UNIVERSITY OF CALIFORNIA,
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Investigations into the Effect of Solvent Polarity on the Stereoselective Synthesis of Carbocycles and Heterocycles *via* the Pinacol-Terminated Prins Cyclization

THESIS

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by

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Committee Chair

University of California, Irvine
2005

DEDICATION

A

mis tres mamás

Elena, Lydia y Margoth

A

mis dos papás

Abuelito Ramón y Tío Reinaldo

&

A

la hermanita mas bella

Lydia Theresa

mi eterno amor

y

gratitud

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ABSTRACT OF THE THESIS

Investigations into the Effect of Solvent Polarity on the Stereoselective Synthesis of Carbocycles and Heterocycles *via* the Pinacol-Terminated Prins Cyclization

By

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Professor Larry E. Overman, Chair

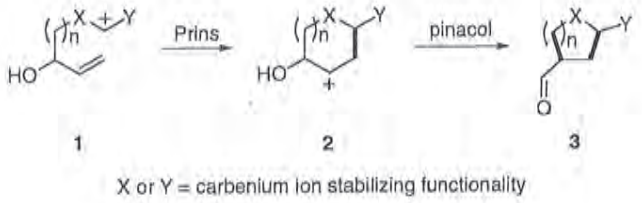
Regardless of the acid employed to promote the pinacol-terminated Prins cyclization of allylic silyl ether **13**, the selective formation of either carbocyclic products is possible. Cyclopentanone **14** is isolated when the reaction is performed in a non-polar reaction medium, while **12** is isolated when an aqueous solvent system is utilized. It is proposed that this reactivity can be attributed to the stereoelectronic effects that the allylic substituents exert on the nucleophilicity of the terminal alkene in the early and late transition states of the Prins cyclization. A shift from an early to a late transition state can be achieved through the use of an aqueous reaction medium, thereby effecting the reversal in stereoselectivity that is observed. The rearrangement of acetal **29** displays the same pattern in reactivity, as both heterocyclic products, **30** and **31**, may be selectively isolated depending upon whether or not an aqueous solvent is employed. Aside from shedding further light upon our mechanistic understanding of the Prins-pinacol reaction, this study expands upon our model for stereoselection and increases its predictive power. This experimental link between solvent and stereoselectivity enhances the synthetic utility and scope of this already powerful tandem reaction sequence.

Chapter 1: Introduction

The goal of organic synthesis is the construction of molecular complexity from relatively simple compounds. The pinacol-terminated Prins cyclization is a method that has been shown to accomplish this objective.[1] The general strategy of this reaction is one which employs a carbenium ion (**1**) that is stabilized by either the X or Y atoms, which typically are O, N, or S (Scheme 1). The Prins cyclization results in the conversion of **1** to carbocation **2**, which forms cyclic carbonyl compound **3** upon the pinacol rearrangement.

This rearranged product, which boasts two newly formed C-C bonds (highlighted in black), may be either a cyclic carbocycle or cyclic heterocycle that can vary in size.

Scheme 1. General Strategy of the Pinacol-Terminated Prins Cyclization

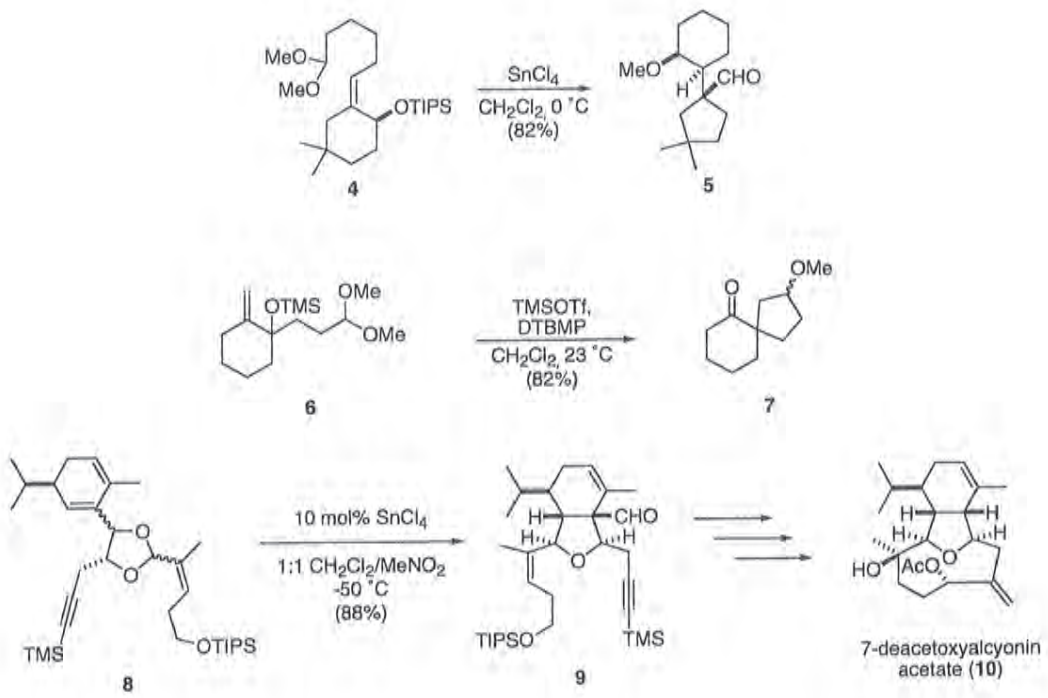


1 2 3

X or Y = carbenium ion stabilizing functionality

As a result of the versatility of the Prins-pinacol reaction, the stereocontrolled synthesis of various carbocycles and heterocycles has been realized (Figure 1). The stereoselective syntheses of attached (**5**), spirocyclic (**7**), and bicyclic carbocycles has been accomplished in high yields.[2] Heterocycles of high complexity can also be formed through the application of the Prins-pinacol reaction.[3] Implementation of this reaction sequence has allowed for the stereocontrolled total syntheses of various natural products, including 7-deacetoxyalcyonin acetate (**10**).[4]

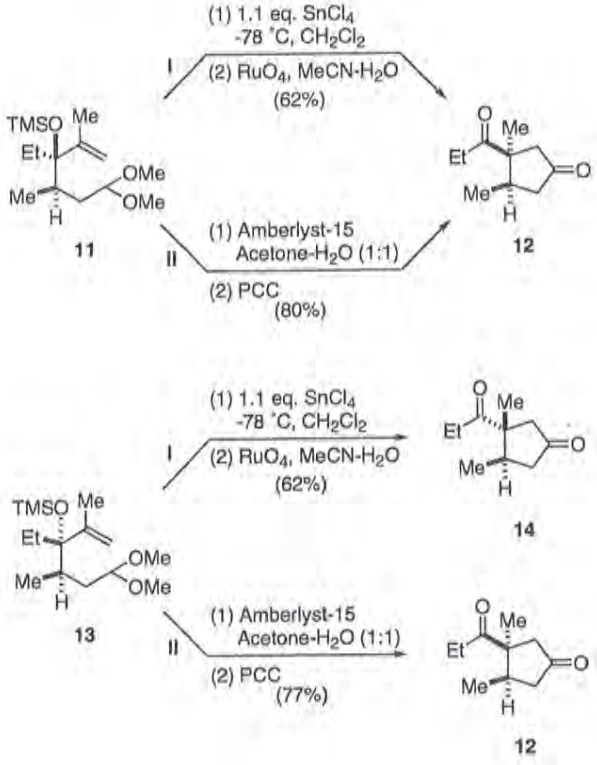
Figure 1. Examples of the Prins-pinacol synthesis of carbocycles and heterocycles.



Recent studies in the Overman group aimed at expanding the scope of the acid promoted Prins-pinacol rearrangement have focused upon the stereoselective synthesis of carbocycles. The general method of initiating the Prins-pinacol reaction sequence is treatment of an appropriate compound with a Lewis acid (typically tin tetrachloride) in a suitable solvent, generally methylene chloride. It was demonstrated by work performed by Timothy Gahman that under these conditions, carbocycle **12** is obtained selectively from acetal **11**, after oxidation (conditions **I**, Scheme 2).[5,6] Treatment of acetal **13** under identical conditions furnished, after oxidation, isomeric ketone **14** as a single stereoisomer. While surveying conditions under which the Prins-pinacol reaction could be promoted, it was found that conducting the rearrangement of **11** with Amberlyst-15 in an acetone/water solvent mixture effectively yields **12**, after oxidation, as a single stereoisomer (conditions **II**). Carrying-out the reaction with epimeric acetal **13** under identical conditions afforded solely diketone **12**, and not the expected carbocycle **14**. In order to understand the unexpected results summarized in Scheme 2, a study was

undertaken probing the effects of both acid and solvent on the stereoselectivity of the Prins-pinacol reaction. The data gathered from these experiments would also serve to further elucidate mechanistic details of the pinacol-terminated Prins cyclization.

Scheme 2. Previous Results of the Rearrangement of Dimethyl Acetals 11 and 13

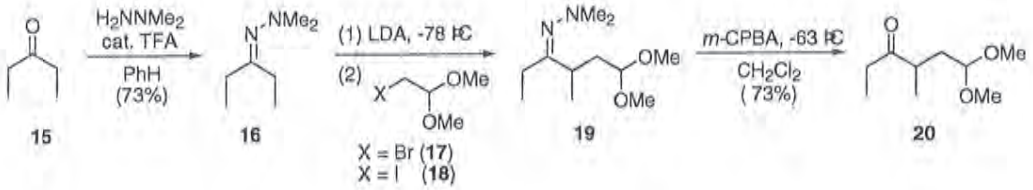


Chapter 2: Results

Preparation of Dimethyl Acetals 11 and 13.[5,6] In order to initiate the study, the syntheses of dimethyl acetals **11** and **13** had to be carried-out. The direct alkylation of 3-pentanone with bromoacetaldehyde dimethylacetal is known to proceed poorly. Therefore, the corresponding hydrazone of 3-pentanone (**16**) was prepared by treatment of 3-pentanone with dimethylhydrazine in refluxing benzene (Scheme 3). Unfortunately, the alkylation of **16** with dimethylacetal **17** consistently furnished low yields. In an attempt to form the more reactive iodoacetaldehyde dimethylacetal *in situ*, tetrabutylammonium iodide was added to the reaction mixture. This reaction

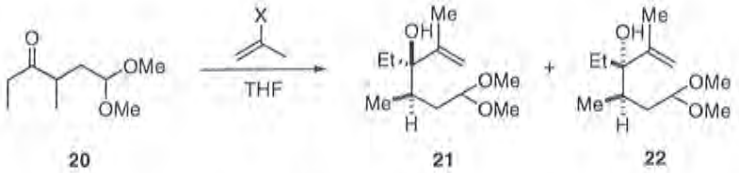
modification did not significantly improve the outcome of the reaction. An efficient solution to this problem was found by direct alkylation of **16** with iodide **18**, furnishing the desired ketone in 73% yield upon removal of the hydrazone moiety with *m*-CPBA.

Scheme 3. Synthesis of Dimethyl Acetals 11 and 13



Installment of the allylic alcohol moiety in the target molecules was performed by the addition of 2-lithiopropene to ketone **20**. It had been previously found that the addition of 2-lithiopropene at –78 °C, followed by warming to room temperature over 6 h, afforded allylic alcohols **21** and **22** in a ratio of 4:1 (entry 1, Table 1).[5] Since the focus of our studies is primarily on the reactivity of dimethylacetal **22**, conditions that improved the diastereoselectivity in favor of this compound were desired. Warming the reaction mixture to 23 °C immediately following the addition of the vinyllithium at –78 °C changed the diastereoselectivity to 2:1 in favor of dimethylacetal **21** (entry 2). The addition of isopropenylmagnesium bromide rather than 2-lithiopropene resulted in a selectivity of 2:1 in favor of **21**, but the yield dropped from 79 to 65% (entry 3). Increasing the temperature at which the addition of 2-lithiopropene takes place to 0 °C did not alter the diastereoselectivity of the reaction, but the yield was improved to 93% (entry 4). Based upon the results displayed in Table 1, it was determined that the method of choice for maximizing the yield of **22** was the procedure described in entry 4.

Table 1. Addition of isopropenyl carbanion to ketone **20**.



20 **21** **22**

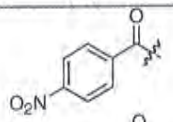
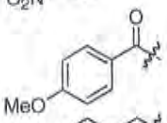
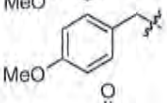
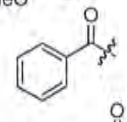
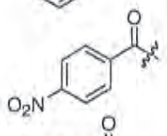
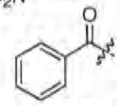
Entry	X	Initial T (°C)	Final T (°C)	t (min)	**21**:**22**	Yield (%)[b]
1[a]	Li	–78	23	360	4:1	82
2	Li	–78	23	5	2:1	79
3	MgBr	0	23	180	2:1	65
4	Li	0	23	5	2:1	93

[a] Gahman, T. C. Ph. D. dissertation, 1994, University of California, Irvine. [b] Isolated yields

In order to finalize the synthesis of the desired silyl ethers, the separation of isomers **21** and **22** had to be performed efficiently. Flash column chromatography on silica gel, with or without added $AgNO_3$, was an unsuccessful method for separating the epimeric alcohols. Separation could only be achieved by HPLC. To improve detection of these isomers some time was invested in the installation of a chromophore. Not surprisingly, a number of conditions for the functionalization of the isomeric tertiary alcohol mixture **23** were unsuccessful (Table 2). Fortunately, it was found that the treatment of **23** with benzoic anhydride, $MgBr_2$, and Et_3N in dichloromethane provided the benzoate derivative in 75% yield (entry 6, Table 2).[7] Various HPLC conditions for separating these benzoates were examined, but none were found suitable for the task.

Table 2. Attempted functionalization of isomeric alcohol **23**.

23 **24**

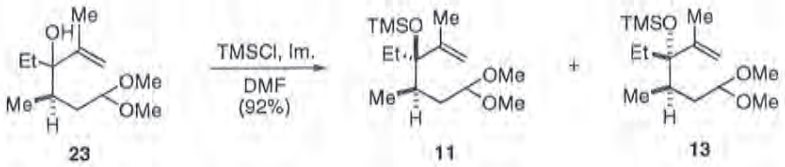
Entry	Conditions	Ar	Yield (%)[a]
1	*p*-NO_2-benzoyl chloride, DIPEA, DMAP, CH_2Cl_2		trace
2	*p*-NO_2-benzoyl chloride, DIPEA, DMAP, CH_2Cl_2		trace
3	PMB-Cl, DIPEA, DMAP,CH_2Cl_2		trace
4	KH; benzoyl Chloride		trace
5	KH; *p*-NO_2-benzoyl chloride		0
6	benzoic anhydride, $MgBr_2$, Et_3N, CH_2Cl_2		75
7	TBDPS-Cl	TBDPS	0

[a] Isolated yields

Silation of the tertiary alcohol mixture with trimethylsilyl chloride proceeded in 92% yield (Scheme 4). Preparative HPLC separation of silyl ethers **11** and **13** could be carried-out by loading 100–150 mg of **23** on a silica gel column and eluting with 10% ethyl acetate in hexanes containing 0.1% triethylamine. Because of the lack of a chromophore, the purity of the collected fractions had to be examined by GLC. As a result of the quality of the HPLC column in use at the time, base-line separation between the two diastereomers was unattainable. In order to obtain isomerically pure **13**, the collected fractions compriseed of >90% of **13** were combined, concentrated, and re-submitted to the purification procedure. The separation time frame for one gram of material (**23**) was on the order of almost a week and a half. The use of a new preparative

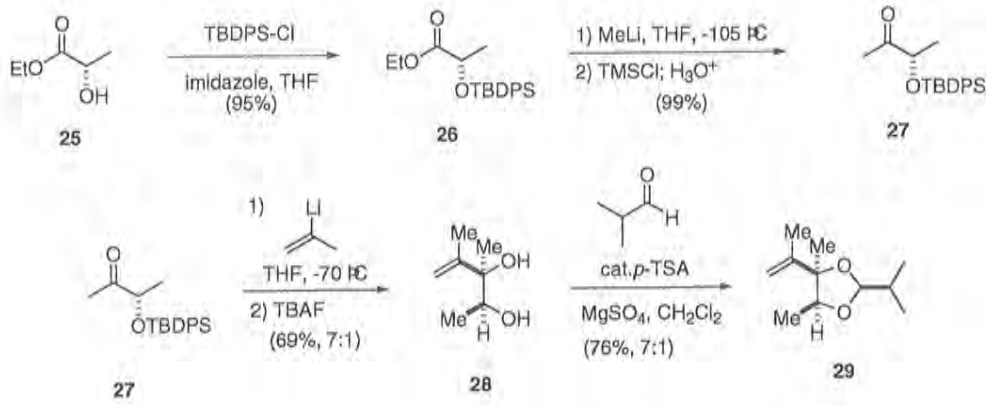
HPLC column resulted in efficient base-line separation of the epimers, thereby allowing for an increase in loading to 300 mg per injection. As a result, the time frame required to separate one gram of crude material was reduced to about one day. An efficient method for obtaining isomerically pure silyl ethers **11** and **13** was now in hand.

Scheme 4. Completion of the Synthesis of Dimethyl Acetals 11 and 13



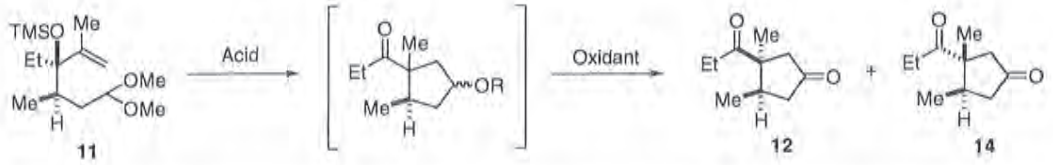
Preparation of Acetal 29.[8] The effect of acid and solvent on the stereoselection in the synthesis of tetrahydrofurans from acetal **29** was examined in order to widen the scope of the study. The first step towards the synthesis of **29** was the protection of isomerically pure (*S*)-ethyl lactate with TBDPS-Cl in a 95% yield (Scheme 5). Addition of MeLi to ester **26** at –105 °C, subsequent silation of the resultant alkoxide, and ensuing desilation at room temperature with 1 N HCl afforded ketone **27**. Addition of 2-propenyllithium to this protected ketone installed the olefinic fragment of the target molecule. Removal of the silyl protecting group with TBAF was performed in the same pot, affording *anti* diol **28** with a 7:1 diastereoselectivity in 69% yield. Following the condensation of isobutyraldehyde with this mixture of diols, the desired acetal **29** was obtained isomerically pure by preparative HPLC purification.

Scheme 5. Synthesis of Acetal 29



Rearrangement of Dimethyl Acetal 11. The results of the rearrangement of dimethyl acetal **11** under various conditions are summarized in Table 3. Studies began by repeating the $SnCl_4$ promoted rearrangement of dimethyl acetal **11** in dichloromethane (Scheme 2).[4,5] It was found that after oxidation the diastereoselectivity was 99:1 in favor of stereoisomer **12** (entry 1, Table 3). Under conditions **II**, **12** was formed with a selectivity of 96:4 (entry 3), in agreement with the previously reported results.[5] The acid utilized to promote the rearrangement was changed to *p*-toluenesulfonic (*p*-TsOH) and trifluoromethane sulfonic acid (TfOH), while the reaction medium was varied to nitromethane and tetrahydrofuran/water mixtures. It was found that cyclopentanone **12** was formed in high stereoselectivity under all the conditions reported in Table 3. These results are consistent with the results obtained by Tim Gahman.[5,6]

Table 3. Rearrangement of dimethyl acetal **11**.



