Development and Applications of Asymmetric Hydroformylation Tandem Reactions: The Total Syntheses of (+)-Patulolide C, (-)-Pyrenophorol, (+)-Decarestrictine L and (+)-Prelog-Djerassi Lactone

by

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Dedication

To my Lord Jesus Christ, without you … I wouldn't be here. Thank you.

Acknowledgments

To Professor Burke, you have taught me that not all syntheses are created equal. You've allowed me the freedom to explore, grow and learn from my mistakes. Thank you. You've always kept the standard high and that forced me to strive to perform at a higher level than I would have otherwise, thank you. You set challenges before me and coached me through them, and that has built confidence in my own abilities. For that I am eternally grateful. You've set the stage for me to discover the great joy of problem solving and the deep satisfaction of synthesizing a challenging complex molecule, thank you. You've taught me that when I think I have a good result, I can probably do just a little bit better and that has given me a spirit of excellence that will guide me throughout my career, thank you. You have been a great blessing to me and I pray God blesses you in ways you cannot even imagine.

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"Proverbs 25:2 It is the glory of God to conceal a matter, but the glory of kings to search out a matter."

I look forward to all the discoveries of the future with great expectation.

Abstract

Three different asymmetric hydroformylation (AHF) tandem reactions have been developed in the context of the total syntheses of (+)-patulolide C, (-)-pyrenophorol, (+)-decarestrictine L and (+)-Prelog-Djerassi lactone. Specifically, a synthesis of (+)-patulolide C has been accomplished in 3 steps utilizing a Rh(I)-catalyzed *Z*-selective *anti*-Markovnikov hydroacetoxylation of a known alkyne to give a *Z*-enol acetate with excellent selectivity (97% *Z*). A Rh(I)-catalyzed AHF/ intramolecular Wittig olefination cascade was utilized to set the C4-hydroxyl stereochemistry, *E*-olefin geometry, and form the macrolactone. Also, both (-)-pyrenophorol and (+)-decarestrictine L have been synthesized from the enantiomeric (4*R*) and (4*S*) 4-*tert*-butyldimethylsiloxy-1-pentyne in five and four steps, respectively. These syntheses feature Ru(II)-catalyzed *Z*-selective *anti*-Markovnikov hydroacetoxylation of the terminal alkynes followed by AHF/ Wittig olefination sequences to rapidly establish functionality and stereogenicity. A synthesis of (+)-Prelog-Djerassi lactone has been accomplished in 3 isolations from the known 1-vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane ortho ester (vinyl-OBO). A Rh(I)-catalyzed AHF/crotylation tandem sequence has been developed and used to set the C2-C4 stereochemistry. A Rh(I)-catalyzed asymmetric hydrogenation was employed to set the C6 stereochemistry, resulting in an unusually short and efficient enantioselective synthesis of this touchstone molecule from achiral starting material. Overall, the strategic application of the Rh(I)- and Ru(II)-*Z*-selective hydroacetoxylation, Rh(I)-catalyzed AHF with the Landis bisdiazaphospholane ligands, and the Rh(I)-catalyzed asymmetric hydrogenation have greatly improved the overall efficiency of these syntheses in terms of atom-economy, catalytic stereoselective transformations, inexpensive reagents, step counts and overall yield.

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Selected Abbreviations and Acronyms

AHF	asymmetric hydroformylation
BDP	bisdiazaphospholane
DMAP	*N,N*-dimethylaminopyridine
EE	ethoxy ethyl
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Bn	benzyl
TPAP	tetrapropylammonium perruthenate
NMO	4-methylmorpholine-*N*-oxide
DCM	dichloromethane
DCC	dicyclohexylcarbodiimide
TsOH	*para*-toluenesulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMSO	dimethylsulfoxide
DMF	*N,N*-dimethylformamide
imid.	imidazole
THF	tetrahydrofuran
Et_2O	diethyl ether
PDC	pyridinium dichromate
PCC	pyridinium chlorochromate
DIBAL-H	diisobutylaluminum hydride
LAH	lithium aluminum hydride

KO*t*-Bu	potassium *tert*-butoxide
m-CPBA	*meta*-chloroperoxybenzoic acid
TBAI	*tetra*-butylammonium iodide
DEAD	diethylazodicarboxylate
DBAD	di-*tert*-butylazodicarboxylate
$PhCH_3$	toluene
PhH	benzene
L-(+)-DIPT	L-(+)-diisopropyltartrate
TBHP	*tert*-butylhydroperoxides
cat.	catalyst
room temp	room temperature
tfacac	trifluoroacetylacetenate
Grubbs 2nd generation catalyst	(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro (phenylmethylene)(tricyclohexylphosphine) ruthenium
Vitride®	sodium bis(2-methoxyethoxy)aluminum dihydride
(*R,R*)- Salen cat.	(*R,R*)-(-)-*N,N'*-bis(3,5-di-*tert*-butyl salicylidene)-1,2-cyclohexane diamine cobalt(II)

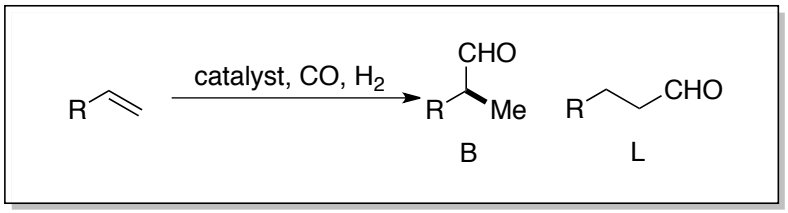
(*S,S*)- Salen cat.	(*S,S*)-(-)-*N,N'*-bis(3,5-di-*tert*-butyl salicylidene)-1,2-cyclohexane diamine cobalt(II)
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
MS	molecular sieves
AIBN	azobisisobutyronitrile
DME	1,2-dimethoxyethane
(S)-CBS	(*S*)-1-Methyl,3,3-diphenyl-tetrahydro-pyrrolo[1,2-*c*][1,3,2]oxazaborole
(R)-YLB	(*R*)-YLi_3tris(binaphthoxide)
pyr.	pyridine
MNBA	2-methyl-6-nitrobenzoic anhydride
T3P®	propylphosphonic anhydride

Chapter 1: Asymmetric Hydroformylation with the Landis' Bisdiazaphospholane Ligands

Chapter 1a: Landis' development of the (*S*,*S*,*S*)/(*R*,*R*,*S*)-Bisdiazaphospholane Ligands

Rhodium(I)-catalyzed asymmetric hydroformylation[1] is a reaction that converts alkenes into aldehydes with the addition of a hydride to one carbon and a formyl group to the other carbon of the alkene (Scheme 1a). The two possible regioisomers formed are the branched (B) and linear (L). The branched aldehyde has an asymmetric center and since the aldehyde is one

Scheme 1a



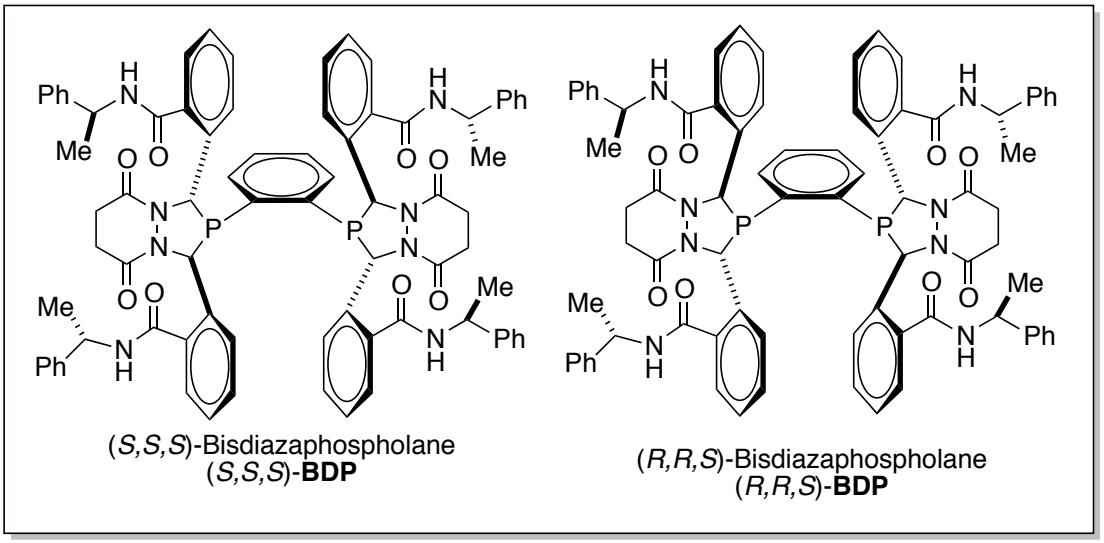
of the most versatile functional groups in organic synthesis,[2] enantioenriched products could serve as highly valuable intermediates in the realm of pharmaceuticals, agrochemicals and materials manufacturing. Asymmetric hydroformylation (AHF) is done with a chiral ligand,[3] usually a bidentate phosphine, on the rhodium center in order to induce asymmetry on the branched chiral aldehyde product.

Hydroformylation is a reaction with many attributes that make it appealing to synthetic chemists. First it uses cheap reagents, hydrogen gas and carbon monoxide, which make it economically feasible. Second it has excellent atom-economy, *i.e.* all the atoms in the alkene, hydrogen gas and carbon monoxide are incorporated into the aldehyde product. Reactions with high atom-economy produce less waste, which makes them more environmentally friendly and amenable to large-scale application.[4] Since billions of pounds of achiral aldehyde are made each year, there is no doubt that AHF has high potential for industrial applications. Furthermore, the ever-increasing demands for scarce resources necessitate the use of catalytic reactions in industrial processes.

Another attribute of AHF is functional group tolerance. The reaction is done under neutral conditions so the newly formed aldehyde as well as any other sensitive functionality in the molecule is relatively safe from epimerization or degradation. Since the aldehyde is such a versatile functional group,[2] it can be used for a variety of subsequent transformations making the formyl group an ideal lynchpin for building molecular complexity efficiently. Once the AHF is complete, the reagents (CO and H_2) are easily removed from solution by venting the reaction vessel. The aldehyde product left in solution is essentially pure, aside from the small amount of catalyst that is generally inert to subsequent transformations, and ready to use without purification. These qualities make the AHF an ideal reaction for developing subsequent tandem transformations. From an industrial perspective, this is highly advantageous, because each step with purification requires time and expensive effort, and generates waste. Therefore eliminating a purification step while building stereochemistry and functionality into the molecule is of great value.

With all these features in mind much research has been done in the field of AHF.[5] When performing an AHF reaction the catalyst must exert both regio- and enantioselectivity in transforming the substrate. Many of the catalyst systems developed for this purpose still suffer from slow rates, especially on internal alkenes, and low regio- and enantioselectivity for a broad range of substrates.[3]

Figure 1a

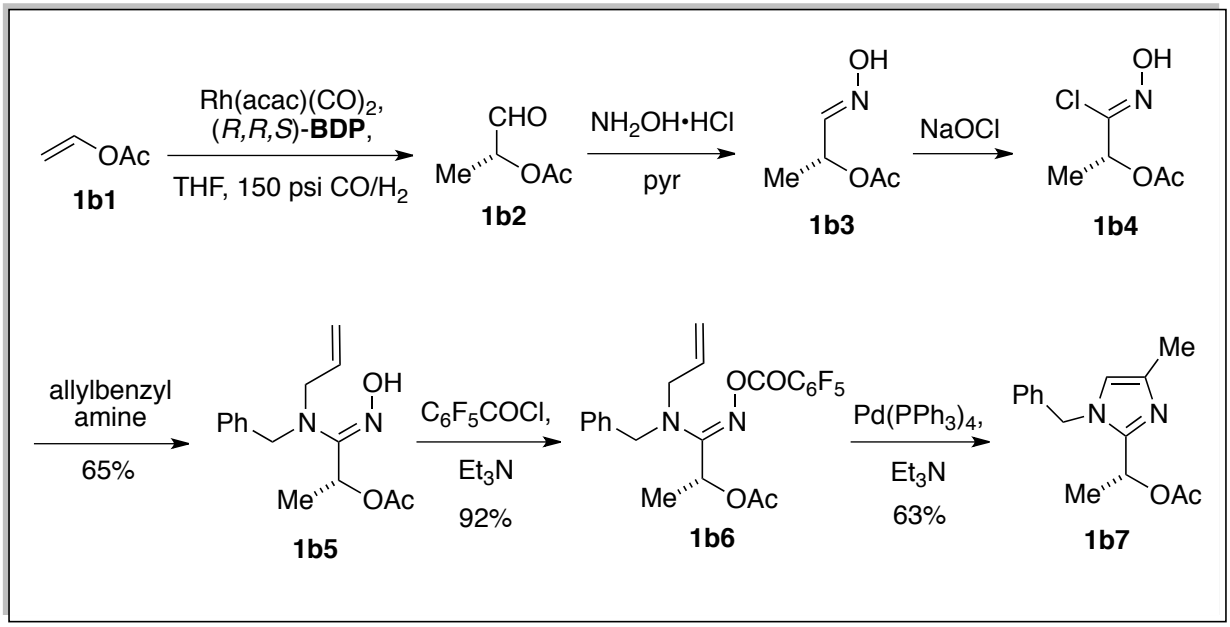


In 2005, the Landis group published a new, highly active AHF ligand,[7] the bis-3,4-diazaphospholanes shown in Figure 1a. Rhodium-catalyzed AHF with the (*S,S,S*)/(*R,R,S*)-bisdiazaphospholanes (**BDP**s) exhibit exceptional reactivity toward a variety of olefins. These state-of-the-art ligands exhibit high turn-over-numbers (TONs), high turn-over-frequency (TOFs) and excellent regio- and enantioselectivity. Vinyl acetate has long been a standard hydroformylation substrate and the Landis group has demonstrated a large scale Rh(I)-catalyzed AHF with the (*S,S,S*)-**BDP** ligand on vinyl acetate generating the chiral (2*S*-acetyloxy)-propanal with excellent regio- and enantioselectivity (41:1 B:L, 92-96 % ee).[7] This catalyst system exhibits outstanding reactivity with the substrate to catalyst ratio of up to 150,000:1 and TOFs averaging 19,400. They have shown that the chirality of the branched aldehyde is determined by the stereochemistry of the phospholane ring, where the rhodium is bound and not the chiral amide moieties.

The Landis group has also demonstrated that these highly enantioenriched aldehydes could be transformed into other functional groups without loss of stereochemical integrity.[8] As shown in Scheme 1b, (2*R*-acetyloxy)-propanal **1b2** was produced via AHF of vinyl acetate **1b1**

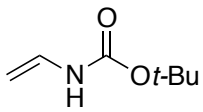
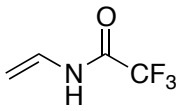
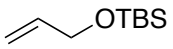
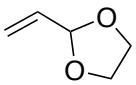
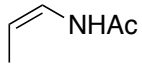
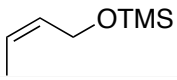
with (*R,R,S*)-**BDP** / $Rh(acac)(CO)_2$ catalyst system. The newly formed chiral aldehyde (94 % ee) was then condensed with NH_2OH and then chlorinated with NaOCl to yield hydroximoyl chloride **1b4**. Coupling with allylbenzyl amine gave **1b5** followed by esterification with pentafluorobenzoyl chloride to give **1b6**. An amino Heck reaction produced the desired chiral imidazole **1b7** (94 % ee) without any loss in ee.[8]

Scheme 1b:



Terminal olefins undergo AHF more readily than 1,2- or 1,1-disubstituted alkenes. The Rh-catalyzed AHF with the **BDP** ligands has shown a broad substrate scope, even on 1,2- or 1,1-disubstituted alkenes, albeit with decreased selectivity. Several examples of 1-alkenes and 1,2-disubstituted alkenes are shown in Table 1a. The **BDP** ligands have displayed supreme regio- and enantioselectivity as well as high TONs and TOFs on a broad range of substrates.[9] These alkenes are just a few examples of low-cost substrates that can be transformed into high value enantioenriched chiral aldehydes in a single step with the Rh-**BDP** system.

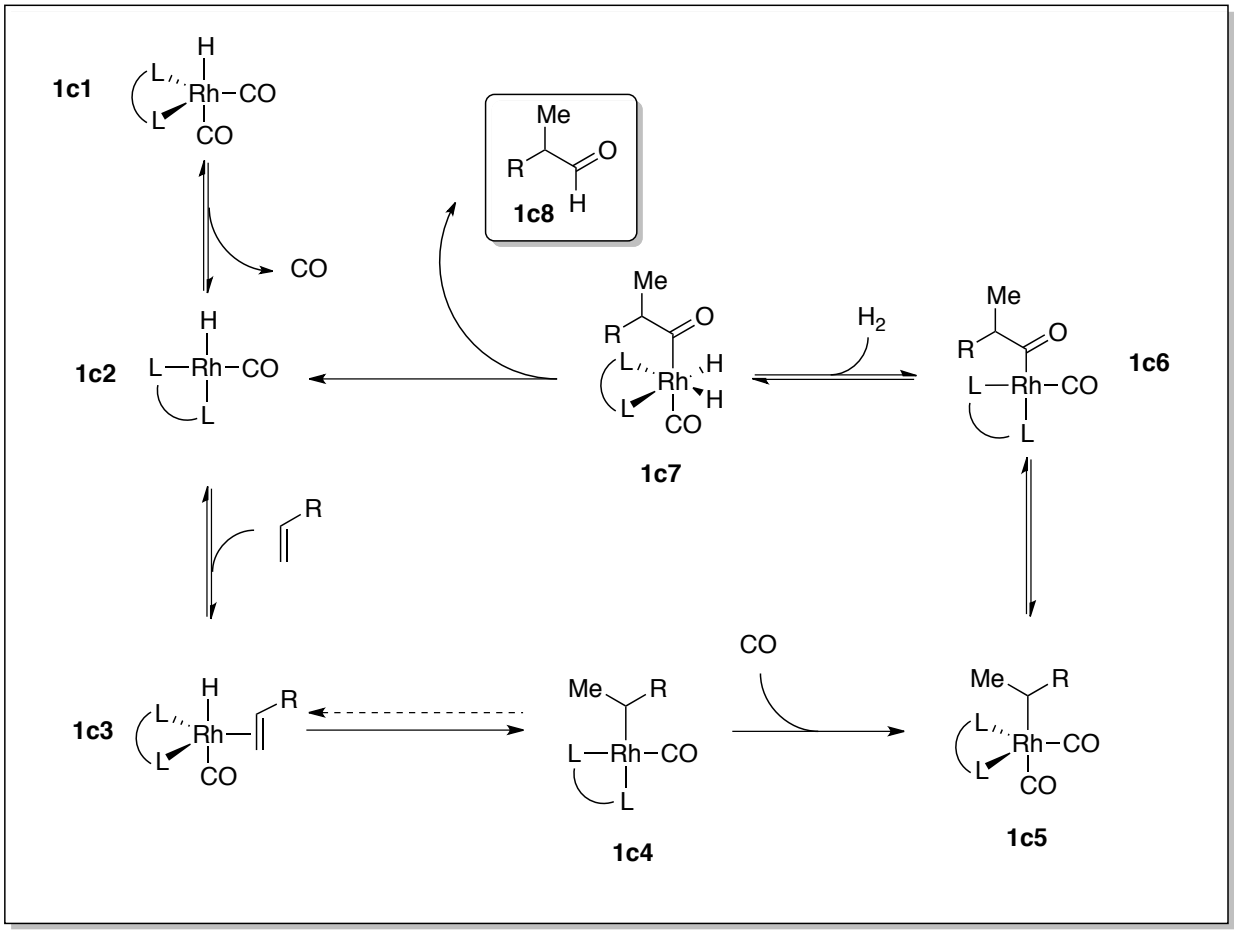
Table 1a:

	time (h)	temp (°C)	conv (%)	B:L	% ee
	12	40	99	33:1	99
	6	40	99	>50:1	99
	4	40	99	2:1	96
	4	40	99	4.2:1	92
	20	70	99	32:1	90
	15	40	99	2.8:1	94

Conditions: 140 psi syngas (CO/H_2 1:1),
0.5 mol% Rh/0.55% (*S*,*S*,*S*)-**BDP**, 0.75 M in toluene

The mechanism for rhodium-catalyzed AHF is depicted in Scheme 1c.[6] The catalyst resting state is the 18 e^- complex rhodium(I) hydrido dicarbonyl **1c1**. Upon dissociation of CO, the active catalyst **1c2** is formed. Alkene coordination yields the π-olefin complex **1c3** that leads (reversibly, vide infra) to the alkyl rhodium specie **1c4**. Another molecule of CO binds to make the pentacoordinate rhodium alkyl specie **1c5** followed by alkyl migration to generate the rhodium-acyl specie **1c6**. Insertion of dihydrogen yields the octahedral rhodium (III) species **1c7**. Finally reductive elimination, for a net hydrogenolysis of **1c6** gives the aldehyde product **1c8** and regenerates the active catalyst **1c2**.

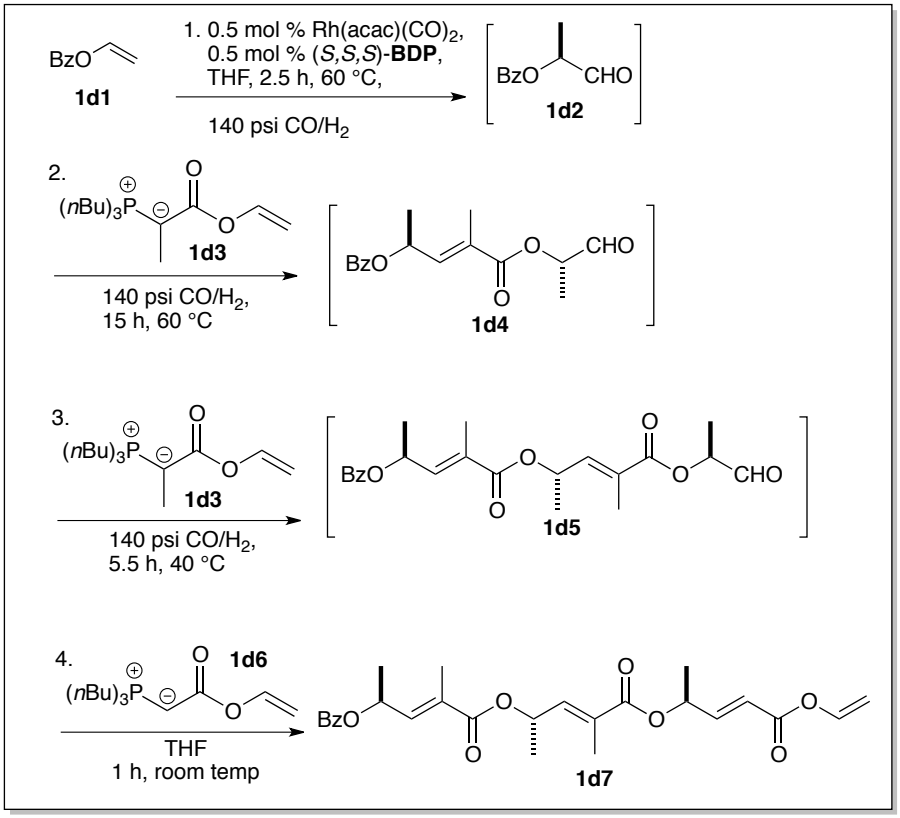
Scheme 1c:



Experiments were conducted probing both the partial pressures of CO and H_2 along with ^{2}H-labelling studies on the AHF of styrene with (*S,S,S*)-**BDP**.[6] They discovered that the regio- and enantioselectivity of the AHF of styrene is dependent and proportional to changes in CO partial pressure from 40 to 120 psi CO and basically unaffected by changes in the H_2 partial pressure. It was also found that at higher CO pressures (> 80 psi CO) a slight inhibition of rate occurred, probably due to the need for CO dissociation from the catalyst resting state to generate the active catalyst (Scheme 1c). They concluded based on extensive incorporation of ^{2}H into the recovered styrene that rhodium-alkyl formation is reversible. Over a broad range of CO pressures the kinetics of the reaction are too complex to identify a single an enantiodetermining step.

Recently Landis and Wong published an account of iterative AHF/ Wittig olefinations[10] to demonstrate the robustness of the catalyst and the ability of stabilized phosphorus ylides to reacts with chiral aldehydes without erosion of enantiopurity at the newly formed asymmetric center. The Wittig olefination of α-chiral aldehydes (as generated by AHF) with carbonyl stabilized phosphorus ylides was shown to proceed in good yield and without loss of stereochemical integrity. As shown in Scheme 1d, vinyl benzoate **1d1** undergoes AHF with very low catalyst loading to afford (2*R*-benzoyloxy)-propanal **1d2**, which is then reacted with ylide **1d3** to generate the Wittig olefination product containing a new vinyl ester, which undergoes a second AHF to yield **1d4**. A second Wittig olefination was done followed by a third AHF to give aldehyde **1d5**. Finally a third Wittig olefination was done with ylide **1d6** to afford the trimer **1d7** in 17 % yield from vinyl benzoate **1d1** without isolation of intermediate products.

Scheme 1d



These results clearly demonstrate the versatility and robust nature of the [Rh-**BDP**] catalyst system for AHF. With these outstanding results in mind, we set out to develop and apply AHF tandem reactions in the context of natural product total synthesis as illustrated in the subsequent chapters.

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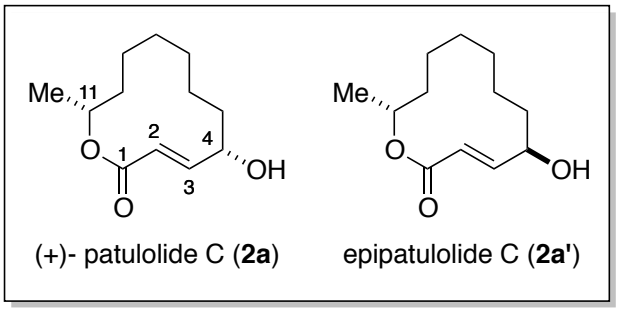
Chapter 2: Background and Previous Syntheses of (+)-Patulolide C

Chapter 2a: Background and Previous Syntheses of (+)-Patulolide C

(+)-Patulolide C (**2a**, Figure 2) was first discovered by Yamada and coworkers in 1985 from the culture filtrate of *Penicillium urticae* S11R59 mutant, along with it's congeners patulolide A and B[1]. (+)-Patulolide C (**2a**) is a 12 membered ring macrocycle containing an *E*-α,β-unsaturated carbonyl, C11 (*R*)-Me substituent and a C4 (*S*)-hydroxyl. Exhibiting both antifungal and antibacterial activities[2], the patulolides have been the targets of several total syntheses. Summaries of those syntheses are presented in the following sections.

Figure 2



(+)- patulolide C (**2a**) epipatulolide C (**2a'**)

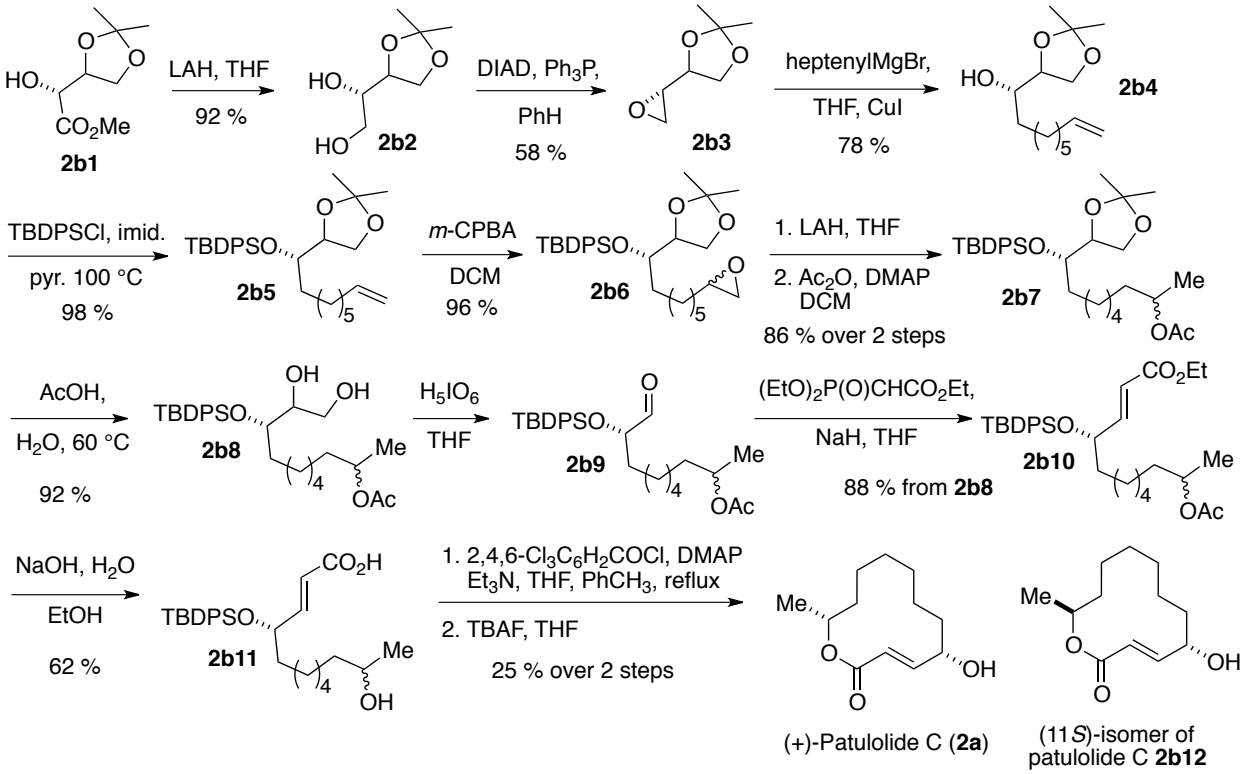
Name, year	Steps (Longest Linear Sequence)	Overall Yield %	Key Reactions
Irie, 1992	13	4.2	Yamaguchi macrolactonization
Zwanenburg, 1993	18	0.97	Rearrang. of diazo-methyl ketone
Takano, 1994	19	2.0	C2-symmetric bis-epoxide
Sabitha, 2010	14	2.1	α-aminooxylation/ HWE tandem
Thomas, 2012*	15	3.8	Diastereoselective aldehyde allylation
Hase, 1999*	8	10	Mitsunobu cyclization
Shibasaki, 2003	9	38	Asymm. cyanation-ethoxycarbonylation
Sharma, 2008	16	3.4	Grubbs II RCM
Mori, 1988	9	21	Yamaguchi macrolactonization

* racemic synthesis

Chapter 2b: Irie's Synthesis of (+)-Patulolide C

Irie's[3] synthesis of (+)-Patulolide C (**2a**) starts with the known ester **2b1**[4] (Scheme 2b), readily available from Vitamin C. Reduction of the ester with LAH gave the primary alcohol **2b2** followed by Mitsunobu reaction with DIAD and Ph_3P to afforded epoxide **2b3**. Ring opening of the epoxide with heptenylmagnesium bromide gave alcohol **2b4** along with protection as the TBDPS-ether to give the fully protected alkene **2b5** and epoxidation with *m*-CPBA to give epoxide **2b6**. Reductive ring opening with LAH and protection with Ac_2O gave the diastereomeric acetates **2b7** folowed by hydrolysis of the acetonide with $AcOH/H_2O$ to give diol **2b8**. Oxidative cleavage of the diol afforded aldehyde **2b9** with subsequent Wittig olefination to produce α,β-unsaturated ester **2b10**. A double hydrolysis of both esters gave hydroxy acid **2b11** followed by Yamaguchi macrolactonization and TBAF mediated desilylation to give (+)-patulolide C (**2a**) and the 11(*S*) isomer **2b12** as a 1:1 mixture.

Scheme 2b: Irie's Synthesis of (+)-Patulolide C

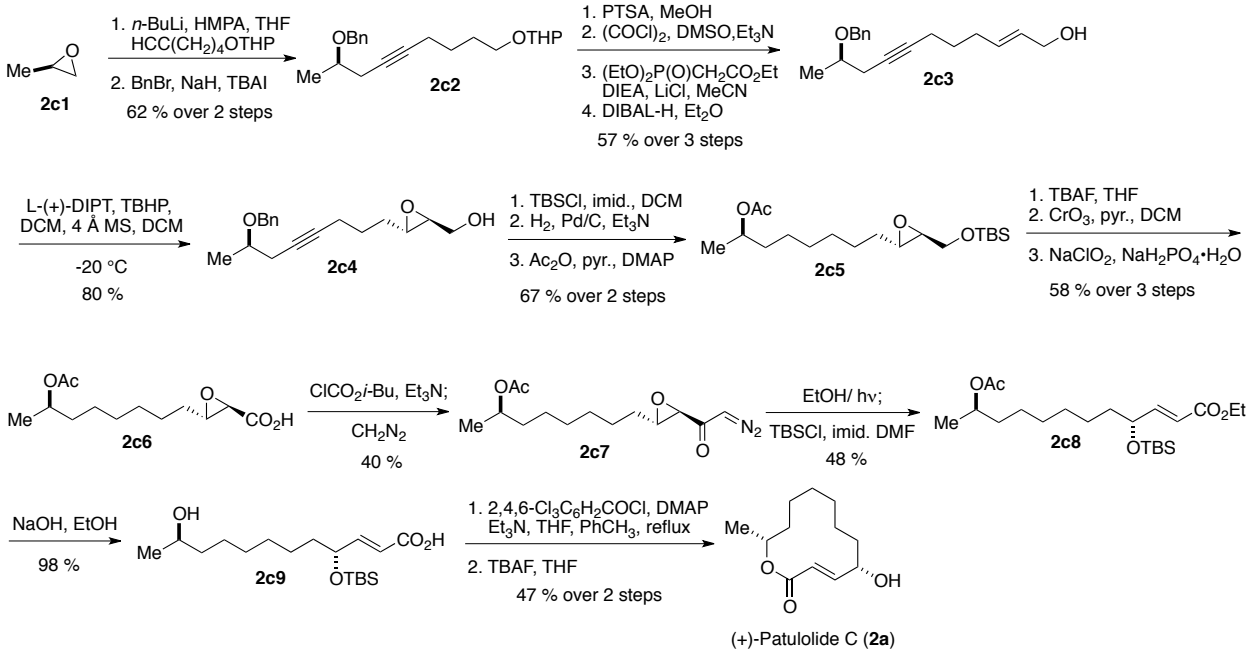


Chapter 2c: Zwanenburg's Synthesis of (+)-Patulolide C

Zwanenburg's[5] synthesis of (+)-patulolide C (**2a**) begins with ring opening of (*R*)-propylene oxide **2c1** (Scheme 2c) with the lithium anion of THP-protected 5-hexyn-1-ol to afford the internal alkyne **2c2**. Next the THP ether was removed, the alcohol oxidized followed by HWE olefination and DIBAL-H reduction to produce allylic alcohol **2c3**. Sharpless asymmetric epoxidation[6] afforded **2c4** followed by protection of the alcohol as the TBS ether, hydrogenation of the alkyne with simultaneous Bn ether cleavage then reprotection of the hydroxyl as the acetate **2c5**. The TBS ether was then removed with TBAF and the alcohol was oxidized to the acid **2c6**. Formation of the mixed anhydride using isobutyl chloroformate preceded the reaction with CH_2N_2 to afford α-diazomethyl ketone **2c7**. Their key photoinduced rearrangement of ketone **2c7** with subsequent TBS silyl ether formation produced the desired γ-

siloxy-α,β-unsaturated ester **2c8** followed by double hydrolysis of both esters gave hydroxy acid **2c9**. Finally Yamaguchi macrolactonization followed by disilylation afforded (+)-patulolide C (**2a**).

Scheme 2c: Zwanenburg's Synthesis of (+)-Patulolide C

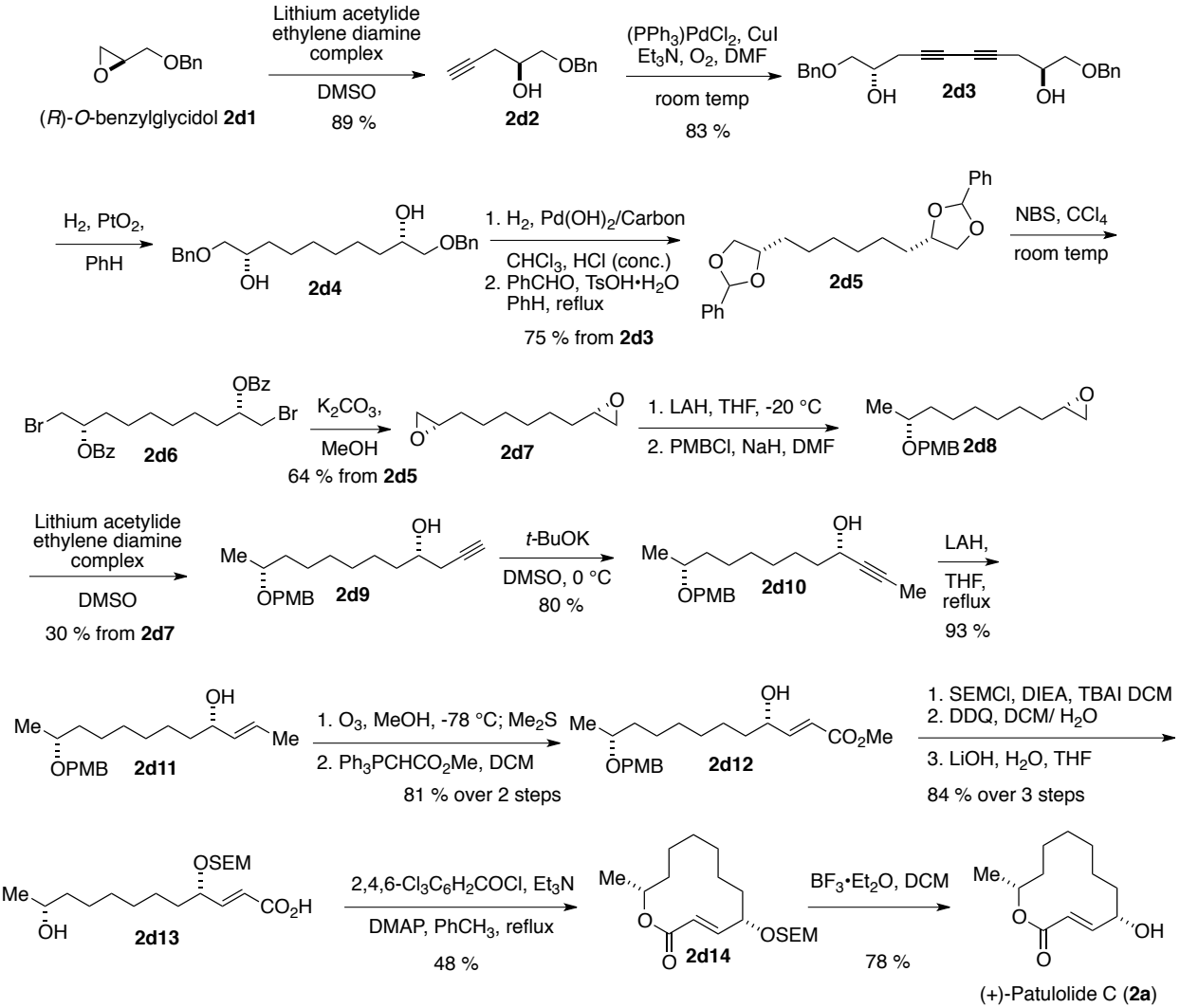


Chapter 2d: Takano's Synthesis of (+)-Patulolide C

In 1994, Takano[7] and coworkers reported a 19 step synthesis of (+)-patulolide C (**2a**) from (*R*)-*O*-benzylglycidol **2d1**[8] (Scheme 2d). Ring opening of the epoxide was affected with lithium acetylide diethylamine complex to give the homopropargylic alcohol **2d2** followed by a Pd(II) catalyzed alkyne dimerization to produce the C2-symmetric bis-alkyne **2d3**. Platinum catalyzed hydrogenation of the alkynes gave the fully saturated diol **2d4** with subsequent hydrogenolysis of the Bn ethers then bis-acetal formation of the tetra-ol to give the C2-symmetric bis-benzylidene acetal **2d5**. Reaction with NBS in CCl_4 oxidatively opens the acetal while brominating the terminal carbon to give dibromide **2d6**. Basic methanolysis cleaves the esters and the intermediate alkoxide displaces the bromide to give the C2-symmetric bis-epoxide

2d7. Careful desymmetrization with LAH followed by PMB protection of the alcohol gave PMB ether **2d8**. Another epoxide opening with lithium acetylide diethylamine complex gave alkyne **2d9** followed by isomerization to the internal alkyne **2d10**. Partial reduction of the alkyne with LAH gave *E*-olefin **2d11**. Ozonolytic cleavage of the alkene followed by Wittig olefination of the aldehyde gave α,β-unsaturated ester **2d12**. Protection of the γ-hydroxy as the SEM ether followed by DDQ mediated deprotection of the C11 hydroxyl and saponification of the methyl ester gave hydroxy acid **2d13**. A Yamaguchi macrocyclization was used to form the 12-membered ring followed by removal of the SEM ether to give (+)-patulolide C (**2a**).

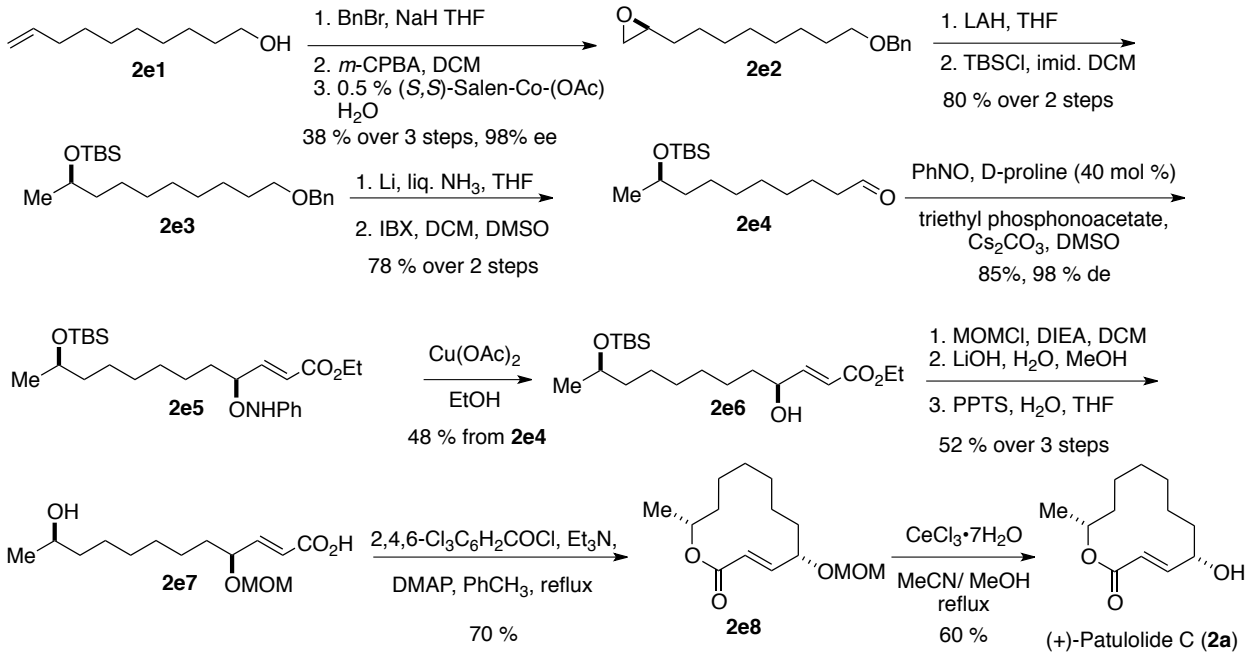
Scheme 2d: Takano's Synthesis of (+)-Patulolide C



Chapter 2e: Sabitha's Synthesis of (+)-Patulolide C

In 2010 Sabitha[9] and coworkers published a synthesis of (+)-patulolide C (**2a**) from 9-decene-1-ol **2e1** (Scheme 2e). Protecting the alcohol as the Bn ether then epoxidizing the alkene followed by a Jacobsen hydrolytic kinetic resolution[10] afforded chiral epoxide **2e2** in 98% ee. Reductive opening of the epoxide with LAH and protection of the hydroxyl as the TBS ether gave **2e3** followed by removal of the Bn ether then IBX oxidation of the alcohol to the aldehyde **2e4**. Next they affected a D-proline catalyzed α-aminooxylation followed by an HWE olefination to give the γ-aminooxy-α,β-unsaturated ester **2e5** with equally high de (98%). Cleavage of the *N, O*-bond was affected with $Cu(OAc)_2$ in EtOH to give γ-hydroxy-α,β-unsaturated ester **2e6**. Protection of the C4 hydroxyl as the MOM ether followed by saponification of the ester and acidic hydrolysis of the TBS ether gave hydroxy acid **2e7**. A Yamaguchi macrocyclization was used to form the 12-membered ring lactone **2e8**. Finally $CeCl_3 \cdot 7H_2O$ mediated cleavage of the MOM ether afforded (+)-patulolide C (**2a**).

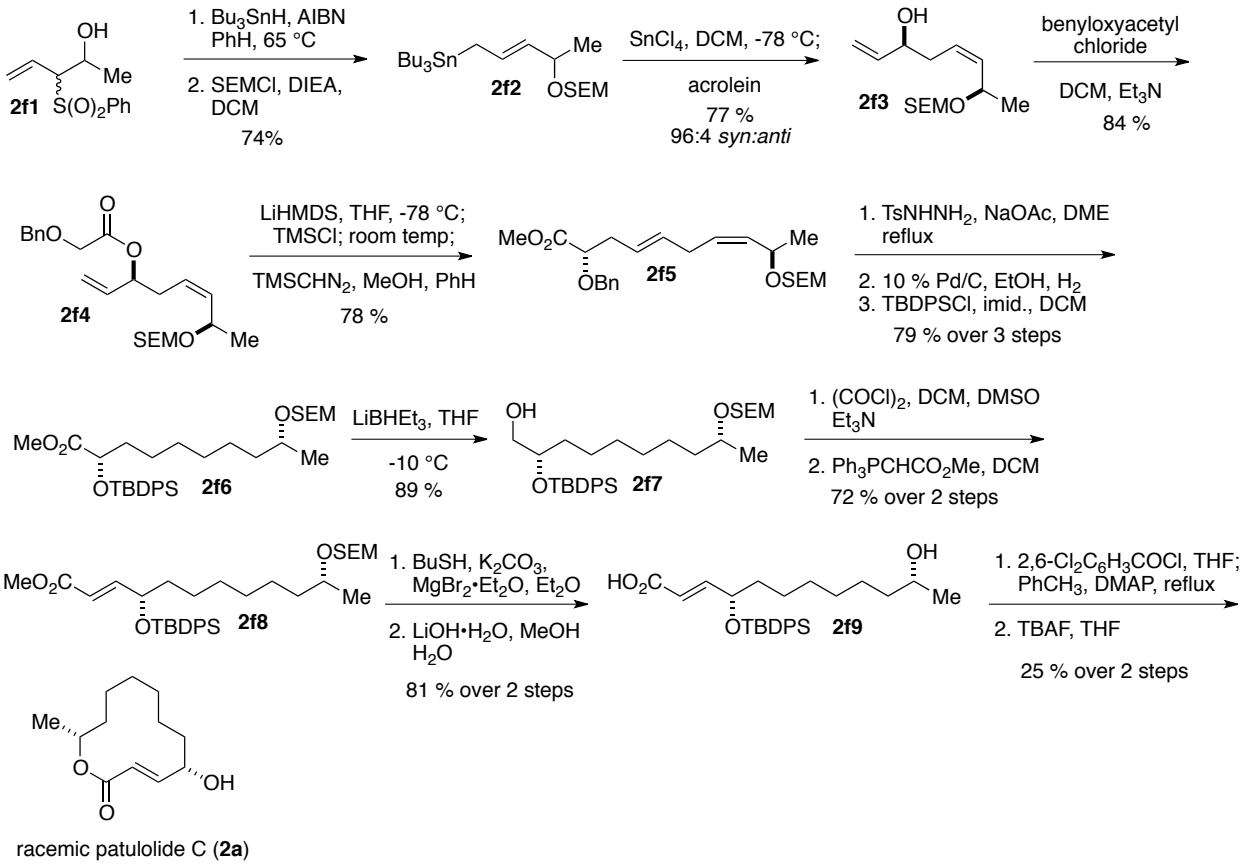
Scheme 2e: Sabitha's Synthesis of (+)-Patulolide C



Chapter 2f: Thomas' Synthesis of Patulolide C

Recently Thomas[11] published a racemic synthesis of patulolide C (**2a**) featuring a diastereoselective aldehyde allylation with allylic tributylstannanes. Beginning with known allylic sulfone **2f1**[12] (Scheme 2f), radical initiated allylic displacement of the sulfone with trapping by the tributyltin radical gave allylic tributylstannane **2f2** after hydroxyl protection as the SEM ether. Next with $SnCl_4$ they affected an allylation of acrolein with great diastereocontrol at -78 °C to give allylic alcohol **2f3** with >96:4 1,5-*syn*: 1,5-*anti*. Esterification with benzyloxyacetyl chloride gave ester **2f4** followed by an Ireland-Claisen rearrangement, via deprotonation with LiHMDS and trapping of the enolate as the TMS ketene acetal then [3,3]-sigmatropic rearrangement. Aqueous work-up followed by reaction of the carboxylic acid with $TMSCH_2N_2$ in MeOH gave α-benzyloxy methyl ester **2f5**. Next a diimide reduction of the olefin followed by a protecting group exchange of the Bn ether to the TBDPS ether gave methyl ester **2f6**. Reduction of the ester to alcohol **2f7** followed by Swern oxidation and Wittig olefination gave α,β-unsaturated ester **2f8**. Removal of the SEM ether and hydrolysis of the methyl ester gave hydroxy acid **2f9** along with Yamaguchi macrocyclization and TBAF-mediated desilylation to afford racemic patulolide C (**2a**).

Scheme 2f: Thomas' Synthesis of Patulolide C

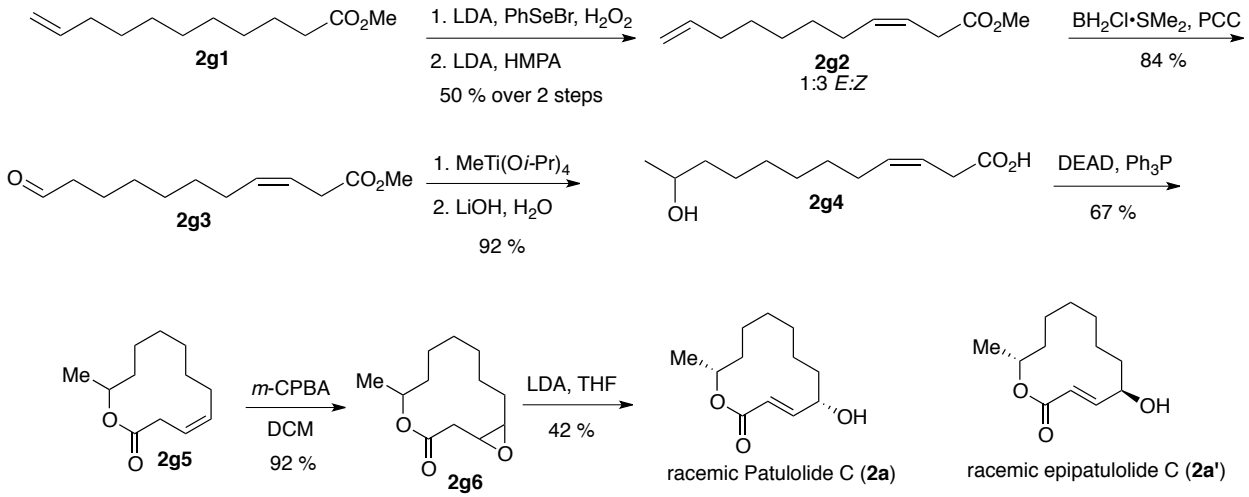


Chapter 2g: Hase's Synthesis of Patulolide C

In 1999 Hase[13] *et. al.* accomplished a racemic synthesis of patulolide C (**2a**) and epipatulolide C (**2a'** Scheme 2g). Beginning with commercially available methyl 10-undecenoate **2g1**, dehydrogenation via the selenoxide, a.k.a. the Reich reaction[14] was affected with LDA, PhSeBr, and H_2O_2. The α,β-unsaturated ester was then deconjugated with LDA and HMPA to give the γ,β-unsaturated ester **2g2** as a mixture of olefins (1:3 *E:Z*). Hydroboration / oxidation with $BH_2Cl{\bullet}SMe_2$ and PCC gave aldehyde **2g3** follwed by nucleophilic addition with $MeTi(O\textit{i}Pr)_4$ to install the C11-Me group. Saponification of the ester along with a Mitsunobu reaction gave γ,β-unsaturated lactone **2g5**. Epoxidation with *m*-CPBA gave epoxide **2g6**

followed by α-deprotonation with LDA and concomitant β,γ-epoxide opening to afford a mixture of racemic patulolide C (**2a**) and epipatulolide C (**2a'**).

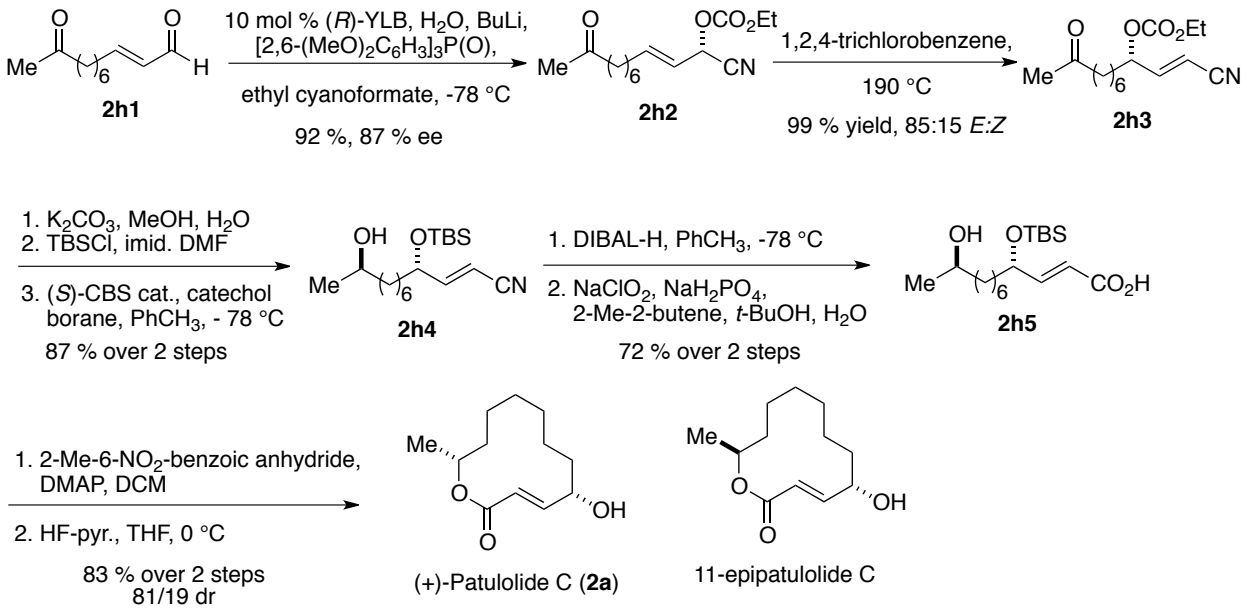
Scheme 2g: Hase's Synthesis of Patulolide C



Chapter 2h: Shibasaki's Synthesis of (+)-Patulolide C

In 2003 Shibasaki[15] and coworkers accomplished a short synthesis of (+)-patulolide C (**2a**) featuring a conversion of an α,β-unsaturated aldehyde to a chiral γ-oxy-α,β-unsaturated nitrile. Beginning with unsaturated aldehyde **2h1**, an asymmetric cyanation-ethoxycarbonylation using a chiral yttrium catalyst and ethyl cyanoformate produced the chiral allylic cyanohydrin carbonate **2h2**. Next a thermal [3,3]-sigmatropic rearrangement proceeded with chirality transfer to give γ-oxy-α,β-unsaturated nitrile **2h3**, with out any loss of enantiopurity. Methanolysis of the carbonate and protection as the TBS ether followed by CBS reduction of the ketone gave alcohol **2h4**. DIBAL-H reduction of the nitrile to the aldehyde followed by oxidation gave α,β-unsaturated acid **2h5**. Macrocyclization with 2-methyl-6-nitrobenzoic anhydride and DMAP with subsequent desilylation afforded (+)-patulolide C (**2a**) in 9 steps from the commercial aldehyde.

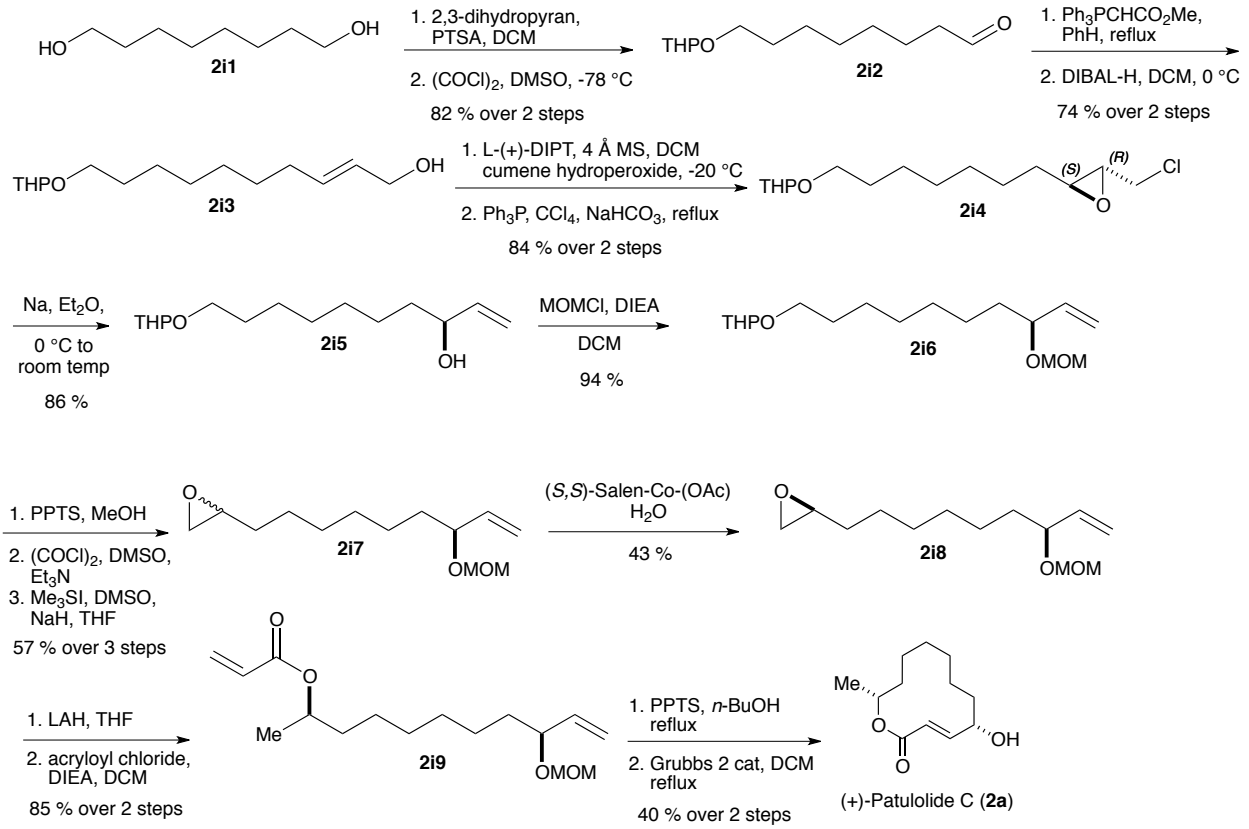
Scheme 2h: Shibaski's Synthesis of (+)-Patulolide C



Chapter 2i: Sharma's Synthesis of (+)-Patulolide C

Sharma[16] and coworkers accomplished a 16 step synthesis of (+)-patulolide C (**2a**) from 1,8-octanediol **2i1** (Scheme 2i). First monoprotection as the THP ether followed by Swern oxidation gave aldehyde **2i2** followed by Wittig olefination to extend the chain then DIBAL-H reduction of the ester to give allylic alcohol **2i3**. A Sharpless asymmetric epoxidation[6] was done next followed by conversion of the hydroxyl to the chloride **2i4** with Ph_3P, $NaHCO_3$ and CCl_4. Sodium metal mediated reductive cleavage of the carbon chlorine bond with concomitant epoxide opening gave allylic alcohol **2i5**. Protection as MOM ether **2i6** followed by removal of the TBS ether, Swern oxidation and reaction with the trimethylsulfonium ylide afforded epoxide **2i7**. A Jacobsen hydrolytic kinetic resolution[10] was used to obtain the diastereomerically enriched epoxide **2i8** followed by reductive opening of the epoxide with LAH then esterification with acryloyl chloride produced acrylate ester **2i9**. Acidic cleavage of the MOM ether followed by ring closing metathesis with Grubbs 2nd generation catalyst[17] produced (+)-patulolide C (**2a**).

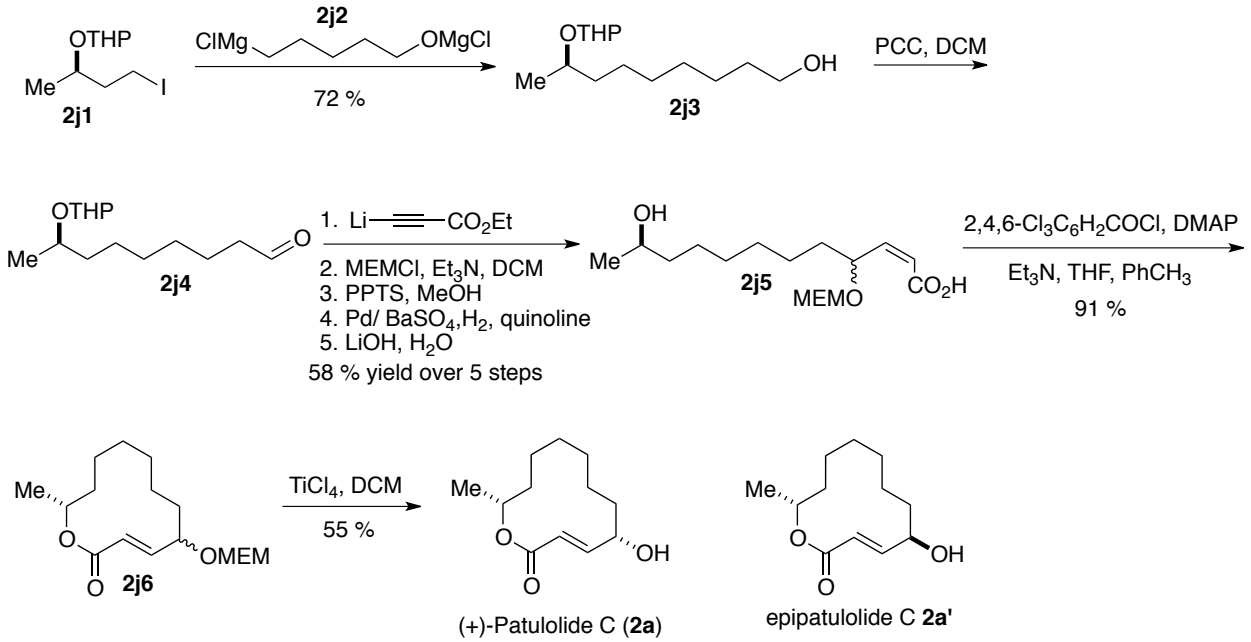
Scheme 2i: Sharma's Synthesis of (+)-Patulolide C



Chapter 2j: Mori's Synthesis of (+)-Patulolide C

In 1998 Mori[2] *et. al.* published a synthesis of (+)-patulolide C (**2a**) and epipatulolide C (**2a'** Scheme 2j). Beginning with known iodide **2j1** they append a carbon chain with Grignard reagent **2j2** affording alcohol **2j3**. Oxidation with PCC gave aldehyde **2j4**, followed by alkynylation of the aldehyde to the propargylic alcohol, which was protected as the MEM ether. Acidic cleavage of the THP ether and a partial reduction of the alkyne followed by hydrolysis of the ester gave *Z*-α,β-unsaturated acid **2j5**. Macrocyclization under Yamaguchi conditions with DMAP promoted olefin isomerization gave *E*-α,β-unsaturated lactone **2j6**. Finally cleavage of the MEM ether with $TiCl_4$ afforded a mixture of (+)-patulolide C (**2a**) and epipatulolide C (**2a'**).

Scheme 2j: Mori's Synthesis of (+)-Patulolide C



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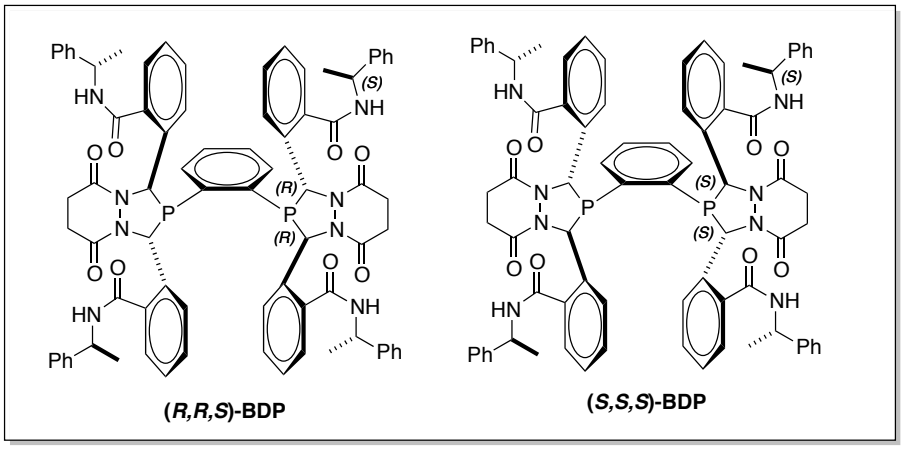
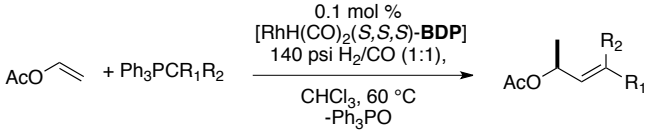
Chapter 3: The Total Synthesis of (+)-Patulolide C via Asymmetric Hydroformylation/ Wittig Olefination

Figure 3a:



Our research program is engaged in exploring the potential uses of AHF/ Olefination tandem reactions in natural product total synthesis. With the high value chiral aldehydes easily accessed via AHF with the BDP ligands (Figure 3a), we set out to develop and apply AHF/ Wittig olefination tandem reactions in the context of natural product total synthesis. Since the Landis ligands worked so well with vinyl acetate (Chapter 1, Scheme 1b) and it was shown that the Wittig olefination with stabilized phosphorus ylides does not erode enantiopurity (Table 3a),[1] we sought to extend this line of research. Landis and Wong have shown that AHF / Wittig olefination produces γ-chiral-α, β-unsaturated carbonyl compounds with high enantiopurity (Table 3a).[1]

Table 3a



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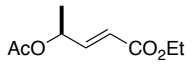
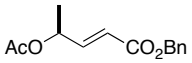
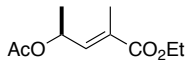
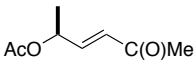
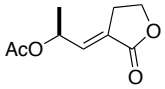
1		18	>95:5	79	99
2		15	>95:5	46	99
3		18	>95:5	68	90
4		21	>95:5	71	97
5		18	>95:5	67	98

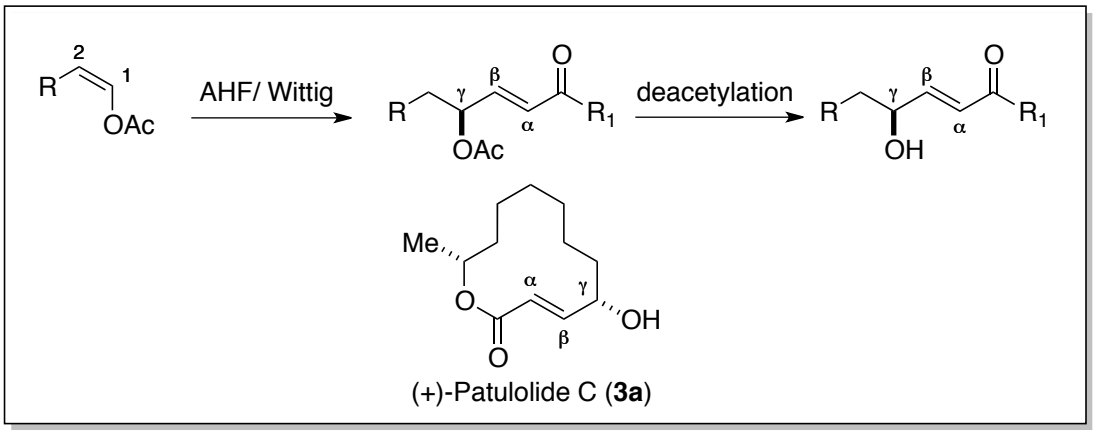
Reaction conditions: Pre-activation of $[Rh(acac)(CO)_2]$ and (*S,S,S*)-**BDP** with 140 psi (1:1) H_2/CO for 0.5 h at 40 °C with subsequent injection of the vinyl acetate/ Wittig ylide solution in $CHCl_3$.

Natural product total synthesis is a mature, yet still growing field of research in the chemical sciences. One can peruse the literature and surmise that with enough material and skill just about any molecule imaginable can be synthesized. One of the greater challenges facing synthetic chemists today is the daunting task of improving the efficiency of complex molecule synthesis. The ever-increasing cost of health care and the diminishing supply of natural resources demand that we innovate the way in which we synthesize complex molecules. Atom-economy describes the overall efficiency of a reaction in terms of the atoms involved.[2] If most of the atoms in the reagents are incorporated into the product then the reaction is highly atom-economical. The hydroformylation reaction is a reaction of perfect atom economy. All the atoms in the reagents, H_2, CO and the alkene, are incorporated into the product. In this respect the AHF is an extremely powerful reaction because of its catalytic nature, perfect atom-economy, and

inexpensive reagents. Because of its versatility in synthesis,[3] the newly formed chiral aldehyde is of extreme value to the synthetic chemist.

The γ-hydroxy-α, β-unsaturated carbonyl motif is common in many natural products. In light of this (+)-patulolide C (Scheme 3a) seemed like a worthy target, wherein the AHF/ Wittig olefination tandem could result in a dramatic improvement in efficiency. Our goal was to efficiently build molecular complexity while keeping the synthetic sequence short. With the success of the AHF/ Wittig olefination of vinyl acetate (Table 3a), we sought to extend this tandem reaction to 1,2-disubstituted *Z*-enol esters for application in the synthesis of natural products, such as (+)-patulolide C. Our rational was that the carbon substituent on the olefin would be in backbone of the target and the acetoxy group would be a masked hydroxyl (Scheme 3a).

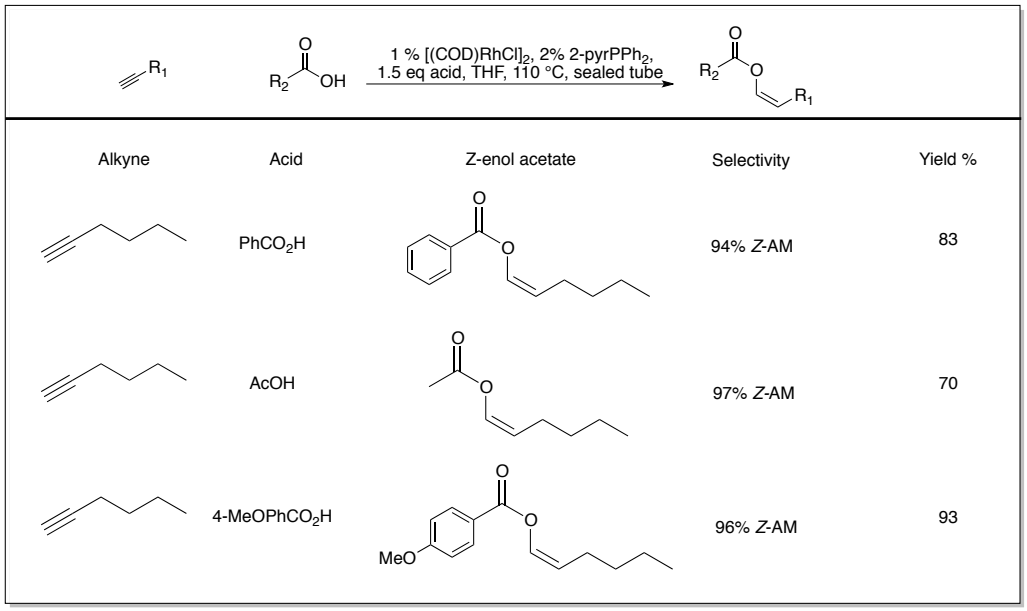
Scheme 3a:



Access to 1,2-disubstituted Z-enol acetates would be done via the Rh(I) catalyzed hydroacetoxylation reaction developed by Breit and coworkers.[4] They have shown that this catalyst system affects an *anti*-Markovnikov hydrocarboxylation of terminal alkynes under Rh(I) catalysis with excellent *Z*-selectivity and substrate scope (Table 3b). With just 1 mol % $[(COD)RhCl]_2$ and 2 mol % 2-pyridyl-diphenylphosphine in THF, the hydrocarboxylation of 1-

hexyne was affected in a sealed tube at 110 °C. Both alkyl (such as acetic acid) and aryl (benzoic and 4-methoxybenzoic acids) carboxylic acids reacted well to give the *anti*-Markovnikov *Z*-enol carboxylates with excellent regio- and stereoselectivity and good yields. Since all the atoms of the acid and alkyne are incorporated into the product, hydroacetoxylation is a reaction with perfect atom economy also.[2]

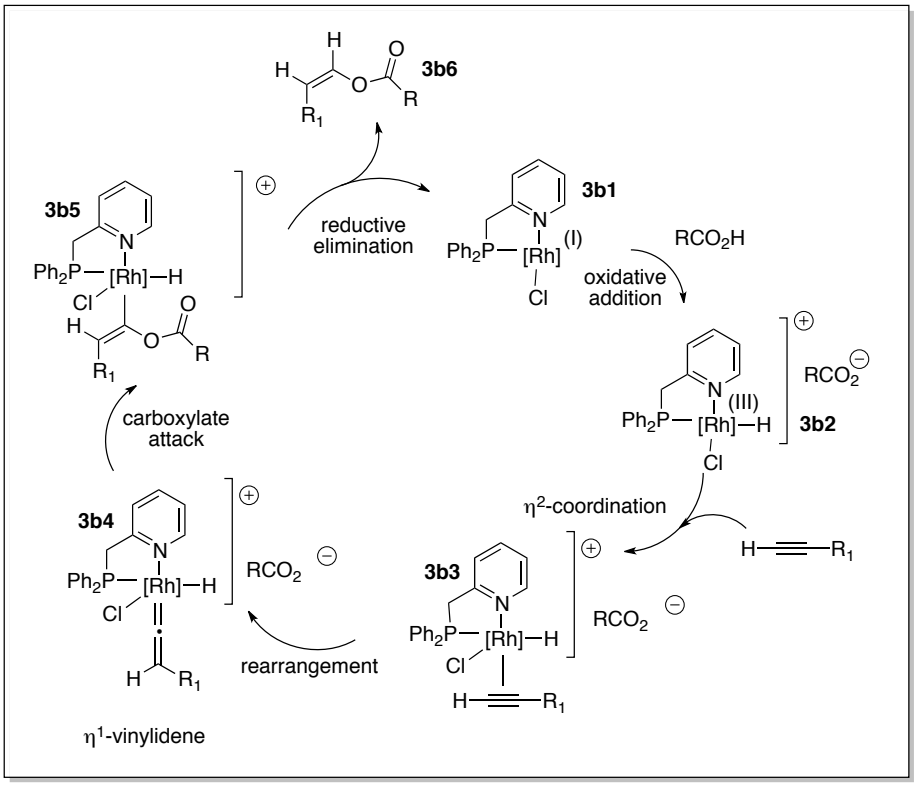
Table 3b:



Alkyne	Acid	Z-enol acetate	Selectivity	Yield %
	$PhCO_2H$		94% *Z*-AM	83
	AcOH		97% *Z*-AM	70
	$4\text{-}MeOPhCO_2H$		96% *Z*-AM	93

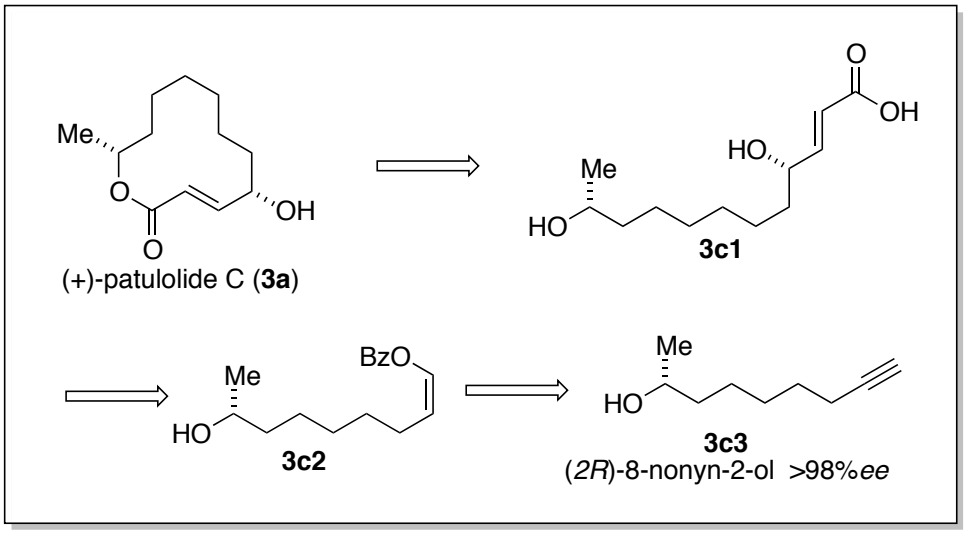
Their proposed mechanism,[4] which accounts for the double contrathermodynamic addition, is shown in Scheme 3b. The ligand bound catalyst **3b1** undergoes oxidative addition into the OH bond of the carboxylic acid to give Rh(III) hydride **3b2**. Next the alkyne coordinates in η^2 fashion to produce **3b3**. Then the alkyne undergoes an η^2 to η^1 rearrangement to give the Rh(III) vinylidene **3b4**. At this point the carboxylate anion attacks at the most electrophilic carbon, the terminal carbon bound to the rhodium to give Rh (III) vinyl ester **3b5**. Finally reductive elimination to produce the *Z*-enol carboxylate and regenerate the active Rh(I) catalyst **3b1**. It is proposed that the facial selectivity of carboxylate attack on the vinylidene is dictated by the bulky diphenylphosphino moiety on the rhodium.

Scheme 3b:



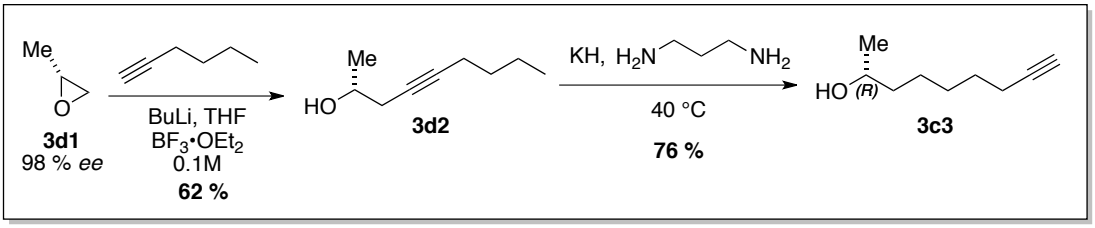
The synthetic strategy of our first approach to (+)-patulolide C is shown in Scheme 3c. We envisioned (+)-patulolide C (**3a**) coming from a macrolactonization of seco-acid **3c1**. The C4-OH stereochemistry would be set via an AHF of *Z*-enol benzoate **3c2** followed by Wittig olefination to bring in the α,β-unsaturated carbonyl moiety and a double hydrolysis would unmask both the C4-hydroxyl and C1 carboxylic acid in **3c1**. We planned to access *Z*-enol benzoate **3c2** from a Rh(I)-catalyzed hydrocarboxylation of known alkyne **3c3** with benzoic acid.

Scheme 3c



Our first approach began with the known synthesis[5] of (2*R*)-8-nonyn-2-ol (**3c3**) as shown in Scheme 3d. Ring opening of (*R*)-propylene oxide (**3d1**) with the lithium anion of 1-hexyne in THF afforded the internal alkyne **3d2** in 62 % yield. Next the internal alkyne was isomerized via a 'zipper' reaction to the terminal alkyne **3d3**. Using KH in 1,3-diaminopropane, the isomerization produced (2*R*)-8-nonyne-2-ol (**3c3**) in 76 % yield, on par with the literature results.[5] With access to this material we began exploring a route to (+)-patulolide C.

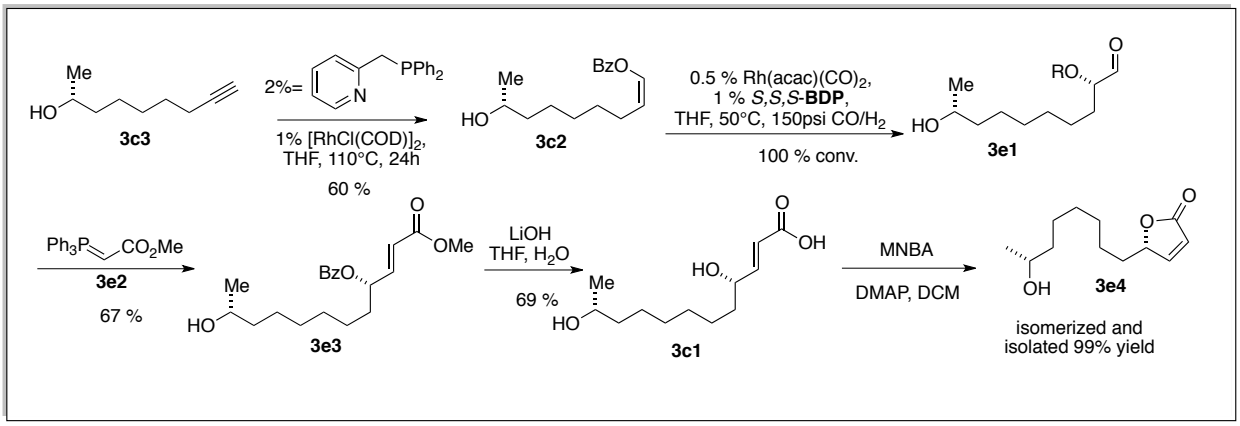
Scheme 3d



In a forward sense, alkyne **3c3** was subjected to the standard hydrocarboxylation conditions developed by Breit (Scheme 3e).[4] After 24 h, all of the alkyne had been consumed and *Z*-enol benzoate **3c2** was isolated in 60 % yield after chromatography. Without protecting the hydroxyl, *Z*-enol benzoate **3c2** underwent AHF with 0.5 mol % [Rh (*S,S,S*)-**BDP**] at 50 °C to

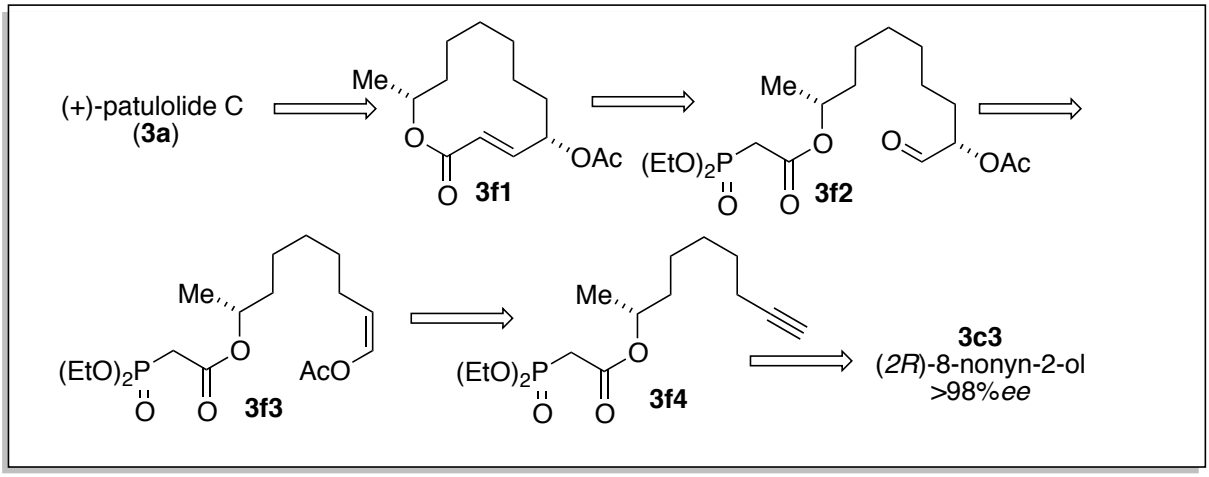
produce α-benzoyloxy aldehyde **3e1** as the sole product by ^{1}H NMR. Methyl (triphenylphosphoranylidene) acetate (**3e2**) was then added to affect the Wittig olefination to yield γ-benzoyloxy-α,β-unsaturated methyl ester **3e3** in 67 % isolated yield with excellent *E*-selectivity (96 % *E*). A global hydrolysis was affected with LiOH to give seco-acid **3c1** in 69 % yield. Dihydroxy acid **3c1** was then slowly added to a stirring DCM solution of MNBA and DMAP via syringe pump to affect the macrolactonization. We were surprised to find that the olefin had isomerized and the 5-membered ring γ-lactone **3e4** was the only product isolated. As evident by this thwarted experiment, the C4-hydroxyl must be protected and enone *E/Z* isomerization had to be avoided in order to affect macrocyclization cleanly.

Scheme 3e



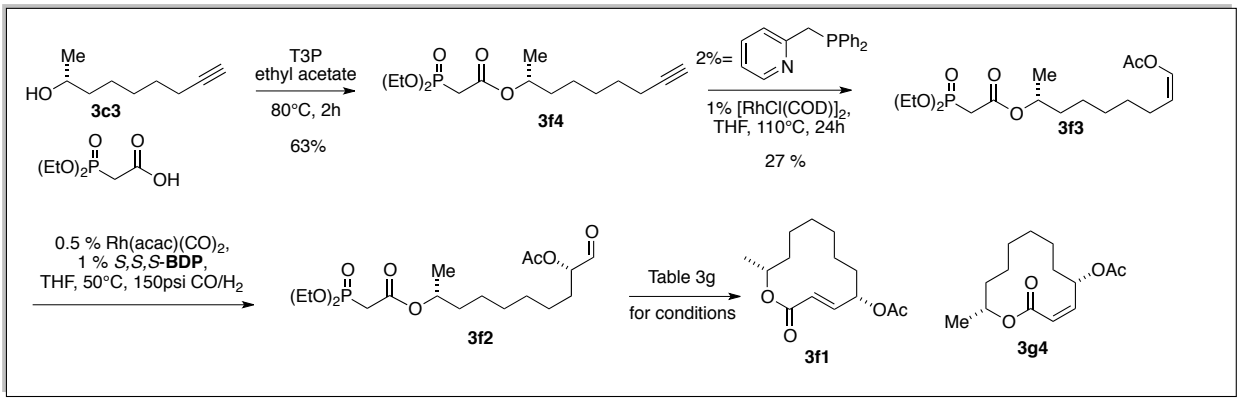
To circumvent these challenges we decided to use the olefination reaction to close the macrocycle and deprotect the OH after cyclization. A new strategy is shown in Scheme 3f. We planned to access (+)-patulolide C from a deacetylation of acetate **3f1**, which would arise from an intramolecular HWE of α-acetoxy aldehyde **3f2**. This aldehyde would be the AHF product from *Z*-enol acetate **3f3** that would be derived from alkyne **3f4** with the β-phosphonate ester already in place.

