Stereoselective Synthesis of Quaternary Carbons via the Dianionic Ireland-Claisen Rearrangement: An Approach to the Synthesis of Briarane Diterpenes

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Abstract

PHILIP S. WILLIAMS: Stereoselective Synthesis of Quaternary Carbons via the Dianionic Ireland-Claisen Rearrangement: An Approach to the Synthesis of Briarane Diterpenes
(Under the direction of Michael T. Crimmins)

Investigation of the dianionic Ireland-Claisen rearrangement has led to the development of a simple method to enantioselectively access quaternary carbon stereocenters via a chelated transition state. This methodology was taken and applied to the synthesis of the core structure of Brianthein A. Peripheral modification of the core structure to complete the total synthesis proved quite challenging and ultimately was unsuccessful in forming the fused butenolide. The work represents the most advanced synthesis of brianthein A to date.

Acknowledgements

"From his neck down a man is worth a couple of dollars a day, from his neck up he is worth anything that his brain can produce."

– Thomas Edison

This is the quote that I was exposed to as I began my graduate chemistry education here at UNC. Filled to the brim with hope and expectations in addition to excitement and uncertainty, Professor Crimmins accepted me into his research group. The journey that began then could never have been predicted, but I am grateful to you Mike for your acceptance, guidance, and soft touch to help make me the scientist I am today – from the "neck up."

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Christie, Dave, Greg, Joe - thanks for making the atmosphere intelligent yet light-hearted.

The atmosphere and professional relationships at work only takes a person so far. I would not be where I am today without the support of my family through the past five years. When reactions didn't go the way I wanted or when I was thought to live in lab, I always was able to share the stresses and struggles of work, even if you didn't really know what I was talking about. There are many who have supported me through the years, thanks to my brother Eric, Aunt Helene, Tom, Michael and Katie, Kristine, Captain Bur, Adam, the Tree of Life family, and many others. To Doug and Kathy, thanks for listening, supporting, and enabling so many opportunities the past 5 years. To Mom, thanks for the unconditional love, even when it meant sacrificing sleep for the late night phone conversations when life was stressful in lab (and when things went right!). Finally, I must thank my beautiful and loving wife, Dawn, for being my solid support on which I have been able to reach for the stars - thank you for being there, sacrificing, and unconditionally loving me all the while.

"If you knew what you were doing it wouldn't be called research!"

- *Albert Einstein*

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Ac	acetyl
AIBN	2,2’-azo bis(isobutyronitrile)
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
bp	boiling point
Bu	butyl
Bz	benzoyl
CM	Cross Metathesis
CSA	camphorsulfonic acid
Cy	cyclohexyl
DCC	dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DIAD	diisobutyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTS	dimethylthexylsilyl

EDC	ethyldimethylaminopropyl carbodiimide
ee	enantiomeric excess
Et	ethyl
Ipc	isopinocampheyl
lut.	2,6-lutidine
LHMDS	Lithium bis(trimethylsilyl)amide
LTMP	Lithium tetramethylpiperidine
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
MOP	methoxypropyl
MS	Molecular Sieves
NIS	*N*-iodo succinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidinone
NR	no reaction
Ph	phenyl
Piv	pivaolyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Pyr	pyridine

RCM	Ring-closing Metathesis
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TS	transition state
p-TSA	*p*-toluenesulfonic acid

Chapter 1

Development of the Dianionic Ireland-Claisen Rearrangement

Introduction:

Organic synthesis has long been challenged by the construction of complex molecules from simple chemical starting materials. One challenge in particular is the stereoselective construction of quaternary carbon stereocenters. The last thirty years has seen a wealth of impressive methodologies developed,[1,2] however the stereoselective synthesis of quaternary carbons remains a significant challenge for organic chemists. These stereocenters pose a challenge due to their inherent steric strain and that they must be made selectively when the bond is formed as they are typically unable to be inverted.

Nonetheless, in the context of natural product synthesis, the stereoselective construction of quaternary carbon centers is a crucial tool for the synthetic chemist's toolbox. In figure 1, a sampling of pharmaceutical agents and natural products containing quaternary carbons is shown. It is the goal of numerous research groups, to develop new methods to synthesize quaternary carbons. Sigmatropic rearrangements are well known and a popular reaction class in the synthesis of complex carbon centers. A key feature of these reactions is the defined and predictable nature in which they proceed. In the

context of the research presented, a brief review of the common [3,3] sigmatropic rearrangements will be presented.

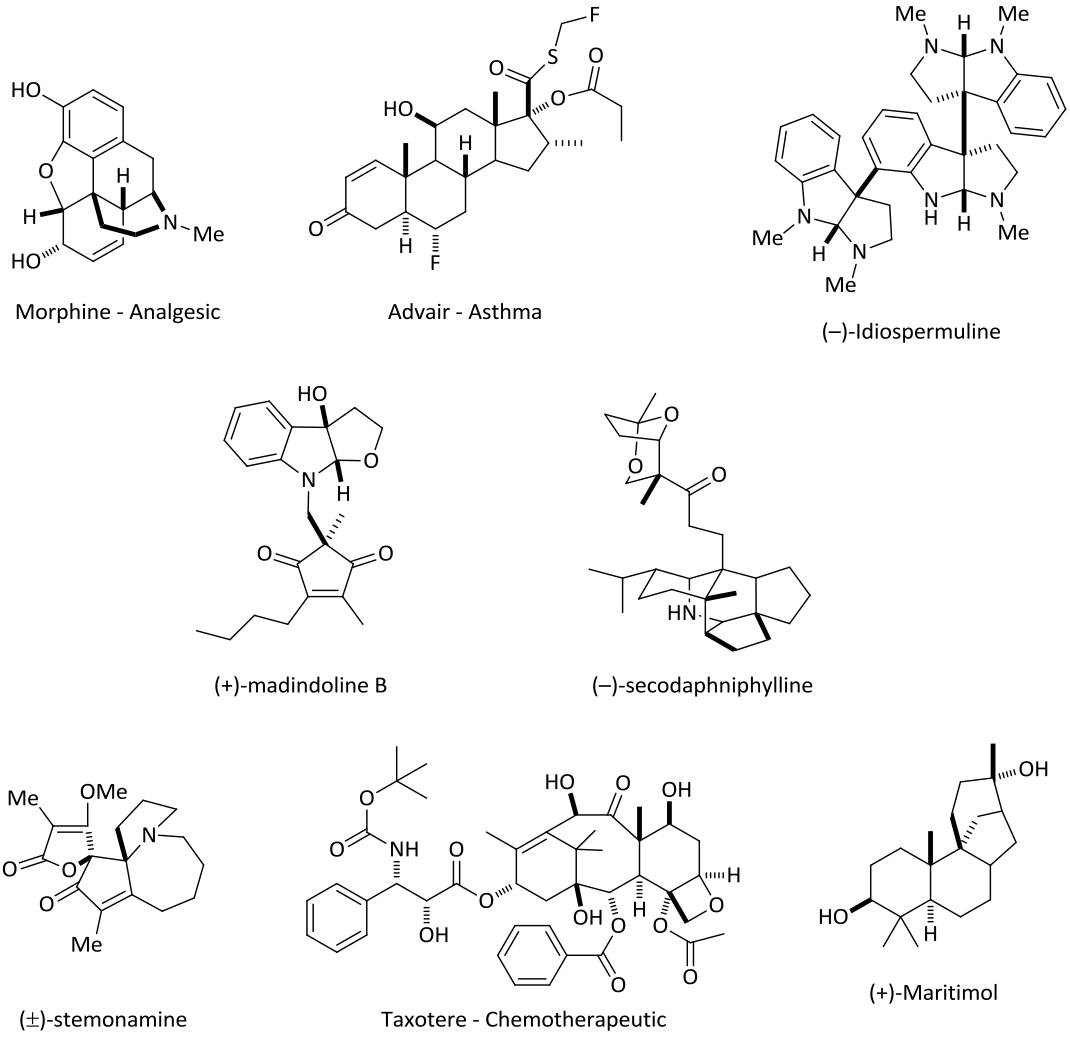
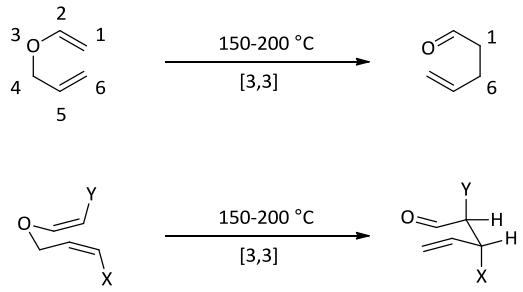


Figure 1: Examples of compounds with quaternary carbon centers

[3,3] Sigmatropic Rearrangements

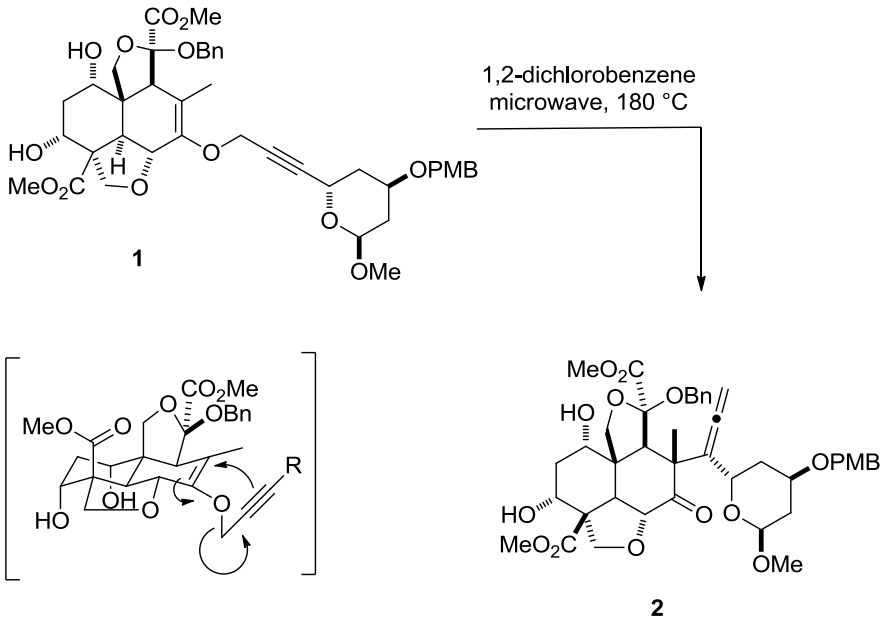
The Claisen rearrangement was discovered in 1912 by Ranier Ludwig Claisen[3,4,5] (scheme 1). The classical Claisen rearrangement is the [3,3] sigmatropic rearrangement of an allyl vinyl ether to afford a γ-δ-unsaturated carbonyl.



Scheme 1: The Claisen rearrangement

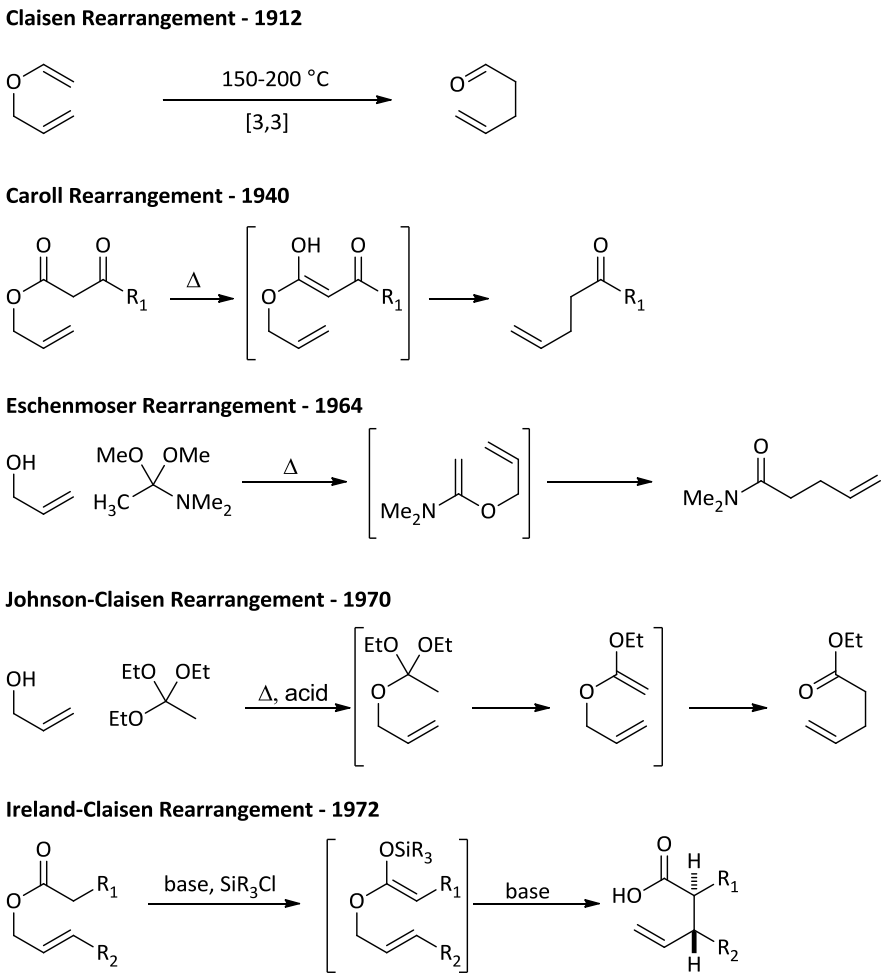
One of the most powerful features of the [3,3] sigmatropic rearrangement is the 1,3 stereogenic transfer due to the chair-like transition state. This can be observed in scheme 1. The ordered transition state defines the stereochemistry of the newly formed bond between carbons 6 and 1.

A significant amount of research has been expended on the Claisen rearrangement. The functional group tolerance remains limited by thermal stability; however, the reaction has been utilized in a number of complex syntheses to achieve the stereoselective synthesis of quaternary carbons. Ley utilized the Claisen rearrangement of propargyl vinyl ether **1** as part of a synthetic sequence leading to the total synthesis of azadirachtin (scheme 2).[6] The substrate based diastereoselectivity was based on the rigid polycyclic structure.



Scheme 2: Claisen rearrangement of propargyl vinyl ether **1**

The greatest limitations to the Claisen rearrangement are the synthesis of the allyl vinyl ether moiety and the harsh temperatures often required to achieve the rearrangement. To this end, a number of research groups have proposed modifications to the reaction to achieve the reaction under milder conditions. The notable examples include the Caroll,[7] Eschenmoser,[8] Johnson,[9] and Ireland[10] variations. The general features of these variations are shown in scheme 3.

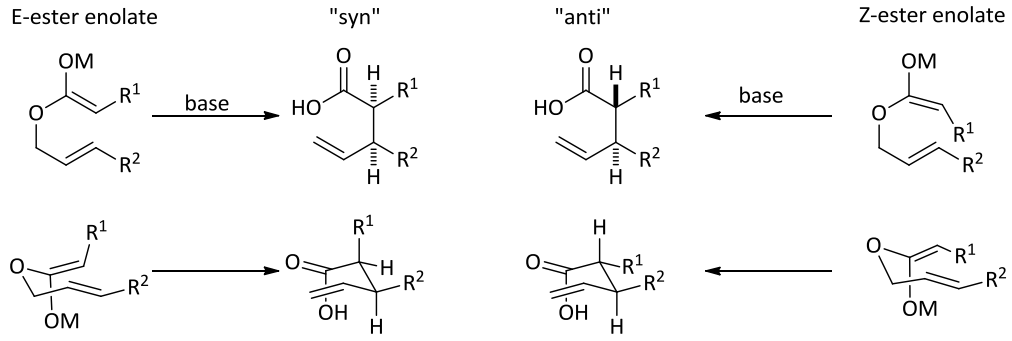


Scheme 3: Major Claisen rearrangement variations

The Ireland-Claisen Rearrangement

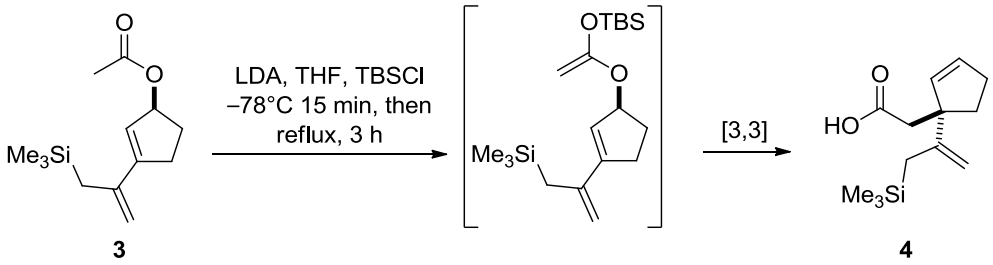
The Ireland-Claisen variation of the Claisen rearrangement is by far one of the most popularly utilized [3,3] sigmatropic rearrangements.[10,11,12] There are three distinct advantages. First, the starting allylic ester functionality is relatively easy to access via standard condensation coupling chemistry. Second, the stereochemistry of the reaction can be influenced by the deprotonation conditions and the stereochemistry of the *in situ* formed ester enolate (Scheme 4). Third,

the temperature necessary for the rearrangement to proceed is significantly lower and typically occurs as the reaction is warmed from –78 °C.



Scheme 4: Ireland-Claisen rearrangement

Corey utilized the Ireland-Claisen rearrangement in the total synthesis of (-)-aspidophytine (scheme 5).[13] Beginning with chiral allyl acetate **3**, deprotonation with LDA and silyl ketene acetal formation with TBSCl proceeded at –78 °C. The reaction mixture was then warmed at reflux to facilitate the rearrangement to provide acid **4**, which was esterified and carried forward.



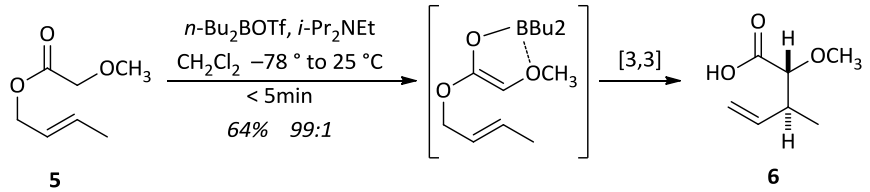
3 **4**

Scheme 5: Corey and co-workers utilize the Ireland-Claisen rearrangement to form the quaternary carbon of (–)-aspidophytine

Stereocontrolled Ireland-Claisen Rearrangements

The benefits of the Ireland-Claisen rearrangement are definite improvements on the Claisen rearrangement. However, without a strong substrate conformational bias, the stereochemical outcome of the reaction is only able to be controlled by the geometry of the ester enolate and the alkene moiety participating in the reaction. A synthetic handle to be able to control the absolute stereochemistry of the Ireland-Claisen rearrangement would prove extremely useful.

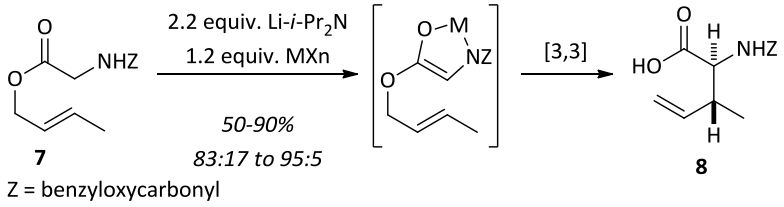
Devine and co-workers demonstrated that soft enolization of **5** with dibutylboron triflate and diisopropylethylamine (DIEA) promoted chelation between the ester enolate and an α-methoxy group.[14] This chelation helped to rigidify the transition state conformation and reinforce a single diastereomer. Moderate yields were achieved (17-64%) with diastereoselectivities up to 99:1.



Scheme 6: Devine and co-workers utilize soft enolization and chelation

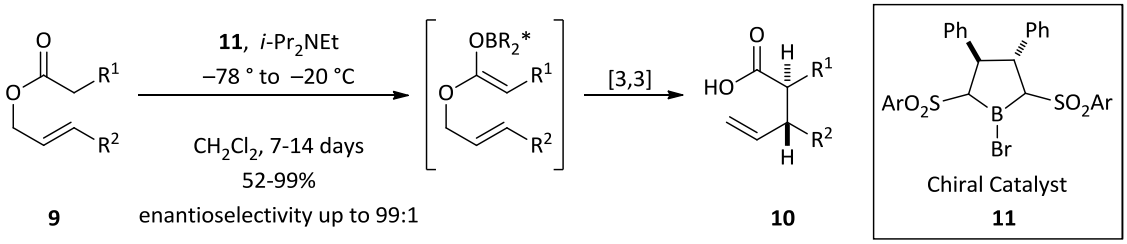
Similarly, Kazmaier and co-workers demonstrated the use of transition metal chelation in the synthesis of amino acids.[15] Strong hindered base was necessary to form the dianionic intermediate, and transition metal chelation occurred between the ester enolate and deprotonated alpha-amine. Once again, this proved to reinforce the conformation of a single diastereomer in the Ireland-Claisen rearrangement. Good to excellent yields (50-90%) with moderate to

excellent diastereoselectivities (up to 95:5) were observed, affording an extremely useful method for the synthesis of aliphatic amino acids.



Scheme 7: Kazmaier achieves excellent selectivity with metal salt chelation

While the chelation work significantly improved the diastereocontrol of the reaction by controlling the formation of the *Z* enolate, the enantiocontrol of the reaction was not achieved. Stated differently, the facial selectivity of the *E* alkene was not controlled. Corey and co-workers disclosed a catalyst controlled Ireland-Claisen rearrangement utilizing chiral boron catalyst **11** (scheme 6).[16] In this reaction, not only was the enolate geometry controlled, but the catalyst created a steric bias for a single face of the enolate. Excellent yields (52-99%) and enantioselectivities (up to 99:1) were observed. However, the reaction times were quite long and impractical.

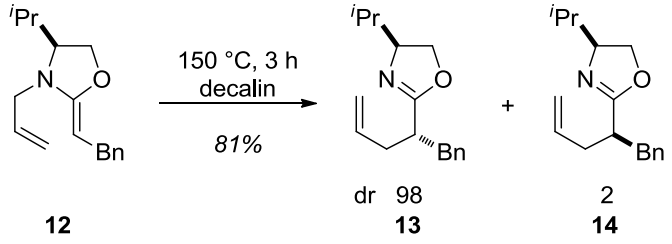


Scheme 8: Chiral boron catalyst controlled Ireland-Claisen rearrangement

Dianionic Ireland-Claisen Rearrangement

Utilizing chelation for the stereocontrol of the Ireland-Claisen rearrangement has had positive results (*vide supra*). Unfortunately, the diasterofacial selectivity of the reaction was not controlled in the work by Kazmaier or Devine, thus the enantioselectivity of the reaction was not fully controlled via the chelated intermediates. Additionally, the presence of the chelating functional group at the alpha position to the ester carbonyl limits the opportunity to fully functionalize the newly formed stereocenters as all carbon quaternary centers.

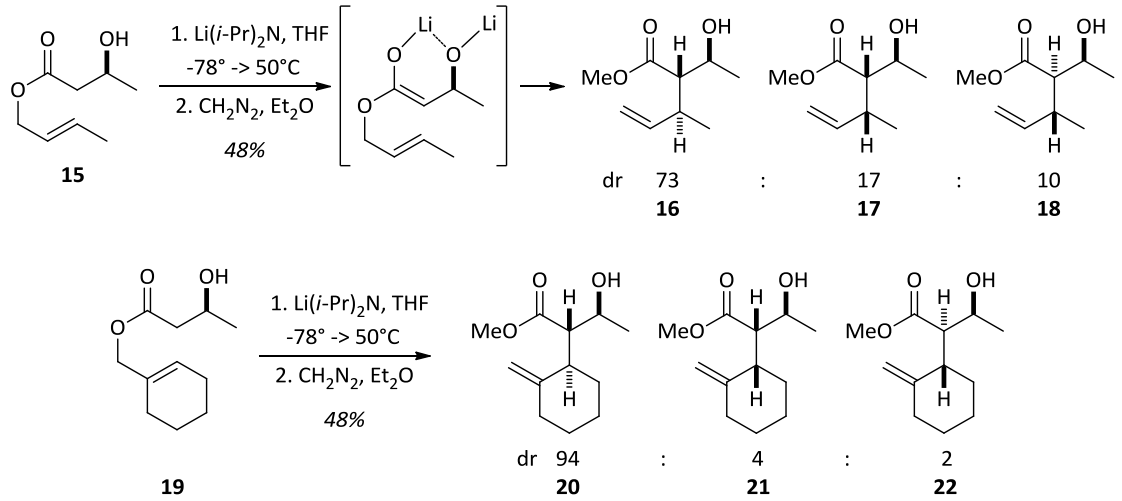
Kurth and co-workers initially observed the effect of intramolecular remote stereocontrol in their investigation of the Claisen rearrangement of *N*-allylketene *N,O*-acetals. (Scheme 9) The reaction required the use of the high boiling solvent decalin. Through the utilization of a chiral auxiliary, Kurth demonstrated the ability to direct the diastereoselectivity of the Claisen rearrangement of *N*-allylketenes.



