PROGRESS TOWARD THE TOTAL SYNTHESIS OF GUANACASTEPENE A VIA A Rh(I)-CATALYZED CYCLOCARBONYLATION REACTION

by

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Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

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Remond Moningka, M.S.

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The cyclocarbonylation reaction or the formal [2 + 2 +1] cycloaddition reaction involving alkynes, allenes, and a carbon monoxide source is a powerful methodology for the formation of cyclopentadienones. More importantly, complex ring systems can be successfully synthesized by employing the intramolecular cyclocarbonylation reaction to allenyne-containing substrates. In this thesis, progress towards the total synthesis of guanacastepene A is reported. The tricyclic skeleton of guanacastepene A has been successfully formed via a Rh(I)-catalyzed cyclocarbonylation reaction. One challenging problem of our synthetic approach is the installation of the angular methyl group at C11. It is predicted that this group can be stereoselectively appended through a hydroxyl directed cyclopropanation, oxidation, and cyclopropyl ring opening reaction sequence. SmI_2 was investigated for the reductive opening of the cyclopropane. However, these conditions gave the ring expanded cyclohexanone instead of the desired angular methyl-containing cyclopentanone. Attempts to affect the cyclopropyl ring opening on a model system were investigated. Both dissolving metal (Li/NH_3) and Bu_3SnH reduction conditions gave ring expansion as the primary product on the model system.

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PREFACE

There are many people whom I would like to thank for a never-ending support and encouragement throughout my graduate education. My research advisor, Professor Kay M. Brummond, provided me with her support, guidance, and understanding during my studies. I also would like to thank my committee member, Dr. Tara Meyer and Dr. Scott Nelson. Thanks to all former and present members of the Brummond group, many of you whom I felt inspired to work with. I especially would like to thank Jamie McCabe for her mentorship and enthusiasm in my early year of studies; Bing Li Yan, Dai Tao Chen, and Jolie DeForrest for the knowledge in chemistry, discussion of various aspects of my research, and support. I truly appreciate it.

Thanks to the Department of Chemistry, University of Pittsburgh, National Institutes of Health, and Johnson & Johnson for the financial support. It was appreciated.

On my personal note, I would like to thank Sandra Kim and Jihyun An for the friendship and incredible support. Hang in there, and I am going to miss you guys.

A special thanks to my dad, Ventje Moningka, my mom, Thio Ai Lan, and my brother, Rendi Moningka, for the endless love end encouragement through my whole life. I could not have accomplished this without all your support. Even though I am away from home, I am forever grateful. You are close to my heart.

ABBREVIATIONS

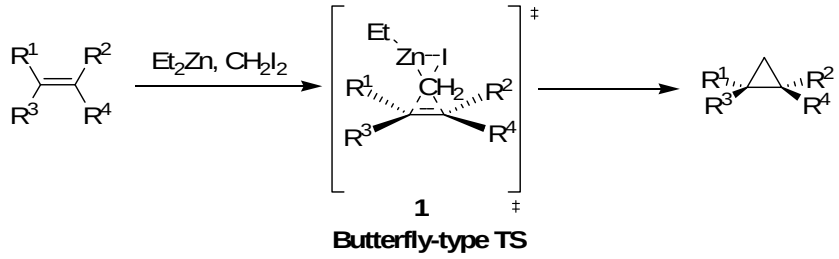
AIBN	2,2'-Azo *bis*isobutyronitrile
BTAF	Benzyltrimethyl ammonium fluoride
BuLi	*n*-Butyllithium
DCE	Dichloroethane
DIBAL-H	Diisobutylaluminum hydride
DMAP	*N,N*-4-dimethylaminopyridine
DMDO	Dimethyl dioxirane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DPS	Dimethylphenylsilyl
EtOAc	Ethyl acetate
GC	Gas Chromatography
h	hour
HMPA	Hexamethylphosphoric triamide
HPLC	High Pressure Liquid Chromatography
iPr_2NH	Diisopropylamine
IR	Infrared
LAH	Lithium aluminum hydride

L-selectride	Lithium tri-*sec*-butylborohydride
MeOH	Methanol
NMO	*N*-methylmorpholine
NMR	Nuclear Magnetic Resonance
PDC	Pyridinium dichromate
PPTS	Pyridinium *p*-toluenesulfonate
Rf	Retention factor
rt	room temperature
SM	starting material
TBAF	Tetra-*n*-butylammonium fluoride
TBS (TBDMS)	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TESOTf	Triethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TPAP	tetra-*n*-propylammonium perruthenate

1.0 INTRODUCTION

1.1 THE CYCLOPROPANATION REACTION

The cyclopropane ring has intrigued chemists due to its ring strain, and its versatility as a synthetic intermediate in syntheses.[1] In 1929, Emschwiller observed that diiodomethane reacts with zinc to give an iodomethylzinc species.[2] Simmons and Smith were the first to report that the reagent, $IZnCH_2I$, could be use for the transformation of alkenes to cyclopropanes.[3] As shown in Scheme 1, the Simmons-Smith cyclopropanation is a concerted process, proceeding through a three-centered "butterfly-type" transition state **1**.[4]

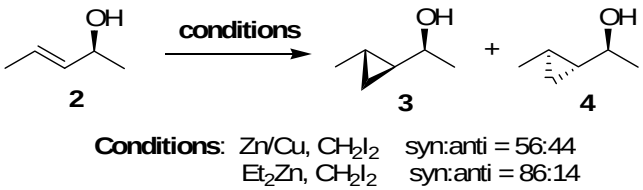


Scheme 1: Transition State of the Cyclopropanation Reaction

1.2 HYDROXYL-DIRECTED CYCLOPROPANATION REACTION

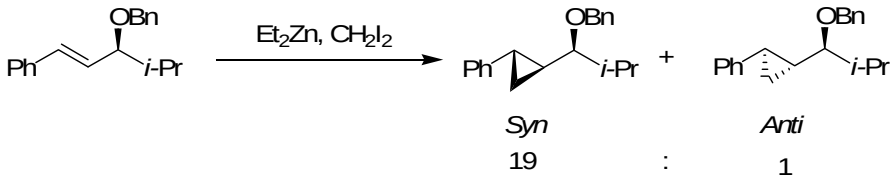
In 1978 Pereyre and coworkers were the first to report a stereoselective cyclopropanation of a chiral, acylic allylic alcohol using the classic Simmons-Smith reagent (Zn-Cu, CH_2I_2).[5] They observed high *syn* selectivities (>200 : 1) with *Z*-disubstituted alkenes, but poor selectivities (<2 : 1) with *E*-disubstituted alkenes.

Charette has shown that the nature of Zn carbenoid species is very important to the high diastereoselectivities of *E*-disubstituted alkenes.[6] As depicted in Scheme 2, Furukawa's reagent (1 : 1 mixture of Et_2Zn : CH_2I_2)[7] is superior and gives a better ratio of the *syn*-isomer **2** compared to the classic Simmons-Smith (Zn/Cu, CH_2I_2).



Scheme 2: Cyclopropanation of *E*-3-Penten-2-ol[1]

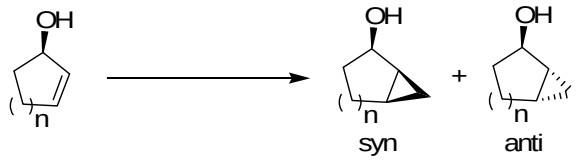
To gain some mechanistic insight into the hydroxyl-directed cyclopropanation reaction, an allylic benzyl ether was used (Scheme 3).[6] The stereochemical outcome of the reaction can be predicted by assuming a hydroxyl-assisted delivery of the reagent from a conformation in which the $A^{1,3}$ strain is minimized.[1,6,8]



Scheme 3: Cyclopropanation of Allylic Benzyl Ether

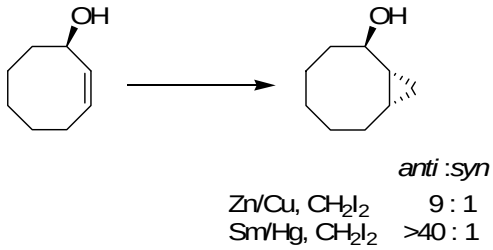
For cyclic alkenes, however, the conformation of the ring is more likely to dictate the stereochemical outcome of the cyclopropane ring. Cyclopropanations of five-, six-, and seven-membered 2-cycloalken-1-ols generally proceed to give a high *syn* : *anti* ratios with either Simmons-Smith or Furukawa's reagents (Table 1).[1] A reversal in the selectivity is observed for eight- and nine-membered rings (Scheme 4). The rationale is based upon the most stable conformation of eight-membered ring adopting a chair-boat shape, in which the bulky hydroxyl group will be oriented in the equatorial position (Figure 1).[1]

Table 1: Diastereoselective Cyclopropanation with Different Reagents and Different Cycloalkenols*



Entry	Reagent	Diastereoselectivity (syn : anti)		
		n = 1	**n = 2**	**n = 3**
1	Zn/Cu	>99 : 1	>99 : 1	90 : 10
2	Et_2Zn, CH_2I_2 (1 : 2)		>99 : 1	
3	Et_2Zn, ICH_2Cl (1 : 2)		>99 : 1	
4	Sm/Hg, CH_2I_2		>99 : 1	>97 : 3

* Lebel, H.; Marcoux, J-F.; Molinaro, C.; Charette, A.B. *Chem. Rev.* **2003**, *103*, 977.

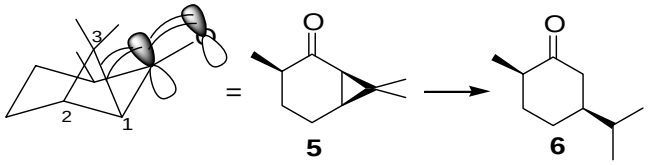


Scheme 4: Reversal of Selectivity for Cyclooctenol

Figure 1: A Chair-Boat Conformation of 2-Cycloocten-1-ol Using Conformer Distribution, MMFF, Macspartan Pro

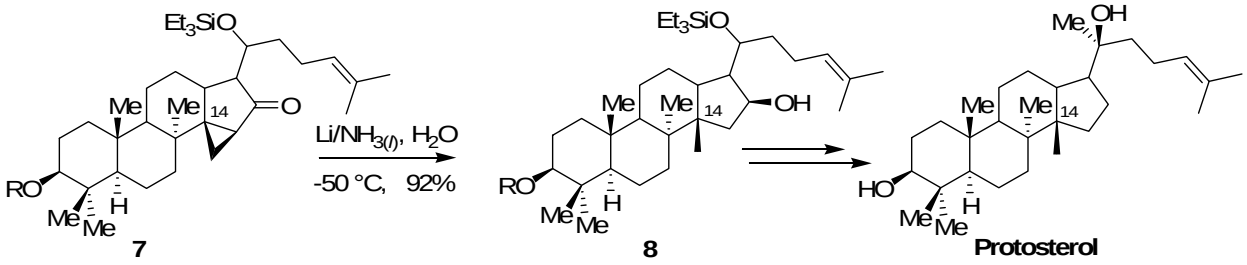
1.3 Sm- or Li-MEDIATED CYCLOPROPYL KETONE RING OPENING

Cyclopropane rings are used as pivotal intermediates in syntheses, especially for the introduction of angular methyl groups. The course of the ring opening of a cyclopropyl ketone is dependent upon the C-C bond of the cyclopropane ring, that has the best orbital overlap with the π-system of the adjacent carbonyl group (Scheme 5).[9] For example, Dauben and coworkers showed in 1966 that the bicyclo[4.1.0]heptane ring system **5** is reductively opened to give 2-methyl-5-isopropylcyclohexanone **6**. This result can be explained by looking at the geometry of the ring system. The external C_1-C_3 orbitals permit excellent overlap with the π-system of the carbonyl group. Alternatively, the orbital overlap between C_1-C_2 and the π-system of the carbonyl is poor. This reaction can be viewed as an overall two-electron reduction to give a carbanion and an enolate ion. Breaking the C_1-C_3 bond will yield the less stable tertiary carbanion in comparison to breaking the internal C_1-C_2 bond, leading to the more stable secondary carbanion.[9] Upon treatment of **5** with lithium in liquid ammonia, the C_1-C_3 bond breaks to yield (-)-carvomenthone **6**.



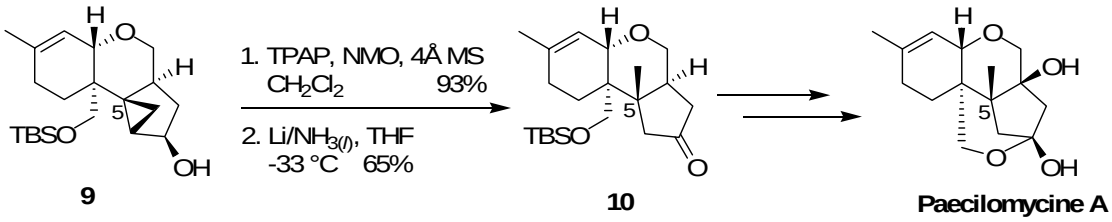
Scheme 5: Orbital Overlap in Bicyclo[4.1.0]heptane Ring System

Corey in his synthesis of protosterol has effectively employed the Li-mediated cyclopropyl ketone ring opening to install an angular methyl group at C14 (Scheme 6).[10] Treatment of **7** with 13 equiv of lithium in THF-NH_3 (1 : 1) containing 10 equiv of H_2O at -50 ºC gives alcohol **8**.



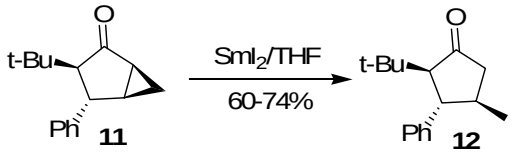
Scheme 6: Li/NH_3-mediated Cyclopropyl Ketone Ring Opening and Ketone Reduction to Afford Protosterol

In 2007, Danishefsky and coworkers demonstrated the utility of dissolving metal reduction to introduce an angular methyl group at C5 of paecilomycine A (Scheme 7).[11] Intermediate **9**, which is obtained from a hydroxyl-directed cyclopropanation reaction, is oxidized to give the corresponding cyclopropyl ketone. Reaction of this substrate with dissolving metal reduction conditions affords cyclopentanone **10**.



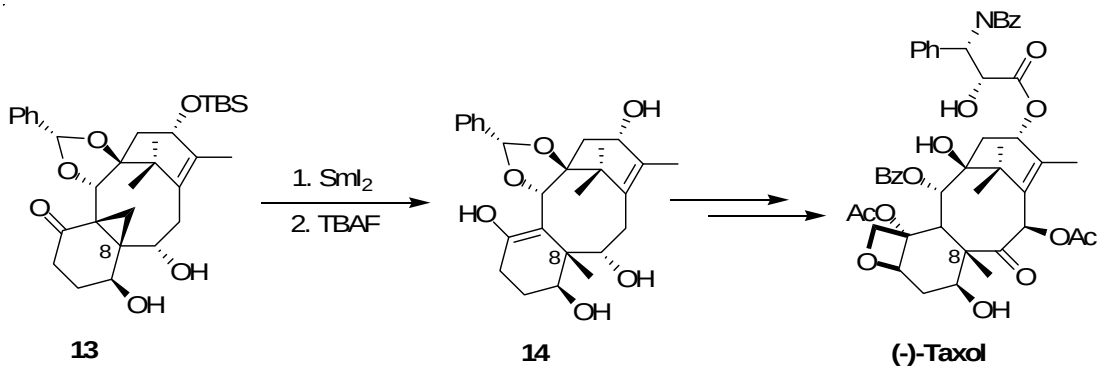
Scheme 7: Reductive Ring Opening to Install Angular Methyl Group of Paecilomycine A

In 1986, Molander and coworkers showed that C-heteroatom cleavage could be easily achieved by SmI_2 when it is vicinal to a carbonyl group.[12,13] Likewise, this methodology can be applied to the C-C bond cleavage as Pericàs et al. successfully demonstrated.[14] As shown in Scheme 8, the reductive ring opening of cyclopropyl ketone **11** with SmI_2 proceeds in 60-74% yield to afford cyclopentanone **12**. Gratifyingly, the reduction occurs with complete regioselectively by cleaving the exocyclic C-C bond of the cyclopropane ring.



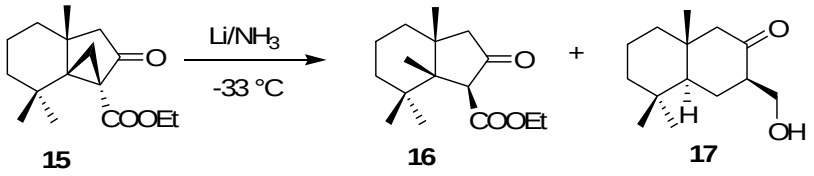
Scheme 8: SmI_2-promoted Reductive Ring Opening of Cyclopropyl Ketone

This SmI_2 protocol has also been used occasionally in total syntheses, such as in the synthesis of (-)-taxol. Kuwajima and coworkers approached the synthesis by introducing the cyclopropyl ketone **13** via cyclopropanation of enone and a subsequent treatment with SmI_2 to afford intermediate **14**, possessing an angular methyl group at C8 (Scheme 9).[15]



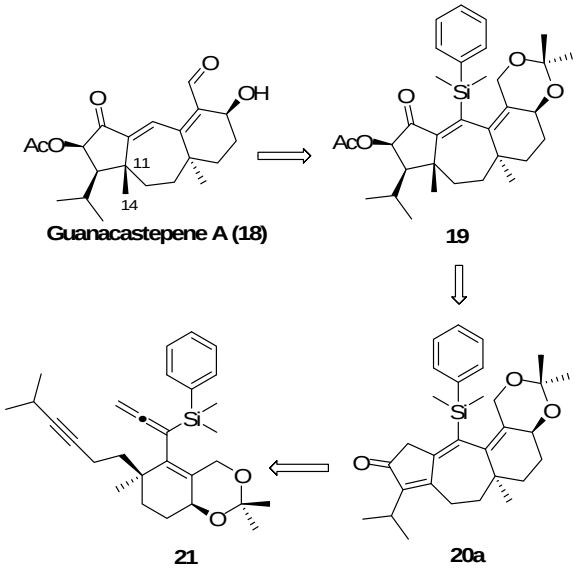
Scheme 9: Installing the C8 Methyl Group of (-)-Taxol via SmI_2 Ring Opening of Cyclopropyl Ketone

Ring expansion products can also be obtained from the dissolving metal reduction. As illustrated by Srikrishna and coworkers, the reductive ring opening of keto-ester **15** with Li/NH_3 at -33 ºC produces a 1:1 mixture of cyclopentanone **16** and cyclohexanone **17** (Scheme 10).[16] This lack of selectivity can be explained by the transfer of electrons either to the carbonyl of the ketone or to the ester. Transfer of electrons to the ketone carbonyl results in the cleavage of the external C-C bond, leading to the formation of cyclopentanone **16**. Conversely, transfer of electrons to the ester carbonyl leads to the cleavage of the internal C-C bond, and subsequently the formation of cyclohexanone **17**.



Scheme 10: Formation of 1:1 Mixture of 5- and 6-membered Rings via Reductive Opening of Cyclopropane

1.4 RETROSYNTHETIC APPROACH TO GUANACASTEPENE A



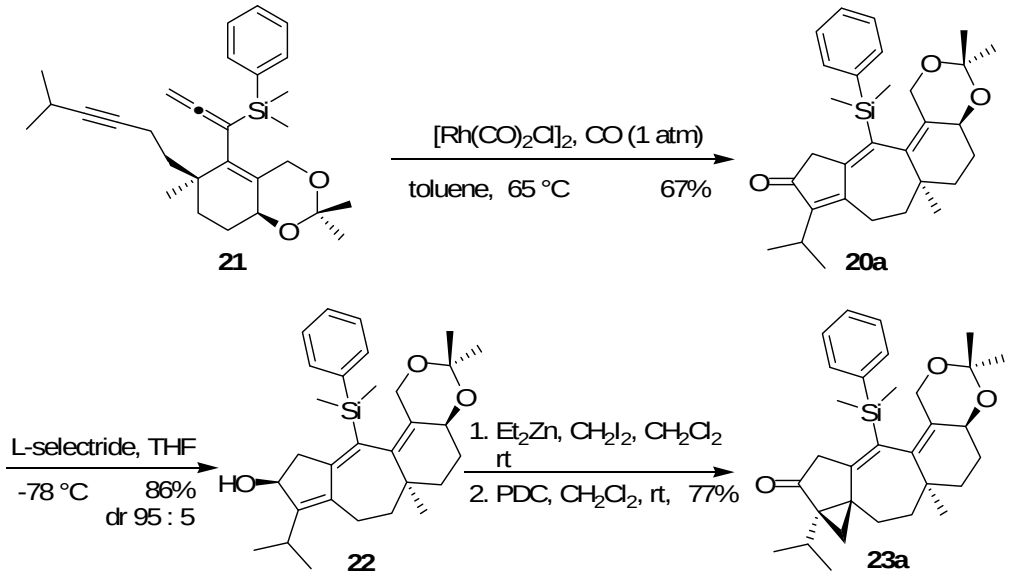
Scheme 11: Retrosynthetic Analysis of Guanacastepene A

Our interest in the reductive ring opening of a cyclopropyl ketone lies within our synthetic approach to guanacastepene A, and the installation of the angular methyl group at C11. It is envisioned that guanacastepene A (**18**) can be prepared from the advanced intermediate **19**, via a deprotection of the acetonide, a selective oxidation of the primary alcohol to the aldehyde and removal of the silyl group (Scheme 11). If successful, this route offers a strategic advantage over that reported by Danishefsky, because the bulky silyl group will prevent the undesired conjugate addition of the primary alcohol to the enone. In turn, compound **19** can be obtained from enone **20a** by a stereoselective installation of the angular methyl group at C11. Next, a hydroxylation reaction will be effected alpha to the carbonyl followed by a thermodynamically favored tautomerization and acetylation of the hydroxyl group. The tricyclic [5-7-6] core ring structure of **20a** can be obtained from allenyne **21** via a Rh(I)-catalyzed allenic cyclocarbonylation reaction, which has been previously developed in our group.

2.0 RESULTS AND DISCUSSIONS

2.1 CYCLOPROPANATION AND RING OPENING: EFFORTS TO INSTALL C-14 ANGULAR METHYL GROUP

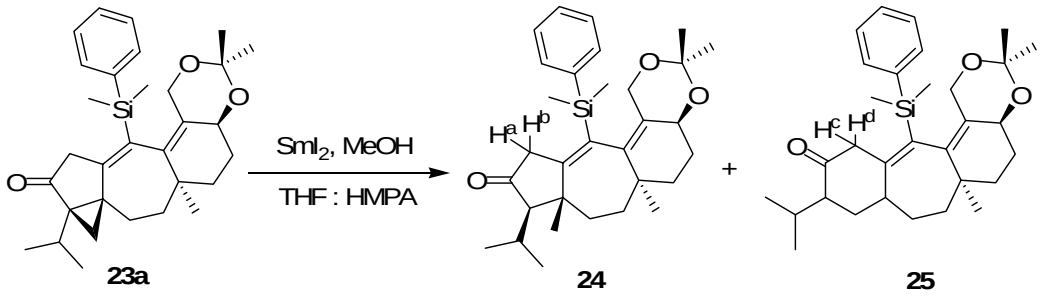
Jamie McCabe[17] successfully converted allenyne **21** to carbocycle **20a**, using a Rh(I)-catalyzed cyclocarbonylation reaction[28] developed in our group (Scheme 12). Reduction of enone **20a** with L-selectride gave allylic alcohol **22** as the major diastereomer in 95 : 5 ratio. The diastereomeric ratio was determined based upon the amount of materials isolated. The hydroxyl-directed Simmons-Smith cyclopropanation reaction allowed for chemoselective installation of the cyclopropyl ring. Subsequent oxidation of the allylic alcohol with pyridinium dichromate (PDC) afforded cyclopropyl ketone **23a** in 77% yield.



Scheme 12: Formation of Cyclopropyl Ketone 23a

With cyclopropyl ketone **23a** in hand, a reductive ring opening of the cyclopropyl group to obtain the angular methyl group of **24** was investigated. It was found that the in situ formation of samarium(II) iodide (SmI_2) from diiodomethane (CH_2I_2) and samarium metal gave a 1:1 ratio of **24** : **25** as determined by crude ^{1}H NMR (entry 1, Table 2).[17] Based upon McCabe's data, the ^{1}H NMR chemical shifts of H^a and H^b alpha to the carbonyl on cyclopentanone **24** are at 3.14 ppm and 3.23 ppm.[17] The formation of cyclohexanone **25** is also evidenced by ^{1}H NMR chemical shifts of H^c and H^d at 2.83 ppm and 3.31 ppm. Unfortunately, the ratio of the reduced products was inconsistent, producing different ratios of **24** to **25** each time the reaction was performed. In my hands, opening the cyclopropyl ring with SmI_2 generated from CH_2I_2 and samarium metal resulted in only cyclohexanone **25** (entry 2, Table 2). When SmI_2 was generated using iodine and samarium metal,[18a] only cyclohexanone **25** was obtained in 57% yield (entry 3, Table 2). Decreasing the temperature to -90 ºC also gave exclusively cyclohexanone **25** (entry 4, Table 2). As seen in entry 5, Table 2, increasing the reaction scale from 5 to 18 mg gave decomposition of the starting material.

Table 2: SmI_2-mediated Cyclopropyl Ring Opening of 23



23a 24 25

Entry	Temp (ºC)	24	:	25	Yield (%)
1[a]	-78	1		1	34[b]
2	-78	0		1	50[b]
3	-78	0		1	57[c]
4[a]	-90	0		1	Undetermined
5[a]	-78	0		0	Decomposition[d]

[a] Reactions were performed by Jamie McCabe. [b] SmI_2 reagent was prepared from $Sm_{(m)}$ and CH_2I_2. [c] SmI_2 reagent was prepared from $Sm_{(m)}$ and I_2. [d] Reaction was scaled up from 5 mg to 18 mg.

2.2 DESILYLATION AND α-OXIDATION OF ENONE 20

It was envisioned that removal of the silyl group from enone **23a** would change the conformation of this tetracyclic system and might in turn affect the regiochemistry of the cyclopropyl ring opening. This hypothesis is supported by the low energy conformers of **23a** and **26a** shown below in Figures 3 and 4. The dihedral angle of bond **a** of the cyclopropyl group and the carbonyl of **23a** is 108.4 º and for cyclopropyl ketone **26a**, 109.9 º. In addition, the endo face of the pentacyclic ring system of **26a** is more open than that of **23a** based upon the computed distance between the methylene carbon of the cyclopropane ring and the β-methyl group of the acetonide, 6.42 Å compared to 5.49 Å for compound **23a**. While, it could not be predicted how this would influence the product ratio of **24** and **25**, we predicted that it would have an effect.

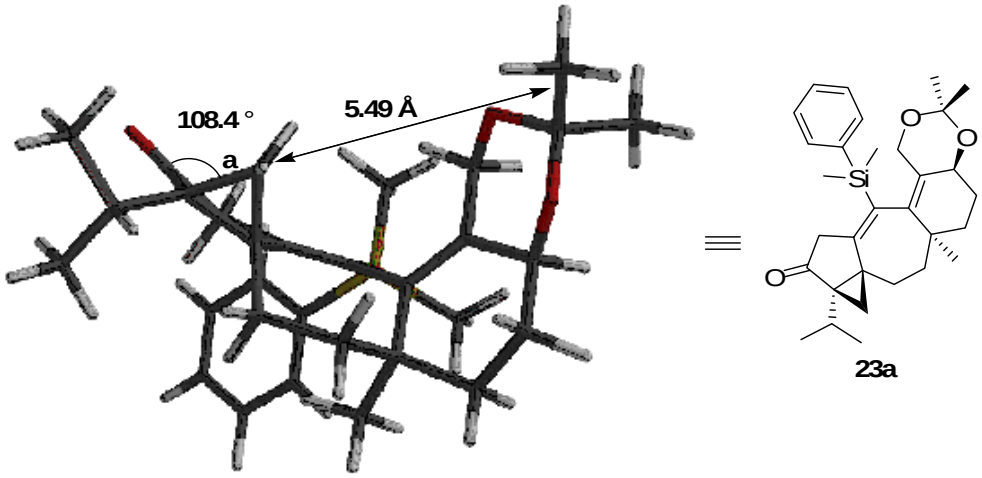


Figure 2: Geometry Optimization of Cyclopropyl Ketone 23a Using Conformer Distribution, MMFF, MacSpartan Pro

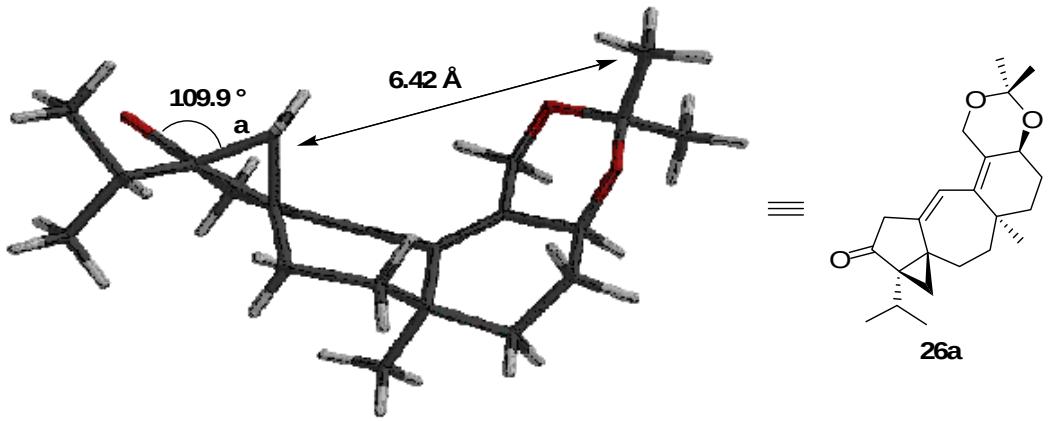
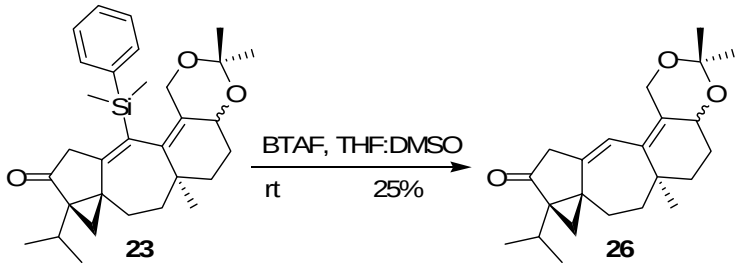


Figure 3: Geometry Optimization of Cyclopropyl Ketone 26a Using Conformer Distribution, MMFF, MacSpartan Pro

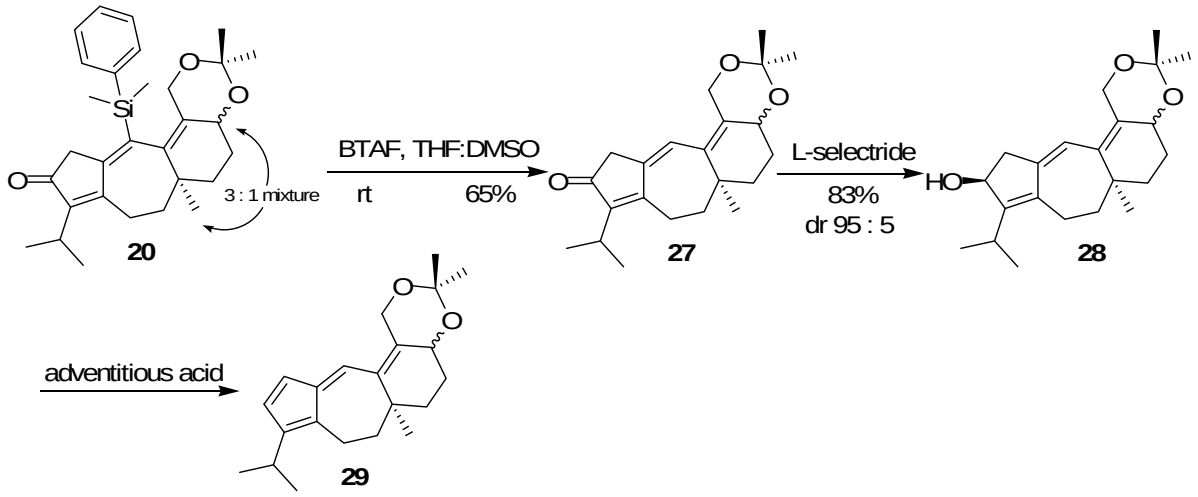
Removal of the DPS group of **23** was performed by McCabe using benzyltrimethylammonium fluoride (BTAF) in THF : DMSO (3 : 1) at room temperature. The TLC of the reaction showed multiple spots, and **26** was isolated in 25% yield (Scheme 13). The low yield for this reaction was attributed to the instability of the vinyl cyclopropane to these nucleophilic conditions.[18b, 18c]



Scheme 13: Desilylation of Cyclopropyl Ketone 23 with BTAF

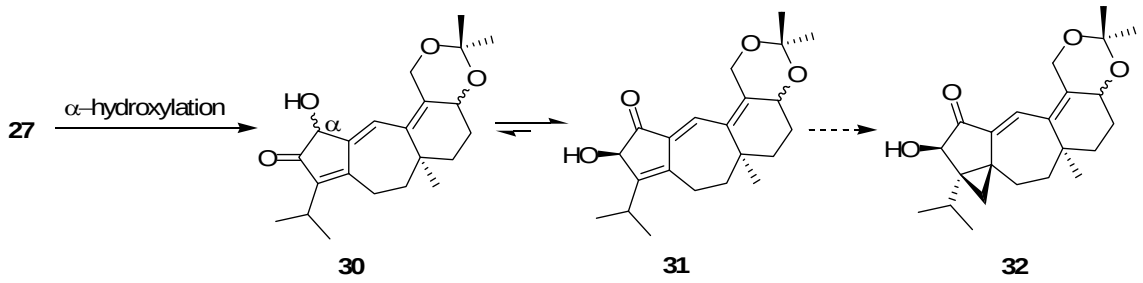
Thus, the DPS group was removed prior to installing the cyclopropyl ring. Enone **20** (dr 3 : 1) was treated with BTAF in THF : DMSO to afford the desilylated product **27** in 65% yield. However, when reduction of trienone **27** was performed with L-selectride, followed by treatment of the allylic alcohol with the Simmons-Smith reagent, fulvene **29** was obtained. This is

attributed to **28** undergoing an elimination reaction (Scheme 14). Unfortunately, due to the instability of **29**, a conclusive ^{1}H NMR could not be obtained.[21a, 21b] The suspected formation of fulvene **29** is based upon the Rf value of 0.72 (20% EtOAc/hexanes) and the color of the material (orange/yellow).



Scheme 14: Instability of Cyclopentenol 28 to Yield Suspected By-product: Fulvene 29

Next, it was thought that α-hydroxylation of **27** followed by tautomerization might afford **31**, which could be selectively cyclopropanated to obtain **32** (Scheme 15). To install the α-hydroxyl group, the Rubottom oxidation protocol was implemented.[19a, 20] Conversion of a 3 : 1 diastereomeric mixture of compound **27** to its silyl enol ether with triethylsilyltrifluoromethanesulfonate (TESOTf), followed by treatment with dimethyl dioxirane (DMDO) yielded *α*-hydroxyl enone **30** as a mixture of four diastereomers approximately in a 3 (δ 204.6 ppm) : 3 (δ 204.3 ppm) : 1 (δ 204.2 ppm) : 1 (δ 204.1 ppm) ratio based upon the integration of the carbonyl peak in the crude ^{13}C NMR spectrum.



Scheme 15: α-Hydroxylation Reaction Followed by the Tautomerization

Only one diastereomer could be separated from the mixture using HPLC and a semipreparative column (Microsorb 100-5 SI, 250 mm x 10 mm), eluting with 3% isopropanol/hexanes at 3.0 mL/min. This diastereomer had the highest retention time and was one of the major diastereomers. The stereochemistry of the hydroxyl group could not be determined. Attempts to crystallize this diastereomer using ethyl acetate (EtOAc) were not successful.

A COSY spectrum (300 MHz) of this diastereomer **30d** is shown in Figure 4. The signal at 6.21 ppm is attributed to olefinic proton H^1. The chemical shift at 4.56 ppm is assigned as H^3 due to an AB splitting pattern and a geminal coupling of 16.5 Hz (Figure 4). The signal at 4.46-4.41 ppm represents three protons of H^2, another H^3, and H^4. However, the splitting pattern of each proton is poorly resolved.

