ASYMMETRIC SYNTHESIS OF PROSTAGLANDINS

by

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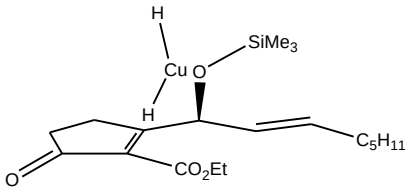
Abstract

Prostaglandins (PGs) are medicinally interesting because of the wide variety of roles they play in the body. PGs are ubiquitous and can be found in the reproductive system, the nervous system, the cardiovascular system, and the immune system. Accordingly, PGs are an important therapeutic target for pharmaceutical companies, and an efficient synthesis is highly desirable. Past research indicates that an approach to prostaglandins via a chiral acetylenic ester or amide provides a promising method for control of C-15 geometry. This project seeks to validate a key stereospecific reduction of an enantiomerically pure cyclopentenone intermediate. This is in turn available from a chiral acetylenic ester or amide via a formal [3+2] cycloaddition step. Several methods have been investigated for asymmetric synthesis of the requisite chiral acetylenic acid derivative including asymmetric conjugate addition, CBS-oxazaborolidine reduction of a ketone, and the separation of diastereomers of a chiral amide. With the optically pure cyclopentenone in hand, we will investigate hydroxyl directed conjugate reduction of the cyclopentenone double bond as shown in the figure.



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Introduction

Prostaglandins (PGs) are medicinally interesting due to their broad spectrum of biological activity. PGs act in many parts of the body, including (but not limited to): the reproductive system (in both males and females), the nervous system, the cardiovascular system, the immune system and gastrointestinal system.[1] Due to their diverse biological activity, there is potential for prostaglandin analogs (prostanoids) to function as effective therapeutic agents. Indeed, there are already PG analogs used as drugs for the treatment of ulcers, hypertension and other conditions.

In the 1960's and 1970's, soon after the core structure of the PGs was determined, many different routes for prostaglandin synthesis were explored.[2,3] However, achieving an asymmetric synthesis of the PGs still presents unique challenges. A wide variety of strategies have been employed, however further investigation is still warranted. Development of a robust, asymmetric route to prostaglandins would greatly benefit development of prostanoids by pharmaceutical companies.

Structure

In the most basic sense, PGs are twenty-carbon molecules made up of a five-membered (cyclopentane) ring with two aliphatic sidechains. The numbering of these molecules is straightforward, and is shown in representative example **1** (Figure 1). Two other structural features are found in all prostaglandins: C-15 is a stereo center with an attached hydroxyl group, and C-9 always has an attached oxygen function (present as a hydroxyl group, ketone, or part of a bridged peroxide moiety). There are a few other distinguishing characteristics of PGs that are not ubiquitous: In most cases, the carbons to which the side chains are attached are stereo centers, and some PGs have a second oxygen function attached to either the C-10 or C-11 positions. Also, PGs can have up to three double bonds present in the sidechains. These structural details separate the known prostaglandins into nine families (or "classes"), while the absence or presence of double bonds in the sidechains separates the PGs into three "series".

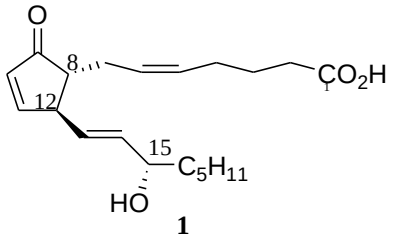

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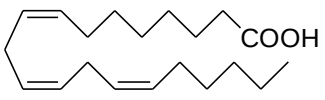
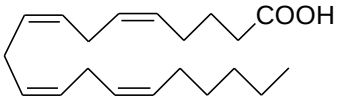
Figure 1. Prostaglandin A_2

As mentioned, prostaglandins are categorized into "series" and "classes". The "series" classification divides PGs up by general structural elements conserved across all classes of prostaglandin as well as indicating from which fatty acid the PG is derived. The "classes" categorize different types PGs by their specific structural elements.

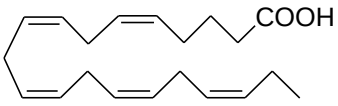
There are three series of prostaglandins, labeled as: PGX_1, PGX_2 and PGX_3, where "X" is a letter indicating the class of a given prostaglandin. The subscripts indicate the number of double bonds in the side chains coming off of C-8 and C-12, which indirectly indicates from what precursor a PG has been generated. Prostanoids are derived from certain essential fatty acids, which are known as the eicosanoic acids. Each series of prostaglandin is derived from a different eicosanoic acid: the 1-, 2-, and 3-series are derived from dihomo-γ-linolenic acid, arachidonic acid (**2**), and 5, 8, 11, 14, 17-eicosapentaenoic acid respectively (Figure 2). The 1-, 2-, and 3- series, "class A" prostaglandins (also known as "PGAs") are shown below in Figure 3 were derived from the corresponding fatty acid in Figure 2.



dihomo-γ-linolenic acid



arachidonic acid (**2**)



5,8,11,14,17-eicosapentaenoic acid

Figure 2. C-20 Fatty Acid PG Precursors

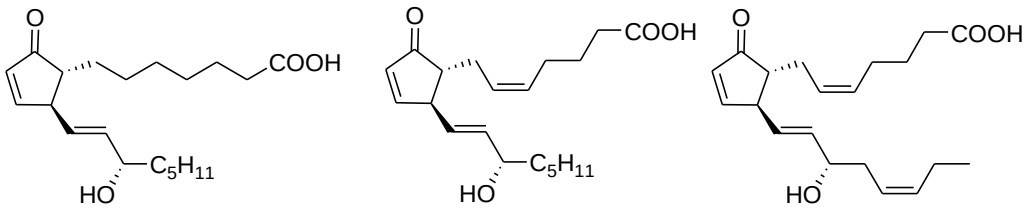


Figure 3. PGA_1, PGA_2, PGA_3 Left to Right

There are nine common classes of prostaglandins, each defined by specific structural elements, named arbitrarily as PGA through PGI. Each class of prostaglandin contains a set of 3 molecules analogous to the PGA series in Figure 3; the 1-series is shown for the rest of the classes of PGs (Figure 4). Precisely one diastereomer of these compounds is found in nature, indicating the importance of the stereochemistry, especially with respect to the C-15 position. Several structural properties are conserved between the various classes of PG.

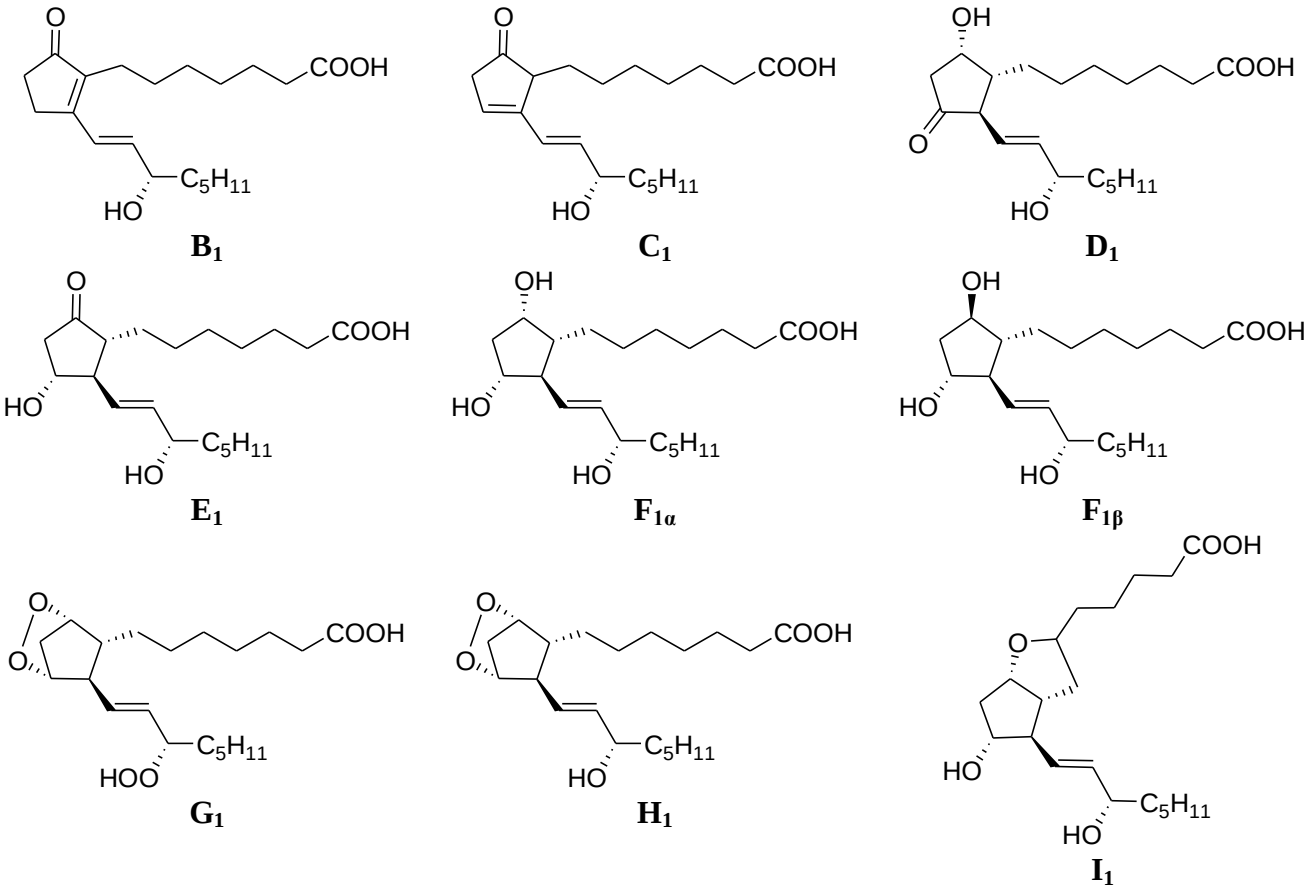


Figure 4. Classes of Prostaglandins

Biosynthesis

Biosynthesis of PGs is often initiated by stimulation (physical, chemical, or neural), and synthesis generally occurs in the region where the PG is to exert influence. For example, one study showed that when guinea pig lung strips are gently rubbed, a large amount of certain types of prostaglandin are released and cause a number of varied responses from the tissue.[4] After stimulation, the concentration of prostaglandins present is much greater than the amount of PG that can be isolated from lung tissue without stimulation, indicating that the prostaglandin is being synthesized on-site. The cycle of synthesis to metabolism *in vivo* is rapid: the prostaglandins are synthesized, exert their influence over a few minutes, and are subsequently metabolized.[1] This rapid metabolism accounts for low equilibrium concentrations of PG *in vivo*. When PGE_1 and/or PGE_2 are passed once through cat, dog, rabbit or guinea pig lung, about 90% of the biological activity is lost.[5] In contrast, seminal fluid is one of the only areas where stores of prostaglandins are held. The concentration of PGs in seminal fluid can reach several hundred μg/mL, but in most other tissues, the concentrations are 10^6 times lower.[6] In the late 1960's and early 1970's the biosynthesis of prostaglandins in the 2-series was studied closely. Since then, the biosynthesis of PG_2s has served as a model for the biosynthesis of other PGs and related compounds.[1,7]

Prostaglandin biosynthesis depends on the availability of the requisite fatty acid. Like many fatty acids, eicosanoic acids are stored mainly as phospholipids in the cell membrane. The release and subsequent metabolism of arachidonic acid (**2**) has been well studied. A stimulus or hormone outside the membrane of the cell leads to activation of the enzyme phospholipase A_2 (PLA_2), shown in Figure 5. Biosynthesis (Modified from Ref. 7). Upon activation, PLA_2 cleaves specific ester bonds of phospholipid molecules, releasing arachidonic acid.

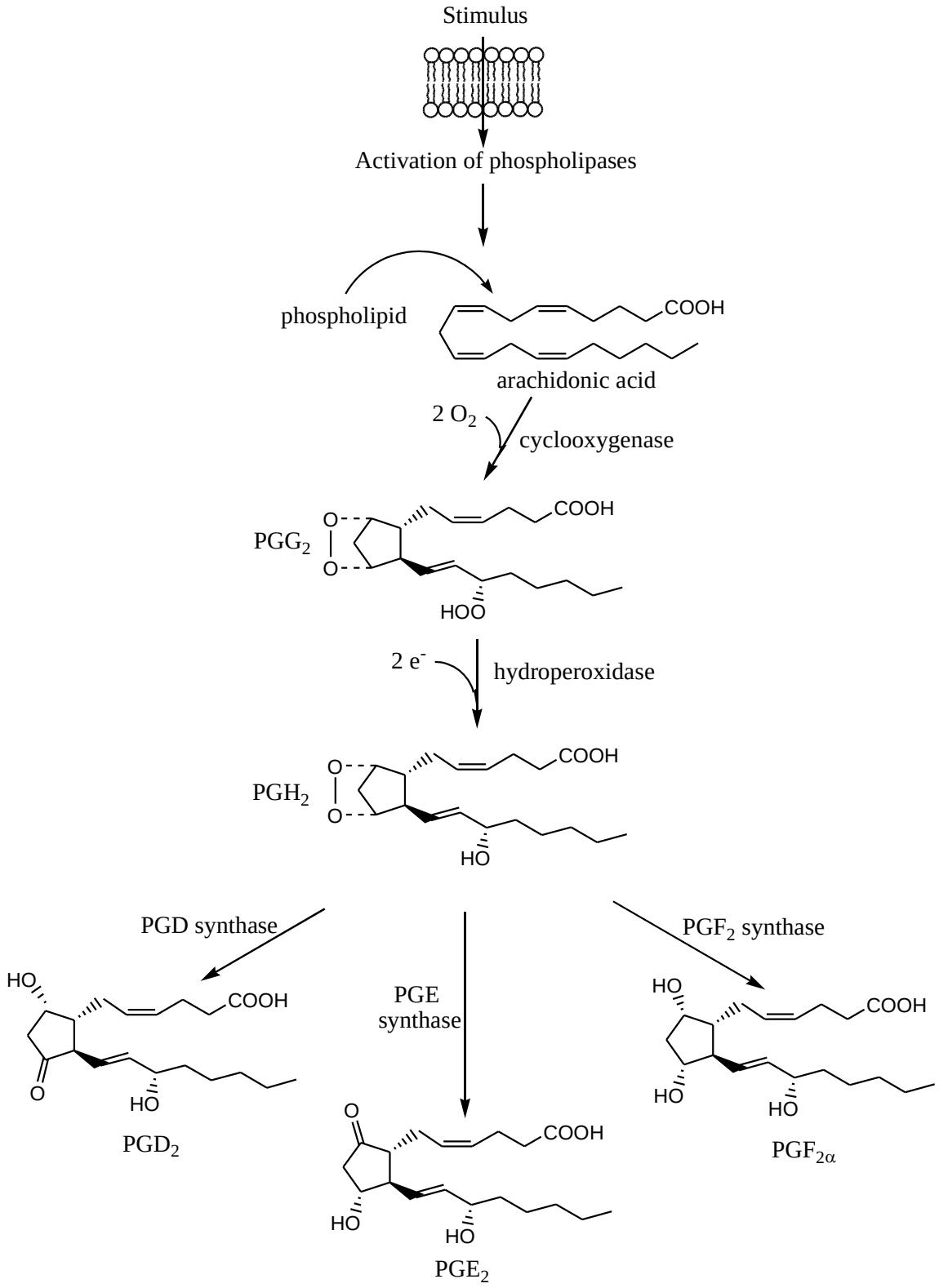


Figure 5. Biosynthesis (Modified from Ref. 7)

Once released, arachidonic acid (**2**) is acted upon sequentially by two enzymes: a cyclooxygenase and a peroxidase (collectively known as "prostaglandin synthase"). The cyclooxygenase enzyme begins to develop the structure of the future prostaglandin; the familiar five-membered ring with *trans*-stereochemistry is formed, and two molecules of oxygen are added to the molecule to form the intermediate PGG_2. The first molecule of oxygen exists in the form of an endoperoxide, while the second molecule of oxygen is added (stereospecifically) as a peroxide group in the C-15 position. The second enzyme, a peroxidase, converts the C-15 peroxide group in to a C-15 hydroxyl group leading to PGH_2 which is both a naturally occurring prostaglandin with its own biological effects and a precursor for further biological derivation.

Once the action of the prostaglandin synthase machinery is complete, the newly formed PGH_2 may be acted on by other enzymes, such as the PGD_2 or PGE_2 synthases to create the other classes of prostaglandin.

Previous Work

Previous research[8] in the laboratory of Professor Dittami has afforded a fairly efficient route to a prostaglandin core (**3**) framework (Figure 6). Key points to note in the structure are the stereo center at C-15 position[a], the *trans*-stereochemistry across the bond between C-8 and C-12 positions, and the ester function at position 8 which serves as a precursor to the C1-C7 sidechain. The stereo centers are common to many PGs and are important to their biological activity, while the ester on C-8 provides a versatile handle for later conversion to analogs.

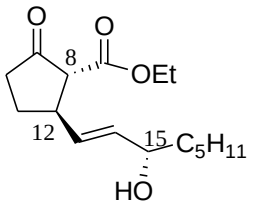


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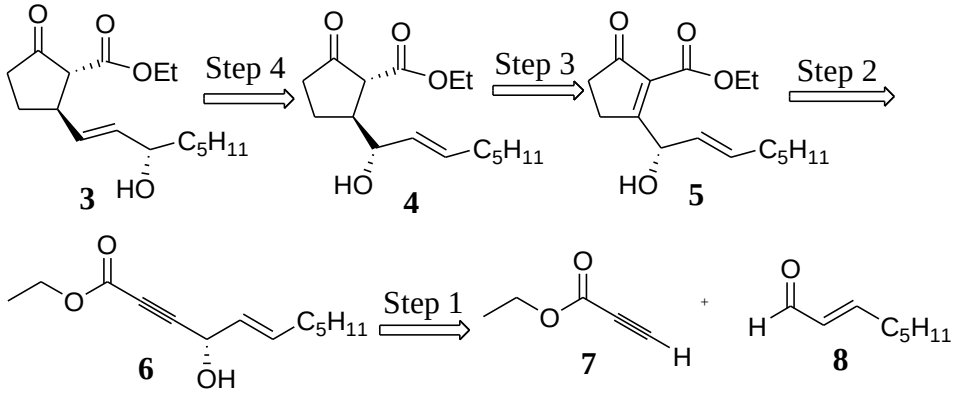
Figure 6. Desired Prostaglandin Core

The retrosynthetic approach is shown below in Scheme 1. In Step 4, a stereospecific [3,3] sigmatropic shift moves the hydroxyl group from the C-13 position to the C-15 position with retention of configuration, providing **3,** the desired core structure.

[a] For simplicity, the same numbering is used for both PGs and for this desired PG core.

Step 3 employs stereospecific reduction of the double bond in the ring, directed by the hydroxyl group on the C-15 stereocenter, yielding **4**. A formal [3+2] cycloaddition of a chiral acetylenic ester creates the substituted cyclopentenone ring in Step 2 (**5**).[9] Step 1 involves formation of an enantiomerically pure chiral acetylenic ester or amide (**6**). Racemic **6** is easily obtained from the commercially available starting materials ethyl propiolate (**7**) and *trans*-2-octenal (**8**). Steps 4 and 2 have been previously carried out and optimized using racemic mixtures or model compounds with good yields. Previous attempts to asymmetrically synthesize the acetylenic ester intermediate **6** in Step 1 have resulted in inadequate enantiomeric excess (ee). Because of this, the stereospecificity in Step 3 remains to be proven, and is therefore the focus of this and future research.



Scheme 1. Retrosynthesis

Establishing the Latent C-15 Hydroxyl Stereochemistry

A key element of our synthesis is to establish the stereochemistry of the hydroxyl center in acetylenic ester **6**. This functional group is expected to serve two roles. (1) It can participate in directing the reduction of the double bond in **5**, giving rise to two new stereo centers at C-8 and C-12. (2) It serves as latent functionality for the C-15 stereocenter via [3,3] sigmatropic shift. The stereochemical integrity of the C-15 center is vital for the biological activity of the PG's. Previous strategies for obtaining this intermediate included derivatization of the racemic intermediate by attaching a chiral group to the hydroxyl moiety (followed by separation of diastereomers), reduction of the corresponding ketone with Alpine borane, and taddol-assisted asymmetric addition of ethyl propiolate (**7**) to *trans*-2-octenal (**8**). None of these methods, however, provided the intermediate with both adequate yield and ee.

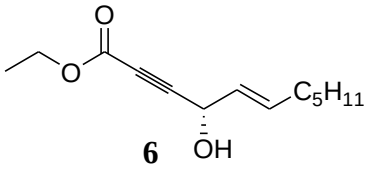
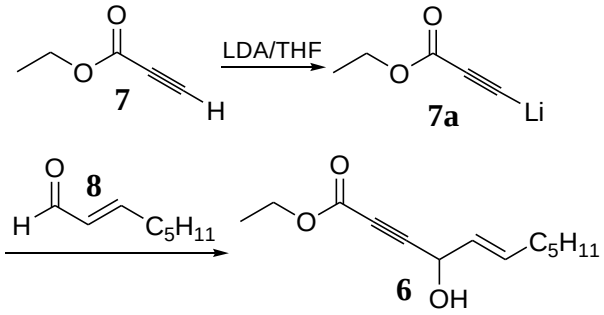


Figure 7. Key Chiral Acetylenic Ester Intermediate

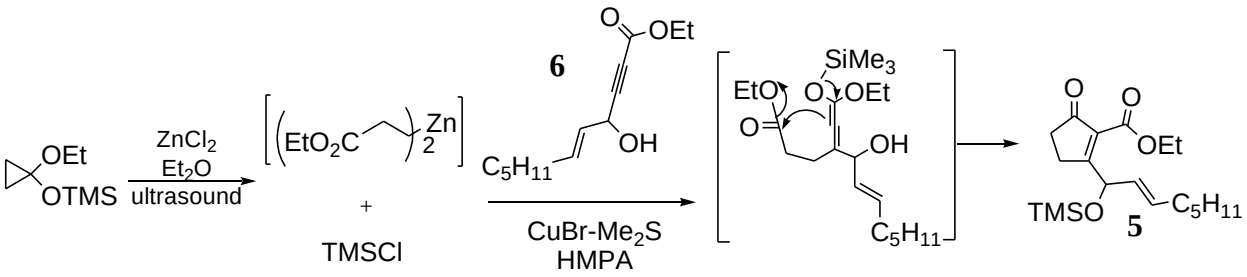
The proof of concept for synthesis of **3** via **6** (Scheme 1) has been demonstrated using racemic acetylenic ester **6** (Scheme 2), which is easily obtained via a two-step one pot coupling. The alkyne **7** is deprotonated by lithium diisopropyl amide (LDA) to yield the lithiated species **7a**, which upon addition of the aldehyde **8** gives rise to racemic intermediate **6**. This coupling step has been carried out with yields up to 93%.



Scheme 2. Racemic Alcohol

Formal [3+2] Cycloaddition

Acetylenic alcohol **6** is employed in formation of pentacyclic ester **5** via a formal [3+2] cycloaddition developed in the laboratory of Michael Crimmins. This step has been carried out providing yields of 85% or greater. The key step is the pre-formation of a zinc homoenolate from a cyclopropyl ether and $ZnCl_2$, which is then added to racemic **6** in the presence of HMPA and CuBr·Me_2S (Scheme 3). Catalytic transmetallation by the copper (I) bromide complex converts the zinc homoenolate into a cuprate. A Michael addition of the homoenolate to the acetylenic ester occurs, followed by cyclization providing racemic **5**.