Scheme 3f



We began by esterifying alkyne **3c3** with diethylphosphonoacetic acid to afford phosphonoate ester **3f4** (Scheme 3g). Since we could only access *Z*-enol esters via the hydrocarboxylation chemistry the γ-oxygen in the AHF/ Wittig olefination product would always be protected as an ester. This approach required an ester protecting group on the C4-OH that could be removed in the presence of the lactone. The acetate was an obvious choice. Therefore the Rh(I)-catalyzed hydroacetoxylation of alkyne **3f4** gave *Z*-enol acetate **3f3** with great selectivity albeit low yield. With the β-phosphonate ester in place the *Z*-enol acetate **3f3** was subjected to AHF conditions to give α-acetoxy aldehyde **3f2** as the only aldehyde observed by ^{1}H-NMR. The crude solution of aldehyde was then diluted and added slowly to a flask with reagents to affect the intramolecular HWE. Several conditions were attempted and the results are summarized in Table 3g. Using KO*t*-Bu in THF afforded the macrolactone in quantitative yield,

Scheme 3g



but the reaction was completely *Z*-selective (Entry 1, Table 3g). The HWE was attempted with 18-crown-6, K_2CO_3 in toluene but the selectivity was only 1.8:1 *E:Z* (Entry 2). Even switching to the bulky isopropyl phosphonate ester only gave a modest increase in *E*-selectivity, 3:1 *E:Z* (Entry 3).

Table 3g

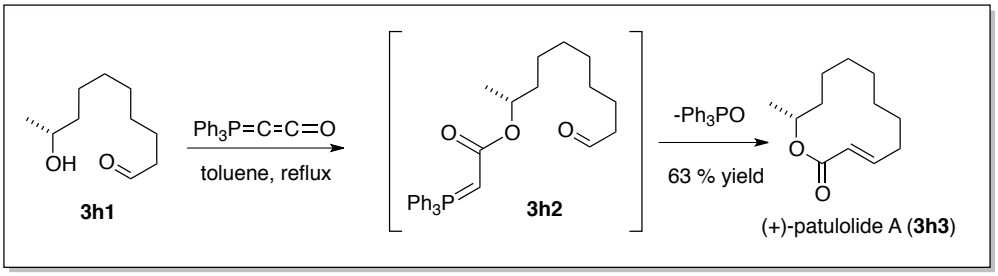
Entry	Reagents	Solvent	Temp.	% yield	*E:Z*
1	KO*t*-Bu	THF	25 °C	99	0:1
2	18-C-6, K_2CO_3	Toluene	65 °C	75	1.8:1
3*	18-C-6, K_2CO_3	Toluene	95 °C	60	3:1

*note: *i*-Pr vs Et on the phosphonate ester

Not satisfied with these results we reexamined our strategy once again. Knowing that the Wittig olefination gave better *E*-selectivity (96:4 *E:Z*), we decided to examine an intramolecular Wittig olefination to close the macrocycle. It turns out Bestmann and coworkers affected a similar Wittig olefination in their synthesis of patulolide A (Scheme 3h).[6] Using ketenylidene triphenylphosphorane to react with the hydroxyl of ω-hydroxyaldehdye **3h1** to generate the

stabilized ylide **3h2** in situ; which in turn reacted with the tethered aldehyde to produce the α,β-unsaturated lactone **3h3** with great *E*-selectivity (96:4 *E:Z*) and good yield (63 %).[6]

Scheme 3h

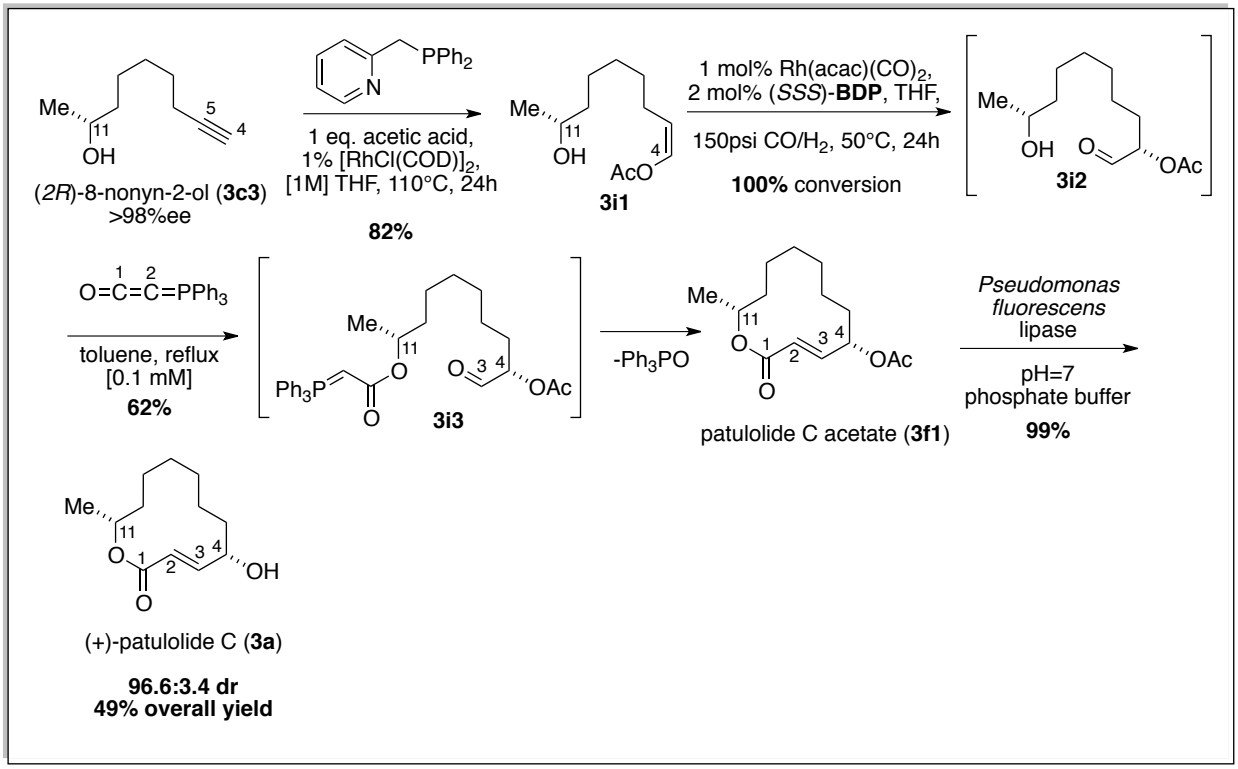


Inspired by Bestmann we decided to use the ketenylidene triphenylphosphorane, also known as the Bestmann ylide in our synthesis of (+)-patulolide C (**3a**). Beginning with alkyne **3c3** (Scheme 3i), hydroacetoxylation afforded hydroxy *Z*-enol acetate **3i1** in 82 % yield. The AHF proceeded with supreme regioselectivity to give α-acetoxyaldehyde **3i2** as the sole product by ^{1}H-NMR along with its hemiacetal. The crude AHF reaction was diluted and added slowly via syringe pump to a refluxing solution of the Bestmann ylide. The ketene carbon was attacked by the hydroxyl to generate stabilized ylide **3i3** *in situ* followed by an intramolecular Wittig olefination to close the macrocycle and give patulolide C acetate **3i4** in 62 % yield from *Z*-enol acetate **3i1**. Typical macrolactonization methods require carboxylic acid activation and a net dehydration; these features are built into the Bestmann ylide and allow the incorporation of the C1-carbonyl and C2-carbon with greater efficiency while setting the *E*-olefin with great selectivity (only *E*-olefin observed).[7]

Several chemical methods (K_2CO_3/MeOH, Et_3N/MeOH, LiOH/H_2O/THF, guanidine/guanidinium acetate/EtOH) were attempted to remove the acetate while leaving the lactone intact, however all of these methods showed poor selectivity between the two esters. On the final step of the synthesis we decide to attempt an enzymatic hydrolysis of the acetate in

hopes of attaining the requisite selectivity. Gratifyingly, lipase from *Pseudomonas fluorescens* catalyzed the hydrolysis of the acetate while leaving the lactone untouched, producing (+)-patulolide C (**3a**) in quantitative yield (Summary Scheme 3i). The diastereomeric ratio of the final product was measured via HPLC and determined to be 96.6:3.4 dr, indicating a highly diastereoselective AHF and no substantial deterioration of dr in subsequent transformations.[7]

Summary Scheme 3i



In summary, a short, highly efficient synthesis of (+)-patulolide C (**3a**, Summary Scheme 3j) has been accomplished in 3 steps from the known alkyne **3c3** with a 49 % overall yield. Two Rh(I)–catalyzed reactions were employed in this synthesis. The first reaction is a Rh(I)–catalyzed hydroacetoxylation of alkyne **3c3** to afford Z-enol acetate **3i1**. Second, a Rh(I)-catalyzed AHF with (*S,S,S*)-**BDP** afforded α-acetoxy aldehyde **3i2**, which was subsequently reacted with the Bestmann ylide[6] to generate a stabilized ylide **3i3** *in situ* followed by intramolecular Wittig olefination to give patulolide C acetate (**3f1**) in 62 % yield. Finally an

enzymatic hydrolysis with lipase from *Pseudomonas fluorescens* of the acetate gave (+)-patulolide C (**3a**) in quantitative yield.[7] This represents the shortest and highest yielding enantioselective synthesis of (+)-patulolide C (**3a**) reported to date when compared to previous enantioselective syntheses (9-19 steps LLS, 2-38 % overall yield). These results validate the hydroacetoxylation/AHF/Wittig olefination sequence as a viable strategy to dramatically increase the efficiency of the synthesis of γ-hydroxy-α,β-unsaturated carbonyl containing natural products.

References:

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2. Marson, C. M. Multicomponent and sequential organocatalytic reactions: diversity with atom-economy and enantiocontrol. *Chem. Soc. Rev.* **2012**, *41*, 7712.
3. (a) Britton, R.; Kang, B. α-Haloaldehydes: versatile building blocks for natural product synthesis. *Nat. Prod. Rep.* **2013**, *30*, 227–236; (b) Reddy, L. V. R.; Kumar, V.; Sagar, R.; Shaw, A. K. Glycal-Derived δ-Hydroxy α,β-Unsaturated Aldehydes (Perlin Aldehydes): Versatile Building Blocks in Organic Synthesis. *Chem. Rev.* **2013**, DOI: 10.1021/cr200016m.
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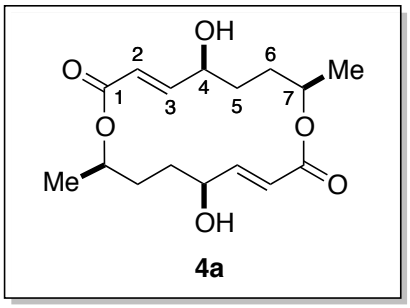
7. Risi, R. M.; Burke, S. D. Synthesis of (+)-Patulolide C via an Asymmetric Hydroformylation/ Macrocyclization Cascade. *Org. Lett.* **2012**, *14*, 1180–1182.

Chapter 4: Background and Previous Syntheses of (-)-Pyrenophorol

Chapter 4a: Isolation and Biological Activity

(-)-Pyrenophorol (**4a**) was first isolated from a plant fungus *Byssachlamys nivea* in 1969[1a] and from culture filtrates of *Stemphylium radicinum* two years later.[1b] This natural product is a 16-membered *C2*-symmetric macrodiolide containing four stereocenters and two α,β-unsaturated esters. It has been shown to have anti-fungal and anthelmintic properties,[1c] and is the subject of a recent Canadian patent application for potential herbicidal use.[1d] Due to its biological activity and interesting functionality, (-)-pyrenophorol (**4a**) has been the target of several total syntheses summarized below.

Figure 4: (-)-Pyrenophorol



4a

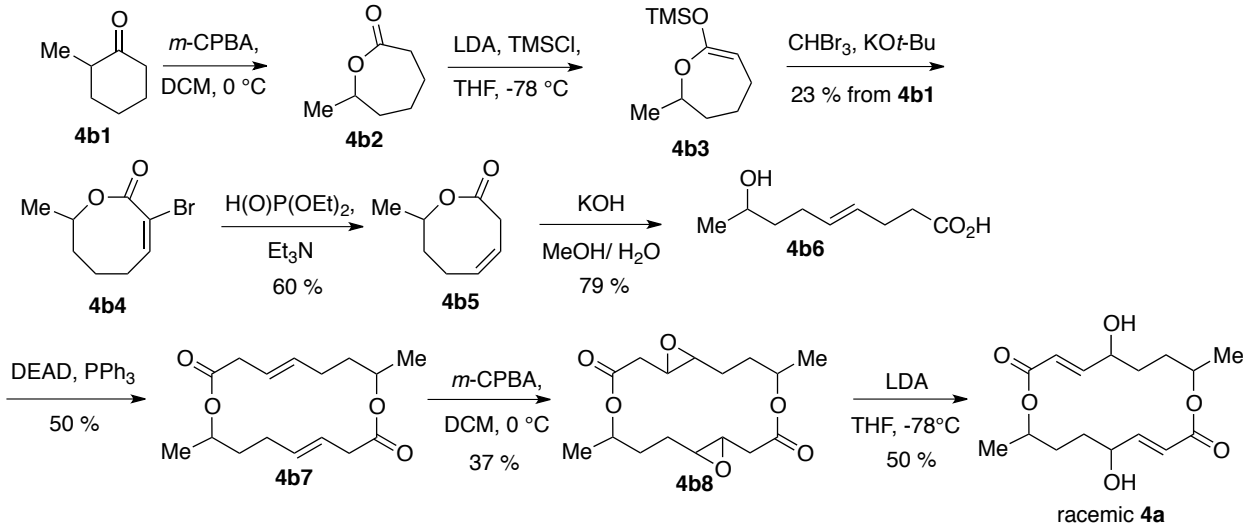
Name, year	Steps (Longest Linear Sequence)	Overall Yield %	Key Reactions
Ohshiro, 1986*	8 steps	3.4 %	Mitsunobu esterification
Zwanenburg, 1991	11 steps	9.8 %	Asymmetric epoxidation
Kibayashi, 1993	14 steps	10.7 %	Sulfoxide pyrolysis
Le Floc'h, 1997**	14 steps	4.5 %	CBS reduction, Wittig olefination
Yadav, 2009	15 steps	3.8 %	Jacobsen kinetic resolution
Kang, 2011	11 steps	1.6 %	Yamaguchi esterification
Yadav, 2012	16 steps	8.2 %	Asym. epoxidation, olefin metathesis

* racemic synthesis, ** enantiomer (+)-pyrenophorol

Chapter 4b: Ohshiro's Synthesis of Racemic Pyrenophorol (4a)

Ohshiro[2a] and coworkers published the first racemic synthesis of pyrenophorol in 1986. The synthesis began with the Baeyer-Villager oxidation of 2-methylcyclohexanone **4b1** (Scheme 4b) to yield heptanolide **4b2**. Next enolization with LDA and trapping with TMSCl gave trimethylsilyl ketene acetal **4b3** which was then reacted with the dibromocarbene generated in situ from bromoform and KO*t*-Bu to effect another ring expansion to give the 8-membered ring lactone **4b4**. The reductive deconjugation of α-bromo-α,β-unsaturated lactone **4b4** was done with diethyl phosphonate and Et_3N to give the β,γ-unsaturated lactone **4b5** followed by saponification to give hydroxy acid **4b6**. Mitsunobu dimerization according to the Gerlach[2b] procedure gave dilactone **4b7** followed by a double epoxidation with *m*-CPBA to give bis-epoxide **4b8**. Finally, LDA mediated epoxide opening installed the α,β-unsaturation and the required C4-hydroxyl in racemic pyrenophorol (**4a**).

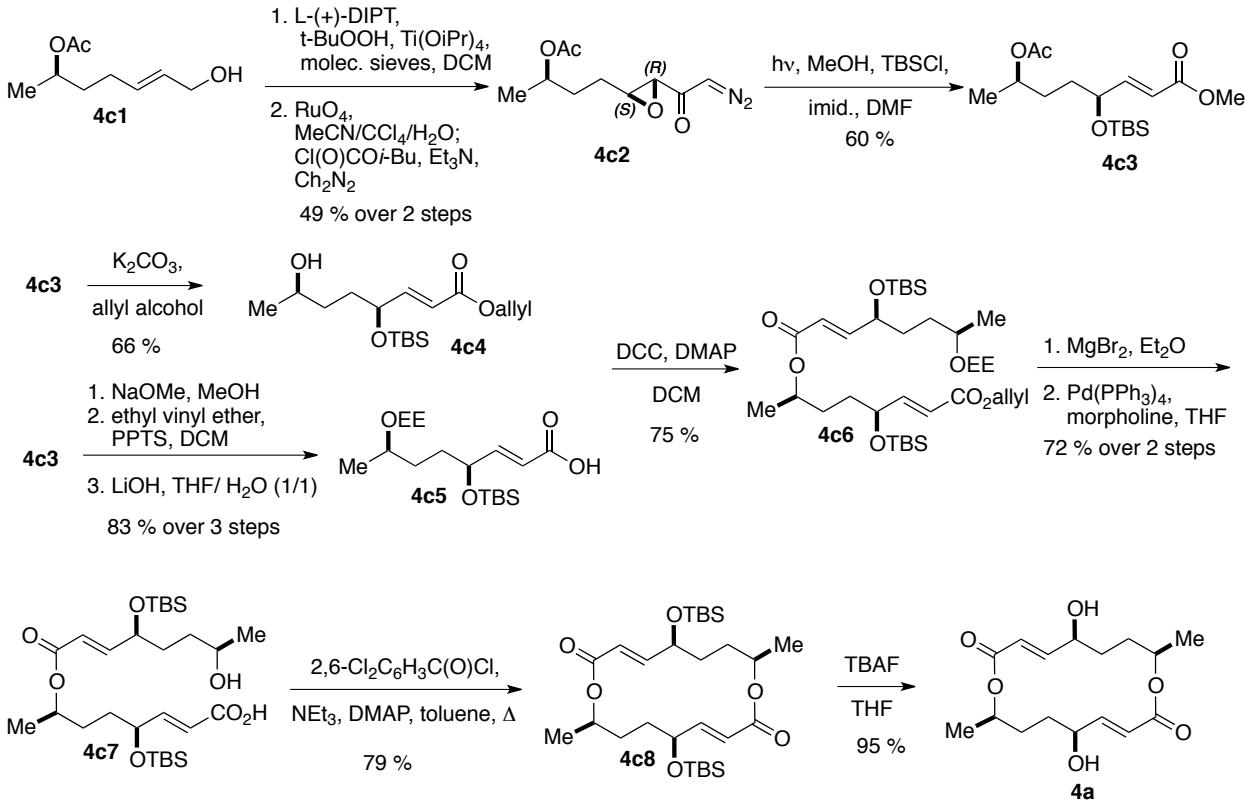
Scheme 4b: Ohshiro's Synthesis of Racemic Pyrenophorol (4a)



Chapter 4c: Zwanenburg's Synthesis of (-)-Pyrenophorol (4a)

The first asymmetric synthesis of (-)-pyrenophorol (**4a**) was published by Zwanenburg[3a] *et. al.* in 1991. Beginning with known allylic alcohol[3b] **4c1** (Scheme 4c), a Sharpless asymmetric epoxidation with L-(+)-DIPT installed the epoxide followed by RuO_4 oxidation of the alcohol to the acid and trapping as a mixed anhydride with isobutyl chloroformate and nucleophilic acyl substitution with CH_2N_2 to afford α-diazomethyl ketone **4c2.** This key substrate was subjected to a photoinduced rearrangement in MeOH to afford *tert*-butylsiloxy α,β-unsaturated ester **4c3** at which point the synthetic route diverged from this common intermediate. Methyl ester **4c3** underwent alcoholysis with allyl alcohol and K_2CO_3 along with simultaneous acetate cleavage to give allyl ester **4c4**. Methanolysis of **4c3** with NaOMe in MeOH removed the acetate while maintaining the methyl ester functionality, then protection of the C7-hydroxyl as the ethoxy ethyl ether followed by saponification gave the coupling partner **4c5**. Carboxylic acid **4c5** and alcohol **4c4** underwent DCC mediated condensation to give the fully protected ester **4c6**, followed by unmasking of the terminal hydroxyl with $MgBr_2$ and then the carboxylic acid with $Pd(PPh_3)_4$ and morpholine to give hydroxy acid **4c7**. A Yamaguchi macrolactonization was then performed to give bis-TBS ether **4c8**, along with TBAF mediated desilylation to give (-)-pyrenophorol (**4a**) in excellent yield.

Scheme 4c: Zwanenburg's Synthesis of (-)-Pyrenophorol (4a)

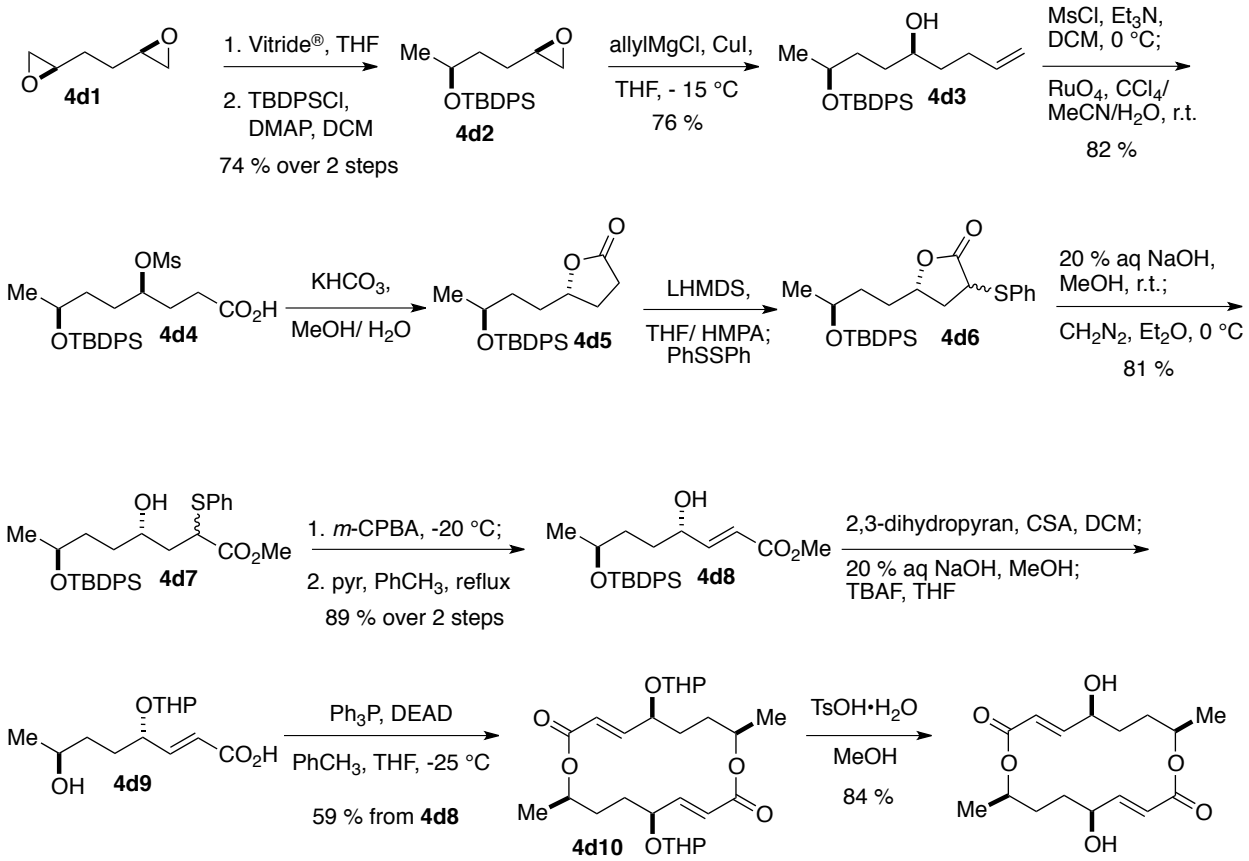


Chapter 4d:Kibayahsi's Synthesis of (-)-Pyrenophorol (4a)

Kibayashi's[4a] synthesis of (-)-pyrenophorol (**4a**) began with the reductive desymmetrization of C2-symmetric bis-epoxide[4b] **4d1** (Scheme 4d) by careful addition of one equivalent of Vitride® to open one epoxide, followed by TBDPS protection to give mono-epoxide **4d2**. Opening of the remaining epoixide with allyl MgCl in the presence of CuI gave homoallylic alcohol **4d3**, followed by protection as the mesylate then RuO_4 oxidation of the alkene to give carboxylic acid **4c4**. An intramolecular Mitsunobu reaction was done to form lactone **4d5** with complete inversion at C4. Lactone **4d5** underwent enolization with trapping by diphenyl disulfide to give **4d6**, followed by hydrolysis of the lactone to the acid then CH_2N_2 mediated esterification to give methyl ester **4d7**. Oxidation of the sulfide followed by pyrolysis installed the α,β-unsaturation in ester **4d8**, along with protection of the hydroxyl as the THP

ether followed by saponification and TBAF desilylation to give hydroxy acid **4d9.** The dimerization was done with a Mitsunobu reaction to give bis-THP pyrenophorol **4d10**, which upon deprotection with TsOH•H_2O in MeOH gave (-)-pyrenophorol (**4a**).

Scheme 4d: Kibayahsi's Synthesis of (-)-Pyrenophorol (4a)

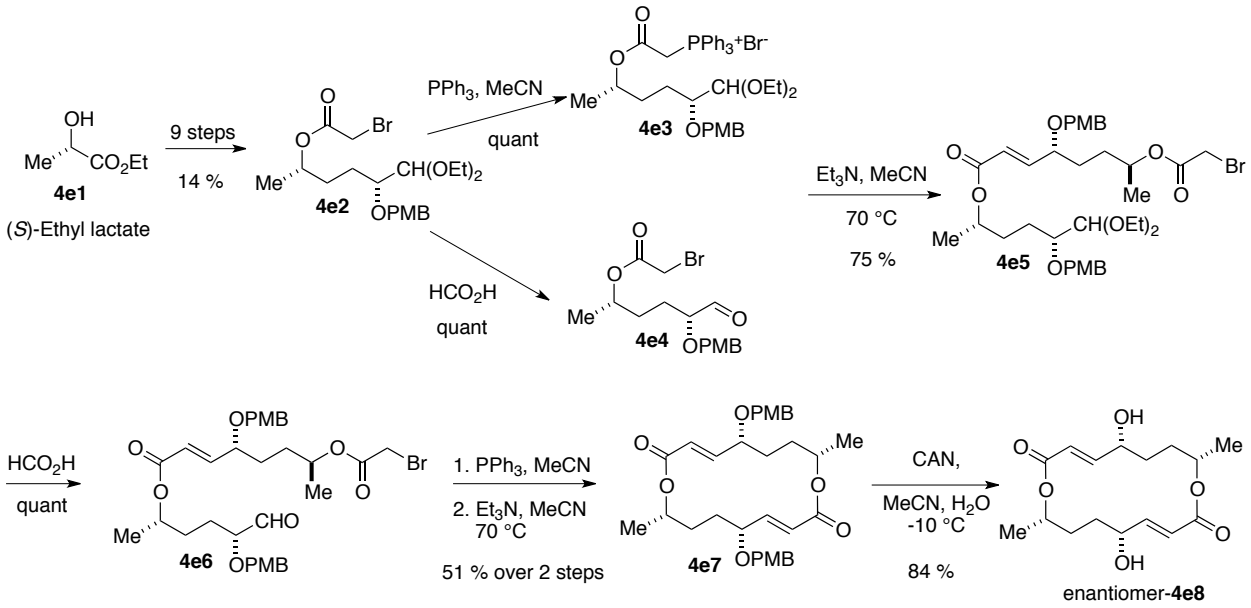


Chapter 4e: Le Floc'h's Synthesis of Enantiomeric (+)-Pyrenophorol (4e8)

The first synthesis of the enantiomer of (-)-pyrenophorol (**4a**) was published by Le Floc'h[5a] *et. al.* using a sequential intermolecular / intramolecular Wittig olefination strategy for macrocycle formation. They had previously synthesized α-bromo ester[5b] **4e2** (Scheme 4e) from (*S*)-ethyl lactate **4e1** in 9 steps. This key material was used to make the 2 coupling pieces of the symmetrical molecule. With a divergent approach the bromine was displaced with Ph_3P to give phosphonium bromide **4e3**, while ester **4e2** was also subjected to acidic cleavage of the acetal to

unmask aldehyde **4e4**. The first of the sequential Wittig olefinations was done with Et_3N in MeCN at 70 °C to give the fully protected α,β-unsaturated ester **4e5**, followed by unveiling of the aldehyde with formic acid gave α-bromo ester **4e6**. The phosphonium salt was made in similar manner as before and intramolecular Wittig olefination afforded bis-PMB ether **4e7**, which was deprotected to give the enantiomer (+)-pyrenophorol (**4e8**).

Scheme 4e: Le Floc'h's Synthesis of Enantiomeric (+)-Pyrenophorol (4e8)

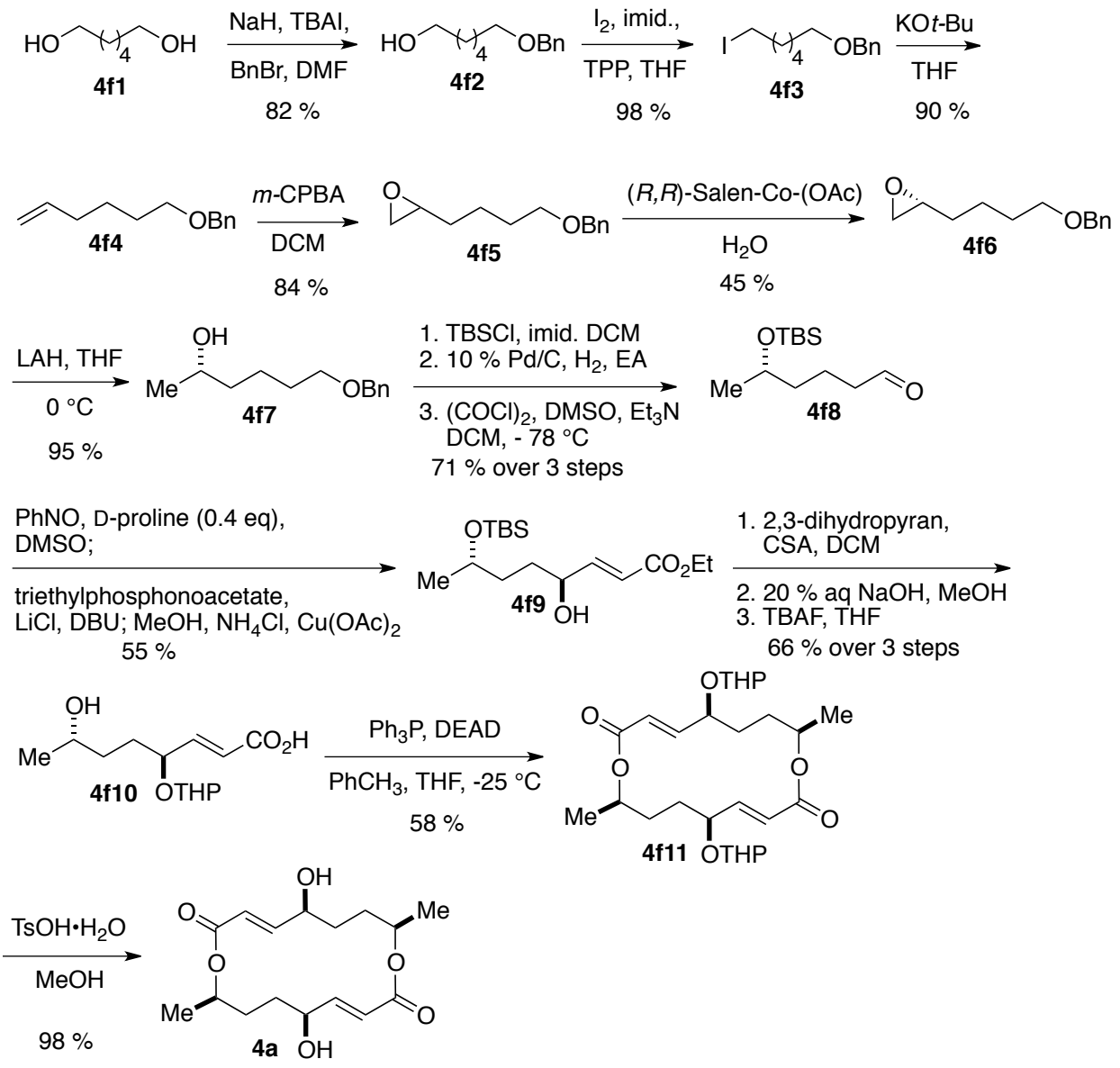


Chapter 4f: Yadav's First Synthesis of (-)-Pyrenophorol (4a)

In 2009 Yadav[6] and coworkers published their first synthesis of (-)-pyrenophorol (**4a**), beginning with the C2-symmetric 1,6-hexanediol **4f1** (Scheme 4f), mono-benzyl ether protection was done followed by iodination of the other alcohol to give iodide **4f3**. Elimination was effected with KO*t*-Bu to make the terminal olefin **4f4** followed by *m*-CPBA epoxidation to give **4f5**. A Jacobsen hydrolytic kinetic resolution was done to obtain enantiomerically enriched epoxide **4f6**. Reductive ring opening with LAH gave **4f7** followed by TBS protection of the alcohol, debenzylation and Swern oxidation to give aldehyde **4f8**. A proline catalyzed MacMillan α-hydroxylation followed by HWE olefination gave δ-hydroxy α,β–unsaturated ethyl ester **4f9**.

Protection of the C4-hydroxyl as the THP ether followed by saponification and desilylation gave hydroxy acid **4f10**. A Mitsunobu dimerization was used to give **4f11** followed by acidic cleavage of the THP ethers to give (-)-pyrenophorol (**4a**).

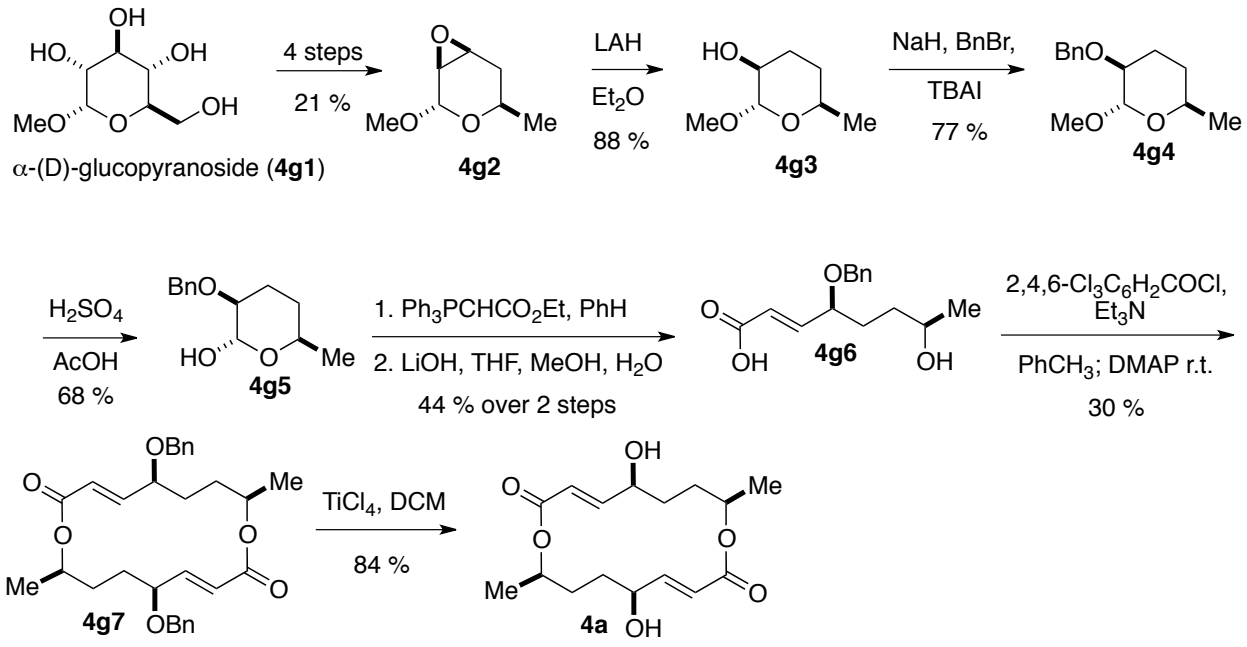
Scheme 4f: Yadav's First Synthesis of (-)-Pyrenophorol (4a)



Chapter 4g: Kang's Synthesis of (-)-Pyrenophorol (4a)

Kang's[7a] synthesis of (-)-pyrenophorol (**4a**) used the chiral pool for starting material, namely α-(D)-glucospyranoside (**4g1**) (Scheme 4g). With removal of some of the functionality via 4 known steps,[7b] glucose **4g1** was converted to epoxide **4g2**. Reductive ring opening with LAH gave alcohol **4g3**, followed by protection as the Bn ether then acidic hydrolysis of the methyl acetal to give the hemiacetal **4g5**. Opening of the hemiacetal was done with a Wittig olefination followed by hydrolysis of the generated ester to give hydroxy acid **4g6**. A Yamaguchi esterification was used to form the macrodiolide **4g7** then removal of the Bn ethers with $TiCl_4$ gave (-)-pyrenophorol (**4a**).

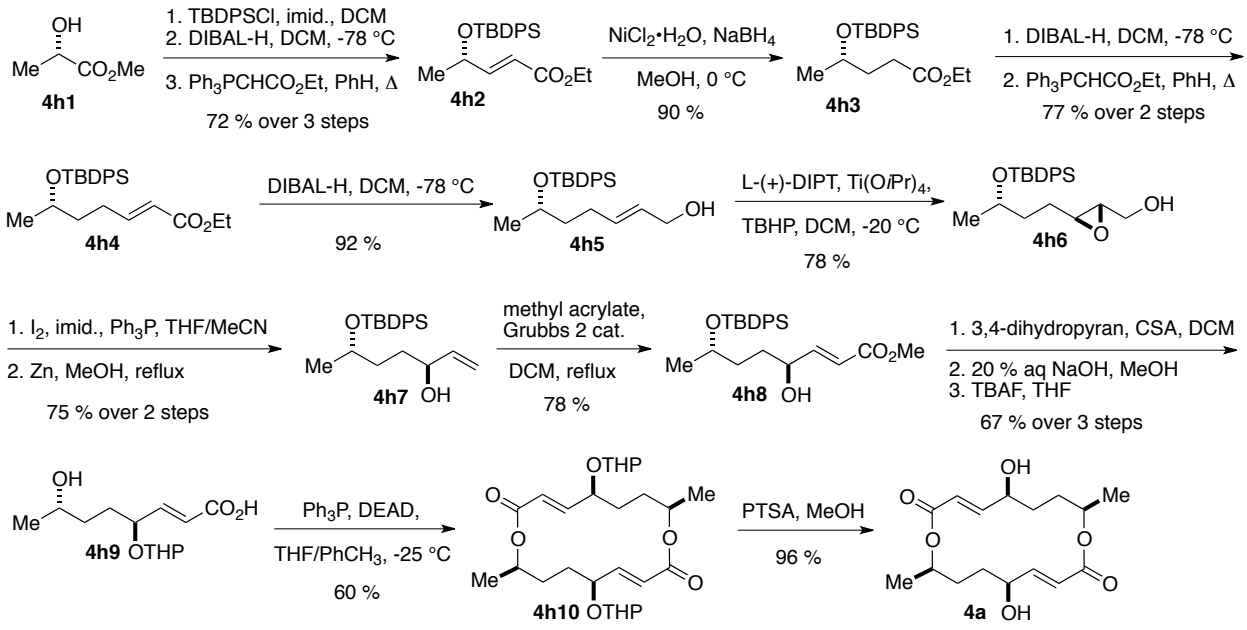
Scheme 4g: Kang's Synthesis of (-)-Pyrenophorol (4a)



Chapter 4h: Yadav's Second Synthesis of (-)-Pyrenophorol (4a)

Yadav's[8] second synthesis of (-)-pyrenophorol (**4a**) began with (*S*)-methyl lactate **4h1** (Scheme 4h). Protection of the hydroxyl as the TBDPS ether followed by DIBAL-H reduction to the aldehyde and Wittig olefination gave α,β-unsaturated ester **4h2**. Reduction of the alkene with $NiCl_2•H_2O$ and $NaBH_4$ gave **4h3**, followed by chain extension with a similar sequence, DIBAL-H reduction to the aldehyde and Wittig olefination gave α,β-unsaturated ester **4h4**. Reduction to alcohol **4h5** followed by Sharpless asymmetric epoxidation afforded epoxide **4h6**. Iodination of the primary alcohol followed by epoxide opening with Zn dust in refluxing MeOH gave allylic alcohol **4h7**. The olefin of (-)-pyrenophorol (**4a**) was uniquely made via a cross metathesis of **4h7** and methyl acrylate with Grubb's 2nd generation catalyst to give **4h8**. Their endgame strategy was similar to that of their first synthesis of (-)-pyrenophorol (**4a**).

Scheme 4h: Yadav's Second Synthesis of (-)-Pyrenophorol (4a)



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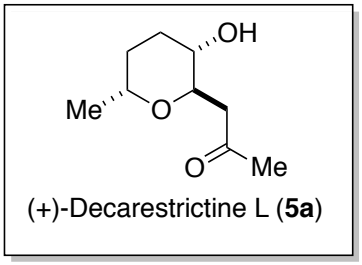
Chapter 5: Background and Previous Syntheses of (+)-Decarestrictine L

Chapter 5a: Isolation and Biological Activity of (+)-Decarestrictine L

(+)-Decarestrictine L (**5a**, Figure 5) is a member of the decarestrictine family of natural products. Originally isolated in 1992[1] from the culture broth of *Penicillium simplicissimum*, (+)-decarestrictine L (**5a**) has a trisubstituted tetrahydropyran (THP) core that sets it apart structurally from its congeners that have a 10-member ring lactone. It has been shown to inhibit cholesterol biosynthesis as an inhibitor of HMG-CoA reductase.[2] (+)-Decarestrictine L (**5a**) consist of a THP ring moderately decorated with a 2'-oxopropyl side chain at C2 in the (*R*) configuration, a C3 (*S*)-hydroxyl and a C6 (*R*)-Me stereocenter. The relative and absolute configuration was first confirmed by Kibayashi[3] *et. al.* in the first total synthesis of the natural product. Due to its biological activity and interesting structure there have been several total syntheses have been published to date and are summarized as follows.

Figure 5: (+)-Decarestrictine L (5a)



(+)-Decarestrictine L (**5a**)

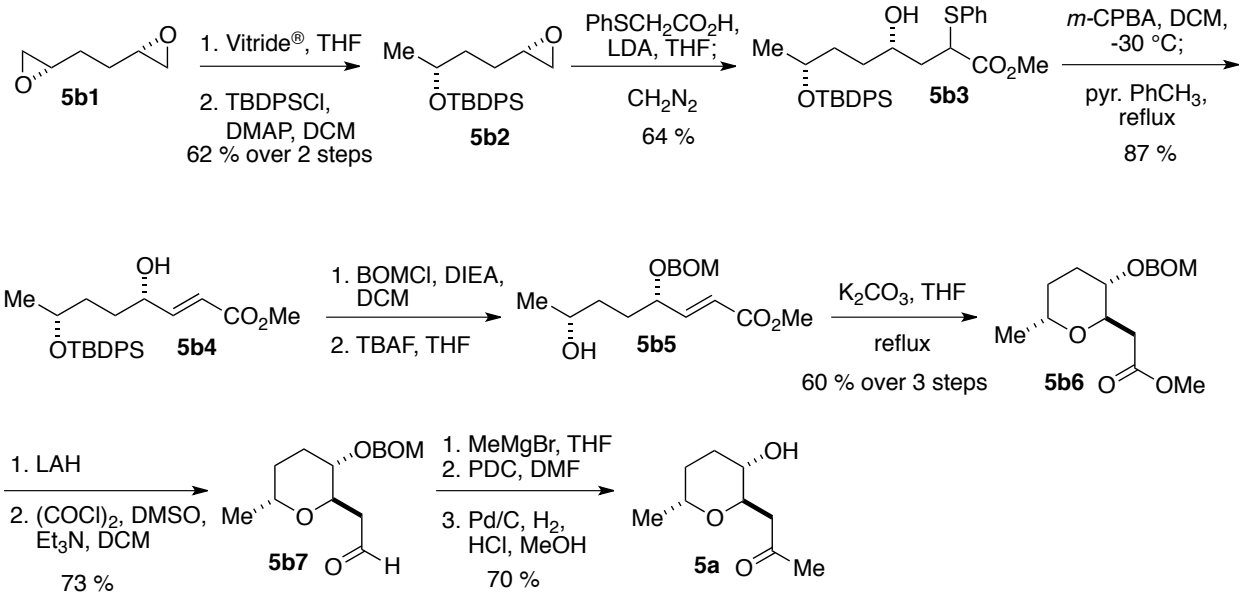
Name, year	Steps (Longest Linear Sequence)	Overall yield %	Key Reactions
Kibayashi, 1993	10 steps	2.3 %	TBAF oxa-Michael
Clark, 1994*	9 steps	5.5 %	Carbenoid insertion ylide rearrangement
Nokami, 1995	7 steps	11 %	Sulfinyl anion addition to aldehyde
Carreno, 1998	18 steps	16 %	Intramolecular S_N2 for THP ring
Hatakeyama, 2000	20 steps	10 %	Sharpless dihydroxylation
Donaldson, 2003	13 steps	6.3 %	Stereoselective axial methylation of tri-O-acetyl-D-glucal
Clark, 2006	10 steps	10 %	Oxonium ylide rearrangement for THP ring
Fall, 2006	12 steps	21 %	Singlet oxygen furan oxidation
Sudalai, 2009	7 steps	22 %	D-Proline catalyzed α-aminooxylation
Fall, 2010	10 steps	4.8 %	Stereoselective Michael addition to tri-O-acetyl-D-glucal

* = racemic synthesis

Chapter 5b: Kibayashi's Synthesis of (+)-Decarestrictine L

In 1993 Kibayashi[3] *et. al.* published the first total synthesis of (+)-decarestrictine L (**5a**, Scheme 5b). This synthesis began with the C2-symmetric bis-epoxide **5b1**, one equivalent of Vitride® affects desymmetrization followed by TBDPS protection to afford the mono-epoxide **5b2**. Ring opening of the epoxide was affected with the lithium dianion of phenylthioacetic acid to give methyl ester **5b3** upon methylation with CH_2N_2. The thioether was then oxidized with *m*-CPBA and pyrolyzed to install the α,β-unsaturation. Next the C3 hydroxyl was protected as the BOM ether followed by TBAF deprotection to give the C6 alcohol **5b5**. Intramolecular oxa-Michael was affected with K_2CO_3 in refluxing THF to give the ester substituted tetrahydropyran **5b6** followed by a reduction/ oxidation sequence to afford aldehyde **5b7**. Finally nucleophilic attack on the aldehyde with MeMgBr and PDC oxidation of the resultant secondary alcohol followed by hydrogenolysis of the BOM ether produced (+)-decarestrictine L (**5a**) in 12 steps.

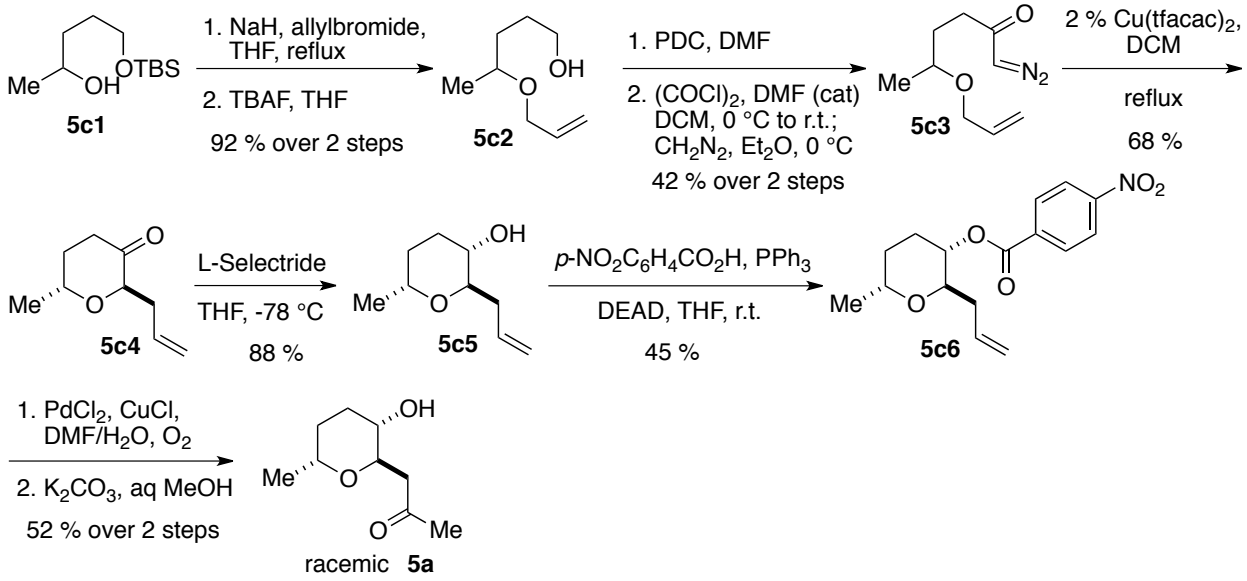
Scheme 5b: Kibayashi's Synthesis of (+)-Decarestrictine L



Chapter 5c: Clark's Synthesis of (+)-Decarestrictine L

Clark[4] and coworkers first published a racemic synthesis of decarestrictine L (**5a**) in 1994. Beginning with the racemic alcohol **5c1** (Scheme 5c), allylation was affected with NaH and allyl bromide followed by TBS removal with TBAF to give allyl ether **5c2**. A two step oxidation, first to the carboxylic acid and then to the acid chloride followed by attack with CH_2N_2 generated the α-diazomethyl ketone **5c3**. Using a catalytic amount of $Cu(tfacac)_2$, the copper carbenoid was first generated followed by insertion into the oxygen lone pair forming an intermediate oxonium species which undergoes rearrangement to the 2,6-dialkyl tetrahydropyran-3-one **5c4**. Ketone reduction with L-Selectride® produced alcohol **5c5** as a single diastereomer followed by Mitsunobu reaction with 4-nitrobenzoic acid with complete inversion of the C3 stereocenter to give **5c6**. The terminal olefin was then subjected to a Wacker oxidation to install the methyl ketone moiety in decarestrictine L (**5a**) along with hydrolysis of the 4-nitrobenzoate ester to give the natural product as a racemate.

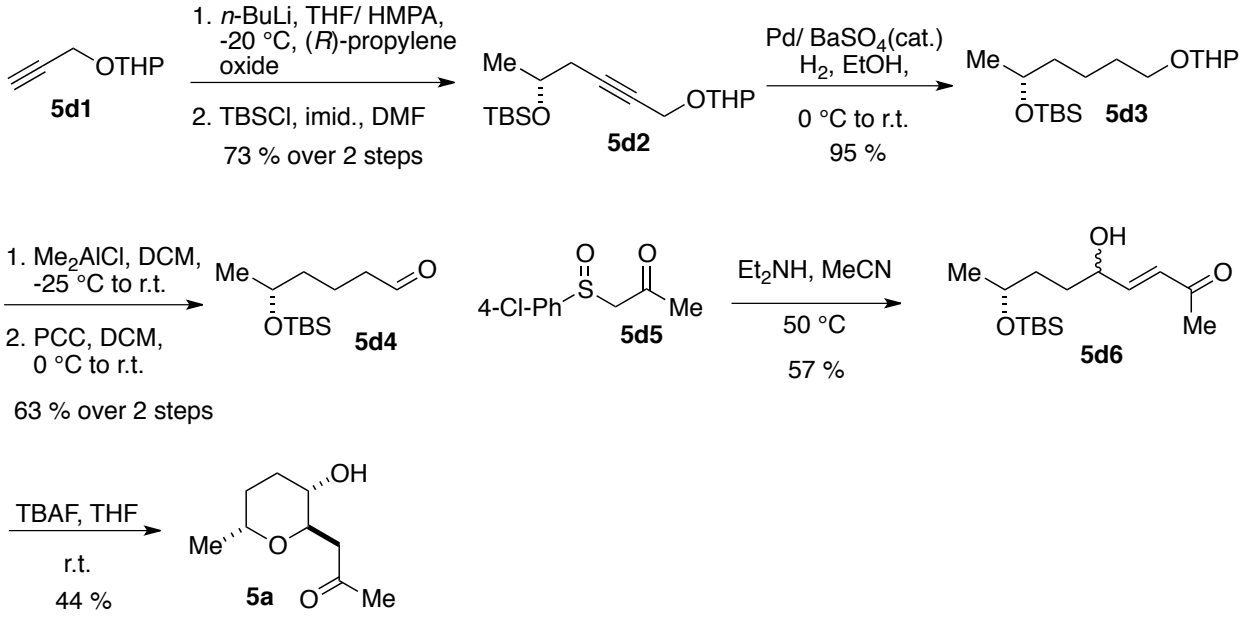
Scheme 5c: Clark's Synthesis of (+)-Decarestrictine L



Chapter 5d: Nokami's Synthesis of (+)-Decarestrictine L

In 1995 Nokami[5] published a seven-step synthesis of (+)-decarestrictine L (**5a**) from the THP protected propynyl ether **5d1** (Scheme 5d). Lithiation of the alkyne with *n*-BuLi followed by attack on (*R*)-propylene oxide produced silyl ether **5d2** after protection with TBSCl. Complete hydrogenation of the internal alkyne with Pd/$BaSO_4$ afforded the fully saturated TBS ether **5d3** followed by removal of the THP ether with Me_2AlCl then PCC oxidation to give aldehyde **5d4**. Now poised to perform their key 3 carbon elongation reaction, aldehyde **5d4** was reacted with sulfoxide **5d5** in the presence of Et_2NH in MeCN at 50 °C to generate aldol-type product with concomitant rearrangement to give the α,β-unsaturated ketone **5b6** as a 1:1 mixture of diasteromers. With all of the atoms in the natural product installed, they affected a TBAF-mediated desilylation oxa-Michael addition to form the THP core of (+)-decarestrictine L (**5a**), completing the synthesis. Interestingly they also reported isolation of the (3*R*)-diastereomer as the open chain diol, not as the cyclized THP.

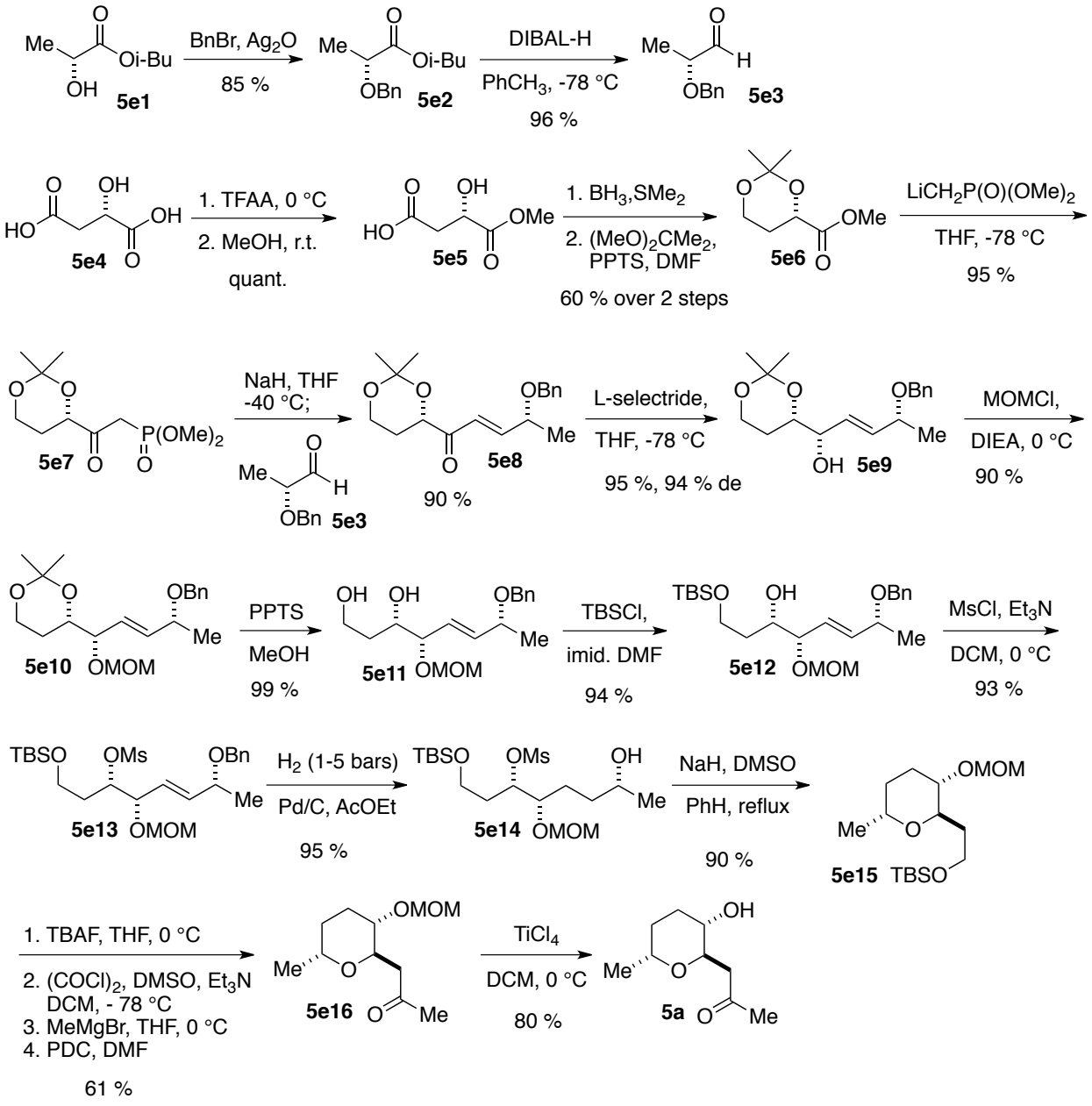
Scheme 5d: Nokami's Synthesis of (+)-Decarestrictine L



Chapter 5e: Carreño's Synthesis of (+)-Decarestrictine L

Carreño's[6] synthesis of (+)-decarestrictine L (**5a**, Scheme 5e) utilized the chiral pool for two out of the three stereocenters. The C6-methyl stereocenter was brought in through (*R*)-isobutyl lactate **5e1**. Protection of the hydroxyl as the Bn ether furnished **5e2** followed by DIBAL-H reduction to afford aldehyde **5e3**. The C2-stereochemistry would be attained via inversion of a mesylate derived from the hydroxyl of (*S*)-malic acid **5e4**. Selective methyl ester formation was affected with TFAA and then MeOH to attain ester **5e5** followed by reduction of the acid with BH_3•SMe_2 to the primary alcohol and then protection as the acetonide **5e6**. Attack with the lithium anion of dimethyl methylphosphonate produced **5e7**; which was reacted with aldehyde **5e3** in a HWE olefination. The C3-hydroxy stereochemistry was obtained via L-Selectride® reduction of ketone **5e8**. Protection as the MOM ether **5e10** and cleavage of the acetonide gave diol **5e11** followed by selective silyl ether formation at the primary hydroxyl to give **5e12**. Hydrogenation of the alkene and simultaneous cleavage of the Bn ether afforded **5e14**, the key substrate for the S_N2 cyclization. The intramolecular S_N2 displacement of the mesylate was affected with NaH in a refluxing mixture of PhH/ DMSO to give tetrahydropyran **5e15**. The primary alcohol was then deprotected, oxidized, methylated and oxidized again to install the methyl ketone moiety over 4 steps. Final deprotection of the MOM ether unmasks the C3-OH in (+)-decarestrictine L (**5a**) completing the synthesis.

Scheme 5e: Carreño's Synthesis of (+)-Decarestrictine L

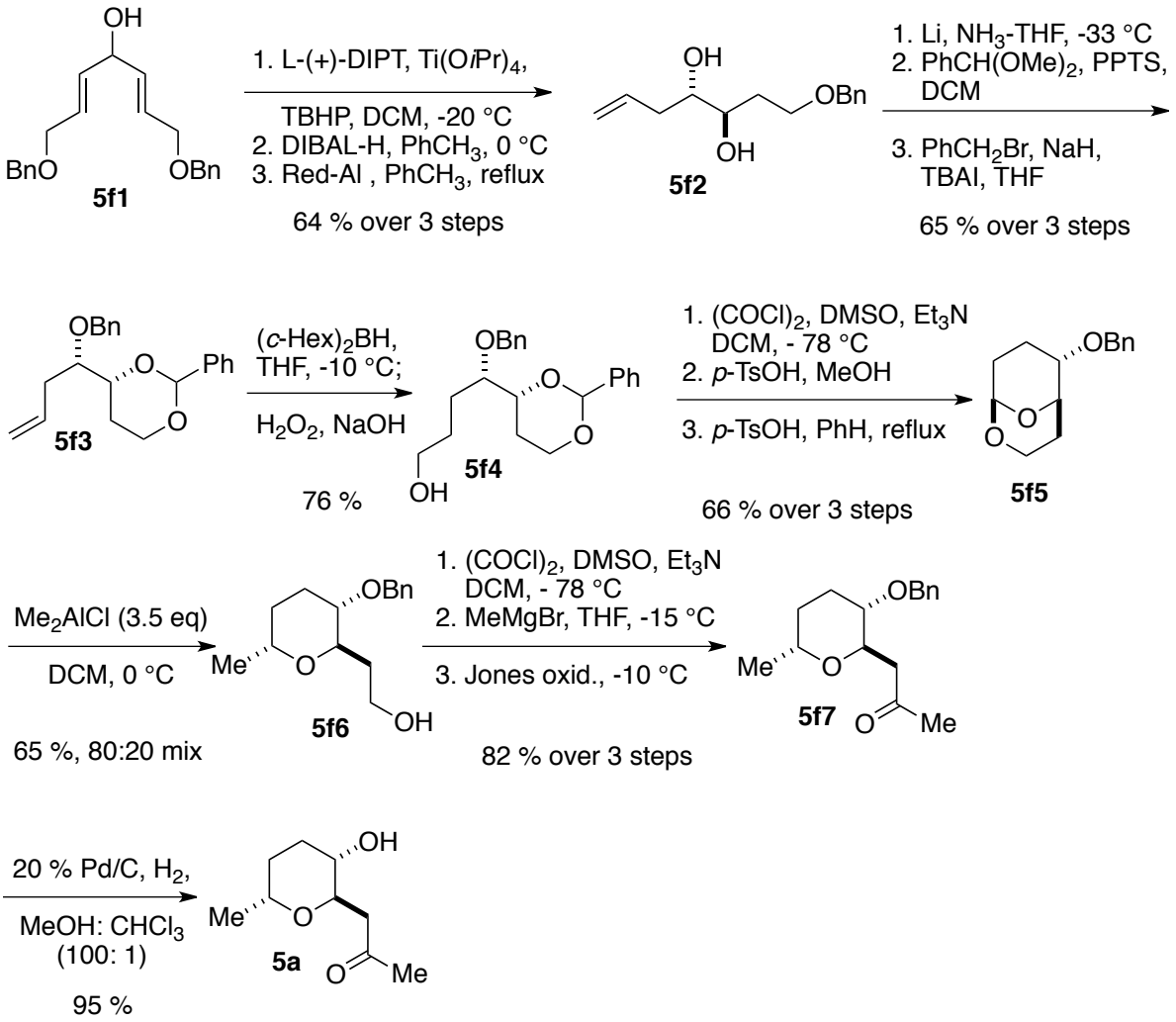


Chapter 5f: Hatakeyama's Synthesis of (+)-Decarestrictine L

Hatakeyama's[7] synthesis of (+)-decarestrictine L (**5a**, Scheme 5f) features a desymmetrization of the C2-symmetric bis-allylic alcohol **5f1** with a Sharpless asymmetric epoxidation. The epoxide was reductively opened with DIBAL-H followed by a Red-Al® mediated reductive debenzylation to give diol **5f2**. Birch reduction of the Bn ether gave a 1,3-

diol that was then protected as the benzylidene acetal. The remaining hydroxyl was then protected as the Bn ether **5f7**. Hydroboration/ oxidation of the terminal alkene gave the primary alcohol **5f4** then oxidation to the aldehyde and methanolic removal of the acetonide followed by acid catalyzed intramolecular acetalization gave the (1*R*,5*R*,6*S*)-6-benzyloxy-2,9-dioxabicyclo [3.3.1] nonane **5f5**. Methylative cleavage with Me_2AlCl installed the C6-methyl stereocenter in **5f6** as an 80:20 mixture of diastereomers. Primary alcohol **5f6** was then subjected to a three-step oxidation/ methylation/ oxidation sequence to install the methyl ketone moiety. Lastly hydrogenolysis of the Bn ether unveiled (+)-decarestrictine L (**5a**) as the final target.

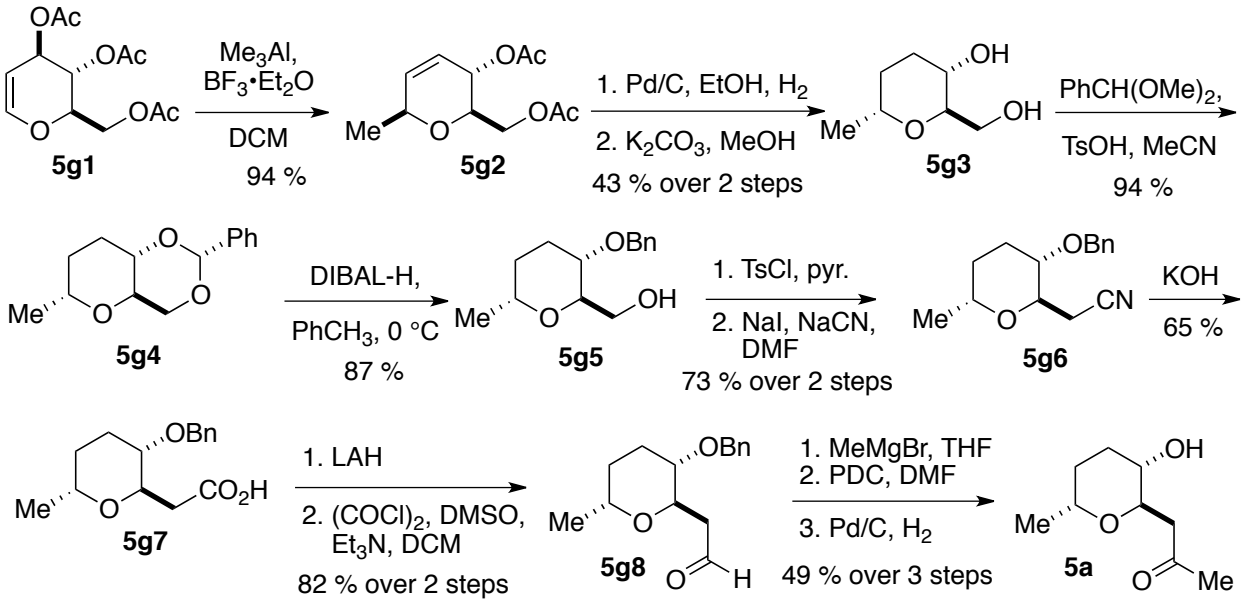
Scheme 5f: Hatakeyama's Synthesis of (+)-Decarestrictine L



Chapter 5g: Donaldson's Synthesis of (+)-Decarestrictine L

Another synthesis that used the chiral pool was Donaldson's[8] synthesis of (+)-decarestrictine L (**5a**, Scheme 5g). Beginning with the commercially available triacetyl-D-glucal **5g1**, an axial methylation with Me_2AlCl and BF_3•Et_2O installed the C6-methyl as an 87:13 mixture, favoring the desired product. The diastereomers were readily separated after hydrogenation of the olefin. Methanolysis of the acetates gave diol **5g3**. Acetalization to **5g4** followed by DIBAL-H reductive opening gave **5g5**. One carbon chain extension was affected with tosylation followed by displacement with NaCN to give **5g6** followed by hydrolysis of the nitrile with KOH to give carboxylic acid **5g7**. In order to install the methyl ketone moiety they first reduced the acid with LAH, followed by oxidation to the aldehyde **5g8** then attack with MeMgBr and oxidation with PDC of the resultant alcohol installed the ketone. They completed the synthesis by unmasking the C3-hydroxyl to give (+)-decarestrictine L (**5a**) in 13 steps.

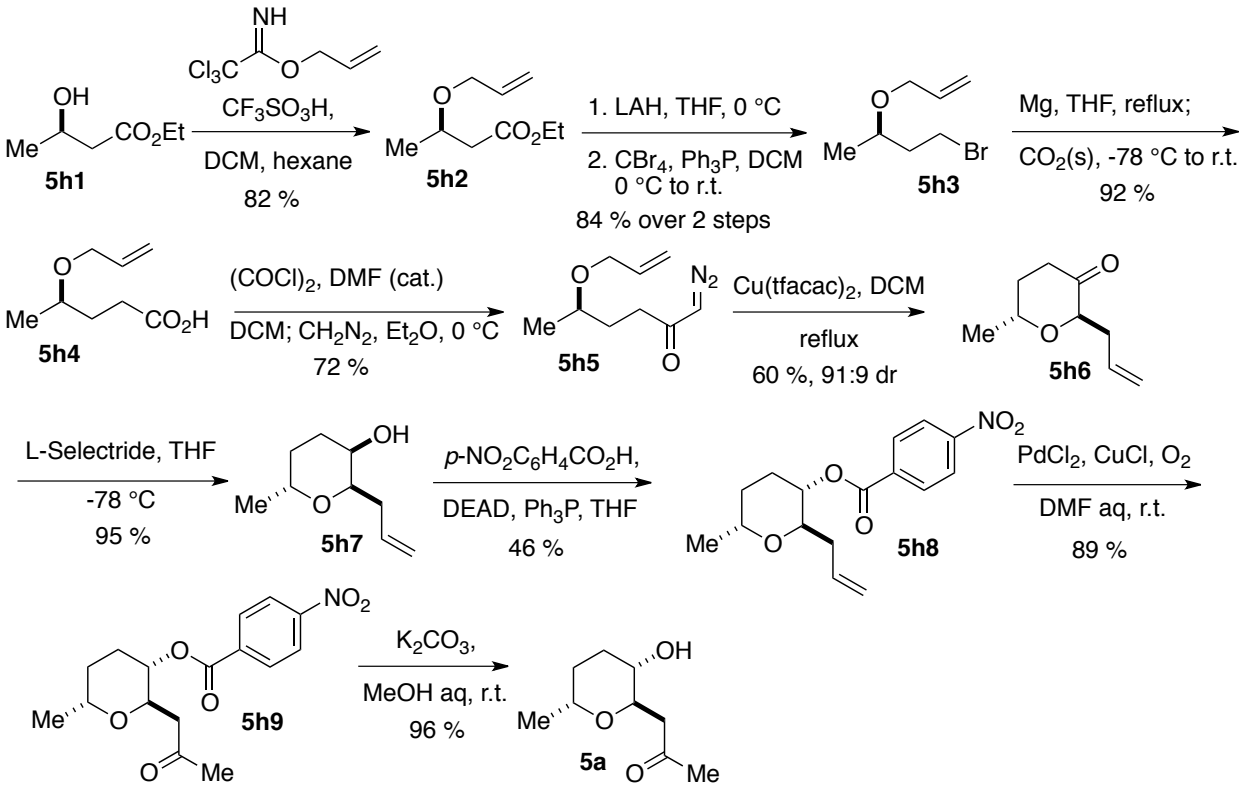
Scheme 5g: Donaldson's Synthesis of (+)-Decarestrictine L



Chapter 5h: Clark's Second Synthesis of (+)-Decarestrictine L

In 2006 Clark[9] *et. al.* published a second synthesis of (+)-decarestrictine L (**5a**, Scheme 5h). They used ethyl (*R*)-3-hydroxybutyrate **5h1** as a commercial starting material in a 10 step asymmetric synthesis. Installation of an allyl ether was affected with allyl trichloroacetimidate to give allyl ether **5h2** followed by reduction of the ester with LAH then conversion of the alcohol to bromide **5h3**. One carbon homologation to carboxylic acid **5h4** was accomplished via $CO_2(s)$ trapping of the Grignard reagent derived from **5h3**. Oxidation to the acid chloride with oxalyl chloride followed by attack with CH_2N_2 generated α-diazomethyl ketone **5h5**. With ketone **5h5** in hand, the $Cu(tfacac)_2$ catalyzed carbenoid insertion and rearrangement gave tetrahydropyran-3-one **5h6**. Reduction of the ketone with L-Selectride® gave alcohol **5h7**, followed by Mitsunobu inversion to the 4-nitrobenzoate ester **5h8** then Wacker oxidation smoothly installed the methyl ketone in **5h9** and hydrolysis of the 4-nitrobenzoate ester produced (+)-decarestrictine L (**5a**).

Scheme 5h: Clark's Second Synthesis of (+)-Decarestrictine L

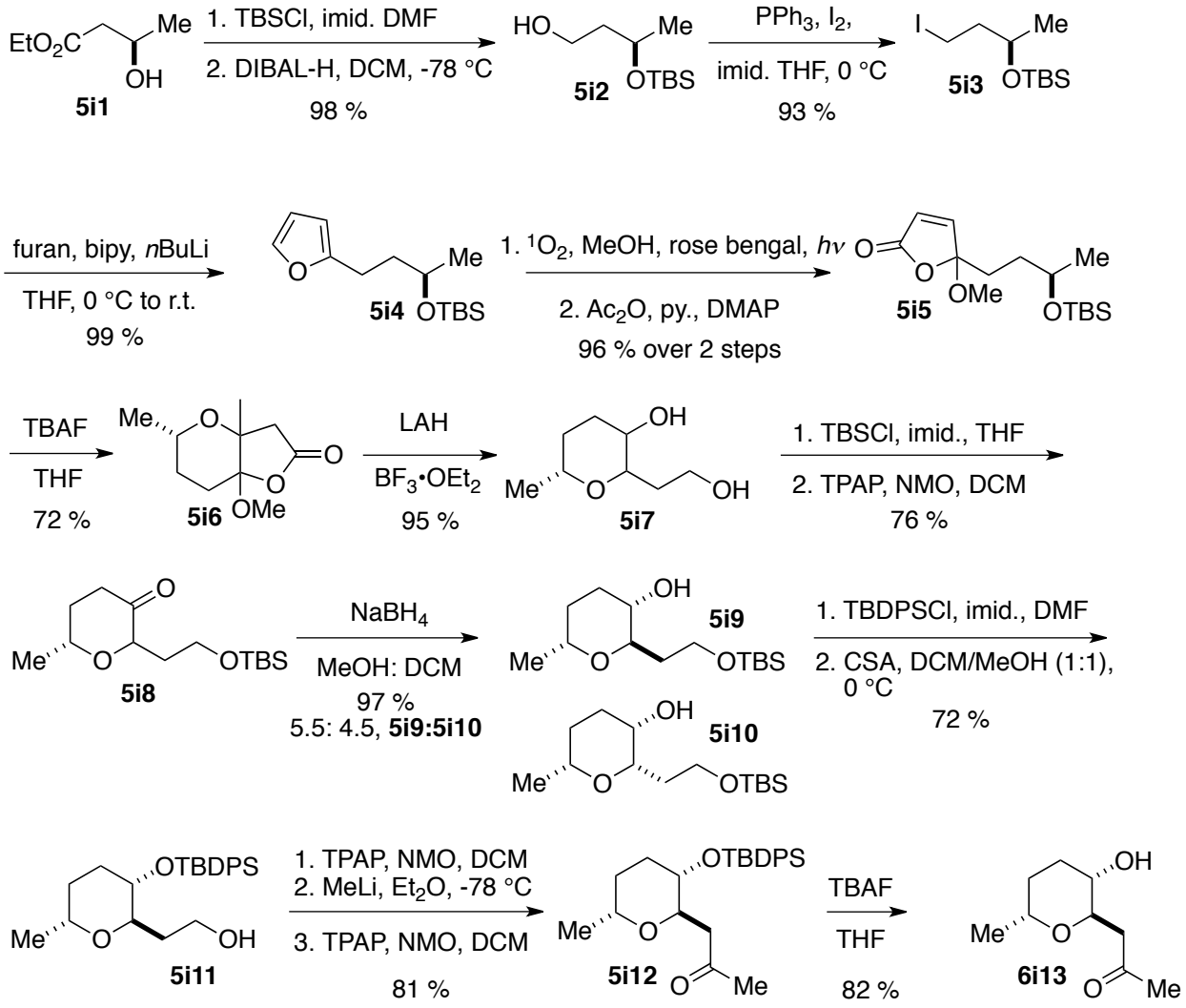


Chapter 5i: Fall's Synthesis of (+)-Decarestrictine L

Fall's[10] synthesis of (+)-decarestrictine L (**5a**, Scheme 5i) features a $^1O_2$ oxidation of a furan. Beginning with (3*R*)-hydroxy-ethyl butyrate **5i1**, DIBAL-H reduction and TBS protection afforded primary alcohol **5i2** followed by conversion to iodide **5i3** with Ph_3P and I_2. Alkylation of lithiated furan with iodide **5i3** afforded the key oxidation substrate **5i4** in quantitative yield. Singlet oxygen mediated oxidation with Rose Bengal then treatment with Ac_2O / pyridine afforded the key butenolide **5i5** followed by TBAF-mediated oxa-Michael addition to give bicyclic lactone **5i6**. Reductive opening of the lactone with LAH produced diol **5i7** along with protection of the primary alcohol as the TBS ether then TPAP/NMO oxidation to give ketone **5i8**. Reduction with $NaBH_4$ produced a mixture of diastereomers **5i9: 5i10** (55:45 respectively), which were separated by chromatography. Protection of the C3-hydroxyl as the TBDPS ether

followed by removal of the TBS ether gave primary alcohol **5i11**. Oxidation to the aldehyde, nucleophilic attack with MeLi followed by TPAP/NMO oxidation installed the methyl ketone moiety of **5i12** in 3 steps. Final desilylation of the C3-hydroxyl with TBAF produced (+)-decarestrictine L (**5a**) in 17 steps.

Scheme 5i: Fall's Synthesis of (+)-Decarestrictine L

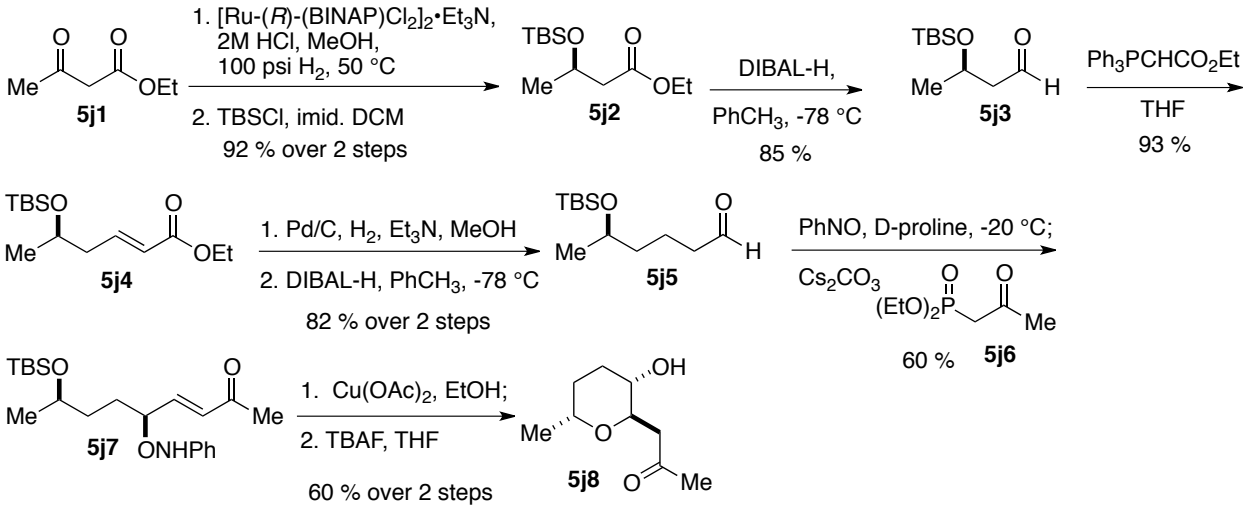


Chapter 5j: Sudalai's Synthesis of (+)-Decarestrictine L

Sudalai's[11] synthesis of (+)-decarestrictine L (**5a**, Scheme 5j) features an α-aminooxylation and HWE olefination sequence to install the C3-hydroxyl stereochemistry and an α,β-unsaturated ketone that was used for intramolecular oxa-Michael addition to form the

tetrahydropyran (THP) core. Beginning with ethyl acetoacetate **5j1** (Scheme 6j), Sudalai used a Noyori hydrogenation followed by TBS protection to access β-siloxy ester **5j2**. Reduction of the ester with DIBAL-H to aldehyde **5j3** followed by Wittig olefination proceeded smoothly to afford ethyl ester **5j4**. The two-carbon homologation was completed by palladium-catalyzed hydrogenation of the olefin and DIBAL-H reduction of the ester to afford the saturated aldehyde **5j5**. Now poised for their key reaction, aldehyde **5j5** was subjected to the α-aminooxylation and HWE sequence with nitrosobenzene and D-proline, aldehyde **5j5** was converted to the α-nitrosoaldehyde, which was immediately reacted with diethyl (2-oxopropyl)-phosphonate **5j6** and Cs_2CO_3 to yield α,β-unsaturated ketone **5j7**. A one pot deprotection of the C3-hydroxyl with $Cu(OAc)_2$ in EtOH followed by TBAF desilylation of the C6-silylether affected the intramolecular oxa-Michael cyclization to form the THP core and complete the synthesis of (+)-decarestrictine L (**5j8**).

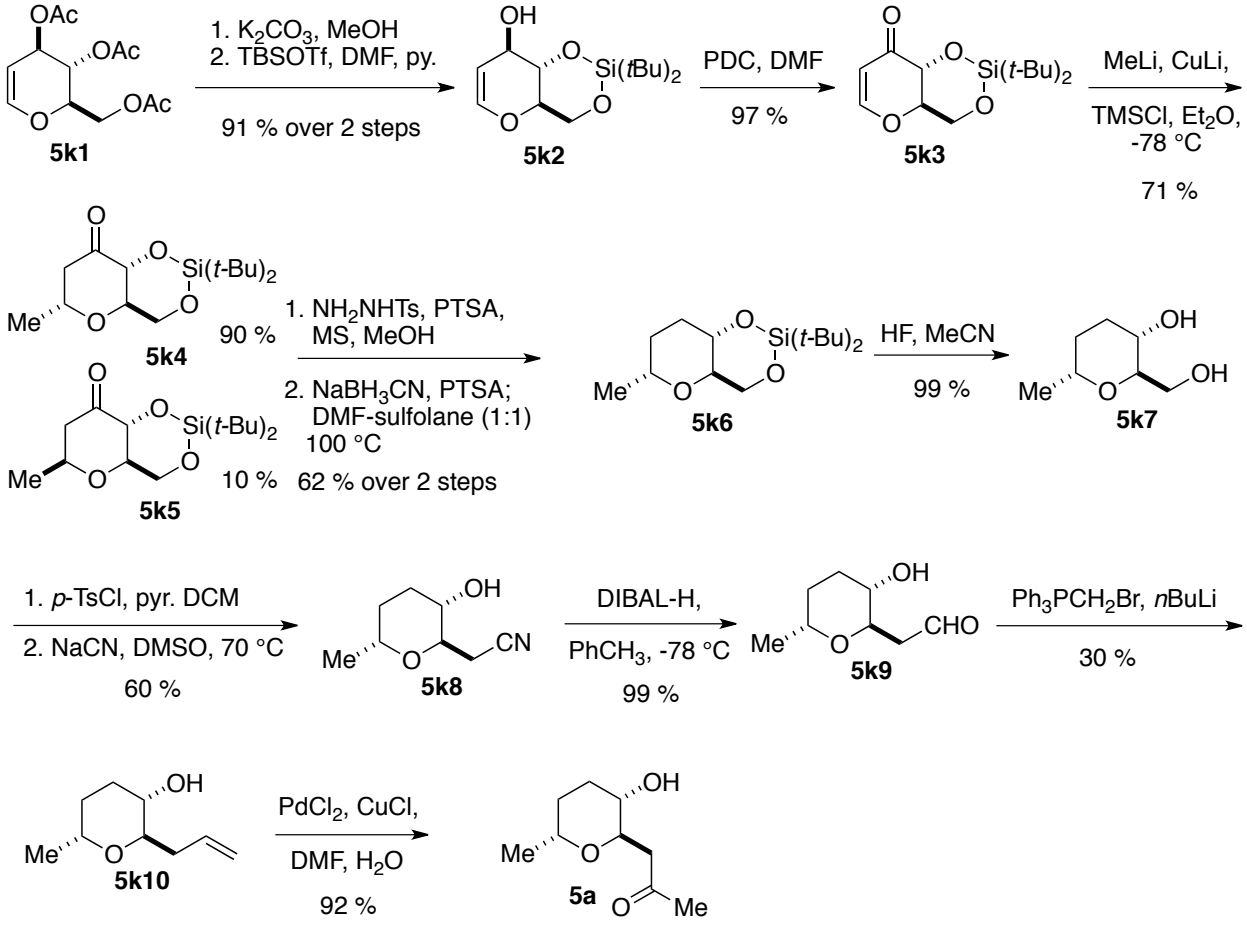
Scheme 5j: Sudalai's Synthesis of (+)-Decarestrictine L



Chapter 5k: Fall's Second Synthesis of (+)-Decarestrictine L

In 2010 Fall[12] *et. al.* published a second synthesis of (+)-decarestrictine L (**5a**, Scheme 5k) also from triacetyl-D-glucal **5k1**. First removing the acetates and then protecting the unmasked 1,3-diol as the bis-silyl ether gave **5k2**. Oxidation to the ketone **5k3** was accomplished with PDC followed by a conjugate addition of the Gillman reagent derived from MeLi/CuLi to afford a 90:10 mixture of diastereomers **5k4**: **5k5**. Ketone **5k4** was subjected to a Wolf-Kishner reduction with *p*-toluenesulfonyl hydrazine followed by $NaBH_3CN$ reduction of the intermediate hydrazine to give tetrahydropyran **5k6**. Desilylation with HF afforded **5k7** followed by a two-step chain extension of the primary alcohol via NaCN displacement of the tosylate. Reduction of the nitrile to the aldehyde with DIBAL-H followed by Wittig olefination gave alkene **5k10**. A Wacker oxidation was then used to install the methyl ketone completing their synthesis of (+)-decarestrictine L (**5a**) 12 steps.

Scheme 5k: Fall's Second Synthesis of (+)-Decarestrictine L



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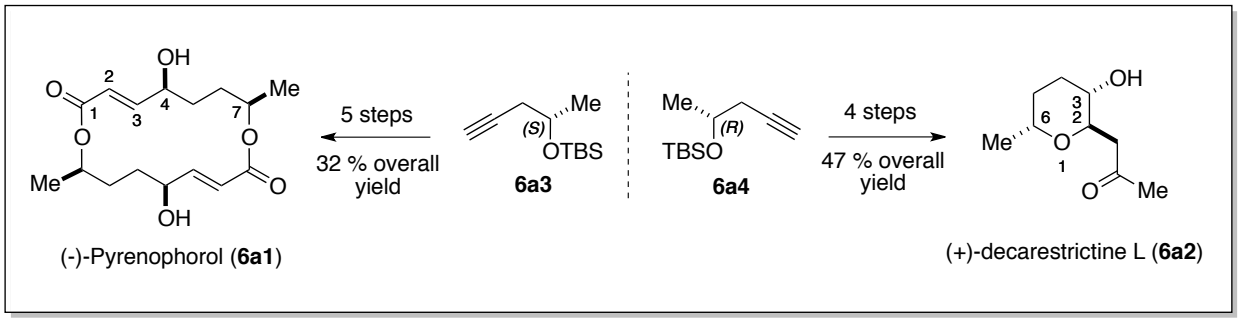
Chapter 6: The Total Syntheses of (-)-Pyrenophorol and (+)-Decarestrictine L via Asymmetric Hydroformylation/ Wittig Olefination

With the successful application of the hydroacetoxylation/ AHF/ Wittig olefination sequence to the synthesis of (+)-patulolide C (Chapter 3),[1] we sought out other targets to demonstrate this powerful chemistry. (-)-Pyrenophorol (**6a1**, Scheme 6a) is a 16-membered macrodiolide natural product containing two γ-hydroxy-α,β-unsaturated ester subunits, making it an excellent target to display the hydroacetoxylation/ AHF/ Wittig olefination sequence. Another small molecule natural product that seemed amenable to this strategy is (+)-decarestrictine L (**6a2**), which contained a trisubstituted tetrahydropyran ring with a masked γ-hydroxy-α,β-unsaturated ketone. With easy access to the (4*S*) and (4*R*)-*tert*-butyldimethylsiloxy-1-pentyne enantiomers **6a3** and **6a4**,[3a] we hoped to develop efficient routes to (-)-pyrenophorol (**6a1**) and (+)-decarestrictine L (**6a2**) respectively.

