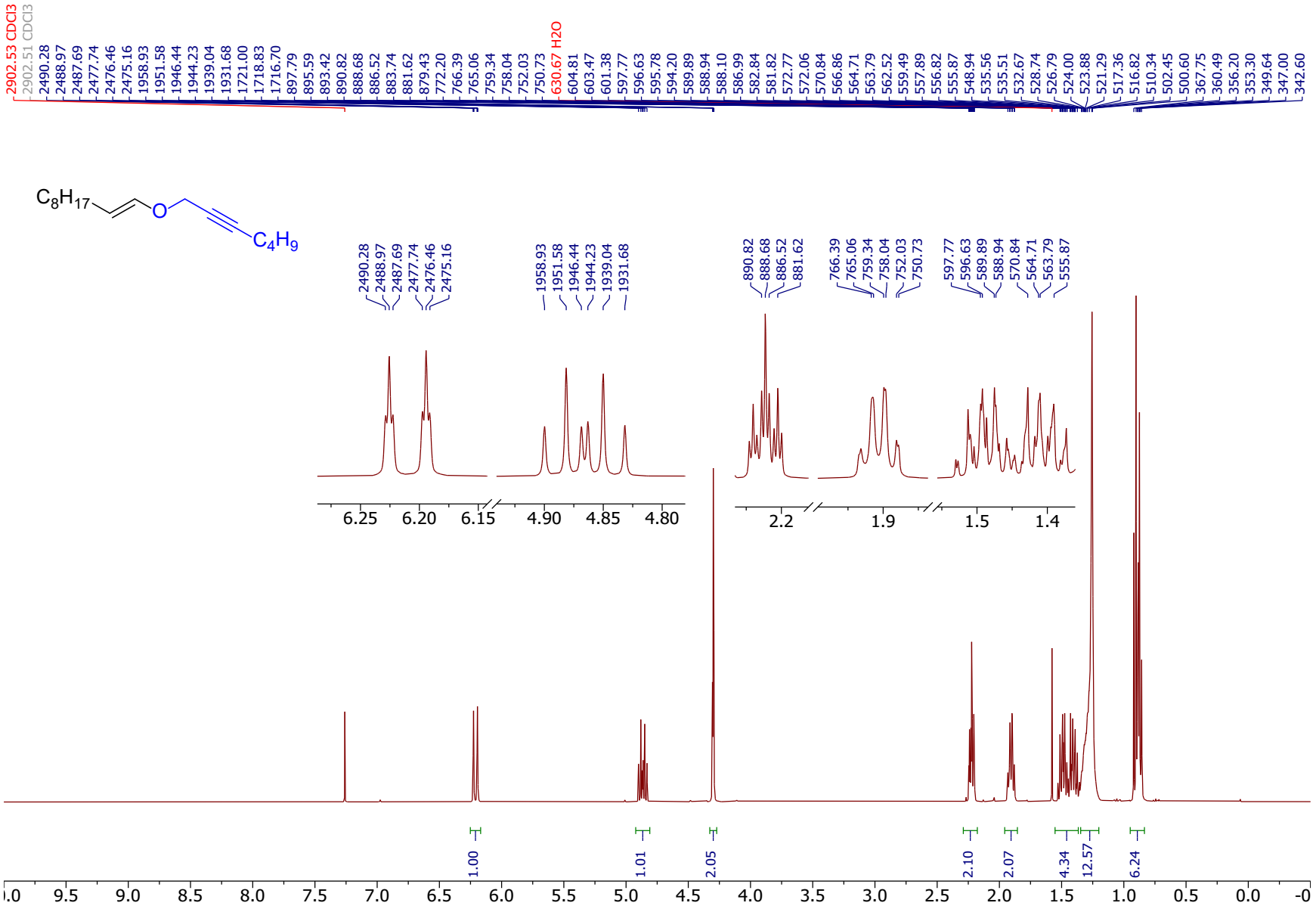
$^{13}C\{^{1}H\}$ NMR Spectrum of **119** (101 MHz, $CDCl_3$)



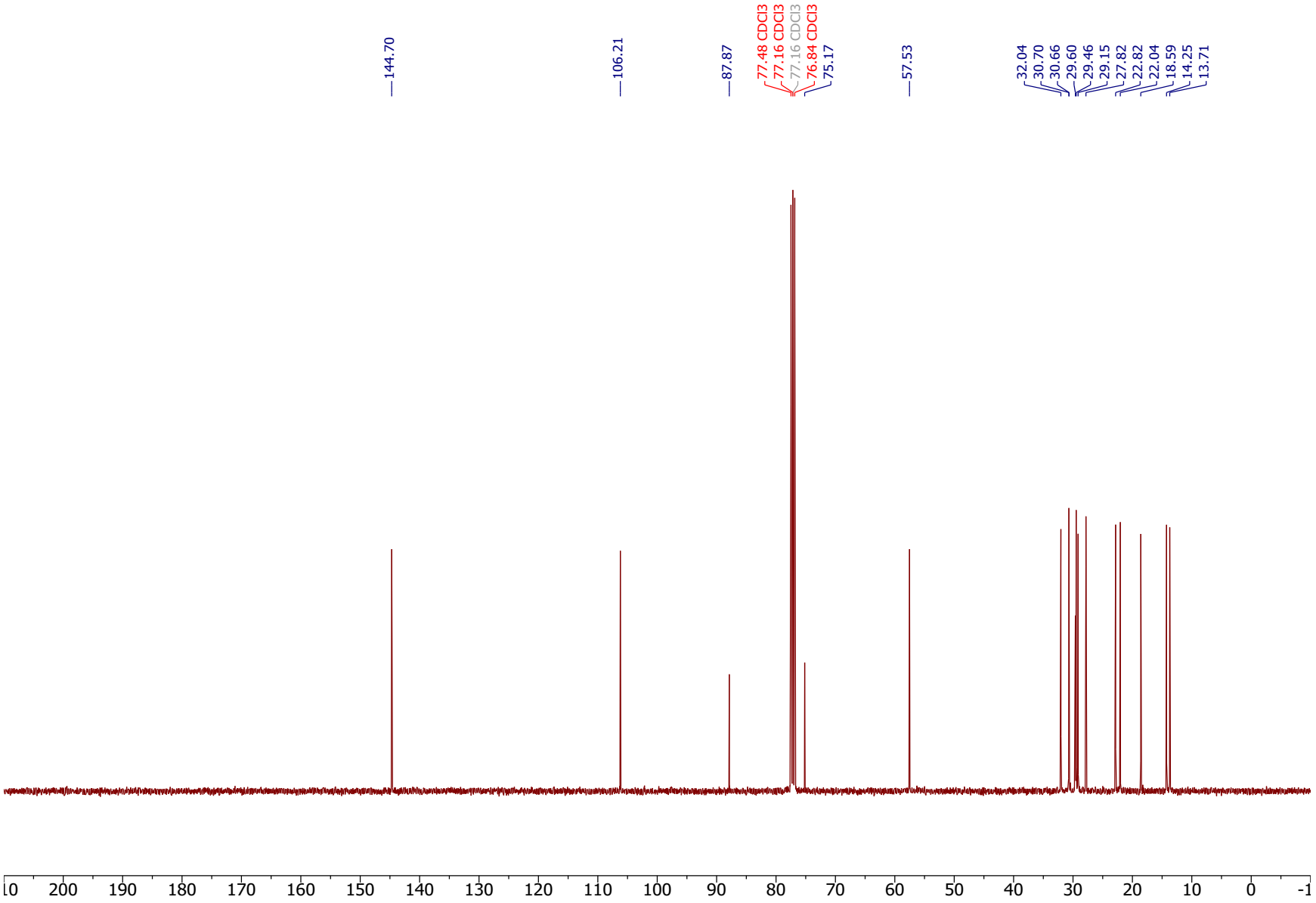
^{19}F NMR Spectrum of **119** (376 MHz, $CDCl_3$)



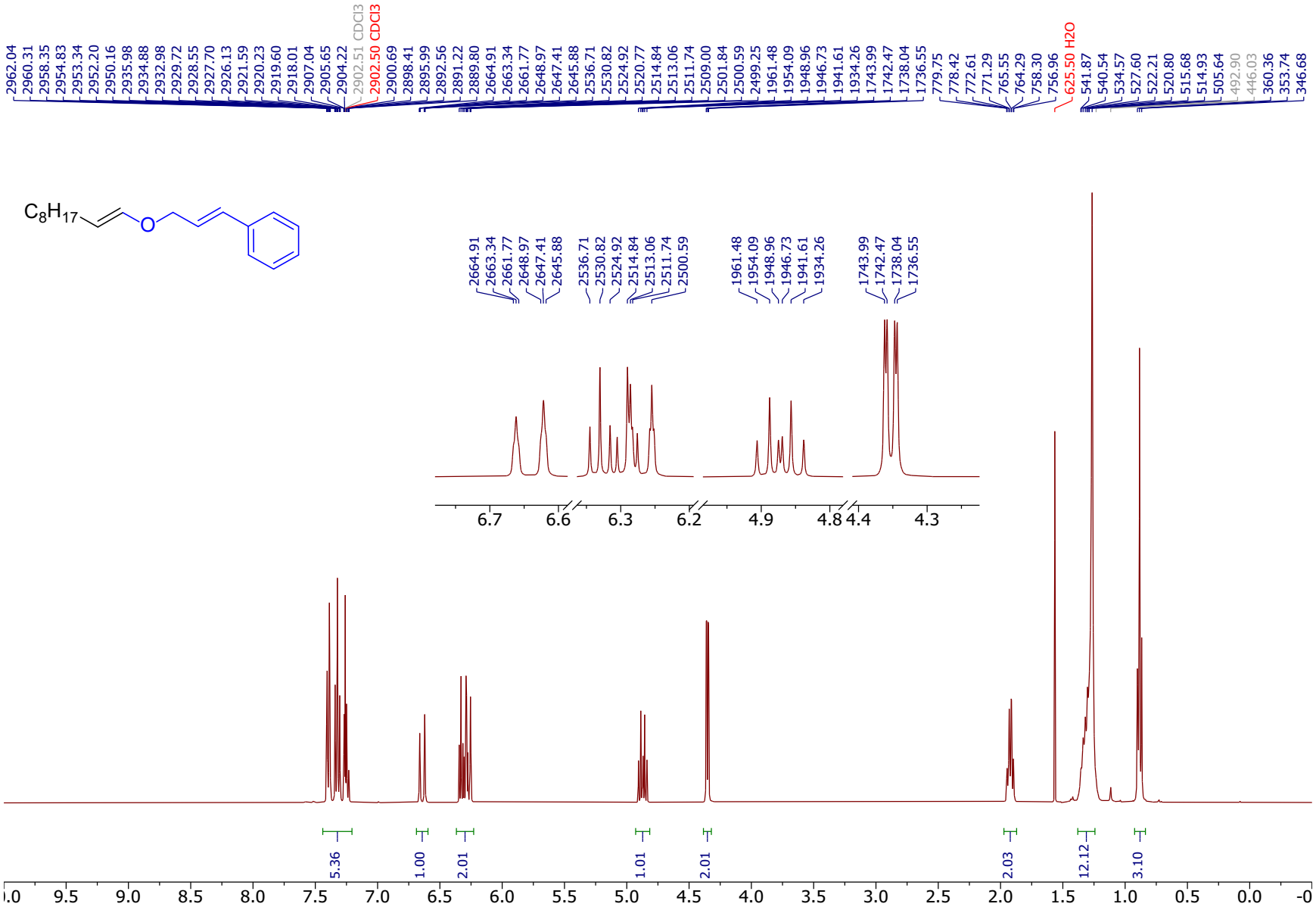
^{1}H NMR Spectrum of **120** (400 MHz, $CDCl_3$)



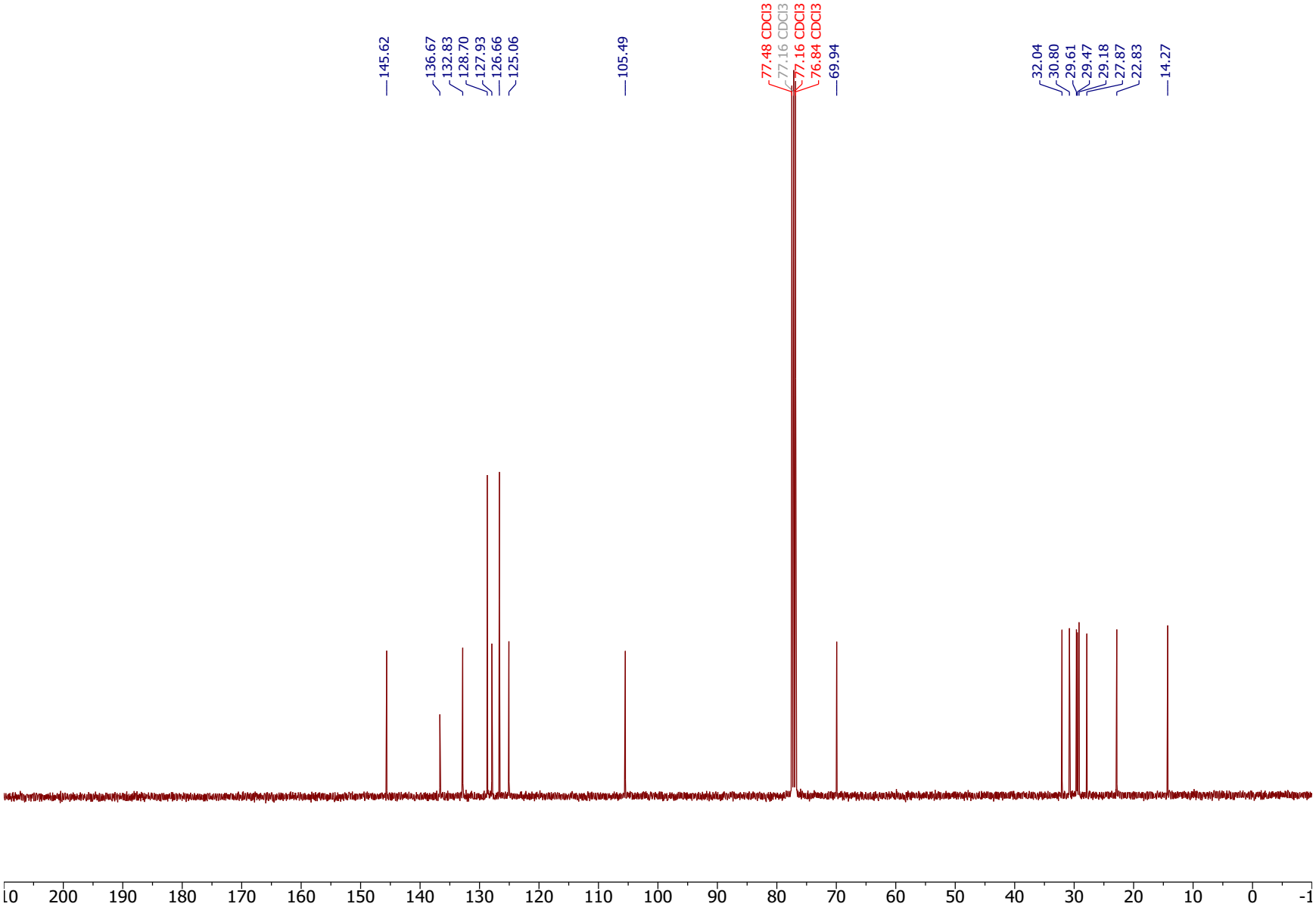
$^{13}C\{^{1}H\}$ NMR Spectrum of **120** (101 MHz, $CDCl_3$)



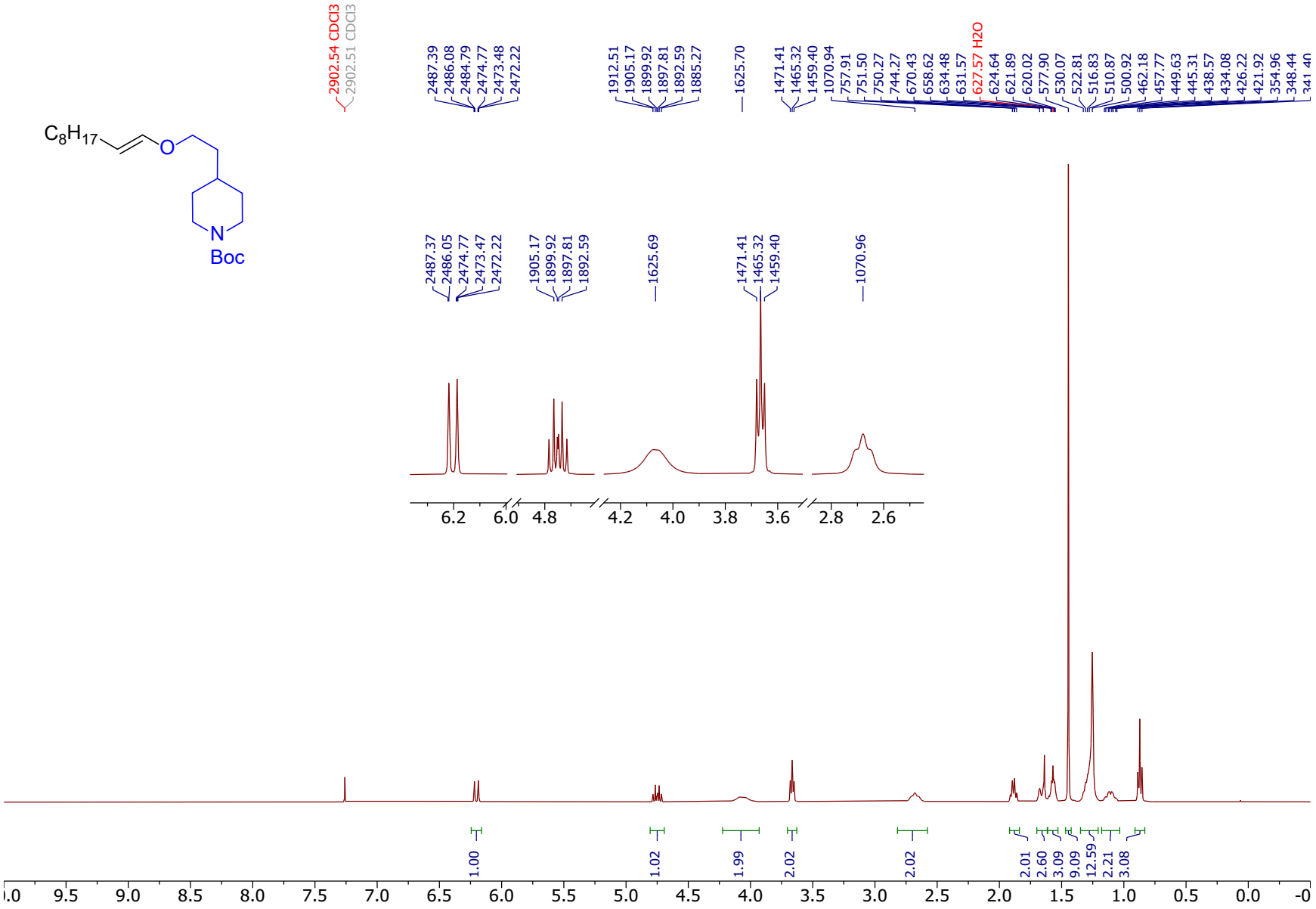
^{1}H NMR Spectrum of **121** (400 MHz, $CDCl_3$)



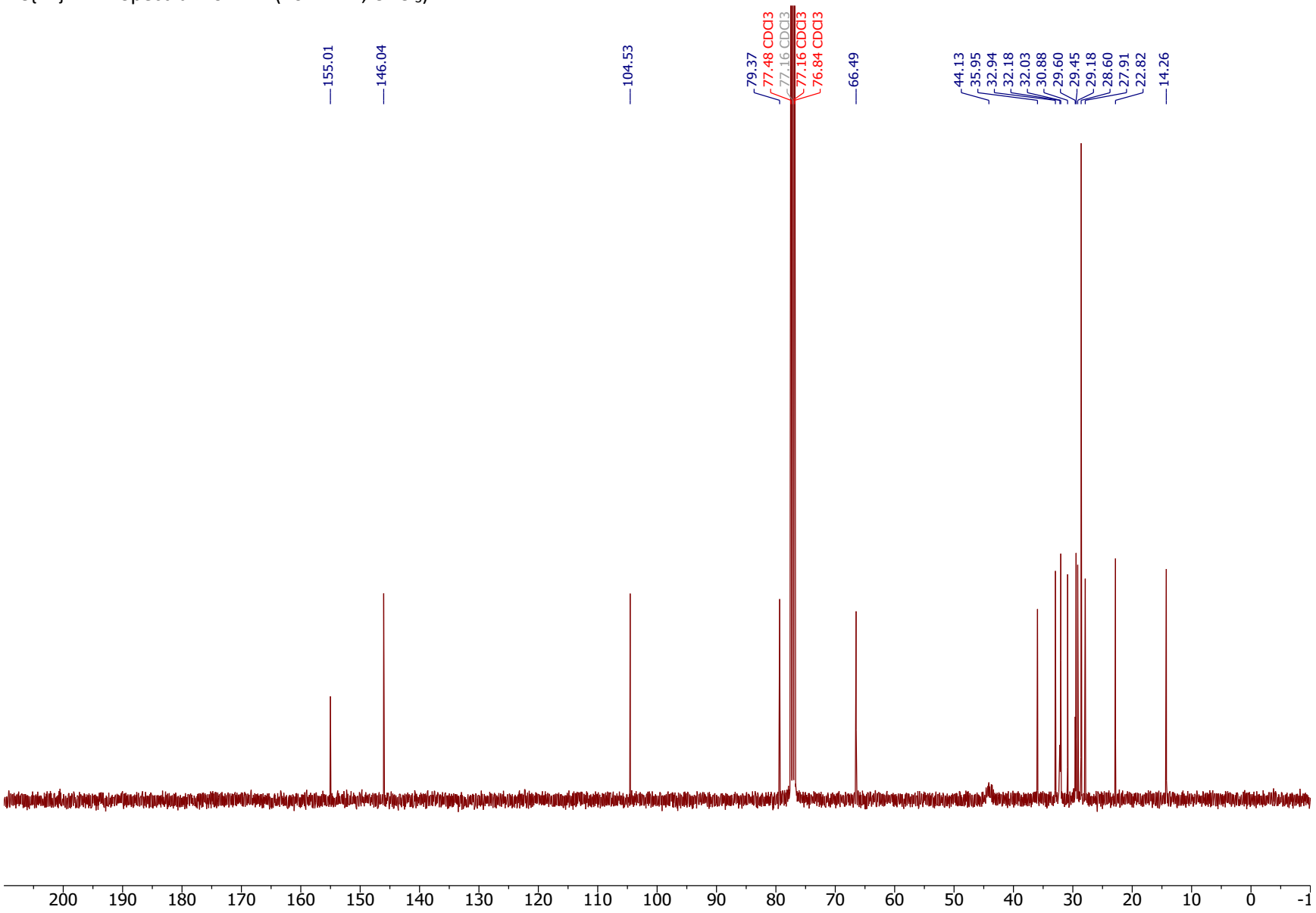
$^{13}C\{^{1}H\}$ NMR Spectrum of **121** (101 MHz, $CDCl_3$)



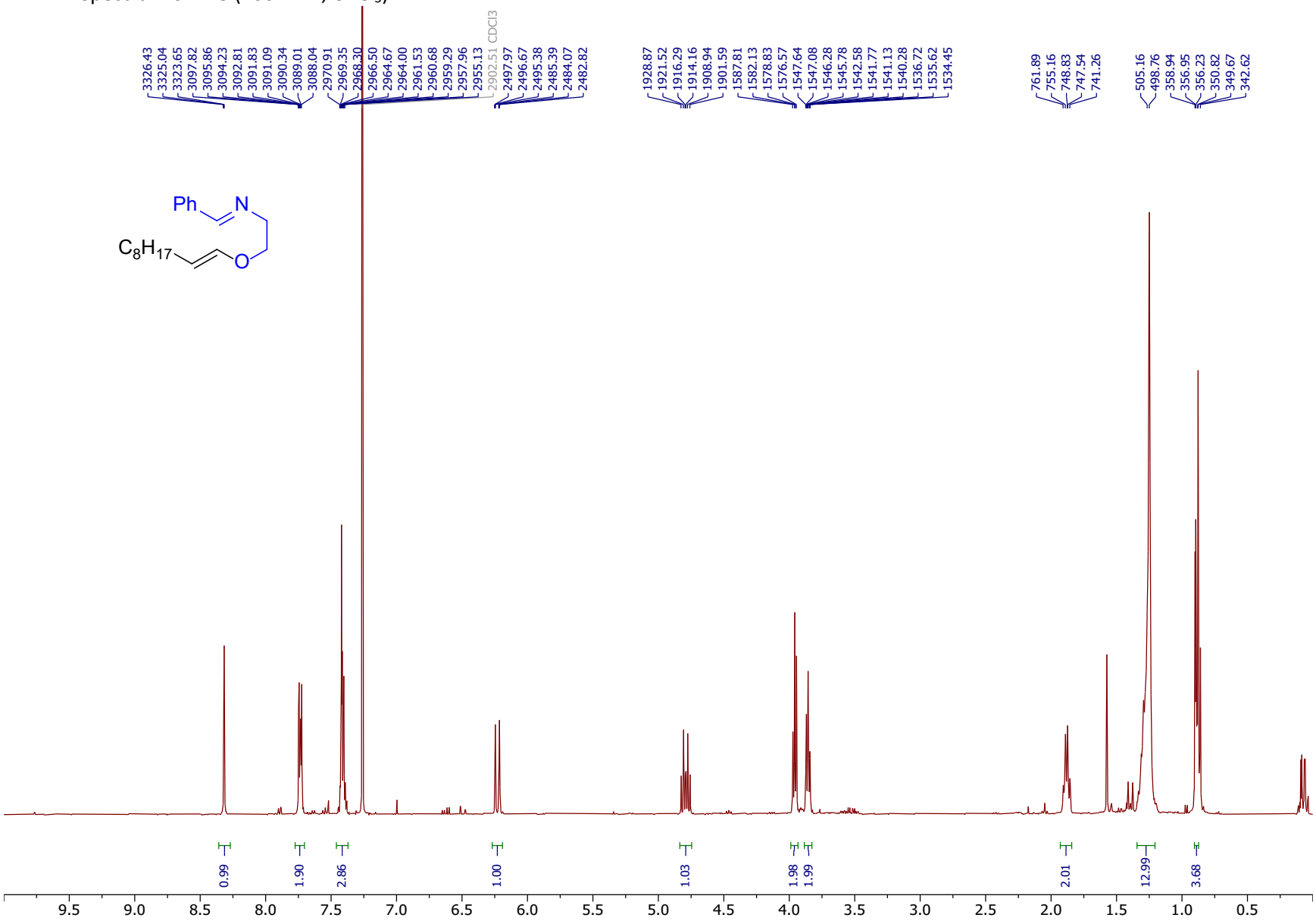
^{1}H NMR Spectrum of **122** (400 MHz, $CDCl_3$)



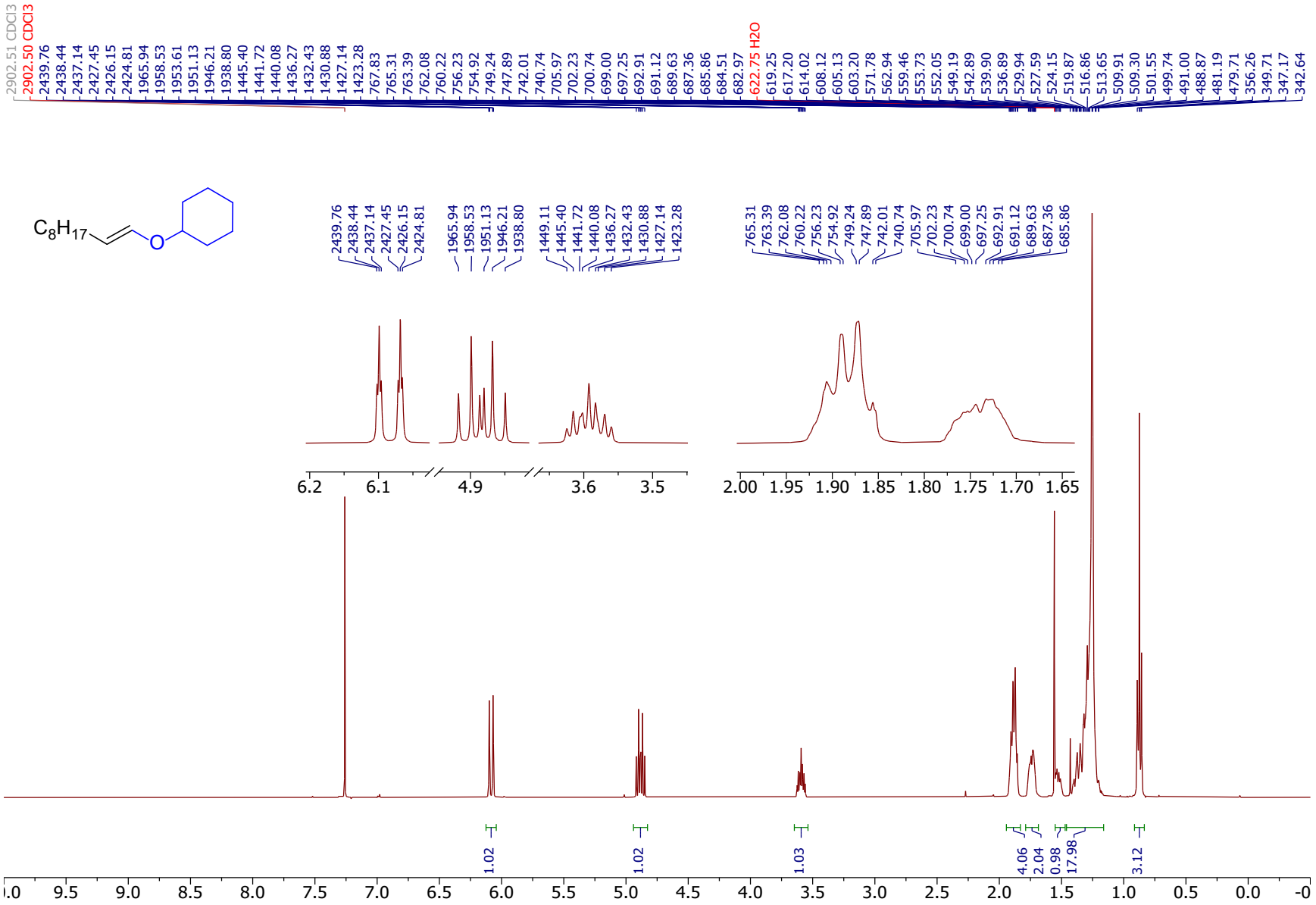
$^{13}C\{^{1}H\}$ NMR Spectrum of **122** (101 MHz, $CDCl_3$)



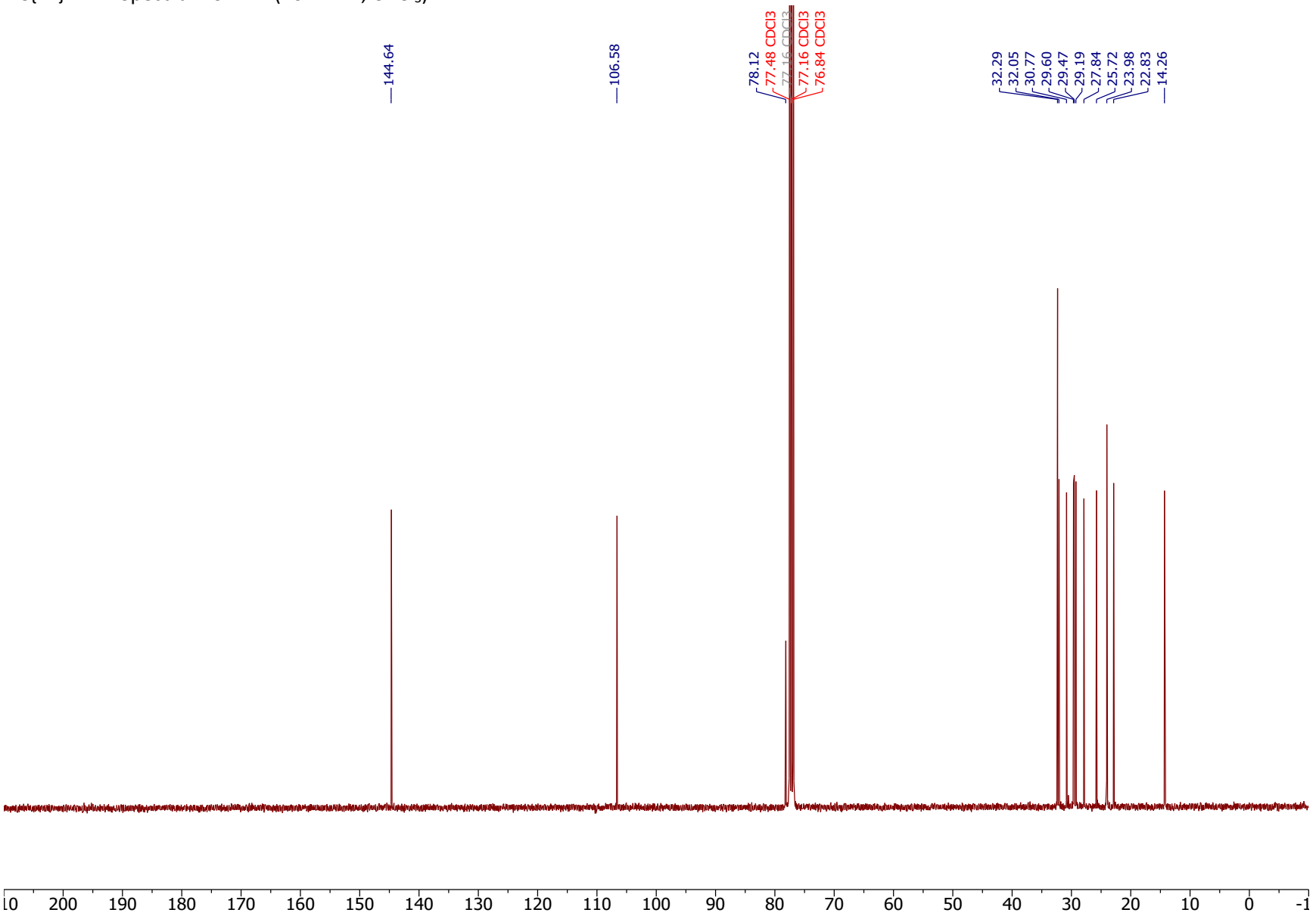
^{1}H NMR Spectrum of **123** (400 MHz, $CDCl_3$)



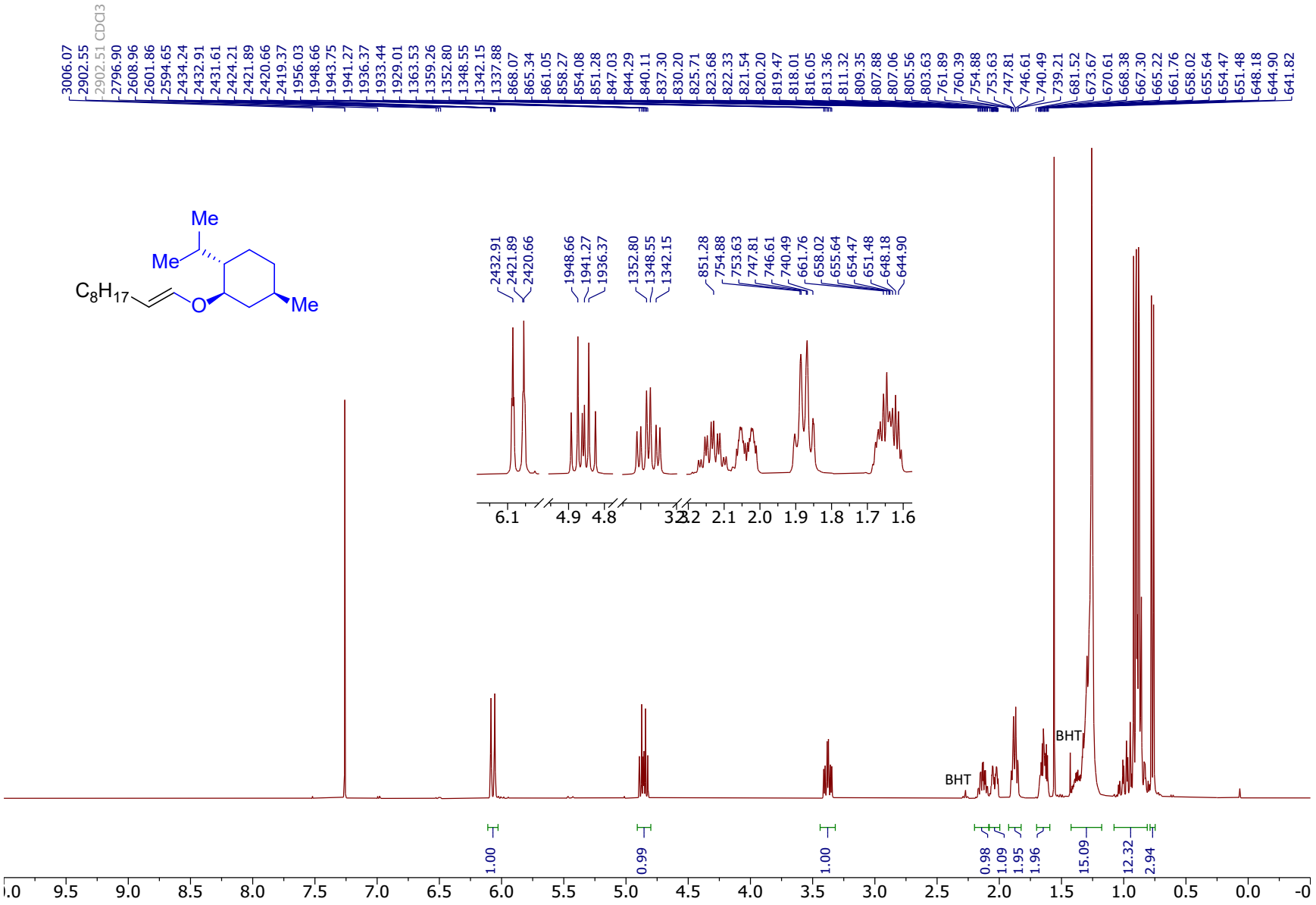
^{1}H NMR Spectrum of **124** (400 MHz, $CDCl_3$)



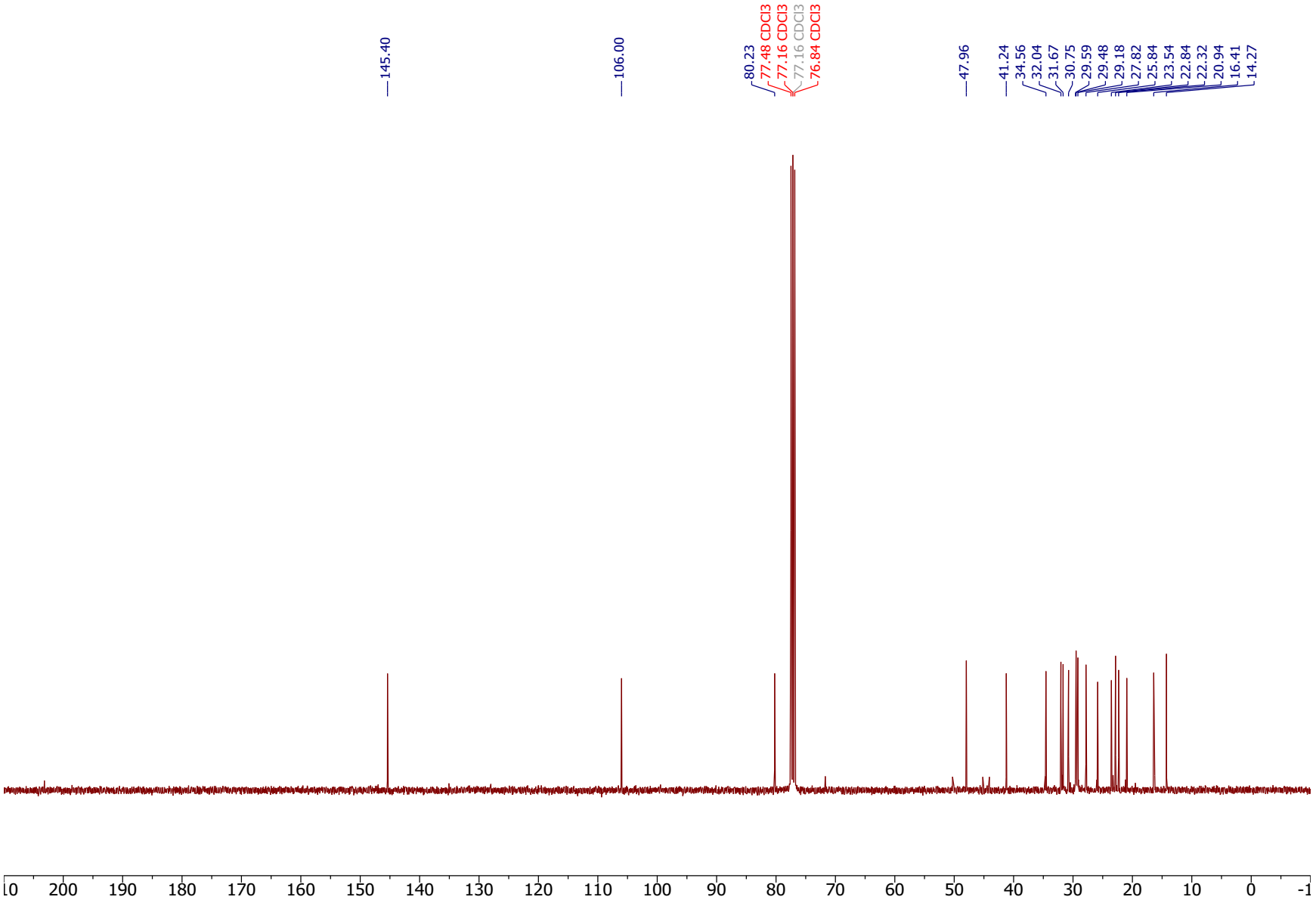
$^{13}C\{^{1}H\}$ NMR Spectrum of **124** (101 MHz, $CDCl_3$)



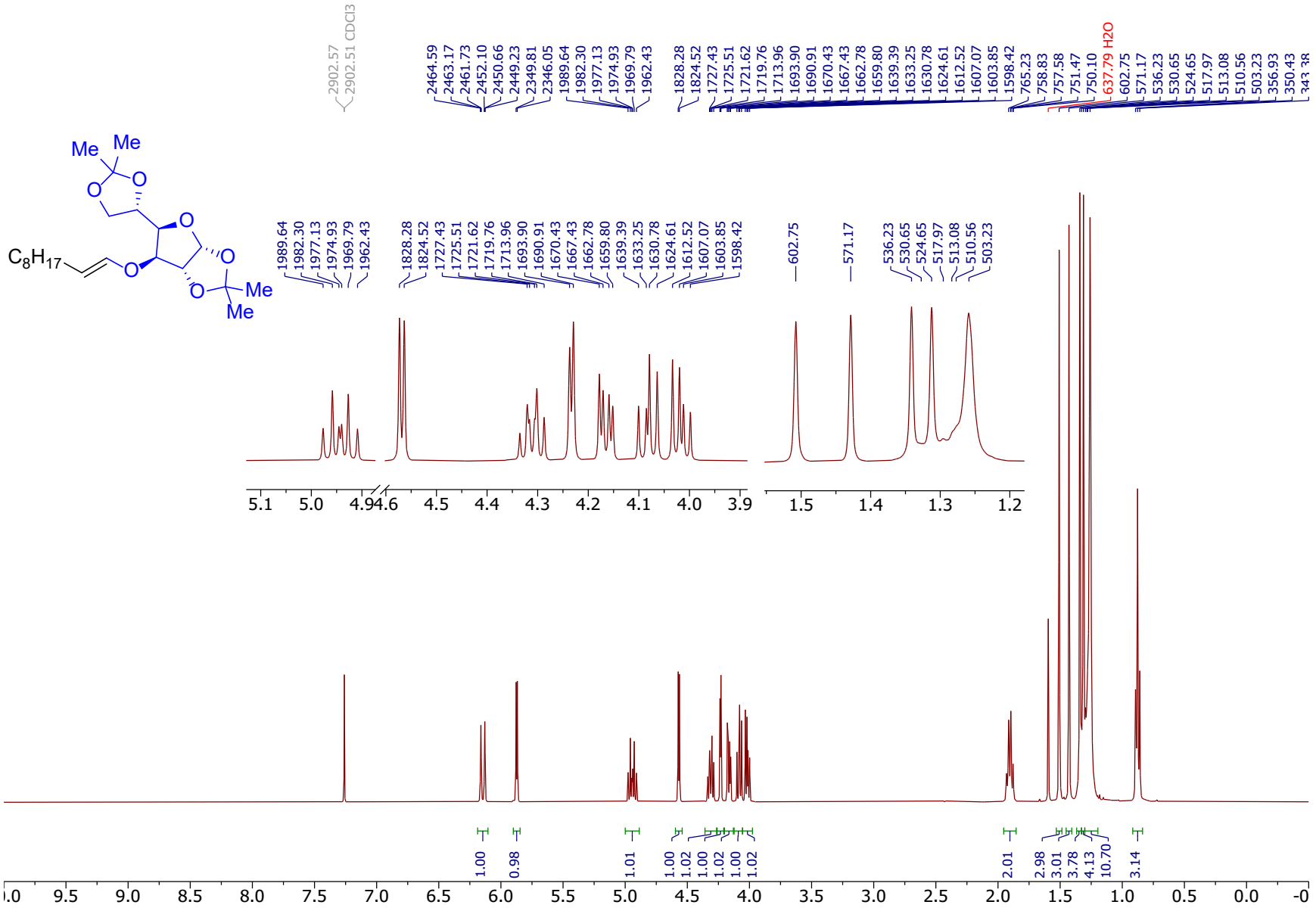
^{1}H NMR Spectrum of **125** (400 MHz, $CDCl_3$)



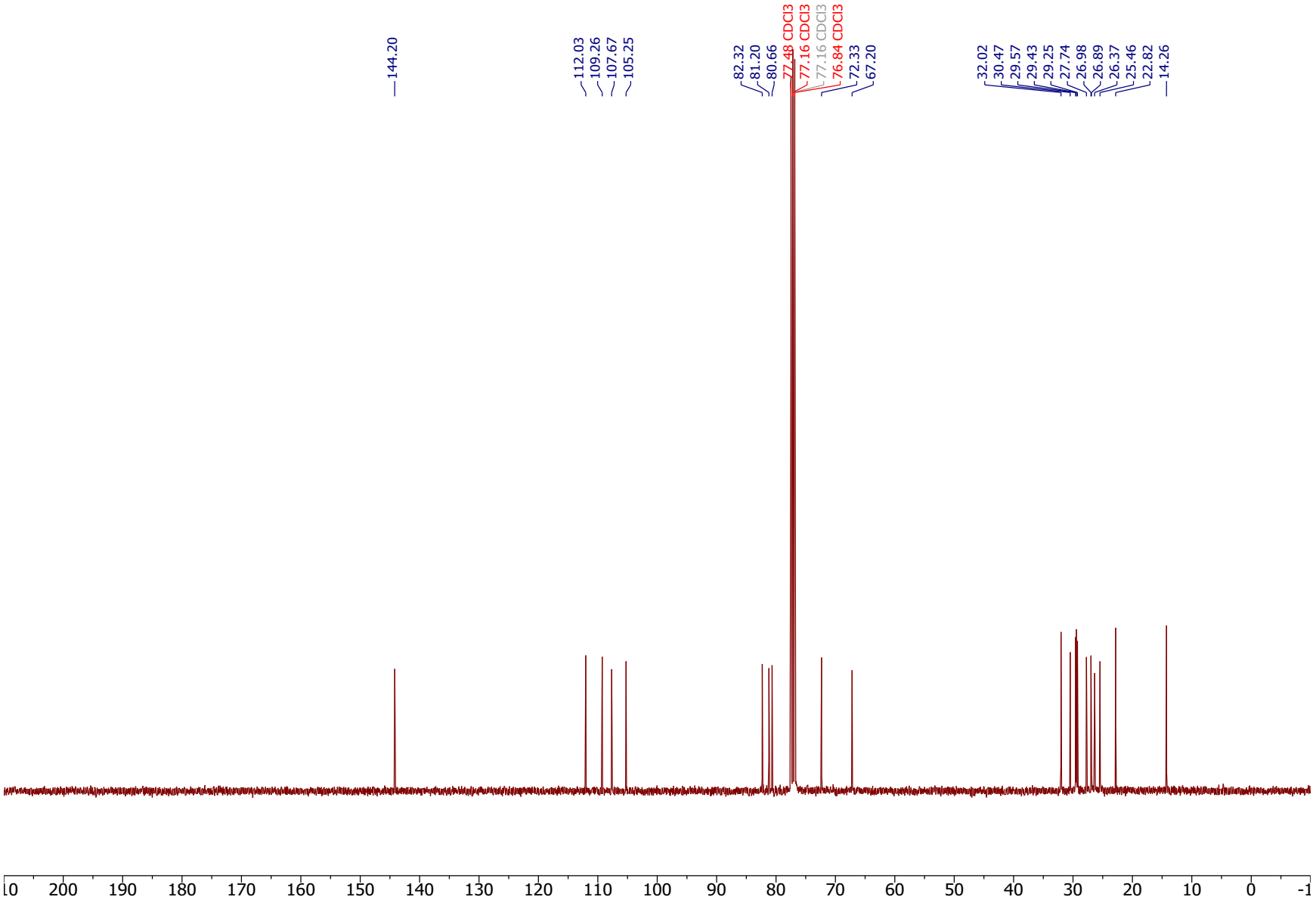
$^{13}C\{^{1}H\}$ NMR Spectrum of **125** (101 MHz, $CDCl_3$)



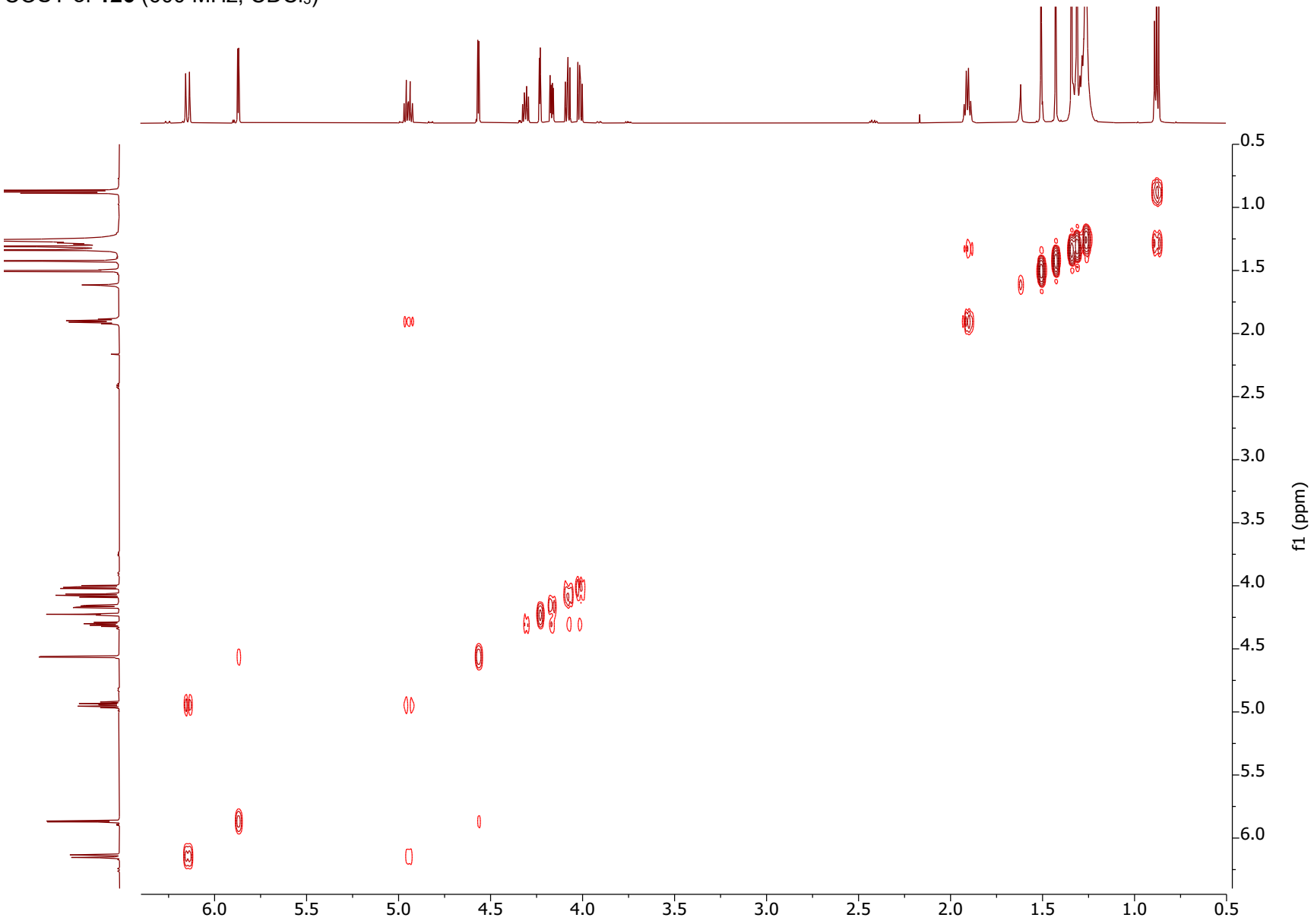
^{1}H NMR Spectrum of **126** (400 MHz, $CDCl_3$)



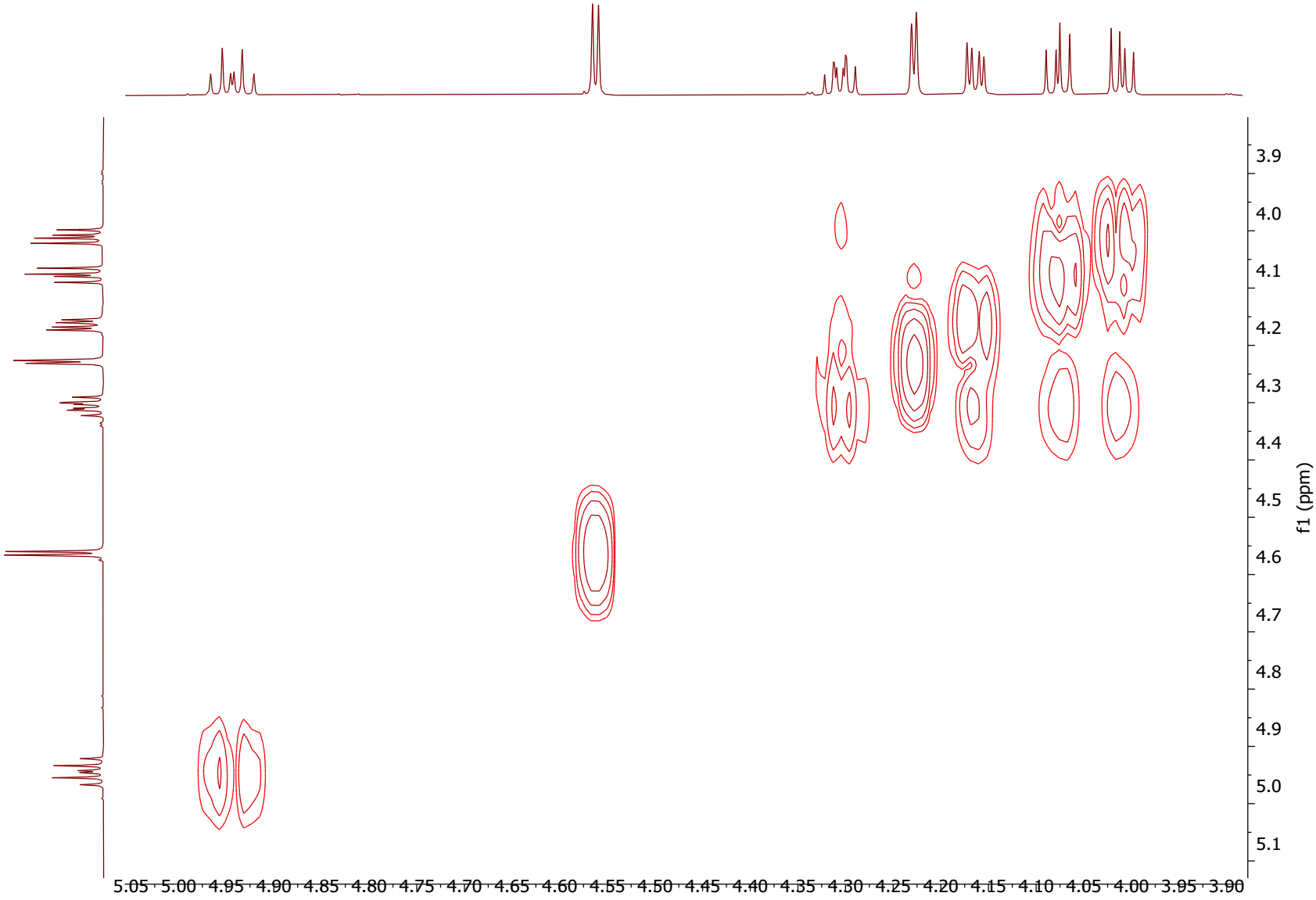
$^{13}C\{^{1}H\}$ NMR Spectrum of **126** (101 MHz, $CDCl_3$)



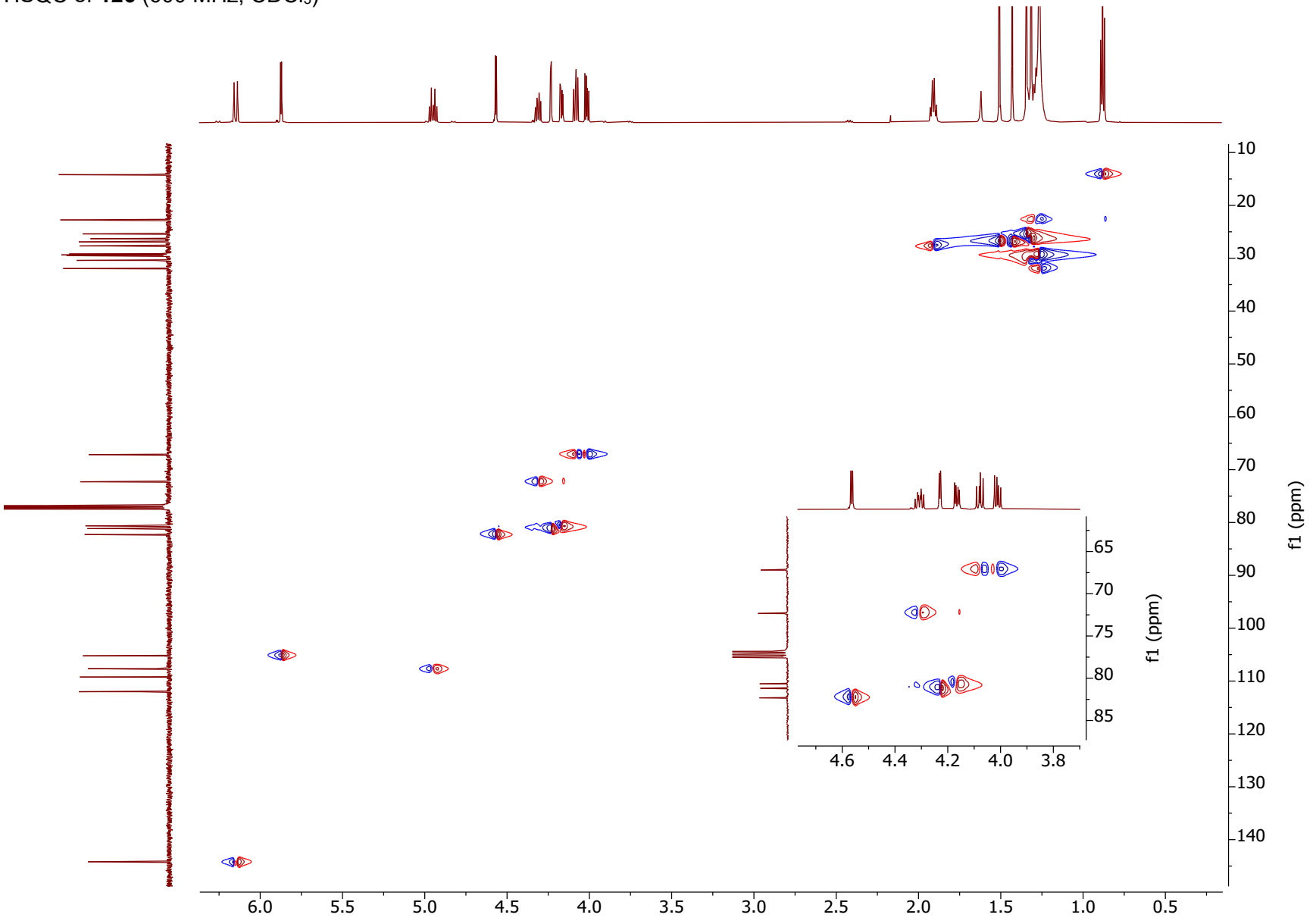
COSY of **126** (600 MHz, $CDCl_3$)