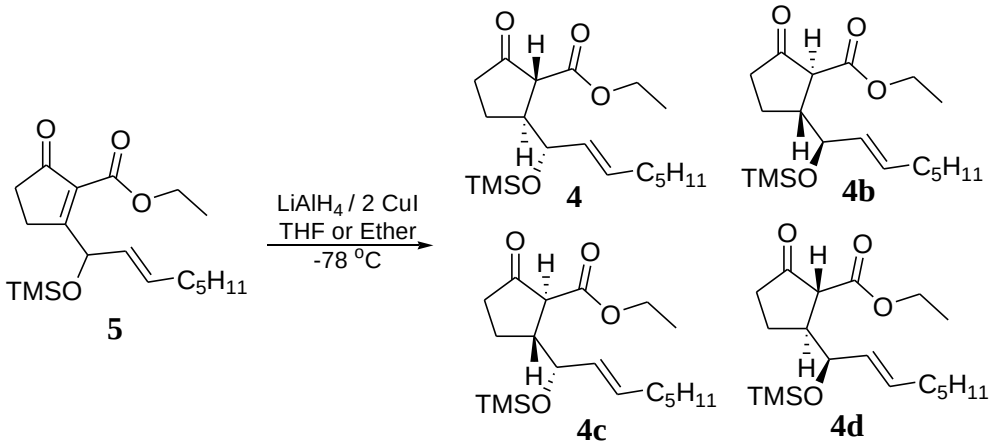
Scheme 3. [3+2] Cycloaddition (Adapted from Ref. 9)

This cyclization provides an elegant route to 2, 3-disubstituted cyclopentenones, which have been historically difficult to synthesize. The hydroxyl-bearing stereocenter in the molecule can now be used to direct a reduction across the double bond in the ring.

Stereospecific Reduction

This step provides two synthetic challenges: The reduction must be specific for the double bond in the ring and it must also be regio- and stereospecific. The conjugate reduction of a racemic mixture of a cyclopentenone starting material could conceivably give rise to eight products (four *cis*-products, and four *trans*-products). However, there is ample precedent to show that formation of *trans*-products occurs predominantly if not exclusively.[10] Thus, four possible products were anticipated (Scheme 4).

In previous work, the conjugate reduction of the trimethylsilyl (TMS) protected alcohol (**5**) was investigated. Several types of reduction conditions were examined, but lithium aluminum hydride and copper (I) iodide in ether or tetrahydrofuran (THF) were found to give the best stereoselectivity for the desired products. These conditions provided up to 98% overall yield. In Scheme 4, the desired pair of enantiomers are shown as compounds **4** and **4b**, and the undesired pair of enantiomers are shown as compounds **4c** and **4d**. In previous work carried out in our laboratory, Cruz reported that 99.5% was recovered as the desired product and 0.5% as undesired product (Ref.8, pg 171). These two sets of diastereoisomers are separable by normal chromatographic methods and are distinguishable by NMR. The diastereomeric excess was determined by relative integrations in the ^{1}H NMR spectrum of the crude mixture. The absolute configurations of each pair of enantiomers were determined by nOe coupling patterns on the pure compounds.



Scheme 4. Stereospecific Reaction Conditions

The proposed intermediate (**9**) for the reaction is shown in Figure 8. The lithium aluminum hydride and copper bromide react to form a copper hydride species which complexes the TMS-ether oxygen in the C-13 position. The complex positions a hydride group in an ideal position for the reduction.

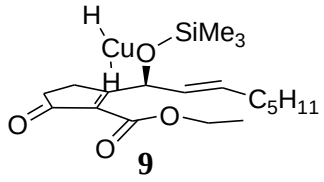


Figure 8. Copper Hydride Complex Directing Reduction (Adapted from Ref. 8)

However, if the oxygen bearing sidechain is not rotationally constrained, the reduction can occur from both faces of the cyclopentenone ring. Given enantiomerically pure starting material, this would lead to two diastereomeric products (Figure 9). The experimental evidence reported above suggests that a conformation leading mainly to only one of the diastereomers is preferred. The two possible diastereomeric products **4** and **4c** are shown in Figure 9. As noted above, the reduction of racemic **5** provided mainly product **4**. By extension a reaction on only one enantiomer should have the same distribution of products as in the reaction with a racemic mixture product: 99.5% desired product **4** and 0.5% undesired diastereomer **4c**.

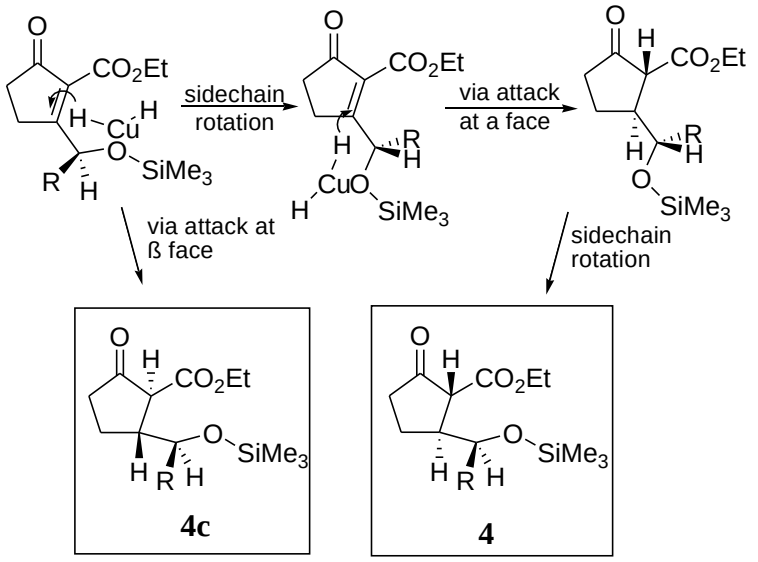
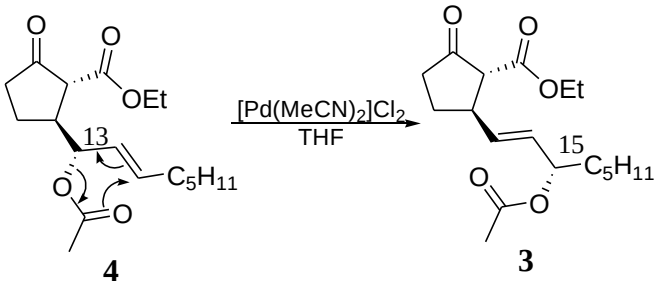


Figure 9. Diastereomeric Products Formed by the Reduction

Stereoselective [3,3] Sigmatropic Shift

The last step of the synthesis is a stereospecific [3,3] sigmatropic rearrangement of **4** to **3** to establish the C-15 hydroxyl with correct stereochemistry. This reaction is performed using the acylated alcohol. This rearrangement is known to provide product with retention of configuration (Scheme 5).[11] It proceeds via a concerted mechanism involving a six-electron rearrangement. Previous results have shown that the yields are relatively good (70%), and that remaining starting material can be recovered for further use.



Scheme 5. [3,3] Sigmatropic Shift

Current Work

The key point of optimization for our PG synthesis is to obtain the intermediate **6** in high yield and good stereochemical purity so that it can be cyclized and used to test the stereospecificity of the reduction of **5** to **4**. Current work in our laboratory involves investigation of several methods for obtaining the intermediate **6** or a similar acetylenic

acid derivative **10** (Figure 10). The methods used are broken down into two categories: direct asymmetric synthesis and separation of diastereoisomers.

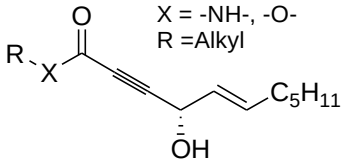


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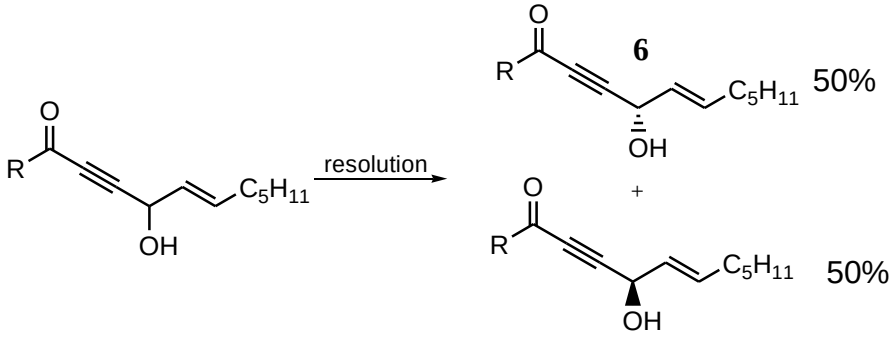
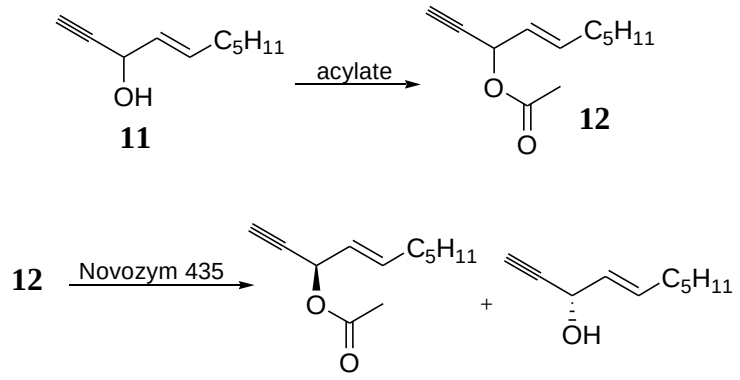
Figure 10. Acetylenic Acid Derivative

Advantages of the separation of stereoisomers include ease of separation (eg. conventional chromatography) and reactions that are relatively insensitive to water and air. The obvious disadvantage: the maximum yield of the desired enantiomer is only 50% (Scheme 6). In this case, however, it is worth investigation: even a small amount of the intermediate can be used to show stereospecificity in the conjugate reduction of **5** (Scheme 4). Two methods for separation of stereoisomers are being investigated: selective deacylation of the intermediate **6** by the commercially available enzyme Novozym 435 and separation of the diastereomers of a chiral acetylenic amide intermediate.



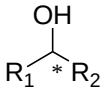
Scheme 6. Separation of Stereoisomers

Novozym 435 consists of a lipase isolated from *Candida antarctica* bound to a solid phase. Past research on the lipase in Novozym 435 has shown that the similar substrate **11** undergoes stereospecific deacylation of one enantiomer with good yield and ee (>95%) as shown in Scheme 7.[12]



Scheme 7. Similar Substrate in Novozym 435 Hydrolysis

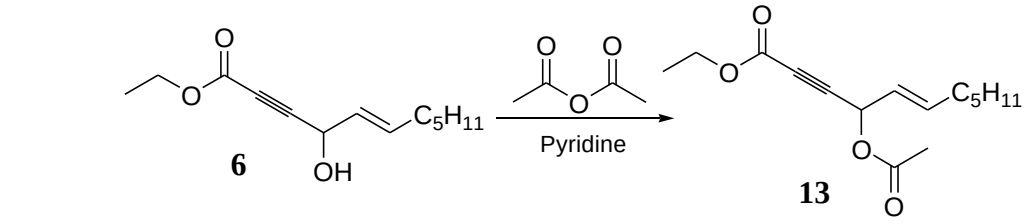
The binding site of the enzyme is composed of two pockets for different sized groups: one large and one small. This binding pocket accommodates molecules of the general structure shown in Figure 11. Based on this analysis, we thought that the intermediate **6** may fit into the binding pocket of the enzyme and undergo selective deacylation.[13]



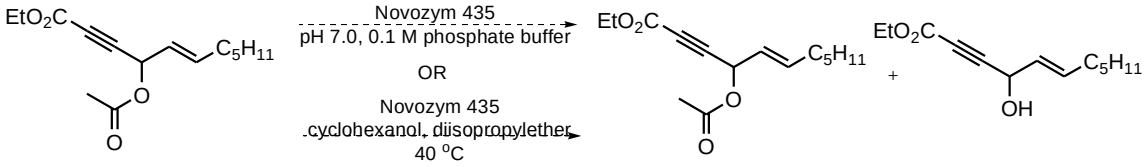
R_1= long aliphatic chain (5-11 carbons)
R_2= short chain (1-2 carbons)

Figure 11. General Structure of Novozym 435 Substrates

Intermediate **6** was acylated with acetic anhydride and pyridine yielding **13** (Scheme 8).[14] The acylated intermediate **13** was then subjected to deacylation by the enzyme. The first set of reaction conditions used aqueous buffer as a solvent. The intermediate **13** is not miscible with water, so the contact between the enzyme (on solid beads, freely moving in the solution) and the substrate was minimal and no reaction occurred. To bring the substrate and the enzyme together, we found similar papers reporting deacylation in organic media.[15] With these conditions, the substrate was dissolved in solution, and there was good contact between the substrate and the enzyme, but no reaction occurred. This result may have been due to interference from the ester group in the pocket of the enzyme, as the other compounds reported generally contained only one ester function. At this point, other options were explored, although resolution of **11** and subsequently adding the ester function is a possibility that may be worth some attention.

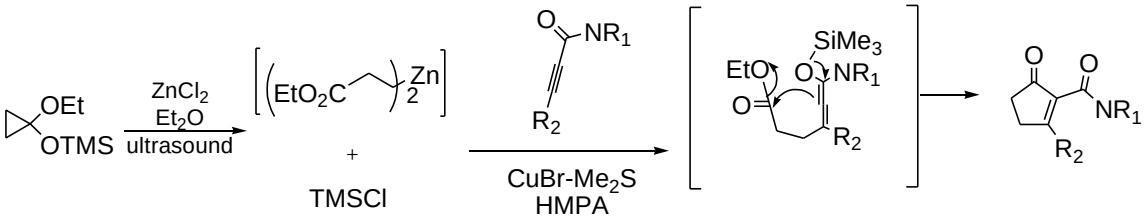


Scheme 8. Acylation



Scheme 9. Novozym 435 Reaction Conditions

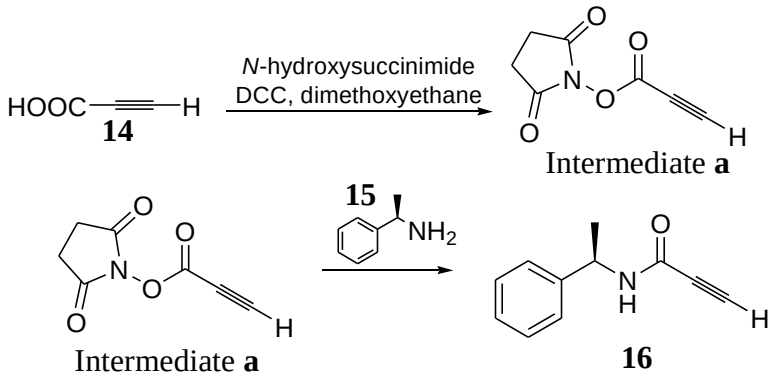
The other separation method being explored involves the use of a chiral acetylenic amide to add a built-in optically pure stereo center. Previous studies have focused on an acetylenic ester intermediate, but using an acetylenic amide intermediate is also possible. Use of acetylenic amides in the construction of disubstituted cyclopentenones (Scheme 10) has been carried out. Reportedly, the yields are improved with these systems.[9]



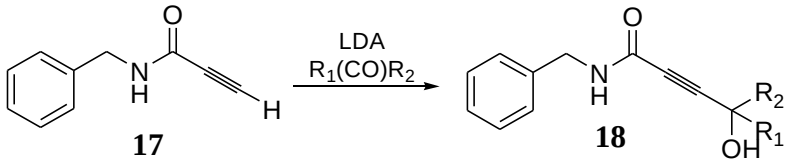
Scheme 10. Cycloaddition with Amides

Using propiolic acid **14** and 1-phenylethanamine **15** in conventional amide bond forming chemistry provides the chiral substituted acetylene **16** (Scheme 11).[16] Both enantiomers of **15** are commercially available and inexpensive. Once formed, the acetylene **16** can then be taken on via addition to *trans*-2-octenal (**8**). There are, however, two acidic protons in **16**: the proton on the nitrogen and the acetylenic proton. Literature searching reveals that two equivalents of LDA will completely remove both of these protons to give a dianion. When an aldehyde such as **8** is added to the reaction mixture, addition occurs via attack of the acetylenic carbon on the aldehyde center as shown for the conversion of the similar compound **17** to **18** in Scheme 12.[17] This method is still being examined in our laboratory. We have thus far synthesized **16**, although in low yield. Optimization of the reaction to form **16** (Scheme 11), followed by addition of

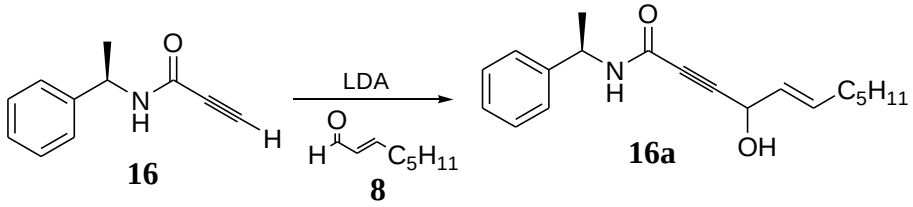
acetylene **16** to **8** may provide an easily separable set of diastereomers that can be resolved and taken on to the cyclization and reduction steps (Scheme 13).



Scheme 11. Formation of Chiral Acetylene

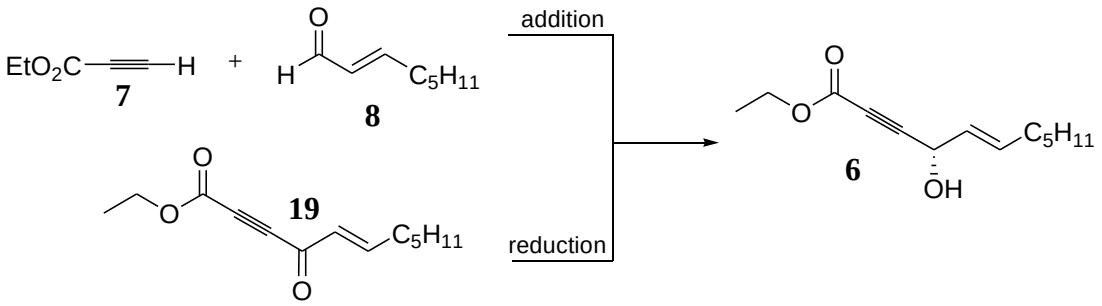


Scheme 12. Addition (Adapted from Ref. 17)



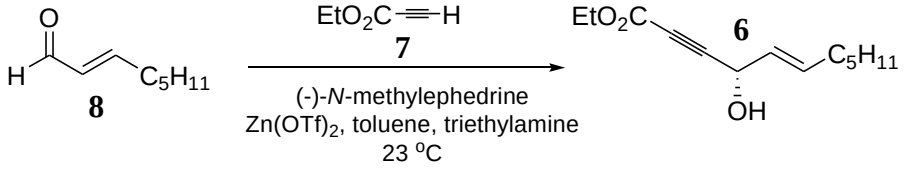
Scheme 13. Proposed Synthesis of 16a

Direct asymmetric synthesis of **6** has the distinct advantage of 100% maximum yield. Two methods were investigated: asymmetric addition of an alkyne to an aldehyde and asymmetric reduction of the ketone of **19** (Scheme 14). Literature searches on asymmetric addition lead to work done in the laboratory of E.M. Carreira.[18] Using *N*-methyl ephedrine as a chiral auxiliary, Carreira has shown that a number of both substituted and unsubstituted acetylenes undergo asymmetric addition to aldehydes.[19,20] In a well-known reaction pioneered by E.J. Corey, ketones such as **19** undergo asymmetric reduction directed by chiral oxazaborolidines in the presence of a reducing agent such as borane-dimethylsulfide.[21] This reaction has since been used in stereospecific syntheses of natural products such as discodermolide and petrofuran.[22,23]

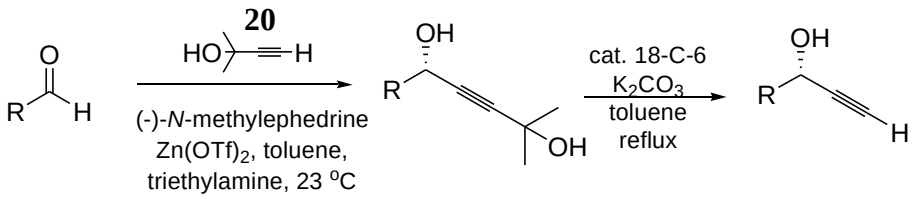


Scheme 14. Direct Asymmetric Synthesis

Using the work of Carreira as a guide, we attempted the addition of ethyl propiolate **7** to *trans*-2-octenal **8** to synthesize intermediate **6** directly (Scheme 15). Formation of product was not observed. Carreira noted improved performance with the acetylene 2-methylbut-3-yn-2-ol (**20**) in this addition. Furthermore, he devised fragmentation conditions for removal of the acetylenic substituent, providing unsubstituted propargylic alcohols (Scheme 16).[20] Attempts to add the Zn-alkynilide of **20** to aldehyde **8** however, did not result in formation of the desired product. Though reactions using unsubstituted aliphatic aldehydes have been reported, the yields are lower than reactions using shorter substituted aliphatic aldehydes or cyclic aldehydes.

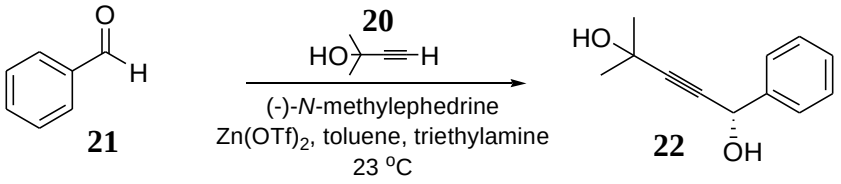


Scheme 15. Direct Synthesis of 6



Scheme 16. Route to Unsubstituted Propargyl Alcohols (From Ref. 20)

As a check on our technique, we attempted to repeat one of the reactions reported in the Carreira paper. The addition of acetylene **20** to benzaldehyde (**21**) had been reported to provide propargyl alcohol **22** in quantitative yield. This reaction was repeated successfully in our laboratory, indicating that the aldehyde **8** was the source of the trouble in our reactions. We concluded that the aldehyde **8** does not easily submit to this type of addition and other methods were explored.



Scheme 17. Addition of Acetylene 20 to Benzaldehyde

Asymmetric reduction of acetylenic enones such as **23** by oxazaborolidines has been reported previously, and there is ample precedent for the successful reduction of compounds similar to our compound **19** (Figure 12).[22,23] However, commercially available oxazaborolidine catalyst is relatively expensive, so a model compound was employed to optimize the reaction conditions. The reduction of similar enone **23** has been reported in quantitative yield and 95% ee.[24] It should be noted that the trimethylsilyl (TMS) group can be easily removed and replaced with the desired ester function. As a model compound, we chose a hybrid between the desired compound **19** and the known compound **23**. In the model compound **24**, the length of the aliphatic chain on the aldehyde is preserved from **19** and the TMS group from **23** is retained (Figure 12).