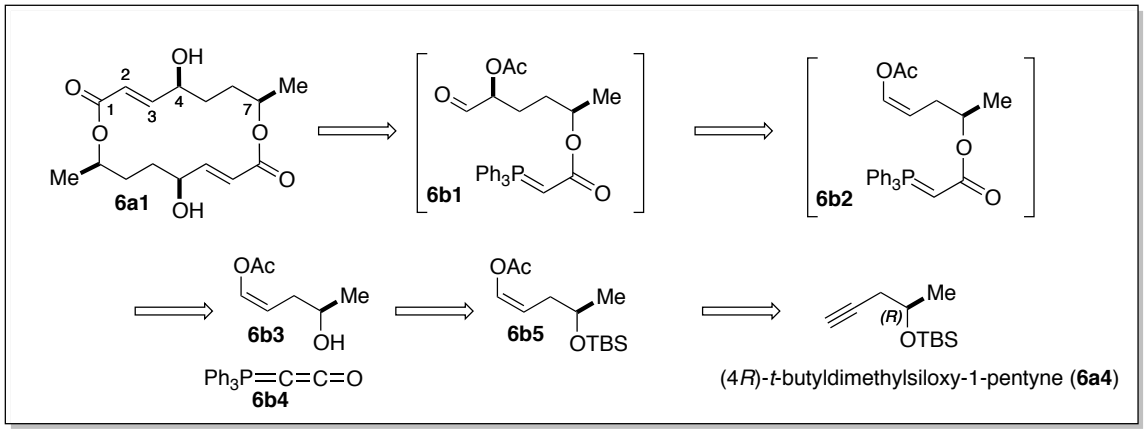
Scheme 6a



Landis and Wong have demonstrated the iterative AHF/Wittig olefination/ AHF/ Wittig olefination in a recent publication.[2] We thought the application of this type of iteration could result in an extremely short synthesis of (-)-pyrenophorol (**6a1**). Our synthetic strategy is outlined in Scheme 6b. In our initial approach we envisioned using the Wittig olefination of α-acetoxy aldehyde **6b1** as the dimerization step to access **6a1** after deacetylation. The α-acetoxy aldehyde **6b1** could be accessed via AHF of *Z*-enol acetate **6b2**, which would arise via esterification of hydroxy Z-enol acetate **6b3** with ketenylidene triphenylphosphorane **6b4**.[3b]

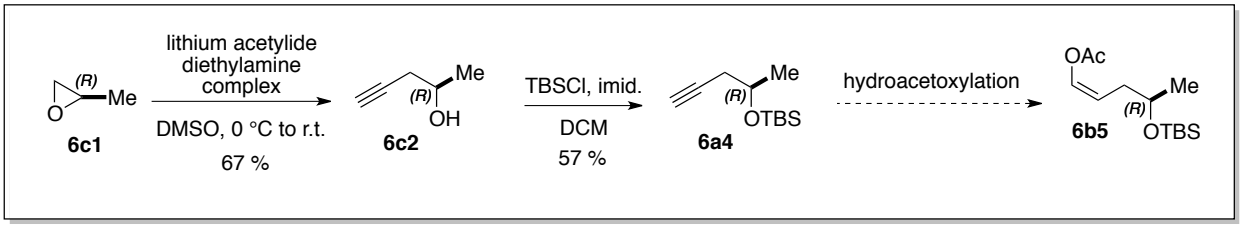
Alcohol **6b3** would be attained from desilylation of TBS ether **6b5**; which would be made via a *Z*-selective hydroacetoxylation of (4*R*)-*tert*-butyldimethylsiloxyl-1-pentyne (**6a4**). Alkyne **6a4** is available in 2 steps from commercially available (*R*)-propylene oxide (> 98 % *ee*) via literature protocol.[3a]

Scheme 6b



Synthesis of alkyne **6a4** began with ring opening of (*R*)-propylene oxide **6c1** by lithium acetylide diethylamine complex to furnish alcohol **6c2** in 67 % yield (Scheme 6c). Protection of the hydroxyl as the TBS ether proceeded smoothly to afford known alkyne **6a4** in 57 % yield. Our previous successful application of the Rh (I)-catalyzed hydroacetoxylation chemistry in our synthesis of (+)-patulolide C[1] (Chapter 3) prompted us to try it on alkyne **6a4** in order to access *Z*-enol acetate **6b5**. Several attempts were made but only resulted in complex mixtures. The

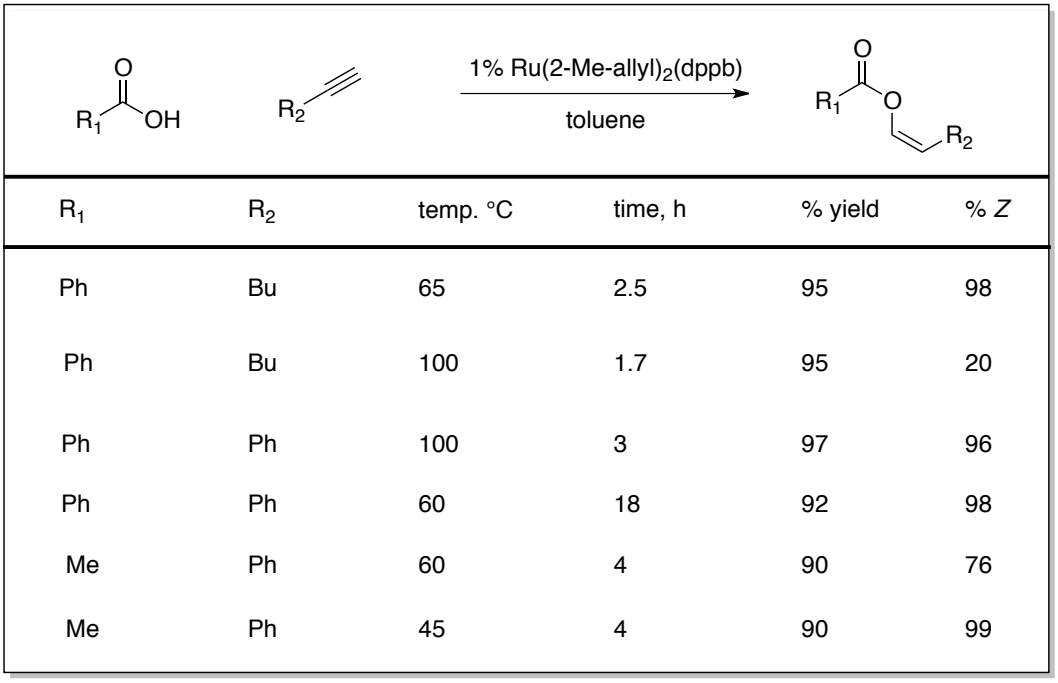
Scheme 6c



higher temperature seemed to be too harsh for this substrate. Searching the literature we found the Ru(II)-catalyzed hydroacetoxylation developed by Dixneuf[4] with equally high *anti*-

Markovnikov *Z*-selectivity at much milder temperatures (ca. 55 °C). They demonstrated the hydroacetoxylation of terminal alkynes with Ru(2-Me-allyl)$_2$dppb, AcOH in toluene and several examples are shown in Table 6a.

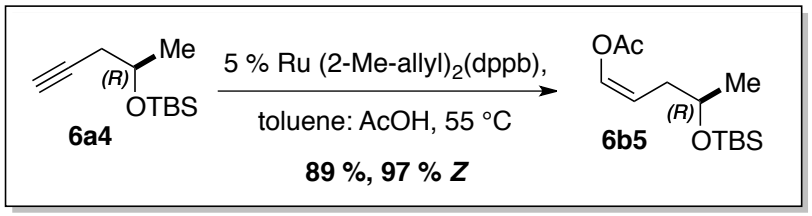
Table 6a



R_1	R_2	temp. °C	time, h	% yield	% *Z*
Ph	Bu	65	2.5	95	98
Ph	Bu	100	1.7	95	20
Ph	Ph	100	3	97	96
Ph	Ph	60	18	92	98
Me	Ph	60	4	90	76
Me	Ph	45	4	90	99

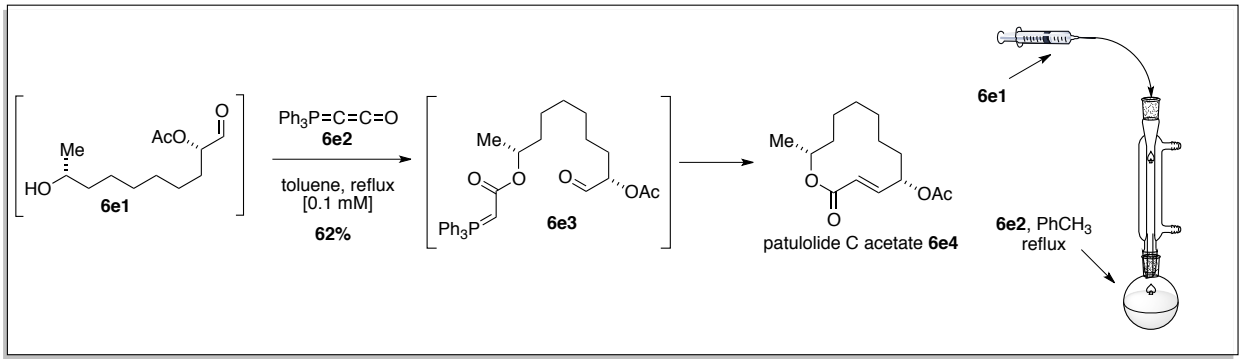
As shown in Table 6a the hydrocarboxylations of hexyne and phenylacetylene that proceeded at lower temperatures were in fact more *Z*-selective in most cases. They propose a similar mechanism to the one put forth by Breit[4b] as shown in Scheme 3b of Chapter 3. The milder conditions prompted us to explore the use of this catalyst system to access *Z*-enol acetate **6b5**. Application of this Ru(II) catalyzed hydroacetoxylation to alkyne **6a4** did form the desired *Z*-enol acetate **6b5**, but some optimization of catalyst loading, time and temperature were required. Indeed with 5 % Ru(2-Me-allyl)$_2$dppb, AcOH in toluene at 55 °C, alkyne **6a4** was transformed into *Z*-enol acetate **6b5** in 89 % yield with 97 % *Z*-selectivity (Scheme 6d).

Scheme 6d



When performing a macrocyclization, concentration is a crucial factor to promote the intramolecular reaction and avoiding the intermolecular reaction. Submillimolar concentrations of substrate are usually necessary for medium sized rings (10-12). One way in which these low concentrations of substrate can be attained is by a slow addition of a solution of the substrate to a dilute solution of reagents as shown in the example of patulolide C acetate in Scheme 6e. As a drop of the hydroxy aldehyde **6e1** is added to the reaction vessel containing Bestmann ylide **6e2** (6 equivalents),[3b] the alcohol **6e1** encounters molecules of **6e2** and the stabilized yilde **6e3** is formed. Since the dropwise addition of substrate **6e1** is slow, the concentration of **6e2** generated in solution is very low (<< 0.1 mM) and the intramolecular Wittig olefination is much faster than a competing intermolecular Wittig olefination. With this method the 12-membered ring macrocycle **6e4** was cleanly formed with the avoidance of dimerization.

Scheme 6e



In the case of (-)-pyrenophorol (**6a1**), we needed to effect a dimerization involving one intermolecular reaction followed by an intramolecular reaction. To accomplish this the rate of

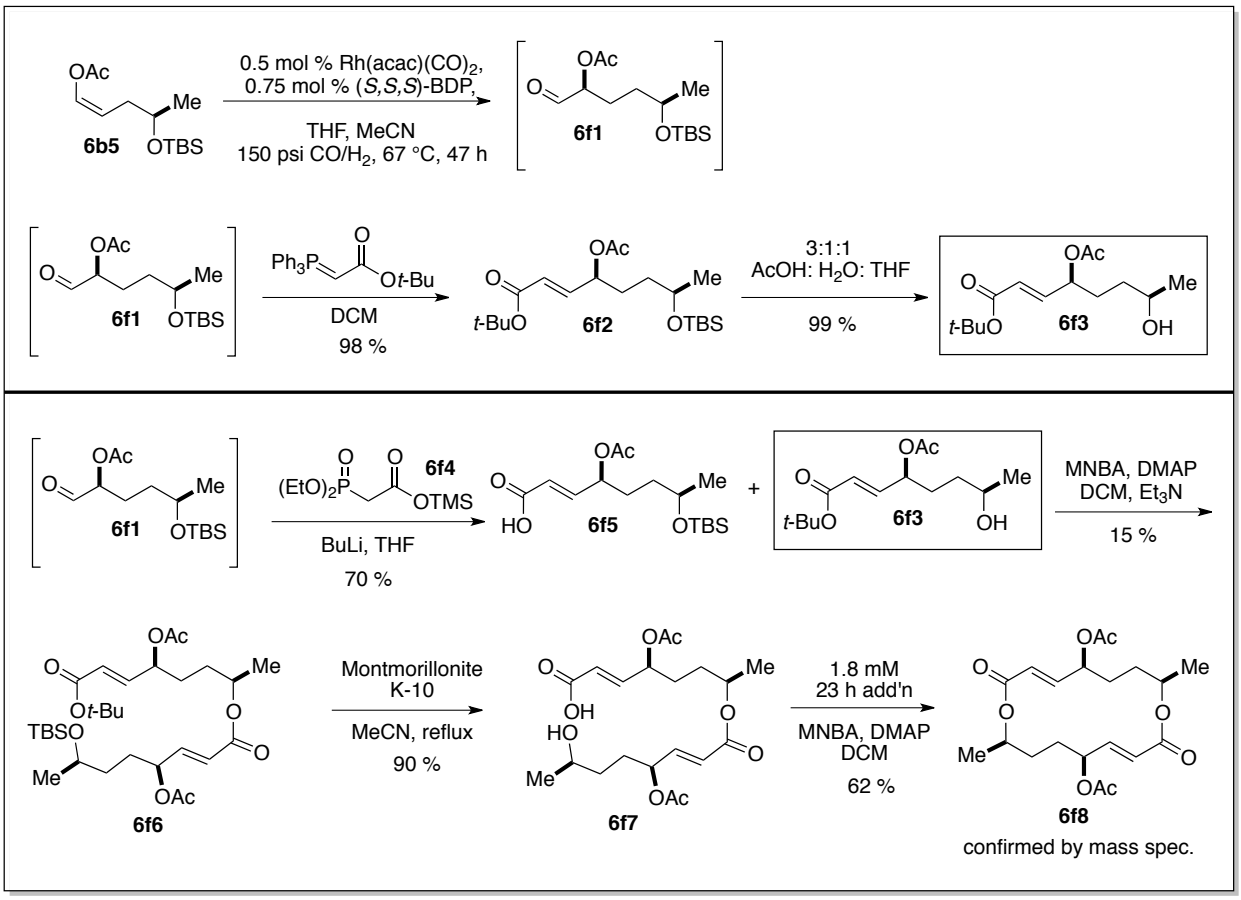
addition and reaction concentration had to be finely tuned in order to favor one intermolecular reaction as soon as the substrate was added to the reaction vessel followed by an intramolucular reaction to effect macrodiolide formation. The concentration should be low enough that the first intermolecular reaction is relatively fast and a second intermolecular reaction (between substrate molecules) would be very slow compared to intramolecular cyclization, thus attaining dimerization and avoiding higher oligomers.

In order to elucidate this narrow window of concentration and rate addition we thought it would be wise to have an authentic sample of the bisacetoxy pyrenophorol **6f8** (Scheme 6f) in hand so as to have key analytical signatures (R_f on TLC plate, ^{1}H-NMR and a mass spectrometry data) to compare with when conducting dimerization experiments. Therefore we synthesized the macrodiolide **6f8** according to the route in Scheme 6f with sequential intermolecular esterification followed by an intramolecular lactonization.

The TBS-protected *Z*-enol acetate **6b5** was subjected to AHF conditions with $Rh(acac)(CO)_2$ and (*S,S,S*)-**BDP** in THF under 150 psi CO/H_2. It was found that the reaction required heating to 67 °C in order to affect complete conversion while maintaining regioselectivity. α-Acetoxy aldehyde **6f1** is the only product observed by ^{1}H-NMR. From aldehyde **6f1** we were able to access carboxylic acid **6f5** and alcohol **6f3** via two different olefination reactions. Wittig olefination with *t*-butoxycarbonylmethylene triphenylphosphorane gave the fully protected α,β-unsaturated *t*-Bu ester **6f2** in 98 % yield (> 95 % *E*) and an HWE olefination with phosphonate ester **6f4** afforded α,β-unsaturated carboxylic acid **6f5** in 70 % yield (> 95 % *E*) upon aqueous workup. The TBS ether of **6f2** was hydrolyzed to yield alcohol **6f3** in 99 % yield. An intermolecular esterification between alcohol **6f3** and acid **6f5** was done under Shiina[5] (MNBA, DMAP in DCM) conditions to afford the open chain fully protected

dimer **6f6**, albeit in low yield. After a variety of cleavage conditions were screened, it was found that reacting substrate **6f6** with Montmorillonite K-10 acidic clay in MeCN at 80 °C affected a simultaneous cleavage of both the *t*-Bu ester and TBS ether to give open chain hydroxy acid **6f7** in 90 % yield with the acetates intact. Slow addition of **6f7** over 23 h to a flask containing 6 equivalents of both MNBA and DMAP in DCM (1.8 mM) cleanly affected macrocyclization to give the bis-acetoxy pyrenophorol **6f8** in 62 % yield with confirmation by mass spectrometry. With an authentic sample in hand, we were able to obtain key analytical signatures such as R_f (for TLC analysis), ^{1}H-NMR, ^{13}C-NMR and mass spectrometry (m.s.) data for comparison in subsequent experiments. The sequential esterification approach (2 steps) to form the macrocycle (Scheme 6f) was sub-optimal considering that several[6] of the previous syntheses of (-)-pyrenophorol (**6a1**) formed the macrodiolide via a head-to-tail dimerization of a hydroxy acid in one step. This route did however provide an authentic sample to reference in the exploration of more efficient routes.

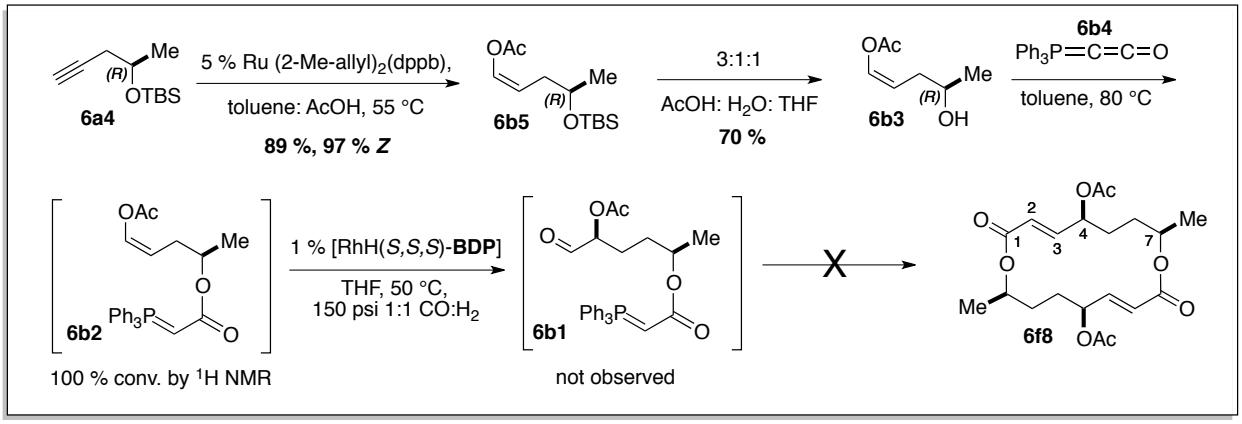
Scheme 6f



With access to *Z*-enol acetate **6b5** and confirmed bis acetoxypyrenophorol **6f8** in hand, we proceeded to explore the iterative AHF/ Wittig olefination dimerization route (Scheme 6g). The TBS ether of **6b5** was removed via AcOH mediated hydrolysis to give hydroxy *Z*-enol acetate **6b3** in 70 % yield. The key AHF/ Wittig dimerization was attempted next. Hydroxy *Z*-enol acetate **6b3** was stirred with one equivalent of the Bestmann ylide **6b4** in toluene at 80 °C to cleanly generate stabilized ylide **6b2** in quantitative yield (NMR yield, not isolated). This *Z*-enol acetate derived stabilized ylide **6b2** was then injected into a solution of pre-reacted [$RhH(CO)_2$(*S,S,S*)-**BDP**] under syngas and reacted at 50 °C in hopes to affect the iterative AHF/ Wittig olefination dimerization. Indeed the AHF catalyst completely consumed all of the alkene, however no dimer **6f8** was detected by TLC, ^{1}H-NMR or mass spectrometry, and only higher

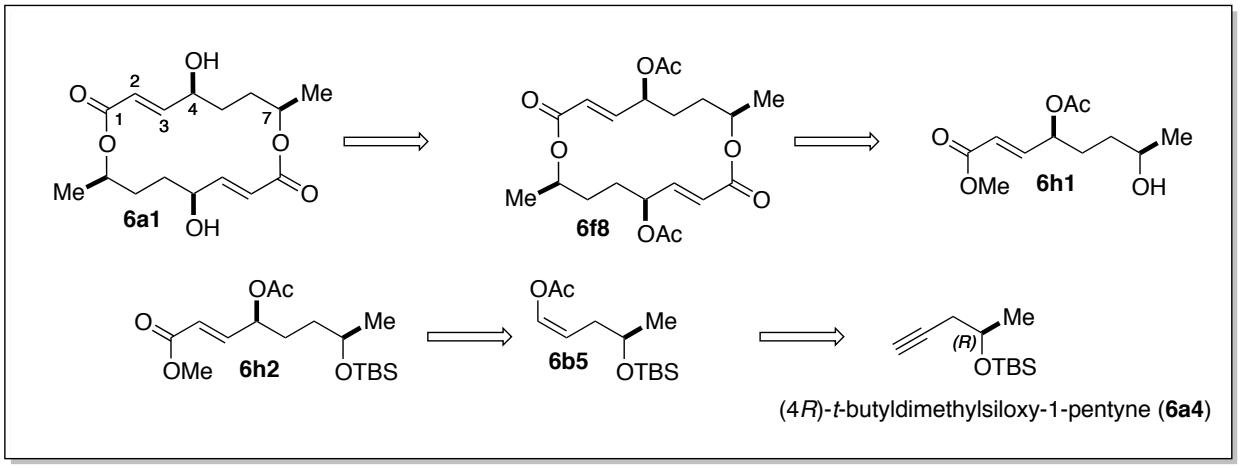
polymers resulted as observed by mass spectrometry. The dimerization reaction needed to be conducted at a much lower concentration (ca. 1 mM in substrate) in order to avoid higher oligomers. The dilute conditions for dimerization proved incompatible with the necessary higher concentration for AHF, thus we had to revise our strategy.

Scheme 6g



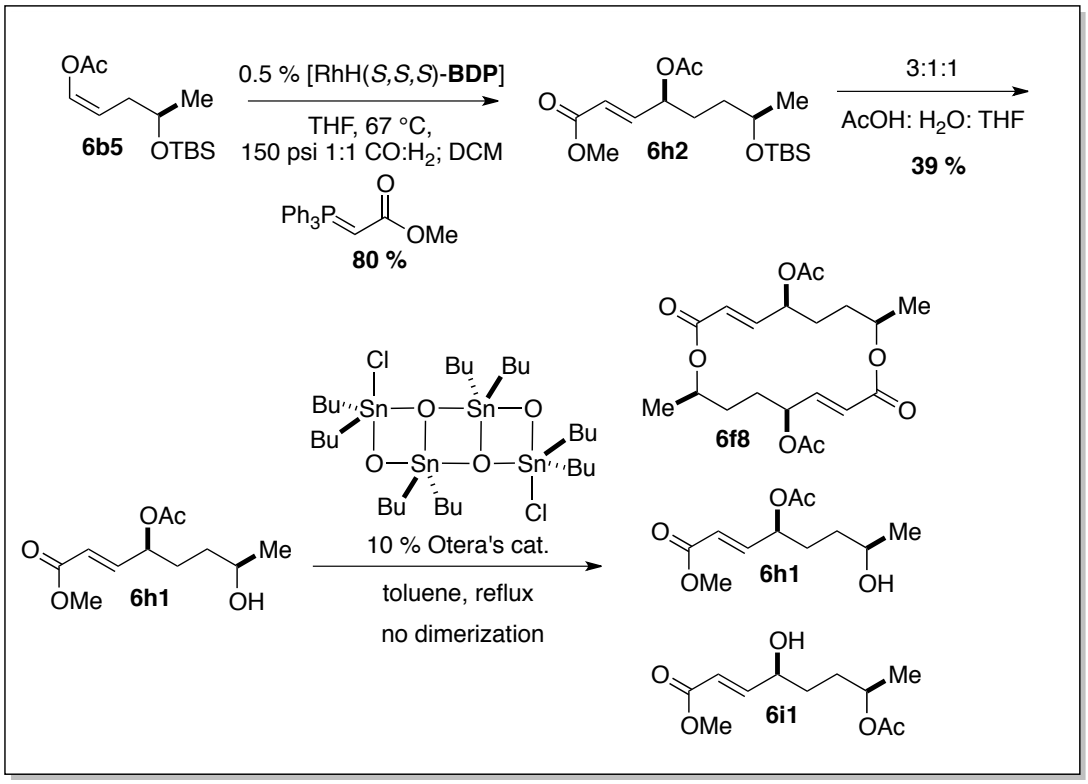
Knowing that the ester bond was used frequently as the disconnection bond for dimerization in previous syntheses,[6] we decided to follow precedent. As shown in Scheme 6h, we planned to access (-)-pyrenophorol (**6a1**) from a double deacetylation of bis-acetate **6f8**; which would come from a dimerization of methyl ester **6h1**. This ester would be accessed from the desilylation of TBS-ether **6h2**; which would come from an AHF/ Wittig olefination of *Z*-enol acetate **6b5**.

Scheme 6h



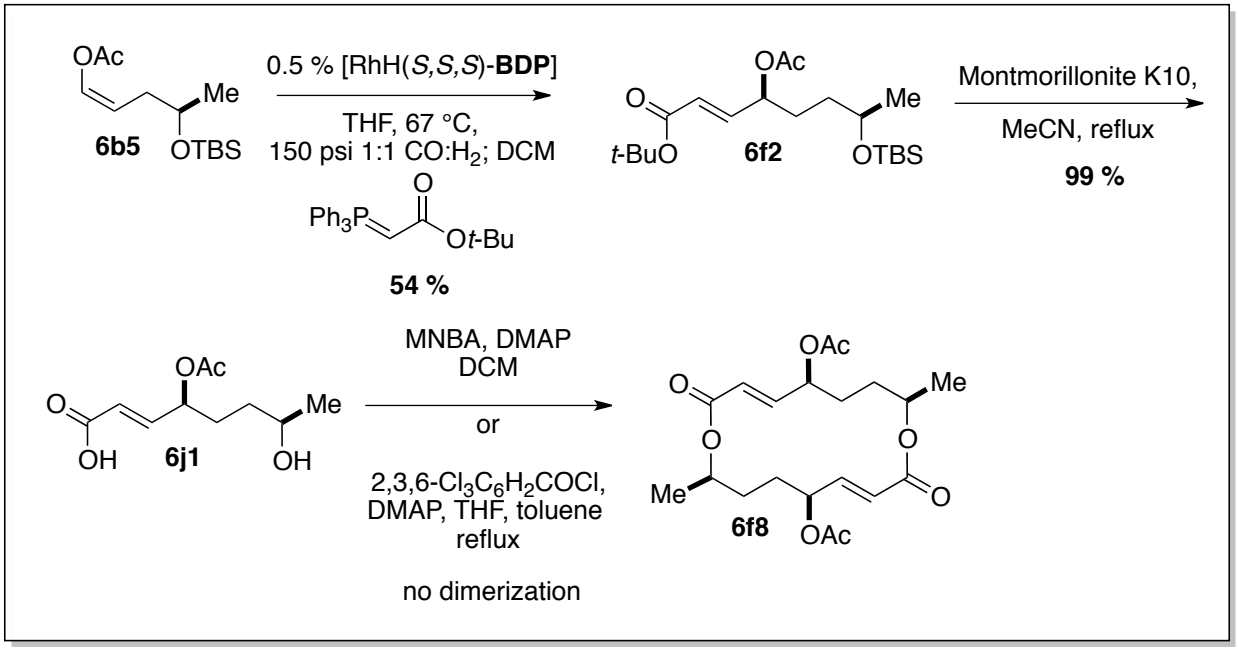
The AHF of *Z*-enol acetate **6b5** (Scheme 6i) proceeded smoothly with 0.5 % catalyst at 67 °C, 150 psi CO/H_2 to give α-acetoxy aldehyde (not shown) as the only observable product by ^1H NMR. The temperature range necessary for the reaction to go to completion and still maintain selectivity was 67–70 °C. Wittig olefination with methoxy acetyl triphenylphosphorane afforded γ-acetoxy-α,β-unsaturated methyl ester **6h2** in 80 % yield. Acidic hydrolysis of the TBS ether produced C7-hydroxy ester **6h1** in 39 % yield (unoptimized). We attempted to affect the dimerization via a neutral transesterification with Otera's catalyst.[7] The transesterification reaction only produced a mixture of acetates **6i1** and **6h1** from partial acetyl transfer and no dimer was detected by TLC or m.s.. Neutral transesterification with Otera's catalyst[7] as a means of dimerization was not a viable option. No other transesterifications were attempted; at this point an esterification reaction, being closer to the precedent, seemed more likely to work.

Scheme 6i



Looking to the preceding syntheses, we knew the dimerization would work with the hydroxy acid. The ester moiety incorporated from the stabilized ylide in the Wittig olefination needed to be cleaved to the carboxylic acid in the presence of the acetate; the *t*-Bu ester was an obvious choice. AHF/ Wittig olefination of *Z*-enol acetate **6b5** (Scheme 6j) proceeded smoothly to afford the α-acetoxy aldehyde (not shown) which was reacted directly with (*tert*-butoxycarbonylmethylene) triphenylphosphorane to afford γ-acetoxy-α,β-unsaturated *t*-butyl ester **6f2** in 54 % yield (unoptimized). Once again refluxing *t*-butyl ester **6f2** in MeCN with Montmorillonite K-10 acidic clay produced C7-hydroxy acid **6j1** in quantitative yield while leaving the acetate untouched.

Scheme 6j



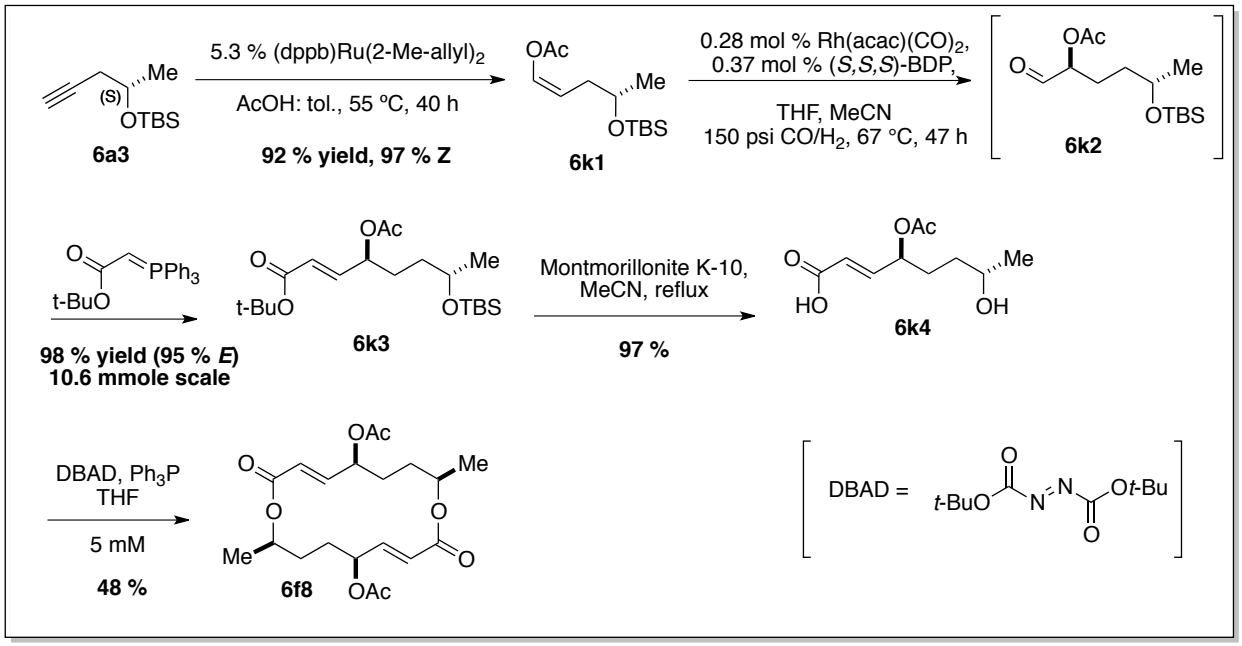
Now poised for the macrodiolide formation, hydroxy acid **6j1** was slowly added to the reagents in the flask to affect either the Shiina[5] or Yamaguchi[8] esterification. A range of concentrations from 1 mM to 100 mM was screened, but none resulted in dimerization, only complex mixtures of inseparable products. None of the dimer was detected by TLC, ^{1}H-NMR or m.s. when compared to the authentic sample previously prepared. Yamaguchi esterification didn't afford the desired bis-acetate dimer **6e1**, but gave a mixture of polymeric products even at low concentrations. Likewise esterification with the Shiina conditions using MNBA/ DMAP in DCM gave only intramolecular Michael addition products and higher oligomers. None of the reported syntheses that used an esterification for the dimerization step had an ester protecting group on the C4 hydroxyl, it is possible that the acetate activated the β-position of the alkene toward Michael addition.

Several syntheses[9] of **6a1** used the Mitsunobu reaction of a C7-hydroxy acid to form the macrodiolide. Since the carboxylate is the nucleophile and the C7-carbon bearing the hydroxyl is

the electrophile in the Mitsunobu reaction, we thought this role reversal (nucleophile/electrophile) from the esterification reaction would avoid the Michael addition. The alternative Mitsunobu reaction strategy required the C7-OH stereocenter to be in the (*S*)-configuration since the Mitsunobu reaction is an S_N2, which proceeds with inversion, and the stereochemistry in (-)-pyrenophorol (**6a1**) is the (*R*) configuration. Therefore a similar route was pursued beginning with (*S*)-propylene oxide to make the enantiomeric (4*S*)-tert-butyldimethylsiloxy-1-pentyne[3a] (**6a3**, Scheme 6h).

The known alkyne **6a3** (Scheme 6k) was prepared in an identical manner to its enantiomer **6a4**. The Ru(II)-catalyzed hydroacetoxylation of alkyne **6a3** afforded *Z*-enol acetate **6k1** in 92 % yield (97 % *Z*). It was found that both the hydroacetoxylation and AHF/ Wittig olefination reactions worked especially well on a large scale. A 58.9 mmol scale hydroacetoxylation afforded plenty of material (14.05 g) to finish the synthesis of (-)-pyrenophorol (**6a1**). The AHF of *Z*-enol acetate **6k1** proceeded smoothly with 0.28 % catalyst at 67 °C, 150 psi syngas (1:1 CO/H_2) on a 10.6 mmole scale to give α-acetoxy aldehyde **6k2** as the sole product. Wittig olefination with (*tert*-butoxycarbonylmethylene) triphenylphosphorane produced (C7-*S*)-*tert*-butyldimethylsiloxy-γ-acetoxy-α,β-unsaturated *tert*-butyl ester **6k3** in 98 % yield with excellent *E*-selectivity (95 % *E*).

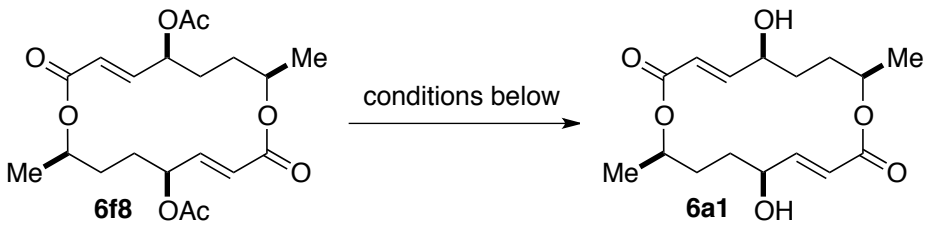
Scheme 6k



Double deprotection of the TBS ether and *t*-Bu ester was done with Montmorillonite K-10 in refluxing acetonitrile to yield C7-hydroxy acid **6k4** in 97 % yield, leaving the acetate in place. The key Mitsunobu dimerization was attempted next with diethylazodicarboxylate (not shown). Hydroxy acid **6k4** was added slowly to a THF/toluene solution of Ph_3P and DEAD at -20 °C over 16 h. The bis-acetate dimer **6f8** was formed, however purification proved troublesome and the product was not isolated from the byproducts. Mitsunobu reactions are notorious for difficult purification of products and the literature showed some research done in order to improve this reaction.[10] The reagent di-*tert*-butylazodicarboxylate (DBAD) was shown by Kiankarimi[10] to facilitate purification the Mitsunobu reaction at room temperature and easily decompose to gaseous byproducts (isobutene, CO_2, and N_2) upon acidic work up. For relatively simple substrates they report mostly pure product after acidic work up and aqueous extraction, however we found that bis-acetate **6f8** still required careful chromatography to attain product of analytical purity. The Mitsunobu reaction was done on hydroxy acid **6k4** with DBAD and Ph_3P

in THF at room temperature and cleanly afforded the bis-acetate dimer **6f8** in 48 % yield after work up and careful chromatography. It was found that the total reaction concentration could be as a high as 5 mM in substrate and the production of trimer or higher oligomers could be avoided. The Mitsunobu reaction was quite fast and the addition could be done over a minimum of 6 h so long as the DBAD and Ph_3P were used in a minimum of 5 equivalents. When the reaction was done at higher concentrations (> 5 mM) or the addition done faster than 6 h, trimer was formed and confirmed by m.s.

Table 6b



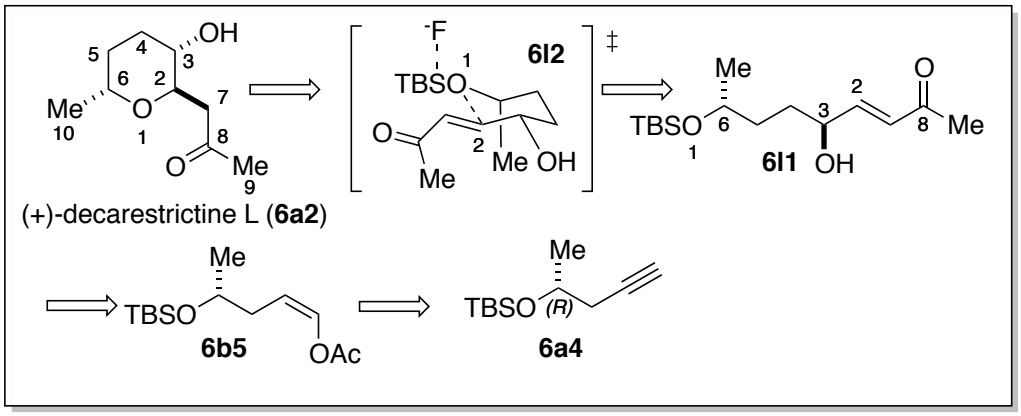
Entry	Reagent	Solvent	Time (d)	Temp. (°C)	% Yield
1	KCN	EtOH	1	50	44
2	Et_3N	MeOH	3	25	25
3	Et_3N	MeOH	10	25	69
4	$TsOH•H_2O$	MeOH	10	25	0
5	*Pseudomonas fluorescens* lipase	pH 7 buffer	14	25	77

With a successful dimerization in hand, deacetylation was all that was left to finish (-)-pyrenophorol (**6a1**). Several conditions were screened and the results are shown in Table 6b. Mild removal with KCN/ EtOH did produce (-)-pyrenophorol (**6a1**) albeit in only 44 % yield. Methanolysis with Et_3N did affect the deacetylation but was slow (3 d, 25 %; 10 d, 69 %) and competitive lactone opening was observed. Acidic cleavage with $TsOH•H_2O$ in MeOH did

remove the acetates, but very slowly and decomposition dominated. Once again enzymatic deacetylation was done in hopes to maintain selectivity and avoid decomposition. Lipase from *Pseudomonas fluorescens* cleanly removed both acetates under neutral conditions without hydrolyzing the lactones. The reaction was slow (14 d), but cleanly and selectively gave the final target (-)-pyrenophorol (**6a1**) in 77 % yield. HPLC analysis of both desilylated t-butyl ester **6k3** and **6a1** showed a diastereomeric ratio of 95:5 indicating excellent selectivity for the AHF as well as no deterioration in the subsequent reactions.

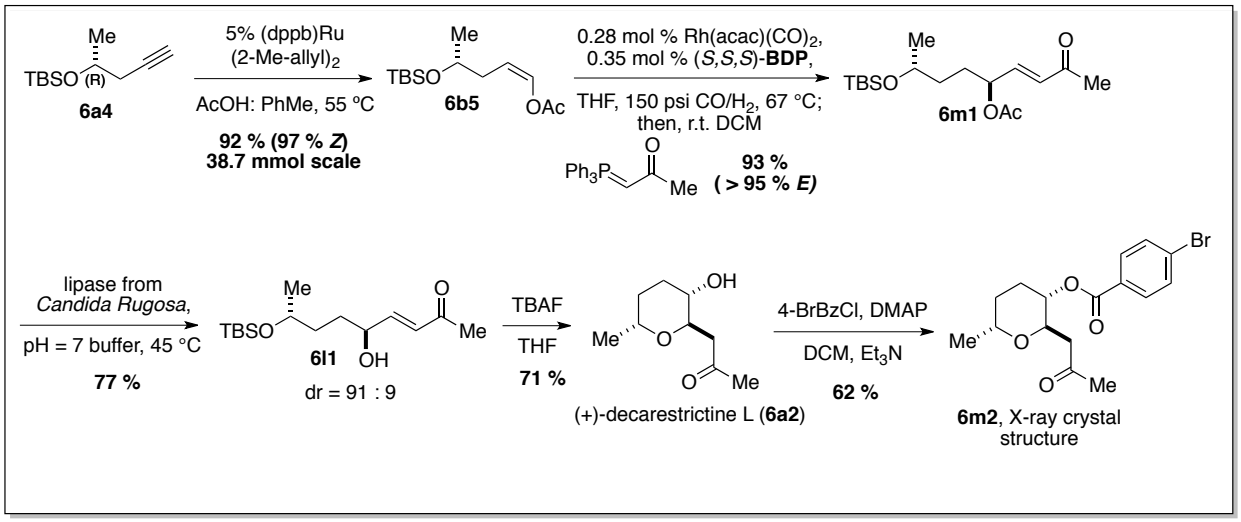
With the successful completion of (-)-pyrenophorol (**6a1**) we had sought to use the hydroacetoxylation/ AHF/ Wittig olefination sequence developed for the (*R*)-enantiomeric alkyne (**6a4**) in a short synthesis of decarestrictine L (**6a2**, scheme 6l). (+)-Decarestrictine L (**6a2**) is a trisubstituted tetrahydropyran (THP) from the decarestrictine family of natural products. With access to *Z*-enol acetate **6b5** we proposed an AHF/Wittig olefination/ deacetylation sequence to produce γ-hydroxy-α,β-unsaturated ketone **6l1**. With all the carbons of the natural product in place the final step would be a TBAF-mediated desilylation/oxa-Michael cyclization via transition state **6l2** to afford decarestrictine L (**6a2**) in a very short synthesis.

Scheme 6l



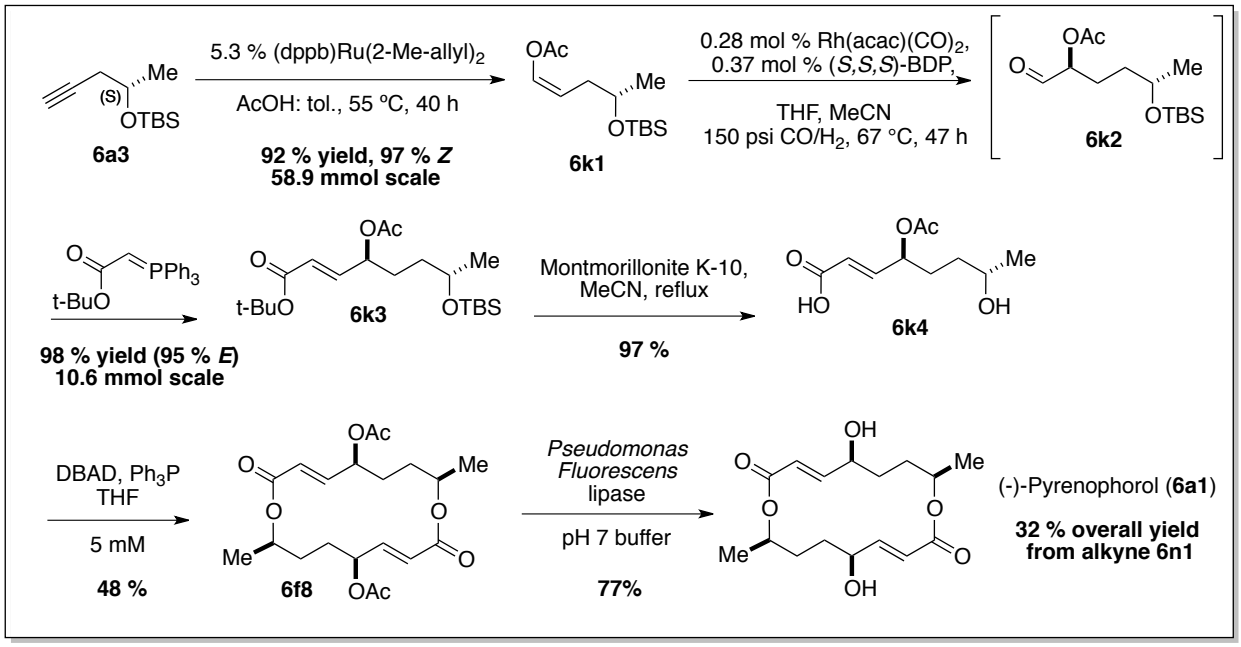
The large scale (38.7 mmol) hydroacetoxylation of **6a4** (Scheme 6m) proceeded well to afford *Z*-enol acetate **6b5** in 92 % yield (97 % *Z*). Next the AHF of *Z*-enol acetate **6b5** was conducted with 0.28 mol % [RhH(*S,S,S*)-**BDP**$(CO)_2$] in THF at 67 °C with 150 psi of syngas (1:1 CO/H_2) followed by Wittig olefination at room temperature with 1-triphenylphosphoranylidene-2-propanone to afford γ-acetoxy-α,β-unsaturated ketone **6m1** in 93 % yield (> 95 % *E*). Several chemical methods were attempted to affect deacetylation, the results were low yield of product and complex mixtures of side reactions. Enzymatic deacetylation with *Pseudomonas fluorescens* lipase in pH 7 buffer resulted in slow conversion and low yields. However, hydrolysis was better affected with lipase from *Candida rugosa* at a slightly elevated temperature (45 °C) to give γ-hydroxy-α,β-unsaturated ketone **6l1** in 77 % yield. Finally the formation of the THP ring was affected by a TBAF-mediated desilylation/ oxa-Michael cascade to afford (+)-decarestrictine L (**6a2**) in 71 % as a single diastereomer after chromatography. It should be noted that the TBAF-mediated desilylation oxa-Michael cascade was done with the acetate in place and produced C3-acetoxy decarestrictine L (not shown) but only as a 4:1 mixture of diastereomers. All characteristic data for synthetic **6a2** closely matched the data reported in the literature, however the 4-bromobenzoate ester (**6m2**) of decarestrictine L was made and both the relative and absolute stereochemistry were confirmed by X-ray crystallography.

Scheme 6m



In summary (-)-pyrenophorol (**6a1**, Summary Scheme 6n) was synthesized in 5 steps from the known alkyne **6a3** (7 steps from commercial material) in 32 % overall yield. A Ru(II)-catalyzed hydroacetoxylation of alkyne **6a3** yielded *Z*-enol acetate **6k1** in 92 % yield (58.9 mmol scale) with 97 % *Z*-selectivity. The AHF of **6k1** with the Landis ligand (*S,S,S*)-**BDP** produced α-acetoxy aldehyde **6k2** as the sole product by ^{1}H-NMR and subsequent Wittig olefination afforded α,β-unsaturated *t*-Bu ester **6k3** in 98 % yield (10.6 mmol scale, 95 % *E*). Simultaneous cleavage of both the TBS ether and *t*-Bu ester were cleanly affected by Montmorillonite K-10 to give hydroxy acid **6k4** in 97 % yield. A head-to-tail Mitsunobu dimerization of hydroxy acid **6k4** was accomplished using DBAD, Ph_3P in THF at 5 mM substrate concentration to produce bis-acetoxy pyrenophorol **6f8** in 48 % yield. Finally enzymatic deacetylation using lipase from *Pseudomonas fluorescens* furnished (-)-pyrenophorol (**6a1**) in 77 %. The relative and absolute configuration of (-)-pyrenophorol (**6a1**) was confirmed by X-ray crystallography and matched the reported crystal structure. Our synthesis of (-)-pyrenophorol (**6a1**, 5 steps LLS, 32 % overall yield) compares very favorably with previous enantioselective syntheses (11-16 steps (LLS), and 1.6-10.7 % overall yield).

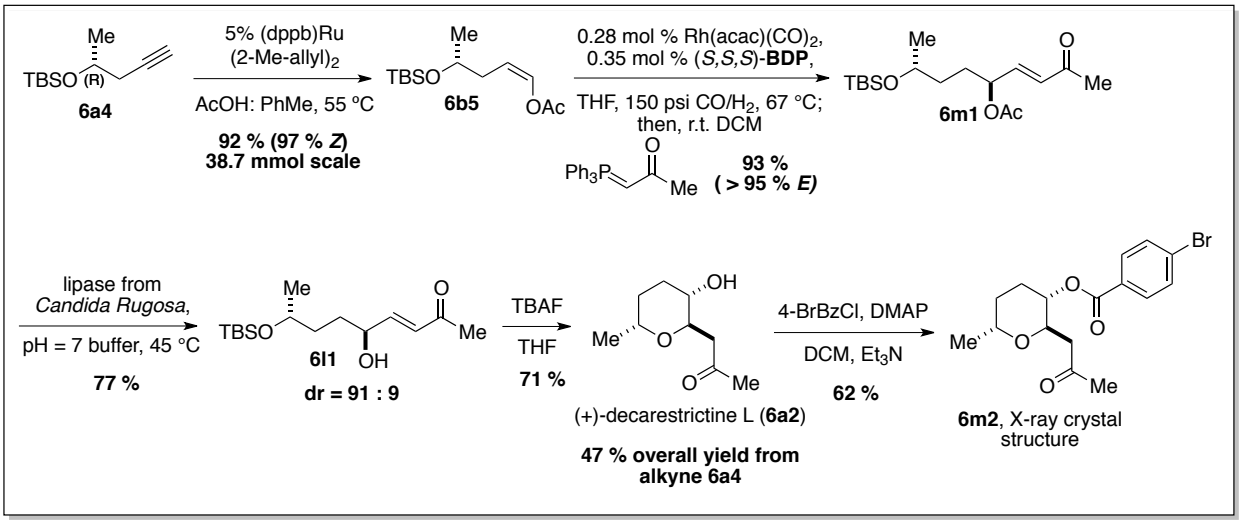
Summary Scheme 6n: (-)-Pyrenophorol



Also, (+)-decarestrictine L (**6a2**, Summary Scheme 6o) was synthesized in 4 steps from known alkyne **6a4** (6 steps from commercial material) in 47 % overall yield. A large scale Ru(II) catalyzed hydroacetoxylation of known alkyne **6a4** proceeded with excellent regio- and stereoselectivity (97 % *Z*) to afford *Z*-enol acetate **6b5** in 92 % yield. The AHF/ Wittig olefination tandem reaction of *Z*-enol acetae **6b5** produced γ-acetoxy-α,β-unsaturated ketone **6m1** in 93 % yield (95 % *E*). An enzymatic hydrolysis of the C3-acetate with lipase from Candida rugosa afforded γ-hydroxy-α,β-unsaturated ketone **6l1** in 77 % yield (91:9 dr by HPLC). Finally a TBAF-mediated desilylation/ oxa-Michael cascade was used to form the THP ring and produce (+)-decarestrictine L (**6a2**) in 71 % yield, and the relative and absolute configuration confirmed by X-ray crystallography of the 4-bromobenzoate ester **6m2**. Our synthesis of (+)-decarestrictine L (**6a2**, 4 steps LLS, 47 % overall yield) compares very favorably with previous enantioselective syntheses (7-20 steps (LLS), and 2.3-22 % overall yield). These two syntheses uniquely demonstrate the dramatic increase in overall efficiency from judicious

incorporation of Rh(I)-catalyzed AHF/ Wittig olefination tandem reactions with the Landis **BDP** ligands and stabilized phosphorus ylides into the synthetic strategy in terms of step counts and overall yields relative to previous efforts.

Summary Scheme 6o: (+)-Decarestrictine L



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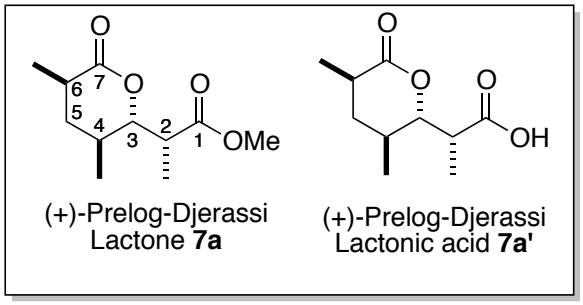
Chapter 7: Background and Previous Syntheses of (+)-Prelog-Djerassi Lactone (Since the 1990 Martin Review)

Chapter7a: Background and Previous Syntheses of (+)-Prelog-Djerassi Lactone (Since the 1990 Martin Review)

The Prelog-Djerassi lactone (**7a**) (Figure 7a) was originally isolated in 1956 by Prelog and Djerassi as an oxidative degradation product from neomethymycin, methymycin, narbomycin, and picromycin.[1, 2] The full stereochemistry was elucidated by Rickards and Smith in 1970.[3,4] Since then, the PD lactone (**7a**) and the PD lactonic acid **7a'** (Figure 7a) have served as benchmark molecules to showcase synthetic methodologies. An instructive variety of strategies have been used to synthesize **7a** including two non-stereoselective approaches,[5a-b] the use of architecturally biased scaffolds,[6-15] and carbohydrate-based syntheses.[16-20] Many methods have been employed to construct this stereochemically rich lactone, including aldol reactions,[8, 9, 21-26] carbonyl crotylations,[27-31] and assorted pericyclic reactions including [4+2] cycloaddition,[32] ene reaction,[33] and Claisen-,[34, 35] [2,3] Wittig-,[36, 37] and Ireland-Claisen rearrangements.[38] Electrophilic additions to alkenes have also been used including mercuric ion induced cyclization,[39] acyclic 1,5-diene hydroboration,[40, 41] Sharpless asymmetric epoxidation,[42, 43] and phenyldimethylsilylcuprate 1,4-addition to an α,β-unsaturated ester.[44] Of the previous syntheses, 14 of them were racemic and required between 5 and 19 steps in the longest linear sequence (LLS).[5a,5b,14-18,28,29,32,37-39,41] Twenty of the previous syntheses relied on the chiral pool to make **7a** with synthetic steps ranging anywhere from 7 to 22 (LLS).[5a,5b,10,12,16-19,21,24,26,27,30,31,34-36,38,43] Among the 9 enantioselective syntheses, the shortest ones took 8 steps and the longest 28 steps (LLS).[8,9b,14,21-23,25,40,44] Clearly the PD lactone (**7a**) has provided a context to display many methods and strategies for polypropionate natural product synthesis. Martin[45] published a comprehensive review of all the syntheses up to 1990. Summaries of the syntheses of the Prelog-Djerassi lactone (**7a**) and PD lactonic acid (**7a'**) since 1990 are presented in the following chapters.

Figure 7a:



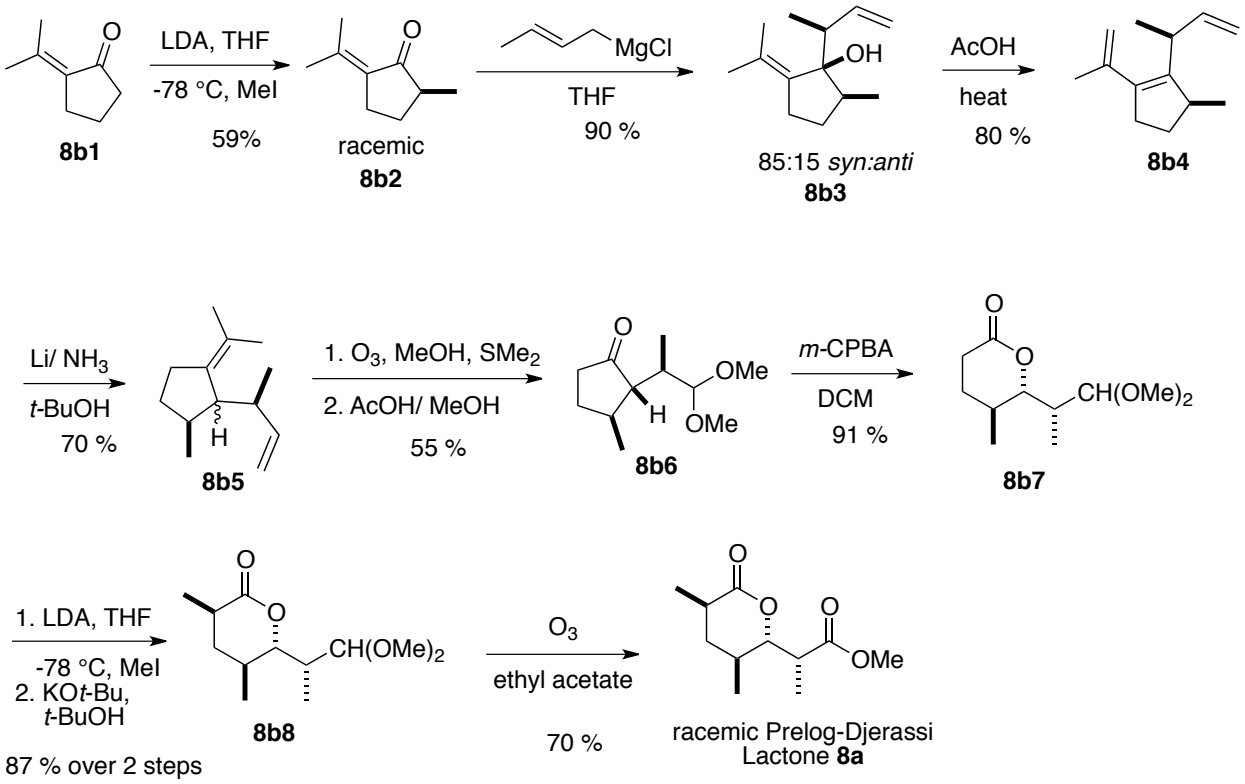
Name/Year	Steps (Longest Linear Sequence)	Yield %	Key Reactions
Santelli/ 1994*	10	9.1	Diastereoselective ketone crotylation
Irie/ 1992	6	40	Methylation of γ,δ-epoxy acrylate
Pilli/ 1996	8	30	Evans aldol
Campagne/ 2001	4	16	Asymmetric vinylogous aldol
Santelli/ 1990	8	41	Baeyer-Villager
Oppolzer/ 1997	8	17	Chiral sultam boron aldol
Parsons/ 1998	14	12	Ireland-Claisen Rearrangement
Fleming/ 1998*	27	0.98	Silyl cuprate S_N2'
Santelli/ 1993	6	56	Dienolate Carroll rearrangement

* racemic synthesis

Chapter 8b: Santelli's Racemic Synthesis of the Prelog-Djerassi Lactone

Several syntheses of the Prelog-Djerassi lactone (PD lactone **8a**) have been published by Santelli[15] and coworkers. They published a racemic synthesis of the PD lactone **8a** from the 2-propanylidene cyclopentanone **8b1** (Scheme 2b). Methylation at the 2-position was effected with LDA, THF and MeI. A diastereoselective crotylation of the ketone was done with crotylmagnesium chloride affording the tertiary alcohol **8b3** with good facial selectivity and decent (85:15 *syn: anti*) selectivity for the new methyl stereocenter. An acid catalyzed dehydration gave the 1,3,6-triene **8b4**, followed by a 1,4-reduction with Li/NH3 to give the 1,6-diene **8b5** as a 1:1 mixture of diastereomers. Ozonolytic cleavage of the 2 alkenes followed by acid catalyzed dimethyl acetal formation gave **8b6** as a single diastereomer. A Baeyer-Villager oxidative ring expansion afforded lactone **8b7**. A common method to install the C6-Me has been enolization of the unsubstituted lactone with LDA and quenching with MeI to give a mixture of diastereomers that is then equilibrated to the desired (6*R*)-Me stereocenter with *t*-BuOK/ *t*-BuOH.[46] Methylation at the C6-position was done in this manner. The mixture of diastereomers was then equilibrated to the desired diastereomer **8b8** with *t*-BuOK/ *t*-BuOH.[46] Finally ozonolysis of the dimethyl acetal gave the PD lactone **8a** as a racemate.

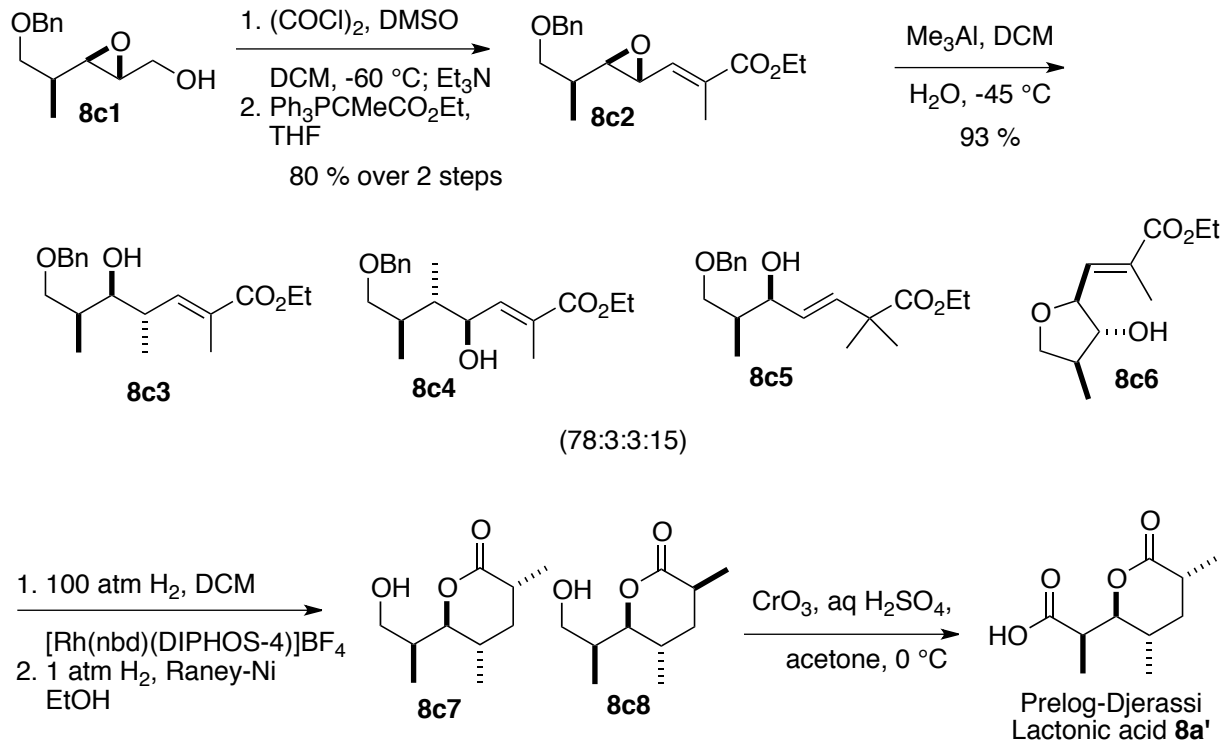
Scheme 8b: Santelli's Racemic Synthesis of the Prelog-Djerassi Lactone



Chapter 8c: Irie's Synthesis of the Prelog-Djerassi Lactonic Acid 8a'

Irie's[43] synthesis of the PD lactonic acid **8a'** began with the known chiral epoxide **8c1**[47](Scheme 2c). Swern oxidation of the primary alcohol followed by Wittig olefination gave α,β–unsaturated ester **8c2**. Their strategic methylative epoxide opening with Me_3Al gave a mixture of alcohols **8c3**, **8c4**, **8c5**, and **8c6** (78:3:3:15 respectively). Alcohols **8c3** and **8c4** could be separated from **8c5** and **8c6** but not from each other. Using a hydroxyl directed Rh-catalyzed asymmetric hydrogenation according to the Evan's procedure[48] the olefin was reduced to set the C6 stereocenter. The separable diastereomeric lactones **8c7** and **8c8** were obtained after Bn ether cleavage. Finally a Jones oxidation of the primary alcohol gave the PD lactonic acid **8a'**.

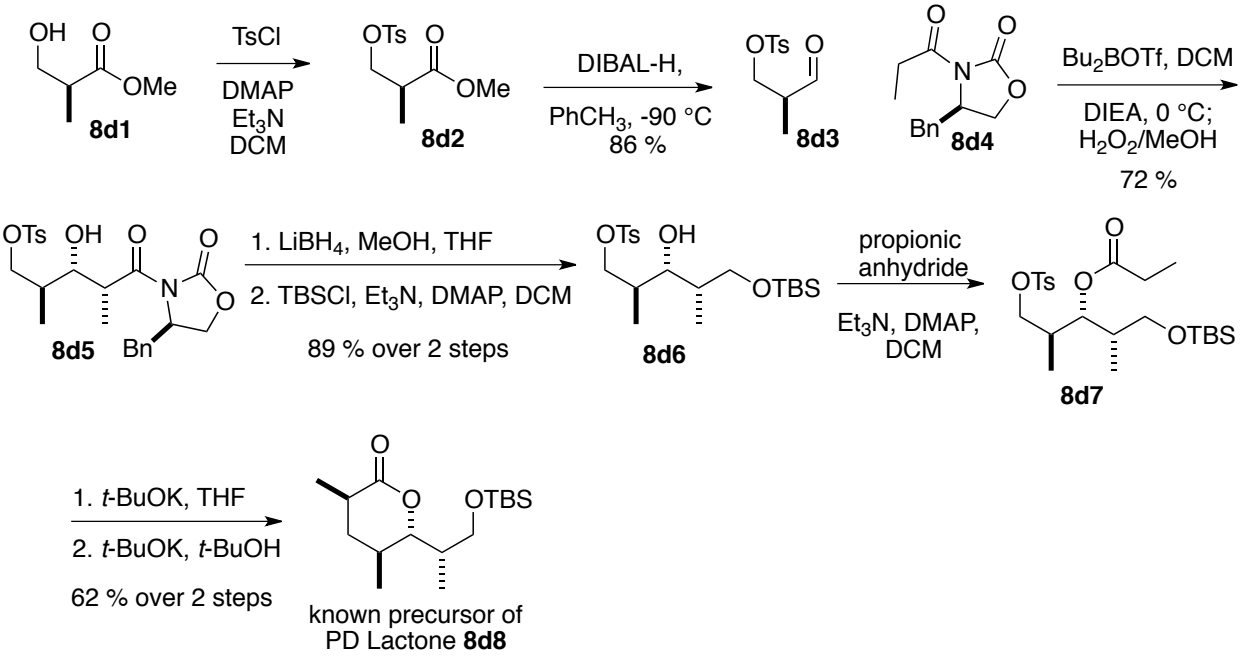
Scheme 8c: Irie's Synthesis of the Prelog-Djerassi Lactonic Acid 8a'



Chapter 8d: Pilli's Synthesis of the Prelog-Djerassi Lactone Known Precursor

In 1996 Pilli[24] and coworkers made a known precursor **8d8**[10](Scheme 2d) of the PD lactone **8a**. Beginning with Roche ester **8d1**, the hydroxyl was protected as the tosylate **8d2** and the ester was reduced with DIBAL-H to give aldehyde **8d3**. Next they did an Evan's chiral auxiliary mediated boron aldol[49] with oxazolidinone **8d3** to give secondary alcohol **8d5** with the desired 2,3-*syn* 3,4-*anti* stereochemistry. Cleavage of the chiral auxiliary was affected with $LiBH_4$ followed by TBS protection of the primary alcohol to afford TBS ether **8d6**. Esterification of the remaining hydroxyl propionic anhydride gave ester **8d7**. Enolization with KO*t*-Bu affected an intramolecular alkylation with displacement of the tosylate and after equilibration of the C6-stereocenter with KO*t*-Bu/ *t*-BuOH gave the known PD lactone precursor **8d8**.

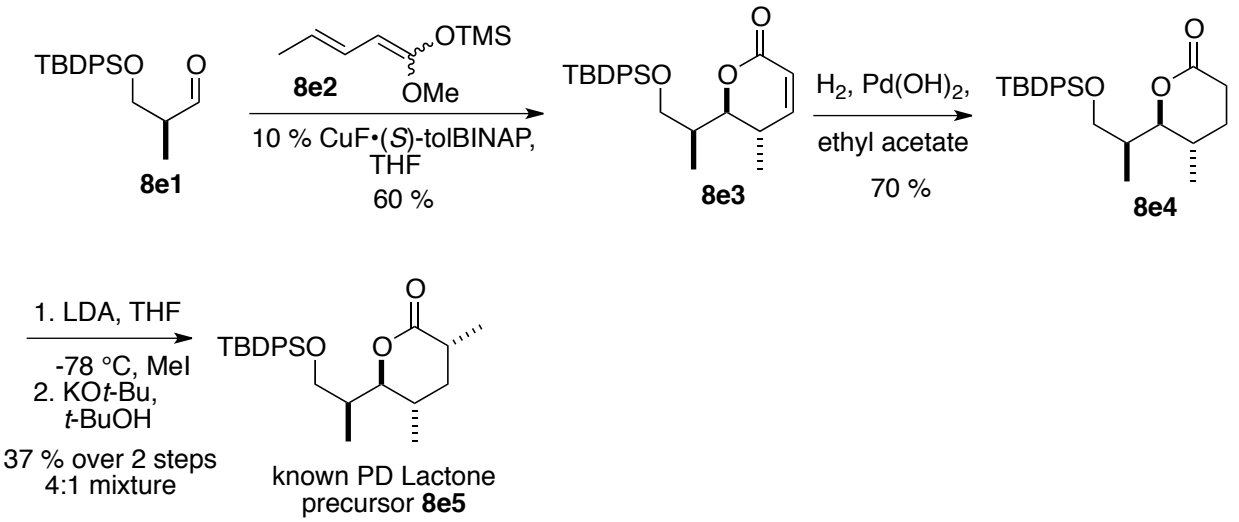
Scheme 8d: Pilli's Synthesis of the Prelog-Djerassi Lactone Known Precursor



Chapter 8e: Campagne's Synthesis of the Prelog-Djerassi Lactone Known Precursor

Campagne's[26] synthesis of the known PD lactone precursor **8e5**[50] (Scheme 2e) began form the TBDPS protected Roche aldehyde **8e1**. They developed an asymmetric vinylogous aldol reaction with the silyl dienylacetal **8e2**.[51] With catalytic CuF•(*S*)-tolBINAP in THF, they affected the aldol reaction to afford the α,β-unsaturated lactone **8e3** directly. Reduction of the alkene gave the saturated lactone **8e4**. Methylation/ equilibration according to known methods gave a 4:1 mixture (desired diasteromer favored) of the known precursor **8e5**.

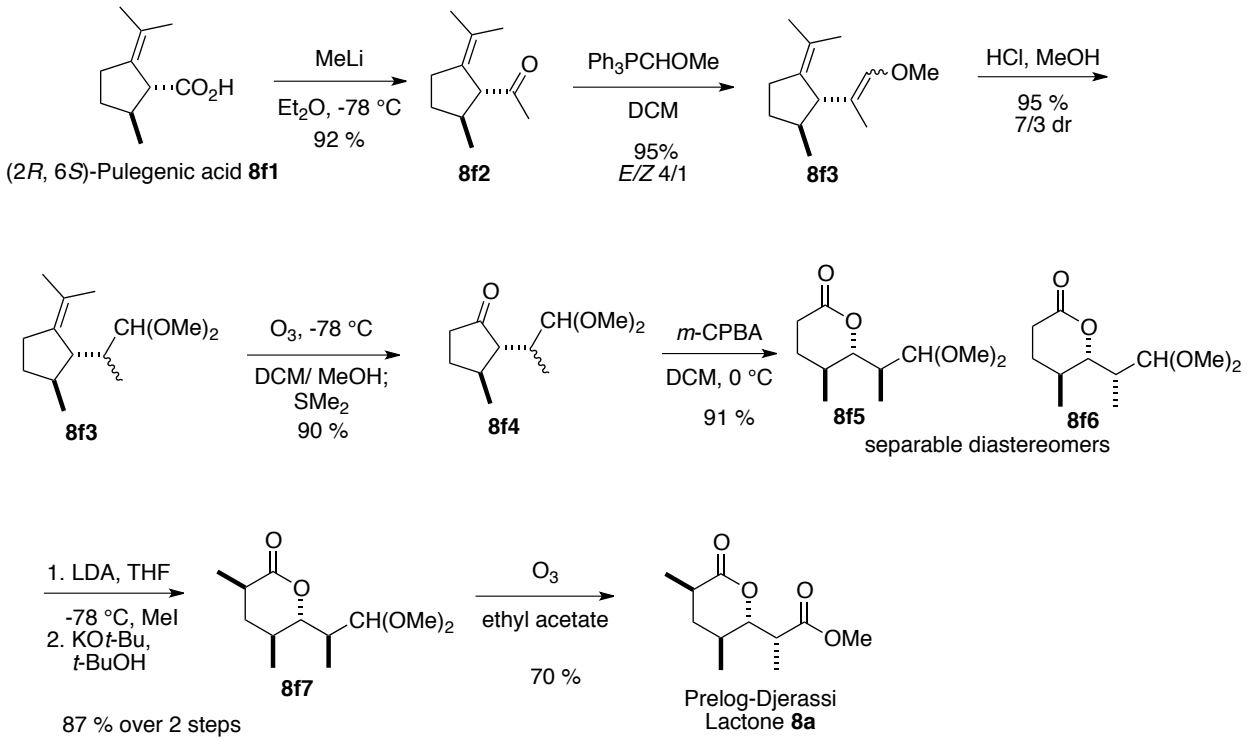
Scheme 8e: Campagne's Synthesis of the Prelog-Djerassi Lactone Known Precursor



Chapter 8f: Santelli's Synthesis of the Prelog-Djerassi Lactone 8a

Santelli[12] also published an asymmetric synthesis of the PD lactone **8a** from (2*R*, 6*S*)-pulegenic acid **8f1** (Scheme 2f). Beginning with an alkylation of the carboxylic acid with MeLi, they obtained the methyl ketone **8f2** in good yield. Wittig olefination fo the ketone gave a 4:1 *E:Z* mixture of methyl enol ether **8f3**. Exposure of the aldehyde with HCl in MeOH and protonation at the α-stereocenter gave a 7:3 mixture of diastereomeric dimethyl acetals **8f3** (favoring the desired diastereomer). Ozonolysis of the alkene gave ketone **8f4**. After Baeyer-Villager oxidation the lactones **8f5** and **8f6** were obtained as separable diastereomers. The desired lactone **8f5** converted to the α-methyl lactone **8f7** via the known protocol.[46] Finally ozonolytic cleavage of the dimethyl acetal gave the methyl ester, completing the synthesis of the PD lactone **8a**.

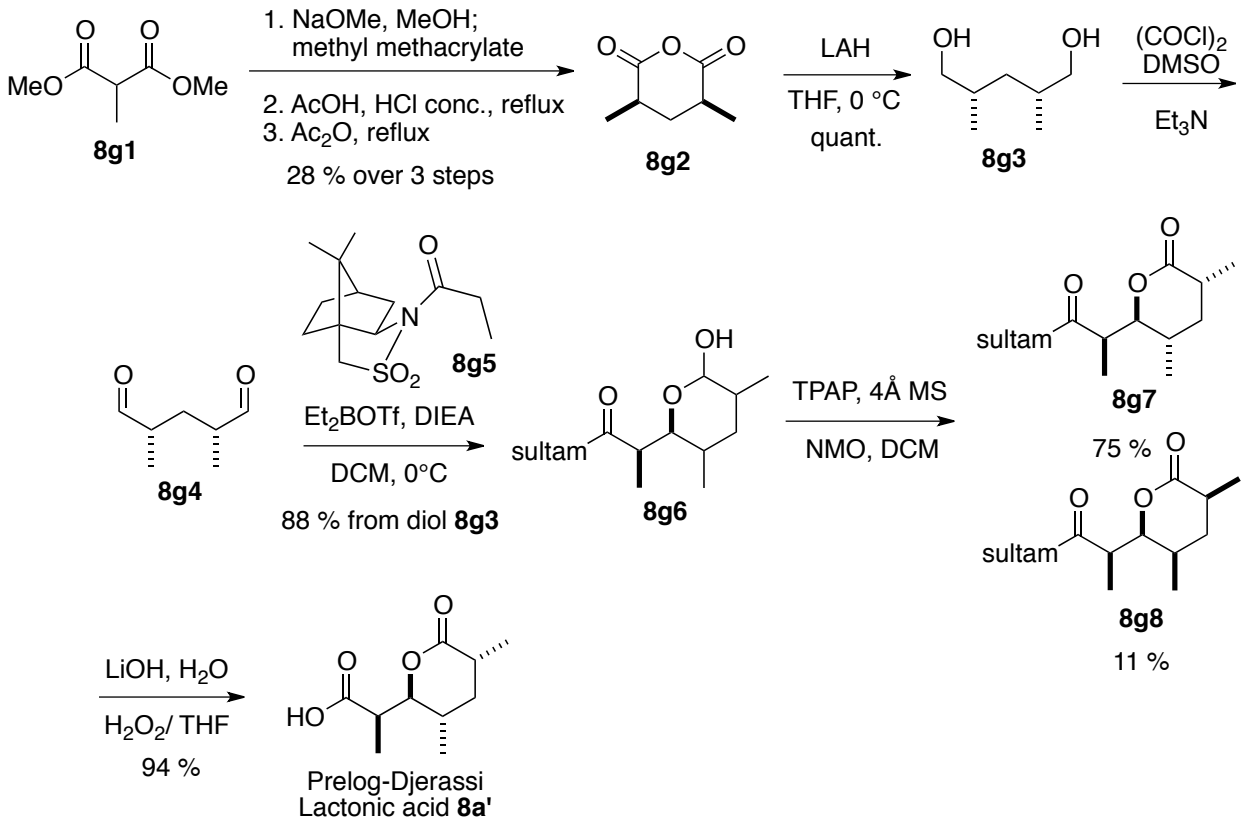
Scheme 8f: Santelli's Synthesis of the Prelog-Djerassi Lactone 8a



Chapter 8g: Oppolzer's Synthesis of the Prelog-Djerassi Lactonic Acid 8a'

In 1997 Oppolzer[25] and coworkers published a synthesis of the PD lactonic acid **8a'** starting from the known *meso*-dialdehyde **8g4**[52] (Scheme 2g), which is available in 5 steps from methyl dimethylmalonate **8g1**. Their synthesis began with a boron aldol reaction of *N*-propionylsultam **8g5** with the *meso*-dialdehyde **8g4** effectively breaking symmetry to give the hemiacetal **8g6** as an inseparable mixture. Oxidation with TPAP/NMO gave the separable lactones **8g7** and **8g8**. Lastly lithium hydroperoxide mediated cleavage of the chiral auxiliary gave the PD lactonic acid 2a'.

Scheme 8g: Oppolzer's Synthesis of the Prelog-Djerassi Lactonic Acid 8a'

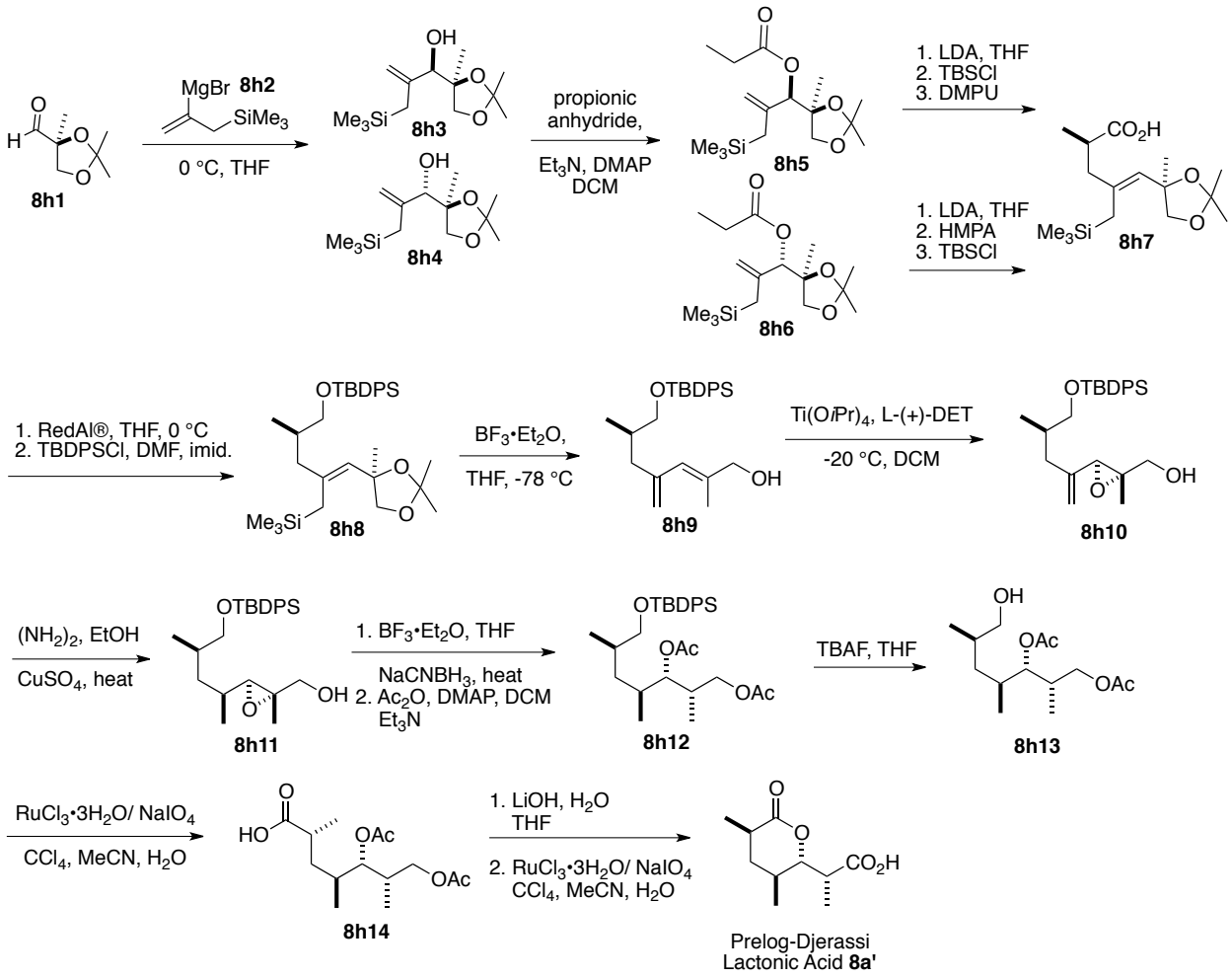


Chapter 8h: Parson's Synthesis of the Prelog-Djerassi Lactonic Acid

Parsons[38] and coworkers accomplished a synthesis of the PD lactonic acid **8a'** featuring an Ireland-Claisen rearrangement[53] and a key fragmentation of a silyl allylic acetal. Beginning with the known aldehyde **8h1**[54] (Scheme 2h), nucleophilic addition with 1-trimethylsilyl-2-propenylmagnesium bromide **8h2** gave the mixture of *syn* and *anti* alcohols **8h3** and **8h4**. Both alcohols were converted to their corresponding propionate esters **8h5** ands **8h6**, respectively. With these diastereomeric esters in hand, they were able to develop conditions to convert both to the desired diastereomeric carboxylic acid **8h7**. Ester **8h5** was first deprotonated with LDA and trapped as the *E*-silyl ketene acetal before the stereospecific Ireland-Claisen rearrangement to give **8h7**. Meanwhile with a slight alteration of conditions, ester **8h6** was enolized then isomerized before trapping as the Z-silyl ketene acetal in order to converge on the same acid **8h7**

via the Ireland-Claisen rearrangement. Reduction of the acid with RedAl® to the primary alcohol and TBDPS protection gave silyl ether **8h8**. Next they affected a BF_3•Et_2O mediated desilylation with concomitant fragmentation of the acetal to afford alcohol **8h9**. Sharpless asymmetric epoxidation[55] with L- (+)-DET gave epoxide **8h10**. A copper mediated diastereoselective diimide reduction of the remaining alkene gave the last Me-stereocenter in **8h11**. Reductive opening of the epoxide followed by the acetalization of both alcohols gave diacetate **8h12**. Desilylation with TBAF gave alcohol **8h13** followed by oxidation to the acid **8h14**. Saponification of the acetates gave the 6-membered ring lactone with the appended primary alcohol, which was oxidized to give PD lactonic acid **8a**.