Scheme 9: Claisen rearrangement of N,O-acetals

By expanding this strategy of utilizing a remote functional group (i.e. beyond the alpha position) to influence the stereochemical outcome of the Ireland-Claisen rearrangement, Kurth and co-workers demonstrated the

rearrangement of beta-hydroxy esters was highly selective for some substrates (Scheme 10). A dianionic, chair-like transition state was proposed, and the proposed transition state was rigidified by the chelation of the ester enolate to the deprotonated hydroxyl group by the lithium counter ion. Additionally, this chelated intermediate was able to provide enantiocontrol of the reaction through the stereodefined beta-hydroxyl group influencing the facial selectivity of the alkene for the [3,3] sigmatropic rearrangement.



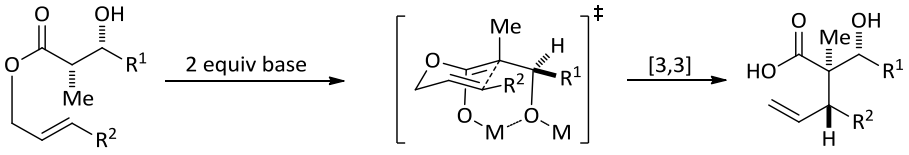
Scheme 10: The dianionic Ireland-Claisen rearrangement

Moderate yields (up to 48%) and moderate to excellent selectivities (up to 98:2) were reported. An obvious trend showed higher selectivities for compounds that were more sterically demanding at the distal carbon of the allyl ether. The poor to moderate yields were somewhat of a surprise because there are many examples of the Ireland-Claisen rearrangement in the literature that show excellent yields[17]. Kurth reported no clear reason for these poor yields.

Enantioselective synthesis of a quaternary carbon via the Dianionic Ireland Claisen Rearrangement

We were inspired by the work of Kurth and co-workers and the ability of a remote stereocenter, beyond the alpha position, to significantly influence the stereochemical outcome of the Ireland-Claisen rearrangement. This was not common in the literature with the exception of substrates utilizing remote chiral auxiliaries. It was proposed that a chelated transition state predominated to control the conformation of the 6-membered chair transition state of the Ireland-Claisen rearrangement.

Kurth's work inspired the investigation of this diastereo- and enantiocontrolled Ireland-Claisen rearrangement being utilized to form quaternary carbon centers. The essential modification to Kurth's precedent is to add an alkyl substituent at the alpha position of the beta-hydroxy allylic ester (scheme 11). It was predicted that this would aid in stabilizing the transition state while also affording a quaternary carbon stereocenter in the product.

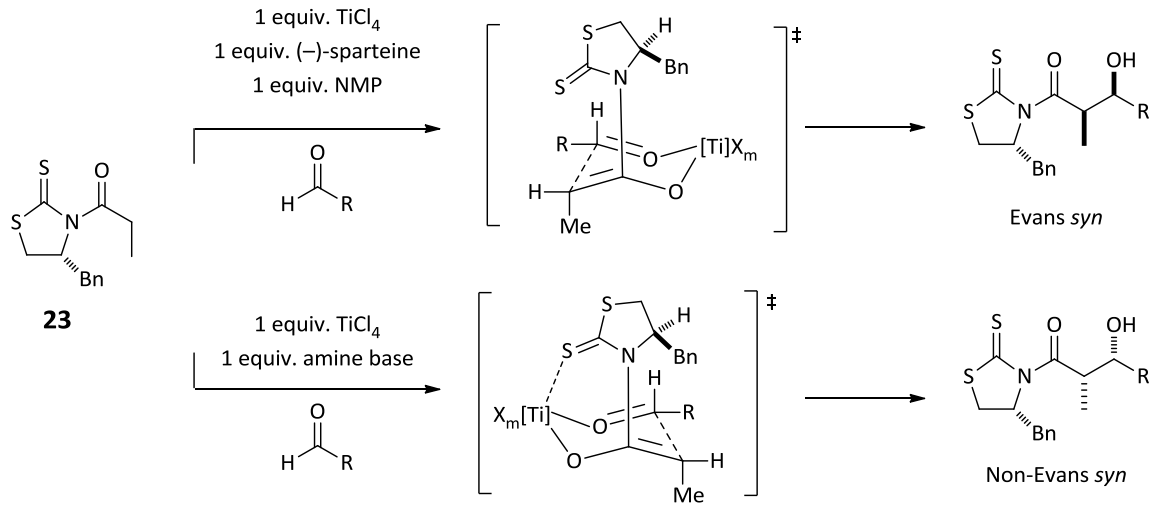


Scheme 11: Proposed quaternary carbon formation via dianionic Ireland-Claisen rearrangement

Synthesis of the dianionic Ireland-Claisen starting material

A significant challenge in all asymmetric synthesis is the achievement of both high yields and high selectivities. Because the β-hydroxyl group is

proposed to control the diastereoselectivity of the reaction, its stereochemistry must be defined by both a highly selective and high yielding reaction. The Crimmins lab has developed the thiazolidinethione-mediated aldol reaction which affords aldol adducts in both very high yields and selectivities. Utilizing soft enolization, titanium tetrachloride coordinates to the amide carbonyl and the auxiliary thionyl allowing a weak, hindered base to deprotonate the alpha-carbon and form a metallated enolate. Upon the addition of *N*-methylpyrrolidinone (NMP), the coordination to the chiral auxiliary is modified allowing for the dipole minimized transition state resulting in the Evans *syn* product upon addition of the aldehyde (scheme 12).



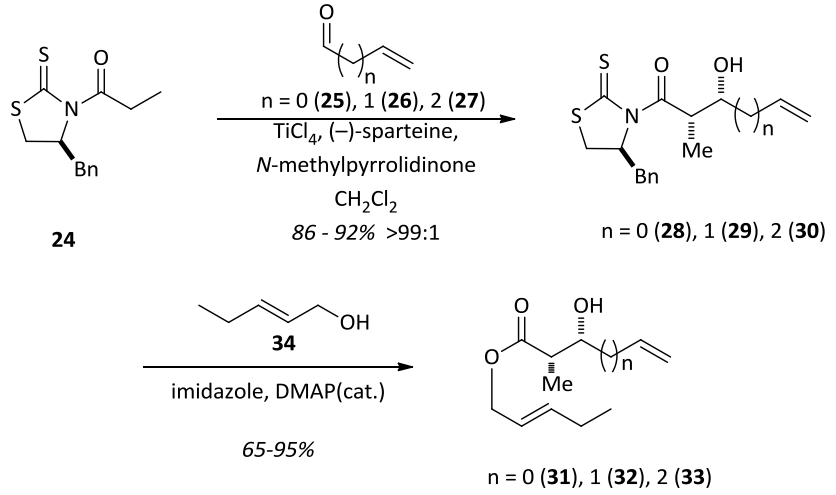
Scheme 12: Crimmins thiazolidinethione mediated aldol methodology

With a stereodefined beta-hydroxyl stereocenter in place, we planned to exploit the versatility inherent in the removal of the thiazolidinethione auxiliary compound compared to the more traditional oxazolidinone auxiliary. Under mild esterification conditions, the chiral auxiliary can be displaced with imidazole and

an allylic alcohol. This quick access to the dianionic Ireland-Claisen rearrangement substrate makes it amenable to variations in functional groups to investigate the scope of the dianionic Ireland-Claisen rearrangement to form quaternary carbon stereocenters.

Optimization of the dianionic Ireland-Claisen rearrangement

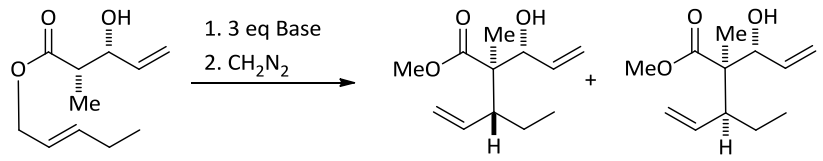
Optimization of the reaction conditions began with the synthesis of ester **31**. Beginning with propionyl thiazolidinethione **24**, titanium tetrachloride ($TiCl_4$) mediated enolization with diisopropylethyl amine (DIEA) and addition of acrolein afforded the desired aldol adduct **28** in 92% yield and 99:1 dr (scheme 13). Displacement of the chiral auxiliary with pentenol **34** afforded the desired dianionic Ireland-Claisen substrate **31** in 95% yield.



Scheme 13: Synthesis of the dianionic Ireland-Claisen model substrate

Investigation of the appropriate base for the dianionic Ireland-Claisen rearrangement was investigated initially. Treatment of **31** with at least two equivalents of lithium diisopropylamine (LDA) to both deprotonate the hydroxyl

and enolize the ester under Kurth's conditions resulted in poor yields. Treatment with a variety of amide bases showed that lithium hexamethyldisilazide (LHMDS) was the base of choice (table 1).



31 **35** **36**

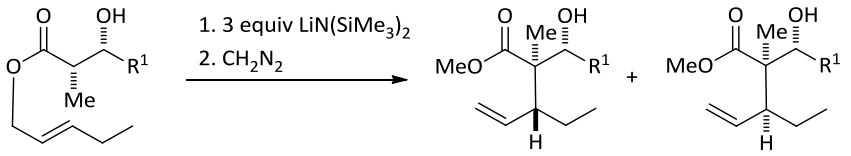
Entry	Base	Yield %
1	LDA	30%
2	LHMDS	40%
3	NaHMDS	16%
4	KHMDS	Decomp.

Table 1: Examination of different bases

The yields of the reaction were all poor, though LHMDS proved reliable and the highest yielding while also being easily prepared for immediate use. The important variable to improved yields turned out to be the regulation of the reaction temperature. As one would expect, enolization occurs well at –78 °C over 2 hours. To attain the energy required for the Ireland-Claisen rearrangement to proceed, the reaction must be warmed. However, the temperature required for a productive reaction was dependent on the specific substrate.

The substrate **31** has fewer degrees of freedom than **32** or **33** and thus is able to undergo the sigmatropic rearrangement at room temperature. However, the addition of one methylene spacer (table 2 entry 3 vs. 4) changes the energy

required to proceed with the [3,3] rearrangement. When **32** was enolized at –78 °C and warmed to room temperature, no product was observed. Interestingly, when the same substrate was warmed immediately to reflux after enolization, a very low yield also resulted. This raised some question of the stability of the ester enolate intermediate which will be discussed later. Heating to reflux over a longer period of time was attempted and a slightly higher isolated yield was observed. The optimized dianionic Ireland-Claisen (DIC) procedure resulting in the best yields for the majority of substrates required the enolization at –78 °C over 2 hours with three equivalents of LHMDS followed by warming over 1-2 hours from –78 °C to room temperature after enolization, then stirring for 4-6 hours at room temperature was essential and finally, heating at reflux overnight for 12-16 hours. These conditions proved compatible with most compounds examined by this study without much need for individual substrate optimization.



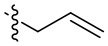
Entry	Cmpd	R^1	Temp	Solvent	Yield %	d.r. (A:B)
1	**31**		–78 → –50°C	THF	0	NA
2	**31**		–78 → 0°C	THF	0	NA
3	**31**		–78°C → rt	THF	40	6:1
4	**32**		–78°C → rt → 50°C	THF	40	>20:1
5	**33**		–78°C → rt → 50°C	THF	55	>20:1
6	**31**		–20°C → rt	Et_2O	0	NA
7	**31**		–78°C → rt	Et_2O:THF 10:1	0	NA
8	**31**		–78°C → rt	Et_2O:THF 5:1	24	2.2:1
9	**31**		–78°C → rt	Et_2O:THF 1:1	35	3.67:1
10	**31**		–78°C → rt	2-Me-THF	34	1.5:1
11	**31**		–78°C → rt	Toluene	51	1.05:1

Table 2: Selected temperature and solvent optimization results of the dianionic Ireland-Claisen rearrangement

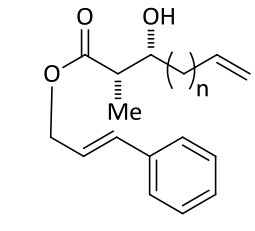
The nature of the reaction was also heavily dependent on the solvent employed. A cursory evaluation of the yields and selectivities of table 2 shows that the inclusion of THF is essential, not only for the reaction to proceed, but also to obtain any useful diastereoselectivity. It is presumed that THF is the best coordinating solvent to support lithium aggregation of the enolate. The utility of 2-methyltetrahydrofuran (table 2, entry 10) was able to achieve a similar overall yield, though the stereoselectivity of the reaction was diminished, presumably due to the lack of a reinforcing lithium aggregate.

To support this theory, less coordinating solvents were examined. When a non-coordinating solvent such as toluene was used, the yield of the DIC improved, yet an unselective reaction was observed, demonstrating that the coordination of solvent was important to achieving a useful stereoselectivity. We also looked to diminish the amount of coordinating solvent by employing solvent mixtures of THF and diethyl ether. In these experiments, the yield of the reaction appeared to be proportional to the ratio of THF to diethyl ether. As the ratio of THF was increased, the yield increased (Table 2, entries 7-9).

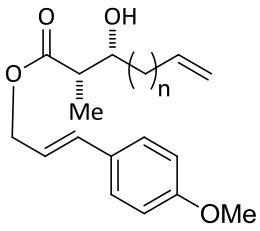
It is rather unclear as to why the reaction yields are higher only after warming to room temperature and stirring for several hours before heating to reflux. It is believed that a key aspect here is the aggregation of the lithium ester enolates. Collum has disclosed examples where the most thermodynamically stable lithium aggregate is formed only after warming from -110 °C to 0 °C; in these mixed lithium aggregates, higher enantioselectivities were observed with the more stable aggregate.[18] In the case of the dianionic Ireland-Claisen rearrangement, as the reaction warms, it is presumed the lithium chelated dianionic intermediate forms a more stable aggregate, which stabilizes the enolate intermediate and reinforces the desired stereochemistry. It is believed that the aggregate not only reinforces the stereochemistry, but also stabilizes the ester enolate intermediate from the potential degradation pathways which will be addressed later.

The external variables of base, temperature, and solvent had still not allowed a significant improvement on the yields of the DIC reported by Kurth. To

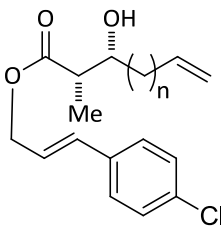
this end, substrates were designed to probe the [3,3] sigmatropic rearrangement. The focus of this design was the alteration of the allylic alcohol employed to examine both steric and electronic variations in the DIC substrate.



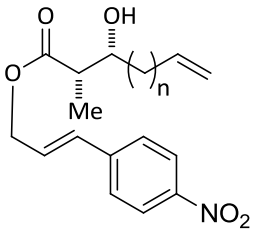
n = 0 (**37**), 1 (**38**), 2 (**39**)



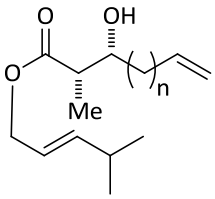
n = 0 (**40**), 1 (**41**), 2 (**42**)



n = 0 (**43**), 1 (**44**), 2 (**45**)



n = 0 (**46**), 1 (**47**), 2 (**48**)

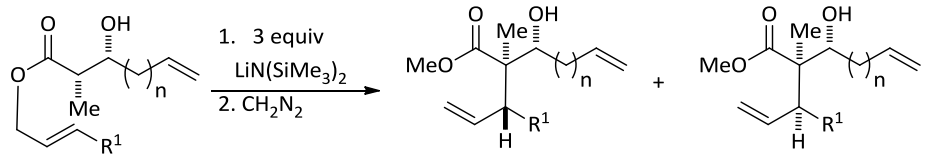


n = 0 (**49**), 1 (**50**), 2 (**51**)

Scheme 14: New substrates for the DIC

We first synthesized the isopropyl variants **49**, **50** and **51**. Unfortunately, the yields were quite low, and did not compare well to the original optimized substrate where ethyl was utilized in place of the isopropyl group. The cause for this result is not clear. However, although the yields suffered, the stereoselectivity did improve where observable (table 3 entry 4 vs 1) due to increased steric demand in the transition state. The cinnamyl alcohol variant allowed us the opportunity to modify the electronic nature of the substrate. Much to our delight, the phenyl substituent (table 3 entries 7-9) did not hinder the reaction sterically and both the yield and selectivity of the reaction improved.

The phenyl ring was then substituted with *p*-chloro, -methoxy, and –nitro functional groups.



A **B**

Entry	Cmpd.	n	R^1	Total Time (h)	Yield %	Selectivity A:B
1	**31**	0	Et	8	40	6:1
2	**32**	1	Et	13	40	>20:1
3	**33**	2	Et	15	55	>20:1
4	**49**	0	*i*-Pr	22	16	>20:1
5	**50**	1	*i*-Pr	20	18	>20:1
6	**51**	2	*i*-Pr	23	21	>20:1
7	**37**	0	Ph	20	44	>20:1
8	**38**	1	Ph	16	55	>20:1
9	**39**	2	Ph	16	60	>20:1
10	**44**	1	*p*-ClPh	6.5	46	>20:1
11	**41**	1	*p*-OMePh	48	8	>20:1
12	**47**	1	*p*-NO_2Ph	--	Decomp.	NA

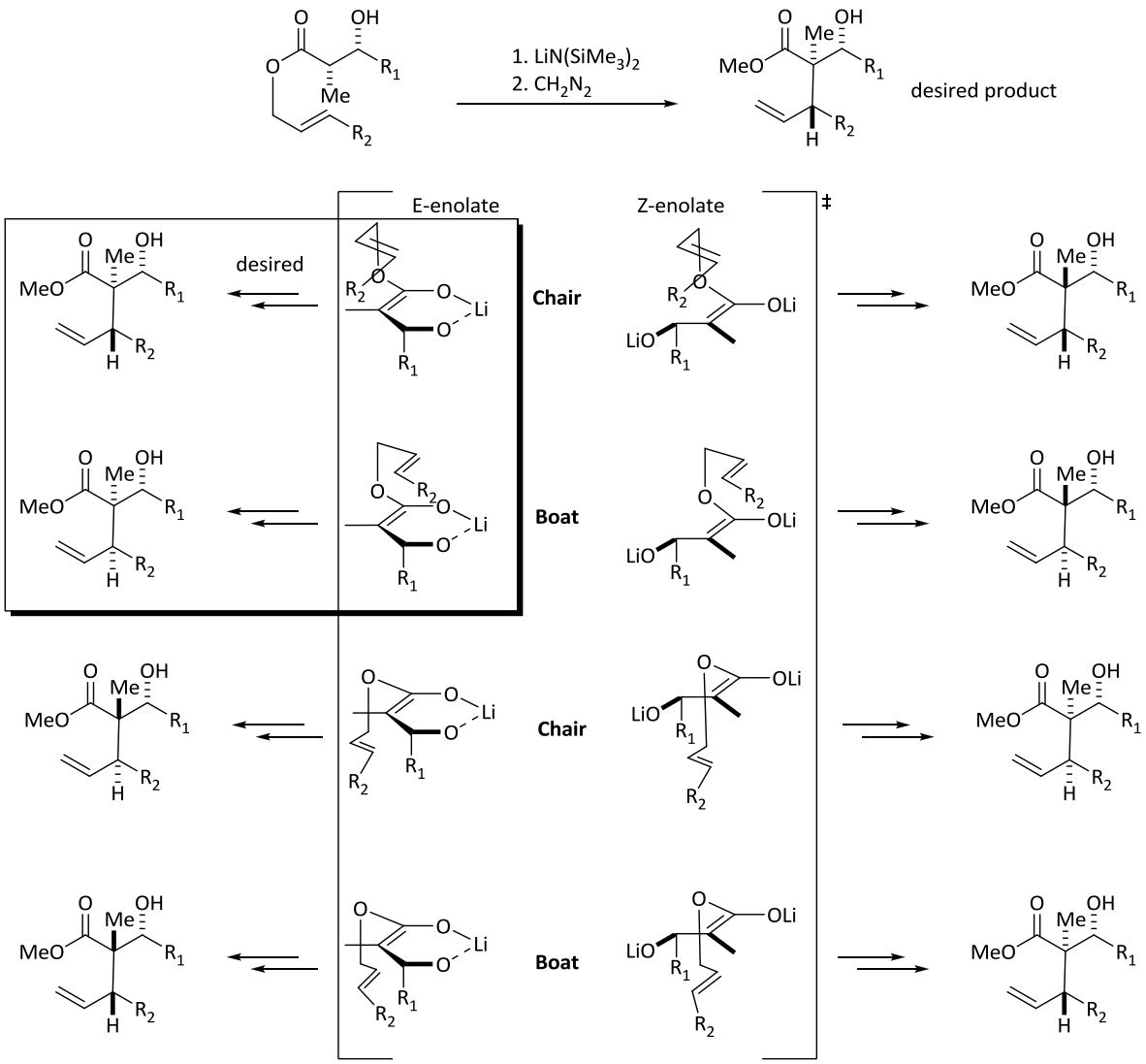
Table 3: Selected results of the dianionic Ireland-Claisen rearrangement

Treatment of the 4-methoxy dianionic Ireland-Claisen substrate **41** with the optimized conditions afforded a lower yield and generally sluggish reaction that did not progress significantly even after 2 days (table 3, entry 11). This was in stark contrast to the 4-chlorophenyl substrate **44** that proceeded in higher yield and significantly shorter total time of 6.5 hours. The total time measures the time beginning with addition of the allylic ester and ending with the consumption of the starting allylic ester and quenching of the reaction. It is believed that the

resonance stabilizing electronic conjugation effects of the aryl ring on the dianionic intermediate were the cause of the improved yields for electron poor aromatic rings. This is in contrast to solely inductive effects of the aryl ring improving the relative rate of the reaction. As shown by Burrow and Carpenter,[19] electron withdrawing groups at the bond forming position of the [3,3] rearrangement actually decreased the rate of reaction. However, we observed an improvement in overall reaction time and yield, which is attributed to conjugative stabilization of the allylic alcohol moiety of the DIC substrate.

Stereochemistry of the Dianionic Ireland-Claisen Rearrangement

The stereochemistry of the β-hydroxy carbon stereocenter is presumed to direct the facial selectivity. A larger interaction between R_1 and R_2 (Scheme 15) should dictate a higher selectivity for the bond forming event to occur from the less hindered face of the chelated intermediate. Kurth showed that with sterically undemanding substrates ($R_1 = R_2$ = methyl), the diastereotopic facial selectivity was good but not exclusive, as evidenced by his isolation of three stereoisomeric products (d.r. = 7.3:1.7:1, Scheme 6). In light of all these factors, the lack of stereospecificity observed in this preliminary research is assumed to largely be a result of the decreased preference between the boat and chair transition states.



Scheme 15: Depiction of stereochemical outcome of the dianionic Ireland-Claisen rearrangement

There are four factors compounding the number of possible transition states from which the product diastereomers can arise: ester enolate geometry, the geometry of the allylic olefin, the diastereotopic facial selectivity (which face of the enolate the olefin approaches) and finally the transition state conformational geometry (boat vs. chair). These variables provide for 16 potential transition states in all (scheme 15). By fixing the geometry of the allylic olefin as the *E* olefin, the number of possible transition states was reduced by half. Moreover, the kinetic enolization of the ester should provide the energetically favorable *E*-ester enolate, further limiting the possible transition states to four. The facial selectivity is predicted to sterically controlled by the steric interaction between the R_1 and R_2 side-chains. The two possible stereoisomeric products remaining are expected to be determined by the chair versus boat energy conformations.