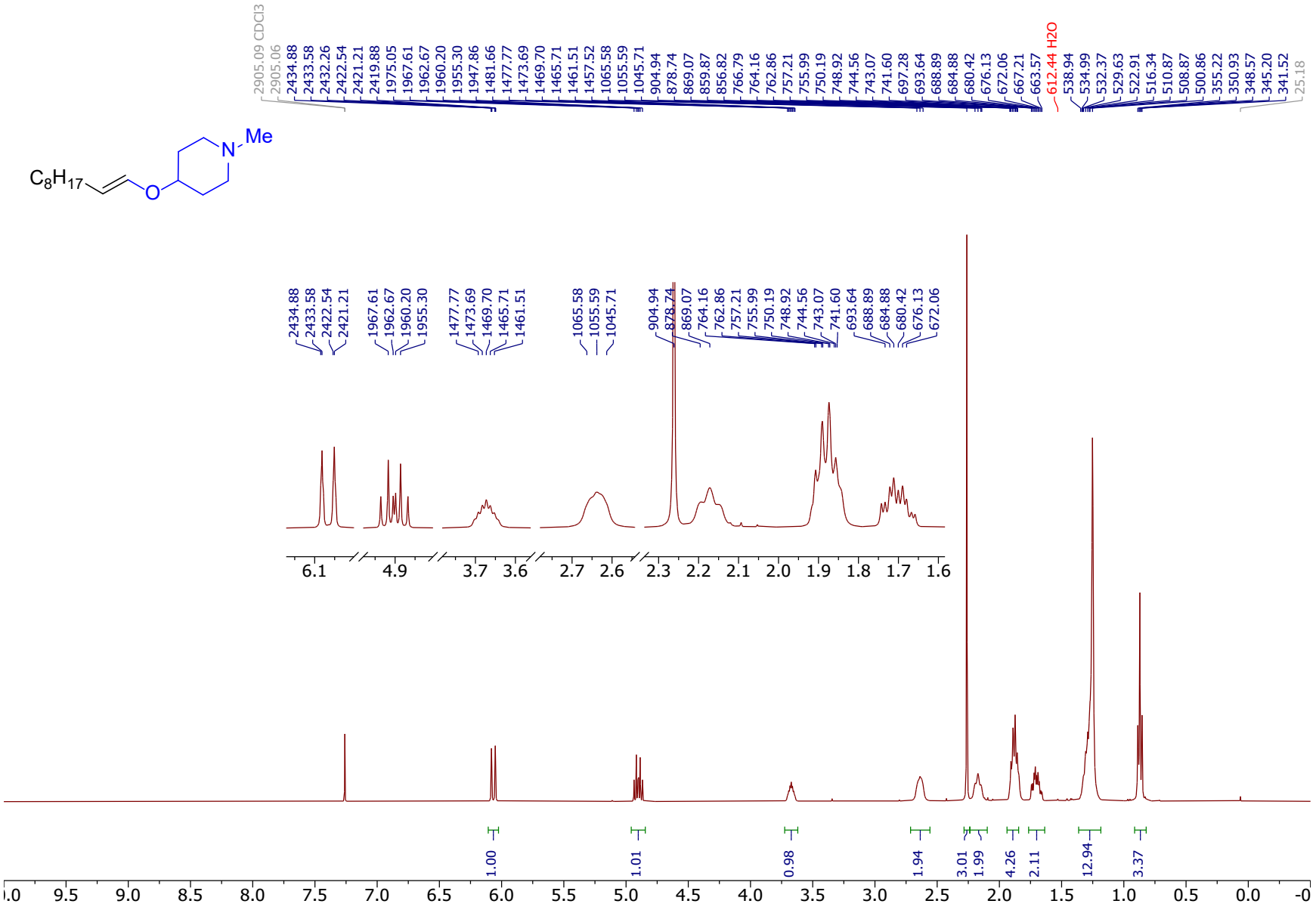
COSY of **126** (600 MHz, $CDCl_3$) Zoom-in



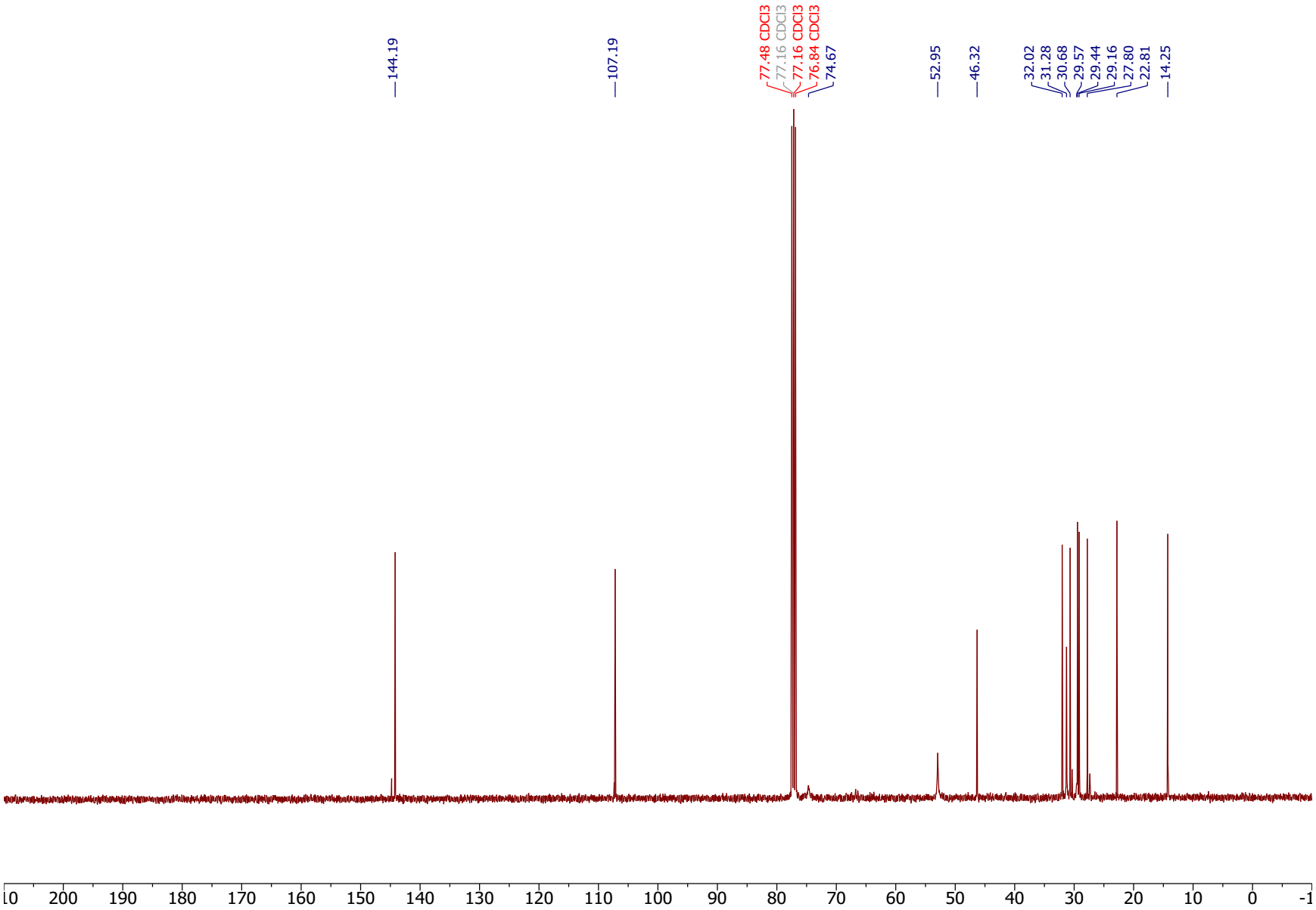
HSQC of **126** (600 MHz, $CDCl_3$)



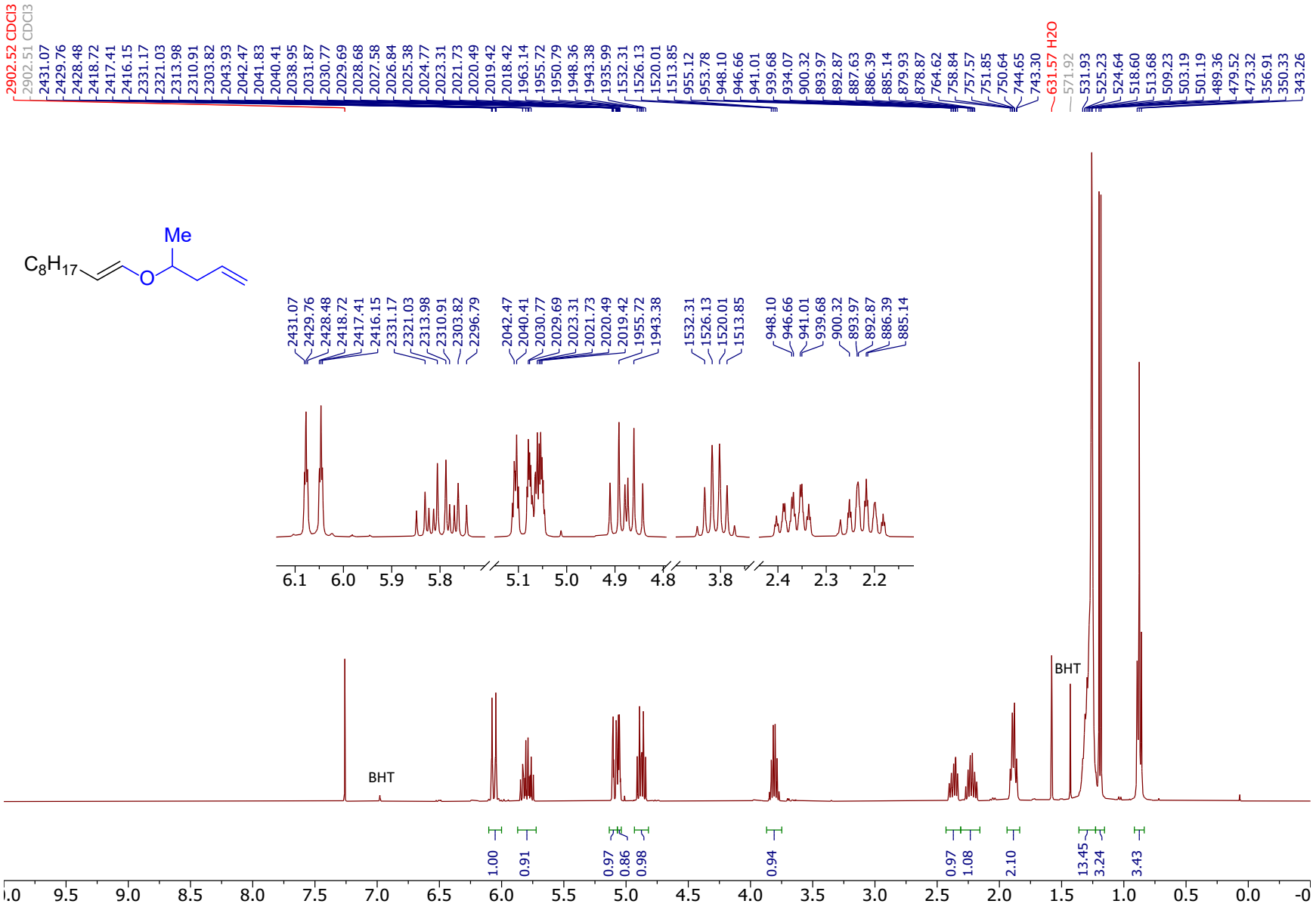
^{1}H NMR Spectrum of **127** (400 MHz, $CDCl_3$)



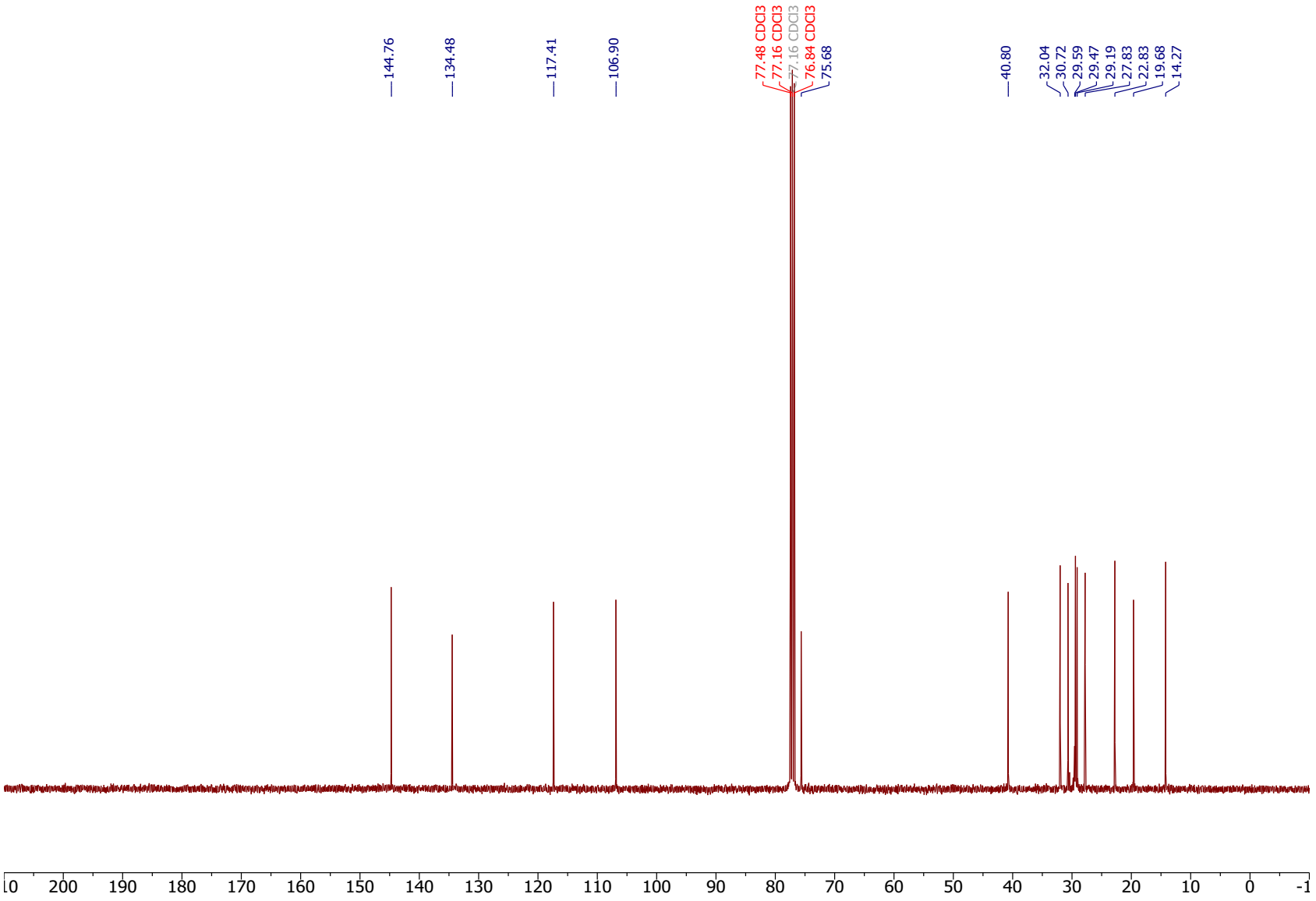
$^{13}C\{^{1}H\}$ NMR Spectrum of **127** (101 MHz, $CDCl_3$)



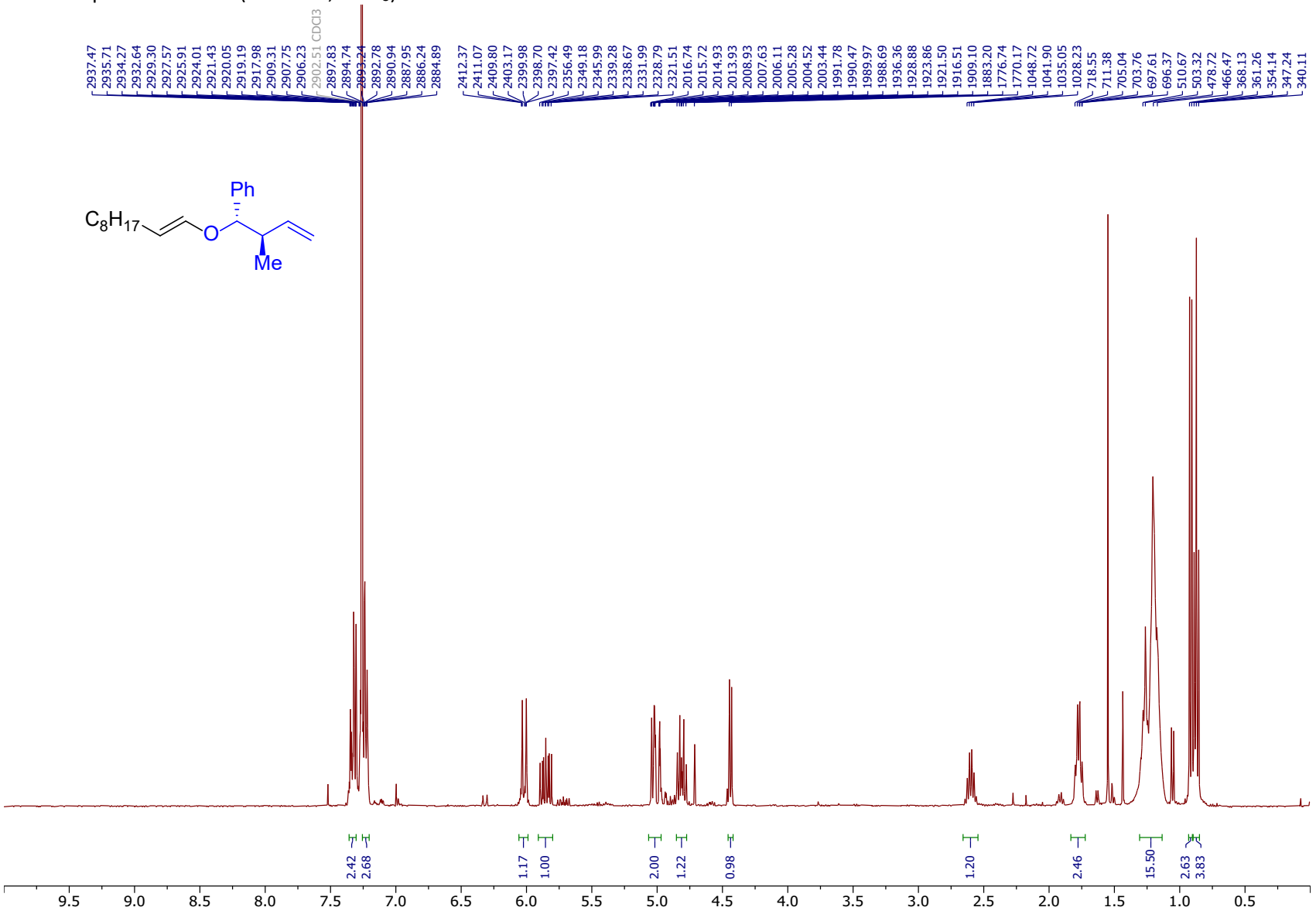
^{1}H NMR Spectrum of **128** (400 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR Spectrum of **128** (101 MHz, $CDCl_3$)



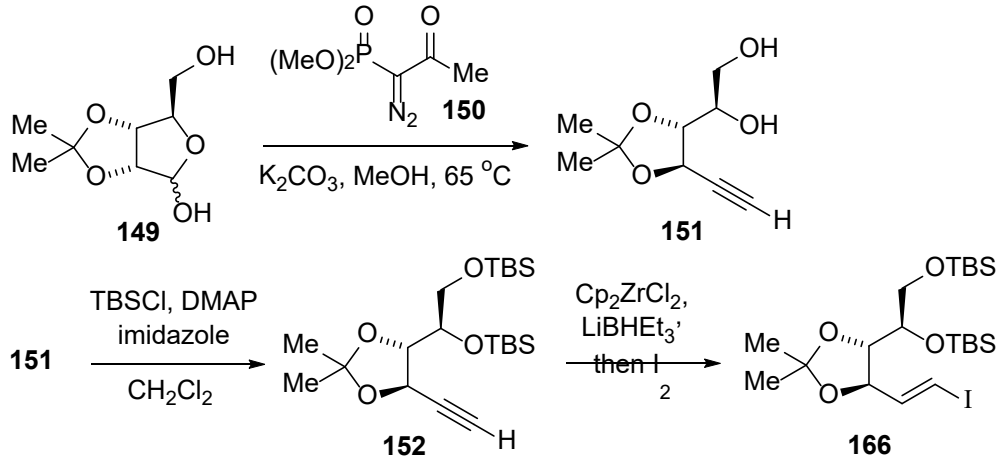
^{1}H NMR Spectrum of **129** (400 MHz, $CDCl_3$)



Experimental for Chapter 3

Experimental for vinylic iodides

Vinylic iodide (166) from D-ribose acetonide (149):



1,2-Dideoxy-3,4-*O*-(isopropylidene)-D-*arabino*-hex-1-ynitol (**151**):

A two-neck round bottom flask with stir bar and reflux condenser was charged with a solution of **149**[11,12] (1.5 g, 7.9 mmol) and K_2CO_3 (2.2 g, 16 mmol) in methanol (39 mL) under argon and heated to reflux in oil bath. A solution of Bestmann-Ohira reagent[5] (**150**, 3.0 g, 16 mmol) dissolved in methanol (20 mL) was added dropwise via syringe pump for over 6 h. After stirring for additional 13 h, the reaction mixture was cooled to room temperature and neutralized with 1M HCl, and the precipitate formed was filtered on filter paper. The filtrate was extracted with EtOAc (× 3). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product **151** was used for the next step without further purification.

For characterization of **151**, a small portion of the crude product was purified by silica gel column chromatography, using a CH_2Cl_2/EtOAc (1:1) eluant. The ^1H NMR spectrum of crude **151** matches the previously reported data[13].

^1H NMR (400 MHz, C_6D_6) δ 4.77 (dd, *J* = 6.3, 2.1 Hz, 1H), 4.11 (t, *J* = 6.1 Hz, 1H), 3.57 – 3.48 (m, 1H), 3.48 – 3.35 (m, 2H), 2.03 (d, *J* = 2.1 Hz, 1H), 1.42 (s, 3H), 1.26 (s, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, C_6D_6) δ 110.9, 82.7, 82.5, 74.4, 72.2, 67.5, 63.4, 27.1, 26.1.

[5,6-Di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*arabino*-hex-1-ynitol (**152**):

Imidazole (1.09 g, 16 mmol, 6 equiv), *t*-butyldimethylsilyl chloride (TBSCl, 1.21 g, 8.1 mmol, 3 equiv), and 4-(dimethylamino)pyridine (DMAP, 0.16 g, 1.3 mmol, 0.5 equiv) were added to a round bottom flask containing a stirring solution of **151** (0.50 g, 2.7 mmol) at 0 °C in CH_2Cl_2. The reaction was allowed to warm up to room temperature and stirred overnight before quenching with saturated aqueous solution of NH_4Cl and water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off the solids, and the filtrates were concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pretreated with 2% triethylamine and hexanes/EtOAc 70:1), followed by a second column chromatography with hexanes/EtOAc (100:1, gradient elution to 20:1) to remove a trace impurity afforded the corresponding TBS-protected alkynyldiol **152** (338 mg, 23% yield from D-ribose acetonide **149**, 2 steps) as a clear colorless oil.

$[\alpha]^{22}_D$ -12.9 (c = 0.1, $CHCl_3$)

^{1}H NMR (400 MHz, C_6D_6) δ 4.98 (dd, *J* = 6.7, 2.1 Hz, 1H), 4.48 (dd, *J* = 6.7, 4.0 Hz, 1H), 4.01 (td, *J* = 5.5, 4.0 Hz, 1H), 3.77 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.67 (dd, *J* = 10.4, 5.4 Hz, 1H), 2.07 (d, *J* = 2.1 Hz, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 0.99 (s, 9H), 0.97 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.07 (s, 6H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 110.4, 83.7, 82.6, 74.2, 73.6, 66.4, 65.5, 27.0, 26.2 (3C), 26.1 (3C), 25.8, 18.6, 18.4, -4.1, -4.5, -5.3 (2C).

HRMS (ESI): *m/z* calcd for $C_{18}H_{39}O_4Si_2^+$ $[M - C_3H_6]^+$ 375.2381; found 375.2379

[5,6-Di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-(*E*)-1-iodo-D-*arabino*-hex-1-enitol (**166**):

An oven-dried 25 mL flask with stir bar, cooled under argon, was charged with Cp_2ZrCl_2 (423 mg, 1.4 mmol, 2 equiv). The flask was vacuum pulled and re-filled with argon, and the cycle was repeated three times. After THF (2.3 mL, 5.5 mL / g of Cp_2ZrCl_2) was added, 1.0 M THF solution of $LiHBEt_3$ (a.k.a Super-hydride, 1.4 mL, 1.4 mmol, 2 equiv) was added dropwise into the stirring solution. The resulting white mixture was wrapped in aluminum foil and stirred at ambient temperature for 1 hr. Alkyne **152** (298 mg, 0.7 mmol) in THF (0.7 mL, 1 M of alkyne) was added dropwise at 0 °C. After 0.5 hr of stirring at 0 °C, the ice bath was removed, and the reaction mixture was stirred at ambient temperature for an additional 0.5 hr. Approximately 1 M solution of iodine (257 mg, 1 mmol, 1.4 equiv) in THF (1 mL) was added dropwise until the brown color persisted. After additional stirring for 0.5 hr, the reaction mixture was quenched with a solution of saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with diethyl ether (50 mL × 3). The combined organic layer was washed successively with saturated solution of $Na_2S_2O_3$ (50 mL),

saturated brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 2% triethylamine, hexanes/EtOAc 100:1 eluant) provided vinylic iodide **166** (296 mg, 75% yield).

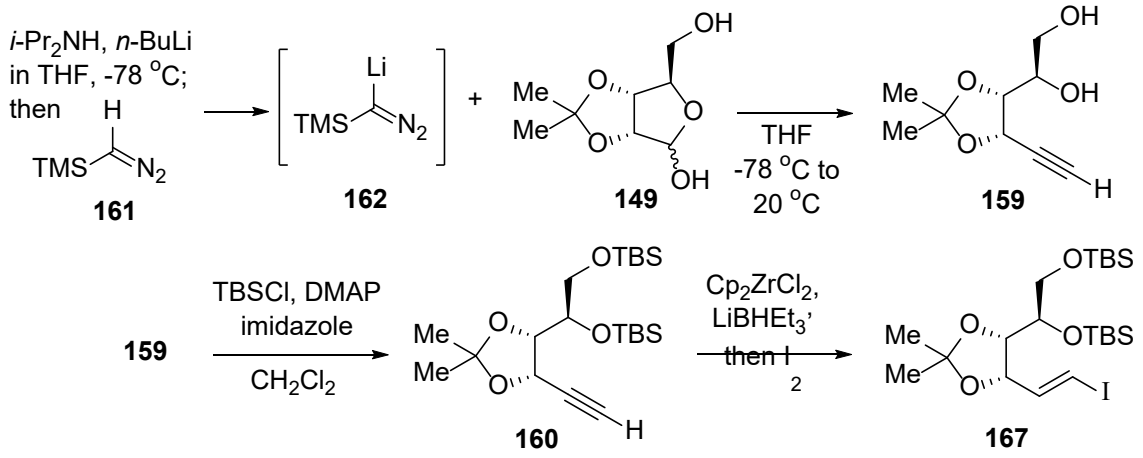
$[\alpha]^{22}_D$ -4.8 (c = 0.1, $CHCl_3$)

^{1}H NMR (400 MHz, C_6D_6) δ 6.76 (dd, *J* = 14.5, 5.8 Hz, 1H), 6.38 (dd, *J* = 14.5, 1.3 Hz, 1H), 4.53 (ddd, *J* = 7.2, 5.9, 1.3 Hz, 1H), 4.04 – 3.95 (m, 2H), 3.64 – 3.59 (m, 1H), 3.59 – 3.54 (m, 1H), 1.41 (s, 3H), 1.25 (s, 3H), 0.99 (s, 9H), 0.95 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 145.4, 109.1, 80.3, 79.2, 79.1, 73.5, 65.3, 27.2, 26.7, 26.2 (3C), 26.1 (3C), 18.6, 18.4, -4.2, -4.3, -5.2, -5.3.

HRMS (APCI): *m/z* calcd for $C_{21}H_{43}IO_4Si_2\ ^{35}Cl^-$ $[M + Cl]^-$ 577.1439; found 577.1445.

Vinylic iodide (167) from D-ribose acetonide (149):



1,2-Dideoxy-3,4-*O*-(isopropylidene)-D-*ribo*-hex-1-ynitol (**159**):

An oven-dried 100-mL round-bottom flask with magnetic stir bar was charged with *i*-Pr_2NH (3.5 mL, 25 mmol), dissolved in THF (18 mL) and cooled to -78 °C with an external cooling bath of dry ice-acetone. *n*-BuLi (2.5 M in hexanes, 7.5 mL, 15 mmol) was slowly added, and the resulting mixture was stirred for 20 min at -78 °C to generate a THF solution of lithium trimethylsilyldiazomethane (**162**)[14].

(2,3-*O*-isopropylidene)-D-ribofuranose **149** (0.95 g, 5.0 mmol) was dissolved in THF (6 mL), and this solution was slowly added to the -78 °C THF solution of **162**. The resulting mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL), and brine (20 mL) was added. The mixture was extracted with EtOAc (50 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product **159** was used in the next step without further purification.

For characterization of **159**, a small portion of the crude product was purified by silica gel column chromatography, using a CH_2Cl_2/EtOAc (1:1) eluant.

^{1}H NMR (400 MHz, C_6D_6) δ 4.74 (dt, *J* = 5.6, 1.9 Hz, 1H, 4.01 (ddd, *J* = 8.7, 5.4, 3.2 Hz, 1H), 3.89 (dd, *J* = 8.7, 5.8 Hz, 1H), 3.72 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.62 (dd, *J* = 11.1, 5.4 Hz, 1H), 2.15 (br s, 1H), 2.01 (s, 1H), 1.48 (s, 3H), 1.15 (s, 3H), 0.54 (br s, 1H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 110.7, 80.5, 77.7, 75.6, 71.3, 68.5, 64.1, 27.4, 25.8.

[5,6-Di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*ribo*-hex-1-ynitol (**160**): Imidazole (2.1 g, 31.1 mmol, 6 equiv), *t*-butyldimethylsilyl chloride (TBSCl, 2.4 g, 17 mmol, 3 equiv), and 4-(dimethylamino)pyridine (DMAP, 0.3 g, 2.5 mmol, 0.5 equiv) were added to a round bottom flask containing a stirring solution of **159** (0.95 g, 5.0 mmol) at 0 °C in CH_2Cl_2 (25 mL, 0.2 M). The reaction was allowed to warm up to room temperature and stirred overnight before quenching with saturated aqueous solution of NH_4Cl and water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off the solids, and the filtrates were concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pretreated with 2% triethylamine and hexanes/EtOAc 70:1), followed by a second column chromatography with hexanes/CH_2Cl_2 (4:1) to remove a trace impurity afforded the corresponding TBS-protected alkynyldiol **160** (798 mg, 39% yield from D-ribose acetonide **149**, 2 steps) as a clear colorless oil.

$[\alpha]^{21}_D$ -38.3 (c = 0.1, $CHCl_3$)

^{1}H NMR (400 MHz, C_6D_6) δ 4.86 (dd, *J* = 5.0, 2.1 Hz, 1H), 4.24 (ddd, *J* = 8.9, 4.4, 2.0 Hz, 1H), 4.14 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.91 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.78 (dd, *J* = 10.8, 4.4 Hz, 1H), 2.01 (d, *J* = 2.1 Hz, 1H), 1.60 (s, 3H), 1.28 (d, *J* = 0.7 Hz, 3H), 1.02 (s, 9H), 0.99 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H), 0.08 (s, 6H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 110.9, 81.9, 77.9, 75.9, 74.3, 69.6, 65.8, 28.0, 26.8, 26.25 (3C), 26.21 (3C), 18.7, 18.5, -3.5, -4.4, -5.2, -5.3.

HRMS (ESI): *m/z* calcd for $C_{21}H_{42}O_4Si_2Na^+$ $[M + Na]^+$ 437.2514; found 437.2530

[5,6-Di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-(*E*)-1-iodo-D-*ribo*-hex-1-enitol (**167**):

An oven-dried 25 mL flask with stir bar, cooled under argon, was charged with Cp_2ZrCl_2 (585 mg, 2 mmol, 2 equiv). The flask was vacuum pulled and re-filled with argon, and the cycle was repeated three times. After THF (3.2 mL, 5.5 mL / g of Cp_2ZrCl_2) was added, 1.0 M THF solution of $LiHBEt_3$ (a.k.a Super-hydride, 2 mL, 2 mmol, 2 equiv) was added dropwise into the stirring solution. The resulting white mixture was wrapped in aluminum foil and stirred at ambient temperature for 1 hr. Alkyne **160** (415 mg, 1 mmol) in THF (1 mL, 1M of alkyne) was added dropwise at 0 °C. After 0.5 hr of stirring at 0 °C, the ice bath was removed, and the reaction mixture was stirred at ambient temperature for an additional 0.5 hr. Approximately 1 M solution of iodine (356 mg, 1.4 mmol, 1.4 equiv) in THF (1.4 mL) was added dropwise until the brown color persisted. After additional stirring for 0.5 hr, the reaction mixture was quenched with a solution of saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with diethyl ether (50 mL × 3).

The combined organic layer was washed successively with saturated solution of $Na_2S_2O_3$ (50 mL), saturated brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 2% triethylamine, hexanes/EtOAc 100:1 eluant) provided vinylic iodide **167** (357 mg, 64% yield).

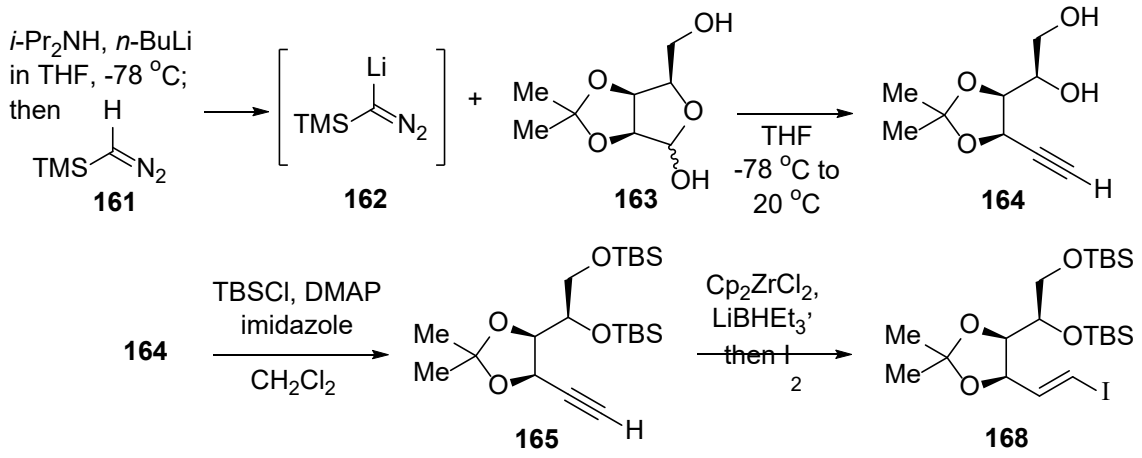
$[\alpha]^{21}_D$ -48.5 (c = 0.1, $CHCl_3$)

^{1}H NMR (400 MHz, C_6D_6) δ 6.87 (dd, *J* = 14.4, 6.5 Hz, 1H), 6.29 (dd, *J* = 14.4, 1.2 Hz, 1H), 4.44 (td, *J* = 6.3, 1.2 Hz, 1H), 4.25 (dd, *J* = 7.7, 6.1 Hz, 1H), 3.80 (dt, *J* = 7.7, 3.6 Hz, 1H), 3.71 (AB dd, *J* = 10.9, 3.1 Hz, 1H), 3.68 (AB dd, *J* = 10.9, 3.7 Hz, 1H), 1.35 (s, 3H), 1.24 (s, 3H), 0.99 (s, 9H), 0.97 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.06 (s, 6H).

^{13}C{^{1}H } NMR (101 MHz, C_6D_6) δ 143.9, 108.7, 80.0, 79.3, 77.4, 72.8, 65.0, 28.0, 26.2 (3C), 26.1 (3C), 25.5, 18.6, 18.5, -3.5, -4.3, -5.2, -5.4.

HRMS (ESI): *m/z* calcd for $C_{21}H_{43}IO_4Si_2\,Na^+$ $[M + Na]^+$ 565.1637; found 565.1647

Vinylic iodide (168) from D-lyxose acetonide (163):



1,2-Dideoxy-3,4-*O*-(isopropylidene)-D-*lyxo*-hex-1-ynitol (**164**):

An oven-dried 100-mL round-bottom flask with magnetic stir bar was charged with *i*-Pr_2NH (3.5 mL, 25 mmol), dissolved in THF (18 mL) and cooled to -78 °C with an external cooling bath of dry ice-acetone. *n*-BuLi (2.5 M in hexanes, 10 mL, 25 mmol) was slowly added, and the resulting mixture was stirred for 20 min at -78 °C. A solution of $TMSCHN_2$ (2.0 M in hexanes, 12.5 mL, 25 mmol) was then added dropwise at -78 °C, and this mixture stirred for 20 minutes to generate a THF solution of lithium trimethylsilyldiazomethane (**162**)[14].

(2,3-*O*-isopropylidene)-D-lyxofuranose **163**[11] (0.95 g, 5.0 mmol) was dissolved in THF (6 mL), and this solution was slowly added to the -78 °C THF solution of **162**. The resulting mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL), and brine (20 mL) was added. The mixture was extracted with EtOAc (50 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (CH_2Cl_2/EtOAc 1:1, gradient elution to 1:2) afforded the

corresponding alkynyl diol **164** (106 mg, 11% yield from lactol **163**). Approximately 10% of compound **163** was recovered.

^{1}H NMR (400 MHz, C_6D_6) δ 4.50 (dd, *J* = 5.8, 2.3 Hz, 1H), 4.07 (ddd, *J* = 7.4, 5.5, 3.6 Hz, 1H), 3.96 (dd, *J* = 7.4, 5.8 Hz, 1H), 3.68 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.59 (dd, *J* = 11.6, 5.4 Hz, 1H), 3.00 (br s, 2H), 2.03 (d, *J* = 2.2 Hz, 1H), 1.53 (s, 3H), 1.19 (d, *J* = 0.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 110.4, 80.2, 78.6, 76.3, 72.4, 67.1, 63.5, 27.7, 26.0.

[5,6-Di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*lyxo*-hex-1-ynitol (**165**):

Imidazole (175 mg, 2.6 mmol, 6 equiv), *t*-butyldimethylsilyl chloride (TBSCl, 194 mg, 1.3 mmol, 3 equiv), and 4-(dimethylamino)pyridine (DMAP, 26 mg, 0.21 mmol, 0.5 equiv) were added to a round bottom flask containing a stirring solution of **164** (80 mg, 0.43 mmol) at 0 °C in CH_2Cl_2. The reaction was allowed to warm up to room temperature and stirred overnight before quenching with saturated aqueous solution of NH_4Cl and water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered off the solids, and the filtrates were concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pretreated with 2% triethylamine and hexanes/EtOAc 70:1) afforded the corresponding TBS-protected alkynyldiol **165** (122 mg, 68% yield from **164**) as a clear colorless oil.

$[\alpha]^{22}_{D}$ 14.0 (c = 0.1, $CHCl_3$)

^{1}H NMR (400 MHz, C_6D_6) δ 4.68 (dd, *J* = 5.1, 2.2 Hz, 1H), 4.28 (ddd, *J* = 8.3, 5.0, 4.2 Hz, 1H), 4.07 (dd, *J* = 8.3, 5.1 Hz, 1H), 3.82 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.64 (dd, *J* = 10.5, 4.2 Hz, 1H), 2.01 (d, *J* =

2.1 Hz, 1H), 1.62 (s, 3H), 1.27 (d, *J* = 0.7 Hz, 3H), 1.10 (s, 9H), 0.95 (s, 9H), 0.32 (s, 3H), 0.27 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, C_6D_6) δ 109.9, 81.6, 80.2, 75.5, 74.2, 67.6, 66.3, 28.0, 26.4, 26.3 (3C), 26.2 (3C), 18.7, 18.6, -3.9, -4.3, -5.26, -5.30.

HRMS (ESI): *m/z* calcd for $C_{18}H_{39}O_4Si_2^+$ $[M - C_3H_6]^+$ 375.2381; found 375.2380

[5,6-Di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-(*E*)-1-iodo-D-*lyxo*-hex-1-enitol (**168**):

An oven-dried 25 mL flask with stir bar, cooled under argon, was charged with Cp_2ZrCl_2 (238 mg, 0.8 mmol, 2 equiv). The flask was vacuum pulled and re-filled with argon, and the cycle was repeated three times. After THF (1.3 mL, 5.5 mL / g of Cp_2ZrCl_2) was added, 1.0 M THF solution of $LiHBEt_3$ (a.k.a Super-hydride, 0.8 mL, 0.8 mmol, 2 equiv) was added dropwise into the stirring solution. The resulting white mixture was wrapped in aluminum foil and stirred at ambient temperature for 1 hr via syringe pump at 5 mL/hr. Alkyne **165** (167 mg, 0.4 mmol) in THF (0.4 mL, 1 M of alkyne) was added dropwise at 0 °C via syringe pump at 5 mL/hr. After 0.5 hr of stirring at 0 °C, the ice bath was removed, and the reaction mixture was stirred at ambient temperature for an additional 0.5 hr. Approximately 1 M solution of iodine (143 mg, 0.56 mmol, 1.4 equiv) in THF (0.56 mL) was added dropwise until the brown color persisted. After additional stirring for 0.5 hr, the reaction mixture was quenched with a solution of saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with diethyl ether (50 mL × 3). The combined organic layer was washed successively with saturated solution of $Na_2S_2O_3$ (50 mL), saturated brine, dried over $MgSO_4$,

filtered, and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 2% triethylamine, hexanes/EtOAc 100:1 eluant) provided vinylic iodide **168** contaminated with terminal alkene byproduct, which was removed with a second column chromatography with silica gel pre-treated with 1% triethylamine, hexanes/CH_2Cl_2 7:1 eluant, to afford vinylic iodide **168** (124 mg, 57% yield).

$[\alpha]^{22}_D$ 10.6 (c = 0.1, $CHCl_3$)

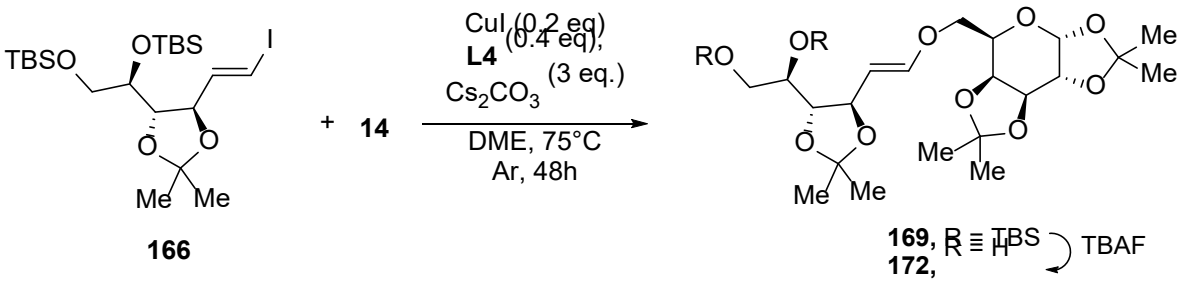
^{1}H NMR (400 MHz, C_6D_6) δ 6.84 (dd, *J* = 14.5, 7.3 Hz, 1H), 6.16 (dd, *J* = 14.5, 1.0 Hz, 1H), 4.29 (ddd, *J* = 7.3, 6.2, 1.1 Hz, 1H), 4.17 (t, *J* = 6.5 Hz, 1H), 3.88 (dt, *J* = 6.8, 5.0 Hz, 1H), 3.68 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.62 (dd, *J* = 10.4, 4.8 Hz, 1H), 1.41 (s, 3H), 1.24 (s, 3H), 1.04 (s, 9H), 0.96 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}C{^{1}H } NMR (101 MHz, C_6D_6) δ 143.5, 108.6, 79.9, 79.7, 79.5, 73.2, 65.6, 27.8, 26.3 (3C), 26.2 (3C), 25.4, 18.6 (2C), -4.0, -4.1, -5.19, -5.22.

HRMS (ESI): *m/z* calcd for $C_{21}H_{43}IO_4Si_2\,^{35}Cl^-$ $[M + Cl]^-$ 577.1439; found 577.1452.

Experimental for the vinylic ethers

C-O cross-coupling to synthesize vinylic ether (*E*)-169:



1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*E*)-[5,6-di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*arabino*-hex-1-enitol]-α-D-galactopyranose ((*E*)-**169**):

An oven-dried 4 mL vial with a stir bar was charged with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**14**, 182 mg, 0.7 mmol, 2 equiv), Cs_2CO_3 (342 mg, 1.1 mmol, 3 equiv), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (CyDMEDA, 22.1 µL, 0.14 mmol, 0.4 equiv), and vinylic iodide **166** (190 mg, 0.35 mmol, 1 equiv). The reaction vial was purged continuously with argon for 5min before CuI (13 mg, 0.07 mmol, 0.2 equiv) was added. Anhydrous 1,2-dimethoxyethane (DME, 0.5mL, 0.7 M based on vinylic iodide) was added, and the reaction mixture was bubbled with argon for 5 minutes. The reaction vial was quickly closed with a solid cap, sealed with Teflon tape and electrical tape, and heated at an internal temperature at 75 °C in an oil bath. The reaction mixture was stirred for 42 hours, cooled to room temperature, and diluted with EtOAc. The mixture was filtered through a Celite® pad and rinsed with EtOAc (100 mL), and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 2% triethylamine, hexanes / EtOAc 12:1 eluent) afforded the vinylic ether (*E*)-**169** (155 mg, 66% yield).

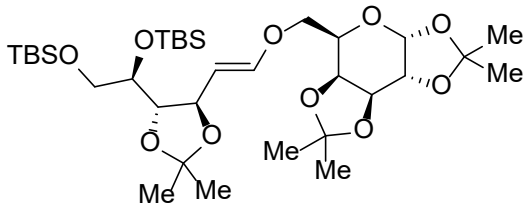
$[\alpha]^{22}_{D}$ -18.1 (c = 0.1, $CHCl_3$)

^{1}H NMR (800 MHz, C_6D_6) δ 6.64 (d, *J* = 12.6 Hz, 1H), 5.48 (d, *J* = 5.0 Hz, 1H), 5.05 (dd, *J* = 12.6, 8.4 Hz, 1H), 4.68 (t, *J* = 8.2 Hz, 1H), 4.47 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.20 (td, *J* = 6.1, 1.9 Hz, 1H), 4.16 – 4.15 (m, 1H), 4.15 – 4.13 (m, 1H), 4.06 (dd, *J* = 8.1, 3.4 Hz, 1H), 4.03 – 4.01 (m, 1H), 4.01 – 3.98 (m, 2H), 3.78 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.71 (dd, *J* = 10.2, 5.8 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 1.02 (s, 9H), 0.97 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 150.6, 109.3, 108.5, 108.0, 103.5, 96.8, 81.6, 75.6, 73.4, 71.4, 71.2, 71.0, 68.6, 66.8, 65.4, 27.6, 27.4, 26.3, 26.2 (7C), 24.9, 24.4, 18.6, 18.5, -4.16, -4.18, -5.2 (2C).

HRMS (ESI): *m/z* calcd for $C_{33}H_{62}O_{10}Si_2$ $^{35}Cl^-$ $[M + Cl]^-$ 709.3576, found 709.3561.

Assignments of diagnostic ^{13}C and ^{1}H NMR resonances for vinylic ether (*E*)-**169**, determined by HSQC, COSY, and HMBC spectroscopy:



169

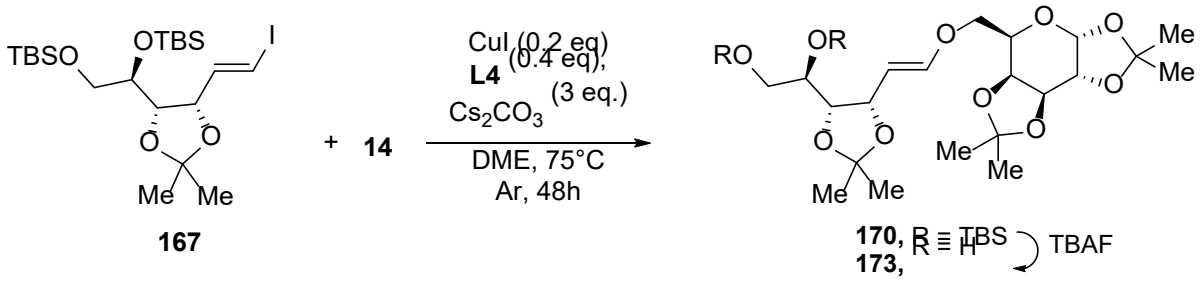
carbon position	δ_C[a]	δ_H[b,c] (*J*, Hz)
1'	150.6	6.64, d (12.6)
2'	103.5	5.05, dd (12.6, 8.4)
3'	75.6	4.68, t (8.2)
4'	81.6	4.06, dd (8.1, 3.4)
5'	73.4	4.15 – 4.13,[d] m
6a'	65.4	3.78, dd (10.2, 6.2)
6b'		3.71, dd (10.2, 5.8)
1	96.8	5.48, d (5.0)
2	71.0	4.16 – 4.15,[d] m
3	71.2	4.47, dd (7.9, 2.4)
4	71.4	4.03 – 4.01,[d] m
5	66.8	4.20, td (6.1, 1.9)
6a	68.6	4.01 – 3.98,[d] m (2H)
6b		
7	108.5	--
8	109.3	--
9	108.0	--

[a] Recorded at 101 MHz in C_6D_6
[b] Recorded at 800 MHz in C_6D_6
[c] Denotes ^{1}H resonance(s) correlating to each ^{13}C for the carbon position
[d] Due to overlapping ^{1}H peaks, these assignments are tentative.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*E*)-[1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*lyxo*-hex-1-enitol]-α-D-galactopyranose (**172**):

An oven-dried 25 mL round-bottom flask with stir bar was charged with vinylic ether **169** (55 mg, 0.08 mmol), dissolved in anhydrous THF (7 mL, 0.01 M), and cooled to 0 °C with an ice bath. A solution of tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 0.25 mL, 0.25 mmol, 3.1 equiv) was added slowly. The ice bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction mixture was cooled to 0 °C and quenched by slow addition of saturated aqueous NH_4Cl solution at room temperature, and then diluting with deionized water and brine. The aqueous layer was extracted with EtOAc (x 3) and the combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (2% triethylamine pre-treated silica gel, hexanes/EtOAc 1:3 eluant) to give the diol-vinylic ether **172** (23 mg, 52% yield).

C-O cross-coupling to synthesize vinylic ether (*E*)-170 followed by desilylation:



1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*E*)-[5,6-di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*ribo*-hex-1-enitol]-α-D -galactopyranose ((*E*)-**170**):

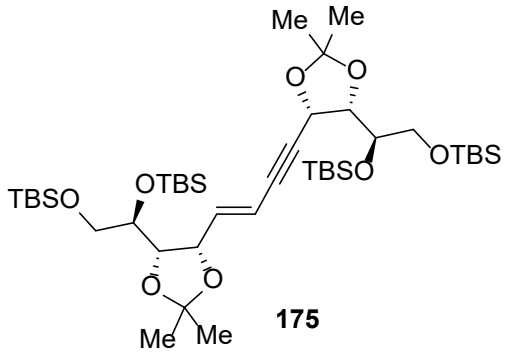
An oven-dried 4 mL vial with a stir bar was charged with 1,2:3,4-di-O-isopropylidene-a-D-galactopyranose (14, 261 mg, 1 mmol, 2 equiv), Cs_2CO_3 (490 mg, 1.5 mmol, 3 equiv), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (CyDMEDA, 31.6 µL, 0.2 mmol, 0.4 equiv), and vinylic iodide (*E*)-**167** (272 mg, 0.5 mmol, 1 equiv). The reaction vial was purged continuously with argon for 5 min before CuI (19 mg, 0.1 mmol, 0.2 equiv) was added. Anhydrous 1,2-dimethoxyethane (DME, 0.7 mL, 0.7 M based on vinylic iodide) was added, and the reaction mixture was bubbled with argon for 5 minutes. The reaction vial was quickly closed with a solid cap, sealed with Teflon tape and electrical tape, and heated at an internal temperature at 75 °C in an oil bath. The reaction mixture was stirred for 46 hours, cooled to room temperature, and diluted with EtOAc. The mixture was filtered through a Celite® pad and rinsed with EtOAc (100 mL), and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 2% triethylamine, hexanes / EtOAc 12:1 eluent) afforded the vinylic ether (*E*)-**170** (162 mg, 48% yield).

$[\alpha]^{22}_D$ -72.1 (c = 0.1, $CHCl_3$)

^{1}H NMR (800 MHz, C_6D_6) δ 6.53 (d, *J* = 12.7 Hz, 1H), 5.48 (d, *J* = 5.0 Hz, 1H), 5.21 (dd, *J* = 12.6, 9.0 Hz, 1H), 4.61 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.47 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.33 (dd, *J* = 7.5, 6.0 Hz, 1H), 4.23 (td, *J* = 6.4, 1.9 Hz, 1H), 4.15 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.09 (dd, *J* = 8.0, 1.8 Hz, 1H), 4.07 (dd, *J* = 9.8, 6.7 Hz, 1H), 4.02 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.93 (ddd, *J* = 7.3, 4.2, 2.9 Hz, 1H), 3.88 (dd, *J* = 10.8, 2.9 Hz, 1H), 3.82 (dd, *J* = 10.8, 4.2 Hz, 1H), 1.463 (s, 3H), 1.460 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, C_6D_6) δ 150.5, 109.2, 108.5, 107.9, 101.9, 96.8, 77.7, 77.0, 73.3, 71.2, 71.13, 71.05, 68.4, 66.7, 65.5, 28.4, 26.32 (3C), 26.28, 26.27, 26.23 (3C), 25.9, 24.9, 24.4, 18.7, 18.5, -3.4, -4.3, -5.15, -5.25.

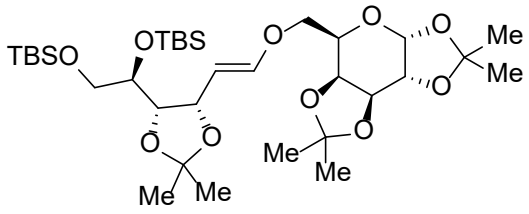
HRMS (ESI): *m/z* calcd for $C_{33}H_{62}O_{10}Si_2\,Na^+$ $[M + Na]^+$ 697.3774, found 697.3806



175

Enyne by-product **175** was isolated as a mixture with the terminal alkene impurity carried over from the synthesis of vinylic iodide. Most protons are accounted for except for the methyl groups on TBS groups. ^{1}H NMR (400 MHz, C_6D_6) δ 6.58 (dd, *J* = 15.8, 6.1 Hz, 1H), 6.04 (dt, *J* = 15.9, 1.7 Hz, 1H), 5.11 (dd, *J* = 5.0, 1.9 Hz, 1H), 4.22 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.97 (dd, *J* = 10.7, 2.0 Hz, 1H), 3.93 – 3.86 (m, 2H), 3.84 (dd, *J* = 10.7, 2.6 Hz, 2H), 3.80 (d, *J* = 4.3 Hz, 1H), 3.78 – 3.73 (m, 2H), 1.67 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.05 (s, 9H), 1.03 (s, 9H).

Assignments of diagnostic ^{13}C and ^{1}H NMR resonances for vinylic ether (*E*)-**170**, determined by HSQC, COSY, and HMBC spectroscopy:



170

carbon position	δ_C[a]	δ_H[b,c] (*J*, Hz)
1'	150.5	6.53, d (12.7)
2'	101.9	5.21, dd (12.6, 9.0)
3'	77.0	4.61, dd (9.0, 6.0)
4'	77.7	4.33, dd (7.5, 6.0)
5'	73.3	3.93, ddd (7.3, 4.2, 2.9)
6a'	65.5	3.88, dd (10.8, 2.9)
6b'		3.82, dd (10.8, 4.2)
1	96.8	5.48, d (5.0)
2	71.05	4.15, dd (5.0, 2.4)
3	71.13[d]	4.47, dd (7.9, 2.4)
4	71.2[d]	4.09, dd (8.0, 1.8)
5	66.7	4.23, td (6.4, 1.9)
6a	68.4	4.07, dd (9.8, 6.7)
6b		4.02, dd (9.8, 6.0)
7	108.5	--
8	109.2	--
9	107.9	--

[a] Recorded at 101 MHz in C_6D_6

[b] Recorded at 800 MHz in C_6D_6

[c] Denotes ^{1}H resonance(s) correlating to each ^{13}C for the carbon position

[d] Due to overlapping ^{13}C peaks, these assignments are tentative.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*E*)-[1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*ribo*-hex-1-enitol]-α-D-galactopyranose ((*E*)-**173**):

A 50 mL round-bottom flask with stir bar was charged with vinylic ether (*E*)-**170** (140 mg, 0.2 mmol), dissolved in anhydrous THF (19 mL, 0.01 M), and cooled to 0 °C with an external cooling bath. A solution of tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 0.7 mL, 0.7 mmol, 3.5 equiv) was added slowly. The external cooling bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction mixture was cooled to 0 °C, and quenched by slow addition of a saturated aqueous NH_4Cl solution at room temperature, and then diluted with deionized water and brine. The aqueous layer was extracted with EtOAc (x 3) and the combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (pre-treated with 2% triethylamine, hexanes/EtOAc 1:3 → 1:5 eluant) to give the diol **173** (61 mg, 65% yield).

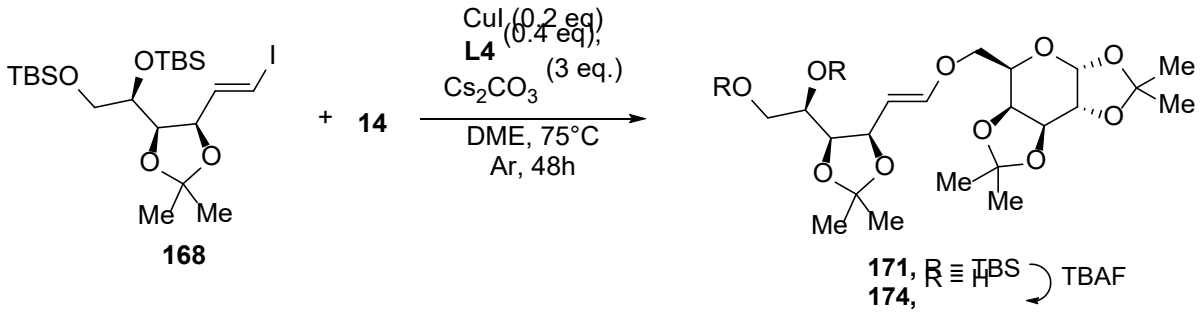
$[\alpha]^{22}_D$ -30.6 (c = 0.1, $CHCl_3$)

^{1}H NMR (800 MHz, C_6D_6) δ 6.46 (d, *J* = 12.4 Hz, 1H), 5.44 (d, *J* = 5.0 Hz, 1H), 5.20 (dd, *J* = 12.5, 9.0 Hz, 1H), 4.59 (dd, *J* = 8.9, 5.9 Hz, 1H), 4.41 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.13 - 4.10 (m, 2H), 4.07 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.98 (d, *J* = 5.9 Hz, 2H), 3.92 (dt, *J* = 7.5, 1.9 Hz, 1H), 3.88 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.84 – 3.75 (m, 2H), 2.9 (br, 1H), 2.4 (br, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.26 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 150.8, 109.5, 108.8, 108.6, 101.6, 96.7, 78.6, 77.0, 71.4, 71.1, 70.9, 70.3, 69.6, 67.7, 65.2, 28.3, 26.20, 26.17, 25.7, 24.8, 24.3.

HRMS (ESI negative): *m/z* calcd for $C_{21}H_{34}O_{10}{}^{35}Cl$ $[M + Cl]^-$ 481.1846, found 481.1858.

C-O cross-coupling to synthesize vinylic ether (*E*)-171 followed by desilylation:



1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*E*)-[5,6-di-*O*-(*tert*-butyldimethylsilyl)]-1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*lyxo*-hex-1-enitol]-α-D-galactopyranose ((*E*)-**171**):

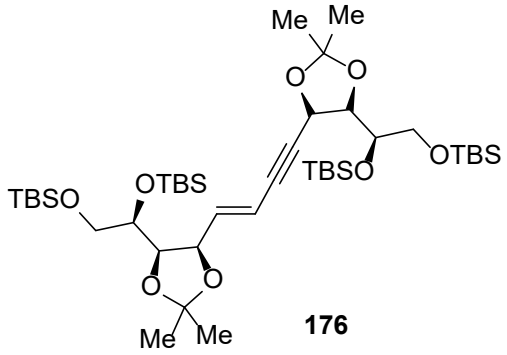
An oven-dried 4 mL vial with a stir bar was charged with 1,2:3,4-di-O-isopropylidene-a-D-galactopyranose (**14**, 156 mg, 0.6 mmol, 2 equiv), Cs_2CO_3 (294 mg, 0.9 mmol, 3 equiv), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (CyDMEDA, 18.9 µL, 0.12 mmol, 0.4 equiv), and vinylic iodide **168** (163 mg, 0.3 mmol, 1 equiv). The reaction vial was purged continuously with argon for 5 min before CuI (12 mg, 0.06 mmol, 0.2 equiv) was added. Anhydrous 1,2-dimethoxyethane (DME, 0.43 mL, 0.7 M based on vinylic iodide) was added, and the reaction mixture was bubbled with argon for 5 minutes. The reaction vial was quickly closed with a solid cap, sealed with Teflon tape and electrical tape, and heated at an internal temperature at 75 °C in an oil bath. The reaction mixture was stirred for 42 hours, cooled to room temperature, and diluted with EtOAc. The mixture was filtered through a Celite® pad and rinsed with EtOAc (100 mL), and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 2% triethylamine, hexanes / EtOAc 12:1 eluent) afforded the vinylic ether (*E*)-**171** (92 mg, 45% yield from compound **168**.