Scheme 8h: Parson's Synthesis of the Prelog-Djerassi Lactonic Acid

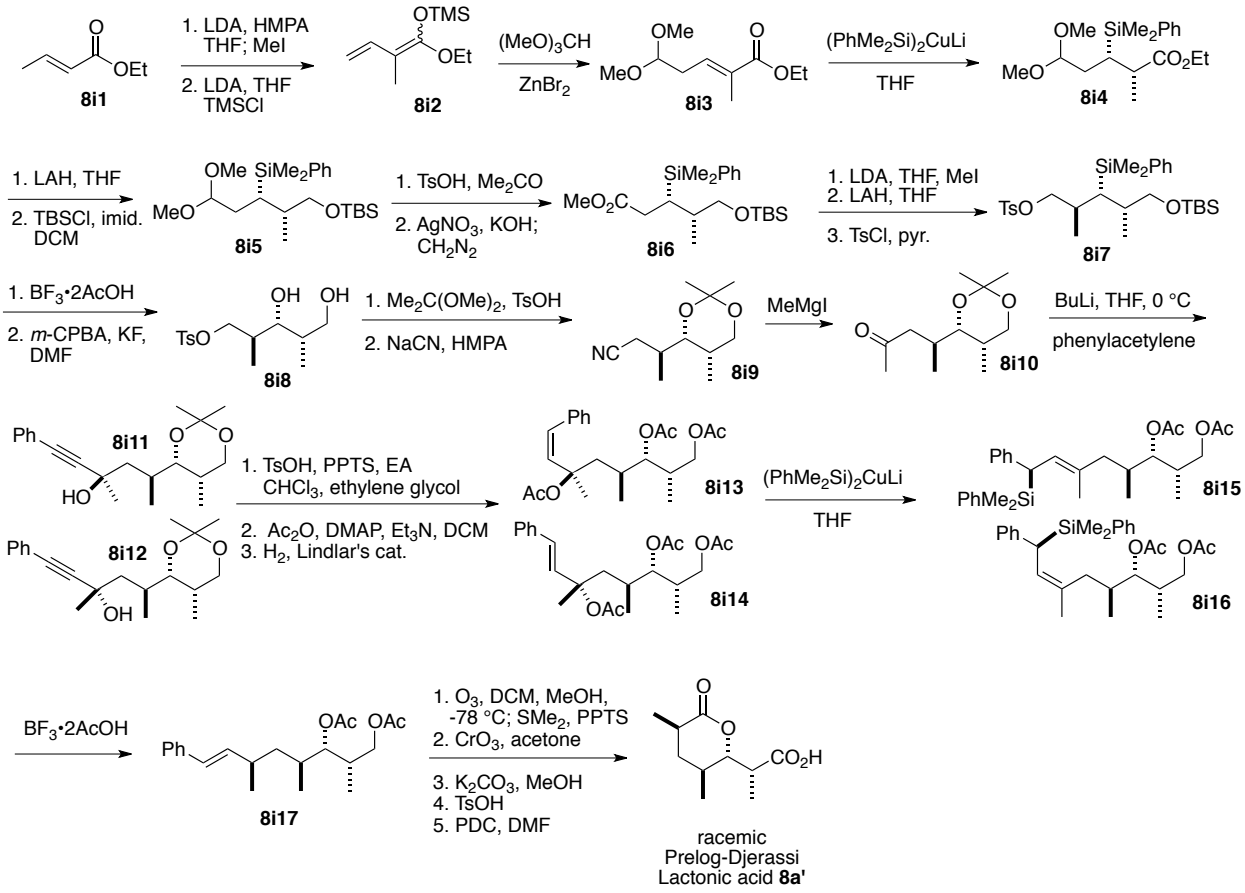


Chapter 8i: Fleming's Synthesis of Racemic Prelog-Djerassi Lactonic Acid

In 1998 Fleming[56] *et. al.* published a racemic synthesis of the PD lactonic acid **8a'**. They started with ethyl crotanoate **8i1** (Scheme 2i) and affected an α-mehtylation with LDA/ MeI followed by another dieneolate formation with trapping as the *tert*-butyldimethylsilyl dieneylacetal **8i2**. Reaction with trimethyl orthoformate under Lewis acid catalysis affected a γ-selective vinylogous aldol to afford ethyl ester **8i3**. Next a conjugate addition with phenyldimethylsilylcuprate gave the β-silane **8i4** with good *syn* selectivity. Reduction of the ester with LAH followed by TBS protection gave **8i5**. Exposure of the aldehyde with TsOH

followed by oxidation to the acid and CH_2N_2 methylation gave methyl ester **8i6**. A diastereoselective α-methylation was done under substrate control to install the α-methyl group *anti* to the silicon stereocenter. Reduction of the ester followed by tosylation gave primary tosylate **8i7**. Next they affected a silyl to hydroxyl conversion via protodesilylation of the phenyl group followed by oxidation with *m*-CPBA and fluoride mediated desilylation to give diol **8i8**. The 1,3-diol was protected as the dimethyl acetal and the tosylate displaced by NaCN to give the primary nitrile **8i9**. Conversion of the nitrile to the methyl ketone was affected with MeMgI to give ketone **8i10**. Nucleophilic attack on the carbonyl with lithiophenylacetylide gave a mixture of the tertiary alcohols **8i11** and **8i12**. Cleavage of the acetal and protection of all three hydroxyls with acetic anhydride gave the triacetates **8i13** and **8i14**. At this point the acetates were displaced via a stereospecific S_N2' with phenyldimethylsilylcuprate to give the *E* and *Z* olefins **8i15** and **8i16** which converged on a single diastereomer **8i17** upon protodesilylation with BF_3•2AcOH. A final sequence of transformations was done to reach the target. First an ozonolysis of the alkene to the aldehyde was followed by Jones oxidation to the acid. Then the acetates were cleaved and TsOH catalyzed lactonization followed by a PDC oxidation of the primary alcohol to the acid **8a'** completing the racemic synthesis.

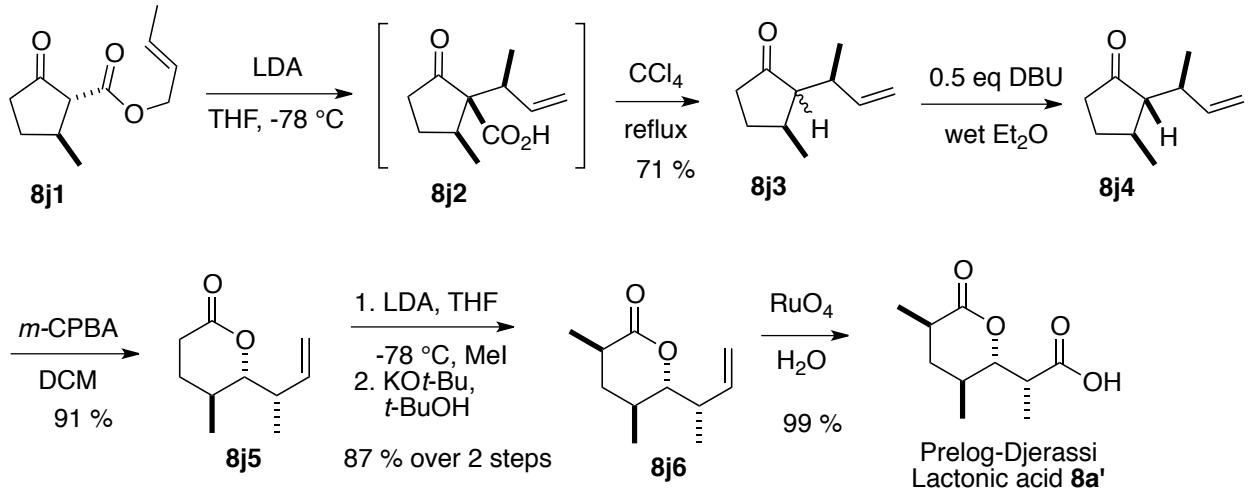
Scheme 8i: Fleming's Synthesis of Racemic Prelog-Djerassi Lactonic Acid



Chapter 8j: Santelli's Synthesis of the Prelog-Djerassi Lactonic Acid

Santelli's[57] third synthesis was of the PD lactonic acid **8a'**, features a dieneolate Carroll[58] rearrangement of the known β-keto ester **8j1**[12](Scheme 2j). The β-keto ester **8j1** was deprotonated with LDA to affect the rearrangement to the β-carboxylic acid **8j2** that underwent decarboxylation to give ketone **8j3** as a mixture of diastereomers. Epimerization with DBU in wet ether affected equilibration of the α-stereocenter to give the favored diastereomer **8j4**. This ketone was reacted with *m*-CPBA to affect the Baeyer-Villager oxidation affording lactone **8j5.** Methylation and equilibration via the known protocol[46] gave **8j6**. Finally, RuO_4 mediated oxidation of the alkene gave PD lactonic acid **8a'** in quantitative yield.

Scheme 8j: Santelli's Synthesis of the Prelog-Djerassi Lactonic Acid



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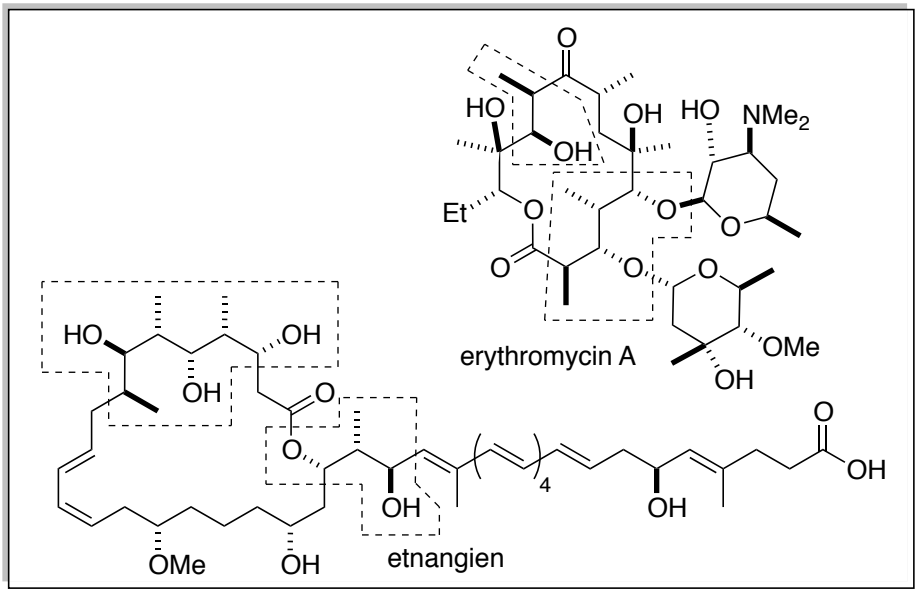
Chapter 8: The Total Synthesis of (+)-Prelog-Djerassi Lactone via Asymmetric Hydroformylation/ Crotylation

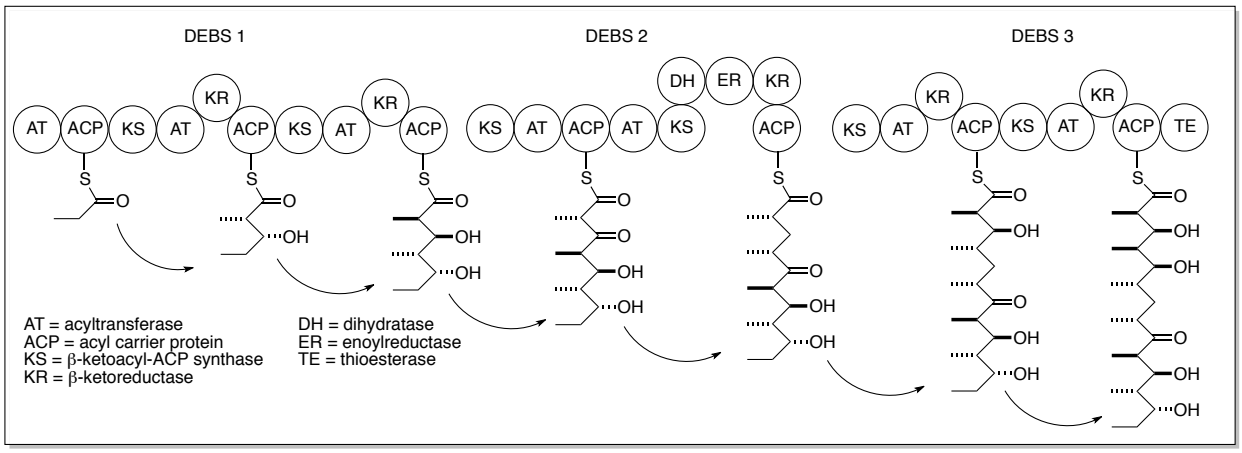
Figure 8a



Polypropionates[1a] are the characteristic structural subunit in polyketide natural products and pharmaceuticals that bear the sequences of methyl- and hydroxyl-bearing stereocenters in the carbon chain. Two examples, erythromycin A and etnangien are shown in Figure 8a with the signature polypropionate segments highlighted. Nature prepares these polypropionate segments via the condensation of propionyl subunits as depicted in Figure 8b. Nature's catalytic system for erythromycin biosynthesis consists of three multifunctional proteins, DEBS 1, DEBS 2, and DEBS 3, each with smaller subunits that perform the specific transformations along the assembly-line style synthetic pathway.[1b] Each of the arrows in Figure 8b represents a condensation cycle containing some or all of the following chemical transformations: transacylation by the acyltransferase enzyme (AT) onto an acyl carrier protein (ACP), ketosynthase (KS) catalyzed β-keto thioester formation, ketoreduction by ketoreductase (KR), dehydration (enoyl dehydratase, DH) and enoyl reduction (enoyl reductase, ER) producing either keto, hydroxy, alkene or methylene centers, respectively. This chain building process is terminated by a thioesterase (TE) that closes the macrocycle yielding 6-deoxyerythronolide B

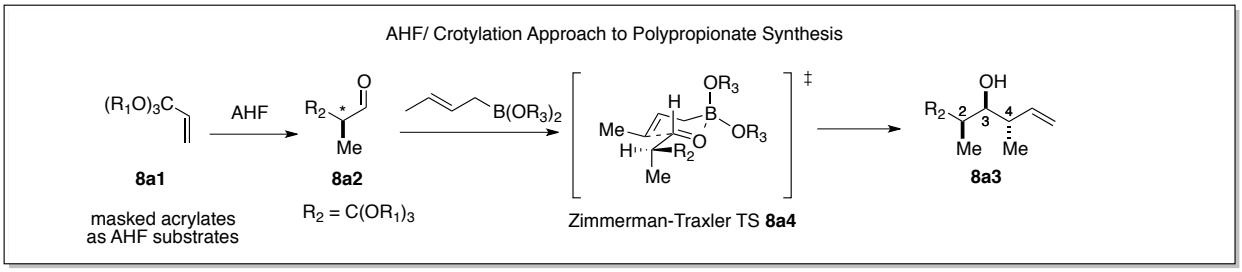
(not shown), which undergoes glycosylation or oxidation to produce various erythromycin antibiotics.[1b] Nature produces these polypropionate antibiotics with great efficiency and exquisite selectivity.

Figure 8b



Many methods for the construction of these polypropionate segments have been developed over the years by synthetic chemists to effect similar transformations as Nature's approach to the alternating methyl-, hydroxyl-, methyl- stereotriads (and higher iterations) including propionate aldol reactions, allenylation, crotylations and epoxide openings to name a few. With the AHF of terminal olefins a new chiral Me-bearing stereocenter is enantioselectively set adjacent to an aldehyde (**8a1** to **8a2**, Scheme 8a). The crotylation of α-methyl chiral aldehydes with crotylboronates has been widely used in polypropionate synthesis[2] (**8a2** to **8a3**) to generate homoallylic alcohols with 3 stereocenters, as such we sought to develop an AHF / crotylation tandem reaction of masked acrylates (**8a1**) to be used in the context of polypropionate natural product total synthesis. Many asymmetric crotylations have been developed using a chiral crotylating reagent as the source of asymmetry.[3] We sought however to combine the high regio- and enantioselectivity of the Rh-**BDP** AHF catalyst system with a substrate controlled crotylation to telescope the influence of the chiral catalyst from the α-methyl bearing

Scheme 8a

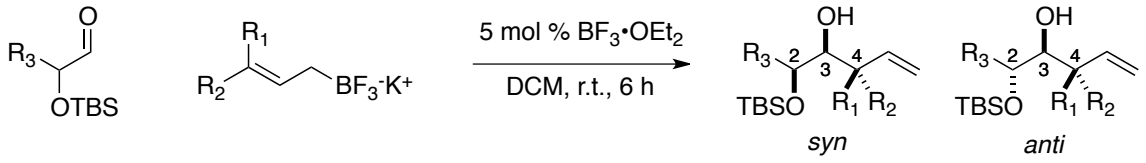


stereocenter (**8a2**) to the other two stereocenters in the homoallylic alcohol (**8a3**) as well. *E*-Crotylboronates are known to react with α-chiral aldehydes with Felkin-Anh selectivity via Zimmerman-Traxler transition state **8a4** to produce the 2,3-*syn*-3,4-*anti*-homoallylic alcohol **8a3**.[4] The facial selectivity is dictated by the large group (R vs Me) being oriented away from the approaching nucleophilic carbon of the *E*-crotylboronate while the α-Me group is oriented to avoid a *syn*-pentane interaction with the methyl group on the *E*-crotylboronate.[5] For the AHF/ crotylation tandem reaction to work well, an AHF-substrate had to be chosen judiciously such that it would undergo AHF with sufficient regio- and enantioselectivity favoring the branched aldehyde as well as having the proper influence on the crotylation reaction.

Batey and coworkers have described diastereoselective substrate controlled allylation and crotylation of α-chiral aldehydes,[6] with representative results shown in Table 8a. Using the potassium allyl- and crotyltrifluoroborate salt as their crotylating reagent they could generate the active crotyl-BF_2 species *in situ* with 5 mol % BF_3•Et_2O in DCM or 10 mol % TBAI in DCM/H_2O. The first two entries show that the allylation only displayed modest diastereoselectivity while the crotylations displayed a higher degree of diastereoselectivity (entries 3-6). The *Z*-crotyl trifluoroborate salt showed excellent 2,3-*anti*-selectivity (entry 3) while the *E*-crotyl trifluoroborate salt only displayed modest 2,3-*syn*-selectivity (entry 4). When R_3 on the aldehyde was Ph (entries 5 and 6), both crotylating reagents favored the *anti*-

diastereomer with similar selectivity (90:10 *anti:syn*) in agreement with a non-chairlike transition state, but rather a Cram-chelate transition state.[7]

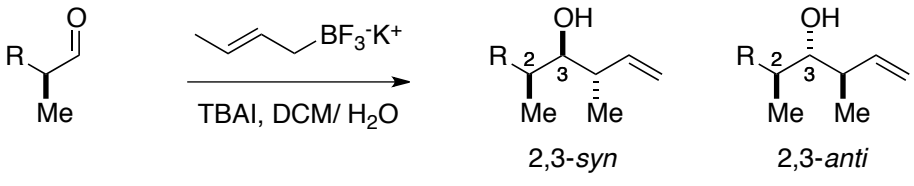
Table 8a

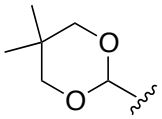
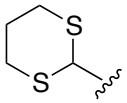
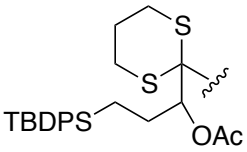


Entry	R_1	R_2	R_3	*syn:anti*	Yield (%)
1	H	H	Me	30:70	69
2	H	H	Ph	35:65	91
3	Me	H	Me	5:95	73
4	H	Me	Me	75:25	72
5	Me	H	Ph	10:90	85
6	H	Me	Ph	10:90	82

Saikawa[8] and coworkers also showed that the crotylation of β-branched α-methylaldehydes proceeds with good to excellent stereoselectivity (Table 8b). Their data is in agreement with Roush's assessment[7] that having a sufficiently large α-substituent in addition to the α-methyl group increases Felkin-Anh diastereoselectivity. They demonstrated that the bulkier the group in the β-position is, the higher the Felkin-Anh selectivity (entry 1 vs 2). The acetal and thioacetal are sufficiently larger than the α-Me group and increase the diastereoselectivity via avoidance of destabilizing gauche pentane interactions in the chair like transition state. They also demonstrated that having another degree of branching (entry 3 vs 2 and 1) significantly increases the diastereoselectivity; producing only one diastereomer.

Table 8b

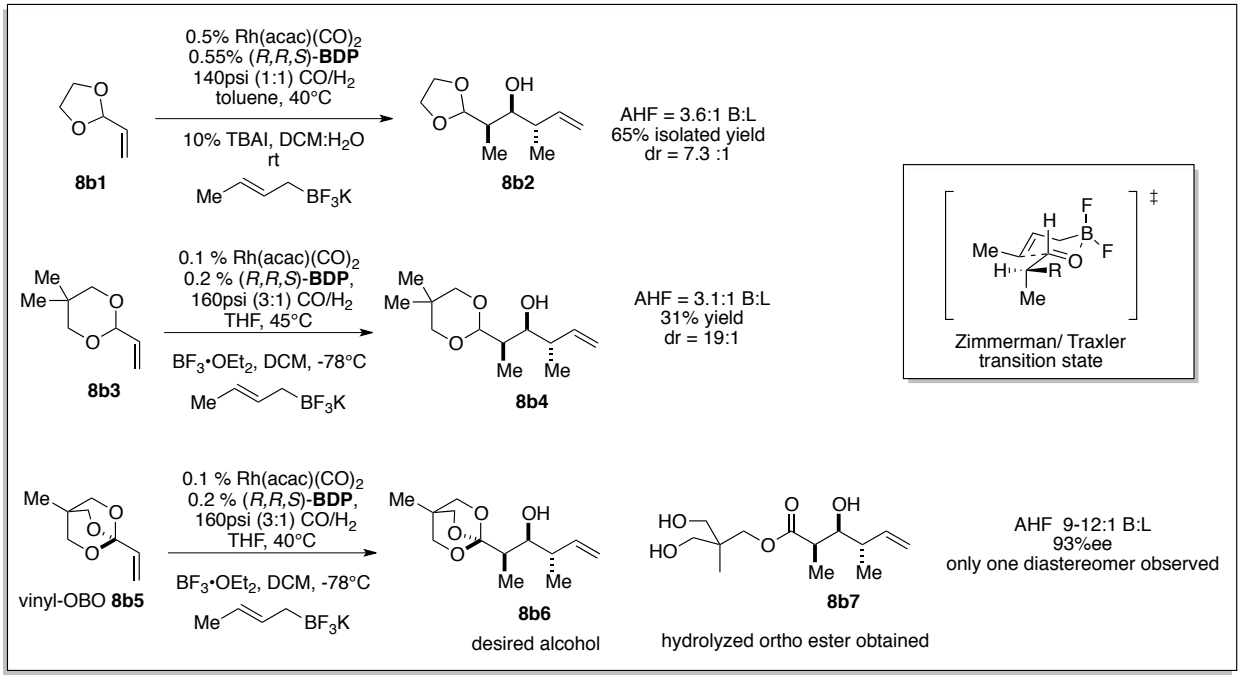


Entry	R	Yield (%)	ratio (2,3-*syn:* 2,3-*anti*)
1		85	11:1
2		97	24:1
3		95	2,3-*syn* only

Our strategy toward a successful AHF/ crotylation tandem reaction began with choosing an appropriate olefin that would react with good regioselectivity in the AHF and exhibit good diastereoselectivity with the potassium crotyltrifluoroborate developed by Batey. Landis[9] *et. al*. have reported the AHF of 2-vinyl-1,3-dioxolane (**8b1**, Scheme 8b) proceeds with good regioselectivity and enantioselectivity (4.2:1 B:L, 92 % ee). With the understanding that the β-branching was necessary to affect good Felkin-Anh diastereoselectivity in the crotylation, we chose 2-vinyl-1,3-dioxolane (**8b1**) as our first AHF/ crotylation substrate. In our hands, the AHF of the 2-vinyl-1,3-dioxolane (**8b1**) proceeded with good regioselectivity (3.6:1 B:L), albeit a little lower than reported, to produce the α-Me chiral aldehyde which was then subjected to crotylation with potassium crotyl trifluoroborate to give homoallylic alcohol **8b2** as a mixture of diastereomers (7.3:1 dr) in favor of the Felkin-Anh product (2,3-*syn*-3,4-*anti*). Desiring a higher diastereoselectivity for the crotylation, the bulkier dioxane **8b3** was used. The AHF proceeded

similarly to that of **8b1** however the diastereoselectivity of the crotylation was much greater (19:1) when the crotylation was done at low temperature. Still convinced we could do better, we switched from an acetal to an ortho ester incorporating an extra point of branching. A perusal of the literature of ortho esters of acrylic acid led us to the 4-methyl-1-vinyl-2,6,7-trioxabicyclo[2.2.2]octane ortho ester (vinyl-OBO **8b5**, Scheme 8b) developed by Corey and coworkers.[10]

Scheme 8b

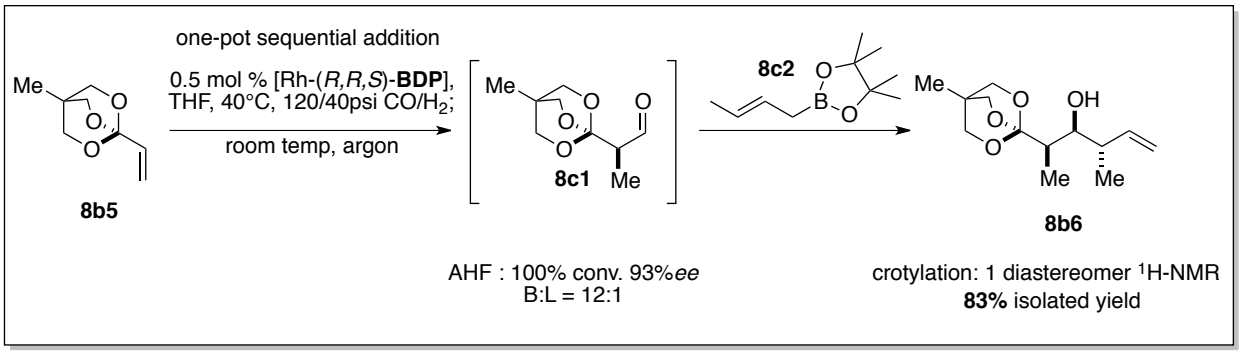


The AHF of vinyl–OBO **8b5** proceeded well with low catalyst loading (0.1 %) and good regio- and enantioselectivity (9-12:1 B:L, 93 % ee). The crotylation with potassium crotyltrifluoroborate gave only the hydrolyzed diol ester **8b7**, but as a single diastereomer. Several attempts were made to prevent the decomposition, but failed to keep the ortho ester intact. Searching for another crotyl boronate that would operate under substrate control we chose *trans*-crotyl pinacolato boronic ester[11] **8c2** (Scheme 8c). The crotylation with **8c2** proceeded

without any decomposition of the ortho ester and with excellent diastereoselectivity, even at room temperature (Scheme 8c).

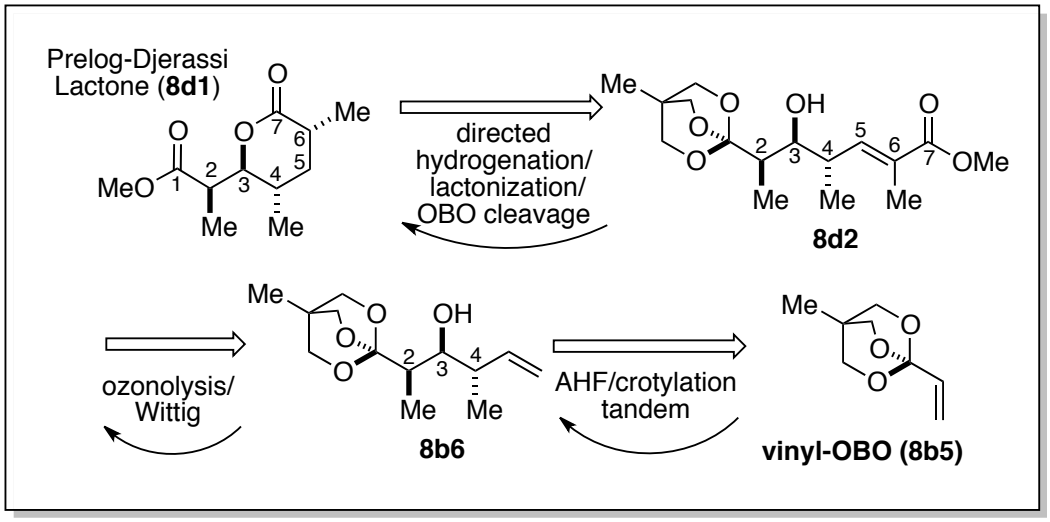
AHF of vinyl-OBO **8b5** proved to be quite sensitive to both temperature and CO-pressure effects. If the temperature was less than 40 °C, the reaction was too slow and if the temperature was higher than 40 °C, the regioselectivity decreased. It was also found that the ideal CO/H_2 ratio was 120/40 CO/H_2 in order to maintain the highest regioselectivity (12:1 B:L). If the total pressure of the reaction lessened during the reaction via consumption of syngas then the regioselectivity would decrease. Therefore a limited amount of vinyl-OBO **8b5** could be reacted in a given vessel so as to maximize regioselectivity. The optimized conditions (40 °C, 120/40 psi CO/H2) afforded the aldehyde **8c1** with maximized regio- and enantioselectivity (12:1 B:L, 93 % ee). Once the AHF was complete, the syngas was vented and *trans*-crotyl pinacolato boronic ester **8c2** was added to the reaction vessel at room temperature to affect the substrate controlled crotylation. After separation via chromatography from the minor linear isomer, the 2,3-*syn*-3,4-*anti*-homoallylic alcohol **8b6** was isolated as a single diastereomer in 83 % yield. The enantioselectivity of the AHF was 93 % ee, as determined via chiral SFC analysis of the PMB ether of the reduced aldehyde.

Scheme 8c



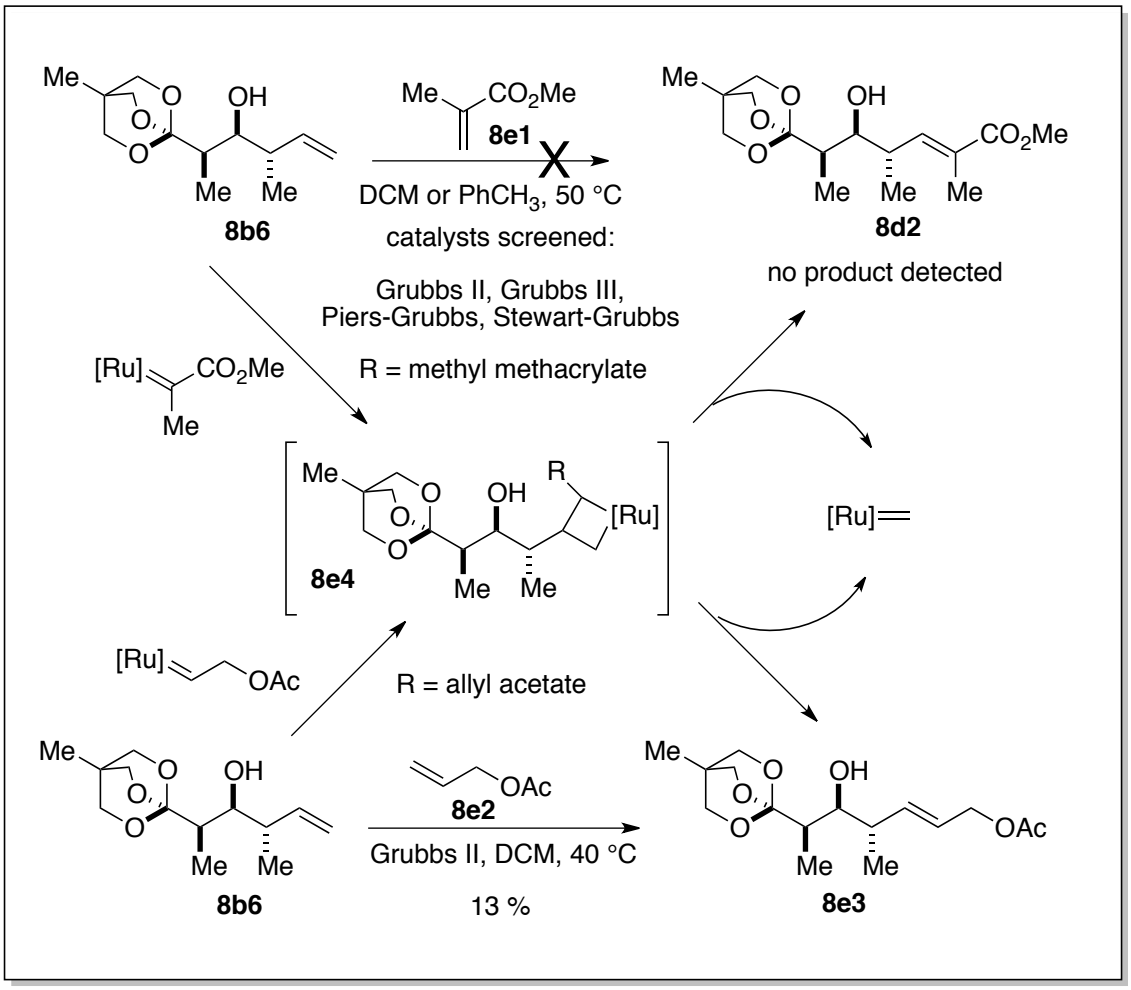
Many methods for polypropionate synthesis have been showcased in the synthesis of the Prelog-Djerassi lactone **8d1** (Scheme 8d), as shown by some of the previous syntheses (Chapter 7). With a successful AHF/ crotylation in hand we sought to apply this to a novel synthesis of **8d1**. As shown by our strategy in Scheme 8d, we saw the AHF/ crotylation tandem reaction as providing the requisite functionality and stereochemistry in C1-C4 positions (PD lactone numbering). The OBO ortho ester would bring in C1 at the proper oxidation state (masked carboxylic acid), avoiding any oxidation step later in the synthesis. The AHF would set the C2-Me stereochemistry with appropriate **BDP** ligand choice, and the substrate controlled diastereoselective crotylation with *trans*-crotyl boronic acid pinacol ester **8c2** would install the C2 hydroxyl and C3 methyl with the correct stereochemistry as well as a terminal olefin at C4-C5. We envisioned a one-step chain homologation from **8b6** to **8d2** via alkene metathesis, incorporating the C6-Me bearing carbon and the C7-Me ester in a single step. Since δ-hydroxy α,β-unsaturated esters such as **8d2** have been shown to undergo hydroxyl directed asymmetric hydrogenation with transfer of stereogenicity,[12] we thought this was an excellent way to set the C6 stereochemistry. In order to access ester **8d2**, we tried a couple of strategies for the incorporation of C6-Me bearing carbon and C7-carbonyl moiety and they are summarized as follows.

Scheme 8d



With homoallylic alcohol **8b6** in hand several attempts were made at a cross-metathesis with methyl methacrylate **8e1** but they all failed (Scheme 8e). When the cross metathesis of alcohol **8b6** and allyl acetate **8e2** was done, the cross metathesis product **8e3** was produced albeit in low yield. This difference in reactivity is probably due to steric hindrance of the OBO-ortho ester along with branching at every carbon on the chain disfavoring Ru-alkylidene formation at the hindered olefin **8b6**. These results suggest that catalyst initiation does not happen at olefin **8b6**. The Ru-alkylidene generated from methyl methacrylate **8e1** is unstable and cross metathesis with the very hindered olefin **8b6** does not proceed. The low yielding (13% yield) cross metathesis with allyl acetate **8e2** suggest that the Ru-alkylidene generated from **8e2** can produce the cross product with **8b6**, just not very well. Convinced that cross metathesis of alcohol **8b6** and methyl methacrylate **8e1** wouldn't proceed successfully, we revised our strategy to a more precedented ozonolysis/ Wittig olefination sequence.

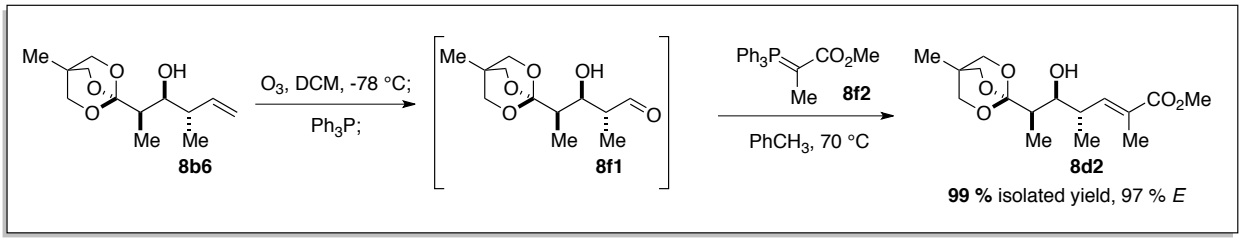
Scheme 8e



A common method for the conversion of terminal olefins into α,β-unsatruated carbonyl moieties is the ozonolysis/ Wittig olefination sequence with stabilized phosphorus ylides. As shown in Scheme 8f, the ozonolysis of alkene **8b6** proceeds without incident to generate β-hydroxy aldehyde **8f1** after workup with Ph_3P. Without isolation of aldehyde **8f1**, Wittig olefination with ylide **8f2** was discovered to require elevated temperatures to proceed. An optimized temperature of 70 °C was found to affect complete conversion while maintaining *E/Z* selectivity (3.79 mmol scale, 91 % yield, 97 % *E*, not shown). This chemistry was found to work even better on a larger scale, alcohol **8b6** (30.95 mmole) was ozonolyzed to the aldehyde **8f1** and

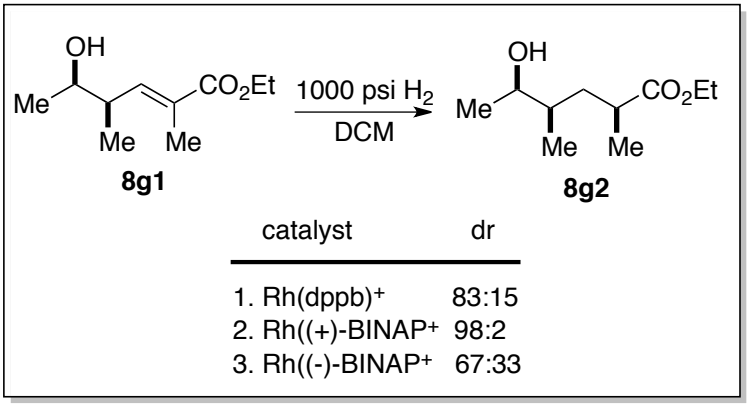
reacted with 2 equivalents of ylide **8f2** to give the desired δ-hydroxy-α,β-unsaturated ester **8d2** in 99 % isolated yield (97 % *E*).

Scheme 8f



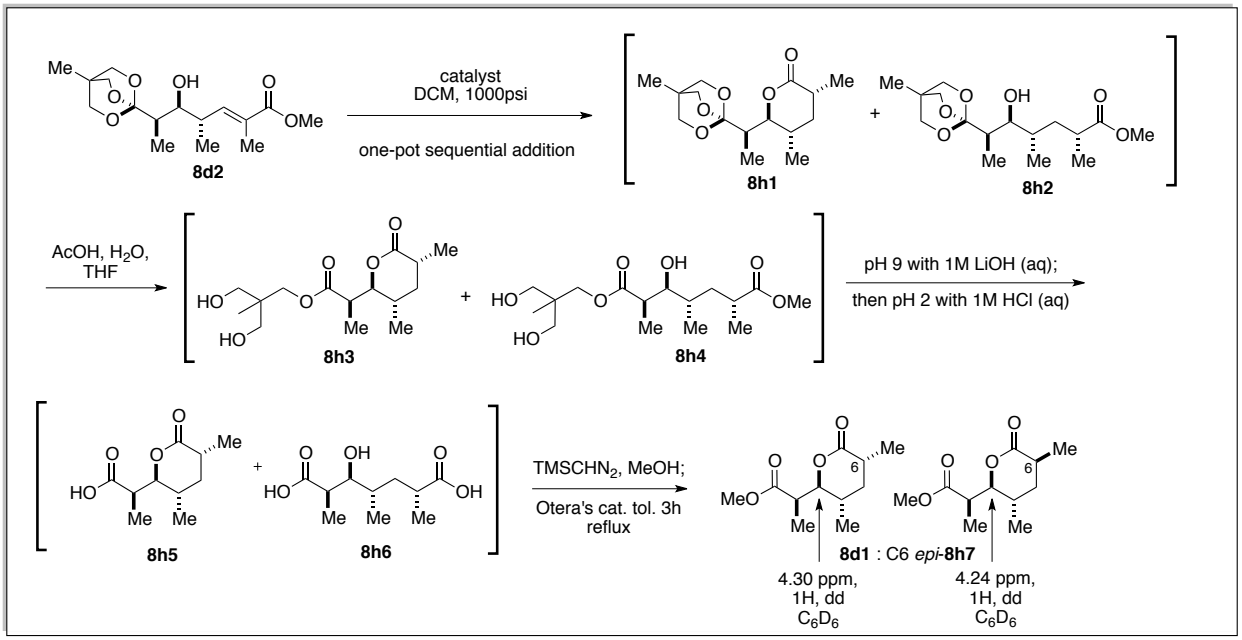
With access to methyl ester **8d2**, we proceeded to explore hydrogenation catalysts to set the C6-methyl stereocenter. Evans[12] and coworkers reported the hydroxyl-directed cationic Rh(I)-catalyzed hydrogenation of δ-hydroxy-α,β-unsaturated ester **8g1** to give fully saturated ester **8g2** (Scheme 8g) with transfer of stereogenicity. With a non-chiral ligand (1,4-diphenylphosphino)-butane (entry 1) they observed a modest diastereoselectivity (83:15 dr). When they incorporated the chiral bisphosphine ligand (*R*)-(+)-BINAP (entry 2) the diastereoselectivity increased dramatically (98:2 dr), however using (*S*)-(-)-BINAP (entry 3) afforded **8g2** at a much lower diastereomeric ratio (67:33) indicating a matched [(+)-BINAP]/ mismatched [(-)-BINAP] case.

Scheme 8g



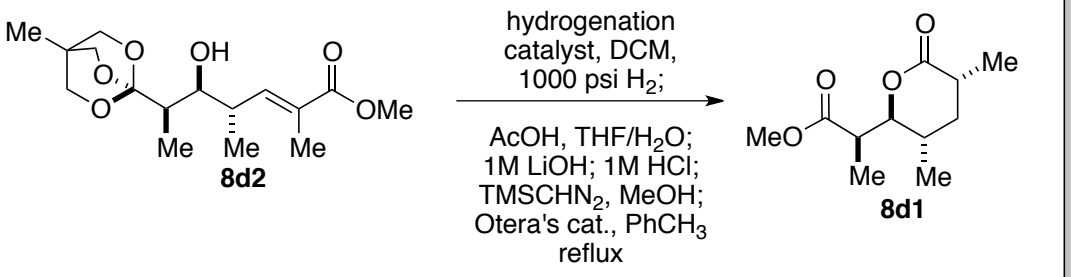
When the hydrogenation was conducted on methyl ester **8d2**, a mixture of lactone **8h1** open chain ester **8h2** was produced (Scheme 8h). Upon completion of the hydrogenation the crude reaction was diluted with THF/H_2O and a catalytic amount of AcOH was added to hydrolyze the OBO ortho esters to diol esters **8h3** and **8h4**. Next the reaction pH was adjusted to 9 with 1M LiOH (aq) to affect saponification to the PD lactonic acid **8h5** and the open chain acid **8h6**, after acidification to pH 2 with 1M HCl (aq). Without isolation this mixture of acids was stirred in MeOH with $TMSCHN_2$ to form the mixture of methyl esters that was heated at reflux in toluene with Otera's transesterification catalyst to converge the mixture of esters to the Prelog-Djerassi lactone **8d1**. At this point ^{1}H-NMR analysis of the PD lactone **8d1** and its C6 epimer **8h7** revealed that the diastereomeric mixture (at C6) showed 2 well-resolved signals for the C3 methine (Scheme 8h). Since the ^{1}H-NMR spectrum of **8d1** is known, we were able to compare our synthetic **8d1**. This method of analysis proved effective for measuring the diastereoselectivity of the hydrogenation of ester **8d2**. Several catalysts were screened in this manner and the results are summarized in Table 8c.

Scheme 8h



We explored several catalyst systems for the hydrogenation (Table 8c) followed by a one-pot conversion of the hydrogenation product to the targeted PD lactone (**8d1**), in which the hydrogenation diastereoselectivity (α-Me desired) was determined. Hydrogenation with Pd/C (entry 1) imparted no diastereoselectivity while [Rh(nbd)(dppb)]BF_4 (entry 2) gave 2.5:1 mixture of products favoring the desired diastereomer. Crabtree's cationic Ir(I)-catalyst (entry 3) gave slightly better selectivity (3:1) and the Burgess catalyst[13] (entry 4) gave lower selectivity (1.6:1). Coupling a chiral ligand with the hydroxyl-directed Rh(I)-catalyzed hydrogenation has been shown to increase the diastereoselectivity via double stereodifferentiation.[12] Using [Rh(COD)]BF_4/(*S*)-BINAP (entry 5) afforded a 5:1 mixture in favor of the PD lactone (**8d1**) C6-stereochemistry. Superior results were obtained when the non-coordinating counter ion ClO_4^- (entry 6) was incorporated into the catalyst, affording a much higher diastereoselectivity (>31:1).

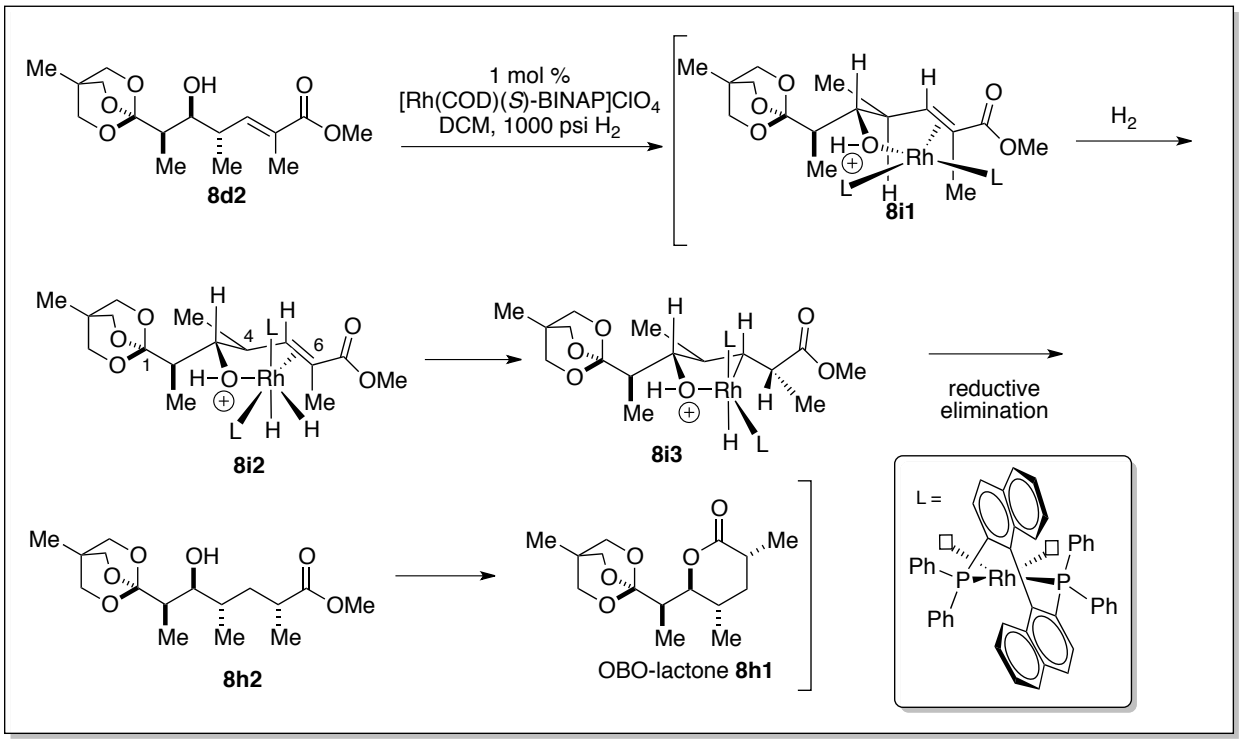
Table 8c



Entry	Catalyst	% Yield	dr (α:β) for C6-Me
1	10 % Pd/C	39	1:1
2	15 % [Rh(norbornadiene)(dppb)]BF_4	61	2.5:1
3	0.9 % [Ir(pyr)(Cy_3P)]PF_6	66	3:1
4	3 % Burgess catalyst	63	1.6:1
5	5 % [Rh(COD)]BF_4/ (*S*)-BINAP	30	5:1
6	1 % [Rh(COD) (*S*)-BINAP]ClO_4	76	>31:1

The diastereoselectivity of the hydroxyl-directed Rh(I)-catalyzed asymmetric hydrogenation can be explained via the proposed mechanism in Scheme 8i.[12] Initial coordination of the hydroxyl and the alkene to the Rh(I)-catalyst would put both the C4-Me and the bulky OBO ortho ester in equatorial positions on the chair-like complex **8i1**. Insertion of dihydrogen would generate Rh(III)-complex **8i2** followed by hydrogen transfer to the coordinated olefin to give **8i3**. Lastly, reductive elimination would afford saturated ester **8h2**, some of which would spontaneously lactonize to **8h1**.

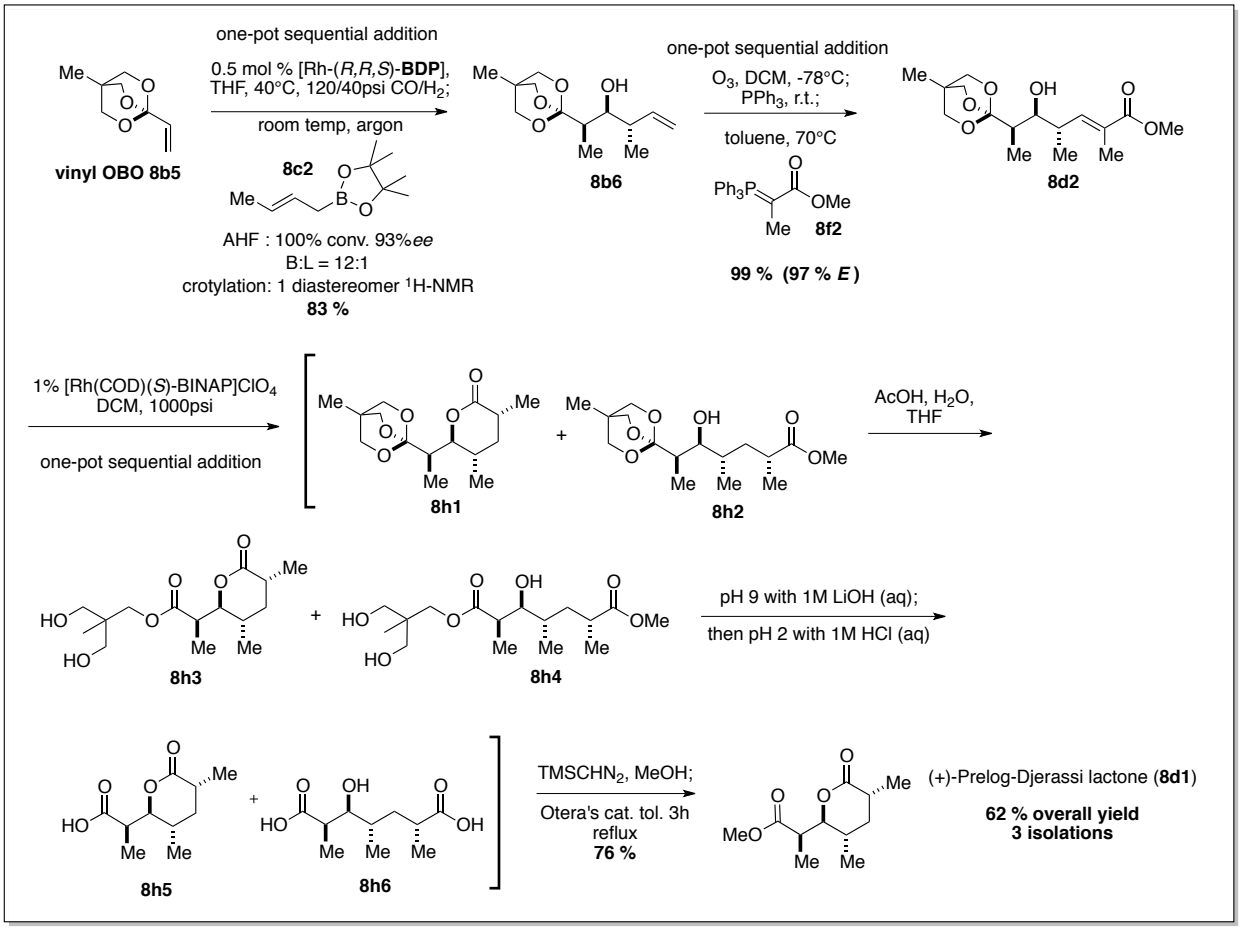
Scheme 8i



In summary a very short and efficient synthesis of the (+)-Prelog-Djerassi lactone (**8d1**, Summary Scheme 8j) has been accomplished.[14] This synthesis features an AHF/ crotylation tandem reaction of vinyl OBO **8b5** with the Landis (*R,R,S*)-**BDP** ligand and *trans*-crotyl boronic acid pinacol ester **8c2** to produce homoallylic alcohol **8b6** in 83 % yield (> 95 % dr) setting 3 of the 4 required stereocenters in a single pot. Ozonolysis/ Wittig homologation with ylide **8f2** afforded δ-hydroxy-α,β-unsaturated methyl ester **8d2** in 99 % yield (97 % *E*). The C6-Me stereocenter was set via a hydroxyl-directed Rh(I)-catalyzed asymmetric hydrogenation with [Rh(COD)(*S*)-BINAP]ClO_4 with excellent diastereoselectivity (>31:1 dr). A one-pot sequence was developed to convert OBO ortho esters **8h1** and **8h2** to the PD lactone (**8d1**). After the hydrogenation was complete the crude mixture was diluted in THF/H_2O and a catalytic amount of AcOH was added to catalyze the hydrolysis of the OBO ortho esters **8h1** and **8h2** to the diol esters **8h3** and **8h4**. Once hydrolysis was complete the pH was adjusted to 9 with 1M LiOH to

affect saponification of the esters followed by acidification to pH 2 in order to protonate the carboxylates and generate a mixture of acids **8h5** and **8h6**. Esterification with $TMSCHN_2$ followed by neutral transesterification with Otera's catalyst in refluxing toluene converged the mixture of esters to the PD lactone (**8d1**) in 76 % yield from α,β-unsaturated ester **8d2**. In light of the brevity of this synthesis and comparison of overall yield (3 isolations and 62 % overall yield from vinyl-OBO **8b5**) with previous syntheses of the PD lactone (**8d1**) from achiral starting material (8-27 steps LLS, 0.98-17 % overall yield), the AHF / crotylation tandem reaction has greatly improved the efficiency of the synthesis of 2,3-*syn*-3,4-*anti* stereotriads for polypropionate synthesis.

Summary Scheme 8j: (+)-Prelog-Djerassi Lactone



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Selected Experimental Procedures:

A. General Methods:

For moisture-sensitive reactions, toluene and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. THF was also subjected to 3 freeze, pump, thaw cycles and stored in a nitrogen filled glove-box prior to use. *Trans*-2-butenyl pinacolato boronic ester (6),[1] Methyl 2-(triphenylphosphoranylidene)propionate,[2] Otera's catalyst,[3] the Burgess catalyst,[4] [Rh(COD)(*S*)-BINAP]ClO_4,[5] (*2R*)-8-Nonyn-2-ol,[6] 2-[(Diphenylphosphino)methyl]pyridine,[7] (1,4-Bis(diphenylphosphino)butane)Ru(η^3-$CH_2MeCH_2)_2$[8] and (4*R*) and (4*S*)-*tert*-butyldimethylsiloxy-1-pentyne[9] were synthesized according to the reported methods. Dicarbonylacetylacetonato rhodium(I), (99%) was purchased from Strem Chemicals Inc. and used as received. (*S*) and (*R*)-Propylene oxide >98% ee were purchased from TCI America and used as received. All other chemicals were purchased from Sigma-Aldrich and used as received.

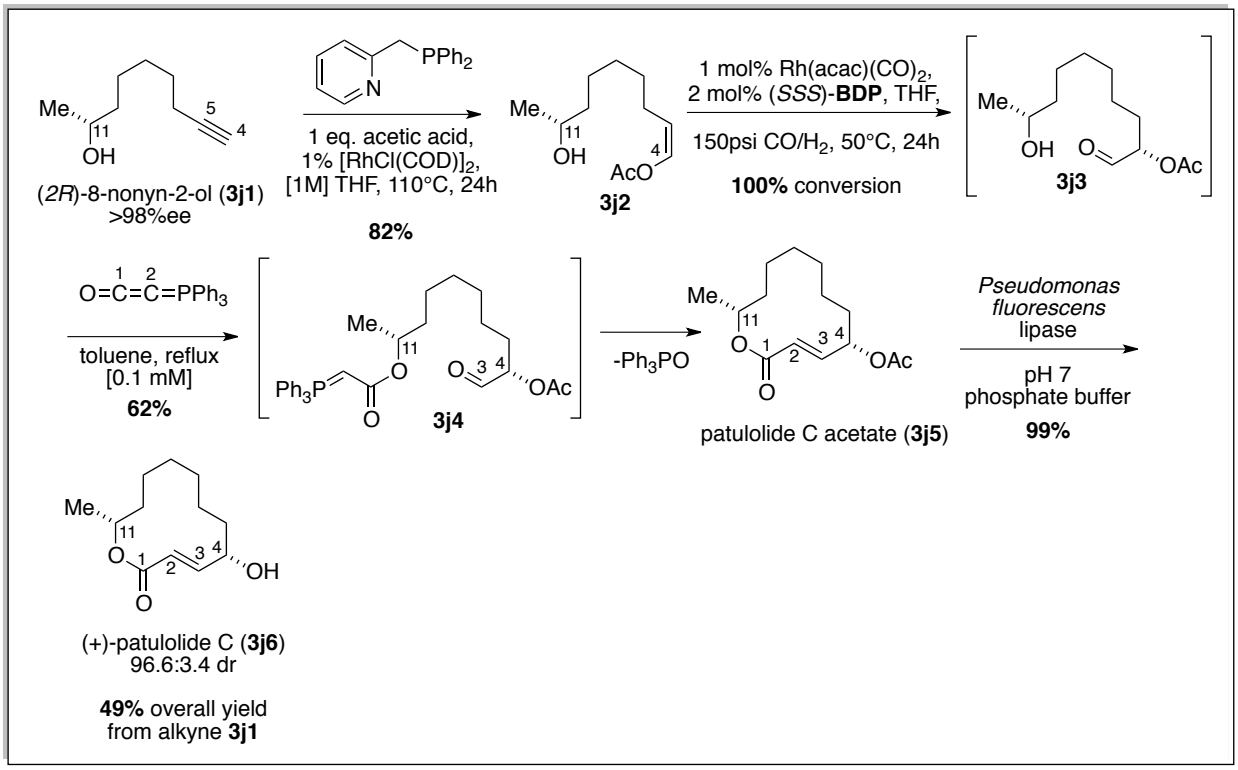
All moisture-sensitive reactions were performed in flame-dried and/or oven-dried glassware under a positive pressure of nitrogen unless otherwise noted. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator at water aspirator pressure. "Dried" refers to addition of ~1g/mmol anhydrous sodium sulfate followed by filtration.

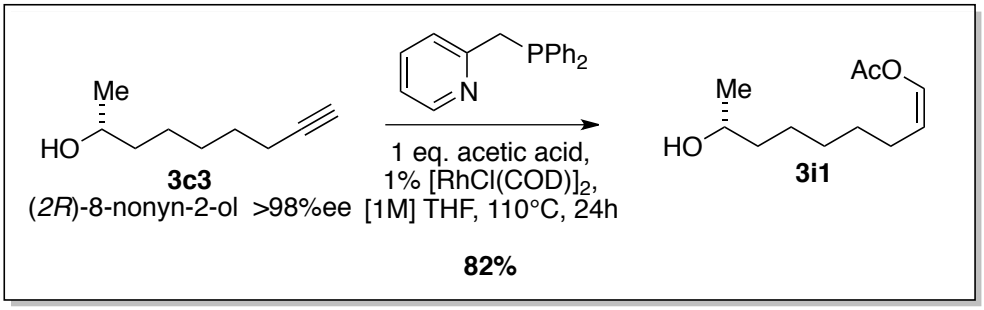
Analytical thin layer chromatography (TLC) was carried out on TLC plates precoated with silica gel 60 F_{254} (0.25 mm layer thickness). Visualization was accomplished using UV light and/or a *p*-anisaldehyde (PAA) or $KMnO_4$ charring solution. Flash column chromatography (FCC) was performed on silica gel 60 (230-400 mesh, 60 Å pore size) Solvent mixtures for FCC are reported as V_1/V_{total} x 100%. Before all compounds containing the OBO ortho ester were subjected to flash column chromatography, the silica gel was deactivated with a 5-10%

triethylamine/hexanes; followed by 100 % ethyl acetate, then equilibrated with the desired eluent for separation before loading the column with the crude material.

Optical rotations were measured on an Autopol III automatic polarimeter. Concentrations (c) are reported in g/100 mL. Infrared spectra (IR) were obtained on a Tensor 27 FT-IR. ^{1}H and ^{13}C NMR spectroscopy were recorded at 300 (^{1}H) or 75 (^{13}C) MHz (NSF Grant CHE-9208463), 500 (^{1}H) or 125 (^{13}C) and 600 (^{1}H) or 150 (^{13}C) MHz (NIH Grants P41RR02301 and P41GM66326) as indicated. $CDCl_3$ used for samples containing the OBO ortho ester was flushed through a plug of basic alumina first to remove trace acid. First order proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), septet (sept), multiplet (m), apparent (ap), and broad (br). Second order proton NMR splitting patterns are designated as AB quartet (ABq), ABX pattern (ABX), etc. All coupling constants were rounded to the nearest 0.1 hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a Waters LCT® (NSF Award #CHE9974839) electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. Exact mass measurements were obtained for all isolated compounds. Super-critical fluid chromatography (SFC) was used with a chiral column (Chiralcel OJ-H) in order to determine enantiomeric excess or Shimadzu UFLC with chiral columns (Chiralcel OJ-H and Chiracel AD-H) in order to determine diastereomeric excess.

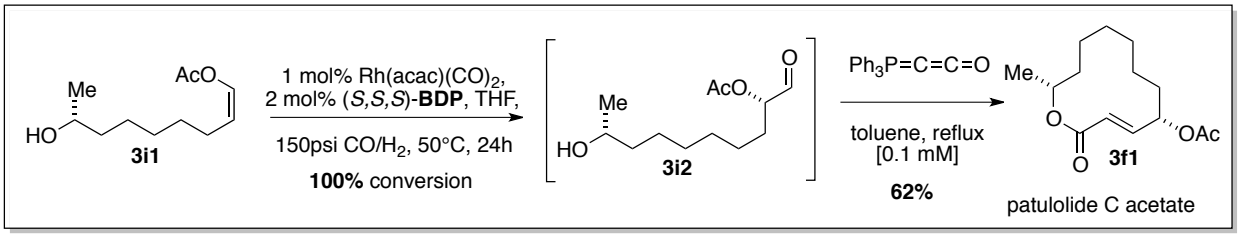
A. The Total Synthesis of (+)-Patulolide C via Asymmetric Hydroformylation/ Wittig Olefination





All reagents were combined in a nitrogen-filled glove-box. To a 15 mL pressure tube (25.4 mm OD x 10.2 cm long rated to 150 psi from Ace Glass Inc.) equipped with a stir bar was added alkyne **3c3** (250 mg, 1.78 mmol), $[Rh(COD)Cl]_2$ (8.8 mg, 0.0178 mmol), 2-[(diphenylphosphino)methyl]pyridine (10 mg, 0.0356 mmol), acetic acid (103 mL, 1.78 mmol), and 1.78 mL of THF (degassed). The pressure tube was then fitted with a septum and removed from the glove-box and purged with Argon (outlet needle equipped). After 1 to 2 min of purging

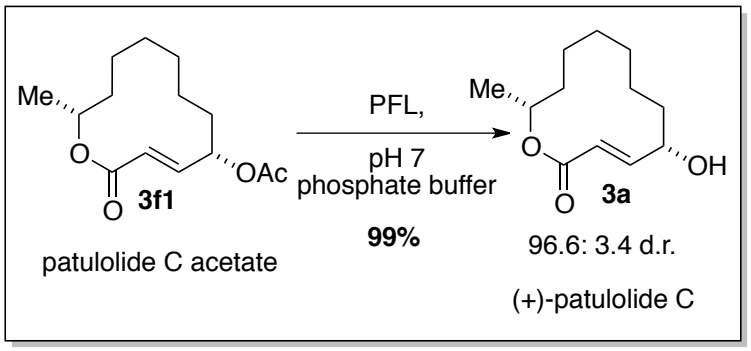
the septum was quickly replaced with a Teflon screw cap fitted with a front-seal O-ring, and tightened by hand. The pressure tube was then placed in a 110 °C oil-bath with stirring and the temperature maintained for 24 h. The tube was then removed from the oil bath and allowed to cool to ambient temperature. The mixture was then filtered through a 1-inch silica plug and rinsed thoroughly with ethyl acetate. The filtrate was concentrated to give a crude oil, which was purified by silica gel flash column chromatography (10% ethyl acetate: hexanes) to yield 292.3 mg of hydroxy-*Z*-enol acetate **3i1** as a yellow oil (82% yield). Kugelrohr distillation (0.1 mm Hg, 120 °C) provided a clear, colorless oil; IR (neat) ν 1062, 1221, 1369, 1671, 1757, 2858, 2931, 3386 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J*=6 Hz, 3H), 1.26-1.49 (m, 9H), 2.11-2.17 (m, 2H), 2.15 (s, 3H), 3.75-3.85 (m, 1H), 4.86 (ABq, *J*=8, 6 Hz, 1H), 7.00 (dt, *J*=6, 2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.0, 23.8, 24.5, 25.7, 29.3, 29.3, 39.5, 68.3, 114.4, 134.3, 168.5; ESI-MS *m/z* calculated:$[M+Na]^+$= 223.1305, measured $[M+Na]^+$= 223.1303; $[\alpha]_D^{23}$ -3.14 (*c* 1.02, $CHCl_3$)(98% ee from epoxide).



All reagents were combined in a nitrogen filled glove-box. To a 48 mL pressure tube (38.1 mm OD x 10.2 cm long rated to 150 psi from Ace Glass Inc.) equipped with a stir bar was added **3i1** (203 mg, 1.01 mmol), $Rh(acac)(CO)_2$ (3 mg, 0.01 mmol), (*S,S,S*)-**BDP** (26 mg, 0.02 mmol) and 1 mL of THF. The pressure tube was then connected to a gauged pressure reactor assembly and removed from the glove-box. The pressure tube was purged five times with syngas (1:1 CO/H_2) and then charged to 150 psi. A blast shield was placed in front of the reactor for safety. The reaction tube was submerged in a 50 °C oil bath with stirring and allowed to react for 24 h. The

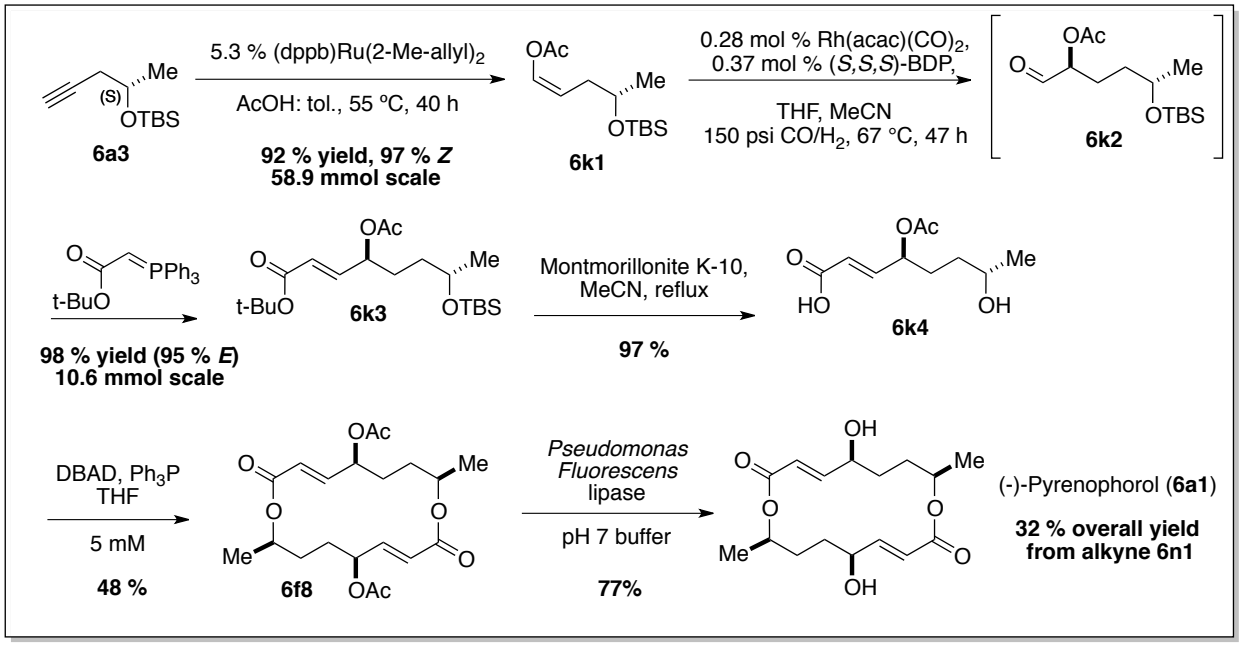
pressure tube was removed form the oil bath and allowed to reach ambient temperature and the pressure was vented to 20 psi. The reactor was equipped with an argon inlet and the remaining syngas was vented through the Schlenk line. A small aliquot was removed from the reaction to confirm 100% consumption of **3i1** by ^{1}H-NMR.

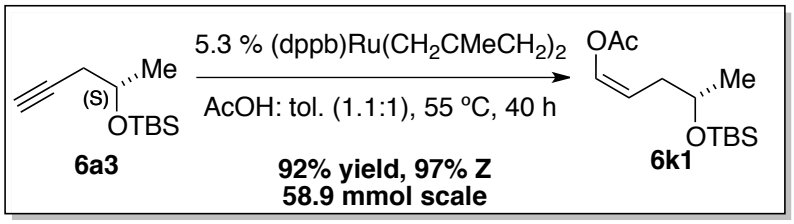
The above solution of aldehyde **3i2** was diluted with toluene (9 mL) and a 0.5 mL (0.05 mmol) sample was removed and diluted with toluene (to 50 mL). This solution was slowly added via syringe pump to a refluxing toluene solution (450 mL) of (triphenylphosphoranylidene)ketene (91 mg, 0.3 mmol) over 20 h. The reaction was allowed to reflux for an additional 1 h and then cooled to ambient temperature. The crude reaction was concentrated and purified via silica gel flash column chromatography (5% ethyl acetate: hexanes) to yield patulolide C acetate (**3f1**) as a yellow oil (7.9 mg, 62%); IR (neat) ν 1462, 1651, 1722, 1743, 2863, 2937 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06-1.82 (m, 12H), 1.29 (d, *J*=7 Hz, 3H), 2.08 (s, 3H), 5.08 (m, 1H), 5.41 (m, 1H), 6.06 (dd, *J*=16, 1 Hz, 1H), 6.83 (dd, *J*=16, 7 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.4, 21.1, 21.3, 22.3, 27.7, 28.1, 32.9, 33.1, 72.8, 73.2, 122.6, 145.6, 167.2, 169.9; ESI-MS *m/z* calculated:$[M+Na]^+$= 277.1411, measured $[M+Na]^+$= 277.1406; $[\alpha]_D^{23}$ -5.3 (*c* 0.57 EtOH).



To a 15 mL round bottom flask equipped with a magnetic stir bar was added patulolide C acetate (**3f1**) (16.9 mg, 0.066 mmol), *Pseudomonas Fluorescens* lipase (8.3 mg), and pH 7 aqueous phosphate buffer (0.7 mL). The reaction was allowed to stir at ambient temperature for 3 d, during which it was monitored by TLC. Upon completion, the product was extracted with diethyl ether (3x), dried and concentrated. The crude oil was purified via silica gel flash column chromatography to yield (+)-patulolide C (**3a**) as a yellow oil (14.0 mg, 99%); IR (neat) ν 1462, 1647, 1718, 2857, 2932, 3426 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) d 1.0-1.8 (m, 12H), 1.29 (d, *J*=7 Hz, 3H), 4.51 (m, 1H), 5.08 (m, 1H), 6.10 (dd, *J*=16, 1 Hz, 1H), 6.85 (dd, *J*=16, 7 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 19.3, 20.7, 22.1, 27.8, 28.3, 32.8, 35.9, 70.9, 73.1, 121.5, 149.6, 168.1; ESI-MS *m/z* calculated: $[M+H]^+$= 213.1486, measured $[M+H]^+$= 213.1480; $[\alpha]_D^{23}$ +4.1 (*c* 0.29 EtOH), lit. $[\alpha]_D^{23}$ +5.0 (*c* 0.32 EtOH).[10]

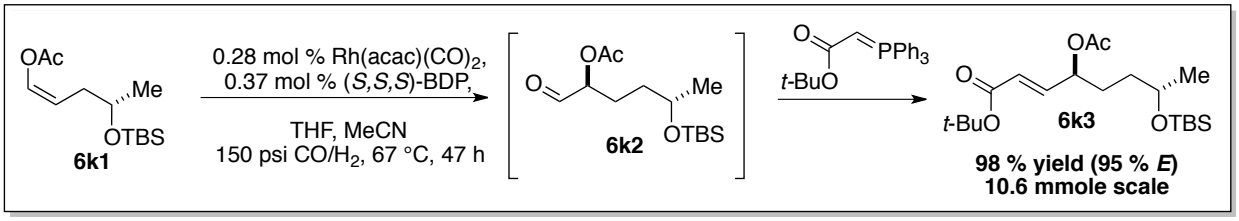
B. The Total Synthesis of (-)-Pyrenophorol and (+)-Decarestrictine L via Asymmetric Hydroformylation/ Wittig Olefination.





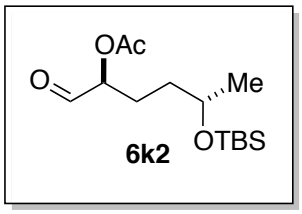
In a nitrogen filled glove box, (4*S*)-*tert*-butyldimethylsiloxy-1-pentyne (**6a3**) (11.7 g, 58.9 mmol) was added to a 50 mL pressure tube containing a stir bar. To the same flask was added (1,4-bis(diphenylphosphino)butane)Ru(η^3-$CH_2MeCH_2)_2$ (2.00 g, 3.14 mmol), acetic acid (10 mL) and toluene (9 mL). The tube was fitted with a rubber septum and removed from the glove box. The headspace of the tube was flushed with Argon for 3 minutes; the septum was replaced with a threaded Teflon stopper and heated in an oil bath for 40 h. The reaction was cooled to ambient temperature and concentrated. The residue was purified via flash column chromatography (2-5% diethylether: hexane) to afford **6k1** as clear colorless oil (14.1 g, 92%, 97% *Z* selectivity by ^{1}H-NMR), R_f = 0.5 (10 % diethylether: hexane); IR (neat) 1056, 1087, 1134, 1221, 1368, 1473,

1673, 1761, 2858, 2896, 2930, 2958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (dt, *J* = 6.5, 1.5 Hz, 1H), 4.93 (td, *J* = 7.6, 6.5 Hz, 1H), 3.85 (h, *J* = 6.1 Hz, 1H), 2.34 – 2.21 (m, 2H), 2.14 (s, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.77, -4.56, 18.15, 20.75, 23.41, 25.85, 34.62, 68.04, 110.43, 135.02, 168.05; ESI-MS *m/z* calculated $[M+NH_4]^+$ = 276.1990, measured $[M+NH_4]^+$ = 276.1980, opt. rot. $[\alpha]_D^{23}$ = -2.2 (*c* 1.0 chloroform).



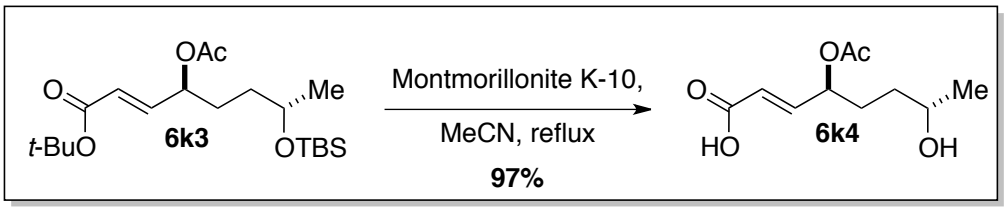
In a nitrogen filled glove box, a 300 mL pressure tube with a stir bar was charged with *Z*-enol acetate **6k1** (2.74 g, 10.6 mmol), (acetylacetonato)dicarbonylrhodium (7.2 mg, 0.028 mmol), (*S,S,S*)-bisdiazaphospholane (61 mg, 0.047 mmol), acetonitrile (1.3 mL) and tetrahydrofuran (1.5 mL). The reaction vessel was fitted with a pressure head and removed from the glove box. It was filled/ purged 5 times with syngas (150 to 40 psi) and then pressurized to 150 psi and placed in a 67 °C oil bath with vigorous stirring behind a blast shield. After 24 h 10 psi of syngas had been consumed, the vessel was pressurized to 150 psi and allowed to react another 23 h. The vessel was then cooled to ambient temperature and the pressure vented down to 20 psi. An aliquot was removed via syringe through the top septum and concentrated for NMR analysis. This aliquot showed complete conversion to the branched aldehyde, it was then purified via flash column chromatography (10% ethyl acetate: hexanes) for full characterization. The data are presented below. The remaining reaction mixture was then fully vented through an Argon Schlenk line, the pressure head removed and replaced with a rubber stopper and Argon needle. To the reaction vessel was added *tert*-butyl 2-(triphenylphosphoranylidene) acetate (6 g, 15.9 mmol) and

dichloromethane (6 mL) and stirred for 3 h. The reaction was monitored by TLC and when complete (3 h), it was concentrated and purified via flash column chromatography (3-5% diethylether: hexane) to afford **6k3** as clear colorless oil (4.02 g, 98 %, 96% *E*); IR (neat) 1155, 1314, 1369, 1463, 1472, 1662, 1719, 1746, 2858, 2931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (dd, *J* = 15.7, 5.6 Hz, 1H), 5.85 (dd, *J* = 15.7, 1.5 Hz, 1H), 5.37 (q, *J* = 5.6Hz, 1H), 3.79 (h, *J* = 6.1 Hz, 1H), 2.09 (s, 3H), 1.83 – 1.71 (m, 1H), 1.70 – 1.58 (m, 1H), 1.48 (s, 9H), 1.44 (m, 2H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.75, -4.39, 18.10, 21.06, 23.68, 25.87, 28.09, 29.91, 34.66, 68.05, 72.60, 80.70, 123.45, 144.05, 165.33, 170.11; ESI-MS *m/z* calculated $[M+NH_4]^+$ = 404.2827, measured $[M+NH_4]^+$ = 404.2827, opt. rot. $[\alpha]_D^{23}$ = -3.5 (*c* 1.04 chloroform).

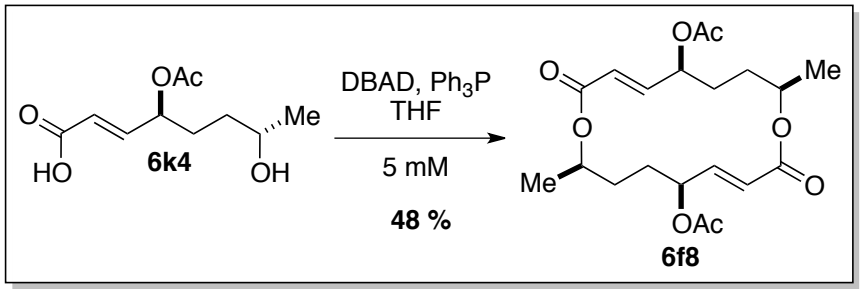


6k2

(2*S*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-2-acetoxy-hexanal (**6k2**); IR (neat) 776, 836, 897, 1055, 1251, 1374, 1469, 1744, 2855, 2929, 2957, 3465 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 4.99 (dd, *J* = 8.4, 4.7 Hz, 1H), 3.82 (h, *J* = 6.0 Hz, 1H), 2.18 (s, 3H), 1.97 (m, 1H), 1.76 – 1.65 (m, 1H), 1.52 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.79, -4.36, 18.08, 20.60, 23.64, 24.86, 25.84, 34.60, 67.90, 78.41, 170.58, 198.16; ESI-MS *m/z* calculated $[M+H]^+$ = 289.1830, measured $[M+H]^+$ = 289.1836, opt. rot. $[\alpha]_D^{23}$ = -4.2 (*c* 0.48 chloroform).

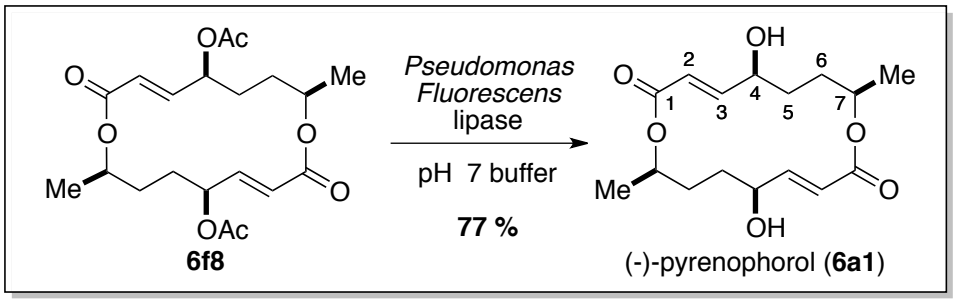


To a 100 mL round bottom flask was added **6k3** (268 mg, 0.69 mmol), Montmorillonite K-10 (138 mg) and acetonitrile (69 mL). The flask was fitted with a reflux condenser and refluxed for 24 h. The reaction was cooled to ambient temperature, filtered through a pad of Celite and the solids were washed with ethyl acetate. The filtrate was concentrated to give viscous oil, which was purified via flash column chromatography (5 % methanol: 94% dichloromethane: 1% acetic acid) to afford the hydroxy acid **6k4** as viscous oil (145 mg, 97%) IR (neat) 982, 1027, 1237, 1375, 1662, 1718, 2930, 2967, 3421(broad) cm^{-1}; ^{1}H NMR (400 MHz, Methanol-d4) δ 6.84 (dd, *J* = 15.7, 5.3 Hz, 1H), 5.91 (dd, *J* = 15.8, 1.6 Hz, 1H), 5.40 (dtd, *J* = 7.1, 5.4, 1.6 Hz, 1H), 3.77 – 3.67 (m, 1H), 2.10 (s, 3H), 1.91 – 1.80 (m, 1H), 1.69 (m, 1H), 1.55 – 1.38 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 20.84, 23.48, 31.19, 35.31, 49.00, 68.19, 73.96, 122.83, 147.10, 169.24, 171.83; ESI-MS *m/z* calculated $[M-H]^-$ = 215.0924, measured $[M-H]^-$= 215.0919, opt. rot. $[\alpha]_D^{23}$ =-3.2 (*c* 0.5 methanol).



To a 100 mL round bottom flask was added hydroxy acid **6k4** (282 mg, 1.31 mmol) and this oil was azeotropically dried with toluene 7 times then placed under argon. To an oven dried 500 mL round bottom flask under argon was added THF (234 mL), triphenylphosphine (1.72 g, 6.55

mmol), and di-*tert*-butyl azodicarboxylate (1.51 g, 6.55 mmol). Hydroxy acid **6k4** was dissolved in 28 mL of THF and added to the reaction flask slowly via syringe pump over 6 h. The reaction was stirred for an additional 1 h, and then concentrated on a rotovap. The residue was dissolved in dichloromethane (50 mL) and trifluoroacetic acid (5 mL) was added and stirred for 3 h. The reaction mixture was then extracted with sodium bicarbonate, washed with brine and dried with $MgSO_4$, filtered and concentrated. The residue was purified via flash column chromatography (15% ethyl acetate: hexane) to afford **6f8** a clear oil which solidified upon standing (126 mg, 48%); IR (neat) 1021, 1233, 1281, 1376, 1653, 1709, 1740, 2876, 2956, 2992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.98 (dd, *J* = 15.8, 1.1 Hz, 1H), 5.22 (m, 1H), 5.10 (m, 1H), 2.08 (s, 3H), 1.93 – 1.79 (m, 2H), 1.79 – 1.68 (m, 1H), 1.67 – 1.57 (m, 1H), 1.26 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.52, 21.12, 27.86, 28.73, 69.78, 72.07, 124.23, 143.73, 164.76, 169.76; ESI-MS *m/z* calculated $[M+H]^+$ = 419.1677, measured $[M+H]^+$ = 419.1677, opt. rot. $[\alpha]_D^{23}$ = -33.2 (*c* 0.47 chloroform), m.p. 119-120°C.



In a 25 mL round bottom flask containing diacetoxypyrenophorol **6f8** (24 mg, 0.0605 mmol) was added lipase from *Pseudomonas fluorescens* (185 mg) and 10 mL of phosphate buffer (pH 7). The reaction was stirred at ambient temperature for 14 days and monitored by TLC. Once complete the mixture was extracted with ethyl acetate, the organic layer was washed with brine and dried over sodium sulfate, filtered and concentrated. The residue was purified via flash column chromatography (40-50 % ethyl acetate: hexane) to yield (-)-pyrenophorol (**6a1**) as clear

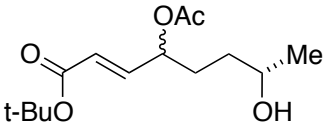
oil, which solidified on standing (14.6 mg, 77 %) IR (neat) 1281, 1647, 2849, 2917, 3442 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 15.7, 5.1 Hz, 1H), 6.00 (dd, *J* = 15.7, 1.6 Hz, 1H), 5.20 – 5.12 (m, 1H), 4.36 – 4.29 (m, 1H), 2.16 (d, *J* = 6.5 Hz, 1H), 1.96 m, 1H), 1.86 (m, 1H), 1.77 – 1.61 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.20, 28.95, 30.45, 69.76, 70.40, 122.12, 149.47, 164.94; ESI-MS *m/z* calculated $[M+Na]^+$ = 335.1466, measured $[M+Na]^+$ = 335.1461, opt. rot. $[\alpha]_D^{23}$ = -4.0 (*c* 0.25 acetone), m.p. 131-133 °C; lit.[11] $[\alpha]_D^{23}$ = -3.2 (*c* 0.25 acetone), m.p. 136-138 °C, A sample of the white solid was recrystallized from $Et_2O/CHCl_3$ for X-ray analysis.[12]

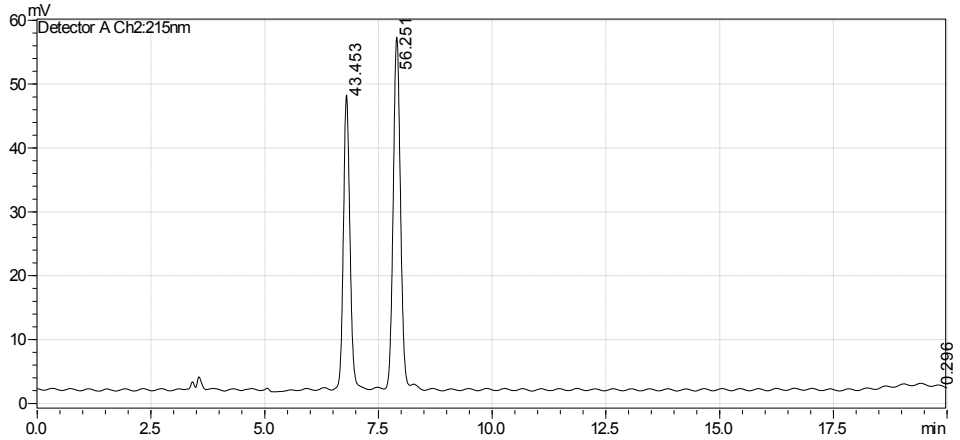
HPLC data for (-)-Pyrenophorol (6a1)

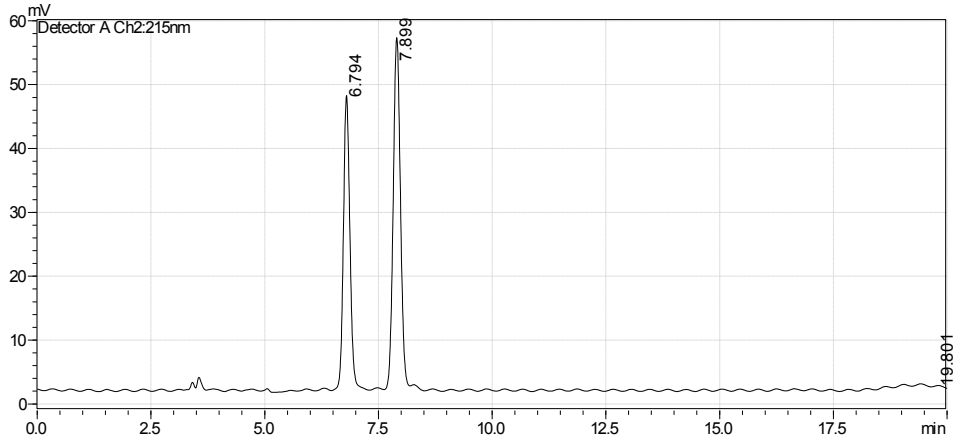
The following HPLC data was obtained on the AHF/Wittig product following desilylation ($AcOH/H_2O$/THF) to measure the diastereoselectivity of the AHF and to determine if any erosion of the newly formed stereocenter occurred during any of the following reactions.

