Catalytic Asymmetric Aldol Equivalents for an Enantioselective Total Synthesis of Apoptolidin C

by

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Apoptolidin C is a biologically active polypropionate macrolide isolated from the soil bacteria *Nocardiopsis* sp. The work presented herein highlights a novel approach to synthesizing the core of the natural product, apoptolidinone C, as well as a de-novo synthesis of the C_9 sacharide. Our synthesis utilizes a catalytic asymmetric approach to the construction of the complex polypropionate arrays contained in apoptolidin through the use of our acyl halide-aldehyde cyclocondensation (AAC) reaction. Employing the AAC technology using *cinchona* alkaloid derived catalysts, as well as the complementary chiral aluminum catalysts, we have successfully demonstrated a catalytic and asymmetric synthesis of the aglycone core of apoptolidin C. In addition, we have demonstrated the asymmetric synthesis of the C_9 saccharide from achiral starting materials.

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LIST OF ABBREVIATIONS

AAC	Acyl Halide-Aldehyde Cyclocondensation
ATP	Adenosine Tri-Phosphate
Bn	Benzyl
Binap	Binapthyl
TBDMS	*t*-Butyldimethylsilyl
DMP	Dess-Martin Periodinane
d.r.	Diastereomeric ratio
DAST	Diethylaminosulfur Trifluoride
DMB	Dimethoxybenzyl
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
NMO	*N*-Methylmorpholine *N*-Oxide
NMP	*N*-Methyl-2-Pyrrolidone
NP	Napthalene
NCI	National Cancer Institute
PCC	Pyridinium Chlorochromate
PPTS	Pyridinium *p*-Toluenesulfonate
RT	Ambient Temperature
THF	Tetrahydrofuran

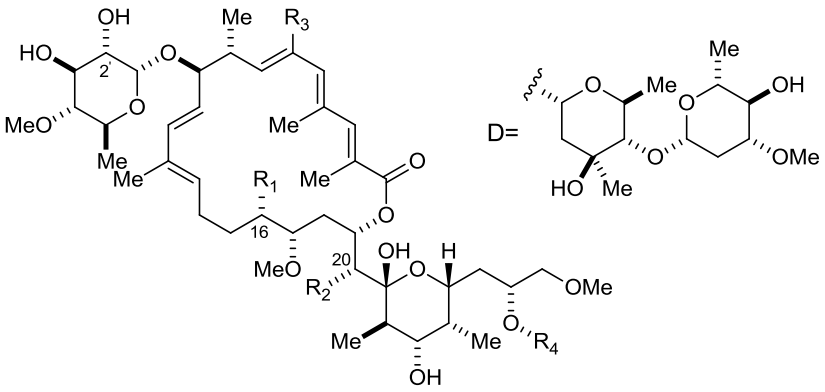
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
TMS	Trimethylsilyl
TMS-Qd	*O*-Trimethylsilylquinidine
TMS-Qn	*O*-Trimethylsilylquinine

1.0 INTRODUCTION

1.1 ISOLATION AND BIOLOGICAL ACTIVITY

Apoptolidin is a highly unsaturated twenty membered macro-lactone isolated in 1997 from the soil bacteria *Nocardiopsis* sp.[1] Seto and coworkers initiated biological studies on apoptolidin A and found it to selectively and potently inhibit of the growth of rat glia cells transformed with the E1A oncogene.[1,2] Apoptolidin has shown potent apoptosis induction in a number of cancer cell lines, and was found to be among the most selective (top 0.1%) agents tested against the National Cancer Institute's (NCI) 60-cell line screening panel.[3] An important aspect of apoptolidin A's selectivity is the almost complete lack of toxicity in normal cells, even at high concentrations (>1 mM).[1] Elucidation of the structure and absolute configuration was achieved by spectral methods as well as chemical degradation.[2] The structure was later confirmed through total synthesis by Nicolaou.[4] In 2005, after numerous synthetic efforts had begun on apoptolidin A, Wender improved upon the original fermentation method of isolation of apoptolidin A, and increased the yield to 130 mg/L from 108 mg/L of fermentation medium.[5] Wender also isolated two additional components from the fermentation mixture that lacked hydroxyl functionality at the C_{16} and C_{20} carbons (Figure 1) in 2-5 mg/L quantities. These additional components were further identified as apoptolidins B and C due to their similarity with the already known macrolide. Further investigation led to the discovery of apoptolidins D-F, which show similar biological activity, excluding apoptolidin F which showed drastically reduced activity due to its lack of the C_{27} disaccharide.[6] The availability of the other members of the apoptolidin family is

limited to a few milligrams per liter of fermentation medium, and as such, biological testing of the other compounds is incomplete.



Apoptolidin A: R_1,R_2=OH, R_3=Me, R_4=D
Apoptolidin B: R_1=H, R_2=OH, R_3=Me, R_4=D
Apoptolidin C: R_1,R_2=H, R_3=Me, R_4=D
Apoptolidin D: R_1,R_2=OH, R_3=H, R_4=D
Apoptolidin E: R_1,R_2=H, R_3=Me, R_4=D, 2'-*epi*
Apoptolidin F: R_1,R_2=H, R_3=Me, R_4=H, 2'-*epi*

Figure 1. Apoptolidins A-F

Biological testing of apoptolidins A-F demonstrated B to be the most potent, with A and C showing similar activity in growth inhibition asssays with the H292 cancer cell line for lung carcinomas (Table 1).[5] Though extensive testing on the complete biological profile of apoptolidin C has not been completed to date, its activity against a number of biological targets is of great interest due to the impressive results shown by apoptolidin A.

Table 1. Tabulated Biological Data

	H292 Cells GI_{50} (μM) (Lung Carcinoma)	F_0F_1-ATPase IC_{50} (μM) (Biological Target)	Ad12-3Y1 IC_{50} (μM) (E1A/B oncogene expressed in 3Y1 cells)	3Y1 Cells IC_{50} (μM)
apoptolidin A	0.032[a]	0.700[b]	0.0065[b]	>1.0[b]
apoptolidin B	0.007[a]	-	-	-
apoptolidin C	0.024[a]	-	-	-
apoptolidin D	0.110[b]	-	-	-
oligomycin	-	1.0[b]	0.0002[b]	3.3[b]

a: Wender, *org. lett.* **2005**, *7*, 3025
b: Wender, *org. lett.* **2007**, *9*, 691
c: Wender, *org. lett.* **2006**, *8*, 589

1.2 MECHANISM OF ACTION

Apoptolidin A has been shown to exhibit an activity profile that is analogous to that of other known F_0F_1-ATPase inhibitors.[7] Khosla hypothesized that the inhibition of mitochondrial ATP synthase is the cause of the anti-proliferative affect exhibited in cells expressing cancer.[3] One problem with this hypothesis is the apparent contradiction between *in vitro* and *in vivo* assays. In cell-free assays of yeast mitochondrial ATP synthase apoptolidin A exhibits micromolar inhibition of ATP hydrolysis.[7] These results however, conflict with the nanomolar inhibition attained in a cell proliferation assay using cells transfected with E1A and E1B oncogenes (table 1).[7] The assay results imply that apoptolidin A is approximately 100 times more potent against whole cancer cells than the biological target within the cell.

There are a few possibilities that could explain the incongruity between the assay results. Since catalysis of ATP hydrolysis is not equivalent to ATP synthesis, it is possible that the cell-free yeast F_0F_1-ATPase assay, which directly measures hydrolysis of ATP, is not an adequate measure of ATP synthesis, and therefore anti-proliferative activity. Another explanation for those conflicting results would be that there is a relevant secondary biological target playing a role in the biological activity of apoptolidin A.[7-9]

There is still much work to be done on elucidating the mechanism of action for apoptolidin A. Due to the structural similarity, the results obtained may correlate well to the action of apoptolidin C, which up to this point demonstrates a very similar inhibition profile to apoptolidin A.[5] Total syntheses of apoptolidin A have been published, along with numerous partial syntheses and fragments, however to date, there are no synthetic studies directed at apoptolidin C apart from our own.[10] Due to the lack of information surrounding this natural product, and the structural complexity it possesses, we found apoptolidin C to be a high profile target to showcase the iterative application of our asymmetric acyl-halide aldehyde cyclocondensation reaction (AAC).

2.0 PREVIOUS TOTAL SYNTHESES OF APOPTOLIDIN A

To date there have been no total syntheses of apoptolidin C or its aglycone. During our research we relied upon precedent from the syntheses of apoptolidin A, which maintains a high degree of structural homology with apoptolidin C. In contrast apoptolidin A has been synthesized in its entirety three separate times by professors K. C. Nicolaou,[4,11-14] Ulrich Koert,[15-19] and most recently by Michael Crimmins.[20-22] There have also been studies on the aglycone synthesis by Professor Gary Sulikowski,[23-26] and extensive fragment syntheses by Professor William Roush,[27,28] amongst others.

2.1 PROFESSOR K. C. NICOLAOU'S SYNTHESIS

Professor Nicolaou completed the first synthesis of apoptolidin A in 2001 utilizing a convergent approach to the aglycone. His retrosynthetic approach was based upon dividing the core structure into two hemispheres, with the upper portion containing the unsaturated triene, along with two stereocenters, while the lower hemisphere containing only a single unsaturation which was used for a Stille cross-coupling, and the fully substituted *c*-bound glycoside (figure 2). Combining the two fragments using a Stille coupling, followed by a Yamaguchi

macrolactonization is a very classical approach, and was utilized subsequently in other syntheses of apoptolidin A.

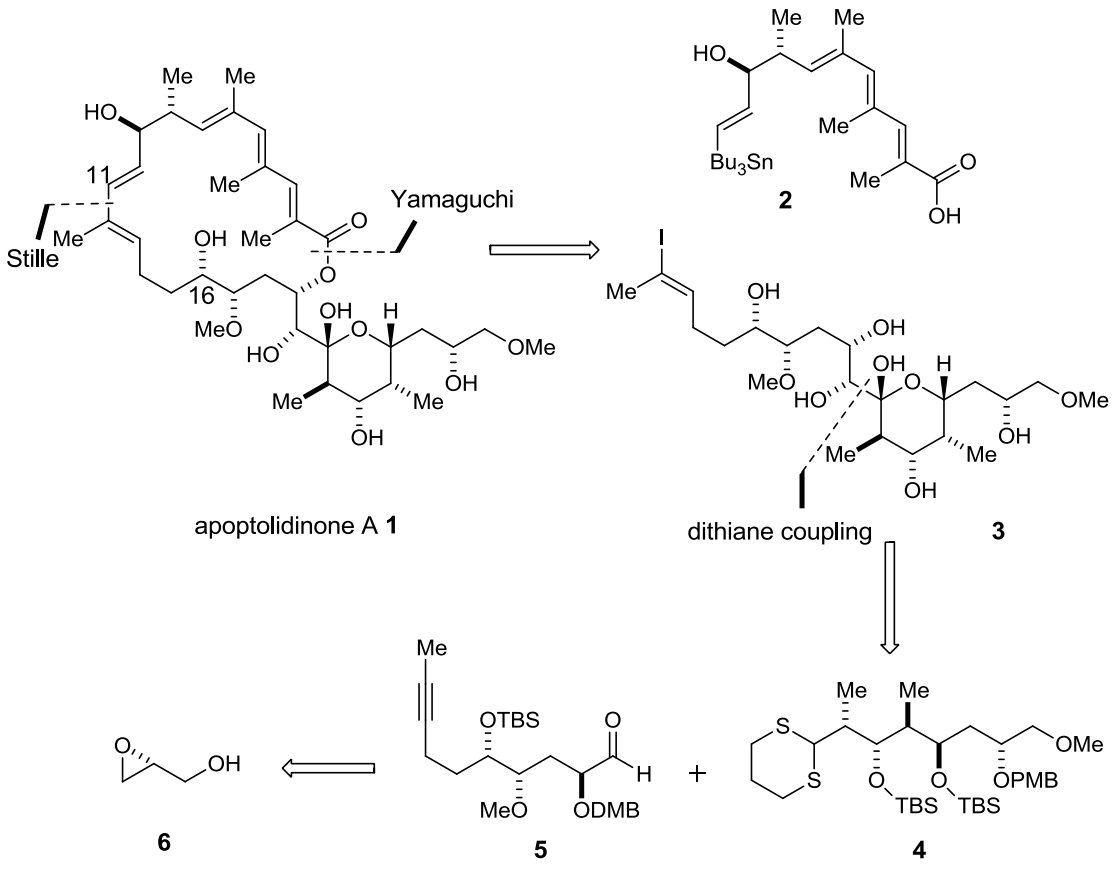


Figure 2. Nicolaou's Retrosynthetic Approach

The C_{12}-C_{28} fragment (**3**) was synthesized by coupling dithiane **4** to aldehyde **5**. This provided the unmasked dithiane after deprotection of the TBS groups, which spontaneously cyclized to the pyran moiety of the natural product. Aldehyde **5** was synthesized from commercially available (+)-glycidol (**6**) using stoichiometric chiral reagents.

Dithiane **4** originated from a similar chiral material, (-)-methylglycidol (Figure 3). Ring opening of the epoxide with lithiodithiane, and subsequent reduction provided the PMB

protected aldehyde **8**. Using Brown's crotylation procedure on **8**, followed by protection with TBS-OTf and oxidative cleavage using $NaIO_4$ and OsO_4 yielded the chiral aldehyde **7**.[12] Subsequently a second crotylation was attempted, however it gave the wrong diastereomer of the product. Employing Evans' oxazolidinone technology, the authors were able to obtain the desired product. After some functional group manipulations, they obtained the desired dithiane **4** with the *syn, anti, syn*-arrangement of contiguous stereocenters.

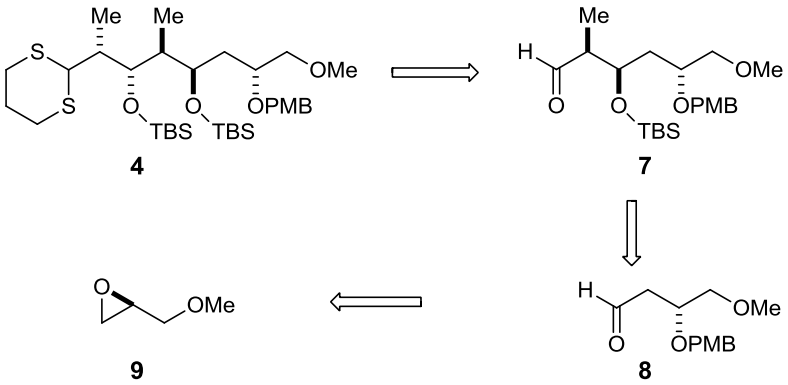
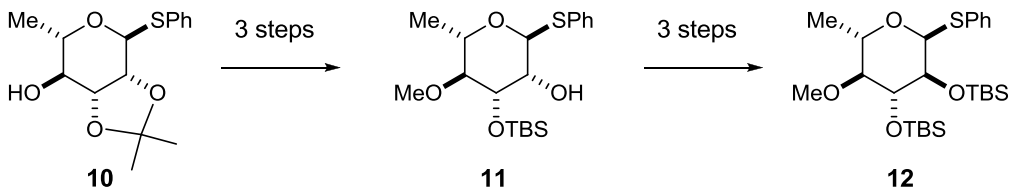


Figure 3. Nicolaou's Dithiane Synthesis

The construction of the three carbohydrate building blocks was accomplished by beginning with readily available L-rhamnose derived thioglycoside **10** to form sugars **12** (Scheme 1), and **14** (scheme 2), while sugar **16** was formed from thioglycoside **17**. In the forward direction, sugar **12** was synthesized by methylation of the C_4 alcohol of thioglycoside **10**, followed by acetal deprotection, and selective C_3 protection with a TBS group. An oxidation/reduction sequence performed on alcohol **11** inverted the C_2 stereochemistry to the all-equitorial β-anomer **12**.

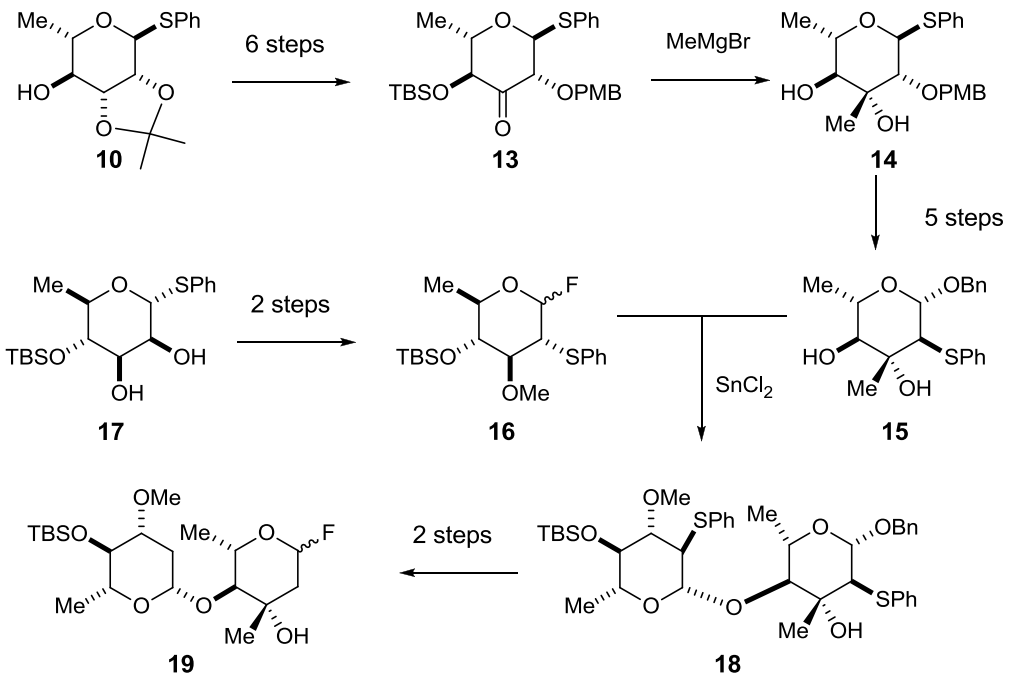
Scheme 1: Nicolaou's Saccharide Synthesis



10 **11** **12**

The disaccharide containing two C_2 deoxy-sugars posed a particular challenge. They began with thioglycoside **10**, which after a series of protecting group manipulations, and one oxidation, gave ketone **13**. Treatment with methyl Grignard gave the correct diastereomer of the tertiary alcohol, presumably under chelate control to PMB ether.[12] The remaining carbohydrate was synthesized very quickly from thioglycoside **17**. A few more functional group manipulations were required to formulate sugar **16** into its active coupling partner. Once accomplished it was coupled with **15** using $SnCl_2$, giving the complete disaccharide (**19**), after treatment of Raney Ni to remove both thiophenyl groups.

Scheme 2: Nicolaou's Disaccharide Synthesis



2.2 PROFESSOR ULRICH KOERT'S SYNTHESIS

Professor Ulrich Koert completed the synthesis of apoptolidinone A in 2001,[17,19] and followed that work by publishing the complete natural product in 2004.[15,16,18] The initial disconnections in Koert's synthesis are identical to those chosen by Nicolaou, including the sp^2-sp^2 coupling between C_{11} and C_{12}, as well as the C_1-O bond of the ester. However, Koert chose to also make a disconnection between C_{15} and C_{16} (Figure 4). He also chose to install the C_{19} and C_{20} hydroxy functionality via dihydroxylation following the cyclization of the furan ring. The cyclized product gave a higher degree of diastereocontrol over the dihydroxylation than was demonstrated on both test substrates, as well as the uncyclized precursor **22**.[18] The α,β-unsaturated ketone was formed from a nucleophilic displacement of the amide (**23**) by a lithiated vinyl Iodide species

that was comprised of C_{12} through C_{15}. The protected polypropionate chain (**22**) could then be deprotected with PPTS in MeOH to close the furan ring.

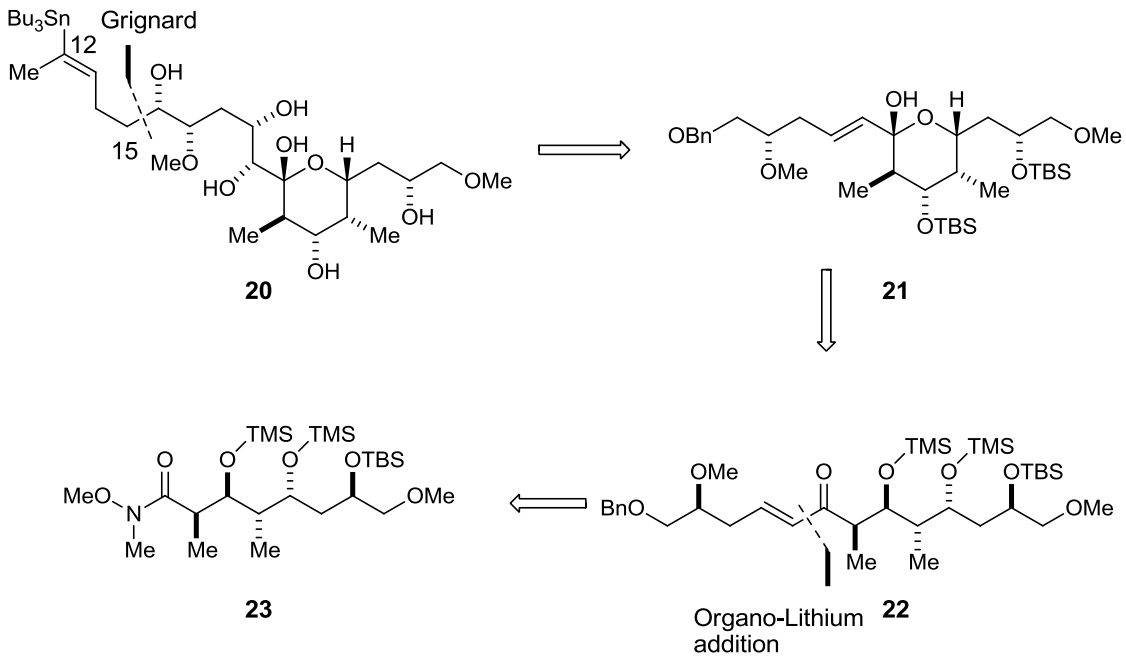
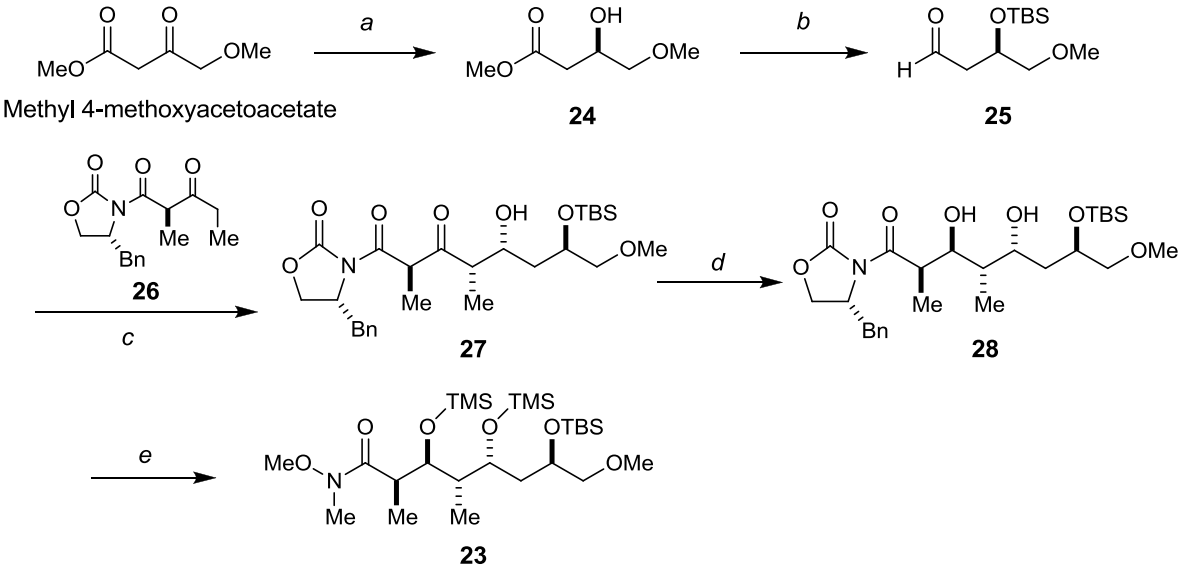


Figure 4. Koert's Retrosynthetic Approach to the C_{12}-C_{28} Fragment

Weinreb amide **23** was constructed in a very short linear sequence starting with methyl 4-methyoxyacetoacetate (Scheme 3). An asymmetric reduction provided ester **24**, followed by a dibal reduction to provide aldehyde **25**. The β-keto imide building block **26** was added to give ketone **27** in 97% yield as a 96:4 diastereomeric ratio. Anti-reduction of the ketone gave the desired *syn, anti, syn*-configuration of the propionate chain. Finishing the sequence with a transamination followed by bis-TMS protection yielded amide **23**. Koert demonstrated an expedient asymmetric synthesis to a complex building block using mainly chiral auxiliaries, with a catalytic asymmetric reduction as the initial stereodefining step.

Scheme 3: Koert's C_{21}-C_{28} Synthesis



a. Ru-(*S*)-Binap, H_2, MeOH, DMF, 95 °C (86%, 97% ee); *b. i*)TBDMSCl, imidazole (95%); *ii*) *i*Bu_2AlH, hexane, (90%); *c.* **26**, $Sn(OTf)_2$, Et_3N, CH_2Cl_2, (97%, 96:4 dr); *d.* $Me_4NBH(OAc)_3$, HOAc, CH_3CN (74%, 95:5 dr); *e. i*) $AlMe_3Me(MeO)NH{\cdot}HCl$, HOAc, CH_2Cl_2 (81%); *ii*) TMSCl, imidazole (86%).

Professor Koert and coworkers approached the three sugar residues with a similar strategy as was previously demonstrated by Nicolaou. The C_9 glycoside (glycoside A) was constructed in a very similar manner starting with the same L-rhamnose derivative. Likewise, the C_{27} sugar (glycoside B) was constructed from the same chiral building block (figure 5).

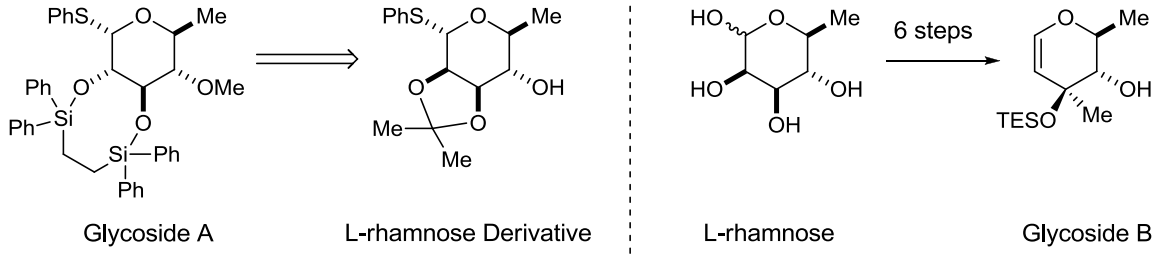
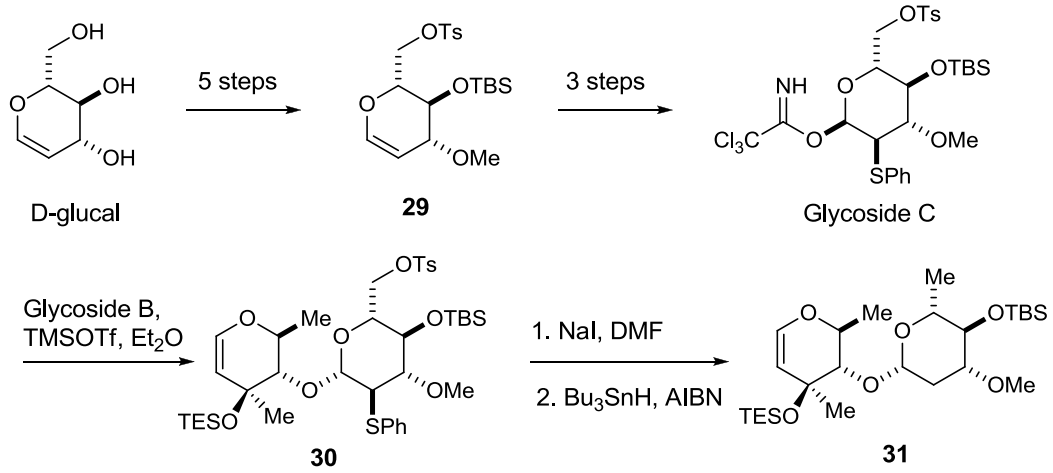


Figure 5. Koert's Approach to Saccharides A and B.

The approach to the terminal residue of the disaccharide appended to C_{27} (glycoside C) bears a resemblance to the synthesis of glycoside B, and is quite concise (scheme 4). Koert is able to use the $C_{3\text{-}5}$ stereocenters from glucose in the unsaturated form of D-glucal to his advantage. After differential funtionalization of the three alcohols in glucal to form **29**, the trichloroacetimidate was formed at C_1 after introduction of the C_2 thiophenol substituent. The *syn*-installation of the C_1/C_2 substituents allowed for selective β-formation of the glycosidic bond. Using trimethylsilyl triflate as a lewis acid activator for the SN2 bond formation provided the complete disaccharide (**30**), which required two manipulations to form the coupling precursor **31**.

Scheme 4: Koert's Disaccharide Synthesis



2.3 PROFESSOR MICHAEL CRIMMINS' SYNTHESIS

Professor Crimmins completed the synthesis of aglycone of apoptolidin A in 2005,[20] along with a separate publication on the synthesis of the three saccharide units.[22] In 2009 he published the complete synthesis of apoptolidin A[21] which combined the previous publications, and really showcased the versatility of his thiazolidinethione chiral auxiliary chemistry.[29] Professor Crimmins published the first de-novo synthesis of apoptolidin A. He was able to use chiral auxiliaries and stoichiometric chiral reagents to form the requisite stereocenters without having to use the chiral pool. His overall strategy for the aglycone was very similar to that of Nicolaou and Koert. After dividing the aglycone into a northern and southern hemisphere he used classic aldol type chemistry to form the polypropionate C_{21}-C_{28} fragment. It is in this fragment (**34**) that the iterative application of his chiral auxiliary chemistry can be seen.

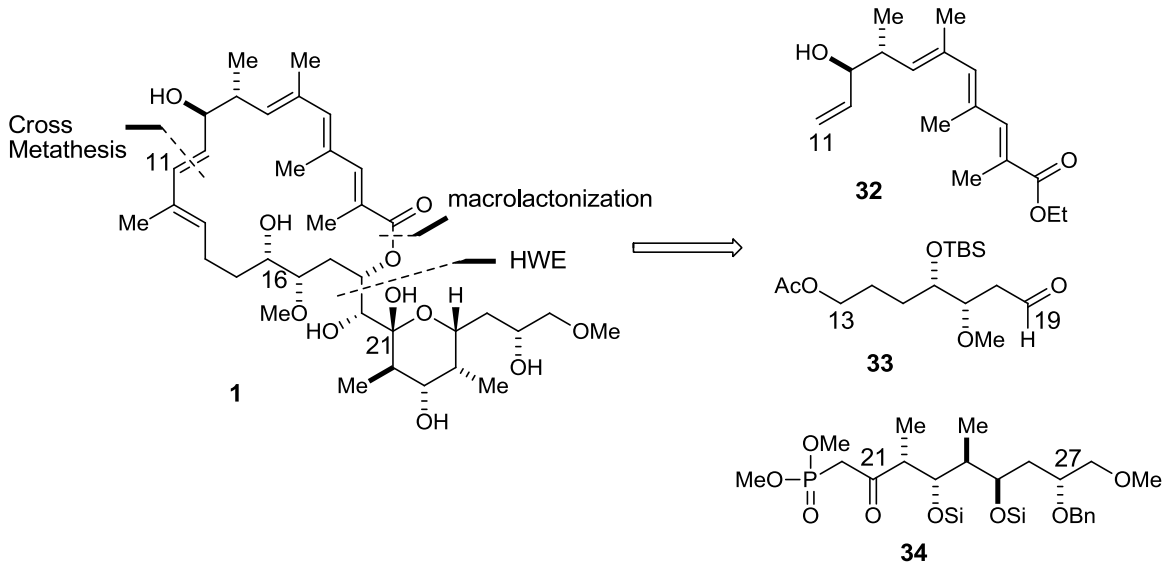
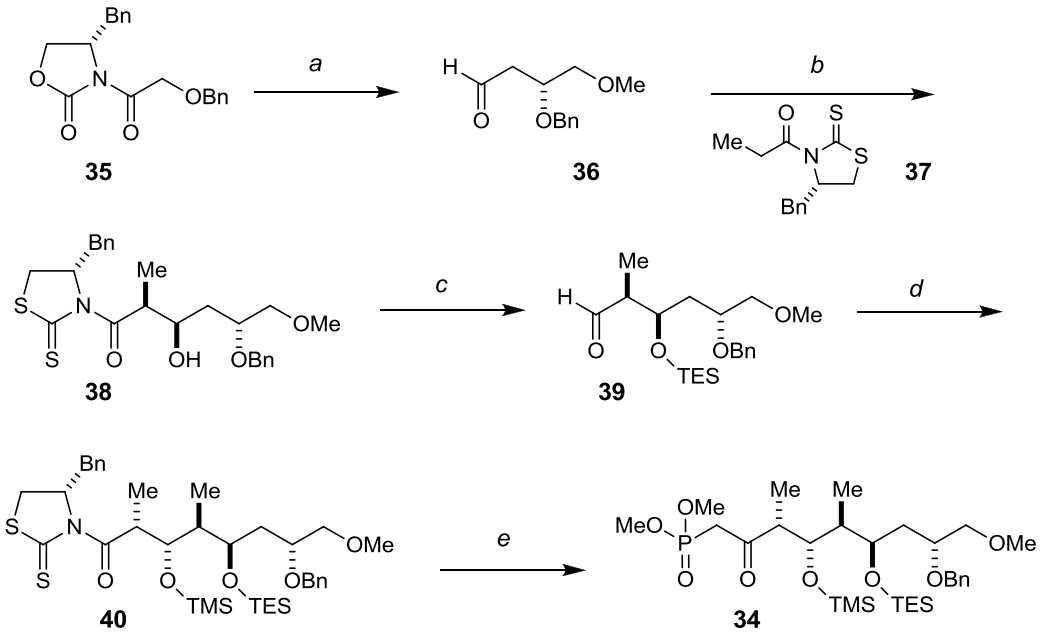


Figure 6. Professor Crimmins' Retrosynthetic Approach

Stereoselective alkylation of **35** (Scheme 5) followed by removal of the chiral auxiliary and subsequent aldol reaction with chiral thiazolidinethione **37** gave excellent stereocontrol in the assembly of alcohol **38** (90%, >98:2 syn). Functional group manipulations led to a second aldol using the same chiral auxiliary as before, however with a reduced yield (62%). Professor Crimmins' approach led to a very efficient synthesis of the complex polypropionate **34** in few linear steps, however, it is plagued by functional group manipulations, use of super stoichiometric metal reagents, and the unmentioned syntheses of the chiral auxiliaries, which are not trivial.

Scheme 5: Crimmins' C_{20}-C_{28} Synthesis



a. *i*) $NaN(SiMe_3)_2$, PhMe, THF, $H_2C{=}CHCH_2I$ (75%); *ii*) $NaBH_4$, THF, H_2O (85%); *iii*) NaH, MeI, THF (88%); *iv*) OsO_4, NMO, THF, H_2O; *v*) $NaIO_4$, H_2O, THF (60% for two steps); *b*. **37**, $TiCl_4$, (–)-sparteine, NMP, CH_2Cl_2, then **36** (90%); *c*. *i*) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2 (97%); *ii*) $^{i}Bu_2AlH$, heptane, CH_2Cl_2 (86%); *d*. **37**, $TiCl_4$, $^{i}Pr_2NEt$, CH_2Cl_2, then **39** (62%); *e*. *i*) Me_3SiCl, Et_3N, DMAP, CH_2Cl_2 (79%); *ii*) $(MeO)_2P(O)Me$, n-BuLi, THF (96%).

It can be seen in the previous syntheses that the sugar residues provide one of the greatest challenges in the synthesis of apoptolidin. The number of reactions required to complete a small synthetic fragment is disproportionately high. Professor Crimmins took a different approach than previously seen in Nicolaou or Koert's work. The similarities between the three sugars in Crimmins' work can be seen in figure 7. All three sugars began with a similar chiral auxiliary which was alkylated, followed by appropriate functionalization, and eventual ring closure.

Glycoside A is formed via a dihydroxylation of alkene **41**, followed by silyl removal, and concurrent cyclization. The approach to glycoside B is extremely similar, however the chiral auxiliary is removed by methyl Grignard addition to yield the methyl ketone **42**. A chelate controlled allylation with allyltributylstannane gives the correct diastereomer with >20:1 selectivity, and nicely sets up an oxidative cleavage of the terminal alkene to form the glycoside upon acidic removal of the triethylsilyl protecting group. The enantiomer of the starting material is used for the synthesis of glycoside C. Arriving at aldehyde **43** provides the proper substrate for another chelate controlled allylation under similar conditions as before. Again, a diastereoselectivity of >20:1 is seen, and the resulting alcohol is methylated, followed by functional group manipulation, and eventual closure to the saccharide.

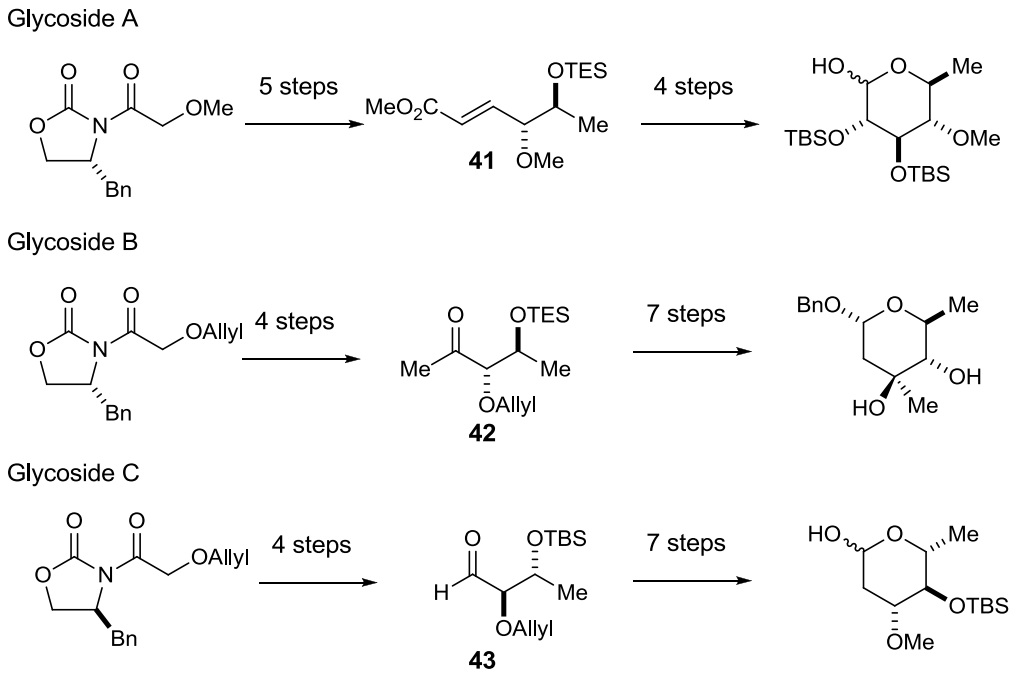


Figure 7. Crimmins' Saccharide Synthesis

2.4 PROFESSOR GARY SULIKOWSKI'S SYNTHESIS

Professor Sulikowski took a different approach to the construction of the aglycone than did the three previous syntheses. The primary disconnections were aimed at creating the shortest linear sequence, coupled with a highly modular approach. In previous syntheses the pyran unit was pre-formed, however Sulikowski appended the C_{20}-C_{28} fragment in a linear form, allowing cyclization upon global deprotection.

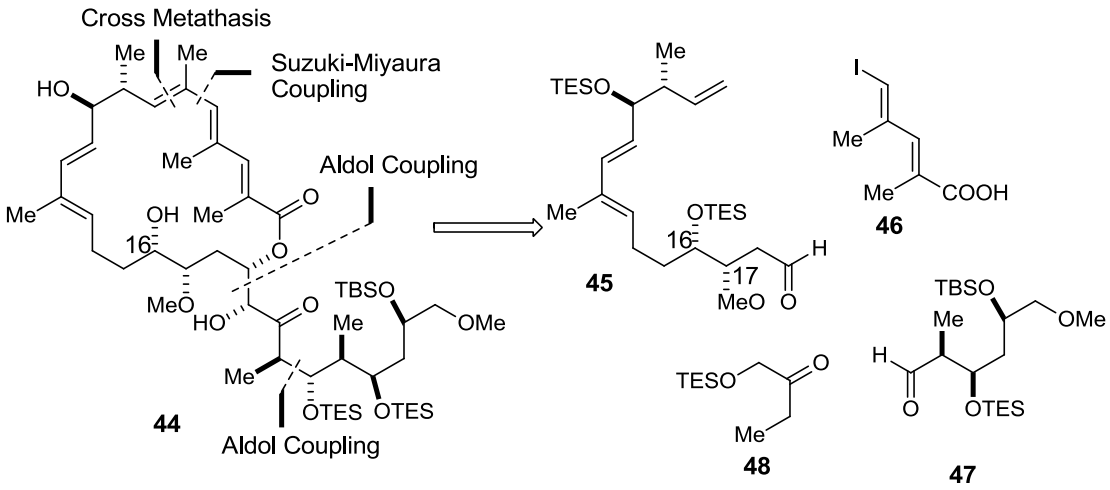


Figure 8. Professor Sulikowski's Retrosynthetic Approach

Triene **45** was synthesized starting from (*S*)-malic acid setting the C_{17} stereo center, followed by a chelate controlled grignard addition to set the hydroxyl group at C_{16}, that was elaborated with a Suzuki-Miyaura coupling to install the upper portion of the triene. Using a diastereoselective Mukaiyama aldol reaction aldehyde **45** was coupled with ketone **48** to give a 50% yield of a 4:1 mixture of diastereomers. Following the aldol, a Yamaguchi esterification appended **46** to the newly formed hydroxyl at C_{19}. The resulting compound was elaborated further via aldol addition with aldehyde **47** before being subjected to the metathasis and Suzuki-Miyaura coupling to yield the macrolactone **44**. Sulikowski's synthesis benefits from a highly modular approach, and therefore is an easily adaptable synthesis that has few long linear sequences, and allows for a rapid construction of analogs.

3.0 CATALYTIC ASYMMETRIC SYNTHESIS OF APOPTOLIDINONE C

Polyacetate and polypropionate architecture is ubiquitous in naturally occurring compounds.[30] Due to their utility in assembling such structures, aldol-based reactions have dominated the field of polypropionate synthesis.[31] Methods have historically been based upon stoichiometric chiral directors, either relying upon chiral reagents, or auxiliaries. Many groups have been occupied with the development of catalytic asymmetric variants of aldol reactions, and to this end we have pursued the construction of aldol equivalents in the form of β-lactones, as building blocks for polypropionate synthesis.

Our group has developed two complimentary methods with which to form chiral β-lactones using either a Lewis basic (*cinchona* alkaloid), or Lewis acidic (chiral aluminum species) catalyst to affect the transformation from aldehyde to β-lactone (Figure 9). Through the use of insitu generated substituted ketene from readily available acyl halides we can form either acetate, or propionate equivalents. We have labeled this reaction the acyl-halide aldehyde cyclocondensation (AAC).

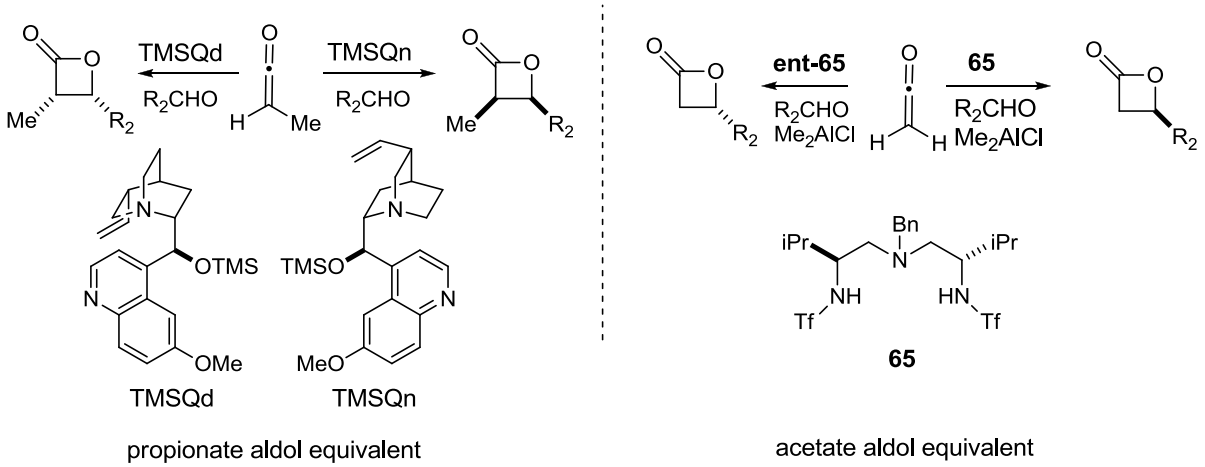


Figure 9. Catalytic Asymmetric Aldol Equivalents.

Apoptolidin A contains much of the same polypropionate architecture, and the efficiency of chiral auxiliaries has been well demonstrated on its core synthesis.[12,20] We have viewed apoptolidin C as a platform from which to evaluate, and demonstrate the iterative application of our AAC technology for synthesizing complex polypropionate arrays. The application of the AAC reaction follows an iterative sequence that is similar to the biosynthetic polyketide assembly. The biosynthetic pathway contains three main steps in route to a polyketide array. (Figure 10) The first step is elongation of the chain as it is transferred from the ketosynthase to the acyl carrier protein. After elongation, there must be a functionalization step to attain the desired structural unit, followed by a transfer step, which allows for a subsequent elongation.

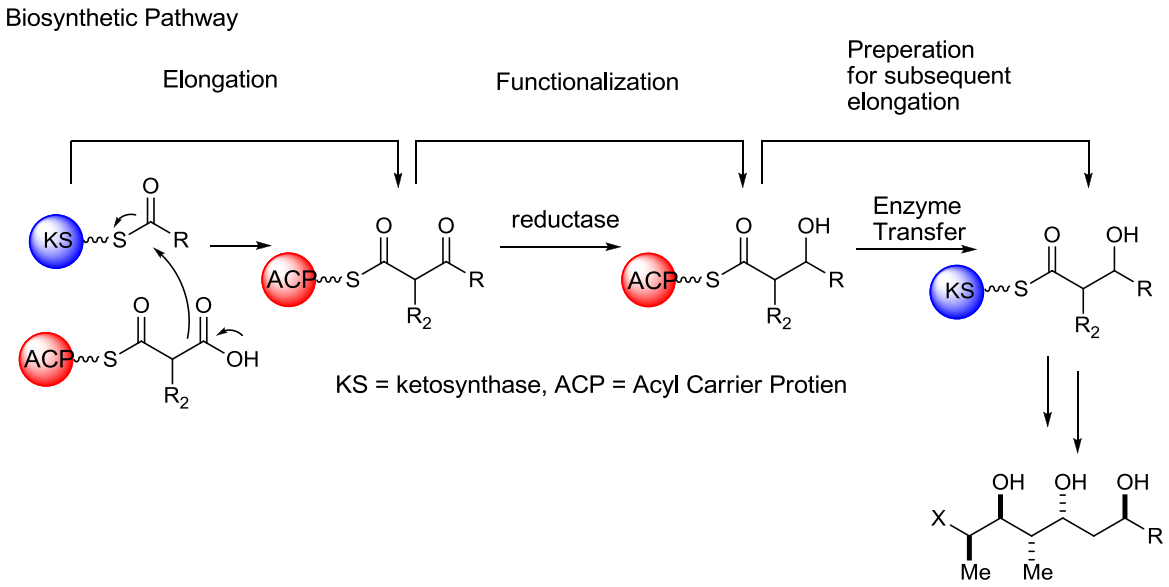


Figure 10. Biosynthetic Pathway for Polyketide Synthesis

Using small molecule catalysis we can mimic the biological pathway for production of these complex units. In our procedure we begin with an aldehyde which can undergo elongation in the first step (Figure 11). In our process we must ring open the β-lactone and protect the free alcohol in order to propagate the chain, which also requires a reduction, as our third and final step.

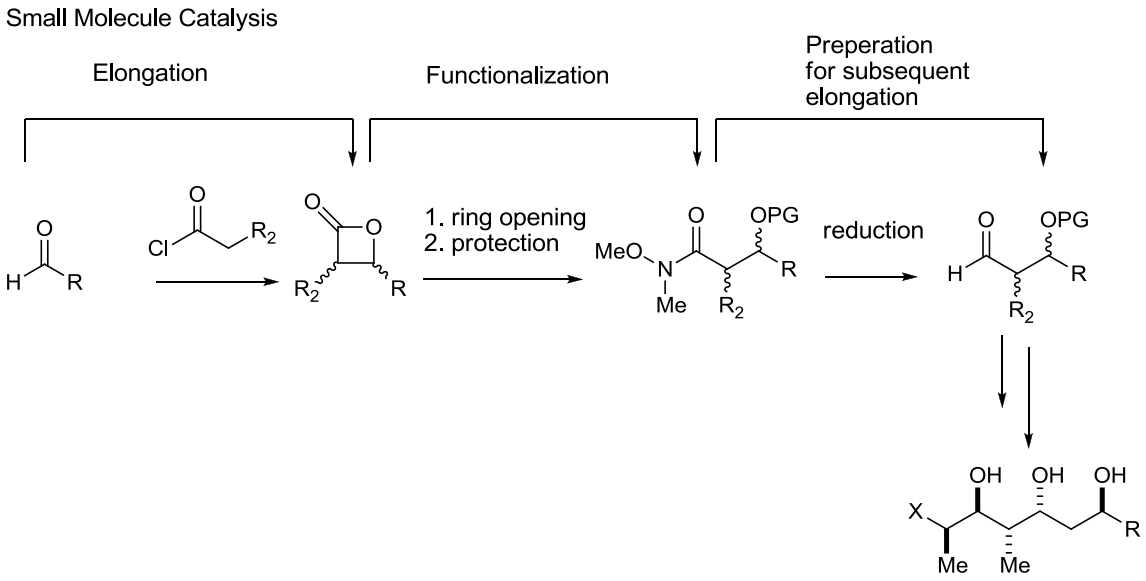


Figure 11. Small Molecule Catalysis Method for Polyketide Synthesis

3.1 RETROSYNTHESIS OF APOPTOLIDIN C

Our retrosynthetic analysis of apoptolidin C begins with the intention of stereocontrol being achieved solely through the use of catalytic asymmetric aldol reactions, notably our AAC technology. We attempted to build flexibility directly into the synthesis by allowing many of the major fragment coupling sequences to occur in a number of different orders. As an example of this flexibility, we required four major coupling reactions: two glycosidations, a Stille Coupling, and a Yamaguchi macrolactonization. We envisioned that these four reactions could be carried out in any order once all the building blocks were in hand. This allowed us to probe the most efficient construction of the aglycone, and subsequently the natural product, while limiting the number of revisions necessary to the individual building blocks. We began by removing the three saccharides, providing a synthetic route to apoptolidinone C. While building the aglycone,

we hoped to draw upon the considerable knowledge available for the construction of apoptolidin A, so we chose the well developed C_{11}-C_{12} disconnection, and the C_{19}-O disconnection, using a Stille coupling, and Yamaguchi macrolactonization, respectively to provide compound **75**.

The synthesis of the C_{12}-C_{28} fragment (**75**), and subsequent construction of the aglycone is the primary focus of this publication, followed by synthetic studies on the C_9 saccharide. Our approach to the C_{12}-C_{28} fragment was a convergent design, hinging upon the use of AAC chemistry for the formation of six of the requisite eight stereocenters, the results of which are compounds **54**, **61**, **64**, and **67**. We disconnected compound **75** via a methyl ketone aldol addition, which leads to two fragments, **58** and **69*a***, both of which can be constructed using AAC technology.

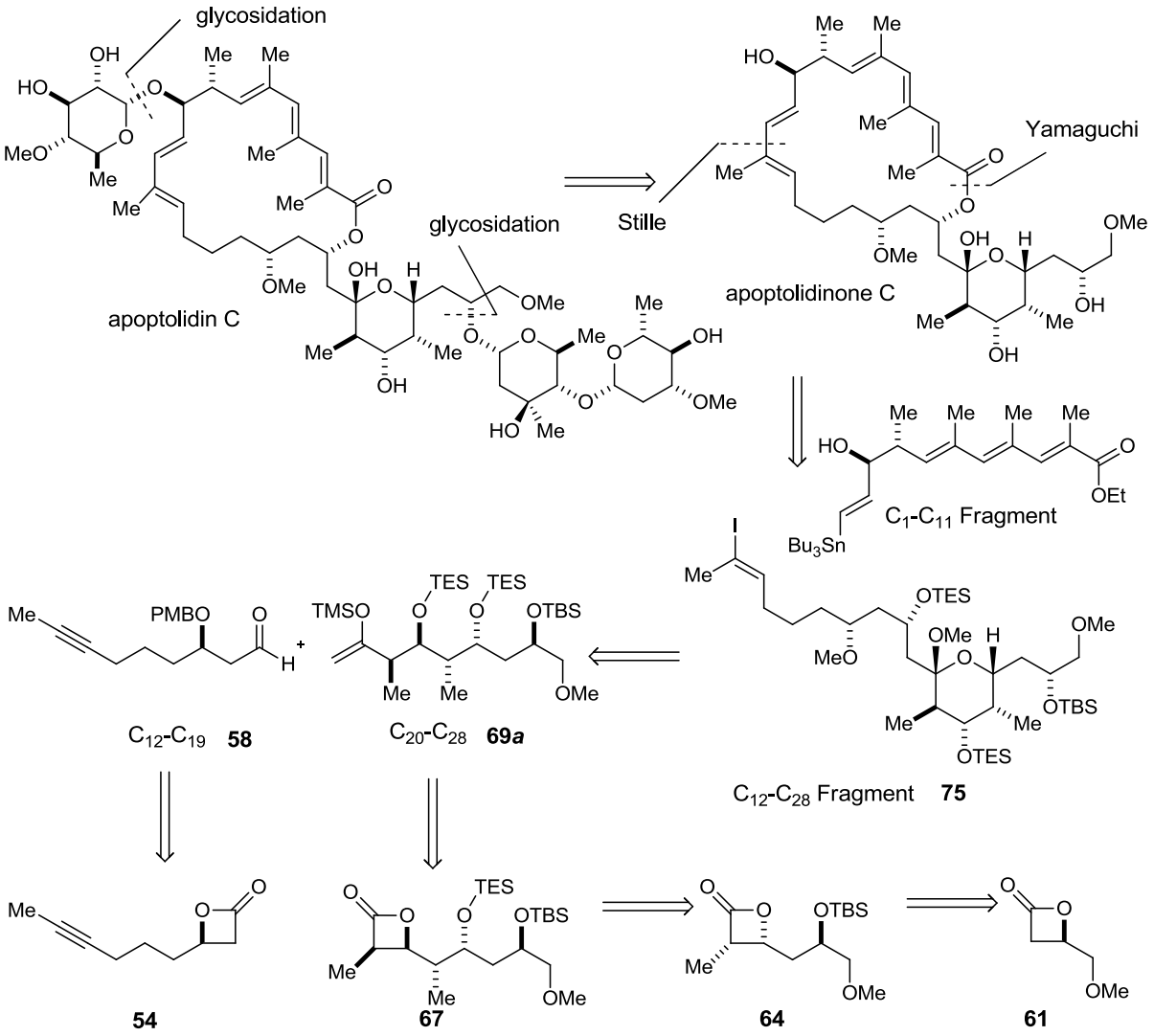
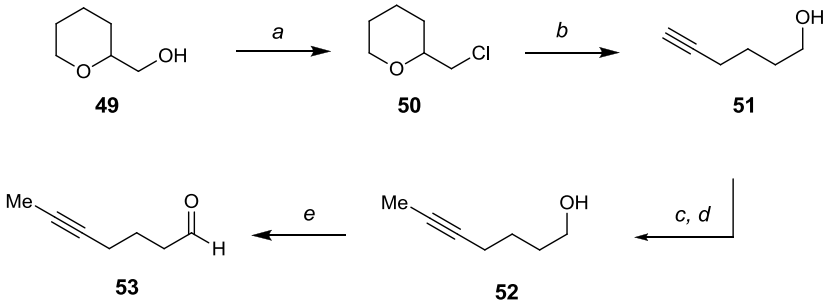


Figure 12. Retrosynthetic Approach

3.2 SYNTHESIS OF THE C_{12}-C_{19} FRAGMENT

Known aldehyde **53** was prepared by a five step sequence beginning with the inexpensive and commercially available alcohol **49** (Scheme 6).[32] Treating **49** with thionyl chloride gave compound **50** in 78%, which was treated with sodium amide in liquid ammonia to provide the terminal alkyne **51**.[33] Trimethylsilyl protection of the primary alcohol followed by methylation of the alkyne yielded alcohol **52** in a 63% yield over three steps. Oxidation (PCC) of this primary alcohol gave very clean conversion to aldehyde **53**, which was used in the following AAC chemistry to form the first stereocenter in this sequence.

Scheme 6: Synthesis of Aldehyde **53**

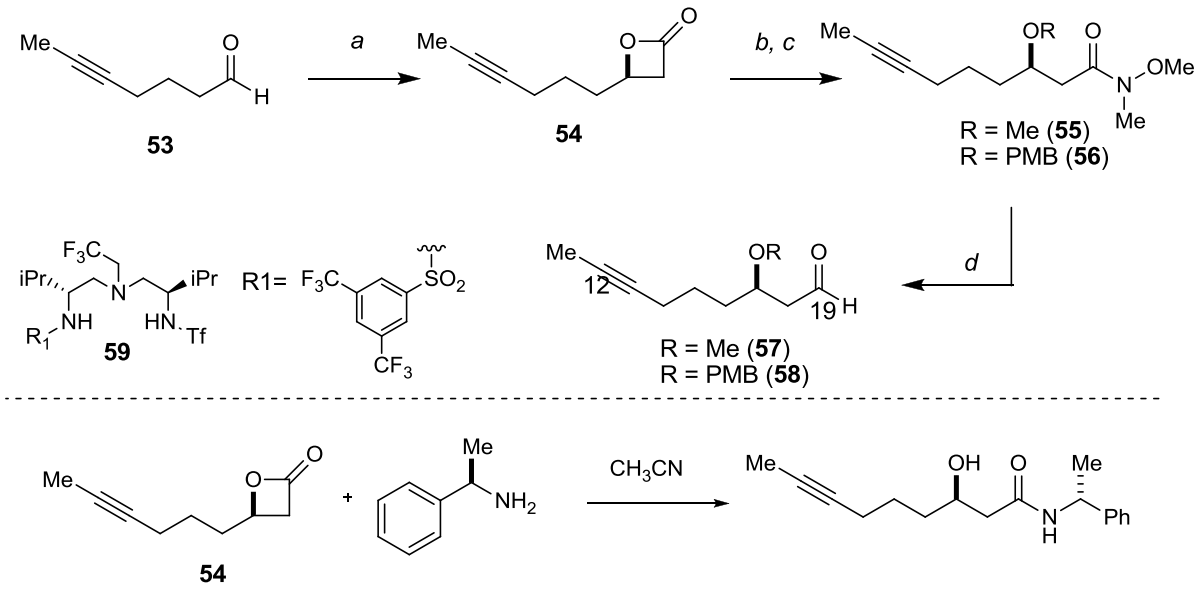


a. $SOCl_2$, pyridine, CH_2Cl_2, 35 °C, 24 h (78%); *b*. Na, $Fe(NO_3)_3$, NH_3, −33 °C, 3 h; *c*. TMSCl, imidazole, CH_2Cl_2, rt, 48 h; *d* nBuLi, MeI, THF, −78 °C - rt, 2 h (63% for 3 steps); *e*. PCC, CH_2Cl_2, 0 °C 3 h.

In order to affect the AAC transformation of aldehyde **53** a second generation aluminum catalyst (**59**) gave the best yields, which was prepared in a published sequence from D-valine (Scheme 7).[34,35] The active catalyst was generated in situ from the tri-amine precursor and Me_2AlCl in CH_2Cl_2 at ambient temperature. It should be noted however, the simpler first generation catalyst can be employed, albeit with slightly lower yields. After generation of

ethenone from acetyl bromide, aldehyde **53** was added, and the resultant β-lactone was formed in 51% yield over two steps (Scheme 7). To ascertain a level of enantioselectivity in this cyclocondensation reaction, the β-lactone was ring opened with enantiomerically pure α-methyl benzylamine, to furnish the β-hydroxy amide. Only a single diastereomer was formed within the limits of detection of NMR, giving a dr of >95:5.

Scheme 7: Synthesis of C_{12}-C_{19} Fragment



a. **59**, Me_2AlCl, $^{i}Pr_2NEt$, acetyl bromide, CH_2Cl_2, −78 °C, 18 h (51% for 2 steps); *b*. N,O-dimethylhydroxylamine hydrochloride, Me_2AlCl, CH_2Cl_2, 0 °C to rt, 3 h (81%); *c*. R = Me: MeI, NaH, DMF, THF, 0 °C, 1 h (80%); R = PMB: PMBOC(NH)CCl_3, 15 mol % BF_3 Et_2O, CH_2Cl_2 (60% for 2 steps); *d*. $^{i}Bu_2AlH$, THF, −78 °C, 2 h (97%).

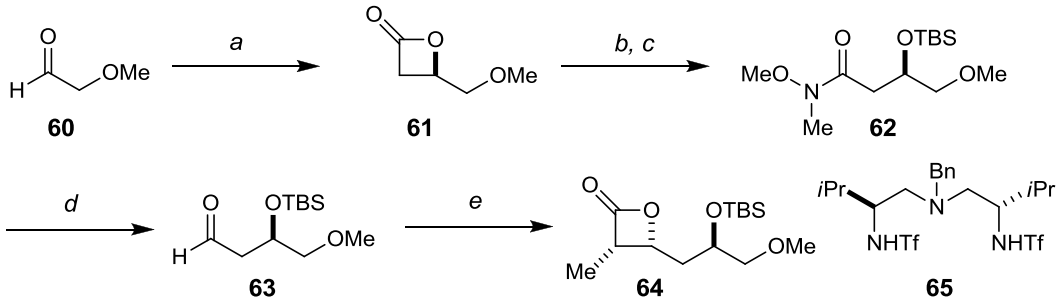
Ring opening of the β-lactone (**54**) with *N,O*-dimethylhydroxyl amine activated by Me_2AlCl gave the β-hydroxy amide. Upon subsequent methylation the β-methoxy amide **55** was obtained in good yield (80%). As will be seen later in the synthesis, the analogous product containing a PMB ether in place of the methyl ether (**56**) was required for diastereocontrol of the subsequent aldol reaction (*vide infra)*. Compound **56** was prepared using the *p*-methoxybenzyl

trichloroacetimidate and boron trifluoride in methylene chloride. Reduction of the Weinreb amide to the aldehyde was accomplished in excellent yield (97%), to provide **58**, while the yield for the reduction of **55** to **57** could not be ascertained due to the instability of the resulting aldehyde.

3.3 SYNTHESIS OF THE C_{20}-C_{28} FRAGMENT

Ketone **69** is characterized by a *syn*,*anti*,*syn*-relationship of four contiguous stereocenters, as well as a 1,3-*anti* relationship between C_{25} and C_{27} (Scheme 9). In the previous syntheses of this portion of apoptolidin A, a number of strategies have been employed, many of which rely on the use of stoichiometric chiral auxiliaries for the installation of the requisite chirality. We chose to avoid the use of chiral auxiliaries and synthesize the fragment from achiral starting materials implementing an iterative application of our AAC technology to demonstrate how efficient and selective the AAC methodology is.

Scheme 8: Synthesis of β-Lactone **64**



a. **65**, Me_2AlCl, $^{i}Pr_2NEt$, acetyl bromide, CH_2Cl_2, −50 °C, 12 h (81%); *b*. N,O-dimethylhydroxylamine hydrochloride, Me_2AlCl, CH_2Cl_2, −35 °C, 12 h (81%); *c*. TBSOTf, 2,6-lutidine, CH_2Cl_2, −60 °C, 12 h (99%); *d*. $^{i}Bu_2AlH$, THF, −78 °C, 2 h (95%); *e*. TMS-Qd, $^{i}Pr_2NEt$, $LiClO_4$, propionyl chloride, CH_2Cl_2/Et_2O, −78 °C, 18 h (78%).

Starting with methoxyacetaldehyde (**60**), prepared from the published procedure using 3-methoxy 1,2-propanediol,[36] the Al-catalyzed AAC reaction was carried out (Scheme 8) with the first generation triamine ligand (**65**) in 81% yield.[34,37] The enantiomeric excess of **61** was established by ring opening with a chiral amine, and analyzed by NMR spectroscopy. The product amide was a single diastereomer within the limits of detection, giving an ee of the β-lactone of greater than 95%. In preparing the aldehyde for the next AAC, the β-lactone was opened with *N,O*-dimethylhydroxyl amine, and the alcohol immediately protected as a TBS ether in 80% yield over the two steps. Reduction of amide **62** with DIBAL proceeded without complication to provide aldehyde **63** in 95% yield.

