Oxidative C-H Bond Activation:

Study on DDQ-Induced Intramolecular Cyclization Reactions

and Application to the Formal Synthesis of Neopeltolide

by

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Submitted to the Graduate Faculty of

School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh
2009

UNIVERSITY OF PITTSBURGH

SCHOOL OF ARTS AND SCIENCES

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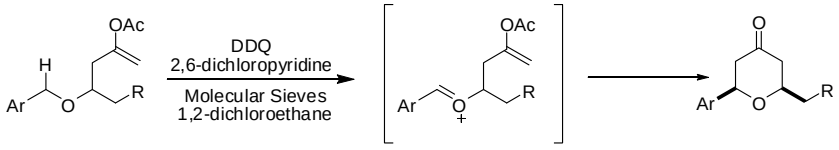
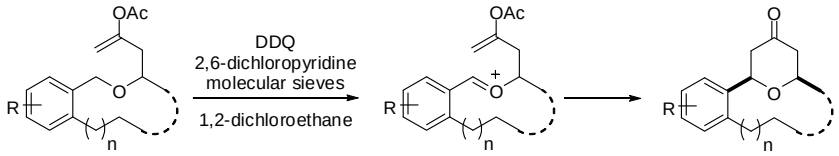
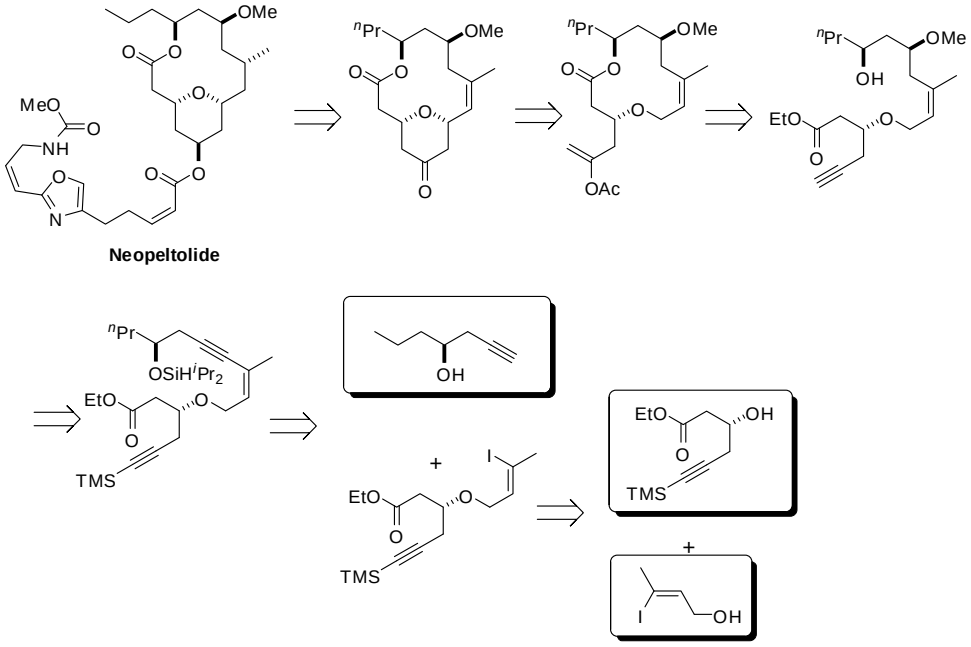
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been found to be an excellent reagent for oxidatively activating benzylic C-H bonds, and the *in-situ* generated oxocarbenium ions can be captured by nucleophiles appended in the molecules. A variety of aromatic methyl ethers with different substituents are shown to be reactive with DDQ, and common protecting groups are well tolerated. The enol acetate group is the most reliable and productive nucleophile compared with other candidates and provides the 2,6-disubstituted tetrahydropyrone product as exclusively the *cis* isomer.



This method has been successfully applied to the macrocyclic systems. The valuable macrocyclic oxocarbenium ions are readily formed when treating the substrates with DDQ. The reactions are generally slower than those of acyclic substrates but the yields are almost unaffected. The ring size has no influence on the diastereoselectivity of cyclization.



A convergent formal synthesis of natural product neopeltolide was accomplished from three building blocks by utilizing the DDQ mediated cyclization reaction as the key transformation. A novel intramolecular hydrosilylation-Tamao oxidation reaction is employed to synthesize the precursor for the key step. This approach to the natural product has minimized the involvement of protecting groups and conveniently provided an opportunity to access the natural product analogues through double bond functionalizations.



Neopeltolide

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
CAN	Cerium(IV) ammonium nitrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dba	Dibenzylideneacetone
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
EI	Electron impact ionization
FG	Functional group
HRMS	High-resolution mass spectrometry
LDA	Lithium diisopropylamide
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MOM	Methoxymethyl
M.S.	Molecule sieves

MTPA	α-Methoxytrifluorophenylacetic acid
Ns	3-Nitrobenzenesulfonyl
PDC	Pyridinium dichromate
PG	Protecting group
PMB	*para*-Methoxylbenzyl
SET	Single electron transfer
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TMSOTf	Trimethylsilyl triflate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TsOH	*p*-Toluenesulfonic acid

PREFACE

First and foremost, I would like to express my most sincere thanks to my research advisor Paul E. Floreancig. Thanks for allowing me to join your group and providing those challenging but exciting research projects to me. I am so appreciated your patience during the period when I was such a green hand; I won't be able to achieve this thesis without your dedicated guidance and directions. I have learned so much from you in these four years – not only the chemistry, but also the attitude, the spirit for exploring the unknowing world. My whole life will benefit from this precious and wonderful experience working with you.

I would like to thank Professor Dennis Curran, Professor Craig Wilcox and Professor Billy Day for your efforts in my comprehensive exam and thesis, and also thanks Professor Kay Brummond for serving as my proposal mentor.

To all the past and current members in Floreancig group, your helps and suggestions are so appreciated. I would especially say thanks to Alex and Shuangyi, you two give me tremendous help and it is such a pleasure to work with you in the same lab. Mike and HHJ, you teach me lots of fantastic lab techniques, and discussing with you gives me a lot of inspirations for my research. Dane, I know you will finish the molecule even without loud heave metal music on 14th floor. Lei, you definitely can extract more stuff from DDQ. Chunliang, Yubo, Gedi, now it is your show time...

Lastly, I would like to thanks my wife Lingling. You sacrifice your career and time to take care of our family; your understanding and encouragement contribute to every single percent of my achievement. And mom and dad, you are the ones who always back me up. I will have nothing without your continuing support. This thesis is the present for you.

1. OXIDATIVE C-H BOND ACTIVATION: DEVELOPMENT OF DDQ INITIATED INTRAMOLECULAR CYCLIZATION REACTIONS ON BENZYLIC ETHERS

1.1 INTRODUCTION OF C-H BOND ACTIVATION

An ideal organic synthetic route is designed to construct the target molecule efficiently through minimum functional group transformations and from an inexpensive material. However, in practice natural product syntheses usually involve many unproductive steps because current synthetic methods mainly rely on reactive functional groups such as heteroatoms and unsaturated bonds.[1] The carbon-hydrogen bond, undoubtedly the most ubiquitous bond in organic molecules, hasn't been considered as a valid functional group for a long period due to its robustness (105 kcal bond energy[2] for H-CH_3, 110 kcal for H-C_6H_5) and chemoselectivity issues. Strategically, C-C bond formation through selectively C-H bond activation is an appealing protocol as it provides the opportunity to straightforwardly access the target with minimum reactivity tuning and high atom economy[3] (Figure 1). In the following section, representative examples of current C-H activation strategies will be briefly discussed.

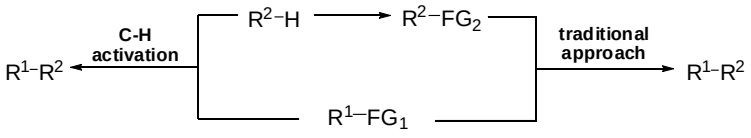


Figure 1. Comparison between C-H functionalization and traditional approach

1.1.1 C-H activation by intramolecular radical reaction

The radical approach is exemplified by the Hofmann-Löffler-Freytag reaction.[5] As shown in Figure 2, an intramolecular hydrogen abstraction by the *in-situ* generated radical cleaves a distal C-H bond, and the resulting radical intermediate can be trapped accordingly to afford the desired product. The critical regioselectivity is dictated by the proximity between the radical and the C-H bond.

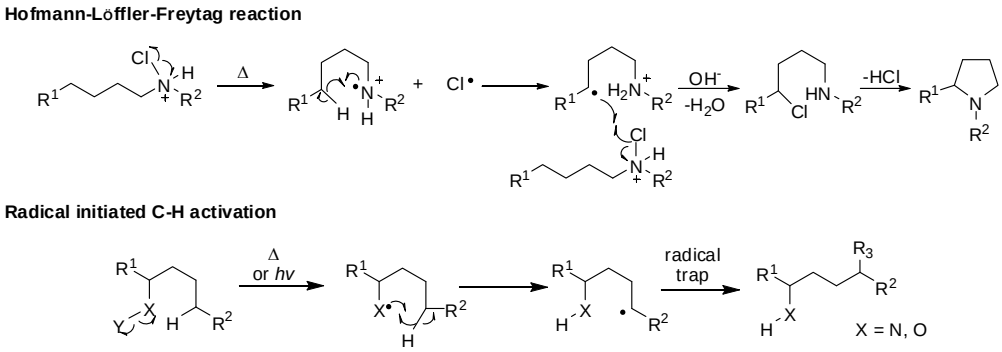
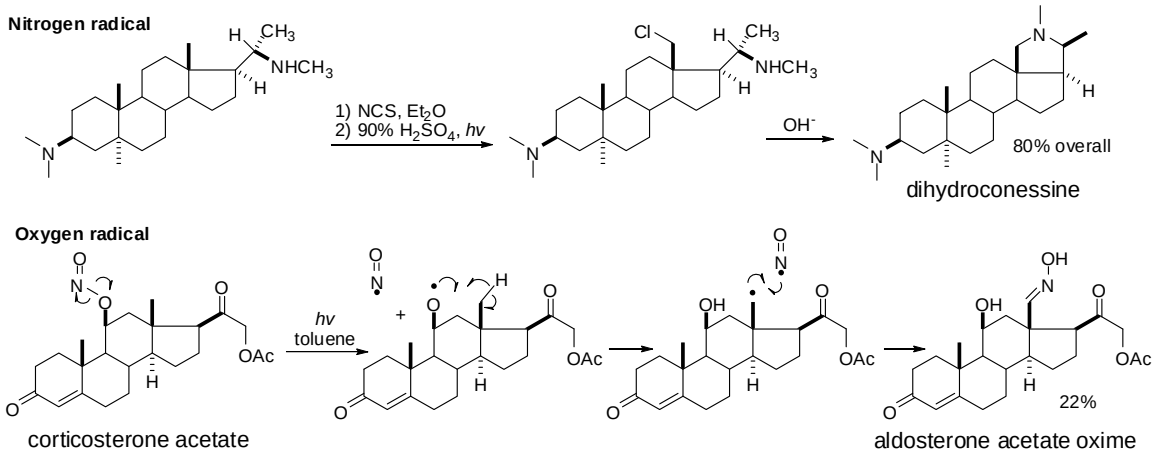


Figure 2. C-H activation by intramolecular radical reaction

Corey has successfully applied the Hofmann-Löffler-Freytag reaction to the synthesis of steroid dihydroconessine[6] (Scheme 1). Another notable application of this C-H activation strategy is the one-step preparation of the aldosterone acetate oxime from the available corticosterone acetate by photolysis of a nitrite ester,[7] which is also known as the Barton reaction. Albeit low yield, direct functionalization of an alkyl group by C-H activation dramatically shortens the synthetic sequence and increases the overall efficiency.



Scheme 1. Radical initiated C-H activation in natural product syntheses

1.1.2 C-H activation by metal carbenoid and nitrenoid insertion

Metal carbenoids, which are readily available from transition metal catalyzed diazo compound decompositions, have been known to interact with C-H bonds for decades.[8] As shown in the general mechanism (Figure 3), the metal atom in the metallocarbene doesn't participate in the C-H insertion process and the metal catalyst is easily regenerated after the insertion.[9]

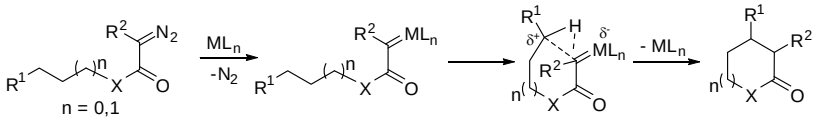
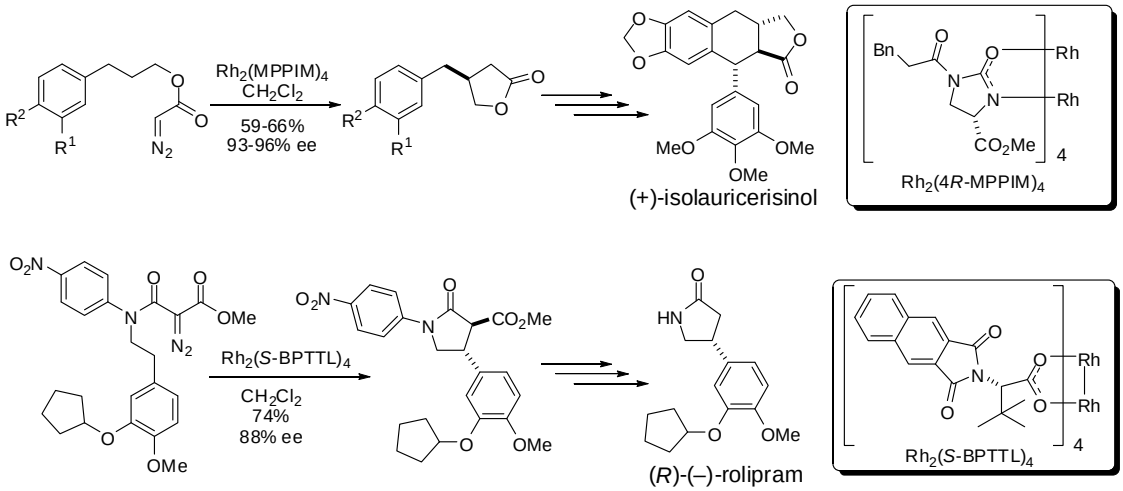


Figure 3. C-H activation by intramolecular metal carbenoid insertion

Intramolecular C-H activation by metal carbenoids has been extensively studied and a variety of cyclic compounds such as lactones[10] and lactams[11] are accessible by this protocol (Scheme 2). In these cases regioselectivity is usually excellent because of the proximity of the

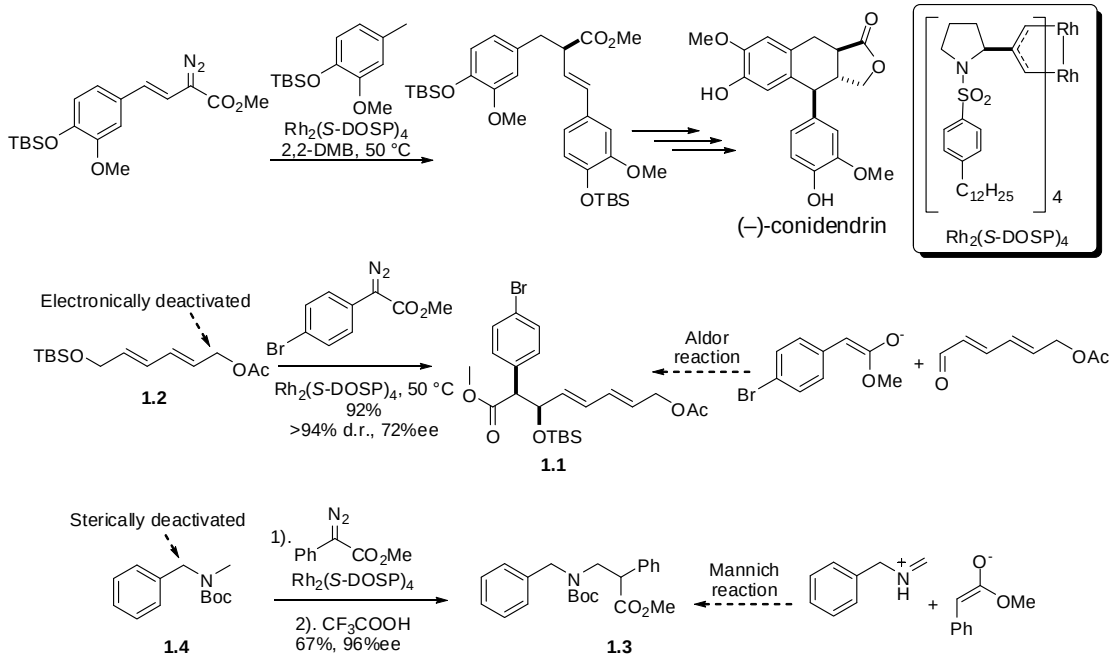
carbenoid and C-H bond. Sites attached to an electron-donating group react preferentially than electron-poor sites as partial positive charge develops during the C-H insertion (Figure 3), though steric interactions and the nature of the metal complex must also be considered.[12] Rhodium(II) complexes are generally the most effective catalysts, and high diastereo- and enantioselectivity can be achieved with proper chiral catalyst selection.[13] Metal carbenoid insertion reactions offer a unique approach to complex molecules because they proceed under neutral reaction conditions, provide high stereoselectivity and, exhibit good functional group compatibility.



Scheme 2. Metal carbenoid insertion in natural product syntheses

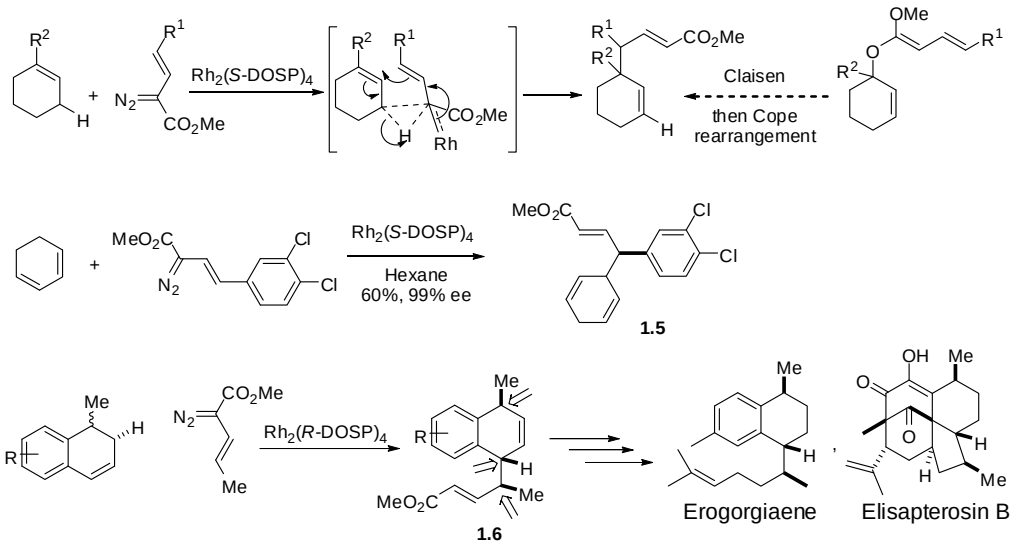
In contrast to the intensive exploration of intramolecular C-H carbenoid insertion, the intermolecular version hasn't been recognized of much synthetic usefulness mainly due to kinetic and chemoselectivity issues.[14] The donor-acceptor substituted metallocarbene (mostly vinyldiazoacetates and aryldiazoacetates) introduced by Davies is an exceptional remedy for these problems.[13b,15] The carbenoid intermediate is effectively stabilized by two substituents so the expected intermolecular C-H insertion can override the aforementioned side reactions to

assure the desired chemo- and stereoselectivity, as demonstrated in the preparation of (–)-conidendrin (Scheme 3). Strategically, this approach could provide a complementary access to the compounds which are usually synthesized by other classic methods, as illustrated by two different designs for preparing compound **1.1**[16] and **1.3**[17].



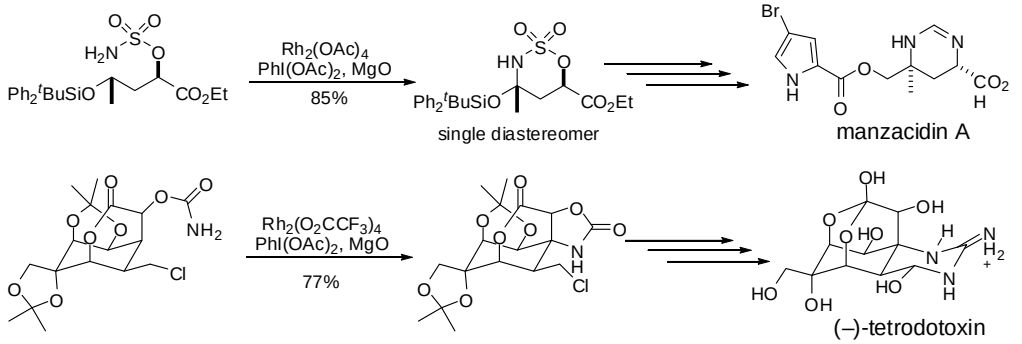
Scheme 3. C-H activation by intermolecular carbenoid insertion

When the vinyldiazoacetate is employed as the donor-acceptor carbenoid precursor, a new cascade reaction has been developed by combining the intermolecular metallocarbene C-H insertion with a Cope rearrangement (Scheme 4).[18] An excellent application of this protocol is the efficient synthesis of **1.6**, the key intermediate for a series of natural products such as erogorgiaene[19] and elisapterosin B.[20] In contrast, traditional synthetic plans[21] suffered from controlling the three highlighted stereocenters in **1.6**.



Scheme 4. Combined intermolecular C-H activation/Cope rearrangement reactions

Analogous to metal carbenoids, metal nitrenoids have also been reported to participate in intramolecular C-H activation reactions.[22] The nitrenoids are usually generated by rhodium catalyzed decomposition of carbamates and sulfamates in the presence of $PhI(OAc)_2$. The mildness and high regio- and stereoselectivity allow a late-stage incorporation of C-N bonds in syntheses. Du Bois has successfully implemented this method in the syntheses of manzacidin A[23] and (–)-tetrodotoxin[24] (Scheme 5).



Scheme 5. Metal nitrenoid insertion in natural product syntheses

1.1.3 C-H activation by coordination directed metallation

Coordination directed metallation is another way to selectively activate the C-H bond in complex molecules. As the general mechanism shows (Figure 4), the transition metal catalyst will coordinate to the heteroatom and activate the remote C-H bond by forming a five or six membered metallacycle. This versatile intermediate can undergo a β-hydride elimination (product not shown), or be utilized to construct a new C-C or C-X bond.

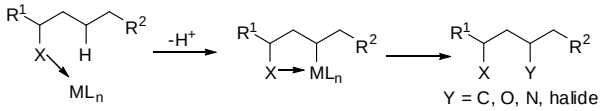
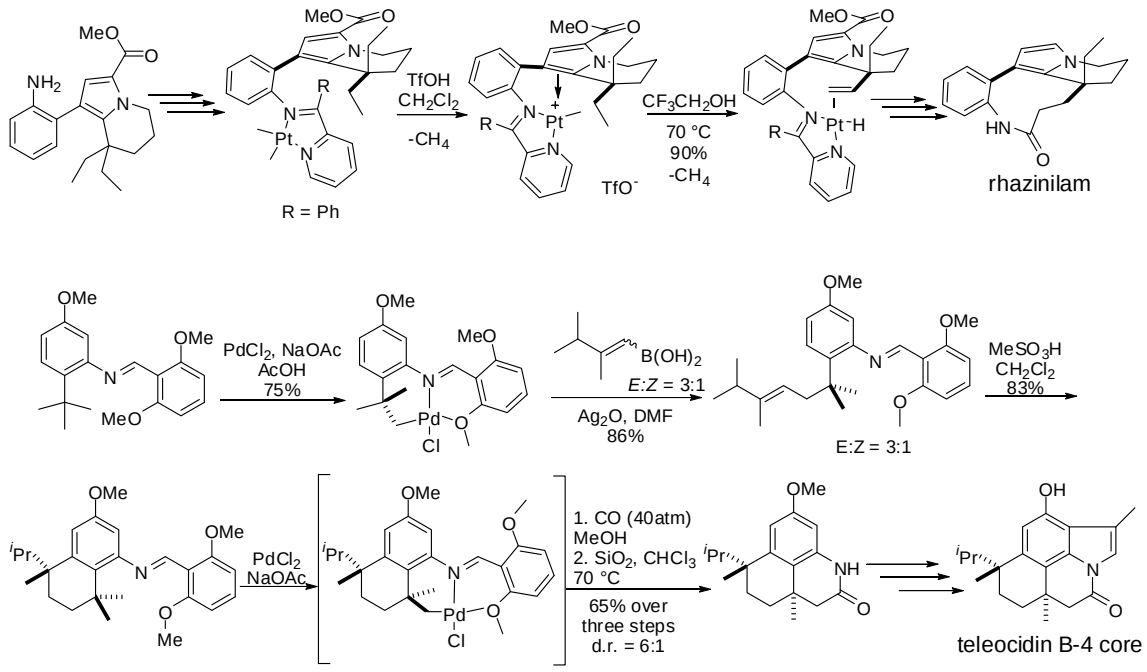


Figure 4. C-H activation by coordination directed metallation

An excellent example of sp^3 C-H activation by metallation can be found in the synthesis of alkaloid rhazinilam (Scheme 6).[25] Coordination of the platinum catalyst to the aniline nitrogen followed by thermolysis successfully dehydrogenates the distant terminal ethyl group in the presence of labile ester and pyrrole groups. Another fantastic example is the synthesis of the teleocidin B-4 core by Sames.[26] Two successive C-H activation reactions are employed in the sequence: the first palladacycle transmetalates with the boronic acid to couple the substrate with the vinyl fragment, and the second one reacts with carbon monoxide to afford the cyclic carbamate. These two examples invoke some unconventional bond disconnections and, on a strategy level, present us a new perspective of designing natural product synthesis.



Scheme 6. Examples of sp^3 C-H activation by coordination directed metallation

Pioneered by Murai group[27a], the directed metallation strategy has also been deployed to activate sp^2 C-H bonds (mostly in arenes) (Figure 5). Various functional groups, such as ketones, α,β-unsaturated esters and imines[27] are able to direct the metal catalysts to insert into the *ortho* C-H bonds, and the *in-situ* generated metallacycles can be utilized in the alkylation,[27a-d] carbonylation,[27e] or arylation[27f] reactions to give the desired products.

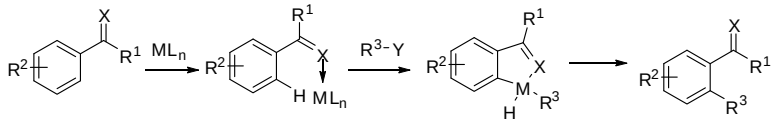
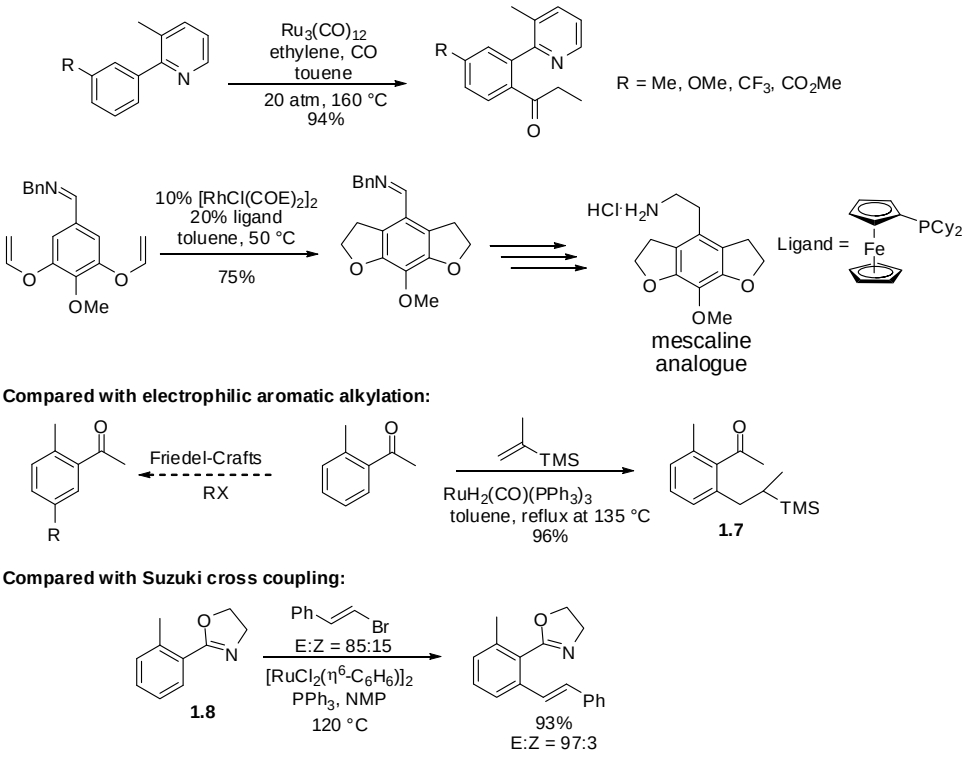


Figure 5. Sp^2 C-H activation by coordination directed metallation

Compared with other *ortho* functionalization methods, this method avoids using strong base like butyl lithium in *ortho*-lithiation, which dramatically enhances the functional group compatibility. Its regioselectivity relies on a totally different mechanism from the electrophilic

aromatic substitutions, therefore certain substitution patterns inaccessible through traditional approaches can be prepared through this C-H activation method, as illustrated by preparation of substrate **1.7** (Scheme 7).[27a] This method also simplifies the substrate preparations for Suzuki cross coupling reactions, as compound **1.8** can be used directly as the coupling partner,[27f] while in traditional Suzuki reactions[28] it needs to be functionalized to a more reactive aryl halide or boronate ester.

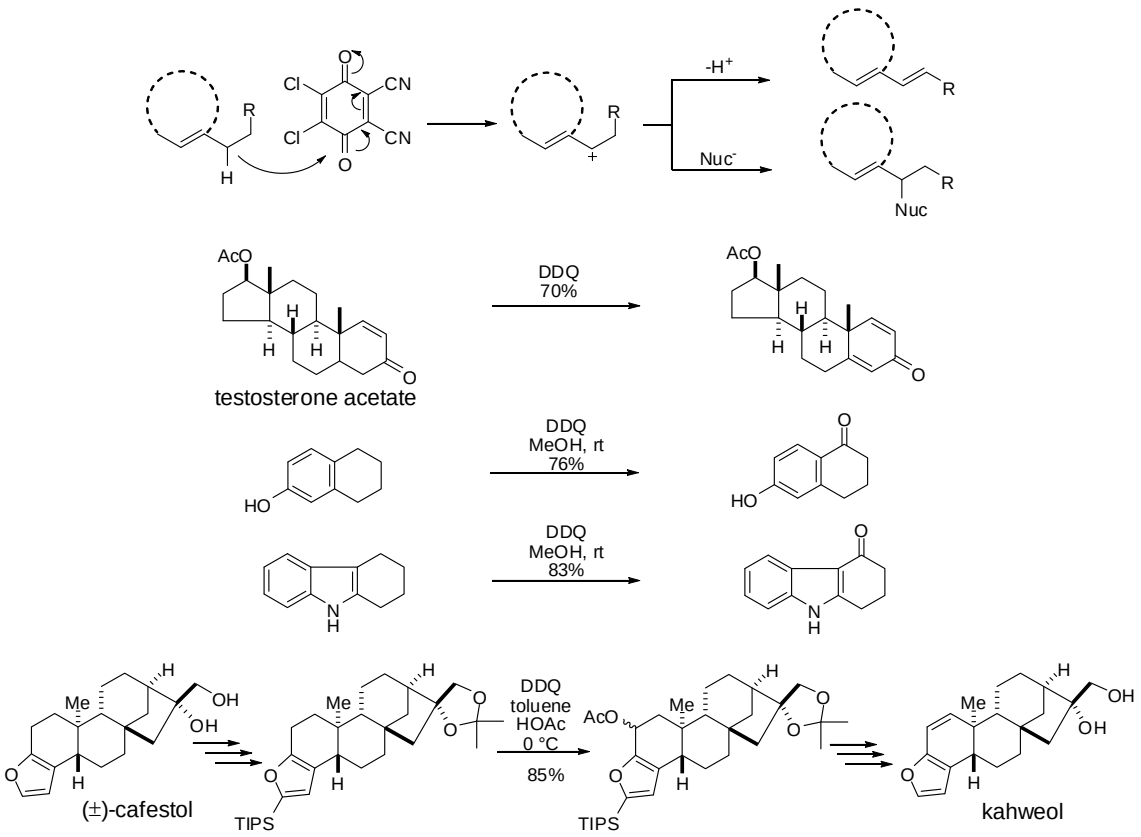


Scheme 7. Examples of sp^2 C-H activation by coordination directed metallation

1.1.4 C-H activation by DDQ oxidation

Quinones with multiple electron-withdrawing substituents such as 3,4,5,6-tetrachloro-1,2-benzoquinone (*o*-chloranil) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) are

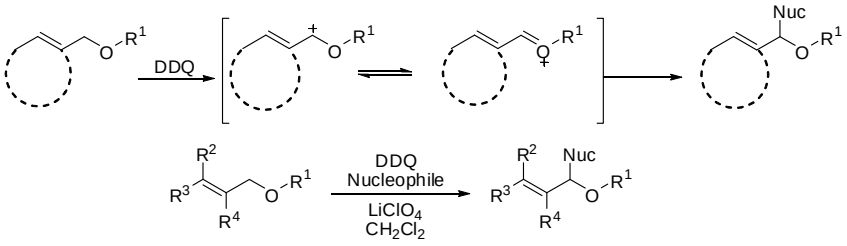
known to be strong oxidants.[29] Early investigations on DDQ showed their potential in dehydrogenating steroid ketones[30] (Scheme 8). The derived dehydro-products serve as useful intermediates for synthesizing other steroid derivatives. Additionally, Tuner has reported that the C-H bond of the methylene group *para* to the hydroxyl group of 6-hydroxytetralin can be selectively cleaved to introduce a new ketone group by DDQ.[31] Yonemitsu has found that DDQ can oxidize the C3 side chain of various indole derivatives.[32] Corey has successfully synthesized kahweol from diterpenoid cafestol by a DDQ mediated acetoxylation reaction.[33] The mechanism of these transformations, though debatable, is believed to be initialized by a formal hydride transfer between the substrate and DDQ. The corresponding carbocation can either be captured by the nucleophiles or deprotonate to afford the final product (Scheme 8).

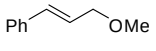
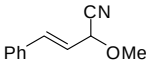
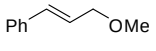
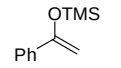
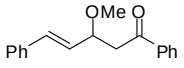
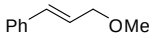
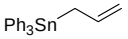
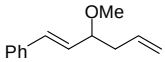
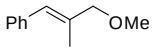
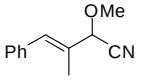
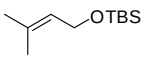
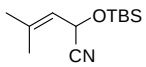


Scheme 8. Mechanism and applications of C-H activation by DDQ

Mukaiyama had captured carbocations from DDQ oxidation of allylic ethers with a variety of carbon nucleophiles to introduce new C-C bonds in the molecules.[34] As shown in Table 1, both the di- and tri- substituted allylic ethers give satisfying results in the C-C coupling reactions. The product in Entry 2 further emphasizes the power of this method as it yields the aldol product in protected form in one step. The order of reagent addition is critical as some nucleophiles (Entry 2 and 3) will decompose in the presence of DDQ. The $LiClO_4$ additive significantly improves the yields, presumably because it increases the electrophilicity of the carbocation/oxocarbenium ions by counter-ion exchanges.

Table 1. C-H activation of allylic ethers by DDQ

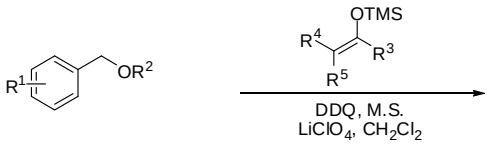


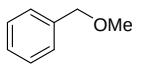
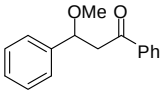
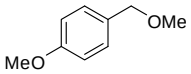
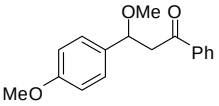
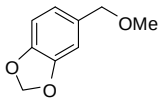
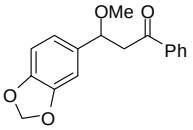
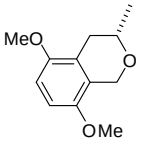
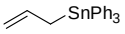
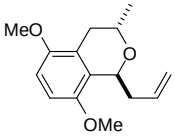
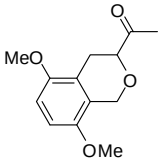
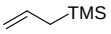
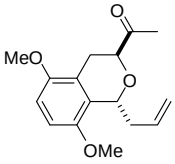
Entry	Substrate	Nucleophile	Product	Yield
1		TMSCN		82%
2				84%
3				79%
4		TMSCN		94%
5		TMSCN		40%

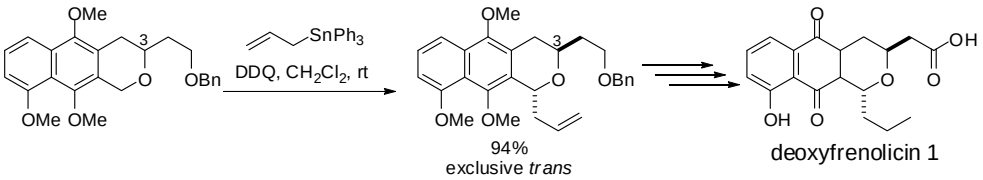
Xu has investigated the DDQ oxidation of cyclic[35] and acyclic benzylic ether systems[36] and found similar reactivities with various carbon nucleophiles (Table 2). The non-substituted benzyl methyl ether doesn't react upon treatment with DDQ (Entry 1), and the electron rich

arene systems are favored in terms of yields (Entry 2 and 3). High *trans* selectivity is observed for chiral substrates especially with strong nucleophiles (Entry 4 and 5), which inspired an efficient formal synthesis of deoxyfrenolicin 1.[37] As shown in Scheme 9, DDQ induced C-H activation followed by treatment with allyltriphenyltin installs the allyl group *trans* to C3 side chain with excellent yield and diastereoselectivity.

Table 2. C-H activation of cyclic and acyclic benzylic ethers by DDQ

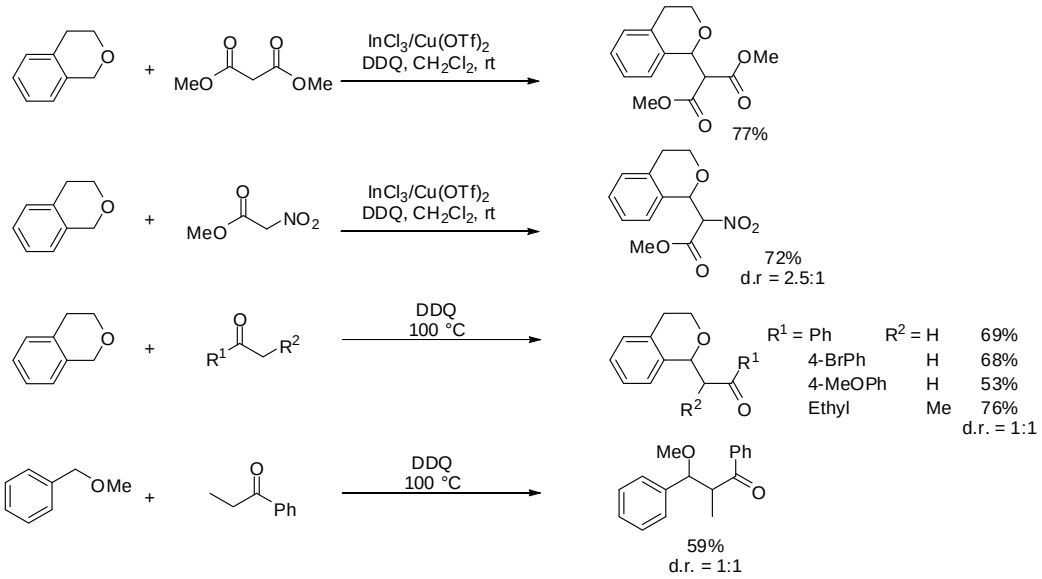


Entry	Substrate	Nucleophile	Product	Yield
1				0%
2				56%
3				84%
4				97% *trans*/*cis* = 13:1
5				78% Exclusive *trans*



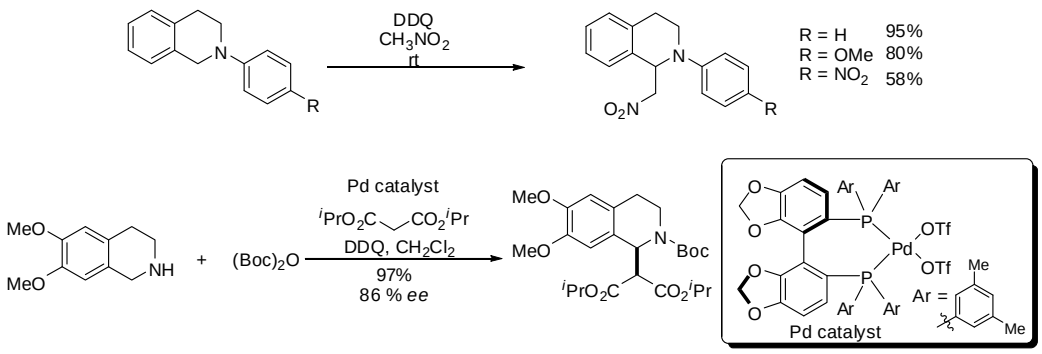
Scheme 9. Formal synthesis of deoxyfrenolicin 1 by DDQ induced C-H activation

Li has further simplified the reaction by replacing the pre-formed strong nucleophiles with readily available dialkyl malonates (Scheme 10).[38] The combination of $InCl_3$ and $Cu(OTf)_2$ catalyzes the enolization of the malonates to serve as the nucleophile sources. Moreover, the simple enolizable ketones can undergo a direct C-C coupling with isochroman when treated with DDQ,[39] though the reactions need to be performed in neat form with vigorous heating.



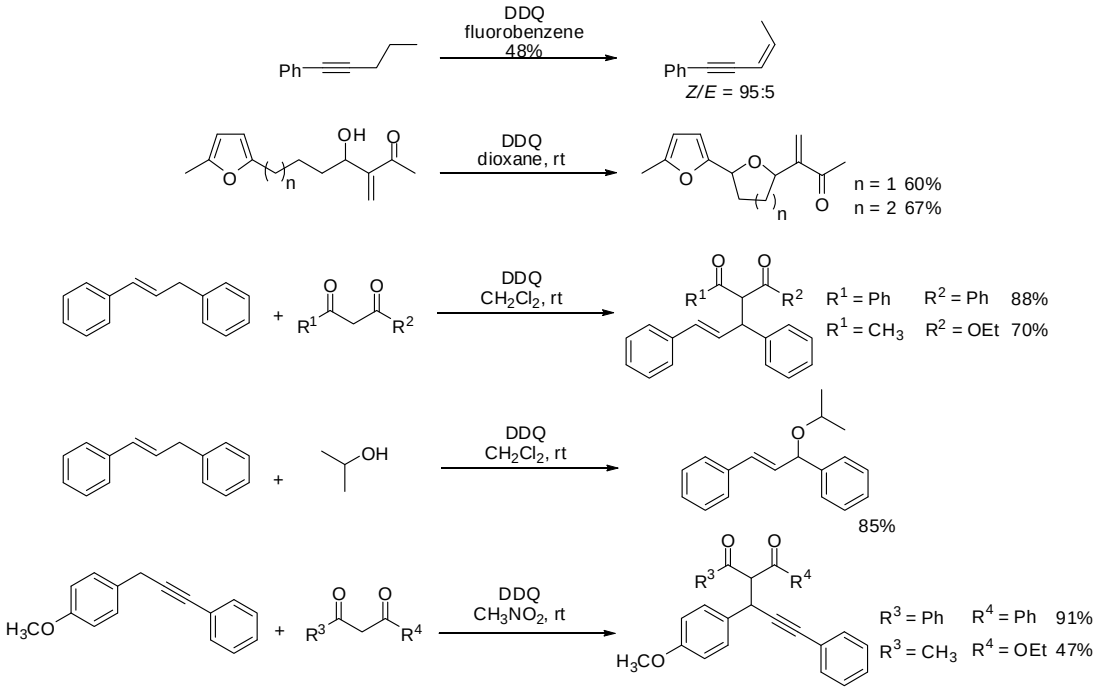
Scheme 10. C-C coupling reactions with enolizable malonates and ketones

Todd has found the benzylic C-H bonds in tetrahydroisoquinolines can be activated similarly by DDQ, and deprotonated nitromethane has been reported to be another suitable carbon nucleophile (Scheme 11).[40] Recently Sodeoka et al. have developed an asymmetric alkylation reaction for tetrahydroisoquinolines with DDQ.[41] These reactions are proposed to start with the DDQ oxidation of the amine or amide, then a nucleophile addition of the enolate to the iminium ion through a Mannich type reaction affords the desired C-C coupled product.



Scheme 11. C-H activation on tetrahydroisoquinolines by DDQ

A C-H bond that is not adjacent to a heteroatom is generally more difficult to activate due to the lack of stabilization of the derived carbocation, but in some cases it can also be functionalized by DDQ. Montevecchi has found refluxing a phenylalkylacetylene with DDQ will dehydrogenate it to afford a (*Z*)-enyne, though the substrate scope is very limited (Scheme 12).[42] Harwood has used DDQ to oxidatively cleave the C-H bond with a vinylogous substituent to initiate an intramolecular cyclization, which produces the novel 2-(2-furanyl)-cyclic ether products in a mild condition.[43] Sp^3 C-H bonds attached to multiple π systems are slightly more reactive than those with single unsaturated substituent, and Bao has shown that they can be efficiently activated by DDQ to couple with carbon and heteroatom nucleophiles.[44]



Scheme 12. Activation of inert C-H bonds by DDQ

1.2 DEVELOPMENT OF DDQ-INDUCED INTRAMOLECULAR CYCLIZATION REACTIONS ON BENZYLIC ETHERS

1.2.1 Introduction: Aim and challenges

Our group has developed the electron transfer initialized cyclization reaction (ETIC) during the investigation of oxidative C-C bond activations, and successfully implemented it in several complex natural product syntheses.[45] Inspired by its mildness and excellent chemoselectivity, we initiated a project to study oxidative C-H activation of benzylic ethers based on the preliminary results from Mukaiyama,[34] Xu,[35-38] and Seiders.[45a] As shown in Figure

6, when substrate **1.9** is subjected to suitable oxidants, the highlighted C-H bond cleaves to give oxocarbenium ion intermediate **1.10**, followed by an intramolecular nucleophilic attack to afford the cyclized product **1.11**. The arene scope, the stereoselectivity in the cyclization, and the functional group compatibility are the major tasks to investigate in this work.

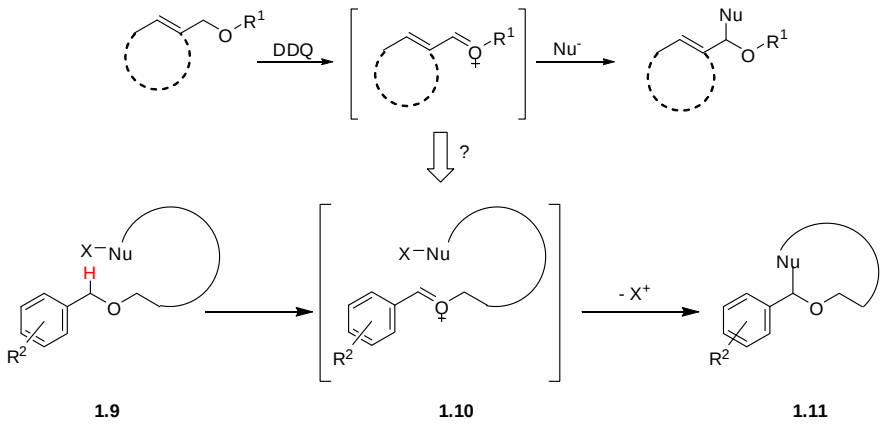


Figure 6. Proposed C-H activation induced cyclization

Several aspects make this project more challenging than the intermolecular C-C coupling reactions discussed in Chapter 1.1.4:

1. The choice of the nucleophile appended in the molecule. The nucleophile is required to survive through the oxidative C-H activation process and be able to capture the transient oxocarbenium ion intermediate. External nucleophiles can be added into the reaction after the generation of cationic intermediate to avoid the co-existence with the oxidizing reagent, but this solution is not plausible in the intramolecular reactions. A screening for compatible nucleophile and oxidant combination is necessary.

2. The over-oxidation problem. The desired product **1.11** still has an intact arene system and a benzylic hydrogen atom. Theoretically it can be oxidized by DDQ to give another oxocarbenium ion, which can react with other nucleophiles or undergo other degradation pathways. Therefore inhibiting over-oxidation is critical to the success of this project.

1.2.2 Substrate preparations

To simplify the reaction parameters, the enol acetate[45a] was chose as the common nucleophile for the first group of substrates and variations are made at the arene substituents and the side chains (Figure 7). The investigation started with *para*-methoxybenzyl ether **1.12**, on which the reagents screening and reaction condition optimizations would be performed. The alkyl side chain was introduced to demonstrate the diastereoselectivity during the cyclization. Compounds with various aromatic systems (**1.13** to **1.18**) were synthesized to test the arene scope. Substrates **1.19** to **1.22** were prepared for two purposes: testing functional group compatibility and studying the influence of competitive cyclization of heteroatom nucleophiles. Substrate **1.23** was designed to test the feasibility of activating C-H bond adjacent to nitrogen atom. Substrates **1.24** to **1.29** in the second group were synthesized to broaden the nucleophile scope for this method.

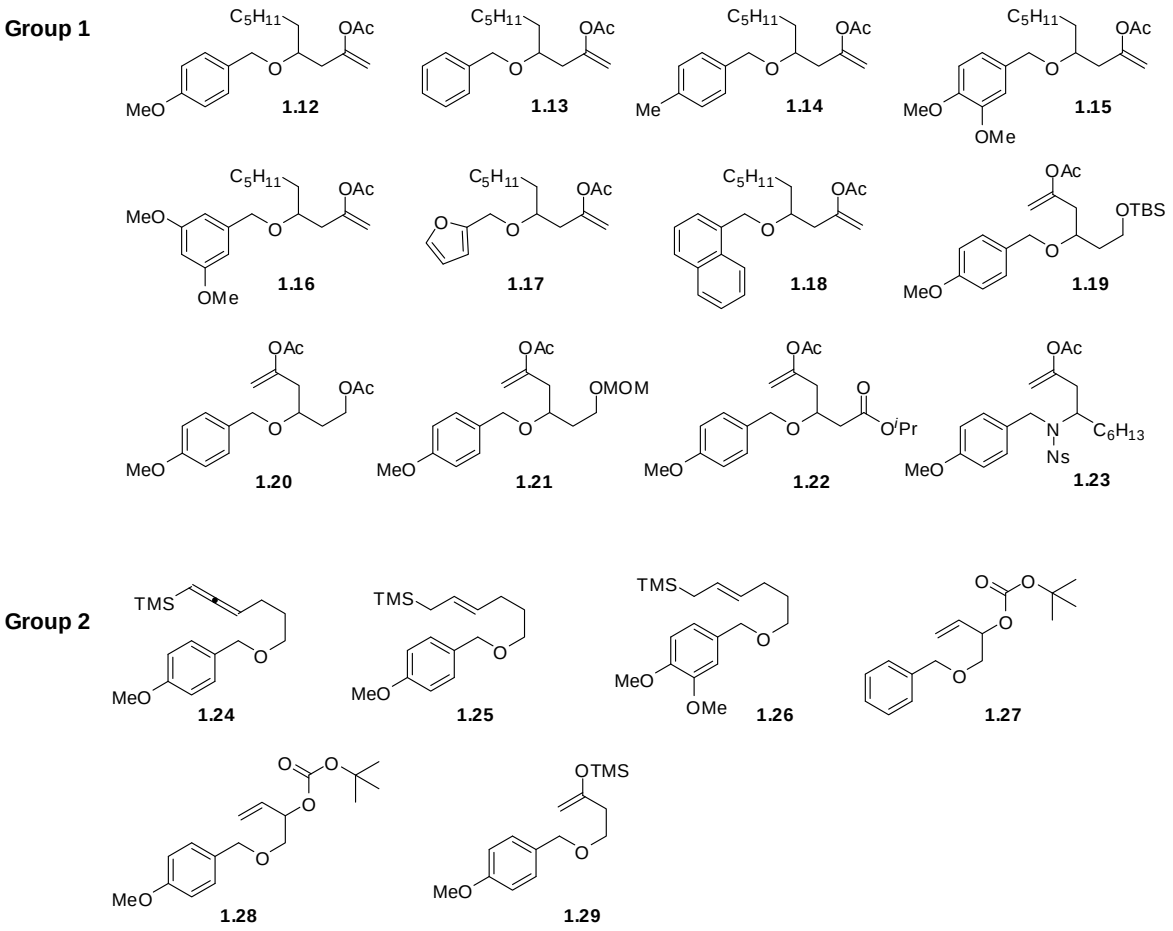
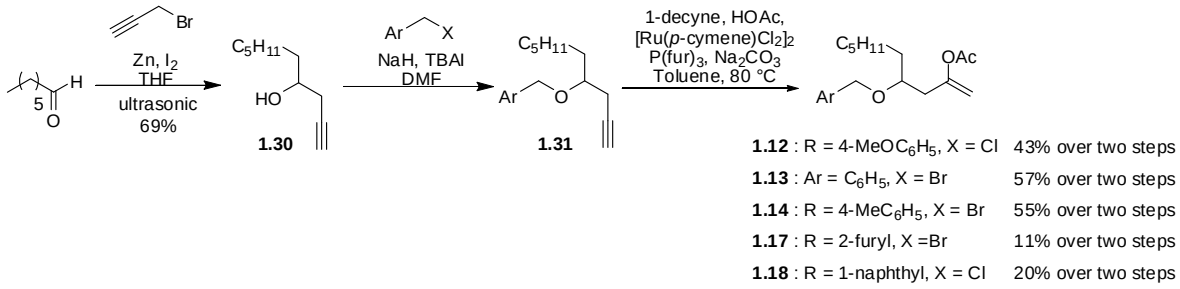


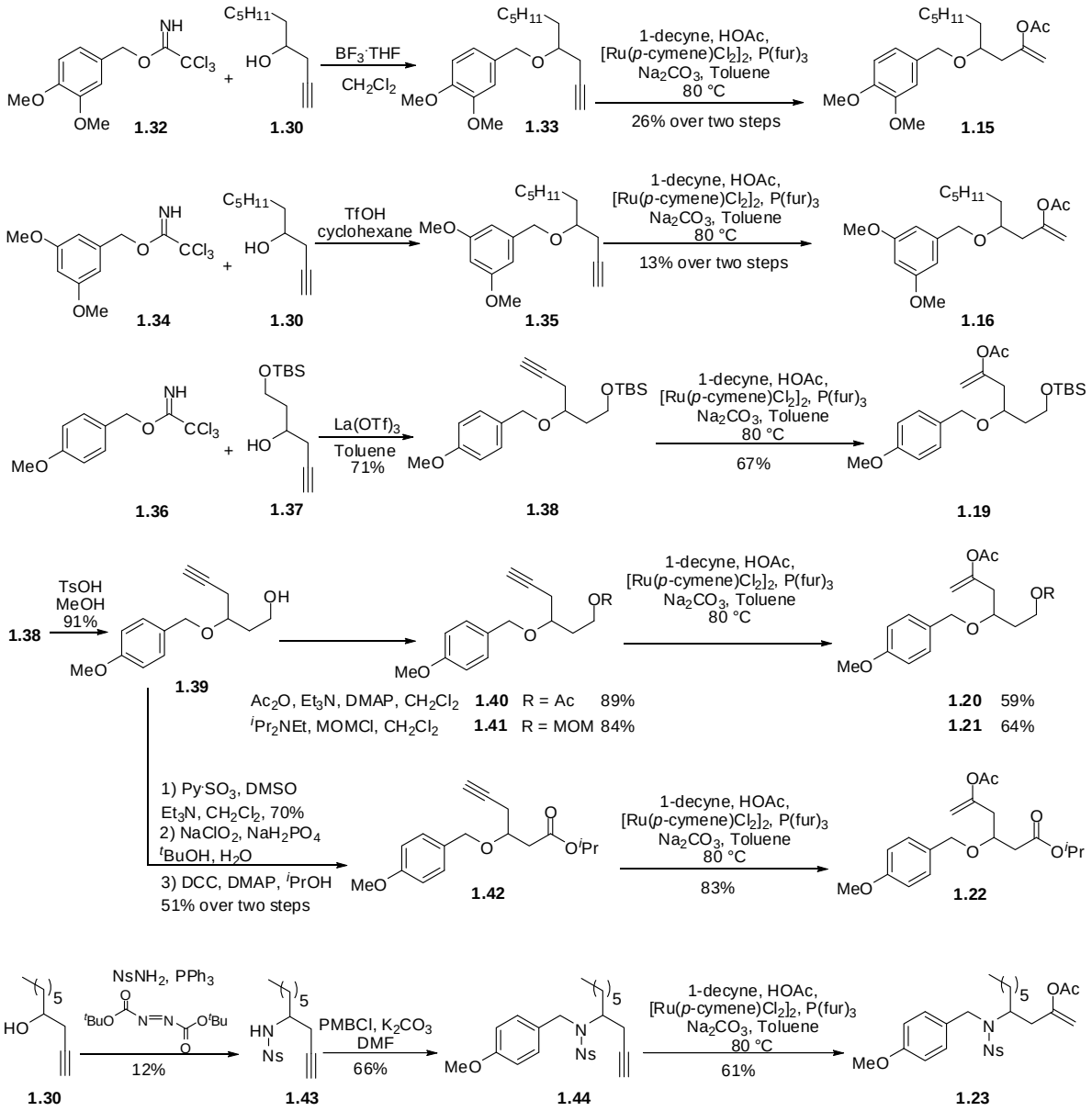
Figure 7. Substrates classification

The preparation of substrates **1.12**-**1.14**, **1.17** and **1.18** shared the same synthetic route (Scheme 13). A Barbier reaction[46] between heptanal and propargyl bromide gave the homopropargylic alcohol **1.30**, which was alkylated with various arylmethyl halides to afford the ether **1.31**. Ruthenium catalyzed Markovnikov addition of acetic acid to the terminal alkyne[47] completed the synthesis of substrate. The low yield in the last two steps for **1.17** was caused by the decomposition of **1.31** intermediate on silica gel column.



Scheme 13. Syntheses of substrates **1.12-1.14**, **1.17** and **1.18**

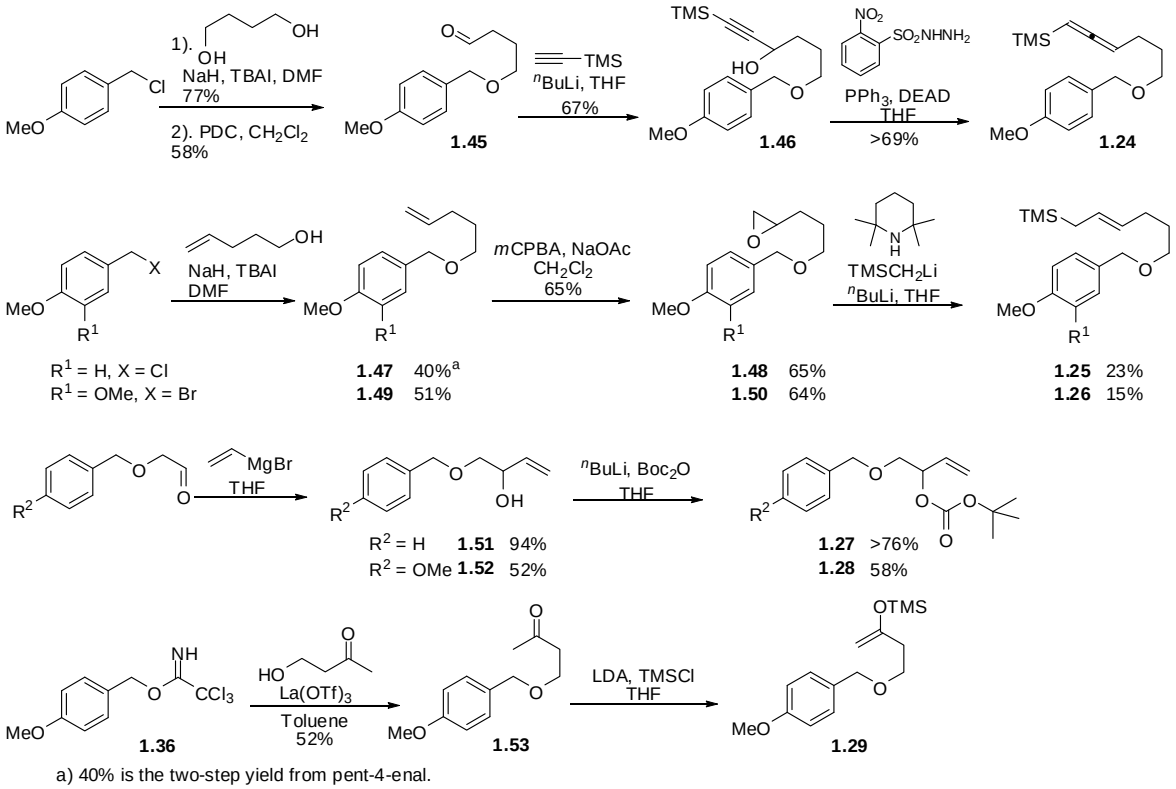
For benzylic ethers with multiple electron-donating groups (**1.15** and **1.16**), a Lewis or Brønsted acid catalyzed etherification reaction between the alcohol and trichloroacetimidate was employed to form the ether bond (Scheme 14).[48] The choice of Lewis acid was critical to the reactions in terms of yields. $La(OTf)_3$ was found to be more productive than other traditionally used Lewis acids[48d] (BF_3·THF and TfOH for **1.15** and **1.16**), and it had been applied to the synthesis of common intermediate **1.38** for substrates **1.19** to **1.23**. The TBS protected homopropargylic alcohol **1.37** was obtained in a similar fashion as **1.30**. The assembling of substrate **1.23** started from a Mitsunobu reaction between **1.30** and nosyl amine to give the Ns-protected amine **1.43**,[49] followed by *N*-deprotonation and alkylation[50] with PMBCl to afford **1.44** as the precursor for enol acetate preparation.



Scheme 14. Syntheses of substrates **1.15**, **1.16** and **1.19**-**1.23**

Syntheses of substrates in the second group are listed in Scheme 15. The trimethylsilyl allene group in substrate **1.24** was prepared from propargylic alcohol **1.46** by employing Myers' protocol.[51] Substrate **1.25** synthesized by cross metathesis reaction[52] was contaminated by some inseparable impurities which were suspected to be the dimers. Alternatively we employed Hodgson's protocol to prepare them from epoxide **1.48** and **1.50**.[53] **1.25** and **1.26** were obtained

from the reactions as exclusive *E* stereoisomers though the yields were low. Carbonates **1.27** and **1.28** were easily prepared by sequential vinyl addition to the aldehyde and Boc protection. The silyl enol ether **1.29** was prepared from **1.53** and the crude material was used without any purification due to its lability.



Scheme 15. Syntheses of substrates **1.24** to **1.29**

1.2.3 Experiment results

I. Cerium(IV) ammonium nitrate (CAN) as the oxidant

Inspired by the report from Freccero[54] we chose photoexcited CAN to be our first oxidant to activate benzylic C-H bonds through a single electron transfer (SET) process (Figure 8). The

irradiation of CAN in solution initiates a homolytic cleavage of the Ce-O bond to give the nitrate radical as the relevant oxidizing agent. A SET between the nitrate radical and the arene **1.54** afforded benzylic radical cation **1.55**. Deprotonation of this transient species, followed by another SET gave rise to oxocarbenium ion **1.57**. Cyclization of the enol acetate nucleophile in **1.57** led to the tetrahydropyrone product **1.58**.

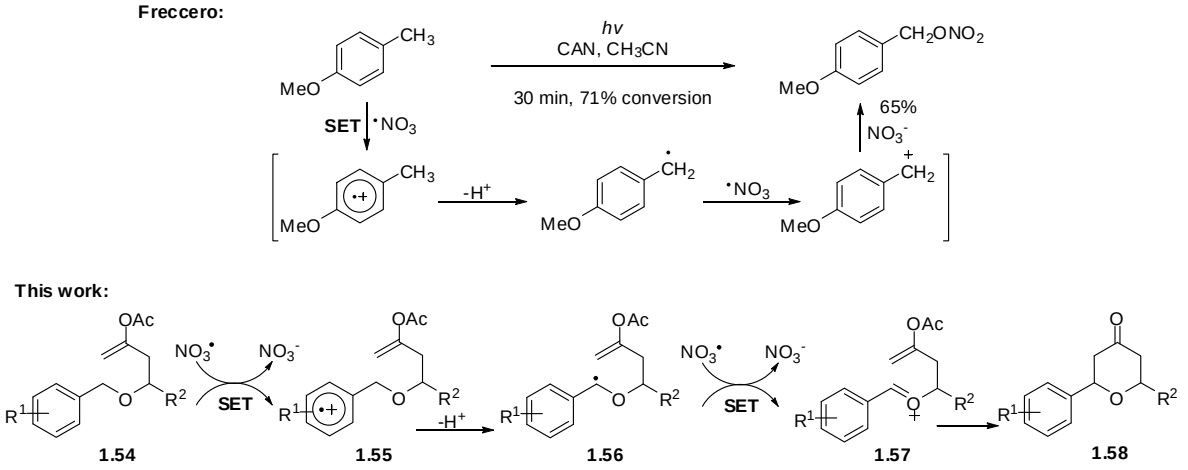
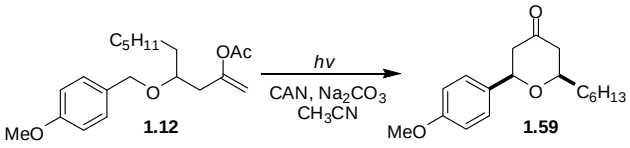


Figure 8. Proposed C-H activation by photoexcited CAN

The first reaction was conducted on *para*-methoxybenzylic ether **1.12** with a stoichiometric amount of CAN and sodium carbonate in anhydrous acetonitrile (Table 3). The reaction stalled after being irradiated for 20 min due to the depletion of Ce^{4+}. The starting material was not completely consumed. After purification, *cis*-tetrahydropyrone **1.59** was obtained in slightly less than 45% yield due to some inseparable anisaldehyde contaminant, and 39% of the starting material was recovered. Another isolated by-product had incorporated a new substituent onto the benzene ring which was suspected to be a nitrate group (three separate groups of proton peaks rather than two for the arene by ^{1}H NMR) and the enol acetate group was intact. Using four equivalents of CAN still could not drive the reaction to completion, and the

yield (brsm) of **1.59** actually decreased. In this case the formation of the over-oxidized product **1.60** was observed (Figure 9). It was found that using deaerated solvent improved the conversion and yield though the reaction was slower. The best result was achieved by using four equivalents of CAN in deaerated acetonitrile (Entry 3, Table 3).

Table 3. Cyclization of PMB ether **1.12** with irradiated CAN



Entry	Equivalents of CAN	Conversion	Time	Yield
1	2	61%	20 min	45% (75% brsm)
2	4	91%	20 min	55% (60% brsm)
3	4[a]	100%	50 min	66%
4	3[a]	81%	80 min	46% (51% brsm)

a. The reaction was deaerated before the irradiation.

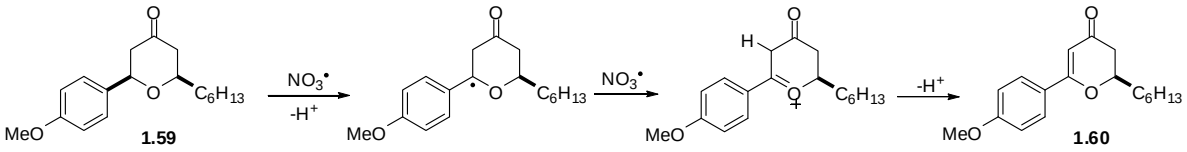
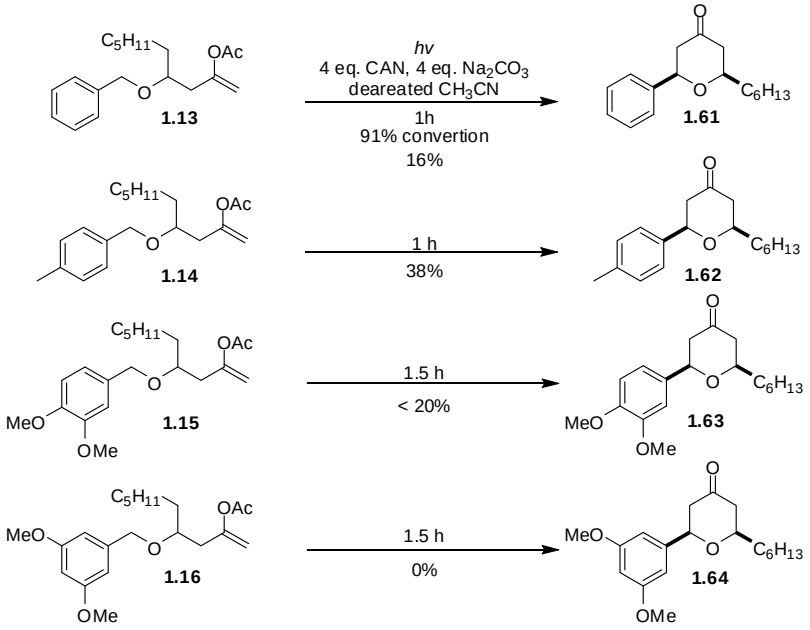


Figure 9. Formation of the over-oxidized product **1.60**

Applying the optimized reaction conditions to other substrates was discouraging (Scheme 16). The majority of the non-substituted benzylic ether **1.13** decomposed to an unidentified compound, and the yield for the desired product **1.61** was a mere 16%. Substrate **1.14** suffered from the nitration reaction of both starting material and the product **1.62** at the *para* methyl group, which dropped the yield to 38%. The nitration issue was much more detrimental on electron-rich benzylic ether **1.15** and **1.16**, as little or no cyclized product was obtained in either

case. Such a limited substrate scope and non-controllable side reactions forced us to choose another oxidizing reagent to replace the over-reactive photoexcited CAN.



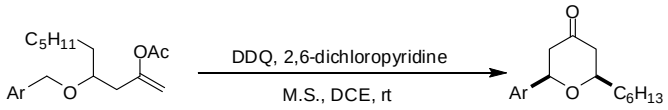
Scheme 16. Cyclization of substrates **1.13-1.16** with photoexcited CAN

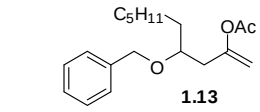
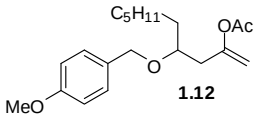
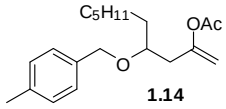
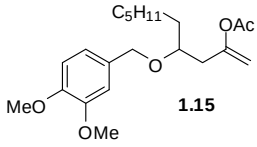
II. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant

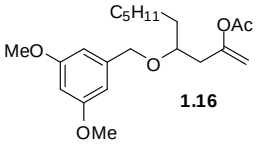
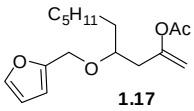
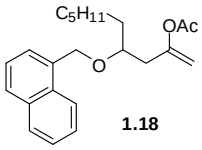
A qualitative screening sequence between readily available substrates and DDQ was performed to optimize the reaction conditions. Two equivalents of DDQ were employed based on the experience with CAN, and it was found that running the reaction in 1,2-dichloroethane with the weak, soluble organic base 2,6-dichloropyridine assured complete consumption of starting material while retaining a high yield. Molecular sieves were added to absorb the trace amount of water in solvent to inhibit the oxidative cleavage of the benzylic group. The dihydropyrone derived from over-oxidation was most likely formed as determined by TLC comparison with the genuine sample but not isolated due to limited quantity.

The cyclization reactions of substrates in group one took place as expected under the optimized conditions to afford the tetrahydropyrone products (Table 4). The diastereoselectivity was excellent as only *cis* isomers were isolated. *para*-Methoxybenzyl ether **1.12** only took 10 min to react completely, and the yield was better than the reaction with photoexcited CAN. *para*-Methylbenzyl ether **1.14** reacted slightly slower but the yield was comparable with that of **1.12**. Substrate **1.13** with no substituent on the arene took 14 hours to complete the reaction. Surprisingly the isolated yield (63%) was very satisfying, especially compared to the results of Xu's study that showed unsubstituted benzyl ether was unreactive with DDQ and external nucleophiles.[36] The reaction of 3,4-dimethoxybenzyl ether **1.15** was almost instant at room temperature but the yield was disappointing (54%). When the reaction was conducted at –20 °C instead of room temperature the yield improved to 83%. Compared with **1.15**, the other di-substituted arene **1.16** took longer time and the yield was mediocre. Furyl and naphthyl substrates behaved similarly to give the corresponding *cis*-tetrahydropyrone products.

Table 4. DDQ-mediated cyclization of arene substrates **1.12-1.18**

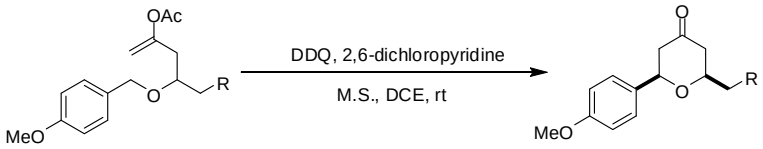


Entry	Substrate	Time	Yield
1	 **1.13**	14 h	63%
2	 **1.12**	10 min	77%
3	 **1.14**	30 min	82%
4	 **1.15**	2 min / rt 10 min / –20 °C	54% 83%

Entry	Substrate	Time	Yield
5	 **1.16**	1.5 h	57%
6	 **1.17**	12 h	63%
7	 **1.18**	4 h	84%

When substrates **1.19-1.22** were treated with DDQ, the same reaction pattern was observed whereas the yields varied with different side chains (Table 5). It was found that 1.5 equiv. of DDQ was sufficient to drive the reactions to completion. The TBS, acetate and isopropyl ester groups (Entry 1 to 3) almost had no impact on the yields, but the reactions were moderately slowed down. The MOM protecting group dropped the yield to 57% (Entry 4). The unprotected aldehyde (**1.65**, Entry 5) survived in this oxidative environment but the yield decreased to 43%.

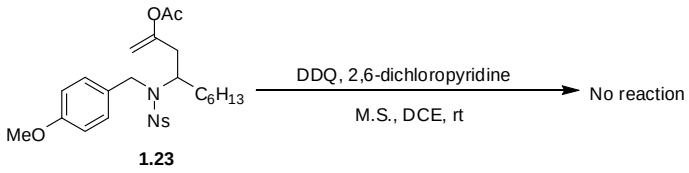
Table 5. DDQ-mediated cyclization of PMB ether with different side chains



Entry	R	Time	Yield
1	CH_2OTBS (**1.19**)	30 min	74%
2	CH_2OAc (**1.20**)	45 min	74%
3	CH_2OMOM (**1.21**)	45 min	57%
4	$CH_2CO_2{}^iPr$ (**1.22**)	45 min	68%
5	CHO (**1.65**)[a]	1 h	43%

a. Synthesized from **1.19**. See the supporting information for detail.

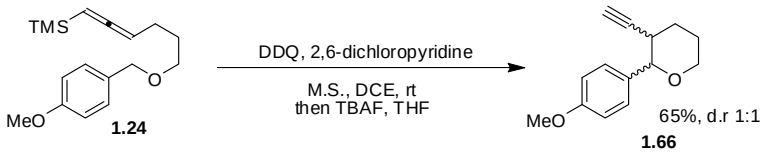
Sulfonylamide substrate **1.23** failed in the reaction with DDQ (Scheme 17). Only starting material was recovered after stirring the reaction for two hours. Further study about this type of substrates is currently being conducted by other group members.



1.23

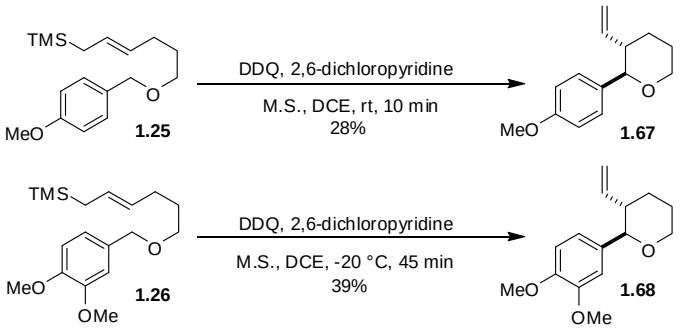
Scheme 17. Reaction of Sulfonylamide **1.23** with DDQ

Substrates with different nucleophiles were also subjected to the optimized reaction conditions. Trimethysilyl allene **1.24** was found to be compatible with DDQ and the desired cyclization occurred to give **1.66** in 65% yield as a 1:1 mixture of diastereomers (Scheme 18). The purpose of treating the crude products with TBAF was to simplify the purification as the silyl group of **1.24** was not completely cleaved during the cyclization reaction.



Scheme 18. Cyclization of substrate with TMS allene nucleophile

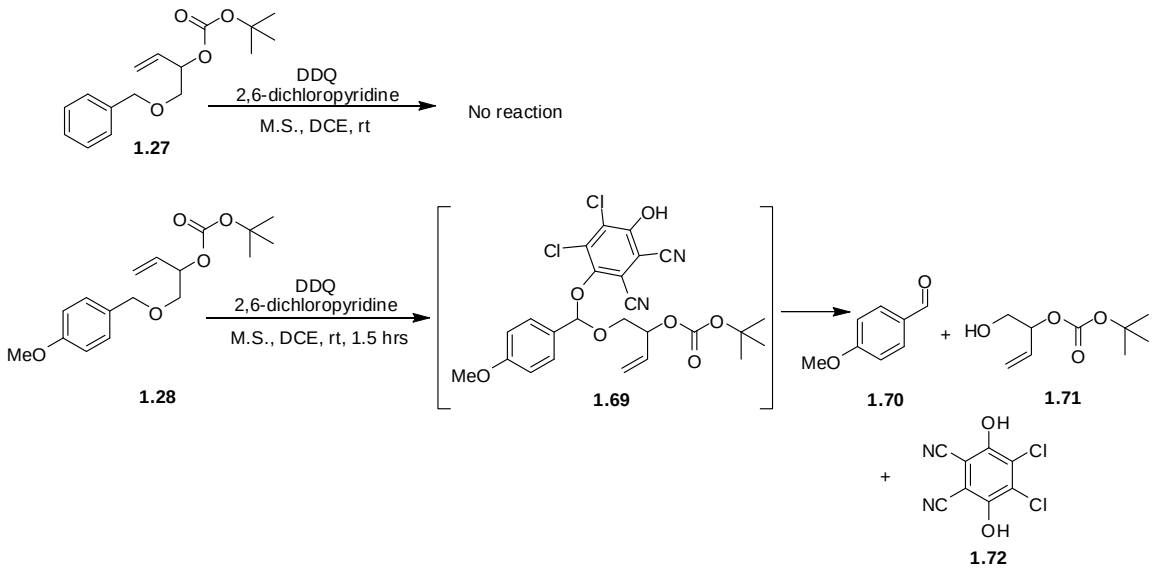
Allyl trimethylsilane substrate **1.25** did not cyclize efficiently with DDQ. Only 28% of cyclized product **1.67** was collected from the reaction at room temperature. Lowering the temperature to –20 °C suppressed the desired reactivity and introduced side reactions. Replacing the electroauxiliary with a more electron-rich 3,4-dimethoxybenzyl group (**1.26**) modestly increased the yield. The diastereoselectivity was excellent in both cases.



Scheme 19. Cyclization of substrates with allyl TMS nucleophile

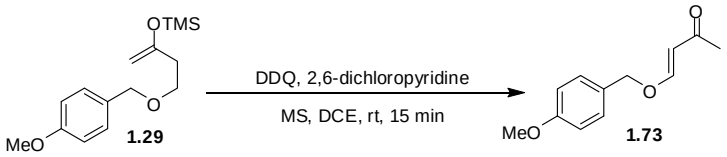
The allylic carbonate groups were not sufficiently nucleophilic to attack the oxocarbenium ion derived from the C-H activation. As shown in Scheme 20, only starting material was recovered from the reaction of substrate **1.27** with DDQ. The result from *para*-methoxybenzyl ether **1.28** was complicated: by TLC all starting material was converted to a single product after 1.5 hours, but the separation of the new product failed. The residue collected from the flash chromatography had a complex proton NMR which suggested it to be a mixture.

The products were tentatively identified as anisaldehyde **1.70** and homoallylic alcohol **1.71**. Considering **1.72** is invisible in ^{1}H NMR, we postulated the product observed during the reaction was compound **1.69.** This unstable benzylic acetal decomposed on the silica gel column during the final purification step, explaining the complicated NMR spectrum.



Scheme 20. Cyclization of substrates with allylic carbonate nucleophile

The reaction of substrate **1.29** with DDQ gave no tetrahydropyrone product but the starting material was consumed within 15 min (Scheme 21). An unexpected product was isolated from the reaction which was tentatively assigned as the enone **1.73** by NMR analysis. This class of nucleophiles was not studied further because they produced the same tetrahydropyrone products as the enol acetate groups.



Scheme 21. Reaction of silyl enol ether **1.29** with DDQ

1.2.4 Discussion

A variety of arenes with different substitution patterns successfully participate in the DDQ induced cyclization reactions. Enol acetate nucleophiles are shown compatible with DDQ and to be highly productive in the cyclization processes. Figure 10 shows the general mechanism for the transformation: a single electron transfer between the starting material and DDQ gives rise to the benzylic radical cation **1.55** and the hydroquinone radical anion **1.74**. A hydrogen atom transfer will take place between the two transient intermediates to afford the oxocarbenium ion intermediate **1.57** (homolytic cleavage), and the nucleophilic attack of enol acetate initiates the cyclization. A six-membered ring transition state is postulated, and both the arene and the side chain R^2 stay on the equatorial positions of the chair conformation which explains the observed exclusive *cis*-diastereoselectivity.

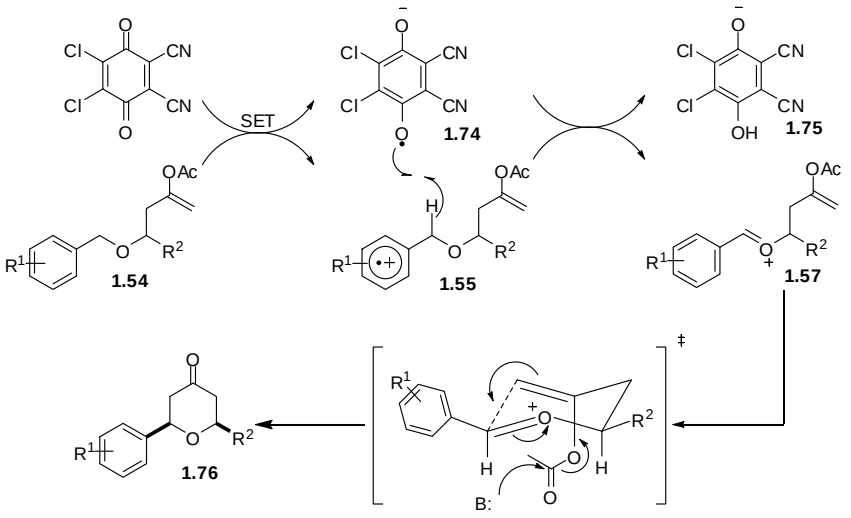


Figure 10. General mechanism of DDQ induced cyclization reaction

An alternative mechanism can also be proposed for the formation of the oxocarbenium ion **1.57**: after the SET oxidation, the intermediate **1.55** deprotonates to give the benzylic radical (heterolytic cleavage), which undergo another SET oxidation to afford the same oxocarbenium ion **1.57**. Both the deprotonation[55] and hydrogen atom abstraction process[56] have been observed for radical cation decay in related systems (Figure 11). We favor the hydrogen atom abstraction mechanism because of the stability of the oxocarbenium ion **1.57** and the low basicity of **1.74**.

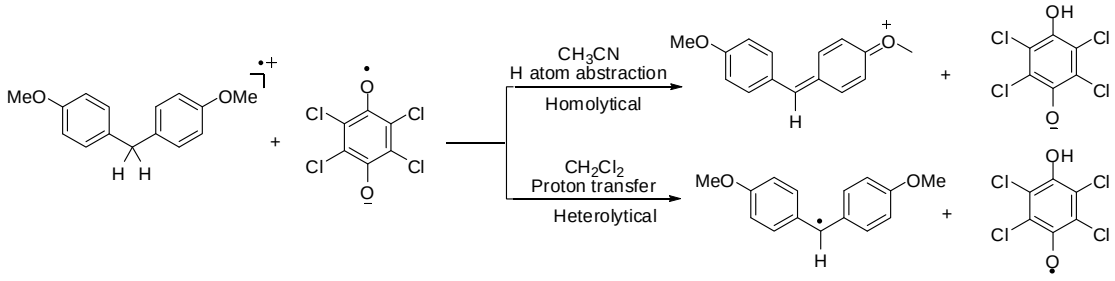


Figure 11. Different mechanisms for diarylmethane radical cation decay

The results in Table 4 show that the substituents on the arene have a significant impact on the rates of the cyclizatios. We postulate that the nucleophilic attacks on the oxocarbenium ions

are always fast, and the observed rate differences are caused by the efficiency of SET oxidation of substrates and subsequent hydrogen atom transfer (Figure 10). Substrates with electron-donating substituents on the arenes are oxidized more easily and cyclize faster. *Para*-Methoxy group on the benzyl ring (**1.15**) can stabilize the oxocarbenium ions better than the *meta* one (**1.16**), facilitating the hydrogen atom transfer process. As a result substrate **1.15** reacts faster than **1.16** with DDQ.

Very limited amount of over-oxidized product **1.81** was observed from any of the reactions in Table 4 and 5, although the tetrahydropyrone **1.76** can be oxidized by DDQ because the substituents of the arenes have barely changed. This can be explained by the strongly disfavored hydrogen atom abstraction of radical cation **1.77**. It is known that the C-H bond in aromatic radical cations is required to be in good alignment with the π electrons to facilitate the bond cleavage.[57] As shown in Figure 12, between the two possible conformers of **1.77**, **1.78** is more stable as it avoids the steric repulsion between the *ortho* hydrogen atom of the arene and the equatorial hydrogen at C2.[58] Such a low-energy conformer has almost no overlap between the π electrons and the axial C-H bond. As a result the hydrogen atom abstraction on **1.77** will not occur and the potential over-oxidation of **1.76** is effectively suppressed.

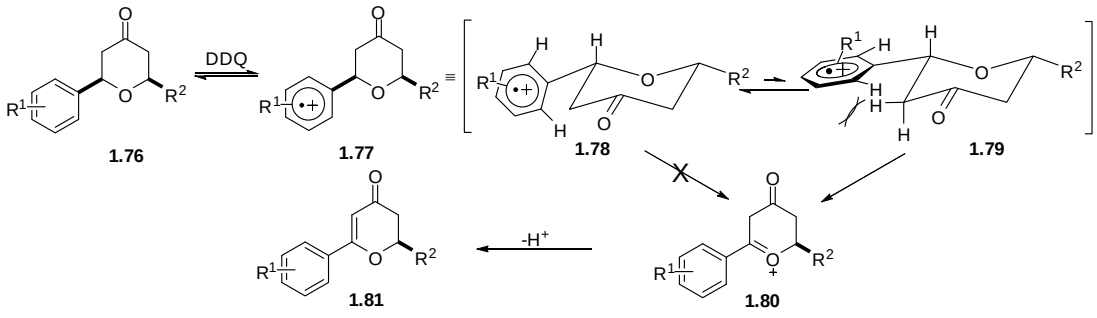


Figure 12. Mechanism of over-oxidation inhibition

Common functional groups such as ester, MOM ether and silyl protecting group (Entry 1 to 4, Table 5) are compatible with this method. The reactions generally took longer time than those with simple alkyl side chains, which was attributed to the inductive destabilization of the oxocarbenium ion intermediate by the heteroatom-containing side chains. More importantly, all the substrates cyclized to give the tetrahydropyrone products even though the heteroatoms could also add to the oxocarbenium ions to produce benzylic acetal (Figure 13). This suggests that the C-O coupling reactions are not favorable, or are reversible. The low yield obtained in Entry 5 was solely due to the instability of the aldehyde motif in this oxidative environment.

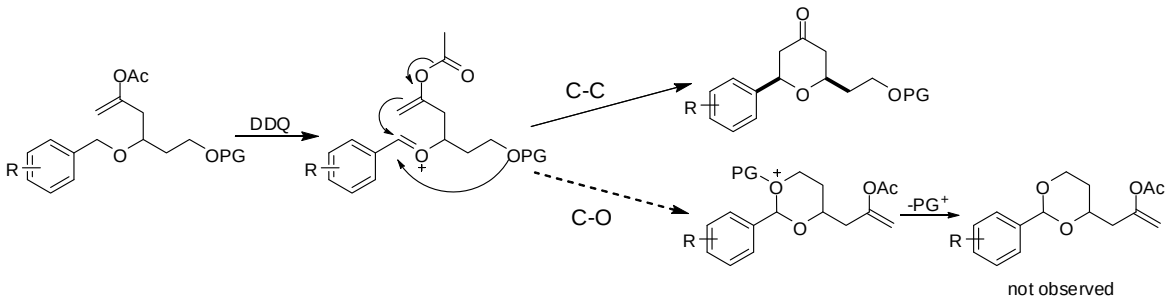


Figure 13. Competition between C-C and C-O bond couplings

Substrate **1.23** was unreactive even the arene and nucleophile were identical to those of **1.12**. The strongly electron-withdrawing nosyl group was not able to stabilize the corresponding cation intermediate **1.83** sufficiently (Figure 14), and consequently the C-H bond cleavage did not occur because of the high energy of **1.83**.

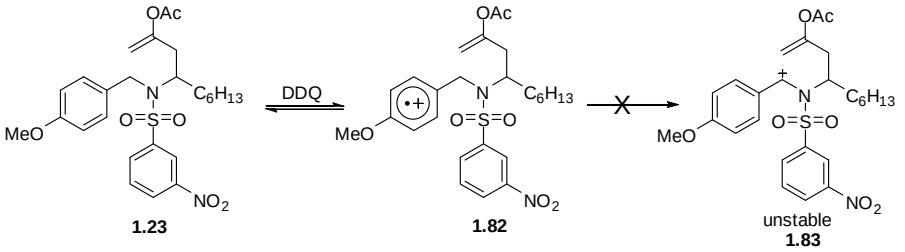
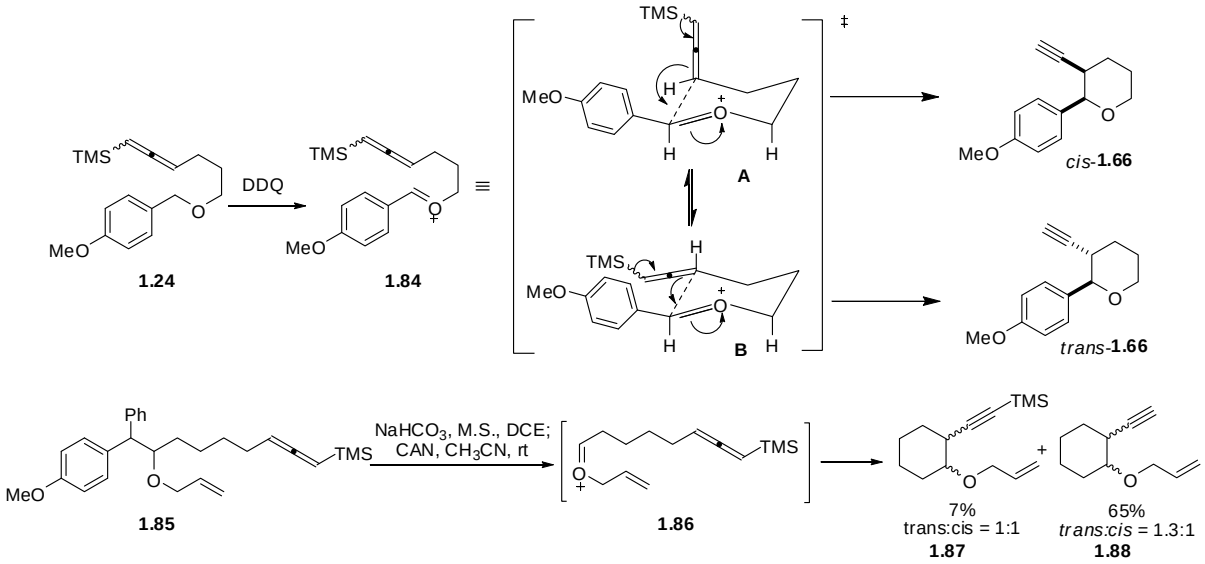


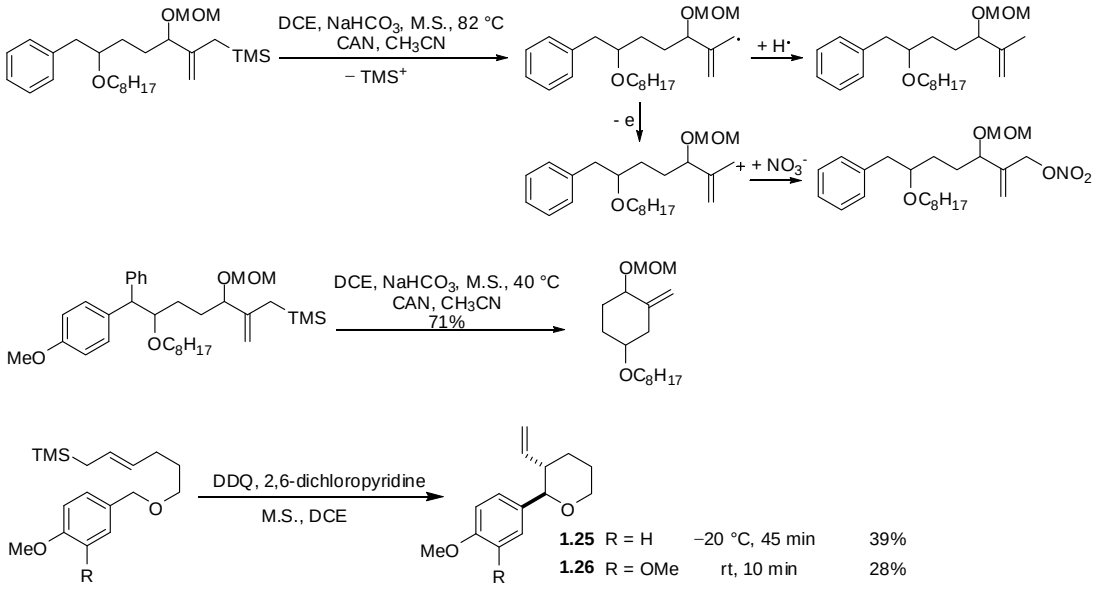
Figure 14. Carbocation destabilization by nosyl group

No stereocontrol was observed when a trimethylsilyl allene group was employed as the nucleophile. As shown in Scheme 22, the small *A* value of the alkynyl group[59] (allenyl group analogue) was not able to differentiate the two transition states A and B, which led to a 1:1 mixture of *cis*/*trans* diastereomer. Wang also observed a similar result for the cyclization of allenyl nucleophile (compound **1.85**) in the study of ETIC reactions.[45a]



Scheme 22. Transition states for cyclization of substrate with allenyl TMS nucleophile

Substrates with allyltrimethylsilane nucleophile (**1.25** and **1.26**) cyclized with low yields. We speculated that the allyl TMS group underwent competitive decomposition with DDQ, therefore the problem could presumably be alleviated by increasing the reactivity of the electroauxiliary. A similar strategy had been utilized by Wang[45a] to suppress the decomposition of allyl TMS nucleophiles with CAN (Scheme 23). Employing the more electron-rich arene (substrate **1.26**) allowed us to perform the reaction at low temperature but the yield improvement was subtle (28% to 39%). The reactions did not produce any isolable by-products.



Scheme 23. Decomposition of allyl TMS in the presence of CAN

The failure of substrate **1.29** to react with DDQ was not unexpected, as Mukaiyama had claimed that silyl enol ether species were unstable in the presence of DDQ.[34] At the same time this nucleophile was considered to be not as important as others because it yielded the same tetrahydropyrone product as the enol acetate and it was too labile to be easily handled.

1.2.5 Summary

We have successfully developed a DDQ-mediated cyclization reaction for a variety of benzylic ethers. The reaction starts from a single electron oxidation of the substrate by DDQ to give an aromatic radical cation, in which the benzylic C-H bond is substantially weakened. Homolytic cleavage of the activated C-H bond affords the oxocarbenium ion intermediate, followed by the attack of the appended nucleophile to complete the cyclization reaction. The reaction rates are correlated to the oxidation potential of the substrates and the stability of *in-situ* generated oxocarbenium ions. A six-membered ring transition state is employed to explain the observed diastereoselectivity. This intramolecular C-C coupling approach is more general and productive than the previously reported intermolecular reactions, as satisfying yields are obtained from arenes with various substitution patterns under the optimal reaction conditions.

The enol acetate is the most reliable nucleophile in this study, which cyclizes to give the tetrahydropyrone product with exclusive *cis*-diastereoselectivity. Allenyl and allyl trimethylsilane could also serve as the carbon nucleophiles but the yield or diastereoselectivity is compromised. Commonly used protecting groups are well tolerated in the reactions, and no product from competitive heteroatom nucleophile is observed in these cases.

2. EXPLORATION OF DDQ-MEDIATED C-H ACTIVATION REACTIONS ON MACROCYCLES

2.1 INTRODUCTION TO MACROCYCLIC OXOCARBENIUM IONS

The oxocarbenium/carbocation ion derived from C-H activation can serve as a versatile intermediate in organic synthesis. Oxidative carbocation formation in macrocycles creates opportunities for transannular nucleophilic attack, and such processes can be used to construct the polycyclic molecules. Thus we initiated a project to study oxocarbenium ion formation in macrocyclic systems by DDQ oxidation (Figure 15).

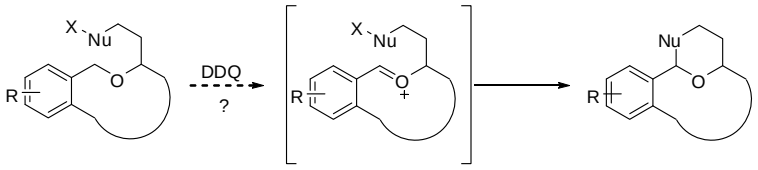
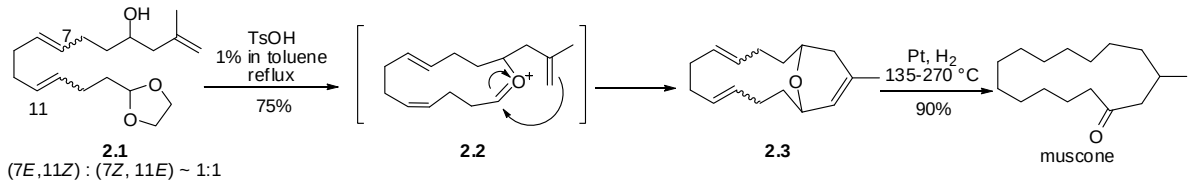


Figure 15. Generation of macrocyclic oxocarbenium ion by DDQ

Macrocyclization by a Prins reaction proceeds through the formation of a macrocyclic oxocarbenium ion, followed by the nucleophilic attack of an internal alkene to close the ring. It has been employed as a unique approach for creating medium sized rings.[60,61,62a-e,63] However this method is highly substrate dependent, and efficient reactions require pre-organization of the substrate into a proper conformer to promote oxocarbenium ion formation.[60,61,63]

In 1979 Ohloff and co-workers reported an acid-catalyzed cyclization of hydroxyacetal **2.1** to bicyclic ether **2.3** in 75% yield (Scheme 24).[60] The reaction needs to be carried out at very low concentration, and the presence and configuration of the two alkenes at C7 and C11 in **2.1** have a profound influence on the efficiency of the cyclization reaction. These observations suggested that the accessibility of optimal conformer is essential for macrocyclic oxocarbenium ion formation in Prins reactions.



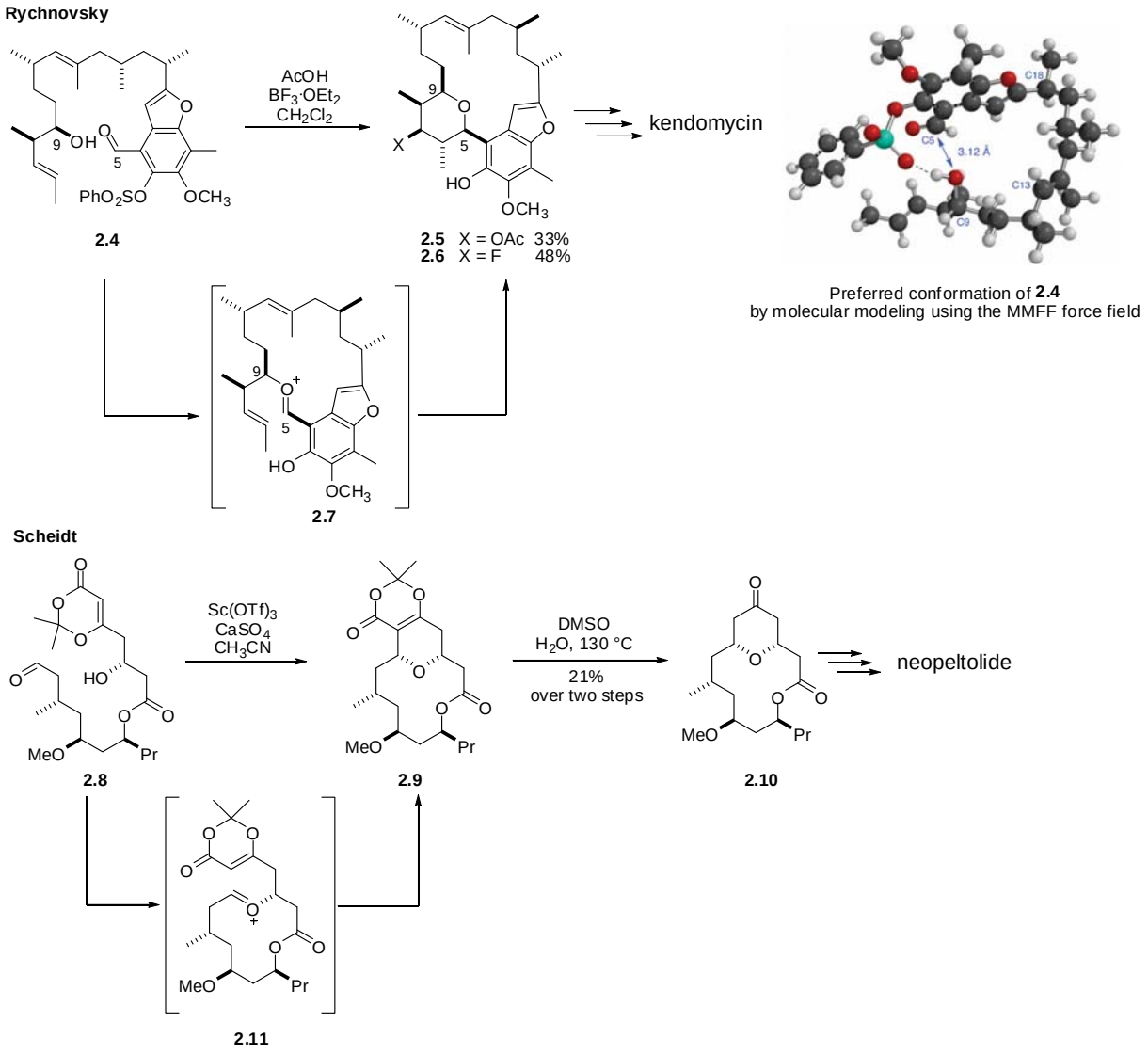
2.1
(7*E*,11*Z*) : (7*Z*, 11*E*) ~ 1:1

2.2

2.3

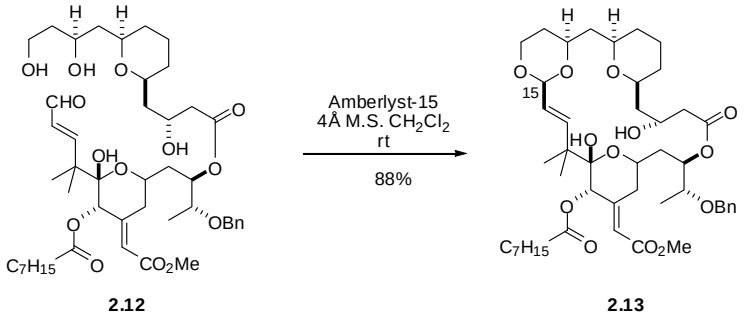
Scheme 24. Macrocyclization *via* oxocarbenium ion in muscone synthesis

Several recent natural product syntheses employ this strategy to construct macrocycles (Scheme 25). Rychnovsky synthesized the kendomycin macrocycle by a Prins cyclization of **2.4**, and obtained a mixture of products **2.5** and **2.6** in a high combined yield (81%).[61] Computational calculations on the conformation of **2.4** predicted the proximity of the hydroxy group and aldehyde group which favored the oxocarbenium ion **2.7** formation. In the synthesis of neopeltolide, Scheidt used a Lewis acid catalyzed Prins reaction to generate the bicyclic product **2.9** from **2.8** through macrocyclic oxocarbenium ion intermediate **2.11**[62a]



Scheme 25. Prins-mediated macrocyclization *via* oxocarbenium ions in natural product syntheses

Wender has developed a macrotransacetalization reaction in the synthesis of biologically active bryostatin analogues (Scheme 26).[63] When substrate **2.12** was treated with Amberlyst-15 acidic resin in CH_2Cl_2, a single diastereomer **2.13** was isolated from the reaction. The acetalization was believed to proceed under thermodynamic control, affording the product **2.13** with an exclusive equatorial configuration at C15.