HPLC 5% isopropanol/hexane Chiracel OJ-H

Racemic AHF/Wittig for pyrenophorol

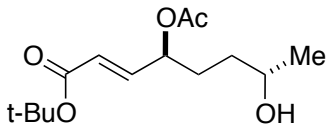


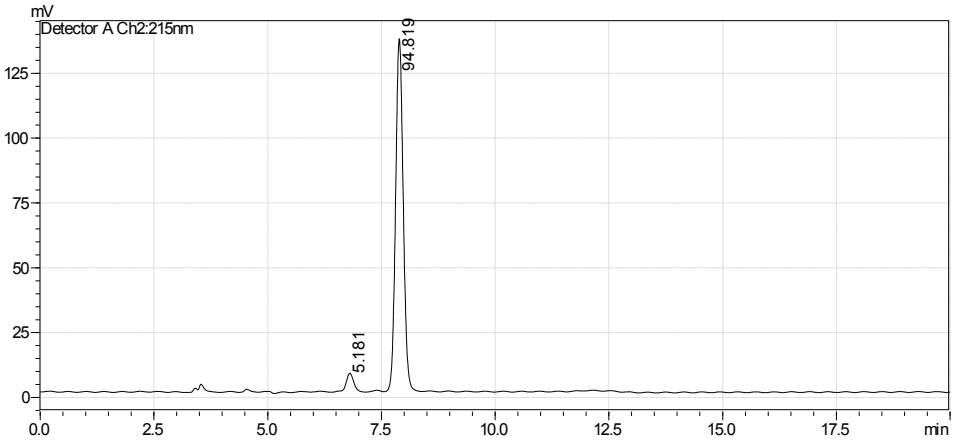


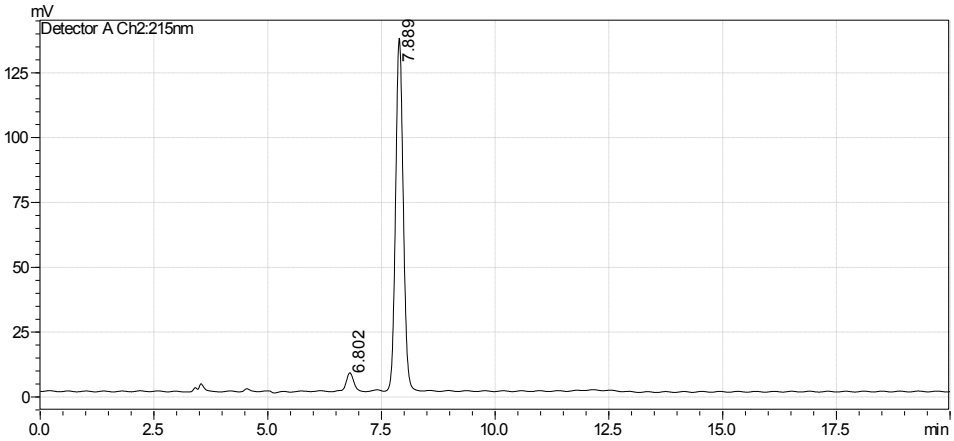


AHF/ Wittig with (*S,S,S*)-BDP

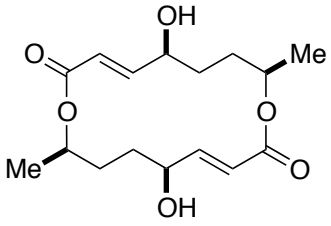
HPLC 5% isopropanol/hexane Chiracel OJ-H



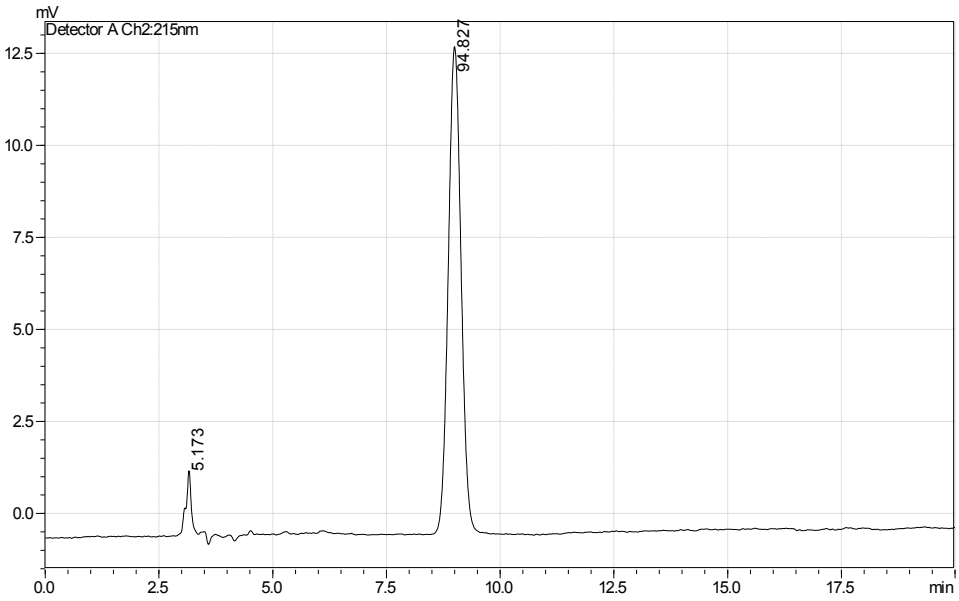


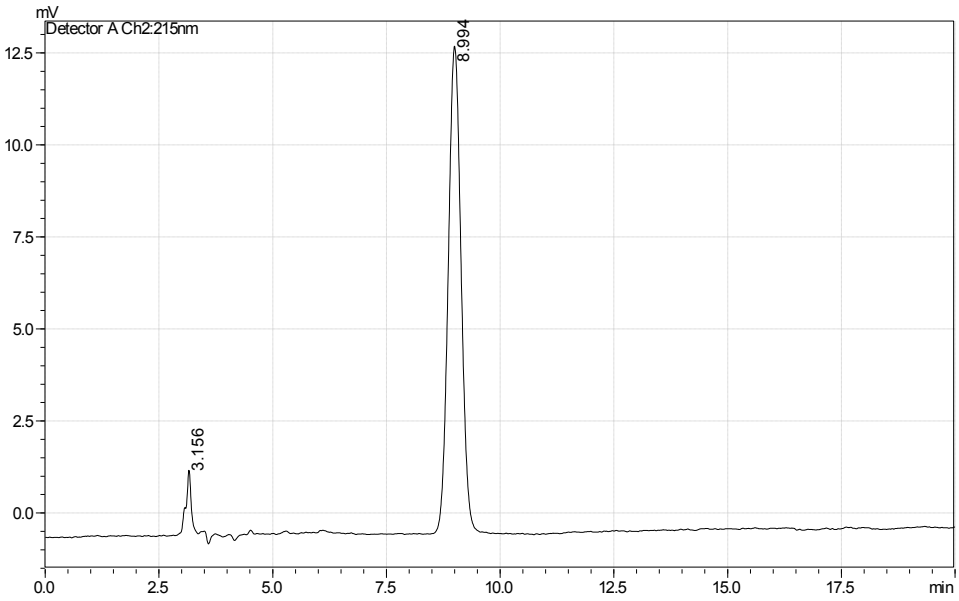


(-)-pyrenophorol (**6a1**)

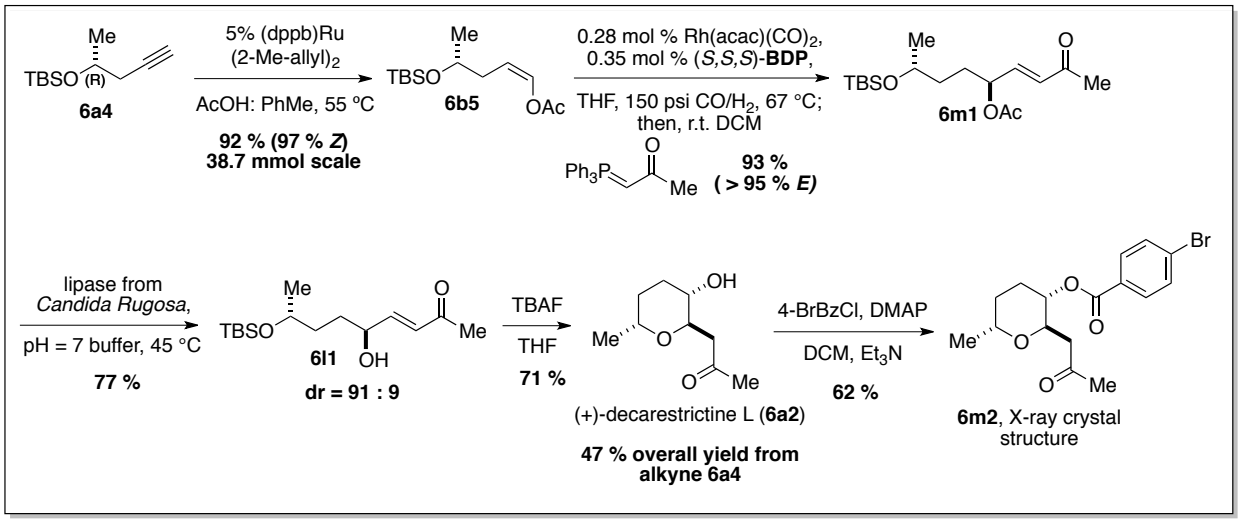


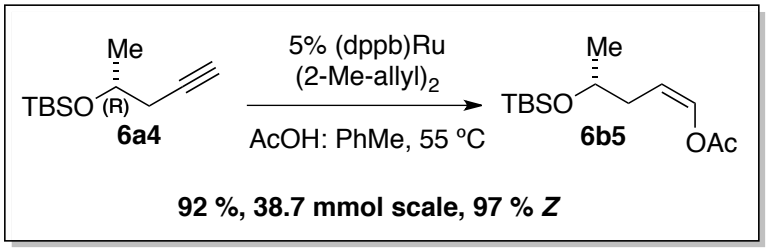
Chiracel OJ-H 20% isopropanol/hexane





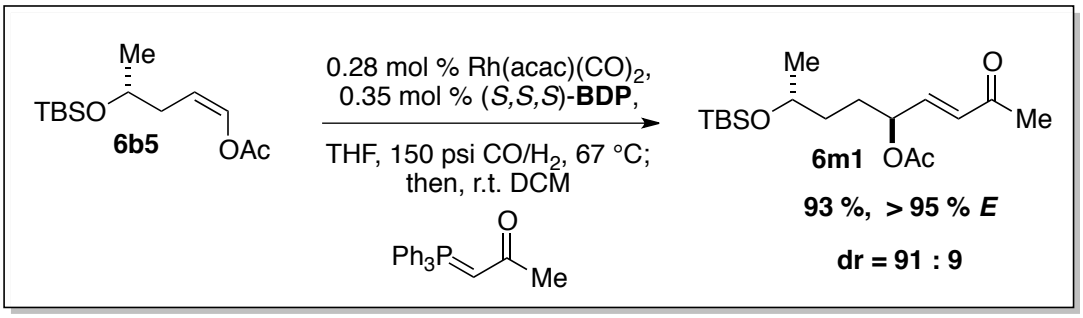
Synthesis of (+)-Decarestrictine L (6a2)





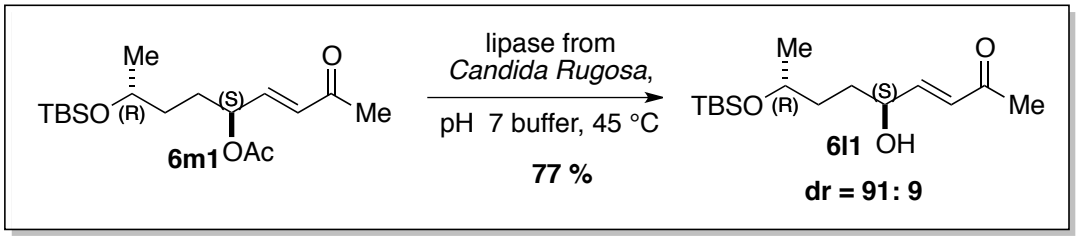
In a nitrogen filled glove box, (4*R*)-*tert*-butyldimethylsiloxy-1-pentyne (**6a4**) (7.68 g, 38.7 mmol) was added to a 100 mL round bottom flask containing a stir bar. To the same flask was added (1,4- bis(diphenylphosphino)butane)Ru(η^3-2-Me-allyl)$_2$ (1.23 g, 1.96 mmol), acetic acid (9 mL) and toluene (8 mL). The flask was fitted with a rubber septum and removed from the glove box, placed under N_2 and heated in an oil bath for 16 h. The reaction was cooled to ambient temperature, diluted with ethyl acetate and washed with $NaHCO_3$. The organic layer was dried with $MgSO_4$, filtered and concentrated. The residue was purified via flash column chromatography (2-5% diethyl ether: hexane) to afford **6b5** as clear colorless oil (9.23 g, 92%, 97% *Z* selectivity by NMR), R_f = 0.5 (10 % diethyl ether: hexane); IR (neat) 1056, 1220, 1368, 1463, 1473, 1674, 1761, 2858, 2896, 2958 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (dt, *J* = 6.5, 1.5 Hz, 1H), 4.93 (td, *J* = 7.6, 6.5 Hz, 1H), 3.85 (h, *J* = 6.1 Hz, 1H), 2.28 (m, 2H), 2.14 (s, 3H),

1.14 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ESI-MS *m/z* calculated $[M+Na]^+$ = 281.1544, measured $[M+Na]^+$ = 281.1544, opt. rot. $[\alpha]_D^{23}$ = +2.6 (*c* 1.0 chloroform).

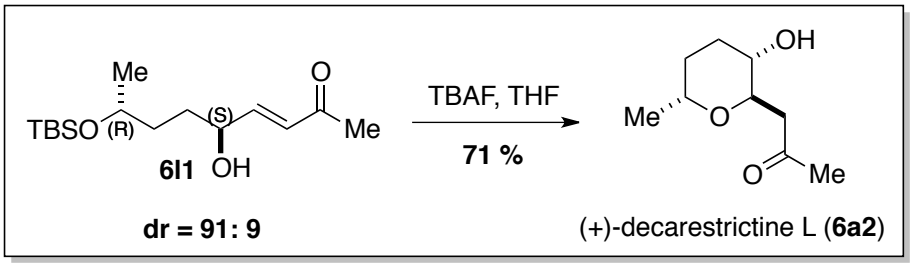


In a nitrogen filled glove box, a 50 mL pressure tube with a stir bar was charged with *Z*-enol acetate **6b5** (2.69 g, 10.4 mmol), (acetylacetonato)dicarbonylrhodium (7.5 mg, 0.029 mmol), (*S,S,S*)-bisdiazaphospholane (48 mg, 0.035 mmol), and tetrahydrofuran (2.5 mL). The reaction vessel was fitted with a pressure head and removed from the glove box. It was purged 5 times with syngas (150 to 40 psi) and then pressurized to 150 psi and placed in a 67 °C oil bath with vigorous stirring behind a blast shield. After 7 h 40 psi of syngas had been consumed, the vessel was pressurized to 150 psi and allowed to react another 40 h. The vessel was then cooled to ambient temperature and the pressure vented down to 20 psi. The reaction mixture was then fully vented through an argon Schlenk line, the pressure head removed and replaced with a rubber stopper and argon needle. To the crude reaction was added 1-(triphenylphosphoranylidene)-2-propanone (5.00 g, 15.7 mmol), dichloromethane (2 mL) and the reaction was stirred overnight. The crude reaction was diluted with ether and flushed through a silica plug, concentrated and purified via flash column chromatography (5-8 % ethyl acetate: hexane) to afford **6m1** as clear colorless oil (3.18 g, 93 %, >95 % *E*); IR (neat) 1140, 1233, 1373, 1473, 1636, 1683, 1704, 1743, 2857, 2930, 2957 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.65 (dd, J = 16.1, 5.3 Hz, 1H), 6.17 (dd, J = 16.1, 1.5 Hz, 1H), 5.42 (dtd, J = 7.0, 5.4, 1.5 Hz, 1H), 3.86 – 3.75 (m, 1H), 2.27 (s, 3H), 2.10

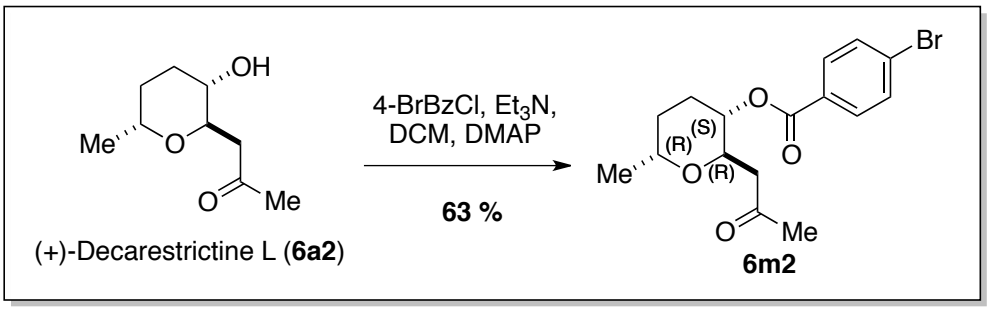
(s, 3H), 1.79 (m, 1H), 1.70 (m, 1H), 1.52 – 1.37 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.75, -4.32, 18.09, 21.02, 23.72, 25.85, 27.42, 29.78, 34.51, 67.79, 72.40, 130.21, 144.06, 170.12, 197.98; ESI-MS *m/z* calculated $[M+NH_4]^+$ = 346.2409, measured $[M+NH_4]^+$ = 346.2411, opt. rot. $[\alpha]_D^{23}$ = -12 (*c* 0.2 chloroform).



To a 100 mL round bottom flask containing ketone **6m1** (1.416 g, 4.31 mmol) was added lipase from *Candida Rugosa* (6 g) and pH = 7 phosphate buffer (30 mL, 0.1 M). The flask was stoppered with plastic cap and placed in a 45 °C oil bath. The reaction was stirred for 32 h and shown to be complete by TLC. The water was removed *in vacuo*, the brown residue was triturated with ethyl acetate and filtered through Celite, concentrated and purified via flash column chromatography (30 % ethyl acetate: hexane) to afford **6l1** as clear colorless oil (959 mg, 77 %); IR (neat) 775, 835, 1050, 1139, 1254, 1362, 1677, 2930, 3427 (broad OH) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 16.0, 4.8 Hz, 1H), 6.30 (dd, *J* = 16.0, 1.7 Hz, 1H), 4.38 – 4.32 (m, 1H), 3.90 (m 1H), 2.68 (d, *J* = 5.1 Hz, 1H), 2.28 (s, 3H), 1.84 – 1.73 (m, 1H), 1.71 – 1.51 (m, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.65, -4.42, 18.13, 23.23, 25.89, 27.55, 31.94, 34.30, 68.29, 70.82, 129.15, 148.95, 198.43; ESI-MS *m/z* calculated $[M+H]^+$ = 287.2037, measured $[M+H]^+$ = 287.2045, opt. rot. $[\alpha]_D^{23}$ = -6 (*c* 0.5 chloroform).

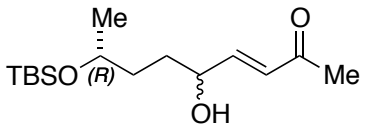


To a 100 mL round bottom flask containing ketone **6l1** (952 mg, 3.32 mmol), in THF (30 mL) under nitrogen was added TBAF (10 mL, 1 M THF) via an addition funnel dropwise over 10 min. After 30 min. of stirring at ambient temperature, the reaction was complete as confirmed by TLC. The reaction was then diluted with ethyl acetate and extracted with NH_4Cl, dried with $MgSO_4$ filtered and concentrated. The residue was purified via flash column chromatography (50 % ethyl acetate: hexane) to yield (+)-decarestrictine L (**6a2**) as clear colorless oil (404 mg, 71 %); IR (neat) 1107, 1543, 1577, 1710, 2970, 3675 (broad OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.02 (q, *J* = 6.4 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.46 – 3.36 (m, 1H), 2.74 (d, *J* = 6.4 Hz, 2H), 2.21 (s, 3H), 2.00 (d, *J* = 6.6 Hz, 1H), 1.93 – 1.82 (m, 1H), 1.78 – 1.66 (m, 2H), 1.63 – 1.51 (m, 1H), 1.22 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.46, 27.07, 28.22, 30.53, 46.33, 67.42, 69.41, 72.04, 207.58; ESI-MS *m/z* calculated $[M+NH_4]^+$ = 190.1438, measured $[M+NH_4]^+$ = 190.1437, opt. rot. $[\alpha]_D^{23}$ = +30.8 (*c* 0.5 chloroform), lit.[13] $[\alpha]_D^{23}$ = +28.8 (*c* 0.5 chloroform).

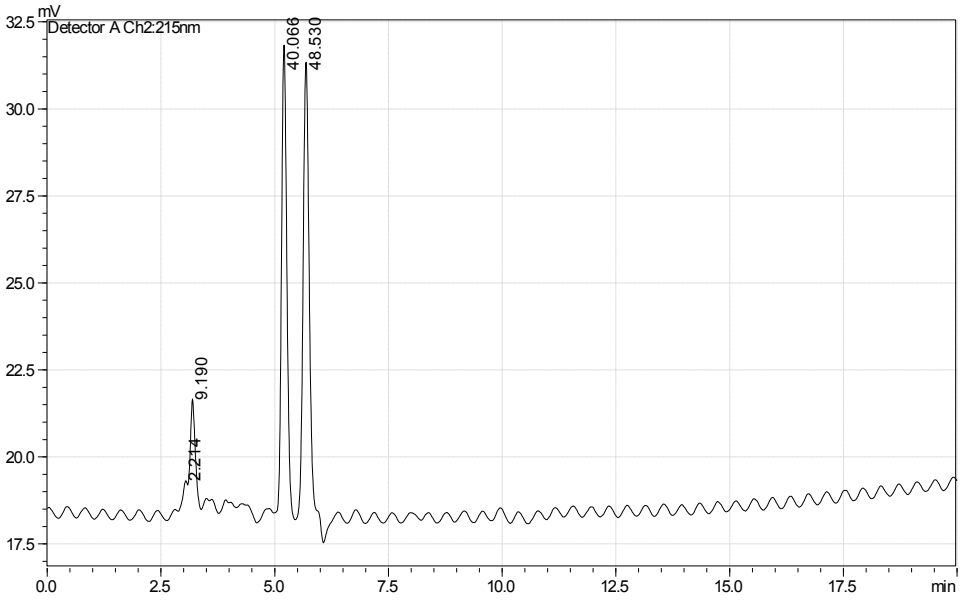


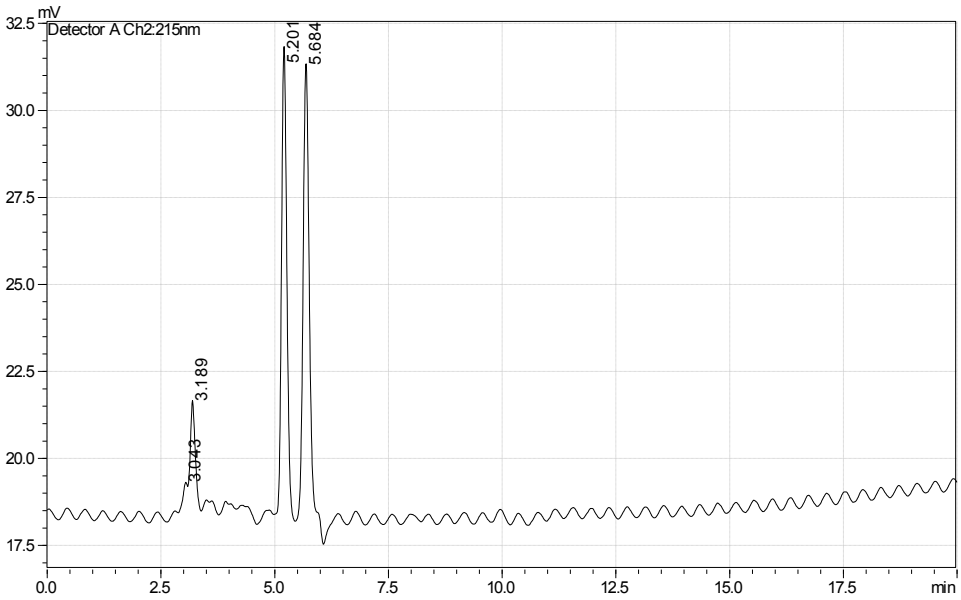
To a 50 mL round bottom flask with **6a2** (310 mg, 1.8 mmol) in dichloromethane (20 mL) under nitrogen was added DMAP (22 mg, 0.18 mmol), Et_3N (0.8 mL, 5.4 mmol) and 4-bromobenzoyl chloride (1.7 g, 7.74 mmol). The reaction was stirred at ambient temperature overnight. Once complete the reaction was washed with saturated $NaHCO_3$, dried and concentrated. The crude residue was purified via flash column chromatography (20 % ethyl acetate/ hexane) to give the 4-bromobenzoate ester of decarestrictine L **6m2** (406 mg, 63%) as a white solid which was recrystallized from hexane as white needles; IR (solid) 540, 668, 757, 848, 972, 1012, 1069, 1102, 1173, 1270, 1398, 1484, 1540, 1590, 1718, 2361, 2849, 2917 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 4.85 – 4.80 (m, 1H), 4.42 (dt, *J* = 9.6, 5.0 Hz, 1H), 3.97 (pd, *J* = 6.5, 4.0 Hz, 1H), 2.81 (dd, *J* = 15.4, 9.2 Hz, 1H), 2.61 (dd, *J* = 15.4, 4.6 Hz, 1H), 2.19 (s, 3H), 2.08 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H), 1.82 – 1.72 (m, 1H), 1.69 – 1.59 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 0.00, 19.22, 24.01, 28.16, 30.45, 45.36, 67.12, 69.92, 71.36, 128.31, 129.00, 131.20, 131.76, 165.13, 206.10; ESI-MS *m/z* calculated $[M+H]^+$ = 355.0540, measured $[M+H]^+$ = 355.0545, opt. rot. $[\alpha]_D^{23}$ = +14.8 (*c* 0.5 chloroform).

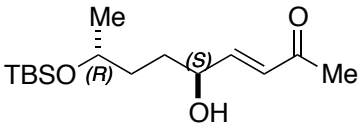
HPLC data for ketone 6l1



5 % isopropanol: hexane Chiracel AJ-H



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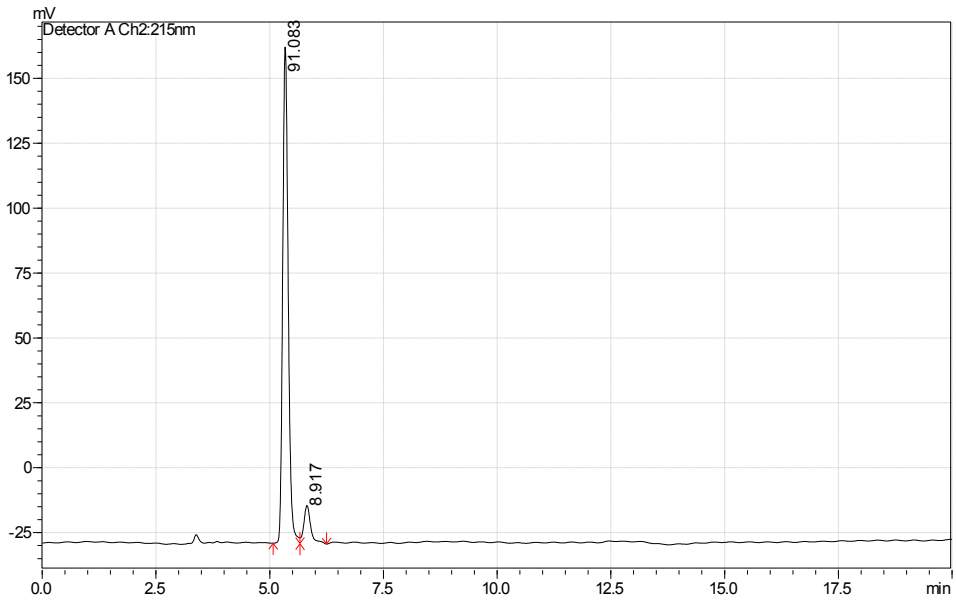
O
TBSO
(R)
(S)
Me
OH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5.0
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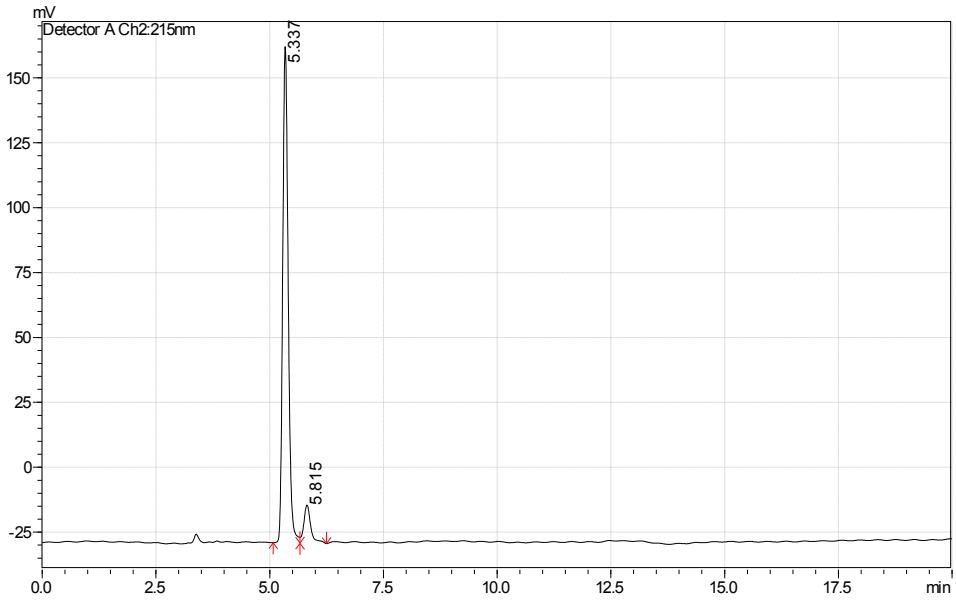
10.0
12.5
15.0
17.5
min


mV
Detector A Ch2:215nm
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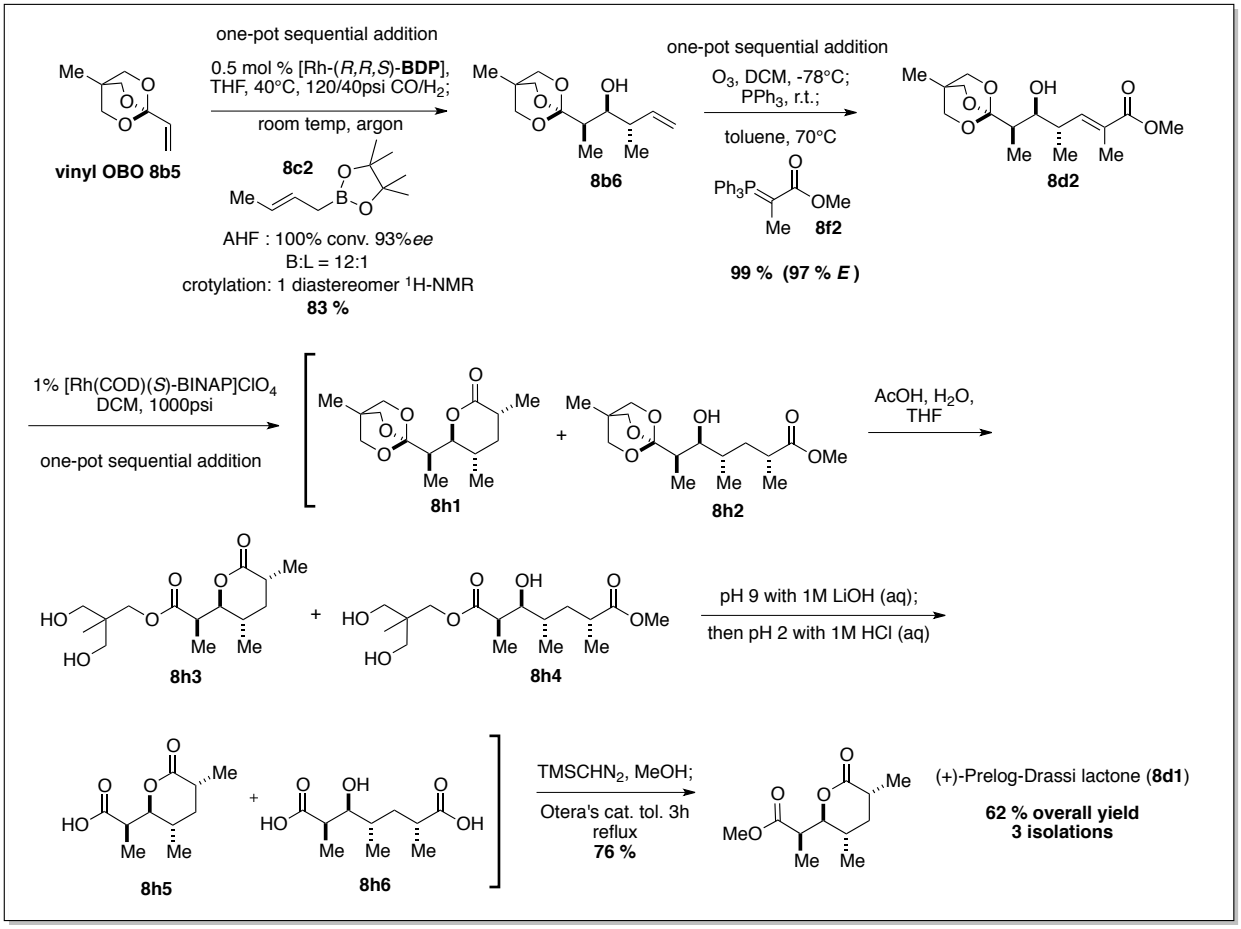
125
100
75
50
25
0
-25
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
min

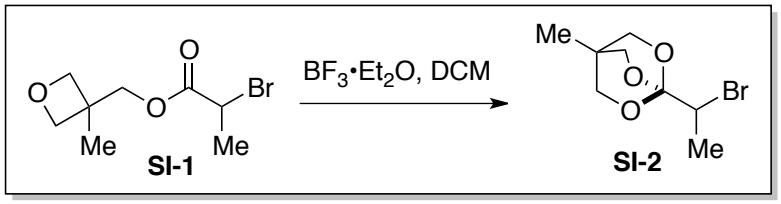
C. The Total Synthesis of (+)-Prelog-Djerassi Lactone via Asymmetric Hydroformylation/ Crotylation



Synthesis of vinyl-OBO (8b5):

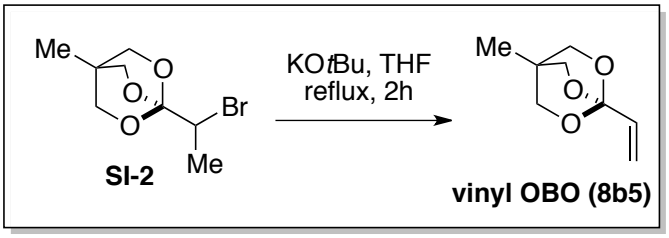
To a dry 100 mL round bottom flask equipped with a stir bar was added 3-methyl-3-oxetanemethanol (1.95 mL, 19.58 mmol), triethylamine (3.3 mL, 23.5 mmol), *N, N*-dimethylaminopyridine (240 mg, 1.96 mmol), and dichloromethane (40 mL). The flask was

cooled to 0 °C and 2-bromopropionyl bromide (2.5 mL, 23.5 mmol) was added slowly over 10 min. The flask was allowed to stir and gradually warm to ambient temperature overnight. The reaction mixture was then poured onto 100 mL of $NaHCO_3$ (sat. aq.) in a 250 mL separatory funnel. The layers were separated and the aqueous layer was extracted 3 times with dichloromethane. The organics were combined, dried, and concentrated. The residue was purified via FCC (10% ethyl acetate: hexanes) to obtain **SI-1** a clear colorless oil (3.52g, 76%), R_f = 0.39, 30% ethyl acetate/ hexanes; IR (neat) 833, 981, 1062, 1098, 1157, 1225, 1259, 1338, 1378, 1447, 1743, 2873, 2935, 2965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.54 (dd, *J* = 6.1, 2.3 Hz, 2H), 4.47 – 4.37 (m, 3H), 4.27 (ABq, *J* = 11.1 Hz, 2H), 1.85 (d, *J* = 6.9 Hz, 2H), 1.37 (s, 3H), ^{13}C-NMR (75 MHz, $CDCl_3$) d 170.2, 79.3, 69.8, 39.7, 39.2, 21.5, 21.0; EI-MS *m/z* calculated: $[M\text{-}CH_2O]^+$= 205.9937, measured $[M\text{-}CH_2O]^+$= 205.9939.



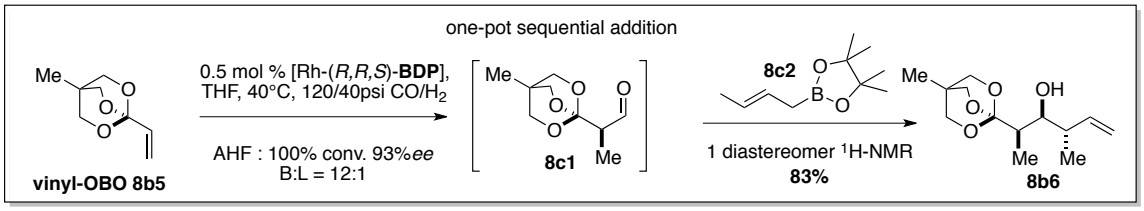
To a dry 100 mL round bottom flask equipped with a stir bar containing 3-methyl-3-oxetanemethyl (2′-bromo) propionate (3.52g, 14.85 mmol) was added dichloromethane (38 mL) and BF_3•Et_2O (0.55 mL, 4.46 mmol) at 0 °C. The reaction was allowed to slowly warm up to ambient temperature overnight. Once the disappearance of starting material was confirmed by TLC analysis, Et_3N (0.64 mL, 4.60 mmol) was added. The mixture was concentrated; the crude residue was triturated with Et_2O and filtered through a plug of Celite and concentrated again. This process was repeated twice to afford a white solid, which was recrystallized from hexanes (3.27g, 93%) R_f = 0.52, 30% ethyl acetate/ hexanes; IR 691, 877, 952, 986, 1082, 1188, 1213, 1268, 1343, 1398, 1471, 1742, 2330, 2357, 2879, 2932, 3005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 4.00 (q, J= 7.0 Hz, 1H), 3.96 (s, 6H), 1.69 (d, *J* = 7.0 Hz, 3H), 0.83 (s, 3H), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 108.1, 73.0, 47.4, 30.5, 20.3, 14.1; EI-MS *m/z* calculated: $[M\text{-}CH_2O]^+$= 205.9937, measured $[M\text{-}CH_2O]^+$= 205.9935, m.p. 87-89 °C.



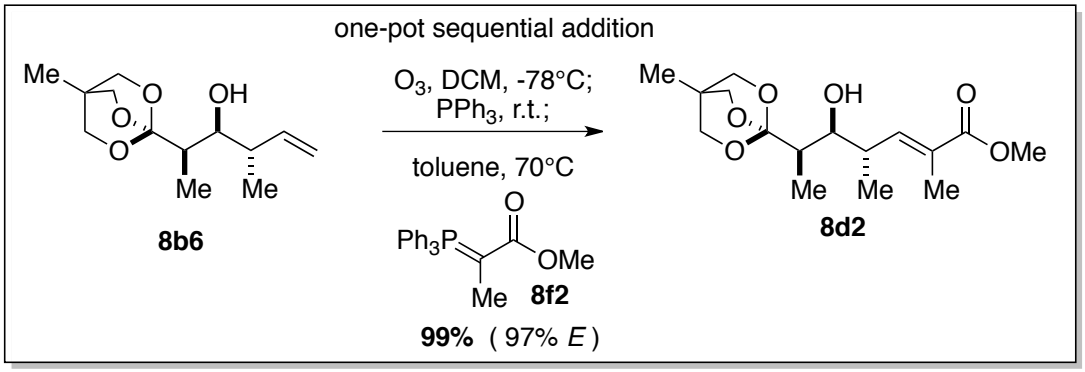
To a dry 500 mL flask equipped with a stir bar containing OBO-bromide **SI-2** (26.95g, 113.7 mmol) was added KO*t*-Bu (30.6g, 274 mmol) and dry THF (280 mL). The flask was fitted with a reflux condenser and the reaction was heated to reflux for 16 h. The reaction was monitored by TLC. Once complete, it was cooled to ambient temperature and diluted with Et_2O to precipitate salts. The suspension was filtered through a plug of Celite and washed 3 times with Et_2O. The filtrate was concentrated to give a crude orange solid. The crude product was purified via Kugelrohr distillation (b.p. 100-110 °C, 1 mTorr) to afford vinyl-OBO **8b5** as a white solid, which was recrystallized from hexanes (12.11g, 68%) R_f = 0.46, 30% ethyl acetate/ hexanes; IR 663, 758, 883, 1065, 1190, 1301, 1356, 1422, 1470, 1660, 1894, 2707, 2741, 2885, 2961, 3044, 3111 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.65 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.31 (dd, *J* = 10.7, 1.5 Hz, 1H), 3.98 (s, 6H), 0.83 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 133.1, 118.7, 105.9, 72.9, 30.5, 14.5; EI-MS *m/z* calculated: $[M]^+$= 156.0781, measured $[M]^+$= 156.0784, m.p. 54-56 °C.

Synthesis of Prelog-Djerassi Lactone:

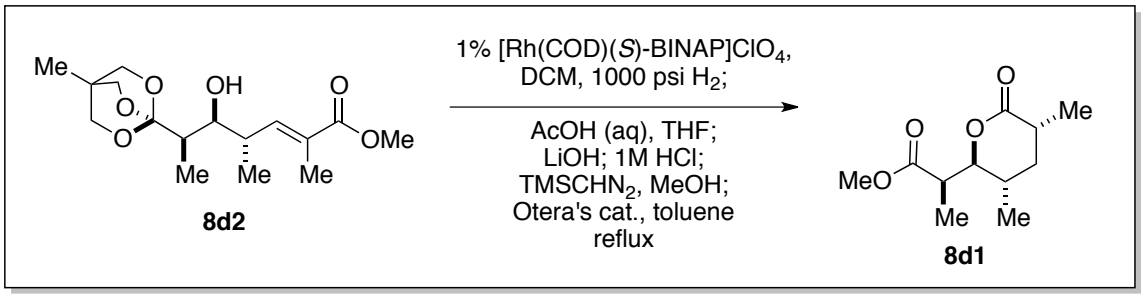


All reagents for the AHF were combined in a nitrogen filled glove box. To a 300 mL pressure tube (Ace Glass #8648-196) equipped with a stir bar was added vinyl-OBO **8b5** (610 mg, 3.90 mmol), $Rh(acac)(CO)_2$ (5 mg, 0.0194 mmol), (*R,R,S*)-**BDP** (Bis[(*R*,*R*,*S*)-DiazaPhos-SPE] Aldrich # 685232) (51 mg, 0.0388 mmol) and 1.94 mL THF. The pressure tube was then connected to a gauged pressure reactor assembly and removed from the glove box. A blast shield was placed in front of the vessel for safety. It was filled/ purged 5 times with CO (120 psi to 40 psi) and then pressurized to 80 psi CO. Then it was charged with 80 psi syngas (1:1 CO: H_2) for a total pressure of 160 psi (3:1 CO: H_2). The vessel was then placed in a 40 °C oil bath and stirred for 43 h during which time the pressure dropped to 155 psi. The reaction vessel was then vented in the fume hood down to 20 psi, removed from the oil bath and allowed to cool to ambient temperature. The remaining pressure was vented into an argon Schlenk line in a fume hood. The pressure head was removed and replaced with a septum. A small aliquot was removed and analyzed by ^{1}H-NMR to confirm completion and obtain an accurate B:L ratio (B:L = 12:1 by ^{1}H-NMR in C_6D_6 RD = 10, 64 scans). Once under argon, the reaction was then transferred to a nitrogen line and *trans*-2-butenyl pinacolato boronic ester (**8c2**) (1.6 mL, 7.8 mmol) was added at rt. The reaction was allowed to stir at ambient temperature for 24 h, transferred to a 100 mL round bottom flask with methanol, then concentrated and purified via FCC (3-20% ethyl acetate: hexanes) to yield **8d2** as a clear colorless oil which solidified upon standing (786 mg, 83 %) R_f = 0.30, 30% ethyl acetate/ hexanes; IR (neat) 1088, 1269, 1310, 1359, 1377, 1411, 1457, 1639,

2885, 2940, 3082, 3539 (broad stretch) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.3, 10.3, 7.8 Hz, 1H), 5.08 (ddd, *J* = 17.2, 1.8, 1.0 Hz, 1H), 5.03 (ddd, *J* = 10.3, 1.8, 0.7 Hz, 1H), 3.91 (s, 6H), 3.84 (d, *J* = 9.4 Hz, 1H), 3.06 (s, 1H), 2.22 (sext, *J* = 7.6 Hz, 1H), 1.96 (qd, *J* = 7.1, 1.1 Hz, 1H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.81 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 142.8, 114.1, 110.9, 73.4, 72.9, 41.0, 40.8, 30.5, 16.7, 14.7, 6.4; ESI-MS *m/z* calculated: $[M+H]^+$ = 243.1591, measured $[M+H]^+$ = 243.1598; m.p. 41-42 °C, opt. rot. $[\alpha]_D^{23}$ = -29.6 (*c* 0.5 ethyl acetate).



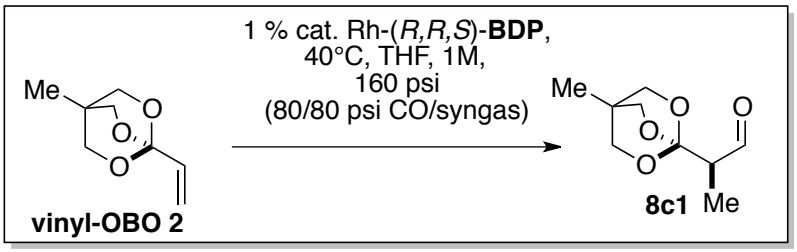
To a 100 mL round bottom flask equipped with a stir bar was added homoallylic alcohol **8b6** (7.5 g, 30.95 mmol) and DCM (100 mL). The flask was cooled to -78 °C. The solution was then sparged with a stream of ozone until a blue color persisted (about 15 min). Then oxygen was bubbled through the solution until the blue color disappeared. The flask was then charged with triphenylphosphine (16.24 g, 61.9 mmol) and allowed to warm to ambient temperature and stirred overnight. The solvent was removed *in vacuo* and replaced with toluene (100 mL) and ylide **8f2** (23.9 g, 68.6 mmol) was added. The mixture was brought to 70 °C and allowed to stir for 16 h. The flask was cooled to ambient temperature and concentrated. The residue was purified via FCC (5-30% ethyl acetate: hexanes) to give **8d2** as a clear colorless oil which solidified upon standing (9.62 g, 91%, >95% *E* isomer) R_f = 0.20, 30% ethyl acetate/ hexanes; IR 947, 1011, 1055, 1092, 1130, 1190, 1227, 1267, 1318, 1360, 1431, 1457, 1649, 1713, 2338, 2362, 2879, 2929, 3509 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (dq, *J* = 9.6, 1.4 Hz, 1H), 3.97 (d, *J* = 9.1 Hz, 1H), 3.90 (s, 6H), 3.70 (s, 3H), 3.03 (s, 1H), 2.59 (tq, *J* = 9.3, 6.9 Hz, 1H), 1.97 (qd, *J* = 7.2, 1.2 Hz, 1H), 1.87 (d, *J* = 1.4 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.80 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.7, 146.2, 127.2, 110.5, 73.5, 72.6, 51.6, 40.6, 36.3, 30.3, 16.0, 14.4, 12.7, 6.3; ESI-MS *m/z* calculated: $[M+H]^+$ = 315.1803, measured $[M+H]^+$ = 315.1805; m.p. 98-99 °C, opt. rot. $[\alpha]_D^{23}$ = -8.4 (*c* 0.5 ethyl acetate).



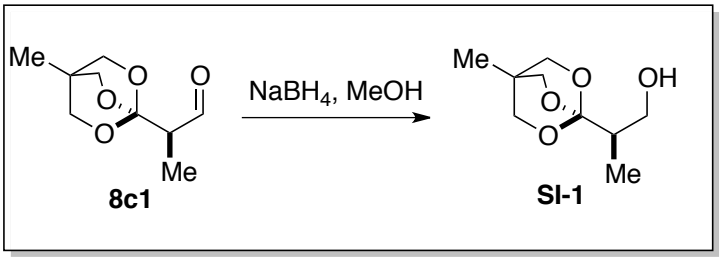
In a nitrogen filled glove box, α,β-unsaturated methyl ester **8d2** (200 mg, 0.636 mmol) was added to a 1.5 dram vial equipped with a magnetic stir bar. To the vial was added [Rh(COD)(*S*)-BINAP]ClO_4 (6 mg, 0.0064 mmol) and DCM (0.636 mL). The vial was then placed in a 100 mL Parr Bomb stainless steel reactor. The reactor was sealed and placed behind a blast shield on top of a stir plate. The reactor was charged with 1000 psi H_2 and stirred for 48 h. The pressure was vented to atmosphere and the vial removed from the Parr bomb. The reaction was concentrated and then dissolved in THF: H_2O (7.7: 1.3 mL) and 2 drops of AcOH was added. The mixture was stirred for 1 h then basified with 1 M LiOH to a pH = 10 and stirred for 1 h. Then the reaction was acidified to pH = 2 with 1M HCl and extracted five times with ethyl acetate, dried and concentrated. The residue was then dissolved in methanol and $TMSCHN_2$ (6 mL, 2.0 M Et_2O) was added. The mixture was stirred for 30 min and concentrated. The residue was then dissolved in toluene (5 mL) and Otera's catalyst (14 mg, 0.013 mmol) was added. The flask was fitted with a reflux condenser and heated to reflux for 4 h, cooled to ambient temperature and concentrated. The residue was purified via FCC (1:1 Et_2O: pentane) to obtain **8d1** as a white solid (103.4 mg, 76 %) which was recrystallized from pentane to white needles, R_f = 0.22, 50% diethyl ether/ hexanes; IR 1180, 1209, 1446, 1730, 2877, 2932, 3004, 3427, 3456 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.54 (dd, *J* = 10.5, 2.9 Hz, 1H), 3.73 (s, 3H), 2.73 (qd, *J* = 7.1, 2.6 Hz, 1H), 2.50 (ddq, (ap. sept.) *J* = 13.6, 7.0, 7.0, 1H), 1.99 – 1.86 (m, 2H), 1.42 (td, (ap. q.) *J* = 13.1, 12.1 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR

(150 MHz, $CDCl_3$) δ 173.7, 173.3, 86.2, 52.2, 41.3, 37.3, 36.2, 30.9, 17.2, 17.0, 8.7; ESI-MS *m/z* calculated: $[M+Na]^+ = 237.1098$, measured $[M+Na]^+ = 237.1096$; m.p. 76-77 °C (lit.[14] 77.0-77.5 °C); opt. rot. $[\alpha]_D^{23} = +39.0$ (*c* 0.2 $CHCl_3$)[lit.[14] $[\alpha]_D^{23} = +39.0$ (*c* 0.2 $CHCl_3$)].

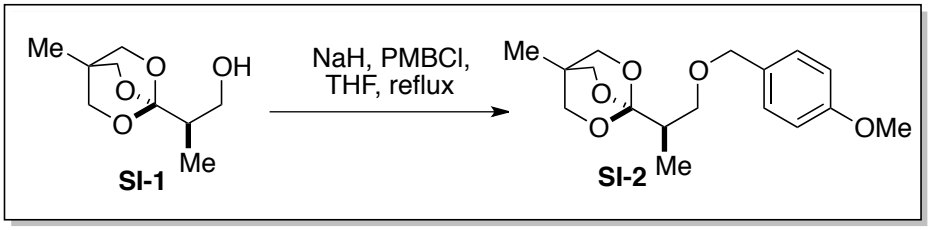
Synthesis of OBO-PMB ether SI-2 for enantiomeric excess determination:



All reagents for the AHF were combined in a nitrogen filled glove box. To a 300 mL pressure tube (Ace Glass #8648-196) equipped with a stir bar was added vinyl-OBO **8b5** (547 mg, 3.5 mmol), $Rh(acac)(CO)_2$ (9 mg, 0.035 mmol), (*R,R,S*)-**BDP** (Bis[(*R*,*R*,*S*)-DiazaPhos-SPE] Alrich # 685232) (51 mg, 0.039 mmol) and 3.5 mL THF. The pressure tube was then connected to a gauged pressure reactor assembly and removed from the glove box. A blast shield was placed in front of the vessel for safety. It was filled/ purged 5 times with CO (120 psi to 40 psi) and then pressurized to 80 psi CO. Then it was charged with 80 psi syngas (1:1 CO: H_2) for a total pressure of 160 psi (3:1 CO: H_2). The vessel was then placed in a 40 °C oil bath and stirred for 24 h during which time the pressure dropped to 155 psi. The vessel was vented to atmosphere in the fume hood and the crude reaction mixture was concentrated and purified via FCC (30% ethyl acetate: hexanes) to yield **8c1** as a white solid (468 mg, 72%) R_f = 0.39, 30% ethyl acetate/ hexanes; IR 1190, 1246, 1300, 1328, 1361, 1391, 1460, 1652, 1725, 2360, 2745, 2852, 2919, 3426 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 10.13 (d, *J* = 1.6 Hz, 1H), 3.47 (s, 6H), 2.78 (qd, *J* = 7.1, 1.6 Hz, 1H), 1.38 (d, *J* = 7.1 Hz, 3H), -0.03 (s, 3H); ^{13}C-NMR (75 MHz, C_6D_6) δ 200.1, 109.3, 72.8, 53.0, 30.4, 14.0, 9.0; ESI-MS *m/z* calculated: $[M+H]^+$ = 187.0965, measured $[M+H]^+$ = 187.0965; m.p. 54-56 °C; opt. rot. $[\alpha]_D^{23}$ = +38.8 (*c* 0.5 ethyl acetate).



To a 25 mL round bottom flask equipped with a stir bar containing OBO-aldehdye **8c1** (437 mg, 2.35 mmol) was added MeOH (5 mL) and $NaBH_4$ (107 mg, 2.81 mmol). The reaction was stir for 30 min and concentrated. The residue was purified via FCC (30% ethyl acetate: hexanes) to yield **SI-1** as a clear, colorless oil (168 mg, 38%), R_f = 0.18, 30% ethyl acetate/ hexanes; IR 916, 950, 990, 1045, 1085, 1118, 1194, 1264, 1352, 1398, 1466, 2362, 2880, 2931, 3447 (broad) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.92 (s, 6H), 3.65 (ddd, *J* = 11.9, 7.6, 4.5 Hz, 1H), 3.56 (ddd, *J* = 11.1, 7.6, 3.3 Hz, 1H), 2.83 (dd, *J* = 7.6, 4.5 Hz, 1H), 2.00 (pd, *J* = 7.2, 3.3 Hz, 1H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.82 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 110.6, 72.5, 64.2, 41.3, 30.3, 14.4, 11.2; ESI-MS *m/z* calculated: $[M+H]^+$ = 189.1122, measured $[M+H]^+$ = 189.1117; opt. rot. $[\alpha]_D^{23}$ = -1.2 (*c* 0.5 ethyl acetate).



To a 25 mL round bottom flask was added OBO-alcohol **SI-1** (80 mg, 0.43 mmol) and THF (2.1 mL). This solution was added via syringe to a flask containing NaH (24 mg, 1 mmol), which was washed with hexanes to remove mineral oil, in THF (2 mL). The flask was fitted with a reflux condenser and heated to 70 °C for 1 h. Then 4-methoxybenzyl chloride (0.14 mL, 1 mmol) was added via syringe and the reaction was stirred at 70 °C for 16 h. The reaction was cooled to ambient temperature and poured onto 50 mL $NaHCO_3$ (sat. aq.) and extracted three times, dried

and concentrated. The crude residue was purified via FCC (5-20% ethyl acetate: hexanes) to yield OBO-PMB **SI-2** (87 mg, 28 %) as oil that solidified upon standing, R_f = 0.41, 30% ethyl acetate/ hexanes; IR 814, 948, 1039, 1086, 1240, 1370, 1399, 1464, 1510, 1612, 2358, 2835, 2858, 2879, 2931, 2977, 3002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 6.89 – 6.84 (m, 2H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.86 (s, 6H), 3.80 (s, 3H), 3.71 (dd, *J* = 9.2, 3.7 Hz, 1H), 3.21 (t, *J* = 9.4 Hz, 1H), 2.10 (dqd, *J* = 9.4, 6.9, 3.7 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.78 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.0, 131.9, 129.1, 113.7, 109.5, 72.5, 72.5, 71.0, 55.2, 40.2, 30.1, 14.5, 12.1; ESI-MS *m/z* calculated: $[M+H]^+$ = 309.1697, measured $[M+H]^+$ = 309.1689; m.p. 57-59 °C; opt. rot. $[\alpha]_D^{23}$ = +18.4 (*c* 0.5 ethyl acetate); SFC 93% ee (Chiracel OJ-H, 10% MeOH, 2 mL/min, see chromatogram below).

PD Lactone dr experiment:

The determination of the diastereomeric ratio via ^1H NMR analysis of the PD Lactone (**8d1**) obtained from the asymmetric hydrogenation / lactonization/ OBO cleavage/ esterification sequence was performed according to the method of Davies.[15] The sample was purified via FCC, which did not separate the diastereomers from each other (or enhance the ratio). The ^1H NMR was recorded on a 600 MHz spectrometer (no spinning to avoid "spinning sidebands") the sample in C_6D_6 in order to resolve (with baseline separation) the diastereomer peaks as shown in spectra on pages 217 and 218. The pulse delay was set to 17 s (>5T_1, T_1= 3 s) to ensure complete (>99%) relaxation of all nuclei observed. The number of scans taken was increased to 64 in order to obtain acceptable signal-to-noise ratio (>10:1) for the smallest peak. The diastereomer ratio was calculated with integrations of the ^{13}C-^1H (satellite of major diastereomer 4.43 ppm) and the ^{12}C-^1H (minor diastereomer 4.24 ppm) according to the equation below. The integrations are divided by 0.0055 (0.01108/2 = 0.0055) in order to account for the ^{13}C natural abundance (1.1%)

and using only one of the satellites. The same analysis was performed on the crystals obtained (pages 219 and 220).

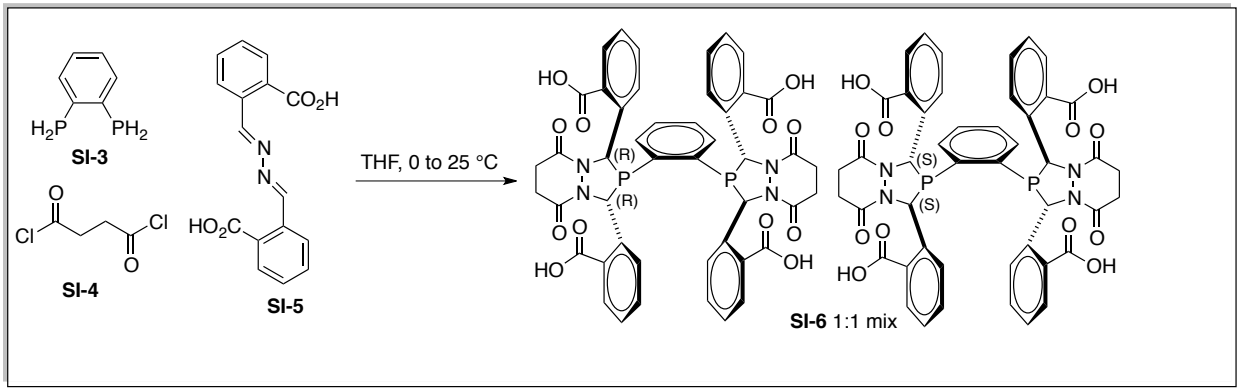
(^{13}C-^{1}H satellite major)/(^{12}C-^{1}H minor)/0.0055 = diast. ratio

1.00/ 5.82/ 0.0055 = 31.2 : 1 (before recrystallization pg. 218)

1.00/ 1.29/ 0.0055 = 140.9 : 1 (after recrystallization pg. 220)

After recrystallization, both ^{1}H (pg.215) and ^{13}C NMR (pg. 216) were recorded in $CDCl_3$ (600 MHz) in order to match the reported data (pg. 229).[7]

Synthesis of (*R*,*R*,*S*)/(*S*,*S*,*S*)-BDP ligands



Tetrahydrofuran (1.1 L) was distilled from sodium/ benzophenone into an oven-dried 2 L round bottom flask under argon. To this flask was added 2,2'-(azinodimethylidyne)bis-benzoic acid **SI-5** (20.86 g, 70.4 mmol). This suspension was stirred at 0 °C. An ampoule with 1,2-bis(phosphino)benzene **SI-3** (5 g, 35.2 mmol from Strem) was opened and immediately fitted with a septum and argon needle. The liquid was transferred to the reaction flask under argon via syringe and the ampoule rinsed with 5 mL of THF to ensure complete transfer. Succinyl chloride **SI-4** (11.7 mL, 106 mmol) was added to the reaction and stirred for 1 h at 0 °C, then at ambient temperature for 24 h. The solid was then collected by filtration and washed with 50 mL of THF before drying under vacuum to afford 16.26 g of racemic tetra acid **SI-6** as white solid (51 %).

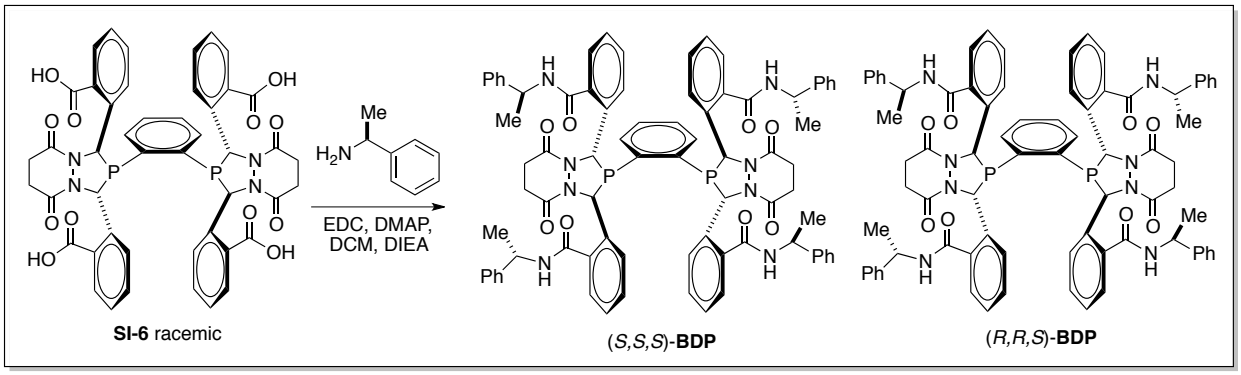
MS-ESI: calc. $(M-H)^-$ = 897.1733, meas 897.1733; m.p. = 250-252 °C (decomp.).

^{1}H NMR (500 MHz, DMSO-d6) δ 12.54 (s, 4H), 8.02 (d, 2H), 7.69 – 7.59 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.31 – 7.19 (m, 4H), 7.16 (s, 2H), 7.13 – 7.07 (m, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.93 – 6.84 (m, 4H), 6.54 – 6.45 (m, 2H), 2.93 – 2.78 (m, 2H), 2.44 – 2.23 (m, 6H).

^{13}C NMR (126 MHz, DMSO) δ 25.18, 29.05, 39.52, 54.38, 57.46, 57.62 (t, *J* = 19.5 Hz), 57.77, 67.07, 125.72, 126.33, 126.55, 126.78, 127.61, 129.06, 129.78, 130.78, 130.90, 130.99, 131.13, 132.89, 138.66, 139.64, 140.65, 140.73 (t, *J* = 10.5 Hz), 140.82, 164.78, 166.97, 167.20, 167.56.

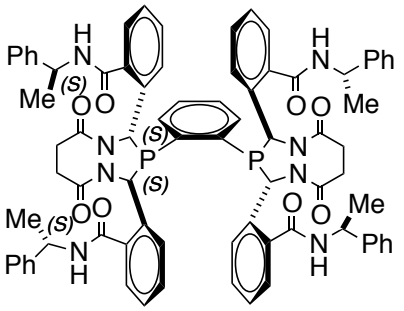
^{31}P NMR (162 MHz, DMSO) δ 4.73.

(*R,R,S*)/(*S,S,S*)-BDP synthesis and purification procedure



To a 250 mL round bottom flask under nitrogen containing the racemic tetra acid **SI-6** (2.7 g, 3.0 mmol) was added *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (2.88 g, 15 mmol, 5 eq.), dichloromethane (150 mL distilled from CaH_2), *N,N*-dimethylaminopyridine (1.83 g, 15 mmol, 5 eq.) and diisopropylethylamine (6.3 mL, 36 mmol, 12 eq.). Next was added (*S*)-(-)-α-methylbenzylamine (1.9 mL, 15 mmol, 5 eq.) and the reaction was stirred for 16 h. The crude reaction mixture was then extracted with 5% HCl (aq.), $NaHCO_3$, H_2O (100 mL each); dried with $MgSO_4$, filtered and concentrated. The crude mixture (4.149g) was dry loaded onto silica gel (5.2g, 122 % of crude mass) and purified via flash column chromatography (column size 70 mm x 8 inches, Silica Gel Spherical Aldrich # 80442, 40-75 mm, 110Å). The diastereomers were separated using dichloromethane: isopropanol: acetic acid (97:2.5:0.5) as an eluent with 14-15 psi of air pressure. The (*R,R,S*) diastereomer eluted first, followed by the (*S,S,S*) diastereomer. Some mixed fractions were obtained and repurified (3 x). The column was monitored with TLC using dichloromethane: isopropanol: acetic acid (95:4:1) and stained with PAA. The (*R,R,S*) diastereomer has an Rf = 0.21 and the (*S,S,S*) diastereomer has an Rf = 0.07. The (*R,R,S*) diastereomer was obtained as a white solid (249 mg, 13 %) and the (*S,S,S*) diastereomer was obtained as a white solid (845 mg, 43 %). No oxidation was detected by ^{31}P NMR or mass spectrometry.

(*S,S,S*)-**BDP**



Chemical Formula: $C_{78}H_{72}N_8O_8P_2$
Molecular Weight: 1311.40

IR 1103.5, 1188.6, 1421.7, 1452.7, 1540.4, 1652.0, 2364.2, 2850.6, 2919.5, 3446.3 cm^{-1};

MS-ESI: calc. $(M+Na)^+$ = 1333.4841, meas 1333.4672; [a] +26.0 (*c* 0.5 $CHCl_3$), m.p. = 165-168 °C

^{1}H NMR (500 MHz, MeOD) δ 9.27 (d, *J* = 7.9 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.47 – 7.43 (m, 4H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.31 – 7.06 (m, 20H), 6.84 (m, 2H), 6.80 (m, 2H), 6.66 (m, 2H), 6.62 – 6.57 (m, 2H), 6.53 (s, 2H), 6.42 – 6.37 (m, 2H), 6.12 – 6.05 (m, 4H), 5.25 (p, *J* = 7.1 Hz, 2H), 4.86 (m, 2H), 2.74 (dt, *J* = 16.0, 10.4 Hz, 2H), 2.52 – 2.42 (m, 2H), 2.42 – 2.33 (m, 2H), 1.82 – 1.75 (m, 2H), 1.48 (d, *J* = 7.1 Hz, 6H), 1.12 – 1.04 (d, *J* = 6.8 Hz , 6H).

^{13}C NMR (126 MHz, MeOD) δ 22.68, 23.04, 27.33, 27.40, 29.97, 30.76, 33.10, 47.36, 47.40, 49.00, 50.65, 51.22, 56.78, 59.18, 126.49, 127.44, 127.65, 128.16, 128.54, 128.80, 129.57, 129.72, 129.80, 130.13, 130.49, 131.71, 132.10, 132.45, 134.39, 135.34, 137.42, 139.26, 144.71, 145.36, 167.63, 168.89, 169.71, 169.82.

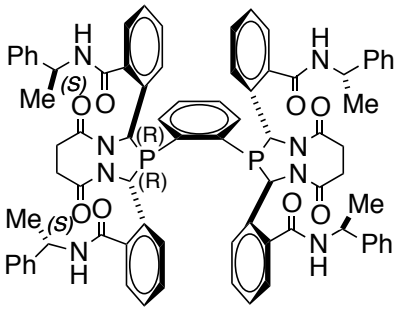
^{31}P NMR (162 MHz, MeOD) δ 6.85.

^{1}H NMR (500 MHz, THF-d8) δ 9.26 (d, *J* = 7.6 Hz, 2H), 7.62 – 7.56 (m, 2H), 7.55 – 7.49 (m, 4H), 7.44 – 7.35 (m, 2H), 7.35 – 7.11 (m, 20H), 6.90 (m, 8H), 6.62 (t, *J* = 7.5 Hz, 4H), 6.16 (m, 2H), 6.07 (m, 4H), 5.37 (m, 2H), 5.02 (m, 2H), 2.57 – 2.28 (m, 8H), 1.55 (d, *J* = 7.0 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, THF-d8) δ 22.34, 23.48, 30.06, 30.27, 30.81, 30.90, 49.52, 49.64, 50.62, 50.72, 56.98, 59.38, 67.57, 79.63, 114.81, 126.22, 127.36, 127.46, 127.81, 128.08, 128.80, 129.19, 129.45, 130.81, 131.65, 132.07, 134.96, 135.33, 137.13, 137.76, 140.69, 145.67, 145.88, 166.80, 168.11.

^{31}P NMR (162 MHz, THF-d8) δ 5.44.

(*R,R,S*)-**BDP**



Chemical Formula: $C_{78}H_{72}N_8O_8P_2$
Molecular Weight: 1311.40

IR 698.9, 1188.2, 1375.8, 1447.1, 1534.8, 1643.7, 2849.4, 2918.0, 2969.6, 3061.0, 3275.4 cm^{-1}; MS-ESI: calc. $(M+Na)^+$ = 1333.4841, meas 1333.4806; [a] -92.4 (*c* 0.5 $CHCl_3$), m.p. = 165-168 °C.

^{1}H NMR (500 MHz, MeOD) δ 9.16 (d, *J* = 8.2 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 2H), 7.56 – 7.48 (m, 4H), 7.40 (m, 4H), 7.32 – 7.14 (m, 20H), 7.13 – 7.06 (m, 4H), 6.88 – 6.73 (m, 6H), 6.52 – 6.42

(m, 4H), 6.42 – 6.34 (m, 2H), 5.27 (m, 2H), 4.76 (m, 2H), 2.76 – 2.59 (m, 4H), 2.56 – 2.32 (m, 4H), 1.47 (d, J = 7.0 Hz, 6H), 1.41 (d, J = 7.0 Hz, 6H).

^{13}C NMR (126 MHz, MeOD) δ 20.82, 22.84, 23.25, 29.48, 29.94, 49.00, 50.78, 50.89, 51.00, 56.61, 58.05, 126.71, 127.13, 127.63, 128.10, 128.35, 129.15, 129.50, 129.62, 130.26, 130.57, 131.58, 131.64, 131.89, 134.86, 135.92, 136.21, 137.89, 138.77, 145.08, 145.10, 167.72, 168.99, 169.53, 169.61, 170.44, 175.26.

^{31}P NMR (162 MHz, MeOD) δ 11.01.

^{1}H NMR (500 MHz, THF-d8) δ 9.20 (s, 2H), 7.93 (d, J = 8.5 Hz, 2H), 7.65 – 7.54 (m, 4H), 7.50 (m, 4H), 7.37 – 7.04 (m, 20H), 6.85 – 6.66 (m, 6H), 6.66 – 6.48 (m, 4H), 6.38 (s, 2H), 5.39 (m, 2H), 5.06 (m, 2H), 2.90 (s, 2H), 2.71 – 2.57 (m, 2H), 2.42 (m, 4H), 1.89 (s, 6H), 1.55 (d, J = 7.0 Hz, 6H), 1.36 (d, J = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, THF-d8) δ 23.19, 23.34, 29.57, 30.19, 30.81, 49.91, 50.10, 50.21, 56.89, 57.46, 67.57, 126.44, 127.40, 127.44, 127.56, 127.72, 128.00, 128.60, 128.80, 129.15, 129.29, 130.65, 130.79, 130.93, 131.50, 134.77, 136.22, 136.90, 138.75, 139.52, 144.85, 146.34, 166.85, 168.06, 168.25, 168.54.

^{31}P NMR (162 MHz, THF-d8) δ 10.2.

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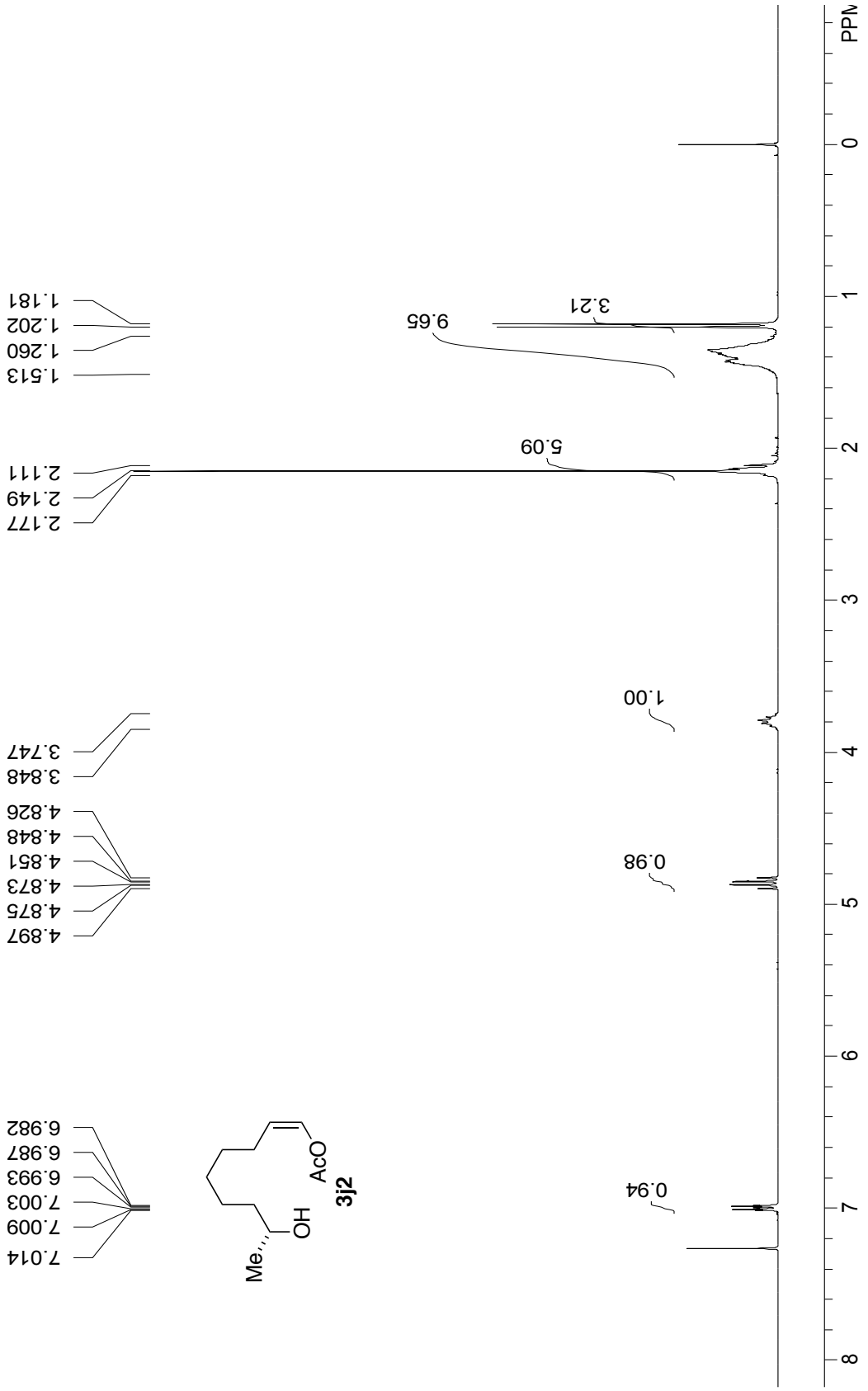
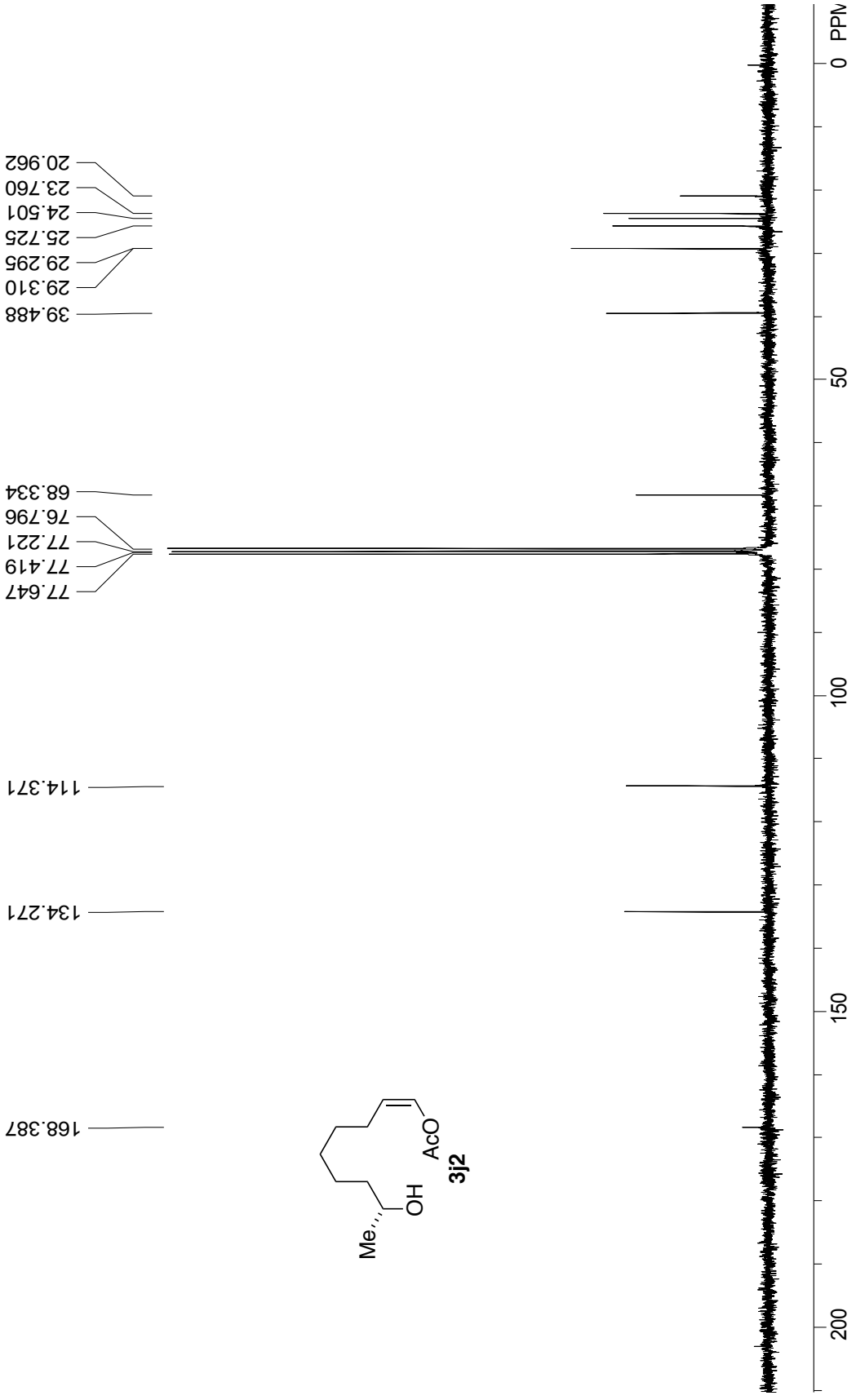
Appendix A: Selected ^{1}H and ^{13}C NMR Spectra

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77.647
77.419
77.221
76.796
68.334
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29.310
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24.501
23.760
20.962
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AcO
3j2
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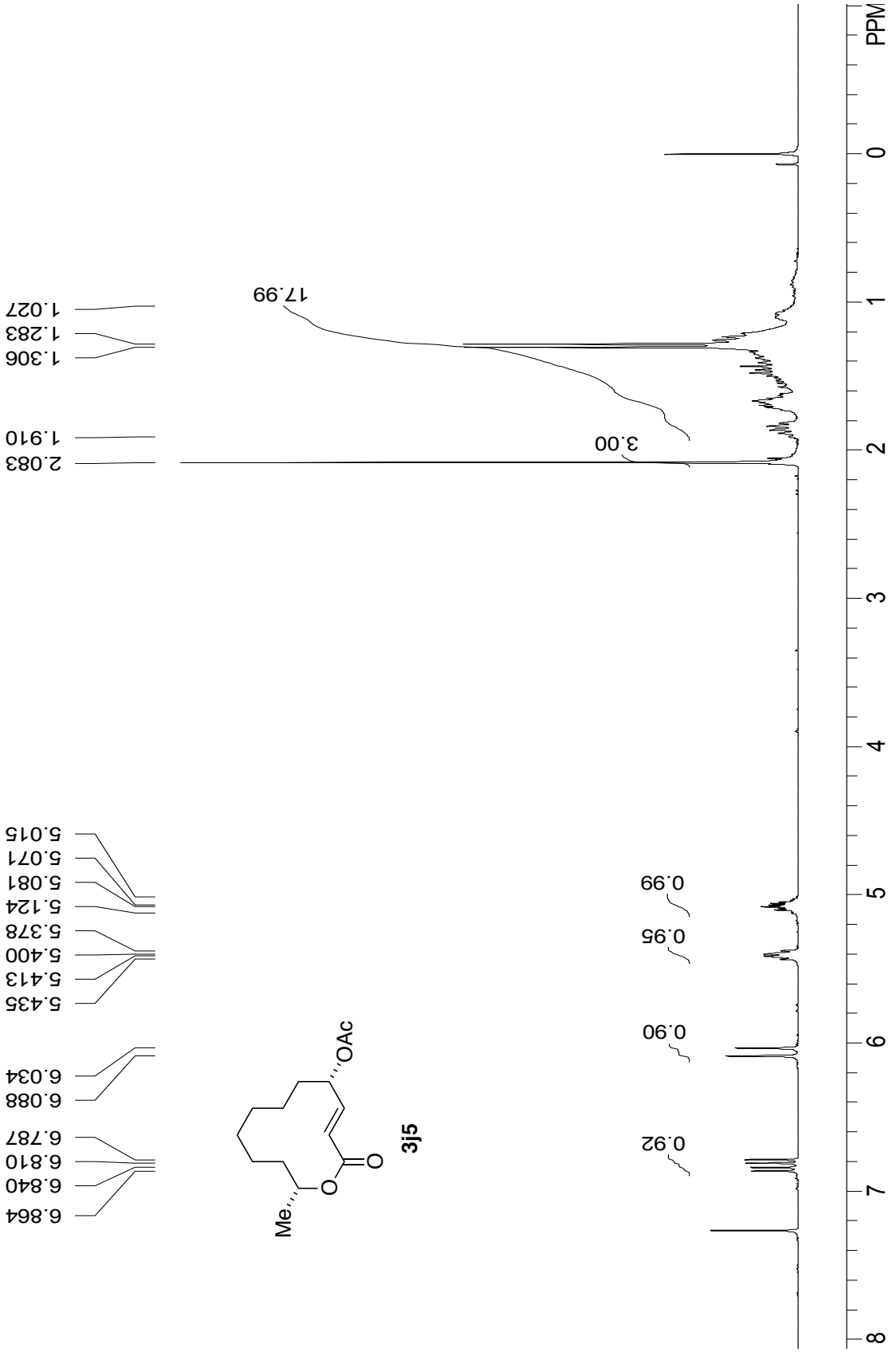
150
100
50
0 PPM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3
4
5
6
7
8
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0.95
0.99
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17.99
2.083
1.910
1.306
1.283
1.027
5.435
5.413
5.400
5.378
5.124
5.081
5.071
5.015
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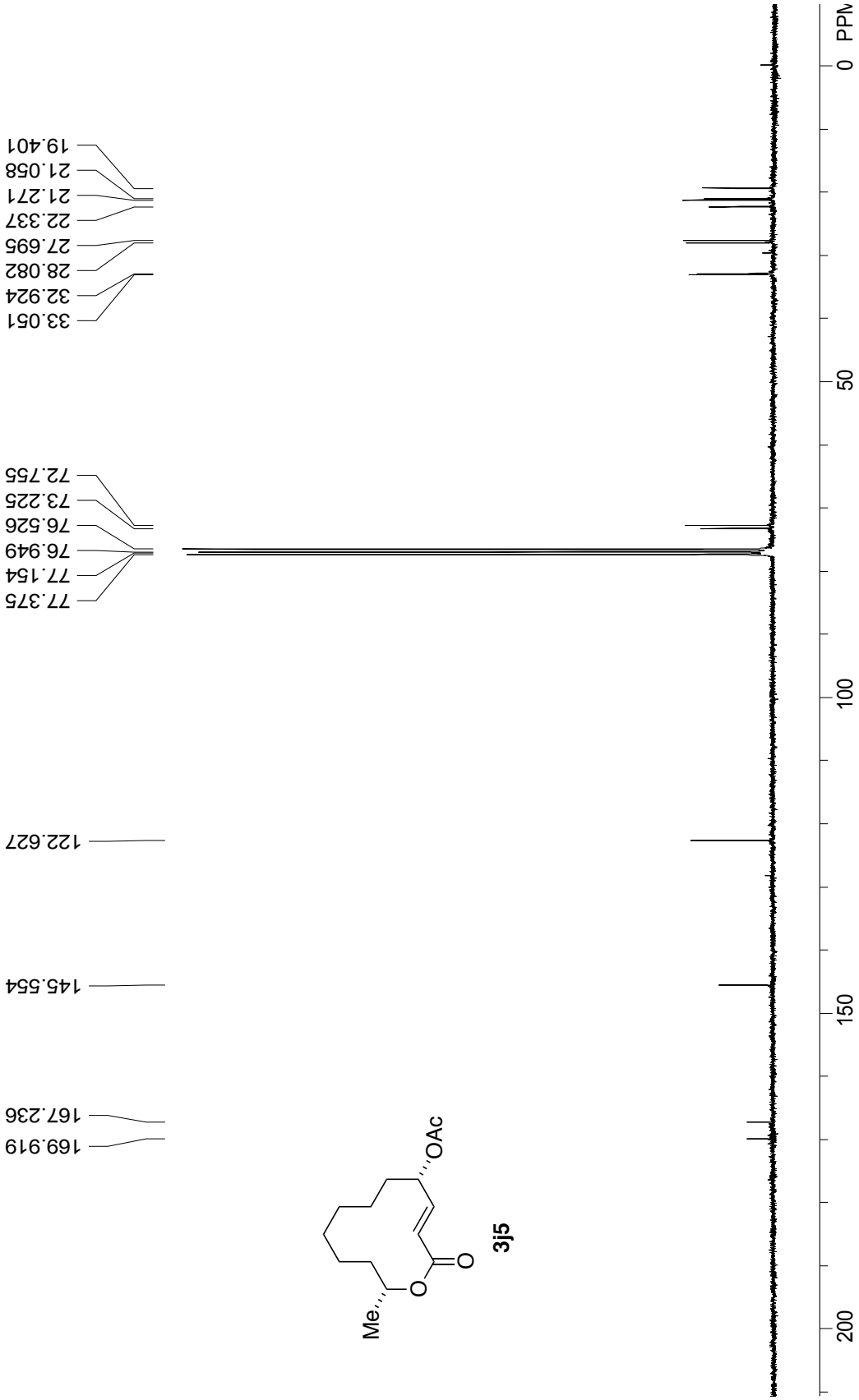
6.840
6.810
6.787
6.088
6.034
Me
OAc
O
O
3j5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77.154
77.375
122.627
145.554
167.236
169.919
Me
O
O
OAc
3j5
200
150
100
50
0 PPM