Following the synthesis of aldehyde **63** we required a second sequential AAC reaction in order to install the C_{24} and C_{25} methyl, and hydroxyl group. This iteration of our AAC chemistry demanded the use of propionyl chloride, providing methylketene in solution, and subsequently yielding a di-substituted β-lactone (**64**). The use of methylketene to form polypropionate arrays often has higher enantiomeric excess when using the Lewis-basic conditions instead of the previously seen aluminum catalysts.[38,39] Therefore, the two remaining β-lactones were formed under the *cinchona* alkaloid conditions (Scheme 9). Unfortunately the AAC reaction of aldehyde **63** under our standard set of conditions[38] (developed for α-unsubstituted aldehydes) gave only small amounts of β-lactone **64** while providing a large amount of ketene dimer as a byproduct.

Previous studies have shown that AAC reactions on α-chiral aldehydes proceed with a high degree of reliability and predictability,[40] and in early studies β-branched substrates gave similar results to unbranched aldehydes. AAC reactions had not been carried out on chiral β-substituted aldehydes until the synthesis of pironetin (figure 13).[40,41] In the pironetin example,

the aldehyde (a β-alkoxy aldehyde with a large protecting group) was unreactive toward *cinchona* alkaloid catalysis, and the aluminum catalyzed reactions were employed with a 20% catalyst loading to afford 25% yield of the desired product. An increase in catalyst loading to 50% provided a usable amount of product (65% yield) with excellent diastereoselectivity. It should be noted that the ketene precursor used in this example is butyryl bromide, thus providing ethyl ketene. The difficulties in accessing high conversion to the AAC product through *cinchona* alkaloid catalysis may have been due to the added steric bulk of the ethyl group.

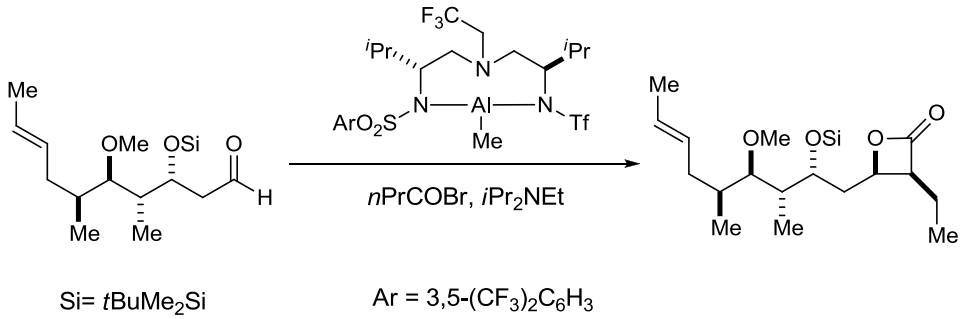
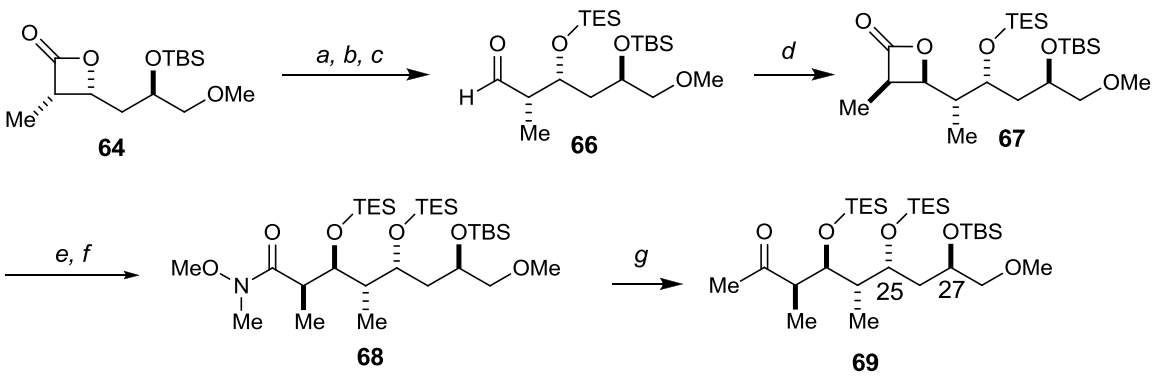


Figure 13. Pironetin's Final AAC Step

In order to optimize the *cinchona* alkaloid catalyzed version of our AAC methodology a number of standard variables were probed such as temperature, concentration, equivalents of ketene precursor, and reaction time. Modifying the Lewis acid used ($MgCl_2$, $LiClO_4$, LiI, ranging from 0.5-2.0 equiv), or increasing the *cinchona* alkaloid catalyst loading gave no benefit, and the competing pathway of ketene dimerization continued to be a significant problem. This was addressed with a much slower addition of propionyl chloride (from 1h to 4h with a 10:1 dilution in DCM). The slow addition of ketene precursor allowed for a very small concentration of ketene to be present in solution at any given point, which allowed for a reduction in the rate of

dimerization relative to cycloaddition. With this modification were able to isolate the desired β-lactone (**64**) in a very good yield (78%) and as a single diastereomer.

Scheme 9: Synthesis of C_{20}-C_{28} Fragment



a. *N,O*-Dimethylhydroxylamine hydrochloride, Me_2AlCl, CH_2Cl_2, −45 °C, 12 h (68%); *b*. TESOTf, 2,6-lutidine, CH_2Cl_2, −60 °C, 2 h (90%); *c*. $^{i}Bu_2AlH$, THF, −78 °C, 3 h (95%); *d*. TMS-Qn, $^{i}Pr_2NEt$, LiI, propionyl chloride, CH_2Cl_2/Et_2O, −78 °C, 18 h (77%); *e*. N,O-dimethylhydroxylamine hydrochloride, Me_2AlCl, CH_2Cl_2, −45 °C, 12 h (99% combined yield); *f*. TESOTf, 2,6-lutidine, CH_2Cl_2, −60 °C, 3 h (88%); *g*. MeMgBr, THF, 0 °C, 3 h (78%).

Continuation of the synthesis required converting β-lactone **64** to aldehyde **66** in order to perform the next AAC reaction. For the synthesis of **66** from β-lactone **64** we employed a standard sequence of *N,O*-dimethylhydroxyl amine ring opening, protection, and amide reduction with $^{i}Bu_2AlH$ to yield aldehyde **66** in 58% yield over the three steps. The final AAC reaction in this sequence provided a good yield of β-lactone **67** (77% of a single diastereomer).

The third iteration of our AAC reaction uses as its substrate, an α-chiral aldehyde, and therefore, the stereocontrol requires more analysis, and is no longer only under catalyst control.[41] In the absence of substrate chirality prediction of the outcome of the cyclocondensation can be achieved using established stereochemical models.[40,42] To predict the outcome of α-chiral aldehyde aldol reactions both the reagent and substrate chirality must be accounted for.

The analysis begins with the addition of the *cinchona* alkaloid into the ketene, and the favored Z-enolate[43] is formed due to a minimization of $A^{1,3}$ strain between the methyl and *cinchona* alkaloid groups. The Zimmerman-Traxler model is oriented in an anti-Felkin/Ahn type approach to avoid the destabilizing syn-pentane interaction (Figure 14).[42] The desired *syn, anti, syn*-aldol outcome is the matched case in which the reagent stereochemistry and the catalyst control are reinforcing, and is formed in very high diastereomeric ratios.

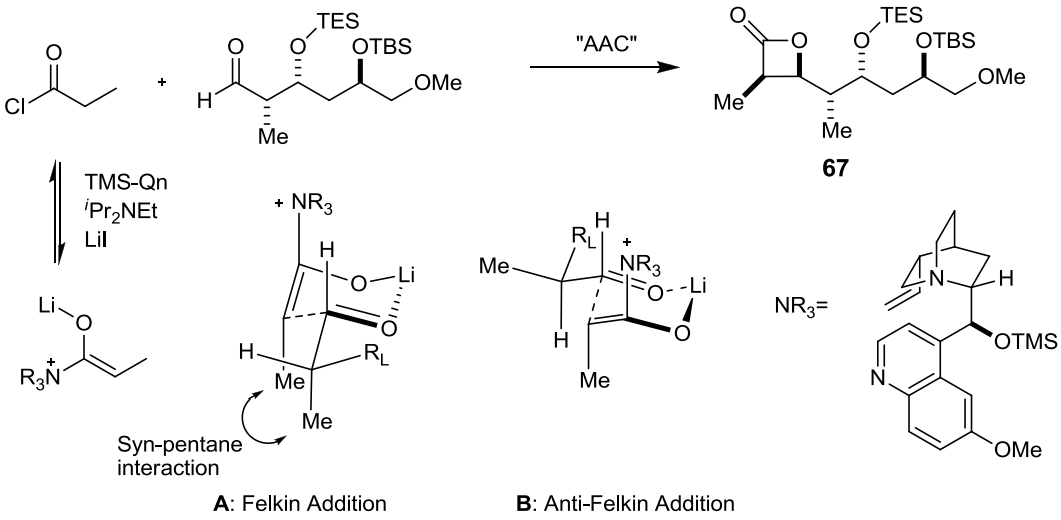


Figure 14. Double Diastereoselective AAC reactions.

Compound **67** was formed from three sequential AAC reactions using both Lewis acid and base catalysis with absolute control over all five stereocenters. Ring opening of the final β-lactone (**67**, Scheme 9) using *N,O*-dimethylhydroxyl amine gave two products, the desired mono alcohol, as well as a diol resulting from the TES-deprotection of the product in a combined yield of 99%. Both products were subjected to the same TESOTf protection, providing 88% of the bis-TES protected amide. Treatment with MeMgBr gave the desired methyl ketone **69** in 78%

yield. The completion of the methyl ketone (**69**) gave us the requisite materials to probe the aldol coupling.

3.4 ALDOL COUPLING OF AGLYCONE FRAGMENTS 58 AND 69

Aldol additions of methyl ketones are often unpredictable in their stereochemical outcome, and thus have rarely seen use in late stage synthetic applications. Recent studies have shed some light on one of the root causes for this unpredictability, [44] namely the tendency for boron enolates to occupy a boat transition state, instead of the more commonly seen chair transition state of the Zimmerman-Traxler model. A major obstacle in the synthesis of apoptolidinone C was the stereoselective C_{19}-C_{20} bond formation. Initial attempts to join the two fragments together provided the desired product (**72**) as the minor component of a mixture of diastereomers at C_{19}. In order to achieve good stereocontrol over the aldol reaction an extensive review of the literature yielded a number of possible stereoinduction methods that may be playing a role in the aldol reaction shown below. A clear understanding of the factors that control the transition state of these methyl ketone aldol additions should provide a path to the optimal conditions to achieve the desired results.

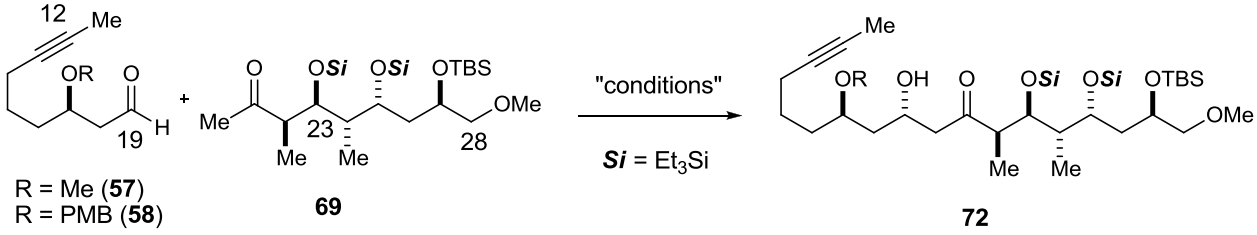
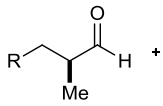
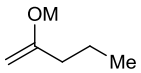
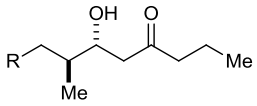
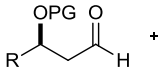
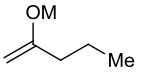
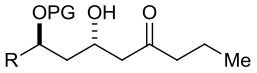
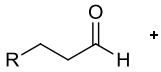
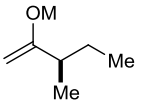
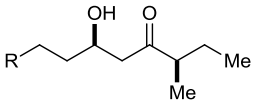
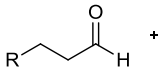
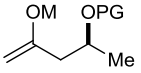
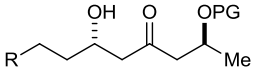
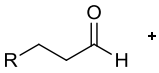
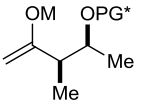
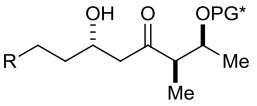
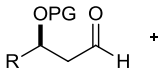
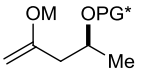
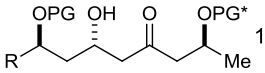
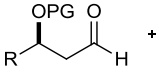
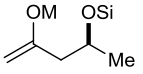
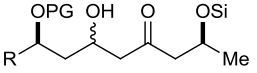
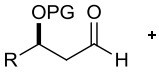
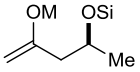
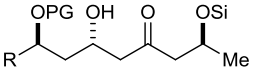


Figure 15. Aldol Reaction for the Formation of Ketone **72**

The following table is a summary of the major modes of stereoinduction in methyl ketone aldol additions, and a more detailed analysis of each model follows the tabular data. Table 2 shows four modes of simple stereoinduction (entries *a*-*d*), as well as doublesteredifferentiating reactions (entries *e*-*h*) which use two of the simple modes of induction together. Some of these modes of induction rely upon closed or open transition states, which is noted under the "induction type" column, while others rely upon particular choices of protecting group.

Table 2. Asymmetric Induction Effects for Methyl Ketone Aldol Additions.

	Induction Type	Aldehyde	Enolate	Major Product Observed		References
a	1,2 Open T.S.				1,2-*anti*	*Tetrahedron Lett*. **1968**, *9,* 2199.
b	1,3 Open T.S.				1,3-*anti*	*J. Am. Chem. Soc.* **1996**, *118*, 4322.
c	1,4 Closed T.S.				1,4-*syn*	*Chem. Comm.* **2007,** 2124.
d	1,5 Closed T.S.				1,5-*anti*	*J. Am. Chem. Soc.* **2003,** *125*, 10893.
e	1,4/1,5 Closed T.S.				1,5-*anti*	*Org. Lett*. **2002**, 4325.
f	1,3/1,5 Closed T.S.				1,3/1,5-*anti*	*J. Am. Chem. Soc.* **2003,** *125*, 10893.
	1,3 and 1,5 reinforcing in a chelated transition state with an alkyl protecting group at the 5 position					
g	1,3/1,5 Closed T.S.				none	*J. Am. Chem. Soc.* **2003**, *125*, 10893.
	erosion of selectivity in many cases with silyl protection at the 5 position					
h	1,3/1,5 Open T.S. with Chelated Aldehyde				1,3/1,5 *anti*	*J. Am. Chem. Soc.* **2003,** *125*, 10893.
	erosion of selectivity in many cases with silyl protection at the 5 position					

* when PG allows for hydrogen bonding

3.4.1 1,2-Stereoinduction

The aldehydes relevant to the synthesis of apoptolidin C (Figure 15, **57** and **58**) don't contain an α-stereocenter, however a discussion of stereoinduction that omits this ubiquitous method would be incomplete. The effect of a stereocenter adjacent to the aldyhyde has been studied extensively with respect to attack of various nucleophiles.[45-47] The accepted transition state model follows "Felkin" selectivity, and is described via transition state structures **A** and **B** (Figure 16). When using a non-chelating Lewis acid ($BF_3 \cdot Et_2O$), this reaction takes place through an open transition state.

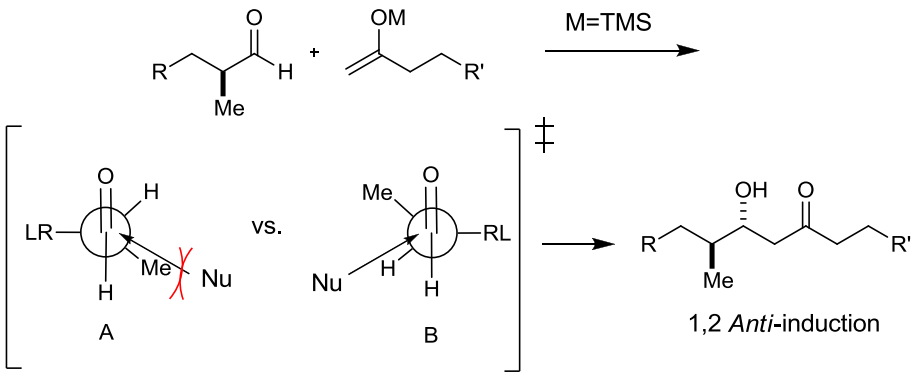


Figure 16. Transition State Describing 1,2 Stereocontrol.

1,2 induction of aldol stereochemistry is well precedented, and generally imparts high selectivity.[48] Using Felkin models to predict the outcome of 1,2 induction is illustrated in Table 2 (entry *a*), and is generally *anti*.

3.4.2 1,3-Stereoinduction

Prediction of product geometry based on reagent stereochemistry and choice of metal for either chelate, or non-chelate control in β-alkoxy aldehydes has been known since the early 1950's.[49-51] A revised transition state structure, was proposed in 1996[48] where the alkoxy substituent is aligned *anti* to the carbonyl group to minimize dipole interactions. The dominant steric interaction in the revised model (Figure 17) is the R group of the chain eclipsing the carbonyl oxygen (**C**). In the other accessible transition structure, the less sterically bulky hydrogen occupies that site (**D**), which leads to the preferred 1,3-*anti* product, as can be seen in example *b* in Table 2.

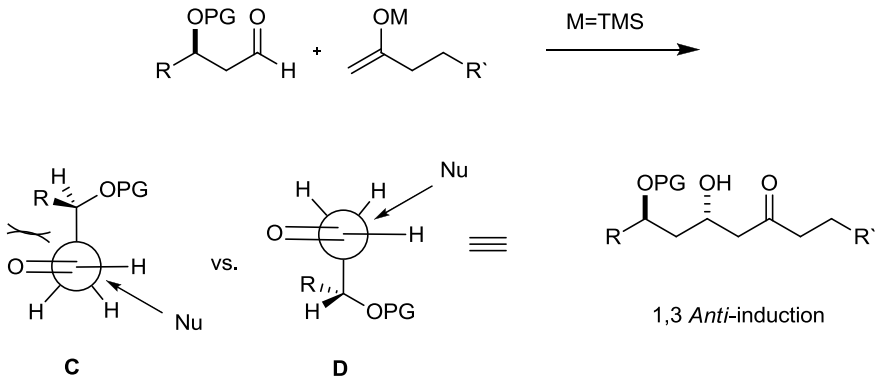


Figure 17. Transition State Model for 1,3 Stereocontrol.

The presence of 1,3 induction as seen above is attained when the system is in an "open" transition state. This is best exemplified in the Mukaiyama aldol reaction where M=TMS, and using a mono-dentate lewis acid, such as BF_3•Et_2O. The use of Bu_2BOTf to form a chelate between the aldehyde and enolate do not show 1,3 induction of stereochemistry.[44]

Alternatively, a widely accepted chelate based model has been proposed that coordinates the aldehyde oxygen with the β-alkoxy substituent to form a rigid six-membered ring capable of directing facial approach of a nucleophile.[51,52] However it is noted that the group that caps the alkoxy substituent plays a significant role in the ordered structure of the transition state.[50] When sterically bulky groups occupy the oxygen, a rigid transition state is formed placing the large bulky group in a pseudo equatorial position. However, with a small protecting group, there is ambiguity in the transition state, leading to significantly lower diastereoselectivities, notably when the β-alkoxy group is capped with CH_3.[50]

3.4.3 1,4-Stereoinduction

Recent computational studies have shown very low energy differences between the boat and chair conformations of unsubstituted enolate additions, when chelating lewis acids are used, such as dibutyl boron triflate.[53] It is their assertion that the minimal energy difference could erode selectivity in many 1,4 induction reactions, however, many such reactions see a strong 1,4 syn dependence.

In boron mediated aldol reactions where a chiral substituent is alpha to the ketone, there can be a strong preference to form the 1,4-*syn* product[54-56] seen in example *c* in Table 2. This preference has been explained via a formyl hydrogen-bonding model,[56] and has been borne out experimentally. The proposed hydrogen-bonding transition state is very similar to that of the 1,5 induction model (Figure 18). It must be pointed out that this induction affect is only noticeable in boron mediated processes, and the affect is negligible in open transition-state processes.

3.4.4 1,5-Stereoinduction

The prediction of stereo induction from an alkoxy substituent at the beta position to the enolate is illustrated in example *d* of Table 2. Recently, Goodman and coworkers proposed a transition state structure that explains levels of 1,5-*anti* induction previously seen.[56] The analysis compared the relative energies of transition state structures for a number of chair and boat conformations for simple unsubstituted aldol reactions, as well as alpha and beta substituted ketones.[53] The explanation given for 1,5-*anti* induction is one of hydrogen-bond stabilization, which they also used successfully to predict the 1,4-*syn* induction. Based on computational calculations the 1,5-*anti* configuration (Figure 18) is lower in energy than the 1,5-*syn* conformation due to the steric interaction imparted by the R` group and the ligands on boron. This affect, as in the 1,4 induction, is only observed in boron mediated aldol reactions.

The formyl hydrogen-bonding models also coincide nicely with an observation made by both Evans[44] and Dias[57] concerning protecting groups on the β-alkoxy group. High levels of 1,5 control are consistent throughout a wide range of protecting groups that allow hydrogen bonding, such as a 1,3 diol acetonide, PMB ether, OBn, and PMP acetal. Accordingly, when a protecting group that blocks chelation, such as TBS is employed, the diastereocontrol is substantially eroded.

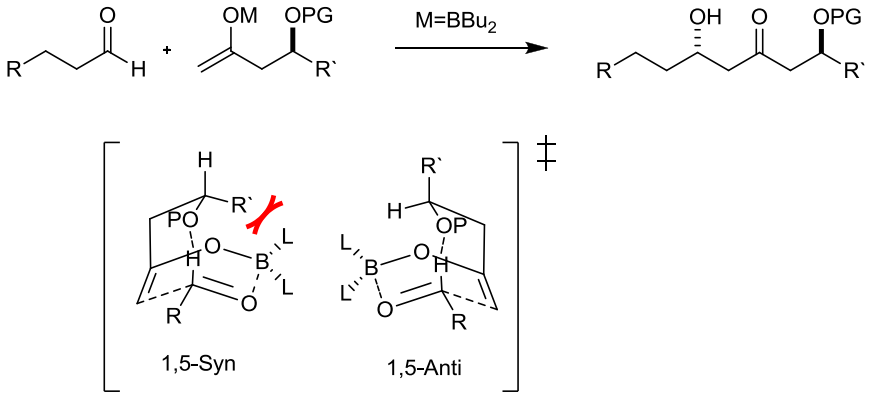


Figure 18. Transition State Model for 1,5-*Anti* Induction.

3.4.5 1,4- and 1,5-Double stereodifferentiating reactions

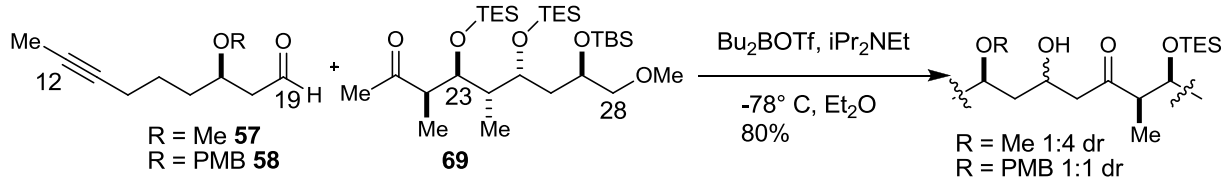
When attempting to control the stereochemistry of an aldol reaction employing an α-methyl, β-alkoxy methylketone the two chiral centers may be reinforcing, or opposed, in their control of the developing alcohol stereocenter, table 2 (entry *e*). Experimental observations have shown that when these two factors are competing against one another, the 1,5 induction will override the 1,4 induction as long as the protecting group of the β-alkoxy substituent meets the requirement of the simple 1,5 induction case, as stated above.[44,53,57] If those requirements are not met, and a silyl protecting group, for example, is used, all diastereoselectivity is eroded.[57] Therefore careful consideration of protecting groups is important.

3.4.6 1,3- and 1,5-Double stereodifferentiating reactions

Stereocontrol in complex aldol couplings with both 1,3 and 1,5 alkoxy substituents can be simplified considerably with the choice of protecting group and lewis acid. This is exemplified

in a series of aldol reactions published by Evans in 2003.[44] When 1,5 anti-induction is desired, the protecting group must be chosen appropriately to allow for coordination to achieve high levels of stereoinduction. However, if a silyl group is occupying the beta oxygen, and 1,3 induction is desired based on an open transition state, very poor selectivities are generally seen. When using chelating conditions, the complexity of the transition state increases dramatically with increased substrate complexity, and the simple stereoinduction models presented here fail to accurately predict the outcome. Strong diastereocontrol is more easily predicted when using open transition states, as the 1,5 induction can be ignored.

Scheme 10: Initial Methyl-Ketone Aldol Coupling



The aldol reaction between ketone **69** and aldehyde **57/58** (scheme 10) using Bu_2BOTf is predicted to have little, to no diastereocontrol. The use of a boron enolate negates any 1,3 control due to a closed transition state, where the stereocenters on the ketone side influence the outcome, and a silyl protecting group on the C_{23} oxygen deters any hydrogen bonding of the formyl hydrogen to that oxygen. This potential lack of hydrogen bonding capability excludes 1,4 as well as 1,5 control. However, treatment of ketone **69** with Bu_2BOTf and $^{i}Pr_2NEt$, in Et_2O followed by aldehyde **57** gave a 4:1 mixture of diastereomers.

Attempting to determine the stereochemistry of the major diastereomer, an analysis of the resultant alcohol was performed by *O*-methylmandelate ester formation.[49] The major

diastereomer was treated with both enantiomers of α-methoxy phenylacetic acid. When comparing the ^{1}H NMR spectrum of the two diastereotopic esters (**70** and **71**, Figure 19), the stereochemistry of the alcohol can be determined by noting which set of protons is shifted downfield relative to the diastereomer. The protons of both products were unequivocally assigned based on ^{1}H and COSY NMR analysis. The shift is influenced by the proximity of the phenyl ring of the ester, and the conformation in solution of the structure. The analysis shown in Figure 18 is the accepted solution state analysis, as the fisher projection is shown in an "extended" view down the length of the ester. The methoxy group is oriented *anti* to the C_{sp2}-O single bond of the ester, to minimize dipoles. The phenyl ring shields the neighboring protons, shifting them upfield relative to the same protons on the diastereomer of the product. This analysis led us to the conclusion that the (*R*) form of the stereocenter is the major diastereomer, which is the un-desired product.

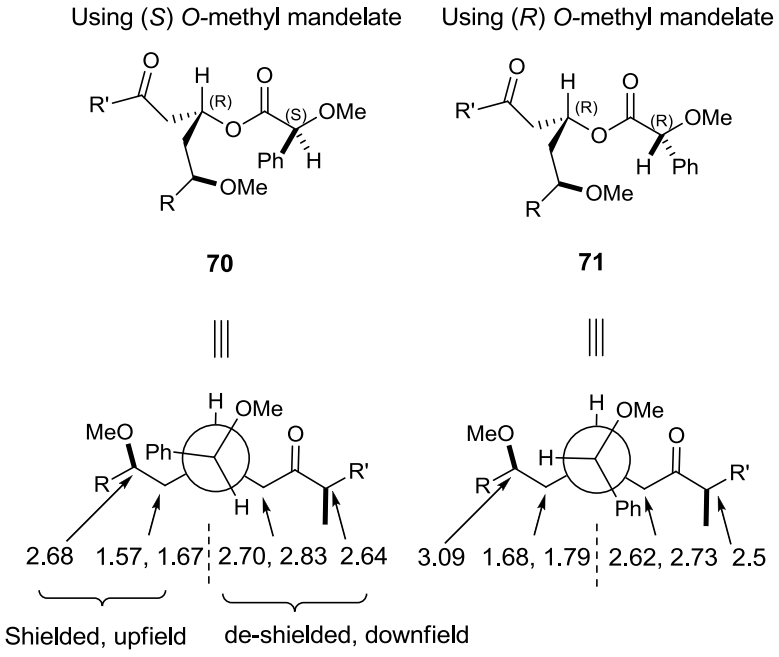
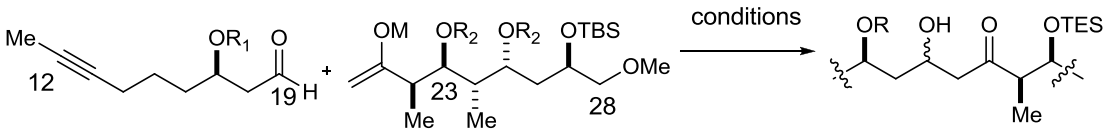


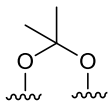
Figure 19. Stereochemical Analysis of the Aldol Product.

In order to gain better control over the selectivity of the aldol transformation, a change in reagents was employed. Treatment of the ketone with TMSCl, and NaHMDS gave only the kinetic enolate,[58] which upon addition to the aldehyde with BF_3•Et_2O gave a 1:1 mixture of diastereomers. The result was disheartening, because analysis of the sterechemical factors would suggest that the only control element in an open transition state of this system should be the 1,3 influence of the β-alkoxy group. Using a mono-dentate lewis acid such as BF_3•Et_2O, the only requirement for control is an anti arrangement of the carbonyl and alkoxy bonds to minimize the dipoles in the transition state and the orientation should not be highly dependant upon the protecting group on oxygen. However, based on Keck's work a chelate controlled addition where the oxygen substituent is a methyl group provides little to no stereochemical bias.

A slightly electron donating protecting group, such as an alkyl methyl group would be just as strong of a directing group as a PMB ether. A very common β-alkoxy substituent seen in many diastereoselectivity studies is a PMB ether, and therefore we chose this as a suitable protecting group to probe the Mukaiyama aldol reaction between the silyl enol ether derived from ketone **69** and aldehyde **58**. Table 3 summarizes the results of various attempts at coupling the two halves of the southern hemisphere of the aglycone, and resulted in the product being formed in good yield as a single diastereomer within the limits of detection of NMR.

Table 3. Summary of Results.



M	Lewis Acid	R_1	R_2	Results
$NiPr_2Et$*	Bu_2BOTf	Me	TES	3.5:1 syn
$NiPr_2Et$*	$TiCl_4$	Me	TES	1:1
LDA*	$MgBr_2$	Me	TES	1:1
$NiPr_2Et$*	Bu_2BOTf	Me		1:1
TMS	$MgBr_2$	PMB	TES	NR
TMS	Me_2AlCl	PMB	TES	1:1
TMS	$SnCl_4$	PMB	TES	Decomposition
TMS	$TiCl_4$	PMB	TES	Decomposition
TMS	BF_3 Et_2O	PMB	TES	>20:1 anti

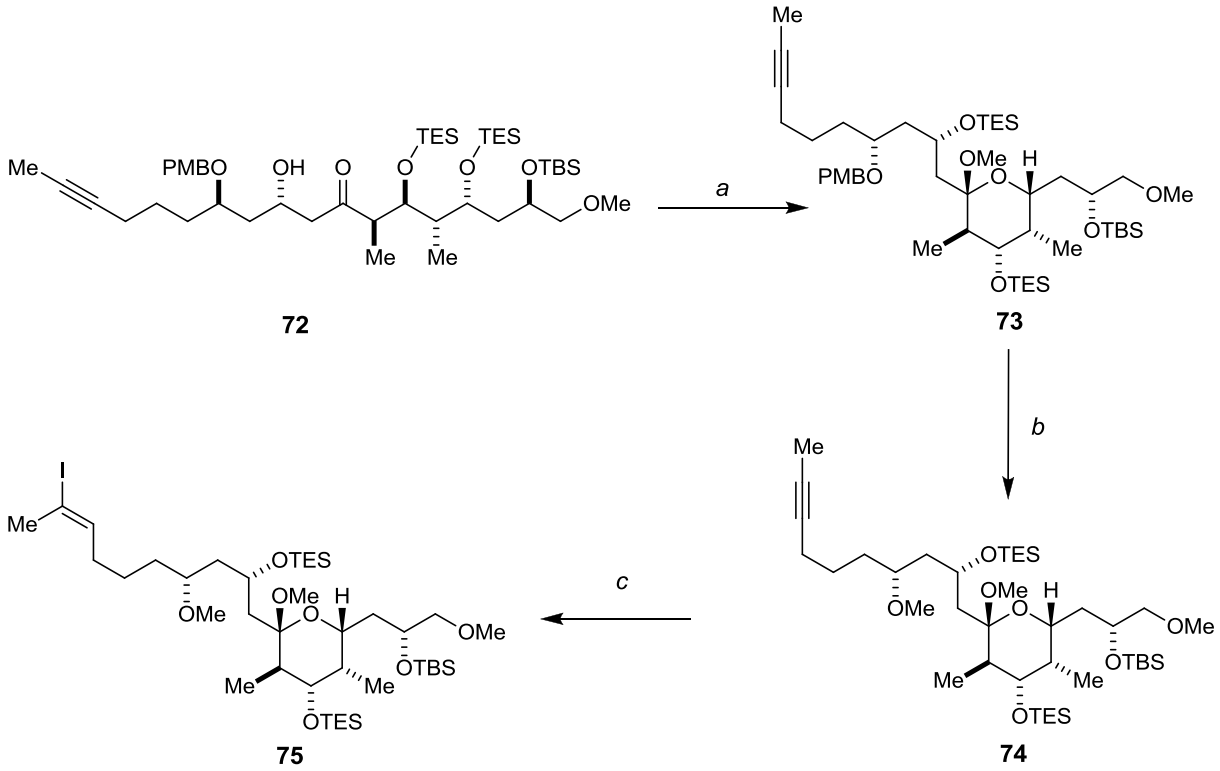
*The ketone was treated with the specified base in the presence of the lewis acid to generate the enolate in-situ

3.5 COMPLETION OF THE AGLYCONE

With the aldol product (**72**, Scheme 11) in hand, we began the final steps to prepare the southern hemisphere of apoptolidinone for coupling. The aldol product (**72**, Scheme 11) was treated with PPTS in a 1:1 mixture of CH_2Cl_2/MeOH, for 12 h at ambient temperature to selectively deprotect the two triethylsilyl groups while retaining the TBS alcohol. Upon deprotection, the free C_{25} alcohol cyclyized onto the ketone to form the desired methoxy ketal (**73**). Protecting the two free alcohols with TESOTf and 2,6-lutidine gave an excellent yield (98%) of the fully protected furan (**74**). Precedent from the aglycone synthesis done by Nicolaou and coworkers provided the procedure for the hydrozirconation/iodination of the internal alkyne with three equivalences of Schwartz's reagent in THF at 55 °C. Due to the expected instability of the vinyl iodide (**75**) the product was not rigorously purified or characterized.

The final fragment coupling leading to apoptolidinone C joined the complete upper (**76** Scheme 12) and lower (**75**) fragments via a Stille coupling utilizing the acetonitrile adduct of $PdCl_2$ providing the *E,E* diene, as the major component of a 12:1 mixture in 75% yield. Of key importance to the success of this reaction was the use of tetrabutylammonium diphenylphosphinate as a tin-halide scavenger.[59] Coupling attempts without this salt resulted in an irreproducible mixture of diene isomers, often as a 1:1 mixture.[60]

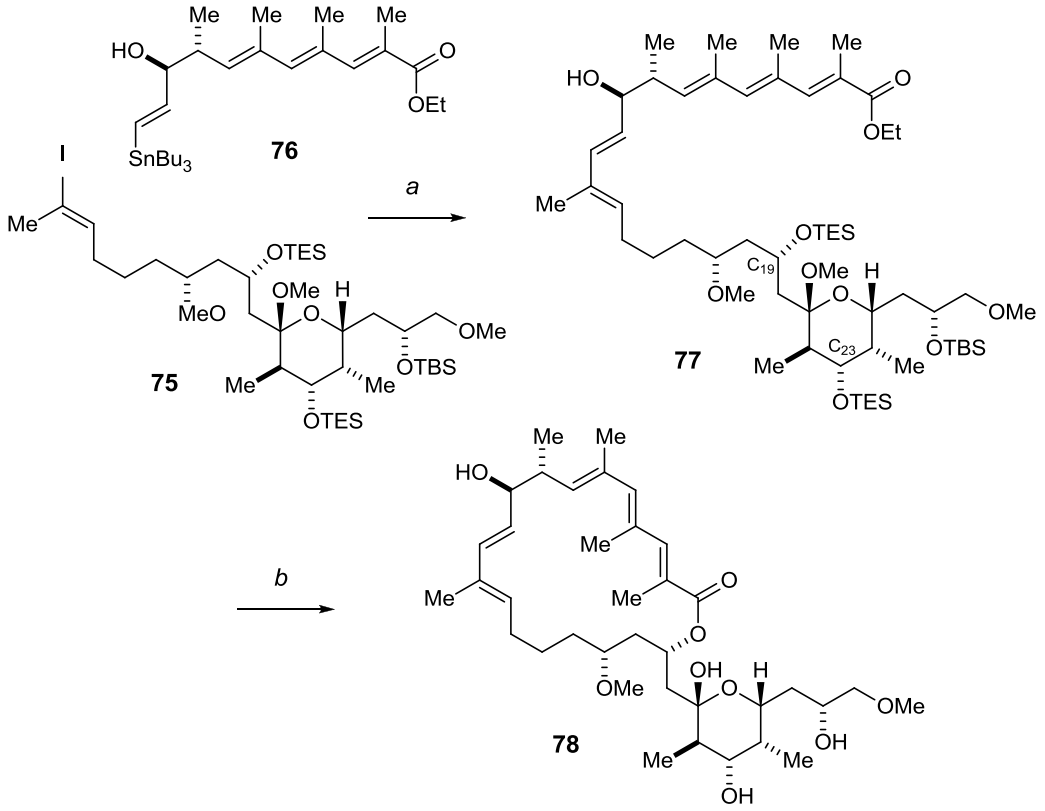
Scheme 11: Completion of the Lower Half



a. *i)* PPTS, MeOH/CH_2Cl_2 1:1, rt, 12 h (75%); *ii)* TESOTf, 2,6-lutidine, CH_2Cl_2, −55 °C, 3 h (98%); *b*. *i)* DDQ, 2:1 CH_2Cl_2:pH7 phosphate buffer; *ii*) Me_3OBF_4, proton sponge, CH_2Cl_2; *c*. Cp_2ZrHCl, THF, 55 °C, 1 h, then I_2, −20 °C.

The successful Stille coupling was followed by a LiOH saponification, which yielded a mixture of products resulting from the partial deprotection of both TES protecting groups at the C_{19} and C_{23} alkoxy groups. In order to simplify the mixture, the crude product was treated with trifluoroacetic acid to complete the deprotection, yielding the seco-acid in 48% yield over two steps. Following the precedent set by previous syntheses of apoptolidinone A, we used standard Yamaguchi macrolactonization conditions, followed by a global deprotection with an acidic fluoride source: H_2SiF_6, yielding the completed aglycone in 57%, and 64% for the final two steps.

Scheme 12: Synthesis of Apoptolidinone C



a. $Pd_2Cl_2(MeCN)_2$, $Ph_2PO_2NBu_4$, DMF, rt (73%); *b*. *i*) LiOH, THF, MeOH, H_2O, rt; *ii*) CF_3CO_2H, CH_2Cl_2/MeOH, −15 °C (48% for 2 steps); *iii*) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, THF, rt (57%); iv) H_2SiF_6, THF, MeCN, −35 °C, 48 h (64%).

4.0 CATALYTIC ASYMMETRIC SYNTHESIS OF THE C_9 SACCHARIDE, AND EFFORTS TOWARDS THE COMPLETION OF APOPTOLIDIN C

4.1 EARLY ATTEMPTS TO SYNTHESIZE THE C_9 SACCHARIDE

The completion of the aglycone gave us the opportunity to focus on the de-novo synthesis of the three saccharides appended to the aglycone, and finish the synthesis of the natural product. Our goal was to generate the three sugars without the use of chiral auxiliaries, or stoichiometric chiral reagents. My efforts were focused on the synthesis of the C_9 sugar, 6-deoxy-4-*O*-methyl-L-glucose (**79**).

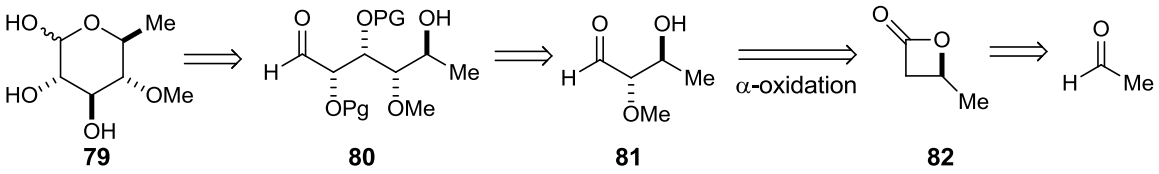


Figure 20. First Retrosynthetic Approach to Glycoside A.

Our first approach to the synthesis of compound **79** was ambitious in its use of new, untested chemistry. We planned on a ring closing reaction from the linear aldehyde **80**, which we believed could be formed from one of two methods: 1. the chelate controlled allylation of aldehyde **81**; 2. the Wittig homologation of the aldehyde followed by an asymmetric

dihydroxylation as seen in professor Crimmins' work.[22] These reactions were predicated upon the formation of the substituted butanaldehyde **81**. Our attempts at synthesizing the sugar became a study in merely synthesizing this α,β-alkoxy aldehyde with correct diastereoselectivity, and high enantiomeric excess.

We saw an opportunity to use our groups AAC chemistry to form the first stereocenter in the form of β-lactone **82**,[61] which, under the right conditions can be alkylated to give the anti-diastereoselectivity that we desired.[62,63] We hoped to translate this behavior to an oxidative reagent such as Davis' oxaziradine.[64] In this manner we could assemble the α,β-anti-stereochemistry that we desired in two simple steps that we predicted would be highly diastereoselective. Unfortunately the α-oxidation product was unattainable under a variety of conditions, and although this would be an excellent reaction to develop, not only for the synthesis at hand, we decided to abandon that route in favor of more reliable chemistry.

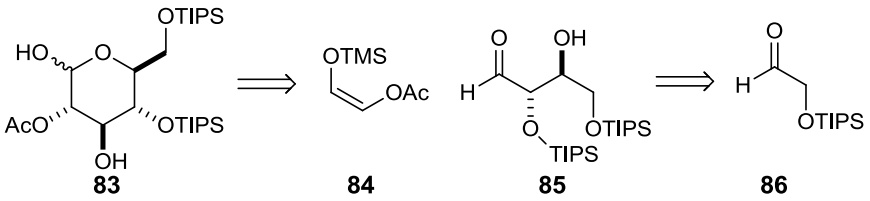


Figure 21. Second Retrosynthetic Approach Utilizing MacMillan's Chemistry.

Our second attempt at installing the correct stereochemistry was through an organocatalytic dimerization of silyloxy acetaldehyde (**86**).[65-67] The proline catalyzed dimerization gives the aldehyde **85**, which when treated with silylenol ether **84** under magnesium chelate conditions can give **83** as the major compound.[66] This procedure fulfilled our requirements, by being a short, precedented route to the basic sugar form, using a chiral catalyst

to set the stereochemistry, and initially we were optimistic about the prospects that this chemistry presented. Unfortunately, upon further experimentation we ran into major problems. Firstly, the formation of aldehyde **86** was low yielding, and difficult to perform on large scale. The dimer product was made in 4:1 diastereomeric ratio, which was only partially separable, and in a much lower yield than reported in the literature. The combination of these facts left us with the need to carry out these reactions on extremely large scale, only to have a few grams of usable product. Following the dimerization, the chelate controlled aldol with **84** gave an approximately 10:1 mixture of diastereomers, providing an inseperable mixture of four compounds. Those four compounds then spontaneously cyclized creating another 1:1 anomeric mixture of each product (Figure 22). The practicality of the synthesis was already being tested, before we approached any of the unknown chemistry.

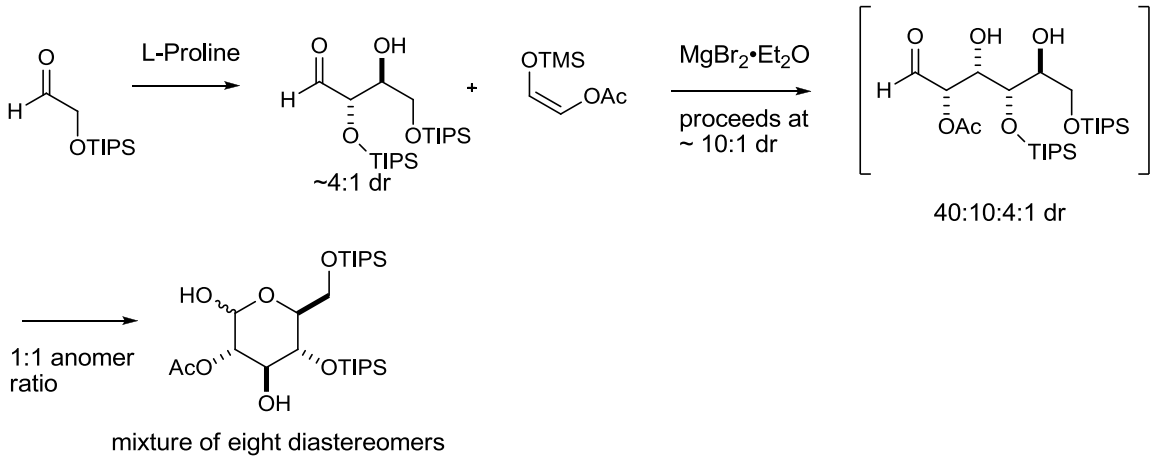


Figure 22. Details of Diasteriomeric Ratio Problems.

A major problem with this route was the inability to separate the diastereomers from each other when run on a large scale. Due to this, we were forced to carry mixtures through the synthesis, and ultimately were left with an unidentifiable mix of hydroxylated compounds.

Secondly, we had envisioned a late stage methylation of the C_4 oxygen, after deprotection, and deoxygenation of the C_5 primary alcohol. The published routes to this sugar show an early installation of this methyl group. During our attempts we noticed a concerning lack of stability when the C_4 oxygen is deprotonated. We attributed this to potential retro-aldol reaction, and attempted various procedures to circumvent the complete deprotonation, which improved the process slightly. This route ultimately proved to be impractical, and we were therefore forced to abandon it in favor of a more traditional approach.

4.2 COMPLETION OF THE C_9 SACCHARIDE

In our final approach we intended to install the methoxy substituent at an early stage, avoid the costly deoxygenation procedures that were necessary in the dimerization route, and use the substrate to control all of the stereodefining steps. To this end we envisioned setting the three contiguous *syn,syn* stereocenters in **90** via a chelate controlled allylation.[68] The strong precedent of this step gave us confidence that our approach would ultimately be successful.

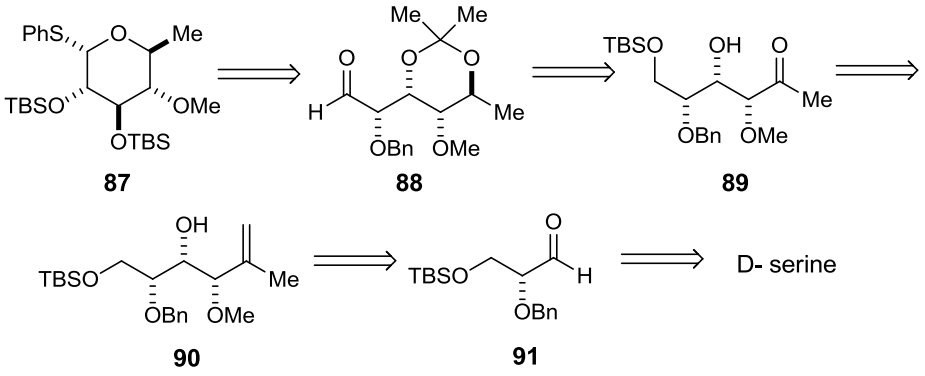
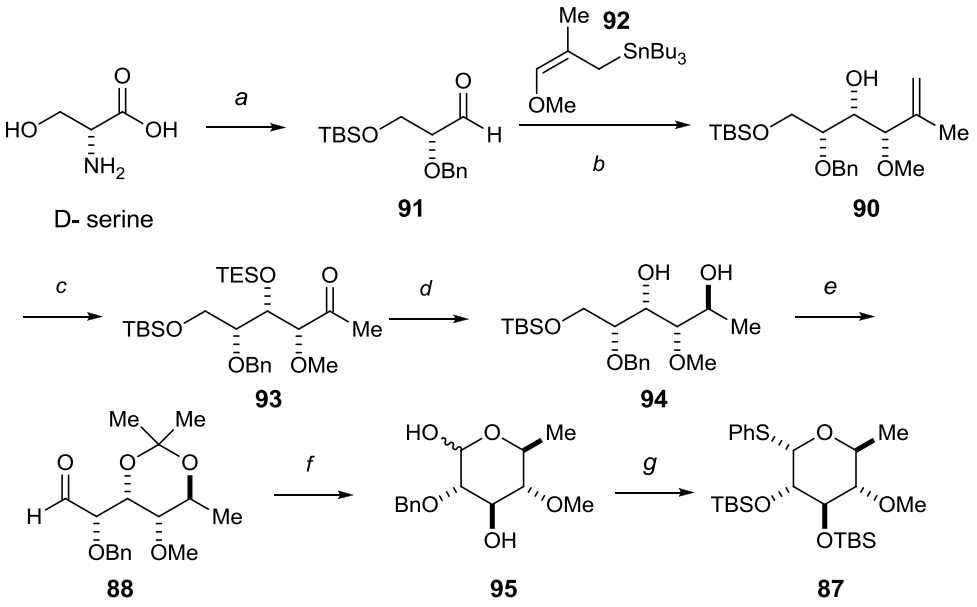


Figure 23. Final Retrosynthetic Approach to Glycoside A.

Following this, we would oxidativly cleave the alkene, and use a directed reduction to install the fourth stereocenter (**88**). From the protected aldehyde, only an acidic deprotection, and functional group manipulation would remain.

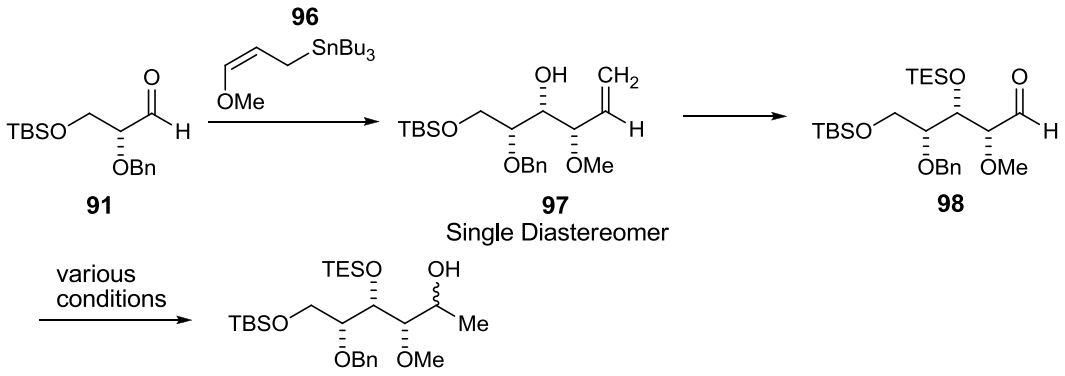
Scheme 13: Synthesis of the C_9 Saccharide



a. i) $NaNO_3$, H_2SO_4; *ii*) TBSCl, imidazole; *iii)* $BnOC(NH)CCl_3$, triflic acid; *iv)* $^{i}Bu_2AlH$ *b*. $MgBr_2{\cdot}Et_2O$, (Z)-tributyl(3-methoxy-2-methylallyl)stannane (**92**), 0 °C *c*. *i)* TESOTf, 2,6-lutidine, CH_2Cl_2; *ii)* O_3, DMS*;* (*d*) *i)* $Zn(BH_4)_2$ *ii)* PPTS, CH_2Cl_2:MeOH *e. i)* dimethoxypropane, PPTS, CH_2Cl_2; *ii)* Bu_4NF; *iii)* DMP, $NaHCO_3$, CH_2Cl_2; *f.* HCl, THF, H_2O; *g. i)* H_2, 20% Pd/C; *ii*) PhSH, TfOH, THF, *iii)* TBSOTf, 2,6-lutidine.

We began with a known route from serine to aldehyde **91** as seen in Mukaiyama's synthesis of taxol.[69] A chelate controlled allylation with **90** gave a 3:1 mixture of diastereomers, which were seperable by column chromatography, giving a 63% yield of a single product. Silyl protection of the resultant secondary alcohol, and chelate controlled reduction of the ketone with $Zn(BH_4)_2$ (95%) gave us the desired *syn,syn,anti* arrangement of stereocenters we desired.

Scheme 14: Initial Tin Allylation Procedure



We initially envisioned an allylation with the known allyl tin species **96**, and this gave us excellent control of the desired alcohol. After oxidative cleavage any attempt to selectively alkylate the aldehyde was met with a mixture of diastereomers, never better than 1.2:1. In contrast, the route we chose to pursue utilized a directed reduction seen in scheme 13 (step *d*) which proceeded with absolute control, and a modified allylation reagent (**92**), which gave 3:1 mixture of diastereomers, which were seperable by column chromatography, and was high yielding.

Selective TES deprotection in the presence of the primary TBS group was achieved in good yield (79%), and the diol was protected with 2,2 dimethoxypropane using PPTS in 93% yield. After removal of the primary TBS group with TBAF (89%), a DMP oxidation gave the aldehyde, which was treated crude with 1M HCl in a mixture of THF and H_2O to yield **95** as a 1:1 mixture of anomers.

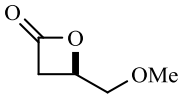
We originally envisioned a thioglycosidation prior to the benzyl deprotection, in order to reduce the polarity of any intermediates, and ease any handling of the compounds, however this proved to be difficult. The initial thioglycosidation proceded under standard conditions (PhSH, TfOH, r.t.), however all attempts at hydrogenolysis of the benzyl group gave

no reaction. To circumvent this problem, we removed the benzyl group first, under standard palladium/H_2 conditions, and without purification of the intervening triol formed the thioglycoside under triflic acid conditions. The resulting thioglycoside was formed as a single anomer, which was later identified as the α-anomer. A bis-TBS protection of the diol gave the known thioglycoside whose NMR spectrum was correlated to the same product as made by both Professor Crimmins, and Nicolaou.

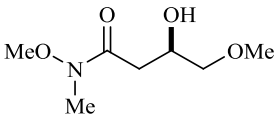
5.0 SUPPORTING INFORMATION

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (c g/100mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300 (300MHz) spectrometer, or a Bruker Avance 500 (500 MHz) with chemical shifts reported relative to residual $CHCl_3$ (7.26 ppm) for ^1H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra.

Unless otherwise stated, all reactions were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvents (CH_2Cl_2, THF, DMF, diethyl ether, pentane and toluene) were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. *N,N*-Diisopropylethylamine, and triethylamine were distilled under nitrogen from CaH_2. Dimethylaluminum chloride (1.0M in hexane) was purchased from Aldrich in Sure/Seal™ bottles. Anhydrous $LiClO_4$ (ReagentPlus) and LiI were purchased from Aldrich. O-trimethylsilyl quinidine (TMS-Qd) and O-trimethylsilyl quinine (TMS-Qn) was prepared according to the literature procedure.[38] Commercially available acetyl bromide, propionyl chloride were redistilled under N_2. Flash chromatography was performed on EM silical gel 60 (230-240 mesh).

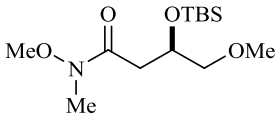


(*R*)-4-(Methoxymethyl)oxetan-2-one (61): To a 0 °C solution of 0.866 g of amine catalyst (**65**) (1.60 mmol, 0.1 equiv) in 190 mL of CH_2Cl_2 was slowly added 1.60 mL of Me_2AlCl (1.60 mmol, 1.0 M solution in hexane). This homogeneous mixture was removed from the ice bath and stirred at ambient temperature for 1 hr before being cooled to −60 °C. To this was added 4.74 mL of $^{i}Pr_2NEt$ (27.2 mmol, 1.7 equiv) followed by a dropwise addition of 2.25 mL of acetyl bromide (30.4 mmol, 1.9 equiv) over a period of 60 seconds. The resulting yellow solution was stirred exactly 120 seconds while maintaining −60 °C whereupon a solution of 1.18 g of methoxyacetaldehyde (16.0 mmol, 1.0 equiv) in approximately 10 mL CH_2Cl_2 was added dropwise. The reaction was maintained at −60 °C for 12 h. Saturated aqueous NH_4Cl (300 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The resulting crude oil was purified by flash chromatography (40% EtOAc/hexanes on silica gel) to afford 1.69 g (91%) of the title compound as a clear colorless oil. $[\alpha]_D^{22}$ −32.9 (*c* 1.68, $CHCl_3$). IR (thin film): 1830, 1455, 1112, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67-4.62 (m, 1H), 3.74 (dd, J = 11.4, 3.0 Hz, 1H), 3.64 (dd, J = 11.7, 4.5 Hz, 1H), 3.47 (dd, J = 16.2, 6.0 Hz, 1H), 3.44 (s, 3H), 3.39 (dd, J = 16.2, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 72.5, 69.9, 60.2, 40.2; HRMS (EI) *m/z* calcd for $C_5H_8O_3$ $(M)^+$: 116.0473; found: 116.0475.

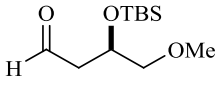


(*R*)-3-Hydroxy-*N*,4-dimethoxy-*N*-methylbutanamide: To a 0 °C solution of 3.08 g of *N*,*O*-dimethylhydroxylamine hydrochloride (31.6 mmol, 2.0 equiv) in 50 mL of CH_2Cl_2 was added 31.6 mL of dimethylaluminum chloride (31.6 mmol of 1 M hexanes solution, 2.0 equiv). The resulting solution was removed from the ice bath following the addition and allowed to warm to ambient temperature and was stirred for 1 h. The resulting solution was cooled to 0°C whereupon 1.84 g of β-lactone (15.8 mmol, 1.0 equiv) was added. The reaction remained in the ice bath, and allowed to warm slowly to ambient temperature overnight. In the morning the reaction mixture was cooled to 0 °C and quenched with 0.5M HCl (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography on silica gel (5% MeOH/CH_2Cl_2) to afford 1.93 g (100%) of the title β-hydroxy amide as a clear

colorless oil. $[\alpha]_D^{21}$ +34.3 (*c* 1.68, $CHCl_3$). IR (thin film): 3440, 2934, 1653, 1445, 1192, 1126, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.24-4.18 (m, 1H), 3.69 (s, 3H), 3.44 (d, J = 5.4 Hz, 2 H), 3.40 (s, 3H), 3.20 (s, 3H), 2.71-2.58 (m, 2 H), 1.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 75.7, 66.9, 61.2, 59.1, 34.9, 31.8; HRMS (ES) *m/z* calcd for $C_7H_{15}NO_4Na$ $(M + Na)^+$: 200.0899; found: 200.0908.

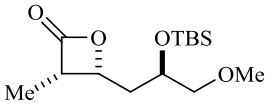


(*R*)-3-(*tert*-Butyldimethylsilyloxy)-*N*,4-dimethoxy-*N*-methylbutanamide (62): To a −60 °C solution of 2.0 g of the β-hydroxy amide (11.3 mmol, 1.0 equiv) in 32.0 mL of CH_2Cl_2 was added 5.26 mL of 2,6 lutidine (45.2 mmol, 4.0 equiv) followed by 3.89 mL of TBDMSOTf (16.9 mmol, 1.5 equiv) dropwise. The resulting solution was maintained at −60 °C overnight. Saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were washed with 1M $NaHSO_4$ (200 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (30% EtOAc/hexanes) to afford 3.28 g (99%) of the title amide as a clear colorless oil. $[\alpha]_D^{21}$ +18.2 (*c* 1.05, $CHCl_3$). IR (thin film): 2930, 1666, 1464, 1386, 1252, 1107, 991, 835, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.37-4.33 (m, 1H), 3.68 (s, 3H), 3.39 (dd, J = 10.0, 4.0 Hz, 1H), 3.34 (s, 3H), 3.33 (dd, J = 10.0, 5.0 Hz, 1H), 3.17 (s, 3H), 2.70 (br dd, J = 15.0, 7.5 Hz, 1H), 2.53 (dd, J = 15.0, 5.0 Hz, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 76.8, 68.4, 61.3, 59.1, 36.9, 31.9, 25.8 (3C), 18.1, −4.7, −4.9; HRMS (ES) *m/z* calcd for $C_{13}H_{29}NO_4NaSi$ $(M + Na)^+$: 314.1764; found: 314.1743.

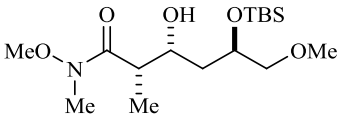


(*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-methoxybutanal (63): To a −78 °C solution of 2.62 g of the amide (9.00 mmol, 1.0 equiv) in 54.0 mL of THF was added 10.8 mL of $^iBu_2AlH$ (10.8 mmol of a 1.0 M solution in hexane, 1.2 equiv) dropwise via syringe pump over 2 h. The resulting colorless solution was maintained at −78 °C for 2 h whereupon saturated aqueous Rochelle salt (100 mL) was added and the resulting emulsion was warmed to ambient temperature, and stirred for 2 h. The resulting mixture was extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated. Purification of the crude oil by flash chromatography on silica gel (10% EtOAc/hexanes) afforded 2.00 g (95%) of the

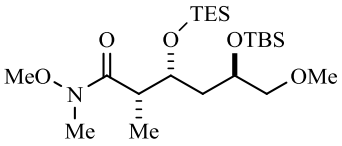
title aldehyde as a clear colorless oil. $[\alpha]_D^{22}$ +7.30 (*c* 1.36, $CHCl_3$). IR (thin film): 17.28, 1469, 1254, 1111, 1009, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.796 (t, J = 2.1 Hz, 1H), 4.34-4.28 (m, 1H), 3.41 (dd, J = 9.6, 5.1 Hz, 1H), 3.35 (s, 3H), 3.30 (dd, J = 9.6, 6.0 Hz, 1H), 2.63 (ddd, J = 15.9, 5.1, 1.8 Hz, 1H), 2.55 (ddd, J = 15.9, 6.6, 2.7 Hz, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 76.5, 67.2, 59.1, 48.8, 25.7 (3C), 18.0, −4.5, −5.0; HRMS (ES) *m/z* calcd for $C_{11}H_{24}O_3NaSi$ $(M + Na)^+$: 255.1392; found: 255.1374.



***(3R, 4S)*-3-Methyl-4-[(2*R*)-2-*tert*-butyldimethylsilyloxy-3-methoxypropanyl]oxetan-2-one (64):** To a solution of 0.457 g of $LiClO_4$ (4.30 mmol, 1.0 equiv) and 0.170 g of TMS-quinidine (0.430 mmol, 0.1 equiv) in Et_2O (7.50 mL) at ambient temperature was added CH_2Cl_2 (22.0 mL) via syringe. The solution was cooled to −78 °C. To this homogeneous solution was added 1.87 mL of Hunig's base (10.8 mmol, 2.5 equiv) followed by 1.0 g of the aldehyde (4.30 mmol, 1.0 equiv). To this solution was added 0.751 mL of propionyl chloride (8.60 mmol, 2.0 equiv) as a solution in 7.5 mL of CH_2Cl_2 over a period of 4 h via syringe pump. The reaction was maintained at −78°C overnight, then quenched with Et_2O (30 mL) and filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure. Purification of the crude oil by flash chromatography on silica gel (10% EtOAc/hexanes) afforded 0.965 g (78%) of the title compound as a clear colorless oil. $[\alpha]_D^{23}$ +63.3 (*c* 0.610, $CHCl_3$). IR (thin film): 1819, 1468, 1249, 1079, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (ddd, J = 10.5, 6.6, 3.0 Hz, 1H), 4.01-3.94 (m, 1H), 3.77 (dq, J = 7.8, 6.6 Hz, 1H), 3.36 (dd, J = 9.6, 4.8 Hz, 1H), 3.34 (s, 3H), 3.30 (dd, J = 9.9, 5.7 Hz, 1H), 1.90 (ddd, J = 14.7, 10.5, 2.7 Hz, 1H), 1.27 (ddd, 14.4, 9.9, 2.7 Hz, 1H), 1.27 (d, 7.8 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 77.1, 72.3, 67.4, 59.1, 47.1, 34.9, 25.1 (3C), 18.1, 8.4, −4.5, −5.0; HRMS (EI) *m/z* calcd for $C_{14}H_{29}O_4Si$ $(M)^+$: 289.1835; found: 289.1827.