Scheme 26. Macrocyclic acetalization *via* oxocarbenium ion

2.2 SUBSTRATE PREPARATIONS

Two general types of structures (**2.14** and **2.15**) were proposed for the macrocyclic substrates (Figure 16). To simplify the reaction parameters, the *para*-methoxy benzyl ether system was selected as the main electroauxiliary. The ring size is the major variable for the investigation. Additional alkyl groups (R_2 in **2.14**) and *trans*-alkene (**2.16**) were also incorporated into the macrocycles to enhance the perturbation of the ring conformation. A control substrate **2.17** was synthesized for a side-by-side comparison with the cyclic substrates.

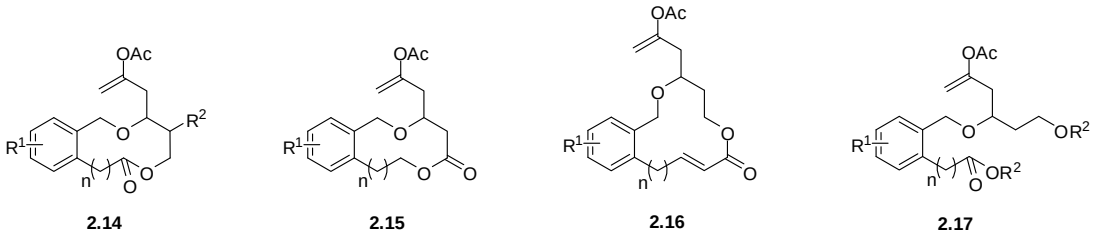


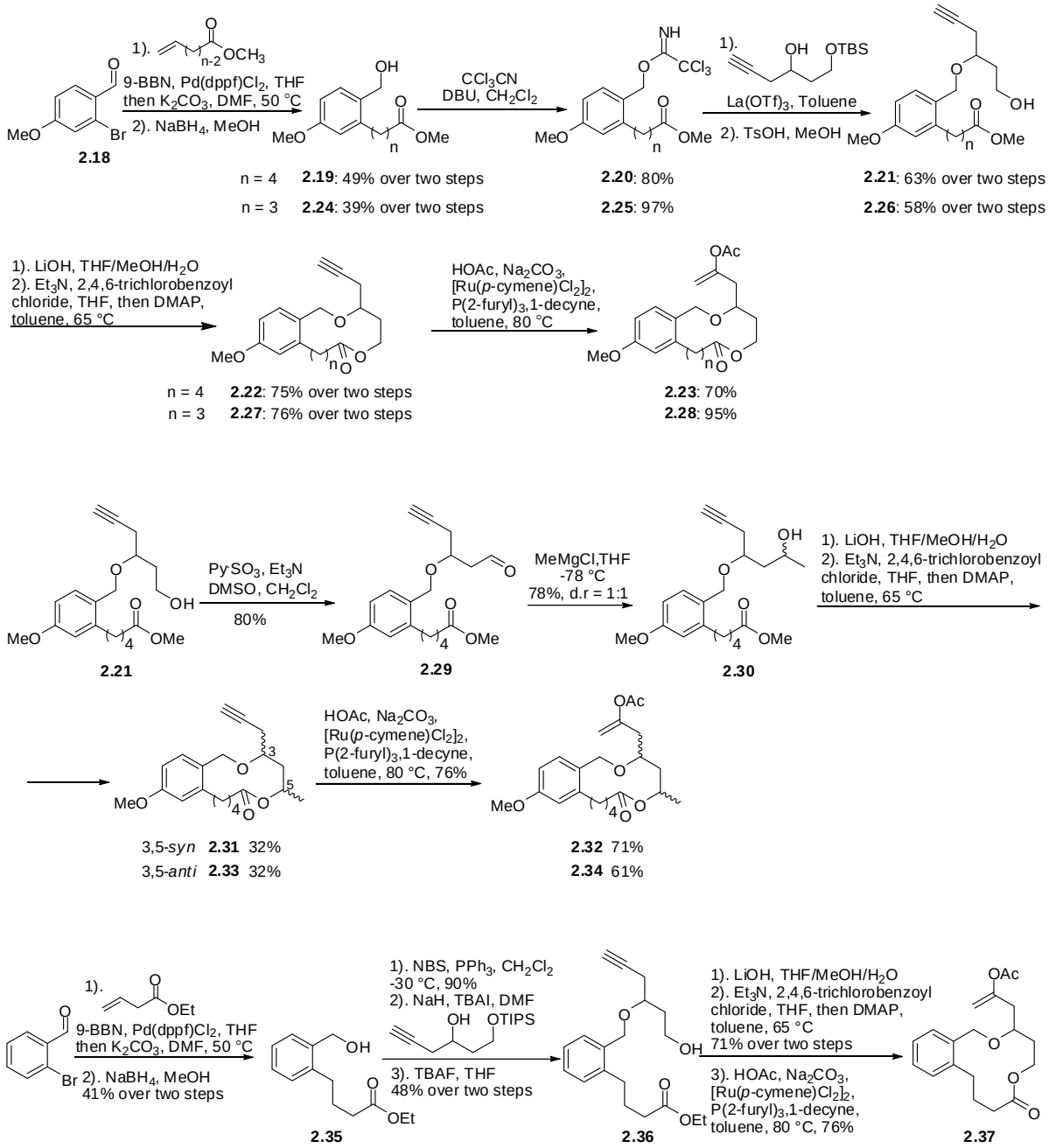
Figure 16. General structures for macrocyclic substrates

Substrates were prepared from the know aldehyde **2.18**[64] (Scheme 27). Suzuki coupling between **2.18** and methyl pentenate gave the *ortho* substituted anisaldehyde, which was reduced by $NaBH_4$ to give **2.19** in 49% yield over two steps. Treating **2.19** with CCl_3CN and DBU[65] afforded the trichloroacetimidate **2.20** (80%). $La(OTf)_3$ catalyzed etherification with the homopropargylic alcohol and subsequent silyl group deprotection gave **2.21** (63% over two steps).[48d] This etherification strategy starting from benzylic alcohol was used as a general method in the preparation of other macrolactones. The methyl ester in **2.21** was saponified, and the derived seco acid was subjected to Yamaguchi macrolactonization protocol[66] to give **2.22** (75% yield over two steps). Finally enol acetate preparation completed the desired 13-membered macrolactone **2.23** (70%). The three-step hydrolysis-macrolactonization-enol acetate preparation sequence was also employed as a common protocol for assembling other substrates from the hydroxy ester. The synthesis of 12-membered macrolactone **2.28** was completed by following the same strategy for **2.23** preparation.

To install the methyl substituent on the macrocycle, the alcohol **2.21** was oxidized to the aldehyde **2.29** in 80% yield. Adding MeMgBr to **2.29** gave product **2.30** as a 1:1 diastereomer mixture in 78% combined yield. The two unseparable diastereomers were hydrolyzed and subjected to the Yamaguchi's protocol. The derived mixture was separated by flash chromatography to give the pure 3,5-*syn* macrolactone **2.31** and 3.5-*anti* **2.33** (the stereochemistry was determined by NOESY spectra of the corresponding cyclized products **2.65** and **2.66**) which were converted to the desired enol acetate **2.32** and **2.34**.

The Suzuki coupling reaction could also be applied to the synthesis of non-substituted benzylic macrolactone **2.37**. As shown in Scheme 27, Suzuki coupling of bromobenzaldehyde with methyl butenate followed by $NaBH_4$ reduction gave the product **2.35** (41% in two steps),

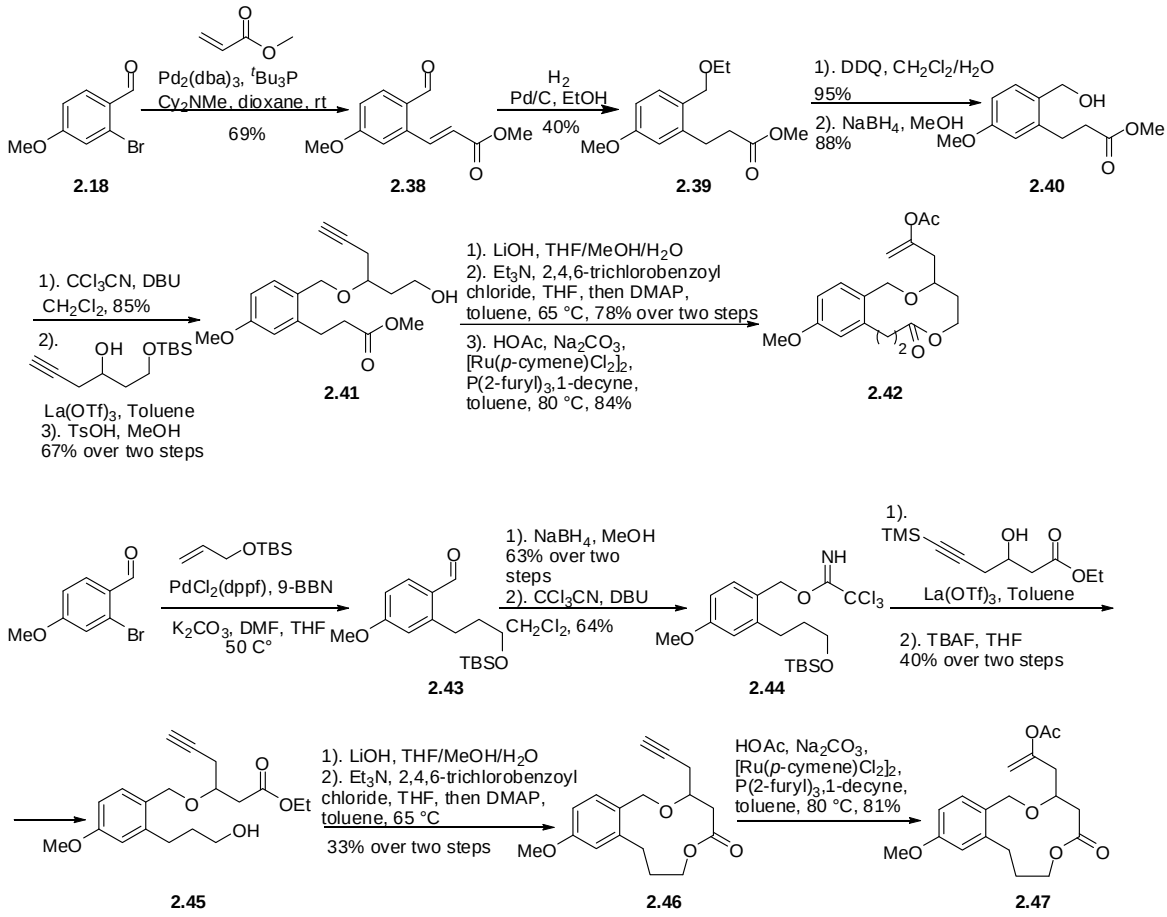
which was converted to an alkyl bromide. Williamson ether preparation and TBS deprotection provided the hydroxy ester **2.36** in 48% yield over two steps. The common three-step sequence was performed on **2.36** to complete **2.37**.



Scheme 27. Syntheses of 13- and 12-membered macrolactones

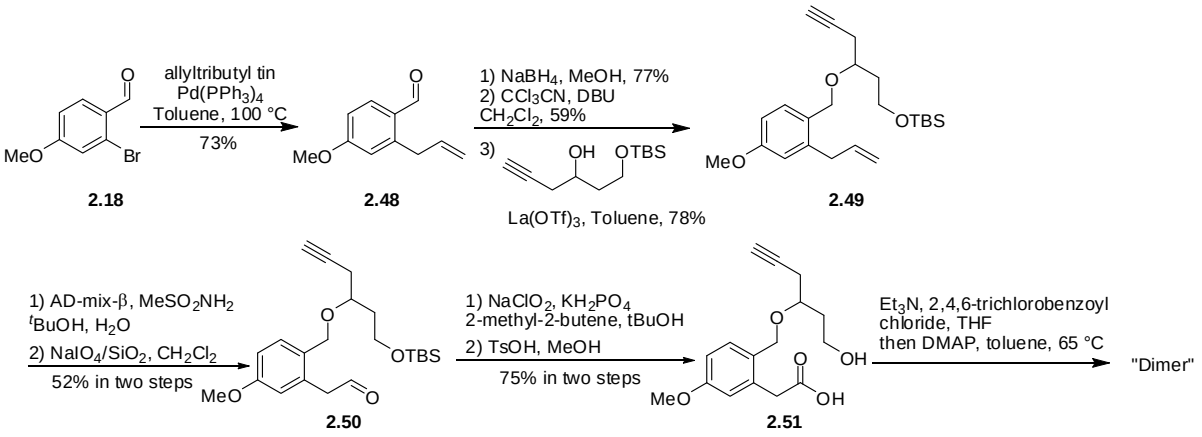
Substrate **2.42** with a 11-membered macrolactone was made from the same starting material **2.18** (Scheme 28). A Heck coupling was used to install the *ortho* alkenyl substituent in **2.18**.[67] The hydrogenation of the α,β-unsaturated ester **2.38** gave an unexpected ethyl ether **2.39**, which was treated with DDQ to recover the aldehyde functional group. With **2.40** in hand, the ether chain was installed and the silyl group in the product was deprotected to give **2.41**. The similar three-step sequence was executed to finish substrate **2.42**.

To synthesize the other 11-membered substrate **2.47**, a protected allylic alcohol was chose for the Suzuki coupling to give compound **2.43**. Reduction of **2.43** followed by the common etherification method and silyl group removal afforded **2.45**. The Yamaguchi macrolactonization reaction on hydrolyzed **2.45** provided the desired product **2.46** in only 33% yield, while another 33% by-product was isolated and tentatively identified as the dimerized macrolactone. The enol acetate preparation finished the synthesis of substrate **2.47**.



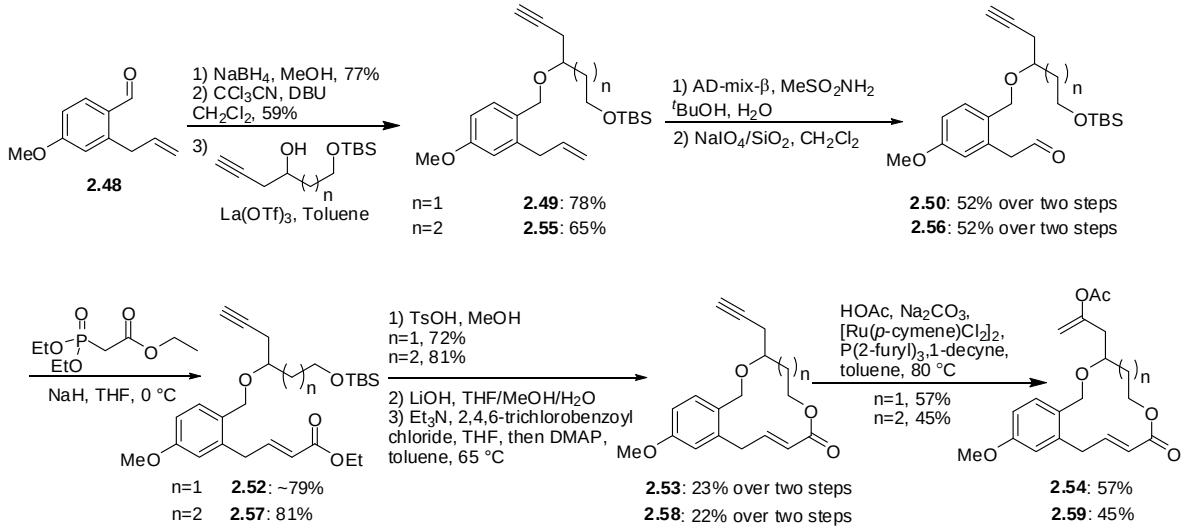
Scheme 28. Syntheses of 11-membered macrolactones

The synthesis of 10-membered macrolactone was unsuccessful. As shown in Scheme 29, treating the seco acid **2.51** with Yamaguchi's protocol gave the dimerized macrolactone as the only isolable product.



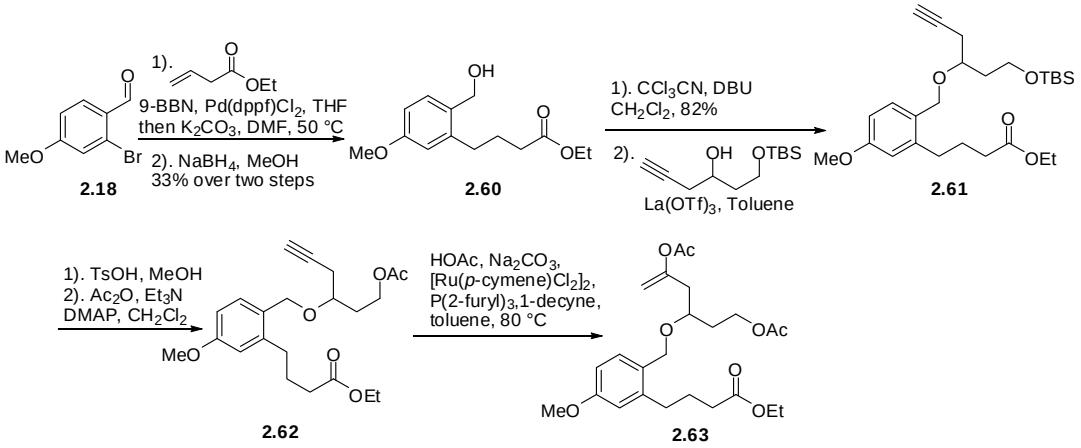
Scheme 29. Effort towards 10-membered macrolactone synthesis

Substrates with a *trans*-alkene in the macrocycle were prepared from **2.48**. Aldehyde **2.50** was obtained from **2.48** through the same sequence as shown in Scheme 29. Horner–Wadsworth–Emmons reaction on **2.50** set up the α,β-unsaturated esters in **2.52**.[68] Deprotection of the TBS group followed by the common ring closing and enol acetate preparation provided the desired substrate **2.54**. The same synthetic sequence was used to prepare substrate **2.59**.



Scheme 30. Syntheses of substrates with *trans* alkene in the macrocycle

The control substrate **2.63** was synthesized straightforwardly from **2.18** (Scheme 31). Suzuki coupling with ethyl butenoate followed by $NaBH_4$ reduction gave benzylic alcohol **2.60**. The same etherification method was used to synthesize **2.61** from **2.60**, and the silyl group in **2.61** was then replaced by an acetate group to give **2.62**. The enol acetate preparation finished the synthesis of **2.63**.



Scheme 31. Synthesis of the control substrate **2.63**

2.3 RESULTS AND DISCUSSION

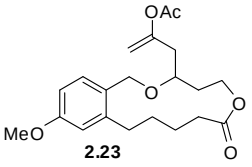
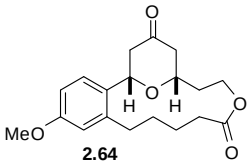
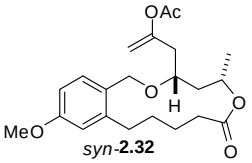
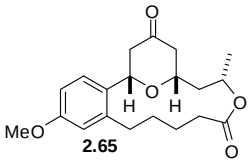
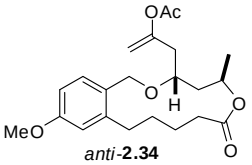
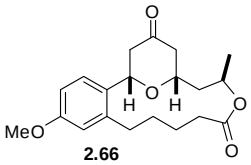
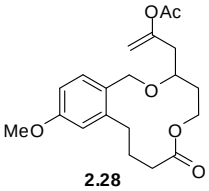
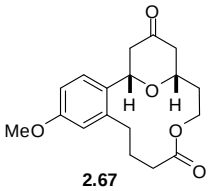
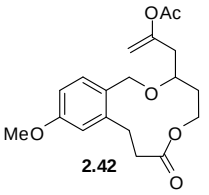
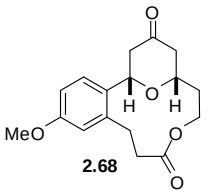
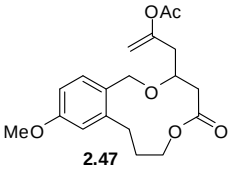
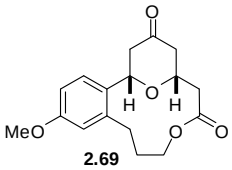
The macrocyclic substrates with *para*-methoxy benzene rings were treated with DDQ under the same conditions as reported in Chapter 1.2 and the results were shown in Table 6. The first substrate **2.23** (Entry 1, Table 6) produced the cyclized product **2.64** as a single diastereomer. The *cis*-relationship between the substituents at C2 and C6 of the tetrahydropyrone was confirmed by the strong cross-peak of the two axial hydrogens in NOESY spectrum. The 73%

yield was comparable with that of acyclic analogue **1.12** (74%), but the reaction was slower (2h v.s. 10 min).

Presence of the methyl group on the macrocycle (Entry 2 and 3) didn't affect the yield of the cyclization reactions, but these reactions took longer time than the cyclization of **2.23**. The products isolated from both *syn*-**2.32** and *anti*-**2.34** had the tetrahydropyrone ring *cis*-fused to the macrolactone, consistent with the results from **2.23**.

For smaller ring substrates, the reactions were slightly slower (Entry 4 and 5), but the yield and stereoselectivity were retained. Substrate **2.47** (Entry 6) with the carbonyl group at a different position on the macrocycle took significantly longer time (28 hours) to finish the cyclization with a slight drop in the yield. The *cis*-diastereoselectivity was still excellent.

Table 6. Reactions of 11- to 13-membered macrolactones with DDQ

Entry	Ring size	Substrate	Product	Time	Yield
1	13	 **2.23**	 **2.64**	2h	73%
2	13	 *syn*-**2.32**	 **2.65**	4h	69%
3	13	 *anti*-**2.34**	 **2.66**	4h	74%
4	12	 **2.28**	 **2.67**	3.25h	76%
5	11	 **2.42**	 **2.68**	4h	73%
6	11	 **2.47**	 **2.69**	28h	65%

From the experience with acyclic benzylic ethers, substrate **2.37** with no electron-donating group on the benzene ring was predicted to be much less reactive than the substrates in Table 6. As shown in Scheme 32, treating **2.37** with 2 equiv. DDQ at room temperature for 72 hours did not consume all the starting material, and the *cis*-cyclized product **2.70** was isolated in

a modest yield (57%). More forcing conditions (3 equiv. DDQ in combination with gentle heating) shortened the reaction time to 24 hours and provided an improved 70% yield.

2.37 **2.70**

1.5 equiv DDQ for 48 h, then 0.5 equiv for 24 h	rt	84% conversion	68% brsm
1.5 equiv DDQ for 48 h, then 0.5 equiv for 24 h	40 °C	100% conversion	67%
3 equiv DDQ, 24 h	50 °C	100% conversion	70%

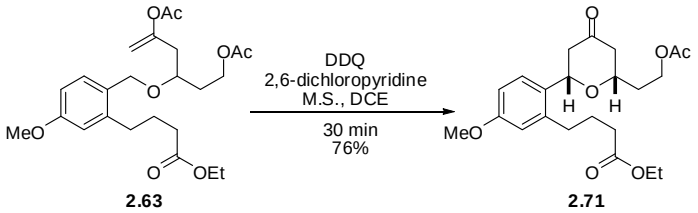
Scheme 32. Optimization of DDQ induced cyclization of benzolactone **2.37**

The two substrates with *trans*-alkene on the macrocycle (**2.54** and **2.59**) didn't produce any cyclized product from the reactions. Based on the TLC two compounds reacted similarly: the starting material was gradually consumed within two hours, but no evident new spot showed up during the reactions.

From the positive results, the DDQ mediated cyclization reaction is applicable to macrocyclic compounds. As illustrated in the general mechanism (Figure 15), the valuable oxocarbenium ions are readily accessible by the oxidative C-H bond activation of macrocyclic benzylic ethers, and the transannular attack by the enol acetate has similar yield and *cis*-diastereoselectivity as in acyclic substrates, presumably following the same six-membered ring transition state.

The ring structure and its size have significant impacts on the reaction rates. Macrocyclic substrates uniformly take longer time than their acyclic analogues in the reactions with DDQ, and the impact is more severe when the ring size is smaller. To exclude the possibility that the slow rates are due to the *ortho* substituent on the aromatic ring, we tested the control substrate

2.63 (Scheme 33). It actually reacts faster than its acyclic analog **1.12** with DDQ, indicating that the conformation of the macrocycles causes the slow reactions.



2.63 **2.71**

Scheme 33. DDQ mediated cyclization of control substrate

The ability to access the conformation in which the π electrons are aligned with C-H σ bond in the radical cations determines the viability and efficiency of the C-H bond activation as discussed in Chapter 1.2.3. Figure 17 shows the energy minimized conformation of **2.42** (MM2). Neither benzylic C-H bond is in good alignment with the π electrons, therefore it is necessary to rotate the aryl group to facilitate the desired C-H activation in the radical cation. However in the macrocyclic system, this rotation is not as facile as in the acyclic substrates, which raises the energy barrier to reach the optimal conformer for hydrogen atom abstraction. As a result, the rate determining C-H bond cleavage[69] is decelerated, and consequently the overall reaction is slowed down.

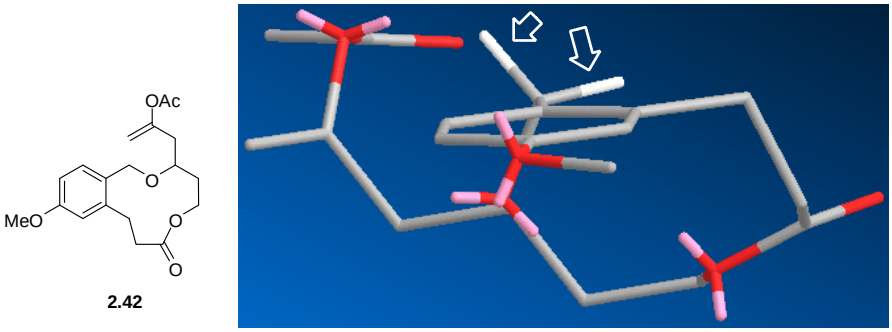


Figure 17. Energy minimized conformation of **2.42**

This explanation also rationalizes the correlation between the reaction rates and the ring size. When the ring size decreases, the ring strain increases and the ring is more rigid. As a result, the substrate will require more energy to reach the optimal conformation for C-H activation, which will cause the cyclization to be slower. Substrates **2.54** and **2.59** are the extreme examples: the *trans*-alkene alters the macrocycle so much that, after they are oxidized to radical cations, the benzylic C-H bonds cannot be activated at all. Without downstream transformations, these unstable and highly reactive intermediates won't be able to survive in the reactions and serious decompositions will take place.

The influence of the oxocarbenium ion stability on the reaction rate is significantly amplified by the macrocycle, as substrate **2.47** with the carbonyl group close to the reactive site takes as long as 28 hours, while substrate **2.42** with identical ring size needs only four hours and the acyclic analog **1.22** needs only 45 min to complete the reaction.

2.4 SUMMARY

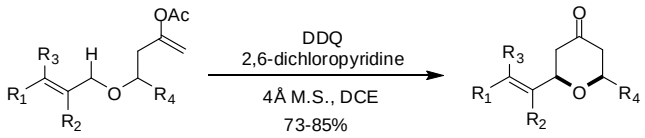
We have discovered that DDQ is an excellent reagent for selective C-H bond activation on cyclic benzylic ethers. The macrocyclic oxocarbenium ions are readily available from DDQ induced C-H bond cleavages, and the cyclization reactions from intramolecular enol acetate nucleophiles have as good yields and *cis*-diastereoselectivity as in acyclic analogues. The reactions are generally slower due to the ring strain, and the destabilization of the oxocarbenium ion has more serious influence on the reaction rates than in acyclic benzylic ethers.

The wide substrate scope, the good functional group compatibility, the excellent diastereoselectivity, all of these advantages highlight this method from other C-H activation protocols, and demonstrate its potential in complex molecule synthesis.

3. FORMAL SYNTHESIS OF NATURAL PRODUCT (+)-NEOPELTOLIDE

3.1 INTRODUCTION TO THE SYNTHESIS OF NEOPELTOLIDE

The scope of our oxidative cyclization reactions was further extended to the allylic ethers by Lei.[70] As shown in Scheme 34, allylic C-H bonds could be selectively cleaved to give oxocarbenium ions, and the yields of the cyclization reactions were similar or better than those of benzylic ethers. Encouraged by these exciting results, we proposed to synthesize natural product neopeltolide to further validate our method's capability of generating oxocarbenium ions in complex macrocycles.



Scheme 34. Cyclization of allylic ethers with DDQ

Neopeltolide (Figure 18) is a macrolide isolated from the genus *Daedalopelta* sponge off the north Jamaican coast by Wright.[71] It is a potent inhibitor of fungal pathogen *Candida albicans* (0.625 μg/mL MIC in liquid culture), and also an extremely potent inhibitor of tumor cell proliferation (1.2 nM IC_{50} against the A549 human lung adenocarcinoma, 5.1 nM against the NCI/ADR-RES ovarian sarcoma, and 0.56 nM against the P388 murine leukemia). Neopeltolide

shares several similar structure features with leucascandrolide A,[72] including the trisubstituted 2,6-*cis*-dialkyl-tetrahydropyran ring, and the same oxazole-containing side chain.

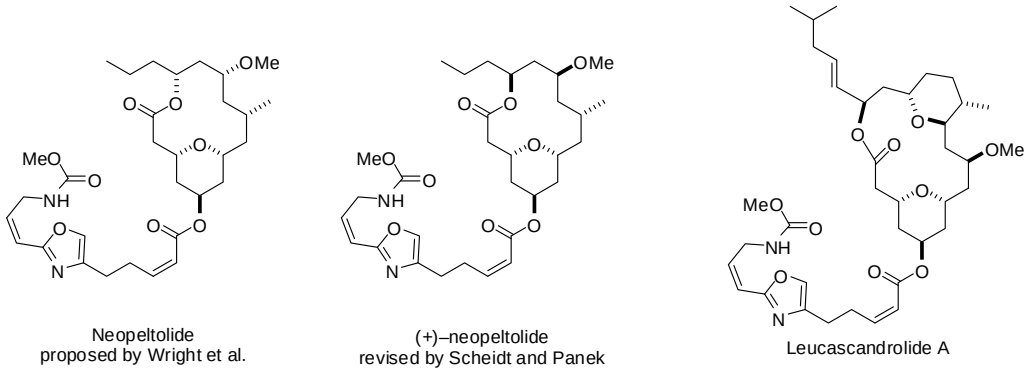
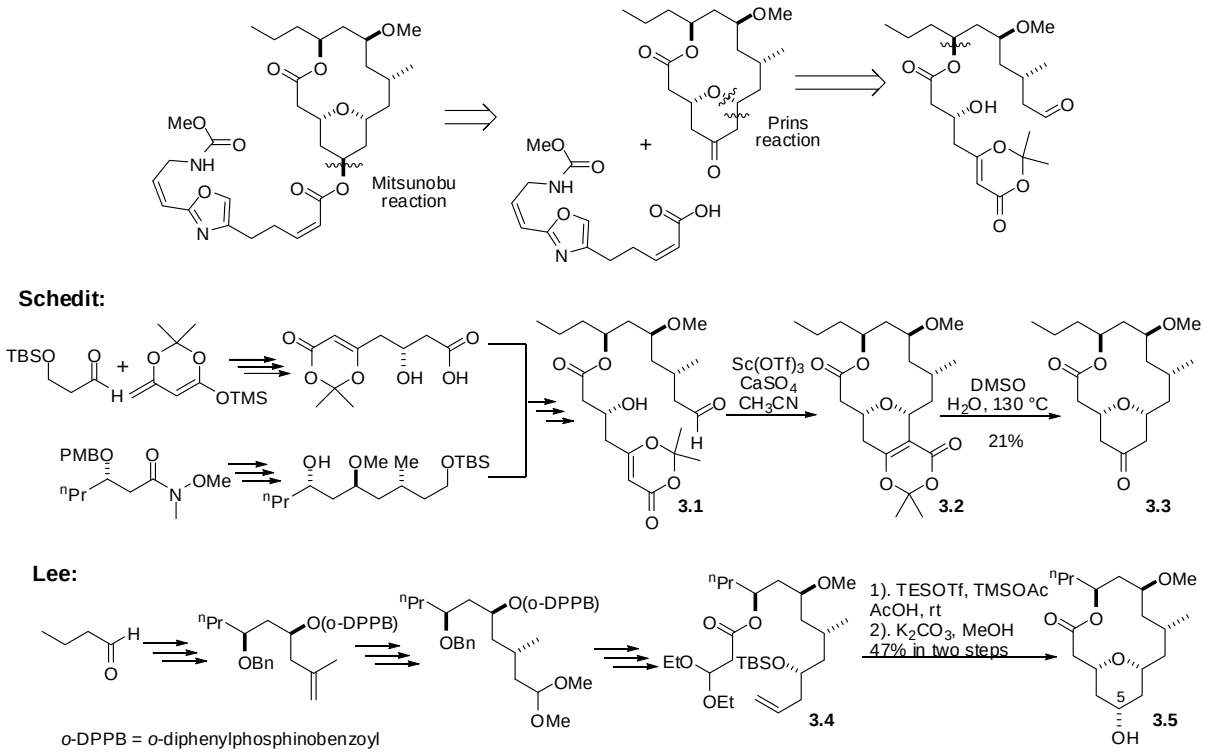


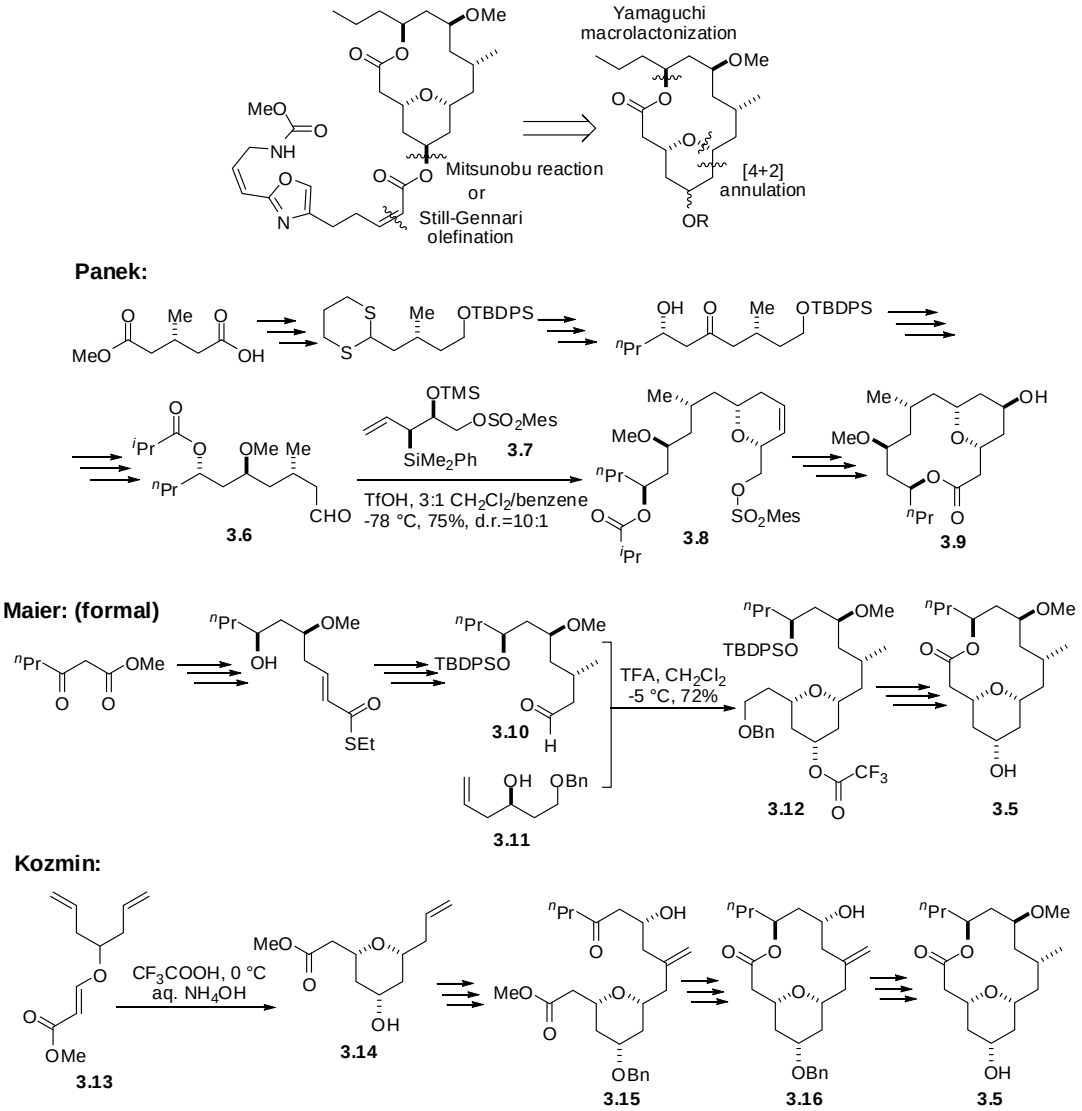
Figure 18. Structure of (+)–neopeltolide and leucascandrolide A

Scheidt[62a] and Panek[62b] independently finished the total syntheses of neopeltolide and revised the incorrectly assigned structure, and several other groups followed up with different approaches to the molecule. These syntheses could be classified by the manner of constructing the tetrahydropyran ring. Most approaches utilized variations of the Prins reaction. Syntheses from Scheidt and Lee[62c] took advantage of the Prins reaction to establish the macrocycle and the tetrahydropyran in one step. As shown in Scheme 35, Scheidt prepared the dioxinone compound **3.1** and treated it with $Sc(OTf)_3$ to give the cyclized intermediate **3.2**, which upon heating in DMSO released the tetrahydropyrone **3.3**. In Lee's synthesis, compound **3.4** with protected hydroxyl group and masked aldehyde was used for Prins cyclization. Harsh conditions were employed to catalyze the reaction, and 10% epimerization at C5 was observed. The derived acetylated *cis*-tetrahydropyranol was hydrolyzed to give **3.5**.



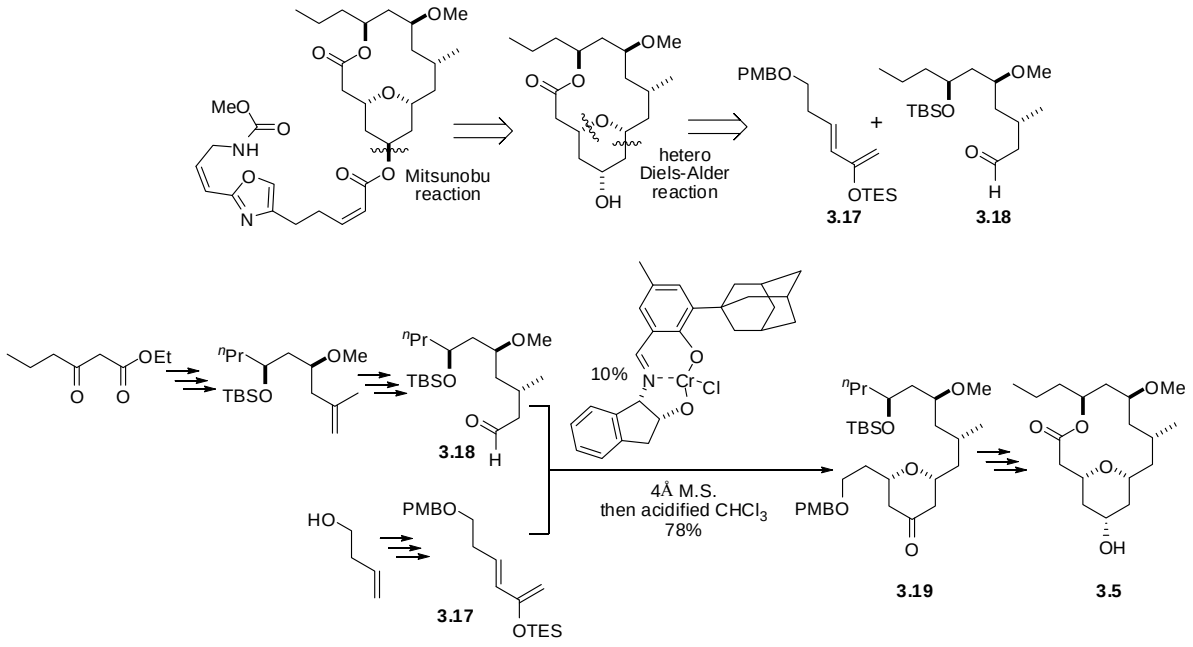
Scheme 35. Syntheses of neopeltolide macrolide by Prins reaction

Several syntheses assembled the tetrahydropyran ring before closing the macrolactone (Scheme 36). The synthesis from Panek used a triflic acid promoted Prins reaction to combine the aldehyde **3.6** and allylsilane **3.7**. The *cis*-dihydropyran was obtained in good yield with excellent diastereoselectivity, and the following oxymercuration installed the hydroxyl group at C5 with correct stereochemistry. In Maier's formal synthesis,[62d] a more classic intermolecular Prins reaction was employed to construct the tri-substituted tetrahydropyran ring from aldehyde **3.10** and homoallylic alcohol **3.11**. Kozmin had applied the Prins reaction at the first step of the synthetic sequence.[62e] When treated with trifluoroacetic acid, the α,β-unsaturated ester **3.13** was protonated to give the oxocarbenium ion for Prins reaction. Cyclization and acid-promoted saponification would afford the tetrahydropyranol **3.14**.



Scheme 36. Syntheses of neopeltolide tetrahydropyran rings by Prins reaction

Paterson et al. used Jacobsen asymmetric Diels-Alder reaction to assemble the tetrahydropyran core from siloxydiene **3.17** and aldehyde **3.18** (Scheme 37).[62f] The reaction proceeded as expected under the catalysis of chiral tridentate chromium (III) salt to provide the *cis*-tetrahydropyrone **3.19** in 78% yield. Compound **3.19** could be easily converted to the common precursor **3.5** for the natural product.



Scheme 37. Synthesis of neopeltolide tetrahydropyran ring by *hetero*-Diels-Alder reaction

3.2 RETROSYNTHETIC ANALYSIS

Since the oxazole-containing acid side chain **3.20** was known, and Patterson et al. had succeeded in converting the tetrahydropyrone **3.3** to the natural product, we would focus on the synthesis of macrolide **3.3**. We proposed that it could be assembled convergently from three simple building blocks (Figure 19). The tetrahydropyrone ring was envisioned to be constructed by a DDQ mediated cyclization of the substituted allylic ether **3.21**. Yamaguchi macrolactonization reaction would be employed to convert **3.22** to **3.21**. The methoxy group in **3.22** would be introduced by hydrosilylation of the enyne group in **3.23**. The enyne could be prepared from homopropargylic alcohol **3.24** and the vinyl iodide **3.25** by Sonogashira coupling reaction. Ether **3.25** could be synthesized from the β-hydroxy ester **3.26** and allylic alcohol **3.27**.

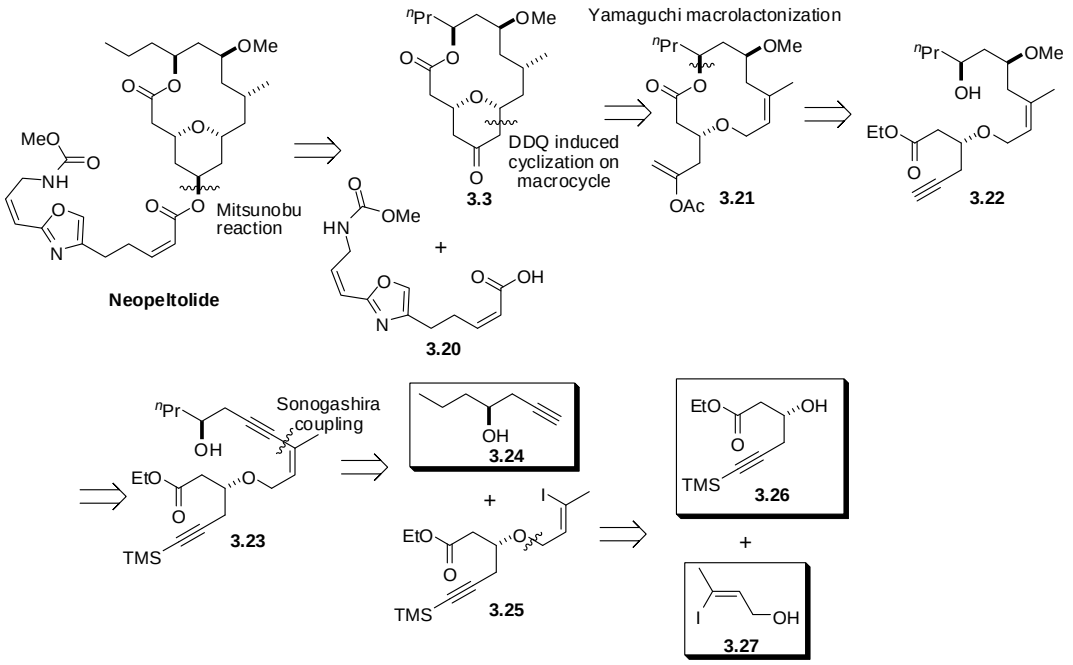
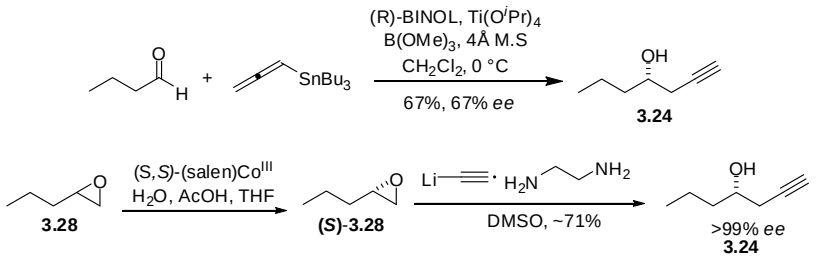


Figure 19. Retrosynthesis of neopeltolide

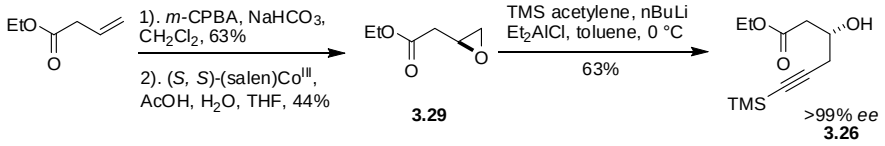
3.3 FORMAL SYNTHESIS OF NEOPELTOLIDE

The building block **3.24** was initially synthesized through a Ti^{4+}-BINOL catalyzed asymmetry addition of allenyl tributyltin to butyraldehyde[73] (Scheme 38). However the enantiomeric excess of the product was only 67% and the removal of excess BINOL was problematic. As a result we turned to the epoxide opening reactions.[74] Epoxide **3.28** is commercially available but it can be easily prepared from inexpensive 1,2-pentanediol.[75] The enantiomerically pure (*S*)-**3.28** was prepared by hydrolytic kinetic resolution[76] of the racemic epoxide, and the enantiomeric excess of the ring-opening product **3.24** was higher than 99% (by NMR analysis of MTPA ester of **3.24**).



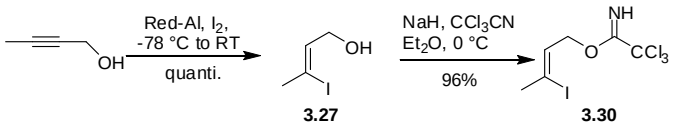
Scheme 38. Synthesis of building blocks **3.24**

β-hydroxy ester **3.26** was synthesized in one step from epoxide **3.29** according to Porco's procedure (Scheme 39).[77] The epoxide **3.29** was also prepared through a hydrolytic kinetic resolution and the homopropargylic alcohol **3.26** had higher than 99% *ee*.



Scheme 39. Synthesis of building blocks **3.26**

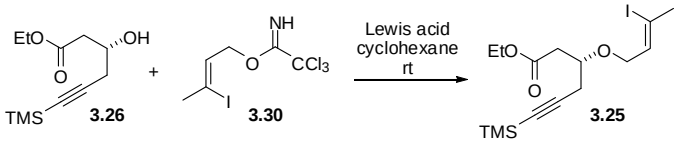
The allylic alcohol **3.27** was prepared from 2-butyn-1-ol by a Red-Al reduction followed by an I_2 quench (Scheme 40).[78] The alcohol was converted to the trichloroacetimidate **3.30** for use in the next step.[79]



Scheme 40. Synthesis of building blocks **3.27**

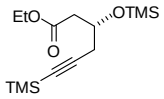
TMSOTf is the commonly used Lewis acid for ether formation between the allylic trichloroacetimidates and alcohols.[80] When we added a catalytic amount of TMSOTf into the mixture of **3.26** and **3.30** in cyclohexane, **3.25** was isolated in 74% yield from the reaction, but the products was an inseparable 4:1 mixture of the *Z* and *E* isomers (Entry 1, Table 7). We attributed the double bond scrambling to product isomerization after prolonged exposure to the Lewis acid, or to a competitive S_N1 reaction pathway during the ether bond formation. Trying to stop the reaction promptly didn't improve the ratios excluding the first explanation (Entry 2). We attempted to favor the desired S_N2 pathway by increasing the reaction concentration. This solution indeed gave a higher *Z*/*E* ratio, but the yield was compromised (Entry 3). At this stage, we postulated that triflic acid generated from TMSOTf caused the side reaction. When 2,6-di-^{t}Bu-pyridine was added into the reaction to neutralize the strong acid, no desired product was formed, which suggested that the catalytic amount of TfOH was the real catalyst for the reaction. Finally we achieved the best result by using TfOH with an excess of **3.30** at a fairly high concentration (0.25 M) (Entry 6).

Table 7. Optimization of the etherification reaction between **3.26** and **3.30**

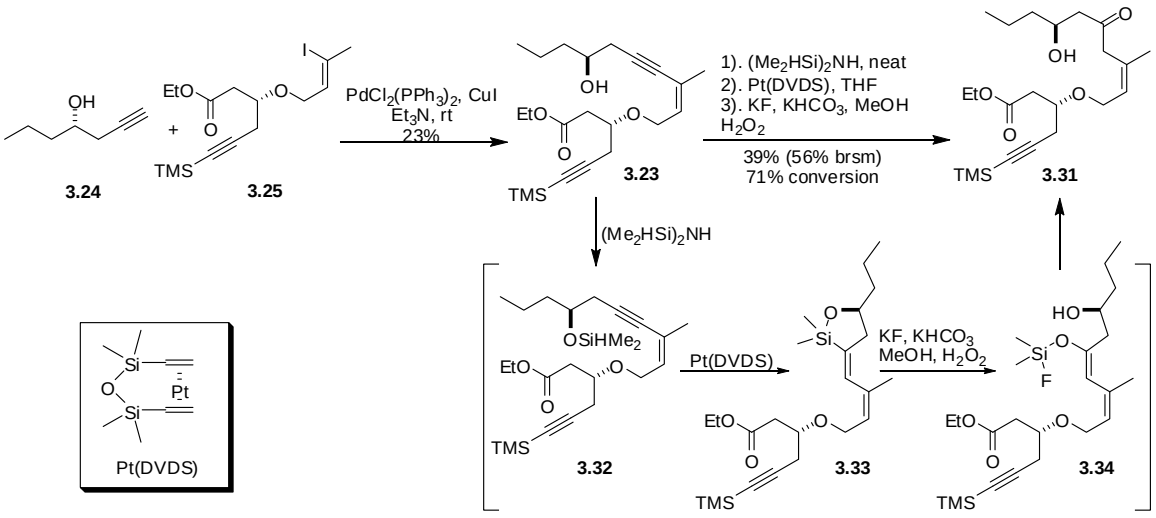


Entry	Equivalent of **3.30**	Concentration of **3.26**	Lewis acid	Time	Yield	*Z*/*E* ratio
1	2	0.09 M	10% TMSOTf	14 h	74%	4:1
2	3	0.09 M	15% TMSOTf	6 h	70%	5:1
3	2	0.3 M	7.5% TMSOTf	2 h	56%	8.5:1
4	3	0.14 M	15% TMSOTf	4 h	59%	4.5:1
5	3	0.09 M	15% TMSOTf[a]	–	Silylated product[b] only	–
6	4	0.25 M	15% TfOH	2 h	77%	7.3:1

a. with excess 2,6-di-^{t}Bu-pyridine

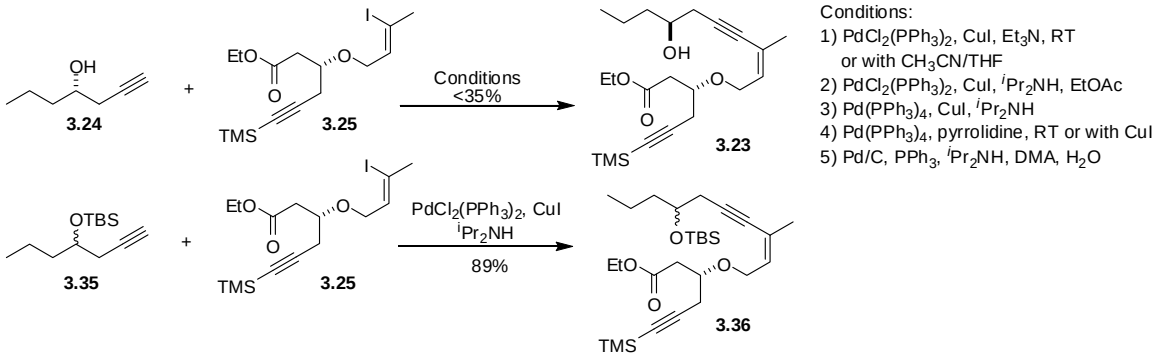
b. The silylated product was 

The next fragment coupling required a Sonogashira reaction between the alkyne **3.24** and vinyl iodide **3.25**. The first try with Pd(II) catalyst and CuI[81a,b] yielded only 23% of the desired enyne **3.23** with a large quantity of an unidentified by-product (Scheme 41). McDonald's one-pot, three-step protocol[82] was used to convert **3.23** to the β-hydroxy ketone **3.31**. Treating **3.23** with tetramethyldisilazane at 60 °C afforded silyl ether **3.32**, which regioselectively added to the internal alkyne under the catalysis of Pt(DVDS).[83] A Tamao-Fleming oxidation[84] opened the siloxane **3.33** and the silyl enol ether **3.34** derived from the Si-O bond migration cleaved to form the ketone product **3.31**. The desired β-hydroxy ketone was isolated in 39% yield (56% brsm), with about 30% starting material recovered from the reaction. Though the yield was modest, it validated our synthetic design and demonstrated the potential of the hydrosilylation reaction in alkyne functionalization.



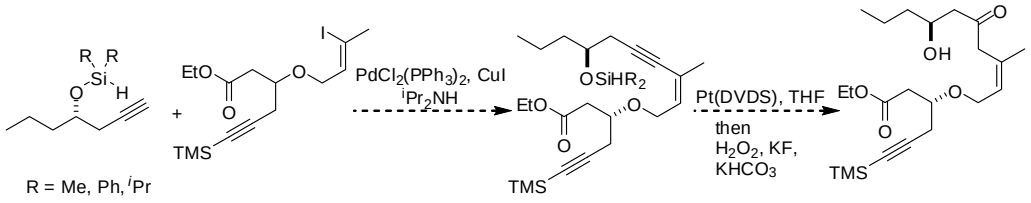
Scheme 41. Sonogashira coupling and hydrosilylation-oxidation reactions

Several conditions were examined to optimize the Sonogashira reaction[81c-h] but none of them gave higher than 35% yield (Scheme 42). In all cases the reaction was clean at the first 15 to 30 min, but the by-product became the dominant product at longer reaction times. Attempts to shorten the reaction time with more Pd catalyst and slow addition of **3.24** were unsuccessful. We suspected that the free hydroxyl group of **3.24** might be incompatible with the reaction, which was confirmed by using **3.35**. The TBS protected homopropargylic alcohol **3.35** reacted smoothly with the vinyl iodide and the enyne **3.36** was obtained in 89% yield within 15 min.



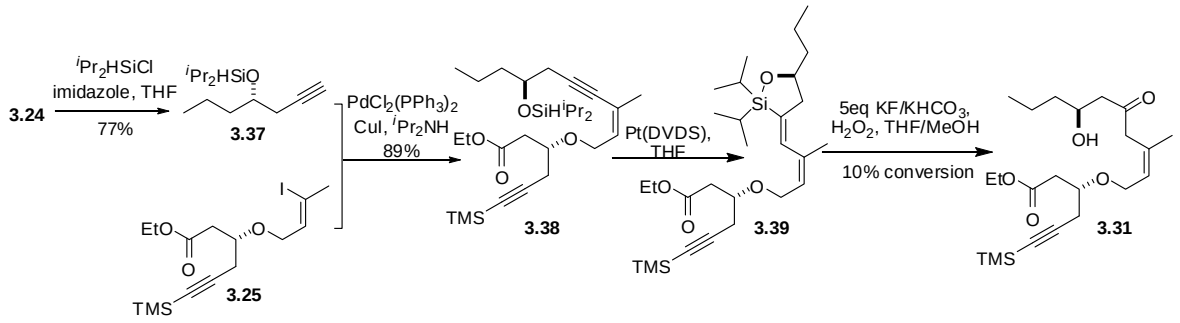
Scheme 42. Optimization of the Sonogashira coupling reaction

The incorporation of the silyl protecting group adds two steps to the sequence, but is necessary for the coupling reaction. Considering that the downstream transformation requires the hydroxyl group to be converted to the dialkylsilyl ether, we proposed to employ a bifunctional protecting group to benefit both the Sonogashira coupling and subsequent hydrosilylation reaction. The special silyl ether was required to be stable during the Sonogashira reaction and the subsequent purification yet possess sufficient reactivity for the hydrosilylation-oxidation sequence (Scheme 43).



Scheme 43. Proposal for the bifunctional silyl protecting group

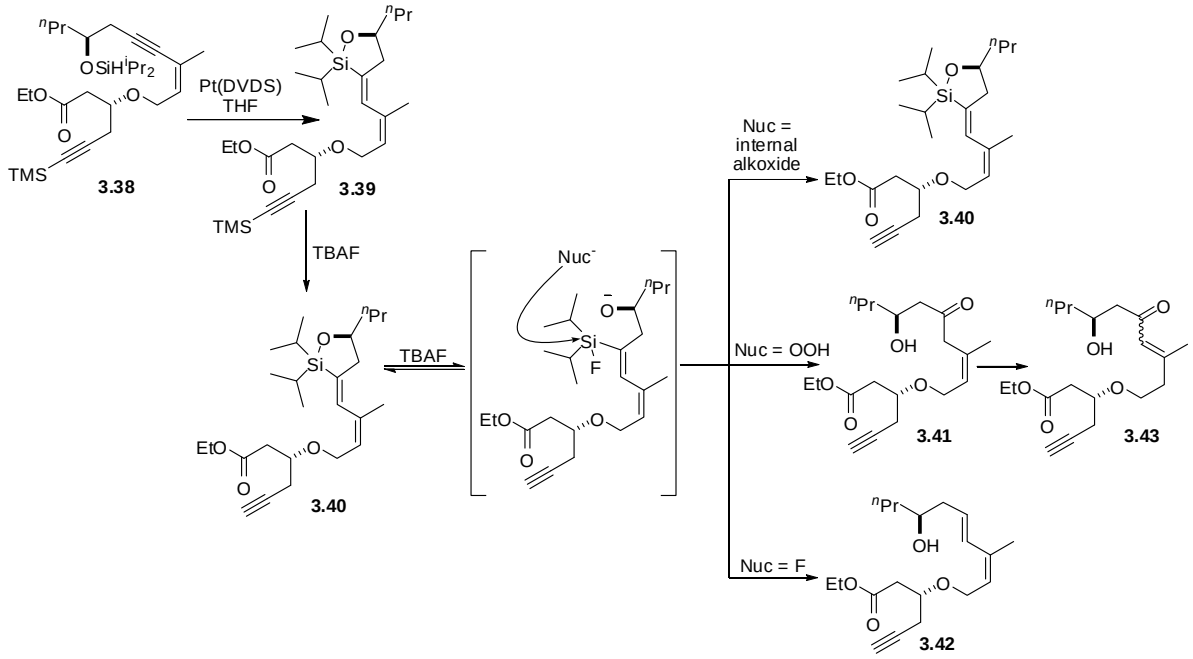
The diisopropylsilyl group was uniquely qualified among several commercial available chlorosilanes. As shown in Scheme 44, the enyne **3.38** was obtained in 89% yield from the diisopropylsilyl protected alcohol **3.37**. When compound **3.38** was subjected to Pt(DVDS) in THF, it cyclized to siloxane **3.39** efficiently at room temperature. However the following Tamao-Fleming oxidation was problematic. The reaction stopped at about 10% conversion when the typical conditions (KF, $KHCO_3$ and H_2O_2) were used. Presumably the bulky isopropyl groups caused the low reactivity of the siloxane, as **3.39** was found to be stable toward TLC and silica gel chromatography. Replacing H_2O_2 with homogeneous ^{t}BuOOH led to no reaction.



Scheme 44. First hydrosilylation/oxidation reaction on diisopropylsilyl ether **3.38**

Stronger bases and fluoride sources had been reported in the literature to oxidize the sterically hindered alkoxysilanes.[85] A strong base would promote the migration of the double bond in the product, so we could only enhance the reactivity by replacing KF with a better fluoride source. After extensive condition screenings (Table 8), we achieved the highest yield of **3.41** by carrying out the reaction in DMF/THF at 40 °C with 2 equiv. TBAF, 7 equiv. KF, 5 equiv. $KHCO_3$ and 20 equiv. H_2O_2 (Entry 5). The oxidation took two hours at 40 °C to consume most of the starting material, providing the product **3.41** in 57% yield as a pure *Z* isomer with 8% inseparable by-product **3.43** (The yield should be corrected to 65% given the existence of unproductive *E* isomer in the starting material). A noticeable fact was that the formation of **3.43** was highly sensitive to the concentration/scale and temperature. When the reaction was scaled up from 0.2 mol to 1.3 mol, the ratio between **3.41** and **3.43** would drop to 5:1 even at the same concentrations. And heating over 50 °C would induce deleterious isomerization of **3.41** to **3.43** (Entry 4).

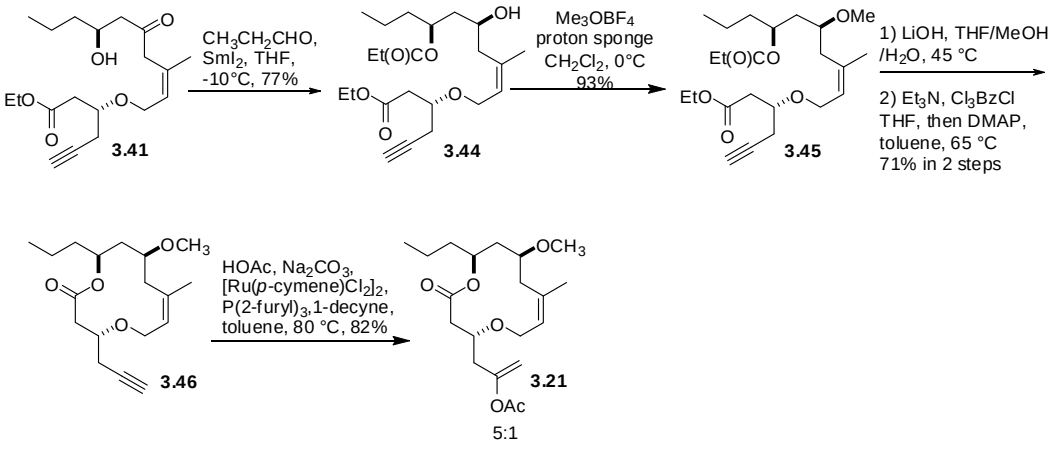
Table 8. Optimization of the hydrosilylation-Tamao oxidation reaction on **3.39**



Entry	Condition	Concentration (M)	Temp (°C)	Time	Products		
					3.40	**3.41**+**3.43**	**3.42**
1	5 equiv. TBAF/$KHCO_3$, H_2O_2, THF/MeOH	0.08	40	2 h	–	36%, 6:1	12%
2	2 equiv. TBAF/$KHCO_3$, H_2O_2, THF/MeOH	0.08	40	2 h	53%	23%, 4:1	–
3	2 equiv. TBAF, 5 equiv. KF/$KHCO_3$, H_2O_2, THF/DMF	0.08	rt	overnight	–	38%, 13:1	–
4	2 equiv. TBAF, 5 equiv. KF/$KHCO_3$, H_2O_2, THF/DMF	0.08	55	20 min	–	N/A, 1:1	–
5	2 equiv. TBAF, 7 equiv. KF/$KHCO_3$, H_2O_2, THF/DMF	0.04	40	2 h	–	57%, 11:1	–

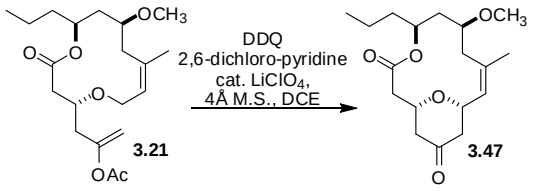
The Tishchenko reduction[86] was performed on the β-hydroxy ketone **3.41** to give *anti* product **3.44** as a single stereoisomer in good yield (77%) (Scheme 45). α,β-Unsaturated ketone **3.43** in the starting material was much less reactive than **3.41** in the reduction reaction thus it was easily removed from **3.44**. This strategy not only set up the correct stereocenter, but also conveniently exposed the reactive site for the next step while keeping the other hydroxyl group protected. The methyl ether formation on **3.44** should not employ a strong base because of the potential acyl migration reaction. Trimethyloxonium tetrafluoroborate provided methyl ether

3.45 in 93% yield.[87] Then two ester groups were hydrolyzed in one step, and the derived seco acid cyclized under Yamaguchi's protocol[66] to give macrolactone **3.46**. The alkyne motif was converted to the enol acetate for the key cyclization. Compound **3.21** was formed as an inseparable 5:1 mixture of two regioisomers arising from addition of the acetic acid. When **3.21** was treated with DDQ in DCE, the expected cyclization of the enol acetate occurred and led to the product **3.47** with a new tetrahydropyrone *cis* fused to the macrolactone. Its structure was further confirmed by the crystallographic analysis. A catalytic amount of $LiClO_4$ was used in the reaction to inhibit the over-oxidation. Compared with the acyclic tri-substituted allylic ether, substrate **3.21** cyclized much slower and less-efficiently with DDQ. After several trials, the best yield was achieved when the reaction was done with 3 equiv. DDQ at room temperature (Entry 3, Table 9). More DDQ or heating would cause severe decomposition of the product, while less DDQ could not deplete the starting material. The 58% yield should be extrapolated to 65% because the minor regioisomer in the starting material would not produce **3.47** in the cyclization reaction.



Scheme 45. Continue of the neopeltolide macrolide synthesis

Table 9. Optimization for DDQ mediated cyclization of **3.21**

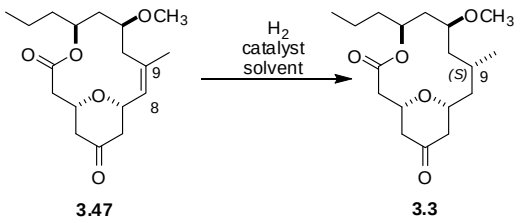


Entry	DDQ	Temp	Time	Conversion	Yield
1	2 equiv.	rt	24 h	86%	48% (56% brsm)
2	2.5 equiv.	rt	36 h	100%	51%
3	3 equiv.	rt	18 h	100%	58%
4	3 equiv.	45 °C to rt[a]	24 h	89%	33% (37% brsm)
5	4 equiv.	rt	24 h	100%	45%

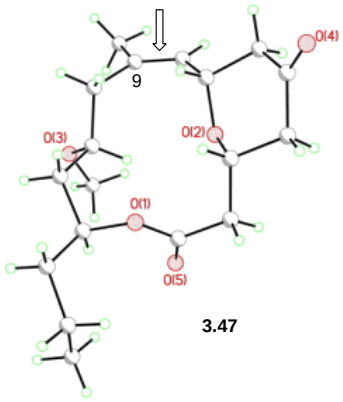
a). The reaction started with 2 equiv. DDQ at 45 °C and was kept for 5 hours. Then another equiv. of DDQ was added in. After two more hours, the heating was stopped and the reaction was stirred at room temperature for another 12 hours.

To complete the synthesis, the alkene between C8 and C9 had to be hydrogenated and the diastereoselectivity was fully controlled by the substrate. From the X-ray structure of **3.47** the conformation of the macrocycle favors the delivery of the hydrogen molecule from marked side to give the desired 9*S* product (Scheme 46). Experimental results validate this postulate: the desired diastereomer was obtained in 74% yield from Pd/C catalyzed hydrogenation reaction, with less than 10% 9*R* by-product. All the characterization data of **3.3** were consistent with those reported by Paterson. Other two catalysts we examined for the hydrogenation reaction were inferior to the simplest Pd/C. $RuCl(PPh_3)_3$ (Wilkinson catalyst)[88] was not able to catalyze the reduction of the tri-substituted olefin. Crabtree's catalyst[89] was more reactive, with the reaction taking less time, but the wrong diastereomer was the major product. We attributed this result to the catalyst coordination to oxygen atom in the tetrahydropyran. From another perspective, this C8-C9 double bond offers us a precious opportunity to diversify the neopeltolide molecule. Numerous methods are available for functionalizing the olefin, and presumably the

stereoselectivity can be manipulated as demonstrated in the hydrogenation reactions. Thus this synthetic strategy provides us a quick access to a variety of neopeltolide analogues.



Catalyst	Yield	**9*S*** : **9*R***
$RuCl(PPh_3)_3$	No reaction	–
$[Ir(Cod)py(PCy_3)]PF_6$	–	1:1.4
Pd/C	74%	>5:1



Scheme 46. Stereoselective hydrogenation of **3.47**

3.4 SUMMARY

A convergent formal synthesis of neopeltolide is accomplished in 13 steps from 2-butyn-1-ol. We utilize our newly developed DDQ-mediated cyclization reaction as the key step to install the *cis*-tetrahydropyrone onto the macrocycle. The convergence of the synthesis originates from the Lewis acid catalyzed etherification and Sonogashira reaction for fragments coupling. Other highlighted steps include the hydrosilylation-Tamao oxidation reaction for alkyne

functionalization and the highly diastereoselective olefin hydrogenation for C9 stereogenic center.

The advantage of the DDQ-induced cyclization is explicitly demonstrated in this work. The ability of DDQ to selectively activate inert C-H bonds allows installing the ether groups at early stage of the synthesis and in turn can minimize the use of protecting groups. In this specific case, no protecting group is introduced to solve the functional group compatibility issue. When properly implemented, this oxidative C-H activation strategy can profoundly benefit the efficiency of natural product syntheses.

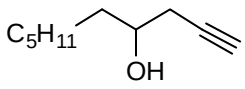
APPENDIX A

OXIDATIVE C-H BOND ACTIVATION: DEVELOPMENT OF DDQ INITIATED INTRAMOLECULAR CYCLIZATION REACTIONS ON BENZYLIC ETHERS

General Experimental Proton (^{1}H NMR) and Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz and 75 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, C_6D_6 = 7.15 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution mass spectra were recorded on a MICROMASS AUTOSPEC (for EI) or WATERS Q-TOF API-US (for ESI) spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Activated 4 Å molecular sieves were obtained through drying in oven at 150 °C overnight. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride and cyclohexane were distilled under N_2 from CaH_2. Toluene and 1,2-dichloroethane were dried over 4 Å molecular sieves overnight

prior to use. Anhydrous DMF was purchased from Acros. Analytical TLC was performed on E. Merck pre-coated (0.25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

Dec-1-yn-4-ol (1.30)

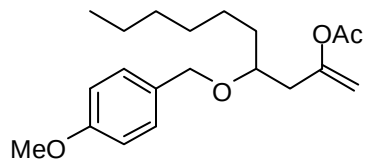


Heptanal (1.00 g, 8.76 mmol), zinc powder(2.86 g, 43.8 mmol), 1,2-diiodoethane (2.47 g, 8.76 mmol) and 3-bromo-1-propyne (1.95 g, 13.1 mmol) were mixed in a 250 mL RBF with 45 mL anhydrous THF. The reaction was sonicated for 2.5 hours, then was quenched by adding 20 mL 2.0 M HCl. The aqueous layer was extracted with Et_2O three times, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then the resulting residue was dissolved in 50 mL EtOAc and washed with aq. $Na_2S_2O_3$ three times to remove the iodine from the crude product. The organic layer was then dried again with $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in Hexane) to give desired product (931 mg, 69%). The spectrum is consistent with the data reported by literature.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71-.3.79 (m, 1H), 3.44 (ddd, *J* = 3.0, 4.5, 16.8 Hz, 1H), 2.31 (ddd, *J* = 2.1, 6.3, 16.8 Hz, 1H), 2.06 (t, *J* = 2.1 Hz, 1H), 1.86 (d, *J* = 5.1 Hz, 1H), 1.56-1.50 (m, 2H), 1.49-1.14 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H).

General Procedure For Enol Acetate Preparation: A RBF was charged with Na_2CO_3 (0.15 equiv.), dichloro(p-cymene)ruthenium(II) dimmer (0.04 equiv.), tri(2-furyl)phosphine (0.08

equiv.). Toluene was added into the flask to dissolve the powder, followed by acetic acid (2 equiv.) and 1-decyne (1 equiv.). The mixture was heated to 80 °C and stirred for one hour. Another 2 equiv. of acetic acid and the substrates (1 equiv.) were dissolved in toluene (the same volume as previously used) and added into the reaction through syringe (overall concentration of substrate in the reaction was about 0.1-0.2 M). The reaction was stirred at the same temperature overnight. Then crude mixture was loaded onto a small plug of silica gel and eluted with Et_2O. The residue was concentrated on a rotary evaporator and purified by flash chromatography to give the desired product.

4-(4-Methoxybenzyloxy)dec-1-en-2-yl acetate (1.12)



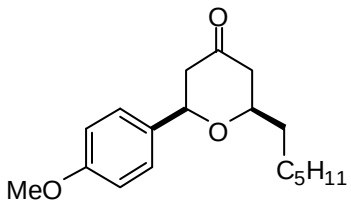
To **1.30** (300 mg, 1.95 mmol) in 5 mL DMF at 0 °C was added NaH (60% dispersed in mineral oil, 93 mg, 2.3 mmol). The mixture was stirred at the same temperature for 30 min, then tetrabutylammonium iodide (77 mg, 0.20 mmol) and 4-methoxybenzyl chloride (317 μL, 2.34 mmol) were added in. The reaction was allowed to room temperature and stirred overnight. The reaction was then quenched by adding water at 0 °C, followed by excess amount of EtOAc. The organic layer was washed with water and brine three times, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5% Et_2O in Hexane) to give 1-((dec-1-yn-4-yloxy)methyl)-4-methoxybenzene (336 mg, 1.22 mmol) with trace 4-methoxybenzyl chloride impurity.

The derived 1-((dec-1-yn-4-yloxy)methyl)-4-methoxybenzene was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (10% $\rightarrow$15% Et_2O in Hexane) to give desired product **1.12** (278 mg, 43% over two steps). ^1H NMR

(300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.84 (s, 1H), 4.82 (s, 1H), 4.51 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 3.81 (s, 3H), 3.54 (quintet, *J* = 6.0 Hz, 1H), 2.54 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.44 (dd, *J* = 5.4, 14.7 Hz, 1H), 2.10 (s, 3H), 1.56-1.46 (m, 2H), 1.43-1.15 (m, 8H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.1, 159.1, 153.6, 130.7, 129.4, 113.6, 103.5, 75.9, 70.7, 55.2, 38.3, 34.0, 31.8, 29.3, 25.2, 22.6, 21.1, 14.0; IR (neat) 2931, 2858, 1754, 1610, 1514, 1464, 1370, 1249, 1033, 825 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{30}O_4$ (M^+) 357.2042, found 357.2039.

General Procedure For The Cyclization Reaction With DDQ: The substrate (1 equiv.), 2,6-dichloropyridine (4 equiv.) and powdered 4 Å molecular sieves (2 mass equiv.) were added to anhydrous 1,2-dichloroethane to give an approximately 0.1 M solution. The mixture was stirred at room temperature for 15 min, then DDQ (see individual examples for equiv.) was added in one portion. The reaction was monitored by TLC at room temperature unless specified, and quenched by Et_3N when complete starting material consumption was observed. The resulting mixture was loaded directly onto a short plug of silica gel and eluted with dichloromethane or EtOAc. The filtrate was concentrated and purified by flash chromatography to give the desired product.

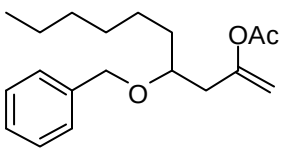
2,6-*cis*-2-Hexyl-6-(4-methoxyphenyl)dihydro-2*H*-pyran-4(3*H*)-one (1.59)



The general cyclization protocol was followed with the substrate **1.12** (105 mg, 0.313 mmol), 2,6-dichloropyridine (185 mg, 1.25 mmol), 4 Å molecular sieves (209 mg), and DDQ (142 mg, 0.626 mmol) in 3 mL anhydrous 1,2-dichloroethane. The reaction was stirred 10 min then purified by

flash chromatography (10% EtOAc in hexane) to give desired product **1.59** (70 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.57 (dd, *J* = 3.9, 10.2 Hz, 1H), 3.80 (s, 3H), 3.78-3.69 (m, 1H), 2.63-2.30 (m, 4H), 1.82-1.70 (m, 1H), 1.65-1.55 (m, 1H), 1.54-1.11 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.2, 159.3, 133.1, 130.0, 114.2, 78.2, 77.3, 55.2, 49.4, 47.7, 36.4, 31.7, 29.1, 25.1, 22.5, 14.0; IR (neat) 2955, 2929, 2856, 1720, 1613, 1515, 1463, 1351, 1249, 1177, 1151, 1036, 829 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{26}O_3$ (M^+) 290.1882, found 290.1878.

4-(Benzyloxy)dec-1-en-2-yl acetate (1.13)

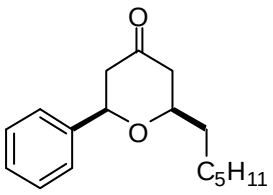


To **1.30** (500 mg, 3.24 mmol) in 6 mL DMF at 0 °C was added NaH (60% dispersed in mineral oil, 156 mg, 3.89 mmol). The mixture was stirred at the same temperature for 30 min, then tetrabutylammonium iodide (128 mg, 0.324 mmol) and benzylbromide (0.77 mL, 6.5 mmol) were added in. The reaction was allowed to room temperature and stirred overnight. The reaction was quenched by adding water at 0 °C, followed by excess amount of EtOAc. The organic layer then washed with water and brine three times, then was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5% Et_2O in Hexane) to give ((dec-1-yn-4-yloxy)methyl)benzene (948 mg, 3.88 mmol) with trace benzyl bromide impurity.

The derived ((dec-1-yn-4-yloxy)methyl)benzene was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (7% Et_2O in Hexane) to give desired product **1.13** (557 mg, 57% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.34 (m, 4H), 7.32-7.27 (m, 1H), 4.83 (s, 1H), 4.82 (s, 1H), 4.57 (d, *J* = 11.4 Hz, 1H),

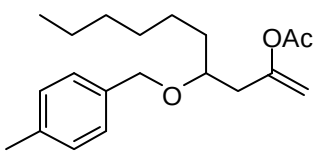
4.51 (d, *J* = 11.4 Hz, 1H), 3.56 (quintet, *J* = 6.0 Hz, 1H), 2.55 (dd, *J* = 6.6, 15.0 Hz, 1H), 2.47 (dd, *J* = 5.4, 14.7 Hz, 1H), 2.08 (s, 3H), 1.60-1.48 (m, 2H), 1.46-1.12 (m, 8H), 0.91 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 168.9, 153.6, 138.6, 128.2, 127.7, 127.4, 76.3, 71.0, 38.2, 33.9, 31.7, 29.2, 25.1, 22.5, 20.9, 14.0; IR (neat) 2929, 2858, 1757, 1665, 1455, 1369, 1195, 1093, 1068, 1022, 736 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{28}O_3Na$ $(M+Na)^+$ 327.1936, found 327.1938.

2,6-*cis*-2-Hexyl-6-phenyldihydro-2*H*-pyran-4(3*H*)-one (1.61)



The general cyclization protocol was followed with the substrate **1.13** (102 mg, 0.335 mmol), 2,6-dichloropyridine (198 mg, 1.34 mmol), 4 Å molecular sieves (204 mg), and DDQ (152 mg, 0.671 mmol) in 3.5 mL anhydrous 1,2-dichloroethane. The reaction was stirred overnight then purified by flash chromatography (50% CH_2Cl_2 in hexane, then 10% EtOAc in hexane) to give desired product **1.61** (55 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.35 (s, 4H), 7.36-7.27(m, 1H), 4.65 (dd, *J* = 3.0, 11.1 Hz, 1H), 3.81-3.73 (m, 1H), 2.67-2.33 (m, 4H), 1.85-1.73 (m, 1H), 1.68-1.54 (m, 1H), 1.52-1.15 (m, 8H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.1, 141.0, 128.5, 127.9, 125.5, 78.5, 77.4, 49.6, 47.7, 36.4, 31.7, 29.1, 25.2, 22.6, 14.0; IR (neat) 2955, 2928, 2857, 1721, 1454, 1349, 1249, 1150, 1061, 754 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{24}O_2$ (M^+) 260.1776, found 260.1781.

4-(4-methylbenzyloxy)dec-1-en-2-yl acetate (1.14)

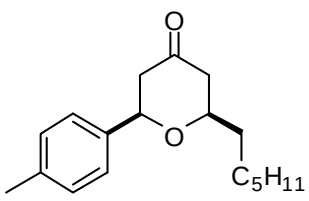


To **1.30** (291 mg, 1.89 mmol) in 6 mL DMF at 0 °C was added NaH (60% dispersed in mineral oil, 113 mg, 2.84 mmol). The mixture was stirred at the same temperature for 30 min, then tetrabutylammonium

iodide (75 mg, 0.19 mmol) and 4-methylbenzyl bromide (700 mg, 3.78 mmol) were added in. The reaction was allowed to room temperature and stirred overnight. The reaction was then quenched by adding water at 0 °C, followed by excess amount of EtOAc. The organic layer was washed with water and brine three times, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (30%→40% CH_2Cl_2 in Hexane) to give 1-((dec-1-yn-4-yloxy)methyl)-4-methylbenzene (334 mg, 1.29 mmol) with trace 4-methylbenzyl bromide impurity.

The derived 1-((dec-1-yn-4-yloxy)methyl)-4-methylbenzene was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (6% →10% Et_2O in Hexane) twice to give desired product **1.14** (330 mg, 55% over two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* =7.5 Hz, 2H), 4.86 (s, 1H), 4.85 (s, 1H), 4.55 (d, *J* = 11.1 Hz, 1H), 4.48 (d, *J* = 11.1 Hz, 1H), 3.57 (quintet, *J* = 6.0 Hz, 1H), 2.57 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.47 (dd, *J* = 5.7, 15.0 Hz, 1H), 2.38 (s, 3H), 2.12 (s, 3H), 1.61-1.52 (m, 2H), 1.45-1.13 (m, 8H), 0.93 (t, *J* = 5.7 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.0, 153.6, 137.1, 135.6, 128.8, 127.9, 103.5, 76.0, 70.9, 38.2, 33.9, 31.7, 29.3, 25.1, 22.5, 21.1, 21.0, 14.0; IR (neat) 2929, 2858, 1758, 1665, 1461, 1369, 1196, 1087, 1021, 872, 803 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{30}O_3Na$ $(M+Na)^+$ 341.2093, found 341.2074.

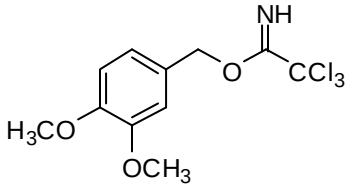
2,6-*cis*-2-Hexyl-6-p-tolyldihydro-2*H*-pyran-4(3*H*)-one (1.62)



The general cyclization protocol was followed with the substrate **1.14** (104 mg, 0.328 mmol), 2,6-dichloropyridine (194 mg, 1.31 mmol), 4 Å molecular sieves (209 mg), and DDQ (149 mg, 0.656 mmol) in 3.5 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 15 min then purified by flash

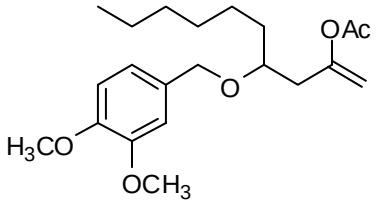
chromatography (40% hexane in CH_2Cl_2 then 15% EtOAc in hexane) to give desired product **1.62** (74 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 4.60 (dd, *J* = 3.3, 10.8 Hz, 1H), 3.80-3.71 (m, 1H), 2.66-2.27 (m, 4H), 2.36 (s, 3H), 1.82-1.72 (m, 1H), 1.66-1.57 (m, 1H), 1.55-1.23 (m, 8H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.2, 138.0, 137.6, 129.2, 125.5, 78.4, 77.3, 49.5, 47.7, 36.4, 33.8, 31.7, 29.1, 25.2, 22.5, 21.1, 14.0; IR (neat) 2955, 2928, 2857, 1721, 1461, 1347, 1248, 1151, 1066, 810 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{26}O_2$ (M^+) 274.1933, found 274.1936.

3,4-Dimethoxybenzyl 2,2,2-trichloroacetimidate (1.32)



To (3,4-dimethoxyphenyl)methanol (1.00 g, 5.95 mmol) in dry Et_2O at 0 °C was added NaH (60% dispersed in mineral oil, 24 mg, 0.60 mmol). The reaction was stirred for 30 min at 0 °C then CCl_3CN (597 μL, 5.95 mmol) was added in. The reaction was allowed to room temperature and stirred for 2.5 hours, then concentrated under reduced pressure. The resulting residue was dissolved in a mixture of 50 mL petroleum ether and 0.2 mL methanol, and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and stored in refrigerator for use. The spectrum is consistent with the data reported in literature.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 6.98 (d, *J* = 9.3 Hz, 1H), 7.00 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 5.28 (s, 3H), 3.88 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 162.5, 149.1, 148.9, 127.9, 120.7, 120.7, 111.2, 110.9, 91.4, 70.7, 55.9, 55.8.

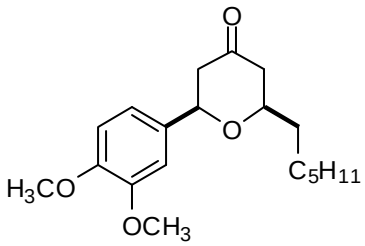
4-(3,4-Dimethoxybenzyloxy)dec-1-en-2-yl acetate (1.15)



To **1.32** (1.22 g, 3.90 mmol) in 6.3 mL cyclohexane was added **1.30** (201 mg, 1.30 mmol) taken up in 1.5 mL anhydrous CH_2Cl_2. The mixture was cooled to 0 °C, then a drop of BF_3·THF was added in through syringe. The reaction was stirred at 0 °C for 10 min, then warmed to room temperature and stirred for 40 min. The reaction was quenched by diluting with 1:2 dichloromethane and cyclohexane, then decanted into aq. $NaHCO_3$. It was extracted with dichloromethane three times, then dried over $MgSO_4$, concentrated and purified by flash chromatography (10% EtOAc in Hexane) to give 4-((dec-1-yn-4-yloxy)methyl)-1,2-dimethoxybenzene (183 mg, 0.602 mmol) with trace amount of dec-1-yn-4-ol impurity.

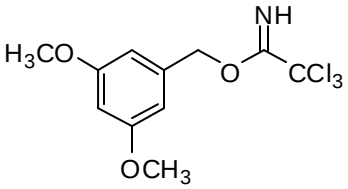
The product derived from previous step was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (15% EtOAc in Hexane) to give desired product **1.15** (125 mg, 26% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 4.79 (s, 2H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.1 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), , 3.50 (quintet, *J* = 5.7 Hz, 1H), 2.50 (dd, *J* = 6.6, 15.0 Hz, 1H), 2.41 (dd, *J* = 5.4, 15.0 Hz, 1H), 2.06 (s, 3H), 1.52-1.43 (m, 2H), 1.39-1.14 (m, 8H), 0.84 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 168.9, 153.6, 148.9, 148.3, 131.2, 120.1, 111.2, 110.7, 103.4, 75.9, 70.9, 55.8, 55.6, 38.2, 33.9, 31.7, 29.2, 25.2, 22.5, 21.0, 14.0; IR (neat) 2928, 2855, 1755, 1515, 1463, 1369, 1264, 1192, 1156, 1138, 1093, 1029 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{32}O_5Na$ $(M+Na)^+$ 387.2147, found 387.2121.

2,6-*cis*-2-(3,4-Dimethoxyphenyl)-6-hexyldihydro-2*H*-pyran-4(3*H*)-one (1.63)



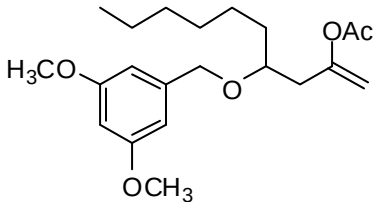
The general cyclization protocol was followed with the substrate **1.15** (39.6 mg, 0.109 mmol), 2,6-dichloropyridine (64.4 mg, 0.435 mmol), 4 Å molecular sieves (79 mg), and DDQ (49.3 mg, 0.217 mmol) in 1.2 mL anhydrous 1,2-dichloroethane at –20 °C. The reaction was stirred at –20 °C for ten min then purified by flash chromatography (20% EtOAc in hexane) to give desired product **1.63** (29 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.90-6.83 (m, 2H), 4.56 (dd, *J* = 3.9, 10.2 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.77-3.69 (m, 1H), 2.62-2.30 (m, 4H), 1.80-1.70 (m, 1H), 1.64-1.52 (m, 1H), 1.50-1.21 (m, 8H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 208.1, 149.0, 148.6, 133.5, 117.8, 111.0, 108.9, 78.3, 77.3, 55.8, 55.8, 49.5, 47.7, 36.3, 31.6, 29.1, 25.1, 22.5, 14.0; IR (neat) 2930, 2856, 1753, 1719, 1594, 1517, 1464, 1419, 1334, 1266, 1161, 1138, 1029, 807 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found 320.1982.

3,5-Dimethoxybenzyl 2,2,2-trichloroacetimidate (1.34)



To (3,5-dimethoxyphenyl)methanol (916 mg, 5.45 mmol) dissolved in dry Et_2O at 0 °C was added NaH (60% dispersed in mineral oil, 22 mg, 0.55 mmol). The reaction was stirred at 0 °C for 30 min, then CCl_3CN (546 μL, 5.45 mmol) was added in. The reaction was allowed to room temperature and stirred for four hours, then concentrated under reduced pressure. The resulting residue was dissolved in a mixture of 25 mL petroleum ether and 0.1 mL methanol, and filtered through a plug of Celite. The filtrate was concentrated on rotary evaporator and stored in refrigerator for use.

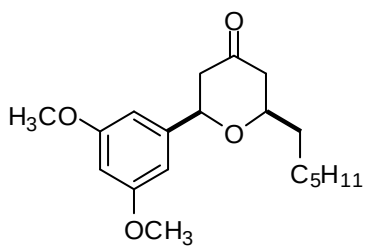
4-(3,5-Dimethoxybenzyloxy)dec-1-en-2-yl acetate (1.16)



To **1.34** (841 mg, 2.69 mmol) in 3 mL cyclohexane was added **1.30** (138 mg, 0.897 mmol). The mixture was cooled to 0 °C, then TfOH (4 μL, 0.04 mmol) was added in. The reaction was allowed to room temperature and stirred overnight, then quenched by decanted into aq. $NaHCO_3$. It was extracted with Et_2O three times, then dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in Hexane) to give 1-((dec-1-yn-4-yloxy)methyl)-3,5-dimethoxybenzene (88 mg, 0.29 mmol) with trace impurity.

The product derived from previous step was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (8% EtOAc in Hexane) to give desired product **1.16** (43 mg, 13% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, *J* = 1.5 Hz, 2H), 6.37 (s, 1H), 4.81 (s, 2H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 3.78 (s, 6H), 3.50 (quintet, *J* = 5.7 Hz, 1H), 2.52 (dd, *J* = 6.3, 14.7 Hz, 1H), 2.44 (dd, *J* = 5.7, 15.3 Hz, 1H), 2.09 (s, 3H), 1.56-1.52 (m, 2H), 1.41-1.06 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 168.9, 160.7, 153.6, 141.0, 105.5, 103.6, 99.6, 76.2, 70.9, 55.2, 38.3, 33.9, 31.8, 29.3, 25.2, 22.6, 21.0, 14.0; IR (neat) 2930, 2856, 1756, 1598, 1463, 1430, 1368, 1203, 1155, 1095, 1065, 1020, 833 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{32}O_5Na$ $(M+Na)^+$ 387.2147, found 387.2123.

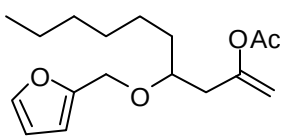
2,6-*cis*-2-(3,5-Dimethoxyphenyl)-6-hexyldihydro-2*H*-pyran-4(3*H*)-one (1.64)



The general cyclization protocol was followed with the substrate **1.16** (43 mg, 0.12 mmol), 2,6-dichloropyridine (70 mg, 0.47 mmol), 4 Å molecular sieves (86 mg), and DDQ (54 mg, 0.24

mmol) in 1.2 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 1.5 hours then purified by flash chromatography (15% EtOAc in hexane) to give desired product **1.64** (21 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 2H), 6.40 (s, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 3.89-3.67 (m, 1H), 3.80 (s, 6H), 2.64-2.31 (m, 4H), 1.78-1.72 (m, 1H), 1.64-1.50 (m, 1H), 1.48-1.22 (m, 8H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.0, 161.0, 143.4, 103.6, 99.6, 78.4, 77.4, 55.3, 49.6, 47.7, 36.4, 31.7, 29.1, 25.2, 22.6, 14.0; IR (neat) 2929, 2855, 1719, 1598, 1463, 1430, 1351, 1205, 1156, 1059, 835 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found 320.1981.

4-(Furan-2-ylmethoxy)dec-1-en-2-yl acetate (1.17)

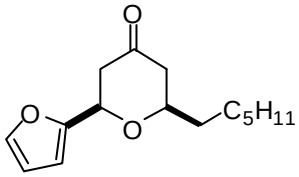


To **1.30** (300 mg, 1.95 mmol) in 5 mL DMF at 0 °C was added NaH (60% dispersed in mineral oil, 104 mg, 2.60 mmol). The mixture was stirred at the same temperature for 30 min, then 2-(bromomethyl)furan (419 mg, 2.60 mmol in dry Et_2O) was added in. The reaction was allowed to room temperature and stirred overnight. The reaction was then quenched by adding water at 0 °C. The aqueous layer was extracted with EtOAc three times, and the combined organic layer was washed with aq. $NaHCO_3$ and water. It was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (7% EtOAc in Hexane, the column was pre-treated with 1% Et_3N in Hexane) to give 2-((dec-1-yn-4-yloxy)methyl)furan (87 mg, 0.37 mmol) with some decomposition.

The product from previous step was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (3% EtOAc in Hexane, the column was pre-treated with 1% Et_3N in Hexane) to give desired product **1.17** (61 mg, 11% over two steps).

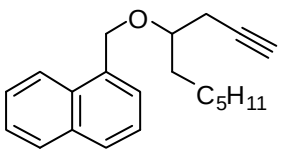
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 0.6, 1.5 Hz, 1H), 6.32 (dd, *J* = 1.8, 3.0 Hz, 1H), 6.28 (d, *J* = 3.0 Hz, 1H), 4.79 (s, 2H), 4.49 (d, *J* = 12.6 Hz, 1H), 4.42 (d, *J* = 12.6 Hz, 1H), 3.51 (quintet, *J* = 6.0 Hz, 1H), 2.46 (dd, *J* = 6.3, 14.7 Hz, 1H), 2.38 (dd, *J* = 5.7, 14.7 Hz, 1H), 2.11 (s, 3H), 1.53-1.40 (m, 2H), 1.35-1.18 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.1, 153.5, 152.2, 142.5, 110.2, 109.0, 103.6, 76.2, 63.2, 38.3, 34.0, 31.8, 29.2, 25.1, 22.6, 21.1, 14.1; IR (neat) 2929, 2857, 1757, 1666, 1461, 1370, 1196, 1151, 1065, 1017, 919, 882, 737 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{26}O_4Na$ $(M+Na)^+$ 317.1729, found 317.1722.

2,6-*cis*-2-(Furan-2-yl)-6-hexyldihydro-2*H*-pyran-4(3*H*)-one



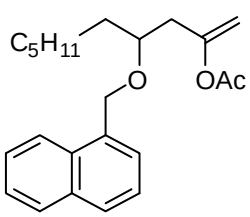
The general cyclization protocol was followed with the substrate **1.17** (22 mg, 0.075 mmol), 2,6-dichloropyridine (45 mg, 0.30 mmol), 4 Å molecular sieves (44 mg), and DDQ (34 mg, 0.15 mmol) in 1 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 12 hours then purified by flash chromatography (40% hexane in CH_2Cl_2 then 8% EtOAc in hexane) to give the desired product (12 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 0.6, 1.8 Hz, 1H), 6.36 (dd, *J* = 1.8, 3.0 Hz, 1H), 6.33 (d, *J* = 3.3 Hz, 1H), 4.68 (dd, *J* = 2.7, 12.0 Hz, 1H), 3.77-3.68 (m, 1H), 2.85 (ddd, *J* = 0.6, 12.0, 14.4 Hz, 1H), 2.59 (dt, *J* = 2.1, 14.7 Hz, 1H), 2.46 (dt, *J* = 2.4, 14.7 Hz, 1H), 2.33 (dd, *J* = 11.4, 14.7 Hz, 1H), 1.81-1.69 (m, 1H), 1.60-1.52 (m, 1H), 1.50-1.15 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 206.3, 152.6, 142.8, 110.3, 107.5, 77.3, 72.0, 47.7, 45.4, 36.3, 31.7, 29.1, 25.2, 22.6, 14.0; IR (neat) 2928, 2857, 1721, 1465, 1346, 1266, 1156, 1058, 1014, 740 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_3$ (M^+) 250.1569, found 250.1573.

1-((Dec-1-yn-4-yloxy)methyl)naphthalene



To **1.30** (300 mg, 1.95 mmol) in 5 mL DMF at 0 °C was added NaH (60% dispersed in mineral oil, 93 mg, 2.3 mmol). The mixture was stirred at the same temperature for 30 min, then tetrabutylammonium iodide (77 mg, 0.20 mmol) and 1-(chloromethyl)naphthalene (350 μL, 2.33 mmol) were added in. The reaction was allowed to room temperature and stirred overnight. The reaction was quenched by adding water at 0 °C and diluted with EtOAc. The organic layer was washed with water and brine three times, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (40% CH_2Cl_2 in Hexane) to give desired product (>162 mg, >28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.91 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.62-7.46 (m, 4H), 5.18 (d, *J* = 11.7 Hz, 1H), 4.97 (d, *J* = 11.7 Hz, 1H), 3.68 (quintet, *J* = 5.7 Hz, 1H), 2.58 (ddd, *J* = 2.4, 5.1, 16.8 Hz, 1H), 2.53 (ddd, *J* = 2.7, 6.0, 16.8 Hz, 1H), 2.10 (t, *J* = 2.7 Hz, 1H), 1.76-1.66 (m, 2H), 1.54-1.27 (m, 10H), 0.94 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 133.9, 133.7, 131.8, 128.5, 128.4, 126.5, 126.0, 125.6, 125.1, 124.2, 81.4, 76.9, 69.9, 69.7, 33.9, 31.7, 29.1, 25.1, 23.7, 22.5, 14.0; IR (neat) 3308, 3047, 2928, 2857, 1464, 1355, 1166, 1091, 1067, 793, 775 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{26}O$ (M^+) 294.1984, found 294.1994.

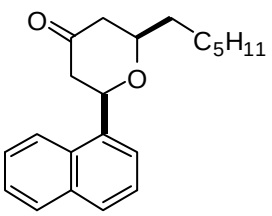
4-(Naphthalen-1-ylmethoxy)dec-1-en-2-yl acetate (1.18)



1-((dec-1-yn-4-yloxy)methyl)naphthalene derived from previous step was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (6% Et_2O in Hexane) to give desired product **1.18** (138 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 1.5, 7.5 Hz,

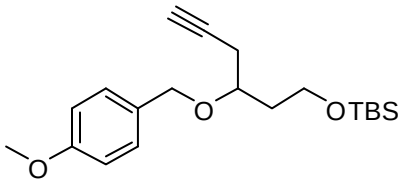
1H), 7.87 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.58-7.42 (m, 4H), 5.05 (d, *J* = 11.7 Hz, 1H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.84 (s, 2H), 3.66 (quintet, *J* = 6.0 Hz, 1H), 2.62 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.51 (dd, *J* = 5.7, 14.7 Hz, 1H), 2.08 (s, 3H), 1.66-1.58 (m, 2H), 1.40-1.23 (m, 8H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.0, 153.5, 134.0, 133.7, 131.7, 128.4, 128.4, 126.5, 125.9, 125.6, 125.1, 124.2, 103.6, 76.1, 69.4, 38.2, 33.9, 31.7, 29.2, 25.1, 22.5, 21.0, 14.0; IR (neat) 3047, 2928, 2857, 1756, 1665, 1464, 1433, 1369, 1194, 1088, 1066, 1020, 874, 794, 776 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{30}O_3$ (M^+) 354.2195, found 354.2210.