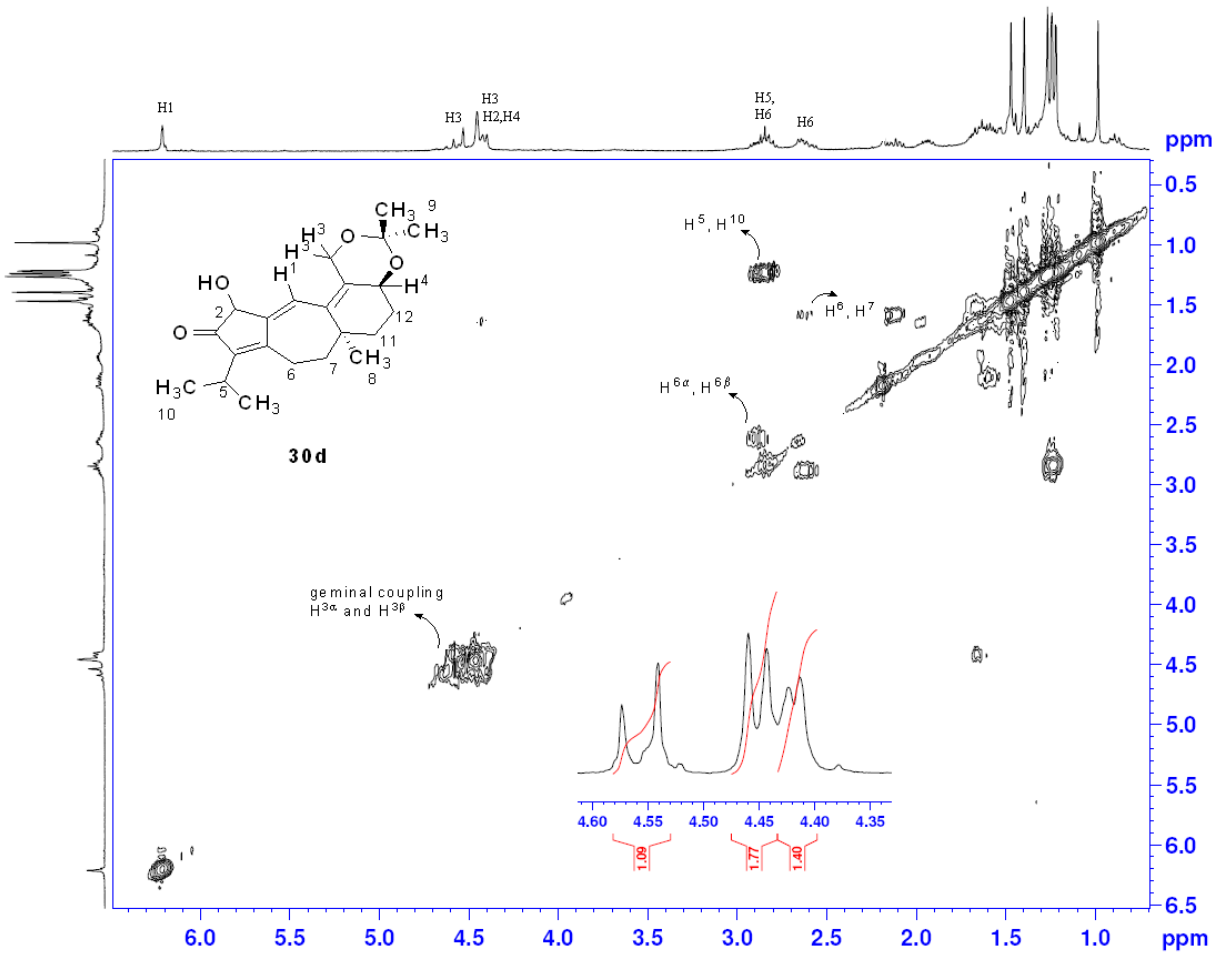


Figure 4: COSY Spectrum of α-Hydroxyl Enone 30d

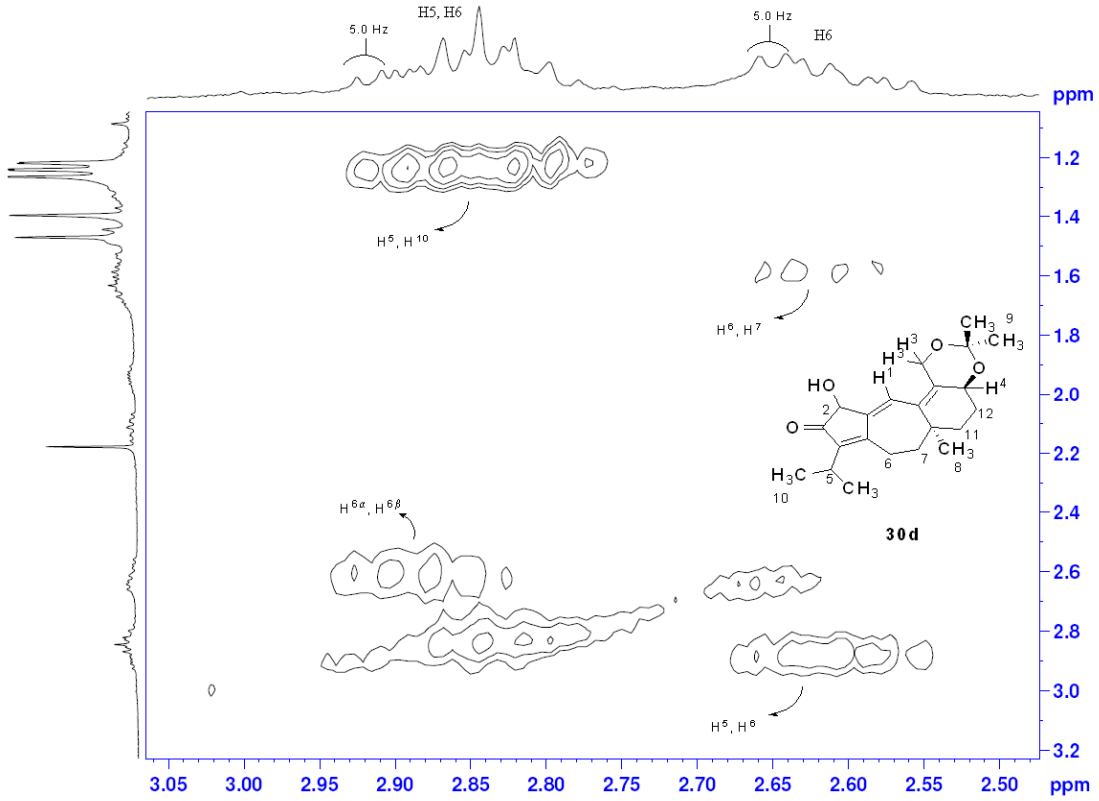


Figure 5: COSY Spectrum of Allylic Protons H^5 and H^6

The upfield signal at 2.90-2.80 ppm is attributed to H^5 and H^6. The COSY spectrum (Figure 5) shows that there is a cross peak between allylic proton H^5 and isopropyl proton H^{10} (J = 7.0 Hz). Allylic proton H^6, which overlaps with H^5, has a strong correlation with another H^6 on the COSY spectrum (Figure 5) at 2.61 ppm. This H^6 is ddd, which results from geminal coupling (14.5 Hz), and vicinal coupling with H^7 (8.5 and 5.0 Hz).

The resonance of H^7 at 1.59 ppm is assigned based upon a cross peak signal with H^6 on the COSY spectrum (Figure 4). In turn, the signal at 2.11 ppm is attributed to another H^7, which has a splitting pattern of ddd, resulting from geminal coupling (14.5 Hz) and vicinal coupling

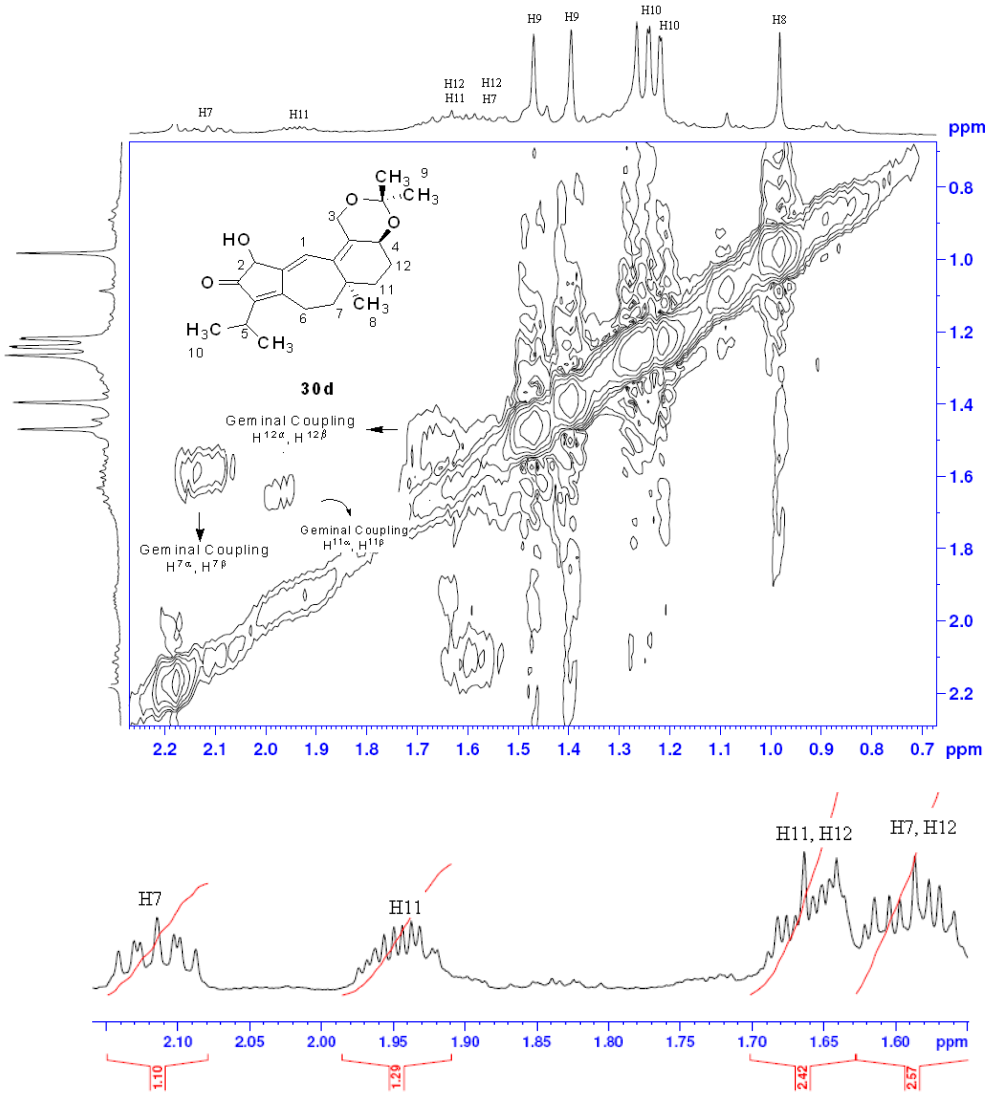


Figure 6: COSY and ^{1}H NMR Spectrum of the Upfield Region

with H^6 (8.0 and 4.8 Hz) (Figure 4). A cross peak between H^4 and H^{12} is also observed on the COSY spectrum, attributed to H^{12} resonance at 1.62-1.54 ppm. The signal at 1.69-1.63 is

assigned as another H^{12} (Figure 6). Unfortunately, due to overlapping signals, the splitting pattern of these two protons is poorly resolved.

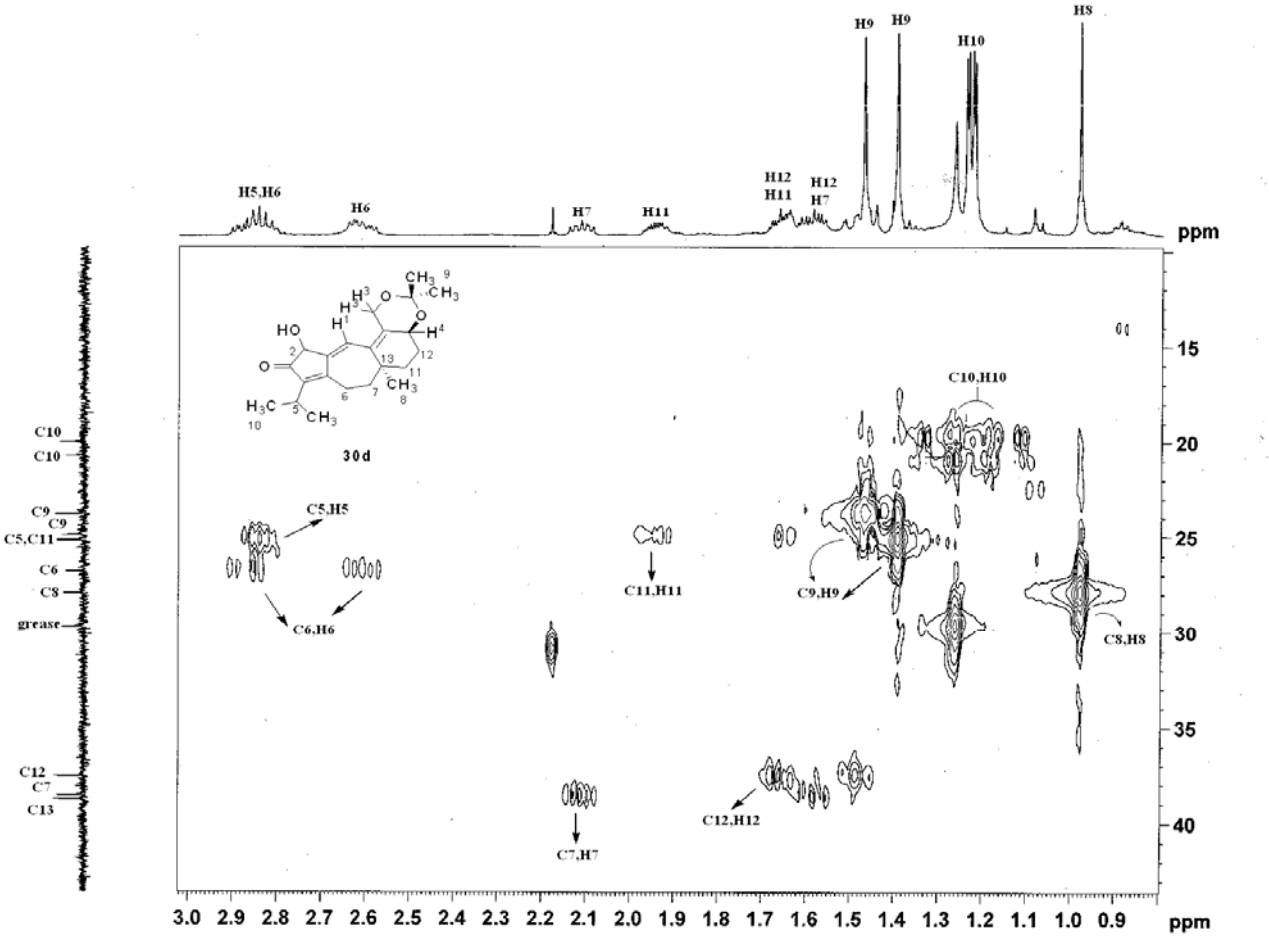
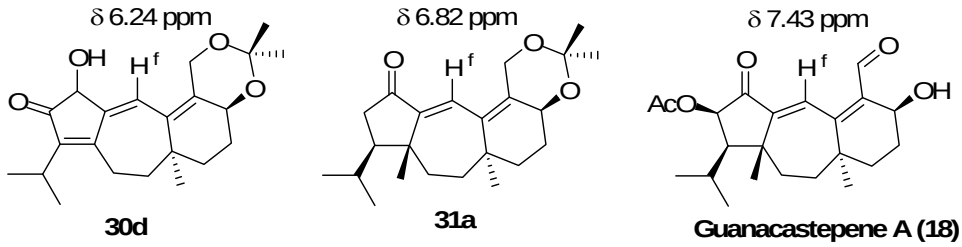


Figure 7: HMQC Spectrum of the Upfield Region

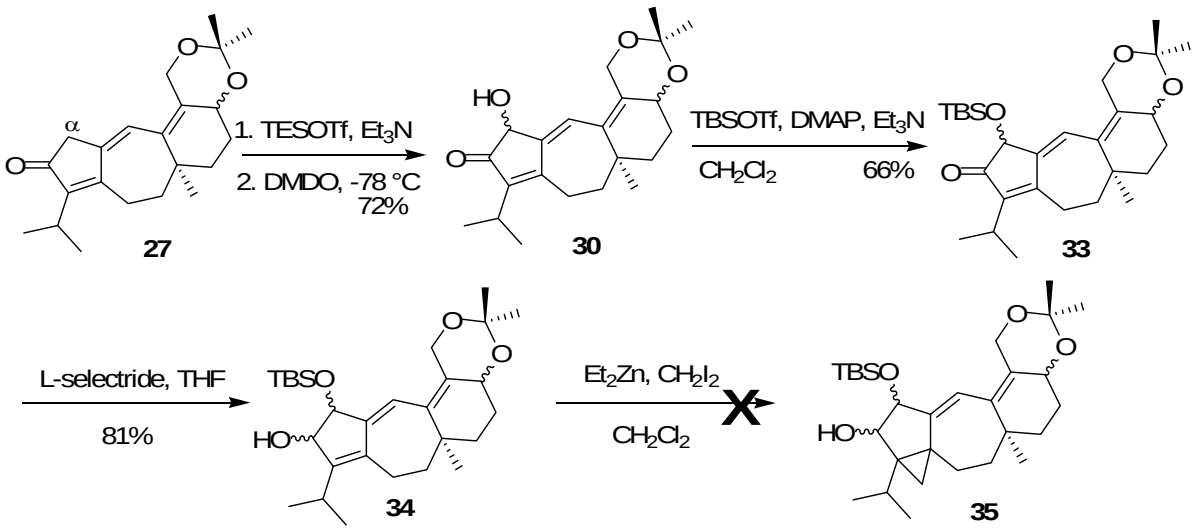
The carbonyl carbon of the cyclopentenone appears at 204.4 ppm on the ^{13}C NMR spectrum. Carbon peaks in the aliphatic region (45-15 ppm) are assigned by using COSY and HMQC experiments (Figure 7).

Unfortunately, the proposed tautomerization did not happen based upon the chemical shift of olefinic proton H^f. The ^1H NMR spectrum of **30d** shows the olefinic proton at 6.24 ppm compared to 6.82 ppm[19b] for compound **31a** and 7.43 ppm[19c] for guanacastepene A (**18**) (Scheme 16).



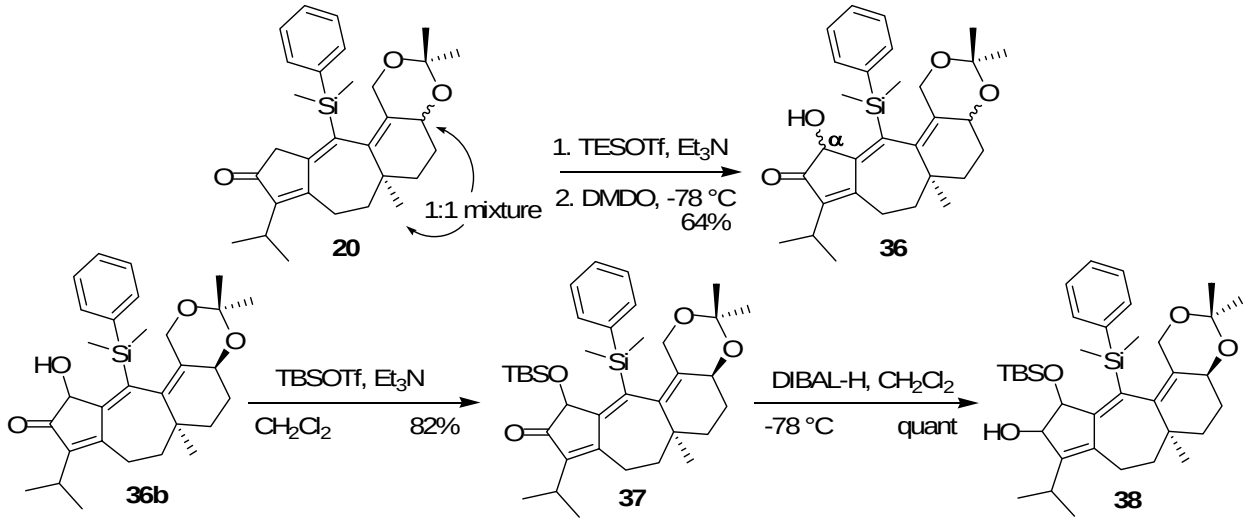
Scheme 16: Comparisons of Olefinic Proton H^f between Compound 30d, 31a, and Guanacastepene A (18)

The hydroxyl group of **30** was then reacted with *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBSOTf) to give silyl ether **33**. With **33** in hand, L-selectride reduction was successfully performed to give a mixture of alcohol **34**. Cyclopropanation of allylic alcohol **34** was performed using the Simmons-Smith condition. However, the reaction was unsuccessful (Scheme 17), and this could be attributed to the instability of compound **34** that presumably decomposed via formation of the fulvene moiety. The ^1H NMR shows multiple olefinic peaks around the chemical shift region of 6.16-5.86 ppm.



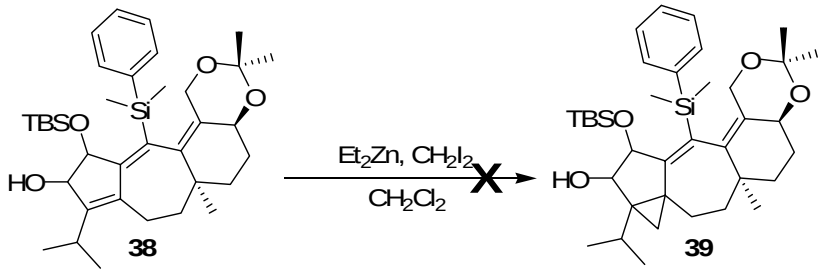
Scheme 17: Cyclopropanation Route without the Dimethylphenyl Silyl (DPS) Moiety

Next, we planned to explore the cyclopropanation reaction again by using substrate **20** (dr 1 : 1). By using Rubottom oxidation conditions, α-hydroxyl enone **36** was obtained from enone **20** in 64% yield as a mixture of four diastereomers (1 : 1 : 1 : 1), calculated by integration of the HPLC peaks. The formation of compound **36** is evidenced by ^{13}C NMR chemical shift at 71.4 ppm. At this stage, all four diastereomers were separated by HPLC using the Varian Pursuit C^8 5μ column, eluting with 30% H_2O/acetonitrile at 23 ^oC. The flow rate was 3.0 mL/min. At this stage, the relative stereochemistry of the hydroxyl group of the four diastereomers was not determined. Protection of the α-hydroxyl moiety of **36b** with TBS-OTf gave **37** in 82% yield. However, L-selectride reduction of enone **37** was unsuccessful. We then opted to perform the reduction reaction with DIBAL-H, and allylic alcohol **38** was obtained in a quantitative yield as a single diastereomer by ^1H NMR (Scheme 18).



Scheme 18: Formation of Cyclopentenol 38

With allylic alcohol **38** in hand, it was reacted to the cyclopropanation conditions using Et_2Zn : CH_2I_2 in a 1 : 2 ratio. However, this only resulted in the recovery of starting material (Scheme 19). By changing the solvent from CH_2Cl_2 to another non-polar, non-coordinating solvent, toluene,[40] again only starting material was recovered. Thus, it was concluded that the bulky TBS protecting group prevents the cyclopropanation reaction from occurring.

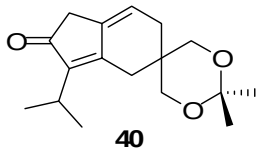


Scheme 19: The Cyclopropanation of Allylic Alcohol 38

2.3 SYNTHESIS OF A MODEL SYSTEM TO TEST RING OPENING OF CYCLOPROPYL KETONE

2.3.1 Li/NH_3-mediated Cyclopropyl Ring Opening

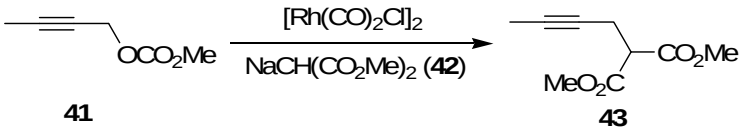
A new method to open the cyclopropyl ring was needed to complete our total synthesis of guanacastepene A. At this stage, we decided to prepare a model system to test the cyclopropyl ring opening of dienones to install the angular methyl group. Cyclocarbonylation product **40** (Scheme 20) was chosen as it could be quickly synthesized.



40

Scheme 20: Design of Model System 40 for Reductive Cleavage of Cyclopropyl Ketone

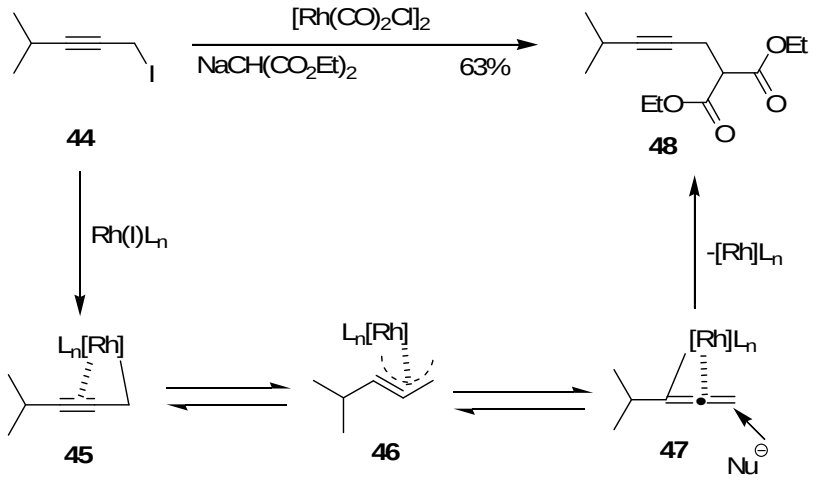
Martin and coworkers have demonstrated the utility of the catalytic Rh(I)-catalyzed alkylation reaction of propargylic carbonates **41** to give homo propargylic malonates **43** with high levels of regioselectivity (Scheme 21).[23,24,38,39] This procedure is advantageous as it avoids over alkylation, which is commonly obtained when sodium malonate **42** is solely employed.



41 **43**

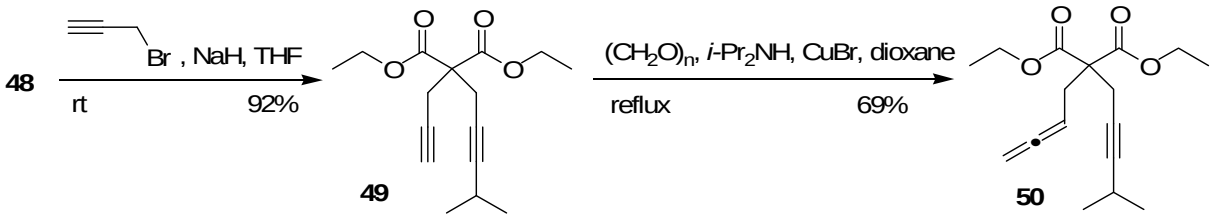
Scheme 21: Alkylation of Dimethyl Malonate Using Rh(I)-catalyzed Conditions

We began the synthesis of our model system **40** by alkylating diethyl malonate with propargylic iodide **44** using 5 mol% of $[Rh(CO)_2Cl]_2$ to obtain the monoalkylation product **48** in 63% yield (Scheme 22). Decreasing the catalyst loading below 5 mol% resulted in a minor amount of dialkylated product, which could be isolated from the monoalkylation product via column chromatography. The proposed mechanism involves an oxidative addition of the rhodium catalyst to generate the corresponding (σ+π) intermediate **45**, which can equilibrate to form the π-allyl-type complex **46**. Presumably, allenic (σ+π) intermediate **47** can be generated from complex **46**, followed by an S_N2' type addition of a nucleophile to give desired propargylic malonate **48**.



Scheme 22: Alkylation with Propargylic Iodide 44 via $[Rh(CO)_2Cl]_2$

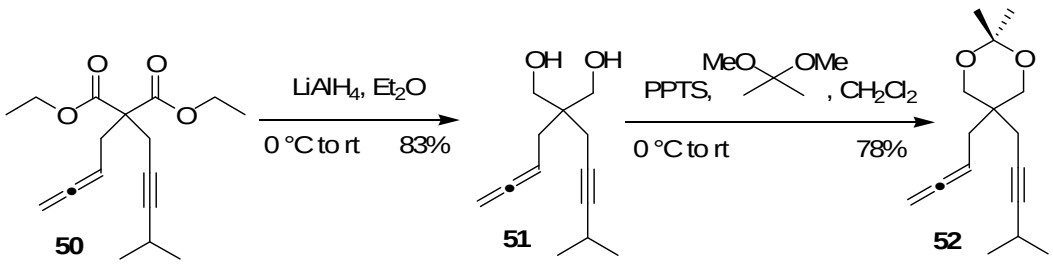
The second alkylation of propargylic malonate **48** with propargylic bromide gave us intermediate **49** in 92% yield (Scheme 23). In order to obtain allenyne **50**, Crabbé homologation procedure was followed.[25,26] When substrate **49** was reacted with paraformaldehyde $(CH_2O)_n$, diisopropylamine (*i*-Pr_2NH), and CuI in refluxing dioxane,[27] allenyne **50** was obtained in only



Scheme 23: Crabbé Homologation Reaction to Obtain Allenyne 50

39% yield. When the reaction was scaled up from 79 mg to 834 mg, the yield decreased to 21% yield. Replacing the CuI with CuBr gave allenyne **50** in 69% yield (Scheme 23).

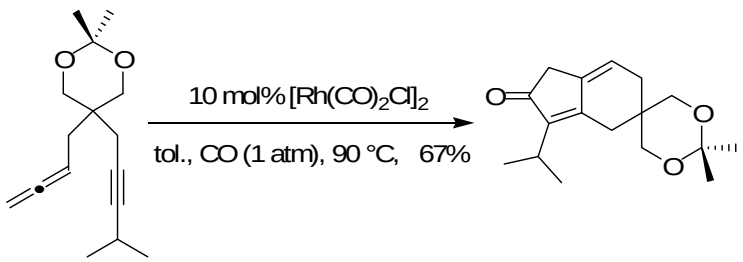
With substrate **50** in hand, lithium aluminum hydride ($LiAlH_4$) reduction of the diester gave diol **51**, which could be protected with 2,2-dimethyoxypropane to afford allenyne **52** as the precursor of the Rh(I)-catalyzed cyclocarbonylation reaction in 78% yield (Scheme 24).



Scheme 24: Formation of Allenyne 52

Allenyne **52** was reacted with 10 mol% $[Rh(CO)_2Cl]_2$, CO(g) (1 atm), and in toluene at 65 ºC to yield the cyclocarbonylation product **40** in 38% yield along with an unidentifiable mixture of compounds (entry 1, Table 4). Due to the low yield obtained, various temperatures were explored. Decreasing the reaction temperature to 50 ºC resulted in full consumption of starting material via TLC after 2.5 h (entry 2, Table 4). However, only a trace amount of **40** was isolated. When the reaction temperature was increased to 90 ºC, the reaction was complete in 6-10 min, and only the desired product **40** was obtained in 67% isolated yield (entry 3, Table 4).

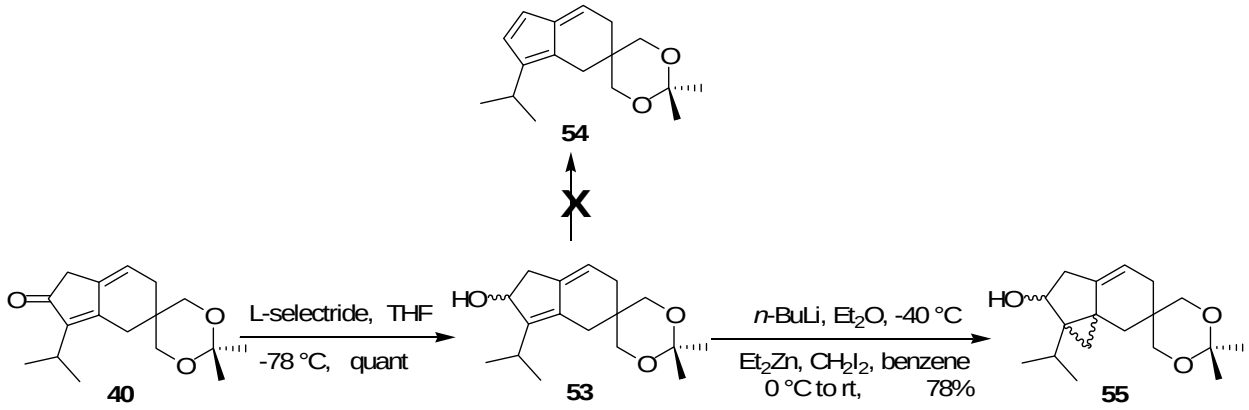
Table 3: Cyclocarbonylation Reaction at Various Temperatures



52 **40**

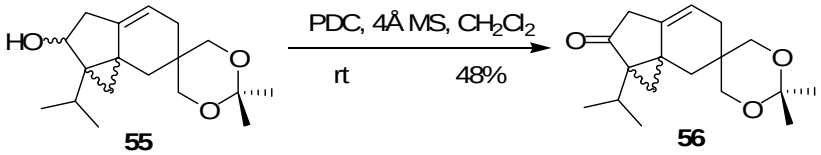
Entry	Temperature (°C)	Reaction Time	Observed Products	Yield
1	65	2.5 h	**40** and Unknown Mixture	38%
2	50	2.5 h	**40** and Unknown Mixture	Trace
3	90	6-10 min	**40**	67%

With advanced intermediate **40** in hand, reduction with L-selectride afforded allylic alcohol **53** in a quantitative yield, which could be cyclopropanated utilizing the alcohol-directed Simmons-Smith cyclopropanation reaction. Allylic alcohol **53** was then treated with *n*-BuLi (*n*-BuLi was used to prevent the elimination of allylic alcohol **53** to fulvene **54**), and added to the pre-mixed Simmons-Smith's reagent. Cyclopropyl alcohol **55** was obtained in 78% yield (Scheme 25).



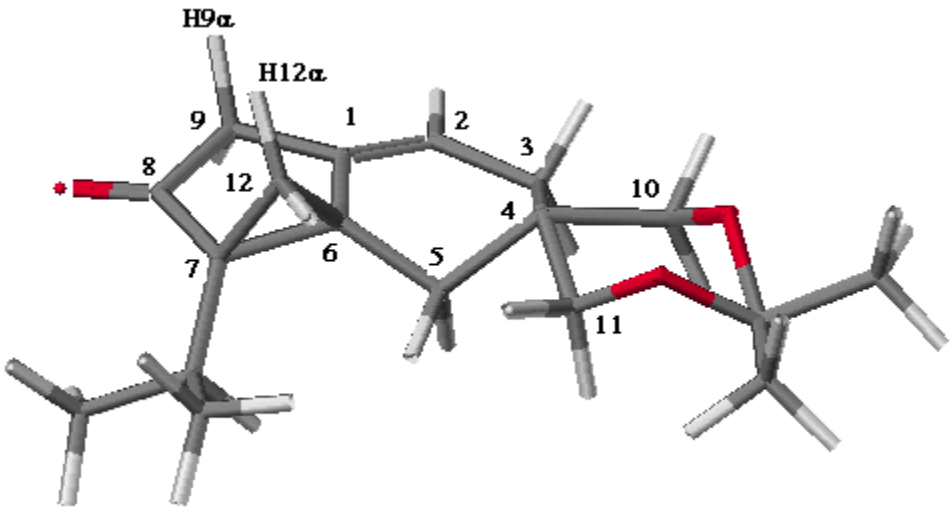
Scheme 25: Hydroxyl-directed Cyclopropanation Reaction

Next, alcohol **55** was oxidized with PDC to yield cyclopropyl ketone **56** in 48% yield (Scheme 26). When the reaction was performed with a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP), and *N*-methylmorpholine oxide (NMO), the reaction did not go to completion.



Scheme 26: PDC Oxidation, Obtaining Cyclopropyl Ketone 56

The formation of the cyclopropyl ring in **56** is evidenced by ^{1}H NMR chemical shifts, coupling constants and DEPT-135. As seen in Figure 8, $H^{9\alpha}$ is 1/2 AB at 2.58 ppm (J = 20 Hz) and $H^{9\beta}$ at 2.82 ppm (J = 20 Hz). $H^{12\beta}$ is a doublet at 1.37 ppm, resulting from geminal coupling with $H^{12\alpha}$ (4.2 Hz). The DEPT-135 spectrum shows six methylene carbons, shown in molecular modeling Figure 8.