$[\alpha]^{22}_{D}$ -7.60 (c = 0.1, $CHCl_3$)

^{1}H NMR (800 MHz, C_6D_6) δ 6.41 (d, *J* = 12.6 Hz, 1H), 5.47 (d, *J* = 5.0 Hz, 1H), 5.19 (dd, *J* = 12.6, 9.6 Hz, 1H), 4.45 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.37 (dd, *J* = 9.6, 6.1 Hz, 1H), 4.21 (apparent t, *J* = 6.4 Hz, 1H), 4.19 (td, *J* = 6.2, 2.0 Hz, 1H), 4.14 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.04 (dd, *J* = 10.1, 5.6 Hz, 1H), 4.01 (dd, *J* = 7.5, 1.7 Hz, 1H), 4.00 – 3.98 (m, 1H), 3.91 (ddd, *J* = 6.8, 5.3, 4.0 Hz, 1H), 3.70 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.68 (dd, *J* = 10.3, 4.0 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.13 (s, 3H), 1.10 (s, 9H), 1.02 (d, *J* = 1.0 Hz, 3H), 0.98 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 150.8, 109.4, 108.5, 107.7, 101.8, 96.8, 79.0, 76.4, 74.0, 71.4, 71.2, 70.9, 68.9, 66.9, 65.6, 28.3, 26.4 (3C), 26.3 (3C), 26.2 (2C), 25.8, 24.8, 24.4, 18.8, 18.7, -3.7, -4.0, -5.1, -5.2.

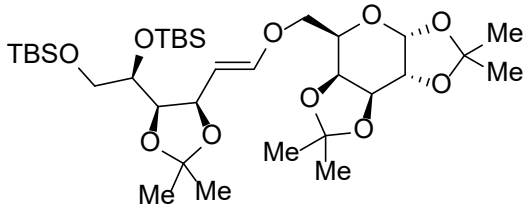
HRMS (APCI): *m/z* calcd for $C_{33}H_{63}O_{10}Si_2^+$ $[M + H]^+$ 675.3954, found 675.3966



176

Enyne by-product **176** was isolated as a mixture with the terminal alkene impurity carried over from the synthesis of vinylic iodide. The following data are the diagnostic peaks: ^{1}H NMR (400 MHz, C_6D_6) δ 6.43 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.82 – 5.76 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H).

Assignments of diagnostic ^{13}C and ^{1}H NMR resonances for vinylic ether **171**, determined by HSQC, COSY, and HMBC spectroscopy:



171

carbon position	δ_C[a]	δ_H[b,c] (*J*, Hz)
1'	150.8	6.41, d (12.6)
2'	101.8	5.19, dd (12.6, 9.6)
3'	76.4	4.37, dd (9.6, 6.1)
4'	79.0	4.21, t (6.4)
5'	74.0	3.91, ddd (6.8, 5.3, 4.0)
6a'	65.6	3.70, dd (10.3, 5.4)
6b'		3.68, dd (10.3, 4.0)
1	96.8	5.47, d (5.0)
2	70.9	4.14, dd (5.0, 2.4)
3	71.2	4.45, dd (7.9, 2.4)
4	71.4	4.00, overlapping m[d]
5	66.9	4.19, td (6.2, 2.0)
6a	68.9	4.04, dd (10.1, 5.6)
6b		3.99, dd (ca. 10, 7)[d]
7	108.5	--
8	109.4	--
9	107.7	--

[a] Recorded at 101 MHz in C_6D_6
[b] Recorded at 800 MHz in C_6D_6
[c] Denotes ^{1}H resonance(s) correlating to each ^{13}C for the carbon position
[d] Due to overlapping ^{1}H peaks, these assignments are tentative.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*E*)-[1,2-dideoxy-3,4-*O*-(isopropylidene)-D-*lyxo*-hex-1-enitol]-α-D-galactopyranose (**174**):

An oven-dried 50 mL round-bottom flask with stir bar was charged with vinylic ether **171** (150 mg, 0.22 mmol), dissolved in anhydrous THF (21 mL, 0.01 M), and cooled to 0 °C with an ice bath. A solution of tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 0.75 mL, 0.75 mmol, 3.5 equiv) was added slowly. The ice bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction mixture was cooled to 0 °C and quenched by slow addition of saturated aqueous NH_4Cl solution at room temperature, and then diluting with deionized water and brine. The aqueous layer was extracted with EtOAc (x 3) and the combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (hexanes/EtOAc 3:7 → 1:5 eluant) to give the diol-vinylic ether **174** (83 mg, 55% yield). $[\alpha]^{23}_D$ -49.1 (c = 0.1, $CHCl_3$)

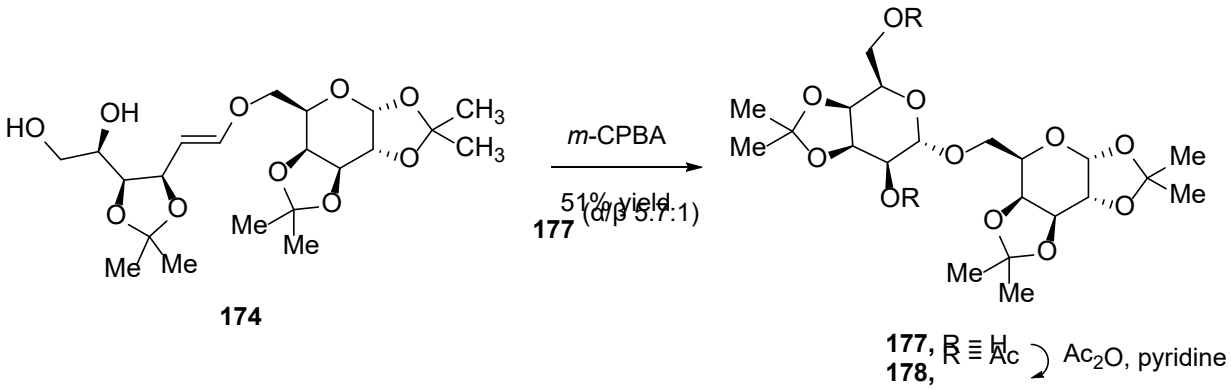
^{1}H NMR (800 MHz, C_6D_6) δ 6.38 (d, *J* = 12.7 Hz, 1H), 5.49 (d, *J* = 5.0 Hz, 1H), 5.25 (dd, *J* = 12.7, 9.4 Hz, 1H), 4.45 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.28 (dd, *J* = 9.4, 7.0 Hz, 1H), 4.21 (ddd, *J* = 7.0, 5.4, 1.9 Hz, 1H), 4.15 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.07 (dd, *J* = 10.3, 6.8 Hz, 1H), 4.02 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.97 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.79 (dd, *J* = 7.0, 3.4 Hz, 1H), 3.51 (d, *J* = 4.2 Hz, 2H), 3.50 – 3.48 (m, 1H), 2.32 (br, 1H), 1.87 (br, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H).

^{13}C{^{1}H } NMR (201 MHz, C_6D_6) δ 151.2, 109.4, 108.6, 107.9, 100.5, 96.8, 78.0, 76.8, 71.3, 71.2, 70.9, 70.3, 68.8, 66.9, 64.7, 27.3, 26.23, 26.19, 24.9, 24.8, 24.3.

HRMS (ESI negative): *m/z* calcd for $C_{21}H_{34}O_{10}$ $^{35}Cl^-$ $[M + Cl]^-$ 481.1846, found 481.1853.

Experimental for disaccharides

Epoxidation-oxacyclization of (*E*)-174 to disaccharide 177 and diacetate derivative 178:



1,2:3,4-Di-*O*-(isopropylidene)-6-*O*-[3,4-*O*-(isopropylidene)-α-D-talopyranosyl]-α-D-galactopyranose (**159**):

A 10 mL round-bottom flask with stir bar was charged with diol-vinylic ether (*E*)-**174** (71 mg, 0.16 mmol) and CH_2Cl_2 (2.5 mL, 0.06 M), and cooled to 0 °C with an external cooling bath. *m*-CPBA (77% w/w) (40 mg, 0.23 mmol, 1.1 equiv) was slowly added to the stirring solution at 0 °C. The resulting suspension was stirred for 15 minutes at 0 °C, the external cooling bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered with a filter paper, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (hexanes/EtOAc 4:6 → 1:4 eluant) to give the disaccharide **177** (33 mg, 51% yield).

$[\alpha]^{22}_D$ -4.60 (c = 0.1, $CHCl_3$)

^{1}H NMR (800 MHz, C_6D_6) δ 5.52 (d, *J* = 5.0 Hz, 1H), 4.95 (d, *J* = 5.9 Hz, 1H), 4.53 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.30 (td, *J* = 6.7, 1.9 Hz, 1H), 4.19 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.17 (dd, *J* = 8.0, 3.4 Hz, 1H), 4.16 (dd, *J* = 5.1, 2.5 Hz, 1H), 4.08 (dd, *J* = 10.9, 6.9 Hz, 1H), 3.98 (dd, *J* = 10.9, 6.4 Hz, 1H), 3.93 (dd, *J* = 11.7, 7.6 Hz, 1H), 3.73 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.63 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.59 (ddd, *J* = 7.6, 3.9, 1.9 Hz, 1H), 3.56 (dd, *J* = 5.9, 3.1 Hz, 1H), 2.57 (br, 1H), 2.40 (br, 1H), 1.49 (s, 3H), 1.45 (s, 6H), 1.18 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 110.1, 109.5, 108.6, 102.5, 96.9, 74.8, 74.6, 71.5, 71.3, 71.2, 71.1, 69.5, 68.0, 66.9, 62.5, 26.31, 26.25, 26.18, 25.2, 24.8, 24.6.

HRMS (ESI): *m/z* calcd for $C_{21}H_{34}O_{11}$ $^{35}Cl^-$ $[M + Cl]^-$ 497.1795, found 497.1809.

1,2:3,4-Di-*O*-(isopropylidene)-6-*O*-[3,4-*O*-(isopropylidene)-α-D-talopyranosyl]-α-D-galactopyranose, 2',6'-bis-*O*-acetyl ester (**178**):

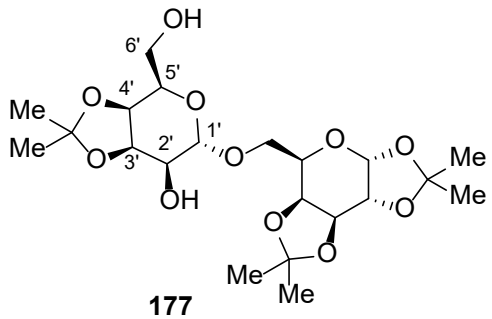
A 100 mL round bottom flask with stir bar was charged with disaccharide diol **177** (17 mg, 0.037 mmol), acetic anhydride (10 mL) was added, followed by pyridine (20 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was then concentrated by rotary evaporation. The crude reaction mixture was quenched with water (20 mL) and brine (10 mL), and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (petroleum ether : EtOAc 2:1 to 1:1) to afford the corresponding diacetate (**178**, 11 mg, 56 % yield).

^{1}H NMR (800 MHz, C_6D_6) δ 5.49 (d, *J* = 5.0 Hz, 1H), 5.20 (d, *J* = 6.1 Hz, 1H), 5.13 (dd, *J* = 6.2, 2.9 Hz, 1H), 4.56 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.45 (dd, *J* = 7.6, 2.9 Hz, 1H), 4.43 (dd, *J* = 11.4, 7.5 Hz, 1H), 4.31 (dd, *J* = 11.4, 4.8 Hz, 1H), 4.29 (td, *J* = 7.0, 1.9 Hz, 1H), 4.21 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.17 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.13 (dd, *J* = 10.2, 6.3 Hz, 1H), 3.97 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.72 (ddd, *J* = 7.1, 4.8, 1.9 Hz, 1H), 3.60 (dd, *J* = 7.6, 1.9 Hz, 1H), 1.78 (s, 3H), 1.71 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H).

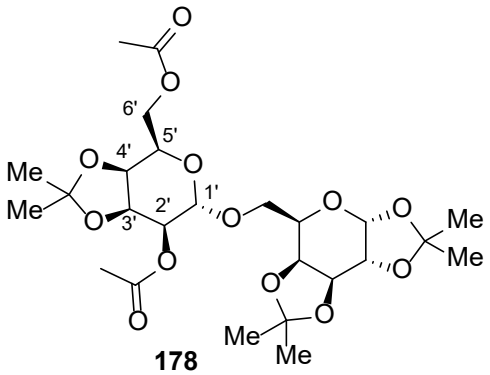
^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 170.1, 169.8, 110.8, 109.2, 108.5, 99.0, 96.9, 74.3, 72.8, 71.5, 71.2, 71.1, 71.0, 68.5, 67.4, 66.6, 63.1, 26.27, 26.25, 26.17, 25.3, 24.9, 24.6, 20.56, 20.55.

HRMS (ESI): *m/z* calcd for $C_{25}H_{38}O_{13}Na^+$ $[M + Na]^+$ 569.2205, found 569.2215

Assignments of diagnostic ^{13}C and ^{1}H NMR resonances for disaccharide **177** and diacetate derivative **178**, determined by HSQC, COSY, and HMBC spectroscopy:



177



178

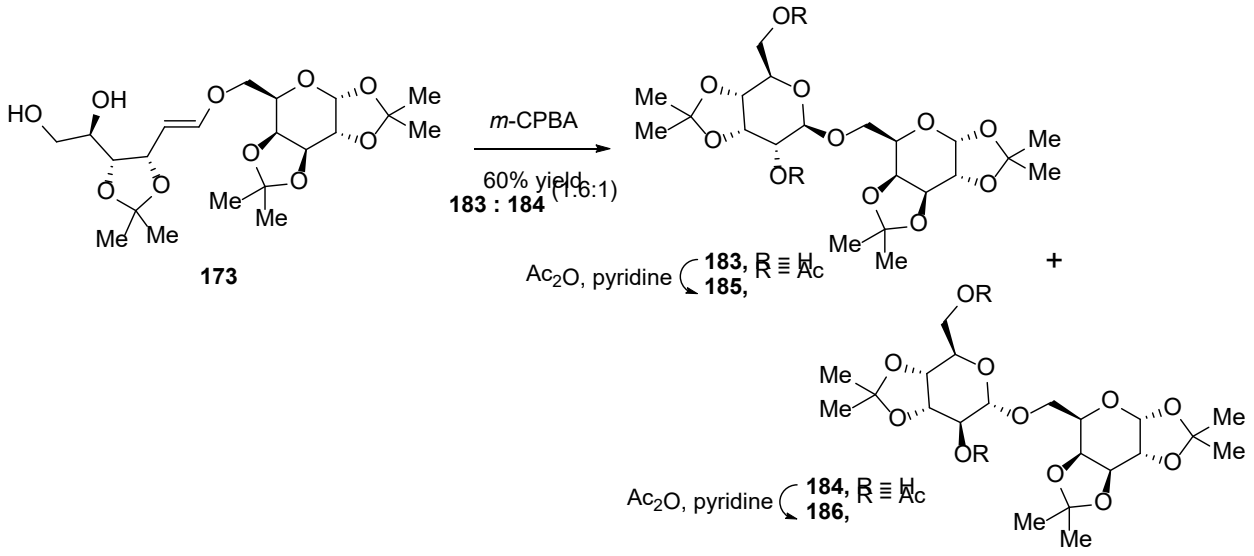
carbon position	δ_C[a]	δ_H[b,c] (*J*, Hz)	δ_C[a]	δ_H[b,c] (*J*, Hz)
1'	102.5	4.95, d (5.9)	99.0	5.20, d (6.1)
2'	69.5	3.56, dd (5.9, 3.1)	71.0	5.13, dd (6.2, 2.9)
3'	74.6	4.17, dd (8.0, 3.4)	72.8	4.45, dd (7.6, 2.9)
4'	74.8	3.63, dd (7.6, 2.0)	74.3	3.60, dd (7.6, 1.9)
5'	71.3	3.59, ddd (7.6, 3.9, 1.9)	68.5	3.72, ddd (7.1, 4.8, 1.9)
6a'	62.5	3.93, dd (11.7, 7.6)	63.1	4.43, dd (11.4, 7.5)
6b'		3.73, dd (11.7, 3.9)		4.31, dd (11.4, 4.8)
1	96.9	5.52, d (5.0)	96.9	5.49, d (5.0)
2	71.1	4.16, dd (5.1, 2.5)	71.1	4.17, dd (5.0, 2.4)
3	71.2	4.53, dd (7.9, 2.4)	71.2	4.56, dd (7.9, 2.4)
4	71.5	4.19, dd (7.9, 1.9)	71.5	4.21, dd (7.9, 1.9)
5	66.9	4.30, td (6.7, 1.9)	66.6	4.29, td (7.0, 1.9)
6a	68.0	4.08, dd (10.9, 6.9)	67.4	4.13, dd (10.2, 6.3)
6b		3.98, dd (10.9, 6.4)		3.97, dd (10.2, 7.2)
7	108.5	--	108.5	--
8	109.4	--	109.2	--
9	107.7	--	110.8	--
2"	--	--	169.8	--
6"	--	--	170.0	--

[a] Recorded at 101 MHz in C_6D_6

[b] Recorded at 800 MHz in C_6D_6

[c] Denotes ^{1}H resonance(s) correlating to each ^{13}C for the carbon position

Epoxidation-oxacyclization of (*E*)-173 to disaccharides 183 and 184:



1) <u>with *m*-CPBA</u>: A 5 mL round-bottom flask with stir bar was charged with diol-vinylic ether (*E*)-**173** (46 mg, 0.1 mmol) and CH_2Cl_2 (1.7 mL, 0.1 M), and cooled to 0 ^oC with an external cooling bath. *m*-CPBA (77% w/w) (36 mg, 0.2 mmol, 1.1 equiv) was slowly added to the stirring solution at 0 °C. The resulting suspension was stirred for 15 minutes at 0 °C, the external cooling bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered with a filter paper, and the filtrate was concentrated by rotary evaporation. ^1H NMR of the crude mixture indicated a 1.6 : 1 ratio of disaccharide diastereomers **183** and **184**. The crude product was purified by silica gel flash chromatography (hexanes/EtOAc 1:3 → 1:5 eluant) to give partial separation of diastereomers **183** and **184**, with the minor diastereomer **184** eluting first (46 mg, 50% combined yield).

2) with TFAA-UHP: A 3 mL conical vial with stir bar was charged with diol-vinylic ether (*E*)-**173** (12 mg, 0.027 mmol) and CH_2Cl_2 (1.2 mL, 0.2 M), and cooled to 0 ^oC with an external cooling bath. Na_2HPO_4 (34 mg, 0.24 mmol, 10 equiv), urea-hydrogen peroxide (UHP, 25 mg, 0.27 mmol, 10 equiv), and then trifluoroacetic anhydride (TFAA, 9.5 µL, 0.068 mmol, 3 equiv) were added at 0 °C. The resulting suspension was stirred for 15 minutes at 0 °C, the external cooling bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. ^1H NMR of the crude mixture indicated a 1.2 : 1 ratio of disaccharide diastereomers **183** and **184**.

3) with cat. $VO(acac)_2$ / TBHP: A 3 mL conical vial with stir bar was charged with diol-vinylic ether (*E*)-**173** (12 mg, 0.027 mmol), $VO(acac)_2$ (17 mg, 0.063 mmol, 2.3 equiv), and CH_2Cl_2 (0.08 mL, 0.3 M), and cooled to 0 ^oC with an external cooling bath. *Tert*-butyl hydrogen peroxide (TBHP, 5.5 M solution in decane, 0.01 mL, 0.054 mmol, 2 equiv.) was slowly added to the stirring solution at 0 °C. The solution turned from blue green to red. The resulting suspension was stirred for 15 minutes at 0 °C, the external cooling bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, and the filtrate was concentrated by rotary evaporation. ^1H NMR of the crude mixture indicated a 4 : 1 ratio of disaccharide diastereomers **183** and **184** along with ~50% of unreacted diol-vinylic ether (*E*)-**173.** Note: An attempt at higher conversion over 18 hrs resulted only in hydrolyzed compounds.

1,2:3,4-Di-*O*-(isopropylidene)-6-*O*-[3,4-*O*-(isopropylidene)-β-D-allopyranosyl]-α-D-galactopyranose (**183**): $[\alpha]^{21}_{D}$ -42.9 (c = 0.1, $CHCl_3$)

^{1}H NMR (800 MHz, C_6D_6) δ 5.47 (d, *J* = 5.0 Hz, 1H), 4.87 (d, *J* = 6.7 Hz, 1H), 4.46 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.23 (dd, *J* = 5.5, 4.4 Hz, 1H), 4.20 (dt, *J* = 6.3, 1.8 Hz, 1H), 4.18 (dd, *J* = 9.0, 6.3 Hz, 1H), 4.13 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.94 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.92 (dd, *J* = 9.1, 5.5 Hz, 1H), 3.82 (ddd, *J* = 11.8, 6.0, 2.7 Hz, 1H), 3.77 (dt, *J* = 6.6, 4.4 Hz, 1H), 3.66 (ddd, *J* = 9.1, 5.5, 2.7 Hz, 1H), 3.61 (dt, *J* = 11.8, 5.9 Hz, 1H), 2.60 (d, *J* = 5.4 Hz, 1H), 2.36 (t, *J* = 6.7 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.29 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 109.9, 109.5, 108.6, 101.4, 96.9, 76.4, 75.0, 72.5, 71.3, 71.2, 71.0, 69.1, 68.3, 67.7, 62.8, 27.9, 26.2 (2C), 25.8, 24.8, 24.2.

HRMS (ESI): *m/z* calcd for $C_{21}H_{34}O_{11}Na^+$ $[M + Na]^+$ 485.1993, found 485.2006

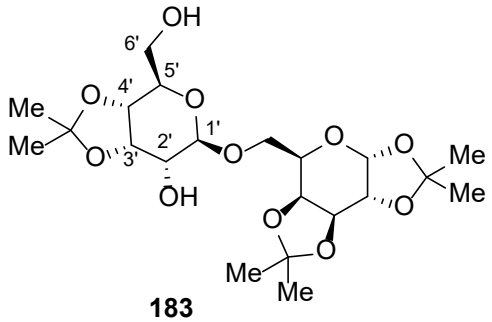
1,2:3,4-Di-*O*-(isopropylidene)-6-*O*-[3,4-*O*-(isopropylidene)-α-D-altropyranosyl]-α-D-galactopyranose (**184**): $[\alpha]^{21}_{D}$ -4.5 (c = 0.1, $CHCl_3$)

^{1}H NMR (800 MHz, C_6D_6) δ 5.51 (d, *J* = 5.1 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 1H), 4.52 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.28 (td, *J* = 6.7, 1.9 Hz, 1H), 4.20 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.16 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.07 (dd, *J* = 10.6, 6.6 Hz, 1H), 4.01 - 3.95 (overlapping m, 4H), 3.91 (t, *J* = 6.6 Hz, 1H), 3.82 (dq, *J* = 12.2, 2.5 Hz, 1H), 3.61 (dt, *J* = 11.4, 5.2 Hz, 1H), 2.37 (br s, 1H), 2.21 (br t, *J* = 6.6 Hz, 1H), 1.46 (s, 4H), 1.46 (s, 3H), 1.38 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H).

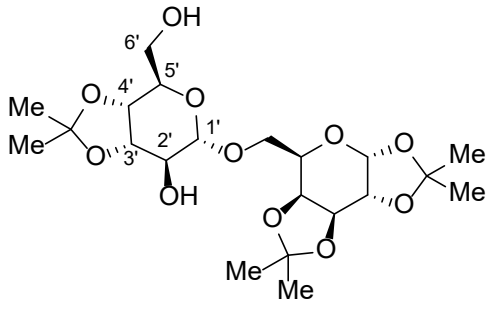
^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 110.5, 109.4, 108.6, 102.7, 96.9, 77.4, 73.7, 72.8, 72.6, 71.4, 71.2, 71.1, 68.2, 67.0, 63.8, 27.5, 26.3, 26.2, 25.2, 24.8, 24.5.

HRMS (ESI): *m/z* calcd for $C_{21}H_{34}O_{11}Na^+$ $[M + Na]^+$ 485.1993, found 485.1990

Assignments of diagnostic ^{13}C and ^{1}H NMR resonances for β-D-*allo*-disaccharide **183** and α-D-*altro*-disaccharide **184**, determined by HSQC, COSY, and HMBC spectroscopy:



183



184

carbon position	δ_C[a]	δ_H[b,c] (*J*, Hz)	δ_C[a]	δ_H[b,c] (*J*, Hz)
1'	101.4	4.87, d (6.7)	102.7	4.67, d (5.9)
2'	69.1	3.77, dt (6.6, 4.4)	73.7	3.91, t (6.6)
3'	75.0	4.23, dd (5.5, 4.4)	77.4[d]	3.98,[d] m
4'	72.5	3.92, dd (9.1, 5.6)	72.6[d]	3.99,[d] m
5'	76.4	3.66, ddd (9.1, 5.5, 2.7)	72.8	3.96,[d] m
6a'	62.8	3.82, ddd (11.8, 6.0, 2.7)	63.8	3.81, ddd (11.8, 6.8, 2.3)
6b'		3.61, dt (11.8, 5.9)		3.60, dt (11.8, 5.9)
1	96.9	5.47, d (5.0)	96.9	5.50, d (5.0)
2	71.0	4.13, dd (5.1, 2.4)	71.1	4.16, dd (5.1, 2.4)
3	71.2	4.46, dd (8.0, 2.4)	71.2	4.52, dd (7.9, 2.4)
4	71.3	4.08, dd (8.0, 1.6)	71.4	4.18, dd (7.9, 1.9)
5	67.7	4.20, td (6.3, 1.8)	67.0	4.28, td (6.7, 1.9)
6a	68.3	4.18, dd (9.0, 6.3)	68.3	4.07, dd (10.6, 6.7)
6b		3.94, dd (8.9, 4.9)		4.00,[d] m
7	108.6	--	108.6	--
8	109.5	--	109.4	--
9	109.9	--	110.5	--

[a] Recorded at 101 MHz in C_6D_6

[b] Recorded at 800 MHz in C_6D_6

[c] Denotes ^{1}H resonance(s) correlating to each ^{13}C for the carbon position

[d] Due to overlapping ^{1}H peaks, including in HMBC, these assignments may be swapped.

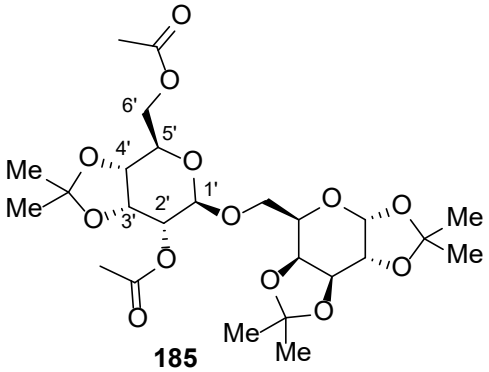
1,2:3,4-Di-*O*-(isopropylidene)-6-*O*-[3,4-*O*-(isopropylidene)-β-D-allopyranosyl]-α-D-galactopyranose, 2',6'-bis-*O*-acetyl ester (**185**):

A 100 mL round bottom flask with stir bar was charged with disaccharide diol **183** (11 mg, 0.024 mmol), acetic anhydride (5 mL) was added, followed by pyridine (10 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was then concentrated by rotary evaporation. The crude reaction mixture was quenched with water (20 mL) and brine (10 mL), and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation to afford the corresponding diacetate **185** (13 mg, quant.).

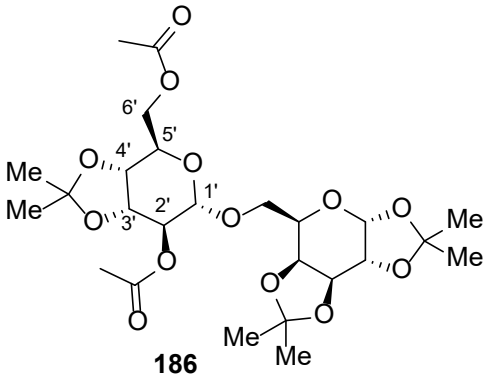
1,2:3,4-Di-*O*-(isopropylidene)-6-*O*-[3,4-*O*-(isopropylidene)-α-D-altropyranosyl]-α-D-galactopyranose, 2',6'-bis-*O*-acetyl ester (**186**):

A 100 mL round bottom flask with stir bar was charged with disaccharide diol **184** (8 mg, 0.017 mmol), acetic anhydride (5 mL) was added, followed by pyridine (10 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was then concentrated by rotary evaporation. The crude reaction mixture was quenched with water (20 mL) and brine (10 mL), and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation to afford the corresponding diacetate **186** (10 mg, quant.).

Assignments of diagnostic ^{13}C and ^{1}H NMR resonances for disaccharide diacetates **185** and **186**, determined by HSQC, COSY, and HMBC spectroscopy:



185



186

carbon position	δ_C[a]	δ_H[b,c] (*J*, Hz)	δ_C[a]	δ_H[b,c] (*J*, Hz)
1'	100.0	5.01, d (7.7)	99.3	4.83, d (3.5)
2'	69.4	5.32, dd (7.7, 4.3)	71.7[d]	5.51, dd (5.6, 3.6)
3'	74.2	4.43, t (4.7)	75.2	4.10, t (6.0)
4'	73.0	3.72, dd (9.3, 4.9)	68.4	4.23, m
5'	73.9	3.68, ddd (9.1, 6.0, 2.7)	71.9[d]	3.99, dd (9.1, 6.5)
6a'	63.8	4.35, dd (11.9, 2.7)	64.2	4.44, d (9.4 Hz)
6b'		4.20, dd (11.9, 6.0)		4.25, m
1	96.8	5.48, d (4.9)	96.8	5.46, d (5.0)
2	71.0	4.13, dd (4.9, 2.4)	71.1[d]	4.16, dd (5.0, 2.3)
3	71.2	4.41, dd (8.0, 2.4)	71.2[d]	4.50, dd (8.0, 2.3)
4	71.6	3.87, dd (8.0, 1.8)	71.3[d]	4.19, dd (7.9, 1.9)
5	68.2	4.12, m	66.8	4.22, m
6a	69.4	4.22, dd (10.9, 6.0)	67.4	4.11, dd (9.8, 6.1)
6b		3.94, dd (10.9, 7.2)		3.87, dd (9.8, 7.1)
7	108.5	--	108.5	--
8	109.3	--	109.2	--
9	110.5	--	110.8	--
2"	169.7	--	168.9	--
6"	170.1	--	170.1	--

[a] Recorded at 101 MHz in C_6D_6

[b] Recorded at 800 MHz in C_6D_6

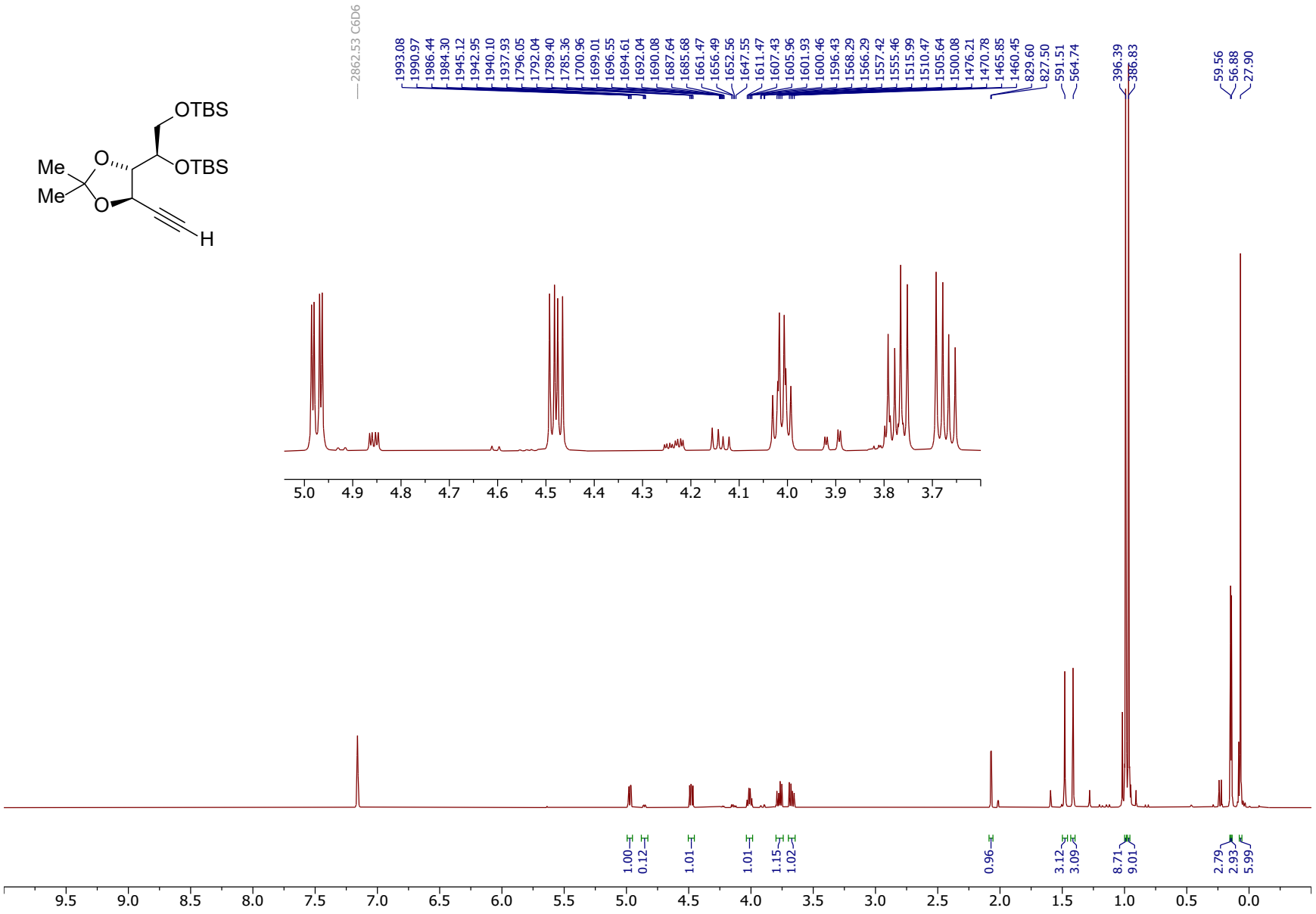
[c] Denotes ^{1}H resonance(s) correlating to each ^{13}C for the carbon position

[d] Due to overlapping ^{13}C peaks in HMBC, these assignments are tentative.

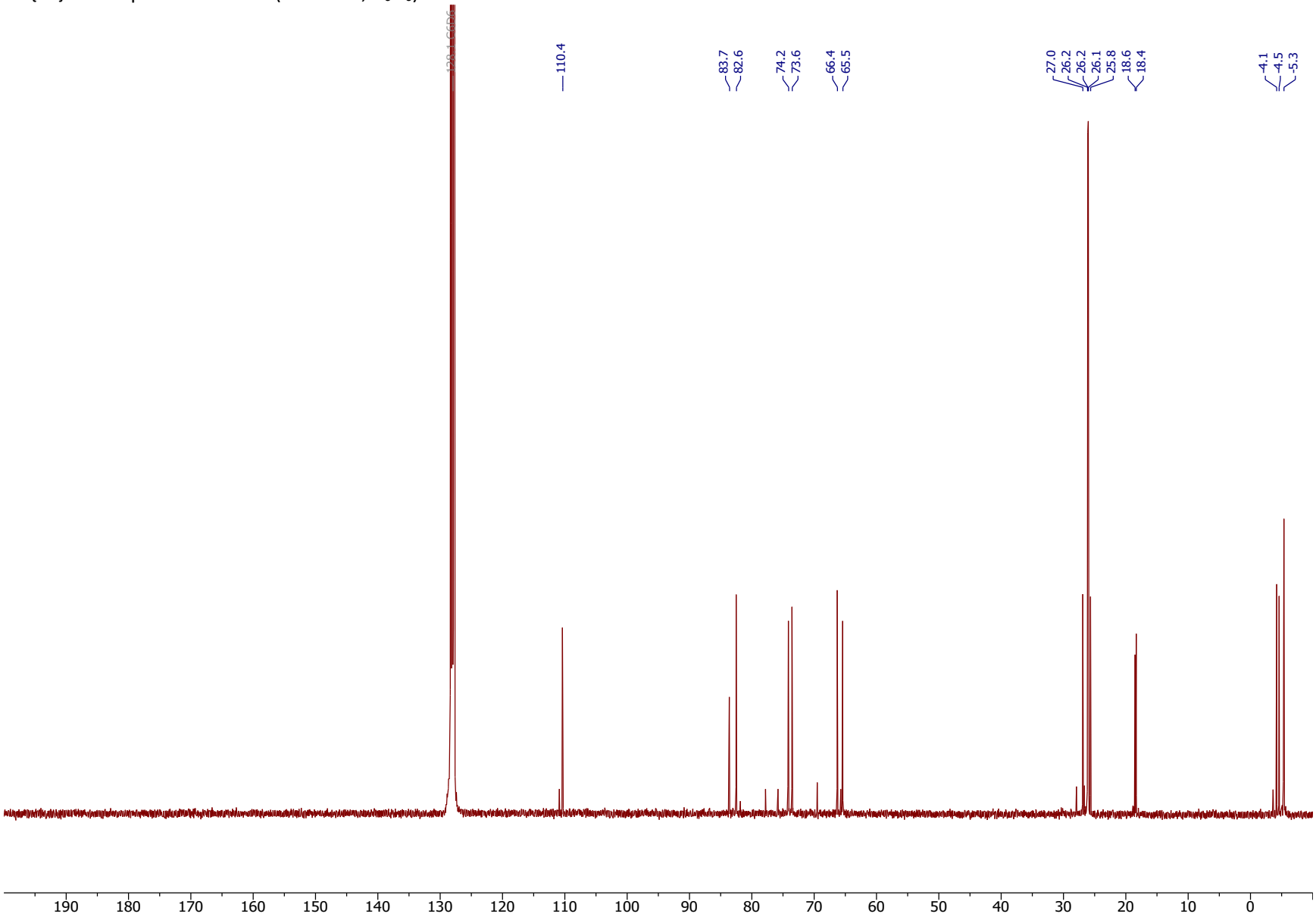
NMR Spectra for Chapter 3

Next page

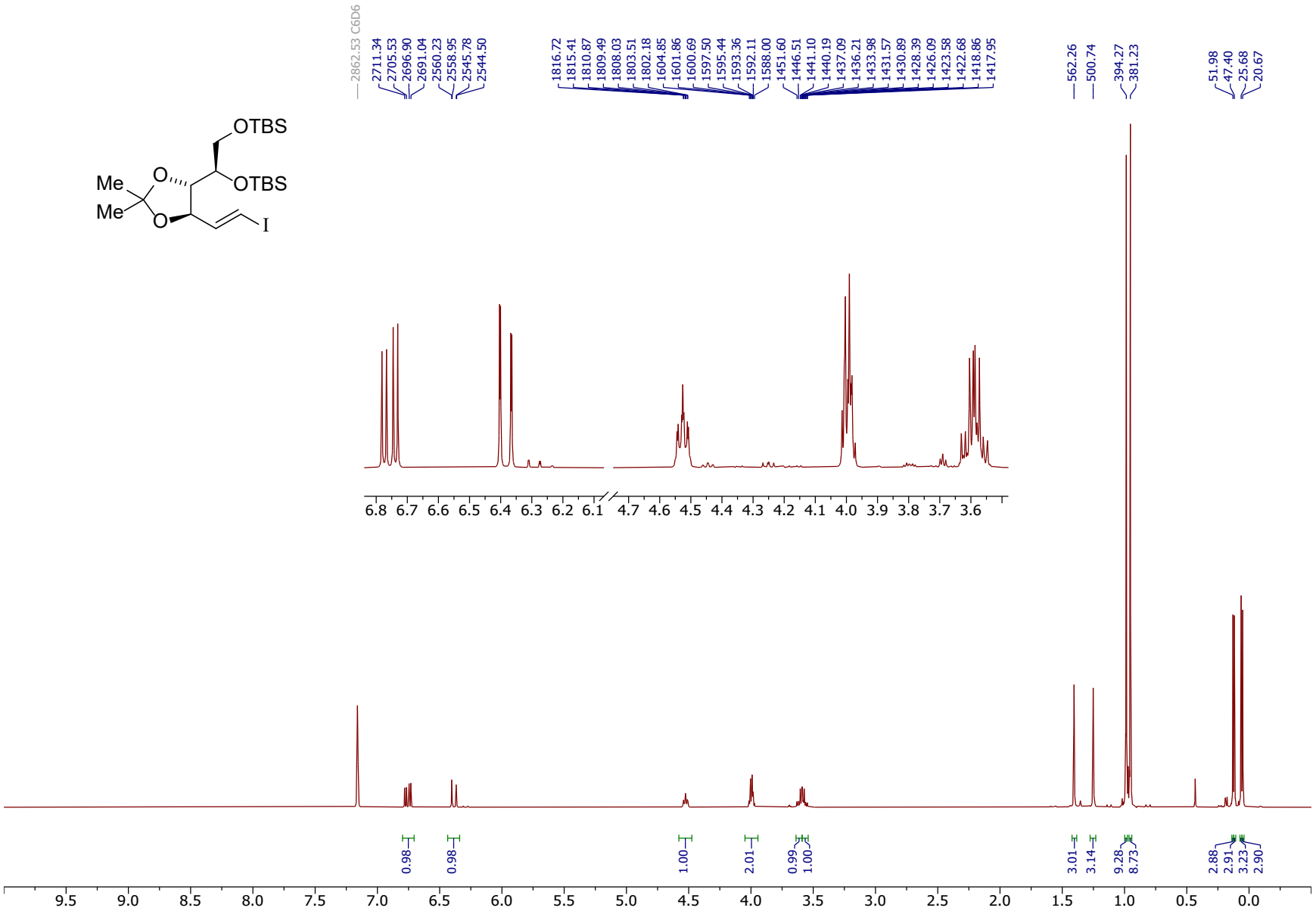
^{1}H NMR Spectrum of **152** (400 MHz, C_6D_6)



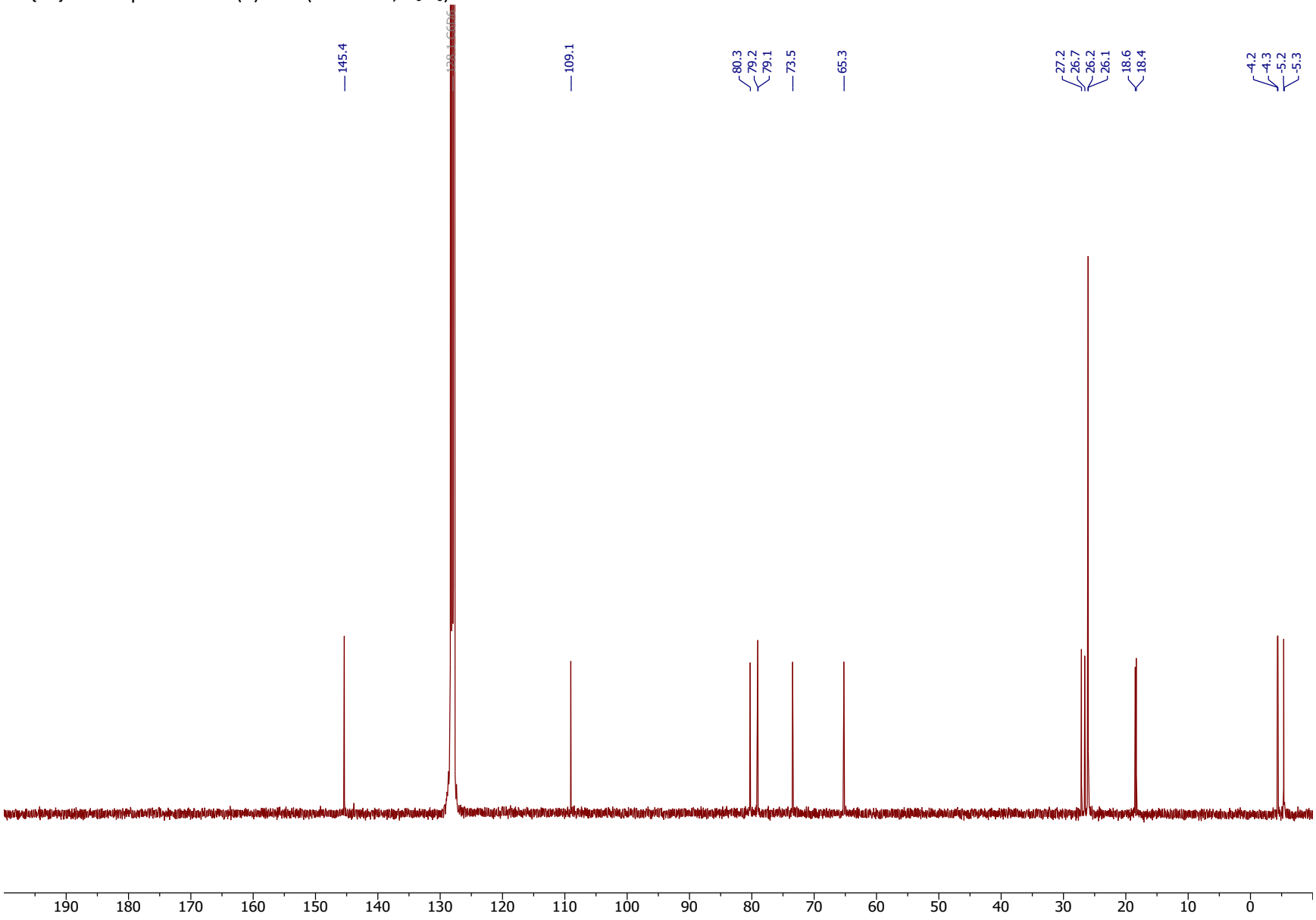
$^{13}C\{^{1}H\}$ NMR Spectrum of **152** (101 MHz, C_6D_6)



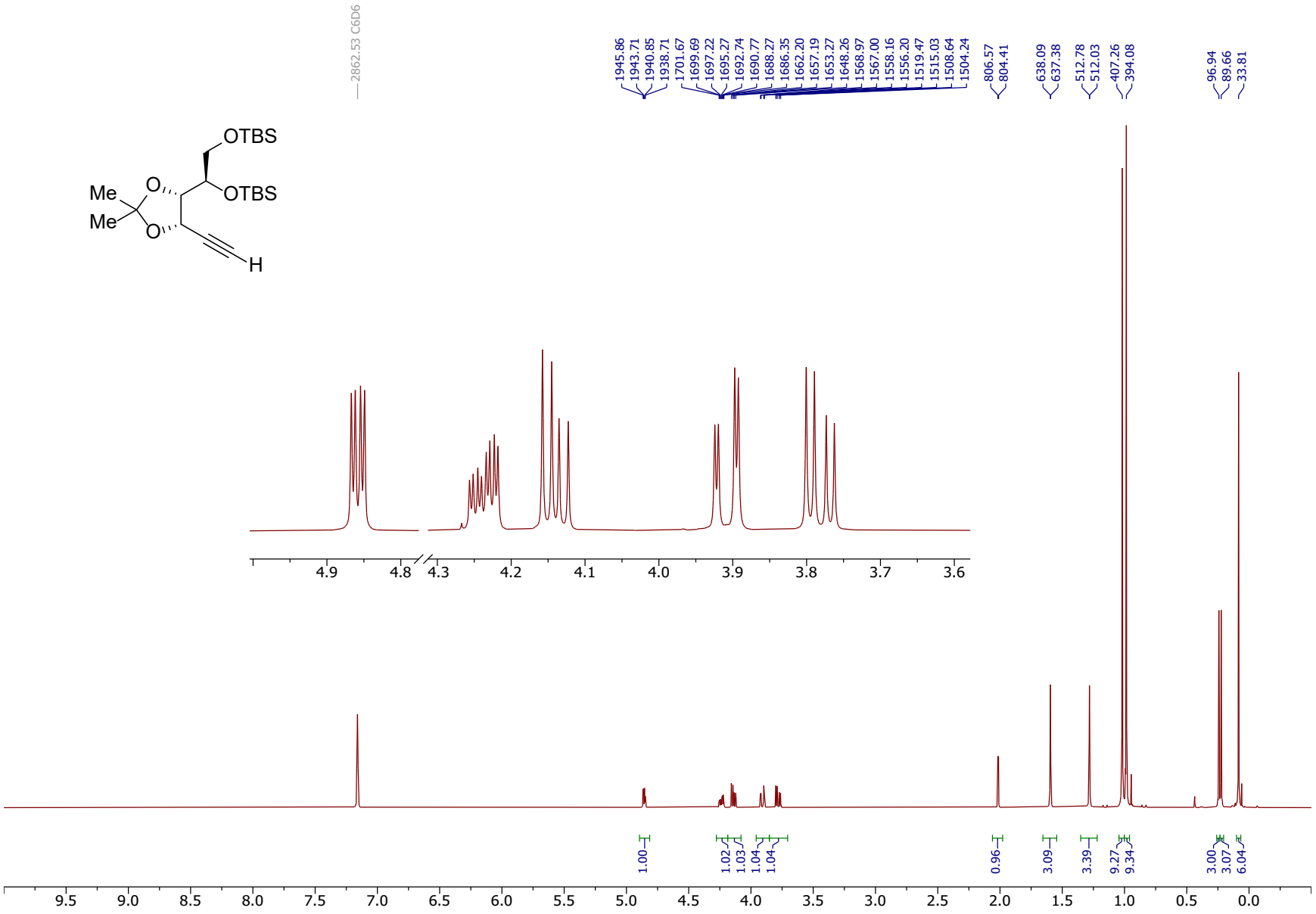
^{1}H NMR Spectrum of (*E*)-**166** (400 MHz, C_6D_6)



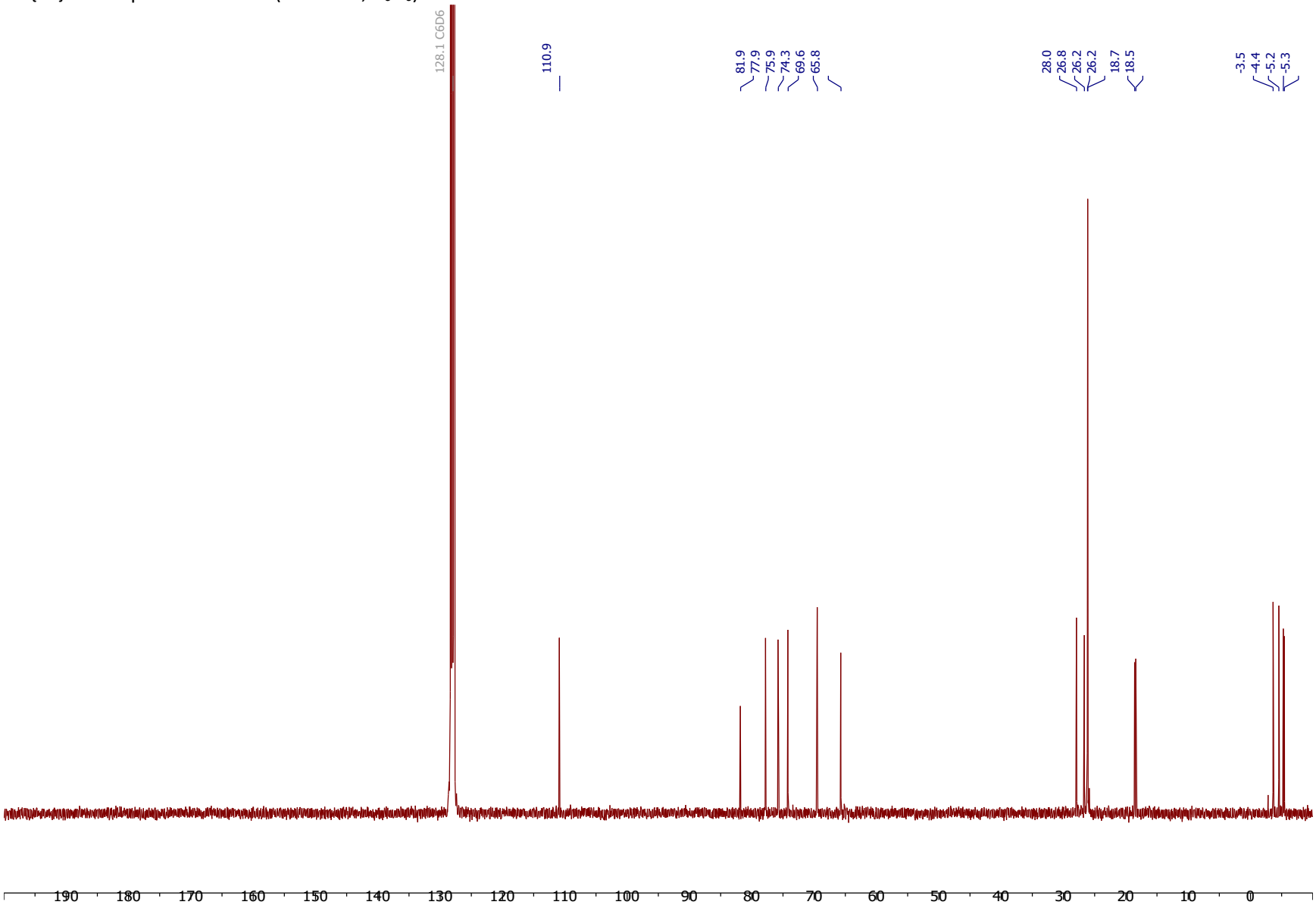
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**166** (101 MHz, C_6D_6)



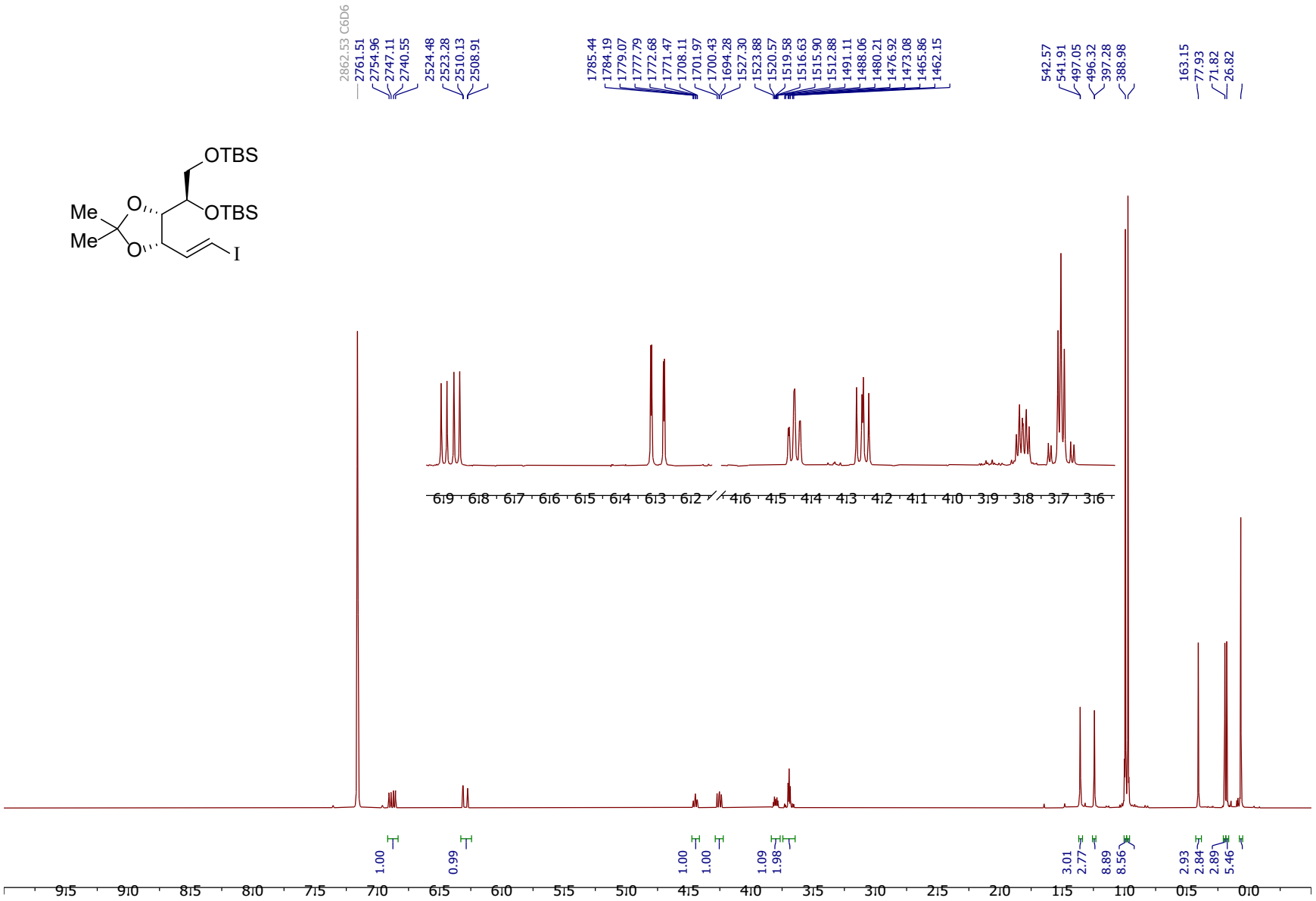
^{1}H NMR Spectrum of **160** (400 MHz, C_6D_6)



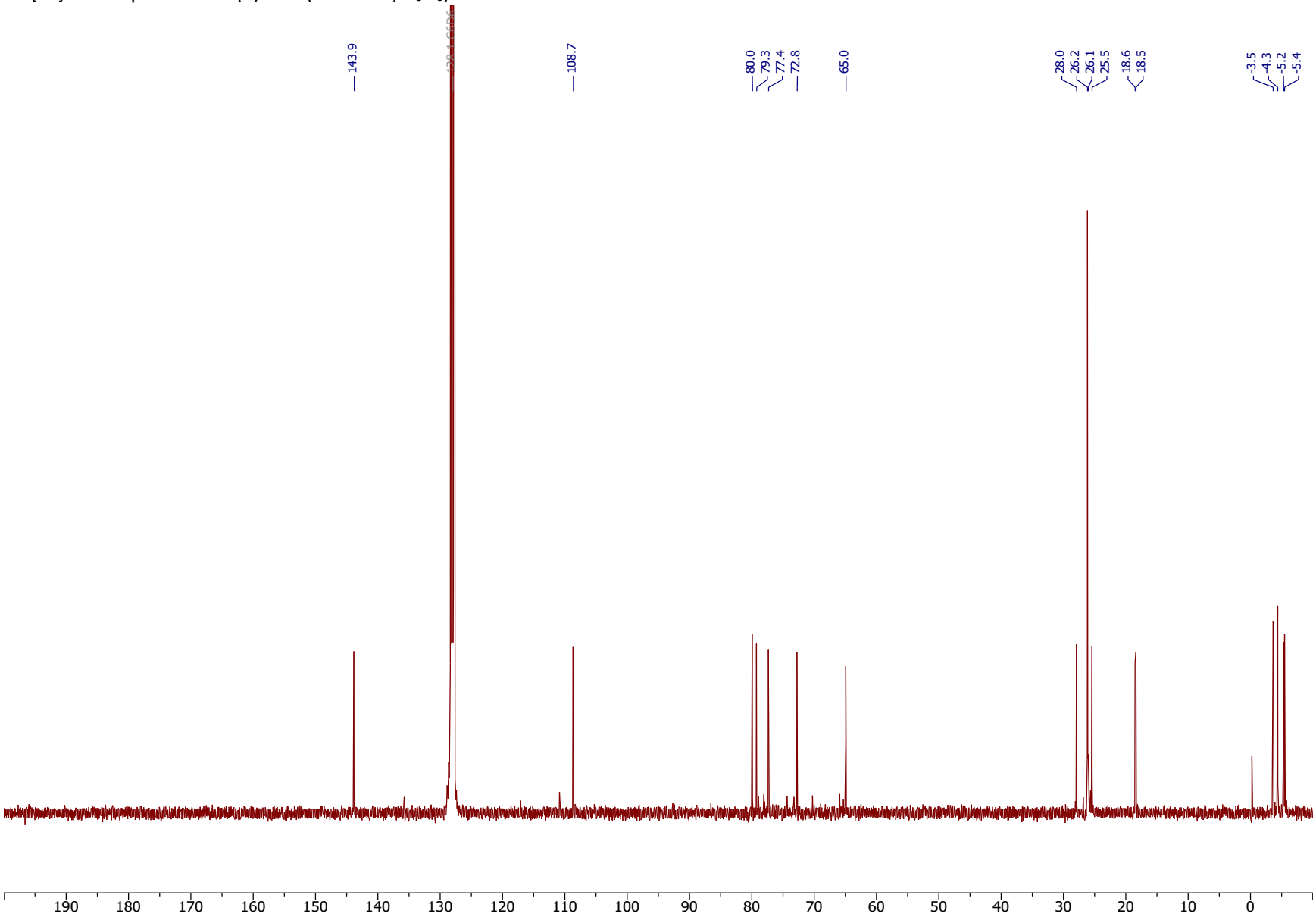
$^{13}C\{^{1}H\}$ NMR Spectrum of **160** (101 MHz, C_6D_6)