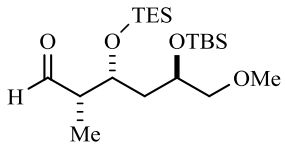


(2*S*,3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-*N*,6-dimethoxy-*N*,2-dimethylhexanamide: To a 0 °C solution of 1.01 g of *N*,*O*-dimethylhydroxylamine hydrochloride (10.4 mmol, 2.0 equiv) in 40.0 mL of CH_2Cl_2 was added 10.4 mL of dimethylaluminum chloride (10.4 mmol of 1M hexanes solution, 2.0 equiv). The resulting solution was allowed to warm to ambient temperature and stirred for 1 h. The resulting solution was cooled to −45 °C whereupon 1.5 g of the β-lactone (5.2 mmol, 1.0 equiv) was added as a solution in 8.00 mL of CH_2Cl_2. The reaction was maintained at −45 °C for 3 h. Saturated aqueous Rochelle salt (60 mL) was added, and the reaction was allowed to warm to ambient temperature and stir for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (40% EtOAc/hexanes) to afford 1.67 g (92.0%) of the β-hydroxy amide as a clear colorless oil. $[\alpha]_D^{23}$ +13.7 (*c* 1.63, $CHCl_3$). IR (thin film): 3469, 2932, 1641, 1462, 1250, 992, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.08-4.10 (m, 2H), 3.86 (br s, 1H), 3.86 (s, 3H), 3.35 (dd, J = 5.1, 0.9 Hz, 2H), 3.33 (s, 3H), 3.17 (s, 3H), 2.83 (br. s, 1H), 1.69 (ddd, 14.1, 10.2, 3.3 Hz, 1H), 1.47 (ddd, 14.1, 7.8, 2.1 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 77.2, 69.1, 68.3, 61.5, 59.0, 40.1, 38.7, 31.9, 25.8 (3C), 18.1, 11.2, −4.5, −4.9; HRMS (ES) *m/z* calcd for $C_{16}H_{35}NO_5NaSi$ $(M + Na)^+$: 372.2182; found: 372.2149.

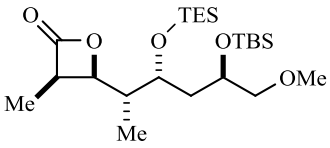


(2*S*,3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-*N*,6-dimethoxy-*N*,2-dimethyl-3-(triethylsilyloxy)hexanamide: To a −60 °C solution of 2.16 g of the β-hydroxy amide (6.18 mmol, 1.0 equiv) in 17.6 mL of CH_2Cl_2 was added 2.88 mL of 2,6 lutidine (24.7 mmol, 4.0 equiv) followed by 2.13 mL of TESOTf (9.27 mmol, 1.5 equiv) dropwise. The resulting solution was maintained at −60 °C for 2 h. Saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture was diluted with CH_2Cl_2 (50 mL) and more aqueous $NaHCO_3$ (50 mL) before being extracted with CH_2Cl_2 (3 x 75 mL). The combined organics were washed with 1M $NaHSO_4$ (3 x 150 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (30%

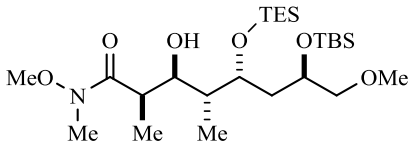
Et_2O/pentane) to afford 2.58 g (90%) of the title amide as a clear colorless oil. $[\alpha]_D^{22}$ −1.46 (*c* 1.88, $CHCl_3$). IR (thin film): 2954, 1669, 1461, 1249, 1110, 834, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (q, J = 5.7 Hz, 1H), 3.83 (ddd, J = 12.6, 6.3, 3.9 Hz, 1H), 3.67 (s, 3H), 3.33 (dd, J = 9.6, 3.6 Hz, 1H), 3.32 (s, 3H), 3.27 (dd, J = 9.9, 6.0 Hz, 1H), 3.17 (s, 3H), 2.92 (m, 1H), 1.67 (t, 6.3 Hz, 2H), 1.13 (d, J = 6.9 Hz, 3H), 0.96 (t, 8.1 Hz, 9H), 0.88 (s, 9H), 0.61 (q, J = 8.1 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 77.6, 70.9, 69.4, 61.1, 58.8, 41.6, 41.5, 32.2, 25.9 (3C), 18.2, 12.8, 6.9 (3C), 5.2 (3C), −3.9, −4.6; HRMS (ES) *m/z* calcd for $C_{22}H_{49}NO_5NaSi_2$ $(M + Na)^+$: 486.3047; found: 486.3007.



(2*S*,3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-6-methoxy-2-methyl-3-(triethylsilyloxy)hexanal (66): To a −78 °C solution of 2.30 g of the amide (4.96 mmol, 1.0 equiv) in 30 mL of THF was added 5.96 mL of $^iBu_2AlH$ (5.96 mmol, 1.0 M hexanes solution, 1.2 equiv) dropwise via syringe pump over 1 h. The resulting colorless solution was maintained at −78 °C for 3 h whereupon saturated aqueous Rochelle salt (30 mL) was added and the resulting emulsion was warmed to ambient temperature, and stirred for 2 h. The resulting mixture was diluted with Et_2O (50 mL) and H_2O (50 mL) before being extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude oil by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 1.90 g (95%) of the title aldehyde as a clear colorless oil. $[\alpha]_D^{22}$ +54.0 (*c* 1.01, $CHCl_3$). IR (thin film): 2955, 1729, 1461, 1251, 1109, 834, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 4.29 (dt, J = 6.0, 3.3 Hz, 1H), 3.90-3.82 (m, 1H), 3.32 (s, 3H), 3.28 (d, J = 5.1 Hz, 2H), 2.50 (ddd, J = 13.8, 6.9, 3.0 Hz, 1H), 1.70-1.63 (m, 2H), 1.05 (d, J = 7.2 Hz, 3H), 0.94 (t, 7.8 Hz, 9H), 0.88 (s, 9H), 0.61 (q, J = 7.8 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 77.6, 69.8, 69.2, 58.8, 52.2, 40.1, 25.8 (3C), 18.2, 7.8, 6.8 (3C), 5.2 (3C), −3.9, −4.7; HRMS (ES) *m/z* calcd for $C_{20}H_{44}O_4NaSi_2$ $(M + Na)^+$: 427.2676; found: 427.2673.

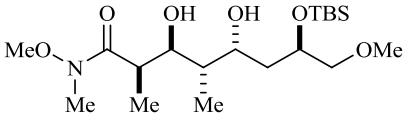


***(3S,4R)*-4-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-3-methyloxetan-2-one (67):** To a solution of 0.501 g of LiI (3.75 mmol, 3.0 equiv) and 0.050 g of TMS-quinine (0.125 mmol, 0.1 equiv) in Et_2O (0.25 mL) at ambient temperature was added CH_2Cl_2 (2.50 mL) via syringe. The solution was cooled to −78 °C. To this homogeneous solution was added 0.544 mL of Hunig's base (3.12 mmol, 2.5 equiv) followed by 0.50 g of the aldehyde (1.25 mmol, 1.0 equiv). To this solution was added 0.218 mL of propionyl chloride (2.5 mmol, 2.0 equiv) as a solution in 2.18 mL of CH_2Cl_2 over a period of 5 h via syringe pump. The reaction was maintained at −78 °C overnight, then quenched with Et_2O (30 mL) and filtered through a plug of silica gel with excess ether. The filtrate was concentrated under reduced pressure. Purification of the crude oil by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 0.445 g (77%) of the title compound as a clear colorless oil. $[\alpha]_D^{21}$ −20.4 (*c* 1.27, $CHCl_3$). IR (thin film): 1829, 1462, 1252, 1118, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (dd, J = 11.1, 6.3 Hz, 1H), 4.05 (dt, J = 6.9, 1.5 Hz, 1H), 3.82-3.69 (m, 2H), 3.33 (s, 3H), 3.28 (dd, J = 5.1, 0.6 Hz, 2H), 1.86-1.72 (m, 1H), 1.75 (t, J = 6.3 Hz, 2H), 1.32 (d, 7.8 Hz, 3H), 0.95 (t, 7.8 Hz, 9H), 0.88 (s, 9H), 0.85 (d, J = 6.6 Hz, 3H), 0.60 (q, J = 8.1 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 77.2, 76.3, 69.4, 67.8, 58.9, 46.4, 40.7, 37.8, 25.8 (3C), 18.1, 8.5, 7.4, 6.9 (3C), 5.1 (3C), −4.2, −5.6; HRMS (ES) *m/z* calcd for $C_{23}H_{48}O_5NaSi_2$ $(M + Na)^+$: 483.2938; found: 483.2942.

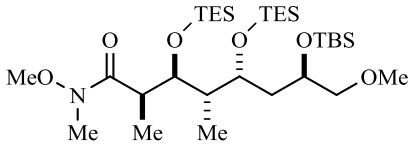


(*2R,3S,4R,5R,7R*)-7-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-*N*,8-dimethoxy-*N*,2,4-trimethyl-5-(triethylsilyloxy)octanamide: To a solution of 0.33 g of *N*,*O*-dimethylhydroxylamine hydrochloride (3.4 mmol, 2.0 equiv) in 15 mL of CH_2Cl_2 at ambient temperature was added 3.4 mL of dimethylaluminum chloride (3.4 mmol of 1M hexanes solution, 2.0 equiv). The resulting solution was allowed to stir at ambient temperature for 1 h. The resulting solution was cooled to −45 °C whereupon 0.80 g of β-lactone (1.77 mmol, 1.0 equiv) was added. The reaction was maintained at −45 °C overnight. Saturated aqueous Rochelle salt (30 mL) was added, and the reaction was allowed to warm to ambient temperature and stir for 4 h. The mixture was diluted with CH_2Cl_2 (40 mL) and H_2O (40 mL) and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined

organics were dried over $MgSO_4$, filtered, and concentrated. The crude material contained 0.818 g of a mixture of TES protection at the C_5 oxygen. The mixture was separated via flash chromatography to yield 0.418 g of the title compound (45% yield), and 0.400 g of the diol (55% yield). $[\alpha]_D^{22}$ −1.2 (*c* 0.98, $CHCl_3$). IR (thin film): 3461, 2954, 1642, 1461, 1249, 1002, 835, 776, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (dt, J = 6.9, 1.8 Hz, 1H), 4.06 (d, J = 2.1 Hz, 1H), 3.81-3.74 (m, 2H), 3.69 (s, 3H), 3.33 (dd, J = 9.9, 3.6 Hz, 1H), 3.32 (s, 3H), 3.26 (dd, J = 9.9, 5.7 Hz, 1H), 3.19 (s, 3H), 3.00-2.96 (m, 1H), 1.77-1.57 (m, 3H), 1.13 (d, J = 7.2 Hz, 3H), 0.94 (t, 8.1 Hz, 9H), 0.88 (s, 9H), 0.81 (d, J = 6.9 Hz, 3H), 0.61 (q, J = 7.8 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 77.1, 72.7, 70.5, 69.4, 61.3, 58.8, 39.6, 39.5, 36.7, 25.9 (3C), 18.2, 10.3, 9.8, 6.8 (3C), 5.1 (3C), −4.1, −4.7; HRMS (ES) *m/z* calcd for $C_{25}H_{55}NO_6NaSi_2$ $(M + Na)^+$: 544.3466; found: 544.3467.



(2*R*,3*S*,4*S*,5*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-3,5-dihydroxy-*N*,8-dimethoxy-*N*,2,4-trimethyloctanamide: Procedure Above. $[\alpha]_D^{21}$ +19.4 (*c* 0.72, $CHCl_3$). IR (thin film): 3440, 1638, 1461, 1252, 1107, 989, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.38 (s br, 1H), 4.10-4.07 (m, 1H), 4.04-4.01 (m, 1H), 3.83 (dt, J = 9.0, 2.4 Hz, 1H), 3.71 (d, J = 6.0 Hz, 1H), 3.68 (s, 3H), 3.36 (dd, J = 5.4, 2.4 Hz, 2H), 3.32 (s, 3H), 3.16 (s, 3H), 3.02 (s br, 1H), 1.80-1.76 (m, 1H), 1.76-1.71 (m, 1H), 1.47 (ddd, J = 13.8, 7.2, 1.2 Hz, 1H), 0.86 (s, 9H), 0.82 (d, J = 7.2 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.3, 77.1, 74.3, 69.9, 69.3, 61.5, 58.9, 39.3, 37.5, 36.0, 31.8, 25.8 (3C), 18.0, 11.9, 10.1, −4.5, −5.0;



(2*R*,3*S*,4*S*,5*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-*N*,8-dimethoxy-*N*,2,4-trimethyl-3,5-bis(triethylsilyloxy) octanamide (68):

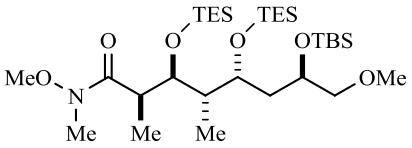
From Mono-alcohol:

To a −60 °C solution of 0.96 g of the mono-alcohol (1.84 mmol, 1.0 equiv) in 5.29 mL of CH_2Cl_2 was added 0.857 mL of 2,6-lutidine (7.36 mmol, 4.0 equiv) followed by 0.624 mL of TESOTf (2.76 mmol, 1.5 equiv) slowly via syringe. The resulting solution was maintained at

−60 °C for 3 hours, whereupon the crude reaction mixture was combined with that of the diol, and quenched concurrently.

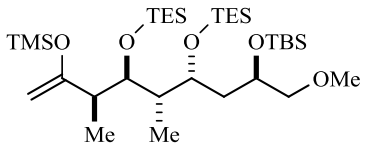
From Diol:

To a −60 °C solution of 0.722 g of the diol (1.77 mmol, 1.0 equiv) in 6.32 mL of CH_2Cl_2 was added 1.23 mL of 2,6-lutidine (10.62 mmol, 6.0 equiv) followed by 1.00 mL of TESOTf (4.42 mmol, 2.5 equiv) slowly via syringe. The resulting solution was maintained at −60 °C for 3 hours. Whereupon the crude mixture was combined with that of the mono-alcohol and quenched with 15 mL of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined and concentrated in vacuo, before being diluted in EtOAc (30 mL) and washed with 1M $NaHSO_4$ (30 mL), dried over $MgSO_4$, and concentrated. The crude colorless oil was purified by column chromatography using 10% to 15% EtOAc in hexane, yielding 2.20 g (95%) of a clear colorless oil. Due to a rapid rearrangement, this compound was carried on without complete characterization.

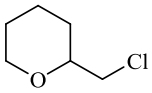


(3*R*,4*S*,5*S*,6*R*,8*R*)-8-(*tert*-Butyldimethylsilyloxy)-9-methoxy-3,5-dimethyl-4,6-bis(triethylsilyloxy)nonan-2-one (69): To a 0 °C solution of 1.68 g of the amide (2.64 mmol, 1.0 equiv) in 16.8 mL of THF was added 3.73 mL of methyl magnesiumbromide (3.17 mmol of a 0.85 M solution, 1.2 equiv) over 1 hour via syring pump. The resulting solution remained in the cold bath and was allowed to warm to ambient temperature over 6 h. Saturated aqueous NH_4Cl (30 mL) was added and the resulting mixture was extracted with Et_2O (3 X 60 mL). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to yield 1.44 g (92%) of a clear colorless oil. $[\alpha]_D^{22}$ −37.8 (*c* 1.25, $CHCl_3$). IR (thin film): 2878, 1714, 1461, 1415, 1383,1359, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.24 (dd, J = 7.2, 1.8 Hz, 1H), 3.97-3.92 (m, 1H), 3.73-3.65 (m, 1H), 3.33 (s, 3H), 3.29-3.26 (m, 2H), 2.67 (dq, J = 6.9, 1.8 Hz, 1H), 2.15 (s, 3H), 1.83-1.74 (m, 2H), 1.73-1.66 (m, 1H), 1.07 (d, 7.2 Hz, 3H), 0.98-0.90 (m, 18H), 0.87 (s, 9H), 0.84 (d, J = 7.2 Hz, 3H), 0.64-0.53 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 76.9, 73.1, 70.2, 69.4, 58.9, 50.3, 42.9, 40.6, 28.6,

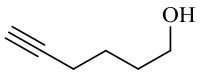
25.8 (3C), 18.2, 9.7, 9.5, 7.1 (3C), 7.0 (3C), 6.0 (3C), 5.6 (3C), 5.4 (3C), −4.3, −4.7; HRMS (ES) *m/z* calcd for $C_{30}H_{66}O_5NaSi_3$ $(M + Na)^+$: 613.4116; found: 613.4160.



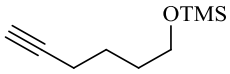
(3*R*,4*S*,5*S*,6*R*,8*R*)-8-(*tert*-butyldimethylsilyloxy)-9-methoxy-3,5-dimethyl-4,6-bis(triethylsilyloxy)-2-trimethylsilyloxy-non-1-ene: To a −78 °C solution of 1.30 g of ketone (2.19 mmol, 1.0 equiv) in 8.64 mL of THF was added 2.42 mL of a 1M solution of NaHMDS (2.42 mmol, 1.1 equiv). The solution was stirred for 30 minutes at −78 °C before warming to 0 °C, and allowing to stir for an additional 30 minutes. After which, 1.27 mL of 2,6-lutidine (10.9 mmol, 5.0 equiv) was added, followed by 0.85 mL of TMSCl (8.76 mmol, 4.0 equiv). The resulting solution was allowed to stir at 0 °C for 30 minutes before warming to ambient temperature and stirring for 2 hours. Saturated aqueous $NaHCO_3$ (20 mL) was added and the resulting mixture was extracted with Et_2O (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated. The clear colorless oil was passed through a plug of IATRO® beads with Et_2O, and used in the following reaction without further purification.



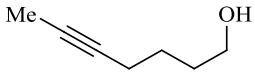
2-(Chloromethyl)-tetrahydro-2H-pyran (50): To a 0 °C solution of 30.0 g of the starting alcohol (.258 mol) in CH_2Cl_2 (240 mL), was added 23.0 mL of pyridine (0.284 mol), then 19.7 mL of thionyl chloride (0.271 mol) was added slowly. The resulting solution was maintained at 0 °C for 30 minutes, before heating to reflux overnight. The resulting dark yellow solution was quenched at 0 °C with H_20 (250 mL) whereupon it was warmed to ambient temperature. The resulting mixture was decanted into a seperatory funnel that contained H_2O (100 mL) and CH_2Cl_2 (100 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 250 mL), dried over $MgSO_4$, filtered, and concentrated. 27.0 g (78%) of a clear colorless oil was isolated from vacuum distillation at 73 °C and 15 mmHg. IR (thin film): 2940, 2850, 1440, 1095, 1046, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07-4.01 (m, 1H), 3.53-3.43 (m, 4H), 1.91-1.85 (m, 1H), 1.72-1.68 (m, 1H), 1.65-1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.3, 68.7, 47.6, 29.2, 25.6, 23.0; HRMS *m/z* calcd for $C_6H_{11}OCl$: 134.0498; found: 134.0499.



Hex-5-yn-1-ol (51): To a −78 °C solution of 0.100 g (0.250 mmol) of $Fe(NO_3)_3$ in 400 mL of NH_3 in a 3-neck flask with dry-ice/acetone coldfinger was added 8.05 g of sodium metal (0.350 mol) in approximately ¼ inch cubes. The resulting grey mixture was maintained at −78 °C for 30 minutes whereupon 13.5 g of the chloride (0.100 mol) was added dropwise. The removal of the dry-ice/acetone bath warmed the mixture to −33 °C and was maintained at this temperature for 3 h. 17.6 g of solid NH_4Cl (0.330 mol) was added, and the coldfinger was removed to allow the evaporation of the ammonia. Et_2O (6 x 100 mL) was used to extract from the powdered remainder of the reaction mixture. 9.00 g of a yellow oil was extracted, and used crude in the following reaction. IR (thin film): 3297, 2942, 2115, 1454, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, J = 6.0 Hz, 2H), 2.23 (dt, J = 6.9, 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.74-1.59 (m, 4H), 1.42 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.5, 68.7, 62.5, 31.9, 24.9, 18.4.

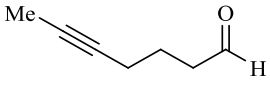


(Hex-5-ynyloxy)trimethylsilane: To a 0 °C solution of 11.2 g of imidazole (165 mmol) in 300 mL of CH_2Cl_2 was added 9.00 g of the alcohol (91.7 mmol), followed by 17.3 g of TMSCl (138 mmol) dropwise. The resulting white, opaque mixture is maintained at ambient temperature for 48 h, whereupon H_2O (300 mL) is added. This mixture is extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were concentrated and filtered through a plug of silica gel. The filtrate was used crude in the next reaction.

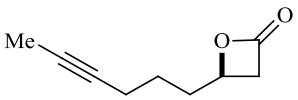


Hept-5-yn-1-ol (52): To a −78 °C solution of 71.3 mL of nBuLi (114 mmol of a 1.60 M solution) in 225 mL of THF was added 13.0 g of the alkyne (76.0 mmol) slowly. The resulting solution was maintained at −78 °C for 1 h, whereupon 14.2 mL of methyliodide (228 mmol) was added via syringe. The reaction was maintained at −78 °C for 1 h before being warmed to ambient temperature for 2 h. A 1M solution of HCl was added (200 mL) at ambient temperature, and after 30 minutes the resulting mixture was extracted with Et_2O (3 x 200 mL) Purification of the crude yellow oil by flash chromatography on silica gel (20% EtOAc/hexanes) afforded 7.15 g (63.1 % 3 steps) of the alcohol as a clear colorless liquid. IR (thin film): 3347, 2939, 1436, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, J =

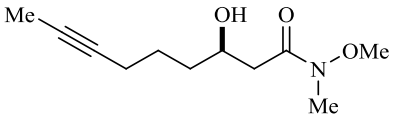
6.0 Hz, 2H), 2.21 (m, 2H), 1.77 (t, J = 2.4 Hz, 3H), 1.72-1.55 (m, 4H), 1.37 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.9, 75.8, 62.5, 31.9, 25.3, 18.5, 3.4.



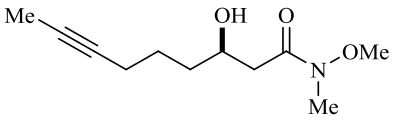
Hept-5-ynal (53): To a solution of 3.35 g of alcohol (29.8 mmol) in 100 mL of CH_2Cl_2 at ambient temperature is added 8.0 g of celite. The resulting mixture is cooled to 0°C whereupon 9.65 g of PCC (44.8 mmol) is added in small portions. The resulting orange/brown mixture is maintained at 0 °C for 1 h before warming to ambient temperature for 2 h. The heterogeneous mixture is filtered through a pad of florisil, and rinsed thoroughly with excess CH_2Cl_2**.** The clear colorless solution is used crude in the following reaction.



(*R*)-4-(Hex-4-ynyl)oxetan-2-one (54): To an ambient temperature solution of 0.246 g of amine catalyst (**59**) (0.363 mmol, 0.1 equiv) in 20 mL of CH_2Cl_2 was slowly added 0.363 mL of Me_2AlCl (0.363 mmol, 1.0 M solution in hexane, 0.1 equiv). This homogeneous mixture was stirred at ambient temperature for 1 hr before being cooled to −78 °C. To this was added 1.07 mL of $^{i}Pr_2NEt$ (6.17 mmol, 1.7 equiv) followed by 0.510 mL of acetyl bromide (6.89 mmol, 1.9 equiv) over a period of 60 seconds. The resulting yellow solution was stirred exactly 120 seconds at −78 °C whereupon 0.400 g of crude aldehyde 3.63 mmol, 1.0 equiv) was added dropwise via syringe as a solution in 5 mL of CH_2Cl_2. The reaction was maintained at −78 °C overnight. Saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford 0.380 g (51% 2 steps) of the β-lactone as a clear colorless oil. $[\alpha]_D^{22}$ +23.07 (*c* 1.66, $CHCl_3$). IR (thin film): 2921, 2863, 1826, 1413, 1133, 870 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54-4.50 (m, 1H), 3.51 (ddd, J = 9.9, 3.6, 0.6 Hz, 1H), 3.08 (ddd, J = 9.9, 2.7, 0.9 Hz, 1H), 2.21-2.18 (m, 2H), 1.95-1.88 (m, 2H), 1.76 (t, J = 2.7 Hz, 3H), 1.66-1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 77.8, 76.5, 70.8, 42.9, 33.6, 24.3, 18.2, 3.3; HRMS (EI) *m/z* calcd for $C_9H_{12}O_2$ $(M)^+$: 152.0837; found: 152.0835.

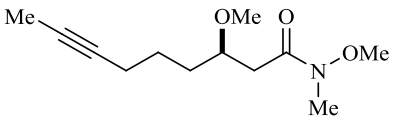


(*R*)-3-Hydroxy-*N*-methoxy-*N*-methylnon-7-ynamide: To a solution of 1.46 g of *N,O*-dimethylhydroxylamine hydrochloride (15.0 mmol, 2.0 equiv) in 50 mL of CH_2Cl_2 at ambient temperature was added 15.0 mL of dimethylaluminum chloride (15.0 mmol of 1M hexanes solution, 2.0 equiv). The resulting solution was allowed to stir at ambient temperature for 1.5 h, then was cooled to 0 °C whereupon 1.15 g of β-lactone (7.50 mmol) was added as a solution in 10 mL of CH_2Cl_2. The reaction remained in the cold bath, and was allowed to warm to ambient temperature over 3 h. To this was added 0.5 N HCl (100 mL), and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (75% EtOAc/hexanes) to afford 1.31 g (81.8%) of the β-hydroxy amide as a clear yellow oil. $[\alpha]_D^{22}$ −33 (*c* 0.73, $CHCl_3$). IR (thin film): 3447, 2920, 1645, 1437, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04-3.98 (m, 1H), 3.81 (d, J = 3.0 Hz, 1H), 3.65 (s, 3H), 3.16 (s, 3H), 2.64 (d, J= 16.5 Hz, 1H), 2.42 (dd, J = 16.8, 9.6 Hz, 1H), 2.18-2.10 (m, 2H), 1.73 (t, J = 2.7 Hz, 3H), 1.66-1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 78.8, 75.6, 67.4, 61.1, 38.1, 35.5, 31.7, 24.9, 18.5, 3.4; HRMS (ES) *m/z* calcd for $C_{11}H_{19}NO_3Na$ $(M + Na)^+$: 236.1263; found: 236.1253.

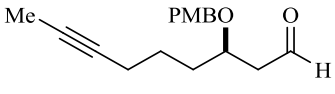


(*R*)-*N*-Methoxy-3-(4-methoxybenzyloxy)-*N*-methylnon-7-ynamide (56): To an ambient temperature solution of 0.75 g of alcohol (3.53 mmol, 1.0 equiv) in 10.7 mL of CH_2Cl_2 was added 2.0 g of freshly prepared p-methoxybenzyl acetimidate (7.08 mmol, 2 equiv) in a small amount of CH_2Cl_2. To this homogeneous solution was added 0.246 g of camphor sulfonic acid (1.06 mmol, 0.3 equiv). The heterogeneous mixture was allowed to stir at ambient temperature for five hours before being quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to a yellowish semi-solid. This semi-solid was triturated with a small amount of CH_2Cl_2 (~2 mL), and cooled on ice. Using pipette filtration the CH_2Cl_2 was removed, leaving behind a white semi-solid. This filtration was repeated twice more, to yield a white crystalline solid, which was discarded. The combined organic filtrates were purified by MPLC (gradient elution 10-40% ethyl acetate in hexanes on silica gel) to afford 1.0 g (74%) of the title

compound as a clear colorless oil. $[\alpha]_D^{22}$ +11.1 (*c* 1.21, $CHCl_3$). IR (thin film): 2937, 1659, 1512, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.25 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.48 (d, J = 2.1 Hz, 2H), 3.99 (app dq, J = 5.4 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.19 (s, 3H), 2.86 (dd, J = 15.3, 7.2 Hz, 1H), 2.46 (dd, J = 15.3, 5.4 Hz, 1H), 2.16-2.10 (m, 2H), 1.78 (t, J = 2.7 Hz, 3H), 1.68-1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 159.0, 130.8, 129.3, 113.6, 78.9, 75.6, 75.5, 71.5, 61.2, 55.2, 37.3, 34.0, 32.0, 24.8, 18.7, 3.4; HRMS (ES) *m/z* calcd for $C_{19}H_{27}NO_4Na$ $(M + Na)^+$: 356.1838; found: 356.1820.

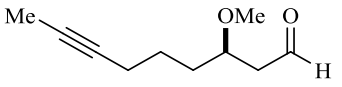


(*R*)-*N*,3-Dimethoxy-*N*-methylnon-7-ynamide (55): To a 0 °C solution of 1.78 g of the beta-alkoxy amide (8.30 mmol, 1.0 equiv) in 54 mL of 3:8 DMF:THF was added 5.17 mL of methyl iodide (83.0 mmol). To the resulting solution is added 0.832 g of sodium hydride (20.8 mmol of 60% dispersion on mineral oil). The resulting heterogeneous mixture is maintained at 0 °C for 1 h, whereupon 20 mL of pH 7 phosphate buffer solution was added, and the mixture was diluted with brine (30 mL), before being extracted with CH_2Cl_2 (3 x 50 mL). The organic fractions were combined and concentrated, taken up in EtOAc (50 mL), before washing with H_2O (2 x 50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. Purification of the crude yellow oil by flash chromatography on silica gel (10% EtOAc in hexanes) afforded 1.51 g (80%) of a yellow oil. $[\alpha]_D^{22}$ −4.3 (*c* 0.55, $CHCl_3$). IR (thin film): 2937, 1662, 1447, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ3.77-3.69 (m, 1H), 3.68 (s, 3H), 3.34 (s, 3H), 3.18 (s, 3H), 2.77 (dd, J = 15.3, 7.2 Hz, 1H), 2.39 (dd, J = 15.3, 6.0 Hz, 1H), 2.16-2.11 (m, 2H), 1.76 (t, J = 2.4 Hz, 3H), 1.68-1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 78.8, 77.3, 75.7, 61.2, 57.2, 36.8, 33.5, 32.1, 24.7, 18.8, 3.4; HRMS *m/z* calcd for $C_{12}H_{21}NO_3Na$: 250.1419; found: 250.1402.

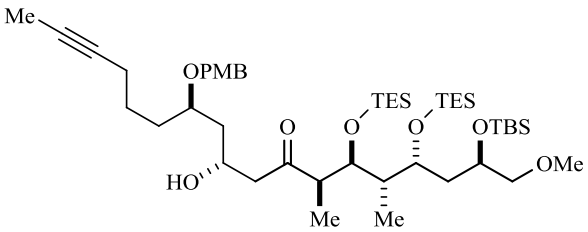


(*R*)-3-(4-Methoxybenzyloxy)non-7-ynal (58): To a solution of 0.190 g of amide (0.500 mmol, 1.0 equiv) in 7.25mL of THF at −78 °C was added 0.60 mL of $^iBu_2AlH$ (0.60 mmol, 1.0 M solution in hexane, 1.2 equiv) over one hour via syringe pump. The resulting solution was stirred at −78 °C for 2 h before being quenched with approximately 20 mL of saturated aqueous Rochelle salt. The heterogeneous mixture was stirred at ambient temperature before being separated. The organic layer was

extracted with CH_2Cl_2 (3 x 20 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford 0.160 g (97%) of a pale yellow oil. $[\alpha]_D^{22}$ −8.80 (*c* 1.14, $CHCl_3$). IR (thin film): 2938, 1723, 1612, 1512, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, J = 2.1 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.47 (d, J = 3.6 Hz, 2H), 3.96 (dtd, J = 5.4, 11.7 Hz, 1H), 3.80 (s, 3H), 2.67 (ddd, J = 9.0, 4.8, 2.4 Hz, 1H), 2.54 (ddd, J = 16.2, 4.8, 1.8 Hz, 1H), 2.18-2.13 (m, 2H), 1.78 (t, J = 2.4 Hz, 3H), 1.72-1.62 (m, 2H), 1.60-1.48 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.6, 159.2, 130.2, 129.4, 113.8, 78.6, 76.0, 73.4, 70.8, 55.2, 48.3, 33.3, 24.5, 18.6, 3.4; HRMS (EI) *m/z* calcd for $C_{17}H_{22}NO_3$ $(M)^+$: 274.156895; found: 274.156129.

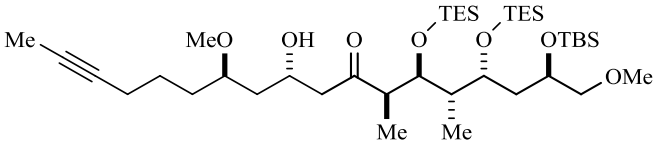


(*R*)-3-Methoxynon-7-ynal (57): To a −78 °C solution of 0.20 g of amide **55** (0.88 mmol) in THF (8.8 mL) was added 1.06 mL of $^iBu_2AlH$ (1.06 mmol of a 1M solution) dropwise via syringe pump over 2 h. The resulting solution was maintained at −78 °C for 1 h, whereupon saturated aqueous Rochelle salt (10 mL) was added, and the mixture was allowed to warm to ambient temperature for 2 h. The mixture was extracted with Et_2O (2 x 25 mL), dried (Na_2SO_4). Solvent was reduced under vacuum to approximately 10 mL, whereupon the solution was filtered through a plug of silica gel, with excess Et_2O rinses. The filtrate was concentrated under vacuum and purified by flash chromatography on silica gel (20% EtOAc in hexanes) to afford 0.120 g of a semi-pure liquid. Due to the instability of the aldehyde product a complete characterization was not completed. ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, J = 2.1 Hz, 1H), 3.78-3.71 (m, 1H), 3.35 (s, 3H), 2.63 (ddd, J = 16.2, 6.9, 2.4 Hz, 1H), 2.52 (ddd, J = 16.5, 5.1, 2.1 Hz, 1H), 2.19-2.13 (m, 2H), 1.77 (t, J = 2.4 Hz, 3H), 1.72-1.62 (m, 2H), 1.60-1.48 (m, 2H).



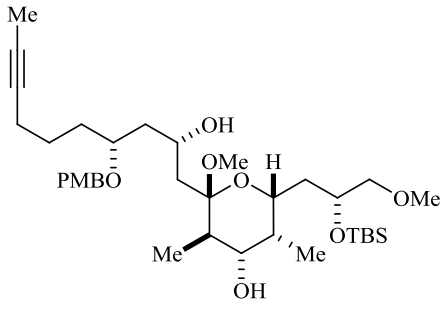
(2*R*,4*R*,5*S*,6*S*,7*R*,10*S*,12*R*)-2-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-1-methoxy-12-(4-methoxybenzyloxy)-5,7-dimethyl-4,6-bis(triethylsilyloxy)octadec-16-yn-8-one (72): To a −78 °C solution of 0.62 g of aldehyde (2.20 mmol, 1.1 equiv) in 20.5 mL of CH_2Cl_2 was added 1.36 g of silyl enol-ether

(2.05 mmol, 1.0 equiv). To this solution was added 0.312 mL of $BF_3{\cdot}Et_2O$ (2.46 mmol, 1.2 equiv) slowly via syringe. The reaction was allowed to stir at −78 °C for 5 hours before being stored in a −78 °C freezer overnight. In the morning 4.0 mL of NEt_3 was added, and the solution was allowed to warm to ambient temperature before quenching with NH_4Cl (20 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel via mPLC with a gradient elution from 5% to 20% EtOAc in hexanes over 30 minutes to afford 1.25 g (66% over two steps) of a clear colorless oil of the title compound as a single diastereomer as assayed by 600 MHz ^{1}H NMR. $[\alpha]_D^{22}$ −17.3 (*c* 0.96, $CHCl_3$). IR (thin film): 3509, 2953, 1702, 1513, 1461, 1248, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.52 (d, J = 11.4 Hz, 1H), 4.45 (d, J = 11.4 Hz, 1H), 4.29-4.26 (m, 1H), 4.23 (dd, J = 7.2, 1.8 Hz, 1H), 3.94 (ddd, J = 9.6, 5.4, 1.2 Hz, 1H), 3.79 (s, 3H), 3.77-3.73 (m, 1H), 3.70-3.67 (m, 1H), 3.45 (d, J = 2.4 Hz, 1H), 3.33 (s, 3H), 3.31 (dd, J = 10.2, 3.0 Hz, 1H), 3.26 (dd, J = 10.2, 5.4 Hz, 1H), 2.66 (dq, J = 6.6, 1.8 Hz, 1H), 2.59-2.56 (m, 2H), 2.15-2.12 (m, 2H), 1.78 (t, J = 2.4 Hz, 3H), 1.81-1.75 (m, 2H), 1.70-1.55 (m, 4H), 1.55-1.48 (m, 2H), 1.08 (d, J = 7.2 Hz, 3H), 0.95 (t, J = 8.4 Hz, 9H), 0.93 (t, J = 7.8 Hz, 9H), 0.88 (s, 9H), 0.83 (d, J 7.2 Hz, 3H), 0.62-0.55 (m, 12H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 159.2, 130.8, 129.5 (2H), 113.8 (2H), 79.0, 75.8, 75.4, 72.9, 71.4, 70.1, 69.4, 64.7, 58.9, 55.3, 50.2, 47.9, 42.9, 41.0, 40.6, 33.3, 25.9 (3H), 24.7, 18.9, 18.2, 9.8, 9.4, 7.1 (3H), 7.1 (3H), 6.0 (3H), 5.4 (3H), 3.5, −4.3, −4.7; HRMS (ES) *m/z* calcd for $C_{47}H_{88}O_8NaSi_3$ (M + Na)$^+$: 887.5685; found: 887.5624.

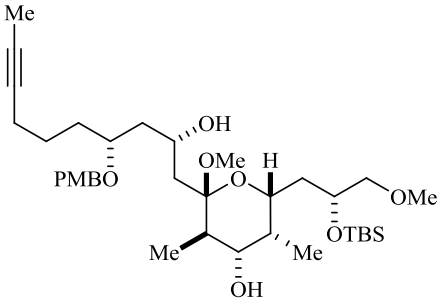


(2*R*,4*R*,5*S*,6*S*,7*R*,10*S*,12*R*)-2-(tert-Butyldimethylsilyloxy)-10-hydroxy-1,12-dimethoxy-5,7-dimethyl-4,6-bis(triethylsilyloxy)octadec-16-yn-8-one: To a solution of 0.30 g of ketone (0.507 mmol) in 5.75 mL of Et_2O at ambient temperature was added 0.097 mL of ^{i}Pr$_2$NEt (0.557 mmol) and subsequently cooled to −78 °C. To this solution was added 0.532 mL of Bu_2BOTf (0.532 mmol of a 1M solution in CH_2Cl_2) dropwise via syringe. The resulting solution was maintained at −78 °C for 1 h, whereupon 0.110 g of aldehyde (0.659 mmol in 3.0 mL of Et_2O) was added via syringe pump over 1 h. The reaction was maintained at −78 °C overnight. A mixture of 1:6 pH

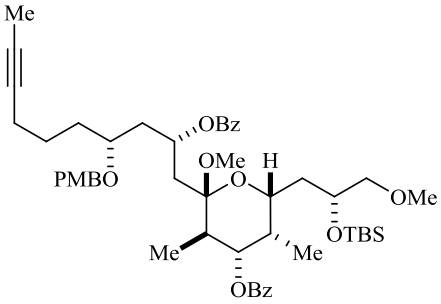
7 phosphate buffer:MeOH (2.0 mL) was added at −78 °C, and the reaction was allowed to warm to 0 °C, whereupon 4 mL of a 1:2 mixture of 30% H_2O_2 : MeOH was added to the reaction. This mixture was then allowed to stir at ambient temperature for 1 h before diluting the mixture with 10 mL of H_2O and extracting with Et_2O (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude oil was subjected to high vacuum overnight to remove any excess MeOH before purification by flash chromatography on silica gel (10% EtOAc in hexanes) yielded 0.307 g (79.7%) of an approximately 4:1 mixture of diastereomers, as well as recovering 0.05 g (16%) of the ketone starting material. $[\alpha]_D^{21}$ −39 (*c* 0.52, $CHCl_3$). IR (thin film): 3490, 2953, 1707, 1460, 1249, 1111, 834, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.23 (dd, J = 7.0, 1.5 Hz, 1H), 4.21-4.17 (m, 1H), 3.95 (ddd, J = 9.0, 5.0, 1.5 Hz, 1H), 3.73 (d, J = 2.0 Hz, 1H), 3.72-3.67 (m, 1H), 3.50-3.43 (m, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.30 (dd, J = 10.0, 4.0 Hz, 1H), 3.26 (dd, J = 9.5, 5.5 Hz, 1H), 2.72 (dq, J = 7.0, 2.0 Hz, 1H), 2.65 (dd, J = 17.0, 8.0 Hz, 1H), 2.57 (dd, J = 16.5, 4.5 Hz, 1H), 2.16-2.13 (m, 2H), 1.77 (t, J = 2.5 Hz, 3H), 1.81-1.75 (m, 2H), 1.70-1.55 (m, 4H), 1.55-1.48 (m, 2H), 1.25 (s, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.94 (t, J = 8.0 Hz, 9H), 0.88 (s, 9H), 0.85 (d, J 7.0 Hz, 3H), 0.63-0.55 (m, 12H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 80.3, 79.4, 77.8, 77.5, 76.4, 73.5, 70.8, 70.0, 67.7, 59.9, 56.7, 51.0, 48.6, 43.6, 41.2, 40.7, 32.7, 26.5 (3C), 24.7, 19.5, 18.8, 10.1, 7.7 (3C), 7.6 (3C), 6.6 (3C), 6.1(3C), 4.0, −3.7, −4.1; HRMS *m/z* calcd for $C_{40}H_{82}O_7NaSi_3$: 781.5266; found: 781.5204.



(2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-2-((2*S*,4*R*)-2-hydroxy-4-(4-methoxybenzyloxy)dec-8-ynyl)-2-methoxy-3,5-dimethyltetrahydro-2H-pyran-4-ol: To a 0 °C solution of 0.060 g of ketone (0.07 mmol, 1.0 equiv) in 0.70 mL of CH_2Cl_2 and 0.70 mL of MeOH, was added 5.2 µL of CF_3CO_2H (0.07 mmol, 1.0 equiv) via syringe. The reaction was allowed to stir at 0 °C for 5 hours before the addition of 5 mL of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were combined and dried over Na_2SO_4, filtered, and concentrated. The clear colorless oil was used crude in the following reaction.

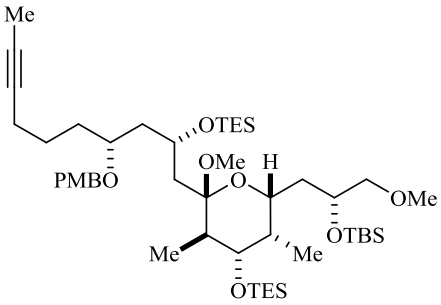


(2*S*,3*R*,4*S*,5*R*,6*R*)-6-[(*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl]-2-[(2*R*,4*R*)-2-hydroxy-4-methoxydec-8-ynyl]-2-methoxy-3,5-dimethyl-tetrahydro-2H-pyran-4-ol: To a solution of 0.225 g of ketone (0.296 mmol) in 3.3 mL of CH_2Cl_2 and 3.3 mL of MeOH at ambient temperature is added 11.1 mg of PPTS (0.044 mmol) as a solid. The resulting mixture is maintained at ambient temperature for 12 h whereupon saturated aqueous $NaHCO_3$ (10 mL) is added. The mixture is diluted with H_2O (5 mL), and extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by flash chromatography on IATRO beads (20% EtOAc in hexanes) to yield 0.120 g (74.5%) of a clear colorless oil. $[\alpha]_D^{23}$ + 64 (*c* 0.35, $CHCl_3$). IR (thin film): 3459, 2930, 1461, 1251, 1096, 985, 834, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.98 (dt, J = 8.5, 3.5 Hz, 1H), 3.95-3.87 (m, 4H), 3.36-3.32 (m, 2H), 3.31 (s, 6H), 3.30-3.27 (m, 2H), 3.20 (s, 3H), 2.17-2.14 (m, 2H), 1.99-1.93 (m, 1H), 1.88-1.83 (m, 2H), 1.81 (dd, J = 13.5, 7.0 Hz, 1H), 1.77 (t, J = 2.5 Hz, 3H), 1.74-1.69 (m, 1H), 1.65-1.61 (m, 1H), 1.61-1.4- (m, 6H), 1.00 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.5, 79.0, 77.6, 77.4, 75.7, 72.1, 69.6, 68.8, 64.8, 58.8, 56.1, 47.6, 41.4, 39.1, 38.7, 38.6, 36.5, 32.5, 25.9 (3C), 24.6, 18.8, 18.2, 11.4, 4.9, 3.4, −3.8, −4.7; HRMS *m/z* calcd for $C_{29}H_{56}O_7NaSi$: 567.3693; found: 567.3659.



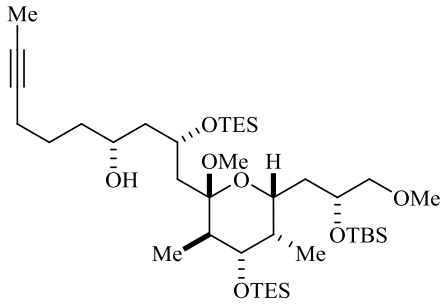
(2*S*,3*R*,4*S*,5*S*,6*R*)-2-((2*S*,4*R*)-2-(Benzoyloxy)-4-(4-methoxybenzyloxy)dec-8-ynyl)-6-((*R*)-2-(tert-butyldimethylsilyloxy)-3-methoxypropyl)-2-methoxy-3,5-dimethyltetrahydro-2H-pyran-4-yl benzoate: To an ambient temperature solution of 0.100 g of the diol (0.153 mmol, 1.0 equiv) in 1.1 mL of pyridine was added 113 mg

of benzoyl bromide (0.614 mmol, 4.0 equiv). The solution was heated to 50 °C for 1 hour. The greenish mixture was quenched with water, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with 0.1N HCl (15 mL), and saturated aqueous $NaHCO_3$ (15 mL), then dried (Na_2SO_4), and concentrated. The crude oil was purified by mPLC using a gradient elution from 2 to 12 % EtOAc in hexanes to yield 60 mg (46%) of a clear colorless oil. $[\alpha]_D^{23}$ + 33.8 (*c* 2.62, $CHCl_3$). IR (thin film): 3019, 1710, 1513, 1215, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.0, 1.0 Hz, 2H), 7.95 (dd, J = 8.0, 1.0 Hz, 2H), 7.60-7.52 (m, 2H), 7.44 (dq, J = 7.5, 7.5 Hz, 4H), 7.30-7.27 (m, 2H), 6.82-6.78 (m, 2H), 5.57-5.51 (m, 1H), 5.27 (dd, J = 11.5, 5.0 Hz, 1H), 4.48 (d, 11.0 Hz, 1H), 4.36 (d, J = 11.0 Hz, 1H), 4.0-3.91 (m, 2H), 3.70 (s, 3H), 3.56-3.51 (m, 1H), 3.37 (dd, J = 9.5, 4.0 Hz, 1H), 3.35 (s, 3H), 10, 6.5 Hz, 1H), 3.17 (s, 3H), 2.31-2.23 (m, 2H), 2.16-2.08 (m, 5H), 1.84-1.80 (m, 1H), 1.78 (t, 2.5 Hz, 3H), 1.75-1.65 (m, 2H), 1.61-1.54 (m, 2H), 1.50-1.42 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.88 (s, 12H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 165.8, 158.9, 132.8, 132.7, 130.9, 130.6, 130.5, 129.5, 129.5, 129.2, 128.3, 113.6, 101.6, 78.9, 77.6, 75.9, 75.7, 74.7, 70.8, 70.1, 69.8, 68.0, 58.8, 55.1, 47.3, 40.3, 38.1, 36.1, 34.9, 33.0, 25.9, 24.1, 18.9, 18.2, 11.5, 5.9, 3.4, -3.9, -4.6; HRMS *m/z* calcd for $C_{50}H_{70}O_{10}NaSi$: 881.4636; found: 881.4636.

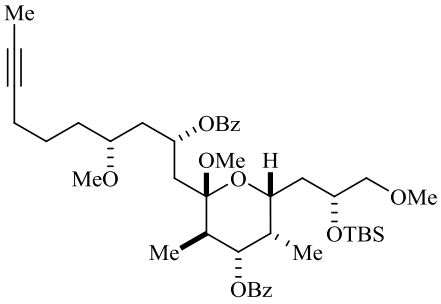


(2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-2-((2*S*,4*R*)-2-triethylsilyloxy-4-(4-methoxybenzyloxy)dec-8-ynyl)-2-methoxy-3,5-dimethyltetrahydro-2H-4-triethylsilyloxypyran (73): To a −55 °C solution of 0.170 g of the diol (0.261 mmol, 1.0 equiv) in 1.8 mL of CH_2Cl_2 was added 0.182 mL of 2,6-lutidine (1.56 mmol, 6.0 equiv), followed by 0.147 mL of TESOTf (0.652 mmol, 2.5 equiv). The reaction was allowed to stir for 12 h at −55 °C. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified via flash chromatography with silica gel (10% EtOAc/Hexanes) to yield 0.223 g (95%, 2 steps) of a clear colorless oil. $[\alpha]_D^{21}$ +32.8 (*c* 0.79, $CHCl_3$). IR (thin film): 1613, 1513, 1460, 1247, 1066 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, J = 9 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.50 (d, J = 10.8 Hz, 1H), 4.35 (d, J = 11.4 Hz, 1H), 4.01-3.96 (m, 1H), 3.92-3.87 (m, 1H), 3.93-3.78 (m, 5H), 3.56

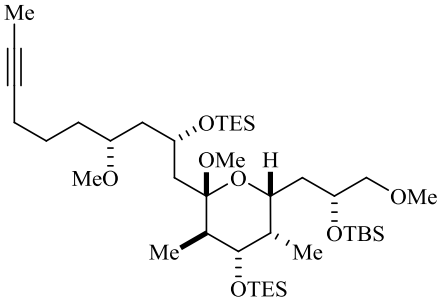
(App. dq, J = 8.4, 4.8 Hz, 1H), 3.37 (dd, J = 9.6, 3.6 Hz, 1H), 3.32 (s, 3H), 2.19 (ddd, J = 14.4, 8.4, 3.6 Hz, 1H), 2.15-2.10 (m, 2H), 1.89 (dd, J = 13.8, 9.0 Hz, 1H), 1.77 (t, J = 2.4 Hz, 3H), 1.77-1.57 (m, 6H), 1.55-1.50 (m, 2H), 1.38 (App. dtd, J = 14.4, 7.2, 3.0 Hz, 2H), 0.97-0.91 (m, 21H), 0.87 (s, 9H), 0.84 (d, J = 6.6 Hz, 3H), 0.62-0.53 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.7, 131.5 (2C), 128.6 (2C), 113.5, 101.7, 79.2, 77.8, 75.5, 75.4, 73.0, 70.3, 69.6, 68.2, 67.0, 58.7, 55.2, 47.0, 43.3, 42.2, 40.1, 38.6, 37.0, 33.0, 26.0 (3C), 24.1, 19.0, 18.2, 12.3, 7.0 (3C), 6.9 (3C), 5.5, 5.3 (3C), 5.1 (3C), 3.5, −3.8, −4.7; HRMS (ES) *m/z* calcd for $C_{48}H_{90}O_8NaSi_3$ $(M + Na)^+$: 901.5841; found: 901.5911.



(2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-2-((2*S*,4*R*)-2-triethylsilyloxy-4-(4-hydroxy)dec-8-ynyl)-2-methoxy-3,5-dimethyltetrahydro-2H-4-triethylsilyloxypyran: To a solution of 0.150 g of PMB ether (0.17 mmol, 1.0 equiv) at 0 °C in 5 mL of a 2:1 mixture of CH_2Cl_2:pH 7 phosphate buffer was added 0.058 g of DDQ (0.25 mmol, 1.5 equiv). The mixture was stirred for 2.5 hours at 0 °C. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were passed through a plug of celite before concentration. The crude oil was purified via flash chromatography on IATRO® beads with 7% EtOAc/Hexanes to yield 117 mg (90.7%) of a clear colorless oil. $[\alpha]_D^{21}$ +60.3 (*c* 0.19, $CHCl_3$). IR (thin film): 3519, 1460, 1247, 1068, 1005 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.15-4.14 (m, 1H), 4.11-4.05 (m, 1H), 3.92 (App. s, 1H), 3.91-3.87 (m, 1H), 3.87-3.82 (m, 2H), 3.34-3.31 (m, 4H), 3.25 (dd, J = 9.6, 6.0 Hz, 1H), 3.15 (s, 3H), 2.30 (dd, J = 13.8, 10.2 Hz, 1H), 2.17-2.12 (m, 2H), 1.82-1.78 (m, 1H), 1.76 (t, J = 3 Hz, 3H), 1.73 (dd, J = 14.4, 3.6 Hz, 1H), 1.70-1.63 (m, 3H), 1.60-1.53 (m, 2H), 1.51-1.37 (m, 3H), 0.98-0.93 (m, 21H), 0.87 (s, 9H), 0.83 (d, J = 6.6 Hz, 3H), 0.63-0.57 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 101.5, 79.1, 77.7, 75.6, 72.8, 70.0, 69.3, 68.2, 68.0, 58.7, 47.2, 41.3, 40.0, 39.2, 38.7, 37.3, 37.0, 26.0 (3C), 25.1, 19.0, 18.2, 12.2, 6.9 (3C), 6.8 (3C), 5.6, 5.0 (3C), 4.7 (3C), 3.5, −3.7, −4.7; HRMS (ES) *m/z* calcd for $C_{40}H_{82}O_7NaSi_3$ $(M + Na)^+$: 781.5266; found: 781.5277.

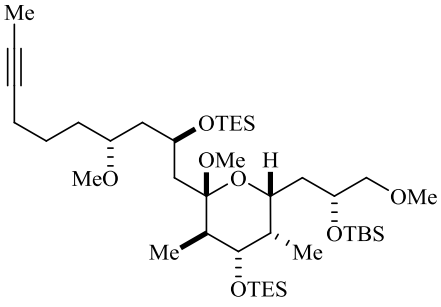


(2*S*,3*R*,4*S*,5*S*,6*R*)-2-((2*S*,4*R*)-2-(Benzoyloxy)-4-methoxydec-8-ynyl)-6-((*R*)-2-(tert-butyldimethylsilyloxy)-3-methoxypropyl)-2-methoxy-3,5-dimethyltetrahydro-2H-pyran-4-yl benzoate: To a 0 °C solution of 60 mg of the pmb ether (0.07 mmol, 1.0 equiv) in 2 mL of 1:2 mixture of pH 7 buffer:DCM was added 23.7 mg of DDQ (0.104 mmol, 1.5 equiv), and the reaction was stirred for 2.5 hours. The reaction was quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were passed through a plug of celite, concentrated. The crude oil was taken up in 0.7 mL of CH_2Cl_2, and to this solution was added 45 mg of proton sponge (0.21 mmol, 3.0 equiv), followed by 31 mg of Me_3OBF_3 (0.21 mmol, 3.0 equiv) at ambient temperature. Upon completion the reaction was quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2 (3 x 5 mL). Wash the combined organic extracts with 1M $NaHSO_4$ (10 mL), then dried (Na_2SO_4), and concentrate. The crude mixture was purified via flash chromatography with silica gel (10 to 20% EtOAc/Hexanes) to yield 40 mg (76%, 2 steps) of a clear colorless oil. $[\alpha]_D^{21}$ + 83.6 (*c* 0.33, $CHCl_3$). IR (thin film): 3019, 1642, 1215, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07-8.05 (m, 2H), 7.98-7.96 (m, 2H), 7.60-7.52 (m, 2H), 7.48-7.39 (m, 4H), 5.48-5.45 (m, 1H), 5.27 (dd, J = 11.0, 4.5 Hz, 1H), 3.99-3.94 (m, 2H), 3.38 (dd, J = 9.5, 4.0 Hz, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 3.30-3.26 (m, 1H), 3.19 (s, 3H), 2.32-2.26 (m, 1H), 2.17-2.04 (m, 6H), 1.81-1.76 (m, 2H), 1.75 (t, J = 2.5 Hz, 3H), 1.65-1.59 (m, 3H), 1.56-1.45 (m, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 165.8, 132.8, 132.7, 130.6, 130.5, 129.5, 129.5, 128.3, 128.2, 101.6, 78.8, 75.9, 75.7, 70.2, 69.8, 67.9, 58.8, 56.9, 47.3, 40.3, 38.1, 38.0, 36.1, 35.0, 32.8, 25.9, 24.2, 18.9, 18.2, 11.6, 5.8, 3.4, -3.9, -4.6; HRMS (ES) *m/z* calcd for $C_{43}H_{64}O_9NaSi$ $(M + Na)^+$: 775.4217; found: 775.4238.



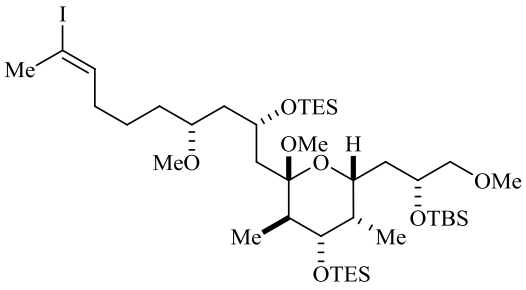
(2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-2-methoxy-2-((2*S*,4*R*)-4-methoxy-2-(triethylsilyloxy)dec-8-ynyl)-3,5-dimethyltetrahydro-2H-4-triethylsilyloxy-pyran (74): To a solution of 382 mg of

the alcohol (0.503 mmol, 1.0 equiv) in 5.2 mL of CH_2Cl_2 at ambient temperature was added 323 mg of H^+ Sponge® (1.51 mmol, 3.0 equiv) and 223 mg of Me_3OBF_4 (1.51 mmol, 3.0 equiv), sequentially. The solution was then stirred at ambient temperature for 1.5 hr, before approximately 5 mL of saturated aqueous NH_4Cl was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined and washed with 20 mL of 1M $NaHSO_4$, dried over Na_2SO_4, filtered, and concentrated. The crude oil was passed through a short plug of silica gel with 20% EtOAc in Hexanes, and concentrated, to yield 382 mg (98%) of a the title compound as a clear colorless oil. $[\alpha]_D^{22}$ +36 (*c* 0.93, $CHCl_3$). IR (thin film): 2953, 1460, 1247, 1067 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.97 (app. dtd, J = 2.7, 8.2 Hz, 1H), 3.91 (app. dtd, J = 4.2, 7.2 Hz, 1H), 3.83-3.78 (m, 2H), 3.37 (dd, J = 3.6, 9.6 Hz, 1H), 3.36-3.32 (m, 1H), 3.32 (s, 3H), 3.28-3.23 (m, 2H), 3.26 (s, 3H), 3.11 (s, 3H), 2.15-2.12 (m, 2H), 2.05 (ddd, J = 3.6, 9.6, 12 Hz, 1H), 1.90 (dd, J = 9.0, 13.8 Hz, 1H), 1.77 (t, 2.4 Hz, 3H), 1.75-1.71 (m, 2H), 1.68-1.60 (m, 2H), 1.50-1.46 (m, 2H), 1.40 (ddd, J = 2.4, 7.2, 13.8 Hz, 1H), 1.32-1.28 (m, 1H), 0.96 (app. dt, J = 2.4, 7,8 Hz, 21H), 0.88 (s, 9H), 0.86 (d, J = 6.6 Hz, 3H), 0.63-0.58 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 101.7, 79.1, 77.9, 76.6, 73.1, 70.3, 68.2, 66.7, 58.7, 55.6, 47.1, 43.0, 42.2, 40.1, 38.7, 36.9, 32.3, 31.6, 26.0 (3H), 24.0, 19.0, 18.2, 12.4, 7.0 (3H), 6.9 (3H), 5.3 (3H), 5.0 (3H), 3.5, −3.8, −4.7; HRMS (ES) *m/z* calcd for $C_{41}H_{84}O_7NaSi_3$ $(M + Na)^+$: 795.5423; found: 795.5435.



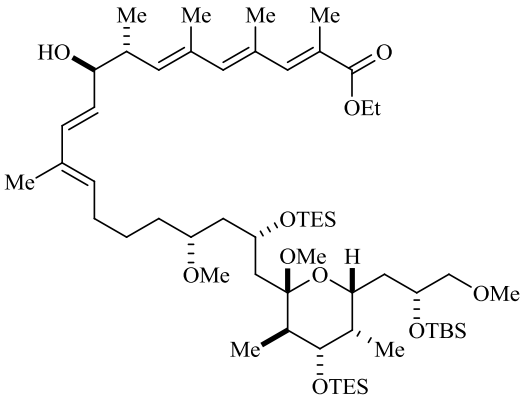
(2*S*,3*R*,4*S*,5*R*,6*R*)-6-[(*R*)-2-(tert-Butyldimethylsilyloxy)-3-methoxypropyl]-2-methoxy-2-[(2*R*,4*R*)-4-methoxy-2-(triethylsilyloxy)dec-8-ynyl]-3,5-dimethyltetrahydro-4-(triethylsilyloxy)-2H-pyran (57): To a −55 °C solution of 0.767 g of hemi-ketal **56** (0.140 mmol) in 0.5 mL of CH_2Cl_2 is added 0.098 mL of 2,6-lutidine (0.84 mmol) followed by 0.079 mL of TESOTf (0.35 mmol) slowly via syringe. The resulting solution was maintained at −55 °C for 3 h. Saturated aqueous $NaHCO_3$ (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification of the crude oil by flash chromatography on silica gel (5% EtOAc in hexanes) afforded 0.106 g (98%) of a clear colorless oil. $[\alpha]_D^{21}$ +63 (*c* 0.33, $CHCl_3$). IR (thin film): 2953, 1460, 1246, 1069, 1008, 835, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.95-3.92 (m,

1H), 3.91-3.86 (m, 1H), 3.85-3.83 (m, 1H), 3.77 (dd, J = 10.5, 5.0 Hz, 1H), 3.33-3.30 (m, 1H), 3.32 (s, 3H), 3.30 (s, 3H), 3.26 (dd, J = 9.5, 6.0 Hz, 1H), 3.12 (s, 3H), 2.16-2.11 (m, 2H), 1.97 (d, J = 14.5 Hz, 1H), 1.84-1.80 (m, 2H), 1.77 (t, J = 2.5 Hz, 3H), 1.70-1.63 (m, 4H), 1.58-1.45 (m, 4H), 1.45-1.40 (m, 2H), 0.97 (t, J = 8.0 Hz, 9H), 0.95 (t, J = 8.0 Hz, 9H), 0.90 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (d, J = 7.2 Hz, 3H), 0.70-0.56 (m, 12H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.2, 79.1, 77.9, 77.8, 75.5, 73.2, 69.8, 67.8, 66.7, 58.7, 56.2, 47.2, 42.9, 41.9, 39.9, 38.6, 37.6, 32.8, 25.9 (3C), 24.7, 18.9, 18.2, 12.2, 7.0 (3C), 6.9 (3C), 5.3, 5.1 (3C), 5.0 (3C), 3.4, −3.7, −4.7; HRMS *m/z* calcd for $C_{41}H_{84}O_7NaSi_3$: 795.5423; found: 795.5399.



(2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(tert-Butyldimethylsilyloxy)-3-methoxypropyl)-2-((2*S*,4*R*,*E*)-9-iodo-4-methoxy-2-(triethylsilyloxy)dec-8-enyl)-2-methoxy-3,5-dimethyltetrahydro-2H-4-triethylsilyloxypyran (75): In a flame dried vessel was placed 100 mg of Cp_2ZrHCl (0.388 mmol, 3.0 equiv) under vacuum for 1 hour before the addition of 100 mg of the alkyne (0.129 mmol, 1.0 equiv) in 1.30 mL of THF. The heterogeneous reaction was stirred at 50° C for 30 minutes before being cooled to 0° C. At this point 45 µL of 2,6-lutidine (0.388 mmol, 3.0 equiv) was added, followed by 98 mg of I_2 (0.388 mmol, as a solution in 0.5 mL of THF, 3.0 equiv), which was added dropwise. The opaque tan mixture turned yellow upon addition of approximately half of the I_2, and a dark purple/brown after complete addition. This mixture was allowed to stir at 0° C for 10 minutes before the addition of approximately 2 mL of saturated aqueous $Na_2S_2O_3$, at which time the reaction turned a pale, clear yellow color. The mixture was partitioned between Et_2O and H_2O (5 mL each), separated and extracted with Et_2O (3 x 10 mL). The organic layers were combined, and passed through a plug of silica gel before concentrating to a clear colorless oil. The crude oil was purified by flash column chromatography on silica gel (3% EtOAc in hexanes) to yield 77 mg (72%) of a clear colorless oil. Product had >17:1 regioselectivity after chromatography, as assayed by 500 MHz ^{1}H NMR. $[\alpha]_D^{22}$ + 32.1 (*c* 1.14, $CHCl_3$). IR (thin film): 1635, 1460, 1381, 1246, 1065, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (App. td, J = 7.5, 1.5 Hz, 1H), 3.99-3.95 (m, 1H), 3.95-3.88 (m, 1H),

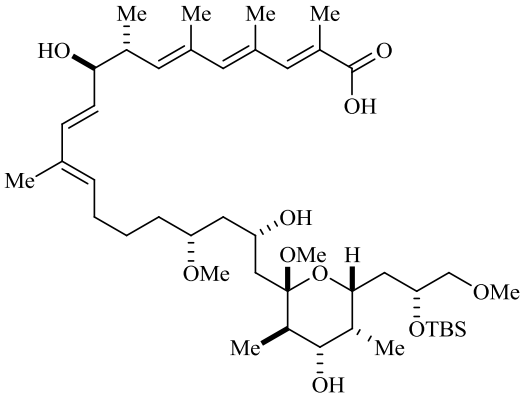
3.83-3.78 (m, 2H), 3.37-3.33 (m, 2H), 3.33 (s, 3H), 3.28-3.23 (m, 4H), 3.12 (s, 3H), 2.36 (s, 3H), 2.07-2.00 (m, 2H), 1.89 (dd, J = 14.0, 9.0 Hz, 1H), 1.77-1.71 (m, 2H), 1.70-1.62 (m, 2H), 1.52-1.36 (m, 5H), 1.32-1.24 (m, 2H), 0.99-0.93 (m, 21H), 0.88 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H), 0.64-0.56 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 101.7, 93.6, 77.9, 73.1, 70.2, 68.1, 66.7, 58.8, 55.7, 47.1, 43.0, 42.2, 40.1, 38.8, 36.9, 32.5, 30.8, 27.5, 25.9 (3C), 23.9, 18.2, 12.4, 7.0 (3C), 6.9 (3C), 5.4, 5.3 (3C), 5.0 (3C), −3.7, −4.7; HRMS (ES) *m/z* calcd for $C_{41}H_{85}O_7NaSi_3I$ $(M + Na)^+$: 923.4546; found: 923.4515.