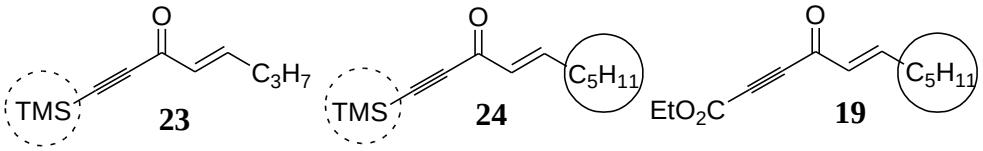
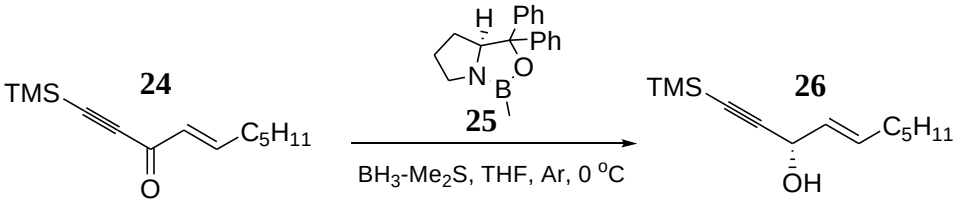


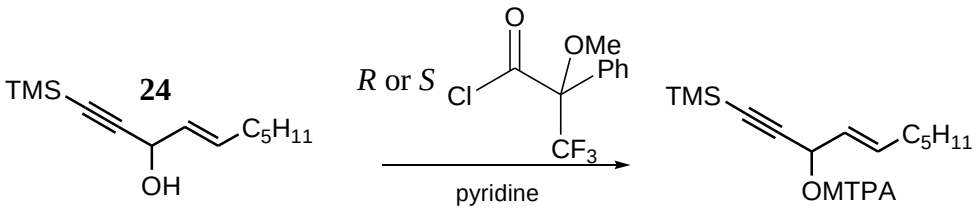
Figure 12. Similar Enone, Model Compound and Desired Compound

Compound **24** was obtained via oxidation of racemic alcohol **26** either by manganese oxide or Jones' reagent.[25,26] Compound **26** was prepared in turn from *n*-butyl lithium promoted addition of trimethylsilylacetylene to *trans*-2-octenal (**8**).[24] Product **24** was subjected to reduction by (*S*)-2-methyl-CBS-oxazaborolidine **25** and borane-dimethylsulfide quantitatively yielding the enantioenriched alcohol **26**. The absolute configuration and ee of this compound were determined using the modified Mosher method as described below.[27]



Scheme 18. Asymmetric Reduction of 24

According to the modified Mosher method reported by Ohtani[27], the (*R*)- and (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters of **26** were produced from the appropriate commercially available MTPA acid chlorides (Scheme 19). It has been shown that MTPA esters adopt a preferred eclipsed conformation creating an "MTPA plane" (Figure 13). Of note is the relative position of the phenyl ring to the substituents on either side of the MTPA plane. The diamagnetic effect of the benzene ring in the MTPA ester causes shifting of proton signals. In one compound, the phenyl ring will affect the trimethylsilyl acetylene substituent and in the other, the effect will be on the unsaturated aliphatic chain. Calculations using the difference between the proton signals for the corresponding hydrogens in each enantiomer of the ester provide enough evidence for assignment of absolute stereochemistry. Integration of the methoxy singlets due to each enantiomer of **24** in either the *R*- or *S*- ester provides the enantiomeric excess. NMR shift data for our mixture was consistent with the absolute stereochemistry shown for **26** with an ee of 80%.



Scheme 19. Formation of MTPA Esters

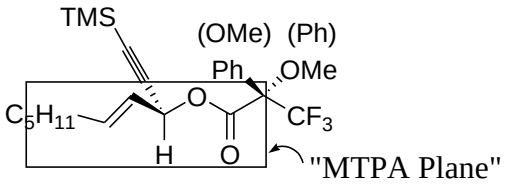
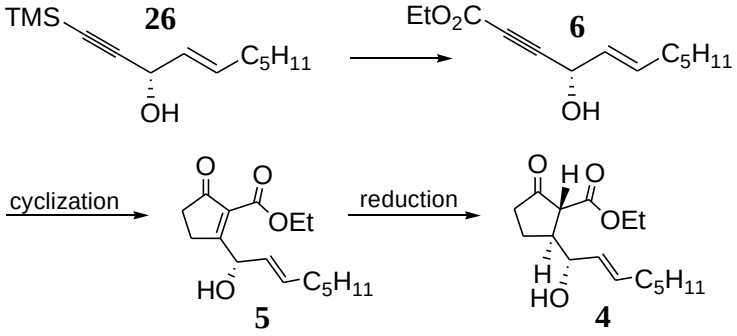


Figure 13. MTPA Plane (From Ref. 27)

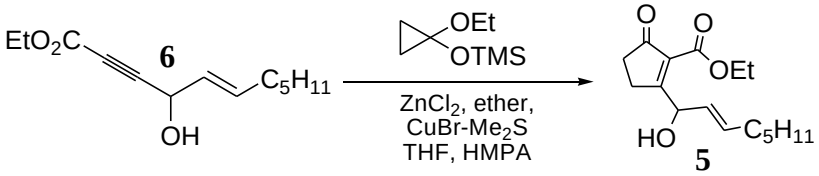
With this result in hand, the desired compound **19** has been oxidized with Jones' reagent. Studies of the asymmetric reduction of **19** to the desired acetylenic intermediate

6 with the oxazaborolidine **25** are currently in progress. The other pathway available from this result is the cleavage of TMS from **26** followed by introduction of the desired ester function for which there is ample precedent.[24,28,29] Both methods are now available to create the key stereo center in the molecule. With this in hand, studies on the asymmetric reduction in Step 3 can be carried out.

We next focused our attention on construction of the cyclopentenone core of the PGs via the aforementioned Crimmins procedure.[9] Our intention was to employ chiral intermediate **26** or **6** to provide **5** which could be used to evaluate the proposed conjugate reduction (Scheme 20). In an effort to evaluate and determine the optimum conditions for the Crimmins reaction, we employed the readily available racemic **6** (Scheme 21). Once we felt confident that the conversion of racemic **6** to racemic **5** went well, we could employ the more precious chiral reagents **26** or **6**.

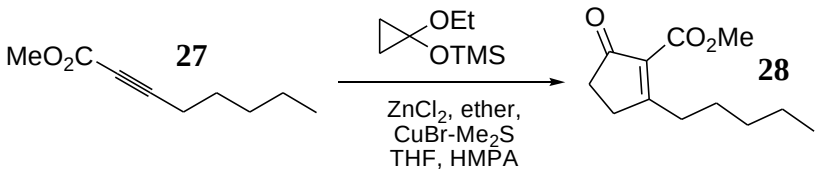


Scheme 20. Cyclization to Provide 5



Scheme 21. Cyclization

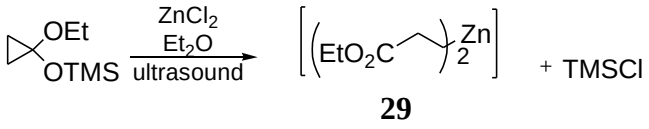
Initial attempts at the synthesis of racemic cyclopentenone intermediate **5** from racemic **6** failed. To diagnose the problem, the inexpensive, commercially available model compound **27** was employed. Methyl octynoate (**27**) was chosen both for its availability and for its similarity to methyl heptynoate, which was used in the original research in the laboratory of Dr. Crimmins (Scheme 22). In our hands, the model compound **28** was produced in 12-15% yield, as compared to the 65% yield originally reported for a similar system by Crimmins.



Scheme 22. Cycloaddition using Methyl Octynoate (27)

Several factors could be responsible for the low yield. Accordingly, we set out to systematically test each variable. Suspecting the copper bromide complex may be bad, we attempted to synthesize and purify fresh material via the published procedure.[30,31] Eventually we bought new commercially available copper bromide-dimethylsulfide complex which was colorless and appeared to be of good purity. Unfortunately, yields for the reaction remained low.

With good copper bromide in hand and confident of the purity of our reaction solvents, we attempted to evaluate the first step – formation of zinc homoenolate **29** via sonication of (1-ethoxycyclopropyloxy)trimethylsilane (Scheme 23). It has been reported that **29** is stable in deuterochloroform solution and can be analyzed by NMR.[32,33] Thus, (1-ethoxycyclopropyloxy)trimethylsilane was sonicated in dry ether in the presence of zinc chloride. Analysis by NMR, however, did not show formation of the expected homoenolate **29**.[32,33] A conversation with Dr. Crimmins confirmed our suspicion that perhaps the zinc chloride reagent was bad.[34] Dr. Crimmins mentioned that in early iterations of the reaction, commercial zinc chloride solutions provided adequate formation of the homoenolate (**29**). He went on to say that later reactions using commercial zinc chloride were unsuccessful, and laboratory prepared zinc chloride was used instead, with success. The zinc chloride employed in our laboratory was obtained commercially as a 1 M solution in diethylether and had been recently purchased. An equivalent solution can be made in the laboratory by fusing solid zinc chloride under vacuum and subsequently sonicating the solid with an appropriate amount of dry diethylether to facilitate dissolution. Alternatively, new zinc chloride solution in ether can be purchased from a different vendor for use in the reaction. Both methods are currently being tested in the laboratory.

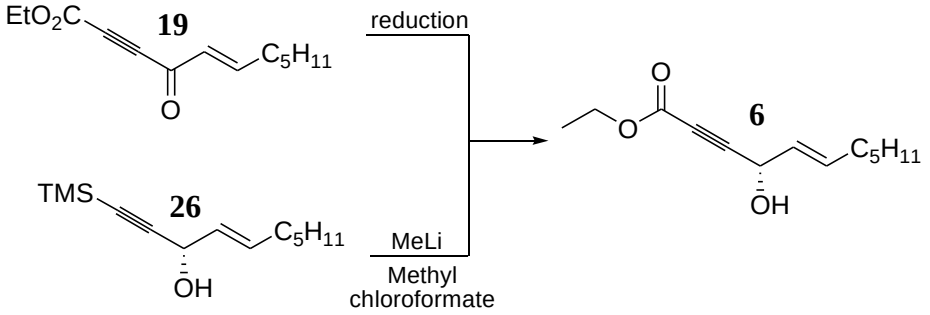


Scheme 23. Formation of Zinc Homoenolate

Future Work

Future work will involve:

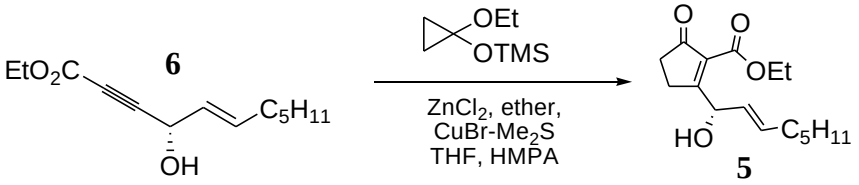
(1) Preparation of optically pure **6** via either direct reduction of intermediate **19** or conversion of 26 (Scheme 24).[35]



Scheme 24. Preparation of Optically Pure 6

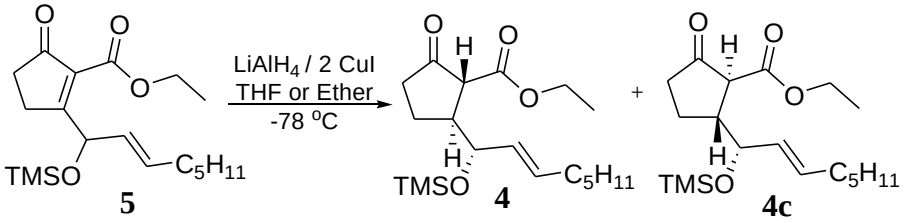
(2) Optimization of the Crimmins conditions for preparation of **5** with racemic **6**.

(3) Synthesis of optically pure **5** from optically pure **6** (Scheme 21).



Scheme 20. Cyclization

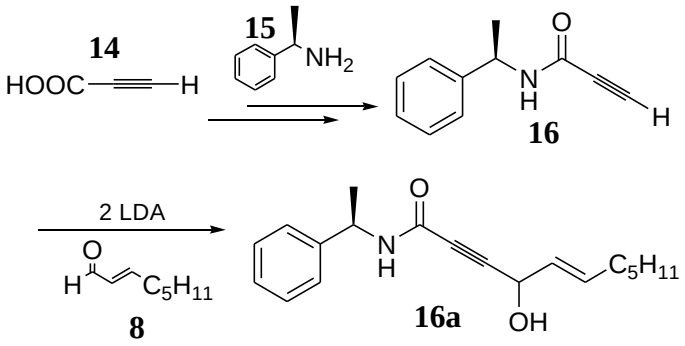
(4) Evaluation of the asymmetric conjugate reduction of **5** to provide the cyclopentenone skeleton **4** (Scheme 25).



Scheme 25. Evaluation of Conjugate Reduction

(5) Evaluation of the corresponding amide analogs of **6** in the overall synthesis plan. These are reported to provide better yields in the Crimmins procedure. There are also a

number of readily available chiral amines which could be used for preparation of chiral amide intermediates **16a** (Scheme 26).



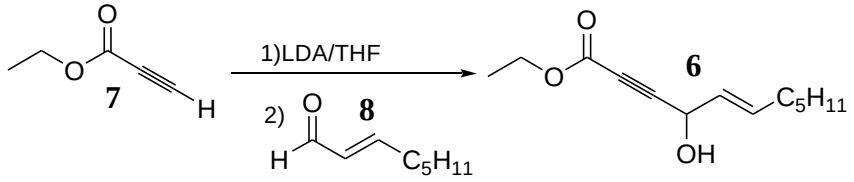
Scheme 26. Creation of Chiral Amides

Experimental

General Procedures

Solvents and chemicals were purchased from Aldrich and other local suppliers and were used as received (unless otherwise noted). NMR Spectra were collected using a Bruker Avance 400 MHz spectrometer. All spectra were acquired using $CDCl_3$ as the solvent referenced to tetramethylsilane at δ 0.00 or to the isotopic impurity peak for the solvent. FT-IR were acquired using a Perkin-Elmer Spectrum One ATR spectrometer. Flash chromatographic separations were done using JT Baker 400 mesh silica gel as the stationary phase. All reactions were monitored by thin-layer chromatography on EM Science 60 F_{254} silica gel. THF used as a solvent was freshly distilled under nitrogen from potassium with benzophenone as an indicator (unless otherwise noted). Glassware for air and moisture sensitive reactions was flame dried, or oven dried at 120 °C for 2 hours and purged with dry nitrogen prior to use (unless otherwise noted).

Synthesis of ethyl 4-hydroxyundec-5-en-2-ynoate (racemic 6)

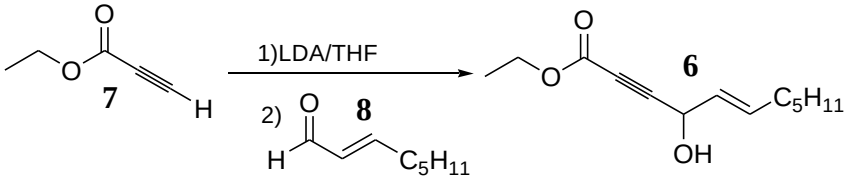


Method A (Ref. 8)

To a stirred solution of LDA (3.0 mL, 6.0 mmol) in THF (20 mL) at –78 °C under nitrogen was added dropwise a solution of ethyl propiolate (**7**) (1.1 mL, 1.1 g, 11 mmol) in THF (10 mL). The brown solution was stirred for 30 minutes at –78 °C after which a solution of *trans*-2-octenal (**8**) (1.5 mL, 1.3 g, 10 mmol) in THF (5 mL) was added. The reaction mixture was stirred at –78 °C until the aldehyde was consumed as observed by TLC (9:1 hexane: ethyl acetate). A saturated solution of ammonium chloride (5 mL) was added and the mixture was allowed to warm to room temperature. The organic phase was concentrated under reduced pressure and dissolved in ethyl ether (10 mL). The solution was washed with water and brine and dried over $MgSO_4$. The crude product was purified by flash chromatography (9:1 hexane: ethyl acetate) to yield **6** as a yellow oil (0.39 g mg, 17%). FT-IR (ATR) 3400 cm^{-1} (OH); 3100 cm^{-1} (C=C-H); 1750 cm^{-1} (C=O); 1050 cm^{-1} (C-O-C). ^{1}H NMR[b] ($CDCl_3$, 400 MHz): δ 0.80 (t, 3H, *J* = 8 Hz); 1.18-1.28 (m, 11 H); 4.18 (q, 2 H); 4.88 (s (br), 1 H); 5.49-5.55 (m, 1 H); 5.84-5.88 (m, 1 H). DEPT-135 ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.42 (CH_3), 14.45 (CH_3), 22.90 (CH_2), 28.79 (CH_2), 31.78 (CH_2), 32.39 (CH_2), 62.64 (CH_2), 63.13 (CH), 127.1 (CH), 136.3 (CH). The NMR spectrum for the ethyl propiolate starting material is shown as **A** in the Appendix, the *trans*-2-octenal starting material is shown as **B** in the Appendix and the pure product **6** is shown as **C** in the Appendix.

[b] The ^{1}H NMR and IR data for this compound agree with the data reported in reference 8, with the exception of the proton in the ^{1}H NMR at δ 4.88, which was not reported previously.

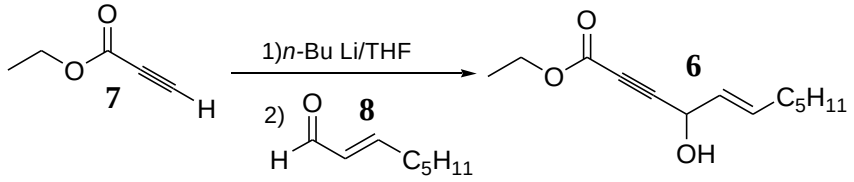
Synthesis of ethyl 4-hydroxyundec-5-en-2-ynoate (racemic 6)



Method B

To a stirred solution of LDA (1.6 mL, 2.8 mmol) in dry THF (1 mL) at –78 °C under nitrogen was added dropwise ethyl propiolate (**7**) (0.11 mL, 0.11 g, 1.1 mmol). The brown solution was stirred for 30 minutes at –78 °C and *trans*-2-octenal (**8**) (0.15 mL, 0.13 g, 1.1 mmol) was added dropwise. The reaction mixture was stirred at –78 °C, and monitored by TLC (9:1 hexane: ethyl acetate) for disappearance of the aldehyde starting material. After 40 minutes a saturated solution of ammonium chloride (0.5 mL) was added and the mixture was allowed to warm to room temperature. The organic phase was extracted with ethyl ether (20 mL). The combined organic phases were washed with water and brine and dried over $MgSO_4$. The crude product was purified by flash chromatography (9:1 hexane: ethyl acetate) to yield **6** as a light yellow oil (0.21 g, 94%).

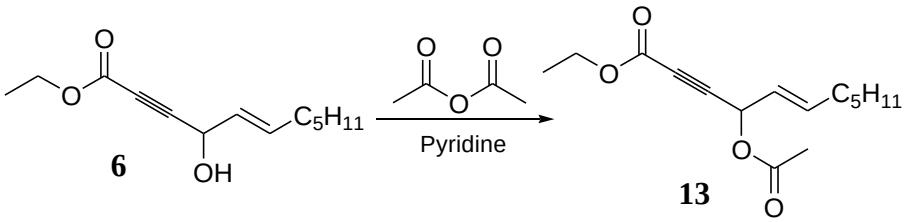
Synthesis of ethyl 4-hydroxyundec-5-en-2-ynoate (racemic 6)



Method C

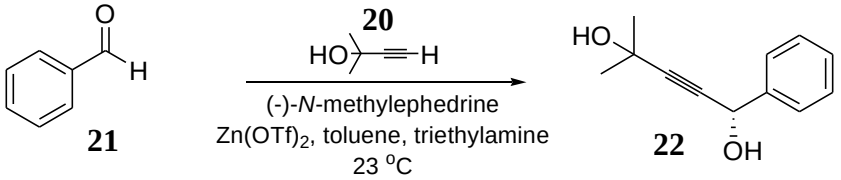
To a flame dried round bottom flask was added dry tetrahydrofuran (10 mL) and ethyl propiolate (**7**) (1.0 mL, 10 mmol). The clear solution was cooled to -78 °C and a 2.0 M of *n*-butyl lithium in cyclohexane (5.6 mL, 11 mmol) was added dropwise. As the base was added, the solution turned from clear and colorless to dark brown. The solution was allowed to stir at -78 °C for 10 minutes and *trans*-2-octenal (**8**) (1.2 mL, 8.2 mmol) was added dropwise. The reaction mixture was stirred for 45 minutes and monitored by TLC (1:9 ethyl acetate: hexanes, *p*-anisaldehyde stain, UV light). After 45 minutes, some of the aldehyde starting material remained. The reaction mixture was warmed to room temperature after which it was poured over pH 7.0 phosphate buffer. The organic layer was extracted with ether (2 x 50 mL) and the combined organic layers were washed with water and brine, dried over $MgSO_4$. Solvent was removed under reduced pressure to give **6** as a brown oil. ^{1}H NMR of the crude oil showed that it contained desired product and aldehyde starting material. The crude product was used directly in the next step without further purification.

Synthesis of ethyl 4-acetoxyundec-5-en-2-ynoate (13)



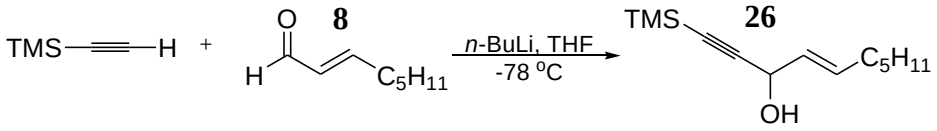
To a stirred solution of pyridine (0.75 mL) and acetic anhydride (0.25 mL) was added ethyl 4-acetoxyundec-5-en-2-ynoate (**6**) (0.12 g, 0.50 mmol). The reaction mixture was allowed to stir at room temperature for one hour and was monitored by TLC (1:9 ethyl acetate: hexanes, uv light) for disappearance of starting material after which the reaction was cooled to 0 °C and saturated aqueous ammonium chloride solution was added. The organic layer was diluted with ether, washed with ammonium chloride solution and brine, dried over magnesium sulfate. Solvent was removed under reduced pressure and excess pyridine was removed by azeotropic distillation with toluene providing **13** as a brown oil (82 mg, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (t, 3H, *J* = 7.1 Hz); 1.19-1.35 (m, 11 H); 2.00 (s, 3 H); 4.18 (q, 2 H); 5.42-5.48 (m, 1 H); 5.84 (d, 1 H, *J* = 6.8 Hz); 5.90-5.97 (m, 1 H). The ^{1}H NMR of this product is found in the Appendix as **D**.