Proton	Chemical Shift (ppm)	Splitting Pattern	*J* Values (Hz)
$H^{9\alpha}$	2.58	1/2 AB	20, 1.5
$H^{9\beta}$	2.89-2.75	1/2 AB	20
$H^{12\alpha}$	1.14	dd	4.2, 1.5
$H^{12\beta}$	1.37	d	4.2

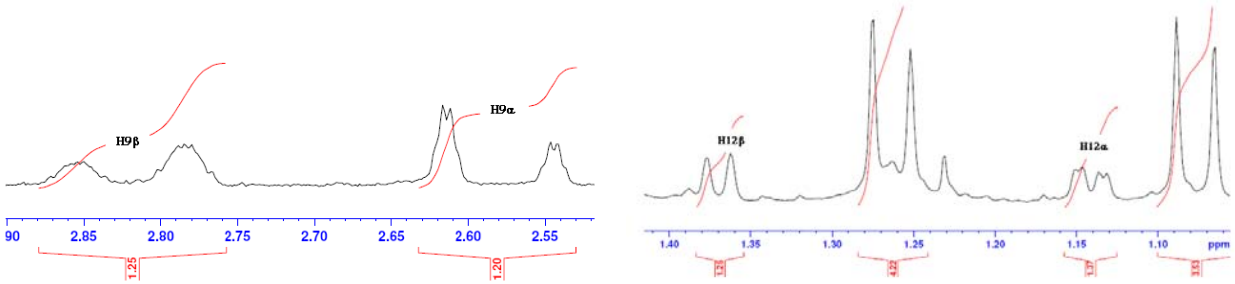
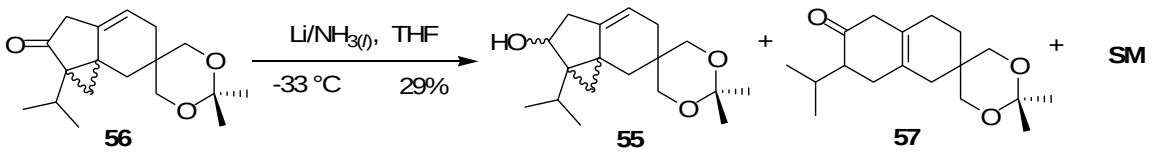


Figure 8: Minimum Energy Conformation (CAChe MM2) of Cyclopropyl Ketone 56, *J* values, and ^{1}H NMR Spectrum of the Upfield Region

Having obtained cyclopropyl ketone **56**, the cyclopropyl ring opening was then investigated. Our first attempt employed a procedure, in which substrate **56** was reacted with 13 equiv of lithium in 1 : 1 ratio of THF : NH_3 and 10 equiv of H_2O at -78 ºC. Unfortunately, the

crude NMR showed only decomposition (entry 1, Table 5). Next, a procedure developed by Danishefsky was followed where the amount of lithium was reduced to 9 equiv,[11] and the reaction was performed in refluxing liquid ammonia (-33 ºC). However, only starting material was recovered (entry 2, Table 5). The third attempt to open the cyclopropyl ring involved increasing the amount of lithium to 20 equiv in refluxing liquid ammonia. Surprisingly, three compounds were obtained in 2 : 1 : 1 ratio (ratio determined by GC-MS). After separation by silica column chromatography, the three compounds corresponded to cyclopropyl alcohol **55** : SM **56** : cyclohexenone **57**, respectively (entry 3, Table 5).

Table 4: Dissolving Metal Reduction with Li/NH_3



56 55 57

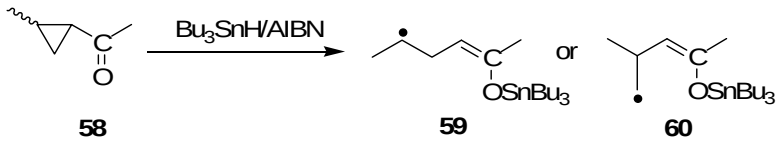
Entry	Reagent	Solvent	Temperature (ºC)	Product
1	Li (13 equiv)/NH_3, H_2O (10 equiv)	THF	-78	Decomposition
2	Li (9 equiv)/NH_3	THF	-33	-
3	Li (20 equiv)/NH_3	THF	-33	**55** (14%) + **56** (17%) + **57** (29%)

The structure of compound **57** is confirmed by DEPT-135 and ^{13}C NMR spectra. According to DEPT-135, there are seven methylene carbons and six carbons of methyl and methine combined. The ring opening to give the angular methyl group can be eliminated, and clearly the ring expansion is the primary product. However, the CH peak of the olefin does not appear on the DEPT-135 spectra. This prompted us to examine the ^{13}C NMR data closely. To

our surprise, there are two olefin resonances at δ 125.8 and 124.8 ppm. This concluded the resonance of the trisubstituted to the tetrasubstituted olefin to give us cyclohexenone **57**.

2.3.2 Bu_3SnH/AIBN-mediated Cyclopropyl Ring Opening

Pereyre and coworkers were the first to demonstrate that neat tributyltin hydride (Bu_3SnH) reagent in the presence of azoisobutyronitrile (AIBN) can be used to convert a cyclopropyl ketone **58** into reduced products **59** and **60**.[29-35] They have also reported experiments regarding the regioselectivity of the cyclopropyl ring opening of *cis*- and *trans*-2-methylcyclopropylcarbinyl radicals (Scheme 27).[34,35] For example, they found that, based on



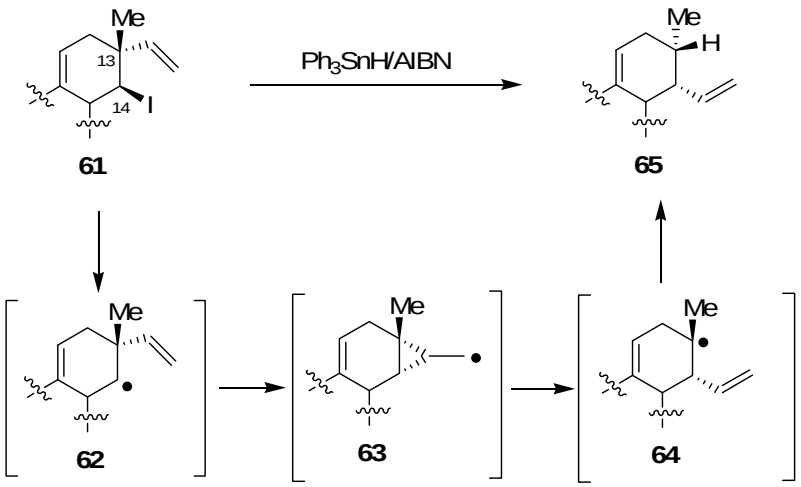
58 **59** **60**

Scheme 27: The Regioselectivity of the Cyclopropyl Ring Opening

electron spin resonance (ESR) spectroscopy, there was a preponderance for the formation of 4-methyl-butan-2-one from *trans*-2-methylcyclopropylmethyl ketone as a result of the primary alkyl radical **60**. In contrast, analysis of the *cis*-counterpart gave hexan-2-one derived from the secondary alkyl radical **59**.[34]

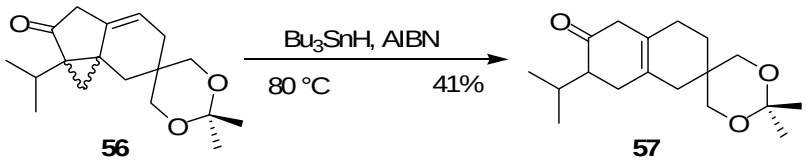
As shown in Scheme 28, Danishefsky and coworkers have also demonstrated that treatment of iodide **61** with triphenyltin hydride in the presence of AIBN gave rise to compound **65**, resulting from a migration of the vinyl group from C-13 to C-14.[36,37] A reasonable explanation involves reduction of iodide at C-14 to give homoallylic radical **62**, which then cyclizes to form cyclopropylcarbinyl radical **63**. Upon electronic rearrangement, the more stable

homoallylic radical **64** is produced, which serves as a locus for hydrogen atom abstraction to afford compound **65**.



Scheme 28: Proposed Radical Mechanism for a Vinyl Migration

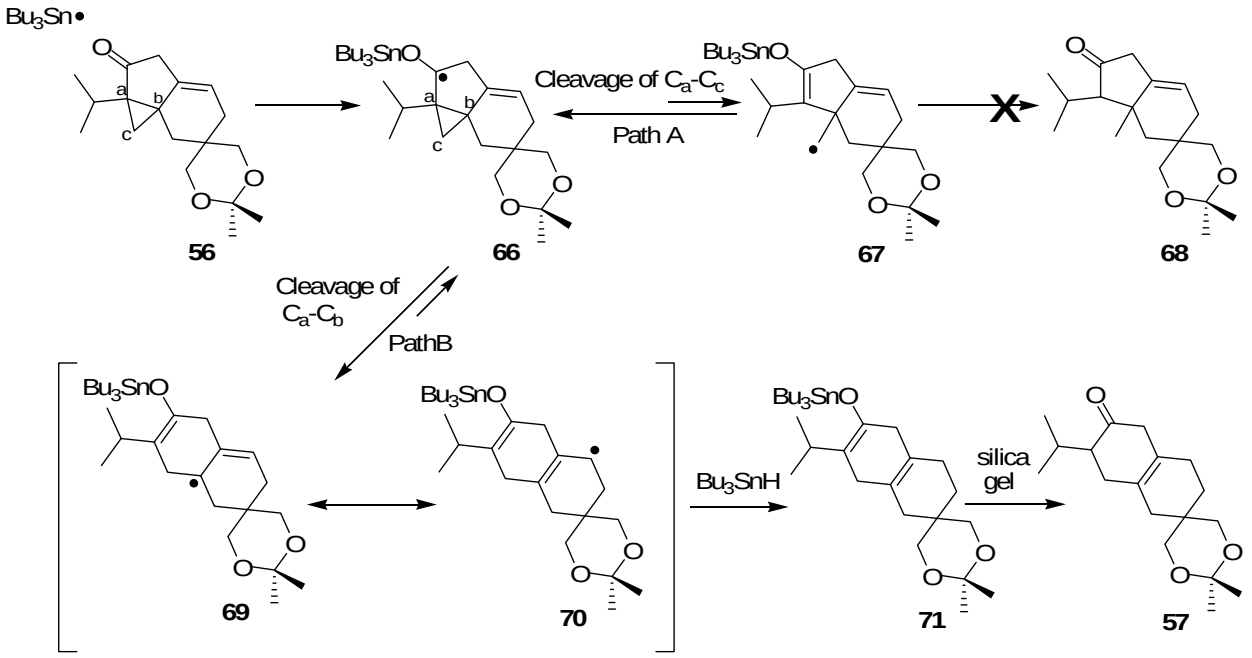
Using conditions developed by Pereyre and Danishefsky, cyclopropyl ketone **56** was reacted with AIBN in neat Bu_3SnH at 80 ºC, which only produced cyclohexenone **57** in 41% yield (Scheme 29).



Scheme 29: Bu_3SnH/AIBN-mediated Cyclopropyl Ring Opening

The proposed mechanism involves the formation of radical species **66**. At this junction, there are two possible pathways in which the radical can react. Path A produces a primary alkyl radical species **67**, which can be trapped with excess of Bu_3SnH to form our desired angular methyl functionality **68**. Ring opening of the cyclopropane by path B gives a more stable tertiary

allylic radical **69**, which is a resonance structure of **70**. This radical **70** serves as a locus for hydrogen atom abstraction to afford compound **71** that eventually gives rise to cyclohexenone **57** (Scheme 30).



Scheme 30: Conversion of Cyclopropyl Ketone 56 to Cyclohexenone 57

3.0 CONCLUSIONS

In summary, we have successfully demonstrated the formation of a tricyclic [5-7-6] ring structure of guancastepene A via a Rh(I)-catalyzed cyclocarbonylation reaction. However, attempts to install the angular methyl group at C11 via the cyclopropyl ring opening with SmI_2 give the ring-expansion product exclusively.

Different reagents were investigated for the cyclopropyl ring opening, such as dissolving metal reduction (Li/NH_3) and Bu_3SnH/AIBN on model system **40** (Scheme 19). The installation of the cyclopropyl ring could be achieved via the hydroxyl-directed Simmons-Smith cyclopropanation reaction. Unfortunately, employing both reducing protocols only resulted in the formation of cyclohexenone **57**.

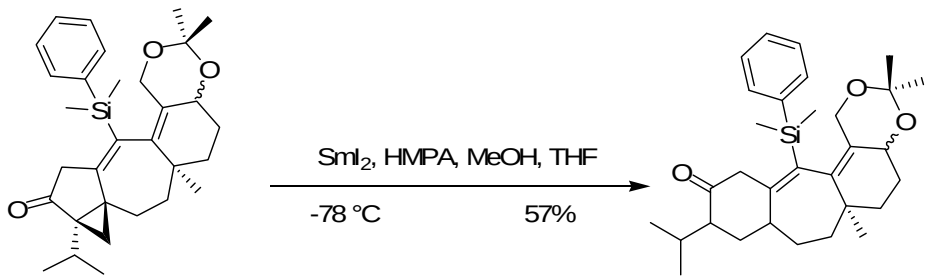
4.0 EXPERIMENTAL

General

All reactions were performed using syringe-septum cap technique under a nitrogen atmosphere, and glassware was flame-dried prior to use. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, and Acros Organics and used as received, unless otherwise specified. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (DCM) were purified with alumina using the Sol-Tek ST-002 solvent purification system. Benzene was freshly distilled from Na(m) and benzophenone under nitrogen. Toluene, triethylamine (TEA), and diisopropylamine were freshly distilled from CaH_2 under nitrogen prior to use. Triethylsilyltrifluoromethanesulfonate (TES-OTf) and tributyldimethylsilyltrifluoromethanesulfonate (TBS-OTf) were distilled under vacuum (4 torr) and stored in septum capped container on bench top. Copper (I) bromide (CuBr) was purified by following the procedure in *Purification of Laboratory Chemicals* by D.D. Perrin and W.L.F. Armarego. Anhydrous methanol was purchased from Aldrich in 100 ml bottle.

Purification of products by flash chromatography was performed using silica gel (32-63 μm particle size, 60 Å pore size) purchased from SAI. TLC analyses were performed on EM Science Silica Gel 60 F254 plates (250 μm thickness). HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5 μm packing, 250 mm x 10 mm) or Varian Pursuit C8 column (5 μm packing, 250 mm x 10 mm).

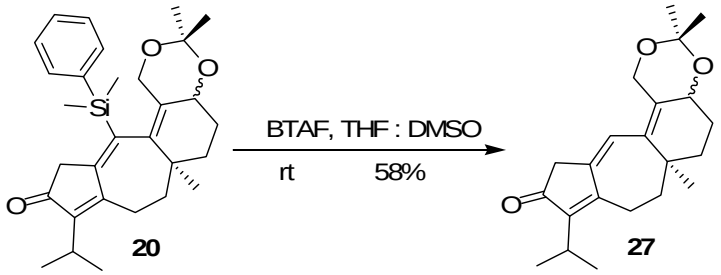
All ^{1}H and ^{13}C spectra were obtained on Bruker Avance 300 MHz, and Bruker Avance DRX 500 MHz instruments, and chemical shift (δ) was reported relative to residual peak of $CDCl_3$ (7.27 ppm) or C_6D_6 (7.15 ppm). All NMR spectra were obtained at room temperature and tabulated as follow: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, qt = quintet, b = broad, dd = doublet of doublet, dt = doublet of triplet, sept = septet of triplet, m = multiplet, etc), coupling constant(s), and number of protons. All IR spectra were obtained from a Nicolet Avatar E.S.P 360 FT-IR. Mass spectra were obtained on a high resolution mass spectrometer using electron impact ionization or ESI Biosystem time of flight.



23a **25**

Cyclohexanone (25): A solution of cyclopropyl ketone **23a** (in a 2 : 1 diastereomeric mixture, 24 mg, 0.050 mmol), MeOH (10 μL, 0.24 mmol), and HMPA (0.17 mL, 1.0 mmol) in THF (2.0 mL) was degassed by bubbling N_2 throughout the solution for 5 min and cooled to -78 ºC. A solution of SmI_2[41] (2.4 mL of 0.1 M concentration in THF, 0.24 mmol) was then added dropwise via syringe to the reaction mixture until the solution remained a deep blue color or purple. After 1 h at -78 ºC, the color of the reaction mixture was pale orange. A saturated NH_4Cl solution was then added, and the reaction mixture was warmed to room temperature then diluted with Et_2O. The aqueous layer was separated, and the organic layer was extracted with

Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, eluting with 10% EtOAc/hexanes to entitle compound **25** (14 mg, 57%) as a pale-yellow oil. ^1H NMR (300 MHz, $CDCl_3$) with trace of silyl impurity: δ 7.58-7.51 (m, 2H), 7.39-7.32 (m, 3H), 4.38-4.33 (m, 1H), 4.29-4.20 (m, 1H), 4.17-4.08 (m, 1H), 3.33 (1/2 ABd, *J* = 14.1 Hz, 0.3H), 3.31 (1/2 ABd, *J* = 14.4 Hz, 1H), 2.87 (1/2 ABd, *J* = 14.1 Hz, 0.3H), 2.83 (1/2 ABd, *J* = 14.1 Hz, 1H), 2.69-2.47 (m, 1H), 2.28-2.16 (m, 2H), 1.97 (ddd, *J* = 12.9, 6.6, 3.6 Hz, 1H), 1.88-1.80 (m, 1H), 1.72-1.64 (m, 2H), 1.62-1.56 (m, 2H), 1.53 (s, 1H), 1.49 (s, 3H), 1.45 (s, 1H), 1.38 (s, 3H), 1.12 (s, 1H), 1.10 (s, 3H), 0.91 (d, *J* = 6.6 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.3 Hz, 1H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.59 (s, 3H), 0.53 (s, 1H), 0.35 (s, 1H), 0.34 (s, 3H).



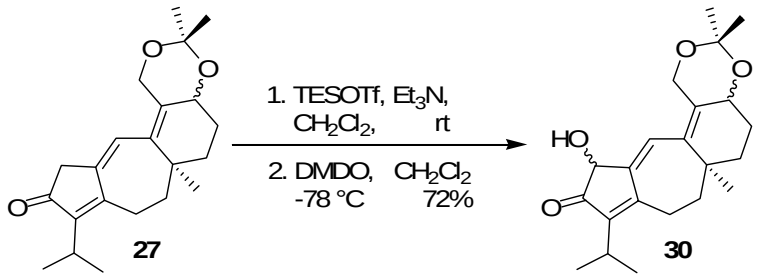
20 **27**

(R,3aZ)-6,7,8,8a,9,10-Hexahydro-1-isopropyl-5,6-dioxane-8a-methyl-benzo[f]azulen-2(3H)-one (27): Enone **20** (in a 3:1 diastereomeric mixture, 128 mg, 0.269 mmol) in THF (3.50 mL) and DMSO (1.20 mL) at room temperature was added benzyltrimethylammonium fluoride hydrate (91.0 mg, 0.537 mmol) in one portion. The reaction mixture was stirred for 45 min then diluted with a saturated NH_4Cl solution and Et_2O. The aqueous layer was separated and extracted with Et_2O (2x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel,

eluting with 20% EtOAc/hexanes to give compound **27** (53 mg, 58%) as a yellow oil in 3:1 diastereomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (s, 0.4H), 5.92 (s, 1H), 4.57-4.32 (m, 4H), 2.97 (s, 3H), 2.89-2.77 (m, 3H), 2.74-2.57 (m, 2H), 2.09-2.01 (m, 1H), 1.97-1.87 (m, 2H), 1.80-1.69 (m, 2H), 1.67-1.48 (m, 6H), 1.45-1.44 (m, 5H), 1.39 (s, 1.5H), 1.37 (s, 3H), 1.21 (d, J = 7.2 Hz, 9H), 1.11 (s, 1H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3*, 204.0**, 165.4*, 165.0**, 149.2**, 148.8*, 137.2 (2C), 136.1**, 135.9*, 135.0*, 134.8**, 120.6*, 120.1**, 99.8*, 99.6**, 67.3**, 66.9*, 60.9*, 60.6**, 42.7**, 41.6*, 38.9 (2C), 38.6*, 38.5**, 37.9, 37.4, 36.7, 28.1, 26.3, 25.4, 25.3, 25.2 (2C), 25.1, 25.0*, 24.3, 23.8*, 20.3, 20.3, 20.0; MS (API-ES) *m/z* (%) 365 ([M+Na]$^+$, 100); HRMS calcd for $C_{22}H_{30}O_3Na$: *m/z* [M+Na]$^+$ 365.2093; found: 365.2078.

*diastereomer 1; **diastereomer 2

General procedure A for preparation of *α*-hydroxy enone.



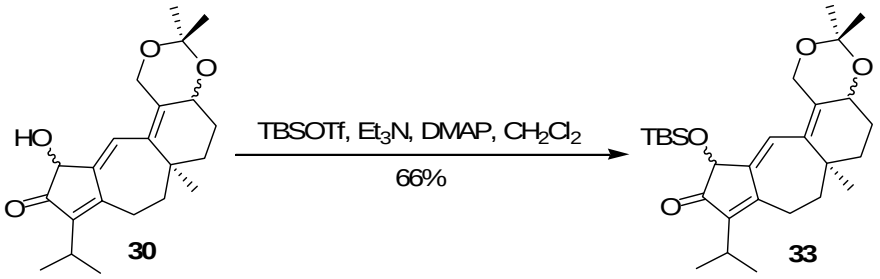
(R,3aZ)-6,7,8,8a,9,10-Hexahydro-3-hydroxy-1-isopropyl-5,6-dioxane-8a-methyl-benzo[f]azulen-2(3H)-one (30): To a solution of enone **27** (as a 3:1 diastereomeric mixture, 17 mg, 0.050 mmol) in CH_2Cl_2 (2.5 mL) at room temperature was added Et_3N (70 μL, 0.50 mmol) followed by triethylsilyltrifluoromethanesulfonate (60 μL, 0.24 mmol) dropwise via syringe. The reaction mixture turned a yellow/orange color, and after 5 min the reaction mixture was

quenched with a saturated $NaHCO_3$ solution and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (2x), and the combined organic layers were dried over Na_2SO_4, filtered, and the solvent removed under vacuum to obtain an orange oil. This crude silylenol ether (23 mg, 0.050 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to -78 ºC. DMDO (0.84 mL of 0.09 M concentration in acetone, 0.075 mmol) was added dropwise via syringe. The orange color disappeared, and after 10-15 min the reaction mixture was quenched with dimethyl sulfide (50 μL, 0.75 mmol), and stirred for an additional 15 min. The reaction mixture was warmed to room temperature and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, eluting with 20% EtOAc/hexanes to afford compound **30** (13 mg, 72%) as a yellow oil. Each diastereomer was separated by HPLC (Microsorb 100-5 SI, 250 mm x 10 mm, 20 μL, 23 ºC, 3% isopropanol/hexanes, flow rate = 3.0 ml/min.); ^{1}H NMR (300 MHz, $CDCl_3$, R_t = 13.7 min and 14.1 min): δ 6.26 (s, 0.6H), 6.21 (s, 1H), 4.64-4.53 (m, 2H), 4.44-4.36 (m, 5H), 2.87-2.70 (m, 7H), 2.05 (ddd, *J* = 14.4, 10.8, 4.5 Hz, 1H), 1.98-1.91 (m, 2H), 1.77-1.65 (m, 5H), 1.62-1.52 (m, 6H), 1.44 (s, 6H), 1.40 (s, 2H), 1.35 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.15 (s, 2H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, R_t = 13.7 min and 14.1 min): δ 204.2*, 204.1**, 164.6**, 164.3*, 144.6*, 144.4**, 138.1, 137.9, 137.8, 137.7, 134.8*, 133.7**, 120.3*, 120.0**, 100.0*, 99.6**, 73.6**, 73.3*, 67.2**, 66.6*, 60.9*, 60.5**, 38.3, 38.1, 38.0, 37.6, 37.2, 36.6, 26.3, 25.4, 25.0, 24.9, 24.7, 24.6, 24.2, 23.7, 20.4, 19.8; IR(thin film): 3410, 2934, 2870, 1696 cm^{-1}; MS (API-ES) *m/z* (%) 381 ([M+Na]$^+$, 100); HRMS calcd for $C_{22}H_{30}O_4Na$: *m/z* [M+Na]$^+$ 381.2042; found: 381.2059.

*diastereomer 1; **diastereomer 2

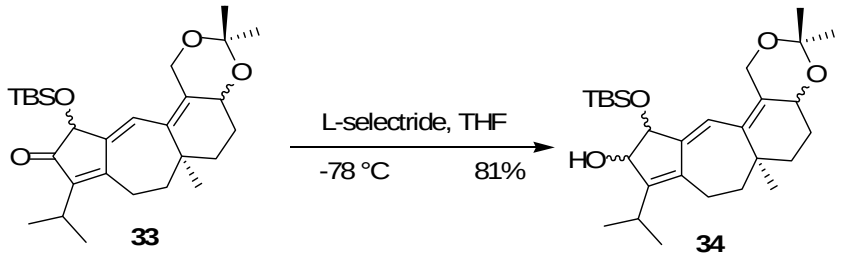
^{1}H NMR (300 MHz, $CDCl_3$, R_t = 15.1 min and 16.5 min): δ 6.21 (s, 1H), 6.19 (s, 0.6H), 4.68-4.62 (m, 1H), 4.58-4.51 (m, 2H), 4.46-4.36 (m, 5H), 2.88-2.69 (m, 7H), 2.09-1.98 (m, 2H), 1.96-1.88 (m, 2H), 1.83 (dd, *J* = 8.7, 6.3 Hz, 1H), 1.78-1.52 (m, 13H), 1.44 (s, 6H), 1.40 (s, 3H), 1.36 (s, 3H), 1.26 (s, 5H), 1.22-1.21 (m, 6H), 1.20 (s, 2H), 1.08 (s, 6H).

^{1}H NMR (500 MHz, $CDCl_3$, R_t = 16.5 min, **30d**): δ 6.21 (s, 1H), 4.56 (1/2 ABd, *J* = 16.5 Hz, 1H), 4.46-4.41 (m, 2H), 4.43 (1/2 ABd, *J* = 15.0 Hz), 2.90-2.80 (m, 2H), 2.61 (ddd, *J* = 15.5, 8.0, 5.0 Hz, 1H), 2.11 (ddd, *J* = 13.5, 7.5, 4.8 Hz, 1H), 1.94 (ddd, *J* = 12.0, 5.5, 2.5 Hz, 1H), 1.69-1.63 (m, 1H), 1.66 (ddd, *J* = 9.5, 6.5, 3.5 Hz, 1H), 1.62-1.54 (m, 1H), 1.59 (ddd, *J* = 14.0, 9.0, 5.0, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, R_t = 16.5 min): δ 204.4, 164.9, 144.4, 139.6, 137.4, 134.6, 120.1, 99.9, 73.8, 67.0, 60.9, 38.8, 38.6, 37.6, 27.9, 26.8, 25.2, 25.1, 24.9, 23.8, 20.7, 20.0.



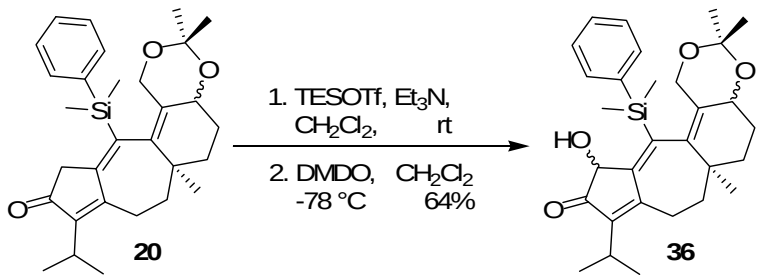
(R,3aZ)-6,7,8,8a,9,10-Hexahydro-3-(tert-butyldimethylsilyl)ether-1-isopropyl-5,6-dioxane-8a-methyl-benzo[f]azulen-2(3H)-one (33): To a solution of α-hydroxyl enone **30** (in a 1 : 1 : 1 : 1 diastereomeric ratio, 29 mg, 0.080 mmol) in CH_2Cl_2 (2.0 mL) at 0 ºC was added *N,N*-4-dimethylaminopyridine (1.0 mg, 0.0080 mmol), Et_3N (40 μL, 0.32 mmol) followed by tributyldimethylsilyltrifluoromethanesulfonate (37 μL, 0.16 mmol) dropwise via syringe. The reaction mixture was stirred for 15 min then quenched with a saturated $NaHCO_3$ solution and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (2x), and the

combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by chromatography on silica gel, eluting with 10% EtOAc/hexanes to give compound **33** (25 mg, 66%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.44-6.40 (m, 1H), 4.71-4.59 (m, 3H), 4.53-4.36 (m, 3H), 2.95-2.85 (m, 1H), 2.72-2.53 (m, 2H), 2.10-1.86 (m, 2H), 1.83-1.53 (m, 8H), 1.44 (s, 4H), 1.39 (s, 2H), 1.36 (s, 1H), 1.35 (s, 1H), 1.23-1.20 (m, 8H), 1.08 (s, 1H), 1.06 (s, 1H), 1.03 (s, 1H), 0.98 (s, 3H), 0.93 (s, 9H), 0.24 (s, 2.5H), 0.22 (s, 3.5H); MS (API-ES) *m/z* (%) 495 ($[M+Na]^+$, 32); HRMS calcd for $C_{28}H_{44}O_4SiNa$: *m/z* $[M+Na]^+$ 495.2907; found: 495.2894.



(R,3aZ)-6,7,8,8a,9,10-Hexahydro-3-(tert-butyldimethylsilyl)ether-1-isopropyl-5,6-dioxane-8a-methyl-benzo[f]azulen-2-ol (34): To a solution of enone **33** (in a 1 : 1 : 2 : 2 diastereomeric ratio, 6.0 mg, 0.013 mmol) in THF (0.1 mL) at -78 ºC was added L-selectride (30 µL of a 1.0 M solution in THF , 0.026 mmol) dropwise via syringe. The reaction mixture was stirred for 45 min then placed in an ice-bath, and quenched with 10 µL of H_2O followed by 30 µL of 3N NaOH and 30 µL of 30% H_2O_2. The reaction mixture was stirred at rt for 30 min, and diluted with Et_2O. The aqueous layer was separated and extracted with Et_2O (2x), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by chromatography on silica gel, eluting with 10% EtOAc/hexanes to

afford compound **34** (5.0 mg, 81%) as a pale yellow oil. ^{1}H NMR (300 MHz, C_6D_6) with trace of impurity of another diastereomer: δ 5.96-5.87 (m, 1H), 4.84 (dd, *J* = 4.2, 2.1 Hz, 1H), 4.75-4.59 (m, 2H), 4.55-4.42 (m, 4H), 2.80-2.69 (m, 2H), 2.41-2.33 (m, 1H), 2.28-2.15 (m, 1H), 1.91-1.80 (m, 3H), 1.75 (dd, *J* = 14.4, 4.8, 1H), 1.47 (s, 2H), 1.44 (s, 5H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.16 (s, 2H), 1.14 (s, 2H), 1.08 (s, 1H), 1.06 (s, 2H), 1.03 (s, 1H), 0.10 (s, 1H), 0.93-0.91 (m, 3H), 0.89-0.88 (m, 9H), 0.45 (s, 1H), 0.05-0.03 (m, 6H); IR(thin film): 3527, 2930, 2856, 1463 cm^{-1}; MS (API-ES) *m/z* (%) 497 ([M+Na]$^+$, 71); HRMS calcd for $C_{28}H_{46}O_4SiNa$: *m/z* [M+Na]$^+$ 497.3063; found: 497.3026.



(R,3aZ)-6,7,8,8a,9,10-Hexahydro-3-hydroxy-1-isopropyl-5,6-dioxane-8a-methyl-4-(dimethyl(phenyl)silyl)benzo[f]azulen-2(3H)-one (36): Prepared by following the general procedure A, using **20** (in 1 : 1 diastereomeric ratio, 176 mg, 0.369 mmol), CH_2Cl_2 (15.0 mL), Et_3N (0.500 mL, 3.69 mmol), triethylsilyltrifluoromethanesulfonate (0.400 mL, 1.85 mmol). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under vacuum to obtain an orange oil as a crude residue.

Prepared by following the general procedure A, using crude silylenol ether (218 mg, 0.369 mmol), CH_2Cl_2 (30.0 mL), DMDO (7.00 mL of 0.08 M concentration in acetone, 0.550

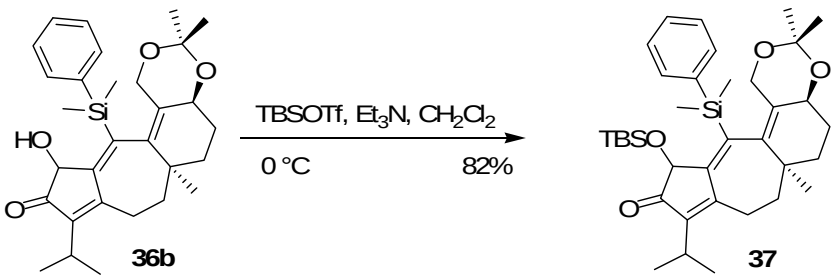
mmol). After 10-15 min the reaction was quenched with dimethyl sulfide (0.400 mL, 5.50 mmol), and stirred for 15 min. The reaction mixture was warmed to room temperature, and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, eluting with 10% EtOAc/hexanes to afford compound **36** (116 mg, 64%) as a white solid and a mixture of four diastereomers. The diastereomers were separated by HPLC (Varian Pursuit C^8 5μ column, 250 mm x 100 mm, 50 μL, 23 ºC, 30% H_2O/acetonitrile, flow rate = 3.0 ml/min.); ^{1}H NMR (300 MHz, $CDCl_3$, R_t = 16.5 min, **36a**): δ 7.77-7.74 (m, 2H), 7.39-7.37 (m, 3H), 4.43-4.37 (m, 1H), 4.36 (dd, *J* = 14.7, 0.6 Hz, 1H), 4.14 (dd, *J* = 15.3, 0.6 Hz, 1H), 3.95 (d, *J* = 3.0 Hz, 1H), 2.73 (qt, *J* = 6.9 Hz, 1H), 2.66 (dt, *J* = 14.4, 3.6 Hz, 1H), 2.25-2.14 (m, 2H), 1.95-1.86 (m, 1H), 1.56 (t, *J* = 3.6 Hz, 3H), 1.51 (s, 3H), 1.42 (s, 3H), 1.23 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.89-0.84 (m, 3H), 0.64 (s, 3H), 0.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, R_t = 16.5 min): δ 204.9, 171.0, 149.3, 144.7, 140.8, 138.0, 137.4, 134.5, 131.0, 129.4, 128.1, 98.9, 69.7, 68.3, 61.0, 41.0, 39.1, 34.3, 29.7, 27.6, 26.8, 25.7, 25.0, 24.0, 21.3, 20.4, 19.8, 0.11, -0.34; IR(thin film): 3366, 2957, 1687 cm^{-1}; MS (API-ES) *m/z* (%) 515 ($[M+Na]^+$, 100); HRMS calcd for $C_{30}H_{40}O_4SiNa$: *m/z* $[M+Na]^+$ 515.2594; found: 515.2612.

^{1}H NMR (300 MHz, $CDCl_3$, R_t = 17.9 min, **36b**): δ 7.67-7.64 (m, 2H), 7.38-7.33 (m, 3H), 4.34-4.27 (m, 1H), 4.20 (dd, *J* = 14.0, 1.5 Hz, 1H), 4.05 (dd, *J* = 14.0, 1.0 Hz, 1H), 4.02 (s, 1H), 2.82 (ddd, *J* = 15.0, 5.5, 1.5 Hz, 1H), 2.78 (qt, 6.9 Hz, 1H), 2.63 (dt, *J* = 15.3, 2.4 Hz, 1H), 2.35 (d, *J* = 3.0 Hz, 1H), 1.98-1.92 (m, 2H), 1.74-1.62 (m, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 120-116 (m, 9H), 0.98 (t, *J* = 7.8, 2H), 0.66 (s, 3H), 0.62 (t, *J* = 7.8 Hz, 1H), 0.40 (s, 3H).

^{1}H NMR (300 MHz, $CDCl_3$, R_t = 20.8 min, **36c**): δ 7.74-7.71 (m, 2H), 7.37-7.34 (m, 3H), 4.44-4.35 (m, 2H), 4.16 (d, *J* = 14.7 Hz, 1H), 3.91 (s, 1H), 2.72 (qt, *J* = 7.2 Hz, 1H), 2.66 (dd, *J* = 5.1, 0.6 Hz, 1H), 2.23-2.14 (m, 1H), 1.92-1.85 (m, 1H), 1.62-1.57 (m, 5H), 1.51 (s, 3H),

1.45 (s, 3H), 1.38 (dt, *J* = 7.2, 0.6 Hz), 1.19 (d, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.08 (s, 3H), 0.89-0.84 (m, 2H), 0.77 (s, 3H), 0.45 (s, 3H).

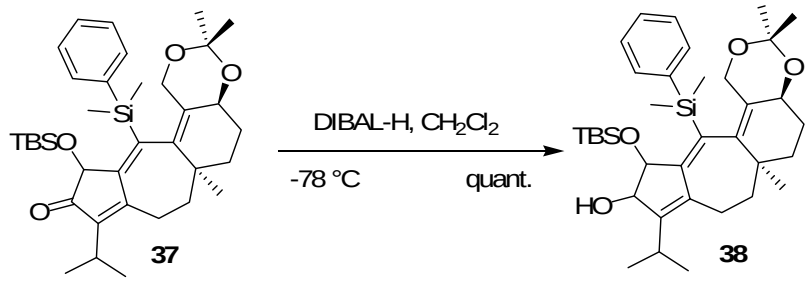
^{1}H NMR (300 MHz, $CDCl_3$, R_t = 21.6 min, **36d**): δ 7.68-7.65 (m, 2H), 7.35-7.33 (m, 3H), 4.46 (t, *J* = 6.0 Hz, 1H), 4.37-4.36 (m, 2H), 3.83 (s, 1H), 2.84-2.71 (m, 2H), 2.57 (m, 1H), 2.39 (d, *J* = 2.7 Hz, 1H), 1.96-1.88 (m, 1H), 1.83 (ddd, *J* = 14.1, 5.7, 2.1 Hz, 1H), 1.77-1.65 (m, 3H), 1.58 (m, 1H), 1.51 (s, 3H), 1.49-1.42 (m, 3H), 1.36 (s, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.12 (s, 3H), 0.91-0.79 (m, 2H), 0.71 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, R_t = 20.8 min): δ 204.7, 168.0, 149.1, 144.0, 139.6, 138.4, 138.3, 134.4, 130.1, 129.1, 127.7, 99.1, 71.4, 68.3, 66.4, 62.8, 41.0, 39.1, 36.3, 29.8, 29.7, 27.3, 26.1, 25.3, 25.1, 22.1, 20.2, 0.94, 0.49.