The stereochemical analysis afforded us an excellent prediction of the expected absolute stereochemistry of the dianionic Ireland-Claisen rearrangement products. Fortunately, throughout the course of optimizing and exploring the reactivity of the DIC, it was discovered that **37** crystallizes when purified. X-Ray crystallography proved that the predicted stereochemistry of the DIC was in fact the observed absolute stereochemistry.

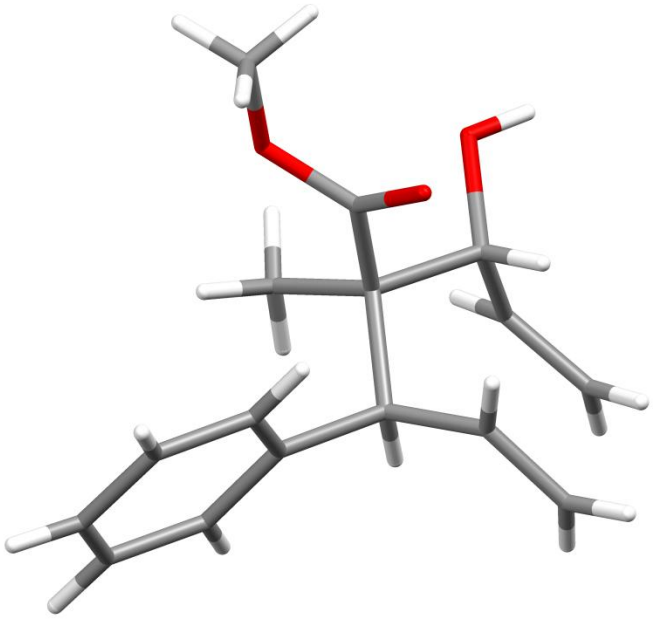
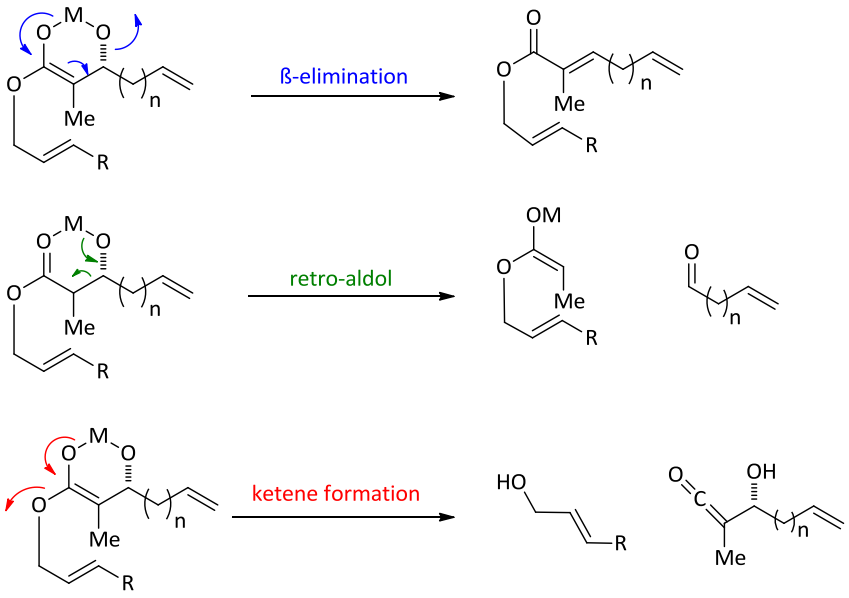


Figure 2: X-Ray crystallography of the product from **37** confirmed the predicted absolute stereochemistry

Degradation Pathways:

Improvement of the reaction yields was welcomed, however developing the DIC into a broadly useful synthetic tool was challenged by the decomposition of the allylic ester. In addition, although yields hovered around 50%, none of the starting allylic ester for any substrate was ever recovered. Thin-layer chromatography (TLC) observation of the reaction showed the complete consumption of the starting allylic ester with all substrate variations. Annoyingly, the analysis of the reaction by-products was not able to identify the major degradation pathway until the phenyl substrate **37** was investigated. With **37**, the free cinnamyl alcohol was able to be observed by TLC. Interestingly, the recovered mass of the free alcohol accounted for the remaining mass balance.

This crucial observation allowed the proposal of more accurate degradation pathways, in addition to elucidating why the yields were unable to be improved much higher than 50%. It was found that the major decomposition of the dianionic Ireland-Claisen substrate occurs after enolization but before the [3,3]-sigmatropic rearrangement. The ester enolate can degrade in a β-elimination pathway where the hydroxyl group is eliminated affording an enone (scheme 16). This expected by-product has been isolated and confirmed by ^{1}H NMR; however, it is a very small yield and typically less than 10%. As with any aldol adduct, treatment with base can induce a retro-aldol reaction. The most applicable degradation pathway is the elimination of the allylic alcohol forming a ketene that then could undergo any number of other degradation reactions. Ketene formation from enolates of esters with bulky alcohols is well-known.[20,21] Although direct evidence for the formation of a ketene is unavailable, the expunged allylic alcohol has been isolated when stable to vacuum and chromatography and the yields typically correspond to the remainder of the mass balance of the reaction.



Scheme 16: Proposed degradation pathways of the dianionic Ireland-Claisen rearrangement

This degradation pathway was interesting as it hasn't been reported in the Ireland-Claisen literature. Typically, the Ireland—Claisen ester enolate is trapped as the silyl enol ether increasing its stability and mitigating allylic alcohol elimination. Often, the enol ether intermediate is stable enough to be isolated. This increased stability was unfortunately unable to be exploited as chelation was critical to the stereoselectivity of the DIC.

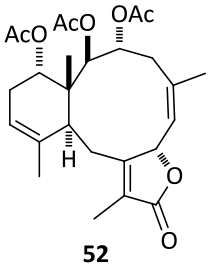
Enolate stabilization

In an attempt to better stabilize the ester enolate intermediate to reduce the propensity of thermal degradation, an investigation into chelating lewis acids was performed. Lithium chloride, magnesium chloride, magnesium bromide, and titanium tetrachloride were examined. Unfortunately, addition of these chelating metals showed no positive effect on the reaction. In the cases of magnesium

and lithium halide salts, the reaction proceeded, although the yields suffered. Utilization of more oxophilic lewis acids such as titanium tetrachloride promoted decomposition of the reaction.

Challenges and Summary

The dianionic Ireland-Claisen rearrangement has been shown to be an excellent vehicle for the creation of quaternary carbons with a high level of stereocontrol. Unfortunately, the stability of the ester enolate intermediate is a significant challenge in promoting the broad utility of the reaction. As will be shown in the next chapter, the high diastereoselectivity of the reaction makes the reaction ideal for applications toward the total synthesis of natural products, specifically the formation of the bridgehead angular quaternary stereocenter of brianthein A.



52

brianthein A

Figure 3: Briarane natural product brianthein A

Chapter 2

Efforts toward the Total Synthesis of Brianthein A

Cyclized Cembranoid-Based Natural Products

Cyclized cembranoid based natural products are complex, often biologically active, and synthetically interesting diterpene secondary metabolites. The Crimmins laboratory has pursued the total synthesis of numerous C2-C11 cyclized cembranoid classes including the eunicellins,[22] briarellins,[23] and asbestinins (Figure 4).[24]

Another related group is the C3-C8 cyclized cembranoids termed the briarane class. Since the discovery of the first briarane-type natural product by Burks[25] in 1977, more than three hundred of these secondary metabolites have been isolated. Many of the briaranes have been assayed for relevant biological activity.[26,27,28] This understudied class of natural products contains a number of synthetic challenges related to their total synthesis. Varying levels of oxidation surround a complex *trans*-fused 6,10 bicyclic core ring structure containing numerous stereocenters and a bridgehead, angular quaternary carbon (figure 5). The synthetic challenges, lack of interest from the synthetic community, and interesting biological activities led to the pursuit of the total synthesis of a representative member of the briarane class: brianthein A.

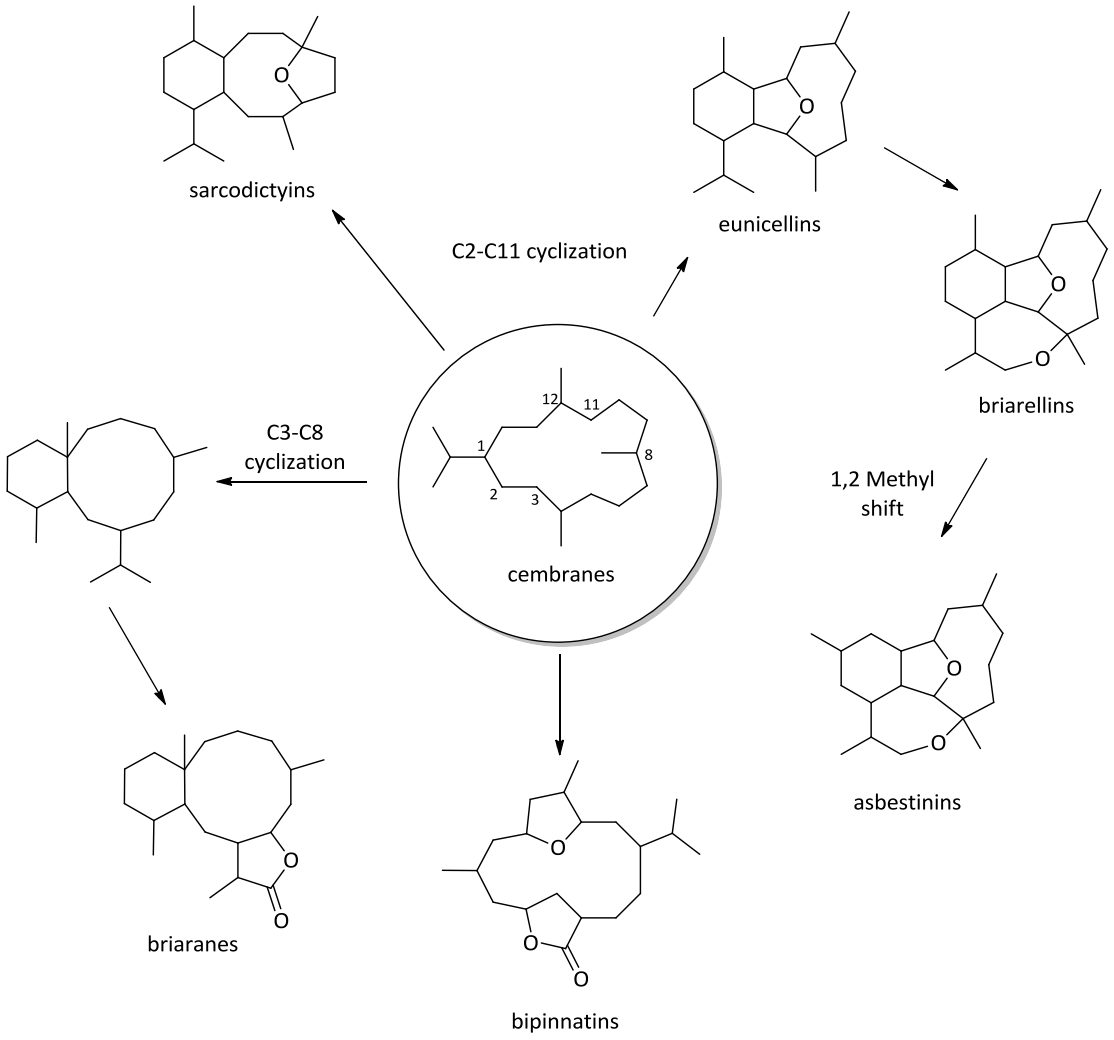


Figure 4: Proposed biosynthetic pathway for cembranoid based natural products

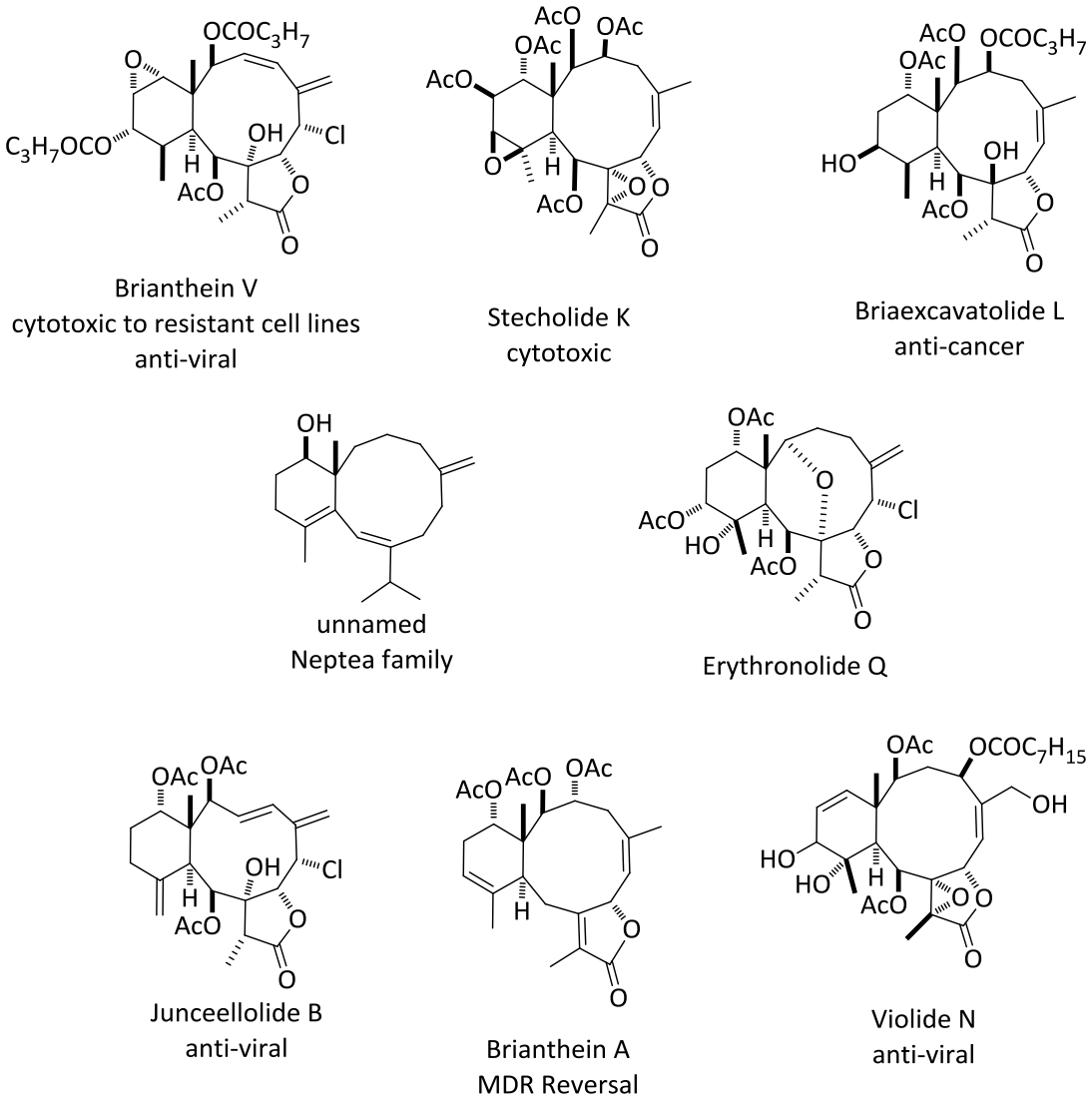
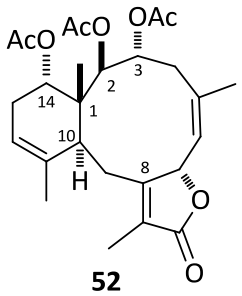


Figure 5: Isolated natural product examples of briarane type diterpenes

Isolation and biological profile of Brianthein A

Brianthein A was originally isolated off the coast of Japan in 2001 by Kobayashi and co-workers.[29] The initial methanol extract of the dried gorgonian *Briareum excavatum* demonstrated multi-drug resistance (MDR) reversal activity at 10 μg/mL when assayed against the human carcinoma KB-C2 cell line.[30] After further extractions and HPLC purifications, the novel briarane diterpene **52** was isolated as the major component.



52

brianthein A

Figure 6: Brianthein A, a briarane diterpene with MDR reversal activity

Brianthein A was isolated as a colorless powder and extensively analyzed by one and two dimensional nuclear magnetic resonance (^{1}H, ^{13}C, COSY, NOESY, and HMBC), high-resolution mass spectroscopy and degradation studies with sodium methoxide. Through the Mosher ester[31] NMR analysis, the stereochemistry of the acetyl protected alcohol moieties at carbons 2, 3 and 14 were able to be identified as R, R and S respectively.

Treatment of human cancer is plagued by the development of multi-drug resistant tumor cells. A major mechanism found to be responsible for this activity is the over-expression of the membrane glycoprotein termed P-glycoprotein (P-

gp).[32] P-glycoprotein functions from the cell cytoplasm signaling pathway to control an ATP-dependent efflux pump of unwanted toxins including anti-cancer drugs such as doxorubicin and vincristine. The biological profile of the isolated brianthein A was found to be quite impressive. In a 96-well plate, the colchicine resistant human carcinoma KB-C2 cell[30] line was added both colchicines and brianthein A. After incubation for 48 hours the samples were measured by means of an (MTT) colorimetric assay.[33] It was found that in the samples where only the anti-cancer drug colchicine or brianthein A was added, the cells survived unscathed. However, where brianthein A was added in concert with colchicine, the complete reversal of multi-drug resistance was observed and the cells were destroyed. Of the numerous briarane-type diterpenes that have been isolated, only brianthein A has shown the efficacy to inhibit MDR activity making it a desirable target for total synthesis and subsequent *in vitro* biological studies.

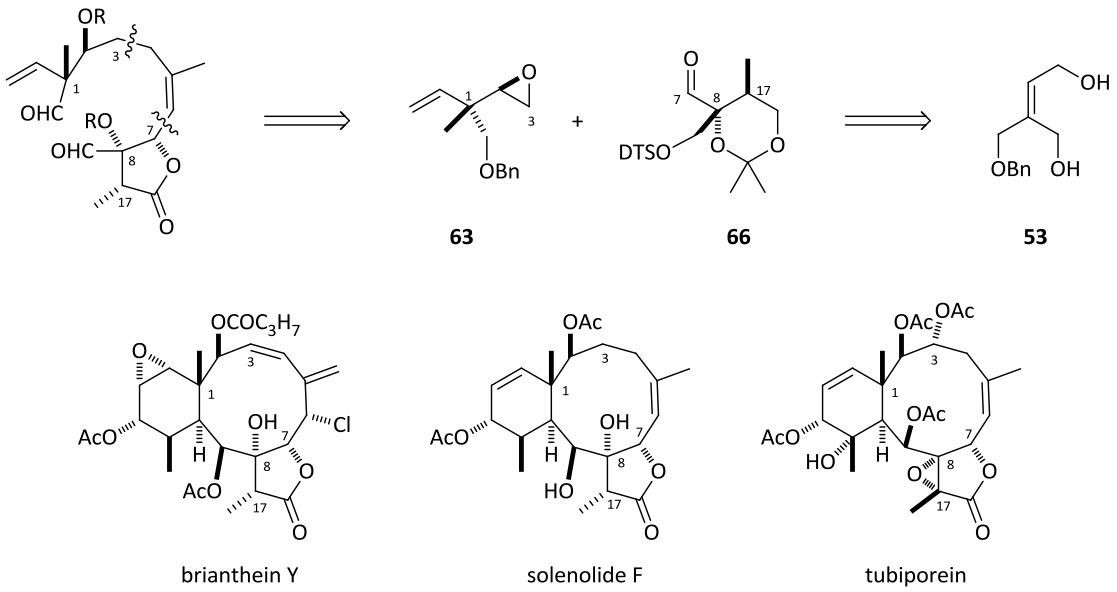
Previous Synthetic Efforts

Currently, a number of publications have been reported which focus on methodology to approach the synthesis of briarane class molecules. However, significant issues remain in accomplishing the total synthesis of the complex briarane core, specifically the formation of the 6,10-fused bicyclic core structure. A brief synopsis of the relevant previous synthetic efforts will be presented.

Nantz' Work toward C1 Quaternary Carbon

In 1997, Nantz and co-workers disclosed new methodology focused on the creation of chiral quaternary carbons.[34] This new methodology was oriented

toward their use in the total synthesis of briarane-type natural products. Their investigation into the regioselective methylation of functionalized 3,3-disubstituted-2,3-epoxy alcohols led to the successful synthesis of the quaternary carbon C1 and C8 of the briarane skeleton.

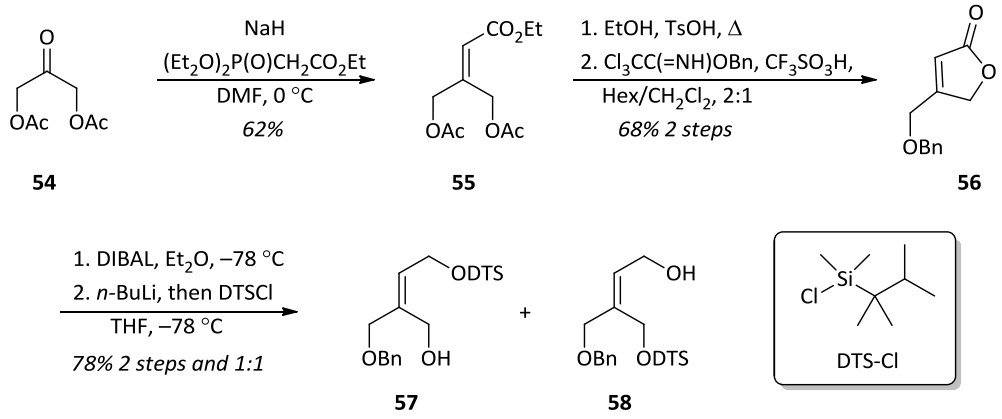


Scheme 17: Retrosynthetic strategy and briarane target molecules

Nantz was initially interested in the briaranes shown in scheme 17, yet efficient access to the core carbon skeleton could enable access to the entire family. Retrosynthetically, he had envisioned accessing the challenging ten-membered ring via a McMurry coupling[35] and the remaining carbon skeleton could be elaborated from diol **53** utilizing the newly developed methodology.