Synthesis of (*S*)-4-methyl-1-phenylpent-2-yne-1,4-diol (22)



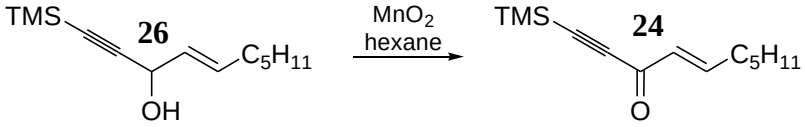
To an oven dried round bottom flask and stirbar was added zinc triflate (0.80 g, 2.2 mmol) and (-)-*N*-methylephedrine (0.41 g, 2.3 mmol). The flask was purged with dry nitrogen for 15 minutes after which toluene (6.0 mL) and triethylamine (0.23 g, 2.3 mmol) were added. The resulting suspension was stirred for 2 hours after which 2-methylbut-3-yn-2-ol (**20**) (0.19 g, 2.3 mmol) was added. The suspension was stirred for 15 minutes followed by the addition of benzaldehyde (**21**) (79 mg, 0.74 mmol). The mixture was stirred overnight after which saturated aqueous ammonium chloride (4 mL) was added. The organic layer was extracted with ether (2 x 20 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the crude product as a yellow oil which was purified by flash chromatography (1:2 ethyl acetate: hexanes) to give **22** as a white solid (0.13 g, 93%). mp 65-68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 6 H); 5.50 (s (br), 1 H); 7.33-7.46 (m, 3 H); 7.54-7.56 (m, 2 H). The ^{1}H NMR of benzaldehyde, 2-methylbut-3-yn-2-ol and (-)-*N*-methylephedrine starting materials can be found in the appendix as **E**, **F**, and **G** respectively. The ^{1}H NMR of **22** can be found in the appendix as **H**.

Synthesis of 1-(trimethylsilyl)dec-4-en-1-yn-3-ol (racemic 26)



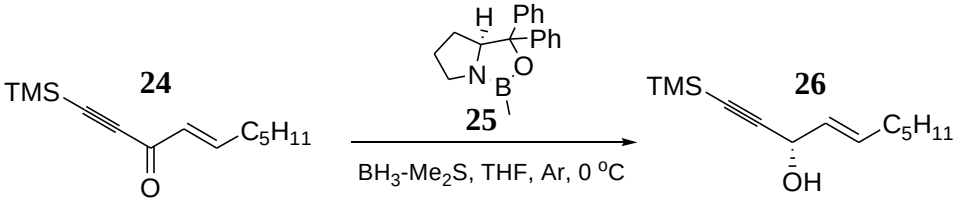
To an oven dried round bottom flask was added trimethylsilylacetylene (0.82 mL, 5.9 mmol) and tetrahydrofuran (6 mL). The solution was cooled to -78 °C and *n*-butyl lithium (2.5 mL, 5.0 mmol) was added dropwise. The solution was stirred for 10 minutes after which *trans*-2-octenal (**8**) (0.75 mL, 5.0 mmol) was added dropwise. After 10 minutes, TLC analysis (2:1 dichloromethane: hexanes, *p*-anisaldehyde stain, UV light) revealed that the starting material had been consumed. The reaction mixture was warmed to room temperature and poured into pH 7.0 phosphate buffer. The organic layer was extracted with dichloromethane (2 x 20 mL), washed with brine and dried over Na_2SO_4. The solvent was removed to give the crude product as a light yellow oil (1.2 g, 92%). ^{1}H NMR of the crude mixture showed that it contained a 1:5 mixture of aldehyde starting material to product. The crude product (**26**) was taken to the next step without further purification. ^{1}H NMR ($CDCl_3$ 400 MHz): δ 0.00 (s, 9 H); 1.10-1.40 (m, 11 H); 4.62-4.65 (m, 1 H); 5.41-5.42 (m, 1 H); 5.67-5.72 (m, 1 H). The ^{1}H NMR of the trimethylsilylacetylene starting material and the product (**26**) can be found in the appendix as **I** and **J** respectively.

Synthesis of 1-(trimethylsilyl)dec-4-en-1-yn-3-one (24)



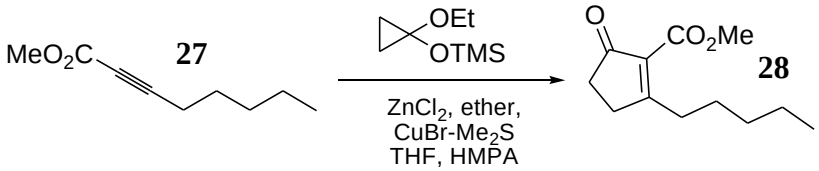
To a crude mixture of *trans*-2-octenal and **26** (1:5 mixture, 0.51 g total, 2.3 mmol) in hexanes (5.0 mL) was added MnO_2 (2.7 g, 31 mmol). The heterogeneous mixture was stirred overnight at room temperature. TLC analysis (1:9 ethyl acetate: hexanes, *p*-anisaldehyde stain, UV light) showed disappearance of the starting material. The mixture was filtered through celite and the solvent removed to give the crude product as a yellow oil, ^{1}H NMR of the crude mixture showed desired product, and *trans*-2-octenal left over from the previous step. The product was purified by flash chromatography (1:9 ethyl acetate: hexanes) to yield **24** as a light yellow oil (0.12 g, 29% yield based on conversion of the starting material **26**). ^{1}H NMR ($CDCl_3$ 400 MHz): δ 0.28 (s, 9 H); 1.28-1.61 (m, 11 H); 6.17 (d, 1 H, J = 15.8 Hz); 7.18-7.28 (m, 1 H). The ^{1}H NMR of the product **24** can be found in the appendix as **K**.

Synthesis of (*S*)-1-(trimethylsilyl)dec-4-en-1-yn-3-ol (26)



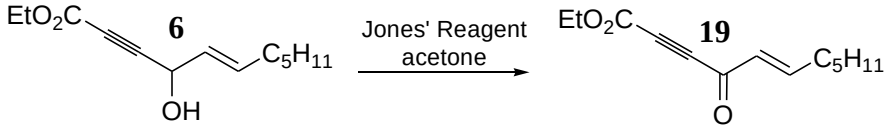
To an oven dried round bottom flask under argon at 0 °C was added tetrahydrofuran (2 mL), a 1 M solution of (*S*)-2-methyl-CBS-oxazaborolidine in toluene (0.50 mL, 0.50 mmol) and 2 M solution of borane-dimethyl sulfide in tetrahydrofuran (0.29 mL, 0.57 mmol). The mixture was stirred for 5 minutes at 0 °C and a solution of 1-(trimethylsilyl)dec-4-en-1-yn-3-one (**24**) (0.12 g, 0.50 mmol) in tetrahydrofuran (1 mL) was added dropwise over 10 minutes. Upon completion of addition, TLC analysis (1:9 ethyl acetate: hexanes, *p*-anisaldehyde stain, UV light) revealed complete disappearance of the starting material. The reaction was cautiously quenched with methanol (1 mL) at 0 °C and then stirred for 15 minutes at room temperature. Solvent was removed under reduced pressure to provide a viscous yellow oil. ^{1}H NMR of the crude mixture showed formation of desired product. The crude oil was purified by flash chromatography (1:9 ethyl acetate: hexanes) to yield **26** quantitatively and with 80% ee. ^{1}H NMR ($CDCl_3$ 400 MHz): δ 0.0 (s, 9 H); 1.1-1.4 (m, 11 H); 4.62-4.65 (m, 1 H); 5.37-5.43 (m, 1 H); 5.68-5.72 (m, 1 H). The ee of the product was analyzed using the modified Mosher method. The ^{1}H NMR data for the product, *R*-MTPA ester and *S*-MTPA ester are found in the appendix as **L**, **M**, and **N** respectively.

Synthesis of methyl 5-oxo-2-pentylcyclopent-1-enecarboxylate (28)



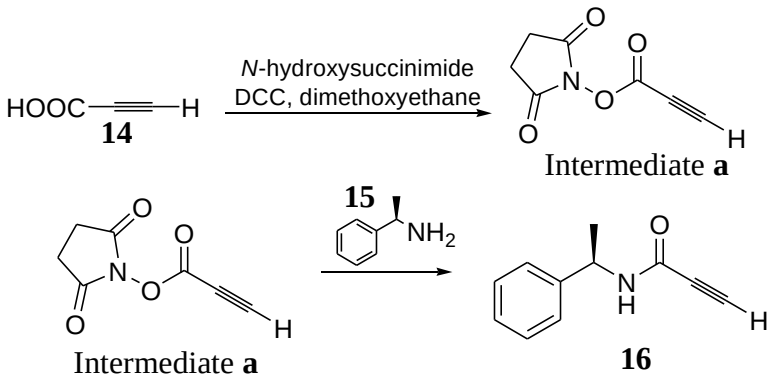
To a flame dried round bottom flask under dry nitrogen was added dry ether (9 mL), (1-ethoxycyclopropoxy)trimethylsilane (2.4 mL, 12 mmol), and a 1 M solution of $ZnCl_2$ in ether (9.0 mL, 9.0 mmol). The solution was sonicated for 40 minutes and stirred for an additional 10 minutes at room temperature. To the heterogeneous mixture was added CuBr-Me_2S (0.15 g, 0.75 mmol), a solution of methyl oct-2-ynoate (**27**) (0.77 g, 5 mmol) in tetrahydrofuran (18 mL) and hexamethylphosphoramide (2.1 mL, 12 mmol). The reaction mixture was stirred at room temperature and monitored by TLC (1:9 ethyl acetate: hexanes, *p*-anisaldehyde stain, UV light). The reaction was quenched by addition of saturated aqueous ammonium chloride solution. The organic layer was washed with half saturated ammonium hydroxide solution until no blue color appeared in the wash. The organic layer was then washed with water and brine, dried over $MgSO_4$. Solvent was removed under reduced pressure to leave a yellow oil. ^{1}H NMR of the crude mixture showed the alkyne starting material present as well as many other peaks. The product was purified by flash chromatography (1:3 ethyl acetate: hexanes) to give **28** as a light yellow oil (0.17 g, 16%). ^{1}H NMR ($CDCl_3$ 400 MHz): δ 0.78-0.81 (m, 3 H); 1.22-1.25 (m, 4 H); 1.38-1.50 (m, 2 H); 2.36-2.39 (m, 2 H); 2.56-2.57 (m, 2 H); 2.63-2.65 (m, 2H); 3.73 (s, 3 H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 14.2, 22.7, 27.8, 30.8, 32.2, 33.0, 35.3, 52.3, 133, 164, 190, 204. The ^{1}H NMR of the (1-ethyoxycyclopropoxy)-trimethylsilane and methyl octynoate starting materials are found in the appendix as **O** and **P** respectively. The ^{1}H and ^{13}C NMR for the product **28** are found in the appendix as **Q** and **R** respectively.

Synthesis of ethyl 4-oxoundec-5-en-2-ynoate (19)



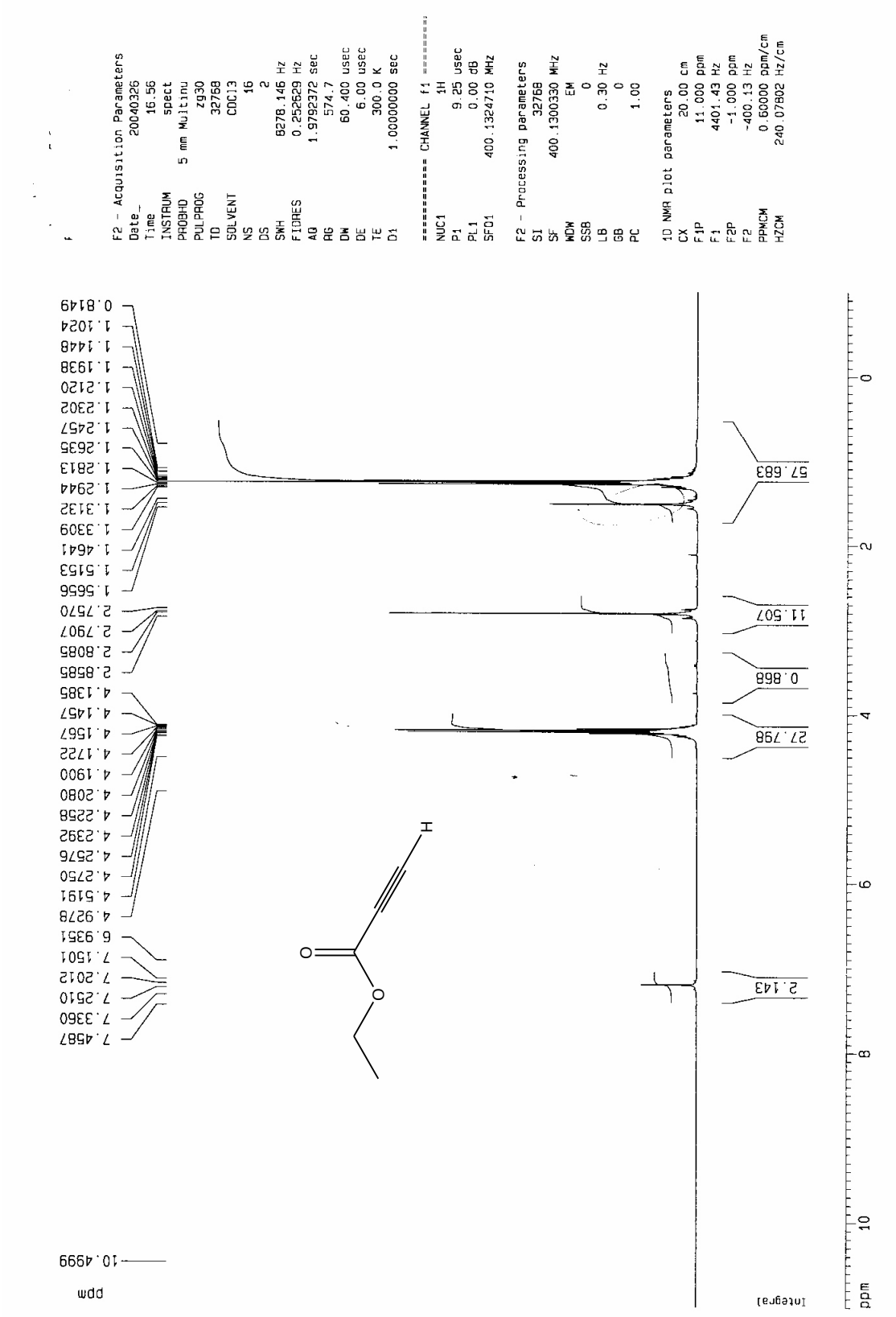
To an oven dried round bottom flask was added ethyl 4-hydroxyundec-5-en-2-ynoate (**6**) (0.15 g, 0.67 mmol) and acetone (2.7 mL). This mixture was stirred and Jones' reagent (0.22 mL, 0.74 mmol) was added dropwise. Upon addition of the first drop of Jones' reagent, the solution changed from clear yellow to clouded greenish yellow. With each subsequent drop of Jones' reagent, the solution turned more green. The mixture was allowed to stir for 5 minutes. After 5 minutes a green solid had precipitated, however there was still evidence of starting material by TLC analysis (1:9 ethyl acetate: hexanes, *p*-anisaldehye stain, UV light). The mixture was stirred for an additional 20 minutes, but no change in TLC was observed. The reaction was quenched with methanol, water was added, and the organic layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with water, brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. ^{1}H NMR of the crude mixture showed desired product **19** and minor impurities. The yellow oil (0.14 g, 93 %) was used directly in the next step without further purification. ^{1}H NMR ($CDCl_3$ 400 MHz): δ 0.73-0.76 (m, 3H); 1.15-1.21 (m, 11 H); 4.11-4.20 (m, 2 H); 6.05 (d, 1 H, J = 15.6 Hz); 7.05-7.12 (m, 1 H). The ^{1}H NMR of the product **19** is found in the appendix as **S**.

Synthesis of (*R*)-*N*-(1-phenylethyl)propiolamide (16)



To an oven dried round bottom flask was added dimethoxyethane (10 mL), propiolic acid (**14**) (0.89 mL, 14 mmol), *N*-hydroxysuccinimide (1.6 g, 14 mmol) and solid dicyclohexylcarbodiimide (DCC) (3.0 g, 14 mmol). Upon addition of DCC, an exothermic reaction ensued resulting in precipitation of a solid. An additional 10 mL of dimethoxyethane was added to facilitate stirring. The reaction mixture was allowed to stir under dry nitrogen for 18 hours. The precipitate was filtered and the solvent removed to give the unstable intermediate **a** as a yellow oil. This oil was used without further purification. To a stirred solution of intermediate **a** (2.1 g, 14 mmol) in dichloromethane (6 mL) was added dropwise (*R*)-1-phenylethanamine (**15**) (1.5 g, 13 mmol). Upon addition of the amine, the reaction mixture heated up. The brown solution was allowed to stir for 24 hours and was then washed with 10 % aqueous sodium carbonate and 1 N HCl. The organic layer was dried over sodium sulfate and the solvent removed under reduced pressure to give a brown oil (3.8 g). ^{1}H NMR of the crude mixture showed presence of the desired product **16**. The crude product was purified by flash chromatography with chloroform as an eluent. About 5% (0.10 g) of the theoretical yield of product was recovered from this purification. mp 86-88 °C. ^{1}H NMR ($CDCl_3$ 400 MHz): 1.54-1.56 (m, 3 H); 2.79 (s, 1 H); 5.15-5.22 (m, 1 H); 6.22 (s (br), 1 H); 7.28-7.40 (m, 5 H). The ^{1}H NMR data of the DCC, (*R*)-1-phenylethanamine, *N*-hydroxysuccinimide, and propiolic acid starting materials is found in the appendix as **T**, **U**, **V**, and **W** respectively. The ^{1}H NMR of the product (**16**) is found in the appendix as **X**.