Entry[a]	Acid	Solvent	Ratio	R	12:14	Yield (%)[d]
1	$SnCl_4$[b]	CH_2Cl_2	---	Me[c]	99:1	80
2	$SnCl_4$	$MeNO_2$	---	Me	98:2	---
3	Amberlyst-15[e]	Acetone:H_2O	1:1	H[f]	96:4	74
4	Amberlyst-15	THF:H_2O	1:1	H	95:5	71
5	TfOH[g]	THF	---	H	96:4	75
6	TfOH	THF:H_2O	10:1	H	95:5	77
7	TfOH	THF:H_2O	1:1	H	97:3	79

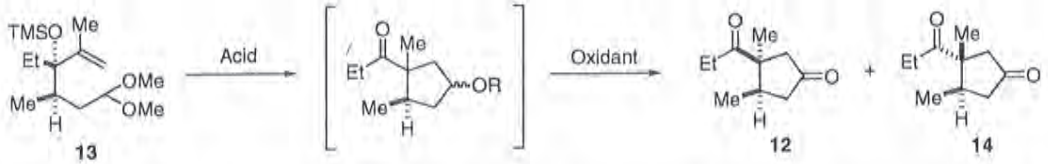
[a] All reactions conducted at [0.1 M] with respect to **11** unless otherwise noted. [b] Conducted with 1.0 eq. of $SnCl_4$ at –78 °C. [c] Oxidant = RuO_4-H_2O. [d] Isolated yields. [e] Conducted with Amberlyst-15 (5x the weight of **5**) at 81 °C & [0.05 M] with respect to **11**. [f] Oxidant = PCC. [g] Conducted with 1.0 eq. of TfOH at 38 °C.

Rearrangement of Dimethyl Acetal 13. Results of the rearrangement of dimethyl acetal **13** with various acids in several solvents are described in Table 4. Treatment of allylic ether **13** with $SnCl_4$ in dichloromethane, followed by oxidation, preferentially afforded carbocycle **14** (entry 1, Table 4), as observed earlier by Timothy Gahman. Performing the reaction in the more polar solvent nitromethane resulted in a drop in the stereoselection from 4:96 to 14:86 also favoring **14**. The use of a sulfonic acid (*p*-TsOH or TfOH) in highly polar mixed solvent systems (acetone/water or tetrahydrofuran/water) changed the outcome of the rearrangement by favoring the formation of **12**, in accord with previous results (entries 3-5).[5]

Performing the rearrangement with trifluoromethanesulfonic acid in tetrahydrofuran with a water content varying from 0 to 100:1, to 10:1, and to 1:1 allows for a more systematic investigation of the effect of water on the stereoselection of the rearrangement. When the reaction was carried-out in THF, the selectivity was 25:75 in favor of **14** (entry 6). The low yield of this reaction is attributed to the presence of a yet to be identified compound that, prior to oxidation, is consistently formed along with the

rearranged product. It was observed that the slightest inclusion of water in the reaction medium (entry 7) significantly altered the selectivity to 80:20 in favor of diketone **12**. Repeating the reaction in a 1:1 mixture of THF/water allows for the highly selective synthesis of **12** (entry 9).

Table 4. Rearrangement of dimethyl acetal **13**.



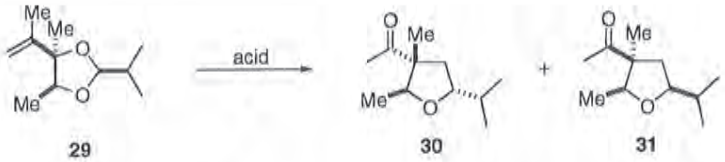
Entry[a]	Acid	Solvent	Ratio	R	**12:14**	Yield (%)[d]
1	$SnCl_4$[b]	CH_2Cl_2	---	Me[c]	4:96	86
2	$SnCl_4$	$MeNO_2$	---	Me	14:86	---
3	Amberlyst-15[e]	Acetone:H_2O	1:1	H[f]	86:14	81
4	Amberlyst-15	THF:H_2O	1:1	H	83:17	75
5	$TsOH•H_2O$[g]	Acetone:H_2O	1:1	H	90:10	78
6	TfOH[h]	THF	---	H	25:75	54
7	TfOH	THF:H_2O	100:1	H	80:20	79
8	TfOH	THF:H_2O	10:1	H	93:7	71
9	TfOH	THF:H_2O	1:1	H	94:6	79

[a] All reactions conducted at [0.1 M] with respect to **13** unless otherwise noted. [b] Conducted with 1.0 eq. of $SnCl_4$ at –78 °C. [c] Oxidant = RuO_4-H_2O. [d] Isolated yields. [e] Conducted with Amberlyst-15 (5x the weight of 7) at 81 °C & [0.05 M] with respect to **13**. [f] Oxidant = PCC. [g] Conducted with 1.1 eq. of $TsOH•H_2O$ at 81 °C & [0.05 M]. [h] Conducted with 1.0 eq. of TfOH at 38 °C.

Rearrangement of Acetal 29. The rearrangement of acetal **29** with different acids in various solvents was investigated (Table 5). Previously, it had been demonstrated that treatment of the *anti* acetal **29** with tin tetrachloride in methylene chloride resulted in the synthesis of tetrahydrofuran **30**.[9] Repeating this reaction also yielded **30** selectively (entry 1, Table 5). Treatment of **29** with TfOH in methylene chloride also resulted in the formation of **30** with a selectivity of 92:8 in a 95% yield (entry 2). Varying the solvent from dichloromethane to a 100:1 tetrahydrofuran/water mixture resulted in a complete

reversal of selectivity, yielding heterocycle **31** in high selectivity and in good yield (entry 4). Moving to a 1:1 mixture also selectively generated **31** (entry 5). The results summarized in Table 5 demonstrate that depending upon the reaction medium utilized in the rearrangement of **29**, either tetrahydrofuran **30** or **31** can be selectively formed.

Table 5. Rearrangement of Acetal **29**.



29 **30** **31**

Entry[a]	Acid	Eq.	Solvent	Ratio	T (°C)	**30**:**31**	Yield (%)[c]
1	$SnCl_4$[b]	1.1	CH_2Cl_2	---	-78	92:8	99
2	TfOH	3.0	CH_2Cl_2	---	-78	92:8	95
3	TfOH[d]	1.0	THF	---	81	*Decomposition*	
4	TfOH[d]	1.0	THF:H_2O	100:1	81	5:95	77
5	TfOH[d]	1.0	THF:H_2O	1:1	81	6:94	80

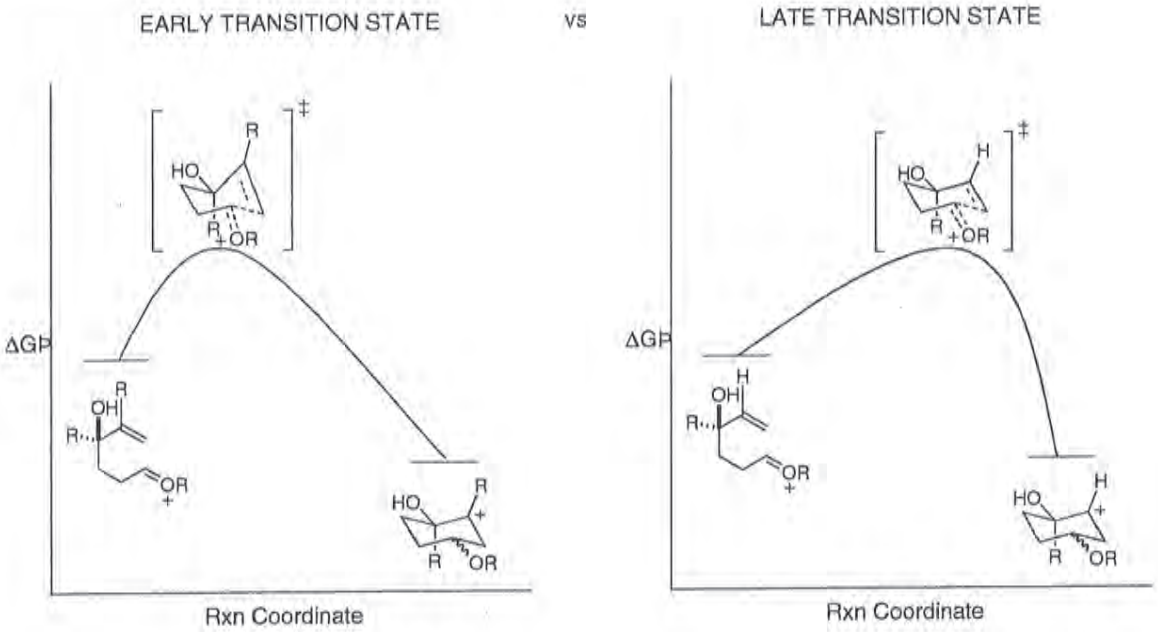
[a] All reactions conducted at [0.01 M] with respect to **29** unless otherwise noted. [b] Cohen, F. *et al* *Org. Lett.* **2001**, *8*, 1225-1228. [c] Isolated yields. [d] Conducted at [0.1 M]. [e] ^1H NMR yield.

Chapter 3: Discussion

The rearrangement of 5-hexenyl acetal **11** under typical Prins-pinacol conditions ($SnCl_4$ in CH_2Cl_2), after oxidation, results in the formation of diketone **12**. From what was known at the time about the stereoselection of this rearrangement, it was expected that treatment of epimeric acetal **13** with acid would result in the selective formation, after oxidation, of cyclopentanone **14**.[2,3,8] For this reason, it was surprising that dimethyl acetal **13** rearranged to cyclopentanone **12** in high selectivity upon changing the reaction medium from dichloromethane to an acetone/water mixture.[5] It is apparent from the results presented in Scheme 2 and in Tables 4 and 5 that the acid utilized in the

rearrangement does not affect the stereoselectivity, but what does do so is the nature of the solvent. In order to better understand these unusual results, it is best to apply our current model for stereoselection of the pinacol-terminated Prins cyclization and establish what can be learned (Figure 3).[9]

Figure 2. Early and Late transition state models of Prins cyclization.



The stereochemical–defining step in the Prins-pinacol reaction is assumed to be the Prins cyclization step due to the low barrier to activation of the pinacol rearrangement.[10,2c] The Prins cyclization could proceed through either an early or late transition state (Figure 2). The Prins portion of the rearrangement is believed to proceed through an early transition state if the terminal double bond present in the substrate is 1,1-disubstituted.[11] Because of the high nucleophilicity of this 1,1-disubstituted double bond,[11] the electron deficient oxocarbenium moiety engages the alkene before appreciable

rehybridization occurs. Therefore, the early transition state of the Prins cyclization can be approximated by the oxocarbenium intermediate.[6,9]

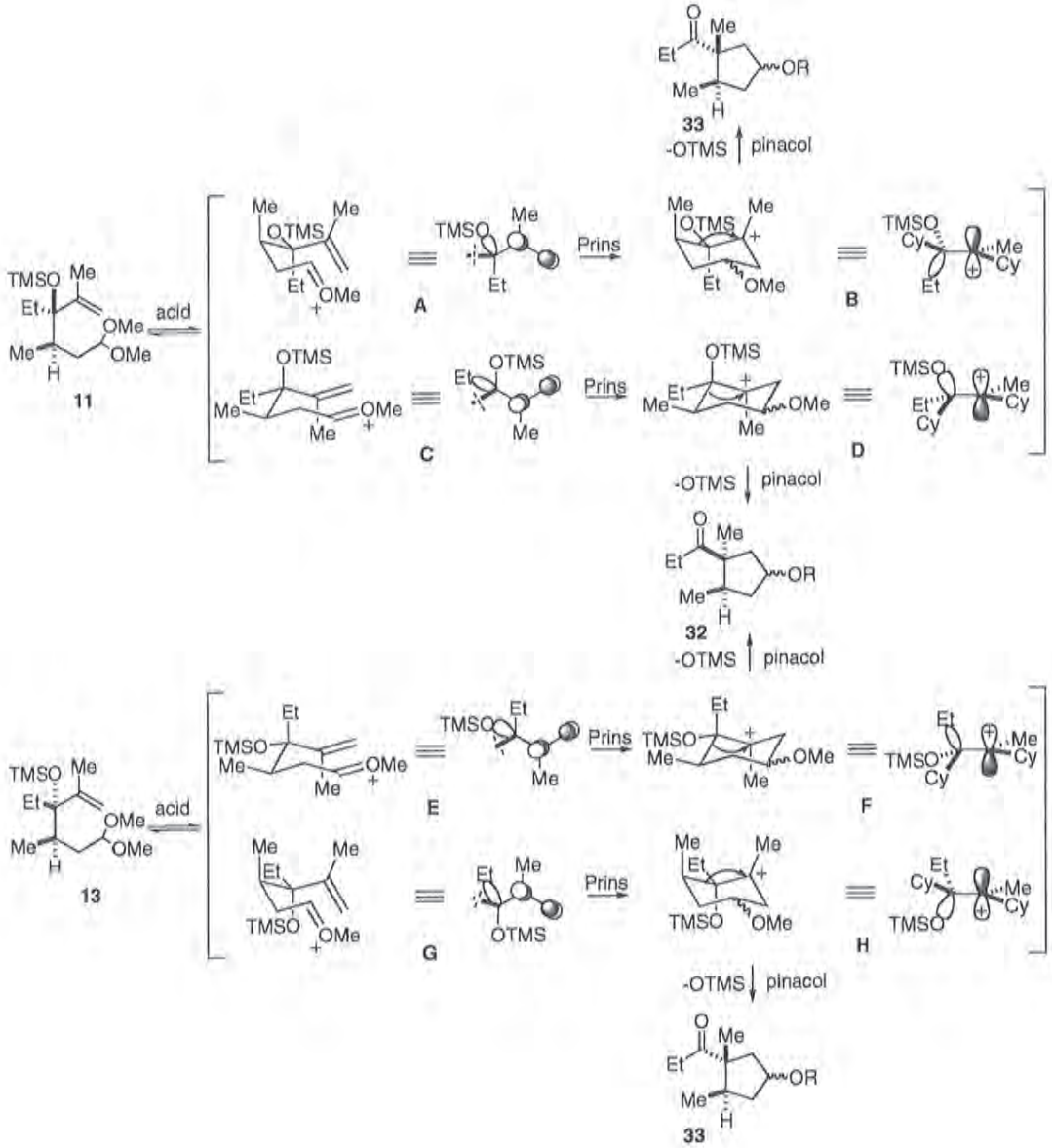
The Prins cyclization is believed to proceed through a late transition state if the double bond incorporated into the substrate is mono-substituted (Figure 2).[11] The low nucleophilicity of this π-bond will result in appreciable bonding with the oxocarbenium moiety only at a later point along the reaction coordinate. Hence, the late transition state of the Prins cyclization is best approximated by the fully cyclized cyclohexyl cation. *Ab initio* calculations at the 6-31G* level support this notion that the position of the transition state of the cyclization comes later on the reaction coordinate when the engaging double bond is 1-substituted, and earlier when the olefin is 1,1-disubstituted.[9]

Because the electron-releasing methyl group is positioned on the internal position of the terminal vinyl group, the Prins cyclization of dimethyl acetal **11** is expected to proceed through an early transition state.[6,9,11] Inspection of the current model for stereoselection depicted in Figure 3 reveals that the cyclization of this compound may advance *via* either of two oxocarbenium ion conformers, **A** or **C**.[9] Comparison of the two conformers shows that oxocarbenium ion **C** is lower in energy than **A**, as both the methyl and ethyl substituents in **C** occupy equatorial positions. Consequently, cyclopentane **32**, which arises from pathway **C**-**D**, should be formed preferentially under either conditions **I** or **II** due to the large energetic difference between the two oxocarbenium conformers.

A stereoelectronic inspection of the proposed model reveals an aspect of the Prins cyclization that aids in understanding the selectivity that is observed in the rearrangement of **11**. A comparison between the two possible oxocarbenium conformers, **A** and **C**, reveals that **C** benefits from maximized hyperconjugation between the allylic $\sigma_{C\text{-}Et}$ and the $\pi^*_{C\text{-}C}$ orbitals (Figure 3). In addition, **C** has a diminished destabilizing interaction between $\sigma^*_{C\text{-}O}$ and $\pi_{C\text{-}C}$. The situation is reversed in comformer **A**, where the interaction between the $\sigma_{C\text{-}Et}$ and the $\pi^*_{C\text{-}C}$ orbitals is reduced and the overlap between the low-lying $\sigma^*_{C\text{-}O}$ and $\pi_{C\text{-}C}$ is maximized. This analysis illustrates that **C** is lower in energy than **D**, and that **C** boasts the more nucleophilic π-bond. Additionally, it can then be concluded that **C** is a more accurate approximation of the transition state of the Prins cyclization.

Therefore, a prediction of which stereoisomer is to be formed preferentially is made by our model by following pathway **C-D**.

Figure 3. Model for stereoselection in pinacol-terminated Prins cyclization.



Both a steric and electronic inspection of the model for stereoselection in the Prins cyclization predicts that the rearrangement of **11** should result in the synthesis of

ketone **32**, which in turn leads to diketone **12** after oxidation (Figure 3). The data gathered in Table 3 demonstrates that irrespective of the acid utilized to initiate the Prins-pinacol reaction, or the nature of the reaction medium in which the rearrangement is carried-out, diketone **12** is selectively formed from **11**; the selectivity of **12** never falling below 95:5. Thus, the results depicted in Scheme 2 and in Table 3 support and validate the prediction made by our model for stereoselection. Though, they stand in stark contrast with those found for the rearrangement of hexenyl dimethyl acetal **13**.

The double bond incorporarted into silyl ether **13** is 1,1-disubstituted, and accordingly, the Prins cyclization of this substrate is expected to proceed through an early transition state. A comparison of oxocarbenium ions **E** and **G** through which the Prins cyclization of **13** may proceed reveals that neither conformer, as a result of sterics, benefits from increased stability. Oxocarbenium ion **E** places an ethyl group in the axial position, while **G** has both a methyl and an alkoxy group in the axial position. The energetic difference between these two oxocarbenium conformers is therefore expected to be minimal. As a result, we must rely on a stereoelectronic argument in order to determine the oxocarbenium ion through which **13** will cyclize.

A stereoelectronic comparison of oxocarbenium ions **E** and **G** reveals that **13** will preferentially cyclize through **G**, resulting in the synthesis of ketone **33**. Conformer **G** benefits from a maximized stabilizing interaction between the allylic $\sigma_{C\text{-}Et}$ and the $\pi^*_{C\text{-}C}$ orbitals, while the overlap between $\sigma^*_{C\text{-}O}$ and $\pi_{C\text{-}C}$ is attenuated (Figure 3). This situation is reversed in conformer **E**, leading to the conclusions that **G** is lower in energy and its terminal double bond is more nucleophilic. Proceeding through pathway **G-H** leads to the formation of **33**, which is converted to diketone **14** after oxidation. As depicted both in Scheme 2 and in Table 4, the treatment of **13** with $SnCl_4$ in CH_2Cl_2 resulted in the formation of diketone **14**, after oxidation, as predicted by this model.

Precedent suggests that neither a change in acid nor solvent has a significant effect on the stereoselectivity of the pinacol terminated Prins cyclization.[1,2,3] Thus, it was surprising that diketone **12**, and not **14**, was isolated upon treatment of silyl ether **13** with Amberlyst-15 in an acetone/water (1:1) solvent system (Scheme 2). This finding contradicts the proposed model, as **12** would arise from cyclization through

oxocarbenium **E**, the less stable conformer. The formulation of the following hypothesis is consequently put forth: The polarity of the reaction medium in which the Prins-pinacol reaction is performed affects its stereoselectivity, increasing its synthetic utility.

