EXPANDING THE SCOPE OF ALLYLBIS(SILANE)-IMINE CYCLIZATIONS. A CONCISE APPROACH TO THE SYNTHESIS OF THE AZATRICYCLIC CORE OF STEMOFOLINE AND ASPARAGAMINE A.

by

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ABSTRACT

The Mannich cyclization has been utilized for the synthesis of a number of heterocyclic compounds since its discovery. In this dissertation, a silane-based variant of the Mannich cyclization is discussed. This Mannich-like cyclization has proven to be a powerful tool in governing regio- and stereo- control in carbon-carbon bond forming reactions, which benefit from enhanced nucleophilicity of the C=C π bond derived from the hyperconjugative effect of the adjacent silicon group. Despite the synthetic utility associated with this transformation, there are comparatively few examples that have explored the intramolecular variant containing silane-based nucleophiles. The utility of a 2-propylidene-1,3-bis(silane) nucleophile in synthesis has also received little attention and it is the goal of this project to further develop this concept, and to apply these findings toward the construction of the azatricyclic core found in the stemona alkaloids Asparagamine A and Stemofoline.

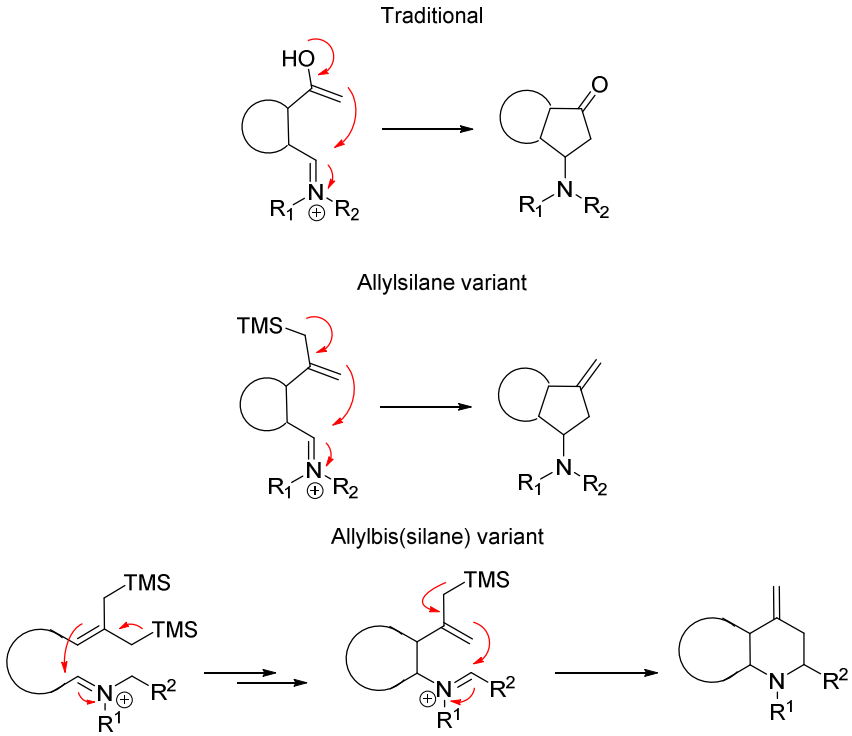
The use of a 2-propylidene-1,3-bis(silane) nucleophile in *N*-acyliminium ion chemistry has been successfully applied towards the construction of the azatricyclodecane cores by employing two cationic desilylative cyclization events. Construction of the requisite nucleophile was accomplished in quantitative yield through a Negishi coupling which employed $ZnCl_2$•$(THF)_2$ and 7 mol% $PdCl_2(PPh_3)_2$. Within this linear synthesis the enantiopure cores were acquired in 16% (**36**) and 12% (**38**) overall yield (16 and 17 steps respectively) from 1,1-dibromo-4-amino-1-butene (**18**).

CHAPTER 1

INTRODUCTION

The Mannich cyclization has been utilized for the synthesis of a number of heterocyclic compounds since its discovery. In this dissertation, a variant of the Mannich cyclization is discussed. Traditionally, an enol as a nucleophile (a terminator) and an iminium ion as an electrophile (an initiator) are united to produce β-amino ketone products. The use of an allylsilane in place of an enol terminator has been exploited by the Fleming, Overman, and Grieco research groups in natural product synthesis toward the construction of strategic bonds (see Scheme 1 for generic examples). This Mannich-like cyclization has proven to be a powerful tool in governing regio- and stereo- control in carbon-carbon bond forming reactions, which benefit from the enhanced nucleophilicity of the C=C π bond derived from the hyperconjugative effect of the adjacent silicon group. Despite the potential associated with this method, there are comparatively few examples that have explored the intramolecular variant containing silane-based nucleophiles.

The utility of a 2-propylidene-1,3-bis(silane) nucleophile in synthesis has also received little attention. It was the goal of this project to further develop this concept, and to apply what is known toward the construction of the azatricyclic core found in the stemona alkaloids Asparagamine A and Stemofoline.



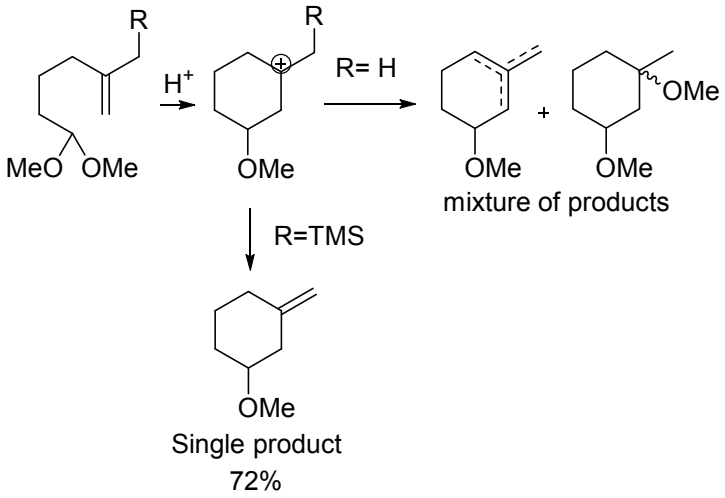
Scheme 1: Generic examples of intramolecular Mannich cyclizations.

The Livinghouse group has advanced this intramolecular variant of the Mannich-like cyclization by the utilization of 2-propylidene-1,3-bis(silane) and 2-(methylthio)-3-(trimethylsilyl)-1-propenyl moieties in cationic desilylative cyclization processes. The examination of a variety of substrates has revealed the optimum conditions for the allylbis(silane)-iminium ion cyclization. Studies by Timothy Kercher showed substrate addition to $TiCl_4$, followed by inverse addition to $KHCO_3$, proved to be most efficient in the monodesilylative process. Formation of the protodesilylation product was not observed under these conditions. In related studies, (*Z*)-Allylsilanes were found to exhibit a loss in stereoselectivity upon cyclization. This problem was circumvented by the enhancement of the allyl silane terminator C=C nucleophilicity through incorporation of a vinylic methylthio substituent. These types of intramolecular cyclization processes have

been shown to produce structurally unique pyrrolidines and have been applied towards turneforcidine[1], the azatricyclic core of the stemona alkaloids, and other targets.

Background: History & Development of Allysilane Iminium Ion Chemistry

The synthetic utility of this Mannich-like methodology was first realized in 1976 by Fleming where allylic trimethylsilane groups were found to dictate the product formation of carbonium ion cyclization reactions.[2] It was found that the relative heterolytic cleavage of Si-C in comparison to H-C is considerably faster[3], this feature prevents the formation of undesired olefins or interception of the resulting carbocation with the *in situ* generated alkoxide. Therefore, one product was exclusively formed when an allylic silane is incorporated (Scheme 2).



Scheme 2: Carbonium ion cyclizations (Ian Fleming).

The strategically placed silyl group was found to stabilize the adjacent developing positive charge through a hyperconjugative interaction involving the overlap of the polarized silicon-carbon bonds with the vacant p orbital (Figure 1).

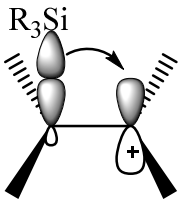
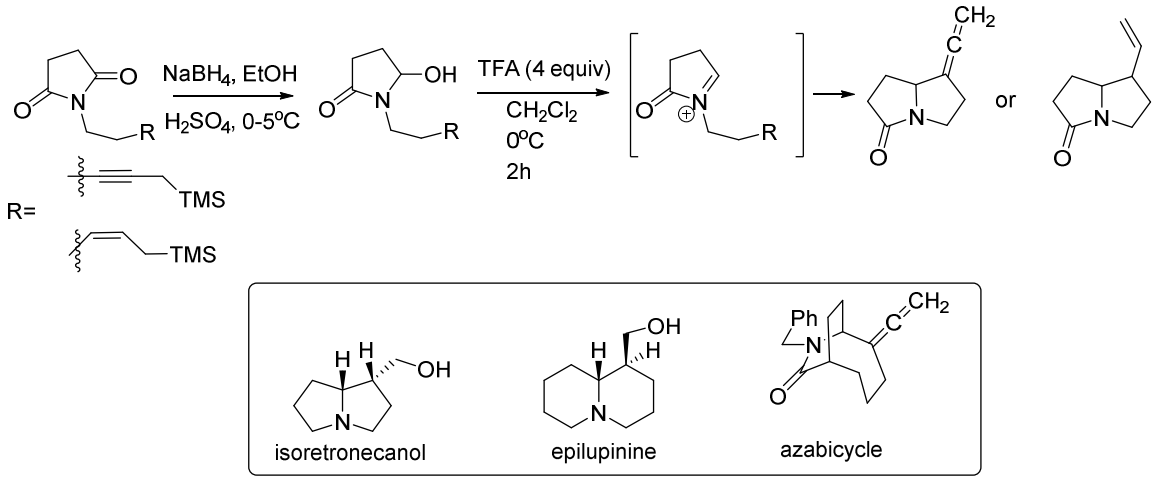


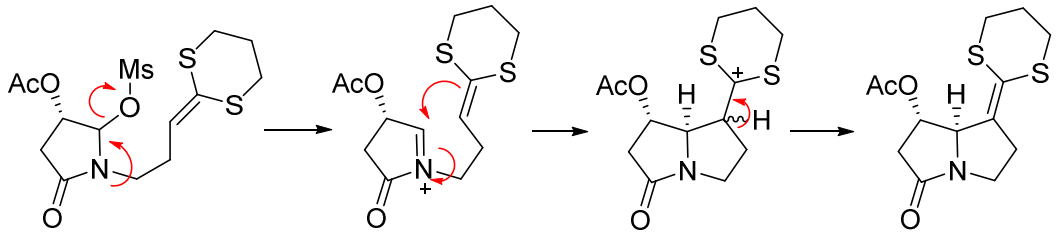
Figure 1: The beta effect.

In the early1980's, further exploration of this regioselective cyclization method was performed by Speckamp and Hiemstra through the cyclization of *N*-acyliminium ions with allyl and propargylsilanes. Following the reduction of the succinimides[4] the acyliminium ions were generated through the use of trifluoroacetic acid, in which protodesilylation was not observed to be a competitive process (Scheme 3).[5] The use of milder conditions involving $SnCl_4$ (1.5 equiv) to induce ring closure was shown to be successful in the construction of 8 membered azabicycles in high yield (81%).[6] These cyclization's proceed with complete stereocontrol and high yield.[7] When incorporating these silane based terminators, regiocontrol was achieved through the directive ability of the β-effect. The ramifications of ring strain were not observed to be a governing factor for the regioselectivity. Their findings were soon after applied towards the synthesis of the azabicyclic natural products such as isoretronecanol and epilupinine.



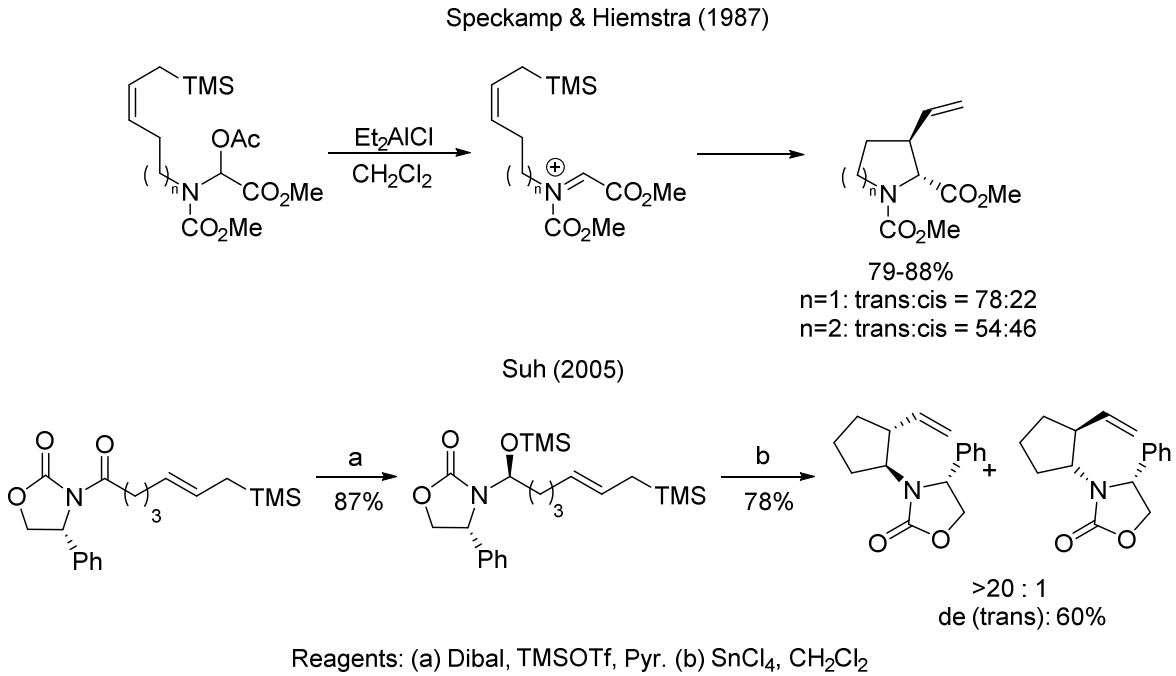
Scheme 3: *N*-acyiminium ion cyclizations (Speckamp and Hiemstra).

In related studies, Chamberlin explored the utility of the acyliminium-ion ketene dithioacetal cyclization methodology towards the construction of the azabicyclic structure found in (+)-Heliotridine and other pyrrolizidines. The cyclization proceeds by employing a ketene dithioacetal group as a nucleophile in the intramolecular ring closure (Scheme 4). Interestingly, the use of an acetoxy group throughout the synthesis had certain benefits. It was speculated that the acetoxy group could play a role in neighboring group participation during the cyclization step, which would provide facial selectivity by blocking one side.[8]



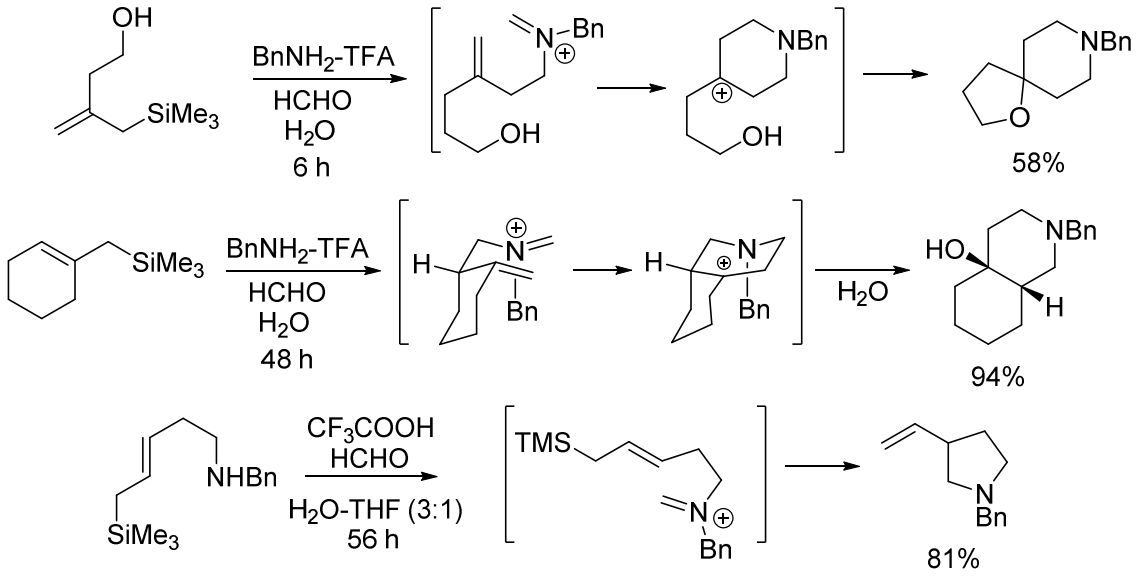
Scheme 4: Chamberlin's approach towards optically active pyrrolizidines.

In addition to this work, Speckamp and Hiemstra also explored the acyclic intramolecular *N*-acyliminium ion cyclization of carbamates containing an ionizable acetate located at the alpha position (Scheme 5).[9] The glyoxylate derived carbamate was shown to provide pyrrolidine or piperidine ring structures containing exocyclic alkenes or allenes in moderate yields with a selectivity preference for the *trans* product. The cyclization conditions that were explored showed comparable results when the Lewis acid mediated route or the thermal method (MsCl, Et_3N, then heat) were used. In 2005, the group of Young-Ger Suh demonstrated a similar method utilizing *N*,*O*-acetal TMS ethers as the *N*-acyliminium ion equivalent.[10] These studies have proven to be highly diastereoselective and the yields moderate (69-74%).



Scheme 5: Acyclic intramolecular allylsilane terminations.

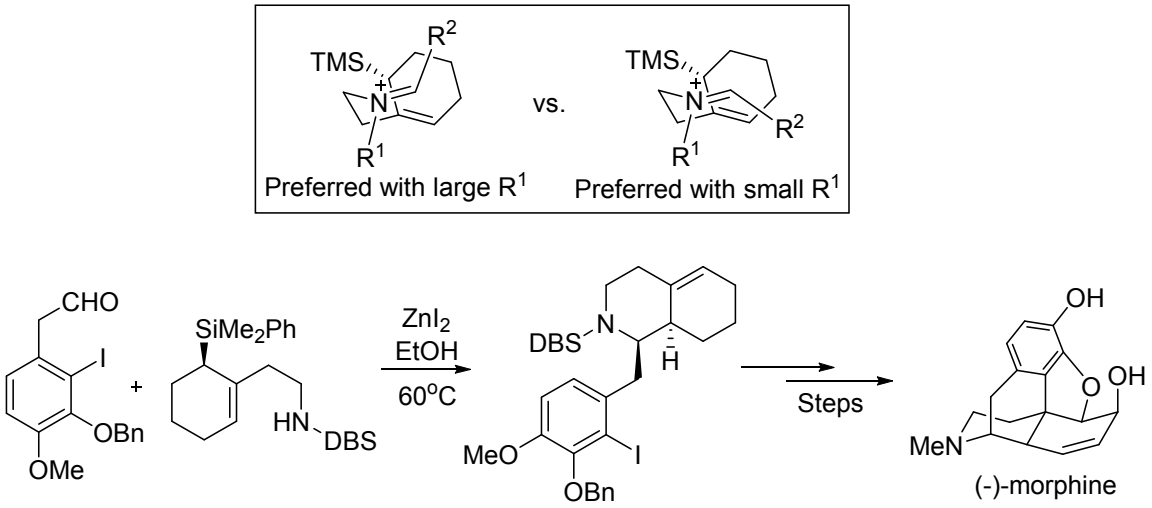
In 1986, Grieco and others reported on intramolecular cyclizations of *in situ* generated iminium-ion allylsilane terminations. Various ring sizes were reported and protodesilylation was not an observed side reaction under the given mannich-like conditions.[11] Additionally, the practicality of conducting iminium ion chemistry in water was explored. Substrates containing additional hydroxyl functionality were found to proceed with faster reaction rates upon cyclization. Furthermore, it was observed that the formation of the homoallylamine was much slower than the cyclization step. These studies provided a route to the synthesis of spirocyclic amines and *cis*-fused bicyclic amine ring structures (Scheme 6).[12]



Scheme 6: Intramolecular Mannich cyclizations (Grieco).

The Overman research group demonstrated the application of this Mannich-like methodology towards the total synthesis of the opiate morphine through the utility of an iminium ion-allylsilane process.[13] In this endeavor, a desired *trans* relationship was required from this transformation. To this end, the bulky DBS (dibenzosuberylamine)

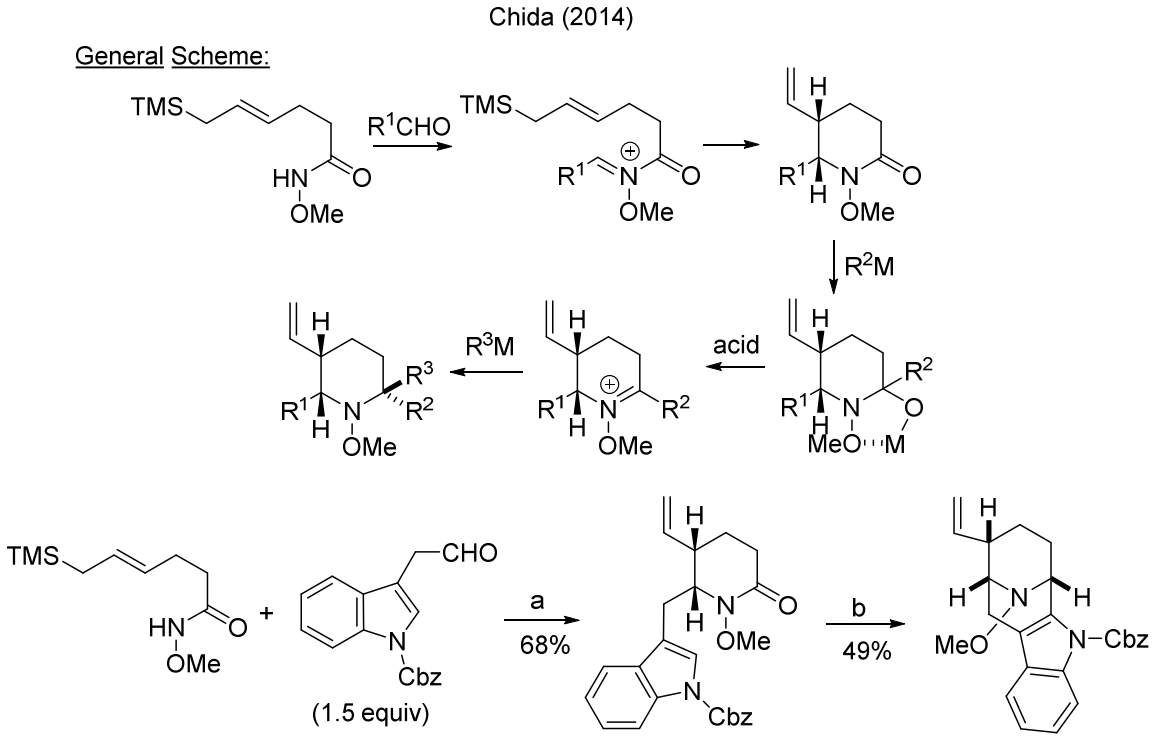
protecting group was employed to control the stereoselection of the cyclization. The resulting diastereoselectivity was explained in terms of sterics (Scheme 7).[14] These investigations have increased our overall understanding of stereocontrol pertaining to these reactions.



Scheme 7: Applications towards morphine (Overman).

An intriguing example of stereoselectivity involving intramolecular iminium-ion allylsilane cyclizations is illustrated in Scheme 8. The synthesis of *cis*-selective multi-substituted piperidines utilizing an *N*-methoxyamide anchor was proven effective towards the construction of the tetracyclic structure observed in kouamine.[15] This chemistry takes advantage of the enhanced nucleophilicity of the amide nitrogen brought on by the electron donating methoxy group to allow condensation onto the desired aldehyde. The resulting *N*-acyl-*N*-oxyiminium ion was observed to provide high *cis*-stereoselectivity which was experimentally shown to be a result of avoiding gauche-type interactions between the allylsilane and alkyl side chain attached to the iminium ion moiety. Similar to Weinreb amide chemistry, the methoxylactam may then be treated with the desired

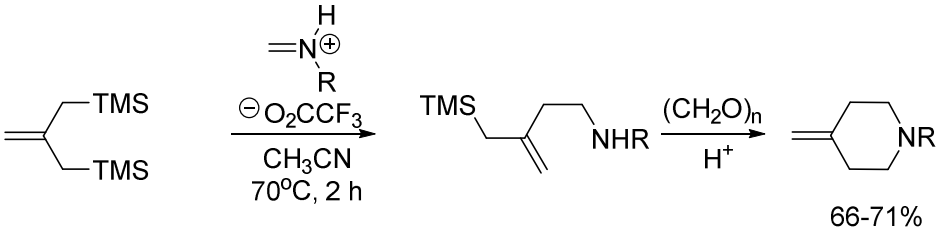
nucleophile to acquire chelation control, *N*-oxyiminium ion formation and following treatment with a 2nd nucleophile to yield functionalized piperidines.



Reagents: (a) BF_3-OEt_2, CH_2Cl_2, -20°C (b) Cp_2ZrHCl, CH_2Cl_2, RT; 10 mol% $Sc(OTf)_3$

Scheme 8: *N*-Methoxyamide based intramolecular allylsilane chemistry.

It was soon realized that the use of an allylbis(trimethylsilane) terminator was not fully explored. Therefore, in 1991, Guyot and Miginiac demonstrated the use of 2-methylenepropane-(1,3-diyl)bis(trimethylsilane) as a nucleophile to obtain unique methylenecyclohexane and methylenepiperidine ring structures (Scheme 9). Lewis acids, $TiCl_4$ or BF_3-Et_2O are utilized to initiate the termination-cyclization process. This methodology has shown to provide moderate to high yields.[16]



Scheme 9: First application of allylbis(silanes).

CHAPTER 2

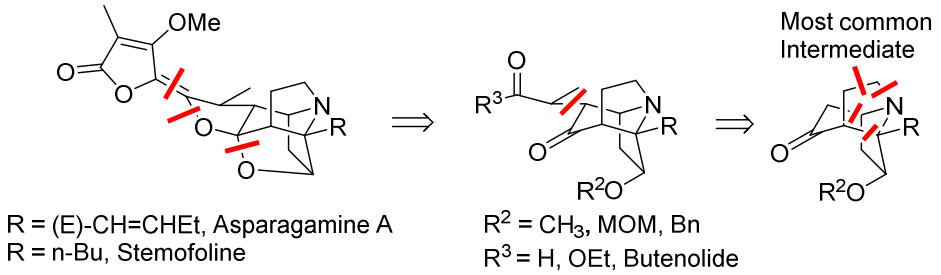
INTRODUCING THE ALKALOIDS

Isolation and Characterization of Stemofoline and Asparagamine A

In 1970, Irie and coworkers[17] isolated a unique alkaloid, Stemofoline, from the plant *Stemona japonica* and acquired structure information from x-ray crystallography examination. Later, in 1994, Sekine and coworkers isolated and completely characterized a similar alkaloid, Asparagamine A, from the roots of *Asparagus racemosus*.[18] Studies on Stemofoline, and Asparagamine A (aka. Didehydrostemofoline), have revealed notable insecticidal properties when administered orally to the larvae of various crop pests such as diamondback moth and silkworm. It was observed that Asparagamine A demonstrated stronger effects, than Stemofoline, isodehydrostemofoline and rotenone (a common pesticide).[19] These findings were reinforced by Kaltenegger[20], and Brem[21], when a wider variety of stemona alkaloids (including tuberostemonine) were tested for their insecticidal properties. Once more, Asparagamine A was found to exhibit higher neurotoxicity than its related derivatives. Additionally, the polycyclic alkaloid, Asparagamine A was found to possess anti-tumor and anti-oxytocin biological activity among the *in vitro* studies examined.[22]

Previous Approaches Towards the Stemona Alkaloids

Shortly after the discovery of Asparagamine A in 1994, the unique biological activity and synthetically challenging cage-like structure of the stemona alkaloids prompted interest towards their total synthesis. The most common bond disconnections are illustrated in red in Scheme 10 among which includes the detachment of the tetrahydrofuranylidene butenolide functionality and disconnection of C-C bonds adjacent to the tertiary amine to form the tropane-like structure.[23]

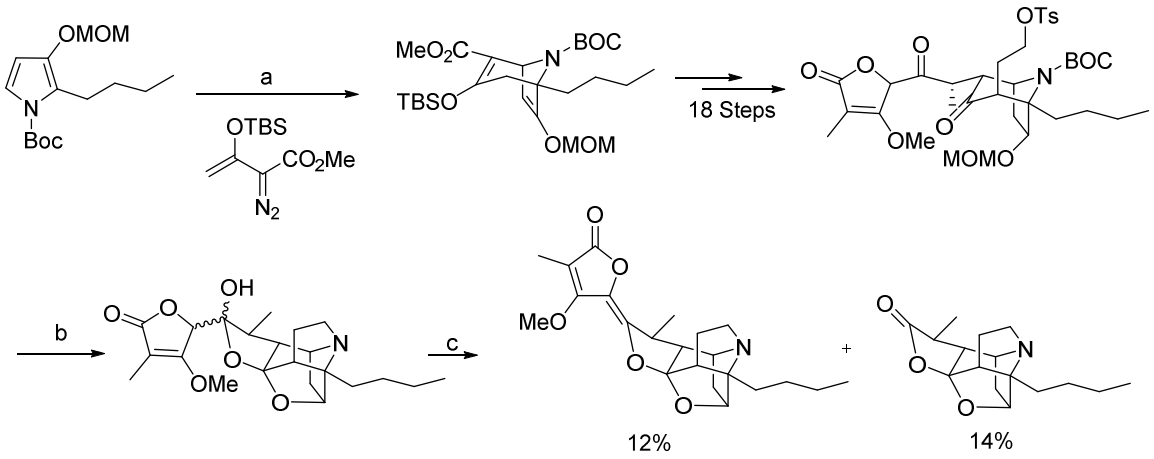


Scheme 10: Common bond disconnections.

[4+3] Cycloaddition Method: Andrew Kende

The earliest attempt towards the cage-like azatricyclic core was investigated by the Livinghouse group[24] in 1996, which will be discussed in detail shortly (see page 17). The first total synthesis of (±)-Isostemofoline was reported by Andrew Kende in 1999.[25] This approach utilized a [4+3] cycloaddition to establish the key tropane ring and a simultaneous triple cyclization to provide the pentacyclic core equipped with the butenolide functionality (Scheme 11). An unfortunate drawback of this method arises at the end of the synthesis where the dehydration with Tf_2O provided retroaldol byproducts

(14%) in addition to the desired alkaloid (12%). Following 26 steps, the natural product (±)-Isostemofoline was obtained in ~0.061% overall yield.



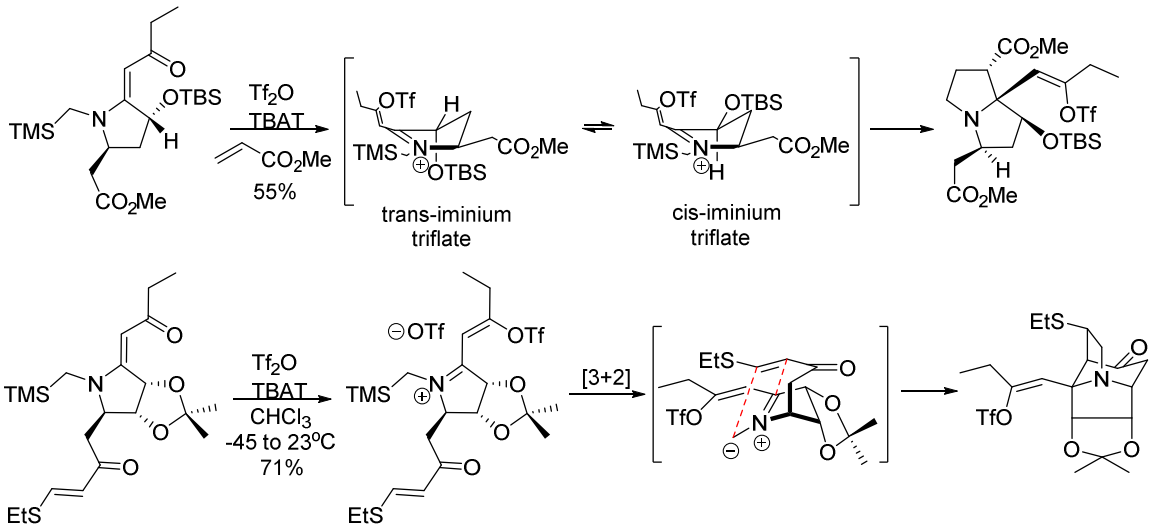
a. rhodium octanoate dimer, pentane, reflux, 90%. b. (1). TFA; (2) saturated aqueous $NaHCO_3$, 67%. c. Tf_2O, CH_2Cl_2

Scheme 11: Andrew Kende's approach.

[3+2] Cycloaddition Method: David Y. Gin

In 2008 at the University of Illinois, David Y. Gin demonstrated a non-racemic approach towards the Stemofoline core by an azomethine ylide [3+2] cycloaddition.[26] The requisite azomethine ylide was generated *in situ* following the treatment of the *N*-(trimethylsilyl)methyl vinylogous amide with Tf_2O/TBAT to initiate the intramolecular [3+2] cycloaddition to yield the polycyclic core (Scheme 12). During the screening stages, studies revealed the stereochemical directing group positioned at C(2) had unexpectedly epimerized to the thermodynamically more stable *cis*-iminium triflate. The fluoride anion was suspected to serve as a base before any desilylation event. This issue was remedied by substituting the TBS directing group for an isopropylidene ketal which is incapable of the epimerization process. Following the treatment of this vinylogous

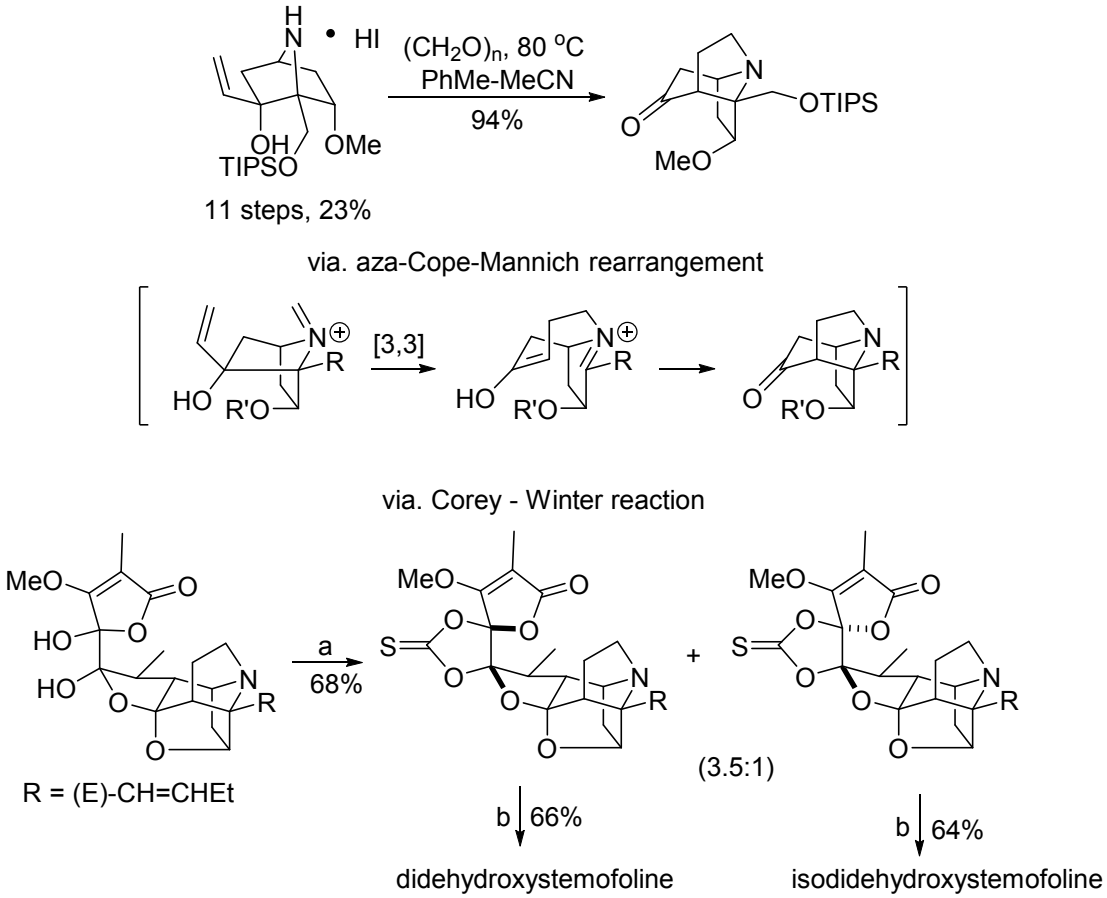
amide with the optimized cyclization conditions (Tf_2O, TBAT, $CHCl_3$, -45 to 23°C) provided the desired core in ~0.090% yield in 11 overall steps.



Scheme 12: David Y. Gin's approach.

Aza-Cope Mannich Method: Larry Overman

In 2003, Overman and workers, reported the first total synthesis of Asparagamine A through a key aza-cope-mannich rearrangement to establish the azatricyclic core in near quantitative yields (Scheme 13).[27] Aside from the key ring forming step, distinguished features about this total synthesis include the use of a Corey-Winter reaction to establish the dialkoxy alkene moiety. This specific sequence was employed to avoid the unfortunate retroaldol observed in Kende's approach. This route improved the overall efficacy for the attachment of the tetrahydrofuranylidene butenolide functionality. The desired stemona alkaloids were successfully produced in approximately 0.65% yield over 27 steps.



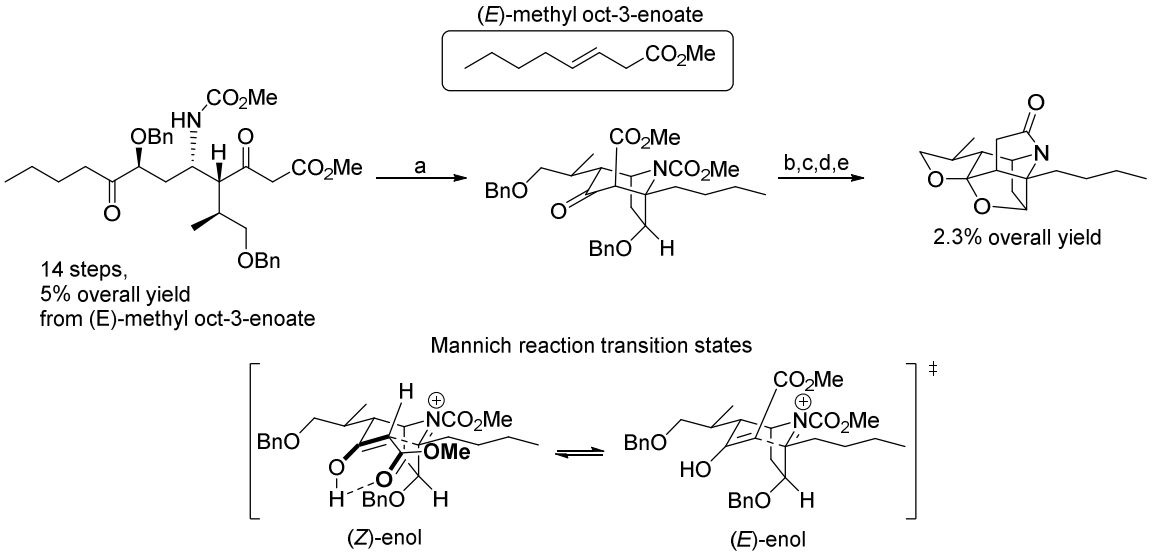
(a) $CSCl_2$, DMAP, CH_2Cl_2, -50 °C; (b) $(MeO)_3P$, 120 °C

Scheme 13: Larry Overman's approach.

Intramolecular Mannich Method: Eric J. Thomas

An asymmetric approach to the pentacyclic core was reported in 2013 by the Eric J. Thomas research group at University of Manchester.[28] This method employs an intramolecular Mannich to form the fully functionalized requisite tropane in 85% yield (Scheme 14). The observed stereoselectivity was presumed to be a result of thermodynamic control where the desired isomer is favored by avoiding syn-gauch interactions with the benzyloxy group. This approach also shares some similarities with

Kende's method, where multiple rings are formed following the removal of the protecting benzyloxy group by hydrogenolysis. Overall the pentacyclic core was established in 2.3% overall yield from 19 steps.



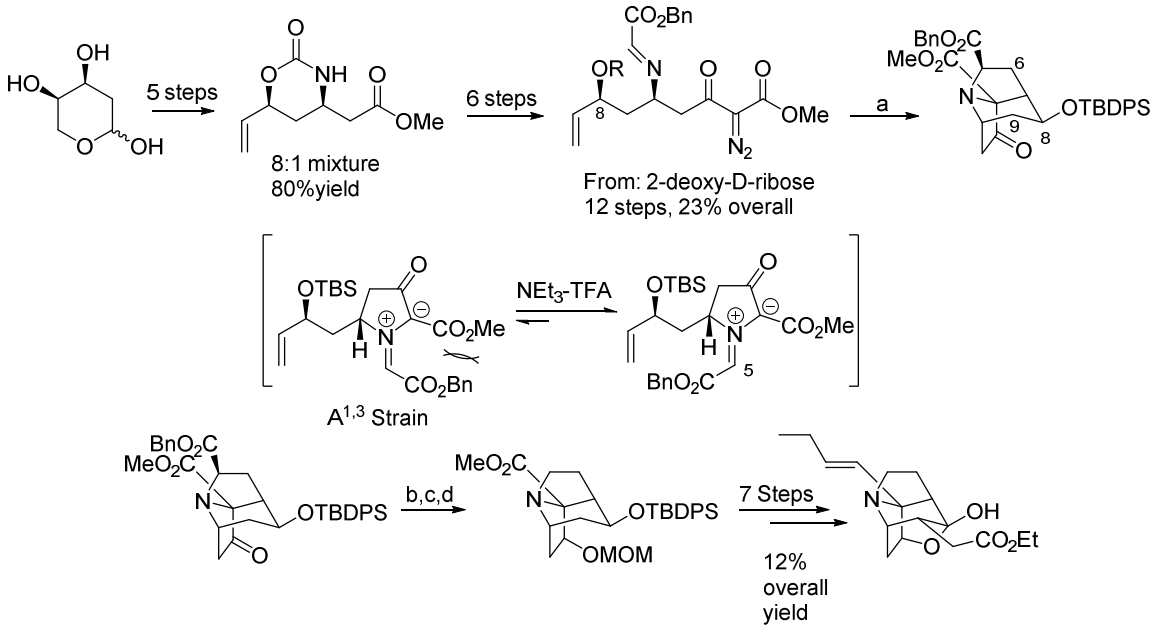
(a) TFA, DCM, -78°C, 12 h , 85%; (b) 10% Pd/C, TFA, EtOAc, rt, 1 h ,82%; (c) DIBAL-H, DCM, -78°C, 1 h ,83%; (d) Ph_3P, imid., I_2, DCM, 35°C, 1 h ,92%; (e) ^tBuLi, hexanes, THF, -78 to 0°C, 5 min ,86%.

Scheme 14: Eric J. Thomas's approach.

Rhodium Initiated azomethine Ylide
Cycloaddition: Stephen F. Martin

Recently, at the University of Texas, the Stephen F. Martin research group reported an asymmetric approach towards the Stemona alkaloids utilizing a rhodium initiated regioselective cycloaddition of an azomethine ylide.[29] Generation of such an azomethine ylide was achieved through a series of steps from commercially available 2-deoxy-D-ribose among which involve a Boord elimination to provide a chiral allylic alcohol followed by a diastereoselective Hirama-Ito cyclization to afford a cyclic carbamate as a 8:1 mixture in 80% yield (Scheme 15). This carbamate may then be

cleaved and transformed to the key diazoacetate using an optimized Claisen condensation process. Extensive studies revealed that the essential azomethine ylide required a readily removable electron withdrawing group at C(5) to assure the regioselectivity of the cycloaddition. The presence of substituents at C(8) and C(9) were shown to be insufficient. The ring closure proceeded preferably by isomerization to the S-shaped ylide due to reduced $A^{1,3}$ strain. Following the cyclization, a Barton decarboxylation process then removed the directing ester group.

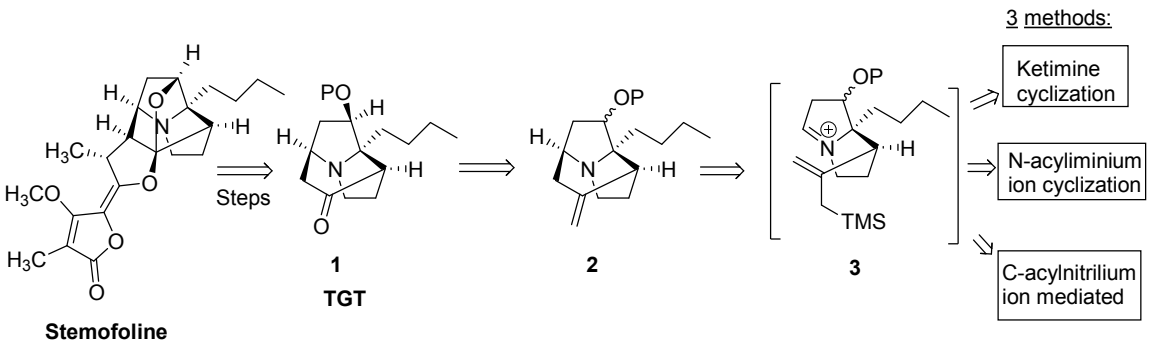


a. $Rh_2(OAc)_4$ (3 mol %), NEt_3-TFA, xylenes, reflux, 75%, b. $NaBH_4$ (3 eq), MeOH, -30°C, 86%; c. MOMCl, NE*t*-Pr_2, DMF, 50°C, 75%; d. 1. Pd/C, H_2, EtOH, 2. N-hydroxy-2-pyridinethione, DCC, DMAP, *t*-BuSH, $CHCl_3$, hv (250 W), 63%.
Scheme 15: Stephen F. Martin's approach.

Allylbis(silane) Iminium Ion Studies:
Tim Kercher & Tom Livinghouse

In 1997, Kercher and Livinghouse[30] demonstrated the applicability of the allylbis(silane)-iminium ion cyclization methodology towards the construction of the

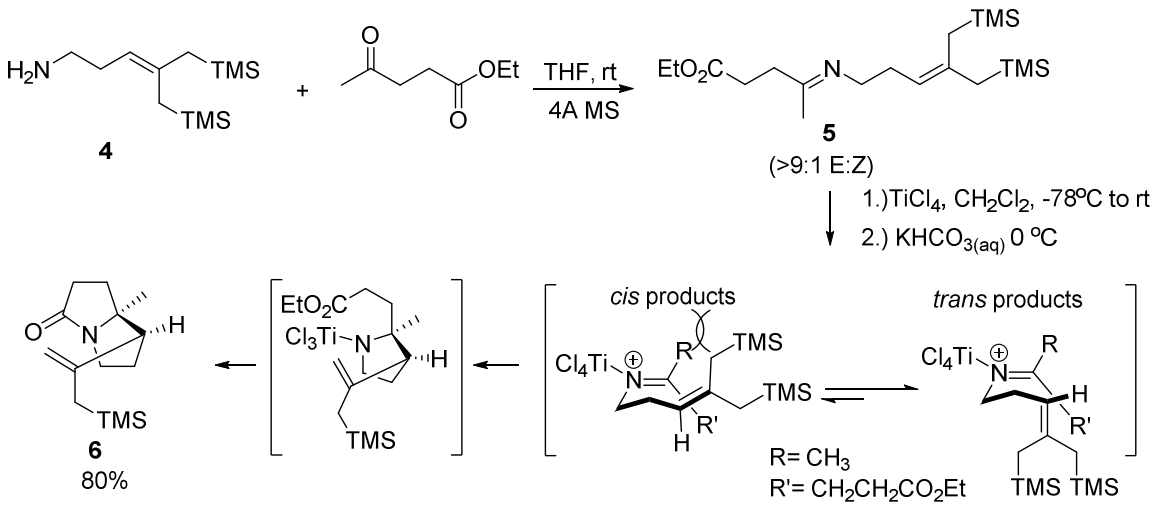
azatricyclic core present in the stemonaceae alkaloid, Stemofoline. During this exploration, the tricyclic synthetic target **1** would be derived from intermediate iminium ion **3** by the key allyl silane-iminium ion cyclization transform (Scheme 16). Generation of iminium ion **3** was approached through three different synthetic strategies which include a ketimine cyclization route, *C*-acylnitrilium-ion mediated polycyclization and an *N*-acyliminium ion-allylbis(silane) cyclization. The exploration began with screening experiments geared towards determining the applicability of using the 2-propylidene-1,3-bis(silane) terminator.



Scheme 16: Tim Kercher's retrosynthetic plan and methods.

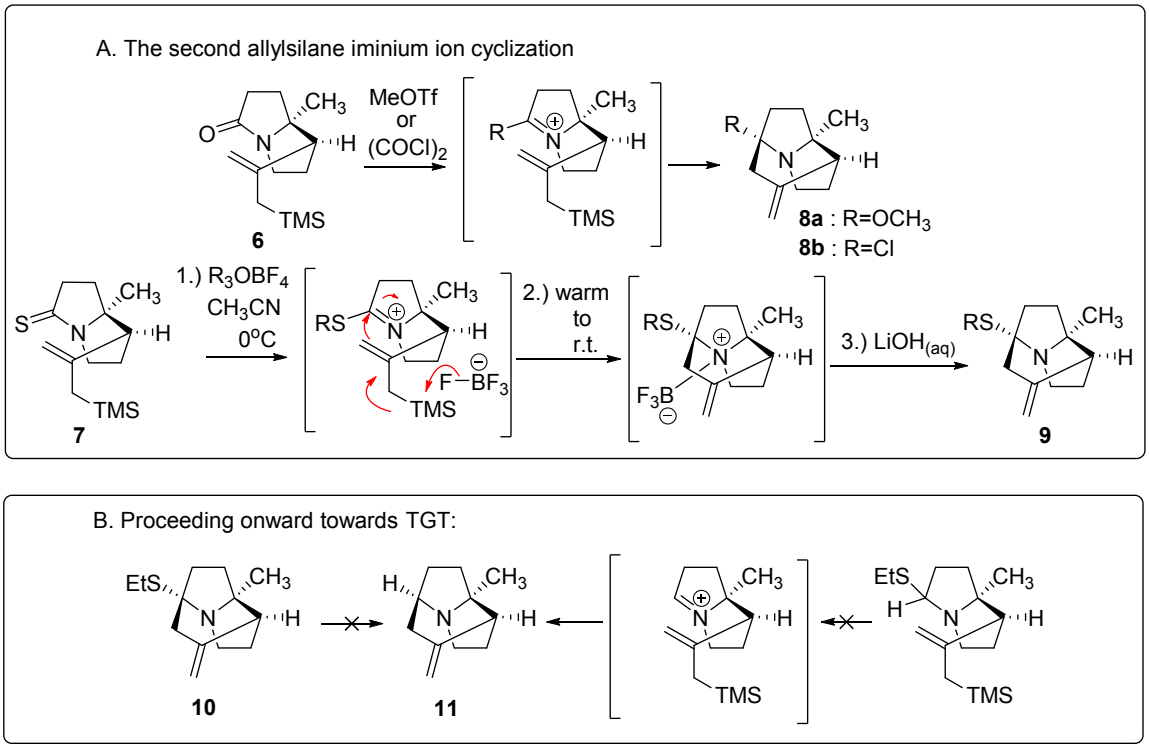
In an initial model study, the ketimine cyclization route began by performing a condensation between ethyl levulinate and amine **4** (Scheme 17). The resultant imine **5** was subjected to cyclization conditions that successfully provided the desired lactam **6** in 80% yield after chromatographic separation over silica. A primary concern at this point was whether or not the necessary *trans* relationship between the methyl group and the allylic TMS group was acquired in sufficient yield and selectivity. The definitive orientations of these groups were determined by the ^{1}H NMR magnetic anisotropic effects exhibited by the shielding cone of the carbonyl on the chemical shift of the

olefinic protons. Using this argument, the undesired diastereomer was shown to not exhibit anisotropic effects and therefore the olefinic peaks of the undesired diastereomer shift downfield.



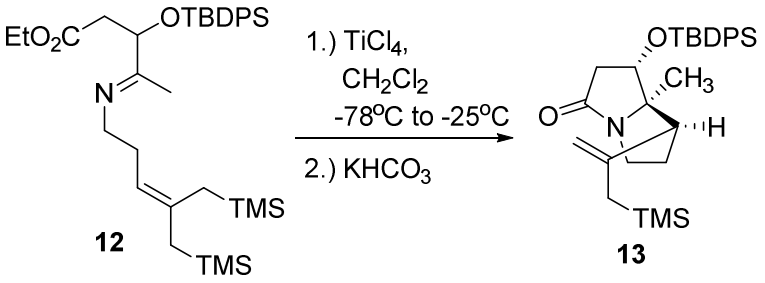
Scheme 17: The ketimine cyclization route.

Focus was then shifted toward executing the second allylsilane iminium ion cyclization. The previously prepared lactam **6** and its thiolactam variant **7** were utilized (Scheme 18). These studies revealed that even electron-rich iminium ions undergo the cyclization readily. Fortunately, competitive alkylation of the product was not observed. The more stable, tricyclic thiopyrrolizidine **9**, was then subjected to a wide variety of desulfurization methods, all of which were unsuccessful to provide the desired bridged pyrrolizidine **11**. Pyrrolizidines **8a** and **8b** were too unstable for isolation and purification.



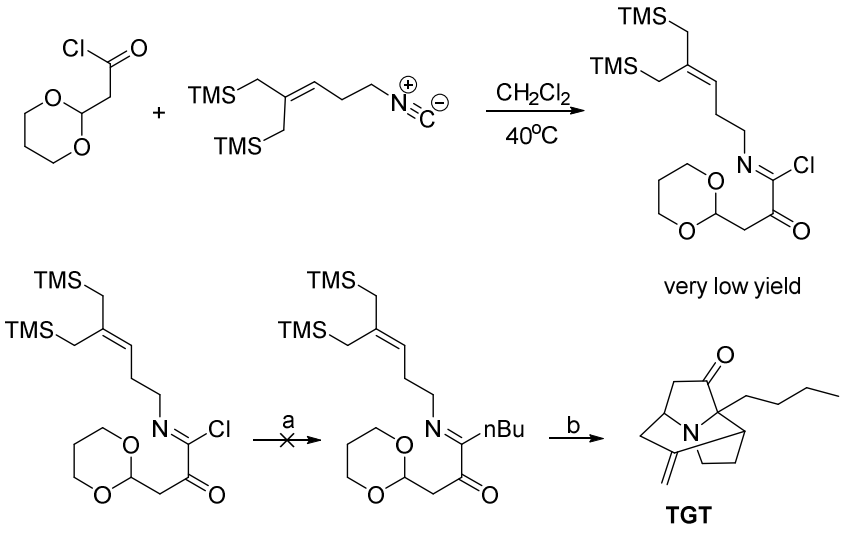
Scheme 18: The second cyclization (Kercher).

Based on the preliminary results from the model cyclization-desulfurization studies an analogous route was attempted. The ketimine cyclization began with preparation of imine **12** containing the appropriate protected alcohol functionality (Scheme 19). Unfortunately, when subjected to the cyclization conditions previously employed, low yields were obtained of the desired lactam **13** (25% using $TiCl_4$ and 34% using $(Me_2S)_2ZrCl_4$).



Scheme 19: Adding the requisite protected alcohol functionality.

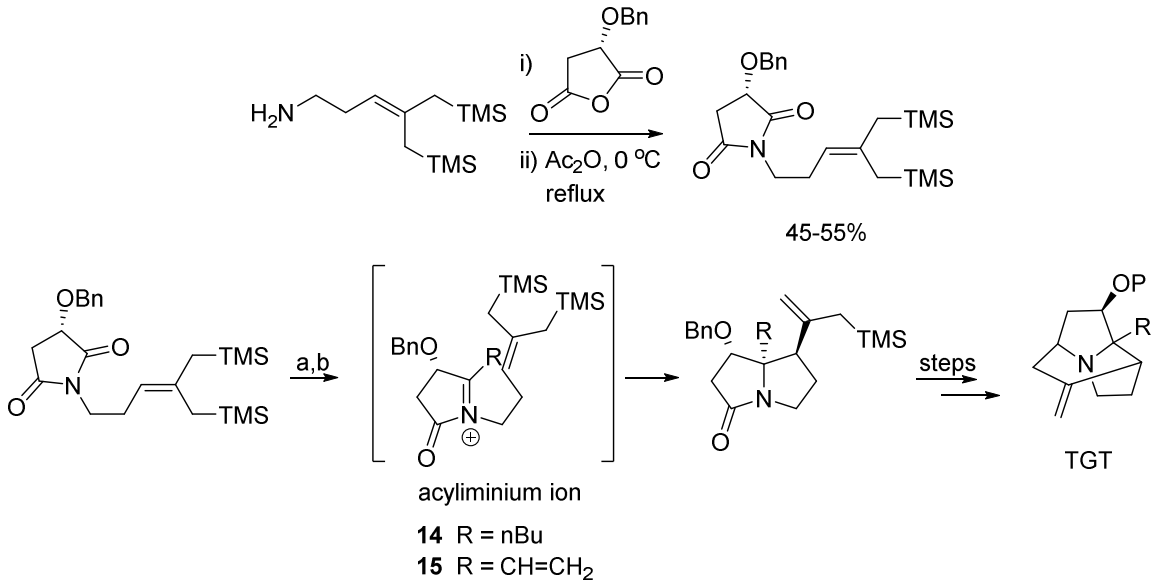
The next method to be explored, utilized a *C*-acyliminium chloride. In this route, propanimidoyl chloride was generated from treating isocyanopropylidene-1,3-bis(silane) with 2-(1,3-dioxan-2-yl)acetyl chloride (Scheme 20). Unfortunately, the required imine was not formed after screening multiple organocuprates. This route was not investigated further.



Scheme 20: *C*-acylnitrilium ion initiated polycyclization.

The final method briefly investigated was the *N*-acyliminium ion – allylbis(silane) cyclization. The studies pertaining to this method reveal that acidic hydrogen's contained

on the butyl side chain of hydroxylactam **14** interfere with the desired cyclization from occurring, resulting in a mixture of elimination and protodesilylation products (Scheme 21). Model experiments that focused on solving this issue utilized ethenyl-magnesium bromide to introduce an alkene substituent (imide **15**). Once more, upon treatment with cyclization conditions no desired bicycle formation occurred. Other issues contained within this method involved low isolated yield (45-55%) of the key Negishi coupled cyclic imide due to decomposition.



Scheme 21: *N*-acyliminium ion cyclization.

Further investigations by the Livinghouse group towards developing this methodology of allyl silane terminated cyclizations has continued beyond the scope of the stemona alkaloids. For instance, Duncan and Livinghouse explored the utility of 2-(methylthio)-3-(trimethylsilyl)-1-propenyl moieties. It was mentioned that (*Z*)-allylsilanes cyclize with trouble and loss of stereoselectivity. This problem was solved by

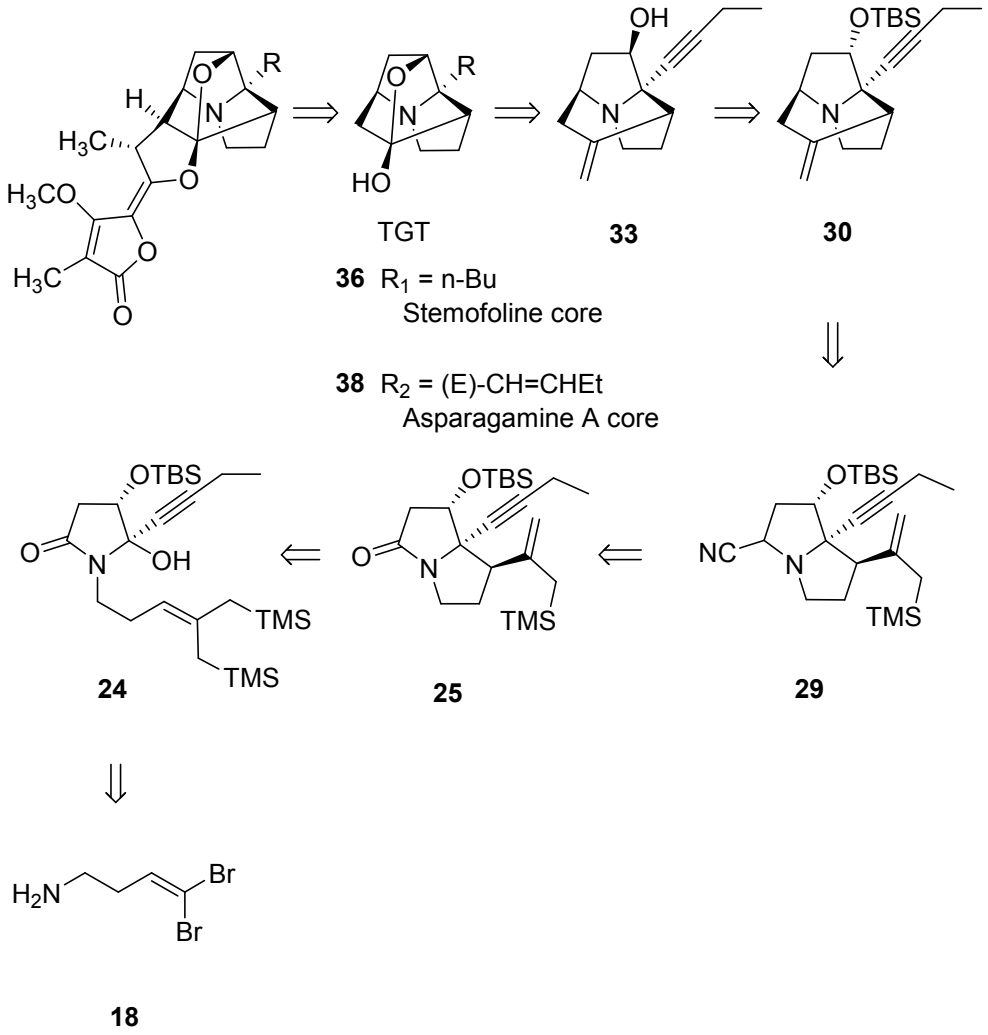
the incorporation of a thioalkyl group in the vinylic position, which increased the nucleophilicity of the terminator and resulted in stereoselective cyclizations with a higher efficacy. The utilization of this strategy was subsequently applied to the total synthesis of turneforcidine[31]

CHAPTER 3

FURTHER STUDIES TOWARDS THE HETEROTRICYCLIC CORE OF THE STEMONA ALKALOIDS: ASPARAGAMINE A AND STEMOFOLINE

Retrosynthetic Plan

A continuation of studies concerned with the *N*-acyliminium ion approach began with the construction of key intermediate **24,** which was envisioned to proceed through a stepwise closure to provide the bridged pyrrolidinone **30** by means of two allylbis(silane)-iminium ion transforms (Scheme 22). The acetylenic side chain contained within precyclization precursor **24** is believed to prevent any formation of elimination or protodesilylation products due to the absence of acidic hydrogens on the hydrocarbon side chain. The bulky TBS group observed in precursor **24** serves not only as a protecting group but also as a stereochemical directing group to enforce the desired stereochemistry observed in lactam **25**. This method of construction is envisioned to provide the enantiopure tetracyclic core observed in Stemofoline **36** and Asparagamine A **38** through a stereochemical modification of the protected alcohol in tricycle **30**, oxidative cleavage of the alkene observed in **33** and a divergent reduction sequence to provide the target compounds in this relay synthesis.

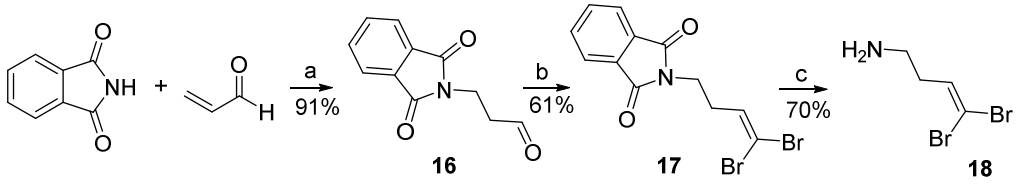


Scheme 22: Retrosynthetic plan.

The Construction of Amine 18 and Vinylidene Dibromide **21**

The synthesis of amine **18** began with the conjugate addition of phthalimide to acrolein in the presence of Triton B at 60 ºC for 15 min to provide aldehyde **16** in 93% crude yield as a white solid (Scheme 23).[32] Alternative methods to aldehyde **16** were not as successful. Treatment of phthalimide with a catalytic amount of potassium phthalimide rather than Triton B provided a mixture of products observed by TLC. This method was

not investigated further. Treatment of phthalimide with a catalytic amount of sodium ethoxide provided the desired aldehyde in high yield (~96%) as a viscous oil upon quenching with glacial acetic acid. The resultant aldehyde from this method contained more impurities by ^{1}H NMR than the Triton B route. Due to the ease of use and apparent low contamination, the use of Triton B was favored. Flash column chromatography and recrystallization methods provided no obvious benefit. In some cases, oxidation of the aldehyde functionality was observed.



Reagents: (a) Triton B, EtOAc, rt. (b) Condition 1: CBr_4, PPh_3, CH_2Cl_2, 0°C, 84% Condition 2: CBr_4, PPh_3, Zn dust, CH_2Cl_2, 0°C, 61% (c) NH_2NH_2, EtOH, reflux.

Scheme 23: Synthesis of primary amine **18**.

Treatment of aldehyde **16** with conditions developed by Ramirez[33] and Corey[34] provided alkylidene dibromide **17** in 84% isolated yield upon purification over silica gel. The utilization of Zn dust[35] provided lower yields (~60%) but allowed for simpler isolation of the product. The purification process was simplified even further by employing a chromatography-free method developed by Gilheany.[36] This simple process uses oxalyl chloride, which serves to convert the formed triphenylphosphine oxide into a sparingly soluble chlorophosphonium salt.

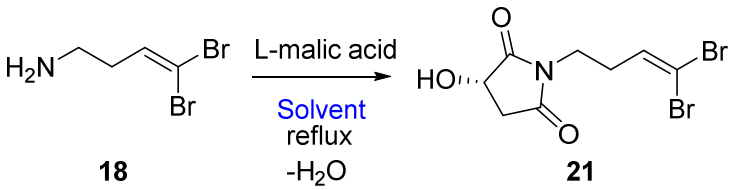
Deprotection of phthalimide **17** with hydrazine monohydrate successfully provided the requisite amine **18** in 85% crude yield (the yield was shown to be capricious due to volatility issues) after soxhlet extraction of the resultant solid. Alternatively, the

amine may simply be placed under vacuum with benzene to remove the ethanol by azeotropic distillation. Due to issues involving the removal of ethanol from the volatile amine, alternative procedures were explored. Interestingly, NMR scale reactions utilizing methyl hydrazine in $CDCl_3$ showed no reaction after 4 days following the traditional temperature ramping scheme (25ºC →45ºC→60ºC).[37] Later, literature searches revealed the formation of the hydrochloride salt to be another method to address the volatility issue.[38] The resulting hydrochloride salt may then be neutralized with 1M KOH and the amine isolated by extraction with diethyl ether. Following the careful removal of the solvent, amine **18** was provided in comparable yields (77-82%) with minimal loss due to evaporation.

The condensation of amine **18** with L-malic acid was then investigated (Table 1). Reports of moderate to high yields (70-85%) in literature when using a variety of amines made this approach seem promising.[39,40] Unfortunately, despite numerous attempts, the highest yields observed were 55-60%. As seen in Table 1, the preferred solvent is *p*-xylene and varying the reaction duration had little effect on the overall yield. The issue seemed to involve decomposition of the amine due to the high temperatures required for reaction. The crude reaction mixtures from these trials were purified by conventional chromatography on silica gel (1:1 ethyl acetate in hexanes) with little separation difficulties. Recrystallization attempts explored provided clean product, but considerably low yield due to poor recovery.

Further studies on this condensation method met with disappointingly low yields of pyrrolidinone **21**. When promoting this condensation with $Ti(O\text{-}^{i}Pr)_4$ in either *p*-xylene

or toluene, yields were 20 and 26% respectively (Table 1).[41] Among alternative methods investigated, the DCC coupling of L-malic acid with amine **18** also failed to provide the target pyrrolidinone **21**.