Appendix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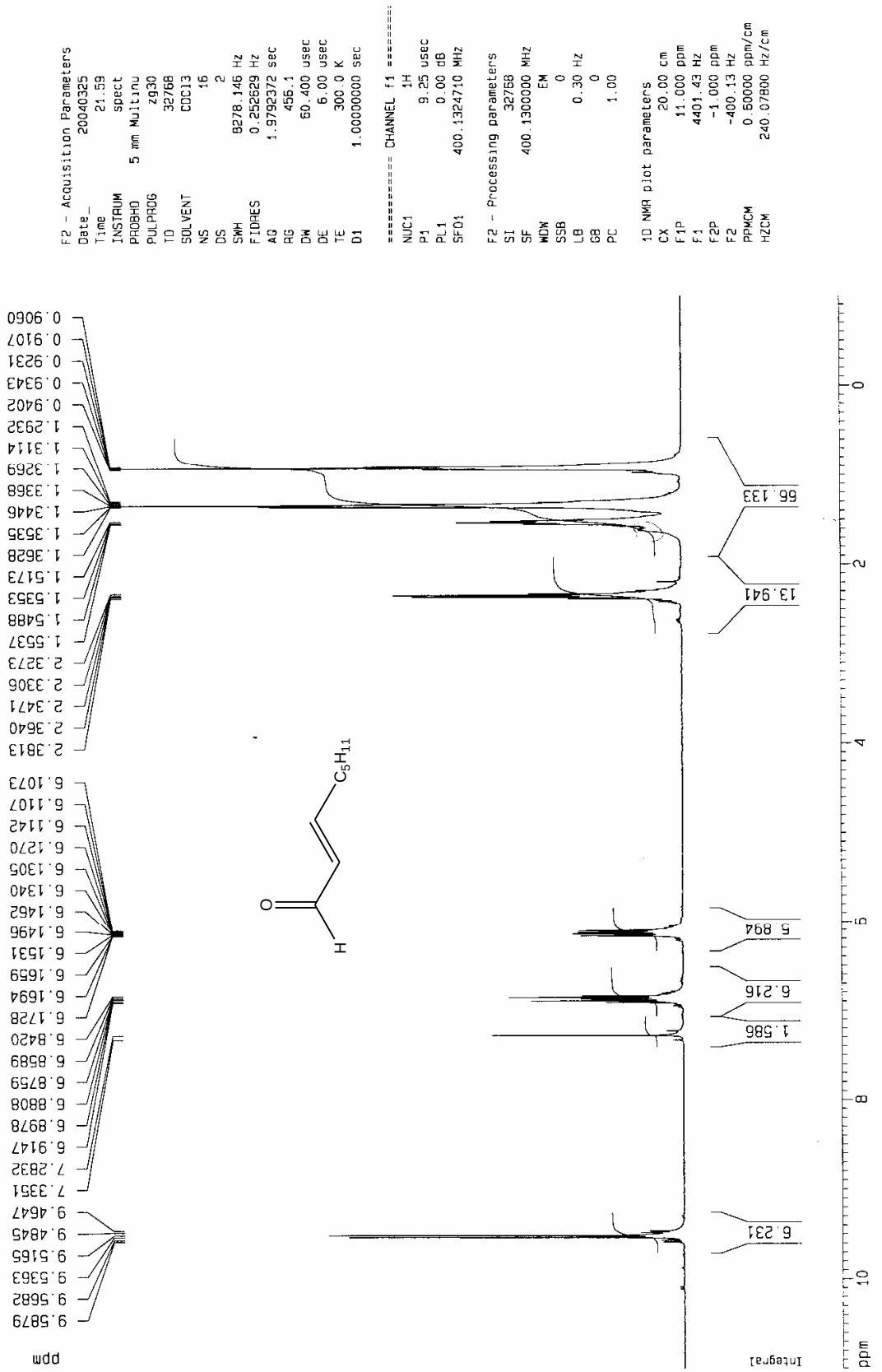
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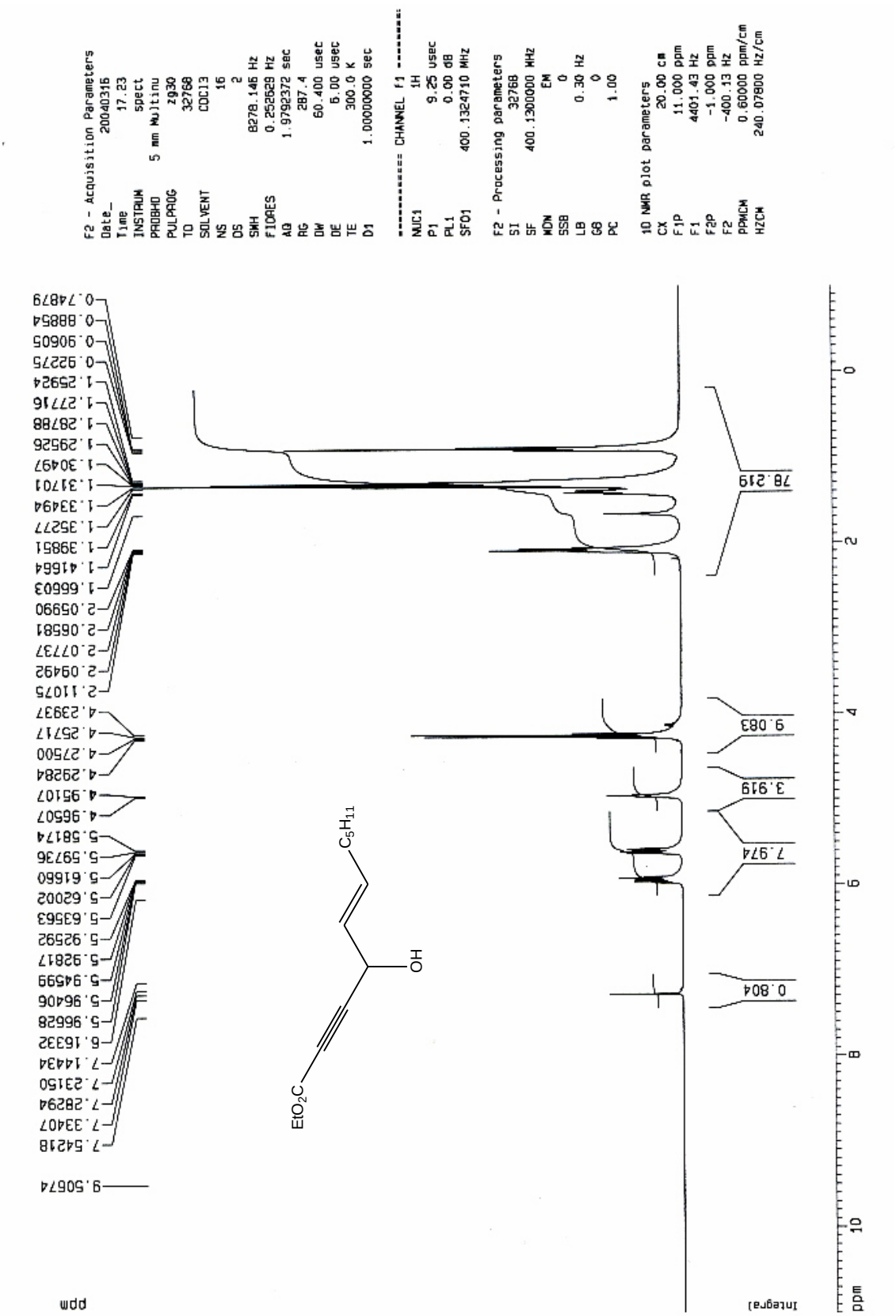
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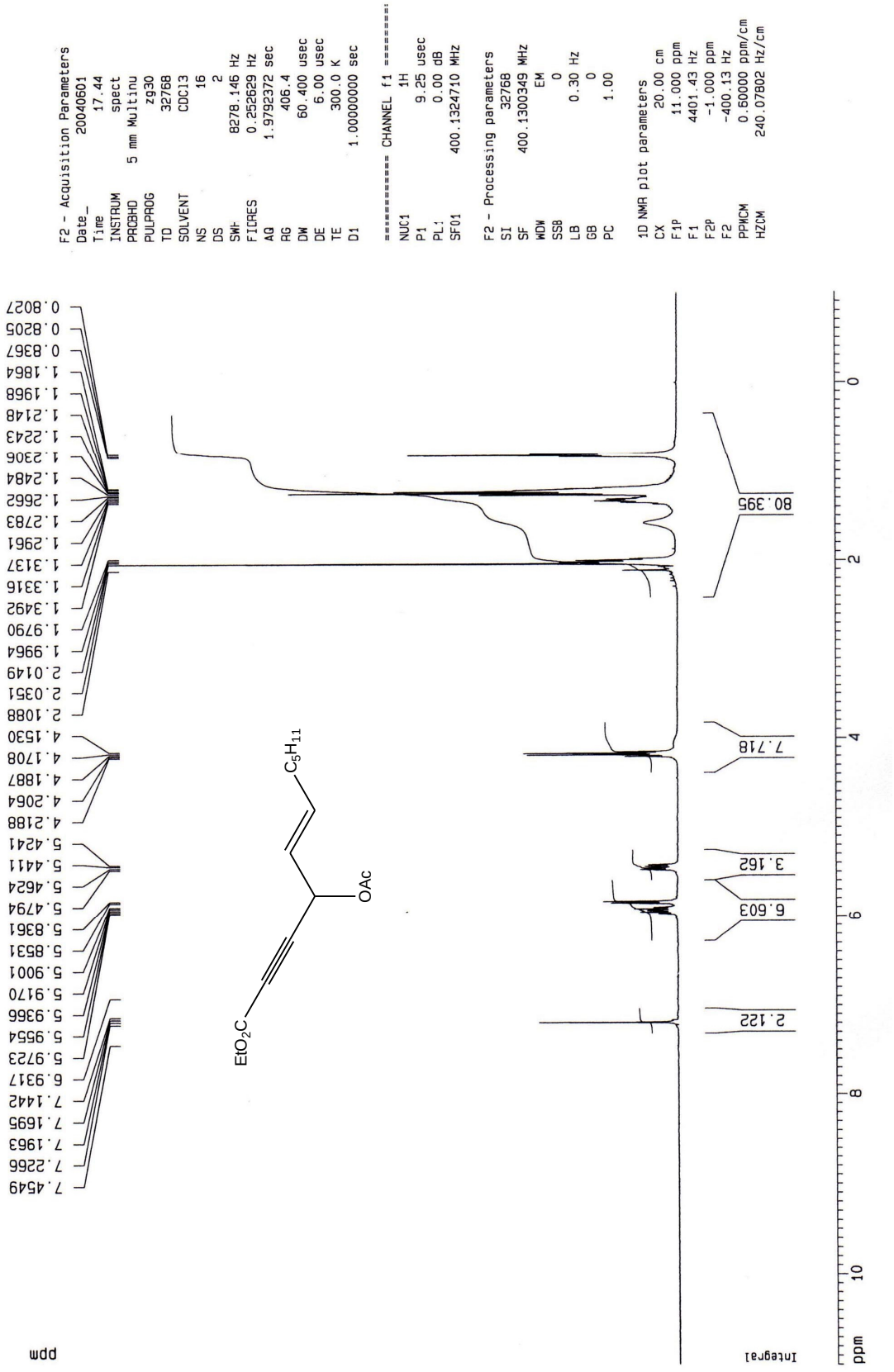
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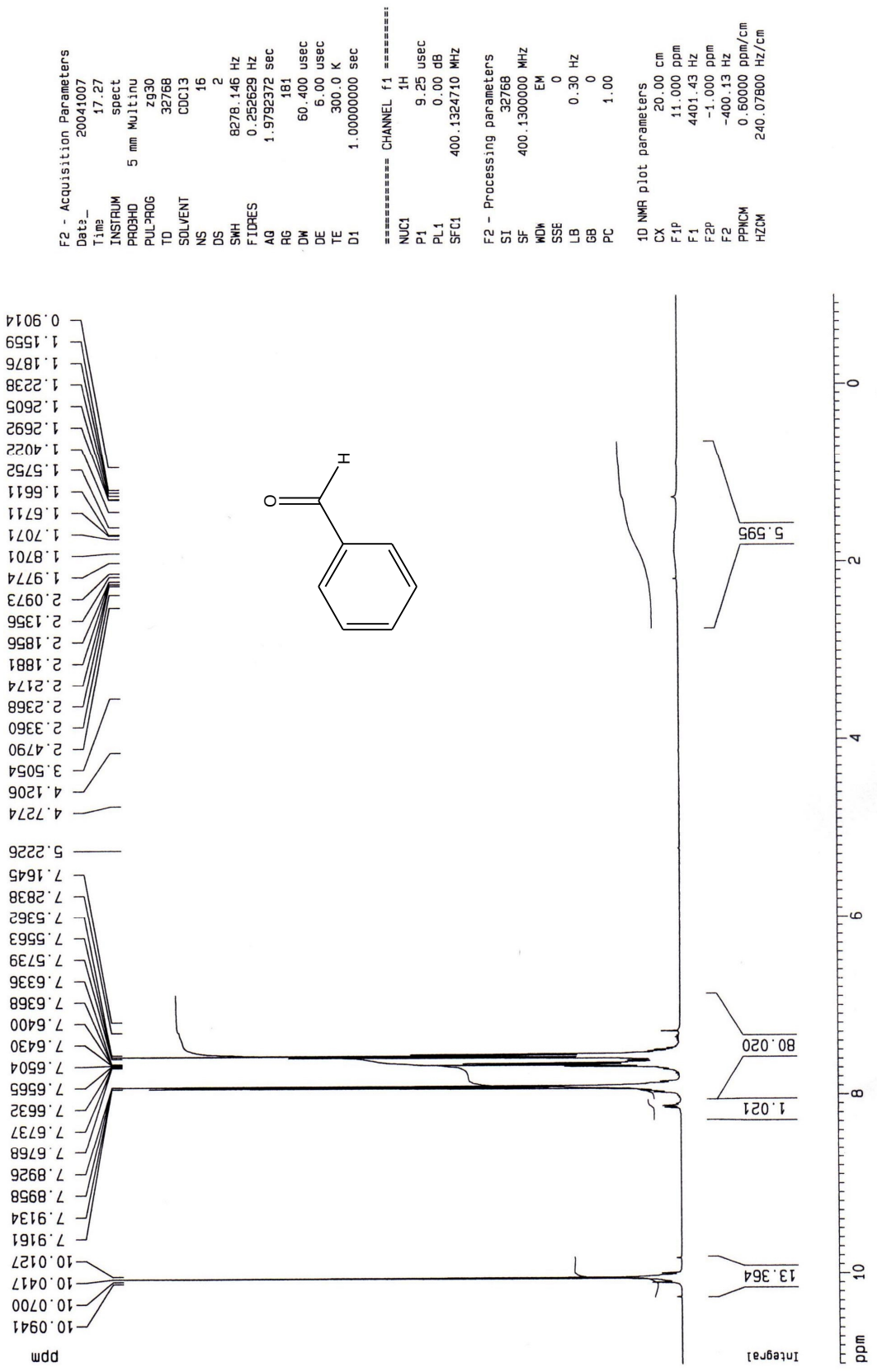
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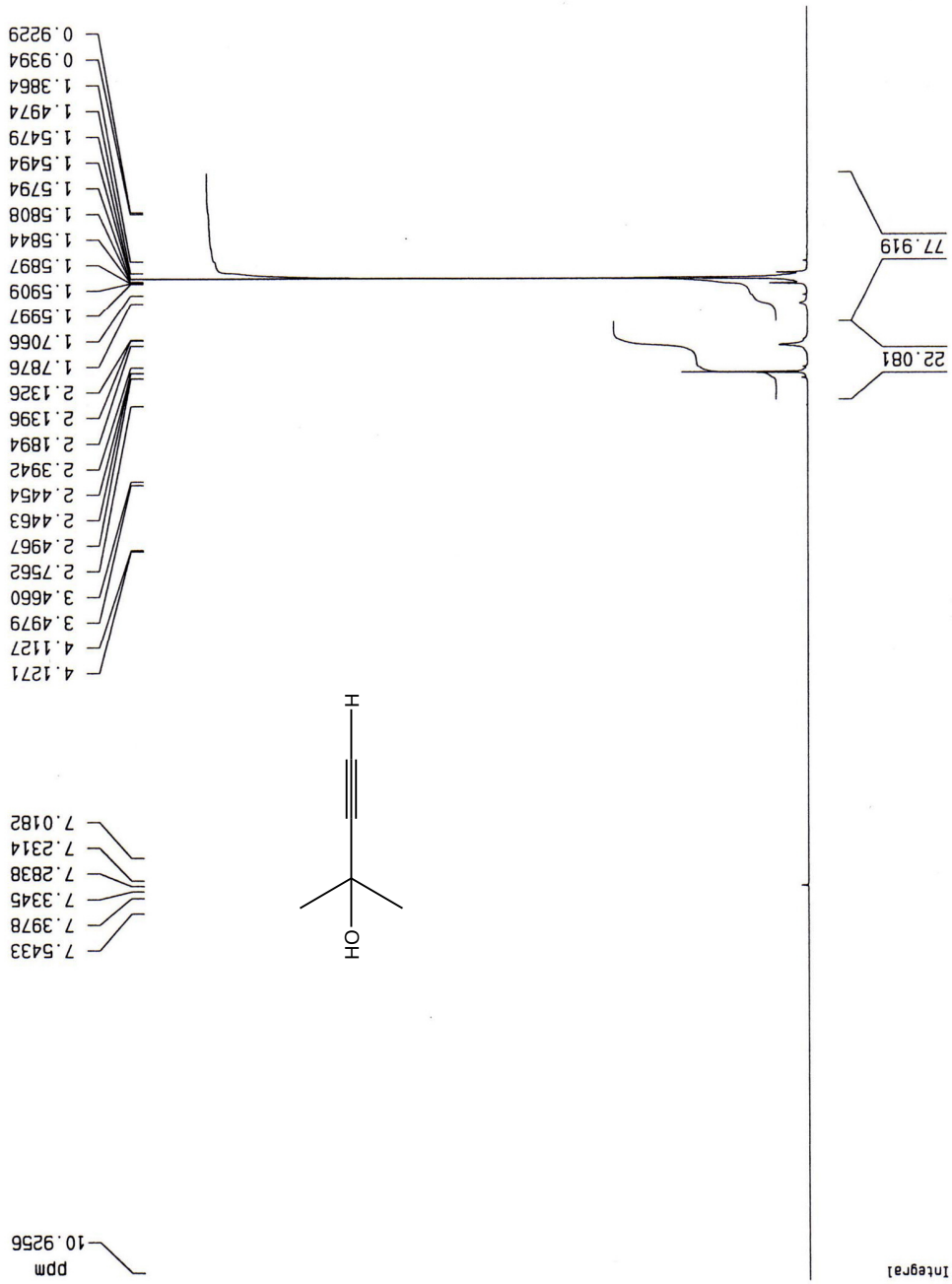
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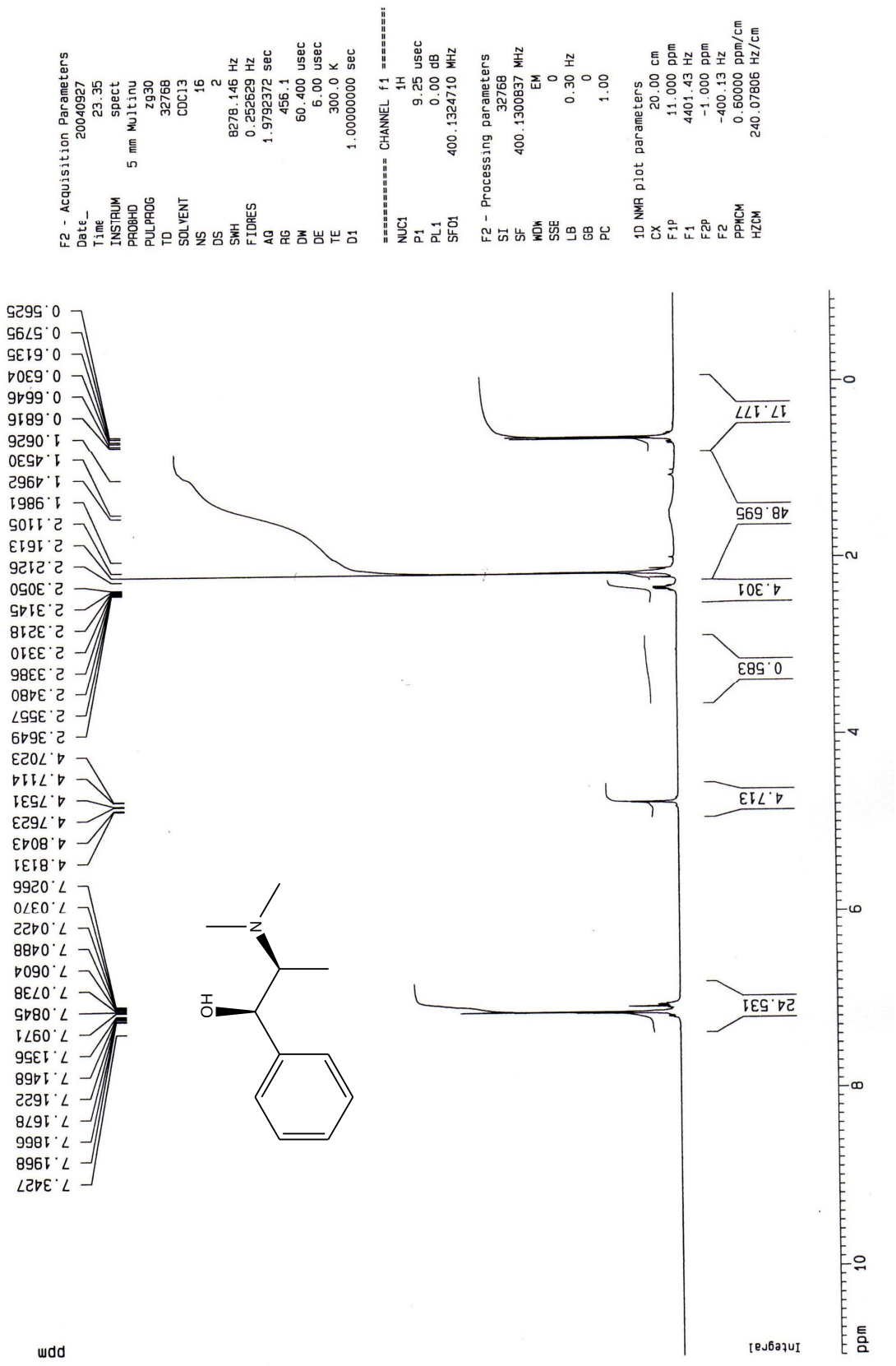
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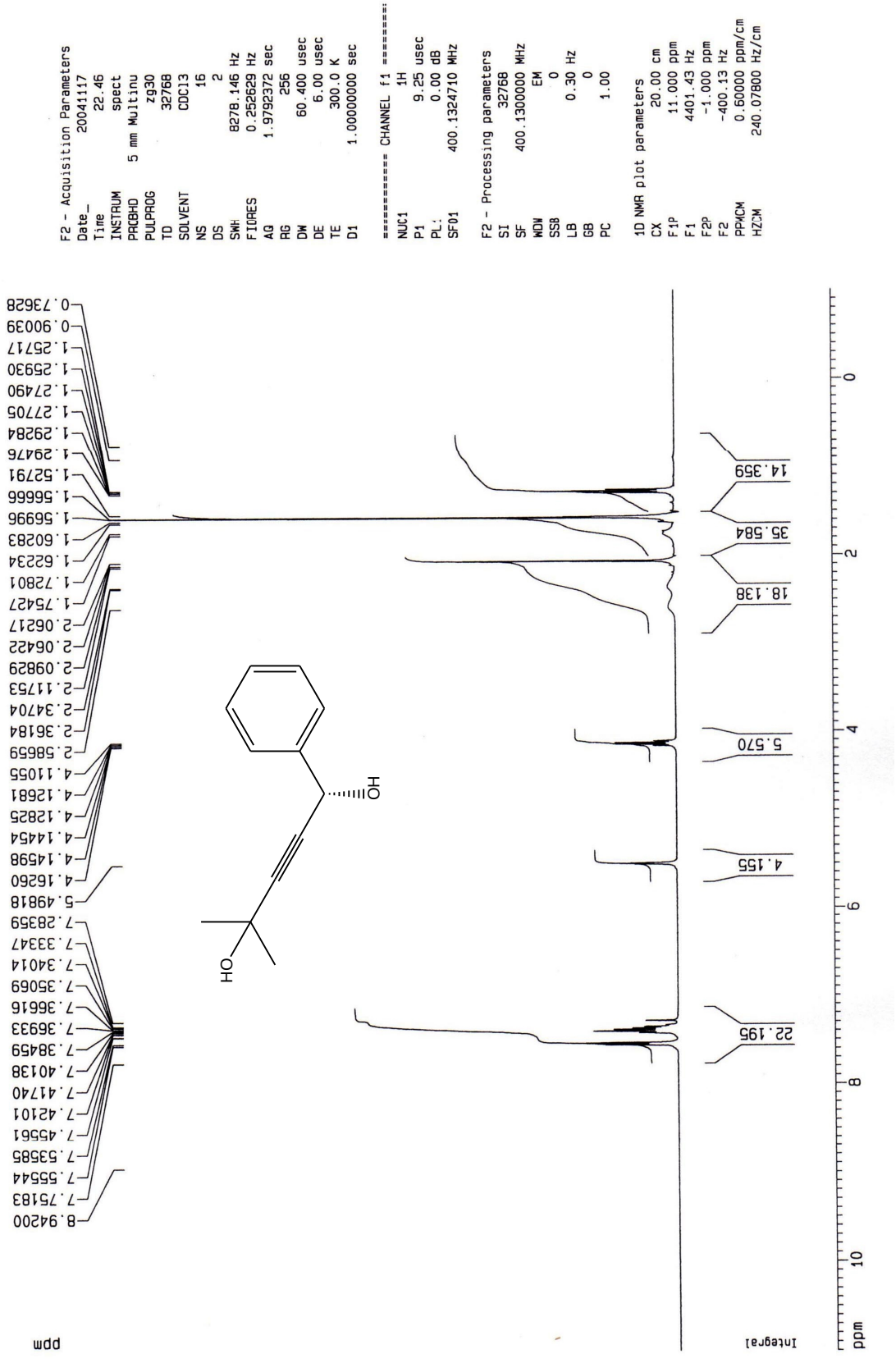
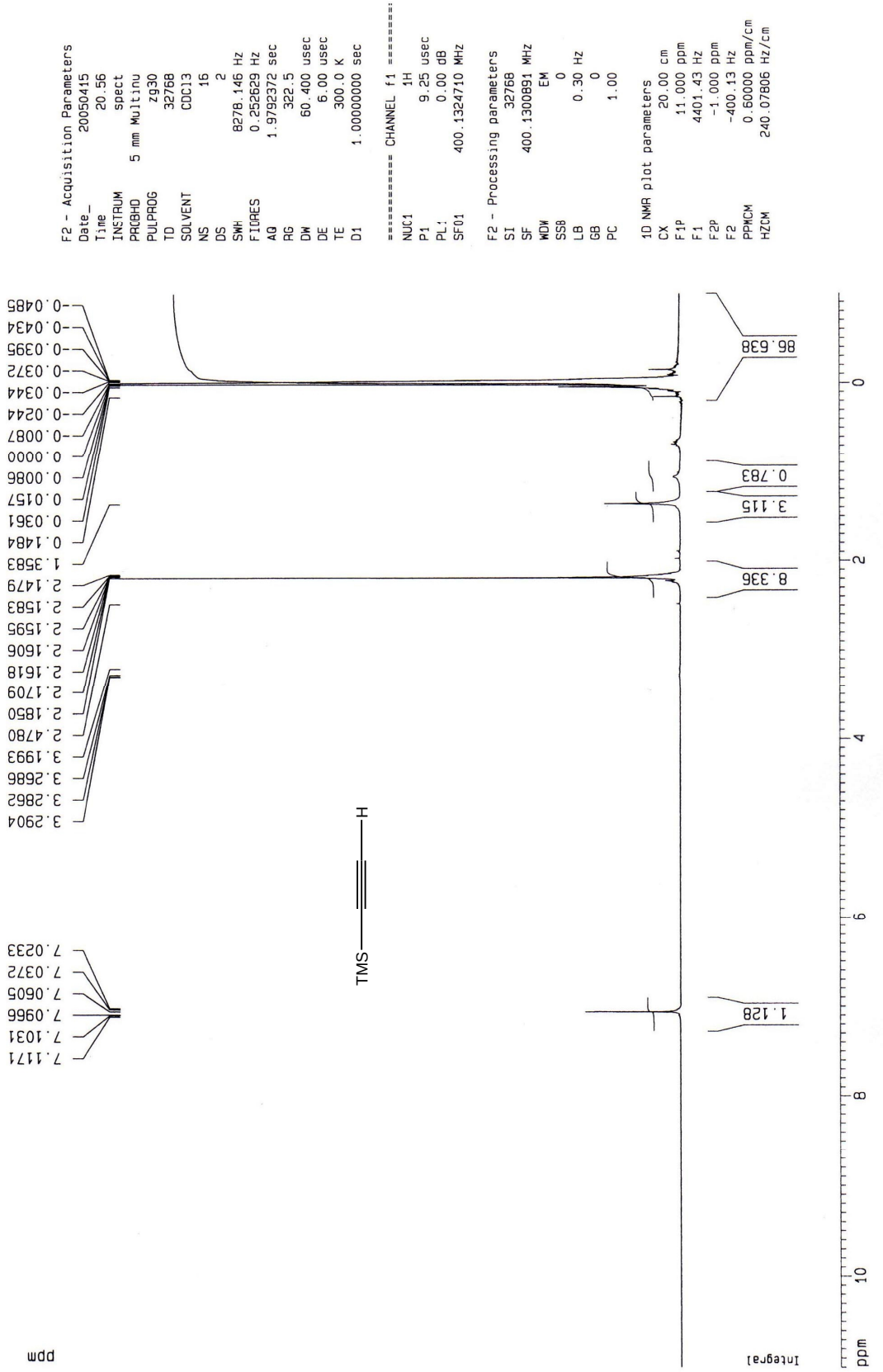
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07806 Hz/cm
7.3427
7.1968
7.1866
7.1678
7.1622
7.1468
7.1356
7.0971
7.0845
7.0738
7.0604
7.0488
7.0422
7.0370
7.0266
4.8131
4.8043
4.7623
4.7531
4.7114
4.7023
2.3649
2.3557
2.3480
2.3386
2.3310
2.3218
2.3145
2.3050
2.2126
2.1613
2.1105
1.9861
1.4962
1.4530
1.0626
0.6816
0.6646
0.6304
0.6135
0.5795
0.5625
17.177
48.695
4.301
0.583
4.713
24.531
OH
N
ppm
Integral