2,6-*cis*-2-Hexyl-6-(naphthalen-1-yl)dihydro-2*H*-pyran-4(3*H*)-one



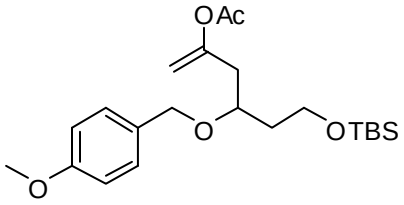
The general cyclization protocol was followed with the substrate **1.18** (84 mg, 0.24 mmol), 2,6-dichloropyridine (140 mg, 0.945 mmol), 4 Å molecular sieves (167 mg), and DDQ (107 mg, 0.473 mmol) in 2.5 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 3.5 hours then purified by flash chromatography (50% CH_2Cl_2 in hexane, then 5% EtOAc in hexane) to give the desired product (61 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.54-7.44 (m, 3H), 5.34 (dd, *J* = 1.8, 10.8 Hz, 1H), 4.00-3.87 (m, 1H), 2.86-2.73 (m, 2H), 2.59-2.37 (m, 2H), 1.88-1.76 (m, 1H), 1.70-1.55 (m, 1H), 1.55-1.15 (m, 8H), 0.90 (t, *J* = 8.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.2, 136.3, 133.8, 130.2, 128.9, 128.6, 126.2, 125.7, 125.4, 123.1, 122.9, 77.7, 75.8, 48.6, 48.0, 36.5, 31.7, 29.2, 25.3, 22.6, 14.0; IR (neat) 3051, 2954, 2928, 2856, 1718, 1511, 1464, 1332, 1265, 1250, 1137, 1057, 798, 776 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{26}O_2$ (M^+) 310.1933, found 310.1936.

tert-Butyl(3-(4-methoxybenzyloxy)hex-5-ynyloxy)dimethylsilane (1.38)



1-(tert-butyldimethylsilyloxy)hex-5-yn-3-ol (1.50 g, 6.57 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (3.34 g, 11.8 mmol) were dissolved in 60 mL dry toluene at room temperature, followed by addition of $La(OTf)_3$ (578 mg, 0.986 mmol). The mixture was stirred at room temperature overnight, then concentrated under reduced pressure and purified by flash chromatography (5% Et_2O in Hexane) to give desired product **1.38** (1.616 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.63 (d, *J* = 11.1 Hz, 1H), 4.48 (d, *J* = 11.1 Hz, 1H), 3.83 (s, 3H), 3.79-3.69 (m, 3H), 2.49 (dd, *J* = 2.4, 5.4 Hz, 2H), 2.04 (t, *J* = 2.4 Hz, 1H), 1.92-1.80 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 159.2, 130.6, 129.4, 113.8, 81.2, 73.8, 71.2, 70.0, 59.4, 55.2, 37.3, 25.9, 24.0, 18.2, –5.3, –5.4; IR (neat) 3309, 2953, 2930, 2857, 1613, 1513, 1466, 1249, 1174, 1094, 1038, 834, 776 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}O_2Na$ $(M–C_8H_{19}OSi+Na)^+$ 212.0813, found 212.0817.

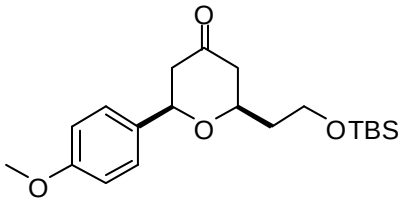
6-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)hex-1-en-2-yl acetate (1.19)



Compound **1.38** (300 mg, 0.861 mmol) was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (6% EtOAc in Hexane) twice to give desired product **1.19** (234 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.82 (d, *J* = 3.9 Hz, 2H), 4.51 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 3.80 (s, 3H), 3.78-3.64 (m, 3H), 2.53 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.46 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.08 (s, 3H), 1.75 (q, *J* = 6.0 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.1, 159.1, 153.5, 130.7, 129.4, 113.7, 103.7, 73.0, 71.2, 59.4, 55.3, 38.5,

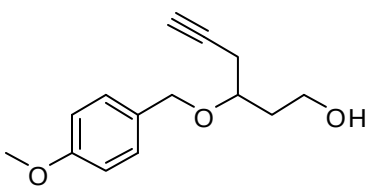
37.4, 25.9, 21.1, 18.2; IR (neat) 2953, 2930, 2857, 2360, 1757, 1665, 1613, 1514, 1467, 1369, 1249, 1200, 1094, 835, 776 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{36}O_5Na$ $(M+Na)^+$ 431.2230, found 431.2215.

2,6-*cis*-2-(2-(tert-Butyldimethylsilyloxy)ethyl)-6-(4-methoxyphenyl)dihydro-2*H*-pyran-4(3*H*)-one



The general cyclization procedure was followed with the substrate **1.19** (101 mg, 0.248 mmol), 2,6-dichloropyridine (147 mg, 0.996 mmol), 4 Å molecular sieves (203 mg), and DDQ (85 mg, 0.37 mmol) in 3 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 30 min then quenched by Et_3N and purified by flash chromatography (8% EtOAc in hexane) to give the desired product (67 mg, 74%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.58 (dd, *J* = 4.5, 9.9 Hz, 1H), 3.94 (ddt, *J* = 4.2, 7.8, 14.7 Hz, 1H), 3.81 (s, 3H), 3.80-3.70 (m, 2H), 2.63-2.51 (m, 2H), 2.50-2.35 (m, 2H), 2.00-1.87 (m, 2H), 1.85-1.74 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 207.1, 159.3, 133.1, 127.0, 113.9, 78.3, 74.0, 59.0, 55.3, 49.5, 47.9, 39.4, 25.9, 18.3, –5.4, –5.4; IR (neat) 2954, 2930, 2857, 1721, 1614, 1466, 1358, 1304, 1251, 1177, 1094, 837, 777 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{23}O_4Si$ $(M-C_4H_9)^+$ 307.1366, found 307.1355.

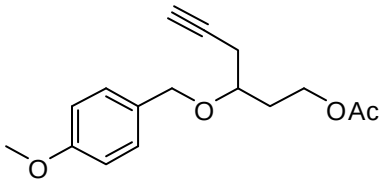
3-(4-Methoxybenzyloxy)hex-5-yn-1-ol (1.39)



Compound **1.38** (1.00 g, 2.87 mmol) was dissolved in 10 mL methanol at room temperature, then a crystal of TsOH was added in. The reaction was stirred for one hour and quenched by adding

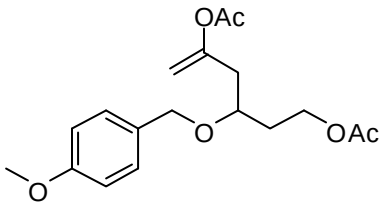
H_2O. The crude mixture was extracted with EtOAc, dried with $MgSO_4$ and filtered. The resulting residue was purified by flash chromatography (40% EtOAc in Hexane) to give desired product **1.39** (609 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.64 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 3.80 (s, 3H), 3.80-3.72 (m, 3H), 2.55 (ddd, *J* = 2.4, 4.8, 16.8 Hz, 1H), 2.45 (ddd, *J* = 2.7, 6.9, 16.8 Hz, 1H), 2.25 (br, 1H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.97-1.81 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 159.3, 129.9, 129.5, 113.9, 80.7, 75.7, 71.1, 70.4, 60.2, 55.2, 36.2, 23.6; IR (neat) 3408, 3291, 2936, 1612, 1513, 1464, 1349, 1302, 1248, 1176, 1034, 822 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1258.

3-(4-Methoxybenzyloxy)hex-5-ynyl acetate (1.40)



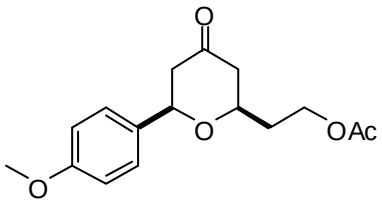
1.39 (309 mg, 1.32 mmol) and DMAP (8 mg, 0.07 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 0 °C, followed by addition of Et_3N (802 mg, 7.92 mmol) and Ac_2O (2.02 g, 19.8 mmol). The reaction was stirred at room temperature overnight then quenched by adding H_2O at 0 °C. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried with $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (8% EtOAc, in Hexane) to give desire product **1.40** (326 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.16 (t, *J* = 5.7 Hz, 2H), 3.79 (s, 3H), 3.68-3.61 (m, 1H), 2.51 (ddd, *J* = 2.7, 5.1, 16.8 Hz, 1H), 2.43 (ddd, *J* = 2.7, 6.3, 17.1 Hz, 1H), 2.03 (t, *J* = 2.7 Hz, 1H), 1.99 (s, 3H), 2.00-1.86 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 171.0, 159.3, 130.0, 129.5, 113.8, 80.6, 73.2, 71.1, 70.4, 61.1, 55.2, 33.1, 23.8, 20.9; IR (neat) 3291, 2917, 1736, 1612, 1513, 1463, 1366, 1245, 1173, 1110, 820 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}O_4$ (M^+) 276.1362, found 276.1361.

3-(4-Methoxybenzyloxy)hex-5-ene-1,5-diyl diacetate (1.20)



Compound **1.40** (326 mg, 1.18 mmol) was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (15% EtOAc in Hexane) twice to give desired product **1.20** (235 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.80 (d, *J* = 5.4 Hz, 2H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.14 (t, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.64-3.58 (m, 1H), 2.55 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.44 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.07 (s, 3H), 1.97 (s, 3H), 1.92-1.75 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 170.8, 168.8, 159.1, 152.8, 130.1, 129.4, 113.6, 104.0, 72.5, 70.8, 61.1, 55.1, 38.1, 33.1, 20.9, 20.8; IR (neat) 2936, 1739, 1666, 1612, 1513, 1464, 1439, 1369, 1248, 1200, 1038, 822 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{24}O_6Na$ $(M+Na)^+$ 359.1471, found 359.1476.

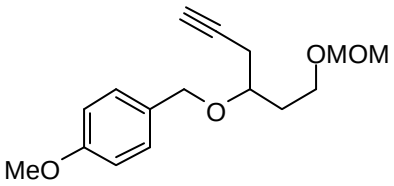
2-((2,6-*cis*)-6-(4-Methoxyphenyl)-4-oxotetrahydro-2*H*-pyran-2-yl)ethyl acetate



The general cyclization procedure was followed with the substrate **1.20** (104 mg, 0.309 mmol), 2,6-dichloropyridine (137 mg, 0.928 mmol), 4 Å molecular sieves (208 mg), and DDQ (105 mg, 0.464 mmol) in 3.5 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 45 min then quenched by Et_3N and purified by flash chromatography (25% EtOAc in hexane) to give the desired product (67 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.59 (dd, *J* = 4.2, 10.2 Hz, 1H), 4.32-4.20 (m, 2H), 3.90 (ddt, *J* = 3.9, 7.8, 14.7 Hz, 1H), 3.81 (s, 3H), 2.66-2.52 (m, 2H), 2.50-2.36 (m, 2H), 2.02 (s, 3H), 2.11-1.87 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 206.4, 171.0, 159.4, 132.7, 127.0, 114.0, 78.3, 74.2, 60.8, 55.3, 49.3, 47.6,

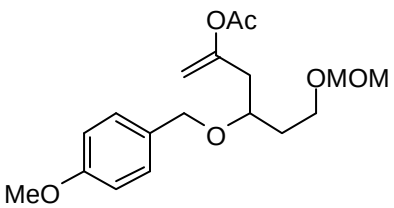
35.3, 20.9; IR (neat) 2962, 2840, 2360, 1736, 1613, 1515, 1368, 1248, 1059, 1035, 832 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}O_5$ (M^+) 292.1311, found 292.1316.

1-Methoxy-4-((1-(methoxymethoxy)hex-5-yn-3-yloxy)methyl)benzene (1.41)



Compound **1.39** (300 mg, 1.28 mmol) and DMAP (8 mg, 0.06 mmol) were dissolved in 6 mL CH_2Cl_2 at 0 °C, followed by addition of $^iPr_2NEt$ (267 μL, 1.53 mmol) and MOMCl (107 μL, 1.41 mmol). Then the reaction was allowed to room temperature and stirred overnight. The reaction was quenched by adding aq. $NaHCO_3$ at 0 °C. The aqueous layer was extracted with EtOAc three times, and the organic layers were combined, dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc, in Hexane) to give desire product **1.41** (300 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.65-4.62 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 6.3 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.45 (d, *J* = 11.1 Hz, 1H), 3.81 (s, 3H), 3.80-3.69 (m, 1H), 3.65 (t, *J* = 5.7 Hz, 2H), 3.36 (s, 3H), 2.52-2.46 (m, 2H), 2.04 (t, *J* = 2.7 Hz, 1H), 2.02-1.85 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 159.2, 130.4, 129.4, 113.7, 96.5, 80.9, 73.9, 71.2, 70.2, 64.2, 55.2, 55.2, 34.3, 23.9; IR (neat) 3288, 2929, 2882, 1612, 1513, 1465, 1349, 1301, 1247, 1174, 1150, 1106, 1036, 918, 820 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_4$ (M^+) 278.1518, found 278.1516.

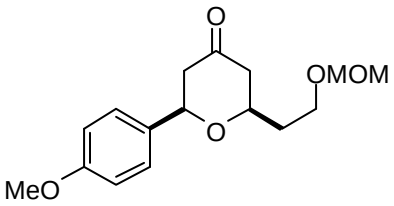
4-(4-Methoxybenzyloxy)-6-(methoxymethoxy)hex-1-en-2-yl acetate (1.21)



Compound **1.41** (300 mg, 1.08 mmol) was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (15% EtOAc in Hexane) to

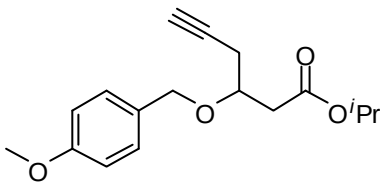
give desire product **1.21** (234 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.85 (s, 2H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.58 (d, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 3.81 (s, 3H), 3.77-3.69 (m, 1H), 3.64 (t, *J* = 6.3 Hz, 2H), 3.36 (s, 3H), 2.57 (dd, *J* = 6.0, 14.7 Hz, 1H), 2.50 (dd, *J* = 5.4, 15.0 Hz, 1H), 2.11 (s, 3H), 1.91-1.79 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 169.0, 159.1, 153.2, 130.5, 129.4, 113.7, 103.8, 96.4, 73.3, 71.1, 64.2, 55.2, 55.1, 38.4, 34.4, 21.0; IR (neat) 2933, 2882, 1755, 1666, 1612, 1514, 1465, 1441, 1370, 1301, 1248, 1201, 1151, 1110, 1038, 918, 822 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{26}O_6Na$ $(M+Na)^+$ 361.1627, found 361.1639.

2,6-*cis*-2-(2-(Methoxymethoxy)ethyl)-6-(4-methoxyphenyl)dihydro-2*H*-pyran-4(3*H*)-one



The general cyclization procedure was followed with the substrate **1.21** (107 mg, 0.317 mmol), 2,6-dichloropyridine (141 mg, 0.951 mmol), 4 Å molecular sieves (215 mg), and DDQ (122 mg, 0.539 mmol) in 3.5 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 45 min then quenched by Et_3N and purified by flash chromatography (25% EtOAc in hexane) to give the desired product (53 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.60 (s, 2H), 4.60 (dd, *J* = 4.2, 9.9 Hz, 1H), 4.01-3.89 (m, 1H), 3.80 (s, 3H), 3.77-3.61 (m, 2H), 3.33 (s, 3H), 2.64-2.74 (m, 2H), 2.49 (dd, *J* = 1.5, 14.4 Hz, 1H), 2.40 (dd, *J* = 11.1, 14.1 Hz, 1H), 2.08-1.96 (m, 1H), 1.95-1.82 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 206.7, 159.3, 132.9, 126.9, 113.9, 96.4, 78.2, 74.2, 63.6, 55.2, 55.1, 49.2, 47.7, 36.4; IR (neat) 2929, 1718, 1613, 1515, 1464, 1354, 1304, 1250, 1177, 1151, 1108, 1046, 918, 829 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_5$ (M^+) 294.1467, found 294.1479.

Isopropyl 3-(4-methoxybenzyloxy)hex-5-ynoate (1.42)



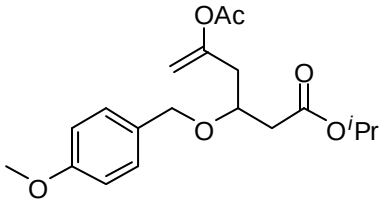
Compound **1.39** (164 mg, 0.699 mmol) was dissolved in 3.5 mL CH_2Cl_2 at 0 °C. Et_3N (292 μL, 2.10 mmol), DMSO (0.9 mL) and $Py{\cdot}SO_3$ (164 mg, 1.05 mmol) were added into the reaction sequentially. The mixture was kept at 0 °C for 15 min, then allowed to room temperature and stirred overnight. The reaction was quenched with H_2O at 0 °C and diluted with EtOAc. The organic layer was washed with H_2O three times, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc in Hexane) to give 3-(4-methoxybenzyloxy)hex-5-ynal (142 mg, 87%).

The product derived from previous step and 2-methyl-2-butene (2.14 g, 30.5 mmol) were dissolved in 10 mL ^{t}BuOH and cooled to 0 °C. A solution of $NaClO_2$ (497 mg, 5.49 mmol) and $NaH_2PO_4{\cdot}H_2O$ (138 mg, 4.27 mmol) in 5.5 mL H_2O was added into the flask dropwisely through syringe. The solution was stirred vigorously and it turned yellow after the addition. The reaction was kept at room temperature for 1.5 hours, then was acidified with 2M HCl until the pH was about 4. The crude mixture was extracted with EtOAc three times, and the combined organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated. The resulting product was used for the next step without further purification.

The acid derived from previous step, DCC (378 mg, 1.83 mmol) and DMAP (15 mg, 0.12 mmol) were dissolved in 4 mL CH_2Cl_2 at room temperature, then isopropanol (110 mg, 1.83 mmol) was added in. The solution turned a little pink and white precipitation formed. The reaction was stirred for 10 min then quenched by adding H_2O at 0 °C. The aqueous layer was extracted with CH_2Cl_2 three times, and the combined organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (7% EtOAc in Hexane) to give

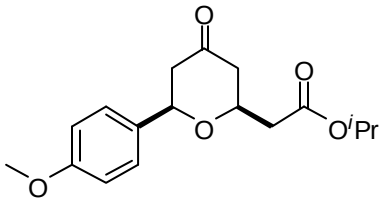
desired product **1.42** (98 mg, 51% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.03 (septet, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.07-3.99 (m, 1H), 3.78 (s, 3H), 2.69 (dd, *J* = 5.1, 15.6 Hz, 1H), 2.60 (dd, *J* = 7.8, 15.6 Hz, 1H), 2.53 (ddd, *J* = 2.4, 5.1, 17.1 Hz, 1H), 2.44 (ddd, *J* = 2.7, 6.6, 16.8 Hz, 1H), 2.04 (t, *J* = 2.4 Hz, 1H), 1.24 (d, *J* = 2.1 Hz, 3H), 1.23 (d, *J* = 2.1 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 170.6, 159.2, 130.0, 129.3, 113.7, 80.2, 73.8, 71.5, 70.6, 67.8, 55.1, 39.7, 23.8, 21.7, 21.7; IR (neat) 3290, 2981, 2934, 1729, 1613, 1514, 1466, 1375, 1304, 1249, 1175, 1108, 1035, 822 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_4$ (M^+) 290.1518, found 290.1503.

Isopropyl 5-acetoxy-3-(4-methoxybenzyloxy)hex-5-enoate (1.22)



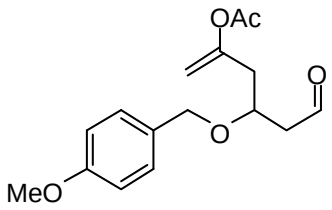
Compound **1.42** (98 mg, 0.33 mmol) was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (10% EtOAc in Hexane) to give desired product **1.22** (97 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.01 (septet, *J* = 6.3 Hz, 1H), 4.82 (d, *J* = 4.5 Hz, 2H), 4.48 (s, 2H), 4.02 (quintet, *J* = 6.3 Hz, 1H), 3.78 (s, 3H), 2.62-2.44 (m, 4H), 2.07 (s, 3H), 1.23 (d, *J* = 2.1 Hz, 3H), 1.21 (d, *J* = 2.1 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 170.8, 169.0, 159.1, 152.6, 130.2, 129.3, 113.6, 104.3, 73.2, 71.5, 67.8, 55.2, 39.8, 38.3, 21.7, 21.7, 21.0; IR (neat) 2980, 2935, 2360, 1756, 1729, 1666, 1613, 1514, 1466, 1372, 1249, 1191, 1109, 1034, 966, 822 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{26}O_6Na$ $(M+Na)^+$ 373.1627, found 373.1617.

Isopropyl 2-((2,6-*cis*)-6-(4-methoxyphenyl)-4-oxotetrahydro-2*H*-pyran-2-yl)acetate



The general cyclization procedure was followed with the substrate **1.22** (94 mg, 0.27 mmol), 2,6-dichloropyridine (119 mg, 0.805 mmol) and 4 Å molecular sieves (188 mg), and DDQ (91 mg, 0.40 mmol) in 3 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 45 min then quenched by Et_3N and was purified by flash chromatography (20% EtOAc in hexane) to give the desired product (56 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.03 (septet, *J* = 6.3 Hz, 1H), 4.63 (dd, *J* = 3.9, 10.5 Hz, 1H), 4.27-4.18 (m, 1H), 3.79 (s, 3H), 2.74 (dd, *J* = 7.2, 15.3 Hz, 1H), 2.66-2.40 (m, 5H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 205.9, 169.6, 159.4, 132.5, 127.0, 113.9, 78.1, 73.6, 68.2, 55.3, 48.8, 46.9, 41.6, 21.7; IR (neat) 2980, 2934, 1725, 1613, 1515, 1372, 1306, 1251, 1180, 1108, 974, 829 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_5Na$ $(M+Na)^+$ 329.1365, found 329.1352.

4-(4-Methoxybenzyloxy)-6-oxohex-1-en-2-yl acetate (1.65)

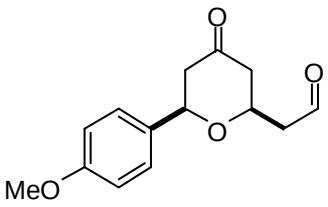


Compound **1.19** (441 mg, 1.08 mmol) was dissolved in 10 mL methanol at room temperature, then a crystal of TsOH was added in. The reaction was stirred for 40 min and quenched by adding H_2O at 0 °C. The crude mixture was extracted with EtOAc and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (45% EtOAc in Hexane) to give 6-hydroxy-4-(4-methoxybenzyloxy)hex-1-en-2-yl acetate (282 mg, 89%).

The product derived from previous step (95 mg, 0.32 mmol) was dissolved in 6 mL CH_2Cl_2 at 0 °C. Et_3N (270 μL, 2.92 mmol), DMSO (400 μL) and $Py{\cdot}SO_3$ (152 mg, 0.972 mmol) were added

into the reaction sequentially. The mixture was kept at 0 °C for 15 min, then allowed to room temperature and stirred overnight. The reaction was quenched with H_2O at 0 °C and diluted with Et_2O. The organic layer was washed with H_2O three times, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc in Hexane) to give desired product **1.65** (50 mg, 53 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.8 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.85 (d, *J* = 1.8 Hz, 1H), 4.83 (d, *J* = 1.8 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.09 (tt, *J* = 6.3, 6.3 Hz, 1H), 3.79 (s, 3H), 2.72 (dd, *J* = 2.4, 7.5 Hz, 1H), 2.67-2.57 (m, 2H), 2.48 (dd, *J* = 6.3, 14.7 Hz, 1H), 2.09 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 200.8, 169.0, 159.3, 152.2, 129.8, 129.5, 113.8, 104.7, 71.3, 71.2, 55.2, 48.0, 38.1, 21.0; IR (neat) 2919, 2839, 2730, 2360, 1754, 1724, 1666, 1612, 1514, 1370, 1302, 1248, 1197, 1083, 1032, 822 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}O_5Na$ $(M+Na)^+$ 315.1208, found 315.1196

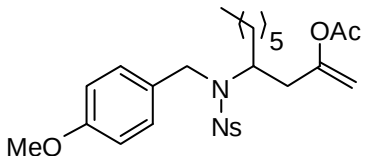
2-((2,6-*cis*)-6-(4-Methoxyphenyl)-4-oxotetrahydro-2*H*-pyran-2-yl)acetaldehyde



The general cyclization procedure was followed with the substrate **1.65** (50 mg, 0.17 mmol), 2,6-dichloropyridine (76 mg, 0.51 mmol) and 4 Å molecular sieves (100 mg), and DDQ (58 mg, 0.26 mmol) in 2 mL anhydrous 1,2-dichloroethane. The reaction was stirred for one hour then quenched by Et_3N and was purified by flash chromatography (20% EtOAc in hexane) to give the desired product (18 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (t, *J* = 1.8 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.66 (dd, *J* = 4.5, 9.9 Hz, 1H), 4.40-4.29 (dddd, *J* = 3.0, 4.8, 7.8, 7.8 Hz, 1H), 3.78 (s, 3H), 2.88 (ddd, *J* = 2.1, 7.5, 16.8 Hz, 1H), 2.68 (ddd, *J* = 1.2, 4.5, 16.8 Hz, 1H), 2.64-2.38 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 205.4, 199.3, 159.5, 132.3, 127.0, 114.0,

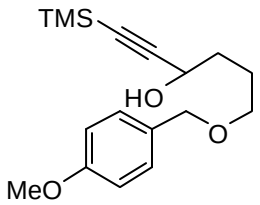
78.5, 72.2, 55.3, 49.4, 49.0, 47.1; HRMS (EI) calcd for $C_{14}H_{16}O_4Na$ $(M+Na)^+$ 271.0946, found 271.0942.

4-(*N*-(4-methoxybenzyl)-3-nitrophenylsulfonamido)dec-1-en-2-yl acetate (1.23)



N-(dec-1-yn-4-yl)-*N*-(4-methoxybenzyl)-3-nitrobenzenesulfonamide (102 mg, 0.222 mmol) was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (30% EtOAc in Hexane) twice to give desired product **1.23** (70 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 0.9 Hz, 1H), 7.67-7.49 (m, 3H), 7.25 (d, *J* = 8.7 Hz, 2H), 6,78 (d, *J* = 8.4 Hz, 2H), 4.71 (s, 1H), 4.70 (s, 1H), 4.60 (d, *J* = 15.9 Hz, 1H), 4.25 (d, *J* = 15.6 Hz, 1H), 4.03-3.92 (m, 1H), 3.78 (s, 3H), 2.48 (dd, *J* = 3.9, 14.1 Hz, 1H), 2.18 (s, 3H), 2.12-1.98 (m, 1H), 1.62-1.34 (m, 2H), 1.25-0.90 (m, 8H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 169.2, 159.2, 152.7, 147.7, 134.3, 133.1, 131.2, 131.2, 129.9, 129.0, 123.9, 113.8, 104.6, 56.4, 55.2, 47.3, 40.1, 31.6, 31.5, 28.8, 25.9, 22.4, 21.0, 14.0; HRMS (EI) calcd for $C_{26}H_{34}N_2O_7NaS$ $(M+Na)^+$ 541.1984, found 541.1962.

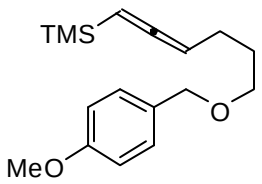
6-(4-Methoxybenzyloxy)-1-(trimethylsilyl)hex-1-yn-3-ol (1.46)



To a stirring THF (30 mL) solution of trimethylsilyl acetylene (1.75 mL, 12.4 mmol) at 0 °C was added ^{n}BuLi (1.6 M, 7.00 mL, 11.2 mmol) dropwisely. The reaction was kept at 0 °C for 45 min then transferred into the solution of 4-(4-methoxybenzyloxy)butanal (517 mg, 2.48 mmol in 15 mL THF) at 0 °C. The mixture was stirred for one hour at 0 °C then quenched with aq. NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over $MgSO_4$ and concentrated.

The resulting residue was purified by flash chromatography (20% EtOAc in Hexane) to give desired product **1.46** (508 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.44 (s, 2H), 4.41-4.32 (m, 1H), 3.76 (s, 3H), 3.61 (d, *J* = 5.4 Hz, 1H), 3.48 (br, 2H), 1.90-1.70 (m, 4H), 0.17 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 158.8, 129.9, 129.0, 113.5, 106.9, 88.4, 72.1, 69.3, 61.9, 54.8, 34.6, 25.1, –0.4; IR (neat) 3399 (br), 2956, 2858, 1612, 1513, 1249, 1173, 1150, 1094, 1034, 843, 760 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{26}O_3NaSi$ $(M+Na)^+$ 329.1549, found 329.1549.

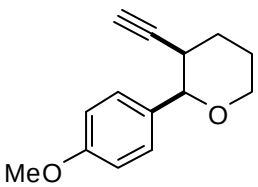
(6-(4-Methoxybenzyloxy)hexa-1,2-dienyl)trimethylsilane (1.24)



To a stirring THF (10 mL) solution of PPh_3 (652 mg, 2.49 mmol) at –10 °C was added DIAD (504 mg, 2.49 mmol) and the reaction was kept at the same temperature for 10 min. Then **1.46** (508 mg, 1.66 mmol) dissolved in 10 mL THF was added into the reaction at –10 °C. After another 10 min, 2-nitrobenzenesulfonohydrazide (901 mg, 4.15 mmol) in 10 mL THF was added into the reaction. The reaction was slowly allowed to room temperature and stirred for 2.5 hours. The crude mixture was directly concentrated under reduced pressure, and the residue was re-dissolved in 10 mL EtOAc. The resulting solution was then added into 400 mL hexane dropwisely to give a pale yellow solution with a lot of precipitation. The mixture was filtered through a plug of silica gel and eluted with 5% EtOAc/Hexane. The filtrate was concentrated and purified by flash chromatography (5% Et_2O in Hexane) to give desired product **1.24** (334 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 4.98 (dt, *J* = 3.9, 7.2 Hz, 1H), 4.85 (dt, *J* = 6.6, 6.9 Hz, 1H), 4.49 (s, 2H), 3.84 (s, 3H), 3.54 (t, *J* = 6.3 Hz, 2H), 2.12 (ddt,

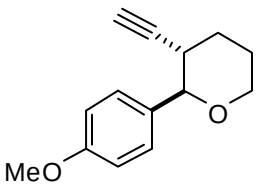
J = 3.9, 6.9, 6.9 Hz 2H), 1.77 (tt, *J* = 6.9, 6.9 Hz, 2H), 0.16 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 209.9, 159.0, 130.6, 129.1, 113.6, 82.8, 82.8, 72.4, 69.4, 55.1, 29.6, 24.3, –0.4.

(2,3-*cis*)-3-Ethynyl-2-(4-methoxyphenyl)tetrahydro-2H-pyran (*cis*-1.66)



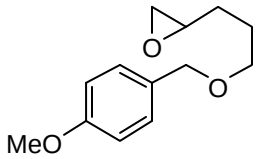
The general cyclization procedure was followed with the substrate **1.24** (101 mg, 0.348 mmol), 2,6-dichloropyridine (206 mg, 1.39 mmol) and 4 Å molecular sieves (202 mg), and DDQ (158 mg, 0.697 mmol) in 3.5 mL anhydrous 1,2-dichloroethane. The reaction was stirred for fifteen min then quenched by Et_3N. The crude mixture was diluted with EtOAc and washed with 4 M HCl three times. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was re-dissolved in 4 mL THF, followed by addition of TBAF (1 M in THF, 4.20 mL, 4.18 mmol). The reaction was stirred at room temperature for two hours, then quenched by adding H_2O. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (60% CH_2Cl_2 in Hexane then 10%→15% EtOAc in Hexane) to give the mixture of *cis*- and *trans*-**1.66** (49 mg, 65% combined yield, d.r. = 1:1 by NMR). The two diastereomers were separated by flash chromatography (1%→1.5% EtOAc in Toluene). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.41 (d, *J* = 2.4 Hz, 1H), 4.22 (dd, *J* = 4.2, 11.8 Hz, 1H), 3.80 (s, 3H), 3.58 (ddd, *J* = 3.0, 11.8, 11.8 Hz, 1H), 2.86 (br, 1H), 2.30-2.05 (m, 2H), 2.00 (d, *J* = 2.1 Hz, 1H), 2.02-1.87 (m, 1H), 1.55-1.44 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 158.8, 133.1, 127.0, 113.3, 83.4, 80.0, 70.7, 69.4, 55.2, 34.4, 29.6, 21.6; IR (neat) 3269, 2946, 2924, 2861, 1612, 1583, 1514, 1458, 1439, 1362, 1305, 1251, 1213, 1176, 1150, 1107, 1086, 1031, 976, 844, 821, 787, 771, 737 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{16}O_2$ (M^+) 216.1150, found 216.1145.

(2,3-*trans*)-3-Ethynyl-2-(4-methoxyphenyl)tetrahydro-2H-pyran (*trans*-1.66)



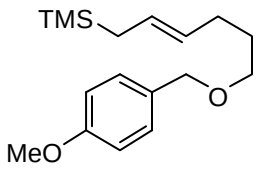
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.13 (d, *J* = 9.9 Hz, 1H), 4.14-4.05 (m, 1H), 3.80 (s, 3H), 3.58 (ddd, *J* = 3.0, 11.4, 11.4 Hz, 1H), 2.62-2.48 (m, 1H), 2.33-2.21 (m, 1H), 1.96 (d, *J* = 2.1 Hz, 1H), 1.84-1.60 (m, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 159.3, 132.9, 129.4, 113.5, 84.6, 83.2, 70.7, 68.7, 55.2, 35.6, 31.2, 25.3; IR (neat) 3289, 2926, 2851, 1613, 1514, 1461, 1302, 1245, 1175, 1090, 1079, 1035, 950, 822 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{16}O_2$ (M^+) 216.1150, found 216.1150.

2-(3-(4-Methoxybenzyloxy)propyl)oxirane (1.48)



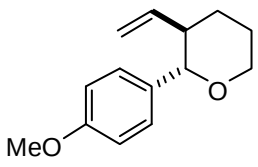
1-Methoxy-4-((pent-4-enyloxy)methyl)benzene (486 mg, 2.36 mmol) was dissolved in 10 mL CH_2Cl_2 at 0 °C, followed by addition of NaOAc (397 mg, 4.72 mmol) and *m*CPBA (70%, 872 mg, 3.54 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction was quenched by adding 1:1 aq. $NaHCO_3$ and $Na_2S_2O_3$ at 0 °C. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (15% EtOAc in Hexane) to give desired product **1.48** (338 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.56-3.42 (m, 2H), 2.96-2.89 (m, 1H), 2.73 (dd, *J* = 4.8, 4.8 Hz, 1H), 2.46 (dd, *J* = 2.7, 4.8 Hz, 1H), 1.82-1.70 (m, 2H), 1.70-1.53 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 159.0, 130.4, 129.1, 113.6, 72.4, 69.3, 55.1, 51.9, 46.9, 29.1, 26.0; IR (neat) 2934, 2857, 1723, 1612, 1513, 1462, 1301, 1247, 1174, 1096, 1034, 822 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1258.

(*E*)-(6-(4-Methoxybenzyloxy)hex-2-enyl)trimethylsilane (1.25)



To 2,2,6,6-tetramethylpiperidine (322 mg, 2.28 mmol) in 15 mL THF at 0 °C was added ^{n}BuLi (1.6 M, 1.43 mL) dropwisely. The mixture was stirred at this temperature for 15 min, then $TMSCH_2Li$ (1.0 M, 7.60 mL) was added into the reaction. After 5 min, **1.48** (338 mg, 1.52 mmol) in 3 mL THF was added into the reaction. Then it was allowed to room temperature and stirred for 15 min while the reaction turned dark red. The reaction was quenched by adding aq. NH_4Cl at 0 °C. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (70% CH_2Cl_2 in Hexane) to give desired product **1.25** (103 mg, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.39 (dt, *J* = 7.8, 15.0 Hz, 1H), 5.21 (dt, *J* = 6.6, 15.0 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.06 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.65 (tt, *J* = 6.9, 6.9 Hz, 2H), 1.39 (d, *J* = 7.5 Hz, 2H), –0.02 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 159.1, 130.8, 129.2, 128.1, 126.6, 113.7, 72.6, 69.6, 55.3, 30.0, 29.3, 22.6, –2.0; IR (neat) 2951, 2852, 1613, 1513, 1247, 1172, 1100, 1038, 846 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{28}O_2Si$ (M^+) 292.1859, found 292.1869.

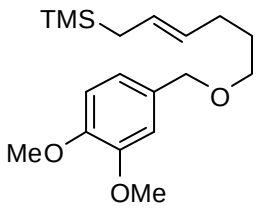
2,3-*trans*-2-(4-Methoxyphenyl)-3-vinyltetrahydro-2*H*-pyran (1.67)



The general cyclization procedure was followed with the substrate **1.25** (103 mg, 0.352 mmol), 2,6-dichloropyridine (208 mg, 1.41 mmol) and 4 Å molecular sieves (206 mg), and DDQ (160 mg, 0.703 mmol) in 4 mL anhydrous 1,2-dichloroethane. The reaction was stirred for 10 min then quenched by Et_3N and was purified by flash chromatography (60% CH_2Cl_2 in Hexane then 8% EtOAc in Hexane) to give the desired product **1.67** (21 mg, 28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz,

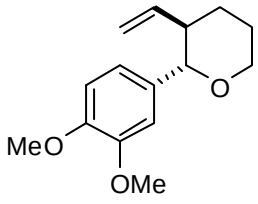
2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.47 (ddd, *J* = 7.2, 9.9, 17.4 Hz, 1H), 4.89-4.80 (m, 2H), 4.10 (ddd, *J* = 1.8, 4.2, 11.1 Hz, 1H), 3.94 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 3H), 3.55 (ddd, *J* = 2.4 Hz, 12.0, 12.0 Hz, 1H), 2.42-2.39 (m, 1H), 2.25-1.93 (m, 1H), 1.83 (ddd, *J* = 4.2, 4.2, 12.6 Hz, 1H), 1.73-1.63 (m, 1H), 1.63-1.48 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 159.1, 139.1, 133.5, 128.6, 115.1, 113.5, 84.5, 68.8, 55.2, 46.4, 29.9, 25.9; IR (neat) 2933, 2838, 1613, 1515, 1302, 1245, 1176, 1099, 1081, 1035, 915, 824 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1306.

(*E*)-(6-(3,4-Dimethoxybenzyloxy)hex-2-enyl)trimethylsilane (1.26)



Compound **1.26** was prepared from 1,2-dimethoxy-4-((pent-4-enyloxy)methyl)benzene similarly as **1.25**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91-6.79 (m, 3H), 5.38 (dt, *J* = 7.8, 15.3 Hz, 1H), 5.22 (dt, *J* = 6.6, 15.0 Hz, 1H), 4.42 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.05 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.65 (tt, *J* = 6.6, 6.6 Hz, 2H), 1.38 (d, *J* = 7.2 Hz, 2H), –0.04 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 148.9, 148.4, 131.2, 127.9, 126.5, 120.1, 110.9, 110.8, 72.7, 69.6, 55.8, 55.7, 30.0, 29.2, 22.5, –2.1; IR (neat) 3000, 2951, 2852, 1593, 1515, 1464, 1418, 1263, 1246, 1156, 1139, 1101, 1031, 850 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{30}O_3Si$ (M^+) 322.1964, found 322.1956.

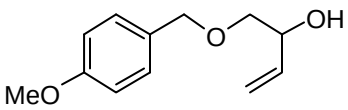
2,3-*trans*-2-(3,4-dimethoxyphenyl)-3-vinyltetrahydro-2*H*-pyran (1.68)



The general cyclization procedure was followed with the substrate **1.26** (68 mg, 0.21 mmol), 2,6-dichloropyridine (125 mg, 0.844 mmol) and 4 Å molecular sieves (136 mg), and DDQ (96 mg, 0.42 mmol) in 2.4 mL anhydrous 1,2-dichloroethane. The reaction was stirred at –20 °C for 45 min then quenched by

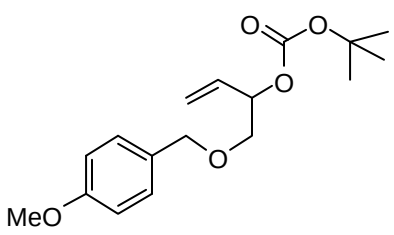
Et_3N. It was purified by flash chromatography (15% EtOAc in Hexane) to give desired product **1.68** (20 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88-6.77 (m, 3H), 5.47 (ddd, *J* = 7.2, 9.9, 17.4 Hz, 1H), 4.89-4.86 (m, 1H), 4.85-4.81 (m, 1H), 4.11 (dddd, *J* = 1.5, 1.5, 4.5, 11.4 Hz, 1), 3.93 (d, *J* = 9.9 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.55 (ddd, *J* = 2.1, 11.7, 11.7 Hz, 1H), 2.42-2.28 (m, 1H), 2.05-1.94 (m, 1H), 1.90-1.74 (m, 1H), 1.73-1.63 (m, 1H), 1.63-1.47 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 148.8, 148.5, 140.0, 133.7, 120.0, 115.1 110.6, 110.3, 84.9, 68.8, 55.8, 46.3, 29.8, 25.8; IR (neat) 2932, 2846, 1516, 1463, 1264, 1233, 1160, 1138, 1080, 1030 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_3$ (M^+) 248.1412, found 248.1414.

1-(4-Methoxybenzyloxy)but-3-en-2-ol (1.52)



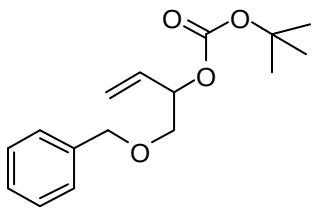
A 50 mL RBF was charged with vinylmagnesium bromide (0.7 M, 11.50 mL) and cooled to 0 °C. Then 2-(4-methoxybenzyloxy)acetaldehyde (1.21 g, 6.73 mmol) in 4 mL THF was added in via syringe. The reaction was stirred at 0 °C for 10 min, then quenched by adding aq. NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in Hexane) to give desired product **1.52** (726 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.84 (ddd, *J* = 5.7, 10.5, 17.1 Hz, 1H), 5.34 (dt, *J* = 1.5, 17.4 Hz, 1H), 5.18 (dt, *J* = 1.2, 10.5 Hz, 1H), 4.50 (s, 2H), 4.40-4.25 (br, 1H), 3.80 (s, 3H), 3.50 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.36 (dd, *J* = 7.8, 9.3 Hz, 1H), 2.90-2.70 (br, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 159.2, 136.6, 129.8, 129.3, 116.1, 113.7, 73.6, 72.9, 71.3, 55.1; IR (neat) 3436 (br), 3003, 2906, 2860, 1612, 1513, 1462, 1361, 1302, 1249, 1176, 1102, 1034, 994, 927, 821 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}O_3$ (M^+) 208.1099, found 208.1101.

***tert*-Butyl 1-(4-methoxybenzyloxy)but-3-en-2-yl carbonate (1.28)**



Compound **1.52** (248 mg, 1.19 mmol) was dissolved in 1.5 mL THF and cooled to -78 °C, followed by dropwise addition of ^{n}BuLi (1.6 M, 0.82 mL). The mixture was stirred for 15 min, then Boc_2O (260 mg, 1.19 mmol) in 1.5 mL THF was added in. The reaction was kept at –78 °C for one hour, then warmed to 0 °C for four hours. The reaction was quenched by adding aq. NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (15% EtOAc in Hexane) to give desired product **1.28** (212 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.84 (ddd, *J* = 6.3, 10.8, 17.1 Hz, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 5.30-5.21 (m, 2H), 4.50 (s, 2H), 3.80 (s, 3H), 3.58 (dd, *J* = 6.9, 10.8 Hz, 1H), 3.53 (dd, *J* = 4.5, 10.8 Hz, 1H), 1.49 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 159.2, 152.8, 133.2, 129.9, 129.2, 118.1, 113.7, 82.1, 76.1, 72.8, 70.9, 55.2, 27.7; IR (neat) 2980, 2936, 2863, 1742, 1613, 1513, 1461, 1368, 1276, 1252, 1167, 1091, 1036, 931, 844 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{24}O_5$ (M^+) 308.1624, found 308.1634.

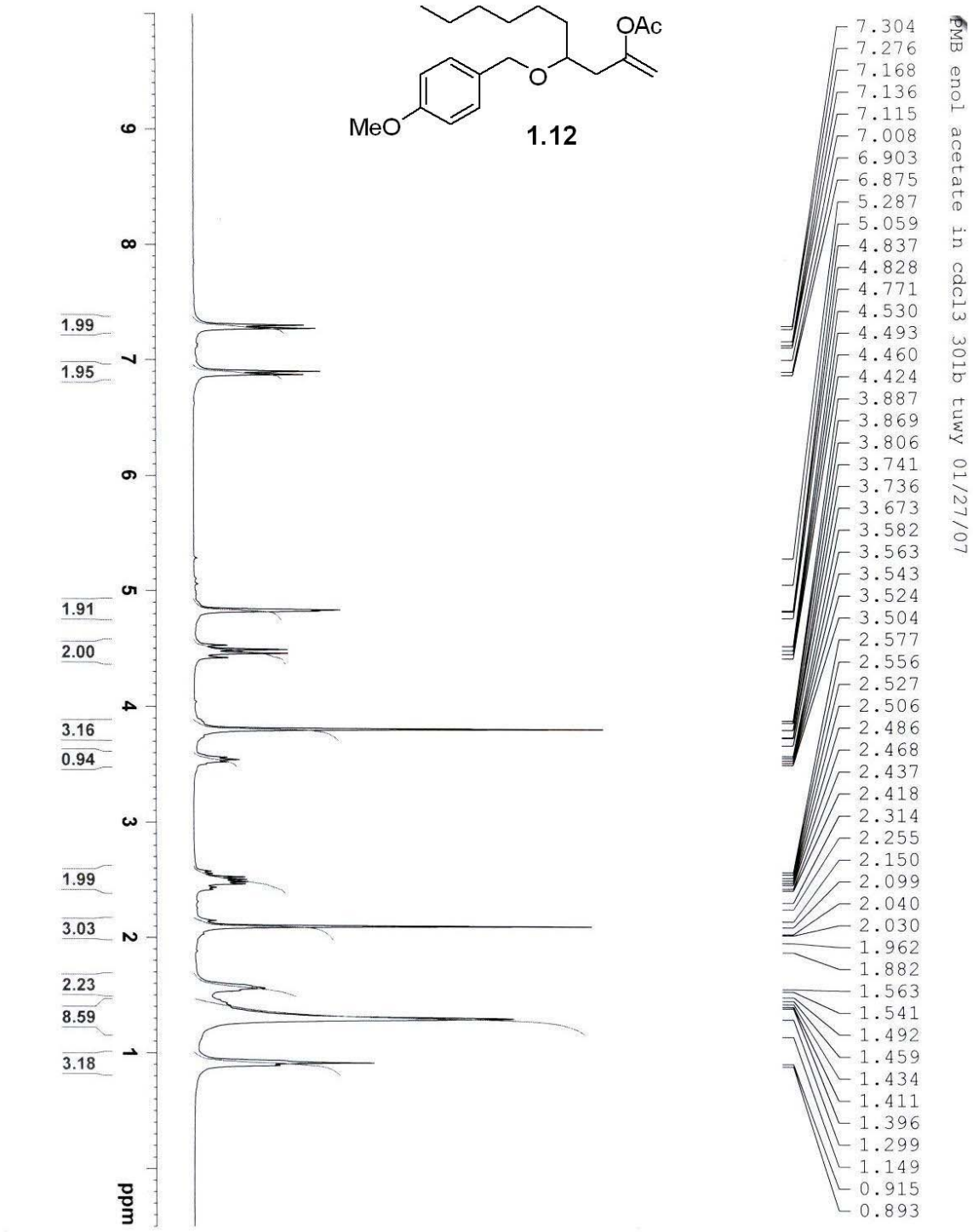
1-(Benzyloxy)but-3-en-2-yl tert-butyl carbonate (1.27)

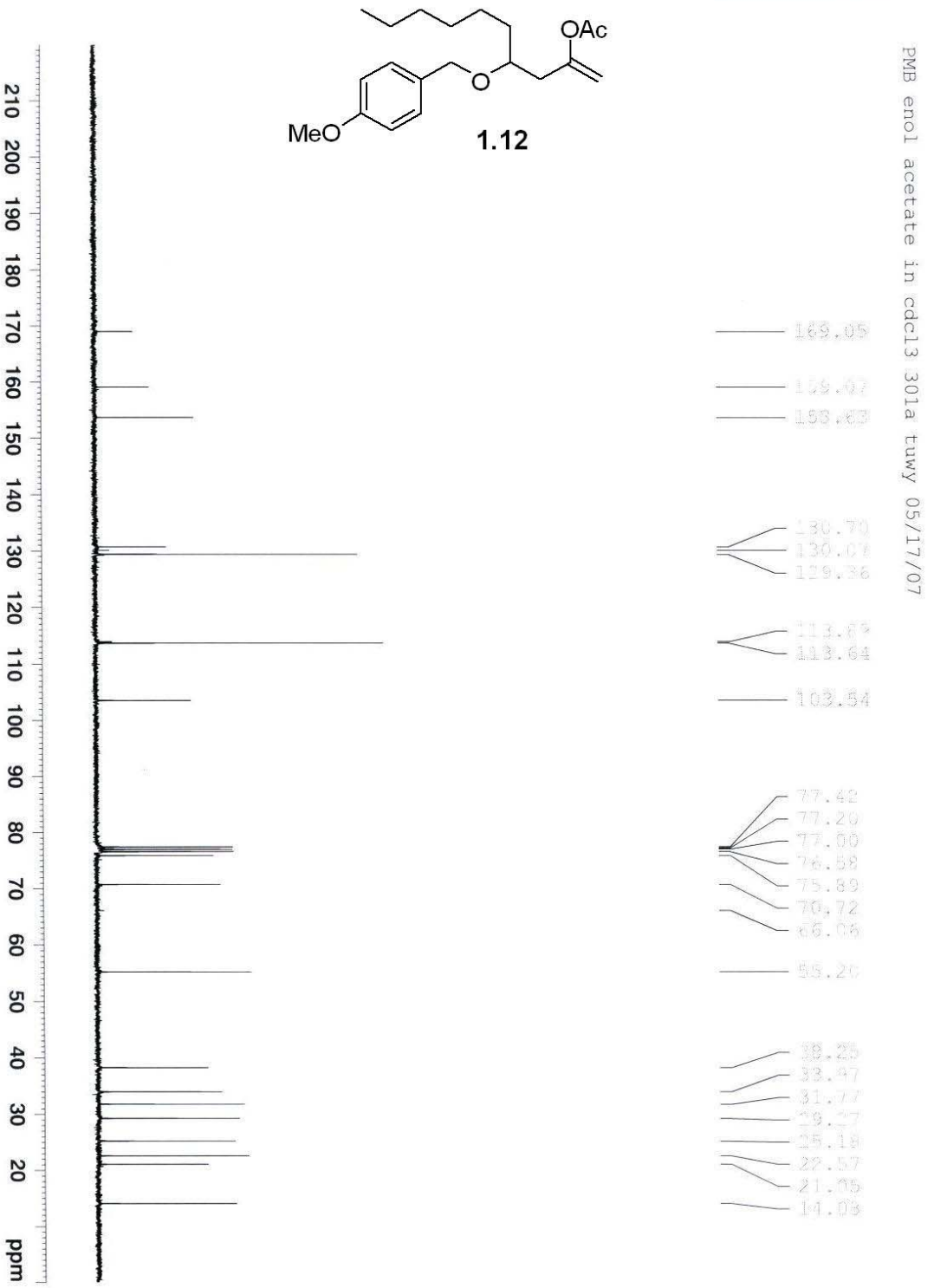


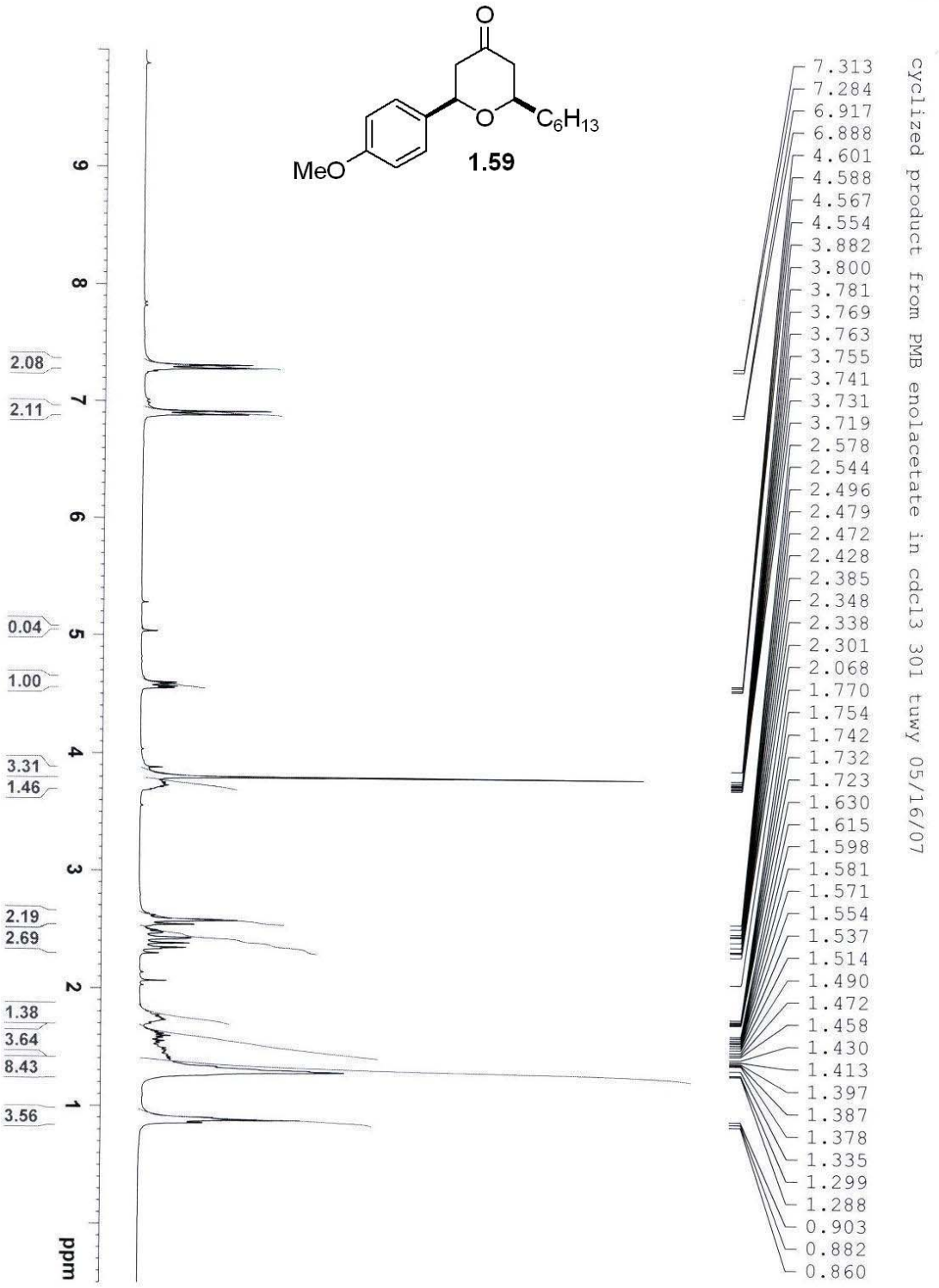
Compound **1.27** was prepared from 2-(benzyloxy)acetaldehyde similarly as **1.28**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.85 (ddd, *J* = 6.3, 10.8, 17.1 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.31-5.19 (m, 2H), 4.57 (s, 2H), 3.66-3.52 (m, 2H), 1.49 (s, 9H).

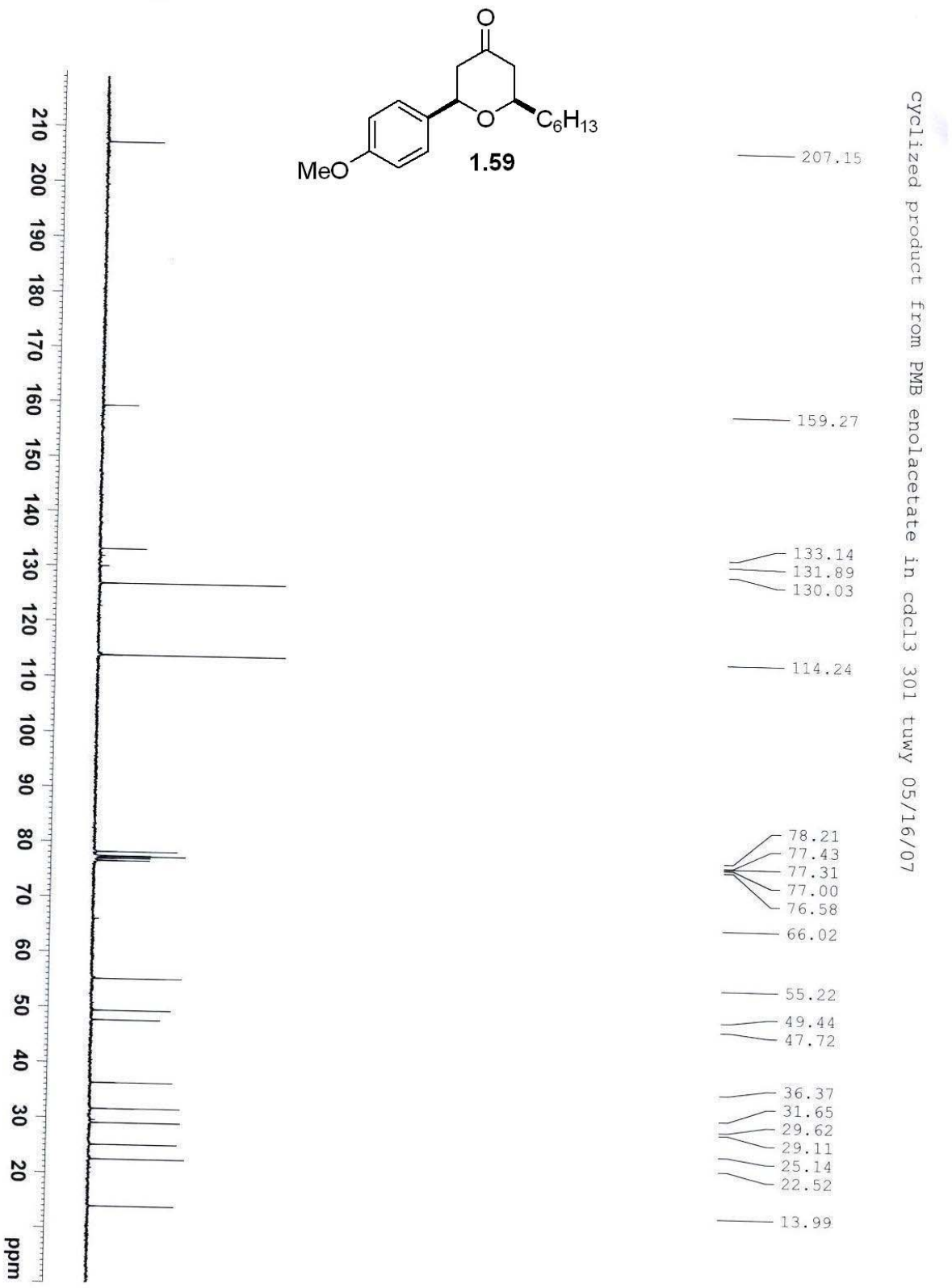
1. Miura, K., Hondo, T., Okajima, S., Nakagawa, T., Takahashi, T., Hosomi, A. *J. Org. Chem.* **2002**, 67, 6082.

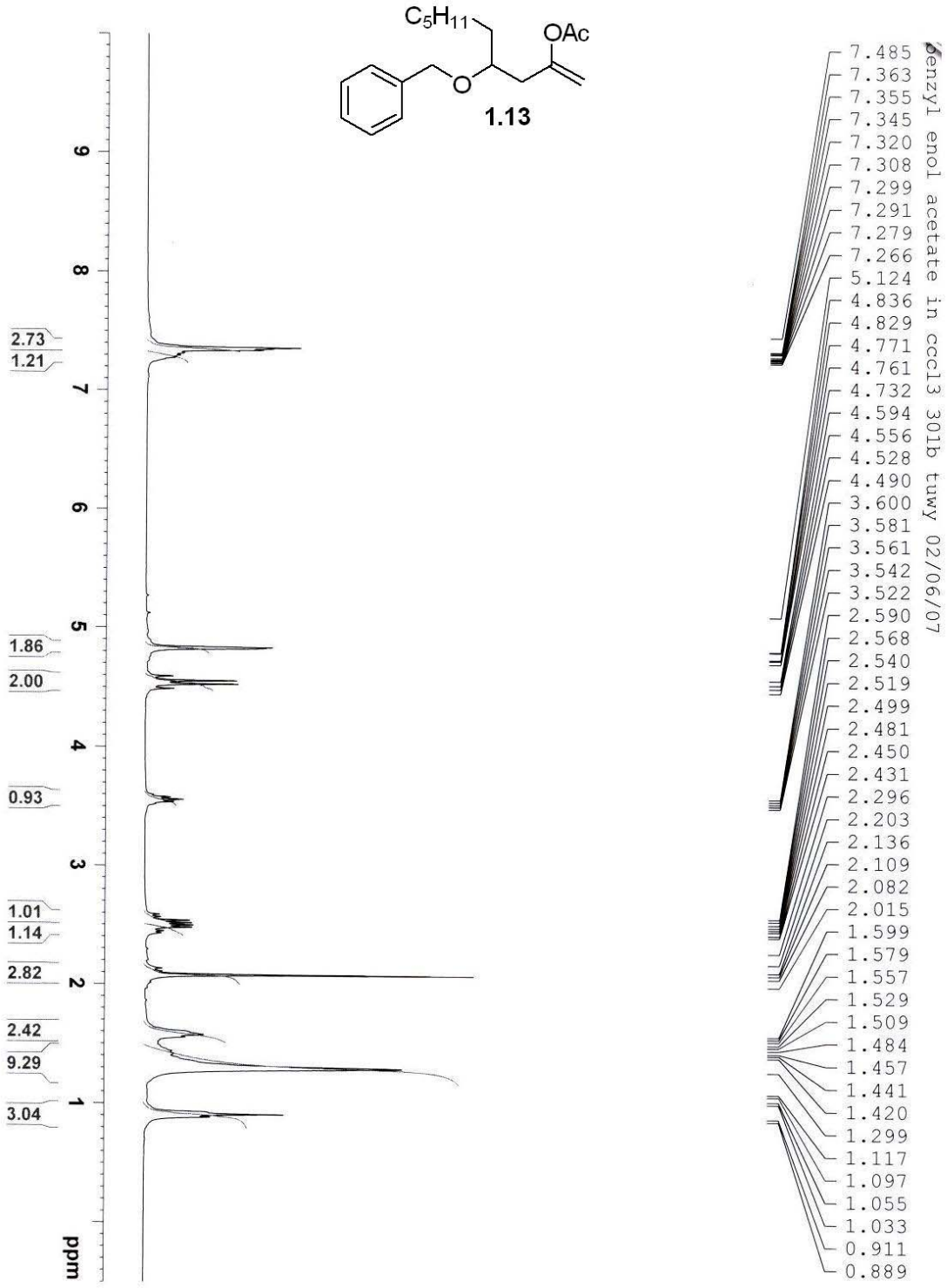
2. Gea, A., Farcy, N., Rossell, N.R., Martins, J.C., De Clercq, P.J., Madder, A. *Eur. J. Org. Chem.* **2006**, 4135.


OAc
O
MeO
1.12
PMB enol acetate in cdcl3 301b tuwy 01/27/07
7.304
7.276
7.168
7.136
7.115
7.008
6.903
6.875
5.287
5.059
4.837
4.828
4.771
4.530
4.493
4.460
4.424
3.887
3.869
3.806
3.741
3.736
3.673
3.582
3.563
3.543
3.524
3.504
2.577
2.556
2.527
2.506
2.486
2.468
2.437
2.418
2.314
2.255
2.150
2.099
2.040
2.030
1.962
1.882
1.563
1.541
1.492
1.459
1.434
1.411
1.396
1.299
1.149
0.915
0.893
1.99
1.95
1.91
2.00
3.16
0.94
1.99
3.03
2.23
8.59
3.18
ppm


OAc
O
MeO
1.12
PMB enol acetate in cdcl3 301a tuwy 05/17/07
169.05
159.07
158.63
130.70
130.07
129.36
113.69
113.64
103.54
77.42
77.20
77.00
76.58
75.89
70.72
66.06
55.20
39.25
33.97
31.77
29.57
25.18
22.57
21.05
14.03
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


O
MeO
O
C_6H_{13}
1.59
cyclized product from PMB enolacetate in cdcl3 301 tuwy 05/16/07
7.313
7.284
6.917
6.888
4.601
4.588
4.567
4.554
3.882
3.800
3.781
3.769
3.763
3.755
3.741
3.731
3.719
2.578
2.544
2.496
2.479
2.472
2.428
2.385
2.348
2.338
2.301
2.068
1.770
1.754
1.742
1.732
1.723
1.630
1.615
1.598
1.581
1.571
1.554
1.537
1.514
1.490
1.472
1.458
1.430
1.413
1.397
1.387
1.378
1.335
1.299
1.288
0.903
0.882
0.860
2.08
2.11
0.04
1.00
3.31
1.46
2.19
2.69
1.38
3.64
8.43
3.56
ppm


cyclized product from PMB enolacetate in cdcl3 301 tuwy 05/16/07
O
O
C_6H_{13}
MeO
1.59
207.15
159.27
133.14
131.89
130.03
114.24
78.21
77.43
77.31
77.00
76.58
66.02
55.22
49.44
47.72
36.37
31.65
29.62
29.11
25.14
22.52
13.99
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


C_5H_{11}
OAc
O
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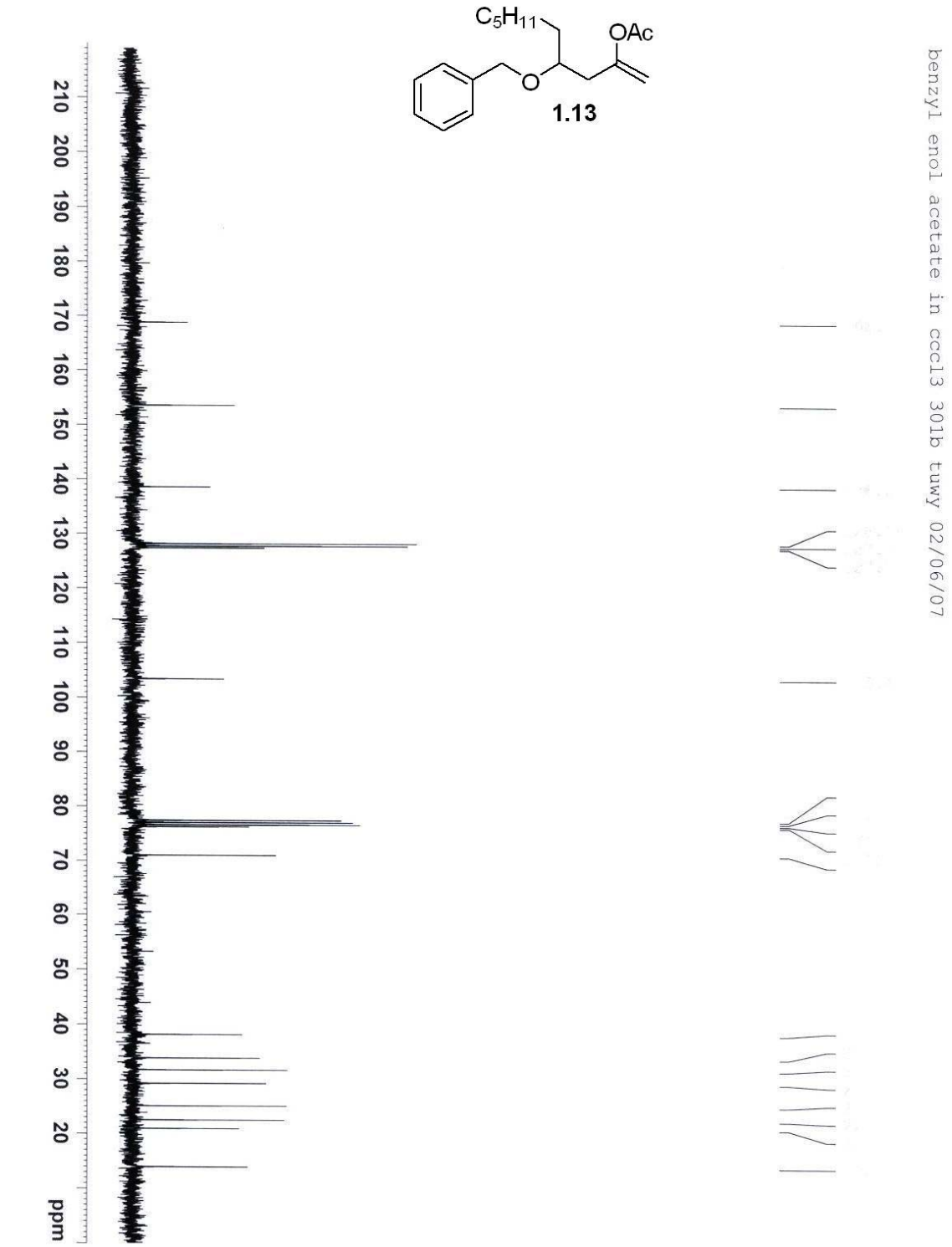
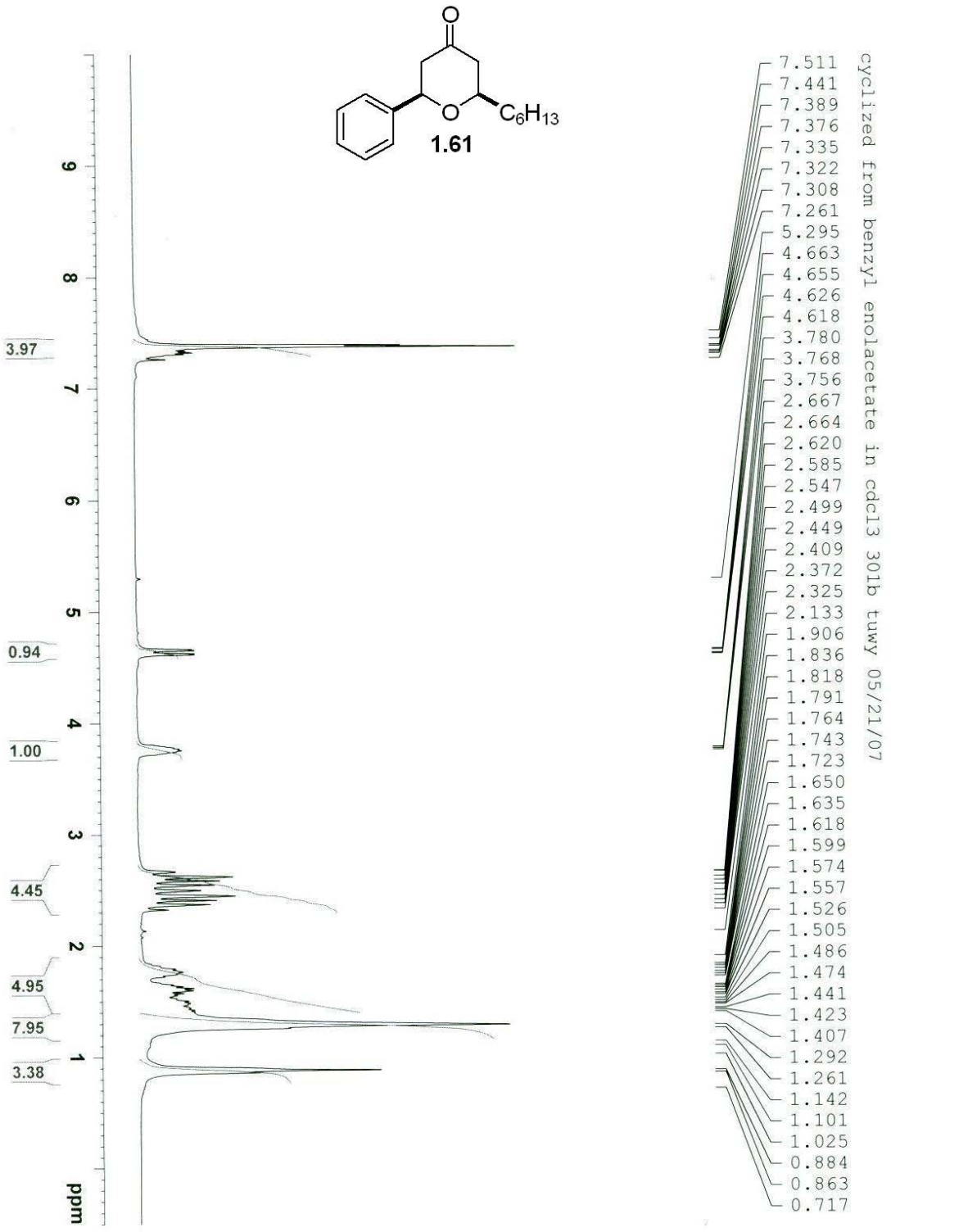
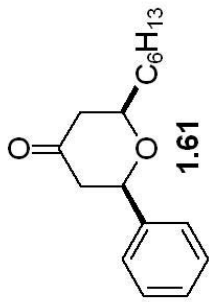
2.73
1.21
1.86
2.00
0.93
1.01
1.14
2.82
2.42
9.29
3.04
ppm
benzyl enol acetate in cccl3 301b tuwy 02/06/07
7.485
7.363
7.355
7.345
7.320
7.308
7.299
7.291
7.279
7.266
5.124
4.836
4.829
4.771
4.761
4.732
4.594
4.556
4.528
4.490
3.600
3.581
3.561
3.542
3.522
2.590
2.568
2.540
2.519
2.499
2.481
2.450
2.431
2.296
2.203
2.136
2.109
2.082
2.015
1.599
1.579
1.557
1.529
1.509
1.484
1.457
1.441
1.420
1.299
1.117
1.097
1.055
1.033
0.911
0.889

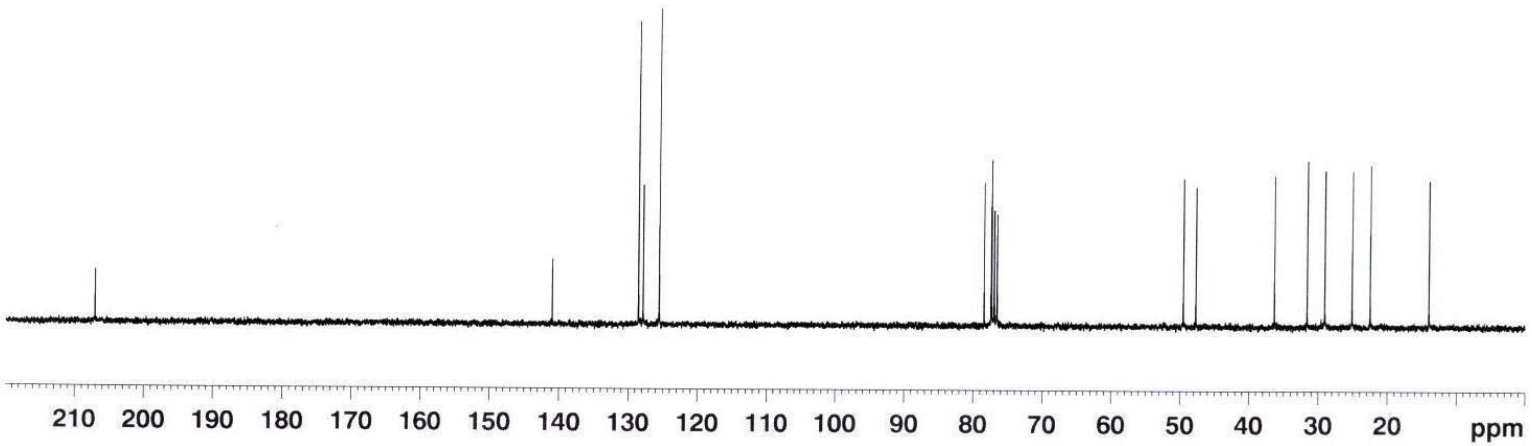

benzyl enol acetate in ccl3 301b tuwy 02/06/07
C5H11
OAc
O
1.13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

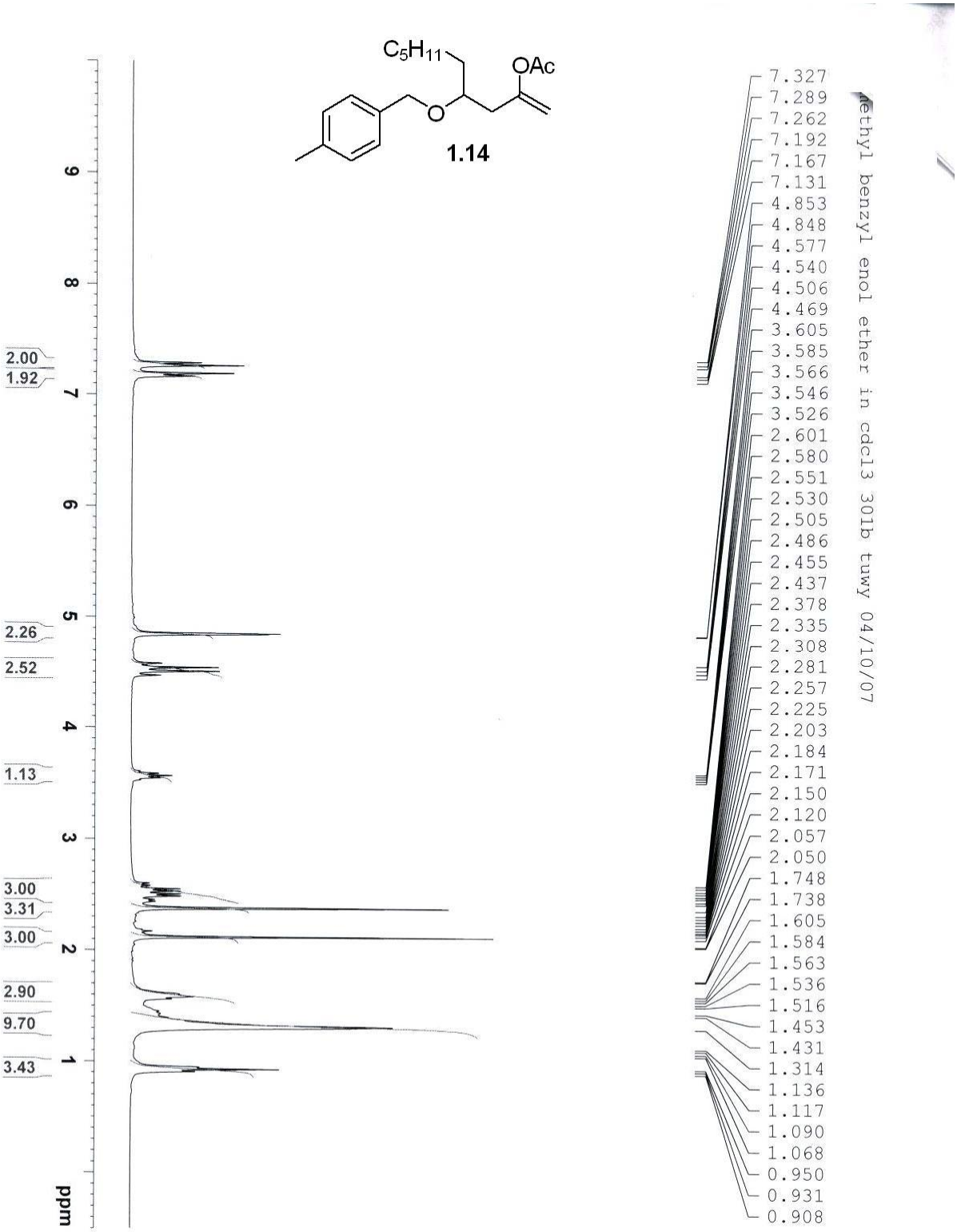

O
O
C_6H_{13}
1.61
3.97
0.94
1.00
4.45
4.95
7.95
3.38
9
8
7
6
5
4
3
2
1
ppm
cyclized from benzyl enolacetate in cdcl3 301b tuwy 05/21/07
7.511
7.441
7.389
7.376
7.335
7.322
7.308
7.261
5.295
4.663
4.655
4.626
4.618
3.780
3.768
3.756
2.667
2.664
2.620
2.585
2.547
2.499
2.449
2.409
2.372
2.325
2.133
1.906
1.836
1.818
1.791
1.764
1.743
1.723
1.650
1.635
1.618
1.599
1.574
1.557
1.526
1.505
1.486
1.474
1.441
1.423
1.407
1.292
1.261
1.142
1.101
1.025
0.884
0.863
0.717

cyclized Benzyl enolacetate in cdcl3 301a tuwy 05/19/07

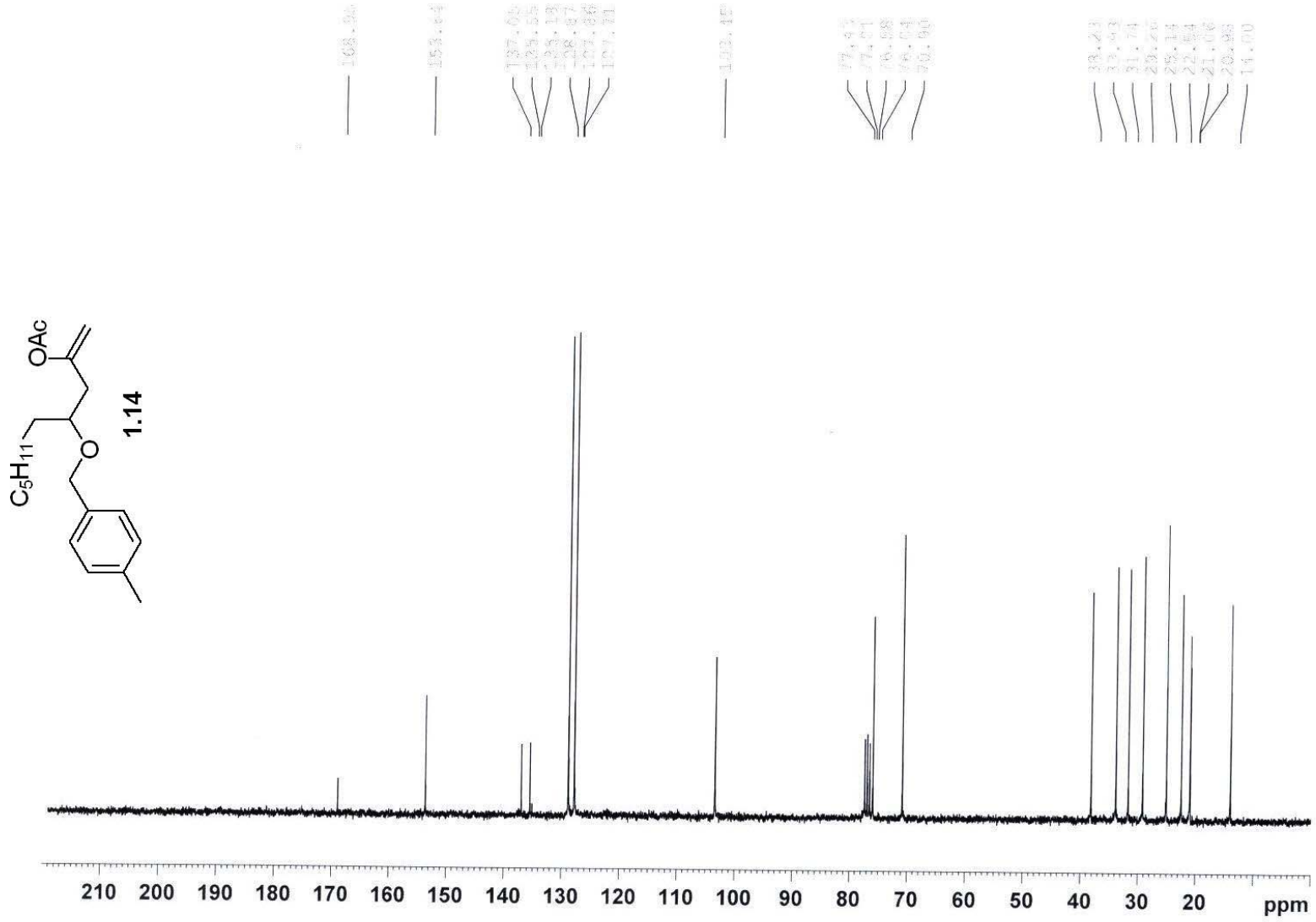


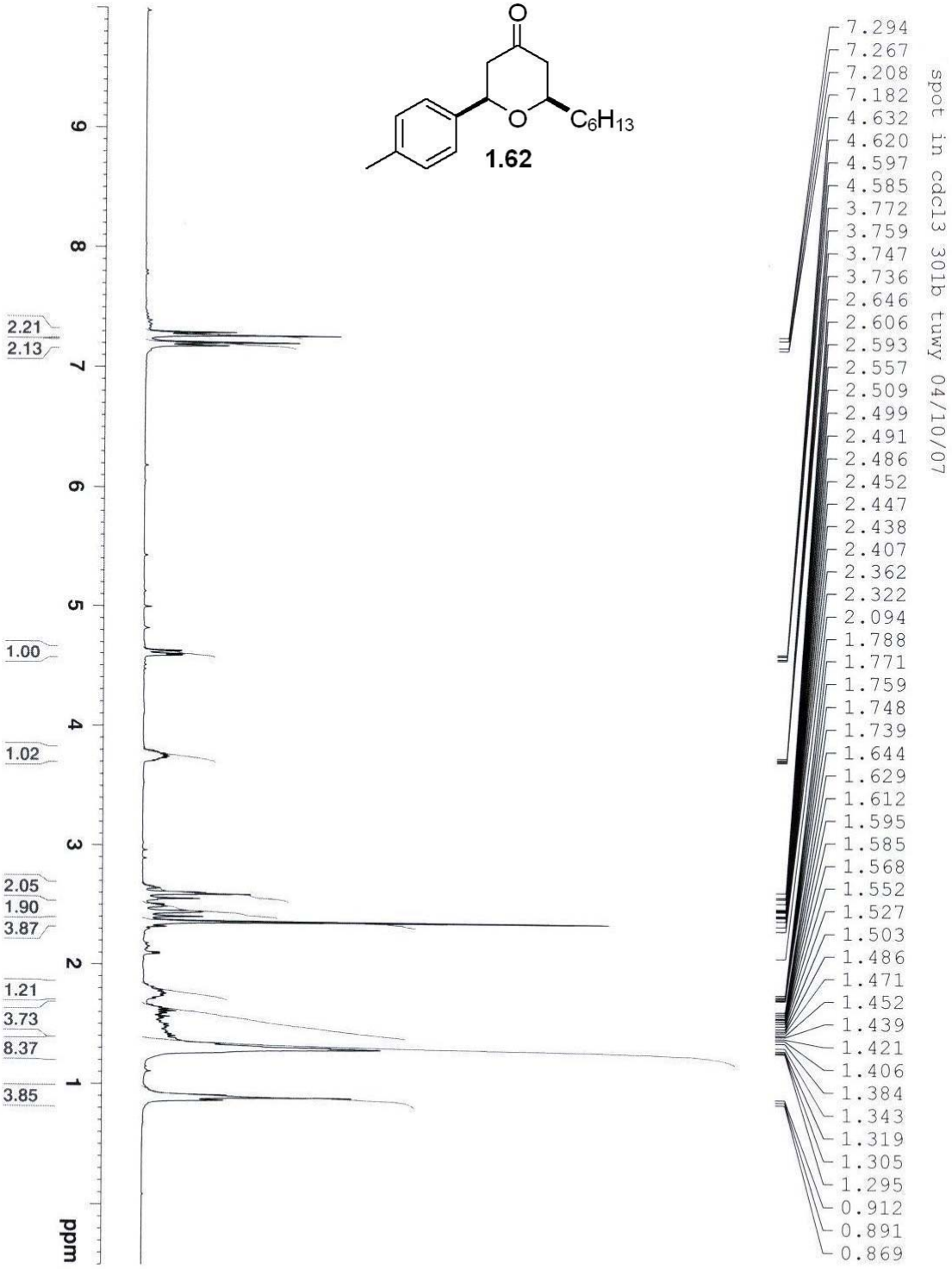
1.61

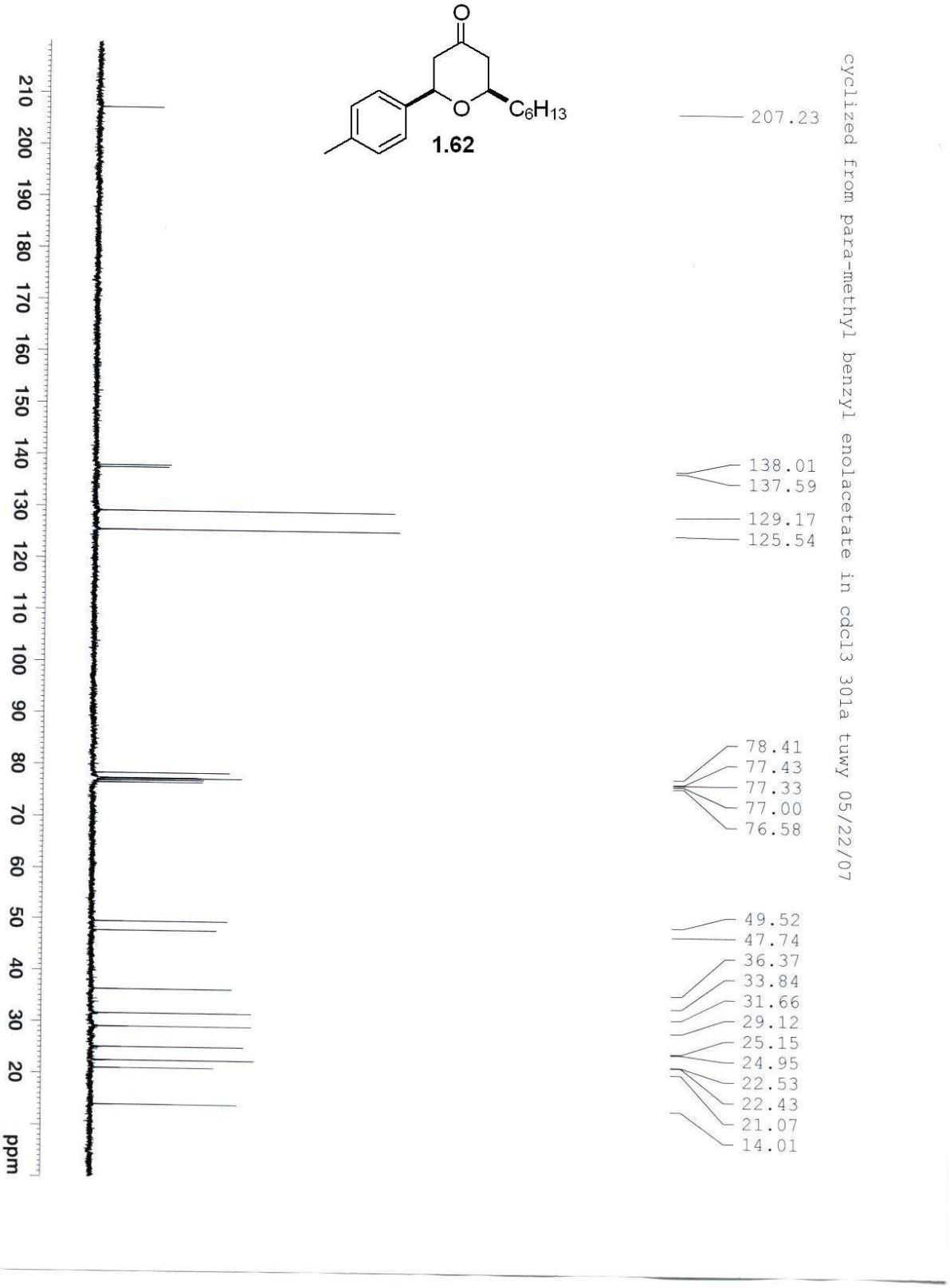


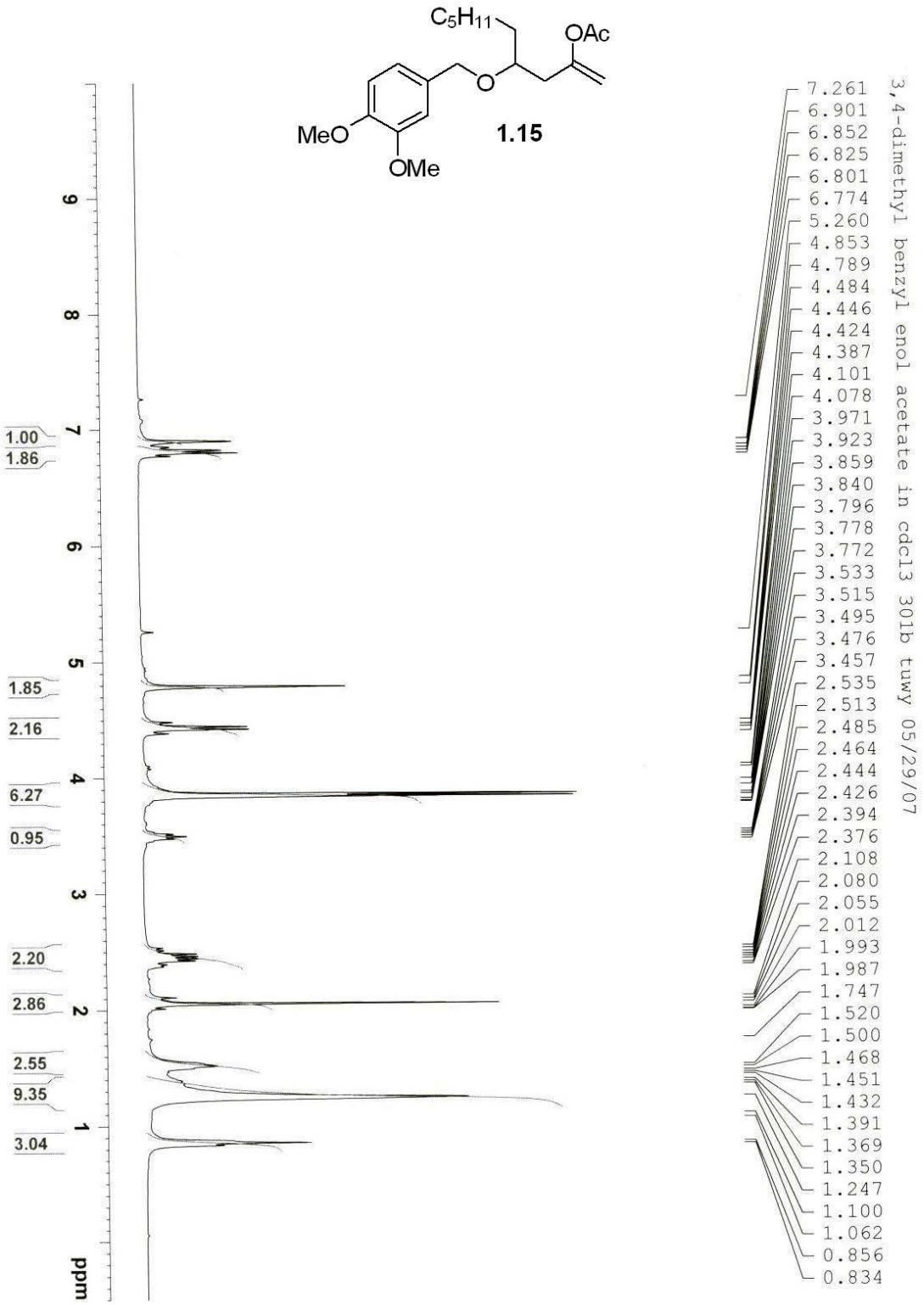

C5H11
OAc
O
1.14
ppm
2.00
1.92
2.26
2.52
1.13
3.00
3.31
3.00
2.90
9.70
3.43
ethyl benzyl enol ether in cdcl3 301b tuwy 04/10/07
7.327
7.289
7.262
7.192
7.167
7.131
4.853
4.848
4.577
4.540
4.506
4.469
3.605
3.585
3.566
3.546
3.526
2.601
2.580
2.551
2.530
2.505
2.486
2.455
2.437
2.378
2.335
2.308
2.281
2.257
2.225
2.203
2.184
2.171
2.150
2.120
2.057
2.050
1.748
1.738
1.605
1.584
1.563
1.536
1.516
1.453
1.431
1.314
1.136
1.117
1.090
1.068
0.950
0.931
0.908

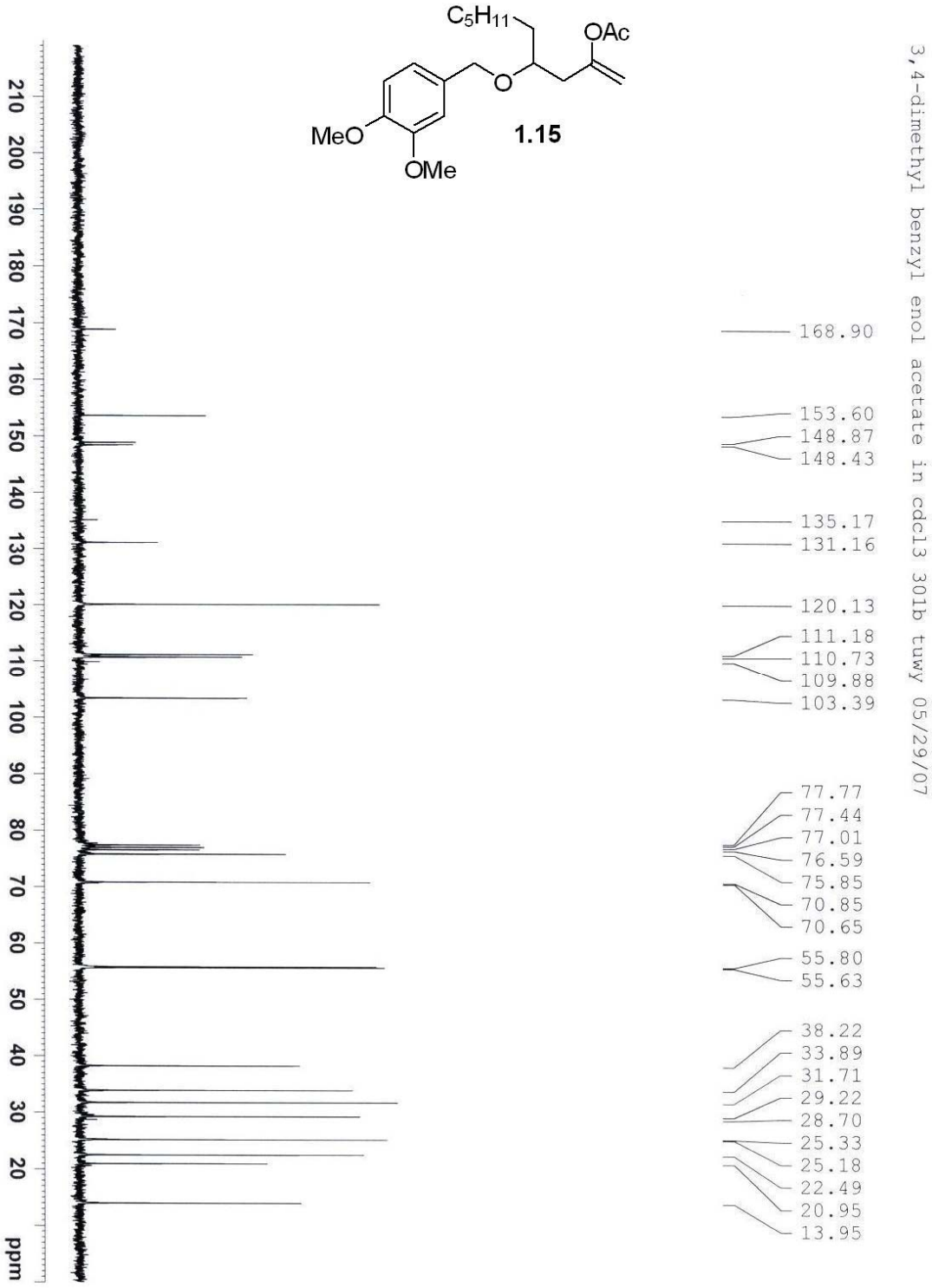
p-methyl benzyl enol ether in cdcl3 301b tuwy 04/10/07

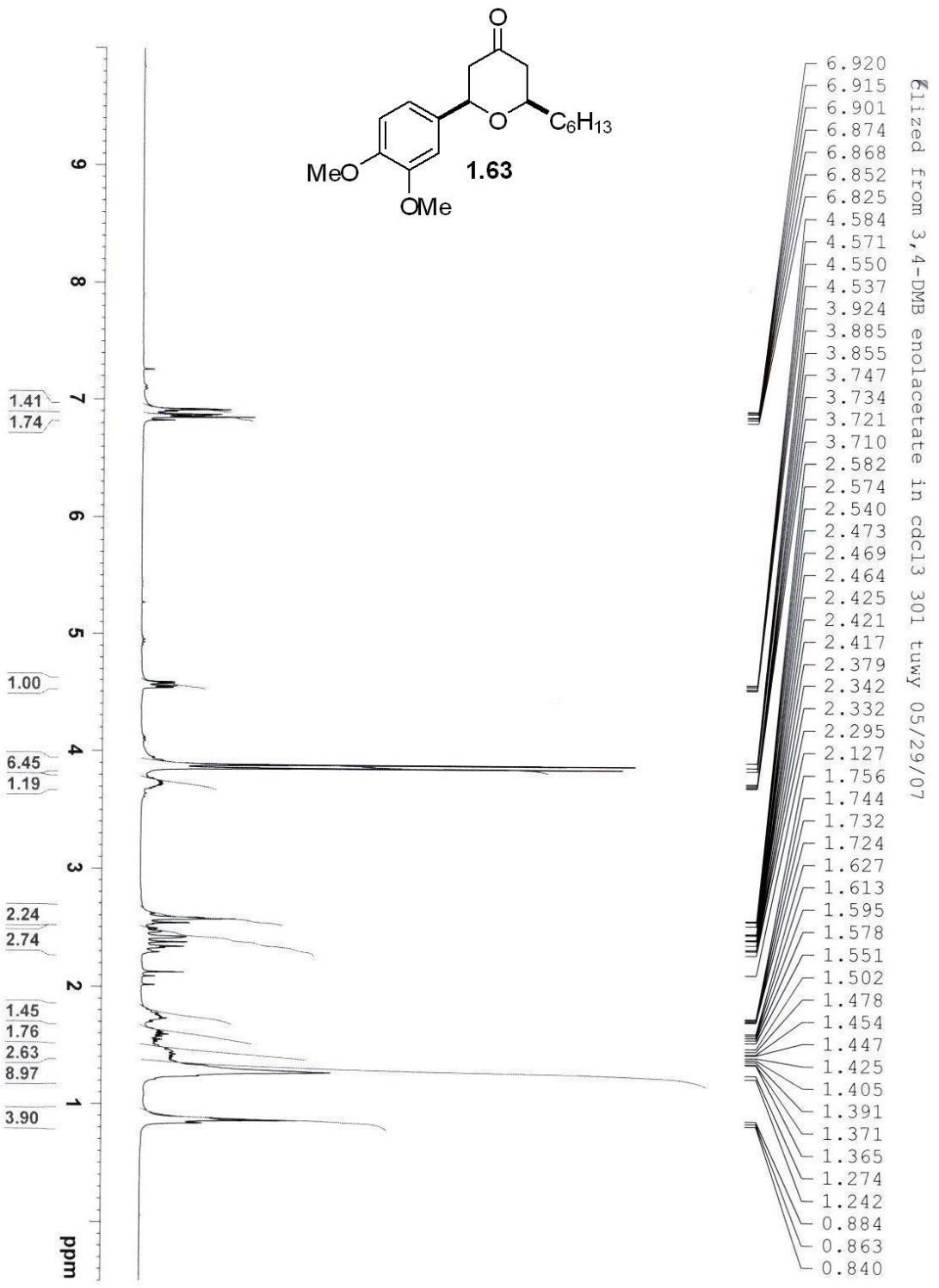



O
O
C6H13
1.62
spot in cdcl3 301b tuwy 04/10/07
7.294
7.267
7.208
7.182
4.632
4.620
4.597
4.585
3.772
3.759
3.747
3.736
2.646
2.606
2.593
2.557
2.509
2.499
2.491
2.486
2.452
2.447
2.438
2.407
2.362
2.322
2.094
1.788
1.771
1.759
1.748
1.739
1.644
1.629
1.612
1.595
1.585
1.568
1.552
1.527
1.503
1.486
1.471
1.452
1.439
1.421
1.406
1.384
1.343
1.319
1.305
1.295
0.912
0.891
0.869
2.21
2.13
1.00
1.02
2.05
1.90
3.87
1.21
3.73
8.37
3.85
ppm