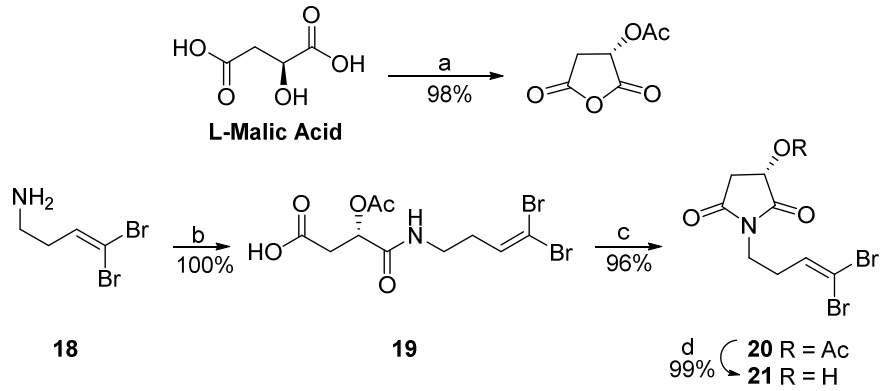
18 **21**

Table 1. Results for condensations with L-malic acid

Entry	Solvent	Additive	Time	Isolated Yield
1	p-Xylene	-	4h	60%
2	p-Xylene	-	~18h	52%
3	Chlorobenzene	-	22h	18%
4	Toluene	-	18h 40min	54%
5	p-Xylene	$Ti(OiPr)_4$	18h	20%
6	Toluene	$Ti(OiPr)_4$	18h	26%

Due to continuously disappointing yields of pyrrolidinone **21** an alternative route was investigated. Procedures outlined by Lee[42] and Chamberlin[43] were explored and the desired imide **21** was ultimately obtained in high yield (Scheme 24). This approach proceeded by nucleophilic opening of the anhydride (derived from L-malic acid) by amine **18**. The intermediate amide (**19)** was then exposed to acylation conditions to form cyclic imide **20** in near quantitative yield. Subsequent removal of the acetate group on imide **20** by generation of HCl *in situ* (AcCl in EtOH) provided the desired cyclic imide **21** in an overall 96% yield from L-malic acid. Unfortunately, excess of amine **18** was required for full consumption of the inexpensive cyclic anhydride due to salt formation. In an effort to minimize the amount of amine **18** utilized in the nucleophilic opening of the anhydride, the use of catalytic amounts of triethylamine (TEA) as a sacrificial amine

proved beneficial (Scheme 24). When employing TEA (0.1 equiv), nearly quantitative yields were obtained. Use of the hydrochloride salt of amine **18** provided elimination products arising from the formation of malic anhydride when amine generation was attempted *in situ* with triethylamine.



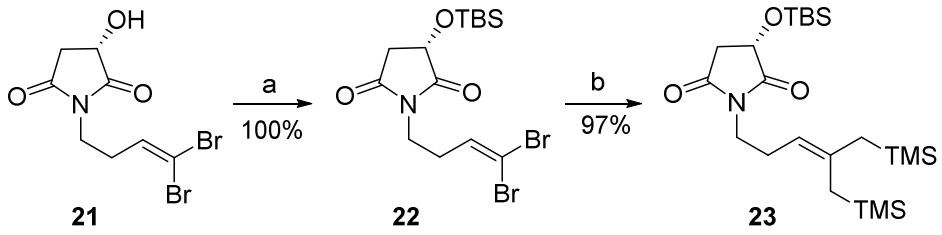
Reagents: (a) AcCl, reflux, 98% (b) 1. anhydride, CH_2Cl_2, 0°C; 2. Et_3N (0.1 equiv), 100% (c) AcCl, reflux, 96% (d) AcCl, EtOH, 99%

Scheme 24: Construction of vinylidene dibromide **21**.

Installation of the 2-propylidene-1,3-bis(silane) and Production of Precycle **24**

With convenient access to succinimide **21,** the procedure developed by Corey[44] for the protection of secondary alcohols was performed to provide the TBS protected succinimide **22** in nearly quantitative yield (Scheme 25). Unfortunately, obtaining the required pyrrolidinone **23** initially proved to be problematic. Following the protocol of Kercher, phthalimide **17** was exposed to a mixture of 7 mol% $PdCl_2(PPh_3)_2$ + TMEDA-$Zn(CH_2TMS)_2$ to provide the Negishi coupled product in 96% yield after purification. $ZnCl_2$-TMEDA was used in place of $ZnCl_2$-$(THF)_2$ due to precedent provided by

Lipshuts, Isobe and Oshima.[45] Unfortunately, when applying these conditions towards succinimide **22**, low yields and complex mixtures were observed.

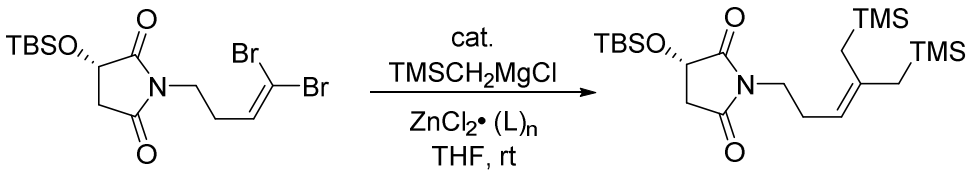


Reagents: (a) TBSCl, Imidazole, DMF (b) $Zn(CH_2TMS)_2$, $PdCl_2(PPh_3)_2$ (7 mol%), THF

Scheme 25: Protection of imide **21** and installation of the 2-propylidene-1,3-bis(silane) moiety.

In order to determine the source of the complications, the catalyst and organozinc sources were investigated. A variety of palladium catalysts were explored and $(PPh_3)_2PdCl_2$ remains the best (Table 2).[46] Among the trials conducted with $ZnCl_2$-TMEDA, the reaction progress tends to slow and eventually halt. Consumption of active catalytic species was initially presumed to be the result of this incomplete conversion. However, addition of more catalyst when the reaction subsided had no effect (not shown in table). Introduction of excess $(TMSCH_2)_2Zn$ also had no added benefit (Entries 2 and 3, Table 2). Solvent effects were also investigated, it was anticipated that the addition of DMF would polarize the Zn-C bond and allow faster transmetallation (not shown in table). An apparent acceleration was initially observed, but the reaction became sluggish after 18 h. The yields remained the same with the DMF additive. Overall, isolation of imide **23** derived from the Negishi cross-coupling utilizing $ZnCl_2$-TMEDA provided the desired product in 11 to 21% yield. The furnished low yields were believed to be a direct result of the $ZnCl_2$-TMEDA complex rendering the organometallic too basic. This feature

led to substantial decomposition. A simple switch to $ZnCl_2$-$(THF)_2$ resulted in dramatic improvements in yield, affording imide **23** in 97% yield (Entry 1, Table 2). Special care should be taken when conducting this reaction because introduction of the slightest impurity has been observed to result in greatly diminished yields.



22 **23**

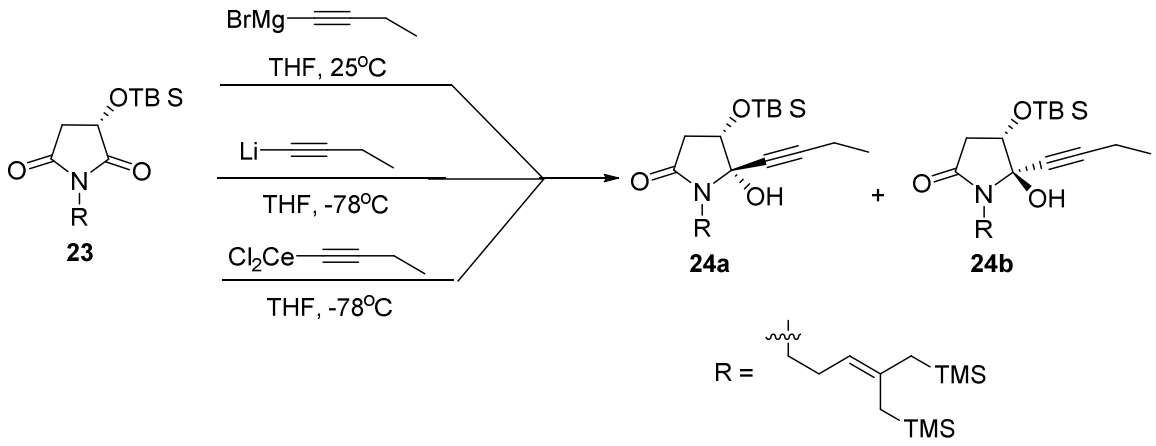
Table 2: Negishi-Coupling Trials

Entry	Catalyst (7mol%)	$ZnCl_2$• $(L)_n$	$TMSCH_2MgCl$	Time	Conv. (%)[a]
1	$PdCl_2(PPh_3)_2$	1 equiv.[b]	2 equiv.	11.5 h	>95 (97)
2	$PdCl_2(PPh_3)_2$	1 equiv.[c]	3 equiv.	15.5 h	41 (21)
3	$PdCl_2(PPh_3)_2$	1 equiv.[c]	4 equiv.	18 h	26 (11)
4	$PdCl_2(PPh_3)_2$	1 equiv.[c]	2 equiv.	69 h	39 (15)
5	$PdCl_2(PMePh_2)_2$	1 equiv.[c]	3 equiv.	11 d	6

[a]As determined by ^1H NMR and/or GC analysis of crude reaction mixtures. Isolated yields in brackets.
[b]L = THF, n = 2
[c]L = TMEDA, n = 1
Other catalyst sources tried: $PdCl_2[P(o\text{-}Tol)_3]_2$, $Pd(OAc)_2 + PPh_3$[47], $Pd(OAc)_2 + P(Cy)_3$, $Pd(OAc)_2 + P(Ph)_2Me$, $NiCl_2(PPh_3)_2$.

The next objective was the nucleophilic alkynylation of pyrrolidinone **23** to produce the requisite cyclization precursor, hydroxylactam **24**. After examining numerous conditions, it was found that exposure of imide **23** to lithiobutyne (3 equiv) in THF at –78 °C for 30 min followed by 16 h at –20 °C provided the desired hydroxylactam in 85 % yield as a diastereomeric mixture (**24a** (85%)/**24b** (15%), Scheme 26**,** see page 42 for identification of diastereomers). During the optimization process, the use of excess lithium reagent was shown to be required for full conversion.[48] Attempts at

utilizing the organocerium or Grignard variants provided nearly exclusive formation of hydroxylactam **24b** or a mixture of products consistent with incomplete Grignard formation by salt metathesis, respectively. The pentyne and hexyne derivatives of the hydroxylactam were formed in a similar manner and utilized as models toward the cationic desilylative cyclization.



Scheme 26: 1,2 addition to pyrrolidinone **23**.

Evaluation of Conditions for the First Cationic Desilylative Cyclization Event

Attention was then shifted towards a crucial step, the cationic desilylative cyclization process. This investigation began with employing methods documented by Speckamp and Hiemstra on their work with the cyclization of allyl and propargylsilanes onto *N*-acyliminium ions. It was envisioned that the bulky TBS group on precycle **24** would serve to direct the ring closure to one face on the molecule, providing a single diastereomer. Literature searches revealed that among the conditions required for iminium ion formation from a tertiary hydroxylactam, strongly acidic conditions such as

TFA, formic acid, BF_3-OEt_2, and 2:3 HCO_2H/AcOH are essential.[49] Interestingly, the work of Evans[50] and Speckamp[51] on the synthesis of perhydrohistrionicotoxin reveal that their requisite cyclization of a tertiary hydroxylactam proceeds via protonation of an enamide rather than immediate ionization to the iminium ion.

Unfortunately, the use of traditional ionizing conditions (TFA, formic acid and BF_3-OEt_2[52]) with hydroxylactam **24** resulted in desilylation of the terminator moiety. Poor results were also observed with $SnCl_4$[53], $Mg(OTf)_2$[54], $FeCl_3$[55], PPTS[56], 5 mol% $LiBF_4$, 4M $LiNTf_2$[57] (in acetone and Et_2O), montmorillonite K10[58] and many others. A complete listing of all the Brønsted and Lewis acids that were examined is shown in Table 3. Conditions previously utilized by Kercher ($TiCl_4$, CH_2Cl_2, -78ºC to rt) provided yields comparable to the fully functionalized ketimine method (25%, see page 20) where the NMR calculated yield was 20% using bis(*t*-butyl)biphenyl as a non-volatile internal standard. In an attempt to attenuate the reactivity of the titanium-centered Lewis acid, *cis*-$[TiF_4(THF)_2]$ was investigated and was shown to provide lower yields that the traditional $TiCl_4$ route (12%).[59]

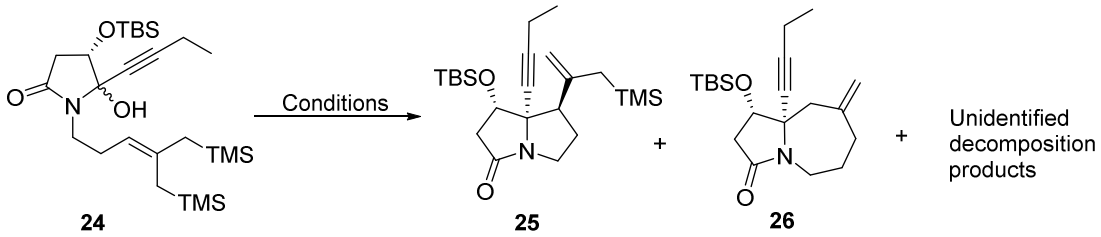


Table 3: Brønsted and Lewis acids screened for the cyclization

Entry	Conditions	**25**, Yield %[a]
1	5M LPDE, 22 °C, 10 h	28%
2	KH, -20 °C then $TiCl_4$, -78 °C, 8 h	20%
3	*Cis*-[$TiF_4(THF)_2$]	12%
4	$ZnCl_2$-$(THF)_2$	10%
5	BF_3-OEt_2, CH_2Cl_2, 0 °C, 1 h	Trace[b]

[a]Yields determined by NMR[60] using t-butylbiphenyl as a non-volatile internal standard.
[b]Product barely observable by NMR. Detected by mass spectroscopy.
Conditions that resulted in protodesilylation/decomposition: TFA, Formic acid, $Mg(OTf)_2$, $Zn(OTf)_2$, $ZrCl_4(SMe)_2$, $FeCl_3$, PPTS, 5 mol% $LiBF_4$, 5 mol% $HClO_4$[61], montmorillonite K10, 4M $LiNTf_2$ in Et_2O, 4M $LiNTf_2$ in acetone, 10 mol% $Mg(NTf_2)_2$ in CH_2Cl_2[62], TMSCl, Me_2AlCl[63], Me_3Al, $SnCl_4$, Ph_3CBF_4[64], Tetrachloroethane[65], F_2BOBn-Et_2O[66], $MeTiCl_3$.[67]

Due to the reported success by the Grieco group on lithium perchlorate-diethyl ether (LPDE) facilitated ring opening of oxabicyclic systems[68,69], and rate acceleration of Diels-Alder cycloaddition reactions[70], this polar medium was investigated. Treatment of hydroxylactam **24** in freshly prepared 5M LPDE provided an inseparable mixture (by traditional column chromatography) of silylated and protodesilylated bicyclic lactams **25** and **26**. Within this crude mixture a 28% calculated yield of the desired lactam **25** was observed by ^1H NMR. Purification by reverse-phase HPLC was successful but resulted in considerable loss due to solubility issues (10% yield).

The formation of protodesilylated lactam **26** suggests the presence of an acid source. Despite thorough drying of the lithium perchlorate (via. drying pistol and heating at reduced pressure, 0.001mmHg at 180°C), freshly distilling diethyl ether from sodium

metal/benzophenone and base washing of glassware, protodesilylation remained to be a problem. Reaction rates seem slower with the dryer solutions (15 h), and product compositions showed marginal improvement. Additionally, resubmitting lactam **25** to the same reaction conditions did not result in further protodesilylation. This result indicates that the formation of undesired lactam **26** occurs by initial protodesilylation followed by cyclization. At this point during the screening process the proton source was speculated to be the tertiary hydroxyl hydrogen. In attempt to improve upon this cyclization process various scavengers and additives were screened (Table 4). A noteworthy trial involving catalytic amounts of TMSCl (Entry 1, Table 4) was employed due to its notable success as a Lewis acid for promoting the ring opening of oxabicyclic systems.[71] This attempt proved to be unsuccessful and complete conversion to the undesired lactam **26** was observed.

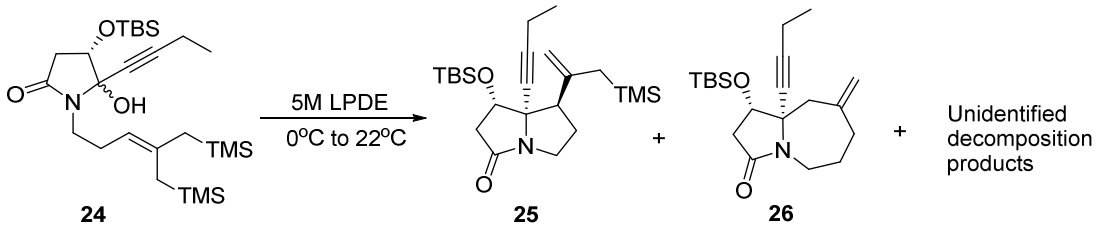


Table 4: Screening for acid scavengers and buffers with 5M LPDE

Entry	Additive	Time	**25**, Yield[a] %
1	TMSCl (0.05 equiv)	3 h	0%
2	TMSCl + Hunigs base (or TMS_2NH)	4 h	27%
3	Hunigs base or TMS_2NH	4 h	No Reaction
4	4Å MS (excess)	24 h	No Reaction
5	Proton Sponge (0.15 equiv)	8 d	3%
6	$SrCO_3$ (0.15 equiv)	4 d	28%
7	LiOH	2 d	No Reaction
8	TMS-methylfuran (**S[1]**)	48 h	28%
9	Allylsilane (**S[2]**)	6 h	28%
10	bis(allylsilane) (**S[3]**)	54 h	28%

[a]Yields determined by NMR and GC using t-butylbiphenyl as a non-volatile internal standard and dodecane as a volatile standard respectively.

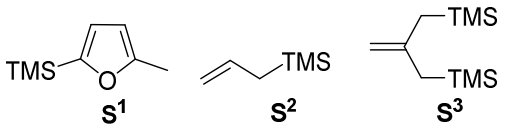
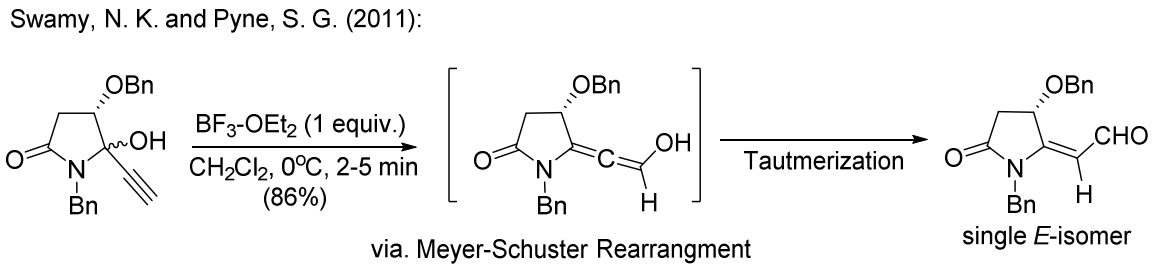


Figure 2. The pictorial representation of **S[1]**, **S[2]**, and **S[3]** functionalities from **Table 4**.

Addition of catalytic amounts of base (TMS_2NH, $(i\text{-Pr})_2NEt$, $SrCO_3$ or LiOH) was explored for possible buffering effects. In the Lewis acid catalyzed trials (Entry 2, Table 4), addition of base provided comparable product compositions to 5M LPDE without any additives, however, experiments lacking TMSCl (Entry 3) resulted in no reaction. Slowly dissolving bases ($SrCO_3$ and LiOH) and silane-based acid scavengers[72] (Entries 8-10, Table 4) resulted either in no reaction or no improvement in yields. The only notable features about these trials are the differing reaction times. Interestingly, the addition of excess 4Å MS to the mixture prevents any reaction from occurring (Entry 4, Table 4). A

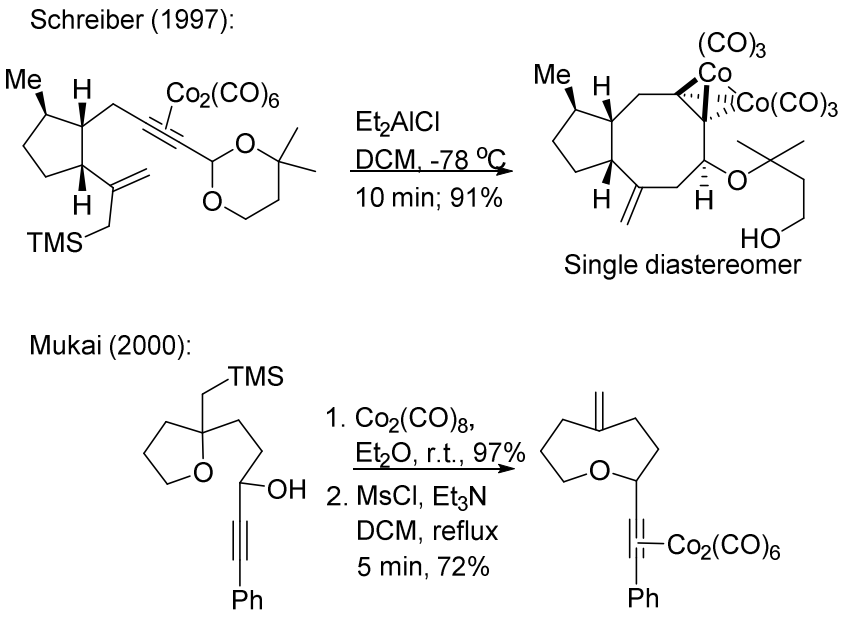
possible explanation of this result is the shielding of the hydroxyl functionality within the pores of the sieves resulting in no interaction with the Lewis acidic solvent.

In 1972, Nicholas and Pettit demonstrated that dicobalt hexacarbonyl stabilized propargylic alcohols are easily ionized and may be trapped with a variety of nucleophiles.[73] This method has the benefits of increased propargylic cation reactivity in comparison to unprotected alkynes and the prevention of possible allene or related side product formation (Scheme 27).[74]



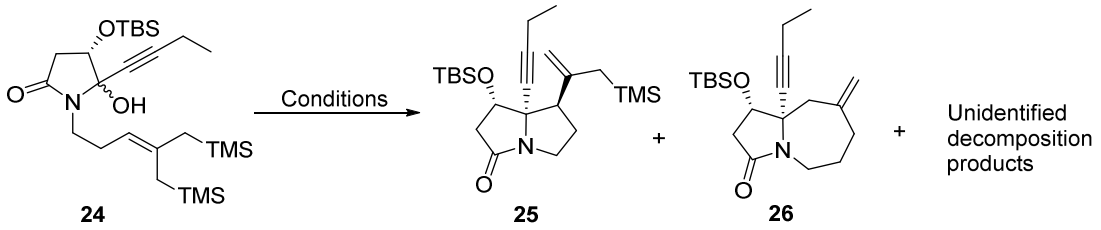
Scheme 27: Meyer-Schuster rearrangement propargyl alcohols.

The application of such methodology utilizing allylsilane nucleophiles has received some attention.[75] For instance, the total synthesis of (+)-epoxydictymene completed by the Schreiber laboratories demonstrated the synthetic applications of the Nicholas reaction by forming the requisite fused 8-membered ring in high yields (Scheme 28). Unfortunately, attempts towards the protection of the alkyne on hydroxylactam **24** utilizing $Co_2(CO)_8$ in diethyl ether was unsuccessful (returned starting material) and was not investigated further.



Scheme 28: Examples of the Nicholas reaction with silanes.

Attenuation of solvent polarity from 5 to 1 M LPDE slowed reaction rates but had no effect on product composition. Trials utilizing 1M LPDE were very slow and never achieved complete conversion even after extended reaction times. Furthermore, alternate solvent combinations with $LiClO_4$ were examined (Table 5). When employing 5M $LiClO_4$-CH_3NO_2 (LPNM) exclusive byproduct formation occurred. Incorporating 5M $LiClO_4$-EtOAc also had detrimental effects, resulting in a mixture of product formation and decomposition. It was originally envisioned that employing less coordinating solvents such as CH_3NO_2 would favor the cationic cyclization process due to the increased Lewis acidity of the Li ion.[76] Overall, opposite effects are observed and more coordinating solvents seem to promote the cyclization. A possible rationalization for the observed trend may involve the degree of acyliminium ion-cation solvation or differences in internal solvent pressure. Further investigation is required to elucidate the observed solvent effects.



24 25 26

Table 5: Screening of various solvent combinations with $LiClO_4$

Entry	Conditions	Time	**25**, Yield (%)[a]
1	5M LPDE	10 h	28
2	4.5M LPDE	18 h	28
3	1M LPDE	2 months	9
4	5M LPNM	7.5 h	5
5	5M $LiClO_4$ in acetone	>3 months	20
6	5M $LiClO_4$ in ethyl acetate	22 h	26
7	5M $LiClO_4$ in Acetonitrile[b]	48 h	0

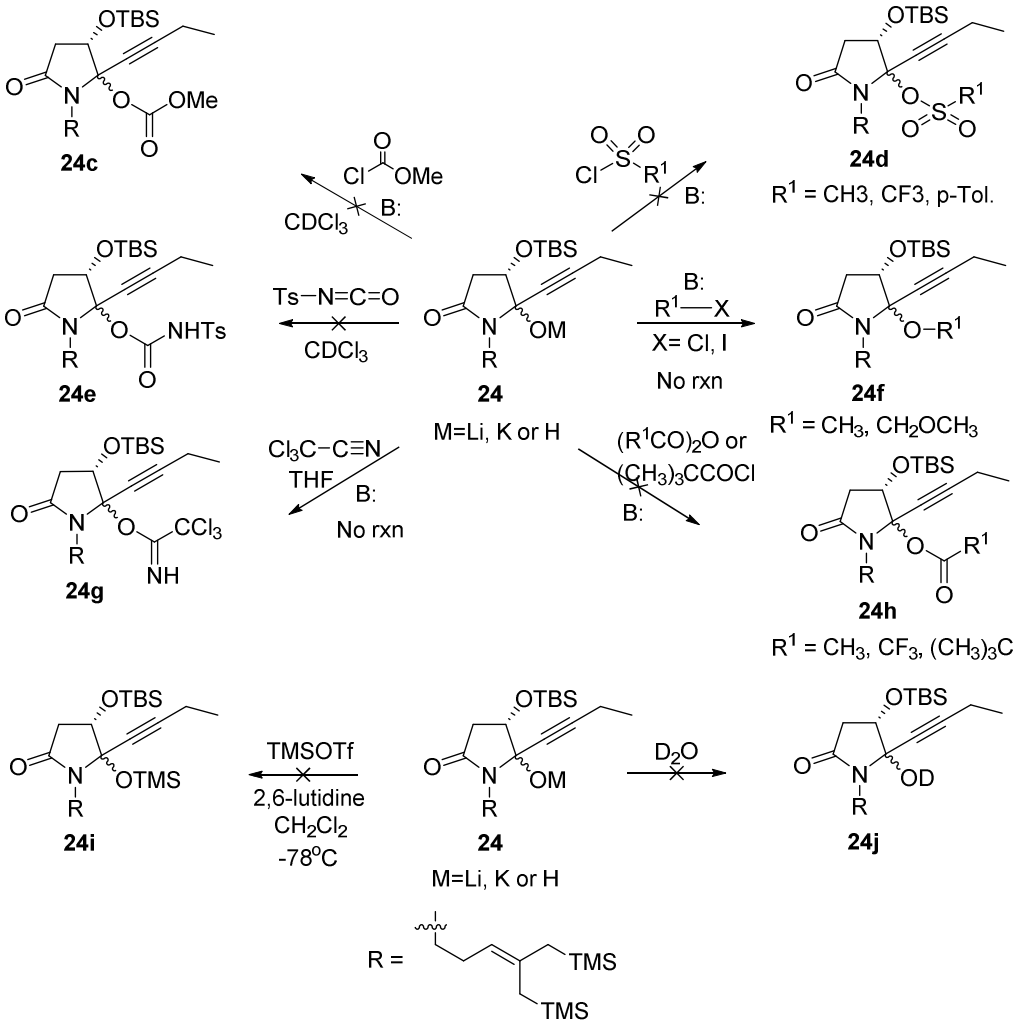
[a]Yields determined by NMR and GC using t-butylbiphenyl as a non-volatile internal standard and dodecane as a volatile standard respectively.
[b]Acetonitrile utilized was from a new and unopened bottle of Acetonitrile-d_3. Observed monodesilylation but no ring closure.
[c]Side note: Attempts employing $LiClO_4$ in tertbutylmethyl ether (MTBE) were unsuccessful due to $LiClO_4$ being very insoluble in MTBE. Similar results were observed when trying CH_2Cl_2 and toluene. Trials with $LiClO_4$-THF returned starting material with minimal decomposition after 4 days.

In addition to the cyclization studies performed on hydroxylactam **24**, functionalization of the alcohol was also pursued (Scheme 29). Conversion of hydroxylactam **24** to its semi-stable acetate derivatives (**24h,** Scheme 29) was unsuccessful and provided decomposition products or returned starting material. A wide range of conditions were evaluated. These include the traditional acetylation conditions (Ac_2O/DMAP/CH_3CN and TFAA/Pyridine/CH_2Cl_2), attempts from the Li and K alkoxides (alkoxide + anhydride or acid chloride), as well as more exotic conditions utilizing 1-methyl-3-pivaloyl-imidazolium chloride as an acylating agent.[77]

Further attempts towards functionalization of the hydroxylactam were unsuccessful and decomposition (as observed with sulfonates **24d**[78]**,** carbonate **24c**, and

carbamate **24e**) or returned hydroxylactam (observed with ethers **24f**, and trichloroacetamide **24g**) was observed (Scheme 29). The silylation of the alcohol using the conditions of Danishefshy [TMSOTf, 2,6-Lutidine, CH_2Cl_2, -78^oC] also proved ineffective and provided unidentified products.[79]

The formation of the deuterated hydroxylactam (**24j**) was also unsuccessful. Attempts involving (1) *in situ* formation of KOD from D_2O + KOtBu and (2) quenching of the lithium alkoxide intermediate formed during the 1,2-addition of lithiobutyne with D_2O also surprisingly provided only non-deuterated hydroxylactam.

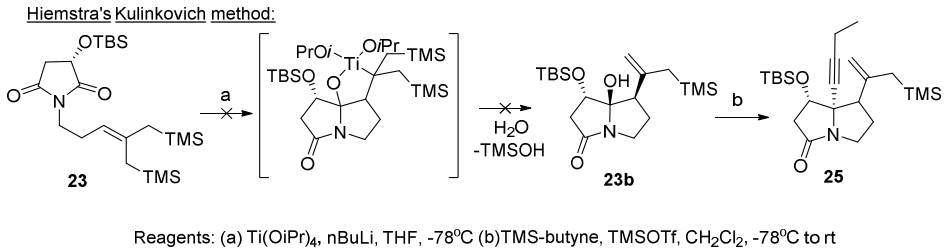


Variety of bases (B:) tried: Et_3N, 2,6-lutidine, pyridine, Hunigs, DMAP, KOtBu, KH, NaHMDS

Scheme 29: Functionalization of hydroxylactam **24**.

Aside from the hydroxylactam-based methods of ring closure, alternative routes to the desired lactam were explored. In 1999, Speckamp and Hiemstra demonstrated a synthetically interesting method for the preparation of functionalized bicyclic lactams using a Kulinkovich reaction (Scheme 30).[80] It was envisioned that from *N*,*O*-acetal **23b** using TMS-butyne, TMSOTf in CH_2Cl_2 at -78°C would furnish the desired lactam **25**.

Unfortunately, treatment of imide **23** to Ti(O*i*Pr)$_4$ /nBuLi in THF at -78^{o}C resulted in substrate decomposition and no ring closure occurred.



Scheme 30: Alternative routes.

After exhausting all options for the removal of the acidic hydroxyl proton on hydroxylactam **24**, an alternative method avoiding the isolation of the hydroxylactam was investigated (Scheme 31). Initially this approach was driven by the need for a purer sample of hydroxylactam due to an undesirable contaminant causing discoloration of the sample. The treatment of imide **23** with lithiobutyne in the presence of 5M LPDE provided a diastereomeric mixture of hydroxylactam **24** as a white solid (26% **24a,** 74% **24b**). The possibility that the initial lithium acetylide adduct could equilibrate was addressed in the following manner. Diastereomer **24b** was subjected to butyl lithium at -30^{o}C for 16 h and the results demonstrate that equilibration can occur under the reaction conditions.

Addition of the lithiobutyne to the desired carbonyl was confirmed by ^{1}H NMR and nOe analysis where the methylene CH_2 and the CH adjacent to the TBS group would show dramatic shifts of these signals depending on which carbonyl was attacked. The signal which is in close proximity to the shielding cone of the carbonyl was expected to be shifted upfield. An even more diagnostic analysis is the positioning of the CH adjacent

to the TBS group due to the magnetic anisotropy of the C-C triple bond. It has shown that a downfield shift of protons positioned adjacent to the triple bond is observed (and upfield shifts for acetylenic hydrogens).[81] This concept not only helps identify which carbonyl is attacked but also which diastereomers are formed. The nOe results are outlined in Figure 3, and application of alkyne magnetic anisotropy support the assignments.

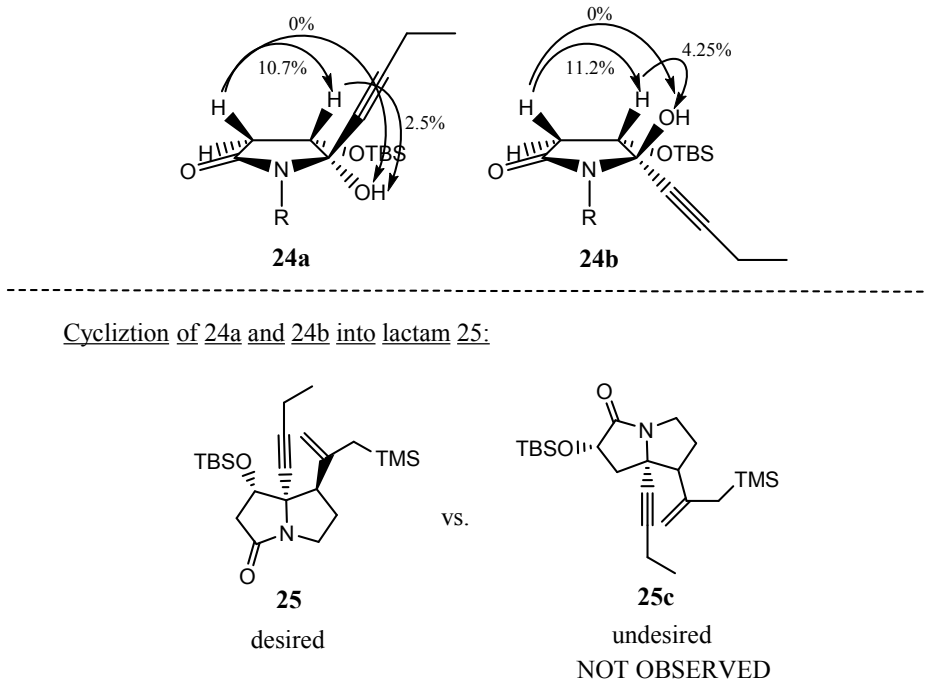
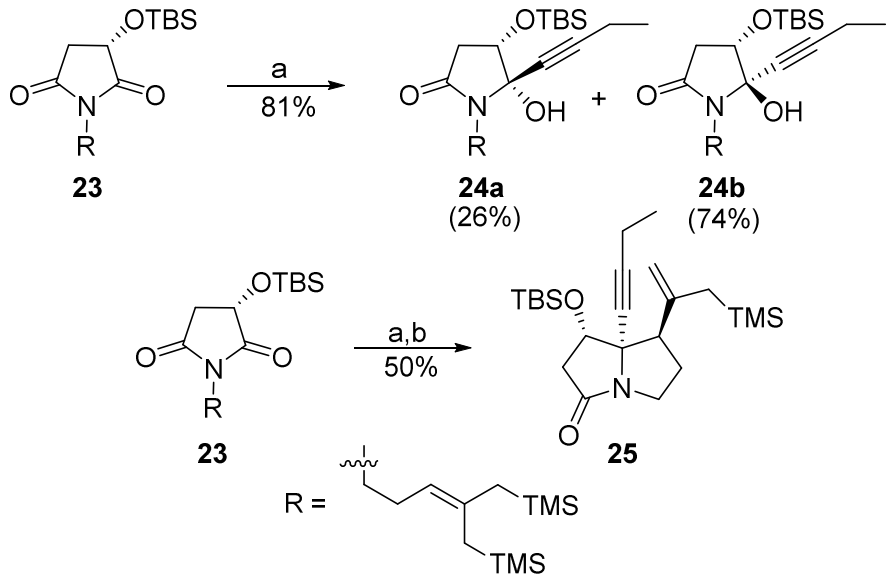


Figure 3: Hydroxylactam 24 nOe results

Additional evidence for the formation of the desired hydroxylactam diastereomers was approached by cyclizing **24a** and **24b** into lactam **25.** The spectrum of the undesired constitutional isomer **25c**, resulting from lithiobutyne addition to the undesired carbonyl,

was expected to have dramatic differences in the methylene and CH signals. The undesired constitutional isomer **25c** (Figure 3) was not observed.

Later studies revealed that treatment of the 5M LPDE reaction mixture with TFAA (1.0 equiv) at 0ºC provided the desired lactam **25** in 50% yield from imide **23** in 12-15 minutes. This sequence has since then been termed the Anderson-Livinghouse pyrrolizidine synthesis. The dramatic difference in rate observed by this method compared to the previous approach is rationalized not only by the effect of the Li^+ Lewis acidity but also the stabilization of the transition state and high internal pressure in this polar medium. Alternatives to TFAA such as benzoic anhydride and dimethyl pyrocarbonate resulted in incomplete conversion or no reaction respectively. The absence of the protodesilated lactam **26** in this one-pot method, compared to the two step sequence, provides compelling evidence that the hydroxyl hydrogen on the hydroxylactam is serving as a proton source.



Reagents: (a) Lithiobutyne, 5M LPDE, 0°C to 22°C, 15 min. (b) TFAA, 0°C to 22°C, 12-15 min.

Scheme 31: The one-pot Anderson-Livinghouse pyrrolizidine synthesis.

The relative stereochemistry of pyrrolizidine **25** was obtained by using nuclear Overhauser effect (nOe) measurements (Figure 3). Irradiation of the proton signal at C6 resulted in a negative nOe enhancement for the proton signal at C4. This lack of peak enhancement, seen in nOe difference spectra, is consistent with a *trans* orientation of the hydrogens at C4/C6. Even though a negative nOe enhancement is not a certain confirmation of stereochemistry, the second cationic cyclization cannot occur with the improper stereochemistry. The success of this second ring closure will support the results observed from the nOe difference spectra and will help confirm the orientation of all three stereocenters at C4, C5 and C6. In the transition state, the allylsilane is directed to the face opposite of the bulky TBS group due to severe steric interference. This feature forces the butyne substituent to the same side as the directing silyl ether (Figure 4). The stereospecificity of the terminating silane is rationalized by stereoelectronic factors

inherent in the intermediate π-complex configurations.[82] More specifically, the stability of the two relevant π-complex configurations are determined by comparing the developing steric interactions observed in the chair or boat-like transitions. The chair-like conformation is preferable due to the avoidance of eclipsing interactions observed in the boat-like alternative.

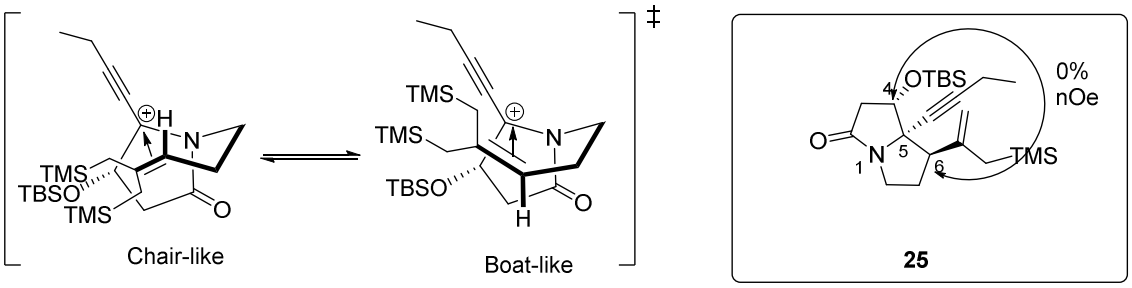


Figure 4: Transition state analysis and nOe measurements.

Investigation into the Partial Reduction of Lactam 25

Partial reduction of lactam **25** proved exceedingly difficult. Among the reducing agents explored by Kercher (DIBALH, K-Selectride[83], Red-Al[84], and Superhydride), all were shown to be ineffective when applied towards analogous lactam **G** (Figure 5).

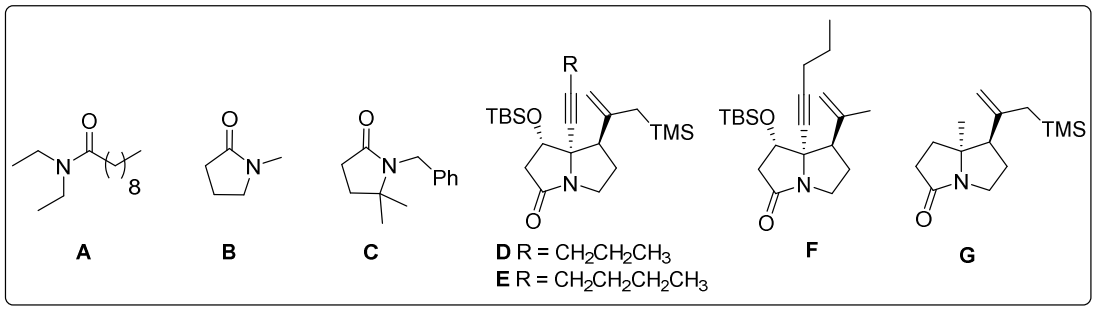
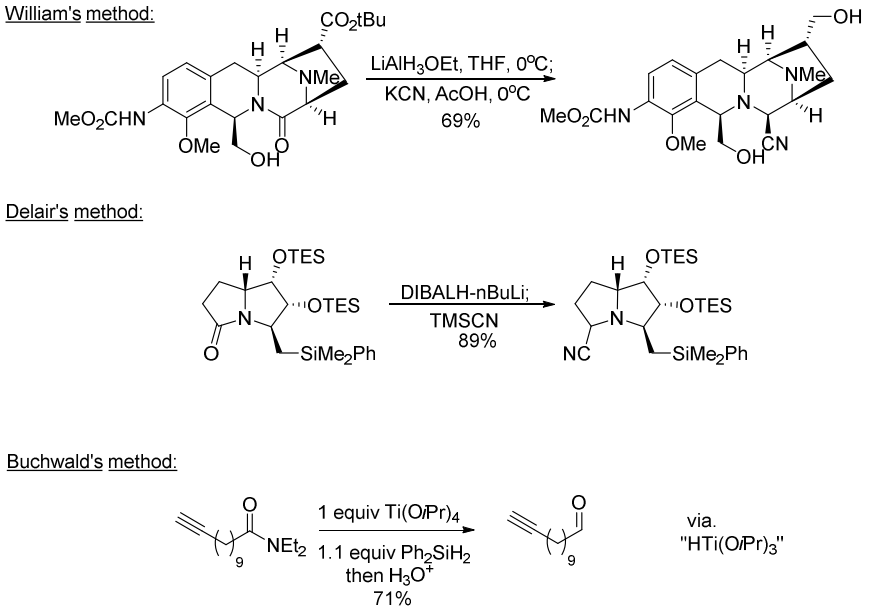


Figure 5: Models used for partial reduction studies.

In literature, Corey[85], Buchwald[86], Delair[87], and Williams[88] successfully achieved partial reduction of lactams followed by immediate transformation to the cyanoamine in excellent yields (Scheme 32). In these studies, specialized reducing agents such as $LiAlH_2(OEt)_2$, $LiAlH_3OEt$, $Ti(OiPr)_4/Ph_2SiH_2$ and DIBALH-nBuLi ate complex[89] were utilized.



Scheme 32: Various partial reduction methods.

To test the viability of these reducing reagents, model studies were conducted using aliphatic, monocyclic and bicyclic tertiary amides (Figure 5). It was found that $LiAlH_3OEt$, $LiAlH_2(OEt)_2$, $LiAlH(OEt)_3$[90], $Ti(OiPr)_4/Ph_2SiH_2$ and DIBAL-nBuLi complex were successful in partially reducing diethyl caprylamide **A** and cyclic amide **B** in near quantitative yields according to GC analysis. However, when utilizing gem-dimethyl amide **C** in combination with the mentioned reducing agents, longer reaction times were required and all provided complex mixtures of partial reduction, complete

reduction, and un-reacted starting materials.[91] When employing the DIBAL-nBuLi/TMSCN conditions towards silylated and protodesilylated analogs (**D**, **E**, and **F**), complex mixtures were observed and a calculated 5% yield (by GC-MS) of the desired cyanoamine was obtained.[92] The traditional lithium ethoxy aluminum hydride reagents, and the selective carboxamide reducing agent lithium tris(diethylamino) aluminum hydride (LTDEA)[93] provided only complex mixtures of degradation products (hydroalumination[94], overreduction, etc.). Lastly, the mild reducing agent Lithium tri-tert-butoxyaluminum hydride provided only returned starting materials in all trials.

Due to the partial success associated with the DIBAL-nBuLi ate complex, this route was investigated further and literature searches revealed that tertiary amides can be partially reduced in near quantitative yields (89-99%) using alkoxy variants of the DIBAL-ate complexes.[95] The procedures outlined by Duk Keun An were explored and lithium diisobutyl-iso-propoxyaluminum hydride (LDBIPA) was proven to be effective in the partial reduction of all the model amides. In an effort to minimize undesired side reactions, the selectivity of such alkoxyaluminum complexes was tuned through introducing additional bulk on the alkoxy substituent (Scheme 33). The ate complexes derived from cyclohexanol and *tert*-amyl alcohol provided comparable results to those subjected to LDBIPA. However, the LDBCA and LDBTAA complexes provided more undesired products and required longer reaction times. After the optimization of conditions, it was found that exposure of pure lactam **25** to LDBIPA (1.5 equiv) in THF at 0 ^{o}C for 24 h followed by treatment with TMSCN (3 equiv) for 7 h provided the

desired cyanoamine **29** in 82 % yield after purification from silica gel as a diastereomeric mixture (75% major & 25% minor diastereomers; diastereomers unassigned).

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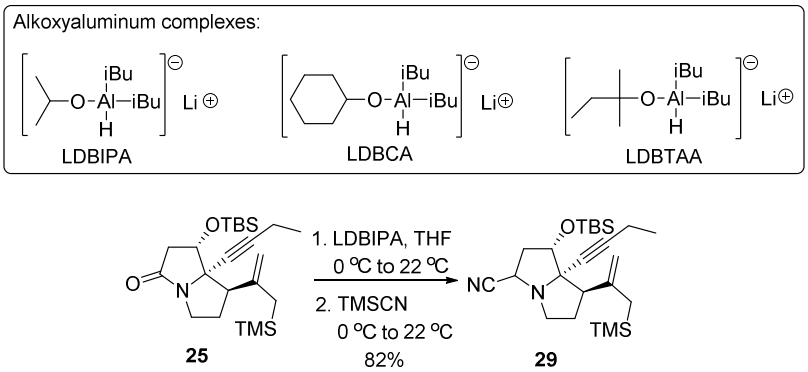
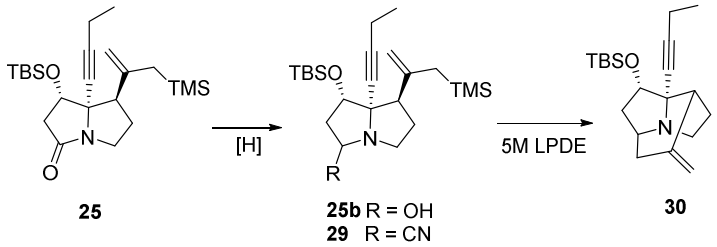


Scheme 33: Formation of cyanoamine **29** from lactam **25**.

Allylsilane Termination to Form the Azatricyclodecane Core

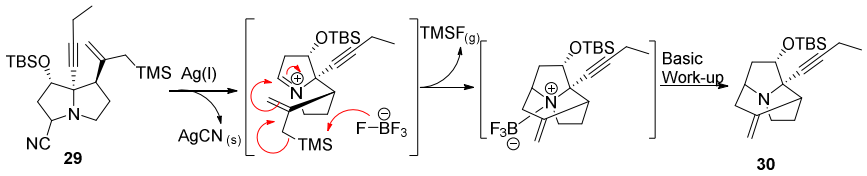
With cyanoamine **29** in hand, conditions to trigger the second iminium ion cyclization were explored. Due to the success encountered in the first cyclization, it was anticipated that partial reduction of lactam **25** to the corresponding hemiaminal **25b** or cyanoamine **29** in the presence of 5M LPDE would furnish the desired pyrrolizidine **30** (Scheme 34). Unfortunately, when treating Lactam **25** with reducing agents such as DIBAL-nBuLi complex or LDBIPA in the presence of 5M LPDE resulted in no reaction. In an alternative approach, complex mixtures of decomposition products resulted when hemiaminal **25b** or cyanoamine **29** were subjected to 5M LPDE. O-alkylation methods of ring closure using MeOTf were also investigated and the results were comparable to Kercher's unsatisfactory trials (see page 19).[96]



25 **25b** R = OH **29** R = CN **30**

Scheme 34: Initial attempts towards azatricyclodecane **30**.

In 2002, Williams and Scott[88] demonstrated the synthetic utility of silver mediated ionization of α-cyanoamines. This alternate route to iminium ion formation was envisioned to provide us with our desired azatricyclodecane core (Table 6). Unfortunately, when employing the conditions of Williams (Entry 6, Table 6) the desired product was not formed and a complex mixture was observed (loss of TBS protecting group was observed). The utility of $AgBF_4$ and AgOTf towards the ionization of cyanopiperidines[97], cyanoquinolizidines[98,99] and promoting *C*-acylnitrilium ion formation[100] has shown to be effective when applied to a variety of systems.



29 **30**

Table 6: Screening of conditions for the second cyclization

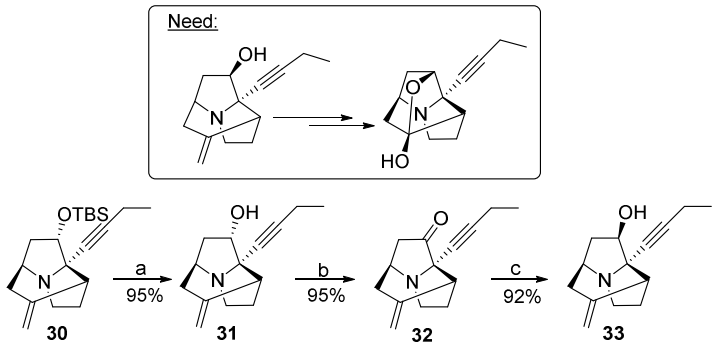
Entry	Conditions	Yield %[a]
1	$AgBF_4$, THF, 5% NH_4OH, 24 h	100 (88)
2	$AgBF_4$, THF, $NaHCO_3$, 24 h	82 (77)
3	AgOTf, THF, $NaHCO_3$, 21 h	87 (45)
4	AgOTf, CH_2Cl_2, $NaHCO_3$	51
5	$AgBF_4$, CH_2Cl_2, $NaHCO_3$	50
6	$AgOCOCF_3$, TFAA/TFA, $ClCH_2CH_2Cl$, 19 h	0

[a]As determined by GC analysis. Isolated yields in brackets.

All trials that utilized these silver (I) reagents provided moderate to high yields (Entries 1-5, Table 6). As demonstrated in Table 6, not only solvent choice but also work-up conditions seem to have a drastic influence on reaction yields. The selection of solvent has been observed to play a role in synthesis of (±)-reserpine by Stork in effecting the formation of a tight ion pair between the cyanide and iminium ion.[101] The use of THF as the reaction solvent has shown to be superior possibly for the same reasons, where a tight ion pair is avoided. Interestingly, when utilizing $NaHCO_3$ rather than NH_4OH for the quench process, a mixture of products were obtained. The utility of NH_4OH however provided only one product as observed by GC and HPLC-MS. Purification of the crude product proved difficult due to excessive adhesion to silica and alumina adsorbents, a common feature of compounds containing a basic amine functionality.

Stereochemical Modification Sequence

Following the construction of the azatricyclodecane core, the alcohol functionality that was originally utilized as a stereochemical directing group must be inverted for the closure of the requisite hemiketal. This was achieved through an oxidation-selective reduction process following the removal of the silane protecting group (Scheme 35). Initially, pyrrolizidine **30** was treated with TBAF in THF for 11 h at 22 ºC to provide tricycle **31** in 73% yield.[102] However, purification of product mixtures using this route was more difficult and less efficient than using an acidic fluoride deprotection method.[103]



(a) Aq. HF/CH_3CN (5:95). (b) DMP, CH_2Cl_2, 22 °C. (c) LDBIPA, THF.

Scheme 35: Stereochemical modification sequence.

Investigations directed toward the alcohol stereo-inversion began with traditional Swern oxidation conditions (Oxalyl Chloride, DMSO, CH_2Cl_2 -78°C then Et_3N).[104] All attempts regarding this method resulted in byproduct formation. Subsequently, Dess-Martin Periodinane was proven to be the optimal oxidant choice, where it has been found effective towards similar 7-azabicyclo[2.2.1]heptane ring systems.[105] The final step in this inversion process was a stereoselective reduction of ketone **32** using the selective reducing agent LDBIPA. This reducing agent was chosen to prevent any hydroalumination (or related processes) from occurring.[106] This reduction procedure was shown to proceed in high yield (92%) at room temperature. Proof of inversion can be seen in the ^1H NMR where the doublet-of-doublets signal produced by the diastereotopic hydrogen opposite to the inverted alcohol is shifted downfield in comparison to the exo derivative. This is due to the placement of this diastereotopic hydrogen in the deshielding zone of the alkyne. X-ray crystallographic studies confirmed this inversion (see Appendix C).

Formation of Hemiketal **35** Following Ozonolysis

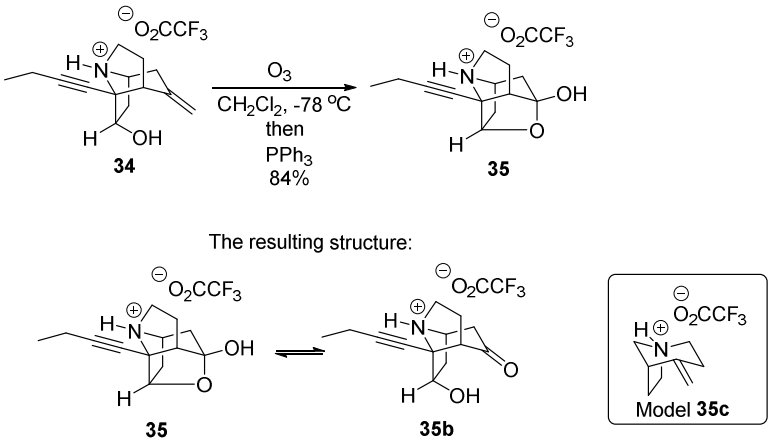
The oxidative cleavage of the exocyclic alkene may, in principle, be accomplished by ozonolysis or osmium tetroxide mediated routes. Due to small quantities of precursor being available late in the synthesis, small scale cleavage methods were desirable. Osmium tetroxide conditions utilizing OsO_4 + Oxone in DMF, OsO_4 + $NaIO_4$ (with and without pyridine/2,6-lutidine), and $OsO_4 + K_2CO_3 + K_3[Fe(CN)_6]$[107] did not result in the diol intermediate nor the ketone cleavage product when applied towards model isotropane **35c** or pyrrolizidineone **33**. The issue associated with this method was determined to be the basic nitrogen preferentially forming the N-oxide (seen with pyrrolizidine **33**).[108]

It is well known that water is essential in order to cleave the intermediate osmate ester.[109] This proved problematic due to the high solubility of the product in aqueous media. Reactions with OsO_4 in 80% AcOH followed by treatment with $NaIO_4$[110] was found to be effective towards the isotropane model **35c** presumably due to the AcOH protonating the 3^o amine and thus preventing N-oxide formation. Even though these conditions have proven effective, isolation of the desired product from the aqueous media without decomposition proved to be difficult.

Literature searches later revealed small-scale ozonolysis (≥7 mg)[111] to be possible through the known solubility of ozone in dichloromethane (saturation of 0.040M at –78 ^{o}C). This small-scale ozonolysis procedure, although useful, was unnecessary for this oxidative cleavage because exposure of tropane **34** to excess amounts of ozone for short periods of time did not result in overoxidation of the alkyne. Similar results were

observed with alkyne containing compounds from the work of Tishchenco[112], Crabbé[113] and McCurry[114]. The alkyne however was not the only concern for overoxidation, the tertiary amine must be masked as the trifluoroacetate salt or N-oxide formation is likely to occur.[115]

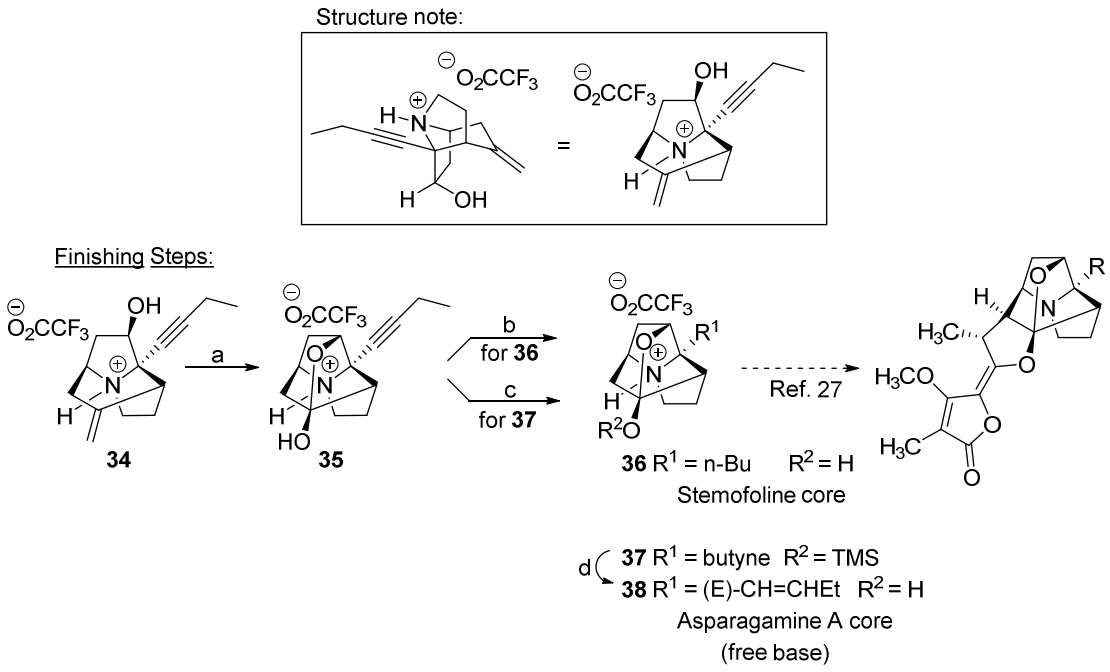
Following the treatment of pyrrolizidine **33** with TFA (1.1 equiv) at 0 ºC for 1h followed by Celite filtration provided the requisite salt **34** in 93% yield. Exposure of salt **34** to excess ozone for 5 min provided the desired hemiketal **35** in 84% yield followed by reductive workup with PPh_3,[116] solvent removal and purification by reverse phase HPLC. The use of Na_2SO_3 in place of the PPh_3 permitted easier purification (silica gel chromatography) but resulted in greatly diminished yields (~60%). Other common reductants such as dimethylsulfide were also successful but removal of the resulting byproducts proved challenging.[117] The product formed was expected to be in equilibrium with its ring opened ketone **35b**[118], however the ring closed hemiketal **35** was confirmed to be the product by ^{13}C NMR (absence of C=O at 210ppm) and IR analysis (lack of ketone C=O required for the ring opened form).



Scheme 36: Ozonolysis of pyrrolizidine salt **34**.

Completion of the Azatricyclic Core of Stemofoline and Asparagamine A

It was originally envisioned that the tricyclic cores **36** and **39** could be utilized to provide the alkaloids Asparagamine A and Stemofoline following the procedure of Overman. The remaining steps in this relay synthesis involve two divergent reduction paths from hemiketal **35** that upon completion will provide the fully functionalized Stemofoline core **36** and Asparagamine A core **39** (Scheme 37).



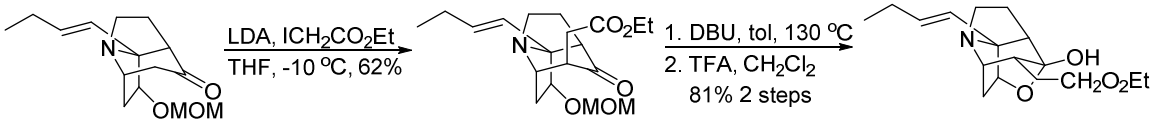
Reagents: (a) O_3, CH_2Cl_2, -78°C then PPh_3, 84%; (b) H_2, Pd-C, 78%; (c) BSTFA; (d) Na/NH_3, 55%.

Scheme 37: Completion of the alkaloid cores.

The final steps of this relay synthesis began with the small scale (11.5mg) reduction of hemiketal **35** using H_2/5% Pd-C in EtOAc for 3h at room temperature to provide the desired Stemofoline core in 78% yield.[119] Silylation of hemiacetal **35** using *N*,*O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) in THF furnished the sensitive TMS

protected alcohol which was used immediately. The TMS protected hemiketal **37** might then be reduced to the (*E*)-butenyl derivative by a dissolving metal reduction or related alkyne reduction conditions. Alkyne reductions employing DIBAL-H were first demonstrated by Granitzer and Stütz in 1979 using various propargylic amine systems and showed high promise for small scale reductions.[120] Interestingly, exposure of the silylated hemiketal **37** to DIBAL-H resulted in no reaction and **37** as the TFA salt was recovered. Following the regiospecific reduction of the alkyne with Na/NH_3, immediate cleavage of the TMS ether was observed and the completed Asparagamine A core **38** was provided in 55% yield as the free-base.

Installation of the functionality α to the azatricyclodecane carbonyl, which is required for the attachment of the butenolide functionality, may be achieved by utilizing methods established by Overman or Martin following the masking of the endo hydroxyl substituent (Scheme 38).



Scheme 38: Installation of the alpha functionality (Stephen Martin's method).

Summary

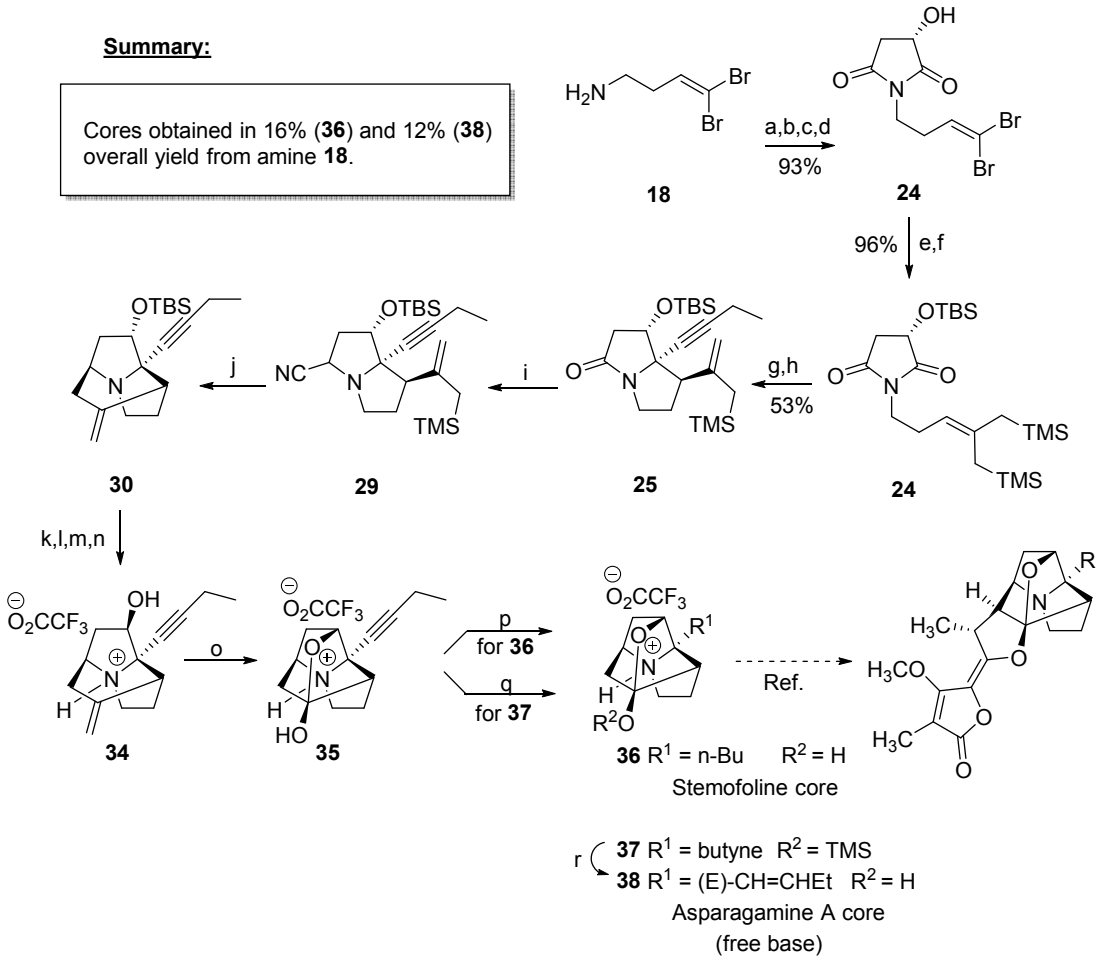
The utility of an 2-propylidene-1,3-bis(silane) nucleophile in *N*-acyliminium ion chemistry has been successfully applied toward the construction of the azatricyclodecane core of the natural products Asparagamine A and Stemofoline. Within this linear

synthesis the enantiopure cores were acquired in 16% (**36**) and 12% (**38**) overall yield (16 and 17 steps respectively) from primary amine **18** (Scheme 39).

The results presented herein are consistent with the findings of Kercher's preliminary work and serve to augment the overall knowledge of allylbis(silane) nucleophiles in *N*-acyliminium ion chemistry. The limitation of this N-acyliminium ion cyclization is contained in the sensitivity of the silane terminator and the commonly employed strongly acidic conditions required for ionization of the tertiary hydroxylactam. Acidic conditions were avoided by rapid ionization to the acyliminium ion *in situ* by treatment of the lithium alkoxide of the hydroxylactam with TFAA while in the presence of 5M LPDE. The success of this cationic desilylative cycization is contingent on many factors which include the condition of the TFAA and dryness of the lithium perchlorate since trace acids will result in the destruction of the allyl silane moiety. The absence of the protodesilated lactam **26** in this one-pot method, compared to the two step sequence, demonstrates that the hydroxyl on the hydroxylactam is serving as a proton source.

Summary:

Cores obtained in 16% (**36**) and 12% (**38**) overall yield from amine **18**.



Reagents: (a) AcCl, reflux, 98% (b) 1. anhydride, CH_2Cl_2, 0°C; 2. Et_3N (0.1 equiv), 100% (c) AcCl, reflux, 96% (d) AcCl, EtOH, 99% (e) TBSCl, Imidazole, DMF, 100%; (f) $Zn(CH_2TMS)_2$, $PdCl_2(PPh_3)_2$ (7 mol%), THF, 97%; (g) Lithiobutyne, 5M LPDE, 0°C to 22°C, 15 min. (h) TFAA, 0°C to 22°C, 12-15 min., 50%; (i) 1.) LDBIPA, THF, 0°C to 22°C; 2. TMSCN 0°C to 22°C, 82%; (j) $AgBF_4$, THF, 88%; (k) Aq. HF/CH_3CN (5:95), 95%; (l) DMP, CH_2Cl_2, 22 °C, 95%; (m) LDBIPA, THF, 92%; (n) TFA, Et_2O, 93%; (o) O_3, CH_2Cl_2, -78°C then PPh_3, 84%; (p) H_2, Pd-C, 78%; (q) BSTFA; (r) Na/NH_3, 55%.

Scheme 39: Completion of the alkaloid cores.