In order to lend credence to this hypothesis, the selectivity of the acid-promoted rearrangements of silyl ether **13** and acetal **30** in the solvents listed in Table 6 were assessed. A change in selectivity as a consequence of the polarity of the solvent system that is utilized would be indicative of a tunable reaction, suggesting that the position of the transition state may be modulated by this solvent property. This ability to affect a fundamental change in the reaction mechanism could then become a powerful method for controlling the outcome of the Prins-pinacol rearrangement. Moreover, the results of these experiments would help expand the scope and validity of current models for stereoselection in the Prins-pinacol reaction.

Table 6.[12] Dielectric constants (ε) for several solvents.

Entry	Solvent	ε^a
1	Water	78.4
2	Nitromethane	35.9
3	Acetone	20.6
4	Dichloromethane	8.9
5	Tetrahydrofuran	7.58

[a] Dielectric constant

A prediction of the outcome of the rearrangement of dimethyl acetal **13** in a polar reaction medium by relying on a model that assumes that the mechanism of the Prins cyclization proceeds through an early transition state has been shown to be inaccurate. Let us, then, analyze this model by inspecting the late transition state of the cylization, which is best represented by the cyclized carbocation. Comparison of the two possible cyclohexyl cations through which the Prins cyclization of **13** could proceed (**F** and **H**) reveals that one could not predict which is lower in energy solely through a steric

argument. A stereoelectronic assessment of the two conformers reveals that as the Prins cyclization evolves from the oxocarbenium ion to the cyclohexyl cation along pathway **E**-**F**, a stabilizing interaction between the developing p orbital and $\sigma_{C\text{-}Et}$ arises in **F** (Figure 3). Meanwhile, the destabilizing interaction between the vacant p orbital and the $\sigma^*_{C\text{-}O}$ progressively decreases. This situation is reversed in carbocation **H**, where the $\sigma_{C\text{-}Et}$ orbital is no longer in the optimal spatial orientation, relative to the empty p orbital, required so that **H** may benefit from hyperconjugation. Concurrently, the destabilizing interaction between the empty p and $\sigma^*_{C\text{-}O}$ orbitals is maximized. Therefore, cyclohexyl cation **F** is lower in energy than **H**, and is a better approximation of the late transition state of the Prins cyclization. A similar analysis of the rearrangement of acetal **11** based upon the late transition state would not change the predicted outcome of its reaction. Such an examination would also result in the prediction of the synthesis of carbocycle **32**, as it would arise from cyclohexyl cation **D**; **D** being the conformer which places the sterically demanding ethyl and methyl groups in an equatorial orientation.

If the rearrangement of **13** were to proceed through a late transition state by being performed in a polar reaction medium, then the Prins cylization should proceed through **F**. This outcome would result in the selective synthesis of cyclopentanone **32** over that of **33**. Indeed such selectivity is observed when the Prins-pinacol reaction is performed in a highly polar reaction medium. It now becomes necessary to expand upon our stated hypothesis:

1) The polarity of the reaction medium in which the Prins-pinacol reaction is performed affects its stereoselectivity;
2) The use of a polar reaction medium stabilizes the carbenium ion intermediate to the extent that the Prins cyclization proceeds through a late transition state.

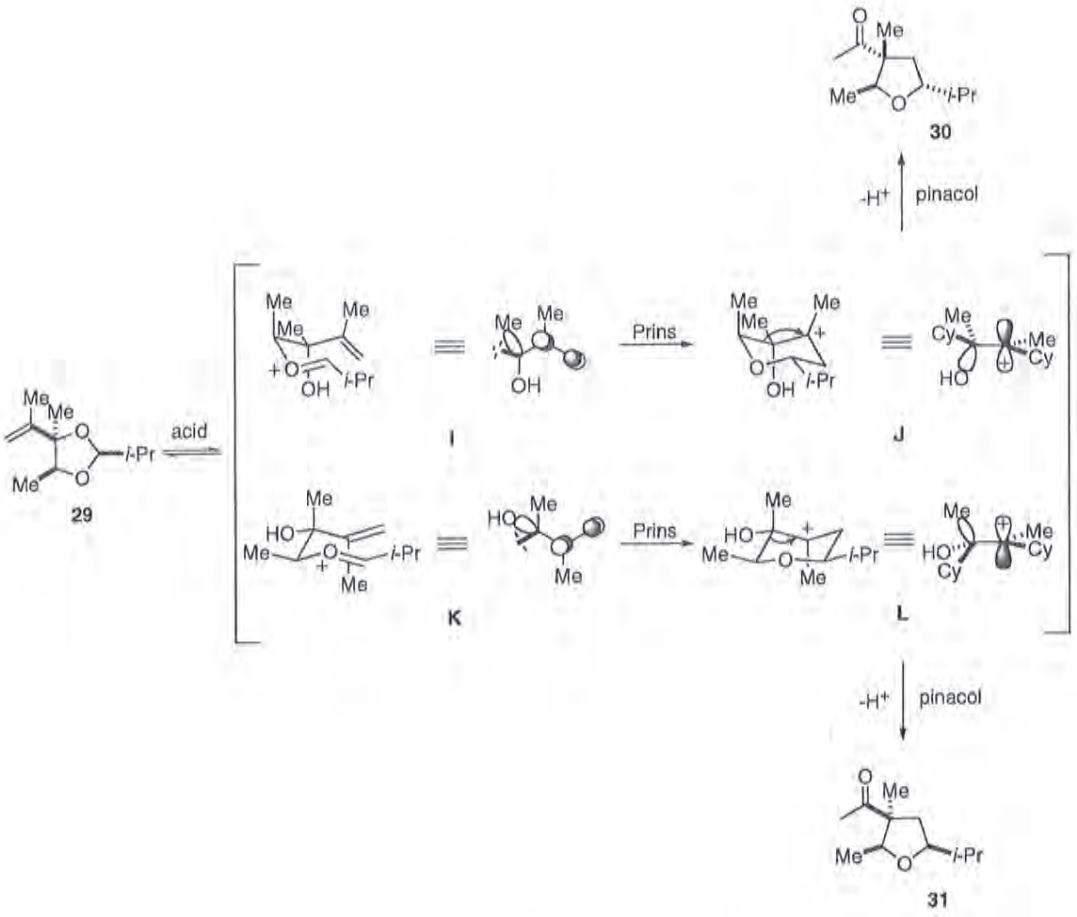
The results of the experiments designed to test the hypothesis are collected in Table 4, and indeed lend support for its validity. Treatment of dimethyl acetal **13** with tin tetrachloride in dichloromethane results in the selective formation of diketone **14**, after

oxidation (entry 1). Changing the reaction medium to the more polar nitromethane results once more in the selective isolation of **14** (entry 2). This result suggests that the polarity of nitromethane is not adequate to significantly shift the position of the transition state, and consequently, the stereoselectivity of the reaction. Performing the reaction in a 100:1 tetrahydrofuran/water mixture does result in a drastic switch in selectivity, favoring the formation of **12** (entry 7). Increasing the water content of the reaction medium to 50% further increases the selectivity of formation of **12** (entry 9). It is apparent from these observations that the slightest inclusion of water in the solvent results in a shift in reactivity, and possibly in transition state position. This shift in selectivity occurs regardless of which acid (i.e. Amberlyst-15, *p*-TsOH, TfOH) is used to promote the rearrangement.

Although the data for the rearrangement of **13** collected in Table 4 is consistent with a shift in reactivity based upon solvent polarity, it was essential to investigate the effect it would have on the stereoselection of the rearrangement of a second substrate. Such an investigation would lend further support to the validity of the predictive power of the model that incorporates the expanded hypothesis. To this end, *anti* acetal **29** was synthesized, and the results of its Prins-pinacol rearrangement under similar conditions were analyzed.

Before discussing the results of this study, let us consider the outcome predicted by this model. The terminal double bond of **29** is 1,1-disubstituted, and it follows that the Prins cyclization should proceed *via* an early transition state when conducted in a solvent of low polarity. A stereoelectronic comparison of oxocarbenium ions **I** and **K** reveals that **I** benefits from maximal hyperconjugation between $\sigma_{C\text{-}Me}$ and $\pi_{C\text{-}C}$, while **K** experiences a maximal interaction between $\sigma_{C\text{-}Me}$ and the $\pi^*_{C\text{-}C}$. Consequently, oxocarbenium **I** has the more nucleophilic propenyl group and is the optimal approximation of the transition state of the Prins cylization. The rearrangement of **29** should proceed through pathway **I-J**, selectively furnishing tetrahydrofuran **30**. Treatment of *anti* acetal **29** with tin tetrachloride in dichloromethane results in the highly selective isolation of **30** (entry 1, Table 5).[9] Changing the acid employed to initiate the reaction sequence to TfOH does not alter the selectivity or yield, as expected (entry 2).

Figure 4. Model for stereoselection of pinacol-terminated Prins cyclization.



Shifting to a more polar solvent system (i.e. THF/H_2O) should alter the position of the transition state along the reaction coordinate and the outcome of the reaction. A stereoelectronic comparison of tetrahydropyranyl cations **J** and **L** reveals that **J** is higher in energy. The destabilizing interaction between the empty p orbital and the neighboring $\sigma^*_{C\text{-}O}$ orbital is maximized. This is not the case for heterocycle **L**, which benefits from hyperconjugation between $\sigma_{C\text{-}Me}$ and the proximal p orbital. The model predicts, then, that in a polar reaction medium, acetal **29** should rearrange to **31** selectively. Treatment of **29** with TfOH in a polar reaction medium indeed results in the isolation of heterocycle **31** in high selectivity, lending credence to the model and its predictive power (entry 4).

Chapter 4: Conclusion

It is apparent from the data in Table 5 that regardless of the acid used, the selectivity of the Prins-pinacol rearrangement of **29** can be tuned by the reaction medium employed. Similar modulation of stereoselection with solvent polarity was observed in the rearrangement of dimethal acetal **13** (Table 4).[5] The only correlation between stereoselection and any reaction parameter appears to be that of the nature of the reaction medium.

The dielectric constant (ε) of nitromethane is about four times greater than both tetrahydrofuran and dichloromethane (Table 6). Yet the difference in selectivity of the

rearrangement of **13** in these solvents was relatively small, always providing carbocycle **14** with high fidelity (Table 4). It may not be unequivocally stated that solvent polarity is solely responsible for the observed changes in selectivity. What may be said for certain, though, is that the slightest inclusion of water in the solvent system results in a complete reversal in selectivity in the rearrangement of both acetals **13** and **29**, and this may be vital to both understanding this phenomenon and exploiting its synthetic utility.

The considerable polarity of water (ε of H_2O ~8x > THF/CH_2Cl_2) may be responsible for the shift in selectivity. It is also conceivable that this major shift may be an artifact of the protic nature of the solvent, and must be considered. Performing the Prins-pinacol rearrangements of **13** and **29** in mediums partially and/or fully composed of polar/protic solvents, i.e. methanol and dimethylformamide, would allow for a robust method of analysis of this reaction parameter. Any resultant changes in selectivity would reveal the extent of influence that both of the above solvent properties have on reaction selectivity, further elucidating a more thorough understanding of this singularity.

The study described in this report has resulted in a more complete examination of the unusual changes in selectivity observed during the investigation of the stereoselective synthesis of carbocyclcic ring systems through the Prins-pinaocl reaction.[5,6] It has been demonstrated that the polarity of the solvent utilized has a marked effect on the stereochemical outcome of the reaction. More specifically, the presence of water in the reaction medium seems to be key in producing the observed effect, and must be examined thoroughly. This change in selectivity highlights the likely existence of a fundamental association between the position of the transition state of the Prins cyclization and the solvent employed for the reaction. This link may serve as an additional tool for controlling the stereochemical outcome of the Prins-pinacol reaction.

This study has established that the stereospecific synthesis of both carbocyles and heterocycles may be easily controlled by the reaction medium utilized. The results described in this study also reveal an opportunity for the further expansion of the synthetic scope and utility of the Prins pinacol rearrangement. Furthermore, this study has shed further light onto the current understanding of the reaction mechanism, expanding the scope of the model for stereoselection (cf. Figure 3). More importantly, it is hoped

that this contribution results in stimulating further investigations into gaining a more complete understanding of this unique, and potentially powerful, reactivity.

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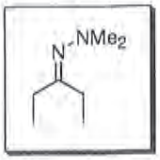
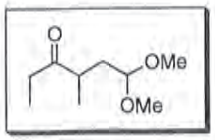
Appendix A: Experimental

General. ^{1}H NMR spectra were recorded in a $CDCl_3$ solution using residual chloroform as an internal standard at 500 MHz with a Nicolet GN-500 or a Nicolet Ω–500 spectrometer. ^{13}C NMR spectra were recorded in a $CDCl_3$ solution using residual chloroform as an internal standard at 125 MHz with a Nicolet GN-500 or a Nicolet Ω–500 spectrometer. TLC analysis was conducted on precoated 250 μm silica plates with 254 nm fluorescent indictor (Whatman K6F or Kiesel 60 F-254). Silica Gel purification (unless otherwise noted) was performed *via* flash column chromatography with 230 mesh Merck Geduran 60 silica. Analytical GLC analysis was performed with a Hewlett

Packard equipped with a flame ionization detector. Solvents for reactions were purified. All glassware was oven dried and cooled under a stream of Ar. $SnCl_4$ was distilled from CaH_2 under Ar and stored in a sealed vessel. 2-Bromopropene was distilled and passed through activity 1 basic alumina immediately prior to use. *n*-Butylithium was used as a solution in hexane, *t*-butylithium as a solution in pentane, and methylithium as a solution in dichloromethane. These reagents were standardized by titration. All other reagents were used as received.



3-Pentanone dimethylhydrazone (16). Following a known procedure,[5] a flask equipped with a Dean Stark trap was charged with 3-pentanone (21.2 mL, 200 mmol), dry benzene (120 mL), and a catalytic amount of trifuoromethanesulfonic aicd (0.8 mL). To this solution was added N,N-dimethylhydrazine (17 mL, 220 mmol), and this reaction mixture was maintained at reflux for 12 h, whereupon GLC analysis indicated the reaction was complete. The solution was cooled, dried over anhydrous $MgSO_4$, and concentrated to provide the crude hydrazone, which was purified *via* distillation (19.3 g, 76 %)). ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 2.39 (q, J = 7.7 Hz, 2H), 2.35 (s, 6H), 2.18 (q, J = 7.5 Hz, 2H), 1.03 (t, J = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 174.6, 47.9, 29.1, 23.0, 11.9, 11.4.



2-(2,2-Dimethoxyethyl)-3-pentanone (20). As previously described,[5] to a solution of diisopropylamine (4.84 mL, 39.3 mmol) in dry THF (27 mL) at –78 °C was added a hexane solution of n-BuLi (11.7 mL, 2.95 M, 34.3 mmol) dropiwse *via* syringe pump over 20 min. This reaction mixture was maintained at -78 °C for 30 min prior to adding a THF (10 mL) solution of **15** (4.21 g, 32.9 mmol) dropwise *via* syringe pump over 30 min. After the addition was complete, the reaction was maintained at -78 °C for 1h and then warmed to 0 °C where it was maintained for an additional hour. The reaction was cooled to –78 °C and iodoacetaldehyde dimethylacetal (4.3 mL, 32.9 mmol) was added dropwise. The solution

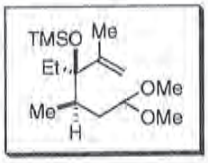
was allowed to warm to room temperature and maintained for 6h, at which time the reaction mixture was partitioned between EtOAc (300 mL) and water (150 mL). The organic layer was separated and the aqueous layer extrtacted with EtOAc (2 x 100 mL). The organic layers were combined and washed with brine (100 mL), dried over Na_2SO_4, and concentrated to yield an oil (7.07 g).

The crude oil was dissolved in CH_2Cl_2 (150 mL) and cooled to –63 °C. To this solution was slowly added *m*-chlorobenzoic acid (7.94 g, 71 %, 46.0 mmol) with vigorous stirring. This reaction mixture was maintained at 63 °C for 25 min, at which time it was poured into cold aqueous saturated $NaHCO_3$ (75 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed successively with cold aqueous saturated $NaHSO_3$ (100 mL), cold aqueous saturated $NaHCO_3$ (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated. Purification by flash chromatography (10% EtOAc in hexanes) yielded 4.31 g (73 %) of the desired ketone as a clear oil. ^{1}H NMR (500 MHZ, $CDCl_3$) ∂ 4.28 (t, J = 6.3 Hz, 1H), 3.20 (s, 3H), 3.27 (s, 3H), 2.66 (m, 1H), 2.47 (m, 2H), 2.05 (ddd, J = 14.2, 6.5, and 0.9 Hz, 1H), 1.56 (app dt, J = 14.2 and 5.3 Hz, 1H), 1.08 (d, J = 7.7 Hz, 3 H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 214.4, 103.2, 53.2, 53.0, 41.6, 36.0, 34.5, 17.3, 7.7.

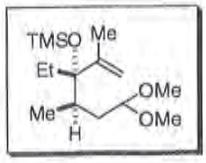
(2*R*,3*R*)-2-(2,2-Dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (11) and (2*R*,3*S*)-2-(2,2-Dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy) pentane (13). To a THF (5 mL) solution of 2-bromopropene (0.18 mL, 2.07 mmol) at –78 °C was added *t*-BuLi (2.4 mL, 4.13 mmol, 1.74 M in pentane) dropwise *via* syringe pump, as described by T. C. Gahman.[5,6] This reaction mixture was maintained at –78 °C for 30 min, followed by warming to 0 °C. At this time a THF (5 mL) solution of **20** (0.18 g, 1.03 mmol) was added dropwise *via* syringe pump over 30 min. The resulting solution was maintained at 0 °C for 5 min, at which time it was quenched by the addition of saturated aqueous NH_4Cl (2 mL) and allowed to warm to room temperature. The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The

combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to afford 1 g (93 %) of crude product. GLC analysis showed a 2:1 ratio of diastereomeric alcohols.

To a solution of the alcohols (**23**) in DMF (1.0 mL) at 0 °C was added imidazole (0.28 g, 4.1 mmol) and TMSCl (0.25 mL, 2.0 mmol). The resulting solution was allowed to warm to room temperature slowly and maintained for 12 h before being partitioned between Et_2O (20 mL) and H_2O (5 mL). The organic layer was separated and washed with water (2 x 5 mL), brine (25 mL), dried over Na_2SO_4, and concentrated. HPLC separation of the epimeric silyl ethers (7% EtOAc in hexanes) afforded the major (**11**) and minor (**13**) silyl ethers as clear oils (0.27 g, 92 %). Each compound a single spot by TLC and GLC analysis.



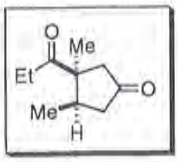
(2*R*,3*R*)-2-(2,2-Dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyl oxy)pentane (11). ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 4.96 (d, J = 2.3 Hz, 1H), 4.90 (t, J = 1.0 Hz, 1H), 4.40 (dd, J = 8.0 and 3.6 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 1.4-1.9 (m, 7H), 1.2-1.3 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.78 (t, J = 7.4 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 147.6, 112.8, 104.4, 85.9, 53.2, 52.3, 36.5, 34.8, 29.07, 20.4, 14.3, 9.0, 2.9.