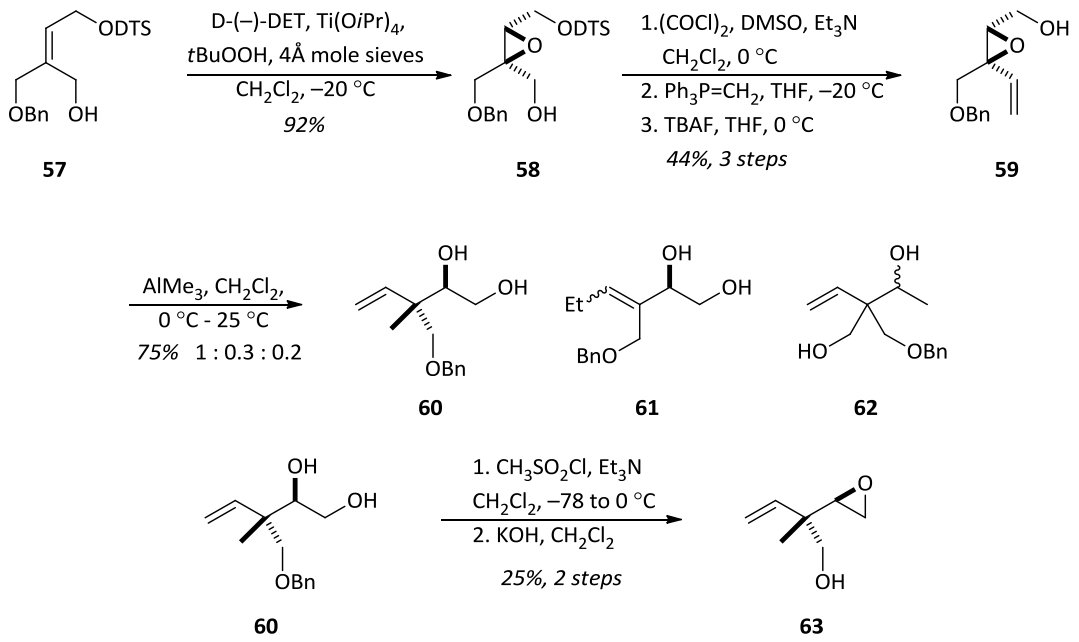
Synthesis of the common precursor diol **53** started with the commercially available 1,3-bisacetate **54** (scheme 18). Horner-Wadsworth-Emmons (HWE) olefination using triethyl phosphonoacetate afforded vinyl ester **55** in a 62% overall yield. Acetate cleavage under acidic conditions in 90% ethanol over a

prolonged time period afforded the butenolide, which was subsequently protected as the benzyl ether **56** with the acidic protocol developed by Bundle and co-workers[36] in a 68% yield over two steps. Butenolide reduction with an excess of diisobutyl aluminum hydride in ether proceeded smoothly in 95% yield. The mono-protection was successful only when the diol was deprotonated with *n*-butyllithium (*n*-BuLi) followed by treatment with dimethylthexysilyl chloride (DTS-Cl) resulting in an 83% yield and a 1:1 mixture of **57** and **58**. This was acceptable because both mono-protected compounds were to be further utilized.



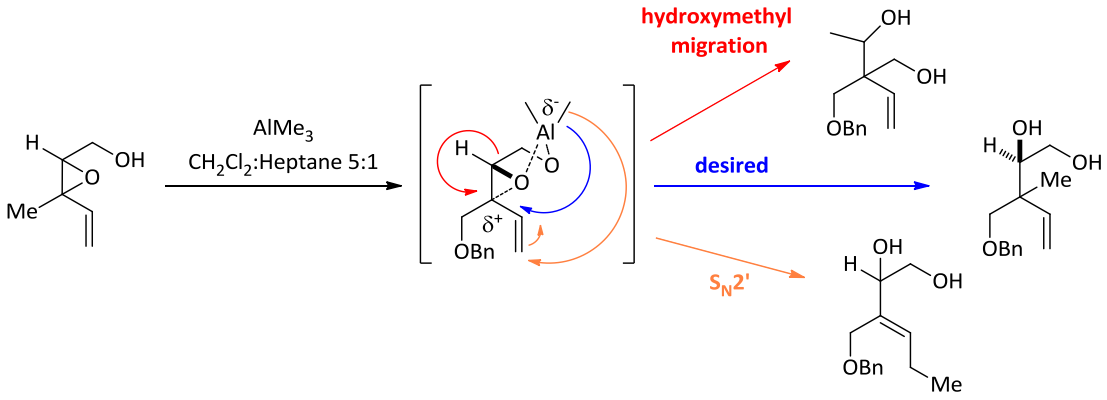
Scheme 18 Synthesis of mono-protected alcohol fragments

To complete the first of two fragments, **57** was treated under Sharpless' asymmetric epoxidation conditions to afford the epoxide **58** in 92% yield (scheme 19). Oxidation of the primary alcohol and subsequent treatment with methylene Wittig conditions afforded the primary alkene.



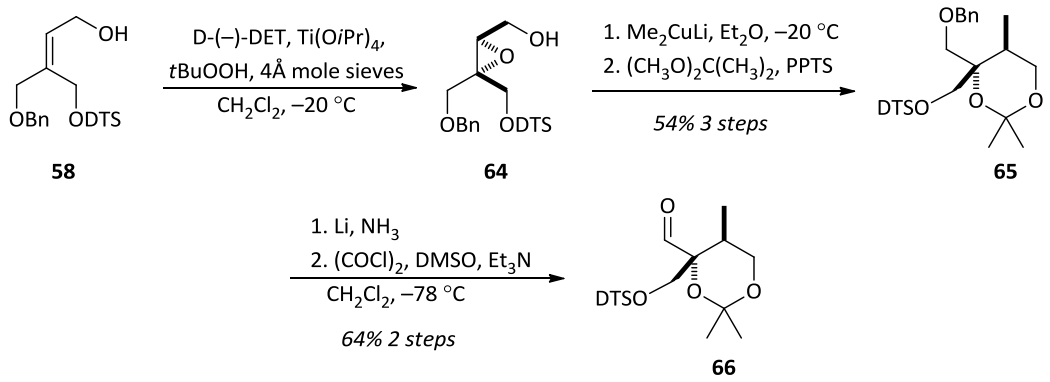
Scheme 19: Synthesis of epoxide fragment containing quaternary carbon **63**

Deprotection with tetra(*n*-butyl)ammonium fluoride produced **59** in a 44% yield over the three steps. Under the newly developed methylation protocol, the allylepoxy alcohol was treated with trimethyl aluminum to afford the desired quaternary carbon product **60** along with two minor products **61** and **62** resulting from S_N2' addition and competitive migration of the C2 hydroxymethyl group respectively (scheme 20).



Scheme 20: Proposed mechanism of methyl addition and side reactions

The synthesis of the second fragment required for the proposed retrosynthesis begins with the monosilyl protected **58** (scheme 21). Again, Sharpless asymmetric epoxidation conditions afforded **64** in 86% yield and a 92% diastereomeric excess. Exposure to an excess of lithium dimethylcuprate in diethyl ether afforded methyl addition to the less substituted epoxide carbon according to the method by Kishi.[37] Subsequent protection of the diol as its acetonide proceeded smoothly utilizing pyridinium *p*-toluenesulfonic acid (PPTS) to give **65** in a 54% yield over three steps. To complete the fragment synthesis, benzyl ether cleavage under lithium and ammonia reducing conditions followed by Swern oxidation to aldehyde **66** proceeded in 64%.

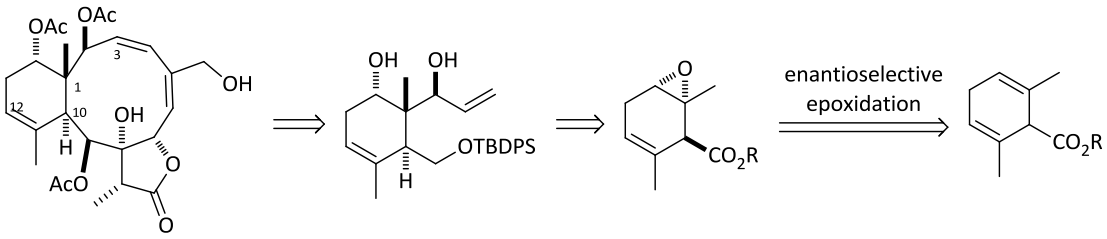


Scheme 21: Synthesis of 66 containing quaternary carbon 8

By controlling the carbon-carbon bond forming events with epoxides **59** and **64** to proceed at either the more or less substituted epoxide carbon, Nantz has demonstrated the ability to synthesize the quaternary carbons of such briarane natural products as brianthein Y, solenolide F, and tubiporein. To date, no report of successful ten-membered ring synthesis has been reported.

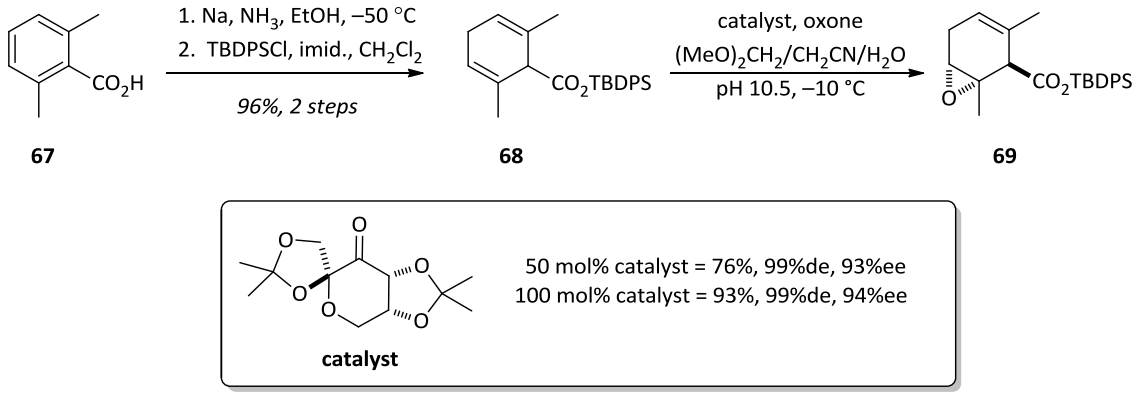
Iguchi's efforts toward Pachyclavulide B

In his synthetic study of the briarane-type diterpene pachyclavulide B (scheme 22), Iguchi and co-workers developed a synthetic strategy aimed at the angular quaternary carbon C1 of the bridgehead stereocenter.[38] As shown by the proposed retrosynthetic analysis, an enantioselective epoxidation would provide access to the cyclohexane ring of the briarane core.



Scheme 22: Retrosynthetic strategy to access the briarane core

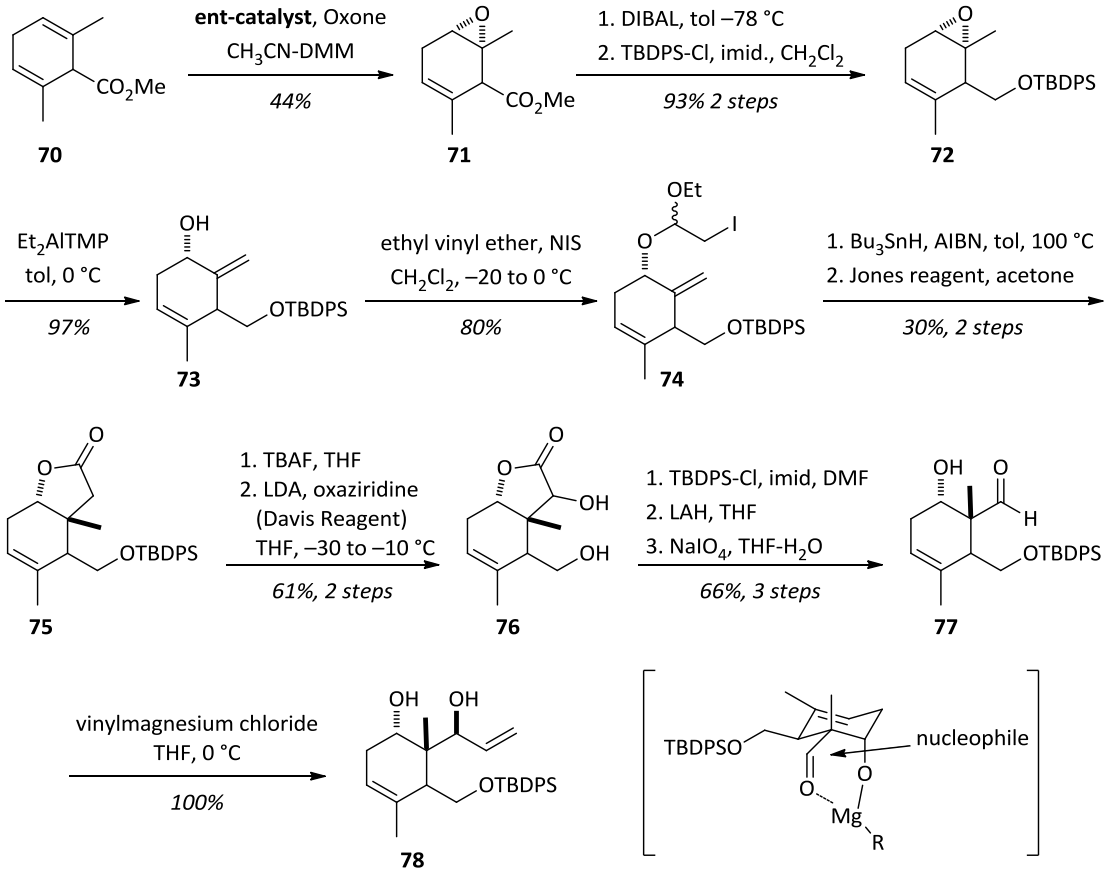
To prepare the epoxidation material, Iguchi began with the commercially available 2,6-dimethylbenzoic acid (**67**) and reduced the aromatic ring under Birch conditions.[39] Exposure of the carboxylic acid to *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) afforded the TBDPS ester **68** in 96% over 2 steps. Oxidation conditions were optimized utilizing the chiral D-fructose derived catalyst[40] developed by Shi to form the epoxide **69**. Higher catalyst loadings were required for improved selectivities (scheme 23).



Scheme 23 Synthesis and optimization of chiral epoxidation

Continuing toward the briarane skeleton, diene **70** was oxidized with the optimized epoxidation conditions. Reduction of the methyl ester **71** and

subsequent protection of the primary alcohol as the TBDPS ether **72** in 93% over 2 steps proceeded smoothly. The hindered Lewis acid diethylaluminum tetramethylpiperidine (Et_2AlTMP) induced the opening of epoxide **72** to allylic alcohol **73** in 97% yield.[41] Exposure of alcohol **73** to ethyl vinyl ether in the presence of *N*-iodosuccinimide afforded the primary iodide **74**.[42]



Scheme 24: Synthesis of cyclohexane portion of briarane skeleton

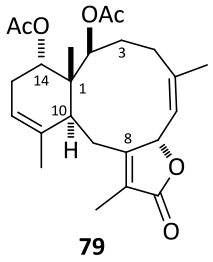
Treatment of **74** with tributyltin hydride and azobisisobutyronitrile (AIBN) at 100 ºC initiated the intramolecular radical cyclization[43] constructing the quaternary carbon stereocenter in a disappointing 32% yield. Oxidation of the resulting hemiacetal with Jones reagent afforded the lactone **75**. Deprotection of

the silyl ether followed by alpha oxidation of the lactone utilizing lithium diisopropylamine and 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis reagent)[44] produced the alpha hydroxyl group on diol **76**. This alpha oxidation was found to be sluggish with the steric repulsion of the TBDPS ether, and thus the TBDPS ether was cleaved prior to oxidation. Once the alpha hydroxyl group was installed, the primary hydroxyl group of diol **76** was protected again as the TBDPS ether. Reduction of the lactone and subsequent oxidation of the resulting vicinal diol afforded the aldehyde **77** in 66% over three steps. Finally, a diastereoselective vinylmagnesium chloride addition was achieved to produce **78** as a single diastereomer in quantitative yield.

Iguchi has demonstrated the ability to synthesize the cyclohexane ring of the briarane skeleton. The elaboration of substrate **78** to the fused 6,10 bicycle remains a significant challenge that has not yet been addressed. Additionally, the key quaternary bond forming step only results in low yields which would make scaling the synthesis challenging.

Bates' Synthesis of the C1 Quaternary Carbon of the Briarane Skeleton

Published in 2010, Bates and co-workers defined an approach to the C1 quaternary carbon stereocenter and northern hemisphere of the briarane carbon skeleton which included a stereocontrolled Claisen rearrangement.[45] The specific target chosen was brianthein W,[46] however the goal was still to define a strategy amenable to the entire briarane class.



79

brianthein W

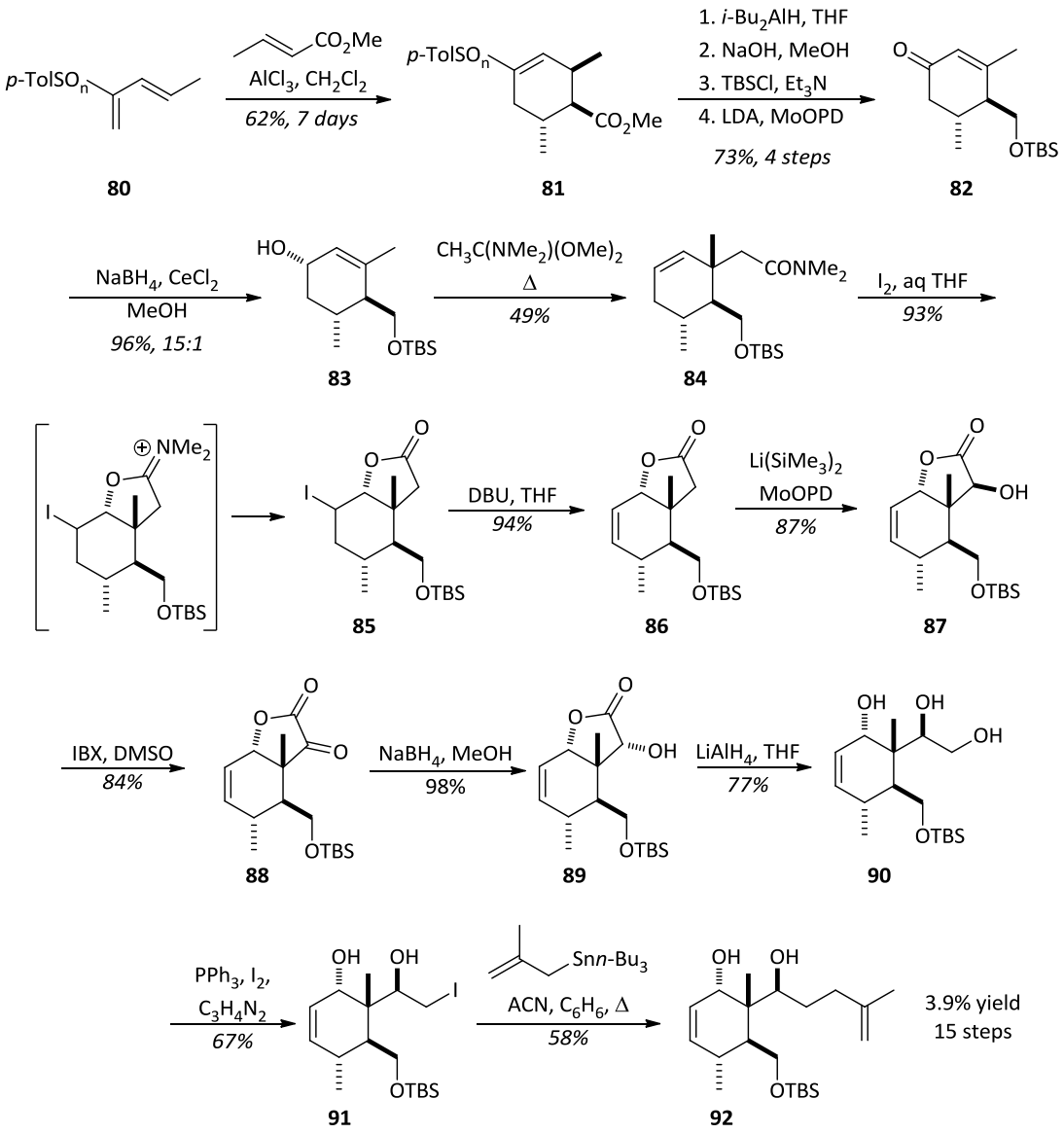
Figure 7: Briarane natural product brianthein W

To construct the desired cyclohexane ring of the briarane skeleton, a chiral sulfoxide auxiliary was installed on diene **80** and utilized in a Diels-Alder reaction with methyl crotonate (scheme 25). While it is known that the Diels-Alder reaction of diene **80** and methyl acrylate is quite rapid with aluminum trichloride as the catalyst,[47] the same reaction with methyl crotonate as the dienophile is far more sluggish and required seven days in refluxing dichloromethane to afford a 62% isolated yield of cyclohexene **81**. This stereocontrolled Diels-Alder reaction succeeded in creating the desired C10 stereocenter of the briarane skeleton.

Treatment of the resulting Diels-Alder adduct **81** with diisobutylaluminum hydride reduced the methyl ester to a primary alcohol. Sodium hydroxide in methanol was utilized to isomerize the double bond within the cyclohexene ring which produced a γ,δ-unsaturated sulfone. Silyl protection of the free alcohol with *tert*-butyldimethylsilyl chloride (TBS-Cl) followed by oxidative desulfurization via lithium diisopropylamine and oxodiperoxymolybdenum(pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (MoOPD) afforded enone **82** in 73% over four synthetic steps. Luche reduction[48] resulted in the 1,2 reduction product in

excellent yield (96%) and selectivity (15:1). Conversion of the allylic alcohol **83** to form the quaternary carbon stereocenter at C1 of the briarane core proved quite challenging. Numerous [3,3] sigmatropic conditions were tested and found unsuccessful including the Johnson-Claisen[49] rearrangement (triethylorthoacetate and propionic acid at reflux), Ireland-Claisen[10] rearrangement (acetate alcohol and treated with base), Claisen[50] rearrangement (treated with mercuric acetate and ethyl vinyl ether and heated) and the method developed by Mandai[51](oxa-michael addition of alcohol **83** to aryl vinyl sulfoxide). Fortunately, the Eschenmoser variation[8] was found to produce amide **84** with the desired quaternary C1 carbon in a modest yield.

Amide **84** was subjected to cycloiodination conditions to afford the iodolactone **85** in 94% yield. Base promoted elimination of H-I followed by alpha oxidation of the lactone resulted in alkene **87** in 82% over 2 steps. Bates required the opposite stereoconfiguration of the alpha hydroxyl group of **87**, and thus effected an epimerization via oxidation with 2-iodoxybenzoic acid (IBX) followed by sodium borohydride ($NaBH_4$) reduction to afford intermediate **89**. Reduction of the lactone with lithium aluminum hydride (LAH) and conversion of the resulting primary alcohol to the alkyl iodide[52] allowed efficient access to the completed fragment **92** via Keck's free radical allylation[53] conditions utilizing methallyltri-*n*-butyltin in the presence of a radical initiator.



Scheme 25: Bates synthesis of the northern fragment of the briarane core

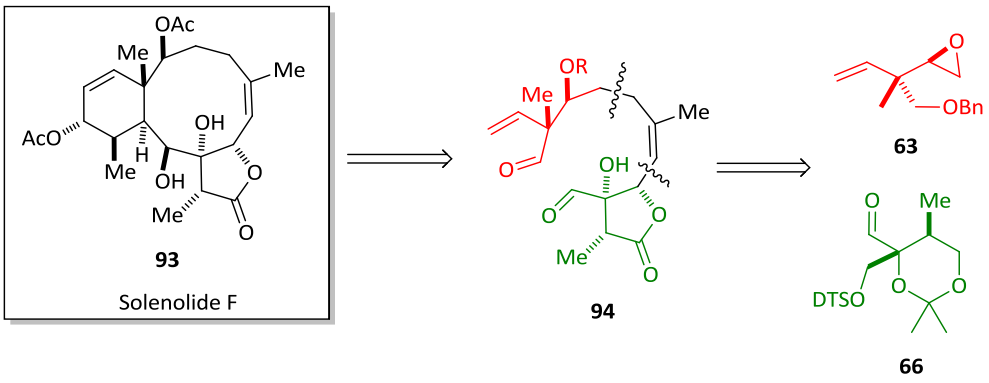
Summary of previous efforts

Bates and co-workers disclosed an advanced substrate toward the total synthesis of the briarane skeleton. They were able to achieve all but three carbons of the ultimate 6,10-bicyclic carbon skeleton with 4 of 5 stereocenters of brianthein W (**79**) installed (Figure 7); however, the cyclodecene synthesis remained a daunting challenge. In all of the synthetic efforts to date, the synthesis of the angular quaternary carbon stereocenter at C1 of the briarane skeleton has been clearly defined as the most challenging feature to address. While Nantz, Iguchi, and Bates have all disclosed syntheses of the C1 stereocenter, the synthesis of the ten membered carbocylic ring has yet to be disclosed leaving a significant challenge in completing the synthesis of the briarane core carbon skeleton.

Previous Syntheses of Ten Membered Rings

Synthesis of the C1 quaternary carbon of the briarane skeleton is certainly a challenging feature of the structure. Additionally, the synthesis of ten membered carbocycles is a significant challenge. There are many examples of larger macrolides synthesized via the formation of an ester linkage, although the formation of ten membered carbocycles calls for the creation of a carbon-carbon bond in their synthesis.