CHAPTER 4

CONCLUSIONS AND SUMMARY

Background

The Mannich cyclization has been utilized for the synthesis of a number of heterocyclic compounds since its discovery. In this dissertation, an allylsilane-based variant of the Mannich cyclization is discussed. This Mannich-like cyclization has proven to be a powerful tool in governing regio- and stereocontrol in carbon-carbon bond forming reactions, which benefit from enhanced nucleophilicity of the C=C π bond derived from the hyperconjugative effect of the adjacent silicon group. Despite the synthetic utility associated with this transformation, there are comparatively few examples that have explored the intramolecular variant containing silane-based nucleophiles.

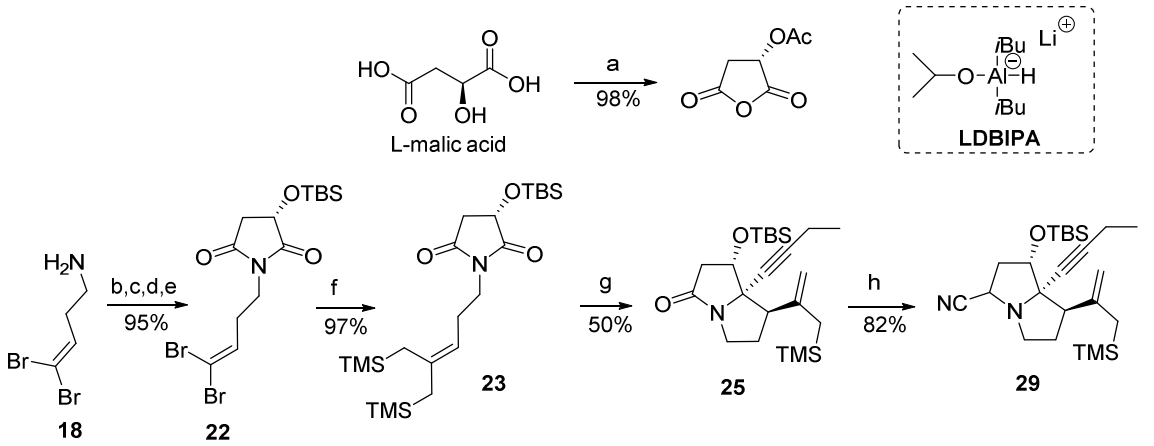
The utility of a 2-propylidene-1,3-bis(silane) nucleophile in synthesis has also received scant attention and it was the goal of this project to further develop this concept, and ultimately to apply these findings toward the construction of the azatricyclic core found in the stemona alkaloids Asparagamine A and Stemofoline. Studies on Stemofoline and Asparagamine A (aka. Didehydrostemofoline), have revealed notable insecticidal properties when administered orally to the larvae of various crop pests such as diamondback moth and silkworm. It was observed that Asparagamine A demonstrated stronger effects, than Stemofoline, isodehydrostemofoline and rotenone (a common

pesticide).[19] Additionally, the polycyclic alkaloid, Asparagamine A was found to possess anti-tumor and anti-oxytocin biological activity among the *in vitro* studies examined.[22]

Summary of Results

During this investigation, the key synthetic targets **36/18** (Scheme 41) were derived from intermediate pyrrolizidine **30** in a stereocontrolled fashion by consecutive allylbis(silane)-iminium ion transforms. Construction of the key intermediate **30** was achieved by acyliminium ion generation following alkynylation of imine **23** in 5M LPDE and ionization of cyanoamine **29** with $AgBF_4$ (Scheme 40 and 41). Preference of $AgBF_4$ over AgOTf was observed and is rationalized by the degree of "cationic character" which is tunable by appropriate selection of the weakly coordinating anion (increasing coordination trend: $SbF_6^- << AsF_6^- < PF_6^- < BF_4^- < OTf^-$). Construction of the requisite cyanoamine **29** was achieved over 7 steps utilizing amine **18** and L-malic acid as a commercial chiral source (Scheme 40). This approach proceeded by nucleophilic opening of an anhydride (derived from L-malic acid) by employing amine **18**. The intermediate that was produced was then exposed to acylation conditions to form an acetate functionalized cyclic imide in near quantitative yield. Subsequent removal of the acetate group by HCl generated *in situ* (AcCl, EtOH) followed by TBS protection of the resulting alcohol provided succinimide **22** in nearly quantitative yields. Alternative conditions of preparation involving the condensation of amine **18** with L-malic acid resulted in modest yields due to decomposition of starting material and product from the high heat required. The installation of the 2-propylidene-1,3-bis(silane) moiety was achieved by exposure of

imide **22** to Negishi cross-coupling conditions utilizing $ZnCl_2 \cdot (THF)_2$, $TMSCH_2MgCl$, and 7 mol% $PdCl_2(PPh_3)_2$ (97% yield). Utilization of $ZnCl_2 \cdot TMEDA$ in place of the THF complex resulted in low yields consistent with the preformed organozinc being too basic.



(a) AcCl, reflux, 98%; (b) anhydride , Et_3N (0.01 equiv), CH_2Cl_2, 0°C, 100%; (c) AcCl, reflux, 96%; (d) AcCl, EtOH, 0°C, 99%; (e) TBSCl, imidazole, DMF, 100%; (f) $ZnCl_2$-$(THF)_2$, $TMSCH_2MgCl$, 7 mol% $PdCl_2(PPh_3)_2$, THF, 97%; (g) Lithiobutyne, 5M LPDE, 0°C to 22°C, 15 min.; then TFAA, 0°C to 22°C, 12-15 min. (h) 1a. LDBIPA, THF, 0°C, 19h, 1b. TMSCN, 22°C, 2h.

Scheme 40: Summary scheme A

Attention was then directed towards the key step, a cationic desilylative cyclization process. Due to the reported success by the Grieco group on lithium perchlorate-diethyl ether (LPDE) facilitated ring opening of oxabicyclic systems[68], and rate acceleration of Diels-Alder cycloaddition reactions[70], this polar medium was investigated. After evaluating several conditions, it was found that exposure of imine **23** to lithiobutyne in 5M LPDE followed by treatment with TFAA provided lactam **25** in 50% yield following purification.

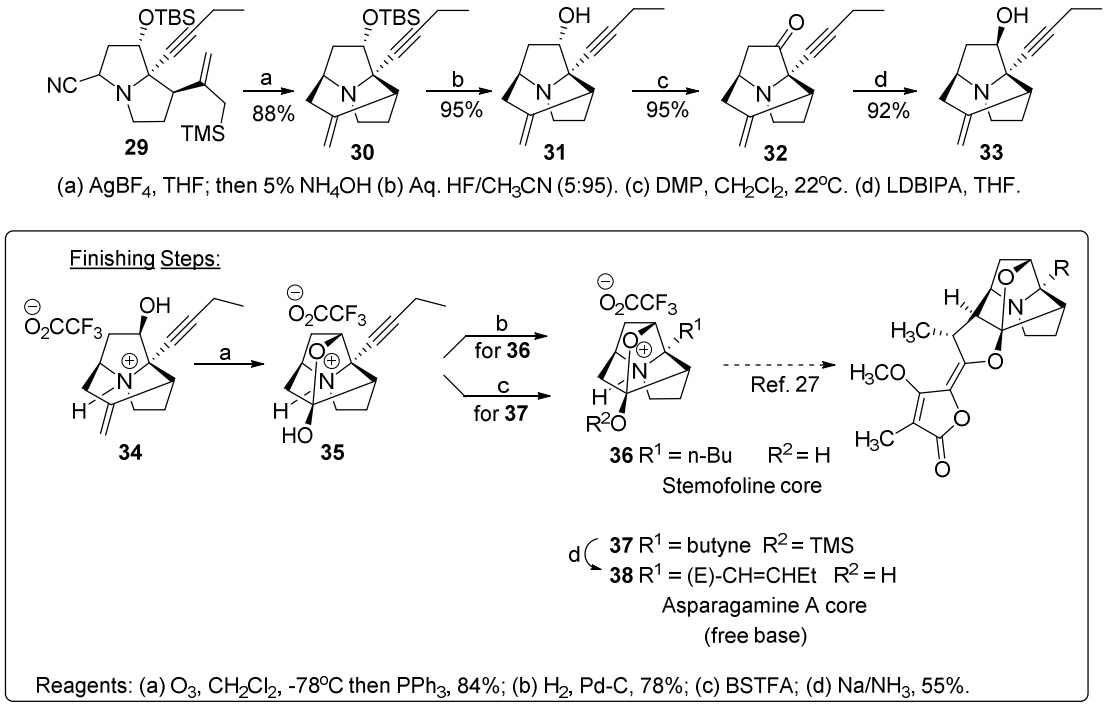
Routes utilizing the intermediate hydroxylactam in 5M LPDE provided yields of lactam **25** no higher than 28% due to extensive protodesilylation/decomposition. Unfortunately, the use of numerous other Lewis acids led only to protodesilylation or

degradation. Optimization attempts using this hydroxylactam route began with screening various solvent combinations with lithium perchlorate which revealed that more coordinating solvent combinations (e.g., diethyl ether and ethyl acetate) proved more effective than less coordinating solvents (e.g., nitromethane). It was originally hypothesized that less coordinating solvents would favor the cationic cyclization process due to the increased Lewis acidity of the lithium cation. Among these solvents, nitromethane has a higher dielectric constant and dipole moment than diethyl ether or ethyl acetate, further supporting the development of ionic intermediates. Due to the opposite effects being observed, a possible rationalization for the observed trend may involve the degree of acyliminium ion-cation solvation or differences in internal solvent pressure. Further investigation is required to elucidate the observed solvent effects.

The issues of protodesilylation were addressed by screening a variety of bases and proton scavengers. The studies showed no improvement in yield but revealed that the removal of the acidic hydroxyl hydrogen resulted in no reaction. Additionally, resubjecting lactam **25** to 5M LPDE did not result in further protodesilylation which suggests that the acidic proton is not present in the solvent but rather the starting substrate. O-alkylation attempts focusing on the removal of this proton were ineffective resulting in returned starting material or unidentified decomposition products.

The relative stereochemistry of pyrrolizidine **25** was obtained by using nuclear Overhauser effect (nOe) measurements where the difference spectra show negative enhancement consistent with a trans orientation. Subjection of the pyrrolizidine **25** to the specialized reducing agent, lithium diisobutyl-isopropoxyaluminum hydride (LDBIPA),

followed by treatment with TMSCN provided the desired cyanoamine **29** in an impressive 82% yield. A variety of reducing agents were evaluated, among which the traditional alkoxy aluminum hydrides provided only decomposition products, which included hydroalumination at the alkyne.



Scheme 41: Summary scheme B

Completion of the bridged pyrrolizidines **36/38** was then accomplished from **30** by stereochemical modification of the hydroxyl substituent and a divergent reduction sequence of the alkyne to yield the enantiopure cores in 16% (Stemofoline core **36**) and 12% (Asparagamine A core **38**) overall yield (16 and 17 steps respectively) from 1,1-dibromo-4-amino-1-butene (**18**). Completion of Asparagamine A and Stemofoline from heterocycle **36/38** could subsequently be accomplished by the method outlined by Overman.[27]

When compared to previous attempts outlined in literature, even though this approach involves a long linear sequence, the fully functionalized azatetracycle is acquired in enantiopure form with yields being comparable or higher. Additionally this methodology is extendable beyond the stemona alkaloids allowing access to a variety of tropane and isotropane ring structures. In comparison to the existing mono allylsilane acyliminium-ion results described by Hiemstra, which are shown to demonstrate high regio- and stereocontrol for the construction of indolizidine, quinolizidine and pyrolizidine alkaloids, the tethered bisallyl(silane) variation allows access to polycyclic alkaloids (>2 rings) by two sequential regio- and stereocontrolled cyclizations. This has advantages over the installation of two nucleophiles at separate intervals since the latter process is more likely to result in loss of regio- and stereocontrol as well as diminished yields typically associated with multiple transformations.

APPENDICES

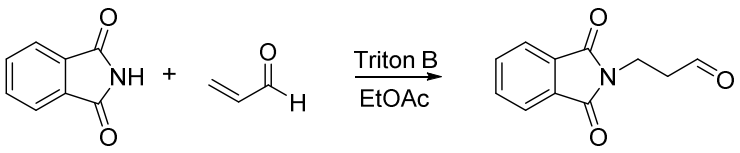
APPENDIX A:

EXPERIMENTAL

Materials and Methods:

Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane and triethylamine were distilled from calcium hydride under nitrogen. Dimethylformamide was distilled from calcium hydride under reduced pressure. Isopropyl alcohol was dried by distillation from calcium hydride after preliminary drying from KOH pellets. $ZnCl_2$ was fused under vacuum using a Bunsen burner prior to use. TBSCl was purified by distillation and imidazole was recrystallized from 1:1 heptane-toluene. $LiClO_4$ and $AgBF_4$ were dried under reduced pressure (0.001mmHg, 120^oC, 24 h) and handled in a drybox. All other materials were used as received from commercial sources. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and visualized with UV light (254 nm), potassium permanganate or 2,4-dinitrophenylhydrazine staining. Flash chromatographic columns were packed with Merck silica gel 60 as a slurry in the initial elution solvent; for compounds containing a basic nitrogen functionality, eluents were treated with NH_4OH to limit sticking. Nuclear magnetic resonance (NMR) data were obtained from a Bruker DRX-300 (300 MHz) and Bruker DRX-500 (500 MHz) spectrometers. Infrared spectra (IR) were obtained from a JASCO FTIR-4100. Melting points were obtained using a Mel-Temp apparatus and are uncorrected. Optical rotations were obtained from a JASCO P-1020 polarimeter. High-resolution mass spectra (HRMS) were obtained from a Bruker MicroTOF with an Agilent 1100 HPLC.

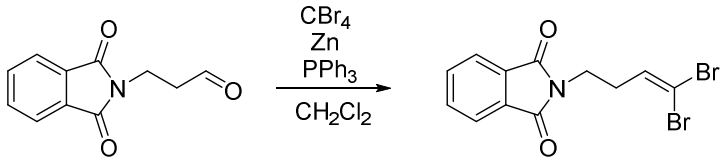
Preparative Procedures:



16

3-Phthalimidopropionaldehyde (**16**): Aldehyde **16** was prepared following an analogous procedure described by Leete:[32] In an oven-dried 250 mL round bottom flask equipped with a magnetic stirring bar, condenser and nitrogen inlet was charged with phthalimide (15.93 g, 108.25 mmol, 1 equiv) and acrolein (6.67 mL, 119.08 mmol, 1.1 equiv) suspended in ethyl acetate (64 mL). The suspension was allowed to stir for 5 min at 65°C prior to the addition of Triton B (40% solution of benzyltrimethylammonium hydroxide in MeOH, 362 μL, 2.165 mmol, 0.02 equiv). Reaction progress was monitored by TLC (25% ethyl acetate in hexanes, 2,4-DNP stain). After 15 minutes, or until the reaction mixture becomes heterogeneous, solvents were removed and the resulting off-white solid was triturated (30 mL ethyl ether) and filtered to afford the product as a white solid (20.12 g, 91%). The product was used without further purification.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.83 (s, 1H), 7.86 (dd, *J* = 5.5, 3.1 Hz, 3H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 4H), 4.05 (t, *J* = 7.0 Hz, 3H), 2.89 (td, *J* = 7.0, 1.4 Hz, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.58, 168.20, 134.32, 132.16, 123.57, 42.57, 31.89; **IR** (film) 2946, 2850, 2739, 2332, 1767, 1708, 1612, 1464, 1442, 1398, 1139, 1028, 891, 714, cm^{-1}.

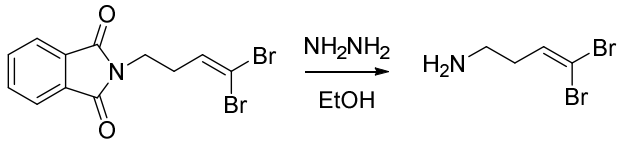


16 **17**

1,1-Dibromo-4-phthalimido-1-butene (**17**): Divinylbromide **17** was prepared following analogous procedures described by Corey[34], and Kercher:[30] In an oven-dried 100 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with carbon tetrabromide (3.264 g, 9.842 mmol, 2 equiv) and zinc dust (0.643 g, 9.842 mmol, 2 equiv) dissolved in dichloromethane (17 mL) freshly distilled from calcium hydride. The grey reaction mixture was cooled to 0ºC prior to the dropwise addition of triphenylphosphine (2.581 g, 9.842 mmol, 2 equiv) in dichloromethane (3 mL) over 30 min. After stirring the resulting olive-green mixture for an additional 10 minutes at 0ºC, aldehyde **16** (1.0 g, 4.921 mmol, 1 equiv) dissolved in dichloromethane (7 ml) was added over 30 min via syringe. The dark burgundy mixture was stirred for 21.5 h at room temperature and monitored by TLC (25% ethyl acetate in hexanes). The reaction mixture was then diluted with hexanes (25 mL) and vigorously stirred for 5 min. The supernatant was decanted and filtered over Celite to provide a crude off white solid. The solid precipitate from the reaction was re-worked four times by re-dissolving in dichloromethane and diluting with hexanes (4x 25 mL). The crude product was then redissolved in CH_2Cl_2 (40 mL) and treated with oxalyl chloride (0.85 mL, 9.842 mmol, 2 equiv) at 0ºC with stirring.[36] After 1h at 22ºC, the reaction mixture was quenched by slow addition of saturated $NaHCO_3$ (40 mL) and diluted with hexanes (30 mL). The

organic phase was dried over MgSO4, filtered and concentrated to provide the title compound as a white solid (1.07 g, 61%).

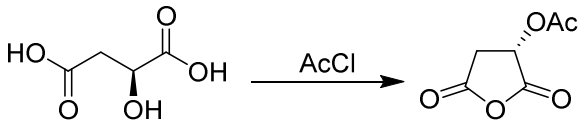
mp = 115-117°C; **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.46 (t, *J* = 7.3 Hz, 1H), 3.81 (t, *J* = 6.8 Hz, 2H), 2.51 (q, *J* = 7.0 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.21, 134.52, 134.13, 132.00, 123.41, 91.69, 35.60, 32.35; IR (film): 3101, 3027, 2942, 2362, 2337, 1767, 1697, 1396, 1364, 1242, 1132, 1043, 988, 873, 747, 718, cm^{-1}.



17 **18**

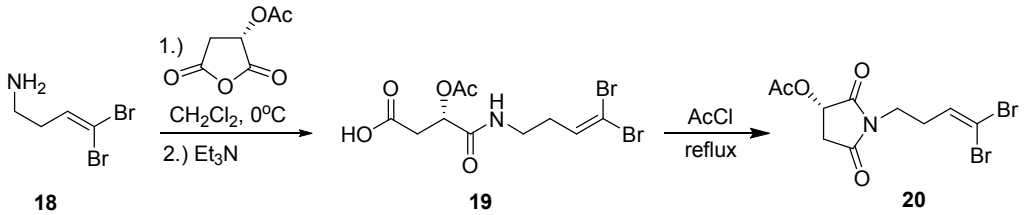
1,1-dibromo-4-amino-1-butene (**18**): In an oven-dried 10 mL round bottom flask equipped with a magnetic stirring bar, condenser and nitrogen inlet was charged with dibromo olefin **17** (4.119 g, 11.473 mmol, 1 equiv) in degassed absolute ethanol (33 mL). Hydrazine monohydrate (1.21 mL, 24.093 mmol, 2.1 equiv) was added all at once with stirring at 60°C and held at that temperature for 20 h or until deemed complete by GC. The phthalhydrazide byproduct was triturated (30 mL ethyl ether) and filtered. The ethanol containing filtrate was concentrated by azeotropic distillation (benzene) to afford the compound as a yellow oil, which may be used without further purification or may be distilled from calcium hydride (63-65 °C, 1.3 mmHg) to provide a colorless liquid (1.83g, 70%)

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.38 (t, *J* = 7.2 Hz, 1H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.17 (q, *J* = 6.8 Hz, 2H), 1.23 (s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.39, 90.29, 40.44, 37.28. **IR** (film): 3438, 3312, 3017, 2861, 2924, 2340, 1563, 1475, 1430, 1383, 1317, 810 cm^{-1}; **HRMS** calcd for $C_4H_7Br_2N$ (M+nH) 227.9018, found 227.9024.



(3S)-2,5-dioxotetrahydrofuran-3-yl acetate: An oven-dried 200 mL round bottom flask equipped with a magnetic stirring bar, condenser and nitrogen inlet was charged with L-malic acid (6.7 g, 43.976 mmol), and acetyl chloride (83.84 mL). The reaction mixture was allowed to stir at reflux for 18 h. Evaporation of solvent under reduced pressure afforded a clear viscous residue, which was triturated with toluene and dried by co-distillation to provide the title compound as an off-white sold. The crude anhydride was recrystallized from benzene to furnish the pure product as a white solid (7.74 g, 98%)

m.p. 56-59^{o}C; $[\alpha]^{20}$ = -23.206 (c 1.6, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$), δ: 5.54 (dd, J = 9.6, 6.4 Hz, 1H), 3.40 (dd, J = 18.9, 9.6 Hz, 1H), 3.04 (dd, J = 18.8, 6.4 Hz, 1H), 2.21 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.82, 167.84, 166.37, 67.73, 35.35, 20.42, 1.24; **IR** (film): 3005, 2957, 2362, 2333, 1874, 1797, 1749, 1405, 1375, 1275, 1216, 1077, cm^{-1}.



(S)-3-acetoxy-4-((4,4-dibromobut-3-en-1-yl)amino)-4-oxobutanoic acid (**19**): In an oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with (3S)-2,5-dioxotetrahydrofuran-3-yl acetate (0.655 g, 4.14 mmol, 1 equiv) dissolved in dichloromethane (16 mL). The reaction mixture was cooled

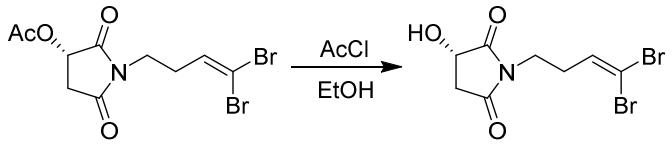
to 0°C prior to the drop wise addition of 1,1-dibromo-4-amino-1-butene (0.949 g, 4.14 mmol, 1 equiv). The solution was allowed to stir at 22°C for 30 minutes and then was treated with triethylamine (61 μL, 0.43 mmol, 0.1 equiv). The reaction mixture was then stirred for 1 h at 22°C and concentrated in vacuo to provide the intermediate acid-amide **19** as a crude yellow oil (1.6 g, 100%). The product was used without further purification.

(S)-3-acetoxy-4-((4,4-dibromobut-3-en-1-yl)amino)-4-oxobutanoic acid (19): **[α]**$^{20.8C}$ = -1.306 (c 1.6, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 6.42 (dd, *J* = 14.4, 7.0 Hz, 2H), 5.48 (t, *J* = 5.8 Hz, 1H), 3.40 (q, *J* = 6.2 Hz, 2H), 3.00 (dd, *J* = 6.0, 2.1 Hz, 2H), 2.37 (q, *J* = 7.0 Hz, 2H), 2.20 (s, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.19, 170.15, 169.43, 135.24, 91.76, 69.90, 51.03, 37.78, 36.35, 36.06, 33.20, 21.25, 20.92; **IR** (film): 3331.43, 3095.19, 2935.13, 2852.2, 2589.93, 2361.41, 2335.37, 1738.51, 1650.77, 1551.45, 1429.26, 1369.21, 1228.43, 1103.08, 1057.76, 943.985, 807.063, 783.922, 738.603, 627.716 cm^{-1}; **HRMS** calcd for $C_{10}H_{13}Br_2NO_5$ (M+nNa) 407.9053, found 407.9057.

(S)-1-(4,4-dibromobut-3-en-1-yl)-2,5-dioxopyrrolidin-3-yl acetate (**20**): In an oven-dried 5 mL round bottom flask equipped with a magnetic stirring bar, condenser and nitrogen inlet was charged with 3-acetoxy-4-(4,4-dibromobut-3-enylamino)-4-oxobutanoic acid **19** (0.462 g, 1.194 mmol, 1 equiv), and acetyl chloride (2.10 mL). The reaction mixture was allowed to stir at reflux for 4 h or until deemed complete by TLC. The reaction mixture was then concentrated, and the resulting dark brown oil was purified by flash chromatography (30% ethyl acetate in hexanes, Rf = 0.40) to provide acetate **20** as a light-yellow oil. Further purification was obtained by recrystallization from ethanol to provide a white solid (0.424 g, 96 %).

(S)-1-(4,4-dibromobut-3-en-1-yl)-2,5-dioxopyrrolidin-3-yl acetate (20): **m.p** 57-59°C; **[α]**^{22C}= -10.281 (c. 1.6, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 6.39 (t, *J* = 7.5 Hz, 1H), 5.43 (dd, *J* = 8.7, 4.7 Hz, 1H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.18 (dd, *J* = 18.4, 8.7 Hz, 1H), 2.68 (dd, *J* = 18.4, 4.7 Hz, 1H), 2.43 (q, *J* = 7.1 Hz, 2H), 2.17 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.38, 173.12, 169.95, 134.19, 92.07, 67.52, 36.67,

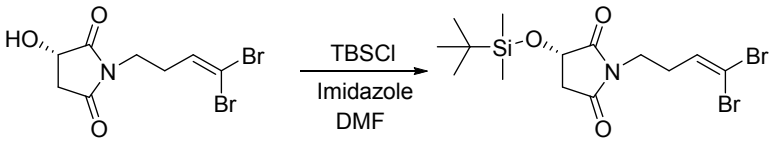
35.82, 31.31, 20.66. **IR** (film): 3486.67, 3027.69, 2947.66, 2946.7, 2850.27, 2360.44, 2337.3, 1789.62, 1749.12, 1716.34, 1714.41, 1712.48, 1635.34, 1558.2, 1540.85, 1507.1, 1438.64, 1436.71, 1402.96, 1371.14, 1352.82, 1316.18, 1249.65, 1225.54, 1164.79, 1105.98, 1040.41, 975.804, 871.667, 790.671, 692.32, 626.752, 591.075, 517.793 cm^{-1}; **HRMS** calcd for $C_{10}H_{11}Br_2NO_4$ (M+nNa) 391.8927 and (M+nH) 369.9108, found 391.8938 and 369.9124 respectively.



20 **21**

(S)-1-(4,4-dibromobut-3-en-1-yl)-3-hydroxypyrrolidine-2,5-dione (**21**): In an oven-dried 10 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with acetate **20** (0.260 g, 0.7045 mmol, 1 equiv) suspended in ethanol (4 mL). The reaction mixture was cooled to 0°C prior to the drop wise addition of acetyl chloride (0.15 mL, 2.147 mmol, 3.048 equiv). The transparent-yellow reaction mixture was allowed to warm to 22°C with stirring over 22 h or until deemed complete by TLC. The reaction mixture was then concentrated in vacuo to provide the title compound as a crude yellow oil. The crude product was purified by flash column chromatography (50% ethyl acetate in hexanes, Rf = 0.34) to provide the title compound as a white solid (0.228 g, 99%).

m.p = 91-93°C; **[α]**^{20C}= -46.081 (c. 1.6, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 6.38 (t, *J* = 7.5 Hz, 1H), 4.68 (ddd, *J* = 8.2, 4.7, 2.9 Hz, 1H), 3.77 (d, *J* = 3.1 Hz, 1H), 3.63 (t, *J* = 6.7 Hz, 2H), 3.10 (dd, *J* = 18.2, 8.4 Hz, 1H), 2.70 (dd, *J* = 18.2, 4.8 Hz, 1H), 2.41 (q, *J* = 7.0 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.56, 174.16, 134.31, 92.10, 77.64, 77.21, 76.79, 67.06, 37.28, 36.58, 31.43; **IR** (film): 3430.74, 3027.69, 2946.7, 2850.27, 2359.48, 2340.19, 1782.87, 1700.91, 1634.38, 1558.2, 1540.85, 1507.1, 1442.49, 1438.64, 1402, 1349.93, 1317.14, 1261.22, 1170.58, 1104.05, 1057.76, 1024.02, 963.269, 902.523, 793.564, 754.995, 692.32, 614.217, 516.829, 509.115 cm^{-1}; **HRMS** calcd for $C_8H_9Br_2NO_3$ (M+nH) 327.9002, found 327.9003.



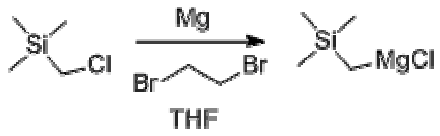
21 **22**

(S)-3-((tert-butyldimethylsilyl)oxy)-1-(4,4-dibromobut-3-en-1-yl)pyrrolidine-2,5-dione (**22**): In an oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with pyrrolidinedione **21** (1.0 g, 3.058 mmol, 1 equiv), TBS-Cl (0.533 g, 3.669 mmol, 1.2 equiv) and imidazole (0.520 g, 7.645 mmol, 2.5 equiv) in dry DMF (2 mL) at room temperature. The yellowish reaction mixture was allowed to stir at 25ºC for 36 h or until deemed complete by TLC (1:1 ethyl acetate in hexanes, Rf = 0.91 (**22**), 0.34 (**21**)). The reaction mixture was then diluted and extracted with 1:1 ether-pentane (3x 15 mL), and the organic layer washed with NH_4Cl (2x 15 mL), brine (15 mL) and dried over anhydrous sodium sulfate. The solvents were then removed under reduced pressure to provide the crude product as a yellow oil. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes, Rf = 0.35) to furnish the title compound **22** as a white solid (1.35 g, 100%).

m.p 27-29ºC; **[α]**$^{19.7C}$= -29.34 (c. 1.6, $CHCl_3$); **^{1}H NMR** (500 MHz, Chloroform-d) δ 6.37 (t, *J* = 7.4 Hz, 1H), 4.58 (dd, *J* = 8.1, 4.5 Hz, 1H), 3.61 (t, *J* = 6.8 Hz, 2H), 3.01 (dd, *J* = 18.0, 8.2 Hz, 1H), 2.60 (dd, *J* = 17.9, 4.5 Hz, 1H), 2.40 (q, *J* = 7.0 Hz, 2H), 0.92 (s, 9H), 0.18 (d, *J* = 7.1 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.58, 174.12, 134.44, 99.72, 91.84, 67.99, 38.95, 36.33, 31.46, 25.79, 18.37, -4.49, -5.09; **IR** (film): 3482.81, 3027.69, 2954.41, 2932.23, 2884.02, 2857.99, 2710.46, 2359.48, 2340.19, 1789.62, 1712.48, 1627.63, 1475.28, 1434.78, 1402, 1349.93, 1253.5, 1161.9, 1102.12, 1035.59, 943.985, 835.99, 781.029, 692.32, 670.142; **HRMS** calcd for $C_{14}H_{23}Br_2NO_3Si$ (M+nH) 441.9867, found 441.9845.

$PdCl_2(PMePh_2)_2$: To a 25 mL round bottom flask equipped with a magnetic stirring bar was charged with $PdCl_2$ (355 mg, 2 mmol, 1 equiv) and KCl (299 mg, 4 mmol, 2 equiv) suspended in deionized H_2O (5 mL) at 22°C. The brown reaction mixture was stirred at 22°C overnight after being flushed with N_2. The resulting deep-red homogeneous solution was treated with acetone (5mL, HPLC grade) prior to the drop wise addition of $PMePh_2$ (0.7443 mL, 4 mmol, 2 equiv). The solution was then allowed to stir at 22°C for 2 h. The reaction mixture was then diluted and extracted with dichloromethane (2x 10 mL), and the organic layer concentrated to afford a crude solid. Trituration of the sample (15 mL Et_2O) followed by filtration furnished the title compound as a yellow solid (1.148g, 99%).

^{31}P NMR (300 MHz, $CDCl_3$), δ: 18.85 (cis), 7.75 (trans).[46b]



To a flame dried 250 mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, condenser and nitrogen inlet was charged with magnesium turnings (3.525 g, 144.5 mmol, 1.1 equiv) and THF (62 mL), followed by 1,2-dibromoethane (0.2 mL, 2.32 mmol). The magnesium suspension was stirred for 10 min and chloromethyltrimethylsilane (18.325 mL, 131.25 mmol, 1 equiv) was added drop wise over 2 h during which exotherms resulted in a gentle reflux of the reaction mixture.

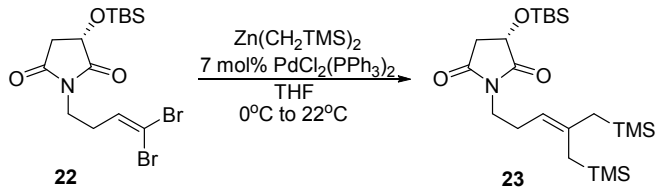
Following addition, the dark grey reaction mixture was stirred for 4 h at 22°C and stirring then stopped. The reaction mixture was allowed to stand overnight. Concentrations were determined by titration using 2-butanol and 1,10-phenanthroline as an indicator.

Preparation for $Zn(CH_2TMS)_2$: A 250 mL flask was charged with $ZnCl_2$ and fused (melted) under high vacuum via a Bunsen burner. The resultant dry $ZnCl_2$ (6.58 g, 48.28 mmol) was dissolved in freshly distilled THF (48 mL) to form a 1M stock solution. This solution was stored under N_2. To a separate 25 mL round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with 1M $ZnCl_2$ (5 mL, 5 mmol, 1 equiv) solution. Over 15 minutes, at 0°C, $TMSCH_2MgCl$ (5.096 mL, 10 mmol, 1.962M, 2 equiv) was added. The reaction mixture becomes thick with a white precipitate, which requires settling before use. The resulting light-grey supernatant is 1M $Zn(CH_2TMS)_2$.

$ZnCl_2$-TMEDA: To a 500 mL round-bottomed flask charged with $ZnCl_2$ (46.5 g, 341 mmol, 1 equiv) was fused (melted) under high vac via a Bunsen burner. Once cooled to room temp, the flask was back-filled with N_2, equipped with a stir bar, and charged with THF (170 mL). The reaction was conducted at 22°C and the reaction mixture quickly became exothermic once dissolving began. After the reaction mixture was homogeneous (30 min), the TMEDA (56 mL, 375 mmol, 1.1 equiv) was added at a steady rate. This increased the exothermic nature of the reaction. After several minutes of vigorous stirring, white solid began to precipitate. The reaction mixture was allowed to

stir over night at 22°C. The reaction was then filtered and the white crystals (80.34 g, 93.2%) washed with cold anhydrous ethyl ether. Recrystallization can be achieved from THF.

m.p. : 176-177°C

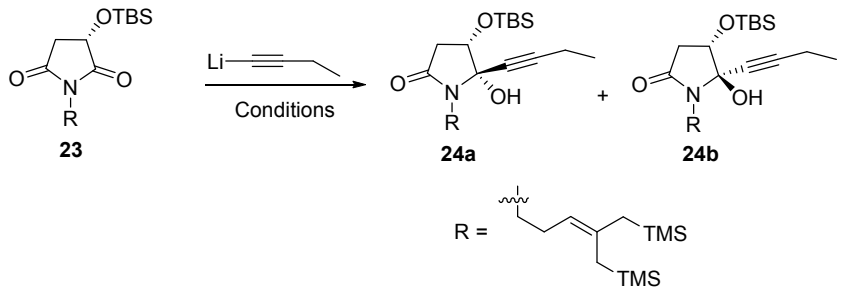


(S)-3-((tert-butyldimethylsilyl)oxy)-1-(5-(trimethylsilyl)-4-((trimethylsilyl)methyl)pent-3-en-1-yl)pyrrolidine-2,5-dione (**23**): To an oven-dried 25 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with gem-dibromide **22** (0.967 g, 2.193 mmol, 1 equiv) dissolved in THF (6.58 mL) freshly distilled from sodium metal. The solution was then treated with $Zn(CH_2TMS)_2$ (4.38 mL, 4.38 mmol, 1 M in THF, 2 equiv) in portions, and stirred for 5 min at 0°C. Afterwards, $PdCl_2(PPh_3)_2$ (0.107 g, 0.153 mmol, 7 mol %) was added all at once, the flask was purged with N_2 and allowed to warm to room temp. The yellow suspension begins to disappear once it reaches 22°C. The reaction was allowed to stir for 11 h 45 min at 22°C. The light-orange reaction mixture was then poured over cold sat. NH_4Cl (25 mL), extracted with ethyl ether (3x 25 mL), and washed with brine (25 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. Trituration of the residue with pentane (2x 10 mL) followed by Celite (1/4 inch) filtration of the supernatant liquid afforded a crude product as a yellow oil, which was

purified by flash column chromatography (SiO_2, gradient: hexanes then 5%→10% ethyl acetate in hexanes) to provide the title compound as a colorless oil (0.228 g, 97%).

[α]^{21C}= -19.1(c. 1.6, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.72 (t, *J* = 7.1 Hz, 1H), 4.55 (dd, *J* = 8.1, 4.5 Hz, 1H), 3.47 (t, *J* = 7.6 Hz, 2H), 2.98 (dd, *J* = 17.9, 8.2 Hz, 1H), 2.58 (dd, *J* = 17.9, 4.5 Hz, 1H), 2.21 (q, *J* = 7.4 Hz, 2H), 1.47 (s, 2H), 1.40 (s, 2H), 0.92 (s, 9H), 0.18 (d, *J* = 3.6 Hz, 6H), 0.02 (s, 9H), -0.01 (s, 8H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.76, 174.33, 138.36, 114.30, 77.57, 77.14, 76.72, 67.97, 38.96, 38.92, 29.65, 26.99, 25.76, 23.92, 18.36, -0.57, -1.04, -4.51, -5.13; **IR** (film): 3480.88, 2954.41, 2928.38, 2359.48, 1787.69, 1715.37, 1468.53, 1400.07, 1361.5, 1251.58, 1152.26, 1091.51, 836.955, 780.065, 623.859; **HRMS** calcd for $C_{22}H_{45}NO_3Si_3$ 456.2780, found 456.2789.

Preparation of lithiobutyne: To a flame dried 100 mL schlenk flask equipped with a magnetic stirring bar and nitrogen inlet was charged with THF (15 mL) and 1-butyne (3.245 g, 60 mmol, 1.2 equiv) at -10ºC (salt-ice bath). The solution was then cooled to -78 ºC and treated drop wise with nBuLi (23.8 mL, 50 mmol, 1 equiv, 2.13 M in hexanes). After allowing to stir for 30 minutes at -78 ºC the solution was allowed to slowly warm to 0ºC. The solvent was then removed to provide lithiobutyne as a white solid.



Method 1:

(S)-4-((tert-butyldimethylsilyl)oxy)-5-(but-1-yn-1-yl)-5-hydroxy-1-(5-(trimethylsilyl)-4-((trimethylsilyl)methyl)pent-3-en-1-yl)pyrrolidin-2-one (24): To an oven-dried 10 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lithiobutyne (47.4 mg, 0.789mmol, 1.2equiv) dissolved in LPDE (5M, 3.3mL) at 0^{o}C. The cooled solution was then treated drop wise with a solution of imide **23** (0.3 g, 0.658 mmol, 1 equiv in 1.5 mL anhydrous ethyl ether) over a period of 2 minutes. Following complete addition, the reaction mixture was allowed to warm to room temp and was stirred for 15 minutes or until deemed complete by TLC (15% ethyl acetate in hexanes). The reaction mixture was then diluted (2 mL Et_2O), poured over cold 5% NH_4OH (10 mL), extracted with Et_2O (3x 10 mL) and dried over magnesium sulfate. Following the removal of solvents, the crude product was provided as a white solid (0.3139 g, 94%) which may be purified and the diastereomers separated by column chromatography (SiO_2, gradient: hexanes then 5%→10% ethyl acetate in hexanes) to provide both as white solids (270 mg, 81%).

Method 2:

To an oven-dried 25 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lithiobutyne (0.153 g, 2.56 mmol, 3.0 equiv) in

tetrahydrofuran (5.3 mL). The reaction mixture was cooled to -78°C prior to the drop wise addition of cyclic imide **23** (0.389 g, 0.855 mmol, 1 equiv in 1.6 mL THF) over 20 min. The red-pink reaction mixture was then allowed to warm to –20°C and was stirred at that temperature for 16 h. The reaction mixture was then quenched by slow addition of 1M Et_3NHOAc in THF (5 mL) and extracted with water (10 mL), ether (3x 10 mL) and the organic layer washed with brine (10 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to provide desired product as a yellow oil. The crude product was purified by flash column chromatography (SiO_2, gradient: hexanes then 5%→10% ethyl acetate in hexanes) to furnish the title compound as a light orange oil (0.368 g, 85%).

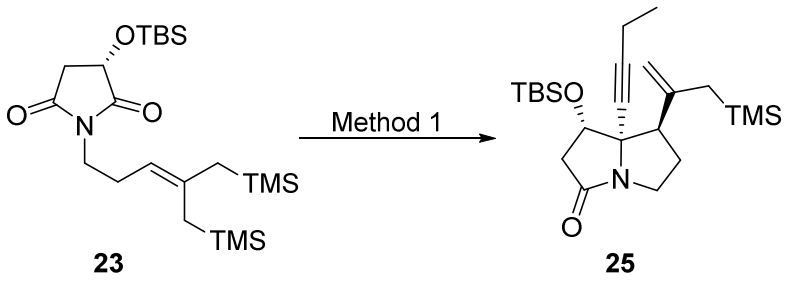
HRMS calcd for $C_{26}H_{51}NO_3Si_3$ (M+nH) 510.3250, found 510.3245.

24a:

[α]$^{18.9C}$= -15.483(c. 0.062, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.79 (t, *J* = 7.2 Hz, 1H), 4.34 (t, *J* = 5.9 Hz, 1H), 3.96 (s, 1H), 3.39 (td, *J* = 12.0, 10.1, 7.5 Hz, 1H), 3.24 (td, *J* = 13.9, 11.7, 7.2 Hz, 1H), 2.63 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.44 – 2.16 (m, 5H), 1.51 (s, 2H), 1.40 (s, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 0.16 (d, *J* = 7.1 Hz, 6H), 0.01 (d, *J* = 9.6 Hz, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.91, 136.65, 115.63, 88.18, 84.62, 77.46, 77.03, 76.61, 73.37, 40.65, 38.28, 29.48, 28.37, 25.68, 23.76, 18.10, 13.44, 12.31, -0.65, -1.15, -4.69, -4.87; **IR** (film): 3478.95, 3334.32, 2950.55, 2932.23, 2893.66, 2856.06, 2239.91, 1711.51, 1403.92, 1361.5, 1316.18, 1247.72, 1145.51, 1080.91, 981.59, 951.698, 924.7, 836.955, 783.922, 700.034, 623.859 cm^{-1}.

24b:

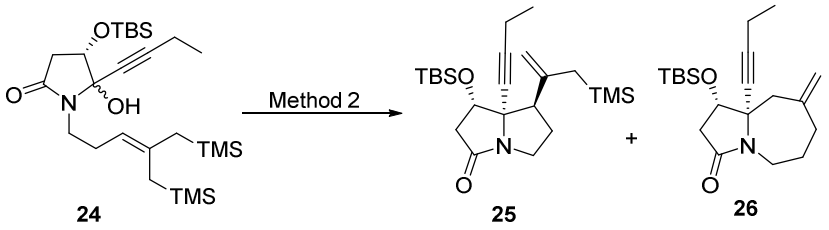
[α]$^{18.4C}$= 14.144(c. 0.152, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.83 (t, *J* = 7.0 Hz, 1H), 4.15 (d, *J* = 5.5 Hz, 1H), 3.55 (dt, *J* = 14.4, 7.6 Hz, 1H), 3.25 (dt, *J* = 14.1, 7.7 Hz, 1H), 2.96 (s, 1H), 2.76 (dd, *J* = 16.5, 5.7 Hz, 1H), 2.28 (q, *J* = 12.8, 10.1 Hz, 5H), 1.47 (dd, *J* = 22.4, 7.4 Hz, 4H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.12 (d, *J* = 4.4 Hz, 6H), 0.02 (d, *J* = 5.0 Hz, 18H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.80, 138.38, 116.23, 91.53, 89.86, 77.64, 77.22, 76.80, 75.62, 74.86, 40.73, 39.19, 29.81, 28.72, 25.88, 24.27, 18.35, 13.63, 12.68, -0.41, -0.91, -4.52, -4.61; **IR** (film): 3139.54, 3056.62, 2954.41, 2927.41, 2893.66, 2852.2, 2245.7, 1654.62, 1453.1, 1389.46, 1362.46, 1317.14, 1244.83, 1138.76, 1078.01, 995.089, 930.485, 843.704, 782.958, 695.212, 627.716 cm^{-1}



23 **25**

Method 1:

(1S,7R,7aS)-7a-(but-1-yn-1-yl)-1-((tert-butyldimethylsilyl)oxy)-7-(3-(trimethylsilyl)prop-1-en-2-yl)hexahydro-3H-pyrrolizin-3-one (**25**): To an oven-dried 50 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lithiobutyne (0.237 g, 3.94 mmol, 1.2 equiv) dissolved in LPDE (5M, 16.45 mL) at 0°C. The cooled solution was then treated drop wise with a solution of imide **23** (1.5 g, 3.29 mmol, 1.0 equiv in 7.5 mL anhydrous ethyl ether) over a period of 2 minutes. Following complete addition, the reaction mixture was allowed to warm to room temp and was stirred for 15 minutes or until deemed complete by TLC (15% ethyl acetate in hexanes). The reaction mixture was then cooled to 0°C and treated with TFAA (0.56 mL, 3.94 mmol, 1.2 equiv). After stirring for 12-15 minutes at room temperature (or until deemed complete by TLC; 15% EtOAc in hexanes) the reaction was quenched by inverse addition over cold 5% NH_4OH (20 mL), extracted with ether (3x 20 mL), and the organic layer washed with brine (30 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to furnish the title compound as an orange oil. The crude product was purified by flash column chromatography (SiO_2, gradient: hexanes then 5%→10%→15% ethyl acetate in hexanes) to furnish the title compound as a light-yellow oil (0.6953 g, 50%).



Method 2:

To an oven-dried 5 mL round bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with hydroxylactam **24** (0.033 g, 0.063 mmol, 1 equiv) in 5M LPDE (0.314 mL, 0.2M in substrate) at 0°C. The reaction mixture was allowed to slowly warm to 22°C and was stirred at that temperature for 15 h or until deemed complete by GC analysis. The reaction mixture was then diluted with cold 5% NH_4OH (5 mL), extracted with ether (3x 10 mL), and the organic layer washed with brine (15 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to furnish a crude mixture of inseparable bicyclic lactams **25** and **26**. The mixture may be partially purified by flash column chromatography (SiO_2, gradient: hexanes then 5%→10%→15% ethyl acetate in hexanes) or separated by reverse phase HPLC to provide a yellow oil (7.62 mg, 28%).

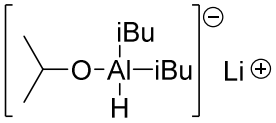
Note: HPLC purifications resulted in diminished yields (~10%)

Reversed phase HPLC purification was performed with a Waters 2487 Dual λ Absorbance detector, 600 controller and pump, and a Phenomenex Synergi 4μ Polar RP 80A HPLC column (250 x 21.2mm) using Waters Empower 3 software. A gradient of A 0.1%TFA, H2O) and B (0.1% TFA, 19:1 CH3CN, H2O) was used.

25:
[α]$^{21.2C}$ = 29.923(c 0.65, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.69 (s, 1H), 4.55 (s, 1H), 4.12 (dd, *J* = 9.9, 7.2 Hz, 1H), 3.76 (ddd, *J* = 11.5, 7.5, 4.1 Hz, 1H), 3.04 (dt, *J* = 11.6, 7.5 Hz, 1H), 2.85 (t, *J* = 7.1 Hz, 1H), 2.71 (dd, *J* = 14.9, 10.3 Hz, 1H), 2.47 (dd, *J* = 15.0, 7.1 Hz, 1H), 2.24 (q, *J* = 7.4 Hz, 2H), 2.12 (dq, *J* = 11.6, 7.0 Hz, 2H), 1.83 (m, *J* = 13.0, 5.9 Hz, 2H), 1.61 (d, *J* = 13.3 Hz, 1H), 1.14 (t, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.03 (s, 15H); **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 171.64, 145.27, 108.55, 88.34, 79.19, 71.16, 70.94, 54.78, 42.90, 41.33, 31.18, 29.41, 25.83, 18.07, 14.15, 12.72, -1.23, -3.52, -4.79; **IR** (film): 3251.4, 3083.62, 2953.45, 2929.34, 2891.74, 2857.02, 2359.48, 2335.37, 2236.06, 1707.66, 1628.59, 1470.46, 1408.75, 1388.5, 1360.53, 1320.04, 1247.72, 1144.55, 917.95, 835.99, 777.172 cm^{-1}; **HRMS** calcd for $C_{23}H_{41}NO_2Si_2$ (M+) 420.2749, found 420.2756.

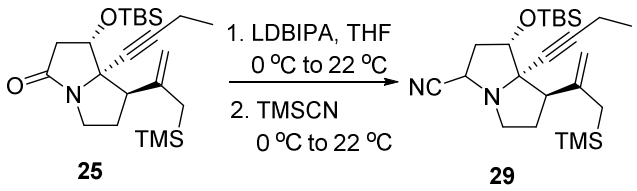
26:

^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.92 (s, 1H), 4.86 (s, 1H), 4.42 (t, *J* = 6.9 Hz, 1H), 3.97 (dt, *J* = 14.1, 5.2 Hz, 1H), 3.05 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.72 – 2.55 (m, 2H), 2.47 – 2.29 (m, 2H), 2.20 (q, *J* = 7.3 Hz, 3H), 1.92 – 1.67 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.12 (d, *J* = 7.6 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.43, 144.77, 115.83, 88.75, 79.31, 77.64, 77.22, 76.79, 75.00, 64.93, 43.20, 39.82, 39.33, 34.94, 25.91, 18.27, 14.12, 12.49, -4.58, -4.63; **IR** (film): 3380.6, 3072.05, 2954.41, 2932.23, 2852.2, 2357.55, 2339.23, 1699.94, 1445.39, 1403.92, 1251.58, 1141.65, 1004.73, 928.557, 889.987, 833.098, 780.065, 666.285 cm^{-1} **HRMS** calcd for C20H33NO2Si (M+nH) 348.2353, found 348.2338.



LDBIPA

The desired reducing agent lithium diisobutyl-iso-propoxyaluminum hydride (LDBIPA) was obtained as a colorless solution from DIBAL (1M in toluene) by the general preparation procedure outlined by Duk An.[92] Concentrations were determined by reaction with excess p-methoxybenzaldehyde and analysis of an aliquot by No-D ^{1}H NMR.[121]



25 **29**

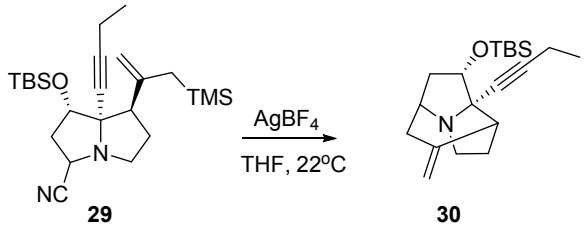
(1S,7R,7aS)-7a-(but-1-yn-1-yl)-1-((tert-butyldimethylsilyl)oxy)-7-(3-(trimethylsilyl)prop-1-en-2-yl)hexahydro-1H-pyrrolizine-3-carbonitrile (**29**): In an oven-dried 5 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lactam **25** (0.4053 g, 0.965 mmol, 1 equiv) dissolved in THF (1.98 mL). The solution was then cooled to 0°C and treated drop wise with LDBIPA (2.49 mL, 1.45 mmol, 0.58 M, 1.5 equiv) over several minutes. The reaction mixture was allowed to slowly warm to 22°C and stir for 24 h or until deemed complete by TLC (15% EtOAc in Hexanes). Upon completion of the partial reduction, the reaction mixture was treated dropwise with freshly distilled TMSCN (0.34 mL, 2.70 mmol, 2.8 equiv) and allowed to stir at 22°C for 7 h or until deemed complete by TLC. The reaction mixture was then quenched by slow addition of water (5mL), filtered over Celite and extracted from ethyl ether (3x 10). The combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to provide desired product as an orange oil. The crude product was purified by flash column chromatography (SiO2, gradient, hexanes then 5%→10% Ethyl acetate in hexanes) to furnish the title compound **29** as a light-yellow oil (0.339 g, 82%).

HRMS calcd for $C_{24}H_{42}N_2OSi_2$ 430.2836, found 430.2827

Major Diastereomer:
[α]^{19C} = -7.034 (c 0.29, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.78 (s, 1H), 4.69 (s, 1H), 4.46 (d, *J* = 5.8 Hz, 1H), 4.05 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.23 – 3.12 (app m, 2H),

2.91 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.39 – 2.19 (m, 4H), 2.15 (d, *J* = 13.4 Hz, 1H), 2.09 – 1.91 (m, 1H), 1.80 – 1.70 (m, 1H), 1.61 (d, *J* = 13.3 Hz, 1H), 1.13 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 1.0 Hz, 6H), 0.04 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.93, 118.45, 108.55, 88.91, 80.85, 77.63, 77.20, 76.78, 72.96, 72.63, 55.43, 50.68, 50.13, 39.05, 28.98, 28.64, 25.85, 18.12, 13.95, 12.82, -1.17, -3.58, -4.70; **IR** (film): 3083.62, 2958.27, 2932.23, 2893.66, 2859.92, 2361.41, 2342.12, 2239.91, 2224.49, 1791.55, 1703.8, 1627.63, 1472.38, 1418.39, 1365.35, 1320.04, 1247.72, 1149.37, 1087.66, 1057.76, 1034.62, 1004.73, 943.985, 916.986, 860.096, 836.955, 776.208, 703.89, 635.43.

Minor Diastereomer:
[α]$^{21.4C}$ = 10.864 (c 0.162, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.63 (d, *J* = 5.8 Hz, 2H), 3.81 (t, *J* = 7.4 Hz, 1H), 3.51 (t, *J* = 8.2 Hz, 1H), 3.22 (dt, *J* = 12.4, 9.3 Hz, 1H), 2.94 – 2.73 (m, 2H), 2.32 – 2.13 (m, 5H), 1.67 (dp, *J* = 10.1, 4.9 Hz, 2H), 1.55 (d, *J* = 13.3 Hz, 1H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.14 – -0.15 (m, 15H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.43, 119.08, 108.08, 88.93, 80.71, 77.63, 77.21, 76.78, 72.67, 55.92, 52.88, 38.68, 28.42, 27.56, 25.83, 18.11, 13.88, 12.90, -1.18, -3.57, -4.74; **IR** (film): 3083.62, 2954.41, 2928.38, 2889.81, 2859.92, 2361.41, 2339.23, 2239.91, 1783.83, 1699.94, 1627.63, 1476.24, 1418.39, 1357.64, 1323.89, 1243.86, 1152.26, 1103.08, 1083.8, 1008.59, 947.842, 901.558, 856.239, 836.955, 780.065, 703.89, 666.285, 643.144.

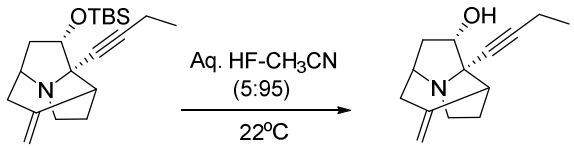


29 **30**

(1R,5S,7S,7aS)-7a-(but-1-yn-1-yl)-7-((tert-butyldimethylsilyl)oxy)-9-methylenehexahydro-1H-1,5-ethanopyrrolizine (**30**): In an oven-dried 5 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with $AgBF_4$ (in a drybox, 30.12 mg, 0.1547 mmol, 1.1 equiv) followed by cyanoamine **29** (60.6 mg, 0.1406 mmol, 1 equiv) dissolved in THF (1.81 mL). The reaction mixture was then protected from light and allowed to stir at 22°C for 22 h or until deemed complete by

GC/TLC. The reaction mixture was then quenched by the addition of 5% NH_4OH (2.5 mL) and extracted from ethyl ether (4x 5 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to provide desired product **30** as a brown oil. The brown oil may then be purified by trituration with pentane (5 mL) followed by passing over a plug of alumina (neutral, activity II, elute with 100% EtOAc) to provide the title compound as a dark orange oil (41.1 mg, 88%).

[α]$^{20.7C}$ = 110.18 (c 0.33, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.65 (app. t, *J* = 2.2 Hz, 1H), 4.59 (app. t, *J* = 2.2 Hz, 1H), 4.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.47 – 3.18 (m, 2H), 3.01 (ddd, *J* = 13.3, 8.6, 5.4 Hz, 1H), 2.69 (d, *J* = 6.2 Hz, 1H), 2.38 – 2.11 (m, 4H), 2.04 (dddd, *J* = 13.3, 6.7, 4.8, 2.1 Hz, 1H), 1.91 (dd, *J* = 12.6, 7.6 Hz, 1H), 1.69 – 1.53 (m, 2H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 4.3 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.15, 107.67, 87.51, 78.38, 77.65, 77.22, 76.80, 75.29, 72.67, 61.96, 54.97, 46.90, 43.43, 34.22, 31.71, 26.08, 18.54, 14.19, 12.87, -4.50, -4.66; IR (film): 3396.03, 2950.55, 2932.23, 2856.06, 2361.41, 2342.12, 1711.51, 1650.77, 1468.53, 1361.5, 1316.18, 1251.58, 1122.37, 1103.08, 1004.73, 936.271, 840.812, 776.208, 666.285; **HRMS** calcd for $C_{20}H_{33}NOSi$ 332.2404, found 332.2407.

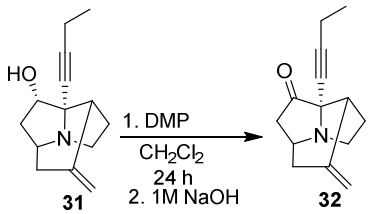


30 **31**

(1R,5S,7S,7aS)-7a-(but-1-yn-1-yl)-9-methylenehexahydro-1H-1,5-ethanopyrrolizin-7-ol (**31**): In a PTFE plastic flask equipped with a magnetic stirring bar was charged with tricycle **30** (0.1173 g, 0.3537 mmol, 1 equiv) dissolved in acetonitrile (11.8 mL). The solution was then treated with aqueous HF (48%, 0.62 mL) and allowed to stir for 24 h at 22°C or until deemed complete by TLC (5% MeOH in DCM + 1% NH_4OH). The reaction mixture was then quenched by the addition of 1M KOH (18 mL) and extracted from ethyl ether (3x 20 mL). The combined extracts were dried over

anhydrous sodium sulfate and concentrated in vacuo to provide the desired product as a yellow solid. The crude product was purified by bulb-to-bulb distillation (1mmHg, 140-160^{o}C) to furnish the title compound **31** as a white solid (73.2 mg, 95%).

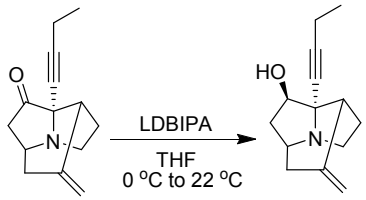
m.p 174-176 (sublime); **[α]**$^{20.3C}$ = 237.69 (c 0.039, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.67 (t, *J* = 2.1 Hz, 1H), 4.63 (t, *J* = 2.1 Hz, 1H), 4.21 (t, *J* = 6.2 Hz, 1H), 3.41 (d, *J* = 4.2 Hz, 1H), 3.26 (ddd, *J* = 12.9, 10.6, 4.2 Hz, 1H), 3.07 (ddd, *J* = 13.3, 8.6, 5.5 Hz, 1H), 2.77 (d, *J* = 6.1 Hz, 1H), 2.44 (s, 1H), 2.35 (s, 1H), 2.33 – 2.20 (m, 3H), 2.03 (ddd, *J* = 5.9, 3.8, 1.3 Hz, 2H), 1.73 – 1.61 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.94, 108.53, 90.41, 77.63, 77.41, 77.21, 76.96, 76.78, 75.95, 71.12, 62.26, 54.39, 46.84, 41.78, 34.19, 31.76, 14.18, 12.72; **IR** (film): 3160.76, 3075.9, 2965.02, 2924.52, 2850.27, 2359.48, 2340.19, 2244.74, 1645.95, 1442.49, 1375.96, 1317.14, 1250.61, 1098.26, 980.625, 906.379, 884.202, 813.813, 722.211, 670.142 cm^{-1} ; **HRMS** calcd for $C_{14}H_{19}NO$ (M+nH) 218.1539, found 218.1547.



(1R,5S,7aS)-7a-(but-1-yn-1-yl)-9-methylenehexahydro-7H-1,5-ethanopyrrolizin-7-one (**32**): To a 10 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with tricycle **31** (73.2 mg, 0.3368 mmol, 1 equiv) in dichloromethane (2.9 mL). To the stirred solution, Dess-Martin periodinane (15% wt in CH_2Cl_2, 1.2 mL, 0.5726 mmol, 1.7 equiv) was added dropwise at room temperature. The reaction progress was monitored TLC analysis (silica gel, 9:1 CH_2Cl_2-MeOH). The reaction mixture was then quenched with the addition of sodium hydroxide (1M, 4 mL) and extracted with CH_2Cl_2 (3x 5 mL). The combined extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate, and concentrated in

vacuo to provide the desired product as a yellow oil. Washing of the viscous oil with pentane (3x 2 mL) followed by concentration of the triturate furnished the title compound (68.5 mg, 95%) as a light-yellow viscous oil. The product was used without further purification.

[α]^{20C} = 227.13 (c 0.29, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.71 (app. d, *J* = 1.9 Hz, 1H), 4.65 (app. t, *J* = 1.8 Hz, 1H), 3.60 (dd, *J* = 6.9, 4.5 Hz, 1H), 3.39 (ddd, *J* = 13.4, 10.8, 4.1 Hz, 1H), 3.20 (ddd, *J* = 13.4, 8.3, 5.6 Hz, 1H), 3.01 (d, *J* = 6.0 Hz, 1H), 2.68 (ddd, *J* = 17.5, 6.9, 1.7 Hz, 1H), 2.55 (ddd, *J* = 14.4, 4.5, 2.2 Hz, 1H), 2.37 – 2.04 (m, 4H), 1.92 – 1.75 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.46, 143.77, 110.79, 88.37, 77.64, 77.22, 76.80, 74.75, 57.04, 56.11, 49.03, 43.82, 33.45, 31.59, 13.88, 12.69; **IR** (film): 3072.05, 2973.7, 2938.98, 2878.24, 2848.35, 2361.41, 2339.23, 2243.77, 1760.69, 1646.91, 1468.53, 1441.53, 1396.21, 1331.61, 1274.72, 1220.72, 1183.11, 1167.69, 1149.37, 1126.22, 1091.51, 1073.19, 1016.3, 997.017, 932.414, 909.272, 860.096, 799.35, 764.637, 723.175, 597.825, 544.792; **HRMS** calcd for $C_{14}H_{17}NO$ [M+nH] 216.1383, found 216.1386.

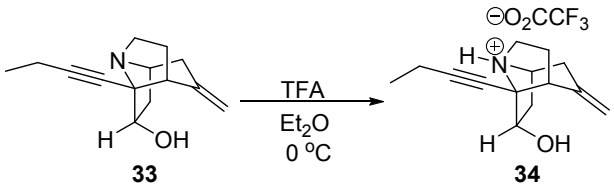


32 **33**

(1R,5S,7R,7aS)-7a-(but-1-yn-1-yl)-9-methylenehexahydro-1H-1,5-ethanopyrrolizin-7-ol (**33**): To a 10 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with tricycle **32** (68.5 mg, 0.3181 mmol, 1 equiv) dissolved in THF (3.2 mL). Then the mixture was cooled to 0ºC prior to the dropwise addition of LDBIPA (0.582 M, 0.820 mL, 0.4772 mmol, 1.5 equiv) and the reaction progress was monitored by TLC (9:1 CH_2Cl_2-MeOH). Upon completion (24 h),

the reaction was then quenched by slow addition of water (4 mL) and extracted from ethyl ether (3x 5 mL). The combined extracts were filtered over a Celite plug, dried over anhydrous magnesium sulfate and concentrated in vacuo to provide desired product as a yellow oil (67.5 mg, 98%). The crude product may then be recrystallized by dissolving in pentane and cooling to -30°C to induce crystallization to provide the desired azatricycle as a white solid (63.5 mg, 92%).

m.p 74-75°C; $[\alpha]^{21.7C}$ = 136.24 (c 0.149, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.91 (s, 1H), 4.77 (s, 1H), 4.58 (ddd, *J* = 13.0, 10.7, 2.7 Hz, 1H), 3.36 (dd, *J* = 6.8, 4.7 Hz, 1H), 3.26 (ddd, *J* = 12.9, 10.5, 4.1 Hz, 1H), 3.03 (ddd, *J* = 13.3, 8.5, 5.5 Hz, 1H), 2.95 (d, *J* = 6.1 Hz, 1H), 2.85 (d, *J* = 12.6 Hz, 1H), 2.69 (dddd, *J* = 13.9, 10.7, 7.0, 1.8 Hz, 1H), 2.50 (ddd, *J* = 14.9, 4.5, 2.3 Hz, 1H), 2.40 – 2.25 (m, 1H), 2.19 (q, *J* = 7.5 Hz, 2H), 1.85 (d, *J* = 14.9 Hz, 1H), 1.62 (ddd, *J* = 12.7, 8.5, 4.1 Hz, 1H), 1.28 (dd, *J* = 14.0, 2.8 Hz, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.18, 108.96, 85.56, 80.07, 78.24, 77.64, 77.22, 76.79, 72.96, 60.77, 52.13, 47.55, 40.34, 34.77, 32.88, 14.14, 12.70; **IR** (film): 3537.77, 3316, 3072.05, 2961.16, 2924.52, 2854.13, 2736.49, 2529.18, 2470.37, 2359.48, 2340.19, 2240.88, 1760.69, 1734.66, 1649.8, 1450.21, 1317.14, 1257.36, 1161.9, 1105.98, 1077.05, 1017.27, 888.059, 799.35, 728.961, 569.862 cm^{-1}; **HRMS** calcd for $C_{14}H_{20}NO^+$ (M) 218.1539, found 218.1529.

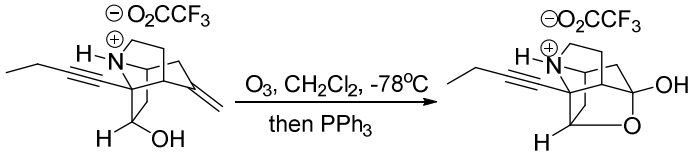


33 **34**

(1R,5S,7R,7aS)-7a-(but-1-yn-1-yl)-9-methylenehexahydro-1H-1,5-ethanopyrrolizin-7-ol ammonium trifluoroacetate (**34**): To a 5 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with tricycle **33** (67.5 mg, 0.3106 mmol, 1 equiv) dissolved in Et_2O (6 mL). The solution was treated with TFA (26.3 µL, 0.3416 mmol, 1.1 equiv) dropwise with stirring at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was concentrated in vacuo and the resulting viscous

oil was washed with pentane (3 x 5 mL). The residue was dissolved in Et_2O and filtered through a Celite plug to furnish the crude compound as a light-yellow oil. The crude oil was then purified by column chromatography (SiO_2, gradient, 100% EtOAc→7:1 EtOAc-MeOH; Rf = 0.37) to provide trifluoroacetate salt **34** as a nearly colorless oil (95.5 mg, 93%).

[α]^{21C} = 58.416 (c 0.24, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 5.08 (s, 1H), 4.96 (s, 1H), 3.86 (s, 1H), 3.71 – 3.57 (app. m, 1H), 3.34 (ddd, *J* = 13.7, 8.6, 6.0 Hz, 1H), 3.16 (d, *J* = 6.1 Hz, 1H), 3.04 – 2.88 (m, 1H), 2.70 (d, *J* = 15.9 Hz, 1H), 2.64 – 2.50 (m, 1H), 2.30 – 2.09 (m, 3H), 1.79 (ddd, *J* = 12.9, 8.7, 4.1 Hz, 1H), 1.53 (dd, *J* = 14.3, 2.9 Hz, 1H), 1.13 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.10, 113.17, 90.58, 75.86, 75.17, 73.55, 60.86, 52.06, 46.47, 38.60, 33.54, 30.81, 13.57, 12.66; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.46; **IR** (film): 3355.53, 2985.75, 2958.27, 2926.93, 2853.65, 2769.76, 2574.99, 2501.7, 2358.52, 2341.16, 2247.15, 1769.85, 1642.46, 1431.89, 1194.69, 1135.38, 1072.71, 1038, 961.341, 905.415, 832.616, 797.421, 720.765; **HRMS** calcd for $C_{14}H_{20}NO^+$ (M) 218.1539, found 218.1529.