PPM
0
1
2
3
4
5
6
7
0.05
1.00
1.00
1.07
1.03
4.25
14.95
1.000
1.284
1.297
1.811
4.502
4.514
5.049
5.107
6.033
6.036
6.065
6.068
6.082
6.084
6.114
6.116
6.828
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6.860
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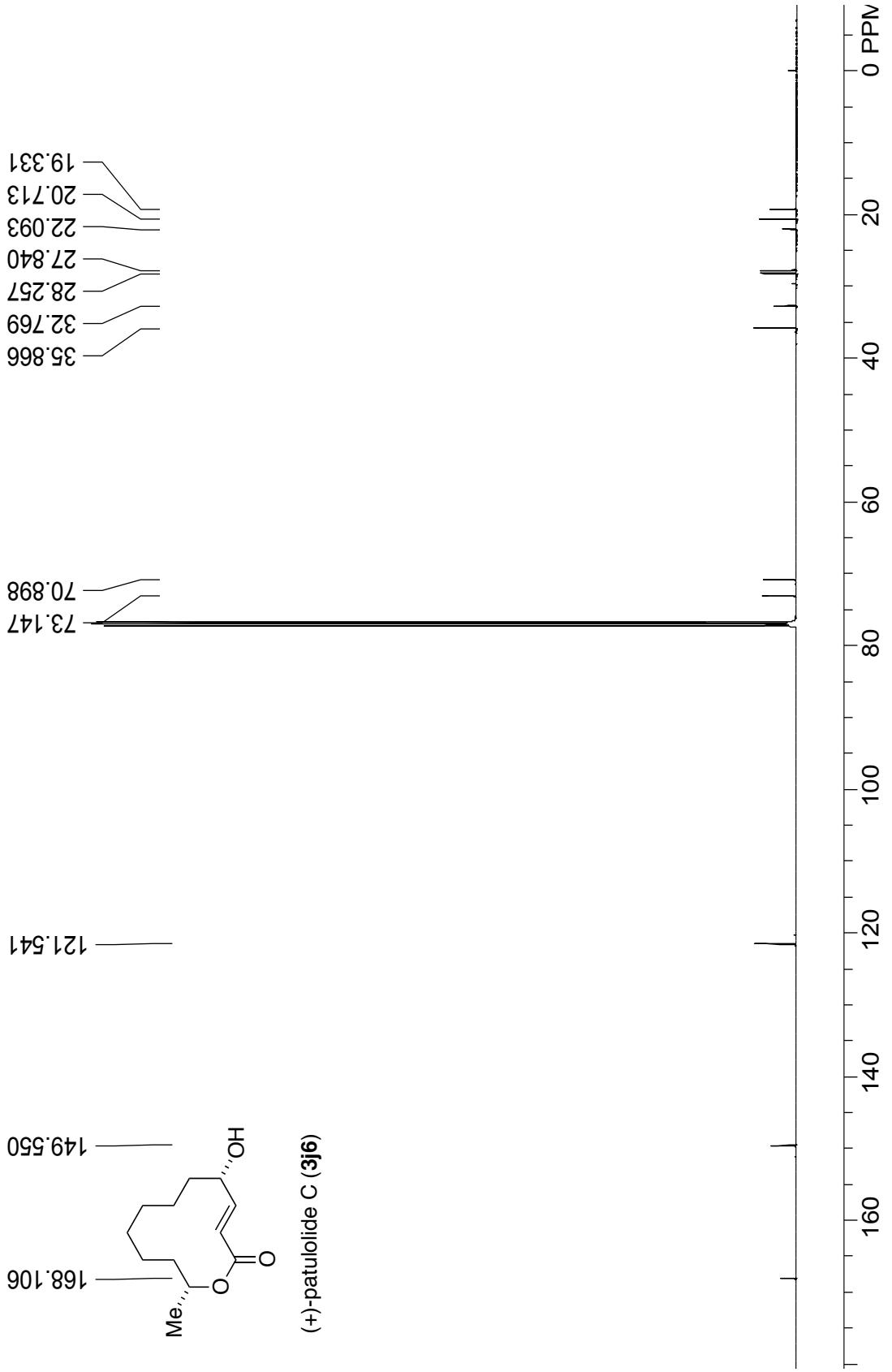
7.030
7.039
Me
O
O
OH
(+)-patulolide C (3j6)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160
140
120
100
80
60
40
20
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Area % Report

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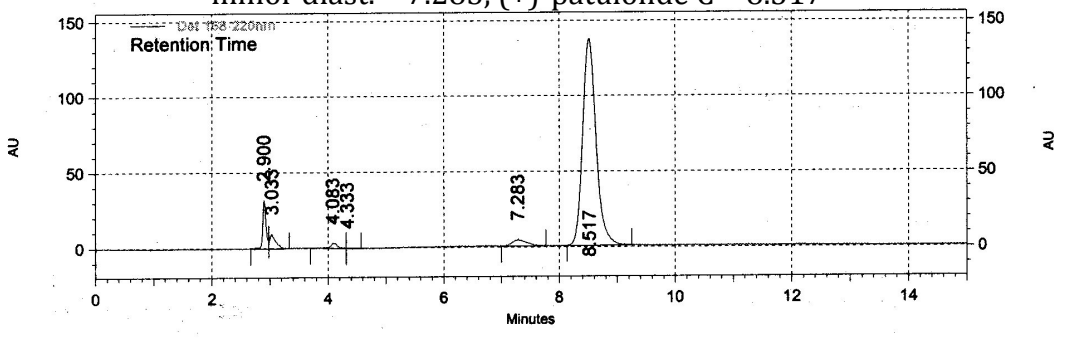
minor diast. = 7.283, (+)-patulolide C = 8.517



Det 168-220nm
Results

Time	Area	Area %	Height	Height %
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4.083	31564	1.26	3354	1.79
4.333	3548	0.14	572	0.31
7.283	78193	3.11	4276	2.29
8.517	2202629	87.74	137259	73.35
Totals	2510407	100.00	187126	100.00

Spectroscopic Data Comparison for (+)-Patulolide C (**1**)

Lit.[a] ^{1}H-NMR 90 MHz	Meas.[b] ^{1}H-NMR 500MHz		Lit.[a] ^{13}C-NMR 100MHz	Meas.[b] ^{13}C-NMR 125MHz
0.93-2.03ppm, 12H, m	1.0-1.81ppm, 12H, m		168.1	168.1
1.32ppm, 3H, d,J=6.6Hz	1.29ppm,3H, d,J=7Hz		121.5	121.5
4.33-4.58ppm, 1H, m	4.51ppm, 1H,m		149.7	149.6
4.85-5.23ppm, 1H, m	5.08ppm,1H,m		70.9	70.9
6.07ppm, 1H, d,J=16.5Hz	6.10ppm, 1H,dd, J=16,1Hz		35.9	35.9
6.82ppm, 1H, dd,J=16.5, 6.3Hz	6.85ppm, 1H,dd, J=16,7Hz		20.7	20.7
			28.3	28.3
			27.8	27.8
			22.2	22.1
			32.8	32.8
			73.2	73.1
			19.3	19.3

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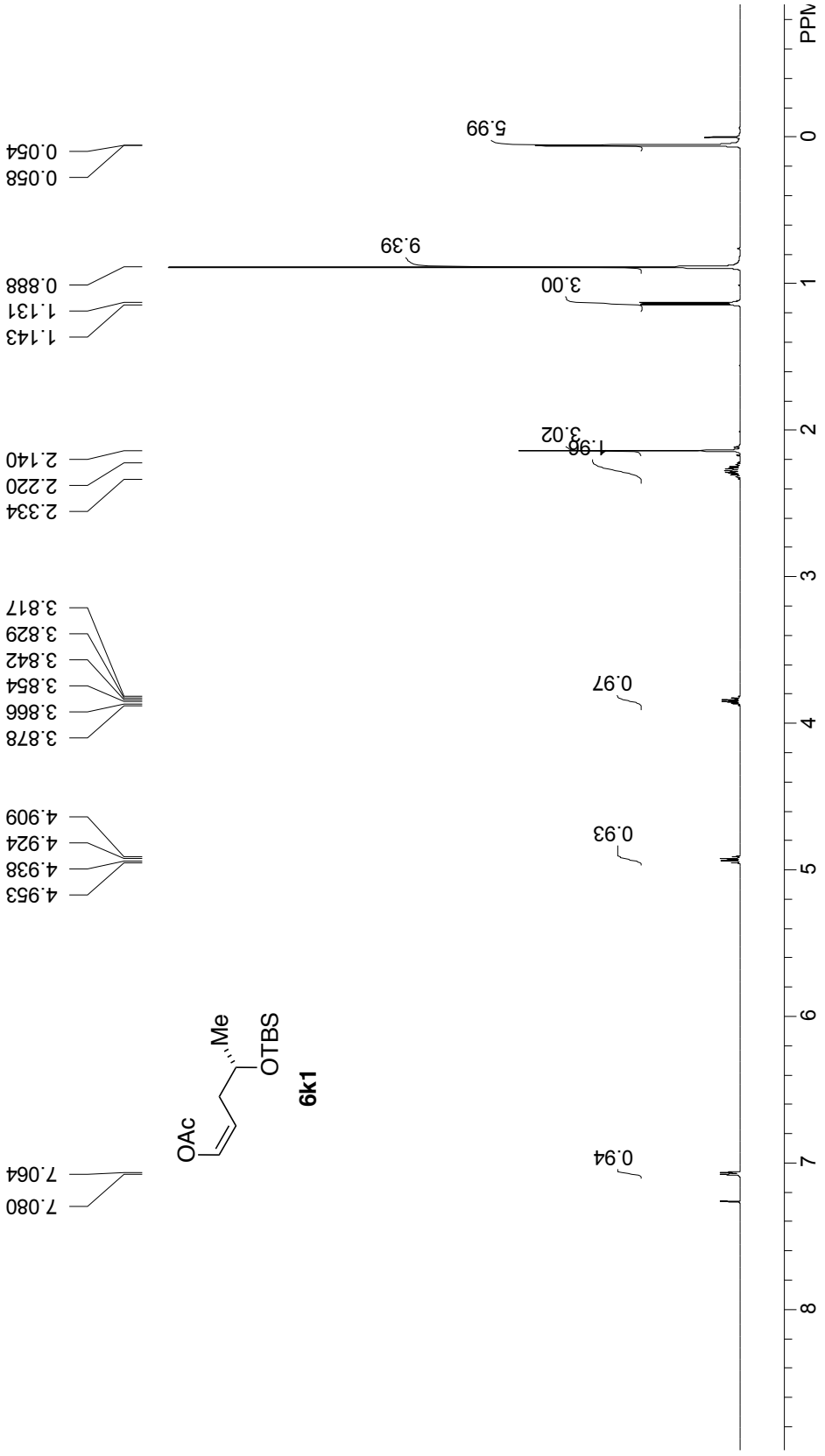
b. This work.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0.93
0.94
0.054
0.058
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1.131
1.143
2.140
2.220
2.334
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3.829
3.842
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OTBS
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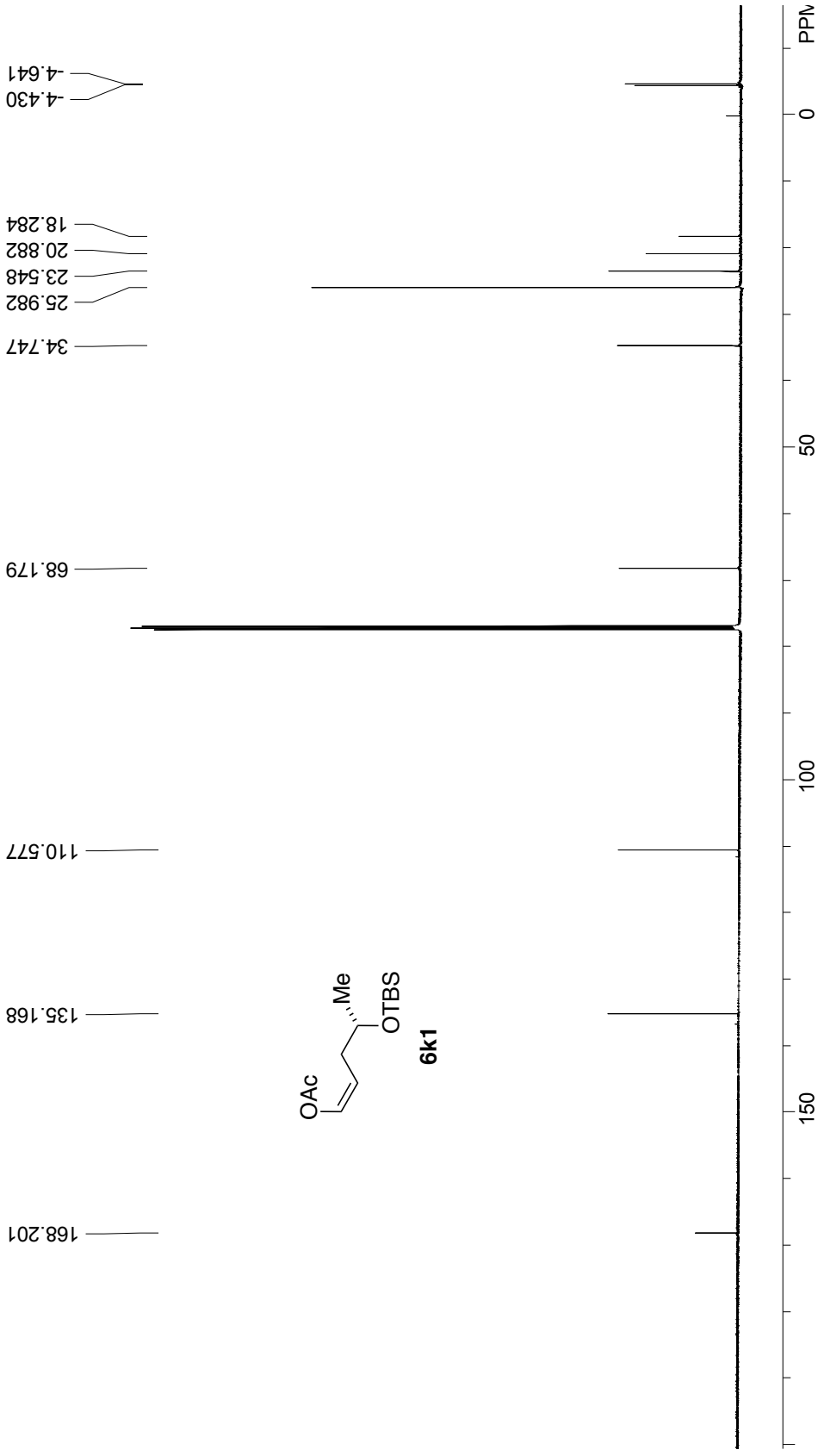
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OTBS
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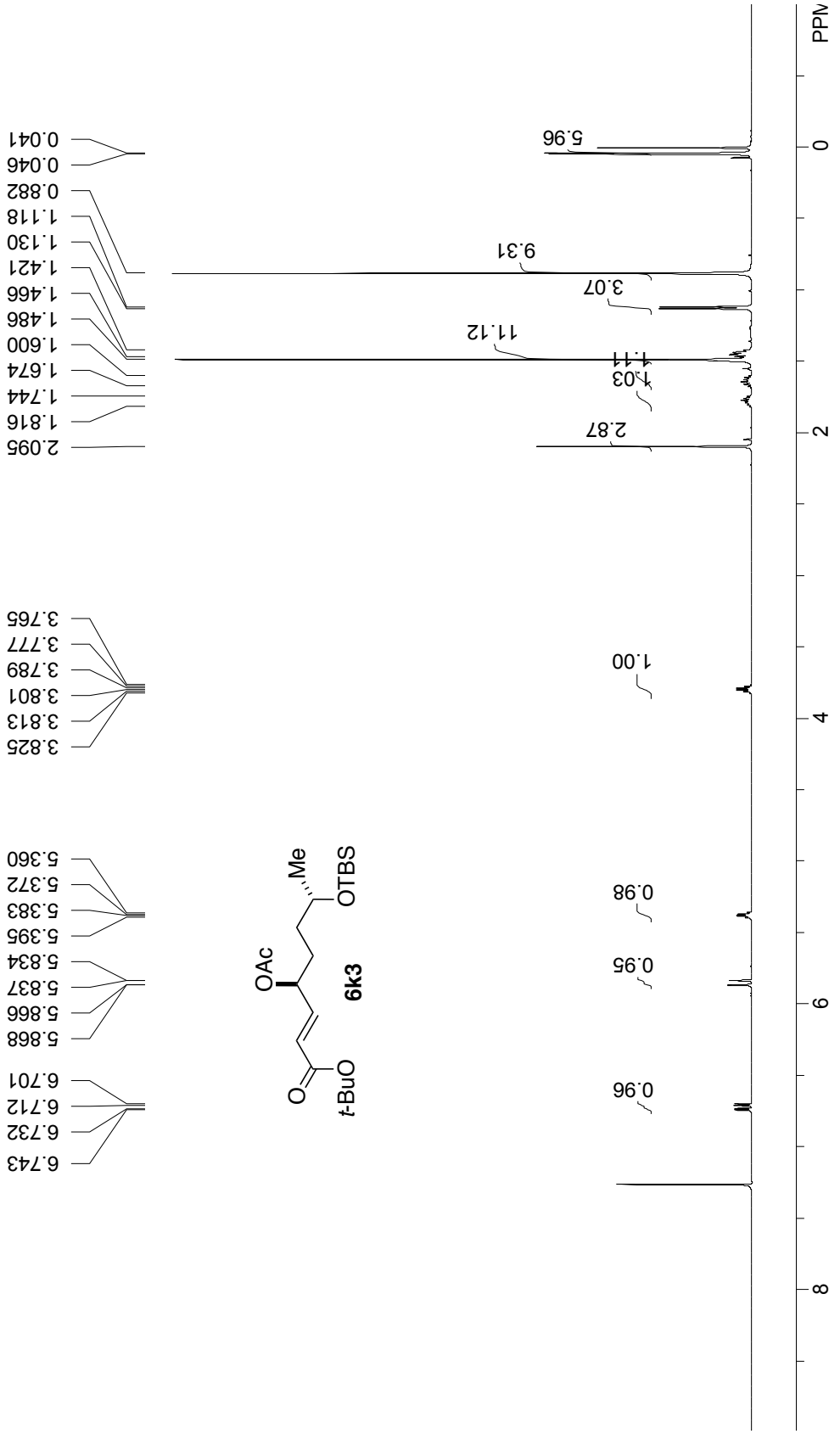
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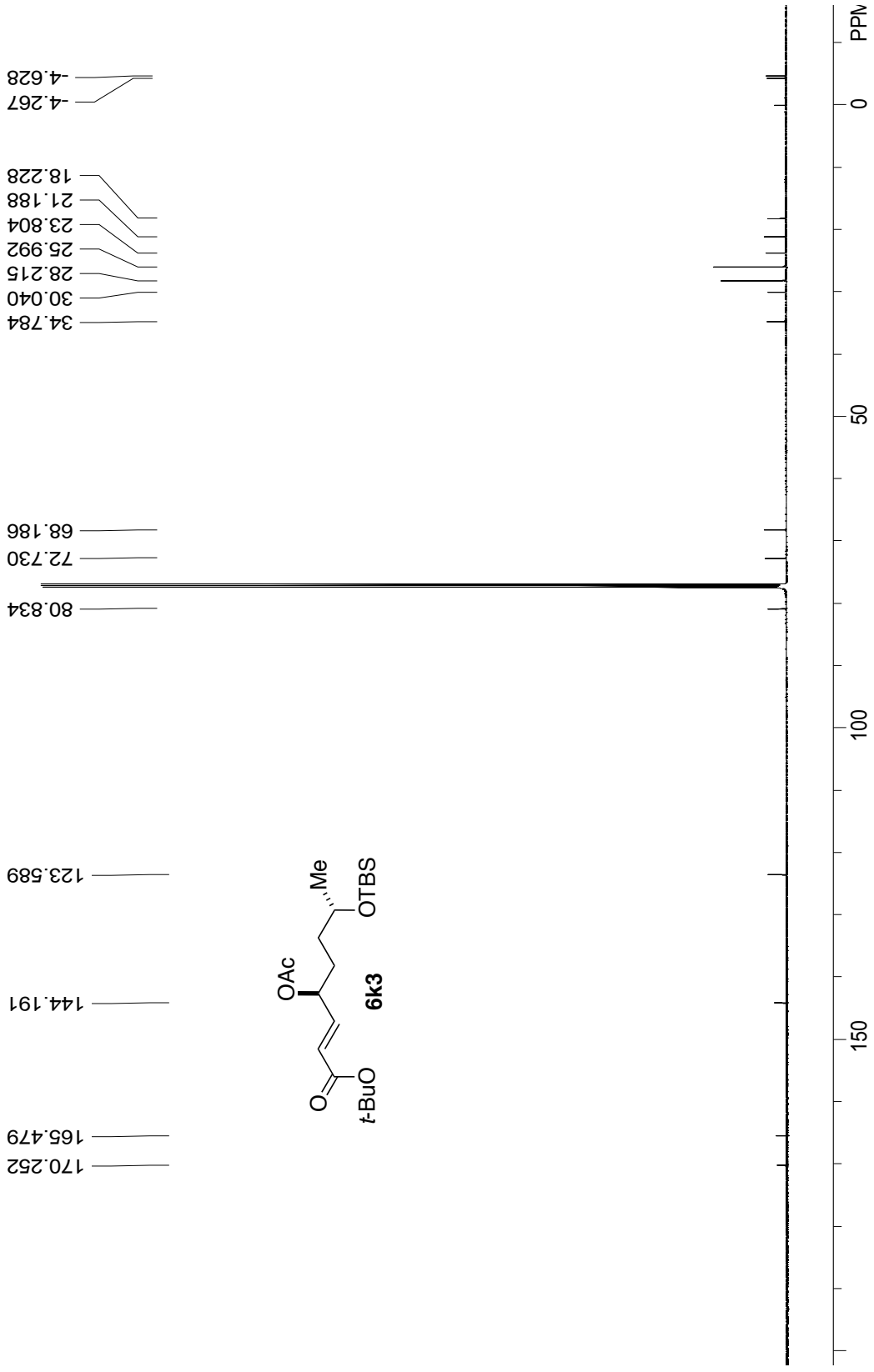
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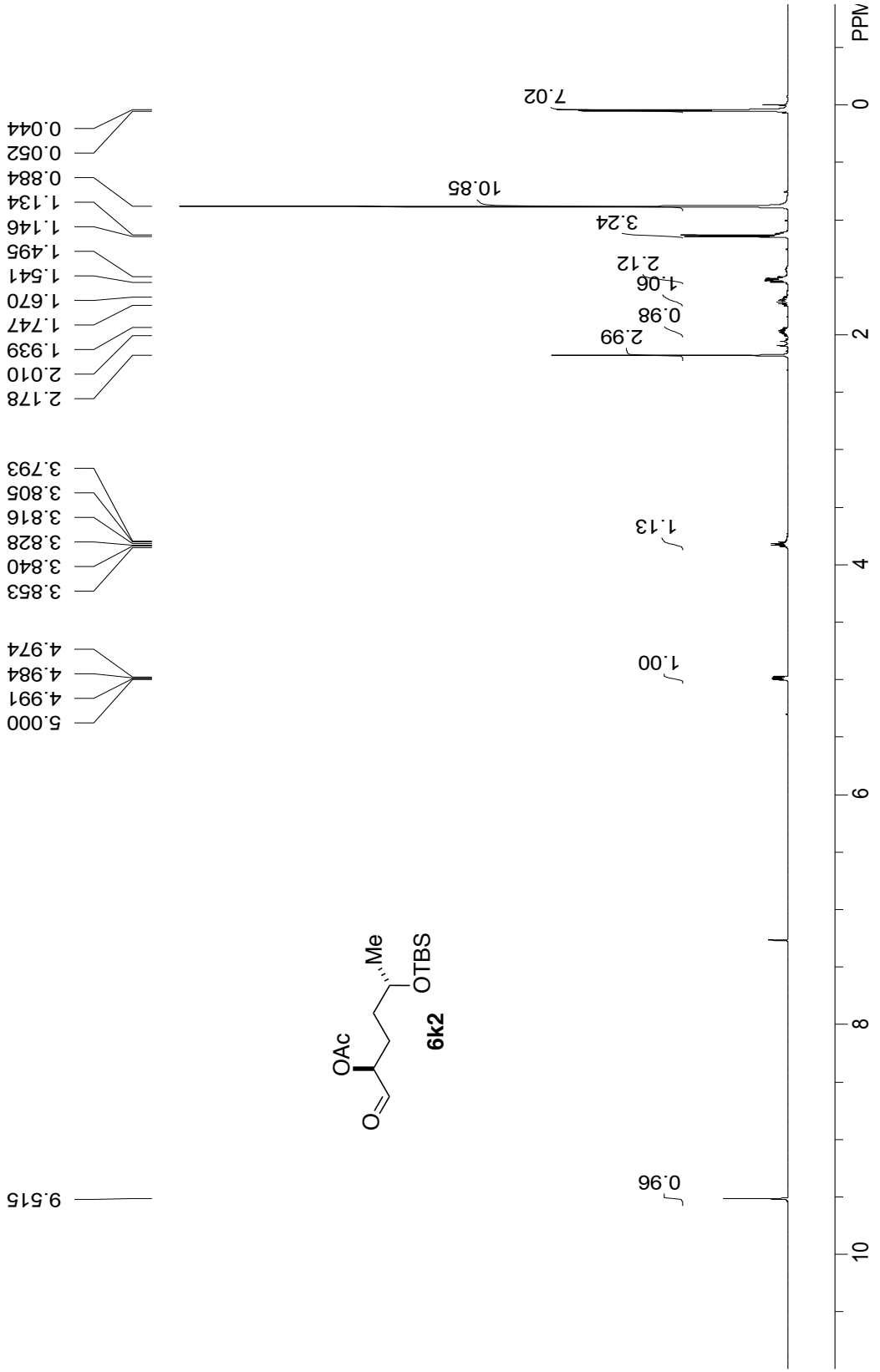
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8
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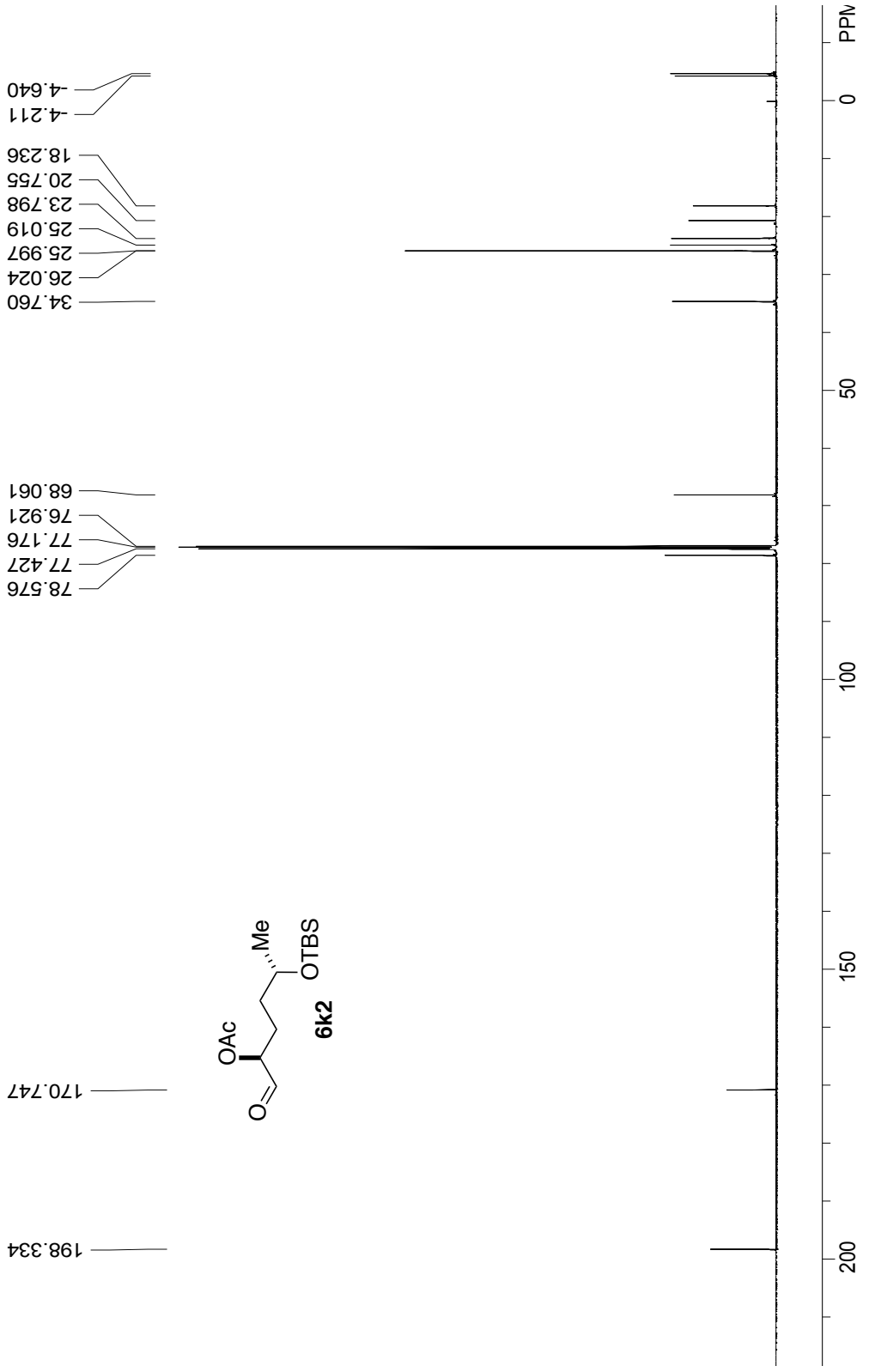
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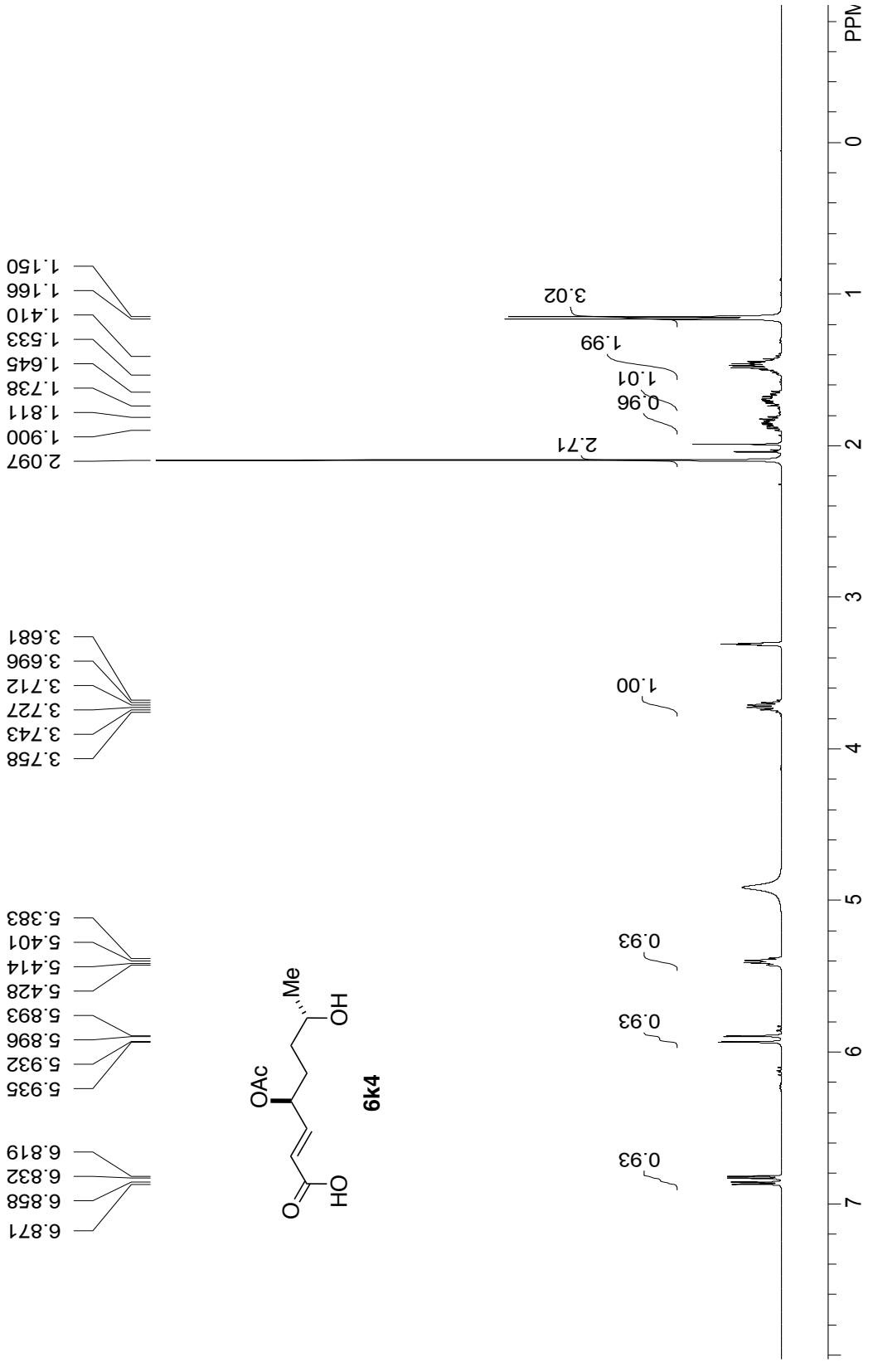
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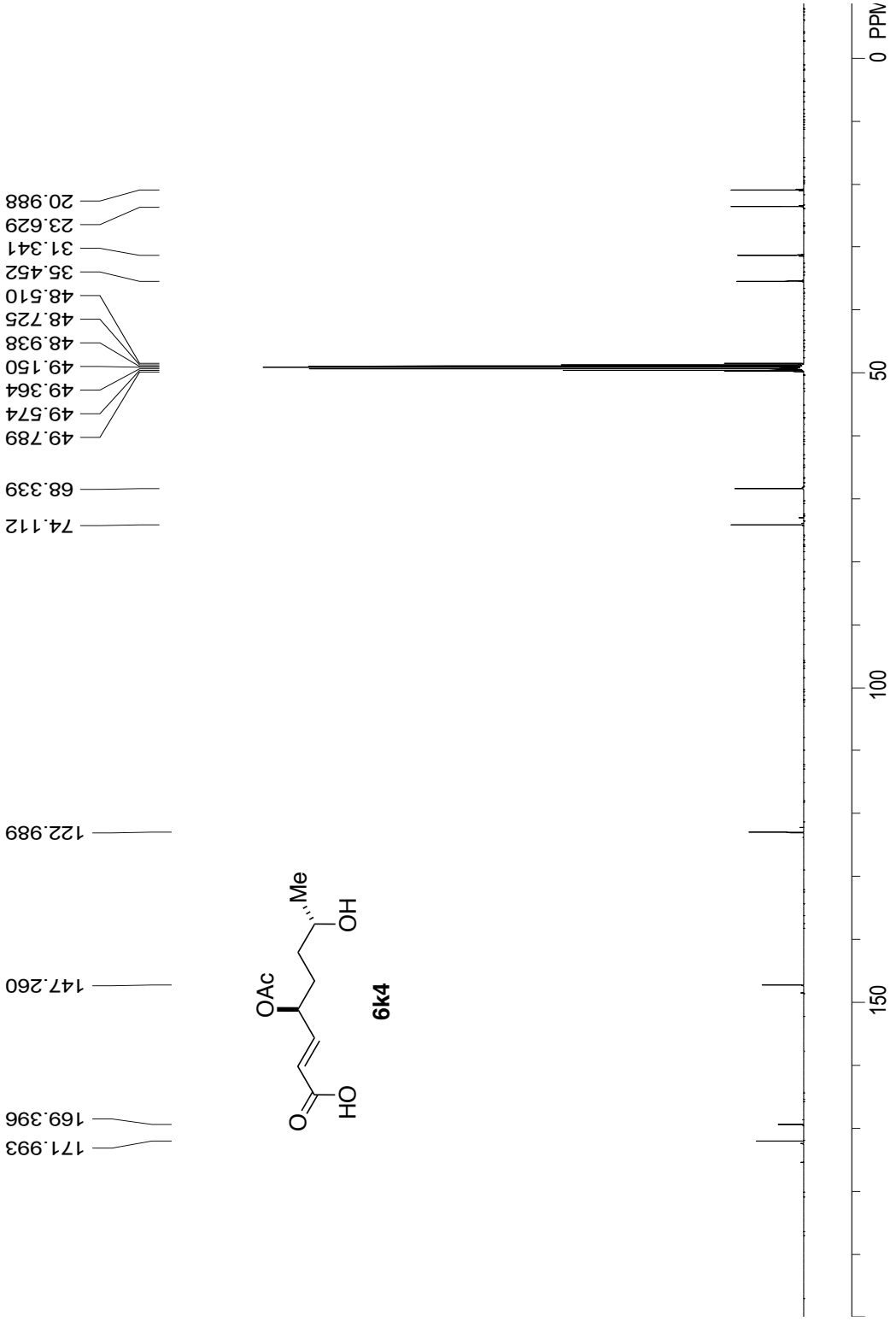
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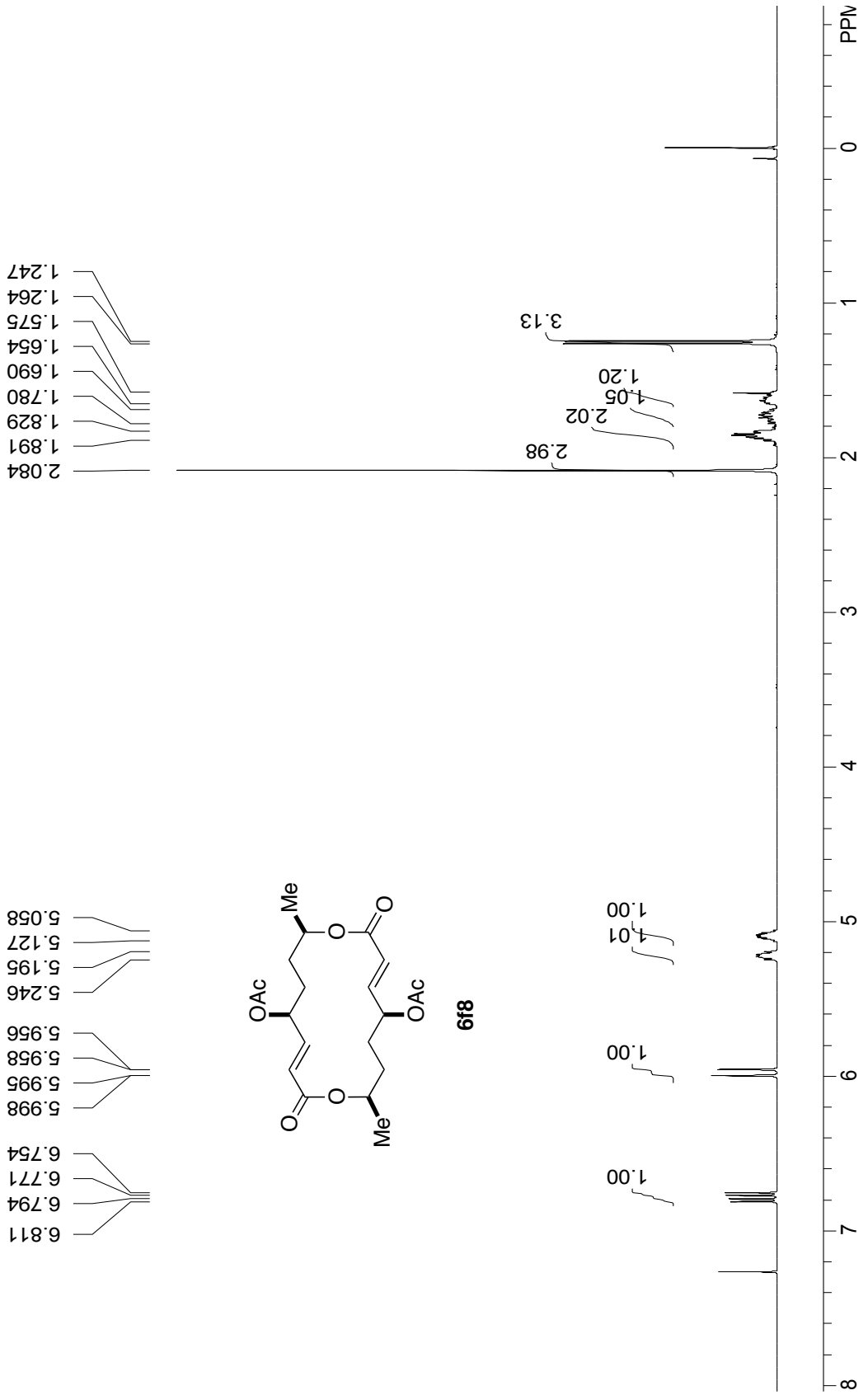
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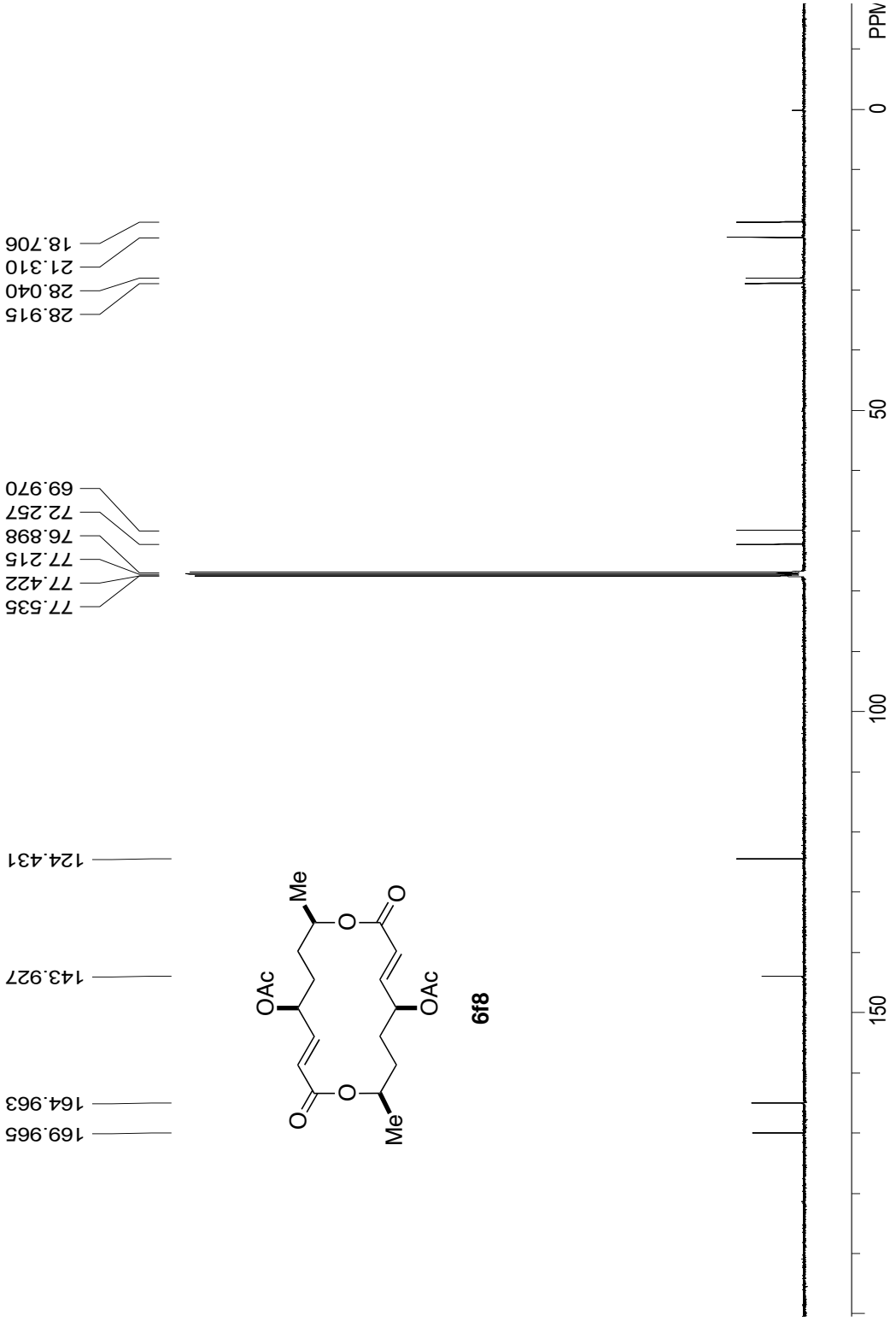
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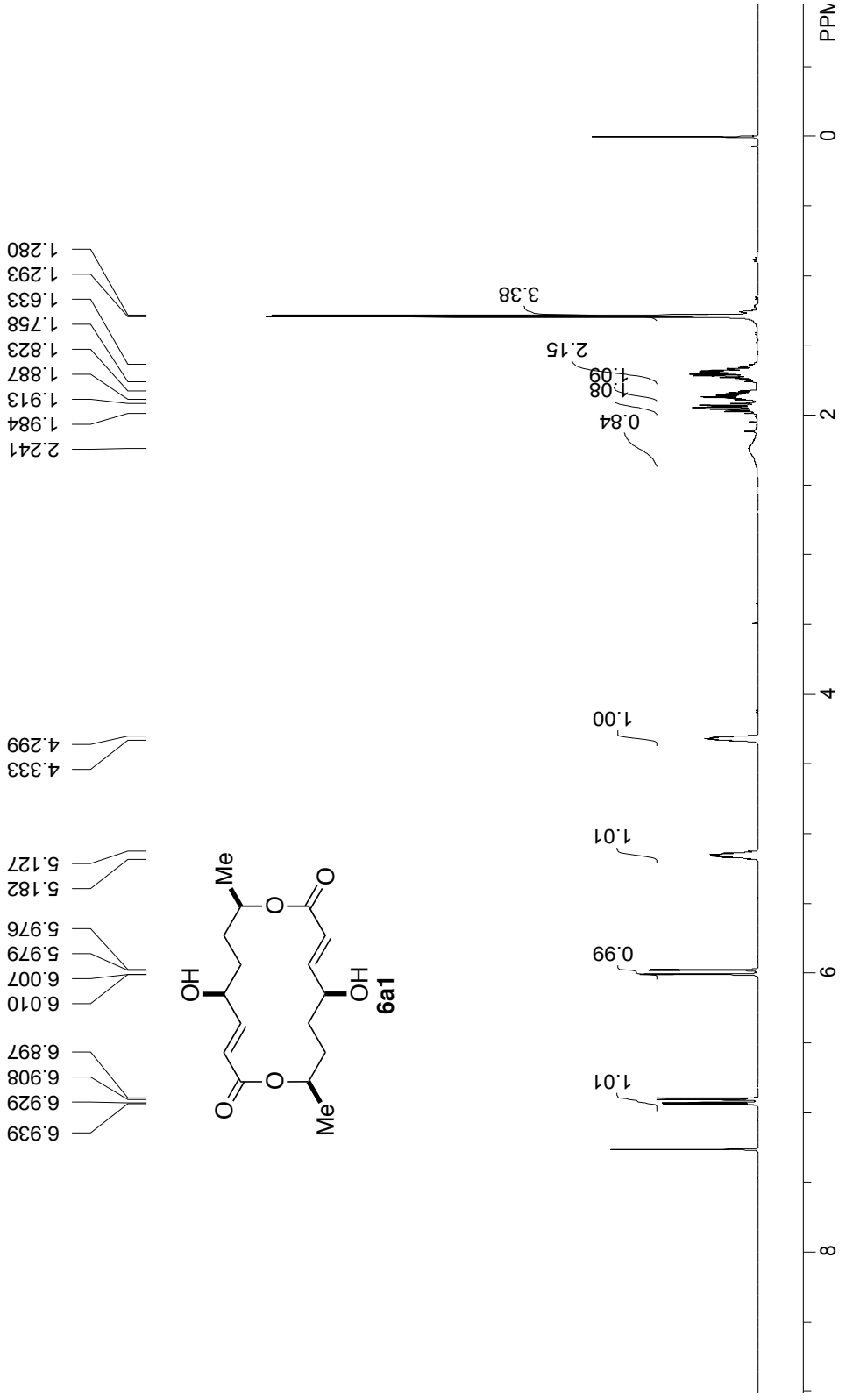
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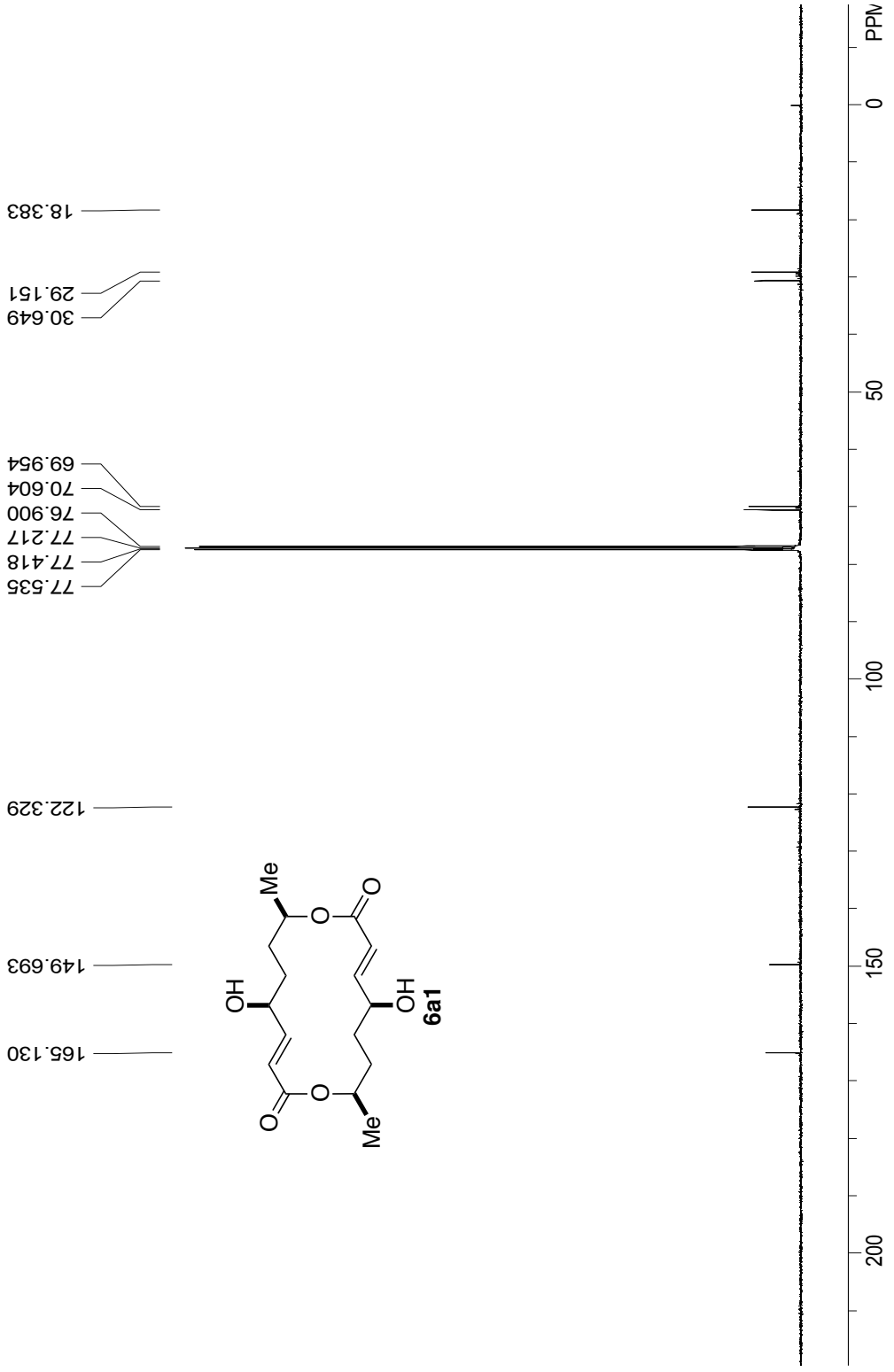
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PPM
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50
100
150
200

PPM
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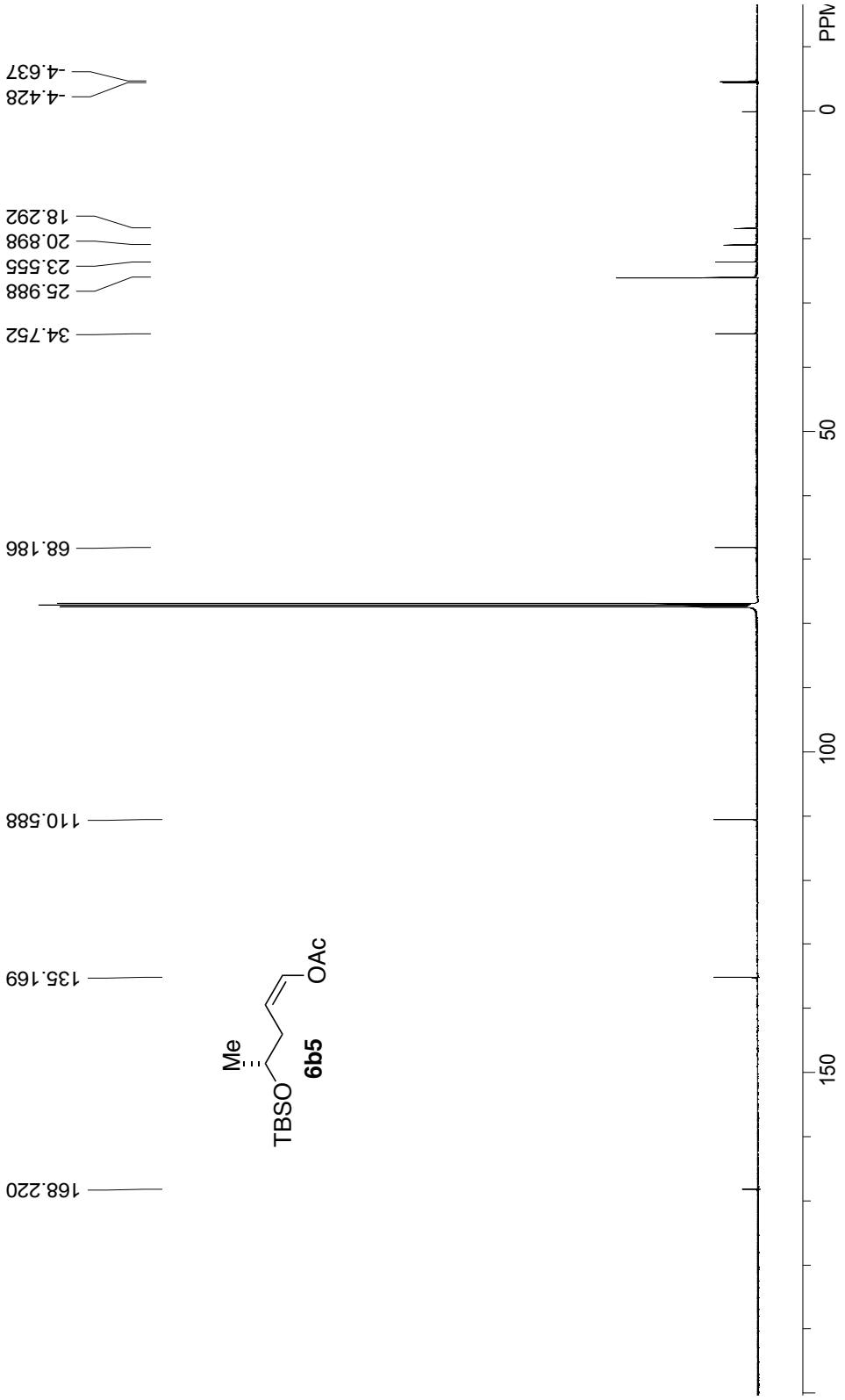
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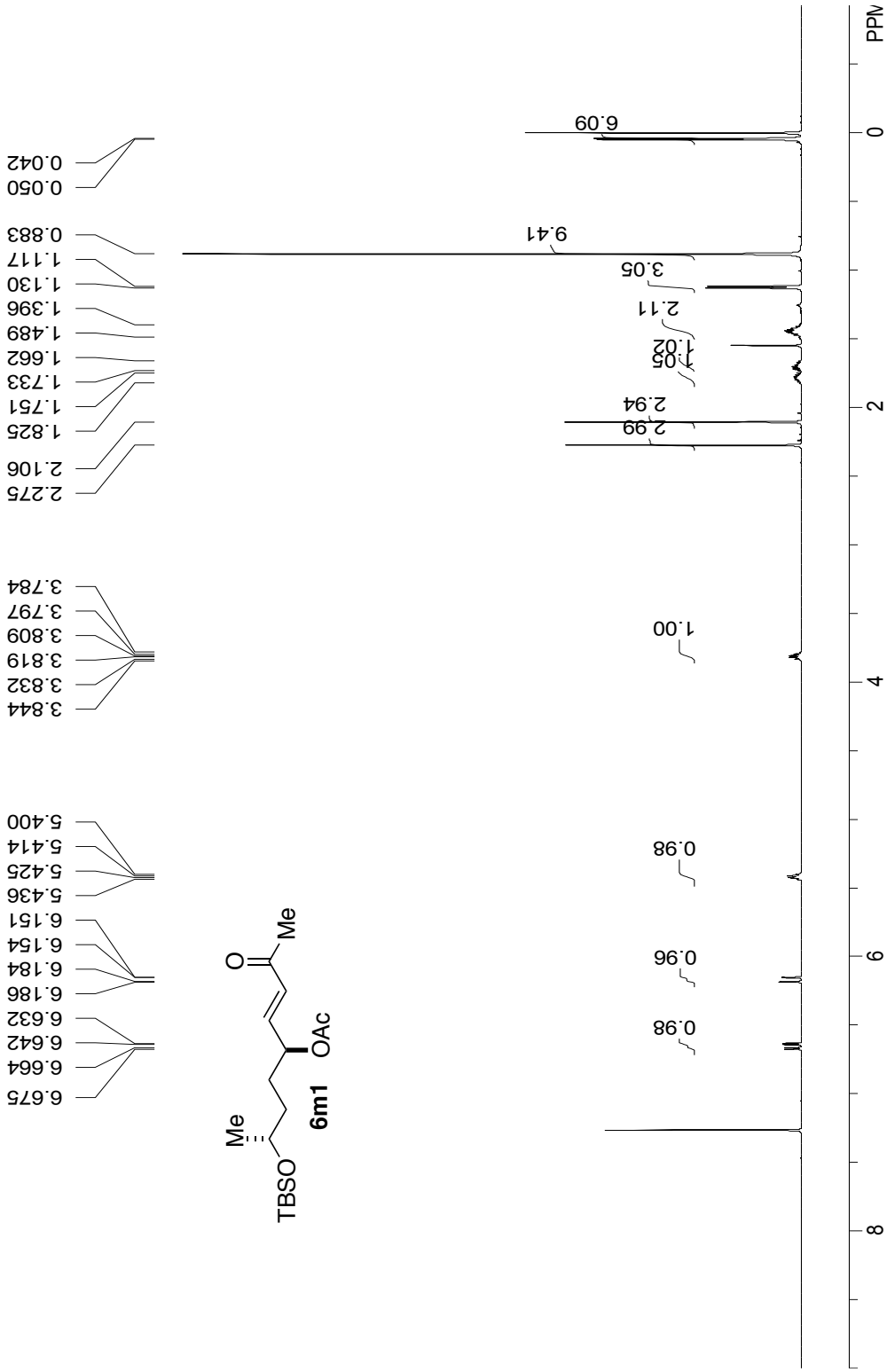
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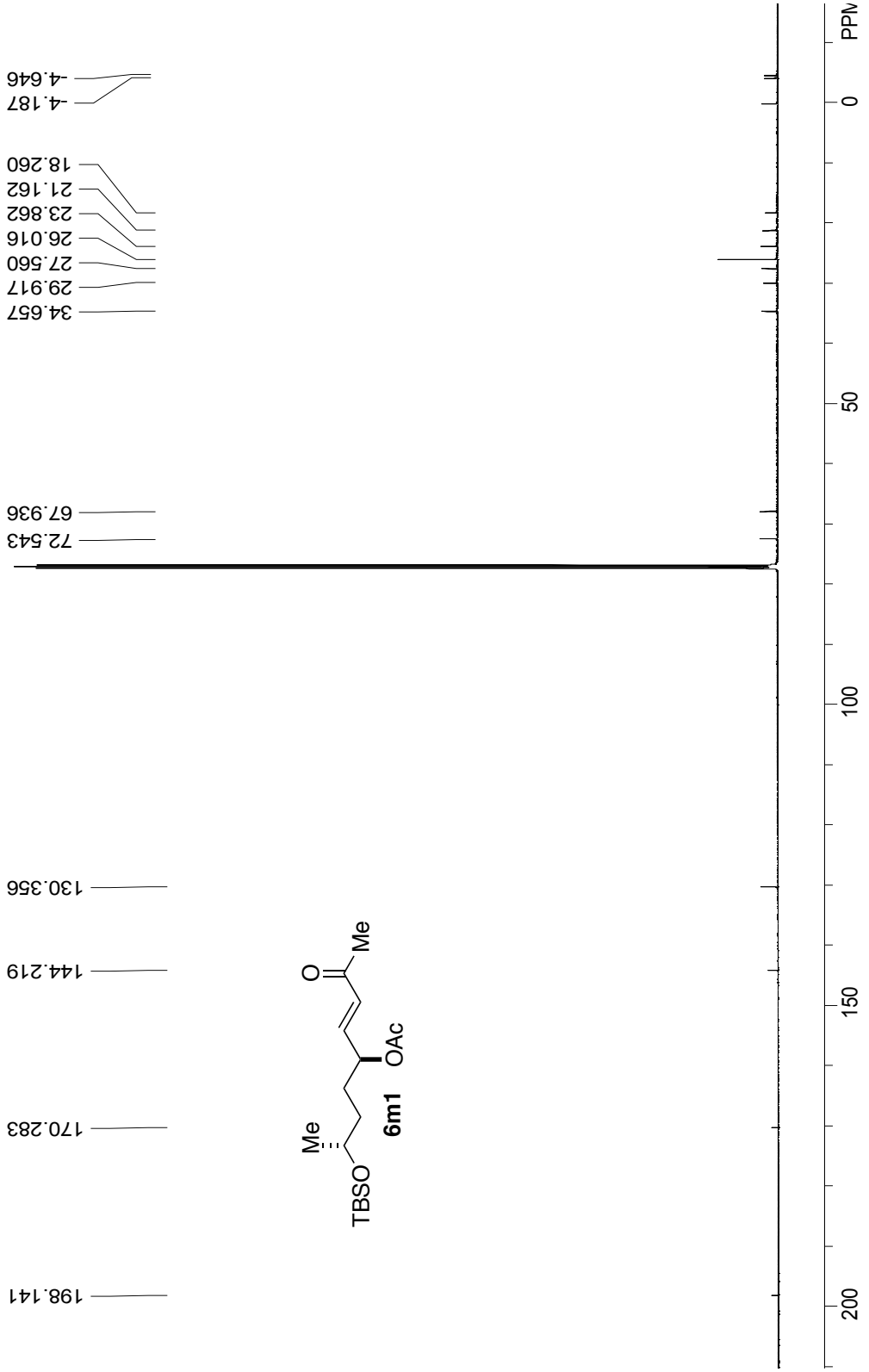
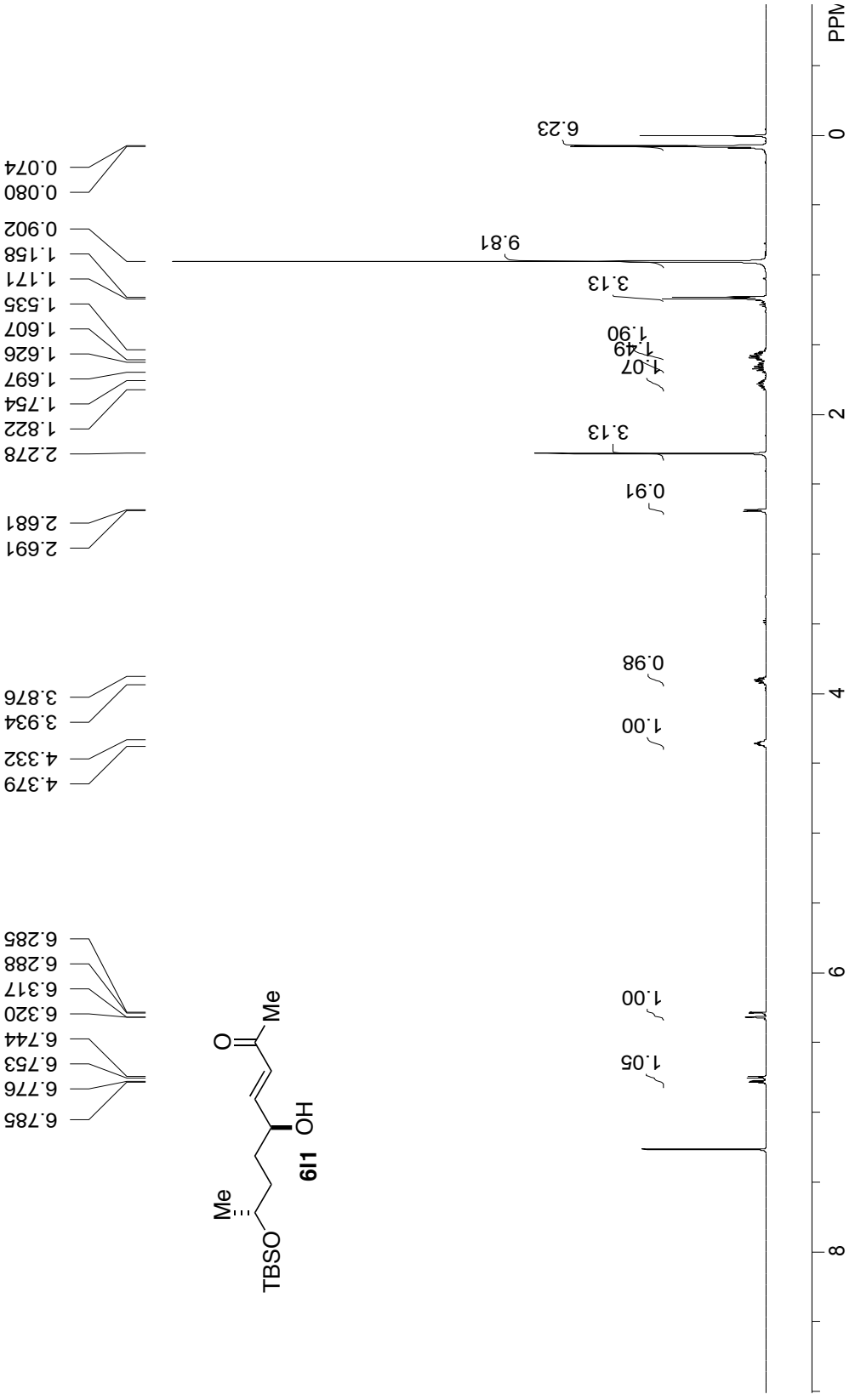
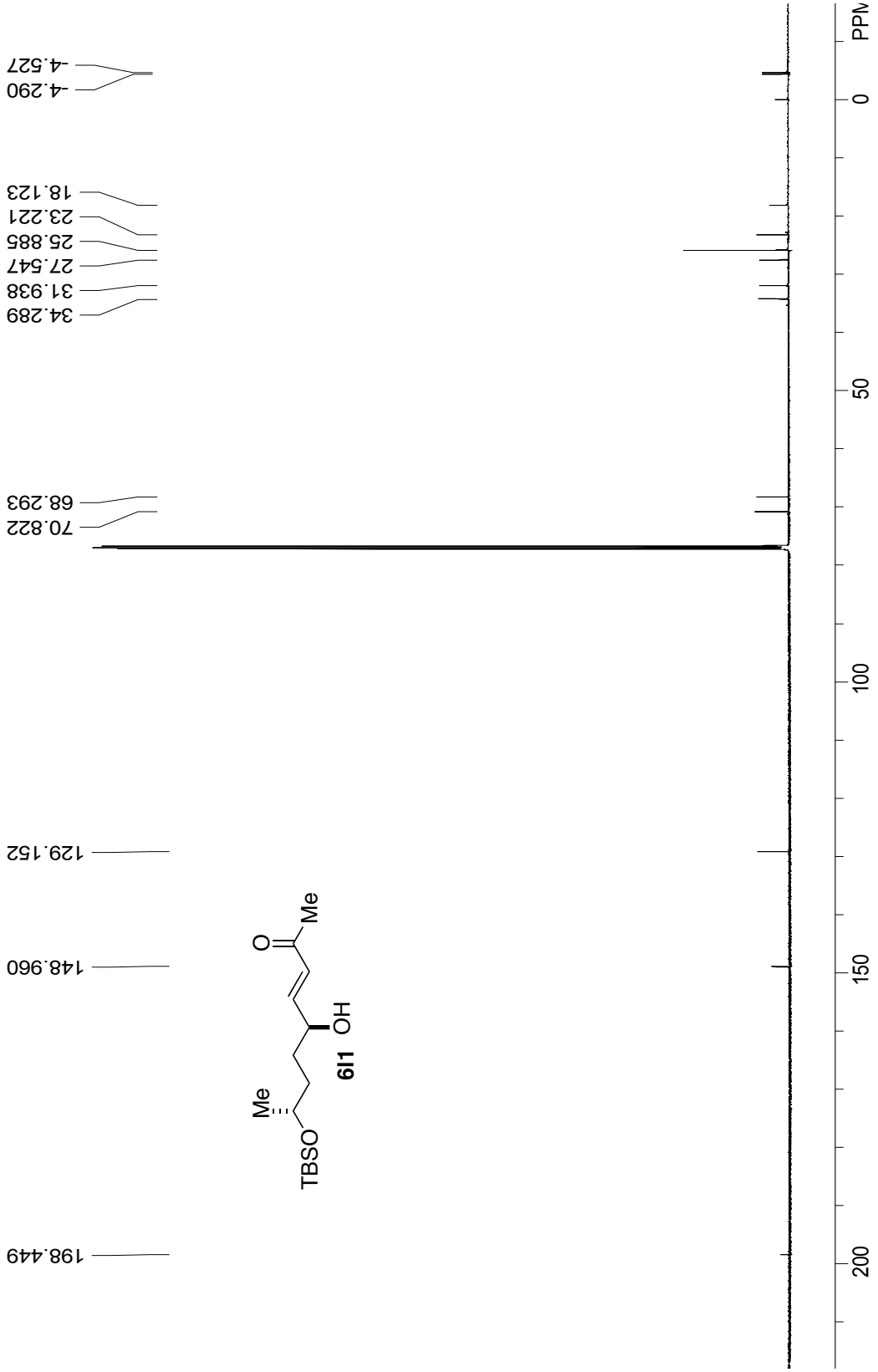
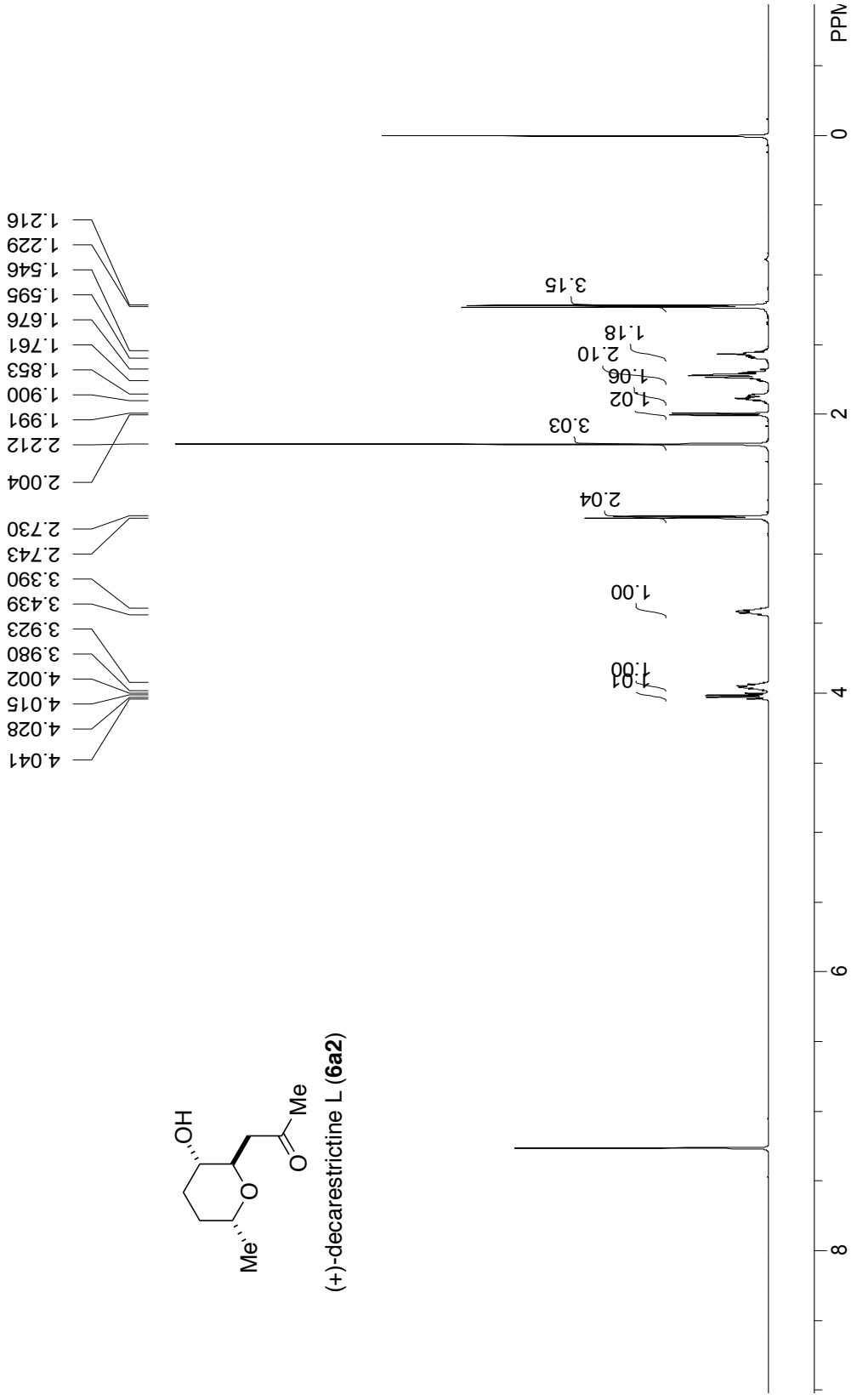
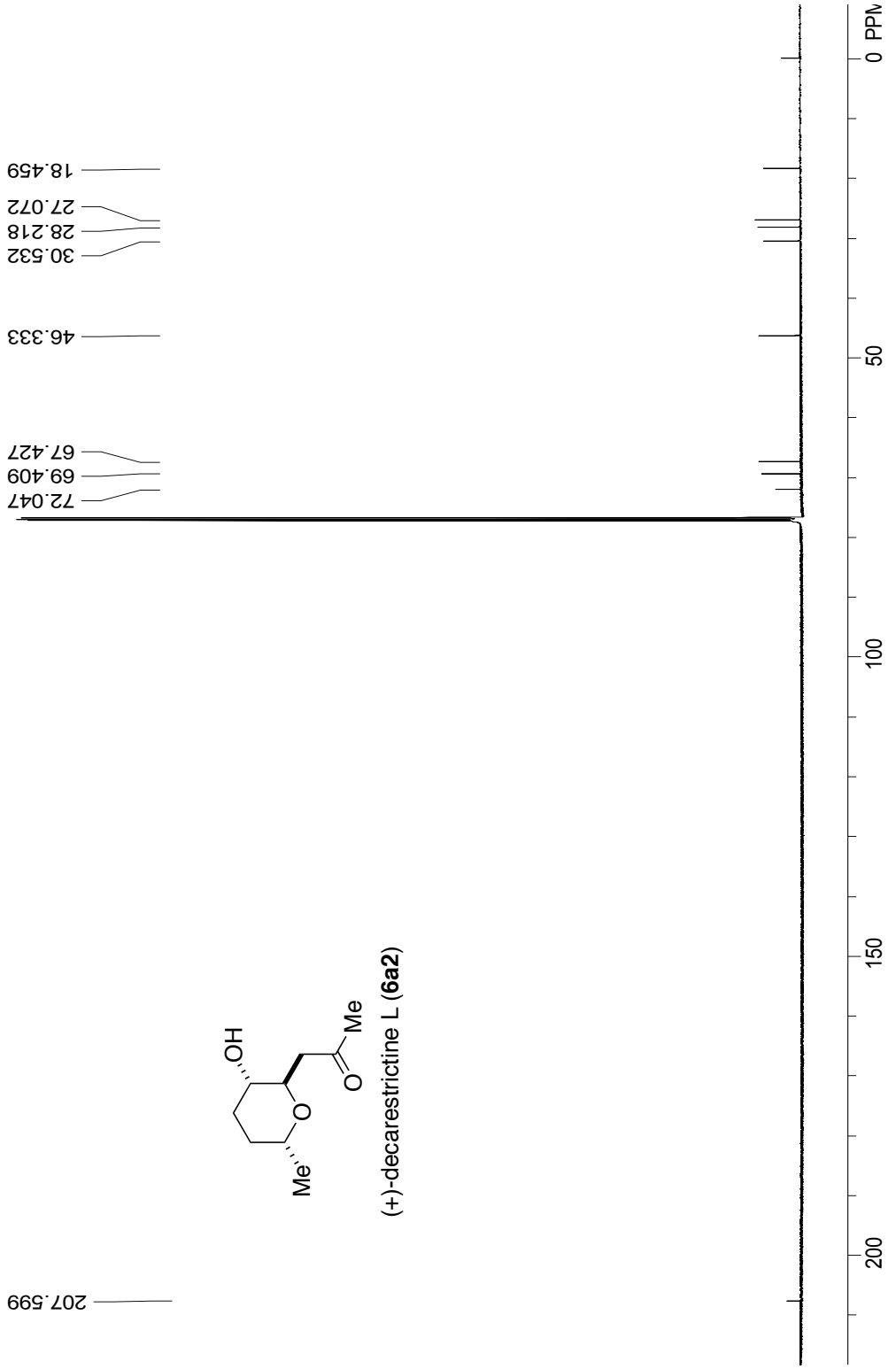
2.275
3.784
3.797
3.809
3.819
3.832
3.844
5.400
5.414
5.425
5.436
6.151
6.154
6.184
6.186
6.632
6.642
6.664
6.675
O
Me
OAc
6m1
Me
TBSO
PPM
0
2
4
6
8

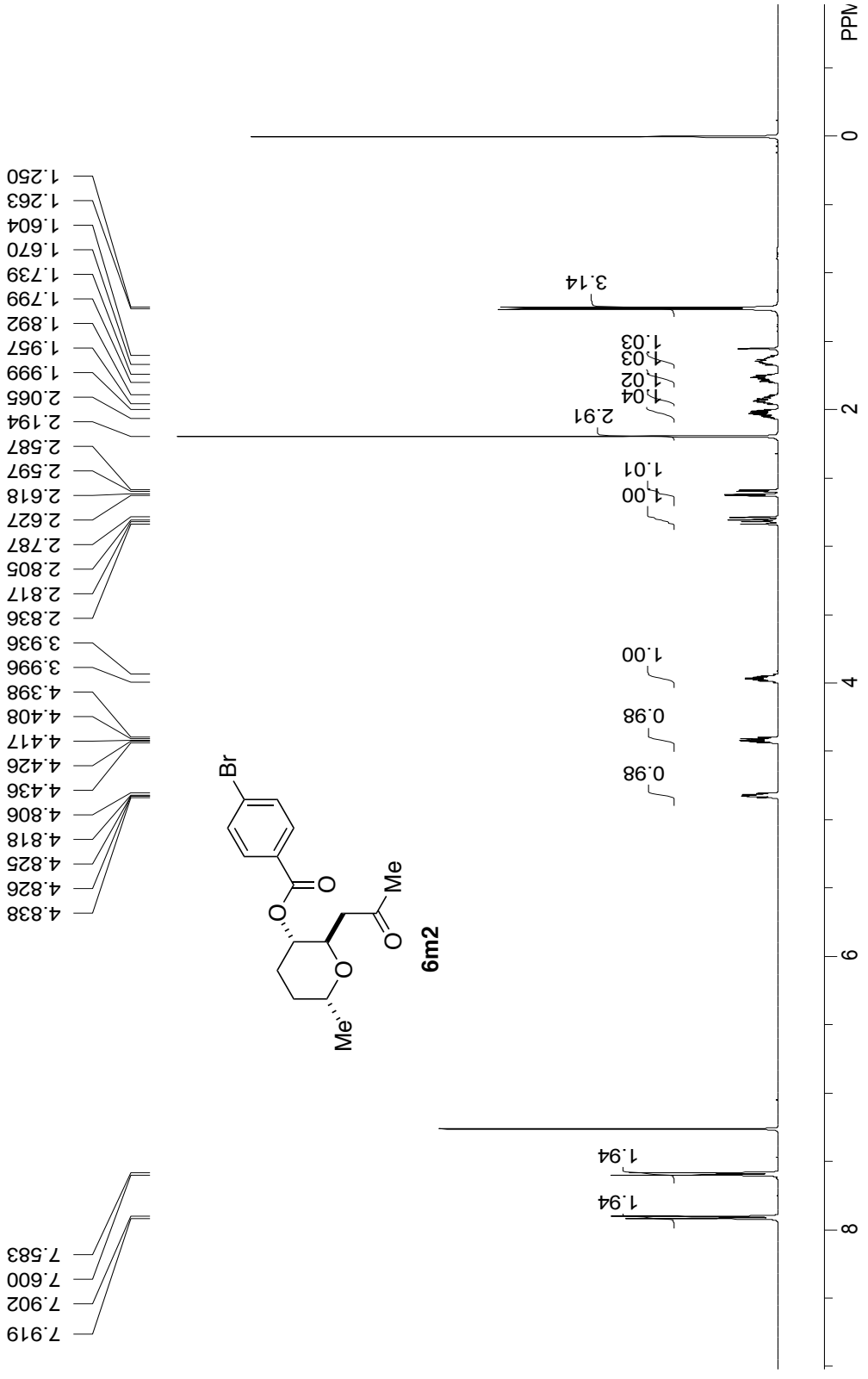

198.141
170.283
144.219
130.356
72.543
67.936
34.657
29.917
27.560
26.016
23.862
21.162
18.260
-4.187
-4.646
PPM
200
150
100
50
0
TBSO
Me
OAc
O
Me
6m1

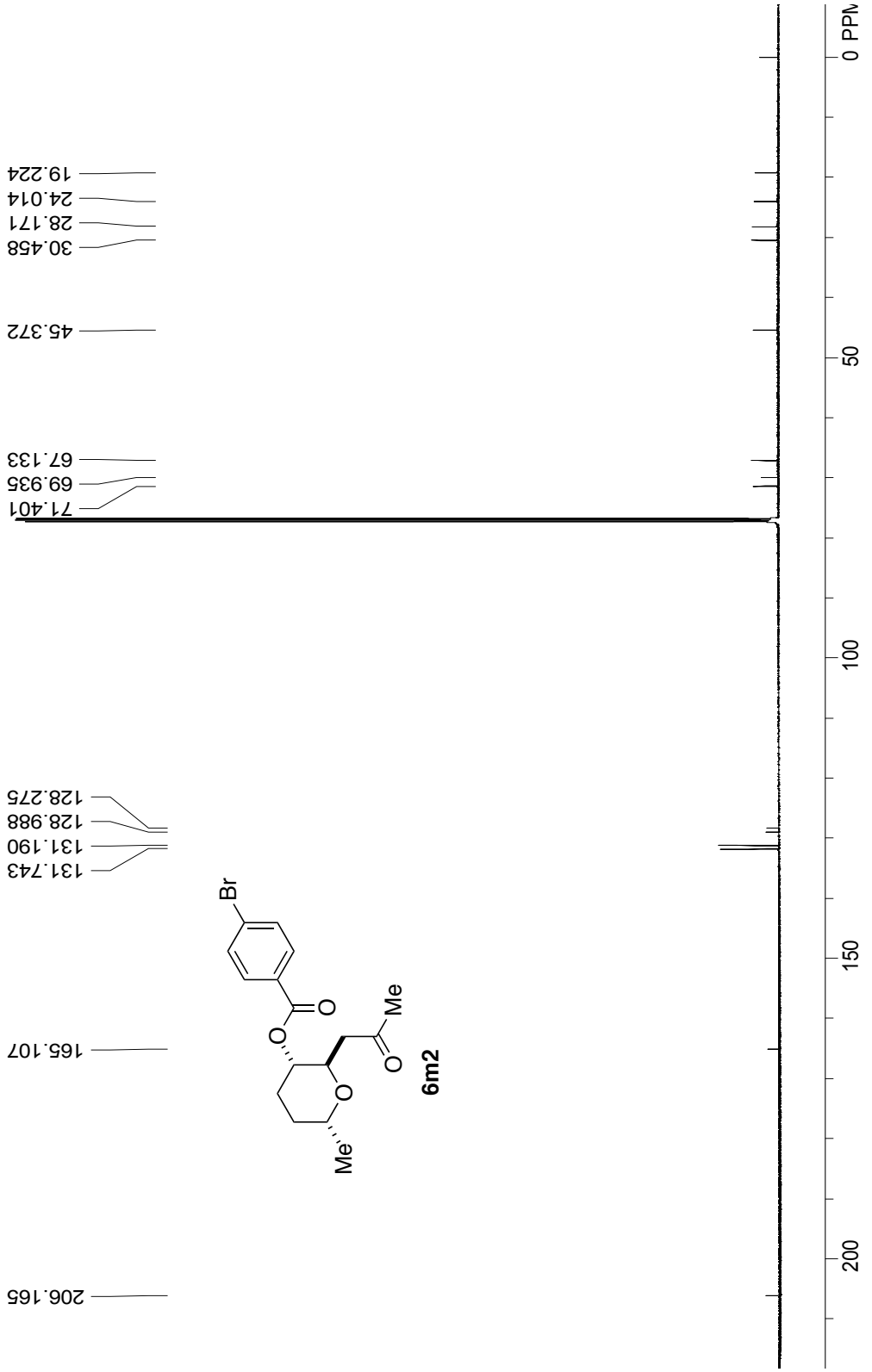

PPM
0
2
4
6
8
6.23
9.81
3.13
1.90
1.49
1.07
3.13
0.91
0.98
1.00
1.05
1.00
0.074
0.080
0.902
1.158
1.171
1.535
1.607
1.626
1.697
1.754
1.822
2.278
2.681
2.691
4.379
4.332
3.934
3.876
6.285
6.288
6.317
6.320
6.744
6.753
6.776
6.785
TBSO
Me
OH
O
Me
6l1