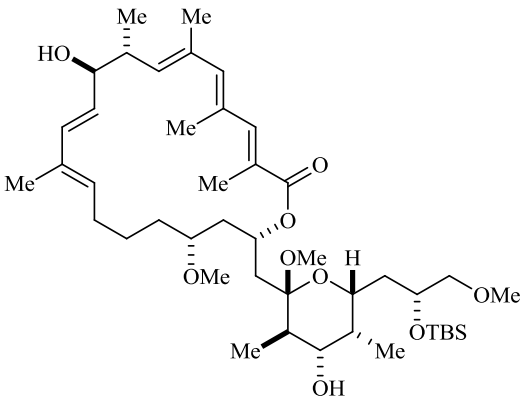
(2*E*,4*E*,6*E*,8*R*,9*R*,10*E*,12*E*,17*R*,19*S*)-ethyl 20-((2*S*,3*R*,4*S*,5*S*,6*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-2-methoxy-3,5-dimethyl-4-(triethylsilyloxy)tetrahydro-2H-pyran-2-yl)-9-hydroxy-17-methoxy-2,4,6,8,12-pentamethyl-19-(triethylsilyloxy)icosa-2,4,6,10,12-pentaenoate (77):

To a flame dried vessel was added 0.151 g of vinyl stannane (0.266 mmol, 4 equiv), and 0.060 g of vinyl iodide (0.066 mmol, 1.0 equiv). The mixture was subjected to high vacuum for one hour before refilling the vessel with $N_{2(g)}$. To this was added 1.3 mL of degassed DMF at ambient temperature, before adding 0.152 g of $Ph_2PO_2NBu_4$ (0.332 mmol, 5 equiv). The vessel was opened to atmosphere momentarily to add 1.7 mg of $Pd_2Cl_2(MeCN)_2$ (0.0066 mmol, 0.1 equiv). The reaction mixture immediately turned black. The reaction was covered in foil and stirred at ambient temperature for 15 hours before being quenched with 13.0 mL of a 1:1 solution of Et_2O to hexanes. This heterogeneous mixture was passed through a plug of celite, rinsing with more of the same 1:1 solution. The yellowish organic eluent was washed with brine (3 x 20 mL) before being dried (Na_2SO_4), and concentrated. The crude yellow oil was purified by flash chromatography (10 % EtOAc/Hex) affording 48 mg (75%) of the title compound as a 12:1 mixture of isomers as assayed by 500 MHz ^{1}H NMR. $[\alpha]_D^{22}$ +54.7 (*c* 0.19, $CHCl_3$). IR (thin film): 2925, 1705, 1460, 1376, 1250, 1068, 1004 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.22 (d, J = 15.5 Hz, 1H), 6.01 (s, 1H), 5.57 (dd, J = 15.5, 7.0 Hz, 1H), 5.47 (t, J = 7.0 Hz, 1H), 5.27 (d, J = 10.0 Hz, 1H), 4.18 (q, J = 5.0 Hz, 2H), 4.05-4.02 (m, 1H), 3.98-3.94 (m, 1H),

3.93-3.88 (m, 1H), 3.83-3.77 (m, 2H), 3.38-3.29 (m, 5H), 3.26-3.22 (m, 4H), 3.10 (s, 3H), 2.70-2.65 (m, 1H), 2.16-2.10 (m, 2H), 2.02 (s, 3H), 1.96 (s, 3H), 1.92-1.86 (m, 1H), 1.79 (s, 3H), 1.76-1.70 (m, 4H), 1.66-1.61 (m, 3H), 1.50-1.44 (m, 2H), 1.42-1.32 (m, 4H), 1.31-1.24 (m, 5H), 1.05 (d, J = 6.5 Hz, 3H), 0.98-0.90 (m, 21H), 0.88 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H), 0.63-0.57 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 143.6, 138.9, 136.5, 133.7, 133.4, 132.9 (2C), 131.8, 136.9, 125.9, 101.7, 77.8, 73.0, 70.2, 68.2, 66.7, 60.6, 58.7, 55.6, 47.0, 43.0, 40.0, 39.4, 36.9, 32.8, 28.4, 27.8, 26.8, 25.9 (3C), 24.5, 18.2, 17.5, 17.3, 16.5, 14.3, 14.1, 13.6, 12.5, 12.3, 7.0 (3C), 6.9 (3C), 5.4, 5.31 (3C), 5.3 (3C), −3.8, −4.7; HRMS (ES) *m/z* calcd for $C_{58}H_{110}O_{10}NaSi_3$ $(M + Na)^+$: 1073.7305; found: 1073.7268.

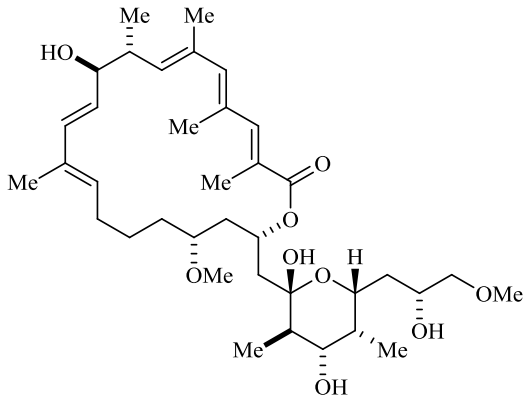


(2*E*,4*E*,6*E*,8*R*,9*R*,10*E*,12*E*,17*R*,19*S*)-20-((2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-4-hydroxy-2-methoxy-3,5-dimethyltetrahydro-2H-pyran-2-yl)-9,19-dihydroxy-17-methoxy-2,4,6,8,12-pentamethylicosa-2,4,6,10,12-pentaenoic acid: The mixture of protected seco-acid (52 mg, 0.0572 mmol, 1.0 equiv) was added to 8.34 mL of a 1:1 mixture of MeOH and CH_2Cl_2. The solution was cooled to −15° C in a MeOH and ice bath. 4.3μL (0.0572 mmol, 1.0 equiv) of CF_3CO_2H dissolved in 0.6 mL of CH_2Cl_2 and added dropwise. The solution was maintained at −15° C for 30 minutes before being quenched with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), the combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column (5% MeOH/CH_2Cl_2), to yield 26.5 mg (58%) of the seco-acid which was combined with the purified material from the previous step, giving an overall yield of 33.5 mg (48% over two steps).

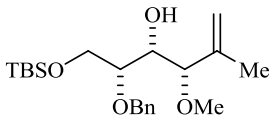


(3*E*,5*E*,7*E*,9*R*,10*R*,11*E*,13*E*,18*R*,20*S*)-20-(((2*S*,3*R*,4*S*,5*R*,6*R*)-6-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxypropyl)-4-hydroxy-2-methoxy-3,5-dimethyltetrahydro-2H-pyran-2-yl)methyl)-10-hydroxy-18-methoxy-3,5,7,9,13-pentamethyloxacycloicosa-3,5,7,11,13-pentaen-2-one: To an ambient temperature solution of 25.0 mg of seco-acid (0.0314 mmol, 1.0 equiv) in 7.44 mL of THF was added 0.174 mL of NEt_3 (1.25 mmol, 4.0 equiv), followed by 19.5 µL of 2,4,6-trichlorobenzoyl chloride (0.125 mmol, 40.0 equiv) dropwise. The reaction was stirred in a foil-covered flask at ambient temperature for 15 hours, whereupon it was diluted with 7.44 mL of toluene, and added to 930 mL of toluene containing 0.767 g of DMAP (6.28 mmol, 200 equiv). The addition took place via syringe pump over 1 hour [followed by two rinses of toluene (1.0 and 0.5 mL) added over 20 and 10 minutes respectively]. The reaction was then allowed to stir at ambient temperature for 24 hours, covered in foil, before being concentrated to approximately 200 mL via rotovap. The toluene solution was then quenched with NH_4Cl (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash column chromatography on IATRO beads with 2% MeOH in CH_2Cl_2 yielding 13.9 mg (57%) of the desired lactone based on HMQC, HMBC, and cosy correlations. The reaction also yielded 2.0 mg (8%) of a minor product believed to be macrolactonization on the pyran oxygen. $[\alpha]_D^{21}$ +10.2 (*c* 0.23, $CHCl_3$). IR (thin film): 3409, 2925, 1693, 1460, 1384, 1248, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 4.2 Hz, 1H), 7.11 (s, 1H), 6.08 (app. d, J = 15 Hz, 1H), 6.07 (app. s, 1H), 5.51 (app. t, J = 7.2 Hz, 1H), 5.34 (dd, J = 15.6, 8.4 Hz, 1H), 5.13 (d, J = 9.6 Hz, 1H), 5.04 (app. t, J = 10.2 Hz, 1H), 3.95-3.89 (m, 2H), 3.86-3.81 (m, 2H), 3.37 (dd, J = 10.2, 4.2 Hz, 1H), 3.35 (s, 3H), 3.33-3.28 (m, 1H), 3.27 (s, 3H), 3.12 (s, 3H), 2.92 (br. q, J = 7.2 Hz, 1H), 2.55-2.50 (m, 1H), 2.27-2.21 (m, 1H), 2.12 (s, 3H), 2.10 (app. d, J = 5.4 Hz, 1H), 2.07 (s, 3H), 2.10-1.90 (m, 3H), 1.88 (s, 3H), 1.86-1.80 (m, 2H), 1.78-1.72 (m, 2H), 1.67-1.63 (m, 4H), 1.46 (ddd, J = 14.4, 7.2, 3.6 Hz, 2H), 1.39 (app. d, J = 5.4 Hz, 1H), 1.35-1.25 (m, 2H), 1.14 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 145.1, 144.5, 140.3, 137.3, 133.0, 132.8, 132.1, 131.8, 128.3,

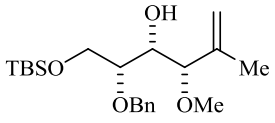
128.2, 127.1, 123.8, 101.5, 79.7, 79.0, 77.8, 72.4, 70.6, 70.0, 68.5, 58.8, 57.3, 47.2, 41.3, 39.5, 38.9, 38.4, 37.0, 33.5, 29.7, 28.0, 26.7, 25.9 (3C), 18.2, 17.5, 17.3, 16.3, 13.7, 12.0, 11.3, 4.9, −3.8, −4.7; HRMS (ES) *m/z* calcd for $C_{44}H_{76}O_9SiNa$ $(M + Na)^+$: 799.5156; found: 799.5152.



(3*E*,5*E*,7*E*,9*R*,10*R*,11*E*,13*E*,18*R*,20*S*)-20-(((2*S*,3*R*,4*S*,5*R*,6*R*)-2,4-Dihydroxy-6-((*R*)-2-hydroxy-3-methoxypropyl)-3,5-dimethyltetrahydro-2H-pyran-2-yl)methyl)-10-hydroxy-18-methoxy-3,5,7,9,13-pentamethyloxacycloicosa-3,5,7,11,13-pentaen-2-one, (Apoptolidinone) (78): Protected aglycone (3.0 mg; 0.00386 mmol, 1.0 equiv) was dissolved in 0.55 mL of acetonitrile and cooled to −35° C in a refrigerator. To this solution was added ~14 mg of H_2SiF_6 (~60 mg of a 20-25% solution in H_2O; 0.0965 mmol, 25 equiv.; measured as 6 drops from a 20 gauge needle). The solution remained in the refrigerator for 40 hours before being quenched at −35° C with 0.100 mL of NEt_3. The resulting mixture was allowed to sit for 30 minutes at −35° C before quenching with sat. aq. $NaHCO_3$ (1 mL) and extracting with EtOAc (5 x 1.0 mL). The organic layer was combined and dried over Na_2SO_4, before being purified by flash chromatography (5% MeOH/CH_2Cl_2 on IATRO beads), yielding 0.7 mg (30%) of the aglycone as a white solid. $[\alpha]_D^{21}$ + (*c*, $CHCl_3$). IR (thin film): cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 4.2 Hz, 1H), 7.11 (s, 1H), 6.08 (app. d, J = 15 Hz, 1H), 6.07 (app. s, 1H), 5.51 (app. t, J = 7.2 Hz, 1H), 5.34 (dd, J = 15.6, 8.4 Hz, 1H), 5.13 (d, J = 9.6 Hz, 1H), 5.04 (app. t, J = 10.2 Hz, 1H), 3.95-3.89 (m, 2H), 3.86-3.81 (m, 2H), 3.37 (dd, J = 10.2, 4.2 Hz, 1H), 3.35 (s, 3H), 3.33-3.28 (m, 1H), 3.27 (s, 3H), 3.12 (s, 3H), 2.92 (br. q, J = 7.2 Hz, 1H), 2.55-2.50 (m, 1H), 2.27-2.21 (m, 1H), 2.12 (s, 3H), 2.10 (app. d, J = 5.4 Hz, 1H), 2.07 (s, 3H), 2.10-1.90 (m, 3H), 1.88 (s, 3H), 1.86-1.80 (m, 2H), 1.78-1.72 (m, 2H), 1.67-1.63 (m, 4H), 1.46 (ddd, J = 14.4, 7.2, 3.6 Hz, 2H), 1.39 (app. d, J = 5.4 Hz, 1H), 1.35-1.25 (m, 2H), 1.14 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, −3.8, −4.7; HRMS (ES) *m/z* calcd for $C_{37}H_{60}O_9Na$ $(M + Na)^+$: 671.4135; found: 671.4108.

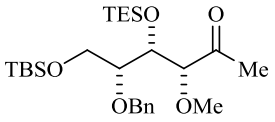


(2*R*,3*R*,4*S*)-2-(Benzyloxy)-1-(tert-butyldimethylsilyloxy)-4-methoxy-5-methylhex-5-en-3-ol (90): To a −25 °C solution of 4.38 g of magnesium bromide diethyl etherate (17.0 mmol, 1.0 equiv) in 38.3 mL of CH_2Cl_2 was added 5.01 g of aldehyde **91** (17.0 mmol, 1.0 equiv). The mixture was allowed to stir for 20 minutes at temperature, before the addition of 7.02 g of stannane **92** (18.7 mmol, 1.1 equiv). The mixture was covered, and allowed to warm slowly over 4-5 hours before being placed in a +4 °C cold room to stir for 12 hours. The reaction was quenched with H_2O (25 mL), and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting crude oil was a mixture of diastereomers (~3:1) which was purified by column chromatography (40 % EtOAc in hexanes on silica gel) to afford 4.12 g (63 %) of the title compound as a single diastereomer. $[\alpha]_D^{22}$ + 3.23 (*c* 1.30, $CHCl_3$). IR (thin film): 3019, 1215, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 5.04 (t, J = 2 Hz, 1H), 4.88 (s, 1H), 4.72 (d, J = 11.5 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 3.83 (dd, J = 10.0, 7.0 Hz, 1H), 3.81-3.76 (m, 2H), 3.74 (d, J = 8.0 Hz, 1H), 3.44 (ddd, J = 7.0, 5.5, 2.0 Hz, 1H), 3.26 (s, 3H), 2.62 (d, 4.0 Hz, 1H), 1.66 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 138.6, 128.3, 127.8, 127.6, 116.7, 86.4, 78.6, 73.0, 71.2, 62.0, 56.3, 25.8, 18.2, 16.9, -5.4, -5.5; HRMS *m/z* calcd for $C_{21}H_{36}O_4NaSi$: 403.2281; found: 403.2294.

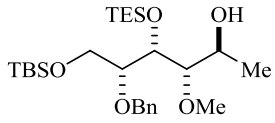


(2*R*,3*R*,4*S*)-2-(Benzyloxy)-1-(tert-butyldimethylsilyloxy)-3-(triethylsilyloxy)-4-methoxy-5-methylhex-5-en (93): To a −45 °C solution of 4.12 g of alcohol **92** (10.8 mmol, 1.0 equiv) in 40.0 mL of CH_2Cl_2 was added 2.51 mL of 2,6-lutidine (2.31 g, 21.6 mmol, 2.0 equiv), followed by 3.73 mL of triethylsilyl triflate (4.29 g, 16.25 mmol, 1.5 equiv). The reaction was allowed to proceed at temperature for 1 hour before being quenched with saturated aqueous sodium bicarbonate (40 mL), and the mixture was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic extracts were washed with 1M $NaHSO_4$ (100 mL), then dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by column chromatography (10 % EtOAc in hexanes on silica gel) to afford 5.34 g (100 %) of the title compound. $[\alpha]_D^{22}$ + 10.4 (*c* 0.67, $CHCl_3$). IR (thin film): 3428 (br), 2929, 1461, 1097, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (m, 5H), 5.00 (t, J = 2.0 Hz, 1H), 4.93 (s, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 3.88 (dd, J = 7.0,

2.5 Hz, 1H), 3.74 (dd, J = 10.0, 6.0 Hz, 1H), 3.73 (t, J = 7.5 Hz, 1H), 3.60 (dd, J = 10.5, 6.0 Hz, 1H), 3.33 (dt, J = 6.5, 3.0 Hz, 1H), 3.18 (s, 3H), 1.64 (s, 3H), 0.94 (t, J = 8.0 Hz, 9H), 0.87 (s, 9H), 0.65-0.55 (m, 6H), 0.00 (3H), -0.01 (3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 139.3, 128.1, 127.6, 127.3, 115.8, 86.6, 80.6, 72.9, 61.9, 55.9, 25.8, 18.1, 17.3, 7.0, 5.3, -5.43, -5.44; HRMS *m/z* calcd for $C_{27}H_{50}O_4NaSi_2$: 517.3145; found: 517.3149.

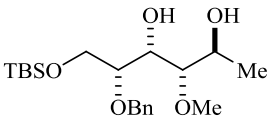


(3*R*,4*S*,5*R*)-5-(Benzyloxy)-6-(tert-butyldimethylsilyloxy)-4-(triethylsilyloxy)-3-methoxyhexan-2-one (93): To a −78 °C solution of 4.14 g of alkene **90** (8.36 mmol, 1.0 equiv) in 62.0 mL of CH_2Cl_2 and 6.2 mL of MeOH was bubbled O_3 until the solution became blue. Upon color change, O_2 was bubbled until clear, followed by bubbling N_2 for 20 minutes. To the solution at −78 °C was added 31 mL of Me_2S, and was allowed to stir at temperature for 4 hours. The solution was then warmed to ambient temperature and stirred for an additional hour. TLC showed only a single product spot, and the solvent was removed in vacuo. The crude oil was combined with other material from similar reactions run at different scales, and purified by column chromatography (10 % EtOAc in hexanes on silica gel) to afford 4.67 g (87 %) of the title compound. $[\alpha]_D^{22}$ +13.9 (*c* 2.92, $CHCl_3$). IR (thin film): 3019, 1215, 1092, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (m, 5H), 4.66 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.08 (t, J = 4.5 Hz, 1H), 3.87 (dd, J = 11.0, 4.0 Hz, 1H), 3.71-3.67 (m, 2H), 3.50 (dt, J = 7.0, 4.0 Hz, 1H), 3.38 (s, 3H), 2.18 (s, 3H), 0.92-0.84 (m, 18H), 0.55 (q, J = 8.0 Hz, 6H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 138.7, 128.2, 127.8, 127.4, 87.8, 81.0, 73.1, 72.9, 62.5, 58.7, 27.7, 25.8, 18.1, 6.75, 4.8, -5.4; HRMS *m/z* calcd for $C_{26}H_{48}O_5NaSi_2$: 519.2938; found: 519.2964.

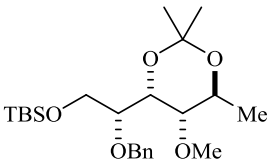


(2*S*,3*S*,4*S*,5*R*)-5-(Benzyloxy)-6-(tert-butyldimethylsilyloxy)-4-(triethylsilyloxy)-3-methoxyhexane-2-ol: To a 0 °C solution of 0.100 g of ketone **93** (0.202 mmol, 1.0 equiv) in 0.404 mL of Et_2O was added 1.61 mL of a .376 M solution of $Zn(BH_4)_2$ (0.606 mmol, 3.0 equiv). The reaction was stirred at 0 °C for 1 hour before being quenched with saturated aqueous NH_4Cl (1 mL), and the mixture was extracted with Et_2O (3 x 2.0 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by column chromatography (20 % EtOAc in hexanes on silica gel) to afford 95 mg (95 %) of the title compound. $[\alpha]_D^{22}$ -9.39 (*c* 0.49,

$CHCl_3$). IR (thin film): 3439, 1641, 1215, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 4.71 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.08 (dd, J = 4.5, 3.0 Hz, 1H), 3.91-3.84 (m, 1H), 3.81 (dd, J = 10.5, 5.5 Hz, 1H), 3.72 (dd, 10.5, 6.0 Hz, 1H), 3.60 (dt, J = 5.5, 3.0 Hz, 1H), 3.43 (s, 3H), 3.33 (s, 1H), 3.02 (dd, J = 7.0, 4.5 Hz, 1H), 1.21 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 6.5 Hz, 9H), 0.90 (s, 9H), 0.61 (q, J = 6.5 Hz, 6H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.2, 127.6, 127.5, 85.0, 79.8, 72.8, 71.1, 68.0, 61.7, 59.2, 25.7, 19.9, 18.0, 6.8, 4.9, -5.4, -5.5; HRMS *m/z* calcd for $C_{26}H_{50}O_5NaSi_2$: 521.3095; found: 521.3105.

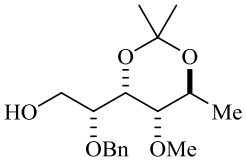


(2*S*,3*S*,4*S*,5*R*)-5-(Benzyloxy)-6-(tert-butyldimethylsilyloxy)-3-methoxyhexane-2,4-diol (94): To a 0 °C solution of 2.68 g of alcohol (5.37 mmol, 1.0 equiv) in 16.5 mL of a 1:1 mixture of CH_2Cl_2:MeOH was added 1.35 g of PPTS (5.37 mmol, 1.0 equiv). The reaction was maintained at 0 °C for 45 minutes. A solution of saturated aqueous sodium bicarbonate (25 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by column chromatography (40 % EtOAc in hexanes on silica gel) to afford 1.62 g (79 %) of the title compound. $[\alpha]_D^{22}$ -16.0 (*c* 1.01, $CHCl_3$). IR (thin film): 3019, 1215, 1112, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 4.77 (d, J = 11.5 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.05-3.97 (m, 2H), 3.87 (dd, J = 11.0, 5.0 Hz, 1H), 3.75 (dd, J = 11.0, 5.0 Hz, 1H), 3.66 (q, J = 5.0 Hz, 1H), 3.47 (s, 3H), 3.14 (dd, J = 4.5, 3.0 Hz, 1H), 3.05 (d, J = 6.5 Hz, 1H), 3.01 (d, J = 4.5 Hz, 1H), 1.22 (d, J = 6.5 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 128.5, 127.9, 127.9, 82.8, 79.7, 72.9, 70.8, 67.2, 62.4, 58.3, 25.8, 19.5, 18.2, -5.4, -5.4; HRMS *m/z* calcd for $C_{20}H_{36}O_5NaSi$: 407.2230; found: 407.2224.

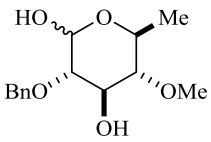


(4*S*,5*S*,6*S*)-5-Methoxy-2,2,4-trimethyl-6-(2–tert-butyldimethylsilyloxy-(*R*)-1-benzyloxyethyl)-1,3-dioxane: To a 0 °C solution of 1.62 g of diol **94** (4.20 mmol, 1.0 equiv) in 20 mL of CH_2Cl_2 was added 2.61 mL of 2,2-dimethoxy propane (21.06 mmol, 5.0 equiv), followed by 0.527 g of PPTS (2.10 mmol, 0.5 equiv). The reaction was maintained at 0 °C for 4 hours. A solution of saturated aqueous sodium bicarbonate (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4),

and concentrated. The resulting crude oil was purified by column chromatography (40 % EtOAc in hexanes on silica gel) to afford 1.66 g (93 %) of the title compound. $[\alpha]_D^{22}$ +7.10 (*c* 2.31, $CHCl_3$). IR (thin film): 3019, 1215, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 4.75 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.00 (dd, J = 8.0, 3.5 Hz, 1H), 3.84-3.80 (m, 2H), 3.73-3.67 (m, 2H), 3.37 (s, 3H), 3.16 (dd, J = 5.5, 3.5 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 1.33 (d, J = 6.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 128.0, 127.6, 127.1, 100.7, 84.2, 80.0, 73.8, 71.4, 69.4, 63.5, 58.2, 25.9, 24.9, 24.0, 21.5, 18.3, -5.2, -5.4; HRMS *m/z* calcd for $C_{23}H_{40}O_5NaSi$: 447.2543; found: 447.2534.

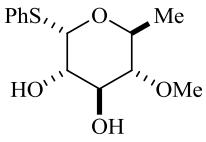


(4*S*,5*S*,6*S*)-5-Methoxy-2,2,4-trimethyl-6-(2–hydroxy-(*R*)-1-benzyloxyethyl)-1,3-dioxane: To a 0 °C solution of 1.66 g of silyl ether (3.90 mmol, 1.0 equiv) in 13 mL of THF was added 7.8 mL of TBAF (1 M solution in hexan, 7.8 mmol, 2.0 equiv). The reaction was allowed to warm to ambient temperature for 4 hours. A solution of saturated aqueous ammonium chloride (20 mL) was added, and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by column chromatography (40 % EtOAc in hexanes on silica gel) to afford 1.07 g (89 %) of the title compound. $[\alpha]_D^{22}$ + 34.9 (*c* 0.98, $CHCl_3$). IR (thin film): 3683, 3019, 1521, 1215, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 4.87 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.01 (dd, J = 8.5, 3.0 Hz, 1H), 3.88-3.72 (m, 3H), 3.58-3.52 (m, 1H), 3.37 (s, 3H), 3.15 (dd, J = 5.5, 3.0 Hz, 1H), 2.24-2.20 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 128.4, 127.8, 127.6, 100.8, 83.7, 79.0, 74.2, 72.2, 69.5, 61.9, 58.1, 24.9, 23.9, 21.6; HRMS *m/z* calcd for $C_{17}H_{26}O_5Na$: 333.1678; found: 333.1684.



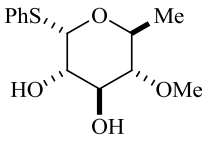
(3*S*,4*R*,5*R*,6*S*)-3-(Benzyloxy)-5-methoxy-6-methyltetrahydro-2H-pyran-2,4-diol (95): To a room temperature solution of 0.968 g of primary alcohol (3.11 mmol, 1.0 equiv) in 19.2 mL of CH_2Cl_2 was added 0.522 g of solid sodium bicarbonate (6.22 mmol, 2.0 equiv), followed by 1.98 g of Des-Martin periodinane (4.66 mmol, 1.5 equiv). The reaction was stirred at ambient temperature for 2 hours, before the addition of water (20 mL). The biphasic mixture was seperated and the aqueous layer was

extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resulting crude oil was passed through a plug of silica with 40 % EtOAc in hexanes, and used in the following reaction without further purification. The crude aldehyde was taken up in 10.8 mL of THF, and cooled to 0 °C. To this solution was added 1.56 mL of 1M HCl (1.56 mmol, 0.5 equiv), and the reaction was allowed to warm to ambient temperature, and stir for 1 hour. A solution of saturated aqueous sodium bicarbonate (10 mL) was added, and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by column chromatography (40 to 75 % EtOAc in hexanes on silica gel) to afford 0.519 g (62 %, over two steps) of the title compound as a white crystalline solid. $[\alpha]_D^{22}$ -28.4 (*c* 0.31, $CHCl_3$). IR (thin film): 3683, 3019, 1521, 1423, 1215, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 5.16 (br s, 0.56H), 4.97 (d, J = 14.5 Hz, 0.44H), 4.74-4.67 (m, 2H), 3.95-3.86 (m, 1H), 3.62-3.55 (m, 1H), 3.57 (s, 3H), 3.42-3.34 (m, 1H), 3.19 (dd, J = 11.5, 9.5 Hz, 0.44Hz), 3.10 (br d, J = 6.5 Hz, 0.41Hz), 2.86-2.76 (m, 1H), 2.47 (br s, 1H), 1.32 (d, J = 8.0 Hz, 1.4H), 1.27 (d, J = 7.5 Hz, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.5, 128.6(2C), 128.2 (2C), 128.0 (2C), 96.8, 90.6, 85.1, 84.7, 82.4, 79.8, 76.0, 74.3, 72.9, 72.7, 71.3, 66.5, 60.7, 60.6, 17.9, 17.8; HRMS *m/z* calcd for $C_{14}H_{20}O_5Na$: 291.1208; found: 291.1211.

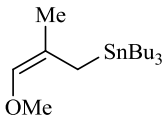


(3*S*,4*S*,5*R*,6*S*)-5-Methoxy-6-methyl-2-(phenylthio)tetrahydro-2H-pyran-3,4-diol: To a room temperature solution of 100 mg of diol **95** (0.373 mmol, 1.0 equiv) in 1.24 mL of MeOH was added 39.6 mg of 10% palladium on carbon (0.0373 mmol, 10 mol %). A balloon filled with hydrogen gas was used to purge the flask, and the reaction was allowed to stir overnight at ambient temperature. After approximately 24 hours, the reaction was complete by TLC. The heterogeneous mixture was diluted with ethyl acetate, and passed through a pad of celite, and concentrated. The crude material was taken up in 1.28 mL of THF and stirred at ambient temperature. To this solution was added 0.381 mL of thiophenol (3.73 mmol, 10.0 equiv), and 112 mg of triflic acid (0.746 mmol, 2.0 equiv). The reaction was allowed to stir at ambient temperature for 40 minutes. A solution of saturated aqueous sodium bicarbonate (5 mL) was added, and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resulting white powder was quickly passed through a plug of silica gel

with 80 % EtOAc in hexanes to afford 98.7 mg (99 % crude yield over two steps) of the title compound as a white crystalline solid. The material was used without further purification in the next step.

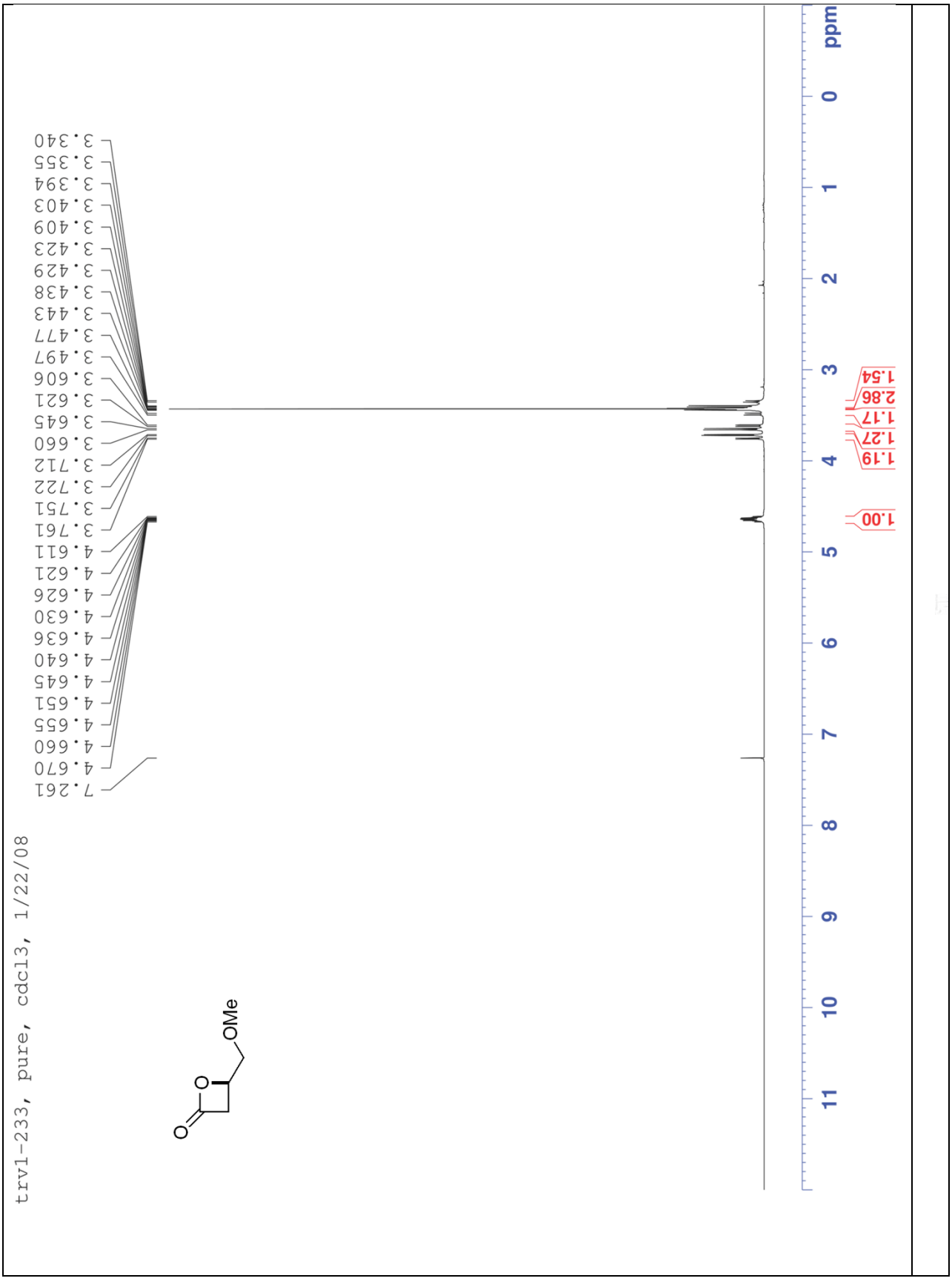


(3*S*,4*S*,5*R*,6*S*)-5-Methoxy-6-methyl-2-(phenylthio)-3,4-(*t*-butyldimethylsilyloxy) tetrahydro-2H-pyran (87): To a 0 °C solution of 0.166 g of diol (0.61 mmol, 1.0 equiv) in 2.5 mL of CH_2Cl_2 was added 0.426 mL of 2,6-lutidine (0.392 g, 3.66 mmol, 6.0 equiv), followed by 0.352 mL of *t*-butyldimethylsilyl triflate (0.405 g, 1.53 mmol, 2.5 equiv). The reaction was allowed to proceed at temperature for 1 hour before being quenched with saturated aqueous sodium bicarbonate (5.0 mL), and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by column chromatography (10 % EtOAc in hexanes on silica gel) to afford 0.290 g (95 %) of the title compound. The proton spectrum matches the known compound for the alpha anomer. $[\alpha]_D^{22}$ -125.5 (*c* 0.72, $CHCl_3$);



(*Z*)-Tributyl(3-methoxy-2-methylallyl)stannane (92): To a −78 °C solution of 3.61 g of 3-methoxy-2-methylprop-1-ene (41.9 mmol, 1.0 equiv) in 103 mL of THF was added 35.9 mL of *sec*-BuLi (50.3 mmol, 1.4 M in cyclohexane, 1.2 equiv) followed by 6.09 g of TMEDA (52.04 mmol, 1.25 equiv). After 15 minutes at −78 °C 15.0 g of Bu_3SnCl (46.09 mmol, 1.1 equiv) was added, and the mixture was allowed to warm to room temperature, and stir at ambient temperature for 30 minutes. The reaction mixture was then poured into 200 mL of hexane, and the organic layer was washed with 100 mL of saturated aqueous NH_4Cl, followed by 100 mL of H_2O. The organic layer was dried with $MgSO_4$, then concentrated. The crude product was partially purified by kugelhrohr distillation under high vacuum at approximately 160 °C to yield a mostly pure product containing only the *Z*-isomer. The product was contaminated with tin by-products, however it was used without further purification in the subsequent reactions.

APPENDIX A: ^{1}H AND ^{13}C SPECTRA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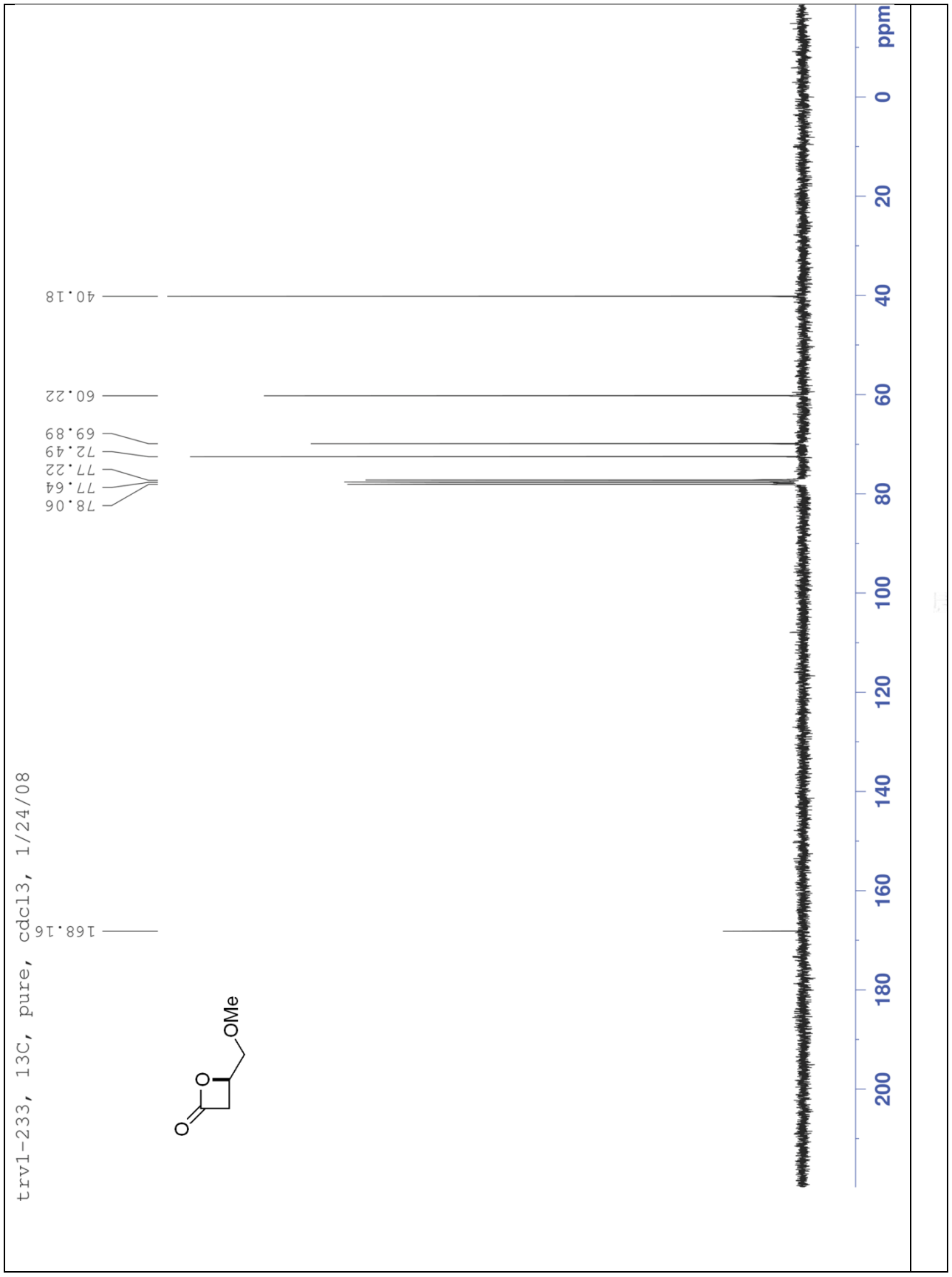
4.670
4.660
4.655
4.651
4.645
4.640
4.636
4.630
4.626
4.621
4.611
3.761
3.751
3.722
3.712
3.660
3.645
3.621
3.606
3.497
3.477
3.443
3.438
3.429
3.423
3.409
3.403
3.394
3.355
3.340
OMe
O
O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
1.54
2.86
1.17
1.27
1.19
1.00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78.06
77.64
77.22
72.49
69.89
60.22
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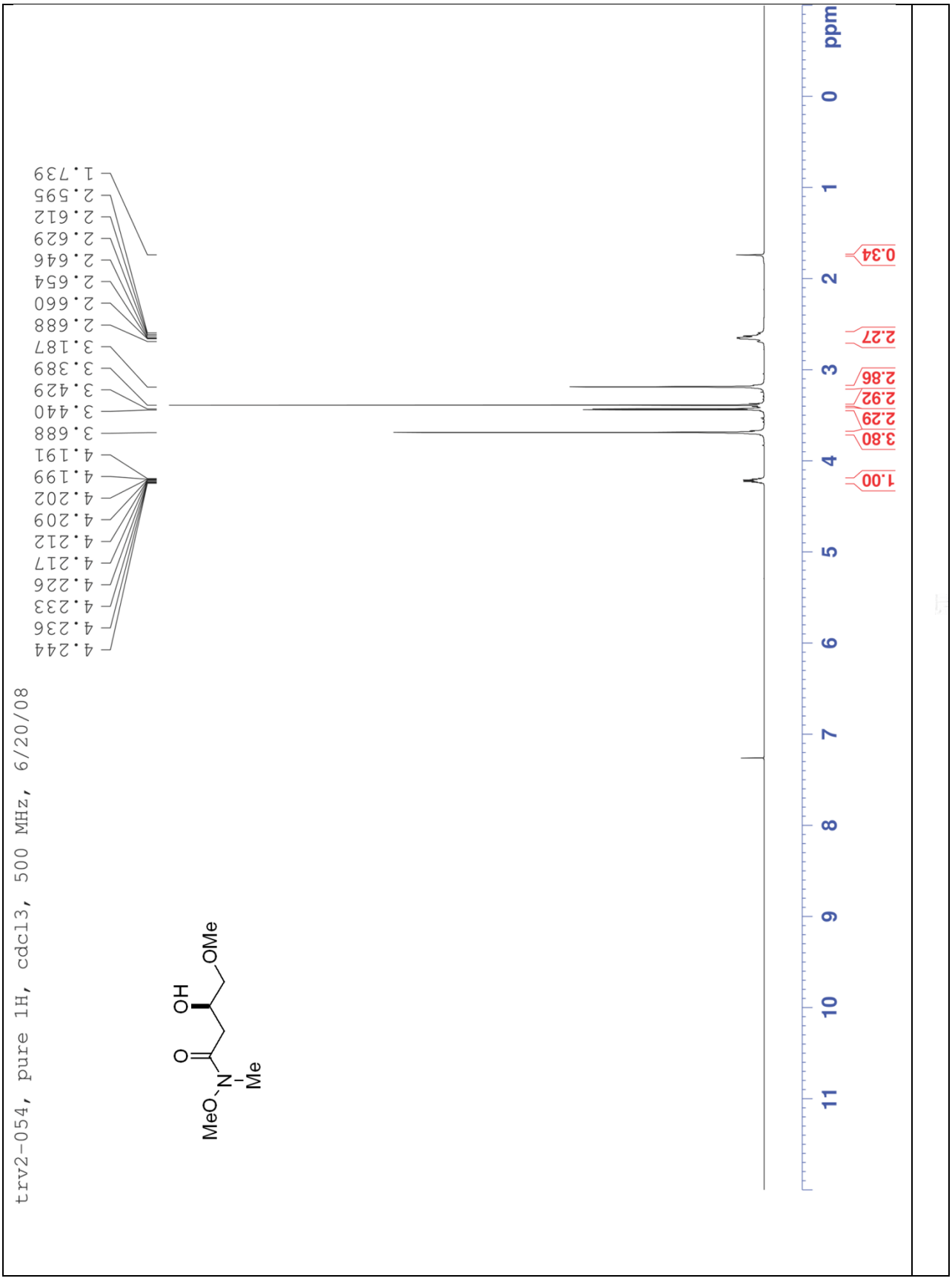
180
160
140
120
100
80
60
40
20
0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4.236
4.233
4.226
4.217
4.212
4.209
4.202
4.199
4.191
3.688
3.440
3.429
3.389
3.187
2.688
2.660
2.654
2.646
2.629
2.612
2.595
1.739
0.34
2.27
2.86
2.92
2.29
3.80
1.00
ppm
0
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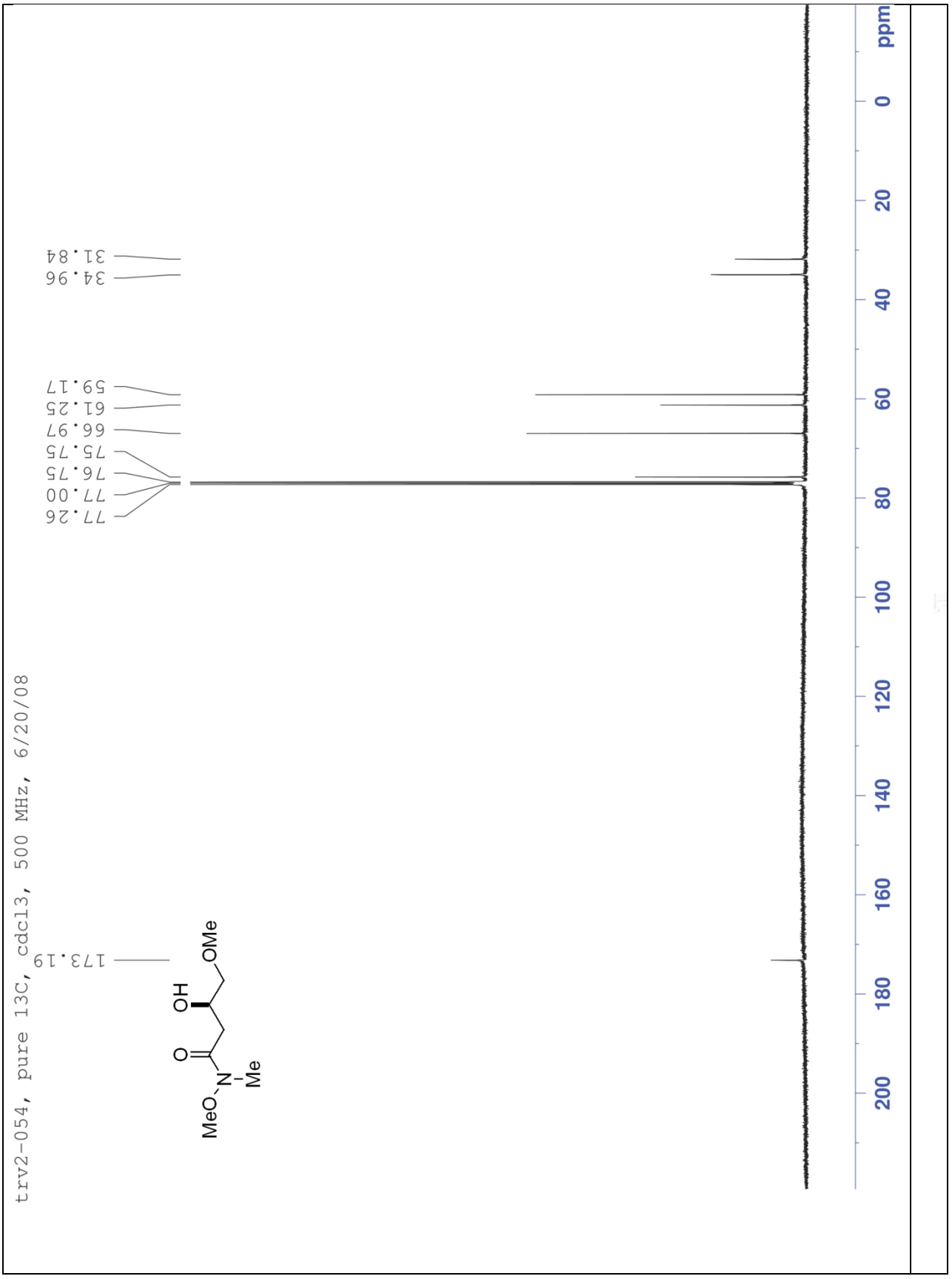
2
3
4
5
6
7
8
9
10
11
OMe
OH
O
N
Me
MeO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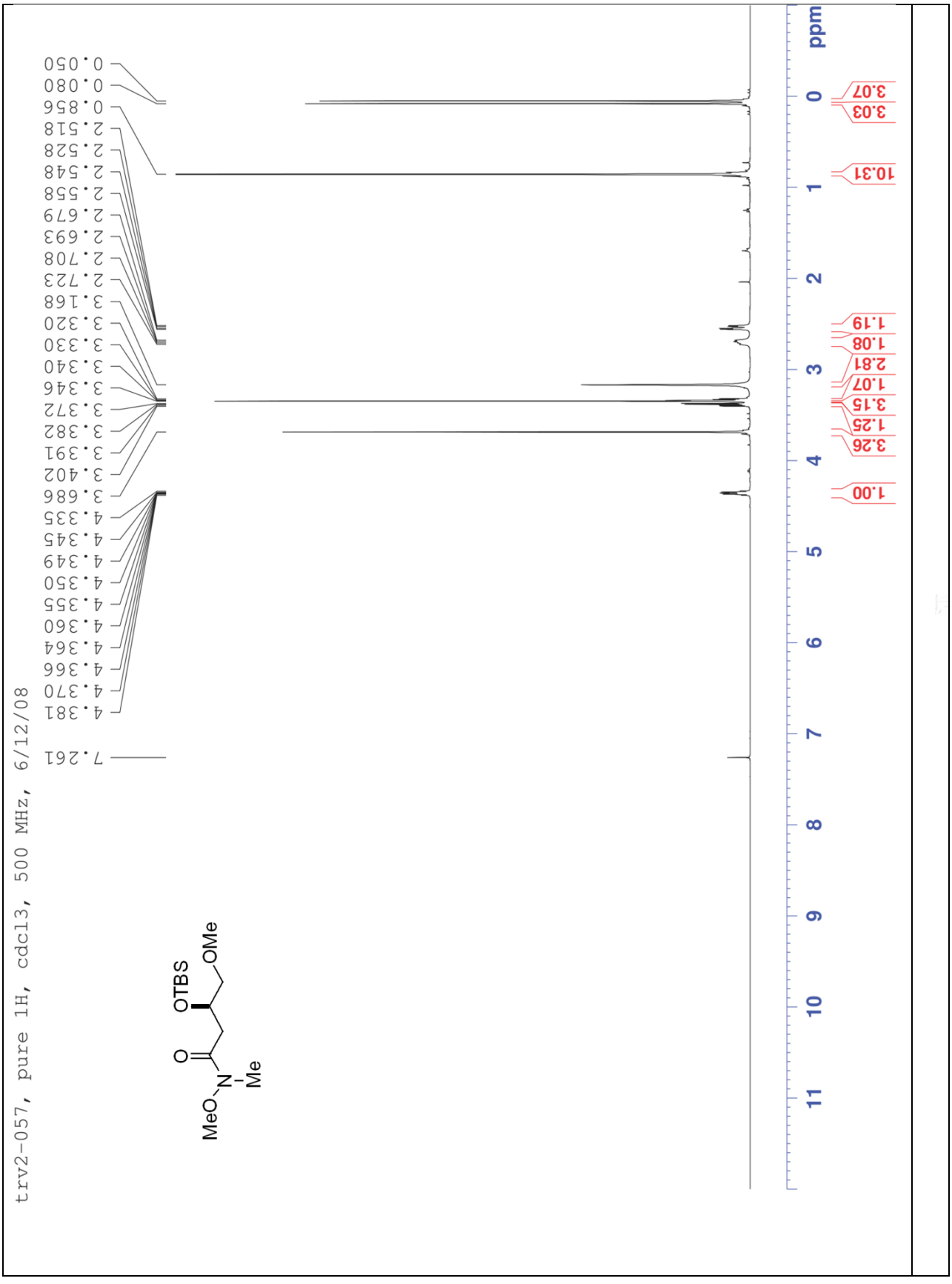
77.26
77.00
76.75
75.75
66.97
61.25
59.17
34.96
31.84
MeO
N
Me
O
OH
OMe
ppm
200
180
160
140
120
100
80
60
40
20
0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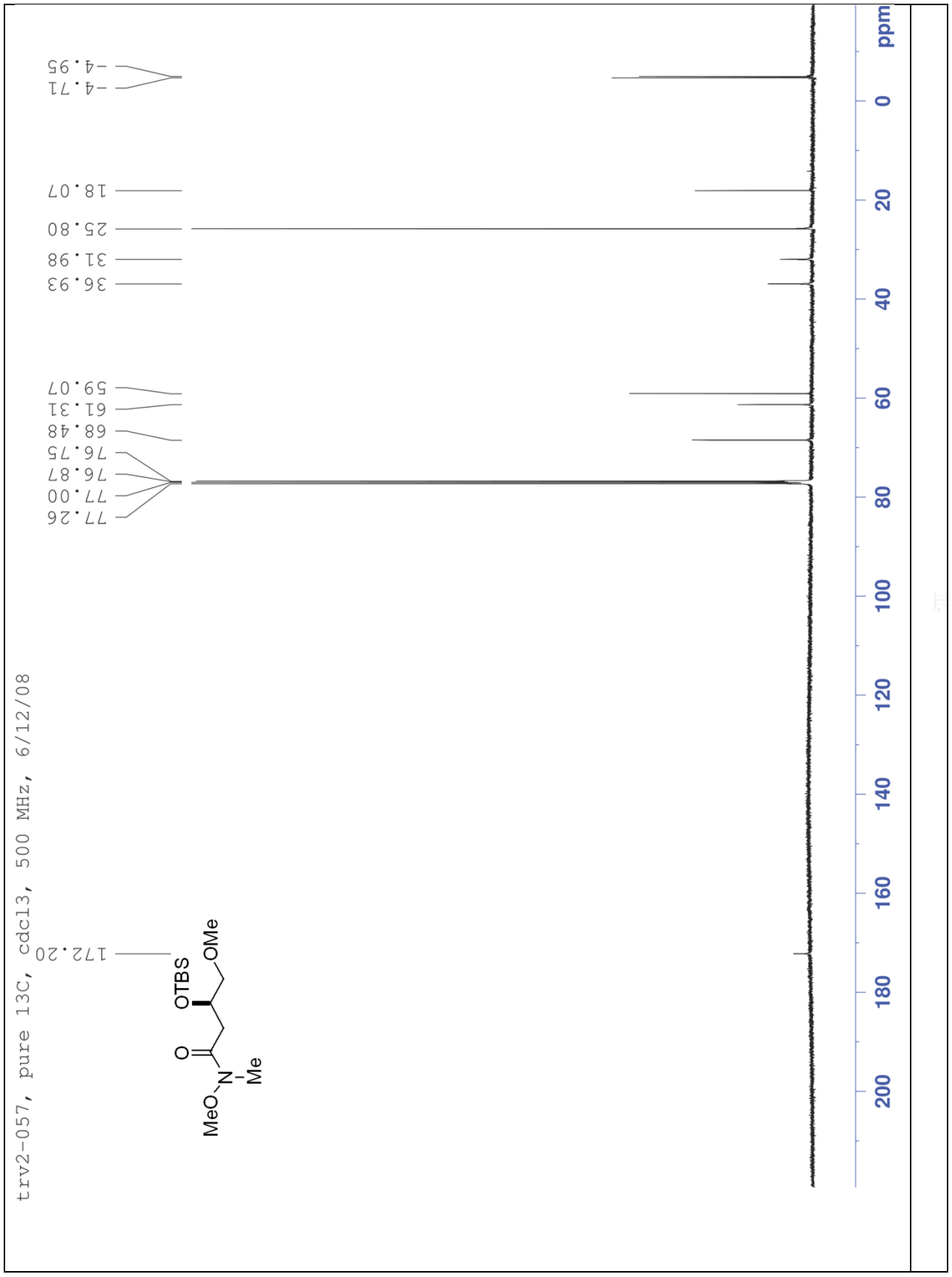
0.080
0.856
2.518
2.528
2.548
2.558
2.679
2.693
2.708
2.723
3.168
3.320
3.330
3.340
3.346
3.372
3.382
3.391
3.402
3.686
4.335
4.345
4.349
4.350
4.355
4.360
4.364
4.366
4.370
4.381
7.261
OTBS
OMe
O
MeO
N
Me
ppm
0
1
2
3
4
5
6
7
8
9
10
11
3.07
3.03
10.31
1.19
1.08
2.81
1.07
3.15
1.25
3.26
1.00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77.00
76.87
76.75
68.48
61.31
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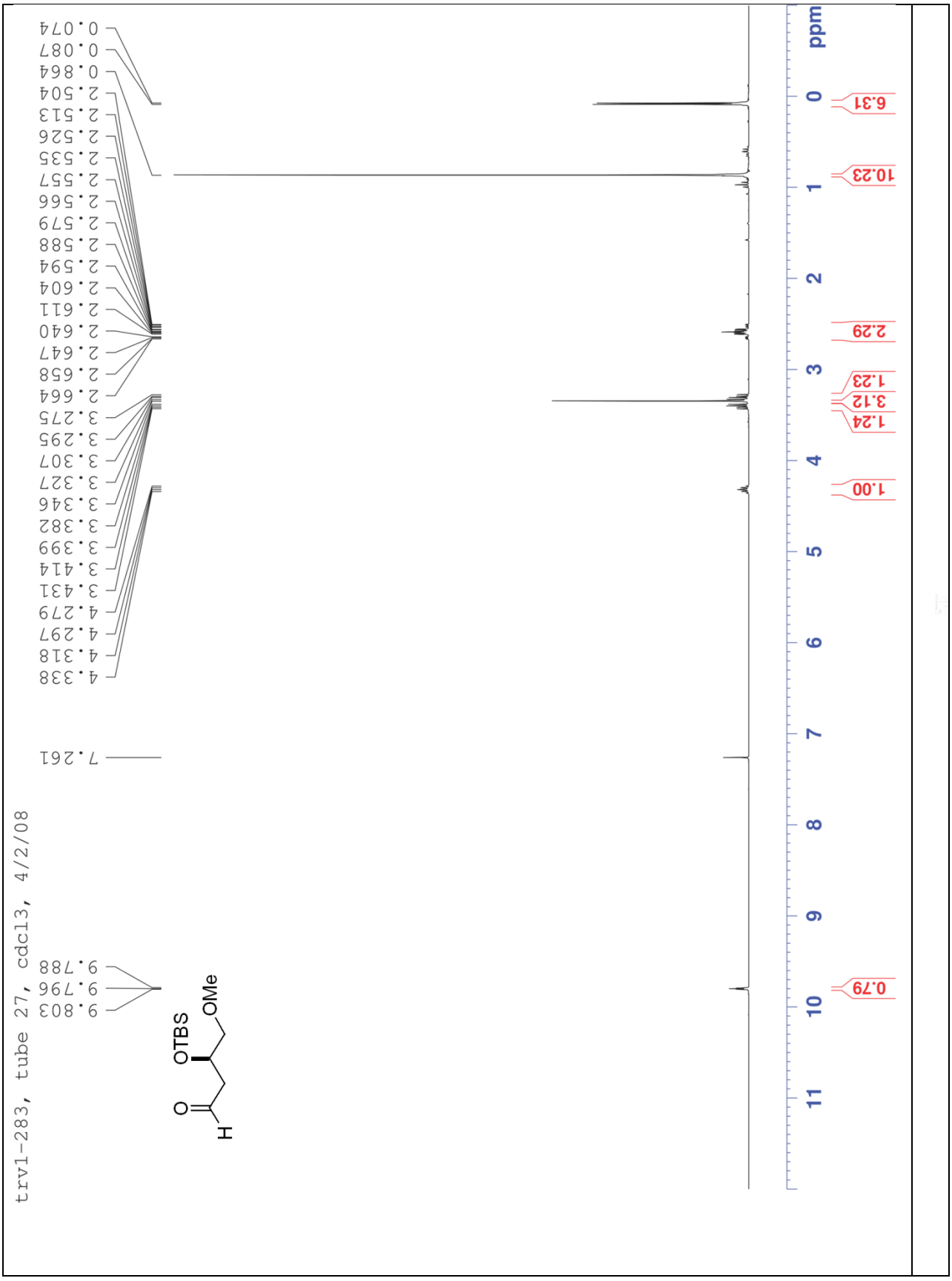
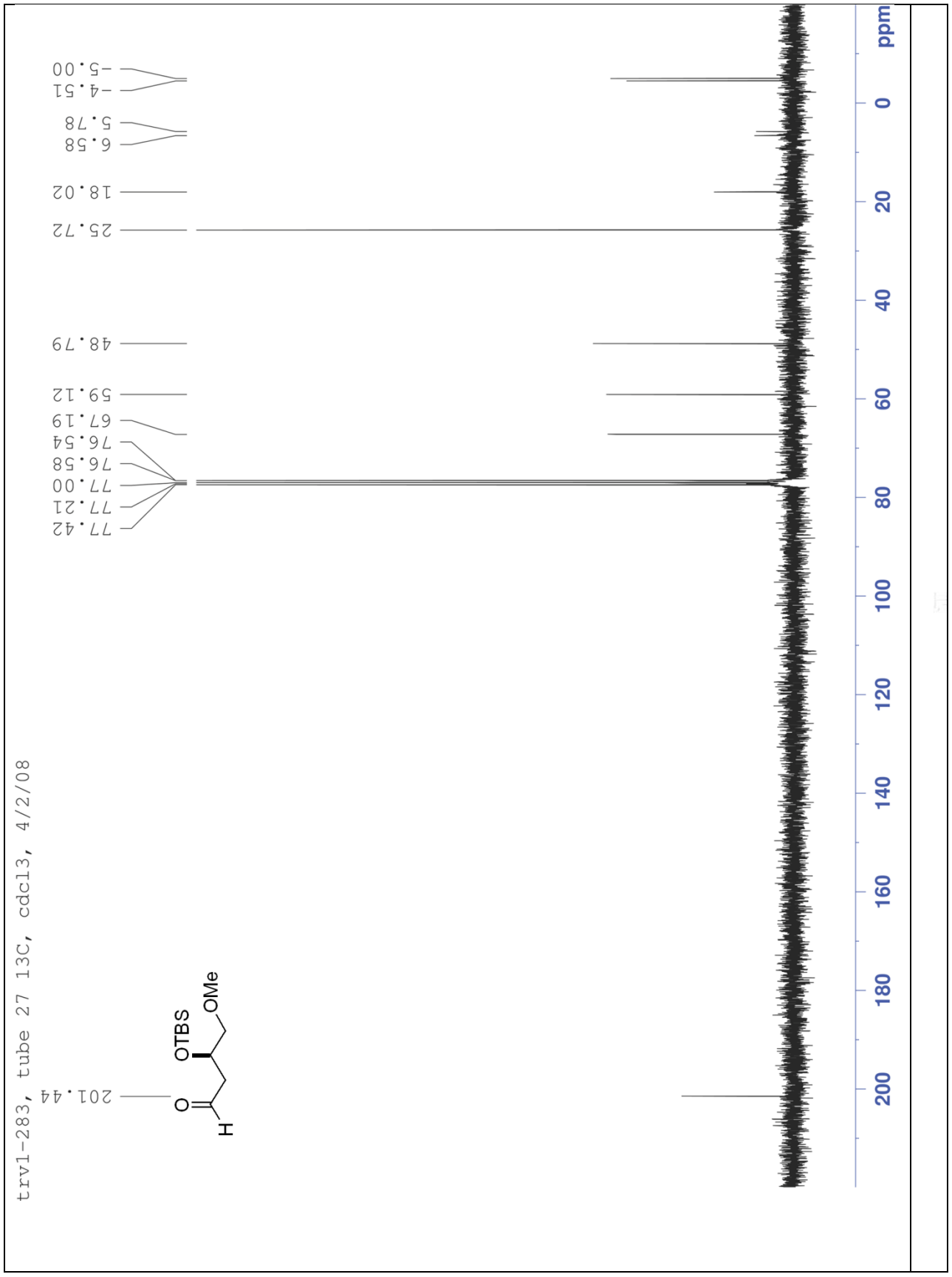
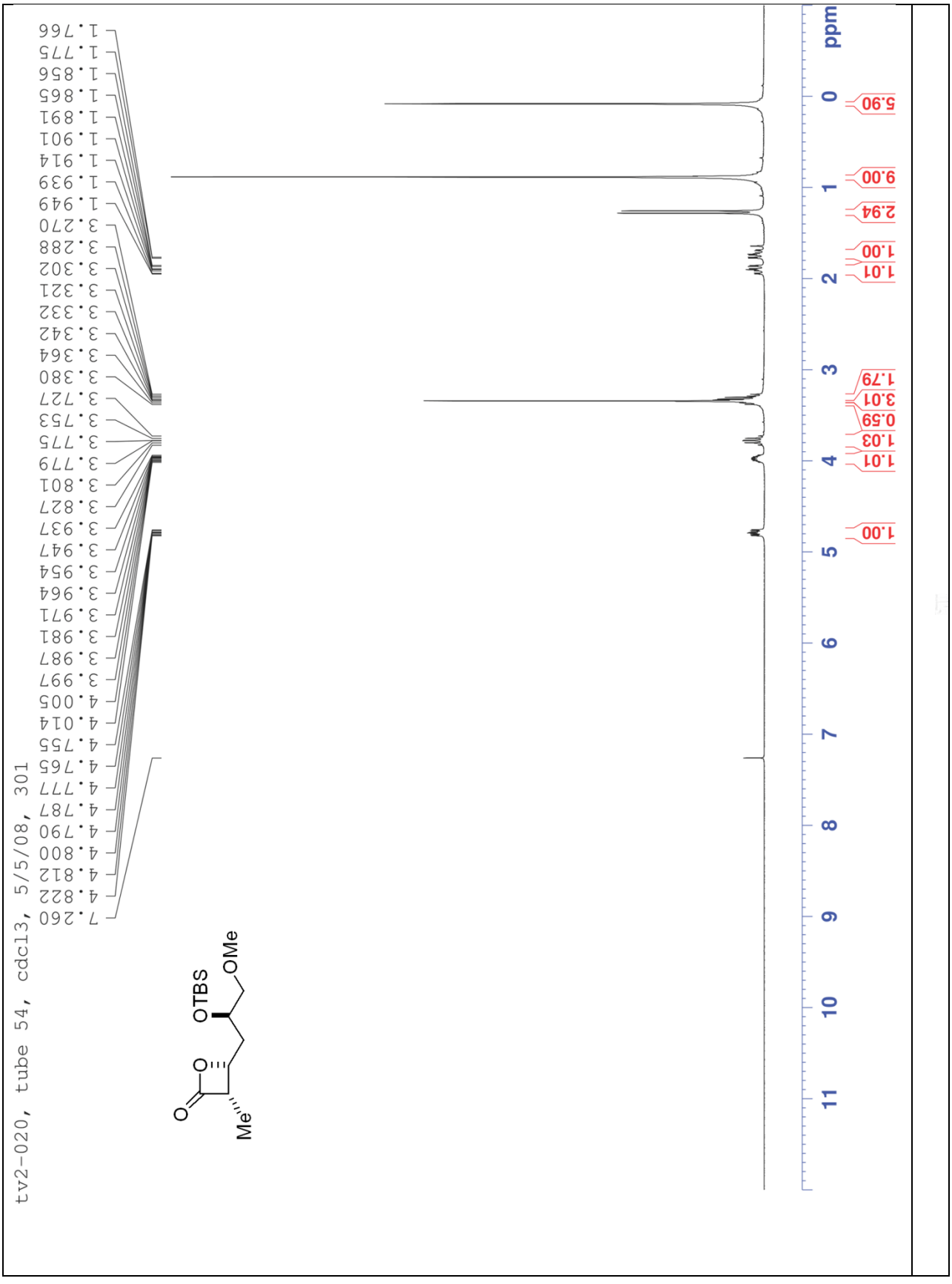
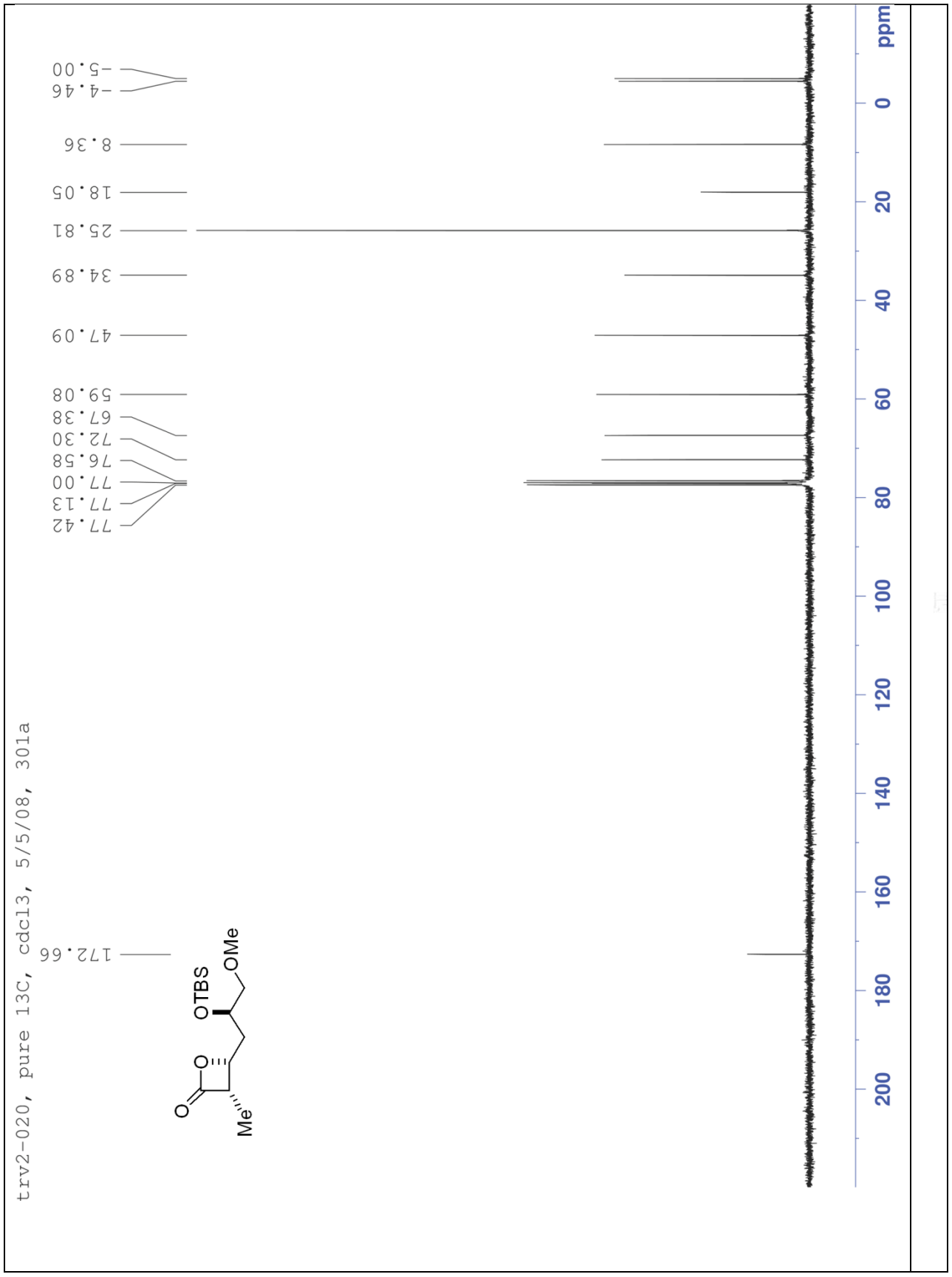
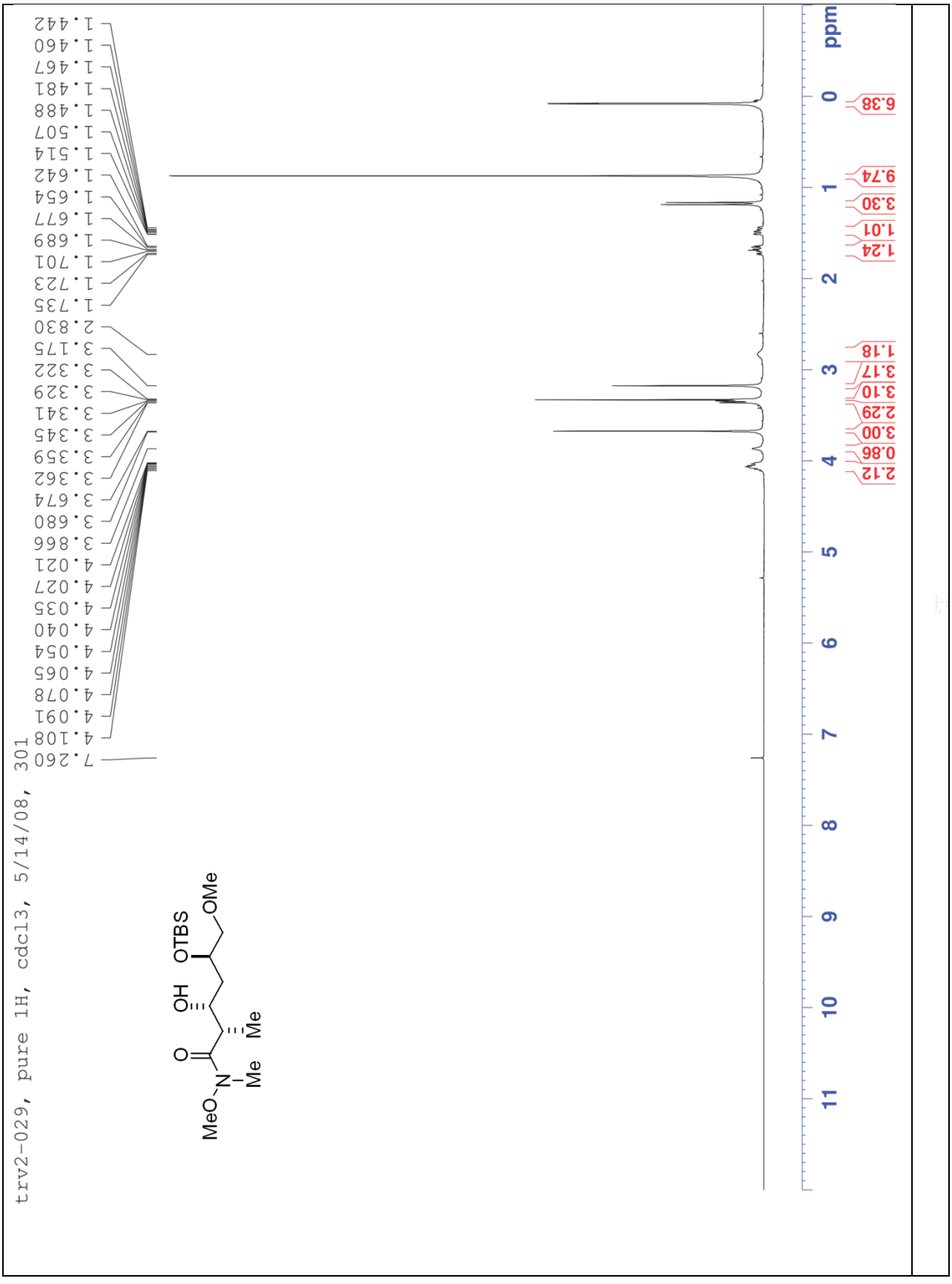
36.93
31.98
25.80
18.07
-4.71
-4.95
OTBS
OMe
O
MeO
N
Me
Me
ppm
0
20
40
60
80
100
120
140
160
180
200