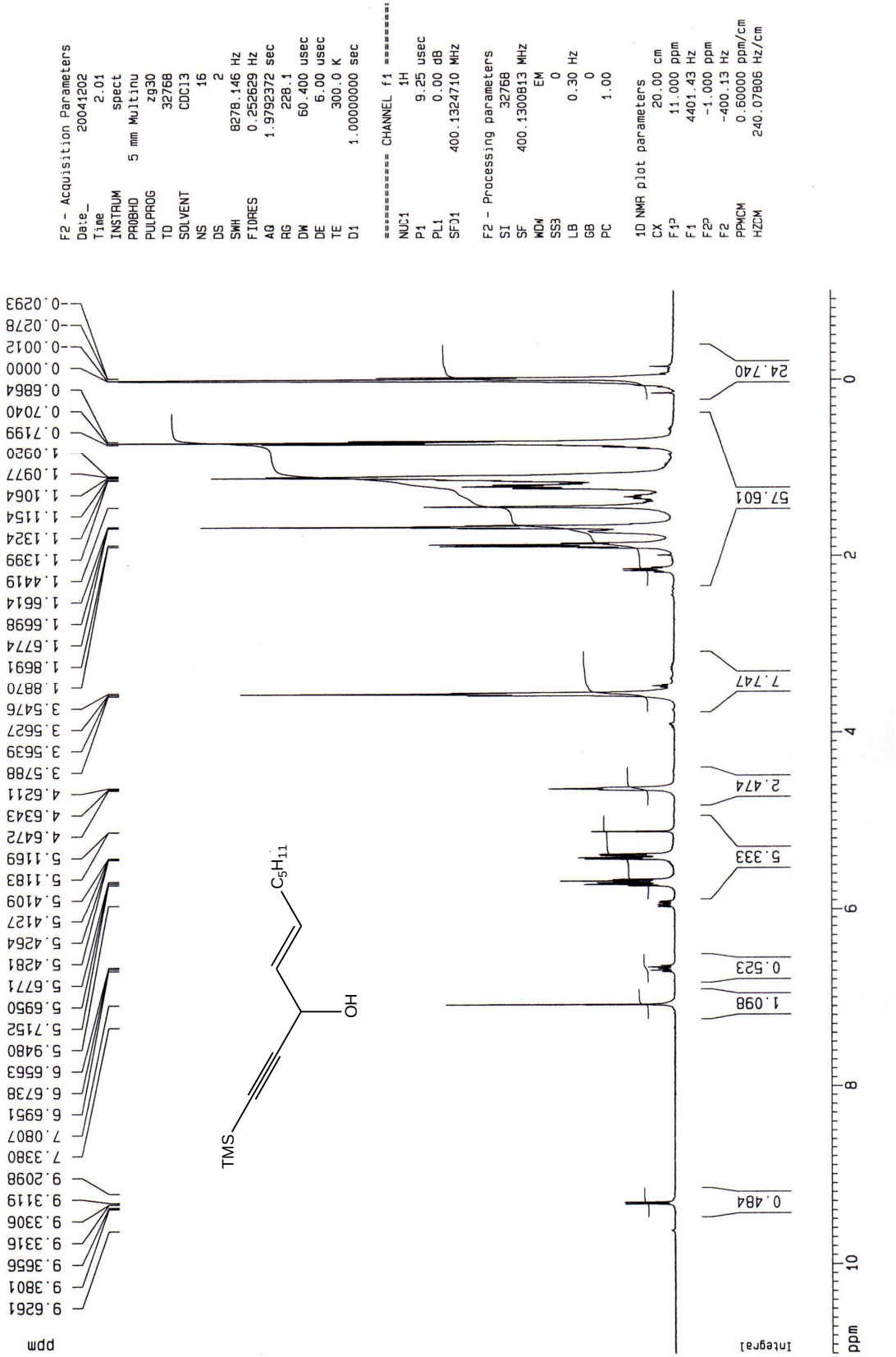
G


F2 - Acquisition Parameters
Date_ 20041117
Time 22.46
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
========== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SF01 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07800 Hz/cm
8.94200
7.75183
7.55544
7.53585
7.45561
7.42101
7.41740
7.40138
7.38459
7.36933
7.36616
7.35069
7.34014
7.33347
7.28359
5.49818
4.16260
4.14598
4.14454
4.12825
4.12681
4.11055
2.58659
2.36184
2.34704
2.11753
2.09829
2.06422
2.06217
1.75427
1.72801
1.62234
1.60283
1.56996
1.56666
1.52791
1.29476
1.29284
1.27705
1.27490
1.25930
1.25717
0.90039
0.73628
14.359
35.584
18.138
5.570
4.155
22.195
OH
HO
ppm
Integral

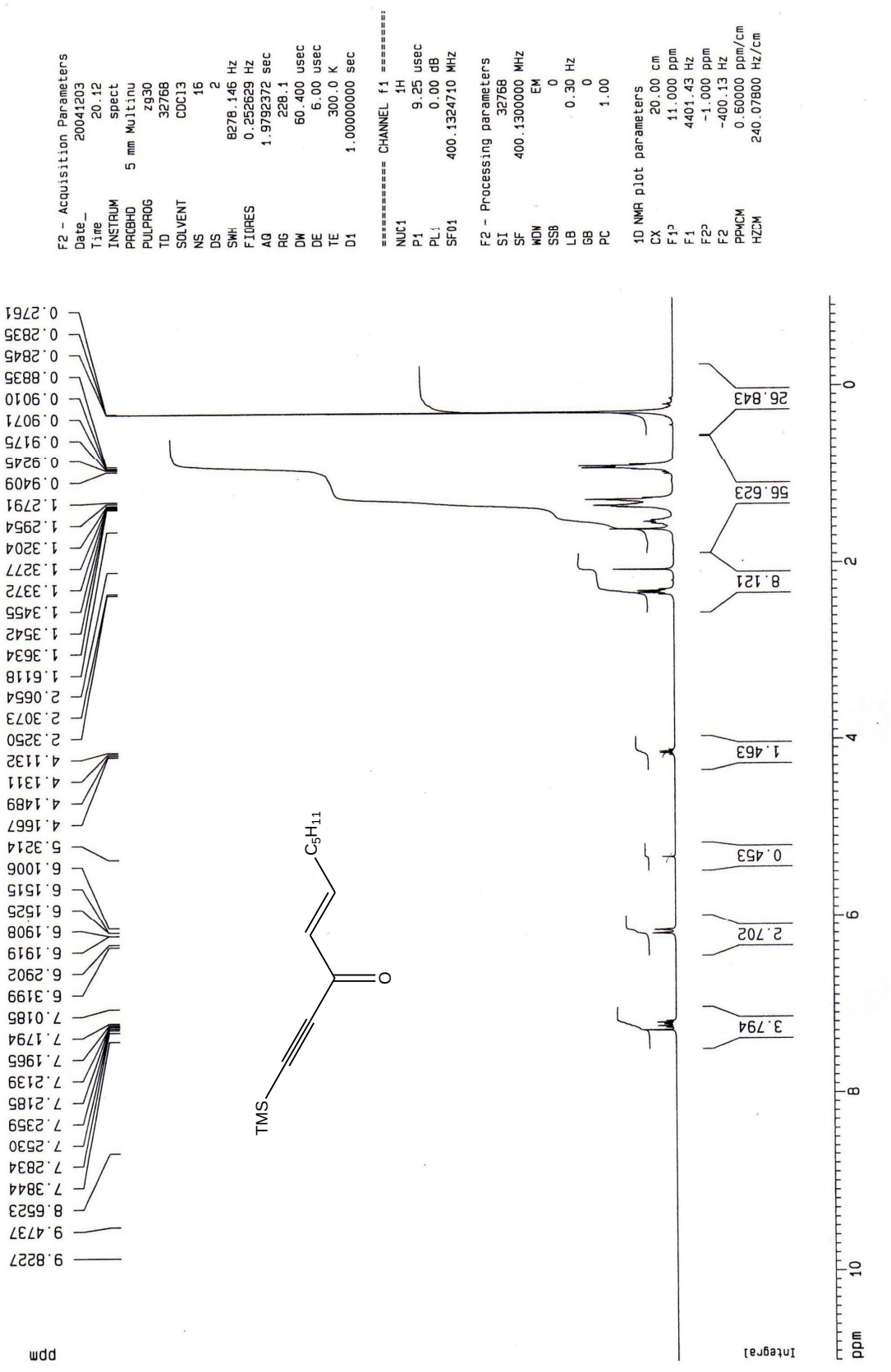
H


F2 - Acquisition Parameters
Date_ 20050415
Time 20.56
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 322.5
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SF01 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300891 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07806 Hz/cm
7.1171
7.1031
7.0966
7.0605
7.0372
7.0233
3.2904
3.2862
3.2686
3.1993
2.4780
2.1850
2.1709
2.1618
2.1606
2.1595
2.1583
2.1479
1.3583
0.1484
0.0361
0.0157
0.0086
0.0000
-0.0087
-0.0244
-0.0344
-0.0372
-0.0395
-0.0434
-0.0485
TMS
H
1.128
8.336
3.115
0.783
86.638
Integral
ppm
10
8
6
4
2
0
ppm

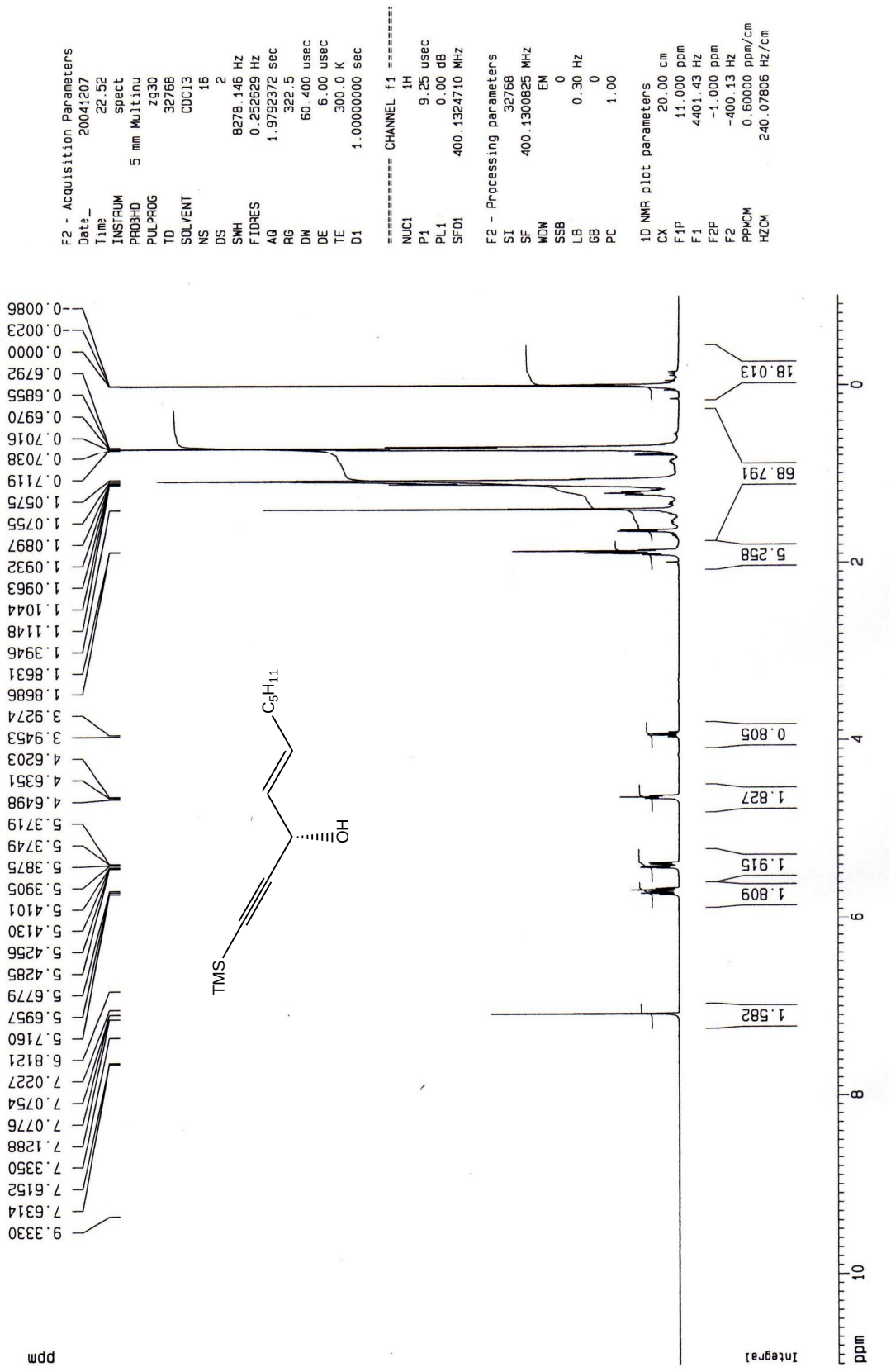
I


F2 - Acquisition Parameters
Date_ 20041202
Time 2.01
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 228.1
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
========== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300813 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07806 Hz/cm
TMS
OH
C_5H_{11}
ppm
Integral
24.740
57.601
7.747
2.474
5.333
0.523
1.098
0.484

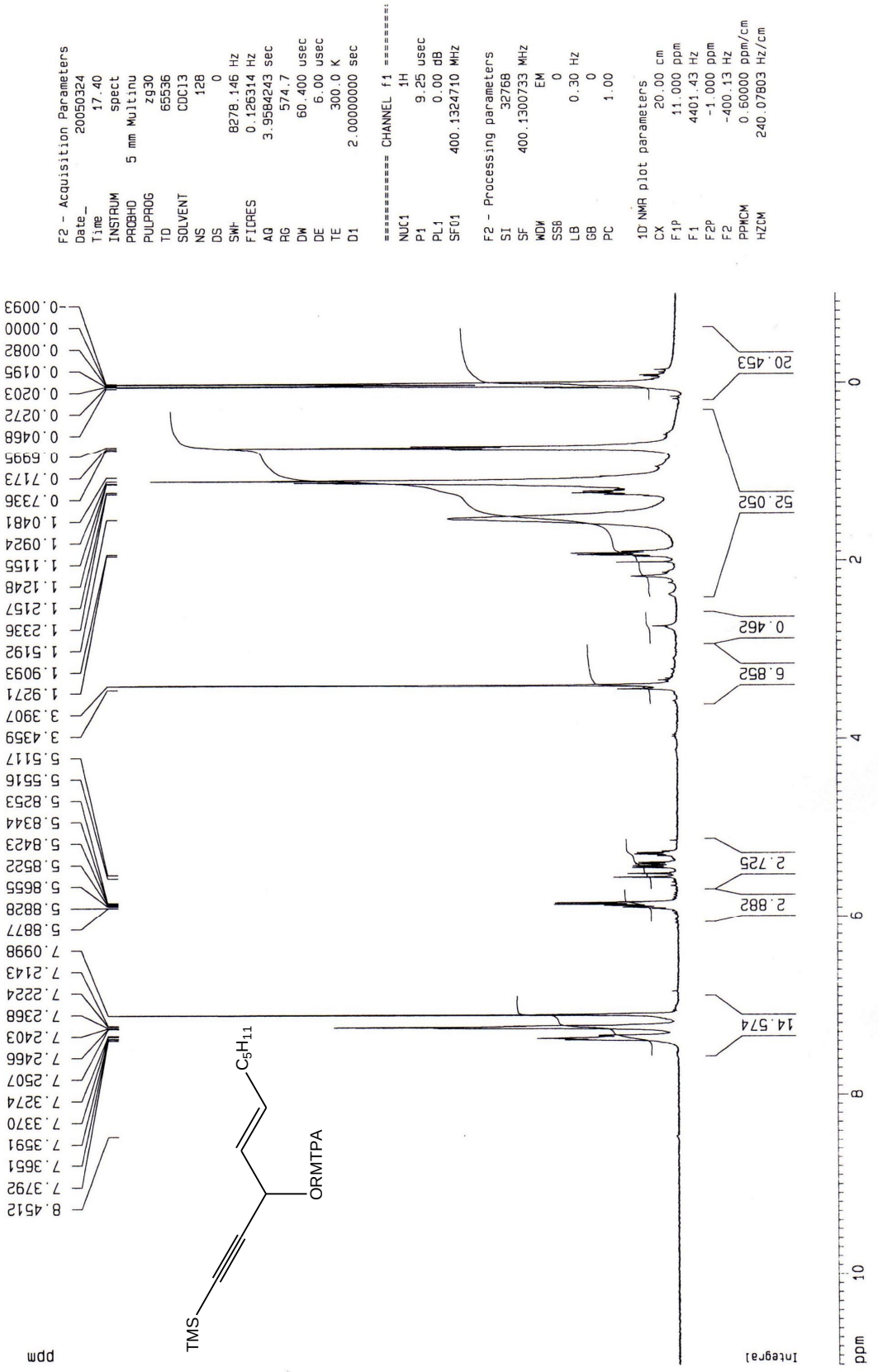
J


F2 - Acquisition Parameters
Date_ 20041203
Time 20.12
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG z930
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 228.1
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SF01 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07800 Hz/cm
9.8227
9.4737
8.6523
7.3844
7.2834
7.2530
7.2359
7.2185
7.2139
7.1965
7.1794
7.0185
6.3199
6.2902
6.1919
6.1908
6.1525
6.1515
6.1006
5.3214
4.1667
4.1489
4.1311
4.1132
2.3250
2.3073
2.0654
1.6118
1.3634
1.3542
1.3455
1.3372
1.3277
1.3204
1.2954
1.2791
0.9409
0.9245
0.9175
0.9071
0.9010
0.8835
0.2845
0.2835
0.2761
TMS
O
C_5H_{11}
26.843
56.623
8.121
1.463
0.453
2.702
3.794
ppm
Integral

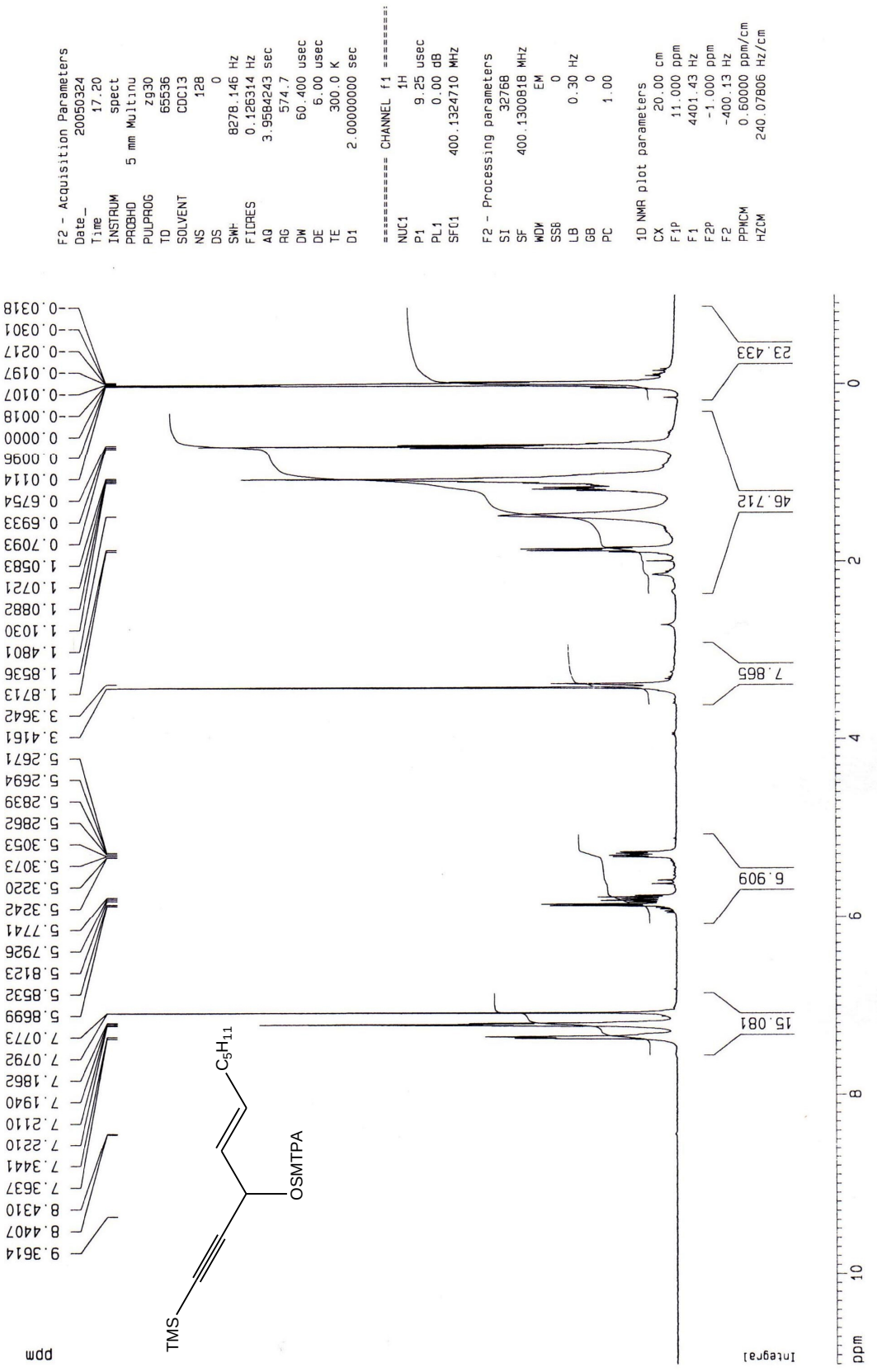
K


F2 - Acquisition Parameters
20041207
22.52
spect
5 mm Multinu
zg30
32768
CDCl3
16
2
8278.146 Hz
0.252629 Hz
1.9792372 sec
322.5
60.400 usec
6.00 usec
300.0 K
1.00000000 sec
CHANNEL f1
1H
9.25 usec
0.00 dB
400.1324710 MHz
F2 - Processing parameters
32768
400.1300825 MHz
EM
0
0.30 Hz
0
1.00
1D NMR plot parameters
20.00 cm
11.000 ppm
4401.43 Hz
-1.000 ppm
-400.13 Hz
0.60000 ppm/cm
240.07806 Hz/cm
9.3330
7.6314
7.6152
7.3350
7.1288
7.0776
7.0754
7.0227
6.8121
5.7160
5.6957
5.6779
5.4285
5.4256
5.4130
5.4101
5.3905
5.3875
5.3749
5.3719
4.6498
4.6351
4.6203
3.9453
3.9274
1.8686
1.8631
1.3946
1.1148
1.1044
1.0963
1.0932
1.0897
1.0755
1.0575
0.7119
0.7038
0.7016
0.6970
0.6855
0.6792
0.0000
-0.0023
-0.0086
18.013
68.791
5.258
0.805
1.827
1.915
1.809
1.582
TMS
OH
C_5H_{11}
ppm
Integral