36b **37**

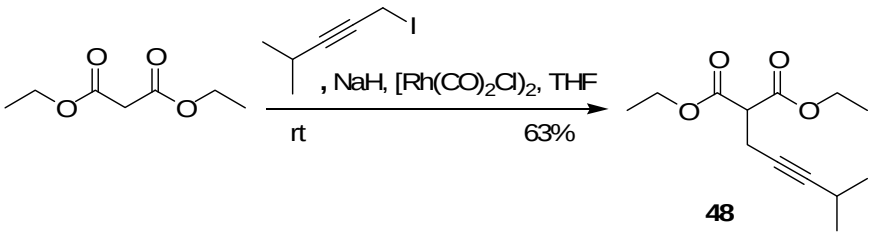
(R,3aZ)-6,7,8,8a,9,10-Hexahydro-3-(tert-butyldimethylsilyl)ether-1-isopropyl-5,6-dioxane-8a-methyl-4-(dimethyl(phenyl)silyl)benzo[f]azulen-2(3H)-one (37): To a solution of α-hydroxyl enone **36b** (R_t = 17.9 min, 6.0 mg, 0.012 mmol) in CH_2Cl_2 (0.30 mL) at 0 ºC was added Et_3N (6.7 μL, 0.048 mmol) followed by tributyldimethylsilyltrifluoromethanesulfonate (5.6 μL, 0.024 mmol) dropwise via syringe. The reaction mixture was stirred for 15 min then quenched with a saturated $NaHCO_3$ solution and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (2x), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by

chromatography on silica gel, eluting with 10% EtOAc/hexanes to give compound **37** (6.0 mg, 82%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) with trace of impurity of one other diastereomer: δ 7.59-7.56 (m, 2H), 7.37-7.33 (m, 3H), 4.29 (s, 1H), 4.21 (t, *J* = 6.9 Hz, 1H), 4.00 (dd, *J* = 14.1, 0.9 Hz, 1H), 3.86 (dd, *J* = 14.1, 0.9 Hz, 1H), 2.84-2.72 (m, 2H), 2.66-2.56 (m, 1H), 1.93-1.82 (m, 2H), 1.79 (dd, *J* = 5.1, 2.1 Hz, 1H), 1.74-1.64 (m, 2H), 1.63-1.56 (m, 2H), 1.51-1.48 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.19-1.17 (m, 9H), 0.85 (s, 9H), 0.63 (s, 3H), 0.39 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 170.5, 150.4, 144.4, 138.5, 138.2, 137.9, 134.7, 129.7, 129.2, 127.8, 99.2, 72.2, 66.4, 62.1, 40.1, 38.6, 36.8, 29.7, 26.9, 26.8, 26.5 (3C), 26.4, 25.4, 24.9, 22.2, 20.3, 20.3, 18.7, 0.84, -0.35, -2.91, -3.16; IR (thin film): 2955, 2931, 2856, 1705, 1583 cm^{-1}; MS (LC-MS) *m/z* (%) 629 ([M+Na]$^{+}$, 24), 322 (100); HRMS calcd for $C_{36}H_{54}O_4Si_2Na$: *m/z* [M+Na]$^{+}$ 629.3458; found: 629.3505.



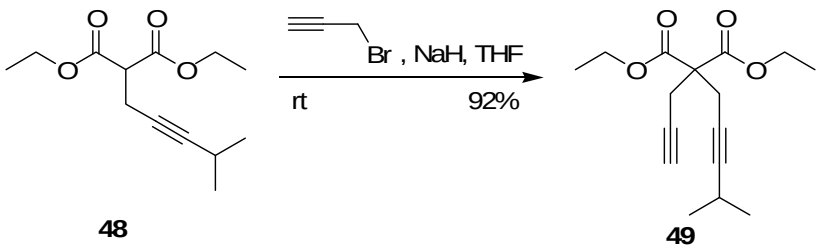
(R,3aZ)-6,7,8,8a,9,10-Hexahydro-3-(tert-butyldimethylsilyl)ether-1-isopropyl-5,6-dioxane-8a-methyl-4-(dimethyl(phenyl)silyl)benzo[f]azulen-2-ol (38): To a solution of enone **37** (4.0 mg, 0.0070 mmol) in CH_2Cl_2 (0.20 mL) at -78 ºC was added DIBAL-H (14 μL of a 1.0 M solution in hexanes , 0.014 mmol) dropwise via syringe. The reaction mixture was stirred for 1.5 hrs then quenched with MeOH at -78 ºC, and slowly warmed to room temperature. The mixture was diluted with H_2O and CH_2Cl_2, and the aqueous layer separated and extracted with

CH_2Cl_2 (2x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel, eluting with 10% EtOAc/hexanes to obtain compound **38** (4.0 mg, 100%) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) with trace of impurity of another diastereomer: δ 758-753(m, 2H), 7.37-7.33 (m, 3H), 4.69 (d, *J* = 3.9 Hz, 1H), 4.44-4.41 (m, 1H), 4.29-4.25 (m, 1H), 4.02-4.01 (m, 2H), 2.70 (qt, *J* = 6.9 Hz, 1H), 2.41-2.37 (m, 2H), 2.27 (d, *J* = 9.9 Hz, 2H), 1.87-1.78 (m, 1H), 1.76-1.67 (m, 3H), 1.63 (t, *J* = 3.9 Hz, 1H), 1.45-1.40 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 1.19 (dd, *J* = 3.9, 2.7 Hz, 1H), 1.15 (d, *J* = 6.9 Hz, 6H), 0.86 (s, 9H), 0.51 (s, 3H), 0.35 (s, 3H), 0.02 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 148.8, 141.7, 139.5, 139.2, 134.3, 129.0, 128.7, 128.5, 127.8 99.3, 66.0, 63.0, 39.4, 38.6, 35.7, 28.4, 27.0, 26.5 (2C), 26.1, 25.3, 23.7, 23.6, 22.2, 22.0, 19.9, 18.8, 1.09, 0.74, -2.44, -2.87; IR (thin film): 3466, 2954, 2930 cm^{-1}; MS (API-ES) *m/z* (%) 631 ([M+Na]$^+$, 100); HRMS calcd for $C_{36}H_{56}O_4Si_2$ Na : *m/z* [M+Na]$^+$ 631.3615; found: 631.3649.



Diethyl 2-(4-methylpent-2-ynyl)malonate (48): To a solution of $[Rh(CO)_2Cl)_2$ (10 mg, 0.025 mmol) in THF (2.5 mL) was added 1-iodo-4-methylpent-2-yne (0.10 g, 0.50 mmol) via a syringe at room temperature. The reaction mixture was stirred for 30 min. In a separate 10 mL flask, diethyl malonate (0.20 mL, 1.3 mmol) was added to a slurry of NaH (40 mg of 60% wt in mineral oil, 1.0 mmol) in THF (2.5 mL), and the mixture was stirred for 20 min. The resulting sodium enolate solution then was added via cannula to the solution of $[Rh(CO)_2Cl]_2$, and the

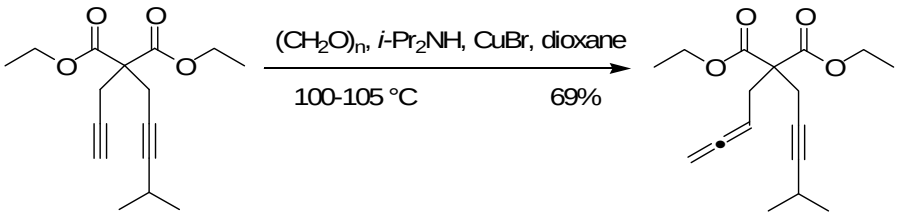
reaction mixture was stirred for an additional 1 hr. The reaction mixture then was filtered through a short plug of silica gel eluting with Et_2O. The filtrate was concentrated, and the residue was purified by chromatography on silica gel, eluting with 10% Et_2O/pentanes to afford **48** (75 mg, 63%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (q, *J* = 6.9 Hz, 4H), 3.50 (t, *J* = 7.8 Hz, 1H), 2.72 (dd, *J* = 7.8, 2.1 Hz, 2H), 2.47 (sept, *J* = 6.9, 2.1 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 6H), 1.10 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 88.0, 74.7, 61.4, 51.8, 23.0, 20.3, 18.7, 13.9; IR (thin film): 2974, 1737 cm^{-1}; MS (EI) *m/z* (%) 240 ($[M]^+$, 50), 195 ($[M-C_2H_5O]^+$, 20), 167 ($[M-C_3H_5O_2]^+$, 100); HRMS calcd for $C_{13}H_{20}O_4$: *m/z* $[M]^+$ 240.1362; found: 240.1370.



48 49

Diethyl 2-(4-methylpent-2-ynyl)-2-(prop-2-ynyl)malonate (49): To a suspension of NaH (13 mg of 60% wt in mineral oil, 0.33 mmol) in THF (2.0 mL) was added solution of **48** (75 mg, 0.31 mmol) in THF (1.0 mL) via cannula. The resulting mixture was stirred for 30 min then propargyl bromide (40 μL of 80% wt in toluene, 0.37 mmol) in THF (0.70 mL) was added dropwise via cannula at room temperature. After 2 h the reaction mixture was quenched with H_2O and diluted with Et_2O. The aqueous layer was separated and extracted with Et_2O (2x), and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under vacuum. The crude mixture was purified by chromatography on silica gel, eluting with 20% EtOAc/hexanes to give **49** (79 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20

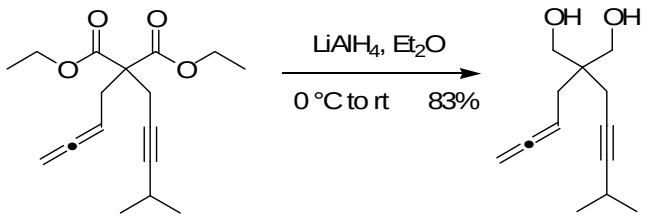
(q, J = 6.9 Hz, 4H), 2.93 (d, J = 2.7 Hz, 2H), 2.90 (d, J = 2.1 Hz, 2H), 2.46 (sept, J = 6.9, 2.1 Hz, 1H), 1.99 (t, J = 2.7 Hz, 1H), 1.24 (t, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 89.5, 78.8, 73.2, 71.3, 61.8, 56.8, 23.1, 22.8, 22.4, 20.4, 14.0; IR (thin film): 3285, 2974, 1739 cm^{-1}; MS (API-ES) *m/z* (%) 301 ([M+Na]$^+$, 75), 217 (100); HRMS calcd for $C_{16}H_{22}O_4Na$: *m/z* [M+Na]$^+$ 301.1416; found: 301.1390.



49 **50**

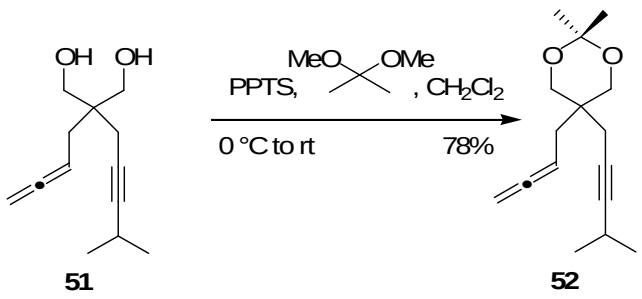
Diethyl 2-(buta-2,3-dienyl)-2-(4-methylpent-2-ynyl)malonate (50): To a solution of alkyne **49** (608 mg, 2.19 mmol) in dioxane (22.0 mL) was added *i*Pr_2NH (0.610 mL, 4.37 mmol) followed by paraformaldehyde (131 mg, 4.37 mmol) and CuBr (94.0 mg, 0.657 mmol). The reaction mixture turned green upon addition of CuBr, and was heated at a gentle reflux for 10 hr. Upon heating the reaction mixture turned brown. Upon completion by TLC, the reaction was quenched with 0.1 M $NaHSO_4$ and diluted with Et_2O. The aqueous layer was separated and extracted with Et_2O (3x), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel, eluting with 10% EtOAc/hexanes to afford **50** (442 mg, 69%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.02-4.92 (m, 1H), 4.67 (dt, J = 6.3, 2,4 Hz, 2H), 4.20 (q, J = 7.2 Hz, 4H), 2.80 (d, J = 2.4 Hz, 2H), 2.76 (dt, J = 8.1, 2.4 Hz, 2H), 2.48 (sept, J = 6.9, 2.4 Hz, 1H), 1.26 (t, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.1, 169.9, 89.3, 84.1, 74.5, 73.5, 61.4, 57.4, 31.6, 23.2, 22.9, 20.4, 14.1; IR (thin film): 2972, 2360, 1956, 1736 cm^{-1}; MS

(API-ES) *m/z* (%) 315 ([M+Na]$^+$, 100); HRMS calcd for $C_{17}H_{24}O_4Na$: *m/z* [M+Na]$^+$ 315.1573; found: 315.1572.



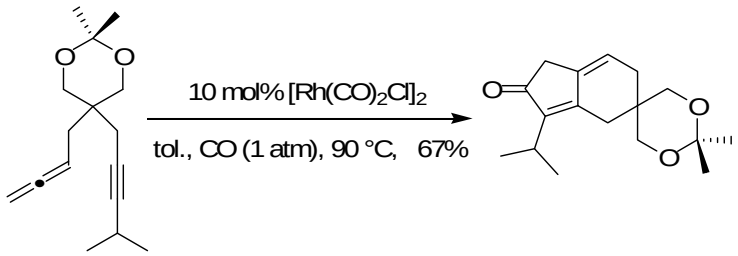
50 **51**

2-(Buta-2,3-dienyl)-2-(4-methylpent-2-ynyl)propane-1,3-diol (51): To a stirred solution of $LiAlH_4$ (59.0 mg, 1.55 mmol) in Et_2O (7.80 mL) in a 25 mL round bottom flask at 0 ºC was added a solution of malonate **50** (181 mg, 0.620 mmol) in Et_2O (1.50 mL) via cannula. The ice-bath was removed, and the reaction mixture was stirred at room temperature for 1.5 hr. The mixture was then cooled to 0 ºC and quenched with H_2O (60.0 μL), 10% NaOH (0.120 mL) and KF solution (0.240 mL) and stirred for 30 min. The reaction mixture was diluted with Et_2O, and the aqueous layer was separated. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated under vacuum, and the crude mixture was purified by chromatography on silica column, eluting with 50% Et_2O/pentanes to give diol **51** (107 mg, 83%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15-5.05 (m, 1H), 4.69 (dt, *J* = 6.9, 2,1 Hz, 2H), 3.71 (1/2 ABd, *J* = 10.8 Hz, 2H), 3.64 (1/2 ABd, *J* = 11.1 Hz, 2H), 2.53 (sept, *J* = 6.9, 2.1 Hz, 1H), 2.22 (d, *J* = 2.1 Hz, 2H), 2.12 (dt, *J* = 8.4, 2.4 Hz, 2H), 2.01 (b, 2H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.8, 89.0, 84.8, 75.2, 74.1, 67.5, 31.3, 30.3, 23.3, 22.0, 20.6; IR (thin film): 3382, 2965, 1955 cm^{-1}; MS (API-ES) *m/z* (%) 247 ([M+K]$^+$, 34), 219 (100); HRMS calcd for $C_{13}H_{20}O_2K$: *m/z* [M+K]$^+$ 247.1100; found: 247.1098.



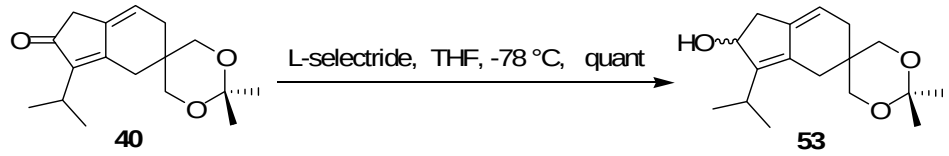
51 52

5-(Buta-2,3-dienyl)-2,2-dimethyl-5-(4-methylpent-2-ynyl)-1,3-dioxane (52): To a stirred solution of diol **51 (**107 mg, 0.510 mmol) in CH_2Cl_2 (5.10 mL) at 0 ºC was added 2,2-dimethyoxypropane (1.30 mL, 10.2 mmol) followed by pyridinium p-toluenesulfonate (26.0 mg, 0.103 mmol). The ice-bath was removed, and the reaction mixture was stirred for 2 hr at room temperature and then quenched with saturated $NaHCO_3$ solution. The mixture was diluted with CH_2Cl_2, and the aqueous layer was separated. The CH_2Cl_2 layer was dried over $MgSO_4$ and filtered. The solvent was removed under vacuum, and the crude mixture was purified by chromatography on silica gel, eluting with 10% Et_2O/pentanes to entitle **52** (98 mg, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09-4.99 (m, 1H), 4.67 (dt, *J* = 6.9, 2.1 Hz, 2H), 3.72 (1/2 ABd, *J* = 11.7 Hz, 2H), 3.65 (1/2 ABd, *J* = 11.7 Hz, 2H), 2.53 (sept, *J* = 6.6, 2.1 Hz, 1H), 2.33 (d, *J* = 2.1 Hz, 2H), 2.15 (dt, *J* = 8.1, 2.4 Hz, 2H), 1.42 (s, 6H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.9, 98.0, 88.9, 84.2, 74.9, 74.1, 66.6, 36.0, 32.2, 24.9, 23.4, 22.7, 22.6, 20.6; IR (thin film): 2966, 1955 cm^{-1}; MS (EI) *m/z* (%) 233 ([M-CH_3]$^+$, 51), 91 (100); HRMS calcd for $C_{15}H_{21}O_2$: *m/z* [M-CH_3]$^+$ 233.1542; found: 233.1533.

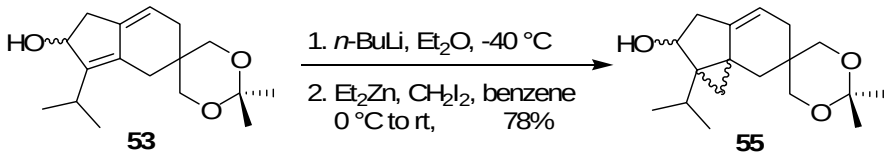


52 **40**

5,6-Dihydro-1,3-dioxane-3-isopropyl-1H-inden-2(4H)-one (40): To a flame-dried test tube (16 x 100 mm) equipped with a magnetic stir bar (8 mm) was added allenyne **52** (110 mg, 0.440 mmol). The test tube was evacuated under vacuum by inserting a needle and charged three times with CO using a balloon. Toluene (4.40 mL) was then added, and the reaction mixture was again evacuated under vacuum and charged three times with a CO balloon. $[Rh(CO)_2Cl]_2$ (17.2 mg, 0.0440 mmol) was added by removing the septa then quickly replacing the septa. A CO balloon was inserted through the septa, and the test tube was immersed in a preheated oil bath at 90 ºC where it was stirred for 6-10 min at which it was done by TLC. The reaction mixture was cooled to room temperature and directly purified by chromatography on silica gel, eluting with 20% EtOAc/hexanes to obtain compound **40** (66 mg, 67%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (t, *J* = 4.2 Hz, 1H), 3.65 (1/2 ABd, *J* = 11.4 Hz, 2H), 3.58 (1/2 ABd, *J* = 11.4 Hz, 2H), 2.94-2.84 (m, 3H), 2.71 (s, 2H), 2.24 (dt, *J* = 4.5, 1.2 Hz, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7, 160.0, 146.6, 135.0, 119.6, 98.4, 68.2, 38.4, 33.4, 31.1, 30.3, 24.4, 23.0, 20.6; IR (thin film): 2960, 1693 cm^{-1}; MS (EI) *m/z* (%) 276 ($[M]^+$, 23), 261 ($[M\text{-}CH_3]^+$, 30), 218 ($[M\text{-}C_3H_5O]^+$, 100); HRMS calcd for $C_{17}H_{24}O_3$: *m/z* $[M]^+$ 276.1725; found: 276.1721.

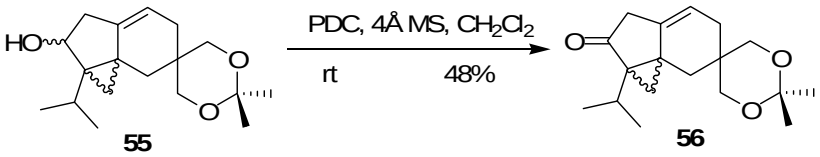


1,2,4,5,6-Pentahydro-1,3-dioxane-3-isopropyl-4H-inden-2-ol (53): To a solution of enone **40** (66 mg, 0.24 mmol) in THF (2.5 mL) at -78 ºC was added L-selectride (0.50 mL of a 1.0 M solution in THF, 0.48 mmol) dropwise via syringe. The reaction mixture was stirred for 1.5 hr then warmed to 0 ºC, and quenched with H_2O (0.40 mL), 3.0 N NaOH (0.80 mL) and 30% H_2O_2 (0.80 mL). The ice bath was removed, and the mixture was stirred at room temperature for 30 min then diluted with H_2O and Et_2O. The aqueous layer was separated and extracted with Et_2O (3x), and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under vacuum. The crude residue was taken on to the next step without further purification.

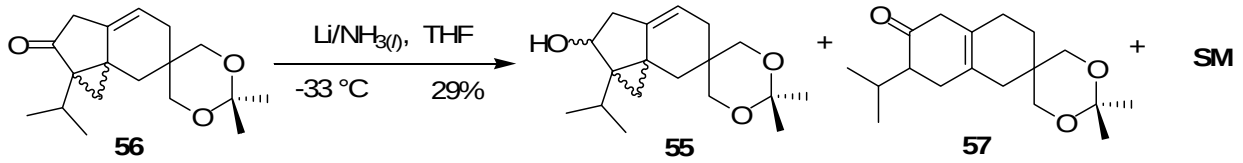


1,2,4,5,6-Pentahydro-1,3-dioxane-3-isopropyl-bicyclo[3.1.0]-4H-inden-2-ol (55): To a solution of Et_2Zn (0.16 mL of a 1.0 M solution in hexanes, 0.17 mmol) in benzene (1.7 mL) at room temperature was added CH_2I_2 (27 μL, 0.33 mmol) dropwise via syringe. Upon addition a white precipitate formed, and the mixture was stirred for 30 min. In a separate 5 ml flask, to a solution of allylic alcohol **53** (31 mg, 0.11 mmol) in Et_2O (1.1 mL) at -40 ºC was added *n*-BuLi (70 μL of a 1.6 M solution in hexanes, 0.11 mmol) dropwise via syringe. The mixture was stirred at -40 ºC for 15 min. The Et_2Zn mixture was cooled to 0 ºC, and to it was added the solution of allylic alcohol **53** dropwise via cannula. The resulting mixture was allowed to warm

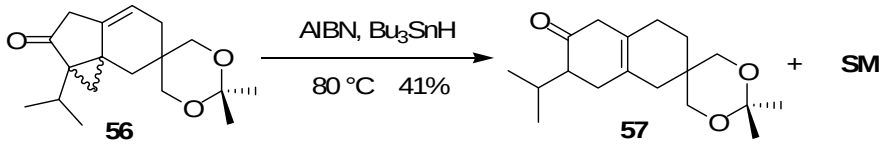
to room temperature and stir for an additional 6 hr. The reaction mixture was quenched with saturated NH_4Cl solution and diluted with Et_2O. The aqueous layer was separated and extracted with Et_2O (3x), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was taken on to the next step without further purification.



5,6-Dihydro-1,3-dioxane-3-isopropyl-bicyclo[3.1.0]-1H-inden-2(4H)-one (56): To a solution of cyclopropyl alcohol **55** (63.0 mg, 0.216 mmol) in CH_2Cl_2 (2.50 mL) at room temperature was added 4Å molecular sieves (138 mg) followed by pyridinium dichromate (138 mg, 0.367 mmol) in one portion. The reaction mixture was stirred for 5 hrs then filtered through a pad of celite. The filtrate was concentrated under vacuum, and the residue was purified by chromatography on silica gel, eluting with 20% Et_2O/pentanes to obtain cyclopropyl ketone **56** (30 mg, 48%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34-5.33 (m, 1H), 3.96 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.75 (d, *J* = 11.7 Hz, 1H), 3.69 (d, *J* = 11.4 Hz, 1H), 3.52 (dd, *J* = 11.4, 1.2 Hz), 2.82 (1/2 ABd, J = 20.0 Hz, 1H), 2.58 (1/2 ABd, *J* = 20.0, 1.5 Hz, 1H), 2.22-2.16 (m, 1H), 1.94-1.86 (m, 1H), 1.83 (s, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.37 (d, *J* = 4.2 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.14 (dd, 4.2, 1.5 Hz, 2H), 1.08 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.1, 135.4, 115.6, 98.9, 71.0, 67.0, 46.9, 40.0, 39.0, 34.2, 32.0, 31.6, 29.5, 27.8, 25.8, 23.1, 20.7, 20.0; IR (thin film): 2960, 1726 cm^{-1}; MS (EI) *m/z* (%) 290 ([M]$^+$, 12), 275 ([M-CH_3]$^+$, 31), 232 ([M-C_3H_6O]$^+$, 100); HRMS calcd for $C_{18}H_{26}O_3$: *m/z* [M]$^+$ 290.1882; found: 290.1885.



3,4,5,6,7,8-Hexahydro-1,3-dioxane-3-isopropylnaphthalen-2(1H)-one (57): To a solution of NH_3/Li[42] (4.0 mL/20 mg, 2.9 mmol) in a 10 mL single-necked conical flask equipped with a magnetic stir bar and a cold-finger was added cyclopropyl ketone **56** (42 mg, 0.15 mmol) in THF (1.5 mL) dropwise at -78 ºC via teflon cannula. Once the addition was complete, the acetone-bath was removed, and the ammonia mixture set to reflux. The deep blue color persisted, and after 1h the reaction mixture was poured onto a saturated NH_4Cl solution, and diluted with Et_2O. The aqueous layer was separated and extracted with Et_2O (3x), and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. The crude mixture was purified by chromatography on silica gel, eluting with 5% EtOAc/CH_2Cl_2 to afford compound **57** (12 mg, 29%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.63-3.55 (m, 4H), 2.81 (1/2 ABd, *J* = 20.0 Hz, 1H), 2.68 (1/2 ABd, *J* = 20.0 Hz, 1H), 2.35 (dd, *J* = 5.5, 15.5 Hz, 1H), 2.29 (q, *J* = 7 Hz, 1H), 2.20 (dd, *J* = 8.5, 15.0 Hz, 1H), 2.11 (oct, *J* = 6.5 Hz, 1H), 1.98 (s, 2H), 1.93 (m, 2H), 1.61 (dt, *J* = 6.5, 13 Hz, 1H), 1.53 (dt, *J* = 7.0, 13.5 Hz, 1H), 1.43 (s, 6H), 0.93 (d, 7 Hz, 3H), 0.91 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.8, 125.8, 124.8, 98.2, 68.7, 68.1, 54.5, 44.8, 35.9, 33.6, 32.0, 27.0, 26.6, 25.8, 24.5, 23.0, 21.2, 19.2; IR (thin film): 2959, 2917, 1715 cm^{-1}; MS (EI) *m/z* (%) 292 ([M]$^+$, 5), 277 ([M-CH_3]$^+$, 26), 234 ([M-C_3H_6O]$^+$, 32), 105 (100); HRMS calcd for $C_{18}H_{28}O_3$: *m/z* [M]$^+$ 292.2038; found: 292.2030.



3,4,5,6,7,8-Hexahydro-1,3-dioxane-3-isopropylnaphthalen-2(1H)-one (57): To a solution of cyclopropyl ketone **56** (32 mg, 0.11 mmol) in tributyltin hydride (3.0 mL) at 80 ºC was added 2,2`-azo *bis*isobutyronitrile (4.0 mg, 0.022 mmol) in one portion. The reaction mixture was stirred at the same temperature for 10 h, then cooled to room temperature, and directly purified by chromatography on silica gel, eluting with 5% EtOAc/hexanes to obtain compound **57** (13 mg, 41%) as a colorless oil.

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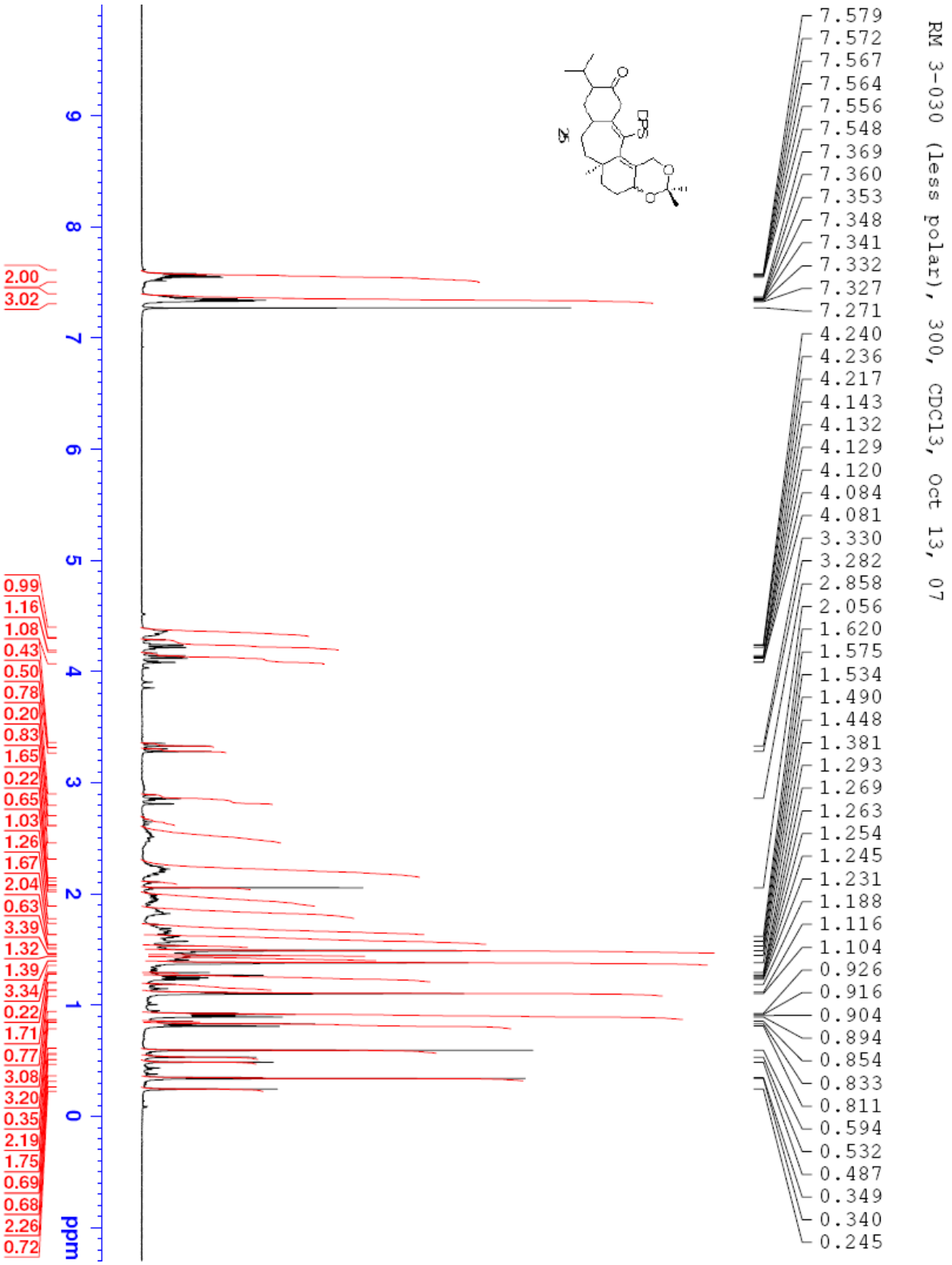
[41]To a flame-dried 25 mL long neck flask equipped with a magnetic stir bar was charged with samarium powder (180 mg, 1.20 mmol) and iodine (127 mg, 1.00 mmol). The flask was evacuated under vacuum and purged with N_2 (2x) then THF (10.0 mL) was added. The flask was immersed in a preheated oil bath at 50-55 ºC. After 10 min, the rusty brown solution turned a cobalt blue color.

[42]Ammonia gas was condensed in a two-necked conical flask, which was immersed in a -78 ºC acetone bath and had been charged with sodium metal. Upon condensation, liquid ammonia turned a deep blue color. The flask was sealed with septa. A separate reaction flask, equipped with a magnetic stir bar, charged with lithium metal, and sealed with a septum, was cooled to -78 ºC. The liquid ammonia was warmed slowly to room temperature, and the gas was distilled over to the reaction flask via teflon cannula. Once in the reaction flask, the liquid ammonia turned a deep blue color.