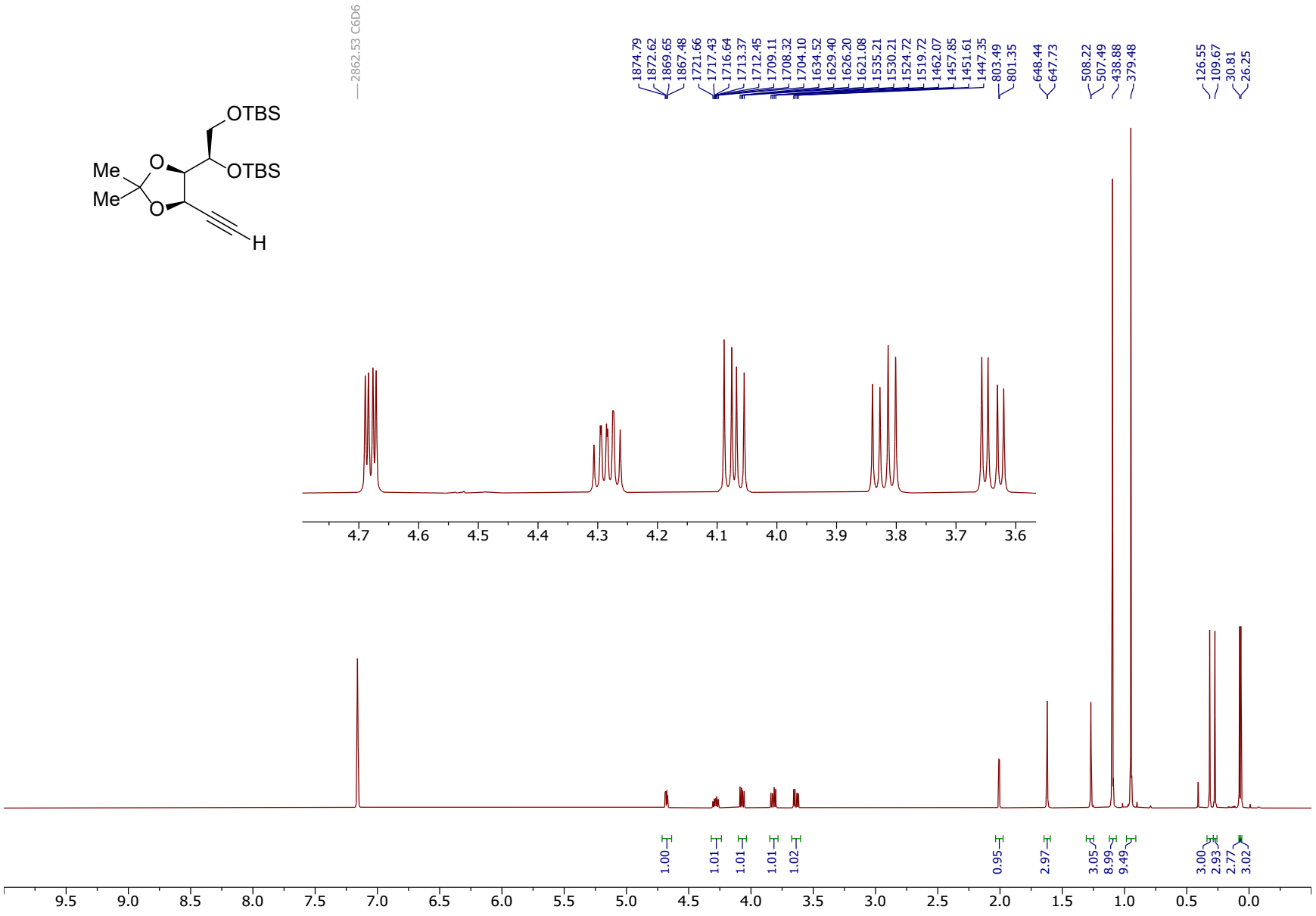
^{1}H NMR Spectrum of (*E*)-**167** (400 MHz, C_6D_6)



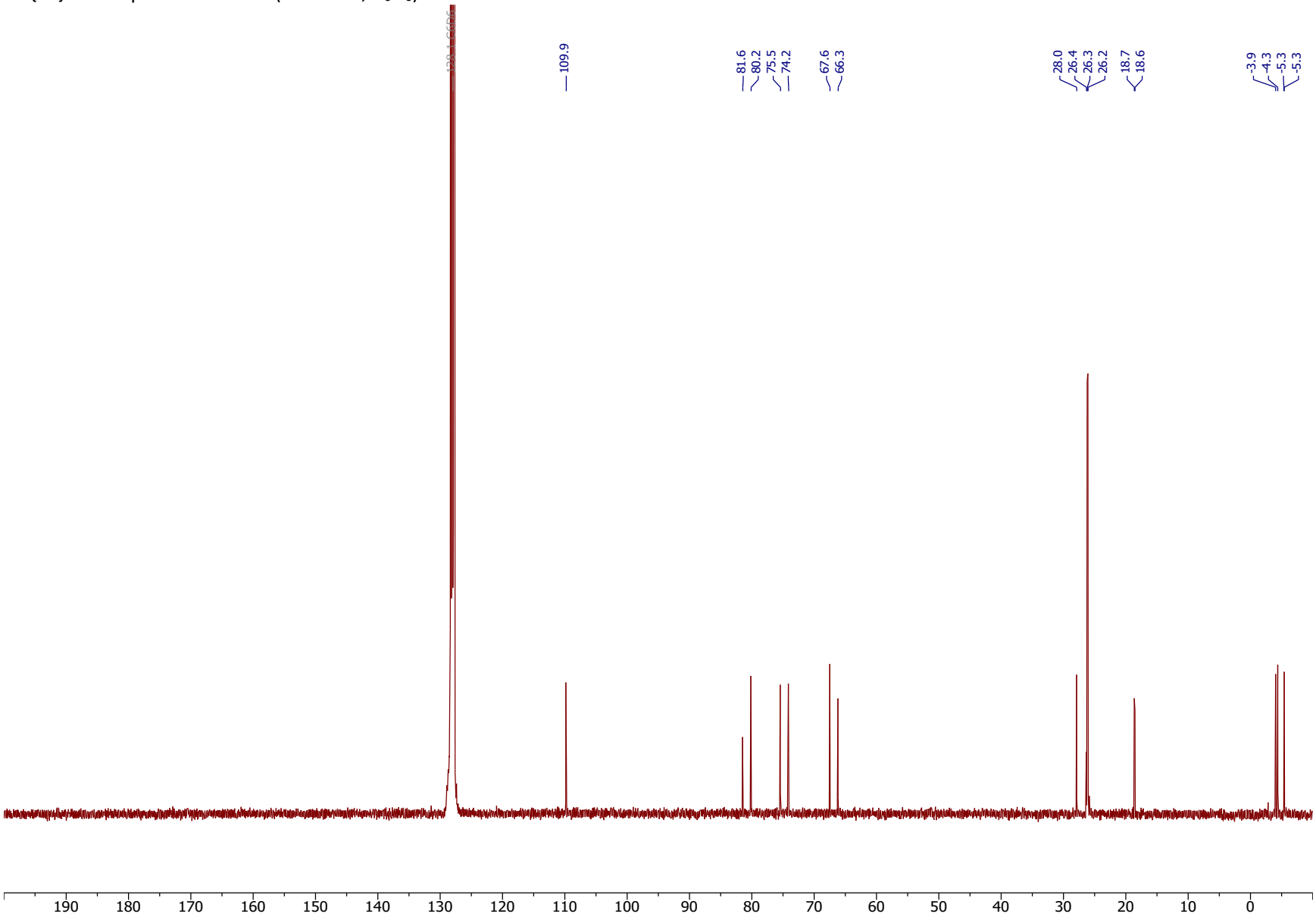
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**167** (101 MHz, C_6D_6)



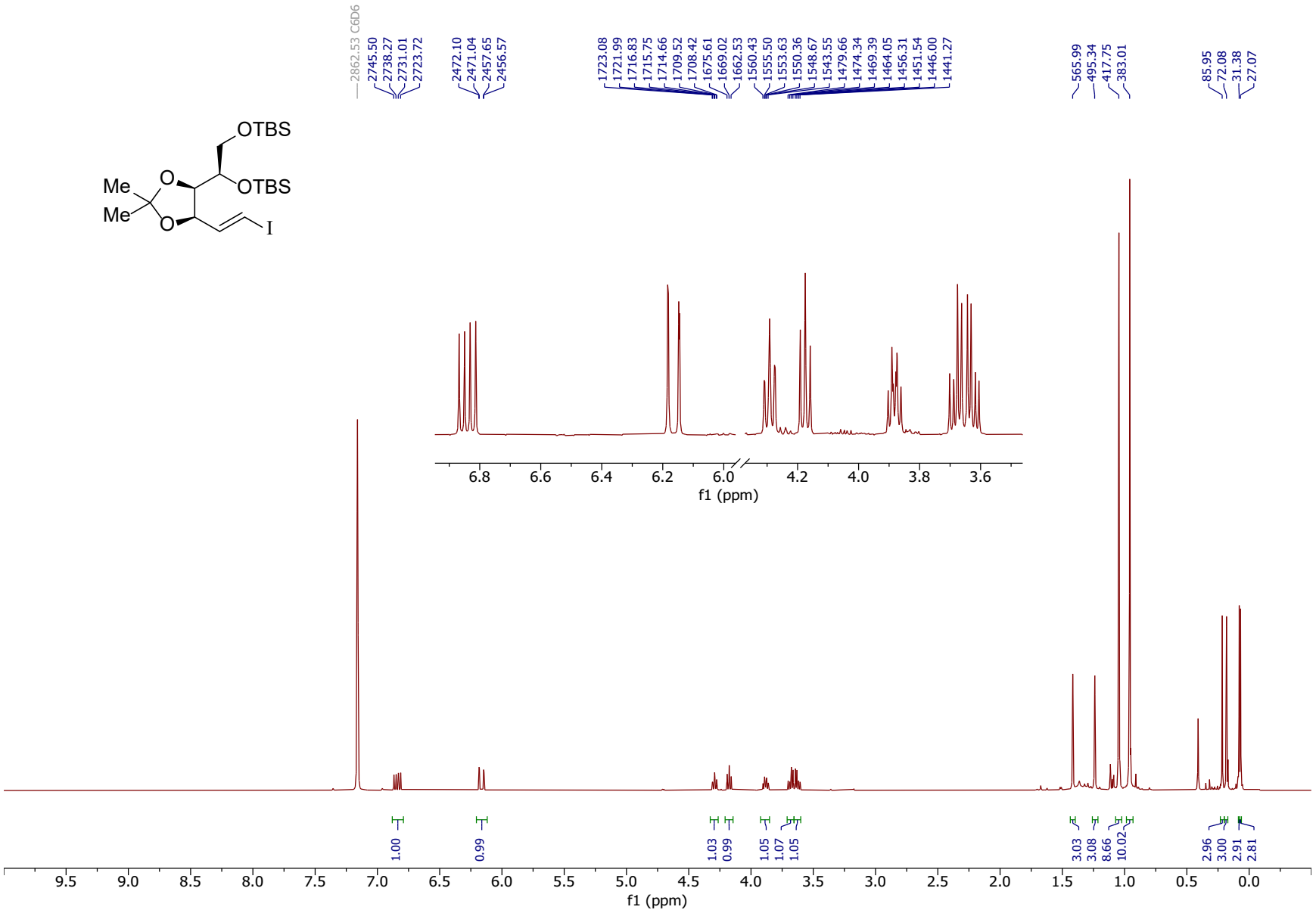
^{1}H NMR Spectrum of **165** (400 MHz, C_6D_6)



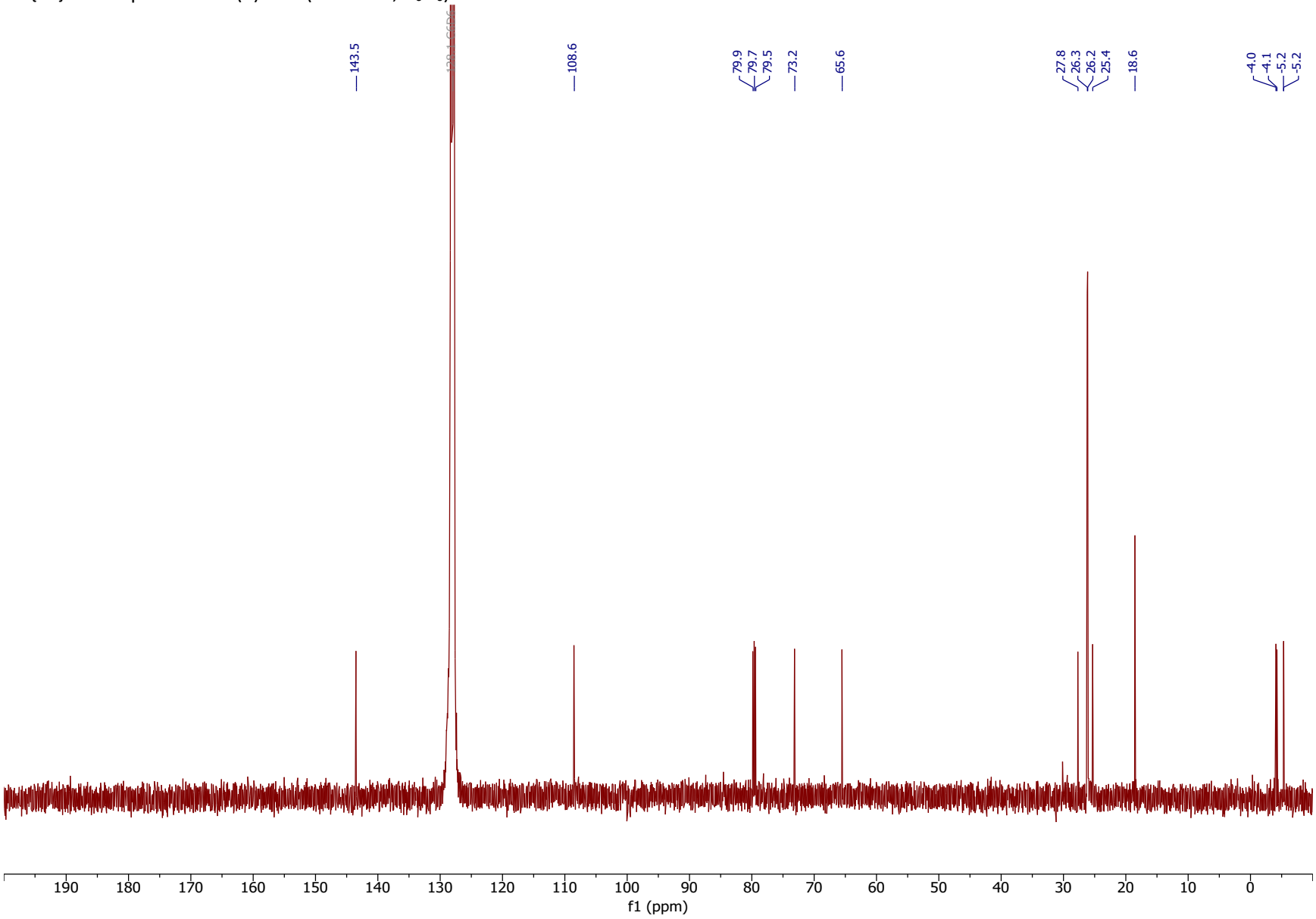
$^{13}C\{^{1}H\}$ NMR Spectrum of **165** (101 MHz, C_6D_6)



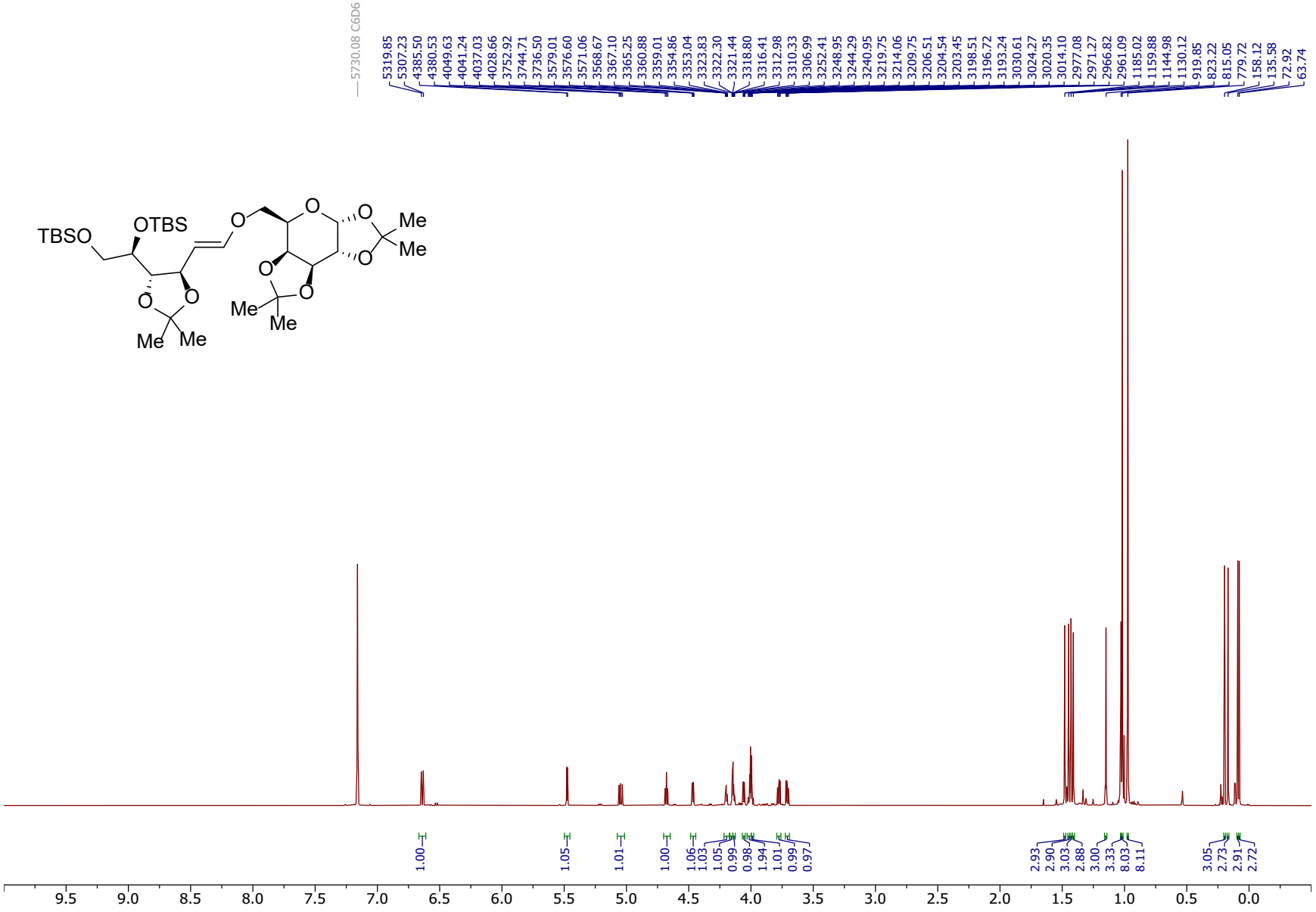
^{1}H NMR Spectrum of (*E*)-**168** (400 MHz, C_6D_6)



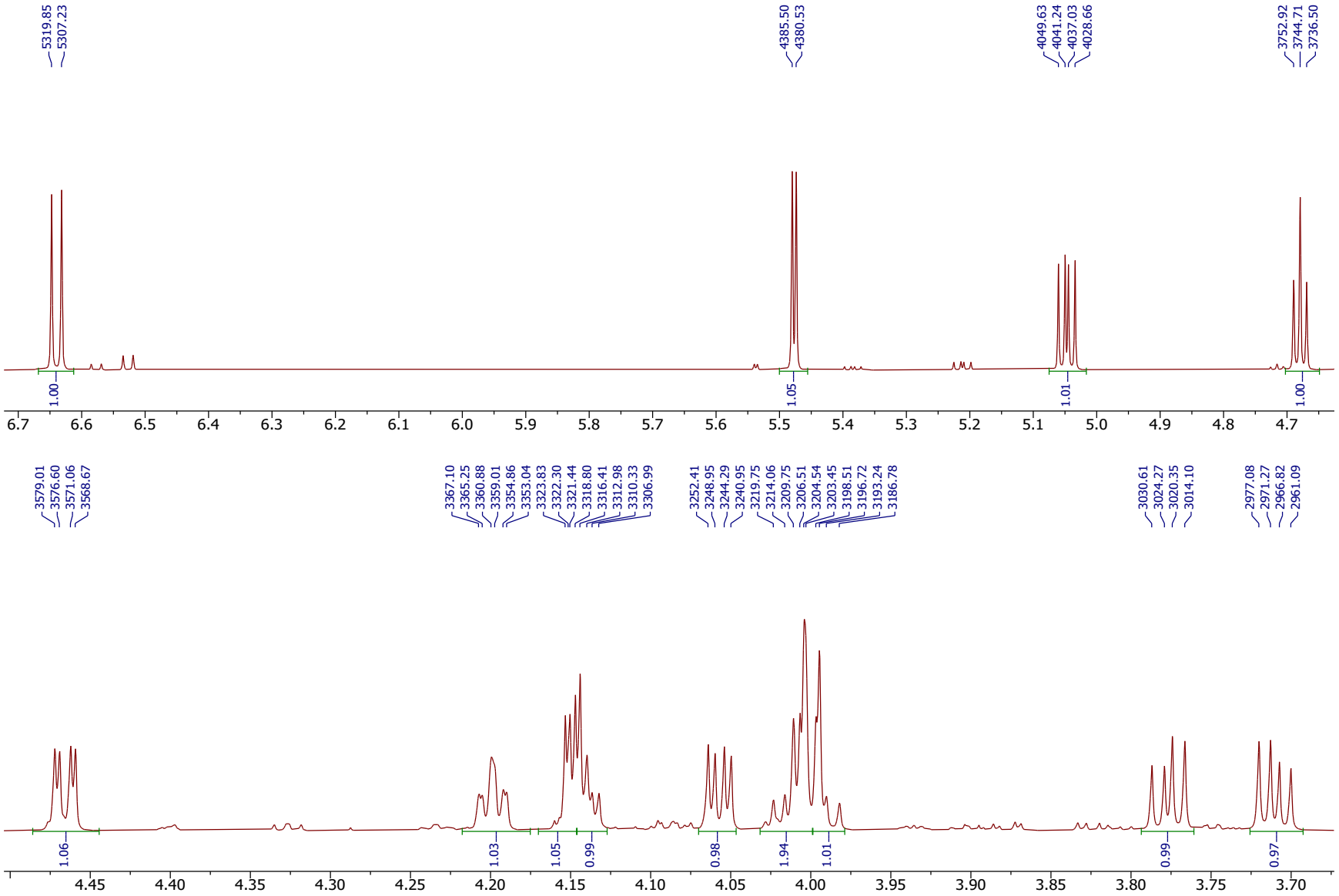
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**168** (101 MHz, C_6D_6)



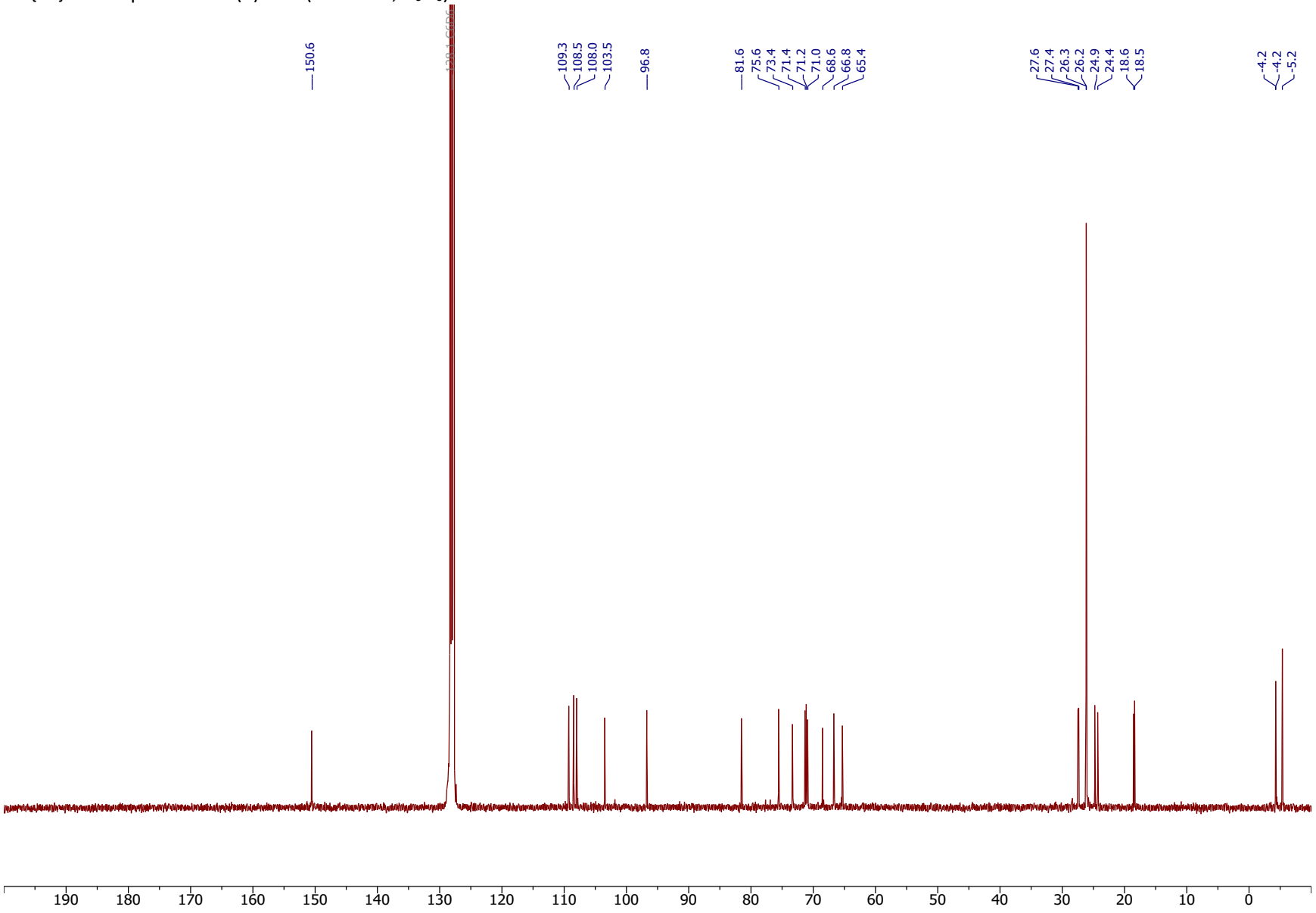
^{1}H NMR Spectrum of (*E*)-**169** (800 MHz, C_6D_6)- full



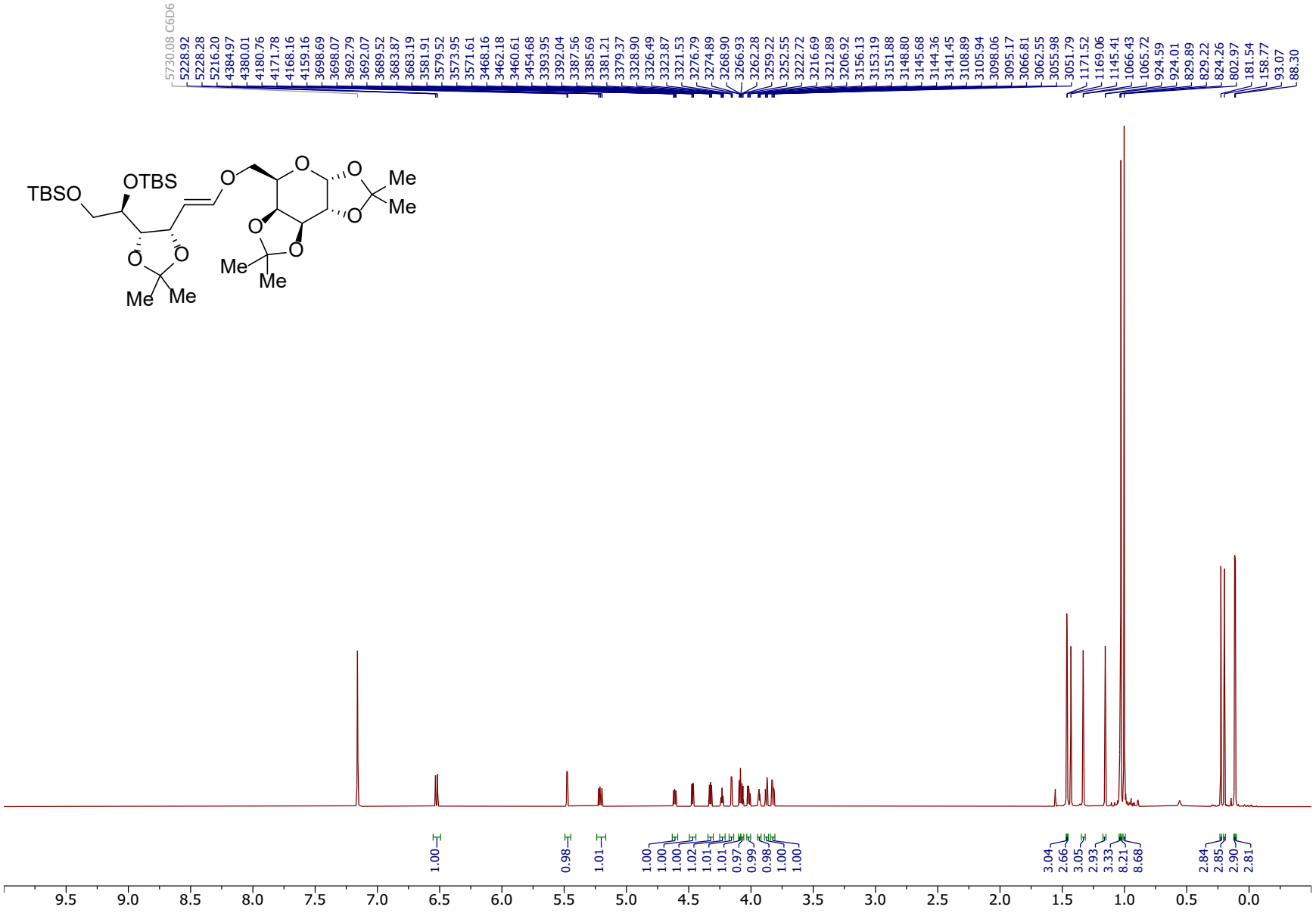
^{1}H NMR Spectrum of (*E*)-**169** (800 MHz, C_6D_6) – expansion



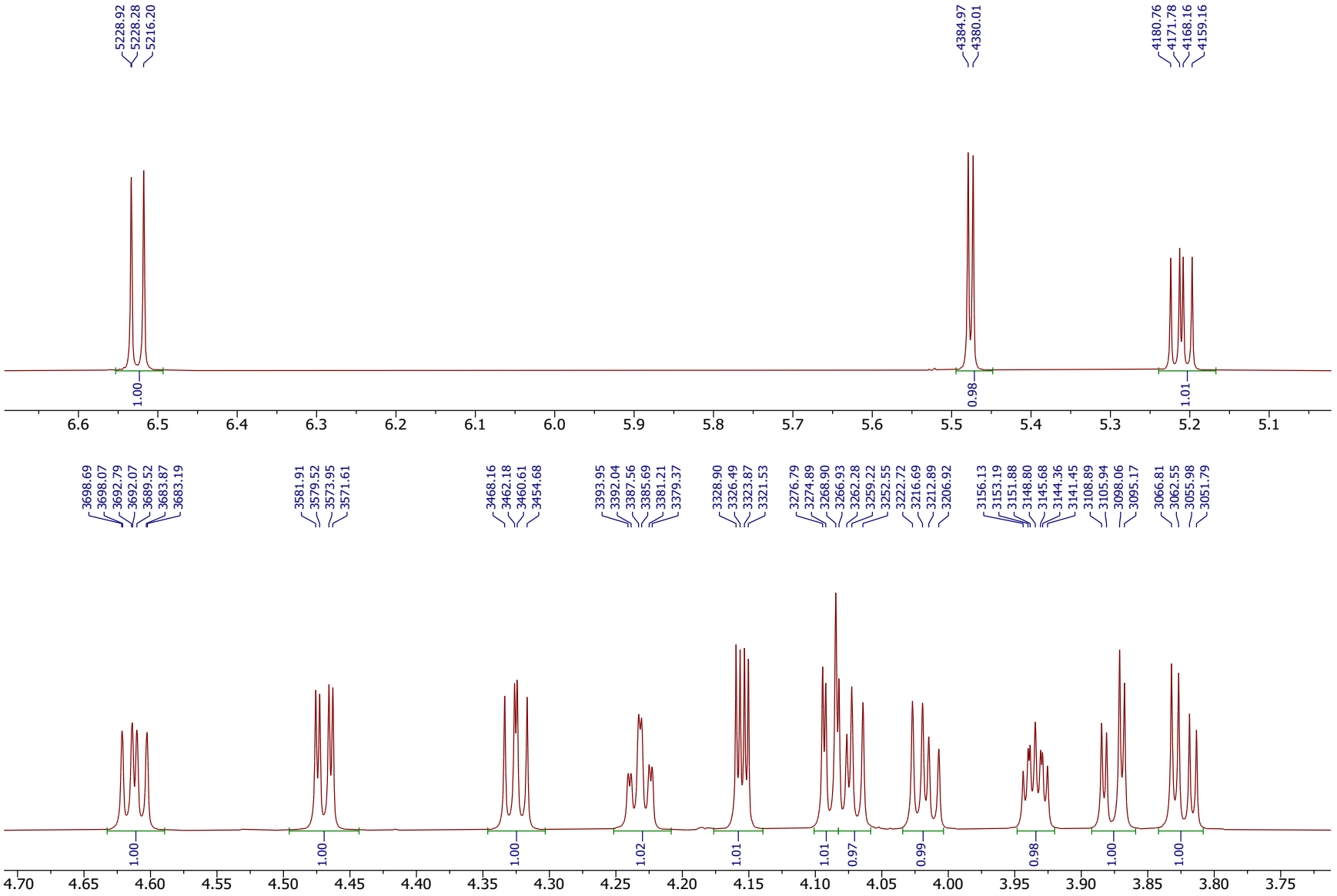
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**169** (101 MHz, C_6D_6)



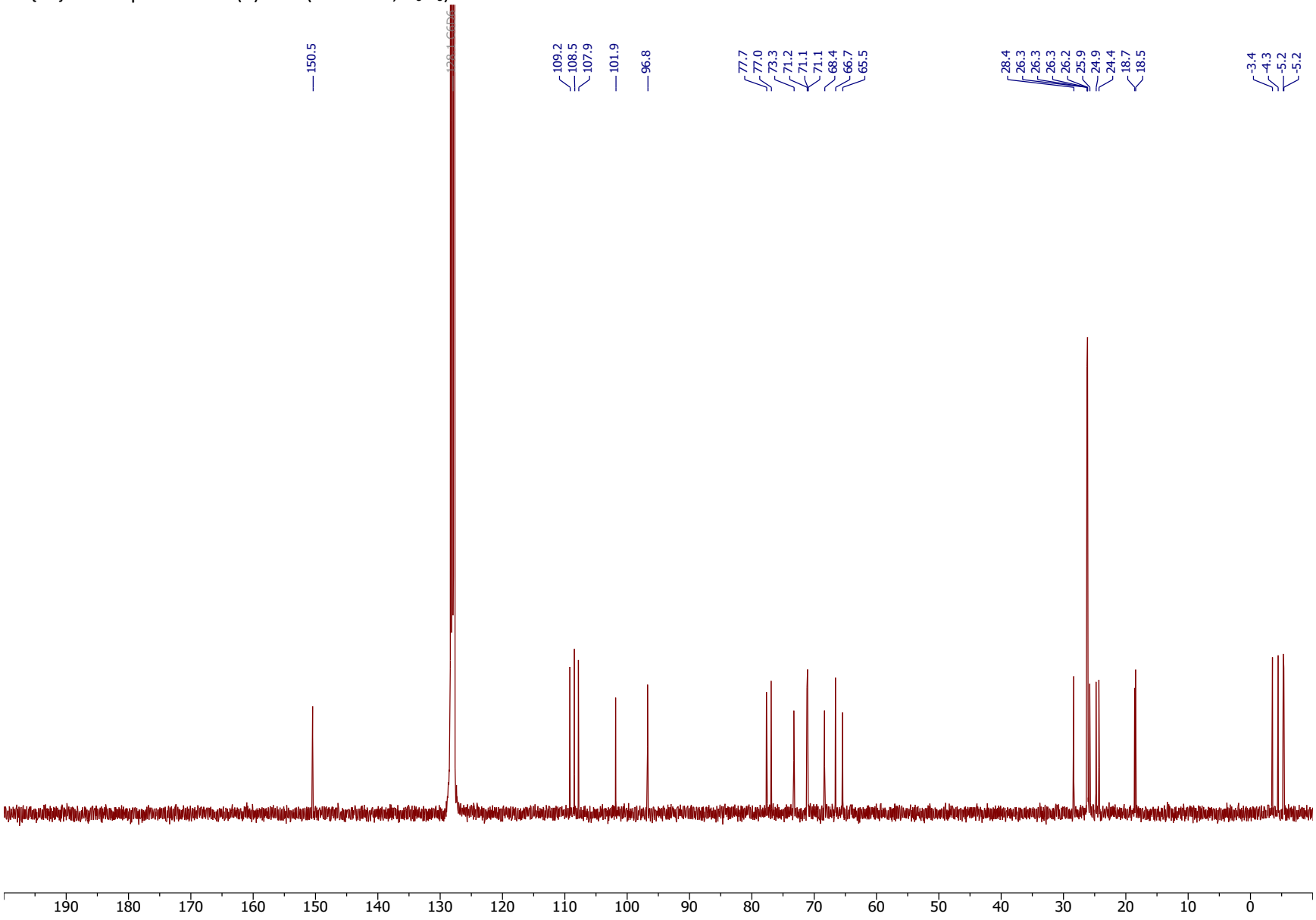
^{1}H NMR spectrum of (*E*)-**170** (800 MHz, C_6D_6) – full



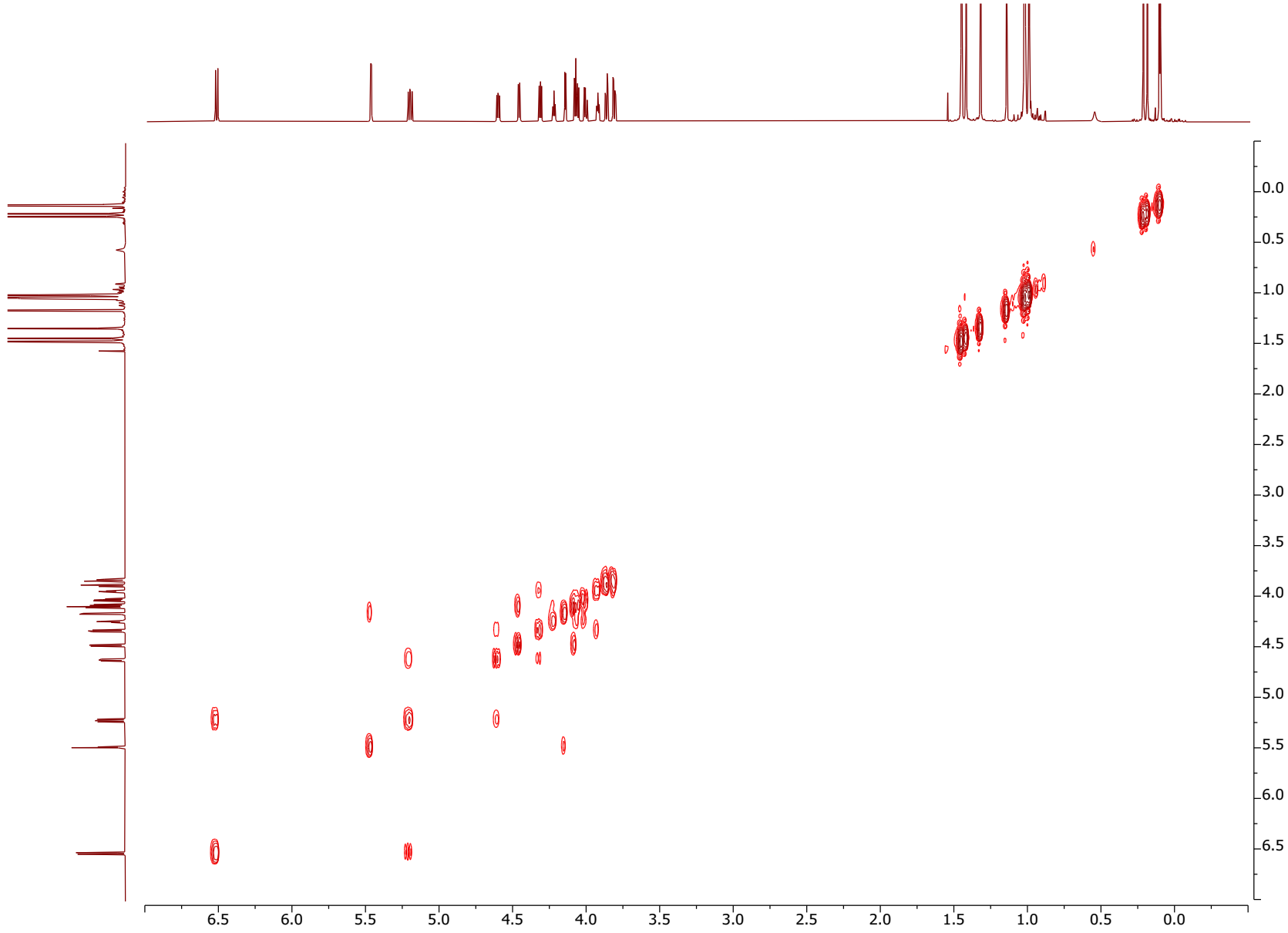
^{1}H NMR spectrum of (*E*)-**170** (800 MHz, C_6D_6) – expansion



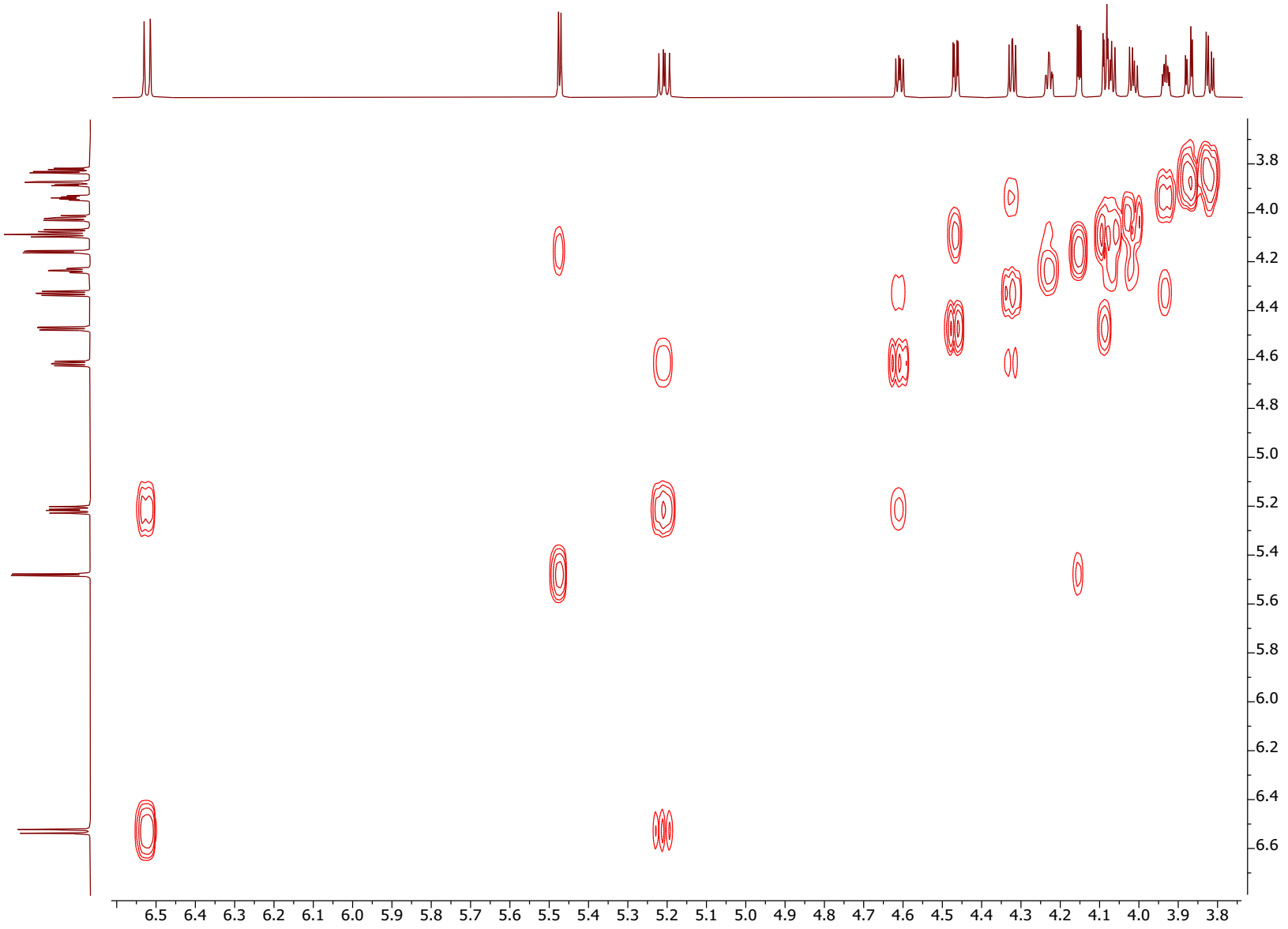
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**170** (101 MHz, C_6D_6)



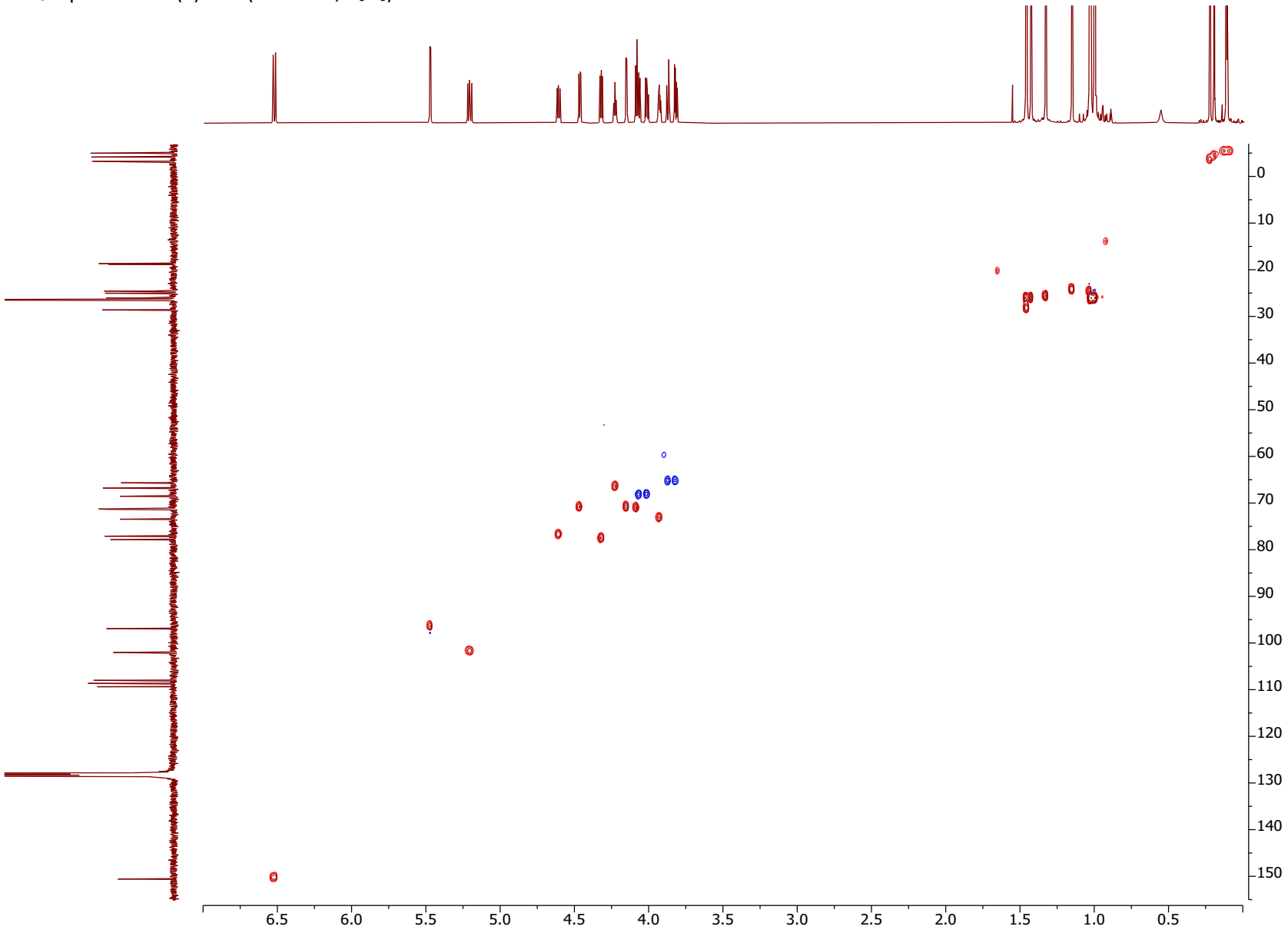
COSY spectrum of (*E*)-**170** (800 MHz, C_6D_6) – full



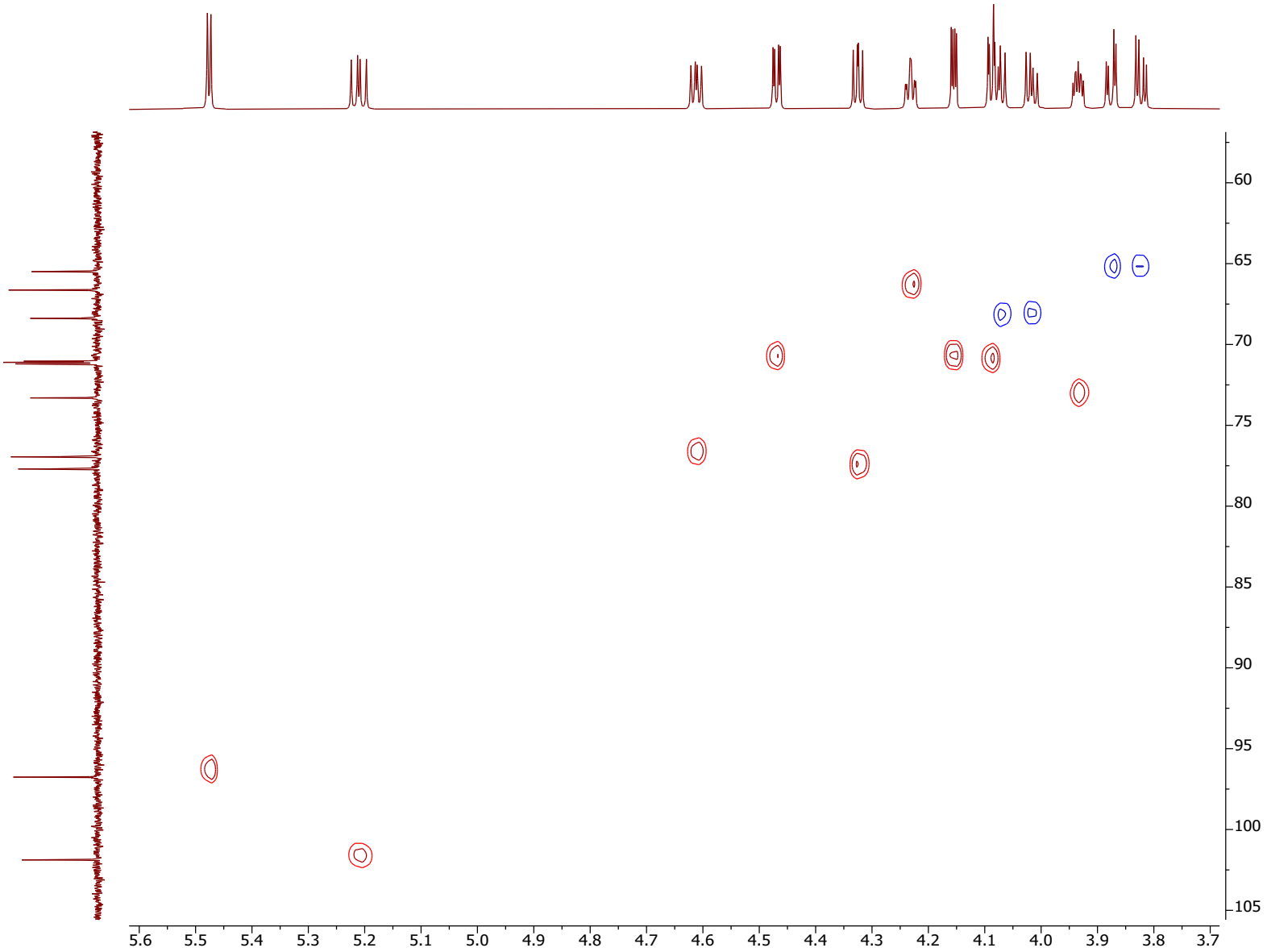
COSY spectrum of (*E*)-**170** (800 MHz, C_6D_6) – expansion



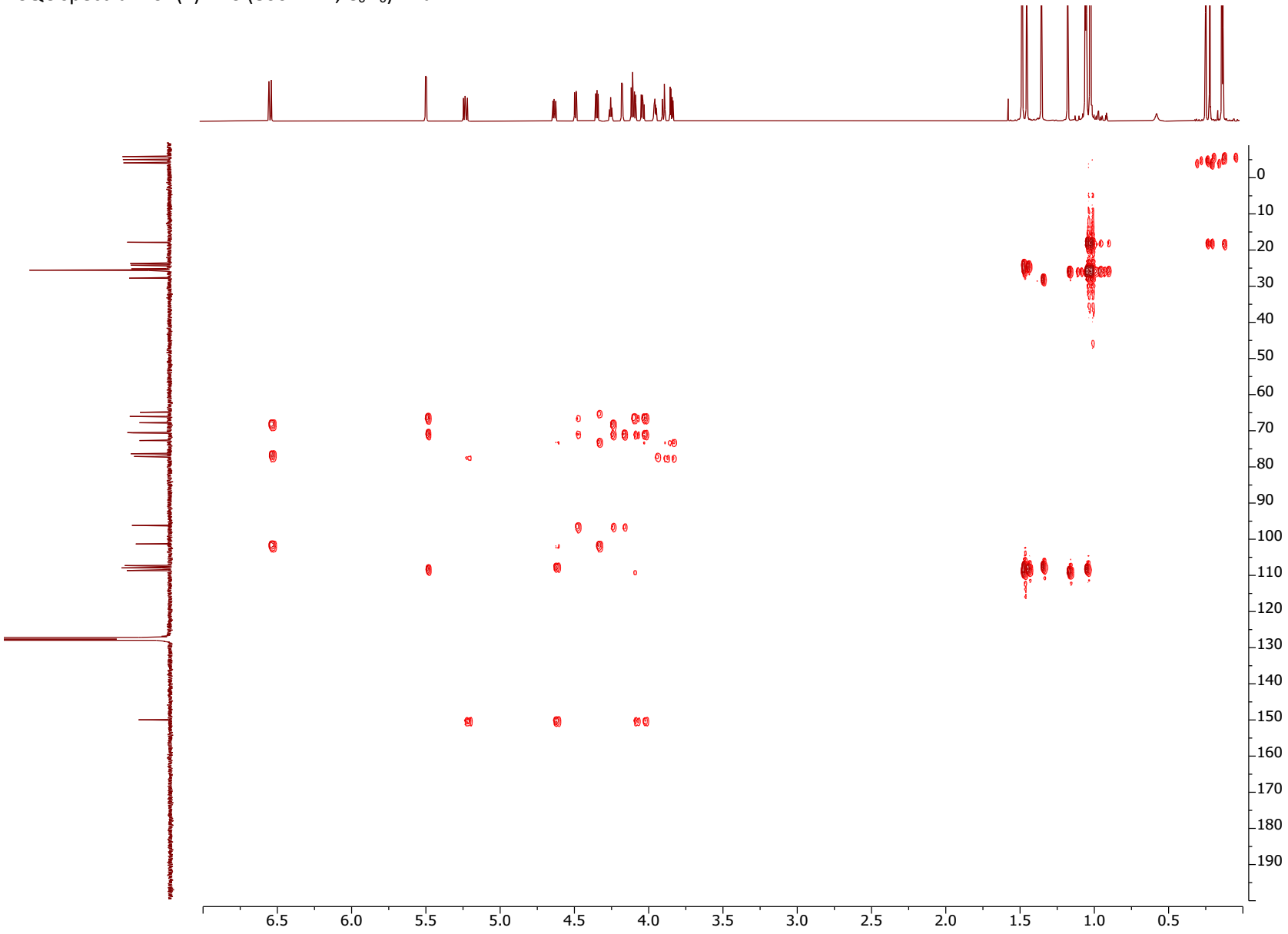
HSQC spectrum of (*E*)-**170** (800 MHz, C_6D_6) – full



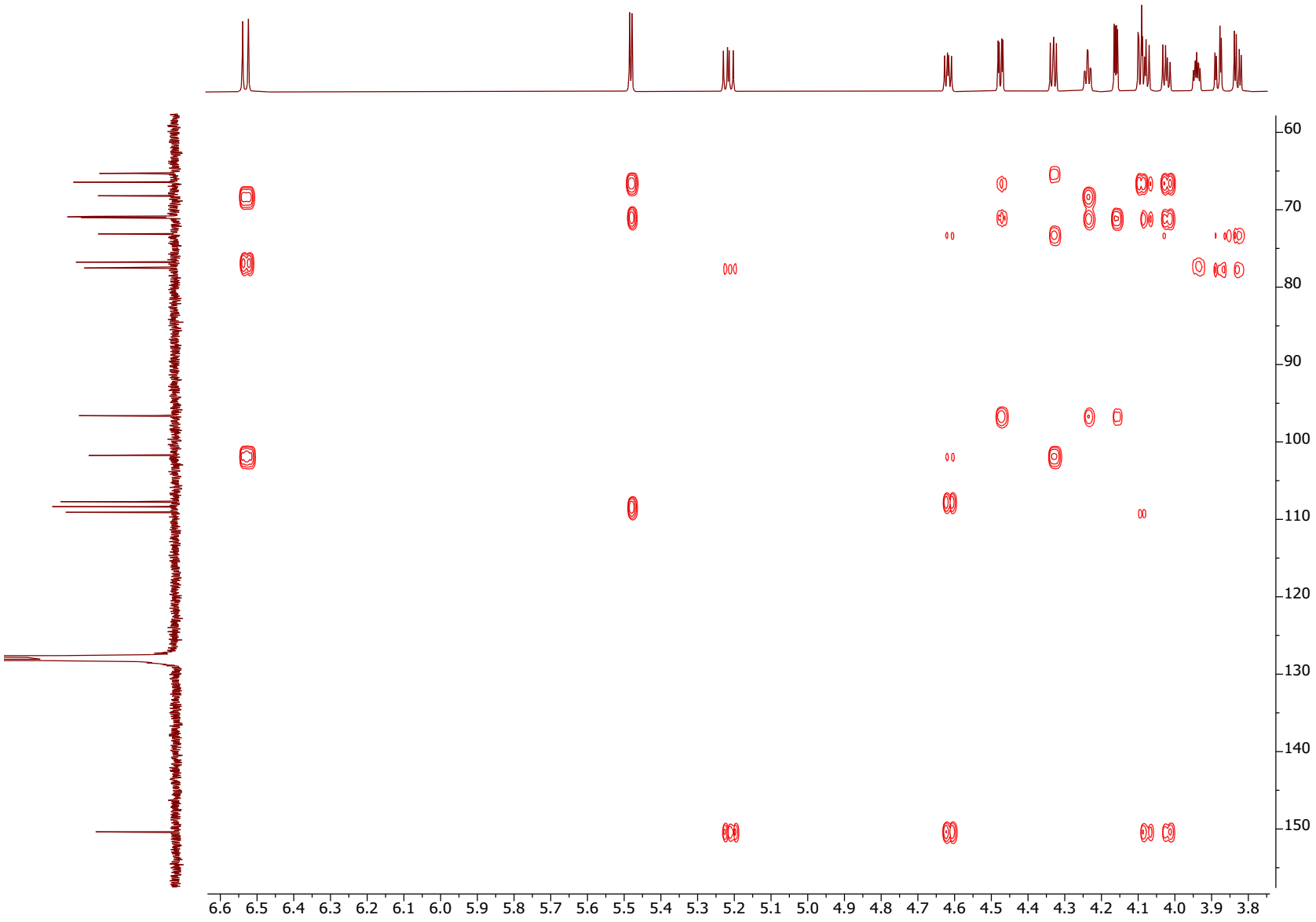
HSQC spectrum of (*E*)-**170** (800 MHz, C_6D_6) – expansion



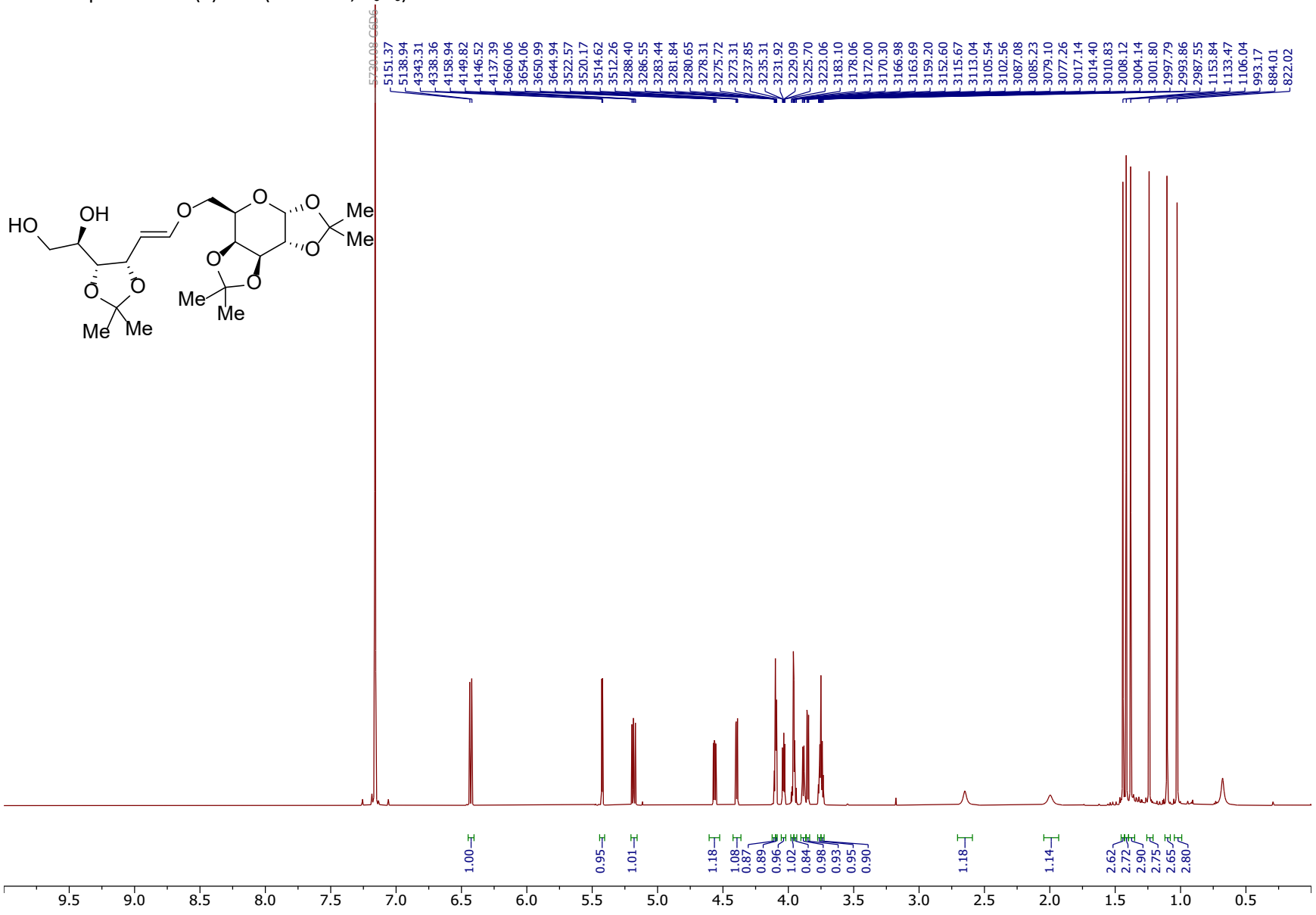
HSQC spectrum of (*E*)-**170** (800 MHz, C_6D_6) – full