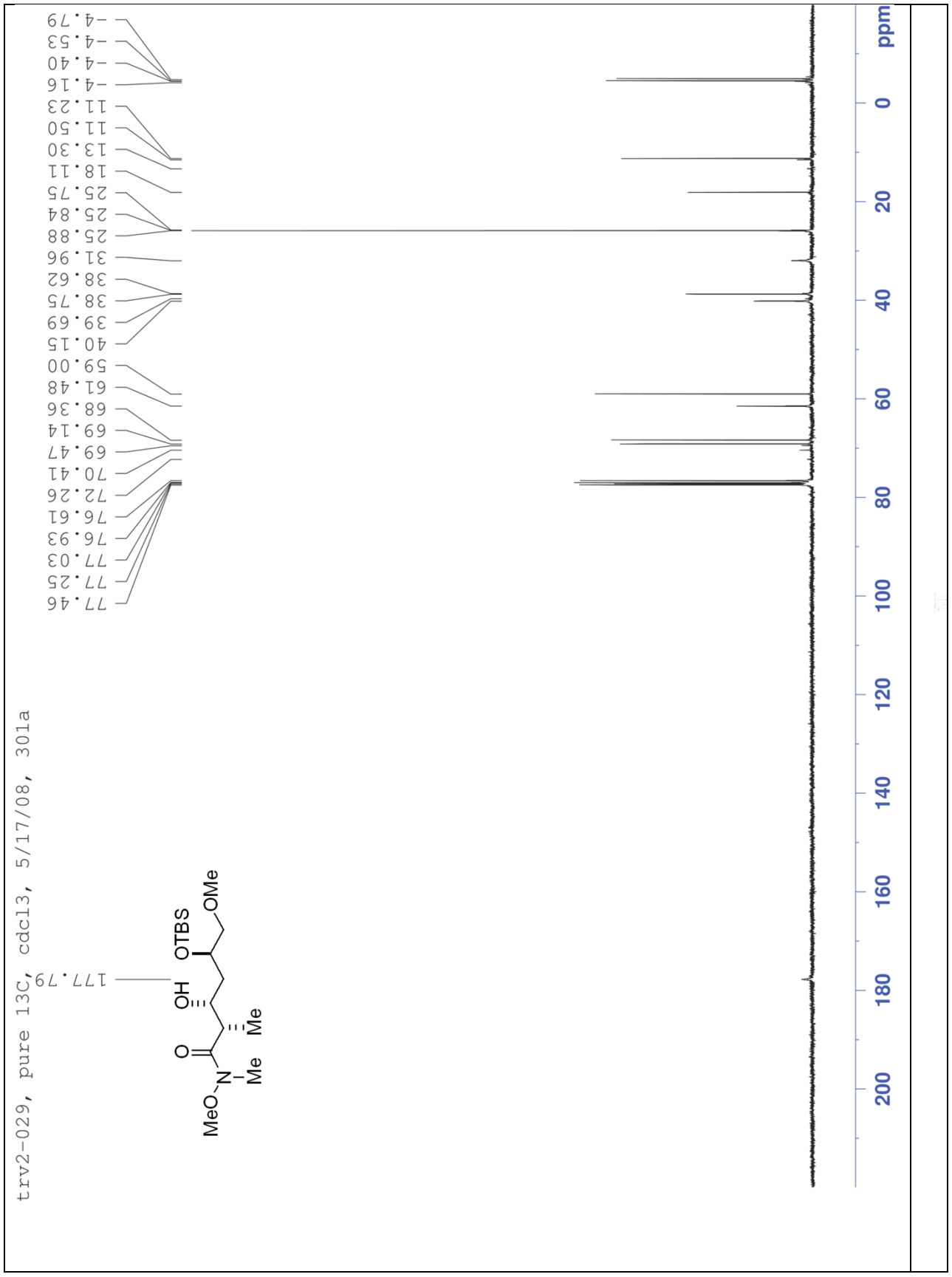

trv1-283, tube 27, cdcl3, 4/2/08
9.803
9.796
9.788
7.261
4.338
4.318
4.297
4.279
3.431
3.414
3.399
3.382
3.346
3.327
3.307
3.295
3.275
2.664
2.658
2.647
2.640
2.611
2.604
2.594
2.588
2.579
2.566
2.557
2.535
2.526
2.513
2.504
0.864
0.087
0.074
OTBS
OMe
O
H
ppm
0.79
10.23
6.31
1.00
2.29
1.23
3.12
1.24

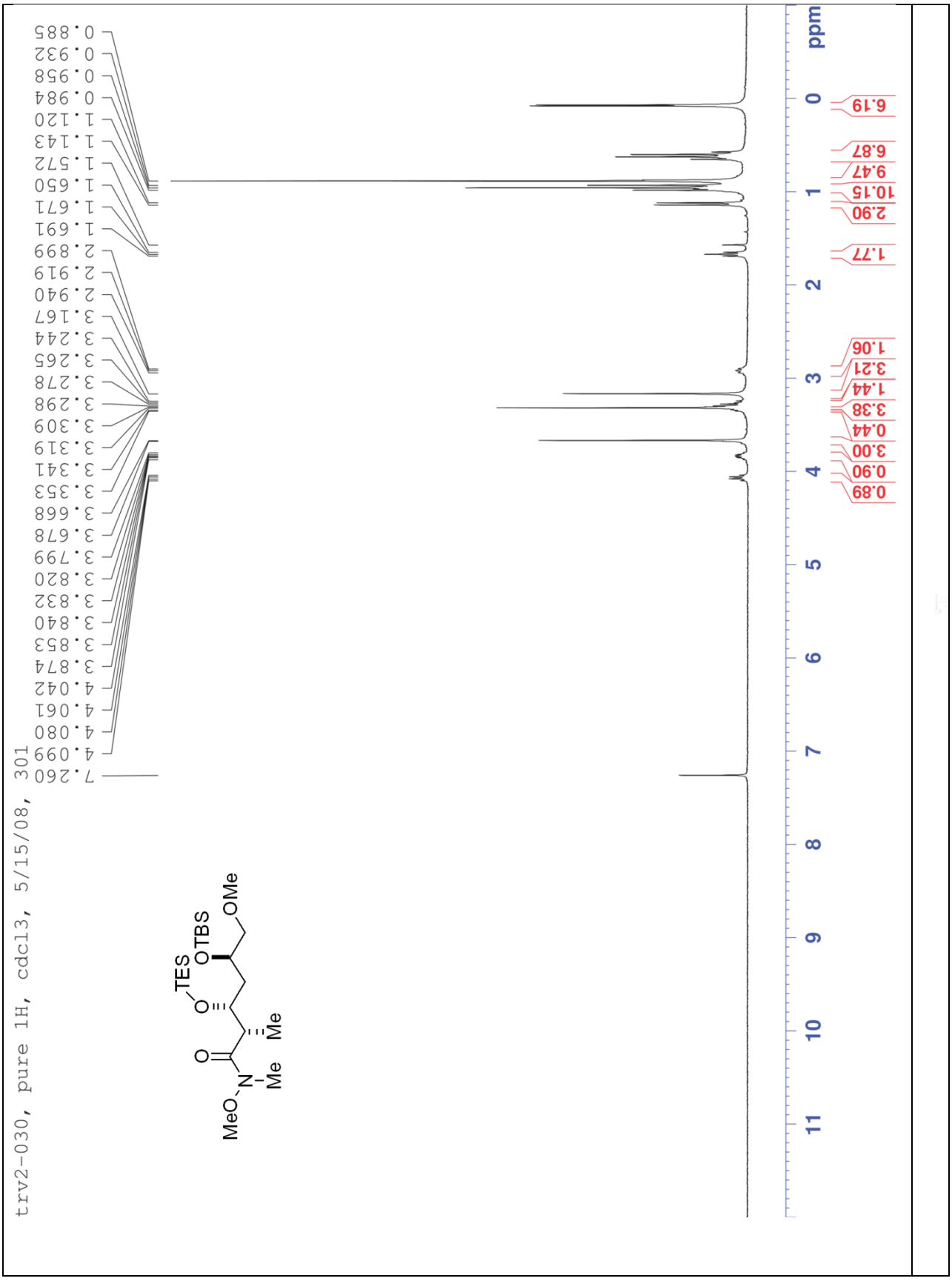

trv1-283, tube 27 13C, cdcl3, 4/2/08
201.44
77.42
77.21
77.00
76.58
76.54
67.19
59.12
48.79
25.72
18.02
6.58
5.78
-4.51
-5.00
OTBS
OMe
O
H
ppm
0
20
40
60
80
100
120
140
160
180
200

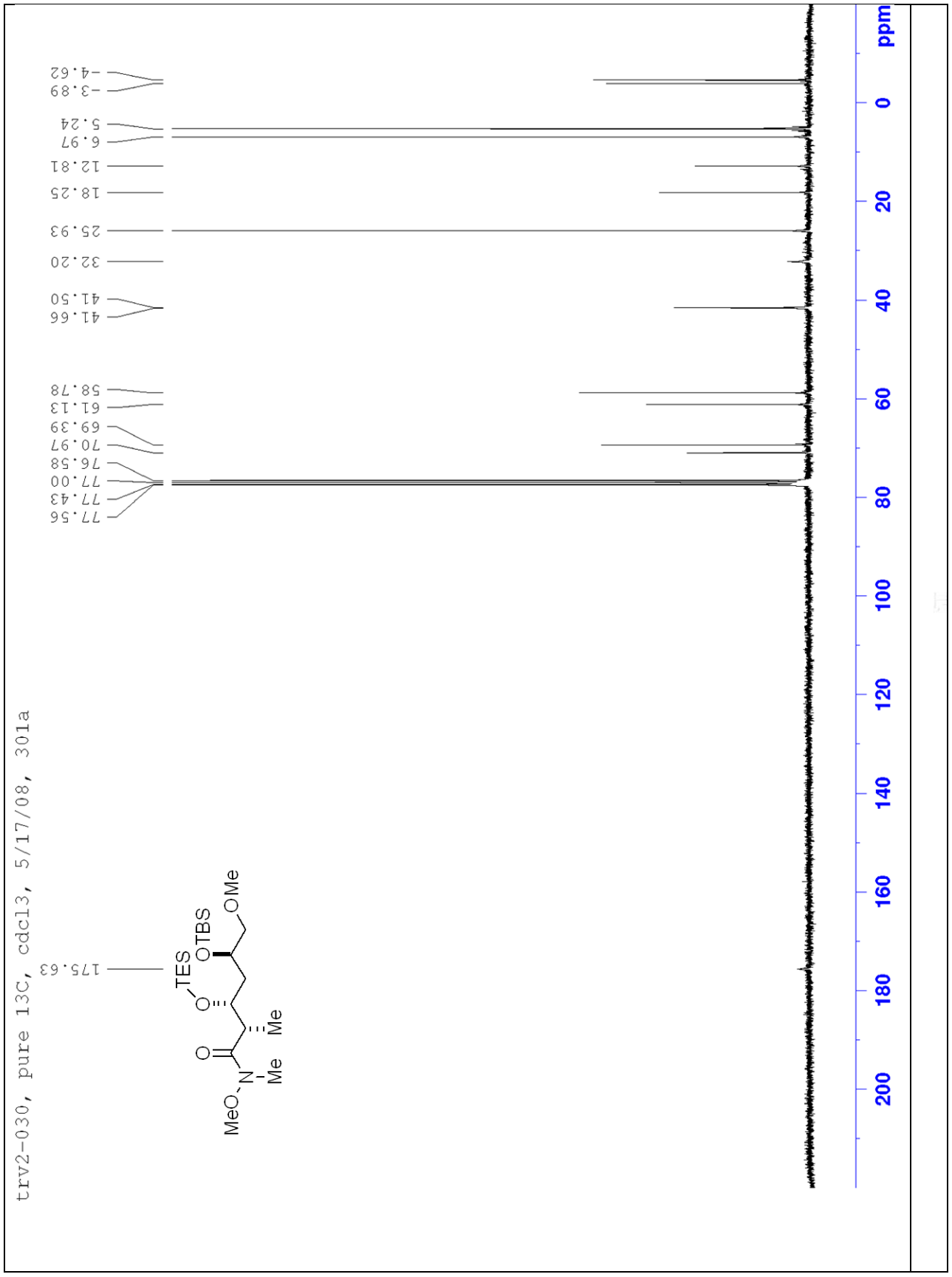

tv2-020, tube 54, cdcl3, 5/5/08, 301
7.260
4.822
4.812
4.800
4.790
4.787
4.777
4.765
4.755
4.014
4.005
3.997
3.987
3.981
3.971
3.964
3.954
3.947
3.937
3.827
3.801
3.779
3.775
3.753
3.727
3.380
3.364
3.342
3.332
3.321
3.302
3.288
3.270
1.949
1.939
1.914
1.901
1.891
1.865
1.856
1.775
1.766
OTBS
OMe
O
O
Me
ppm
0
1
2
3
4
5
6
7
8
9
10
11
5.90
9.00
2.94
1.01
1.00
1.79
3.01
0.59
1.03
1.01
1.00

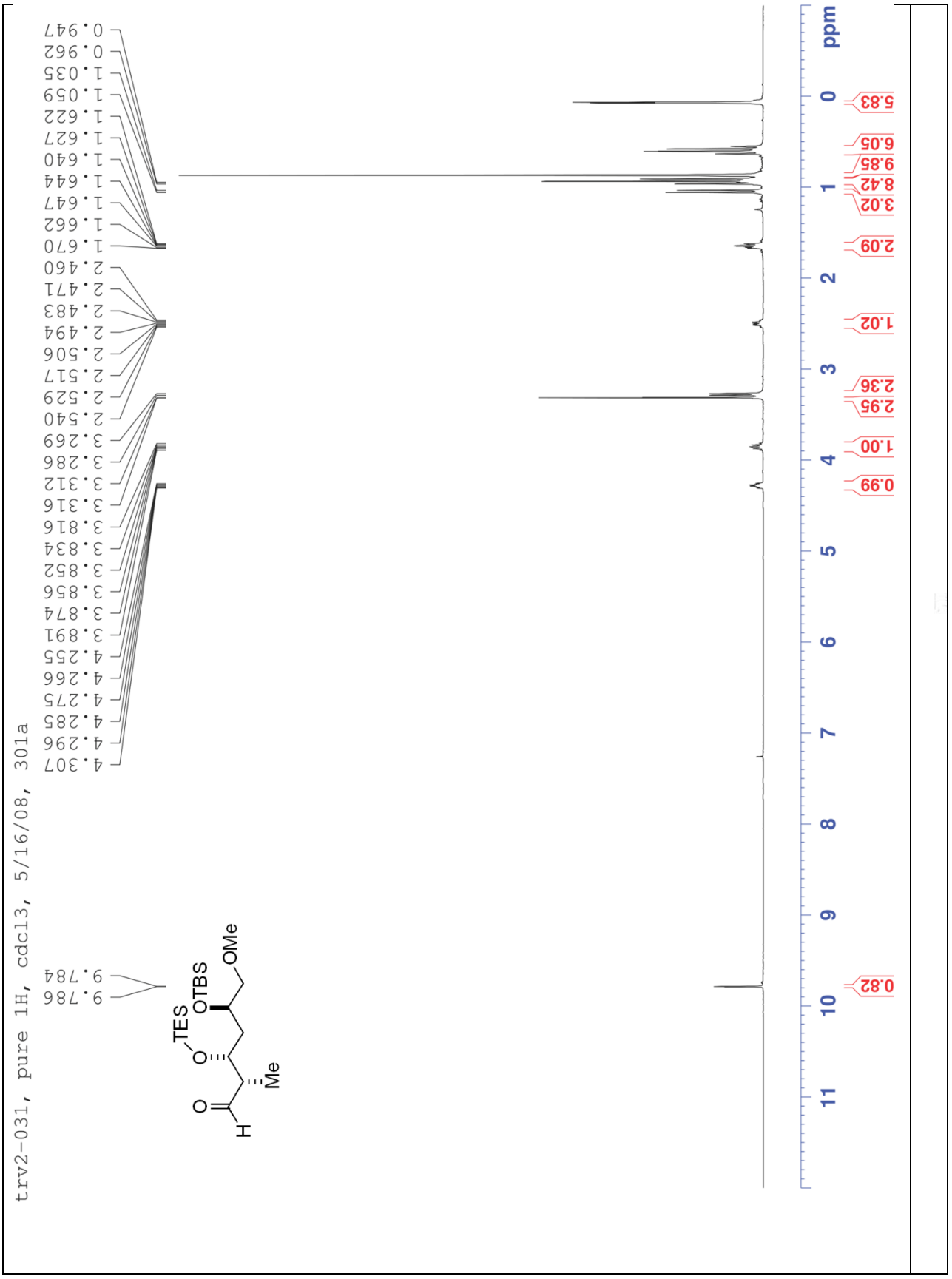

trv2-020, pure 13C, cdcl3, 5/5/08, 301a
172.66
77.42
77.13
77.00
76.58
72.30
67.38
59.08
47.09
34.89
25.81
18.05
8.36
-4.46
-5.00
OTBS
OMe
Me
O
O
ppm
200
180
160
140
120
100
80
60
40
20
0

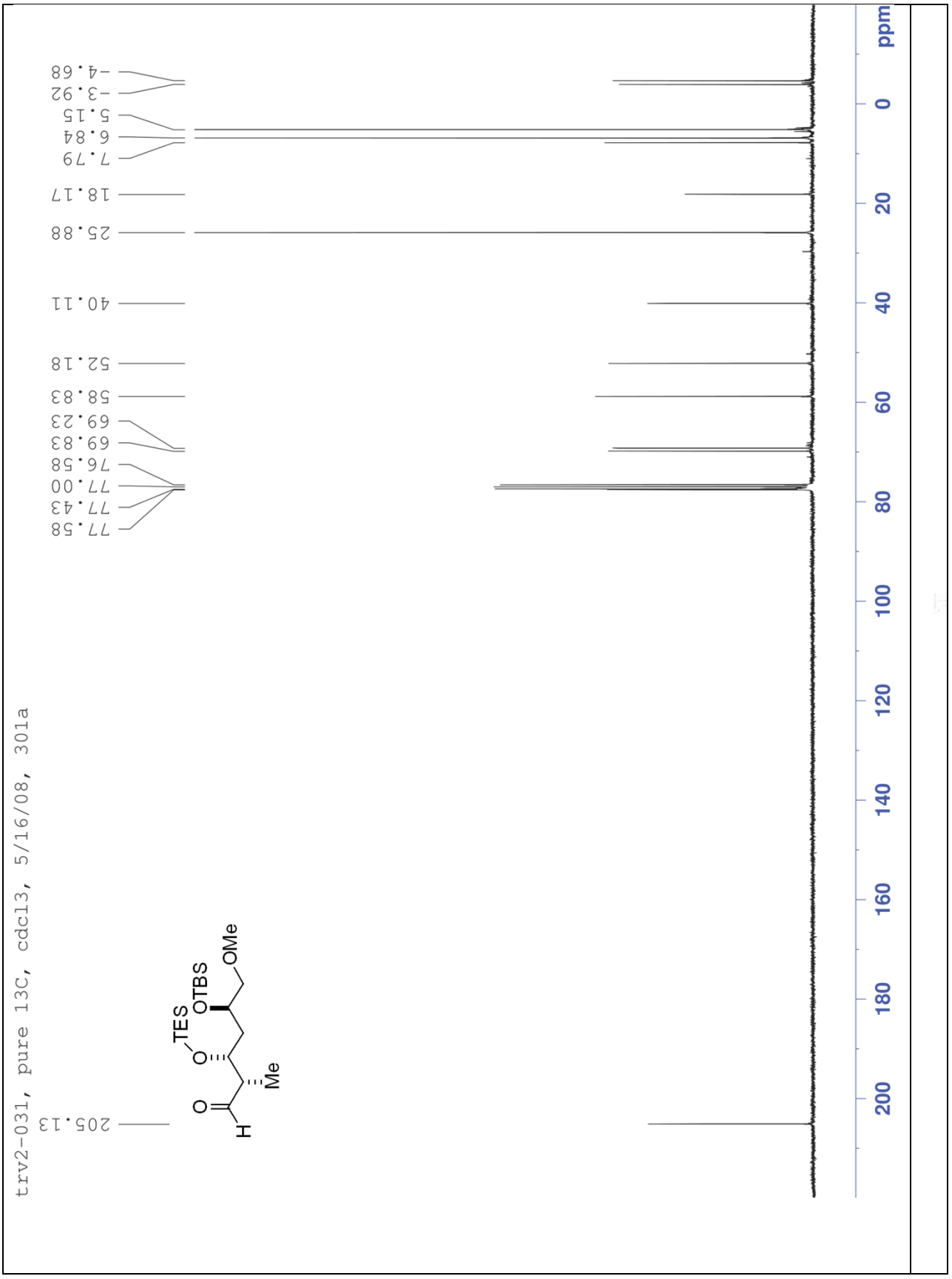

trv2-029, pure 1H, cdcl3, 5/14/08, 301
7.260
4.108
4.091
4.078
4.065
4.054
4.040
4.035
4.027
4.021
3.866
3.680
3.674
3.362
3.359
3.345
3.341
3.329
3.322
3.175
2.830
1.735
1.723
1.701
1.689
1.677
1.654
1.642
1.514
1.507
1.488
1.481
1.467
1.460
1.442
OH
OTBS
OMe
O
N
MeO
Me
Me
Me
ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.38
9.74
3.30
1.01
1.24
1.18
3.17
3.10
2.29
3.00
0.86
2.12

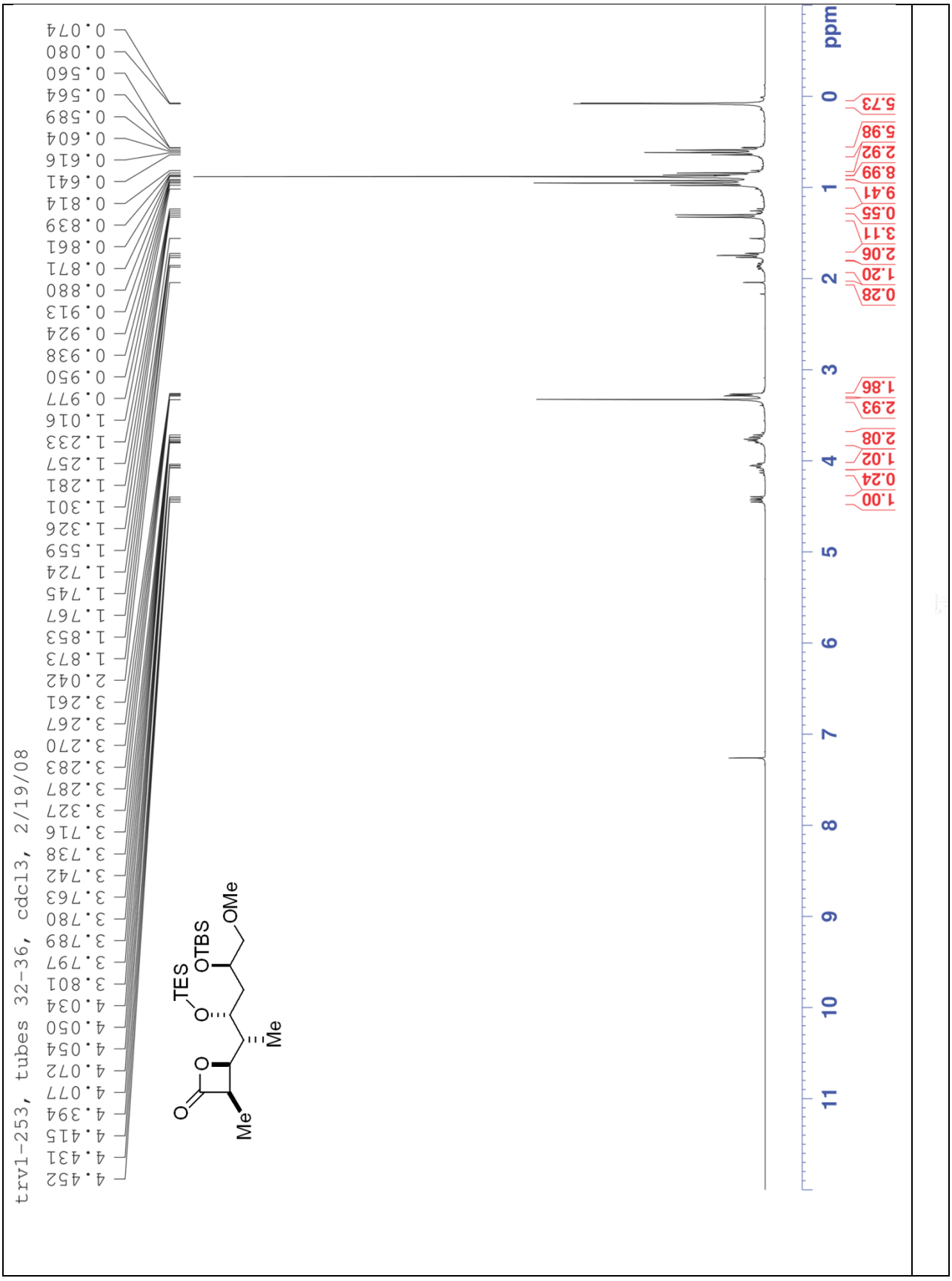

trv2-029, pure 13C, cdcl3, 5/17/08, 301a
177.79
77.46
77.25
77.03
76.93
76.61
72.26
70.41
69.47
69.14
68.36
61.48
59.00
40.15
39.69
38.75
38.62
31.96
25.88
25.84
25.75
18.11
13.30
11.50
11.23
-4.16
-4.40
-4.53
-4.79
O
OH
OTBS
OMe
MeO
N
Me
Me
Me
ppm
200
180
160
140
120
100
80
60
40
20
0

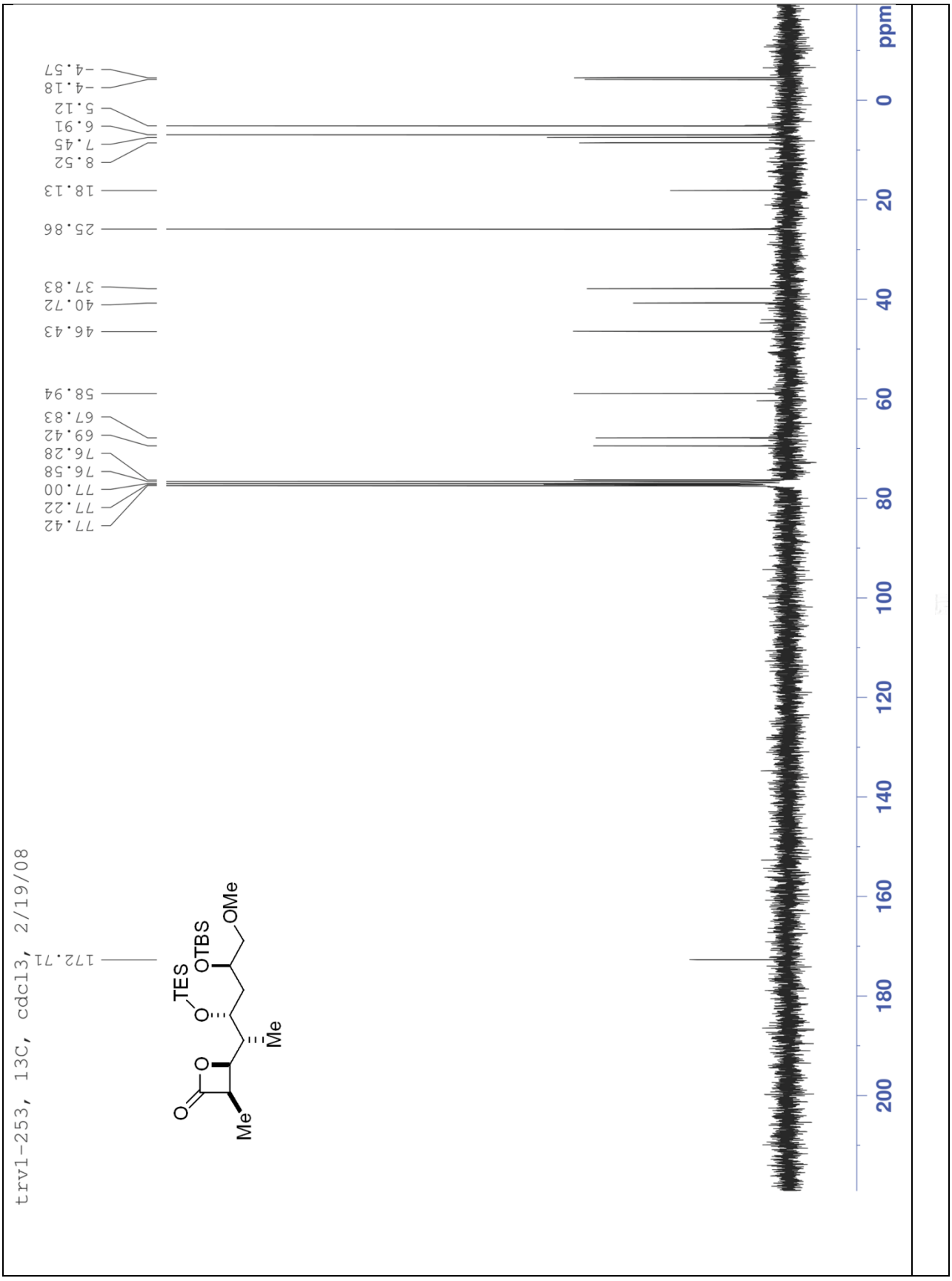

trv2-030, pure 1H, cdcl3, 5/15/08, 301
7.260
4.099
4.080
4.061
4.042
3.874
3.853
3.840
3.832
3.820
3.799
3.678
3.668
3.353
3.341
3.319
3.309
3.298
3.278
3.265
3.244
3.167
2.940
2.919
2.899
1.691
1.671
1.650
1.572
1.143
1.120
0.984
0.958
0.932
0.885
TES
OTBS
OMe
O
O
N
MeO
Me
Me
ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.19
6.87
9.47
10.15
2.90
1.77
1.06
3.21
1.44
3.38
0.44
3.00
0.90
0.89

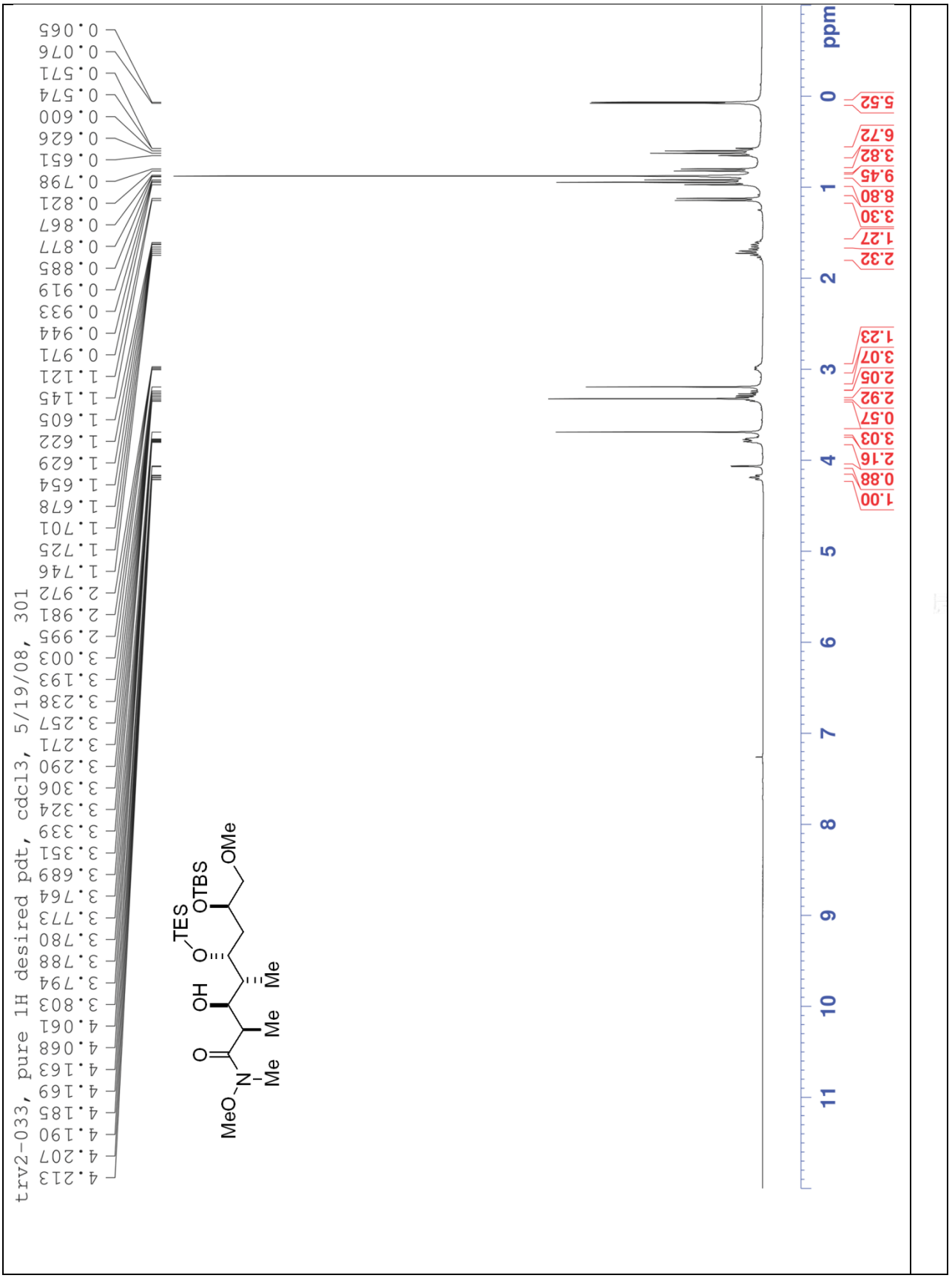

trv2-030, pure 13C, cdcl3, 5/17/08, 301a
175.63
77.56
77.43
77.00
76.58
70.97
69.39
61.13
58.78
41.66
41.50
32.20
25.93
18.25
12.81
6.97
5.24
-3.89
-4.62
TES
OTBS
OMe
MeO
N
Me
Me
Me
ppm
0
20
40
60
80
100
120
140
160
180
200

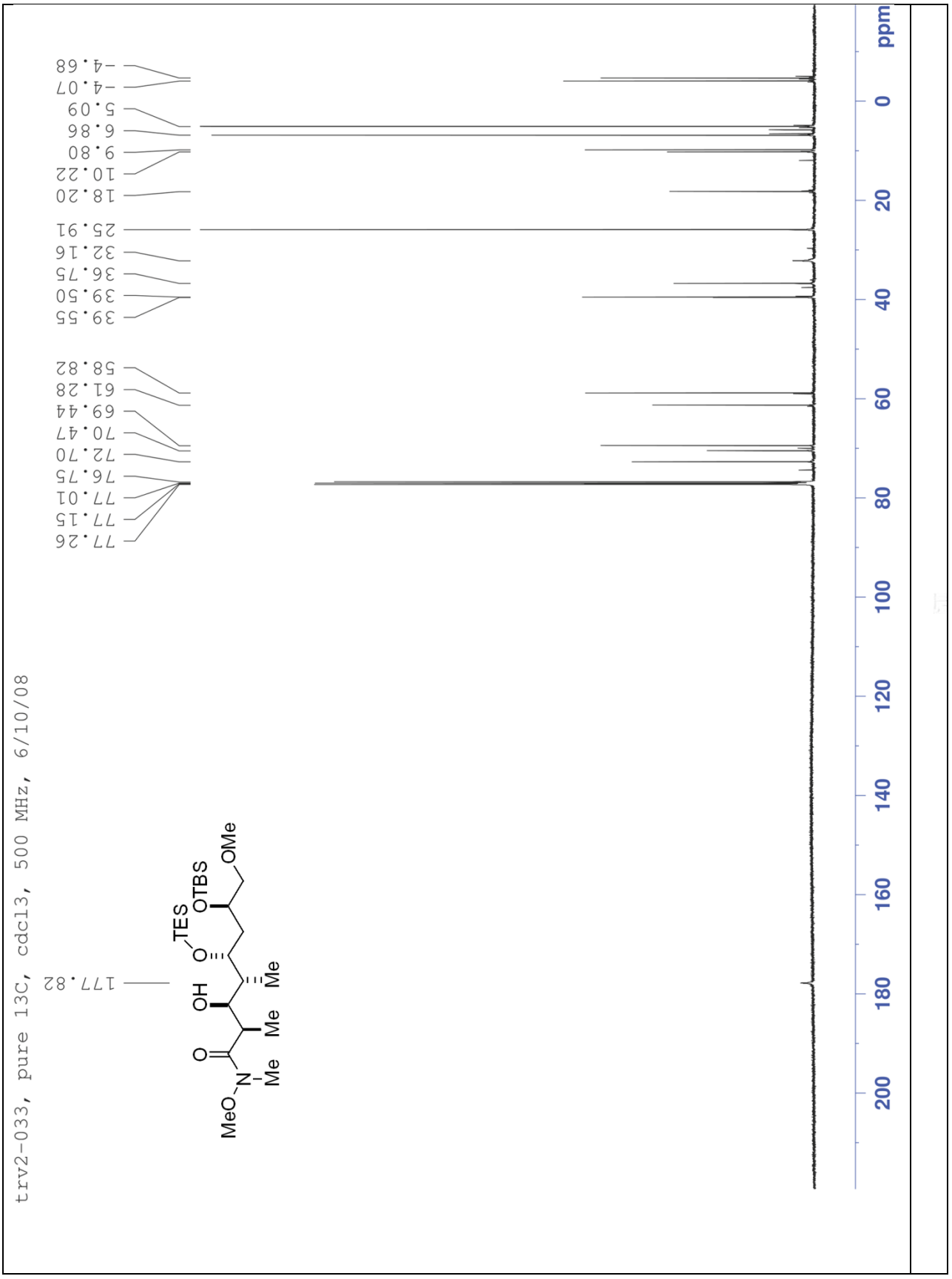

trv2-031, pure 1H, cdcl3, 5/16/08, 301a
TES
OTBS
OMe
Me
O
H
ppm
0.947
0.962
1.035
1.059
1.622
1.627
1.640
1.644
1.647
1.662
1.670
2.460
2.471
2.483
2.494
2.506
2.517
2.529
2.540
3.269
3.286
3.312
3.316
3.816
3.834
3.852
3.856
3.874
3.891
4.255
4.266
4.275
4.285
4.296
4.307
9.784
9.786
5.83
6.05
9.85
8.42
3.02
2.09
1.02
2.36
2.95
1.00
0.99
0.82

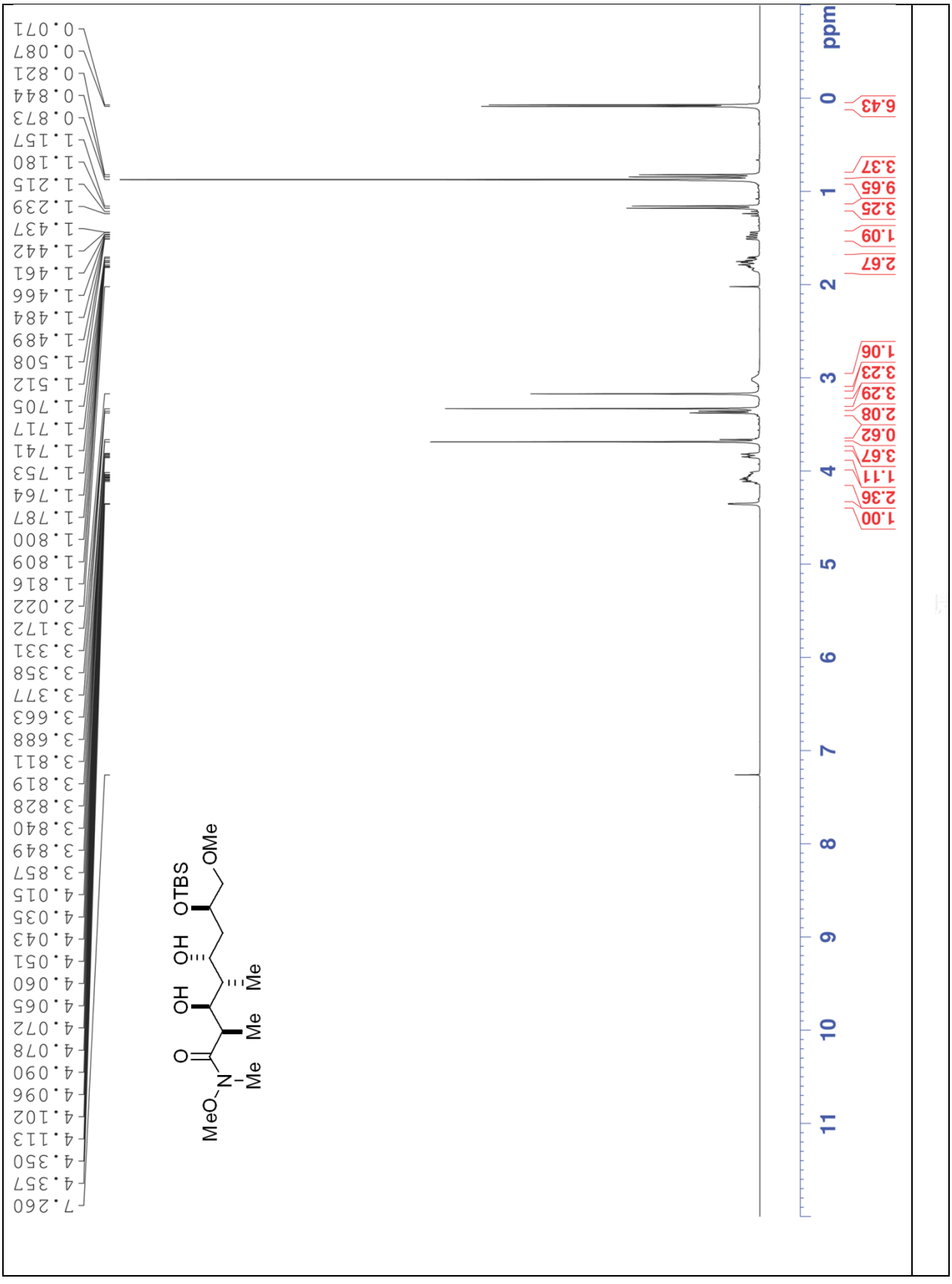

trv2-031, pure 13C, cdcl3, 5/16/08, 301a
205.13
77.58
77.43
77.00
76.58
69.83
69.23
58.83
52.18
40.11
25.88
18.17
7.79
6.84
5.15
-3.92
-4.68
TES
OTBS
OMe
Me
O
H
ppm
0
20
40
60
80
100
120
140
160
180
200

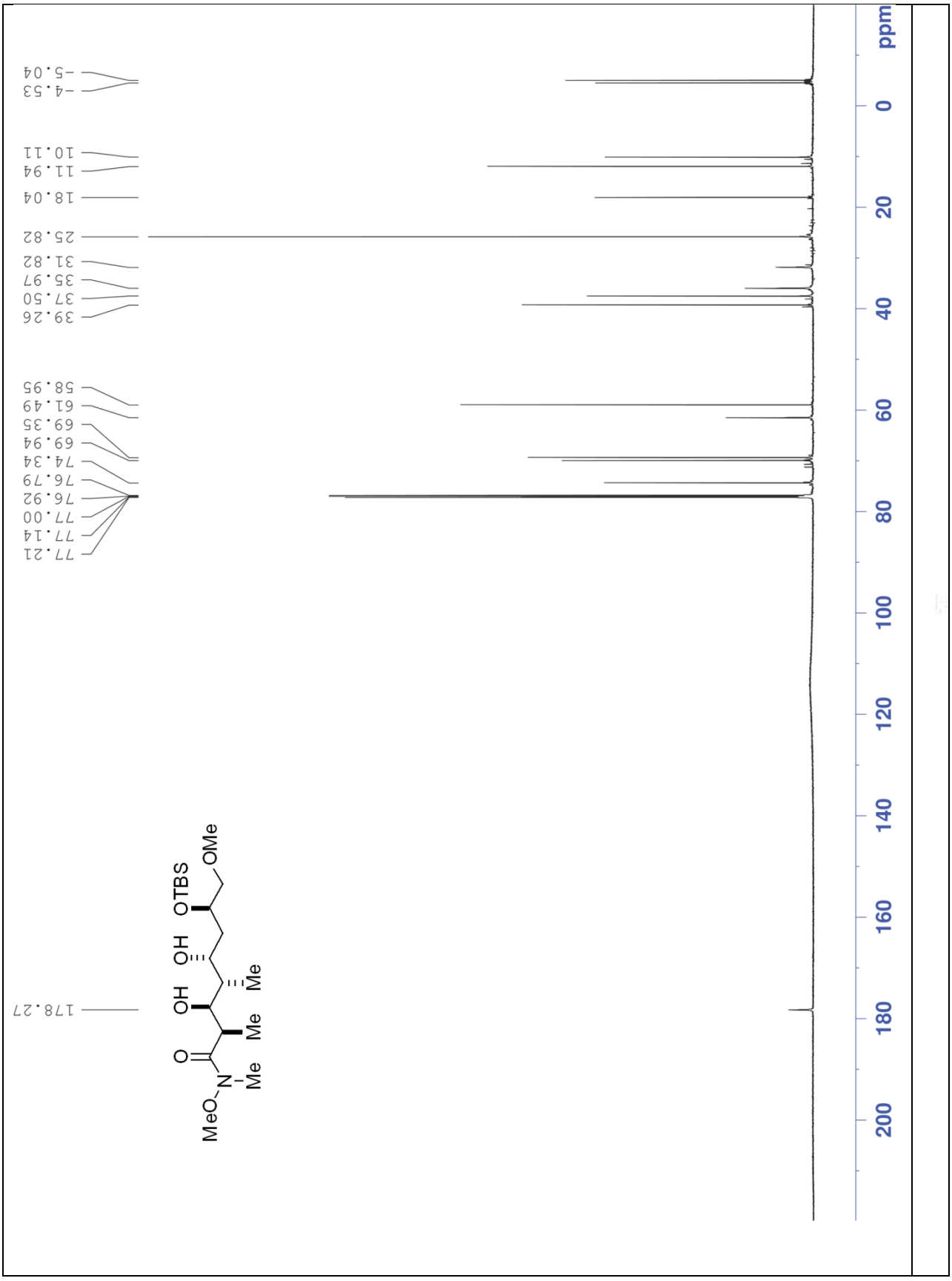

trv1-253, tubes 32-36, cdcl3, 2/19/08
0.074
0.080
0.560
0.564
0.589
0.604
0.616
0.641
0.814
0.839
0.861
0.871
0.880
0.913
0.924
0.938
0.950
0.977
1.016
1.233
1.257
1.281
1.301
1.326
1.559
1.724
1.745
1.767
1.853
1.873
2.042
3.261
3.267
3.270
3.283
3.287
3.327
3.716
3.738
3.742
3.763
3.780
3.789
3.797
3.801
4.034
4.050
4.054
4.072
4.077
4.394
4.415
4.431
4.452
TES
OTBS
OMe
Me
Me
O
O
O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
5.73
5.98
2.92
8.99
9.41
0.55
3.11
2.06
1.20
0.28
1.86
2.93
2.08
1.02
0.24
1.00

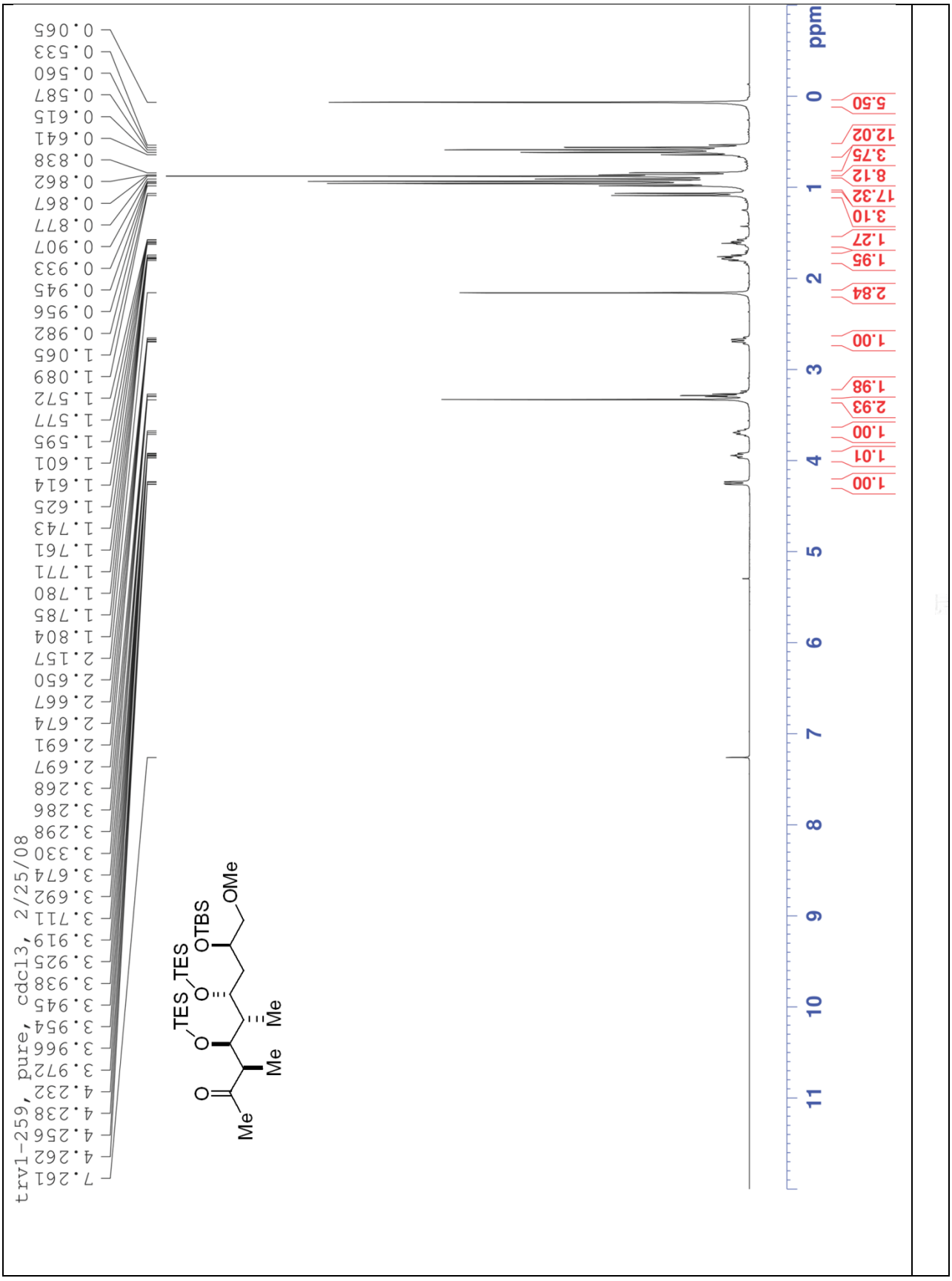

trv1-253, 13C, cdcl3, 2/19/08
-4.57
-4.18
5.12
6.91
7.45
8.52
18.13
25.86
37.83
40.72
46.43
58.94
67.83
69.42
76.28
76.58
77.00
77.22
77.42
172.71
TES
OTBS
OMe
Me
Me
O
O
O
ppm
0
20
40
60
80
100
120
140
160
180
200

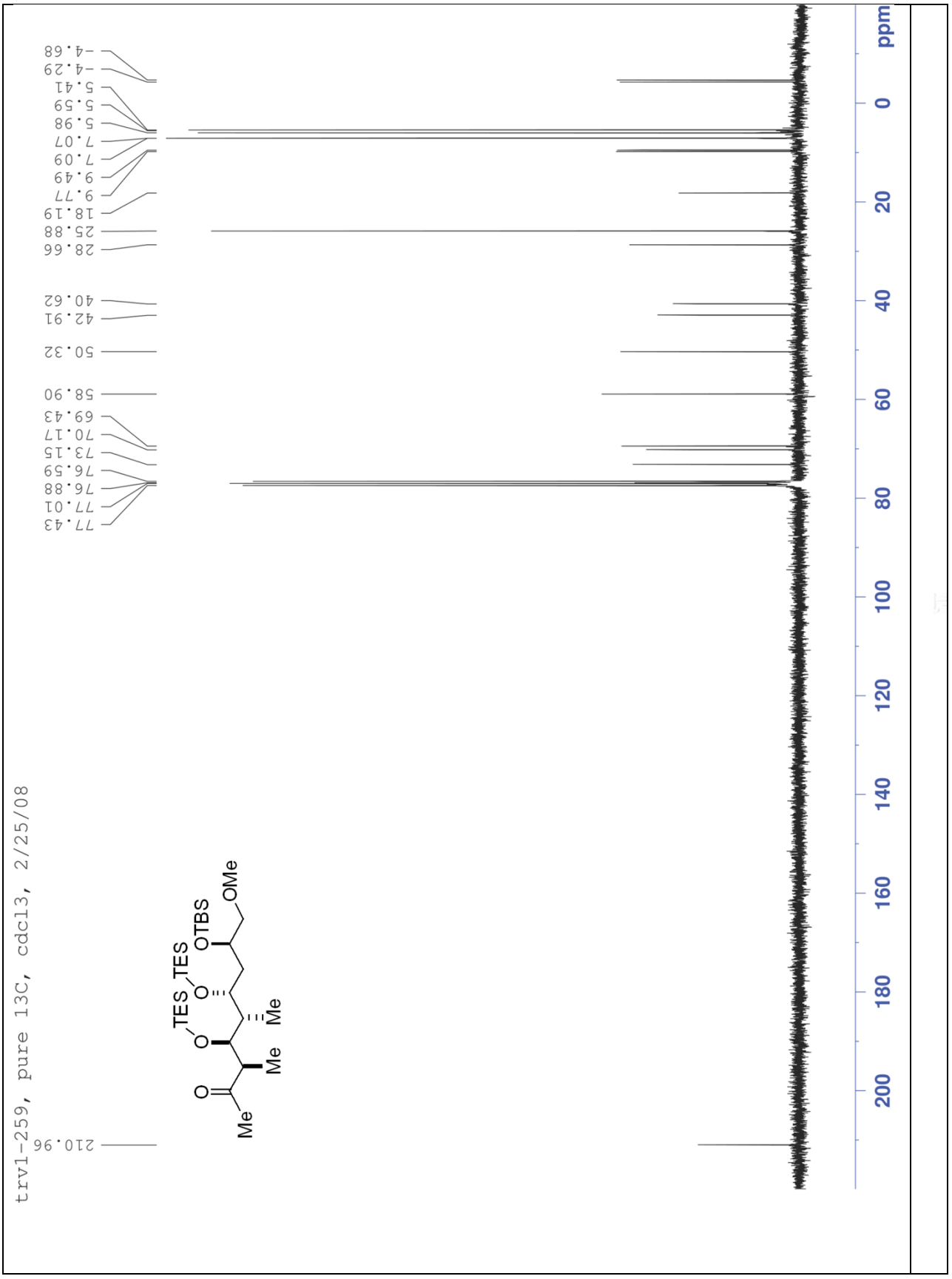

trv2-033, pure 1H desired pdt, cdcl3, 5/19/08, 301
0.065
0.076
0.571
0.574
0.600
0.626
0.651
0.798
0.821
0.867
0.877
0.885
0.919
0.933
0.944
0.971
1.121
1.145
1.605
1.622
1.629
1.654
1.678
1.701
1.725
1.746
2.972
2.981
2.995
3.003
3.193
3.238
3.257
3.271
3.290
3.306
3.324
3.339
3.351
3.689
3.764
3.773
3.780
3.788
3.794
3.803
4.061
4.068
4.163
4.169
4.185
4.190
4.207
4.213
TES
OTBS
OMe
OH
O
Me
Me
Me
Me
MeO
N
O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
5.52
6.72
3.82
9.45
8.80
3.30
1.27
2.32
1.23
3.07
2.05
2.92
0.57
3.03
2.16
0.88
1.00