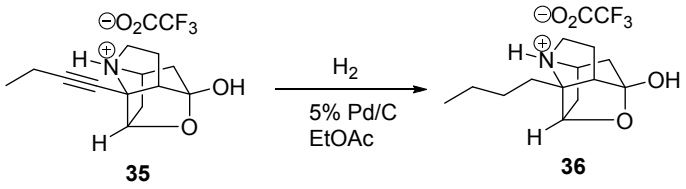
34 **35**

(1S,2a1S,4R,5S,7aS)-2a1-(but-1-yn-1-yl)hexahydro-1,4-methanofuro[2,3,4-gh]pyrrolizin-1(2aH)-ol ammonium trifluoroacetate (**35**): To a 10-mL double necked round-bottomed flask equipped with a magnetic stirring bar and oxygen inlet was charged with tropane trifluoroacetate salt **34** (28.8 mg, 0.0869 mmol, 1 equiv) in dichloromethane (2.2 mL) at -78 ^oC (dryice-acetone bath). Ozone was bubbled into the solution at an oxygen pressure of 8 p.s.i., 110 volts, and a flow rate of 0.040 cu. ft./min. for 2 minutes or until a light-blue color persists. The reaction mixture was then purged of excess ozone

for 5 min using a stream of N_2, and treated with PPh_3 (25.0 mg, 0.0956 mmol, 1.1 equiv in 0.5 mL CH_2Cl_2). After stirring for an additional 2 min, the reaction mixture was allowed to slowly warm to 22 ^oC and solvent was removed to provide the crude mixture as a light-yellow oil. The crude product was purified by reverse phase HPLC (gradient, 25% CH_3CN to 5% CH_3CN in H_2O) to furnish the title compound **35** as a faint-yellow oil (24.3 mg, 84%).

Reversed phase HPLC purification was performed with a Waters 2487 Dual λ Absorbance detector, 600 controller and pump, and a Phenomenex Synergi 4µ Polar RP 80A HPLC column (250 x 21.2mm) using Waters Empower 3 software. A gradient of A 0.1%TFA, H2O) and B (0.1% TFA, 19:1 CH3CN, H2O) was used.

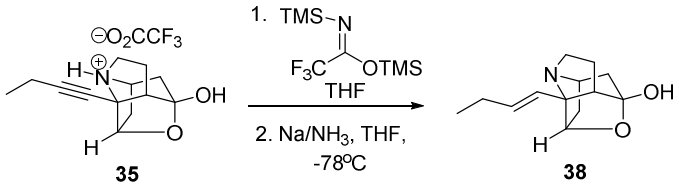
[α]^{19C} = 19.831 (c 0.238, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.74 (s, 1H), 4.13 (s, 1H), 3.84 (td, *J* = 12.5, 5.4 Hz, 1H), 3.49 (td, *J* = 9.0, 4.6 Hz, 1H), 2.82 (d, *J* = 5.6 Hz, 1H), 2.56 – 2.34 (m, 2H), 2.27 (q, *J* = 7.5 Hz, 2H), 2.23 – 1.94 (m, 4H), 1.15 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.57, 162.11, 161.64, 118.73, 114.85, 103.77, 95.43, 81.03, 78.49, 69.88, 61.88, 59.25, 47.48, 36.87, 32.17, 23.79, 13.21, 12.73; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.32; **IR** (film): 3224.4, 2981.41, 2942.84, 2924.52, 2882.09, 2852.2 2760.6, 2601.5, 2551.36, 2361.41, 2339.23, 2251.49, 1670.05, 1480.1, 1456.96, 1429.96, 1357.64, 1282.43, 1198.54, 1133.94, 1077.05, 1061.62, 977.733, 897.701, 833.098, 799.35, 719.318, 662.428, 570.826, 537.078; **HRMS** calcd for $C_{13}H_{18}NO_2$ 220.1332, found 220.1333.



35 **36**

(1S,2a1R,4R,5S,7aS)-2a1-butylhexahydro-1,4-methanofuro[2,3,4-gh]pyrrolizin-1(2aH)-ol ammonium trifluoroacetate (**36**): To a 10-mL round-bottomed flask equipped with a magnetic stirring bar and hydrogen inlet was charged with Pd/C (5wt%, 27.6 mg, 0.0130 mmol, 0.2 equiv), hemiketal trifluoroacetate salt **35** (21.7 mg, 0.0651 mmol, 1 equiv) in ethyl acetate (5.6 mL) at 22°C. Reaction progress was monitored by TLC (7:1 EtOAc in MeOH). Following reaction completion (approx. 3h), the reaction mixture was filtered over Celite and concentrated invacuo to afford the title compound as a crude oil. The product was then purified by column chromatography (SiO_2, gradient, 100% EtOAc to 7:1 EtOAc in MeOH) to furnish the pure Stemofoline core as the trifluoroacetate salt 36 (17.1 mg, 78%).

[α]$^{19.1C}$ = 28.101 (c 0.079, $CHCl_3$); **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 4.55 (s, 1H), 4.10 (s, 1H), 3.71 (ddd, *J* = 13.6, 11.1, 5.8 Hz, 2H), 3.44 (ddt, *J* = 19.5, 9.0, 5.3 Hz, 1H), 2.65 (d, *J* = 6.1 Hz, 1H), 2.33 – 2.05 (m, 7H), 2.03 – 1.89 (m, 3H), 1.76 (dt, *J* = 16.6, 6.6 Hz, 1H), 1.40 (dp, *J* = 16.2, 5.7 Hz, 6H), 0.97 – 0.87 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 104.02, 86.94, 78.10, 77.65, 7, 62.10, 54.51, 46.93, 36.45, 32.77, 28.75, 26.91, 23.42, 22.90, 14.00; **^{19}F NMR** (282 MHz, C_6D6) δ -75.45; **IR** (film): 3270.68, 2961.16, 2935.13, 2870.52, 2768.31, 2614.04, 2545.58, 2360.44, 2342.12, 1672.95, 1465.63, 1427.07, 1359.57, 1196.61, 1132.97, 1087.66, 1023.05, 981.59, 837.919, 796.457, 721.247 cm^{-1}; **HRMS** calcd for $C_{13}H_{21}NO_2$ (M+nH) 224.1645, found 224.1652.



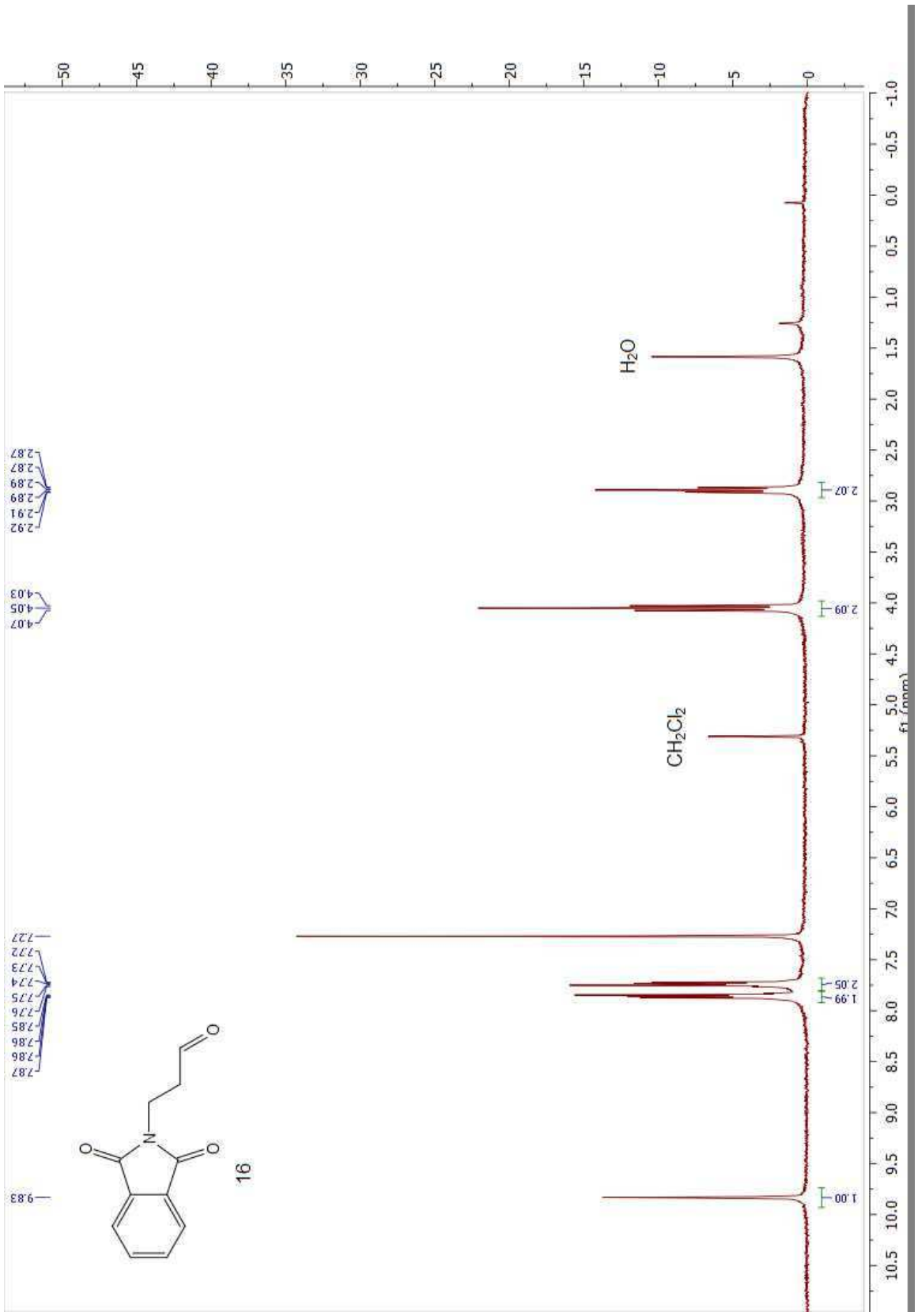
(1S,2a1R,4R,5S,7aS)-2a1-((E)-but-1-en-1-yl)hexahydro-1,4-methanofuro[2,3,4-gh]pyrrolizin-1(2aH)-ol ammonium trifluoroacetate (**38**): To a 10mL double-necked round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with hemiketal trifluoroacetate salt **35** (12.9 mg, 0.0387 mmol, 1 equiv) dissolved in THF (2 mL) at room temperature. To the stirred solution, *N*,*O*-Bis(trimethylsilyl)trifluoroacetamide (10.2 μL, 0.0387 mmol, 1 equiv) was added all-at-once and was allowed to stir until completion (3h). Upon completion, solvent and volatile byproducts were removed under high vacuum to provide the sensitive intermediate TMS protected hemiketal **37** as a colorless oil which must be used immediately.

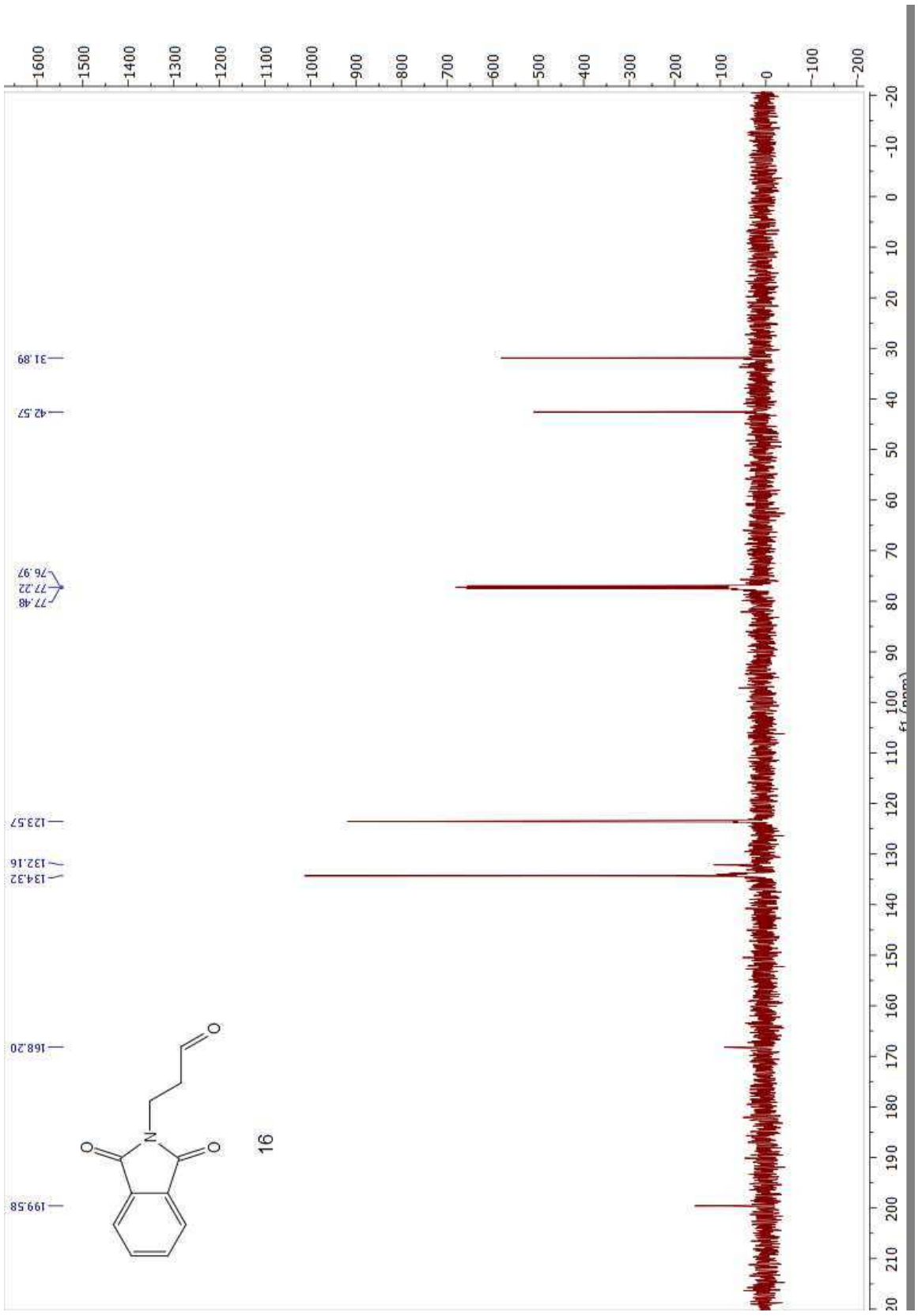
The TMS protected hemiketal **37** (15.6 mg, 0.0387 mmol, 1 equiv) was then dissolved in THF (1 mL) at room temperature. The stirred solution was cooled to -78ºC, equipped with a dry ice condenser, and charged with anhydrous liquid ammonia (3 mL). The cooled solution was then treated piece wise with sodium metal (8.7 mg, 0.3947 mmol, 10.2 equiv) to provide a dark blue reaction mixture. The reaction mixture turned clear after 35 minutes and was then quenched by cautious addition of saturated NH_4Cl (1 mL), the ammonia evaporated by removal of the condenser and extracted using Et_2O (4x 3 mL). The combined extracts were dried over anhydrous magnesium sulfate, concentrated in vacuo, and purified by extraction (3x MeOH/Hexanes, product in MeOH) to provide desired product as a colorless oil (4.71 mg, 55%).

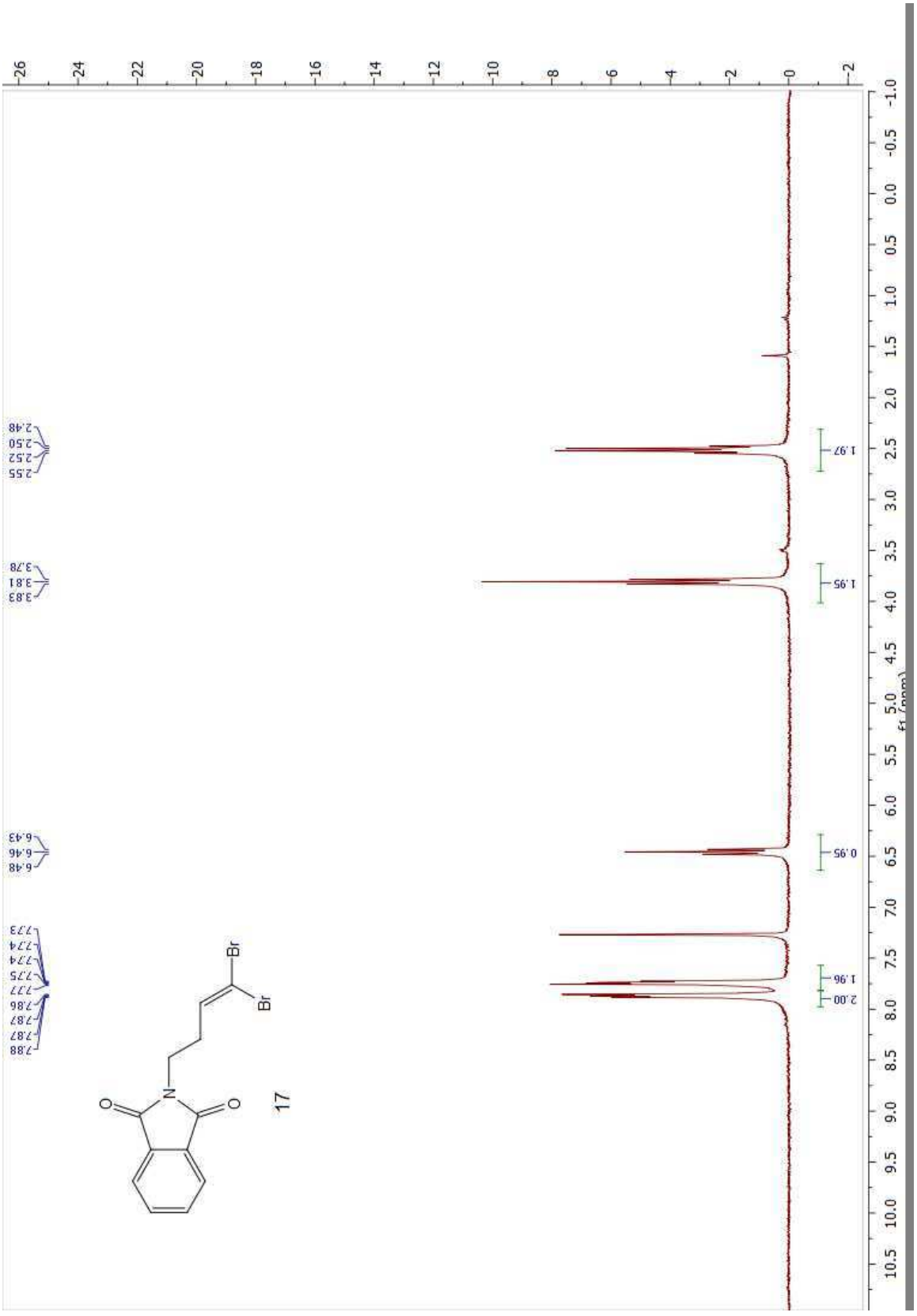
[α]$^{20.6C}$ = 2.290 (c 0.131, $CHCl_3$); **^{1}H NMR** (300 MHz, C_6D_6) δ 5.83 (dt, *J* = 15.5, 6.4 Hz, 1H), 5.56 – 5.42 (m, 1H), 4.26 (s, 1H), 3.09 (s, 1H), 2.94 (ddd, *J* = 13.1, 9.7, 6.0 Hz, 1H), 2.61 (ddd, *J* = 13.1, 8.0, 5.2 Hz, 1H), 2.32 (d, *J* = 5.6 Hz, 1H), 1.95 (dq, *J* = 8.5, 6.6 Hz, 2H), 1.83 – 1.44 (m, 7H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 132.46, 128.99, 105.92, 83.27, 82.91, 61.46, 57.95, 48.78, 38.35, 35.38, 27.31, 26.04, 14.20; **IR** (film): 3338.18, 3026.73, 2962.13, 2874.38, 2749.03, 2601.5, 2361.41, 1742.37, 1670.05, 1559.17, 1472.38 1453.1, 1347.03, 1327.75, 1296.89, 1285.32, 1259.29, 1224.58, 1194.69, 1133.94, 1095.37, 1057.76, 1023.05, 977.733, 943.985, 901.558, 875.524, 807.063, 722.351, 734.746, 700.034, 658.571, 586.254, 566.969, 540.935; **HRMS** calcd for $C_{13}H_{20}NO_2$ (M+) 222.1489, found 222.1483.

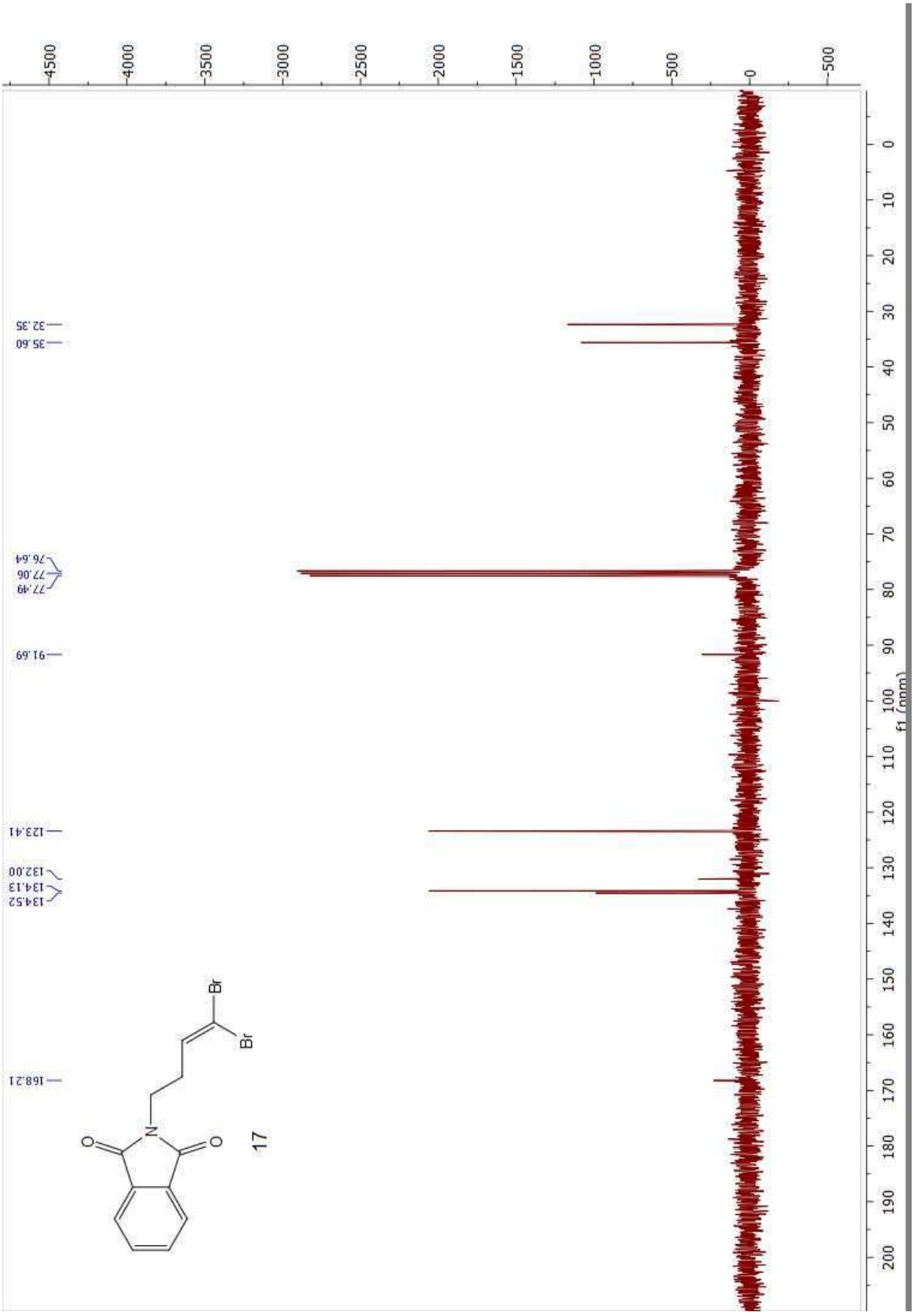
APPENDIX B:

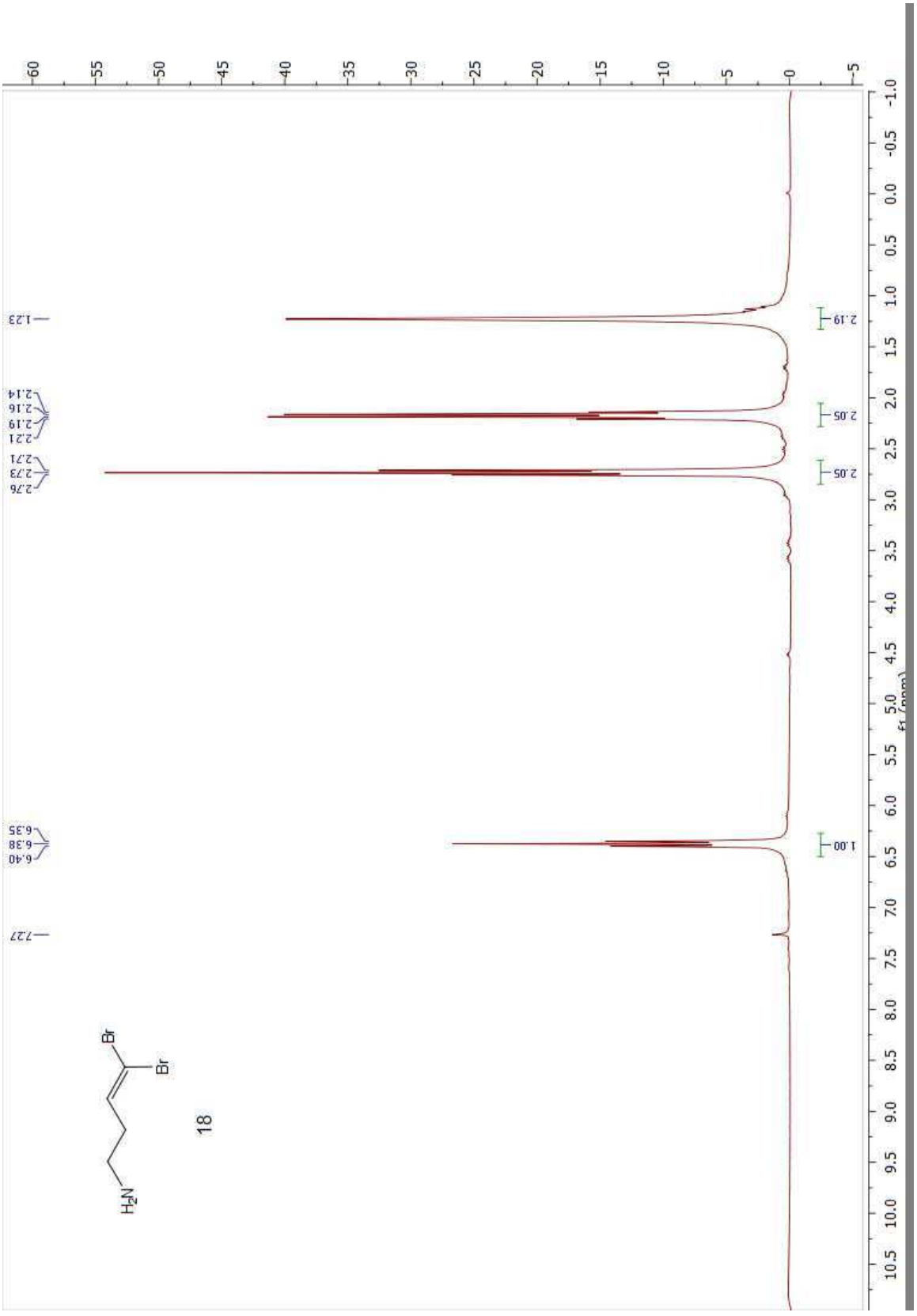
REPRESENTATIVE SPECTRA

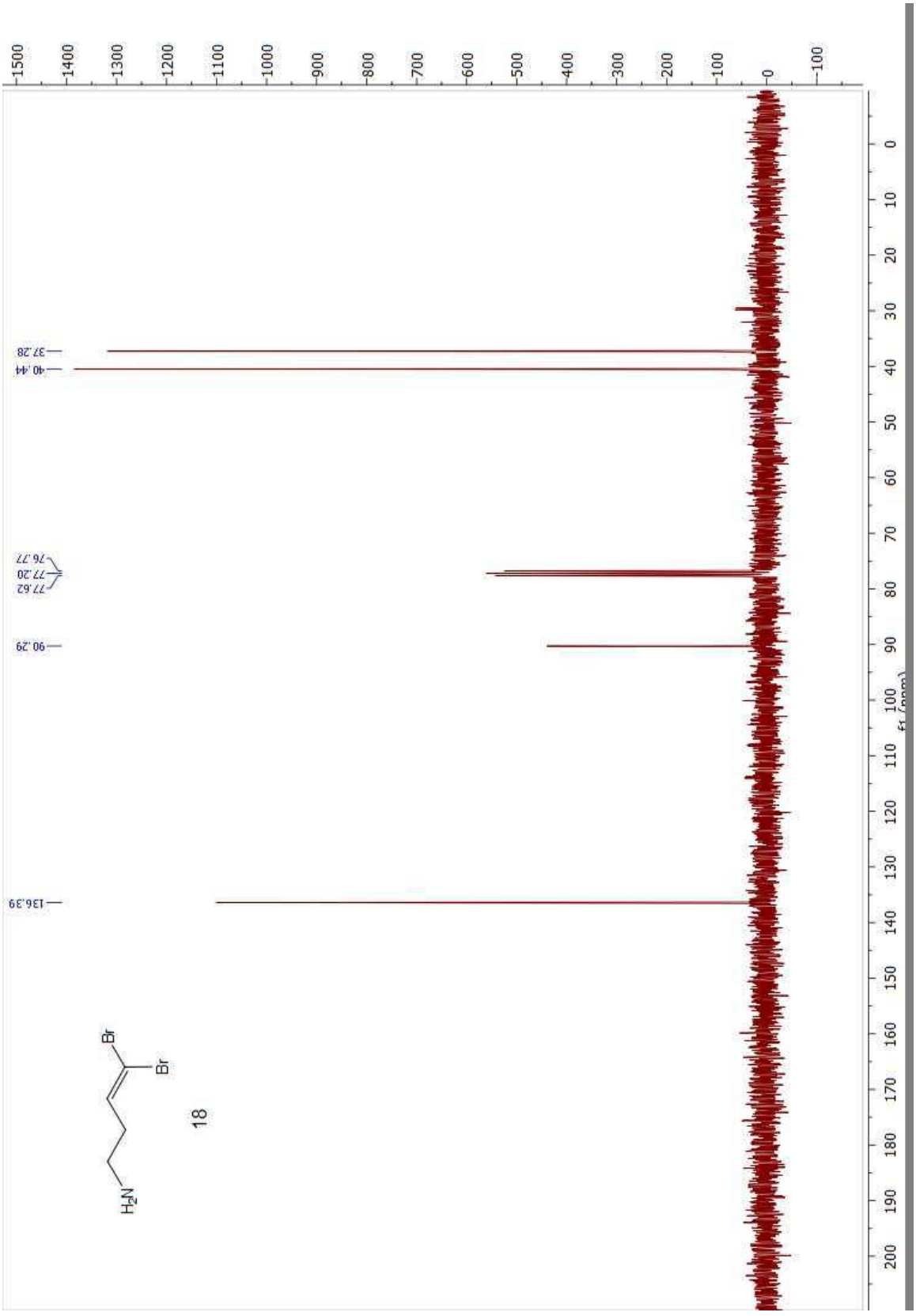

H2O
CH2Cl2
16
f1 (ppm)

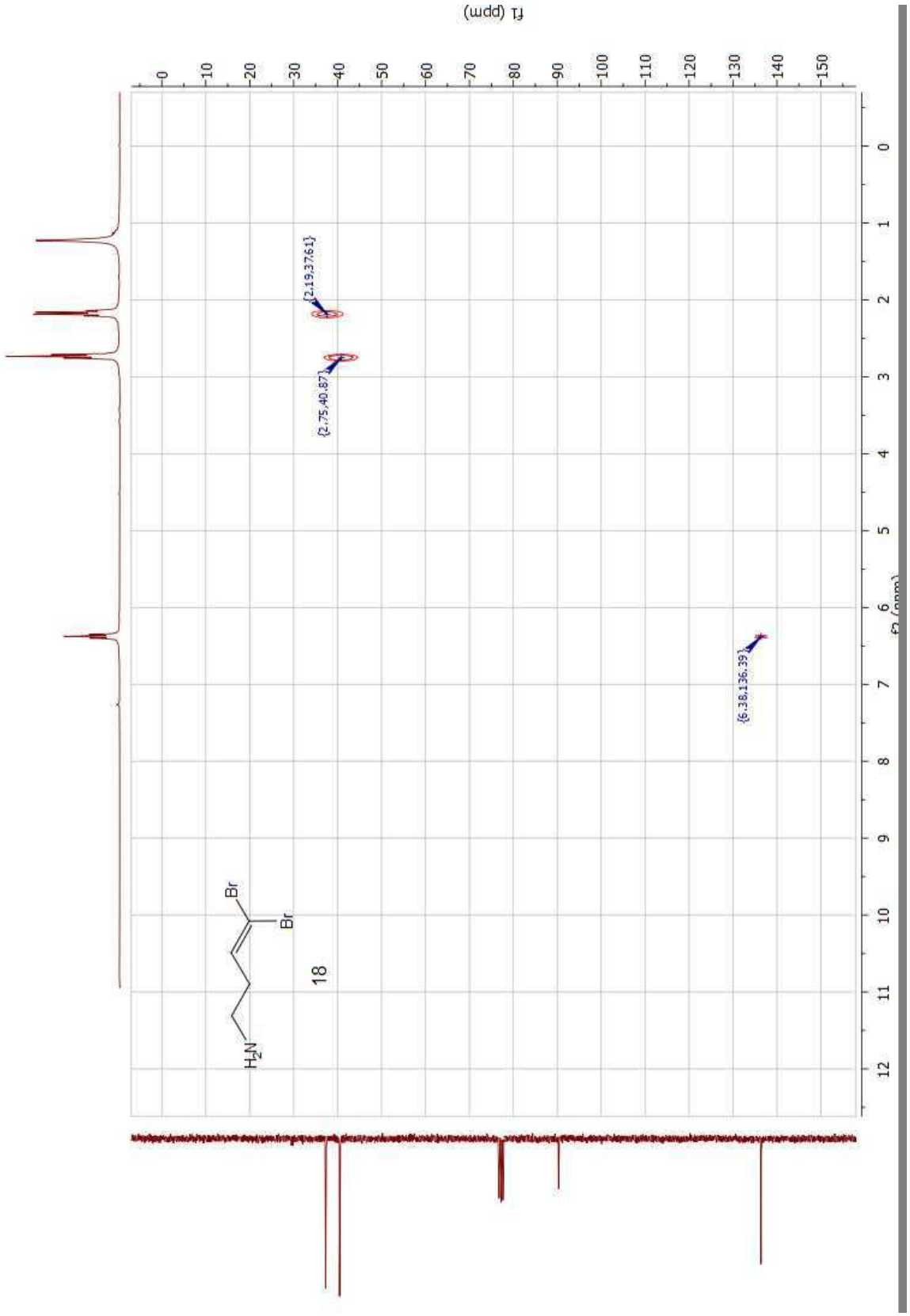

199.58
168.20
134.32
132.16
123.57
77.48
77.22
76.97
42.57
31.89
16


Br
Br
N
O
O
17
7.88
7.87
7.87
7.86
7.77
7.75
7.74
7.74
7.73
6.48
6.46
6.43
3.83
3.81
3.78
2.55
2.52
2.50
2.48
1.97
1.95
0.95
1.96
2.00
f1 (ppm)


168.21
134.52
134.13
132.00
123.41
91.69
77.49
77.06
76.64
35.60
32.35
Br
Br
O
N
O
17
f1 (ppm)


Br
Br
H2N
18
7.27
6.40
6.38
6.35
2.76
2.73
2.71
2.21
2.19
2.16
2.14
1.23
1.00
2.05
2.05
2.19
f1 (ppm)


136.39
90.29
77.62
77.30
76.77
40.44
37.28
Br
Br
H2N
18
f1 (ppm)


f1 (ppm)
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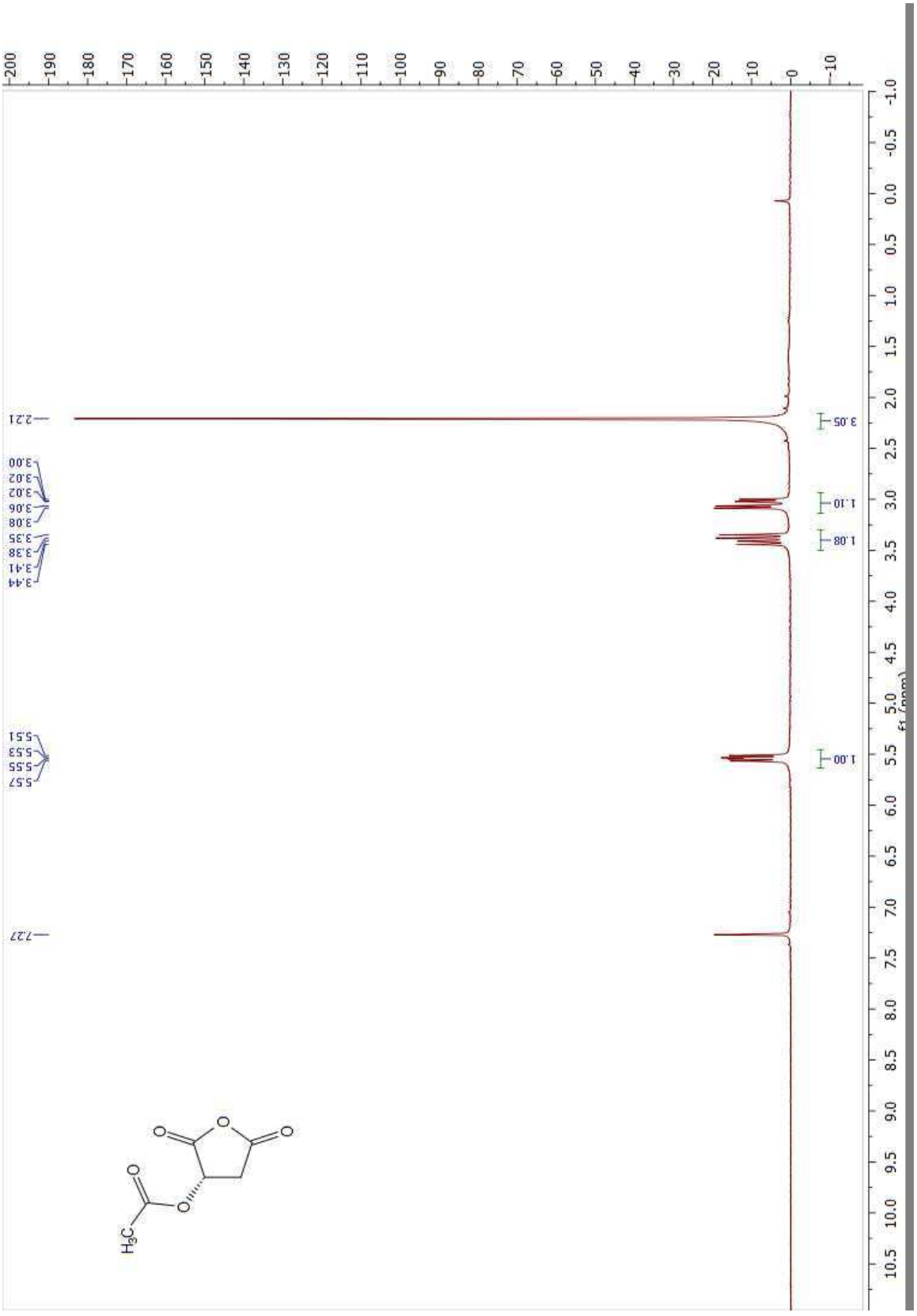
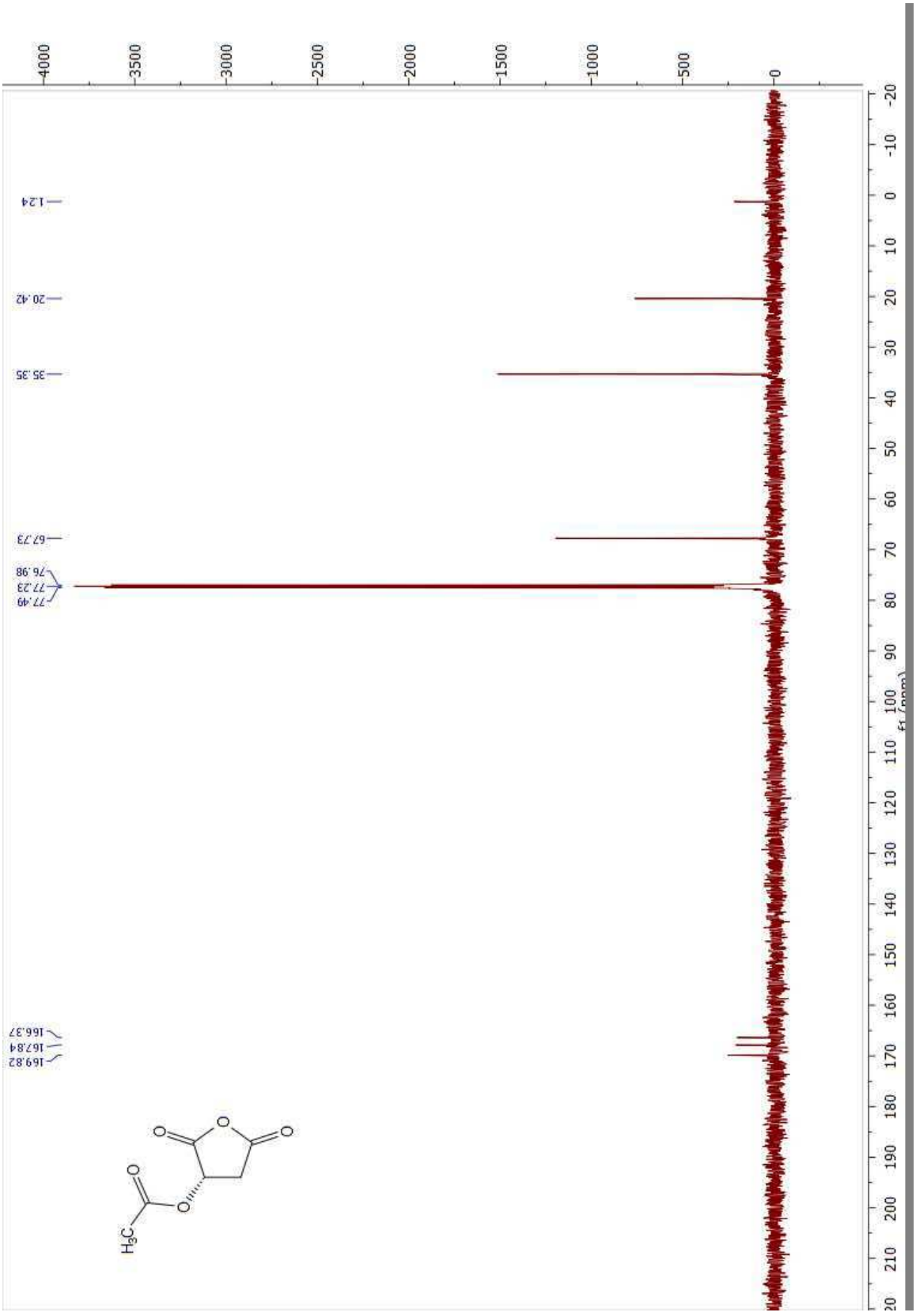
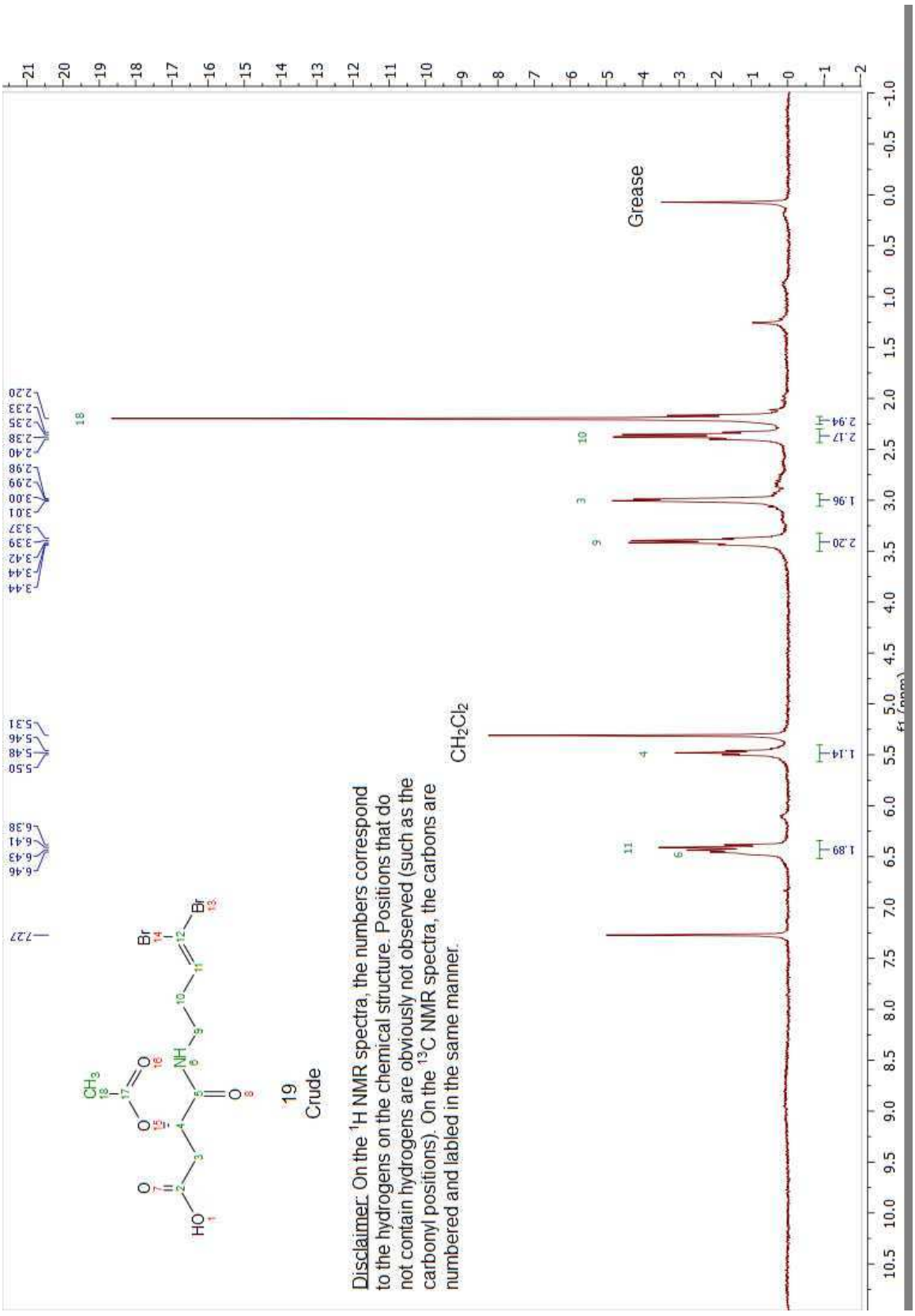
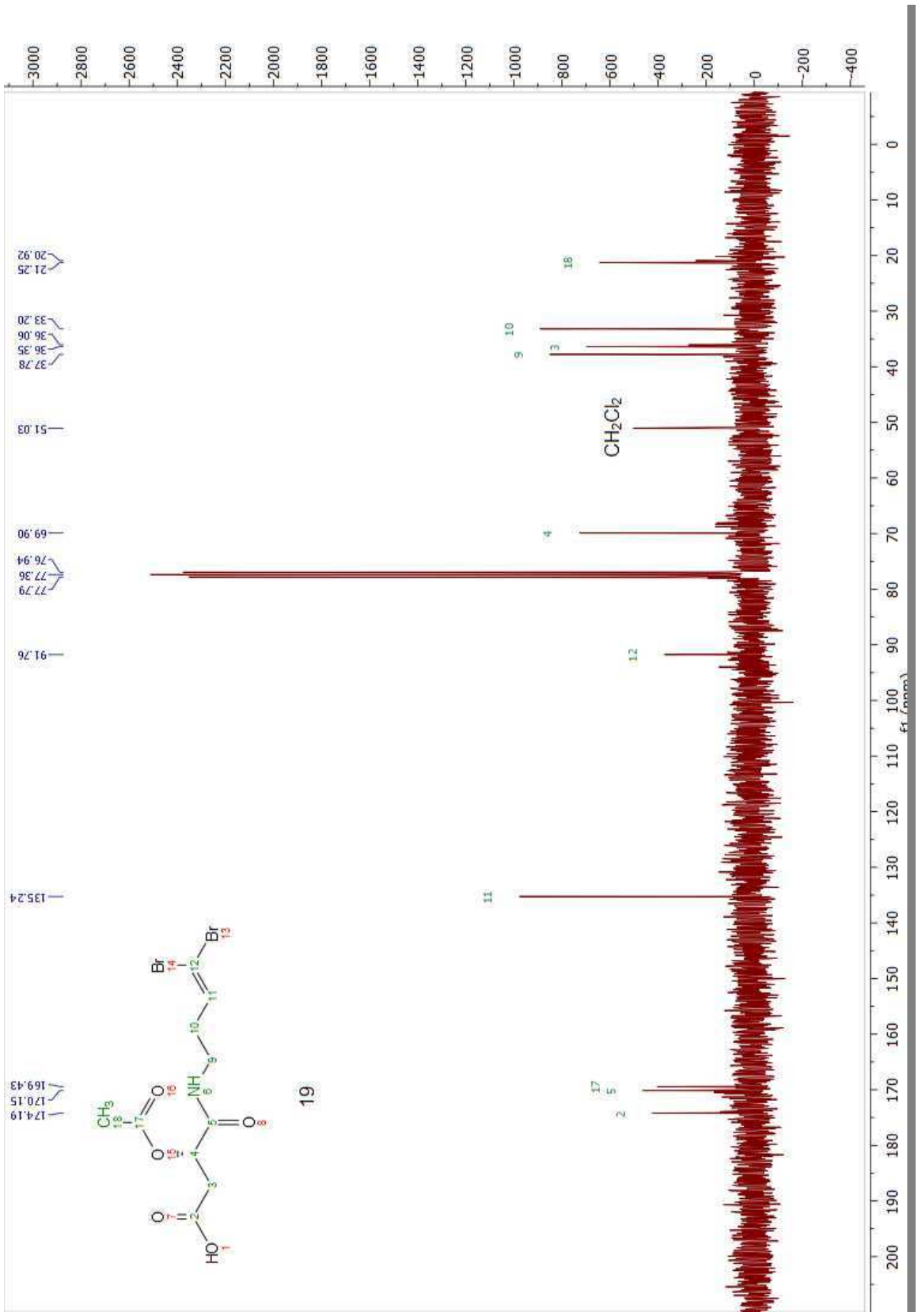
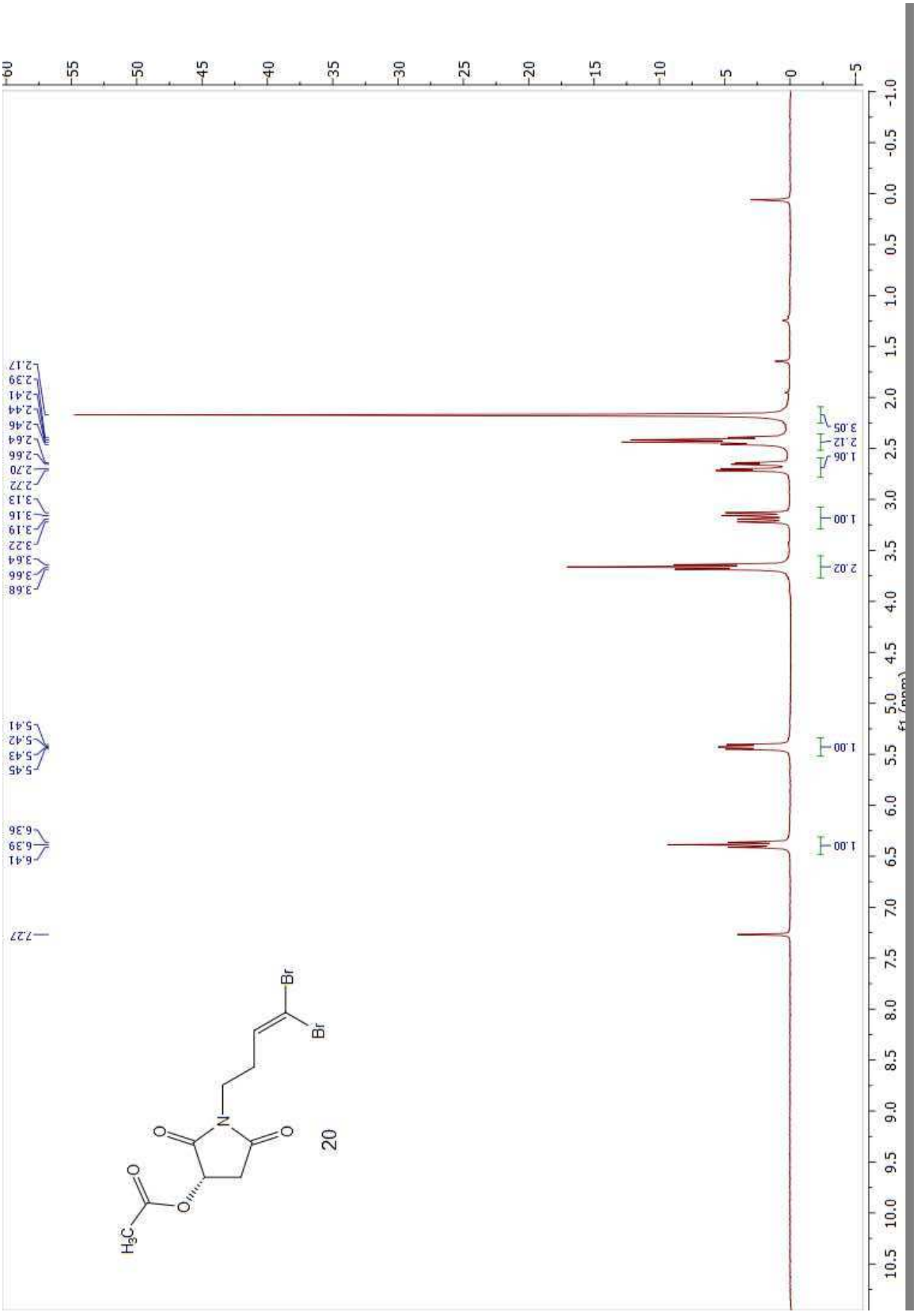
{2.75,40.87}
{6.38,136.39}
Br
Br
H_2N
18

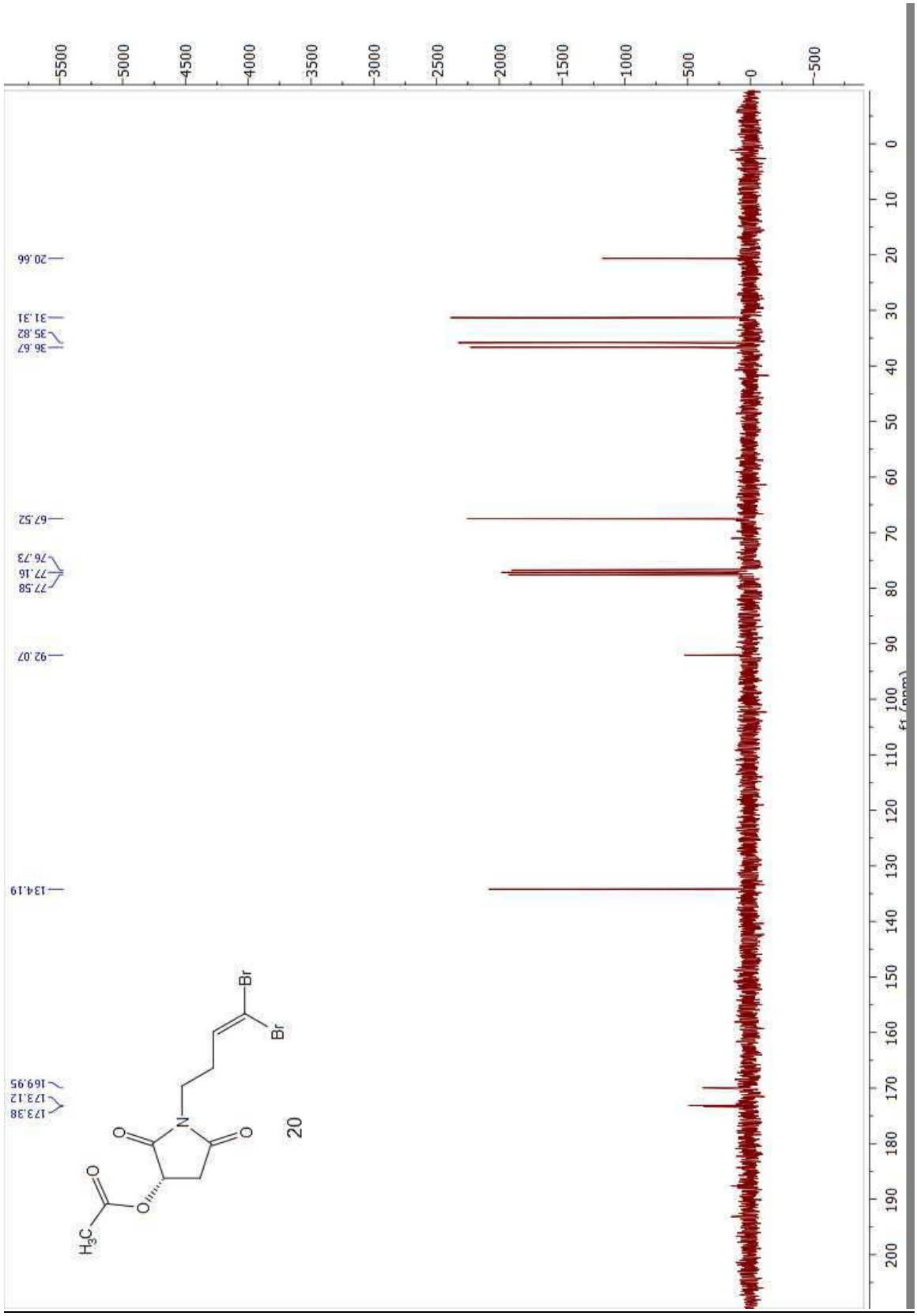

2.21
3.00
3.02
3.02
3.06
3.08
3.35
3.38
3.41
3.44
5.51
5.53
5.55
5.57
7.27
3.05
1.10
1.08
1.00
f1 (ppm)

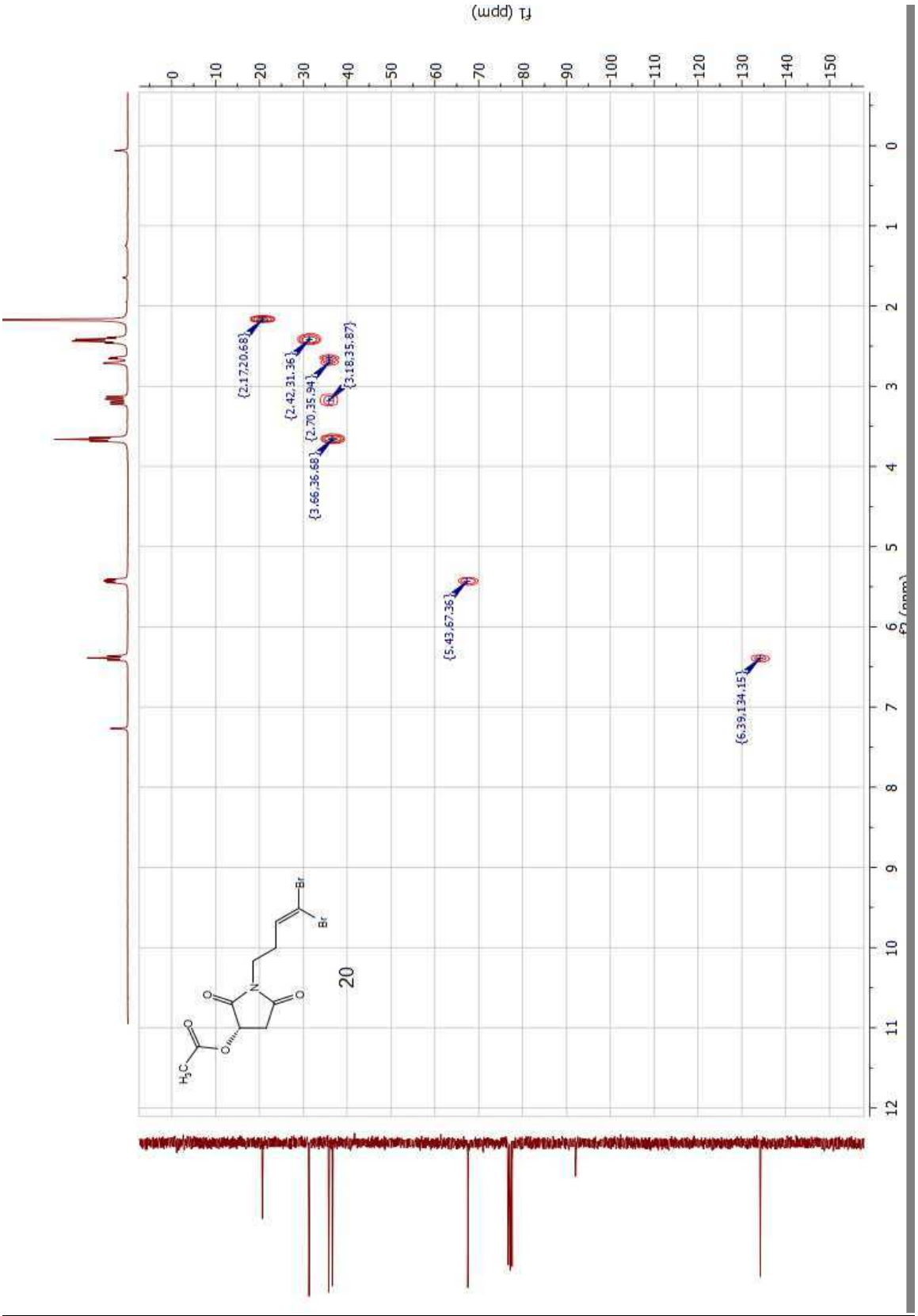

169.82
167.84
166.37
77.49
77.23
76.98
67.73
35.35
20.42
1.24
H3C
f1 (ppm)

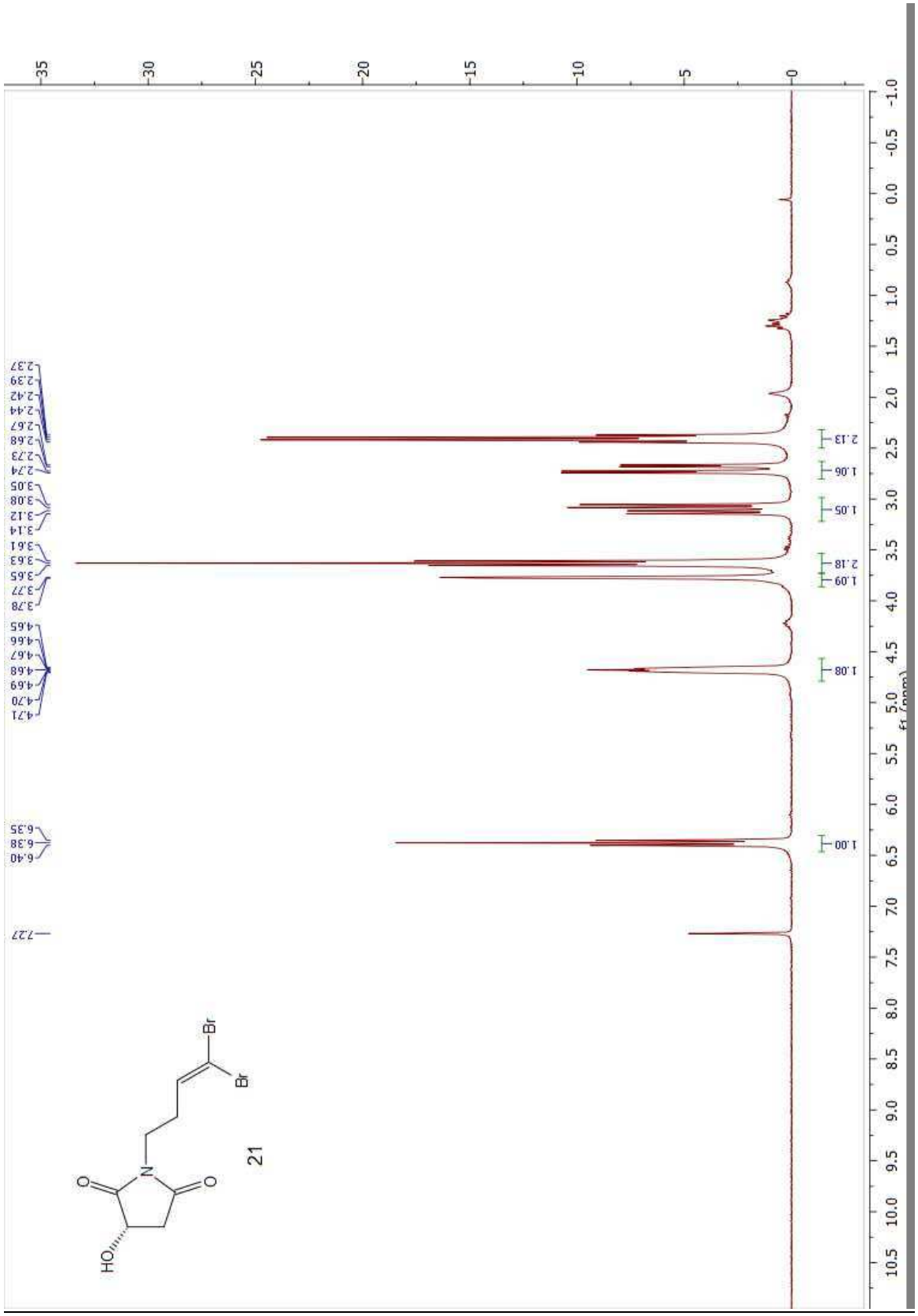

19
Crude
Disclaimer: On the ^{1}H NMR spectra, the numbers correspond to the hydrogens on the chemical structure. Positions that do not contain hydrogens are obviously not observed (such as the carbonyl positions). On the ^{13}C NMR spectra, the carbons are numbered and labled in the same manner.
CH_2Cl_2
Grease
f1 (ppm)