(2*R*,3*S*)-2-(2,2-Dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyl oxy)pentane (13). ^{1}H NMR (500 MHz, CDCl3) ∂ 4.92 (d, J = 2.3 Hz, 1H), 4.88 (app dd, J = 1.3 and 2.3 Hz, 1H), 4.45 (dd, J = 8.2 and 3.5 Hz, 1H), 3.34 (s, 3H), 3.32 (s, 3H), 1.9-2.0 (m, 1H), 1.64 (s, 3H), 1.2-1.8 (m, 4H), 0.80 (m, 6H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 147.5, 112.4, 104.2, 85.5, 52.9, 52.3, 36.6, 34.1, 29.0, 20.4, 14.8, 8.8, 2.8.

General procedure for the rearrangement of (2*R*,3*R*)-2-(2,2-dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (11) with Stannic Chloride. Preparation of (3*S*,4*R*)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanone (12). Following the procedures described by Timothy Gahman,[5,6] to a solution of the allylic silyl ether **11** (23 mg, 0.080 mmol) in CH_2Cl_2 (0.8 mL) at –78 °C was added $SnCl_4$ (9.3 μL, 0.080 mmol) in one portion. The resulting solution was maintained at –78 °C for 15 min and was quenched by the addition of saturated aqueous NaCl (2 mL) and warmed to 23 °C. The resulting mixture was diluted with CH_2Cl_2 (5 mL), and the separated aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to be taken-on to the next step.

This crude residue was added to a mixture of CCl_4 (0.2 mL), CH_3CN (0.2 mL), H_2O (0.3 mL), and $NaIO_4$ (86 mg, 0.40 mL). After stirring for 15 min, $RuCl_3 \cdot 3H_2O$ (0.3 mg) was added and the mixture was stirred overnight. At this time, the reaction mixture was diluted with Et_2O (15 mL) and H_2O (5 mL). The aqueous layer was separated and extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with H_2O (2 x 5 mL), brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was analyzed by GLC and purified by flash chromatography (25% EtOAc in hexanes) to furnish 11 mg (99:1, 80 %) the diketone **12**.



(3*S*,4*R*)-3,4-Dimethyl-3-(1-oxopropyl)cyclopentanone (12). ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 2.82 (d, J = 18.3 Hz, 1H), 2.53 (m, 3H), 2.34 (dddd, J = 7.0, 7.1, and 14.1 Hz, 1H), 2.09 (app dd, J = 8.6 and 6.6 Hz, 1H), 1.94 (d, J = 18.3 Hz, 1H), 1.42 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 216.7, 214.3, 55.3, 48.0, 44.8, 41.2, 33.1, 23.6, 16.9, 7.9.

General procedure for the rearrangement of (2*R*,3*S*)-2-(2,2-dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (13) with Amberlyst-15. Preparation of (3*S*,4*R*)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanone (14).[5,6] To a flask fitted with a

reflux condenser and charged with the allylic silyl ether **11** (20 mg, 0.070 mmol), Amberlyst-15 (100 mg), acetone (1.1 mL), and H_2O (1.1 mL) were combined and heated at 81 °C for 2h. After allowing to cool to room temperature, the reaction mixture was filtered, concentrated, and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to be taken-on to the next step.

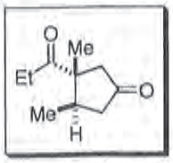
To this crude mixture of alcohols (0.070 mmol) in CH_2Cl_2 (1.5 mL) was added pyridinium chlorochromate (23 mg, 0.110 mmol). The resulting mixture was maintained at 23 °C for 2 h, at which time it was filtered through a plug of silica, eluting with 100% EtOAc. The residue was analyzed by GLC and purified by flash chromatography (25% EtOAc in hexanes) to furnish 9 mg (96:4, 74 %) of the diketone **12**.

General procedure for the rearrangement of (2*R*,3*R*)-2-(2,2-dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (11) with trifluoromethanesulfonic acid. Preparation of (3*S*,4*R*)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanone (12). To a sealed vessel charged with the silyl ether **11** (28 mg, 0.097 mmol), THF (0.45 mL), and H_2O (0.45 mL) at 38 °C was added the trifluoromethanesulfonic acid (9 μL, 0.097 mmol) and maintained for 20 h. At this time the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL) and concentrated to remove the THF. The aqueous suspension was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to be taken on to the next step.

To this crude mixture of alcohols (0.097 mmol) in CH_2Cl_2 (1.95 mL) was added pyridinium chlorochromate (31 mg, 0.146 mmol). The resulting mixture was maintained at 23 °C for 2 h, at which time it was filtered through a plug of silica, eluting with 100% EtOAc. The residue was analyzed by GLC and purified by flash chromatography (25% EtOAc in hexanes) to furnish 12.9 mg (97:3, 79%) of the diketone **12**.

General procedure for the rearrangement of (2*R*,3*S*)-2-(2,2-dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (13) with stannic chloride. Preparation of (3*R*,4*R*)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanone (14).[5,6] To a solution of the allylic silyl ether **13** (23 mg, 0.080 mmol) in CH_2Cl_2 (0.8 mL) at –78 °C was added $SnCl_4$ (9.3 μL, 0.080 mmol) in one portion. The resulting solution was maintained at –78 °C for 15 min and was quenched by the addition of saturated aqueous NaCl (2 mL) and warmed to 23 °C. The resulting mixture was diluted with CH_2Cl_2 (5 mL), and the separated aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to be taken-on to the next step.

This crude residue was added to a mixture of CCl_4 (0.2 mL), CH_3CN (0.2 mL), H_2O (0.3 mL), and $NaIO_4$ (86 mg, 0.40 mL). After stirring for 15 min, $RuCl_3 \cdot 3H_2O$ (0.3 mg) was added and the mixture was stirred overnight. At this time, the reaction mixture was diluted with Et_2O (15 mL) and H_2O (5 mL). The aqueous layer was separated and extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with H_2O (2 x 5 mL), brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was analyzed by GLC and purified by flash chromatography (25% EtOAc in hexanes) to furnish 11.6 mg (96:4, 86 %) the diketone **14**.



(3*R*,4*R*)-3,4-Dimethyl-3-(1-oxopropyl)cyclopentanone (14). ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 2.68 (m, 2H), 2.55 (dddd, J = 7.2 and 12.8 Hz, 2H), 2.45 (dd, J = 8.3, 1H), 2.15 (d, J = 17.8 Hz, 1H), 1.22 (s, 3H), 1.08 (t, J = 7.2, 3H), 1.05 (d, J = 7.3, 3H), 0.92 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 216.2, 213.9, 54.7, 50.5, 44.6, 36.7, 31.8, 17.4, 15.6, 8.5.

General procedure for the rearrangement of (2*R*,3*S*)-2-(2,2-dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (13) with Amberlyst-15. Preparation of (3*S*,4*R*)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanone (12).[5,6] To a flask fitted with a

reflux condenser and charged with the allylic silyl ether **13** (21 mg, 0.073 mmol), Amberlyst-15 (105 mg), acetone (1.2 mL), and H_2O (1.2 mL) were combined and heated at 81 °C for 2h. After allowing to cool to room temperature, the reaction mixture was filtered, concentrated, and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to be taken-on to the next step.

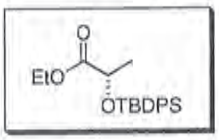
To this crude mixture of alcohols (0.073 mmol) in CH_2Cl_2 (1.5 mL) was added pyridinium chlorochromate (24 mg, 0.110 mmol). The resulting mixture was maintained at 23 °C for 2 h, at which time it was filtered through a plug of silica, eluting with 100% EtOAc. The residue was analyzed by GLC and purified by flash chromatography (25% EtOAc in hexanes) to furnish 10 mg (86:14, 81%) of the diketone **12.**

General procedure for the rearrangement of (2*R*,3*S*)-2-(2,2-dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (13) with *p*-toluenesulfonic acid. Preparation of (3*S*, 4*R*)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanone (12). To a flask fitted with a reflux condenser and charged with the allylic silyl ether **13** (19 mg, 0.066 mmol), *p*-toluenesulfonic acid (14 mg, 0.072 mmol), acetone (1.2 mL), and H_2O (1.2 mL) were combined and heated at 81 °C for 2h. After allowing to cool to room temperature, the reaction mixture was filtered, concentrated, and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to be taken-on to the next step.

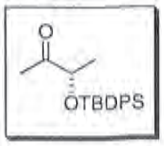
To this crude mixture of alcohols (0.066 mmol) in CH_2Cl_2 (1.3 mL) was added pyridinium chlorochromate (21 mg, 0.099 mmol). The resulting mixture was maintained at 23 °C for 2 h, at which time it was filtered through a plug of silica, eluting with 100% EtOAc. The residue was analyzed by GLC and purified by flash chromatography (25% EtOAc in hexanes) to furnish 9 mg (90:10, 78%) of the diketone **12.**

General procedure for the rearrangement of (2*R*,3*S*)-2-(2,2-dimethoxyethyl)-3-(2-propenyl)-3-(trimethylsilyloxy)pentane (13) with trifluoromethanesulfonic acid. Preparation of (3*S*,4*R*)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanone (12). To a sealed vessel charged with the silyl ether **13** (23 mg, 0.080 mmol), THF (0.4 mL), and H_2O (0.4 mL) at 38 °C was added the trifluoromethanesulfonic acid (7 μL, 0.080 mmol) and maintained for 20 h. At this time the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL) and concentrated to remove the THF. The aqueous suspension was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated to be taken on to the next step.

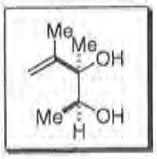
To this crude mixture of alcohols (0.080 mmol) in CH_2Cl_2 (1.5 mL) was added pyridinium chlorochromate (26 mg, 0.120 mmol). The resulting mixture was maintained at 23 °C for 2 h, at which time it was filtered through a plug of silica, eluting with 100% EtOAc. The residue was analyzed by GLC and purified by flash chromatography (25% EtOAc in hexanes) to furnish 12.9mg (94:6, 79%) of the diketone **12.**



Ethyl (*S*)-2-(*t*-butyl-diphenylsiloxy)propanoate (26). Following a known procedure,[8] to a round bottom flask charged with imidazole (7.2 g, 105.8 mmol) and THF (25 mL) was added (*S*)-ethyl lactate (4.8 mL, 42.3 mmol) and TBDPS-Cl (11.0, 42.3 mmol). The resulting white suspension was stirred vigorously at RT for 1.25 h, at which time it was filtered through glass wool into H_2O (200 mL). The solids were rinsed with THF (2 x 15 mL). The resulting aqueous suspension was extracted with EtOAc (2 x 100 mL), and the organics were washed with H_2O (2 x 200 mL), dried over Na_2SO_4, and concentrated in *vacuo* to yield a colorless oil., Purification by flash chromatography (5 % EtOAc in heaxanes) yielded 14.3 g (95 %) of **26**. ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 7.84 (m, 2H), 7.80 (m, 2H), 7.45 (m, 6H), 4.42 (ddd, J = 6.7 Hz, 1H), 4.10 (app ddd, J = 7.1 Hz, 2H), 1.50 (d, J = 6.7 Hz, 3H), 1.24 (s, 9H), 1.21 (t, J = 7.1, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 173.5, 135.9, 135.7, 133.6, 129.8, 129.78, 127.7, 126.6, 69.0, 60.4, 26.9, 21.3, 19.3, 14.1.

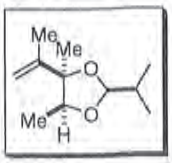


(*S*)-3-(*t*-butyl-diphenylsiloxy)-2-butanone (27).[8] A flask fitted with an internal thermometer charged with ester **26** (13.1 g, 36.8 mmol) and THF (170 mL) was cooled to –105 °C using a minimum amount of liquid N_2 in a dewar. To this reaction mixture was added halogen free MeLi (30 mL, 47.84 mmol) dropwise *via* syringe pump over 35 min while not allowing the internal temperature to rise over –100 °C. Upon completion of the addition, the TMSCl (11.2 g, 103.04 mmol) was injected in one portion and the resulting solution is warmed to 23 °C over 20 min. with the aid of a water bath. At this time, 1N HCl (171 mL) was added and vigorous stirring was continued for 1.5 h. The resulting aqueous supension was poured slowly into a flask containing solid $NaHCO_3$ (20 g) and concentrated to remove the THF. The aqueous suspension was extracted with EtOAc (2 x 300 mL), dried over Na_2SO_4, and concentrated to furnish 11.98 g (99%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 7.74 (m, 4H), 7.47 (m, 2H), 7.43 (m, 4H), 4.27 (ddd, J = 6.8 Hz, 1H), 2.22 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 212.0, 135.8, 133.7, 133.1, 130.0, 127.9, 27.04, 25.0, 20.7, 19.3.

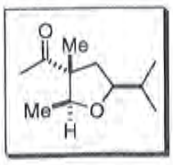


(2,3*R*)-dimethyl-1-penten-(3,4*S*)-diol (28). As described previously by Rishton and Overman,[8] to a flask charged with 2-bromopropene (4.3 g, 35.8 mmol) and THF (45 mL) at –78 °C was added *t*-BuLi (43 mL, 72.4 mmol) dropwise *via* syringe pump over 20 min. The resulting yellow solution was maintained at –78 °C for an additional 20 min., at which time a solution of the ketone **27** (7.3 g, 22.4 mmol) in THF (30 mL) was added dropwise *via* syringe pump over 40 min. This reaction mixture was maintained at –78 °C for an additional 45 min., at which time a 1.0 M solution of TBAF in THF (67.1 mL) was added in one portion. The mixture was warmed to 23 °C and maintained for 1 h, and poured into a flask with saturated aqueous ammonium chloride (90 mL) and concentrated. The aqueous suspension was extracted with EtOAc (2 x 90 mL), and the combined organic extracts were washed with brine (5 x 45 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (1:1 EtOAc:Hexanes) to furnish 2.5 g (7:1, 86%) of an oil. ^{1}H NMR

(500 MHz, CDCl3) ∂ 5.04 (s, 1H), 4.82 (app t, J = 1.5 Hz, 1H), 3.72 (ddd, J = 6.4 Hz, 1H), 2.46 (bs, 2H), 1.70 (s, 3H), 1.31 (s, 3H), 1.04 (d, J = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 148.4, 111.8, 71.7, 70.6, 60.5, 19.8, 17.4.

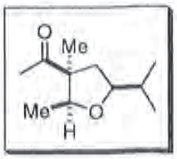


(2*S*,4*R*,5*S*)-4-Isopropenyl-4,5-dimethyl-2-isopropyl-1,3-dioxolane (29).[8] The mixture of diols **28** (1.3 g, 10.0 mmol), isobutyraldehyde (9.1 mL, 99.9 mmol), anhydrous $MgSO_4$ (30 g), *p*-TsOH•H_2O (0.2 g, 1.0 mmol), and CH_2Cl_2 (500 mL) was maintained at room temperature for 5 h, at which time it was poured into saturated aqueous ammonium chloride (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL), and the combined organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (5% EtOAc in hexanes) furnishing 1.4 g (7:1, 76%) of **29**. HPLC separation with a column of the epimeric acetals (5% EtOAc in hexanes) afforded pure *anti* acetal **29** as a clear oil (a single spot by TLC and GLC analysis). ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 4.94 (app d, J = 0.8 Hz, 1H), 4.87 (app t, J = 1.5 Hz, 1H), 4.61 (d, J = 5.8 Hz, 1H), 3.76 (ddd, J = 6.4 Hz, 1H), 1.81 (m, 1H), 1.70 (s, 3H), 1.32 (s, 3H), 1.06 (d, J = 6.4 Hz), 0.95 (d, J = 3.7 Hz, 3H), 0.93 (d, J = 3.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 146.5, 111.9, 106.1, 84.1, 81.3, 32.1, 20.9, 17.7, 17.6, 16.6.



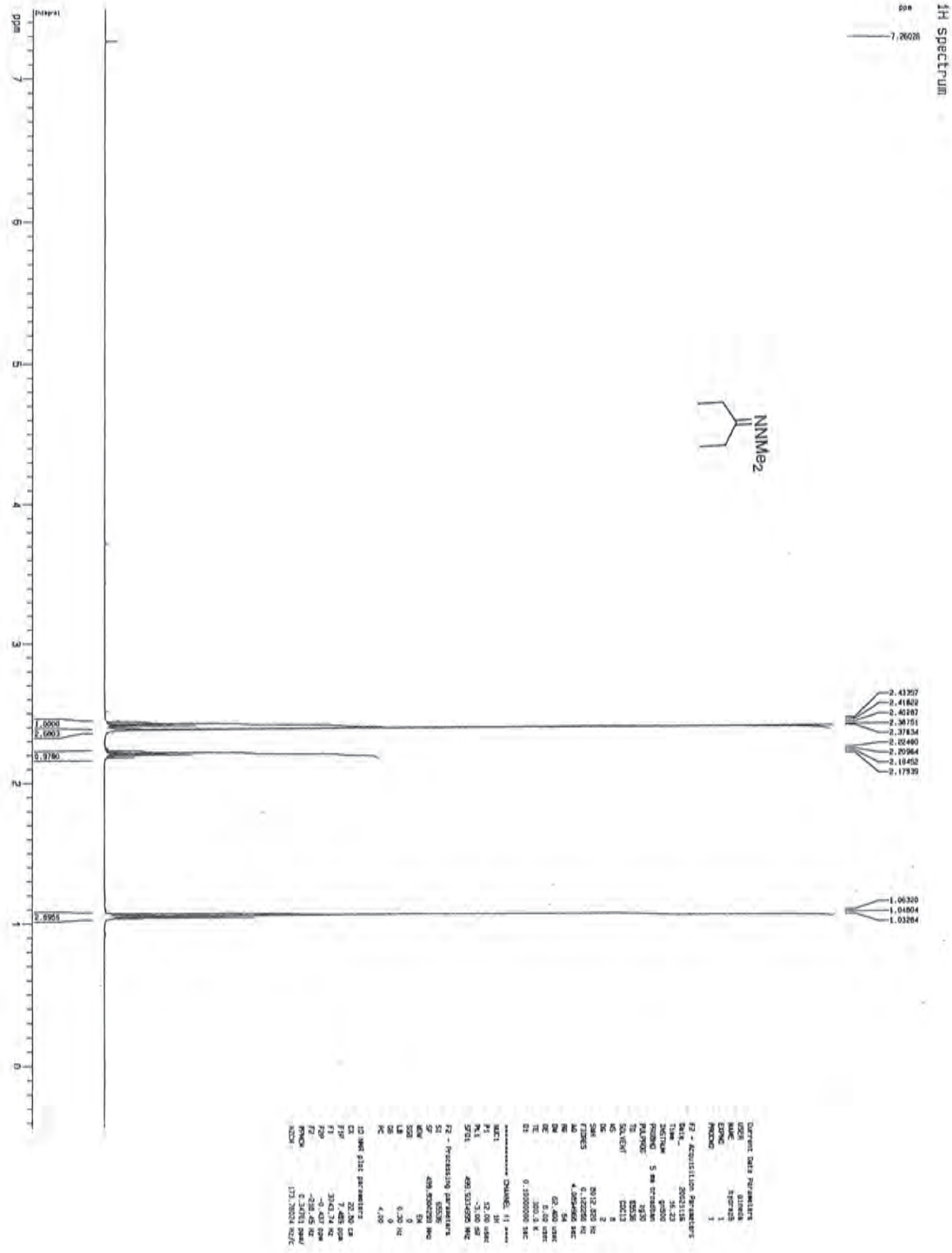
General procedure for the rearrangement of (2*S*,4*R*,5*S*)-4-isopropenyl-4,5-dimethyl-2-isopropyl-1,3-dioxolane (29) with trifluoromethanesulfonic acid. Preparation of (2*S*,3*S*,5*S*)-1-(tetrahydro-2,3-dimethyl-5-isopropyl-3-furanyl)-ethanone (30).[8,9] To a flask charged with the *anti* acetal **29** (20 mg, 0.11 mmol) and CH_2Cl_2 (11 mL) at –78 °C was added the TfOH (29 μL, 0.33 mmol) in one portion. This reaction mixture was maintained at –78 °C for 21 h, at which time it was poured into saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated to furnish 19 mg (92:8, 95%) of ketone **30** as

an oil. ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 4.18 (ddd, J = 6.3 Hz, 1H), 3.75 (m, 1H), 2.17 (s, 3H), 2.03 (m, 1H), 1.84 (dd, J = 6.5 Hz, 1H), 1.69 (m, 1H), 1.19 (s, 3H), 1.15 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 211.1, 84.5, 83.5, 60.0, 40.0, 34.1, 28.7, 22.8, 20.2, 19.1, 17.2.