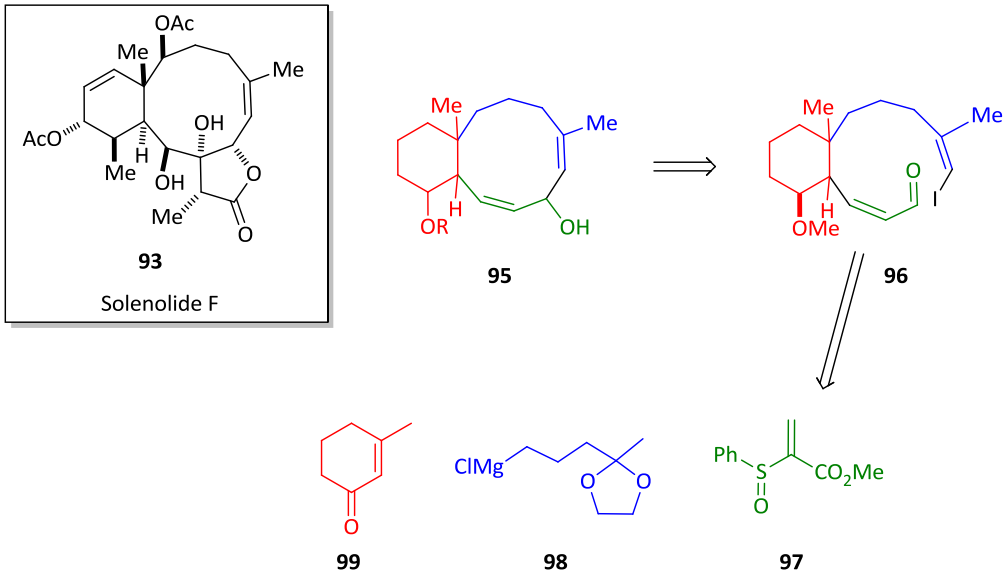
In the previous example by Nantz (scheme 18), the formation of his quaternary carbon methodology was described. To complete the proposed synthesis of solenolide F, the ten membered ring of the briarane skeleton was to be formed via a McMurry coupling.[35] This synthetic route has not yet been achieved, though remains a viable option to utilize the fragments synthesized in the previous work.



Scheme 26: Nantz' proposed formation of ten membered ring

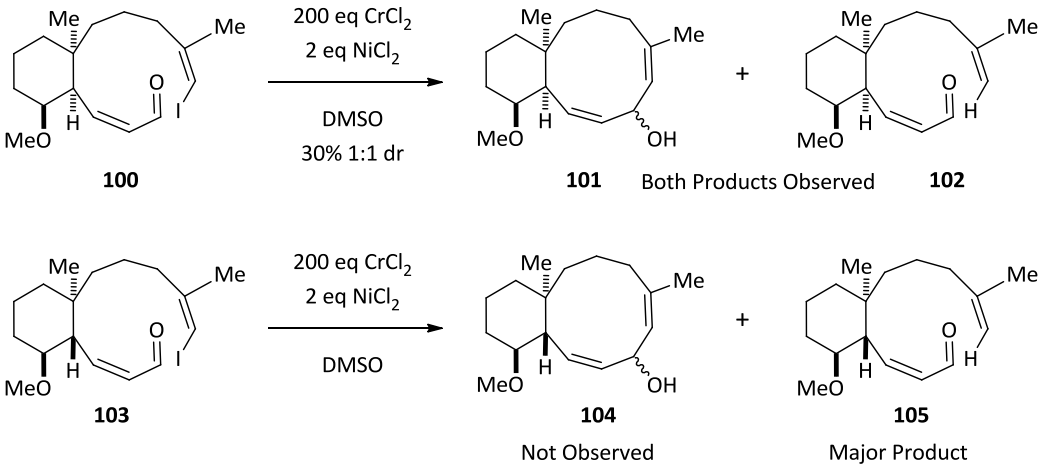
Procter NHK Coupling toward Solenolide F

Solenolide F was also a molecule of interest for the Proctor group.[54] The proposed formation of the carbon skeleton focused on the formation of the ten membered ring via a Nozaki-Hiyama-Kishi (NHK) coupling reaction.



Scheme 27: Proposed Retrosynthesis of solenolide F core

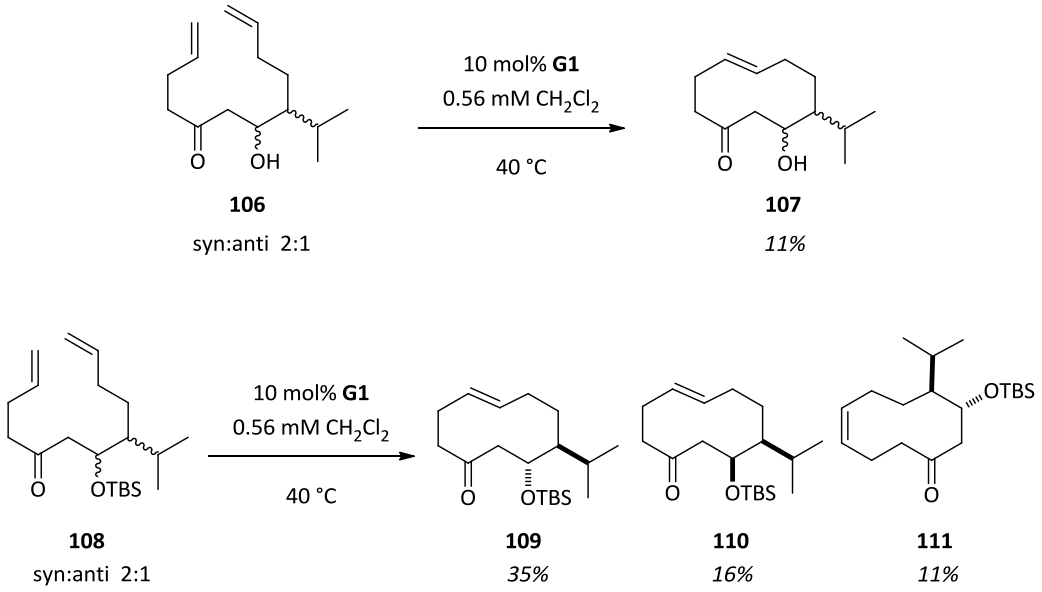
Attempts at closing the ten membered ring were found to be highly dependent on the bridgehead stereochemistry being *cis*. As shown in scheme 28, the NHK coupling formed a 1:1 mixture of diastereomers at the newly formed carbinol position only in the reactants in the *cis* position. With a *trans* bridgehead orientation, the metallated vinyl center and the carbonyl were presumably not able to react due to the conformation of the molecule.



Scheme 28: Nozaki-Hiyama-Kishi conditions to form 10 membered ring

Ring Closing Metathesis to form 10 Membered Rings

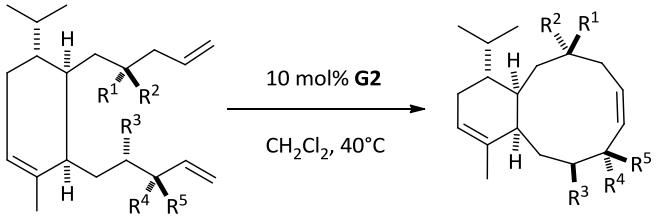
The synthesis of larger carbocycles via ring closing metathesis is not well known due to the entropic challenge of bringing two distant alkenes into proximity with one another. Koskinen and co-workers demonstrated the ability to form these larger carbocycles when the correct steric constraints were employed on the starting diene (scheme 29).[55]



Scheme 29: Koskinen ring closing metathesis of 10 membered ring

By the addition of the bulky silyl protecting group on the alcohol, the acyclic conformation was modified so that the two alkenes were more able to react. Interestingly, this resulted in an additional challenge. Now, because of the larger ring size, the conformational flexibility allows for the formation of both the *E* and the *Z* alkene geometries.

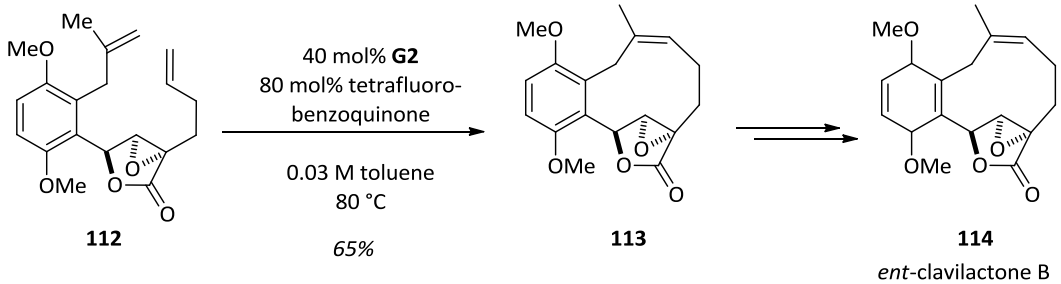
Gennari showed the ability to form a ten membered ring via ring closing metathesis as well (table 4).[56] His formation of a 6,10 fused bicycle is very similar to that of the briarane skeleton, with the exception of the stereochemistry of the bridgehead, which in this case is *cis* and lacks a quaternary carbon stereocenter at C1. Molding the results of both Procter and Koskinen by utilizing the *cis* bridgehead stereochemical relationship and selectively modifying the protecting groups around the diene, Gennari was able to form the 10 membered ring (table 4).



R^1	R^2	R^3	R^4	R^5	Yield
OTBDPS	H	OH	H	OPMP	82%
OTBDPS	H	OPiv	H	OPMP	52%
H	OAc	OTBDPS	OMe	H	N.R.
H	OPiv	-(OC(Me)$_2$O)-		H	N.R.

Table 4: RCM optimization by Gennari

A final example of ring closing metathesis being utilized in the formation of 10 membered rings is the work by Barrett in the synthesis of *ent*-clavilactone B (scheme 30).[57] After extensive experimentation and optimization, the ten-membered ring was achieved through the addition of 40 mol% Grubbs' 2nd generation catalyst in the presence of 80 mol% tetrafluorobenzoquinone while heated in toluene to 80 C. The removal of the ethylene formed by reaction with the terminal alkene was found to be crucial in driving the reaction toward the desired macrocycle. In this example, the stereochemistry of the bridgehead position was more restricted due to the presence of sp^2 carbons.



Scheme 30: Barrett's synthesis of *ent*-clavilactone B

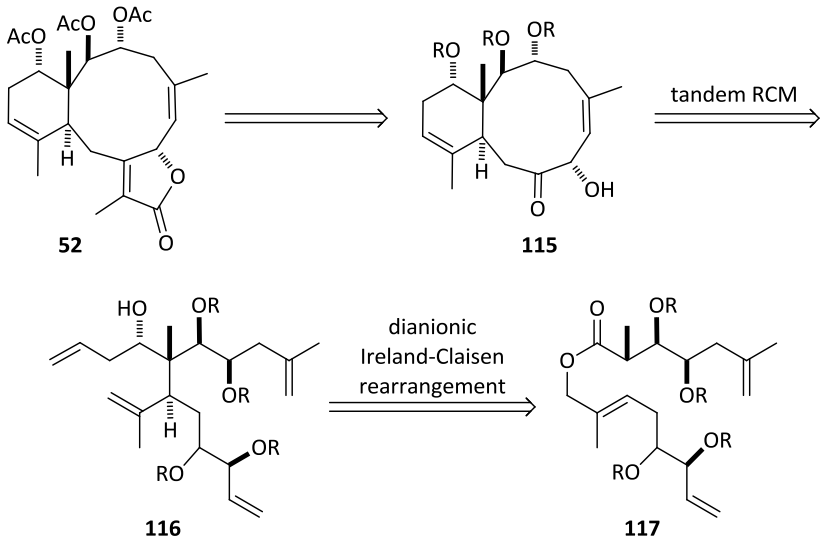
Summary of the synthesis of 10 membered rings

The formation of large carbocycles presents a number of challenges not found with the synthesis of smaller rings. Entropic effects of the acyclic reactants often outweigh the thermodynamic ability of the two intramolecular reactants to react with each other. The conformation of the molecule can ultimately control the capability of the molecule to undergo the necessary carbon-carbon bond forming step, whether with a RCM reaction, NHK coupling reaction, or other carbon-carbon bond forming reaction. Additionally, in the cases where ring closing metathesis is used, the formation of both alkene geometries is possible bringing an additional challenge.

Crimmins' Efforts toward Brianthein A

1st Generation Synthesis

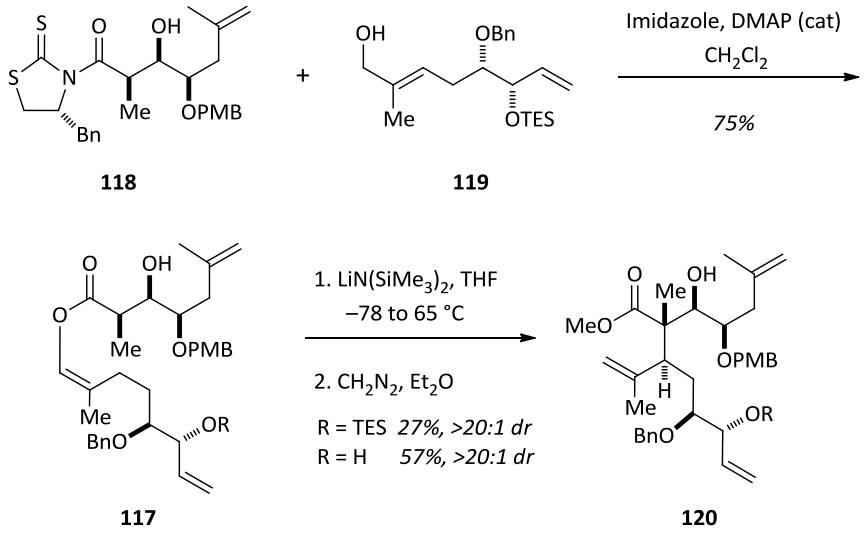
The Crimmins laboratory, having consistently looked to synthesize complex, biologically active natural products, viewed the briarane class as a formidable challenge. The opportunity to apply the dianionic Ireland-Claisen methodology as a synthetic handle toward the briarane bicyclic core was appealing. Scheme 31 defines the first generation retrosynthesis explored by Dr. Yan Zhang.[58]



Scheme 31: 1st Generation Retrosynthesis of Brianthein A

The butenolide was to be appended at a late stage from hydroxyketone **115**. One of the two key reactions was the tandem ring closing metathesis of tetraene **116** to form the 6,10 fused bicycle. The tetraene substrate containing the C1 quaternary carbon stereocenter in place would be prepared via the dianionic Ireland-Claisen rearrangement of ester **117**.

This strategy was extremely appealing due to the short number of synthetic steps required to access the complex 6,10 carbon skeleton of the entire briarane family. In addition, upon successful tandem ring closing metathesis, the general strategy could be applied to many of the over three hundred briaranes currently known.[28]



Scheme 32: 1st generation dianionic Ireland-Claisen rearrangement

The dianionic Ireland-Claisen substrate **117** was prepared over an 8 longest linear step sequence and 34% overall yield (scheme 32). Optimization of the substrate by removing the triethylsilyl ether protecting group allowed for a 57% yield from the dianionic Ireland-Claisen rearrangement. Elaboration to tetraene **116** proceeded smoothly in 3 steps (not shown). Unfortunately, treatment with a variety of ring closing metathesis catalysts did not produce the desired 6,10 fused bicycle. The synthesis of 10-membered rings in the literature is very dependent on the conformational restraints of the individual substrate. Without the optimal steric constraints, the 10-membered ring typically will not

form.[55,59,57] Thus, the focus was shifted to protecting group manipulation of the hydroxyl groups in order to manipulate the conformation of the substrate.

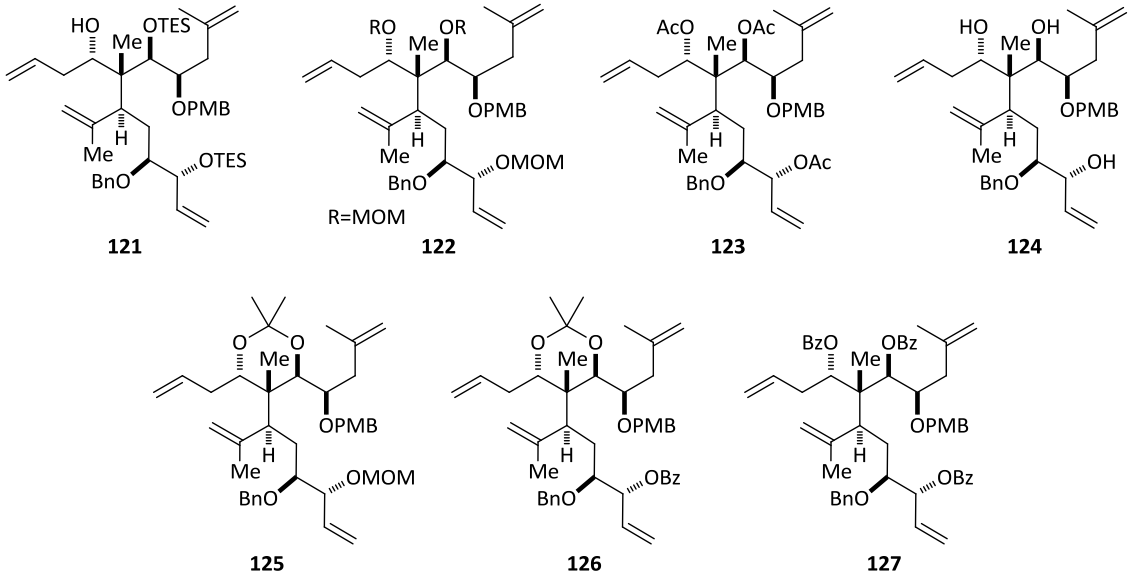


Figure 8: Hydroxyl protecting group variations to effect the tandem ring closing metathesis of the brianthein core

Not only did the synthetic strategy of the tandem ring closing metathesis prove unsuccessful, none of the substrates tested ever formed the ten membered ring. To probe solely the formation of the ten membered carbocycle, the cyclohexene ring was closed efficiently. The resulting triene (figure 9) was also probed to form the desired briarane bicycle to no avail. Closer analysis of the conformation of the triene **128** showed that the two acyclic alkenes required for the formation of the ten membered ring were oriented in opposite directions. Through this same conformational analysis, Zhang developed a method to utilize the 1,3 acetonide as a conformational constraint to reinforce the necessary orientation of the two acyclic alkenes for the ring closing metathesis.

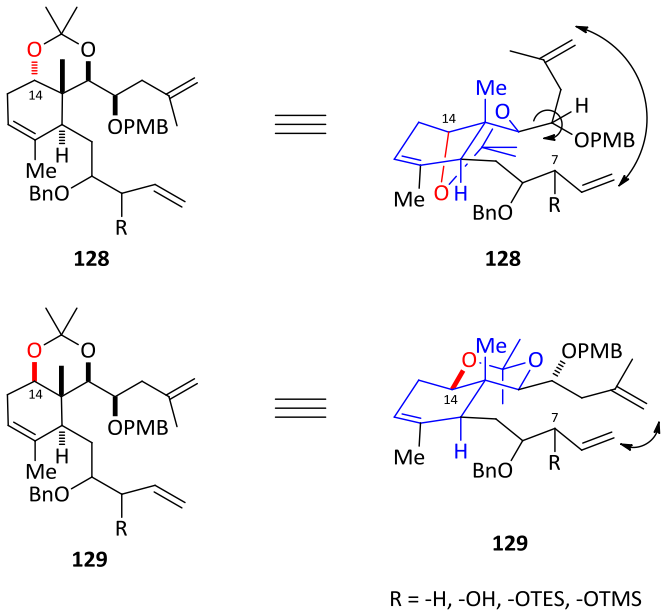


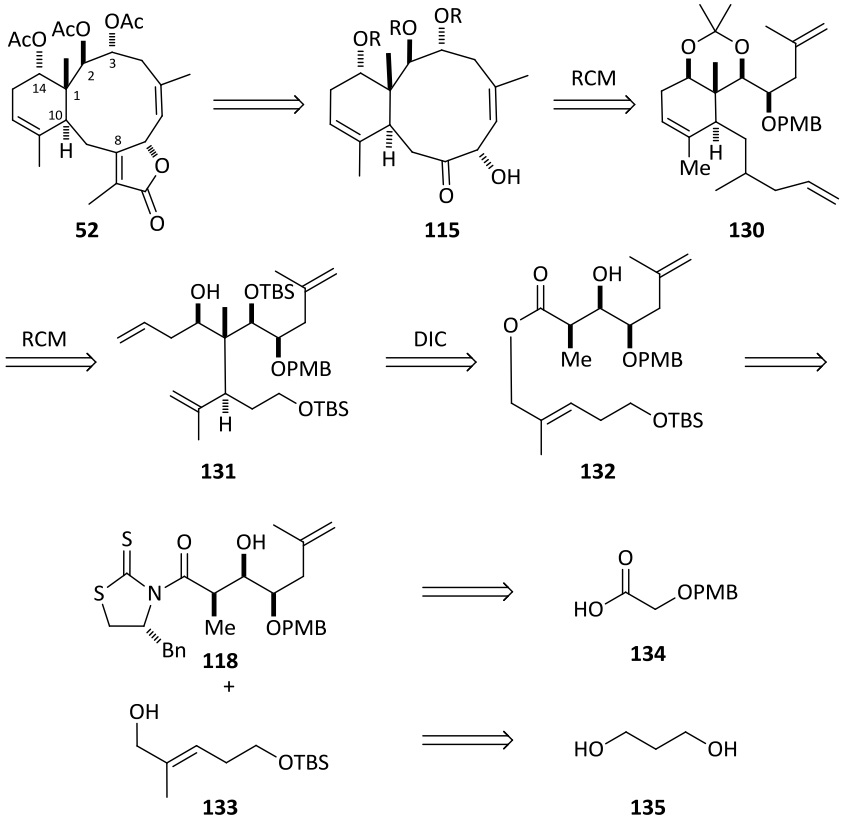
Figure 9: Proposed conformational restraints to effect a the 10-membered ring closing metathesis

By inverting the hydroxyl stereocenter at C14 of the briarane skeleton and forming an acetonide between two hydroxyls, a very rigid, planar, *trans*-decalin type conformation was rationalized. This structure of **129** oriented the two reactive alkenes in better proximity to each other. With this conformation, the desired RCM reaction was successful, but only with substrates with no functionality at C7 of the brianthein A core (R=H in figure 9).[58]

Second Generation Synthesis

The development of the ten membered ring closing metathesis reaction toward the synthesis of the briarane skeleton led to a revised, second generation retrosynthesis depicted in scheme 33. Performing the RCM reactions to form the cyclohexene and cyclodecene rings sequentially added linear synthetic steps,

however also potentially allowed for maximum flexibility in future synthetic modifications toward other briarane natural product targets.



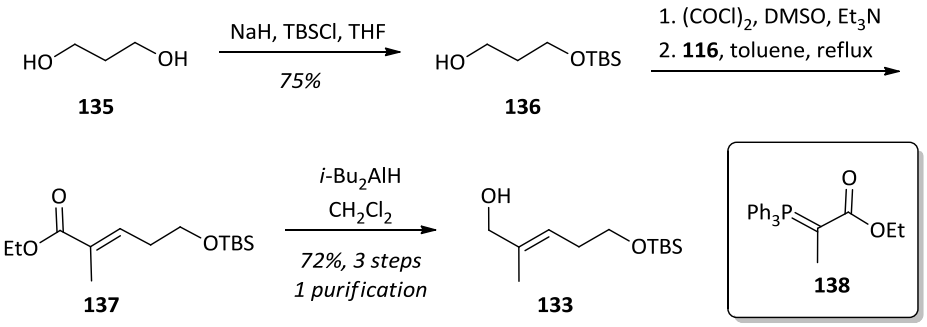
Scheme 33: Second generation retrosynthesis of brianthein A

The revised retrosynthetic analysis required additional late-stage protecting group manipulations to epimerize C14 to the desired stereochemistry of brianthein A. The butenolide would be constructed from hydroxyketone **115** which would be accessed by an alpha-oxidation as opposed to carrying the masked hydroxyketone from an early stage in the synthesis as in the first generation route. Ring closing metathesis would be utilized to form both the ten and six membered rings. The bridgehead carbon-carbon bond including the quaternary angular methyl group would be synthesized via the dianionic Ireland-

Claisen methodology. The DIC substrate **132** is formed by coupling the aldol adduct **118** with the revised allylic alcohol **133**.