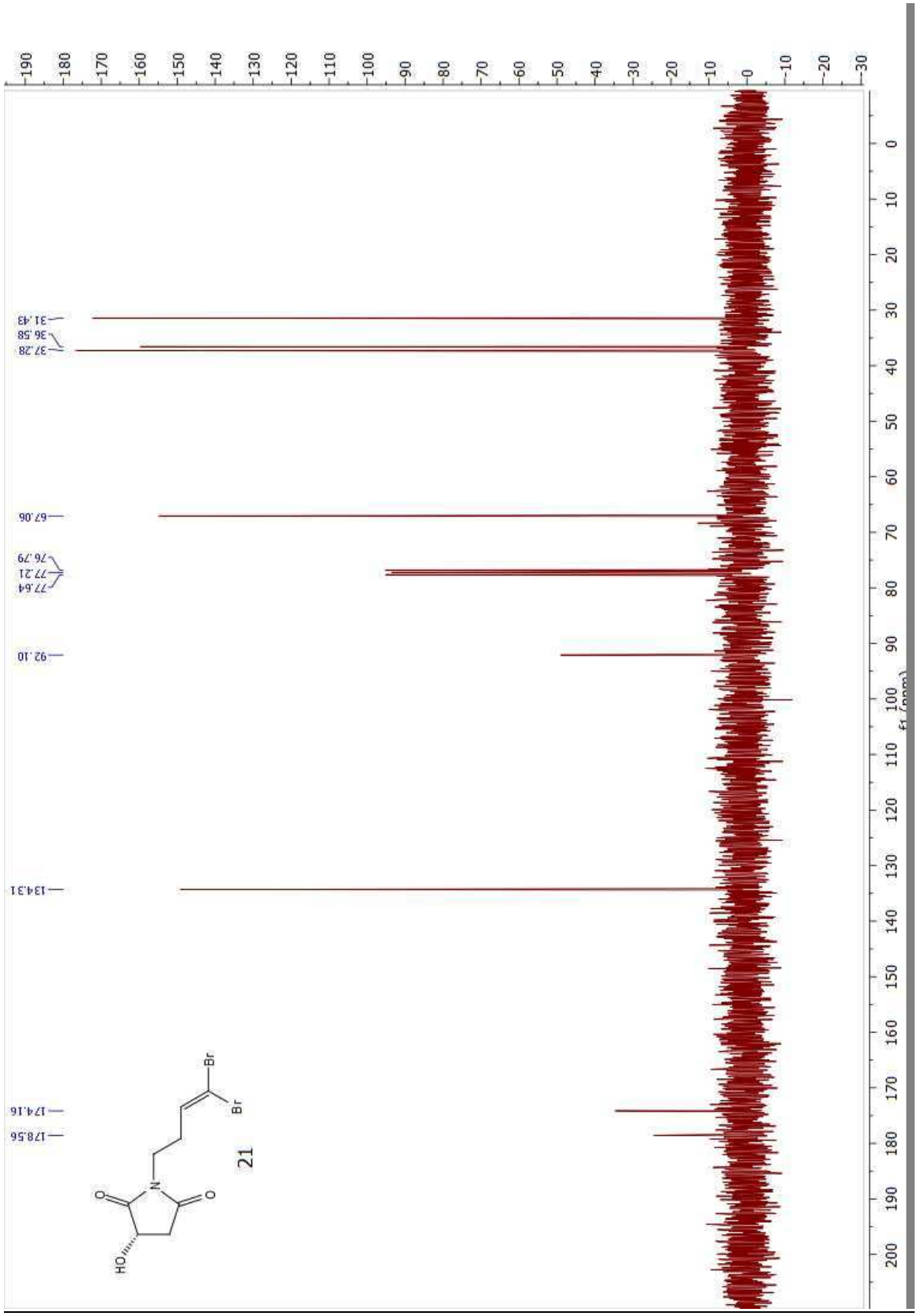

19
CH2Cl2
f1 (ppm)

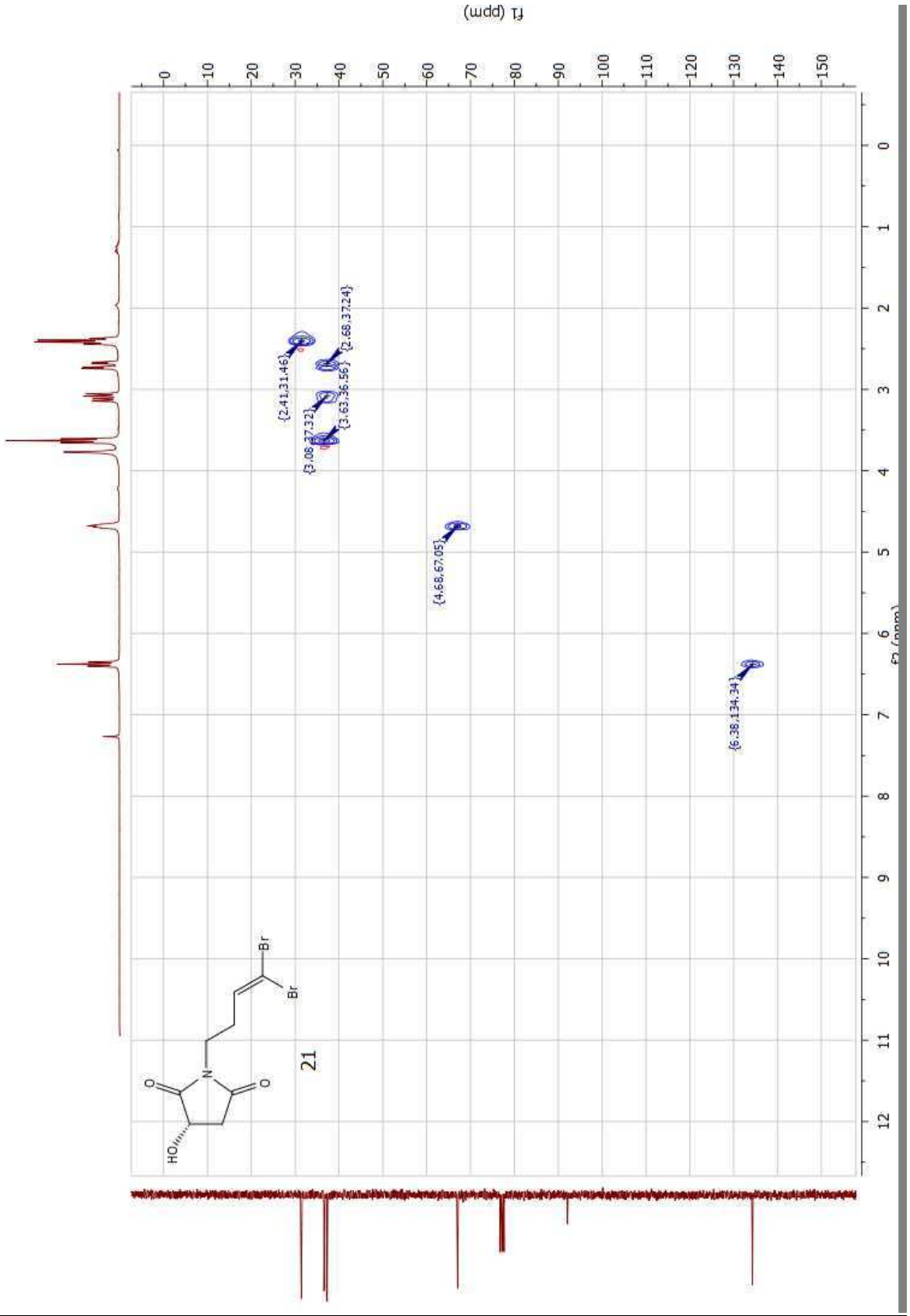

20
Br
Br
O
O
O
O
N
H3C
7.27
6.41
6.39
6.36
5.45
5.43
5.42
5.41
3.68
3.66
3.64
3.22
3.19
3.16
3.13
2.72
2.70
2.66
2.64
2.46
2.44
2.41
2.39
2.17
3.05
2.12
1.06
1.00
2.02
1.00
1.00
f1 (ppm)

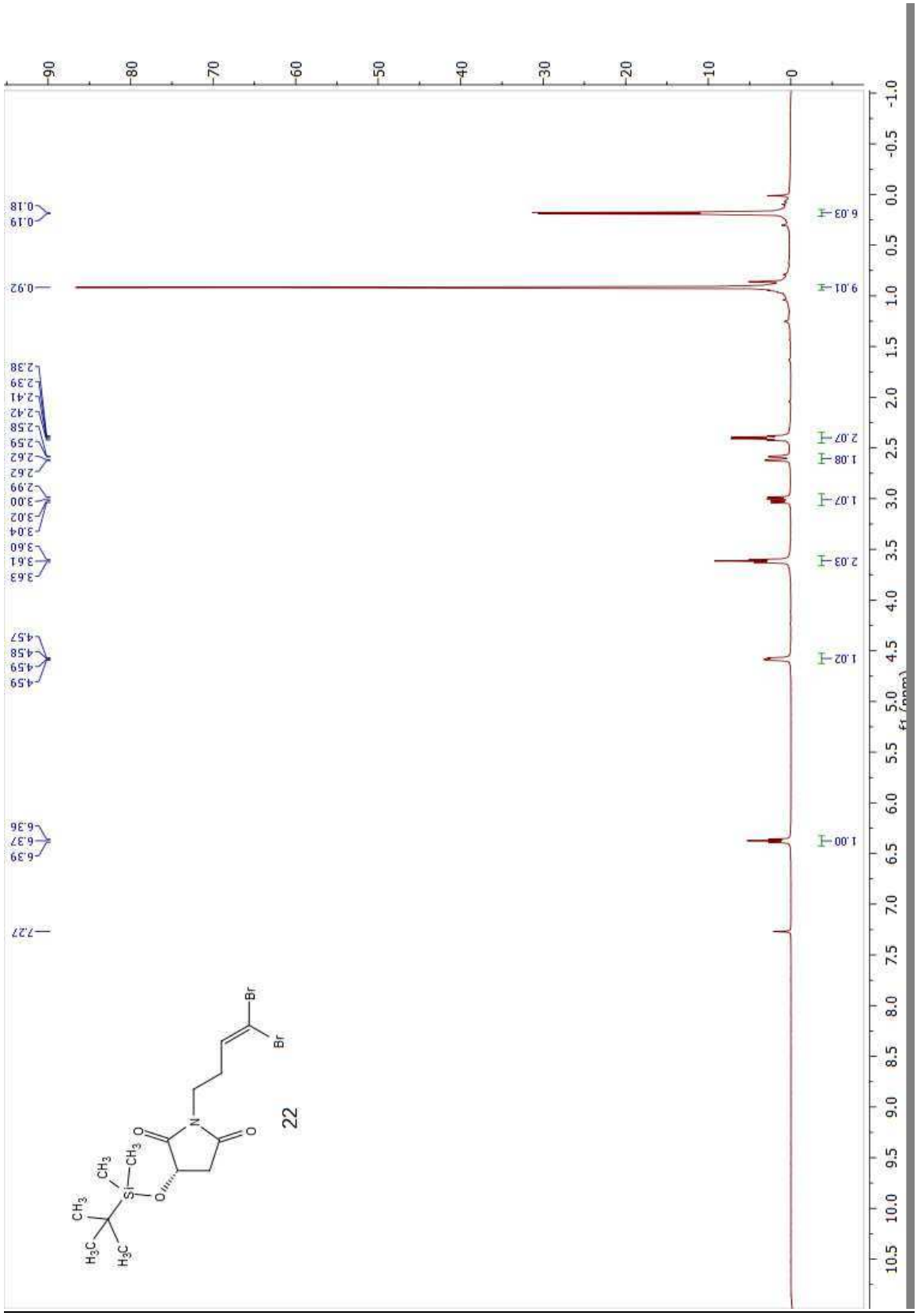

20.66
31.31
35.82
36.67
67.52
76.73
77.16
77.58
92.07
134.19
169.95
173.12
173.38
Br
Br
O
O
O
O
N
O
H3C
20
f1 (ppm)

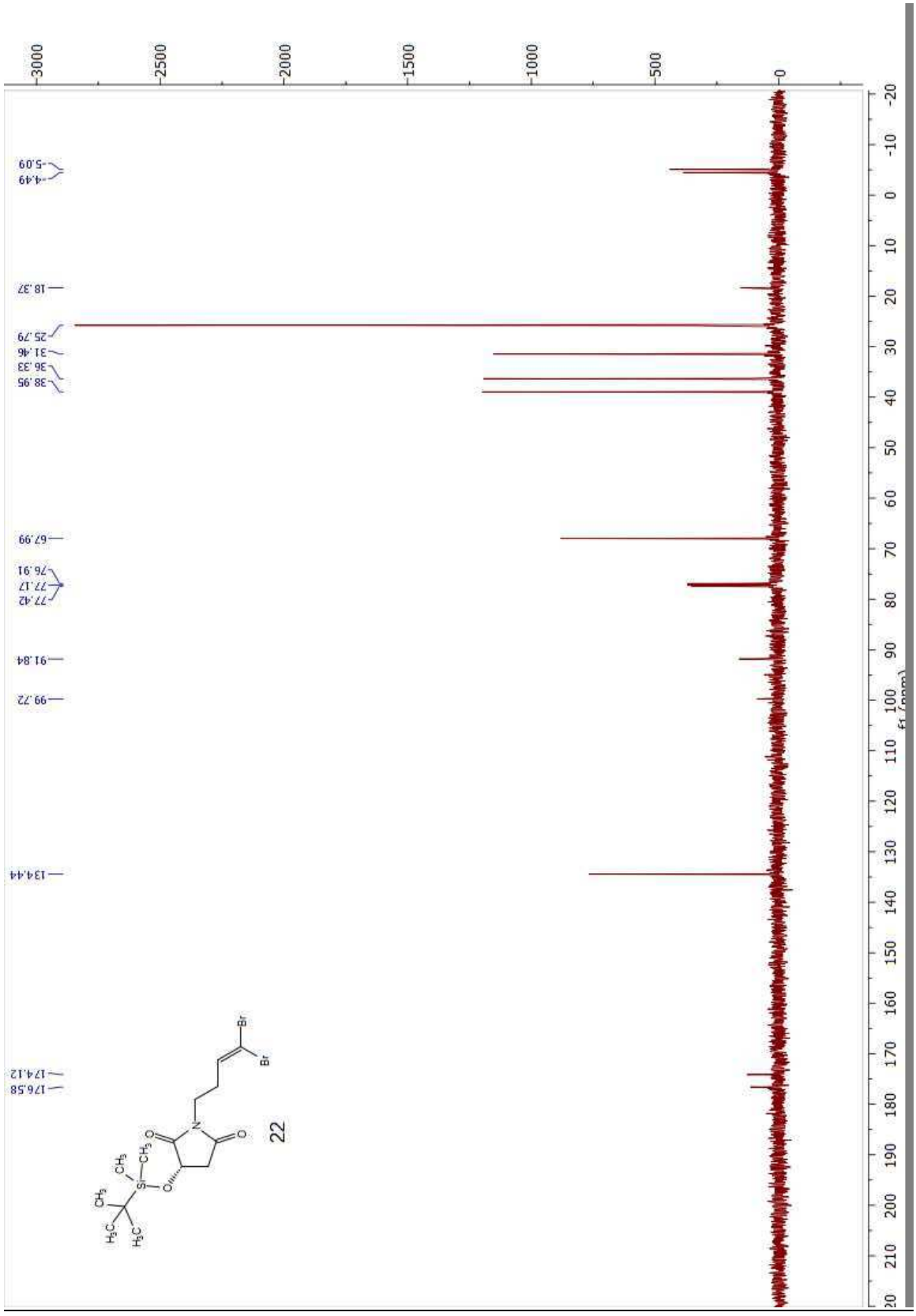

f1 (ppm)
{2.17,20.68}
{2.42,31.36}
{2.70,35.94}
{3.18,35.87}
{3.66,36.68}
{5.43,67.36}
{6.39,134.15}
20
Br
Br
O
N
O
O
O
O
H3C

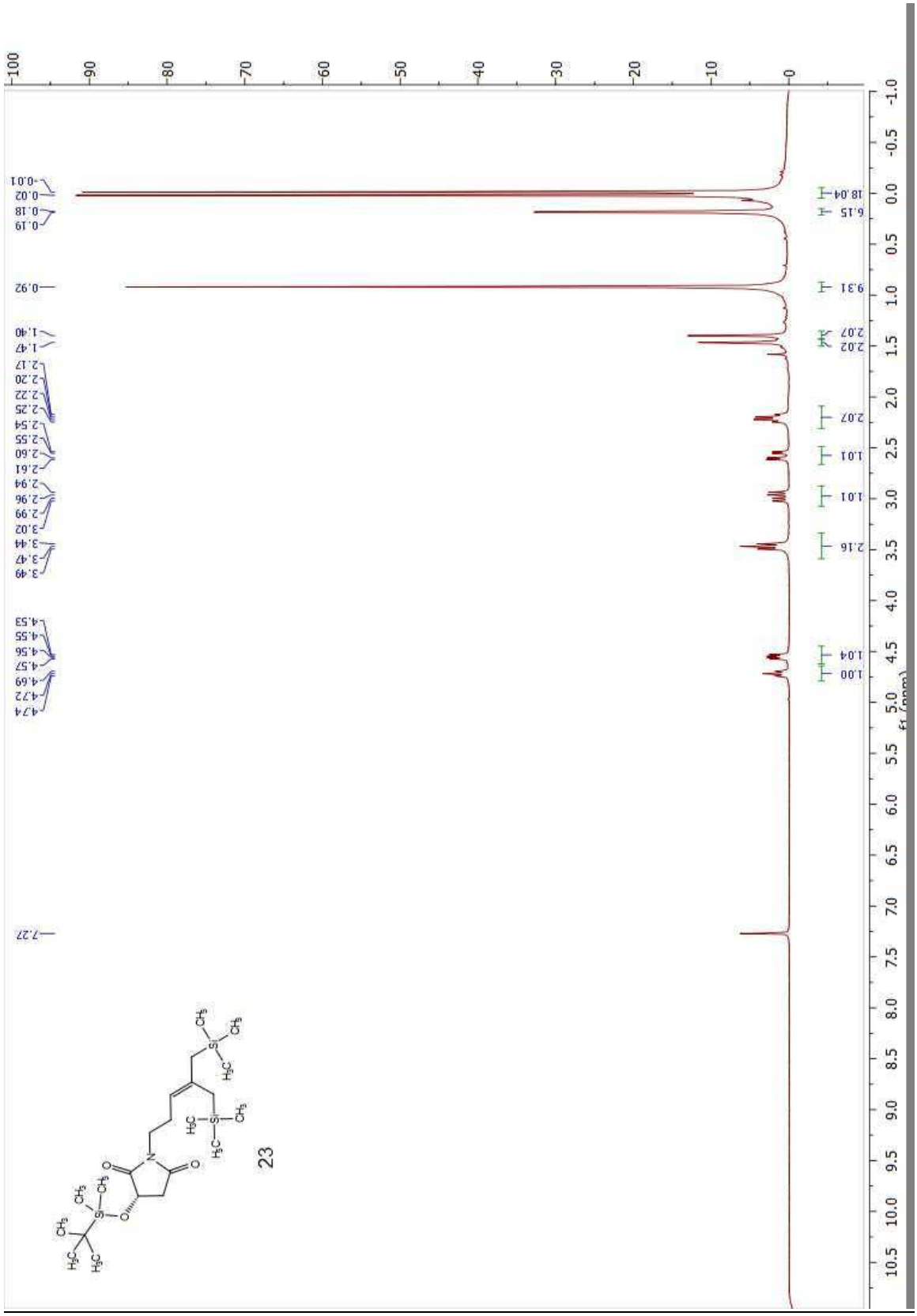

Br
Br
N
O
O
HO
21

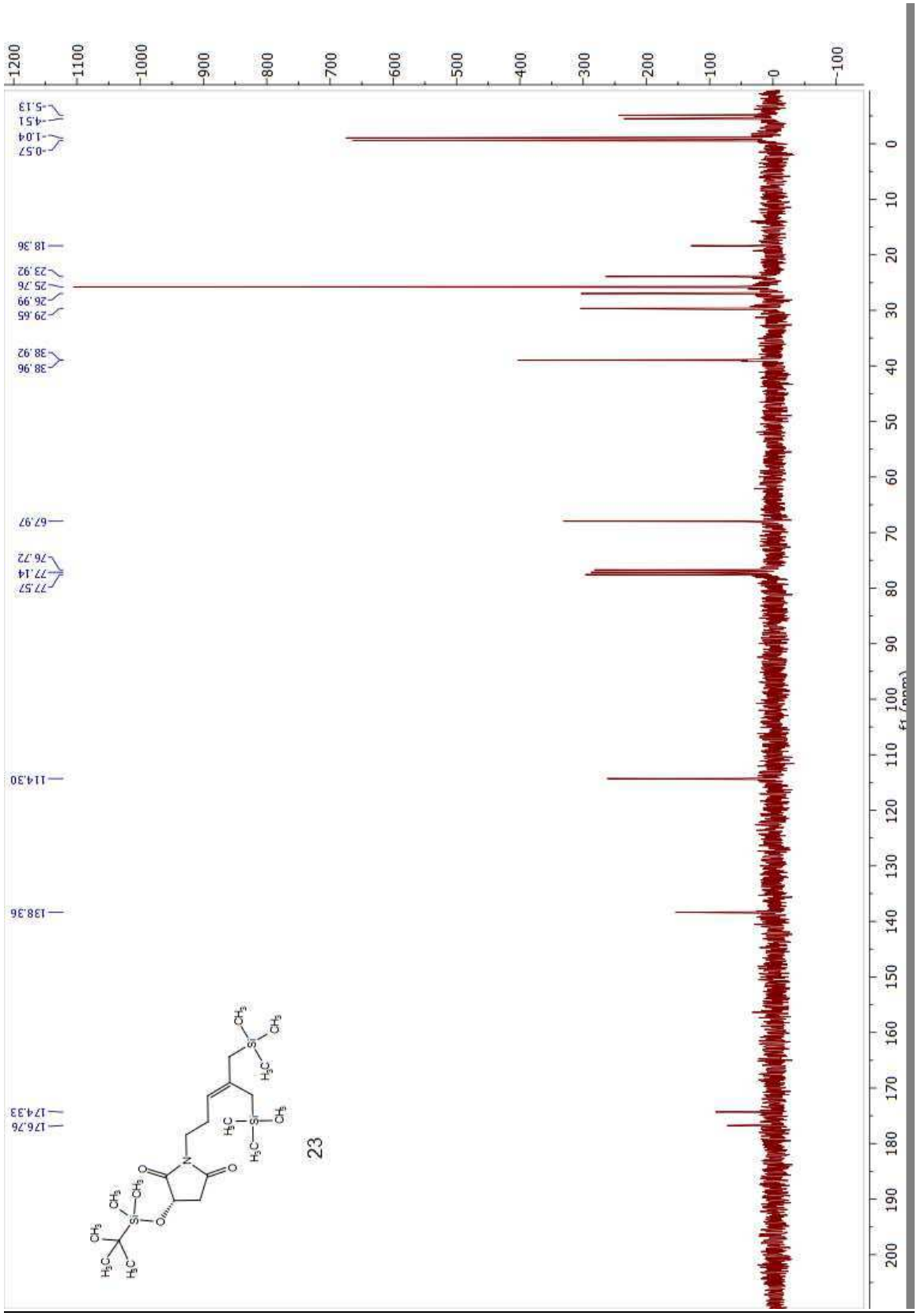

31.43
36.58
37.28
67.06
76.79
77.21
77.64
92.10
134.31
174.16
178.56
Br
Br
O
O
N
O
HO
21
f1 (ppm)

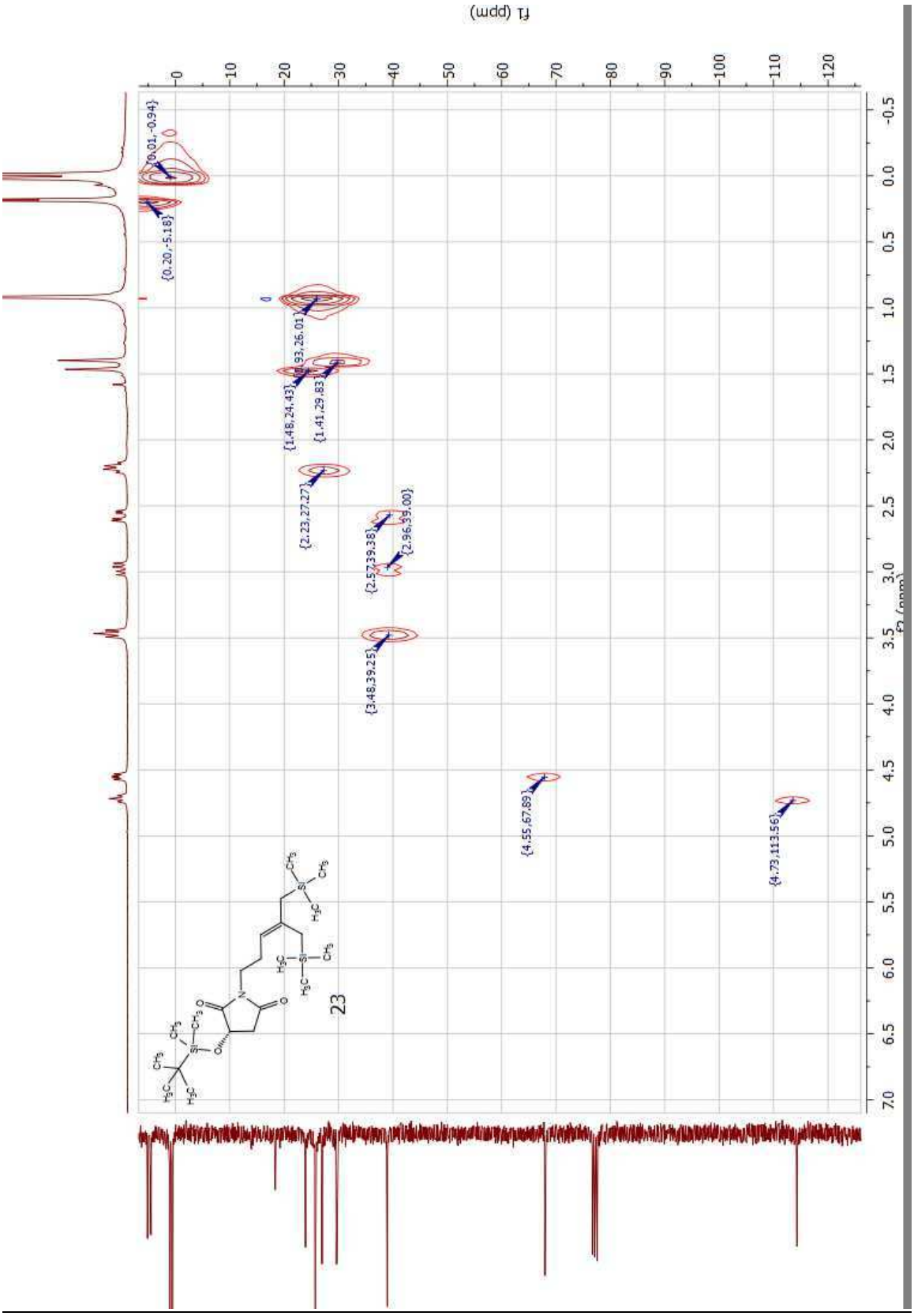

f1 (ppm)
{2.41.31.46}
{2.68.37.24}
{3.08.37.32}
{3.63.36.56}
{4.68.67.05}
{6.36.134.34}
f2 (ppm)
21
HO
O
N
O
Br
Br


22
Br
Br
O
O
N
O
Si
CH3
CH3
H3C
CH3
H3C
0.18
0.19
0.92
2.38
2.39
2.41
2.42
2.58
2.59
2.62
2.62
2.99
3.00
3.02
3.04
3.60
3.61
3.63
4.57
4.58
4.59
4.59
6.36
6.37
6.39
7.27
6.03
9.01
2.07
1.08
1.07
2.03
1.02
1.00
f1 (ppm)


-4.49
-5.09
18.37
25.79
31.46
36.33
38.95
67.99
76.91
77.17
77.42
91.84
99.72
134.44
174.12
176.58
22


23


-5.13
-4.51
-1.04
-0.57
18.36
23.92
25.76
26.99
29.65
38.92
38.96
67.97
76.72
77.14
77.57
114.30
138.36
174.33
176.76
23


f1 (ppm)
f2 (ppm)
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{0.20,-5.18}
{1.48,24.43}
{1.93,26.01}
{1.41,29.83}
{2.23,27.27}
{2.57,39.38}
{2.96,39.00}
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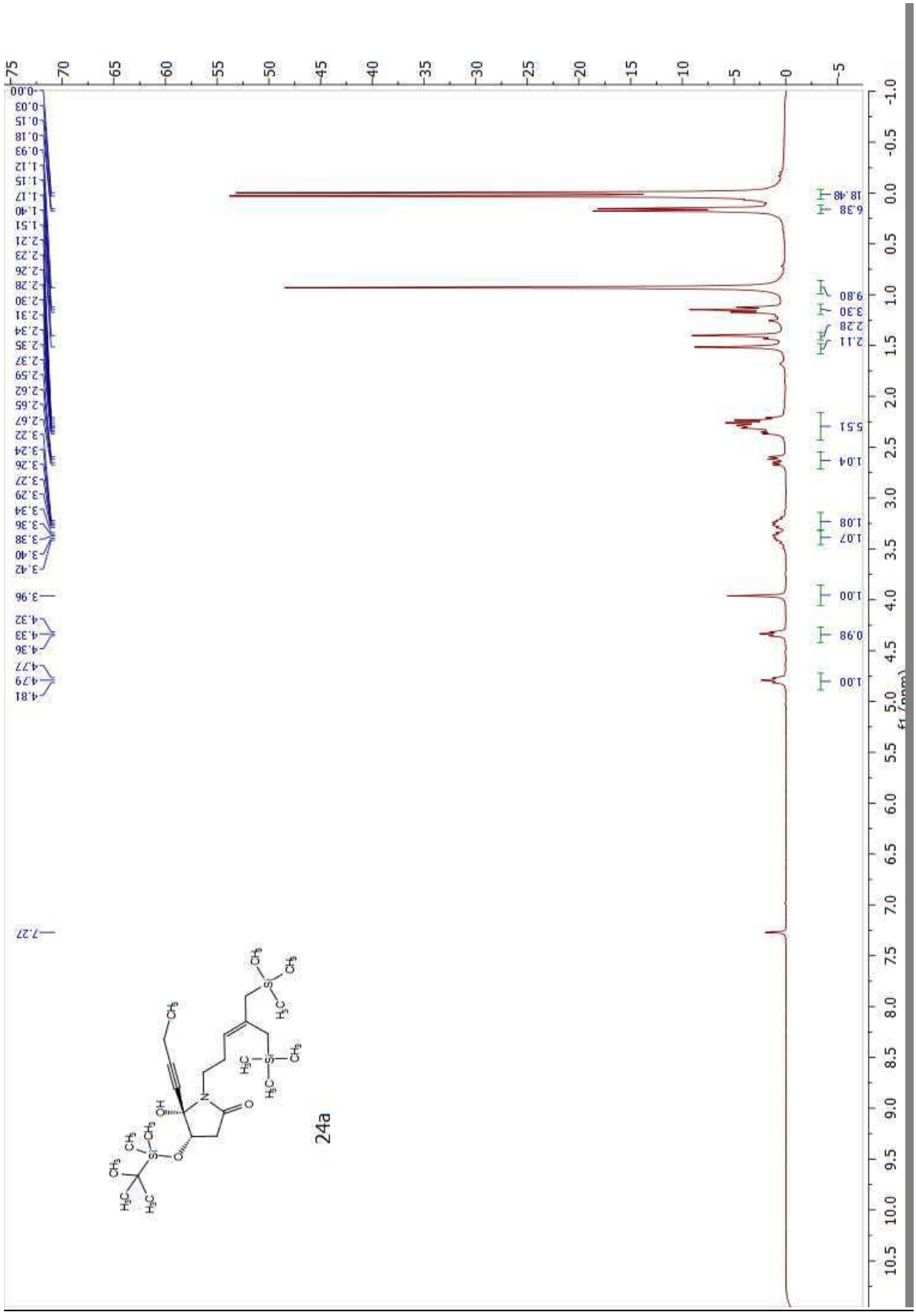
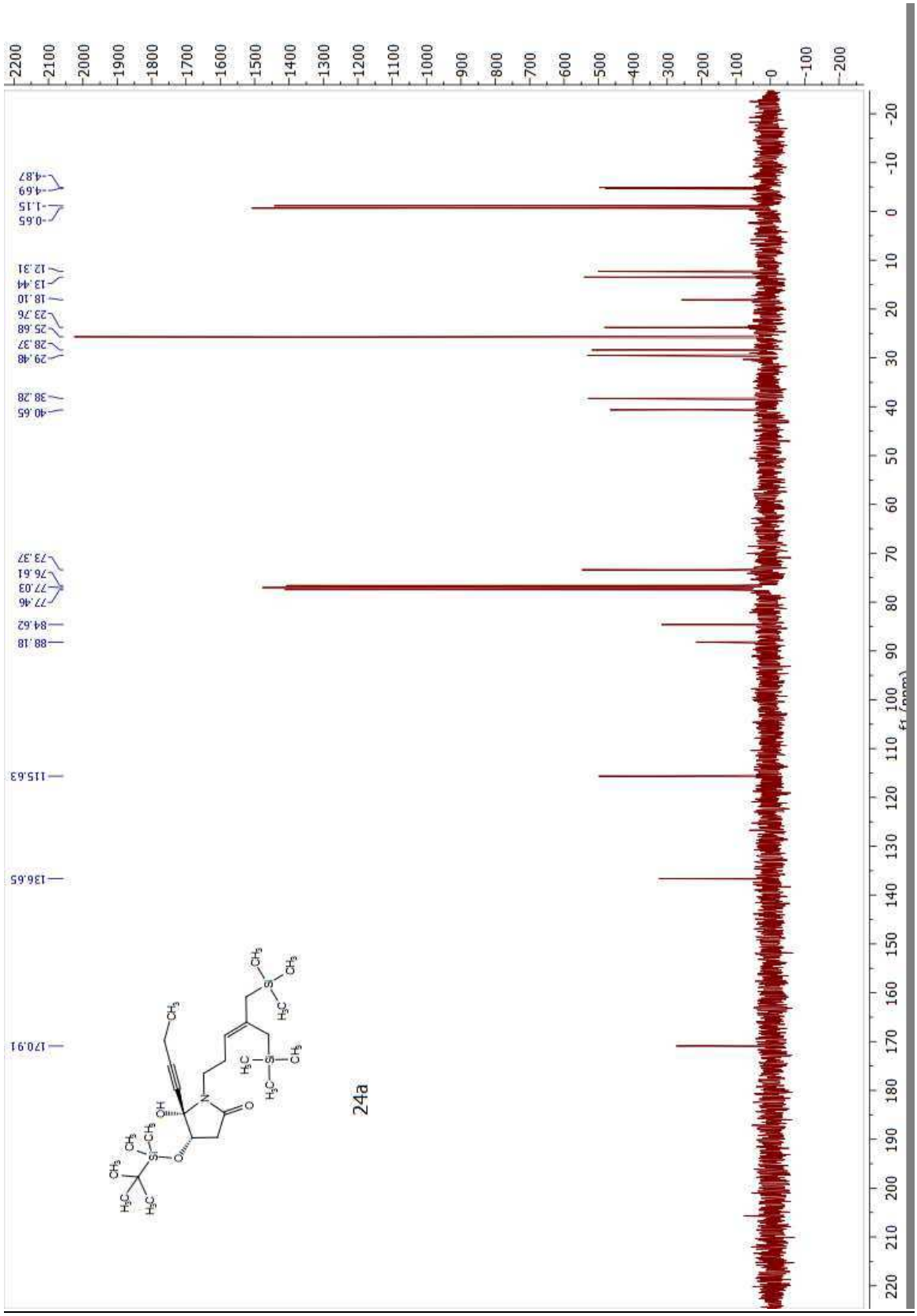
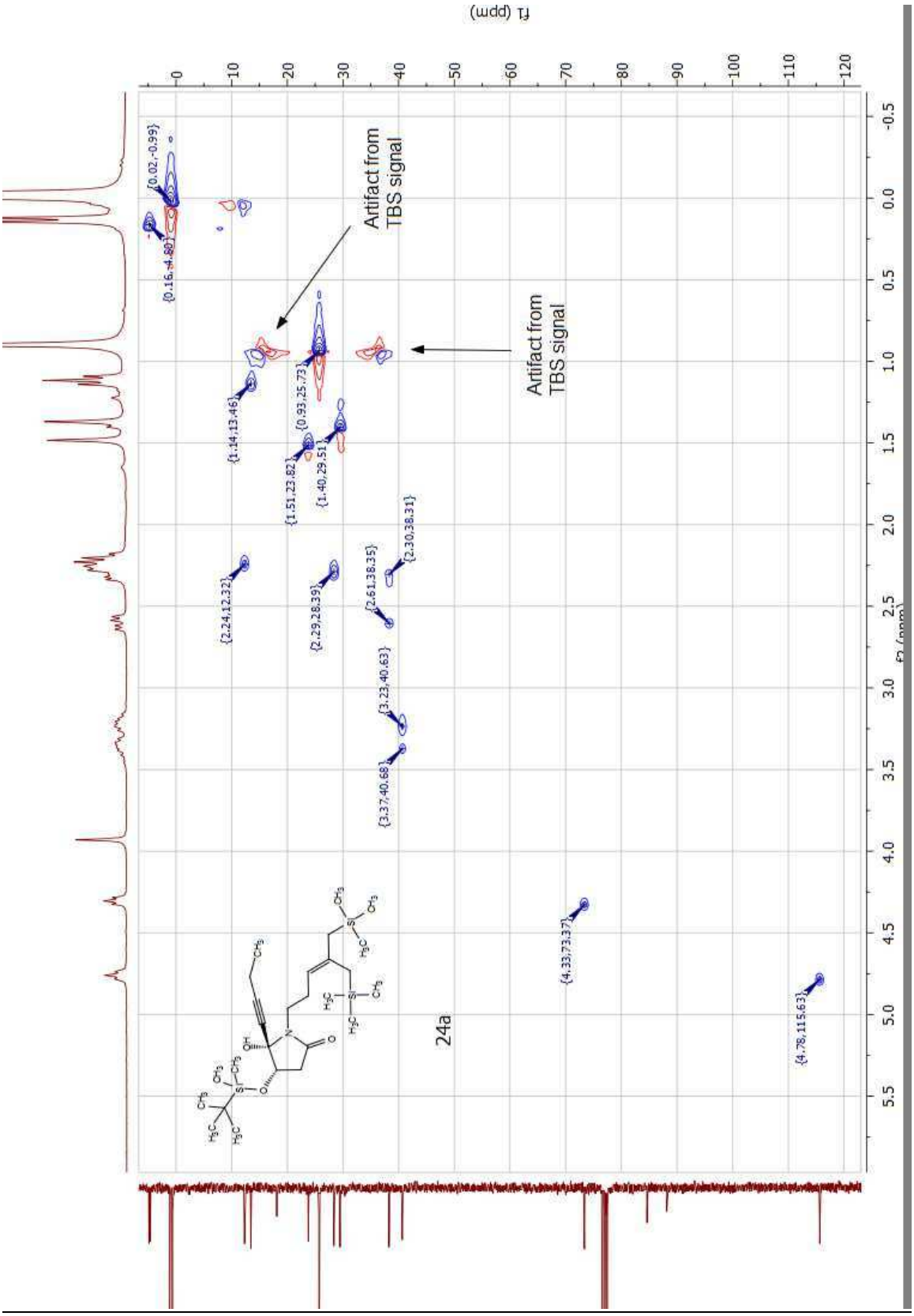
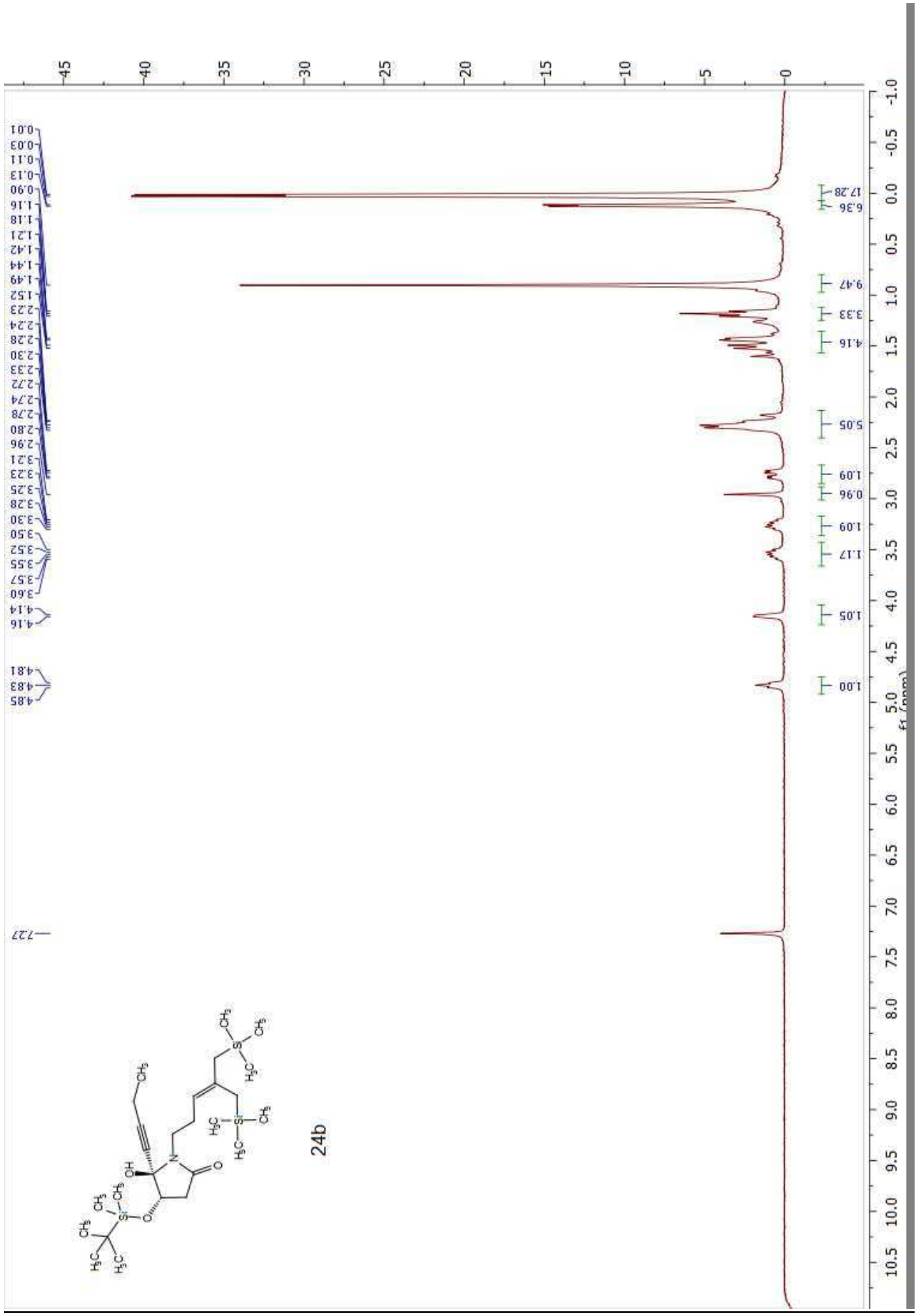
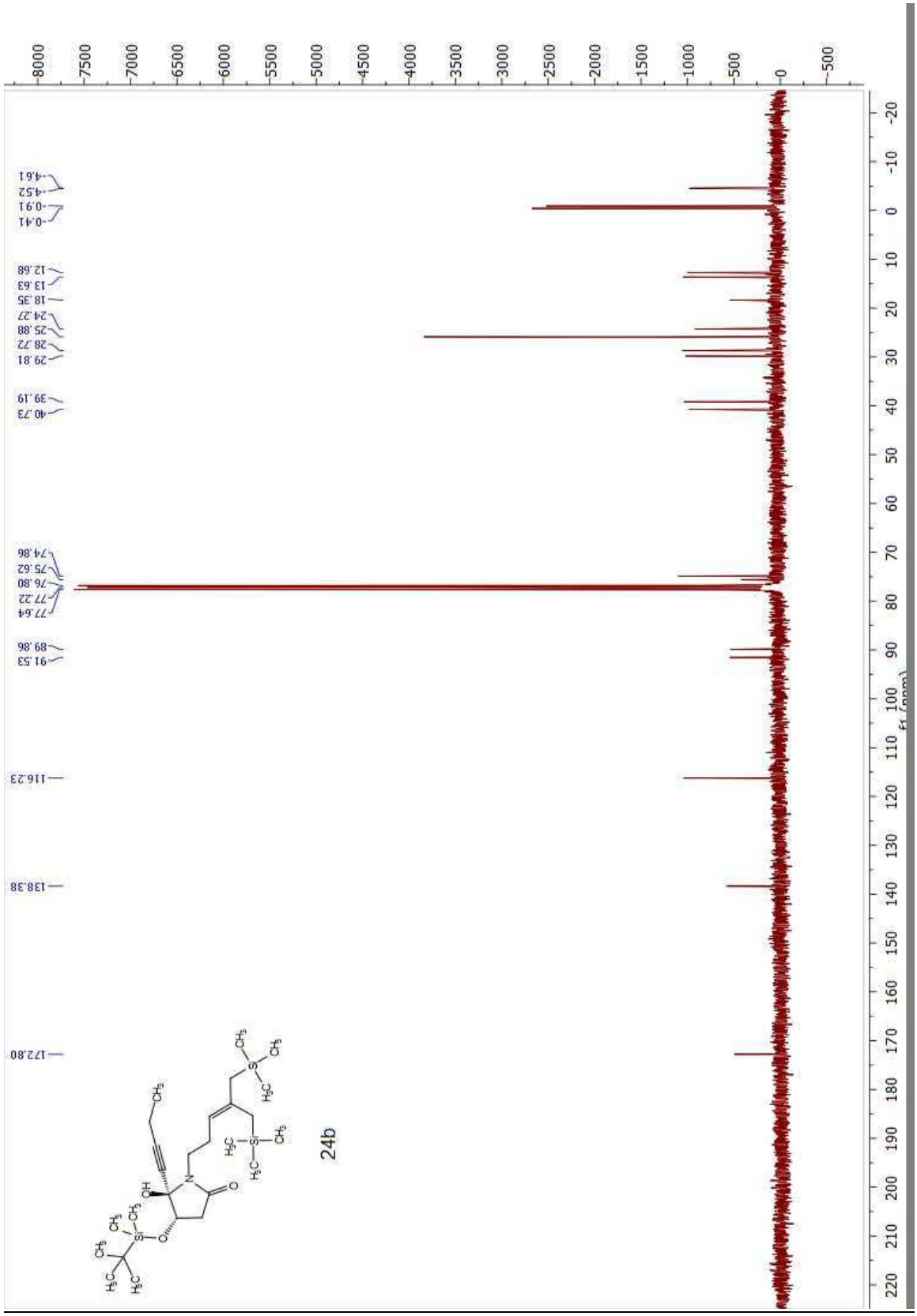
{4.55,67.89}
{4.73,113.56}
23


24a


-0.65
-1.15
-4.69
-4.87
12.31
13.44
18.10
23.76
25.68
28.37
29.48
38.28
40.65
73.37
76.61
77.03
77.46
84.62
88.18
115.63
136.65
170.91
24a
f1 (ppm)


Artifact from TBS signal
Artifact from TBS signal
24a
{0.02,-0.99}
{0.16,4.80}
{1.14,13.46}
{1.51,23.82}
{0.93,25.73}
{1.40,29.51}
{2.24,12.32}
{2.29,28.39}
{2.61,36.35}
{2.30,38.31}
{3.23,40.63}
{3.37,40.68}
{4.33,73.37}
{4.78,115.63}
f1 (ppm)
f2 (ppm)


24b


-0.41
-0.91
-4.52
-4.61
12.68
13.63
18.35
24.27
25.88
28.72
29.81
39.19
40.73
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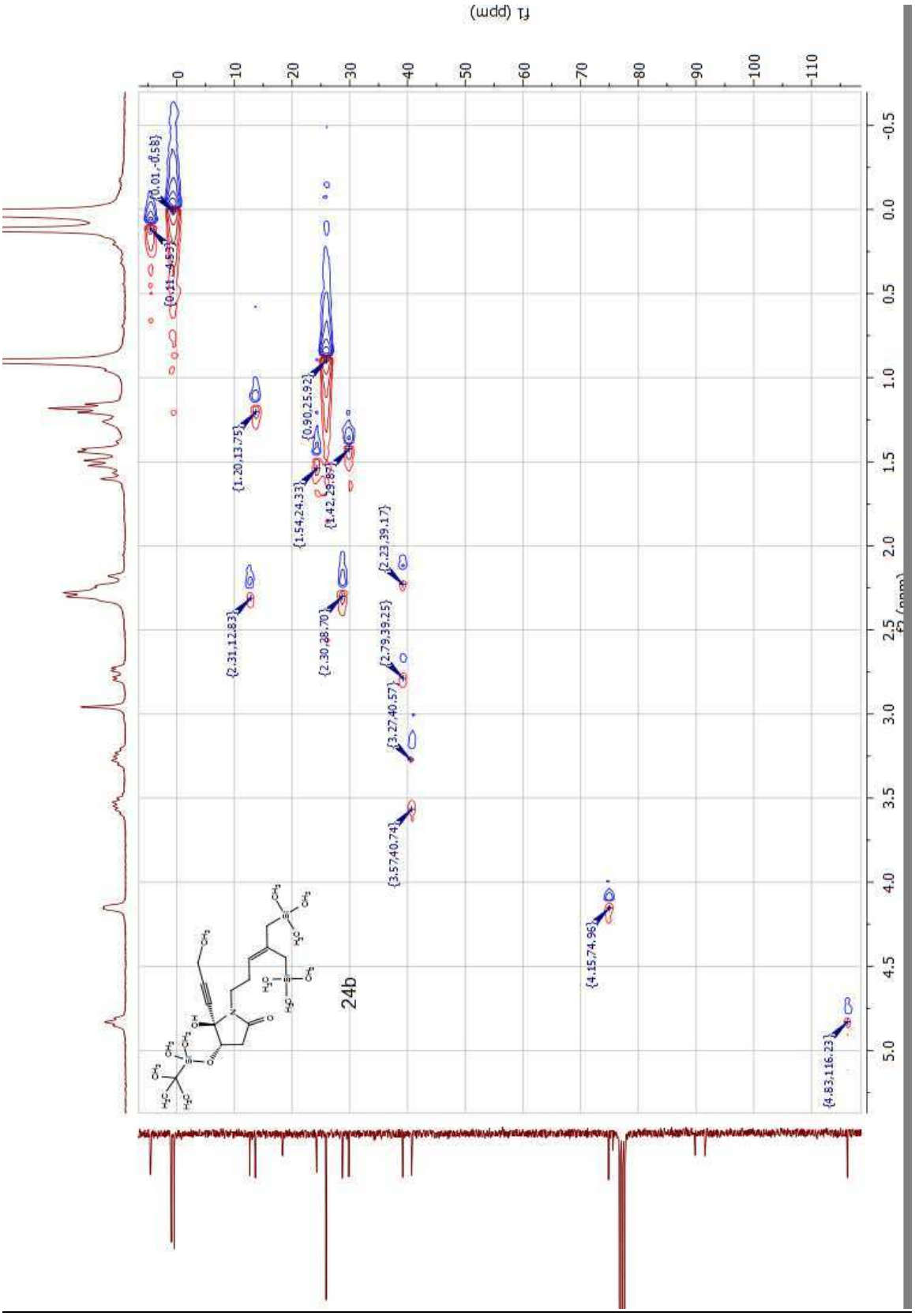
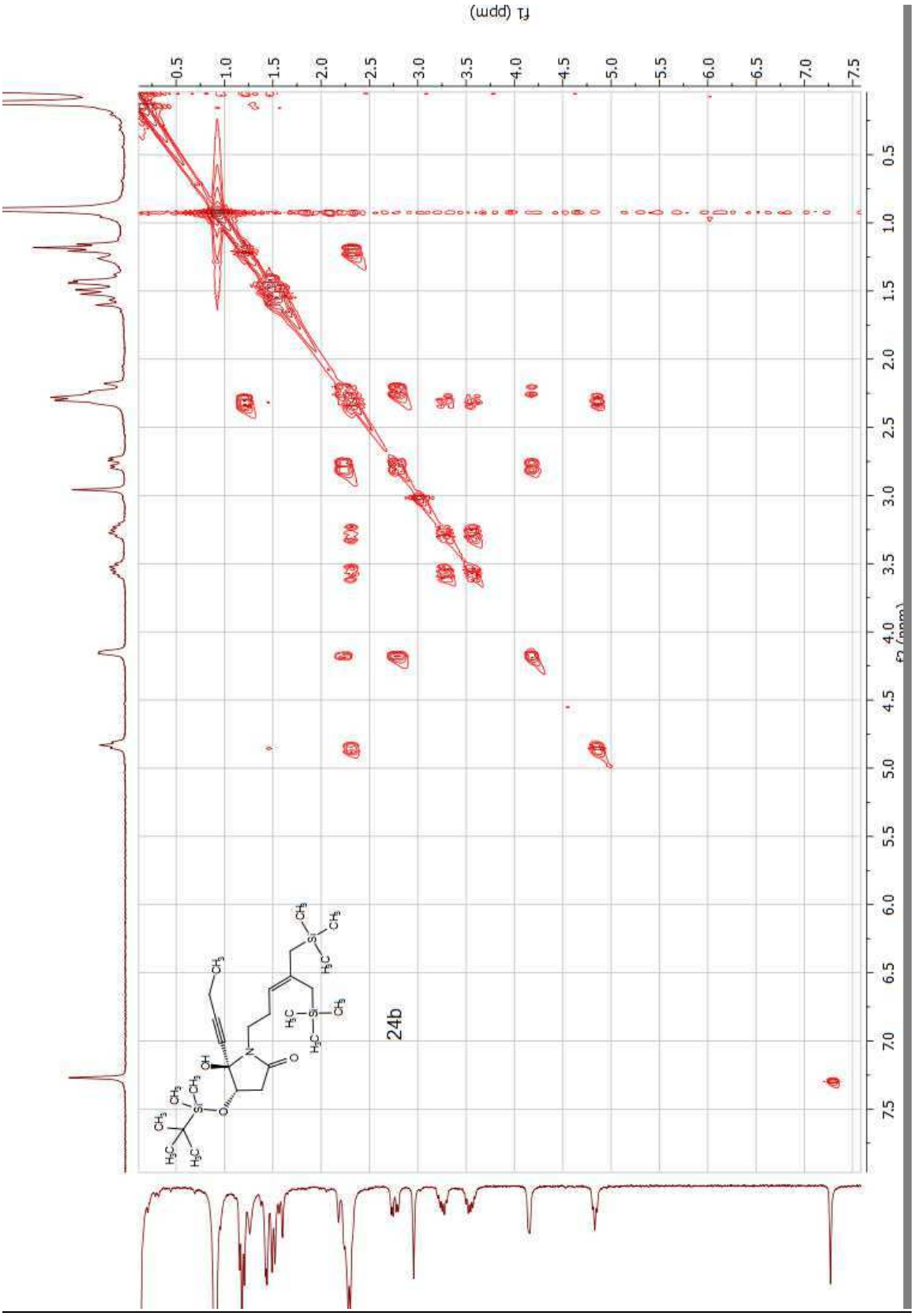
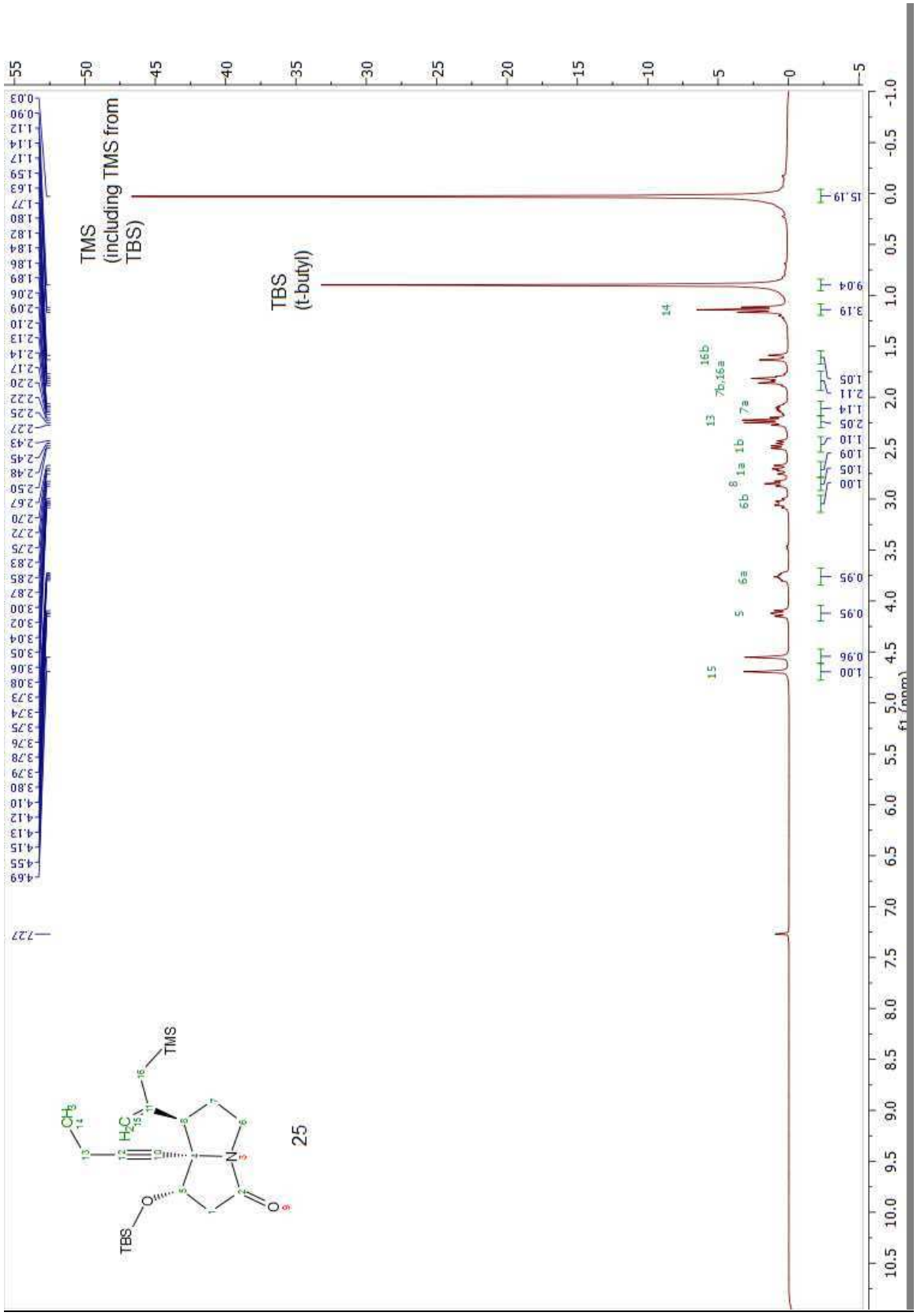
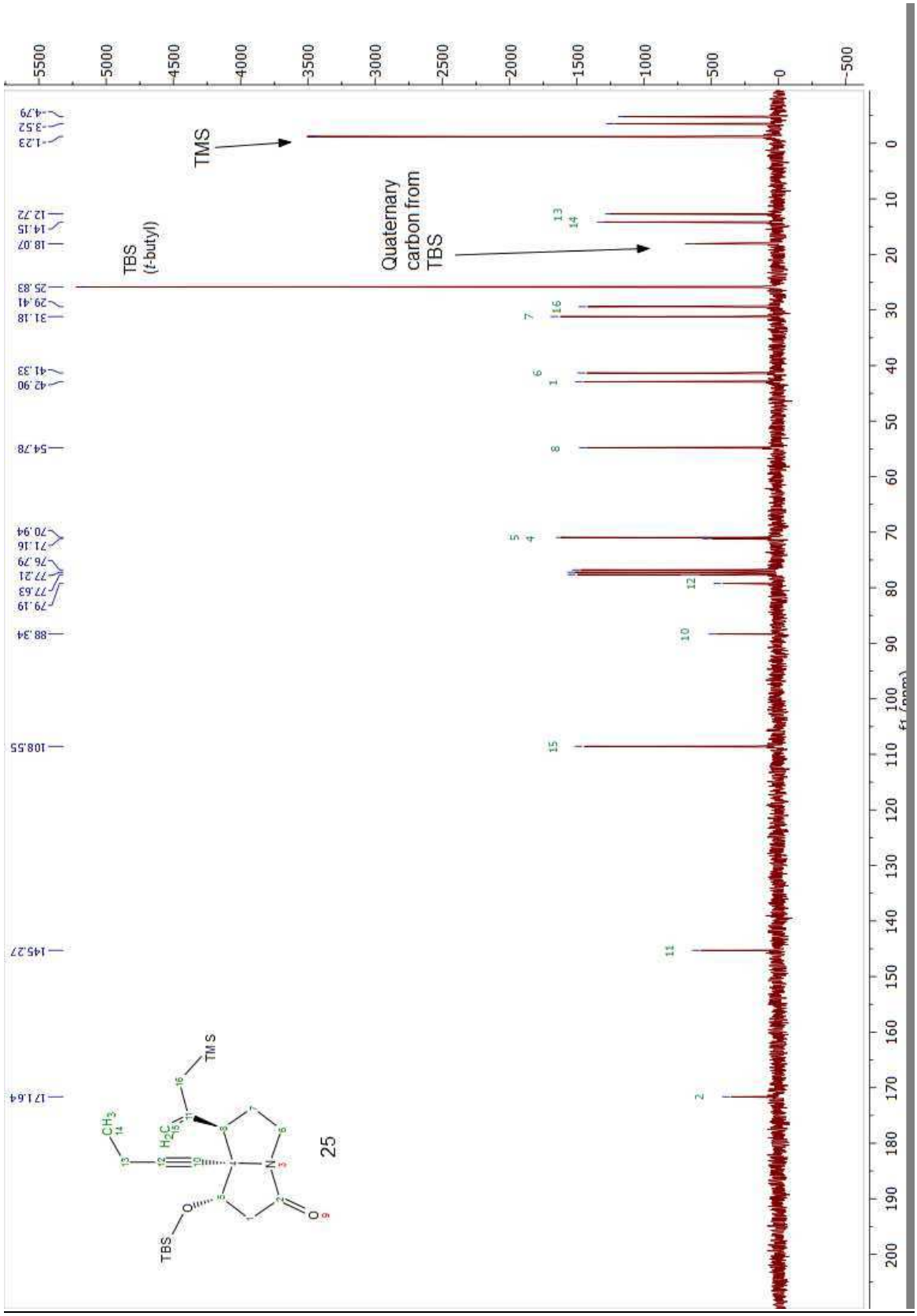
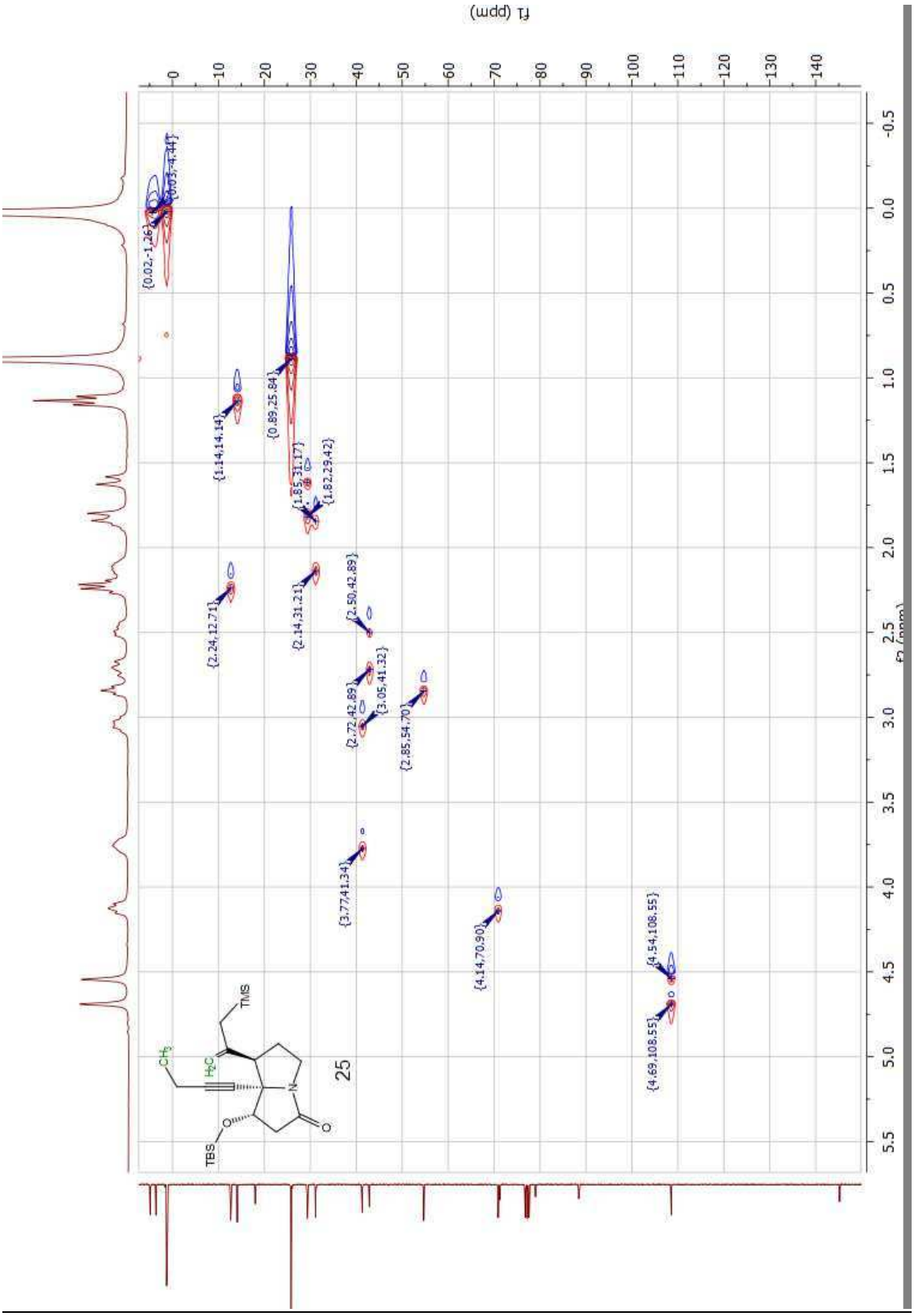
89.86
91.53
116.23
138.38
172.80
24b

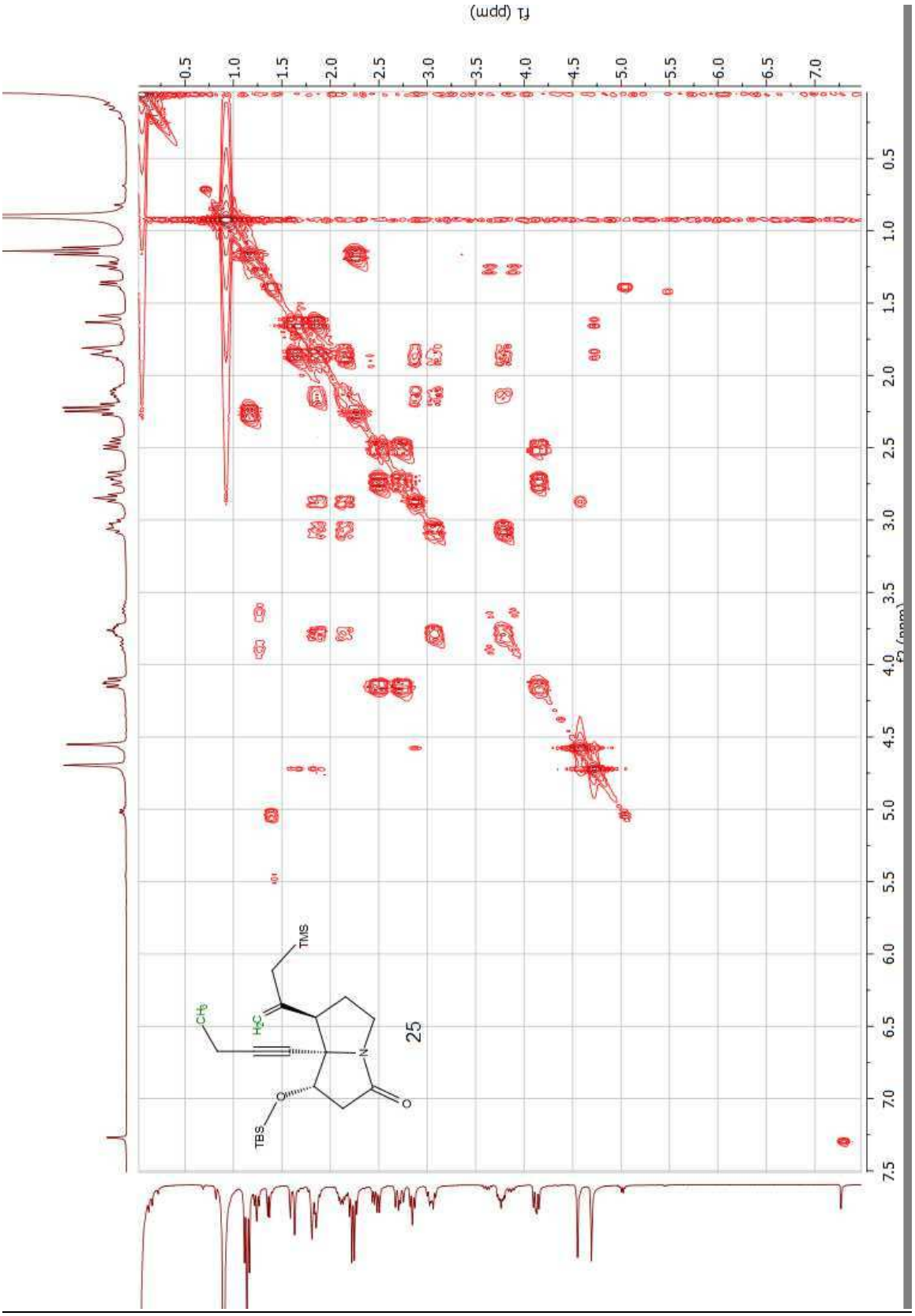

f1 (ppm)
f2 (ppm)
{0.01,-0.58}
{0.11,-4.63}
{1.20,13.75}
{0.90,25.92}
{1.54,24.33}
{1.42,29.85}
{2.31,12.83}
{2.30,28.70}
{2.23,39.17}
{2.79,39.25}
{3.27,40.57}
{3.57,40.74}
{4.15,74.96}
{4.83,116.23}
24b