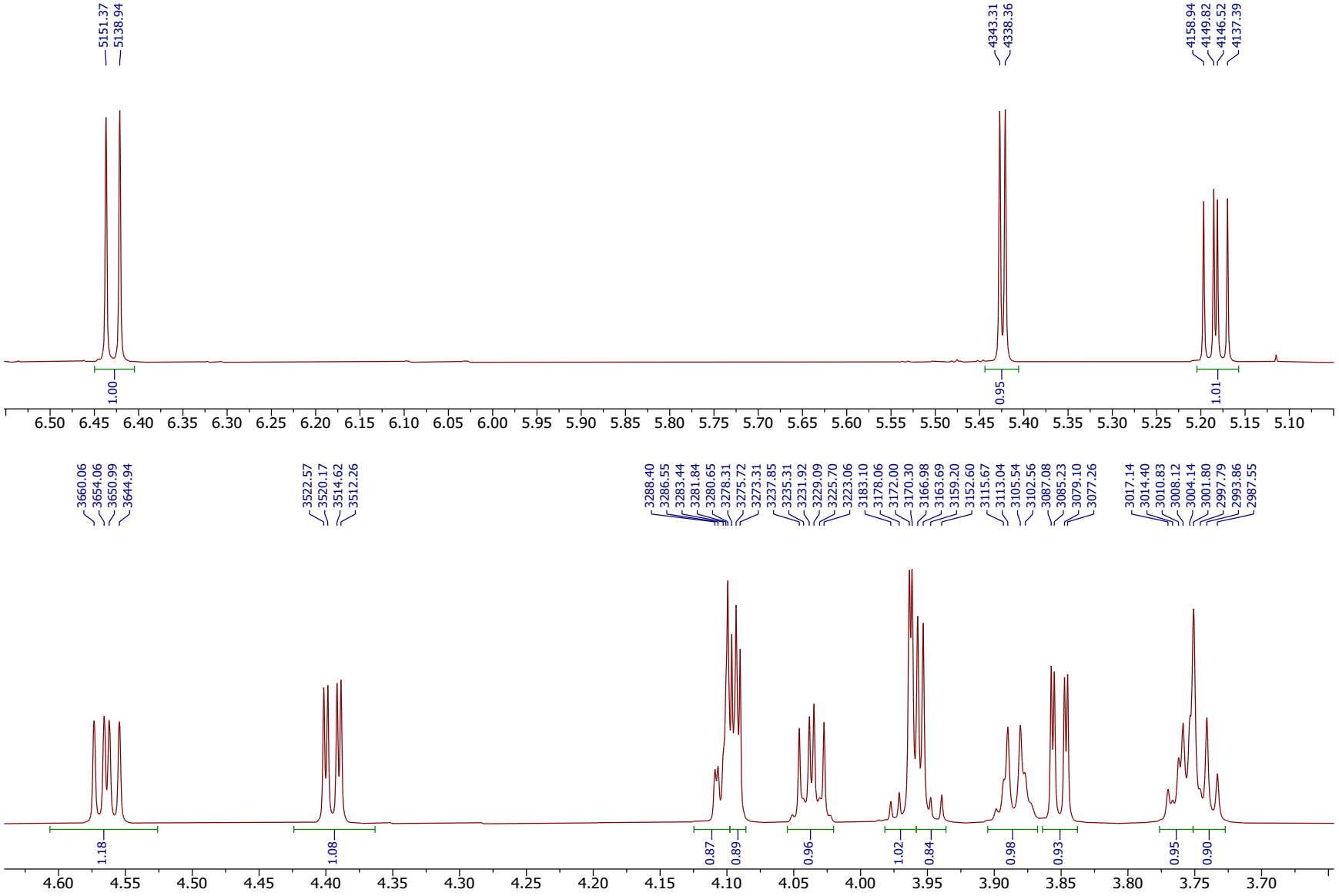
HSQC spectrum of (*E*)-**170** (800 MHz, C_6D_6) – expansion



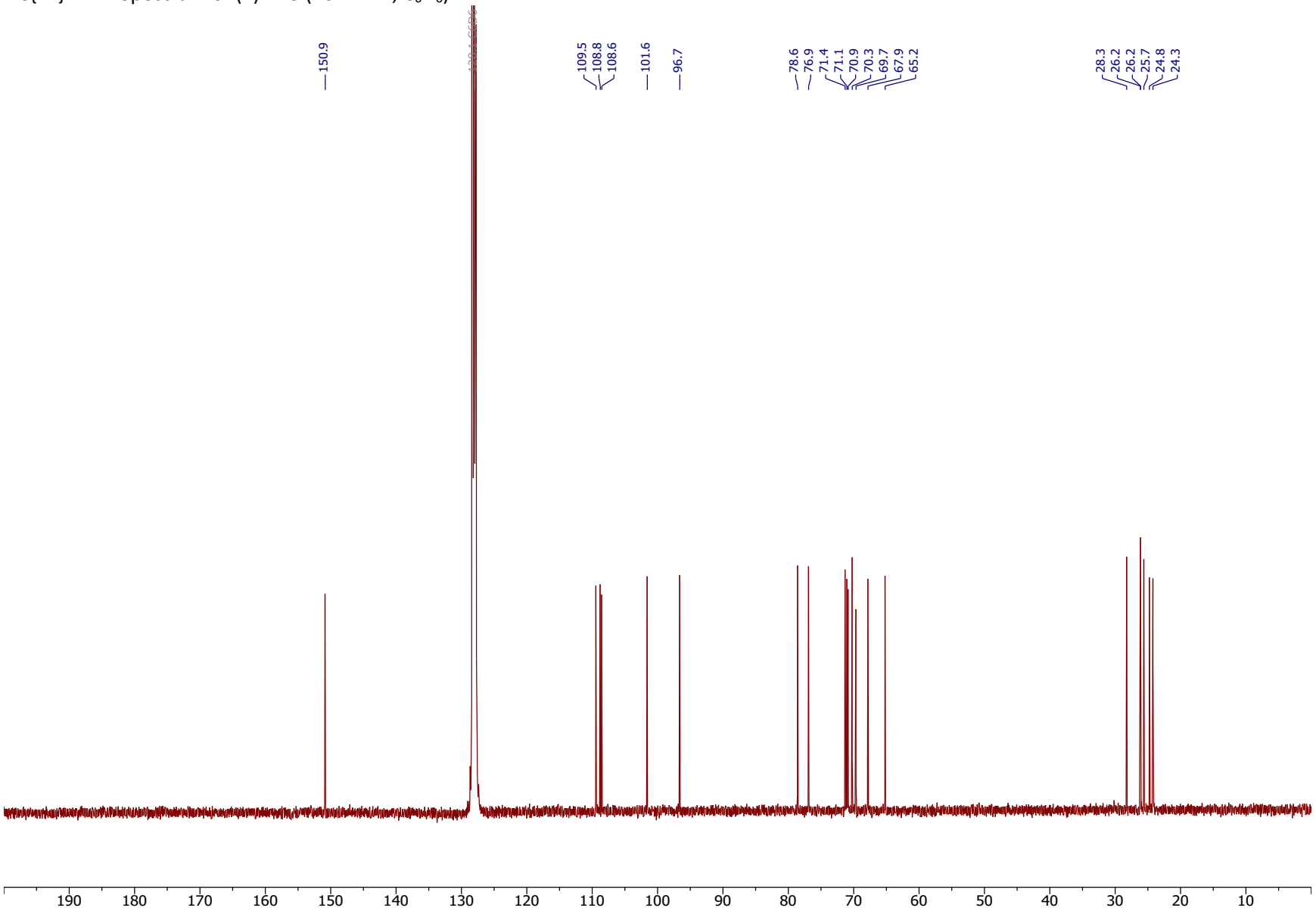
^{1}H NMR spectrum of (*E*)-**173** (800 MHz, C_6D_6) – full



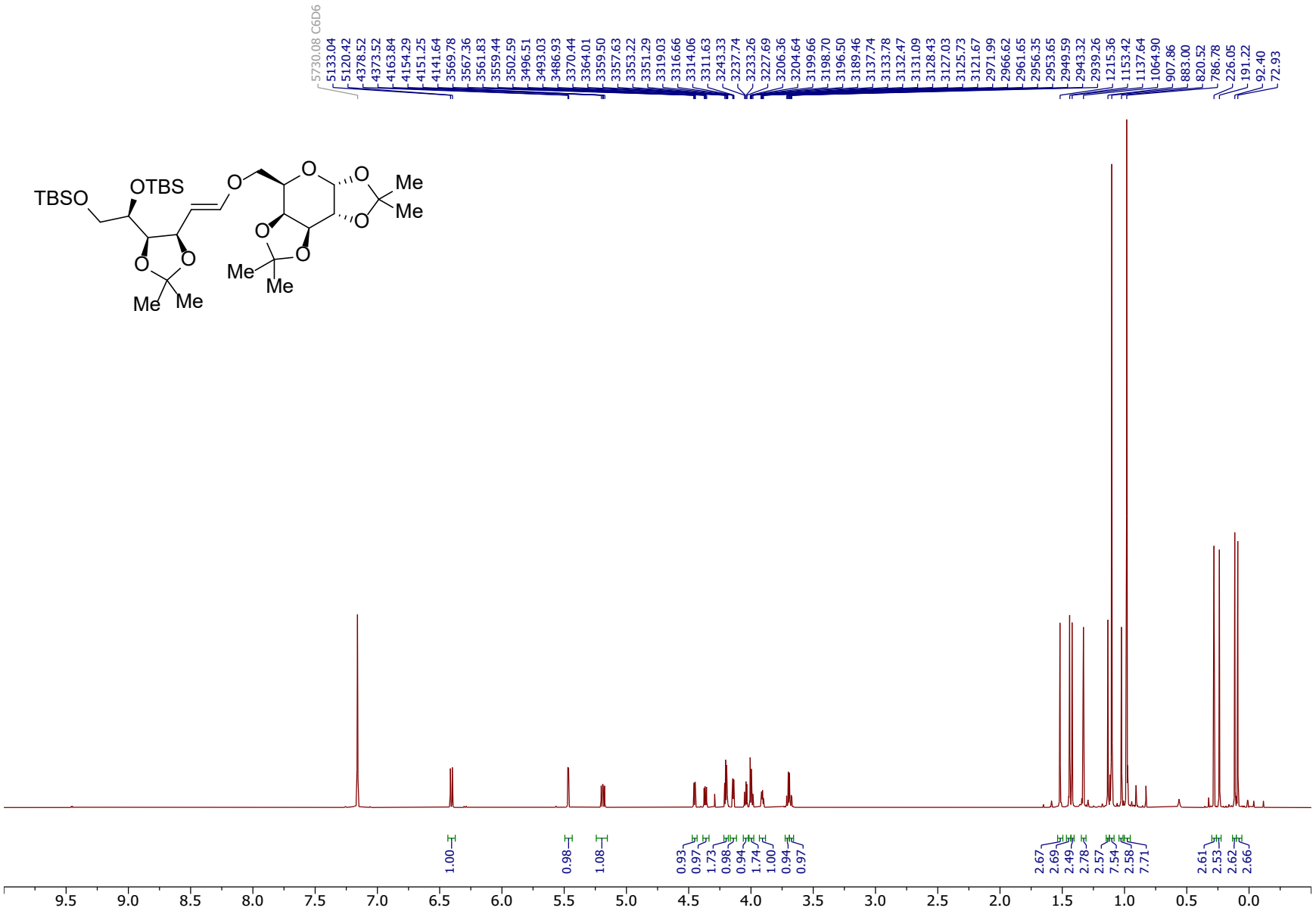
^{1}H NMR Spectrum of (*E*)-**173** (800 MHz, C_6D_6) – expansion



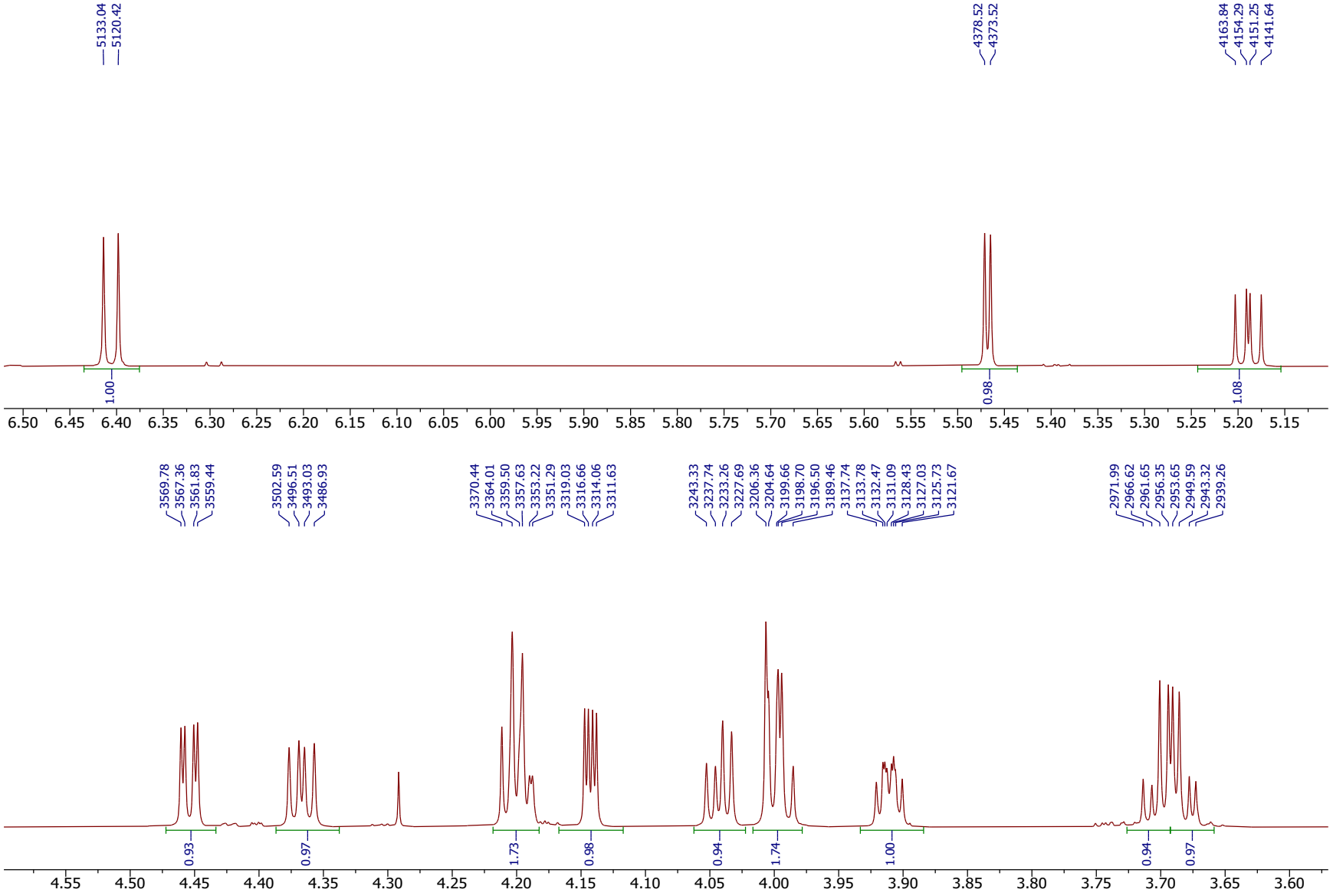
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**173** (101 MHz, C_6D_6)



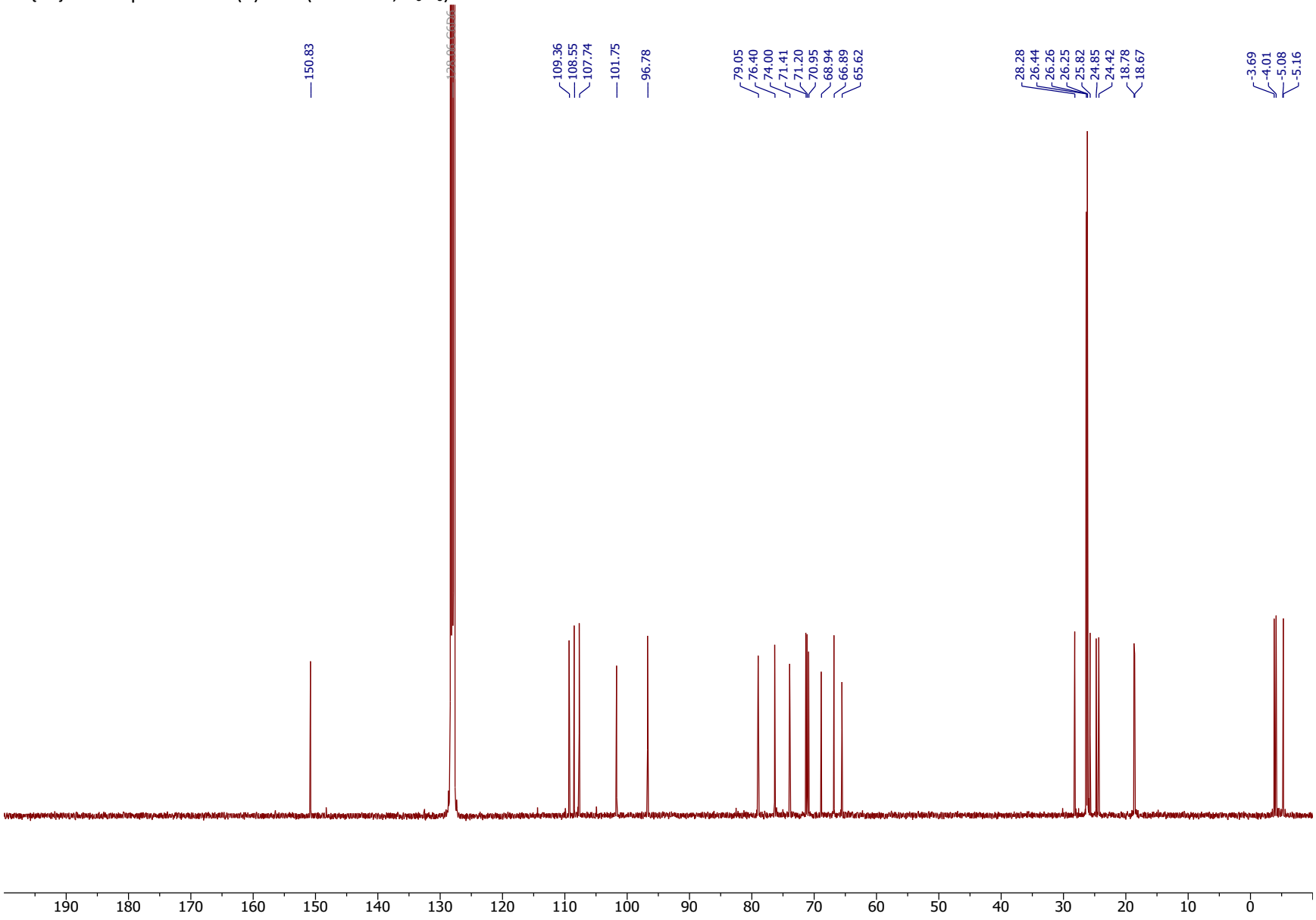
^{1}H NMR Spectrum of (*E*)-**171** (800 MHz, C_6D_6) – full



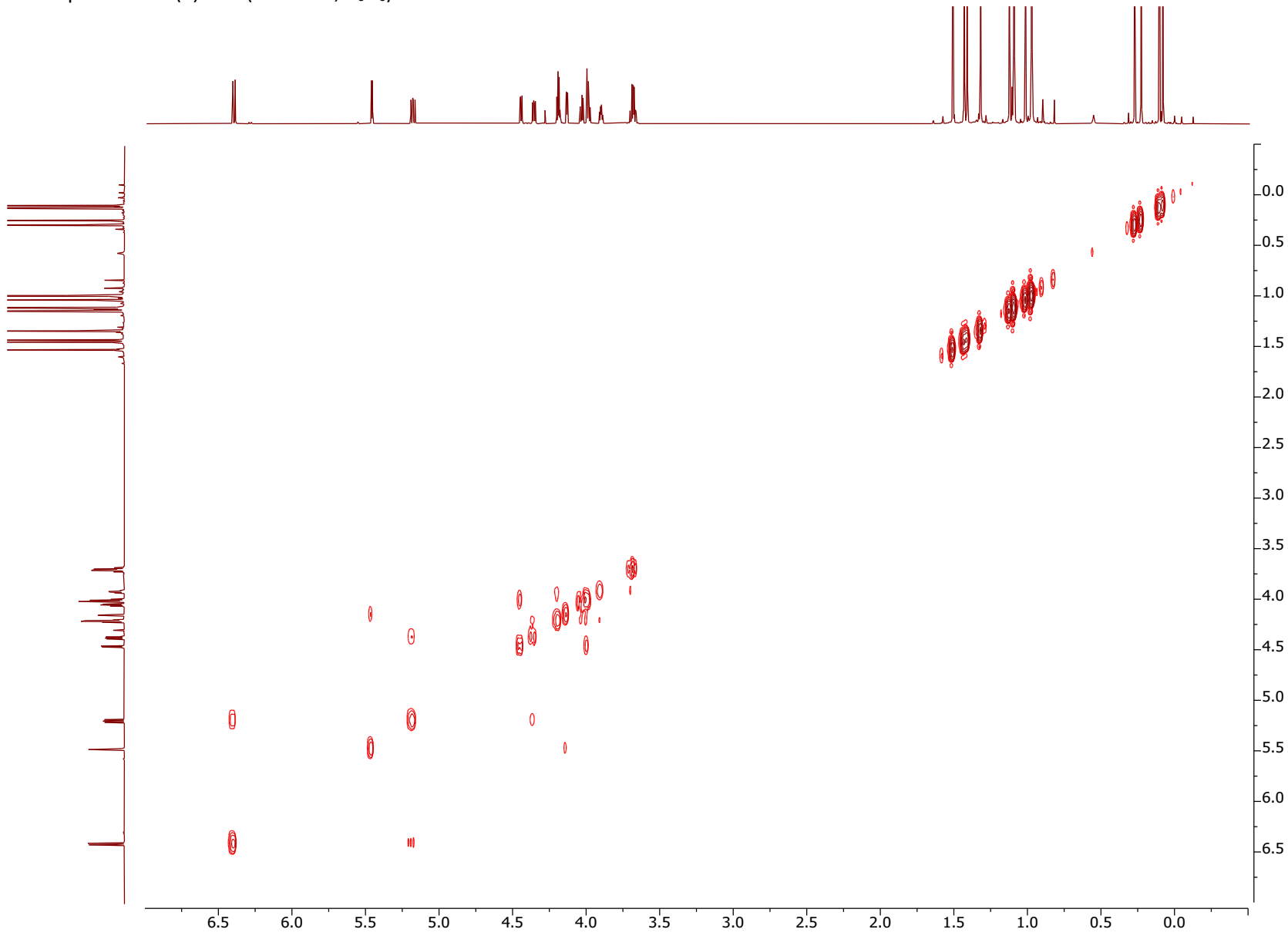
^{1}H NMR Spectrum of (*E*)-**171** (800 MHz, C_6D_6) – expansion



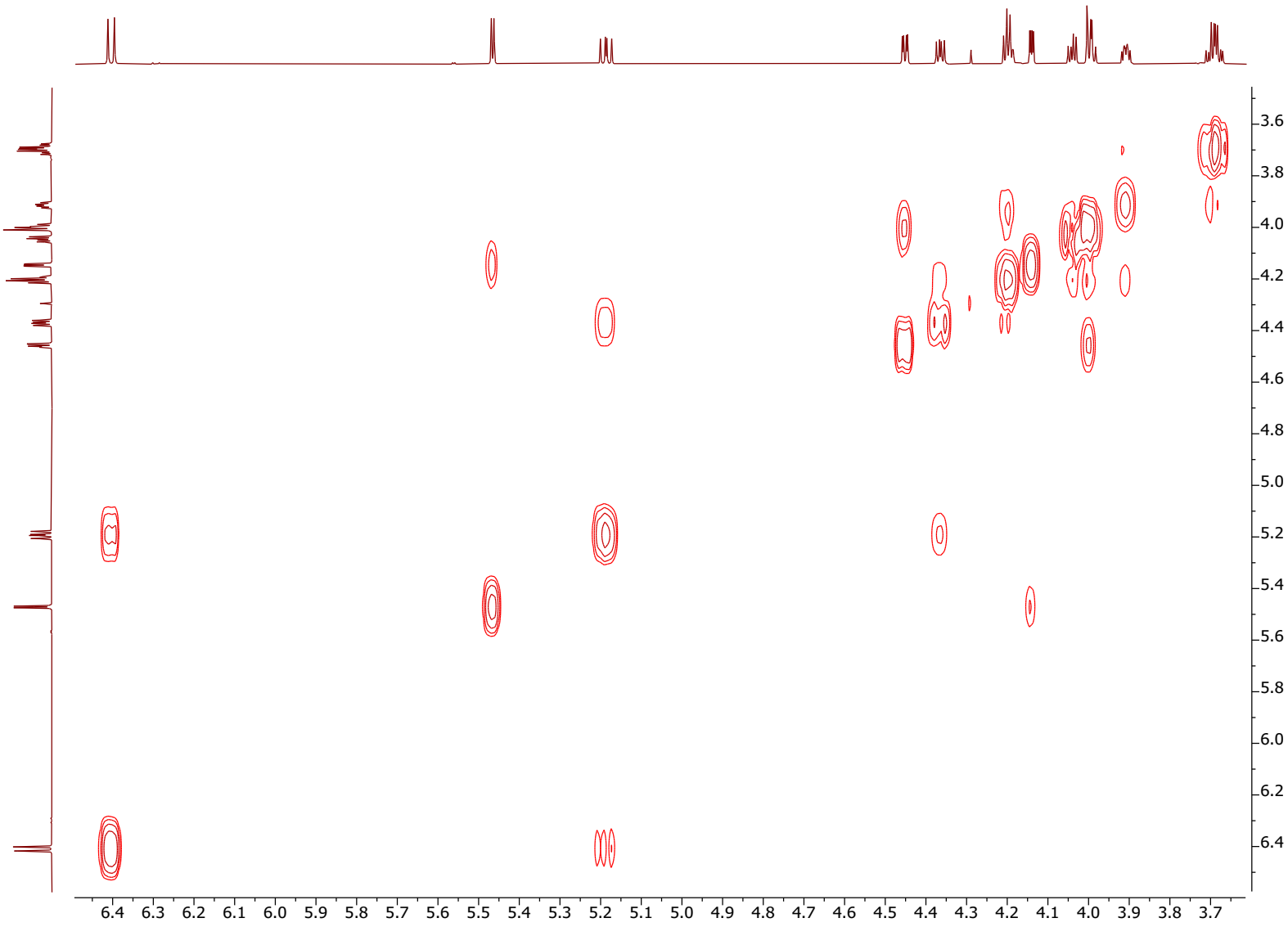
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**171** (101 MHz, C_6D_6)



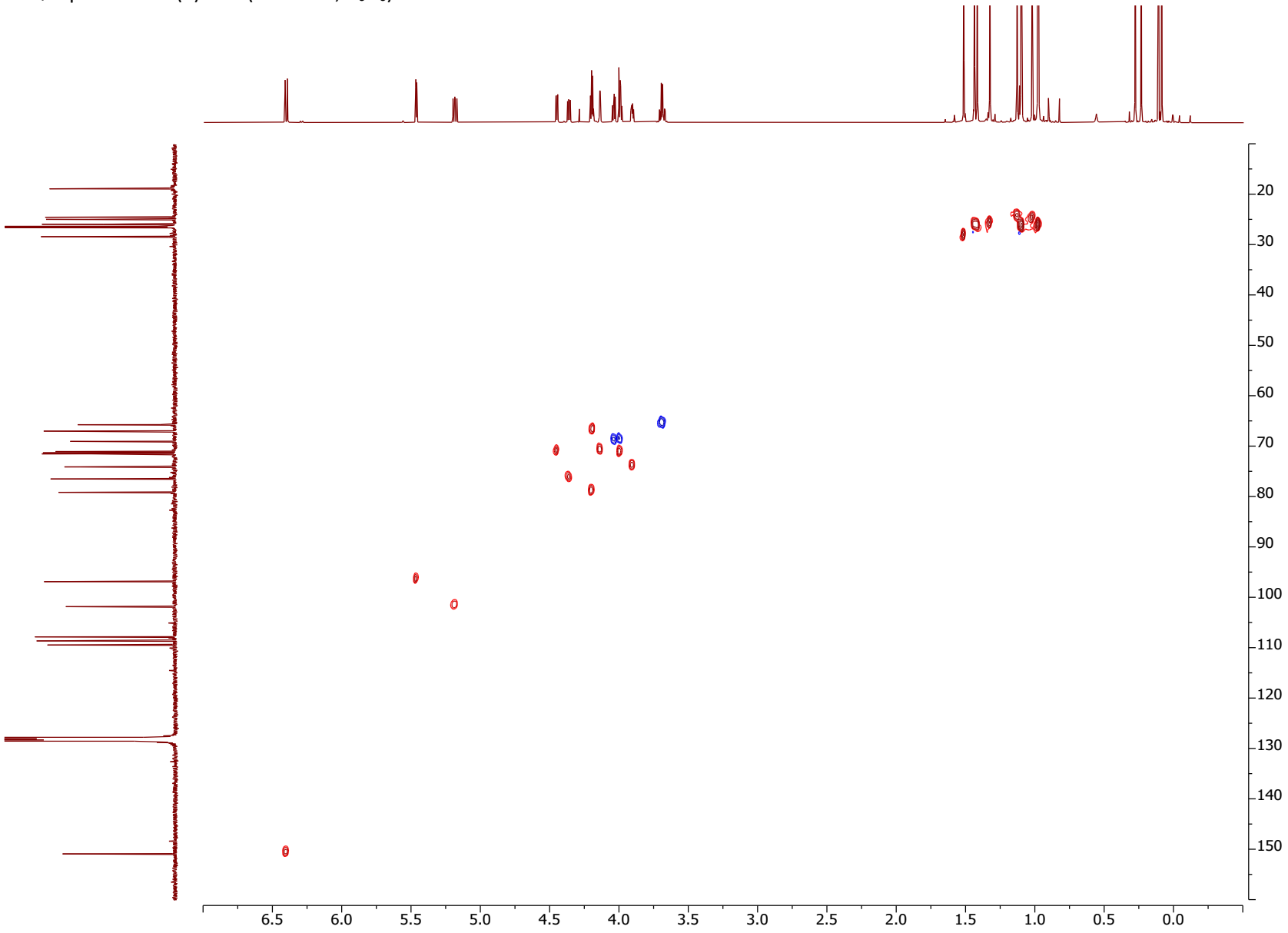
COSY spectrum of (*E*)-**171** (800 MHz, C_6D_6) – full



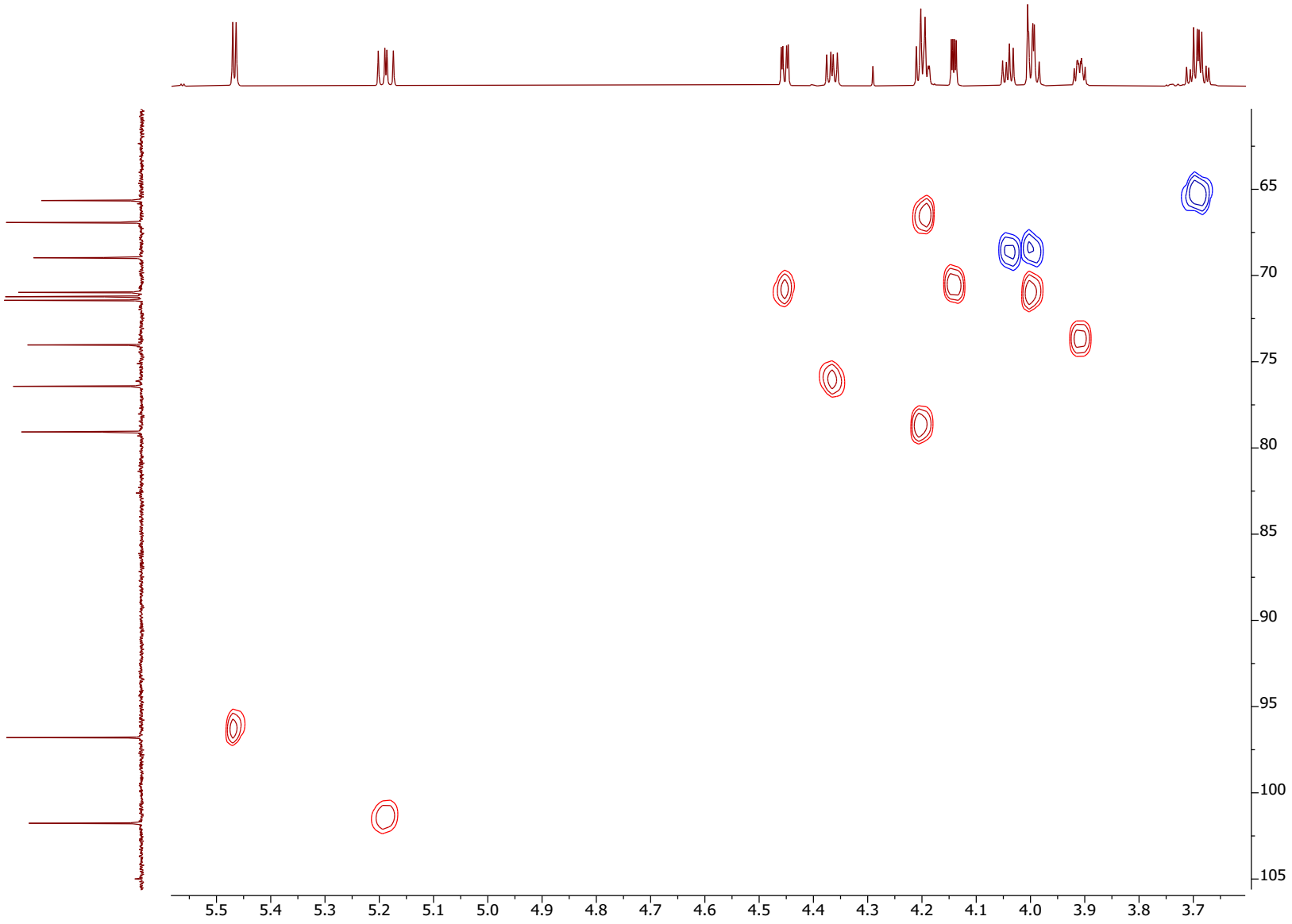
COSY spectrum of (*E*)-**171** (800 MHz, C_6D_6) – expansion



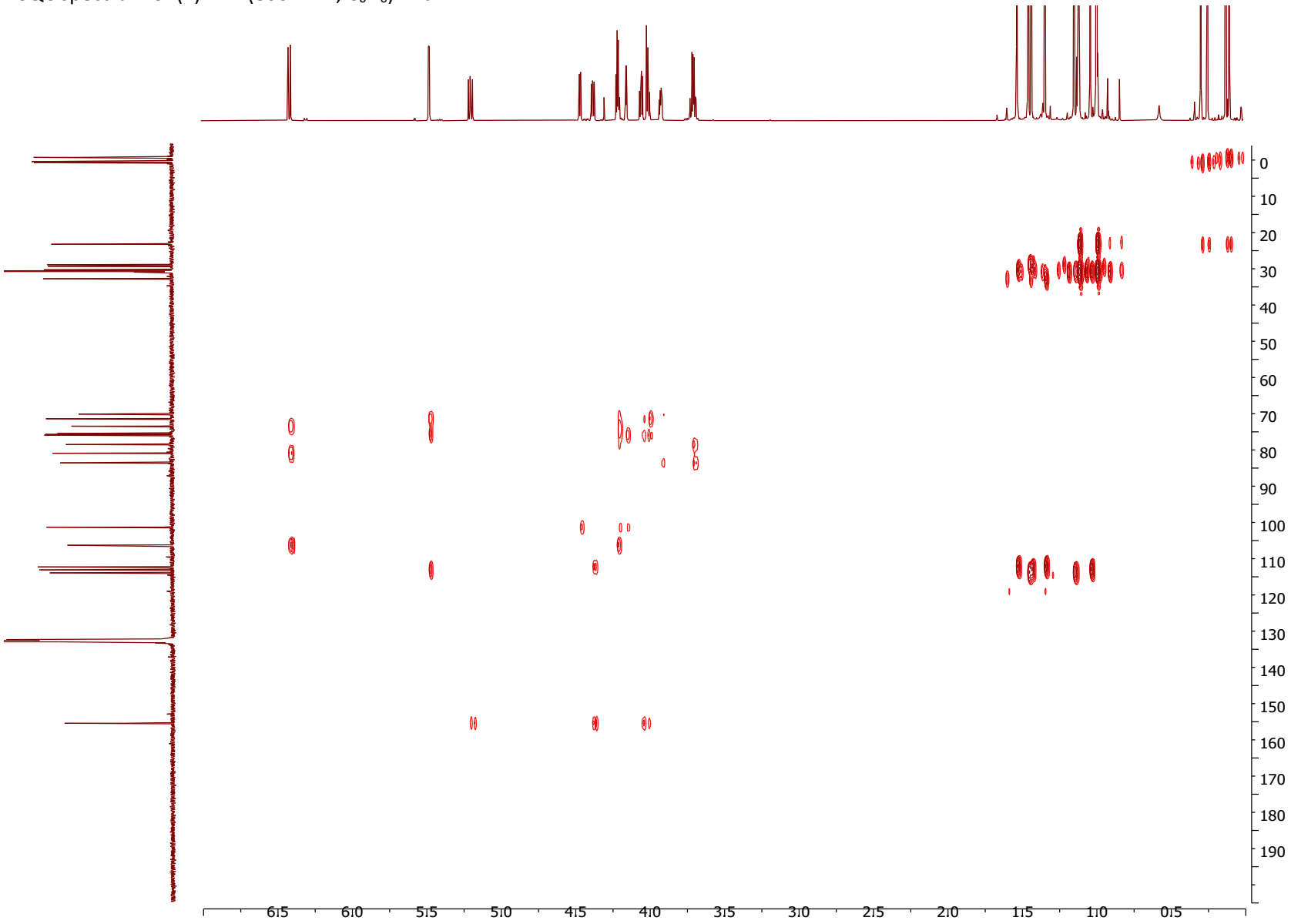
HSQC spectrum of (*E*)-**171** (800 MHz, C_6D_6) – full



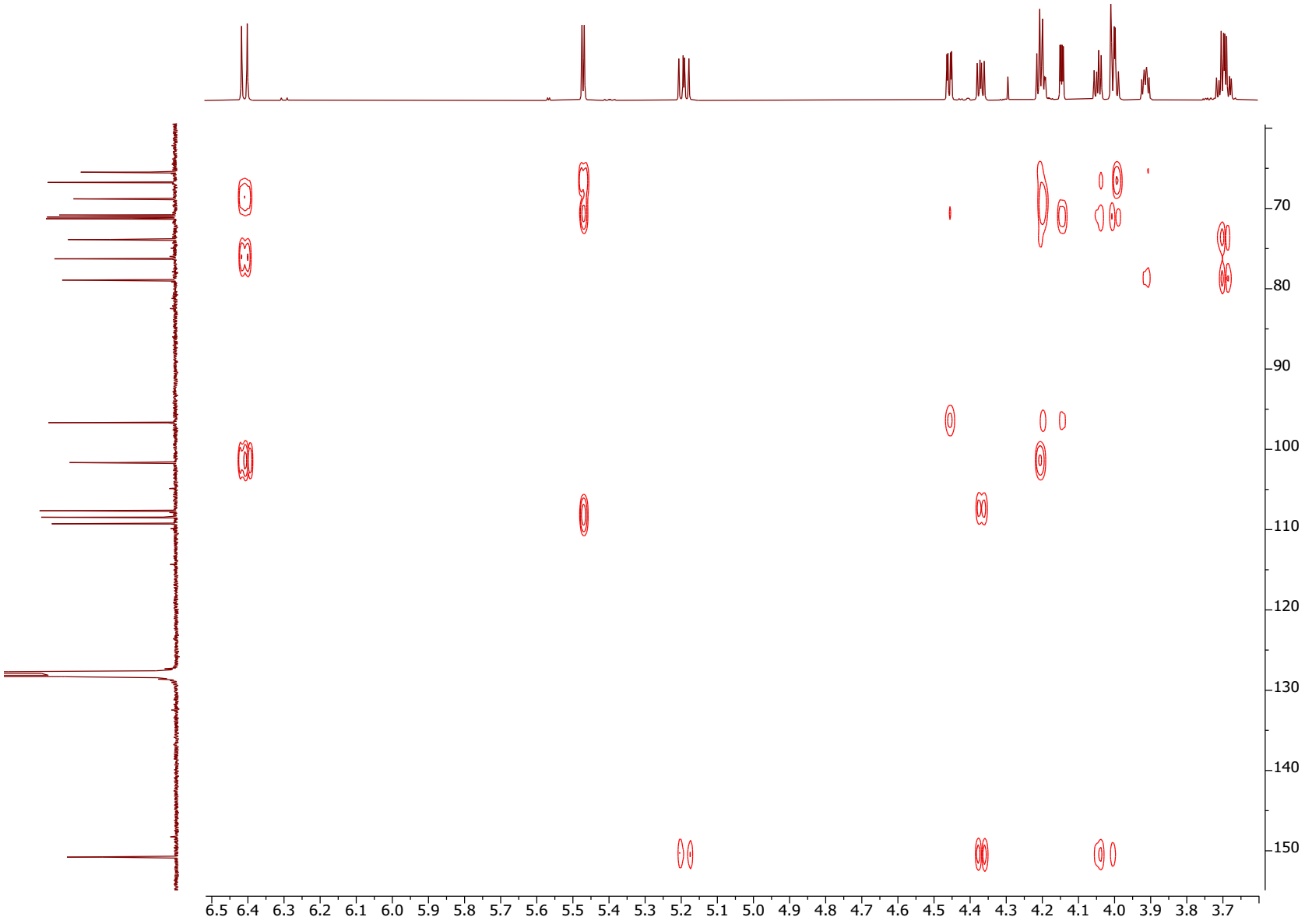
HSQC spectrum of (*E*)-**171** (800 MHz, C_6D_6) – expansion



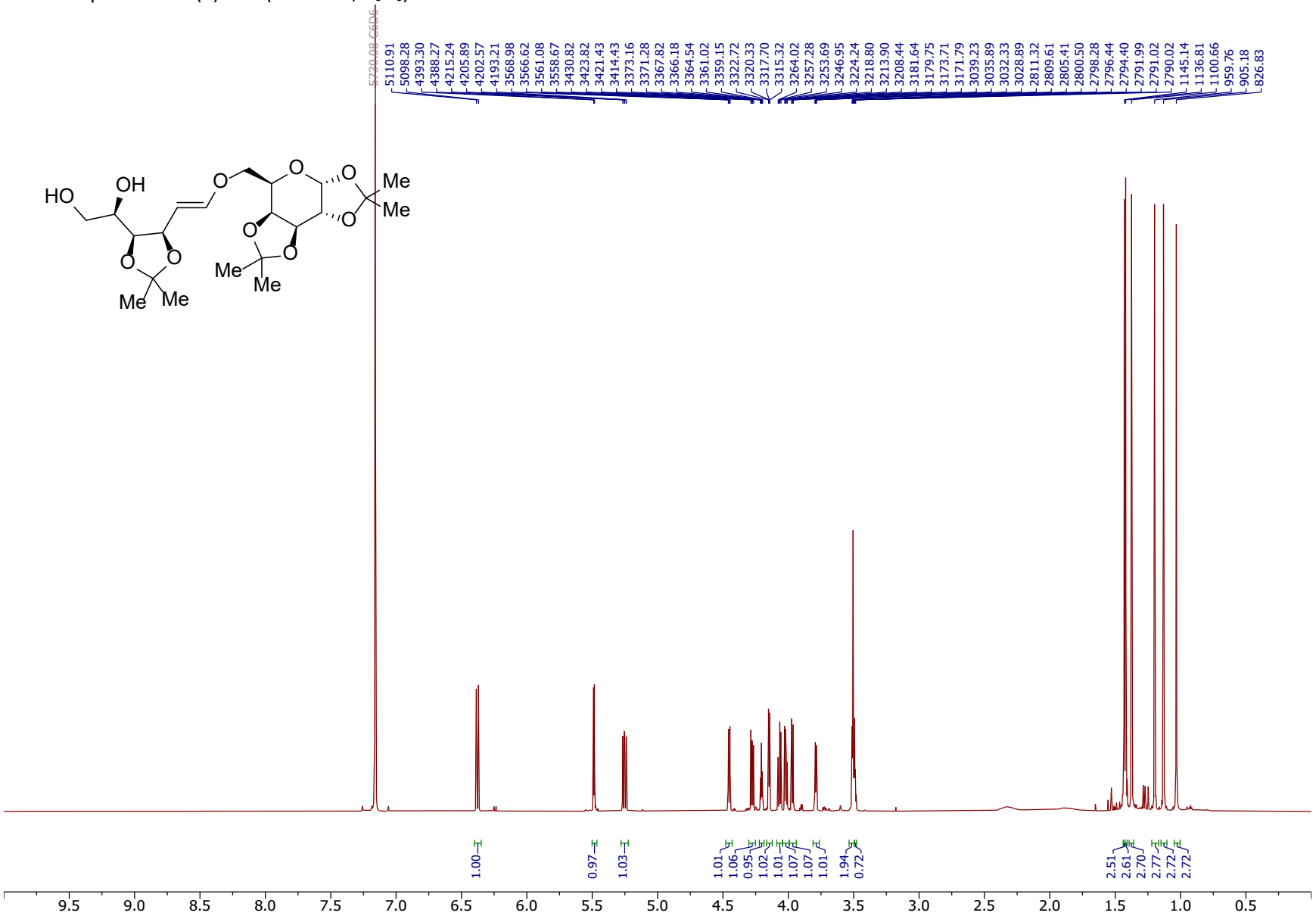
HSQC spectrum of (*E*)-**171** (800 MHz, C_6D_6) – full



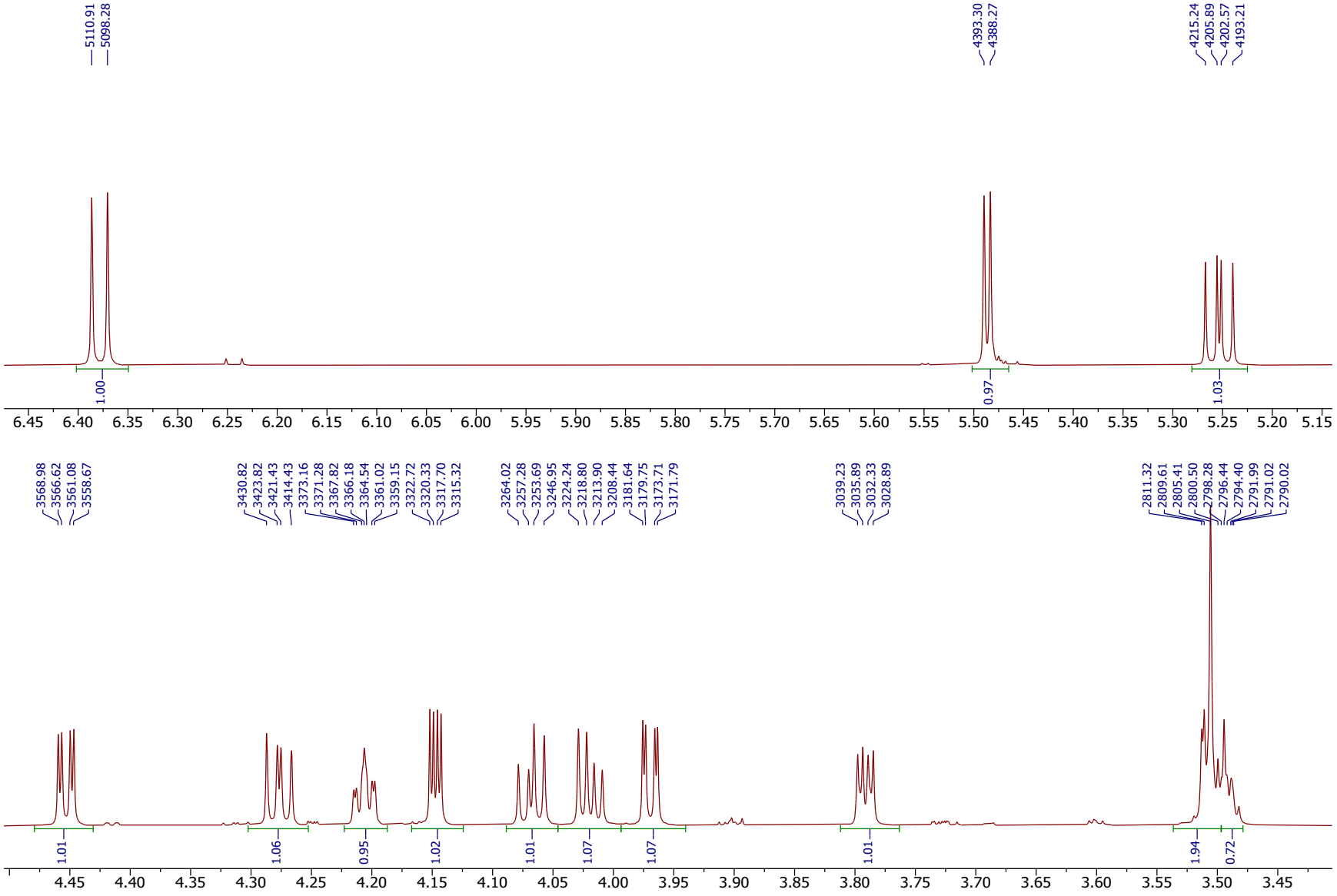
HSQC spectrum of (*E*)-**171** (800 MHz, C_6D_6) – expansion



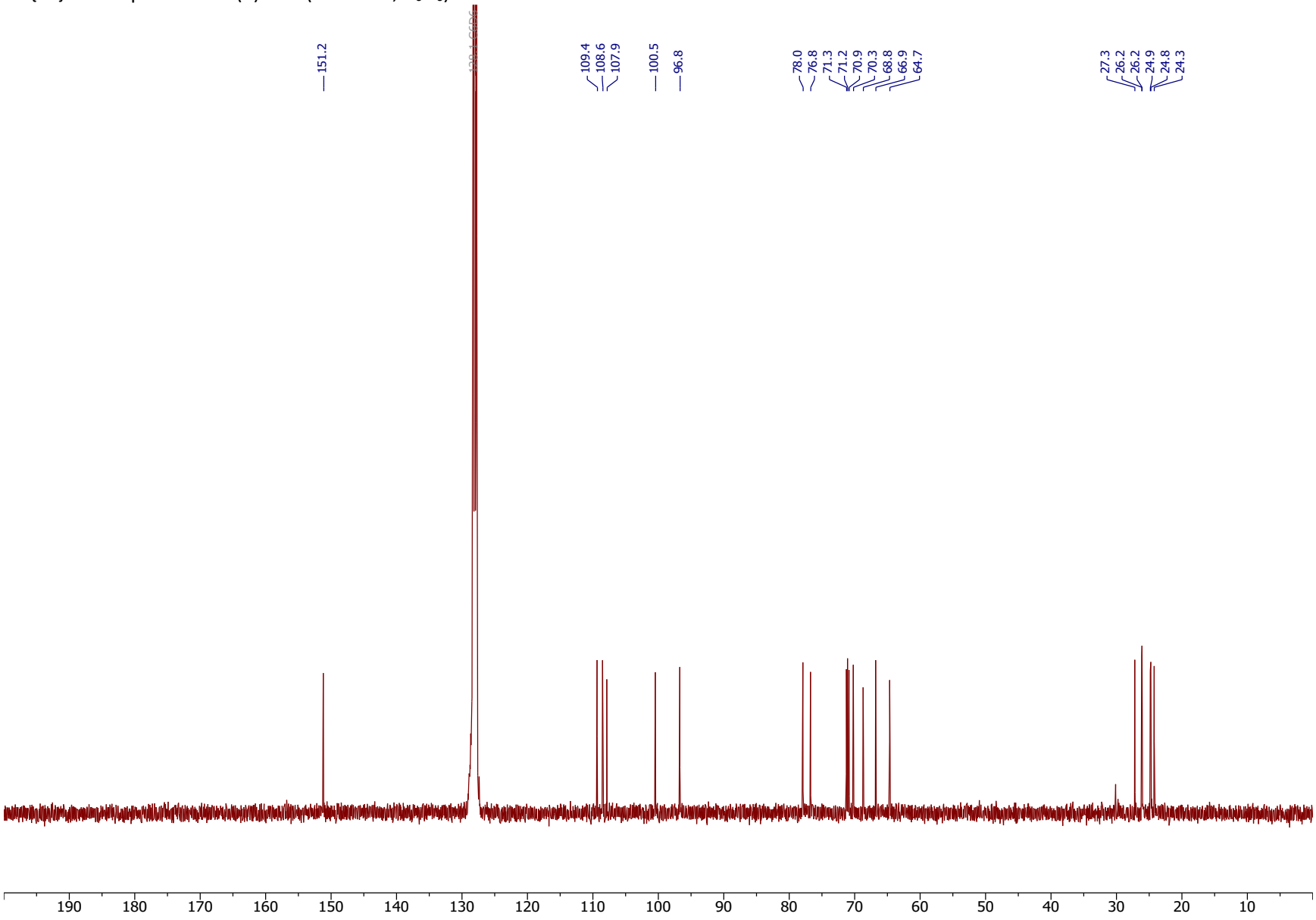
^{1}H NMR Spectrum of (*E*)-**174** (800 MHz, C_6D_6) – full



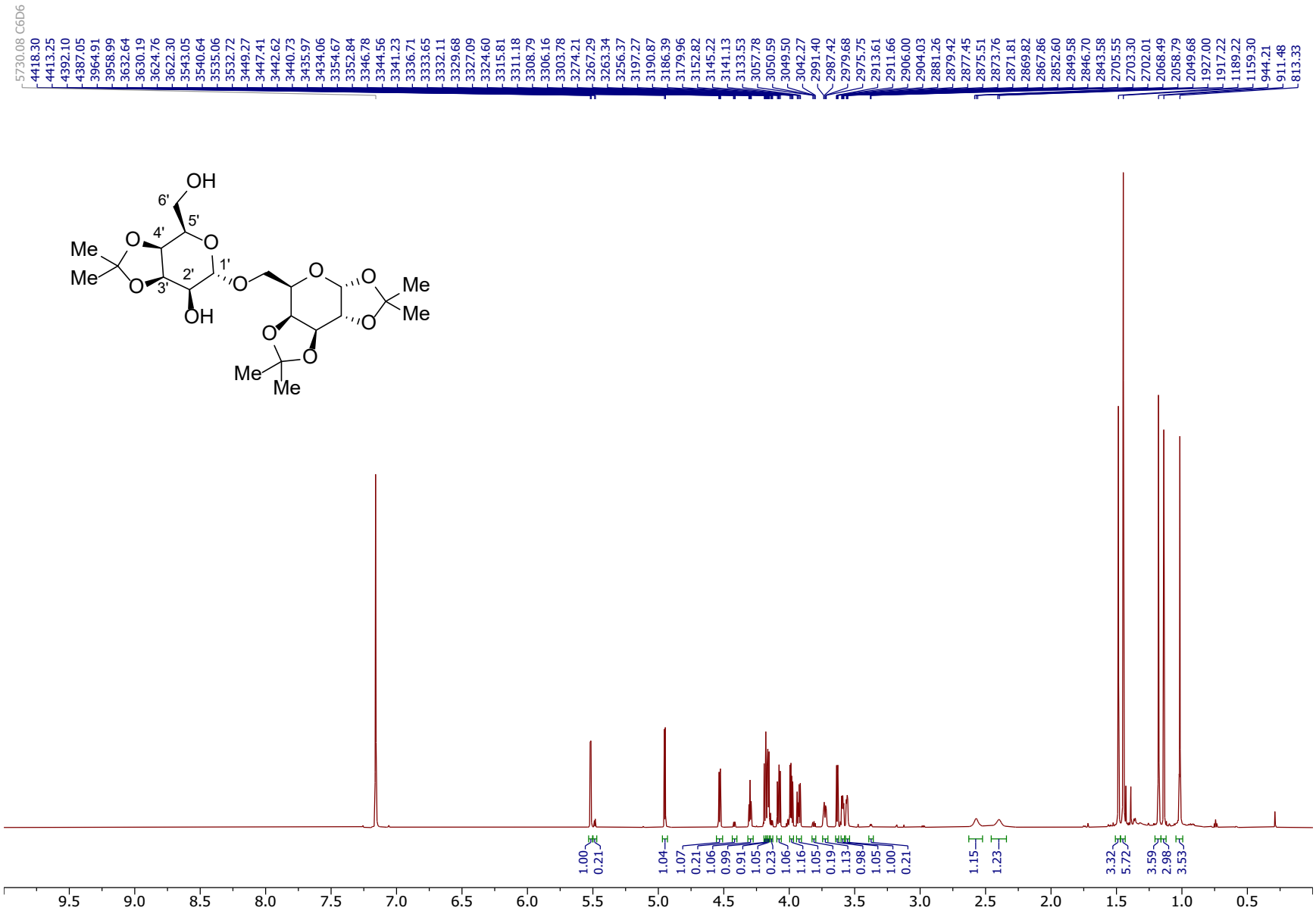
^{1}H NMR Spectrum of (*E*)-**174** (800 MHz, C_6D_6) – expansion



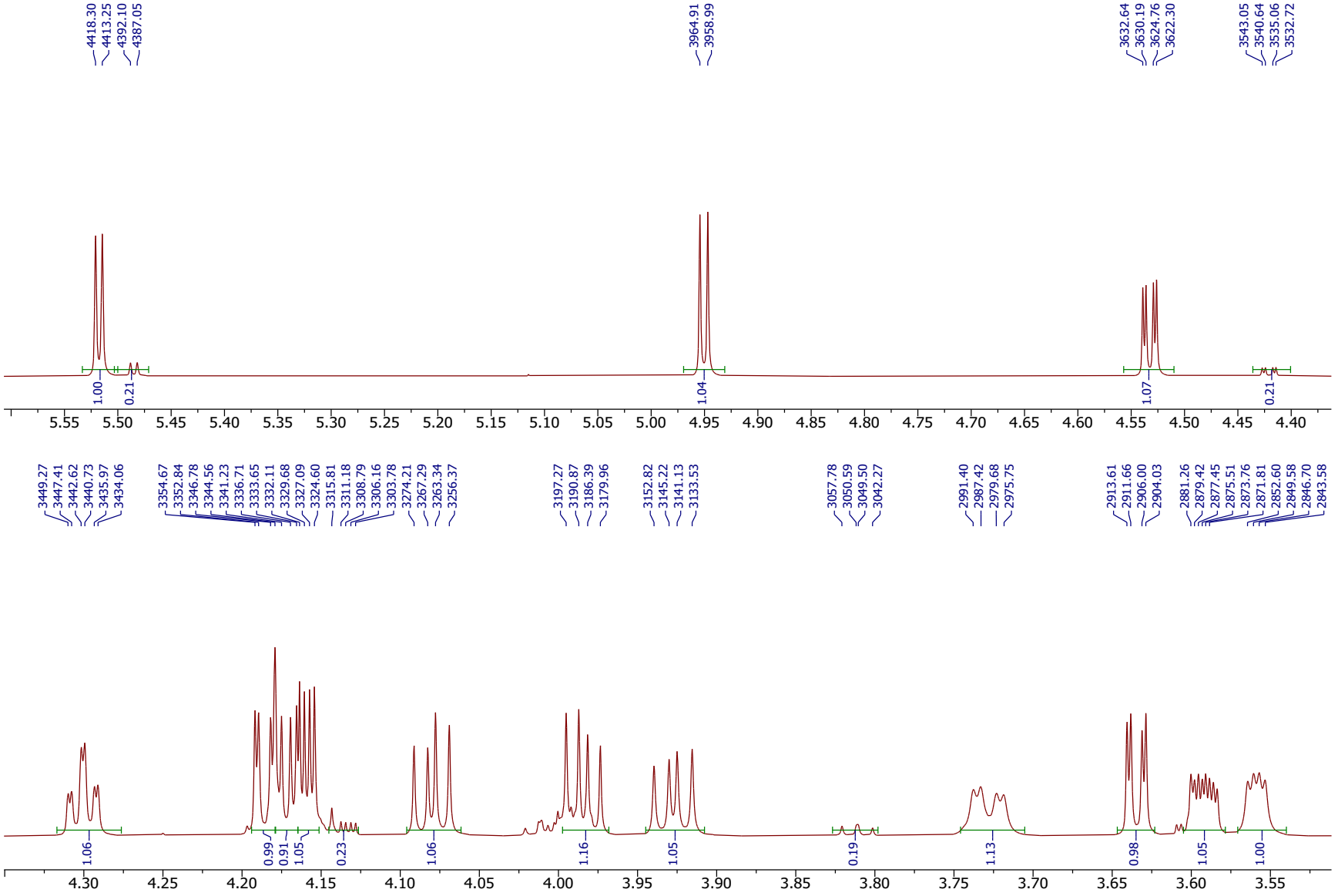
$^{13}C\{^{1}H\}$ NMR Spectrum of (*E*)-**174** (101 MHz, C_6D_6)