General procedure for the rearrangement of (2*S*,4*R*,5*S*)-4-isopropenyl-4,5-dimethyl-2-isopropyl-1,3-dioxolane (29) with trifluoromethanesulfonic acid. Preparation of (2*S*,3*R*,5*S*)-1-(tetrahydro-2,3-dimethyl-5-isopropyl-3-furanyl)-ethanone (31).[8,9] To a sealed vessel charged with the *anti* acetal **29** (20 mg, 0.11 mmol), THF (0.55 mL), and H_2O (0.55 mL) at 81 °C was added the TfOH (10 μL, 0.11 mmol) in one portion. This reaction mixture was maintained at 81 °C for 24 h, at which time it was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL), diluted with CH_2Cl_2 (5 mL), and cooled to 23 °C. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated to afford 16.2 mg (96:4, 80%) of ketone **31**. ^{1}H NMR (500 MHz, $CDCl_3$) ∂ 3.73 (ddd, J = 4.4 Hz, 1H), 3.61 (m, 1H), 2.14-2.18 (m, 4H), 1.72-1.80 (m, 1H), 1.68 (dd, J = 6.4 Hz, 1H), 1.25 (s, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.02 (J = 6.5 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) ∂ 211.0, 84.3, 83.2, 58.8, 39.8, 33.9, 28.5, 22.6, 20.0, 18.9, 17.0.

Appendix B: Spectra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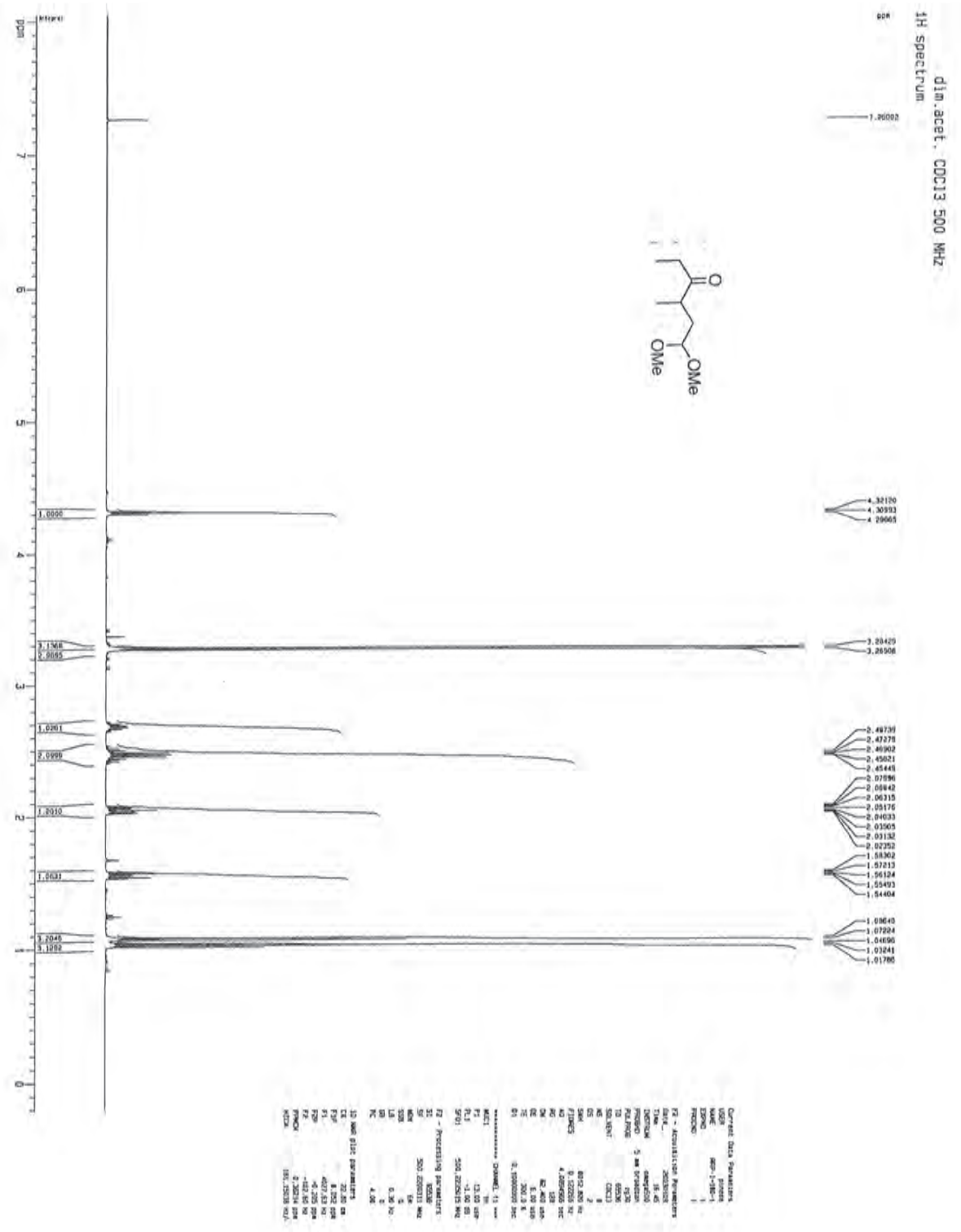
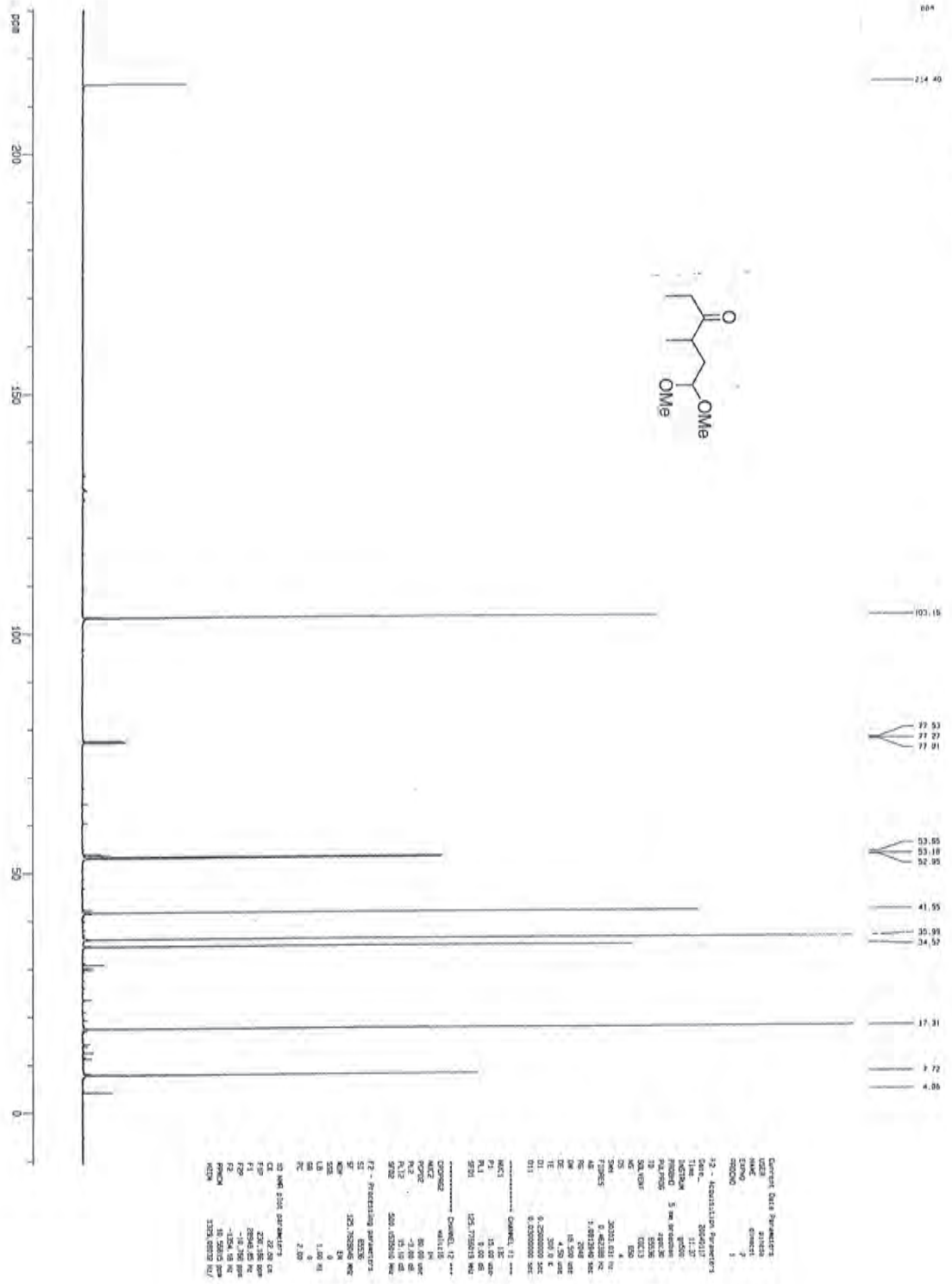
2.43357
2.41822
2.40287
2.38751
2.37834
2.22460
2.20964
2.19452
2.17939
1.06320
1.04804
1.03284
1.0000
2.0803
0.9780
2.0955

Hydrazone 125MHz CDCl3
13C spectrum with 1H decoupling
ppm
200
150
100
50
0
174.55
77.68
77.43
77.18
47.86
32.25
28.39
28.12
23.84
22.97
14.36
11.80
11.39
2-NNO2