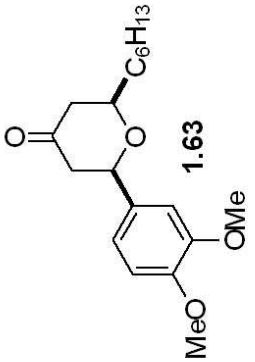

cyclized from para-methyl benzyl enolacetate in cdcl3 301a tuwy 05/22/07
1.62
207.23
138.01
137.59
129.17
125.54
78.41
77.43
77.33
77.00
76.58
49.52
47.74
36.37
33.84
31.66
29.12
25.15
24.95
22.53
22.43
21.07
14.01
ppm

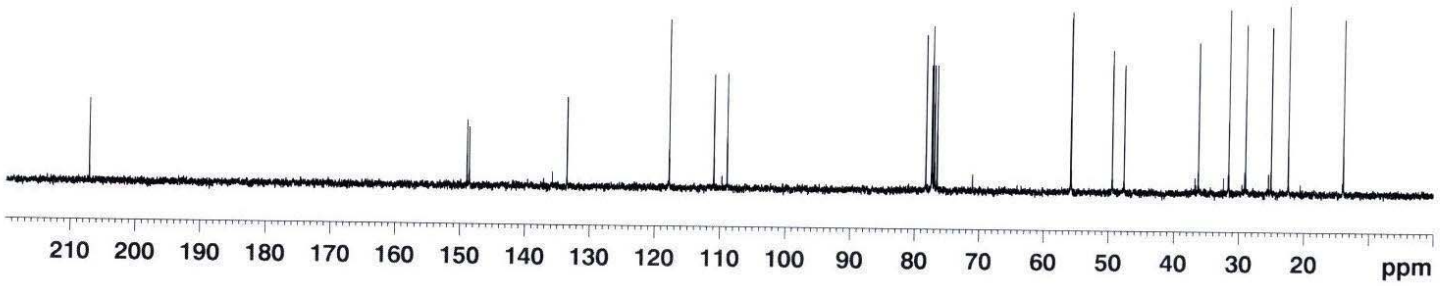

C5H11
OAc
O
MeO
OMe
1.15
1.00
1.86
1.85
2.16
6.27
0.95
2.20
2.86
2.55
9.35
3.04
ppm
3,4-dimethyl benzyl enol acetate in cdcl3 301b tuwy 05/29/07
7.261
6.901
6.852
6.825
6.801
6.774
5.260
4.853
4.789
4.484
4.446
4.424
4.387
4.101
4.078
3.971
3.923
3.859
3.840
3.796
3.778
3.772
3.533
3.515
3.495
3.476
3.457
2.535
2.513
2.485
2.464
2.444
2.426
2.394
2.376
2.108
2.080
2.055
2.012
1.993
1.987
1.747
1.520
1.500
1.468
1.451
1.432
1.391
1.369
1.350
1.247
1.100
1.062
0.856
0.834

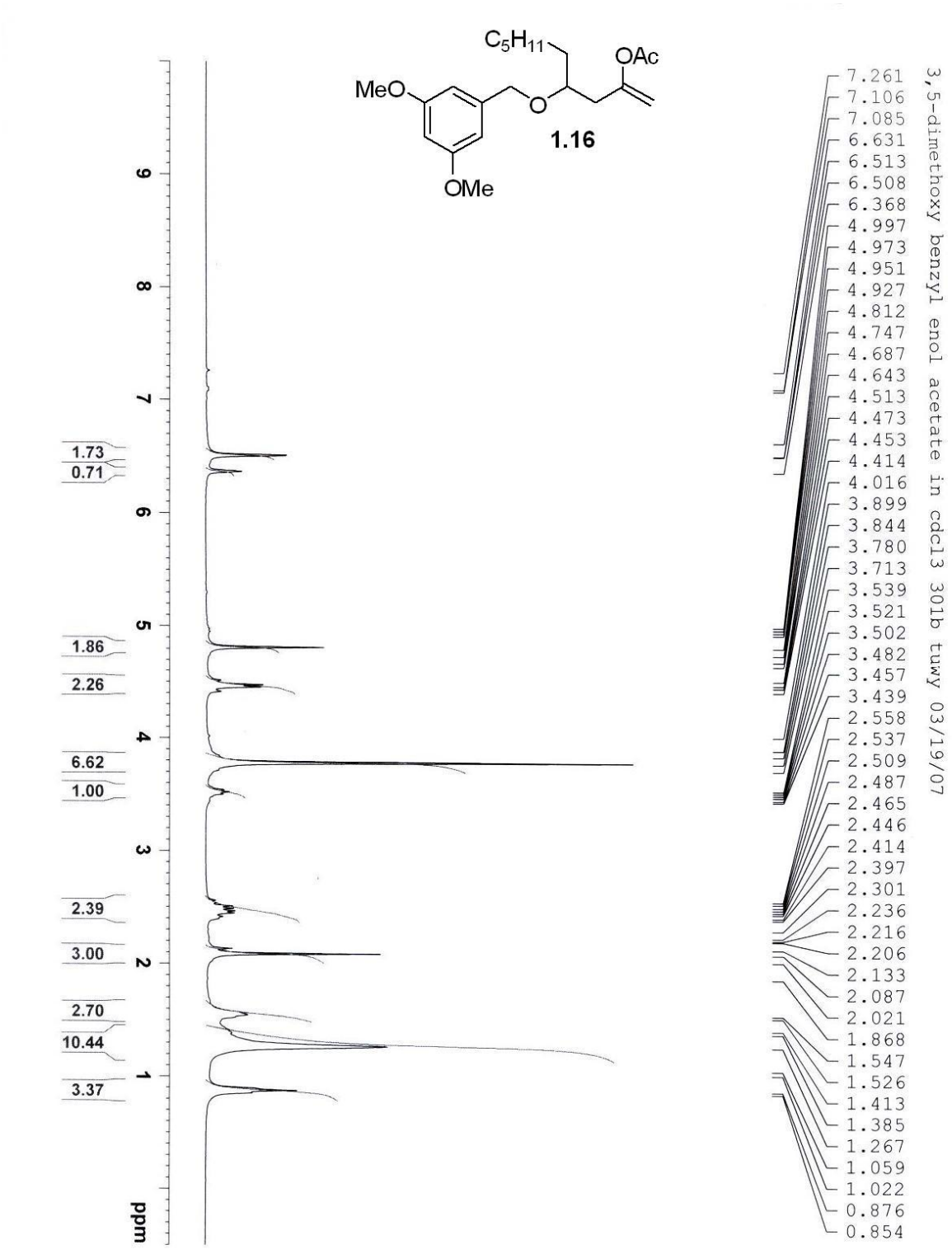

C5H11
OAc
O
MeO
OMe
1.15
3,4-dimethyl benzyl enol acetate in cdcl3 301b tuwy 05/29/07
168.90
153.60
148.87
148.43
135.17
131.16
120.13
111.18
110.73
109.88
103.39
77.77
77.44
77.01
76.59
75.85
70.85
70.65
55.80
55.63
38.22
33.89
31.71
29.22
28.70
25.33
25.18
22.49
20.95
13.95
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

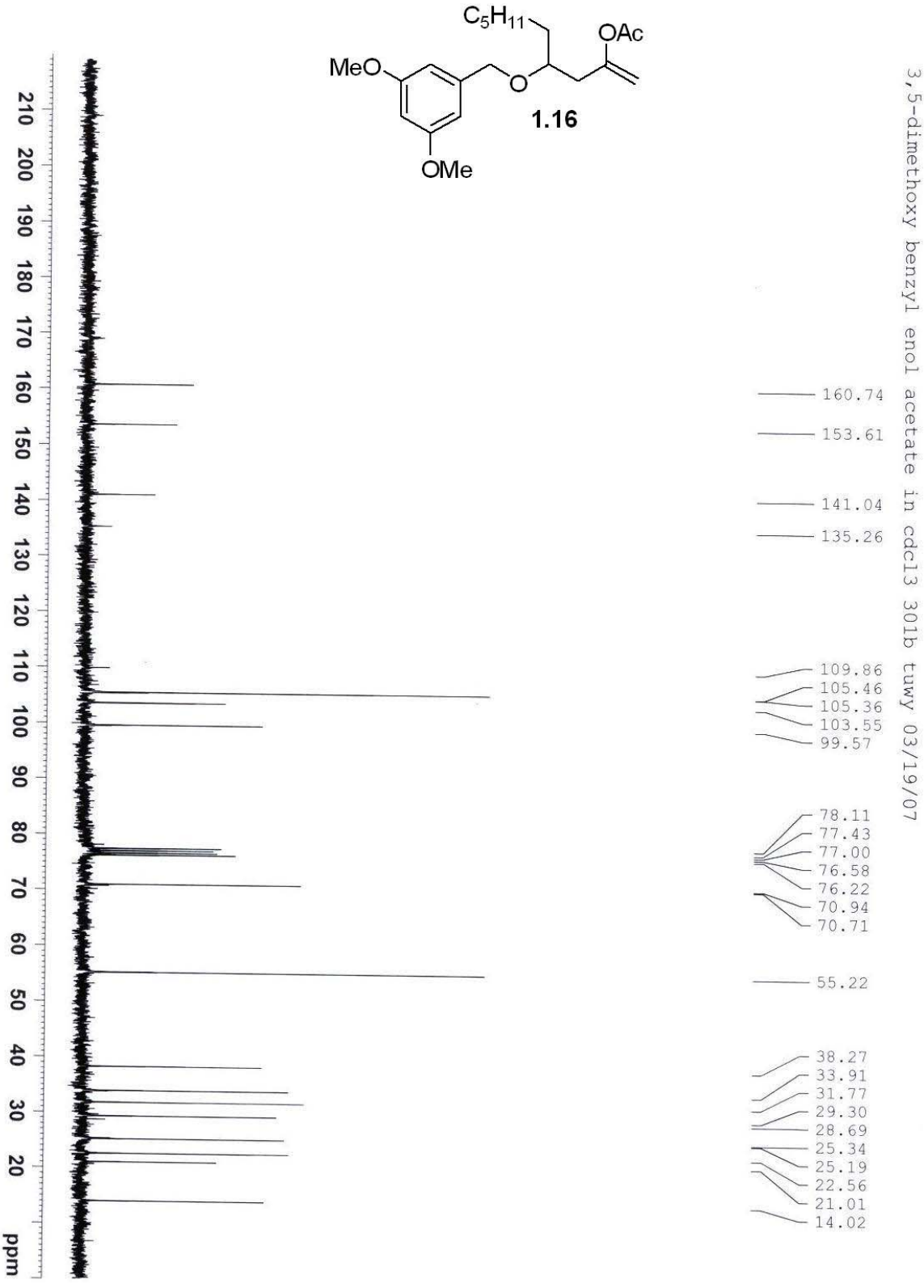

O
O
C6H13
MeO
OMe
1.63
1.41
1.74
1.00
6.45
1.19
2.24
2.74
1.45
1.76
2.63
8.97
3.90
ppm
6.920
6.915
6.901
6.874
6.868
6.852
6.825
4.584
4.571
4.550
4.537
3.924
3.885
3.855
3.747
3.734
3.721
3.710
2.582
2.574
2.540
2.473
2.469
2.464
2.425
2.421
2.417
2.379
2.342
2.332
2.295
2.127
1.756
1.744
1.732
1.724
1.627
1.613
1.595
1.578
1.551
1.502
1.478
1.454
1.447
1.425
1.405
1.391
1.371
1.365
1.274
1.242
0.884
0.863
0.840
lized from 3,4-DMB enolacetate in cdcl3 301 tuwy 05/29/07

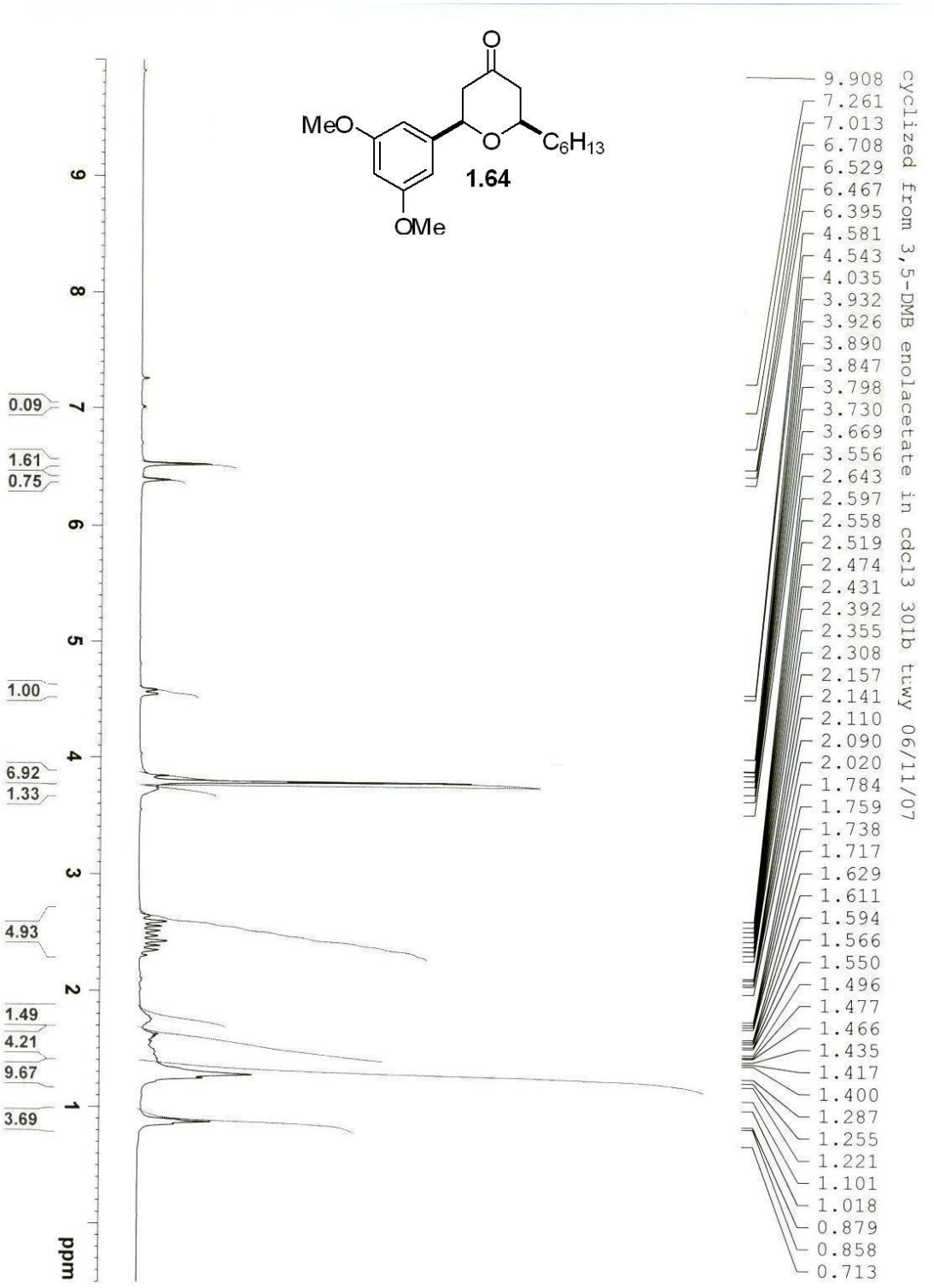
cyclized from 3,4-DMB enolacetate in cdcl3 301a tuwy 05/29/07





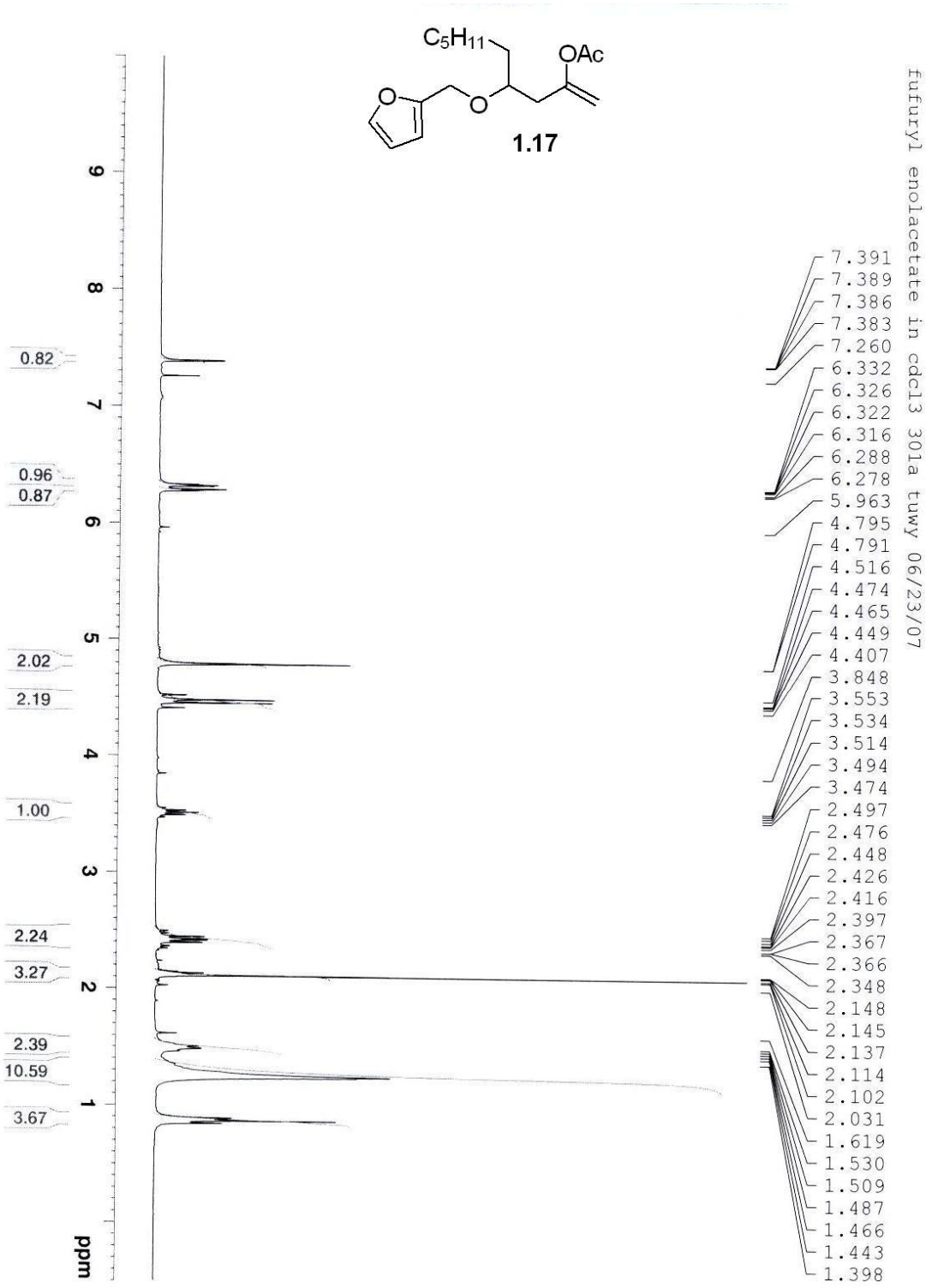

C5H11
OAc
MeO
O
OMe
1.16
1.73
0.71
1.86
2.26
6.62
1.00
2.39
3.00
2.70
10.44
3.37
ppm
3,5-dimethoxy benzyl enol acetate in cdcl3 301b tuwy 03/19/07
7.261
7.106
7.085
6.631
6.513
6.508
6.368
4.997
4.973
4.951
4.927
4.812
4.747
4.687
4.643
4.513
4.473
4.453
4.414
4.016
3.899
3.844
3.780
3.713
3.539
3.521
3.502
3.482
3.457
3.439
2.558
2.537
2.509
2.487
2.465
2.446
2.414
2.397
2.301
2.236
2.216
2.206
2.133
2.087
2.021
1.868
1.547
1.526
1.413
1.385
1.267
1.059
1.022
0.876
0.854

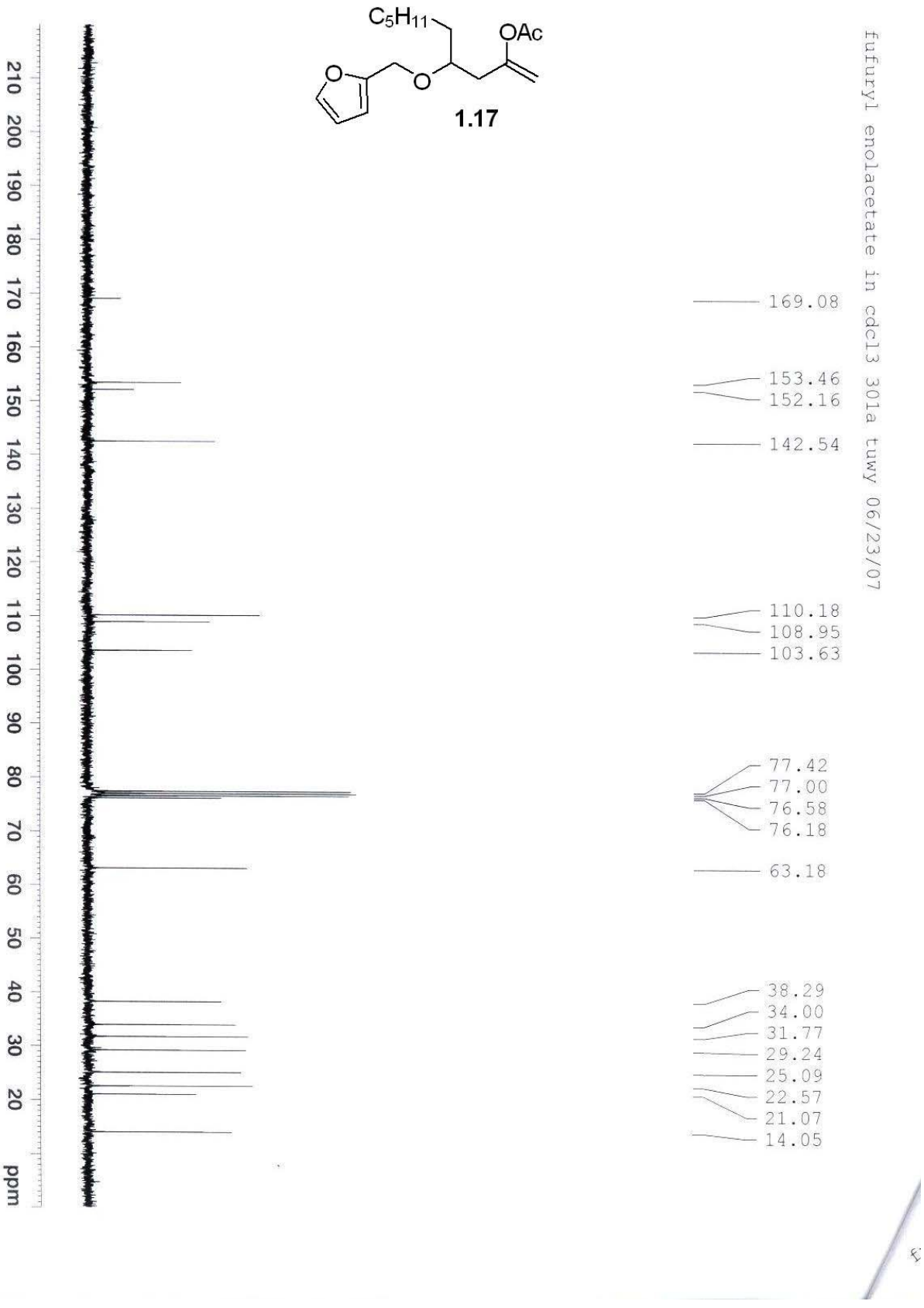

3,5-dimethoxy benzyl enol acetate in cdcl3 301b tuwy 03/19/07
C5H11
OAc
MeO
O
OMe
1.16
160.74
153.61
141.04
135.26
109.86
105.46
105.36
103.55
99.57
78.11
77.43
77.00
76.58
76.22
70.94
70.71
55.22
38.27
33.91
31.77
29.30
28.69
25.34
25.19
22.56
21.01
14.02
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

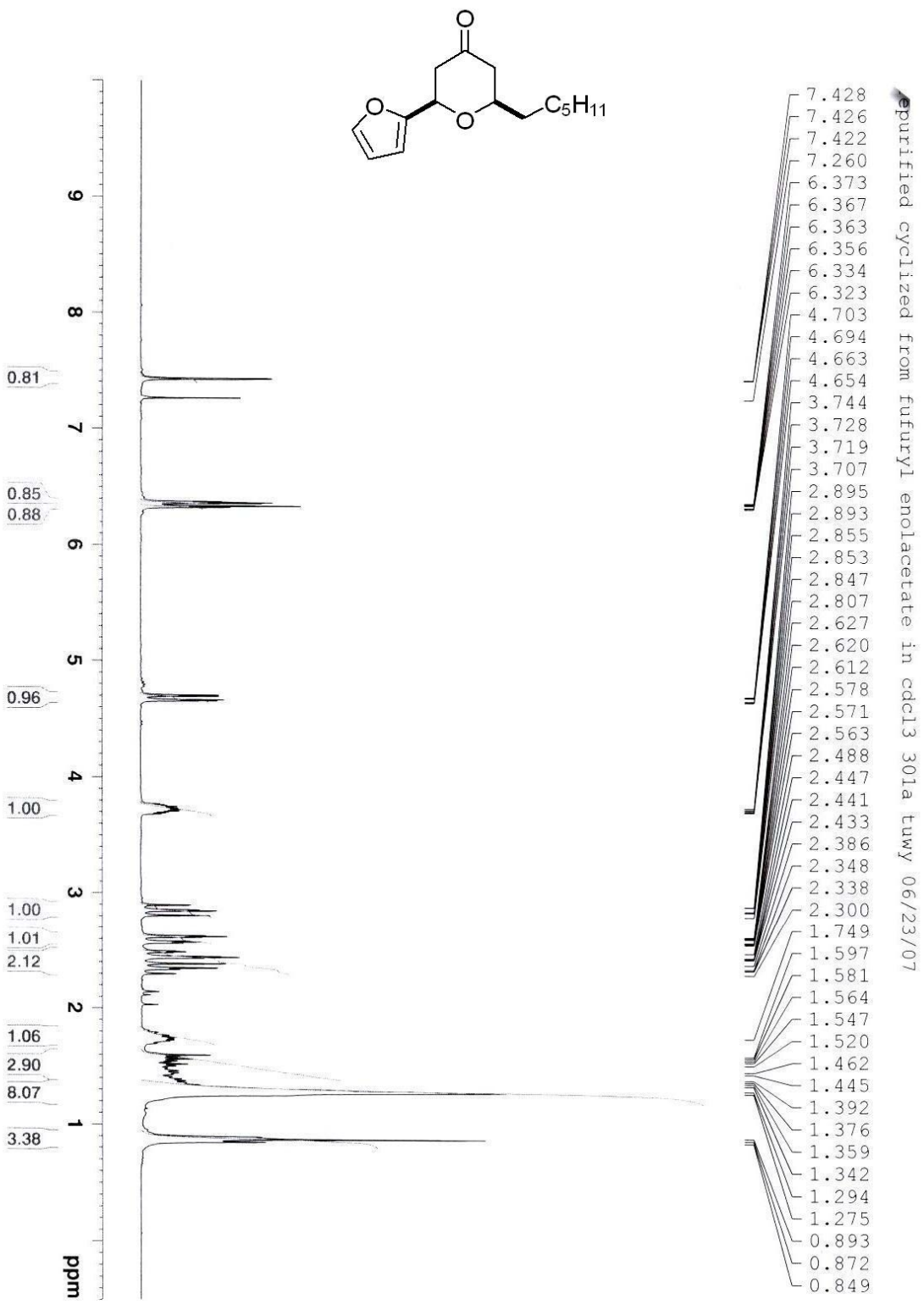

MeO
O
O
C_6H_{13}
1.64
OMe
cyclized from 3,5-DMB enolacetate in cdcl3 301b tuwy 06/11/07
9.908
7.261
7.013
6.708
6.529
6.467
6.395
4.581
4.543
4.035
3.932
3.926
3.890
3.847
3.798
3.730
3.669
3.556
2.643
2.597
2.558
2.519
2.474
2.431
2.392
2.355
2.308
2.157
2.141
2.110
2.090
2.020
1.784
1.759
1.738
1.717
1.629
1.611
1.594
1.566
1.550
1.496
1.477
1.466
1.435
1.417
1.400
1.287
1.255
1.221
1.101
1.018
0.879
0.858
0.713
0.09
1.61
0.75
1.00
6.92
1.33
4.93
1.49
4.21
9.67
3.69
ppm

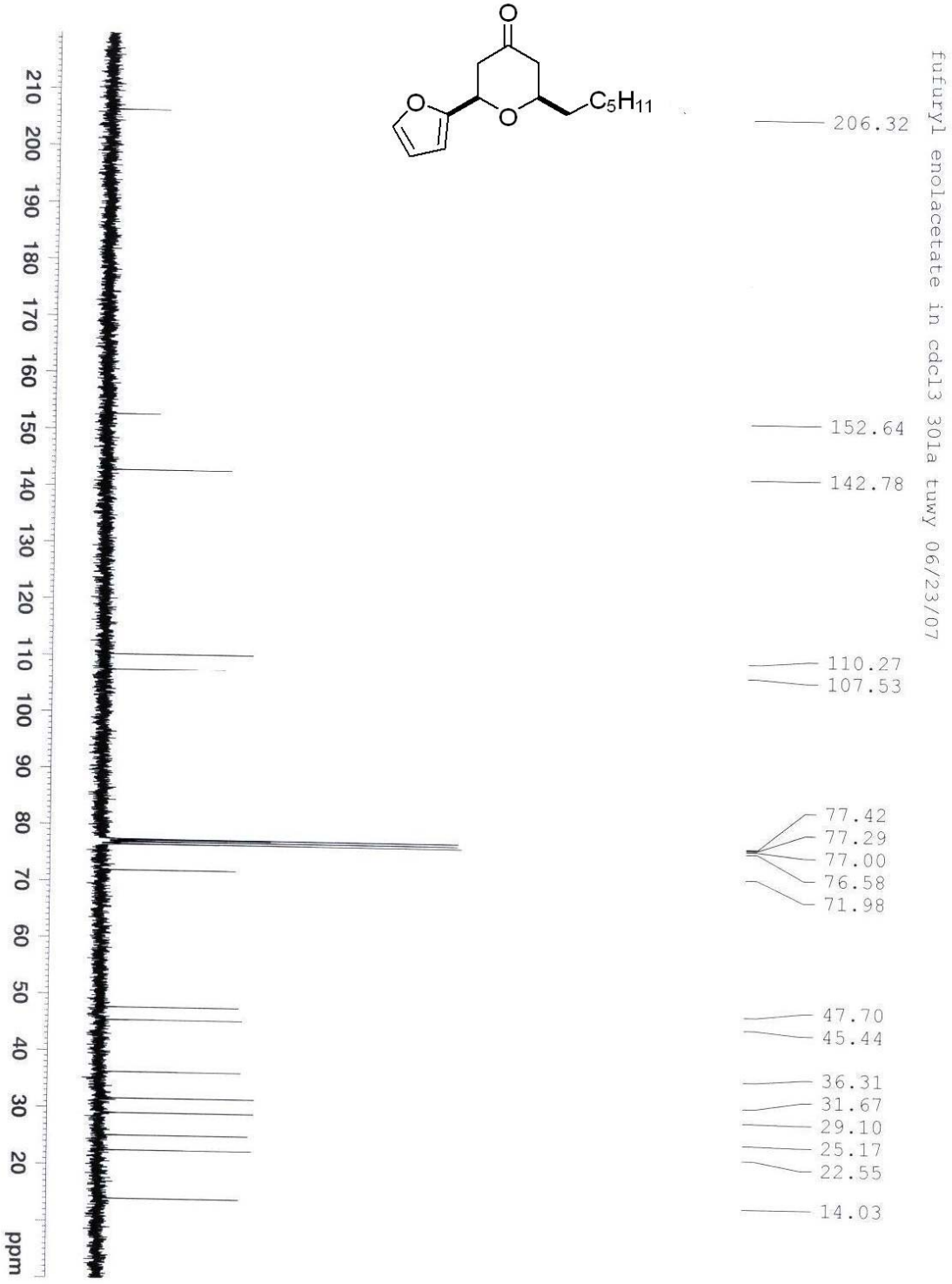
cyclized from 3,5-DMB enolacetate in cdcl3 301b tuwy 06/11/07

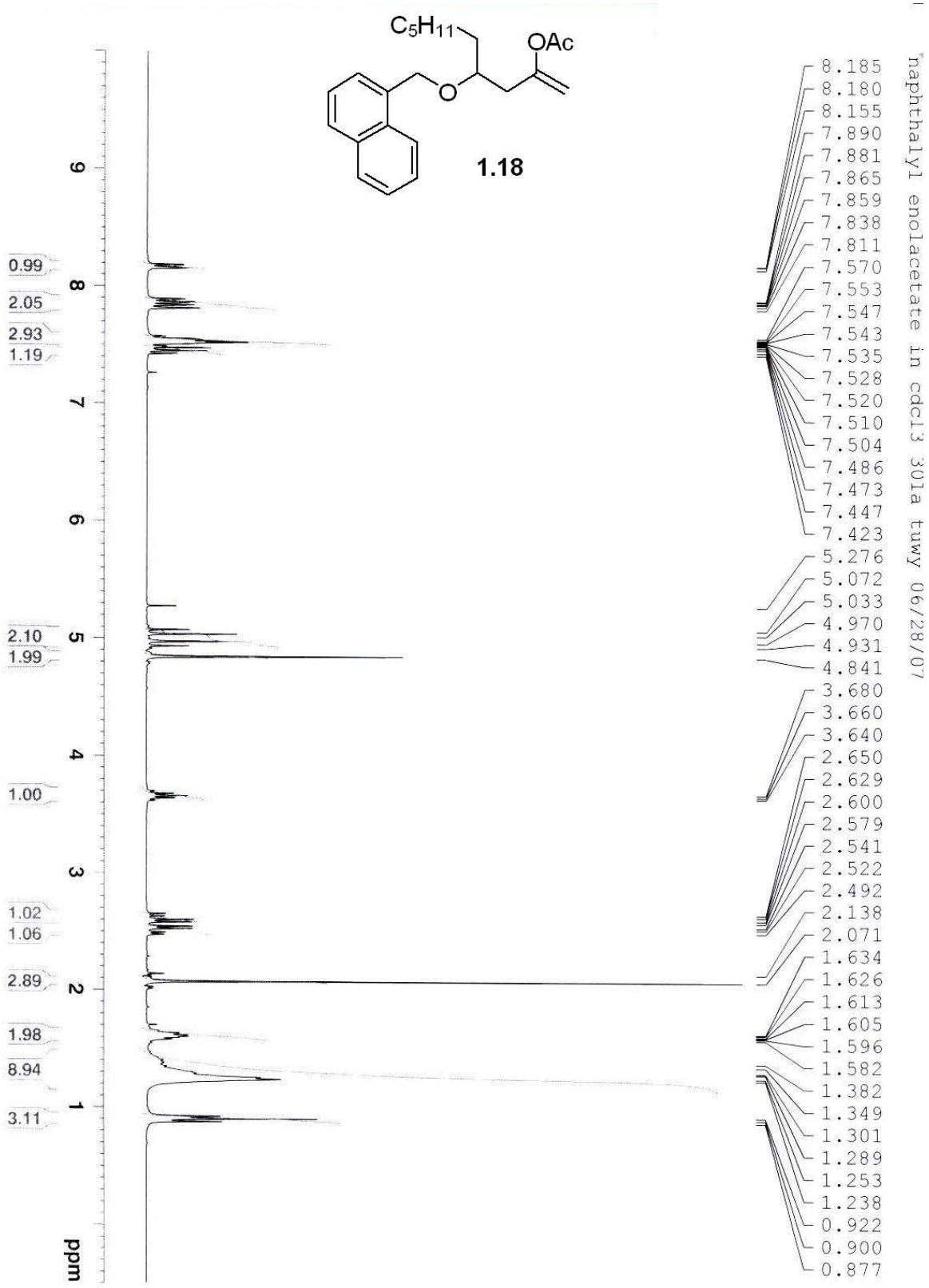
1.64

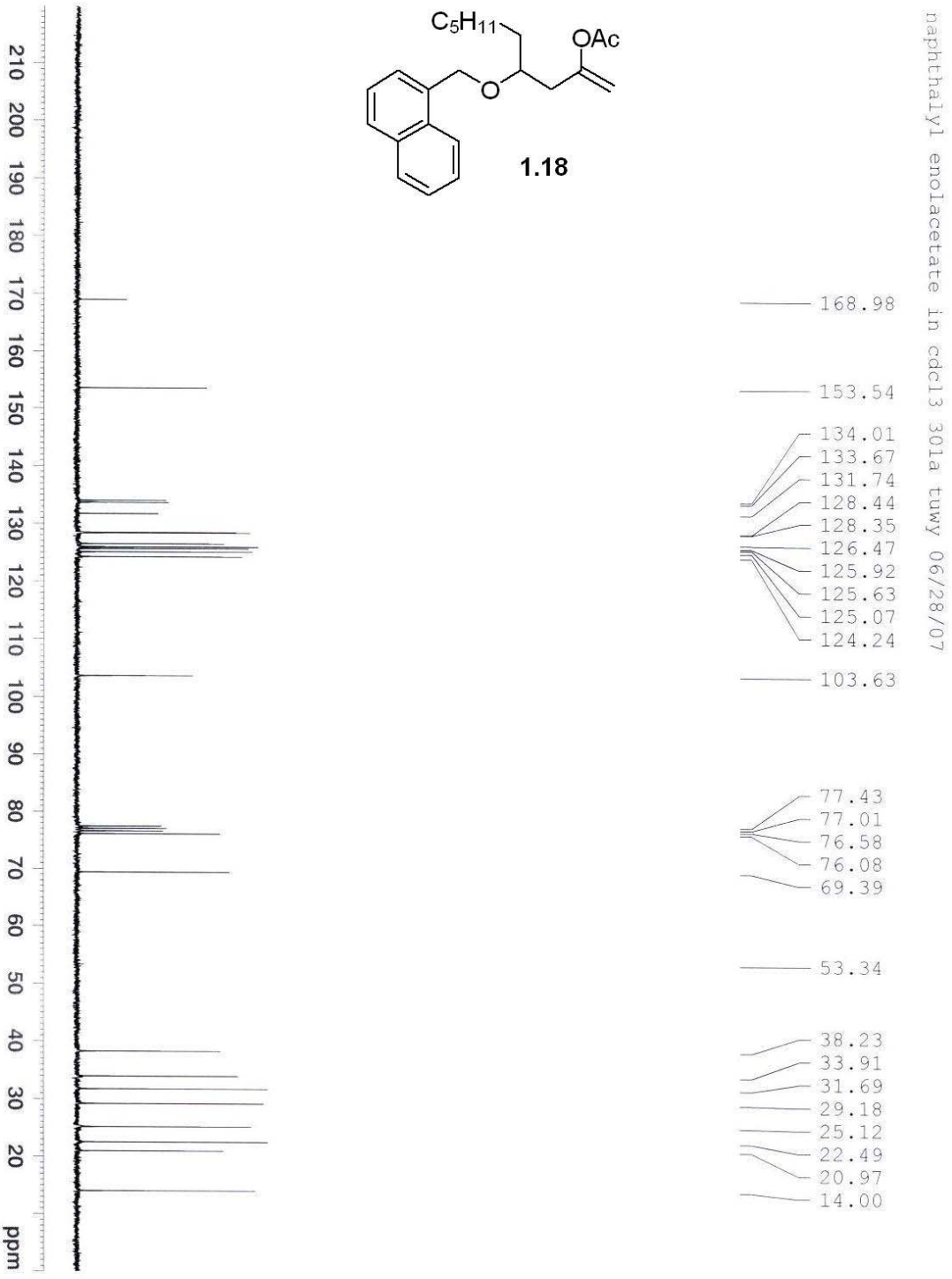

C5H11
OAc
O
O
1.17
fufuryl enolacetate in cdcl3 301a tuwy 06/23/07
7.391
7.389
7.386
7.383
7.260
6.332
6.326
6.322
6.316
6.288
6.278
5.963
4.795
4.791
4.516
4.474
4.465
4.449
4.407
3.848
3.553
3.534
3.514
3.494
3.474
2.497
2.476
2.448
2.426
2.416
2.397
2.367
2.366
2.348
2.148
2.145
2.137
2.114
2.102
2.031
1.619
1.530
1.509
1.487
1.466
1.443
1.398
0.82
0.96
0.87
2.02
2.19
1.00
2.24
3.27
2.39
10.59
3.67
ppm

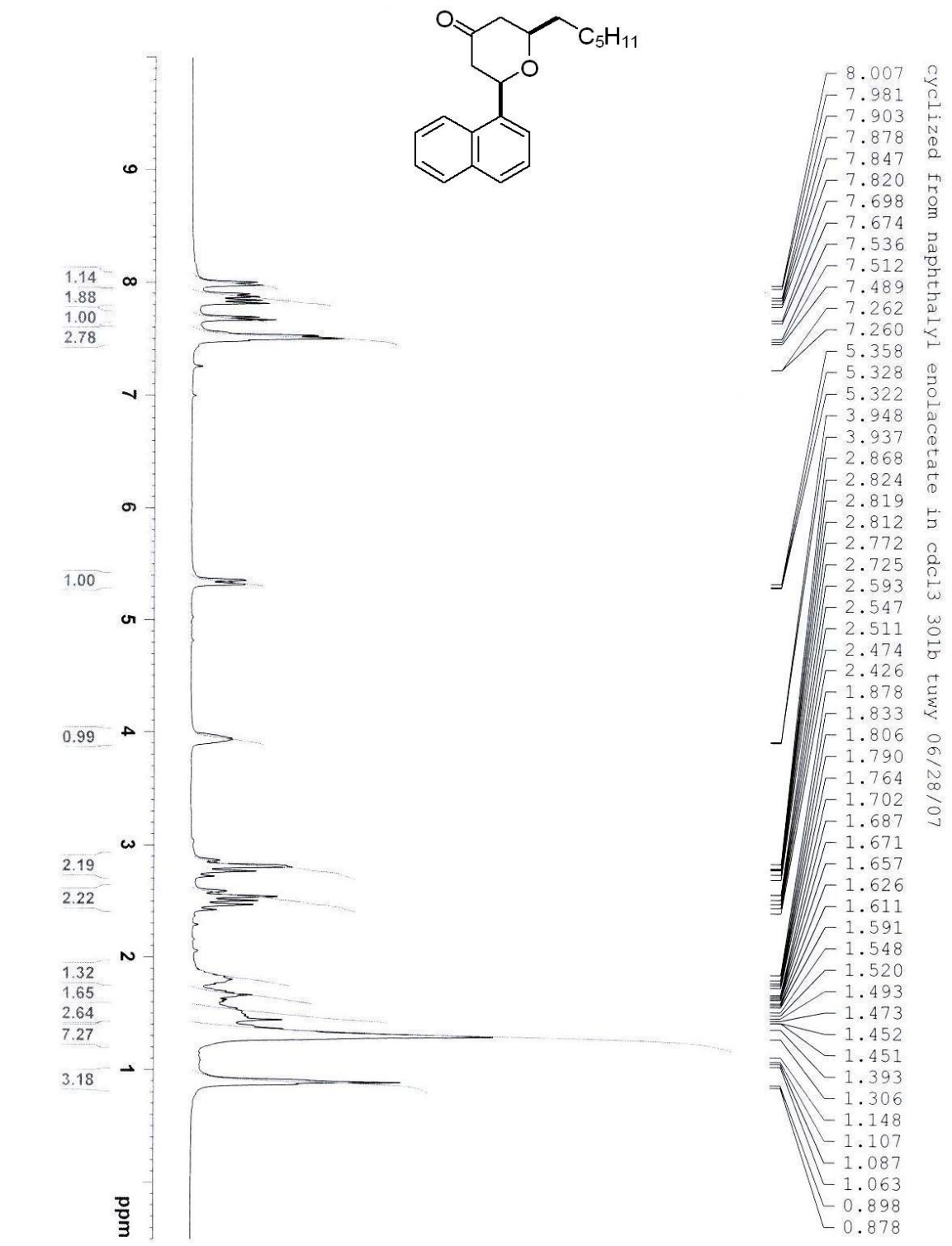

C5H11
OAc
O
O
1.17
fufuryl enolacetate in cdcl3 301a tuwy 06/23/07
169.08
153.46
152.16
142.54
110.18
108.95
103.63
77.42
77.00
76.58
76.18
63.18
38.29
34.00
31.77
29.24
25.09
22.57
21.07
14.05
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


O
O
O
C_5H_{11}
0.81
0.85
0.88
0.96
1.00
1.00
1.01
2.12
1.06
2.90
8.07
3.38
9
8
7
6
5
4
3
2
1
ppm
7.428
7.426
7.422
7.260
6.373
6.367
6.363
6.356
6.334
6.323
4.703
4.694
4.663
4.654
3.744
3.728
3.719
3.707
2.895
2.893
2.855
2.853
2.847
2.807
2.627
2.620
2.612
2.578
2.571
2.563
2.488
2.447
2.441
2.433
2.386
2.348
2.338
2.300
1.749
1.597
1.581
1.564
1.547
1.520
1.462
1.445
1.392
1.376
1.359
1.342
1.294
1.275
0.893
0.872
0.849
epurified cyclized from fufuryl enolacetate in cdcl3 301a tuwy 06/23/07

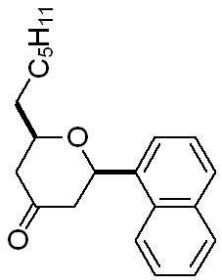

fufuryl enolacetate in cdcl3 301a tuwy 06/23/07
206.32
152.64
142.78
110.27
107.53
77.42
77.29
77.00
76.58
71.98
47.70
45.44
36.31
31.67
29.10
25.17
22.55
14.03
ppm

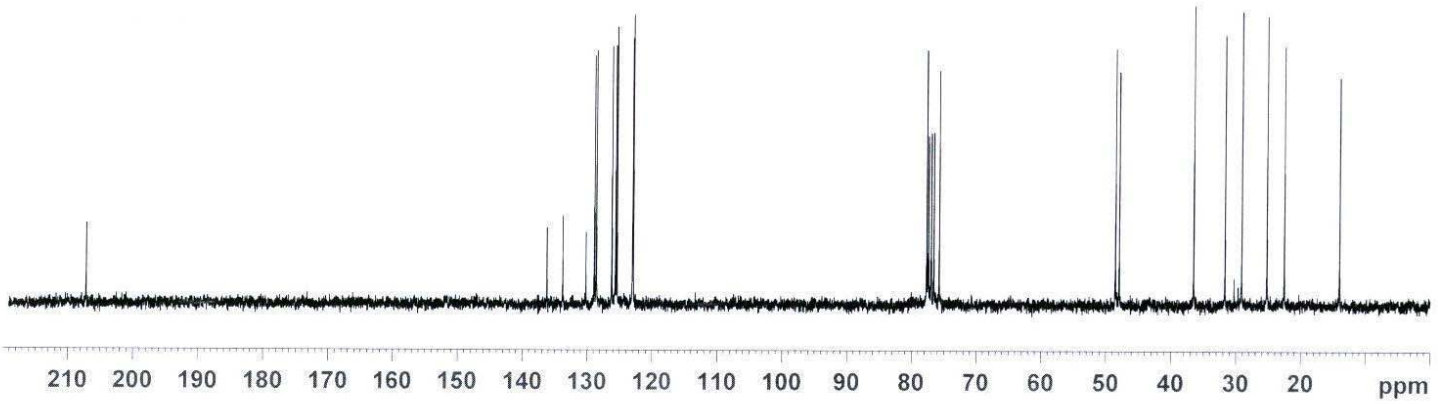

C5H11
OAc
O
1.18
naphthalyl enolacetate in cdcl3 301a tuwy 06/28/07
8.185
8.180
8.155
7.890
7.881
7.865
7.859
7.838
7.811
7.570
7.553
7.547
7.543
7.535
7.528
7.520
7.510
7.504
7.486
7.473
7.447
7.423
5.276
5.072
5.033
4.970
4.931
4.841
3.680
3.660
3.640
2.650
2.629
2.600
2.579
2.541
2.522
2.492
2.138
2.071
1.634
1.626
1.613
1.605
1.596
1.582
1.382
1.349
1.301
1.289
1.253
1.238
0.922
0.900
0.877
0.99
2.05
2.93
1.19
2.10
1.99
1.00
1.02
1.06
2.89
1.98
8.94
3.11
ppm

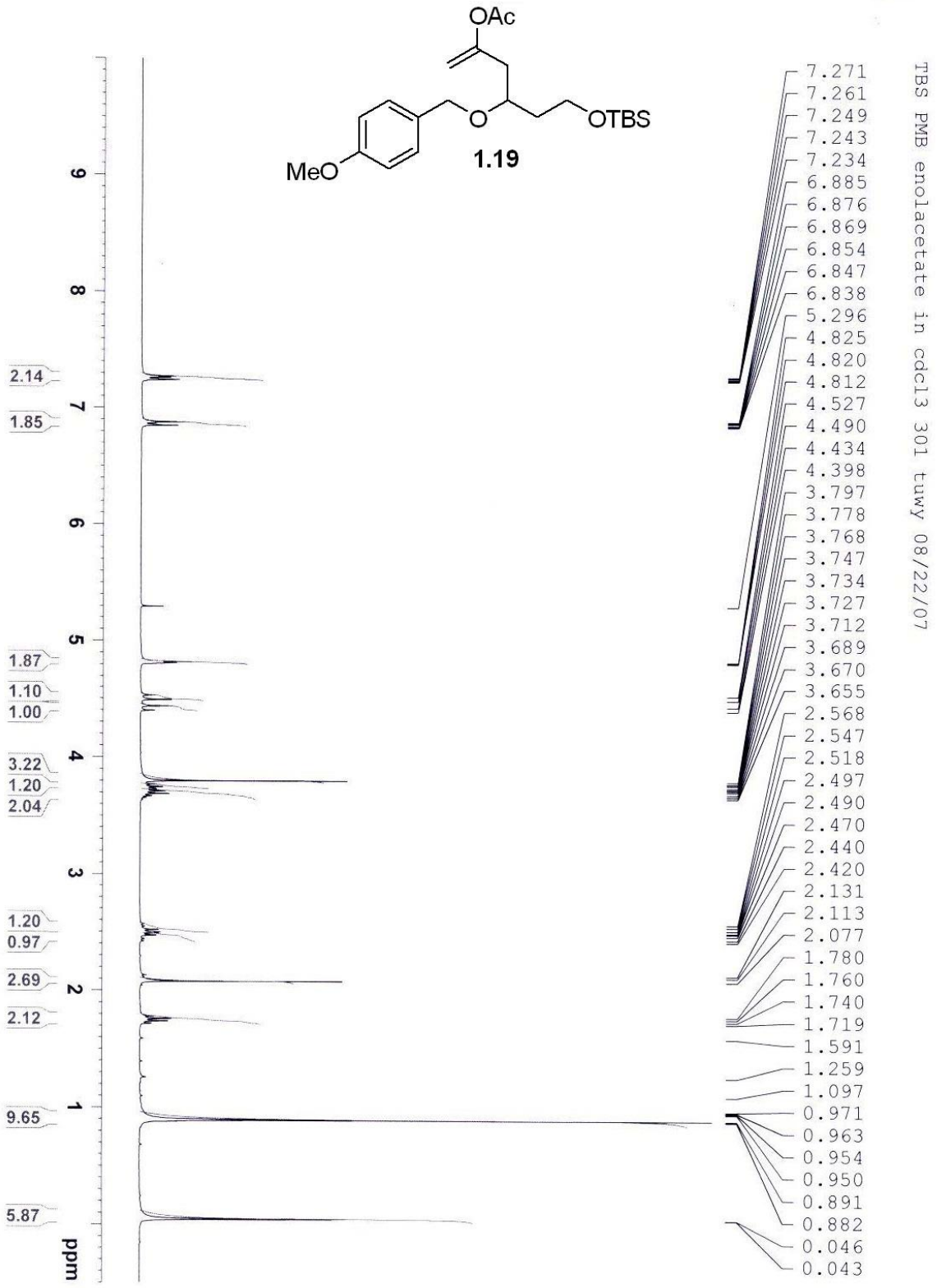

C5H11
OAc
O
1.18
naphthalyl enolacetate in cdcl3 301a tuwy 06/28/07
168.98
153.54
134.01
133.67
131.74
128.44
128.35
126.47
125.92
125.63
125.07
124.24
103.63
77.43
77.01
76.58
76.08
69.39
53.34
38.23
33.91
31.69
29.18
25.12
22.49
20.97
14.00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

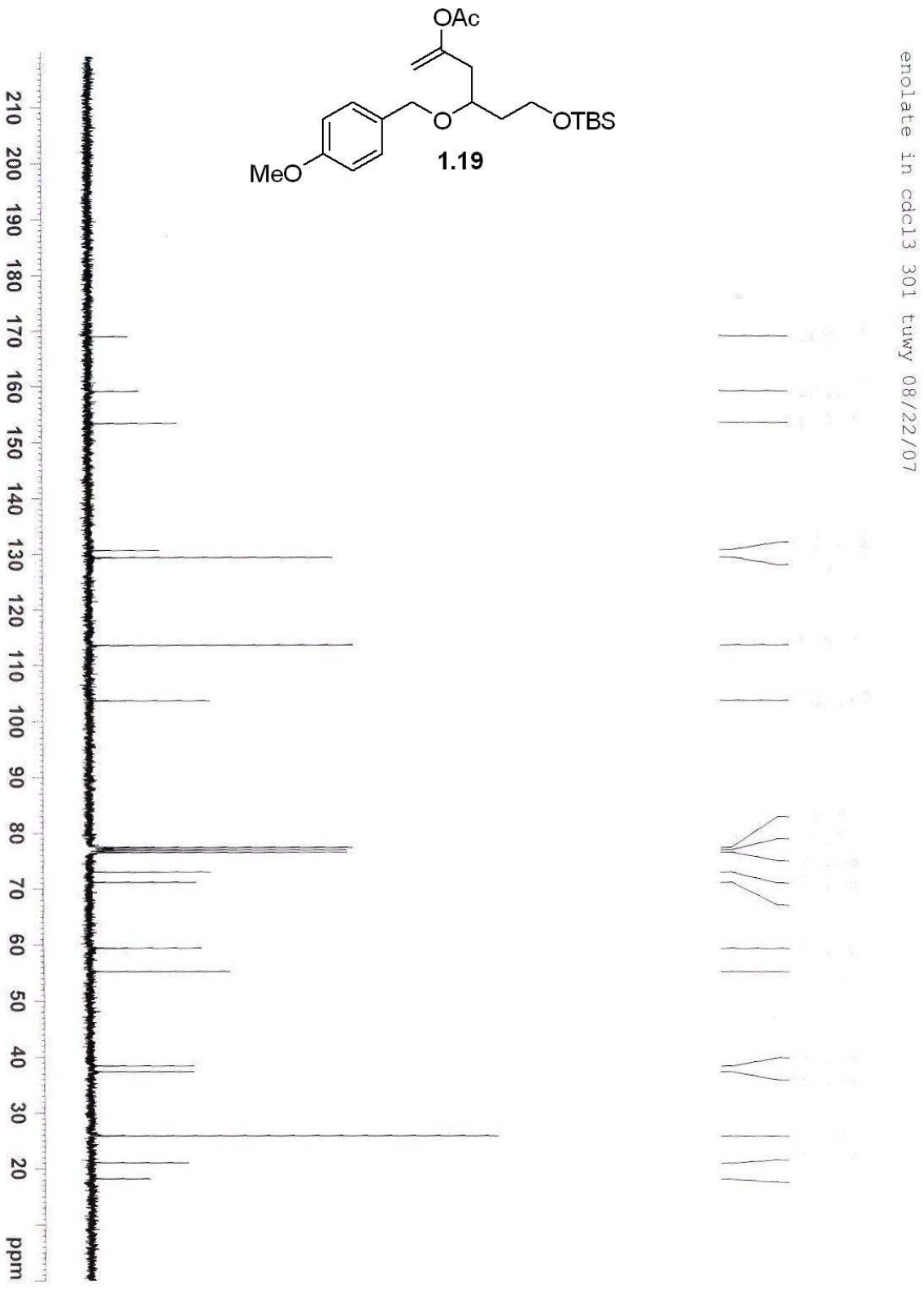

cyclized from naphthalyl enolacetate in cdcl3 301b tuwy 06/28/07
8.007
7.981
7.903
7.878
7.847
7.820
7.698
7.674
7.536
7.512
7.489
7.262
7.260
5.358
5.328
5.322
3.948
3.937
2.868
2.824
2.819
2.812
2.772
2.725
2.593
2.547
2.511
2.474
2.426
1.878
1.833
1.806
1.790
1.764
1.702
1.687
1.671
1.657
1.626
1.611
1.591
1.548
1.520
1.493
1.473
1.452
1.451
1.393
1.306
1.148
1.107
1.087
1.063
0.898
0.878
1.14
1.88
1.00
2.78
1.00
0.99
2.19
2.22
1.32
1.65
2.64
7.27
3.18
ppm

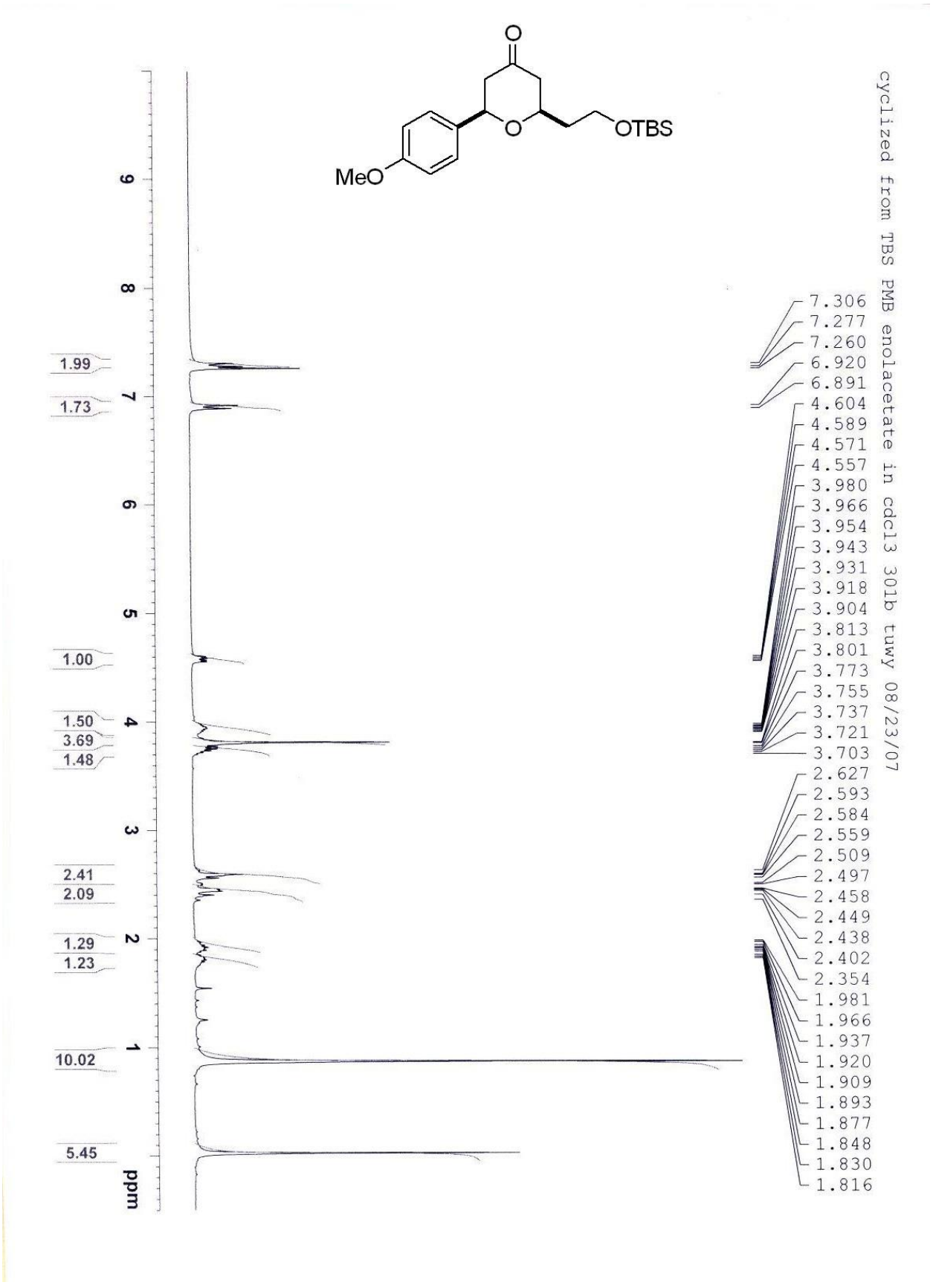
cyclized from naphthalyl enolacetate in cdcl3 301b tuwy 06/28/07

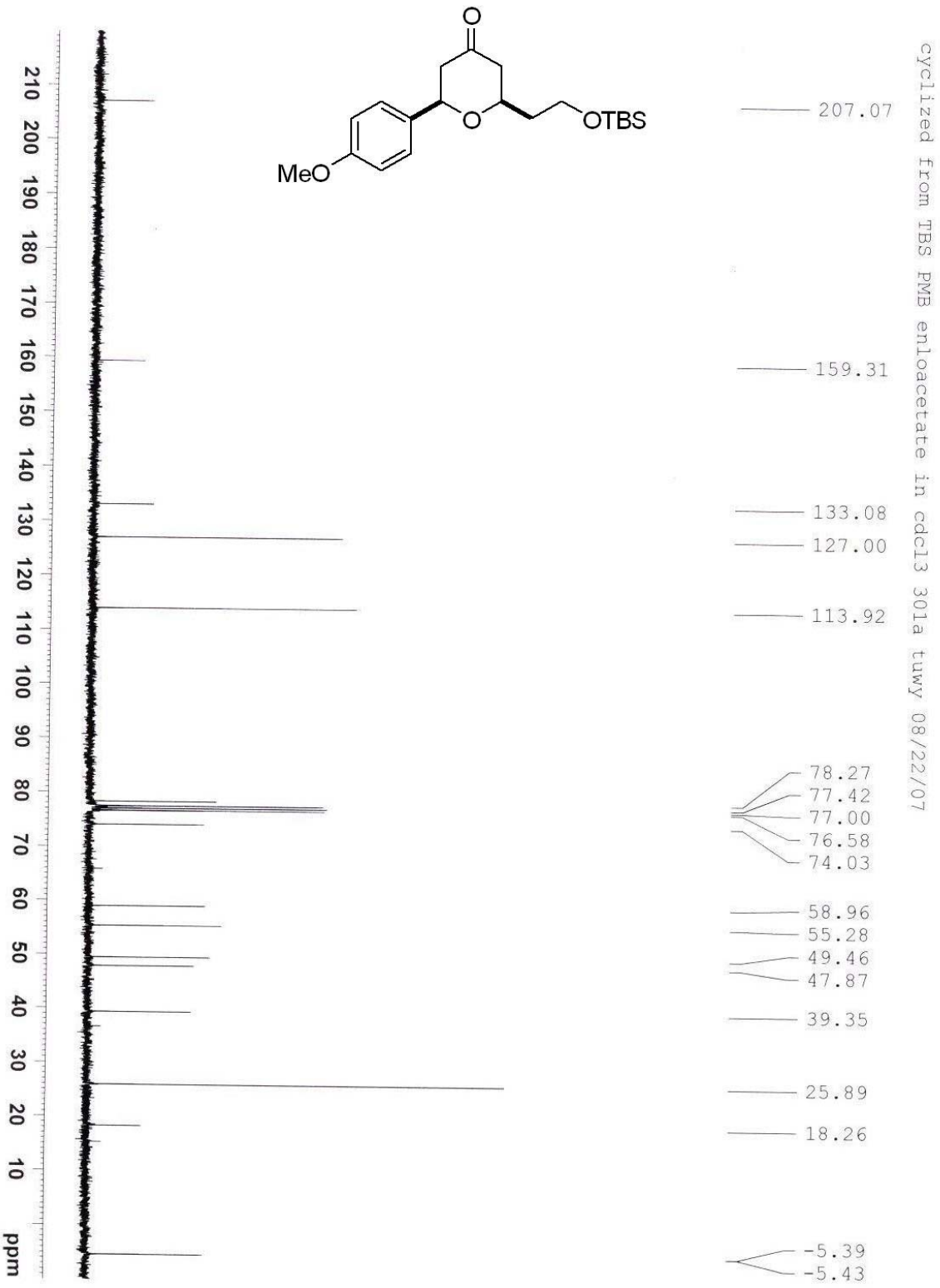


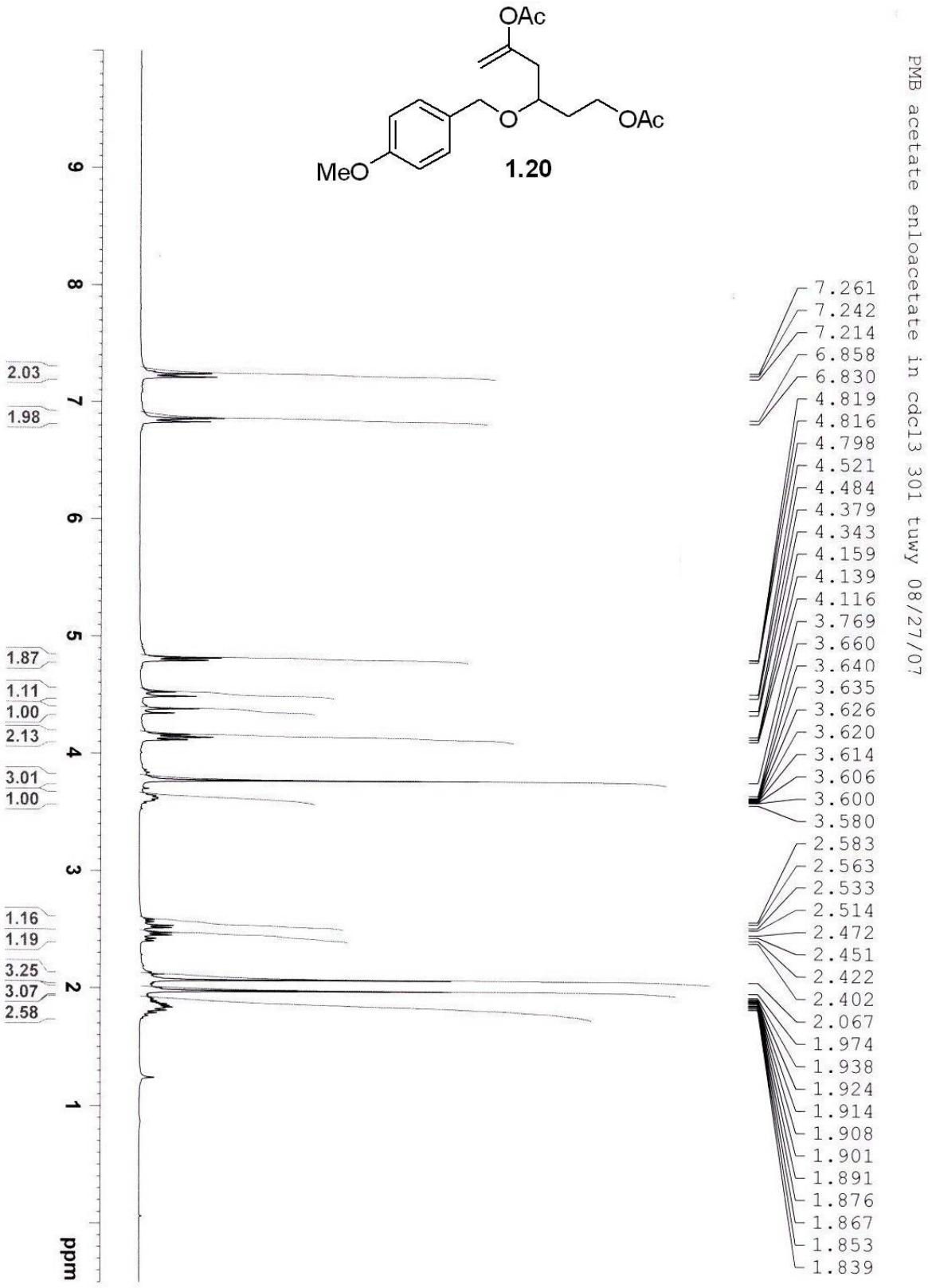


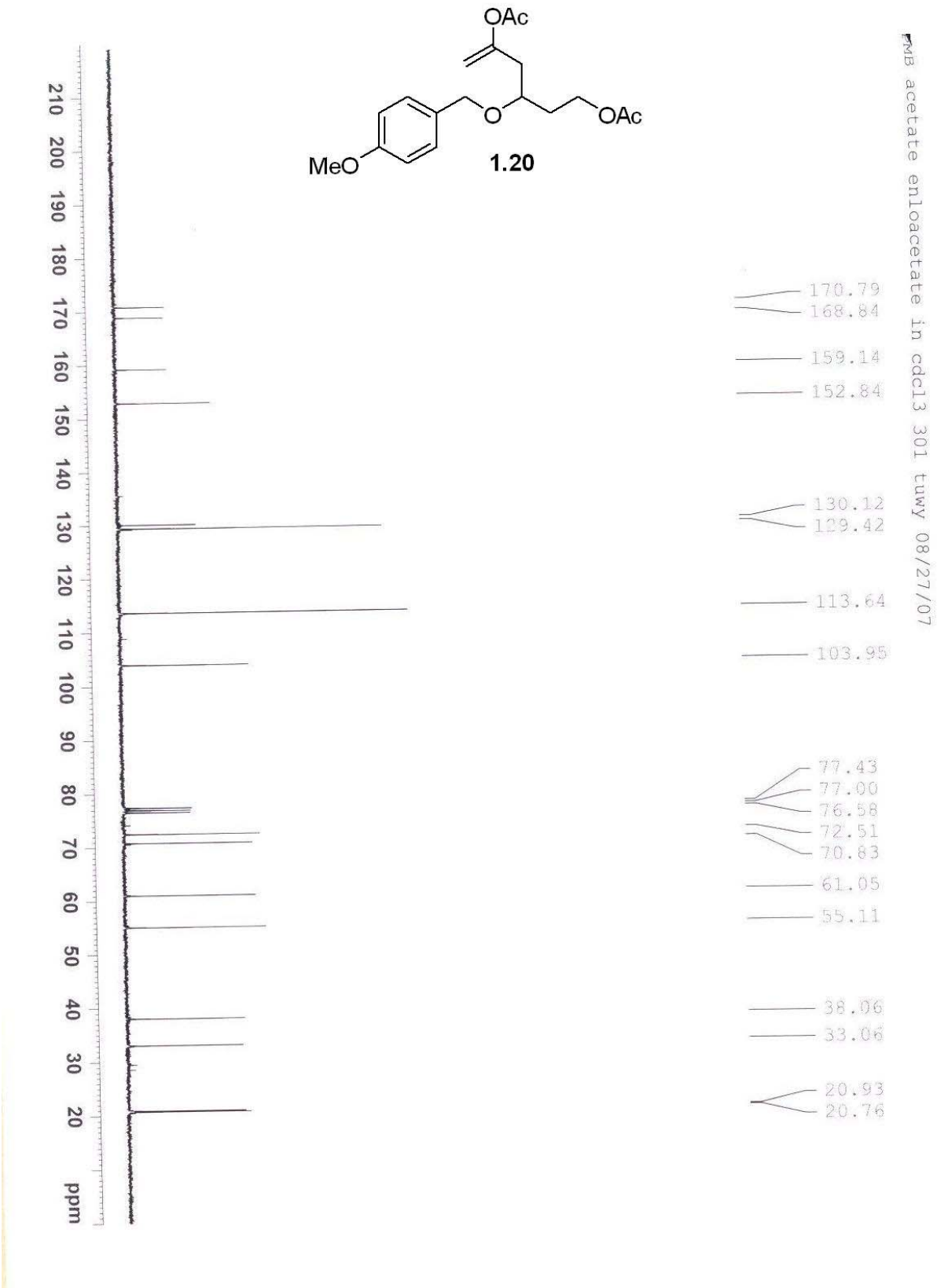

OAc
OTBS
O
MeO
1.19
TBS PMB enolacetate in cdcl3 301 tuwy 08/22/07
7.271
7.261
7.249
7.243
7.234
6.885
6.876
6.869
6.854
6.847
6.838
5.296
4.825
4.820
4.812
4.527
4.490
4.434
4.398
3.797
3.778
3.768
3.747
3.734
3.727
3.712
3.689
3.670
3.655
2.568
2.547
2.518
2.497
2.490
2.470
2.440
2.420
2.131
2.113
2.077
1.780
1.760
1.740
1.719
1.591
1.259
1.097
0.971
0.963
0.954
0.950
0.891
0.882
0.046
0.043
2.14
1.85
1.87
1.10
1.00
3.22
1.20
2.04
1.20
0.97
2.69
2.12
9.65
5.87
ppm

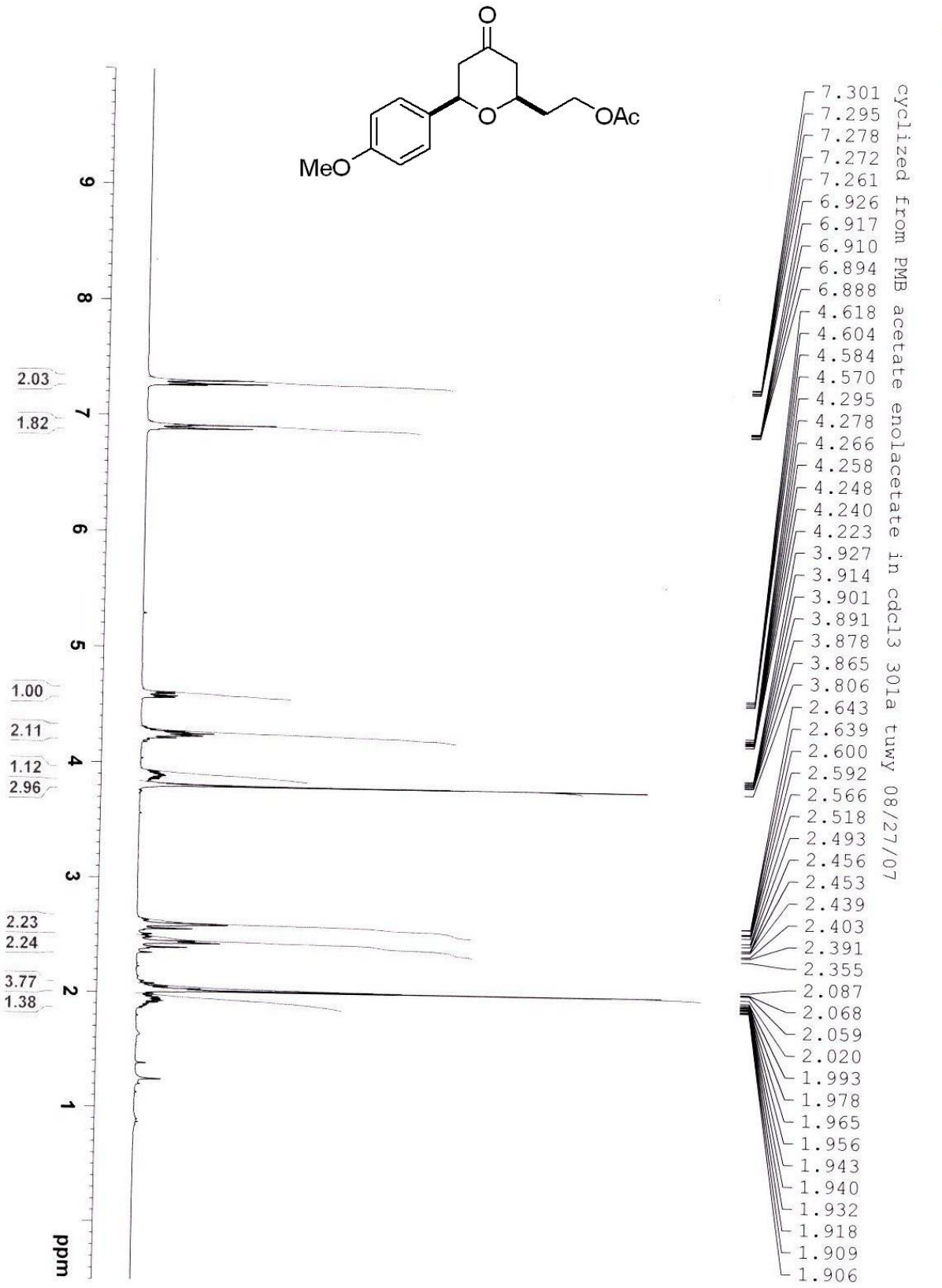

OAc
OTBS
O
MeO
1.19
enolate in cdcl3 301 tuwy 08/22/07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

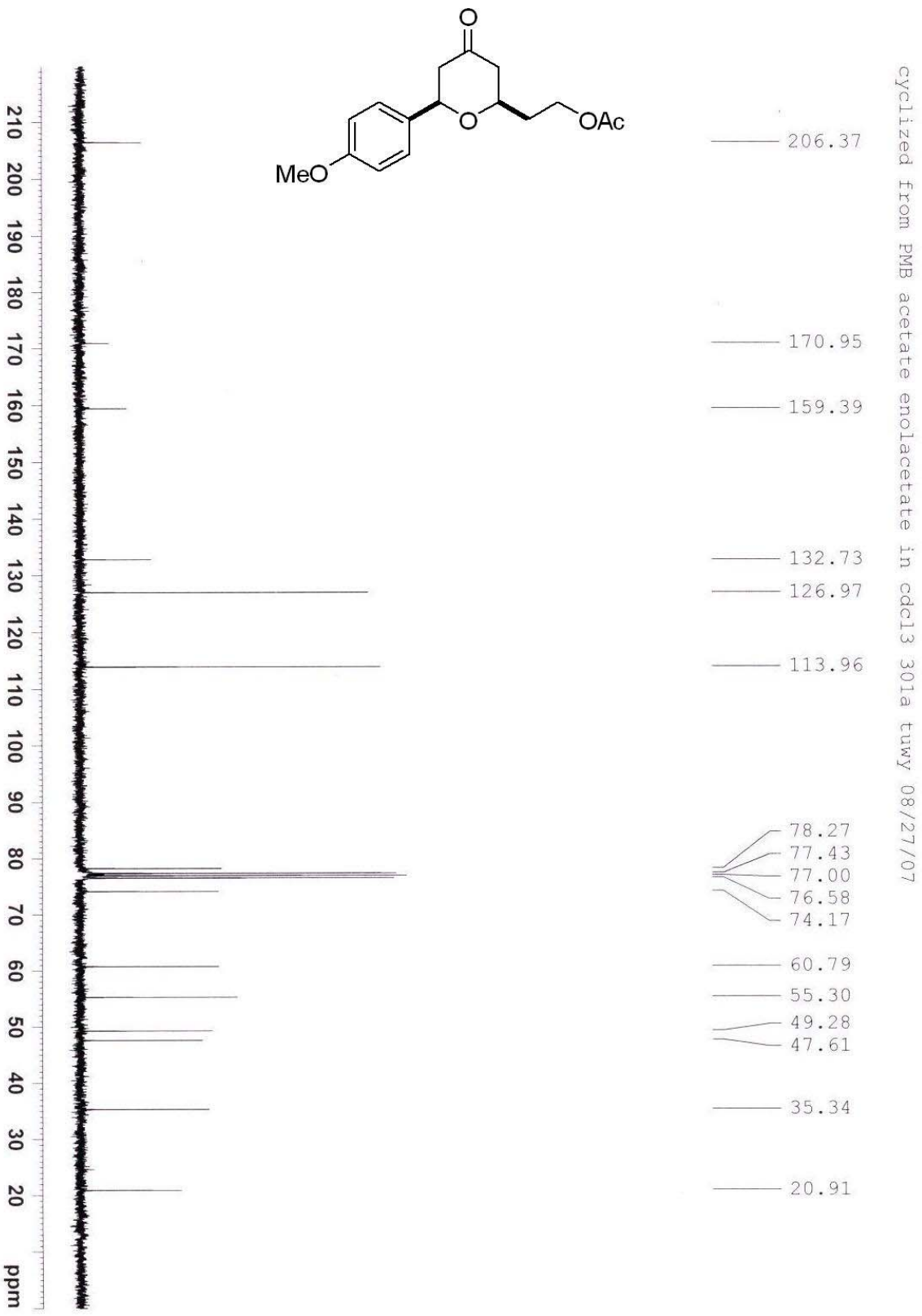

cyclized from TBS PMB enolacetate in cdcl3 301b tuwy 08/23/07
MeO
O
OTBS
7.306
7.277
7.260
6.920
6.891
4.604
4.589
4.571
4.557
3.980
3.966
3.954
3.943
3.931
3.918
3.904
3.813
3.801
3.773
3.755
3.737
3.721
3.703
2.627
2.593
2.584
2.559
2.509
2.497
2.458
2.449
2.438
2.402
2.354
1.981
1.966
1.937
1.920
1.909
1.893
1.877
1.848
1.830
1.816
1.99
1.73
1.00
1.50
3.69
1.48
2.41
2.09
1.29
1.23
10.02
5.45
ppm

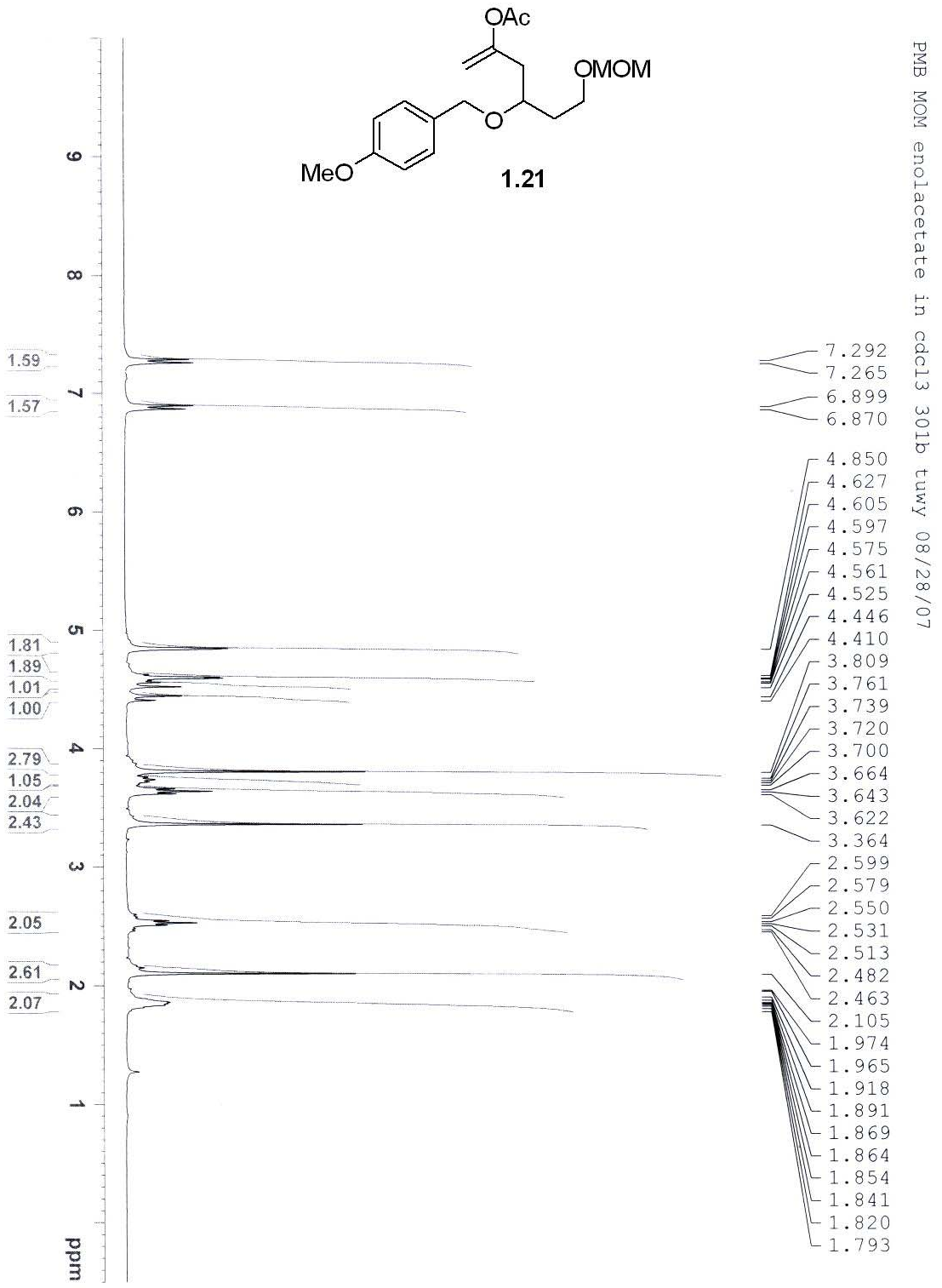

cyclized from TBS PMB enloacetate in cdcl3 301a tuwy 08/22/07
207.07
159.31
133.08
127.00
113.92
78.27
77.42
77.00
76.58
74.03
58.96
55.28
49.46
47.87
39.35
25.89
18.26
-5.39
-5.43
MeO
O
OTBS
ppm

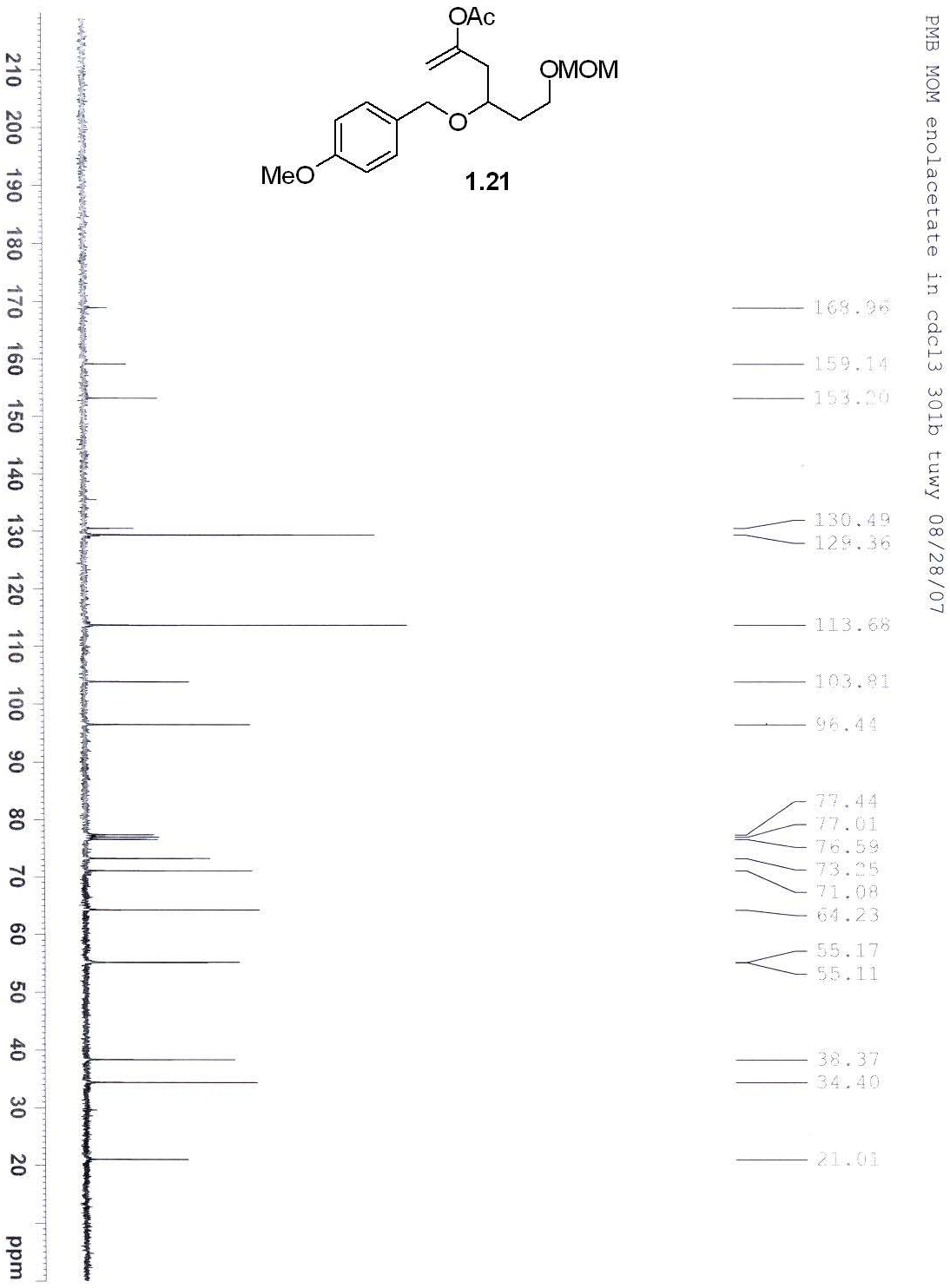

OAc
OAc
MeO
O
1.20
PMB acetate enloacetate in cdcl3 301 tuwy 08/27/07
7.261
7.242
7.214
6.858
6.830
4.819
4.816
4.798
4.521
4.484
4.379
4.343
4.159
4.139
4.116
3.769
3.660
3.640
3.635
3.626
3.620
3.614
3.606
3.600
3.580
2.583
2.563
2.533
2.514
2.472
2.451
2.422
2.402
2.067
1.974
1.938
1.924
1.914
1.908
1.901
1.891
1.876
1.867
1.853
1.839
2.03
1.98
1.87
1.11
1.00
2.13
3.01
1.00
1.16
1.19
3.25
3.07
2.58
ppm

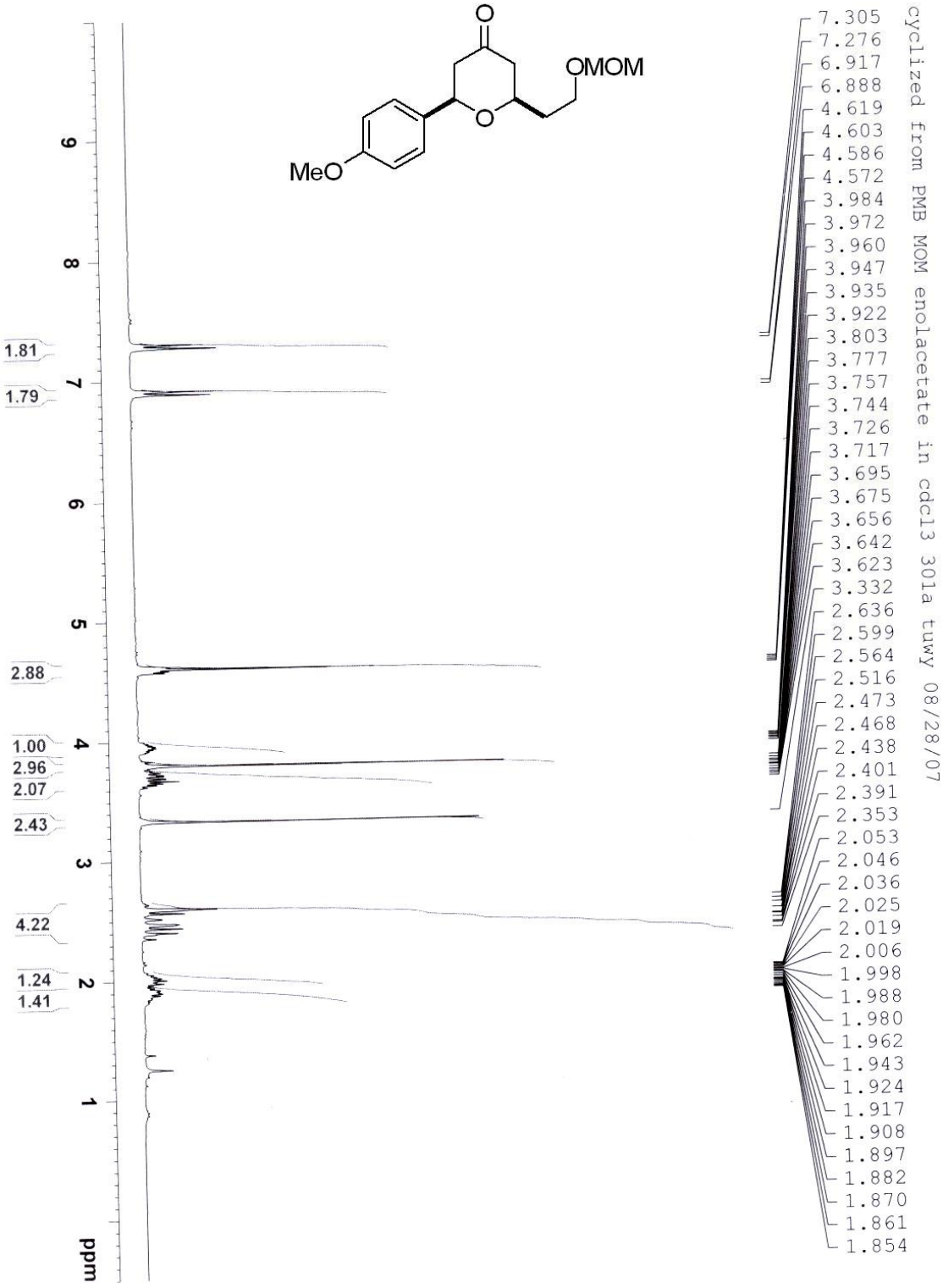

OAc
OAc
MeO
O
1.20
PMB acetate enloacetate in cdcl3 301 tuwy 08/27/07
170.79
168.84
159.14
152.84
130.12
129.42
113.64
103.95
77.43
77.00
76.58
72.51
70.83
61.05
55.11
38.06
33.06
20.93
20.76
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

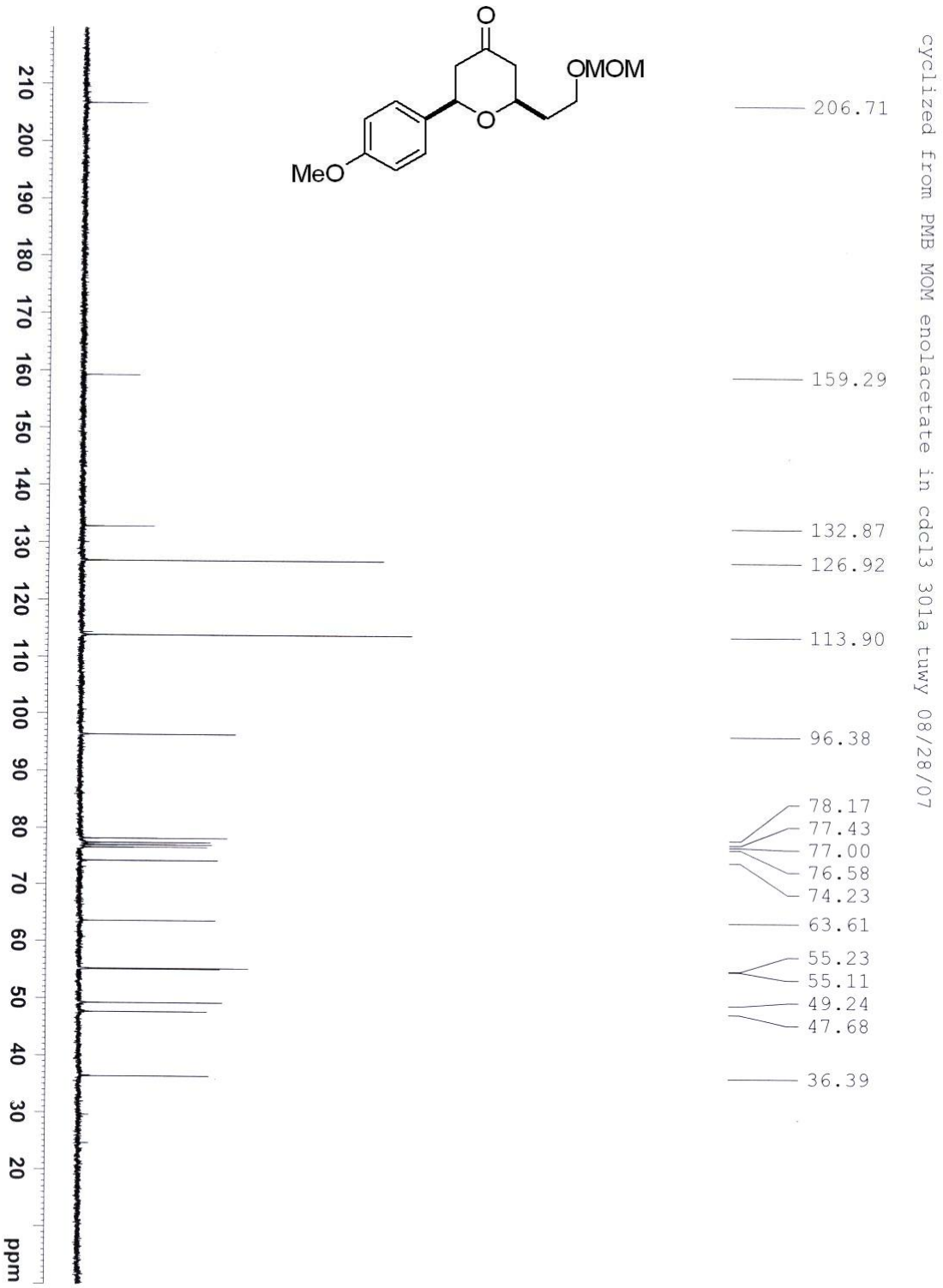

O
O
OAc
MeO
cyclized from PMB acetate enolacetate in cdcl3 301a tuwy 08/27/07
7.301
7.295
7.278
7.272
7.261
6.926
6.917
6.910
6.894
6.888
4.618
4.604
4.584
4.570
4.295
4.278
4.266
4.258
4.248
4.240
4.223
3.927
3.914
3.901
3.891
3.878
3.865
3.806
2.643
2.639
2.600
2.592
2.566
2.518
2.493
2.456
2.453
2.439
2.403
2.391
2.355
2.087
2.068
2.059
2.020
1.993
1.978
1.965
1.956
1.943
1.940
1.932
1.918
1.909
1.906
2.03
1.82
1.00
2.11
1.12
2.96
2.23
2.24
3.77
1.38
ppm

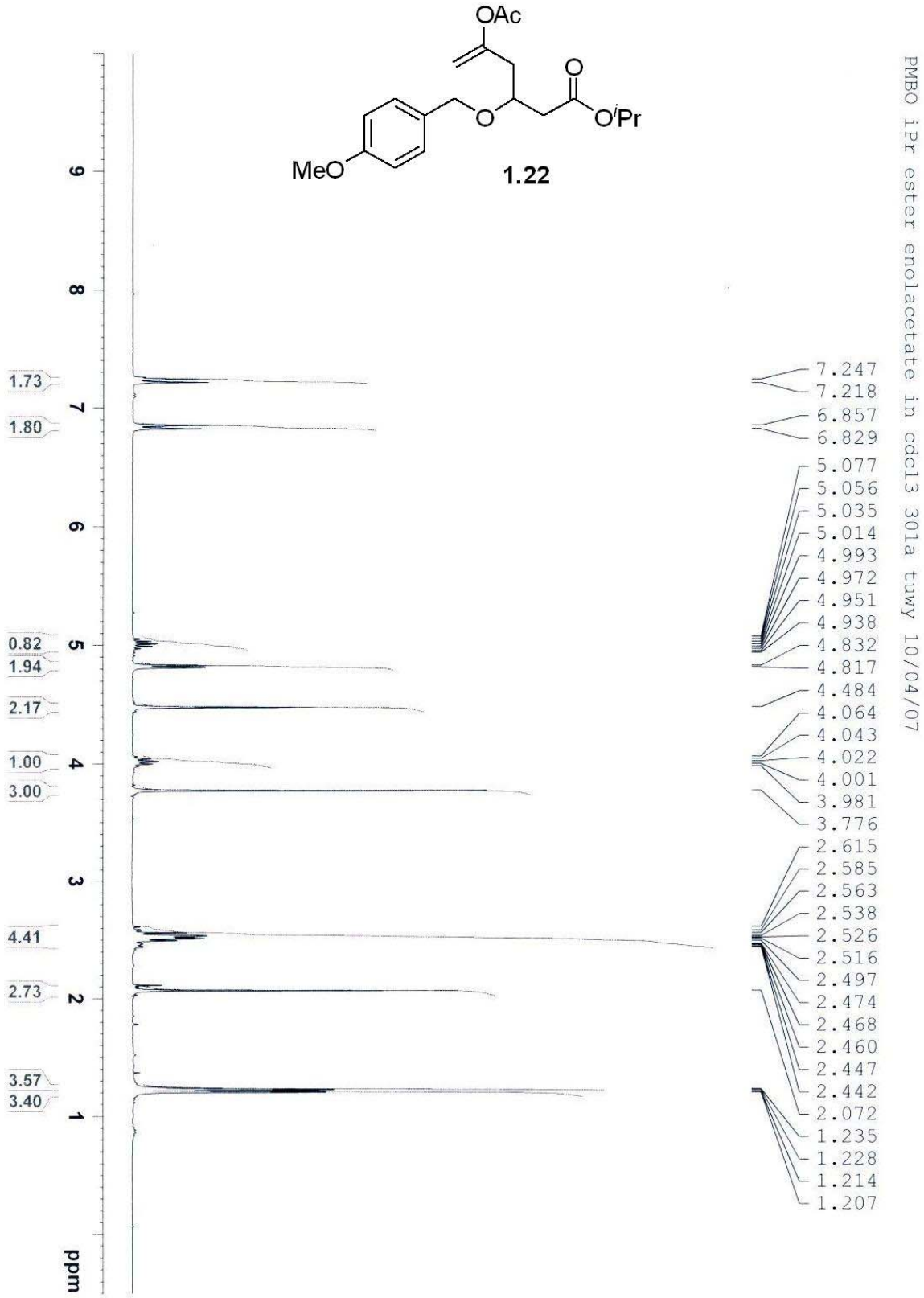

cyclized from PMB acetate enolacetate in cdcl3 301a tuwy 08/27/07
206.37
170.95
159.39
132.73
126.97
113.96
78.27
77.43
77.00
76.58
74.17
60.79
55.30
49.28
47.61
35.34
20.91
MeO
OAc
O
O
ppm