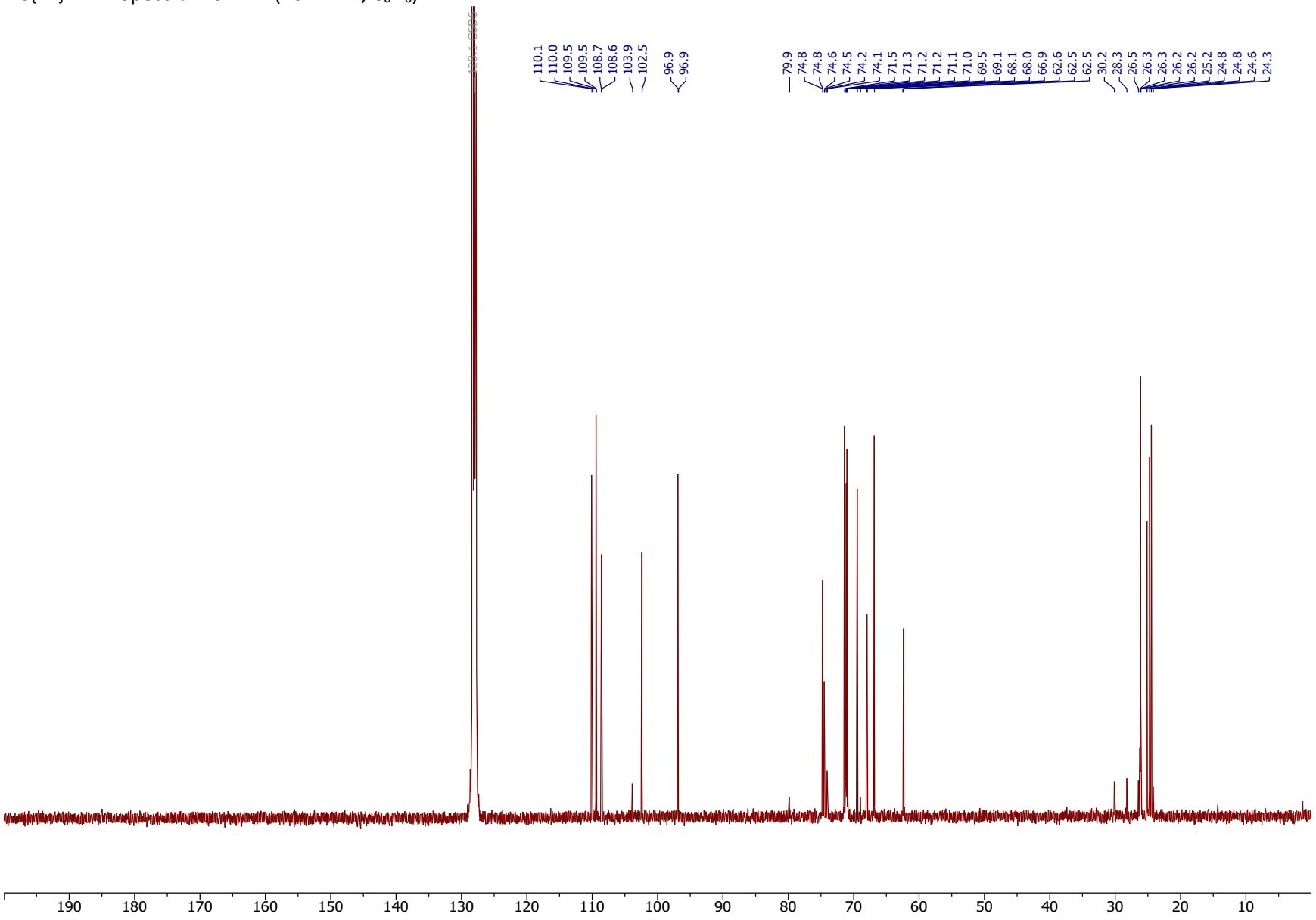
^{1}H NMR Spectrum of **177** (800 MHz, C_6D_6) – full



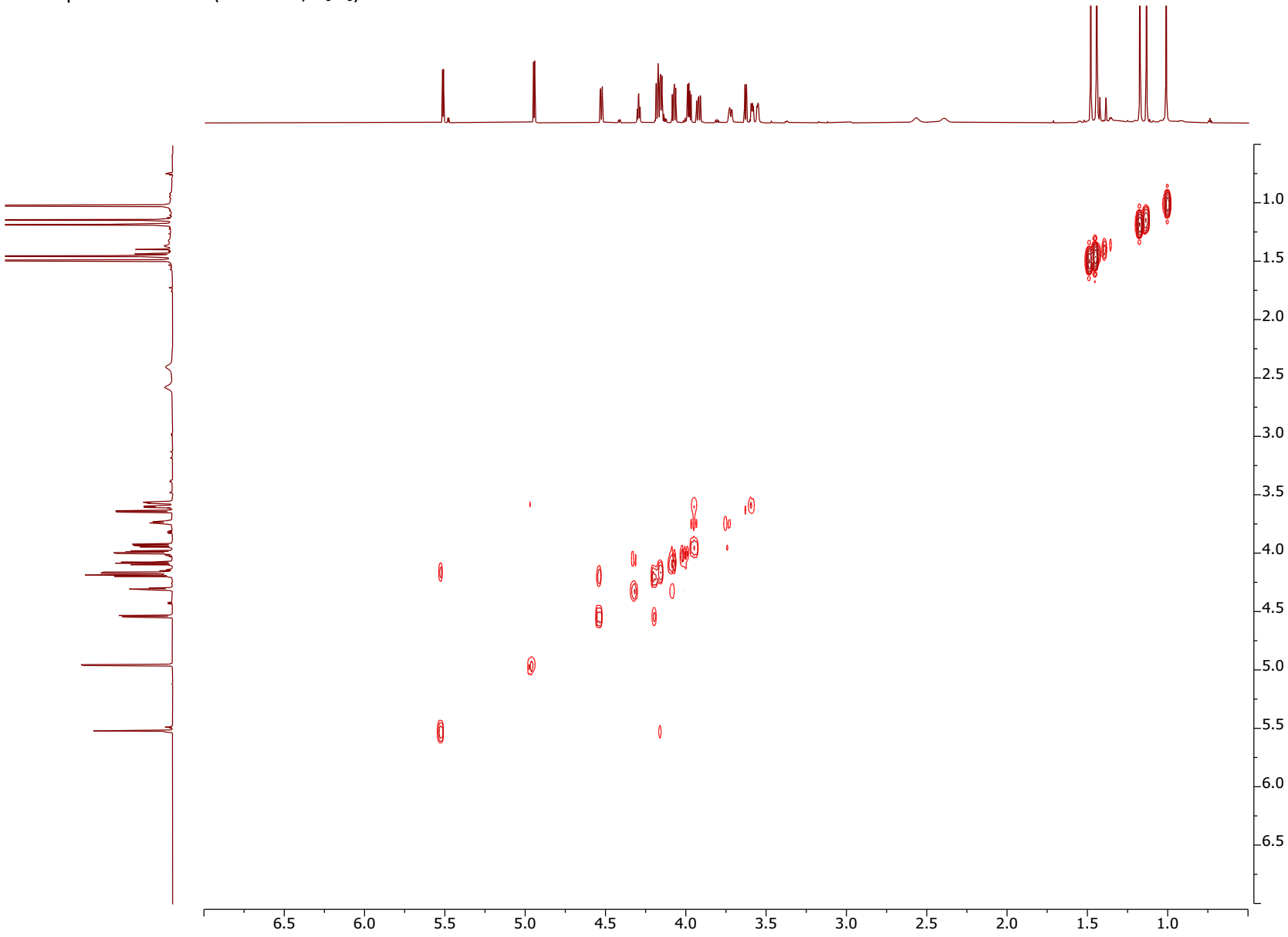
^{1}H NMR Spectrum of **177** (800 MHz, C_6D_6) – expansion



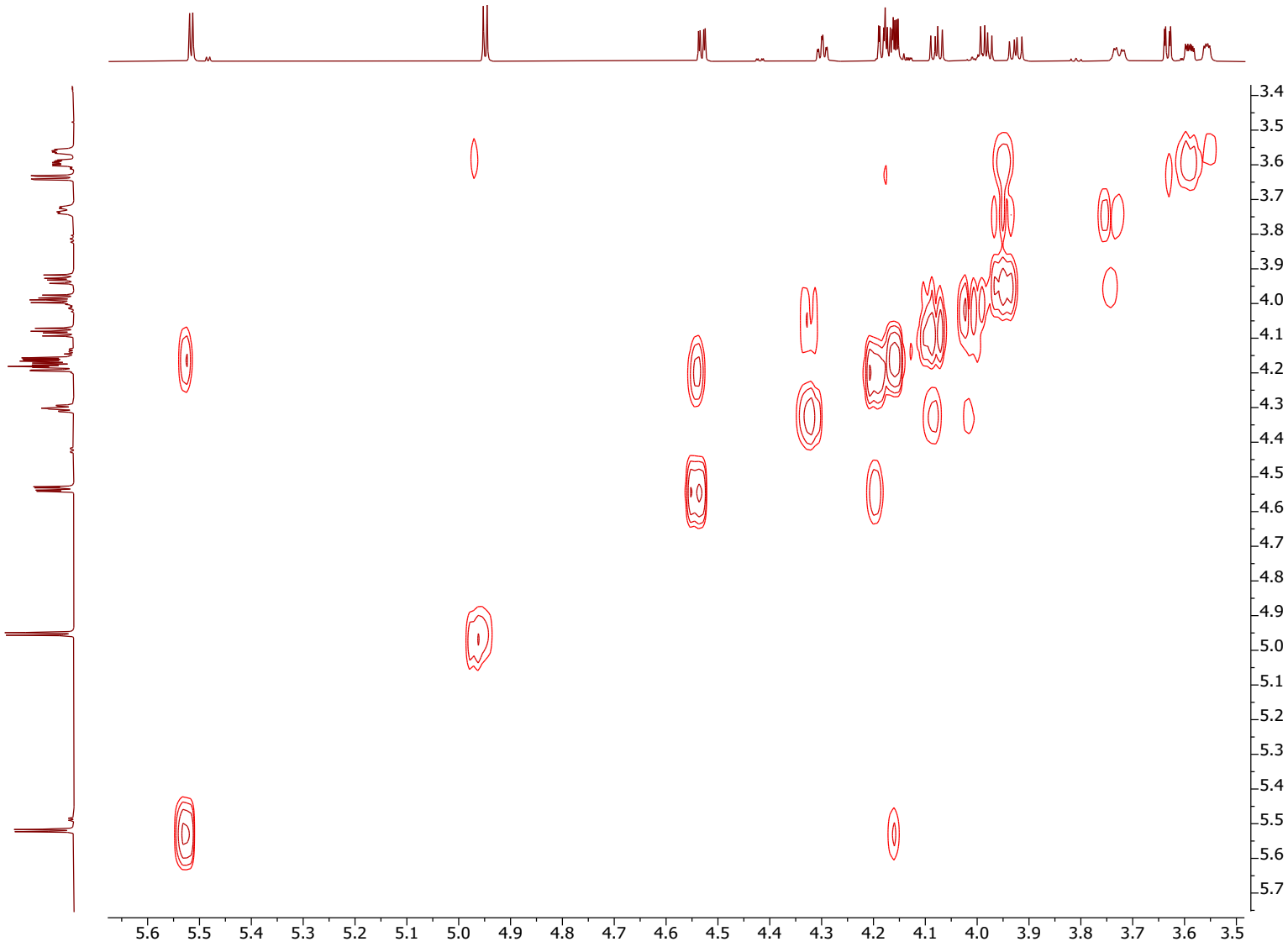
$^{13}C\{^{1}H\}$ NMR Spectrum of **177** (101 MHz, C_6D_6)



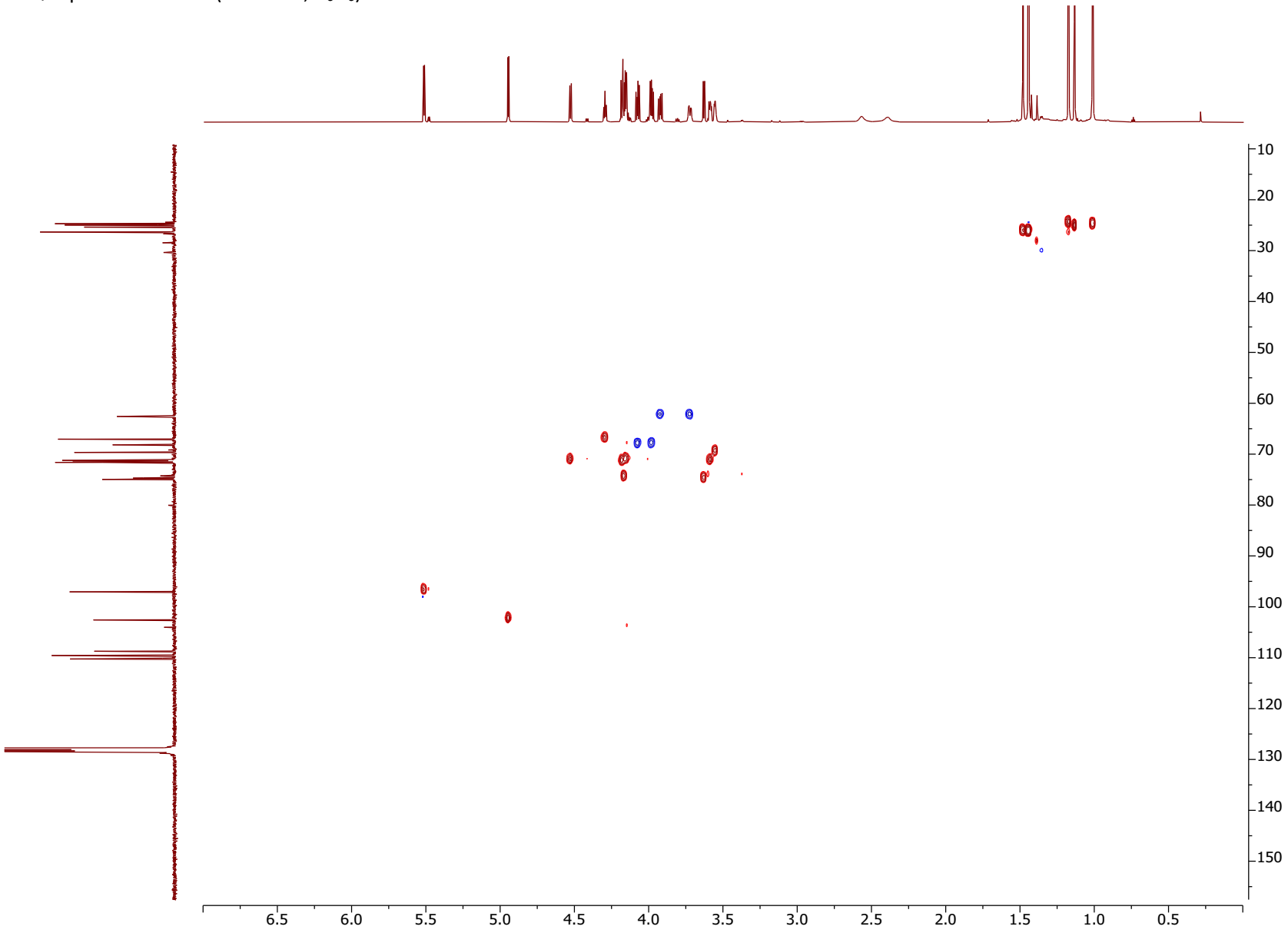
COSY spectrum of **177** (800 MHz, C_6D_6) – full



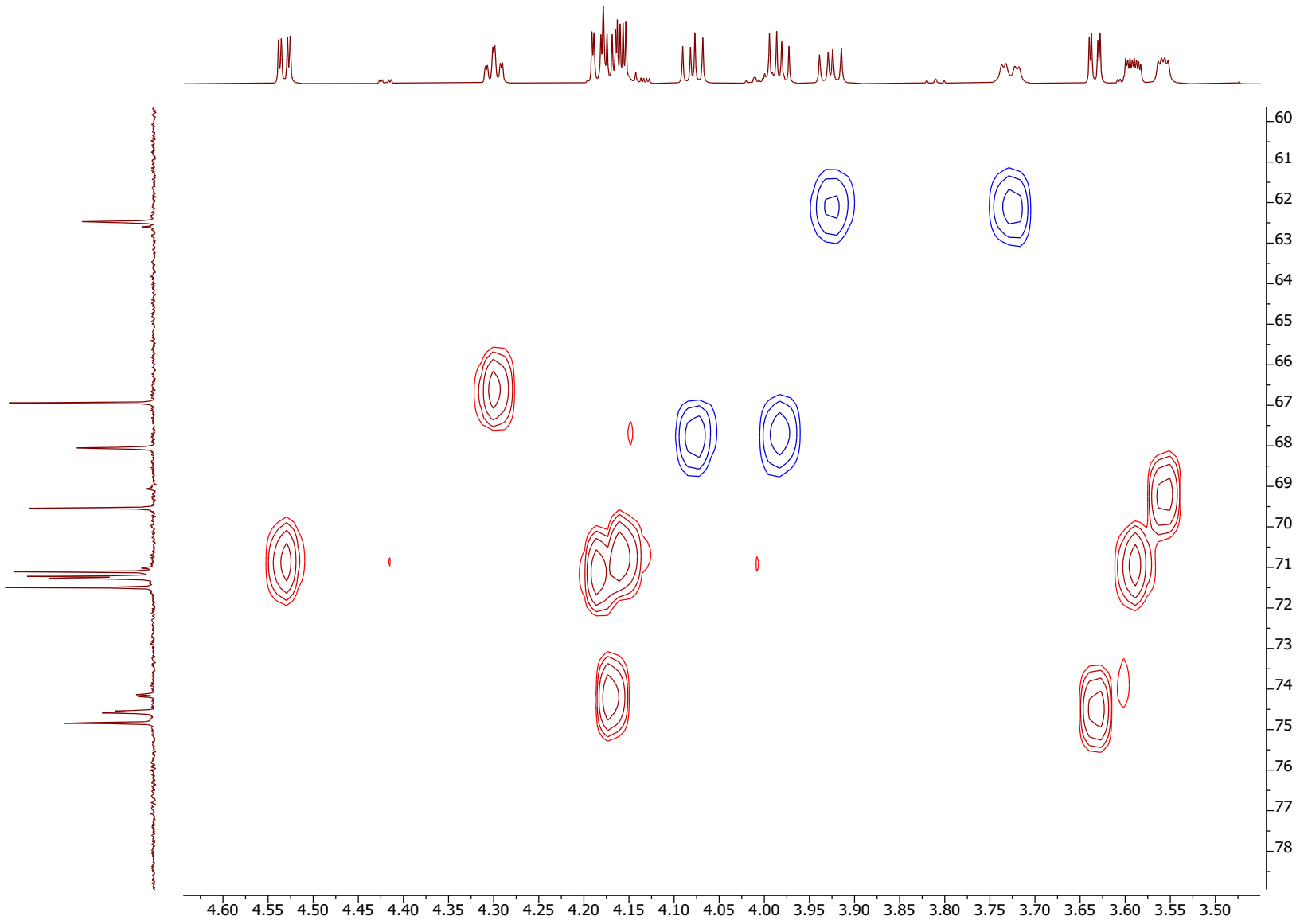
COSY spectrum of **177** (800 MHz, C_6D_6) – expansion



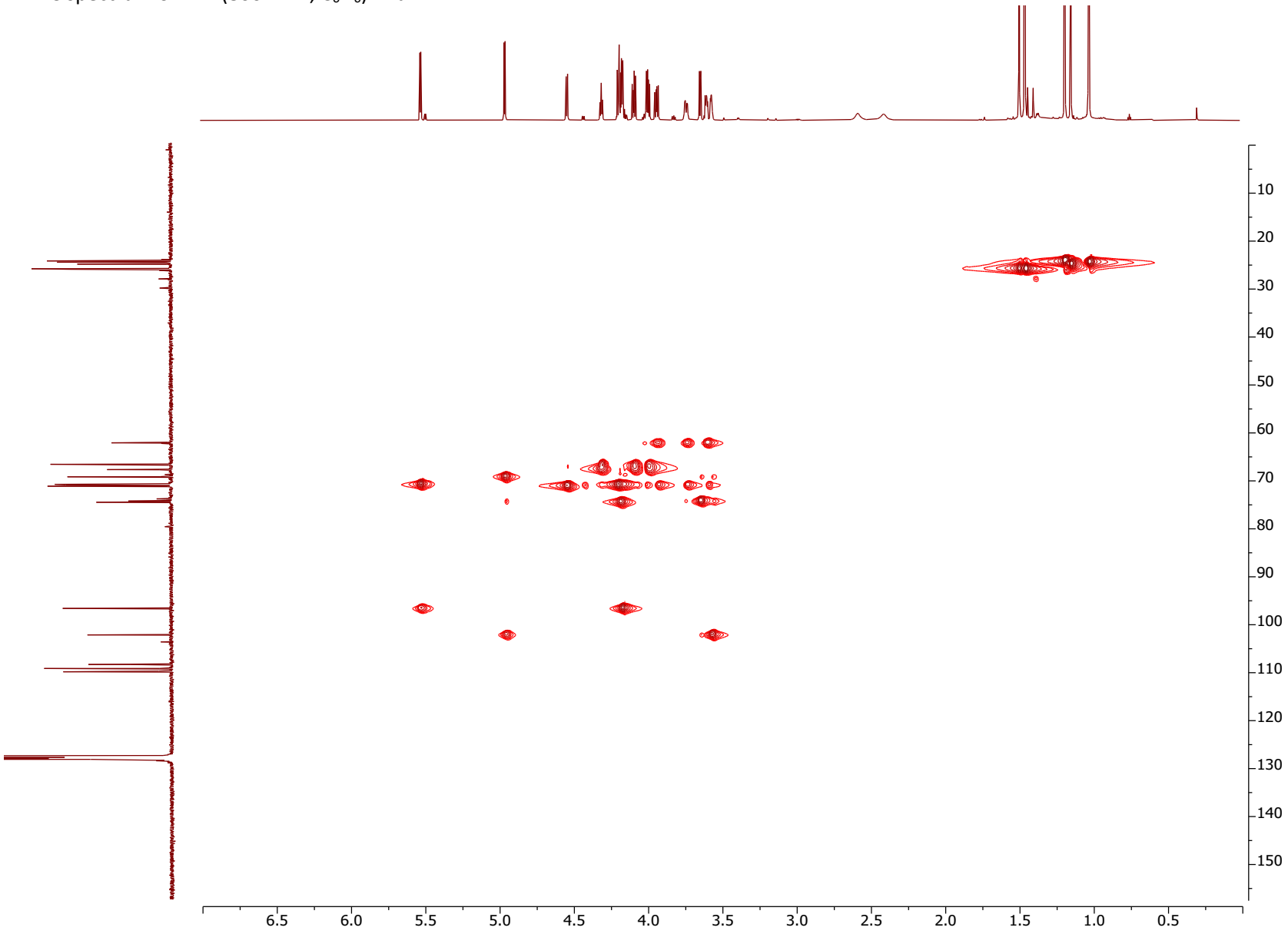
HSQC spectrum of **177** (800 MHz, C_6D_6) – full



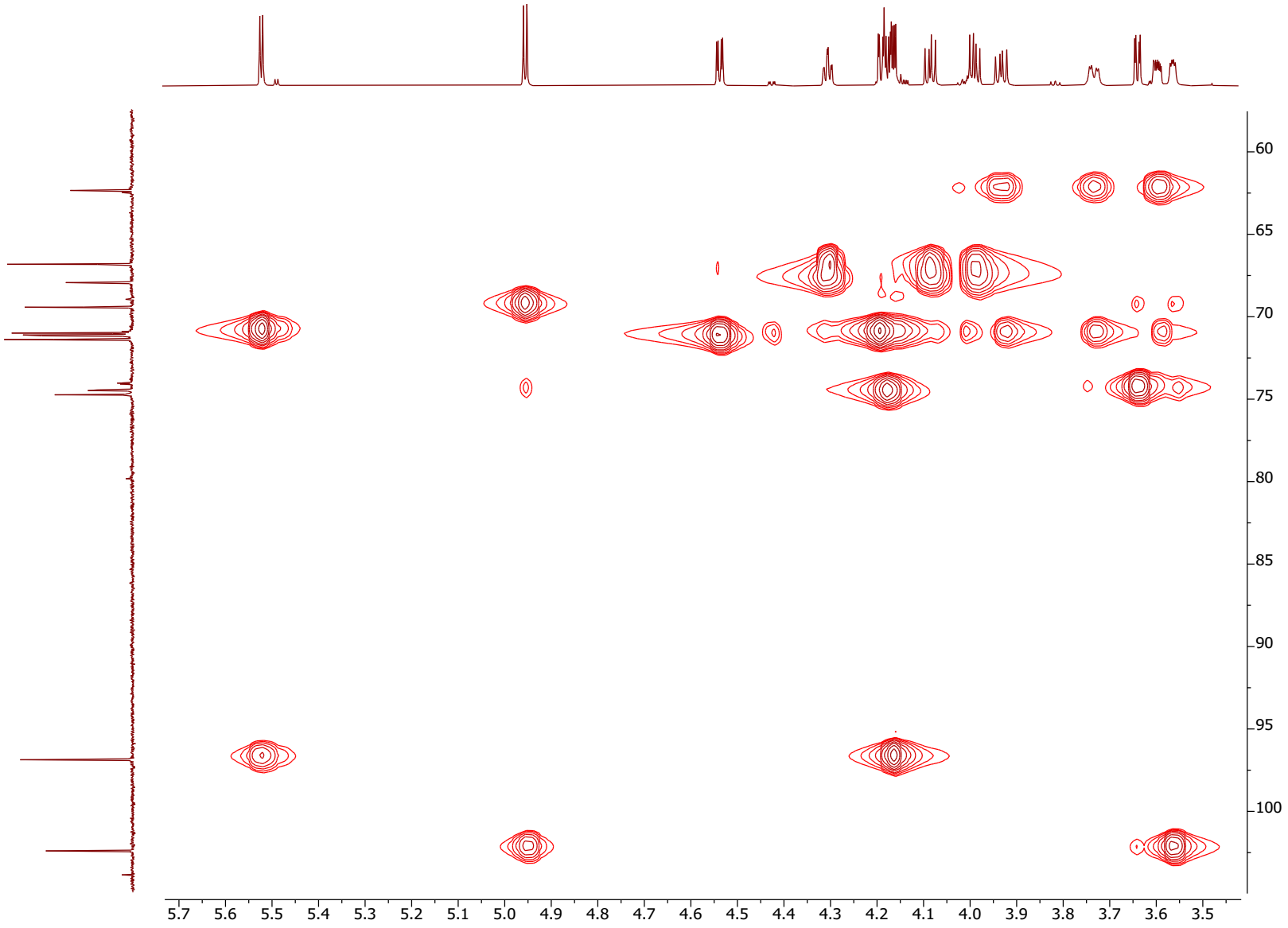
HSQC spectrum of **177** (800 MHz, C_6D_6) – expansion



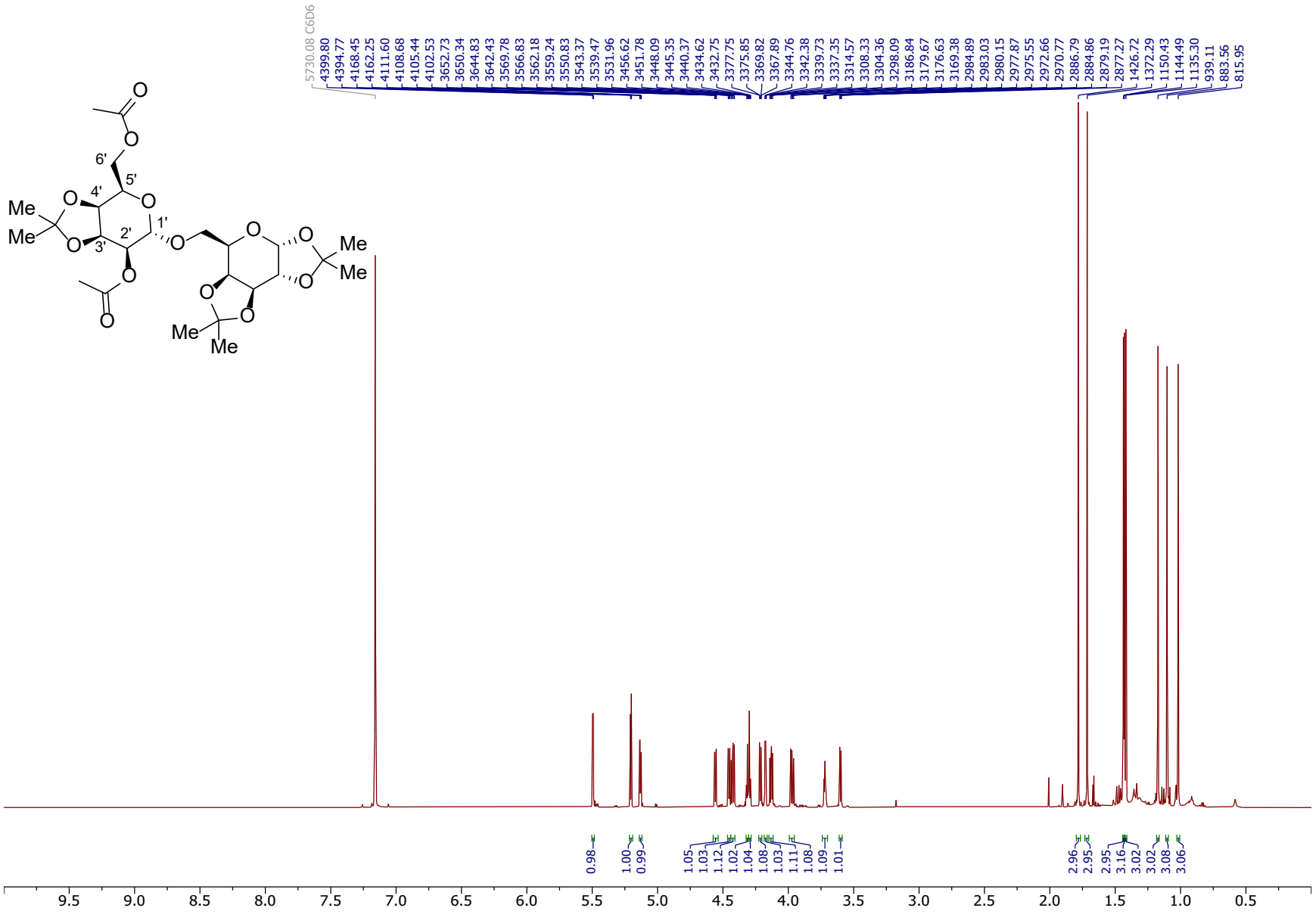
HMBC spectrum of **177** (800 MHz, C_6D_6) – full



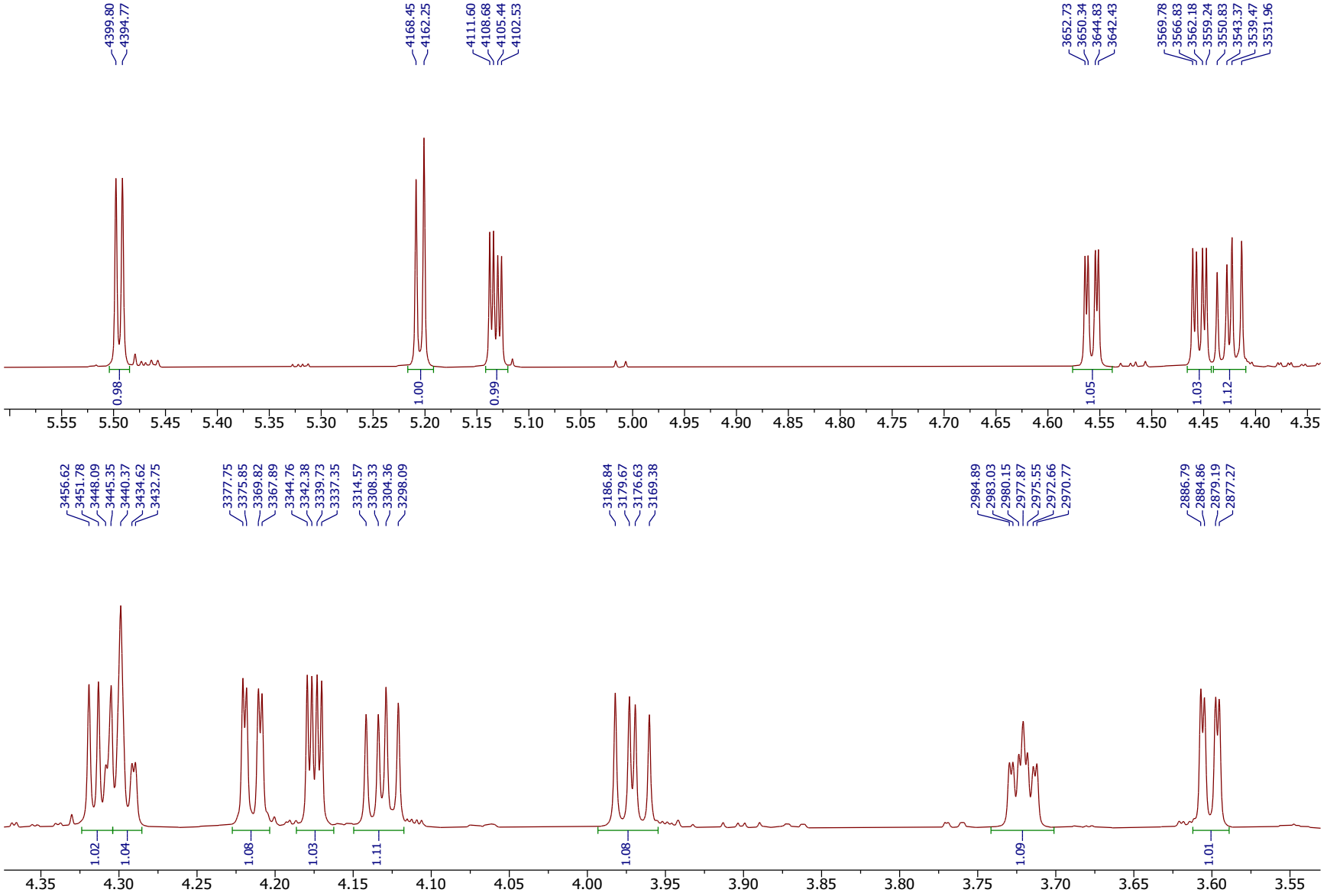
HMBC spectrum of **177** (800 MHz, C_6D_6) – expansion



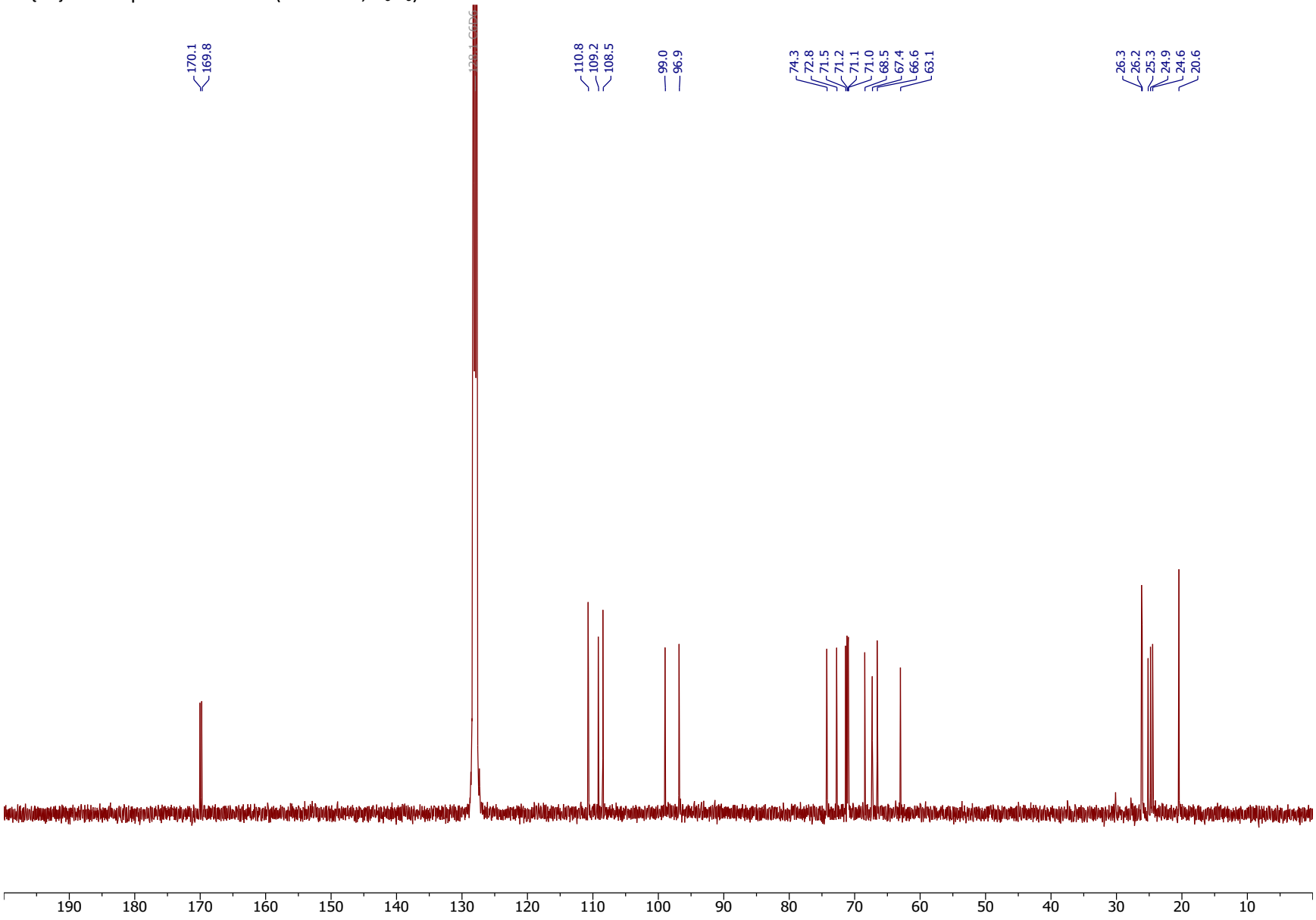
^{1}H NMR Spectrum of **178** (800 MHz, C_6D_6) – full



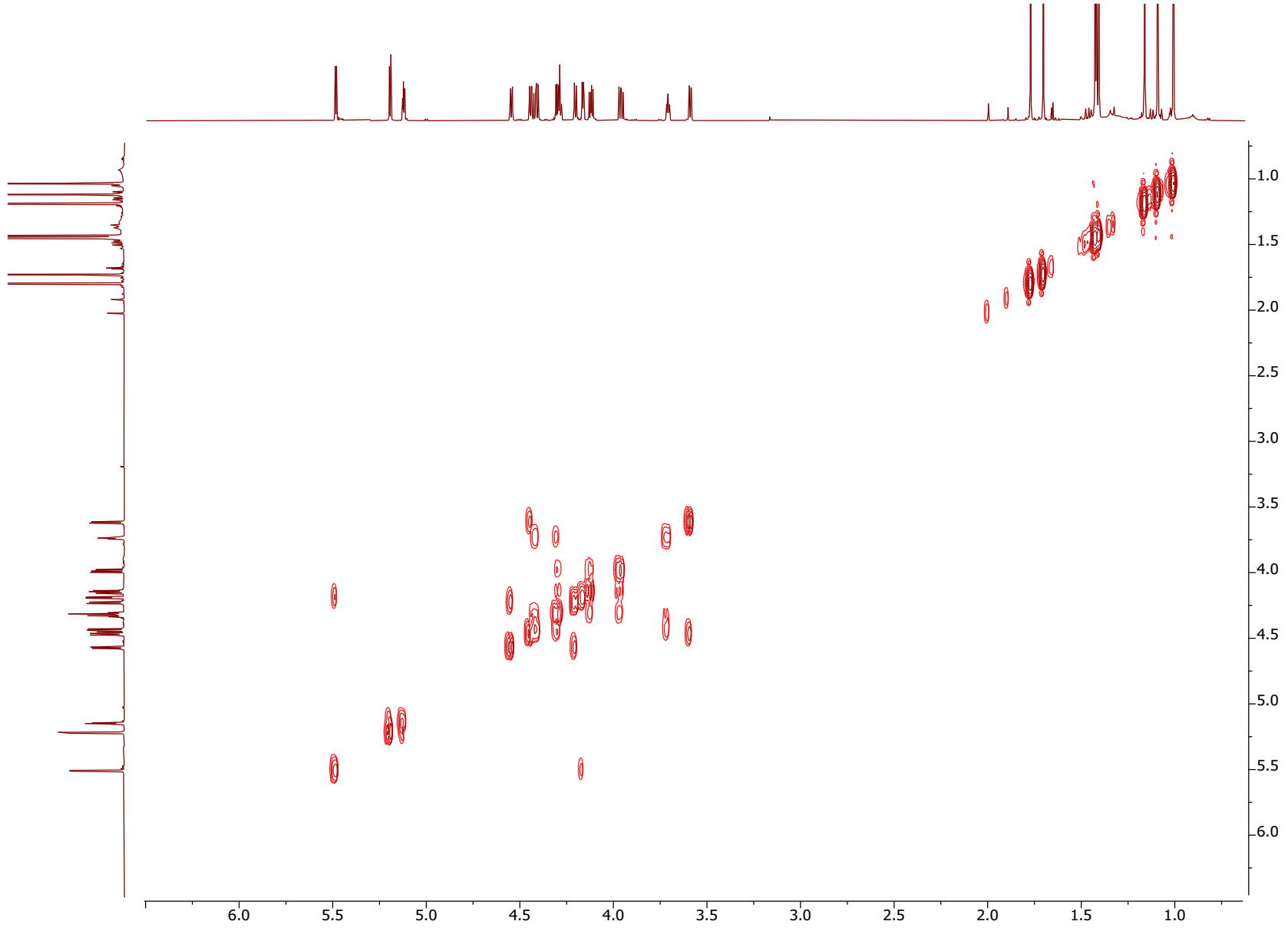
^{1}H NMR Spectrum of **178** (800 MHz, C_6D_6) – expansion



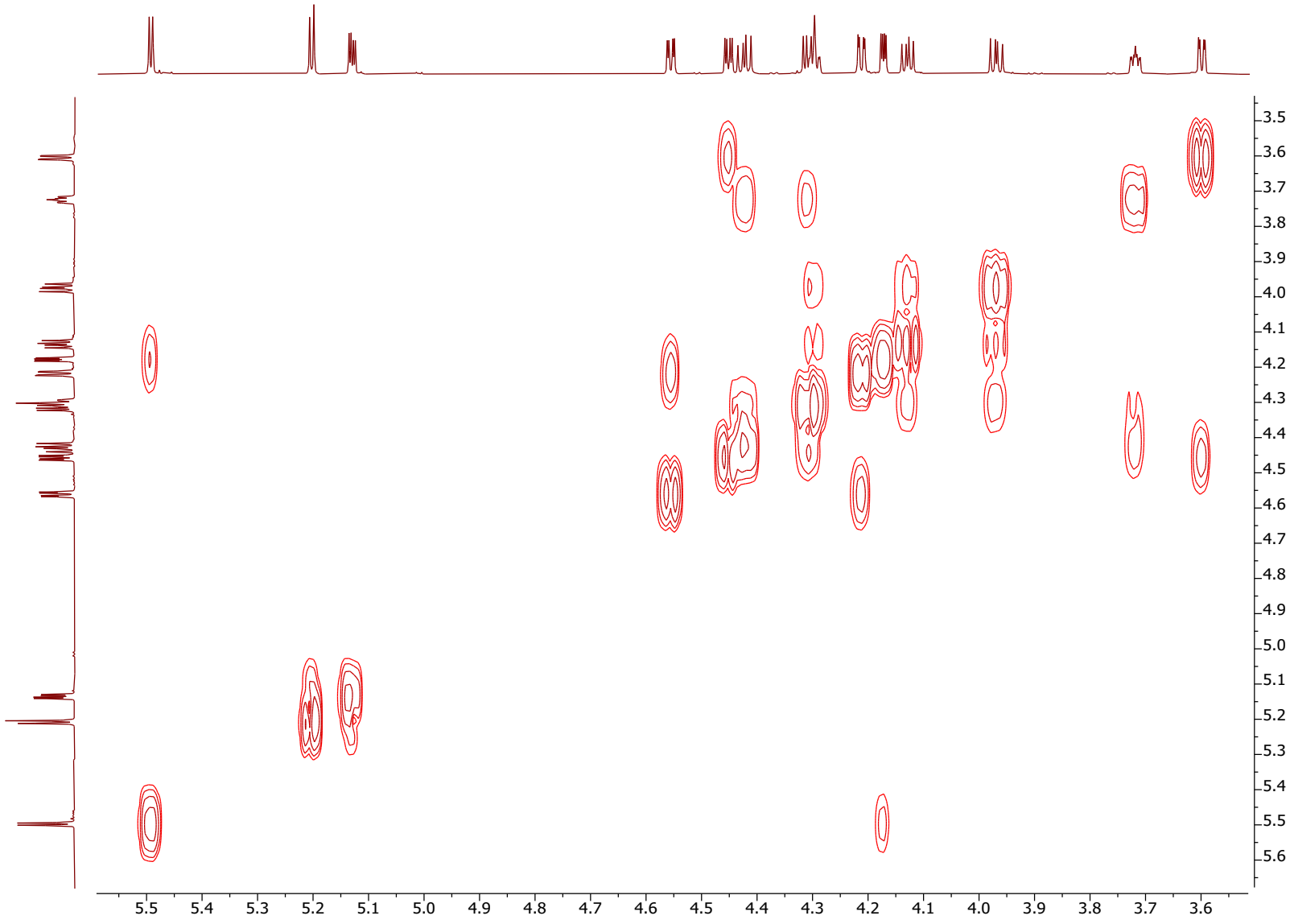
$^{13}C\{^{1}H\}$ NMR Spectrum of **178** (101 MHz, C_6D_6)



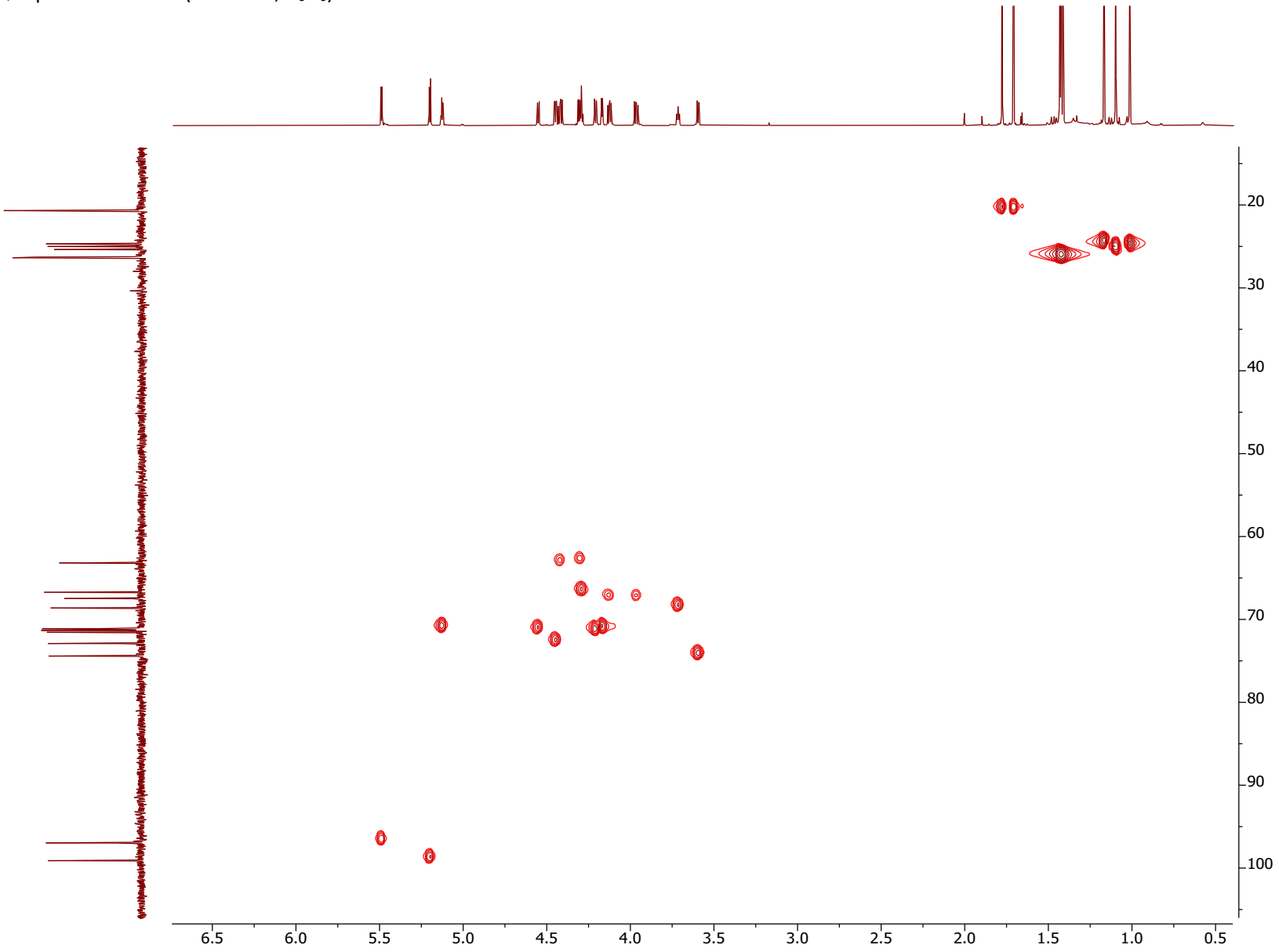
COSY spectrum of **178** (800 MHz, C_6D_6) – full



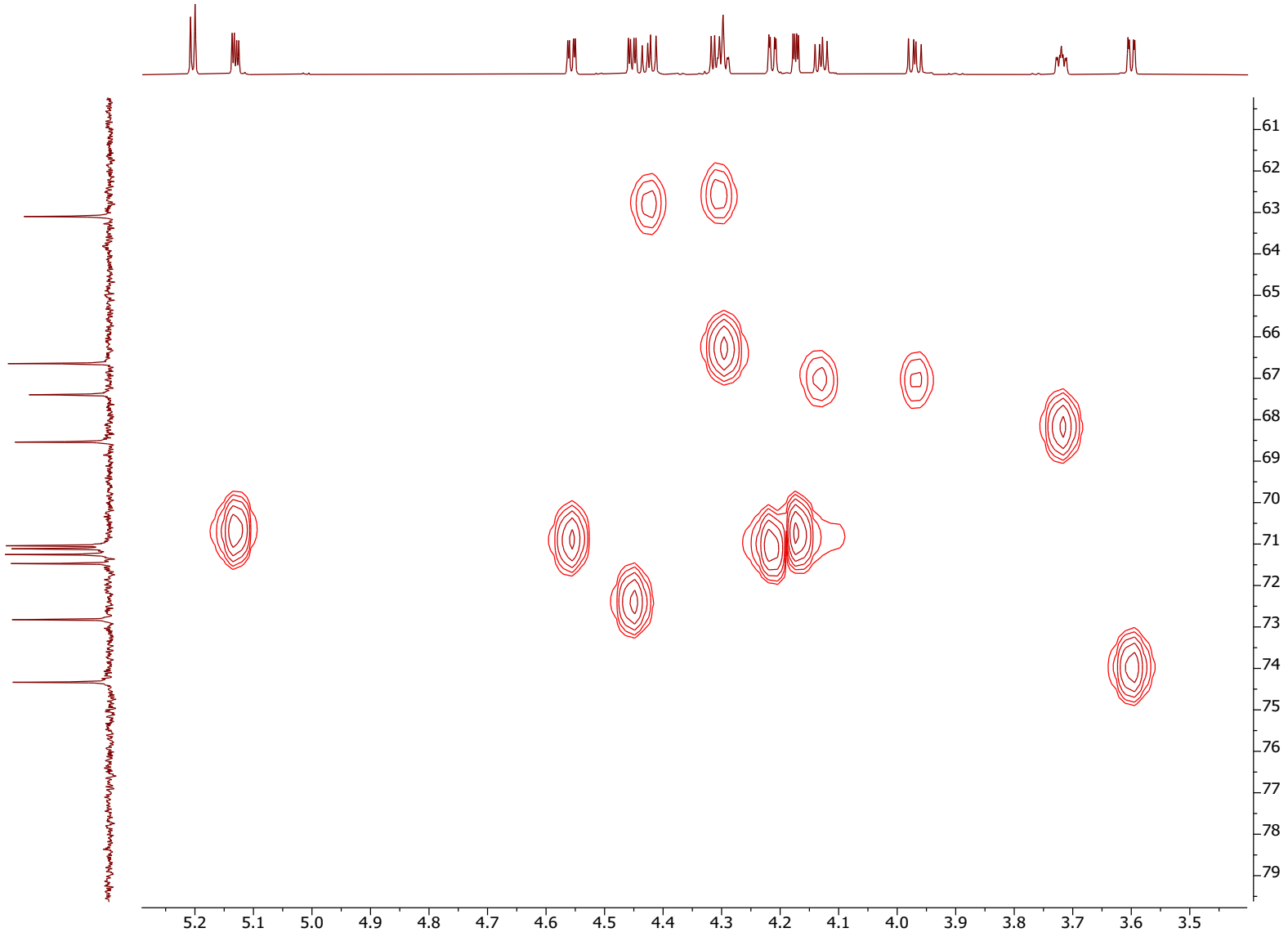
COSY spectrum of **178** (800 MHz, C_6D_6) – expansion



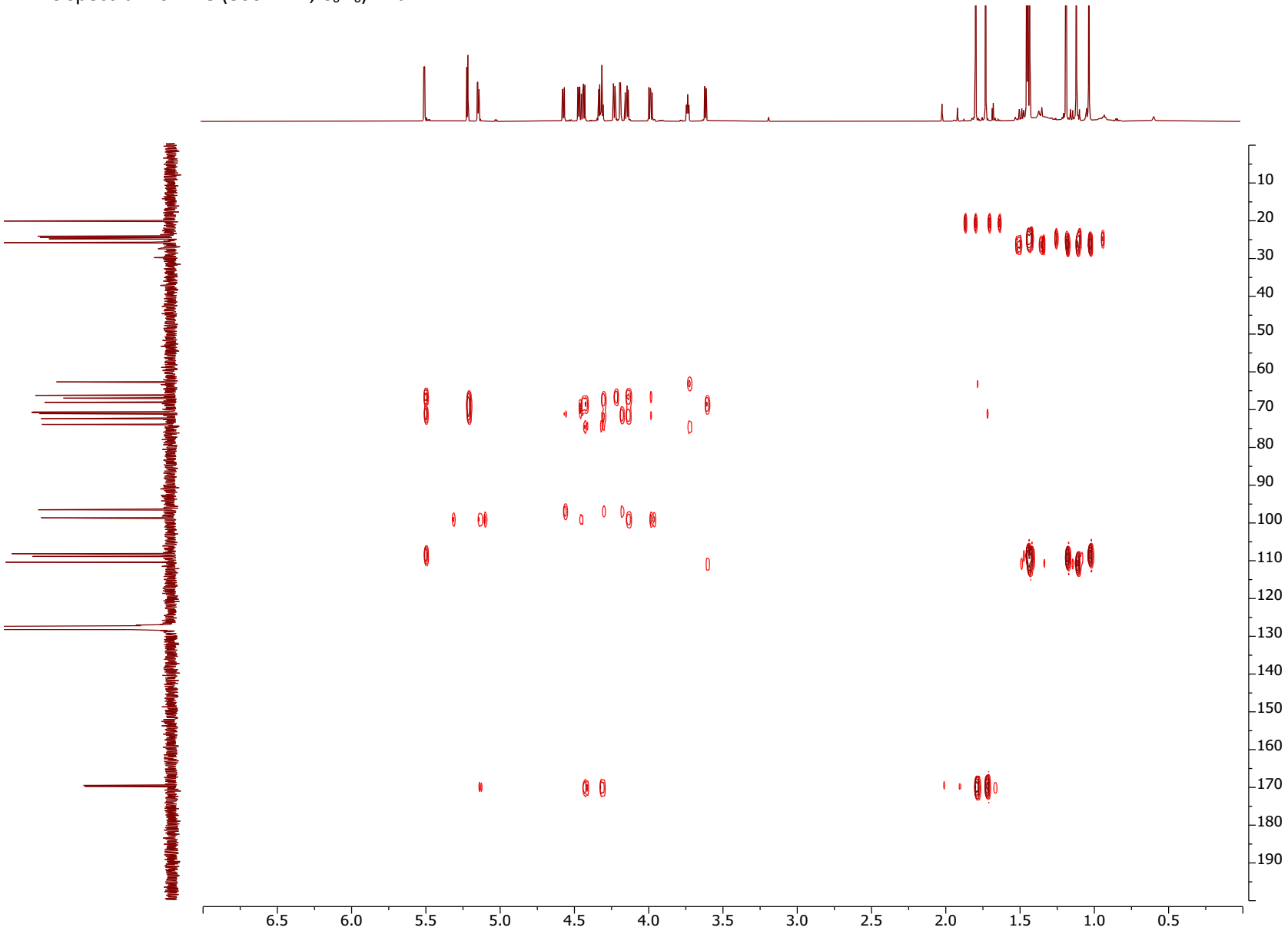
HSQC spectrum of **178** (800 MHz, C_6D_6) – full



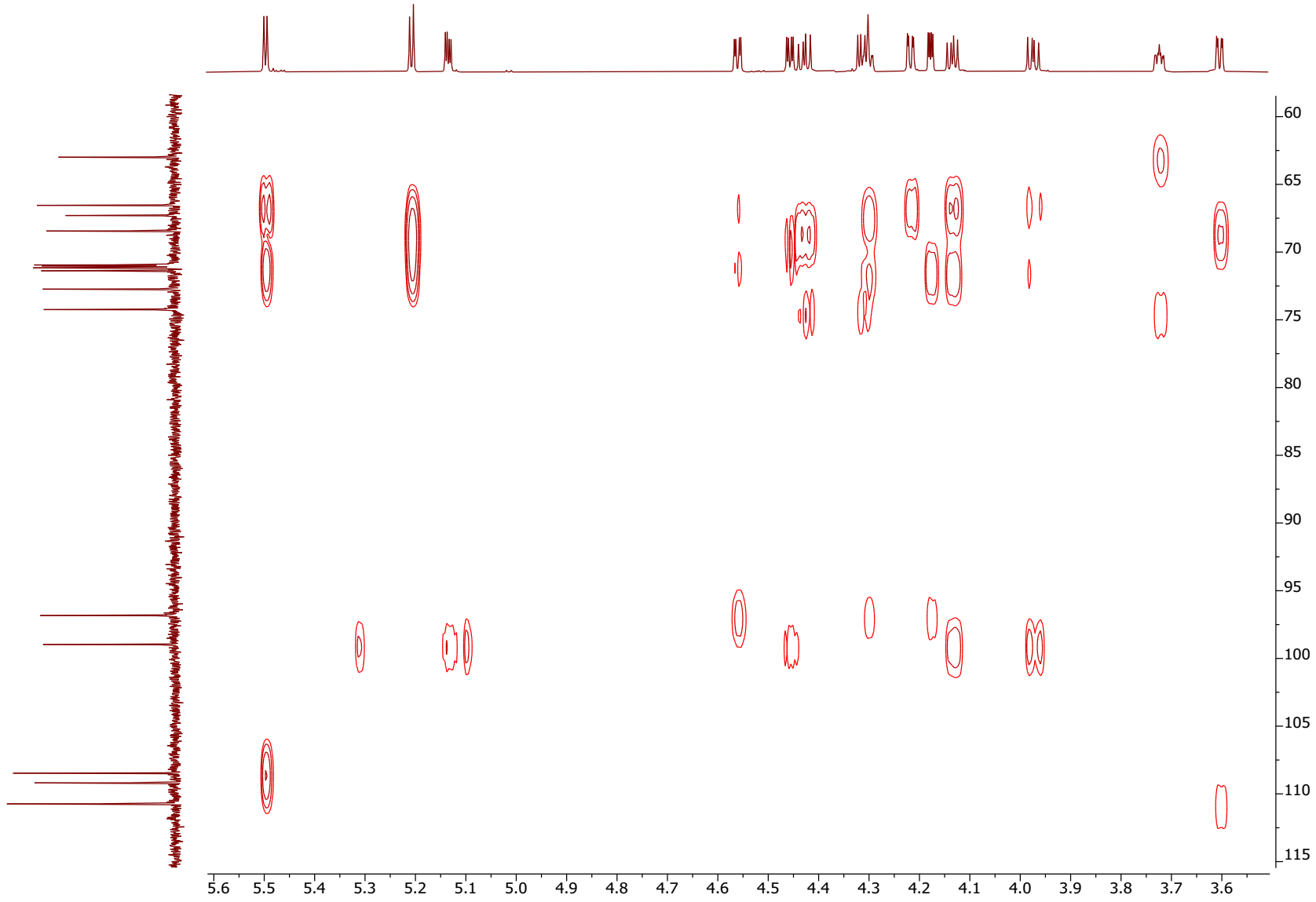
HSQC spectrum of **178** (800 MHz, C_6D_6) – expansion