1H spectrum
dim-acet. CDCl3 500 MHz
OMe
OMe
O


dim. acet. 125MHz CDCl3
13C spectrum with 1H decoupling
OMe
OMe
214.40
103.15
77.53
77.22
77.01
53.85
53.18
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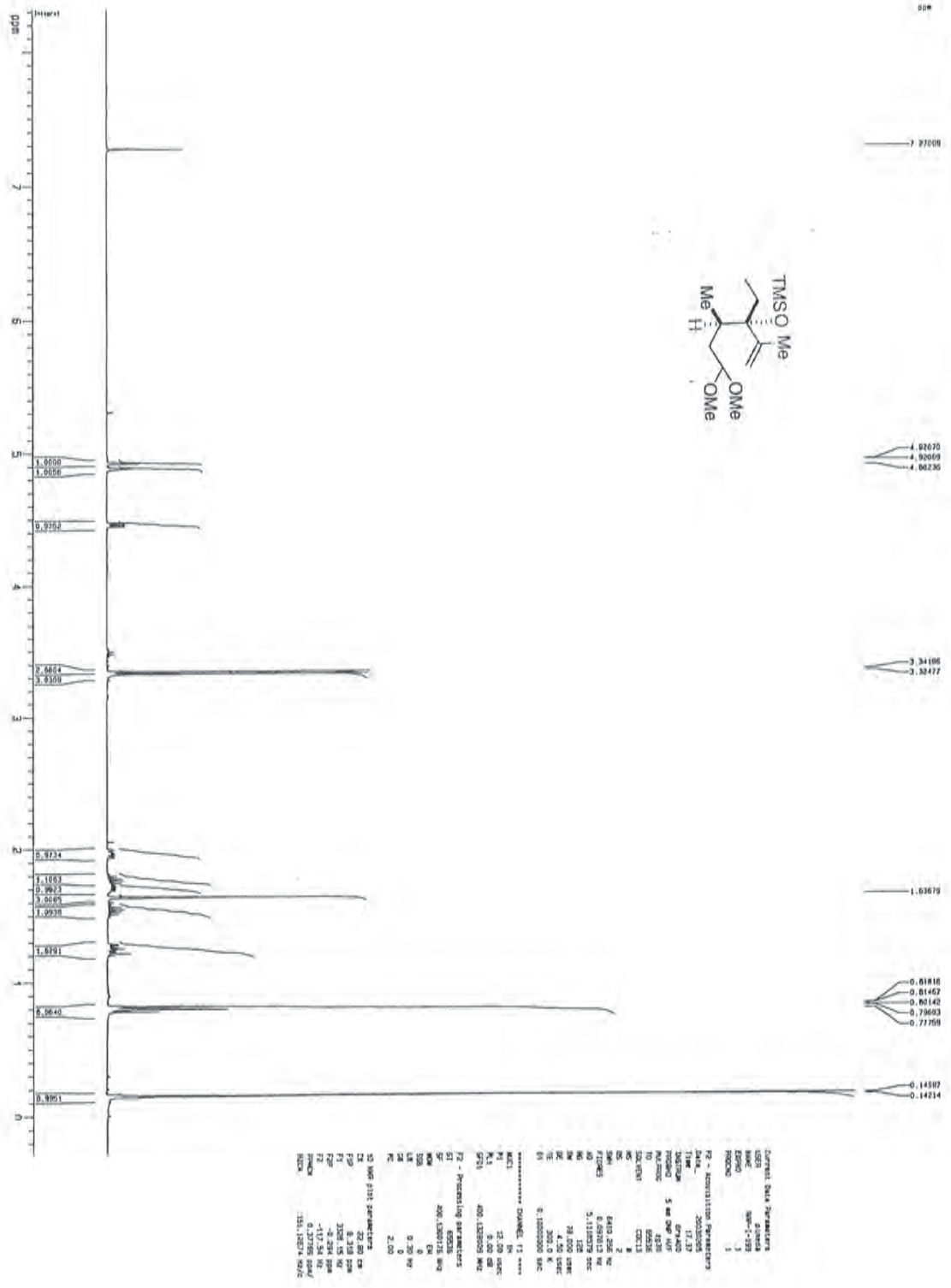
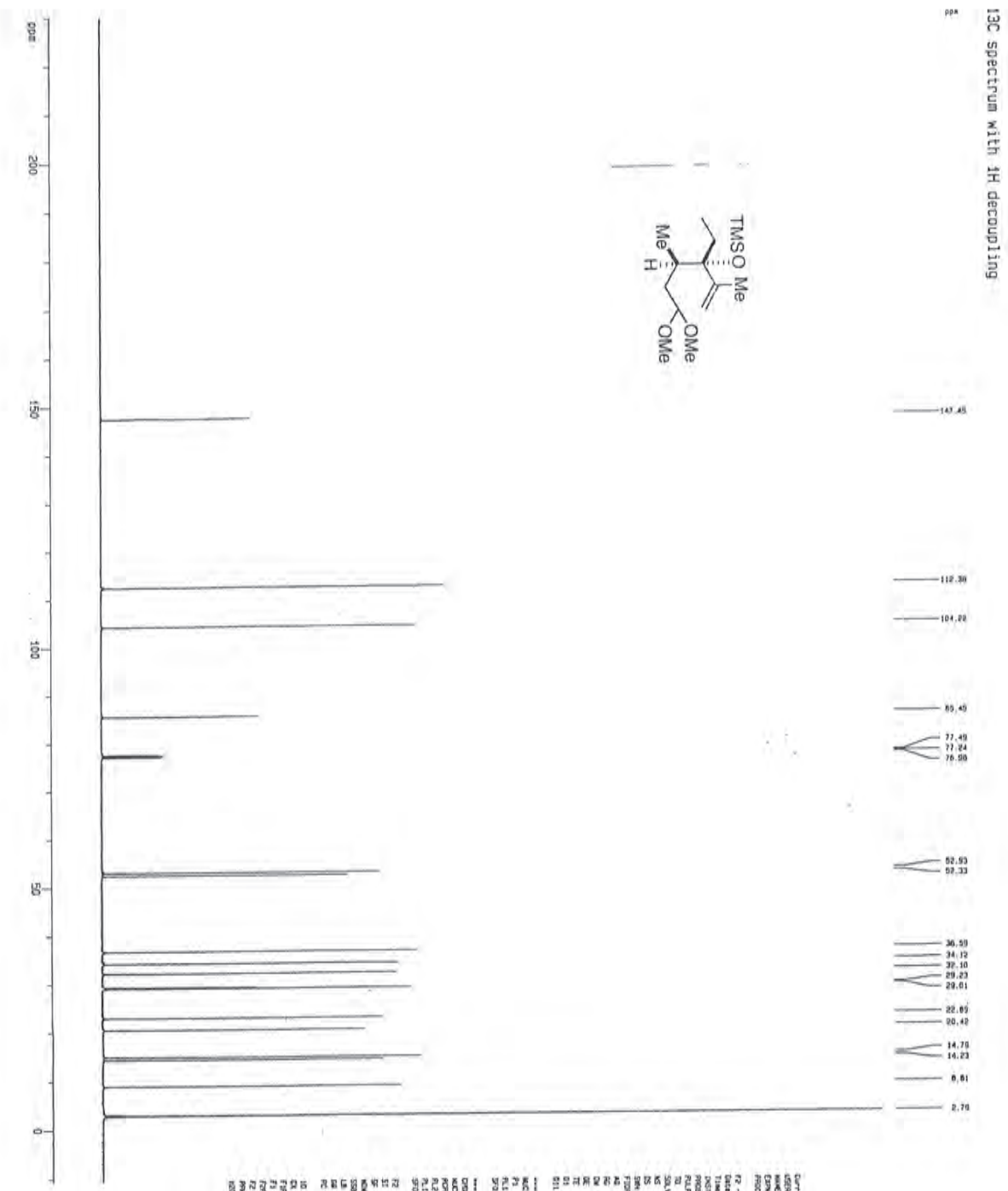
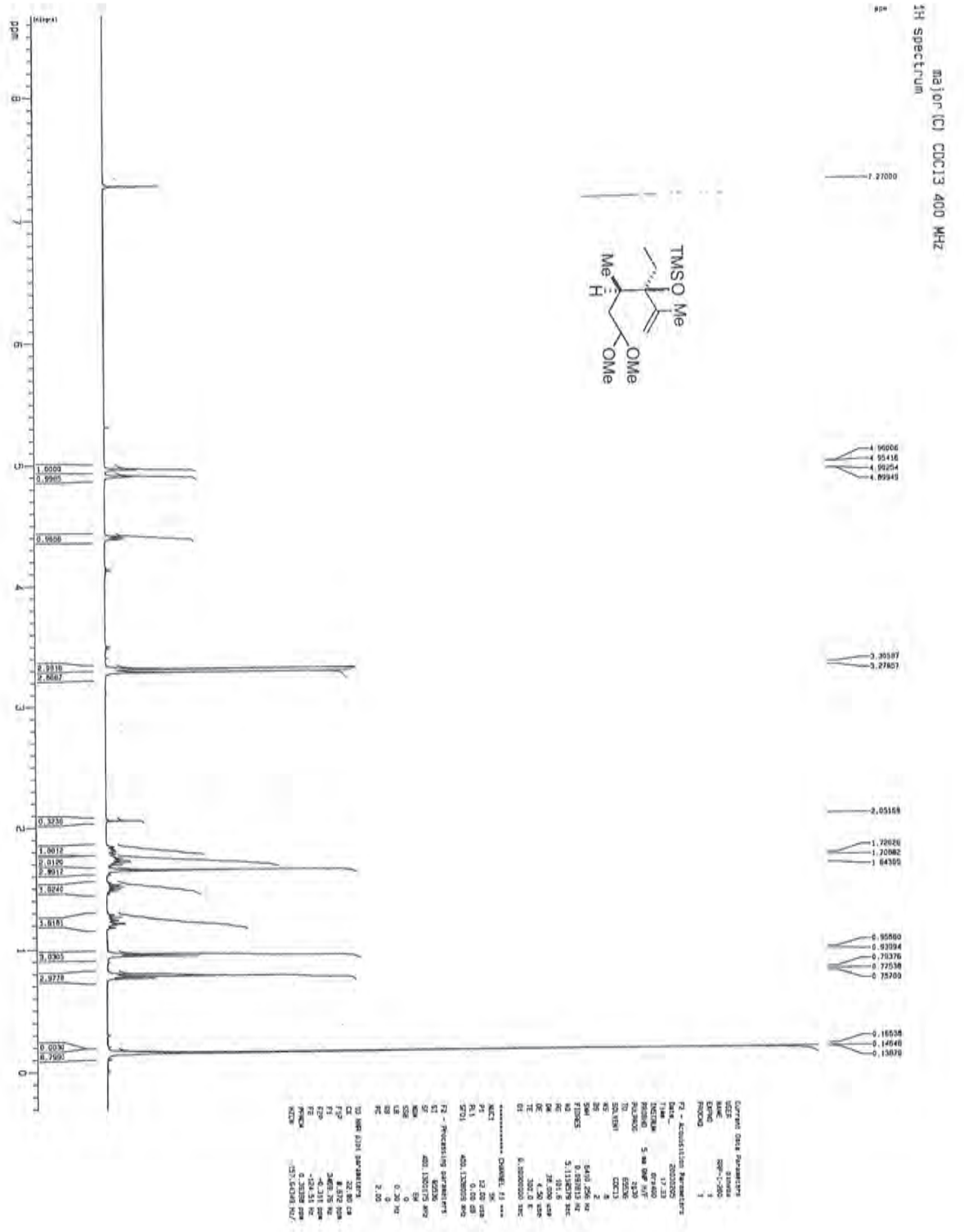
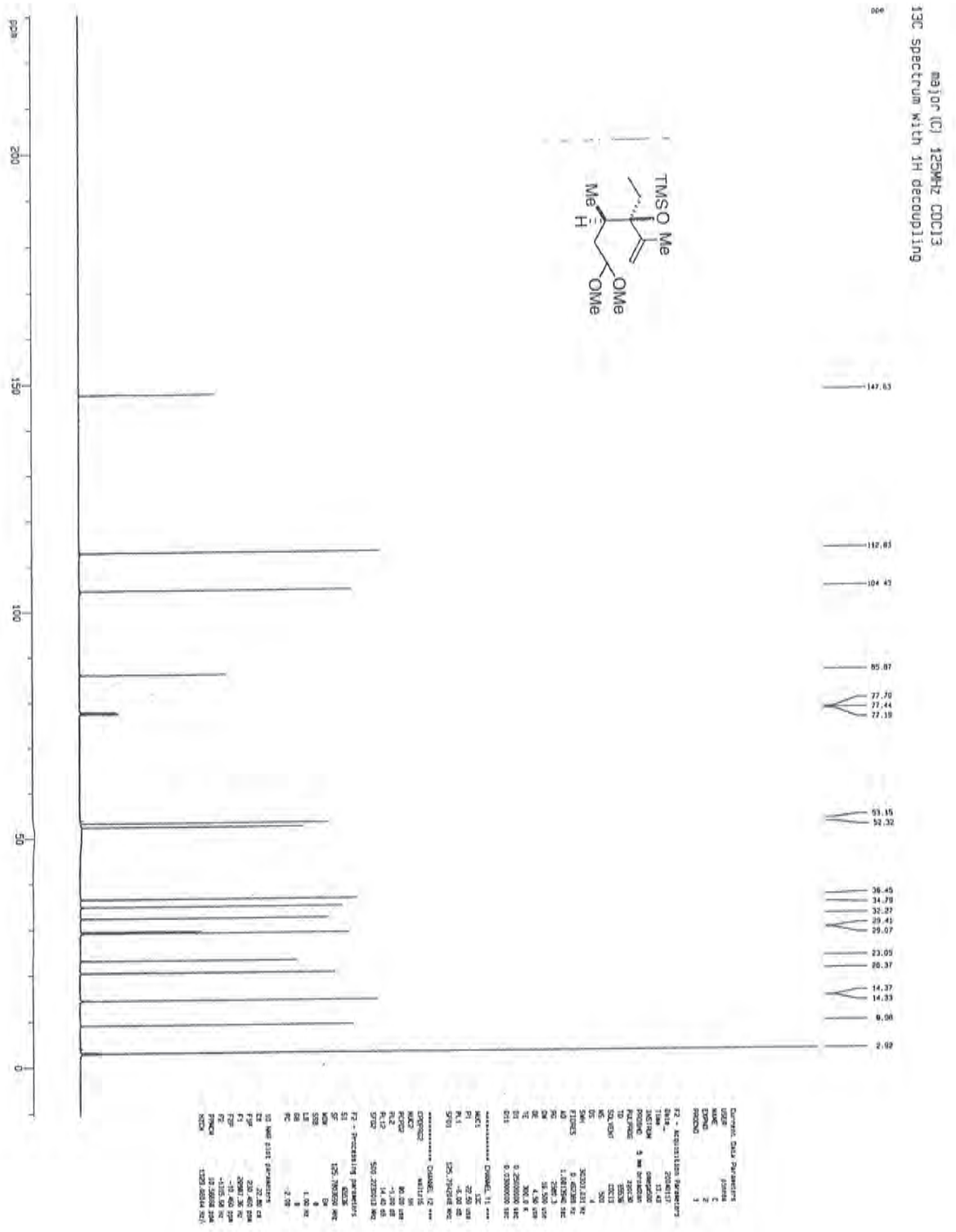
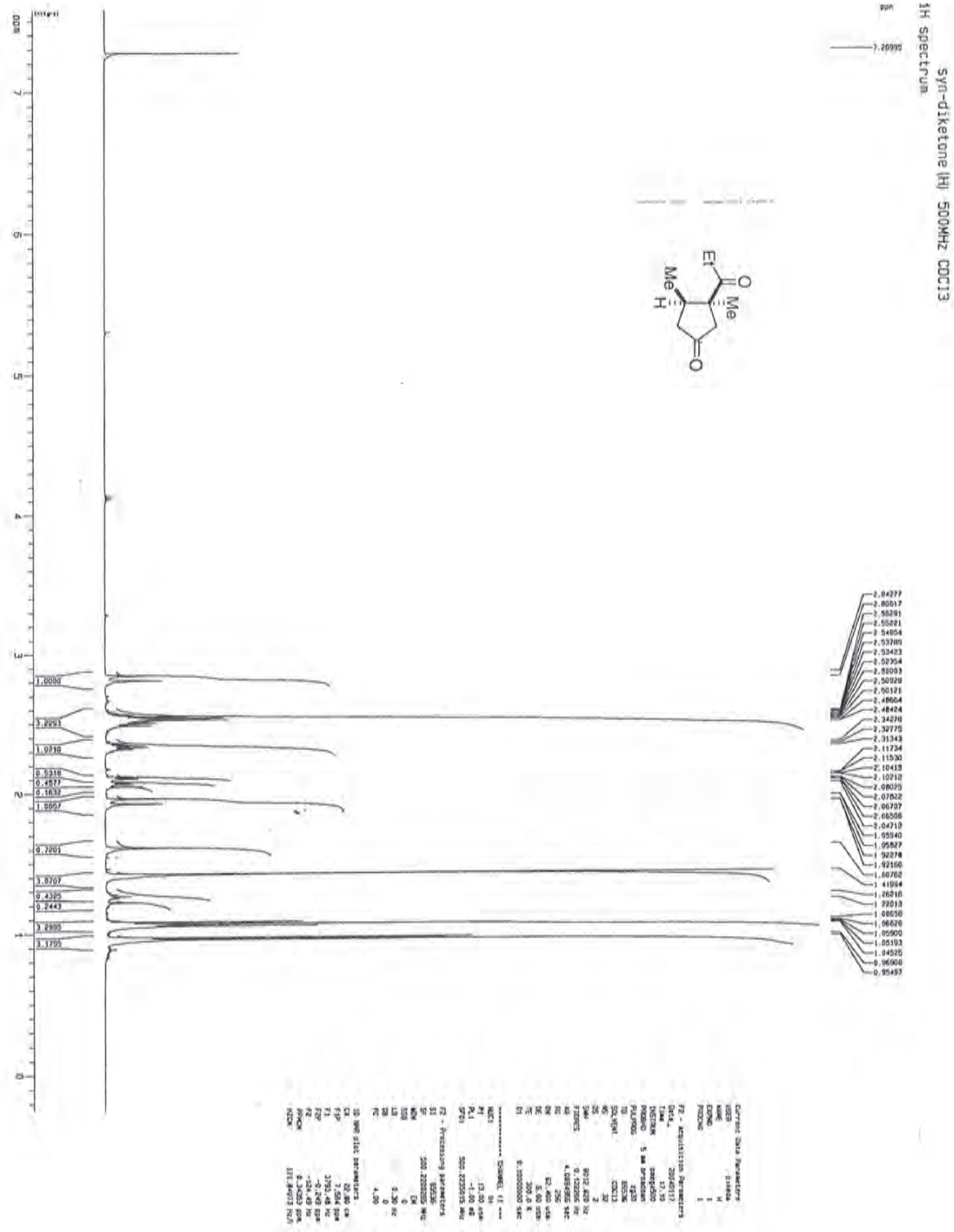
41.55
35.99
34.52
17.31
9.72
4.06
ppm
200
150
100
50
0


1H spectrum
minor (B) CDCl3 400 MHz
TMSO Me
Me
H
OMe
OMe

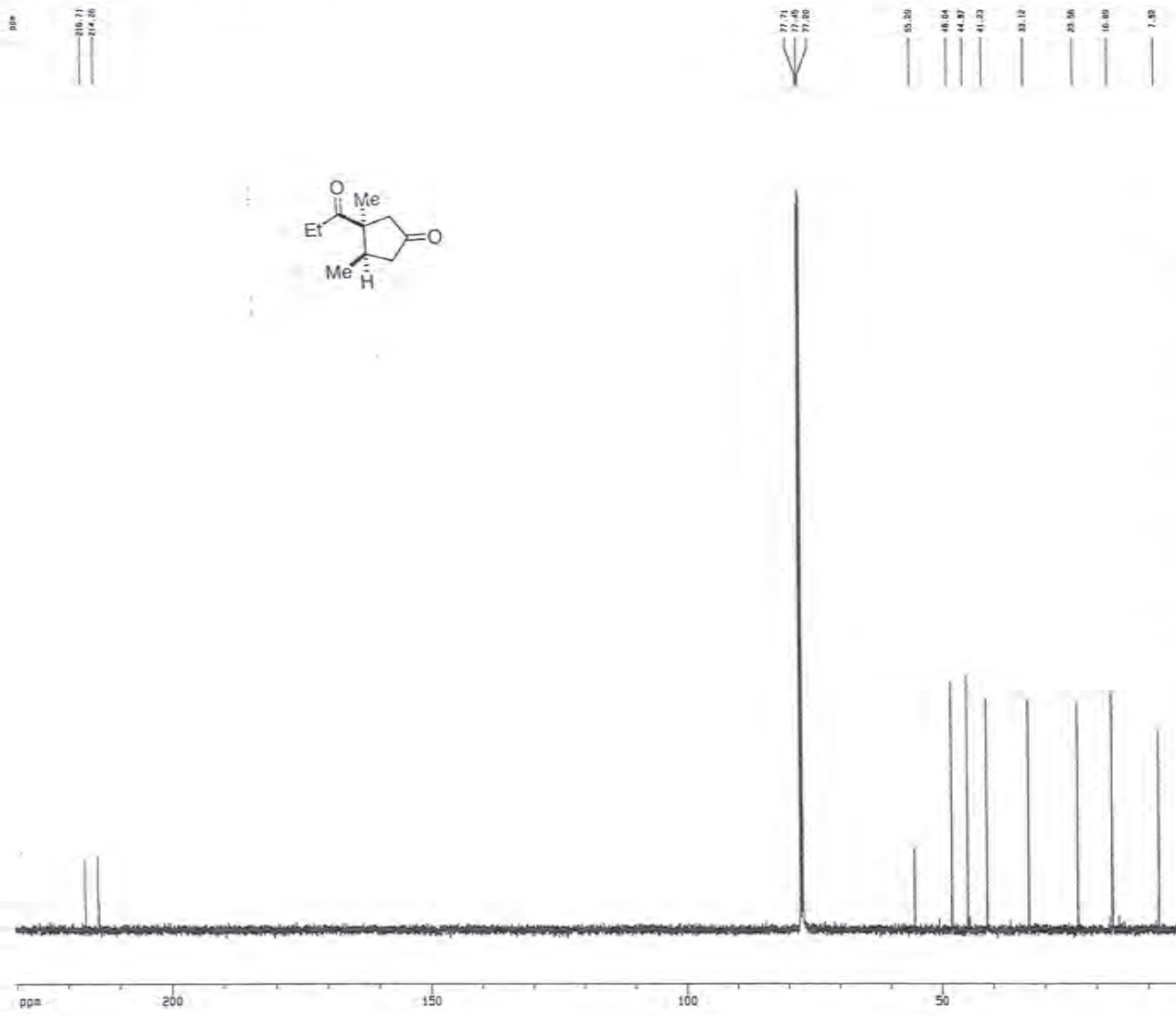

13C spectrum with 1H decoupling
ppm
TMSO Me
Me
H
OMe
OMe
147.45
112.30
104.28
85.49
77.49
77.24
76.98
62.93
62.33
36.59
34.12
32.10
29.23
29.01
22.89
20.42
14.75
14.23
0.61
2.76
0
50
100
150
200


major (C) CDCl3 400 MHz
1H spectrum
TMSO Me
Me
H
OMe
OMe


major (C) 125MHz CDCl3
13C spectrum with 1H decoupling
TMSO
Me
Me
H
OMe
OMe
147.63
112.83
104.43
85.87
77.70
77.44
77.19
53.15
52.32
36.45
34.78
32.27
29.41
29.07
23.05
20.37
14.37
14.33
9.08
2.92
ppm
200
150
100
50
0


1H spectrum
Syn-diketone (H) 500MHz CDCl3
ppm
7.26995
Et
O
Me
Me
H
O
1.0000
3.2293
1.9316
0.5316
0.4577
0.1632
1.9957
0.7201
3.8707
0.4325
0.2443
3.2995
3.1755

syn-diketone 125MHz CDCl3
13C spectrum with 1H decoupling



Current Data Parameters
USER pyneta
NAME N
EXPNO 2
PROCNO 1

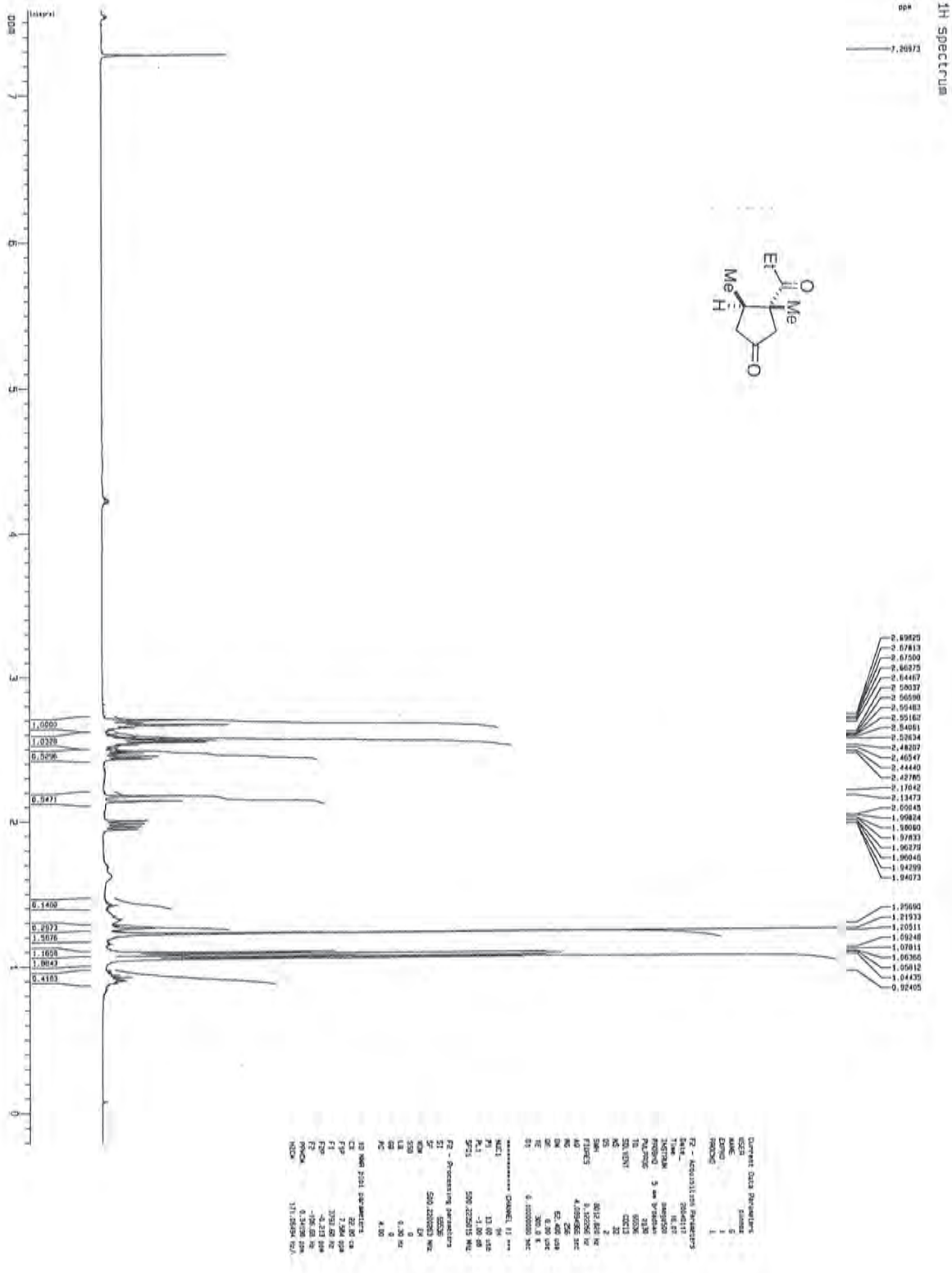
F2 - Acquisition Parameters
Date_ 20040107
Time 18.26
INSTRUM omega500
PROBHD 5 mm broadban
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 1356
DS 4
SWH 30303.031 Hz
FIDRES 0.462368 Hz
AQ 1.0813840 sec
RG 2580.3
DW 35.500 usec
DE 4.50 usec
TE 300.0 K
D1 0.25000000 sec
D11 0.03000000 sec

========== CHANNEL f1 ====
NUC1 13C
P1 22.50 usec
PL1 -5.00 dB
SFO1 125.7942048 MHz

========== CHANNEL f2 ====
CPDPRG2 waltz65
NUC2 1H
PCPD2 80.00 usec
PL2 -1.00 dB
PL12 14.40 dB
SFO2 500.2230013 MHz