APPENDIX A

^{1}H AND ^{13}C NMR DATA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7.360
7.353
7.348
7.341
7.332
7.327
7.271
4.240
4.236
4.217
4.143
4.132
4.129
4.120
4.084
4.081
3.330
3.282
2.858
2.056
1.620
1.575
1.534
1.490
1.448
1.381
1.293
1.269
1.263
1.254
1.245
1.231
1.188
1.116
1.104
0.926
0.916
0.904
0.894
0.854
0.833
0.811
0.594
0.532
0.487
0.349
0.340
0.245
2.00
3.02
0.99
1.16
1.08
0.43
0.50
0.78
0.20
0.83
1.65
0.22
0.65
1.03
1.26
1.67
2.04
0.63
3.39
1.32
1.39
3.34
0.22
1.71
0.77
3.08
3.20
0.35
2.19
1.75
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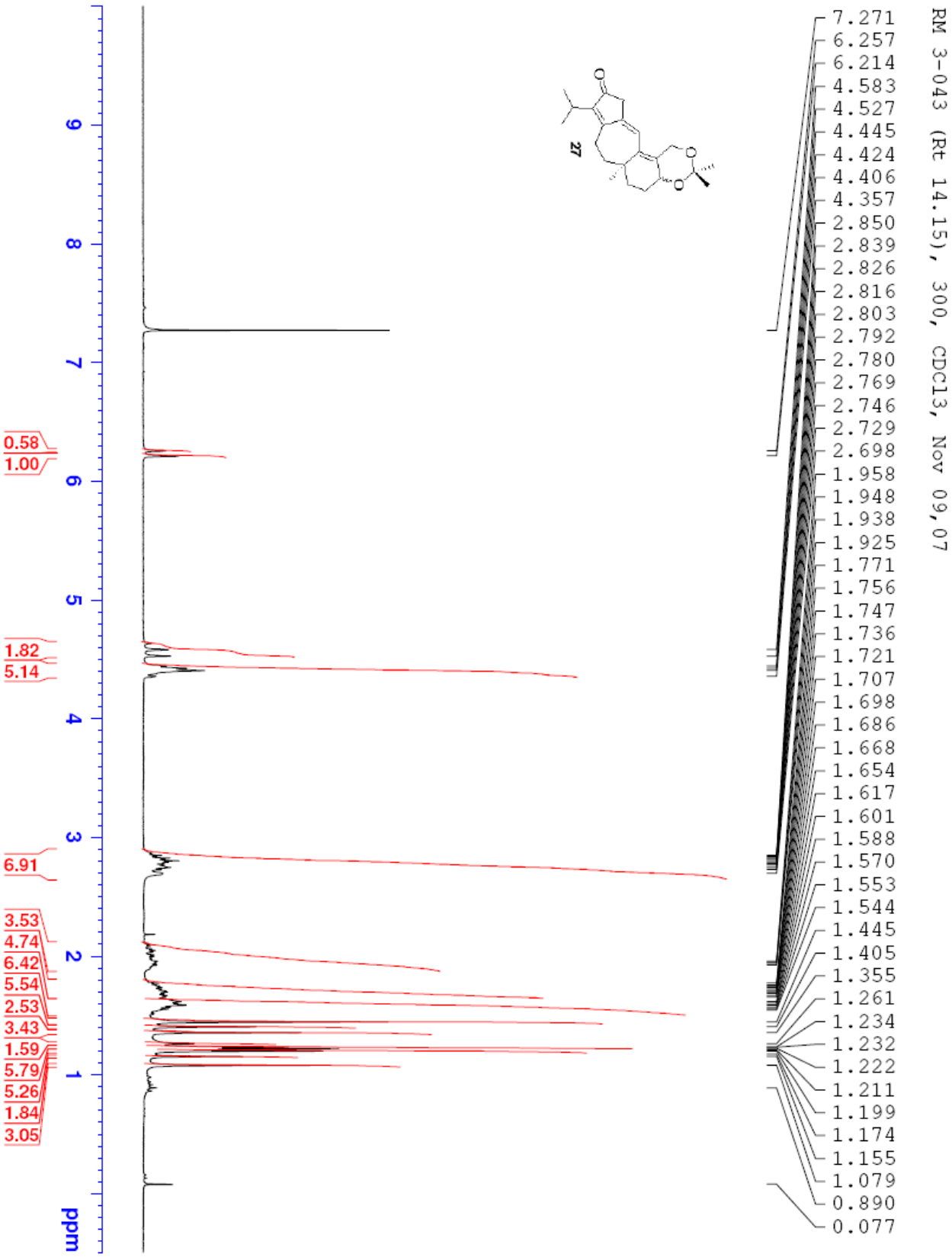
0.72
ppm
9
8
7
6
5
4
3
2
1
0
OPS
25


RM 3-043 (Rt 14.15), 300, CDCl3, Nov 09,07
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6.214
4.583
4.527
4.445
4.424
4.406
4.357
2.850
2.839
2.826
2.816
2.803
2.792
2.780
2.769
2.746
2.729
2.698
1.958
1.948
1.938
1.925
1.771
1.756
1.747
1.736
1.721
1.707
1.698
1.686
1.668
1.654
1.617
1.601
1.588
1.570
1.553
1.544
1.445
1.405
1.355
1.261
1.234
1.232
1.222
1.211
1.199
1.174
1.155
1.079
0.890
0.077
0.58
1.00
1.82
5.14
6.91
3.53
4.74
6.42
5.54
2.53
3.43
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5.26
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3.05
ppm
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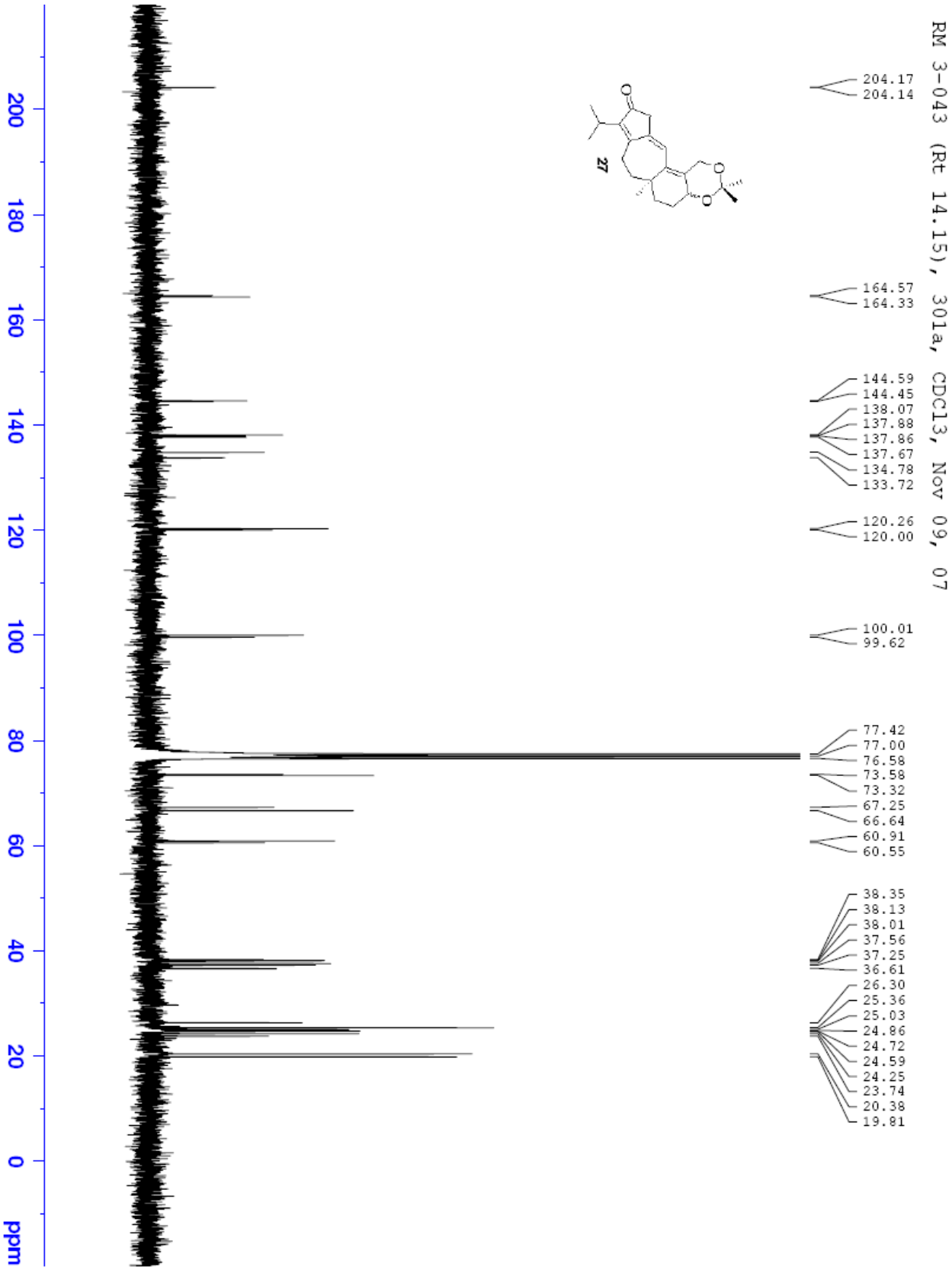
8
7
6
5
4
3
2
1
27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164.57
164.33
144.59
144.45
138.07
137.88
137.86
137.67
134.78
133.72
120.26
120.00
100.01
99.62
77.42
77.00
76.58
73.58
73.32
67.25
66.64
60.91
60.55
38.35
38.13
38.01
37.56
37.25
36.61
26.30
25.36
25.03
24.86
24.72
24.59
24.25
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20.38
19.81
27
200
180
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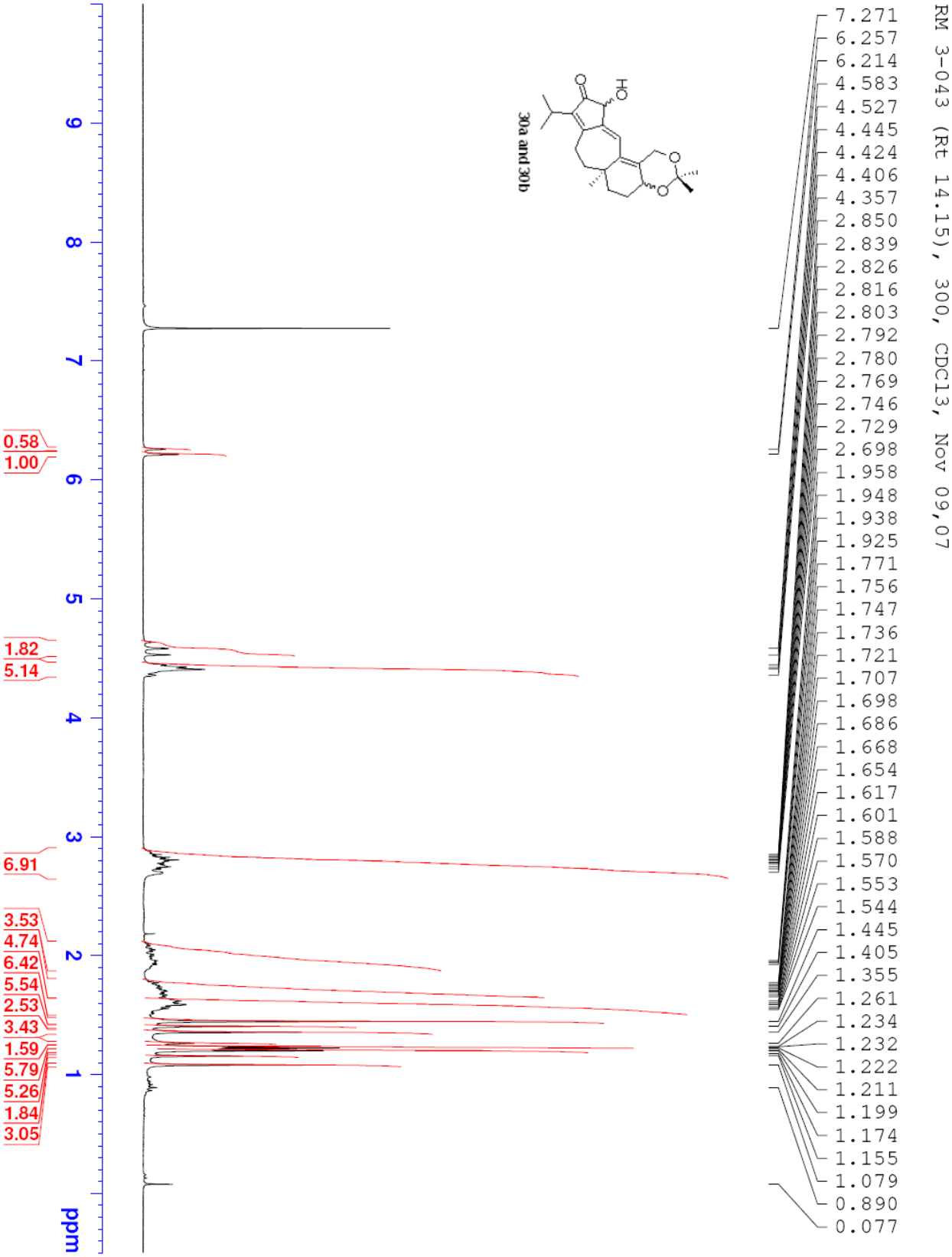
140
120
100
80
60
40
20
0
ppm


RM 3-043 (Rt 14.15), 300, CDC13, Nov 09,07
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6.257
6.214
4.583
4.527
4.445
4.424
4.406
4.357
2.850
2.839
2.826
2.816
2.803
2.792
2.780
2.769
2.746
2.729
2.698
1.958
1.948
1.938
1.925
1.771
1.756
1.747
1.736
1.721
1.707
1.698
1.686
1.668
1.654
1.617
1.601
1.588
1.570
1.553
1.544
1.445
1.405
1.355
1.261
1.234
1.232
1.222
1.211
1.199
1.174
1.155
1.079
0.890
0.077
HO
30a and 30b
0.58
1.00
1.82
5.14
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5.79
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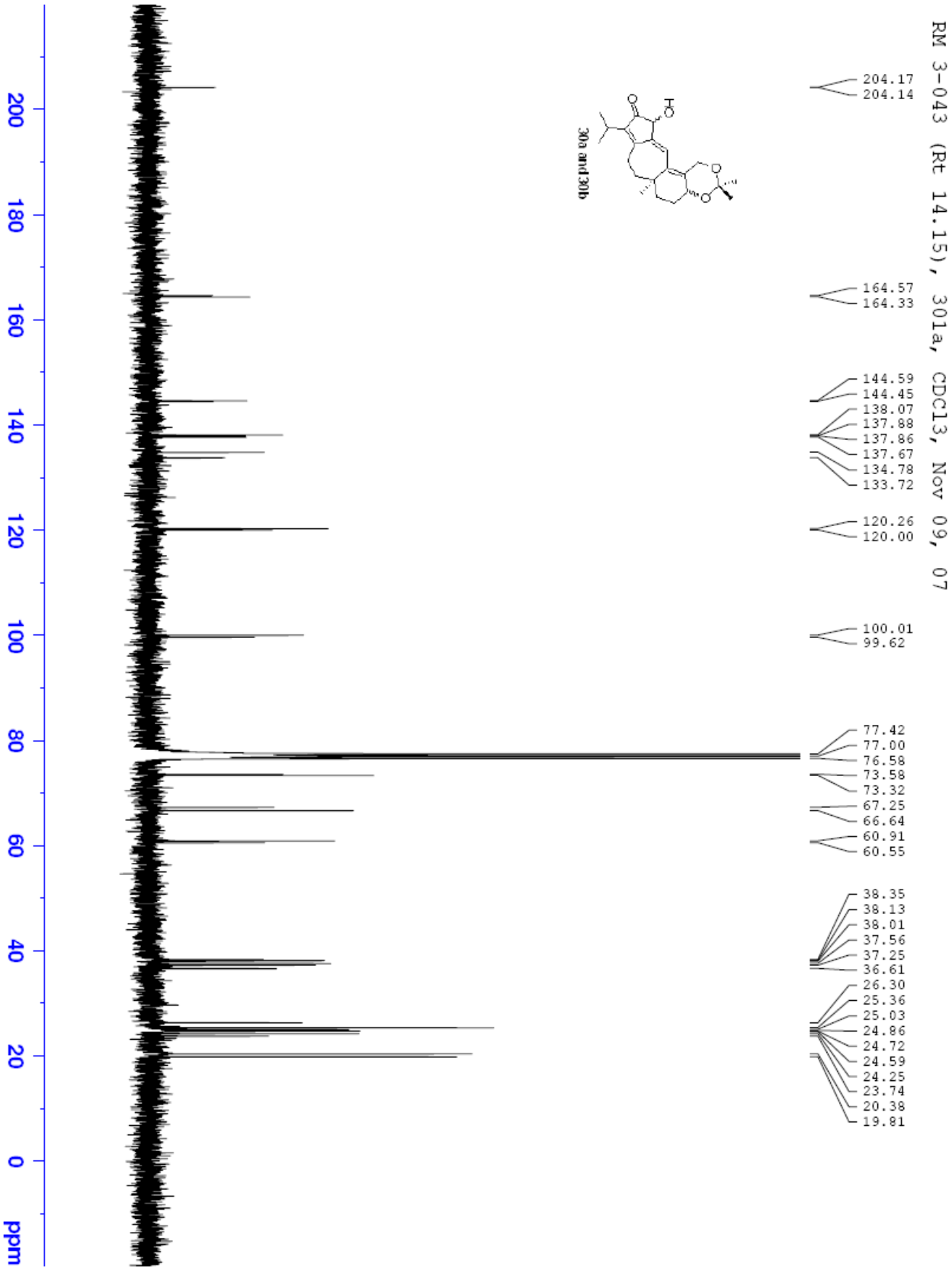
ppm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204.14
164.57
164.33
144.59
144.45
138.07
137.88
137.86
137.67
134.78
133.72
120.26
120.00
100.01
99.62
77.42
77.00
76.58
73.58
73.32
67.25
66.64
60.91
60.55
38.35
38.13
38.01
37.56
37.25
36.61
26.30
25.36
25.03
24.86
24.72
24.59
24.25
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19.81
301a and 130b
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120
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40
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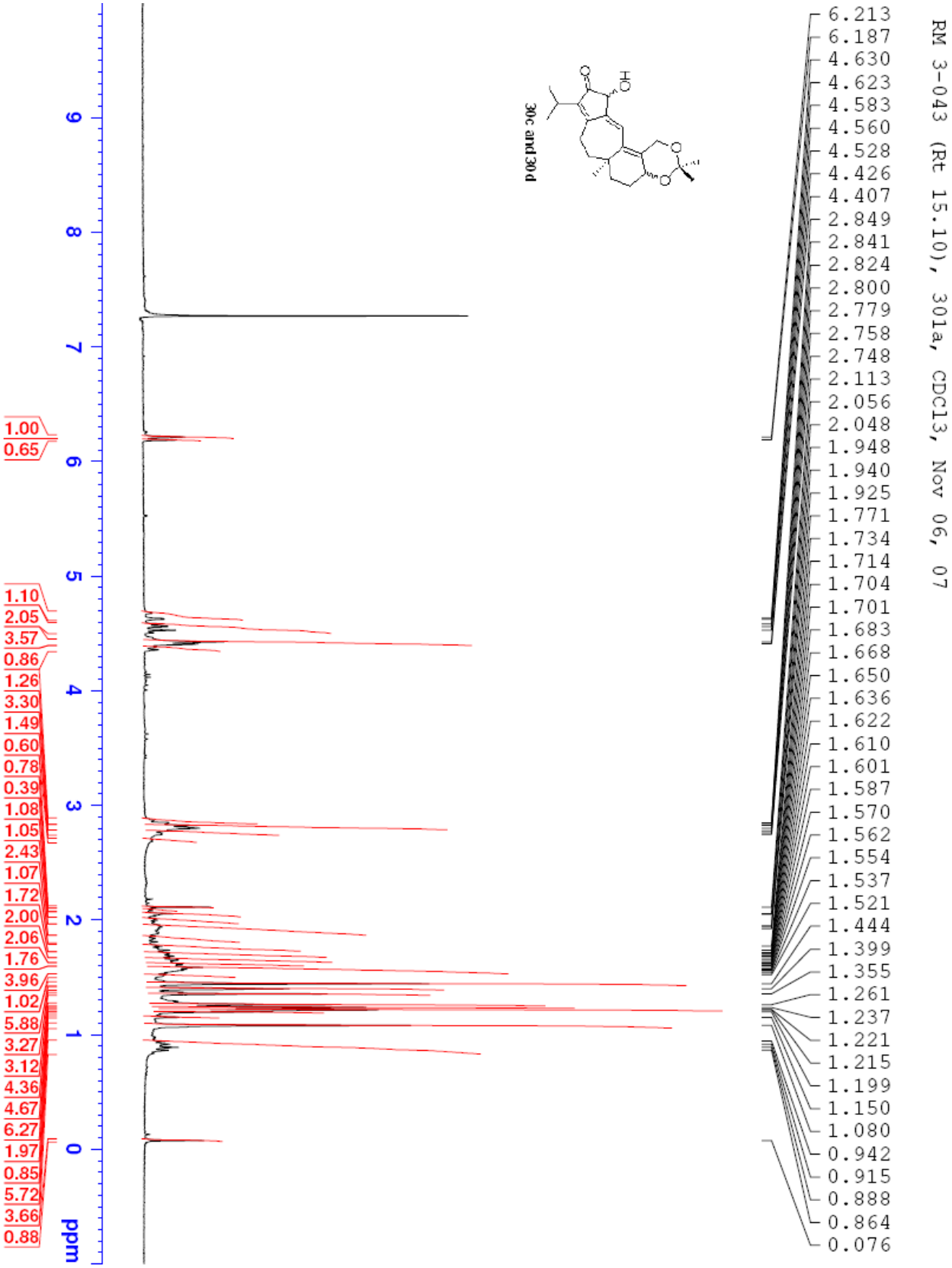
ppm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4.583
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4.528
4.426
4.407
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2.841
2.824
2.800
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2.758
2.748
2.113
2.056
2.048
1.948
1.940
1.925
1.771
1.734
1.714
1.704
1.701
1.683
1.668
1.650
1.636
1.622
1.610
1.601
1.587
1.570
1.562
1.554
1.537
1.521
1.444
1.399
1.355
1.261
1.237
1.221
1.215
1.199
1.150
1.080
0.942
0.915
0.888
0.864
0.076
30c and 30d
1.00
0.65
1.10
2.05
3.57
0.86
1.26
3.30
1.49
0.60
0.78
0.39
1.08
1.05
2.43
1.07
1.72
2.00
2.06
1.76
3.96
1.02
5.88
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3.12
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4.67
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0.85
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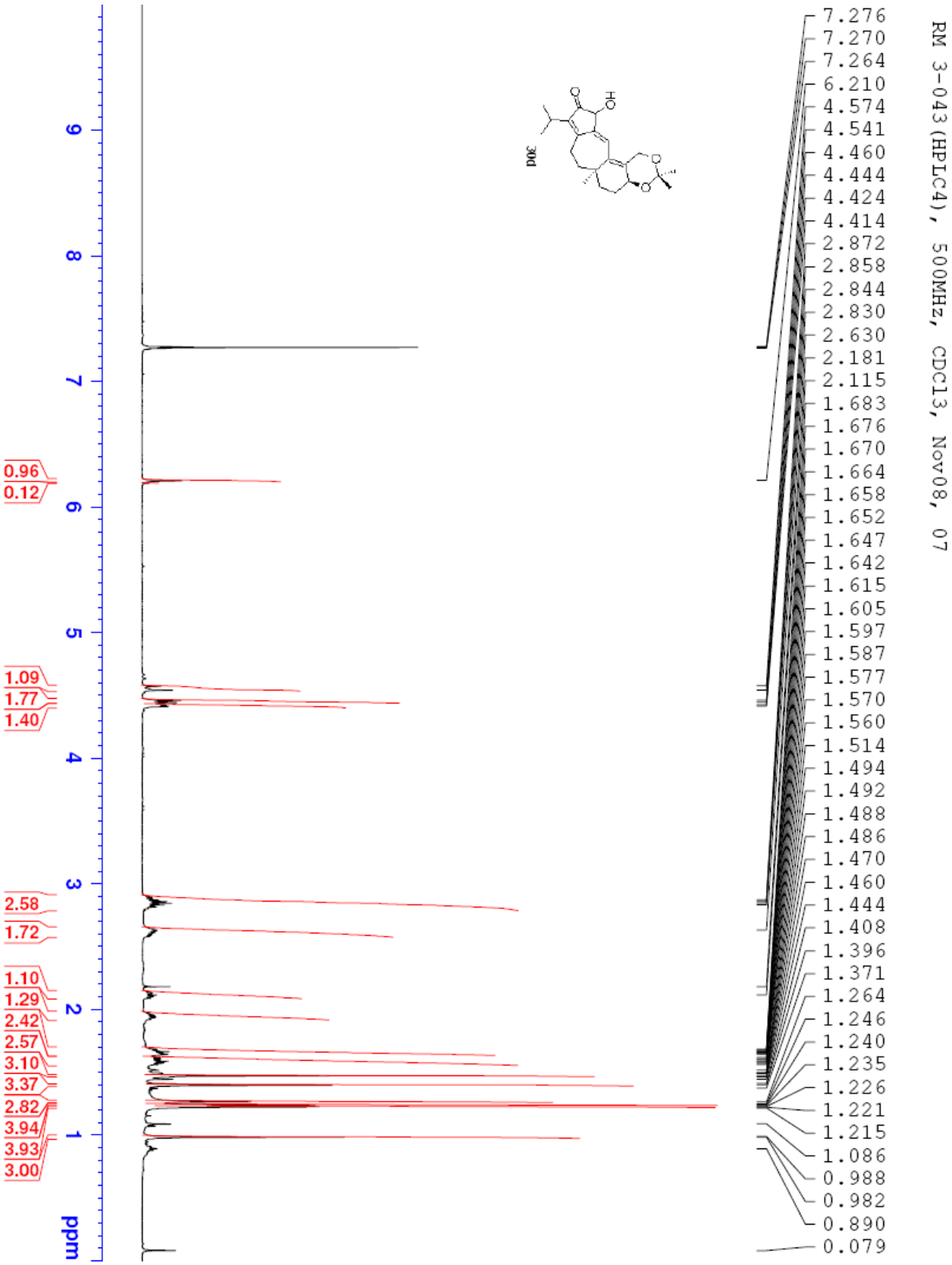
3.66
0.88
ppm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4.424
4.414
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2.858
2.844
2.830
2.630
2.181
2.115
1.683
1.676
1.670
1.664
1.658
1.652
1.647
1.642
1.615
1.605
1.597
1.587
1.577
1.570
1.560
1.514
1.494
1.492
1.488
1.486
1.470
1.460
1.444
1.408
1.396
1.371
1.264
1.246
1.240
1.235
1.226
1.221
1.215
1.086
0.988
0.982
0.890
0.079
0.96
0.12
1.09
1.77
1.40
2.58
1.72
1.10
1.29
2.42
2.57
3.10
3.37
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6
7
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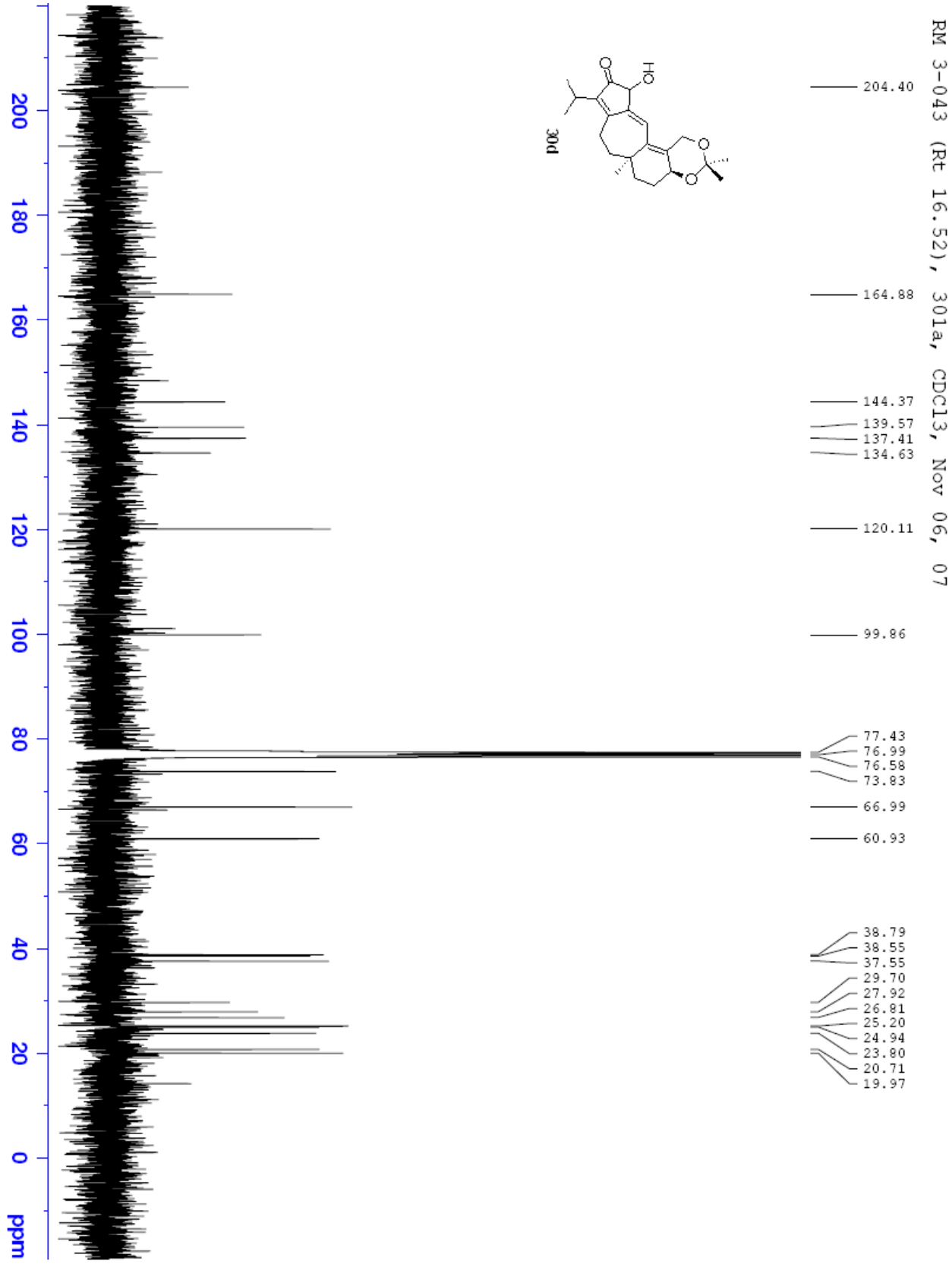
OH
O
O
O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30d
HO
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120.11
99.86
77.43
76.99
76.58
73.83
66.99
60.93
38.79
38.55
37.55
29.70
27.92
26.81
25.20
24.94
23.80
20.71
19.97
200
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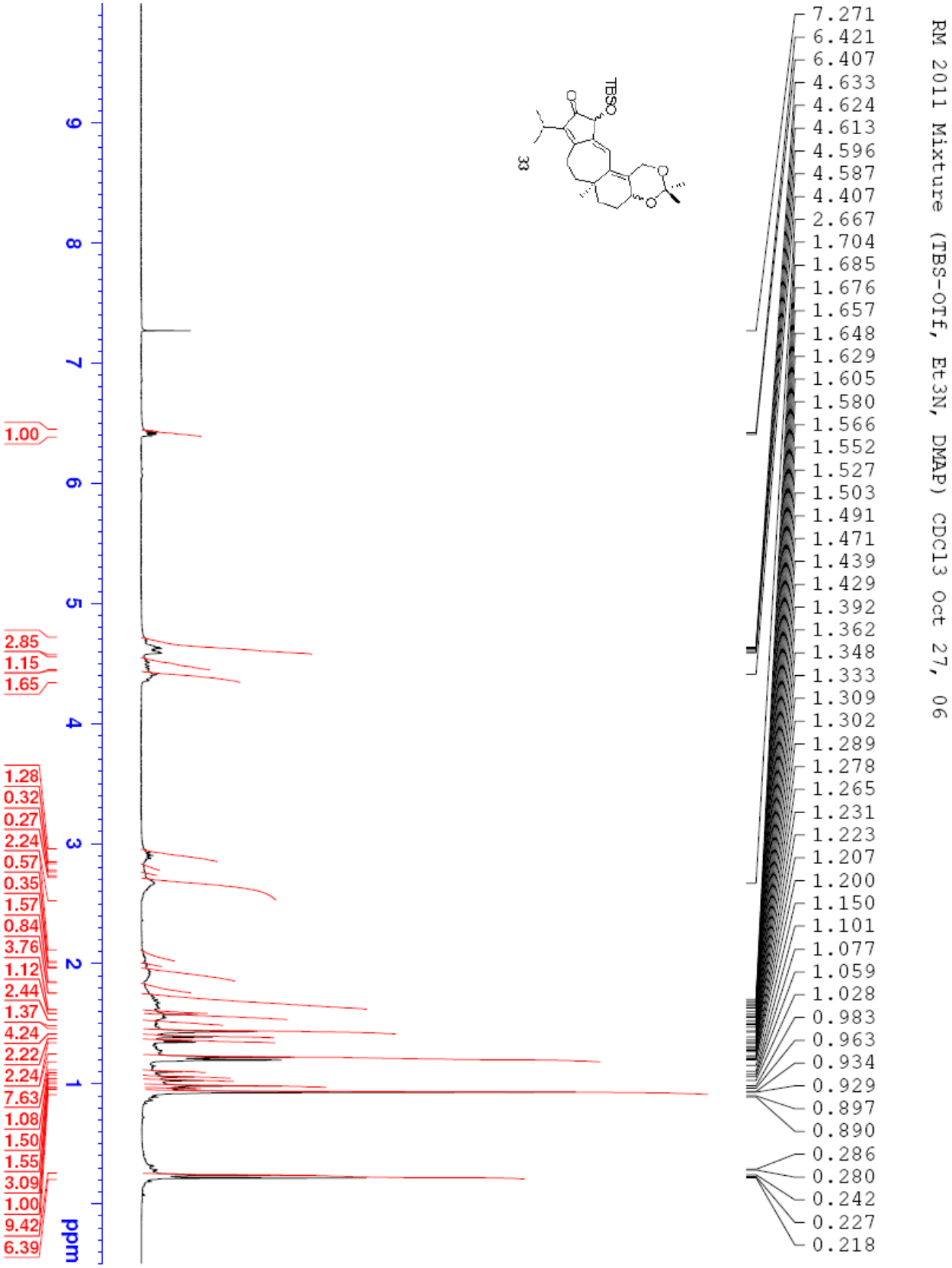
160
140
120
100
80
60
40
20
0
ppm