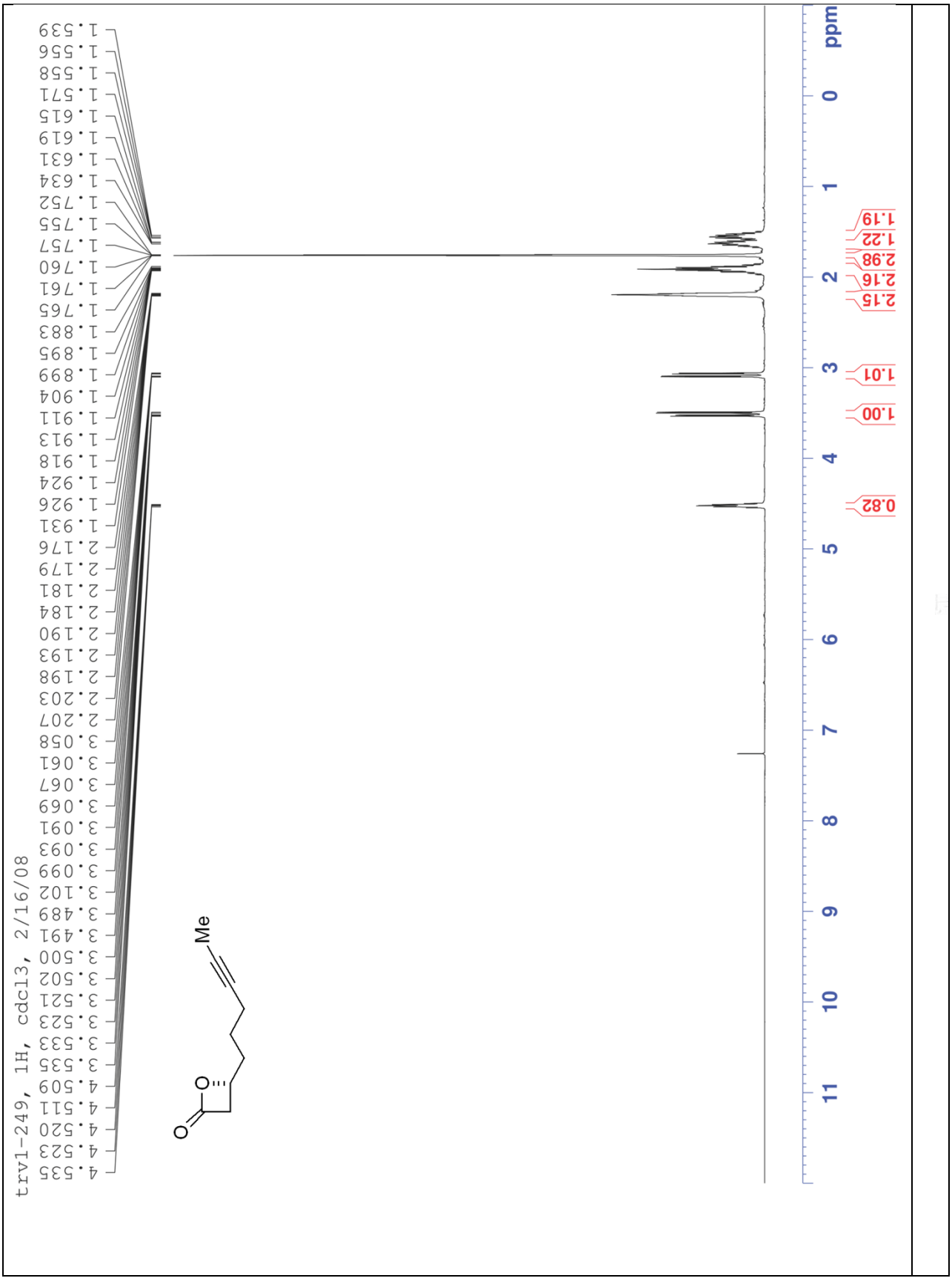

trv2-033, pure 13C, cdcl3, 500 MHz, 6/10/08
-4.68
-4.07
5.09
6.86
9.80
10.22
18.20
25.91
32.16
36.75
39.50
39.55
58.82
61.28
69.44
70.47
72.70
76.75
77.01
77.15
77.26
177.82
TES
OTBS
OMe
OH
O
Me
Me
Me
Me
MeO
N
ppm
0
20
40
60
80
100
120
140
160
180
200

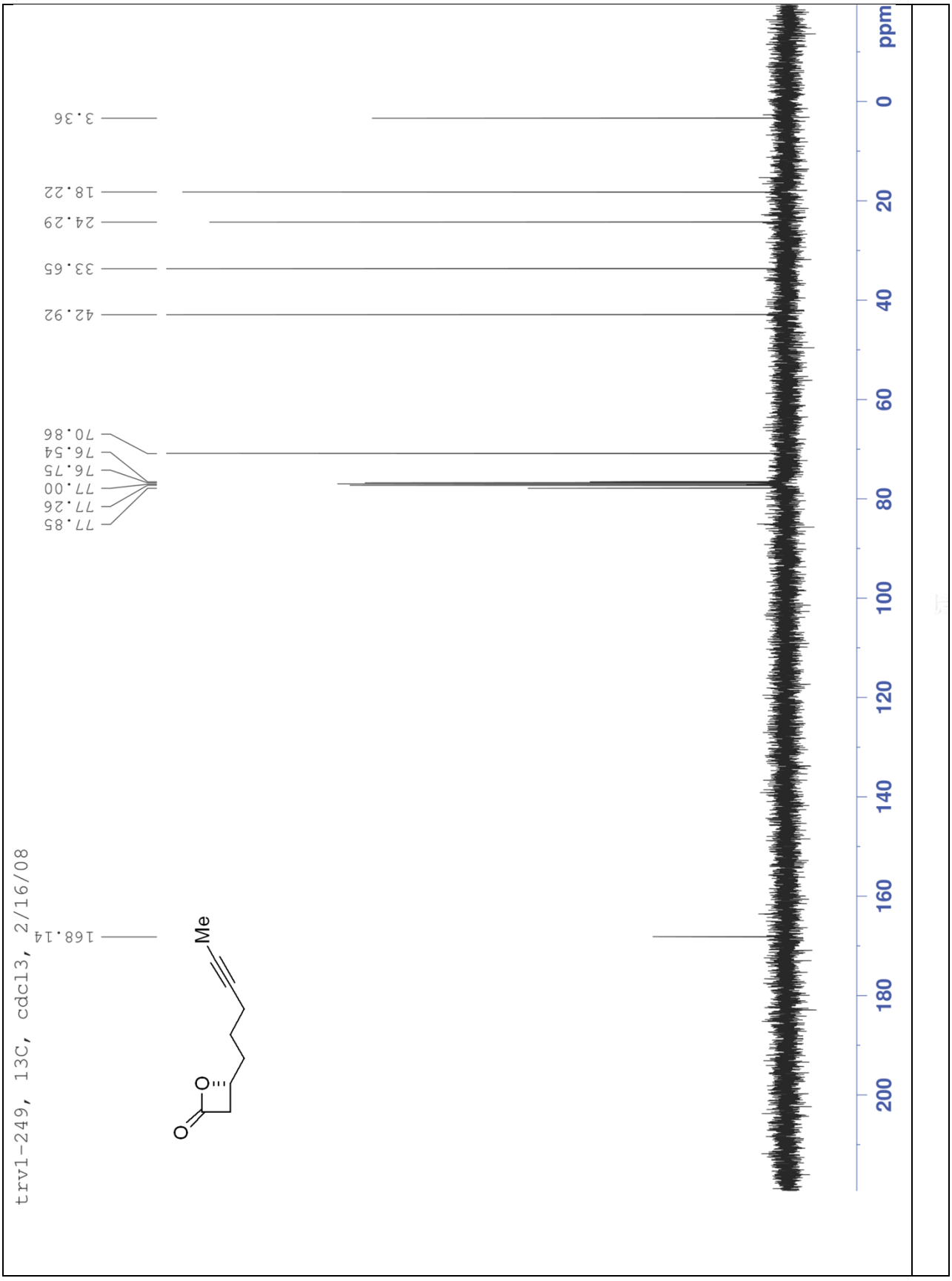

ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.43
3.37
9.65
3.25
1.09
2.67
1.06
3.23
3.29
2.08
0.62
3.67
1.11
2.36
1.00
OMe
OTBS
OH
OH
Me
Me
Me
O
N
MeO

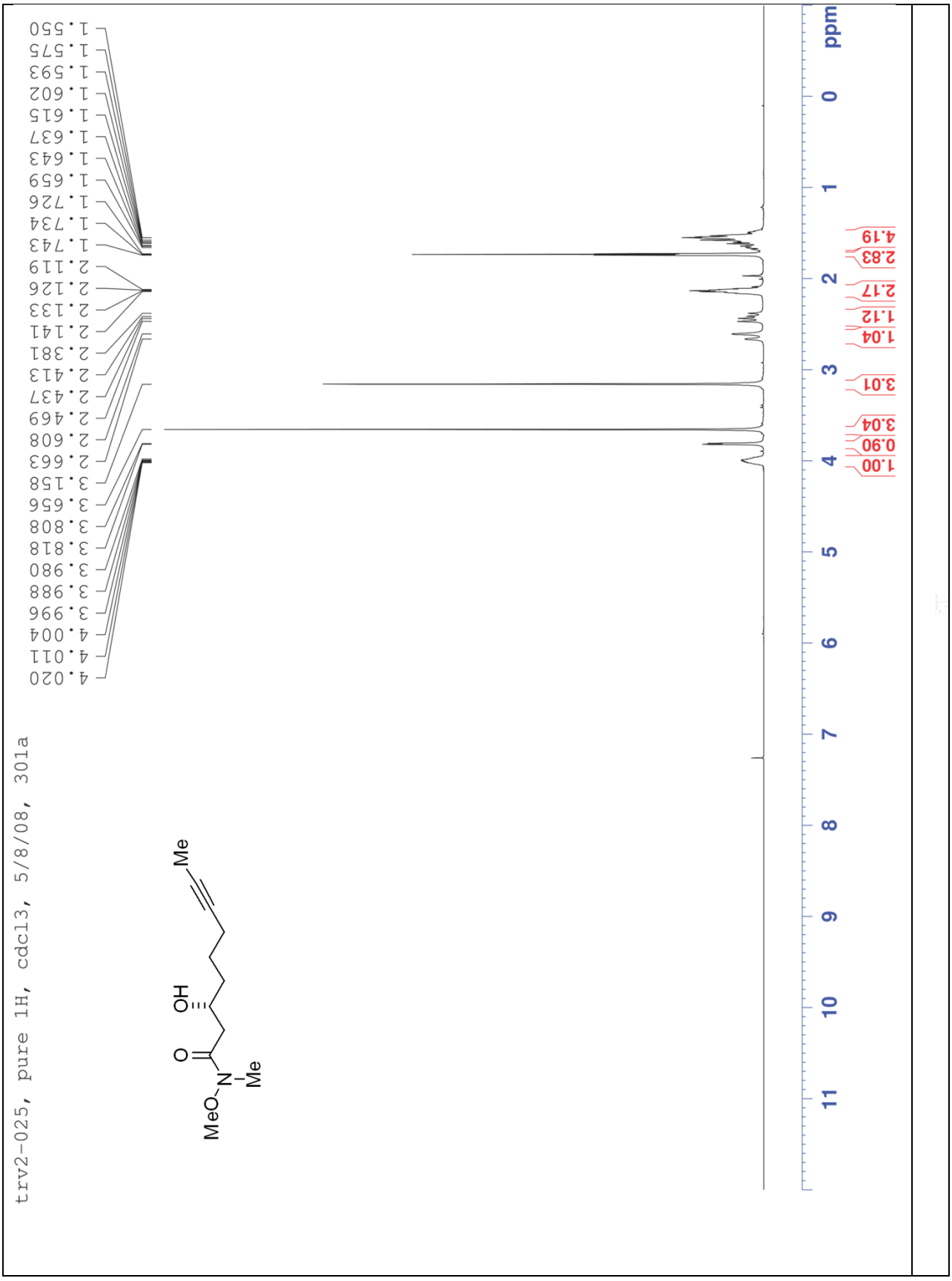

-5.04
-4.53
10.11
11.94
18.04
25.82
31.82
35.97
37.50
39.26
58.95
61.49
69.35
69.94
74.34
76.79
76.92
77.00
77.14
77.21
178.27
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
N
Me
O
OH
Me
Me
OH
OTBS
OMe

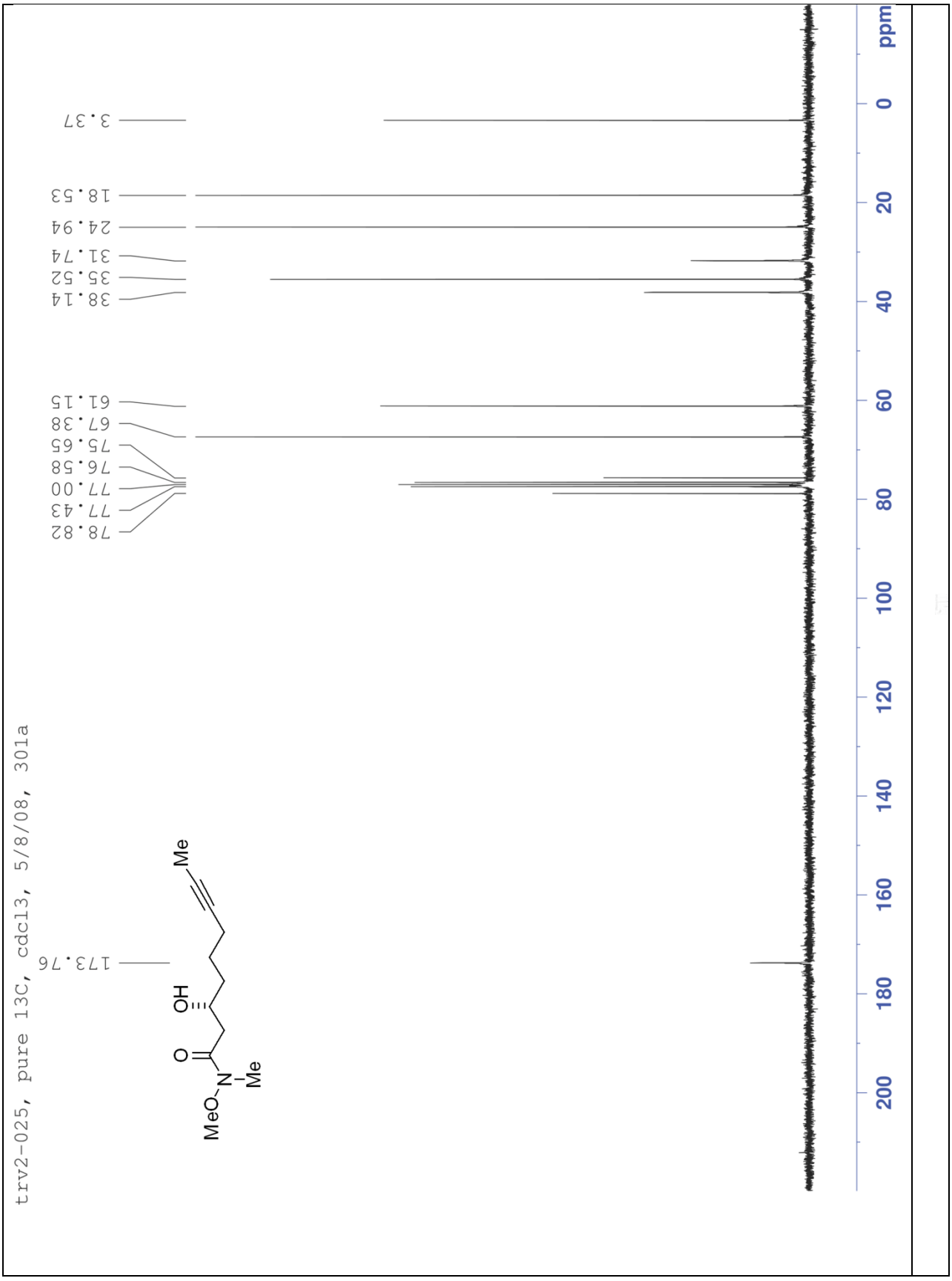

trv1-259, pure, cdc13, 2/25/08
0.065
0.533
0.560
0.587
0.615
0.641
0.838
0.862
0.867
0.877
0.907
0.933
0.945
0.956
0.982
1.065
1.089
1.572
1.577
1.595
1.601
1.614
1.625
1.743
1.761
1.771
1.780
1.785
1.804
2.157
2.650
2.667
2.674
2.691
2.697
3.268
3.286
3.298
3.330
3.674
3.692
3.711
3.919
3.925
3.938
3.945
3.954
3.966
3.972
4.232
4.238
4.256
4.262
7.261
TES
TES
OTBS
OMe
Me
Me
Me
O
O
O
ppm
5.50
12.02
3.75
8.12
17.32
3.10
1.27
1.95
2.84
1.00
1.98
2.93
1.00
1.01
1.00

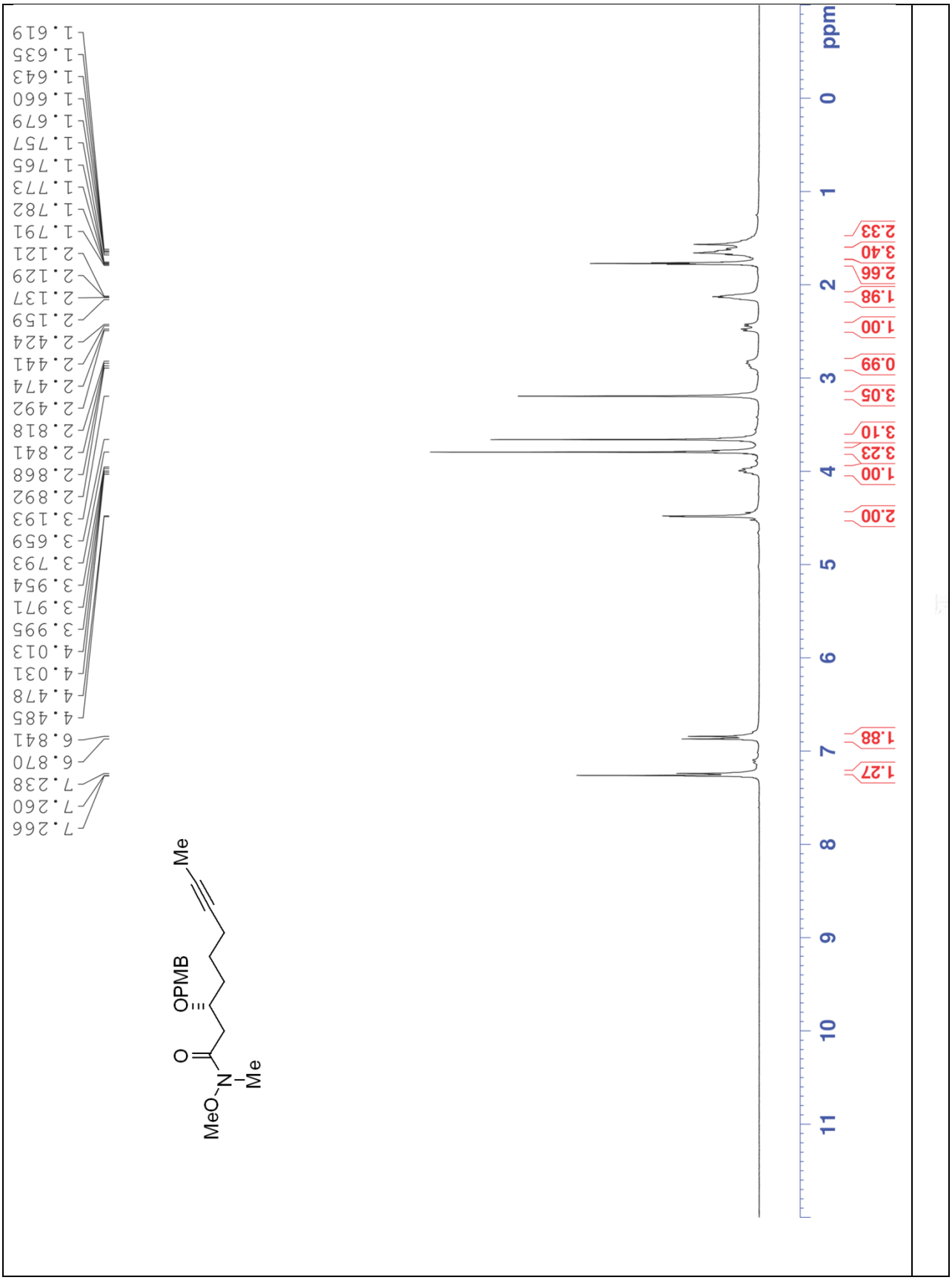

trv1-259, pure 13C, cdcl3, 2/25/08
-4.68
-4.29
5.41
5.59
5.98
7.07
7.09
9.49
9.77
18.19
25.88
28.66
40.62
42.91
50.32
58.90
69.43
70.17
73.15
76.59
76.88
77.01
77.43
210.96
TES
TES
O
OTBS
OMe
O
Me
Me
Me
ppm
0
20
40
60
80
100
120
140
160
180
200

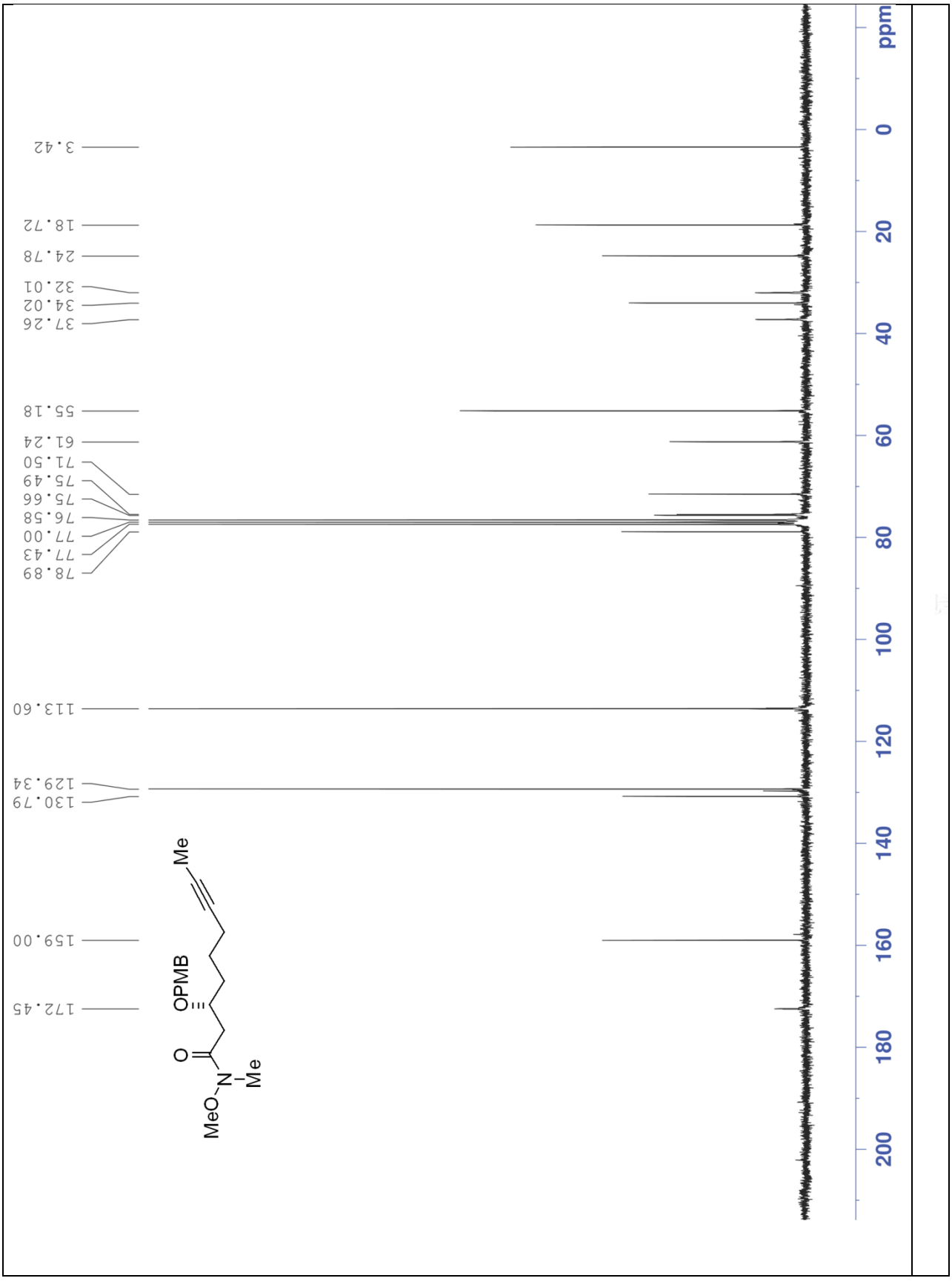

trv1-249, 1H, cdcl3, 2/16/08
1.539
1.556
1.558
1.571
1.615
1.619
1.631
1.634
1.752
1.755
1.757
1.760
1.761
1.765
1.883
1.895
1.899
1.904
1.911
1.913
1.918
1.924
1.926
1.931
2.176
2.179
2.181
2.184
2.190
2.193
2.198
2.203
2.207
3.058
3.061
3.067
3.069
3.091
3.093
3.099
3.102
3.489
3.491
3.500
3.502
3.521
3.523
3.533
3.535
4.509
4.511
4.520
4.523
4.535
Me
O
O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
0.82
1.00
1.01
2.15
2.16
2.98
1.22
1.19

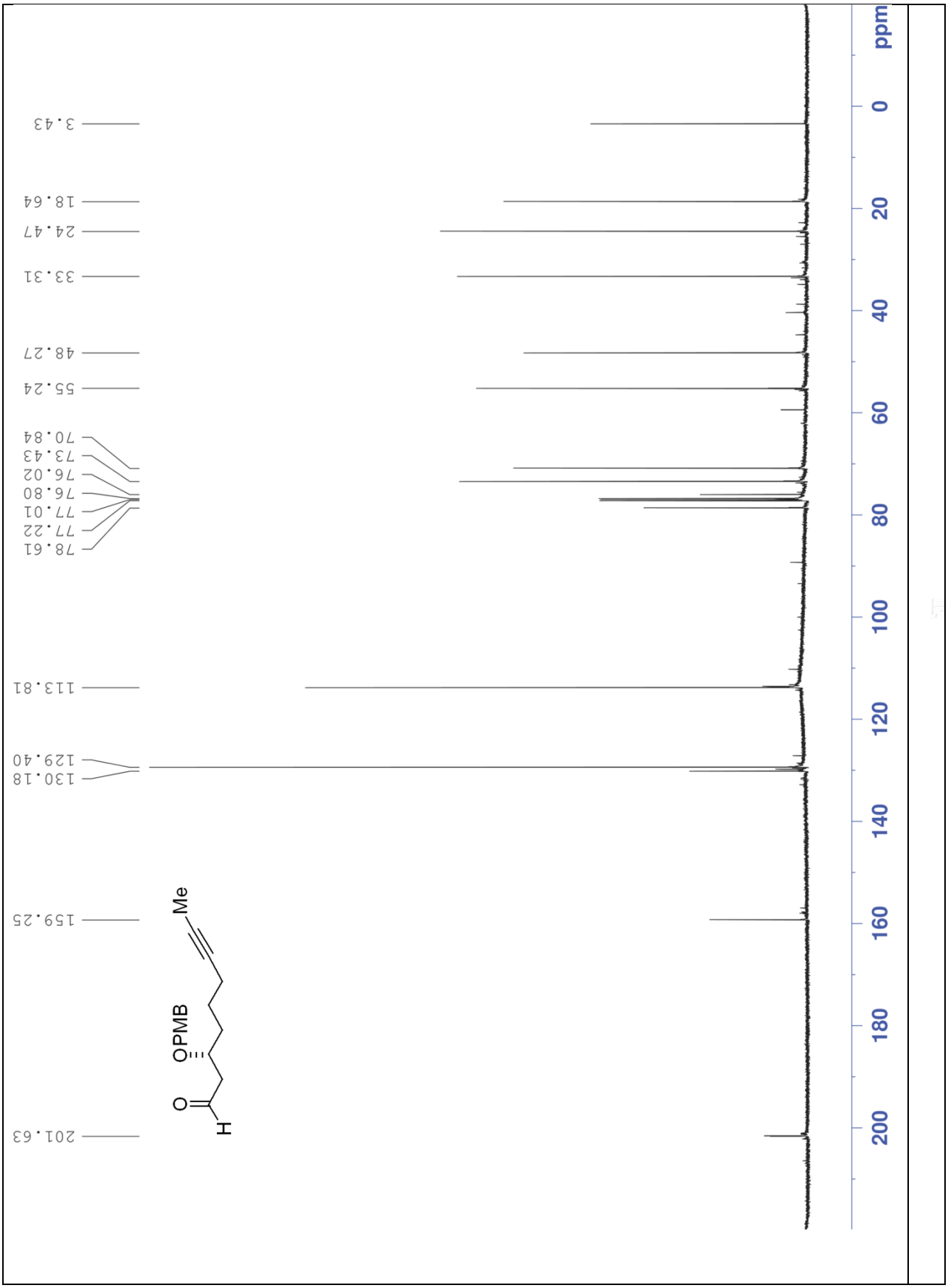

trv1-249, 13C, cdcl3, 2/16/08
168.14
77.85
77.26
77.00
76.75
76.54
70.86
42.92
33.65
24.29
18.22
3.36
Me
O
O
ppm
0
20
40
60
80
100
120
140
160
180
200

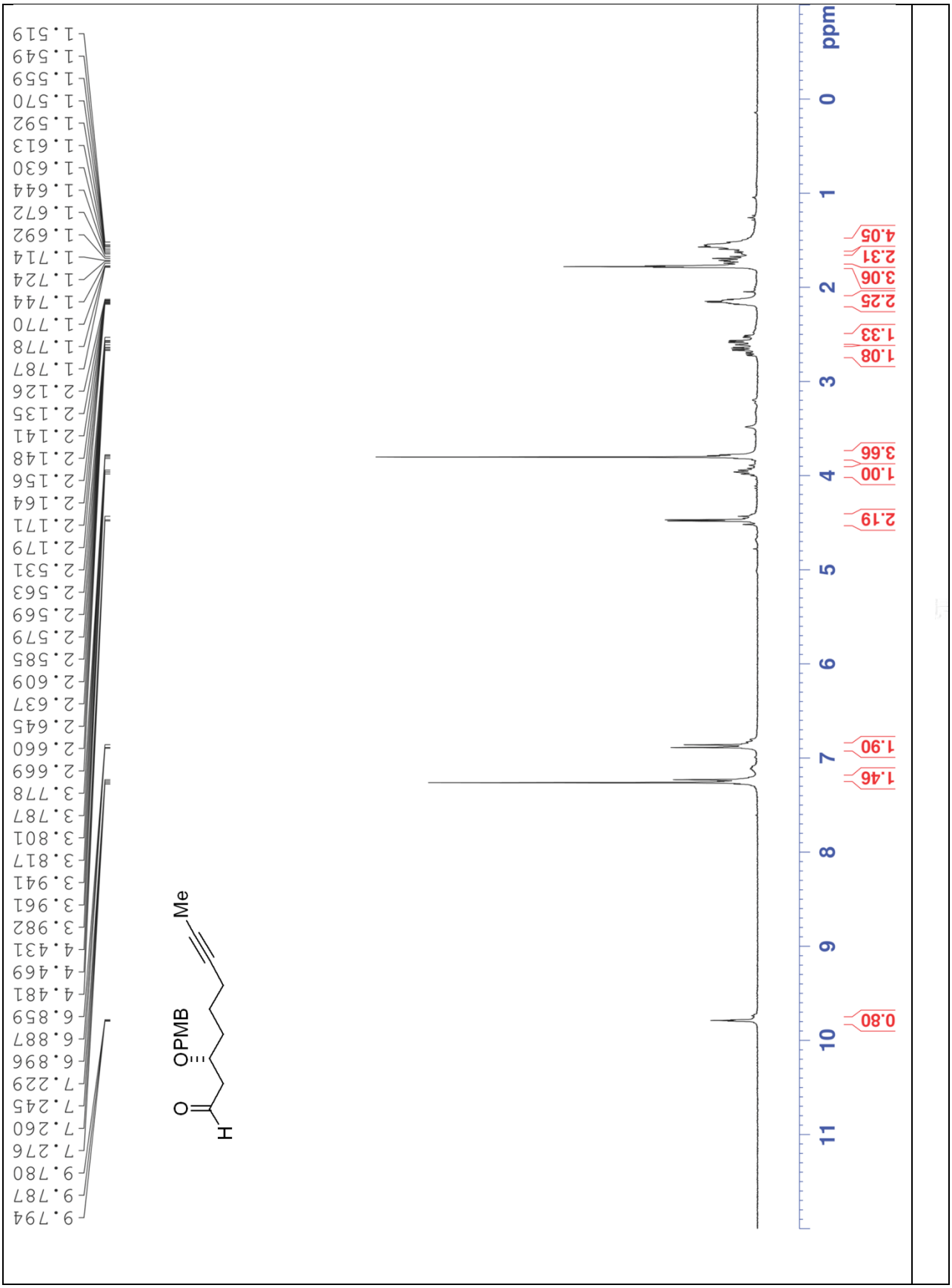

trv2-025, pure 1H, cdcl3, 5/8/08, 301a
1.550
1.575
1.593
1.602
1.615
1.637
1.643
1.659
1.726
1.734
1.743
2.119
2.126
2.133
2.141
2.381
2.413
2.437
2.469
2.608
2.663
3.158
3.656
3.808
3.818
3.980
3.988
3.996
4.004
4.011
4.020
1.00
0.90
3.04
3.01
1.04
1.12
2.17
2.83
4.19
ppm
0
1
2
3
4
5
6
7
8
9
10
11
Me
OH
O
N
Me
MeO

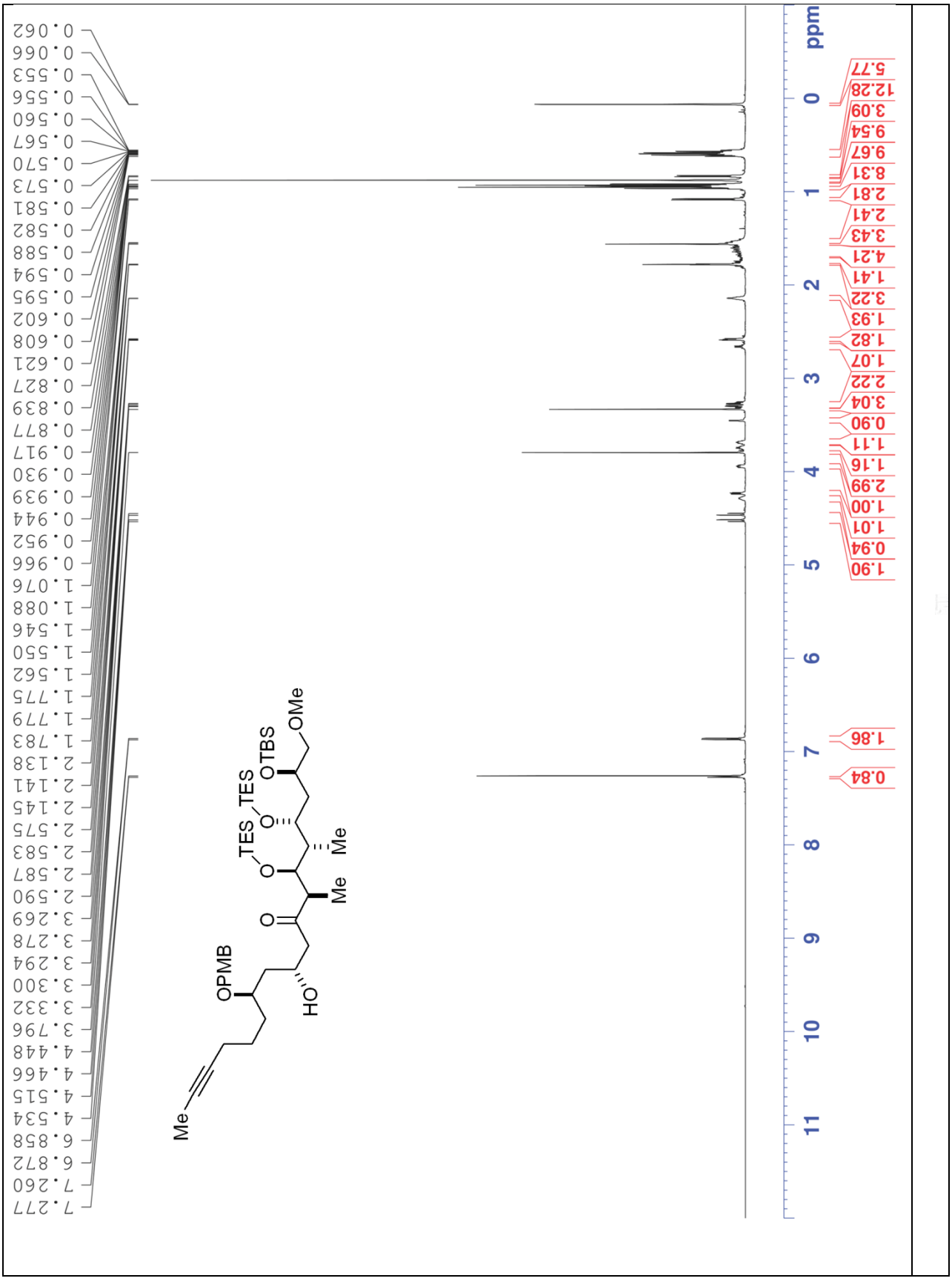

trv2-025, pure 13C, cdcl3, 5/8/08, 301a
173.76
78.82
77.43
77.00
76.58
75.65
67.38
61.15
38.14
35.52
31.74
24.94
18.53
3.37
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
OH
O
N
Me
MeO

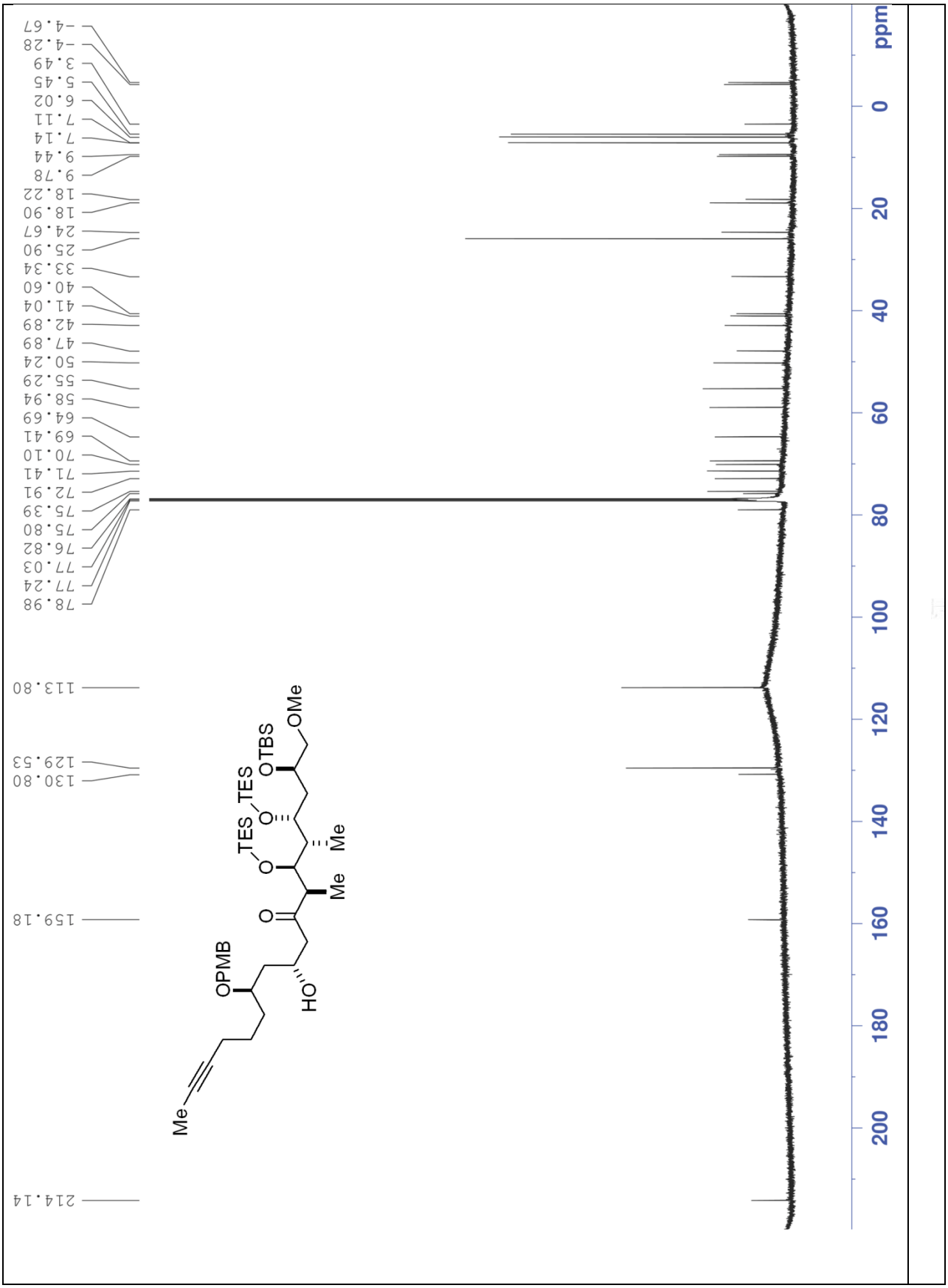

ppm
0
1
2
3
4
5
6
7
8
9
10
11
2.33
3.40
2.66
1.98
1.00
0.99
3.05
3.10
3.23
1.00
2.00
1.88
1.27
1.619
1.635
1.643
1.660
1.679
1.757
1.765
1.773
1.782
1.791
2.121
2.129
2.137
2.159
2.424
2.441
2.474
2.492
2.818
2.841
2.868
2.892
3.193
3.659
3.793
3.954
3.971
3.995
4.013
4.031
4.478
4.485
6.841
6.870
7.238
7.260
7.266
Me
OPMB
O
MeO
N
Me

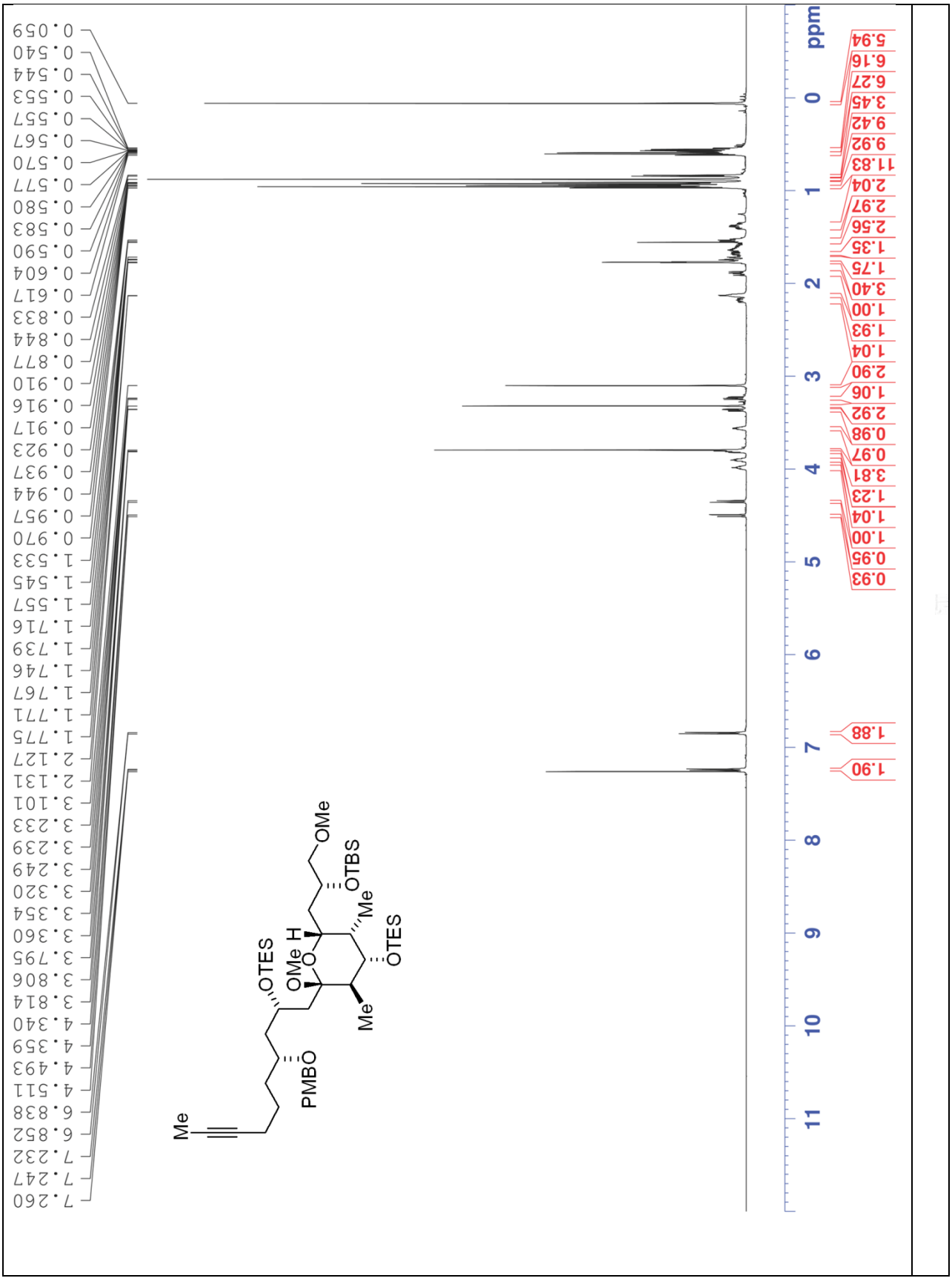

3.42
18.72
24.78
32.01
34.02
37.26
55.18
61.24
71.50
75.49
75.66
76.58
77.00
77.43
78.89
113.60
129.34
130.79
159.00
172.45
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
OPMB
O
MeO
N
Me

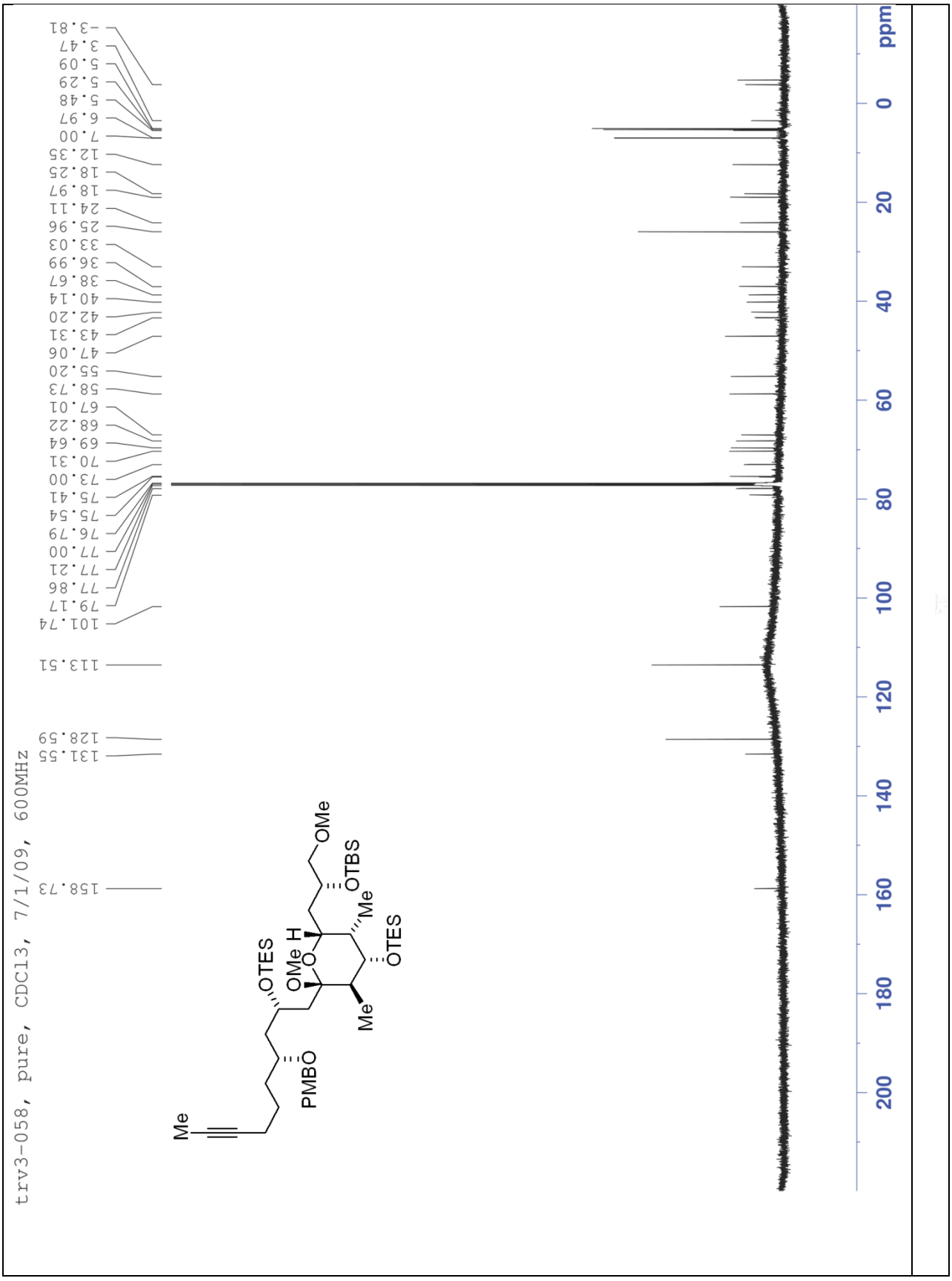

3.43
18.64
24.47
33.31
48.27
55.24
70.84
73.43
76.02
76.80
77.01
77.22
78.61
113.81
129.40
130.18
159.25
201.63
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
OPMB
O
H

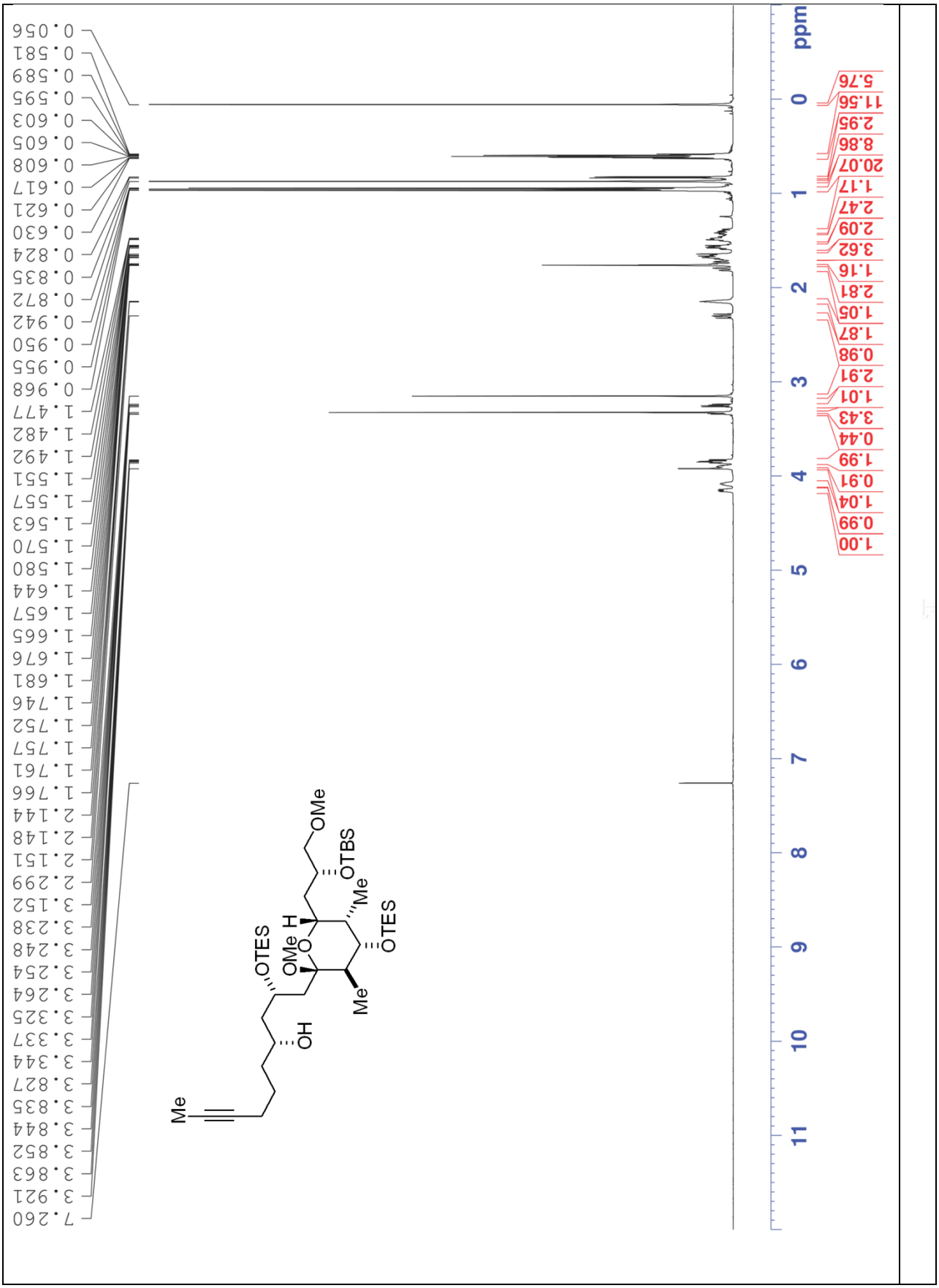

Me
OPMB
O
H
ppm
0.80
1.46
1.90
2.19
1.00
3.66
1.08
1.33
2.25
3.06
2.31
4.05
9.794
9.787
9.780
7.276
7.260
7.245
7.229
6.896
6.887
6.859
4.481
4.469
4.431
3.982
3.961
3.941
3.817
3.801
3.787
3.778
2.669
2.660
2.645
2.637
2.609
2.585
2.579
2.569
2.563
2.531
2.179
2.171
2.164
2.156
2.148
2.141
2.135
2.126
1.787
1.778
1.770
1.744
1.724
1.714
1.692
1.672
1.644
1.630
1.613
1.592
1.570
1.559
1.549
1.519

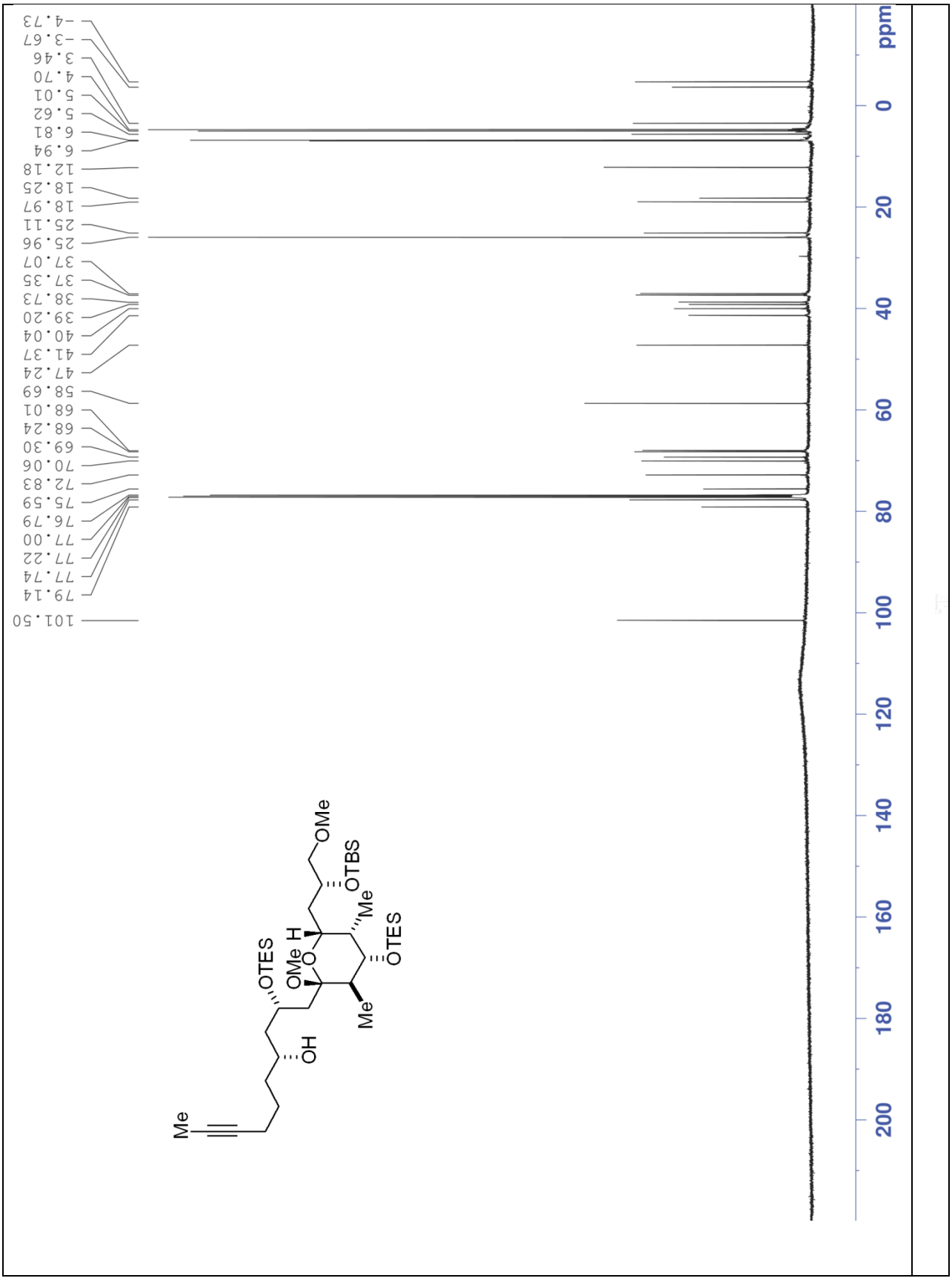

ppm
0 1 2 3 4 5 6 7 8 9 10 11
5.77
12.28
3.09
9.54
9.67
8.31
2.81
2.41
3.43
4.21
1.41
3.22
1.93
1.82
1.07
2.22
3.04
0.90
1.11
1.16
2.99
1.00
1.01
0.94
1.90
1.86
0.84
OPMB
HO
O
O
TES
TES
OTBS
OMe
Me
Me
Me

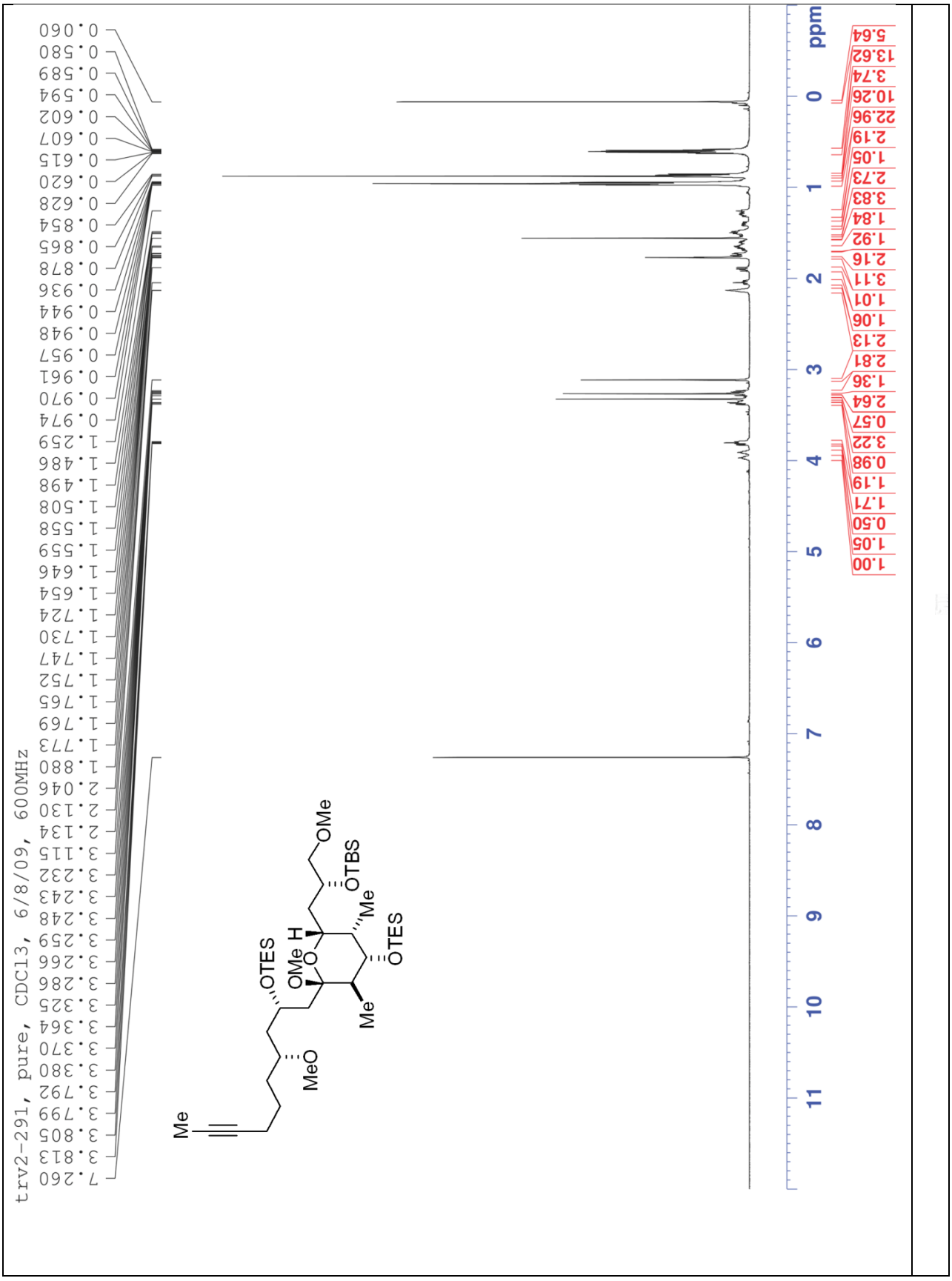

-4.67
-4.28
3.49
5.45
6.02
7.11
7.14
9.44
9.78
18.22
18.90
24.67
25.90
33.34
40.60
41.04
42.89
47.89
50.24
55.29
58.94
64.69
69.41
70.10
71.41
72.91
75.39
75.80
76.82
77.03
77.24
78.98
113.80
129.53
130.80
159.18
214.14
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
OPMB
HO
O
Me
Me
O
TES
TES
O
OTBS
OMe

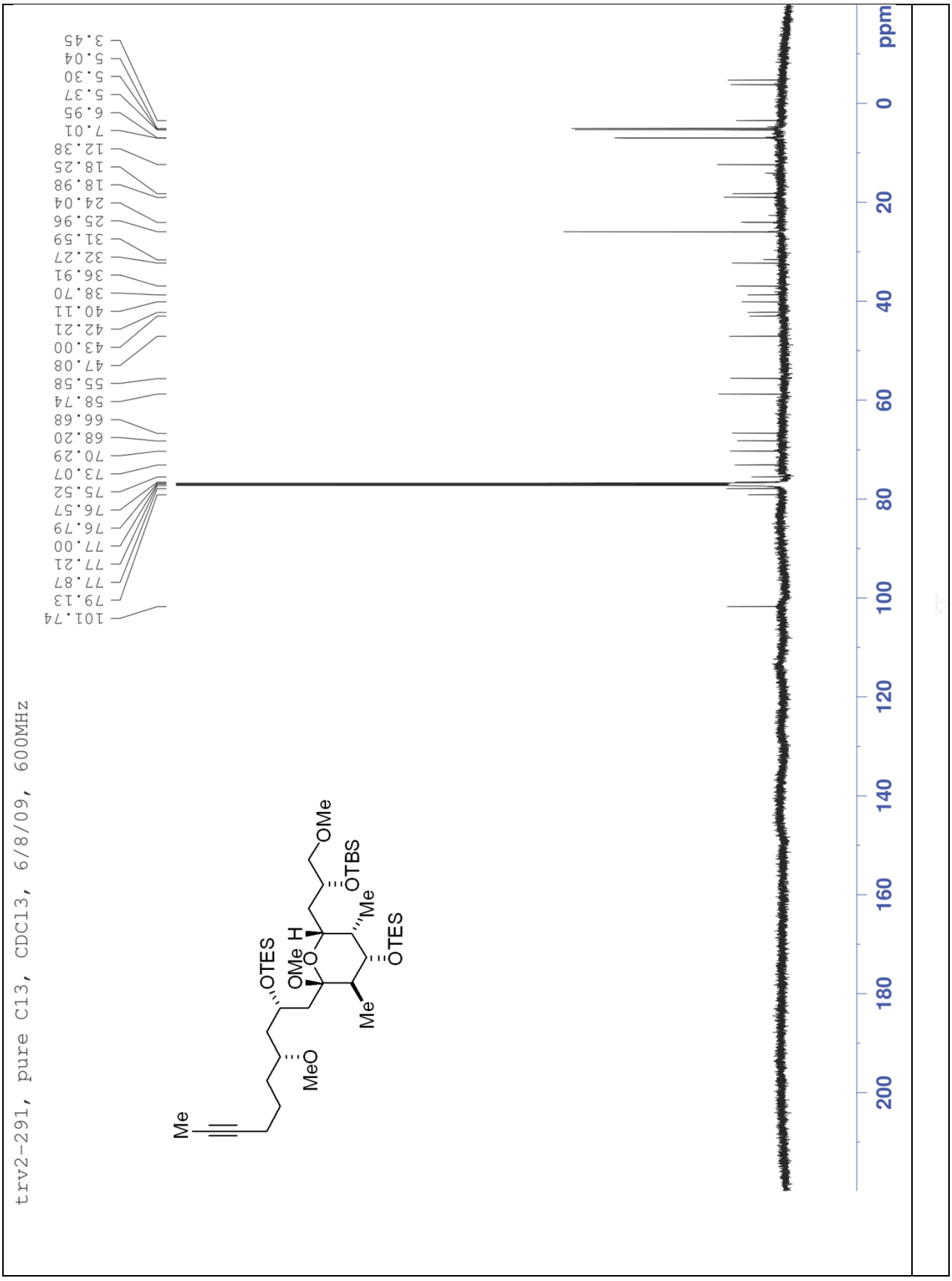

Me
PMBO
OTES
OMe H
O
Me
Me
OTES
OTBS
OMe
ppm
0.93
0.95
1.00
1.04
1.23
3.81
0.97
0.98
2.92
1.06
2.90
1.04
1.93
1.00
3.40
1.75
1.35
2.56
2.97
2.04
11.83
9.92
9.42
3.45
6.27
6.16
5.94
1.88
1.90