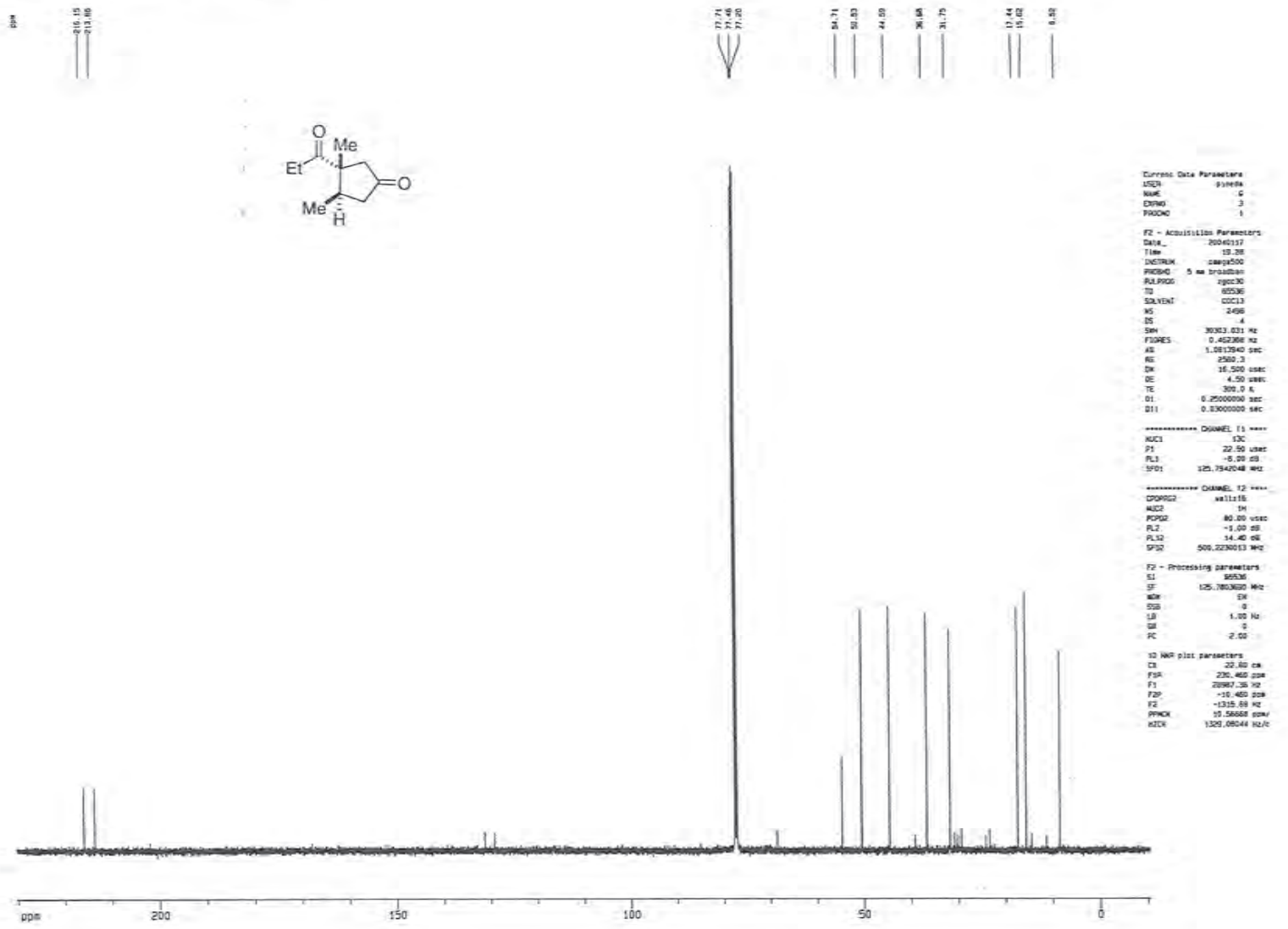
F2 - Processing parameters
SI 65536
SF 125.7803690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

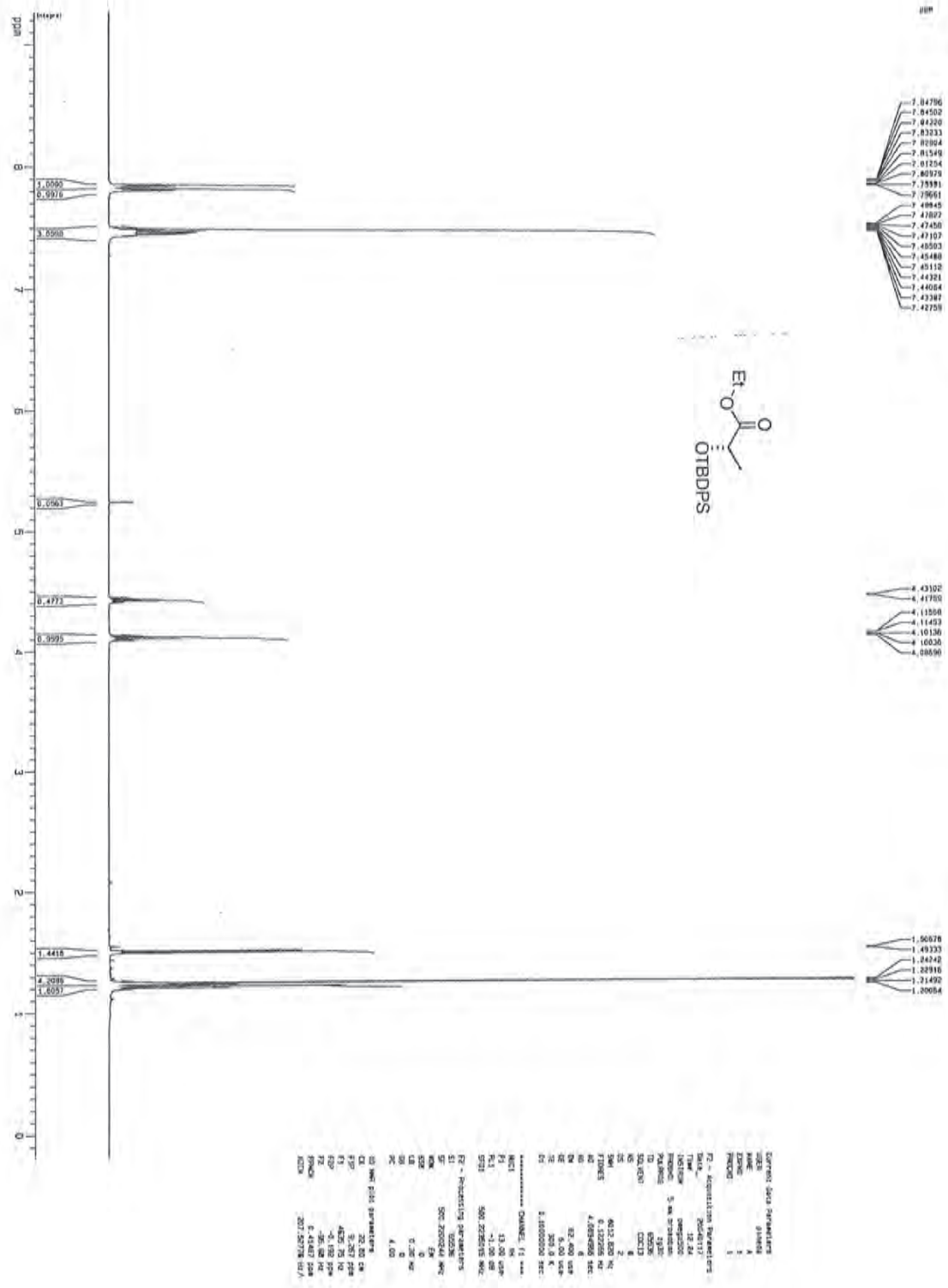
1D NMR plot parameters
CX 22.80 cm
F1P 230.460 ppm
F1 28987.36 Hz
F2P -10.460 ppm
F2 -1315.58 Hz
PPMCM 10.58668 ppm/
HZCM 1329.08644 Hz/c