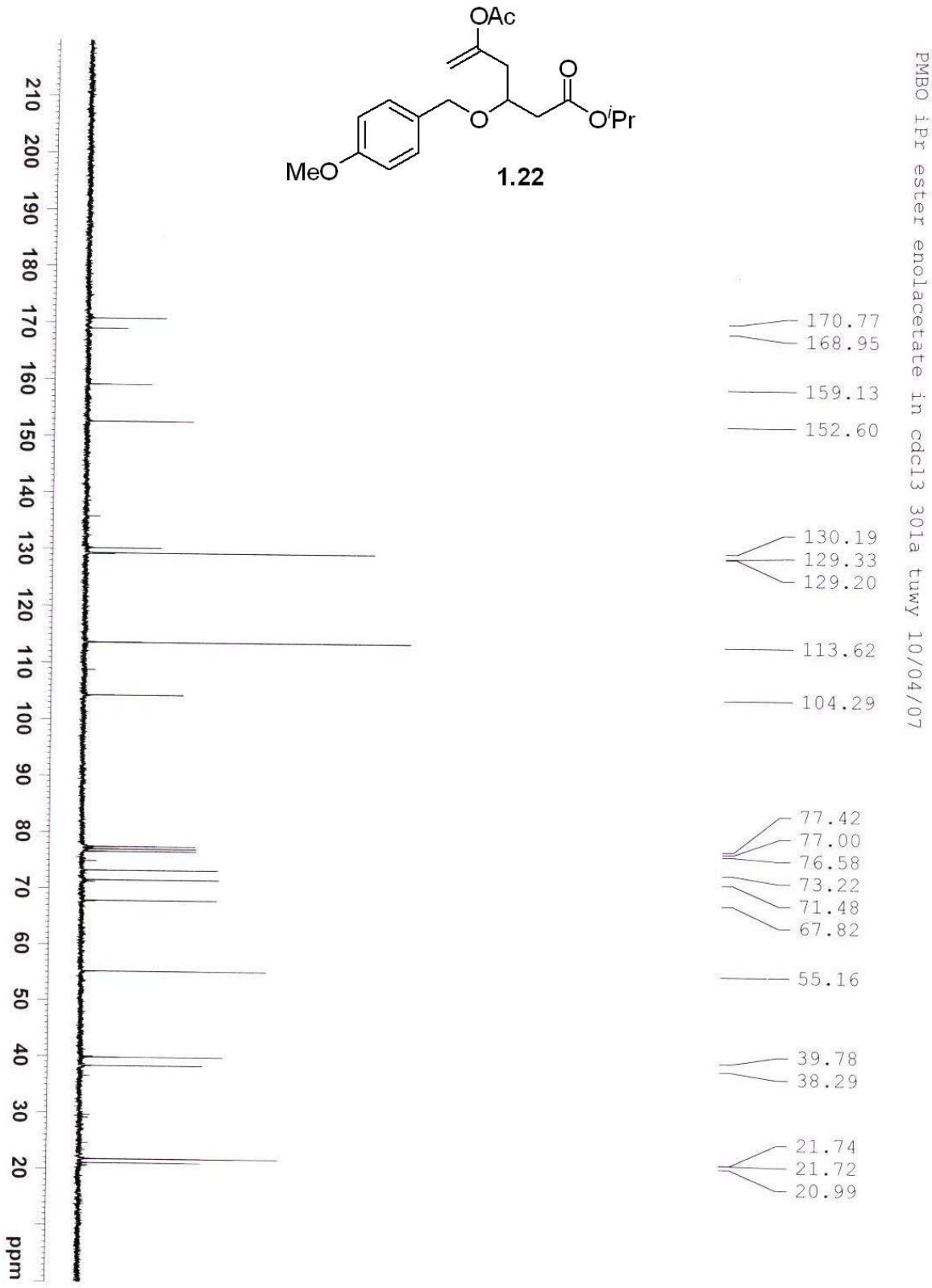

OAc
OMOM
O
MeO
1.21
PMB MOM enolacetate in cdcl3 301b tuwy 08/28/07
1.59
1.57
1.81
1.89
1.01
1.00
2.79
1.05
2.04
2.43
2.05
2.61
2.07
ppm
7.292
7.265
6.899
6.870
4.850
4.627
4.605
4.597
4.575
4.561
4.525
4.446
4.410
3.809
3.761
3.739
3.720
3.700
3.664
3.643
3.622
3.364
2.599
2.579
2.550
2.531
2.513
2.482
2.463
2.105
1.974
1.965
1.918
1.891
1.869
1.864
1.854
1.841
1.820
1.793

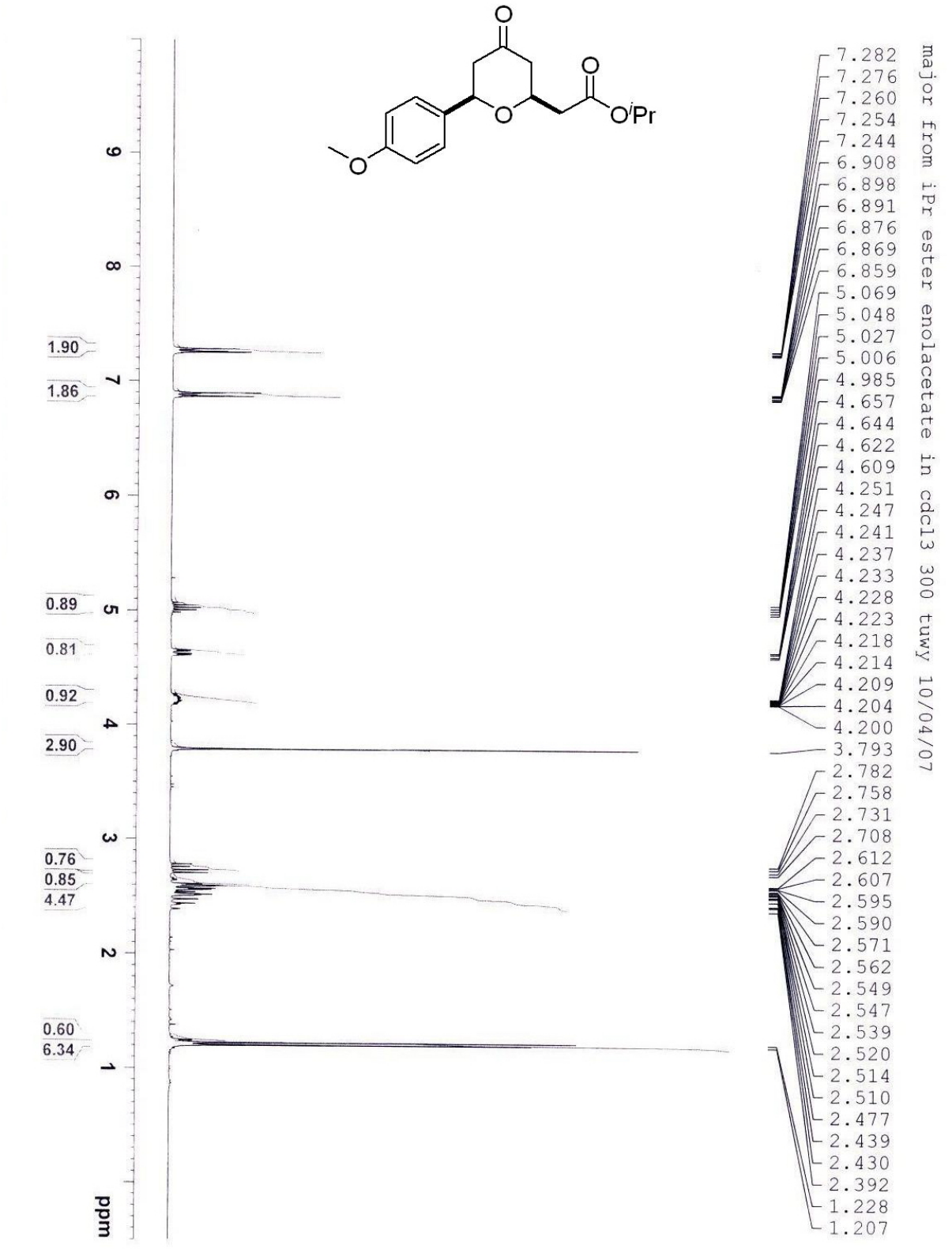

PMB MOM enolacetate in cdcl3 301b tuwy 08/28/07
OAc
OMOM
O
MeO
1.21
169.96
159.14
153.20
130.49
129.36
113.68
103.81
96.44
77.44
77.01
76.59
73.25
71.08
64.23
55.17
55.11
38.37
34.40
21.01
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

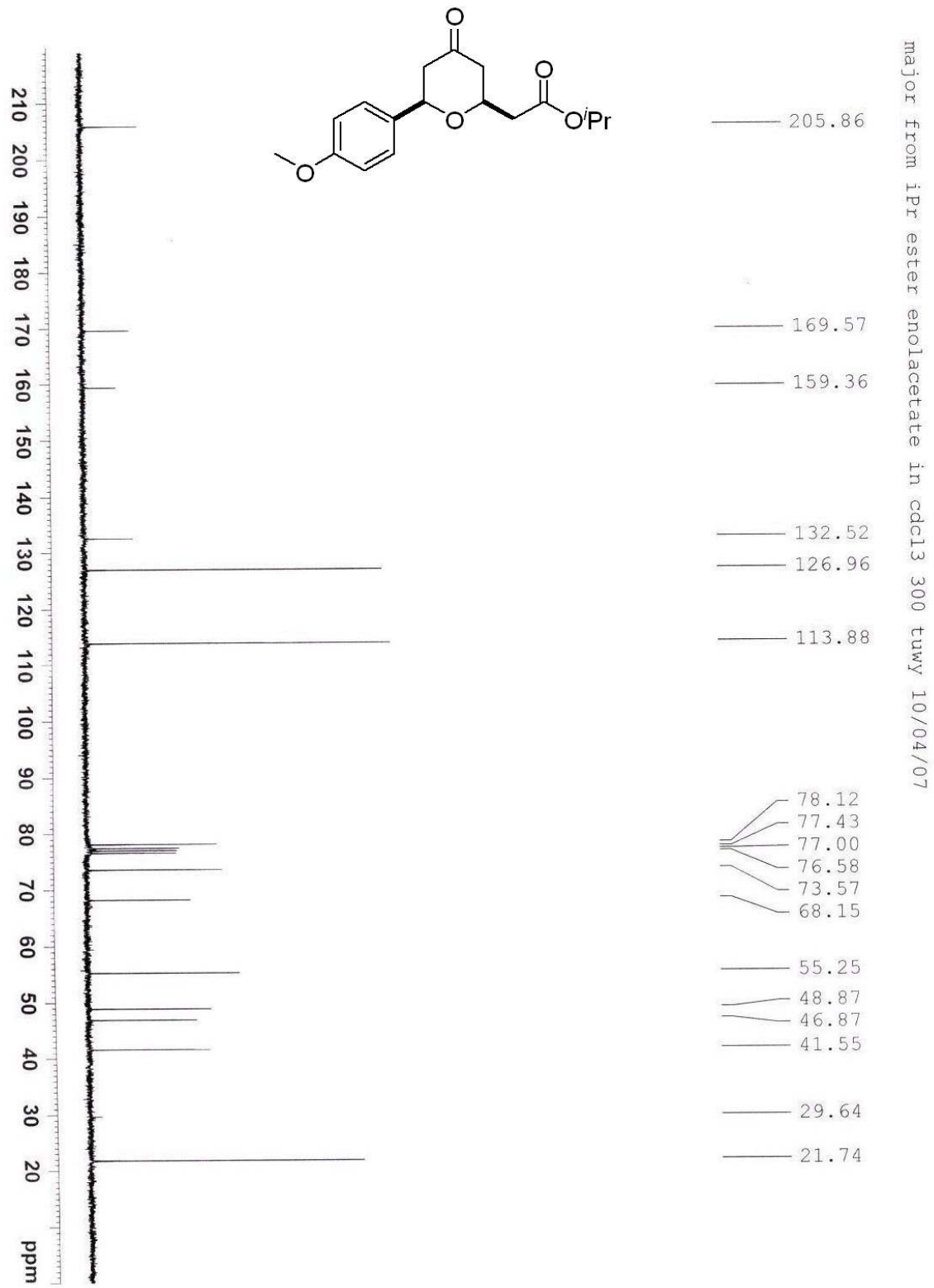

O
OMOM
O
MeO
1.81
1.79
2.88
1.00
2.96
2.07
2.43
4.22
1.24
1.41
ppm
cyclized from PMB MOM enolacetate in cdcl3 301a tuwy 08/28/07
7.305
7.276
6.917
6.888
4.619
4.603
4.586
4.572
3.984
3.972
3.960
3.947
3.935
3.922
3.803
3.777
3.757
3.744
3.726
3.717
3.695
3.675
3.656
3.642
3.623
3.332
2.636
2.599
2.564
2.516
2.473
2.468
2.438
2.401
2.391
2.353
2.053
2.046
2.036
2.025
2.019
2.006
1.998
1.988
1.980
1.962
1.943
1.924
1.917
1.908
1.897
1.882
1.870
1.861
1.854

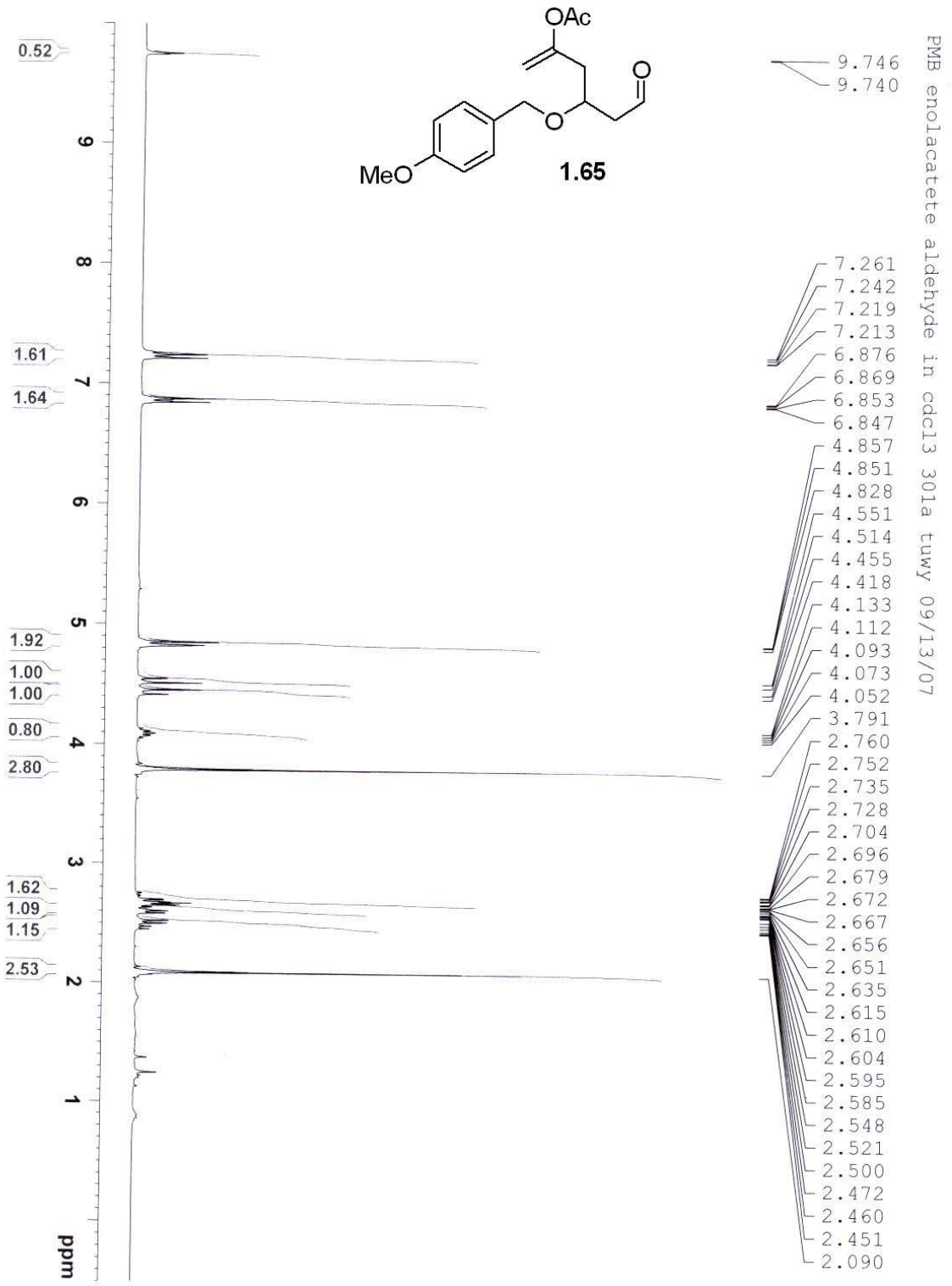

cyclized from PMB MOM enolacetate in cdcl3 301a tuwy 08/28/07
206.71
159.29
132.87
126.92
113.90
96.38
78.17
77.43
77.00
76.58
74.23
63.61
55.23
55.11
49.24
47.68
36.39
OMOM
MeO
O
O
ppm

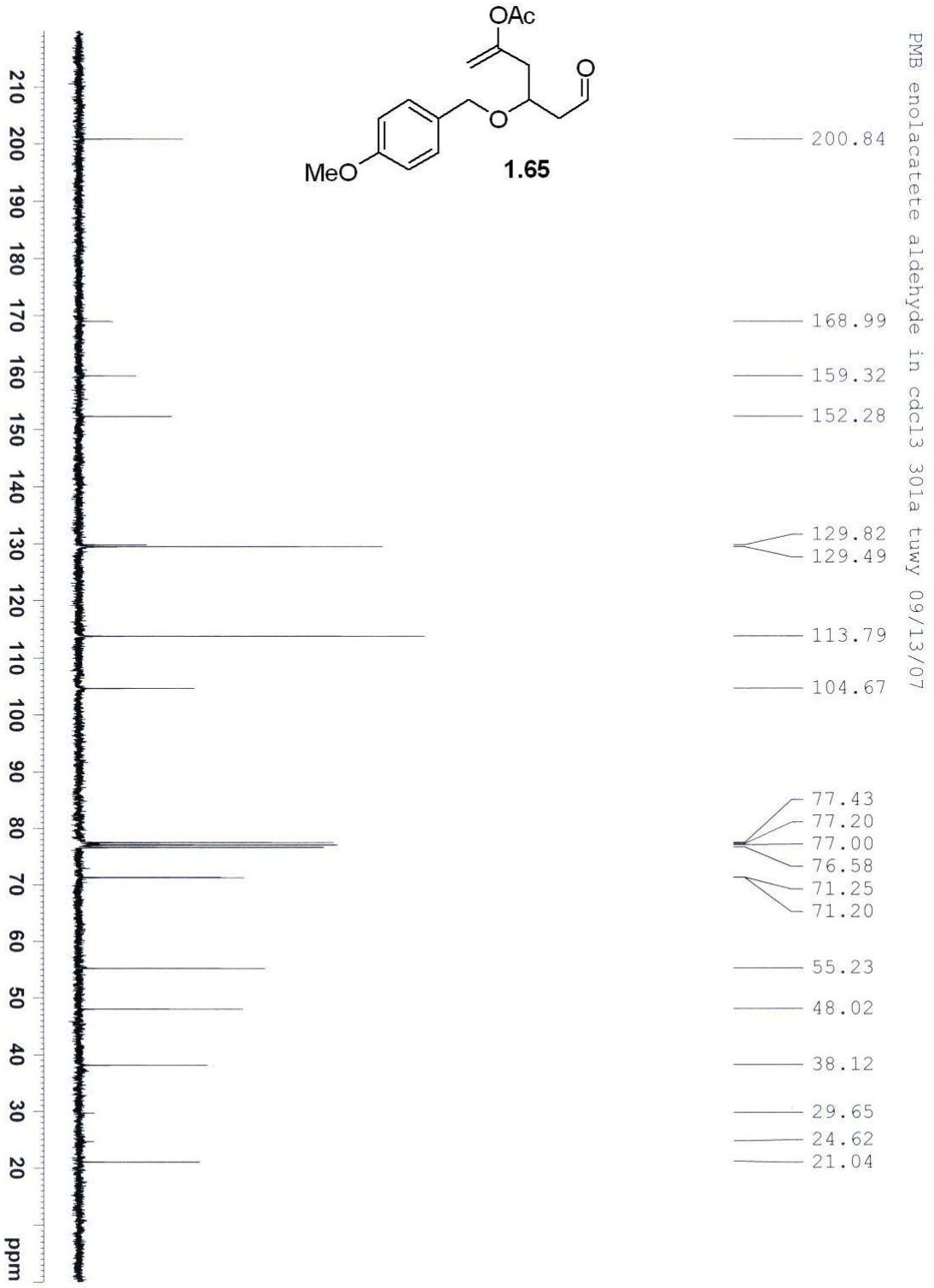

OAc
O
O
O
O'Pr
MeO
1.22
PMBO iPr ester enolacetate in cdcl3 301a tuwy 10/04/07
7.247
7.218
6.857
6.829
5.077
5.056
5.035
5.014
4.993
4.972
4.951
4.938
4.832
4.817
4.484
4.064
4.043
4.022
4.001
3.981
3.776
2.615
2.585
2.563
2.538
2.526
2.516
2.497
2.474
2.468
2.460
2.447
2.442
2.072
1.235
1.228
1.214
1.207
1.73
1.80
0.82
1.94
2.17
1.00
3.00
4.41
2.73
3.57
3.40
ppm

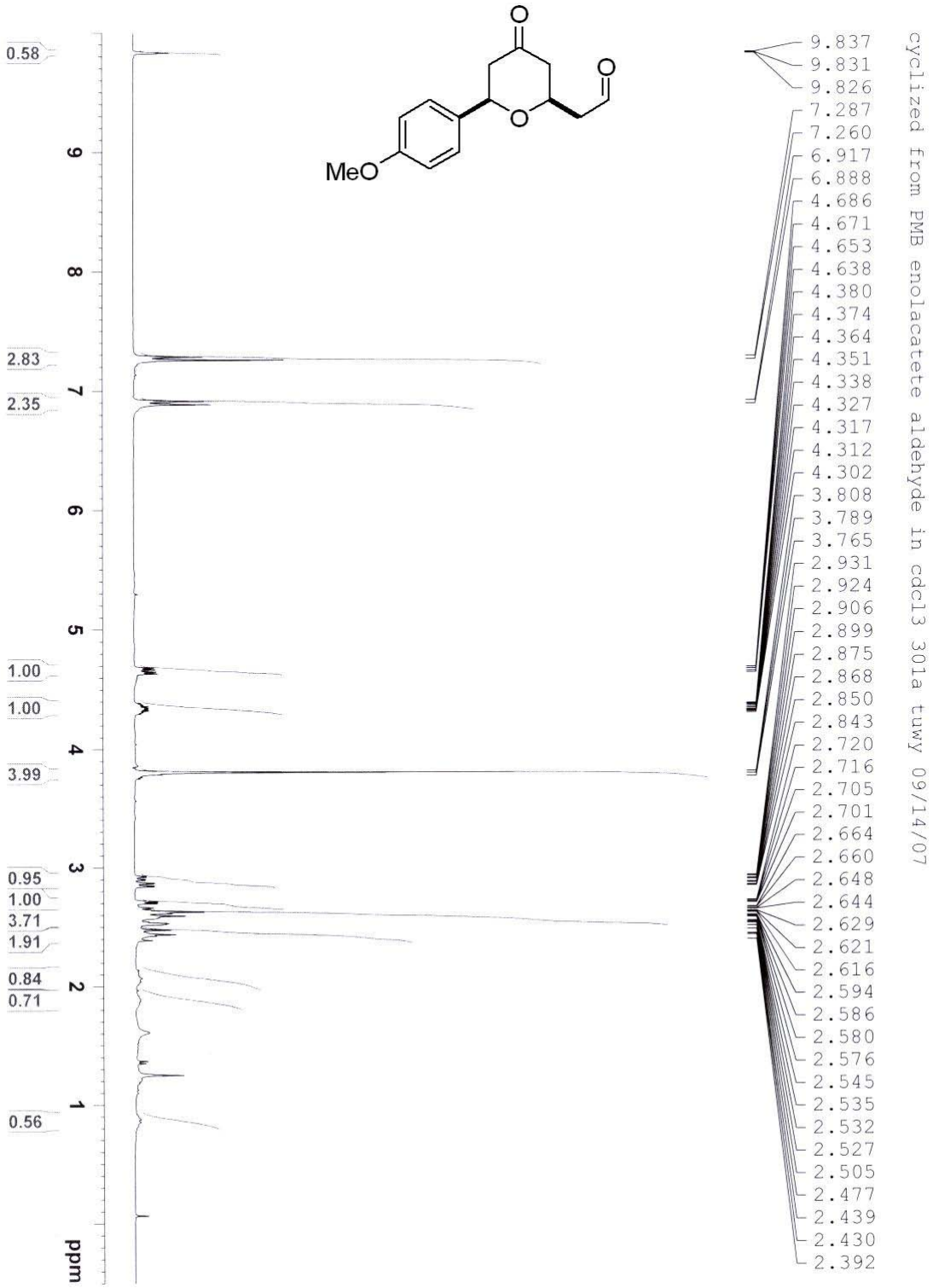

OAc
O
O
O
iPr
MeO
1.22
PMBO iPr ester enolacetate in cdcl3 301a tuwy 10/04/07
170.77
168.95
159.13
152.60
130.19
129.33
129.20
113.62
104.29
77.42
77.00
76.58
73.22
71.48
67.82
55.16
39.78
38.29
21.74
21.72
20.99
ppm

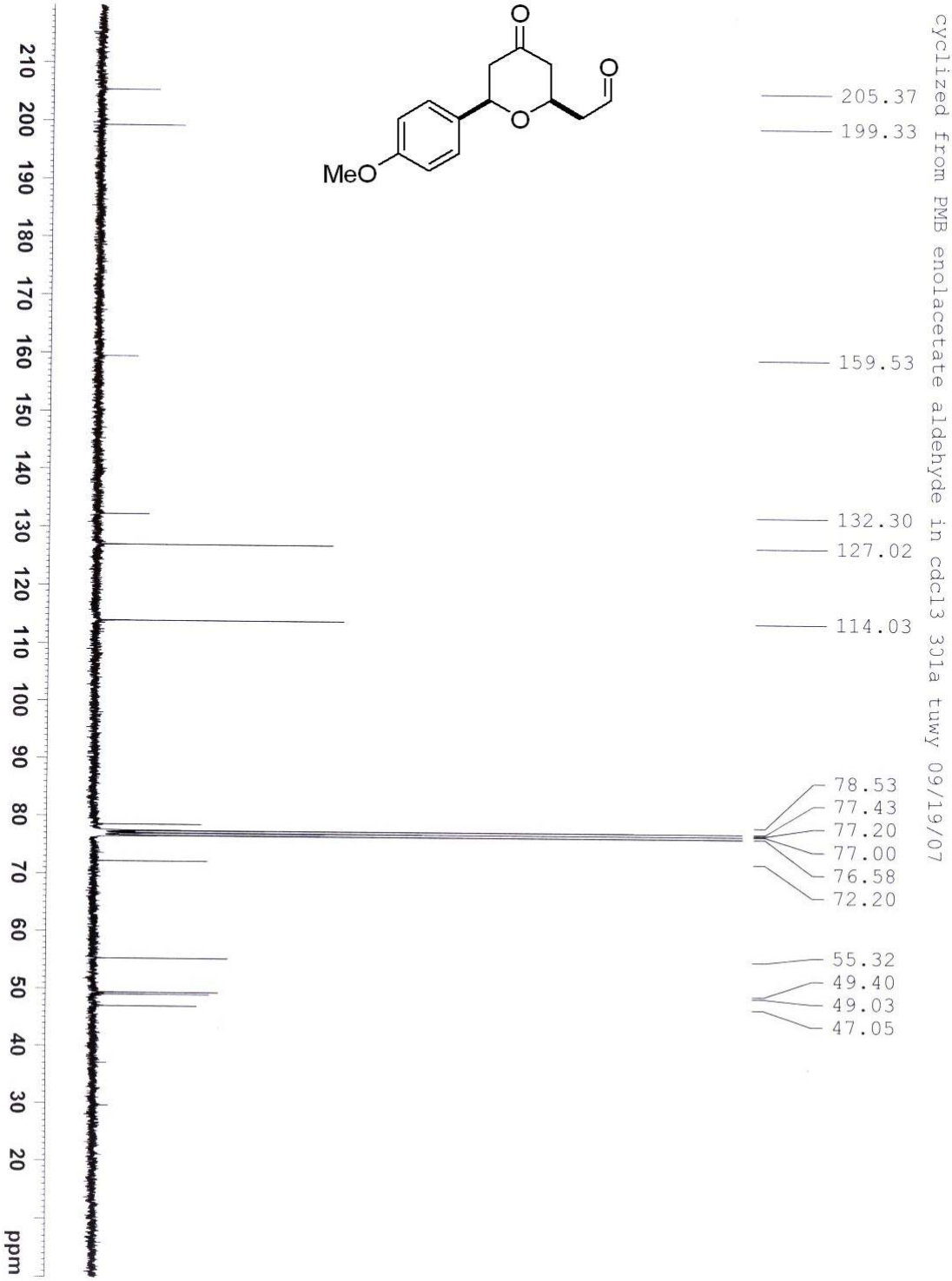

major from iPr ester enolacetate in cdcl3 300 tuwy 10/04/07
7.282
7.276
7.260
7.254
7.244
6.908
6.898
6.891
6.876
6.869
6.859
5.069
5.048
5.027
5.006
4.985
4.657
4.644
4.622
4.609
4.251
4.247
4.241
4.237
4.233
4.228
4.223
4.218
4.214
4.209
4.204
4.200
3.793
2.782
2.758
2.731
2.708
2.612
2.607
2.595
2.590
2.571
2.562
2.549
2.547
2.539
2.520
2.514
2.510
2.477
2.439
2.430
2.392
1.228
1.207
1.90
1.86
0.89
0.81
0.92
2.90
0.76
0.85
4.47
0.60
6.34
ppm

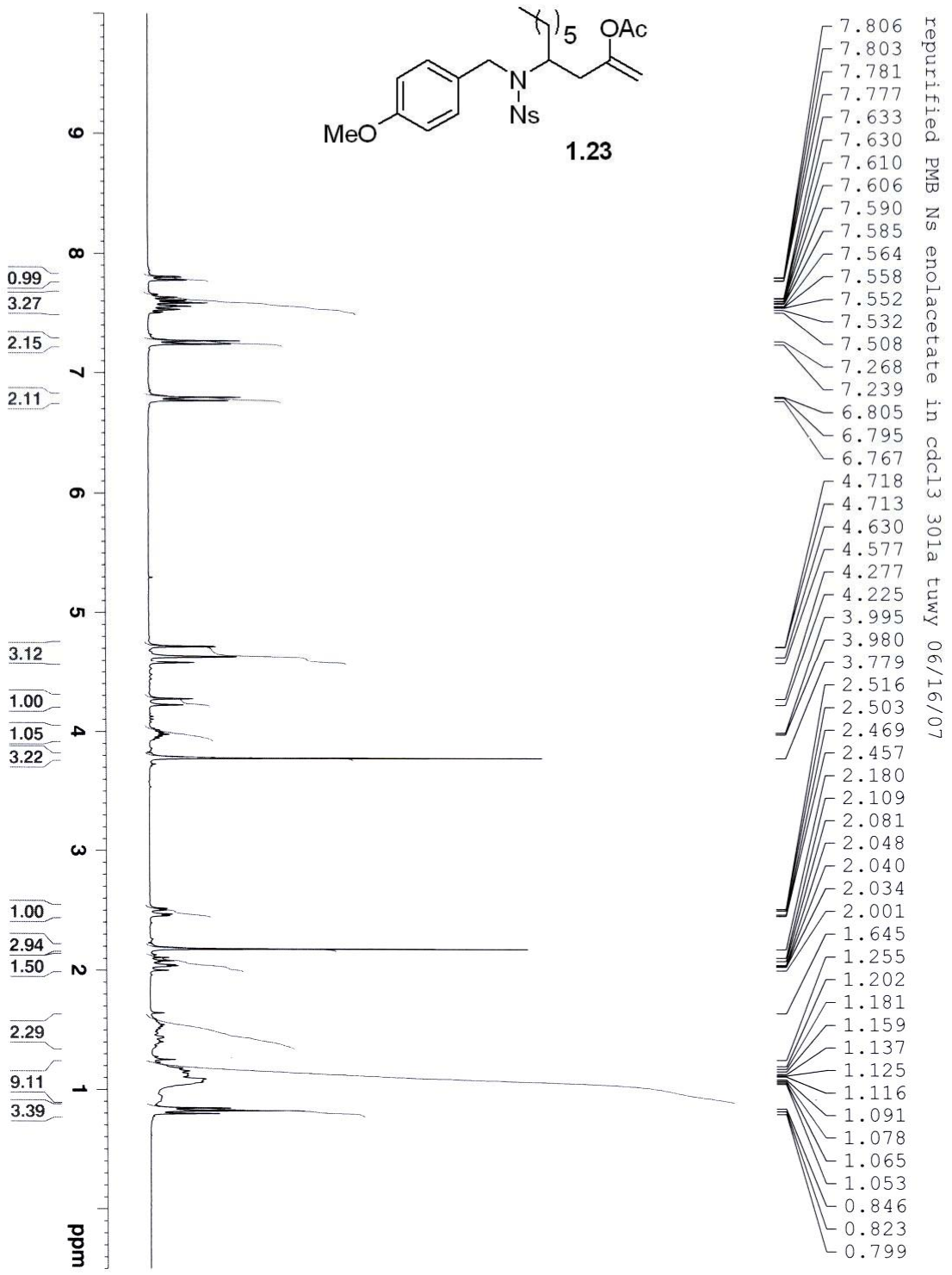

major from iPr ester enolacetate in cdcl3 300 tuwy 10/04/07
205.86
169.57
159.36
132.52
126.96
113.88
78.12
77.43
77.00
76.58
73.57
68.15
55.25
48.87
46.87
41.55
29.64
21.74
ppm

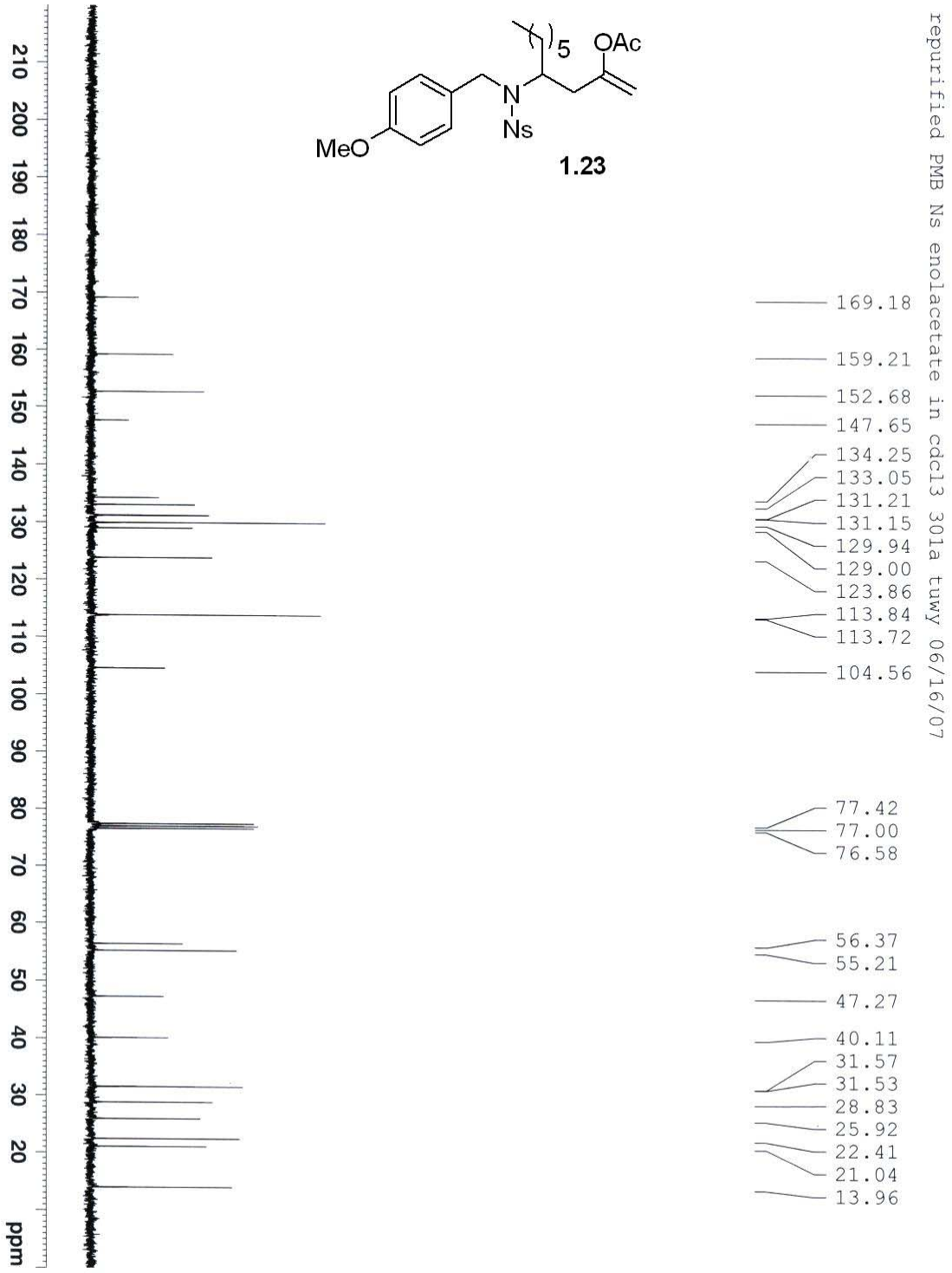

PMB enolacatete aldehyde in cdcl3 301a tuwy 09/13/07
OAc
O
O
MeO
1.65
9.746
9.740
7.261
7.242
7.219
7.213
6.876
6.869
6.853
6.847
4.857
4.851
4.828
4.551
4.514
4.455
4.418
4.133
4.112
4.093
4.073
4.052
3.791
2.760
2.752
2.735
2.728
2.704
2.696
2.679
2.672
2.667
2.656
2.651
2.635
2.615
2.610
2.604
2.595
2.585
2.548
2.521
2.500
2.472
2.460
2.451
2.090
0.52
1.61
1.64
1.92
1.00
1.00
0.80
2.80
1.62
1.09
1.15
2.53
ppm

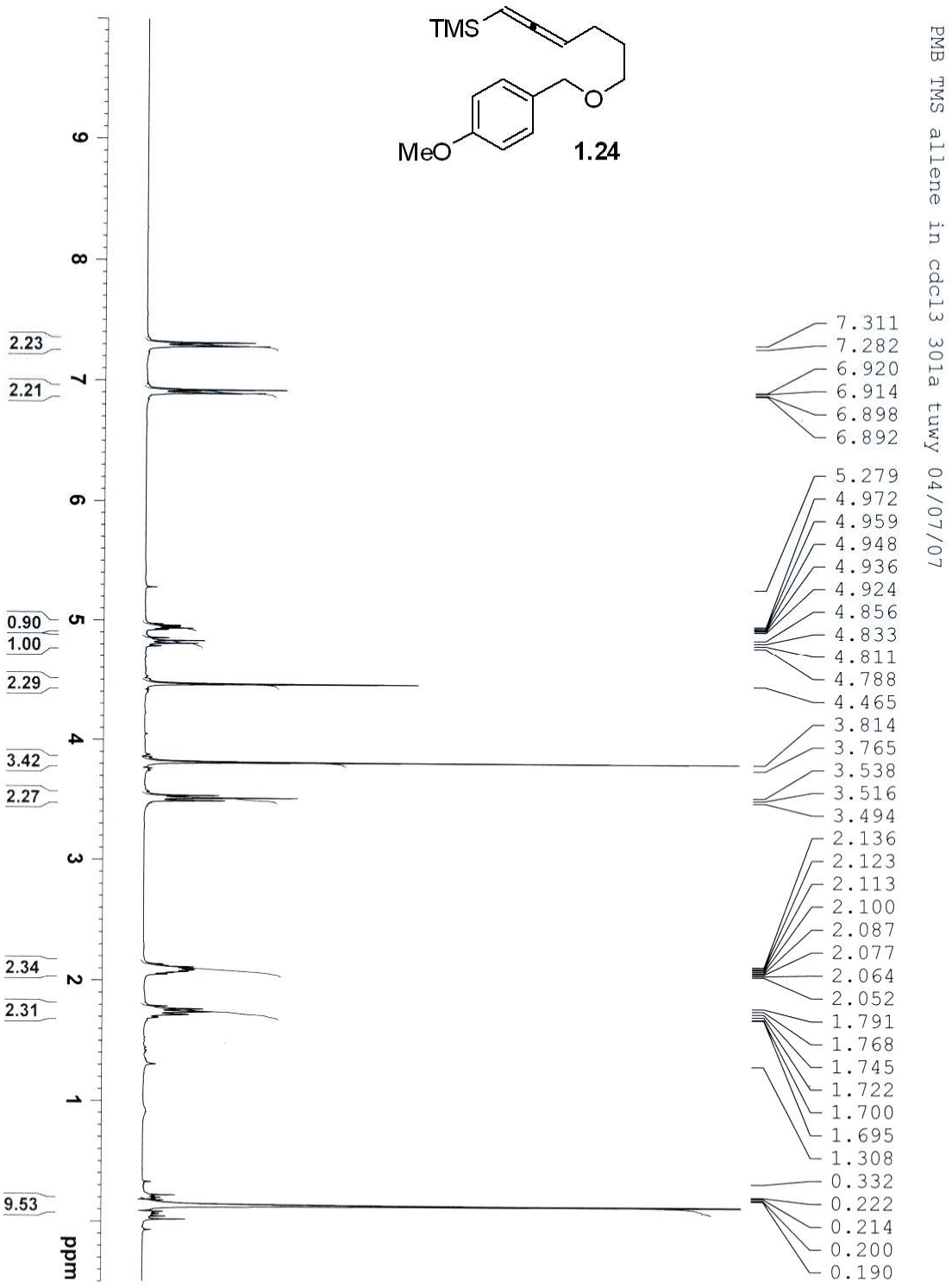

OAc
O
O
MeO
1.65
PMB enolacatete aldehyde in cdcl3 301a tuwy 09/13/07
200.84
168.99
159.32
152.28
129.82
129.49
113.79
104.67
77.43
77.20
77.00
76.58
71.25
71.20
55.23
48.02
38.12
29.65
24.62
21.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

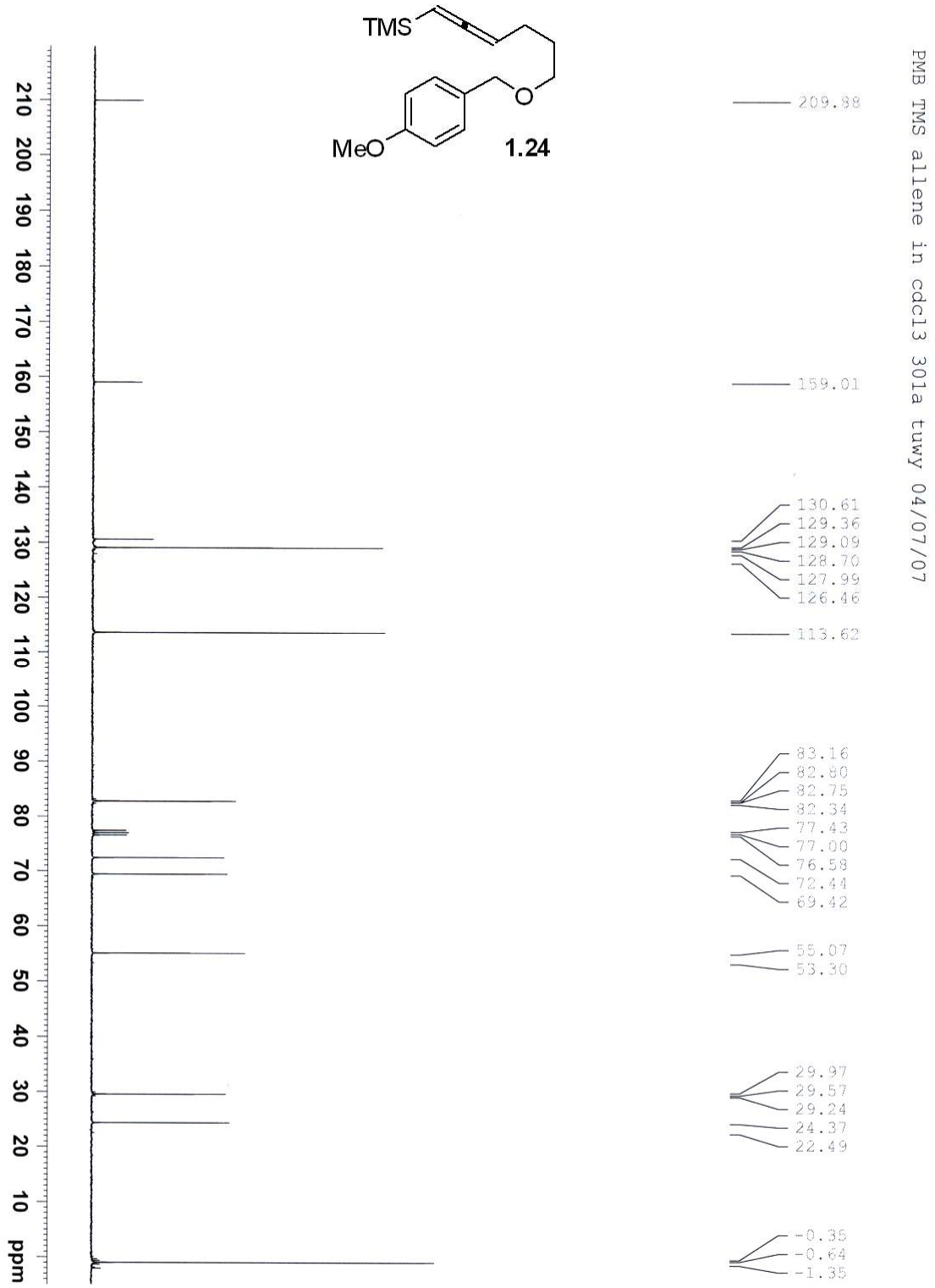

cyclized from PMB enolacatete aldehyde in cdcl3 301a tuwy 09/14/07
9.837
9.831
9.826
7.287
7.260
6.917
6.888
4.686
4.671
4.653
4.638
4.380
4.374
4.364
4.351
4.338
4.327
4.317
4.312
4.302
3.808
3.789
3.765
2.931
2.924
2.906
2.899
2.875
2.868
2.850
2.843
2.720
2.716
2.705
2.701
2.664
2.660
2.648
2.644
2.629
2.621
2.616
2.594
2.586
2.580
2.576
2.545
2.535
2.532
2.527
2.505
2.477
2.439
2.430
2.392
MeO
O
O
O
0.58
2.83
2.35
1.00
1.00
3.99
0.95
1.00
3.71
1.91
0.84
0.71
0.56
ppm

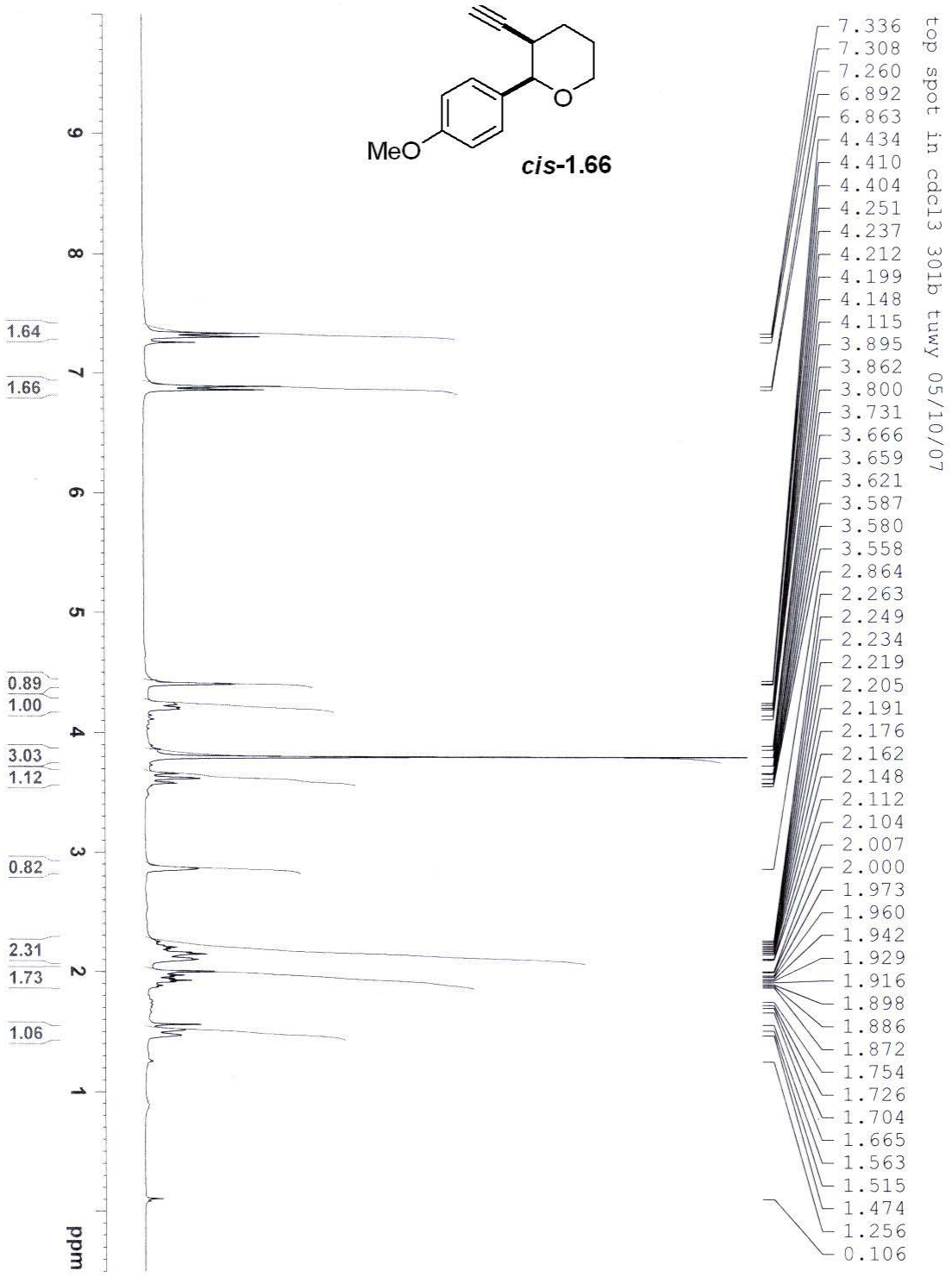

cyclized from PMB enolacetate aldehyde in cdcl3 301a tuwy 09/19/07
205.37
199.33
159.53
132.30
127.02
114.03
78.53
77.43
77.20
77.00
76.58
72.20
55.32
49.40
49.03
47.05
MeO
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


repurified PMB Ns enolacetate in cdcl3 301a tuwy 06/16/07
7.806
7.803
7.781
7.777
7.633
7.630
7.610
7.606
7.590
7.585
7.564
7.558
7.552
7.532
7.508
7.268
7.239
6.805
6.795
6.767
4.718
4.713
4.630
4.577
4.277
4.225
3.995
3.980
3.779
2.516
2.503
2.469
2.457
2.180
2.109
2.081
2.048
2.040
2.034
2.001
1.645
1.255
1.202
1.181
1.159
1.137
1.125
1.116
1.091
1.078
1.065
1.053
0.846
0.823
0.799
MeO
N
Ns
5
OAc
1.23
0.99
3.27
2.15
2.11
3.12
1.00
1.05
3.22
1.00
2.94
1.50
2.29
9.11
3.39
ppm

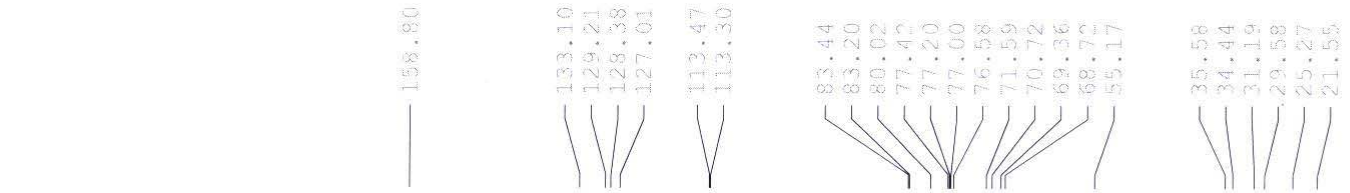

repurified PMB Ns enolacetate in cdcl3 301a tuwy 06/16/07
169.18
159.21
152.68
147.65
134.25
133.05
131.21
131.15
129.94
129.00
123.86
113.84
113.72
104.56
77.42
77.00
76.58
56.37
55.21
47.27
40.11
31.57
31.53
28.83
25.92
22.41
21.04
13.96
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm
MeO
N
Ns
5
OAc
1.23

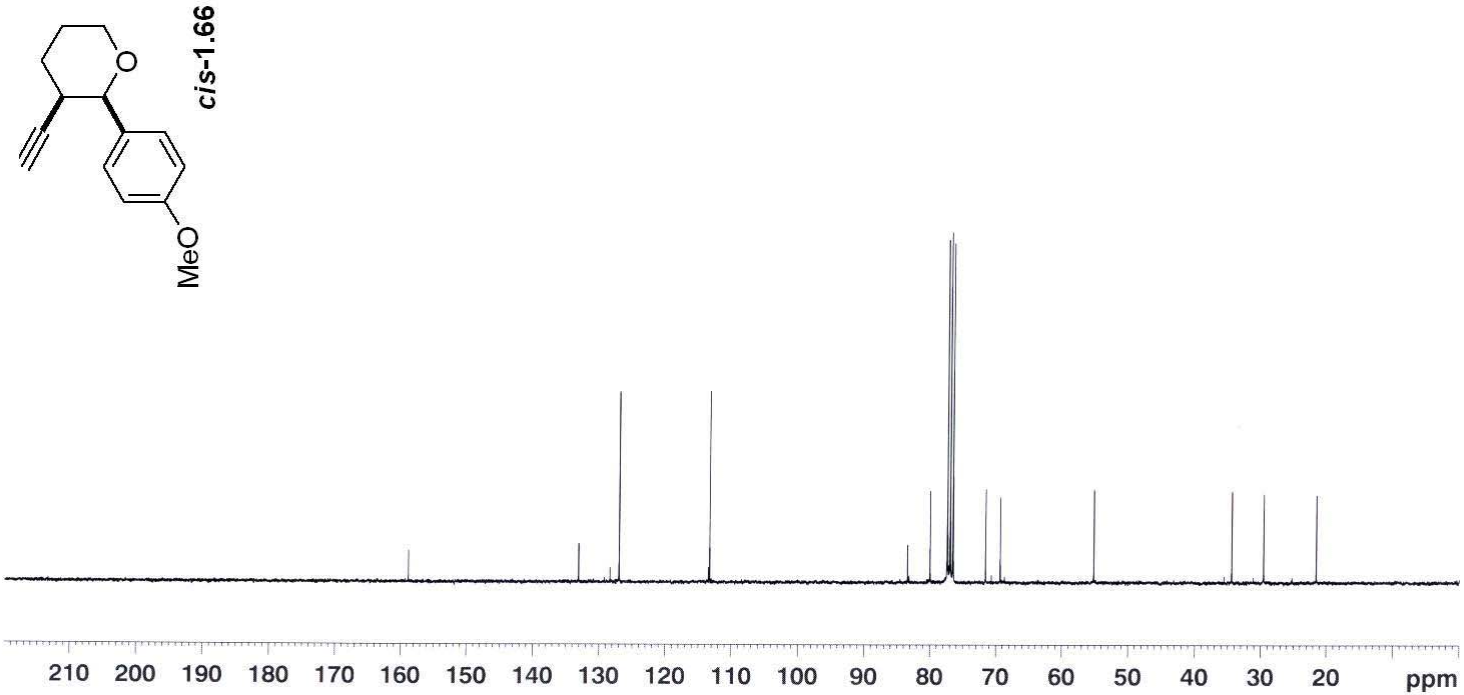

TMS
MeO
1.24
PMB TMS allene in cdcl3 301a tuwy 04/07/07
2.23
2.21
0.90
1.00
2.29
3.42
2.27
2.34
2.31
9.53
ppm
7.311
7.282
6.920
6.914
6.898
6.892
5.279
4.972
4.959
4.948
4.936
4.924
4.856
4.833
4.811
4.788
4.465
3.814
3.765
3.538
3.516
3.494
2.136
2.123
2.113
2.100
2.087
2.077
2.064
2.052
1.791
1.768
1.745
1.722
1.700
1.695
1.308
0.332
0.222
0.214
0.200
0.190

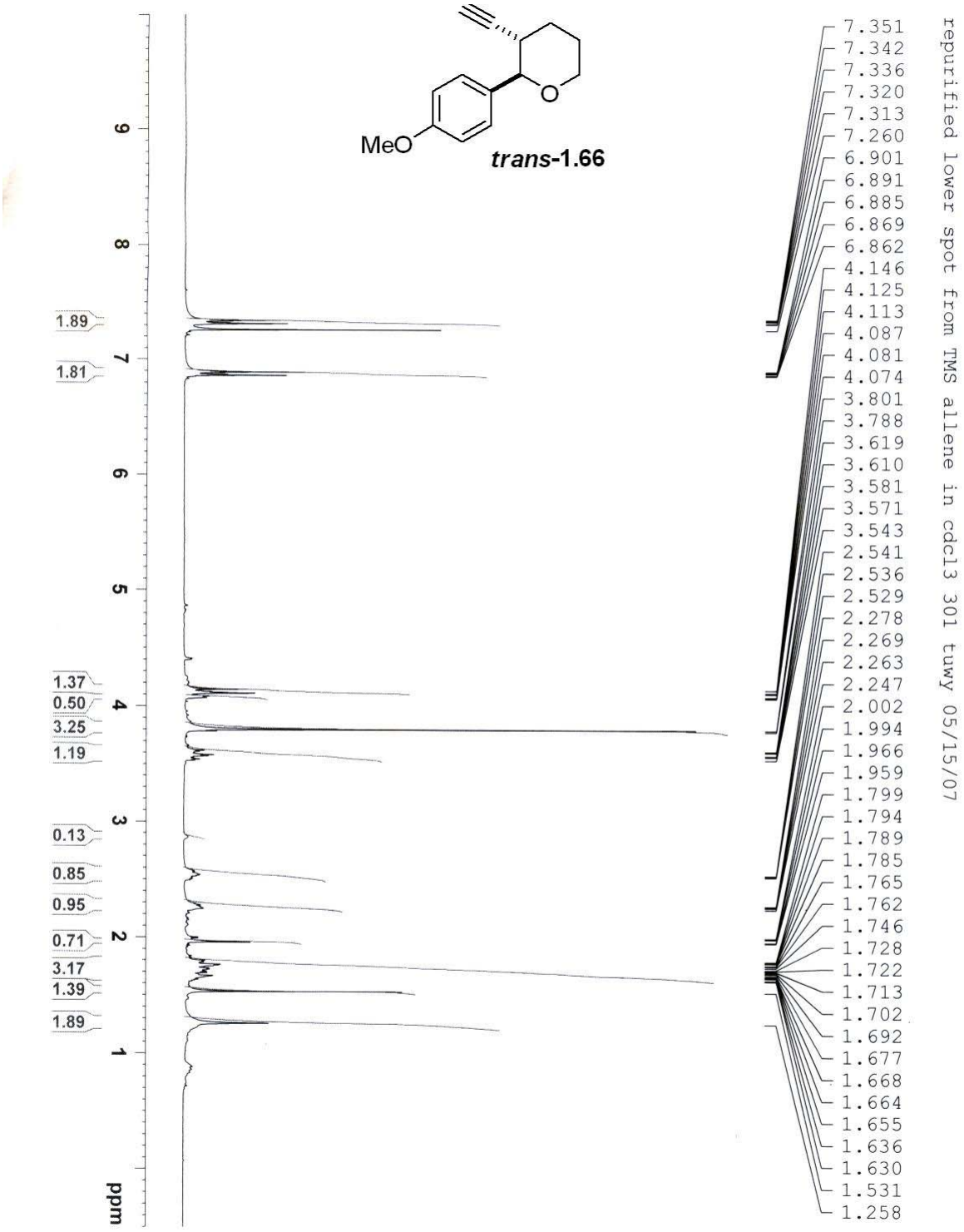

PMB TMS allene in cdcl3 301a tuwy 04/07/07
TMS
O
MeO
1.24
209.88
159.01
130.61
129.36
129.09
128.70
127.99
126.46
113.62
83.16
82.80
82.75
82.34
77.43
77.00
76.58
72.44
69.42
55.07
53.30
29.97
29.57
29.24
24.37
22.49
-0.35
-0.64
-1.35
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

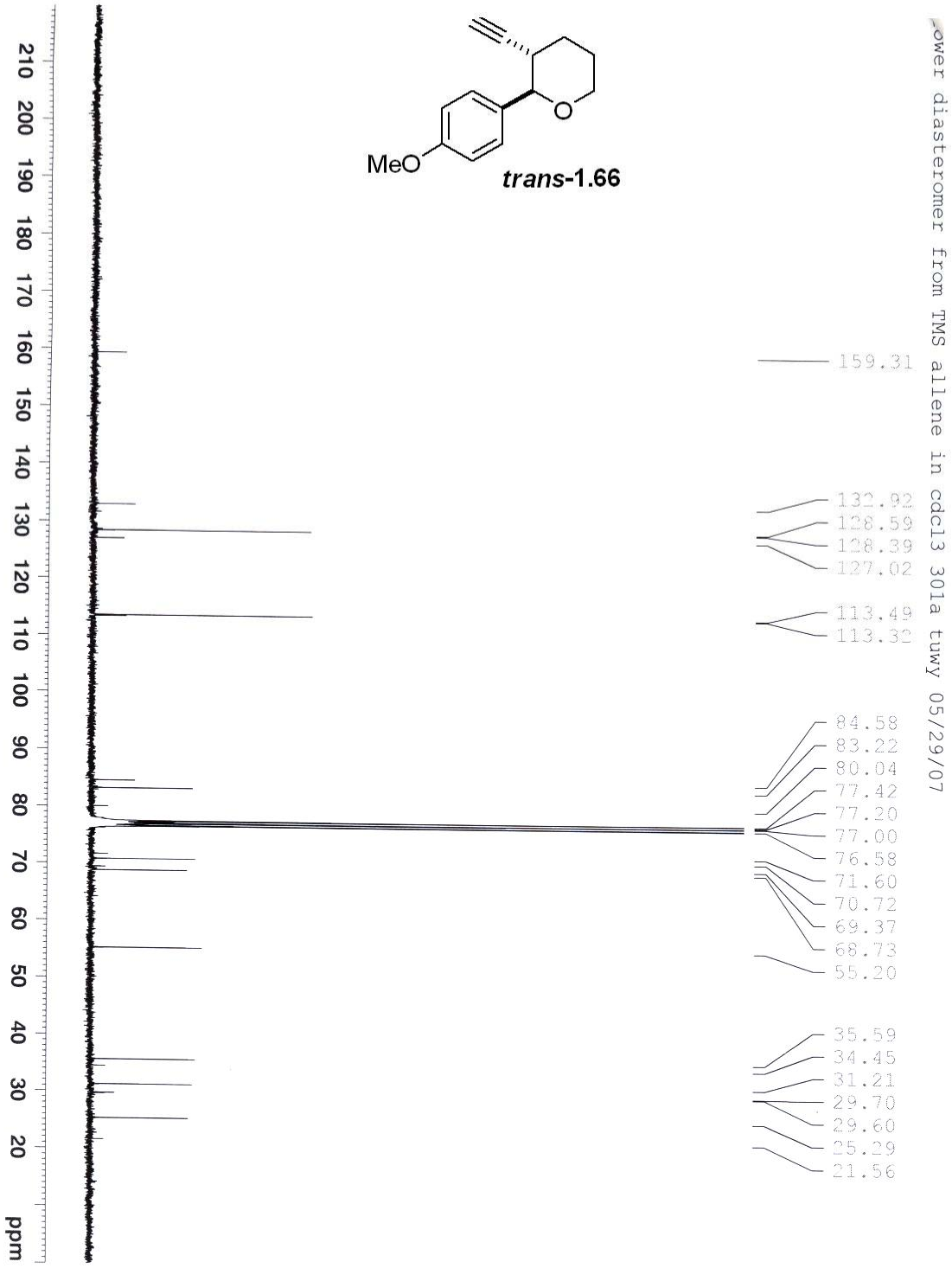

MeO
O
cis-1.66
top spot in cdcl3 301b tuwy 05/10/07
7.336
7.308
7.260
6.892
6.863
4.434
4.410
4.404
4.251
4.237
4.212
4.199
4.148
4.115
3.895
3.862
3.800
3.731
3.666
3.659
3.621
3.587
3.580
3.558
2.864
2.263
2.249
2.234
2.219
2.205
2.191
2.176
2.162
2.148
2.112
2.104
2.007
2.000
1.973
1.960
1.942
1.929
1.916
1.898
1.886
1.872
1.754
1.726
1.704
1.665
1.563
1.515
1.474
1.256
0.106
1.64
1.66
0.89
1.00
3.03
1.12
0.82
2.31
1.73
1.06
ppm

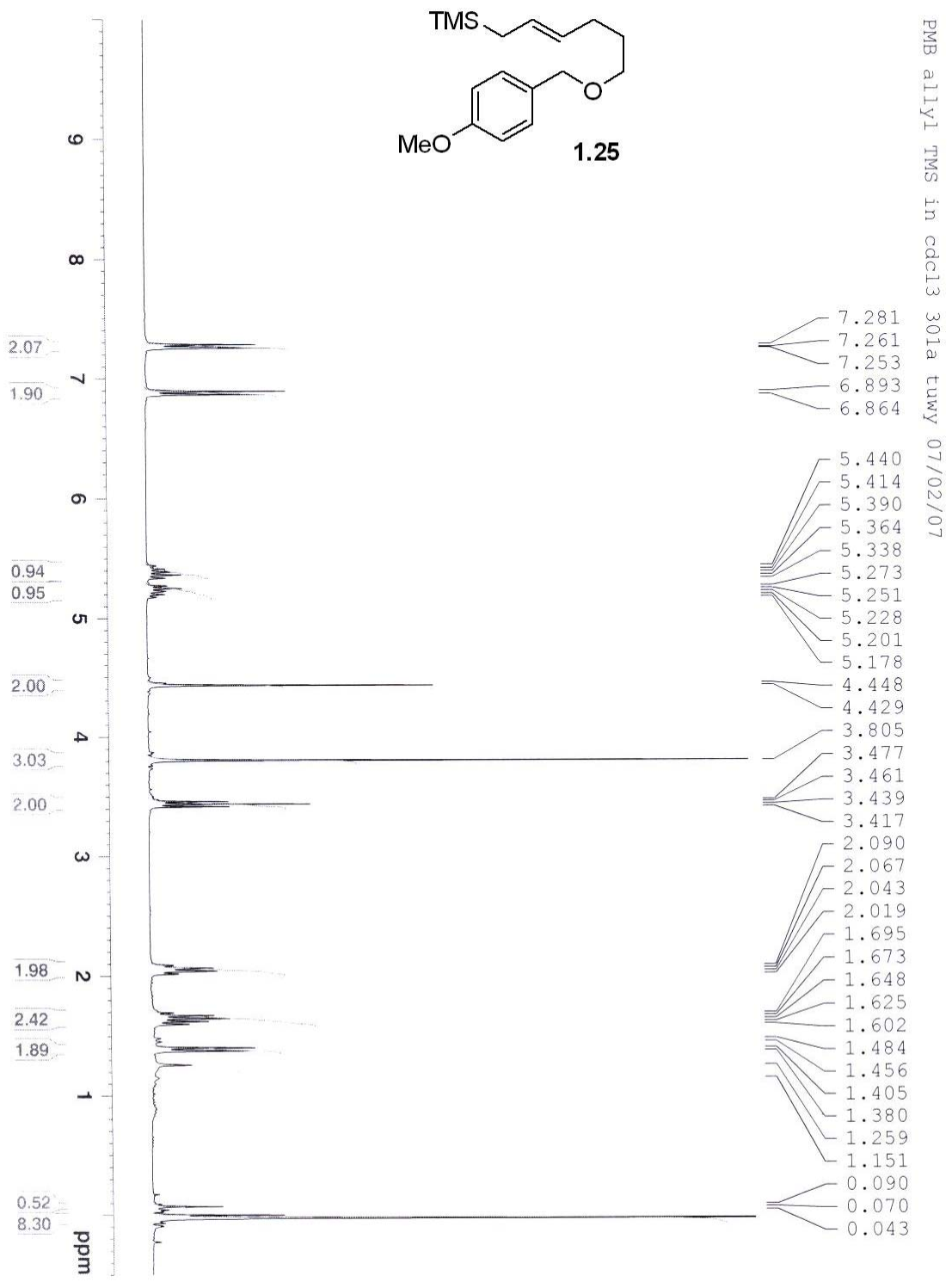
nstop spot from allene in cdcl3 301a tuwy 05/14/07

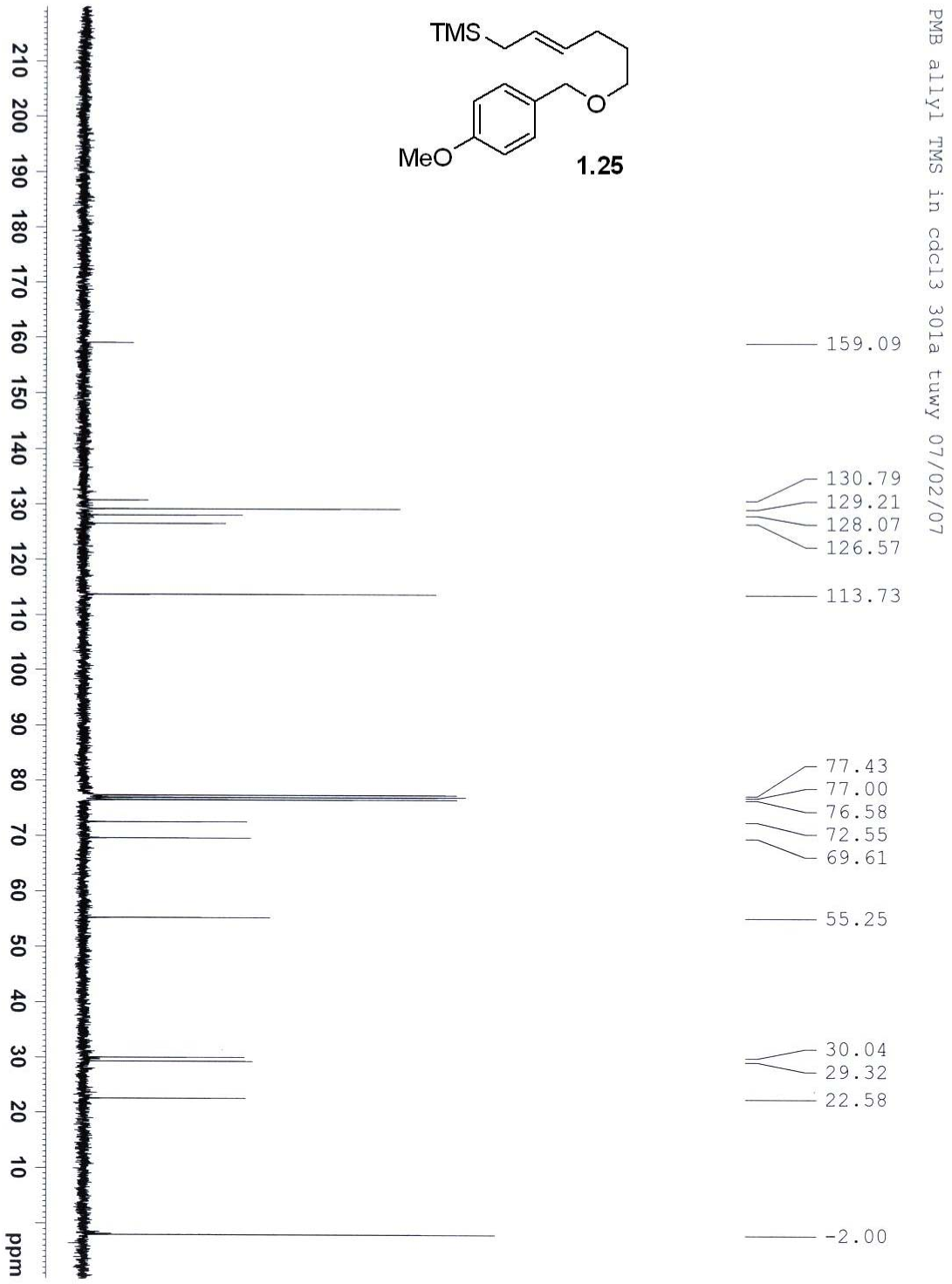


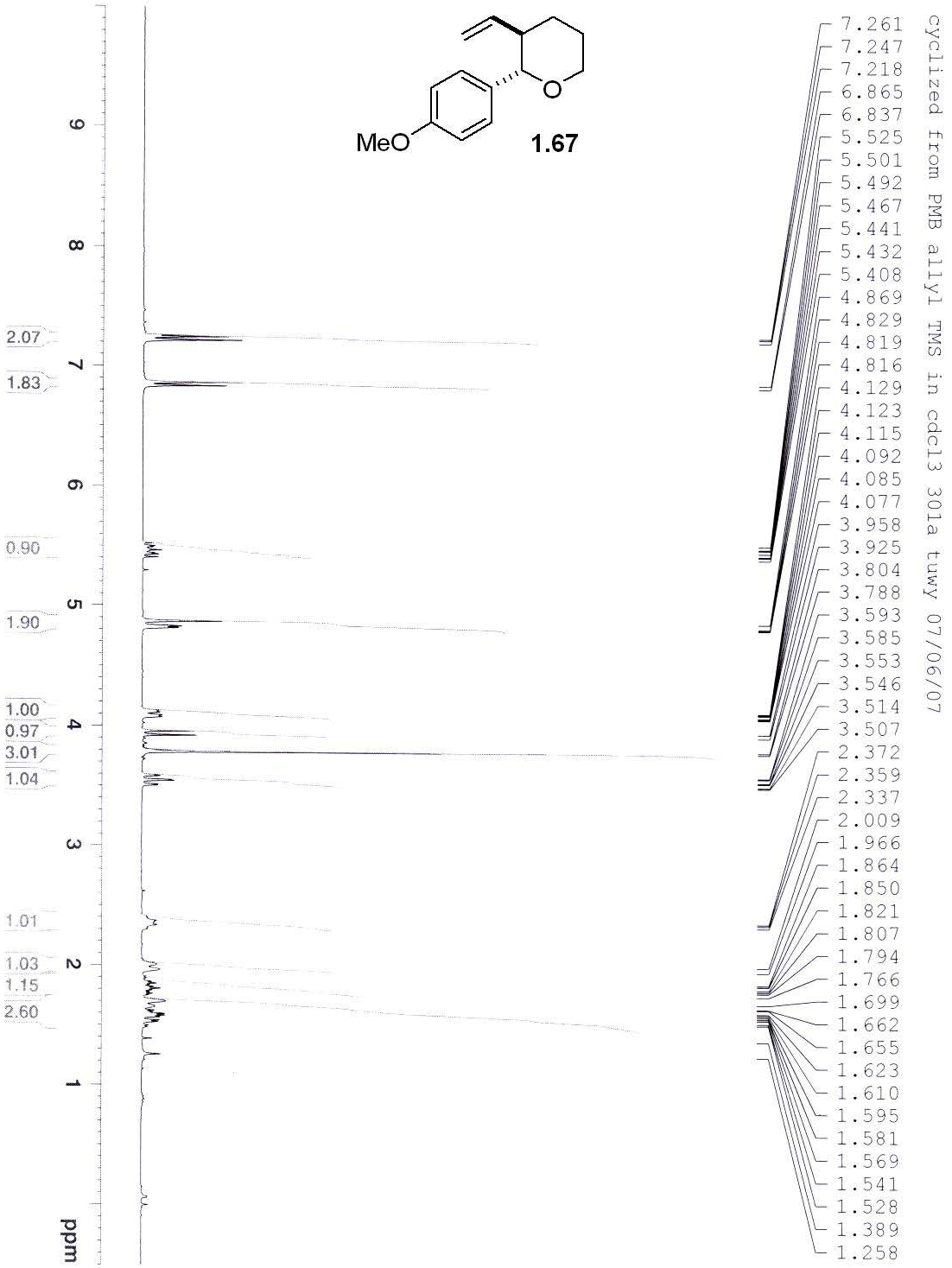



MeO
O
trans-1.66
repurified lower spot from TMS allene in cdcl3 301 tuwy 05/15/07
7.351
7.342
7.336
7.320
7.313
7.260
6.901
6.891
6.885
6.869
6.862
4.146
4.125
4.113
4.087
4.081
4.074
3.801
3.788
3.619
3.610
3.581
3.571
3.543
2.541
2.536
2.529
2.278
2.269
2.263
2.247
2.002
1.994
1.966
1.959
1.799
1.794
1.789
1.785
1.765
1.762
1.746
1.728
1.722
1.713
1.702
1.692
1.677
1.668
1.664
1.655
1.636
1.630
1.531
1.258
1.89
1.81
1.37
0.50
3.25
1.19
0.13
0.85
0.95
0.71
3.17
1.39
1.89
ppm

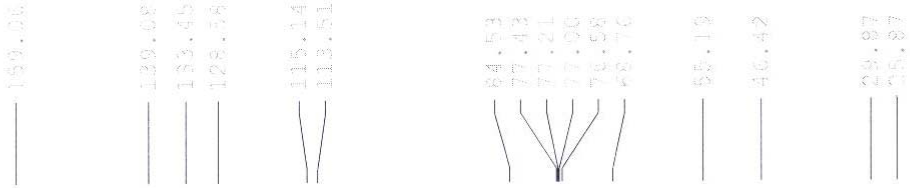

MeO
trans-1.66
ower diasteromer from TMS allene in cdcl3 301a tuwy 05/29/07
159.31
132.92
128.59
128.39
127.02
113.49
113.30
84.58
83.22
80.04
77.42
77.20
77.00
76.58
71.60
70.72
69.37
68.73
55.20
35.59
34.45
31.21
29.70
29.60
25.29
21.56
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

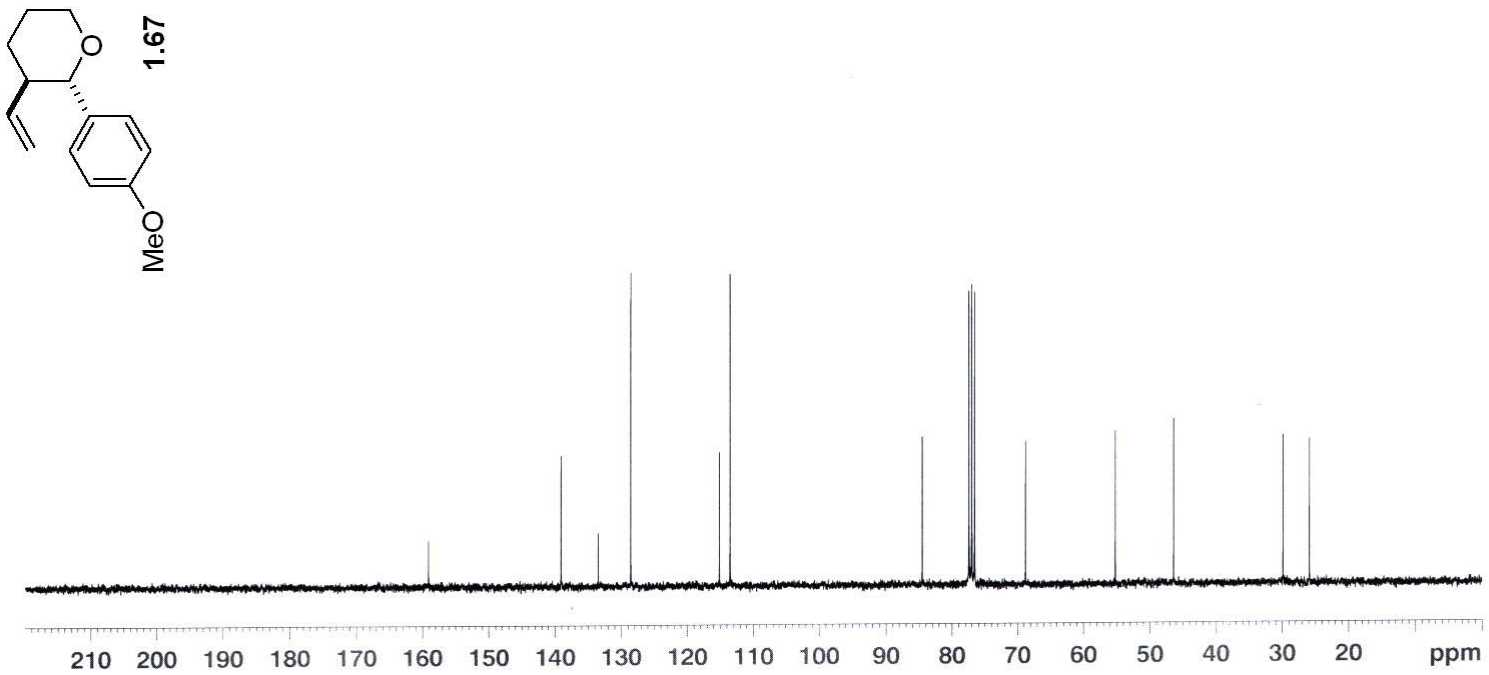

TMS
MeO
O
1.25
PMB allyl TMS in cdcl3 301a tuwy 07/02/07
7.281
7.261
7.253
6.893
6.864
5.440
5.414
5.390
5.364
5.338
5.273
5.251
5.228
5.201
5.178
4.448
4.429
3.805
3.477
3.461
3.439
3.417
2.090
2.067
2.043
2.019
1.695
1.673
1.648
1.625
1.602
1.484
1.456
1.405
1.380
1.259
1.151
0.090
0.070
0.043
2.07
1.90
0.94
0.95
2.00
3.03
2.00
1.98
2.42
1.89
0.52
8.30
ppm

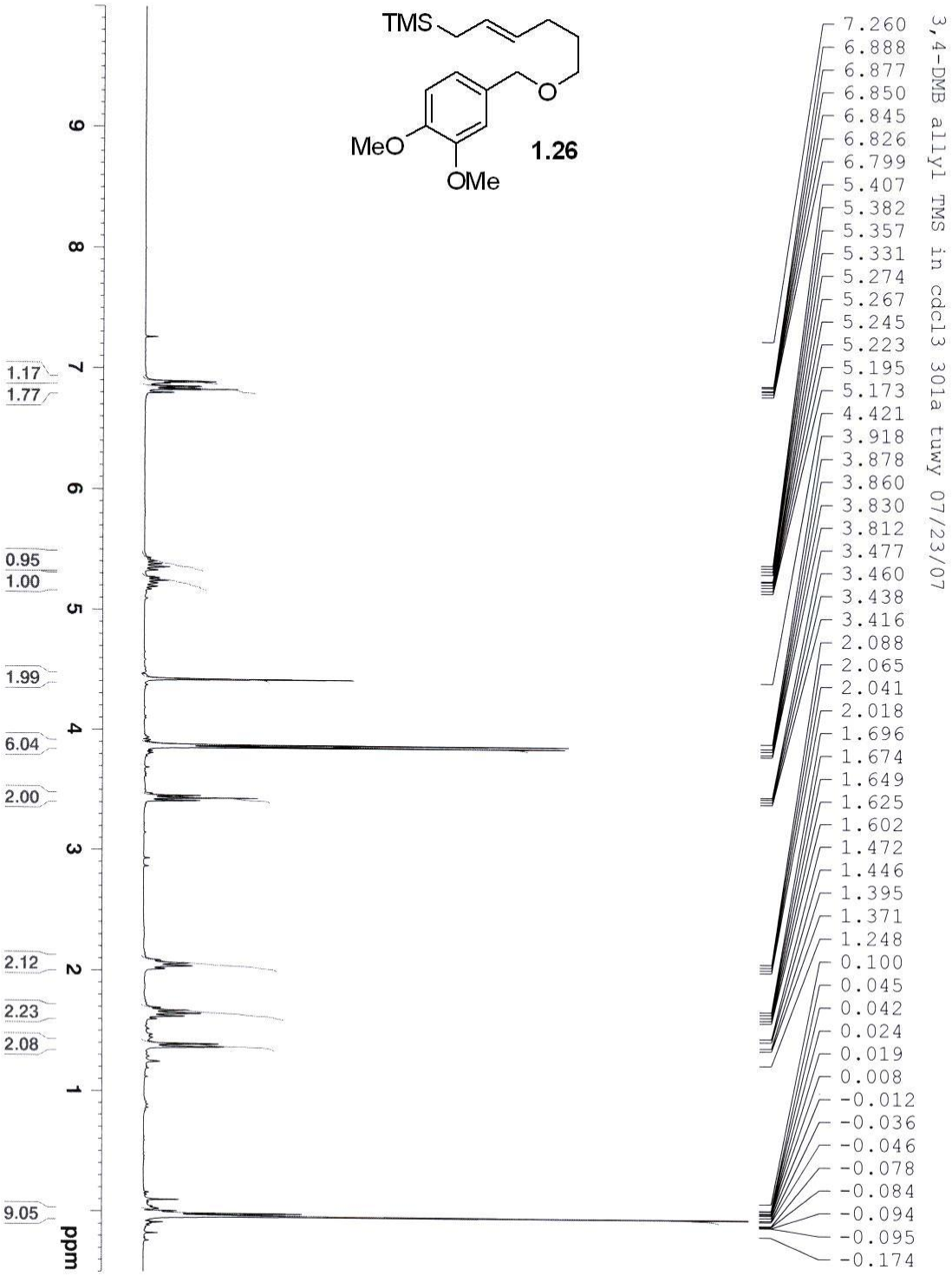

TMS
MeO
1.25
PMB allyl TMS in cdcl3 301a tuwy 07/02/07
159.09
130.79
129.21
128.07
126.57
113.73
77.43
77.00
76.58
72.55
69.61
55.25
30.04
29.32
22.58
-2.00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


cyclized from PMB allyl TMS in cdcl3 301a tuwy 07/06/07
7.261
7.247
7.218
6.865
6.837
5.525
5.501
5.492
5.467
5.441
5.432
5.408
4.869
4.829
4.819
4.816
4.129
4.123
4.115
4.092
4.085
4.077
3.958
3.925
3.804
3.788
3.593
3.585
3.553
3.546
3.514
3.507
2.372
2.359
2.337
2.009
1.966
1.864
1.850
1.821
1.807
1.794
1.766
1.699
1.662
1.655
1.623
1.610
1.595
1.581
1.569
1.541
1.528
1.389
1.258
MeO
O
1.67
2.07
1.83
0.90
1.90
1.00
0.97
3.01
1.04
1.01
1.03
1.15
2.60
ppm

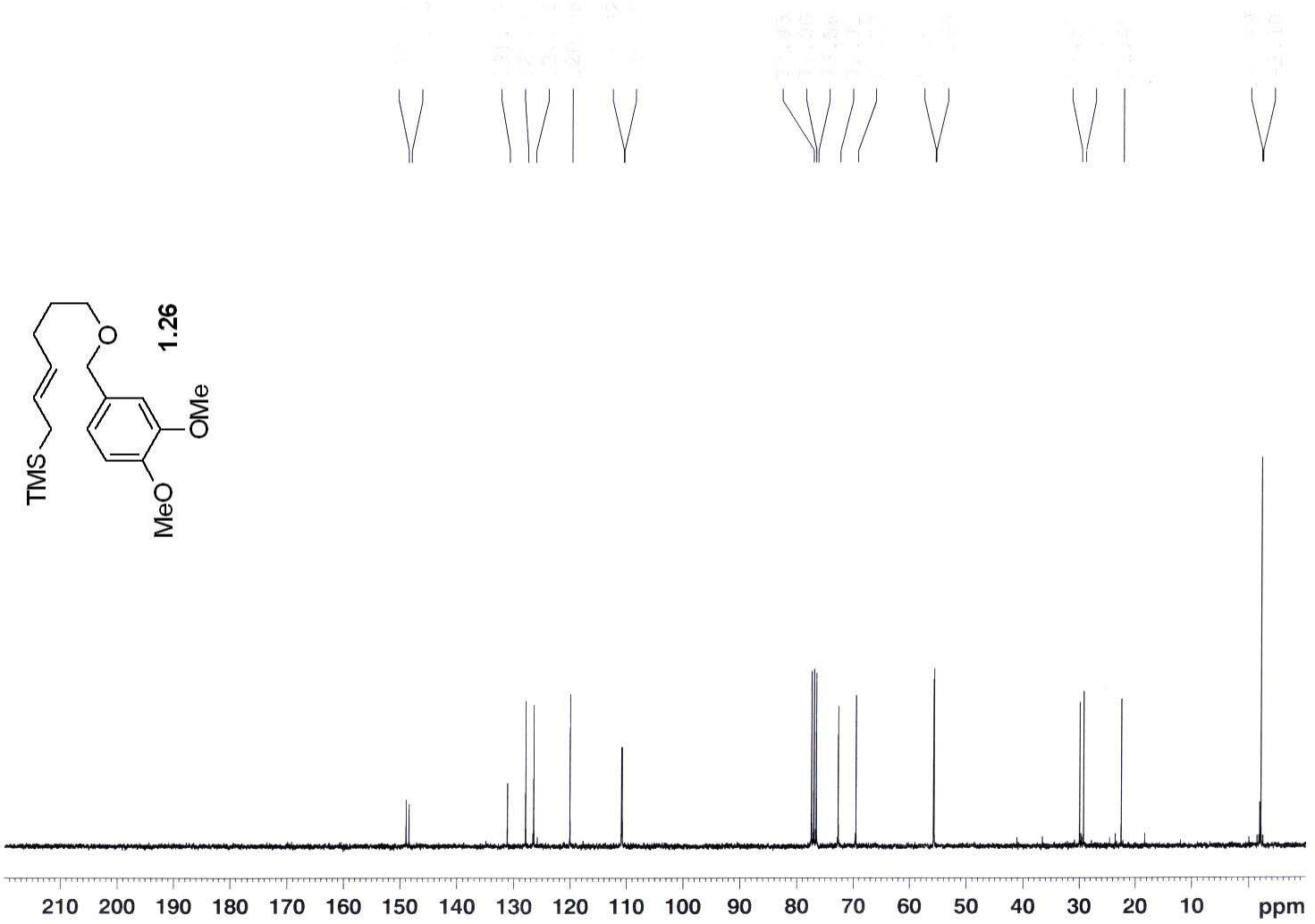
cyclized from PMB allyl TMS in cdcl3 301a tuwy 07/06/07

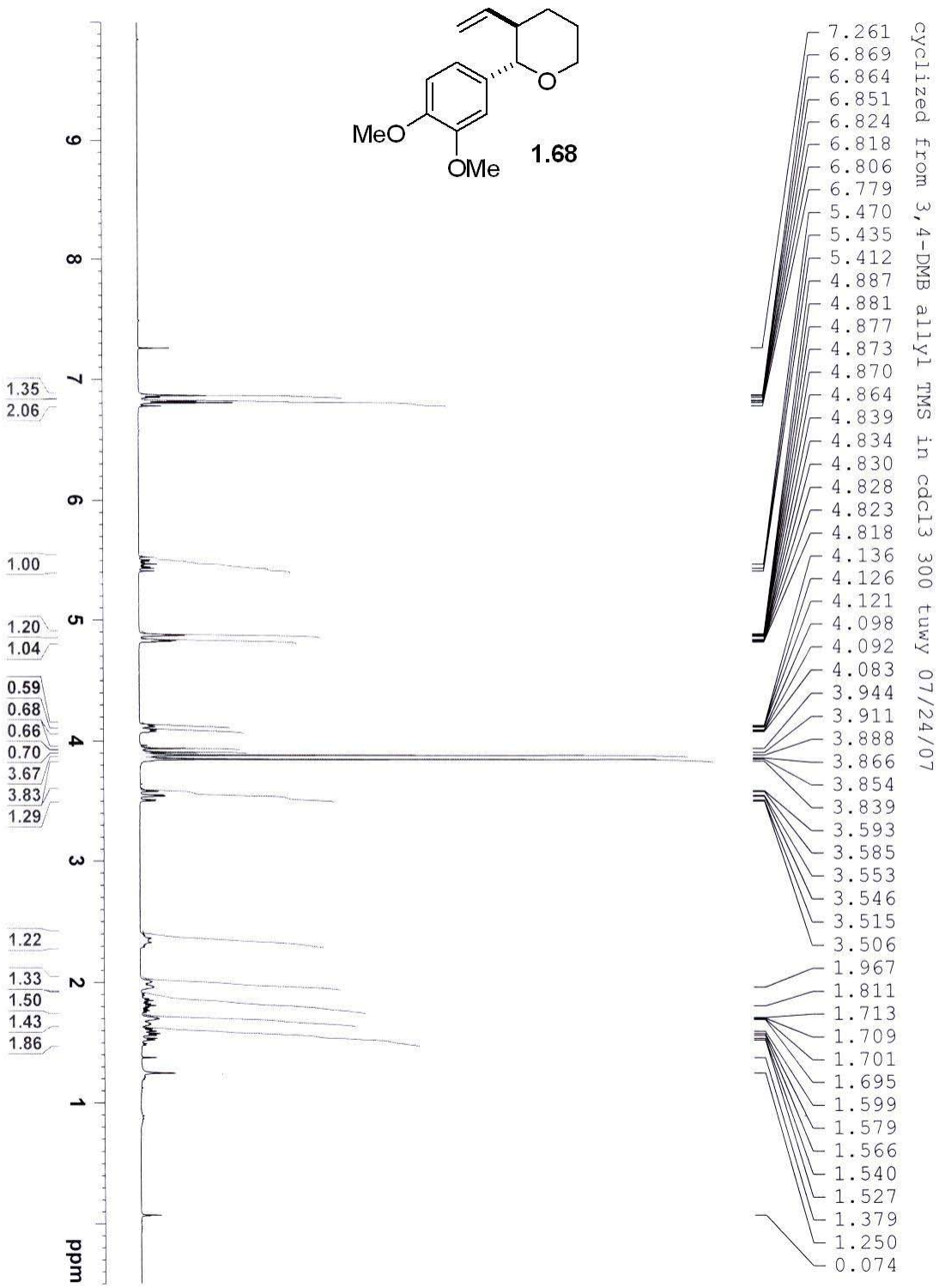




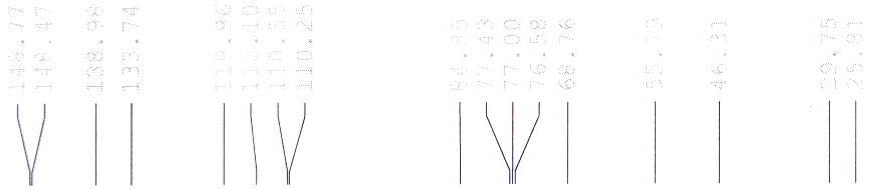

TMS
O
MeO
OMe
1.26
3,4-DMB allyl TMS in cdcl3 301a tuwy 07/23/07
7.260
6.888
6.877
6.850
6.845
6.826
6.799
5.407
5.382
5.357
5.331
5.274
5.267
5.245
5.223
5.195
5.173
4.421
3.918
3.878
3.860
3.830
3.812
3.477
3.460
3.438
3.416
2.088
2.065
2.041
2.018
1.696
1.674
1.649
1.625
1.602
1.472
1.446
1.395
1.371
1.248
0.100
0.045
0.042
0.024
0.019
0.008
-0.012
-0.036
-0.046
-0.078
-0.084
-0.094
-0.095
-0.174
1.17
1.77
0.95
1.00
1.99
6.04
2.00
2.12
2.23
2.08
9.05
ppm

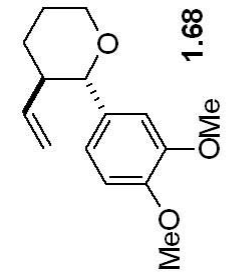
3,4-DMB allyl TMS in cdcl3 301a tuwy 07/23/07

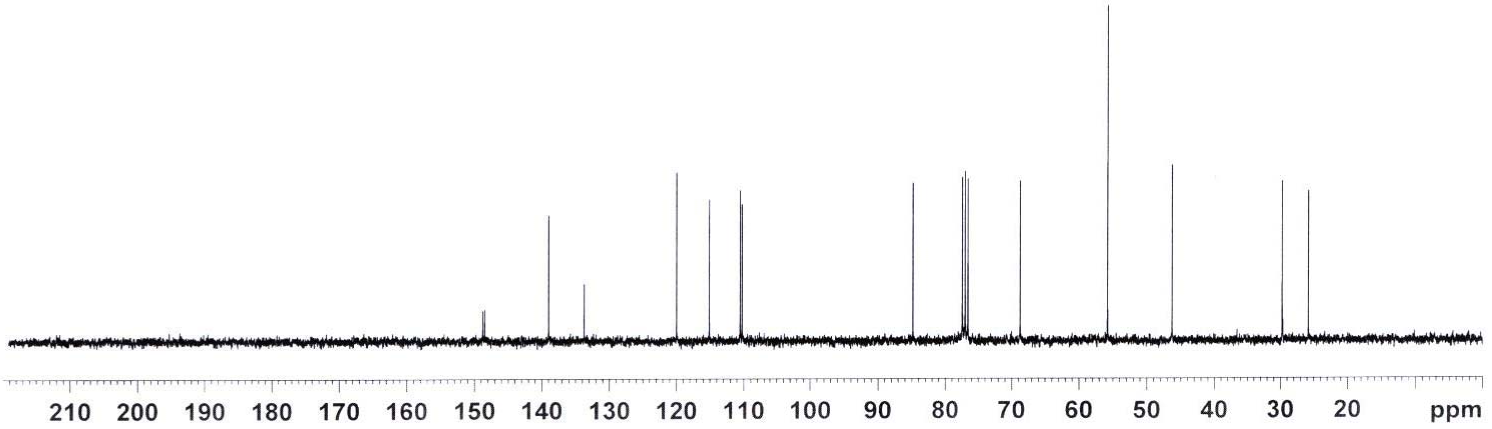


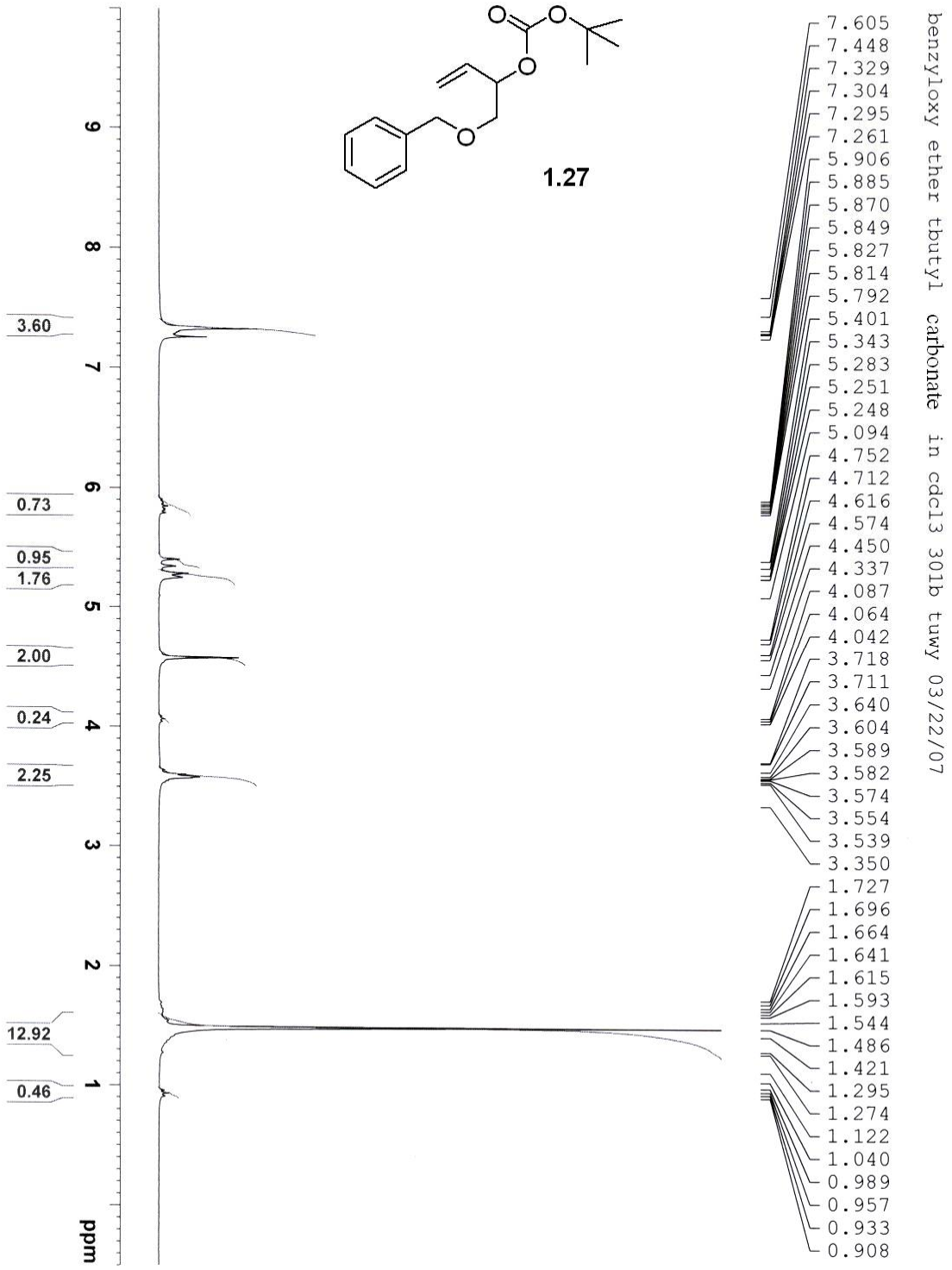

MeO
OMe
O
1.68
cyclized from 3,4-DMB allyl TMS in cdcl3 300 tuwy 07/24/07
7.261
6.869
6.864
6.851
6.824
6.818
6.806
6.779
5.470
5.435
5.412
4.887
4.881
4.877
4.873
4.870
4.864
4.839
4.834
4.830
4.828
4.823
4.818
4.136
4.126
4.121
4.098
4.092
4.083
3.944
3.911
3.888
3.866
3.854
3.839
3.593
3.585
3.553
3.546
3.515
3.506
1.967
1.811
1.713
1.709
1.701
1.695
1.599
1.579
1.566
1.540
1.527
1.379
1.250
0.074
1.35
2.06
1.00
1.20
1.04
0.59
0.68
0.66
0.70
3.67
3.83
1.29
1.22
1.33
1.50
1.43
1.86
ppm

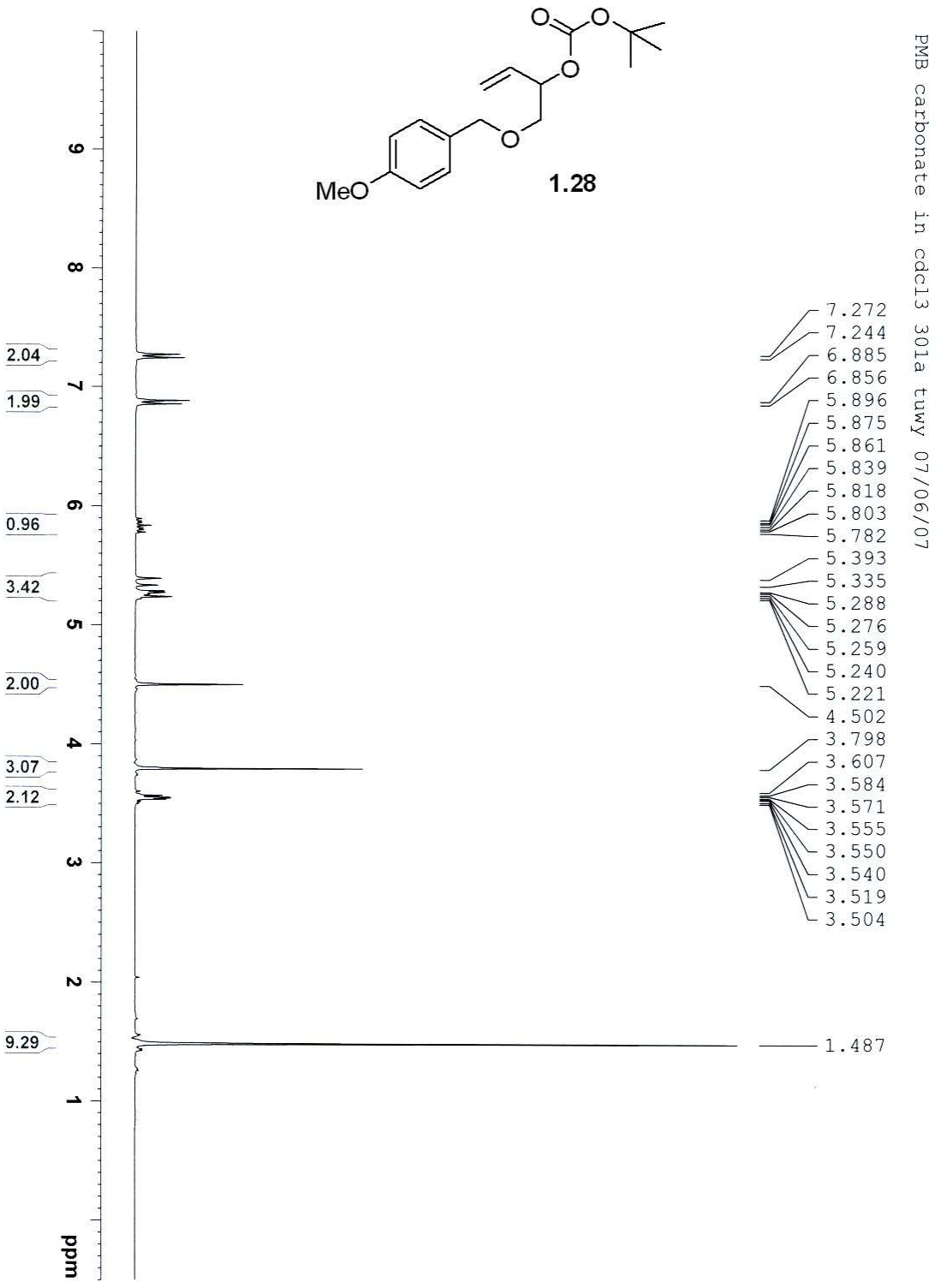
cyclized from 3,4-DMB allyl TMS in cdcl3 300 tuwy 07/24/07

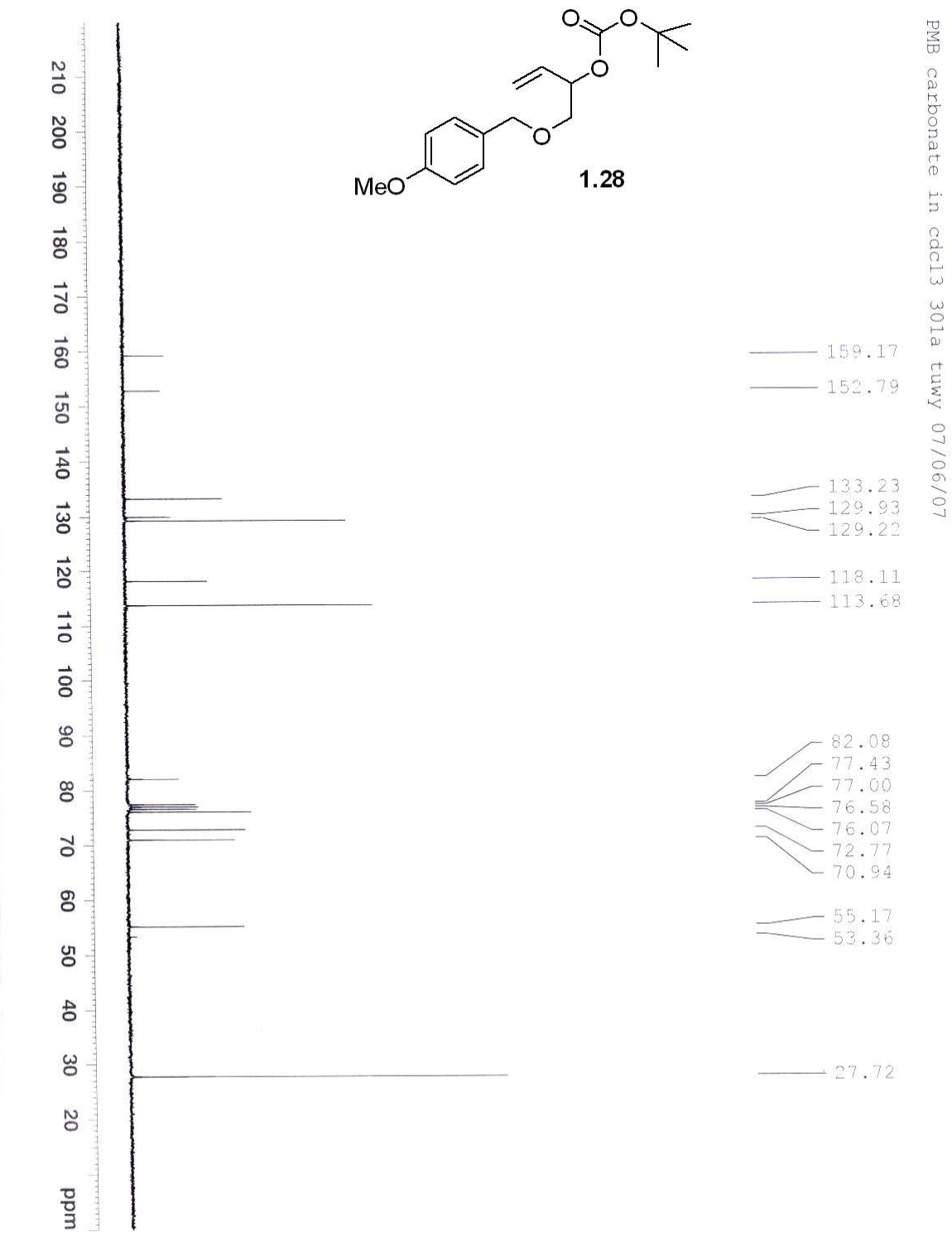







benzyloxy ether tbutyl carbonate in cdcl3 301b tuwy 03/22/07
1.27
7.605
7.448
7.329
7.304
7.295
7.261
5.906
5.885
5.870
5.849
5.827
5.814
5.792
5.401
5.343
5.283
5.251
5.248
5.094
4.752
4.712
4.616
4.574
4.450
4.337
4.087
4.064
4.042
3.718
3.711
3.640
3.604
3.589
3.582
3.574
3.554
3.539
3.350
1.727
1.696
1.664
1.641
1.615
1.593
1.544
1.486
1.421
1.295
1.274
1.122
1.040
0.989
0.957
0.933
0.908
3.60
0.73
0.95
1.76
2.00
0.24
2.25
12.92
0.46
ppm


PMB carbonate in cdcl3 301a tuwy 07/06/07
MeO
1.28
7.272
7.244
6.885
6.856
5.896
5.875
5.861
5.839
5.818
5.803
5.782
5.393
5.335
5.288
5.276
5.259
5.240
5.221
4.502
3.798
3.607
3.584
3.571
3.555
3.550
3.540
3.519
3.504
1.487
2.04
1.99
0.96
3.42
2.00
3.07
2.12
9.29
ppm


PMB carbonate in cdcl3 301a tuwy 07/06/07
MeO
1.28
159.17
152.79
133.23
129.93
129.22
118.11
113.68
82.08
77.43
77.00
76.58
76.07
72.77
70.94
55.17
53.36
27.72
ppm

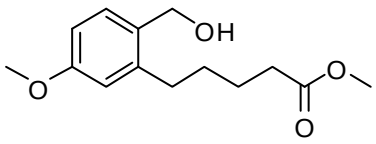
APPENDIX B

EXPLORATION OF THE DDQ-MEDIATED C-H ACTIVATION REACTION ON MACROCYCLES

General Experimental Proton (^{1}H NMR) and Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz and 75 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, C_6D_6 = 7.15 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution mass spectra were recorded on a MICROMASS AUTOSPEC (for EI) or WATERS Q-TOF API-US (for ESI) spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Activated 4 Å molecular sieves were obtained through drying in oven at 150 °C overnight. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride and cyclohexane were distilled under N_2 from CaH_2. Toluene and 1,2-dichloroethane were dried over 4 Å molecular sieves overnight

prior to use. Anhydrous DMF was purchased from Acros. Analytical TLC was performed on E. Merck pre-coated (0.25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

Methyl 5-(2-(hydroxymethyl)-5-methoxyphenyl)pentanoate (2.19)

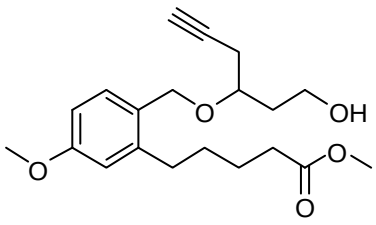


To the solution of methyl pent-4-enoate (250 mg, 2.19 mmol) in 1.2 mL anhydrous THF at 0 °C was added 9-BBN (0.5 M in THF, 6.40 mL). The reaction was allowed to room temperature after the addition and stirred for 4 hours. Then the reaction was diluted with 12 mL anhydrous DMF and treated with $PdCl_2(dppf)\cdot CH_2Cl_2$ (49 mg, 0.060 mmol), **2.18** (428 mg, 2.00 mmol) and K_2CO_3 (552 mg, 4.0 mmol). The mixture was heated to 50 °C and stirred overnight. The reaction was quenched by decanting the crude mixture into H_2O, and the aqueous layer was then extracted with EtOAc and washed with H_2O three times. The combined organic layer was dried with $MgSO_4$, filtered and concentrated. The residue was finally purified by flash chromatography (20% EtOAc in Hexane) to give desired coupled product methyl 5-(2-formyl-5-methoxyphenyl)pentanoate (354 mg, contaminated by borate derivatives).