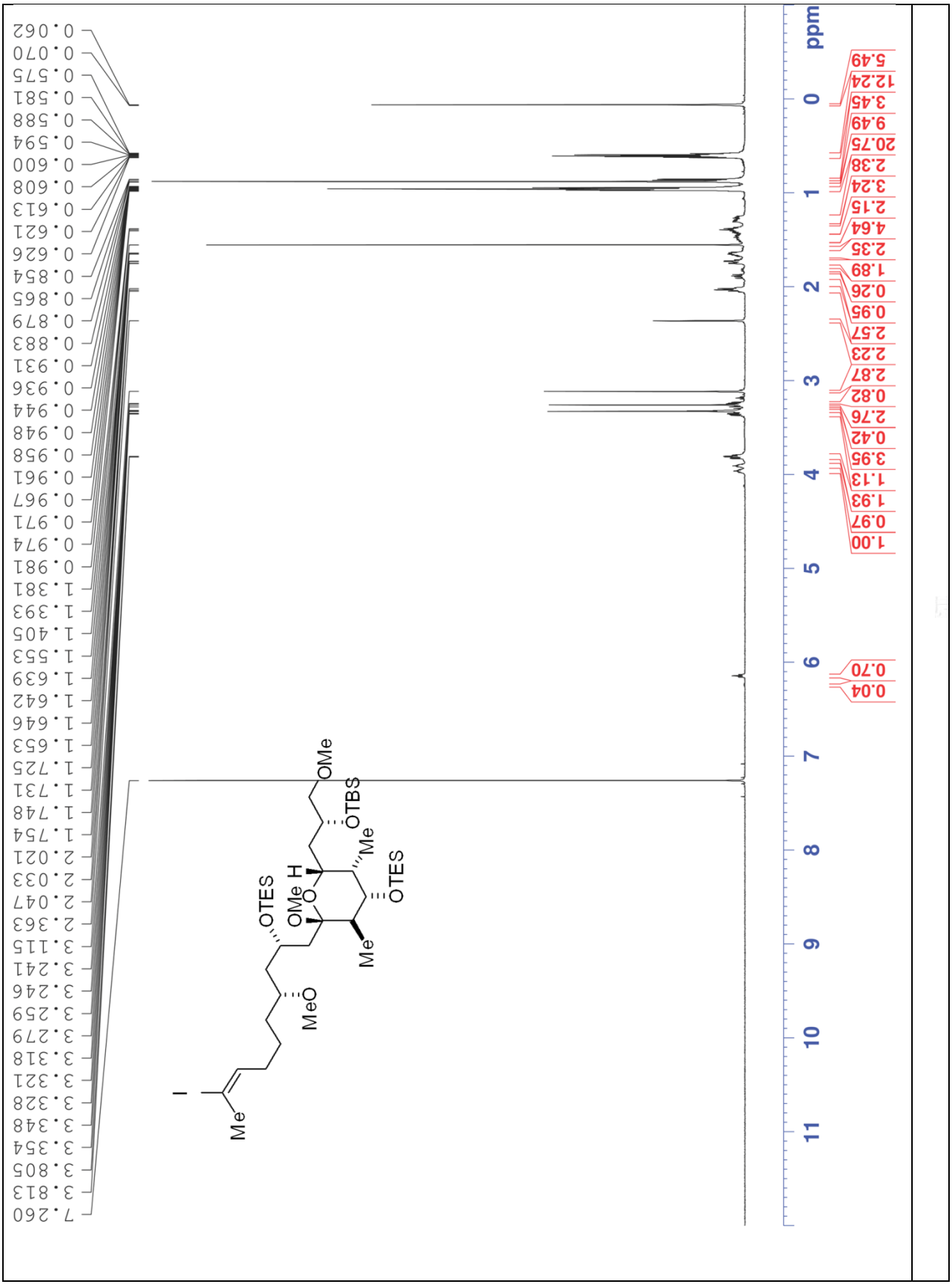

trv3-058, pure, CDC13, 7/1/09, 600MHz
-3.81
3.47
5.09
5.29
5.48
6.97
7.00
12.35
18.25
18.97
24.11
25.96
33.03
36.99
38.67
40.14
42.20
43.31
47.06
55.20
58.73
67.01
68.22
69.64
70.31
73.00
75.41
75.54
76.79
77.00
77.21
77.86
79.17
101.74
113.51
128.59
131.55
158.73
Me
PMBO
OTES
OMe H
O
Me
OTBS
OMe
Me
OTES
ppm
200
180
160
140
120
100
80
60
40
20
0

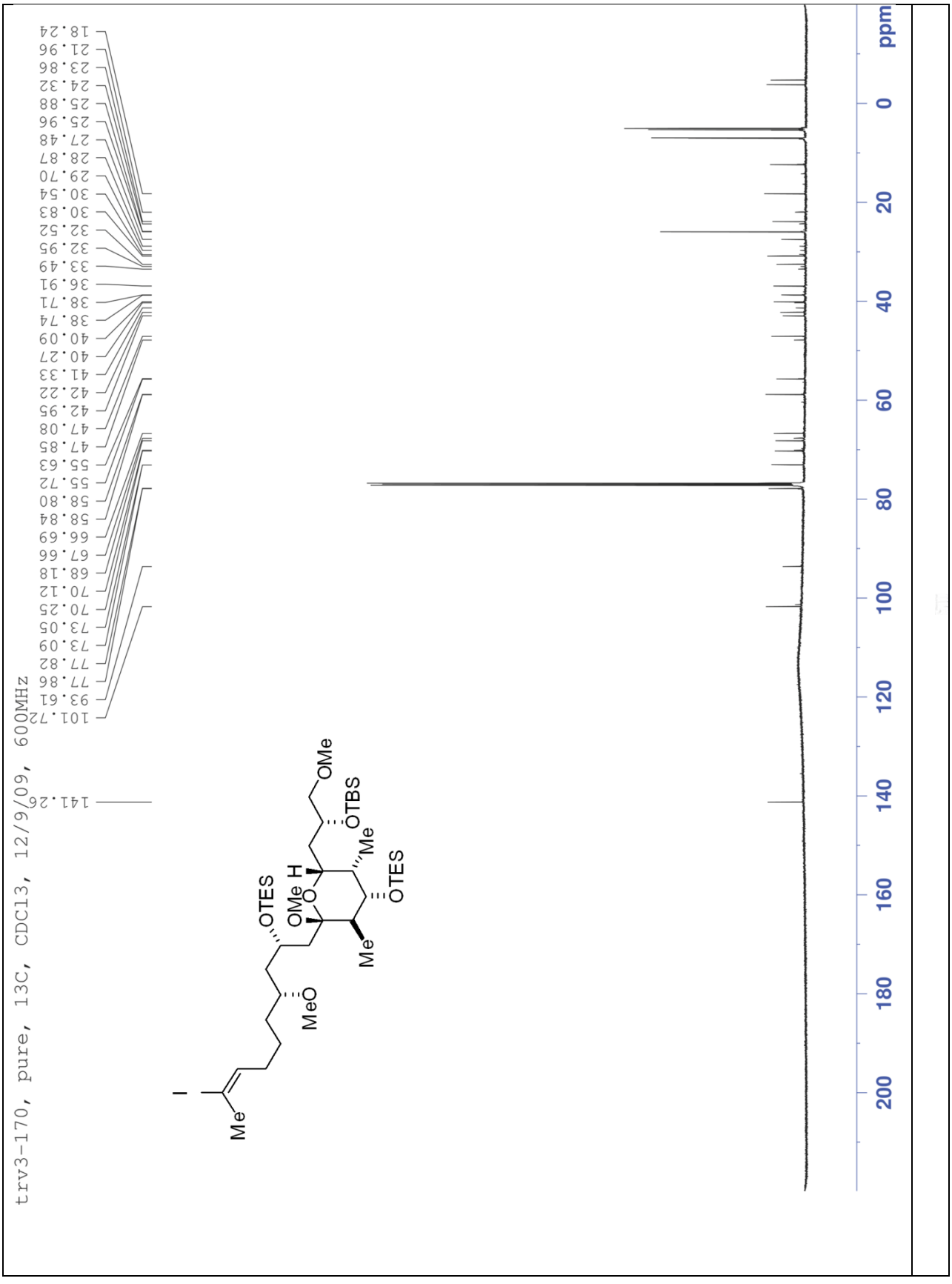

ppm
0 1 2 3 4 5 6 7 8 9 10 11
5.76
11.56
2.95
8.86
20.07
1.17
2.47
2.09
3.62
1.16
2.81
1.05
1.87
0.98
2.91
1.01
3.43
0.44
1.99
0.91
1.04
0.99
1.00
OMe
OTBS
Me
OTES
Me
OMe H
O
OTES
OH
Me

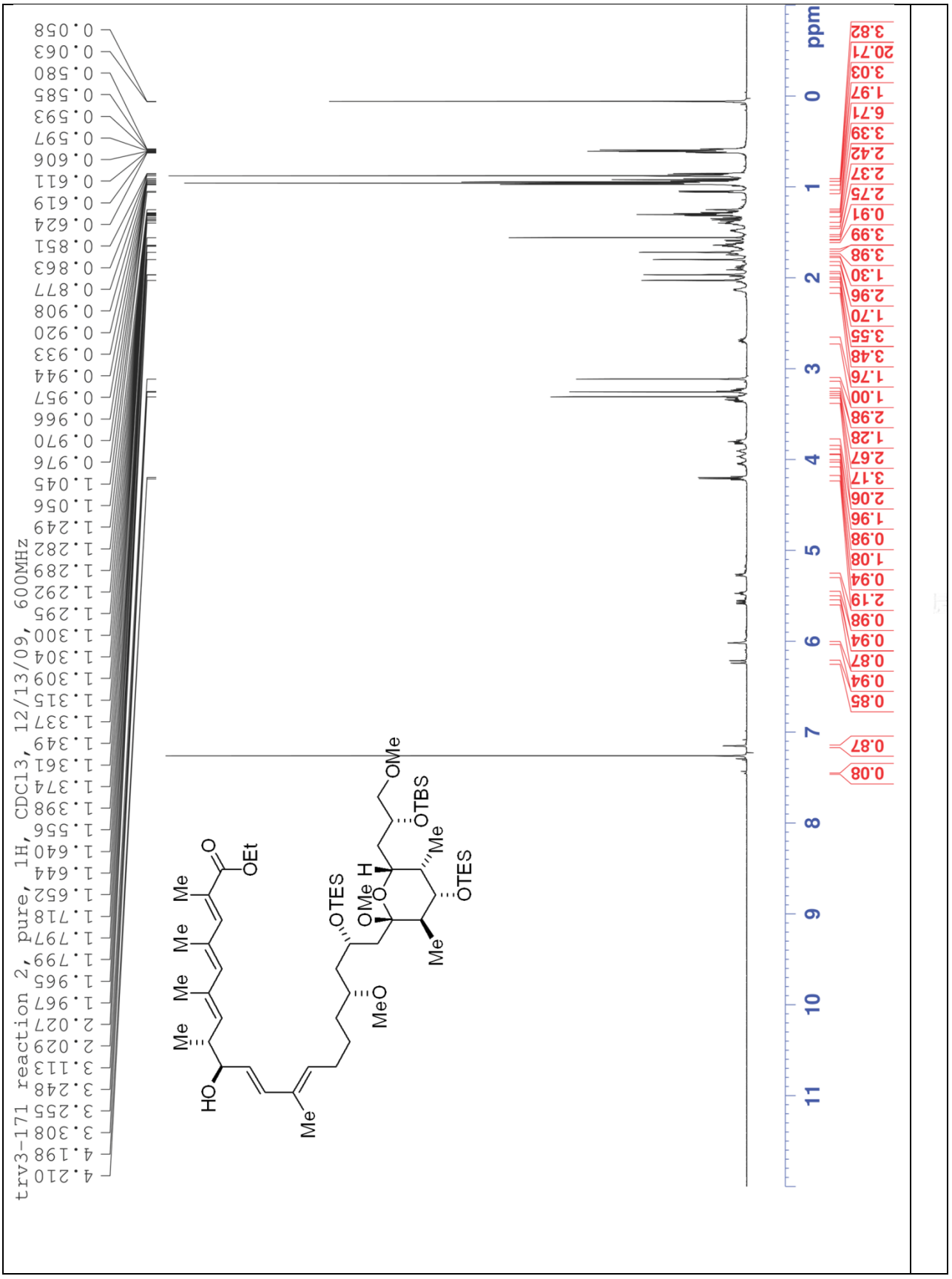

-4.73
-3.67
3.46
4.70
5.01
5.62
6.81
6.94
12.18
18.25
18.97
25.11
25.96
37.07
37.35
38.73
39.20
40.04
41.37
47.24
58.69
68.01
68.24
69.30
70.06
72.83
75.59
76.79
77.00
77.22
77.74
79.14
101.50
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
OH
OTES
OMe
H
O
Me
OTES
Me
OTBS
OMe

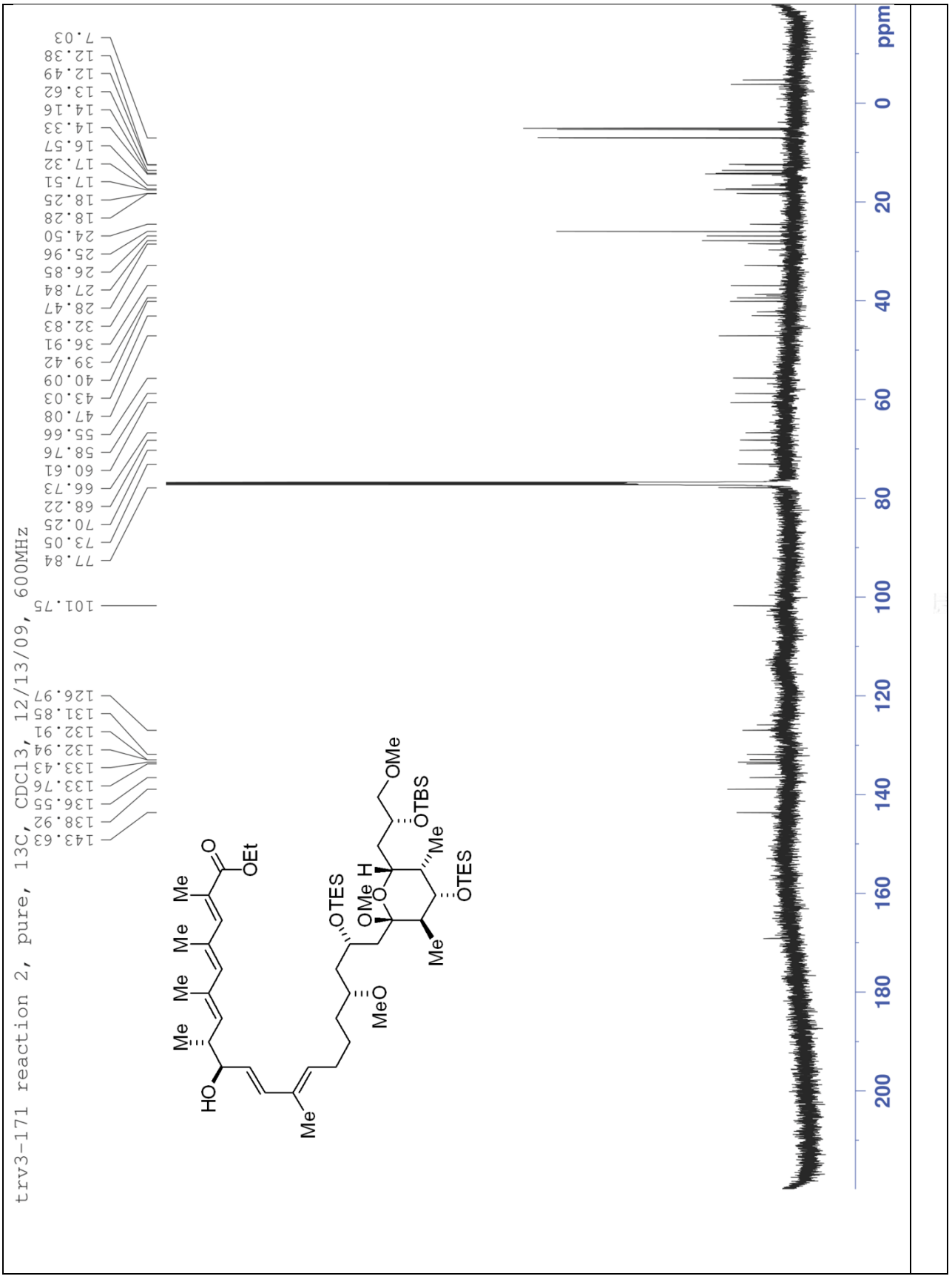

trv2-291, pure, CDC13, 6/8/09, 600MHz
Me
MeO
OTES
OMe H
O
Me
OTBS
OMe
Me
OTES
ppm

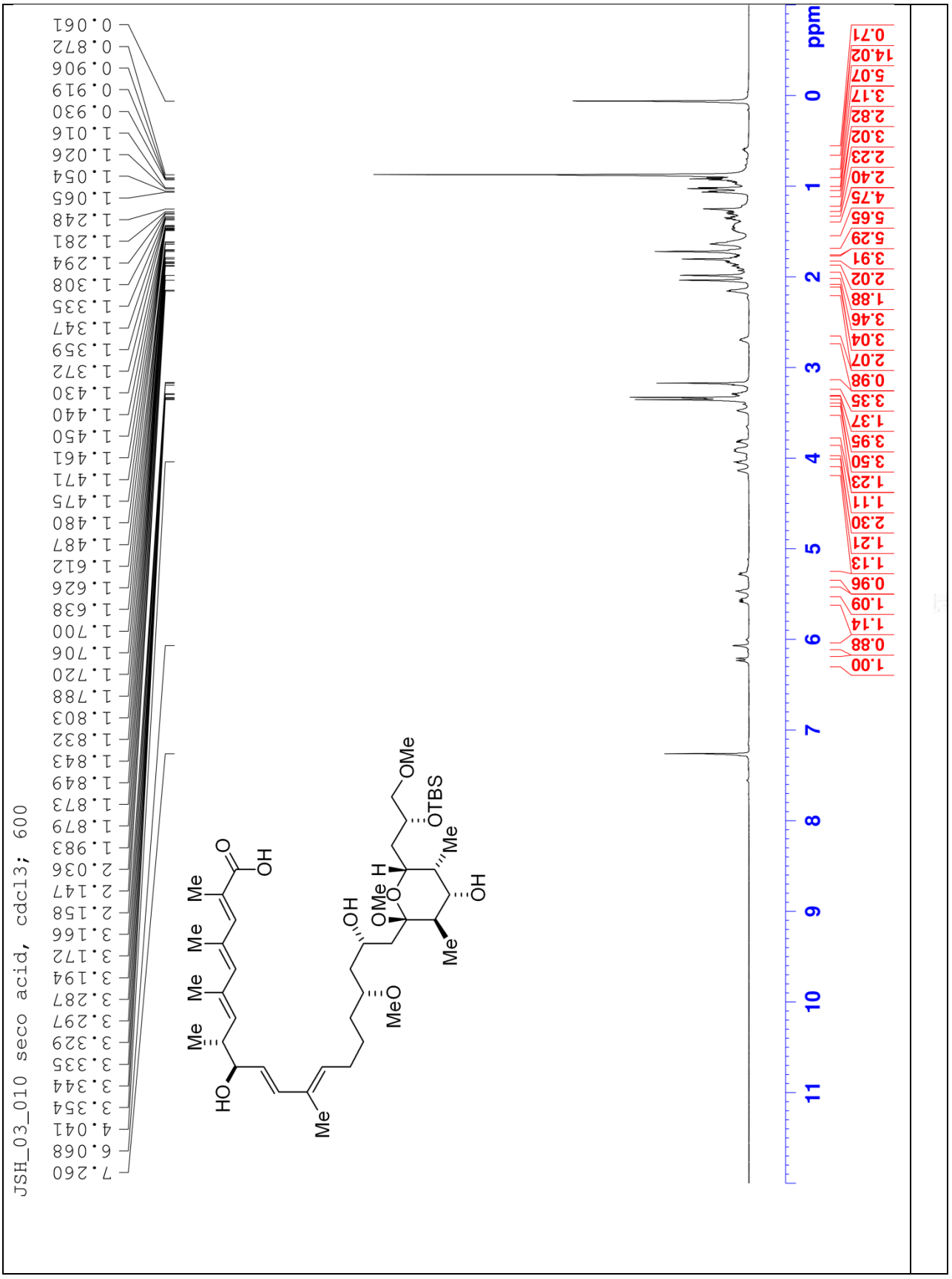

trv2-291, pure C13, CDCl3, 6/8/09, 600MHz
3.45
5.04
5.30
5.37
6.95
7.01
12.38
18.25
18.98
24.04
25.96
31.59
32.27
36.91
38.70
40.11
42.21
43.00
47.08
55.58
58.74
66.68
68.20
70.29
73.07
75.52
76.57
76.79
77.00
77.21
77.87
79.13
101.74
Me
MeO
OTES
OMe H
O
Me
Me
OTBS
OMe
OTES
ppm
200
180
160
140
120
100
80
60
40
20
0

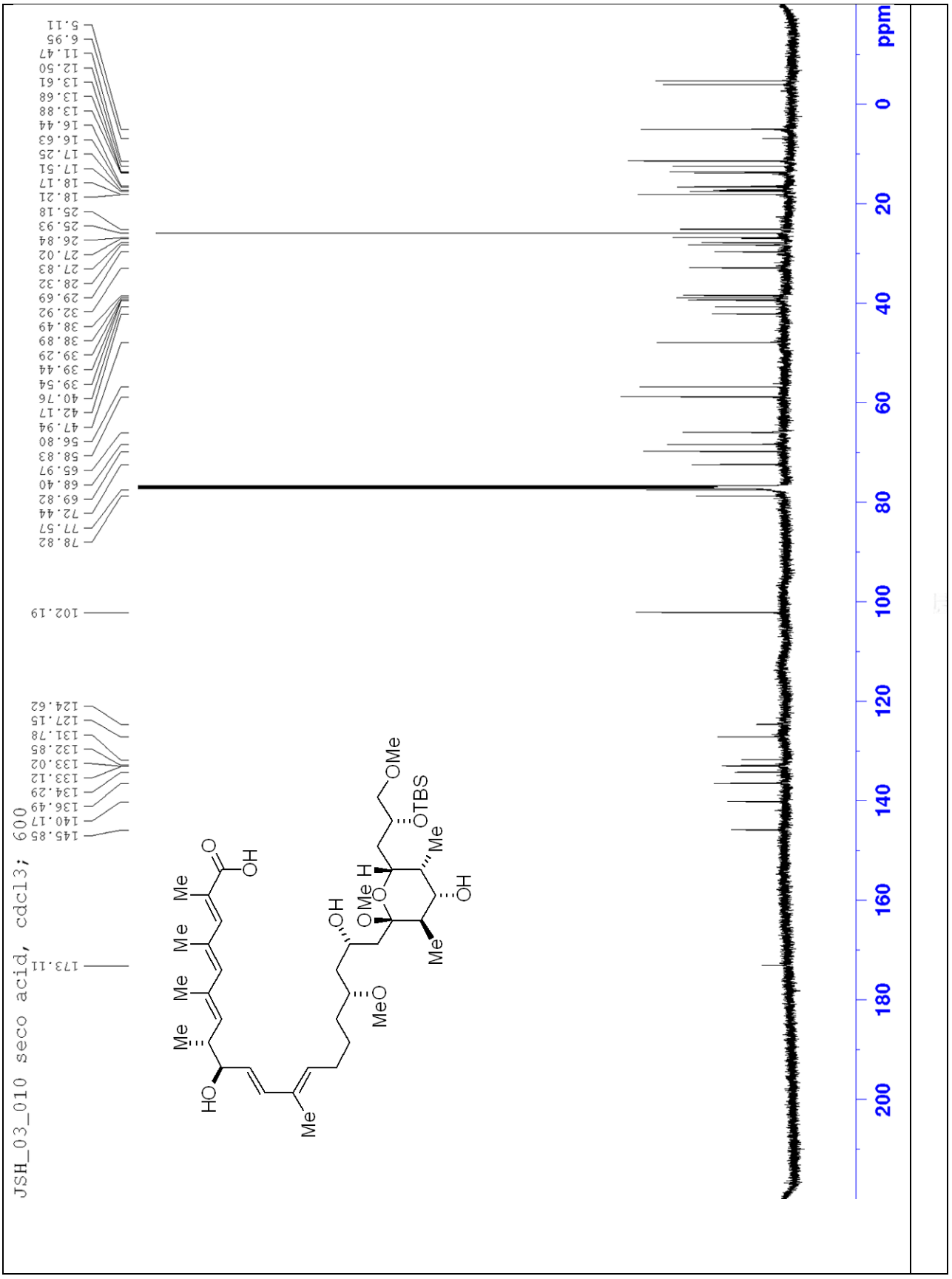

ppm
0 1 2 3 4 5 6 7 8 9 10 11
5.49
12.24
3.45
9.49
20.75
2.38
3.24
2.15
4.64
2.35
1.89
0.26
0.95
2.57
2.23
2.87
0.82
2.76
0.42
3.95
1.13
1.93
0.97
1.00
0.04
0.70
I
Me
MeO
OTES
OMe H
O
Me
Me
OTES
OTBS
OMe

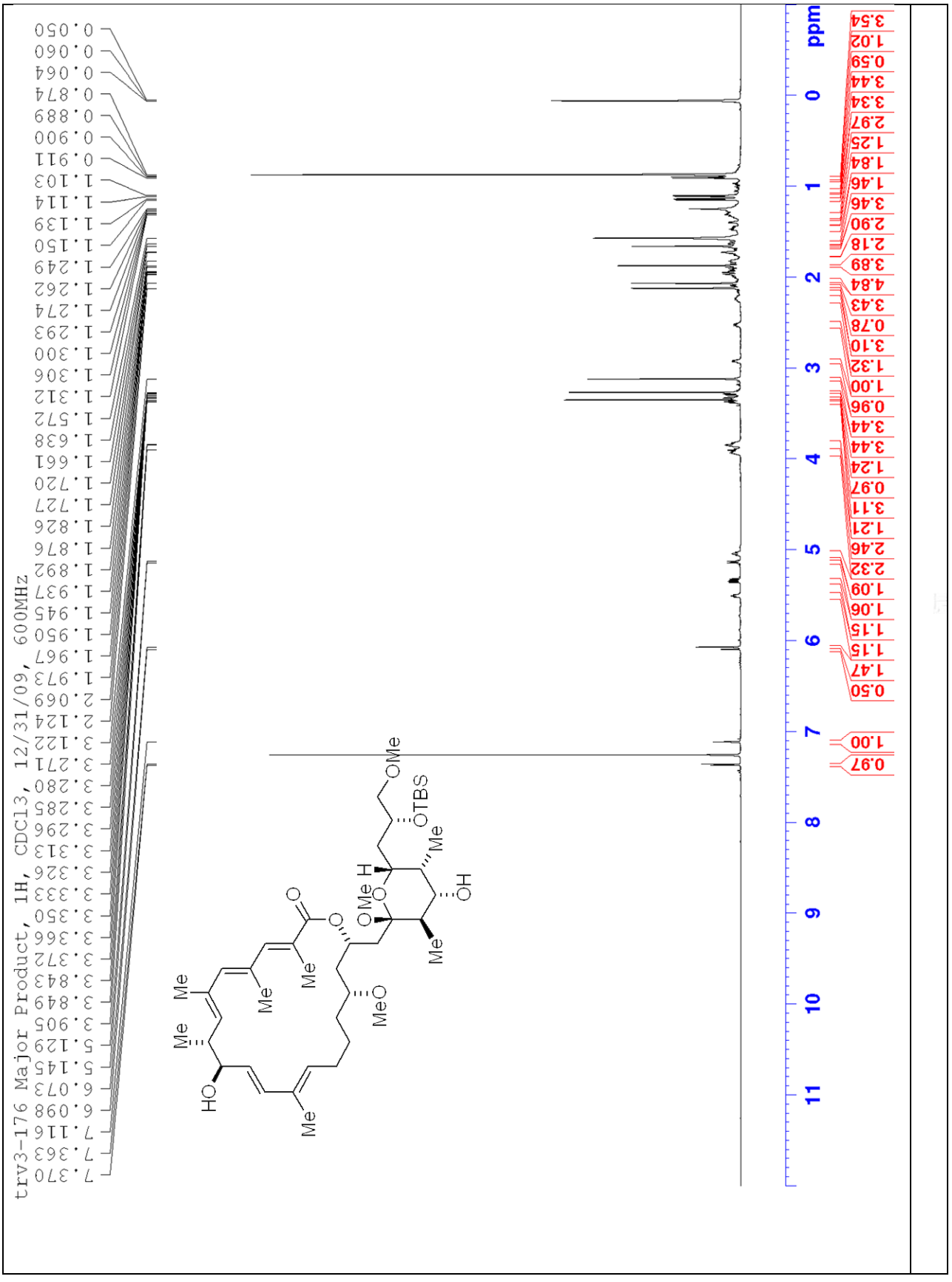

trv3-170, pure, 13C, CDCl3, 12/9/09, 600MHz
141.26
101.72
93.61
77.86
77.82
73.09
73.05
70.25
70.12
68.18
67.66
66.69
58.84
58.80
55.72
55.63
47.85
47.08
42.95
42.22
41.33
40.27
40.09
38.74
38.71
36.91
33.49
32.95
32.52
30.83
30.54
29.70
28.87
27.48
25.96
25.88
24.32
23.86
21.96
18.24
I
Me
MeO
OTES
OMe H
O
Me
Me
OTES
OTBS
OMe
ppm
200
180
160
140
120
100
80
60
40
20
0

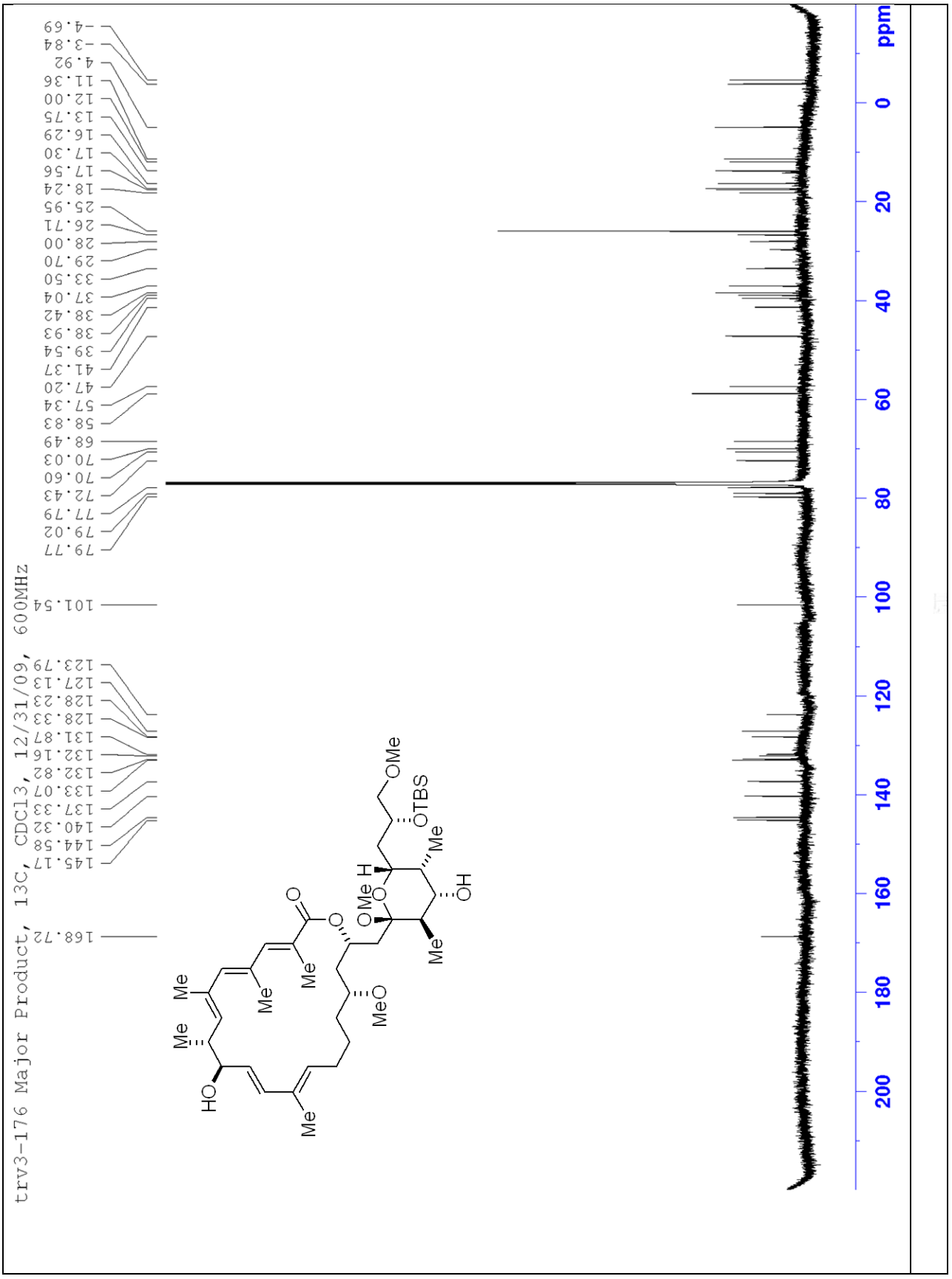

trv3-171 reaction 2, pure, 1H, CDCl3, 12/13/09, 600MHz
ppm
Me
Me
Me
Me
OEt
O
HO
Me
OTES
OMe
H
O
MeO
OMe
OTBS
Me
Me
OTES

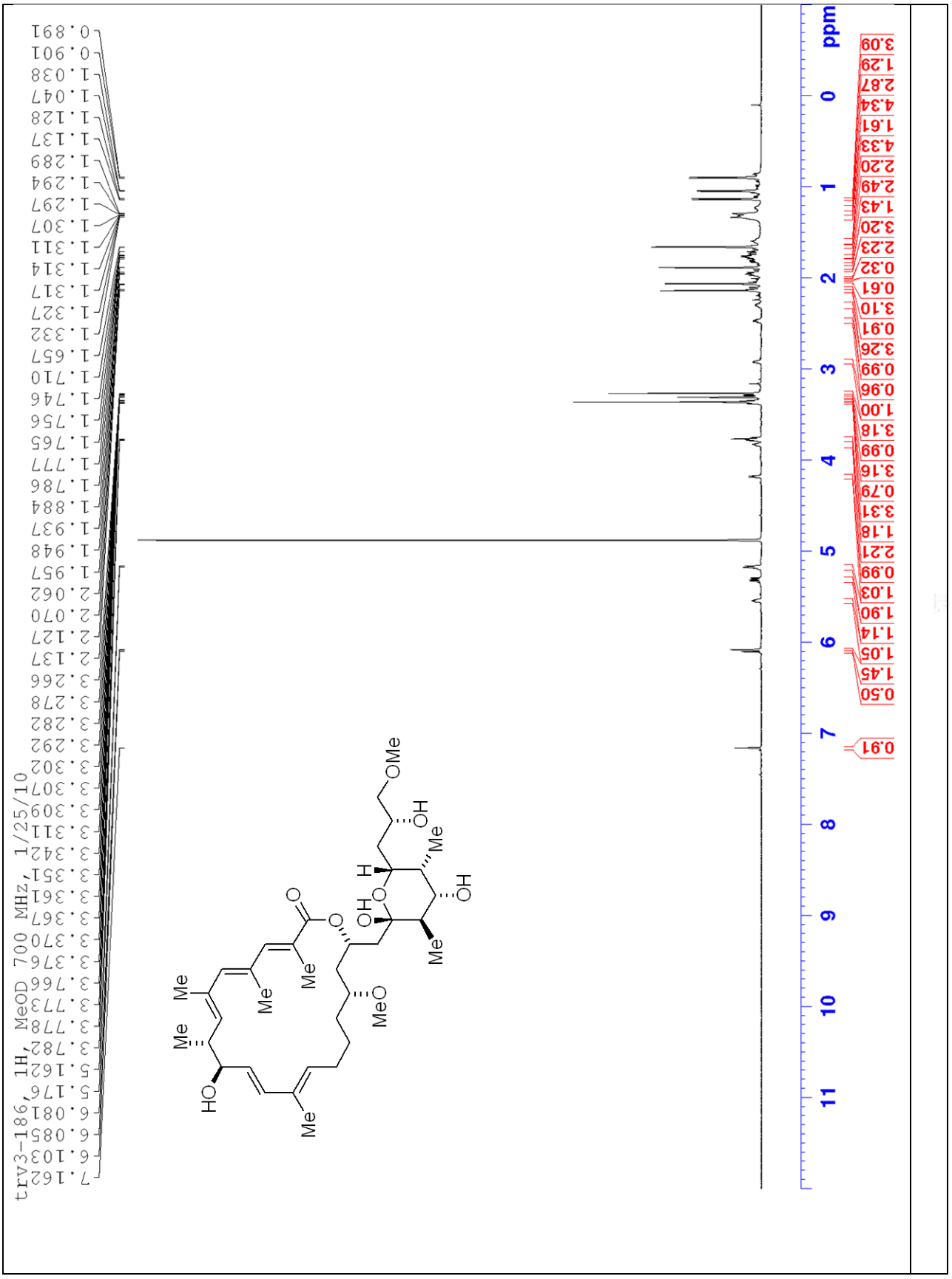

trv3-171 reaction 2, pure, 13C, CDCl3, 12/13/09, 600MHz
143.63
138.92
136.55
133.76
133.43
132.94
132.91
131.85
126.97
101.75
77.84
73.05
70.25
68.22
66.73
60.61
58.76
55.66
47.08
43.03
40.09
39.42
36.91
32.83
28.47
27.84
26.85
25.96
24.50
18.28
18.25
17.51
17.32
16.57
14.33
14.16
13.62
12.49
12.38
7.03
ppm
0
20
40
60
80
100
120
140
160
180
200
HO
Me
Me
Me
Me
Me
O
OEt
MeO
OTES
OMe
H
O
Me
Me
OTBS
OMe
OTES

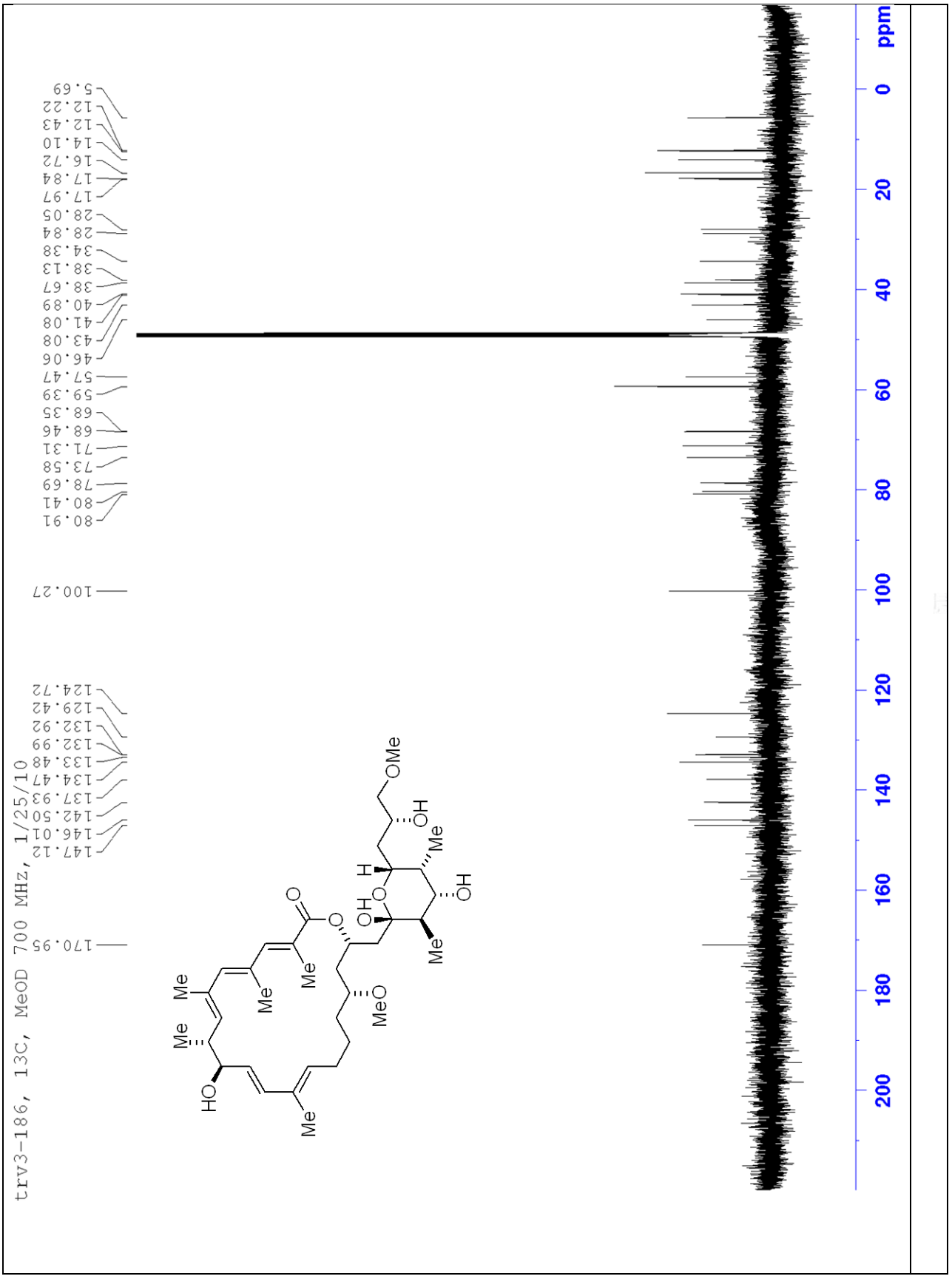

JSH_03_010 seco acid, cdcl3; 600
0.061
0.872
0.906
0.919
0.930
1.016
1.026
1.054
1.065
1.248
1.281
1.294
1.308
1.335
1.347
1.359
1.372
1.430
1.440
1.450
1.461
1.471
1.475
1.480
1.487
1.612
1.626
1.638
1.700
1.706
1.720
1.788
1.803
1.832
1.843
1.849
1.873
1.879
1.983
2.036
2.147
2.158
3.166
3.172
3.194
3.287
3.297
3.329
3.335
3.344
3.354
4.041
6.068
7.260
ppm
0 1 2 3 4 5 6 7 8 9 10 11
1.00
0.88
1.14
1.09
0.96
1.13
1.21
2.30
1.11
1.23
3.50
3.95
1.37
3.35
0.98
2.07
3.04
3.46
1.88
2.02
3.91
5.29
5.65
4.75
2.40
2.23
3.02
2.82
3.17
5.07
14.02
0.71
HO
Me
Me
Me
Me
Me
O
OH
Me
MeO
OH
OMe
H
O
Me
OH
Me
OTBS
OMe

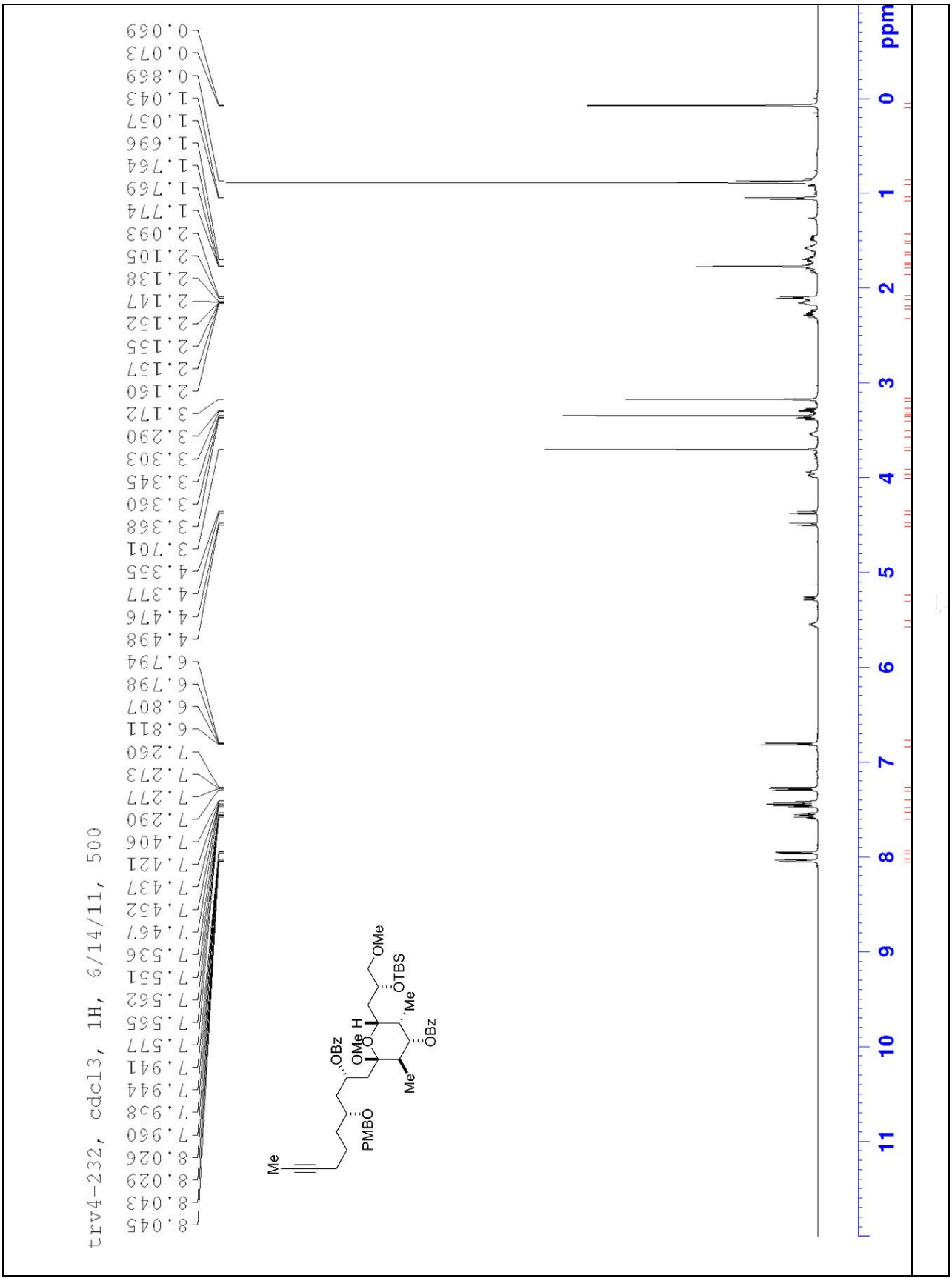

JSH_03_010 seco acid, cdcl3; 600
173.11
145.85
140.17
136.49
134.29
133.12
133.02
132.85
131.78
127.15
124.62
102.19
78.82
77.57
72.44
69.82
68.40
65.97
58.83
56.80
47.94
42.17
40.76
39.54
39.44
39.29
38.89
38.49
32.92
29.69
28.32
27.83
27.02
26.84
25.93
25.18
18.21
18.17
17.51
17.25
16.63
16.44
13.88
13.68
13.61
12.50
11.47
6.95
5.11
ppm
200
180
160
140
120
100
80
60
40
20
0
Me
Me
Me
Me
HO
O
OH
Me
OH
OMe H
O
MeO
OMe
OTBS
Me
Me
OH

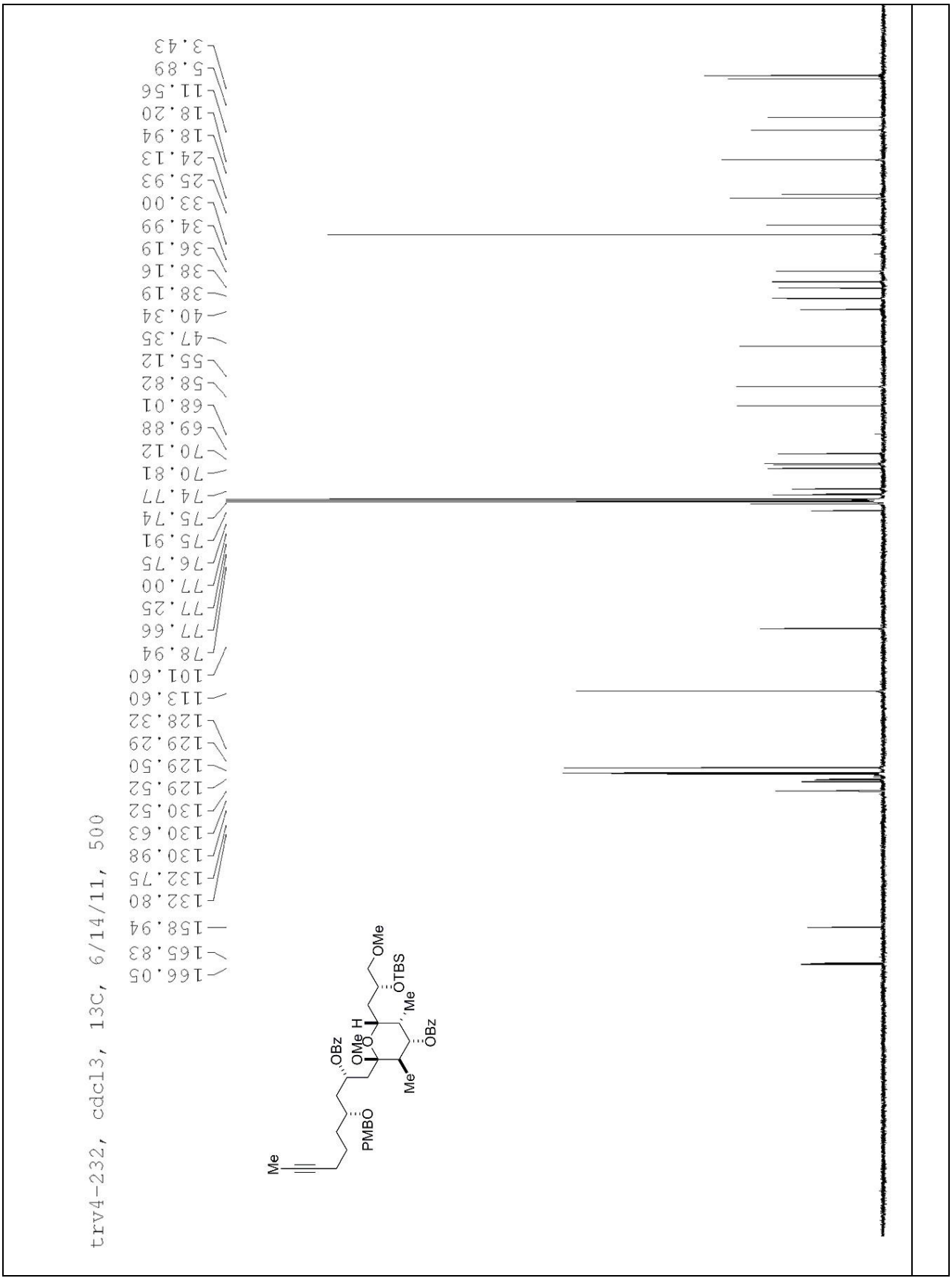

trv3-176 Major Product, 1H, CDCl3, 12/31/09, 600MHz
ppm
Me
Me
Me
Me
HO
MeO
OMe
H
O
O
O
OTBS
Me
Me
OH
OMe

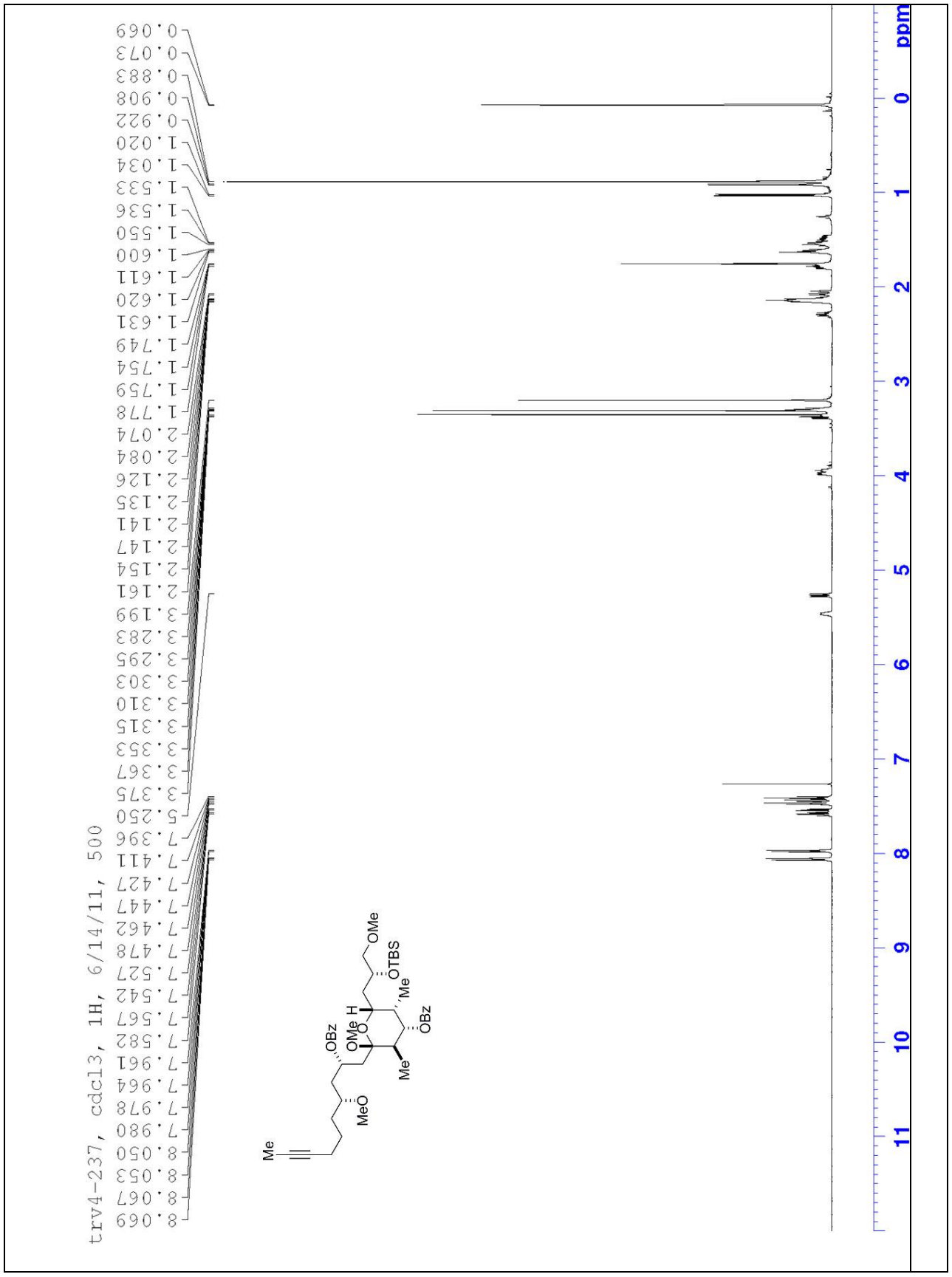

trv3-176 Major Product, 13C, CDCl3, 12/31/09, 600MHz
-4.69
-3.84
4.92
11.36
12.00
13.75
16.29
17.30
17.56
18.24
25.95
26.71
28.00
29.70
33.50
37.04
38.42
38.93
39.54
41.37
47.20
57.34
58.83
68.49
70.03
70.60
72.43
77.79
79.02
79.77
101.54
123.79
127.13
128.23
128.33
131.87
132.16
132.82
133.07
137.33
140.32
144.58
145.17
168.72
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
Me
Me
Me
Me
HO
O
O
MeO
OMe
H
O
OTBS
Me
Me
OH
OMe

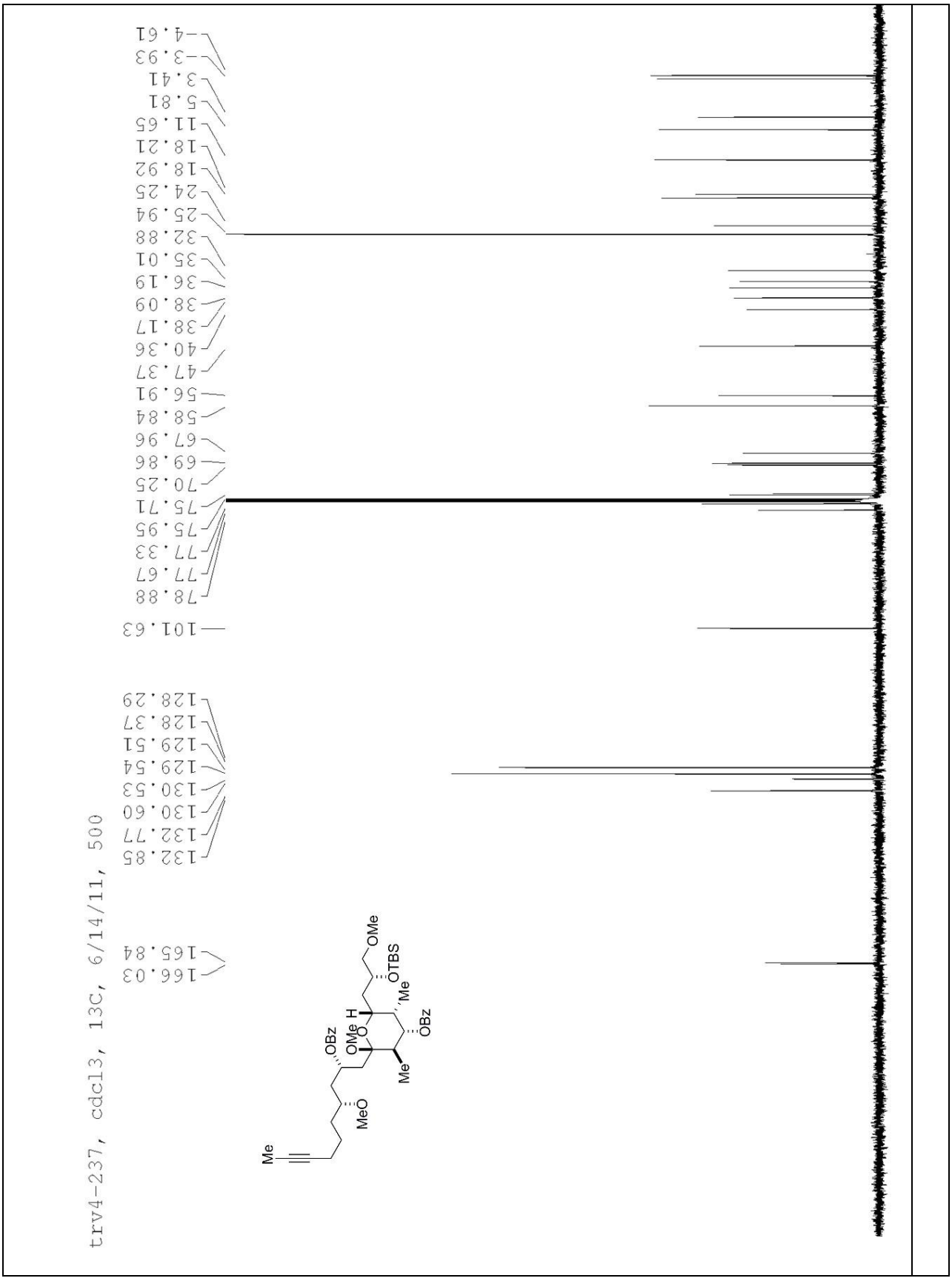

trv3-186, 1H, MeOD 700 MHz, 1/25/10
ppm
Me
Me
Me
Me
HO
Me
O
O
OH
H
O
MeO
Me
OH
Me
OMe

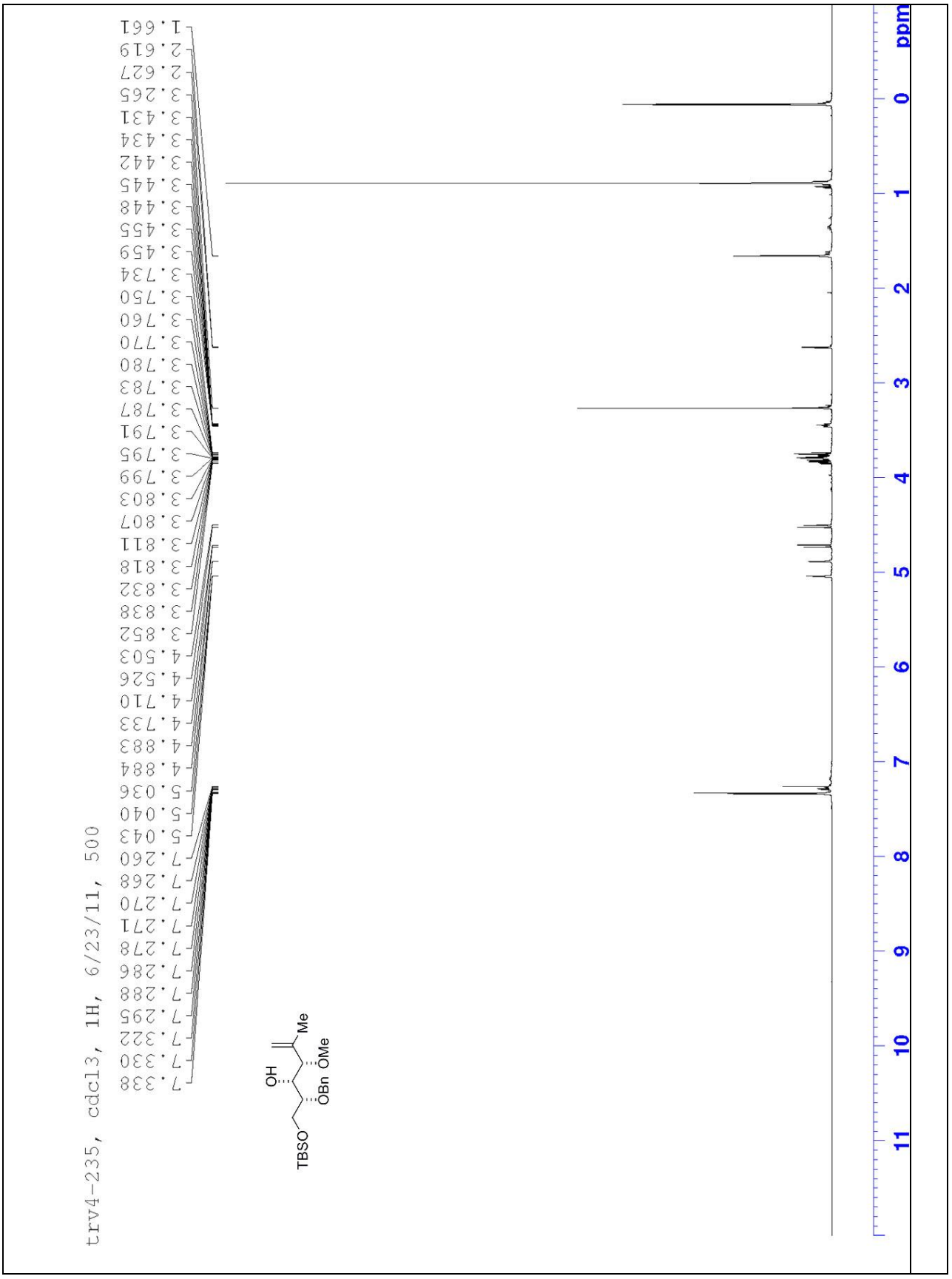

trv3-186, 13C, MeOD 700 MHz, 1/25/10
170.95
147.12
146.01
142.50
137.93
134.47
133.48
132.99
132.92
129.42
124.72
100.27
80.91
80.41
78.69
73.58
71.31
68.46
68.35
59.39
57.47
46.06
43.08
41.08
40.89
38.67
38.13
34.38
28.84
28.05
17.97
17.84
16.72
14.10
12.43
12.22
5.69
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
Me
Me
Me
Me
HO
MeO
O
O
OH
H
O
Me
OH
Me
OH
OMe