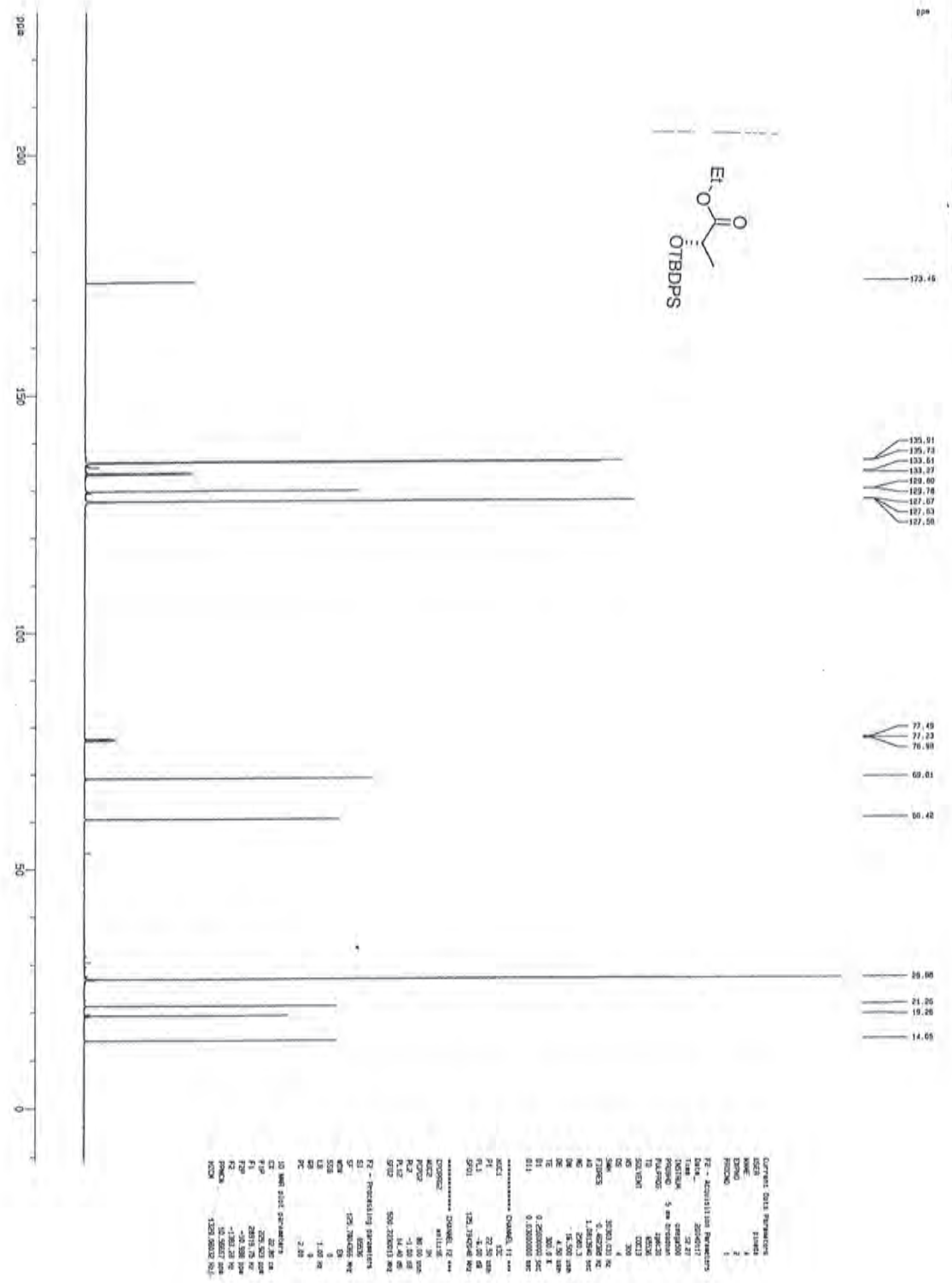

1H spectrum
Et
Me
Me
H
O
O

anti-diketone (G) 125MHz CDCl3

13C spectrum with 1H decoupling

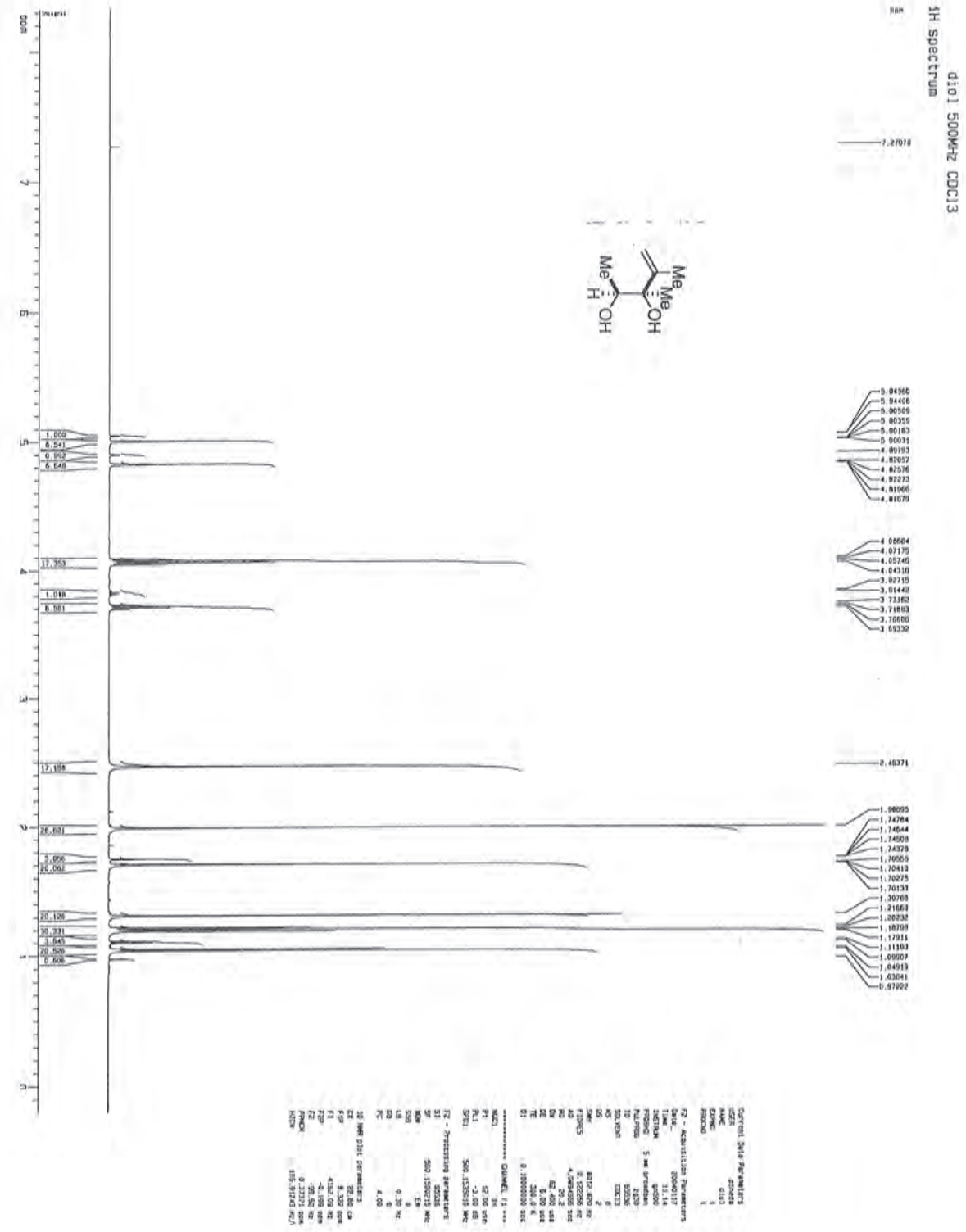


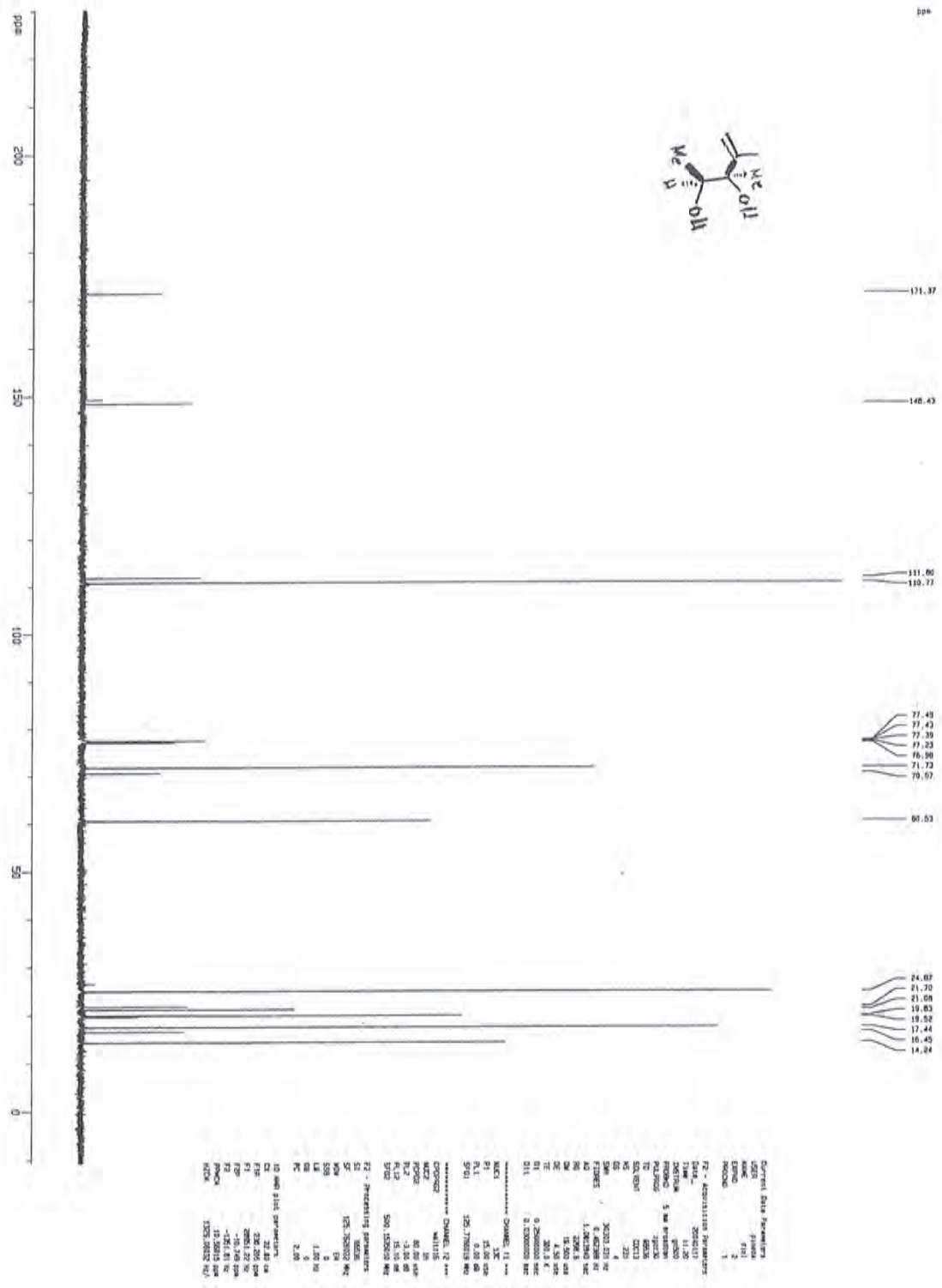

ester (A) 500MHz CDCl3
1H spectrum
ppm
Et
O
OTBDPS

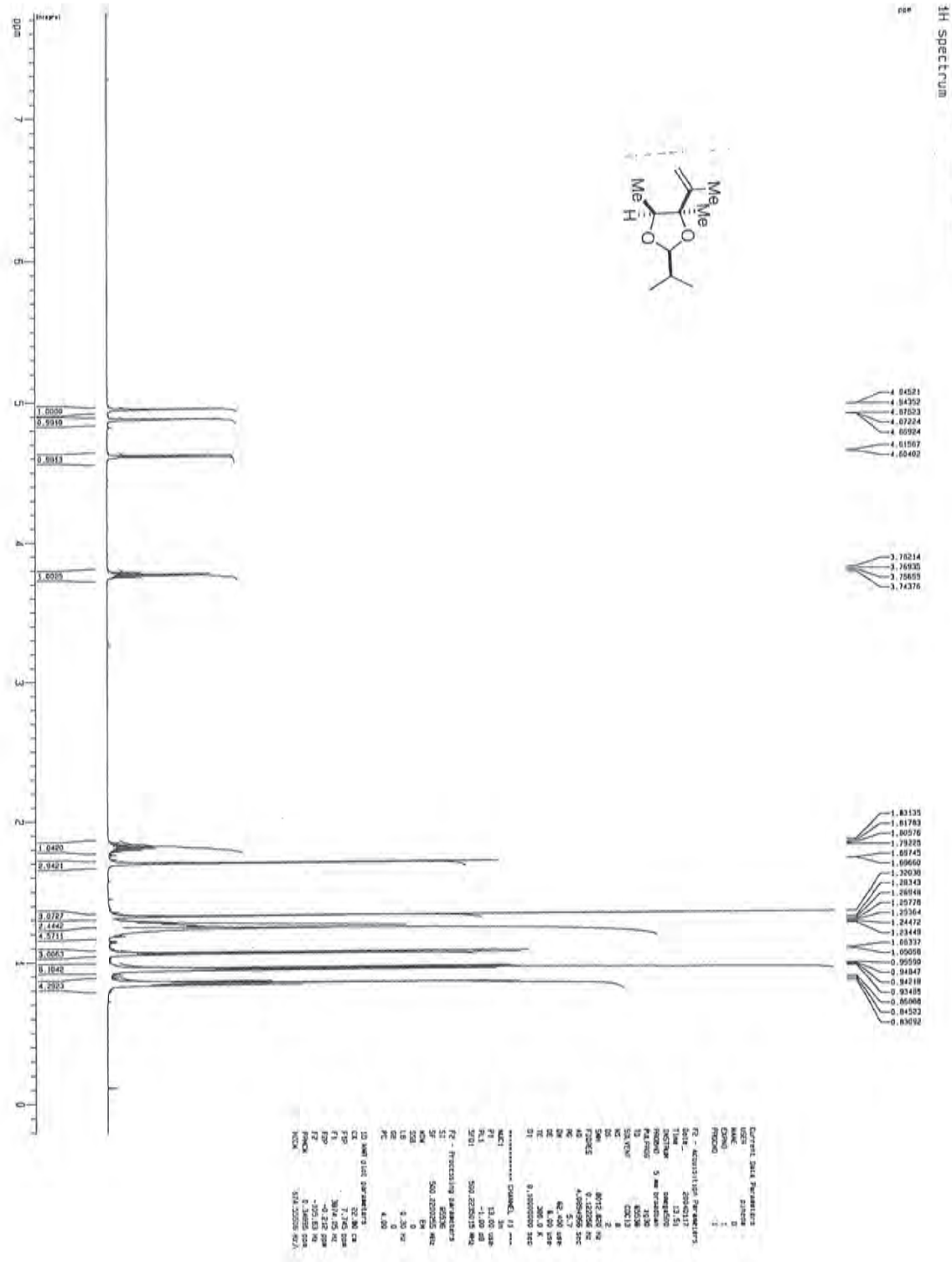

ester(A) 125MHz CDCl3
13C spectrum with 1H decoupling
ppm
173.46
135.91
135.73
133.61
133.27
129.80
129.78
127.67
127.63
127.58
77.45
77.33
76.98
60.81
60.42
28.06
21.26
19.26
14.05
OTBDPS
Et
O
O
O

ketone 500MHz CDCl3
1H spectrum
OTBDPS

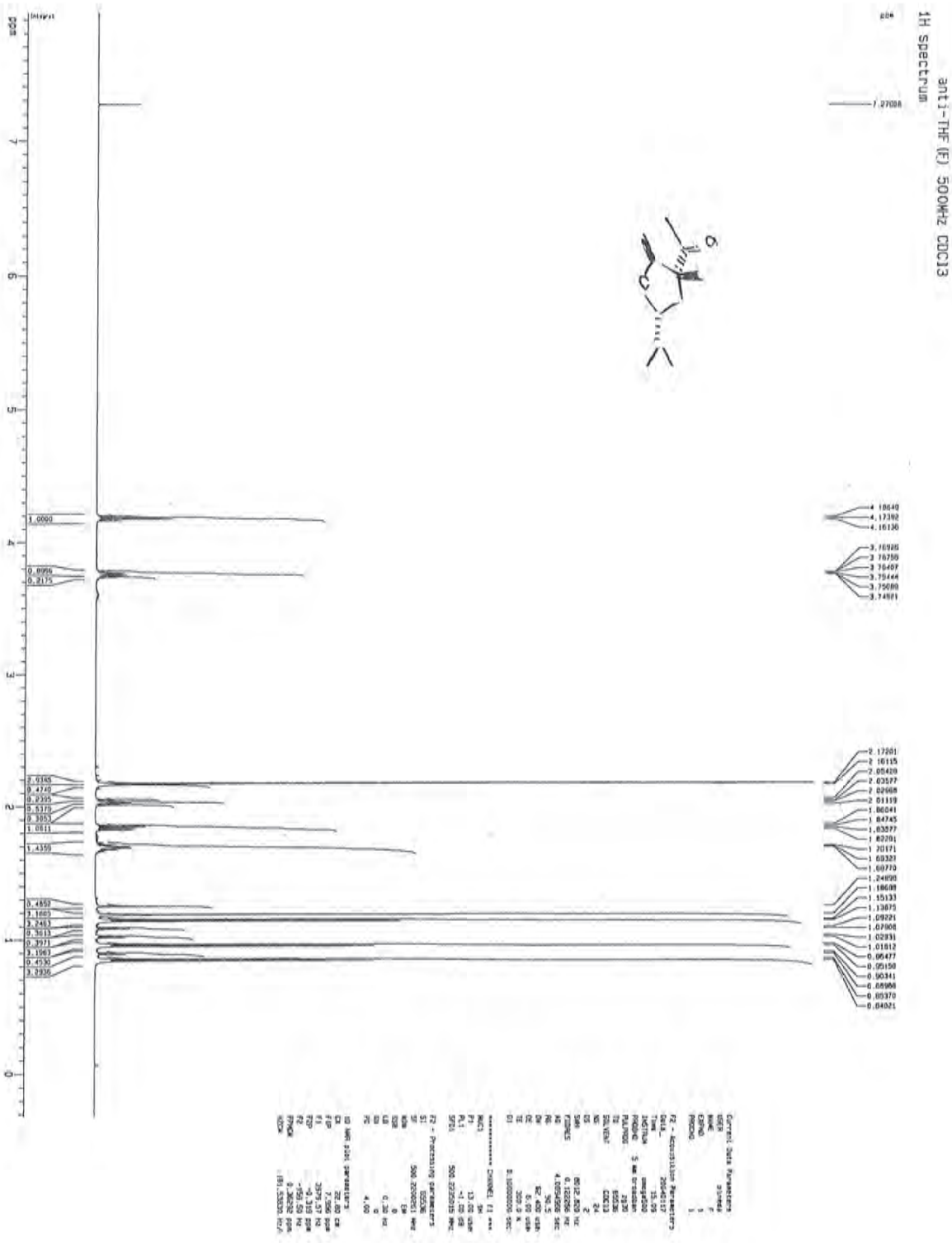
Ketone 125MHz CDCl3
13C spectrum with 1H decoupling
SDQ840
ppm
200
150
100
50
0
135.01
133.67
133.05
130.08
129.00
127.91
127.80
77.61
27.04
25.00
20.65
19.39


diol 500MHz CDCl3
1H Spectrum
Me
Me
OH
Me
H
OH

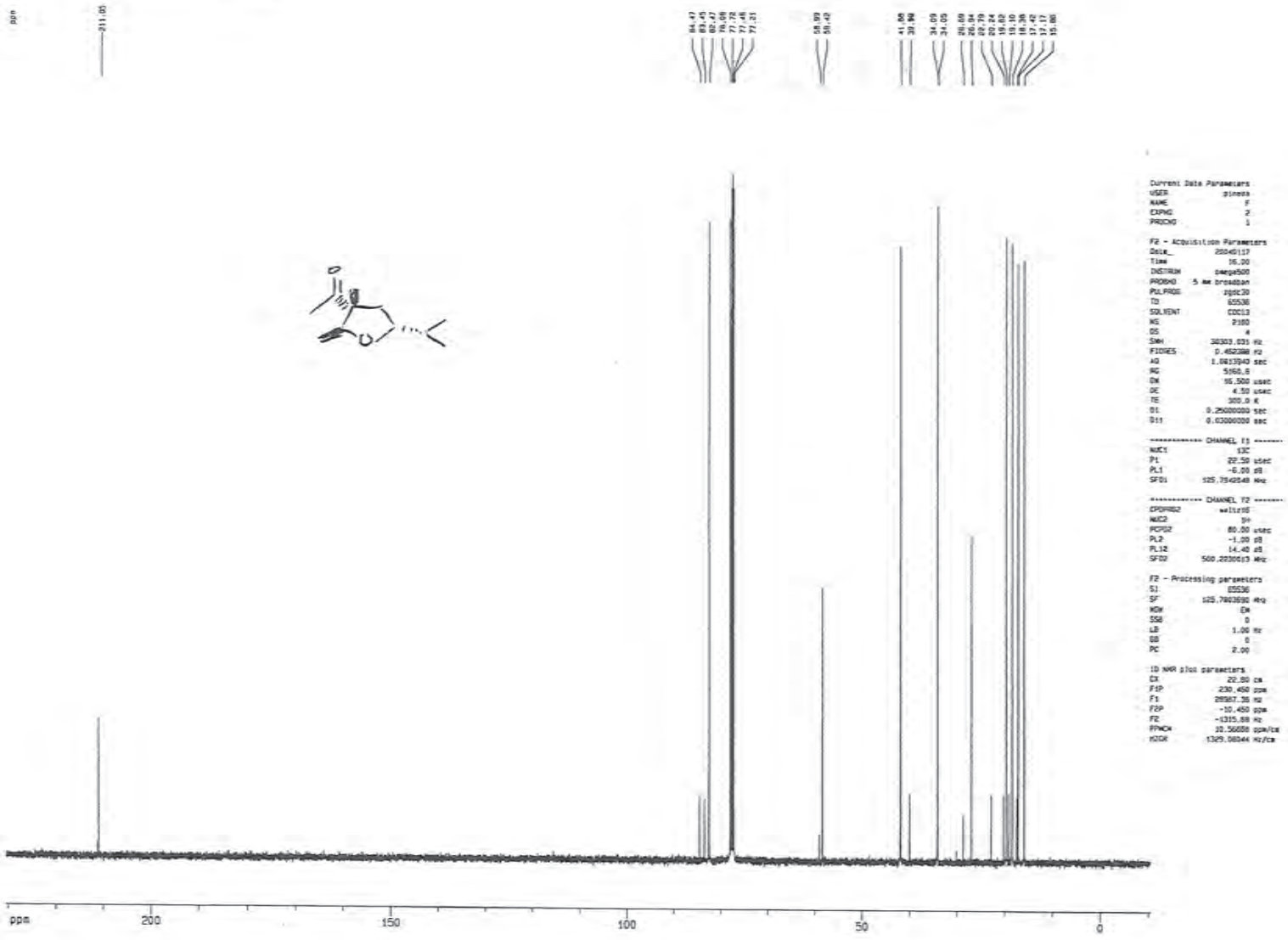

diol 125MHz CDCl3
13C spectrum with 1H decoupling
ppm
171.37
148.43
111.80
110.77
77.48
77.43
77.39
77.23
76.98
71.73
70.67
60.53
24.87
21.70
21.08
19.83
19.52
17.44
16.45
14.24
200
150
100
50
0


acetal 101 500MHz CDCl3
1H Spectrum
Me
Me
Me
H
O
O
4.84521
4.84352
4.67523
4.67224
4.60924
4.61567
4.60402
3.78214
3.76935
3.75655
3.74376
1.83135
1.81763
1.80576
1.79328
1.69745
1.69660
1.32038
1.28343
1.26948
1.25726
1.23364
1.24472
1.23449
1.06337
1.05058
0.95559
0.94847
0.94218
0.93485
0.85068
0.84503
0.83092
1.0000
0.9916
0.9913
1.0005
1.0420
2.9421
3.0797
2.4442
4.5711
3.0063
5.1042
4.2923

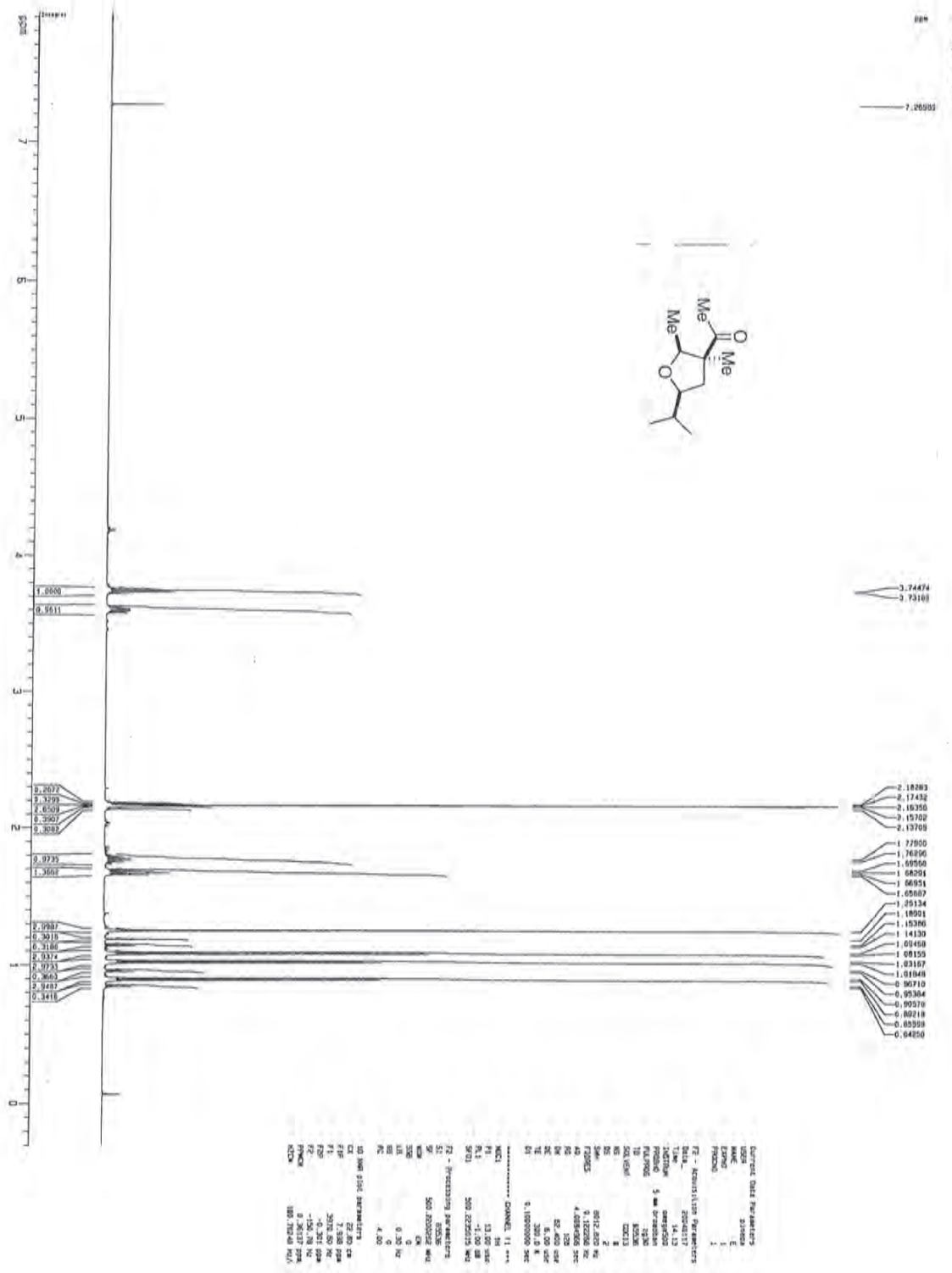
acetal(D) 125MHz CDCl3
13C spectrum with 1H decoupling
ppm
200
150
100
50
0
146.47
111.85
106.14
84.11
81.33
77.48
77.23
76.97
32.20
32.08
29.22
23.37
22.84
20.92
17.64
17.55
16.58
14.12
Me
Me
Me
H
O
O


anti-THF (E) 500MHz CDCl3
1H spectrum
ppm
7.27088
1.0000
0.0956
0.2175
2.0385
0.4740
0.2395
0.5378
0.3053
1.0811
1.4359
0.4852
1.1603
0.2463
0.3613
0.2971
1.1963
0.4530
3.2936
4.18640
4.17392
4.16136
3.76926
3.76756
3.76467
3.75444
3.75089
3.74681
2.17201
2.16115
2.05429
2.03577
2.02968
2.01119
1.86041
1.84745
1.83577
1.82201
1.70171
1.69321
1.68770
1.24898
1.18698
1.15133
1.13675
1.09221
1.07906
1.02931
1.01812
0.95477
0.95150
0.90341
0.88966
0.85370
0.84021

anti-THF (F) 125MHz CDCl3
13C spectrum with 1H decoupling




```
Current Data Parameters
USER                 pineda
NAME                      F
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20040117
Time                   16.00
INSTRUM            omega500
PROBHD    5 mm broadban
PULPROG              zgdc30
TD                    65536
SOLVENT               CDCl3
NS                     2100
DS                        4
SWH                30303.031 Hz
FIDRES             0.462288 Hz
AQ                 1.0813940 sec
RG                    5958.8
DW                   16.500 usec
DE                    4.50 usec
TE                   300.0 K
D1                 0.25000000 sec
D11                0.03000000 sec

========== CHANNEL f1 ========
NUC1                     13C
P1                     22.50 usec
PL1                    -6.00 dB
SFO1             125.7542548 MHz

========== CHANNEL f2 ========
CPDPRG2              waltz65
NUC2                     1H
PCPD2                 80.00 usec
PL2                    -1.00 dB
PL12                   14.40 dB
SFO2             500.2230013 MHz

F2 - Processing parameters
SI                       65536
SF               125.7803690 MHz
WDW                         EM
SSB                          0
LB                      1.00 Hz
GB                           0
PC                        2.00

1D NMR plot parameters
CX                      22.00 cm
F1P                   230.450 ppm
F1                   28987.36 Hz
F2P                   -10.450 ppm
F2                   -1315.88 Hz
PPMCM                10.56000 ppm/cm
HZCM                 1329.08044 Hz/cm
```


1H spectrum
syn-THF (E) 125MHz CDCl3
Me
Me
O
Me
O

syn-THF (E) 125MHz CDCl3
13C spectrum with 1H decoupling