RM 2011 Mixture (TBS-OTf, Et3N, DMAP) CDCl3 Oct 27, 06
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4.407
2.667
1.704
1.685
1.676
1.657
1.648
1.629
1.605
1.580
1.566
1.552
1.527
1.503
1.491
1.471
1.439
1.429
1.392
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1.348
1.333
1.309
1.302
1.289
1.278
1.265
1.231
1.223
1.207
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1.150
1.101
1.077
1.059
1.028
0.983
0.963
0.934
0.929
0.897
0.890
0.286
0.280
0.242
0.227
0.218
TBSO
33
1.00
2.85
1.15
1.65
1.28
0.32
0.27
2.24
0.57
0.35
1.57
0.84
3.76
1.12
2.44
1.37
4.24
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2.24
7.63
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3.09
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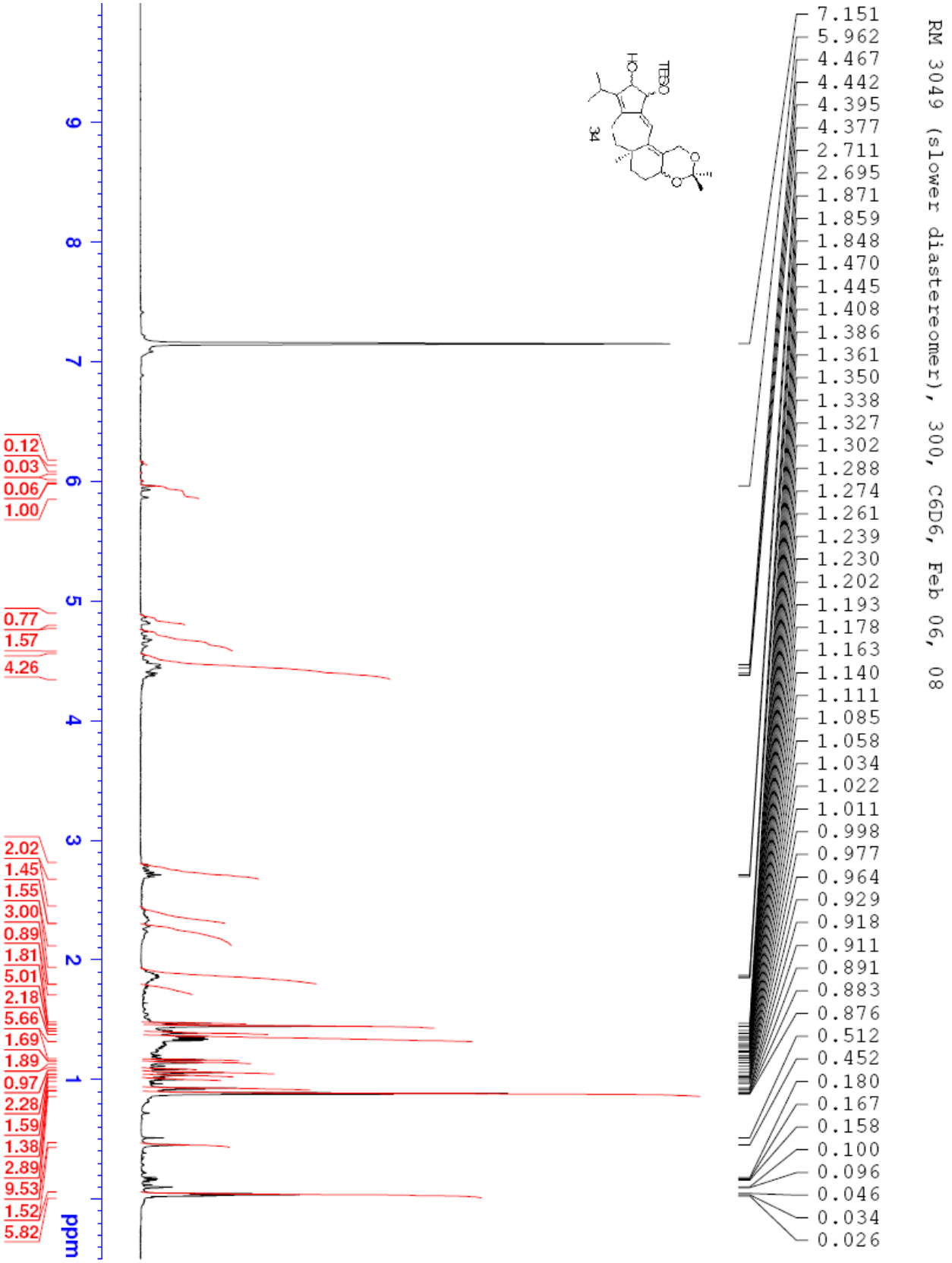
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4.377
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2.695
1.871
1.859
1.848
1.470
1.445
1.408
1.386
1.361
1.350
1.338
1.327
1.302
1.288
1.274
1.261
1.239
1.230
1.202
1.193
1.178
1.163
1.140
1.111
1.085
1.058
1.034
1.022
1.011
0.998
0.977
0.964
0.929
0.918
0.911
0.891
0.883
0.876
0.512
0.452
0.180
0.167
0.158
0.100
0.096
0.046
0.034
0.026
0.12
0.03
0.06
1.00
0.77
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4.26
2.02
1.45
1.55
3.00
0.89
1.81
5.01
2.18
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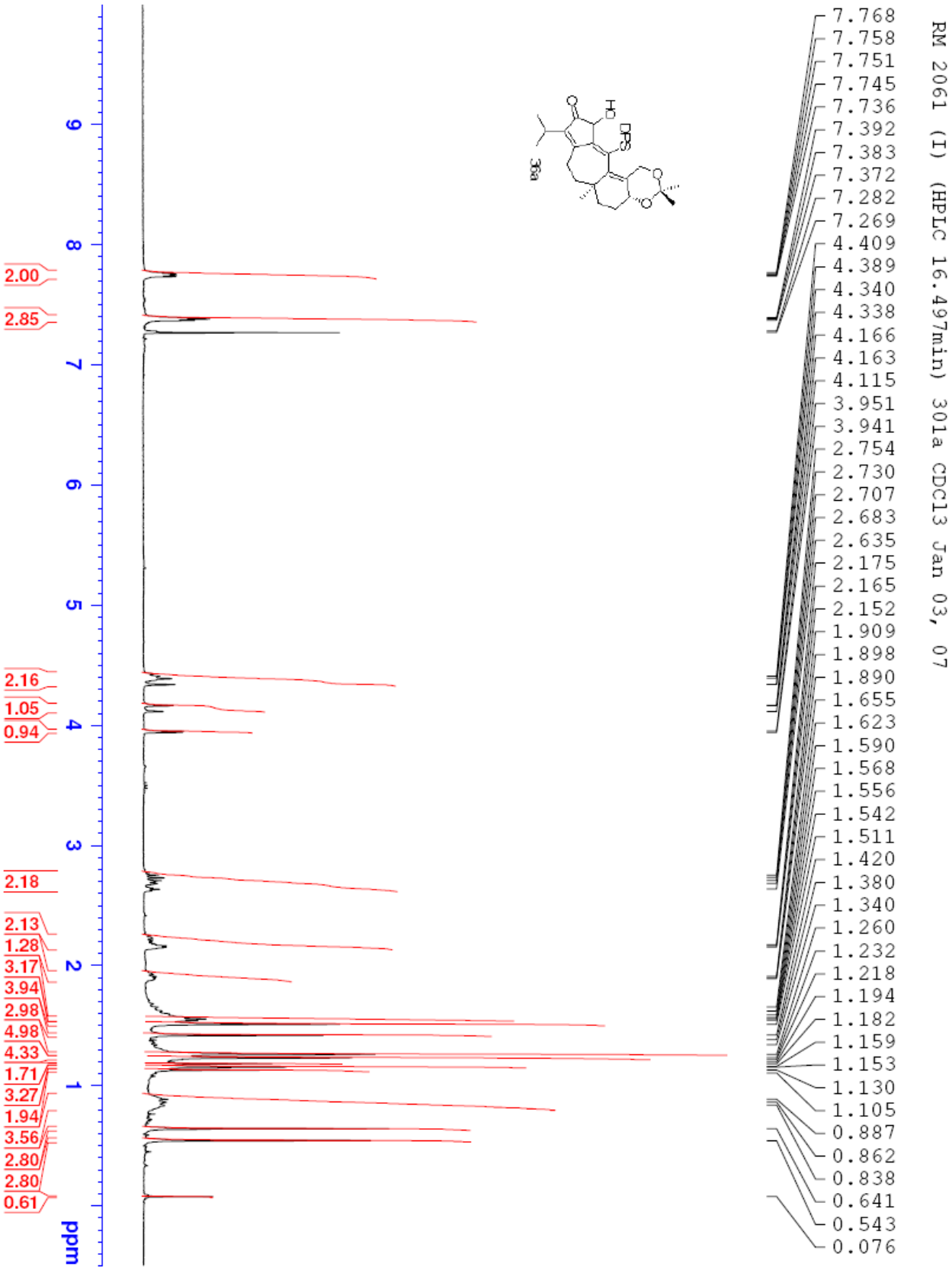
TESO
HO
34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7.282
7.269
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4.338
4.166
4.163
4.115
3.951
3.941
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2.730
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2.683
2.635
2.175
2.165
2.152
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1.898
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1.542
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1.218
1.194
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1.153
1.130
1.105
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0.862
0.838
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0.543
0.076
2.00
2.85
2.16
1.05
0.94
2.18
2.13
1.28
3.17
3.94
2.98
4.98
4.33
1.71
3.27
1.94
3.56
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0.61
ppm
9
8
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6
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4
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2
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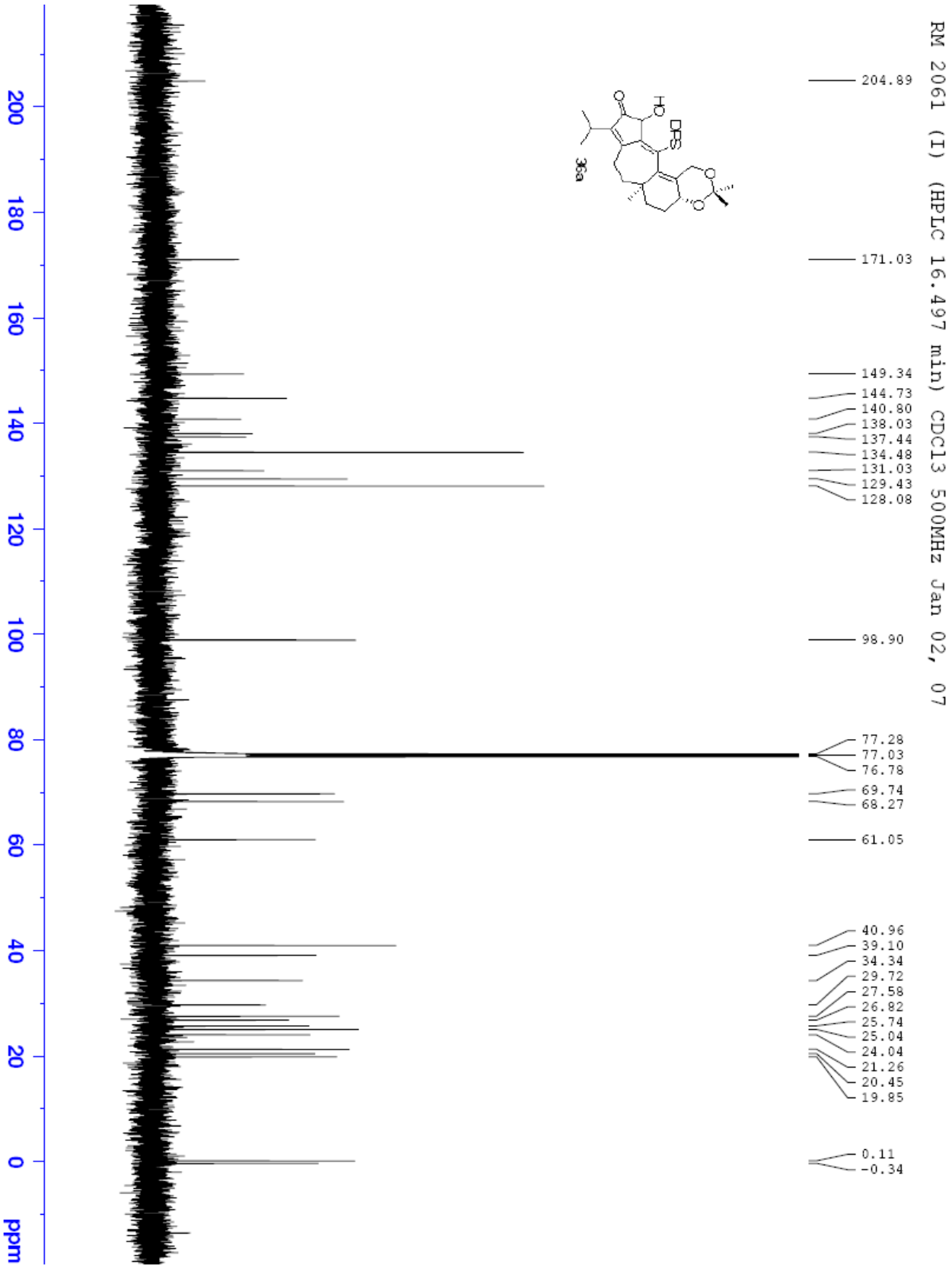
OH
OBS
36a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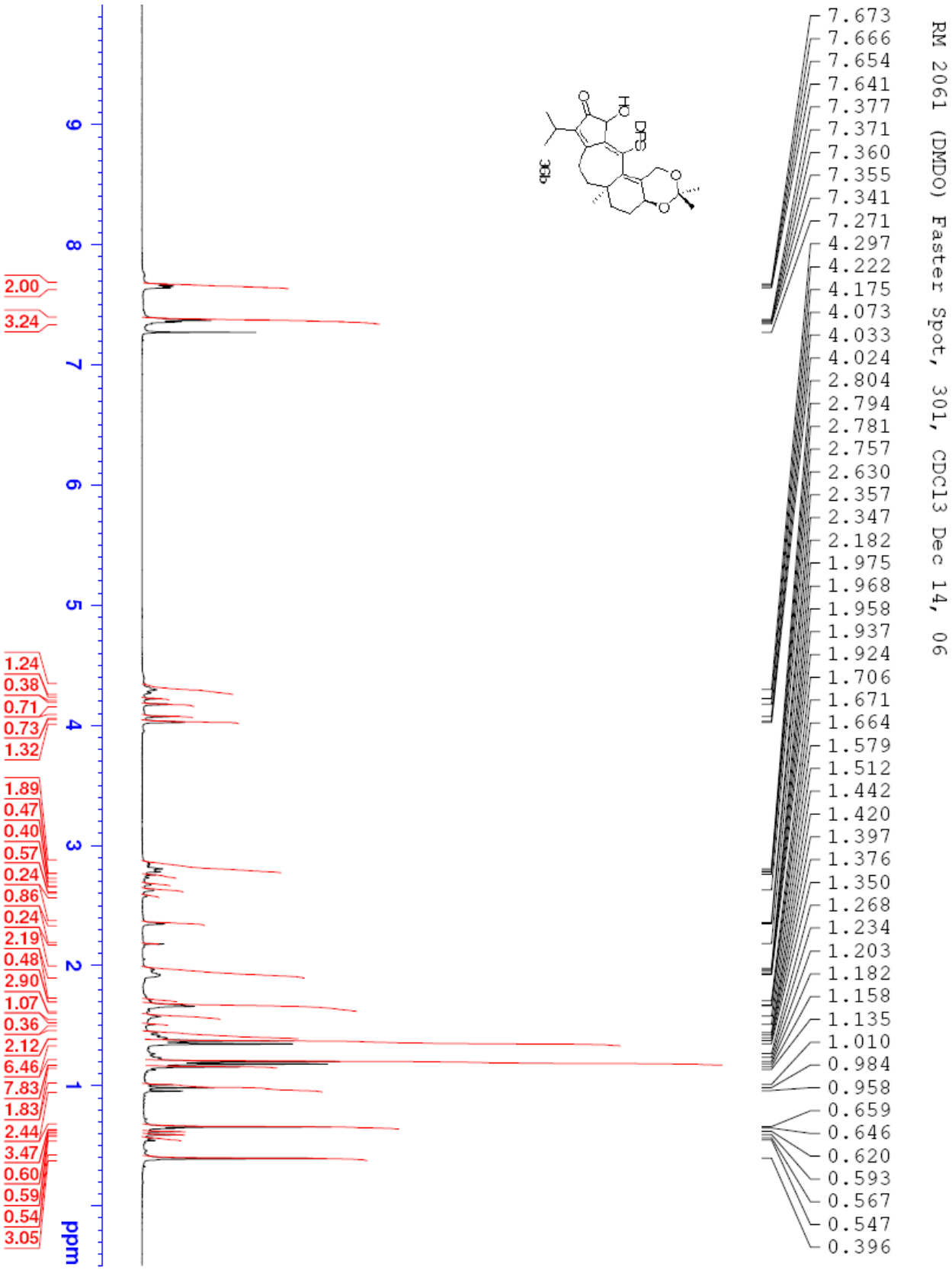
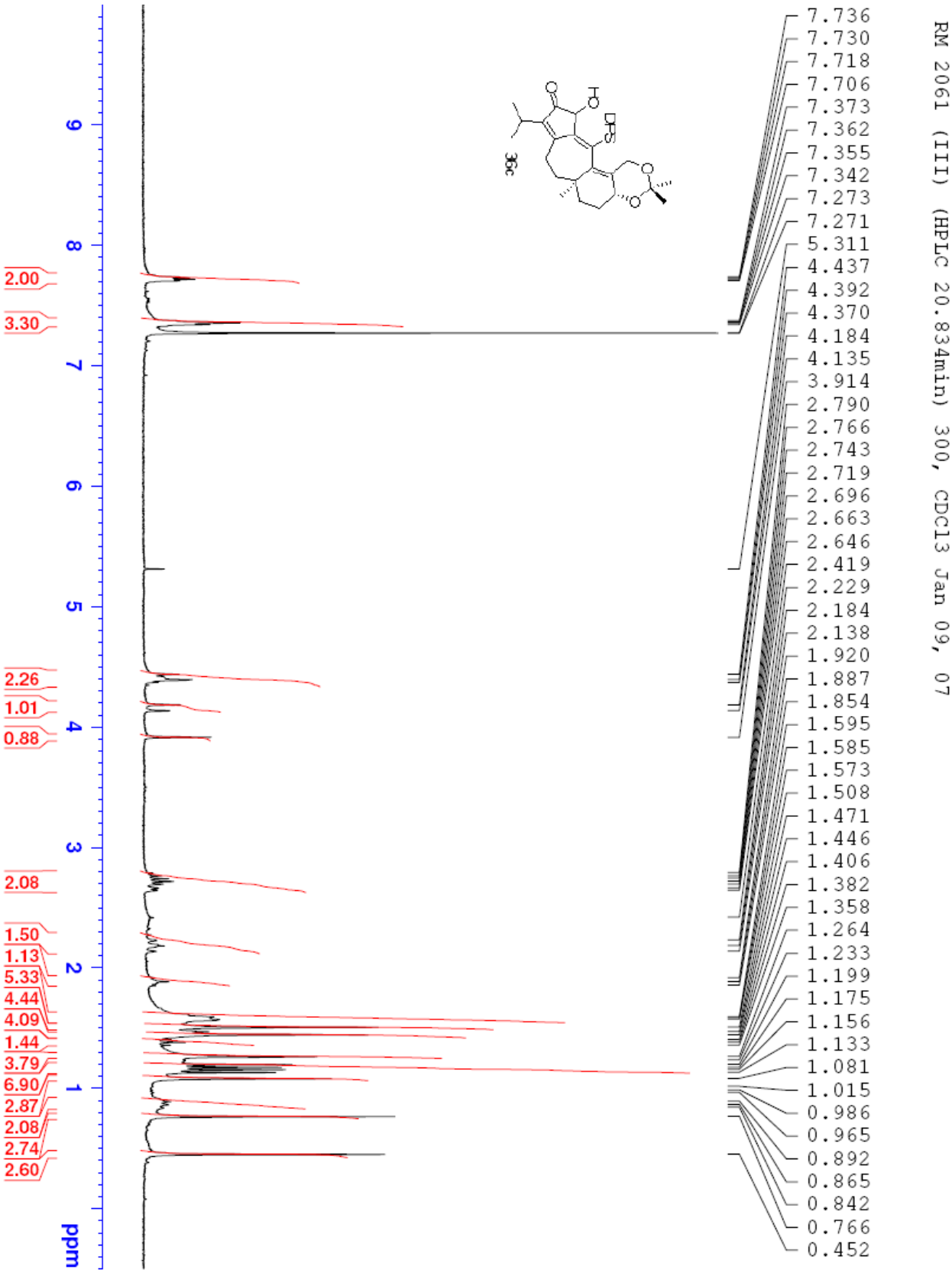
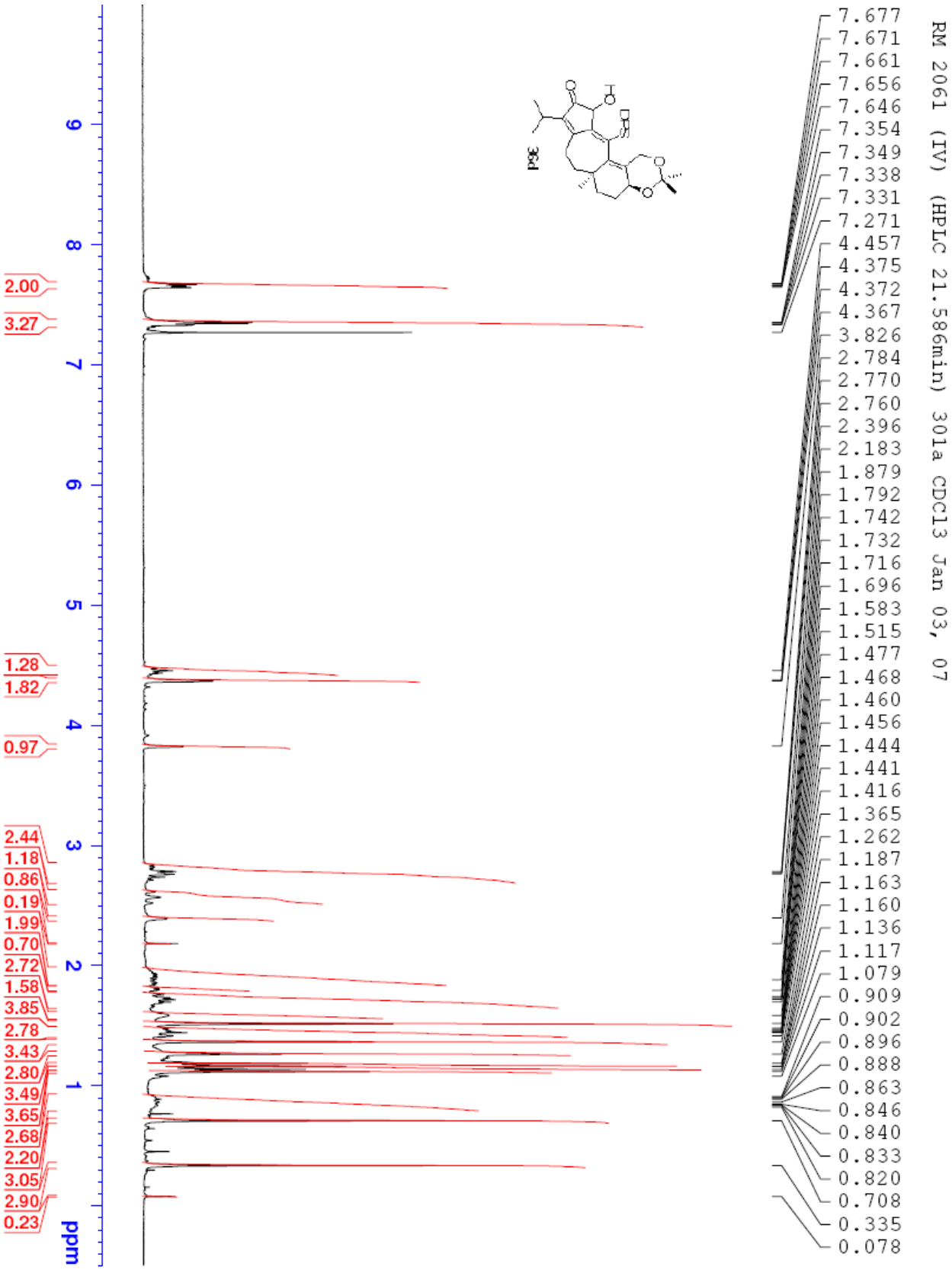
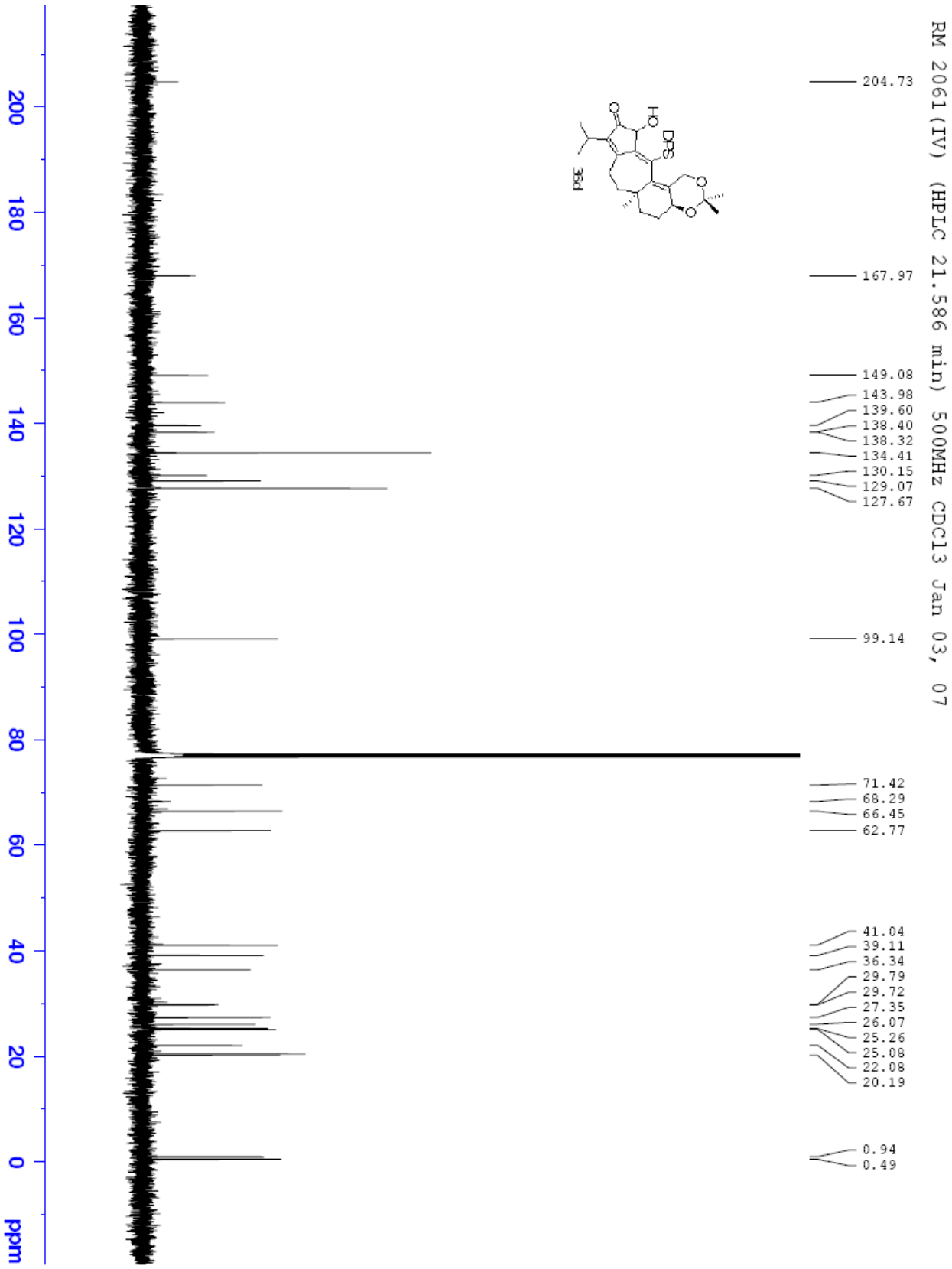
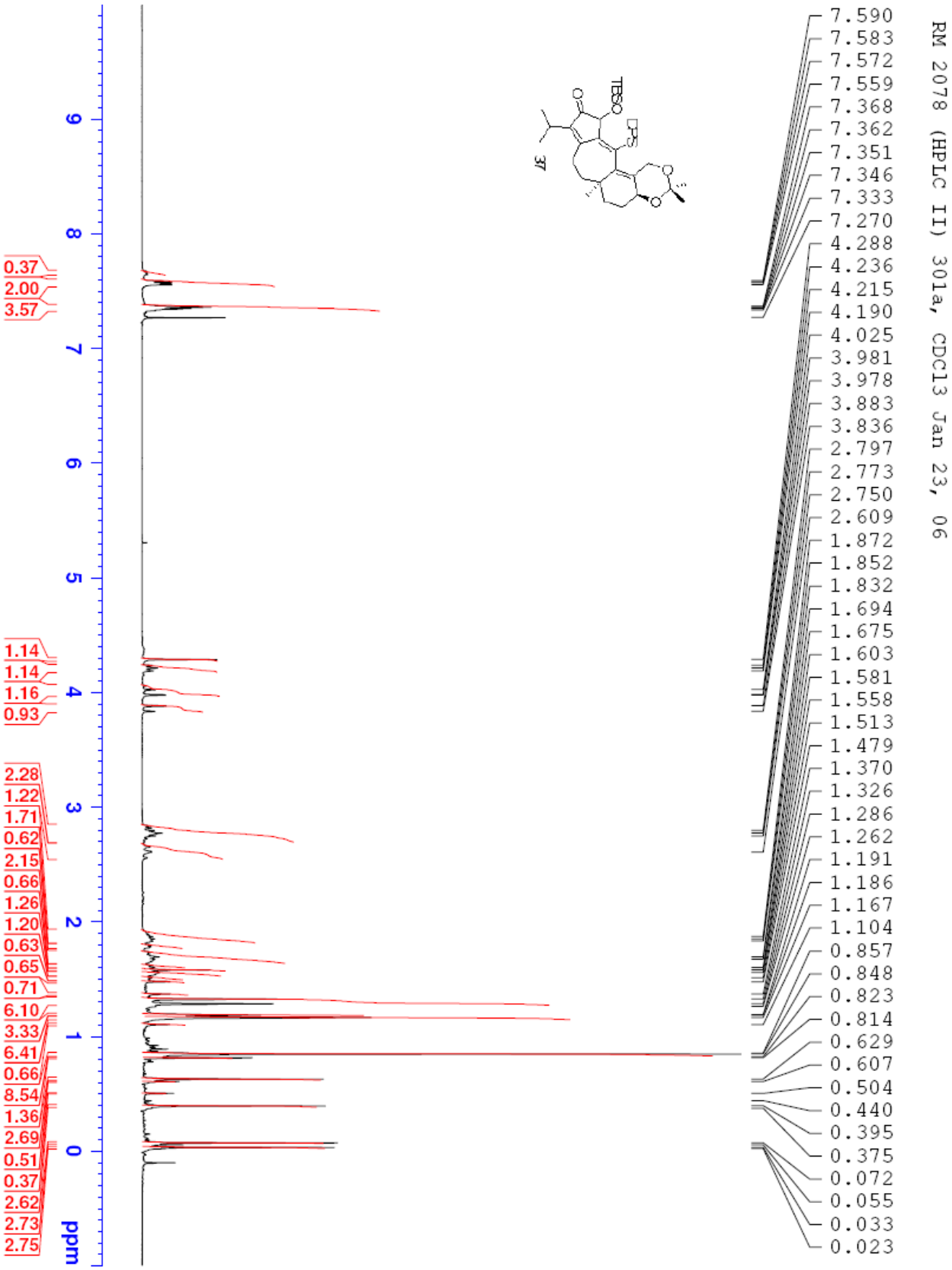
131.03
129.43
128.08
98.90
77.28
77.03
76.78
69.74
68.27
61.05
40.96
39.10
34.34
29.72
27.58
26.82
25.74
25.04
24.04
21.26
20.45
19.85
0.11
-0.34
200
180
160
140
120
100
80
60
40
20
0
ppm

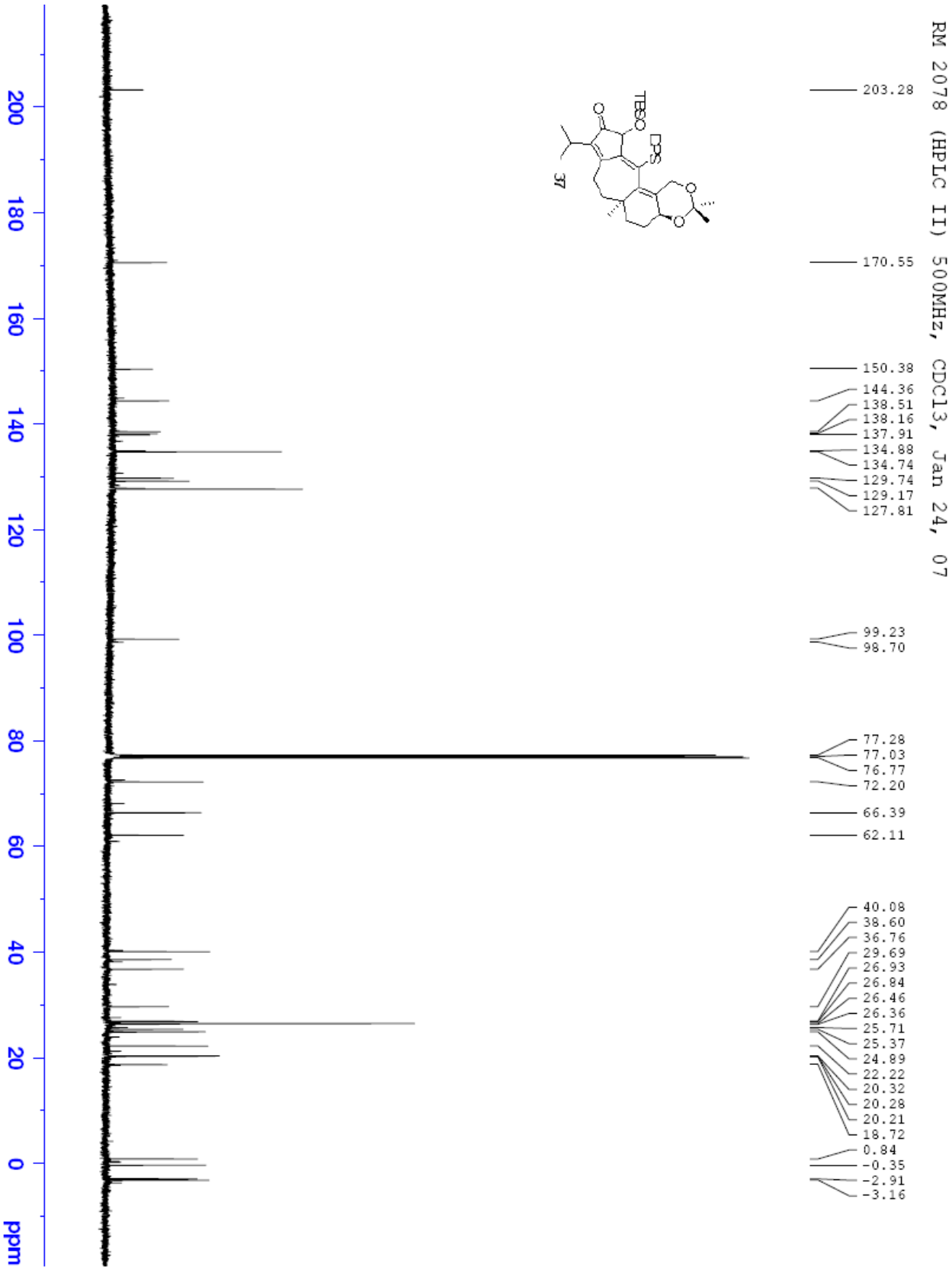

RM 2061 (DMDO) Faster Spot, 301, CDC13 Dec 14, 06
7.673
7.666
7.654
7.641
7.377
7.371
7.360
7.355
7.341
7.271
4.297
4.222
4.175
4.073
4.033
4.024
2.804
2.794
2.781
2.757
2.630
2.357
2.347
2.182
1.975
1.968
1.958
1.937
1.924
1.706
1.671
1.664
1.579
1.512
1.442
1.420
1.397
1.376
1.350
1.268
1.234
1.203
1.182
1.158
1.135
1.010
0.984
0.958
0.659
0.646
0.620
0.593
0.567
0.547
0.396
HO
OBn
2.00
3.24
1.24
0.38
0.71
0.73
1.32
1.89
0.47
0.40
0.57
0.24
0.86
0.24
2.19
0.48
2.90
1.07
0.36
2.12
6.46
7.83
1.83
2.44
3.47
0.60
0.59
0.54
3.05
ppm

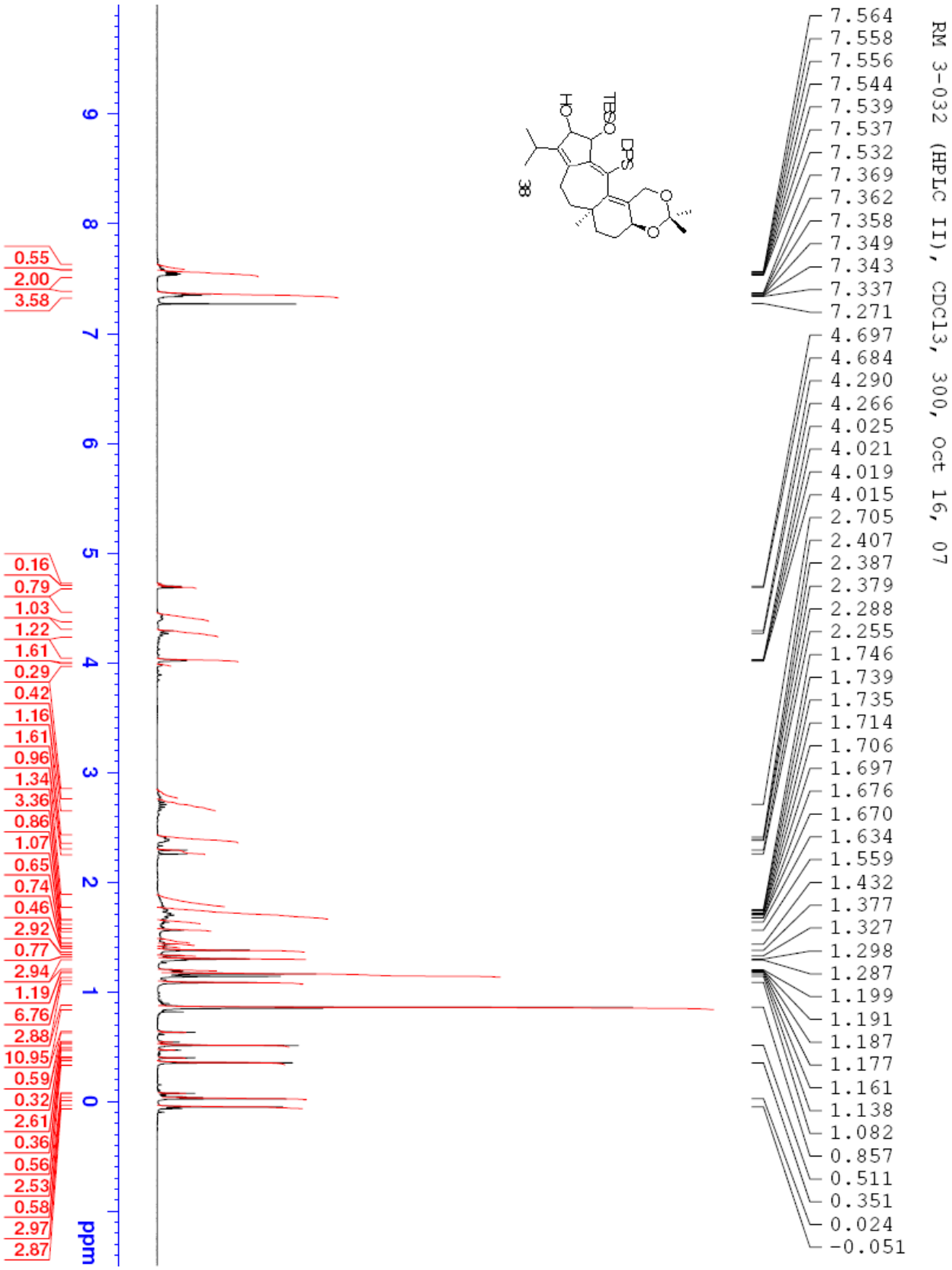

RM 2061 (III) (HPLC 20.834min) 300, CDC13 Jan 09, 07
7.736
7.730
7.718
7.706
7.373
7.362
7.355
7.342
7.273
7.271
5.311
4.437
4.392
4.370
4.184
4.135
3.914
2.790
2.766
2.743
2.719
2.696
2.663
2.646
2.419
2.229
2.184
2.138
1.920
1.887
1.854
1.595
1.585
1.573
1.508
1.471
1.446
1.406
1.382
1.358
1.264
1.233
1.199
1.175
1.156
1.133
1.081
1.015
0.986
0.965
0.892
0.865
0.842
0.766
0.452
2.00
3.30
2.26
1.01
0.88
2.08
1.50
1.13
5.33
4.44
4.09
1.44
3.79
6.90
2.87
2.08
2.74
2.60
ppm
HO
OPS
36c