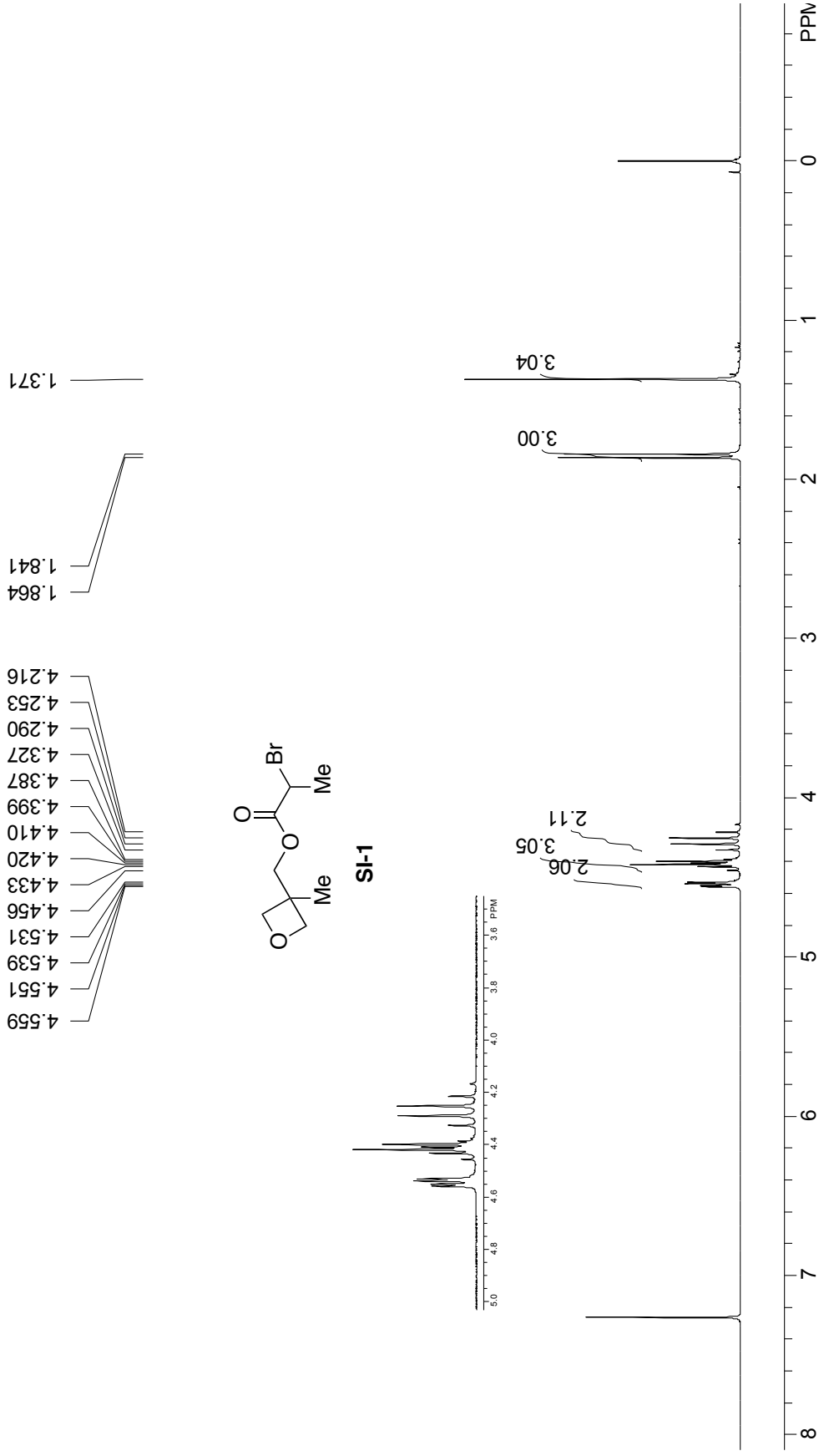

198.449
148.960
129.152
70.822
68.293
34.289
31.938
27.547
25.885
23.221
18.123
-4.290
-4.527
PPM
200
150
100
50
0
TBSO
Me
O
Me
OH
6l1

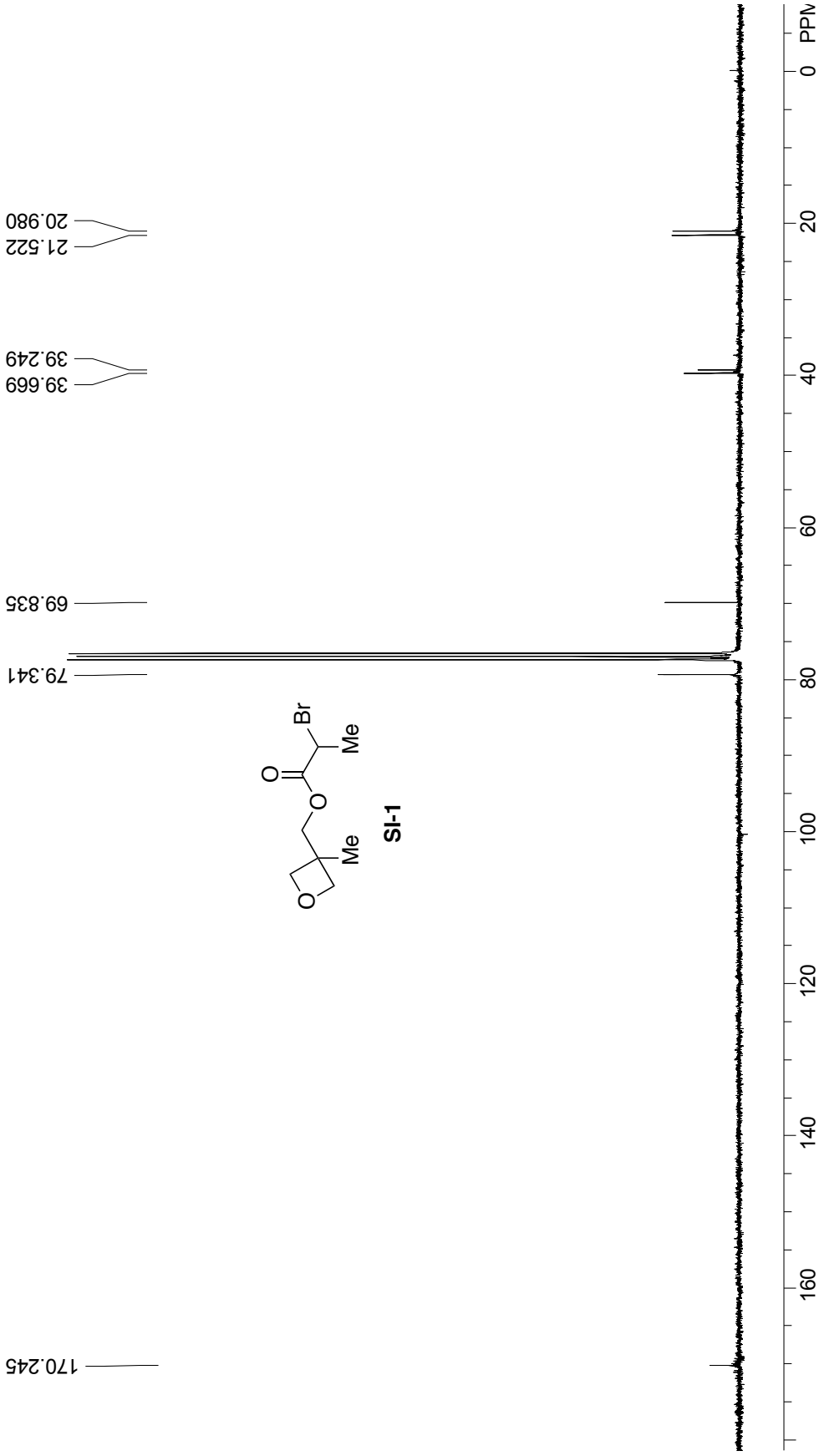

(+)-decarestrictine L (6a2)
OH
O
Me
O
Me
PPM
0
2
4
6
8
1.00
1.01
2.04
3.03
1.02
1.06
2.10
1.18
3.15
4.041
4.028
4.015
4.002
3.980
3.923
3.439
3.390
2.743
2.730
2.004
2.212
1.991
1.900
1.853
1.761
1.676
1.595
1.546
1.229
1.216


207.599
72.047
69.409
67.427
46.333
30.532
28.218
27.072
18.459
200
150
100
50
0 PPM
OH
Me
O
O
Me
(+)-decarestrictine L (6a2)

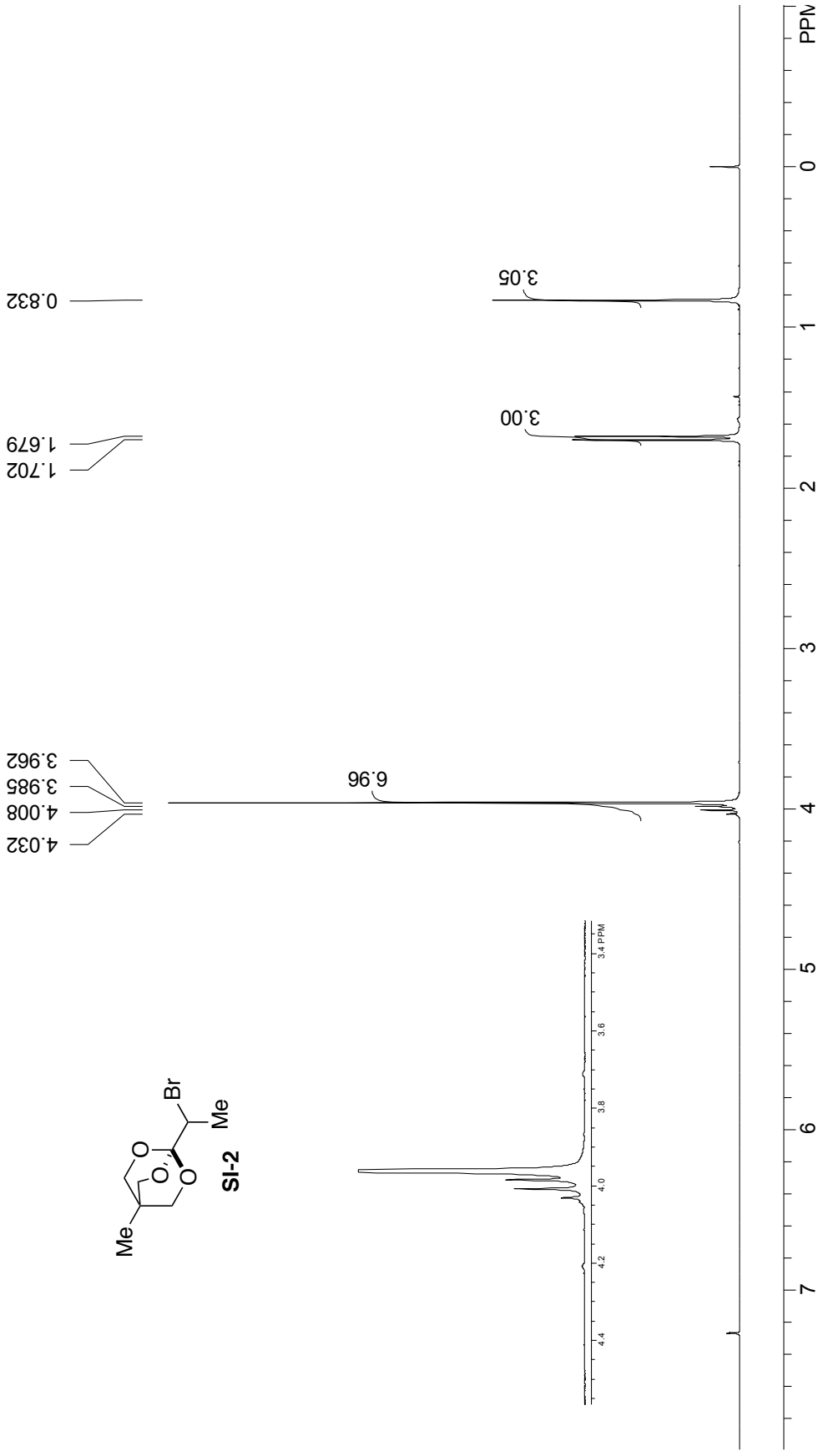

6m2
Br
O
O
O
Me
Me
O
PPM
0
2
4
6
8
1.250
1.263
1.604
1.670
1.739
1.799
1.892
1.957
1.999
2.065
2.194
2.587
2.597
2.618
2.627
2.787
2.805
2.817
2.836
3.936
3.996
4.398
4.408
4.417
4.426
4.436
4.806
4.818
4.825
4.826
4.838
7.583
7.600
7.902
7.919
1.94
1.94
0.98
0.98
1.00
1.00
1.01
2.91
3.14
1.03
1.03
1.02
1.04

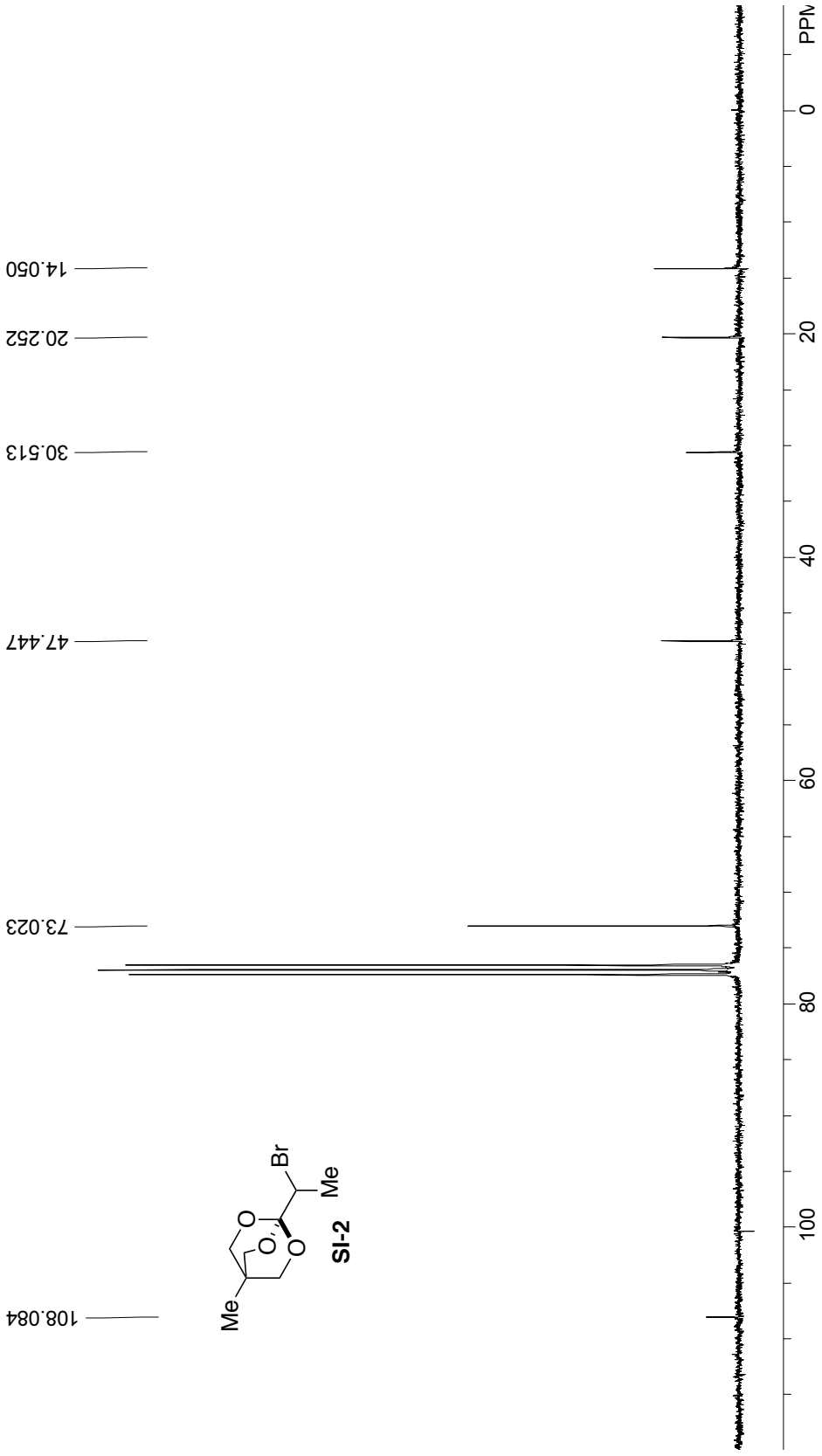

206.165
165.107
131.743
131.190
128.988
128.275
71.401
69.935
67.133
45.372
30.458
28.171
24.014
19.224
Br
O
O
O
Me
O
Me
6m2
200
150
100
50
0 PPM

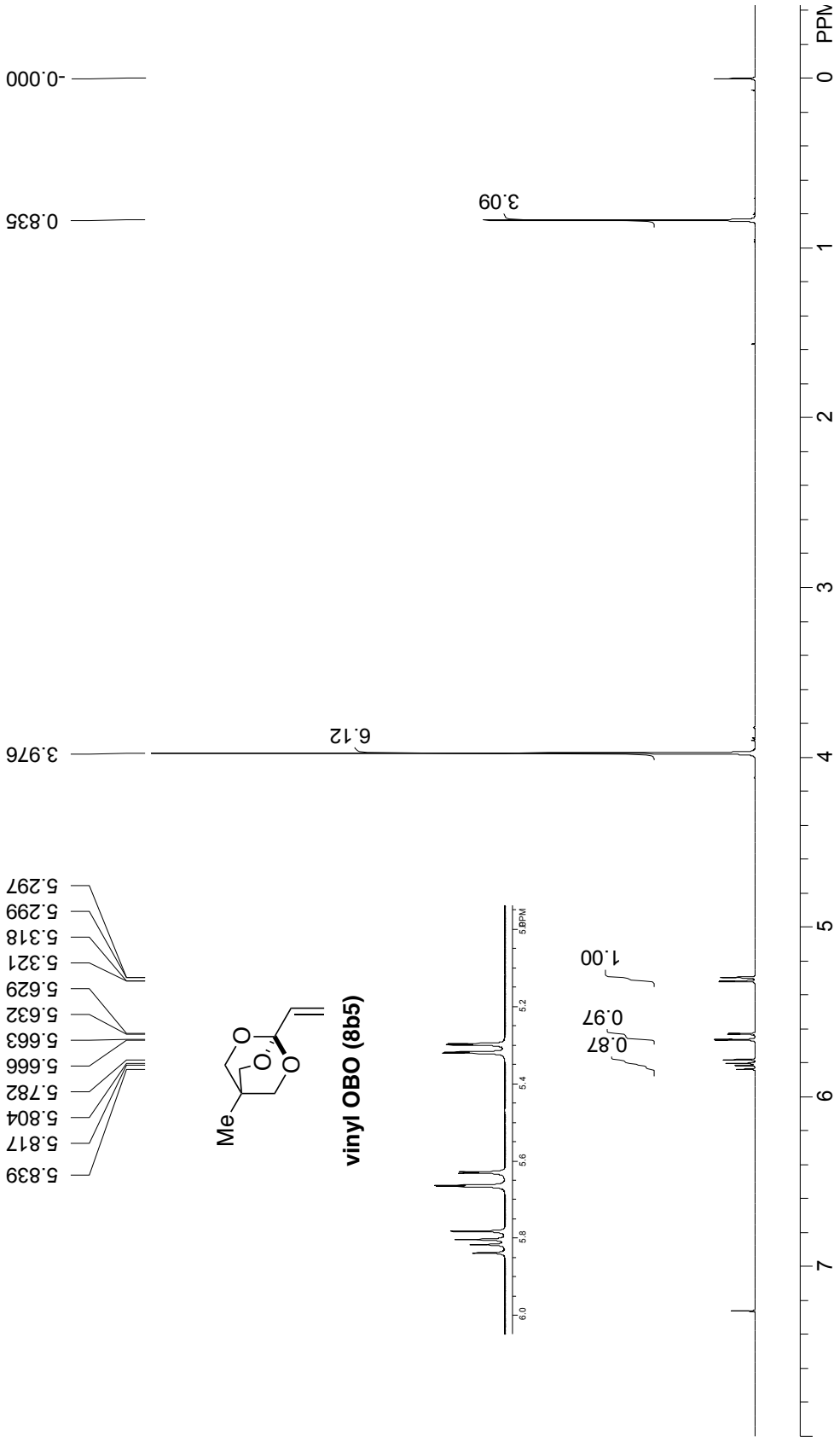

PPM
0
1
2
3
4
5
6
7
8
3.04
3.00
2.11
3.05
2.06
1.371
1.864
1.841
4.559
4.551
4.539
4.531
4.456
4.433
4.420
4.410
4.399
4.387
4.327
4.290
4.253
4.216
SI-1
Br
Me
O
O
Me
O
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0

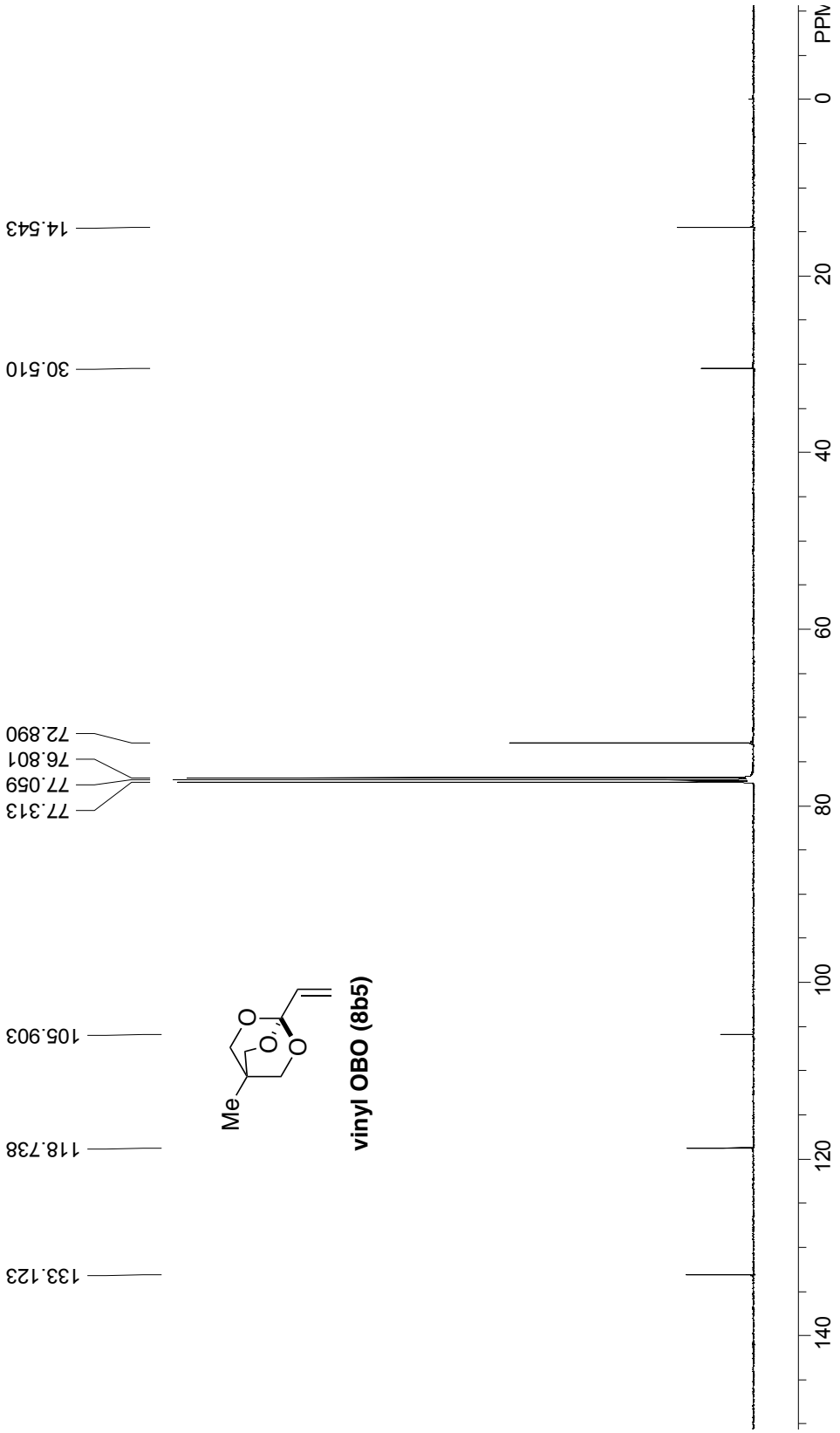

170.245
79.341
69.835
39.669
39.249
21.522
20.980
Br
Me
O
O
Me
O
PPM
0
20
40
60
80
100
120
140
160

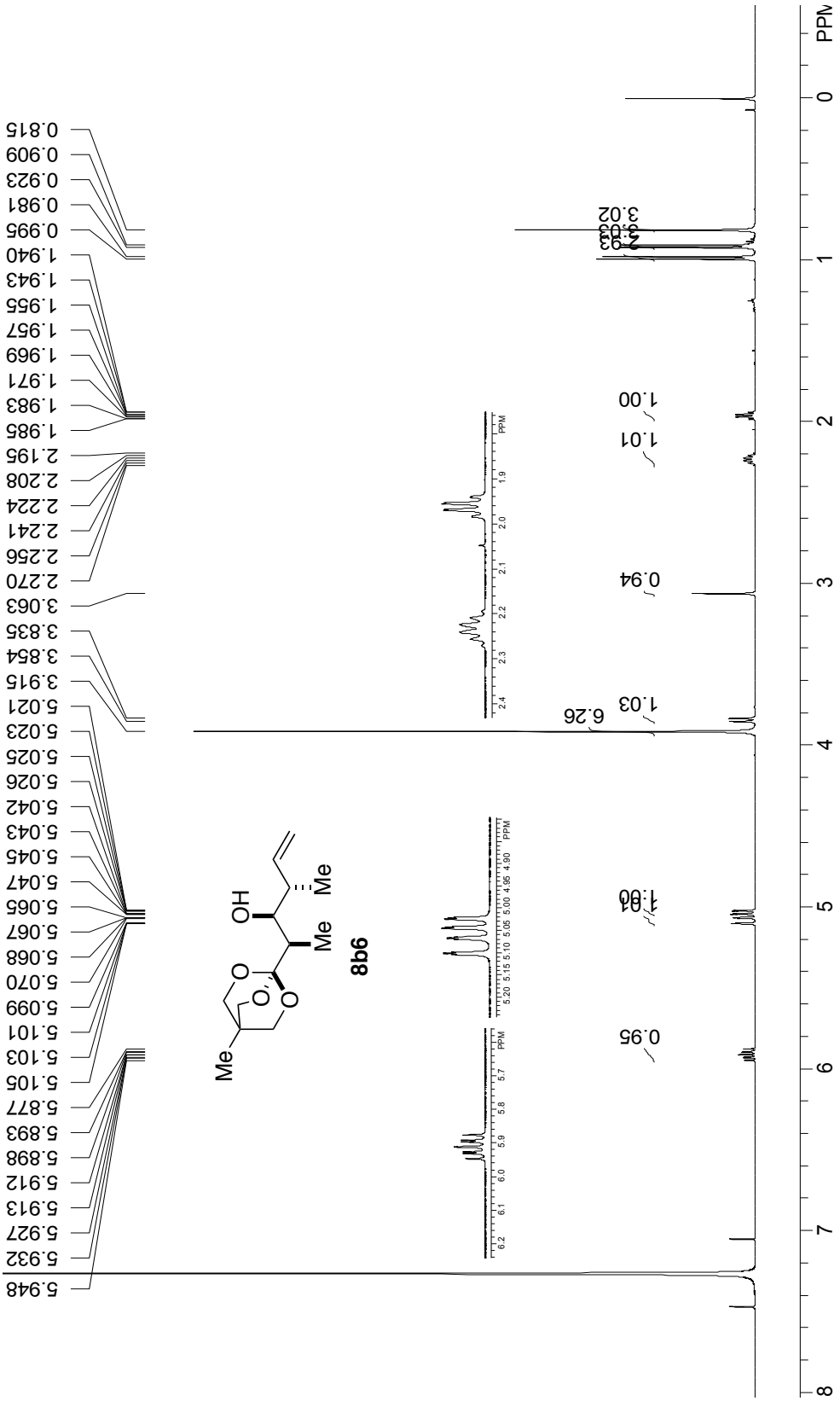
SI-1

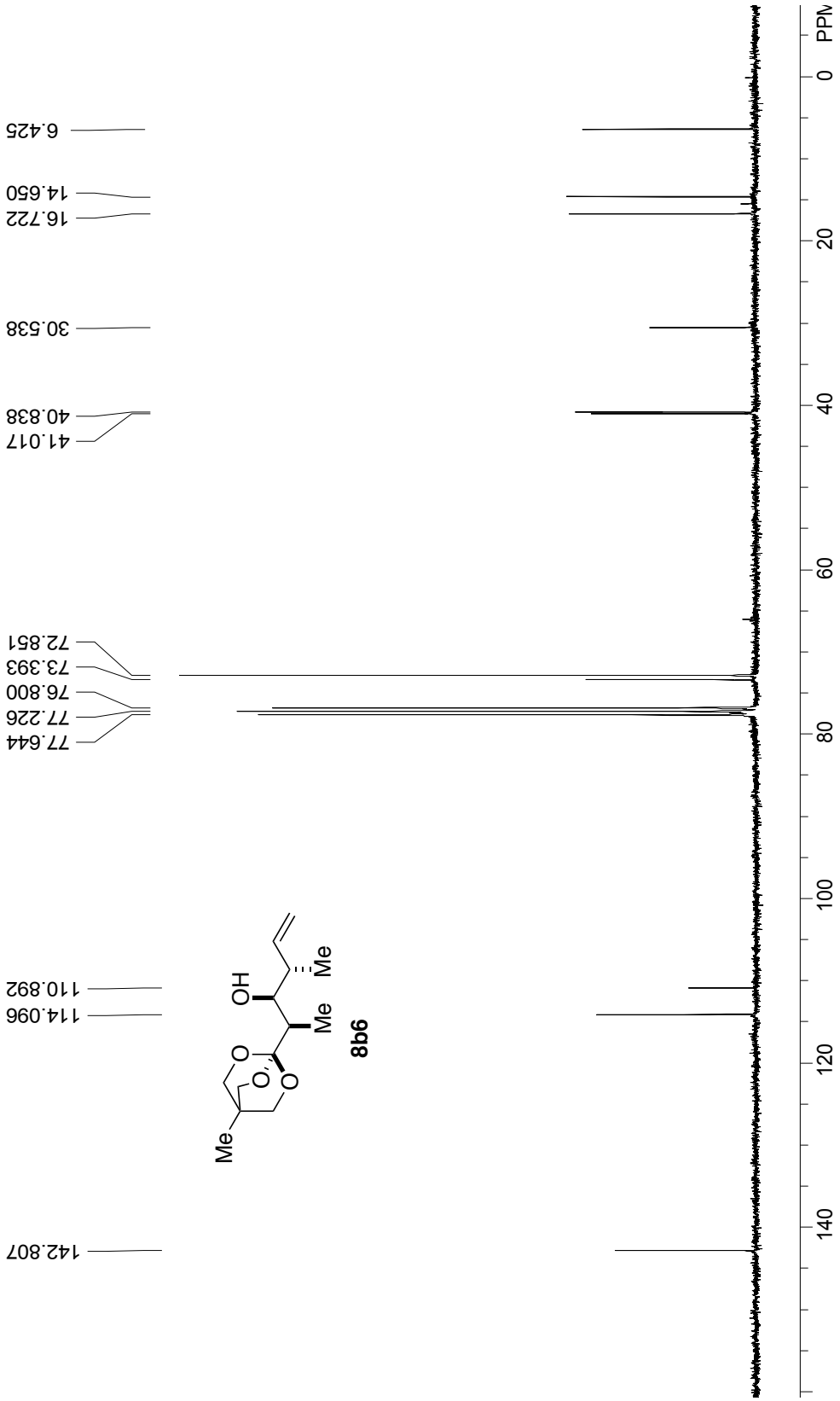

PPM
0
1
2
3
4
5
6
7
3.05
3.00
6.96
4.032
4.008
3.985
3.962
1.702
1.679
0.832
3.4 PPM
3.6
3.8
4.0
4.2
4.4
Me
O
O
O
Me
Br
SI-2

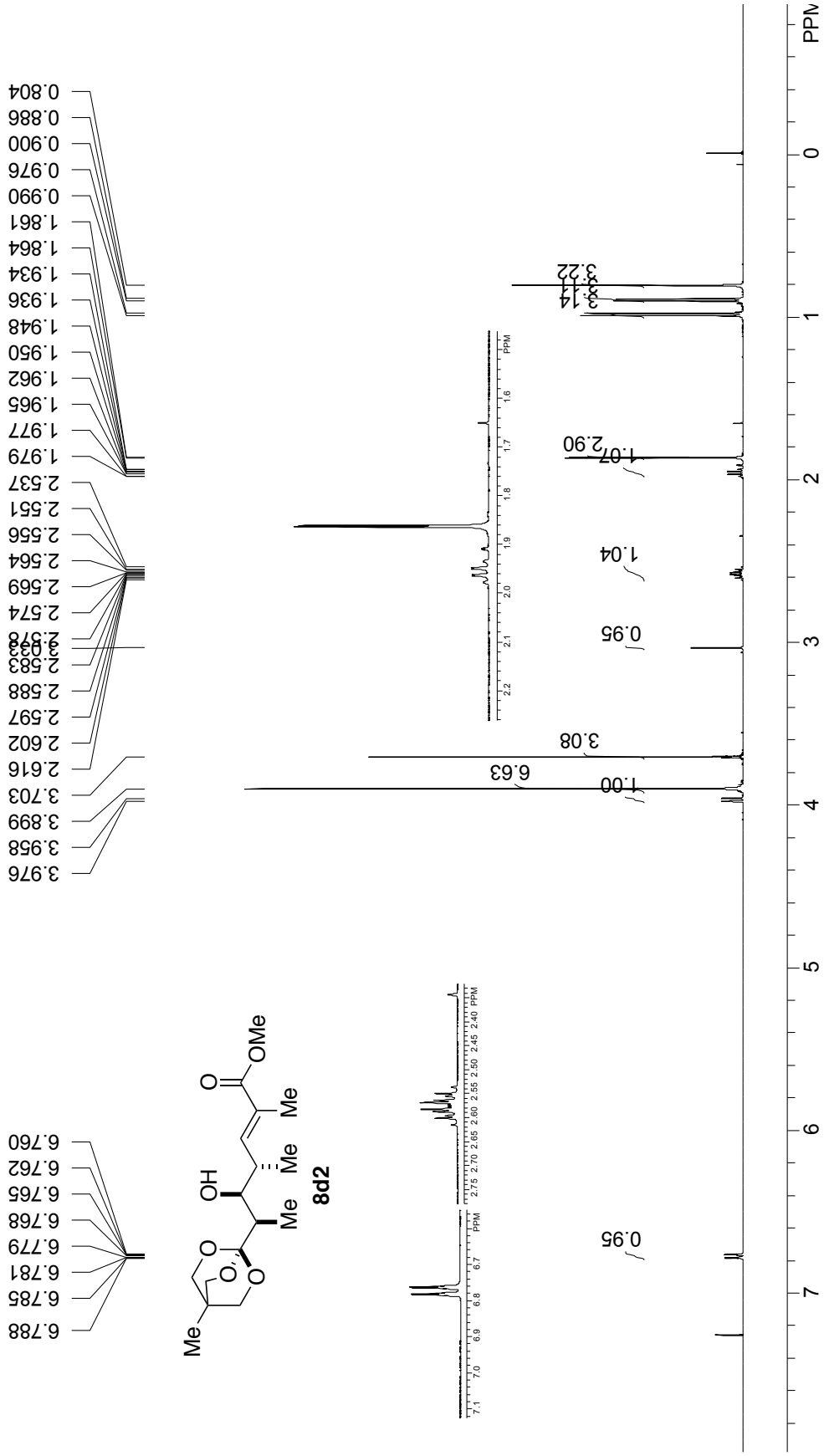

14.050
20.252
30.513
47.447
73.023
108.084
Me
Br
Me
O
O
O
Me
SI-2
PPM
0
20
40
60
80
100

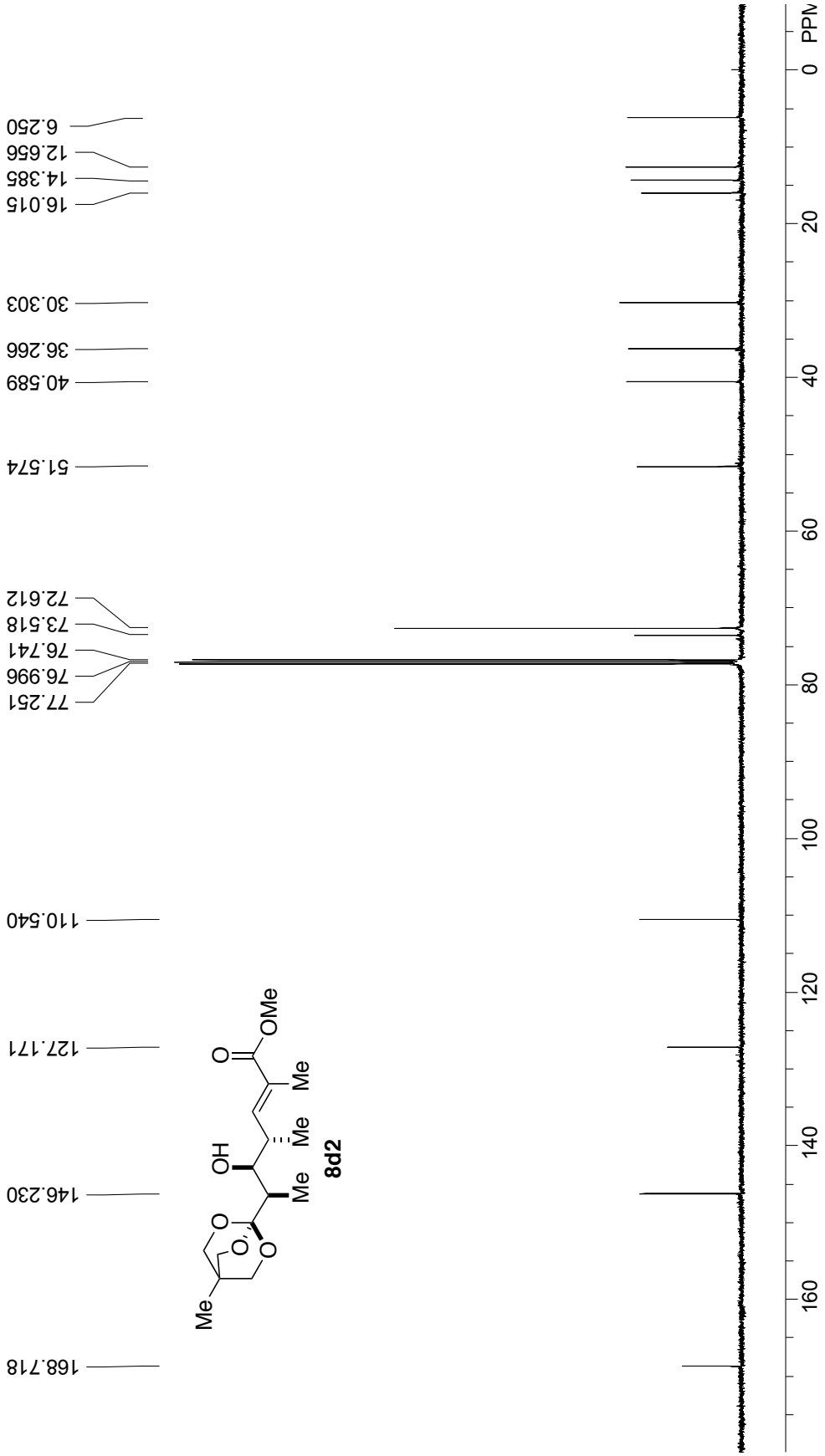

PPM
0
1
2
3
4
5
6
7
3.09
6.12
1.00
0.87
0.97
5.297
5.299
5.318
5.321
5.629
5.632
5.663
5.666
5.782
5.804
5.817
5.839
3.976
0.835
-0.000
Me
vinyl OBO (8b5)

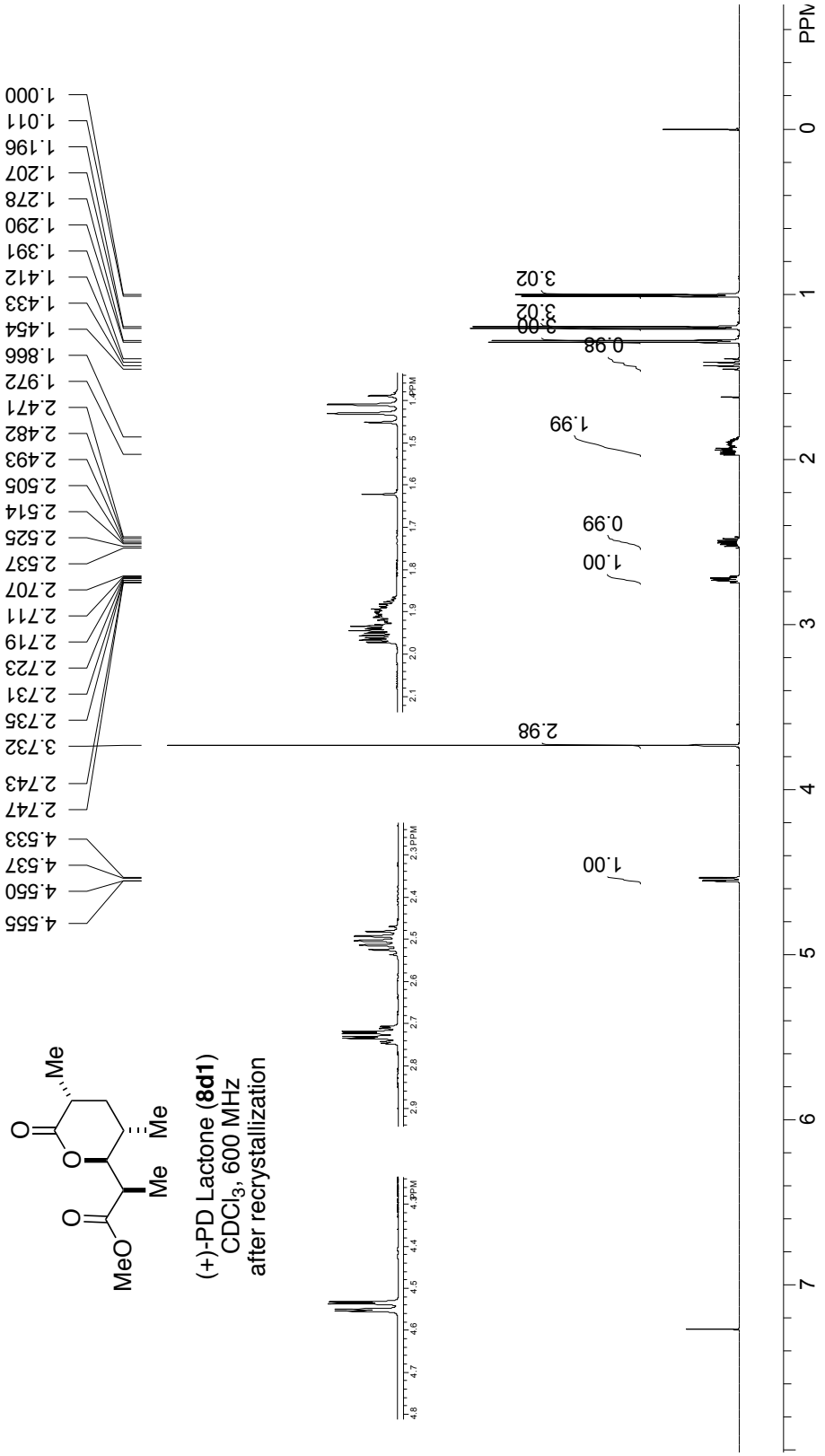

14.543
30.510
72.890
76.801
77.059
77.313
105.903
118.738
133.123
Me
O
O
O
vinyl OBO (8b5)
PPM
0
20
40
60
80
100
120
140

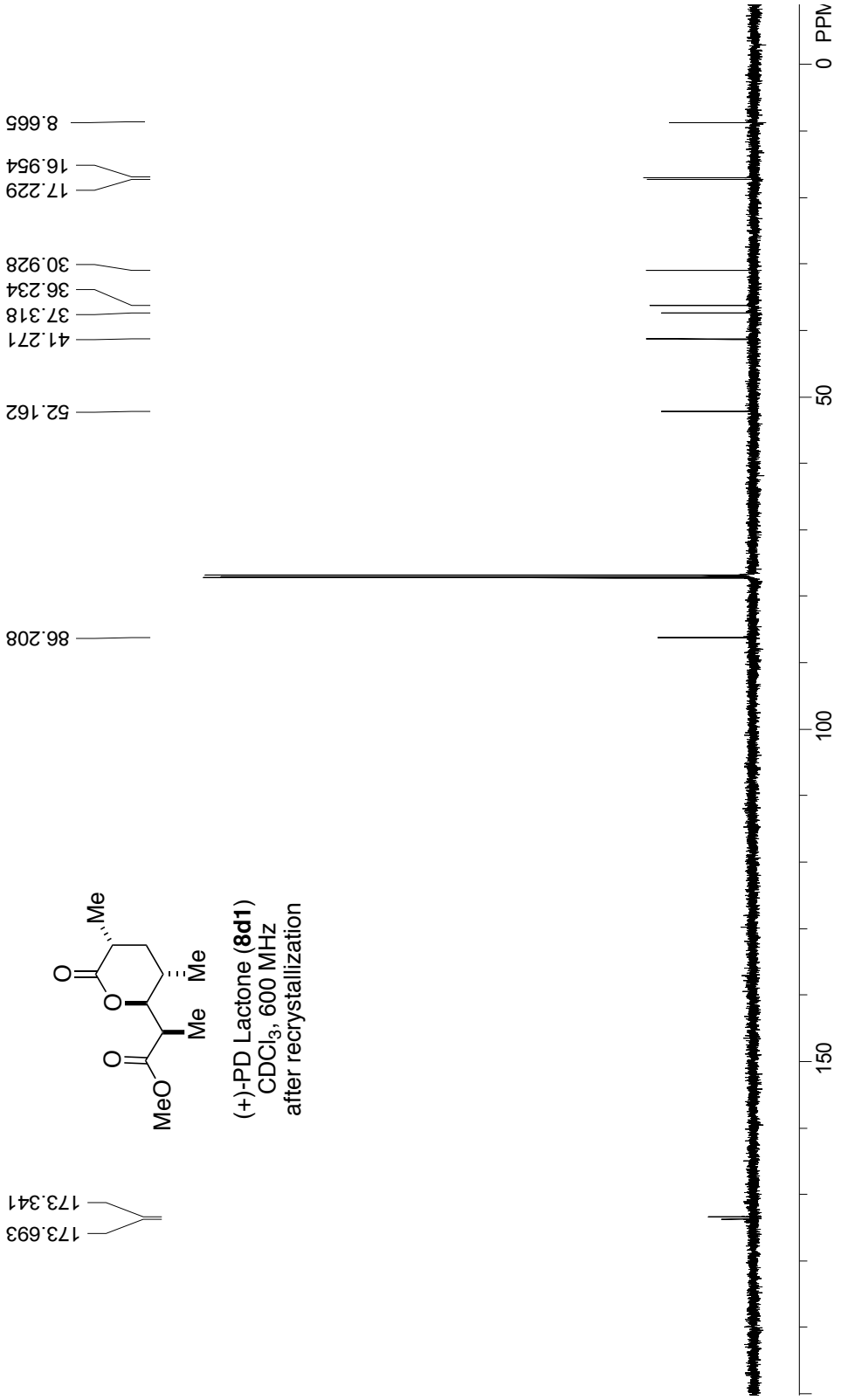

8b6
9g8
PPM

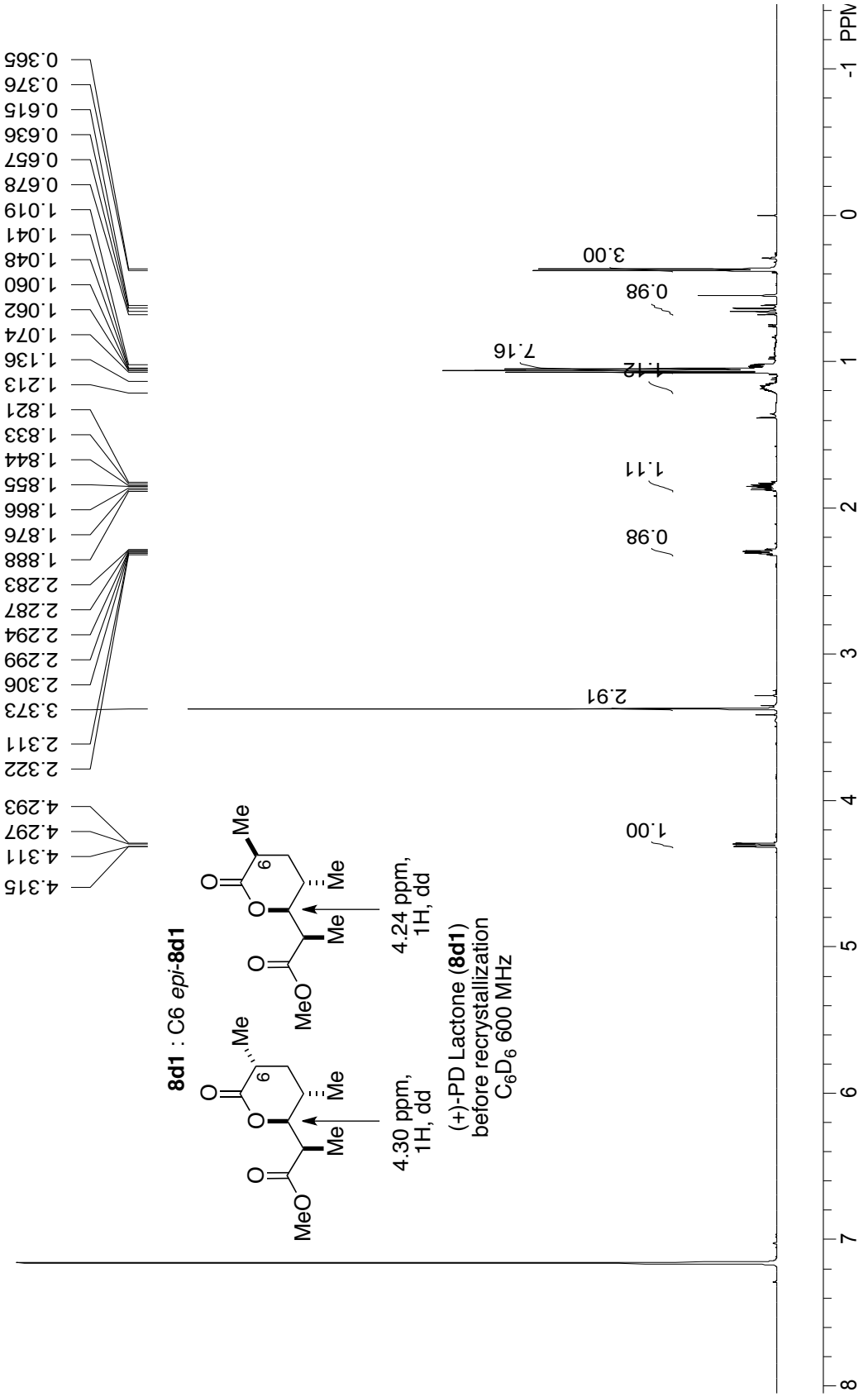

142.807
114.096
110.892
77.644
77.226
76.800
73.393
72.851
41.017
40.838
30.538
16.722
14.650
6.425
PPM
0
20
40
60
80
100
120
140
Me
O
O
O
OH
Me
Me
8b6

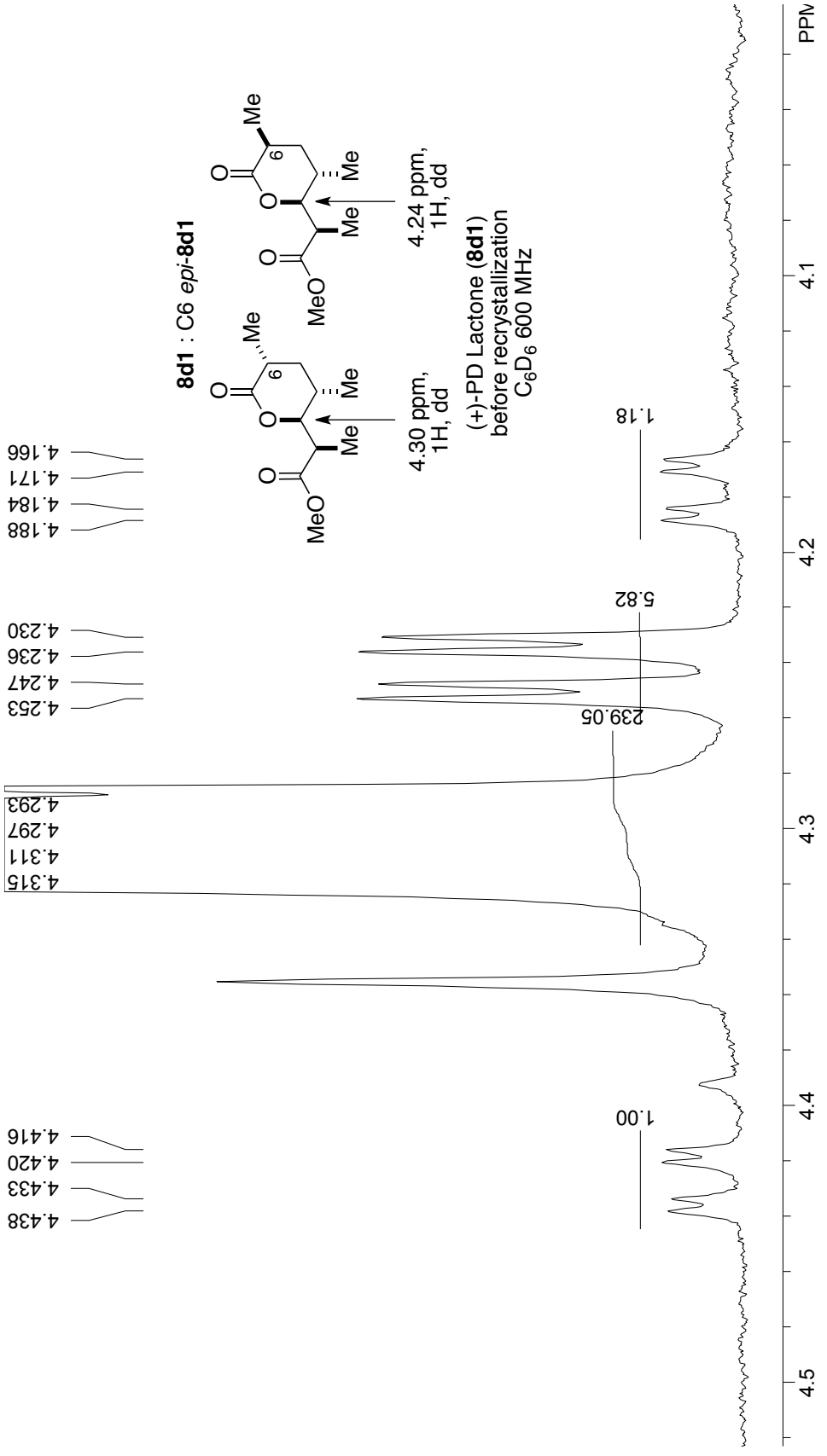

8d2
Me
Me
Me
OH
Me
OMe
O
PPM
0.95
1.00
6.63
3.08
0.95
1.04
1.07
2.90
3.14
3.11
3.22
6.788
6.785
6.781
6.779
6.768
6.765
6.762
6.760
3.976
3.958
3.899
3.703
2.616
2.602
2.597
2.588
2.583
2.574
2.569
2.564
2.556
2.551
2.537
1.979
1.977
1.965
1.962
1.950
1.948
1.936
1.934
1.864
1.861
0.990
0.976
0.900
0.886
0.804

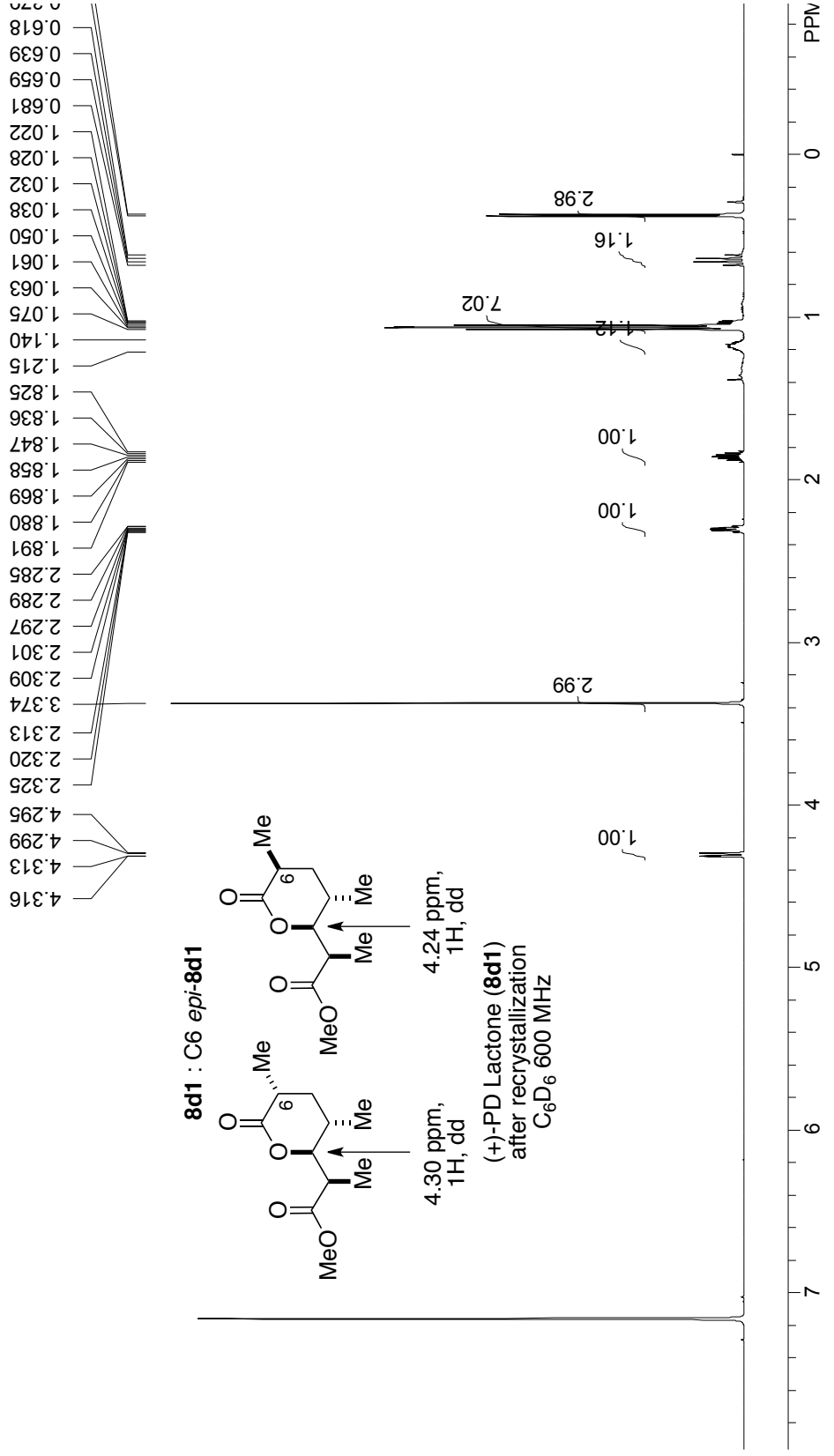

168.718
146.230
127.171
110.540
77.251
76.996
76.741
73.518
72.612
51.574
40.589
36.266
30.303
16.015
14.385
12.656
6.250
8d2
OMe
O
Me
Me
Me
OH
Me
O
O
O
O
Me
PPM
0
20
40
60
80
100
120
140
160

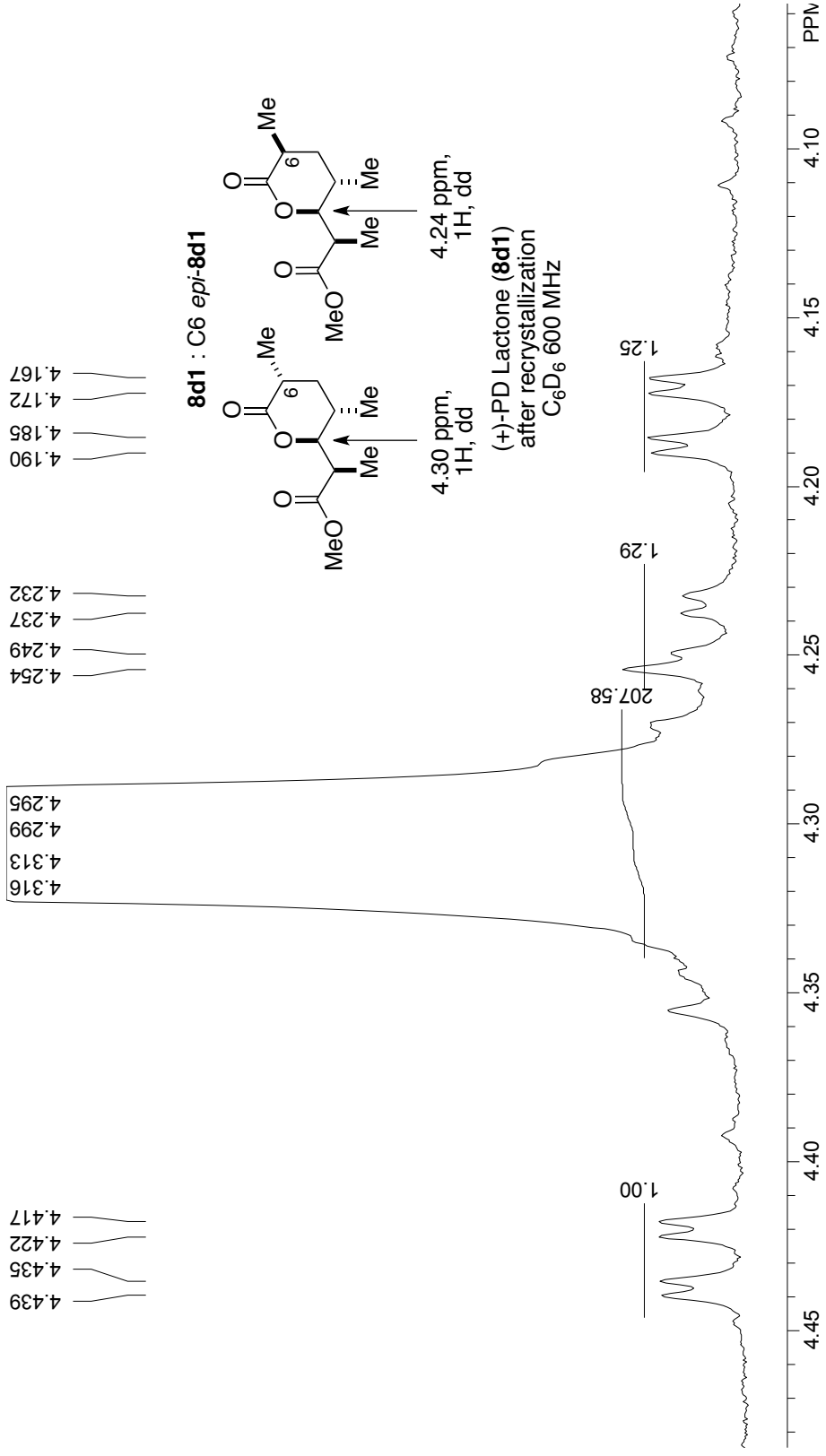

(+)-PD Lactone (8d1)
CDCl3, 600 MHz
after recrystallization
MeO
Me
Me
Me
4.555
4.550
4.537
4.533
2.747
2.743
3.732
2.735
2.731
2.723
2.719
2.711
2.707
2.537
2.525
2.514
2.505
2.493
2.482
2.471
1.972
1.866
1.454
1.433
1.412
1.391
1.290
1.278
1.207
1.196
1.011
1.000
2.98
1.99
1.00
0.99
1.00
0.98
3.00
3.02
3.02
PPM


(+)-PD Lactone (8d1)
CDCl3, 600 MHz
after recrystallization
MeO
Me
Me
Me
O
O
O
8.665
16.954
17.229
30.928
36.234
37.318
41.271
52.162
86.208
173.341
173.693
0
50
100
150
PPM

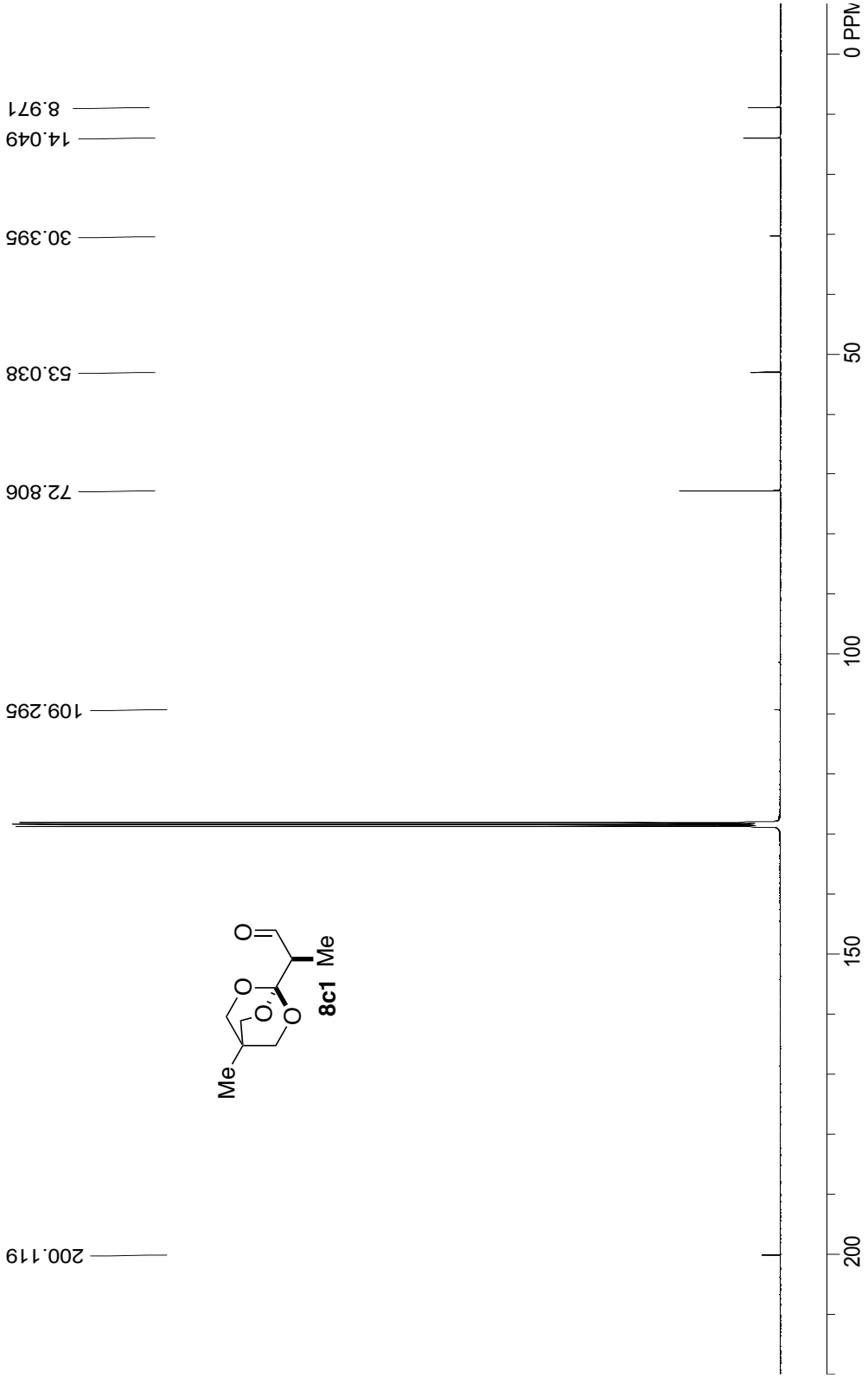

(+)-PD Lactone (8d1)
before recrystallization
C6D6 600 MHz
8d1 : C6 epi-8d1
4.24 ppm, 1H, dd
4.30 ppm, 1H, dd
MeO
Me
PPM
1.00
2.91
0.98
1.11
1.12
7.16
0.98
3.00
4.315
4.311
4.297
4.293
2.322
2.311
3.373
2.306
2.299
2.294
2.287
2.283
1.888
1.876
1.866
1.855
1.844
1.833
1.821
1.213
1.136
1.074
1.062
1.060
1.048
1.041
1.019
0.678
0.657
0.636
0.615
0.376
0.365

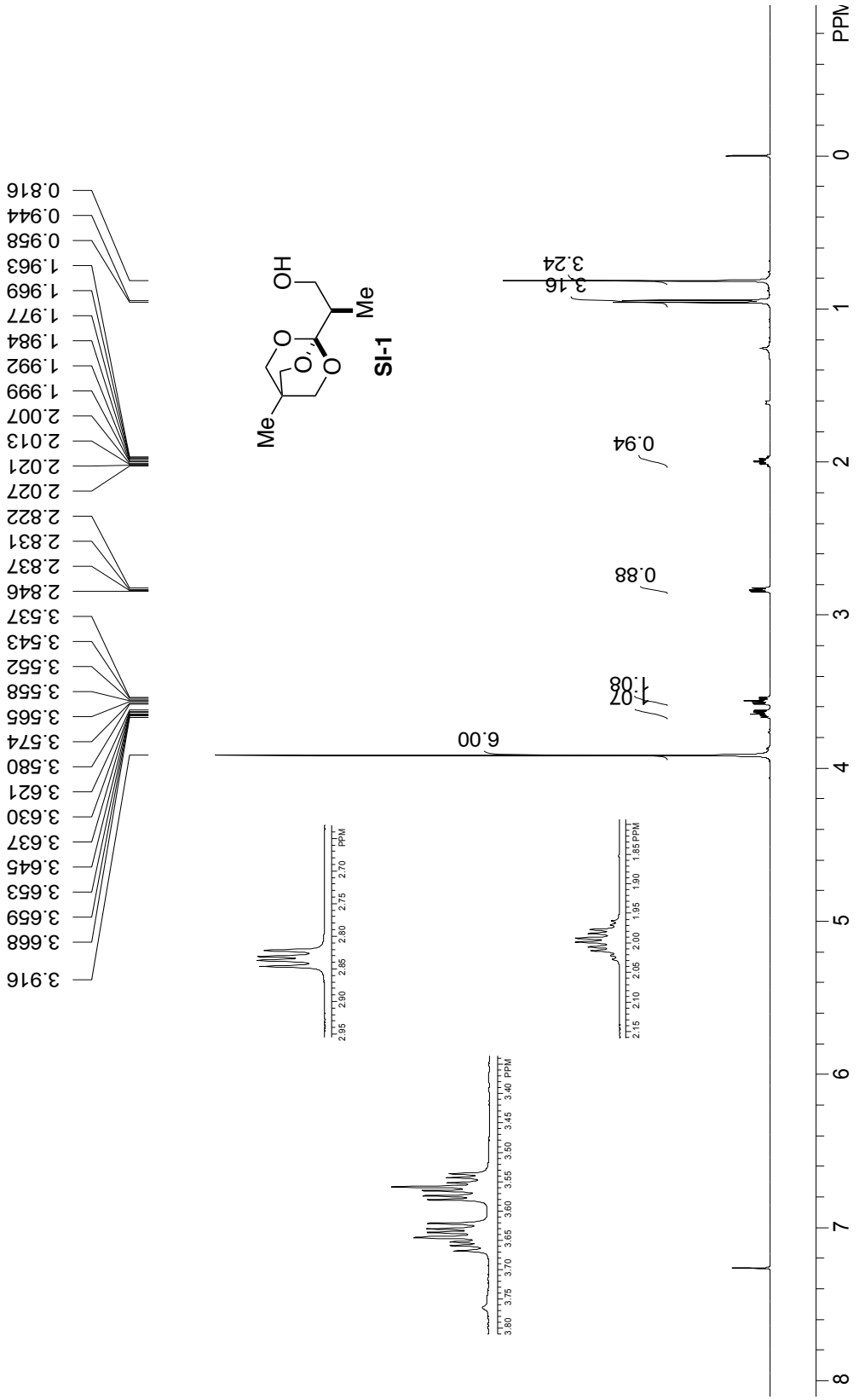

(+)-PD Lactone (8d1)
before recrystallization
C6D6 600 MHz
8d1 : C6 epi-8d1
4.30 ppm, 1H, dd
4.24 ppm, 1H, dd
MeO
Me
O
6
4.166
4.171
4.184
4.188
4.230
4.236
4.247
4.253
4.293
4.297
4.311
4.315
4.416
4.420
4.433
4.438
1.18
5.82
239.05
1.00
4.5
4.4
4.3
4.2
4.1
PPM

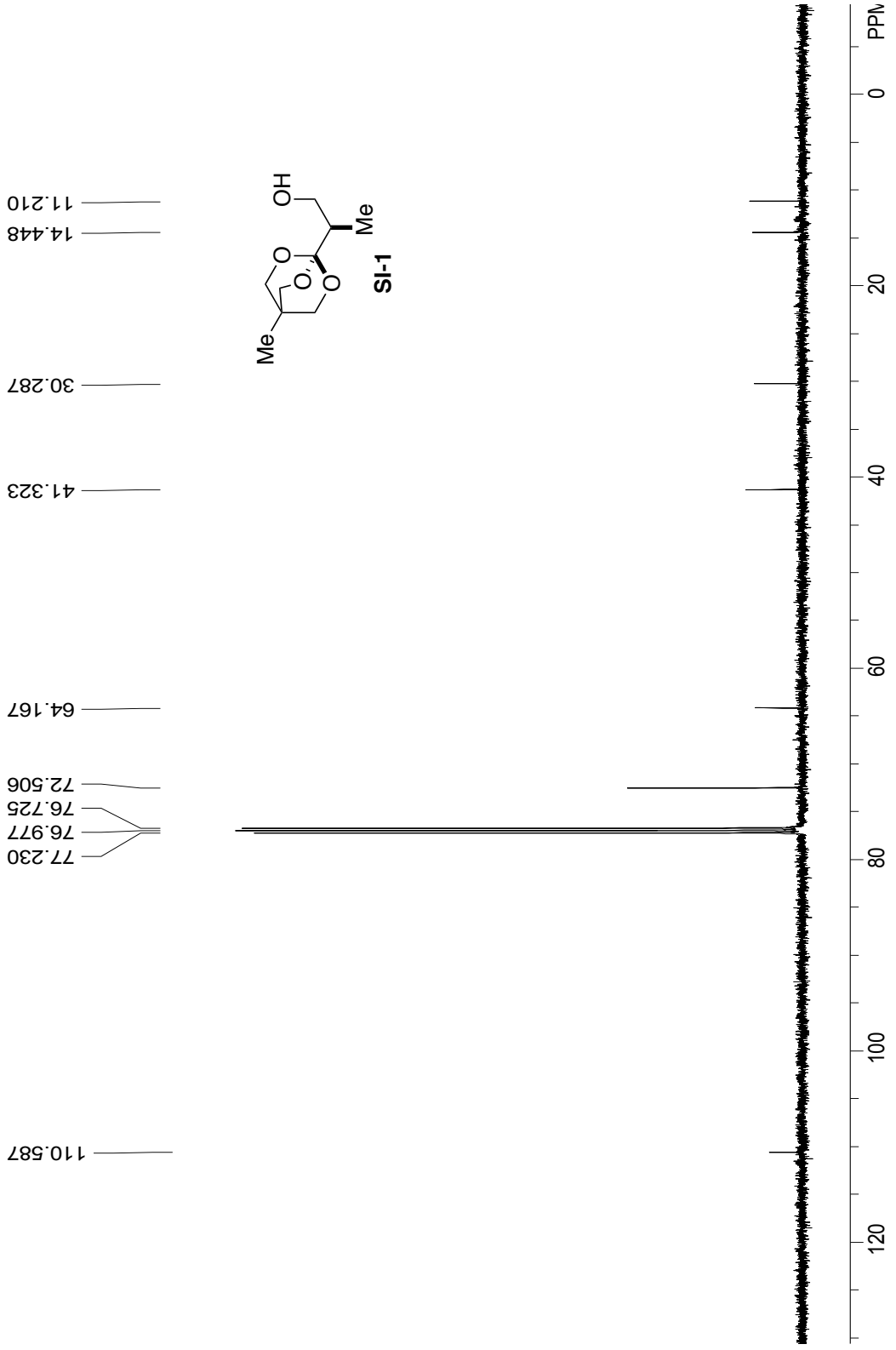

(+)-PD Lactone (8d1)
after recrystallization
C6D6 600 MHz
4.24 ppm,
1H, dd
4.30 ppm,
1H, dd
8d1 : C6 epi-8d1
MeO
Me
Me
Me
Me
O
O
O
O
6
9
PPM
0
1
2
3
4
5
6
7
1.00
1.00
1.00
1.16
1.42
2.98
7.02
2.99
4.316
4.313
4.299
4.295
2.325
2.320
2.313
3.374
2.309
2.301
2.297
2.289
2.285
1.891
1.880
1.869
1.858
1.847
1.836
1.825
1.215
1.140
1.075
1.063
1.061
1.050
1.038
1.032
1.028
1.022
0.681
0.659
0.639
0.618

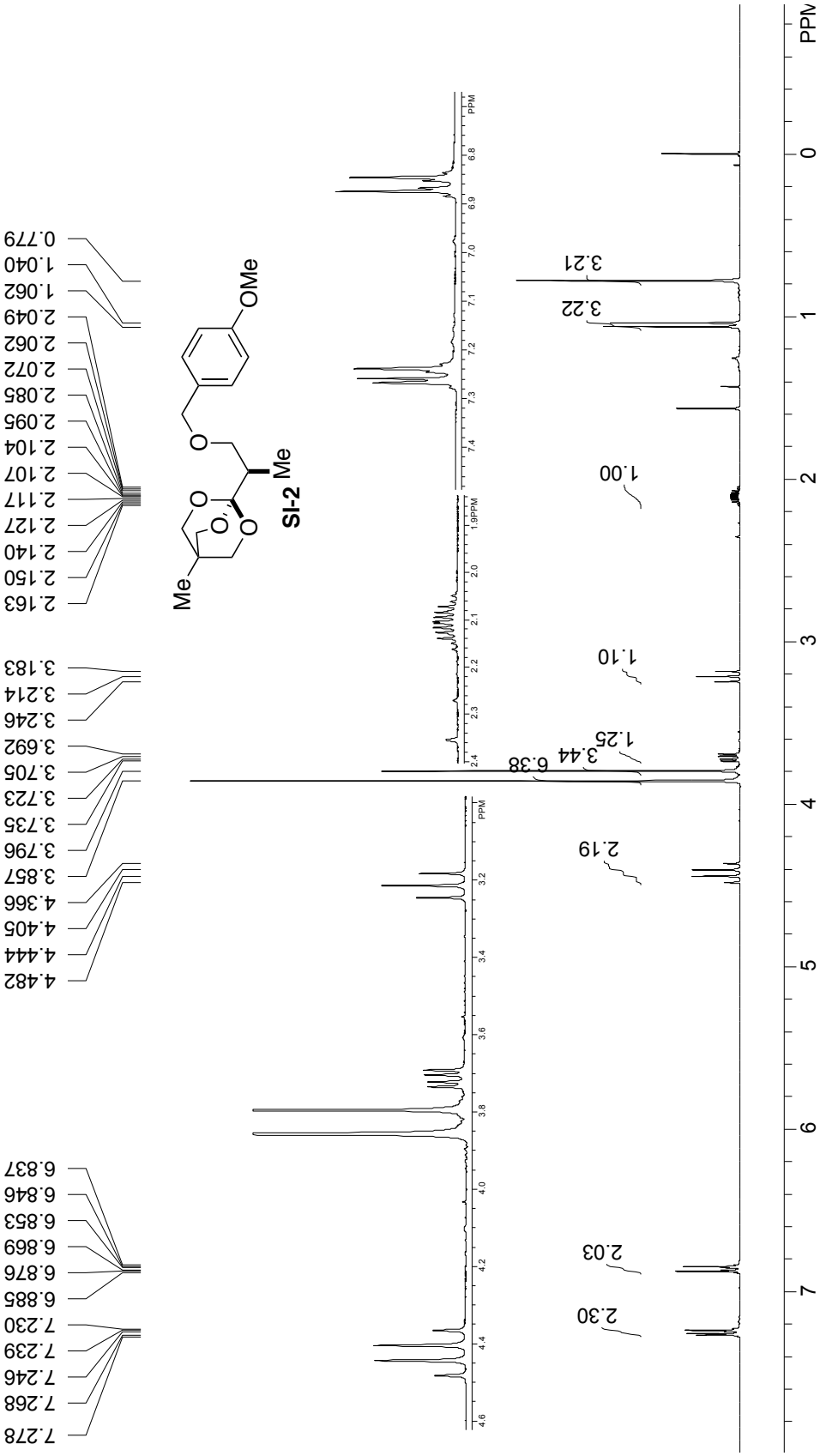

4.439
4.435
4.422
4.417
4.316
4.313
4.299
4.295
4.254
4.249
4.237
4.232
4.190
4.185
4.172
4.167
1.00
207.58
1.29
1.25
4.45
4.40
4.35
4.30
4.25
4.20
4.15
4.10
PPM
(+)-PD Lactone (8d1)
after recrystallization
C6D6 600 MHz
8d1 : C6 epi-8d1
4.30 ppm,
1H, dd
4.24 ppm,
1H, dd
MeO
Me
O
O
O
O
6
9

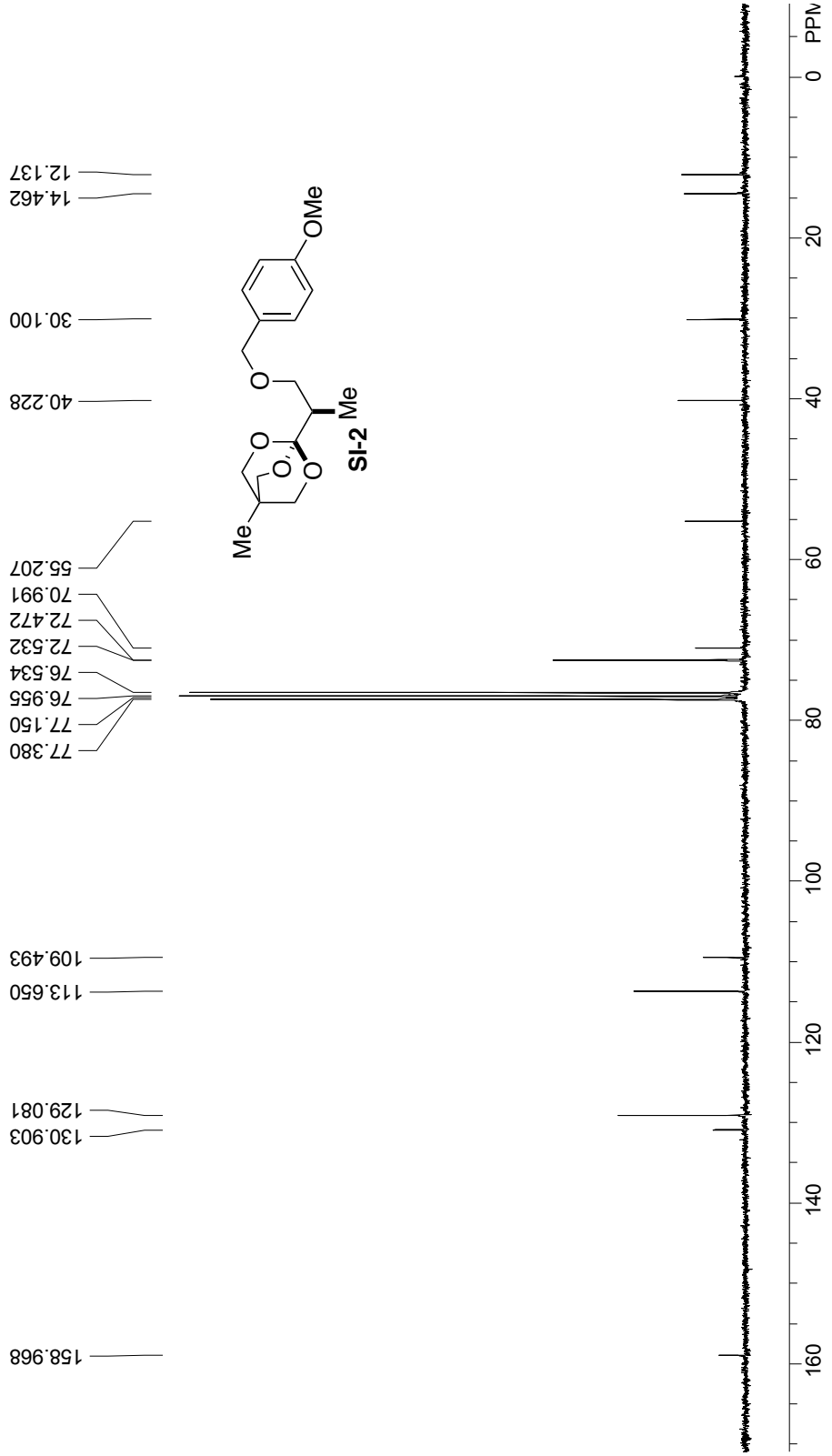
10.136
10.132
1.02
1.00
3.46
3.18
6.92
3.471
2.813
2.808
2.790
2.784
2.765
2.761
2.742
2.737
1.394
1.371
-0.028
8c1 Me
Me
PPM


8.971
14.049
30.395
53.038
72.806
109.295
200.119
8c1 Me
Me
O
O
O
O
200
150
100
50
0 PPM

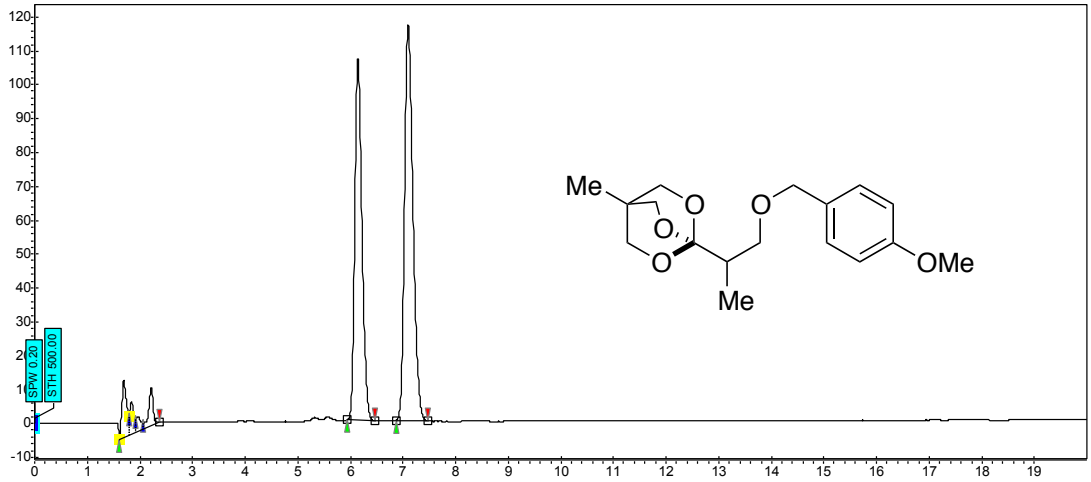

SI-1
OH
Me
Me
O
O
O
O
6.00
1.07
1.08
0.88
0.94
3.16
3.24
PPM
0
1
2
3
4
5
6
7
8
3.916
3.668
3.659
3.653
3.645
3.637
3.630
3.621
3.580
3.574
3.565
3.558
3.552
3.543
3.537
2.846
2.837
2.831
2.822
2.027
2.021
2.013
2.007
1.999
1.992
1.984
1.977
1.969
1.963
0.958
0.944
0.816


11.210
14.448
30.287
41.323
64.167
72.506
76.725
76.977
77.230
110.587
SI-1
Me
OH
Me
O
O
O
O
PPM
0
20
40
60
80
100
120


SI-2
Me
OMe
Me
PPM
0.779
1.040
1.062
2.049
2.062
2.072
2.085
2.095
2.104
2.107
2.117
2.127
2.140
2.150
2.163
3.183
3.214
3.246
3.692
3.705
3.723
3.735
3.796
3.857
4.366
4.405
4.444
4.482
6.837
6.846
6.853
6.869
6.876
6.885
7.230
7.239
7.246
7.268
7.278
2.30
2.03
2.19
6.38
3.44
1.25
1.10
1.00
3.22
3.21


158.968
129.081
130.903
113.650
109.493
77.380
77.150
76.955
76.534
72.532
72.472
70.991
55.207
40.228
30.100
14.462
12.137
SI-2
OMe
Me
Me
PPM
0
20
40
60
80
100
120
140
160

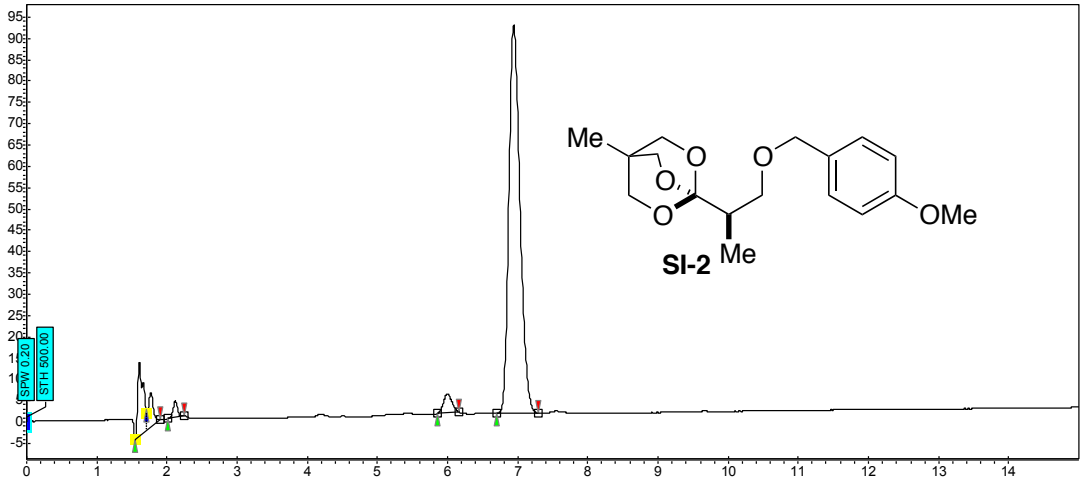
SFC Column Chiracel OJ-H 10% MeOH, 2 mL/min
OBO-PMB ether partially racemic



#	Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]		Quantity [% Area]	Height [µV]	Area [µV.Min]	Area [%]
1	UNKNOWN	1.61	1.70	1.79	0.00	4.02	16.8	1.7	4.018
2	UNKNOWN	1.79	1.84	1.91	0.00	1.99	9.7	0.9	1.994
3	UNKNOWN	1.91	1.96	2.07	0.00	1.21	4.4	0.5	1.214
4	UNKNOWN	2.07	2.22	2.36	0.00	2.48	11.3	1.1	2.480
5	UNKNOWN	5.93	6.14	6.46	0.00	39.46	106.5	17.0	39.456
6	UNKNOWN	6.87	7.10	7.46	0.00	50.84	116.6	21.9	50.838
Total					100.00	265.3	43.0	100.000		

The partially racemic OBO-PMB ether shown above was synthesized in the same manner as **SI-2** except the AHF was performed with ~1:1 mixture of the (*S,S,S*)-**BDP**: (*R,R,S*)-**BDP** ligands yielding a 39.46:50.84 mixture of enantiomers. This material was made for the purpose of resolving enantiomers for quantitative enantiomeric excess determination.