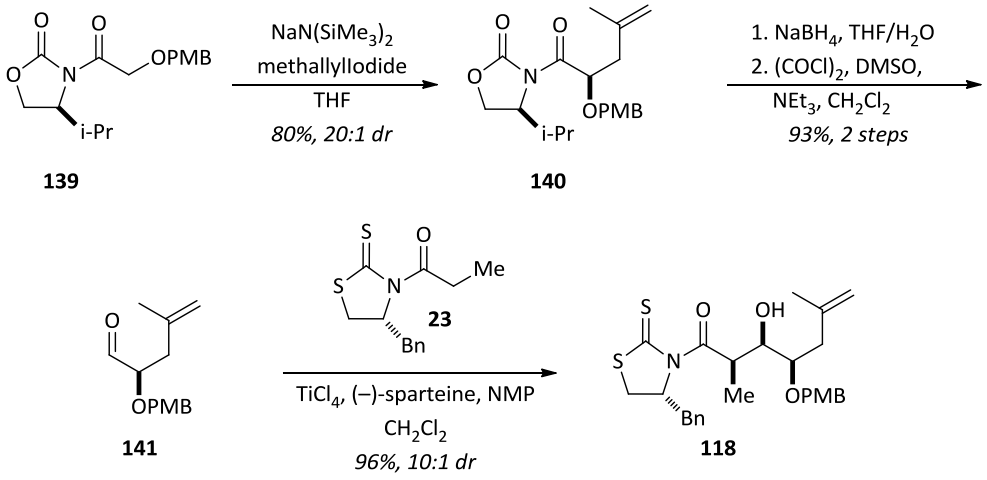
Synthesis of Quaternary Carbon C1

The synthesis of the allylic alcohol began with 1,3-propane diol (**135**) (scheme 34). Initially disclosed by Zhang,[58] the current publication reports an optimized synthetic route to improve scalability. Mono *tert*-butyldimethylsilyl protection after sodium hydride deprotonation proceeded well with a minor amount of di-protected side-product. Swern oxidation of the resulting primary alcohol **136** was taken forward without purification to the Wittig olefination with stabilized phosphorane **138**. The crude reaction mixture from the olefination could again be carried forward without chromatographic purification. After filtration of the phosphine oxide by-product, the crude material was reduced with excess DIBAL to afford the allylic alcohol **133** in good yield after flash column silica gel purification.



Scheme 34: Synthesis of the allylic alcohol fragment **133**

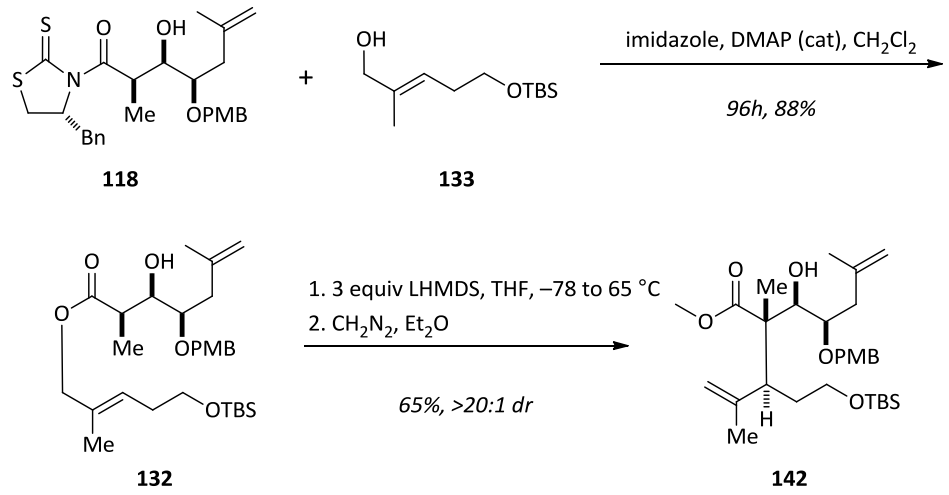
Synthesis of the aldol adduct **118** began with glycolate **139** (scheme 35). Treatment with alkylation conditions of sodium hexamethyldisilazane and excess freshly prepared methallyliodide afforded the desired product **140** in 80% yield as a single detectable diastereomer by ^{1}H NMR spectroscopy. Reduction of the oxazolidinone chiral auxiliary with sodium borohydride followed by Swern oxidation afforded aldehyde **141**. The chiral thiazolidinethione-mediated aldol could be employed with the unpurified aldehyde, however optimal yields were achieved after flash chromatography purification of the aldehyde before addition to the aldol reaction.



Scheme 35: Synthesis of the aldol fragment **118**

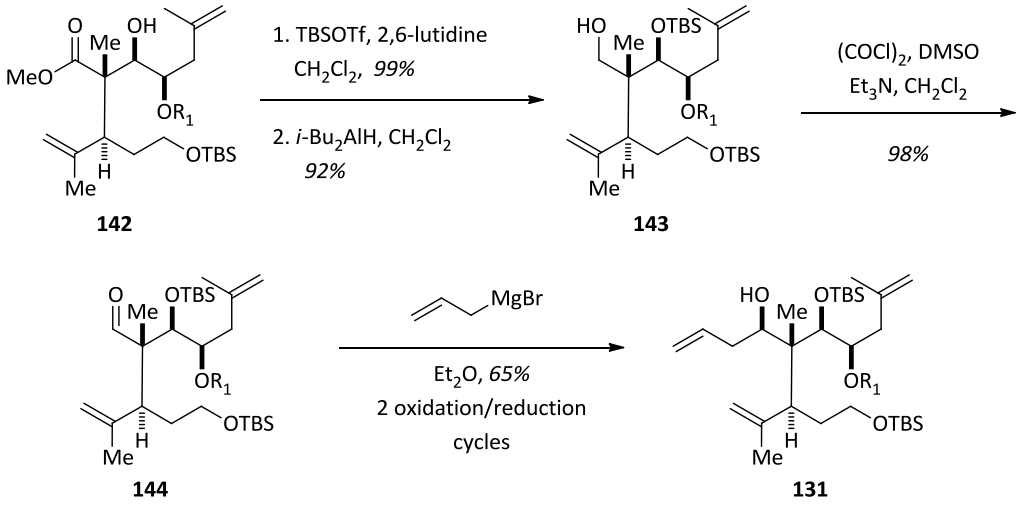
The coupling of the allylic alcohol **133** and the aldol adduct **118** was performed in the same manner as with the model systems described in chapter one (scheme 13). By combining both the allylic alcohol and aldol product with imidazole and DMAP, up to an 88% yield of **132** could be achieved if allowed to react for 96 hours (scheme 36). A 75% yield was achieved after stirring for a weekend (60 hours). The dianionic Ireland-Claisen rearrangement was

optimized to proceed in a maximum 65% yield by Zhang.[58] This moderate yield was tolerated because of the synthetic complexity added to the substrate in single operation.



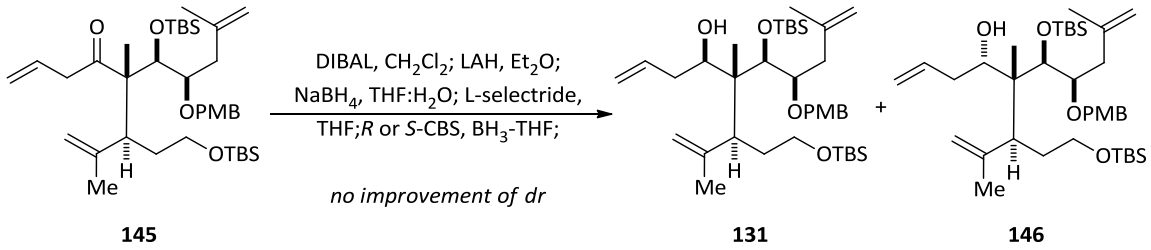
Scheme 36: Coupling to form the dianionic Ireland-Claisen substrate

Methyl ester **142** was elaborated to the homoallylic alcohol after protecting the free hydroxyl group as the TBS ether (scheme 37). Reduction with excess DIBAL afforded the primary alcohol **143** which was oxidized under Swern conditions to aldehyde **144**. Allylmagnesium bromide addition to **144** formed a 3:1 mixture favoring the undesired (*S*) diastereomer at C14 when cooled below 0 ºC. Executing the Grignard addition at 0 ºC afforded a 1:1 separable mixture.



Scheme 37: Synthesis of the C14 stereocenter via Grignard addition

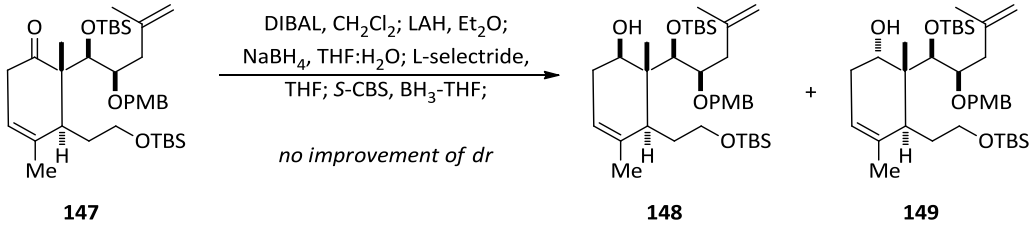
In attempts to improve on the isolated yield of the desired *R* diastereomer (**131**), a range of reducing conditions was investigated. When ketone **145** (acyclic) was reduced with DIBAL, LAH, $NaBH_4$, or L-selectride (*s*-Bu_3BHLi) no improvement above a 1:1 diastereomeric ratio was observed.



Scheme 38: Attempts to improve yield of desired alcohol diastereomer **131**

Belief that perhaps the cyclic ketone **147** would allow for some improved selectivity, examination again with DIBAL and $NaBH_4$ demonstrated no improvement, and in fact, resulted in poorer diastereomeric ratios.

Experimentation with the (*S*)-CBS chiral reducing catalyst in conjunction with borane•THF complex gave a 1:1 mixture of products.



147 **148** **149**

Scheme 39: Attempts to improve ratio of the *R* diastereomer at C14

Use of the (*R*)-CBS enantiomer afforded the undesired diastereomer almost selectively and will prove important later in the synthesis when this stereocenter must be inverted to match the natural product. The cause for this drastically different result can be understood by conformational analysis of the cyclic ketone **147**. With the presumed flagpole position of the angular quaternary carbon methyl group in a twist-boat conformation, the approach of the hydride source to achieve the (*R*) diastereomer at C14 would interact significantly with the cyclohexene ring (figure 10).

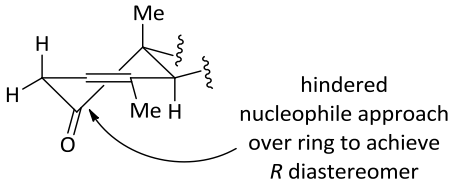
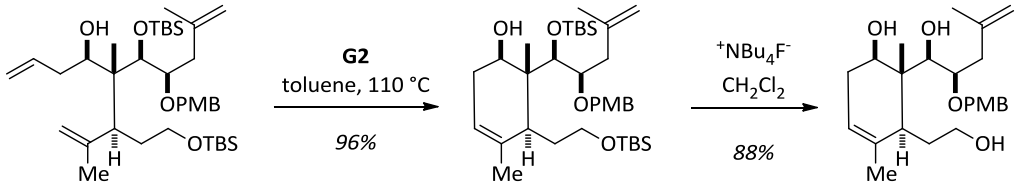


Figure 10: Depiction of unfavorable hydride approach with cyclic ketone **125**

Ring closing metathesis of diene **131** proceeded smoothly in degassed, refluxing toluene over the course of an hour (scheme 40). Global silyl deprotection of **150** utilizing TBAF afforded the triol **151** in 88% yield.

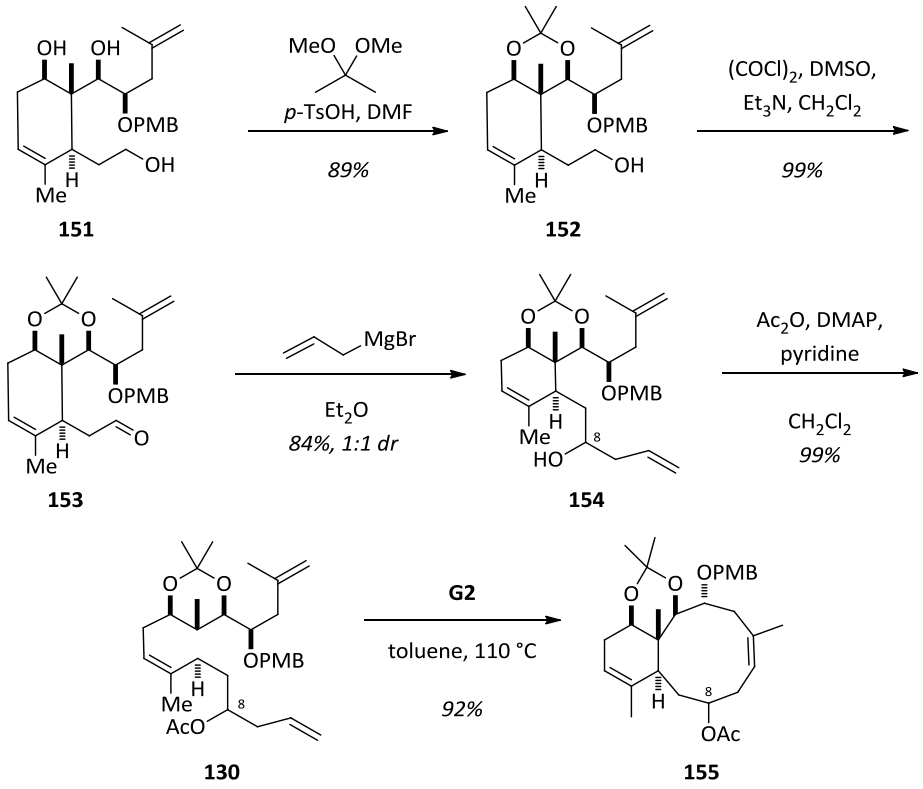


131 **150** **151**

Scheme 40: Synthesis of crystalline triol **151**

At this point, triol **151** was selectively protected as the 1,3 acetonide with dimethoxypropane and PTSA. X-ray crystallography confirmed the absolute stereochemistry of the crystalline **152** of the stereocenters at C1, C2, C3, C10, and C14. Swern oxidation of the resulting primary alcohol and subsequent allylmagnesium bromide addition afforded a 1:1 mixture of diastereomers at the C8 stereocenter. This was unfortunate, since only one of the two stereoisomers were capable of undergoing the ten membered ring closing metathesis. In previous studies,[58] a variety of chiral allylation substrates were examined to improve on the diastereomeric ratio of the allylation, however Zhang found no improvement was observed. Subsequent personal efforts to epimerize the C8 hydroxyl group and convert directly to the acetyl protected alcohol via Mitsunobu conditions ultimately failed after extensive experimentation. Further complicating the efforts to achieve a level of selectivity with the allylation of C8, the stereoisomer which was capable of forming the cyclodecene could not be determined by NMR after chemical derivitization (Mosher ester analysis) nor could a crystal structure be isolated after aryl acylation of the alcohol. However, the mixture of alcohols was able to be separated and recycled via an oxidation/reduction sequence of the alcohol.

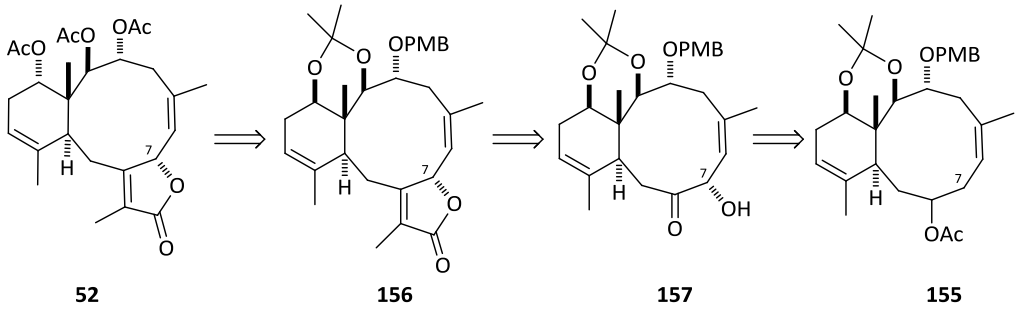
Acetate protection of the desired alcohol of unknonwn stereochemistry proceeded smoothly to give acetyl alcohol **130**. Exposure to Grubbs second generation catalyst in refluxing toluene for 15 minutes consumed the starting material and afforded a 96% yield of bicycle **155**.



Scheme 41: Completion of the bicyclic core of brianthein A

Endgame Strategy 1

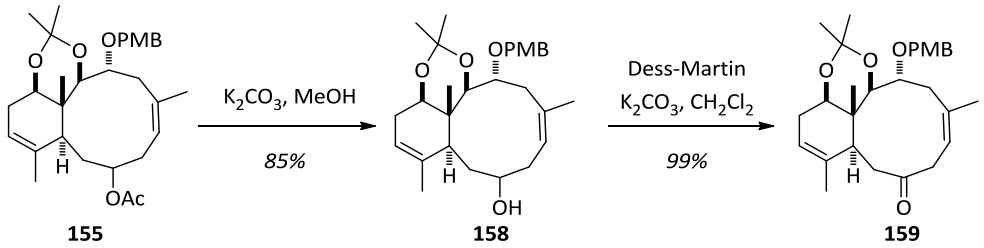
The synthesis of the 6,10 fused bicyclic core of brianthein A was an important achievement. The key synthetic challenges remaining to complete the total synthesis included the formation of the butenolide and epimerization of the hydroxyl group at C14. Elaboration to the butenolide was investigated and the planned endgame strategy is shown in scheme 42.



52 156 157 155

Scheme 42: Initial endgame strategy to complete brianthein A

The first challenge was to install the stereocenter at C7 by means of an alpha-hydroxylation reaction. Toward that end, bicycle **155** was treated with potassium carbonate and methanol to remove the acetate protecting group (scheme 43). Subsequent oxidation proceeded in excellent yield to afford ketone **159**.



155 158 159

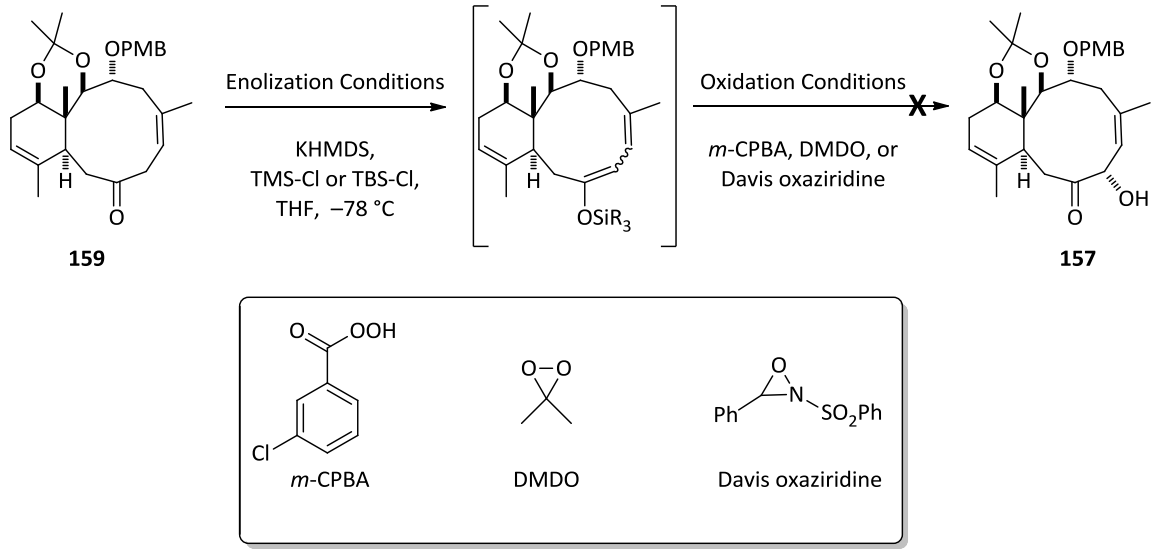
Scheme 43: Synthesis of ketone **159**

Alpha-oxidation studies

Standard conditions to form hydroxyketones involve the oxidation of an enolate intermediate. This can be performed directly after enolization with strong base, or the oxidation can be performed on an isolated enol intermediate, for example a silyl enol ether as is found in the Rubottom oxidation.[60] The deprotonation of ketone **159** was predicted to be complicated by a number of

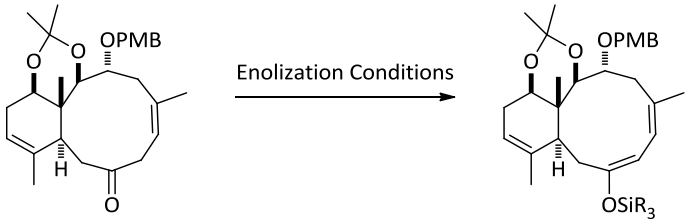
factors including the perceived flexibility of the cyclodecene ring and the regioselectivity of the enolization. The hydrogens at C7 were expected to be more reactive to deprotonation due to their higher acidity when compared to the hydrogens at C9. The option to isolate and purify the enol intermediate could be desirable with the late stage complexity of the synthesis; thus, Rubottom oxidation conditions were investigated first.

Initial experiments utilized potassium hexamethyldisilazide (KHMDS) to enolize ketone **159** and trap the enolate *in situ* as the trimethylsilyl enol ether (scheme 44). Without purification, treatment with *m*-chloroperoxybenzoic acid (*m*-CPBA), dimethyldioxirane (DMDO), or Davis oxaziridine as oxidant sources only resulted in complex mixtures from which very little could be discerned and the formation of the hydroxyketone was not able to be proven. In the event that multiple enol ether geometries or regioisomers were formed, an unselective oxidation of that mixture would result in potentially four or even more products if γ or δ oxidation also occurred due to activation by the formed enolate.



Scheme 44: Rubottom oxidation attempts to form hydroxyketone **157**

To better control the reaction conditions, the silyl enol ether intermediate was isolated and analyzed to determine and ensure its formation and purity. Deprotonation with potassium hexamethyldisilazide and subsequent trapping as the *tert*-butyldimethylsilyl ether afforded a 2:1 mixture of inseparable TBS silyl enol ethers **160** (Table 5). Attempts to synthesize the TMS enol ether were successful, however the resulting mixture was impossible to isolate due to its acid sensitivity. Identification of the components of the TBS enol ether **160** mixture proved difficult. ^{1}H NMR analysis showed multiple varying signals in the alkene region leading to the conclusion that either the base was not regioselective for C7 deprotonation or that both the *Z* and *E* enolate geometries were formed. Unfortunately, due to the presumed flexibility of the cyclodecene ring, any analysis of alkene *J*-coupling constants to determine enolate geometry was found to be inconsistent and difficult to obtain.



159 **160**

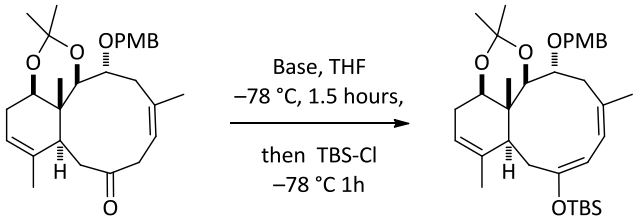
Base	Temperature	Ratio
$KN(SiMe_3)_2$/TBSCl	0 °C	2:1
$KN(SiMe_3)_2$/TBSCl	–78 °C	2:1
NEt_3/TBSOTf	–78 °C to rt	1.5:1
TMP/TBSOTf	–78 °C to rt	1:1
LTMP/TBSCl	–78 °C	N.R.