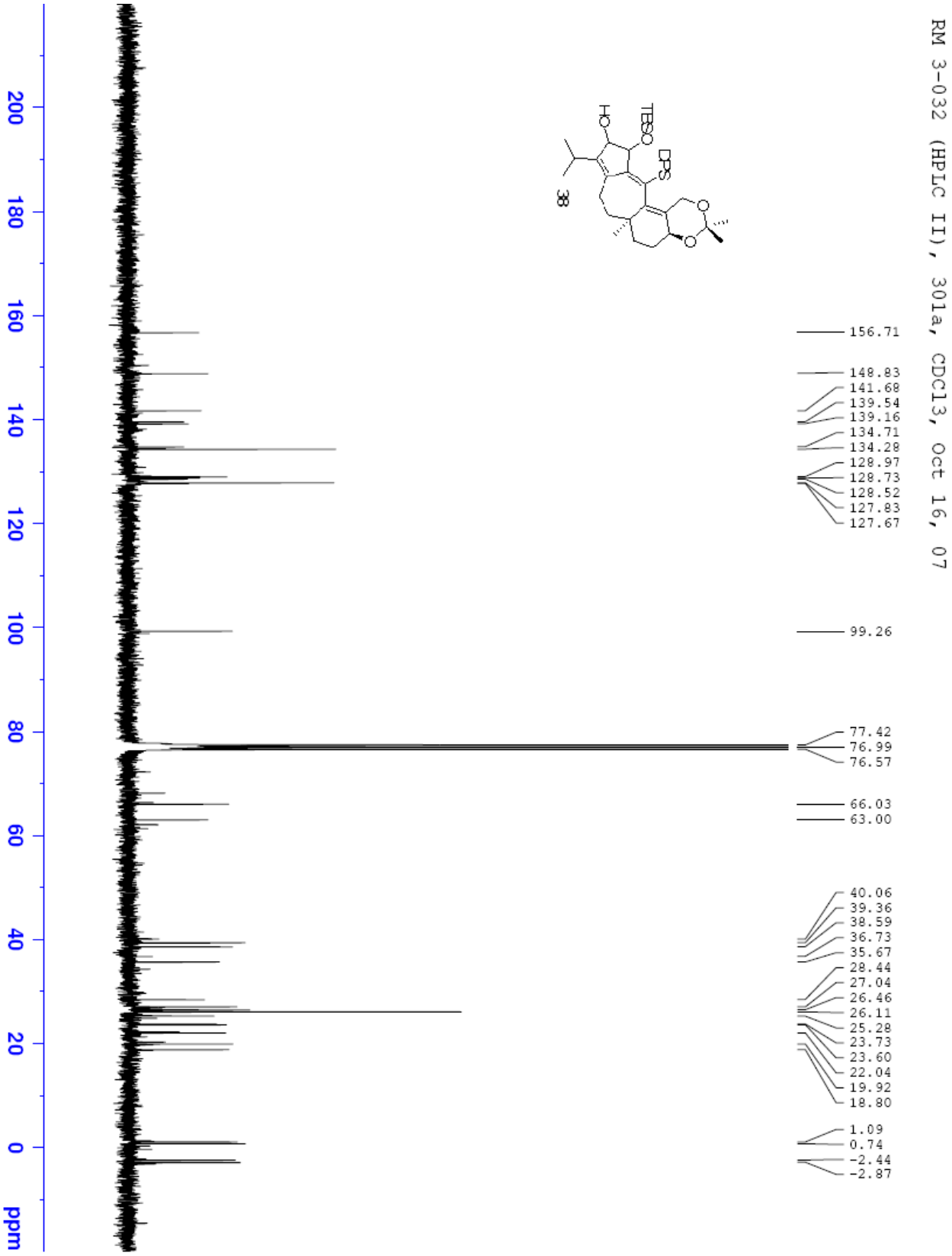

RM 2061 (IV) (HPLC 21.586min) 301a CDCl3 Jan 03, 07
7.677
7.671
7.661
7.656
7.646
7.354
7.349
7.338
7.331
7.271
4.457
4.375
4.372
4.367
3.826
2.784
2.770
2.760
2.396
2.183
1.879
1.792
1.742
1.732
1.716
1.696
1.583
1.515
1.477
1.468
1.460
1.456
1.444
1.441
1.416
1.365
1.262
1.187
1.163
1.160
1.136
1.117
1.079
0.909
0.902
0.896
0.888
0.863
0.846
0.840
0.833
0.820
0.708
0.335
0.078
2.00
3.27
1.28
1.82
0.97
2.44
1.18
0.86
0.19
1.99
0.70
2.72
1.58
3.85
2.78
3.43
2.80
3.49
3.65
2.68
2.20
3.05
2.90
0.23
ppm
9
8
7
6
5
4
3
2
1
TBS
OH
O
O
O
364

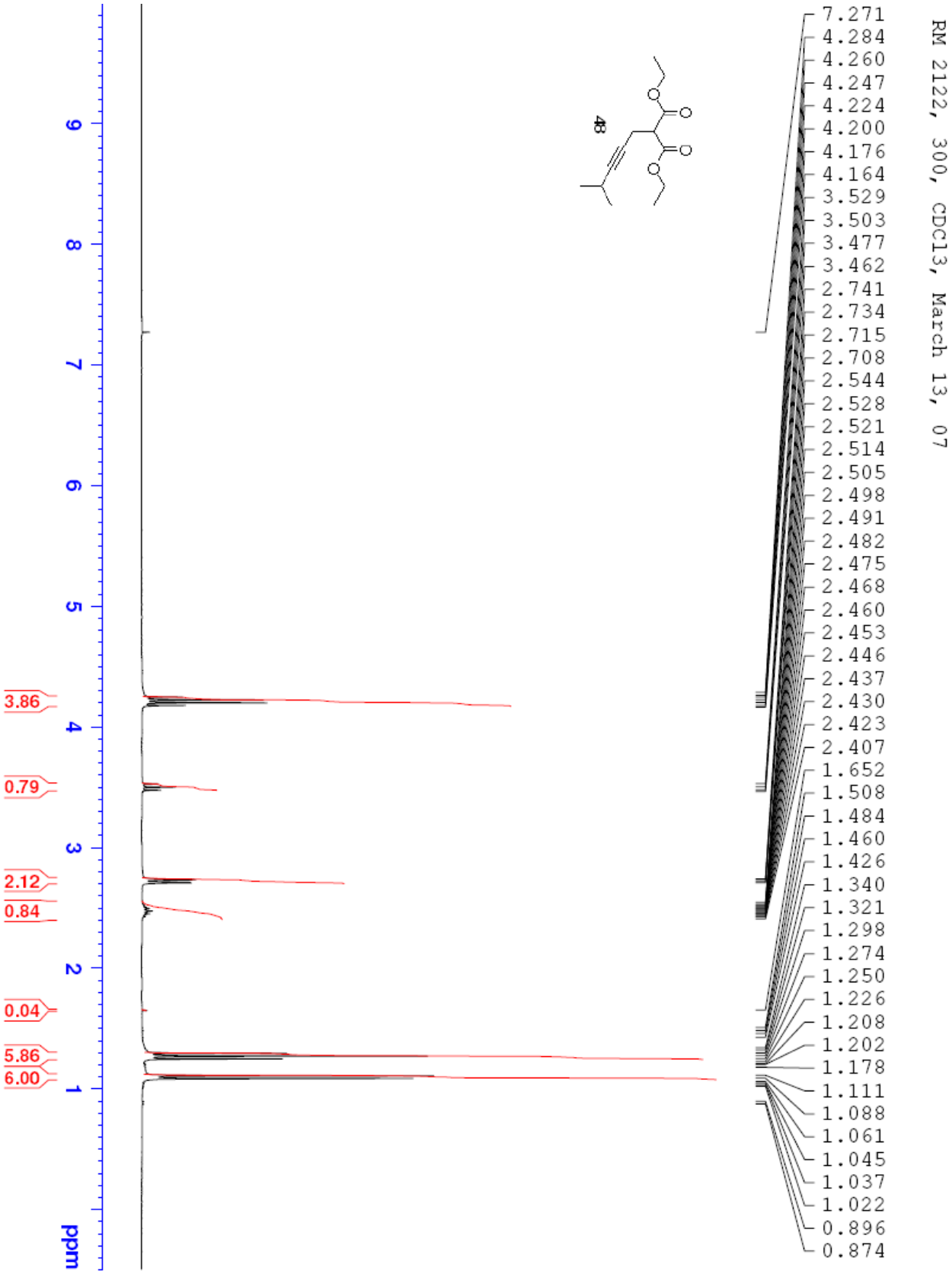

RM 2061(IV) (HPLC 21.586 min) 500MHz CDCl3 Jan 03, 07
204.73
167.97
149.08
143.98
139.60
138.40
138.32
134.41
130.15
129.07
127.67
99.14
71.42
68.29
66.45
62.77
41.04
39.11
36.34
29.79
29.72
27.35
26.07
25.26
25.08
22.08
20.19
0.94
0.49
200
180
160
140
120
100
80
60
40
20
0
ppm

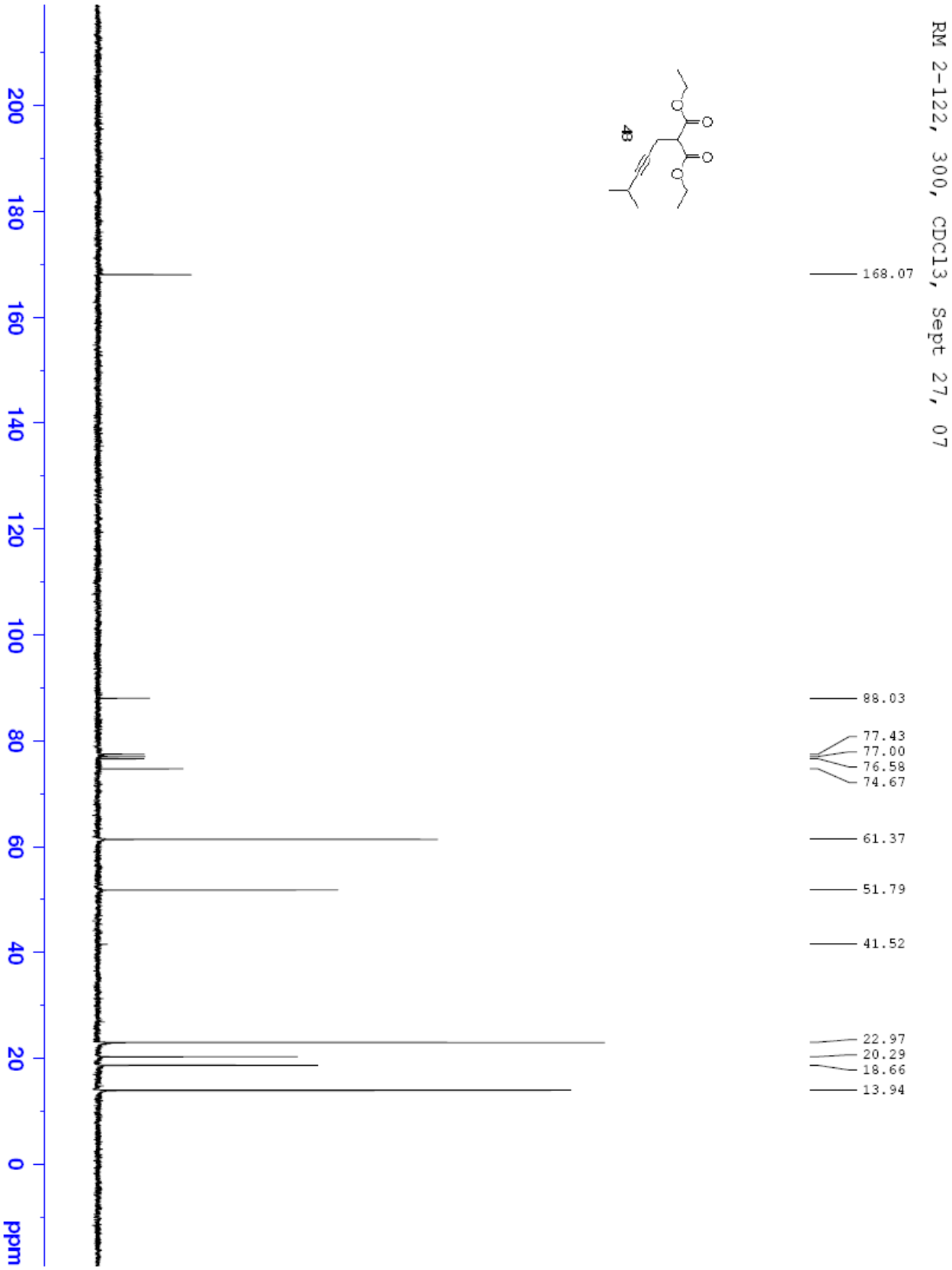

RM 2078 (HPLC II) 301a, CDC13 Jan 23, 06
7.590
7.583
7.572
7.559
7.368
7.362
7.351
7.346
7.333
7.270
4.288
4.236
4.215
4.190
4.025
3.981
3.978
3.883
3.836
2.797
2.773
2.750
2.609
1.872
1.852
1.832
1.694
1.675
1.603
1.581
1.558
1.513
1.479
1.370
1.326
1.286
1.262
1.191
1.186
1.167
1.104
0.857
0.848
0.823
0.814
0.629
0.607
0.504
0.440
0.395
0.375
0.072
0.055
0.033
0.023
0.37
2.00
3.57
1.14
1.14
1.16
0.93
2.28
1.22
1.71
0.62
2.15
0.66
1.26
1.20
0.63
0.65
0.71
6.10
3.33
6.41
0.66
8.54
1.36
2.69
0.51
0.37
2.62
2.73
2.75
ppm
TBSO
OPS
3E

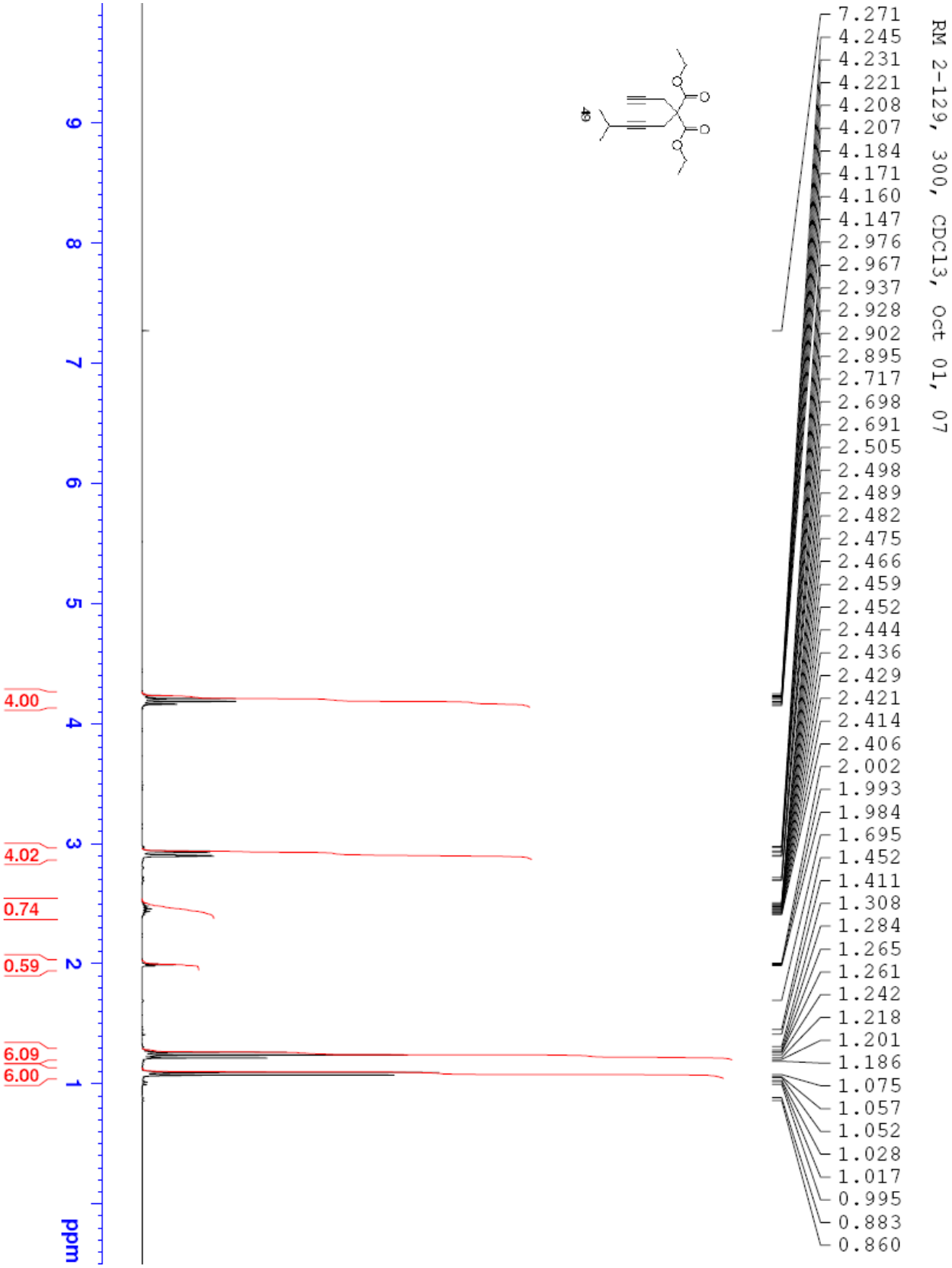

RM 2078 (HPLC II) 500MHz, CDCl3, Jan 24, 07
203.28
170.55
150.38
144.36
138.51
138.16
137.91
134.88
134.74
129.74
129.17
127.81
99.23
98.70
77.28
77.03
76.77
72.20
66.39
62.11
40.08
38.60
36.76
29.69
26.93
26.84
26.46
26.36
25.71
25.37
24.89
22.22
20.32
20.28
20.21
18.72
0.84
-0.35
-2.91
-3.16
TBSO
OBn
3E
200
180
160
140
120
100
80
60
40
20
0
ppm

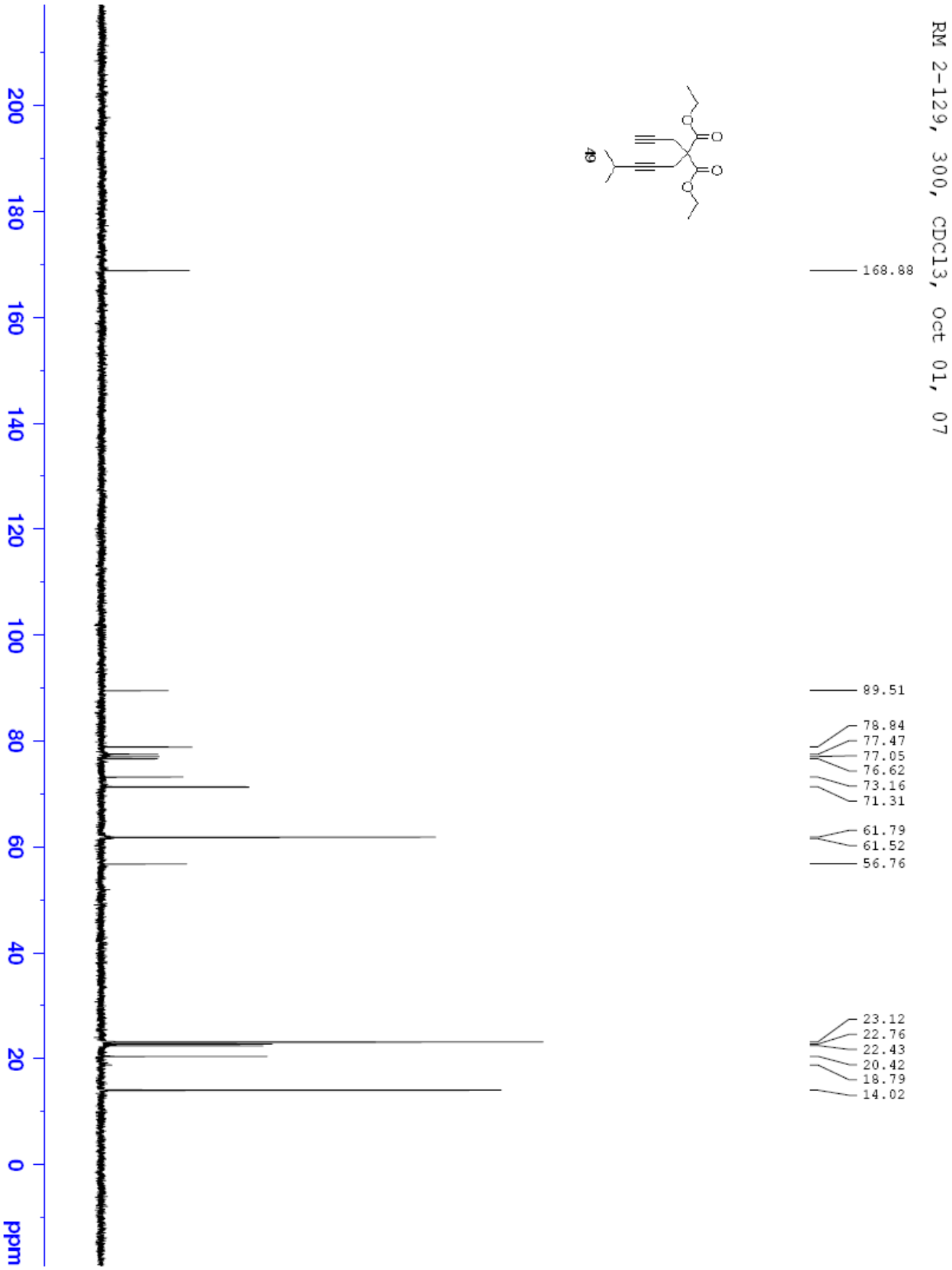

RM 3-032 (HPLC II), CDC13, 300, Oct 16, 07
7.564
7.558
7.556
7.544
7.539
7.537
7.532
7.369
7.362
7.358
7.349
7.343
7.337
7.271
4.697
4.684
4.290
4.266
4.025
4.021
4.019
4.015
2.705
2.407
2.387
2.379
2.288
2.255
1.746
1.739
1.735
1.714
1.706
1.697
1.676
1.670
1.634
1.559
1.432
1.377
1.327
1.298
1.287
1.199
1.191
1.187
1.177
1.161
1.138
1.082
0.857
0.511
0.351
0.024
-0.051
HO
TBSO
DPS
38
0.55
2.00
3.58
0.16
0.79
1.03
1.22
1.61
0.29
0.42
1.16
1.61
0.96
1.34
3.36
0.86
1.07
0.65
0.74
0.46
2.92
0.77
2.94
1.19
6.76
2.88
10.95
0.59
0.32
2.61
0.36
0.56
2.53
0.58
2.97
2.87
9
8
7
6
5
4
3
2
1
0
ppm

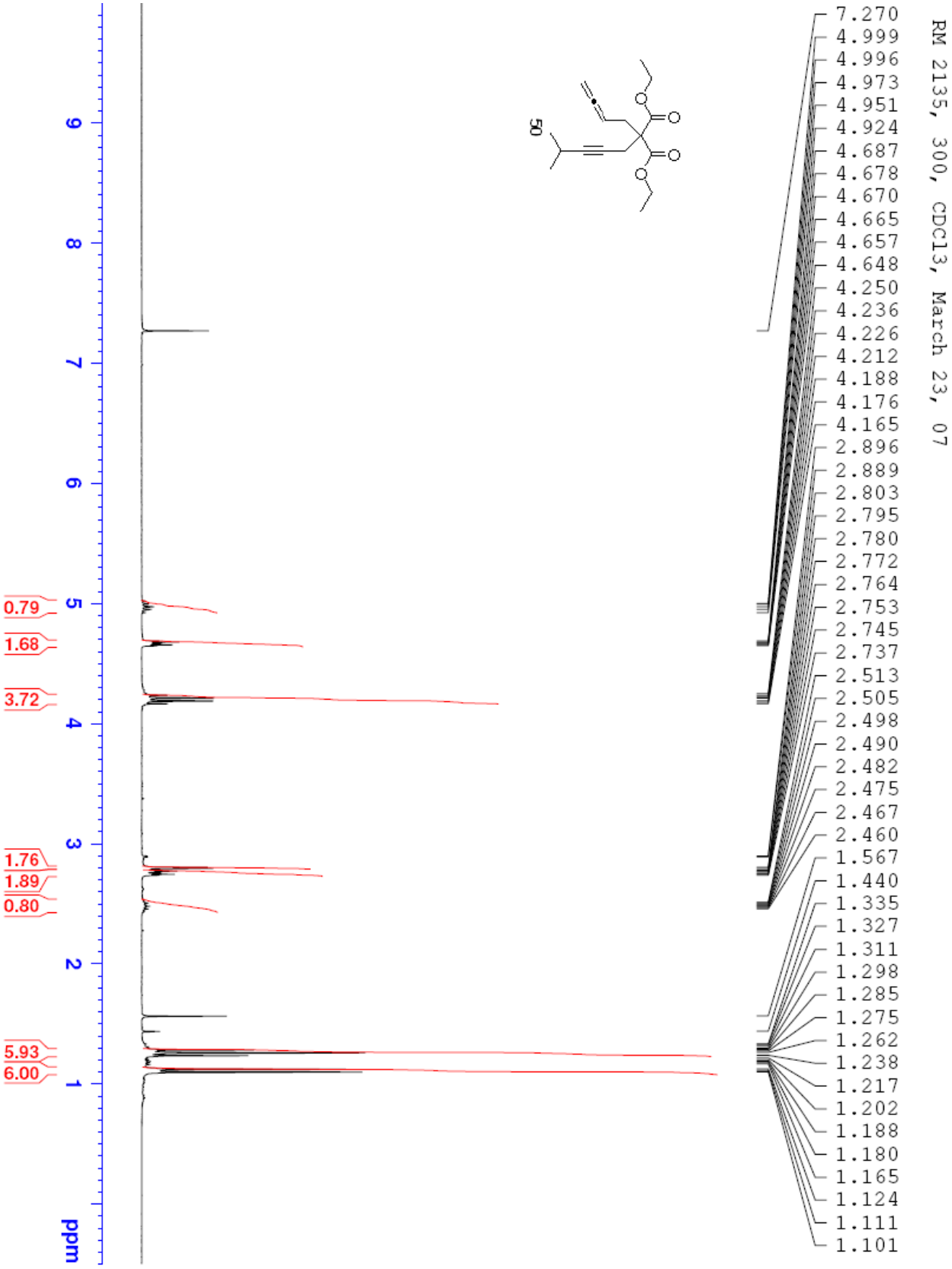

RM 3-032 (HPLC II), 301a, CDC13, Oct 16, 07
38
HO
TBSO
OPS
156.71
148.83
141.68
139.54
139.16
134.71
134.28
128.97
128.73
128.52
127.83
127.67
99.26
77.42
76.99
76.57
66.03
63.00
40.06
39.36
38.59
36.73
35.67
28.44
27.04
26.46
26.11
25.28
23.73
23.60
22.04
19.92
18.80
1.09
0.74
-2.44
-2.87
200
180
160
140
120
100
80
60
40
20
0
ppm

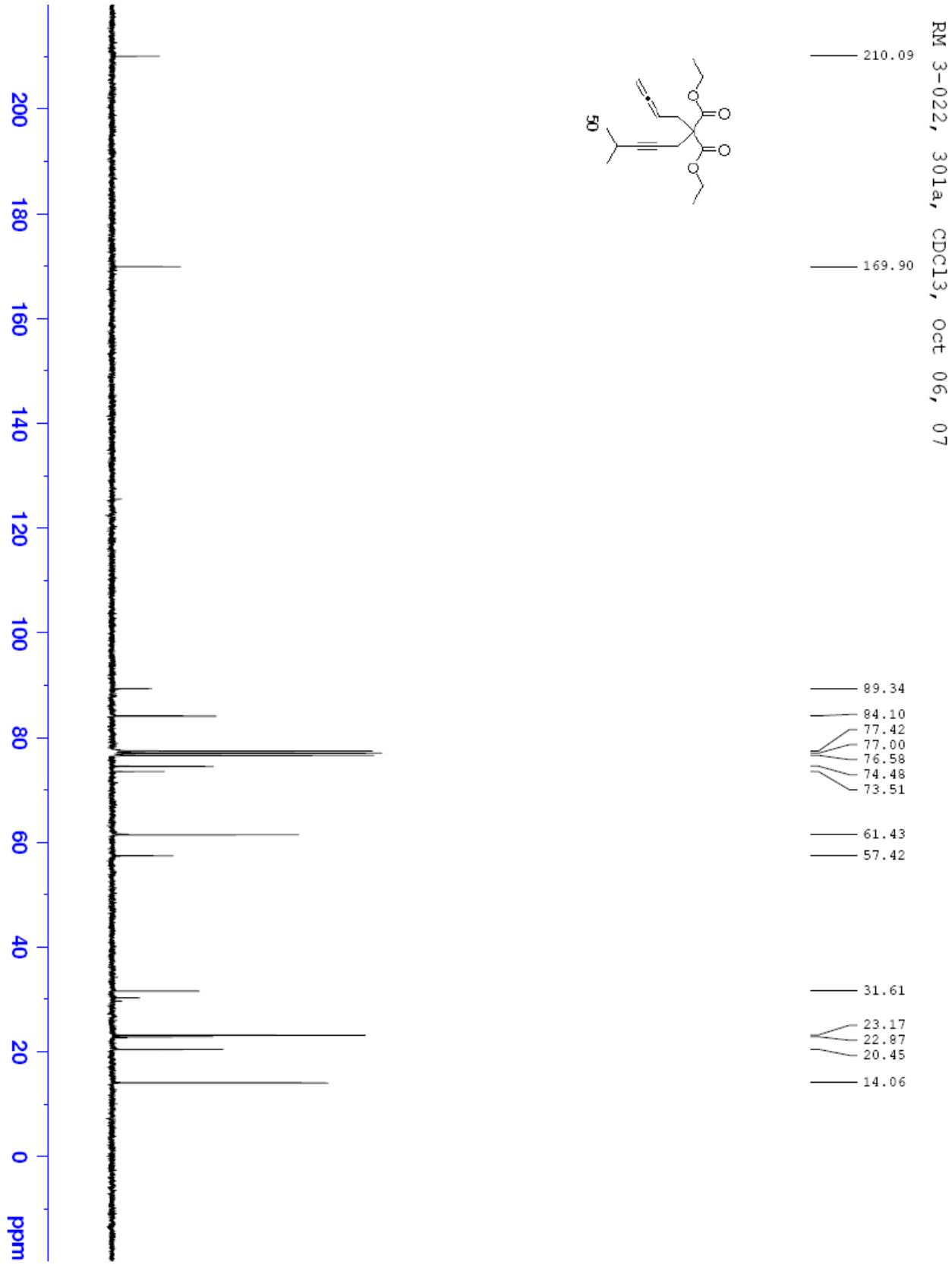

RM 2122, 300, CDC13, March 13, 07
7.271
4.284
4.260
4.247
4.224
4.200
4.176
4.164
3.529
3.503
3.477
3.462
2.741
2.734
2.715
2.708
2.544
2.528
2.521
2.514
2.505
2.498
2.491
2.482
2.475
2.468
2.460
2.453
2.446
2.437
2.430
2.423
2.407
1.652
1.508
1.484
1.460
1.426
1.340
1.321
1.298
1.274
1.250
1.226
1.208
1.202
1.178
1.111
1.088
1.061
1.045
1.037
1.022
0.896
0.874
48
3.86
0.79
2.12
0.84
0.04
5.86
6.00
ppm


RM 2-122, 300, CDCl3, Sept 27, 07
4B
168.07
88.03
77.43
77.00
76.58
74.67
61.37
51.79
41.52
22.97
20.29
18.66
13.94
200
180
160
140
120
100
80
60
40
20
0
ppm

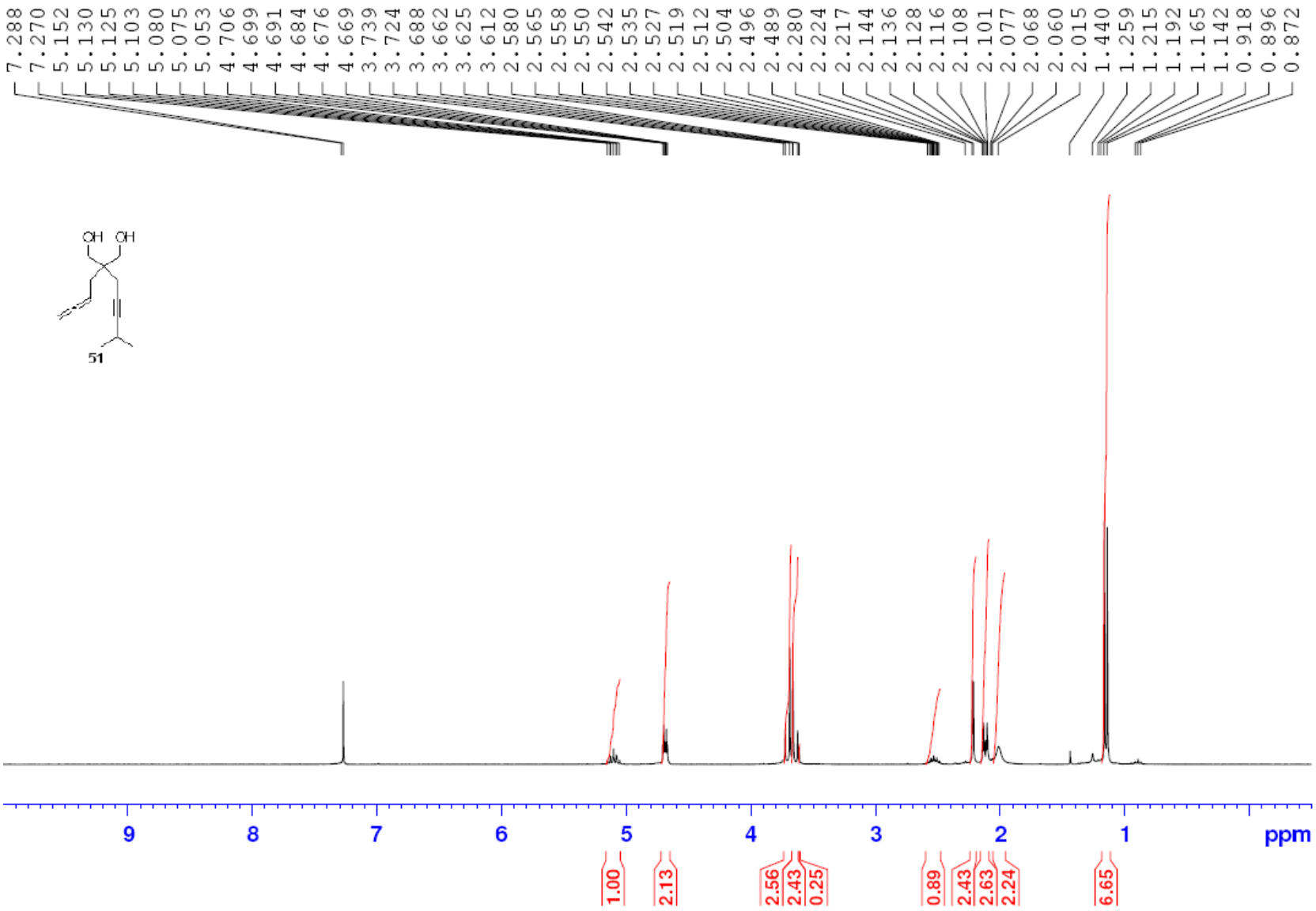

RM 2-129, 300, CDC13, Oct 01, 07
7.271
4.245
4.231
4.221
4.208
4.207
4.184
4.171
4.160
4.147
2.976
2.967
2.937
2.928
2.902
2.895
2.717
2.698
2.691
2.505
2.498
2.489
2.482
2.475
2.466
2.459
2.452
2.444
2.436
2.429
2.421
2.414
2.406
2.002
1.993
1.984
1.695
1.452
1.411
1.308
1.284
1.265
1.261
1.242
1.218
1.201
1.186
1.075
1.057
1.052
1.028
1.017
0.995
0.883
0.860
4.00
4.02
0.74
0.59
6.09
6.00
ppm

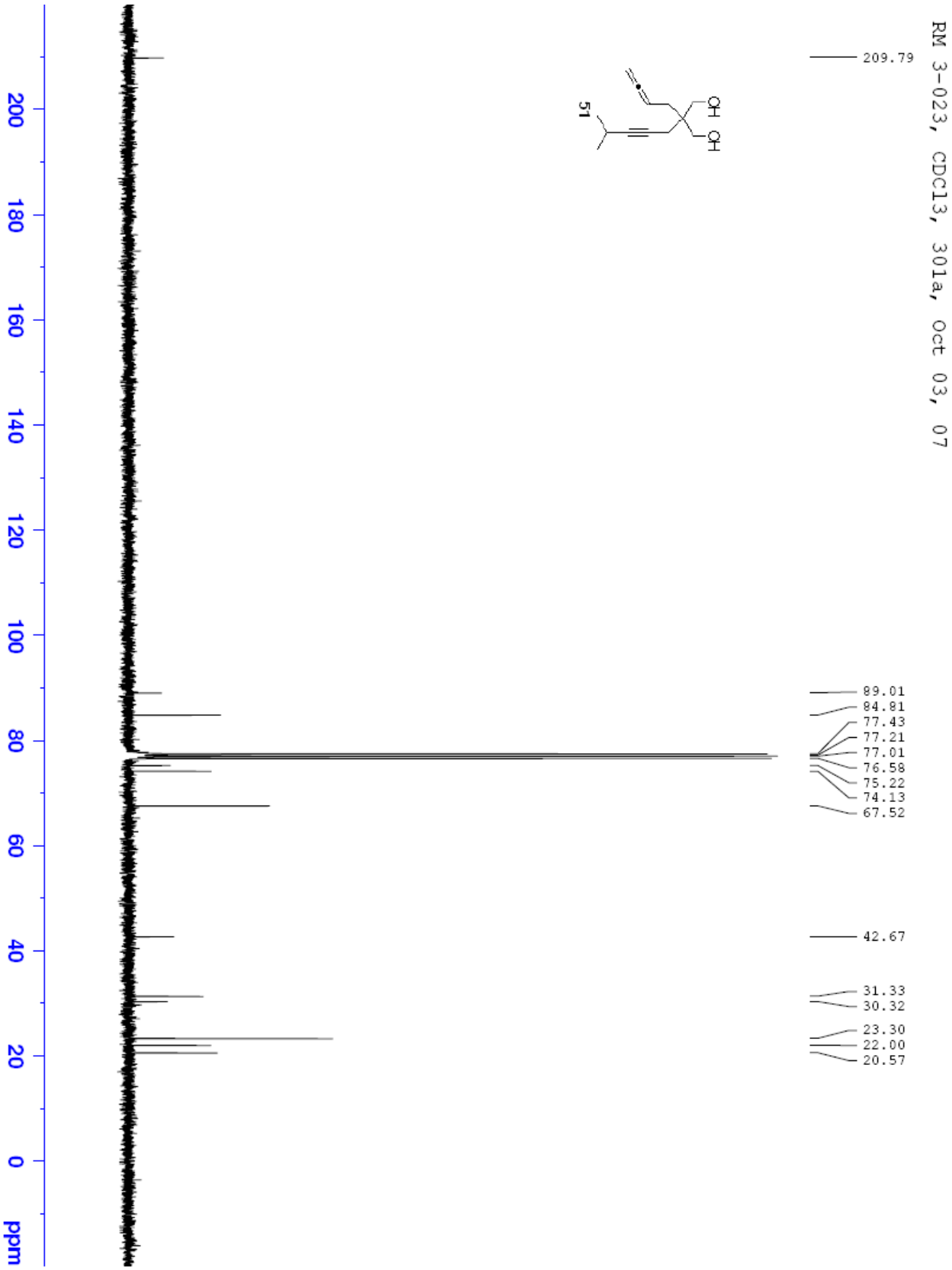

RM 2-129, 300, CDCl3, Oct 01, 07
49
168.88
89.51
78.84
77.47
77.05
76.62
73.16
71.31
61.79
61.52
56.76
23.12
22.76
22.43
20.42
18.79
14.02
200
180
160
140
120
100
80
60
40
20
0
ppm