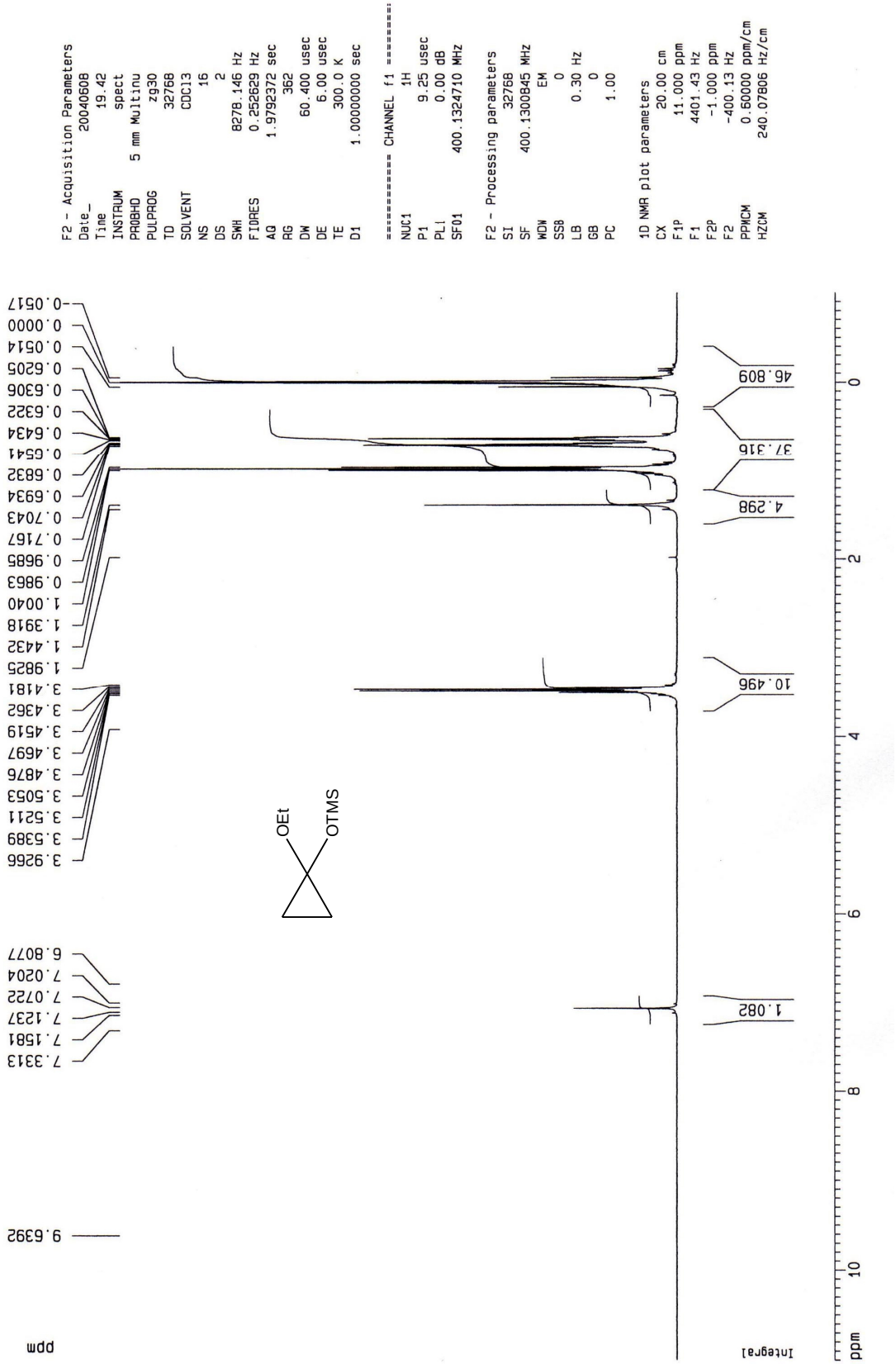
L


F2 - Acquisition Parameters
Date_ 20050324
Time 17.40
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 128
DS 0
SWH 8278.146 Hz
FIRES 0.126314 Hz
AQ 3.9584243 sec
RG 574.7
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300733 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07803 Hz/cm
-0.0093
0.0000
0.0082
0.0195
0.0203
0.0272
0.0468
0.6995
0.7173
0.7336
1.0481
1.0924
1.1155
1.1248
1.2157
1.2336
1.5192
1.9093
1.9271
3.3907
3.4359
5.5117
5.5516
5.8253
5.8344
5.8423
5.8522
5.8655
5.8828
5.8877
7.0998
7.2143
7.2224
7.2368
7.2403
7.2466
7.2507
7.3274
7.3370
7.3591
7.3651
7.3792
8.4512
20.453
52.052
0.462
6.852
2.725
2.882
14.574
TMS
C_5H_{11}
ORMTPA
ppm
Integral

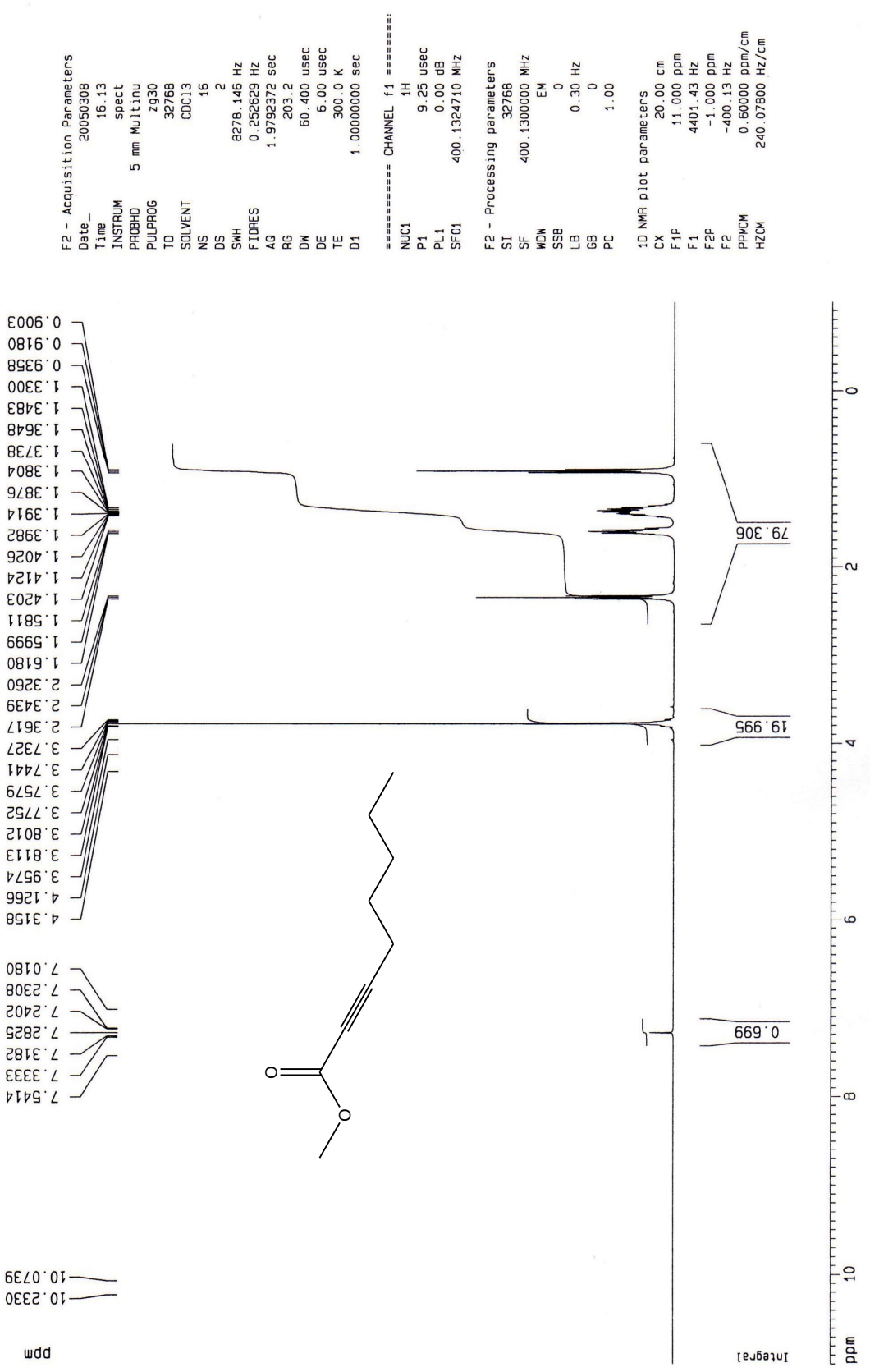
M


F2 - Acquisition Parameters
Date_ 20050324
Time 17.20
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 128
DS 0
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 574.7
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300818 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07806 Hz/cm
9.3614
8.4407
8.4310
7.3637
7.3441
7.2210
7.2110
7.1940
7.1862
7.0792
7.0773
5.8699
5.8532
5.8123
5.7926
5.7741
5.3242
5.3220
5.3073
5.3053
5.2862
5.2839
5.2694
5.2671
3.4161
3.3642
1.8713
1.8536
1.4801
1.1030
1.0882
1.0721
1.0583
0.7093
0.6933
0.6754
0.0114
0.0096
0.0000
-0.0018
-0.0107
-0.0197
-0.0217
-0.0301
-0.0318
ppm
Integral
15.081
6.909
7.865
46.712
23.433
TMS
OSMTPA
C_5H_{11}
ppm

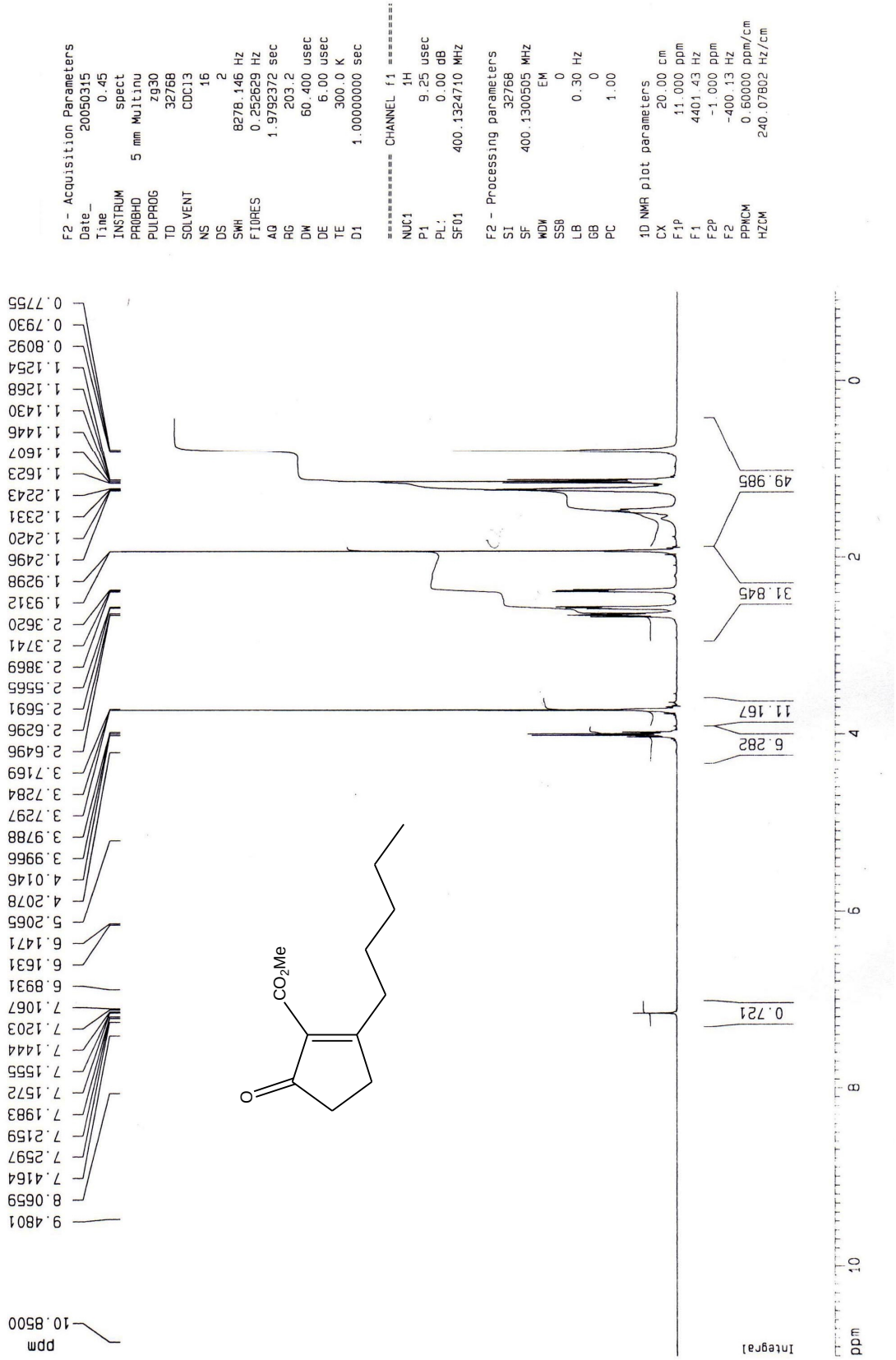
N


F2 - Acquisition Parameters
Date_ 20040608
Time 19.42
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
========== CHANNEL f1 ==========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SF01 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300845 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07806 Hz/cm
-0.0517
0.0000
0.0514
0.6205
0.6306
0.6322
0.6434
0.6541
0.6832
0.6934
0.7043
0.7167
0.9685
0.9863
1.0040
1.3918
1.4432
1.9825
3.4181
3.4362
3.4519
3.4697
3.4876
3.5053
3.5211
3.5389
3.9266
6.8077
7.0204
7.0722
7.1237
7.1581
7.3313
9.6392
OEt
OTMS
46.809
37.316
4.298
10.496
1.082
ppm
Integral

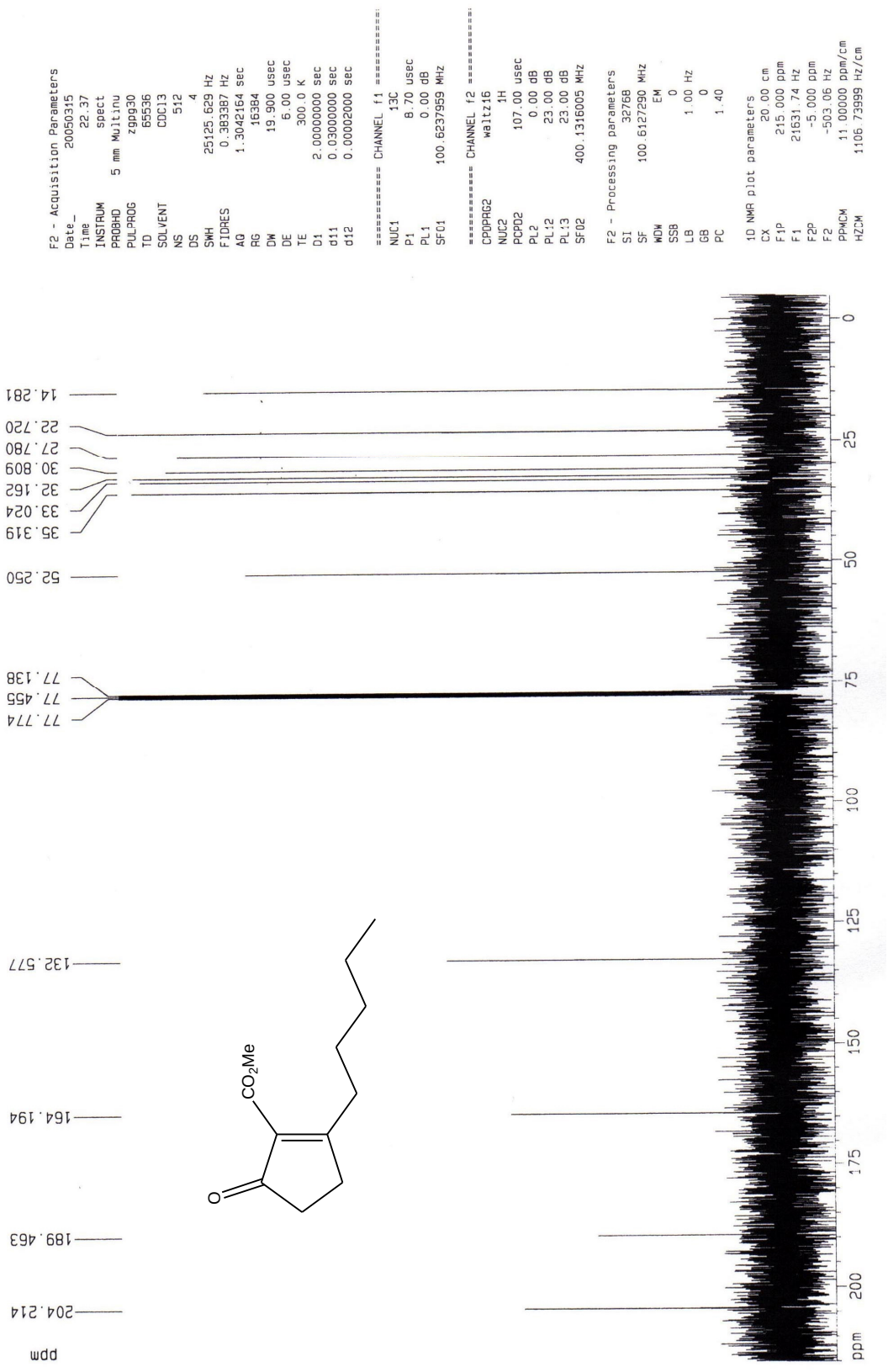
O


F2 - Acquisition Parameters
Date_ 20050308
Time 16.13
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 203.2
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
========== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFC1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07800 Hz/cm
10.2330
10.0739
7.5414
7.3333
7.3182
7.2825
7.2402
7.2308
7.0180
4.3158
4.1266
3.9574
3.8113
3.8012
3.7752
3.7579
3.7441
3.7327
2.3617
2.3439
2.3260
1.6180
1.5999
1.5811
1.4203
1.4124
1.4026
1.3982
1.3914
1.3876
1.3804
1.3738
1.3648
1.3483
1.3300
0.9358
0.9180
0.9003
79.306
19.995
0.699
ppm
Integral

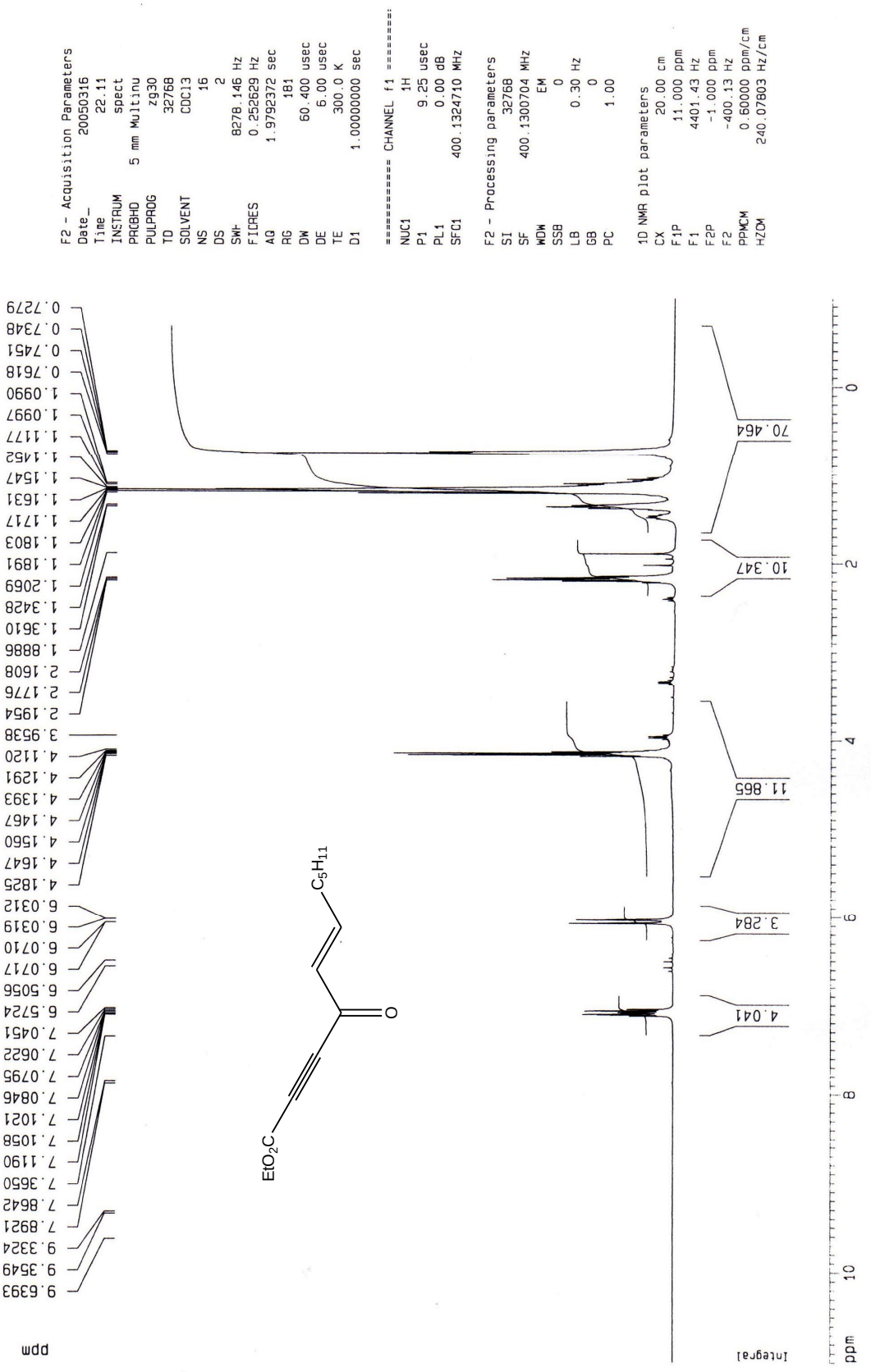
P


F2 - Acquisition Parameters
Date_ 20050315
Time 0.45
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 203.2
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SF01 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300505 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07802 Hz/cm
0.7755
0.7930
0.8092
1.1254
1.1268
1.1430
1.1446
1.1607
1.1623
1.2243
1.2331
1.2420
1.2496
1.9298
1.9312
2.3620
2.3741
2.3869
2.5565
2.5691
2.6296
2.6496
3.7169
3.7284
3.7297
3.9788
3.9966
4.0146
4.2078
5.2065
6.1471
6.1631
6.8931
7.1067
7.1203
7.1444
7.1555
7.1572
7.1983
7.2159
7.2597
7.4164
8.0659
9.4801
10.8500
ppm
49.985
31.845
11.167
6.282
0.721
Integral
ppm
CO2Me
O