Table 5: Synthesis of silyl enol ether for the Rubottom oxidation

Attempts to control the reactivity of the deprotonation conditions with temperature or increased steric repulsion were unable to form a single product. Soft enolization with triethylamine and TBS triflate afforded the same silyl enol ether mixture in a 1.5:1 ratio (table 5). Conformational analysis and molecular modeling led to the understanding that deprotonating at C9 would likely involve a high amount of steric repulsion due to the proximity to both the bridgehead C10 and the protruding vinyl methyl group at C11. Exposure to the highly hindered lithium tetramethylpiperidine (LTMP) resulted in no reaction at –78 or 0 °C (table 5).

The puzzling result of no reaction with LTMP was a crucial observation in ultimately understanding the reactivity of the enolization of ketone **159**. A counterion study was performed utilizing the three major variants of metallated hexamethyldisilazides (table 6). In side-by-side reactions to maintain

consistency and reduce environmental variables, ketone **159** was treated to 3 equivalents each of lithium, sodium, and potassium hexamethyldisilazide at –78 °C for 1.5 hours. At that point, TBS chloride was added to the reactions and stirred for one hour while maintaining the temperature.



159 **161**

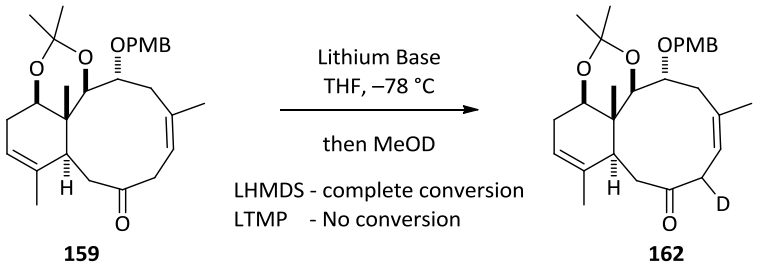
Base	**Conversion**
$LiN(SiMe_3)_2$	None
$NaN(SiMe_3)_2$	~50%
$KN(SiMe_3)_2$	100%

Table 6: Counterion study in formation of the silyl enol ether

Upon quench and isolation of the resulting mixtures, the approximate conversion of each reaction to silyl enol ether **161** was analyzed and found to correlate as expected. As previously observed with the potassium counterion, complete conversion to a mixture of silyl enol ethers resulted. No conversion was observed in the case of the lithium counterion and a 50% yield was obtained from the sodium counterion. Interestingly, increasing the temperature did not aid in the formation of the silyl enol ether before decomposition of the lithium enolate.

The counterion effect had shown some promise in understanding the reactivity of the enolization, albeit without any regioselectivity information. Yet,

the lack of conversion with the lithium counterion raised the question of whether enolization was occurring or if the enolate was not sufficiently reactive to the enol ether. To probe this question, a deuterium quenching study was performed to observe the reactivity of LHMDS with ketone **159**. Two dimensional NMR studies allowed for the successful assignment of the hydrogens at C7.

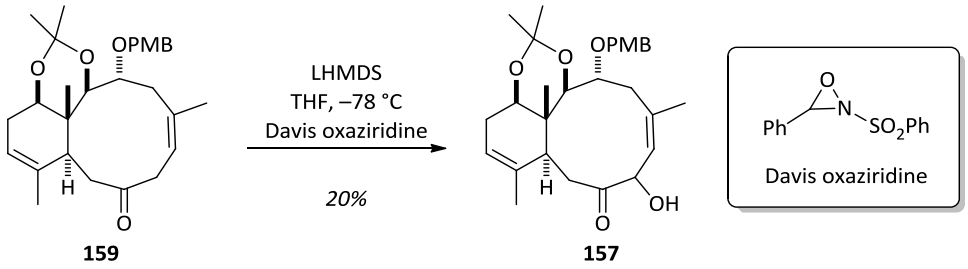


Scheme 45: Deuterium quenching study

Exposure of **159** (ketone) to three equivalents of LHMDS at –78 °C for one hour was followed by addition of deuterated methanol to quench the reaction. After workup and isolation of the crude product, ^{1}H NMR showed the complete consumption of the desired hydrogen signal at C7. In addition, no evidence of any side reactions or deprotonation at C9 was observed (scheme 45). Interestingly, the same deuterium quenching experiment performed with the more hindered LTMP base did not deprotonate at either C7 or C9, which supported the results observed previously (tables 5 and 6).

The results of the deuterium quenching study ruled out the feasibility of utilizing LHMDS as a base to effect the conversion of **159** to a silyl enol ether. However, successful and selective enolization with LHMDS could allow for the direct oxidation of the lithium enolate to the desired hydroxyketone. Toward this

end, ketone **159** was deprotonated with LHMDS at –78 °C for 1 hour and treated with an excess of Davis oxaziridine. The resulting crude mixture resulted in a 20% yield of the desired hydroxyketone **157**, which unfortunately was extremely difficult to purify due to the similar polarity of the phenylsulfonylimine byproduct from the oxaziridine reagent. Only if carried forward could the material be completely purified.

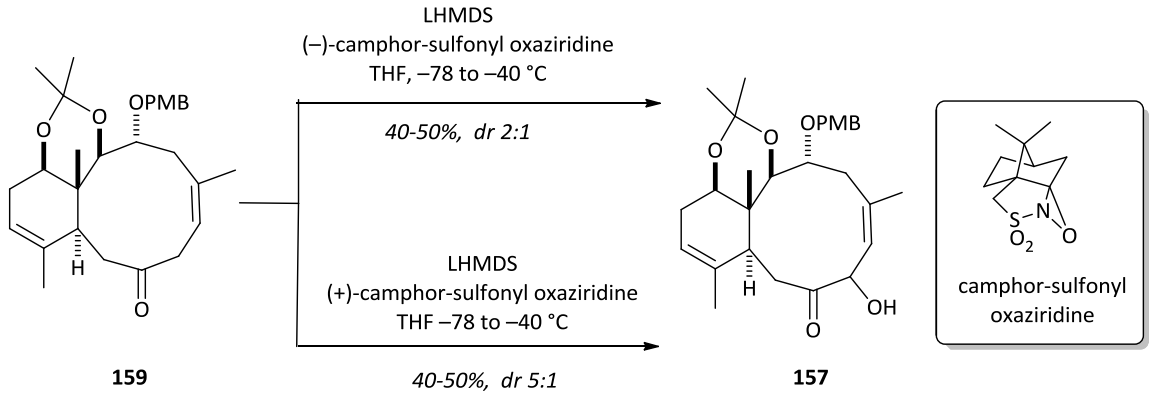


Scheme 46: Synthesis of the hydroxyketone **157**

The diastereoselectivity of the enolate oxidation was expected to be controlled significantly by the substrate's conformation. The diastereomeric ratio of the impure hydroxyketone could not be determined with significant confidence. Modification of the reaction conditions to utilize the chiral camphorsulfonyl oxaziridine in place of the racemic phenylsulfonyl oxaziridine was expected to improve the diastereoselectivity.

Ketone **159** was oxidized with both enantiomers of camphorsulfonyl oxaziridine (scheme 47). As expected, the polarity change of the imine byproduct changed significantly to allow for complete purification of the resulting hydroxyketone. In both cases, the yield of the oxidation was a quite disappointing 50%. Interestingly, both enantiomers afforded the same major

stereoisomeric product. The (+)-camphorsulfonyl oxaziridine provided a 5:1 mixture and the (–)-camphorsulfonyl oxaziridine afforded a 2:1 mixture. In all cases, the mixture of diastereomers was inseparable. Further extensive optimization of the reaction conditions were unable to significantly improve the yield, however the diastereoselectivity was improved to a single detectable diastereomer by ^{1}H NMR through careful synthesis and purification of the (+)-camphorsulfonyl oxaziridine.[61]



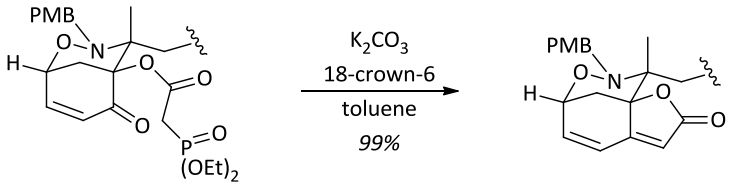
Scheme 47: Improved synthesis of hydroxyketone **157**

Literature precedent for butenolide synthesis

The hydroxyketone functional group was the desired handle needed to access the butenolide moiety.[62] It was anticipated that by esterifying the hydroxyl group with a phosphonate, a beta-ketophosphonate could be accessed allowing for a Horner-Wadsworth-Emmons (HWE) olefination reaction to form the butenolide. There existed numerous examples in the literature of this reaction with a variety of conditions. A number of examples will be reported for clarity.

In their attempt to synthesize natural products from the securinega alkaloid family, Carson and Kerr achieved the synthesis of the butenolide

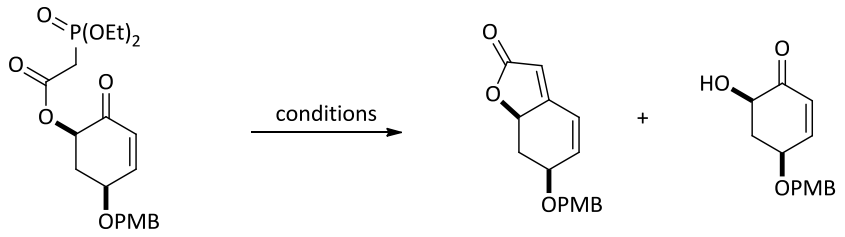
containing (+)-phyllantidine via a HWE olefination (scheme 48).[63] Utilizing 18-crown-6 to sequester the potassium ion, an excellent yield of the butenolide **164** was achieved.



163 **164**

Scheme 48: Carson and Kerr synthesize butenolide **164**

Another example of employing the HWE olefination toward accessing the butenolide functional group in natural product synthesis was in the synthesis of Phyllanthurinolactone (table 7).[64] Ueda was challenged by competing reactions. Lithium bromide (LiBr) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) conditions or only DBU as the employed basic conditions, exhibited a high propensity to deacylate the phosphonate **165** giving hydroxyketone **167**. Employing stronger basic conditions with sodium hydride (NaH) afforded the best yields of the desired butenolide **166**.

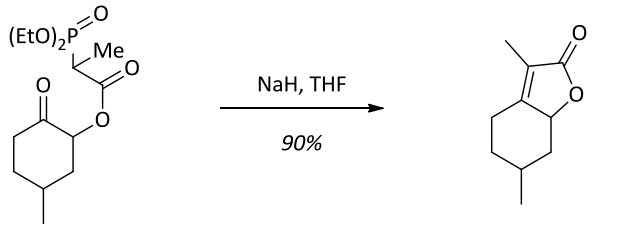


165 **166** **167**

Entry	Conditions	Prod. Yield%
1	LiBr:DBU (2:1 equiv.), THF –78 to –30 ^{o}C	**167** (59%) Hydroxyketone
2	DBU (1.0 equiv), THF, rt	Complex mixture
3	NaHMDS (1.0 equiv.), THF, –78 ^{o}C	Complex mixture
4	K_2CO_3 (1.2 equiv.), THF, rt	**166** (29%) Butenolide
5	NaH (0.5 equiv), THF, 0 ^{o}C	**166** (42%) butenolide

Table 7: Sampled conditions for synthesis of butenolide **166** by Ueda

A notable difference between the previous examples and the desired butenolide for brianthein A, was the methyl substitution at the alpha-position of the fused butenolide (**52**). However, in their synthesis of racemic mintlactone,[65] Tanyeli and co-workers described the synthesis of an alpha-methyl substituted butenolide, again with sodium hydride as base (scheme 49).

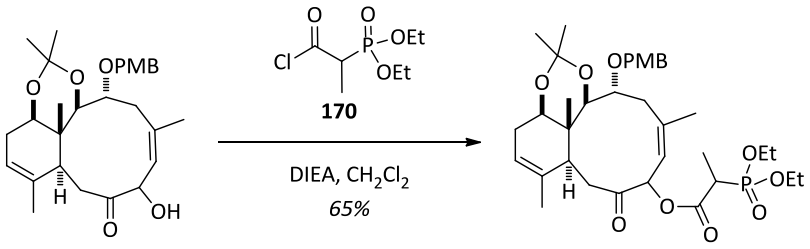


168 **(±)-mintlactone**

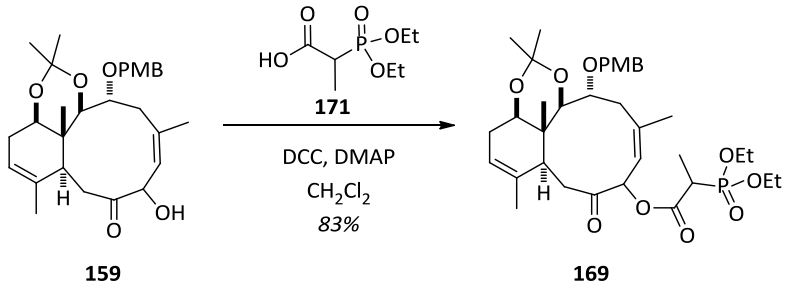
Scheme 49: Tanyeli synthesis of mintlactone

Attempted formation of butenolide

Acylation of the hydroxyketone **157** with the acid chloride **170** proceeded acceptably in 65% yield. Standard coupling conditions utilizing the carboxylic acid **171** in conjunction with DCC and DMAP to afford the desired *beta*-keto-phosphonate **169** was successful in an improved 83% yield (scheme 50).



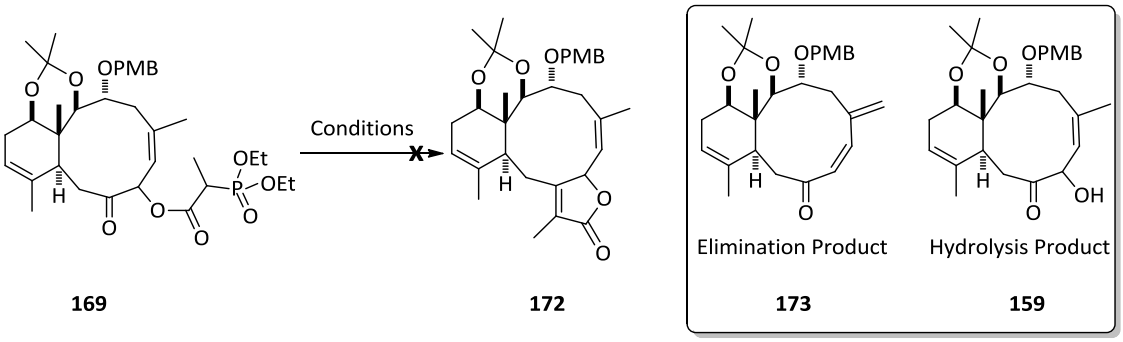
Scheme 50: Acid chloride acylation of hydroxyketone **157**



Scheme 51: Improved phosphonate formation via carbodiimide coupling

At this point, conditions for the HWE olefination were examined. Unfortunately, no evidence for the successful formation of the butenolide was ever obtained. Treatment with potassium *tert*-butoxide in dimethoxyethane resulted in the elimination product **173** (table 8). If the strength of the basic

conditions were tamed, less elimination was observed, but then the major problem became hydrolysis to the hydroxyketone **159**. The elimination of the allylic ester position is easily understood to be favorable due to the steric accessibility of the vinyl methyl group to strong hindered bases, in addition to the excellent leaving group characteristics inherent to the phosphonate moiety. Extensive experimentation with various conditions yielded only undesired products or no reaction at all.



169 **172** **173** **159**

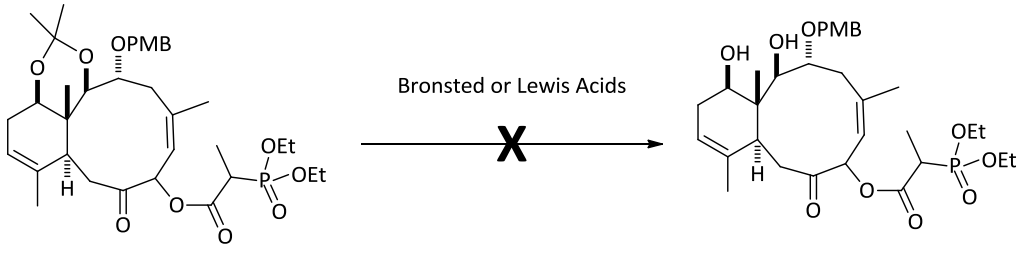
Base	Solvent	Temperature	Result
t-BuOH/K_2CO_3	DME	reflux	Elimination
t-BuOH/K_2CO_3	DME	rt	Elimination
$Ba(OH)_2$	THF/H_2O	rt	Hydrolysis
K_2CO_3/18-crown-6	THF	rt	No reaction
LiCl/DBU	acetonitrile	0 °C, rt, reflux	elimination and hydrolysis

Table 8: Attempts to synthesize butenolide **172**

Conformational analysis of the olefination reaction led to the observation that perhaps the structure was *too* rigid to allow for successful butenolide synthesis. Up to this point, the substrate had been rigidified to reinforce the conformational restraints necessary to achieve the ring closing metathesis reaction of the ten membered ring. It was believed that the same conformational

restraints could now be hindering the formation of the butenolide ring. To test to this theory, it was proposed that deprotection of the acetonide to diol **174** would afford a less rigid substrate (table 9).

Attempts to remove the 1,3-acetonide protecting group proved to be quite challenging. Initially, beta-ketophosphonate **169** was treated with various acids in methanol with no success, only hydrolysis of the ester to revert to the hydroxyketone **157** was able to be isolated. Subsequent experiments with **157** were also unable to obtain any of the desired diol product.



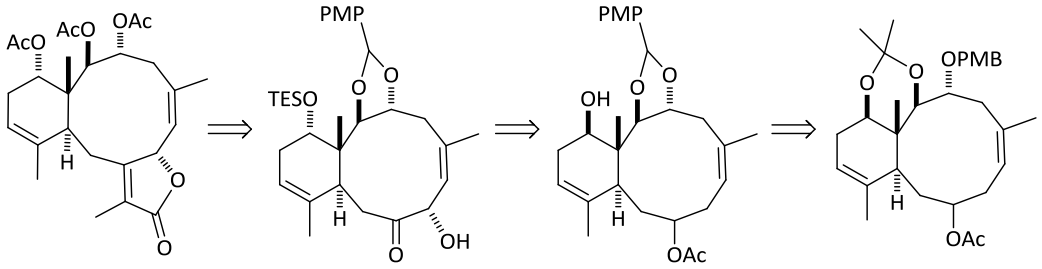
169 **174**

Acid	Solvent	Temperature	Result
10 % *aq.* HCl	MeOH	rt/60 °C	Decomposition
PPTS	MeOH	rt /60 °C	No Reaction
PMA	MeOH	rt	No Reaction
p-TsOH	MeOH	rt	Decomposition
CSA	MeOH	rt	Decomposition
Dowex Resin	MeOH	rt	Decomposition
Amberlyst Resin	MeOH	rt	Decomposition
BCl_3	CH_2Cl_2	rt	Hydrolysis
$BiCl_3$	CH_2Cl_2	rt	No Reaction

Table 9 Attempts to remove the acetonide protecting group

Endgame Strategy 2

The struggles with installing the hydroxyketone and butenolide amplified the need to modify the endgame strategy to complete the total synthesis of brianthein A. Reverting back to intermediate bicycle **155**, a revised endgame strategy was conceived.



52 **175** **176** **155**

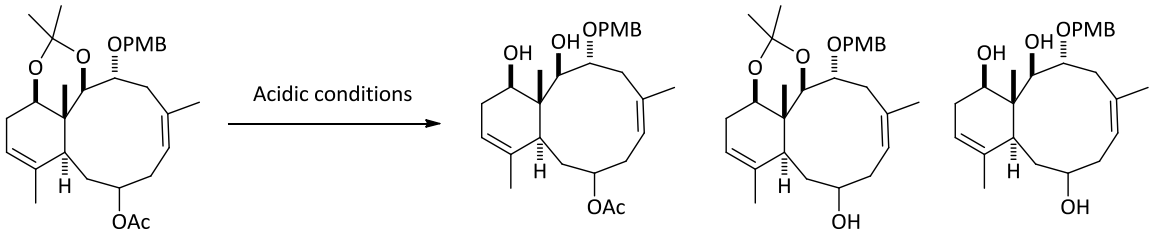
brianthein A

Scheme 52: Revised endgame strategy to complete brianthein A

In this strategy, the northern section of the molecule would be elaborated to include the correct hydroxyl stereochemistry at C14 before incorporating the butenolide (scheme 52). Conformational analysis supported the theory that with a less rigid substrate and the correct stereochemistry of brianthein A, formation of the butenolide could be more favorable.

First, acetonide deprotection conditions were investigated (table 10). As found previously, the 1,3-acetonide protecting group was quite stable and difficult to selectively remove. In many cases, the acetate protecting group of the hydroxyl at C8 was removed in addition to the acetonide. With *p*-TSA, it was observed that acetonide deprotection occurred slightly faster than acetate deprotection. This effect was not as apparent with any other acetonide

deprotection conditions. Thus, with limiting the time of the reaction and recycling the recovered starting material, an overall 60% yield could be obtained through two recycles. By limiting the reaction to 6 hours, the yield of the desired diol **178** was maximized and the amount of recovered triol **179** was minimized. The triol formed in a significant quantity if the reaction was allowed to progress over an extended period of time because the product of either the acetate or acetonide deprotection (**158** or **178**) remains susceptible to further acid catalyzed deprotection.