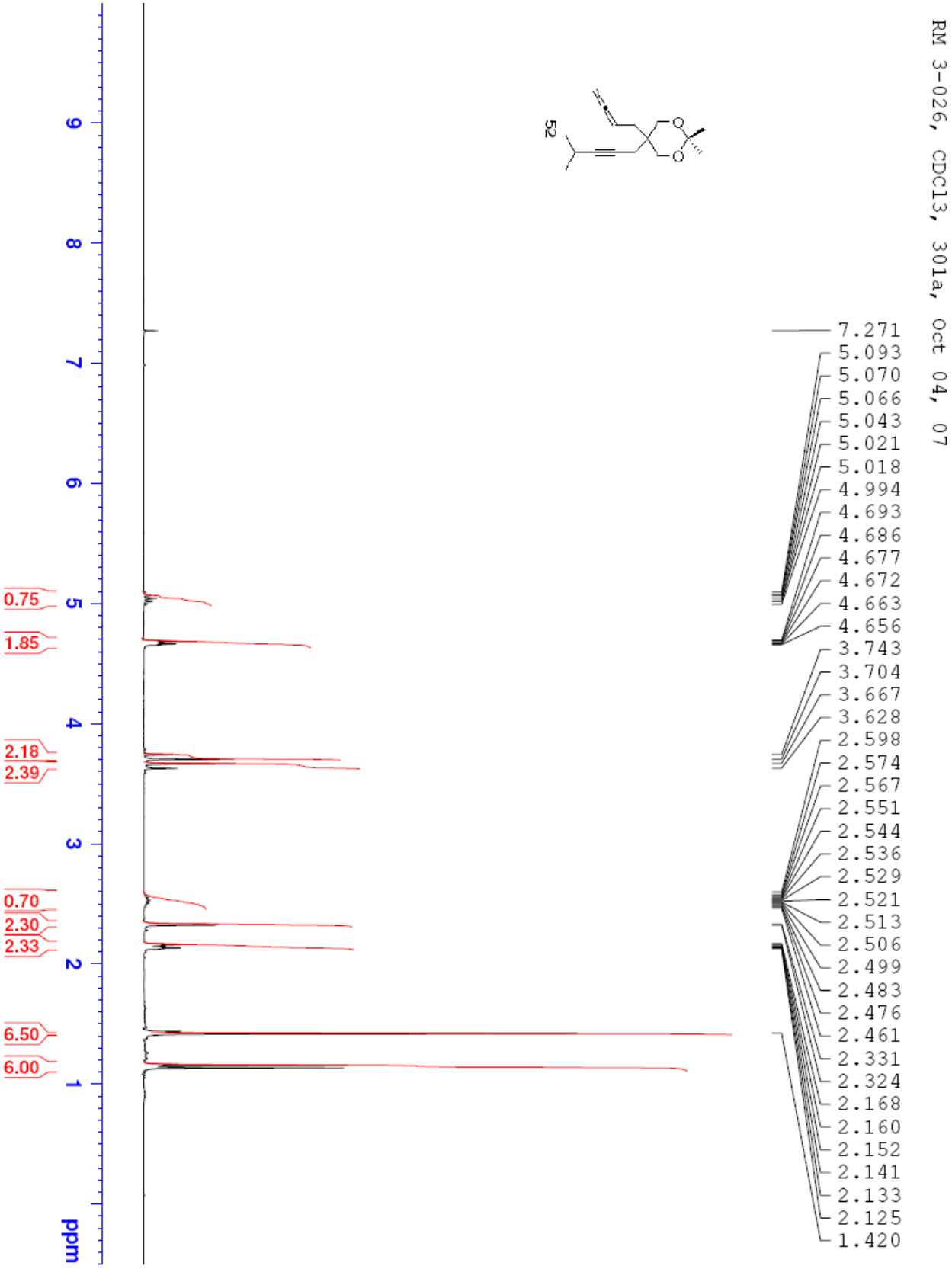

RM 2135, 300, CDCl3, March 23, 07
7.270
4.999
4.996
4.973
4.951
4.924
4.687
4.678
4.670
4.665
4.657
4.648
4.250
4.236
4.226
4.212
4.188
4.176
4.165
2.896
2.889
2.803
2.795
2.780
2.772
2.764
2.753
2.745
2.737
2.513
2.505
2.498
2.490
2.482
2.475
2.467
2.460
1.567
1.440
1.335
1.327
1.311
1.298
1.285
1.275
1.262
1.238
1.217
1.202
1.188
1.180
1.165
1.124
1.111
1.101
50
0.79
1.68
3.72
1.76
1.89
0.80
5.93
6.00
ppm


RM 3-022, 301a, CDCl3, Oct 06, 07
50
210.09
169.90
89.34
84.10
77.42
77.00
76.58
74.48
73.51
61.43
57.42
31.61
23.17
22.87
20.45
14.06
200
180
160
140
120
100
80
60
40
20
0
ppm

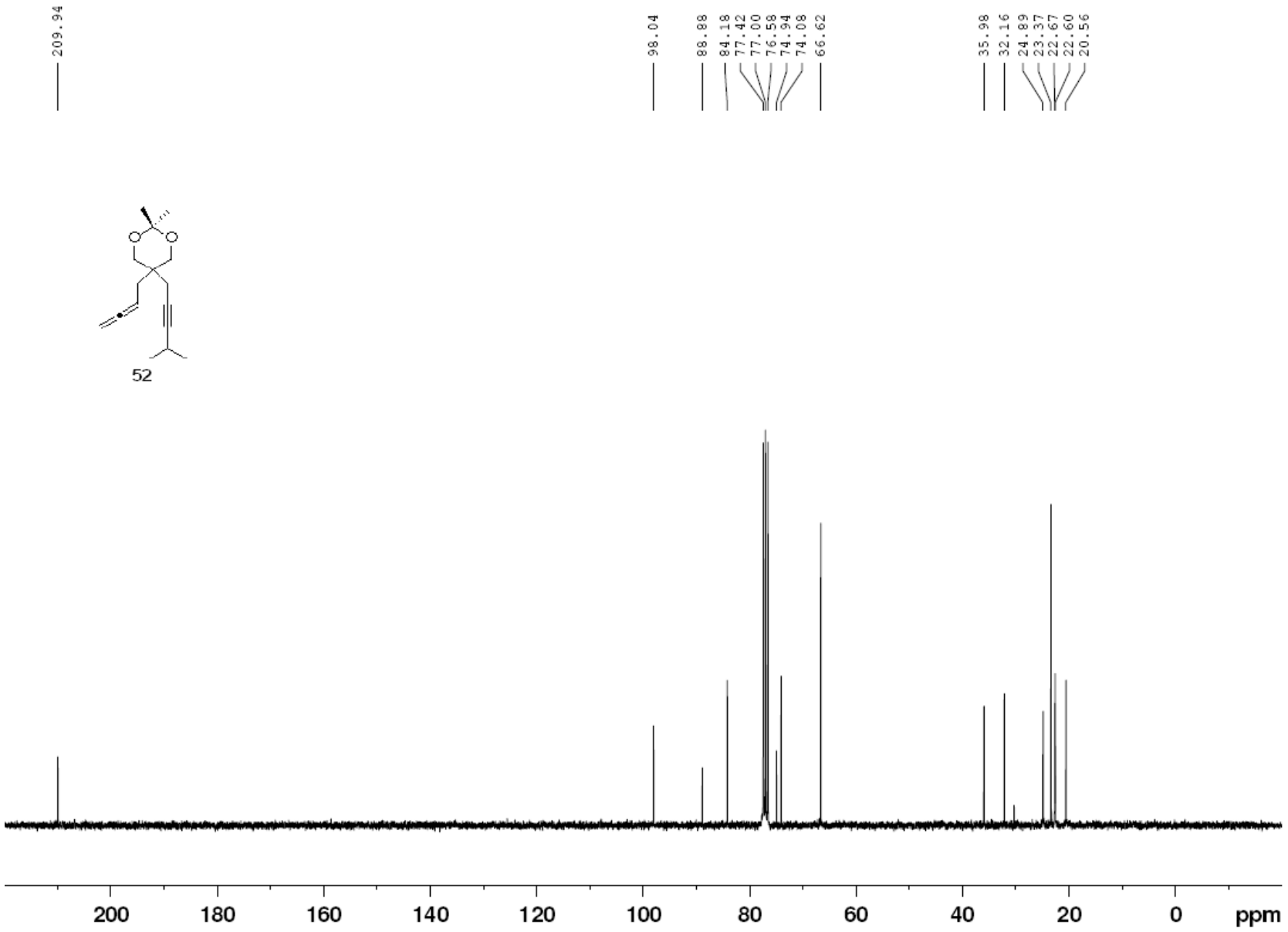
RM 2137, 300, CDCl3, March 27, 07



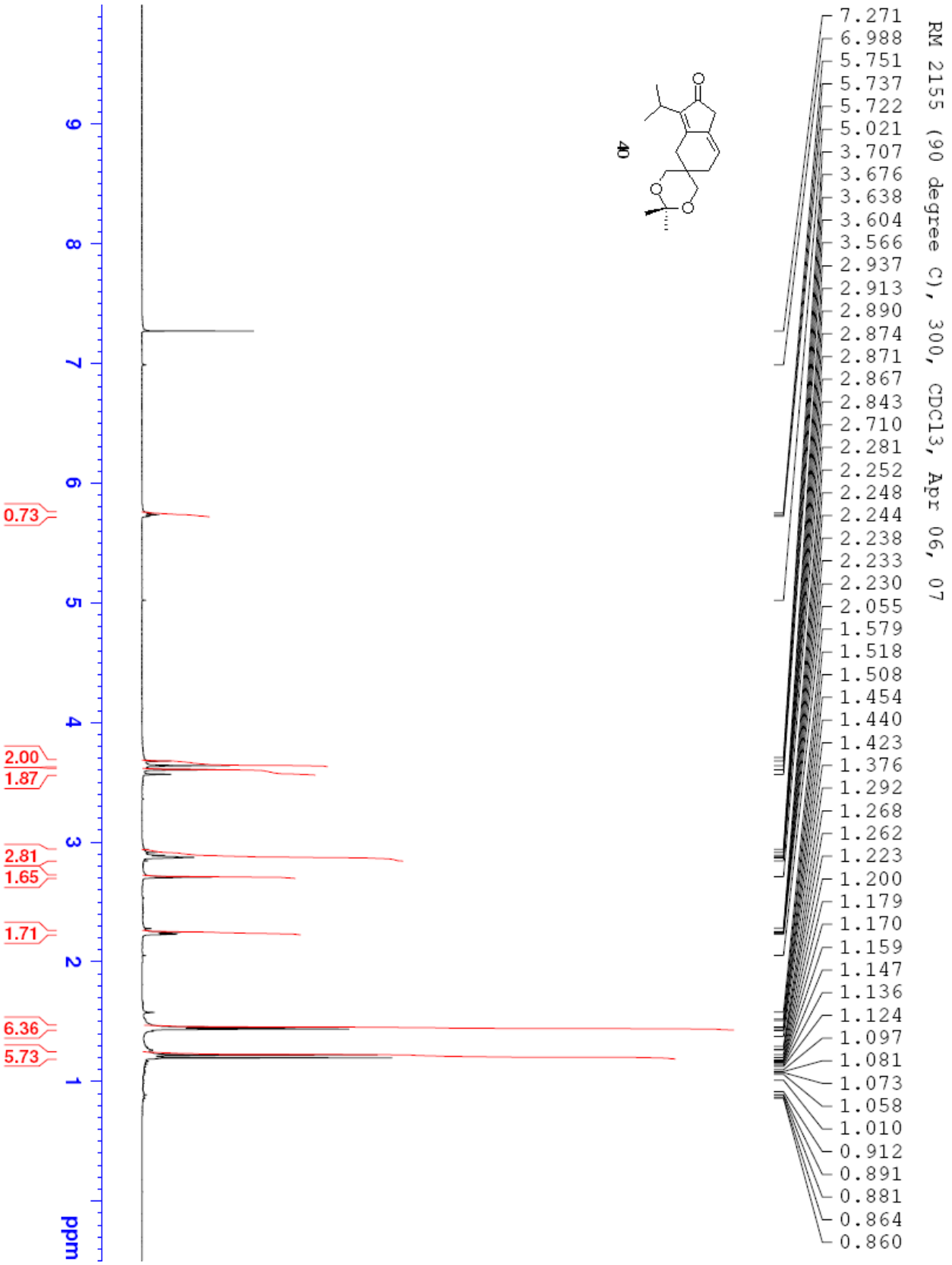

RM 3-023, CDCl3, 301a, Oct 03, 07
209.79
89.01
84.81
77.43
77.21
77.01
76.58
75.22
74.13
67.52
42.67
31.33
30.32
23.30
22.00
20.57
OH
OH
51
200
180
160
140
120
100
80
60
40
20
0
ppm

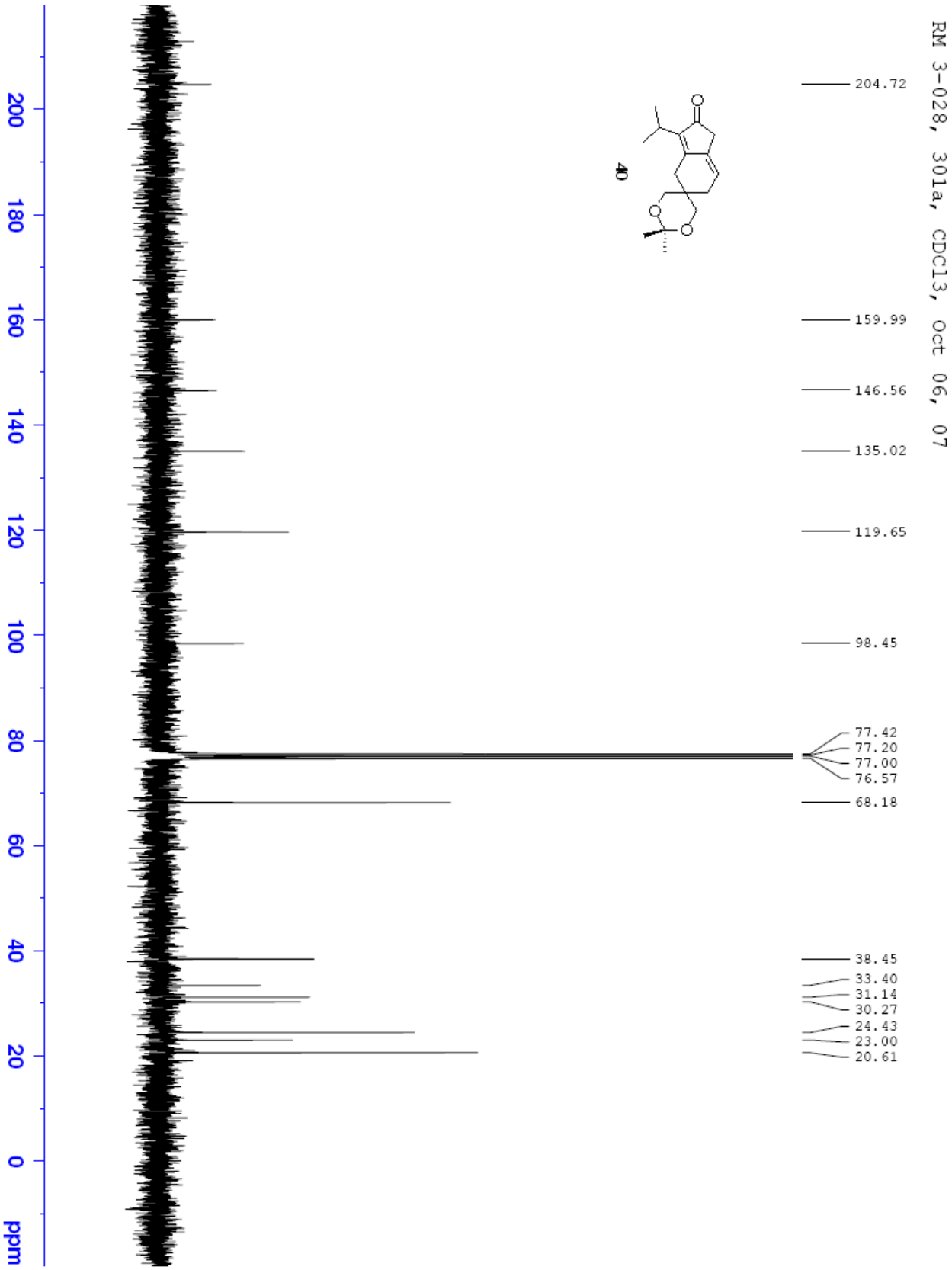

RM 3-026, CDC13, 301a, Oct 04, 07
52
7.271
5.093
5.070
5.066
5.043
5.021
5.018
4.994
4.693
4.686
4.677
4.672
4.663
4.656
3.743
3.704
3.667
3.628
2.598
2.574
2.567
2.551
2.544
2.536
2.529
2.521
2.513
2.506
2.499
2.483
2.476
2.461
2.331
2.324
2.168
2.160
2.152
2.141
2.133
2.125
1.420
0.75
1.85
2.18
2.39
0.70
2.30
2.33
6.50
6.00
ppm

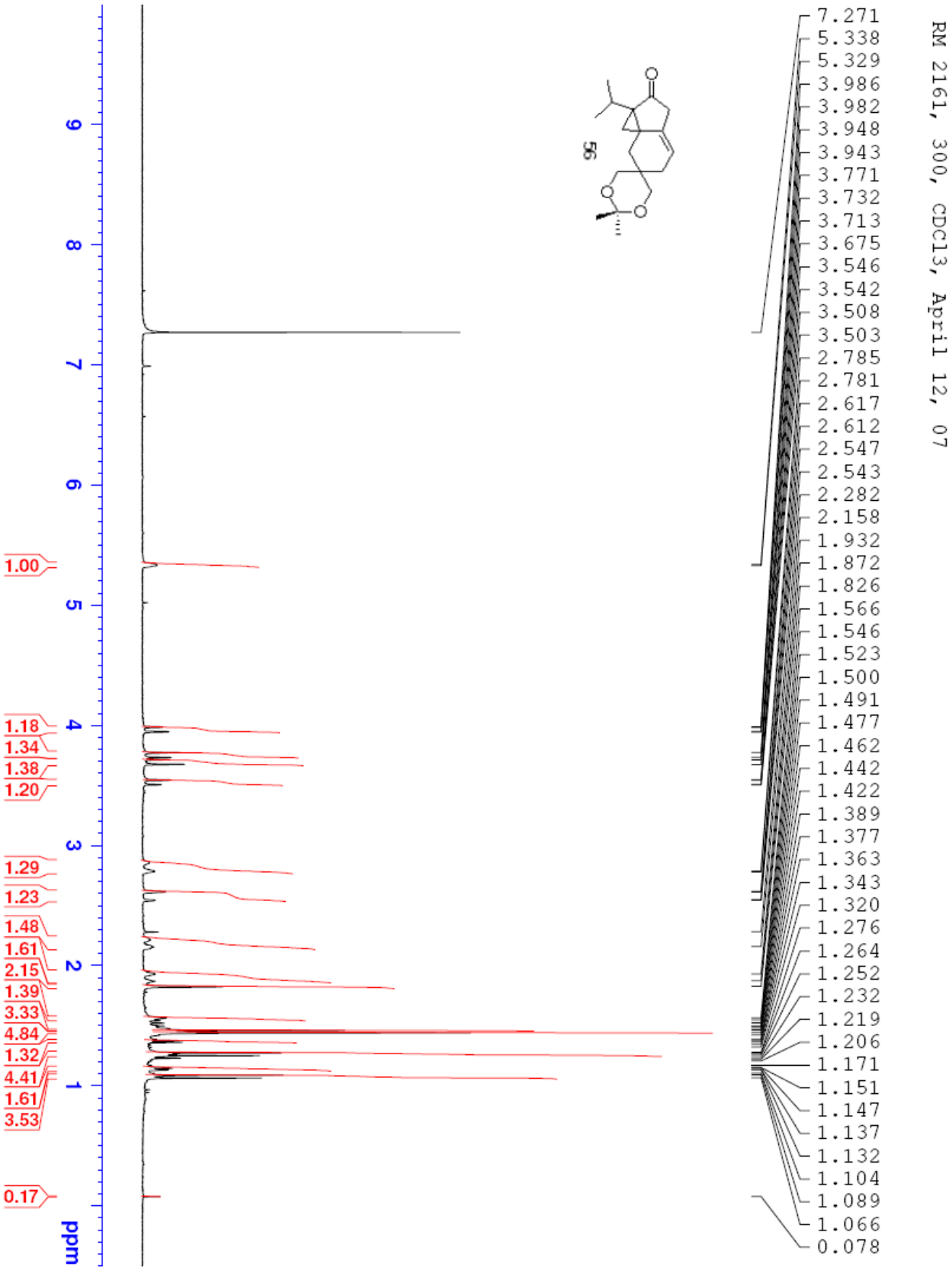
RM 3-026, CDCl3, 301a, Oct 04, 07

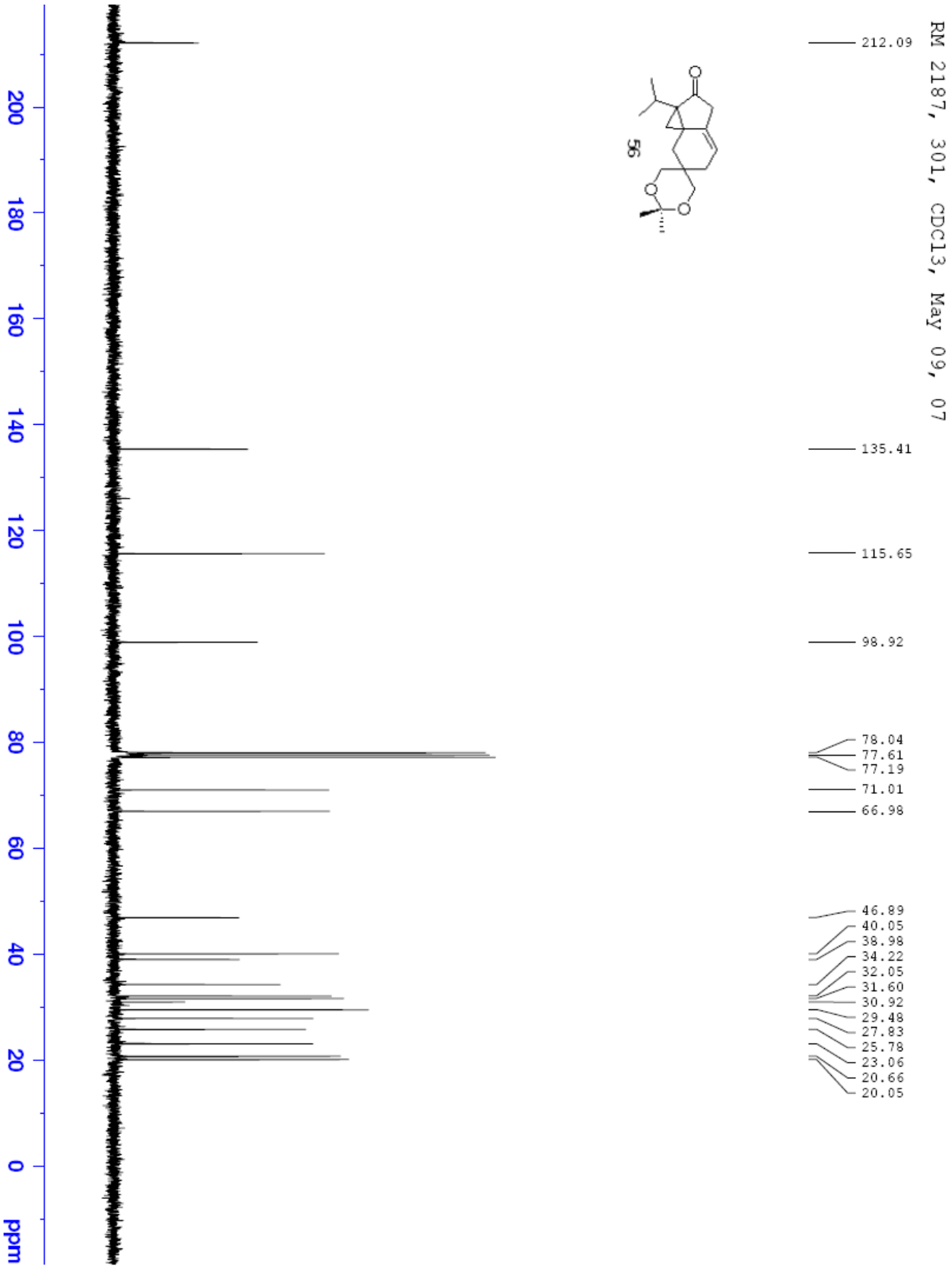


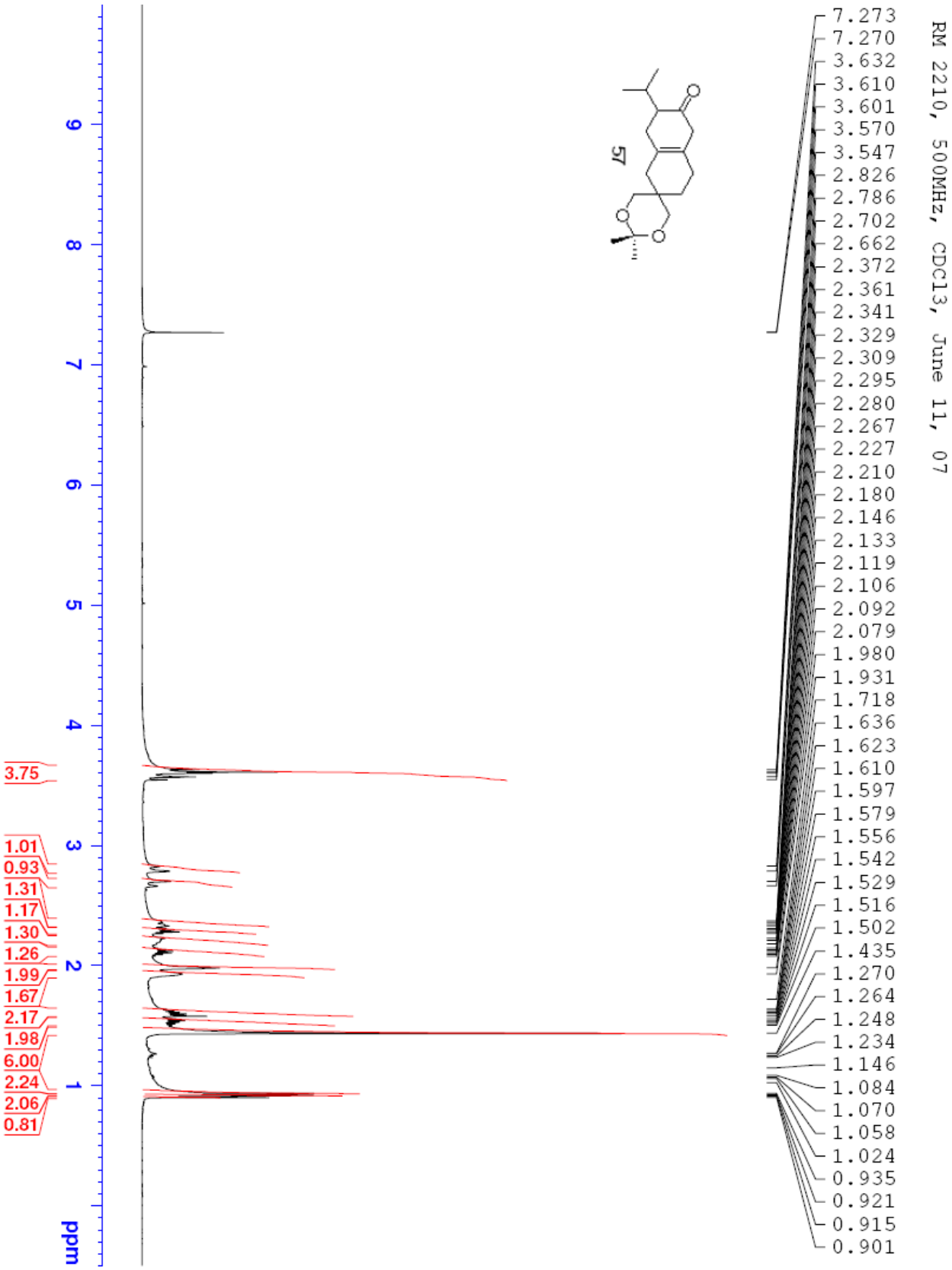
52

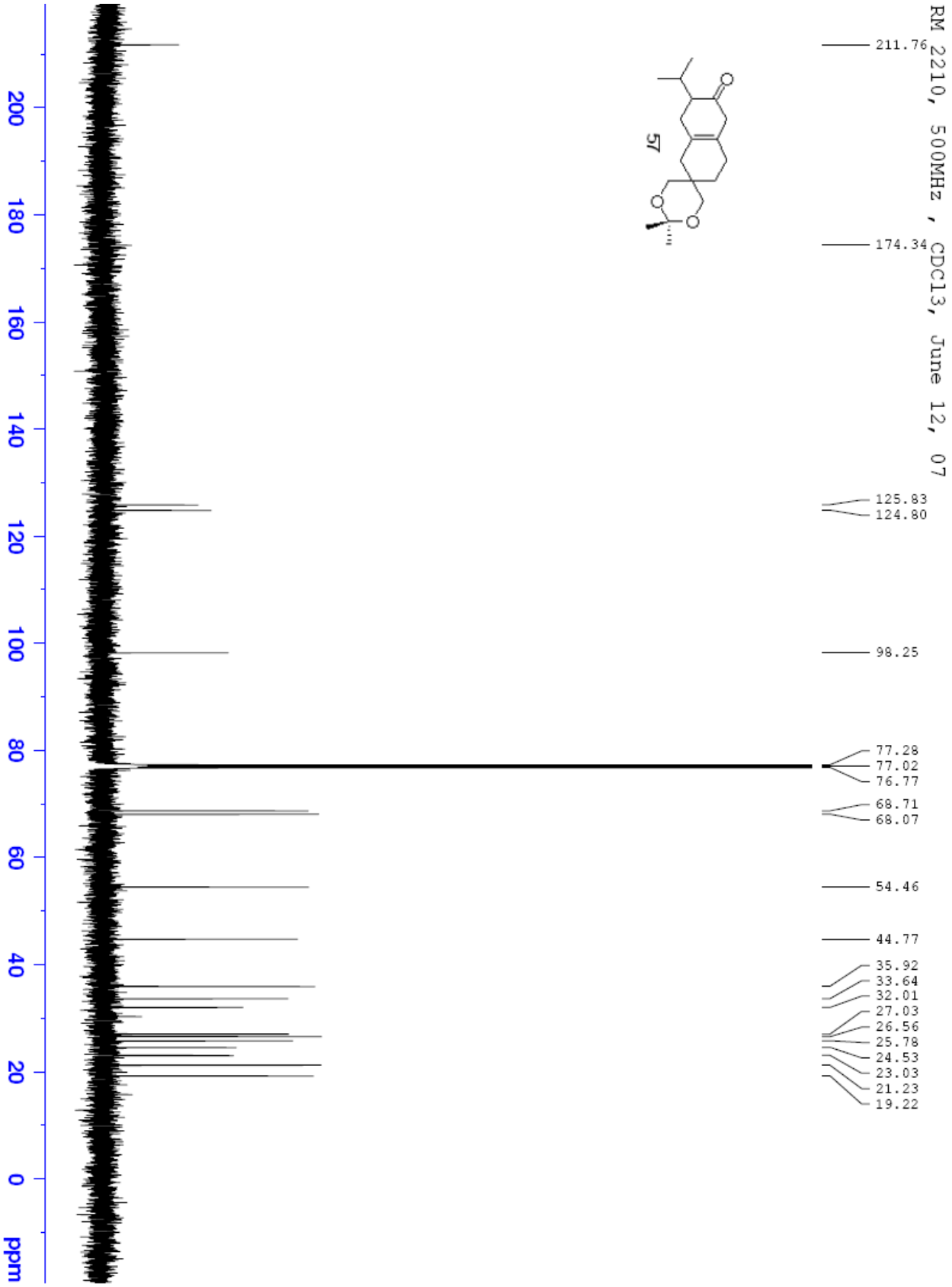

RM 2155 (90 degree C), 300, CDC13, Apr 06, 07
7.271
6.988
5.751
5.737
5.722
5.021
3.707
3.676
3.638
3.604
3.566
2.937
2.913
2.890
2.874
2.871
2.867
2.843
2.710
2.281
2.252
2.248
2.244
2.238
2.233
2.230
2.055
1.579
1.518
1.508
1.454
1.440
1.423
1.376
1.292
1.268
1.262
1.223
1.200
1.179
1.170
1.159
1.147
1.136
1.124
1.097
1.081
1.073
1.058
1.010
0.912
0.891
0.881
0.864
0.860
40
0.73
2.00
1.87
2.81
1.65
1.71
6.36
5.73
ppm


RM 3-028, 301a, CDCl3, Oct 06, 07
40
204.72
159.99
146.56
135.02
119.65
98.45
77.42
77.20
77.00
76.57
68.18
38.45
33.40
31.14
30.27
24.43
23.00
20.61
200
180
160
140
120
100
80
60
40
20
0
ppm


RM 2161, 300, CDC13, April 12, 07
7.271
5.338
5.329
3.986
3.982
3.948
3.943
3.771
3.732
3.713
3.675
3.546
3.542
3.508
3.503
2.785
2.781
2.617
2.612
2.547
2.543
2.282
2.158
1.932
1.872
1.826
1.566
1.546
1.523
1.500
1.491
1.477
1.462
1.442
1.422
1.389
1.377
1.363
1.343
1.320
1.276
1.264
1.252
1.232
1.219
1.206
1.171
1.151
1.147
1.137
1.132
1.104
1.089
1.066
0.078
56
1.00
1.18
1.34
1.38
1.20
1.29
1.23
1.48
1.61
2.15
1.39
3.33
4.84
1.32
4.41
1.61
3.53
0.17
ppm


RM 2187, 301, CDC13, May 09, 07
56
212.09
135.41
115.65
98.92
78.04
77.61
77.19
71.01
66.98
46.89
40.05
38.98
34.22
32.05
31.60
30.92
29.48
27.83
25.78
23.06
20.66
20.05
200
180
160
140
120
100
80
60
40
20
0
ppm


RM 2210, 500MHz, CDCl3, June 11, 07
7.273
7.270
3.632
3.610
3.601
3.570
3.547
2.826
2.786
2.702
2.662
2.372
2.361
2.341
2.329
2.309
2.295
2.280
2.267
2.227
2.210
2.180
2.146
2.133
2.119
2.106
2.092
2.079
1.980
1.931
1.718
1.636
1.623
1.610
1.597
1.579
1.556
1.542
1.529
1.516
1.502
1.435
1.270
1.264
1.248
1.234
1.146
1.084
1.070
1.058
1.024
0.935
0.921
0.915
0.901
57
3.75
1.01
0.93
1.31
1.17
1.30
1.26
1.99
1.67
2.17
1.98
6.00
2.24
2.06
0.81
ppm


RM 2210, 500MHz , CDCl3, June 12, 07
211.76
174.34
125.83
124.80
98.25
77.28
77.02
76.77
68.71
68.07
54.46
44.77
35.92
33.64
32.01
27.03
26.56
25.78
24.53
23.03
21.23
19.22
57
200
180
160
140
120
100
80
60
40
20
0
ppm

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