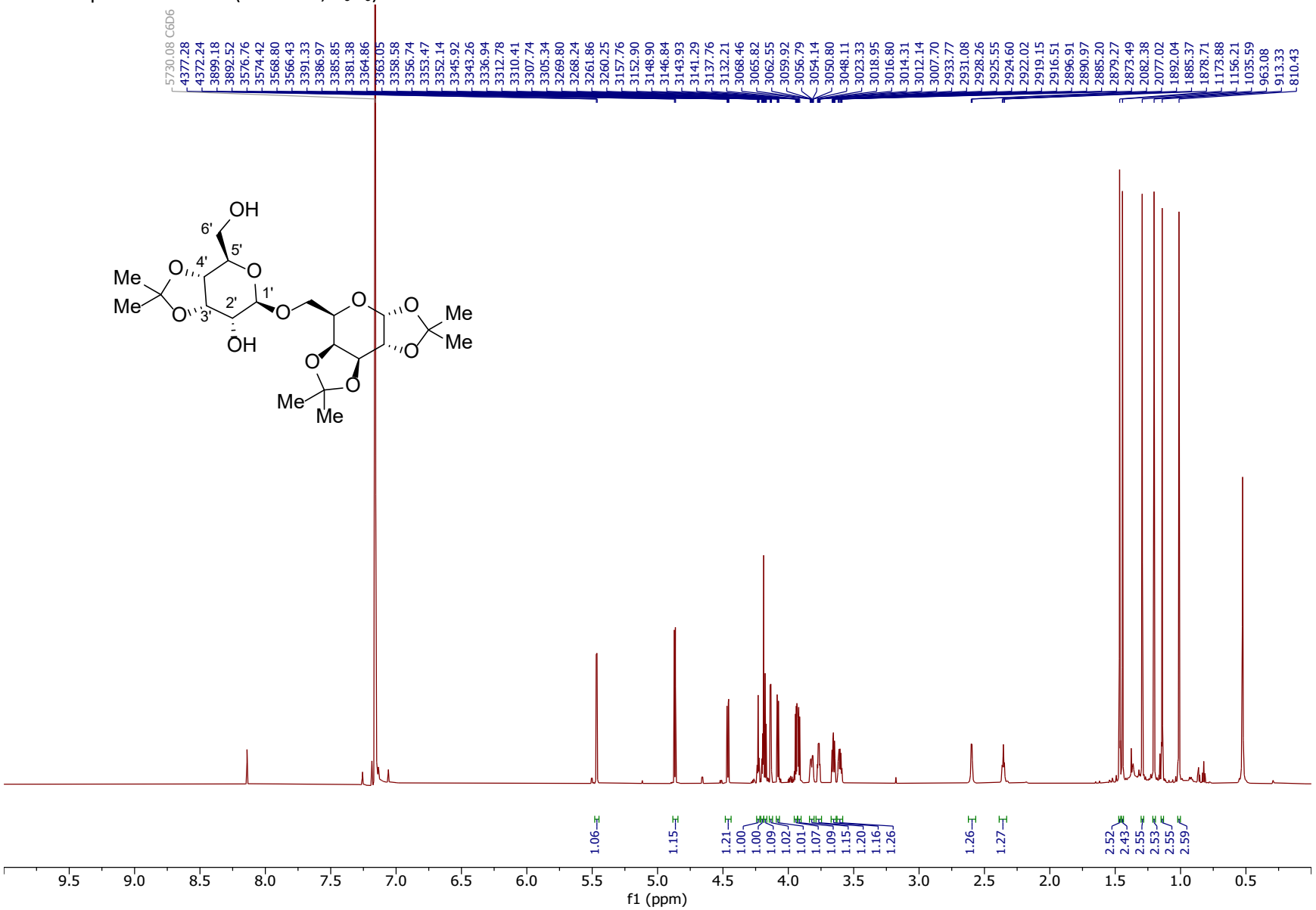
HMBC spectrum of **178** (800 MHz, C_6D_6) – full



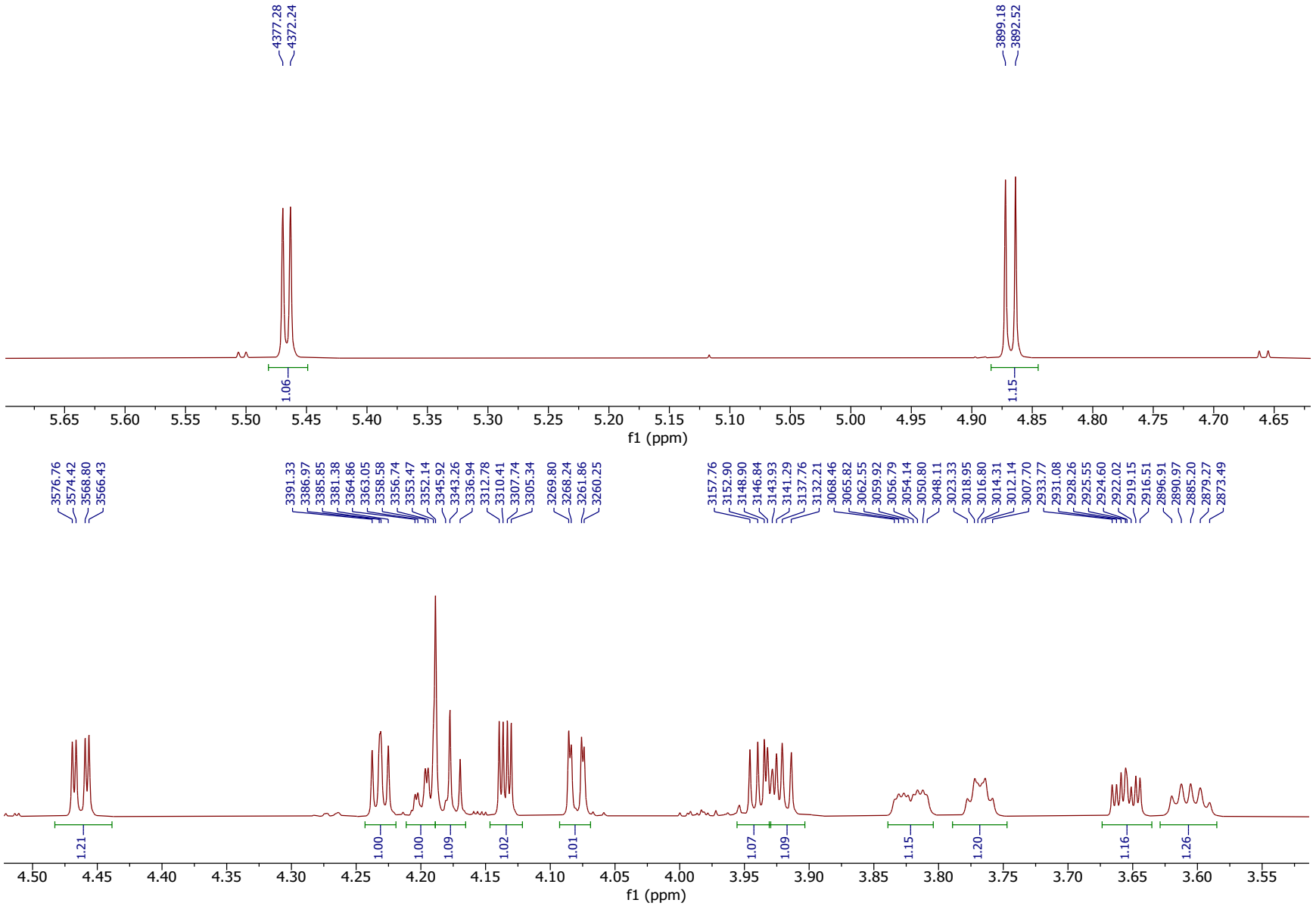
HMBC spectrum of **178** (800 MHz, C_6D_6) – expansion



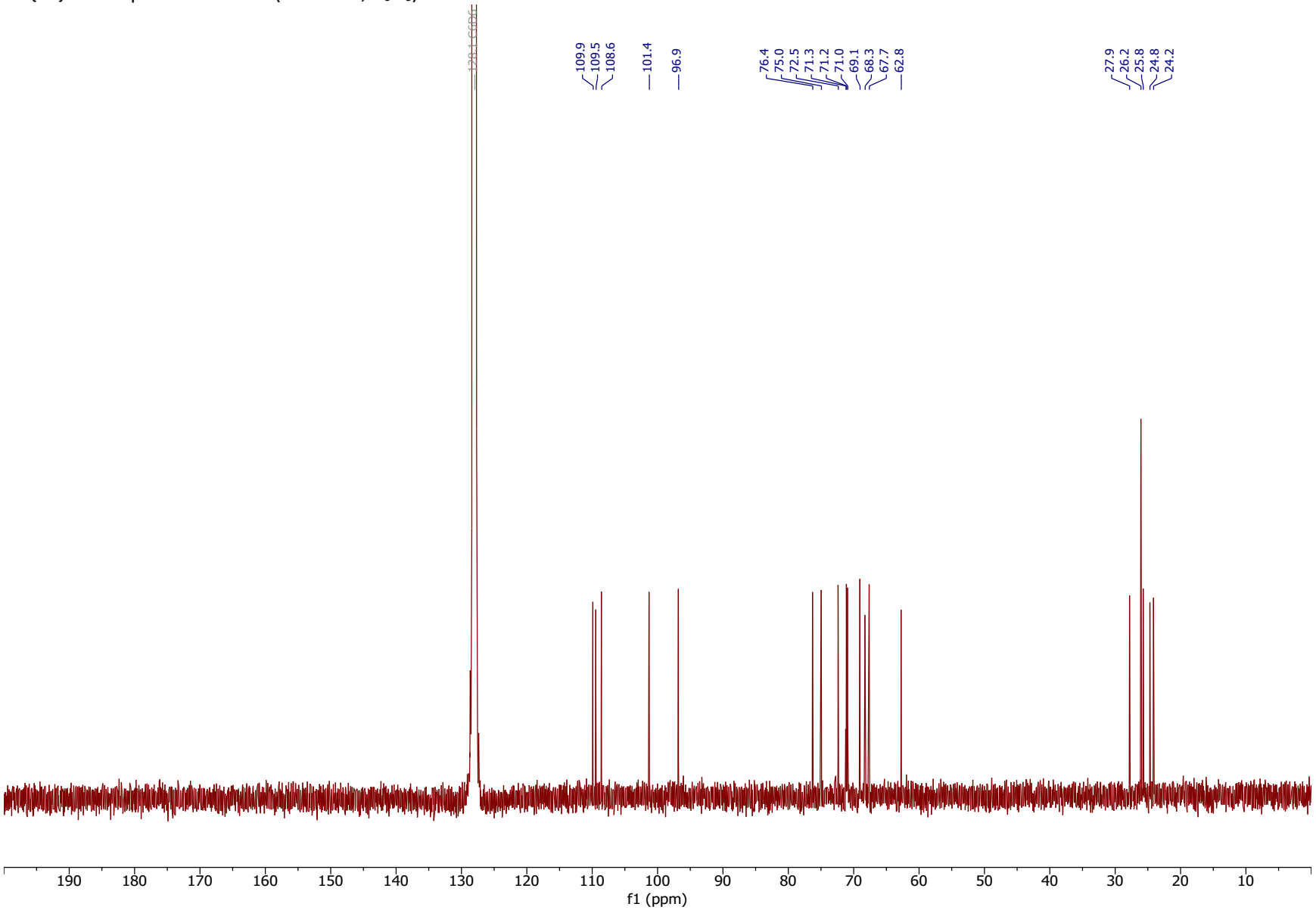
^{1}H NMR Spectrum of **183** (800 MHz, C_6D_6) – full



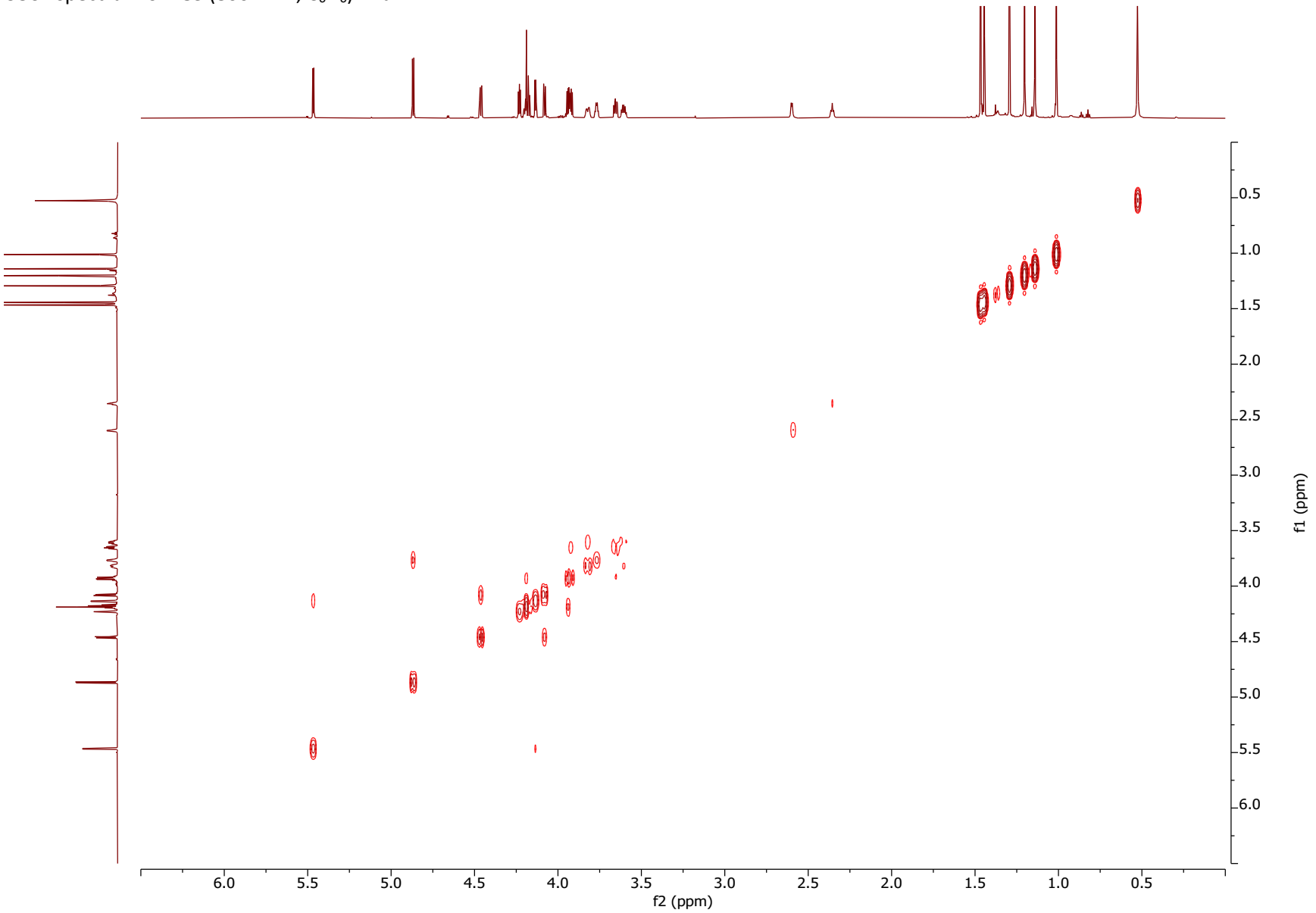
^{1}H NMR Spectrum of **183** (800 MHz, C_6D_6) – expansion



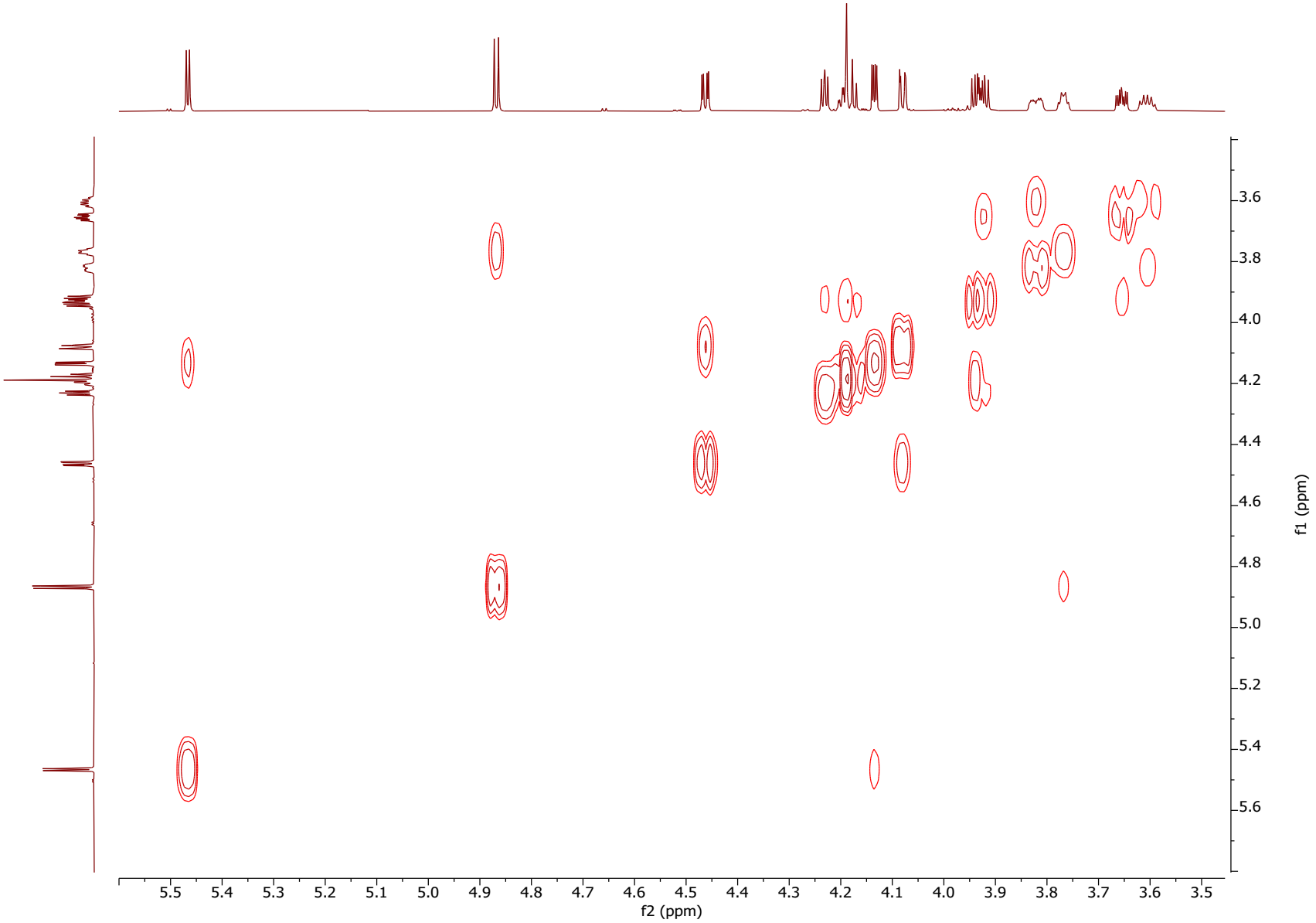
$^{13}C\{^{1}H\}$ NMR Spectrum of **183** (101 MHz, C_6D_6)



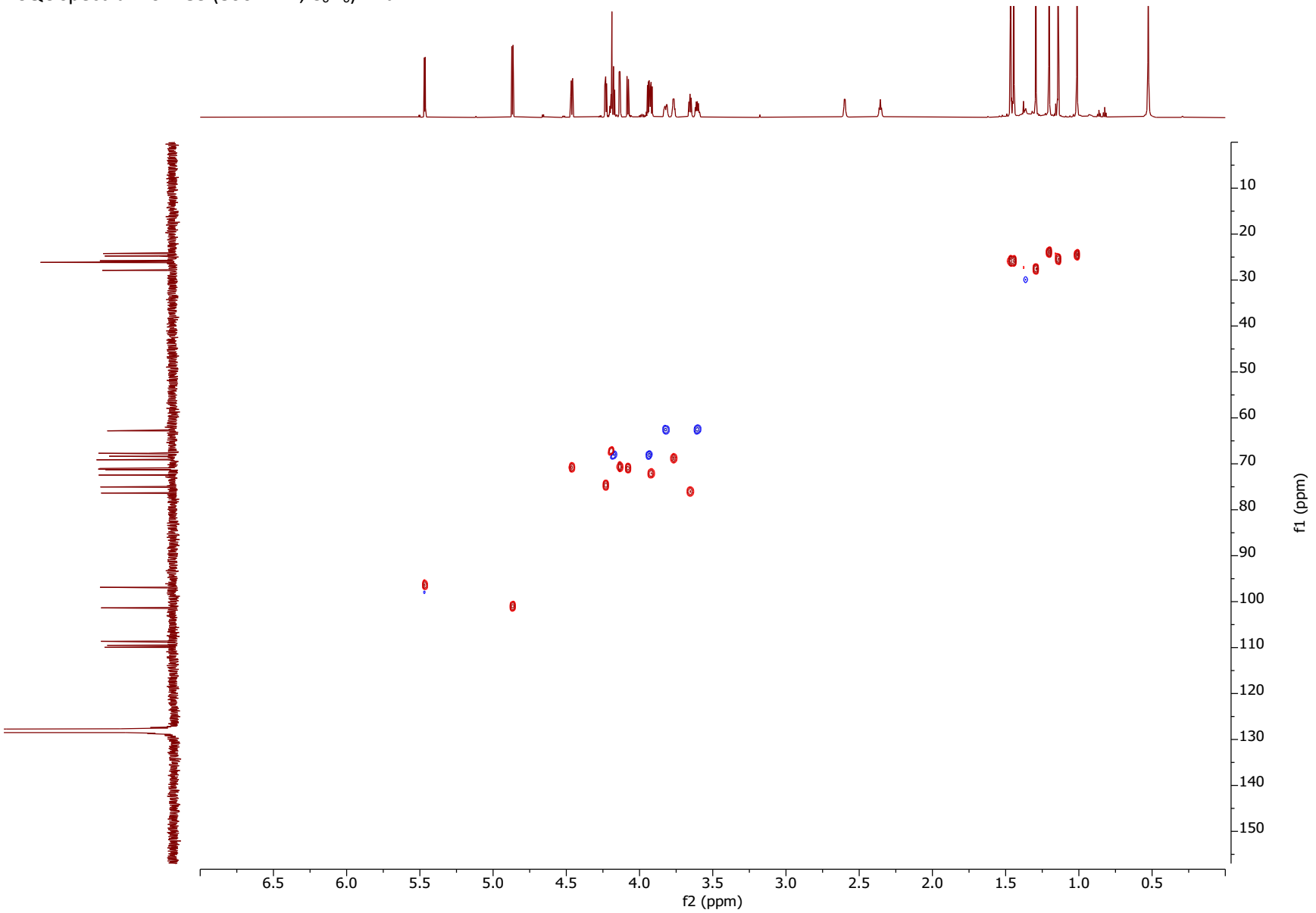
COSY spectrum of **183** (800 MHz, C_6D_6) – full



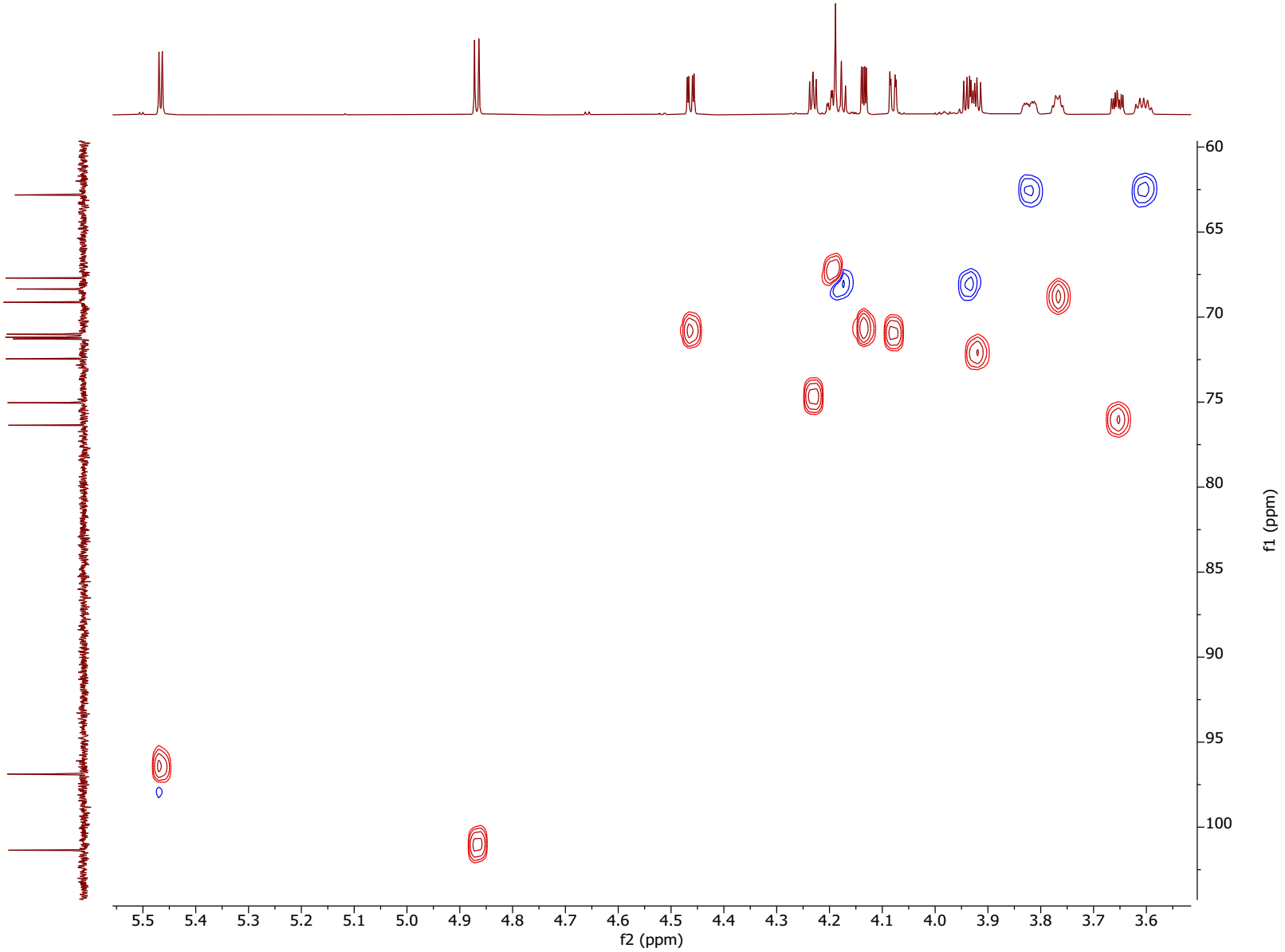
COSY spectrum of **183** (800 MHz, C_6D_6) – expansion



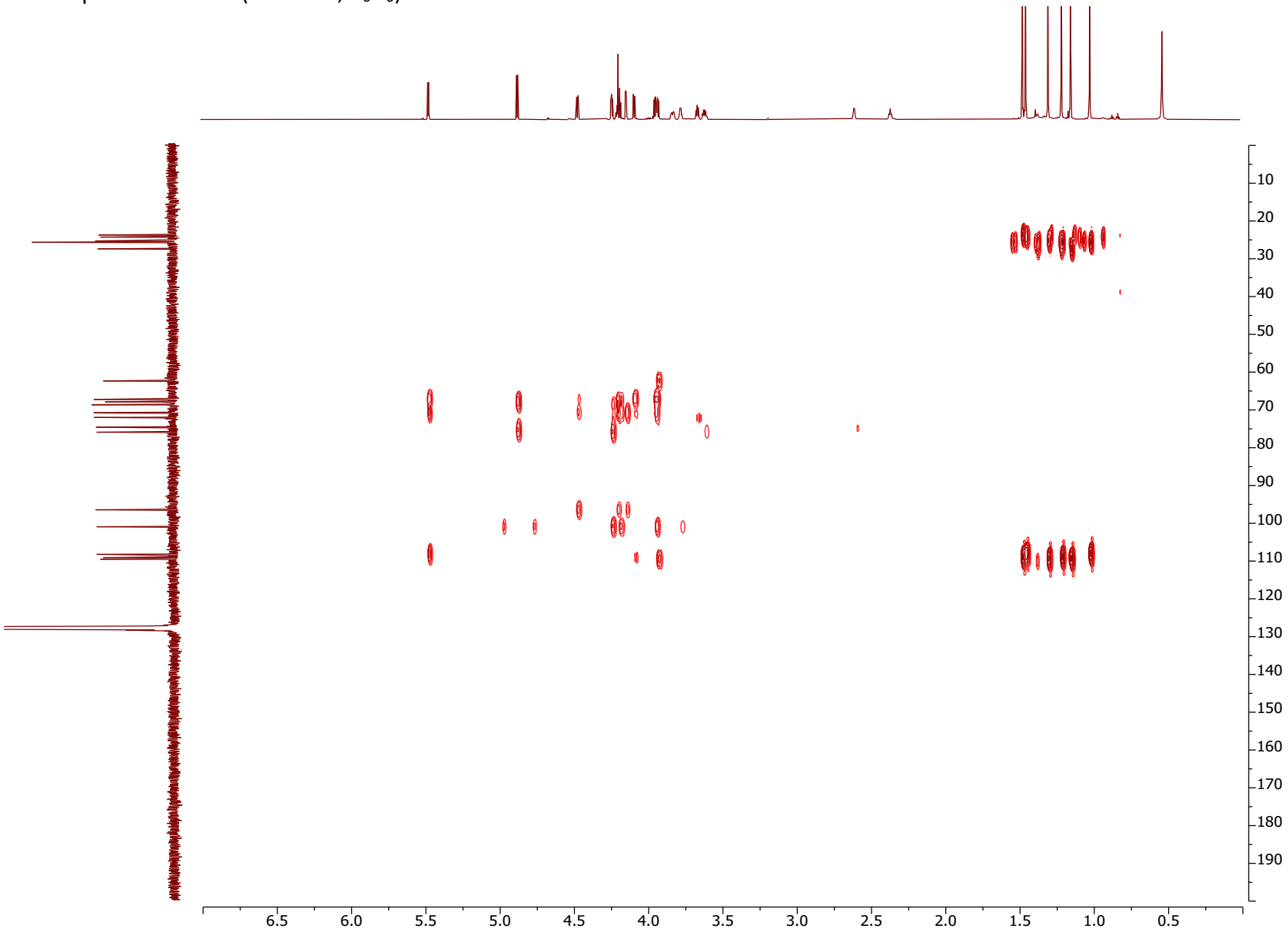
HSQC spectrum of **183** (800 MHz, C_6D_6) – full



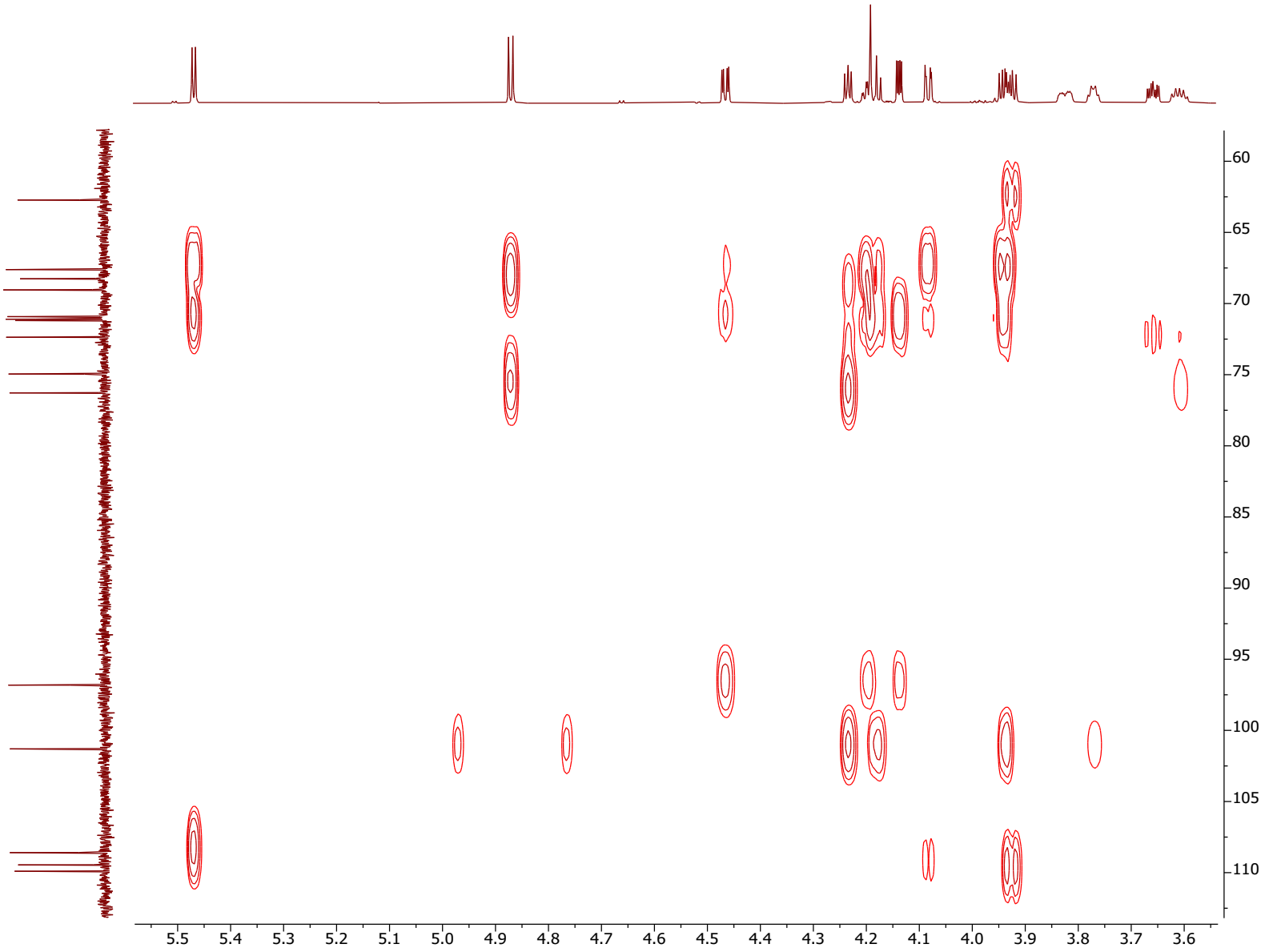
HSQC spectrum of **183** (800 MHz, C_6D_6) – expansion



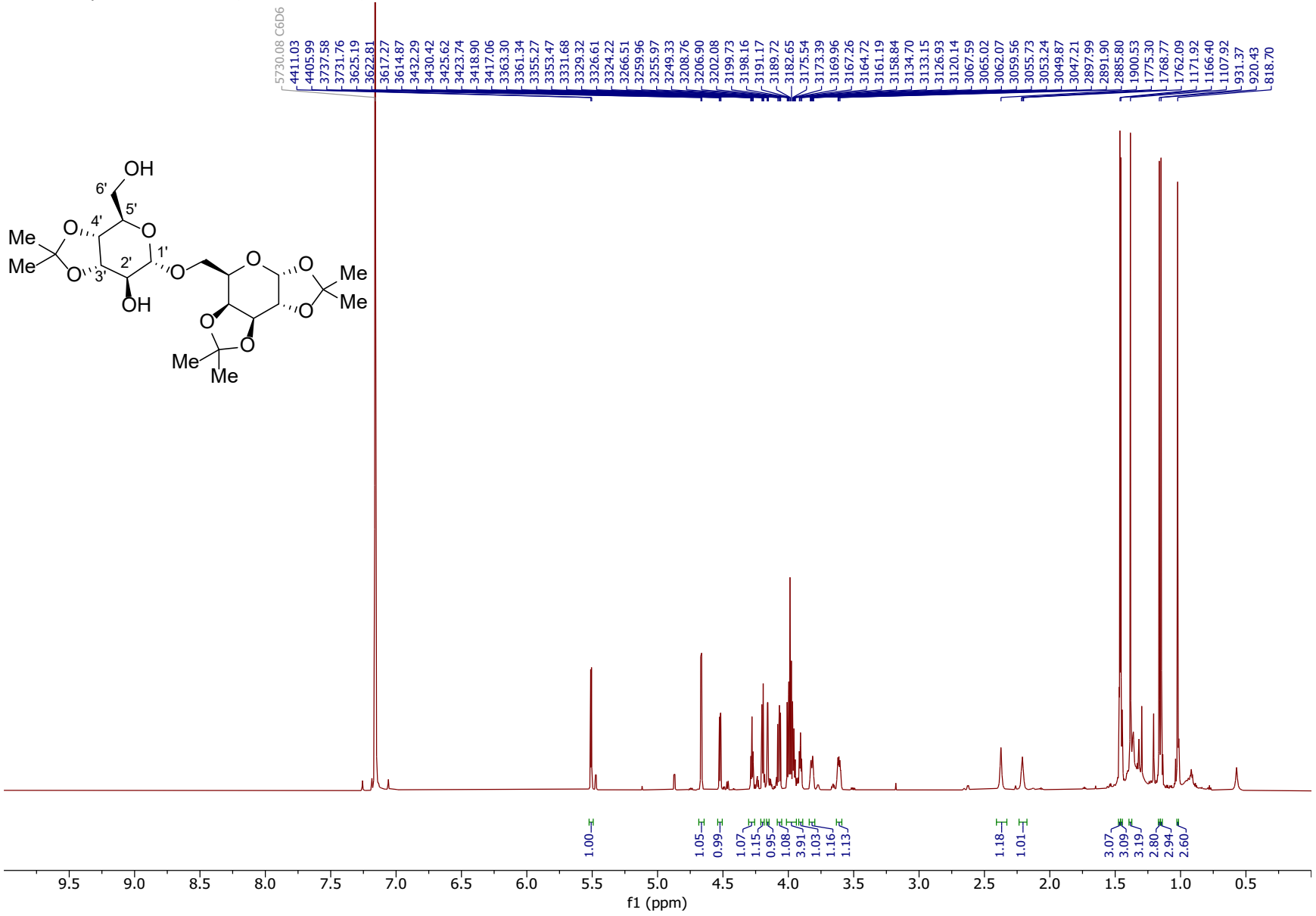
HMBC spectrum of **183** (600 MHz, C_6D_6) – full



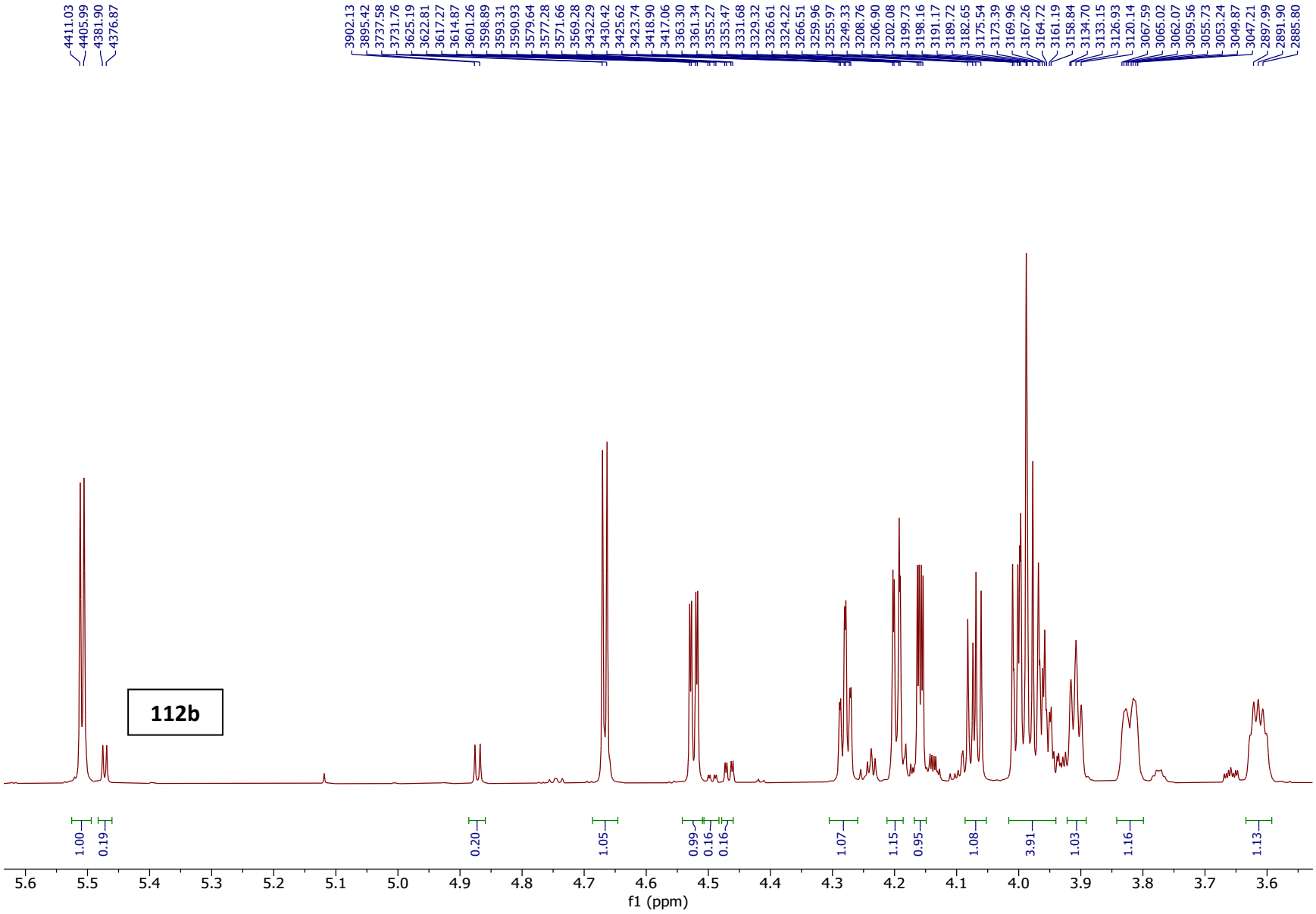
HMBC spectrum of **183** (600 MHz, C_6D_6) – expansion



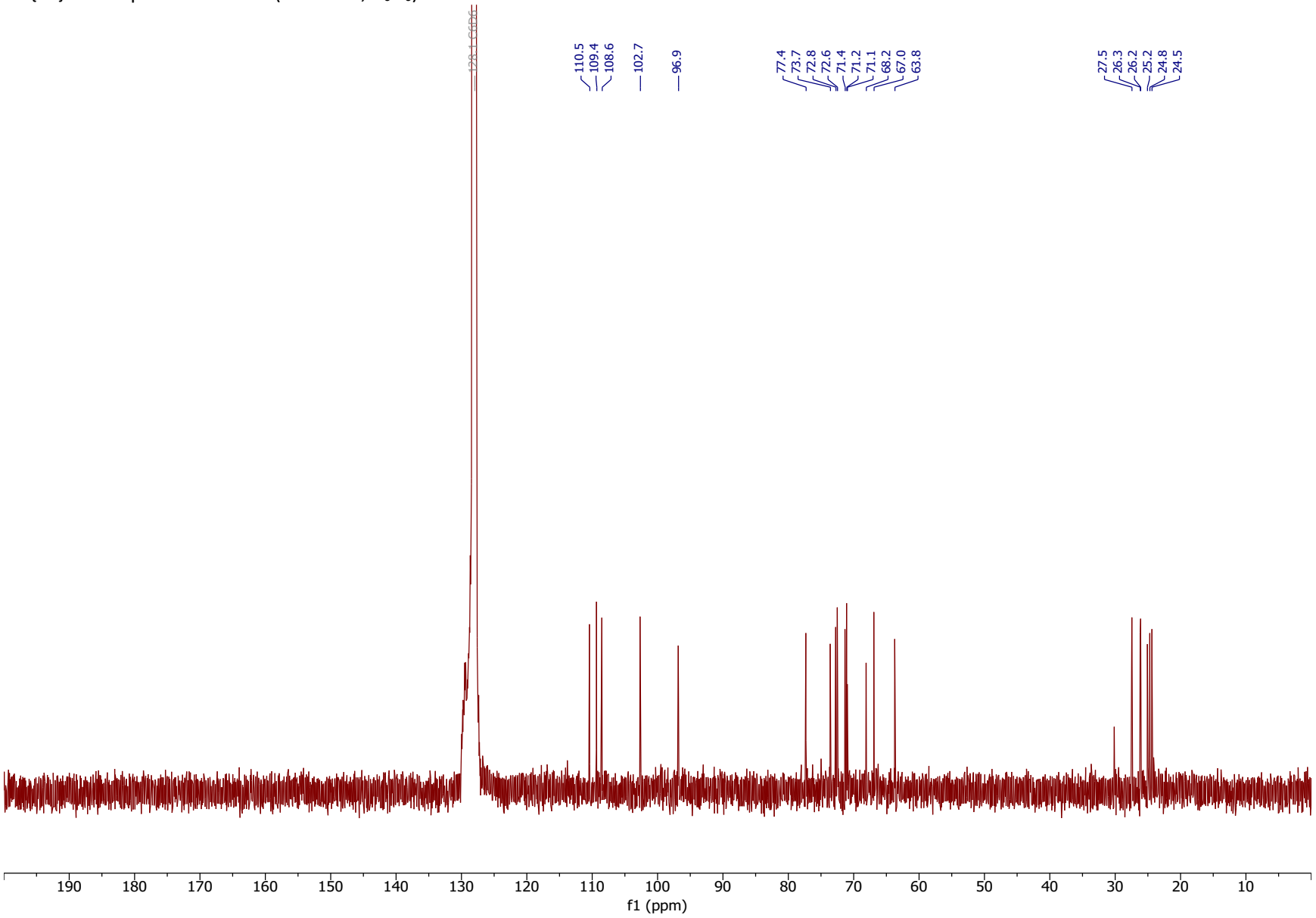
^{1}H NMR Spectrum of **184** (800 MHz, $_{6}D_{6}$)



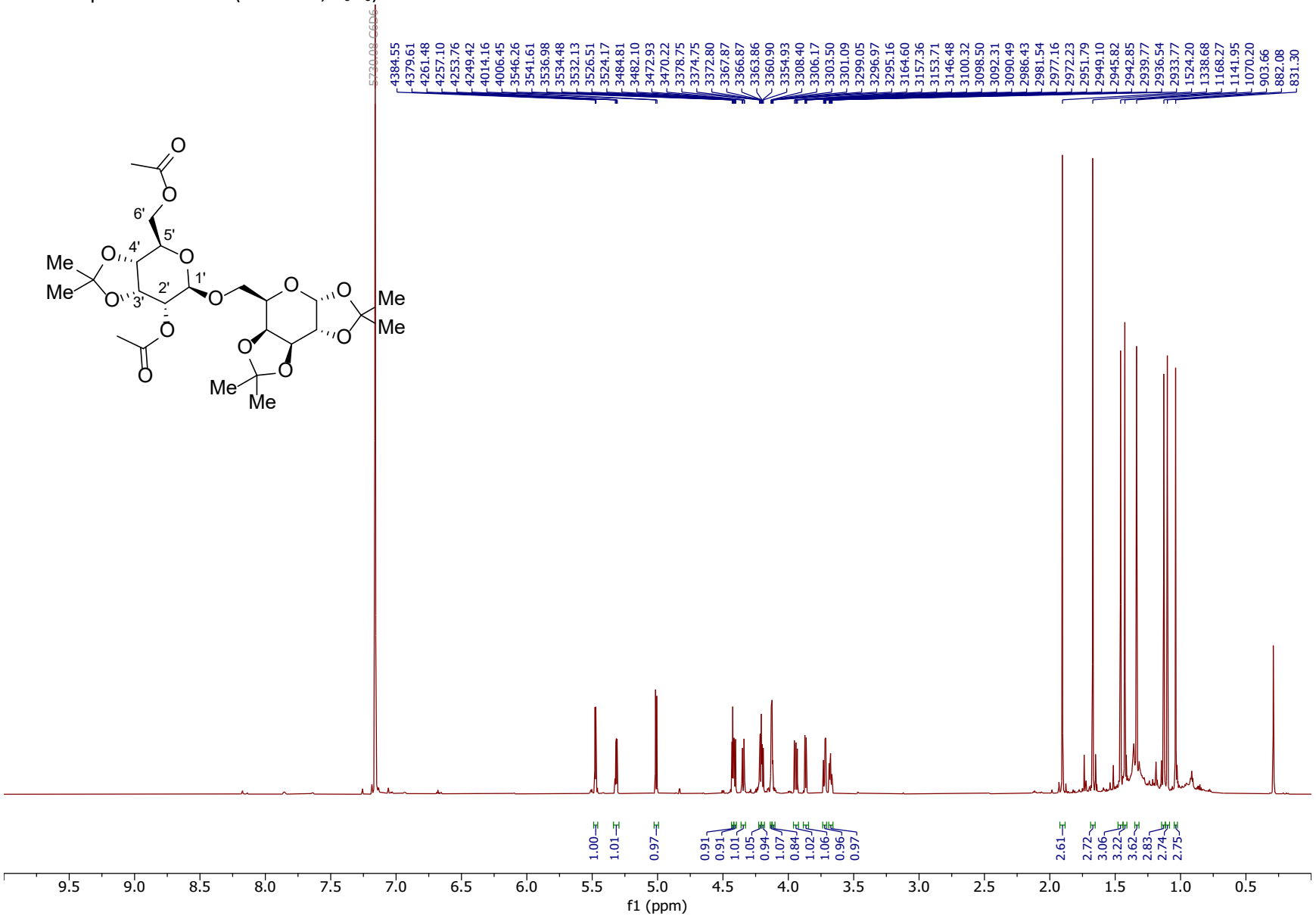
^{1}H NMR Spectrum of **184** (800 MHz, $_{6}D_{6}$) – expansion



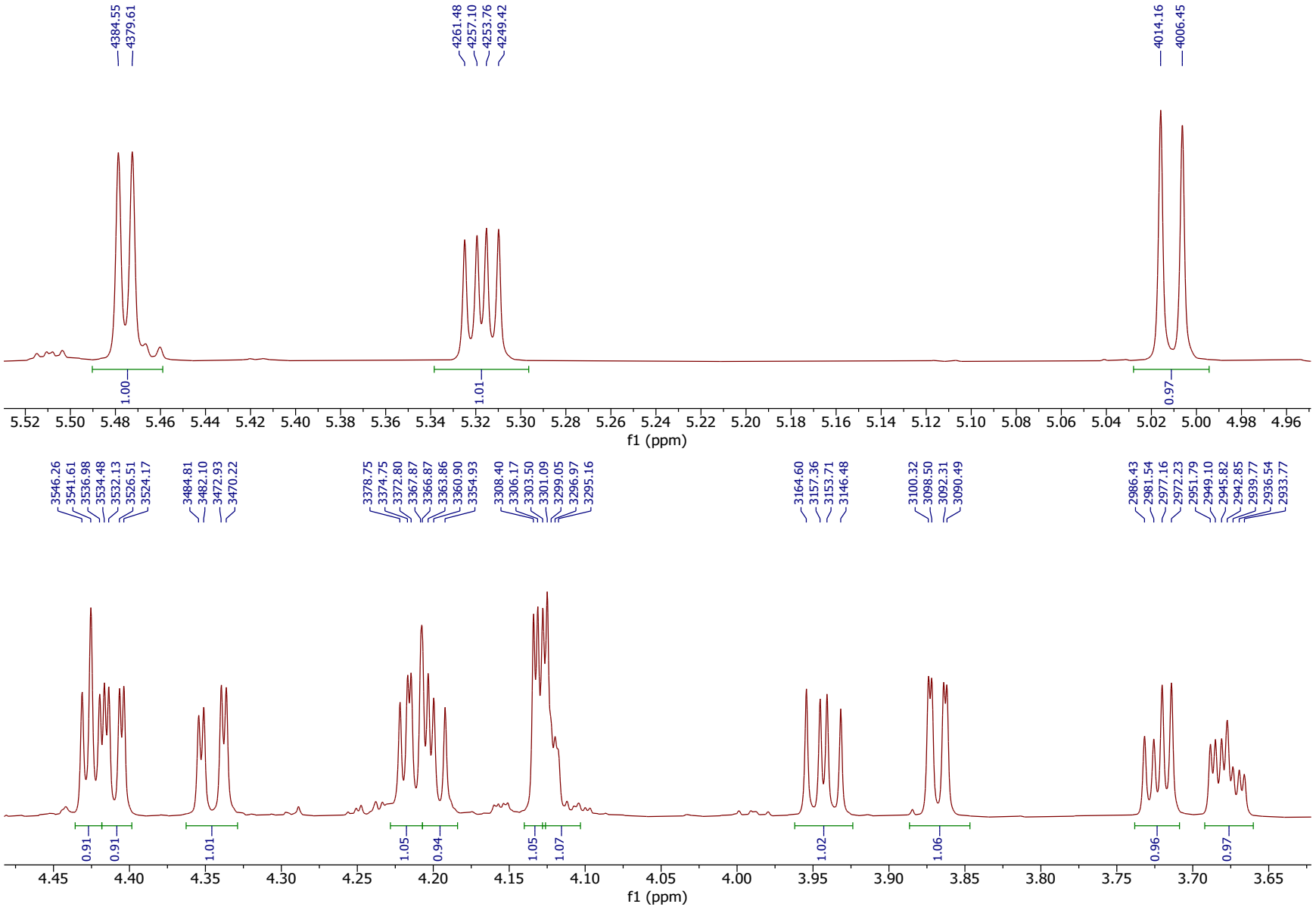
$^{13}C\{^{1}H\}$ NMR Spectrum of **184** (101 MHz, C_6D_6)



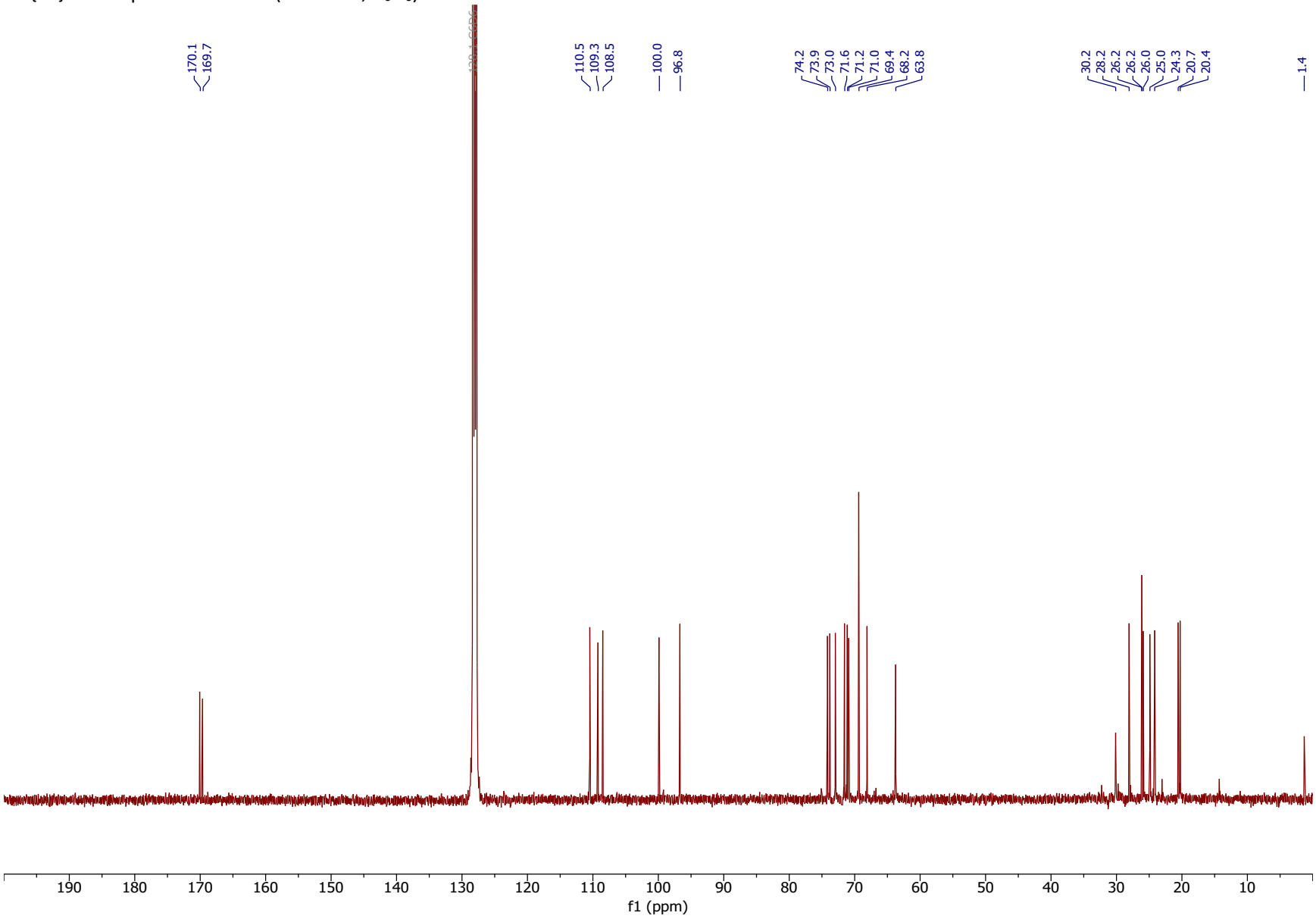
^{1}H NMR Spectrum of **185** (800 MHz, C_6D_6) – full



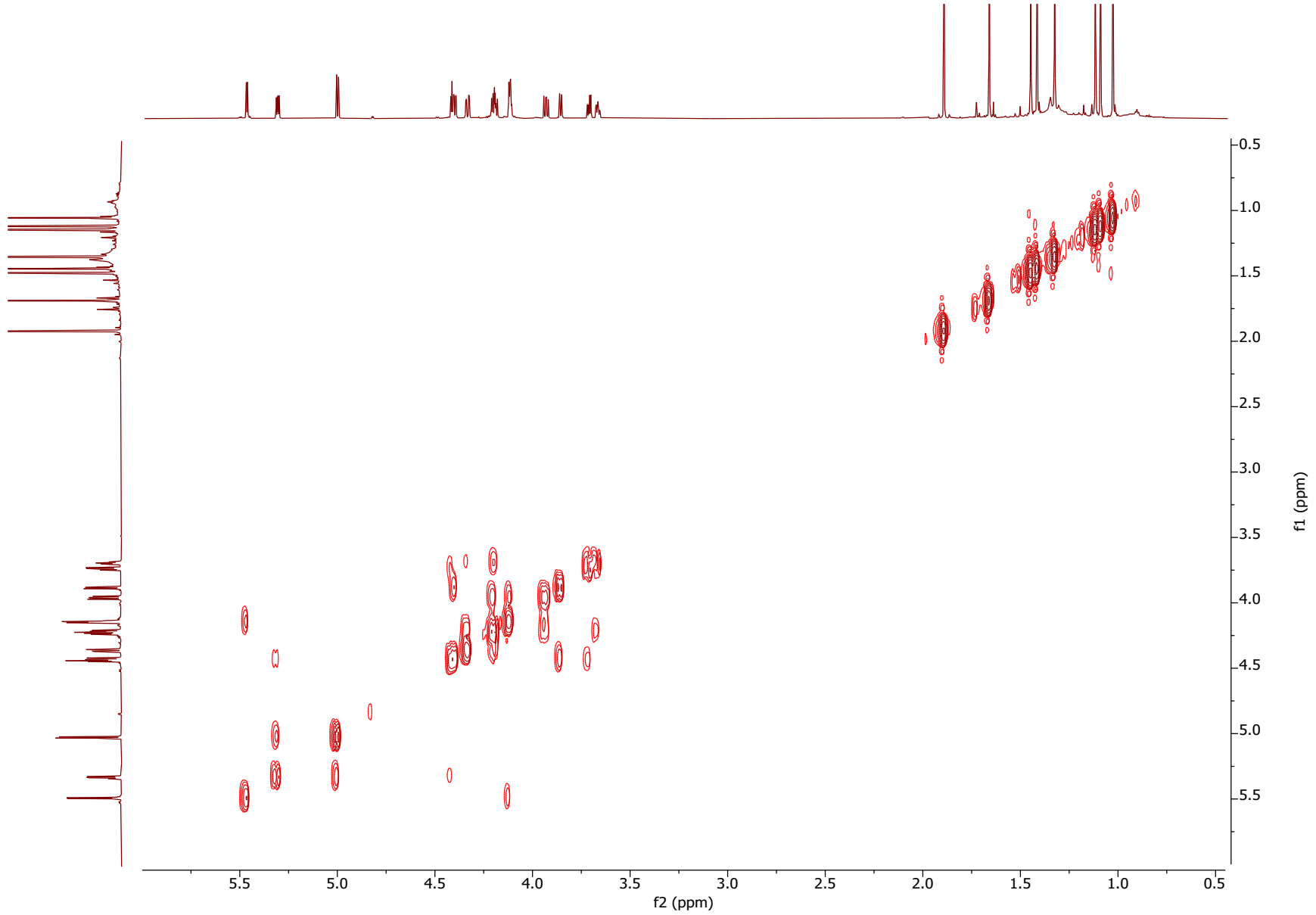
^{1}H NMR Spectrum of **185** (800 MHz, C_6D_6) – expansion



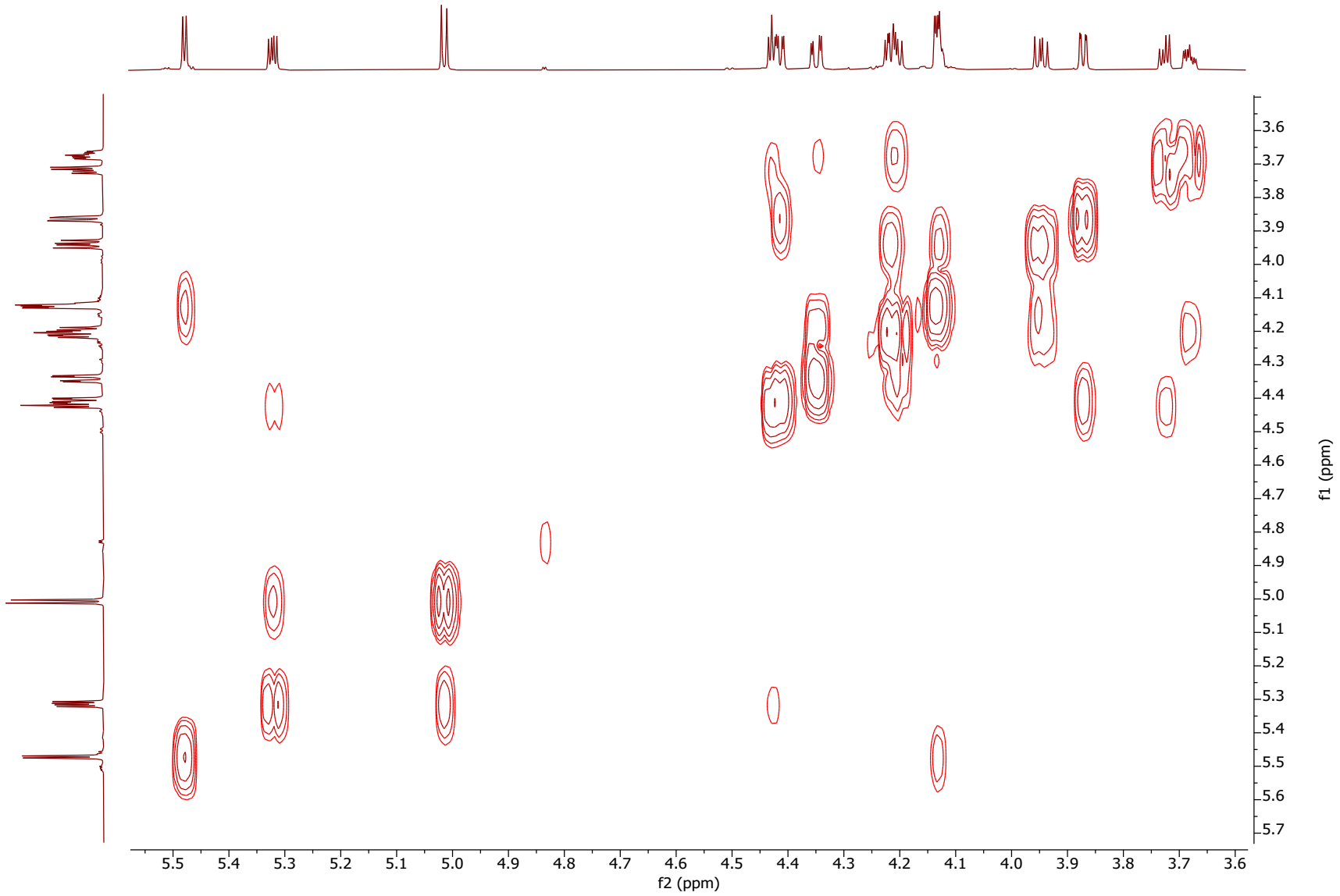
$^{13}C\{^{1}H\}$ NMR Spectrum of **185** (101 MHz, C_6D_6)