Q


F2 - Acquisition Parameters
Date_ 20050315
Time 22.37
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 25125.629 Hz
FIDRES 0.383387 Hz
AQ 1.3042164 sec
RG 16384
DW 19.900 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.70 usec
PL1 0.00 dB
SFO1 100.6237959 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.00 usec
PL2 0.00 dB
PL12 23.00 dB
PL13 23.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127290 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 215.000 ppm
F1 21631.74 Hz
F2P -5.000 ppm
F2 -503.06 Hz
PPMCM 11.00000 ppm/cm
HZCM 1106.73999 Hz/cm
14.281
22.720
27.780
30.809
32.162
33.024
35.319
52.250
77.138
77.455
77.774
132.577
164.194
189.463
204.214
ppm
0
25
50
75
100
125
150
175
200
CO2Me
O

R


F2 - Acquisition Parameters
Date_ 20050316
Time 22.11
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
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RG 181
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
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NUC1 1H
P1 9.25 usec
PL1 0.00 dB
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F2 - Processing parameters
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07803 Hz/cm
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9.3549
9.3324
7.8921
7.8642
7.3650
7.1190
7.1058
7.1021
7.0846
7.0795
7.0622
7.0451
6.5724
6.5056
6.0717
6.0710
6.0319
6.0312
4.1825
4.1647
4.1560
4.1467
4.1393
4.1291
4.1120
3.9538
2.1954
2.1776
2.1608
1.8886
1.3610
1.3428
1.2069
1.1891
1.1803
1.1717
1.1631
1.1547
1.1452
1.1177
1.0997
1.0990
0.7618
0.7451
0.7348
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4.041
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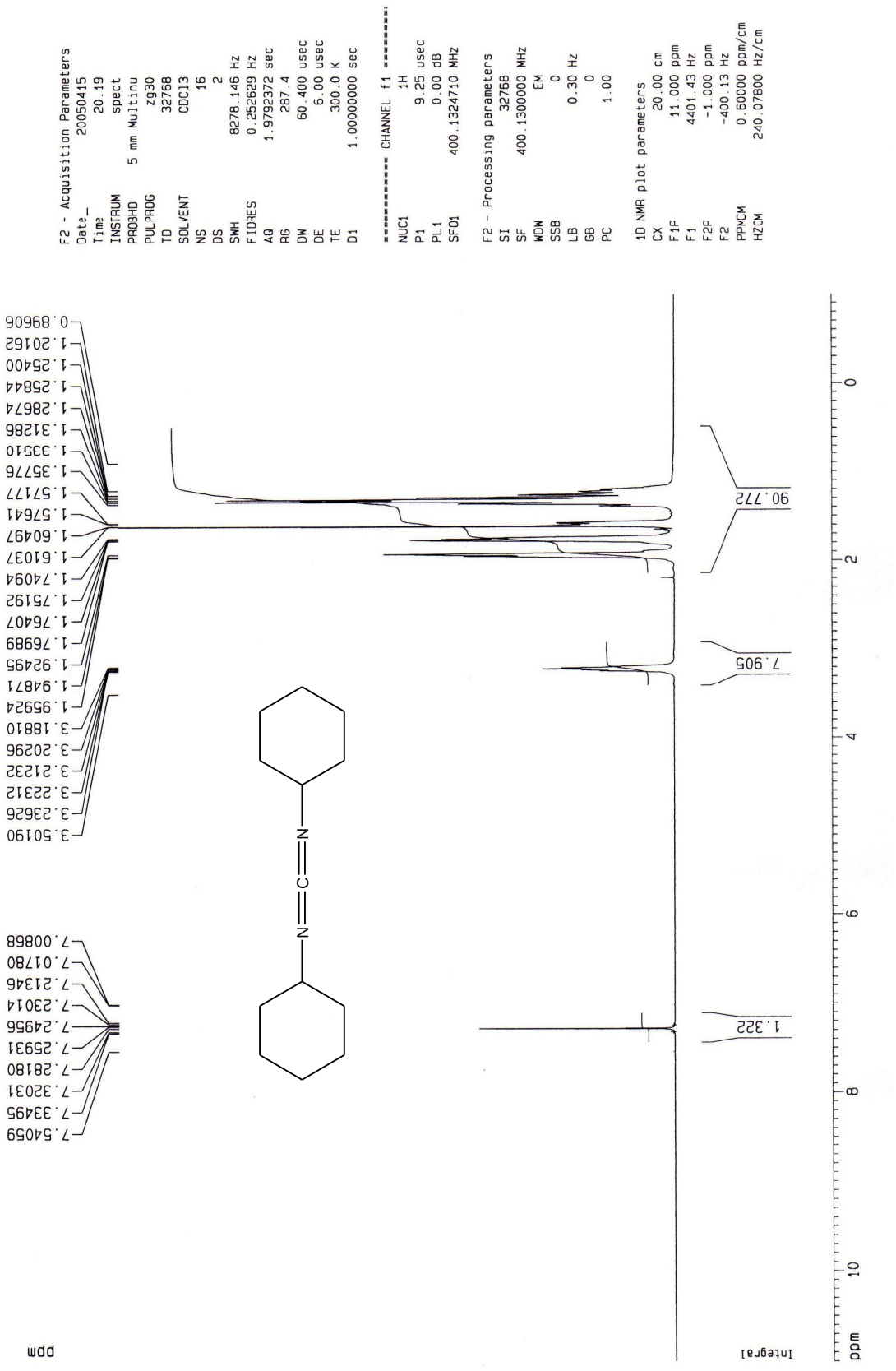
O
ppm
Integral

S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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07800 Hz/cm
0.89606
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1.25400
1.25844
1.28674
1.31286
1.33510
1.35776
1.57177
1.57641
1.60497
1.61037
1.74094
1.75192
1.76407
1.76989
1.92495
1.94871
1.95924
3.18810
3.20296
3.21232
3.22312
3.23626
3.50190
7.00868
7.01780
7.21346
7.23014
7.24956
7.25931
7.28180
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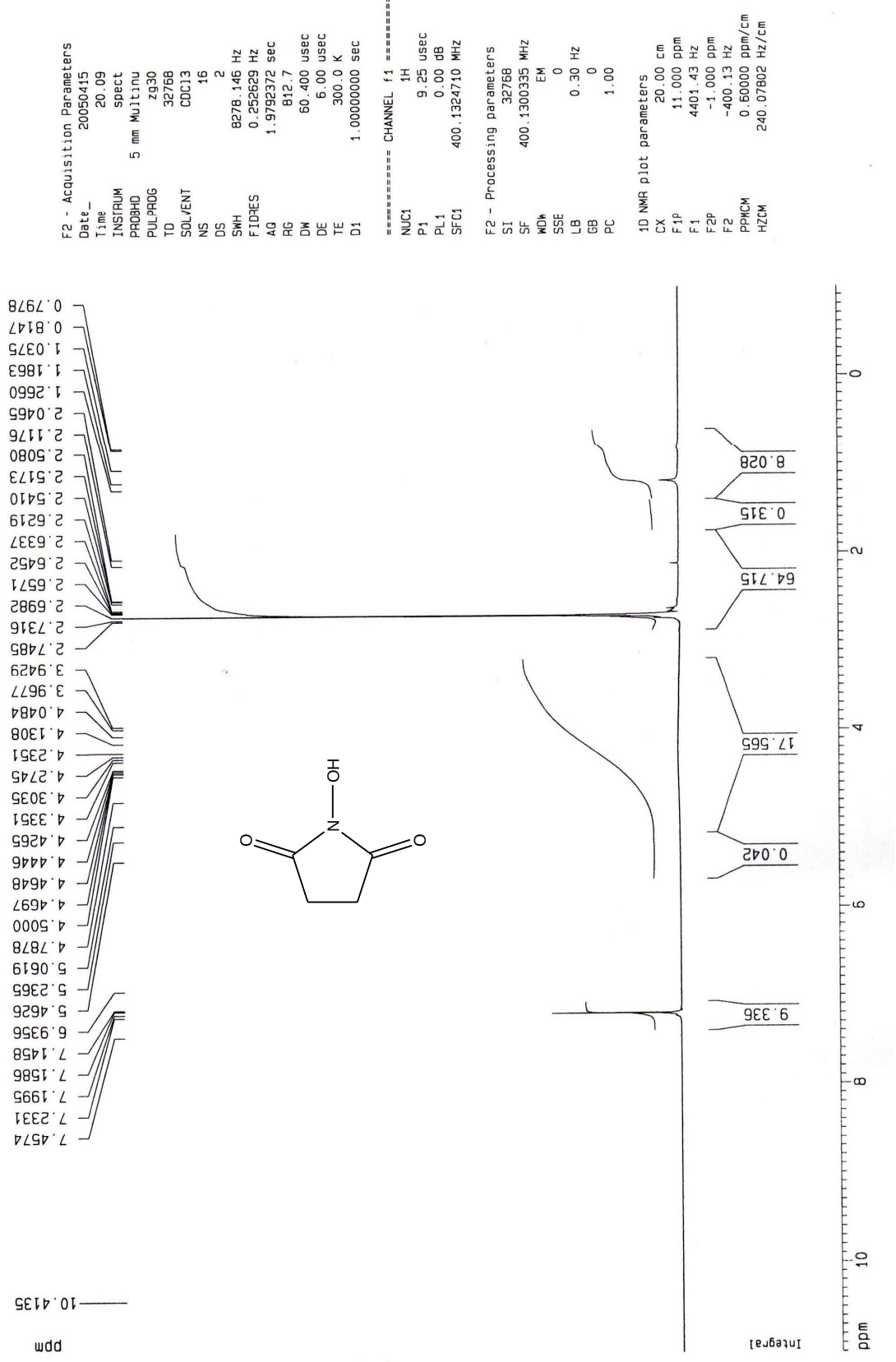
7.33495
7.54059
90.772
7.905
1.322
N
C
N
ppm
Integral

T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SOLVENT CDCl3
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DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 812.7
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
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NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300335 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07802 Hz/cm
ppm
Integral
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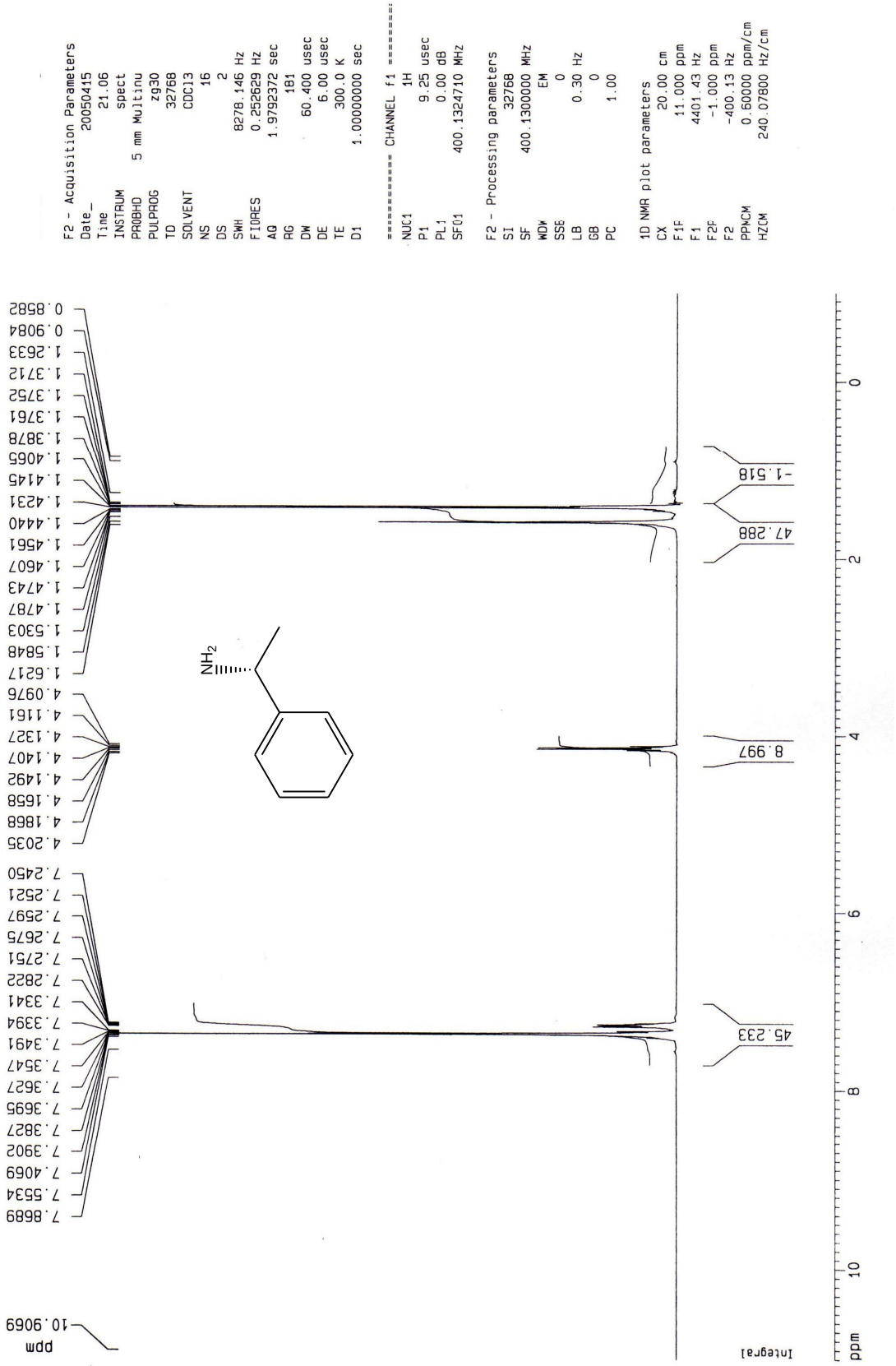
17.565
0.042
9.336
HO
N
O
O

V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DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 181
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
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HZCM 240.07800 Hz/cm
ppm
Integral
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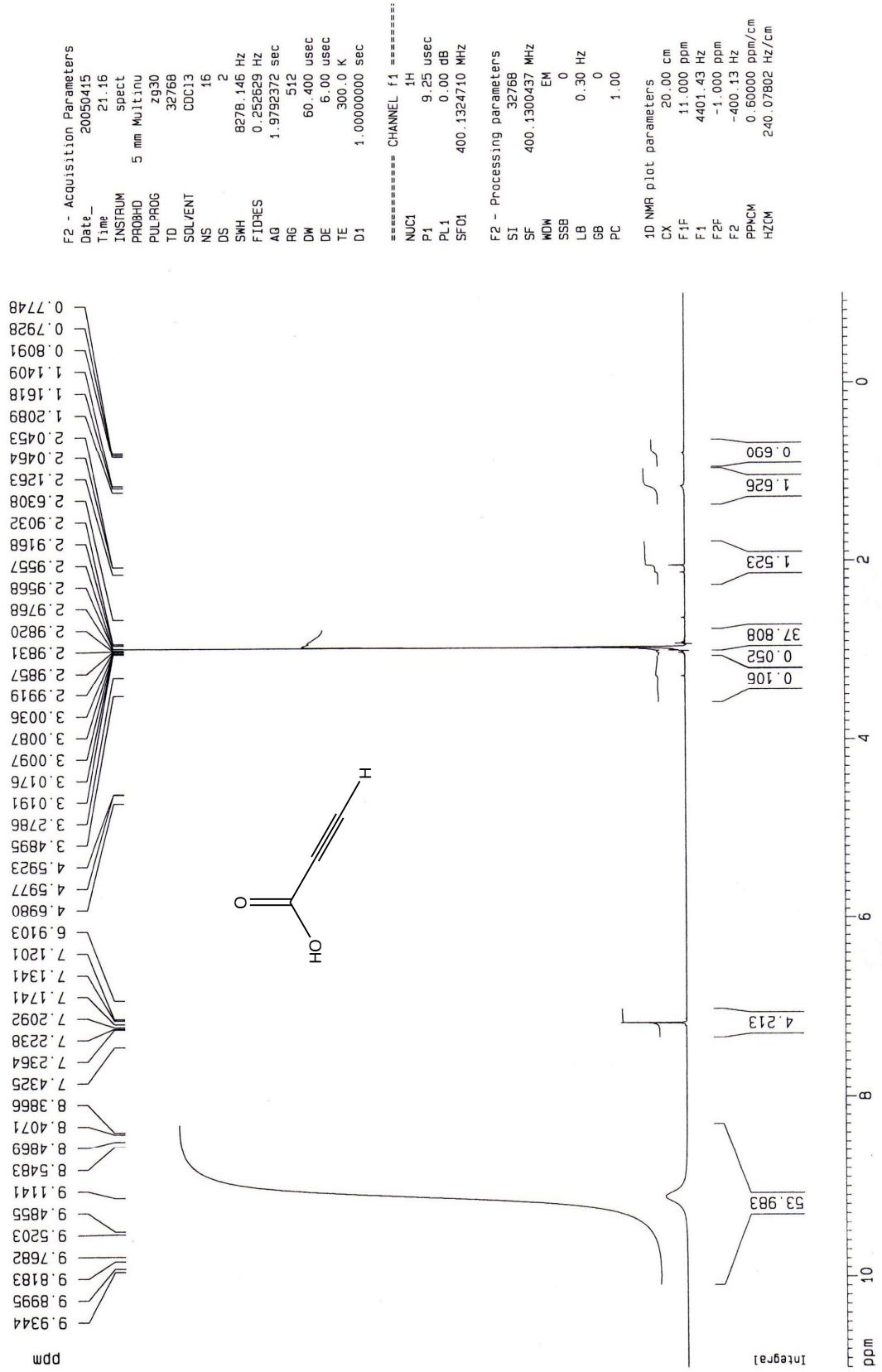
8.997
47.288
-1.518
NH2

U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TD 32768
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NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 512
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300437 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07802 Hz/cm
ppm
Integral
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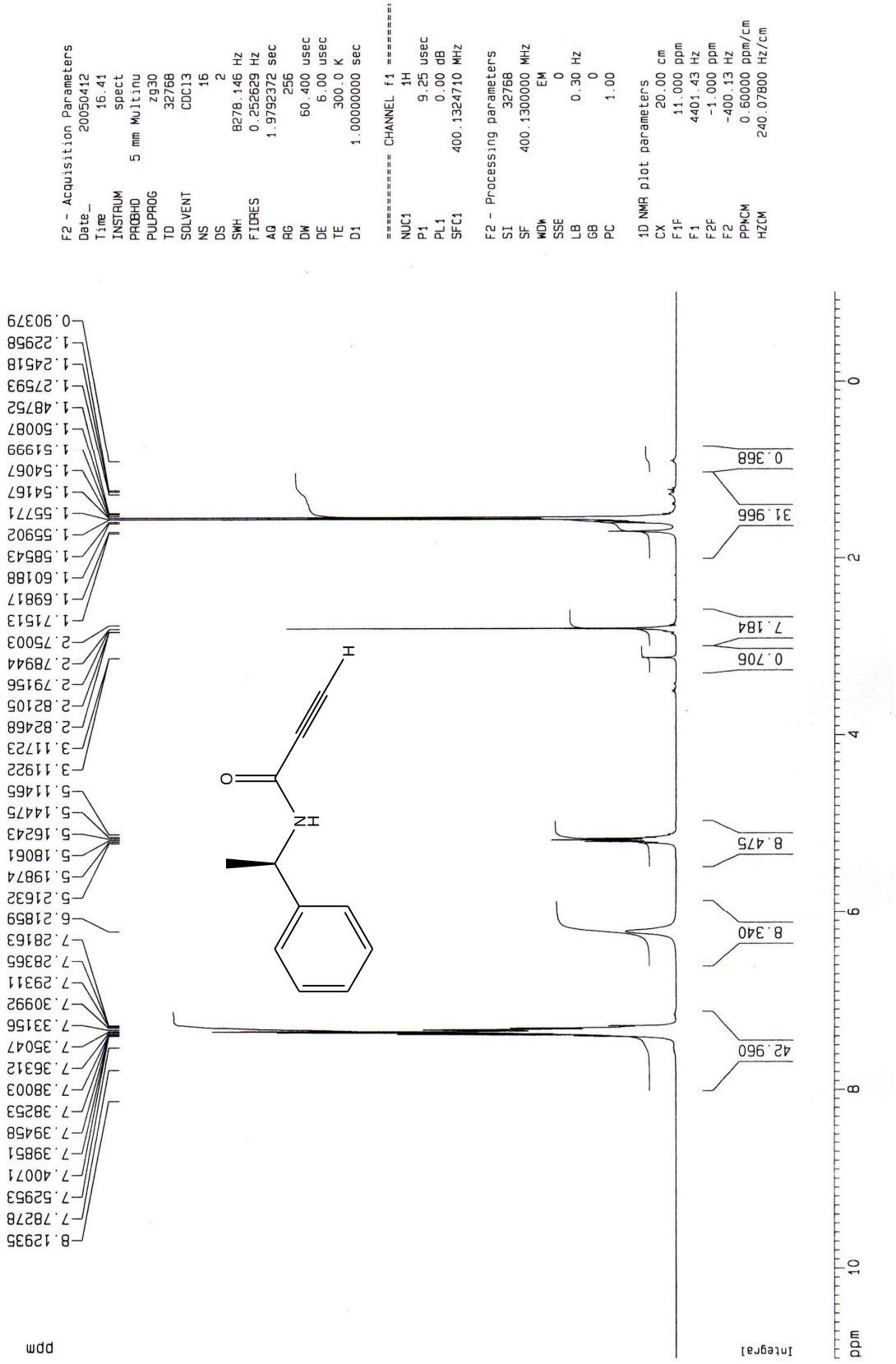
37.808
0.052
0.106
4.213
53.983
OH
O
H

W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PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07800 Hz/cm
ppm
Integral
8.12935
7.78278
7.52953
7.40071
7.39851
7.39458
7.38253
7.38003
7.36312
7.35047
7.33156
7.30992
7.29311
7.28365
7.28163
6.21859
5.21632
5.19874
5.18061
5.16243
5.14475
5.11465
3.11922
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1.71513
1.69817
1.60188
1.58543
1.55902
1.55771
1.54167
1.54067
1.51999
1.50087
1.48752
1.27593
1.24518
1.22958
0.90379
42.960
8.340
8.475
0.706
7.184
31.966
0.368
O
NH
H

X

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