The product from previous Suzuki coupling reaction was dissolved in 3 mL MeOH and cooled to 0 °C, followed by addition of $NaBH_4$ (54 mg, 1.4 mmol). The reaction was kept at 0 °C for 10 min, then was quenched by aq. $NaHCO_3$. The crude mixture was extracted with EtOAc, dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (30%

EtOAc in Hexane) to give **2.19** (244 mg, 49% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 1H), 6.73 (dd, *J* = 2.7, 7.8 Hz, 1H), 4.64 (d, *J* = 4.8 Hz, 2H), 3.81 (s, 3H), 3.68 (s, 3H), 2.70 (t, *J* = 7.8 Hz, 2H), 2.37 (t, *J* = 6.9 Hz, 2H), 1.79-1.60 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 174.1, 159.3, 142.1, 130.7, 130.1, 115.2, 110.9, 62.7, 55.1, 51.5, 33.8, 32.1, 30.6, 24.8; IR (neat) 3421, 2945, 2866, 1735, 1610, 1579, 1500, 1437, 1253, 1162, 1110, 1034, 1005 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{20}O_4$ (M^+) 252.1362, found 252.1351.

Methyl 5-(2-((1-hydroxyhex-5-yn-3-yloxy)methyl)-5-methoxyphenyl)pentanoate (2.21)



To a solution of **2.19** (800 mg, 3.17 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added DBU (711 μL, 4.76 mmol) and Cl_3CCN (954 μL, 9.51 mmol). The reaction was warmed to rt and stirred for 1h. The mixture was directly concentrated to give a very viscous brown oil, and purified by neutralized silica gel flash chromatography (10% EtOAc in hexane) to give the trichloroacetimidate of **2.19** (989 mg, 80%).

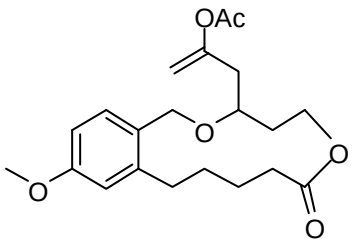
The trichloroacetimidate and 1-(tert-butyldimethylsilyloxy)hex-5-yn-3-ol (356 mg, 1.56 mmol) were dissolved in toluene (30 mL) at rt. $La(OTf)_3$ (137 mg, 0.234 mmol) was added. The reaction was stirred at rt for 8 hours, then was filtered through a plug of silca gel using Et_2O as the eluent. The filtrate was concentrated and partially purified by flash chromatography (10% EtOAc in hexane) to give the desired homopropargylic ether (628 mg, containing some unreacted homopropargylic secondary alcohol).

The crude ether was dissolved in MeOH (10 mL) and treated with a crystal of p-TsOH. The reaction was stirred at rt for 1.5 h, then was concentrated and purified by flash chromatography (45% EtOAc in hexane) to give **2.21** (339 mg, 63% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.22 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 2.7 Hz, 1H), 6.70 (dd, *J* = 2.7, 10.8 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.41 (d, *J* = 11.1 Hz, 1H), 3.78 (s, 3H), 3.81-3.69 (m, 3H), 3.66 (s, 3H), 2.68 (t, *J* = 8.1 Hz, 2H), 2.54 (ddd, *J* = 2.4, 4.8, 16.8 Hz, 1H), 2.46 (ddd, *J* = 2.7, 3.9, 14.1 Hz, 1H), 2.35 (t, *J* = 6.9 Hz, 2H), 2.30-2.19 (m, 1H), 2.04 (t, *J* = 2.4 Hz, 1H), 1.98-1.80 (m, 2H), 1.78-1.58 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 174.1, 159.5, 142.7, 131.2, 127.6, 115.1, 110.8, 80.8, 75.8, 70.4, 69.1, 60.1, 55.2, 51.5, 36.3, 33.9, 32.2, 30.6, 24.9, 23.6; IR (neat) 3447, 3288, 2947, 2869, 1734, 1610, 1579, 1502, 1437, 1349, 1260, 1164, 1063 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{28}O_5$ (M^+) 348.1925, found 348.1937.

General Procedure For Enol Acetate Preparation: A RBF was charged with Na_2CO_3 (0.15 equiv.), dichloro(p-cymene)ruthenium(II) dimmer (0.04 equiv.), tri(2-furyl)phosphine (0.08 equiv.). Toluene was added into the flask to dissolve the powder, followed by acetic acid (2 equiv.) and 1-decyne (1 equiv.). The mixture was heated to 80 °C and stirred for one hour. Another 2 equiv. of acetic acid and the substrates (1 equiv.) were dissolved in toluene (the same volume as previously used) and added into the reaction through syringe (overall concentration of substrate in the reaction was about 0.1-0.2 M). The reaction was stirred at the same temperature overnight. Then crude mixture was loaded onto a small plug of silica gel and eluted with Et_2O. The residue was concentrated on a rotary evaporator and purified by flash chromatography to give the desired product.

3-(13-Methoxy-7-oxo-3,4,5,7,8,9,10,11-octahydro-1H-2,6-benzodioxacyclotridecin-3-yl)prop-1-en-2-yl acetate (2.23)



To a solution of **2.21** (339 mg, 0.974 mmol) in a mixture of THF, MeOH, and H_2O (3 mL, 1 mL, and 1 mL, respectively) at RT was added $LiOH \cdot H_2O$ (164 mg, 3.90 mmol). The reaction was stirred at rt for one hour, then was acidified with 0.5 M HCl until the pH was between 3 and 4. The aqueous solution was extracted with EtOAc three times, and the combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated and was carried to the next step without purification.

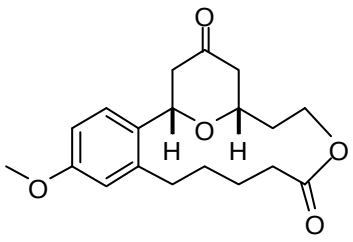
The crude acid (120 mg, 0.359 mmol) was dissolved in anhydrous THF (2.5 mL) followed by the addition of anhydrous Et_3N (250 μL, 1.80 mmol) at rt. The mixture was stirred for 20 min, then a solution of trichlorobenzoyl chloride (127 mg, 0.539 mmol) in THF (2.5 mL) was added. A precipitate formed after several min, and the stirring was continued for 2 h. The crude mixed acid anhydride was filtered through a pad of Celite and washed with toluene (160 mL total). The toluene solution of the mixed anhydride was added dropwise into a solution of DMAP (175 mg, 1.44 mmol) in toluene (50 mL) at 65 °C over a period of 5 hours. After the addition, the crude mixture was concentrated, re-dissolved in Et_2O and washed with aq. $NaHCO_3$. The organic layer was dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (15% EtOAc in hexane) to give desired product **2.22** (79 mg, 70% over two steps).

Compound **2.22** was treated with general enol acetate preparation procedure, and the crude mixture was purified by flash chromatography (15% Et_2O in Hexane) to give desired product **2.23** (65 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 7.8 Hz, 1H), 6.71 (s, 1H), 6.69

(dd, *J* = 2.4, 7.8 Hz, 1H), 4.85 (s, 1H), 4.83 (s, 1H), 4.58 (d, *J* = 9.6 Hz, 1H), 4.41 (ddd, *J* = 3.3, 7.2, 11.7 Hz, 1H), 4.32 (d, *J* = 9.6 Hz, 1H), 4.03 (ddd, *J* = 3.3, 7.5, 11.4 Hz, 1H), 3.78 (s, 3H), 3.81-3.70 (m, 1H), 2.75 (ddd, *J* = 3.9, 12.3, 12.3 Hz, 1H), 2.67 (dd, *J* = 5.4, 14.7 Hz, 1H), 2.54 (ddd, *J* = 4.8, 11.7, 11.7 Hz, 1H), 2.45 (dd, *J* = 6.6, 15.0 Hz, 1H), 2.50-2.34 (m, 2H), 2.09 (s, 3H), 2.05-1.84 (m, 3H), 1.84-1.73 (m, 2H), 1.70-1.59 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 174.1, 169.1, 159.6, 153.0, 143.9, 132.5, 127.8, 115.4, 111.0, 104.2, 75.5, 69.6, 62.3, 55.2, 38.4, 33.4, 32.6, 32.3, 30.5, 25.5, 21.1; IR (neat) 2931, 2866, 1754, 1729, 1665, 1610, 1579, 1503, 1446, 1369, 1349, 1263, 1200, 1067, 1027 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{28}O_6Na$ $(M+Na)^+$ 399.1784, found 399.1790.

General Procedure For The Cyclization Reaction With DDQ: The substrate (1 equiv.), 2,6-dichloropyridine (4 equiv.) and powdered 4 Å molecular sieves (2 mass equiv.) were added to anhydrous 1,2-dichloroethane to give an approximately 0.1 M solution. The mixture was stirred at room temperature for 15 min, then DDQ (see individual examples for equiv.) was added in one portion. The reaction progress was monitored by TLC at room temperature unless specified, and quenched by Et_3N when complete starting material consumption was observed. The resulting mixture was loaded directly onto a short plug of silica gel and eluted with dichloromethane or EtOAc. The filtrate was concentrated and the residue product was purified by flash chromatography to give the desired product.

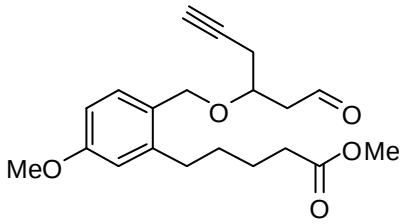
1,16-*cis*-5-Methoxy-13,20-dioxatricyclo[14.3.1.$0^{2,7}$]icosa- 2,4,6-triene-12,18-dione (2.64)



The general procedure for the cyclization reaction was followed with **2.23** (64 mg, 0.17 mmol), 2,6-dichloropyridine (76 mg, 0.51

mmol) and 4 Å molecular sieves (128 mg) in 1,2-dichloroethane (2 mL). DDQ (58 mg, 0.26 mmol) was initially added, and after 1.75 h DDQ (7.7 mg, 0.034 mmol) was added. The reaction was stirred 15 more min then was quenched and purified by flash chromatography (35% EtOAc in hexane) to give the desired product **2.64** (41 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 2.7, 11.1 Hz, 1H), 6.75 (s, 1H), 4.73 (dd, *J* = 1.8, 12.3 Hz, 1H), 4.23-4.11 (m, 2H), 4.05 (ddd, *J* = 4.5, 8.7, 12.9 Hz, 1H), 3.79 (s, 3H), 3.00 (t, *J* = 15.0 Hz, 1H), 2.76 (tt, *J* = 3.0, 10.2 Hz, 1H), 2.65-2.55 (m, 1H), 2.55-2.40 (m, 4H), 2.39-2.28 (m, 1H), 1.96 (quintet, *J* = 4.8 Hz, 1H), 2.01-1.90 (m, 1H), 1.83-1.66 (m, 3H), 1.64-1.49 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 207.0, 173.6, 159.6, 143.9, 128.3, 127.6, 115.9, 111.1, 75.4, 74.2, 60.6, 55.2, 48.1, 46.6, 34.1, 32.6, 30.4, 25.6; IR (neat) 2959, 2938, 2869, 1719, 1615, 1577, 1500, 1463, 1422, 1371, 1315, 1255, 1148, 1062, 1044, 1030, 803 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{24}O_5$ (M^+) 332.1624, found 332.1615.

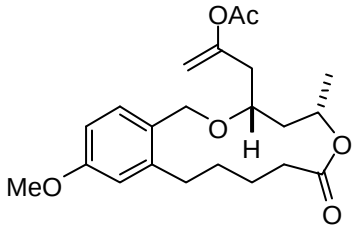
Methyl 5-(5-methoxy-2-((1-oxohex-5-yn-3-yloxy)methyl)phenyl)pentanoate (2.29)



Compound **2.21** (476 mg, 1.37 mmol) was dissolved in 8 mL CH_2Cl_2 at 0 °C. Et_3N (572 μL, 4.10 mmol), DMSO (1.73 mL) and Py·SO_3 (320 mg, 2.05 mmol) were added into the reaction sequentially. The mixture was kept at 0 °C for 15 min, then allowed to room temperature and stirred overnight. The reaction was quenched with H_2O at 0 °C and diluted with EtOAc. The organic layer was washed with H_2O three times, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (25% EtOAc in Hexane) to give desired product **2.29** (417 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H),

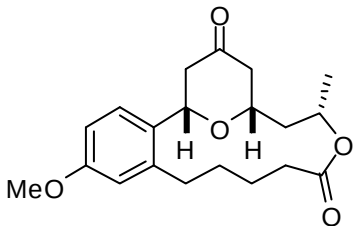
6.68 (dd, *J* = 2.7, 8.4 Hz, 1H), 4.61 (d, *J* = 10.8 Hz, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.10 (tt, *J* = 5.7, 6.9 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 2.80-2.73 (m, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 2.57 (ddd, *J* = 2.7, 4.8, 17.1 Hz, 1H), 2.47 (ddd, *J* = 2.7, 6.9, 16.8 Hz, 1H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.77-1.53 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 200.5, 173.9, 159.5, 142.7, 131.3, 127.3, 115.1, 110.7, 79.9, 71.9, 71.1, 69.3, 55.1, 51.4, 48.0, 33.8, 32.1, 30.5, 24.8, 23.6; IR (neat) 3285, 2922, 1733, 1612, 1505, 1458, 1435, 1260, 1157, 1114, 1092, 1033 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{25}O_4$ $(M–OH)^+$ 329.1753, found 329.1741.

3-[(3,5-*cis*)-13-Methoxy-5-methyl-7-oxo-3,4,5,7,8,9,10,11-octahydro-1H-2,6-benzodioxacyclotridecin-3-yl]prop-1-en-2-yl acetate (2.32)



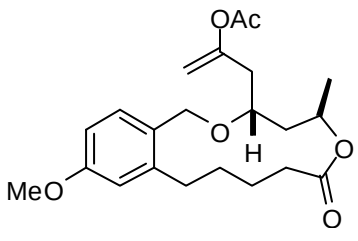
Compound **2.32** was prepared from **2.30** by following the same protocol for converting **2.21** to **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 3.9, 9.3 Hz, 1H), 6.74-6.66 (m, 2H), 5.07 (ddq, *J* = 0.9, 5.5, 7.2 Hz, 1H), 4.83 (d, *J* = 1.5 Hz, 1H), 4.81 (s, 1H), 4.40 (d, *J* = 10.5 Hz, 1H), 4.35 (d, *J* = 10.5 Hz, 1H), 3.77 (s, 3H), 3.63 (ddt, *J* = 3.9, 3.9, 6.6 Hz, 1H), 2.75-2.56 (m, 3H), 2.49-2.35 (m, 3H), 2.07 (s, 3H), 2.04-1.85 (m, 2H), 1.85-1.60 (m, 4H), 1.22 (d, *J* = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 173.7, 169.1, 159.4, 152.8, 143.3, 132.5, 128.0, 115.1, 110.9, 104.2, 75.5, 70.6, 68.1, 55.1, 41.3, 38.9, 33.7, 31.9, 29.4, 24.4, 21.6, 21.0; IR (neat) 2933, 2869, 1755, 1724, 1665, 1610, 1579, 1503, 1449, 1369, 1262, 1205, 1084 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{30}O_6Na$ $(M+Na)^+$ 413.1940, found 413.1920.

(1*S*,14*S*,16*S*)-5-Methoxy-14-methyl-13,20-dioxatricyclo[14.3.1.0^{2,7}]icosa-2,4,6-triene- 12,18-dione (2.65)



The general procedure for cyclization reaction was followed with **2.32** (88 mg, 0.22 mmol), DDQ (76 mg, 0.34 mmol) 2,6-dichloropyridine (100 mg, 0.67 mmol) and 4 Å molecular sieves (175 mg) in 1,2-dichloroethane (2.5 mL). The mixture was stirred for 4 hours then was purified by flash chromatography (30% EtOAc in hexane) to give the desired product **2.65** (53 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.7 Hz, 1H), 6.80 (dd, *J* = 3.0, 8.7 Hz, 1H), 6.71 (d, *J* = 2.7 Hz, 1H), 5.10 (ddq, *J* = 3.0, 6.3, 12.6 Hz, 1H), 4.68 (dd, *J* = 2.1, 12.0 Hz, 1H), 3.88-3.75 (m, 1H), 3.80 (s, 3H), 3.02 (dd, *J* = 3.0, 8.4 Hz, 1H), 2.96 (t, *J* = 12.3, 13.8 Hz, 1H), 2.55-2.40(m, 4H), 2.38-2.29(m, 2H), 2.10 (ddd, *J* = 6.6, 11.4, 15.6 Hz, 1H), 1.90-1.75 (m, 1H), 1.71-1.55 (m, 3H), 1.54-1.40 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 206.9, 173.5, 159.5, 142.2, 129.2, 127.6, 116.4, 111.3, 76.3, 74.3, 70.3, 55.2, 49.0, 46.3, 43.0, 35.0, 33.4, 28.3, 23.9, 20.9; IR (neat) 2922, 2856, 1721, 1611, 1579, 1504, 1456, 1423, 1371, 1309, 1266, 1151, 1095, 1068, 1045 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{26}O_5$ (M^+) 346.1780, found 346.1775.

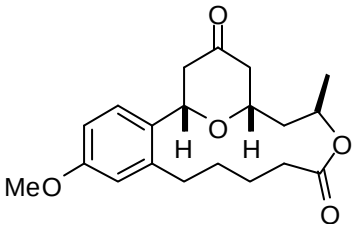
3-[(3,5-*trans*)-13-Methoxy-5-methyl-7-oxo-3,4,5,7,8,9,10,11-octahydro-1H-2,6-benzodioxacyclotridecin-3-yl]prop-1-en-2-yl acetate (2.34)



Compound **2.34** was prepared from **2.30** by following the same protocol for converting **2.21** to **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.1 Hz, 1H), 6.70 (s, 1H), 6.68 (dd, *J* = 2.7, 8.4 Hz, 1H), 5.12 (ddq, *J* = 3.6, 6.3, 6.3 Hz, 1H), 4.82 (s, 2H), 4.60 (d, *J* =

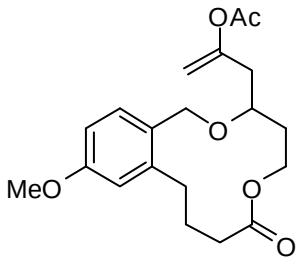
9.9 Hz, 1H), 4.22 (d, *J* = 9.9 Hz, 1H), 3.84 (ddt, *J* = 3.0, 6.6, 6.6 Hz, 1H), 3.77 (s, 3H), 2.77 (dt, *J* = 3.9, 12.0 Hz, 1H), 2.66 (dd, *J* = 5.4, 15.0 Hz, 1H), 2.52-2.30 (m, 4H), 2.06 (s, 3H), 2.00-1.53 (m, 6H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 173.7, 169.0, 159.6, 153.1, 144.1, 132.5, 127.9, 115.4, 110.9, 104.1, 73.6, 70.0, 67.5, 55.2, 38.7, 38.3, 33.5, 32.4, 30.8, 25.4, 21.1, 20.3; IR (neat) 2933, 2866, 1755, 1726, 1665, 1610, 1579, 1504, 1446, 1369, 1263, 1199, 1117, 1084, 1028 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{30}O_6Na$ $(M+Na)^+$ 413.1940, found 413.1941.

(1*S*,14*R*,16*S*)-5-Methoxy-14-methyl-13,20-dioxatricyclo[14.3.1.0^{2,7}]icosa-2,4,6-triene-12,18-dione (2.66)



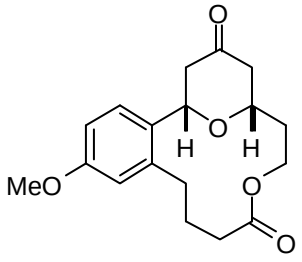
The general procedure for the cyclization reaction was followed with **2.34** (77 mg, 0.20 mmol), DDQ (67 mg, 0.30 mmol), 2,6-dichloropyridine (88 mg, 0.59 mmol), and 4 Å molecular sieves (154 mg) in 1,2-dichloroethane (2 mL). The mixture was stirred for 4 hours then was purified by flash chromatography (30% EtOAc in hexane) to give the desired product **2.66** (51 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 2.4, 8.1 Hz, 1H), 6.74 (s, 1H), 4.90 (ddq, *J* = 2.1, 6.0, 6.3 Hz, 1H), 4.72 (dd, *J* = 1.2, 12.1 Hz, 1H), 4.09 (ddt, *J* = 3.6, 3.6, 9.9 Hz, 1H), 3.79 (s, 3H), 3.00 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.73-2.55 (m, 2H), 2.55-2.40 (m, 4H), 2.35-2.23 (m, 1H), 2.05-1.90 (m, 1H), 1.89-1.54 (m, 5H), 1.28 (d, *J* = 6.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 207.1, 173.3, 159.7, 144.2, 128.2, 127.4, 115.7, 111.2, 75.3, 73.3, 67.8, 55.2, 48.4, 46.5, 42.1, 34.5, 32.6, 30.5, 25.6, 20.3; IR (neat) 2931, 2869, 1722, 1610, 1578, 1504, 1461, 1370, 1256, 1153, 1123, 1059, 962 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{26}O_5$ (M^+) 346.1780, found 346.1783.

3-(12-Methoxy-7-oxo-1,3,4,5,7,8,9,10-octahydro-2,6-benzodioxacyclododecin-3-yl)prop-1-en-2-yl acetate (2.28)



Compound **2.28** was prepared similarly as **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 2.4, 8.1 Hz, 1H), 4.82 (s, 2H), 4.65 (d, *J* = 9.9 Hz, 1H), 4.50-4.37 (m, 1H), 4.27 (d, *J* = 9.6 Hz, 1H), 4.18 (ddd, *J* = 2.7, 5.4, 11.1 Hz, 1H), 3.75 (s, 3H), 3.72-3.64 (m, 1H), 2.81-2.59 (m, 3H), 2.42 (dd, *J* = 7.2, 14.7 Hz, 1H), 2.36-2.25 (m, 2H), 2.06 (s, 3H), 2.02-1.80 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 173.2, 168.9, 159.5, 152.9, 143.1, 132.3, 127.8, 114.8, 110.7, 104.0, 76.6, 69.4, 62.2, 55.0, 37.7, 33.3, 32.2, 30.5, 26.6, 20.9; IR (neat) 3383 (br), 2953, 1754, 1728, 1665, 1611, 1578, 1504, 1457, 1432, 1369, 1258, 1197, 1116, 1070, 1041, 875, 803 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{26}O_6Na$ $(M+Na)^+$ 385.1627, found 385.1620.

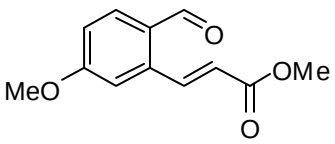
(1,15-*cis*)-5-Methoxy-12,19-dioxatricyclo[13.3.1.0^{2,7}]nonadeca-2,4,6-triene-11,17-dione (2.67)



The general procedure for the cyclization reaction was followed with **2.28** (117 mg, 0.323 mmol), DDQ (110 mg, 0.48 mmol), 2,6-dichloropyridine (143 mg, 0.969 mmol) and 4 Å molecular sieves (234 mg) in 1,2-dichloroethane (3.5 mL). The mixture was stirred for 3.25 h then was purified by flash chromatography (35% EtOAc in hexane) to give the desired product **2.67** (78 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 6.68 (dd, *J* = 2.7, 8.7 Hz, 1H), 4.52 (ddd, *J* = 2.4, 11.1, 11.1 Hz, 1H), 4.45 (dd, *J* = 2.4, 12.0 Hz, 1H), 3.74 (ddd, *J* = 3.9, 3.9, 11.7 Hz, 1H), 3.56 (ddd, *J* = 3.6, 7.8, 10.8 Hz, 1H), 3.43 (s, 3H), 2.86 (ddd, *J* = 8.1, 8.1, 13.2 Hz, 1H), 2.63 (dd, *J* = 12.3, 12.3 Hz, 1H), 2.54 (ddd, *J* = 3.6,

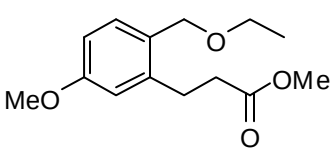
8.1, 12.3 Hz, 1H), 2.36 (ddd, *J* = 1.8, 1.8, 13.8 Hz, 1H), 2.20-2.10 (m, 4H), 1.79-1.58 (m, 2H), 1.50-1.35 (m, 1H), 1.03 (ddd, *J* = 3.3, 3.3, 12.0 Hz, 1H); ^{13}C (75 MHz, C_6D_6) δ 205.1, 173.2, 160.5, 143.9, 115.9, 111.6, 77.2, 76.1, 61.3, 55.1, 48.2, 46.9, 36.1, 32.6, 29.9, 27.6; IR (neat) 2916, 2852, 1716, 1613, 1575, 1501, 1444, 1326, 1251, 1150, 1110, 1050 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{22}O_5$ (M^+) 318.1467, found 318.1464.

Methyl (2*E*)-3-(2-formyl-5-methoxyphenyl)prop-2-enoate (2.38)



A 50 mL RBF was charged with **2.18** (600 mg, 2.79 mmol) and $Pd_2(dba)_3$ (128 mg, 0.140 mmol). The flask was vacuumed and back-filled with argon three times. Degassed Cy_2NMe (657 μL, 3.07 mmol), ^{t}Bu$_3$P (10% weight in Hexane, 830 μL, 0.279 mmol), methyl acrylate (502 μL, 5.58 mmol) and anhydrous dioxane (3 mL) were added sequentially into the flask. The reaction was stirred at room temperature overnight, then diluted with EtOAc and filtered through a plug of silica gel. The filtrate was concentrated and purified by flash chromatography (25% EtOAc in Hexane) to give desired product **2.38** (424 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.52 (d, *J* = 15.9 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 7.02 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H).

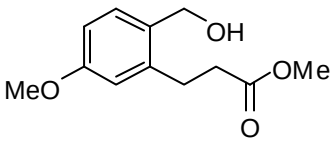
Methyl 3-(2-(ethoxymethyl)-5-methoxyphenyl)propanoate (2.39)



Compound **2.38** (519 mg, 2.35 mmol) and 10% Pd/C (250 mg, 0.234 mmol) were dissolved in 10 mL EtOH, and the reaction was stirred under H_2 atmosphere for three hours, then the crude mixture was filtered through a plug of silica gel and eluted with Et_2O. The filtrate was concentrated and

purified by flash chromatography (10% EtOAc in Hexane) to give **2.39** (235 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 2.7 Hz, 1H), 6.72 (dd, *J* = 2.7, 8.1 Hz, 1H), 4.45 (s, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 3.53 (q, *J* = 6.9 Hz, 2H), 2.98 (t, *J* = 8.7 Hz, 2H), 2.65 (t, *J* = 8.4 Hz, 2H), 1.22 (t, *J* = 6.9 Hz, 3H).

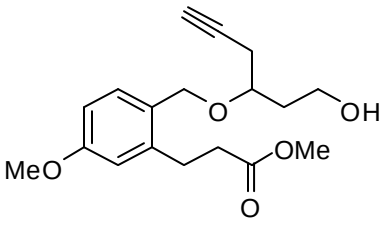
Methyl 3-(2-(hydroxymethyl)-5-methoxyphenyl)propanoate (2.40)



Compound **2.39** (235 mg, 0.931 mmol) was dissolved in a mixture of CH_2Cl_2 (5 mL) and H_2O (0.27 mL) and cooled to 0 °C. DDQ (253 mg, 1.12 mmol) was added into the solution and the reaction was stirred at room temperature for 1.5 hours, then quenched with aq. $NaHCO_3$. The crude mixture was filtered through a plug of silica gel and eluted with Et_2O. The filtrate was dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (25% EtOAc in Hexane) to give methyl 3-(2-formyl-5-methoxyphenyl)propanoate (197 mg, 95%).

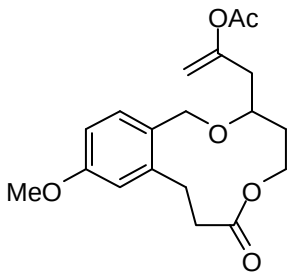
The aldehyde derived from previous step was dissolved in 2 mL MeOH at 0 °C, followed by addition of $NaBH_4$ (37 mg, 0.98 mmol). The reaction was kept at 0 °C for 10 min, then quenched by aq. $NaHCO_3$. The crude mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (40% EtOAc in Hexane) to give desired product **2.40** (176 mg, 88%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 1H), 6.75-6.68 (m, 2H), 4.61 (s, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.65-2.45 (br, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 173.6, 159.3, 140.5, 130.9, 130.6, 114.8, 111.3, 62.7, 55.1, 51.7, 35.1, 27.1; IR (neat) 3413 (br), 2951, 2838, 1733, 1610, 1579, 1502, 1438, 1367, 1255, 1157, 1111, 1042 cm^{-1}.

Methyl 3-(2-((1-hydroxyhex-5-yn-3-yloxy)methyl)-5-methoxyphenyl)propanoate (2.41)



Compound **2.41** was prepared from **2.40** by following the same protocols for converting **2.21** to **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 1H), 6.76-6.68 (m, 2H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 10.5 Hz, 1H), 3.87-3.68 (m, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.55 (ddd, *J* = 2.7, 5.1, 17.1 Hz, 1H), 2.48 (ddd, *J* = 2.7, 6.6, 16.8 Hz, 1H), 2.39-2.28 (br, 1H), 2.02 (t, *J* = 2.7 Hz, 1H), 2.00-1.77 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 173.5, 159.7, 141.2, 131.5, 127.7, 114.9, 111.3, 80.7, 75.7, 70.4, 69.4, 59.7, 55.2, 51.7, 36.3, 35.3, 27.6, 23.5; IR (neat) 3418 (br), 3288, 2923, 1732, 1610, 1579, 1503, 1436, 1348, 1258, 1155, 1114, 1093, 1040 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{24}O_5Na$ $(M+Na)^+$ 343.1521, found 343.1523.

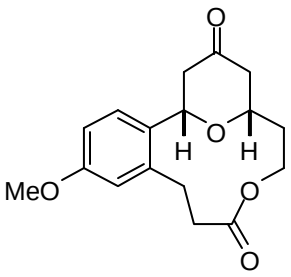
3-(11-Methoxy-7-oxo-3,4,5,7,8,9-hexahydro-1H-2,6-benzodioxacycloundecin-3-yl)prop-1-en-2-yl acetate (2.42)



Compound **2.42** was prepared from **2.41** by following the same protocols for converting **2.21** to **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 2.7 Hz, 1H), 6.69 (dd, *J* = 2.7, 8.4 Hz, 1H), 4.83 (d, *J* = 1.5 Hz, 1H), 4.81 (s, 1H), 4.53 (d, *J* = 10.8 Hz, 1H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.35-4.24 (m, 1H), 4.05 (dt, *J* = 3.3, 11.1 Hz, 1H), 3.78 (s, 3H), 3.64 (ddt, *J* = 1.8, 5.1, 7.5 Hz, 1H), 3.12-2.94 (m, 2H), 2.77-2.64 (m, 2H), 2.56 (ddd, *J* = 3.0, 7.8, 14.1 Hz, 1H), 2.34 (dd, *J* = 7.5, 14.7 Hz, 1H), 2.13 (s, 3H), 2.08-1.92 (m, 1H), 1.75 (ddd, *J* = 3.3, 5.4, 15.3 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 172.3, 169.0, 159.8, 153.0, 142.4, 132.4, 128.0, 115.5, 111.4, 104.1, 73.5, 67.7, 62.4, 55.1, 38.0, 36.8, 31.9, 28.0, 21.1; IR (neat) 2922, 1753, 1732,

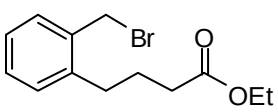
1665, 1611, 1505, 1454, 1429, 1370, 1318, 1198, 1147, 1068, 1043 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{24}O_6$ (M^+) 348.1573, found 348.1589.

(1,14-*cis*)-5-Methoxy-11,18-dioxatricyclo[12.3.1.0^{2,7}]octadeca-2,4,6-triene-10,16-dione (2.68)



The general procedure for the cyclization reaction was followed with **2.42** (63 mg, 0.18 mmol), 2,6-dichloropyridine (81 mg, 0.55 mmol) and 4 Å molecular sieves (127 mg) were dissolved in 2 mL anhydrous 1,2-dichloroethane. DDQ (62 mg, 0.27 mmol) was initially added. After 4 h another 4 mg DDQ was added. The mixture was stirred two more hours then was purified by flash chromatography (40% EtOAc in hexane) to give the desired product **2.68** (41 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 6.73 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.72 (dd, *J* = 2.1, 12.0 Hz, 1H), 4.44 (dd, *J* = 5.4, 11.1 Hz, 1H), 4.18 (ddd, *J* = 5.1, 11.4, 11.4 Hz, 1H), 4.06 (dt, *J* = 5.1, 9.3 Hz, 1H), 3.79 (s, 3H), 3.16 (dd, *J* = 10.5, 12.6 Hz, 1H), 3.00-2.81 (m, 3H), 2.64 (d, *J* = 12.9 Hz, 1H), 2.49-2.25 (m, 4H), 1.62 (dd, *J* = 4.5, 15.0 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 206.7, 173.0, 159.9, 143.5, 128.8, 126.4, 116.8, 111.3, 75.1, 74.2, 61.6, 55.2, 48.1, 45.4, 37.5, 33.7, 28.7; IR (neat) 3016, 2950, 2898, 2857, 2817, 1724, 1613, 1575, 1508, 1456, 1427, 1387, 1352, 1310, 1288, 1267, 1150, 1118, 1061, 805 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{20}O_5Na$ $(M+Na)^+$ 327.1208, found 327.1202.

Ethyl 4-(2-(bromomethyl)phenyl)butanoate



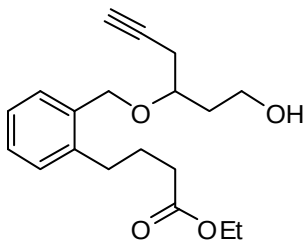
To the solution of ethyl but-3-enoate (814 mg, 7.13 mmol) in 3.5 mL anhydrous THF at 0 °C was added 9-BBN (0.5 M in THF, 19.6 mL). The reaction was allowed to room temperature after the addition and stirred for four hours. Then the

reaction was diluted with 35 mL anhydrous DMF and treated with $PdCl_2(dppf)\cdot CH_2Cl_2$ (157 mg, 0.192 mmol), 2-bromobenzaldehyde (1.20 g, 6.40 mmol) and K_2CO_3 (1.77 g, 12.8 mmol). The mixture was heated to 50 °C and stirred overnight. The reaction was quenched by decanting the crude mixture into H_2O, and the aqueous layer was then extracted with EtOAc and washed with H_2O three times. The combined organic layer was dried with $MgSO_4$, filtered and concentrated. The residue was finally purified by flash chromatography (10% EtOAc in Hexane) to give desired coupled product ethyl 4-(2-formylphenyl)butanoate (1.09 g, contaminated by borate derivatives).

The product from previous Suzuki coupling reaction was dissolved in 6 mL MeOH and cooled to 0 °C, followed by addition of $NaBH_4$ (225 mg, 5.96 mmol). The reaction was kept at 0 °C for ten min, then was quenched by aq. $NaHCO_3$. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (30% EtOAc in Hexane) to give desired ethyl 4-(2-(hydroxymethyl)phenyl)butanoate (597 mg, 41% over two steps).

The product derived from previous step and PPh_3 (645 mg, 2.46 mmol) were dissolved in 6 mL CH_2Cl_2 and cooled to –30 °C, then NBS (438 mg, 2.46 mmol) was added into the reaction. The mixture was stirred at –30 °C for 20 min, then allowed to room temperature and kept for 1.5 hours. Then the crude mixture was dumped into 25 mL hexane and filtered through a plug of Celite. The filtrate was concentrated and purified by flash chromatography (10% EtOAc in Hexane) to give desired ethyl 4-(2-(bromomethyl)phenyl)butanoate (632 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.15 (m, 4H), 4.57 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 2.77 (t, J = 7.8 Hz, 2H), 2.41 (t, J = 7.2 Hz, 2H), 2.00 (tt, J = 7.5, 7.5 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H).

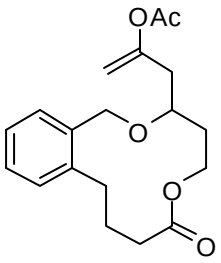
Ethyl 4-(2-((1-hydroxyhex-5-yn-3-yloxy)methyl)phenyl)butanoate (2.36)



Ethyl 4-(2-(bromomethyl)phenyl)butanoate (613 mg, 2.15 mmol) and 1-(triisopropylsilyloxy)hex-5-yn-3-ol (484 mg, 1.79 mmol) were dissolved in 8 mL anhydrous DMF at 0 °C, followed by addition of TBAI (71 mg, 0.18 mmol) and NaH (60% dispersed in mineral oil, 86 mg, 2.2 mmol). The mixture was allowed to room temperature and stirred overnight. The reaction was then quenched by adding water at 0 °C, followed by dilution with EtOAc. The organic layer was washed with water and brine three times, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (8%→10% Et_2O in Hexane) to give ethyl 4-(2-((1-(triisopropylsilyloxy)hex-5-yn-3-yloxy)methyl)phenyl) butanoate (589 mg, 1.24 mmol).

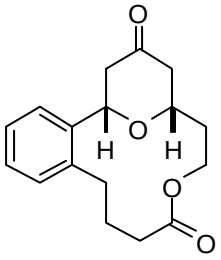
The product derived from previous step was dissolved in 3 mL THF at 0 °C and treated with TBAF (1M in THF, 1.61 mL, 1.61 mmol). The reaction was allowed to room temperature and stirred for one hour, then was directly concentrated under reduced pressure. The residue was purified by flash chromatography (30%→40% EtOAc in Hexane) to give desired product **2.36** (273 mg, 48% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.16 (m, 4H), 4.75 (d, *J* = 11.1 Hz, 1H), 4.53 (d, *J* = 10.8 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.90-3.80 (m, 1H), 3.80-3.67 (m, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.59 (ddd, *J* = 2.7, 4.8, 16.8 Hz, 1H), 2.51 (ddd, *J* = 2.7, 6.6, 16.8 Hz, 1H), 2.39 (t, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 5.7 Hz, 1H), 2.04 (t, *J* = 2.7 Hz, 1H), 2.00-1.85 (m, 4H), 1.27 (t, *J* = 6.9 Hz, 3H).

3-(7-Oxo-1,3,4,5,7,8,9,10-octahydro-2,6-benzodioxacyclododecin-3-yl)prop-1-en-2-yl acetate (2.37)



Compound **2.37** was prepared from **2.36** by following the same protocols for converting compound **2.21** to **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.11 (m, 4H), 4.85 (s, 2H), 4.56 (d, *J* = 9.6 Hz, 1H), 4.45 (ddd, *J* = 3.3, 8.7, 11.7 Hz, 1H), 4.35 (d, *J* = 9.3 Hz, 1H), 4.21 (ddd, *J* = 3.0, 5.7, 11.4 Hz, 1H), 3.73 (ddt, *J* = 2.4, 5.4, 7.2 Hz, 1H), 2.86-2.65 (m, 3H), 2.46 (dd, *J* = 7.2, 15.0 Hz, 1H), 2.40-2.29 (m, 2H), 2.08 (s, 3H), 2.05-1.84 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 173.2, 169.0, 152.9, 141.6, 135.3, 131.1, 129.3, 128.5, 125.9, 104.2, 76.9, 70.1, 62.2, 37.8, 33.5, 32.2, 30.4, 26.7, 21.0; IR (neat) 2922, 1754, 1728, 1665, 1433, 1369, 1251, 1197, 1151, 1110, 1069, 879 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{24}O_5Na$ $(M+Na)^+$ 355.1521, found 355.1509.

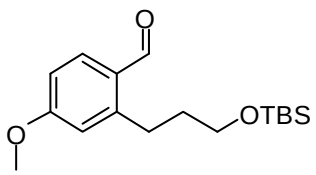
(1,15-*cis*)-12,19-Dioxatricyclo[13.3.1.0^{2,7}]nonadeca-2,4,6-triene-11,17-dione (2.70)



The general procedure for the cyclization reaction was followed except that the process was conducted at 50 °C with **2.37** (27 mg, 0.081 mmol), DDQ (55 mg, 0.24 mmol), 2,6-dichloropyridine (72 mg, 0.48 mmol) and 4 Å molecular sieves (54 mg) in 1,2-dichloroethane (1.2 mL). The reaction was stirred for 24 hours then was purified by flash chromatography (30% EtOAc in hexane) to give the desired product **2.70** (16 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.19 (m, 4H), 4.76 (dd, *J* = 2.4, 12.0 Hz, 1H), 4.69 (ddd, *J* = 2.1, 11.4, 11.4 Hz, 1H), 4.17 (ddd, *J* = 3.9, 3.9, 11.7 Hz, 1H), 4.02 (dddd, *J* = 1.5, 2.4, 7.8, 11.7 Hz, 1H), 2.97 (dd, *J* = 13.5, 13.5 Hz, 1H), 2.94-2.83 (m, 1H), 2.75 (ddd, *J* = 3.9, 9.0, 12.6 Hz, 1H), 2.58 (dd, *J* = 14.1, 14.1 Hz, 1H), 2.52 (dt, *J* = 2.1, 14.1 Hz, 1H), 2.39 (dt, *J* = 2.1, 14.1 Hz, 1H), 2.42-2.30 (m, 1H), 2.24 (dd, *J* = 2.1, 10.5 Hz, 1H), 2.20-2.03 (m,

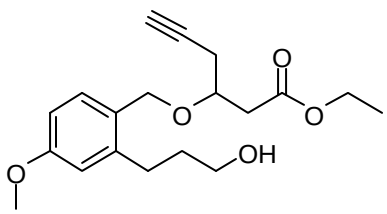
2H), 1.96-1.77 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 206.6, 173.4, 141.4, 136.4, 130.1, 128.8, 126.5, 126.2, 77.2, 76.5, 60.9, 47.7, 46.3, 35.4, 32.4, 29.3, 26.9; IR (neat) 2959, 2918, 2857, 1723, 1326, 1257, 1153, 1071, 1048, 754 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{20}O_4$ (M^+) 288.1362, found 288.1369.

2-(3-(tert-Butyldimethylsilyloxy)propyl)-4-methoxybenzaldehyde (2.43)



To the solution of allyloxy(tert-butyl)dimethylsilane (882 mg, 5.12 mmol) in 2.5 mL anhydrous THF at 0 °C was added 9-BBN (0.5 M in THF, 12.1 mL, 6.05 mmol). The reaction was allowed to room temperature after the addition and stirred for 4 hours. Then the reaction was diluted with 25 mL anhydrous DMF and treated with $PdCl_2(dppf)\cdot CH_2Cl_2$ (114 mg, 0.140 mmol), **2.18** (1.00 g, 4.65 mmol) and K_2CO_3 (1.29 g, 9.30 mmol). The mixture was heated to 50 °C and stirred overnight. The reaction was quenched by decanting the crude mixture into H_2O, and the aqueous layer was then extracted with Et_2O and washed with H_2O three times. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was finally purified by flash chromatography (6% EtOAc in Hexane) to give desired product **2.43** (1.141 g with some borate impurity). ^1H NMR (300 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 6.84 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 3.87 (s, 3H), 3.67 (t, *J* = 6.0 Hz, 1H), 3.07 (t, *J* = 7.8 Hz, 1H), 1.86-1.78 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H).

Ethyl 3-(2-(3-hydroxypropyl)-4-methoxybenzyloxy)hex-5-ynoate (2.45)



Compound **2.43** (1.141 g) was dissolved in 5 mL MeOH and cooled to 0 °C, followed by addition of $NaBH_4$ (168 mg, 4.44

mmol). The reaction was kept at 0 °C for 30 min then quenched by aq. $NaHCO_3$. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in Hexane) to give (2-(3-(tert-butyldimethylsilyloxy)propyl)-4-methoxyphenyl)methanol (915 mg, 63% over two steps).

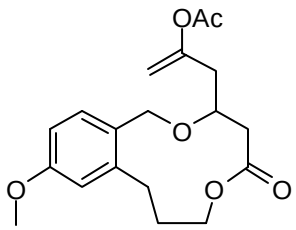
The alcohol derived from previous step (915 mg, 2.95 mmol) was dissolved in 6 mL anhydrous CH_2Cl_2 at 0 °C, followed by dropwise addition of DBU (661 μL, 4.42 mmol) and CCl_3CN (886 μL, 8.84 mmol). The reaction was allowed to room temperature and stirred for one hour. Then it was directly concentrated under reduced pressure to give a very viscous brown oil, and purified by 1% Et_3N neutralized silica gel flash chromatography (10% EtOAc in Hexane) to give desired trichloroacetimidate (854 mg, 64%).

The product from previous step and ethyl 3-hydroxy-6-(trimethylsilyl)hex-5-ynoate (268 mg, 1.18 mmol) were dissolved in 12 mL dry toluene at room temperature, then $La(OTf)_3$ (103 mg, 0.176 mmol) was added in. The reaction was stirred at rt overnight then filtered through a plug of silica gel with Et_2O as eluent to remove the metal salt. The filtrate was concentrated and roughly purified by flash chromatography (8%→10% Et_2O in Hexane) to give ethyl 3-(2-(3-(tert-butyldimethylsilyloxy)propyl)-4-methoxybenzyloxy)-6-(trimethylsilyl)hex-5-ynoate (449 mg, containing some unreacted homopropargylic secondary alcohol).

The product from previous step was dissolved in 6 mL THF at 0 °C and treated with TBAF·$3H_2O$ (816 mg, 2.59 mmol). The reaction was allowed to room temperature and stirred for one hour and directly concentrated under reduced pressure. The residue was purified by flash chromatography (45%→50% EtOAc in Hexane) to give desired product **2.45** (159 mg, 40% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 2.7 Hz, 1H), 6.70 (dd, J = 2.7, 8.4 Hz, 1H), 4.60 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 4.14 (q, J =

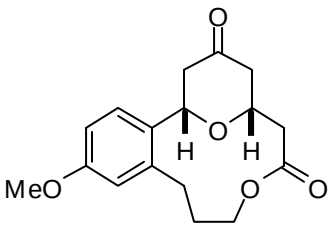
7.2 Hz, 2H), 4.14-4.05 (m, 1H), 3.79 (s, 3H), 3.66 (dt, *J* = 6.0, 6.0 Hz, 2H), 2.76 (t, *J* = 8.1 Hz, 2H), 2.75-2.61 (m, 2H), 2.57 (ddd, *J* = 2.7, 4.8, 16.8 Hz, 1H), 2.48 (ddd, *J* = 2.7, 6.6, 16.8 Hz, 1H), 2.13 (t, *J* = 5.7 Hz, 1H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.92-1.81 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

3-(11-Methoxy-5-oxo-3,4,5,7,8,9-hexahydro-1H-2,6-benzodioxacycloundecin-3-yl)prop-1-en-2-yl acetate (2.47)



Compound **2.47** was prepared from **2.45** by following the same protocols for converting compound **2.21** to **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 6.65 (dd, *J* = 2.7, 8.1 Hz, 1H), 4.87 (s, 2H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.40-4.30 (m, 1H), 4.10-3.99 (m, 1H), 3.97 (dt, *J* = 3.3, 10.5 Hz, 1H), 3.78 (s, 3H), 2.87-2.60 (m, 4H), 2.50-2.38 (m, 2H), 2.16 (s, 3H), 2.10-1.85 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 171.2, 169.0, 159.9, 152.3, 143.5, 132.3, 127.3, 115.1, 110.4, 104.6, 74.2, 70.7, 62.8, 55.1, 40.9, 38.0, 29.0, 26.6, 21.1; IR (neat) 2921, 1738, 1665, 1610, 1578, 1503, 1454, 1370, 1261, 1193, 1070, 1020 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{24}O_6$ (M^+) 348.1573, found 348.1561.

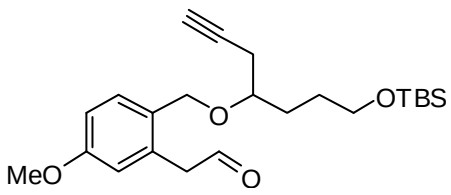
(1,14-*cis*)-5-Methoxy-11,18-dioxatricyclo[12.3.1.0^{2,7}]octadeca-2,4,6-triene-12,16-dione (2.69)



The general procedure for the cyclization reaction was followed with **2.47** (43 mg, 0.12 mmol), DDQ (42 mg, 0.19 mmol), 2,6-dichloropyridine (55 mg, 0.37 mmol) and 4 Å molecular sieves (86 mg) in 1,2-dichloroethane (1.5 mL). The mixture was stirred for 28 h then was purified by flash chromatography (35% EtOAc in hexane) to give the desired product **2.69** (24 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 2.7 Hz,

1H), 6.71 (dd, *J* = 2.7, 8.4 Hz, 1H), 4.88 (ddd, *J* = 2.7, 2.7, 10.8 Hz, 1H), 4.75 (dd, *J* = 1.8, 12.3 Hz, 1H), 4.33 (dddd, *J* = 2.7, 4.2, 11.4, 11.4 Hz, 1H), 3.79 (s, 3H), 3.73 (dd, *J* = 12.3, 12.3 Hz, 1H), 2.97 (dd, *J* = 12.9, 12.9 Hz, 1H), 2.82 (dd, *J* = 4.5, 14.7 Hz, 1H), 2.79-2.68 (m, 2H), 2.66-2.55 (m, 2H), 2.48 (dd, *J* = 11.4, 15.0 Hz, 1H), 2.36 (dd, *J* = 11.7, 14.4 Hz, 1H), 2.05-1.89 (m, 1H), 1.80-1.63 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 205.9, 170.2, 159.9, 145.1, 127.1, 126.2, 115.9, 110.3, 75.5, 74.3, 64.2, 55.2, 47.1, 45.0, 42.0, 30.9, 27.6; IR (neat) 2963, 2920, 1726, 1709, 1615, 1575, 1503, 1453, 1424, 1371, 1329, 1245, 1145, 1063, 1012, 814 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{20}O_5$ (M^+) 304.1311, found 304.1318.

2-(2-((7-(tert-Butyldimethylsilyloxy)hept-1-yn-4-yloxy)methyl)-5-methoxyphenyl) acetaldehyde (2.56)



Compound **2.18** (1.36 g, 6.32 mmol) and allyltributyltin (2.30 g, 6.96 mmol) were dissolved in 25 mL degassed dry toluene, followed by addition of $Pd(PPh_3)_4$ (731 mg, 0.632 mmol). The solution was purged again with argon. The reaction was heated to 100 °C and kept for 24 hours. The crude mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (10% EtOAc in Hexane) to give desired Stille coupling product **2.48** (820 mg, 74%).

Compound **2.48** from previous step was dissolved in 8 mL MeOH and cooled to 0 °C, followed by addition of $NaBH_4$ (194 mg, 5.12 mmol). The reaction was kept at 0 °C for 30 min then quenched by aq. $NaHCO_3$. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in Hexane) to give (2-allyl-4-methoxyphenyl)methanol (638 mg, 77%).

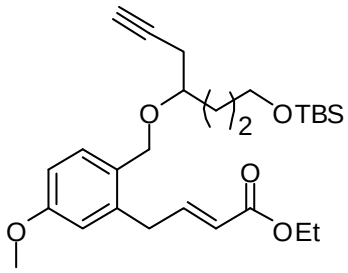
The alcohol from previous step was dissolved in 7 mL anhydrous CH_2Cl_2 at 0 °C, followed by dropwise addition of DBU (803 μL, 5.37 mmol) and CCl_3CN (1.08 mL, 10.7 mmol). The reaction was allowed to rt and stirred for two hours. Then it was directly concentrated under reduced pressure to give a very viscous brown oil, and purified by 1% Et_3N neutralized silica gel flash chromatography (10% EtOAc in Hexane) to give desired trichloroacetimidate (919 mg, 80%).

The trichloroacetimidate (677 mg, 2.10 mmol) derived from previous step and 7-(tert-butyldimethylsilyloxy)-hept-1-yn-4-ol (299 mg, 1.23 mmol) were dissolved in 5 mL dry toluene at room temperature, then $La(OTf)_3$ (108 mg, 0.185 mmol) was added in. The reaction was stirred at room temperature overnight then filtered through a plug of silica gel with Et_2O to remove the metal salt. The filtrate was concentrated and roughly purified by flash chromatography (5% Et_2O in Hexane) to give **2.55** (321 mg, 65%).

AD-mix-β (1.115 g) was dissolved in a mixture of 4 mL H_2O and 2 mL ^{t}BuOH at 0 °C, followed by addition of $CH_3SO_2NH_2$ (76 mg, 0.80 mmol). Compound **2.55** (321 mg, 0.796 mmol) was diluted with 2 mL ^{t}BuOH and added into the reaction. The mixture was allowed to room temperature and stirred overnight. The reaction was quenched by adding aq. $Na_2S_2O_3$. The aqueous layer was then extracted with EtOAc and the combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (45% EtOAc in Hexane) to give desired 3-(2-((7-(tert-butyldimethylsilyloxy)hept-1-yn-4-yloxy)methyl)-5-methoxyphenyl)propane-1,2-diol (103 mg) and unreacted starting material (105.4 mg). The latter was re-subjected to the dihydroxylation reaction and the products were combined.

The diol derived from previous step (160 mg, 0.367 mmol) was dissolved in 4 mL CH_2Cl_2 and treated with $NaIO_4/SiO_2$ (1.100 g) at room temperature. The reaction was stirred for four hours, then filtered through a plug of silica gel and eluted with Et_2O. The filtrate was concentrated and the residue was purified by flash chromatography (10% EtOAc in Hexane) to give desired product **2.56** (132 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.84-6.70 (m, 2H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 5H), 3.66-3.51 (m, 3H), 2.42 (dd, *J* = 2.4, 5.4 Hz, 2H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.76-1.48 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 199.8, 159.8, 133.3, 131.7, 129.2, 116.8, 112.5, 81.2, 77.1, 70.1, 69.5, 62.9, 55.3, 48.0, 30.1, 28.4, 26.0, 23.6, 18.3, -5.3; IR (neat) 2953, 2929, 2856, 1722, 1611, 1506, 1460, 1254, 1096, 1044, 836, 776 cm^{-1}.

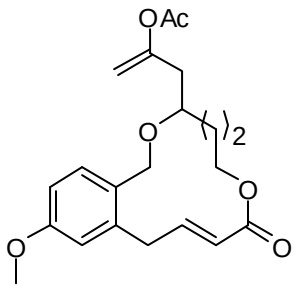
(*E*)-Ethyl 4-(2-((7-(tert-butyldimethylsilyloxy)hept-1-yn-4-yloxy)methyl)-5-methoxyphenyl) but-2-enoate (2.57)



Ethyl 2-(diethoxyphosphoryl)acetate (146 mg, 0.653 mmol) was dissolved in 2 mL THF at 0 °C, followed by addition of NaH (60% dispersed in mineral oil, 26 mg, 0.65 mmol). The mixture was kept at 0 °C for 20 min, then **2.56** (132 mg, 0.327 mmol) in 3 mL THF was added into the reaction. It was stirred at 0 °C for one hour, then quenched by adding aq. NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (6% EtOAc in Hexane) to give desired product **2.57** (125 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 1H), 7.11 (dt, *J* = 6.3, 15.3 Hz, 1H), 6.75 (dd, *J* = 2.7, 8.1 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 5.73 (d, *J* = 15.6 Hz, 1H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 11.1 Hz, 1H),

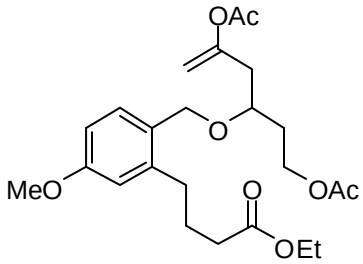
4.16 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.68-3.48 (m, 5H), 2.51-2.35 (m, 2H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.80-1.45 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 166.4, 159.6, 147.1, 138.3, 131.4, 128.3, 122.3, 115.9, 111.5, 81.2, 76.7, 70.0, 69.0, 62.9, 60.2, 55.2, 35.2, 30.1, 28.4, 25.9, 23.7, 18.2, 14.2, -5.4; IR (neat) 3393 (br), 2928, 2856, 1717, 1616, 1464, 1258, 1156, 1096, 1041 cm^{-1}.

3-(13-Methoxy-8-oxo-3,4,5,6,8,11-hexahydro-1H-2,7-benzodioxacyclotridecin-3-yl)prop-1-en-2-yl acetate (2.59)



Compound **2.59** was prepared from **2.57** by following similar protocols for converting **2.21** to **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.06 (m, 2H), 6.88-6.68 (m, 2H), 6.28 (dt, *J* = 6.9, 15.0 Hz, 1H), 4.83 (d, *J* = 0.9 Hz, 1H), 4.82 (s, 1H), 4.47 (s, 2H), 4.18-3.96 (m, 2H), 3.81 (s, 3H), 3.56-3.46 (m, 1H), 3.34 (d, *J* = 6.6 Hz, 2H), 2.61 (dd, *J* = 5.7, 14.7 Hz, 1H), 2.41 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.10 (s, 3H), 1.95-1.78 (m, 1H), 1.78-1.50 (m, 3H).

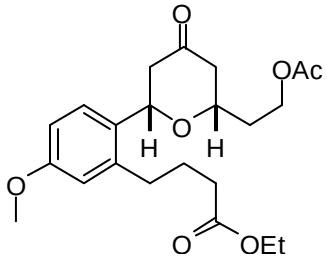
3-(2-(4-Ethoxy-4-oxobutyl)-4-methoxybenzyloxy)hex-5-ene-1,5-diyl diacetate (2.63)



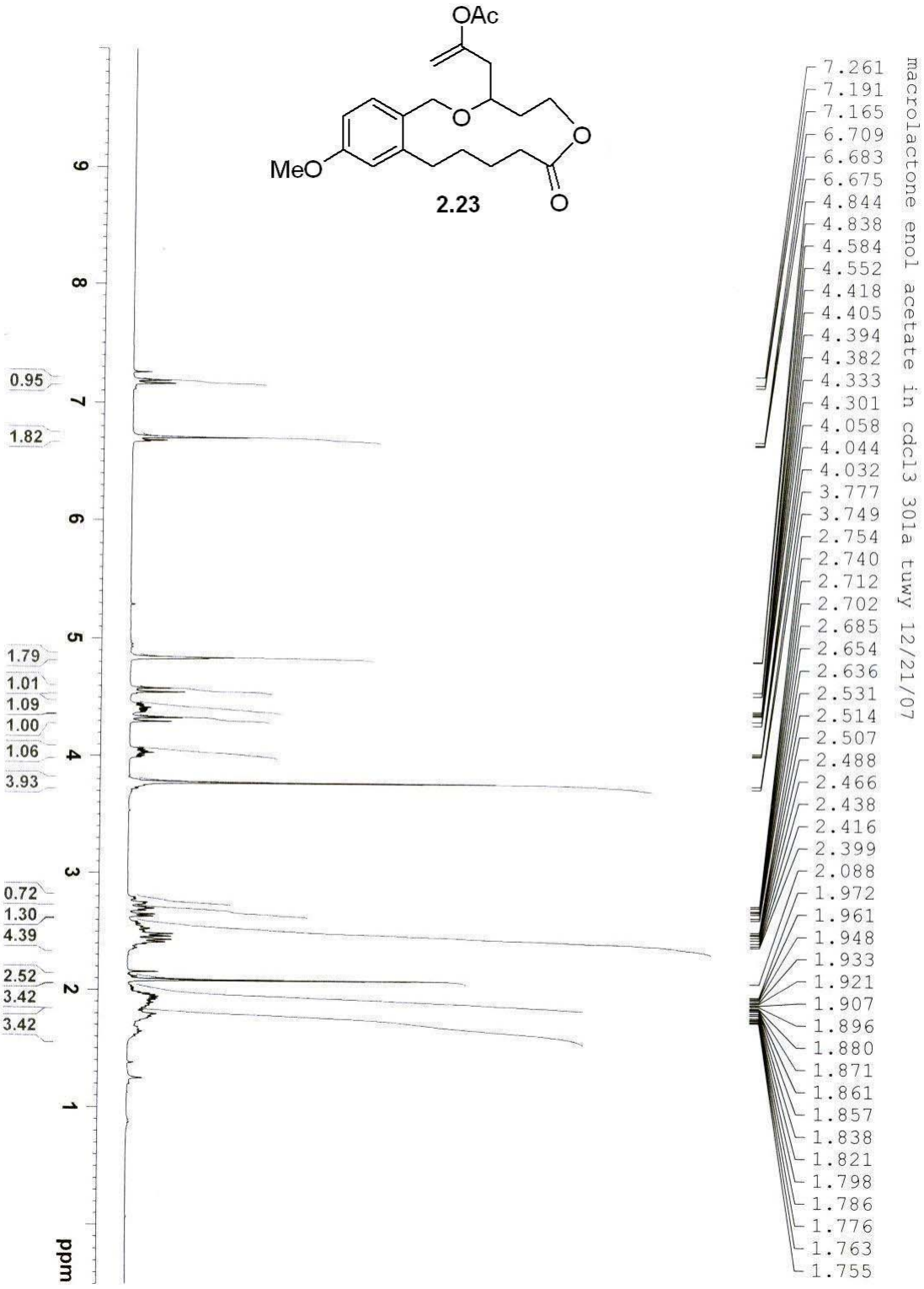
Compound **2.63** was prepared from **2.18** by following similar protocols for synthesizing **2.23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 1H), 6.72 (s, 1H), 6.71 (d, *J* = 9.6 Hz, 1H), 4.83 (s, 1H), 4.82 (s, 1H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 11.1 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 4H), 3.78 (s, 3H), 3.70-3.58 (m, 1H), 2.68 (dt, *J* = 4.5, 7.5 Hz, 2H), 2.57 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.45 (dd, *J* = 6.0, 14.7 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.09 (s, 3H), 2.00 (s, 3H), 2.00-1.75 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ

173.4, 170.9, 169.0, 159.4, 152.9, 142.0, 131.3, 127.9, 115.1, 111.0, 104.1, 72.7, 68.7, 61.1, 60.3, 55.2, 38.2, 33.8, 33.1, 31.8, 26.2, 21.1, 20.9, 14.2; IR (neat) 2921, 1734, 1666, 1610, 1579, 1504, 1459, 1370, 1162, 1096, 1026 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{34}O_8$ (M^+) 450.2254, found 450.2250.

Ethyl 4-(2-((2,6-*cis*)-6-(2-acetoxyethyl)-4-oxotetrahydro-2H-pyran-2-yl)-5-methoxyphenyl) butanoate (2.71)



The general procedure for the cyclization reaction was followed with **2.63** (46 mg, 0.10 mmol), DDQ (35 mg, 0.15 mmol), 2,6-dichloropyridine (45 mg, 0.31 mmol), and 4 Å molecular sieves (92 mg) in 1,2-dichloroethane (1.2 mL). The mixture was stirred for 30 min then was purified by flash chromatography (30% EtOAc in hexane) to give the desired product **2.71** (32 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.7 Hz, 1H), 6.79 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 4.80 (dd, *J* = 2.4, 11.7 Hz, 1H), 4.30-4.15 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.95 (ddt, *J* = 3.6, 7.5, 7.5 Hz, 1H), 3.80 (s, 3H), 2.72-2.60 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.56-2.50 (m, 1H), 2.50-2.39 (m, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.01 (s, 3H), 2.08-1.83 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 206.6, 173.1, 170.9, 159.3, 140.4, 130.2, 127.2, 115.1, 111.9, 74.9, 74.2, 60.7, 60.4, 55.2, 48.6, 47.6, 35.3, 33.7, 31.8, 26.4, 20.9, 14.2; IR (neat) 2959, 2921, 1718, 1610, 1579, 1505, 1459, 1370, 1148, 1036 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{30}O_7$ (M^+) 406.1992, found 406.1986.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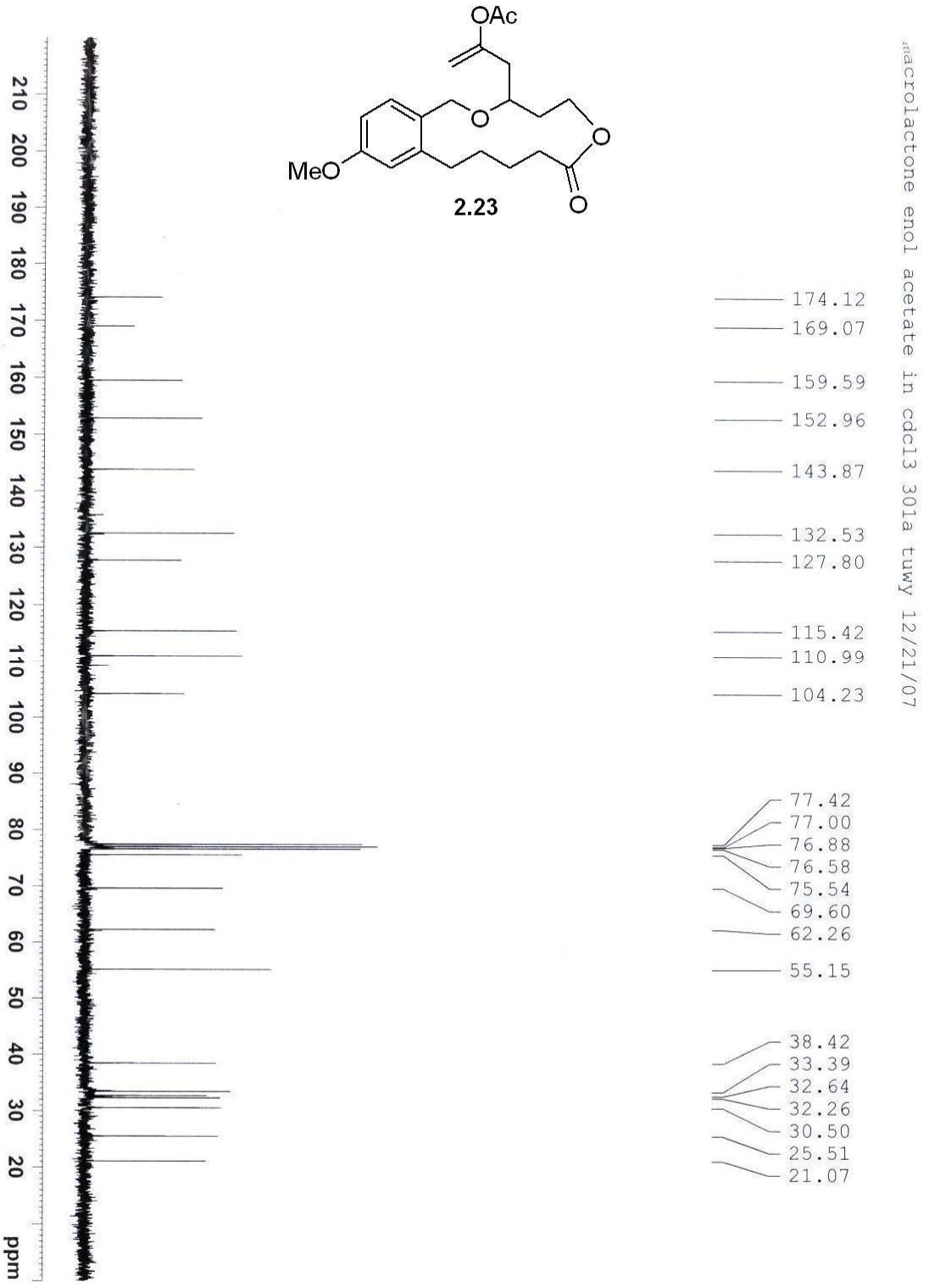
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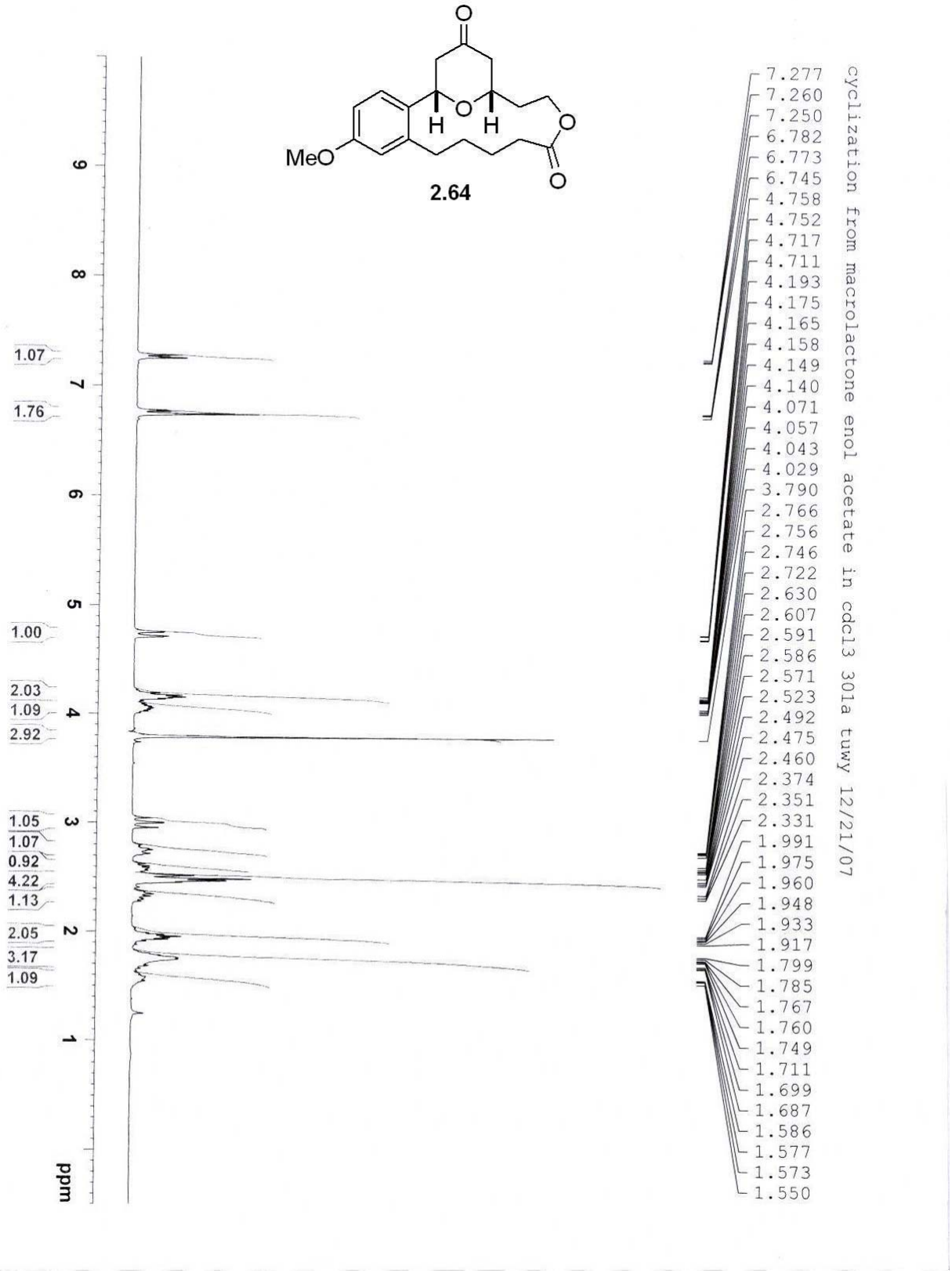
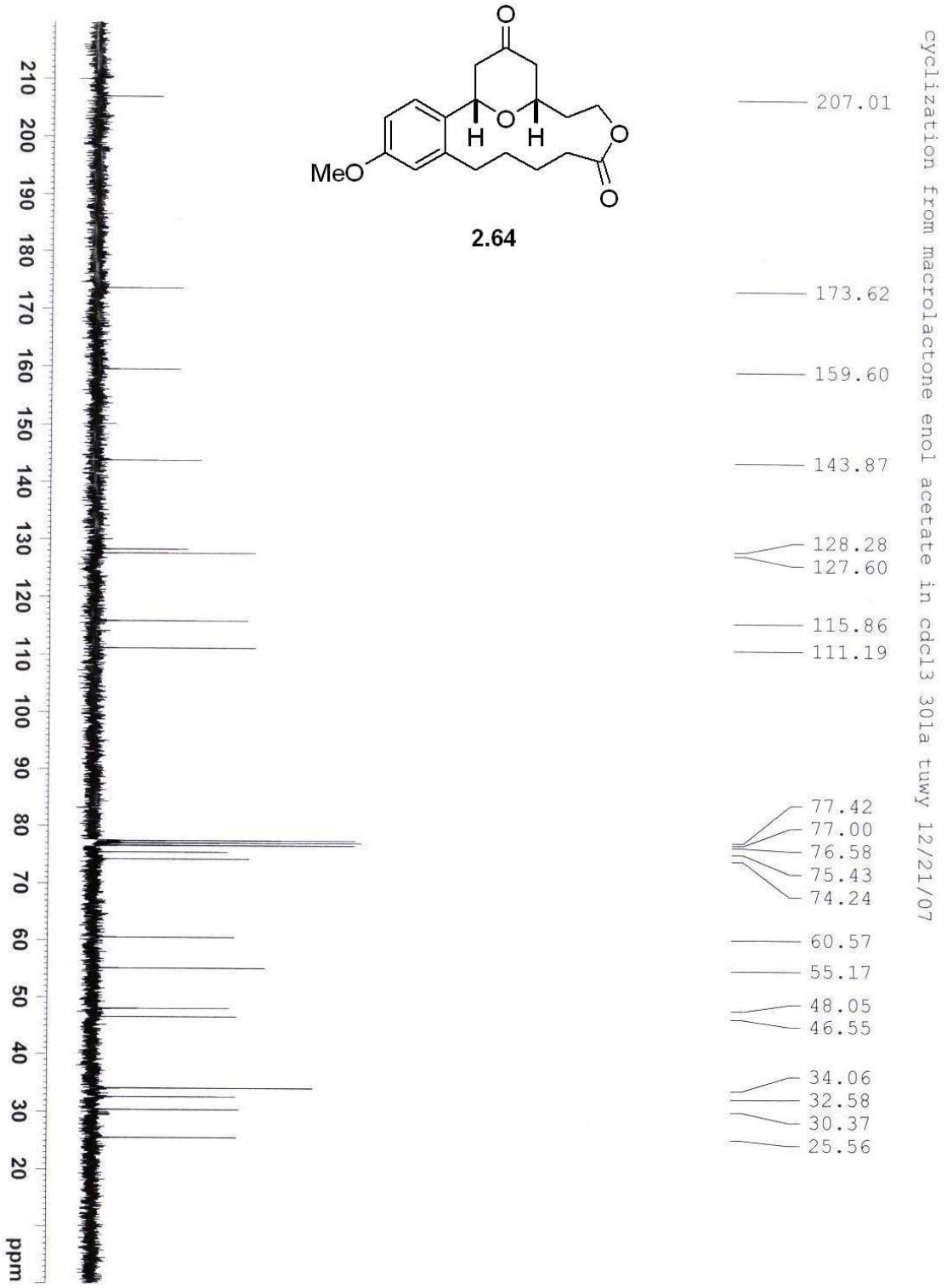
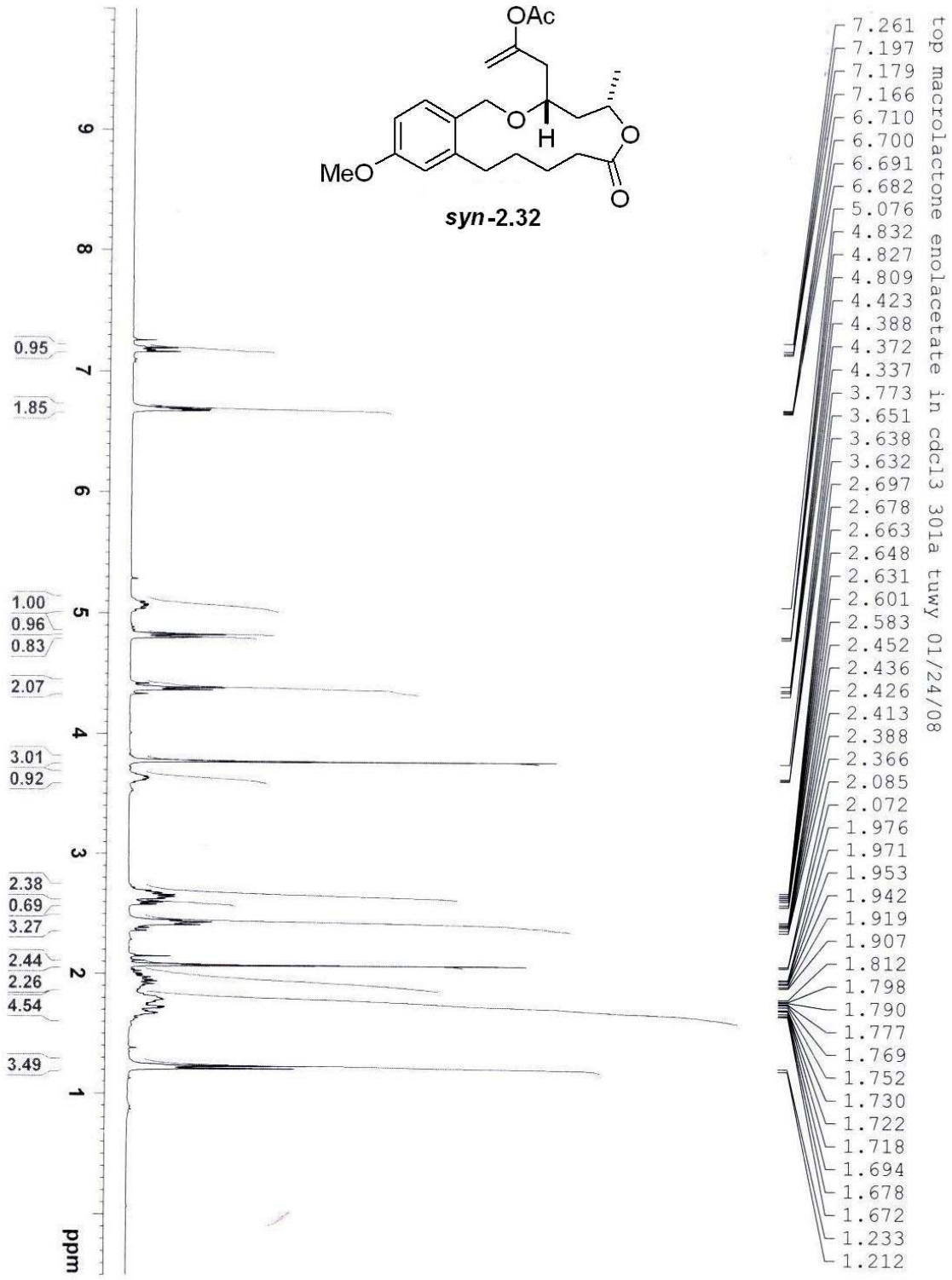
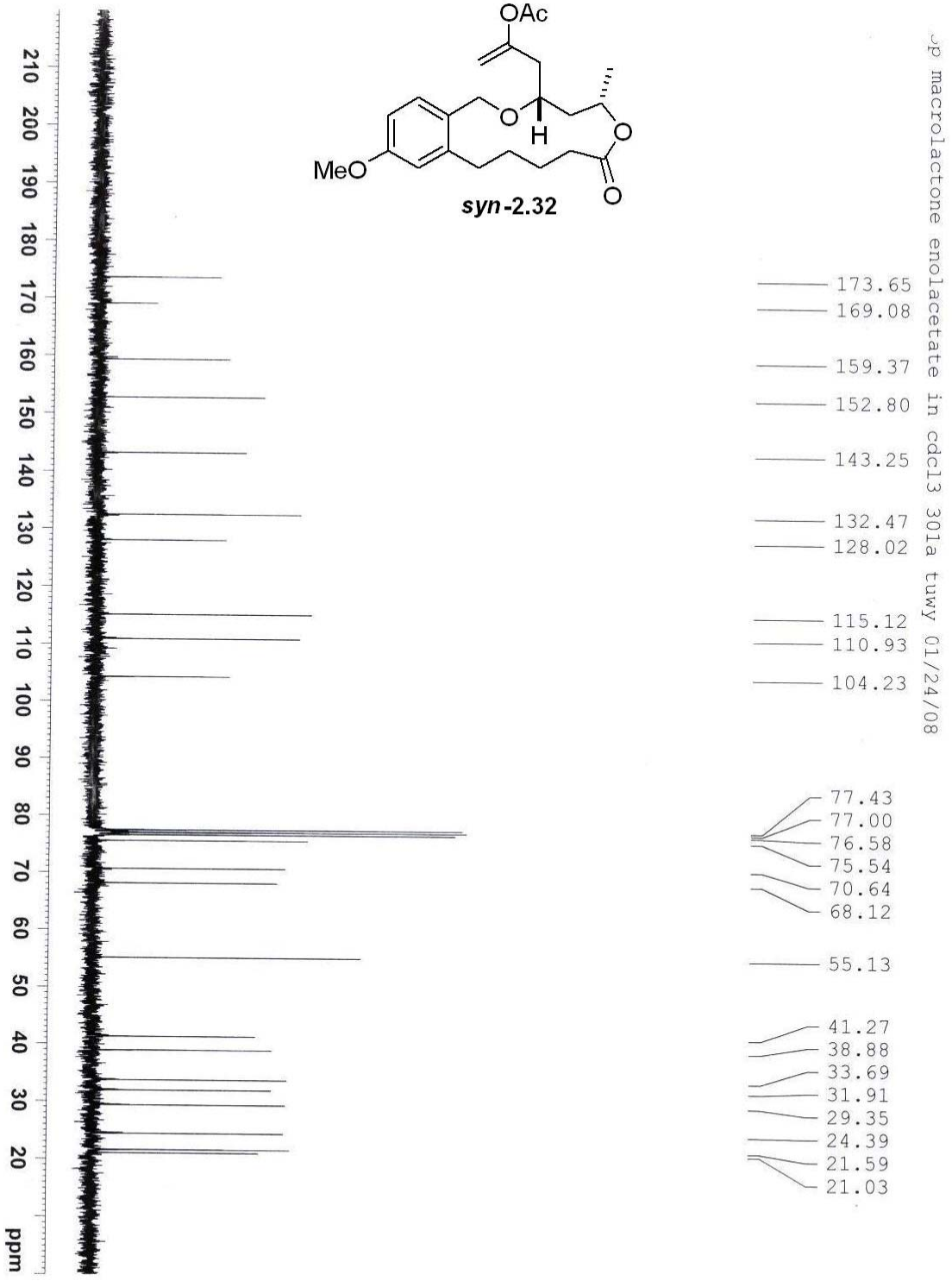
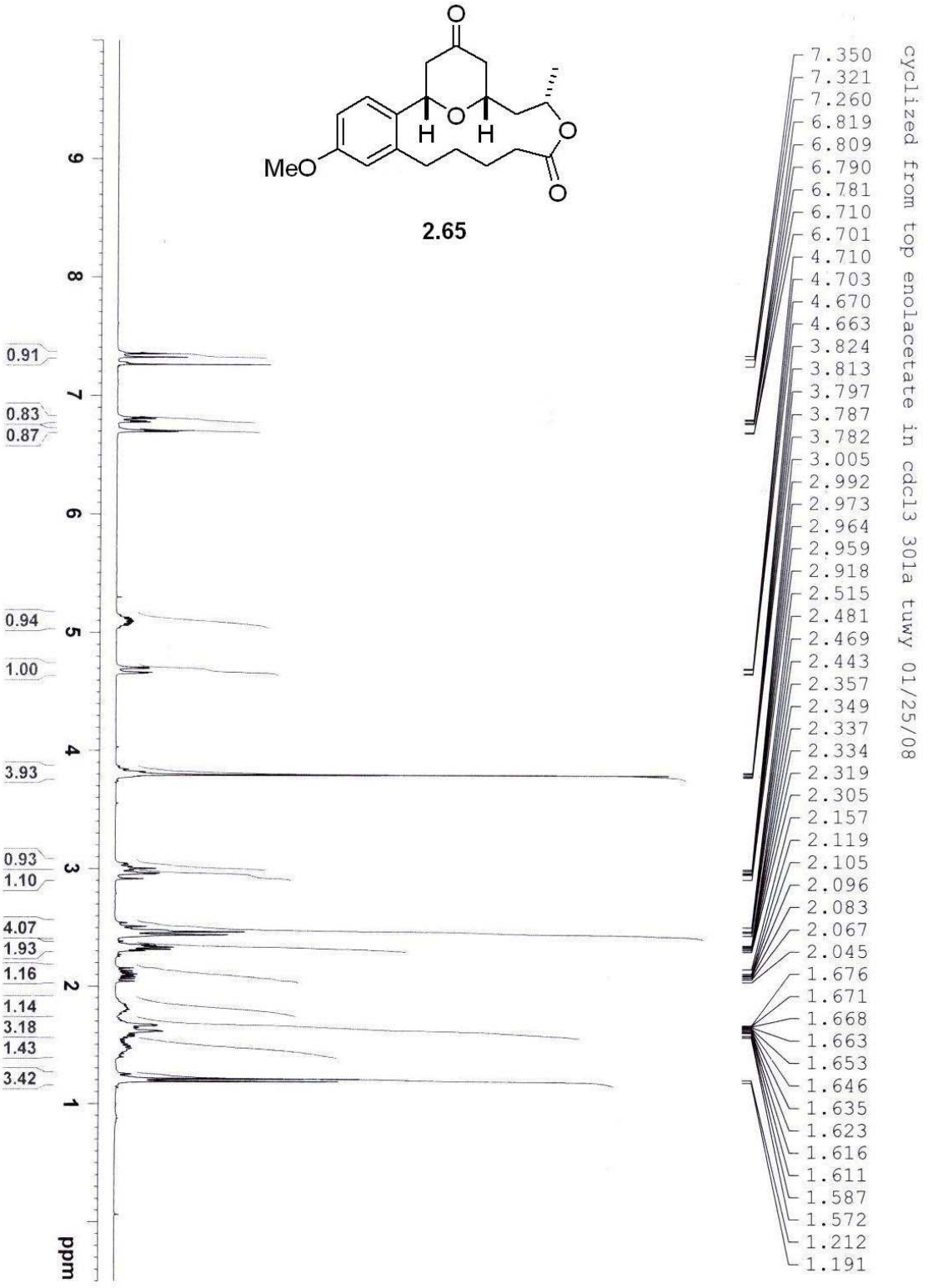
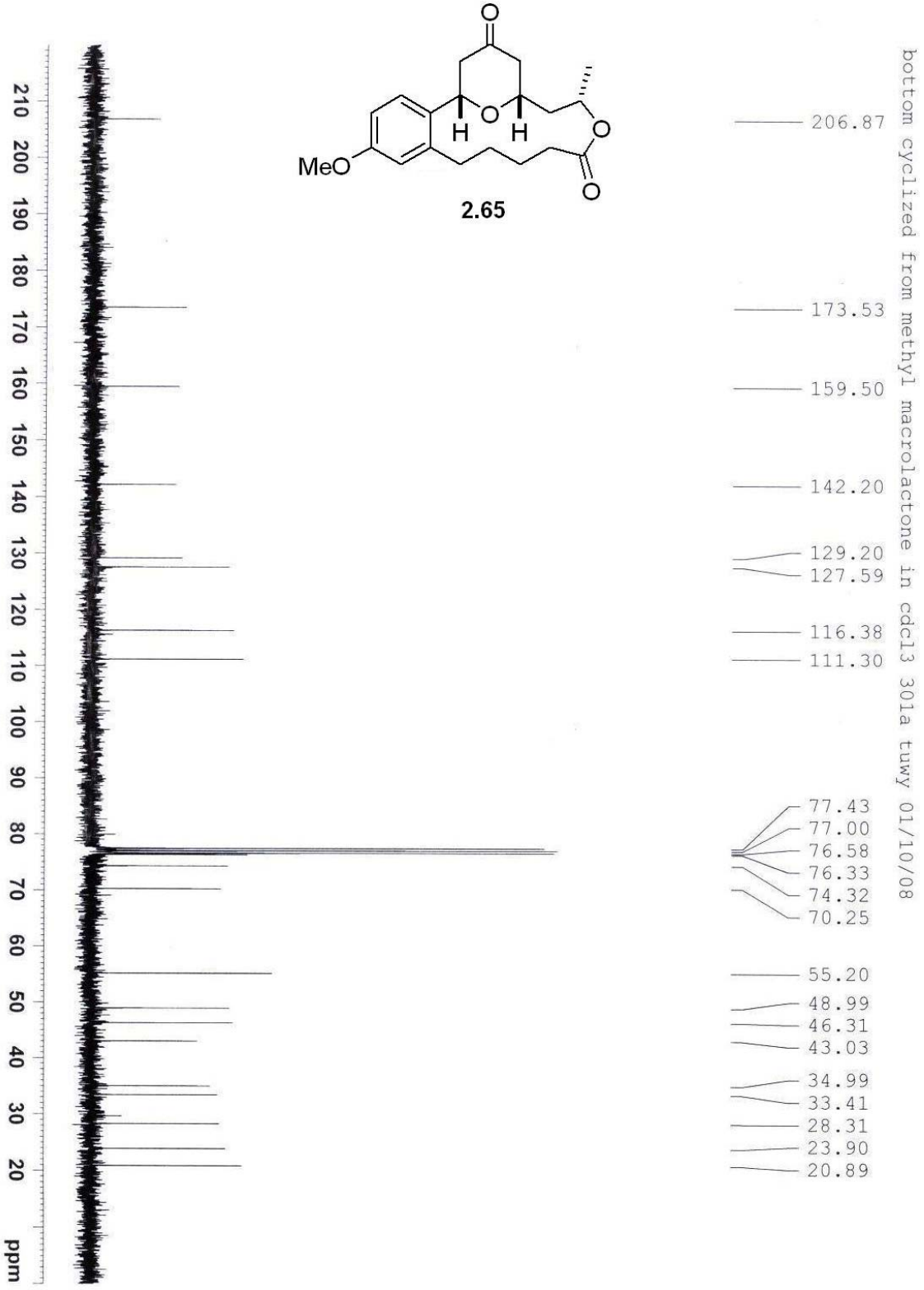

O
O
H
H
O
MeO
O
2.64
cyclization from macrolactone enol acetate in cdcl3 301a tuwy 12/21/07
7.277
7.260
7.250
6.782
6.773
6.745
4.758
4.752
4.717
4.711
4.193
4.175
4.165
4.158
4.149
4.140
4.071
4.057
4.043
4.029
3.790
2.766
2.756
2.746
2.722
2.630
2.607
2.591
2.586
2.571
2.523
2.492
2.475
2.460
2.374
2.351
2.331
1.991
1.975
1.960
1.948
1.933
1.917
1.799
1.785
1.767
1.760
1.749
1.711
1.699
1.687
1.586
1.577
1.573
1.550
1.07
1.76
1.00
2.03
1.09
2.92
1.05
1.07
0.92
4.22
1.13
2.05
3.17
1.09
ppm

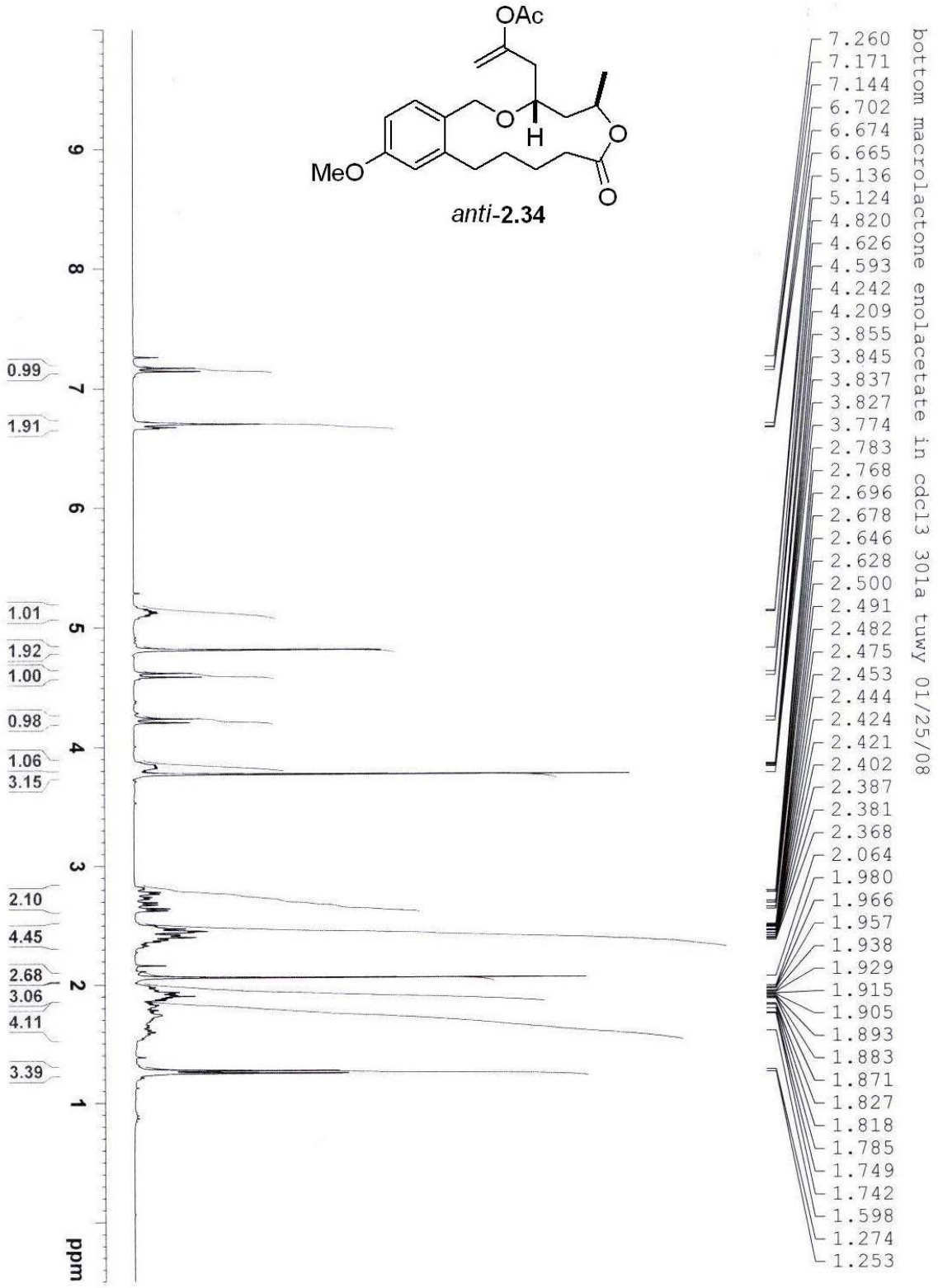

cyclization from macrolactone enol acetate in cdcl3 301a tuwy 12/21/07
207.01
173.62
159.60
143.87
128.28
127.60
115.86
111.19
77.42
77.00
76.58
75.43
74.24
60.57
55.17
48.05
46.55
34.06
32.58
30.37
25.56
MeO
H
H
O
O
O
O
2.64
ppm