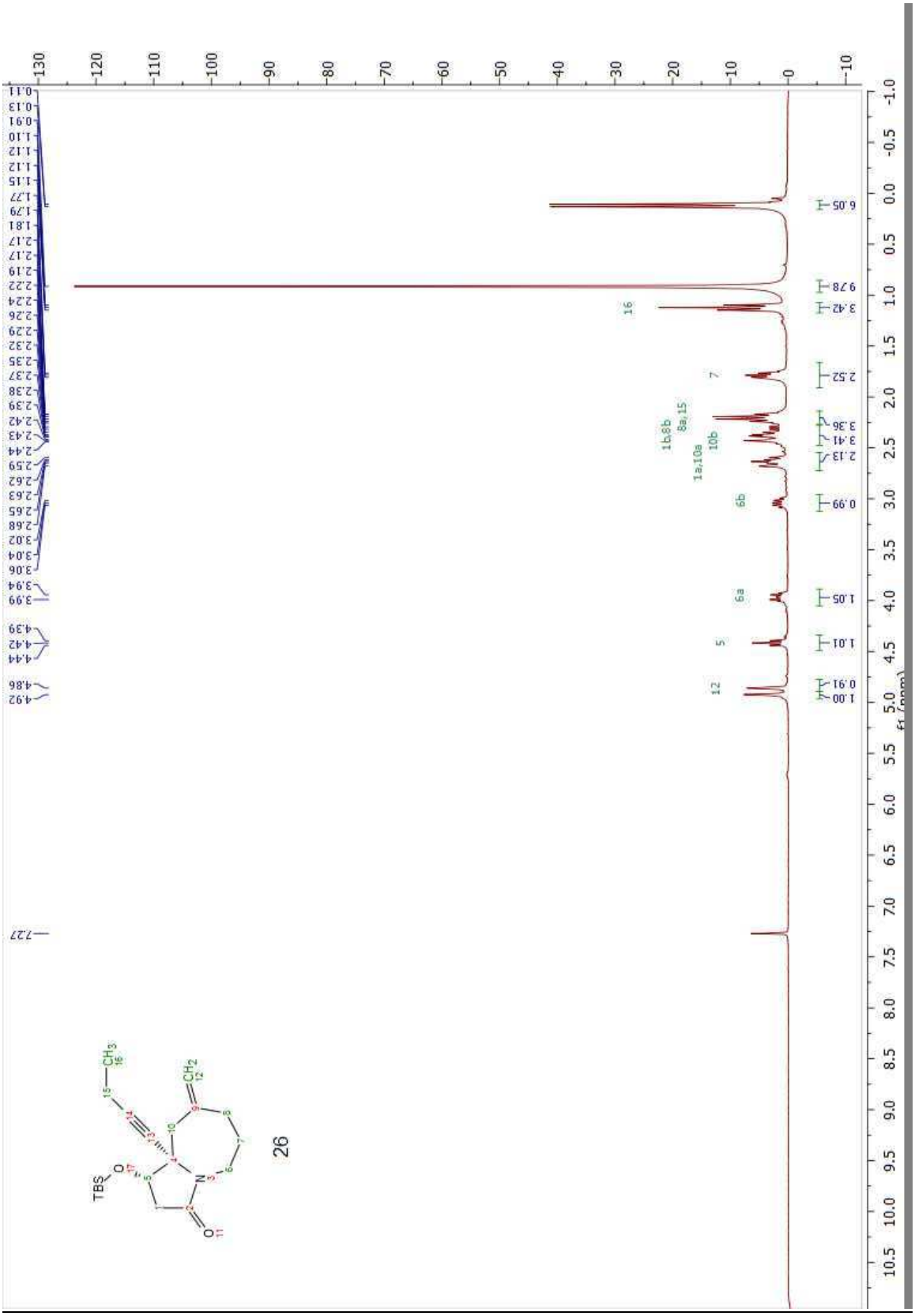

f1 (ppm)
f2 (ppm)
24b

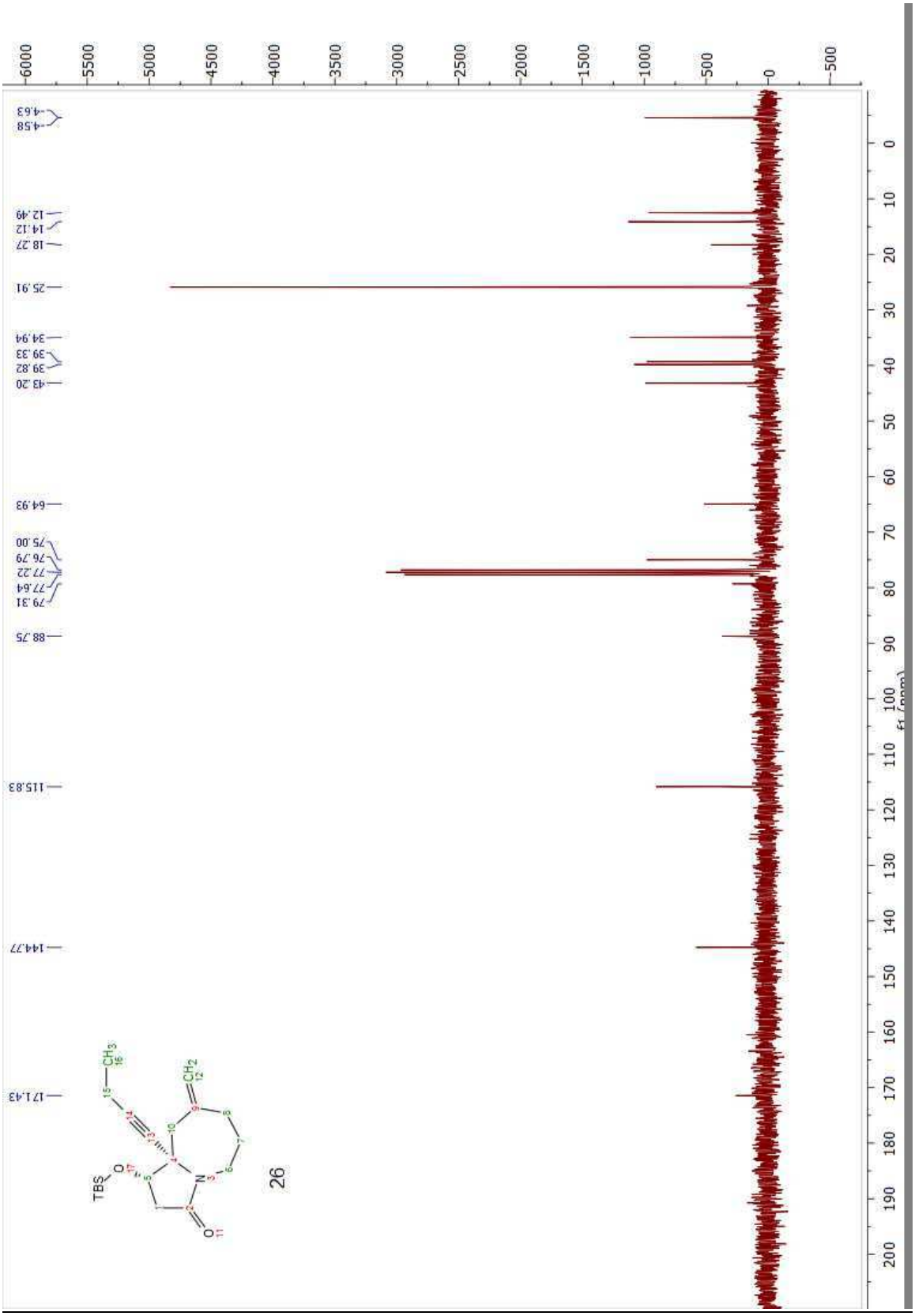

TMS
(including TMS from TBS)
TBS
(t-butyl)
25
TBS
TMS
f1 (ppm)

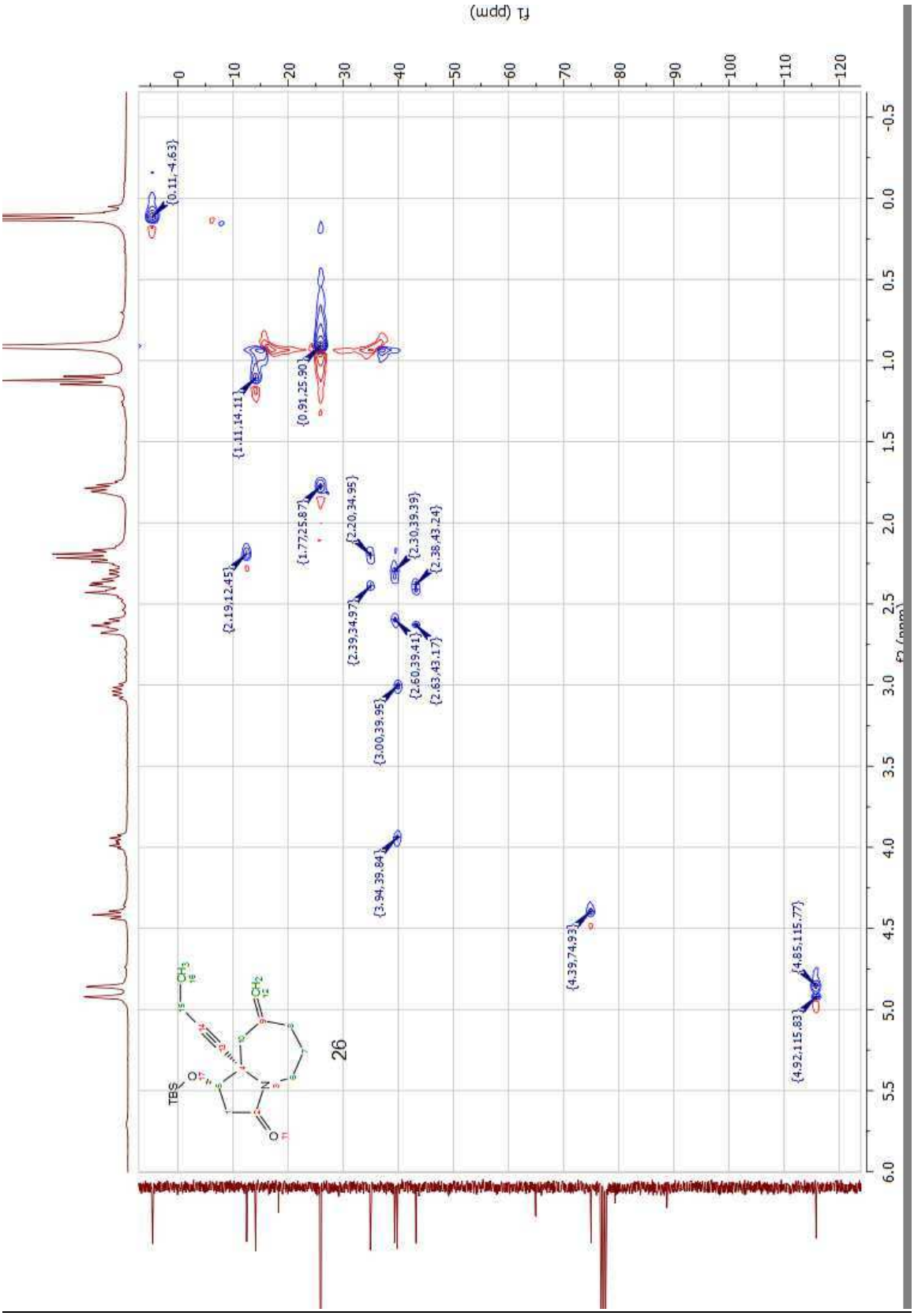

TMS
Quaternary carbon from TBS
TBS (t-butyl)
25
TBS
TMS
f1 (ppm)

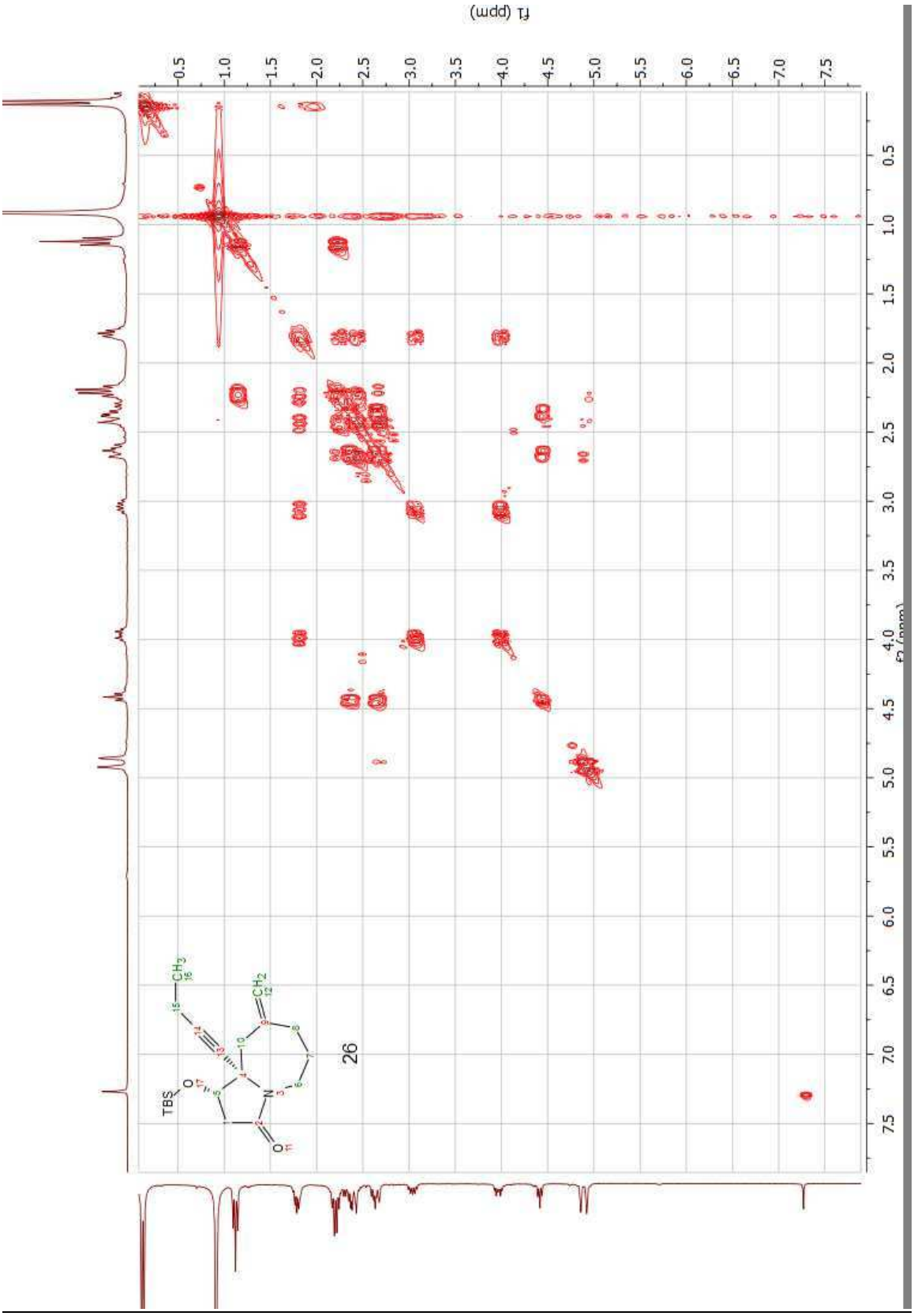

f1 (ppm)
f2 (ppm)
{0.02,-1.26}
{0.03,-4.44}
{1.14,14.14}
{0.89,25.84}
{1.85,31.17}
{1.82,29.42}
{2.24,12.71}
{2.14,31.21}
{2.50,42.89}
{2.72,42.89}
{3.05,41.32}
{2.85,54.70}
{3.77,41.34}
{4.14,70.90}
{4.54,108.55}
{4.69,108.55}
TMS
TBS
25

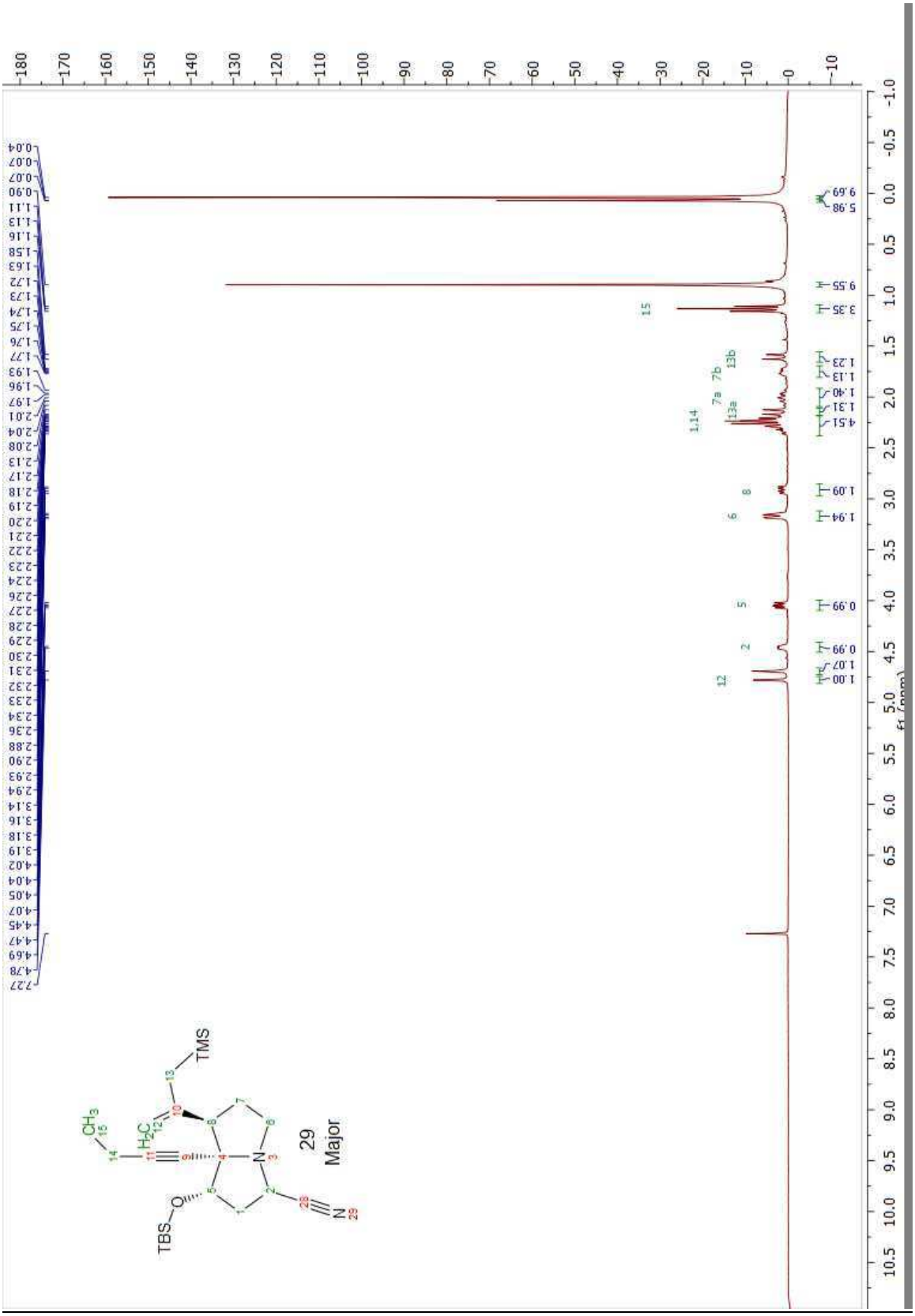

f1 (ppm)
f2 (ppm)
TMS
TBS
O
N
25

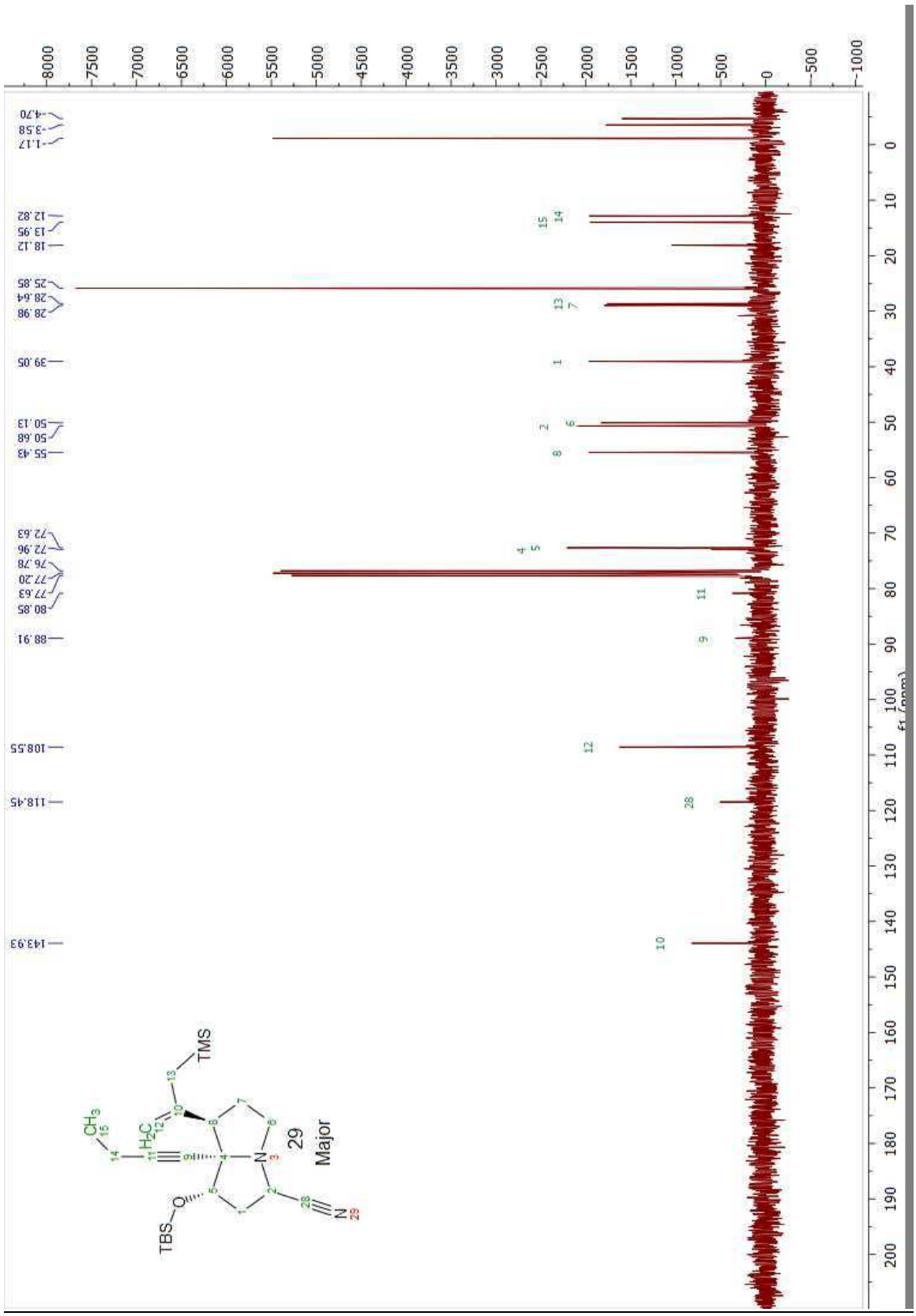

TBS
O
O
N
O
O
CH3
CH2
26

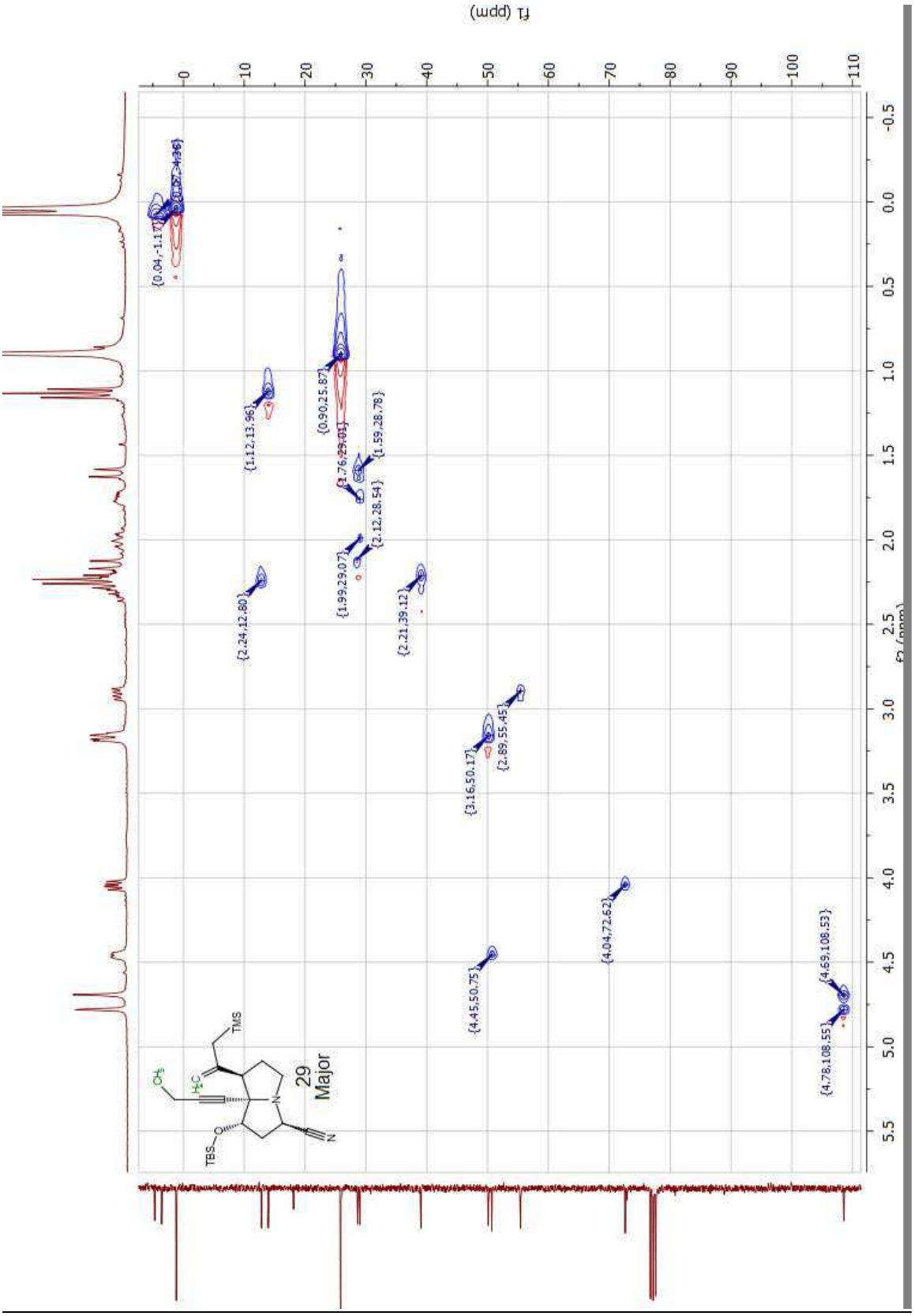

-4.63
-4.58
12.49
14.12
18.27
25.91
34.94
39.33
39.82
43.20
64.93
75.00
76.79
77.22
77.64
79.31
88.75
115.83
144.77
171.43
TBS
O
O
N
O
CH3
CH2
26

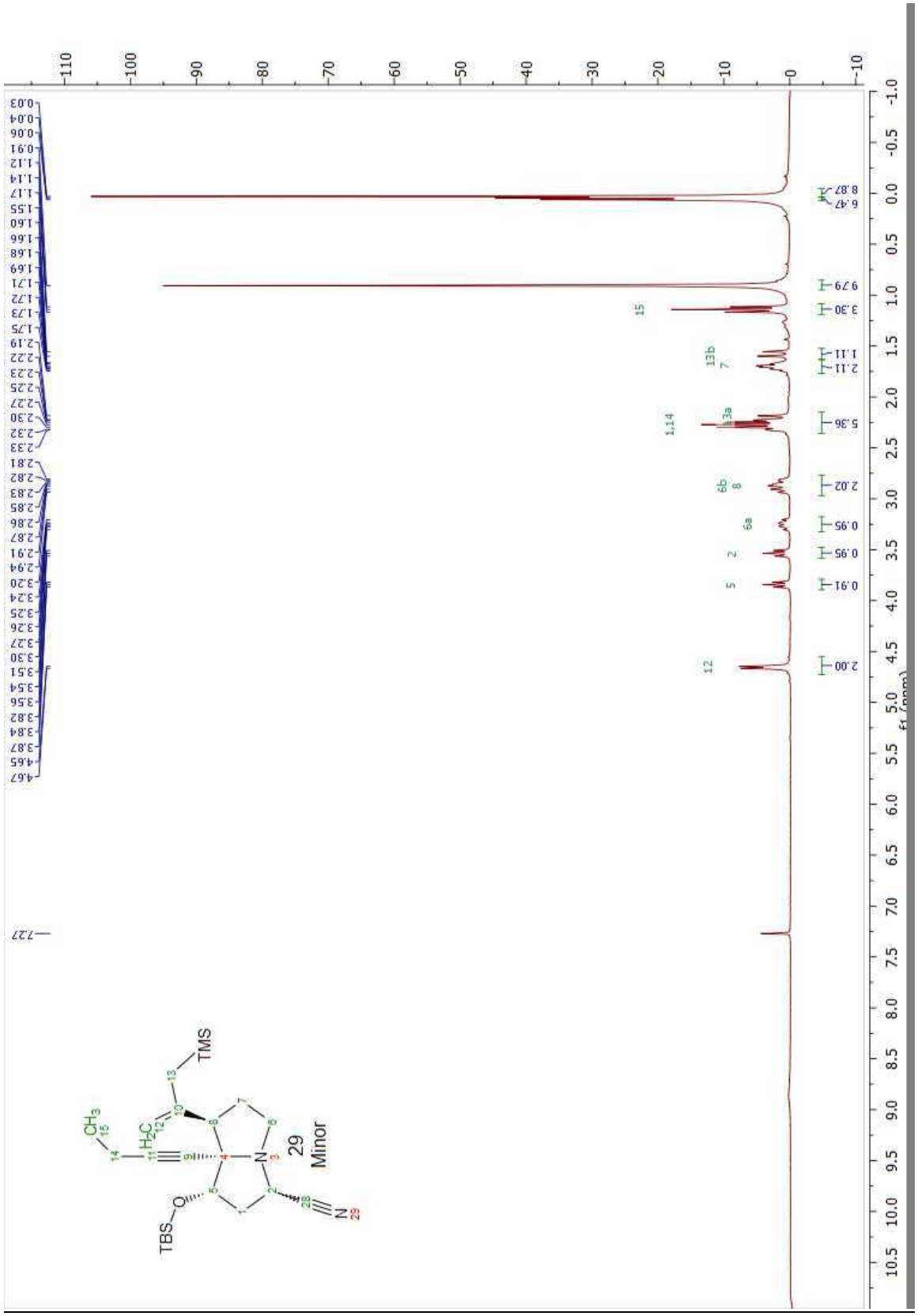

f1 (ppm)
f2 (ppm)
{0.11,-4.63}
{1.11,14.11}
{0.91,25.90}
{1.77,25.87}
{2.19,12.45}
{2.20,34.95}
{2.30,39.39}
{2.38,43.24}
{2.39,34.97}
{2.60,39.41}
{2.63,43.17}
{3.00,39.95}
{3.94,39.84}
{4.39,74.93}
{4.85,115.77}
{4.92,115.83}
TBS
26

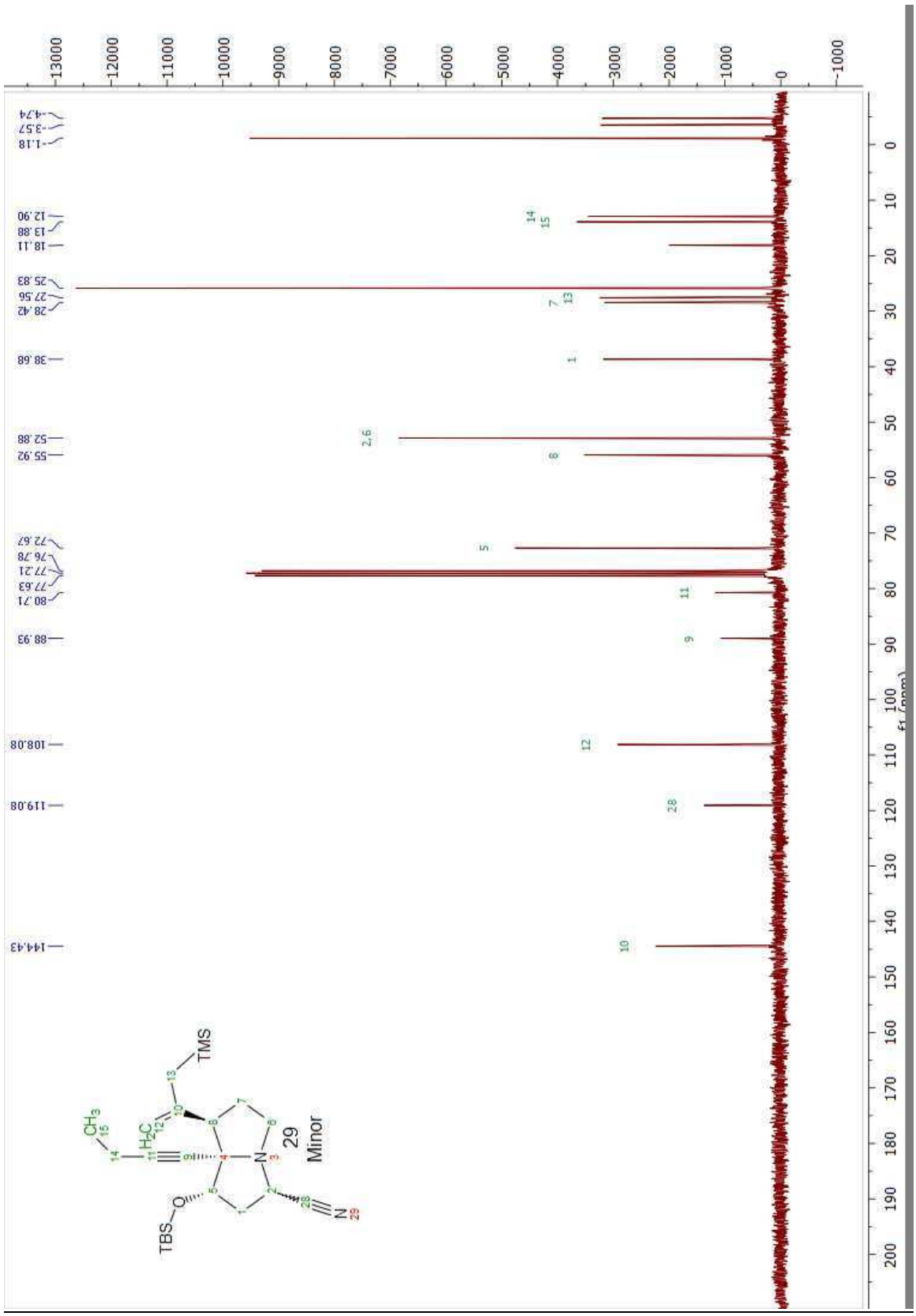

f1 (ppm)
f2 (ppm)
TBS
O
N
CH2
CH3
26

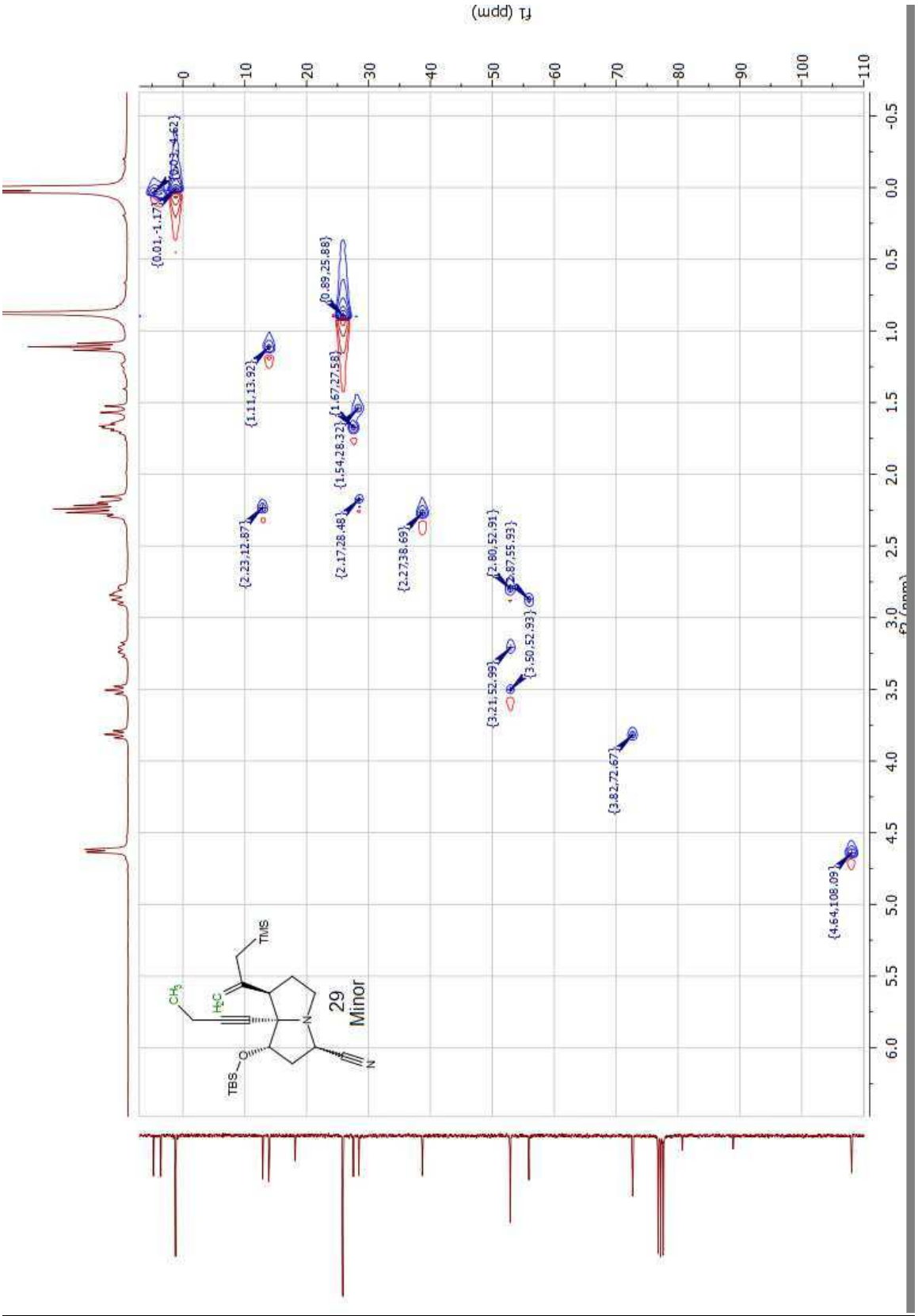

TMS
CH3
H2C
TBS
O
N
29
Major

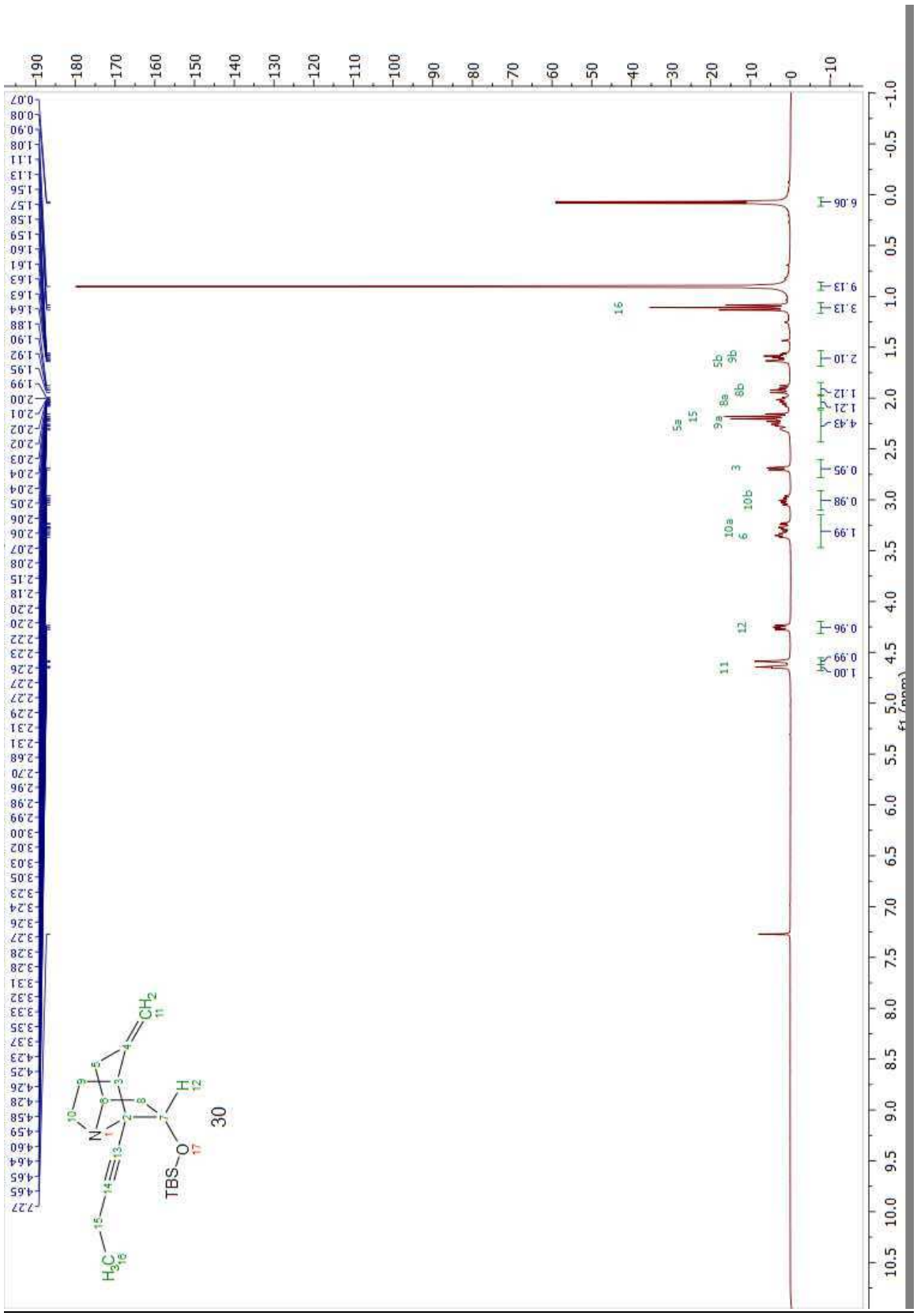

-4.70
-3.58
-1.17
12.82
13.95
18.12
25.85
28.64
28.98
39.05
50.13
50.68
55.43
72.63
72.96
76.78
77.20
77.63
80.85
88.91
108.55
118.45
143.93
TMS
TBS
O
N
29
Major
f1 (ppm)

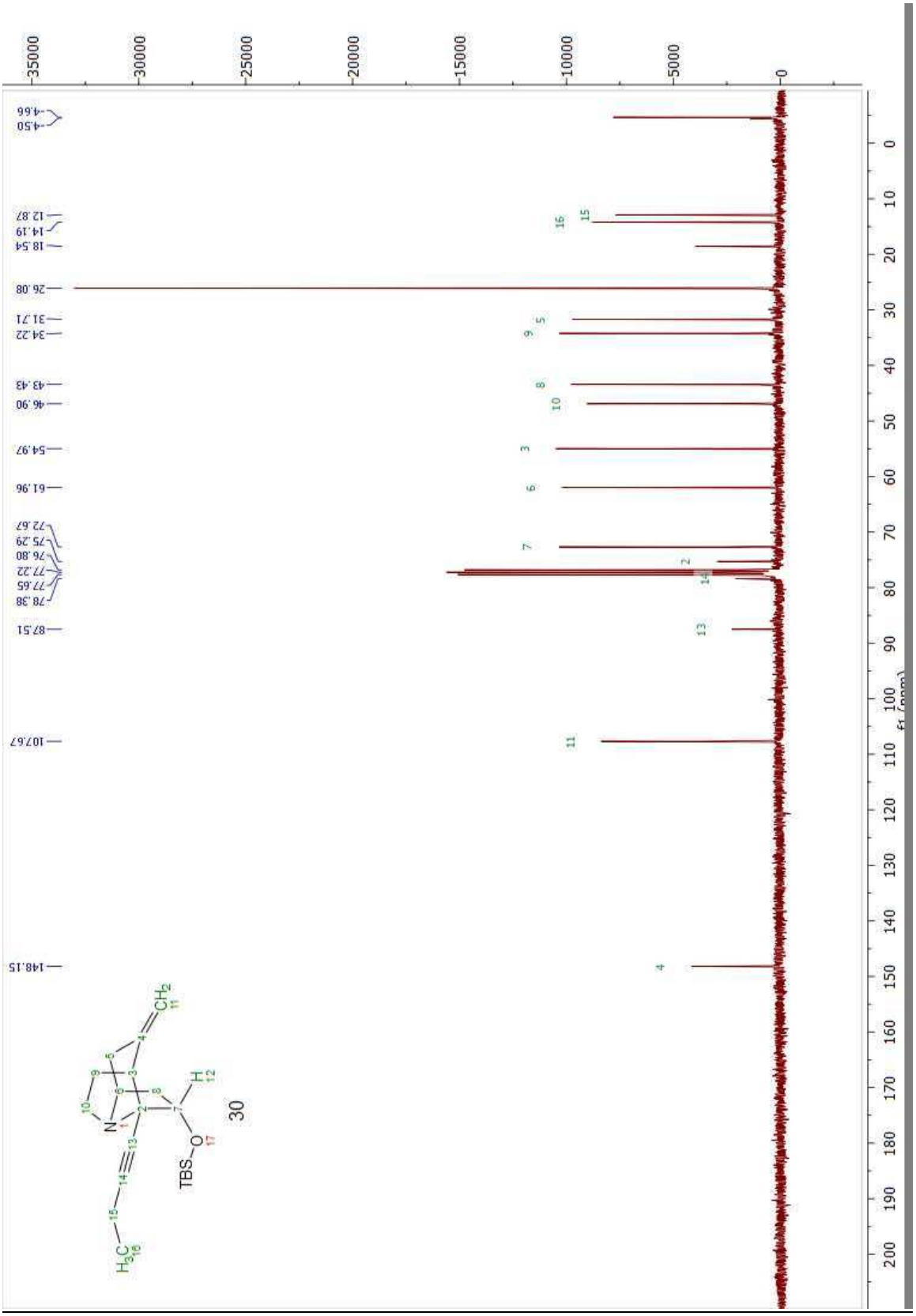

f1 (ppm)
{0.04,-1.17}
{1.12,13.96}
{0.90,25.87}
{2.76,29.01}
{1.59,28.78}
{2.12,28.54}
{1.99,29.07}
{2.24,12.80}
{2.21,39.12}
{3.16,50.17}
{2.89,55.45}
{4.45,50.75}
{4.04,72.62}
{4.69,108.53}
{4.78,108.55}
TMS
TBS
29
Major

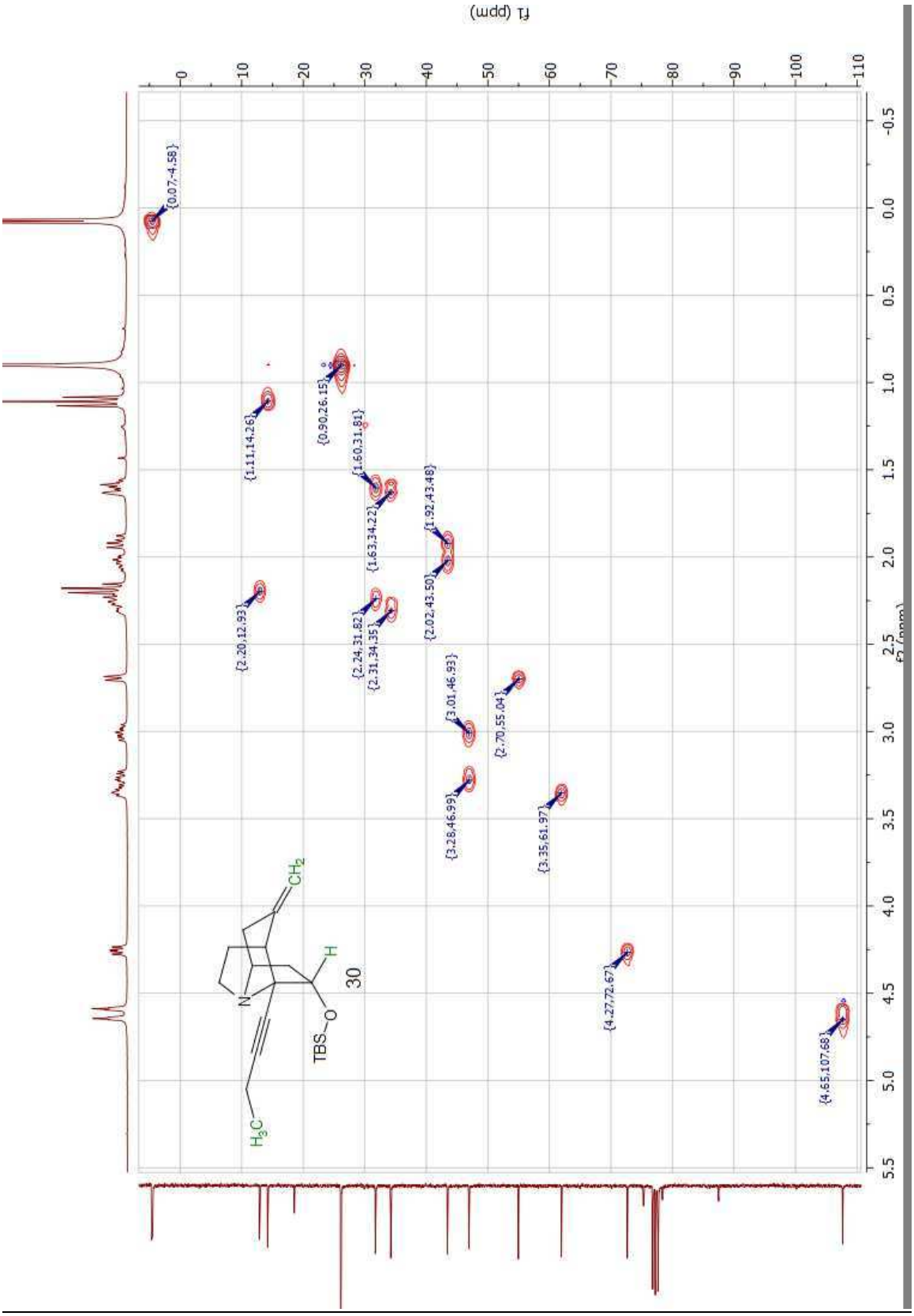

TMS
CH3
H2C
TBS
O
N
29
Minor

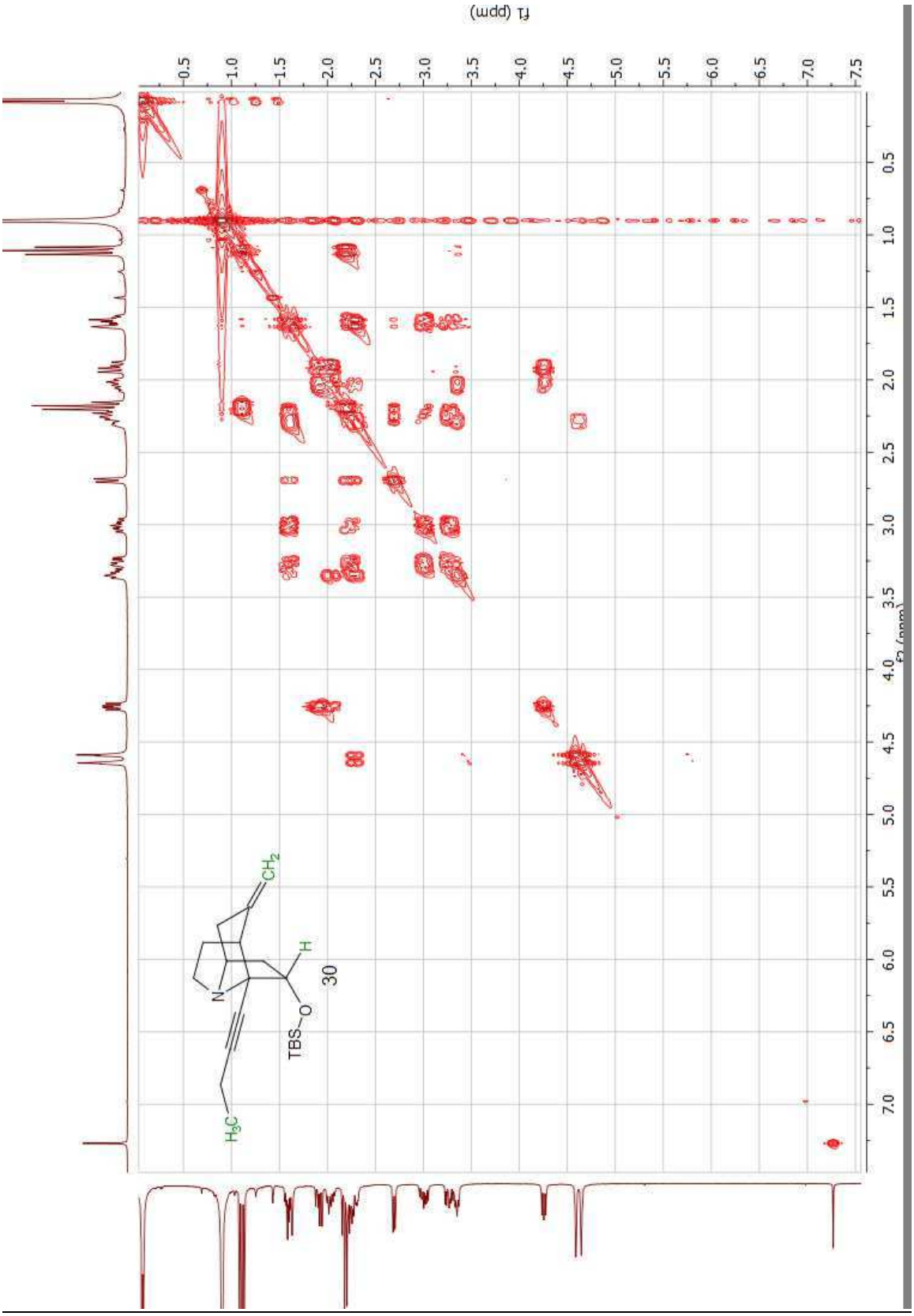

-4.74
-3.57
-1.18
12.90
13.88
18.11
25.83
27.56
28.42
38.68
52.88
55.92
72.67
76.78
77.21
77.63
80.71
88.93
108.08
119.08
144.43
TMS
CH3
H2C
TBS
O
N
29
Minor
f1 (ppm)

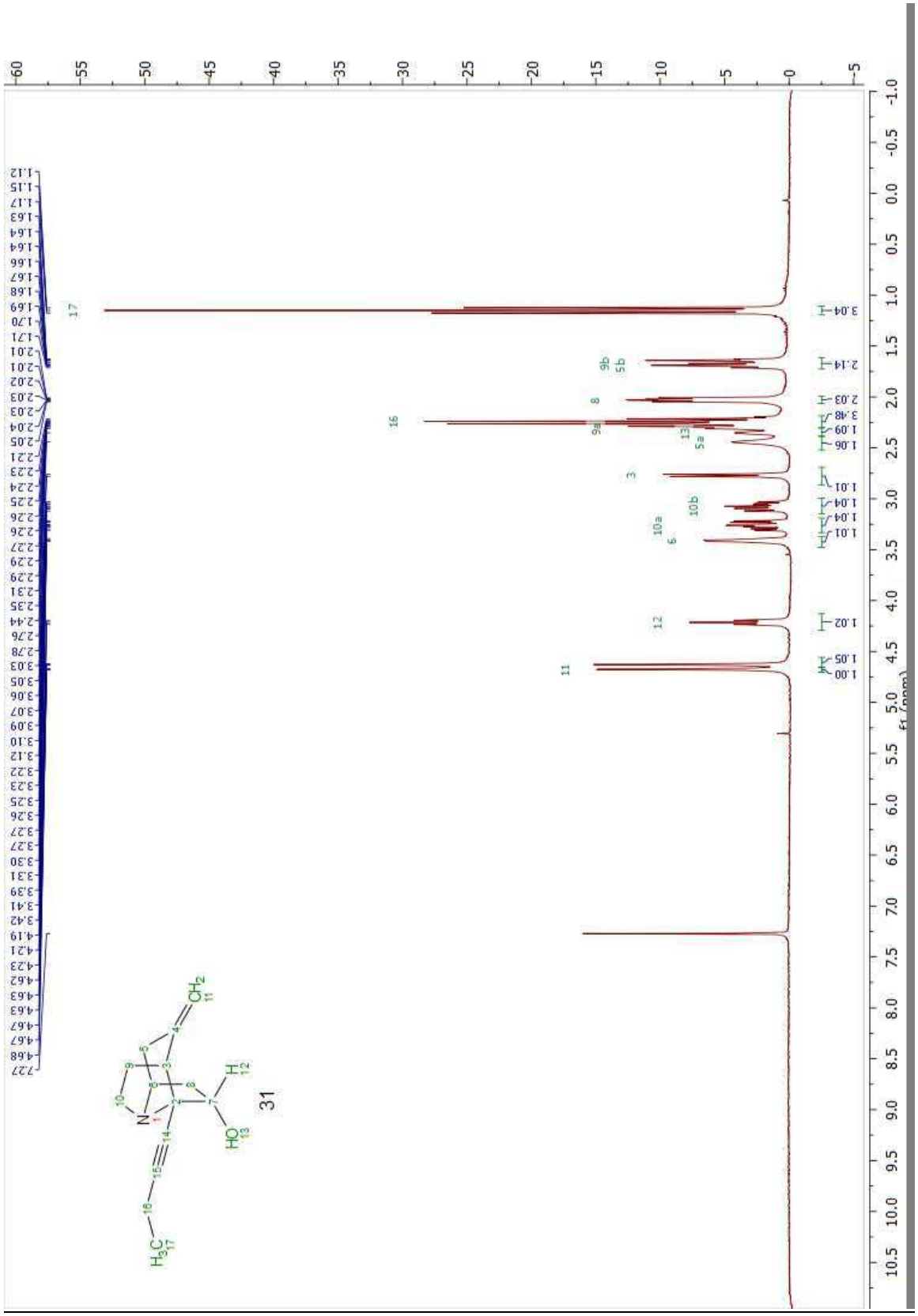

f1 (ppm)
{0.01,-1.17}
{0.89,25.88}
{1.11,13.92}
{1.67,27.58}
{1.54,28.32}
{2.23,12.87}
{2.17,28.48}
{2.27,38.69}
{2.80,52.91}
{2.87,55.93}
{3.50,52.93}
{3.21,52.99}
{3.82,72.67}
{4.64,108.09}
TMS
TBS
29
Minor

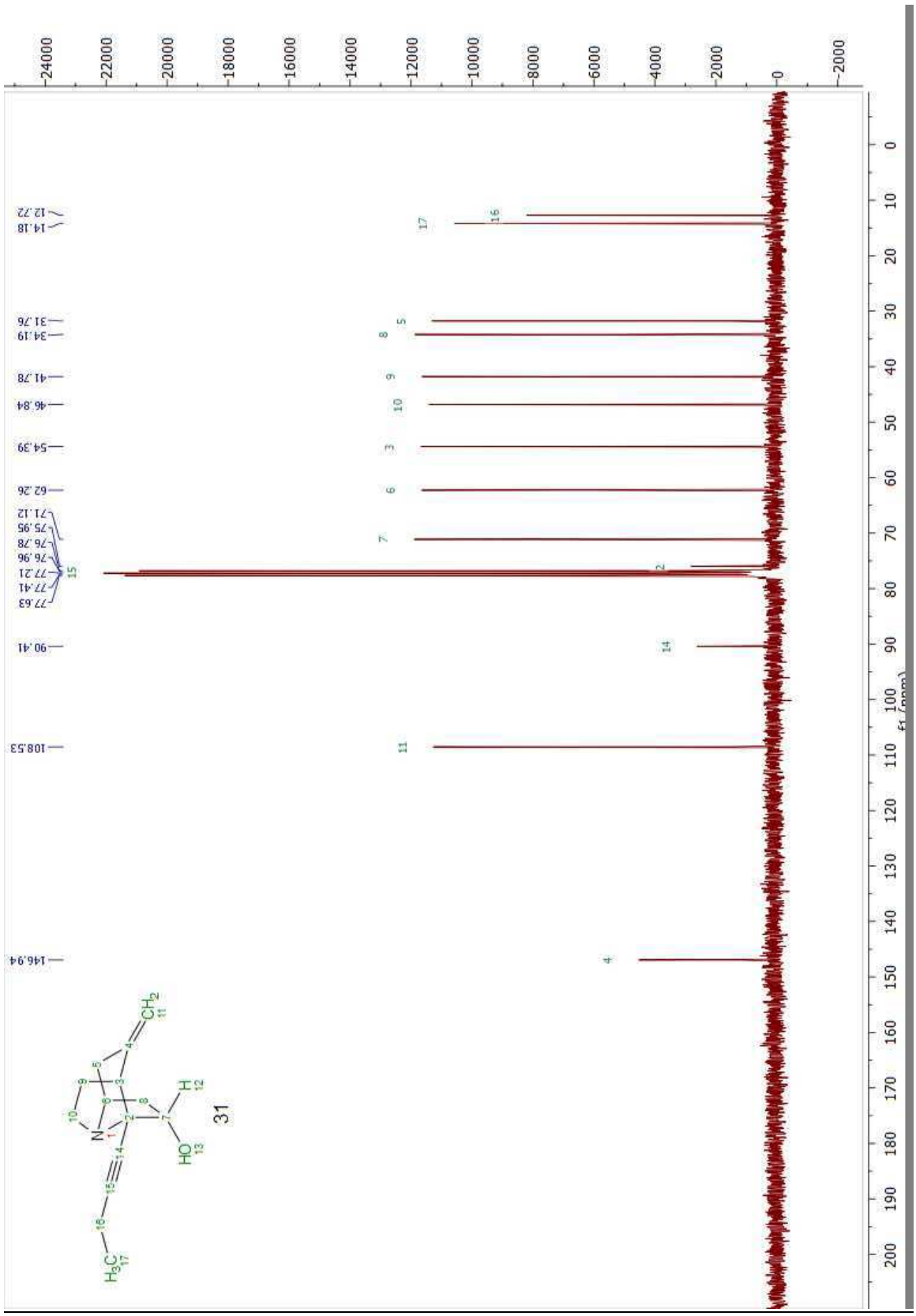

TBS
O
H
CH2
H3C
N
30

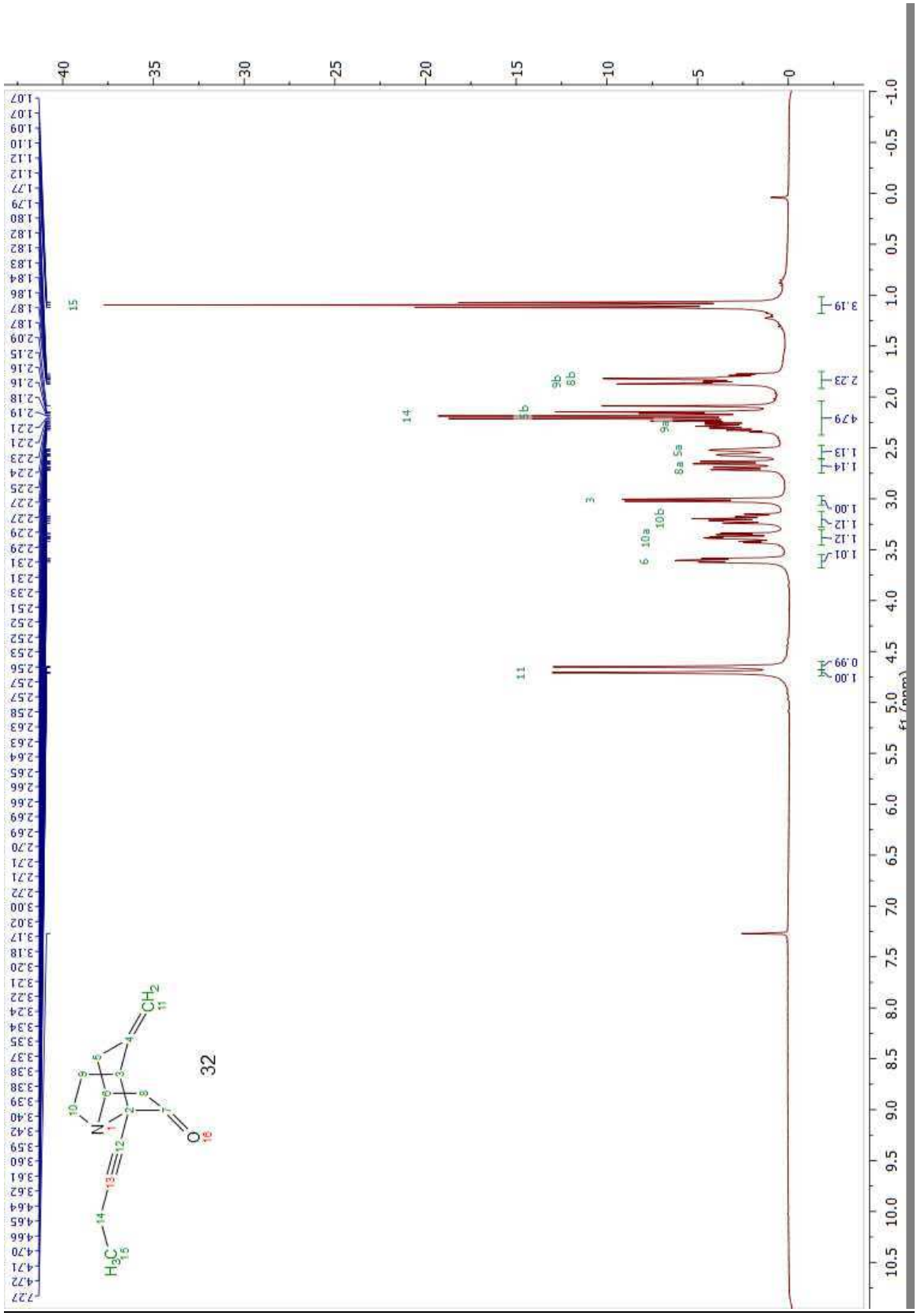

-4.66
-4.50
12.87
14.19
18.54
26.08
31.71
34.22
43.43
46.90
54.97
61.96
72.67
75.29
76.80
77.22
77.65
78.38
87.51
107.67
148.15
TBS
O
N
H
CH2
H3C
30

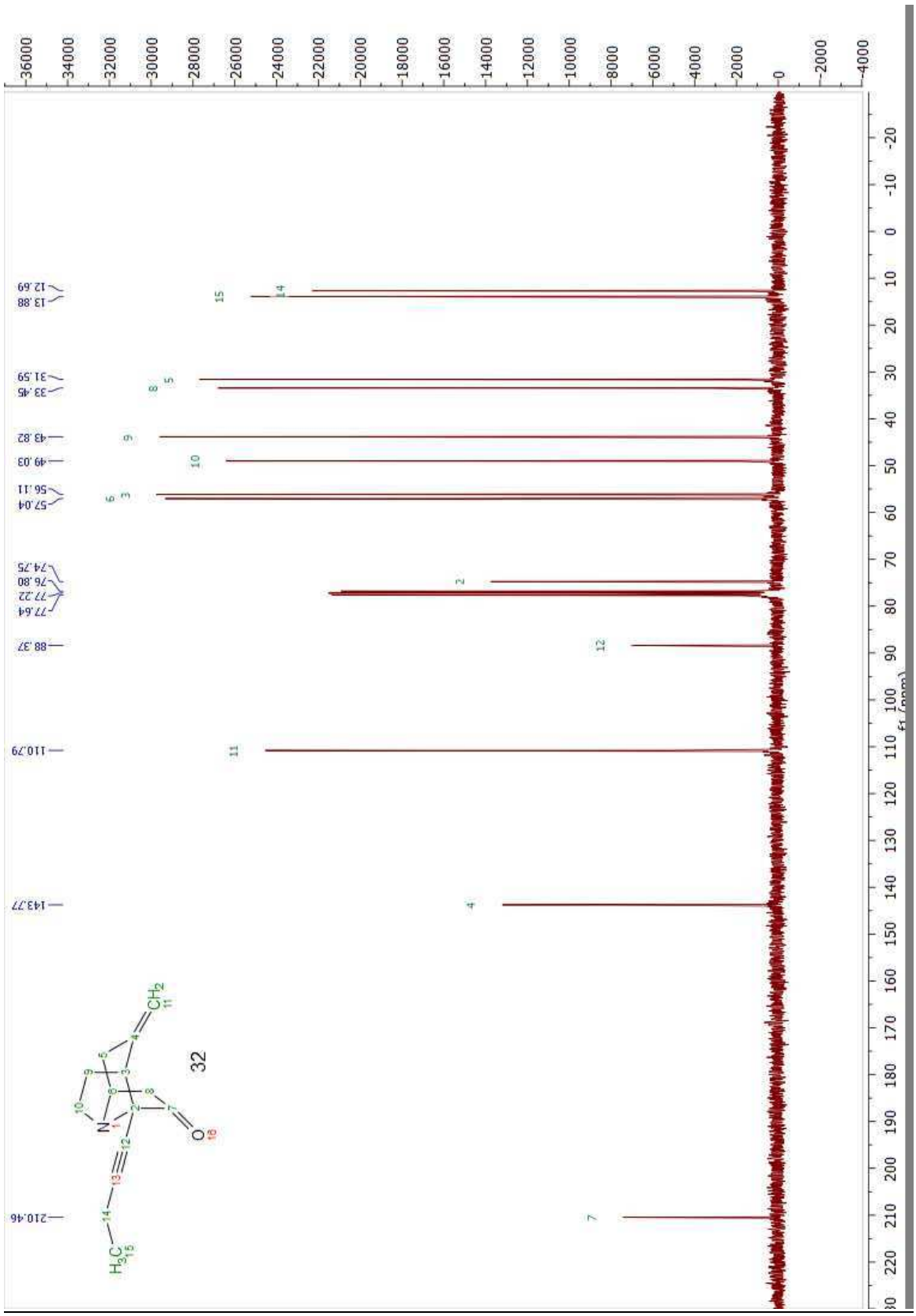

f1 (ppm)
{0.07,-4.58}
{0.90,26.15}
{1.11,14.26}
{1.60,31.81}
{1.63,34.22}
{1.92,43.48}
{2.02,43.50}
{2.20,12.93}
{2.24,31.82}
{2.31,34.35}
{3.01,46.93}
{3.26,46.99}
{2.70,55.04}
{3.35,61.97}
{4.27,72.67}
{4.65,107.68}
CH2
H
N
O
TBS
H3C
30