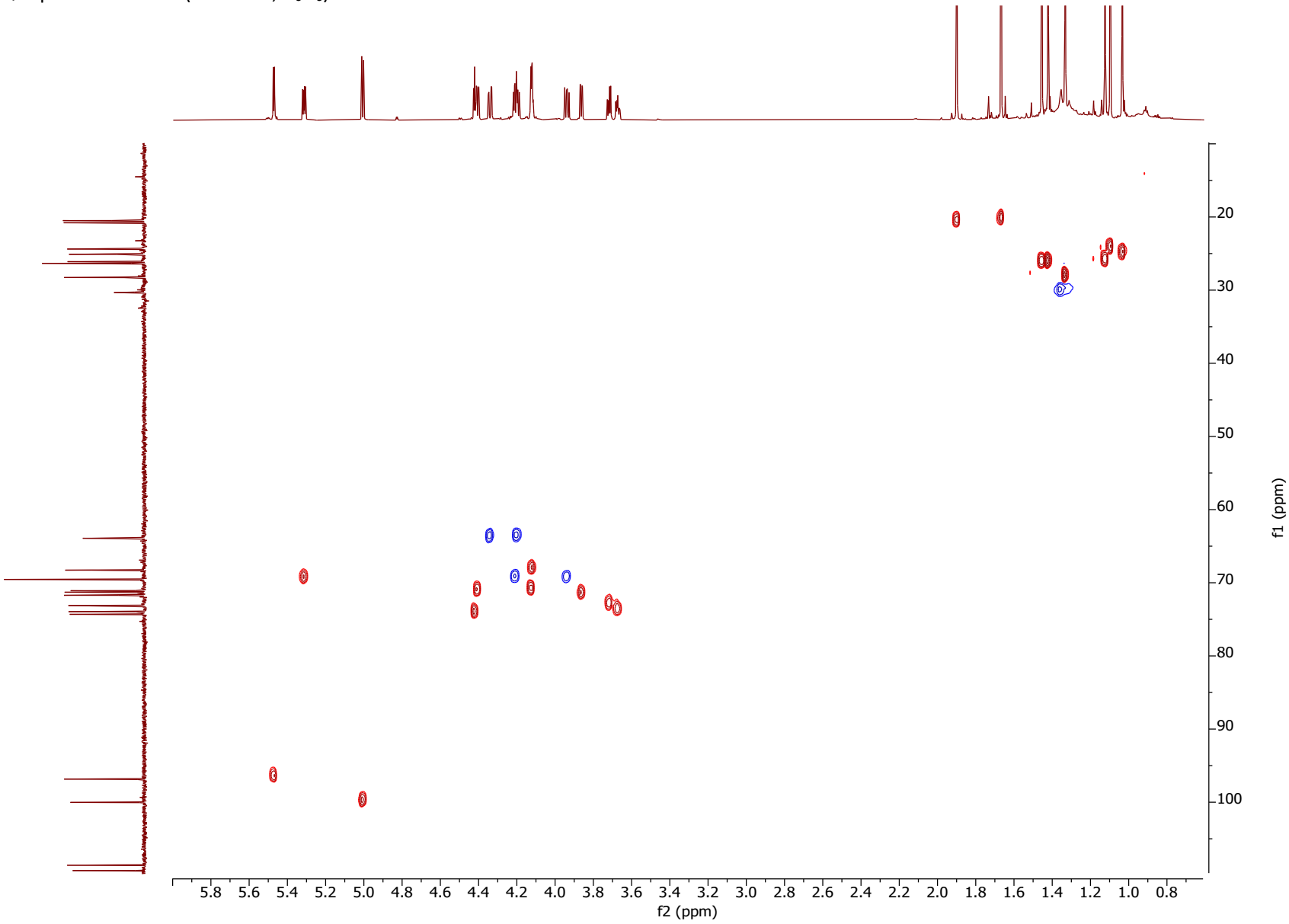
COSY spectrum of **185** (800 MHz, C_6D_6) – full



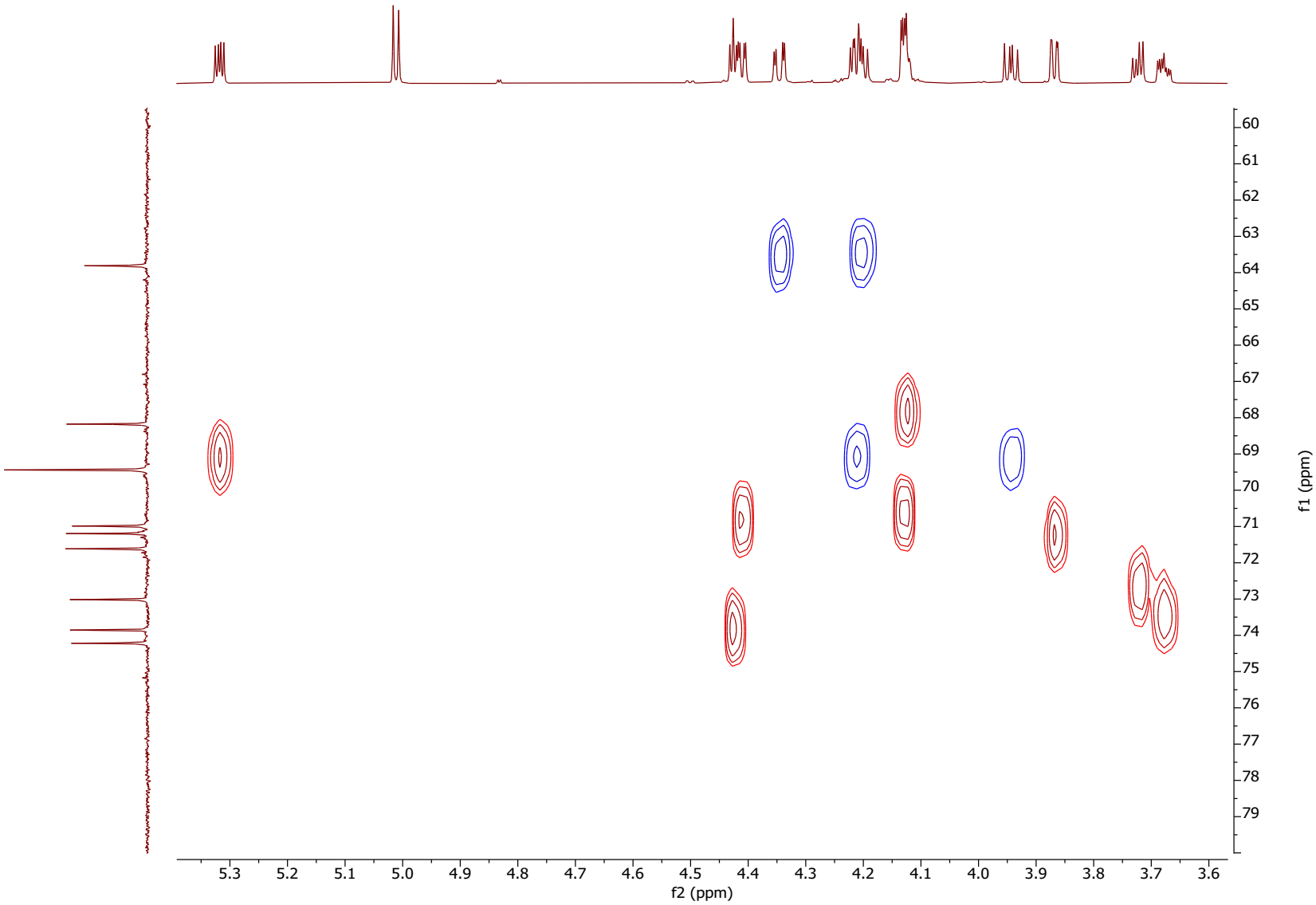
COSY spectrum of **185** (800 MHz, C_6D_6) – expansion



HSQC spectrum of **185** (800 MHz, C_6D_6) – full



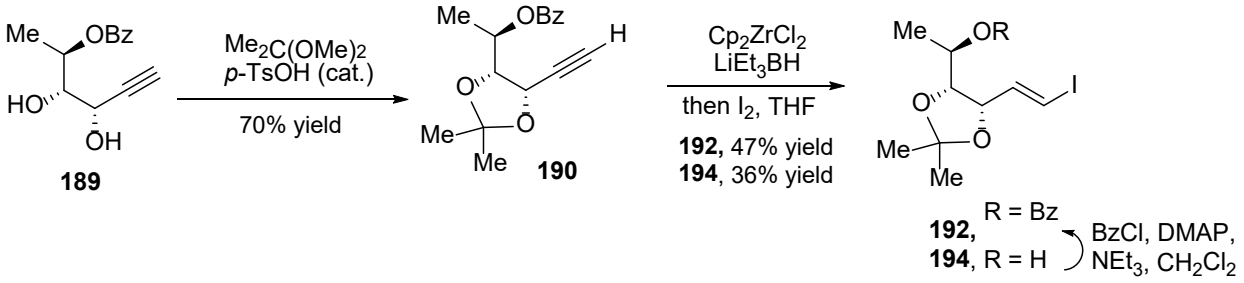
HSQC spectrum of **185** (800 MHz, C_6D_6) – expansion



Experimental for Chapter 4

Experimental for vinylic iodides

Synthesis of acetonide-vinylic iodide 192



(R)-1-((4R,5S)-5-((E)-2-iodovinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl benzoate (**192**):

Alkyne **190** was prepared according to a reported procedure from alkynyl diol **189** [15–17].

190, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.56 (ddt, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.50 – 7.39 (m, 2H), 5.37 (dq, *J* = 8.0, 6.2 Hz, 1H), 4.94 (dd, *J* = 6.0, 2.2 Hz, 1H), 4.32 – 4.22 (m, 1H), 2.45 (d, *J* = 2.2 Hz, 1H), 1.57 (s, 3H), 1.51 (d, *J* = 6.2 Hz, 3H), 1.42 – 1.38 (s, 3H).

An oven-dried 25 mL flask with stir bar, cooled under argon, was charged with Cp_2ZrCl_2 (731 mg, 2.5 mmol, 2.5 equiv). The flask was vacuum pulled and re-filled with argon, and the cycle was repeated three times. After THF (10 mL, 4 mL / mmol of Cp_2ZrCl_2) was added, 1.0 M THF solution of $LiHBEt_3$ (a.k.a Super-hydride, 2.5 mL, 2.5 mmol, 2.5 equiv) was added dropwise into the stirring solution via syringe pump at 10 mL/hr. The resulting white mixture was wrapped in aluminum foil and stirred at an ambient temperature for 1 hr. Alkyne **190** (274 mg, 1 mmol) in THF (2.0 mL, 0.5 M of alkyne) was added dropwise via syringe pump at 5 mL/hr. After 1 hr, the reaction mixture was cooled to 0 °C, and approximately 1 M solution of iodine (355 mg, 1.4 mmol, 1.4 equiv) in

THF (1.4 mL) was added dropwise at until the brown color persisted. After additional stirring for 15 min., the reaction mixture was quenched with a solution of saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with diethyl ether (75 mL × 3). The combined organic layer was washed successively with $Na_2S_2O_3$ (75 mL) and saturated brine (75 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (hexanes/DCM 1:2 eluant) to afford *E*-vinylic iodide **192** (124 mg, 57% yield). The column was washed with CH_2Cl_2 to isolate alcohol **194** (110 mg, 36% yield).

192, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.96 (m, 2H), 7.62 – 7.54 (m, 1H), 7.47 (dd, *J* = 8.4, 7.1 Hz, 2H), 6.59 (dd, *J* = 14.5, 7.2 Hz, 1H), 6.45 (dd, *J* = 14.4, 0.7 Hz, 1H), 5.26 (quint, *J* = 6.4 Hz, 1H), 4.35 (apparent t, *J* = 7.5 Hz, 1H), 3.90 (dd, *J* = 7.8, 6.5 Hz, 1H), 1.43 (s, 3H), 1.43 (d, *J* = 6.2 Hz, 3H), 1.40 (s, 3H).

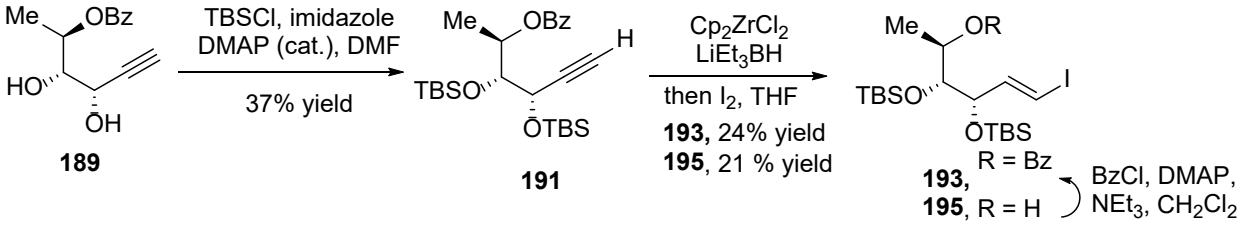
194, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 14.5, 6.8 Hz, 1H), 6.48 (dd, *J* = 14.5, 1.1 Hz, 1H), 4.62 (td, *J* = 6.5, 1.2 Hz, 1H), 3.91 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.83 (t, *J* = 6.3 Hz, 1H), 1.48 – 1.46 (m, 3H), 1.36 – 1.35 (m, 3H).

Benzoylation of alcohol **194**:

To a solution of triethylamine (0.39 mL, 2.8 mmol, 4.6 equiv), **194** (110 mg, 0.23 mmol of **194** + 0.38 mmol of benzyl alcohol), and DMAP (35 mg, 1.3 mmol, 0.47 equiv) in CH_2Cl_2 (1.1 mL, 0.5M), benzoyl chloride (0.24 mL, 2.1 mmol, 3.4 equiv) was added slowly and stirred for overnight. The mixture was quenched with $NaHCO_3$ (aq. saturated) and then extracted with ethyl acetate (x 3). The organic layer was dried with $MgSO_w$, filtered, and the solvent was removed by rotary

evaporation. Purification of the crude product by silica gel flash chromatography (hexanes/CH_2Cl_2 1:2 eluant) to afford *E*-vinylic iodide **192** (98 mg, quant. yield).

Synthesis of TBS-vinylic iodide 193



(2R,3R,4S)-3,4-bis((tert-butyldimethylsilyl)oxy)hex-5-yn-2-yl benzoate (**193**):

Alkyne **191** was prepared according to a reported procedure from alkynyl diol **189** [16,17].

191, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.55 (tt, *J* = 7.0, 1.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 3H), 5.46 (qd, *J* = 6.4, 3.4 Hz, 1H), 4.34 (dd, *J* = 5.2, 2.1 Hz, 1H), 4.00 (dd, *J* = 5.2, 3.5 Hz, 1H), 2.40 (d, *J* = 2.1 Hz, 1H), 1.37 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 9H), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H).

An oven-dried 25 mL flask with stir bar, cooled under argon, was charged with Cp_2ZrCl_2 (731 mg, 2.5 mmol, 2.5 equiv). The flask was vacuum pulled and re-filled with argon, and the cycle was repeated three times. After THF (0.2 mmol / mL of Cp_2ZrCl_2) was added, 1.0 M THF solution of $LiHBEt_3$ (a.k.a Super-hydride, 2 mL, 2 mmol, 2 equiv) was added dropwise into the stirring solution via syringe pump at 10 mL/hr. The resulting white mixture was wrapped in aluminum foil and stirred at an ambient temperature for 1.5 hr. Alkyne **191** (463 mg, 1 mmol) in THF (2.0 mL, 0.5 M of alkyne) was added dropwise via syringe pump at 5 mL/hr. After 1 hr, the reaction mixture was

cooled to 0 °C, and approximately 1 M solution of iodine (355 mg, 1.4 mmol, 1.4 equiv) in THF (1.4 mL) was added dropwise at until the brown color persisted. After additional stirring for 30 min., the reaction mixture was quenched with a solution of saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with diethyl ether (30 mL × 3). The combined organic layer was washed successively with $Na_2S_2O_3$ (50 mL) and saturated brine (50 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. Purification of the crude product by 1% triethylamine pre-treated silica gel flash chromatography (hexanes/CH_2Cl_2 8:1 eluant) to afford *E*-vinylic iodide **193** (139 mg, 24% yield). The column was washed with hexanes/CH_2Cl_2 2:1 to isolate alcohol **195** (117 mg, 21% yield)

193, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.98 (m, 2H), 7.60 – 7.51 (m, 1H), 7.49 – 7.39 (m, 2H), 6.55 (dd, *J* = 14.5, 7.2 Hz, 1H), 6.27 (dd, *J* = 14.5, 0.9 Hz, 1H), 5.36 (qd, *J* = 6.5, 3.7 Hz, 1H), 4.02 (ddd, *J* = 7.1, 5.7, 1.0 Hz, 1H), 3.84 (dd, *J* = 5.5, 3.6 Hz, 1H), 1.33 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 18H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H).

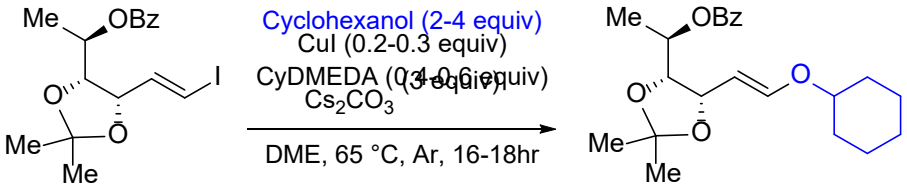
195, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 14.4, 7.4 Hz, 1H), 6.25 (dd, *J* = 14.6, 0.9 Hz, 1H), 4.07 (ddd, *J* = 7.4, 5.5, 1.0 Hz, 1H), 3.86 (p, *J* = 4.7 Hz, 2H), 3.49 (t, *J* = 5.1 Hz, 1H), 1.99 (d, *J* = 5.3 Hz, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.89 – 0.86 (m, 18H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H).

Benzoylation of alcohol **195**: To a solution of triethylamine (0.51 mL, 3.7 mmol, 4 equiv), **195** (418 mg, 0.86 mmol), and DMAP (43 mg, 0.35 mmol, 0.4 equiv) in CH_2Cl_2 (4 mL, 0.2M), benzoyl chloride (0.25 mL, 2.2 mmol, 2.5 equiv) was added slowly and stirred for overnight. The mixture was transferred to a 20-mL vial. The solvent was removed by rotary evaporation. Purification of

the crude product by 1% triethylamine pre-treated silica gel flash chromatography (hexanes/CH_2Cl_2 6:1 eluant) to afford *E*-vinylic iodide **193** (268 mg, 52% yield).

Experimental for the vinylic ethers

(*E*)-Vinylic ether 196 from (*E*)-vinylic iodide 192

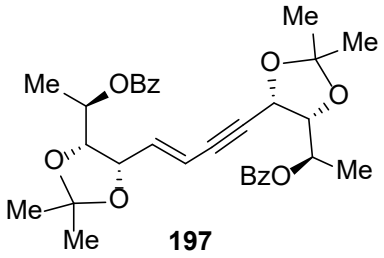


192 **196**

(R)-1-((4R,5S)-5-((E)-2-(cyclohexyloxy)vinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl benzoate (**196**): An oven-dried 4 mL vial with a stir bar was charged with cyclohexanol (88 mg, 0.88 mmol, 4 equiv), Cs_2CO_3 (218 mg, 3 equiv), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (CyDMEDA, 21 µL, 0.6equiv), and *E*-vinyl iodide **192** (90 mg, 0.22 mmol, 1 equiv). The reaction vial was purged continuously with argon for 5 min before CuI (13 mg, 0.3 equiv) was added. Anhydrous 1,2-dimethoxyethane (DME, 0.32 mL, 0.7 M based on vinylic iodide) was added, and the reaction mixture was bubbled with argon for 5 minutes. The reaction vial was quickly closed with a solid cap, sealed with Teflon tape and electrical tape, and placed in a metal heat block, whose internal temperature was controlled by digital thermometer and set at 65 °C. The reaction mixture was stirred for 18 hours and cooled to room temperature. The mixture was filtered through a Celite® pad and rinsed with EtOAc (100 mL), and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 1%

triethylamine, hexanes / EtOAc 15:1 eluent) afforded the (*E*)-vinylic ether **196** (62 mg, 74% yield) along with enyne **197** as a by-product (3% yield).

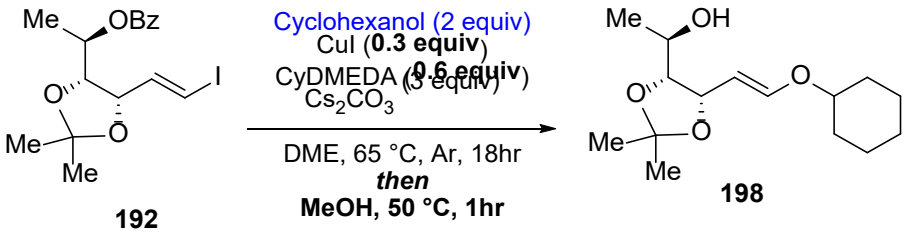
196, ^{1}H NMR (400 MHz, C_6D_6) δ 8.17 – 8.08 (m, 2H), 7.13 – 7.07 (m, 1H), 7.07 – 7.01 (m, 2H), 6.20 (d, *J* = 12.4 Hz, 1H), 5.47 (dq, *J* = 8.0, 6.2 Hz, 1H), 5.13 (dd, *J* = 12.5, 9.4 Hz, 1H), 4.57 (dd, *J* = 9.3, 6.2 Hz, 1H), 4.16 (dd, *J* = 7.9, 6.2 Hz, 1H), 3.31 (tt, *J* = 9.0, 3.6 Hz, 1H), 1.56 – 1.37 (m, 4H), 1.49 (d, *J* = 6.2 Hz, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.20 (m, 4H), 0.96 (m, 2H).



197

Enyne **197** by-product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dt, *J* = 8.4, 1.3 Hz, 4H), 7.56 – 7.47 (m, 2H), 7.38 (ddd, *J* = 8.8, 5.4, 2.5 Hz, 4H), 5.98 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.63 (dt, *J* = 15.8, 1.5 Hz, 1H), 5.26 (dq, *J* = 6.3, 7.1 Hz 1H), 5.03 (quint, *J* = 6.3 Hz, 1H), 4.92 (dd, *J* = 6.1, 1.6 Hz, 1H), 4.63 (td, *J* = 6.6, 1.4 Hz, 1H), 4.26 (t, *J* = 6.6 Hz, 1H), 4.22 (dd, *J* = 7.3, 6.1 Hz, 1H), 1.49 (s, 3H), 1.48 (s, 3H), 1.43 (d, *J* = 6.3 Hz, 3H), 1.37 (d, *J* = 1.4 Hz, 6H), 1.34 (d, *J* = 6.3 Hz, 3H).

(*E*)-Vinylic ether 198 from (*E*)-vinylic iodide 192 in one-pot synthesis

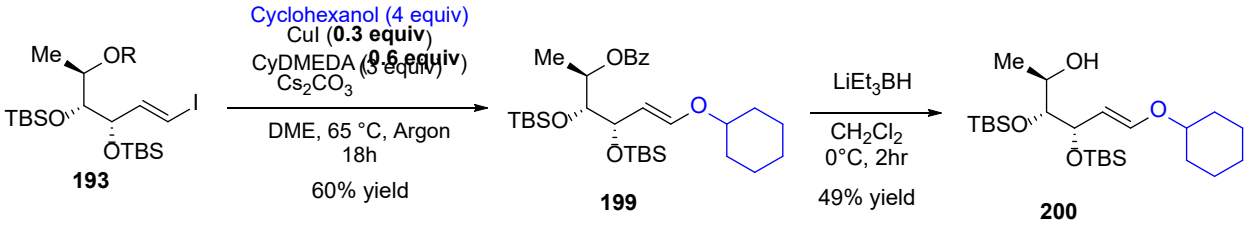


(R)-1-((4R,5S)-5-((E)-2-(cyclohexyloxy)vinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (**198**):

An oven-dried 4 mL vial with a stir bar was charged with cyclohexanol (319 mg, 1.6 mmol, 2 equiv), Cs_2CO_3 (778 mg, 3 equiv), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (CyDMEDA, 75 µL, 0.6equiv), and *E*-vinyl iodide **192** (320 mg, 0.8 mmol, 1 equiv). The reaction vial was purged continuously with argon for 5 min before CuI (45 mg, 0.3 equiv) was added. Anhydrous 1,2-dimethoxyethane (DME, 1.1 mL, 0.7 M based on vinylic iodide) was added, and the reaction mixture was bubbled with argon for 5 minutes. The reaction vial was quickly closed with a solid cap, sealed with Teflon tape and electrical tape, and placed in a metal heat block, whose internal temperature was controlled by digital thermometer and set at 65 °C. The reaction mixture was stirred for 19 hours, cooled to room temperature. To the reaction mixture was added MeOH (0.36mL, 2 equiv). The reaction was heated to 50 °C and stirred for 1 hr. After cooling it to room temperature, the mixture was filtered through a Celite® pad and rinsed with EtOAc (100 mL), and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (DCM/ Pentane / diethyl ether 5:4.5:1 → 0:1:1 eluent) afforded the vinylic ether **198** (102 mg, 47 % yield from compound **192**).

198, ^{1}H NMR (400 MHz, C_6D_6) δ 6.23 (d, *J* = 12.4 Hz, 1H), 5.26 (dd, *J* = 12.4, 9.3 Hz, 1H), 4.56 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.84 (dd, *J* = 3.8, 2.2 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.38 (td, *J* = 8.8, 4.3 Hz, 1H), 1.64 (br s, 1H), 1.69 – 1.59 (m, 2H), 1.56 – 1.47 (m, 2H), 1.45 (s, 3H), 1.33 (d, *J* = 5.9 Hz, 3H), 1.31 (s, 3H), 1.07 – 0.94 (m, 6H).

(*E*)-Vinylic ether 200 from (*E*)-vinylic iodide 193



(2R,3R,4S,E)-3,4-bis((tert-butyldimethylsilyl)oxy)-6-(cyclohexyloxy)hex-5-en-2-yl benzoate (**199**)

An oven-dried 4 mL vial with a stir bar was charged with cyclohexanol (94 mg, 4 equiv), Cs_2CO_3 (230 mg, 3 equiv), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (CyDMEDA, 22 µL, 0.6 equiv), and *E*-vinyl iodide **193** (139mg, 0.23 mmol, 1 equiv). The reaction vial was purged continuously with argon for 5 min before CuI (13 mg,0.3 equiv) was added. Anhydrous 1,2-dimethoxyethane (DME, 0.34 mL, 0.7 M based on vinylic iodide) was added, and the reaction mixture was bubbled with argon for 5 minutes. The reaction vial was quickly closed with a solid cap, sealed with Teflon tape and electrical tape, and placed in a metal heat block, whose internal temperature was controlled by digital thermometer and set at 65 °C. The reaction mixture was stirred for 18 hours, cooled to room temperature. The mixture was filtered through a Celite® pad and rinsed with EtOAc (100 mL), and the filtrate was concentrated by rotary evaporation. Purification of the crude product by silica gel flash chromatography (pre-treated with 1% triethylamine, hexanes / EtOAc 95:5 → 9:1 eluent) afforded the (*E*)-vinylic ether **199** (77 mg, 60% yield).

199, ^{1}H NMR (400 MHz, C_6D_6) δ 8.30 – 8.19 (m, 3H), 7.11 – 7.05 (m, 4H), 6.24 (d, *J* = 12.6 Hz, 1H), 5.78 (qd, *J* = 6.4, 3.8 Hz, 1H), 5.15 (dd, *J* = 12.6, 9.0 Hz, 1H), 4.14 (dd, *J* = 9.0, 5.2 Hz, 1H), 4.09 (dd, *J* = 5.2, 3.8 Hz, 1H), 3.54 (tt, *J* = 8.5, 3.7 Hz, 1H), 1.86 – 1.67 (m, 2H), 1.58 (m, 2H), 1.46 (d, *J* = 6.4 Hz, 3H), 1.44 – 1.35 (m, 2H), 1.34 – 1.18 (m, 2H), 1.07 (s, 9H), 1.05 (s, 9H), 0.19 (s, 3H), 0.18 (s, 6H), 0.15 (s, 3H).

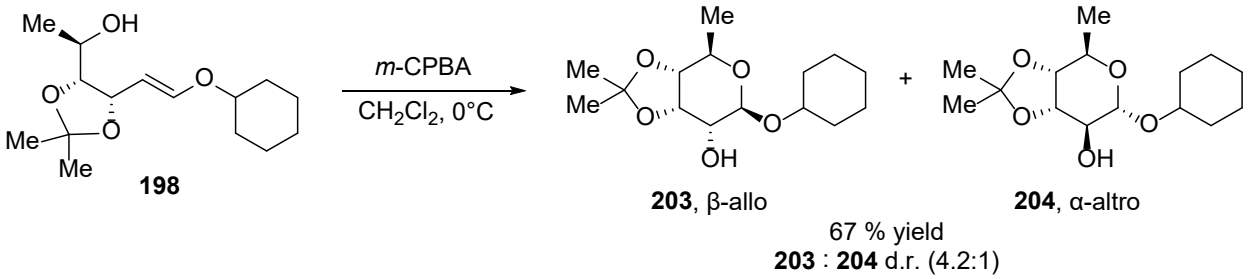
(2R,3R,4S,E)-3,4-bis((tert-butyldimethylsilyl)oxy)-6-(cyclohexyloxy)hex-5-en-2-ol (**200**)

$LiBEt_3H$ (0.36 mL, 3 equiv, 1 M solution in THF) was added dropwise to a solution of benzoate **199** (68 mg, 0.12 mmol) in THF (1.7 mL, 0.07 M based on **199**) at 0 °C under argon. After stirring for 2 h a few drops of acetone were added, followed by diethyl ether and water. The organic phase was separated and the aqueous one extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was concentrated by rotary evaporation. The residue was purified by flash chromatography (1% pre-treated silica gel, hexanes/EtOAc 8:1 → 4:1) to give compound **200** (27 mg, 0.059 mmol, 49% yield).

200, ^{1}H NMR (400 MHz, C_6D_6) δ 6.25 (d, *J* = 12.5 Hz, 1H), 5.11 (dd, *J* = 12.6, 9.3 Hz, 1H), 4.21 (dd, *J* = 9.3, 5.0 Hz, 1H), 3.96 (p, *J* = 6.2 Hz, 1H), 3.61 (t, *J* = 5.2 Hz, 1H), 3.55 (tt, *J* = 8.4, 4.1 Hz, 1H), 1.83 – 1.69 (m, 2H), 1.65 – 1.53 (m, 2H), 1.49 – 1.34 (m, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.12 – 1.04 (m, 2H), 1.02 (s, 9H), 1.01 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H).

Experimental for the 6-deoxy- and 2,6-dideoxy glycosides

6-deoxyglycoside synthesis from vinylic ether 198

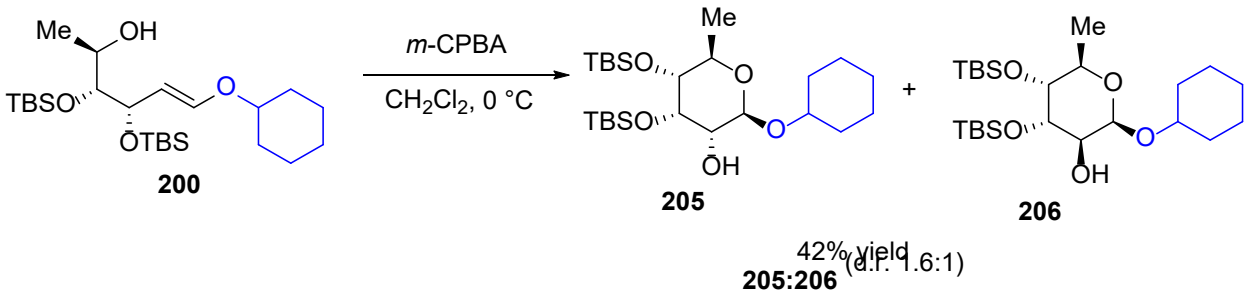


A 10 mL round-bottom flask with stir bar was charged with hydroxy vinylic ether **198** (6 mg, 0.02 mmol) and CH_2Cl_2 (0.22 mL, 0.1 M), and cooled to 0 °C with an external cooling bath. *m*-CPBA (77% w/w) (4.5 mg, 1.1 equiv) was slowly added to the stirring solution at 0 °C. The resulting suspension was stirred for 10 minutes at 0 °C, the external cooling bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL). The aqueous layer was extracted with EtOAc (3 x 2 mL) and the combined organic layers were dried over $MgSO_4$, filtered with a filter paper, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (hexanes/EtOAc 4:1 eluant) to give a mixture of diastereomers **203** and **204** in d.r. 4.2 : 1 (4 mg, 67% yield). Compound **204** was isolated in an insufficient amount. It was not feasible to characterize it thoroughly.

203, ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, C_6D_6) δ 4.83 (d, *J* = 7.1 Hz, 1H), 4.22 (t, *J* = 4.8 Hz, 1H), 3.74 (dd, *J* = 7.2, 4.5 Hz, 1H), 3.72 – 3.64 (m, 1H), 3.62 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.48 (dd, *J* = 9.0, 5.0 Hz, 1H), 2.04 – 1.88 (m, 2H), 1.77 (d, *J* = 5.4 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.57 – 1.47 (m, 2H), 1.39 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.19 (s, 3H).

- Note: peaks in 1.47 – 2.04 ppm are overlapping

6-deoxyglycoside synthesis from vinylic ether 200



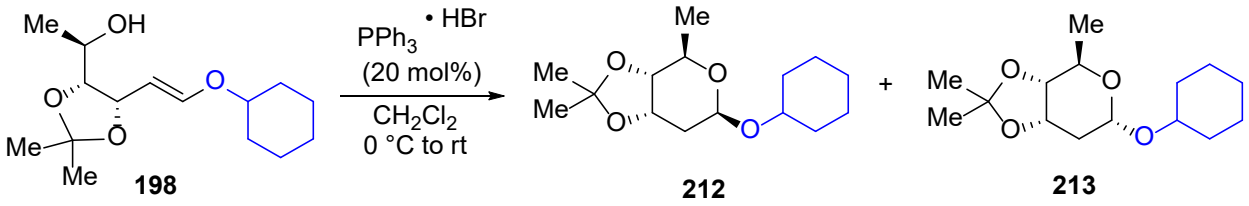
A 10 mL round-bottom flask with stir bar was charged with hydroxy vinylic ether **200** (9 mg, 0.02 mmol) and CH_2Cl_2 (0.35 mL, 0.06 M), and cooled to 0 °C with an external cooling bath. *m*-CPBA (77% w/w) (5 mg, 1.1 equiv) was slowly added to the stirring solution at 0 °C. The resulting suspension was stirred for 10 minutes at 0 °C, the external cooling bath was removed, and the reaction mixture stirred for 5 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (1% triethylamine pre-treated silica gel, hexanes/EtOAc 19:1 → 4:1 eluant) to give a mixture of diastereomers **205** and **206** in d.r. 1.6 : 1 (4 mg, 42% yield).

205, ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, *J* = 7.6 Hz, 1H), 4.19 (d, *J* = 2.0 Hz, 1H), 4.18 – 4.13 (m, 1H), 3.77 (td, *J* = 9.2, 4.5 Hz, 1H), 3.48 (d, *J* = 7.6 Hz, 1H), 3.31 (dd, *J* = 8.8, 2.1 Hz, 1H), 2.16 (s, 1H), 2.08 – 2.00 (m, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.65 – 1.47 (m, 2H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 10H), 0.94 (s, 9H), 0.35 (s, 3H), 0.29 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H).

206, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (apparent t, *J* = 1.1 Hz, 1H), 4.44 (qd, *J* = 13.2, 6.5 Hz, 1H), 3.94 (dd, *J* = 4.2, 2.9 Hz, 1H), 3.78 (dd, *J* = 8.1, 2.7 Hz, 1H), 3.75 (dd, *J* = 4.3, 1.9 Hz, 1H), 3.55 (ddd,

J = 13.5, 9.4, 3.9 Hz, 1H), 2.02 (d, *J* = 12.3 Hz, 1H), 1.81 (d, *J* = 12.5 Hz, 1H), 1.73 – 1.58 (m, 2H), 1.58 – 1.43 (m, 1H), 1.43 – 1.32 (m, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.10 (s, 9H), 1.00 (s, 9H), 0.20 (s, 3H), 0.20 (s, 3H), 0.12 (s, 3H), 0.07 (s, 3H).

Synthesis of 2,6-dideoxyglycoside from vinylic ether 198



1) With *m*-CPBA: A conical vial with stir bar was charged with hydroxy vinylic ether **198** (12 mg, 0.04 mmol) and CH_2Cl_2 (0.2 mL, 0.2 M), and cooled to 0 °C with an external cooling bath. Added 0.09 mL of triphenylphosphonium hydrogen bromide stock solution (0.1 M, 0.009 mmol, 0.2 equiv) was slowly added to the stirring solution at 0 °C. The resulting suspension was stirred at 0 °C, allowed to warm up to room temperature, and the reaction mixture stirred for 4.5 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 1 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (1% triethylamine pre-treated silica gel, pentane/diethyl ether 9:1 → 3:1 eluant) to give a mixture of diastereomers **212** and **213** in 3.3:1 ratio (3 mg, 22% yield).

2) With HFIP: Hydroxy vinylic ether **198** (49 mg, 0.18 mmol) was dissolved in HFIP (1 mL, 0.18 M). Transferred 0.27 mL of the solution of **198** in HFIP (0.05 mmol of **198**) into an oven-dried test tube (12 x 75 mm) with stir bar. The test tube was capped with rubber septum, heated to 50 °C,

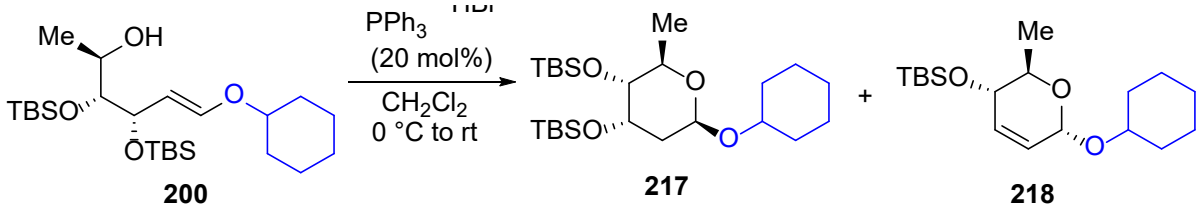
and stirred for 18 hrs. The reaction was cooled and transferred to 20 mL vial, by washing it with EtOAc. The solvent was removed by rotary evaporation. The crude product was purified by silica gel flash chromatography (hexane/EtOAc 9:1) to give a mixture of diastereomers **212** and **213** in 2.6 : 1 ratio (7 mg, 56% yield).

Below ^{1}H NMR data includes only the diagnostic peaks in the spectrum of the diastereomeric mixture.

212, ^{1}H NMR (400 MHz, C_6D_6) δ 4.96 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.05 (td, *J* = 5.0, 2.7 Hz, 1H), 3.76 – 3.69 (m, 1H), 3.55 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.48 (dd, *J* = 9.1, 5.0 Hz, 1H), 2.25 (dt, *J* = 14.6, 2.6 Hz, 1H), 1.94 (ddd, *J* = 14.6, 8.8, 4.9 Hz, 1H), 1.45 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.22 (s, 3H)

213, ^{1}H NMR (400 MHz, C_6D_6) δ 5.12 (s, 0H), 4.80 (t, *J* = 5.7 Hz, 0H), 4.11 – 4.07 (m, 0H), 4.02 – 3.97 (m, 0H), 3.66 – 3.58 (m, 0H), 3.26 (q, *J* = 7.0 Hz, 0H), 3.17 (s, 0H), 2.08 – 2.04 (m, 0H), 2.04 – 2.02 (m, 0H), 1.47 (s, 3H), 1.37 (m, 3H), 1.26 (s, 3H).

Synthesis of 2,6-dideoxyglycoside from vinylic ether 200



200 **217** **218**

An oven-dried test tube (12 x 75 mm) with stir bar was charged with hydroxy vinylic ether **200** (9 mg, 0.02 mmol) and CH_2Cl_2 (0.5 mL, 0.04 M), and cooled to 0 °C with an external cooling bath. Added 0.04 mL of triphenylphosphonium HBr stock solution (0.1 M, 0.004 mmol, 0.2 equiv) was slowly added to the stirring solution at 0 °C. The resulting suspension was stirred for 10 minutes

at 0 °C, the external cooling bath was removed, and the reaction mixture stirred for 24 h at room temperature. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (1% triethylamine pre-treated silica gel, hexanes/CH_2Cl_2 6:1 → 3:2 eluant) to give compound **217** and **218** separately. **218** was less polar than **217**. Although the two compounds were separable on a column chromatography, the combined yield was calculated due to a small scale (4 mg, 43% yield in ~ 1:1 ratio). Their ratio was determined from the crude spectrum.

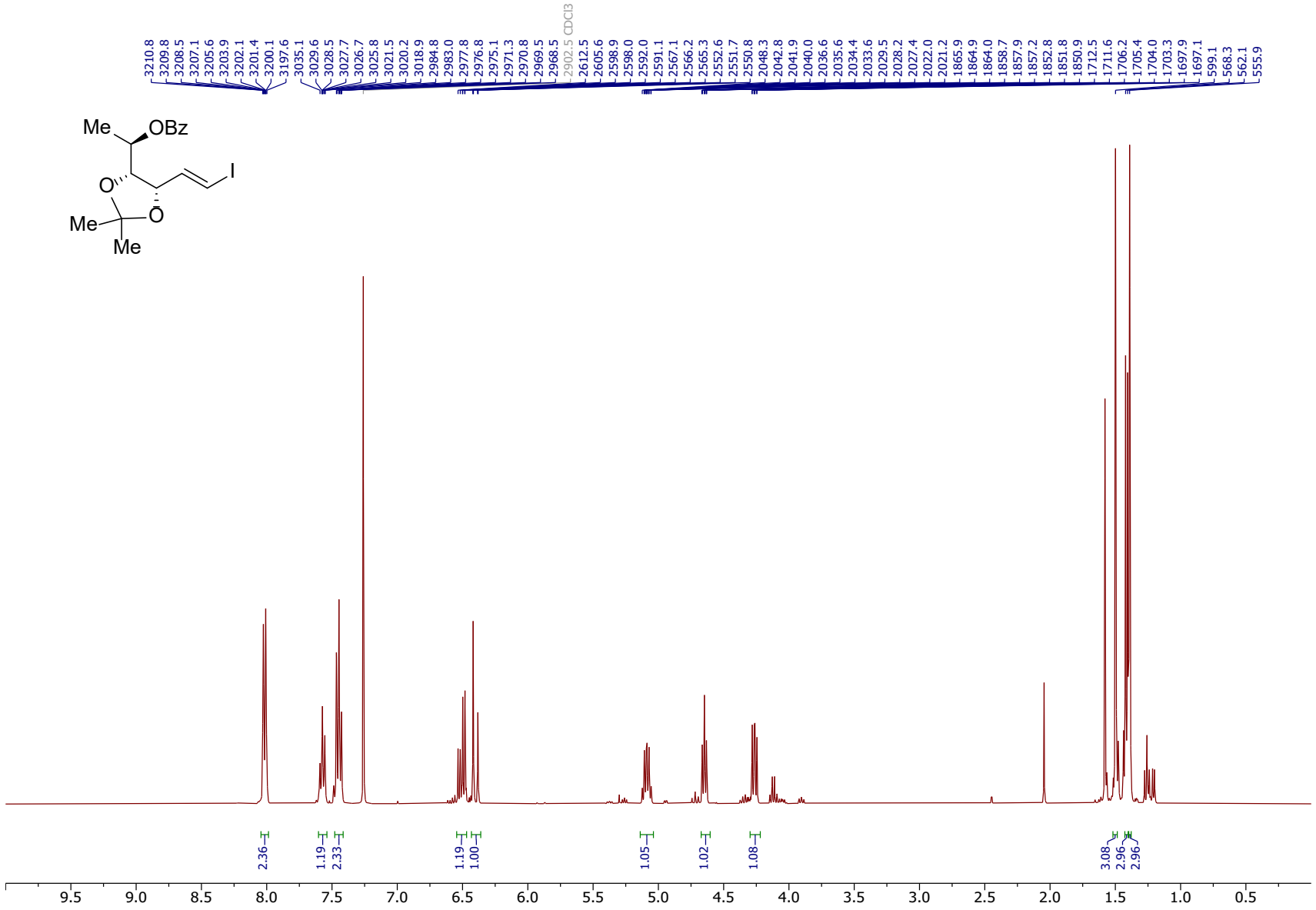
217, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (dd, *J* = 9.5, 2.1 Hz, 1H), 3.99 (br s, 1H), 3.87 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.63 (m, 1H), 3.29 (dd, *J* = 9.0, 2.4 Hz, 1H), 1.91 – 1.82 (m, 2H), 1.69 (dd, *J* = 13.0, 3.4 Hz, 1H), 1.25 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H).

218, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (d, *J* = 10.2 Hz, 1H), 5.64 (dt, *J* = 10.3, 2.3 Hz, 1H), 5.06 (s, 1H), 3.89 – 3.81 (m, 1H), 3.75 (q, *J* = 6.1 Hz, 1H), 3.60 (dt, *J* = 9.3, 5.1 Hz, 1H), 1.90 (br s, 2H), 1.87 – 1.83 (m, 2H), 1.73 (br s, 2H), 1.25 (m, 6H), 1.23 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

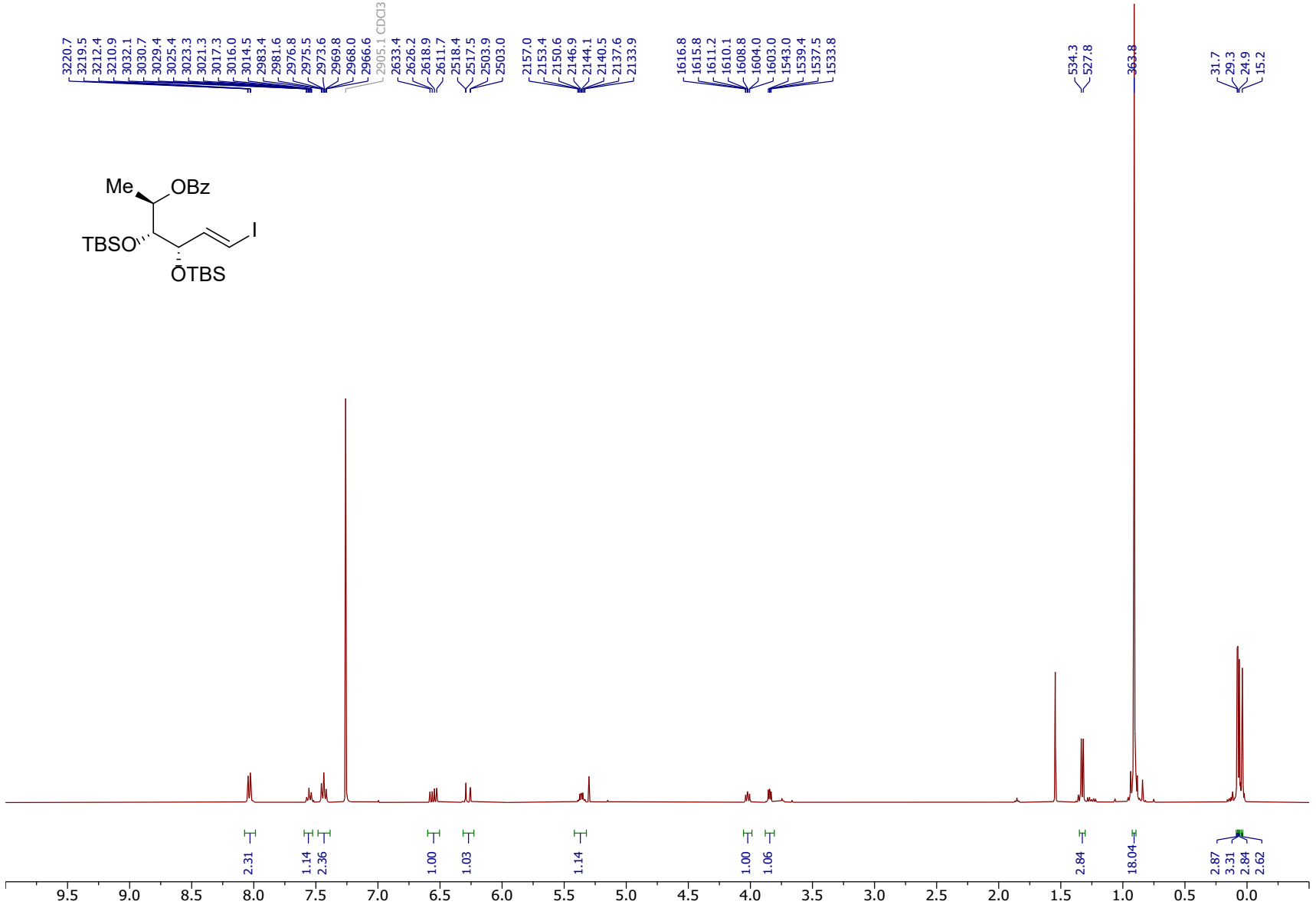
NMR spectra for Chapter 4

(next page)

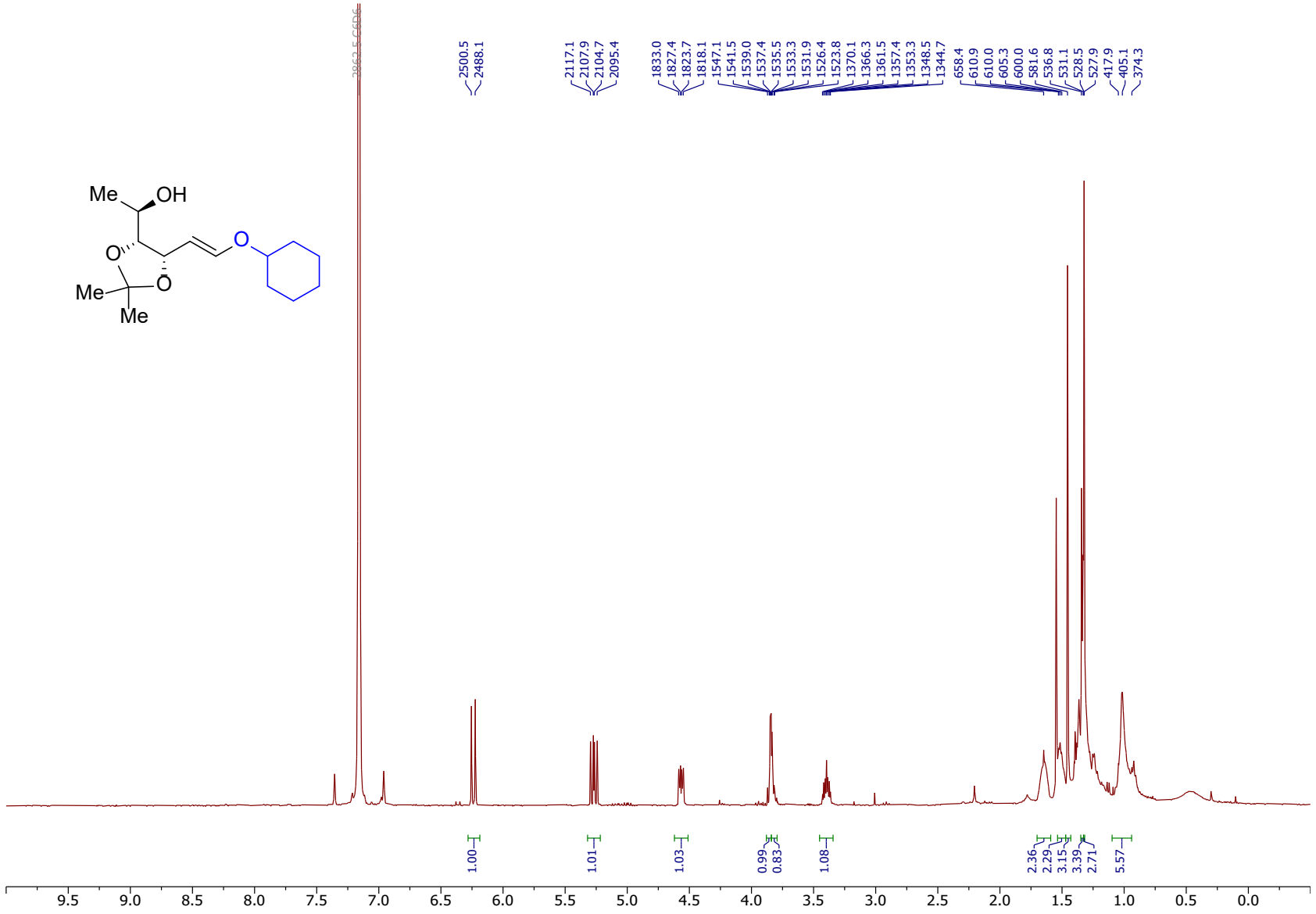
^{1}H NMR Spectrum of **192** (400 MHz, $CDCl_3$)



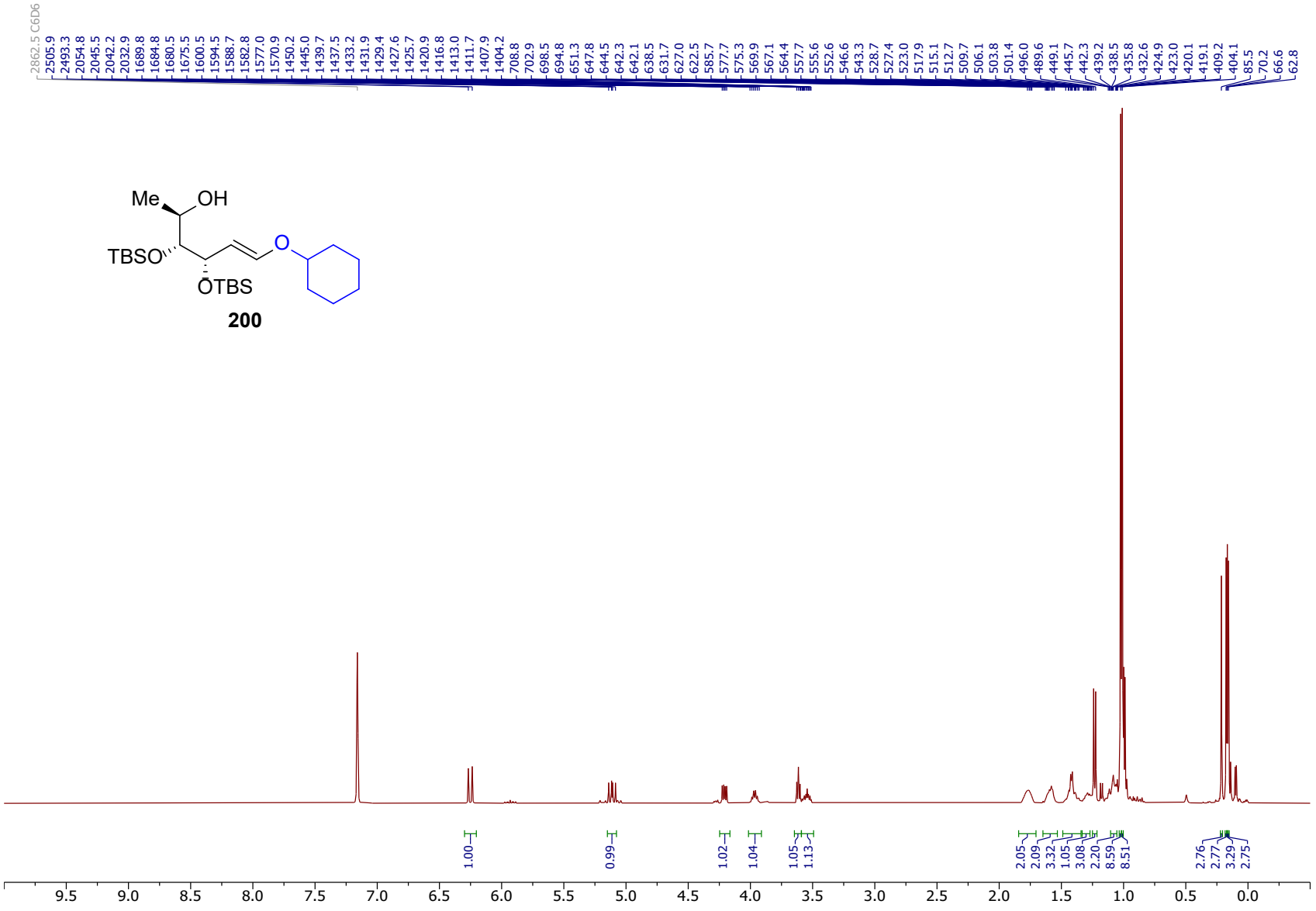
^{1}H NMR Spectrum of **193** (400 MHz, $CDCl_3$)



^{1}H NMR Spectrum of **198** (400 MHz, C_6D_6)



^{1}H NMR Spectrum of **200** (400 MHz, C_6D_6)



References

(1) Zhao, Y.; Snieckus, V. A Practical in Situ Generation of the Schwartz Reagent. Reduction of Tertiary Amides to Aldehydes and Hydrozirconation. *Org. Lett.* **2014**, *16* (2), 390–393.

(2) Pradal, A.; Evano, G. A Vinylic Rosenmund–von Braun Reaction: Practical Synthesis of Acrylonitriles. *Chem. Commun.* **2014**, *50* (80), 11907–11910.

(3) Skotnitzki, J.; Kremsmair, A.; Keefer, D.; Gong, Y.; De Vivie-Riedle, R.; Knochel, P. Stereoselective Csp^3 −Csp^2 Cross-Couplings of Chiral Secondary Alkylzinc Reagents with Alkenyl and Aryl Halides. *Angew. Chem. Int. Ed.* **2020**, *59* (1), 320–324.

(4) Wu, Y.-D.; Lai, Y.; Dai, W.-M. Synthesis of Two Diastereomeric C1–C7 Acid Fragments of Amphidinolactone B Using B-Alkyl Suzuki–Miyaura Cross-Coupling as the Modular Assembly Step. *ChemistrySelect* **2016**, *1* (5), 1022–1027.

(5) Pietruszka, J.; Witt, A. Synthesis of the Bestmann-Ohira Reagent. *Synthesis* **2006**, *24*, 4266–4268.

(6) Mames, A.; Stecko, S.; Mikołajczyk, P.; Soluch, M.; Furman, B.; Chmielewski, M. Direct, Catalytic Synthesis of Carbapenams via Cycloaddition/Rearrangement Cascade Reaction: Unexpected Acetylenes' Structure Effect. *J. Org. Chem.* **2010**, *75* (22), 7580–7587.

(7) Nitelet, A.; Evano, G. A General Copper-Catalyzed Vinylic Halogen Exchange Reaction. *Org. Lett.* **2016**, *18* (8), 1904–1907.

(8) Yang, C.; Nolan, S. P. Regio- and Stereoselective Dimerization of Terminal Alkynes to Enynes Catalyzed by a Palladium/Imidazolium System. *J. Org. Chem.* **2002**, *67* (2), 591–593.

(9) Nordmann, G.; Buchwald, S. L. A Domino Copper-Catalyzed C−O Coupling−Claisen Rearrangement Process. *J. Am. Chem. Soc.* **2003**, *125* (17), 4978–4979.

(10) Fürstner, A.; Shi, N. Nozaki−Hiyama−Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118* (49), 12349–12357.

(11) Mahankali, B.; Srihari, P. A Carbohydrate Approach for the First Total Synthesis of Cochliomycin C: Stereoselective Total Synthesis of Paecilomycin E, Paecilomycin F and 6'-*Epi* -Cochliomycin C: Total Synthesis of Cochliomycin C. *Eur. J. Org. Chem.* **2015**, *18*, 3983–3993.

(12) Song, W.-S.; Liu, S.-X.; Chang, C.-C. Synthesis of L-Deoxyribonucleosides from d-Ribose. *J. Org. Chem.* **2018**, *83* (24), 14923–14932.

(13) Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. 1,5-α-d-Mannoseptanosides, Ring-Size Isomers That Are Impervious to α-Mannosidase-Catalyzed Hydrolysis. *Org. Lett.* **2009**, *11* (4), 851–854.

(14) McDonald, F. E.; Ding, D.; Ephron, A. J.; Bacsa, J. Alkynylation of Pentose Derivatives with Stereochemical Fidelity: Implications for the Regioselectivity of Alkynyl Diol Cycloisomerizations to Cyclic Enol Ethers. *Org. Lett.* **2019**, *21* (9), 3295–3298.