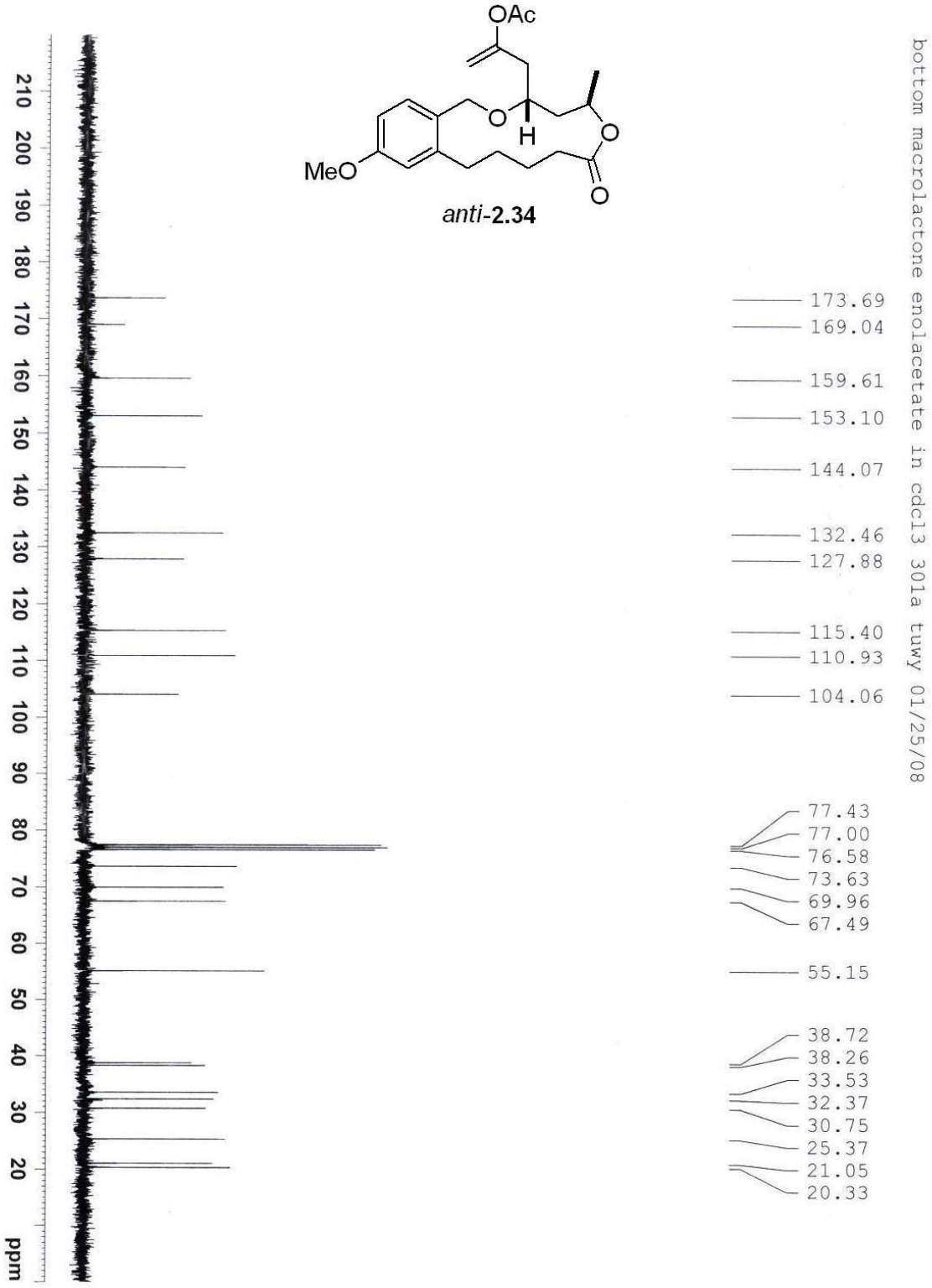

OAc
O
H
O
MeO
O
syn-2.32
0.95
1.85
1.00
0.96
0.83
2.07
3.01
0.92
2.38
0.69
3.27
2.44
2.26
4.54
3.49
ppm
top macrolactone enolacetate in cdcl3 301a tuwy 01/24/08
7.261
7.197
7.179
7.166
6.710
6.700
6.691
6.682
5.076
4.832
4.827
4.809
4.423
4.388
4.372
4.337
3.773
3.651
3.638
3.632
2.697
2.678
2.663
2.648
2.631
2.601
2.583
2.452
2.436
2.426
2.413
2.388
2.366
2.085
2.072
1.976
1.971
1.953
1.942
1.919
1.907
1.812
1.798
1.790
1.777
1.769
1.752
1.730
1.722
1.718
1.694
1.678
1.672
1.233
1.212

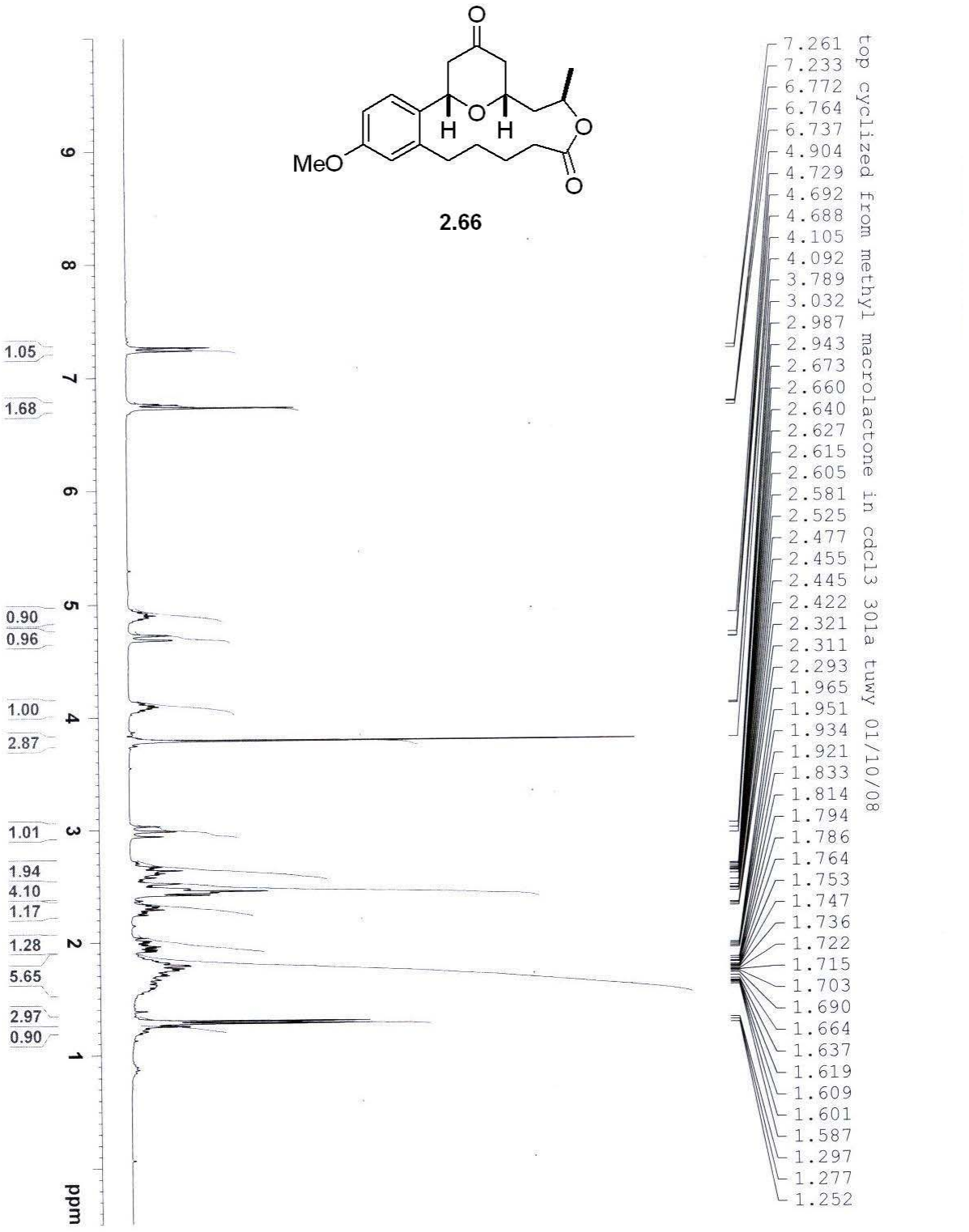

OAc
O
H
O
MeO
O
syn-2.32
jp macrolactone enolacetate in cdcl3 301a tuwy 01/24/08
173.65
169.08
159.37
152.80
143.25
132.47
128.02
115.12
110.93
104.23
77.43
77.00
76.58
75.54
70.64
68.12
55.13
41.27
38.88
33.69
31.91
29.35
24.39
21.59
21.03
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

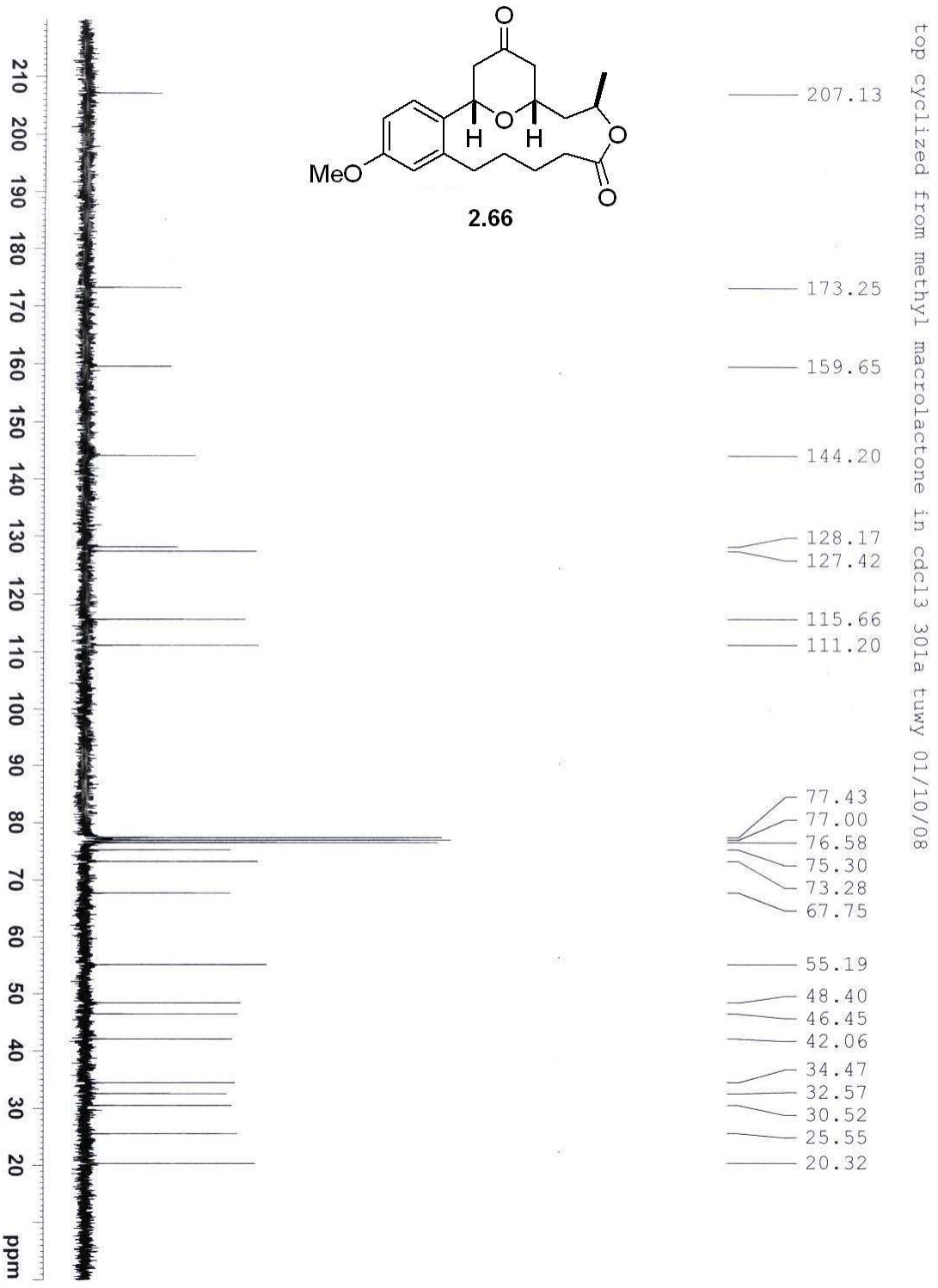

cyclized from top enolacetate in cdcl3 301a tuwy 01/25/08
7.350
7.321
7.260
6.819
6.809
6.790
6.781
6.710
6.701
4.710
4.703
4.670
4.663
3.824
3.813
3.797
3.787
3.782
3.005
2.992
2.973
2.964
2.959
2.918
2.515
2.481
2.469
2.443
2.357
2.349
2.337
2.334
2.319
2.305
2.157
2.119
2.105
2.096
2.083
2.067
2.045
1.676
1.671
1.668
1.663
1.653
1.646
1.635
1.623
1.616
1.611
1.587
1.572
1.212
1.191
0.91
0.83
0.87
0.94
1.00
3.93
0.93
1.10
4.07
1.93
1.16
1.14
3.18
1.43
3.42
ppm
MeO
H
H
O
O
O
O
2.65

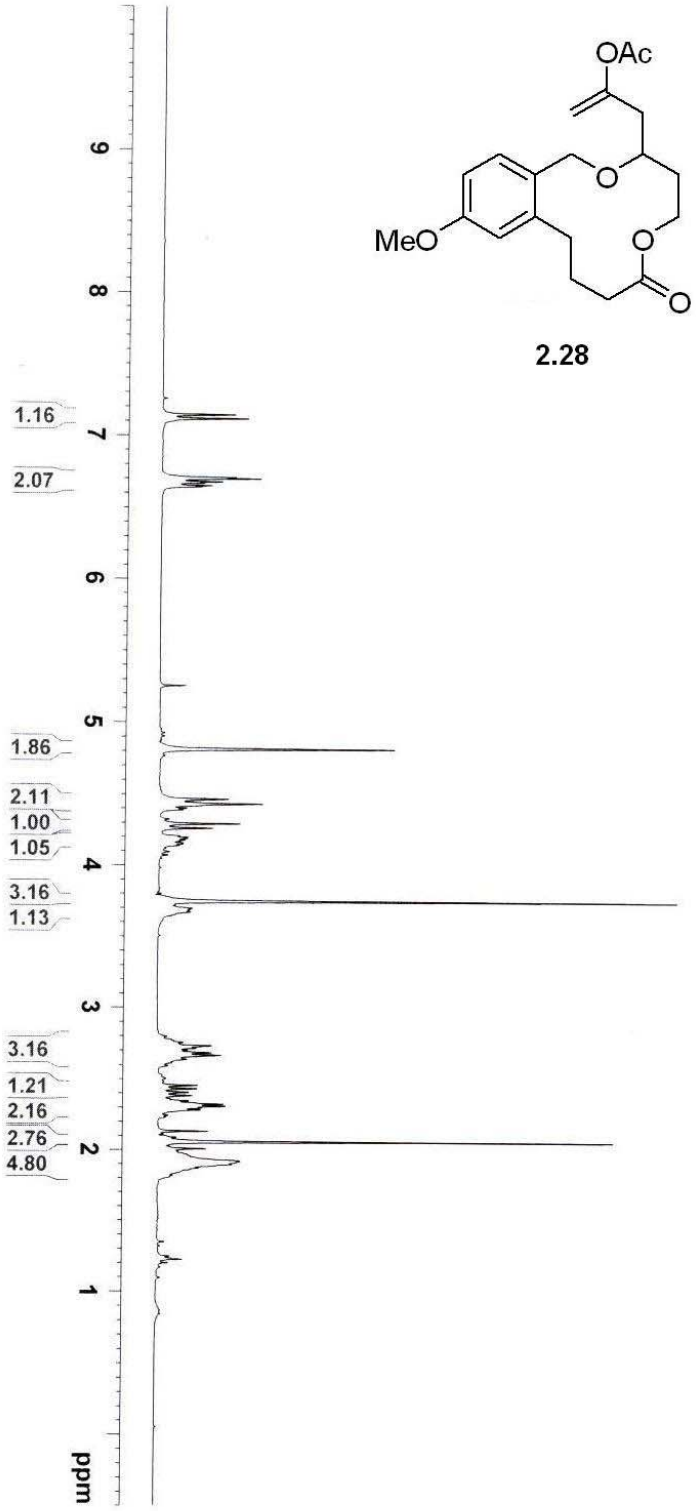

bottom cyclized from methyl macrolactone in cdcl3 301a tuwy 01/10/08
206.87
173.53
159.50
142.20
129.20
127.59
116.38
111.30
77.43
77.00
76.58
76.33
74.32
70.25
55.20
48.99
46.31
43.03
34.99
33.41
28.31
23.90
20.89
MeO
H
H
O
O
O
O
2.65
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


OAc
O
H
O
O
MeO
O
anti-2.34
bottom macrolactone enolacetate in cdcl3 301a tuwy 01/25/08
7.260
7.171
7.144
6.702
6.674
6.665
5.136
5.124
4.820
4.626
4.593
4.242
4.209
3.855
3.845
3.837
3.827
3.774
2.783
2.768
2.696
2.678
2.646
2.628
2.500
2.491
2.482
2.475
2.453
2.444
2.424
2.421
2.402
2.387
2.381
2.368
2.064
1.980
1.966
1.957
1.938
1.929
1.915
1.905
1.893
1.883
1.871
1.827
1.818
1.785
1.749
1.742
1.598
1.274
1.253
0.99
1.91
1.01
1.92
1.00
0.98
1.06
3.15
2.10
4.45
2.68
3.06
4.11
3.39
ppm

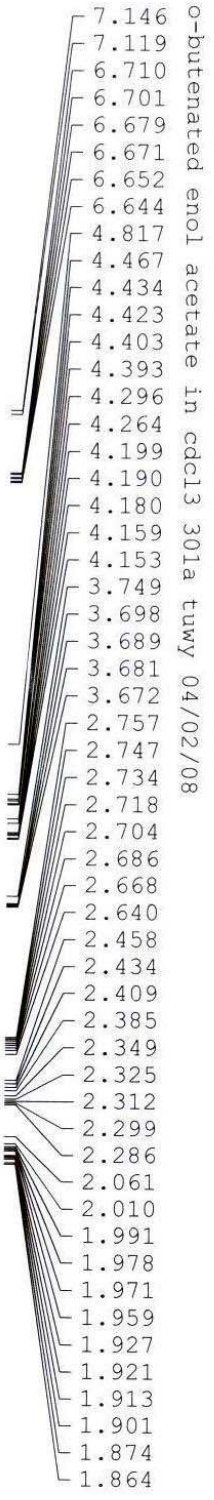

OAc
O
H
O
O
MeO
O
anti-2.34
bottom macrolactone enolacetate in cdcl3 301a tuwy 01/25/08
173.69
169.04
159.61
153.10
144.07
132.46
127.88
115.40
110.93
104.06
77.43
77.00
76.58
73.63
69.96
67.49
55.15
38.72
38.26
33.53
32.37
30.75
25.37
21.05
20.33
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

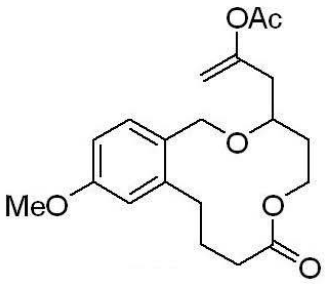

O
O
H
H
O
O
O
MeO
2.66
top cyclized from methyl macrolactone in cdcl3 301a tuwy 01/10/08
7.261
7.233
6.772
6.764
6.737
4.904
4.729
4.692
4.688
4.105
4.092
3.789
3.032
2.987
2.943
2.673
2.660
2.640
2.627
2.615
2.605
2.581
2.525
2.477
2.455
2.445
2.422
2.321
2.311
2.293
1.965
1.951
1.934
1.921
1.833
1.814
1.794
1.786
1.764
1.753
1.747
1.736
1.722
1.715
1.703
1.690
1.664
1.637
1.619
1.609
1.601
1.587
1.297
1.277
1.252
1.05
1.68
0.90
0.96
1.00
2.87
1.01
1.94
4.10
1.17
1.28
5.65
2.97
0.90
ppm


top cyclized from methyl macrolactone in cdcl3 301a tuwy 01/10/08
207.13
173.25
159.65
144.20
128.17
127.42
115.66
111.20
77.43
77.00
76.58
75.30
73.28
67.75
55.19
48.40
46.45
42.06
34.47
32.57
30.52
25.55
20.32
MeO
H
H
O
O
O
O
2.66
ppm

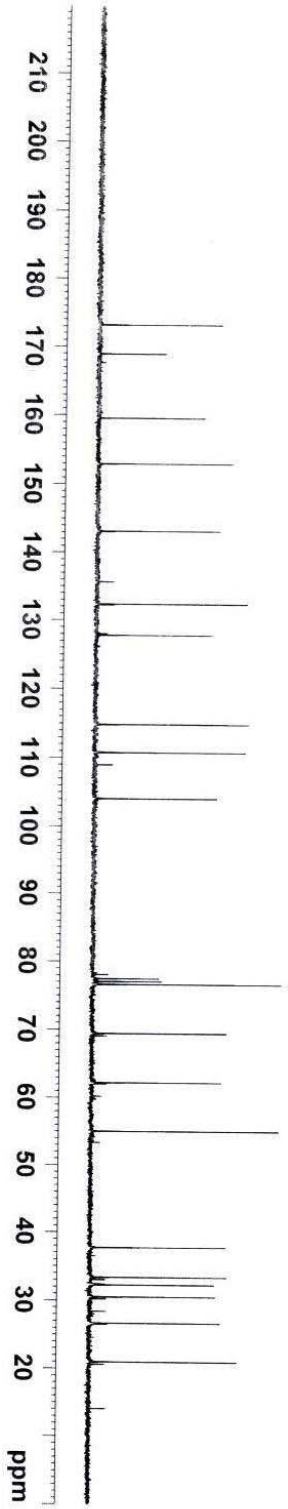

OAc
MeO
O
O
O
1.16
2.07
1.86
2.11
1.00
1.05
3.16
1.13
3.16
1.21
2.16
2.76
4.80
ppm

2.28


o-butenated enol acetate in cdcl3 301a tuwy 04/02/08
7.146
7.119
6.710
6.701
6.679
6.671
6.652
6.644
4.817
4.467
4.434
4.423
4.403
4.393
4.296
4.264
4.199
4.190
4.180
4.159
4.153
3.749
3.698
3.689
3.681
3.672
2.757
2.747
2.734
2.718
2.704
2.686
2.668
2.640
2.458
2.434
2.409
2.385
2.349
2.325
2.312
2.299
2.286
2.061
2.010
1.991
1.978
1.971
1.959
1.927
1.921
1.913
1.901
1.874
1.864

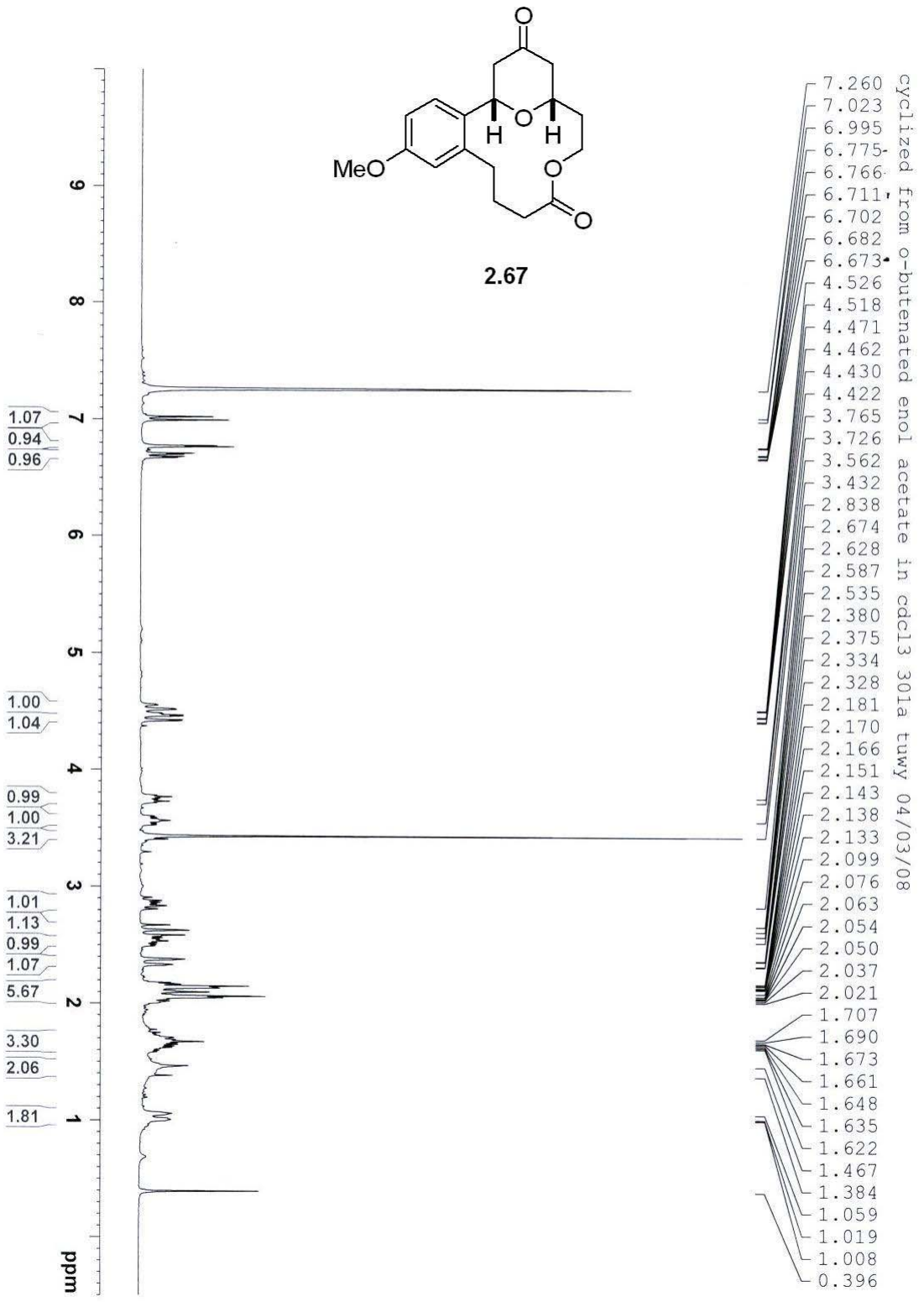


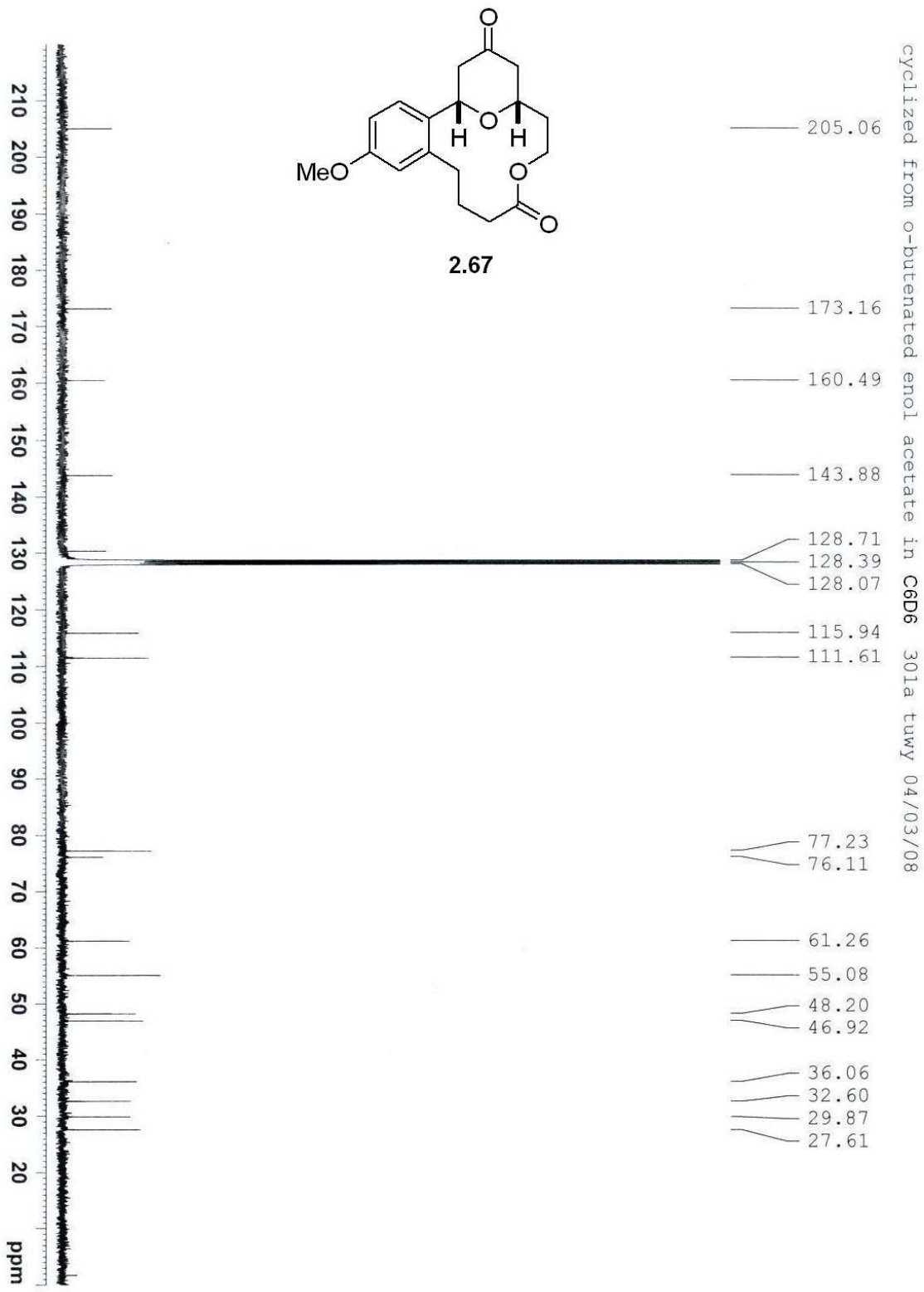
2.28

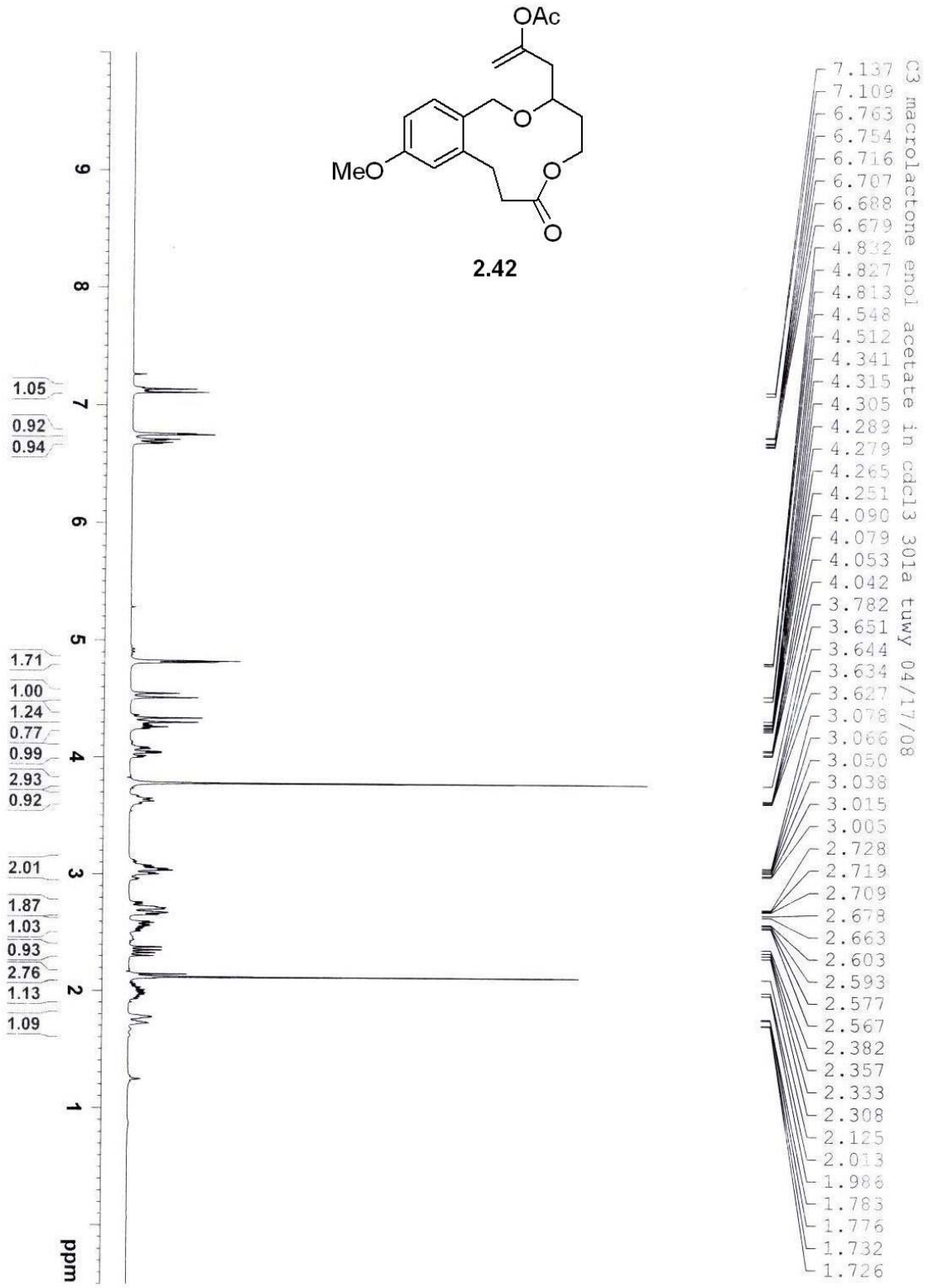


o-butenated enol acetate in cdcl3 301a tuwy 04/02/08

173.16
168.93
159.54
152.93
143.12
132.33
127.79
114.81
110.72
104.03
77.43
77.00
76.56
69.40
62.21
54.98
37.66
33.30
32.20
30.46
26.61
20.93


cyclized from o-butenated enol acetate in cdcl3 301a tuwy 04/03/08
7.260
7.023
6.995
6.775
6.766
6.711
6.702
6.682
6.673
4.526
4.518
4.471
4.462
4.430
4.422
3.765
3.726
3.562
3.432
2.838
2.674
2.628
2.587
2.535
2.380
2.375
2.334
2.328
2.181
2.170
2.166
2.151
2.143
2.138
2.133
2.099
2.076
2.063
2.054
2.050
2.037
2.021
1.707
1.690
1.673
1.661
1.648
1.635
1.622
1.467
1.384
1.059
1.019
1.008
0.396
1.07
0.94
0.96
1.00
1.04
0.99
1.00
3.21
1.01
1.13
0.99
1.07
5.67
3.30
2.06
1.81
ppm
MeO
H
O
H
O
O
O
2.67


cyclized from o-butenated enol acetate in C6D6 301a tuwy 04/03/08
205.06
173.16
160.49
143.88
128.71
128.39
128.07
115.94
111.61
77.23
76.11
61.26
55.08
48.20
46.92
36.06
32.60
29.87
27.61
MeO
H
H
O
O
O
O
2.67
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


OAc
MeO
O
O
O
2.42
1.05
0.92
0.94
1.71
1.00
1.24
0.77
0.99
2.93
0.92
2.01
1.87
1.03
0.93
2.76
1.13
1.09
9
8
7
6
5
4
3
2
1
ppm
C3 macrolactone enol acetate in cdcl3 301a tuwy 04/17/08
7.137
7.109
6.763
6.754
6.716
6.707
6.688
6.679
4.832
4.827
4.813
4.548
4.512
4.341
4.315
4.305
4.289
4.279
4.265
4.251
4.090
4.079
4.053
4.042
3.782
3.651
3.644
3.634
3.627
3.078
3.066
3.050
3.038
3.015
3.005
2.728
2.719
2.709
2.678
2.663
2.603
2.593
2.577
2.567
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1.986
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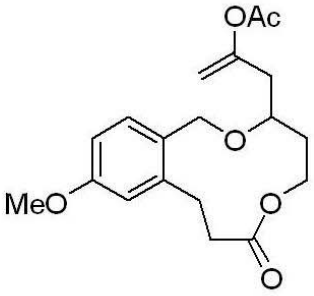
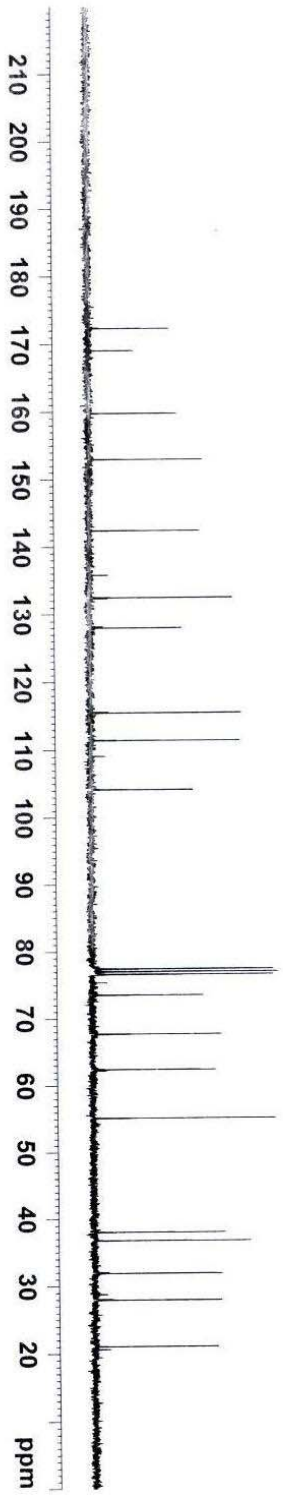
1.732
1.726

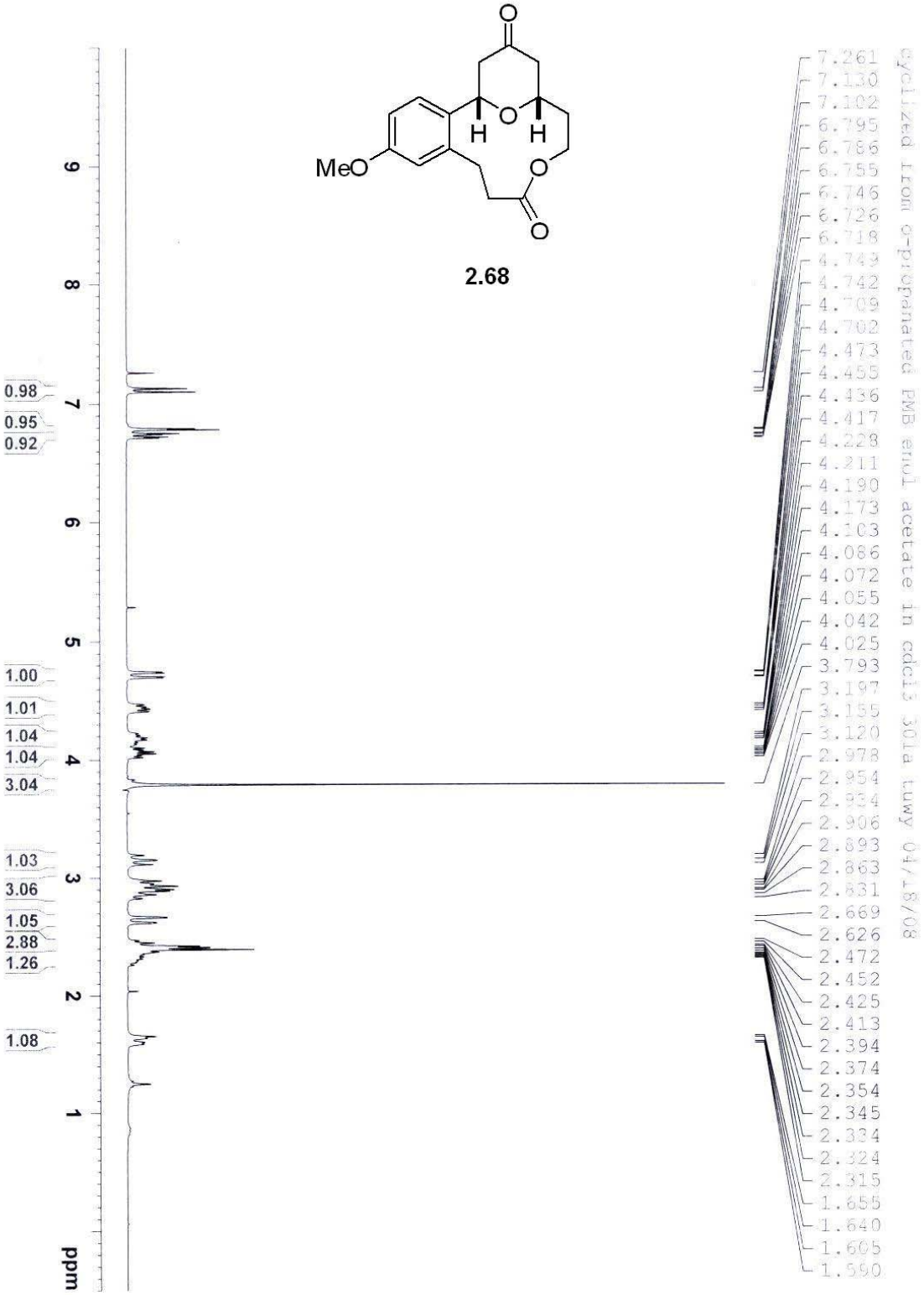


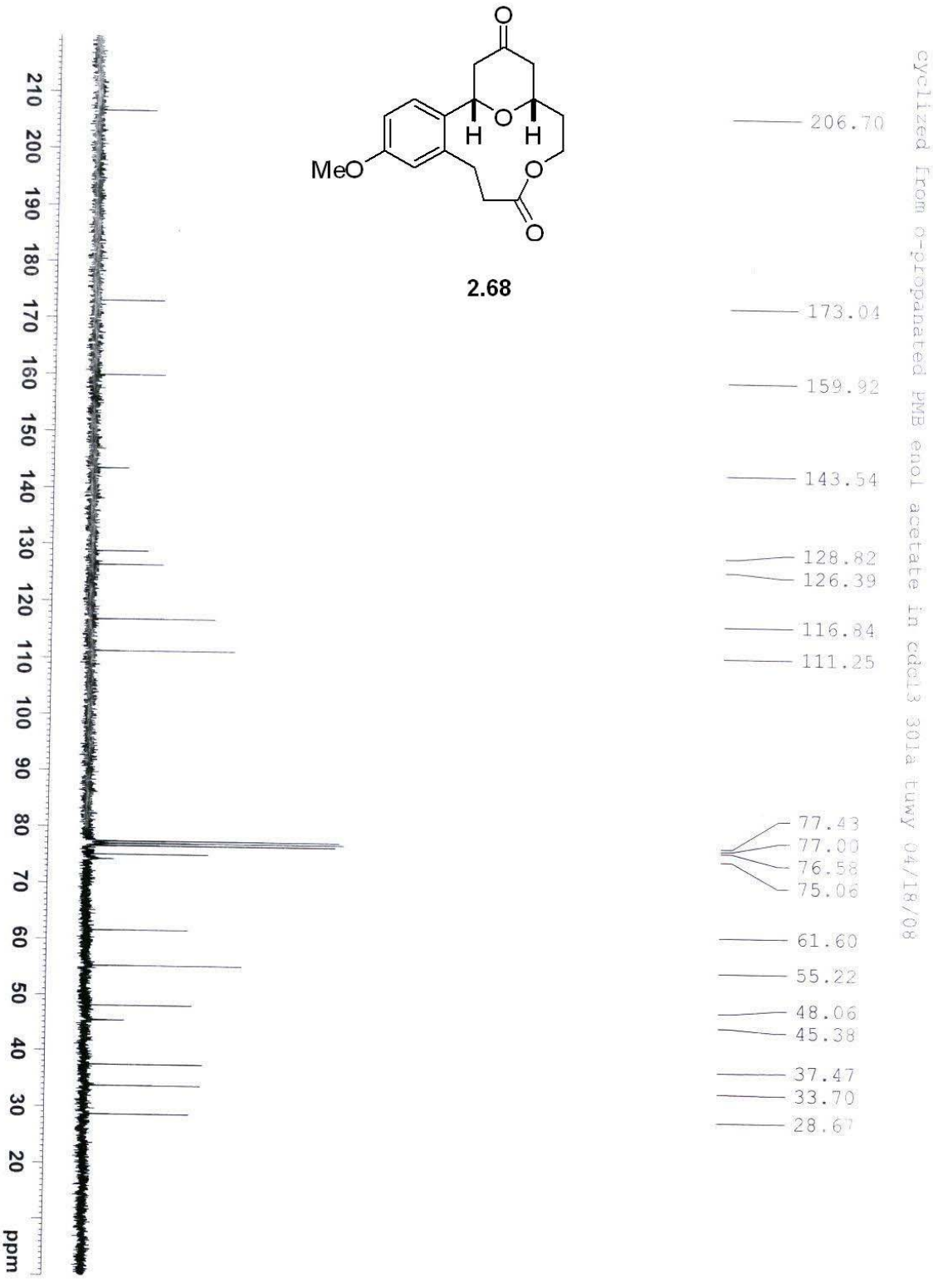
2.42

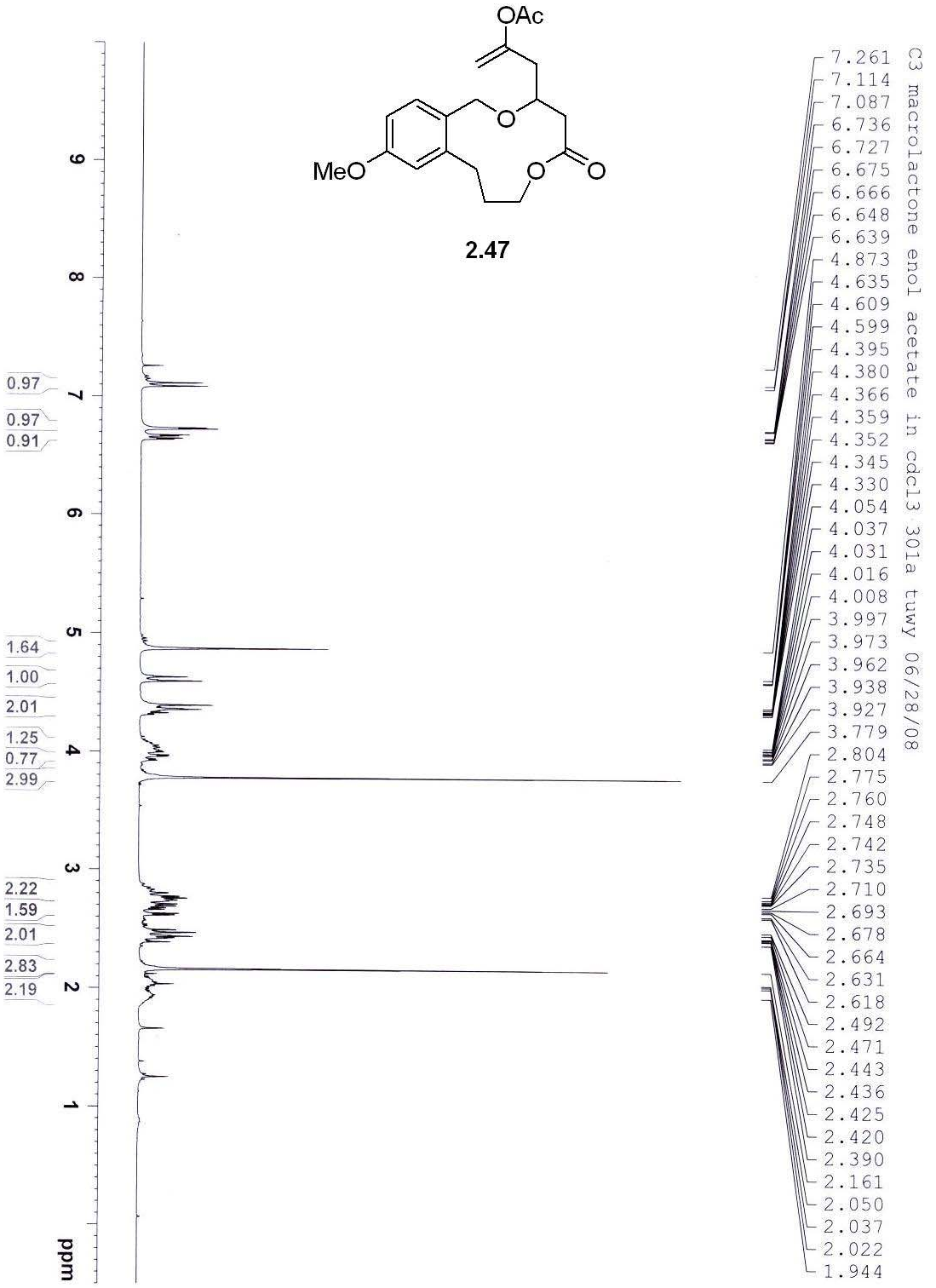


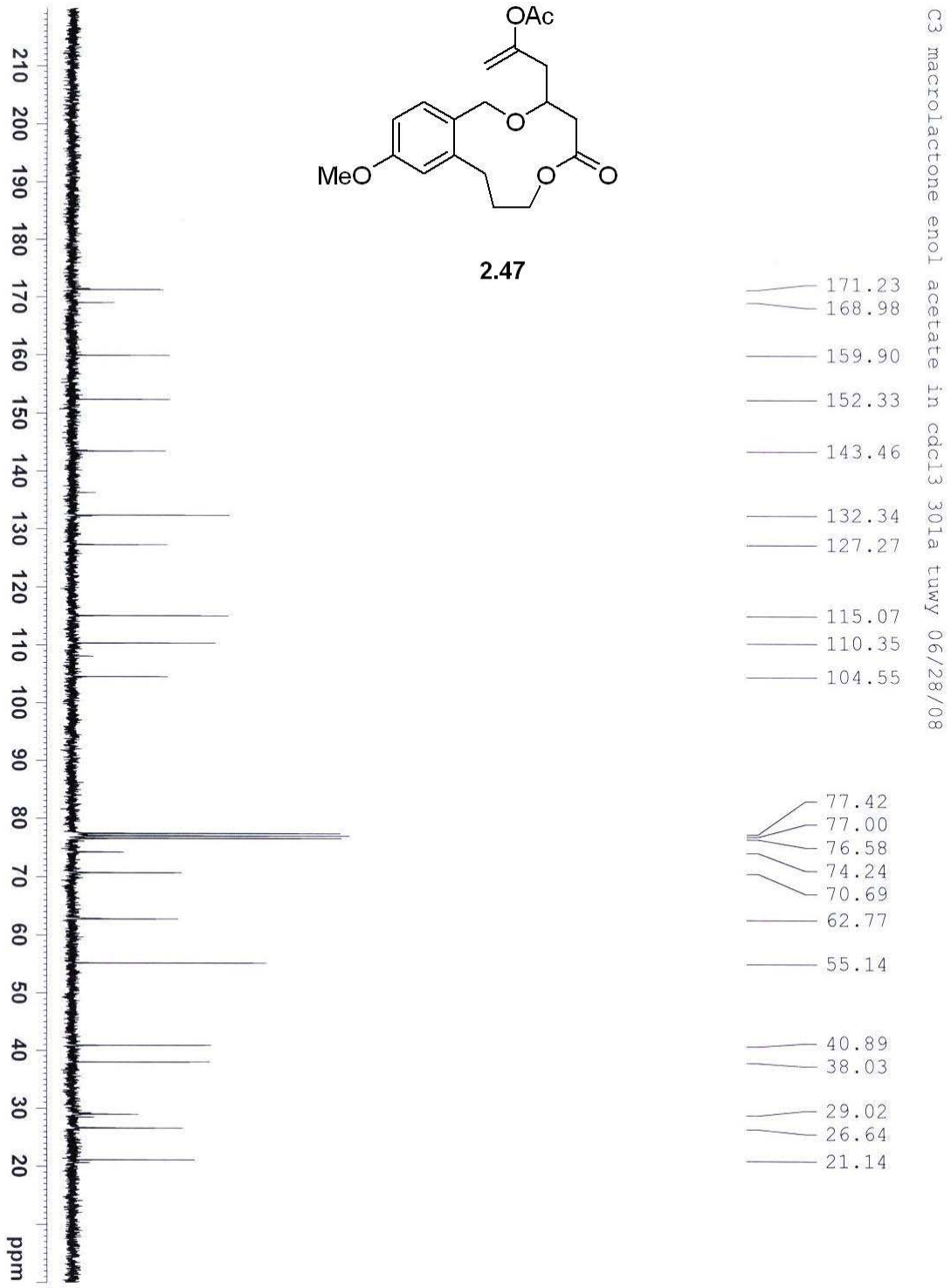
C3 macrolactone enol acetate in cdcl3 301a tuwy 04/17/08

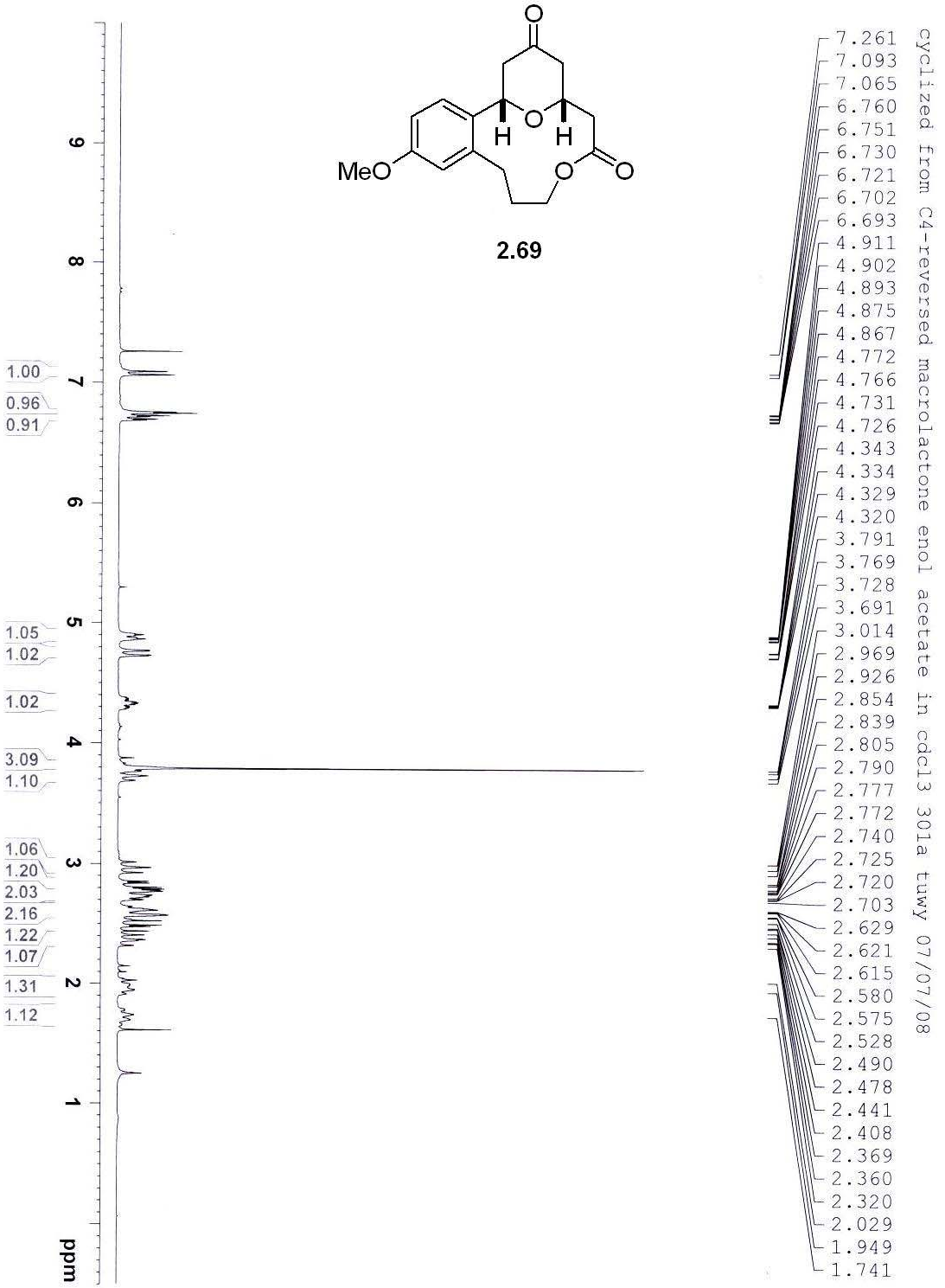
172.28
169.04
159.75
152.95
142.38
132.44
128.00
115.49
111.42
104.12
77.43
77.00
76.58
73.51
67.71
62.42
55.13
38.04
36.79
31.91
27.98
21.09

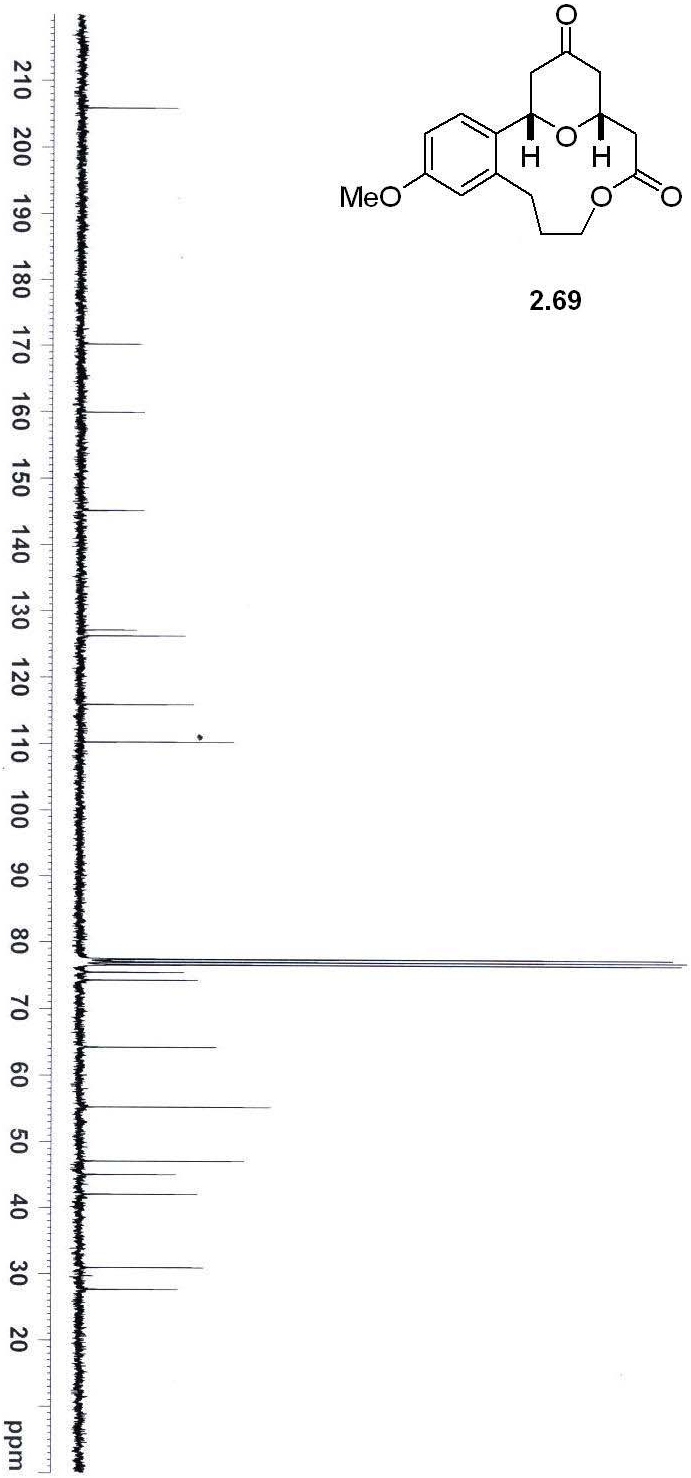

MeO
H
H
O
O
O
O
2.68
cyclized from o-propanated PMB enol acetate in cdcl3 30ja tuwy 04/18/08
7.261
7.130
7.102
6.795
6.786
6.755
6.746
6.726
6.718
4.743
4.742
4.709
4.702
4.473
4.455
4.436
4.417
4.228
4.211
4.190
4.173
4.103
4.086
4.072
4.055
4.042
4.025
3.793
3.197
3.155
3.120
2.978
2.954
2.934
2.906
2.893
2.863
2.831
2.669
2.626
2.472
2.452
2.425
2.413
2.394
2.374
2.354
2.345
2.334
2.324
2.315
1.655
1.640
1.605
1.590
0.98
0.95
0.92
1.00
1.01
1.04
1.04
3.04
1.03
3.06
1.05
2.88
1.26
1.08
ppm


cyclized from o-propanated PMB enol acetate in cdcl3 301a tuwy 04/18/08
206.70
173.04
159.92
143.54
128.82
126.39
116.84
111.25
77.43
77.00
76.58
75.06
61.60
55.22
48.06
45.38
37.47
33.70
28.67
MeO
H
H
O
O
O
O
2.68
ppm


OAc
MeO
O
O
O
2.47
C3 macrolactone enol acetate in cdcl3 301a tuwy 06/28/08
7.261
7.114
7.087
6.736
6.727
6.675
6.666
6.648
6.639
4.873
4.635
4.609
4.599
4.395
4.380
4.366
4.359
4.352
4.345
4.330
4.054
4.037
4.031
4.016
4.008
3.997
3.973
3.962
3.938
3.927
3.779
2.804
2.775
2.760
2.748
2.742
2.735
2.710
2.693
2.678
2.664
2.631
2.618
2.492
2.471
2.443
2.436
2.425
2.420
2.390
2.161
2.050
2.037
2.022
1.944
0.97
0.97
0.91
1.64
1.00
2.01
1.25
0.77
2.99
2.22
1.59
2.01
2.83
2.19
ppm


OAc
MeO
O
O
O
2.47
C3 macrolactone enol acetate in cdcl3 301a tuwy 06/28/08
171.23
168.98
159.90
152.33
143.46
132.34
127.27
115.07
110.35
104.55
77.42
77.00
76.58
74.24
70.69
62.77
55.14
40.89
38.03
29.02
26.64
21.14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

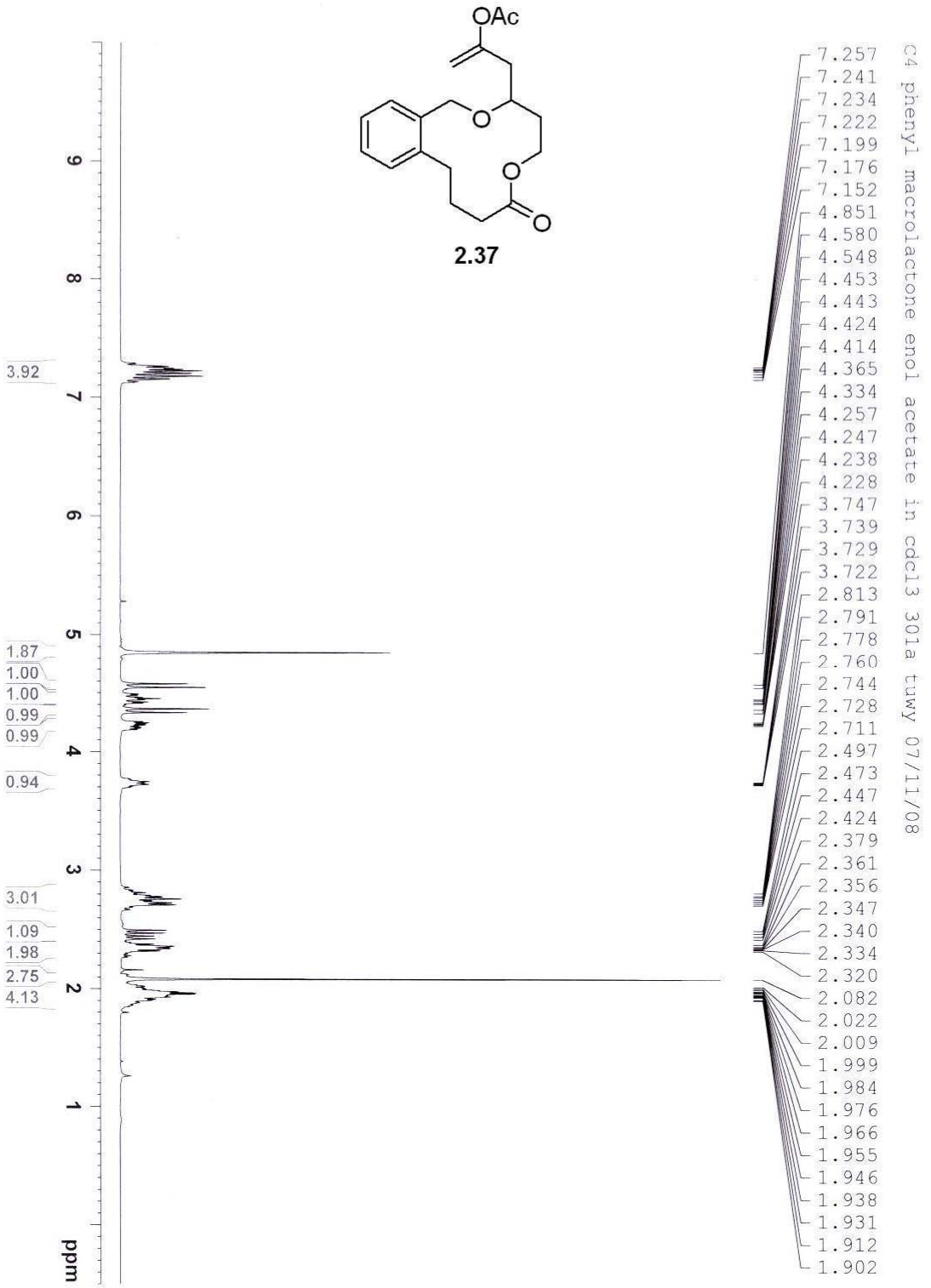

cyclized from C4-reversed macrolactone enol acetate in cdcl3 301a tuwy 07/07/08
7.261
7.093
7.065
6.760
6.751
6.730
6.721
6.702
6.693
4.911
4.902
4.893
4.875
4.867
4.772
4.766
4.731
4.726
4.343
4.334
4.329
4.320
3.791
3.769
3.728
3.691
3.014
2.969
2.926
2.854
2.839
2.805
2.790
2.777
2.772
2.740
2.725
2.720
2.703
2.629
2.621
2.615
2.580
2.575
2.528
2.490
2.478
2.441
2.408
2.369
2.360
2.320
2.029
1.949
1.741
MeO
O
H
H
O
O
O
2.69
1.00
0.96
0.91
1.05
1.02
1.02
3.09
1.10
1.06
1.20
2.03
2.16
1.22
1.07
1.31
1.12
ppm



2.69

cyclized from C4-reversed macrolactone enol acetate in cdcl3 301a tuwy 07/08/08

205.88
170.19
159.90
145.13
127.10
126.22
115.92
110.27
77.42
77.00
76.58
75.46
74.28
64.24
55.22
47.08
45.02
42.03
30.92
27.63


OAc
O
O
O
2.37
C4 phenyl macrolactone enol acetate in cdcl3 301a tuwy 07/11/08
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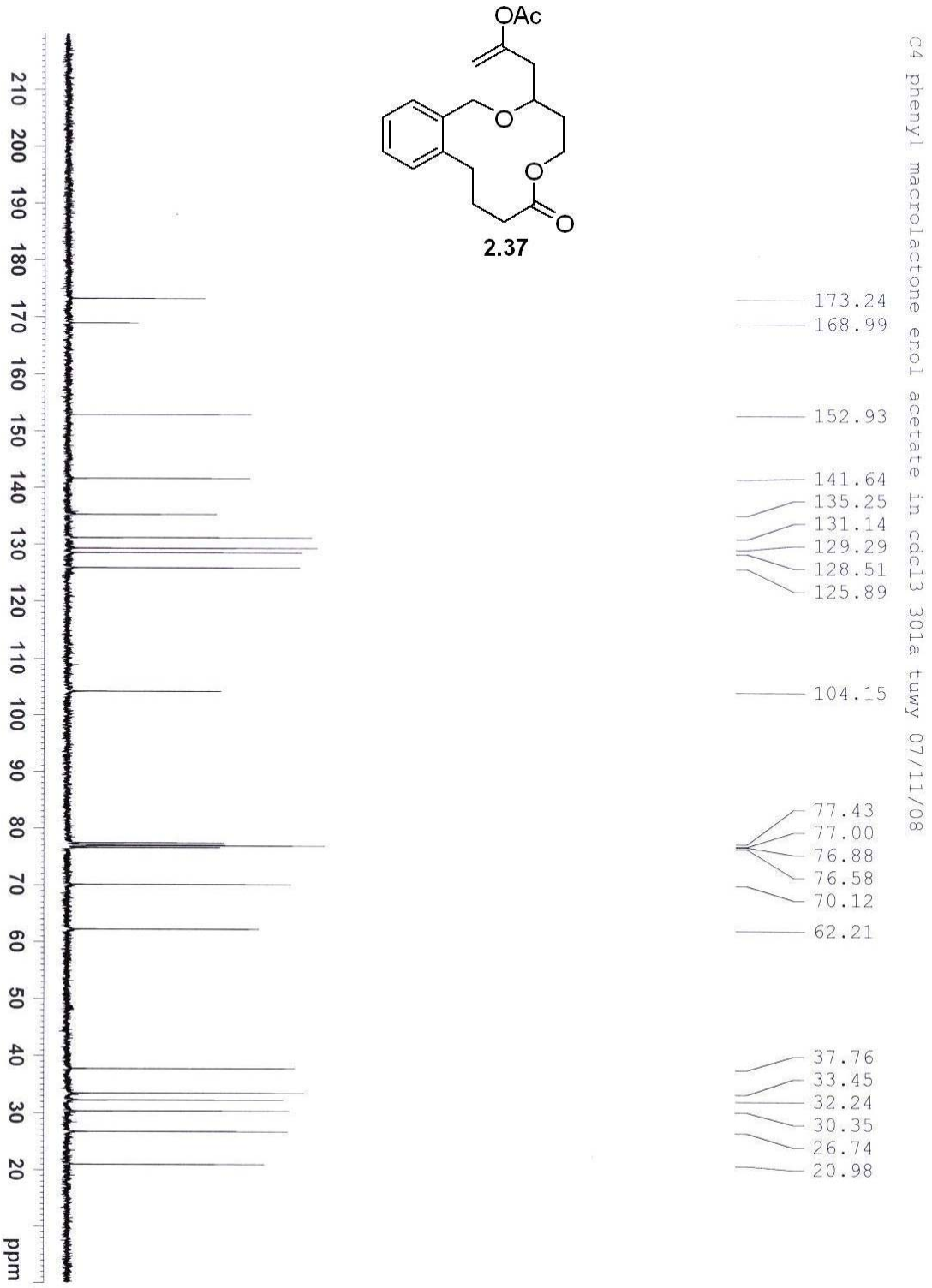
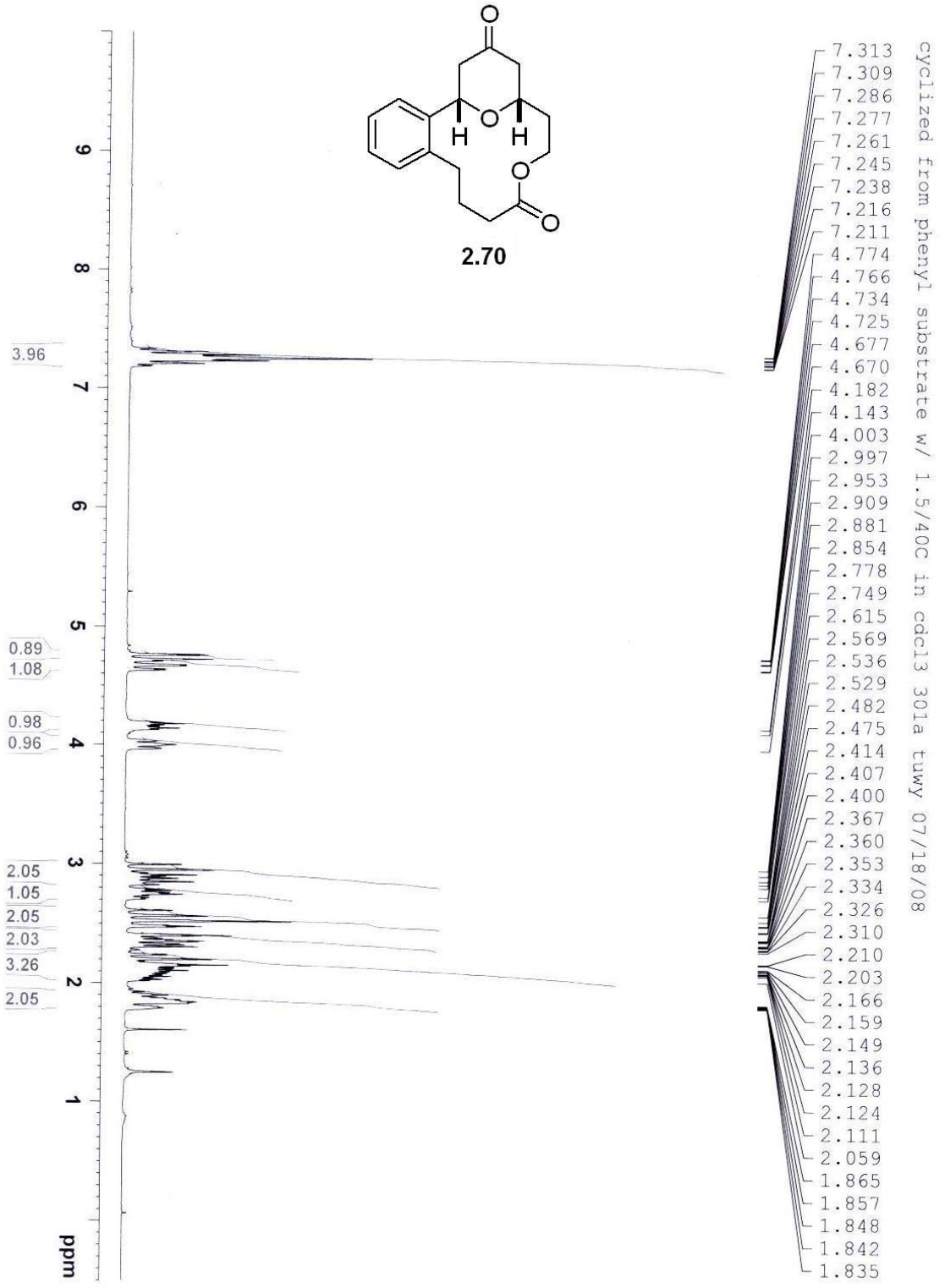
7.241
7.234
7.222
7.199
7.176
7.152
4.851
4.580
4.548
4.453
4.443
4.424
4.414
4.365
4.334
4.257
4.247
4.238
4.228
3.747
3.739
3.729
3.722
2.813
2.791
2.778
2.760
2.744
2.728
2.711
2.497
2.473
2.447
2.424
2.379
2.361
2.356
2.347
2.340
2.334
2.320
2.082
2.022
2.009
1.999
1.984
1.976
1.966
1.955
1.946
1.938
1.931
1.912
1.902
3.92
1.87
1.00
1.00
0.99
0.99
0.94
3.01
1.09
1.98
2.75
4.13
ppm


OAc
O
O
O
2.37
c4 phenyl macrolactone enol acetate in cdcl3 301a tuwy 07/11/08
173.24
168.99
152.93
141.64
135.25
131.14
129.29
128.51
125.89
104.15
77.43
77.00
76.88
76.58
70.12
62.21
37.76
33.45
32.24
30.35
26.74
20.98
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


2.70
cyclized from phenyl substrate w/ 1.5/40C in cdcl3 301a tuwy 07/18/08
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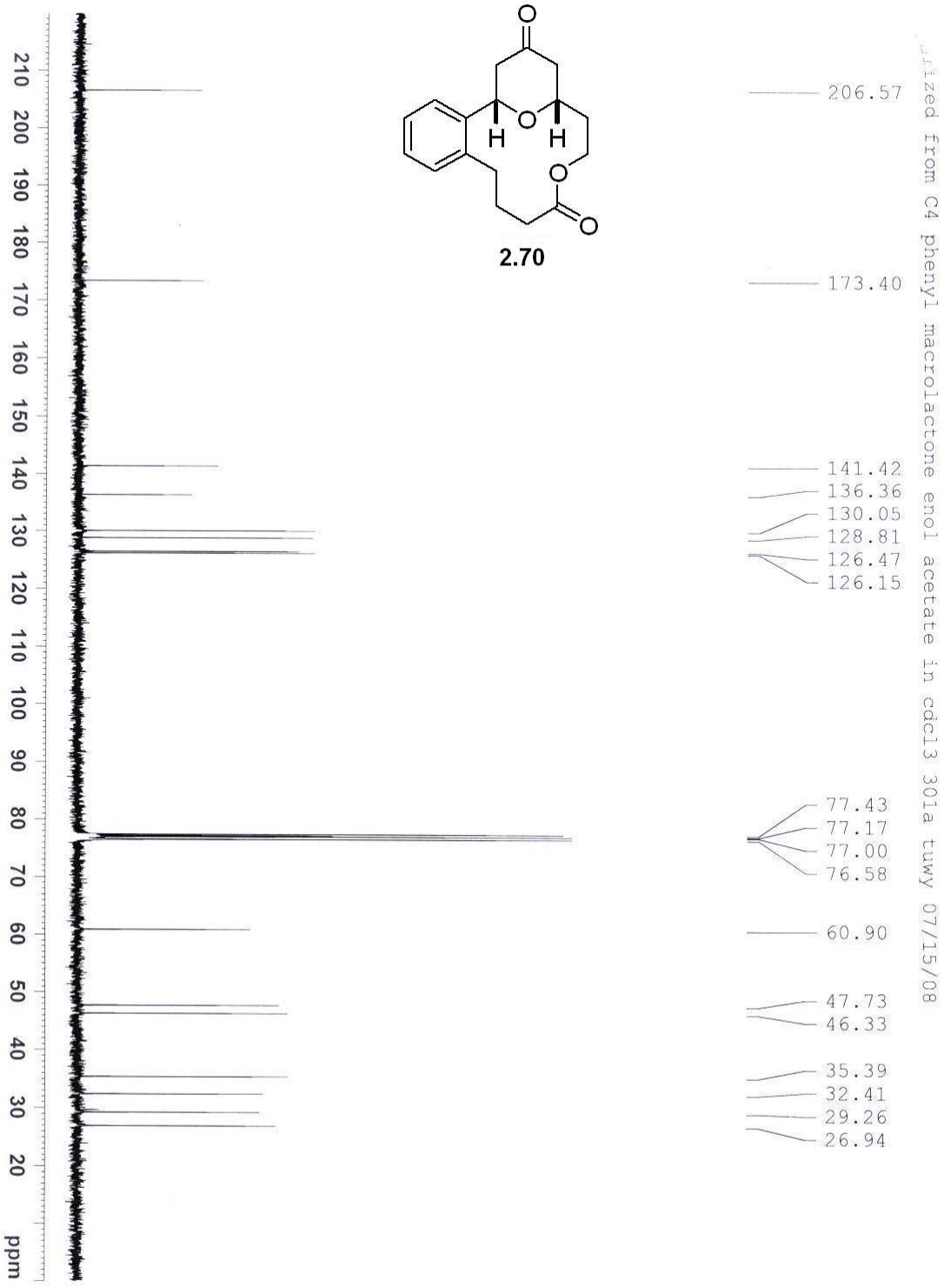
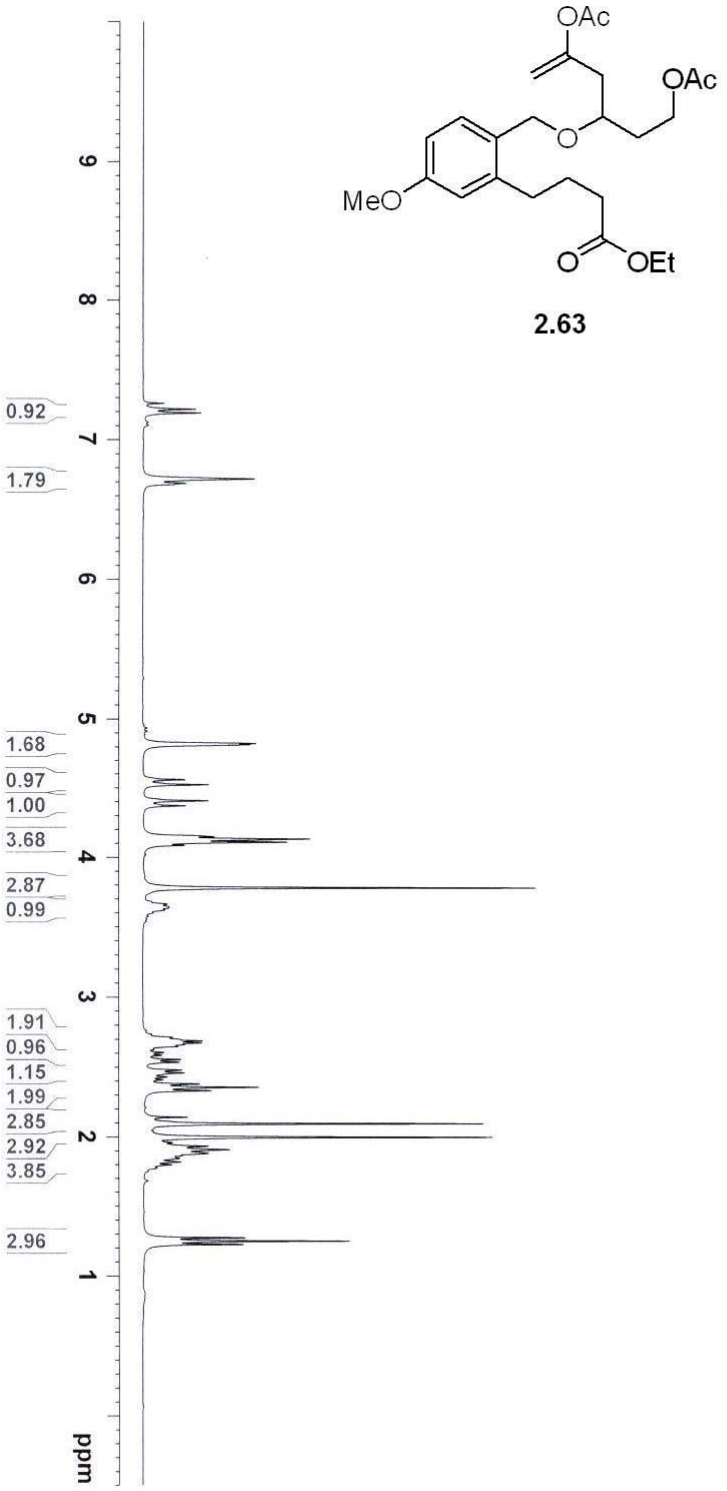
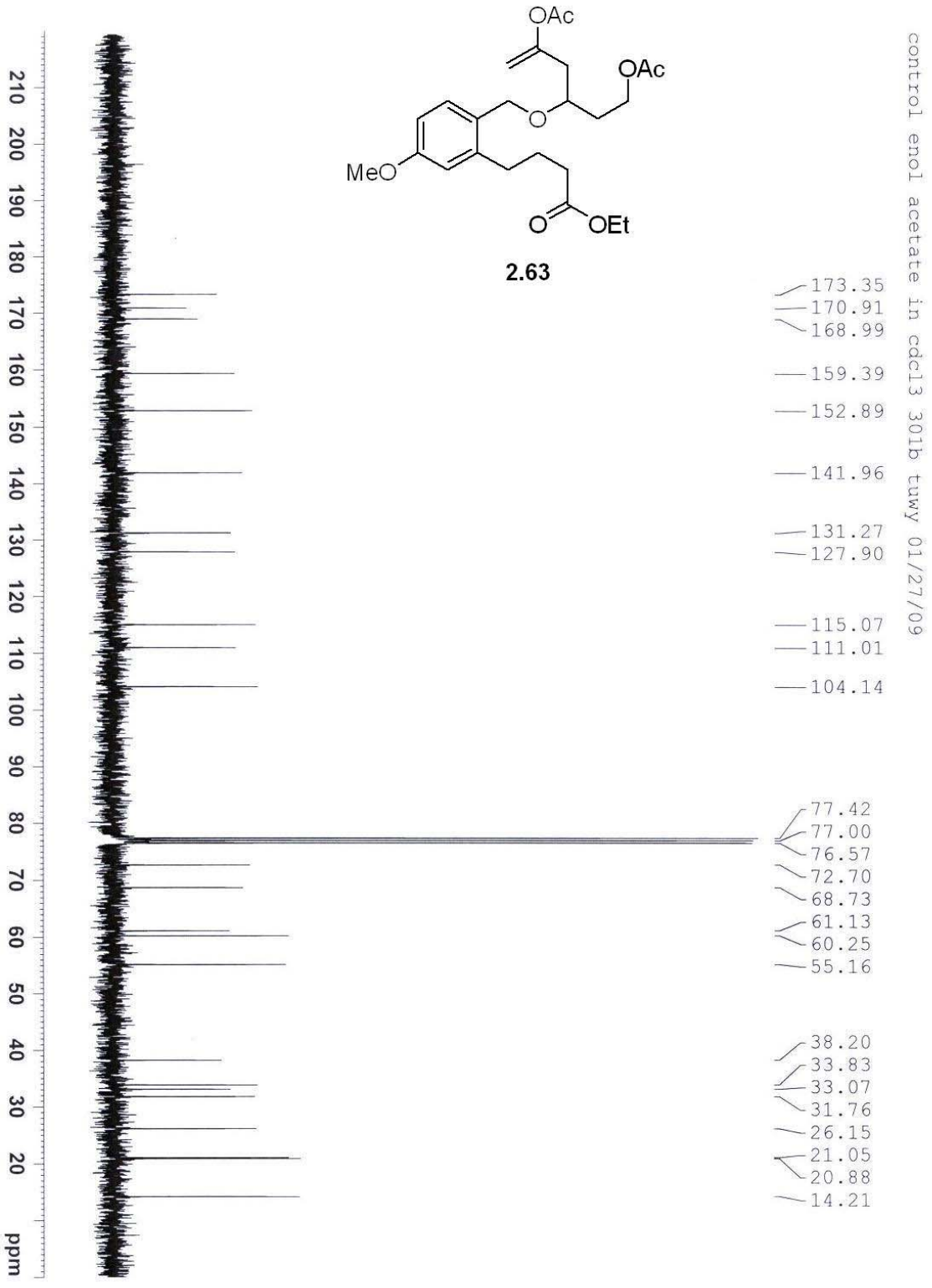
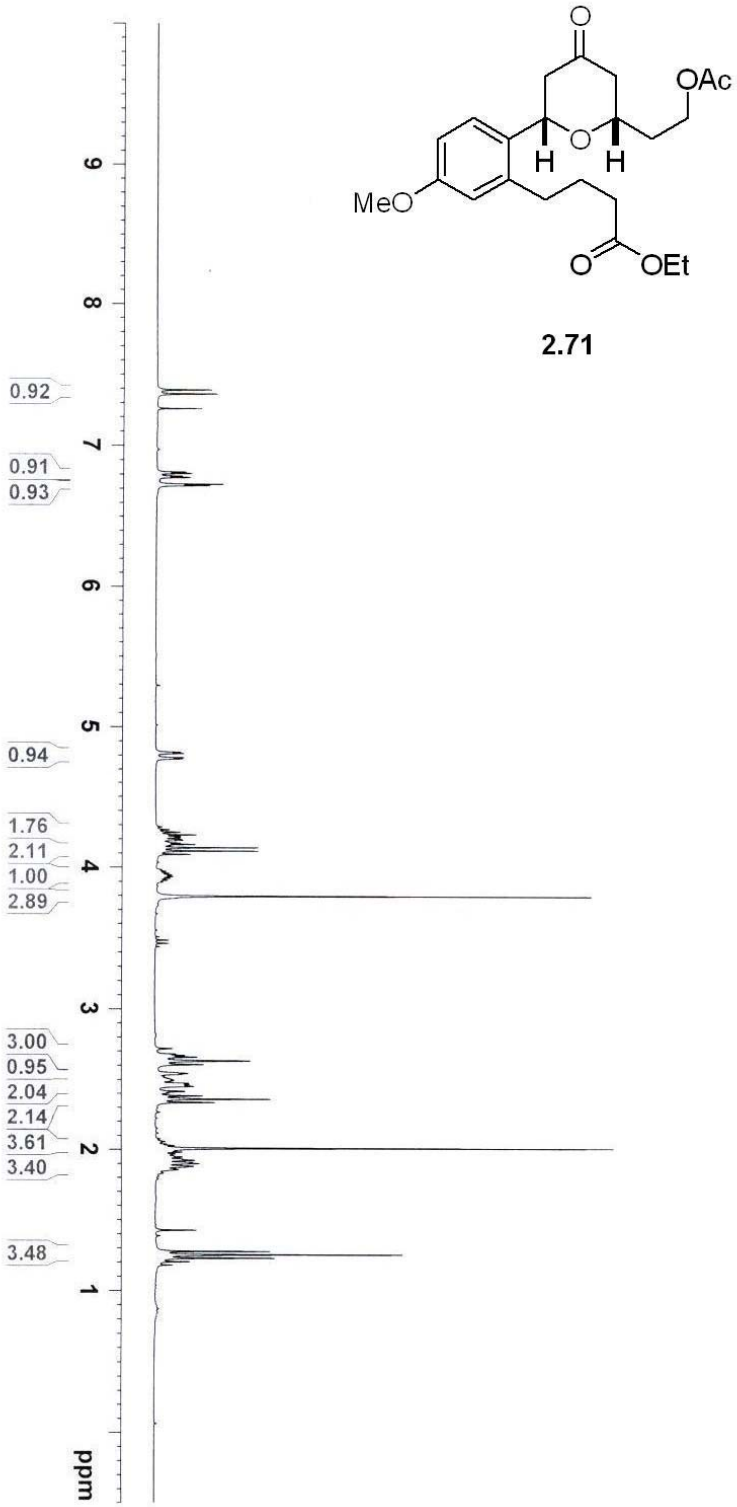
7.277
7.261
7.245
7.238
7.216
7.211
4.774
4.766
4.734
4.725
4.677
4.670
4.182
4.143
4.003
2.997
2.953
2.909
2.881
2.854
2.778
2.749
2.615
2.569
2.536
2.529
2.482
2.475
2.414
2.407
2.400
2.367
2.360
2.353
2.334
2.326
2.310
2.210
2.203
2.166
2.159
2.149
2.136
2.128
2.124
2.111
2.059
1.865
1.857
1.848
1.842
1.835
3.96
0.89
1.08
0.98
0.96
2.05
1.05
2.05
2.03
3.26
2.05
ppm

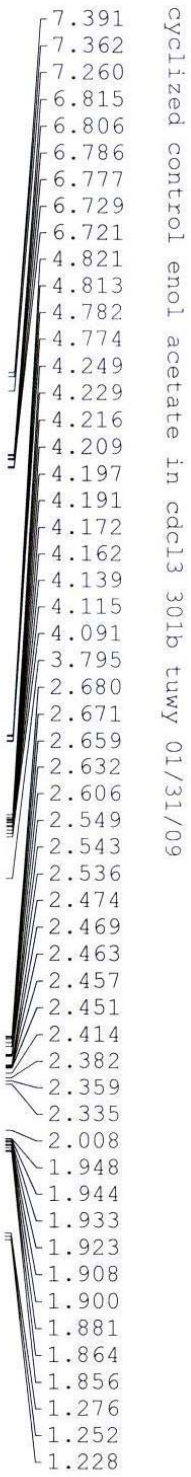

2.70
206.57
173.40
141.42
136.36
130.05
128.81
126.47
126.15
77.43
77.17
77.00
76.58
60.90
47.73
46.33
35.39
32.41
29.26
26.94
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
lized from C4 phenyl macrolactone enol acetate in cdcl3 301a tuwy 07/15/08

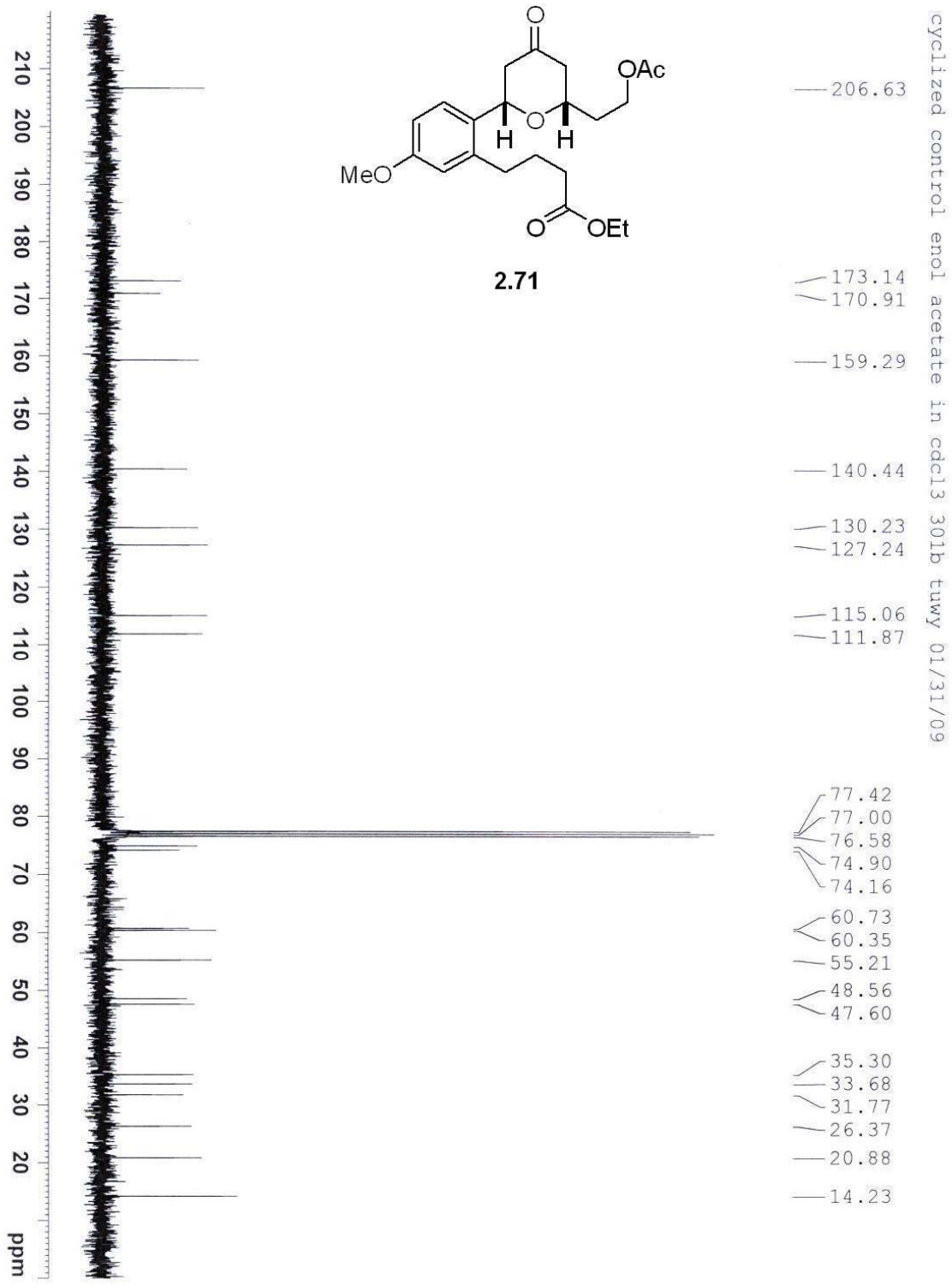

OAc
OAc
MeO
O
O
OEt
2.63
0.92
1.79
1.68
0.97
1.00
3.68
2.87
0.99
1.91
0.96
1.15
1.99
2.85
2.92
3.85
2.96
9
8
7
6
5
4
3
2
1
ppm


control enol acetate in cdcl3 301b tuwy 01/27/09
7.260
7.218
7.191
6.723
6.691
4.824
4.816
4.559
4.522
4.407
4.370
4.148
4.132
4.109
4.086
3.780
3.662
3.644
3.637
3.621
3.600
2.714
2.699
2.689
2.674
2.663
2.650
2.628
2.606
2.587
2.557
2.537
2.480
2.460
2.431
2.410
2.380
2.355
2.331
2.141
2.093
2.035
1.996
1.959
1.933
1.908
1.882
1.866
1.845
1.819
1.799
1.778
1.272
1.248
1.225


OAc
OAc
MeO
O
O
OEt
2.63
control enol acetate in cdcl3 301b tuwy 01/27/09
173.35
170.91
168.99
159.39
152.89
141.96
131.27
127.90
115.07
111.01
104.14
77.42
77.00
76.57
72.70
68.73
61.13
60.25
55.16
38.20
33.83
33.07
31.76
26.15
21.05
20.88
14.21
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


O
OAc
O
H
H
MeO
O
OEt
2.71
0.92
0.91
0.93
0.94
1.76
2.11
1.00
2.89
3.00
0.95
2.04
2.14
3.61
3.40
3.48
ppm


cyclized control enol acetate in cdcl3 301b tuwy 01/31/09
7.391
7.362
7.260
6.815
6.806
6.786
6.777
6.729
6.721
4.821
4.813
4.782
4.774
4.249
4.229
4.216
4.209
4.197
4.191
4.172
4.162
4.139
4.115
4.091
3.795
2.680
2.671
2.659
2.632
2.606
2.549
2.543
2.536
2.474
2.469
2.463
2.457
2.451
2.414
2.382
2.359
2.335
2.008
1.948
1.944
1.933
1.923
1.908
1.900
1.881
1.864
1.856
1.276
1.252
1.228


cyclized control enol acetate in cdcl3 301b tuwy 01/31/09
206.63
173.14
170.91
159.29
140.44
130.23
127.24
115.06
111.87
77.42
77.00
76.58
74.90
74.16
60.73
60.35
55.21
48.56
47.60
35.30
33.68
31.77
26.37
20.88
14.23
ppm
MeO
OAc
OEt
H
H
O

2.71

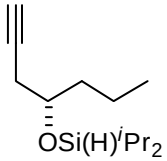
APPENDIX C

FORMAL SYNTHESIS OF NATURAL PRODUCT (+)-NEOPELTOLIDE

General Experimental Proton (^{1}H NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz or on a Brucker Avance 700 spectrometer at 700 MHz. Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 75 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, C_6D_6 = 7.15 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution mass spectra were recorded on a MICROMASS AUTOSPEC (for EI) or WATERS Q-TOF API-US (for ESI) spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Activated 4 Å molecular sieves were obtained through drying in oven at 150 °C overnight. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride and cyclohexane were distilled under N_2 from CaH_2. Toluene and 1,2-dichloroethane were dried

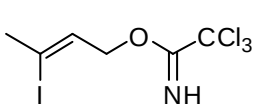
over 4 Å molecular sieves overnight prior to use. Anhydrous DMF was purchased from Acros. Analytical TLC was performed on E. Merck pre-coated (0.25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

(*S*)-(Hept-1-yn-4-yloxy)diisopropylsilane (3.37)



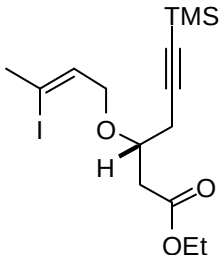
Compound **3.24** (2.21 g, 19.7 mmol) and imidazole (2.68 g, 39.4 mmol) were dissolved in THF (120 mL). A solution of $^{i}Pr_2Si(H)Cl$ (3.56 g, 23.6 mmol) in THF (15 mL) was added dropwise into the reaction mixture, and a white precipitate formed immediately. The reaction was stirred at rt for 30 min, then was quenched with H_2O at 0 °C. The organic layer was extracted with Et_2O. The combined organic layer was washed with H_2O, dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (6% Et_2O in hexane) to give the desired product **3.37** (3.31 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (s, 1H), 3.90-3.79 (m, 1H), 2.40 (ddd, *J* = 2.7, 5.4, 16.8 Hz, 1H), 2.34 (ddd, *J* = 2.7, 6.6, 16.8 Hz, 1H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.70-1.30 (m, 4H), 1.03 (s, 14H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 81.5, 72.8, 69.9, 38.5, 26.8, 18.4, 17.5, 17.4, 17.4, 14.1, 12.6, 12.5; IR (neat) 3314, 2957, 2941, 2867, 2092, 1463, 1366, 1243, 1111, 1091, 1040, 1002, 882, 841, 802 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{25}OSi$ $(M–H)^+$ 225.1675, found 225.1676; $[\alpha]_D^{25} = –26.8$ ($CHCl_3$, *c* = 1.0).

(*Z*)-3-iodobut-2-enyl 2,2,2-trichloroacetimidate (3.30)



To a suspension of NaH (60% suspension in mineral oil, 10 mg, 0.25 mmol) in 1.5 mL anhydrous Et_2O at room temperature was added 1 mL Et_2O solution of **3.27** (500 mg, 2.53 mmol) dropwisely. The reaction bubbled for about five min, then it was cooled to 0 °C, followed by addition of CCl_3CN (254 μL, 2.53 mmol). After 10 min, the reaction was allowed to room temperature and concentrated directly under reduced pressure. A mixture of 25 mL pentane and 0.1 mL methanol was added into the crude residue and the RBF was shaken well to give a yellow suspension, which was filtered through a plug of Celite and eluted with 10 mL pentane. The filtrate was concentrated without further purification (826 mg, 95%).