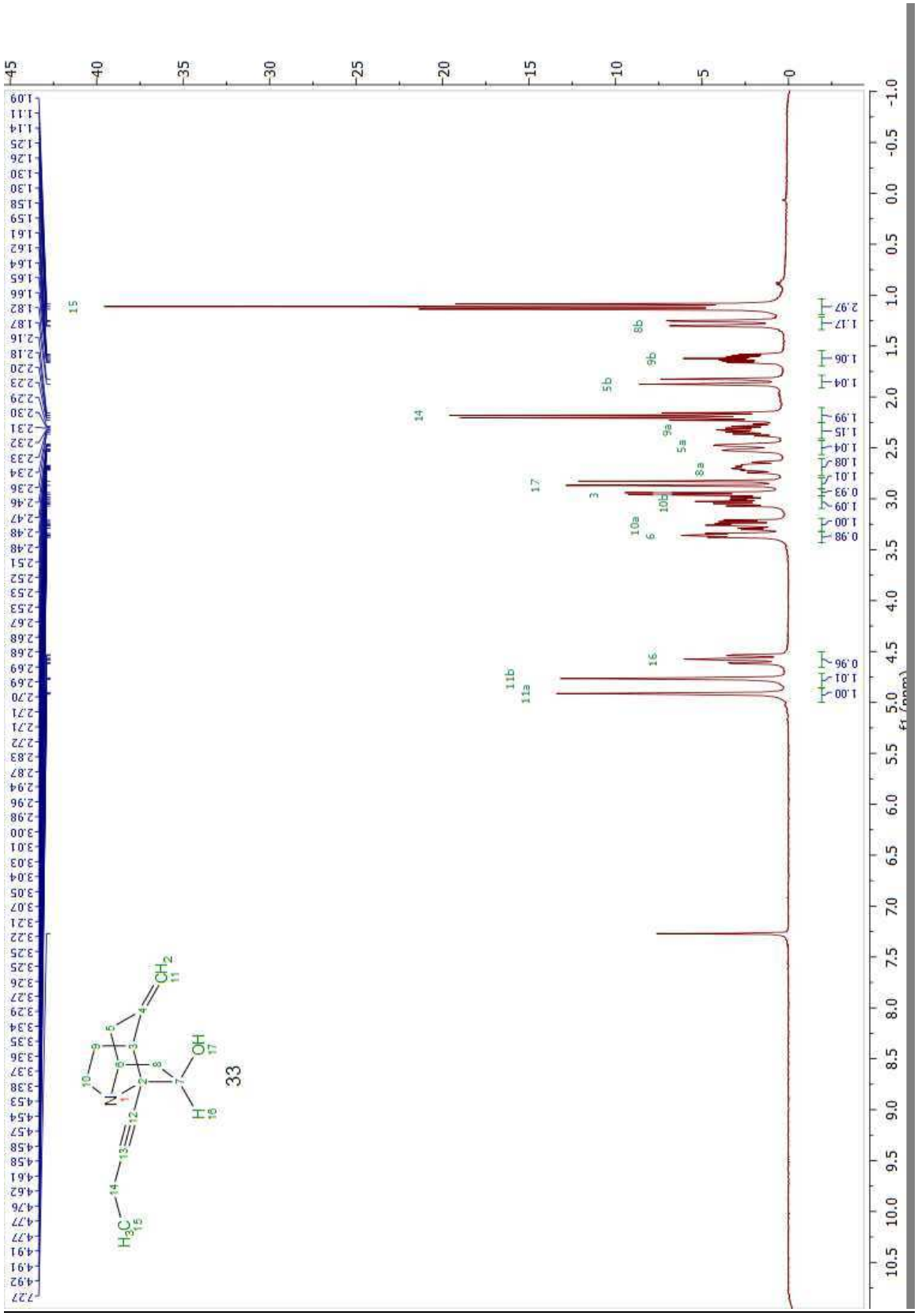

f1 (ppm)
f2 (ppm)
CH2
H
N
TBS—O
H3C
30

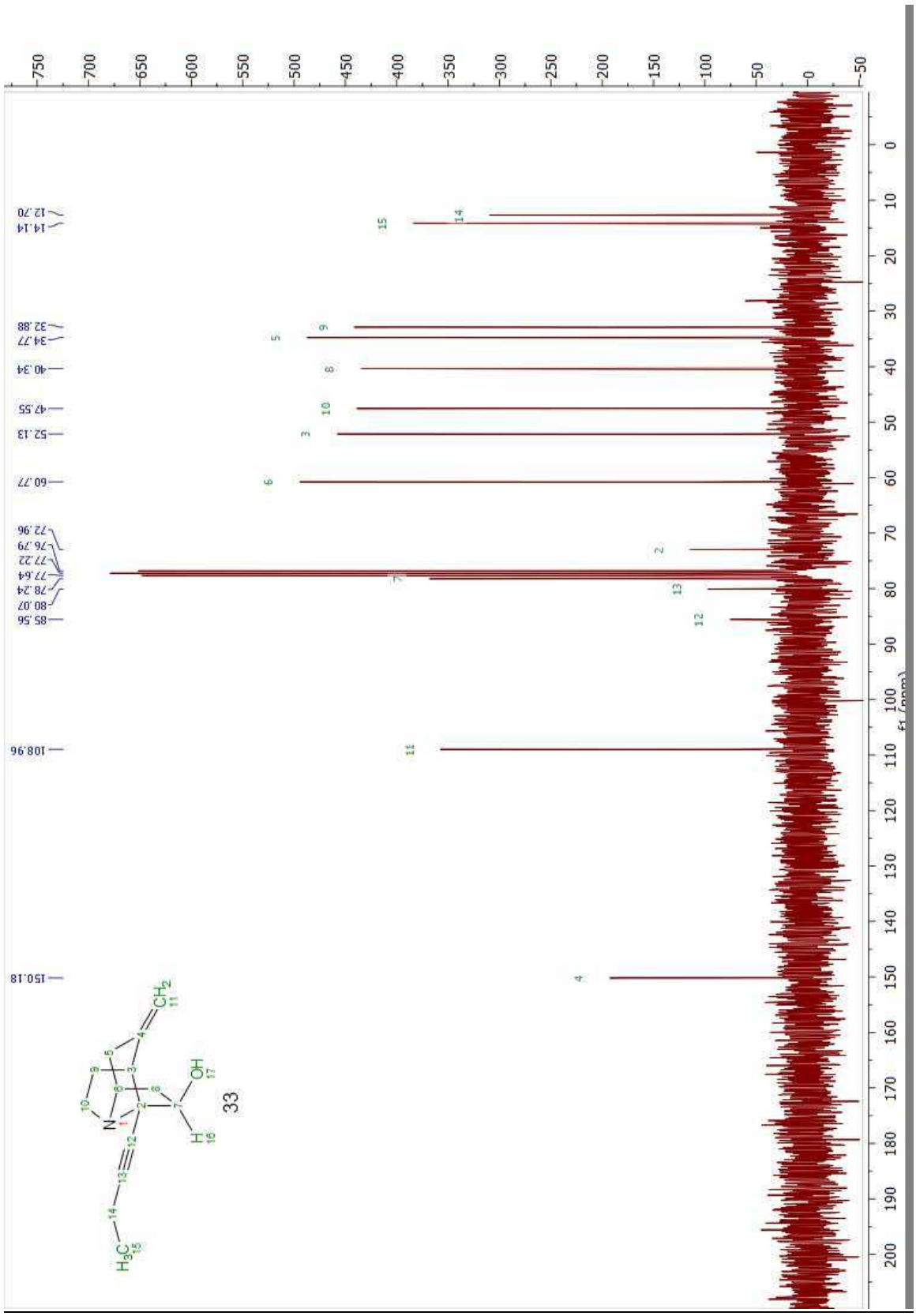

31

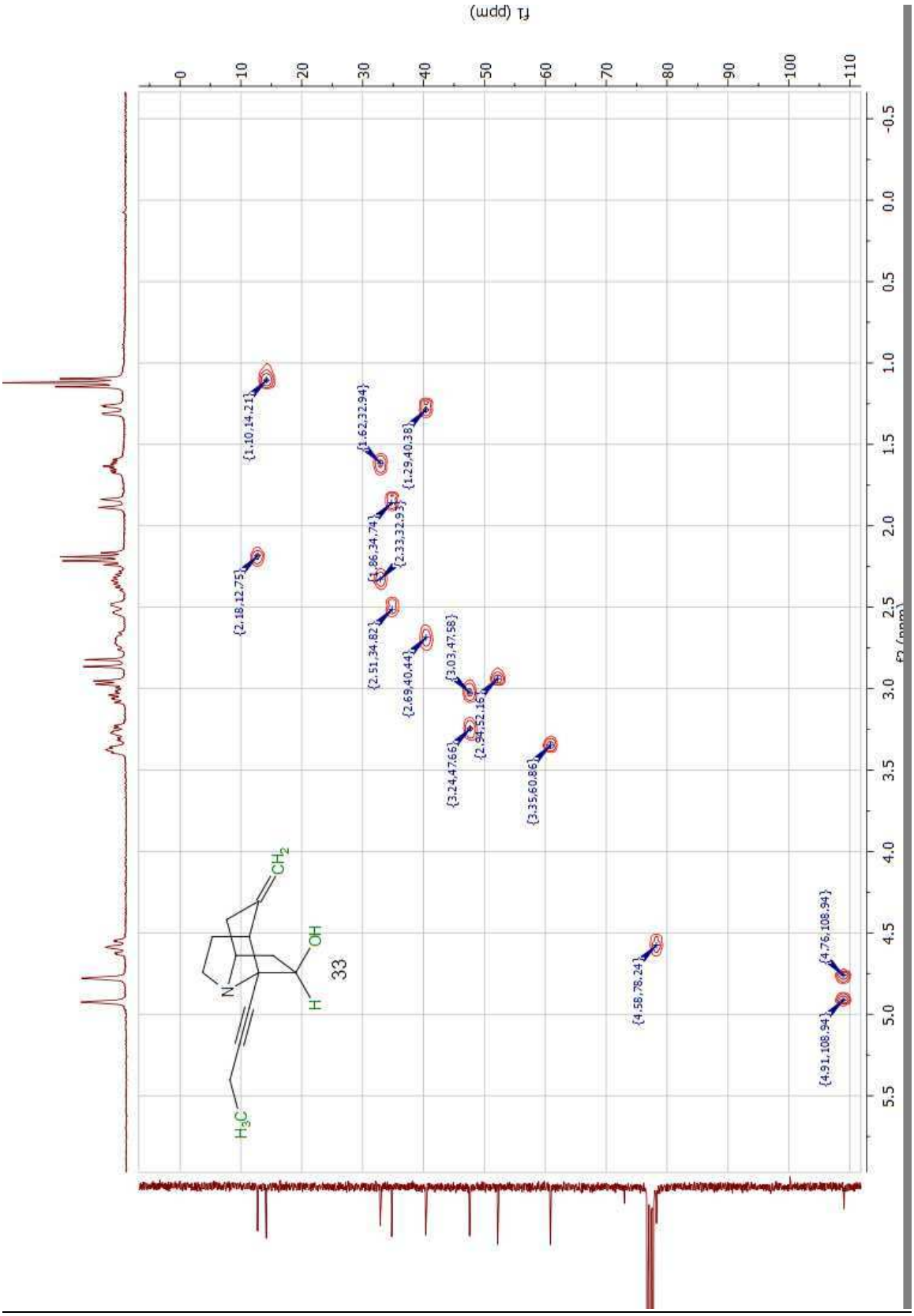

12.72
14.18
31.76
34.19
41.78
46.84
54.39
62.26
71.12
75.95
76.78
76.96
77.21
77.41
77.63
90.41
108.53
146.94
f1 (ppm)
31

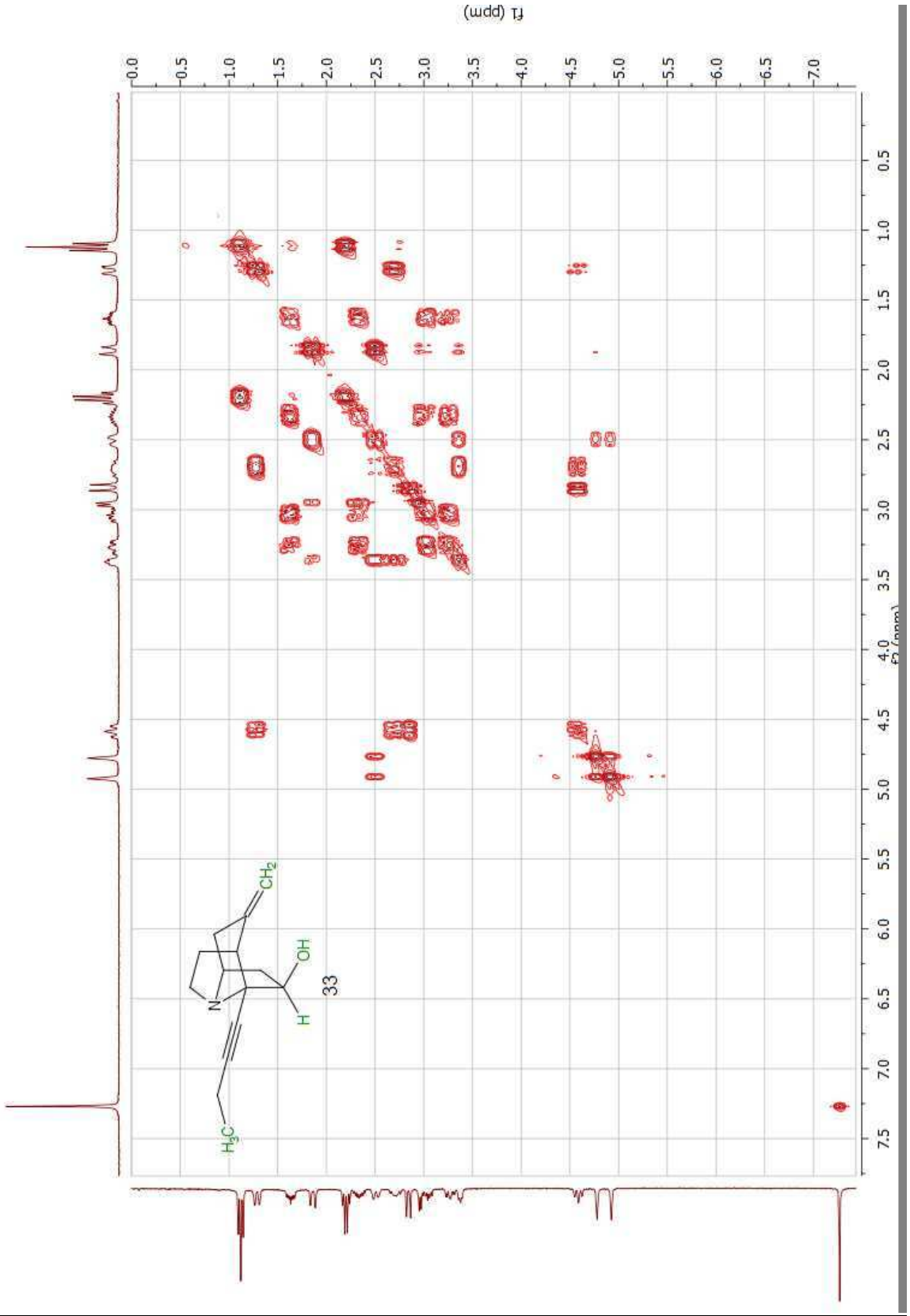

32
f1 (ppm)

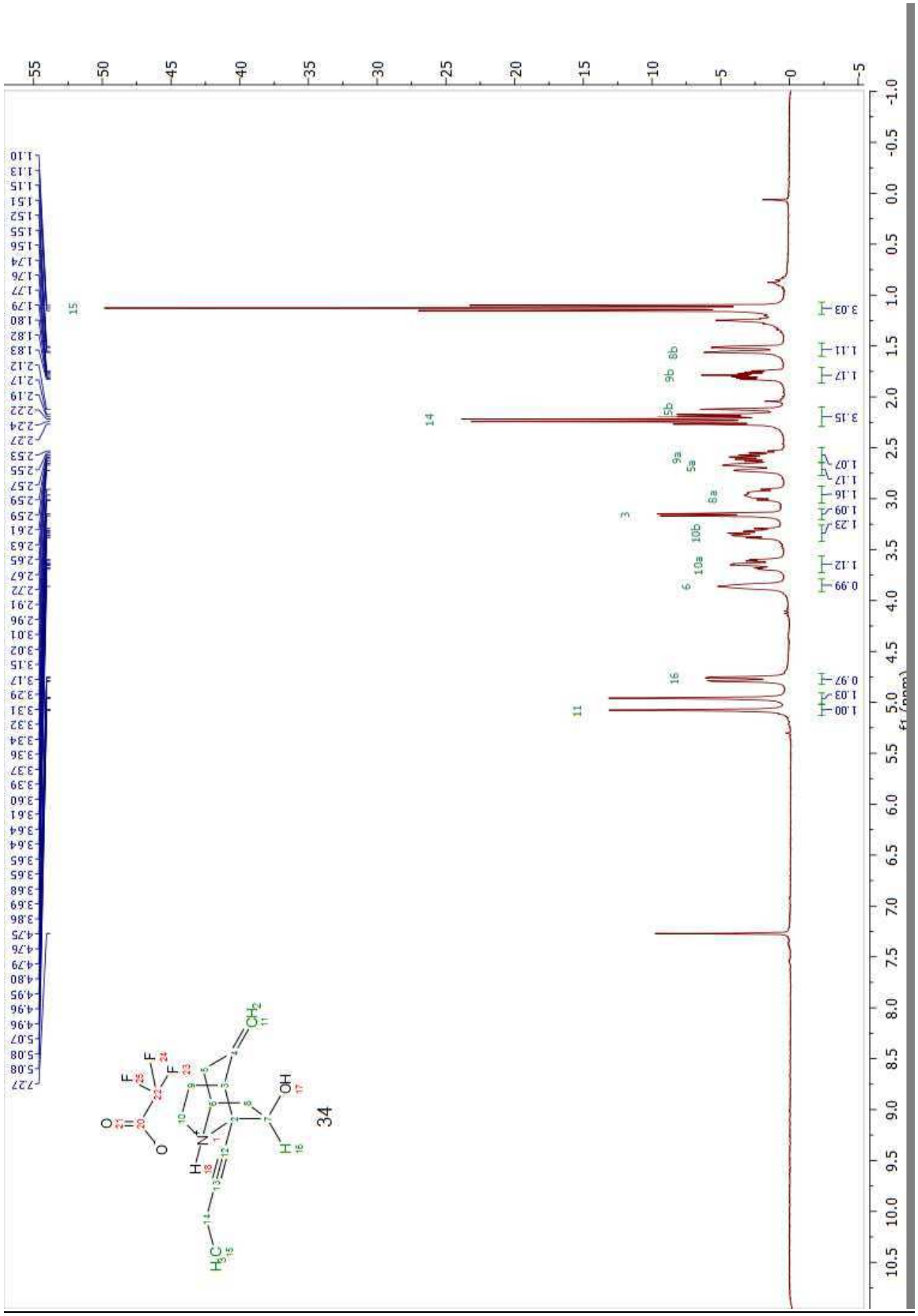

210.46
143.77
110.79
88.37
77.64
77.22
76.80
74.75
57.04
56.11
49.03
43.82
33.45
31.59
13.88
12.69
32
CH2
H3C
N
O

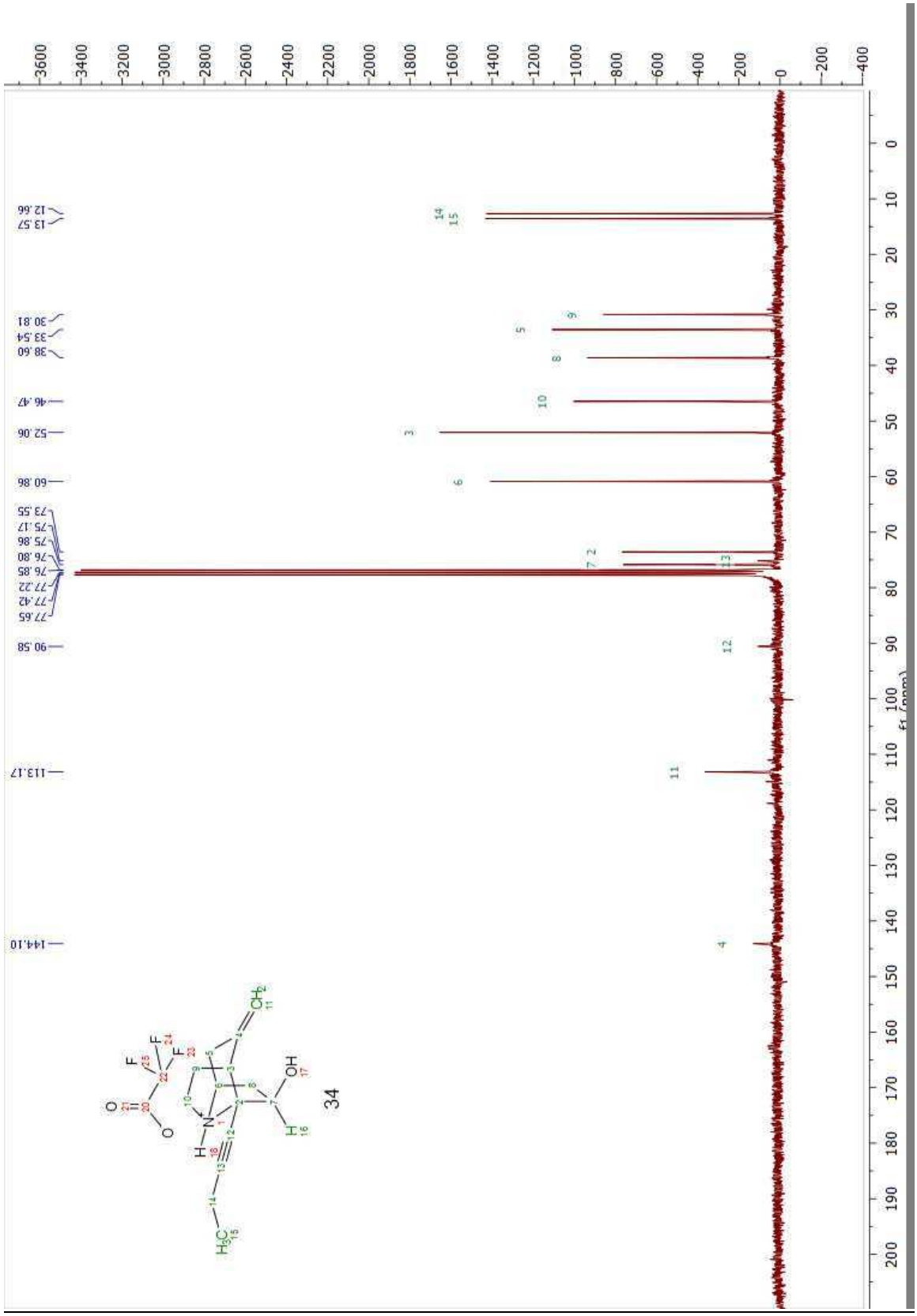

33

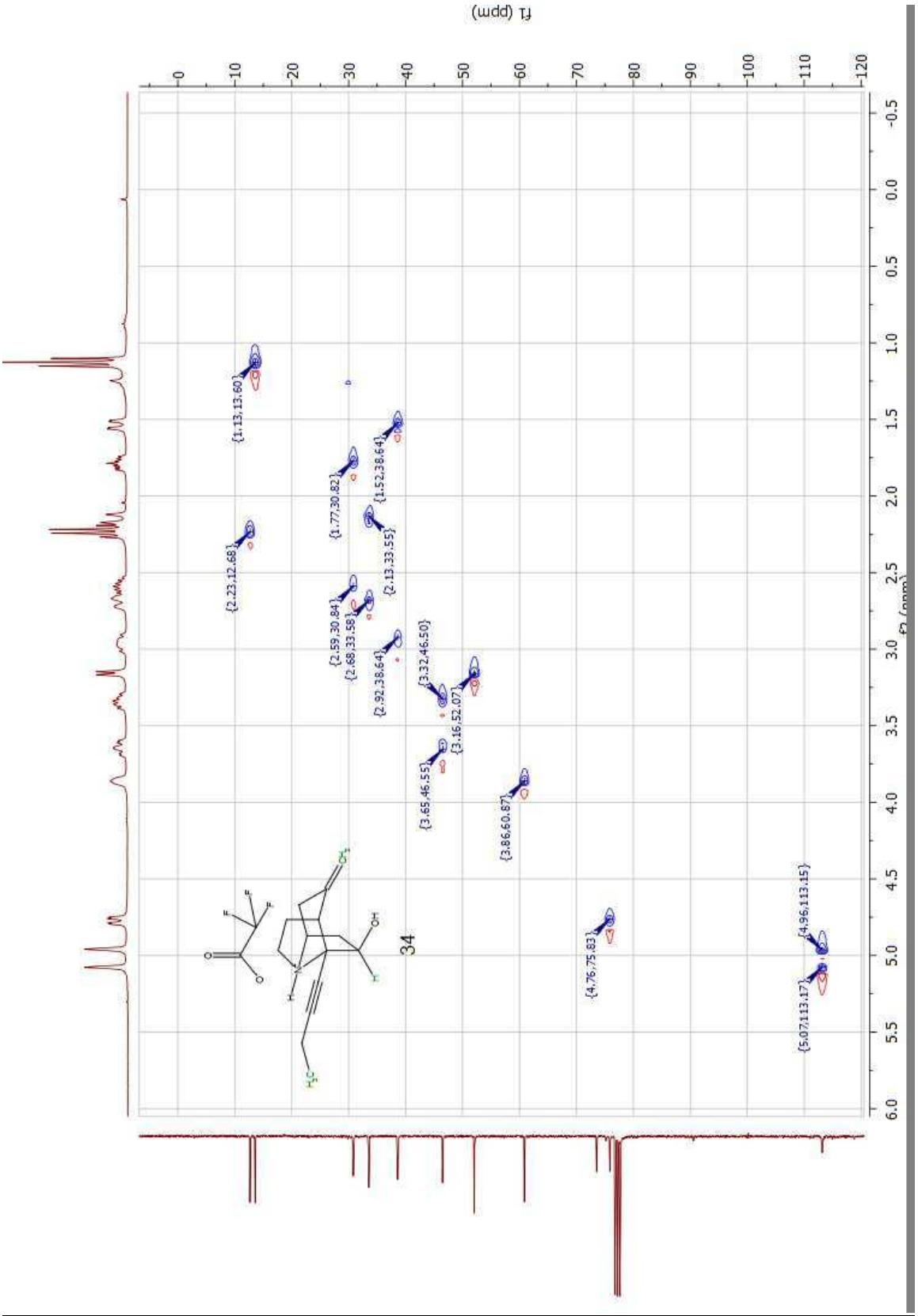

12.70
14.14
32.88
34.77
40.34
47.55
52.13
60.77
72.96
76.79
77.22
77.64
78.24
80.07
85.56
108.96
150.18
33

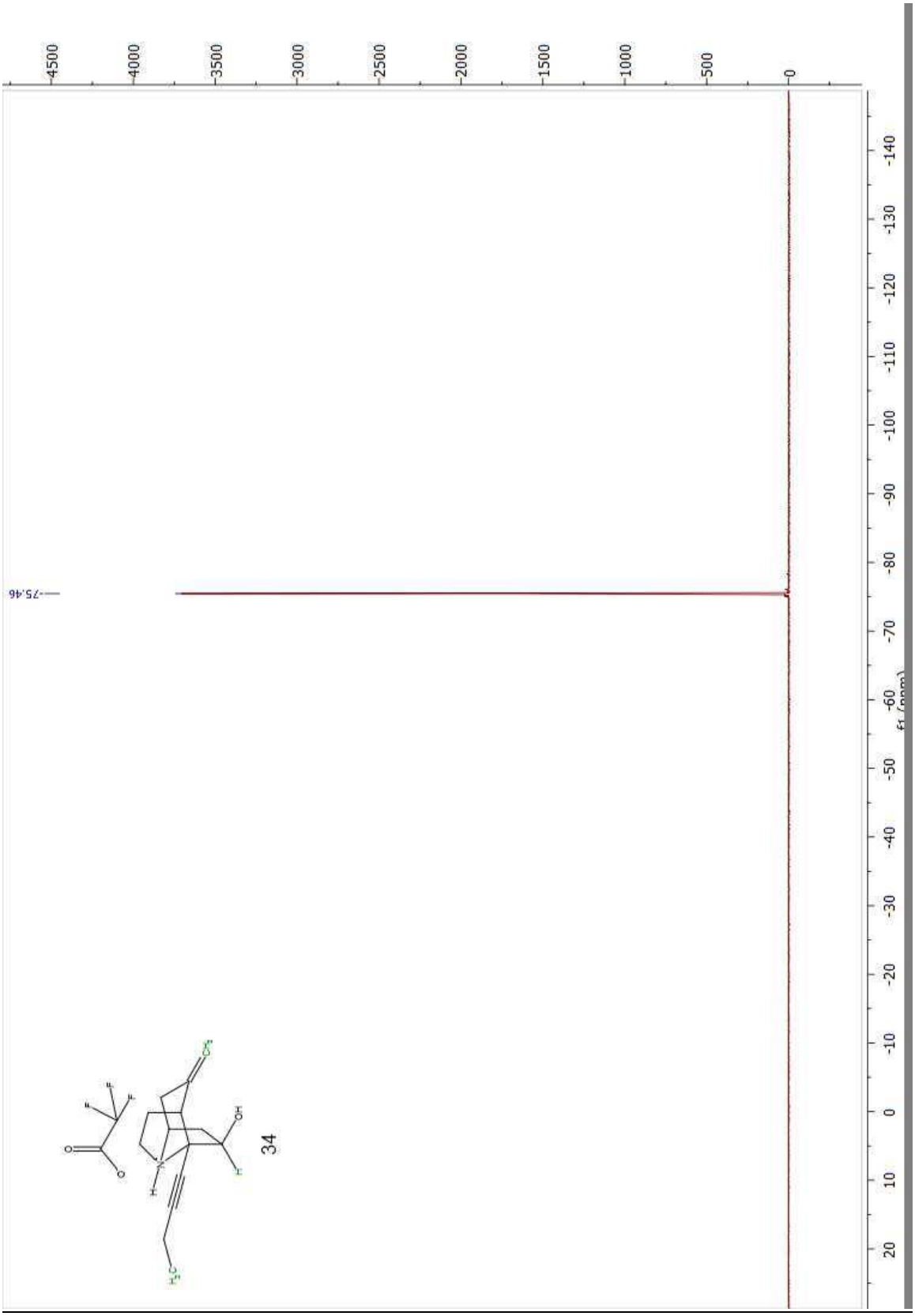

f1 (ppm)
f2 (ppm)
{1.10,14.21}
{1.62,32.94}
{1.29,40.38}
{1.86,34.74}
{2.33,32.93}
{2.18,12.75}
{2.51,34.82}
{2.69,40.44}
{3.03,47.58}
{3.24,47.66}
{2.94,52.16}
{3.35,60.86}
{4.58,78.24}
{4.76,108.94}
{4.91,108.94}
CH2
OH
H
N
H3C
33

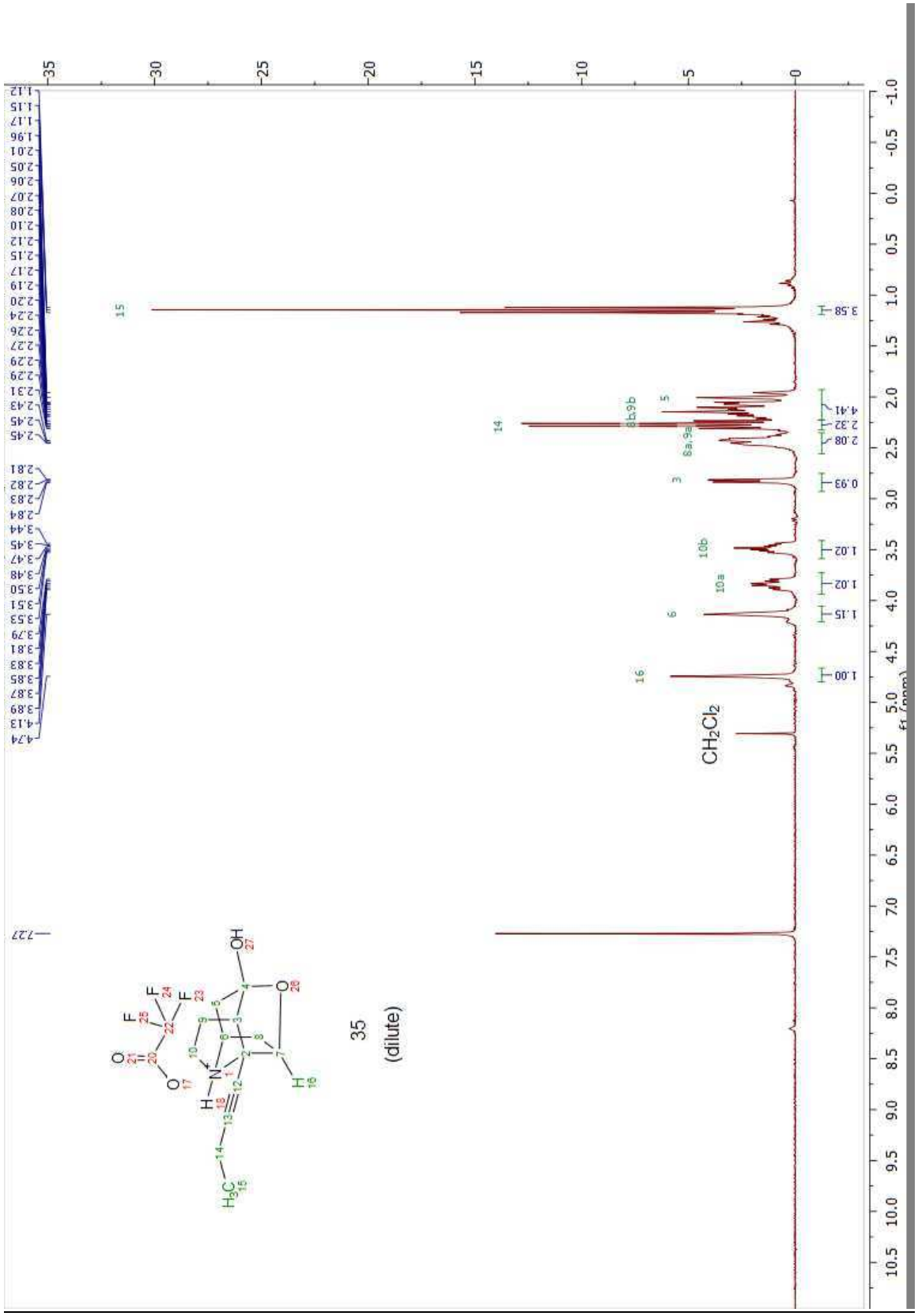

f1 (ppm)
f2 (ppm)
CH2
OH
H
N
H3C
33

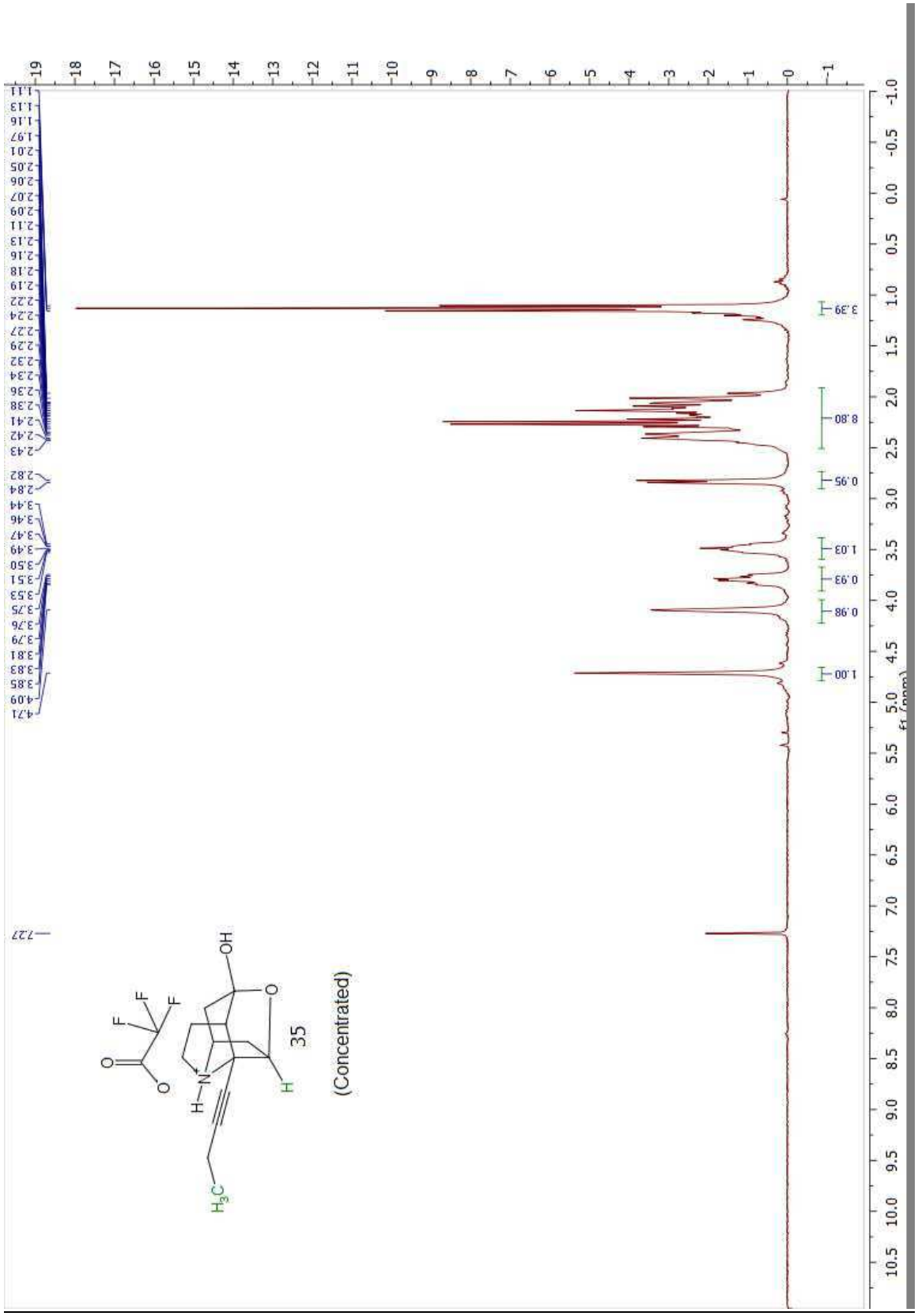

34

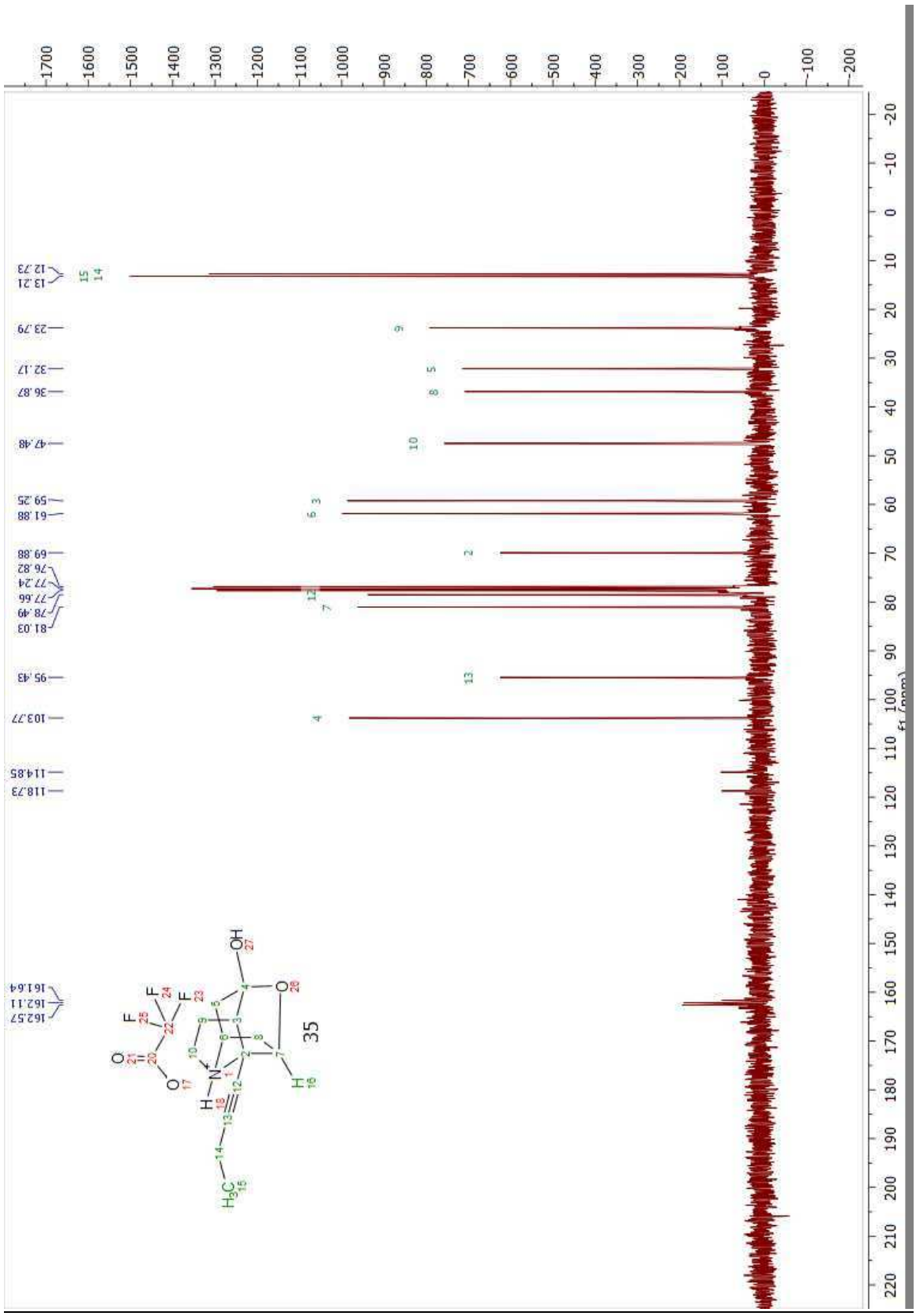

12.66
13.57
30.81
33.54
38.60
46.47
52.06
60.86
73.55
75.17
75.86
76.80
76.85
77.22
77.42
77.65
90.58
113.17
144.10
34

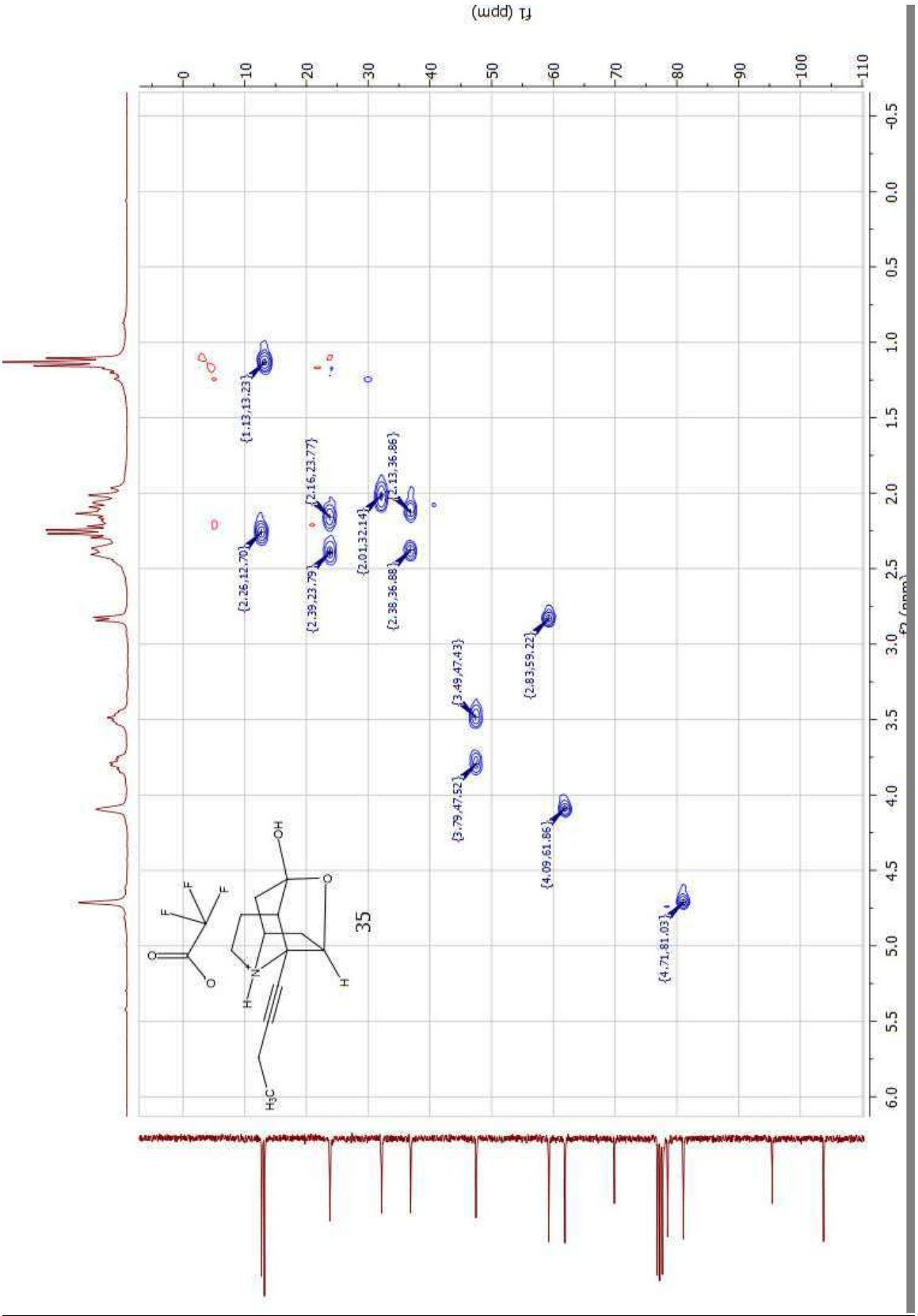

f1 (ppm)
f2 (ppm)
{1.13,13.60}
{2.23,12.68}
{1.77,30.82}
{1.52,38.64}
{2.13,33.55}
{2.59,30.84}
{2.68,33.58}
{2.92,38.64}
{3.32,46.50}
{3.16,52.07}
{3.65,46.55}
{3.86,60.87}
{4.76,75.83}
{4.96,113.15}
{5.07,113.17}
34

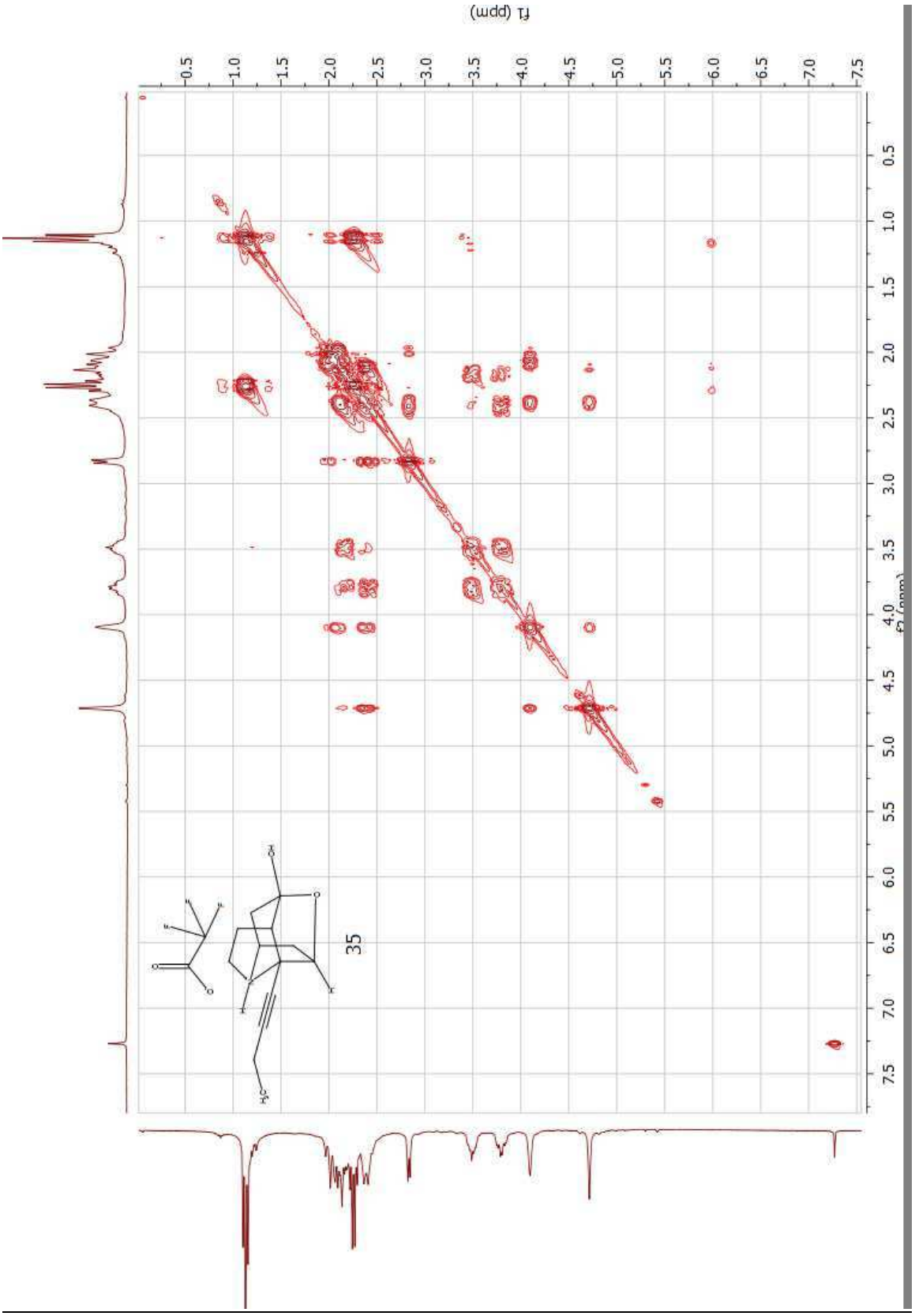

-75.46
f1 (ppm)
34

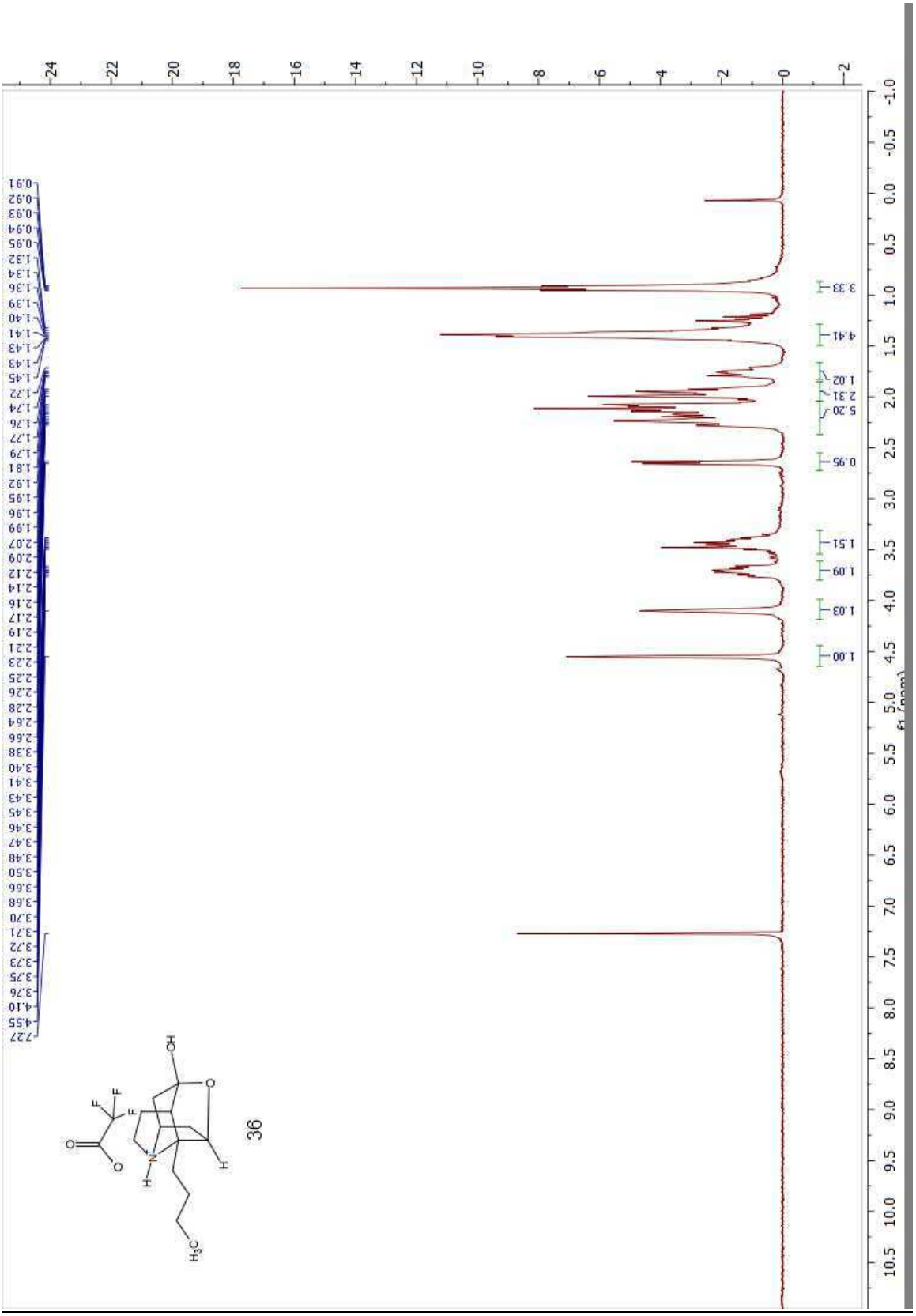

35
(dilute)
CH2Cl2

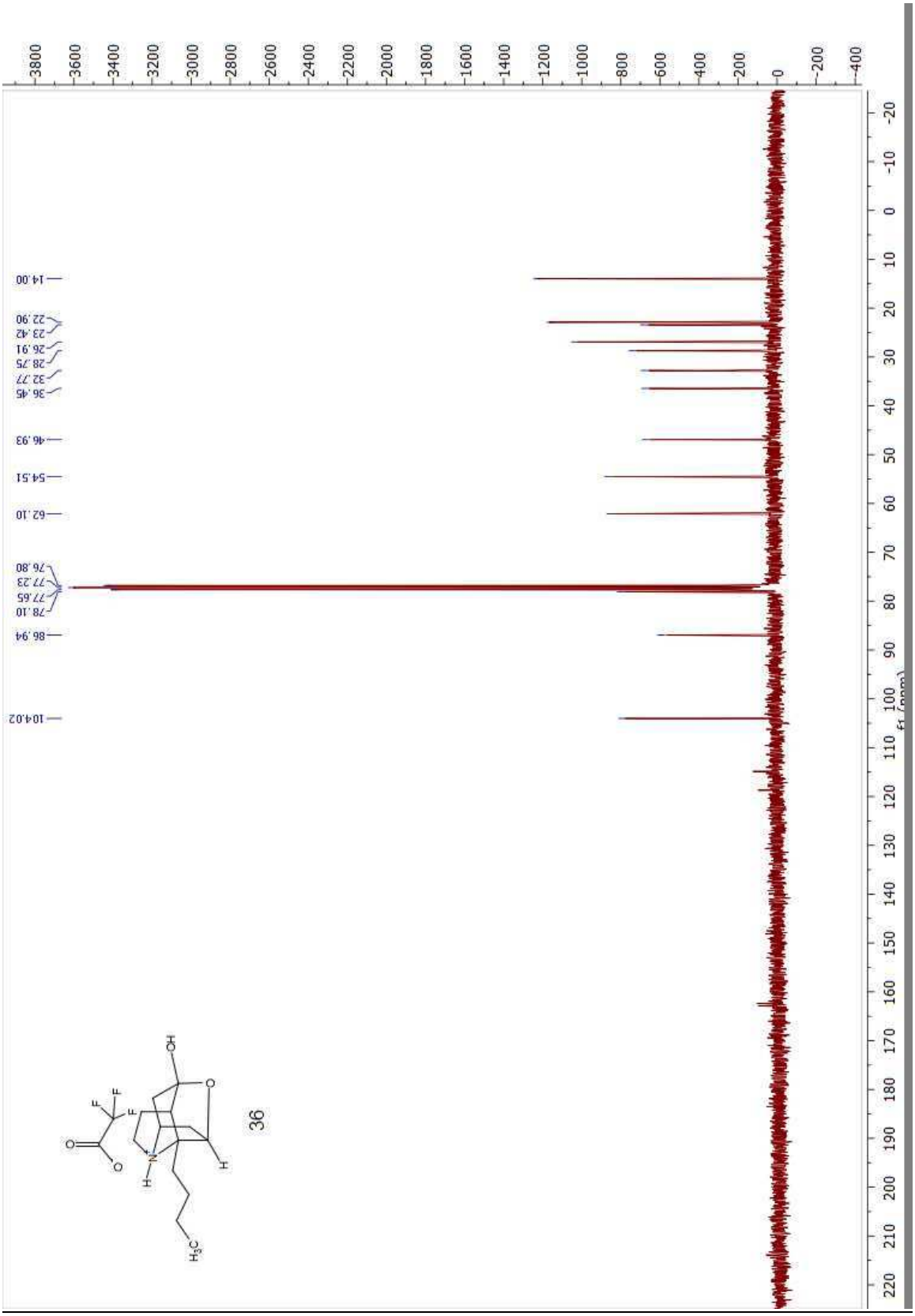

35
(Concentrated)

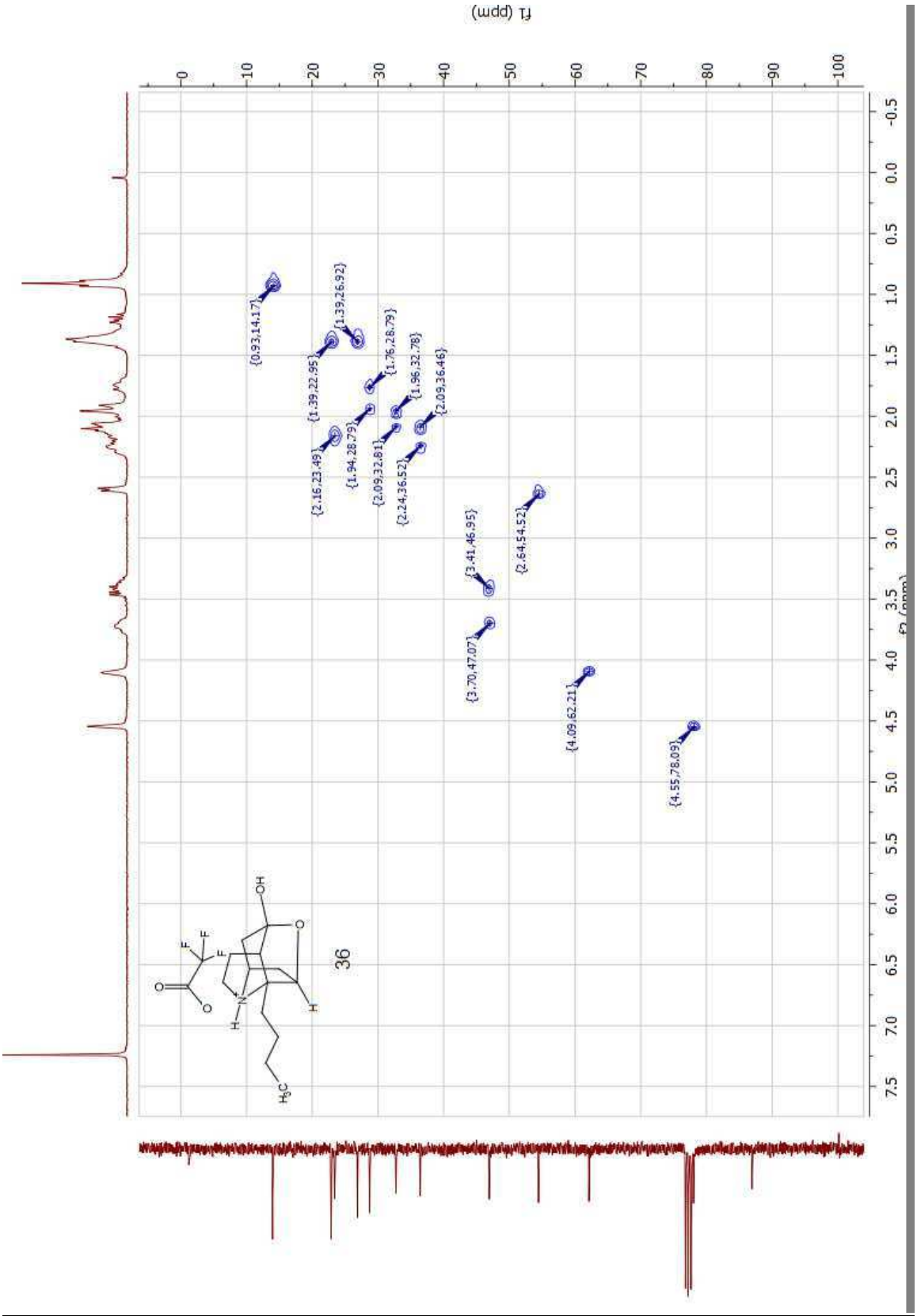

13.21
12.73
23.79
32.17
36.87
47.48
59.25
61.88
69.88
76.82
77.24
77.66
78.49
81.03
95.43
103.77
114.85
118.73
162.57
162.11
161.64
35

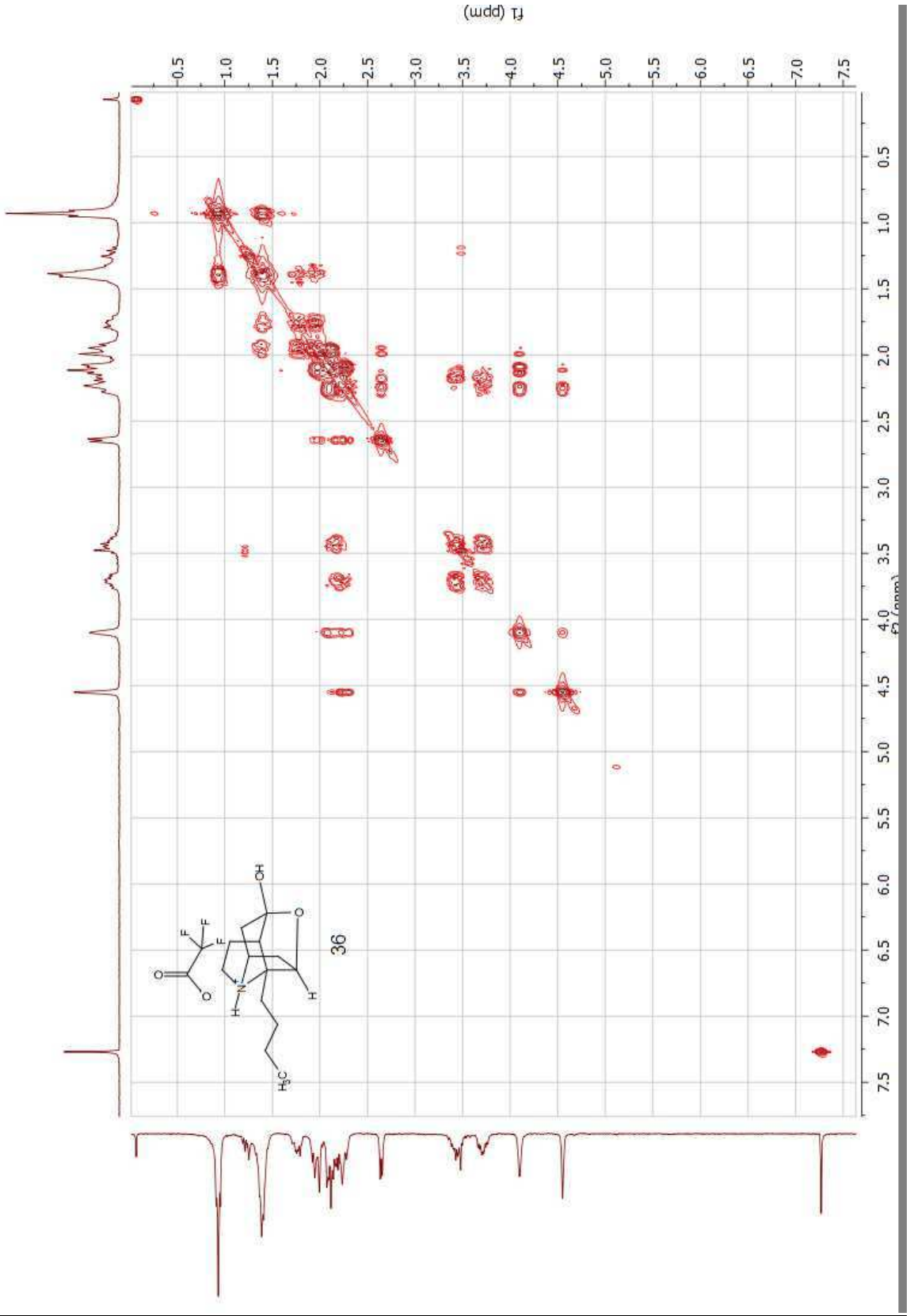

f1 (ppm)
f2 (ppm)
{1.13,13.23}
{2.26,12.70}
{2.39,23.79}
{2.16,23.77}
{2.01,32.14}
{2.13,36.86}
{2.38,36.88}
{3.49,47.43}
{3.79,47.52}
{2.83,59.22}
{4.09,61.86}
{4.71,81.03}
35