SFC Column Chiracel OJ-H 10% MeOH, 2 mL/min
Enantioenriched OBO-PMB ether **SI-4**



#	Name	Start [Min]	Time [Min]	End [Min]	RT Offset [Min]		Quantity [% Area]	Height [µV]	Area [µV.Min]	Area [%]
1	UNKNOWN	1.55	1.60	1.72	0.00	7.95	17.2	1.6	7.955
2	UNKNOWN	1.72	1.77	1.90	0.00	3.39	8.1	0.7	3.392
3	UNKNOWN	2.01	2.12	2.24	0.00	1.35	3.8	0.3	1.350
4	UNKNOWN	5.86	6.00	6.17	0.00	3.19	4.4	0.6	3.195
5	UNKNOWN	6.71	6.94	7.29	0.00	84.11	91.0	16.7	84.108
Total					100.00	124.5	19.9	100.000		

Calculation:

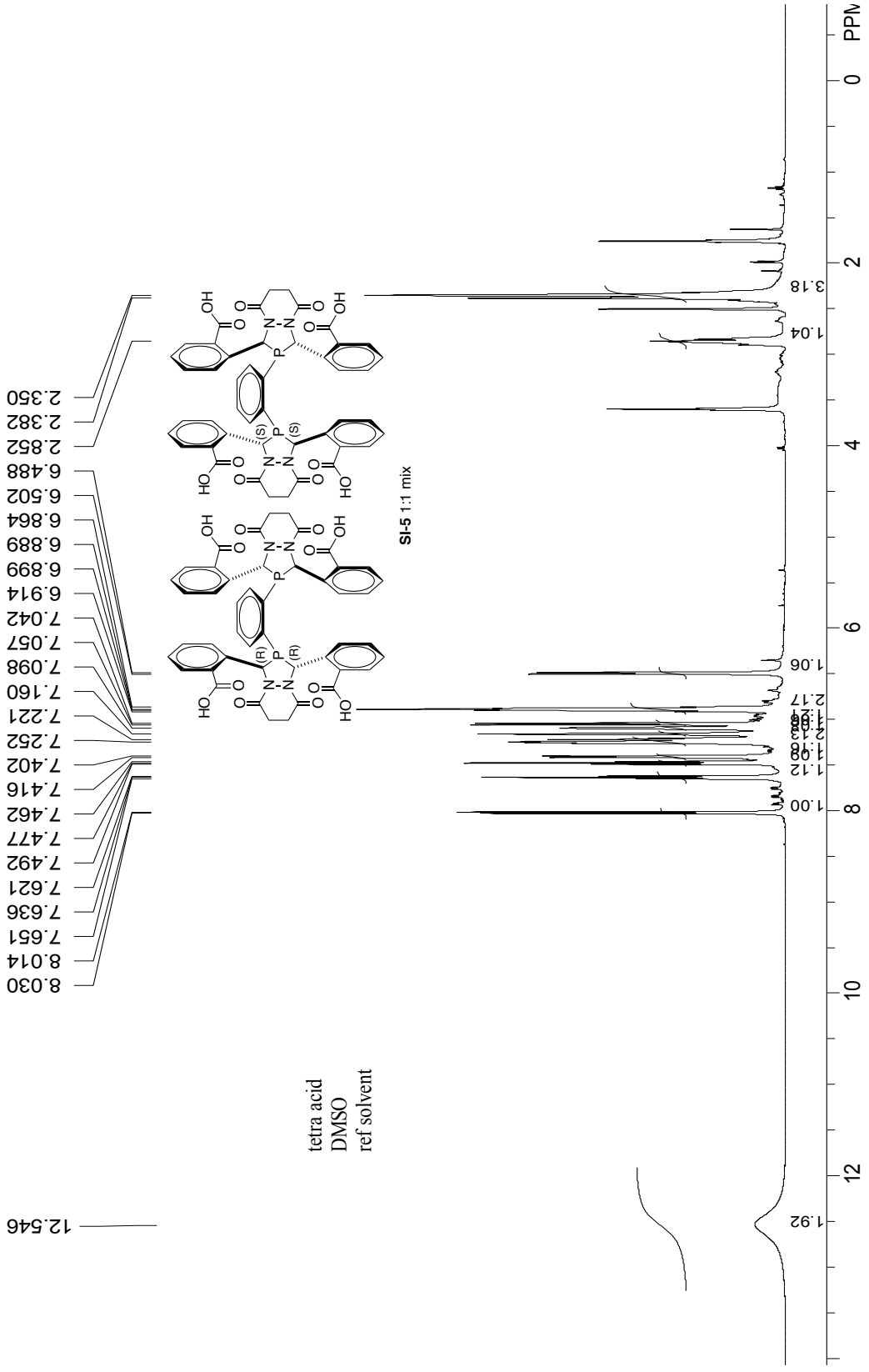
(84.11-3.19)/(84.11+3.19) x 100% = 92.7%ee

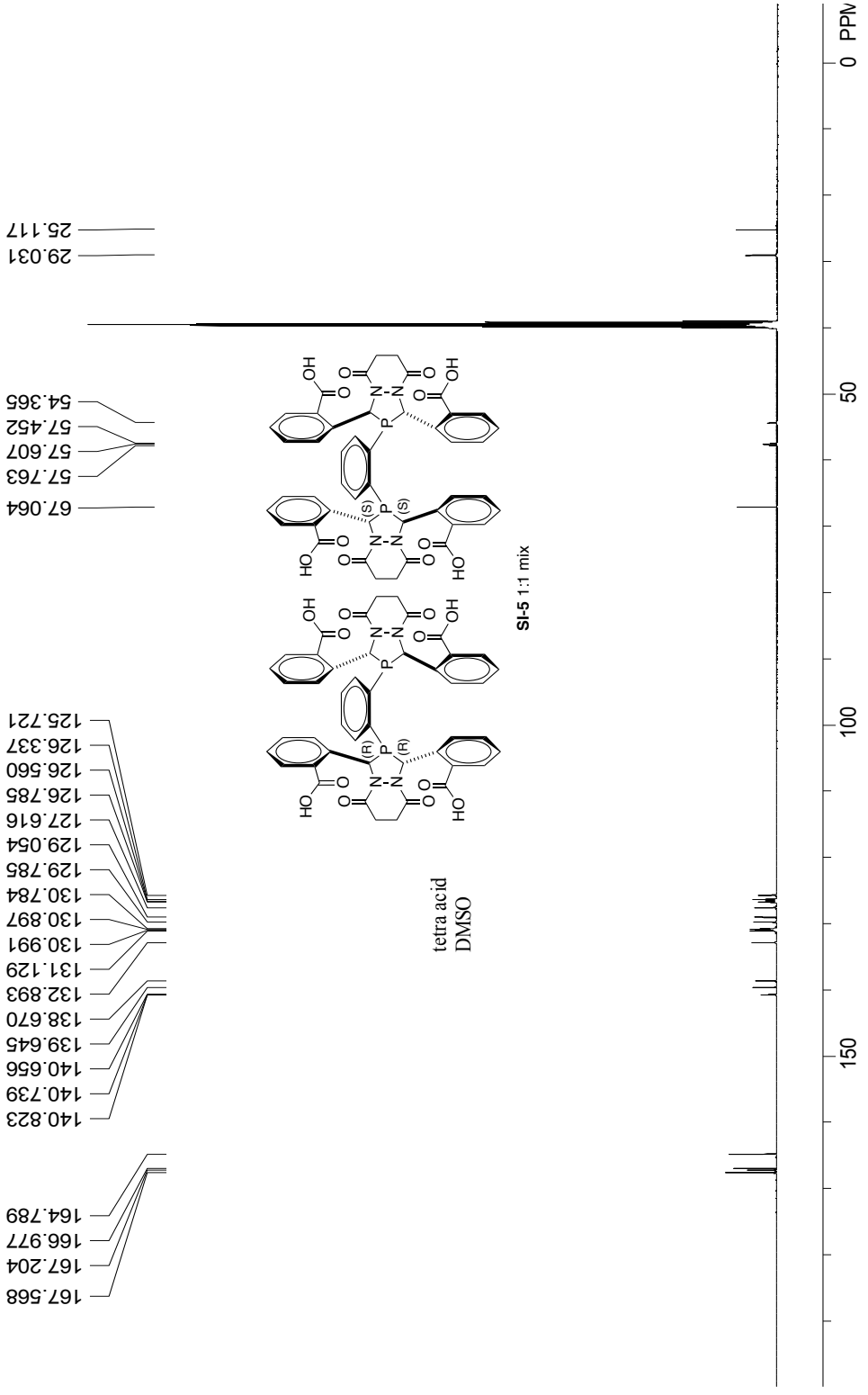
^{1}H NMR Data Comparison Table for (+)-PD Lactone:

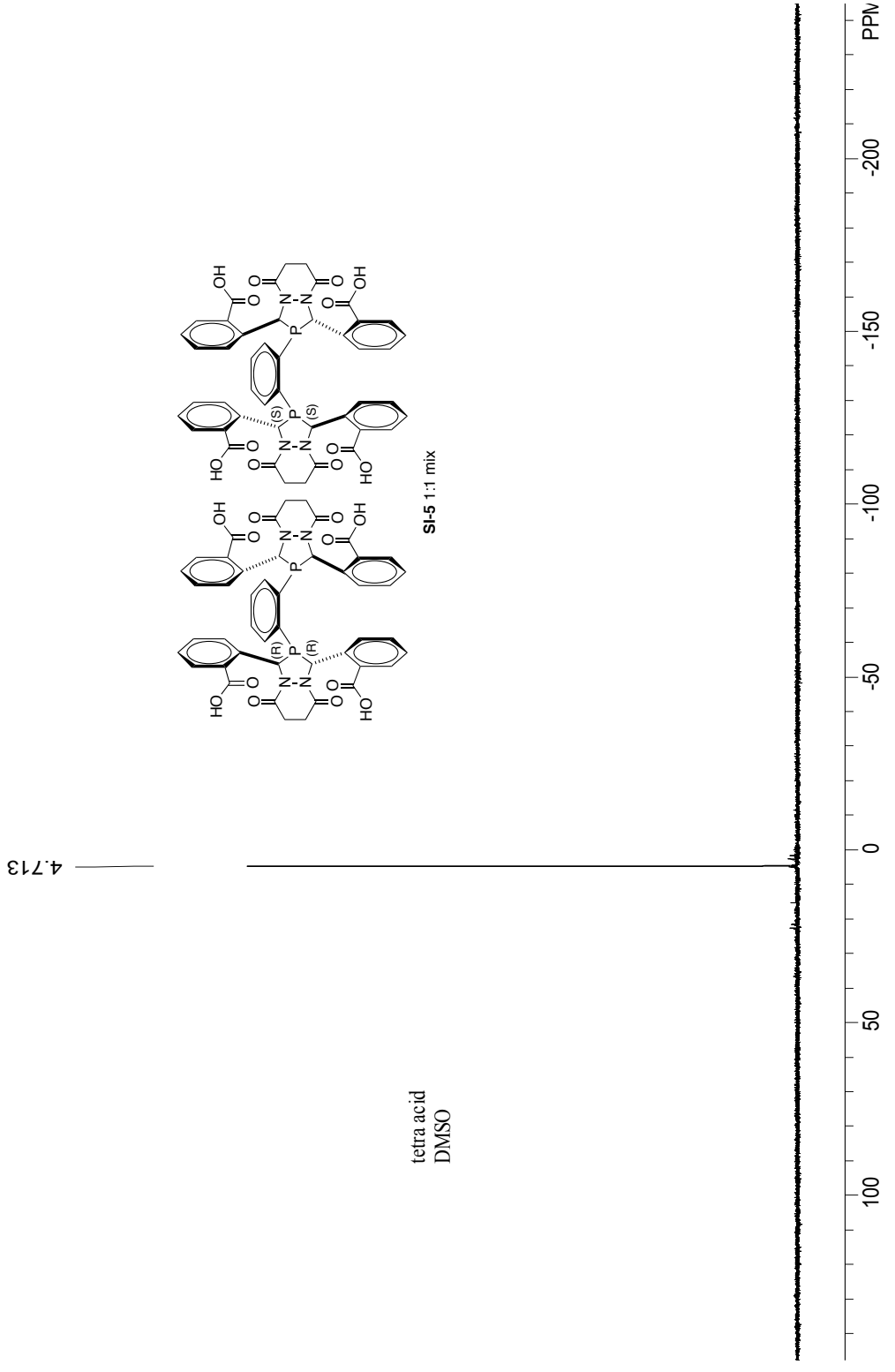
Carbon	reference[7] (200 MHz)	measured (600 MHz)	Δδ	ref.[7] mult/J(Hz)	meas. mult/J(Hz)
MeO	3.73	3.73	0.00	s/none	s/none
C1	-	-	-	-	-
C2	2.73	2.73	0.00	qd/7.1,2.6	qd/7.1,2.6
C3	4.54	4.54	0.00	dd/2.6,10.4	dd/2.9,10.5
C4	1.80-2.05	1.86-1.97	-	-	-
C5(eq)	1.80-2.05	1.86-1.97	-	-	-
C5(ax)	1.45	1.42	0.03	dd/12.0,12.0	dt/12.1, 13.1(ap. q)
C6	2.49	2.50	-0.01	ddq/12.0,6.0,7.1	ddq/13.6,7.0,7.0 (ap. sept)
C7	-	-	-	-	-
C2-Me	1.20	1.20	0.00	d/7.1	d/7.0
C4-Me	1.00	1.01	-0.01	d/6.4	d/6.5
C6-Me	1.29	1.29	0.00	d/7.1	d/6.8

^{13}C NMR Data Comparison Table for (+)-PD Lactone:

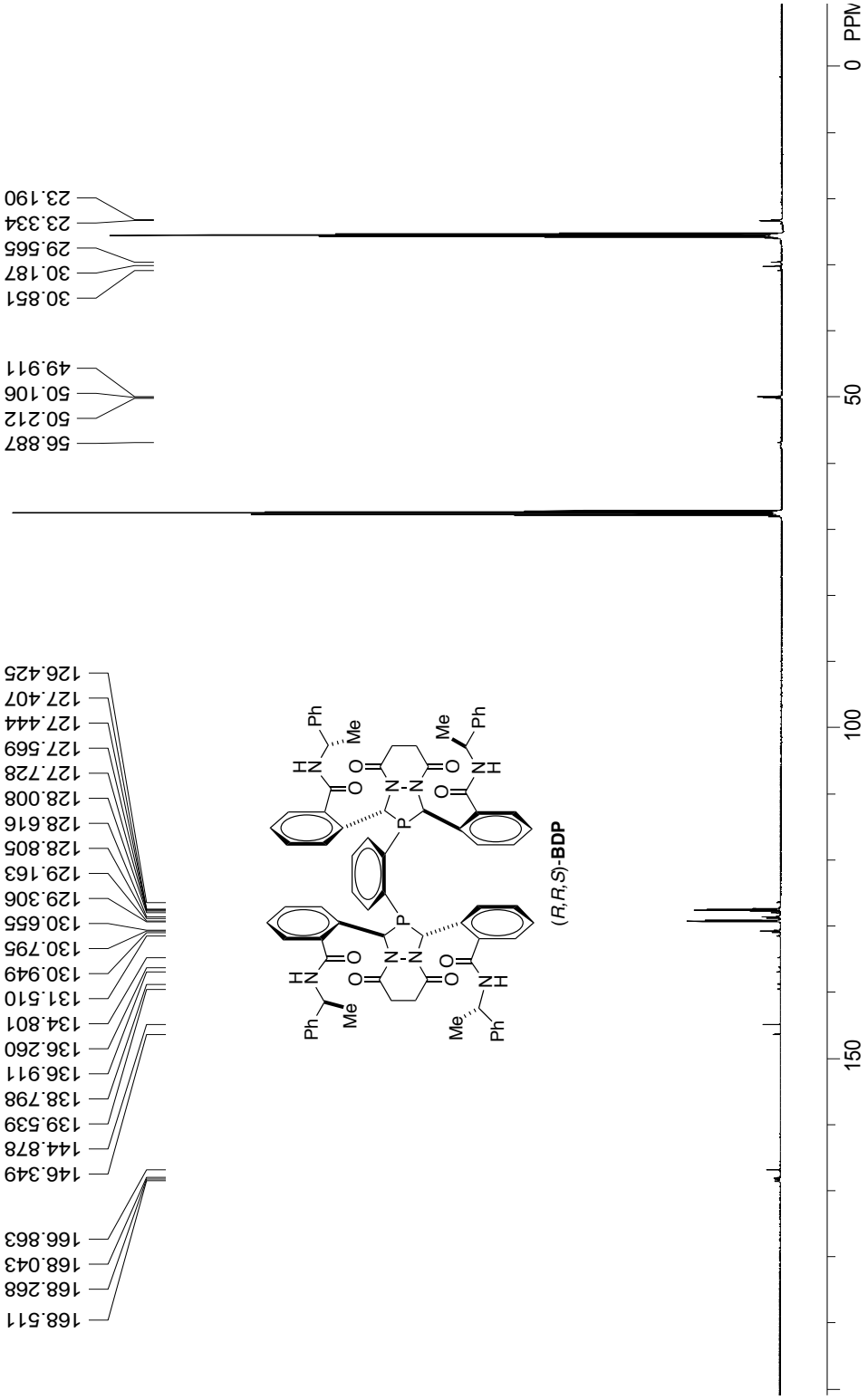
Carbon	reference[7]	measured	Δδ
1	173.6	173.7	-0.1
2	173.3	173.3	0.0
3	86.2	86.2	0.0
4	52.2	52.2	0.0
5	41.4	41.3	0.1
6	37.4	37.3	0.1
7	36.3	36.2	0.1
8	31.0	30.9	0.1
9	17.3	17.2	0.1
10	17.0	17.0	0.0
11	8.8	8.7	0.1

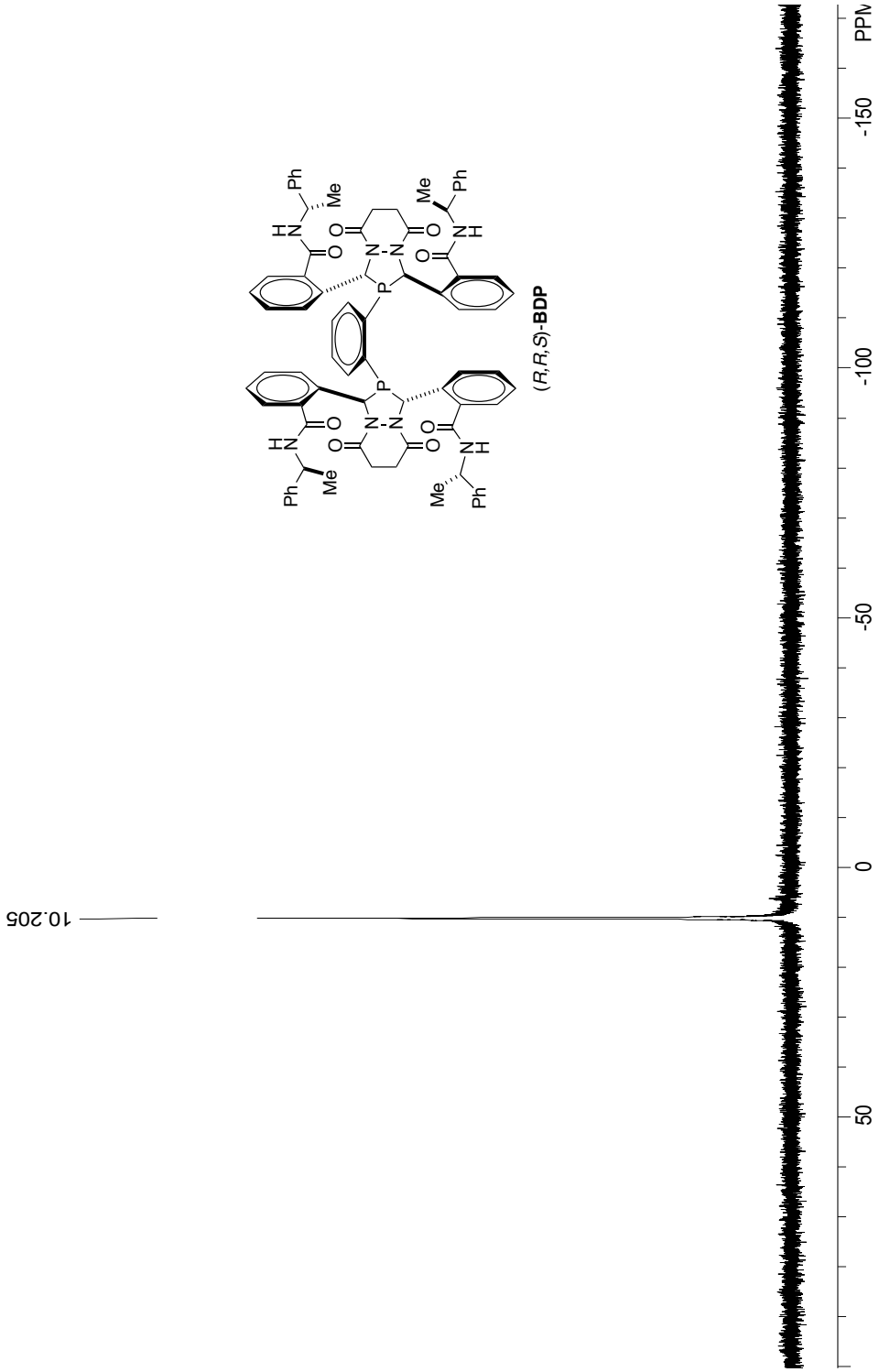

SI-5 1:1 mix
tetra acid
DMSO
ref solvent
PPM
0
2
4
6
8
10
12
3.18
1.04
1.06
2.17
1.00
1.12
1.92
2.350
2.382
2.852
6.488
6.502
6.864
6.889
6.899
6.914
7.042
7.057
7.098
7.160
7.221
7.252
7.402
7.416
7.462
7.477
7.492
7.621
7.636
7.651
8.014
8.030
12.546

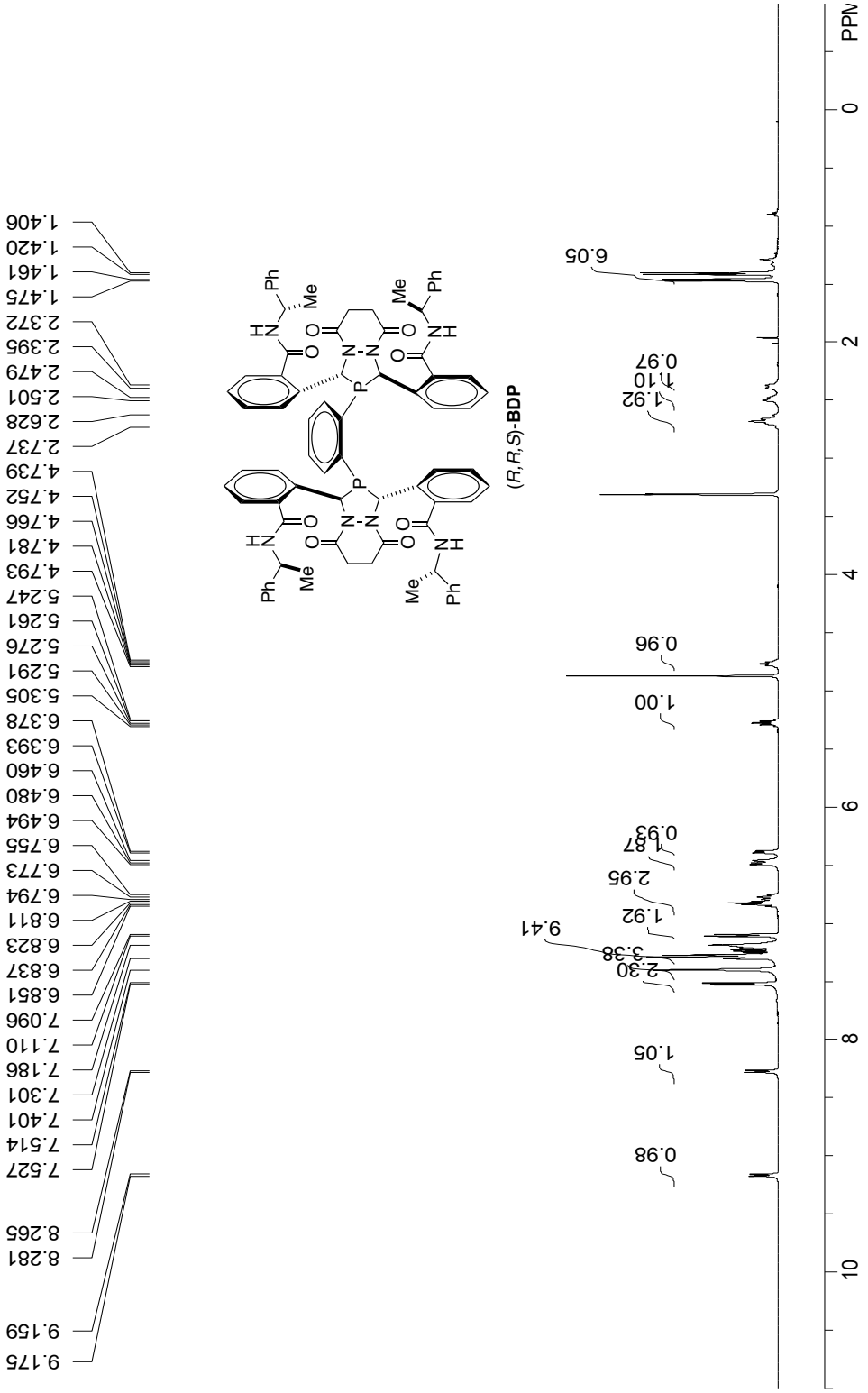

SI-5 1:1 mix
tetra acid
DMSO
25.117
29.031
54.365
57.452
57.607
57.763
67.064
125.721
126.337
126.560
126.785
127.616
129.054
129.785
130.784
130.897
130.991
131.129
132.893
138.670
139.645
140.656
140.739
140.823
164.789
166.977
167.204
167.568
0
50
100
150

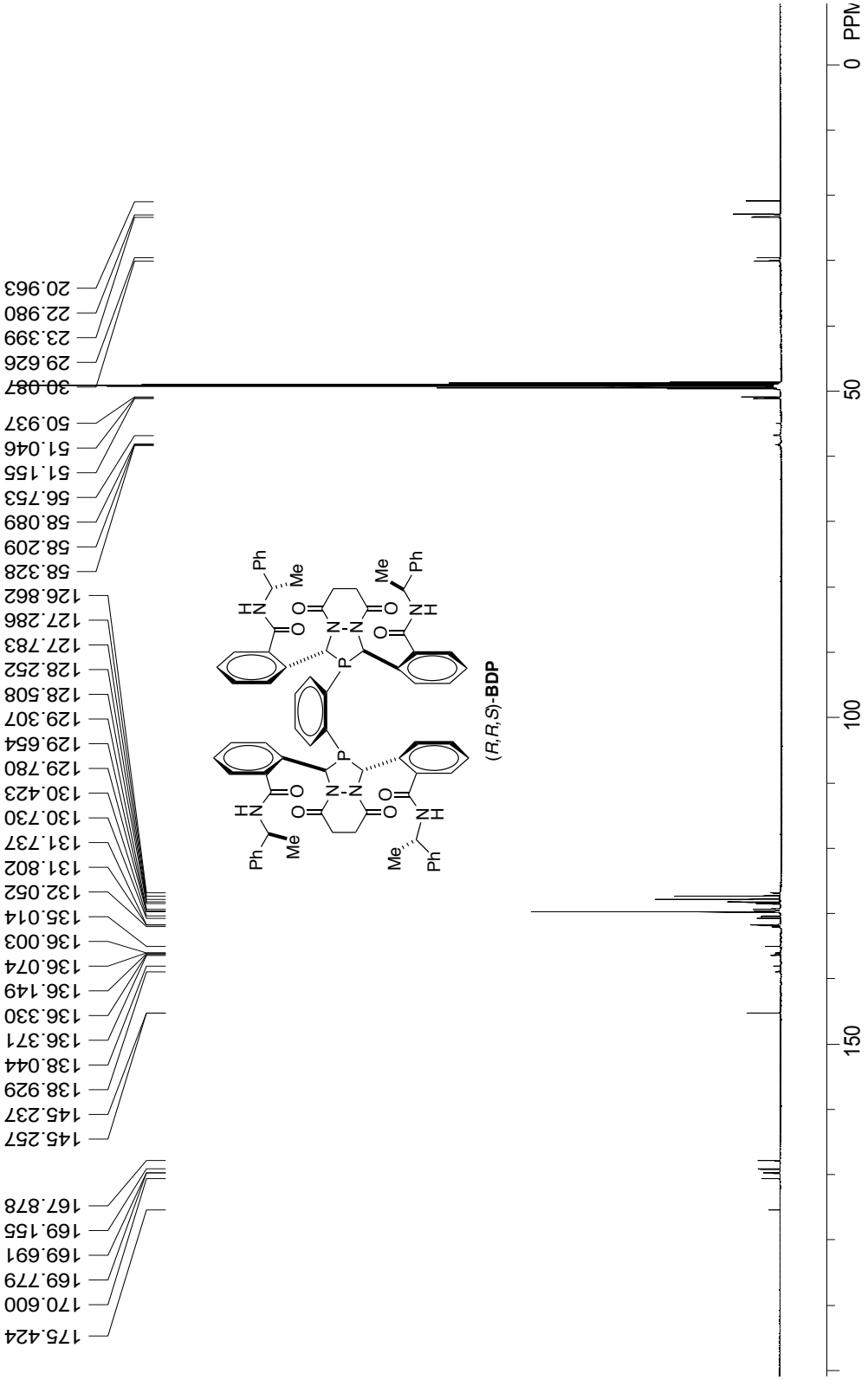

4.713
tetra acid
DMSO
SI-5 1:1 mix
100
50
0
-50
-100
-150
-200
PPM

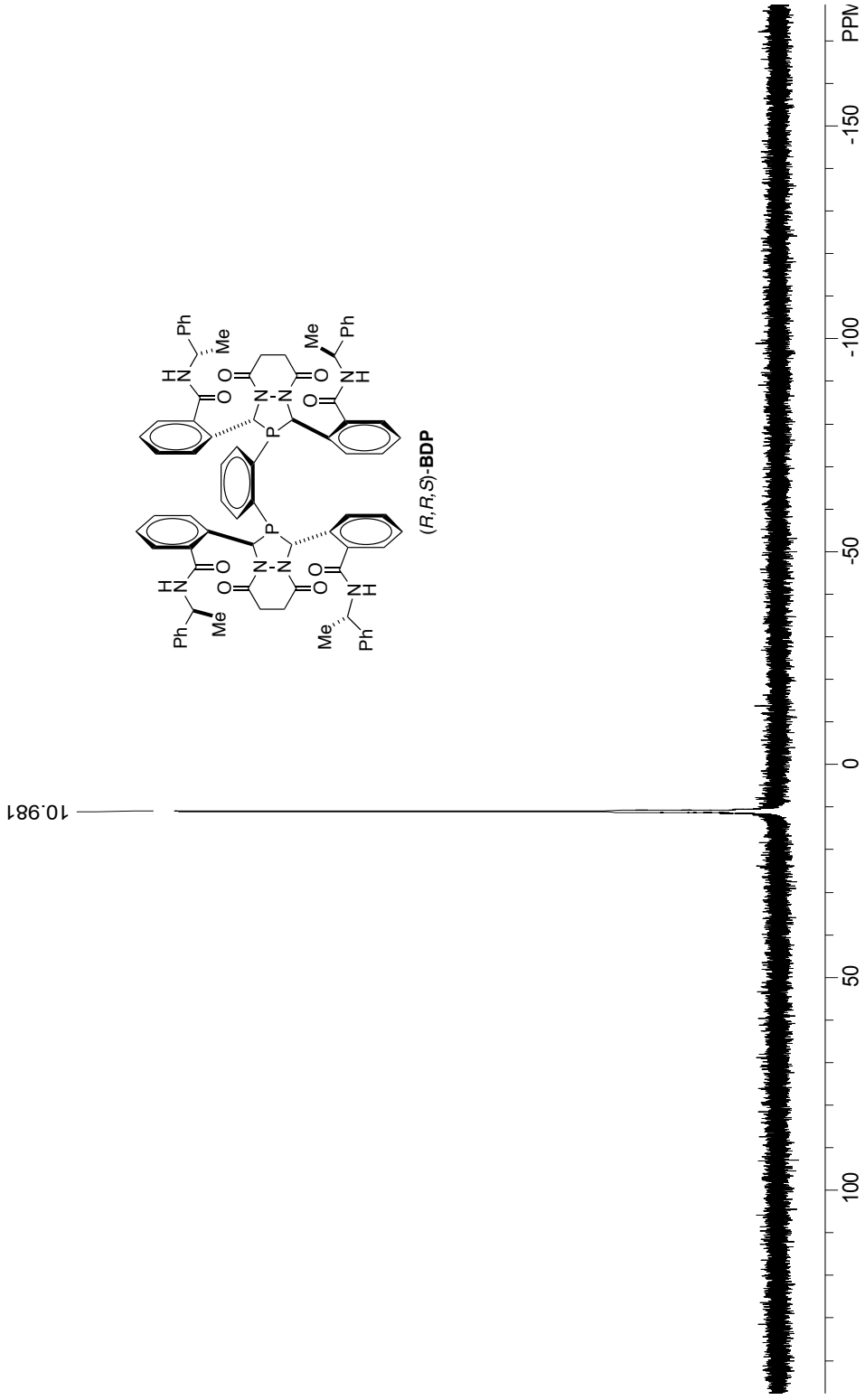
(R,R,S)-BDP
PPM
0
2
4
6
8
10
0.86
1.19
2.37
1.16
13.76
2.84
1.70
0.80
1.00
0.99
0.91
1.06
2.08
1.05
3.07
3.41
9.220
9.220
7.955
7.941
7.599
7.584
7.511
7.500
7.325
7.099
6.801
6.727
6.611
6.556
6.387
5.427
5.414
5.400
5.385
5.371
5.075
5.075
5.061
5.047
5.047
2.888
2.656
2.625
2.602
2.501
2.369
2.341
1.566
1.552
1.372
1.358

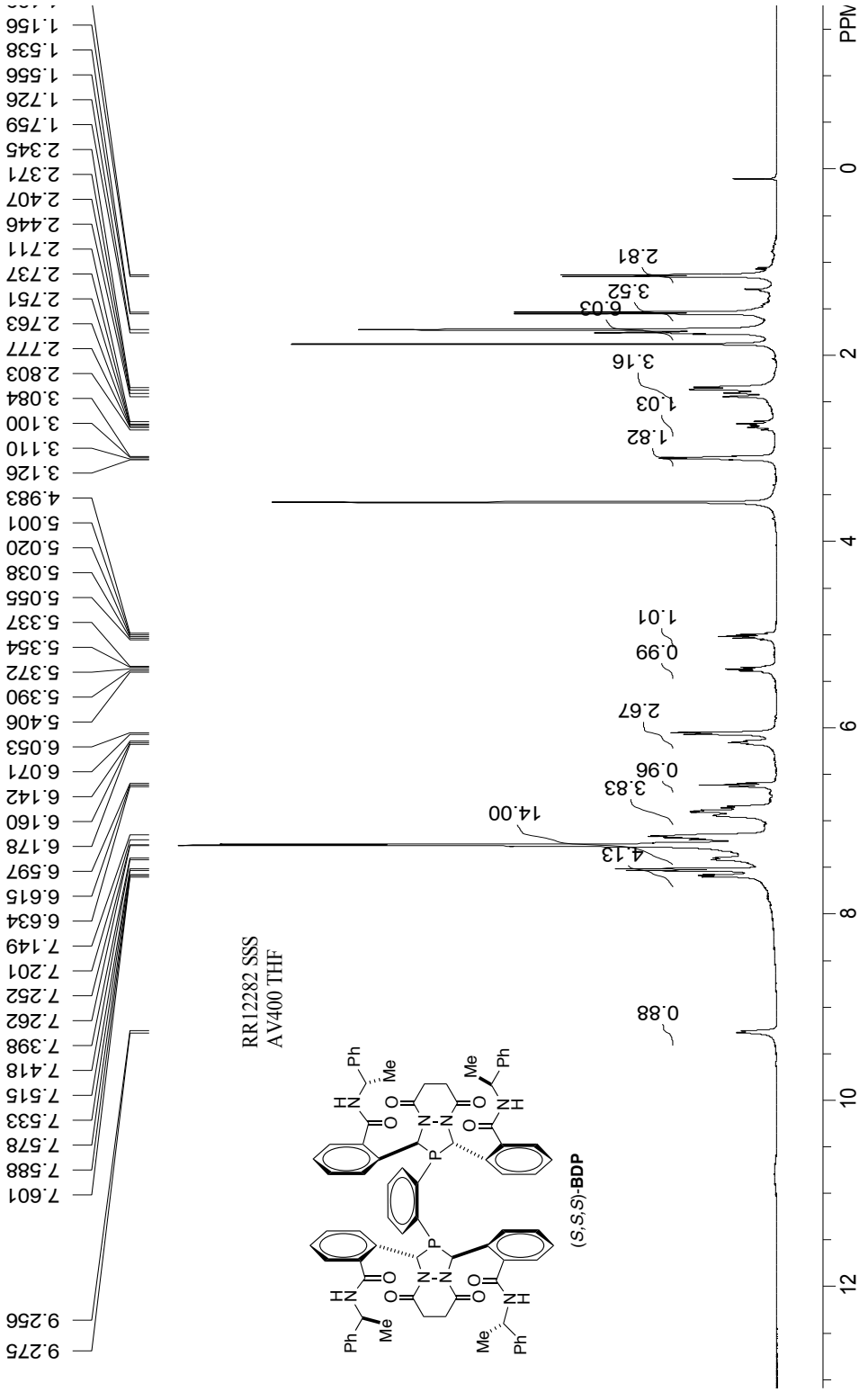

23.190
23.334
29.565
30.187
30.851
49.911
50.106
50.212
56.887
126.425
127.407
127.444
127.569
127.728
128.008
128.616
128.805
129.163
129.306
130.655
130.795
130.949
131.510
134.801
136.260
136.911
138.798
139.539
144.878
146.349
166.863
168.043
168.268
168.511
(R,R,S)-BDP
0
50
100
150


10.205
50
0
-50
-100
-150
PPM
(R,R,S)-BDP


(R,R,S)-BDP
PPM
0
2
4
6
8
10
6.05
0.96
1.00
0.93
1.87
2.95
1.92
9.41
3.38
2.30
1.05
0.98
4.92
3.10
0.97
9.175
9.159
8.281
8.265
7.527
7.514
7.401
7.301
7.186
7.110
7.096
6.851
6.837
6.823
6.811
6.794
6.773
6.755
6.494
6.480
6.460
6.393
6.378
5.305
5.291
5.276
5.261
5.247
4.793
4.781
4.766
4.752
4.739
2.737
2.628
2.501
2.479
2.395
2.372
1.475
1.461
1.420
1.406


20.963
22.980
23.399
29.626
30.087
50.937
51.046
51.155
56.753
58.089
58.209
58.328
126.862
127.286
127.783
128.252
128.508
129.307
129.654
129.780
130.423
130.730
131.737
131.802
132.052
135.014
136.003
136.074
136.149
136.330
136.371
138.044
138.929
145.237
145.257
167.878
169.155
169.691
169.779
170.600
175.424
(R,R,S)-BDP
0
50
100
150
PPM


10.981
(R,R,S)-BDP
PPM
100
50
0
-50
-100
-150


RR12282 SSS
AV400 THF
(S,S,S)-BDP
PPM
0.88
14.00
4.13
3.83
0.96
2.67
0.99
1.01
1.82
1.03
3.16
6.03
3.52
2.81
9.275
9.256
7.601
7.588
7.578
7.533
7.515
7.418
7.398
7.262
7.252
7.201
7.149
6.634
6.615
6.597
6.178
6.160
6.142
6.071
6.053
5.406
5.390
5.372
5.354
5.337
5.055
5.038
5.020
5.001
4.983
3.126
3.110
3.100
3.084
2.803
2.777
2.763
2.751
2.737
2.711
2.446
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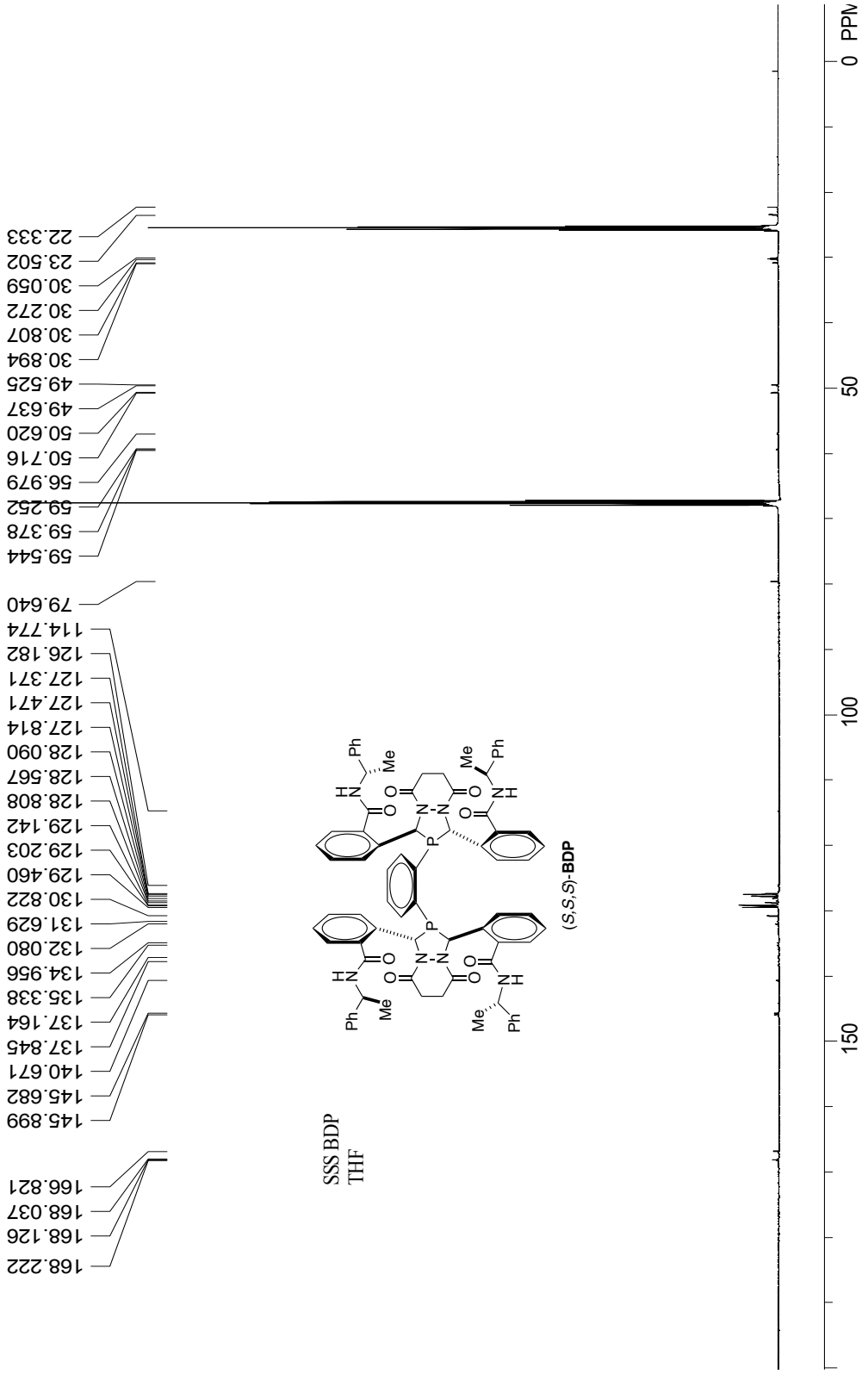
2.345
1.759
1.726
1.556
1.538
1.156


SSS BDP
THF
(S,S,S)-BDP
0 PPM
50
100
150
22.333
23.502
30.059
30.272
30.807
30.894
49.525
49.637
50.620
50.716
56.979
59.252
59.378
59.544
79.640
114.774
126.182
127.371
127.471
127.814
128.090
128.567
128.808
129.142
129.203
129.460
130.822
131.629
132.080
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137.164
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145.899
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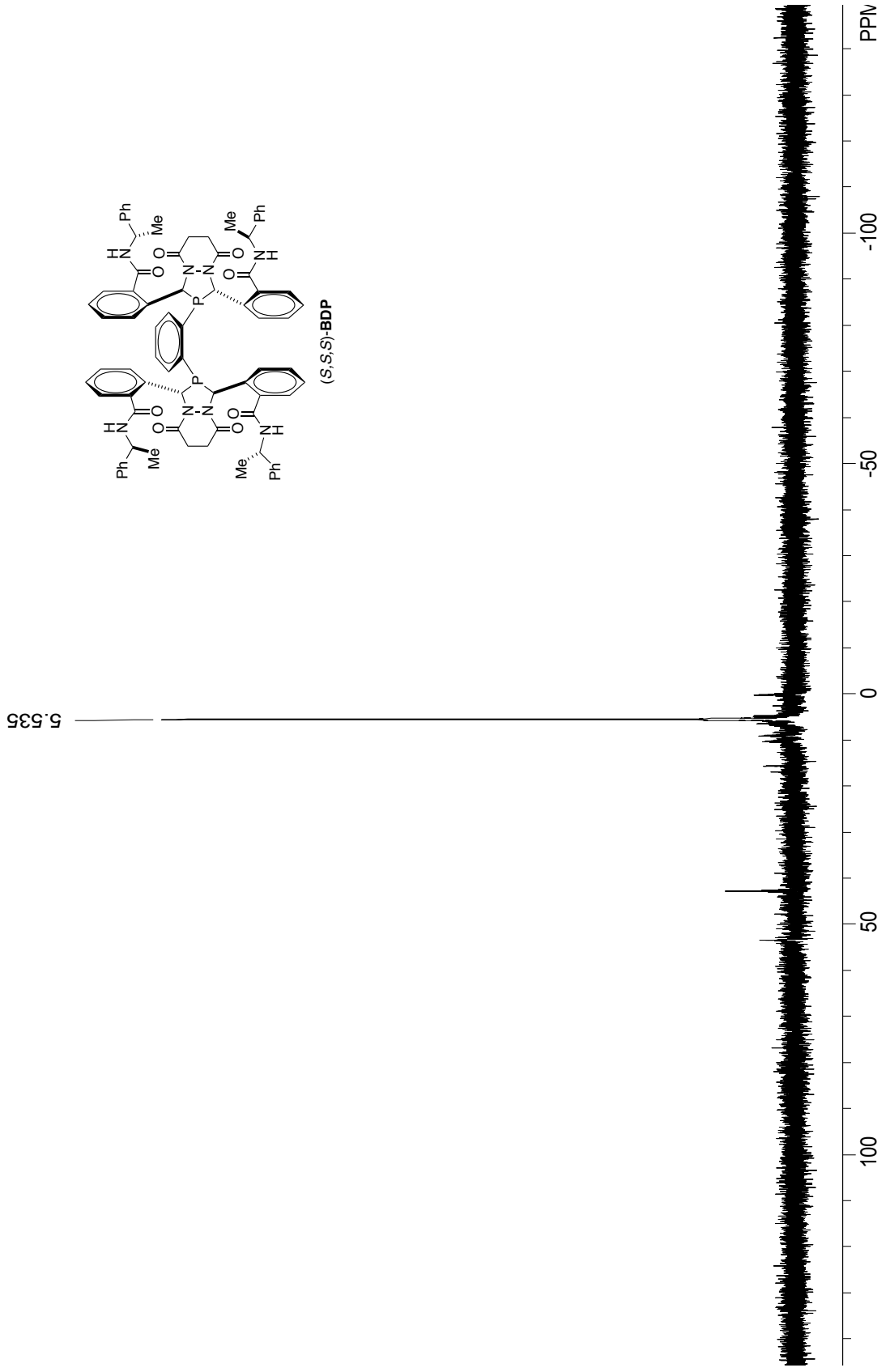
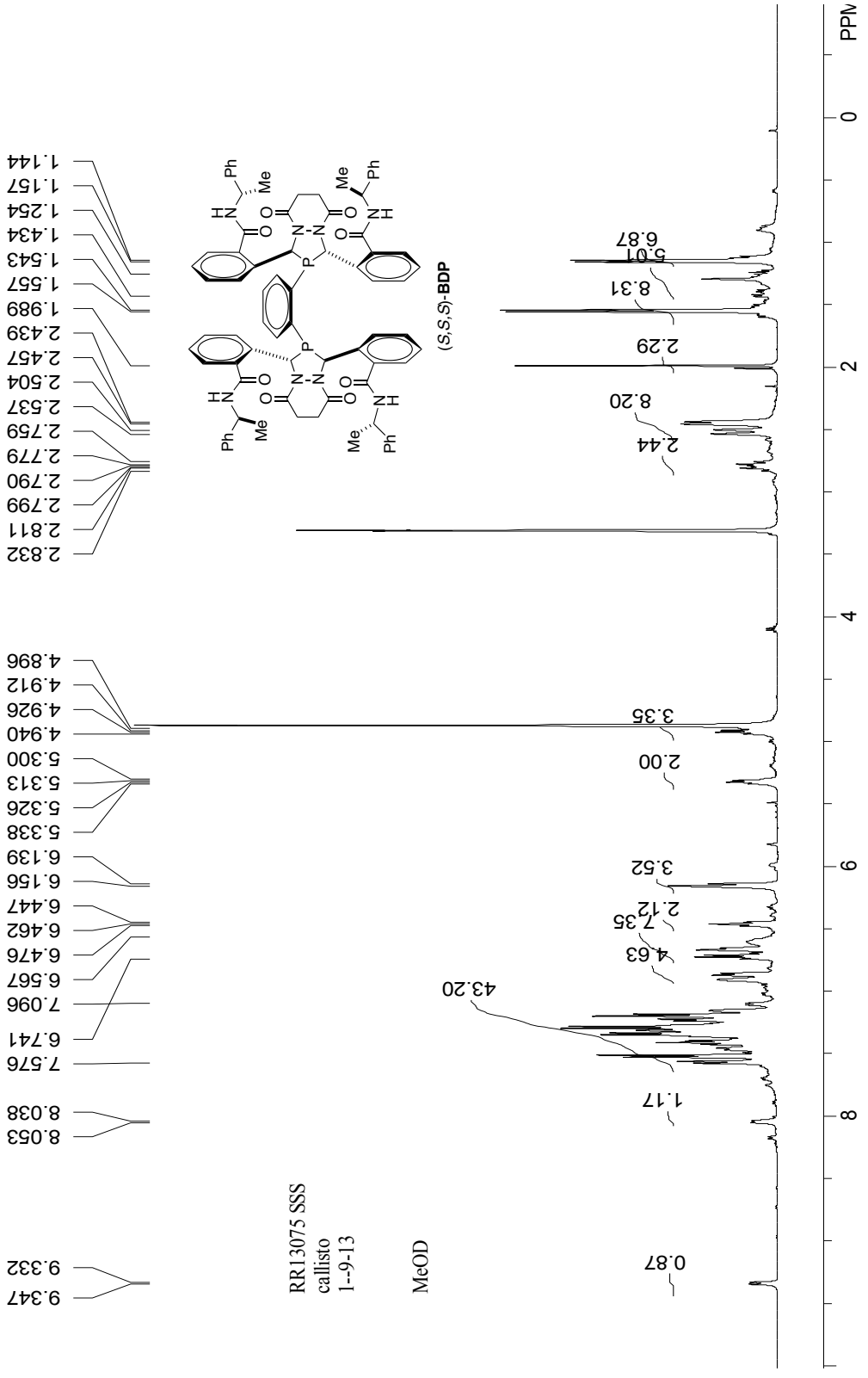
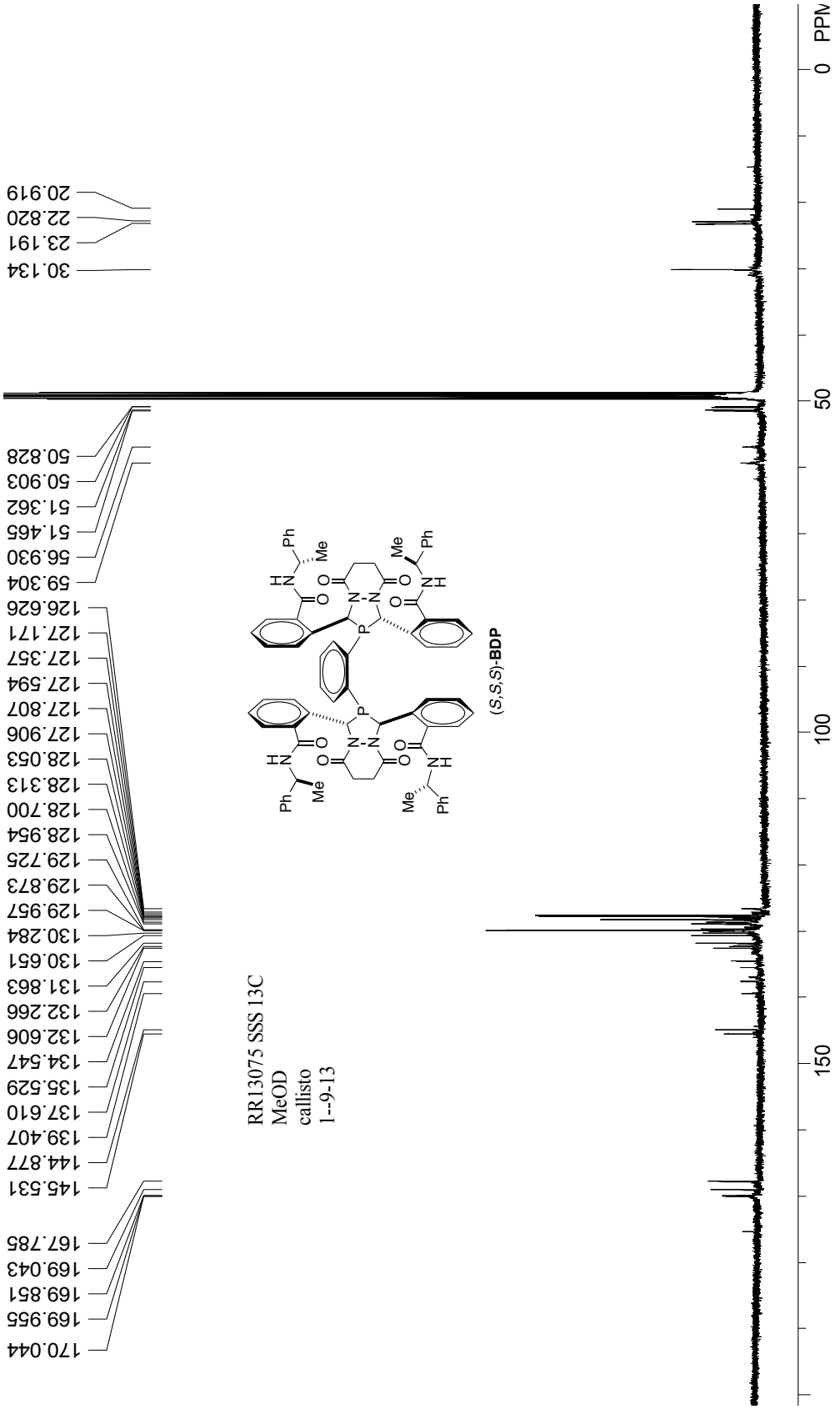
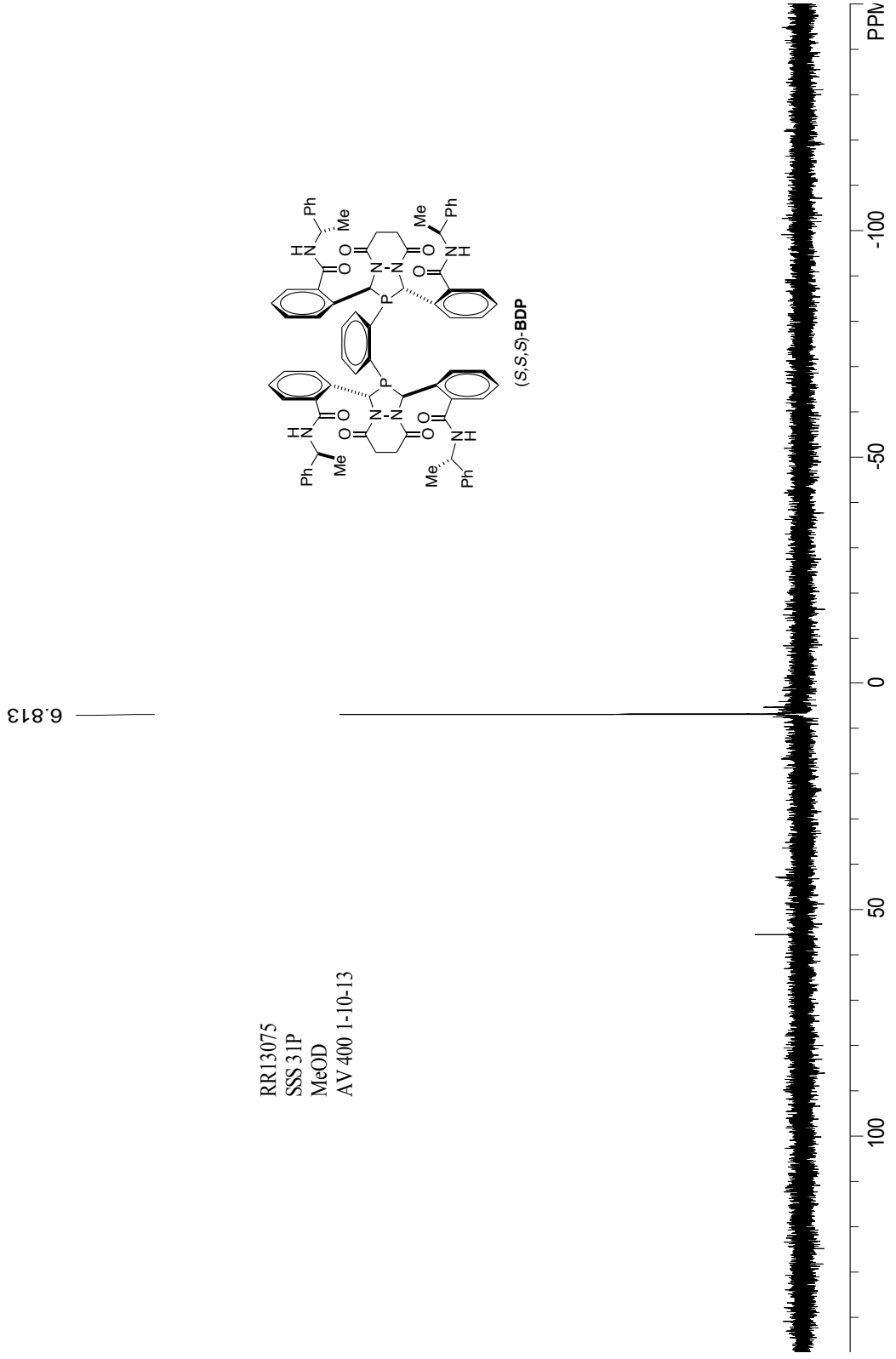
168.037
168.126
168.222


5.535
PPM
100
50
0
-50
-100
(S,S,S)-BDP


RR13075 SSS
callisto
1--9-13
MeOD
(S,S,S)-BDP
PPM
0
2
4
6
8
0.87
1.17
43.20
4.63
7.35
2.12
3.52
2.00
3.35
4.940
2.44
8.20
2.29
8.31
5.01
6.87
9.347
9.332
8.053
8.038
7.576
6.741
7.096
6.567
6.476
6.462
6.447
6.156
6.139
5.338
5.326
5.313
5.300
4.926
4.912
4.896
2.832
2.811
2.799
2.790
2.779
2.759
2.537
2.504
2.457
2.439
1.989
1.557
1.543
1.434
1.254
1.157
1.144


RR13075 SSS 13C
MeOD
callisto
1--9-13
(S,S,S)-BDP
170.044
169.955
169.851
169.043
167.785
145.531
144.877
139.407
137.610
135.529
134.547
132.606
132.266
131.863
130.651
130.284
129.957
129.873
129.725
128.954
128.700
128.313
128.053
127.906
127.807
127.594
127.357
127.171
126.626
59.304
56.930
51.465
51.362
50.903
50.828
30.134
23.191
22.820
20.919
0
50
100
150
PPM


6.813
RR13075
SSS 31P
MeOD
AV 400 1-10-13
(S,S,S)-BDP
100
50
0
-50
-100
PPM

Appendix B: Crystallographic Data

MOLECULAR STRUCTURE LABORATORY

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University of Wisconsin-Madison
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Madison, WI 53706

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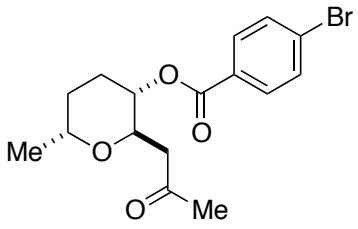
E-mail: iguzei@chem.wisc.edu

Structural report on **6m2**



6m2

MARCH 18, 2013

Crystallographic Experimental Section

Data Collection

A colorless crystal with approximate dimensions 0.395 × 0.041 × 0.04 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker Quazar SMART APEXII diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.96 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 12 frames collected at intervals of 0.5º in a 6º range about ω with the exposure time of 30 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program suite. The final cell constants were calculated from a set of 9917 strong reflections from the actual data collection.

The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.70 Å. A total of 35047 data were harvested by collecting 5 sets of frames with 0.5º scans in ω and φ with exposure times of 90 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1]

Structure Solution and Refinement

The systematic absences in the diffraction data and the *E*-statistics were consistent for the space groups *C*2 and *C*m. Only the chiral space group *C*2 was consistent with the proposed structure. It was chosen for the refinement and yielded chemically reasonable and computationally stable results of refinement [2-4].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

There are two chemically equivalent molecules with the same handedness but slightly different conformations in the asymmetric unit. The molecules can be superimposed with a rms of 0.214 Å. The absolute configuration was unequivocally established by anomalous dispersion as C8(S), C11(R), C13(R).

The final least-squares refinement of 384 parameters against 8541 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0305 and 0.0616, respectively. The final difference Fourier map was featureless.

Summary

Crystal Data for $C_{16}H_{19}O_4Br$ (M =355.22): monoclinic, space group C2 (no. 5), a = 28.650(11) Å, b = 4.9547(18) Å, c = 22.409(8) Å, β = 97.901(13)°, V = 3151(2) Å^3, Z = 8, T = 100.0 K, μ(Mo Kα) = 2.622 mm^{-1}, *Dcalc* = 1.498 g/mm^3, 35047 reflections measured ($2.87 \leq 2\Theta \leq 58.572$), 8541 unique ($R_{int}$ = 0.0430) which were used in all calculations. The final R_1 was 0.0305 ($I > 2\sigma(I)$) and wR_2 was 0.0616 (all data).

References

[1] Bruker-AXS. (2009) APEX2, SADABS, and SAINT Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

[2] Sheldrick, G. M. (2008) SHELXL. *Acta Cryst.* **A64**, 112-122.

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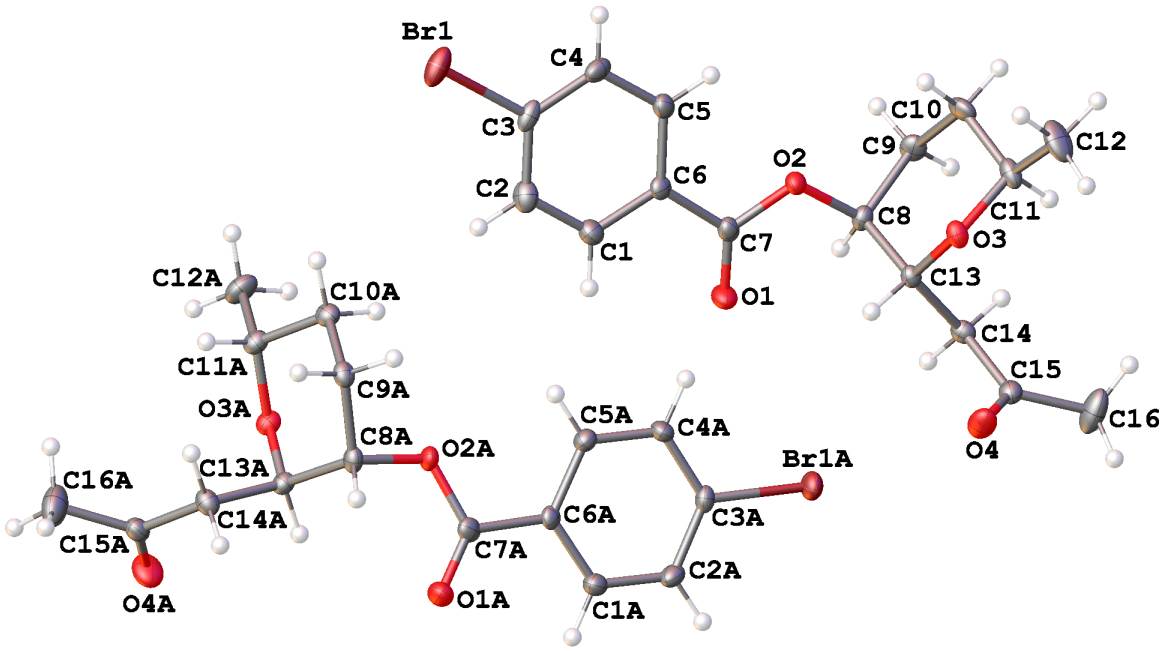

Figure 1. A molecular drawing of Burke25 shown with 50% probability ellipsoids.

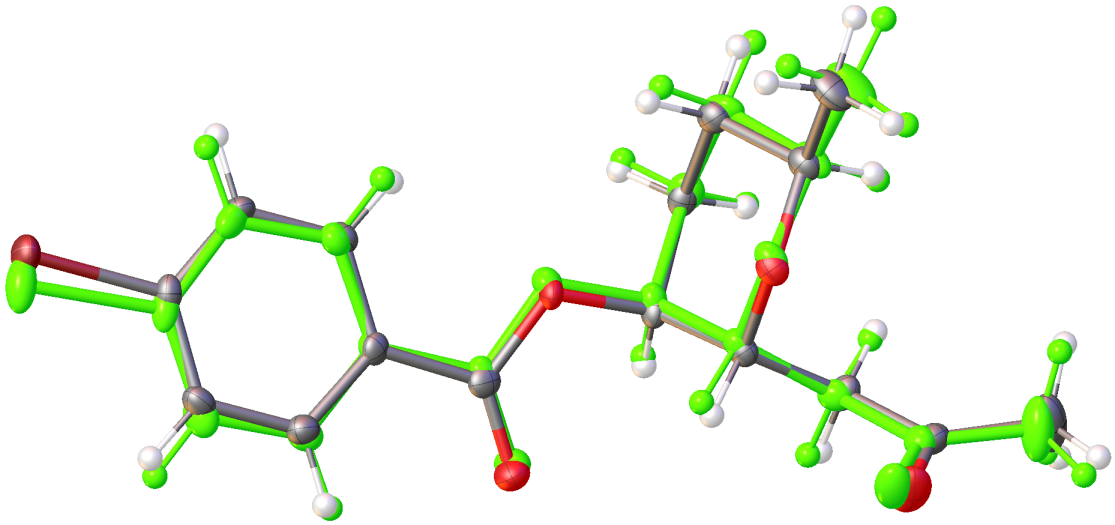

Figure 2. The two molecules of Burke25 superimposed. Shown with 50% probability ellipsoids.

Table 1 Crystal data and structure refinement for Burke25

Identification code	Burke25
Empirical formula	$C_{16}H_{19}O_4Br$
Formula weight	355.22
Temperature/K	100.0
Crystal system	monoclinic
Space group	C2
a/Å	28.650(11)
b/Å	4.9547(18)
c/Å	22.409(8)
α/°	90
β/°	97.901(13)
γ/°	90
Volume/Å^3	3151(2)
Z	8
ρ_{calc}mg/mm^3	1.498
m/mm^{-1}	2.622
F(000)	1456.0
Crystal size/mm^3	0.395 × 0.041 × 0.04
2Θ range for data collection	2.87 to 58.572°
Index ranges	-38 ≤ h ≤ 38, -6 ≤ k ≤ 6, -30 ≤ l ≤ 30
Reflections collected	35047
Independent reflections	8541[R(int) = 0.0430]
Data/restraints/parameters	8541/1/384
Goodness-of-fit on F^2	1.021
Final R indexes [I>=2σ (I)]	R_1 = 0.0305, wR_2 = 0.0595
Final R indexes [all data]	R_1 = 0.0379, wR_2 = 0.0616
Largest diff. peak/hole / e Å^{-3}	0.49/-0.32
Flack parameter	0.004(6)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Burke25. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
Br1	2116.2(2)	9856.8(6)	9542.8(2)	29.20(9)

O1	1968.0(7)	124(5)	7354.5(10)	24.1(5)
O2	1203.4(7)	493(4)	7472.5(9)	16.3(4)
O3	650.4(7)	791(4)	6229.7(9)	16.4(4)
O4	1278.4(8)	-201(6)	5200.5(10)	29.6(5)
C1	2203.9(10)	4375(6)	8176.5(14)	20.3(7)
C2	2309.6(12)	6333(6)	8612.1(15)	23.5(7)
C3	1964.1(10)	7207(6)	8935.2(13)	18.8(6)
C4	1509.9(11)	6201(7)	8825.5(13)	20.6(7)
C5	1403.9(10)	4226(6)	8389.1(13)	18.3(7)
C6	1752.7(10)	3290(6)	8062.1(13)	15.4(6)
C7	1663.3(10)	1166(6)	7595.6(13)	17.2(6)
C8	1096.9(10)	-1757(6)	7055.2(13)	16.4(6)
C9	639(1)	-2992(6)	7191.7(14)	20.4(7)
C10	216.9(10)	-1208(7)	6966.9(15)	21.9(7)
C11	216.3(10)	-533(6)	6308.4(14)	19.8(6)
C12	-176.6(11)	1362(7)	6056.8(19)	34.8(9)
C13	1066.6(9)	-772(5)	6403.2(13)	13.4(6)
C14	1108(1)	-3143(6)	5979.9(13)	16.9(6)
C15	1093.3(9)	-2268(7)	5332.0(13)	18.2(6)
C16	839.8(15)	-4091(8)	4866.8(17)	38.2(10)
Br1A	2207.3(2)	2581.1(6)	5710.8(2)	23.12(8)
O1A	4059.3(8)	10852(5)	6808(1)	25.1(5)
O2A	3593.8(7)	11098(4)	7539.1(9)	17.2(4)
O3A	4207.4(7)	10562(4)	8716.3(9)	16.3(4)
O4A	5295.2(8)	11222(5)	8649.0(12)	32.6(6)
C1A	3438(1)	6865(6)	6210.5(13)	19.0(6)
C2A	3104.7(10)	5112(7)	5914.9(13)	19.9(6)
C3A	2676.1(10)	4848(7)	6124.2(12)	17.0(5)
C4A	2572.6(10)	6273(6)	6620.7(14)	18.5(6)
C5A	2906.3(10)	8001(6)	6915.7(13)	17.6(6)
C6A	3344.9(10)	8308(6)	6711.3(13)	14.9(6)
C7A	3706.6(10)	10184(6)	7007.2(13)	17.2(6)
C8A	3880(1)	13253(6)	7837.6(13)	16.3(6)
C9A	3557.7(10)	14686(7)	8222.0(13)	16.6(6)
C10A	3462.3(9)	12869(6)	8743.8(13)	17.5(6)
C11A	3921.4(10)	11928(6)	9102.7(13)	17.7(6)
C12A	3847.6(12)	9930(8)	9595.0(13)	26.8(7)
C13A	4320.6(9)	12118(6)	8214.6(12)	15.3(6)

C14A	4670.6(10)	14383(6)	8415.4(14)	18.4(6)
C15A	5124.5(10)	13345(6)	8769.1(14)	19.8(7)
C16A	5356.7(13)	15146(9)	9255.8(17)	39.1(9)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for Burke25. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
Br1	46.5(2)	18.13(15)	19.32(16)	-2.42(14)	-8.47(14)	3.28(15)
O1	16.1(10)	29.5(13)	26.9(12)	-9.0(11)	3.9(9)	2.7(10)
O2	13.1(9)	18.6(11)	16.7(10)	-1.5(8)	0.3(8)	0.9(8)
O3	15(1)	12.5(9)	20.6(11)	2.5(8)	-1.6(8)	-0.8(8)
O4	35.1(12)	34.0(13)	20.7(11)	1.4(12)	7.1(9)	-15.8(12)
C1	16.6(14)	22.5(18)	21.8(15)	0.0(13)	1.9(12)	0.9(12)
C2	25.0(16)	17.2(16)	26.6(17)	-1.5(13)	-2.4(14)	-0.9(13)
C3	30.1(15)	11.0(14)	13.2(13)	-0.1(11)	-4.6(11)	2.3(12)
C4	23.0(15)	26.4(17)	11.9(14)	0.5(13)	1.1(12)	7.7(13)
C5	15.1(14)	23.0(18)	15.9(15)	1.3(12)	-0.7(11)	-0.2(12)
C6	14.3(13)	17.0(15)	13.8(14)	2.0(11)	-1.3(11)	2.8(10)
C7	15.6(14)	20.5(16)	14.8(14)	2.5(12)	-0.3(11)	-1.1(11)
C8	18.7(14)	15.9(15)	13.9(14)	-0.1(11)	-0.2(11)	-1.6(11)
C9	23.7(15)	18.6(17)	19.5(15)	4.3(12)	4.9(12)	-6.0(12)
C10	15.1(14)	21.0(15)	31.0(18)	-2.9(14)	8.2(13)	-6.4(12)
C11	13.8(13)	13.8(15)	30.1(16)	-1.3(13)	-3.2(12)	-0.6(11)
C12	19.1(16)	25.5(18)	56(2)	1.3(18)	-9.3(16)	5.8(14)
C13	12.9(13)	12.2(14)	14.9(14)	1.5(11)	0.7(11)	-1.1(10)
C14	16.3(13)	14.3(14)	20.5(15)	1.2(11)	4.0(11)	-1(1)
C15	16.5(12)	19.2(14)	19.0(14)	-3.3(14)	2.5(10)	0.7(13)
C16	60(3)	26.1(19)	24.2(19)	-3.0(15)	-8.5(18)	-10.1(18)
Br1A	20.91(14)	24.43(16)	23.12(16)	-7.52(14)	-0.14(11)	-4.33(13)
O1A	19.5(11)	34.0(13)	22.4(12)	-3.4(10)	5.5(9)	-6.5(10)
O2A	16.7(10)	20.0(11)	14.6(10)	-3.9(9)	0.2(8)	-5.2(8)
O3A	20.2(10)	12.4(10)	16.2(10)	-0.2(8)	2.0(8)	2.4(8)
O4A	21.9(12)	32.3(14)	42.3(15)	-7.6(12)	0.1(11)	9.8(10)
C1A	15.8(13)	24.1(17)	17.4(15)	-0.3(12)	3.4(11)	0.5(11)
C2A	19.0(14)	25.5(17)	15.3(14)	-3.6(14)	2.3(11)	5.1(13)
C3A	17.7(13)	16.2(13)	15.8(13)	-0.9(14)	-3.1(10)	-0.8(12)

C4A	12.3(13)	24.2(16)	19.4(15)	-2.5(13)	3.8(12)	-0.2(11)
C5A	17.6(13)	19.8(17)	15.4(14)	-2.7(13)	2.5(11)	0.6(12)
C6A	12.6(13)	17.5(15)	13.3(14)	1.1(11)	-2.5(11)	2(1)
C7A	15.6(13)	21.0(16)	14.3(13)	4.5(12)	-0.7(11)	2.3(12)
C8A	17.4(13)	14.4(14)	16.0(14)	-0.1(11)	-1.4(11)	-3.3(10)
C9A	14.7(12)	14.1(13)	20.0(14)	-0.8(13)	-1.5(11)	1.8(12)
C10A	18.4(13)	15.6(14)	18.8(14)	-3.4(13)	3.8(11)	0.1(12)
C11A	21.6(14)	15.1(15)	16.5(14)	-1.8(11)	3.3(12)	0.9(11)
C12A	39.6(18)	25.5(16)	15.9(14)	2.0(15)	6.0(13)	1.8(16)
C13A	17.2(12)	14.1(15)	14.4(13)	-1.5(11)	2.2(10)	0.7(11)
C14A	15.7(13)	15.2(16)	23.9(16)	-0.4(12)	0.8(12)	-0.3(11)
C15A	14.9(14)	24.6(17)	19.9(16)	1.5(12)	2.8(12)	-0.9(11)
C16A	35(2)	42(2)	35.2(19)	-11.1(19)	-13.6(16)	10.6(18)

Table 4 Bond Lengths for Burke25.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Br1	C3	1.898(3)	Br1A	C3A	1.893(3)
O1	C7	1.204(4)	O1A	C7A	1.206(4)
O2	C7	1.350(3)	O2A	C7A	1.355(4)
O2	C8	1.460(3)	O2A	C8A	1.452(3)
O3	C11	1.438(3)	O3A	C11A	1.440(3)
O3	C13	1.430(3)	O3A	C13A	1.436(3)
O4	C15	1.208(4)	O4A	C15A	1.206(4)
C1	C2	1.380(4)	C1A	C2A	1.390(4)
C1	C6	1.391(4)	C1A	C6A	1.387(4)
C2	C3	1.374(4)	C2A	C3A	1.380(4)
C3	C4	1.383(4)	C3A	C4A	1.384(4)
C4	C5	1.387(4)	C4A	C5A	1.382(4)
C5	C6	1.397(4)	C5A	C6A	1.404(4)
C6	C7	1.480(4)	C6A	C7A	1.479(4)
C8	C9	1.517(4)	C8A	C9A	1.522(4)
C8	C13	1.532(4)	C8A	C13A	1.526(4)
C9	C10	1.526(4)	C9A	C10A	1.530(4)
C10	C11	1.513(4)	C10A	C11A	1.518(4)
C11	C12	1.514(4)	C11A	C12A	1.518(4)
C13	C14	1.525(4)	C13A	C14A	1.531(4)

C14	C15	1.510(4)	C14A	C15A	1.517(4)
C15	C16	1.491(4)	C15A	C16A	1.493(5)

Table 5 Bond Angles for Burke25.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C7	O2	C8	115.6(2)	C7A	O2A	C8A	117.6(2)
C13	O3	C11	115.0(2)	C13A	O3A	C11A	115.3(2)
C2	C1	C6	120.7(3)	C6A	C1A	C2A	120.8(3)
C3	C2	C1	119.4(3)	C3A	C2A	C1A	118.8(3)
C2	C3	Br1	119.0(2)	C2A	C3A	Br1A	119.6(2)
C2	C3	C4	121.4(3)	C2A	C3A	C4A	121.6(3)
C4	C3	Br1	119.6(2)	C4A	C3A	Br1A	118.7(2)
C3	C4	C5	119.3(3)	C5A	C4A	C3A	119.3(3)
C4	C5	C6	120.1(3)	C4A	C5A	C6A	120.2(3)
C1	C6	C5	119.2(3)	C1A	C6A	C5A	119.2(3)
C1	C6	C7	118.1(3)	C1A	C6A	C7A	119.1(3)
C5	C6	C7	122.6(3)	C5A	C6A	C7A	121.7(3)
O1	C7	O2	123.3(3)	O1A	C7A	O2A	123.2(3)
O1	C7	C6	123.8(3)	O1A	C7A	C6A	125.3(3)
O2	C7	C6	112.9(2)	O2A	C7A	C6A	111.5(2)
O2	C8	C9	106.8(2)	O2A	C8A	C9A	104.8(2)
O2	C8	C13	110.3(2)	O2A	C8A	C13A	110.8(2)
C9	C8	C13	112.6(2)	C9A	C8A	C13A	112.2(2)
C8	C9	C10	111.6(2)	C8A	C9A	C10A	110.1(3)
C11	C10	C9	110.1(2)	C11A	C10A	C9A	110.7(2)
O3	C11	C10	109.6(2)	O3A	C11A	C10A	110.4(2)
O3	C11	C12	106.4(3)	O3A	C11A	C12A	106.1(2)
C10	C11	C12	113.7(3)	C10A	C11A	C12A	112.8(3)
O3	C13	C8	111.6(2)	O3A	C13A	C8A	111.9(2)
O3	C13	C14	112.4(2)	O3A	C13A	C14A	111.9(2)
C14	C13	C8	110.4(2)	C8A	C13A	C14A	110.5(2)
C15	C14	C13	112.5(2)	C15A	C14A	C13A	112.6(2)
O4	C15	C14	121.5(3)	O4A	C15A	C14A	121.6(3)
O4	C15	C16	122.1(3)	O4A	C15A	C16A	122.1(3)
C16	C15	C14	116.4(3)	C16A	C15A	C14A	116.3(3)

Table 6 Torsion Angles for Burke25.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
Br1	C3	C4	C5	-178.7(2)	Br1A	C3A	C4A	C5A	-178.0(2)
O2	C8	C9	C10	73.6(3)	O2A	C8A	C9A	C10A	69.5(3)
O2	C8	C13	O3	-71.7(3)	O2A	C8A	C13A	O3A	-66.9(3)
O2	C8	C13	C14	162.5(2)	O2A	C8A	C13A	C14A	167.7(2)
O3	C13	C14	C15	56.2(3)	O3A	C13A	C14A	C15A	57.1(3)
C1	C2	C3	Br1	178.9(2)	C1A	C2A	C3A	Br1A	177.6(2)
C1	C2	C3	C4	-1.2(5)	C1A	C2A	C3A	C4A	-0.3(5)
C1	C6	C7	O1	8.1(4)	C1A	C6A	C7A	O1A	10.0(5)
C1	C6	C7	O2	-172.6(3)	C1A	C6A	C7A	O2A	-170.2(3)
C2	C1	C6	C5	0.7(4)	C2A	C1A	C6A	C5A	-0.6(5)
C2	C1	C6	C7	-179.1(3)	C2A	C1A	C6A	C7A	-179.1(3)
C2	C3	C4	C5	1.4(5)	C2A	C3A	C4A	C5A	-0.1(5)
C3	C4	C5	C6	-0.6(4)	C3A	C4A	C5A	C6A	0.2(5)
C4	C5	C6	C1	-0.5(4)	C4A	C5A	C6A	C1A	0.1(4)
C4	C5	C6	C7	179.3(3)	C4A	C5A	C6A	C7A	178.6(3)
C5	C6	C7	O1	-171.7(3)	C5A	C6A	C7A	O1A	-168.5(3)
C5	C6	C7	O2	7.6(4)	C5A	C6A	C7A	O2A	11.3(4)
C6	C1	C2	C3	0.1(5)	C6A	C1A	C2A	C3A	0.6(5)
C7	O2	C8	C9	154.7(2)	C7A	O2A	C8A	C9A	154.3(2)
C7	O2	C8	C13	-82.7(3)	C7A	O2A	C8A	C13A	-84.5(3)
C8	O2	C7	O1	4.5(4)	C8A	O2A	C7A	O1A	8.6(4)
C8	O2	C7	C6	-174.8(2)	C8A	O2A	C7A	C6A	-171.2(2)
C8	C9	C10	C11	52.8(3)	C8A	C9A	C10A	C11A	54.2(3)
C8	C13	C14	C15	-178.4(2)	C8A	C13A	C14A	C15A	-177.5(2)
C9	C8	C13	O3	47.5(3)	C9A	C8A	C13A	O3A	49.9(3)
C9	C8	C13	C14	-78.3(3)	C9A	C8A	C13A	C14A	-75.5(3)
C9	C10	C11	O3	-57.9(3)	C9A	C10A	C11A	O3A	-56.6(3)
C9	C10	C11	C12	-176.8(3)	C9A	C10A	C11A	C12A	-175.2(3)
C11	O3	C13	C8	-55.2(3)	C11A	O3A	C13A	C8A	-53.9(3)
C11	O3	C13	C14	69.5(3)	C11A	O3A	C13A	C14A	70.8(3)
C13	O3	C11	C10	60.9(3)	C13A	O3A	C11A	C10A	57.5(3)
C13	O3	C11	C12	-175.8(3)	C13A	O3A	C11A	C12A	-179.9(2)
C13	C8	C9	C10	-47.6(3)	C13A	C8A	C9A	C10A	-50.8(3)
C13	C14	C15	O4	37.2(4)	C13A	C14A	C15A	O4A	35.8(4)
C13	C14	C15	C16	-142.9(3)	C13A	C14A	C15A	C16A	-146.6(3)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Burke25.

Atom	*x*	*y*	*z*	U(eq)
H1	2442	3763	7952	24
H2	2618	7070	8688	28
H4	1273	6856	9047	25
H5	1094	3510	8313	22
H8	1354	-3133	7132	20
H9A	655	-3253	7632	24
H9B	596	-4786	6997	24
H10A	-78	-2159	7020	26
H10B	232	477	7206	26
H11	189	-2243	6069	24
H12A	-153	3038	6291	52
H12B	-482	504	6081	52
H12C	-149	1769	5635	52
H13	1343	435	6380	16
H14A	1408	-4104	6109	20
H14B	847	-4423	6010	20
H16A	500	-3963	4878	57
H16B	944	-5955	4949	57
H16C	909	-3553	4467	57
H1A	3733	7077	6068	23
H2A	3171	4113	5574	24
H4A	2275	6066	6757	22
H5A	2839	8982	7258	21
H8A	3974	14532	7530	20
H9AA	3256	15148	7971	20
H9AB	3708	16385	8383	20
H10C	3276	13875	9011	21
H10D	3276	11282	8583	21
H11A	4097	13530	9289	21
H12D	3688	8320	9414	40
H12E	3654	10764	9872	40
H12F	4154	9416	9817	40
H13A	4475	10874	7950	18

H14C	4745	15364	8055	22
H14D	4522	15677	8668	22
H16D	5649	14303	9447	59
H16E	5144	15431	9557	59
H16F	5429	16886	9082	59