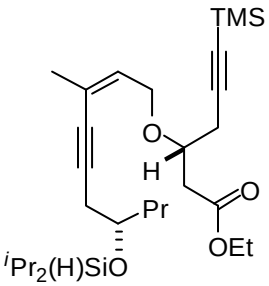
(*R*,*Z*)-Ethyl 3-(3-iodobut-2-enyloxy)-6-(trimethylsilyl)hex-5-ynoate (3.25)



Compound **3.26** (115 mg, 0.504 mmol) was dissolved in 2 mL anhydrous cyclohexane, then **3.30** (690 mg, 2.01 mmol) was added into the solution. To the mixture at room temperature was added TfOH (8.7 μL, 0.076 mmol). A yellow precipitation formed in several min after the addition. The reaction was stirred at rt for two hours then filtered through a small plug of Celite and eluted with hexane. The filtrate was concentrated and purified by flash chromatography (4%→5% Et_2O in Hexane) to give **3.25** (159 mg, 77%, *Z*/*E* = 7.3:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (qt, *J* = 1.5, 5.7 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.10 (ddq, *J* = 1.5, 5.7, 11.4 Hz, 1H), 4.14-4.01 (m, 1H), 4.01-3.90 (m, 1H), 2.69 (dd, *J* = 4.5, 15.9 Hz, 1H), 2.65-1.38 (m, 3H), 2.53 (t, *J* = 1.5 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.15 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 171.1, 132.2, 102.5, 102.1, 87.2, 74.2, 74.1, 60.1, 39.5, 33.6, 25.2, 14.2, –0.0; IR (neat) 2959, 2176, 1737, 1250, 1208, 1159, 1100, 1046, 844,

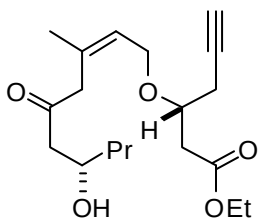
760 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_3SiI$ $(M–CH_3)^+$ 393.0383, found 393.0386; $[\alpha]_D^{25}$ = –10.4 ($CHCl_3$, *c* = 1.0).

(*R*)-ethyl 3-((*S,Z*)-7-(diisopropylsilyloxy)-3-methyldec-2-en-4-ynyloxy)-6-(trimethylsilyl)hex -5-ynoate (3.38)



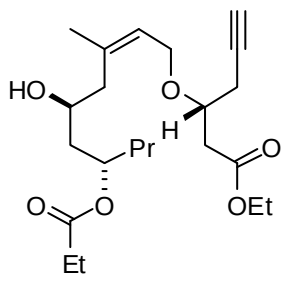
Under nitrogen atmosphere, **3.25** (250 mg, 0.612 mmol) was dissolve in 4 mL $^iPr_2NH$, followed by addition of $PdCl_2(PPh_3)_2$ (22 mg, 0.031 mmol) and CuI (18 mg, 0.092 mmol). The mixture was purged with argon for 15 min, then **3.37** (222 mg, 0.980 mmol) was added into the reaction via syringe. After 15 min the reaction turned to be dark yellow/black slurry, which was filtered through a plug of silica gel and eluted with Et_2O. The filtrate was concentrated and purified by flash chromatography (4%→5% Et_2O in Hexane) to give **3.38** (275 mg, 89%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (qt, *J* = 1.2, 6.3 Hz, 1H), 4.31-4.10 (m, 2H), 4.22 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.93 (ddd, *J* = 4.8, 8.1, 12.6 Hz, 1H), 2.84 (ddt, *J* = 1.2, 5.1, 11.7 Hz, 1H), 2.71 (dd, *J* = 4.5, 15.6 Hz, 1H), 2.66-2.49 (m, 4H), 2.42 (dd, *J* = 7.5, 17.1 Hz, 1H), 1.84 (s, 3H), 1.68-1.50 (m, 2H), 1.50-1.32 (m, 2H), 1.27 (t, *J* = 6.9 Hz, 3H), 1.03 (s, 14H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.14 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 171.3, 132.1, 121.8, 102.7, 92.4, 87.0, 80.4, 73.9, 73.0, 68.0, 60.4, 39.5, 38.8, 27.9, 25.0, 23.4, 18.4, 17.5, 17.4, 17.4, 14.2, 14.2, 12.6, 12.5, 0.0; IR (neat) 2957, 2866, 2177, 2091, 1739, 1462, 1375, 1250, 1205, 1158, 1091, 1038, 843, 760 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{50}O_4Si$ (M^+) 506.3248, found 506.3236; $[\alpha]_D^{25}$ = –13.9 ($CHCl_3$, *c* = 1.0).

(*R*)-Ethyl 3-((*S*,*Z*)-7-hydroxy-3-methyl-5-oxodec-2-enyloxy)hex-5-ynoate (3.41)



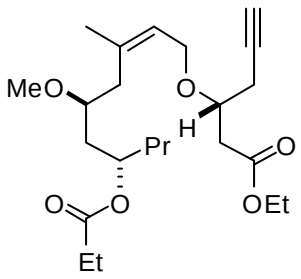
To **3.38** (100 mg, 0.194 mmol) in 1 mL anhydrous THF was added Pt(DVDS) (2% Pt in xylene, 7 μL, 0.6 μmol) at room temperature. The reaction was stirred for one hour, then another 7 μL Pt(DVDS) was appended. After three hours, the crude mixture was filtered through a plug of silica gel and eluted with Et_2O. The filtrate was concentrated and re-dissolved in 1.6 mL anhydrous THF, followed by addition of exact 0.40 mL TBAF solution (1 M in THF, 0.40 mmol) at room temperature. The reaction was stirred for 15 min, then 2 mL anhydrous DMF was added in, followed by immediate and sequential addition of $KHCO_3$ (138 mg, 1.38 mmol), 0.3 mL H_2O_2 (30% aqueous solution) and KF (80 mg, 1.4 mmol). Then the reaction was heated to 40 °C. After 30 min, another 0.2 mL H_2O_2 was added in. After another 1.5 hours, the reaction was cooled to 0 °C and aq. Na_2SO_3 was slowly added into the flask to quench the reaction. The crude mixture was stirred at 0 °C for 15 min then extracted with EtOAc three times. The combined organic layer was washed with brine three times, dried over $MgSO_4$, concentrated and purified by flash chromatography (25% EtOAc in Hexane) to give **3.41** (38 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (qt, *J* = 0.9, 6.9 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 2H), 4.15-3.99 (m, 3H), 3.98-3.88 (m, 1H), 3.23 (s, 2H), 2.97 (d, *J* = 3.6 Hz, 1H), 2.68 (dd, *J* = 5.1, 16.2 Hz, 1H), 2.64-2.53 (m, 3H), 2.52-2.43 (m, 2H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.76 (s, 3H), 1.55-1.32 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 209.1, 171.2, 133.7, 125.1, 80.2, 73.8, 70.7, 67.4, 66.1, 60.6, 48.6, 47.4, 39.4, 38.6, 24.3, 23.8, 18.6, 14.2, 13.9; IR (neat) 3506, 3283, 2959, 2930, 2873, 1733, 1377, 1312, 1213, 1164, 1072, 1029 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{30}O_5$ (M^+) 338.2093, found 338.2078; $[\alpha]_D^{25}$ = +12.0 ($CHCl_3$, *c* = 0.5).

(*R*)-Ethyl 3-((5*S*,7*S*,*Z*)-5-hydroxy-3-methyl-7-(propionyloxy)dec-2-enyloxy)hex-5-ynoate (3.44)



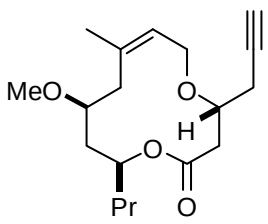
A solution of **3.41** (455 mg, 1.34 mmol) and freshly distilled propionaldehyde (970 μL, 13.4 mmol) in THF (10 mL) was cooled to –10 °C. A freshly prepared SmI_2 solution (5.4 mL, 0.1 M in THF, 0.54 mmol) was added. The reaction was stirred under argon for 4 hours, then was quenched with aq. $NaHCO_3$ at –10 °C. The crude mixture was extracted with EtOAc three times. The combined organic layer was dried with $MgSO_4$, concentrated and purified by flash chromatography (20% EtOAc in hexane) to give desired product **3.44** (411 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (t, *J* = 6.6 Hz, 1H), 5.09 (ddd, *J* = 4.8, 8.4, 12.9 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.12-3.97 (m, 2H), 3.97-3.87 (m, 1H), 3.60 (dddd, *J* = 4.2, 4.2, 8.4, 12.6 Hz, 1H), 2.93 (d, 1H), 2.67 (dd, *J* = 5.1, 15.9 Hz, 1H), 2.57 (dd, *J* = 7.5, 15.3 Hz, 1H), 2.56-2.46 (m, 1H), 2.41 (ddd, *J* = 2.4, 6.6, 16.8 Hz, 1H), 2.32 (q, *J* = 7.5 Hz, 2H), 2.39-2.28 (m, 1H), 2.06 (dd, *J* = 4.8, 13.5 Hz, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.74 (s, 3H), 1.63-1.45 (m, 4H), 1.40-1.27 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.14 (dt, *J* = 0.6, 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 175.3, 171.2, 137.8, 124.0, 80.3, 73.7, 71.3, 70.6, 65.8, 65.5, 60.5, 42.7, 40.0, 39.4, 37.0, 27.8, 23.9, 23.8, 18.6, 14.2, 13.8, 9.3; IR (neat) 3507 (br), 3289, 2961, 2937, 2875, 1733, 1377, 1201, 1072, 1026 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{36}O_6$ (M^+) 397.2590, found 397.2571; $[\alpha]_D^{25} = -8.8$ ($CHCl_3$, *c* = 1.0).

(*R*)-Ethyl 3-((5*S*,7*S*,*Z*)-5-methoxy-3-methyl-7-(propionyloxy)dec-2-enyloxy)hex-5-ynoate (3.45)



Compound **3.44** (111 mg, 0.280 mmol) was dissolved in 3 mL anhydrous CH_2Cl_2 at 0 °C, followed by addition of proton sponge (175 mg, 0.814 mmol) and Me_3OBF_4 (125 mg, 0.814 mmol). The mixture was stirred at 0 °C for 48 hours, then quenched by adding aq. NH_4Cl. The crude mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (15% EtOAc in Hexane) to give **3.45** (106 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (t, *J* = 6.6 Hz, 1H), 5.10 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.07 (t, *J* = 7.2 Hz, 1H), 4.15-4.00 (m, 1H), 3.98-3.88 (m, 1H), 3.30 (s, 3H), 3.22 (dddd, *J* = 3.0, 3.0, 6.3, 12.3 Hz, 1H), 2.67 (dd, *J* = 5.1, 15.9 Hz, 1H), 2.57 (dd, *J* = 7.5, 15.6 Hz, 1H), 2.57-2.40 (m, 2H), 2.40-2.30 (m, 1H), 2.35 (dd, *J* = 7.8, 14.1 Hz, 1H), 2.29 (dd, *J* = 7.5, 15.0 Hz, 1H), 2.10 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.74 (s, 3H), 1.62-1.38 (m, 4H), 1.36-1.20 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.8 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 174.0, 171.2, 136.8, 124.2, 80.2, 76.4, 73.7, 70.9, 70.6, 66.1, 60.5, 57.5, 39.6, 39.4, 37.3, 36.8, 27.9, 24.1, 23.8, 18.4, 14.2, 13.9, 9.4; IR (neat) 3275, 2962, 2935, 2876, 1734, 1462, 1376, 1263, 1194, 1094, 1029 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{38}O_6$ (M^+) 410.2668, found 410.2665; $[\alpha]_D^{25} = -1.0$ ($CHCl_3$, *c* = 1.0).

(4*R*,10*S*,12*S*,*Z*)-10-Methoxy-8-methyl-4-(prop-2-ynyl)-12-propyl-1,5-dioxacyclododec-7-en-2-one (3.46)

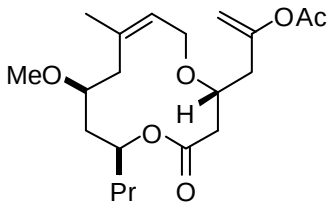


To a solution of **3.45** (173 mg, 0.421 mmol) in a mixture of THF, MeOH, and H_2O (1.5 mL/0.5 mL/0.5 mL, respectively), was added $LiOH{\cdot}H_2O$

(106 mg, 2.53 mmol). The reaction was stirred at 45 °C for 4 hours, then was cooled to 0 °C and treated with 0.5 M aq. HCl solution until the pH was between 3 and 4. The crude mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and filtered. The residue was concentrated without purification for next step.

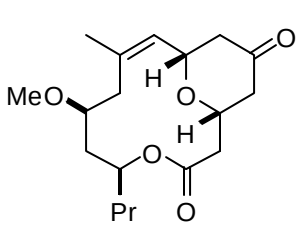
To the crude acid in THF (2.5 mL) was added Et_3N (294 μL, 2.11 mmol). The mixture was stirred for 20 min, then a solution of trichlorobenzoyl chloride (154 mg, 0.632 mmol) taken in THF (2.5 mL) was added into the reaction. A precipitate formed after several min, and the stirring was continued for 2 h. The crude mixed anhydride was filtered through a pad of Celite and washed with toluene (150 mL total). The resulting solution was then added dropwise into a solution of DMAP (206 mg, 1.69 mmol) in toluene (150 mL) at 65 °C over a period of 5 h. After the addition, the crude mixture was concentrated, re-dissolved in Et_2O and washed with aq. $NaHCO_3$. The organic layer was dried over MgSO4, filtered and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexane) to give **3.46** (92 mg, 71% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (t, *J* = 7.8 Hz, 1H), 5.21 (dddd, *J* = 2.4, 5.1, 5.1, 12.9 Hz, 1H), 4.09-4.00 (m, 1H), 4.00-3.87 (m, 2H), 3.41 (dddd, *J* = 3.0, 5.4, 5.4, 11.1 Hz, 1H), 3.35 (s, 3H), 2.84 (dd, *J* = 3.6, 14.4 Hz, 1H), 2.64-2.52 (m, 2H), 2.43 (ddd, *J* = 2.7, 8.1, 16.8 Hz, 1H), 2.31 (dd, *J* = 7.8, 13.8 Hz, 1H), 2.18 (dd, *J* = 5.1, 13.5 Hz, 1H), 2.06 (t, *J* = 2.4 Hz, 1H), 1.87 (s, 3H), 1.71 (ddd, *J* = 2.4, 6.0, 14.7 Hz, 1H), 1.63 (dd, *J* = 3.3, 10.8 Hz, 1H), 1.59-1.41 (m, 2H), 1.41-1.23 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 170.3, 146.1, 120.3, 80.8, 80.0, 73.0, 72.6, 70.9, 63.8, 57.3, 40.8, 40.2, 38.4, 37.2, 26.4, 22.5, 18.6, 13.8; IR (neat) 3342, 2955, 2929, 2858, 1469, 1388, 1254, 1095, 1040, 837, 775 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{28}O_4$ (M^+) 308.1988, found 308.1991; $[\alpha]_D^{25} = -72.8$ ($CHCl_3$, *c* = 1.0).

3-((2*R*,6*S*,8*S*,*Z*)-8-Methoxy-10-methyl-4-oxo-6-propyl-1,5-dioxacyclododec-10-en-2-yl)prop-1-en-2-yl acetate (3.21)



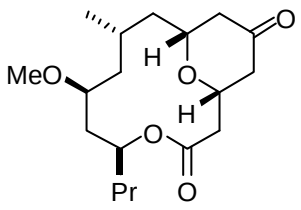
To a mixture of $[(p\text{-cymene})RuCl_2]_2$ (5 mg, 0.008 mmol), tri(2-furyl)phosphine (4 mg, 0.02 mmol), and Na_2CO_3 (3 mg, 0.03 mmol), in toluene (2 mL) were added acetic acid (24 μL, 0.41 mmol) and 1-decyne (37 μL, 0.20 mmol). The mixture was then heated to 80 °C and stirred for one hour. Another 24 μL acetic acid and **3.46** (63 mg, 0.20 mmol) were dissolved in toluene (2 mL) and added into the reaction mixture. The reaction was stirred at 80 °C overnight. Then crude mixture was loaded onto a small plug of silica gel and eluted with Et_2O. The residue was concentrated and purified by flash chromatography (15% Et_2O in hexane) to give **3.21** (61 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (dt, *J* = 1.2, 7.8 Hz, 1H), 5.17 (dddd, *J* = 2.7, 5.7, 7.8, 10.5 Hz, 1H), 4.87 (s, 1H), 4.85 (d, *J* = 1.8 Hz, 1H), 4.01-3.83 (m, 3H), 3.40-3.31 (m, 1H), 3.34 (s, 3H), 2.76 (dd, *J* = 3.9, 14.4 Hz, 1H), 2.66 (dd, *J* = 4.8, 14.7 Hz, 1H), 2.52-2.41 (m, 2H), 2.28 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.20 (dd, *J* = 7.8, 14.1 Hz, 1H), 2.15 (s, 3H), 1.86 (d, *J* = 1.5 Hz, 3H), 1.74 (ddd, *J* = 2.7, 5.4, 14.7 Hz, 1H), 1.68-1.44 (m, 3H), 1.30 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 170.4, 169.0, 152.5, 145.8, 120.5, 104.6, 81.2, 73.3, 72.4, 64.1, 57.2, 40.6, 39.7, 38.7, 37.3, 37.2, 26.3, 21.1, 18.6, 13.9; IR (neat) 2961, 2930, 2874, 1757, 1733, 1665, 1437, 1371, 1195, 1068, 1020 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{32}O_6$ (M^+) 368.2199, found 368.2188; $[\alpha]_D^{25} = -39.8$ ($CHCl_3$, *c* = 0.25).

(1*R*,5*S*,7*S*,11*S*,*Z*)-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadec-9-ene-3,13-dione (3.47)



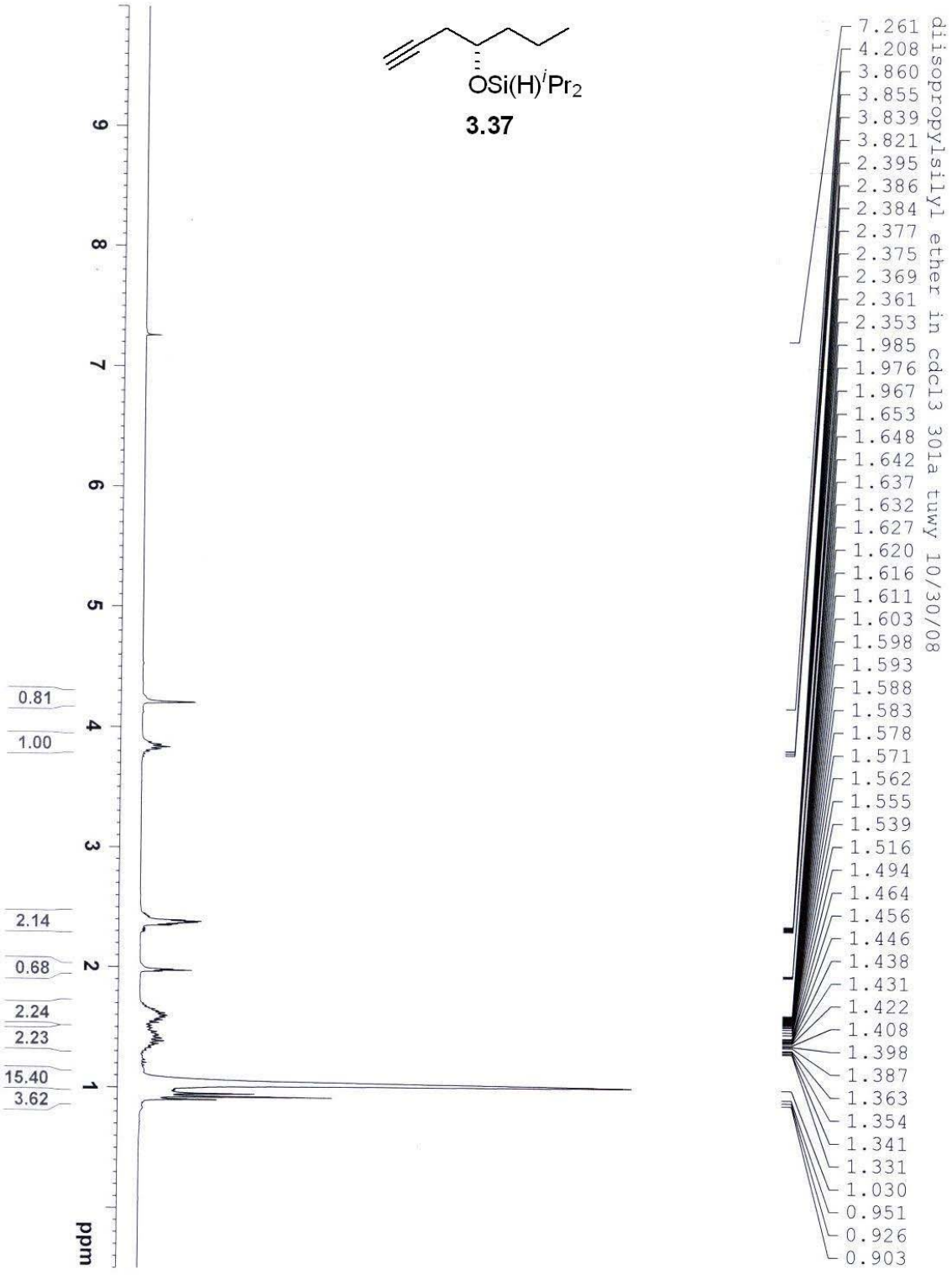
A mixture of **3.21** (30 mg, 0.081 mmol), 2,6-dichloropyridine (72 mg, 0.49 mmol), $LiClO_4$ (2 mg, 0.02 mmol), and 4 Å molecular sieves (60 mg) in 1,2-dichloroethane (1 mL) was stirred for 15 min, then DDQ (55 mg, 0.24 mmol) was added in one portion. The reaction stirred at RT for 18 hours, then was quenched by Et_3N. The crude mixture was filtered through a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and purified by flash chromatography (20% EtOAc in hexane) to give **3.47** (15 mg, 58 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (dddd, *J* = 2.7, 5.7, 7.8, 11.7 Hz, 1H), 5.28 (d, *J* = 7.2 Hz, 1H), 4.23-4.11 (m, 2H), 3.53 (ddddd, *J* = 1.5, 1.5, 5.1, 5.1, 10.5 Hz, 1H), 3.37 (s, 3H), 2.69 (dd, *J* = 3.6, 15.0 Hz, 1H), 2.58 (dd, *J* = 10.8, 15.3 Hz, 1H), 2.52-2.31 (m, 4H), 2.67 (dd, *J* = 12.0, 14.7 Hz, 1H), 2.04 (dd, *J* = 10.2, 13.5 Hz, 1H), 1.89 (d, *J* = 0.6 Hz, 3H), 1.93-1.83 (m, 1H), 1.69 (ddd, *J* = 3.3, 11.7, 15.0 Hz, 1H), 1.57-1.47 (m, 1H), 1.41-1.23 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 205.7, 169.5, 148.3, 124.3, 81.7, 74.3, 73.4, 72.9, 57.9, 47.2, 46.8, 43.0, 42.4, 41.8, 37.3, 25.3, 18.6, 13.8; IR (neat) 2961, 2930, 2874, 1728, 1370, 1319, 1267, 1233, 1185, 1131, 1099, 1072, 807 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{28}O_5$ (M^+) 324.1937, found 324.1946; $[\alpha]_D^{25}$ = –92.3 ($CHCl_3$, *c* = 1.0); m.p. = 95-97 °C.

(1*R*,5*S*,7*S*,9*S*,11*R*)-7-Methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecane-3,13-dione (3.3)



A mixture of **3.47** (46 mg, 0.14 mmol) and 10% Pd/C (15 mg, 0.014 mmol) in EtOH (3 mL) was evacuated and back-filled with H_2 three

times. The mixture was stirred under an H_2 atmosphere for 6 hours, then was filtered through a plug of silica gel using EtOAc as the eluent. The filtrate was concentrated and the residue was purified by flash chromatography (6%→8% Et_2O in CH_2Cl_2) to give **3.3** (34 mg, 74%). ^{1}H NMR (700MHz, $CDCl_3$) δ 5.21 (dt, *J* = 4.9, 9.1 Hz, 1H), 4.04 (dddd, *J* = 2.8, 4.2, 10.5, 11.2 Hz, 1H), 3.58 (dddd, *J* = 2.1, 2.8, 9.1, 11.2 Hz, 1H), 3.50 (ddd, *J* = 2.8, 8.4, 9.8 Hz, 1H), 3.33 (s, 3H), 2.71 (dd, *J* = 3.5, 14.7 Hz, 1H), 2.51 (dd, *J* = 11.2, 14.7 Hz, 1H), 2.43 (ddd, *J* = 1.4, 2.8, 14.7 Hz, 1H), 2.33 (ddd, *J* = 1.4, 2.8, 14.0 Hz, 1H), 2.29 (dd, *J* = 11.2, 14.7 Hz, 1H), 2.24 (dd, *J* = 11.9, 14.7 Hz, 1H), 1.85 (ddd, *J* = 1.4, 10.5, 14.7 Hz, 1H), 1.71-1.59 (m, 3H), 1.54-1.47 (m, 2H), 1.41 (ddd, *J* = 1.4, 9.1, 15.4 Hz, 1H), 1.39-1.32 (m, 3H), 1.19 (ddd, *J* = 2.8, 11.2, 13.3 Hz, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 205.8, 169.9, 79.7, 75.7, 73.4, 73.4, 56.3, 48.8, 47.0, 44.3, 42.6, 41.9, 40.0, 37.0, 31.1, 25.4, 18.9, 13.9; IR (neat) 2958, 2923, 2872, 1726, 1459, 1368, 1257, 1091, 798 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{30}O_5$ (M^+) 326.2093, found 326.2096; $[\alpha]_D^{25} = -16.3$ ($CHCl_3$, *c* = 0.16).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0.903

3.37

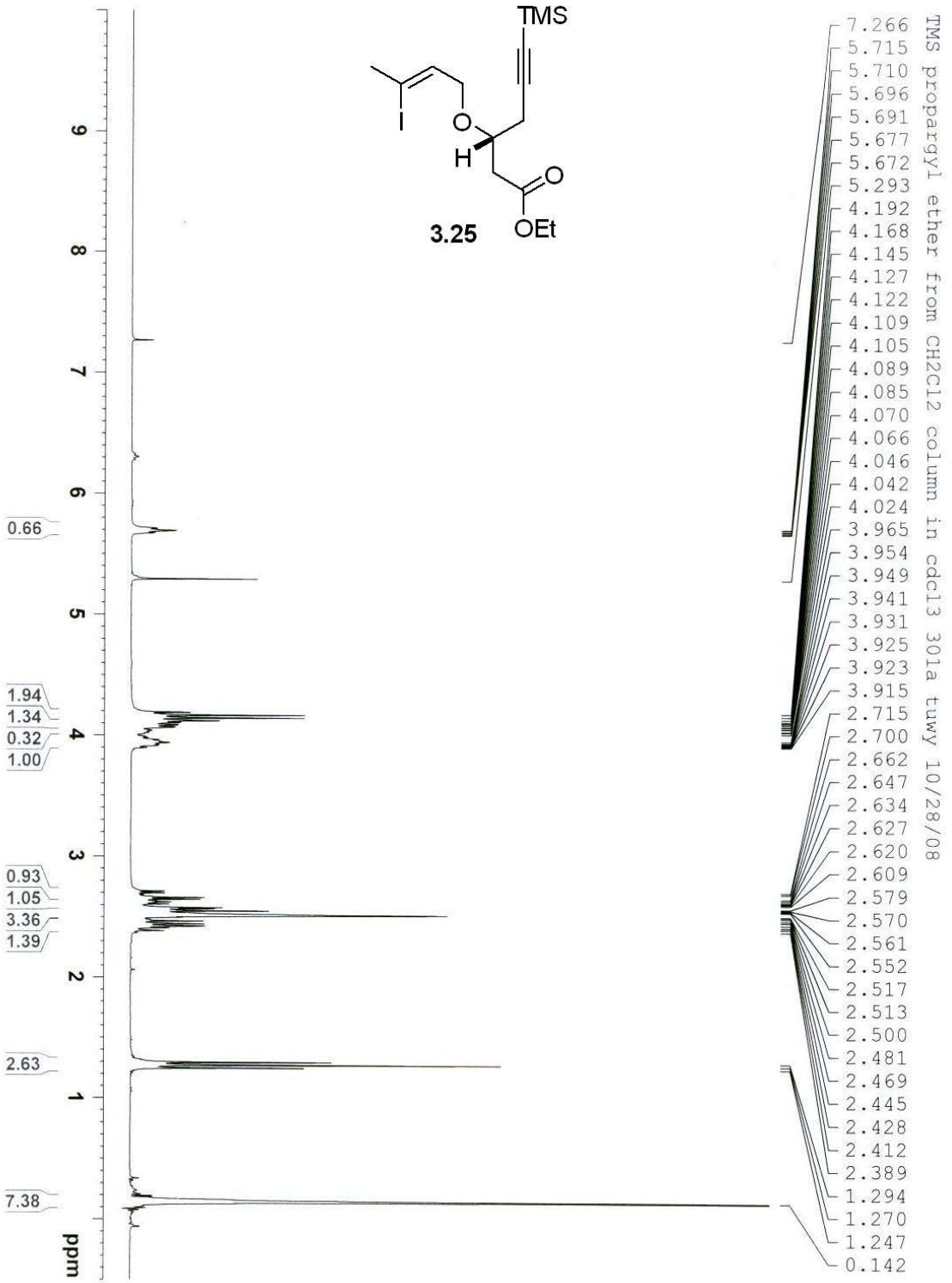
diisopropylsilyl ether in cdcl3 301a tuwy 10/30/08

81.48
77.43
77.00
76.58
72.81
69.91

38.54

26.84
18.38
17.48
17.38
17.35
14.11
12.60
12.53

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


TMS
I
O
H
O
OEt
3.25
TMS propargyl ether from CH2Cl2 column in cdcl3 301a tuwy 10/28/08
7.266
5.715
5.710
5.696
5.691
5.677
5.672
5.293
4.192
4.168
4.145
4.127
4.122
4.109
4.105
4.089
4.085
4.070
4.066
4.046
4.042
4.024
3.965
3.954
3.949
3.941
3.931
3.925
3.923
3.915
2.715
2.700
2.662
2.647
2.634
2.627
2.620
2.609
2.579
2.570
2.561
2.552
2.517
2.513
2.500
2.481
2.469
2.445
2.428
2.412
2.389
1.294
1.270
1.247
0.142
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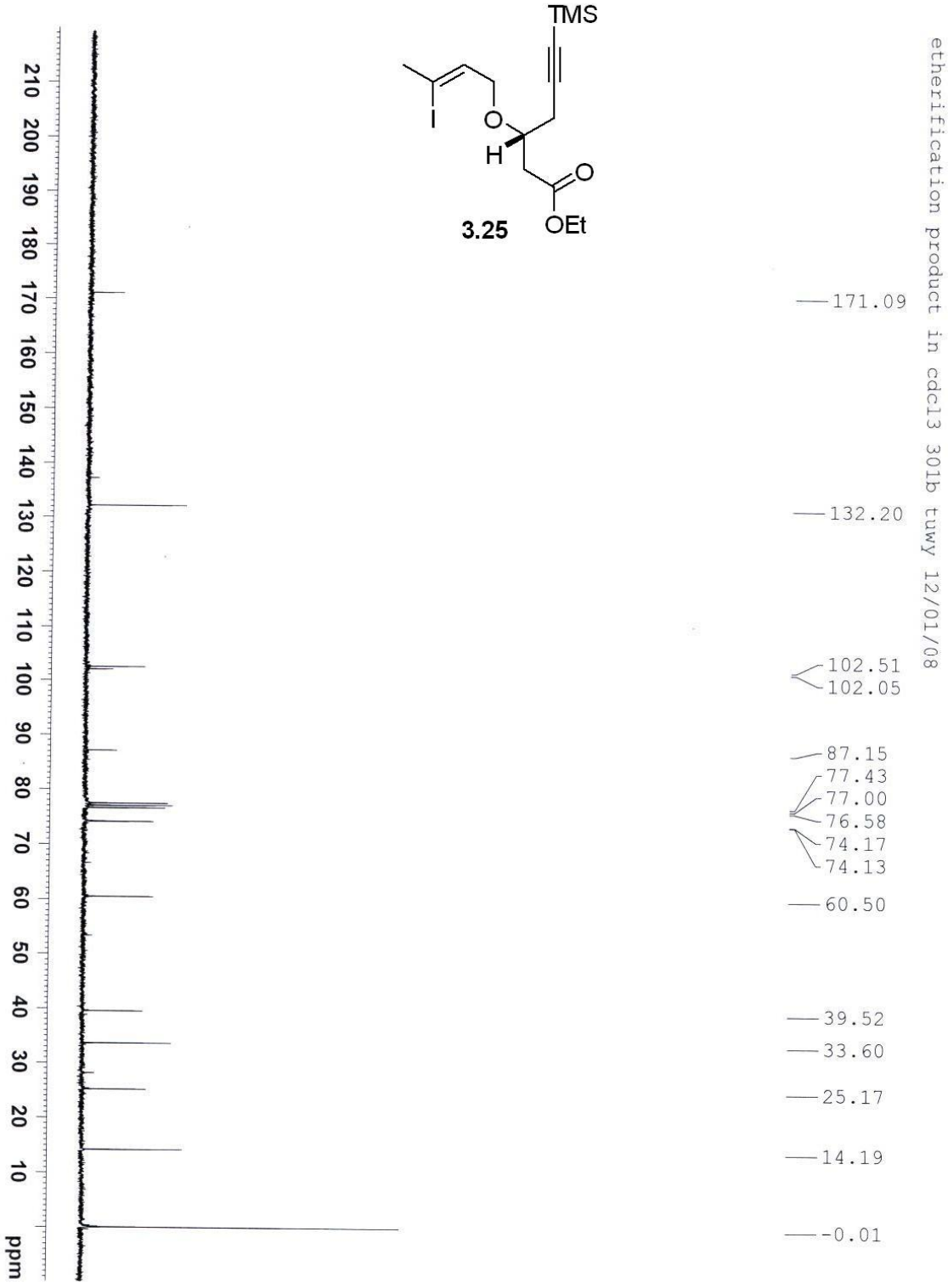
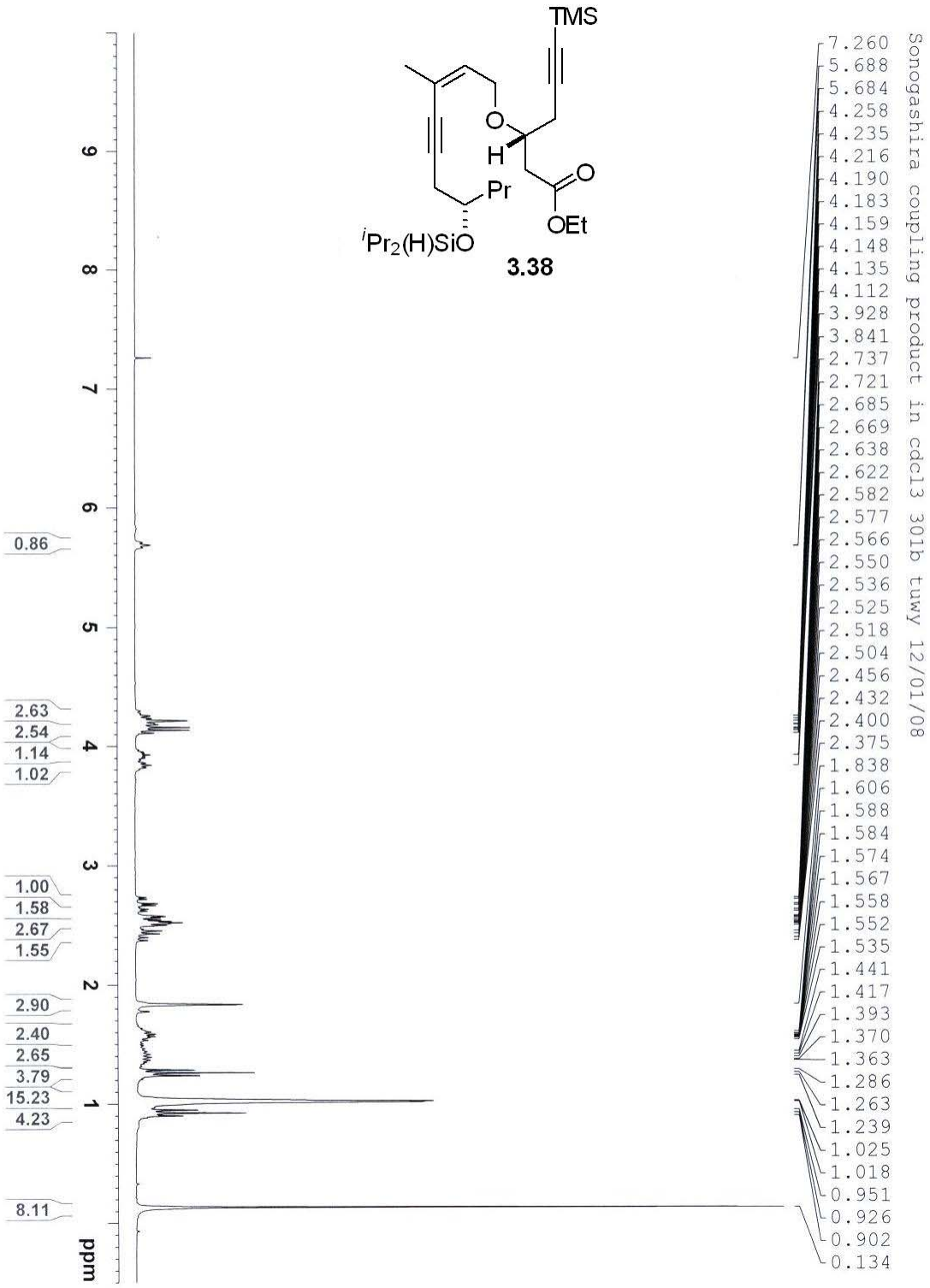
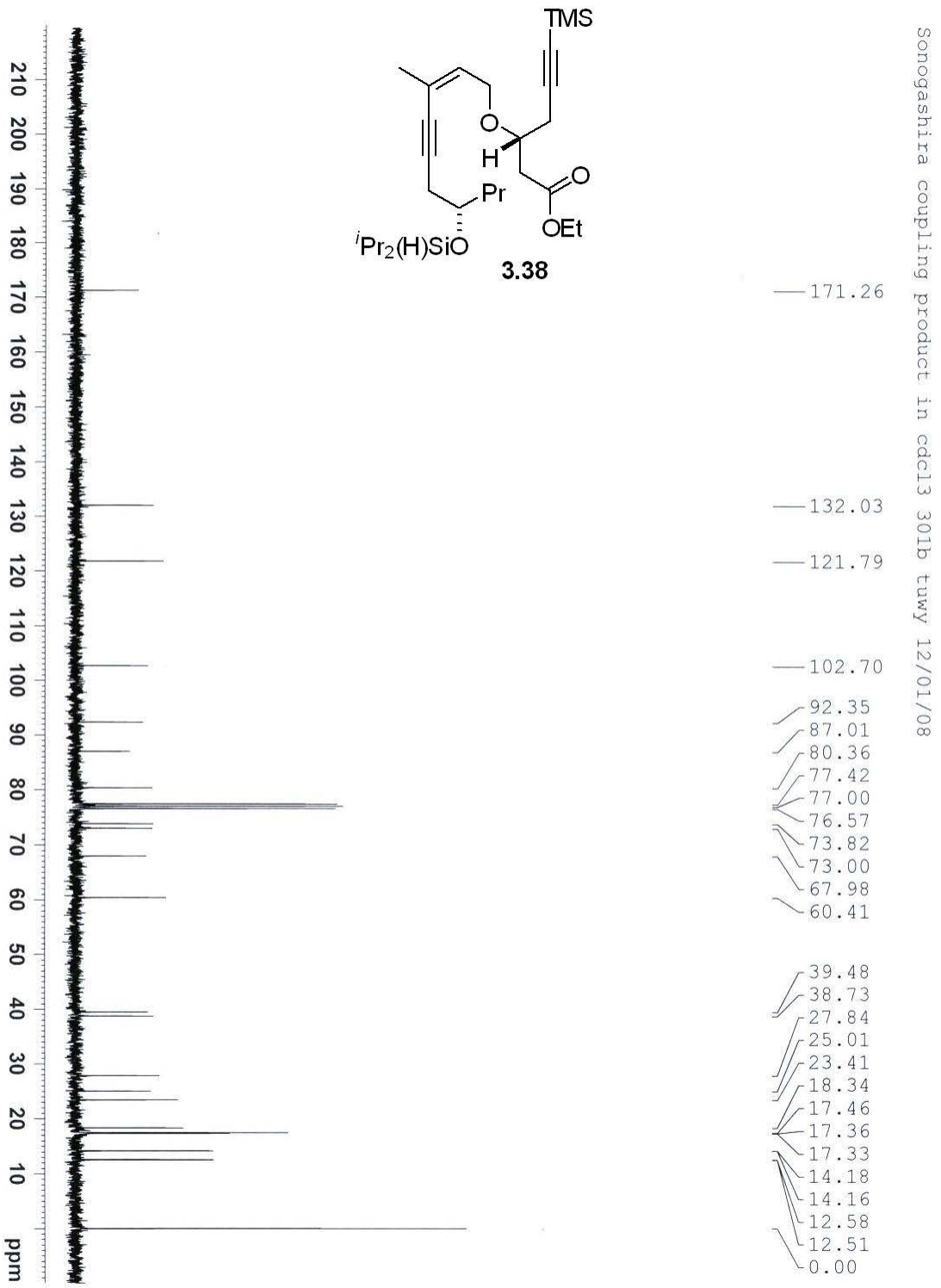
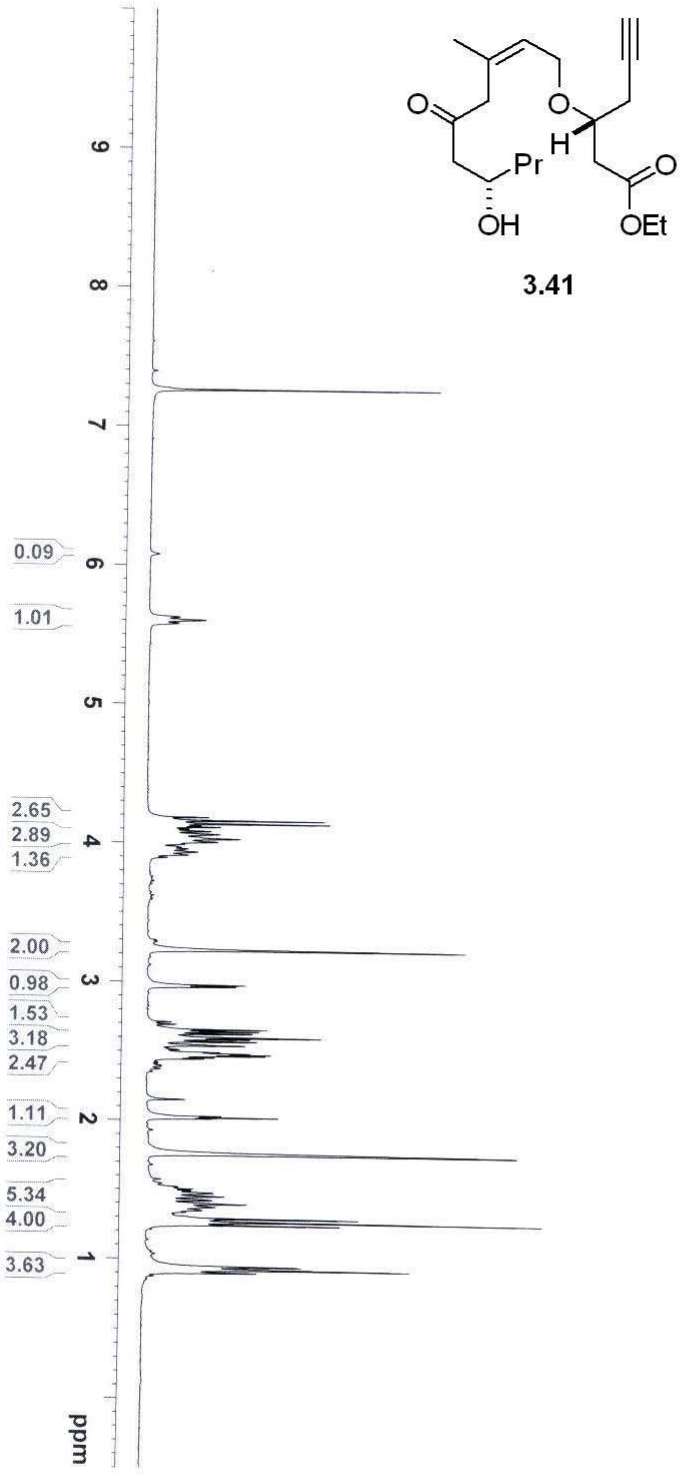
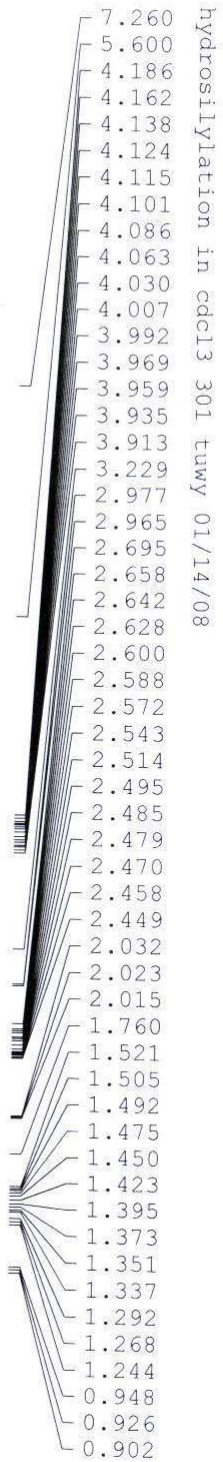
1.34
0.32
1.00
0.93
1.05
3.36
1.39
2.63
7.38
ppm

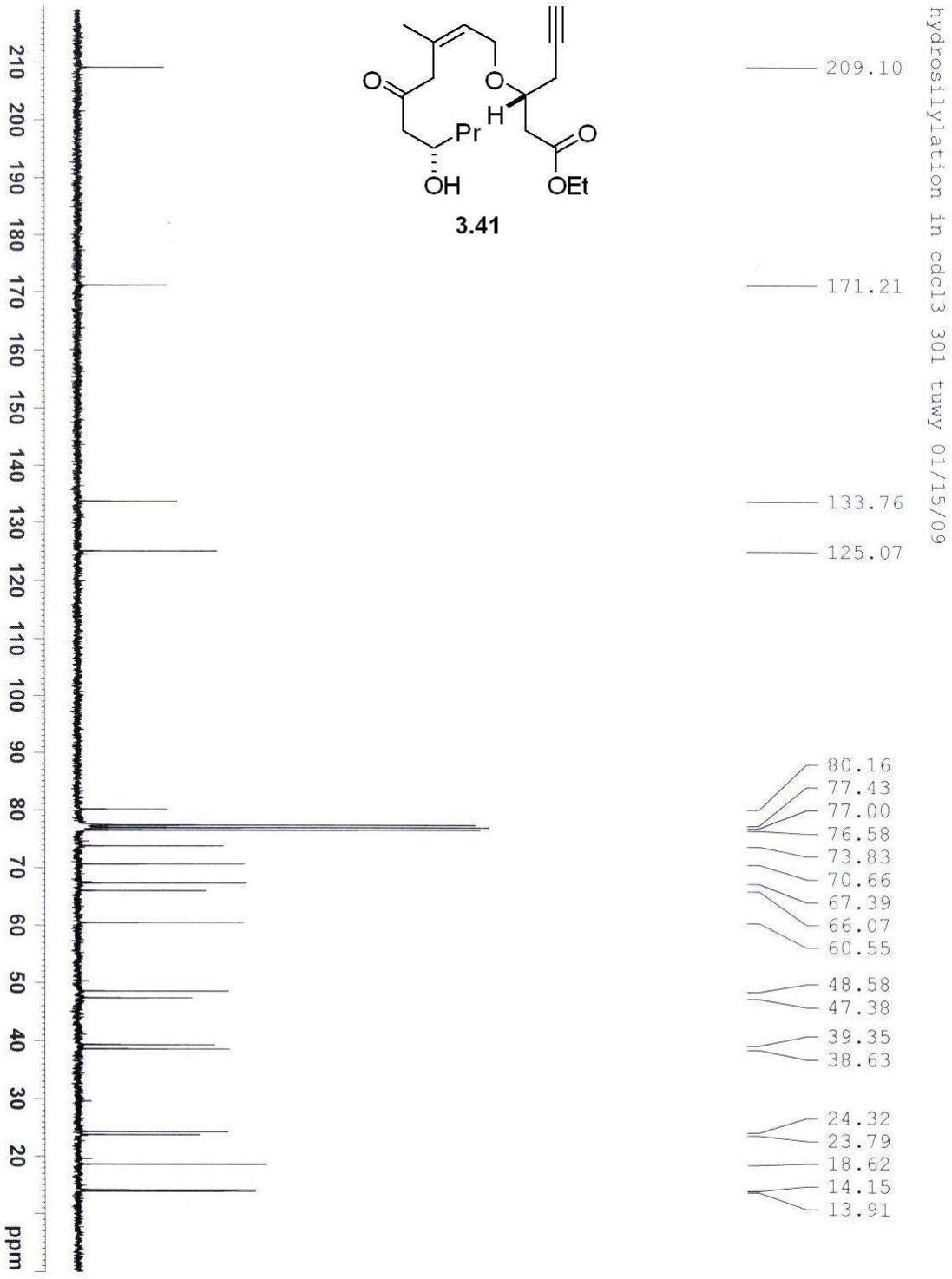

TMS
I
O
H
O
OEt
3.25
etherification product in cdcl3 301b tuwy 12/01/08
171.09
132.20
102.51
102.05
87.15
77.43
77.00
76.58
74.17
74.13
60.50
39.52
33.60
25.17
14.19
-0.01
ppm

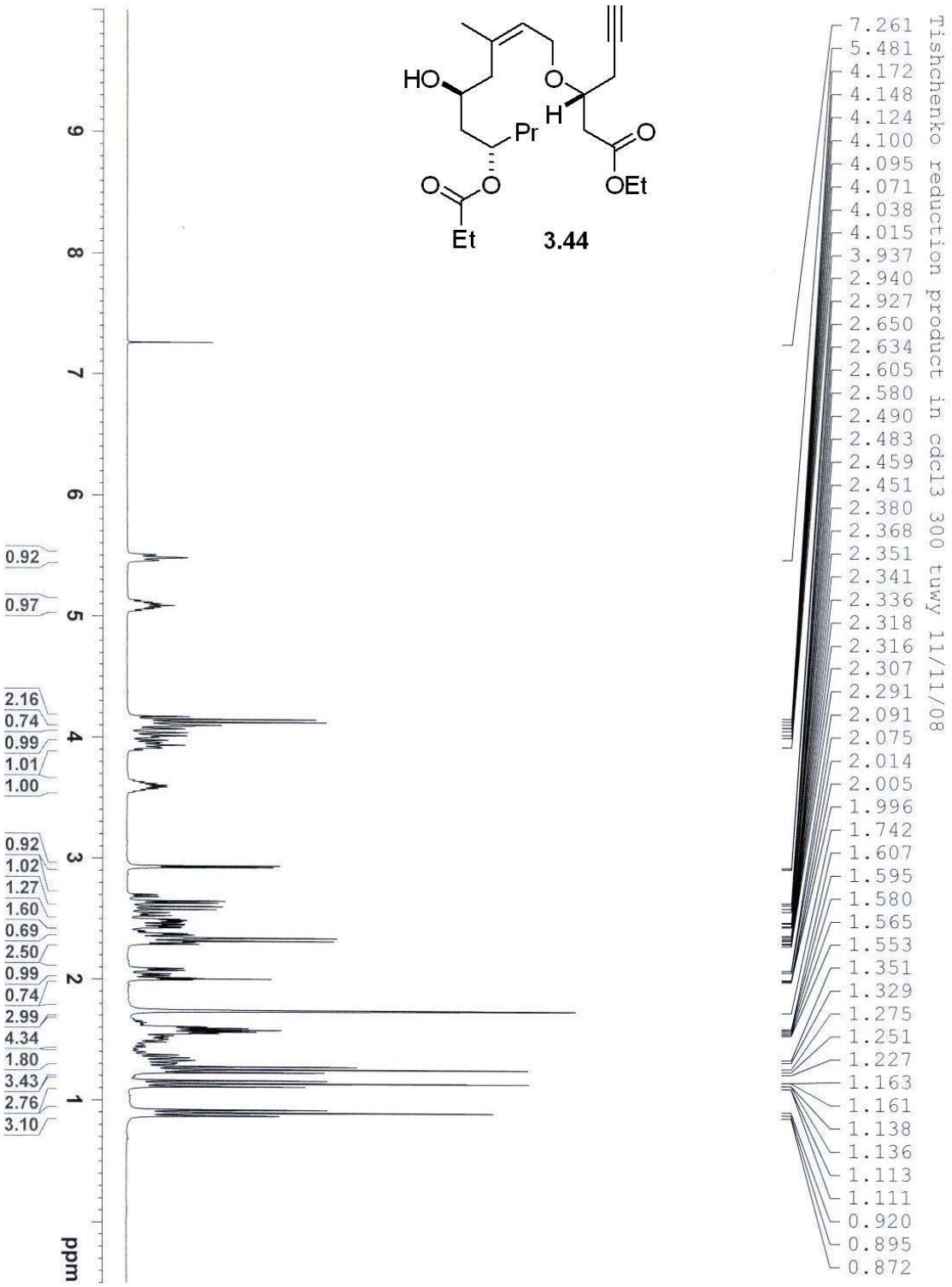

TMS
O
H
Pr
O
OEt
$^{i}Pr_2(H)SiO$
3.38
Sonogashira coupling product in cdcl3 301b tuwy 12/01/08
7.260
5.688
5.684
4.258
4.235
4.216
4.190
4.183
4.159
4.148
4.135
4.112
3.928
3.841
2.737
2.721
2.685
2.669
2.638
2.622
2.582
2.577
2.566
2.550
2.536
2.525
2.518
2.504
2.456
2.432
2.400
2.375
1.838
1.606
1.588
1.584
1.574
1.567
1.558
1.552
1.535
1.441
1.417
1.393
1.370
1.363
1.286
1.263
1.239
1.025
1.018
0.951
0.926
0.902
0.134
0.86
2.63
2.54
1.14
1.02
1.00
1.58
2.67
1.55
2.90
2.40
2.65
3.79
15.23
4.23
8.11
ppm

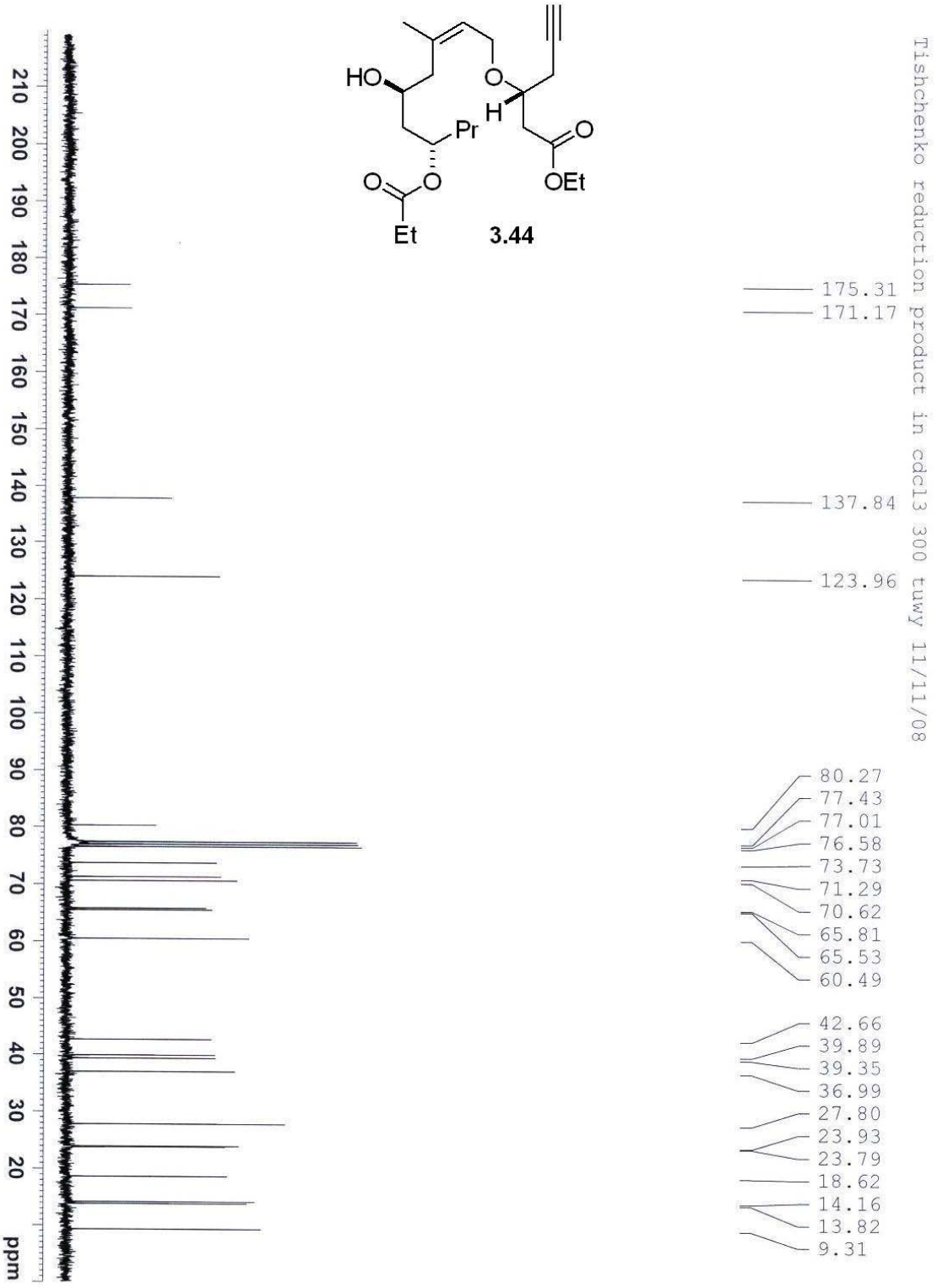

TMS
O
H
Pr
O
OEt
$^{i}Pr_2(H)SiO$
3.38
171.26
132.03
121.79
102.70
92.35
87.01
80.36
77.42
77.00
76.57
73.82
73.00
67.98
60.41
39.48
38.73
27.84
25.01
23.41
18.34
17.46
17.36
17.33
14.18
14.16
12.58
12.51
0.00
ppm
Sonogashira coupling product in cdcl3 301b tuwy 12/01/08

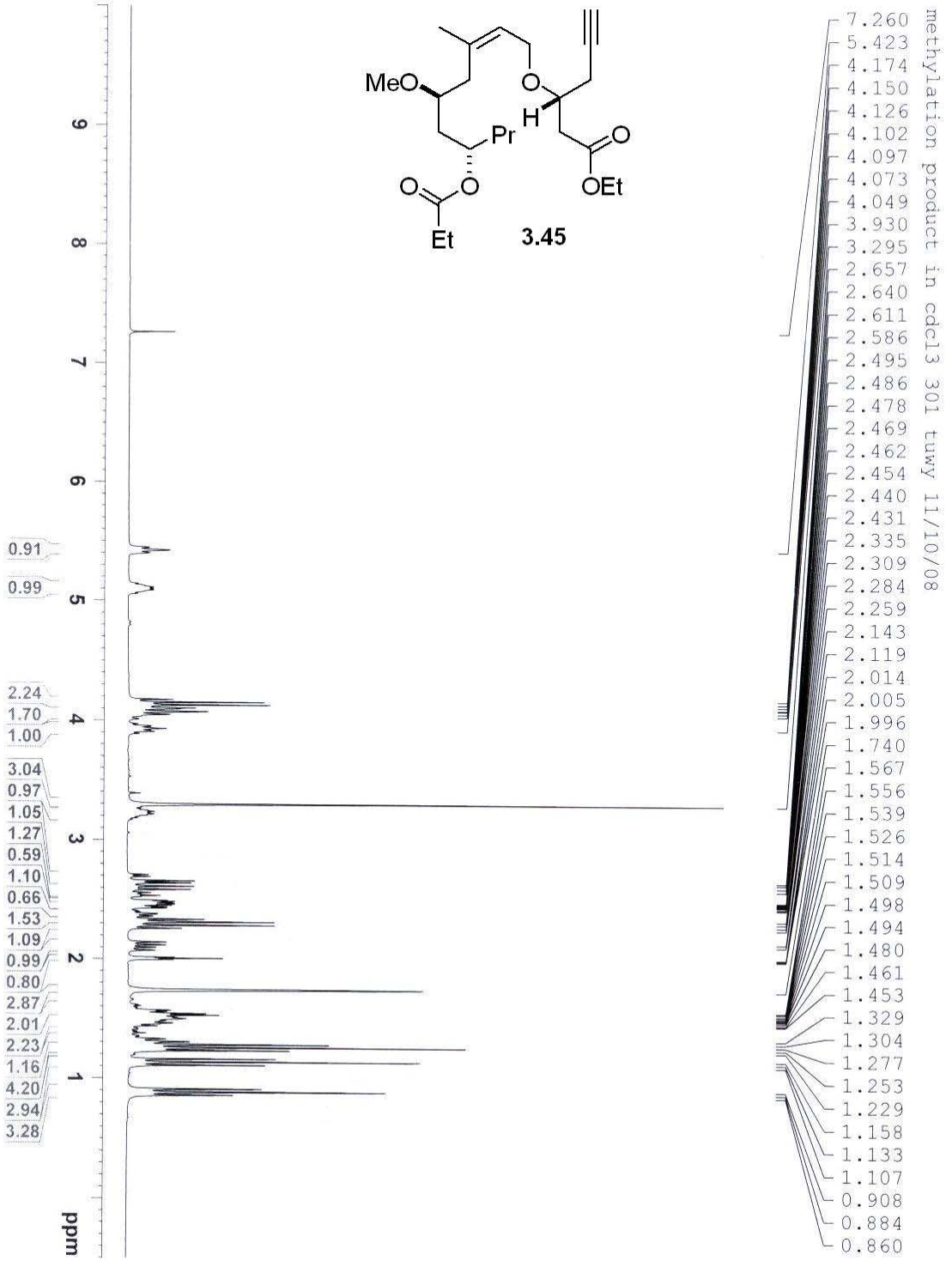

O
O
H
Pr
OH
O
OEt
3.41
0.09
1.01
2.65
2.89
1.36
2.00
0.98
1.53
3.18
2.47
1.11
3.20
5.34
4.00
3.63
ppm
9
8
7
6
5
4
3
2
1

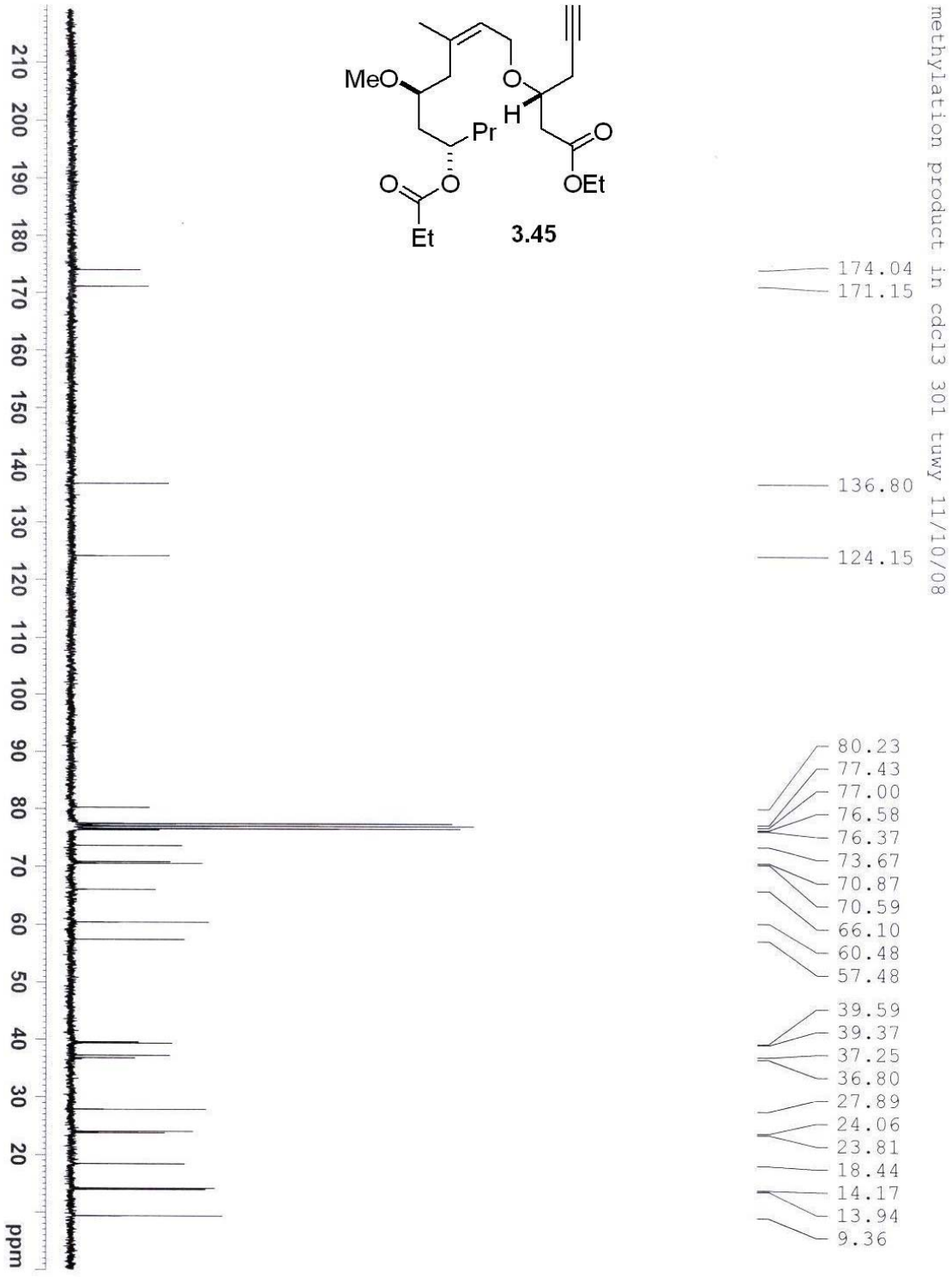

hydrosilylation in cdcl3 301 tuwy 01/14/08
7.260
5.600
4.186
4.162
4.138
4.124
4.115
4.101
4.086
4.063
4.030
4.007
3.992
3.969
3.959
3.935
3.913
3.229
2.977
2.965
2.695
2.658
2.642
2.628
2.600
2.588
2.572
2.543
2.514
2.495
2.485
2.479
2.470
2.458
2.449
2.032
2.023
2.015
1.760
1.521
1.505
1.492
1.475
1.450
1.423
1.395
1.373
1.351
1.337
1.292
1.268
1.244
0.948
0.926
0.902

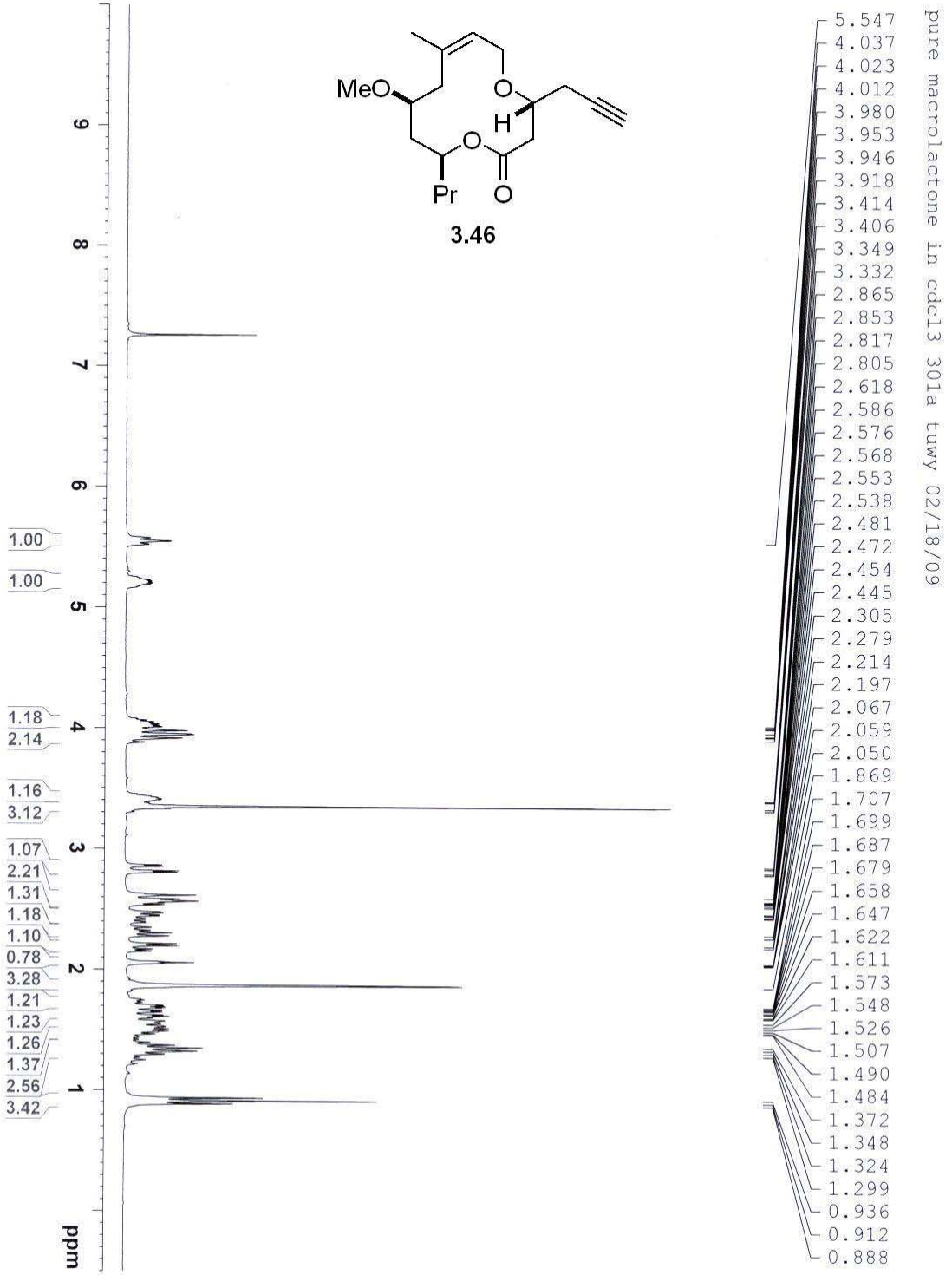

hydrosilylation in cdcl3 301 tuwy 01/15/09
209.10
171.21
133.76
125.07
80.16
77.43
77.00
76.58
73.83
70.66
67.39
66.07
60.55
48.58
47.38
39.35
38.63
24.32
23.79
18.62
14.15
13.91
O
O
H
Pr
OH
O
OEt
3.41
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

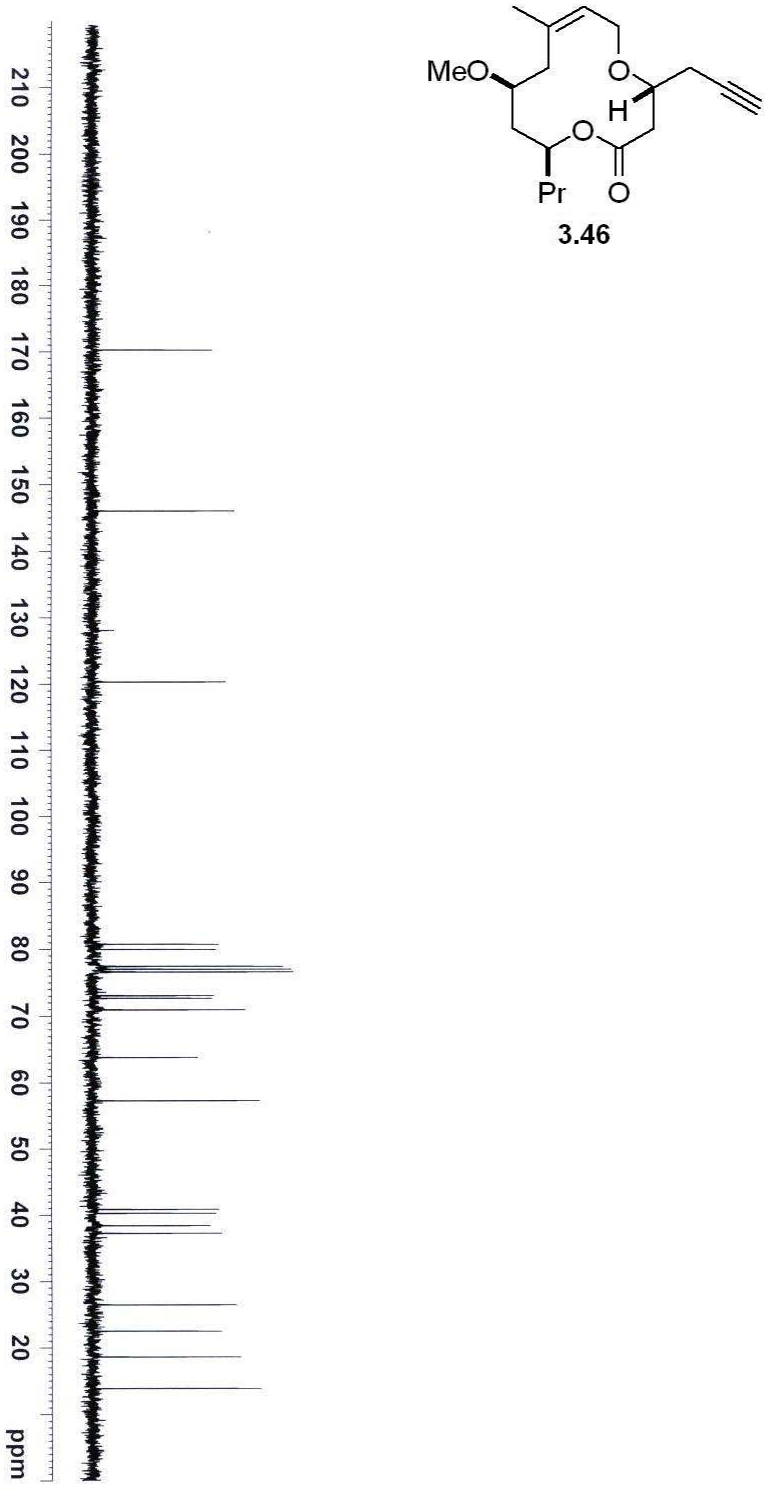

HO
O
H
Pr
O
O
OEt
O
O
Et
3.44
Tishchenko reduction product in cdcl3 300 tuwy 11/11/08
7.261
5.481
4.172
4.148
4.124
4.100
4.095
4.071
4.038
4.015
3.937
2.940
2.927
2.650
2.634
2.605
2.580
2.490
2.483
2.459
2.451
2.380
2.368
2.351
2.341
2.336
2.318
2.316
2.307
2.291
2.091
2.075
2.014
2.005
1.996
1.742
1.607
1.595
1.580
1.565
1.553
1.351
1.329
1.275
1.251
1.227
1.163
1.161
1.138
1.136
1.113
1.111
0.920
0.895
0.872
0.92
0.97
2.16
0.74
0.99
1.01
1.00
0.92
1.02
1.27
1.60
0.69
2.50
0.99
0.74
2.99
4.34
1.80
3.43
2.76
3.10
ppm

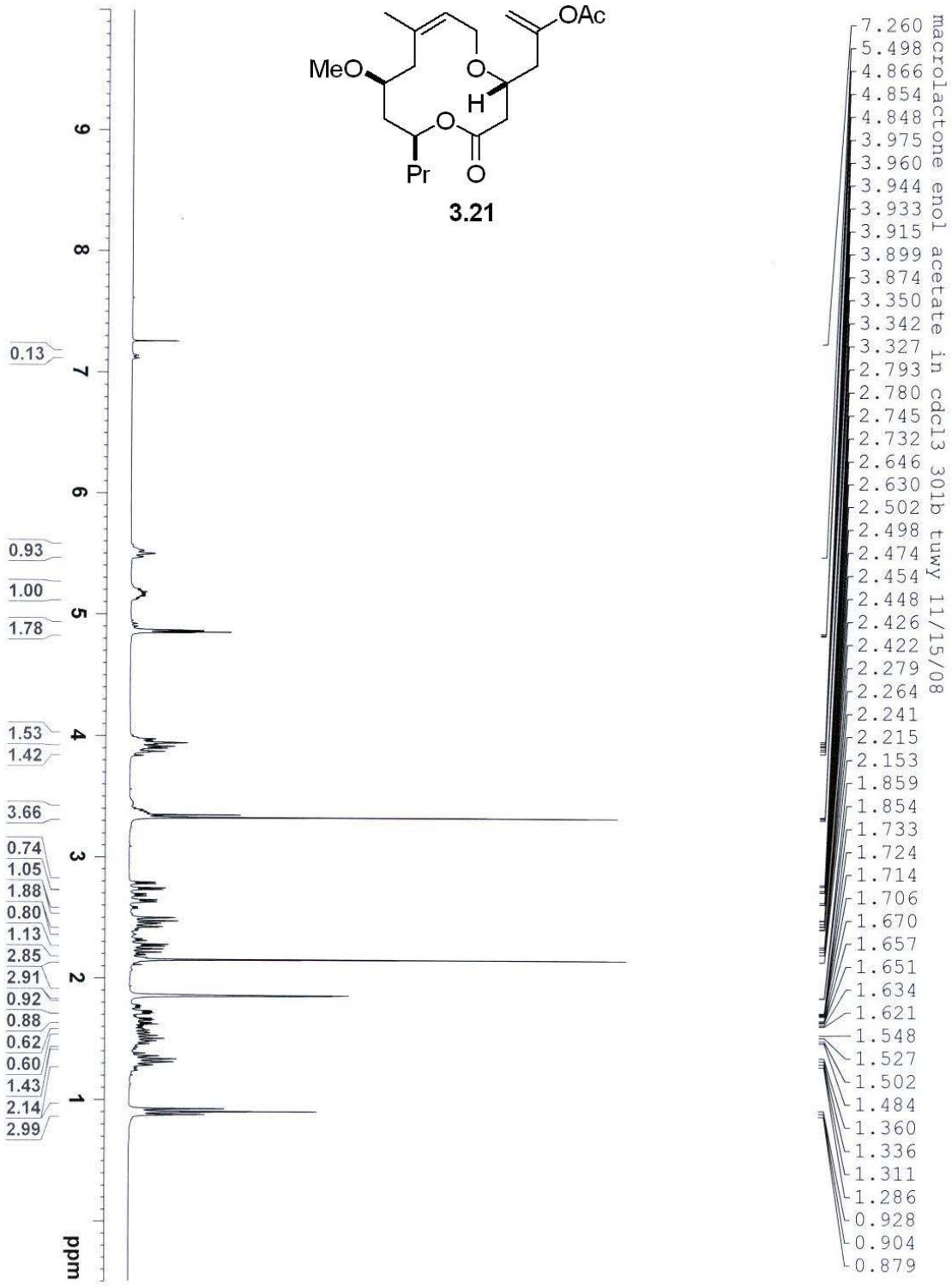

HO
O
H
Pr
O
O
OEt
O
Et
3.44
Tishchenko reduction product in cdcl3 300 tuwy 11/11/08
175.31
171.17
137.84
123.96
80.27
77.43
77.01
76.58
73.73
71.29
70.62
65.81
65.53
60.49
42.66
39.89
39.35
36.99
27.80
23.93
23.79
18.62
14.16
13.82
9.31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


MeO
O
H
Pr
O
O
OEt
O
O
Et
3.45
methylation product in cdcl3 301 tuwy 11/10/08
7.260
5.423
4.174
4.150
4.126
4.102
4.097
4.073
4.049
3.930
3.295
2.657
2.640
2.611
2.586
2.495
2.486
2.478
2.469
2.462
2.454
2.440
2.431
2.335
2.309
2.284
2.259
2.143
2.119
2.014
2.005
1.996
1.740
1.567
1.556
1.539
1.526
1.514
1.509
1.498
1.494
1.480
1.461
1.453
1.329
1.304
1.277
1.253
1.229
1.158
1.133
1.107
0.908
0.884
0.860
0.91
0.99
2.24
1.70
1.00
3.04
0.97
1.05
1.27
0.59
1.10
0.66
1.53
1.09
0.99
0.80
2.87
2.01
2.23
1.16
4.20
2.94
3.28
9
8
7
6
5
4
3
2
1
ppm


methylation product in cdcl3 301 tuwy 11/10/08
MeO
O
H
Pr
O
O
OEt
O
Et
3.45
174.04
171.15
136.80
124.15
80.23
77.43
77.00
76.58
76.37
73.67
70.87
70.59
66.10
60.48
57.48
39.59
39.37
37.25
36.80
27.89
24.06
23.81
18.44
14.17
13.94
9.36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


MeO
O
H
O
Pr
O
3.46
pure macrolactone in cdcl3 301a tuwy 02/18/09
5.547
4.037
4.023
4.012
3.980
3.953
3.946
3.918
3.414
3.406
3.349
3.332
2.865
2.853
2.817
2.805
2.618
2.586
2.576
2.568
2.553
2.538
2.481
2.472
2.454
2.445
2.305
2.279
2.214
2.197
2.067
2.059
2.050
1.869
1.707
1.699
1.687
1.679
1.658
1.647
1.622
1.611
1.573
1.548
1.526
1.507
1.490
1.484
1.372
1.348
1.324
1.299
0.936
0.912
0.888
1.00
1.00
1.18
2.14
1.16
3.12
1.07
2.21
1.31
1.18
1.10
0.78
3.28
1.21
1.23
1.26
1.37
2.56
3.42
ppm


MeO
O
H
O
Pr
O
3.46
macrolactone in cdcl3 301b tuwy 11/14/08
170.26
146.06
120.33
80.75
79.96
77.43
77.00
76.58
73.04
72.64
70.92
63.79
57.30
40.82
40.23
38.37
37.21
26.44
22.48
18.61
13.84
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


OAc
MeO
O
H
O
Pr
O
3.21
0.13
0.93
1.00
1.78
1.53
1.42
3.66
0.74
1.05
1.88
0.80
1.13
2.85
2.91
0.92
0.88
0.62
0.60
1.43
2.14
2.99
ppm
macrolactone enol acetate in cdcl3 301b tuwy 11/15/08
7.260
5.498
4.866
4.854
4.848
3.975
3.960
3.944
3.933
3.915
3.899
3.874
3.350
3.342
3.327
2.793
2.780
2.745
2.732
2.646
2.630
2.502
2.498
2.474
2.454
2.448
2.426
2.422
2.279
2.264
2.241
2.215
2.153
1.859
1.854
1.733
1.724
1.714
1.706
1.670
1.657
1.651
1.634
1.621
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1.502
1.484
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1.336
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1.286
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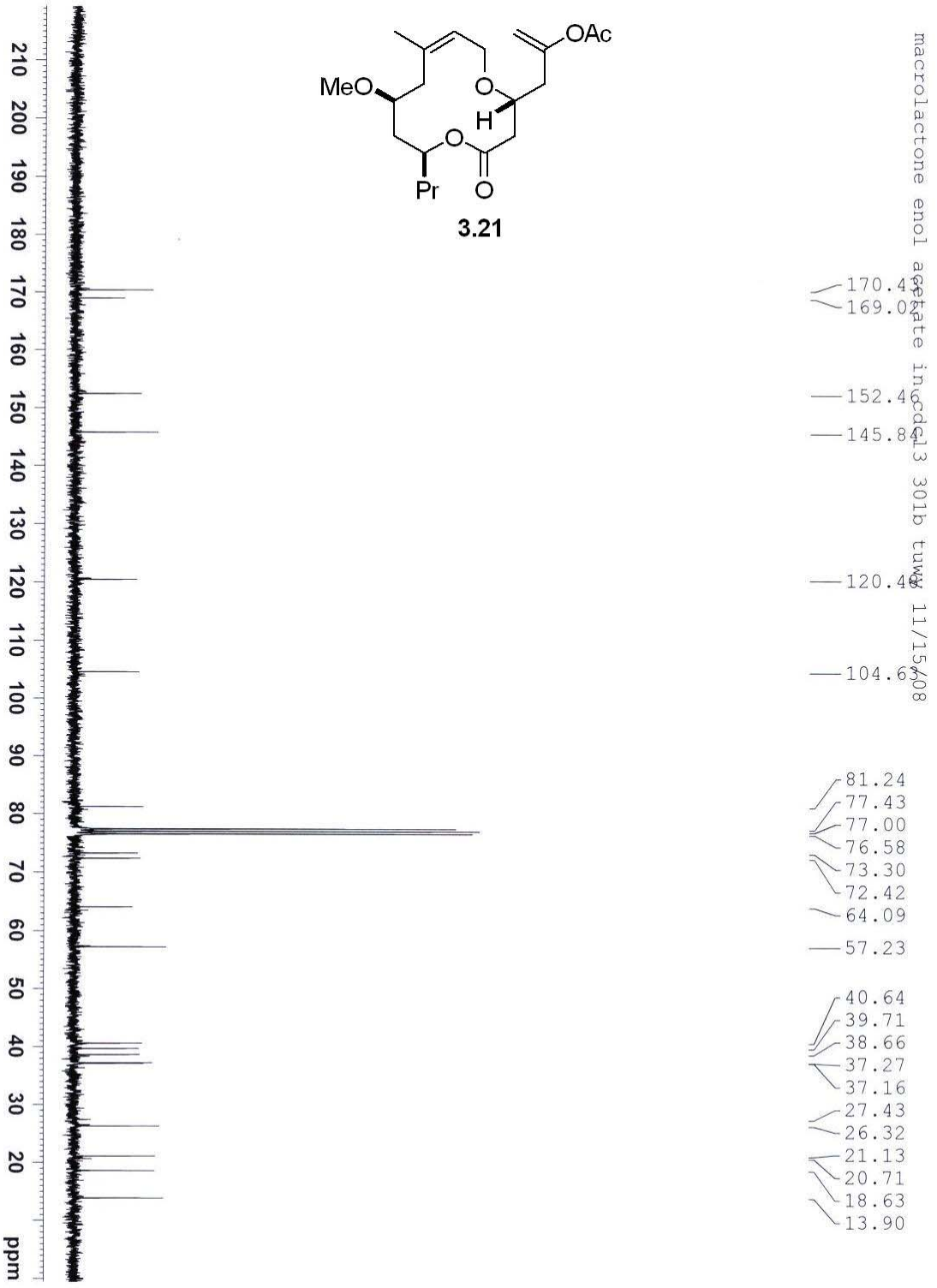
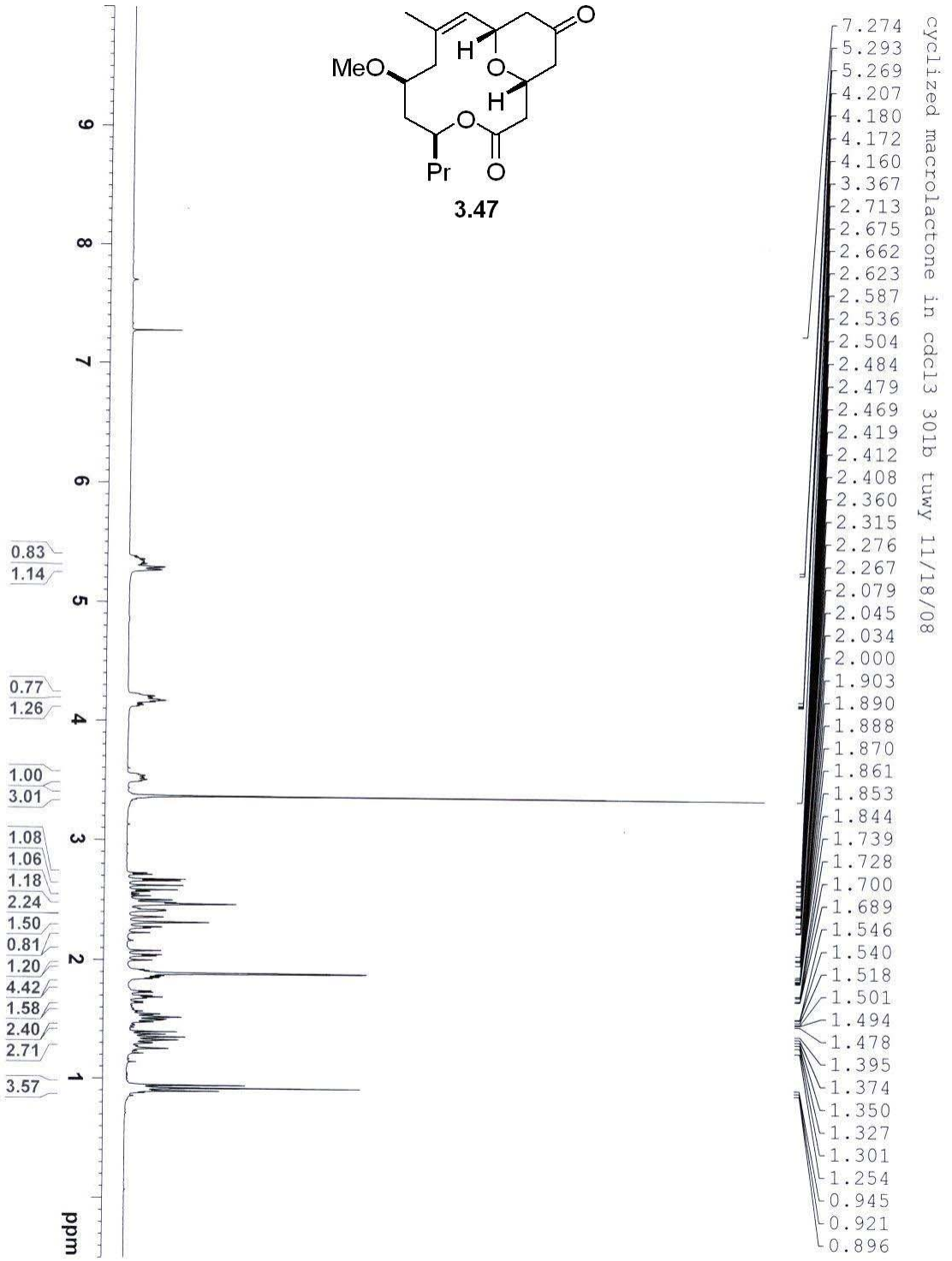
0.904
0.879


macrolactone enol acetate in cdcl3 301b tuw 11/15/08
170.42
169.02
152.41
145.82
120.48
104.63
81.24
77.43
77.00
76.58
73.30
72.42
64.09
57.23
40.64
39.71
38.66
37.27
37.16
27.43
26.32
21.13
20.71
18.63
13.90
ppm

OAc
MeO
O
H
O
Pr
O

3.21


MeO
H
O
H
O
Pr
O
O
3.47
cyclized macrolactone in cdcl3 301b tuwy 11/18/08
7.274
5.293
5.269
4.207
4.180
4.172
4.160
3.367
2.713
2.675
2.662
2.623
2.587
2.536
2.504
2.484
2.479
2.469
2.419
2.412
2.408
2.360
2.315
2.276
2.267
2.079
2.045
2.034
2.000
1.903
1.890
1.888
1.870
1.861
1.853
1.844
1.739
1.728
1.700
1.689
1.546
1.540
1.518
1.501
1.494
1.478
1.395
1.374
1.350
1.327
1.301
1.254
0.945
0.921
0.896
0.83
1.14
0.77
1.26
1.00
3.01
1.08
1.06
1.18
2.24
1.50
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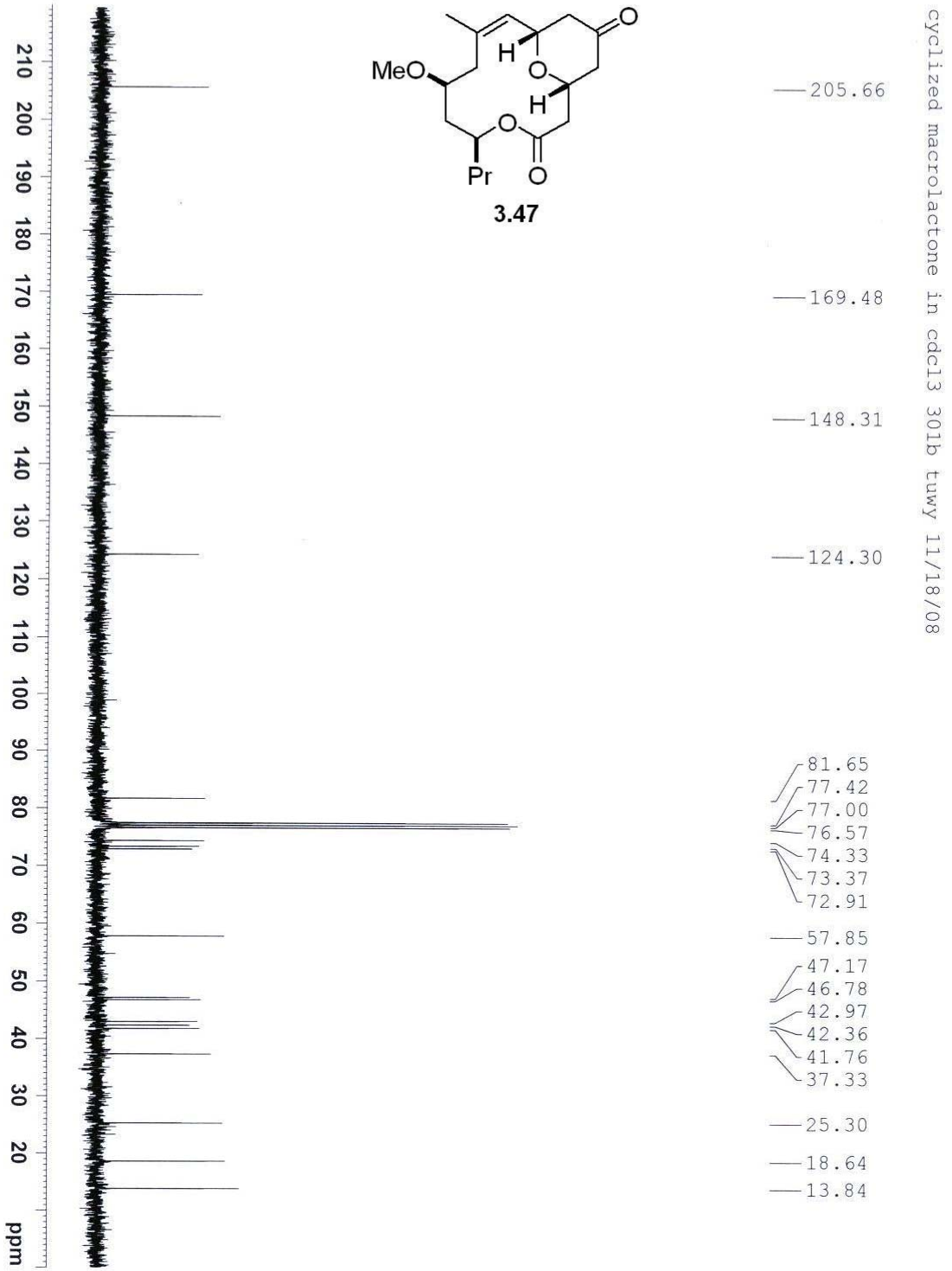
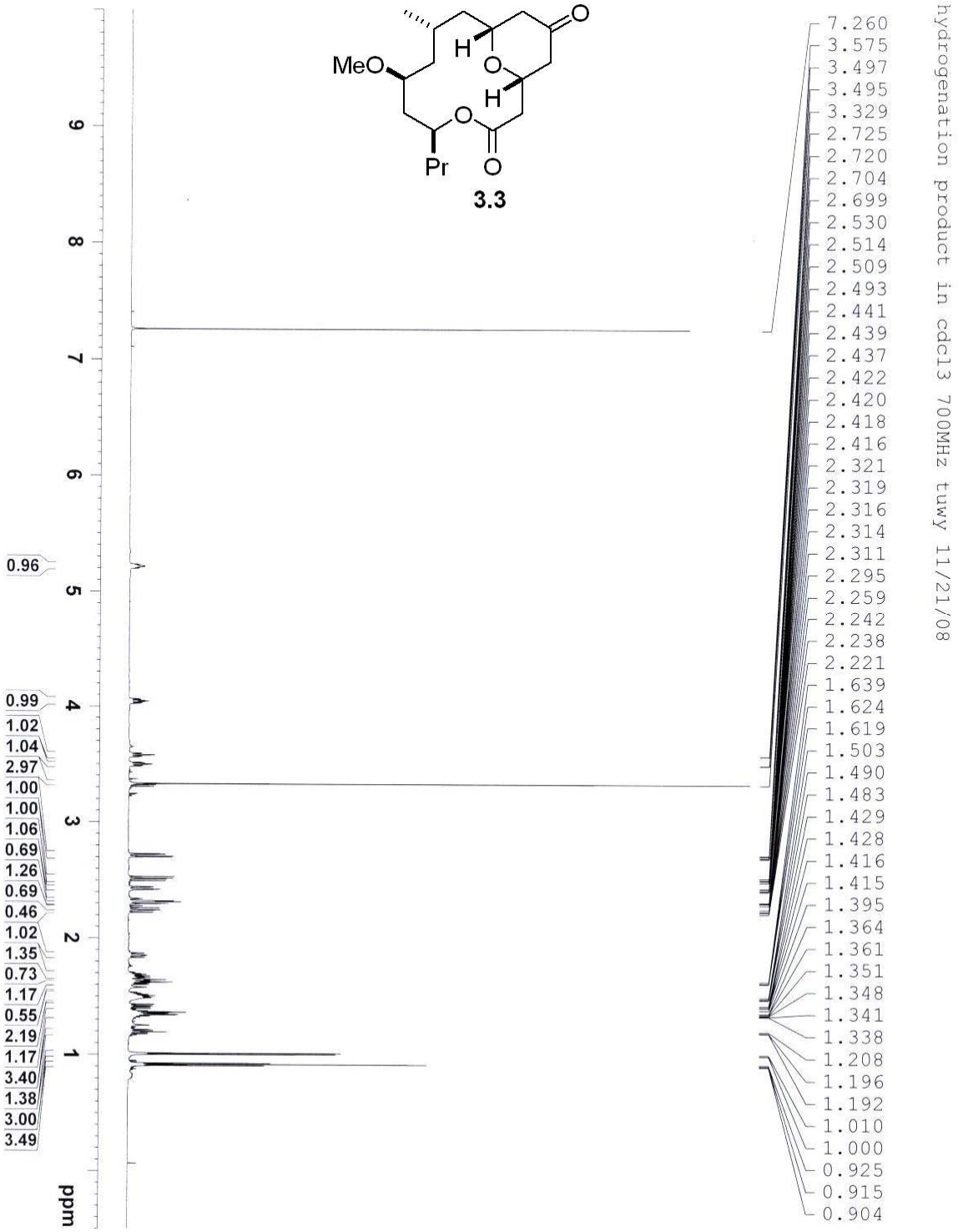
1.20
4.42
1.58
2.40
2.71
3.57
ppm


cyclized macrolactone in cdcl3 301b tuwy 11/18/08
MeO
H
O
H
O
Pr
O
O
3.47
205.66
169.48
148.31
124.30
81.65
77.42
77.00
76.57
74.33
73.37
72.91
57.85
47.17
46.78
42.97
42.36
41.76
37.33
25.30
18.64
13.84
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


MeO
H
O
H
O
O
Pr
O
3.3
hydrogenation product in cdcl3 700MHz tuwy 11/21/08
7.260
3.575
3.497
3.495
3.329
2.725
2.720
2.704
2.699
2.530
2.514
2.509
2.493
2.441
2.439
2.437
2.422
2.420
2.418
2.416
2.321
2.319
2.316
2.314
2.311
2.295
2.259
2.242
2.238
2.221
1.639
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1.619
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1.490
1.483
1.429
1.428
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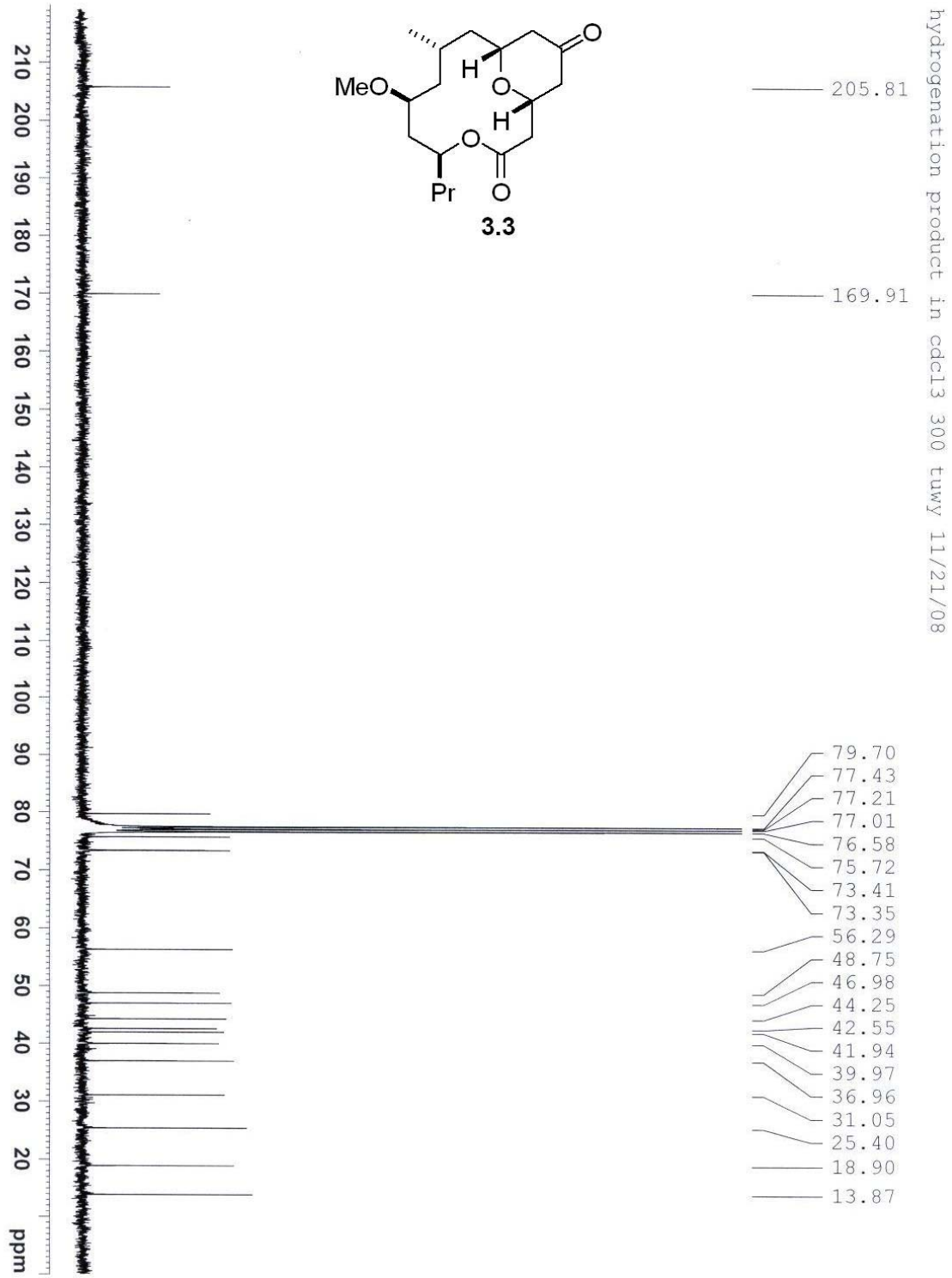
1.415
1.395
1.364
1.361
1.351
1.348
1.341
1.338
1.208
1.196
1.192
1.010
1.000
0.925
0.915
0.904
0.96
0.99
1.02
1.04
2.97
1.00
1.00
1.06
0.69
1.26
0.69
0.46
1.02
1.35
0.73
1.17
0.55
2.19
1.17
3.40
1.38
3.00
3.49
ppm


hydrogenation product in cdcl3 300 tuwy 11/21/08
205.81
169.91
79.70
77.43
77.21
77.01
76.58
75.72
73.41
73.35
56.29
48.75
46.98
44.25
42.55
41.94
39.97
36.96
31.05
25.40
18.90
13.87
MeO
H
O
H
O
Pr
O
O
3.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

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