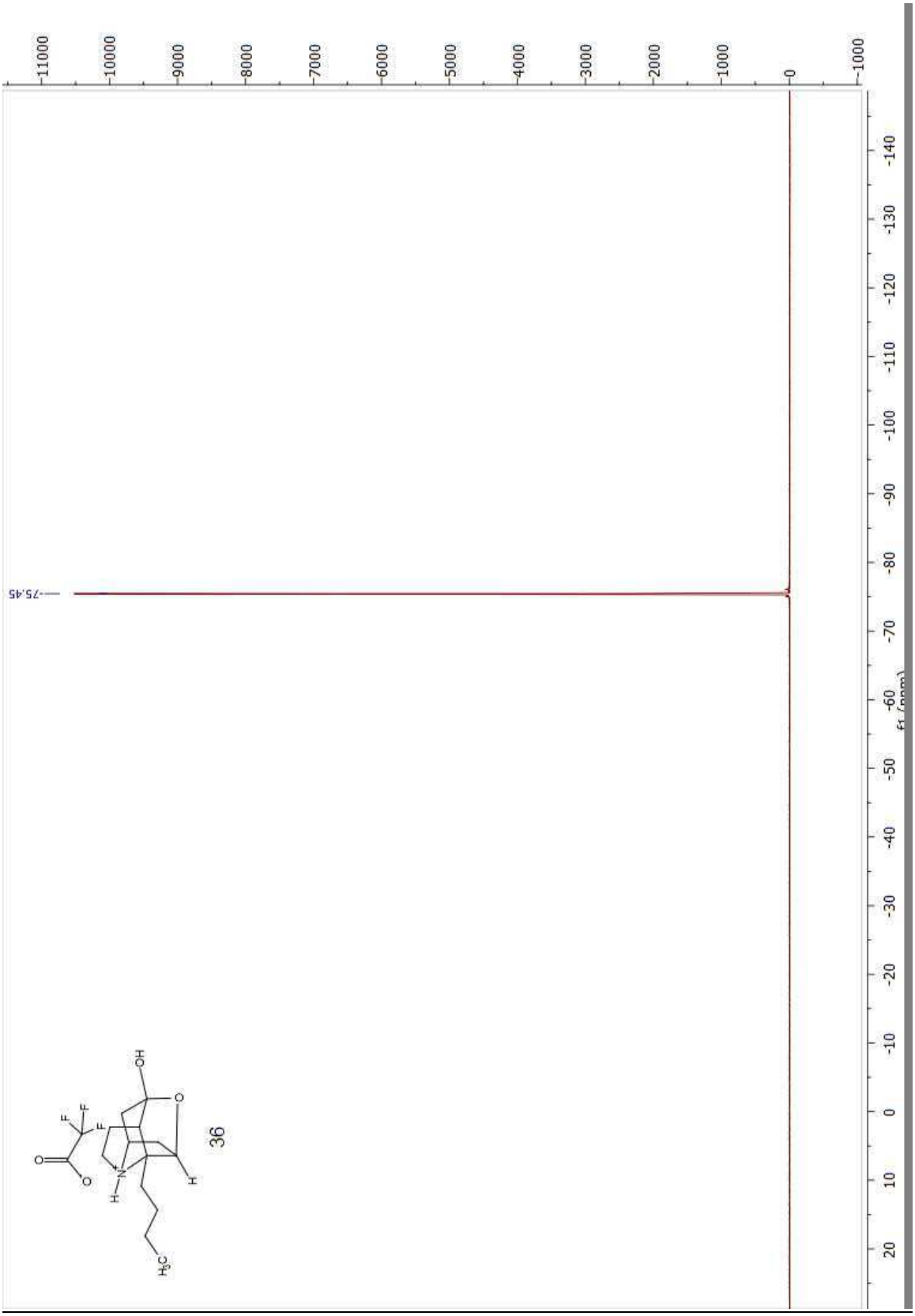

f1 (ppm)
f2 (ppm)
35

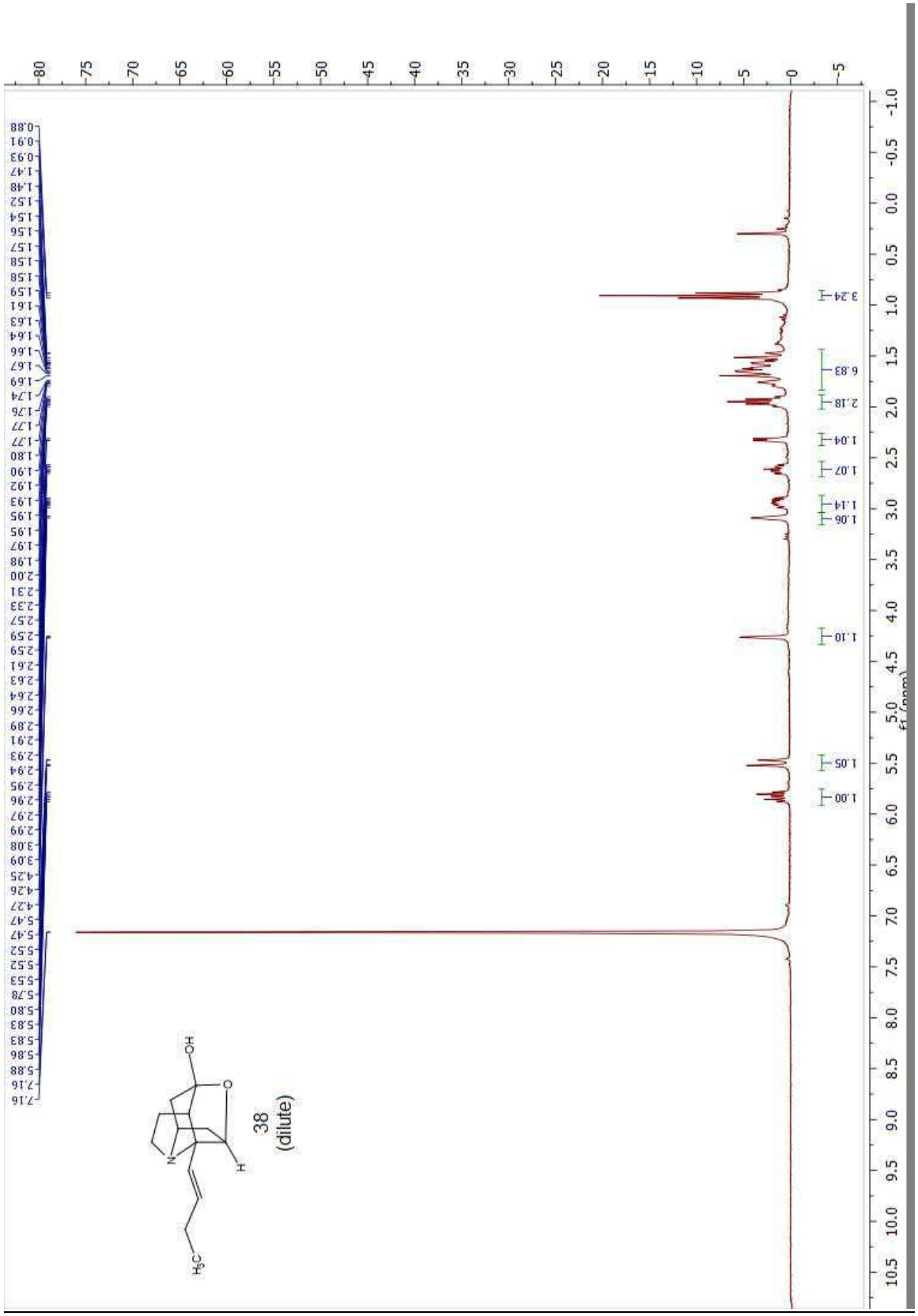

36

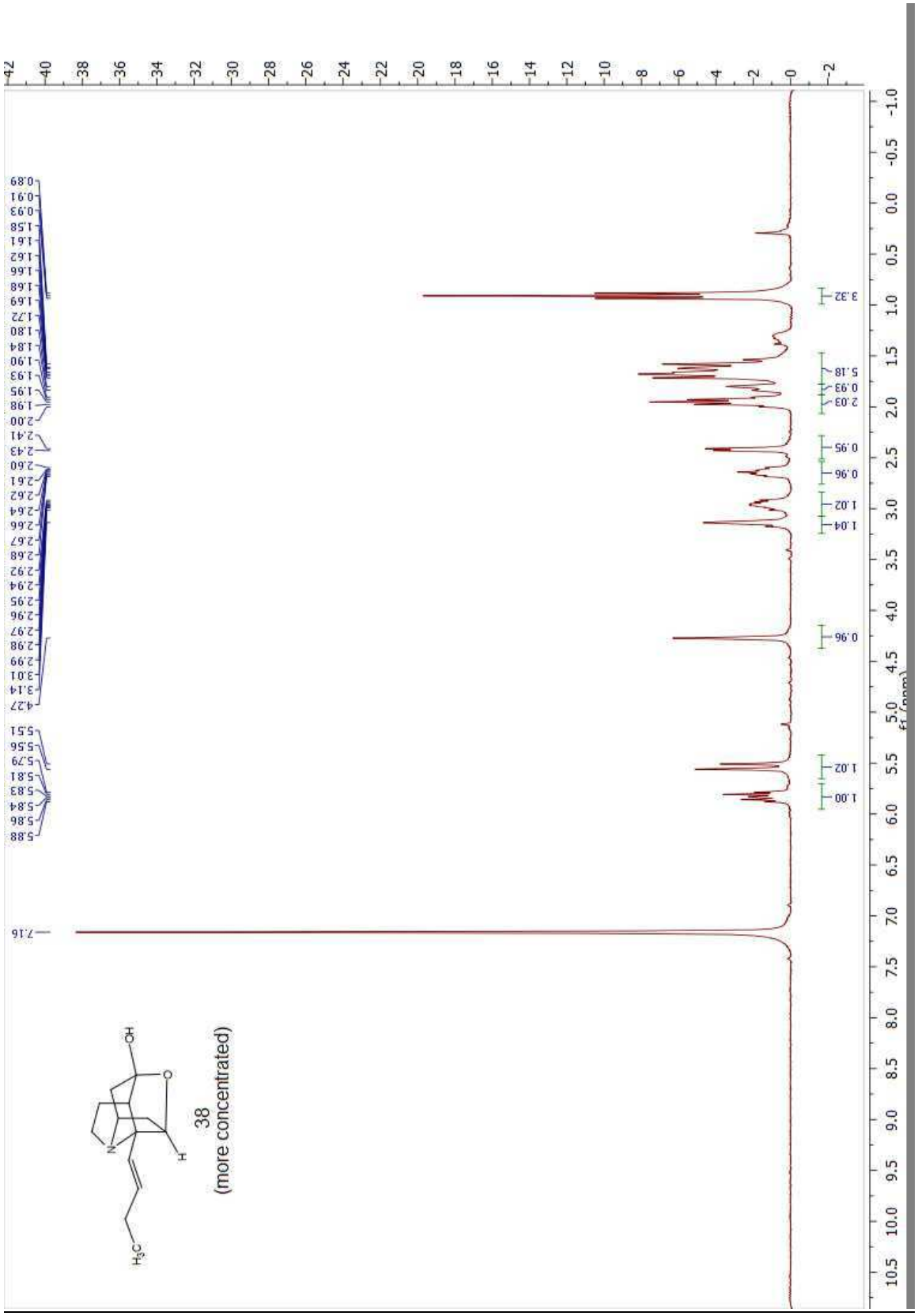

14.00
22.90
23.42
26.91
28.75
32.77
36.45
46.93
54.51
62.10
76.80
77.23
77.65
78.10
86.94
104.02
f1 (ppm)
36

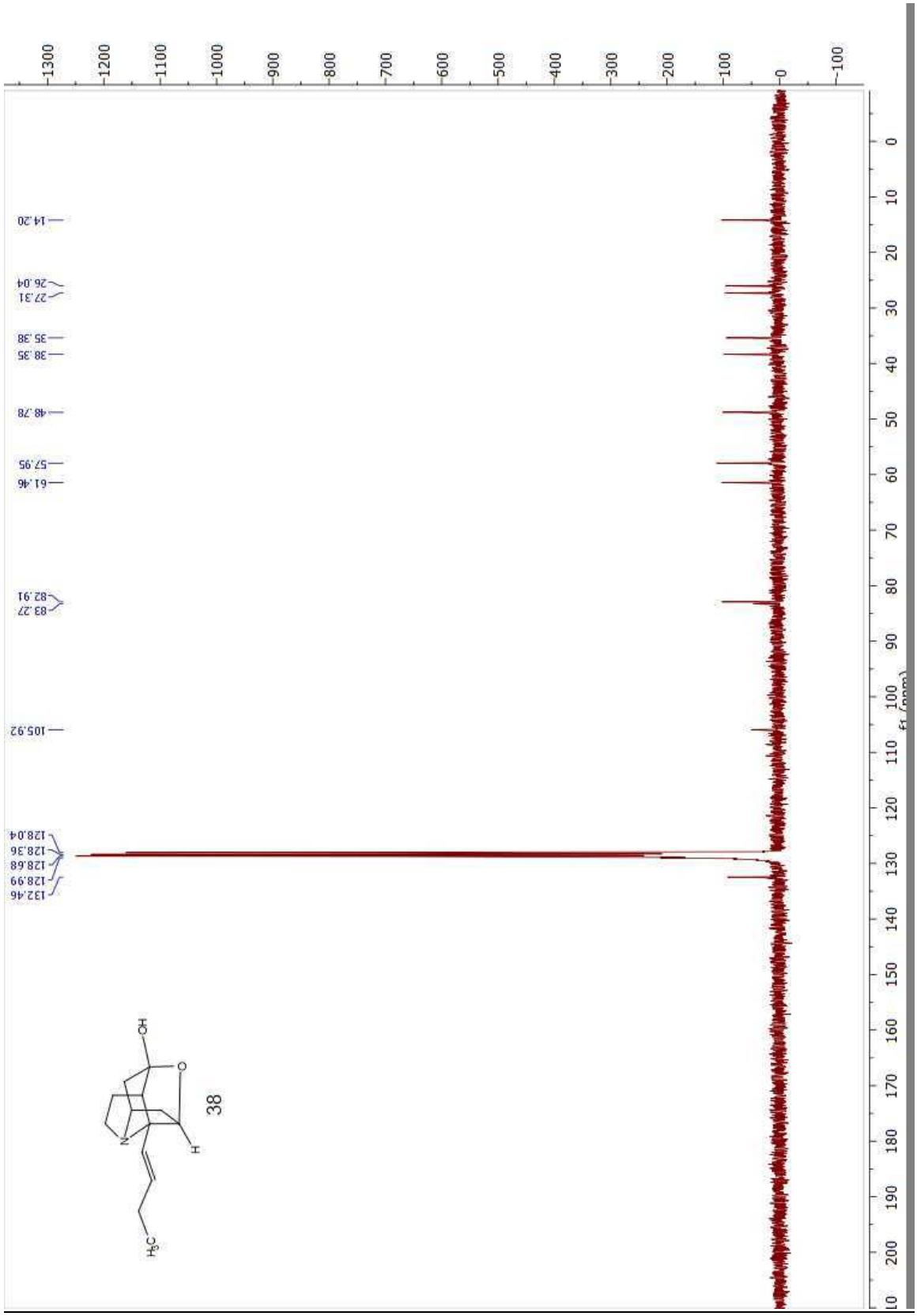

f1 (ppm)
{0.93,14.17}
{1.39,22.95}
{1.39,26.92}
{1.76,28.79}
{1.96,32.78}
{2.09,36.46}
{2.16,23.49}
{1.94,28.79}
{2.09,32.81}
{2.24,36.52}
{3.41,46.95}
{2.64,54.52}
{3.70,47.07}
{4.09,62.21}
{4.55,78.09}
OH
O
F
F
F
O
O
H
N+
H
H3C
36

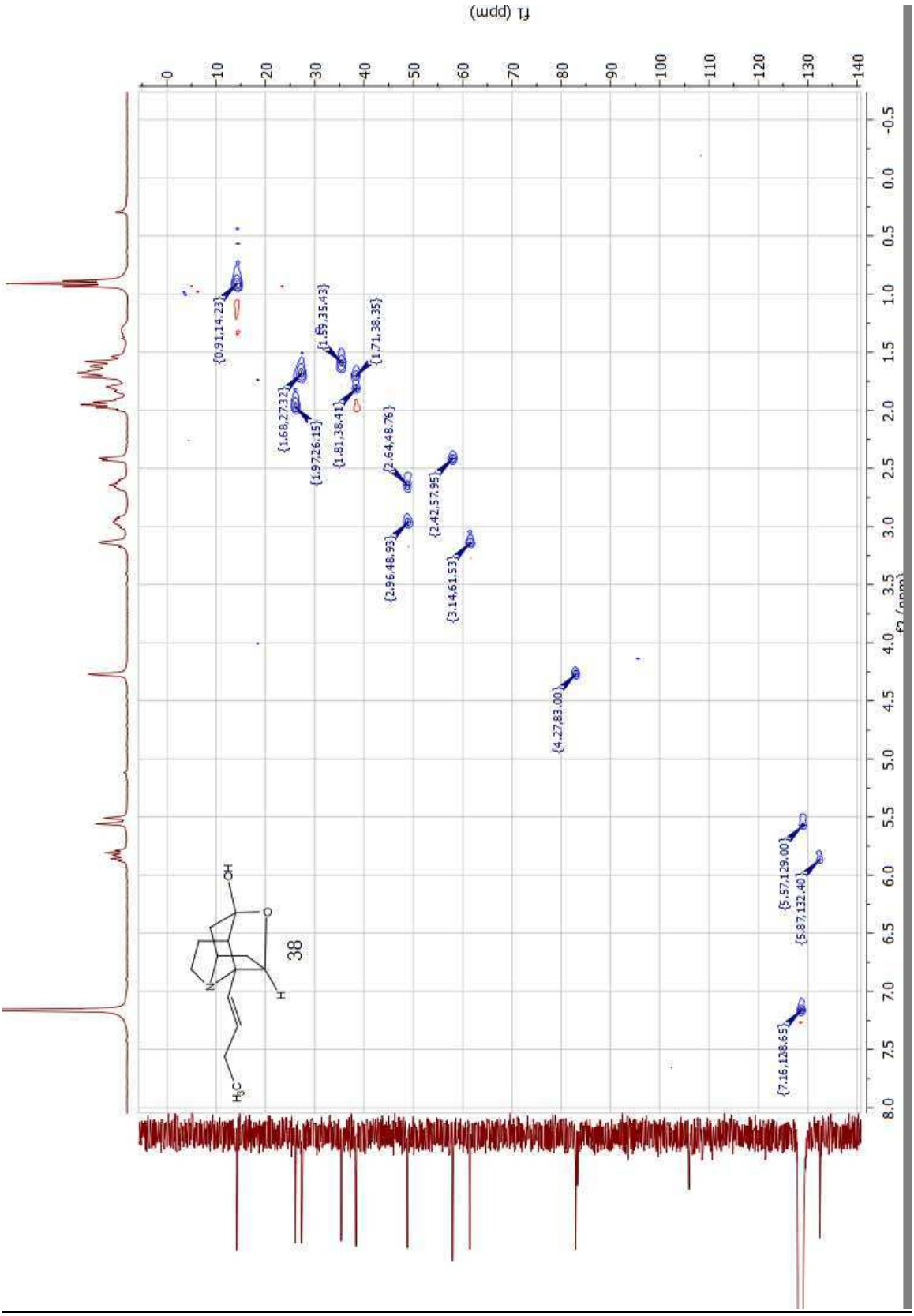

f1 (ppm)
f2 (ppm)
36

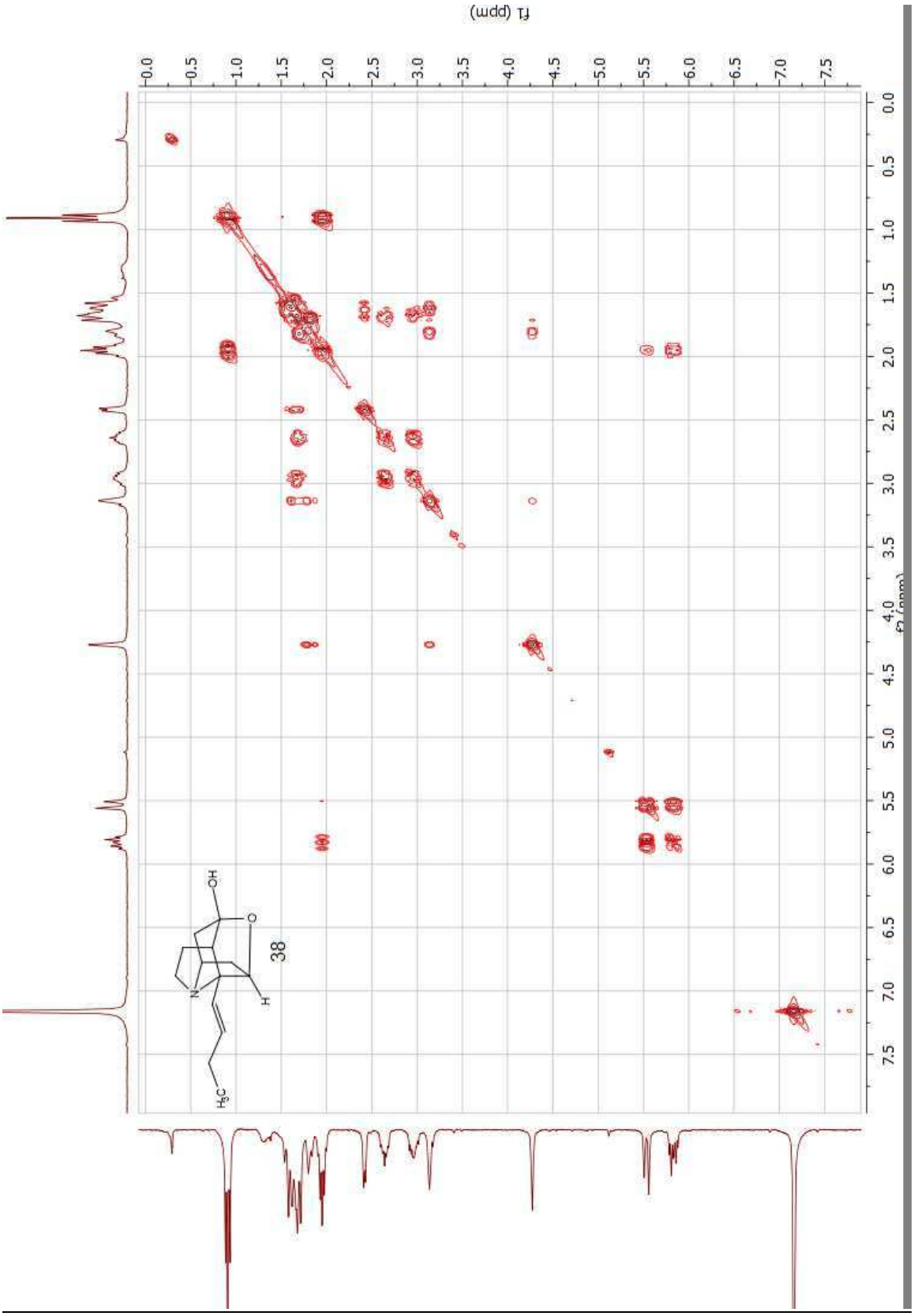

-75.45
f1 (ppm)
36


38
(dilute)
f1 (ppm)


38
(more concentrated)


14.20
26.04
27.31
35.38
38.35
48.78
57.95
61.46
82.91
83.27
105.92
128.04
128.36
128.68
128.99
132.46
OH
O
N
H
H3C
38
f1 (ppm)

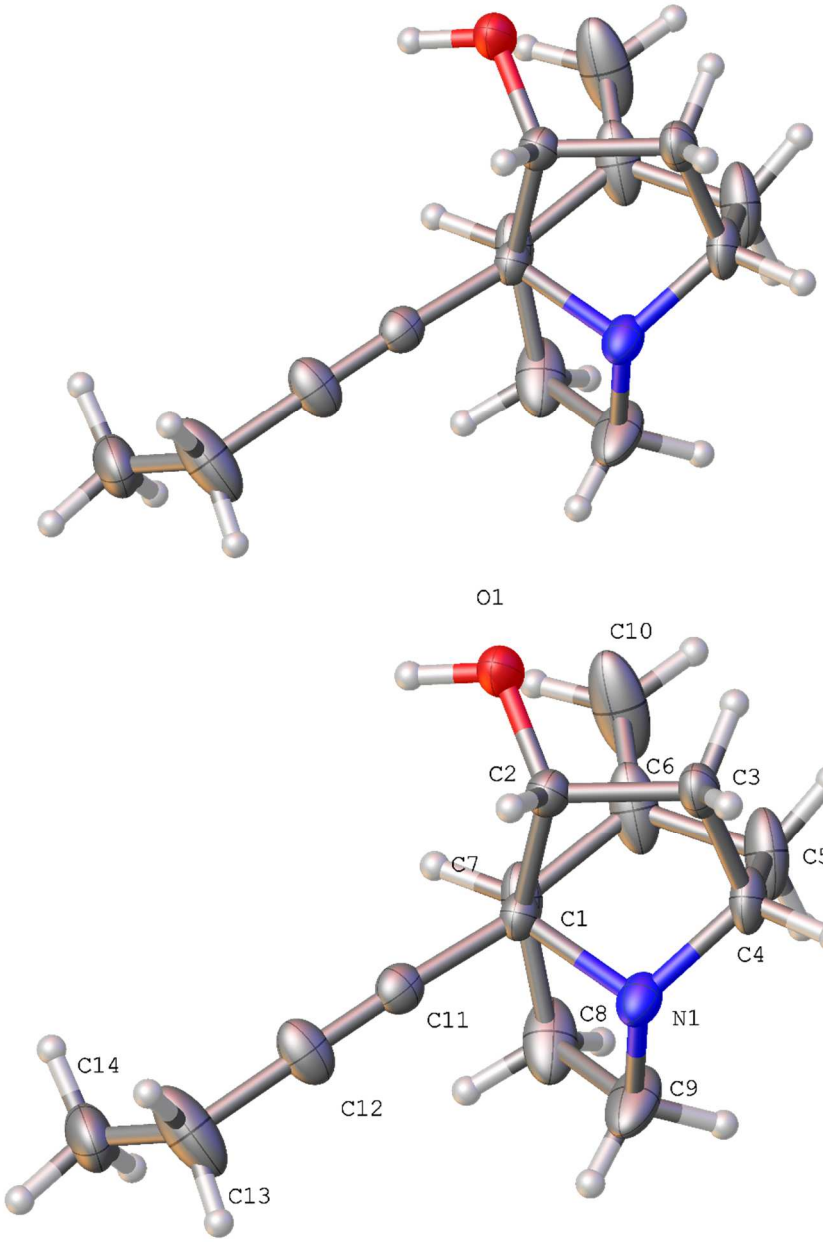

f1 (ppm)
f2 (ppm)
{0.91,14.23}
{1.59,35.43}
{1.71,38.35}
{1.68,27.32}
{1.97,26.15}
{1.81,38.41}
{2.64,48.76}
{2.42,57.95}
{2.96,48.93}
{3.14,61.53}
{4.27,83.00}
{5.57,129.00}
{5.87,132.40}
{7.16,128.65}
OH
O
N
H
H3C
38

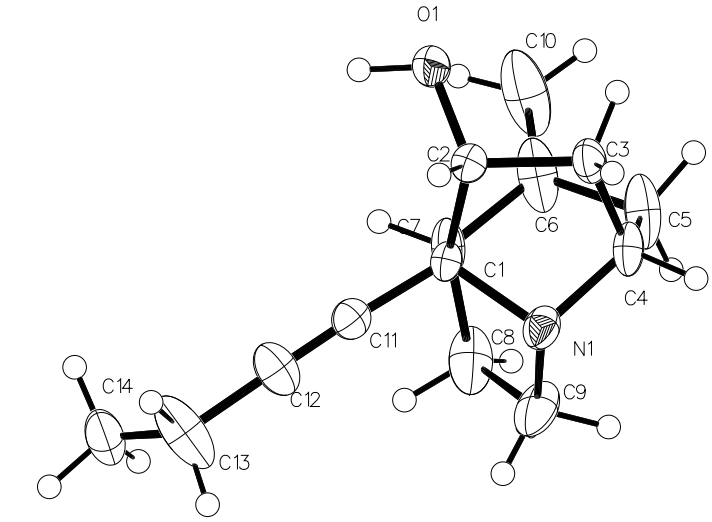

f1 (ppm)
f2 (ppm)
38

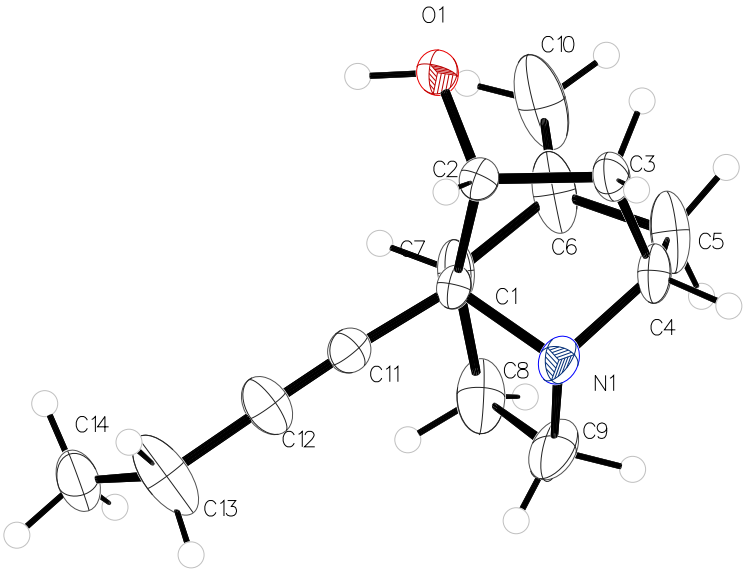
APPENDIX C:

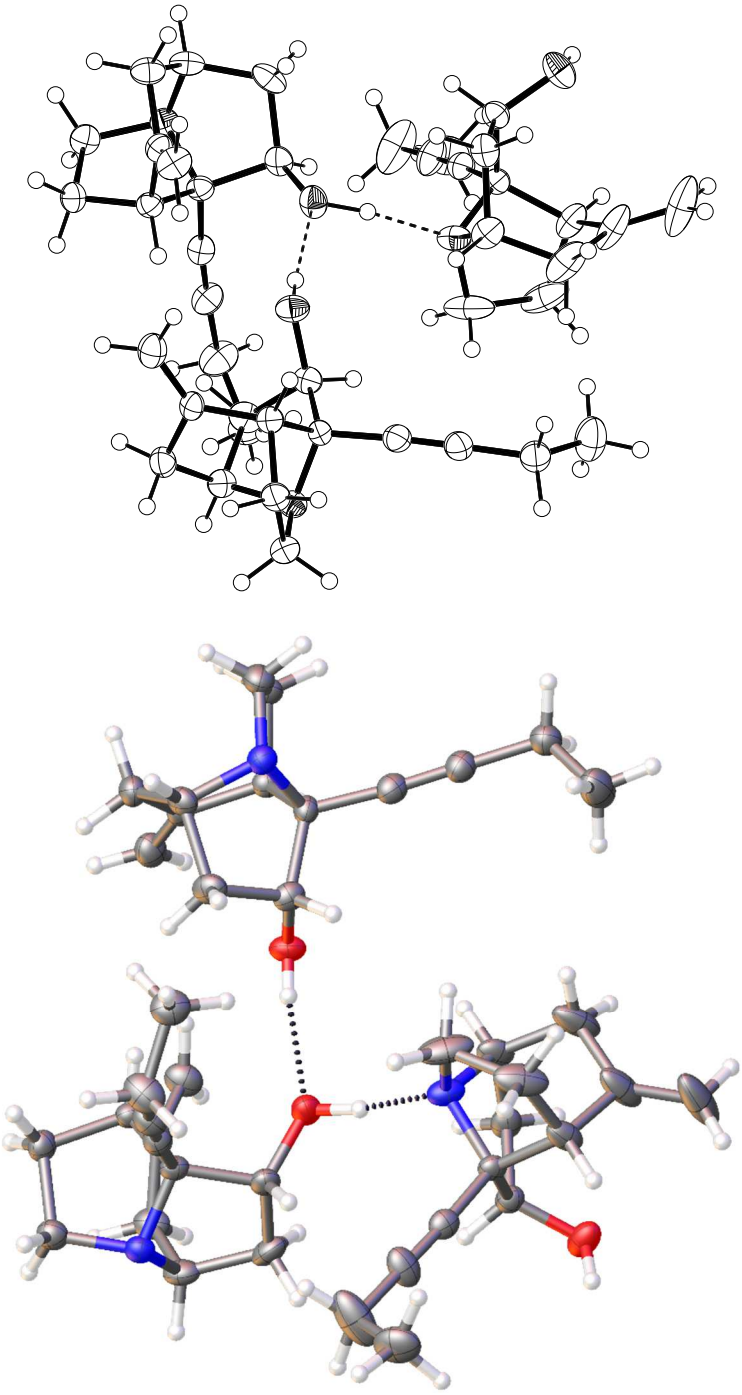
X-RAY CRYSTALLOGRAPHY DATA FOR AZATRICYCLODECANE **33**

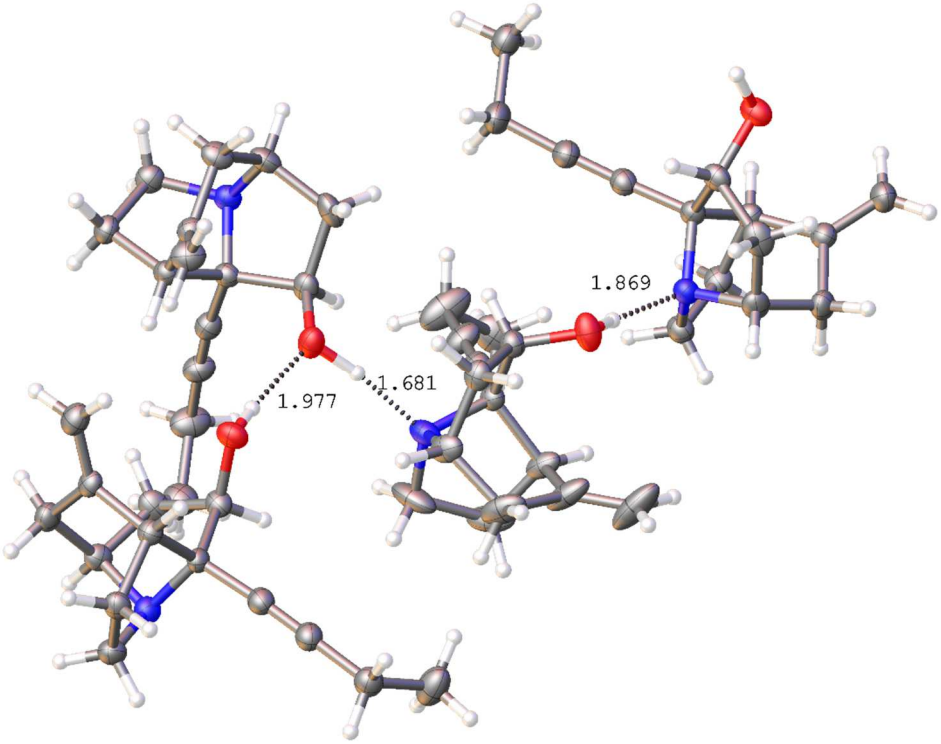
MSU_BA2

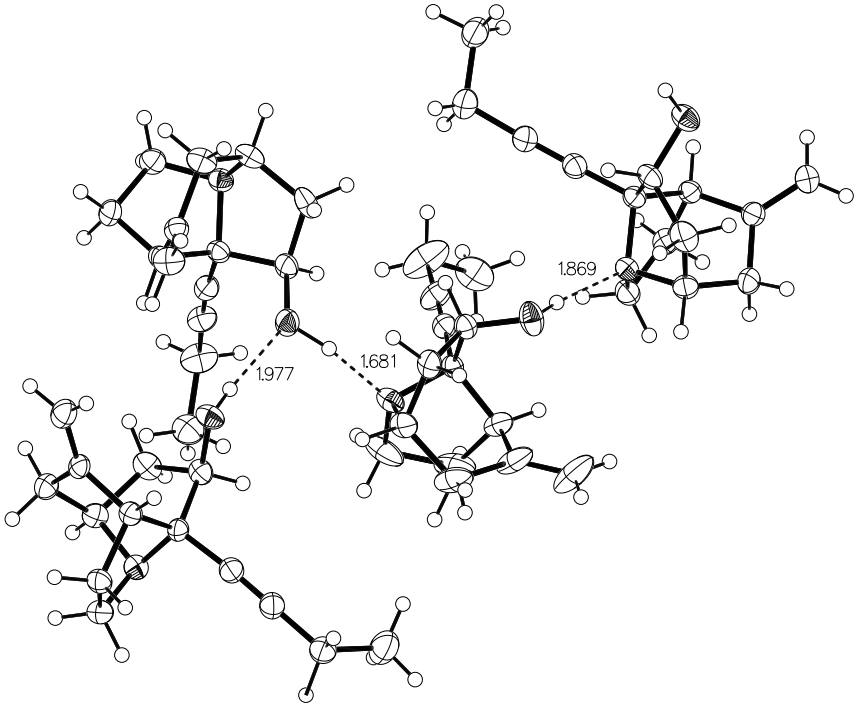


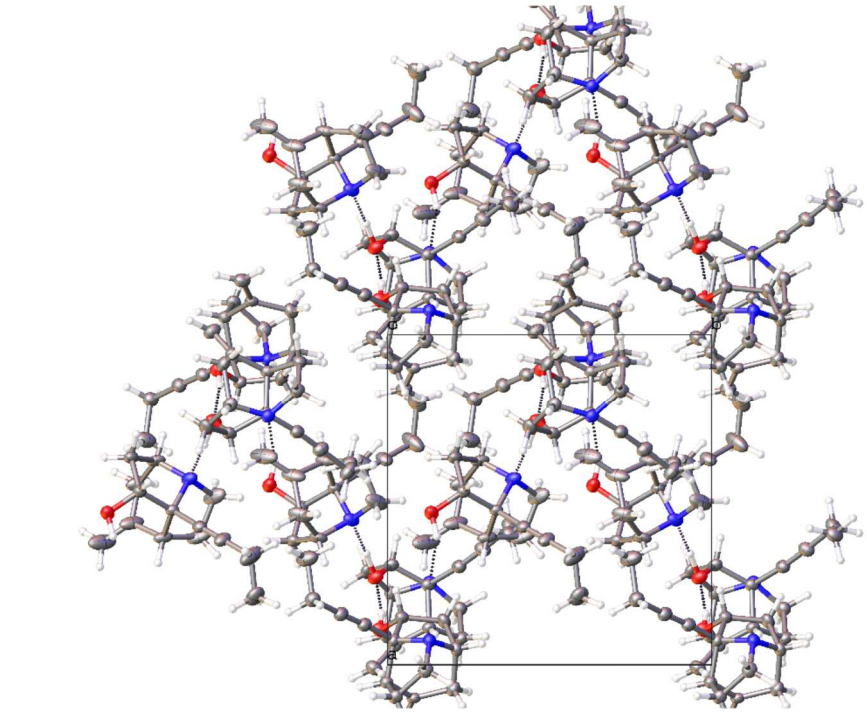

O1
C10
C2
C3
C6
C5
C7
C1
C4
C11
C8
N1
C14
C12
C9
C13

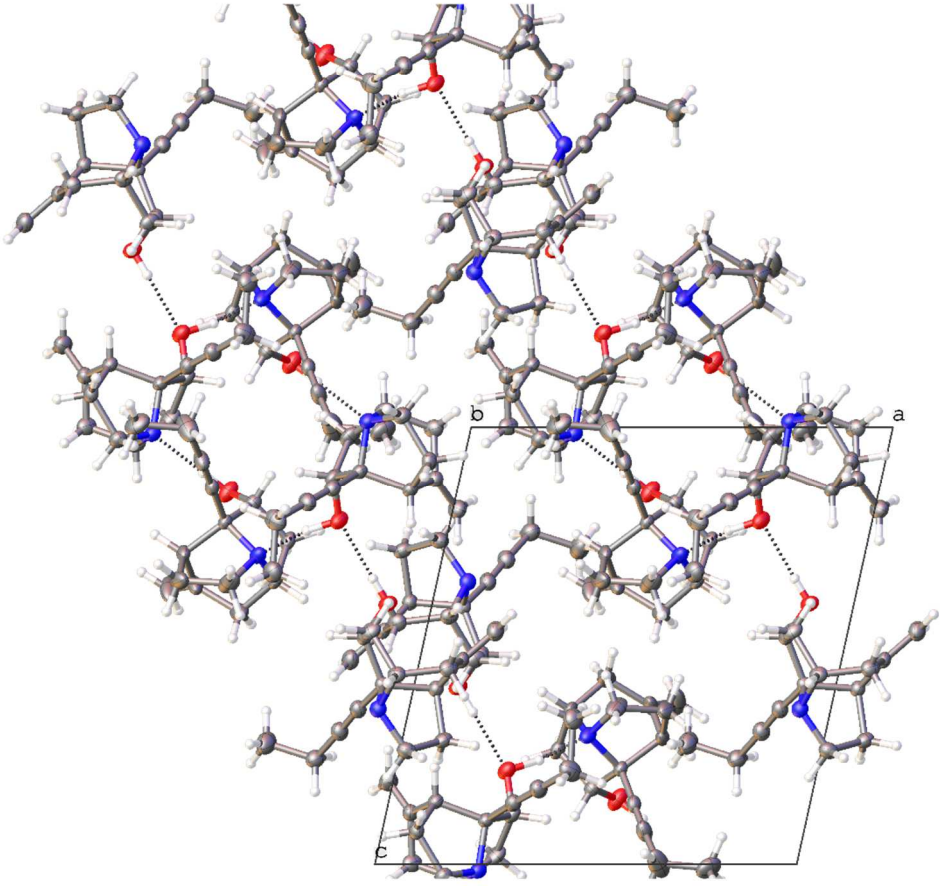

O1
C10
C2
C3
C6
C5
C7
C1
C4
C11
C8
N1
C14
C12
C9
C13

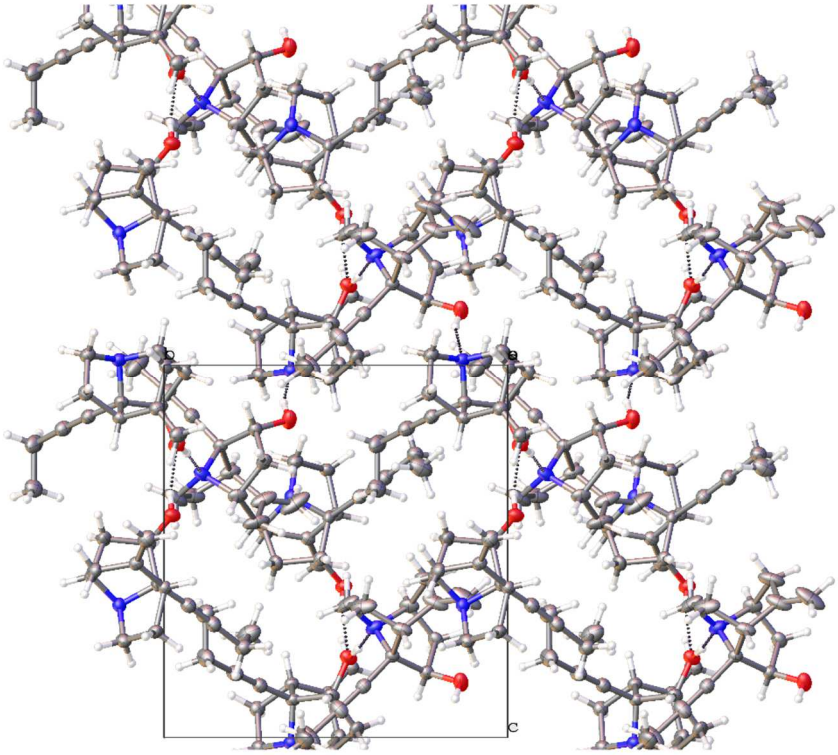



1.869
1.681
1.977


1.869
1.681
1.977




b
a
c


b
a
c

MSU_BA2

Table 1 Crystal data and structure refinement for MSU_BA2.

Identification code	MSU_BA2
Empirical formula	$C_{42}H_{57}N_3O_3$
Formula weight	651.90
Temperature/K	120.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	12.2572(9)
b/Å	11.7318(9)
c/Å	13.0251(10)
α/°	90
β/°	102.397(4)
γ/°	90
Volume/Å^3	1829.3(2)
Z	2
ρ_{calc}g/cm^3	1.184
μ/mm^{-1}	0.573
F(000)	708.0
Crystal size/mm^3	0.25 × 0.221 × 0.076
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.948 to 133.29
Index ranges	$-14 \leq h \leq 14$, $-13 \leq k \leq 13$, $-15 \leq l \leq 15$
Reflections collected	58666
Independent reflections	6436 [R_{int} = 0.0699, R_{sigma} = 0.0441]
Data/restraints/parameters	6436/1/448
Goodness-of-fit on F^2	1.100
Final R indexes [I>=2σ (I)]	R_1 = 0.0411, wR_2 = 0.0864
Final R indexes [all data]	R_1 = 0.0595, wR_2 = 0.0931
Largest diff. peak/hole / e Å^{-3}	0.30/-0.26
Flack parameter	0.00(9)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for MSU_BA2. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1"	1049.4(17)	4769.3(18)	5953.2(17)	30.6(5)
O1'	2637.3(17)	4631.6(18)	7858.8(15)	31.7(5)
O1	5416.8(17)	1358.9(17)	8517.5(17)	36.1(5)
N2"	731.1(18)	6301(2)	3548.3(17)	25.6(6)
N1'	2483.9(18)	6312(2)	10145.6(17)	25.5(6)
N1	4380.7(19)	3883(2)	7055.1(18)	29.6(6)
C7'	1114(2)	6288(3)	8564(2)	23.7(6)
C7"	-533(2)	4974(2)	4012(2)	23.9(7)
C1'	2403(2)	6246(3)	8990(2)	23.3(7)
C2	4760(2)	2346(2)	8260(2)	25.4(7)
C11	5826(2)	4195(3)	8623(2)	25.9(7)
C1"	741(2)	5200(2)	4100(2)	23.0(7)
C6"	-1012(2)	5812(2)	4667(2)	23.7(7)
C9"	-164(2)	6180(3)	2598(2)	31.3(7)
C6'	576(2)	5213(2)	8819(2)	26.0(7)
C11'	2962(2)	7210(3)	8602(2)	27.4(7)
C8"	-975(2)	5251(3)	2835(2)	28.2(7)
C2'	3007(2)	5121(2)	8871(2)	27.2(7)
C2"	1435(2)	5451(2)	5209(2)	26.2(7)
C9'	1694(2)	7225(3)	10273(2)	29.4(7)
C11"	1206(2)	4295(3)	3542(2)	28.6(7)
C1	5330(2)	3358(2)	7818(2)	22.5(7)
C4"	471(2)	7122(3)	4334(2)	26.1(7)
C12	6216(2)	4902(3)	9243(3)	36.2(8)
C3	3738(2)	2086(3)	7386(2)	29.1(7)
C4'	2136(2)	5137(3)	10387(2)	30.6(7)
C4	3835(2)	2862(3)	6475(2)	31.7(8)
C8'	808(2)	7286(3)	9230(2)	28.0(7)
C3"	1311(3)	6743(2)	5326(2)	31.2(8)
C12'	3486(3)	7939(3)	8279(2)	32.6(8)
C5'	880(2)	4932(3)	9973(2)	30.9(7)
C12"	1528(2)	3566(3)	3036(2)	30.5(7)
C10"	-1644(2)	5508(3)	5326(2)	34.8(8)
C3'	2817(3)	4394(3)	9797(2)	34.5(8)
C5"	-728(2)	7026(3)	4474(2)	30.1(7)
C13"	1966(3)	2691(3)	2411(2)	33.0(8)

C7	6159(2)	3076(3)	7107(2)	32.7(8)
C10'	-104(2)	4587(3)	8112(2)	35.3(8)
C14'	3941(3)	8797(3)	6678(3)	40.1(8)
C13'	4147(3)	8787(3)	7864(3)	43.3(9)
C5	4529(3)	2316(4)	5766(2)	49.8(10)
C6	5717(3)	2098(4)	6378(3)	47.7(10)
C9	4918(3)	4663(3)	6424(3)	51.3(10)
C8	6120(3)	4188(4)	6485(3)	51(1)
C14	7931(3)	5913(3)	10077(3)	49.8(10)
C14"	3205(3)	2524(3)	2770(3)	51.3(10)
C13	6719(3)	5787(4)	9983(3)	63.5(12)
C10	6301(3)	1190(4)	6275(3)	69.0(13)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for MSU_BA2. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1"	29.4(11)	36.6(13)	23.1(11)	2.7(10)	-0.1(10)	-3.7(10)
O1'	26.3(11)	36.5(13)	29.6(12)	-5.7(10)	-0.2(10)	5.4(10)
O1	28.8(11)	27.9(12)	45.1(13)	-3.0(11)	-6.6(11)	1.4(10)
N2"	25.5(13)	24.1(14)	27.0(13)	0.7(12)	5.2(11)	-1.6(11)
N1'	24.7(12)	27.9(14)	22.6(13)	-1.2(12)	2.2(11)	-1.8(11)
N1	24.8(13)	36.9(16)	25.6(13)	9.0(12)	1.7(11)	-4.8(11)
C7'	21.5(14)	27.2(16)	21.4(15)	1.5(14)	2.2(12)	0.7(13)
C7"	21.8(14)	25.2(17)	24.4(15)	0.0(13)	3.9(12)	-1.1(12)
C1'	21.9(14)	26.7(16)	20.1(15)	1.3(14)	1.7(12)	-0.2(13)
C2	23.3(15)	25.9(17)	25.5(15)	0.3(13)	2.1(13)	0.9(13)
C11	19.7(14)	29.7(18)	29.1(17)	3.2(16)	7.0(14)	-0.8(14)
C1"	24.5(15)	20.7(16)	24.7(15)	1.5(14)	7.5(13)	3.2(12)
C6"	16.5(14)	29.1(17)	24.7(16)	-2.5(13)	2.7(13)	1.1(13)
C9"	36.2(16)	32.8(18)	25.8(16)	1.8(15)	8.7(14)	3.0(14)
C6'	23.1(15)	29.0(18)	26.1(16)	-1.4(15)	5.7(13)	-0.6(13)
C11'	24.7(15)	29.4(18)	27.7(16)	-3.5(15)	4.7(14)	-0.2(15)
C8"	28.8(15)	30.3(18)	23.0(15)	-2.6(14)	0.1(13)	1.4(13)
C2'	22.4(15)	31.8(18)	24.2(16)	-3.2(14)	-2.3(13)	2.2(13)
C2"	21.1(15)	28.0(17)	28.7(16)	3.1(14)	4.0(13)	-2.3(12)
C9'	28.2(16)	31.3(18)	27.6(16)	-3.3(15)	3.4(14)	-1.9(15)
C11"	25.8(16)	30.9(19)	29.7(17)	4.0(16)	7.1(14)	0.9(14)

C1	17.6(14)	27.4(17)	21.1(15)	0.2(13)	1.0(12)	0.0(12)
C4"	29.9(16)	22.7(16)	25.0(16)	-3.5(14)	4.0(13)	-3.9(13)
C12	28.3(16)	42(2)	42(2)	-12.6(18)	15.7(15)	-8.5(15)
C3	20.5(15)	31.8(18)	32.1(17)	-5.6(15)	-0.9(14)	-1.4(13)
C4'	35.3(17)	31.2(18)	22.7(15)	6.6(14)	0.9(14)	-4.2(14)
C4	17.9(15)	50(2)	25.1(16)	-3.2(15)	-1.3(13)	-5.0(14)
C8'	23.1(15)	29.8(17)	31.3(17)	-0.5(15)	6.7(13)	3.0(14)
C3"	33.1(17)	26.7(18)	30.1(17)	-3.0(14)	-1.5(15)	-6.5(13)
C12'	30.5(17)	37(2)	31.1(18)	-4.1(16)	8.5(15)	-5.4(16)
C5'	34.3(16)	28.2(17)	29.5(17)	2.9(14)	5.2(14)	-8.7(14)
C12"	28.7(16)	30.9(19)	32.4(18)	3.3(16)	7.8(14)	2.3(14)
C10"	27.4(16)	40(2)	37.2(18)	-4.4(16)	6.7(15)	2.5(14)
C3'	32.9(16)	29.6(18)	34.9(18)	6.8(15)	-6.1(15)	4.8(14)
C5"	32.6(16)	28.0(18)	29.6(17)	-2.7(15)	6.3(14)	5.1(14)
C13"	32.4(17)	35.0(19)	30.4(18)	-1.8(15)	4.5(15)	1.9(14)
C7	18.3(15)	55(2)	24.7(17)	-10.0(16)	4.7(13)	-5.7(15)
C10'	31.9(17)	40(2)	33.3(18)	-3.7(16)	5.4(15)	-9.6(15)
C14'	36.9(18)	42(2)	42(2)	5.1(17)	10.4(16)	-6.9(16)
C13'	48(2)	41(2)	44(2)	-5.2(17)	16.7(17)	-16.5(17)
C5	31.6(18)	90(3)	27.2(17)	-18(2)	4.5(15)	-14(2)
C6	25.6(17)	85(3)	35.1(19)	-27(2)	12.8(16)	-10.2(19)
C9	39.6(19)	71(3)	38.8(19)	31(2)	-2.5(16)	-16.7(19)
C8	35.6(19)	87(3)	30.5(19)	8(2)	8.4(16)	-24(2)
C14	50(2)	49(2)	42(2)	-7.4(18)	-6.6(18)	-16.1(18)
C14"	36.1(19)	68(3)	48(2)	-15(2)	5.4(18)	9.8(18)
C13	54(2)	71(3)	73(3)	-41(2)	32(2)	-31(2)
C10	34.8(19)	109(4)	66(3)	-57(3)	16.6(19)	-7(2)

Table 4 Bond Lengths for MSU_BA2.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1"	C2"	1.414(3)	C6"	C5"	1.501(4)
O1'	C2'	1.420(3)	C9"	C8"	1.551(4)
O1	C2	1.409(3)	C6'	C5'	1.505(4)
N2"	C1"	1.478(4)	C6'	C10'	1.324(4)
N2"	C9"	1.474(4)	C11'	C12'	1.200(4)
N2"	C4"	1.489(4)	C2'	C3'	1.536(4)
N1'	C1'	1.489(3)	C2"	C3"	1.534(4)
N1'	C9'	1.477(4)	C9'	C8'	1.547(4)

N1'	C4'	1.496(4)	C11"	C12"	1.197(4)
N1	C1	1.492(3)	C1	C7	1.551(4)
N1	C4	1.495(4)	C4"	C3"	1.535(4)
N1	C9	1.476(4)	C4"	C5"	1.522(4)
C7'	C1'	1.559(4)	C12	C13	1.460(5)
C7'	C6'	1.494(4)	C3	C4	1.520(4)
C7'	C8'	1.551(4)	C4'	C5'	1.538(4)
C7"	C1"	1.564(4)	C4'	C3'	1.524(4)
C7"	C6"	1.501(4)	C4	C5	1.525(4)
C7"	C8"	1.547(4)	C12'	C13'	1.458(5)
C1'	C11'	1.467(4)	C12"	C13"	1.481(5)
C1'	C2'	1.537(4)	C13"	C14"	1.504(5)
C2	C1	1.549(4)	C7	C6	1.514(5)
C2	C3	1.531(4)	C7	C8	1.531(5)
C11	C1	1.470(4)	C14'	C13'	1.511(4)
C11	C12	1.184(4)	C5	C6	1.524(5)
C1"	C2"	1.539(4)	C6	C10	1.306(6)
C1"	C11"	1.469(4)	C9	C8	1.562(5)
C6"	C10"	1.322(4)	C14	C13	1.471(5)

Table 5 Bond Angles for MSU_BA2.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1"	N2"	C4"	102.2(2)	C3'	C2'	C1'	103.9(2)
C9"	N2"	C1"	104.5(2)	O1"	C2"	C1"	109.7(2)
C9"	N2"	C4"	114.1(2)	O1"	C2"	C3"	115.8(2)
C1'	N1'	C4'	101.8(2)	C3"	C2"	C1"	103.7(2)
C9'	N1'	C1'	104.4(2)	N1'	C9'	C8'	106.8(2)
C9'	N1'	C4'	114.9(2)	C12"	C11"	C1"	175.9(3)
C1	N1	C4	101.9(2)	N1	C1	C2	102.4(2)
C9	N1	C1	104.5(2)	N1	C1	C7	102.0(2)
C9	N1	C4	114.8(2)	C2	C1	C7	117.6(2)
C6'	C7'	C1'	110.9(2)	C11	C1	N1	110.1(2)
C6'	C7'	C8'	110.0(2)	C11	C1	C2	113.4(2)
C8'	C7'	C1'	100.0(2)	C11	C1	C7	110.2(2)
C6"	C7"	C1"	110.7(2)	N2"	C4"	C3"	100.8(2)
C6"	C7"	C8"	109.2(2)	N2"	C4"	C5"	112.9(2)
C8"	C7"	C1"	99.7(2)	C5"	C4"	C3"	111.6(2)
N1'	C1'	C7'	101.6(2)	C11	C12	C13	178.1(3)

N1'	C1'	C2'	102.6(2)	C4	C3	C2	105.8(2)
C11'	C1'	N1'	112.0(2)	N1'	C4'	C5'	112.3(2)
C11'	C1'	C7'	111.4(2)	N1'	C4'	C3'	102.1(2)
C11'	C1'	C2'	110.9(2)	C3'	C4'	C5'	110.4(2)
C2'	C1'	C7'	117.6(2)	N1	C4	C3	100.8(2)
O1	C2	C1	116.0(2)	N1	C4	C5	113.3(3)
O1	C2	C3	110.3(2)	C3	C4	C5	111.6(3)
C3	C2	C1	103.8(2)	C9'	C8'	C7'	104.3(2)
C12	C11	C1	177.4(3)	C2"	C3"	C4"	105.4(2)
N2"	C1"	C7"	102.0(2)	C11'	C12'	C13'	177.5(3)
N2"	C1"	C2"	103.5(2)	C6'	C5'	C4'	109.3(2)
C2"	C1"	C7"	116.3(2)	C11"	C12"	C13"	177.8(3)
C11"	C1"	N2"	110.8(2)	C4'	C3'	C2'	105.7(2)
C11"	C1"	C7"	109.2(2)	C6"	C5"	C4"	110.8(2)
C11"	C1"	C2"	114.1(2)	C12"	C13"	C14"	112.3(3)
C10"	C6"	C7"	123.2(3)	C6	C7	C1	110.2(2)
C10"	C6"	C5"	123.7(3)	C6	C7	C8	110.4(3)
C5"	C6"	C7"	113.1(2)	C8	C7	C1	100.6(3)
N2"	C9"	C8"	107.1(2)	C12'	C13'	C14'	113.6(3)
C7'	C6'	C5'	112.4(2)	C6	C5	C4	110.4(2)
C10'	C6'	C7'	123.8(3)	C7	C6	C5	111.9(3)
C10'	C6'	C5'	123.8(3)	C10	C6	C7	123.6(3)
C12'	C11'	C1'	174.8(3)	C10	C6	C5	124.5(3)
C7"	C8"	C9"	104.0(2)	N1	C9	C8	106.2(3)
O1'	C2'	C1'	112.1(2)	C7	C8	C9	104.6(2)
O1'	C2'	C3'	115.7(2)	C12	C13	C14	113.8(3)

Table 6 Hydrogen Bonds for MSU_BA2.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O1"	H1"	O1'	0.84(4)	1.98(4)	2.811(3)	169(4)
O1	H1	N1'[1]	0.95(4)	1.87(4)	2.781(3)	161(3)
O1'	H1'	N1	1.05(5)	1.68(5)	2.719(3)	171(4)

[1]1-X,-1/2+Y,2-Z

Table 7 Torsion Angles for MSU_BA2.

A	B	C	D	Angle/°	A	B	C	D	Angle/°

O1" C2" C3" C4"	-114.7(3)	C11' C1' C2' O1'	-85.8(3)
O1' C2' C3' C4'	-123.8(3)	C11' C1' C2' C3'	148.6(2)
O1 C2 C1 N1	146.0(2)	C8" C7" C1" N2"	46.3(2)
O1 C2 C1 C11	-95.4(3)	C8" C7" C1" C2"	158.2(2)
O1 C2 C1 C7	35.2(3)	C8" C7" C1" C11"	-71.0(3)
O1 C2 C3 C4	-119.7(3)	C8" C7" C6" C10"	119.6(3)
N2" C1" C2" O1"	148.5(2)	C8" C7" C6" C5"	-58.8(3)
N2" C1" C2" C3"	24.2(3)	C9' N1' C1' C7'	-44.9(3)
N2" C9" C8" C7"	6.0(3)	C9' N1' C1' C11'	74.0(3)
N2" C4" C3" C2"	-32.7(3)	C9' N1' C1' C2'	-167.0(2)
N2" C4" C5" C6"	50.7(3)	C9' N1' C4' C5'	40.5(3)
N1' C1' C2' O1'	154.5(2)	C9' N1' C4' C3'	158.7(2)
N1' C1' C2' C3'	28.9(3)	C11" C1" C2" O1"	-91.0(3)
N1' C9' C8' C7'	4.3(3)	C11" C1" C2" C3"	144.7(2)
N1' C4' C5' C6'	53.7(3)	C1 N1 C4 C3	49.4(3)
N1' C4' C3' C2'	-27.9(3)	C1 N1 C4 C5	-70.0(3)
N1 C1 C7 C6	-71.0(3)	C1 N1 C9 C8	24.8(3)
N1 C1 C7 C8	45.5(3)	C1 C2 C3 C4	5.2(3)
N1 C4 C5 C6	51.1(4)	C1 C7 C6 C5	52.7(4)
N1 C9 C8 C7	4.1(3)	C1 C7 C6 C10	-128.6(4)
C7' C1' C2' O1'	44.1(3)	C1 C7 C8 C9	-29.9(3)
C7' C1' C2' C3'	-81.5(3)	C4" N2" C1" C7"	75.3(2)
C7' C6' C5' C4'	-43.1(3)	C4" N2" C1" C2"	-45.8(2)
C7" C1" C2" O1"	37.5(3)	C4" N2" C1" C11"	-168.5(2)
C7" C1" C2" C3"	-86.8(3)	C4" N2" C9" C8"	-87.1(3)
C7" C6" C5" C4"	-39.4(3)	C3 C2 C1 N1	24.9(3)
C1' N1' C9' C8'	25.4(3)	C3 C2 C1 C11	143.5(2)
C1' N1' C4' C5'	-71.7(3)	C3 C2 C1 C7	-85.9(3)
C1' N1' C4' C3'	46.6(2)	C3 C4 C5 C6	-61.9(4)
C1' C7' C6' C5'	53.6(3)	C4' N1' C1' C7'	74.9(2)
C1' C7' C6' C10'	-127.3(3)	C4' N1' C1' C11'	-166.1(2)
C1' C7' C8' C9'	-30.4(3)	C4' N1' C1' C2'	-47.2(2)
C1' C2' C3' C4'	-0.5(3)	C4' N1' C9' C8'	-85.2(3)
C2 C1 C7 C6	40.0(4)	C4 N1 C1 C2	-46.4(3)
C2 C1 C7 C8	156.5(2)	C4 N1 C1 C11	-167.3(2)
C2 C3 C4 N1	-33.1(3)	C4 N1 C1 C7	75.7(2)
C2 C3 C4 C5	87.5(3)	C4 N1 C9 C8	-85.9(3)
C11 C1 C7 C6	172.1(3)	C4 C5 C6 C7	-40.8(4)
C11 C1 C7 C8	-71.4(3)	C4 C5 C6 C10	140.5(4)
C1" N2" C9" C8"	23.7(3)	C8' C7' C1' N1'	46.2(3)

C1"	N2"	C4"	C3"	48.5(2)	C8'	C7'	C1'	C11'	-73.2(3)
C1"	N2"	C4"	C5"	-70.7(3)	C8'	C7'	C1'	C2'	157.2(2)
C1"	C7"	C6"	C10"	-131.5(3)	C8'	C7'	C6'	C5'	-56.0(3)
C1"	C7"	C6"	C5"	50.1(3)	C8'	C7'	C6'	C10'	123.1(3)
C1"	C7"	C8"	C9"	-31.2(3)	C3"	C4"	C5"	C6"	-62.0(3)
C1"	C2"	C3"	C4"	5.5(3)	C5'	C4'	C3'	C2'	91.7(3)
C6"	C7"	C1"	N2"	-68.6(3)	C10"	C6"	C5"	C4"	142.2(3)
C6"	C7"	C1"	C2"	43.3(3)	C3'	C4'	C5'	C6'	-59.6(3)
C6"	C7"	C1"	C11"	174.1(2)	C5"	C4"	C3"	C2"	87.5(3)
C6"	C7"	C8"	C9"	84.9(3)	C10'	C6'	C5'	C4'	137.8(3)
C9"	N2"	C1"	C7"	-43.9(2)	C6	C7	C8	C9	86.5(3)
C9"	N2"	C1"	C2"	-165.1(2)	C9	N1	C1	C2	-166.3(2)
C9"	N2"	C1"	C11"	72.2(3)	C9	N1	C1	C11	72.8(3)
C9"	N2"	C4"	C3"	160.7(2)	C9	N1	C1	C7	-44.1(3)
C9"	N2"	C4"	C5"	41.5(3)	C9	N1	C4	C3	161.7(2)
C6'	C7'	C1'	N1'	-69.8(3)	C9	N1	C4	C5	42.3(3)
C6'	C7'	C1'	C11'	170.8(2)	C8	C7	C6	C5	-57.5(3)
C6'	C7'	C1'	C2'	41.2(3)	C8	C7	C6	C10	121.2(4)
C6'	C7'	C8'	C9'	86.3(3)					

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for MSU_BA2.

Atom	*x*	*y*	*z*	U(eq)
H7'	917	6462	7794	28
H7"	-687	4167	4183	29
H2	4500	2608	8898	30
H9"A	154	5951	1992	38
H9"B	-563	6912	2429	38
H8"A	-1750	5542	2708	34
H8"B	-955	4567	2394	34
H2'	3824	5282	8976	33
H2"	2236	5267	5232	31
H9'A	2090	7962	10416	35
H9'B	1334	7048	10865	35
H4"	634	7919	4141	31
H3A	3737	1276	7173	35
H3B	3040	2246	7627	35
H4'	2350	4985	11160	37

H4	3076	3065	6059	38
H8'A	848	8025	8874	34
H8'B	46	7188	9358	34
H3"A	2038	7130	5374	37
H3"B	1028	6922	5964	37
H5'A	698	4125	10082	37
H5'B	445	5417	10361	37
H10A	-1945	6073	5708	42
H10B	-1796	4725	5416	42
H3'A	2403	3689	9541	41
H3'B	3539	4181	10260	41
H5"A	-823	7504	5075	36
H5"B	-1244	7313	3835	36
H13A	1795	2922	1662	40
H13B	1583	1958	2467	40
H7	6926	2916	7530	39
H10C	-273	4815	7395	42
H10D	-422	3910	8321	42
H14D	3157	8987	6386	60
H14E	4108	8043	6427	60
H14F	4424	9368	6452	60
H13C	4949	8637	8152	52
H13D	3973	9551	8109	52
H5A	4181	1586	5486	60
H5B	4546	2826	5164	60
H9A	4951	5446	6713	62
H9B	4494	4681	5686	62
H8A	6252	4042	5773	61
H8B	6691	4732	6852	61
H14G	8089	6030	9378	75
H14H	8312	5223	10392	75
H14I	8200	6571	10524	75
H14A	3464	1974	2309	77
H14B	3373	2236	3493	77
H14C	3587	3254	2743	77
H13E	6574	5607	10684	76
H13F	6353	6524	9754	76
H10E	7045	1118	6671	83
H10F	5981	601	5805	83
H1"	1530(30)	4820(30)	6520(30)	59(12)

H1	6120(40)	1520(30)	8960(30)	67(12)
H1'	3350(40)	4340(40)	7620(30)	94(15)

MSU_BA2

X-ray diffraction data for **MSU_BA2** were collected at 120 K on a Bruker D8 Venture using CuKα (λ = 1.54178) radiation. Data have been corrected for absorption using SADABS[1] area detector absorption correction program. Using Olex2[2], the structure was solved with the ShelXT structure solution program using Direct Methods and refined with the ShelXL refinement package using least squares minimization. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms attached to heteroatoms were found from the residual density maps and refined with isotropic thermal parameters. All other hydrogens atoms were refined in calculated positions using a ridged group model. The absolute structure was determined by refinement of the Flack Parameter[3], based on anomalous scattering. All calculations and refinements were carried out using APEX[4], SHELXTL[5], and Olex2 software.

Crystallographic Data for **MSU_BA2** C42H57N3O3, M =651.90, monoclinic, space group P21, a = 12.2572(9), b = 11.7318(9), c = 13.0251(10), β = 102.397(4)°, V = 1829.3(2), Z = 2, T = 120.0 K, μ(CuKα) = 0.573 mm^{-1}, ρ_{calcd} == 1.184 g ml^{-1}, $2\Theta_{max}$= 133.29, 58666 reflections collected, 6436 unique (R_{int} = 0.0699, R_{sigma} = 0.0441), R1 = 0.0411 (I > 2σ(I)), wR2 = 0.0931 (all data), Flack Parameter = 0.00(9).

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