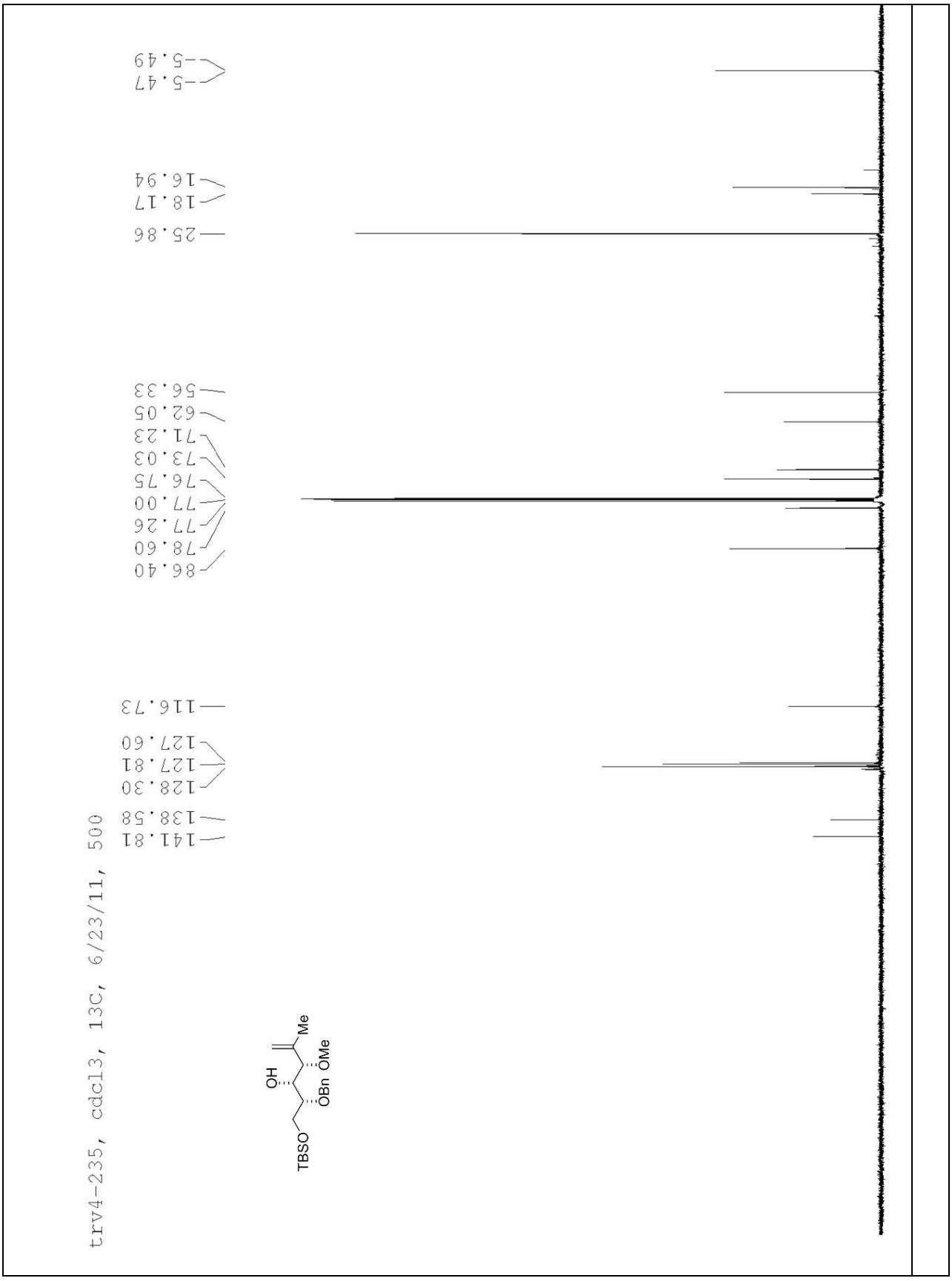

trv4-232, cdcl3, 1H, 6/14/11, 500
0.069
0.073
0.869
1.043
1.057
1.696
1.764
1.769
1.774
2.093
2.105
2.138
2.147
2.152
2.155
2.157
2.160
3.172
3.290
3.303
3.345
3.360
3.368
3.701
4.355
4.377
4.476
4.498
6.794
6.798
6.807
6.811
7.260
7.273
7.277
7.290
7.406
7.421
7.437
7.452
7.467
7.536
7.551
7.562
7.565
7.577
7.941
7.944
7.958
7.960
8.026
8.029
8.043
8.045
Me
PMBO
OBz
OMe
H
O
Me
OBz
Me
OTBS
OMe
ppm

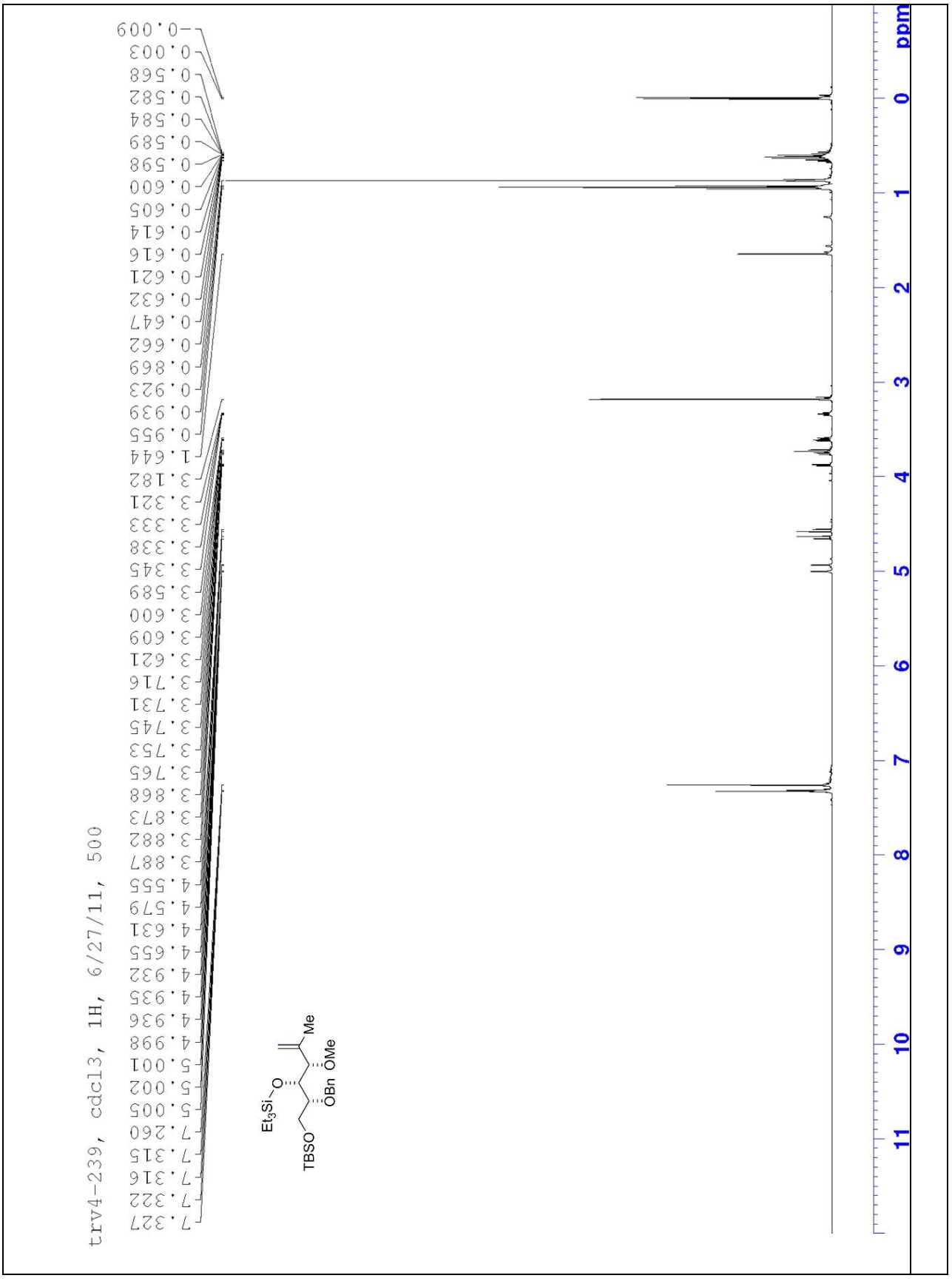

trv4-232, cdcl3, 13C, 6/14/11, 500
166.05
165.83
158.94
132.80
132.75
130.98
130.63
130.52
129.52
129.50
129.29
128.32
113.60
101.60
78.94
77.66
77.25
77.00
76.75
75.91
75.74
74.77
70.81
70.12
69.88
68.01
58.82
55.12
47.35
40.34
38.19
38.16
36.19
34.99
33.00
25.93
24.13
18.94
18.20
11.56
5.89
3.43
Me
PMBO
OBz
OMe
H
O
Me
OBz
Me
OTBS
OMe

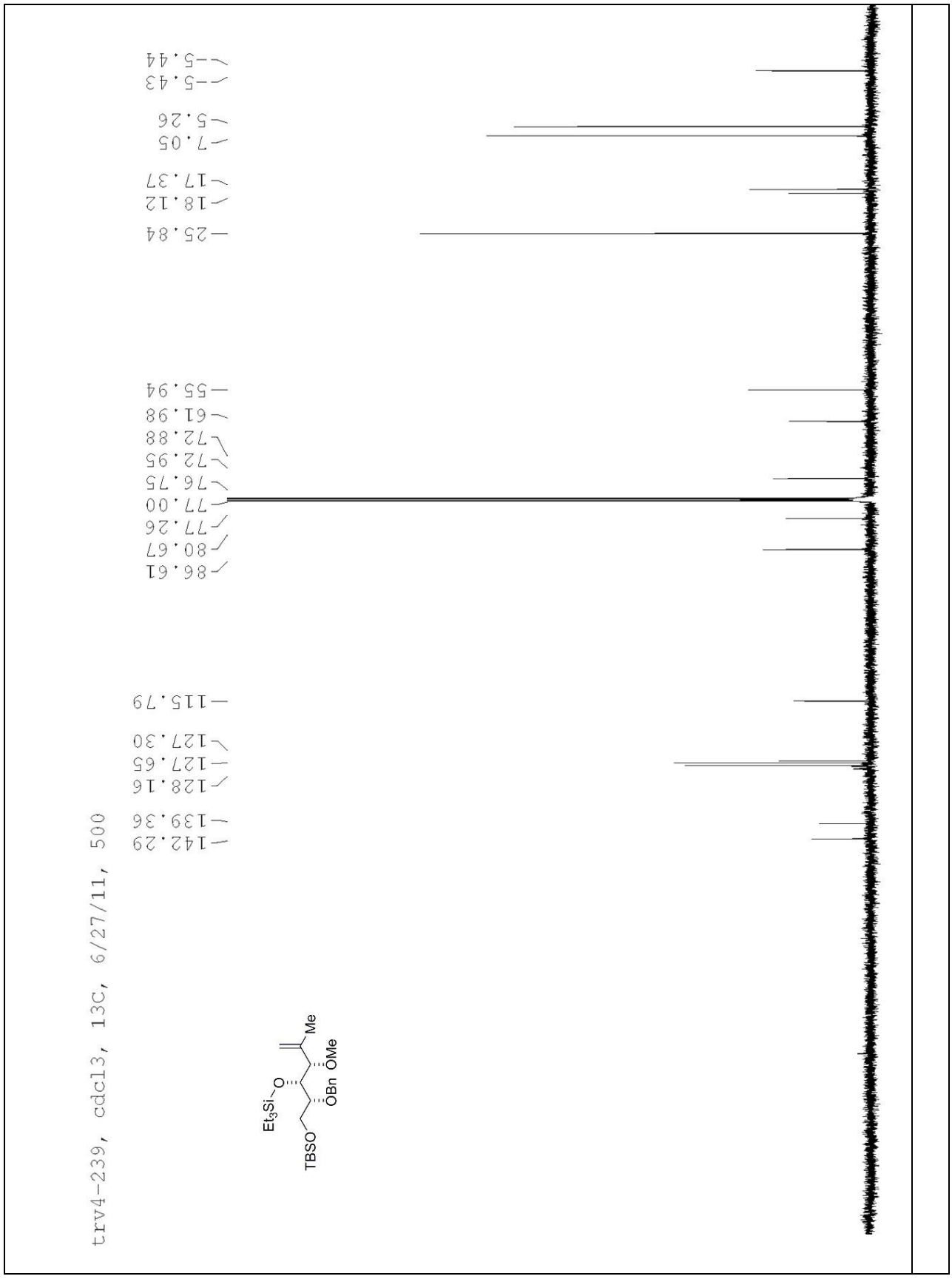

trv4-237, cdcl3, 1H, 6/14/11, 500
8.069
8.067
8.053
8.050
7.980
7.978
7.964
7.961
7.582
7.567
7.542
7.527
7.478
7.462
7.447
7.427
7.411
7.396
5.250
3.375
3.367
3.353
3.315
3.310
3.303
3.295
3.283
3.199
2.161
2.154
2.147
2.141
2.135
2.126
2.084
2.074
1.778
1.759
1.754
1.749
1.631
1.620
1.611
1.600
1.550
1.536
1.533
1.034
1.020
0.922
0.908
0.883
0.073
0.069
ppm
Me
MeO
OBz
OMe H
O
Me
OBz
Me
OTBS
OMe

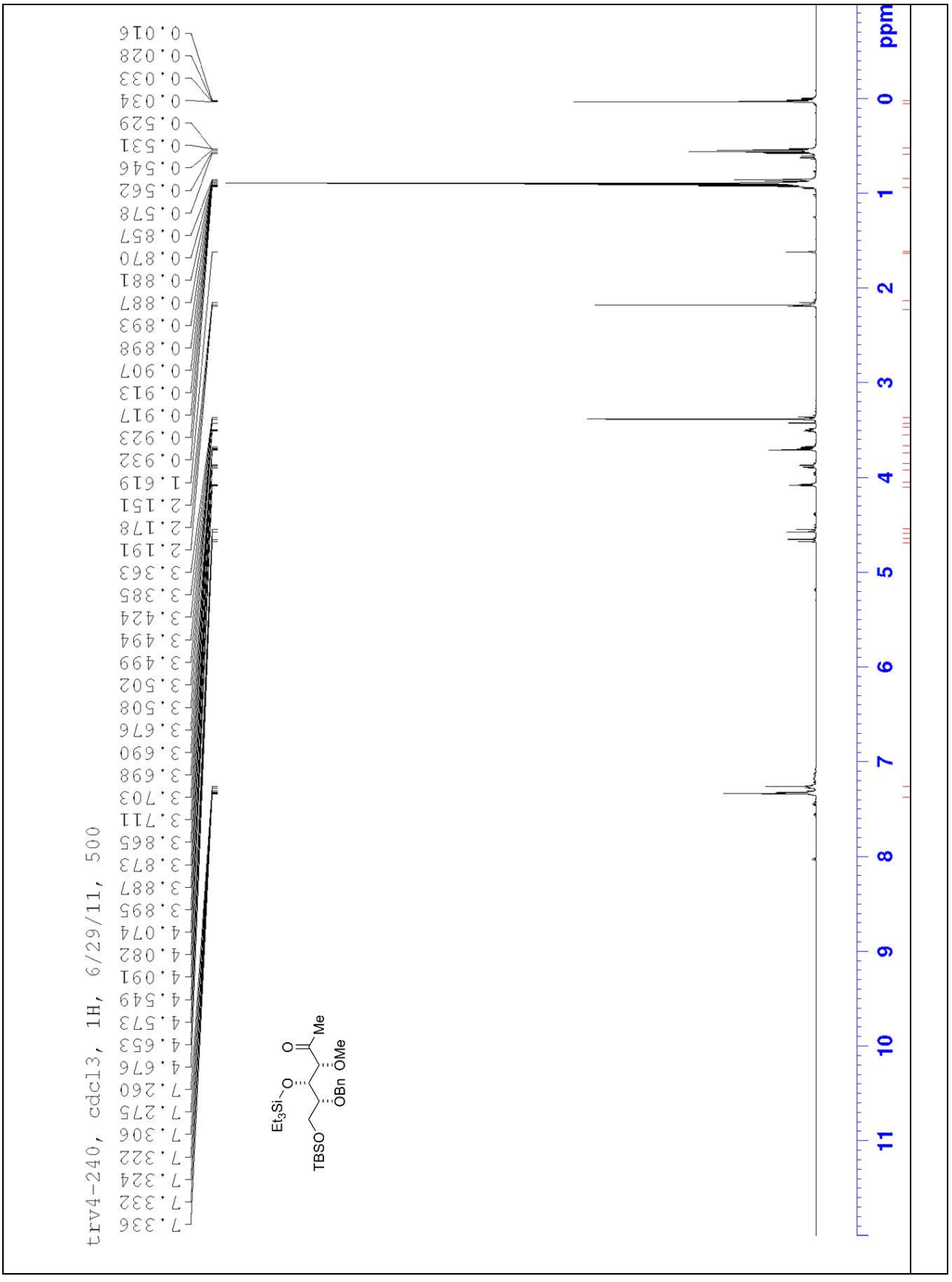

trv4-237, cdcl3, 13C, 6/14/11, 500
-4.61
-3.93
3.41
5.81
11.65
18.21
18.92
24.25
25.94
32.88
35.01
36.19
38.09
38.17
40.36
47.37
56.91
58.84
67.96
69.86
70.25
75.71
75.95
77.33
77.67
78.88
101.63
128.29
128.37
129.51
129.54
130.53
130.60
132.77
132.85
165.84
166.03
Me
MeO
OBz
OMe
H
O
Me
OBz
Me
OTBS
OMe

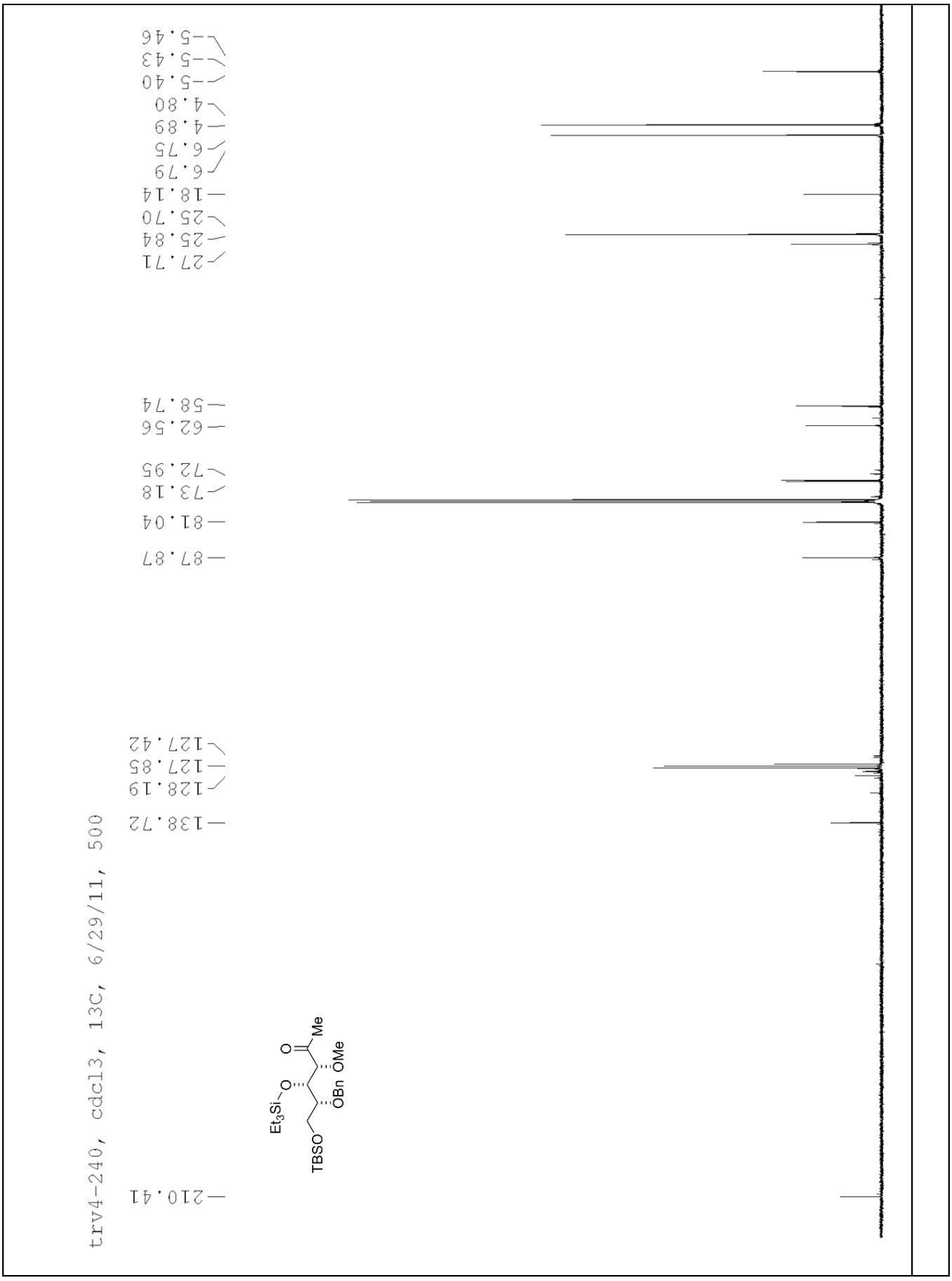

trv4-235, cdcl3, 1H, 6/23/11, 500
7.338
7.330
7.322
7.295
7.288
7.286
7.278
7.271
7.270
7.268
7.260
5.043
5.040
5.036
4.884
4.883
4.733
4.710
4.526
4.503
3.852
3.838
3.832
3.818
3.811
3.807
3.803
3.799
3.795
3.791
3.787
3.783
3.780
3.770
3.760
3.750
3.734
3.459
3.455
3.448
3.445
3.442
3.434
3.431
3.265
2.627
2.619
1.661
OH
Me
OBn OMe
TBSO
ppm
0
1
2
3
4
5
6
7
8
9
10
11

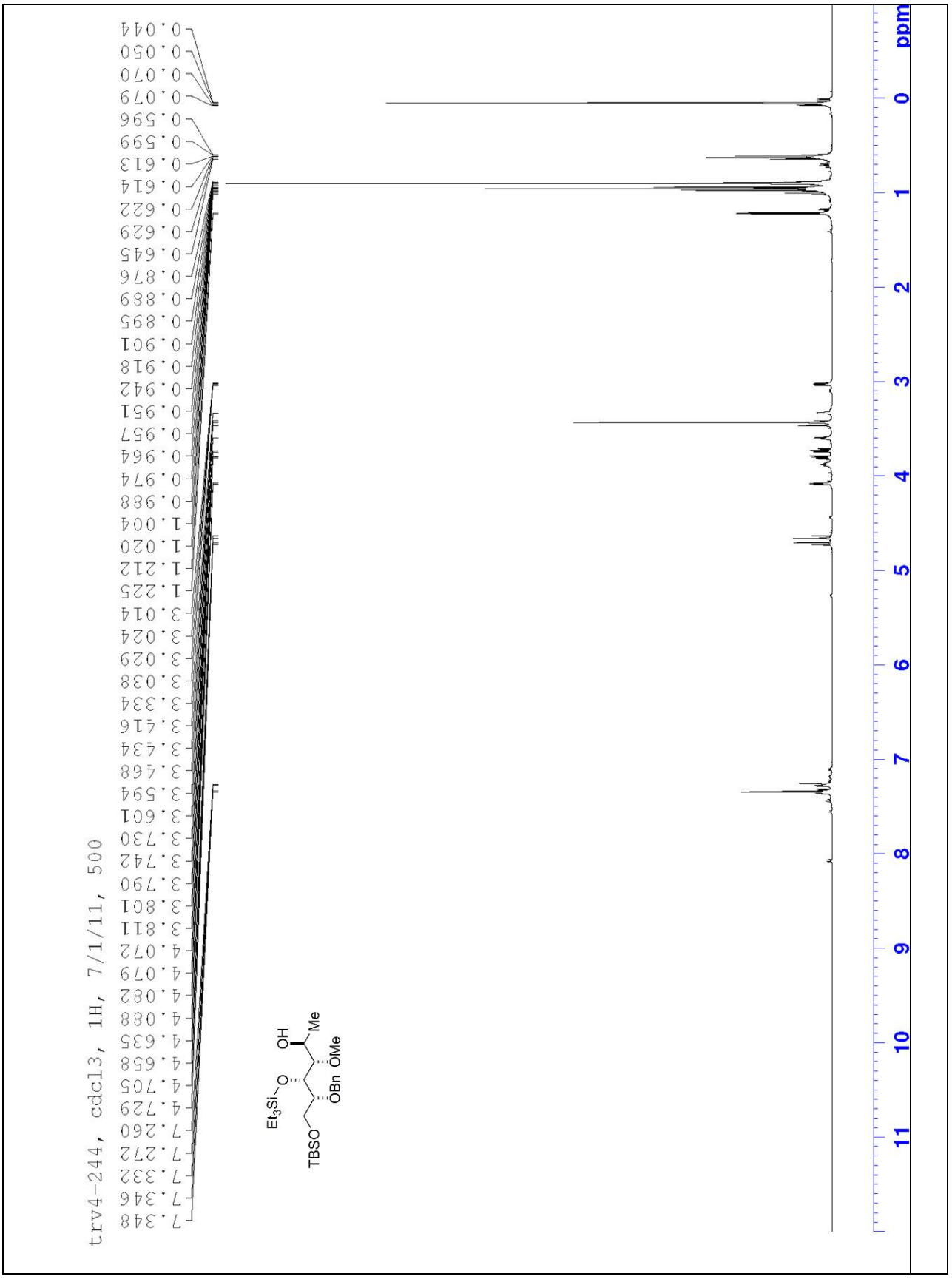

trv4-235, cdcl3, 13C, 6/23/11, 500
141.81
138.58
128.30
127.81
127.60
116.73
86.40
78.60
77.26
77.00
76.75
73.03
71.23
62.05
56.33
25.86
18.17
16.94
-5.47
-5.49
OH
Me
OBn
OMe
TBSO

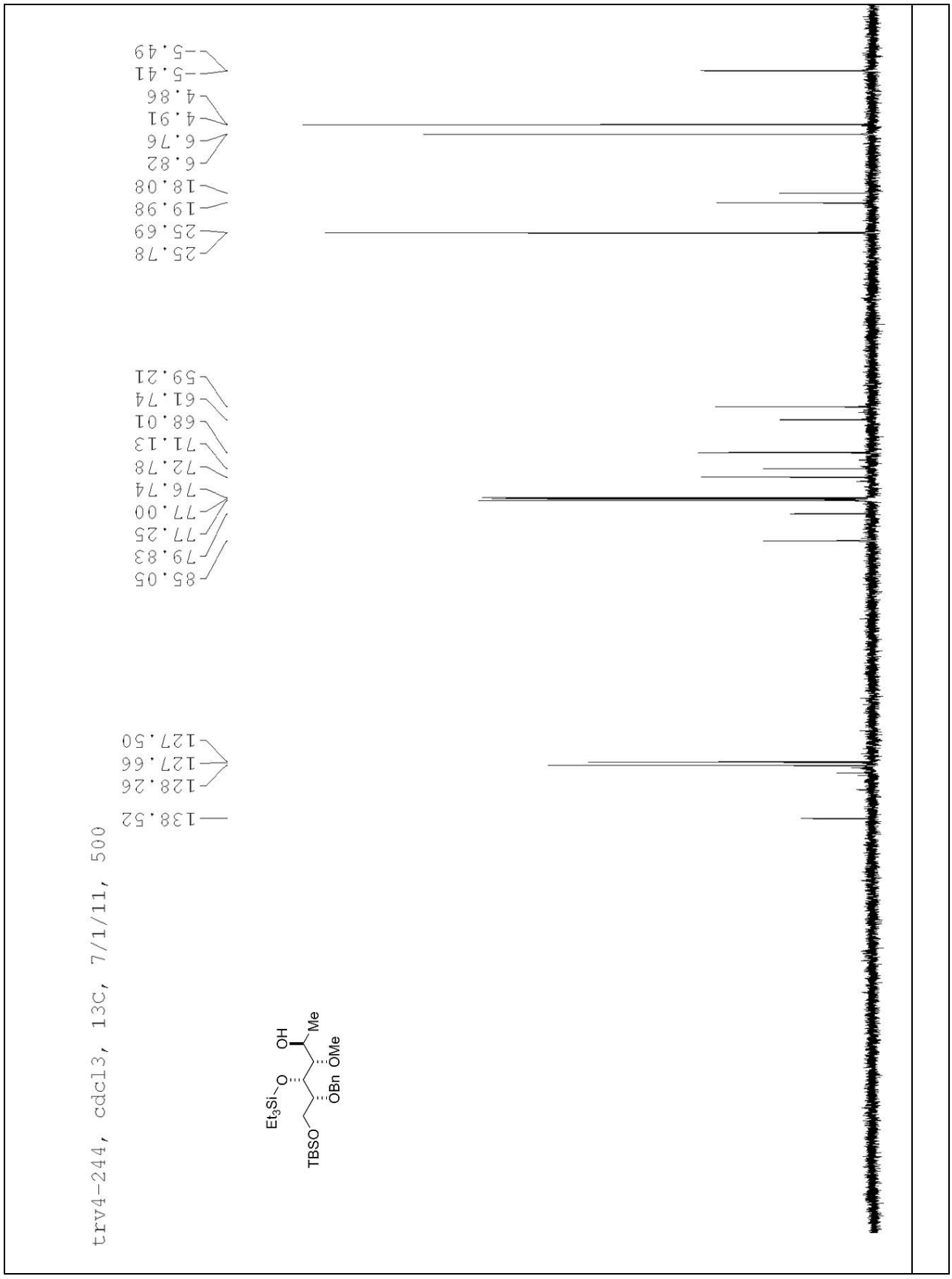

trv4-239, cdcl3, 1H, 6/27/11, 500
-0.009
0.003
0.568
0.582
0.584
0.589
0.598
0.600
0.605
0.614
0.616
0.621
0.632
0.647
0.662
0.869
0.923
0.939
0.955
1.644
3.182
3.321
3.333
3.338
3.345
3.589
3.600
3.609
3.621
3.716
3.731
3.745
3.753
3.765
3.868
3.873
3.882
3.887
4.555
4.579
4.631
4.655
4.932
4.935
4.936
4.998
5.001
5.002
5.005
7.260
7.315
7.316
7.322
7.327
Et3Si
O
TBSO
Me
OBn
OMe
ppm
0
1
2
3
4
5
6
7
8
9
10
11

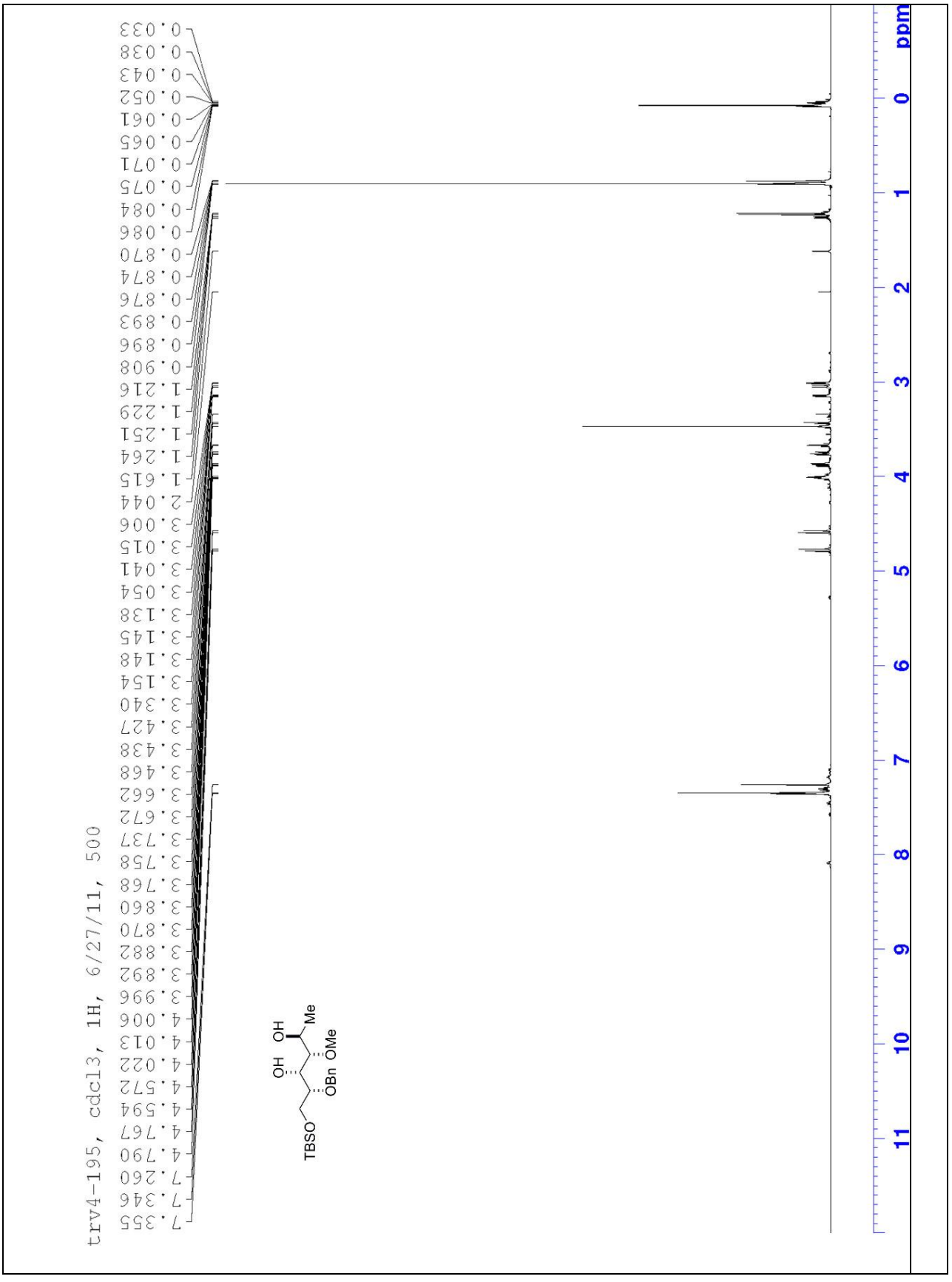

trv4-239, cdcl3, 13C, 6/27/11, 500
142.29
139.36
128.16
127.65
127.30
115.79
86.61
80.67
77.26
77.00
76.75
72.95
72.88
61.98
55.94
25.84
18.12
17.37
7.05
5.26
-5.43
-5.44
Et3Si
O
TBSO
OBn
OMe
Me

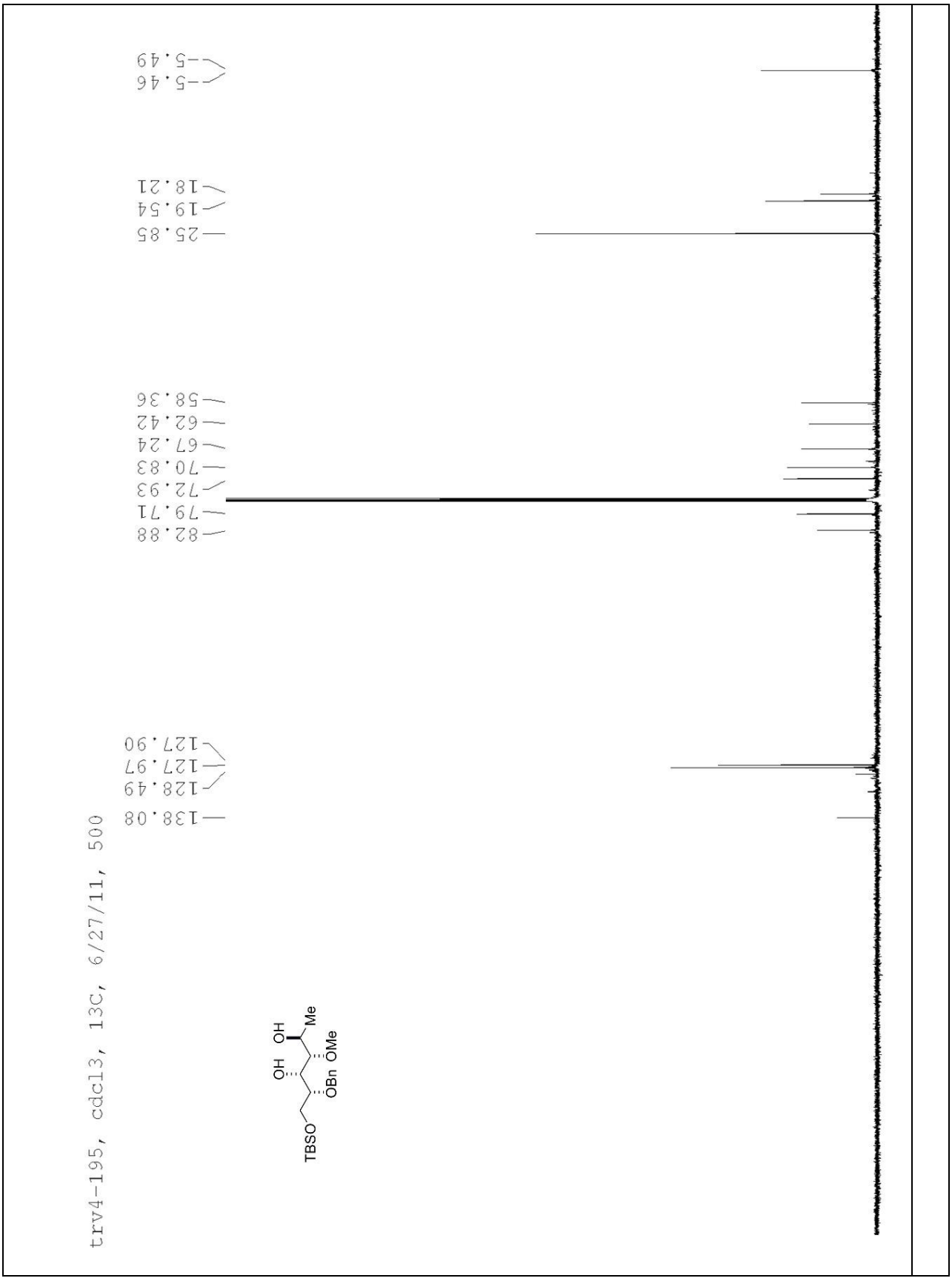

trv4-240, cdcl3, 1H, 6/29/11, 500
0.016
0.028
0.033
0.034
0.529
0.531
0.546
0.562
0.578
0.857
0.870
0.881
0.887
0.893
0.898
0.907
0.913
0.917
0.923
0.932
1.619
2.151
2.178
2.191
3.363
3.385
3.424
3.494
3.499
3.502
3.508
3.676
3.690
3.698
3.703
3.711
3.865
3.873
3.887
3.895
4.074
4.082
4.091
4.549
4.573
4.653
4.676
7.260
7.275
7.306
7.322
7.324
7.332
7.336
Et3Si
O
O
Me
TBSO
OBn
OMe
ppm
0
1
2
3
4
5
6
7
8
9
10
11

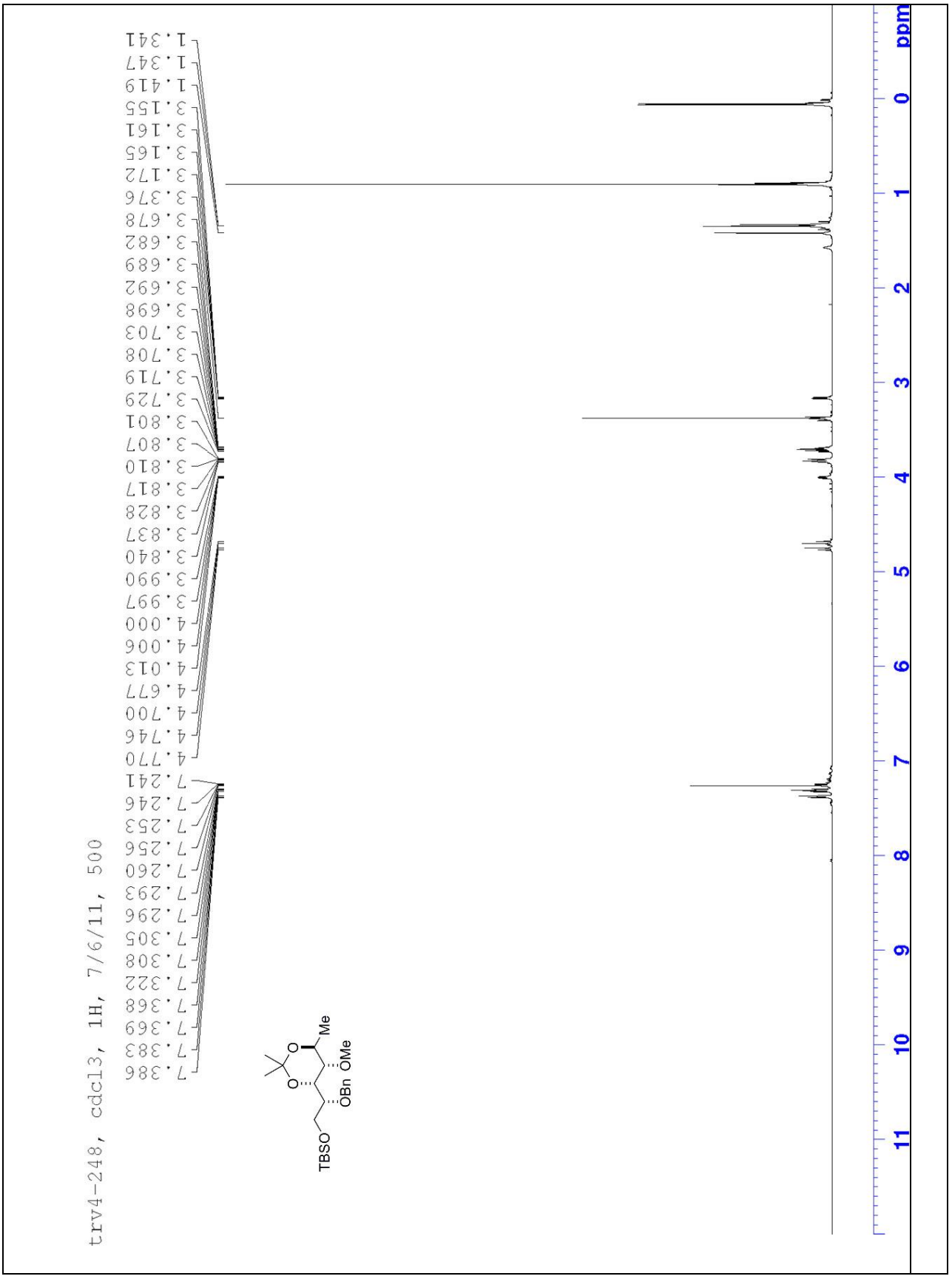

trv4-240, cdcl3, 13C, 6/29/11, 500
210.41
138.72
128.19
127.85
127.42
87.87
81.04
73.18
72.95
62.56
58.74
27.71
25.84
25.70
18.14
6.79
6.75
4.89
4.80
-5.40
-5.43
-5.46
Et3Si
O
TBSO
OBn
OMe
Me
O

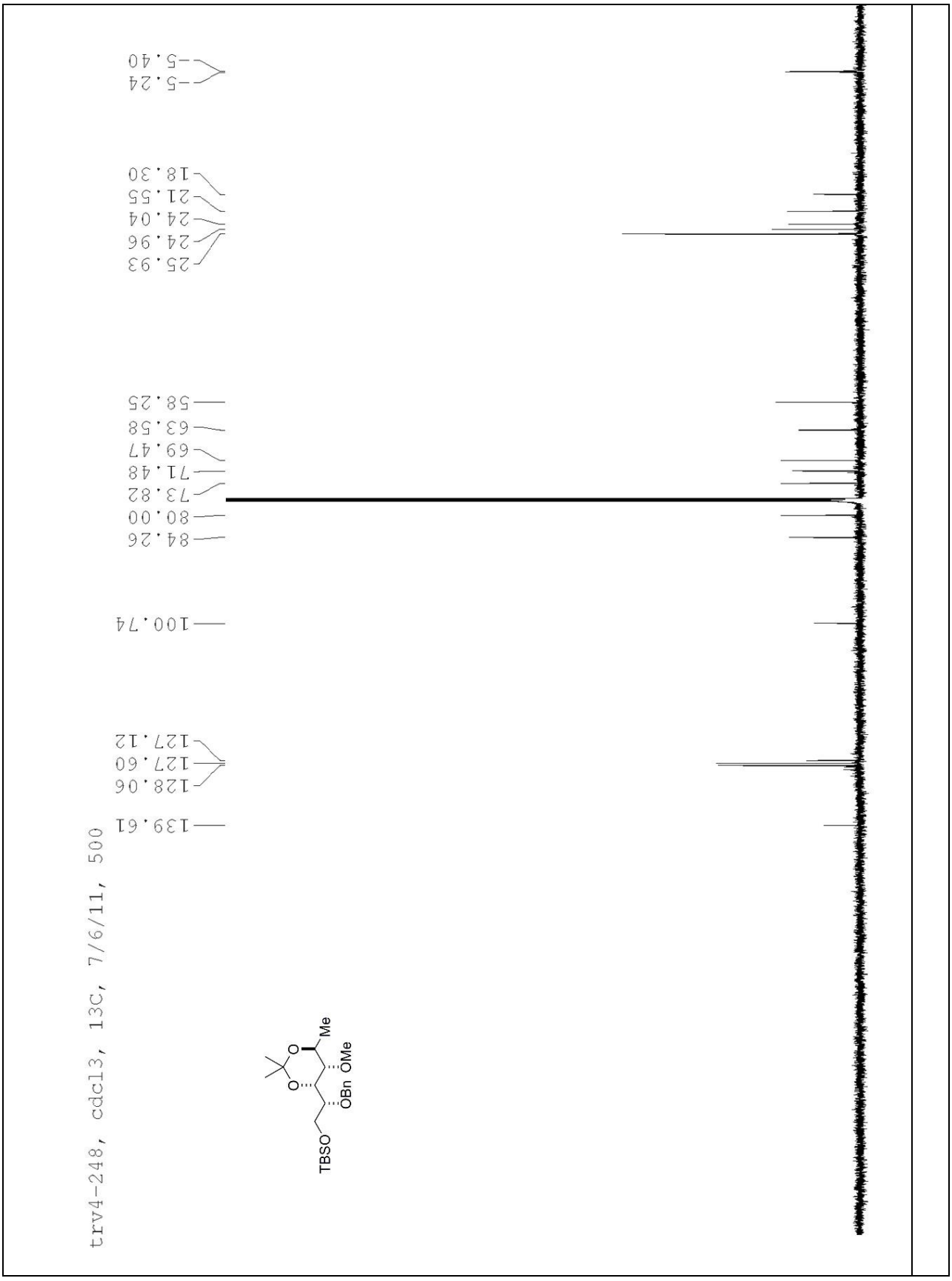

trv4-244, cdcl3, 1H, 7/1/11, 500
0.044
0.050
0.070
0.079
0.596
0.599
0.613
0.614
0.622
0.629
0.645
0.876
0.889
0.895
0.901
0.918
0.942
0.951
0.957
0.964
0.974
0.988
1.004
1.020
1.212
1.225
3.014
3.024
3.029
3.038
3.334
3.416
3.434
3.468
3.594
3.601
3.730
3.742
3.790
3.801
3.811
4.072
4.079
4.082
4.088
4.635
4.658
4.705
4.729
7.260
7.272
7.332
7.346
7.348
Et3Si
O
OH
Me
TBSO
OBn
OMe
ppm
0
1
2
3
4
5
6
7
8
9
10
11

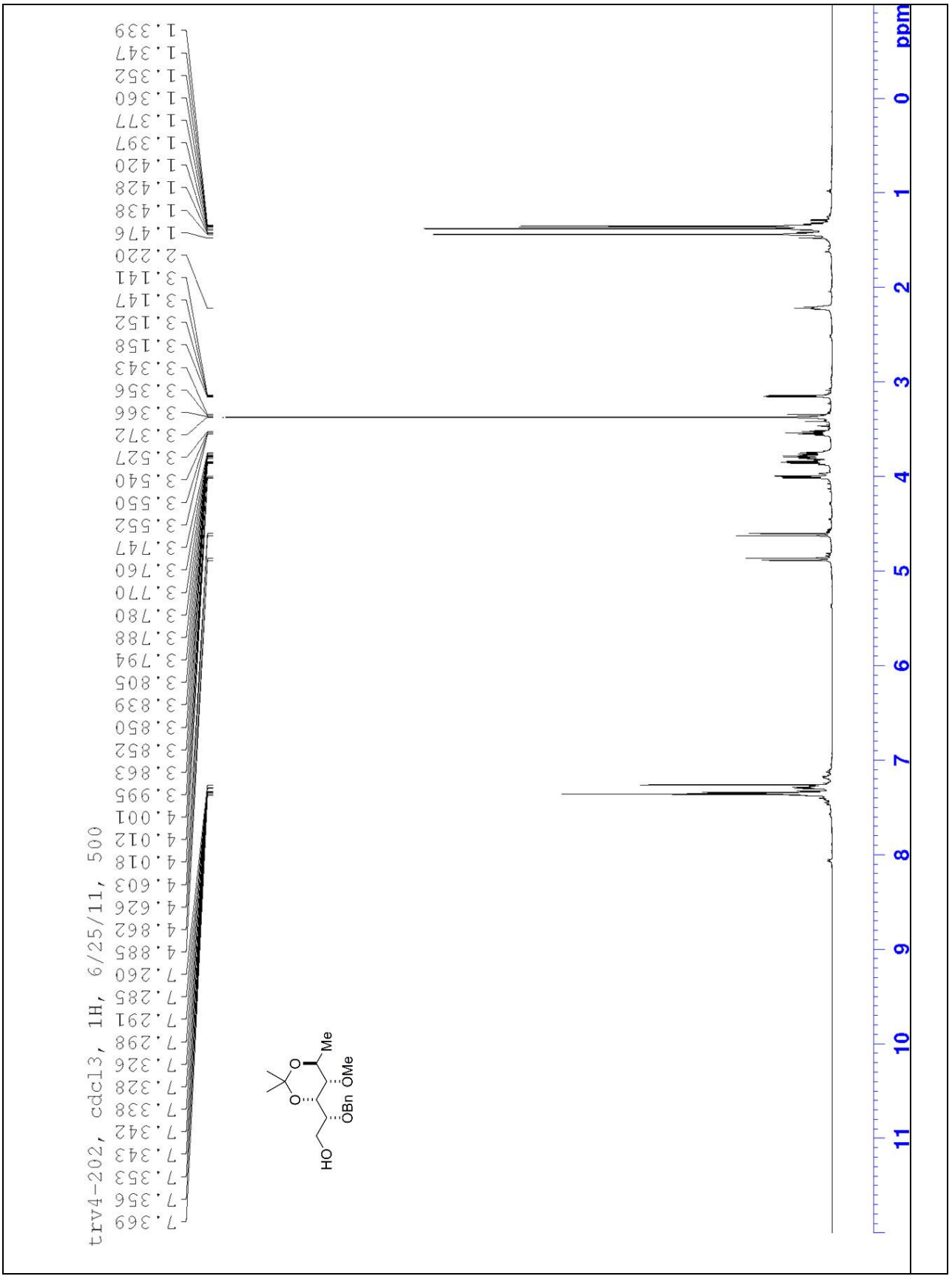

trv4-244, cdcl3, 13C, 7/1/11, 500
-5.49
-5.41
4.86
4.91
6.76
6.82
18.08
19.98
25.69
25.78
59.21
61.74
68.01
71.13
72.78
76.74
77.00
77.25
79.83
85.05
127.50
127.66
128.26
138.52
Et3Si
O
OH
Me
OBn
OMe
TBSO

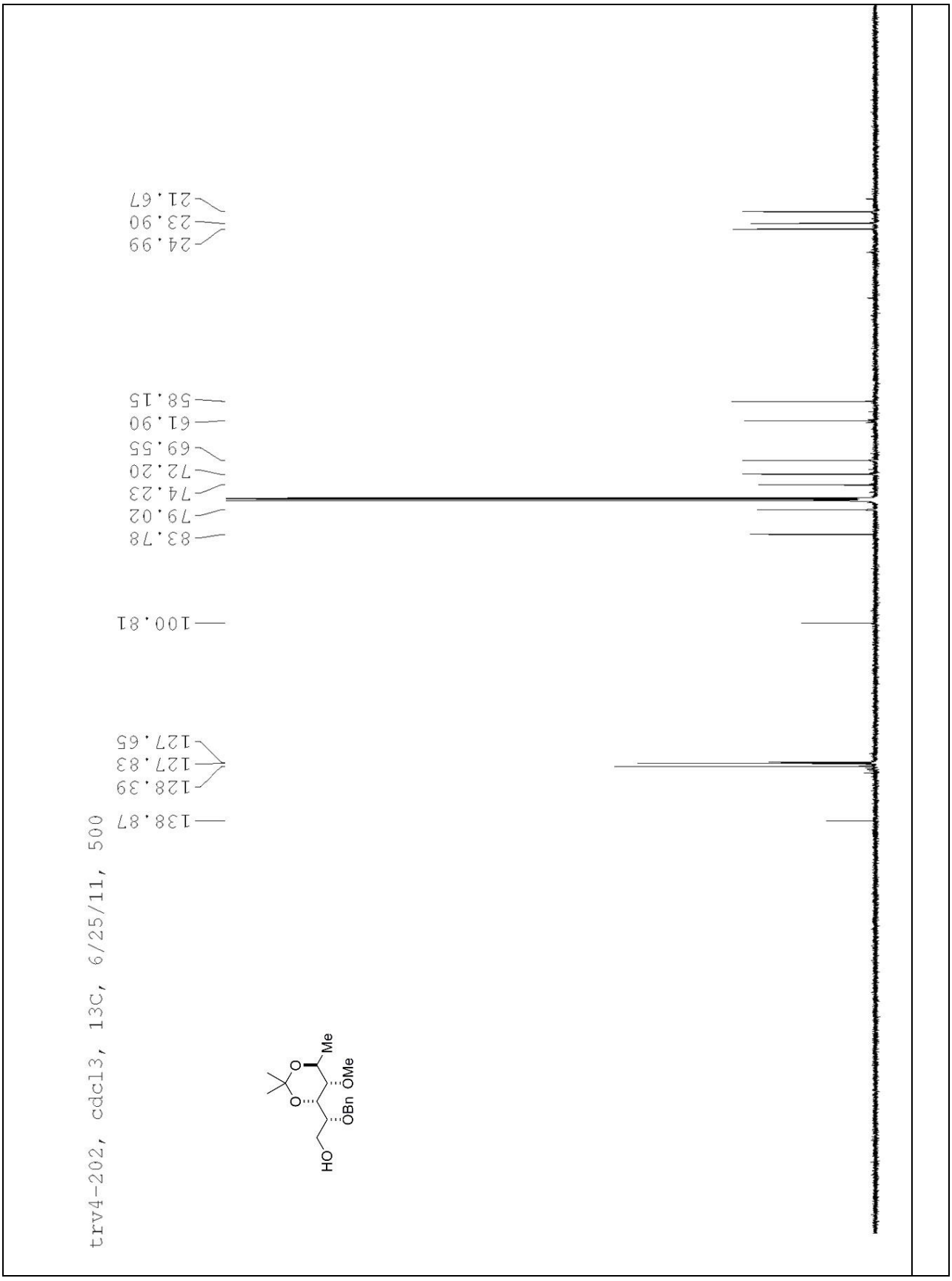

trv4-195, cdcl3, 1H, 6/27/11, 500
0.033
0.038
0.043
0.052
0.061
0.065
0.071
0.075
0.084
0.086
0.870
0.874
0.876
0.893
0.896
0.908
1.216
1.229
1.251
1.264
1.615
2.044
3.006
3.015
3.041
3.054
3.138
3.145
3.148
3.154
3.340
3.427
3.438
3.468
3.662
3.672
3.737
3.758
3.768
3.860
3.870
3.882
3.892
3.996
4.006
4.013
4.022
4.572
4.594
4.767
4.790
7.260
7.346
7.355
OH
OH
Me
TBSO
OBn
OMe
ppm
0
1
2
3
4
5
6
7
8
9
10
11

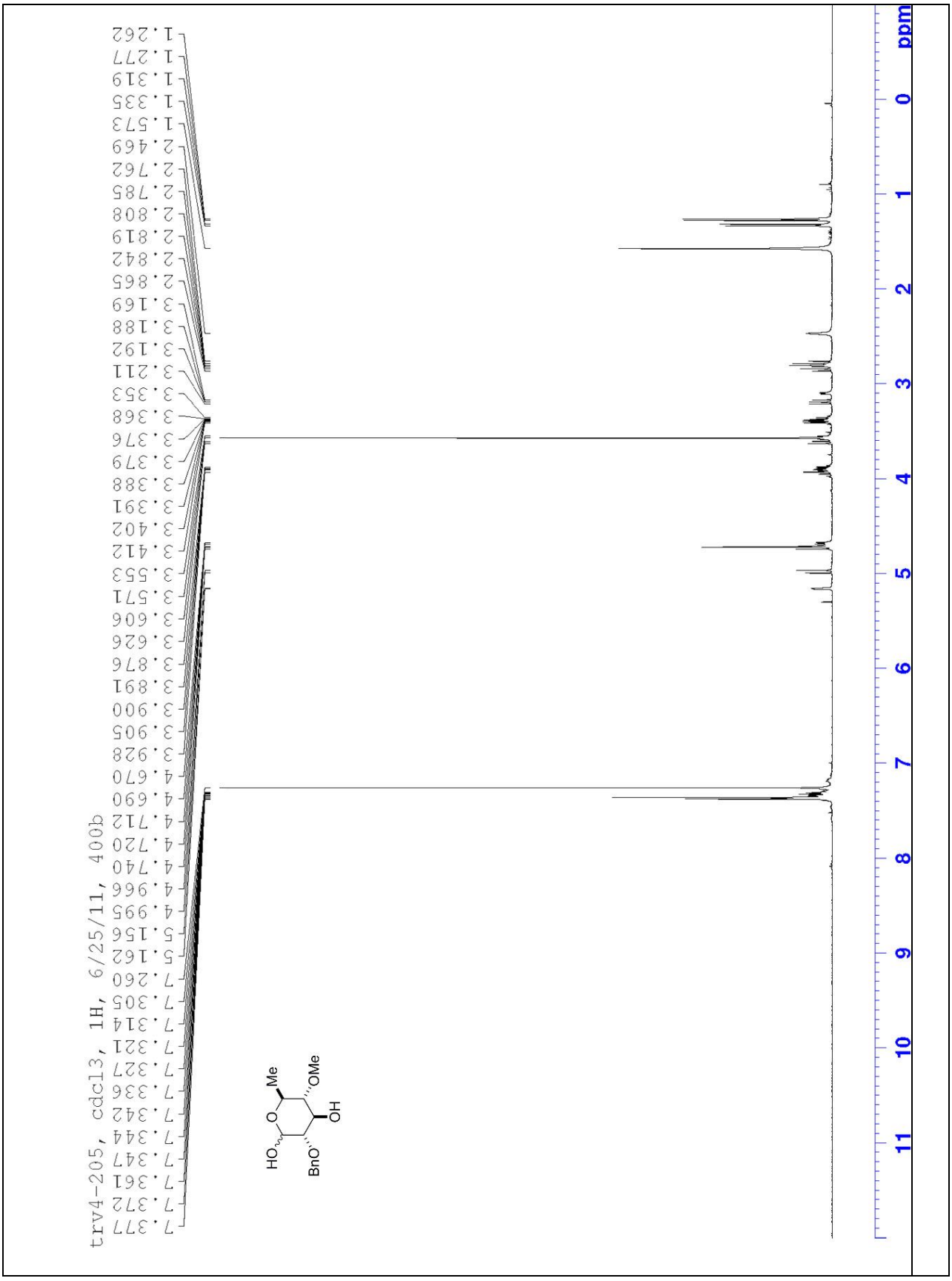

trv4-195, cdcl3, 13C, 6/27/11, 500
138.08
128.49
127.97
127.90
82.88
79.71
72.93
70.83
67.24
62.42
58.36
25.85
19.54
18.21
-5.46
-5.49
TBSO
OBn
OMe
OH
OH
Me


trv4-248, cdcl3, 1H, 7/6/11, 500
7.386
7.383
7.369
7.368
7.322
7.308
7.305
7.296
7.293
7.260
7.256
7.253
7.246
7.241
4.770
4.746
4.700
4.677
4.013
4.006
4.000
3.997
3.990
3.840
3.837
3.828
3.817
3.810
3.807
3.801
3.729
3.719
3.708
3.703
3.698
3.692
3.689
3.682
3.678
3.376
3.172
3.165
3.161
3.155
1.419
1.347
1.341
TBSO
OBn
OMe
Me
ppm


trv4-248, cdcl3, 13C, 7/6/11, 500
-5.40
-5.24
18.30
21.55
24.04
24.96
25.93
58.25
63.58
69.47
71.48
73.82
80.00
84.26
100.74
127.12
127.60
128.06
139.61
TBSO
OBn
OMe
Me
O
O


trv4-202, cdcl3, 1H, 6/25/11, 500
7.369
7.356
7.353
7.343
7.342
7.338
7.328
7.326
7.298
7.291
7.285
7.260
4.885
4.862
4.626
4.603
4.018
4.012
4.001
3.995
3.863
3.852
3.850
3.839
3.805
3.794
3.788
3.780
3.770
3.760
3.747
3.552
3.550
3.540
3.527
3.372
3.366
3.356
3.343
3.158
3.152
3.147
3.141
2.220
1.476
1.438
1.428
1.420
1.397
1.377
1.360
1.352
1.347
1.339
Me
OMe
OBn
HO
ppm
0
1
2
3
4
5
6
7
8
9
10
11


trv4-202, cdcl3, 13C, 6/25/11, 500
138.87
128.39
127.83
127.65
100.81
83.78
79.02
74.23
72.20
69.55
61.90
58.15
24.99
23.90
21.67
Me
OMe
OBn
HO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1.319
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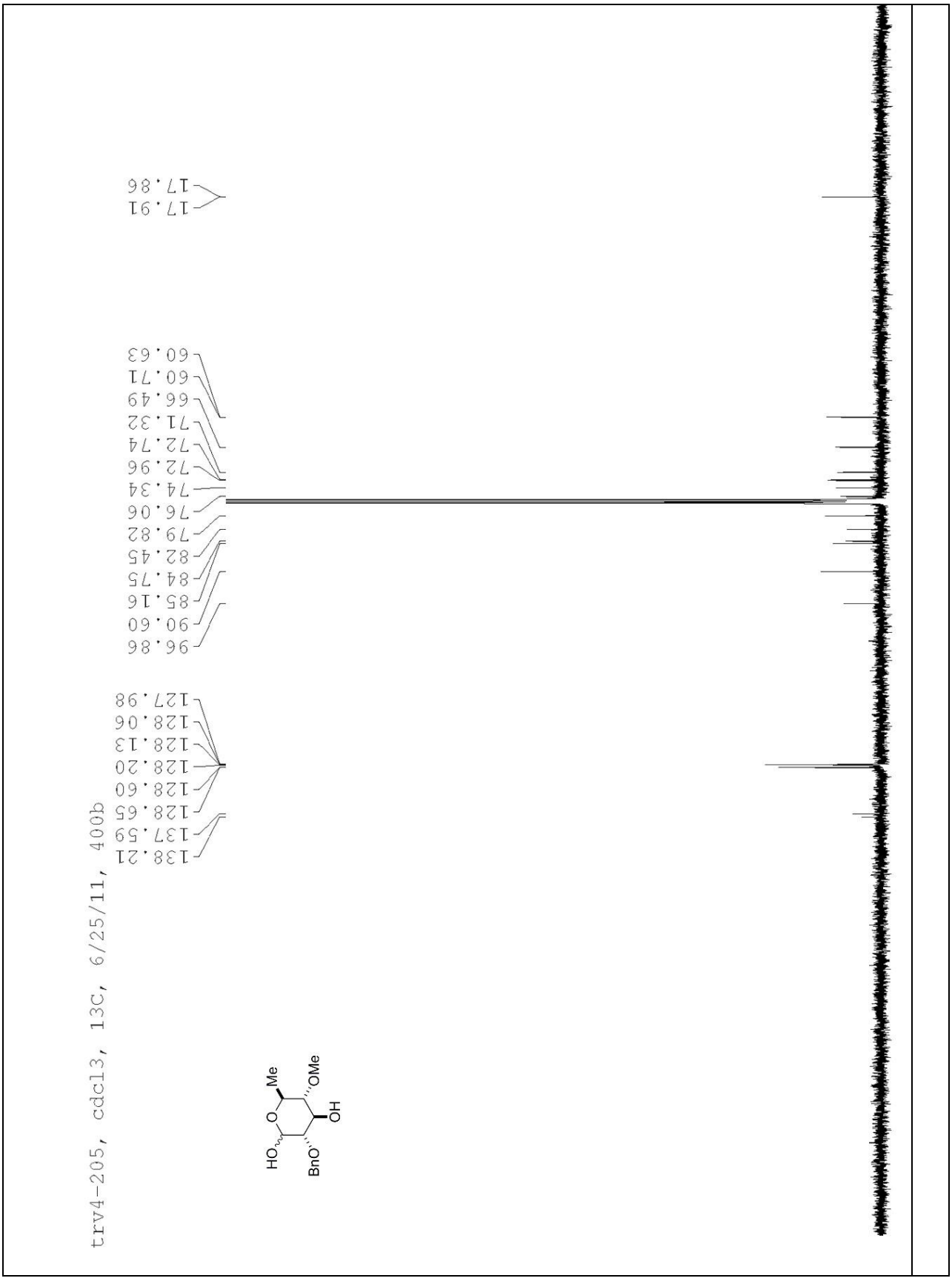
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O

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