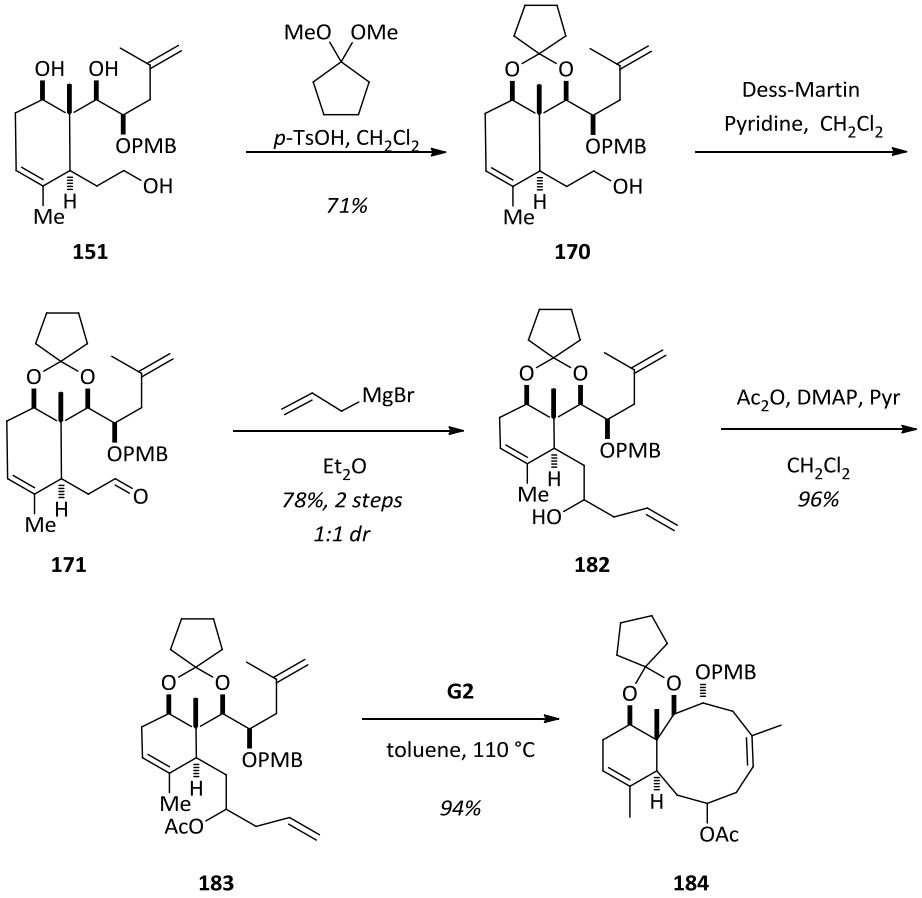
155 **178** **168** **179**

desired product acetate deprotected triol

Acid	Solvent	Temperature	Result
10 % *aq.* HCl	MeOH	rt/60 °C	Decomposition and triol
PPTS	MeOH	rt/60 °C	No reaction
PMA	MeOH	rt	Decomposition
p-TsOH	MeOH	rt	34% diol (6h)
CSA	MeOH	rt	Triol only
Dowex Resin	MeOH	rt	Decomposition
Amberlyst-15 Resin	MeOH	rt	Decomposition
BCl_3	CH_2Cl_2	rt	Decomposition
$BiCl_3$	CH_2Cl_2	rt	Decomposition

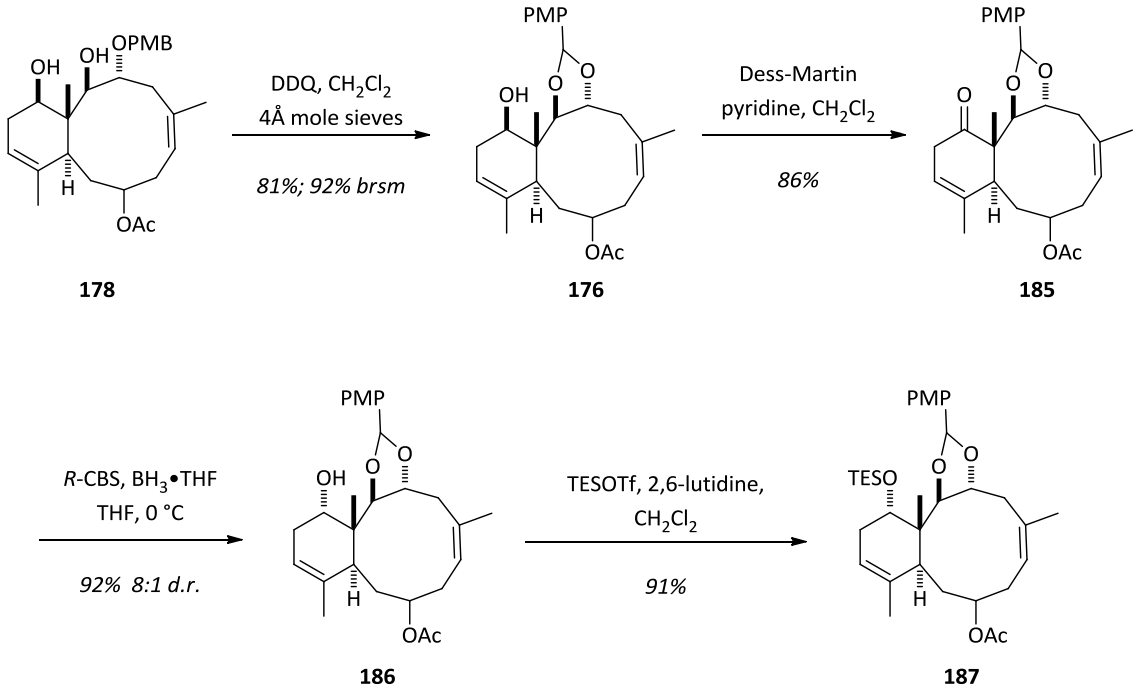
Table 10: Attempt at removing the acetonide protecting group

In an effort to improve the selectivity of the acetonide deprotection, the structure of the acetonide was examined. As shown previously, the characteristics and functional groups required to achieve the ring closing metathesis reaction to form bicycle **155** were very specific. Modifying the protecting group to the cyclopentylidine acetal (scheme 53) proved to be amenable to the ring closing metathesis conditions and the ten membered ring product **184** was formed in 94% yield. Unfortunately, the cyclopentylidine acetal did not improve the yield of diol obtained with *p*-TSA in methanol.



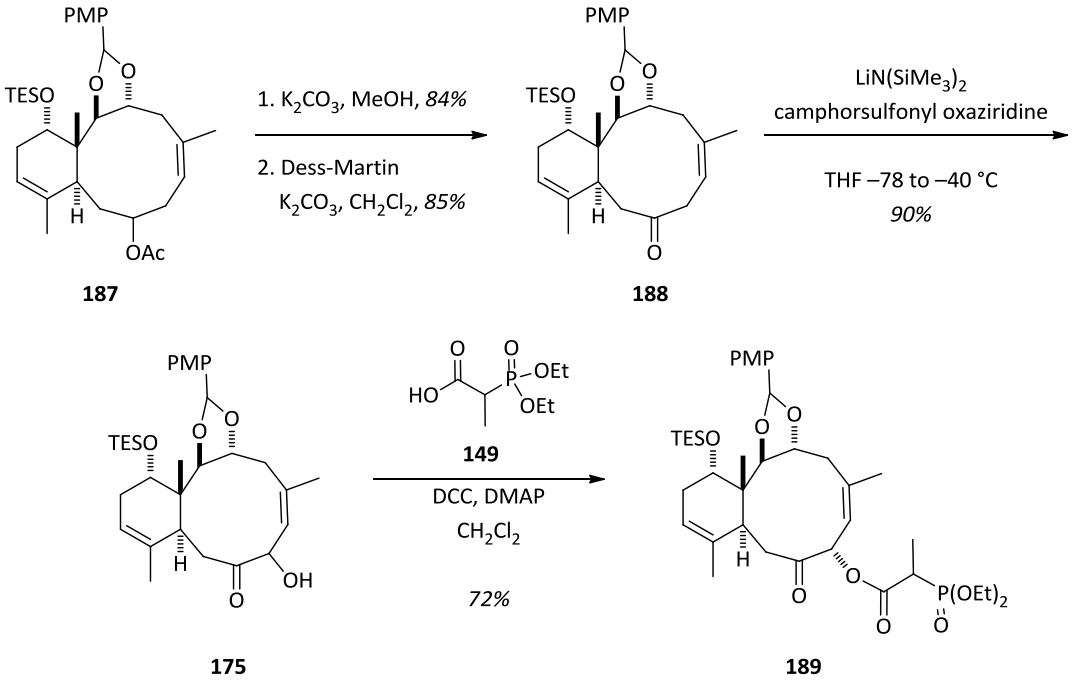
Scheme 53: Synthesis of cyclopentylidine acetal **184**

Diol **178** was converted to the *para*-methoxybenzilidine acetal through exposure to DDQ in dilute methylene chloride with 4Å mole sieves (scheme 54).[66] Achieving complete conversion was an unexpected challenge. Recrystallized DDQ did not improve the rate of conversion to acetal **176**; only by adding excess quantities of DDQ did the acetal formation proceed to near completion in 81% yield. Oxidation of the C14 hydroxyl group to ketone **185** was achieved smoothly in 86% with Dess-Martin periodinane buffered with pyridine in dichloromethane. A number of reduction conditions were investigated to achieve the reduction to the desired hydroxyl diastereomer **186**. Standard achiral metal hydride reductions were unsuccessful in creating any useful diastereomeric ratio. Fortunately, the use of the chiral oxazaborolidine Corey-Bakshi-Shibata catalyst (CBS) in combination with borane-tetrahydrofuran (BH_3 • THF) complex afforded significant diastereoselectivity as was observed previously (scheme 34). Treatment of ketone **185** with *R*-CBS in tetrahydrofuran followed by addition of BH_3 • THF complex afforded in 92% yield an 8:1 mixture of diastereomers favoring the desired *S* configuration (**186**). Protection of the resulting alcohol as triethylsilyl ether **187** was successful in 91% yield.



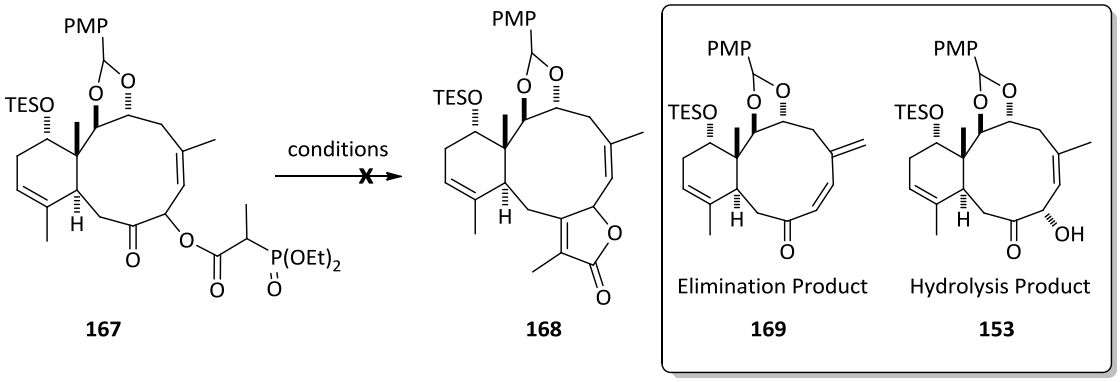
Scheme 54: Synthesis of the correct stereoisomer at C14

The entire northern section of intermediate **187** matched the stereoconfiguration of the target brianthein A (**52** figure 3). Elaboration of the acetate protected hydroxyl group at C8 to the butenolide was carried out as before. Deprotection of the acetate with potassium carbonate and methanol afforded the alcohol, which was then oxidized to ketone **188** with potassium carbonate buffered Dess-Martin oxidation conditions in methylene chloride in a 71% yield over the two steps (scheme 55). Formation of the hydroxyketone **175** proceeded in an improved yield of 90% with varying amounts of recovered starting ketone. The basis for this improvement in reaction yield and conservation of the starting material was unclear, yet presumed to be substrate related. Acylation of the hydroxyketone with DCC, DMAP and the carboxylic acid **171** afforded *beta*-ketophosphonate **189** in 72% yield.



Scheme 55: Synthesis of phosphonate **189**

Phosphonate **189** needed only to be treated with base to undergo the desired Horner-Wadsworth-Emmons olefination reaction. Unfortunately, after extensive investigation of reaction conditions, no evidence for butenolide formation could be realized. The reactivity patterns were very similar as with the previous endgame strategy. With stronger bases, elimination product **191** prevailed. The use of metals and weaker bases resulted in either no reaction or hydrolysis of the ester to revert back to the hydroxyketone (**175** table 11).

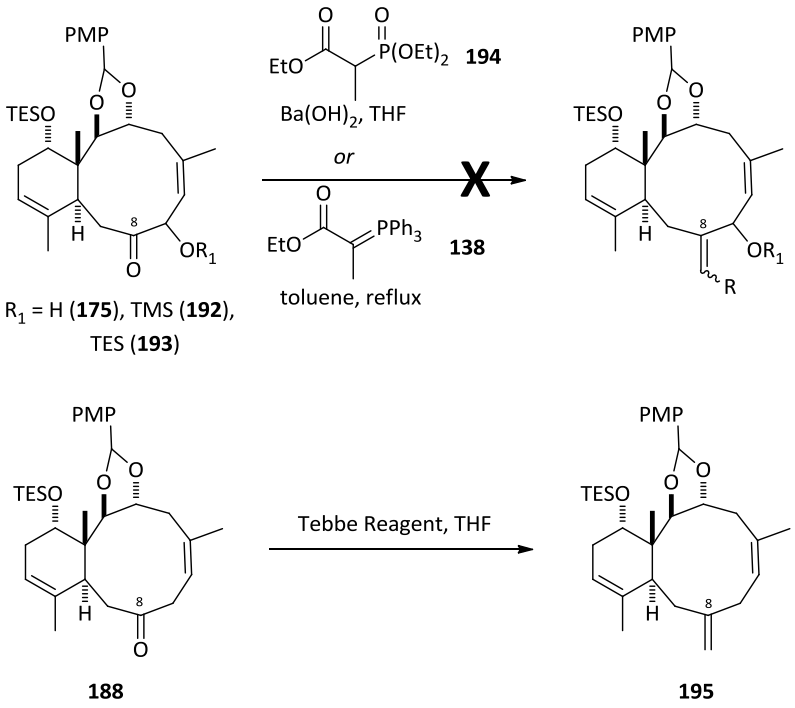


167 168 169 153

Base	Solvent	Temperature	Result
LHMDS	THF	rt	Elimination
NaH	THF	rt	Elimination
LiBr	TEA	rt	No reaction
K_2CO_3/18-crown-6	THF	rt	No reaction
K_2CO_3/18-crown-6	THF	reflux	No reaction
K_2CO_3/18-crown-6	toluene	reflux	No reaction
LiCl/DBU	acetonitrile	0 °C, rt, reflux	elimination and hydrolysis

Table 11: Attempts to synthesis butenolide **168**

These disappointing results led to the consideration of a number of other strategies to synthesize the butenolide ring. To examine the ability of the ketone at C8 to form an sp^2 carbon-carbon bond, a number of intermolecular olefination conditions were examined.

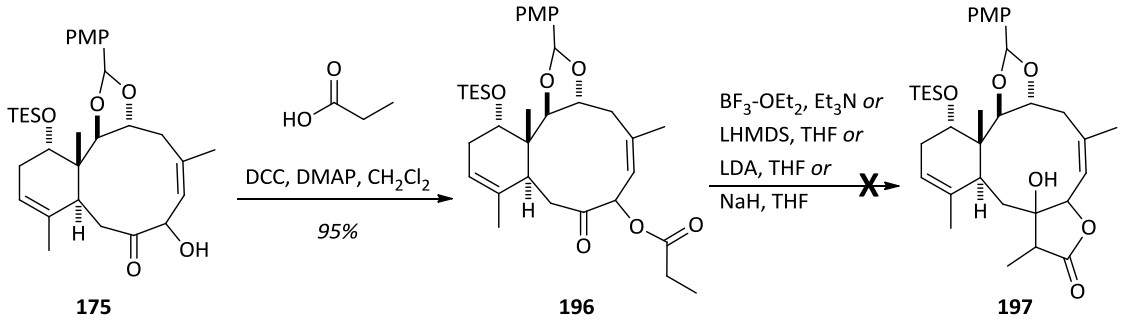


Scheme 56: Investigation of sp^2 carbon-carbon bond formation at C8

Only the Tebbe reagent was able to react with ketone **188** and only under specific substrate conditions. The presence of the alpha-hydroxyl group to the ketone presumably imparted too much of a steric challenge for any of the intermolecular olefination conditions, including the Tebbe olefinating reagent. However, the *exo*-methylene was formed when the alpha-hydroxyl group was removed.

This formation of an exo-olefin (**195**) only proved that an sp^2 carbon could be synthetically added at that position, but the sterics effects of the substrate, especially the hydroxyl group, seemed to play a very significant role in the accessibility of the C8 carbon. Understanding that the acylation of the

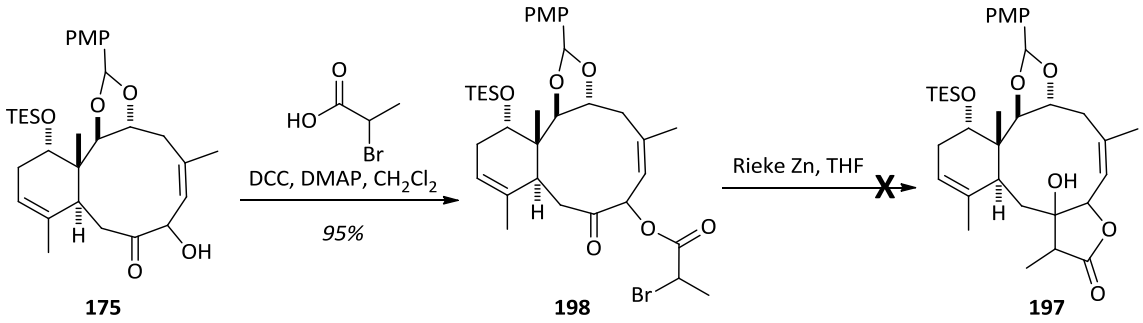
hydroxyketone was possible, a number of other strategies utilizing the hydroxyketone moiety as a synthetic handle were pursued.



Scheme 57: Attempts to form lactone via aldol chemistry

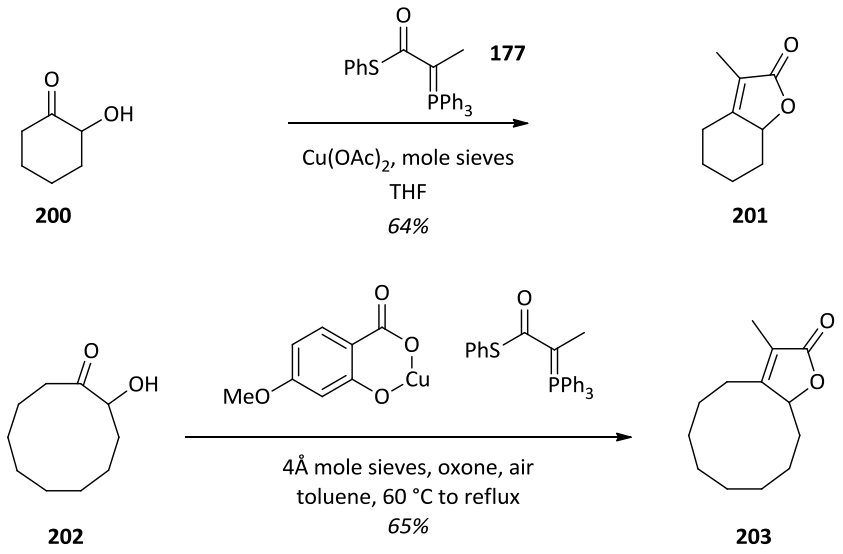
In an attempt to achieve an aldol reaction to form a tertiary hydroxyl group that could then be eliminated to result in the desired butenolide, hydroxyketone **175** was successfully acylated with propionic acid under the same DCC coupling conditions previously reported (scheme 57). Treatment of the resulting ester **196** with basic conditions including LHMDS, LDA, and NaH all led to complete decomposition of the substrate or elimination products as was previously observed. Soft enolization utilizing boron trifluoroetherate ($BF_3 \bullet OEt_2$) and triethylamine (TEA) resulted in decomposition and hydrolysis of the ester reverting backwards to the hydroxyketone.

In a similar manner, Reformatsky conditions were investigated. Acylation with the 2-bromopropionic acid was successful with the same DCC coupling conditions (scheme 53). Treatment with Rieke zinc consumed the starting material, yet yielded the hydrolysis and elimination products (**191**, **175**).



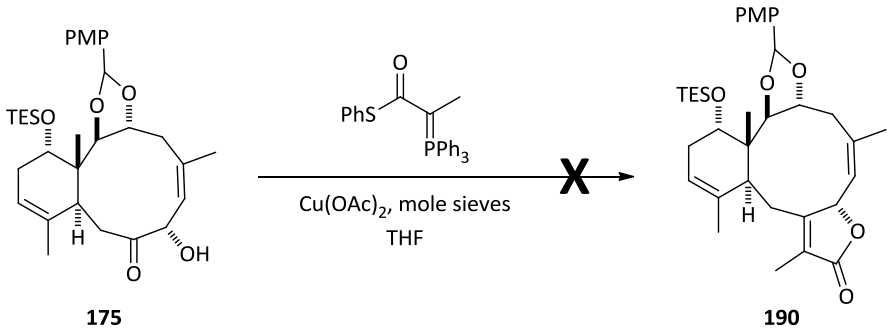
Scheme 58: Reformatsky conditions to form lactone **197**

The lack of successful butenolide closure was disappointing; however, a review of the literature provided a new reagent and conditions which had recently been developed by Shindo to synthesize butenolides in a single synthetic step from the hydroxyketone functional group.[67] Utilizing thioester tethered triphenylphosphine ylide **199**, Shindo had reported the mechanism of action to involve first a fast acylation of the hydroxyketone with the thioester (scheme 59). Following acylation, heating of the reaction would promote intramolecular Wittig olefination affording butenolides in a variety of substrates. In reviewing the substrates and published procedures, the variability of the hydroxyketone complexity was encouraging for the application of the methodology to the brianthein A synthesis.



Scheme 59: Investigation of Shindo's conditions to form butenolides

Initial catalyst preparation and experimentation on model substrates was successful, however required a fair amount of optimization. Unfortunately, when the optimized conditions utilizing the copper(II) salicylate catalyst were applied to the brianthein A substrate, no reaction was observed (scheme 60). Extensive attempts to modify Shindo's reaction conditions failed to produce any fruitful reaction. Attempts to solely acylate the hydroxyketone moiety **175** without effecting the Wittig reaction were equally unsuccessful. Without the acylation of the hydroxyketone, the Wittig olefination would not be successful as previous research had demonstrated (scheme 54).



Scheme 60: Attempt to synthesize butenolide **168**

Summary

Although the 6,10-fused carbon bicyclic core of brianthein A (**52**) has been successfully synthesized, the total synthesis of brianthein A continues to remain an elusive challenge. The challenges associated with specific peripheral functional group modification on a highly complex substrate is a significant challenge in organic synthesis. All stereocenters with the exception of that at C7 have been confirmed as matching that of the natural product brianthein A. Being unable to successfully elaborate the fused butenolide ring has created the need to prepare new synthetic strategies to access the briarane class of natural products. Efforts toward achieving the total synthesis of brianthein A, utilizing the quaternary carbon forming dianionic Ireland-Claisen rearrangement, yet allowing for installation of the butenolide at an earlier phase of the synthesis, are ongoing.

Chapter 3

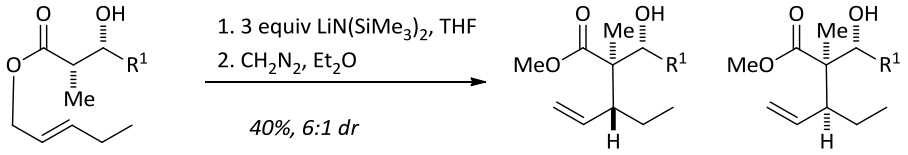
Experimental

Materials and Methods

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Nulear magnetic resonance (^{1}H, ^{13}C, COSY, NOESY) spectra were recorded on Bruker model Avance 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker model Avance 600 (^{1}H at 600 MHz; ^{13}C at 150MHz) instruments. Optical rotations were determined using a Jasco P1010 polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad with non-electrospray ionization. Thin-layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from EMD Chemicals Inc. Flash column chromatography was carried out using Ultra Pure Silica Gel Silia-P (40-64 μm) purchased from SiliCycle Inc. Diethyl ether (Et2O), tetrahydrofuran (THF), dichloromethane (CH2Cl2), and toluene (tol) were dried by being passed through a colun of netural alumina under nitrogen immediately prior to use. Alkylamines were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under reduced pressure and stored over 4Å molecular sieves. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich chemical company in 1L

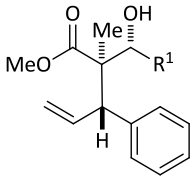
Sure/Seal™ bottles. Pivaloyl chloride was distilled and stored over 4Å molecular sieves. Methallyl iodide was isolated and stored over copper wire at -20 °C. Dess-Martin periodinane was prepared according to literature procedures and stored at -20 °C. Sodium bis(trimethylsilyl)amide was prepared according to literature procedures and stored under argon and protected from light. Grubbs second generation catalyst was purchased from Aldrich Chemical Company and stored under argon. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of argon and conducted under an argon atmosphere.

Experimental



To a flame dried flask with stir-bar was added HMDS (0.412g, 2.55mmol) and THF (8mL). After cooling to -78 C, *n*-BuLi (1.467M, 1.7mL, 2.5mmol) was added and stirred for 2 hours. Allylic ester **31** was diluted in THF (2mL) and added dropwise by syringe to the stirring reaction. After 2 hours, the reaction was warmed to room temperature over another 2 hours and stirred overnight. Quenched with 10% aq. HCl until pH=2. Layers separated and the aqueous was extracted with ethyl acetate (3x10mL). Combined organics were dried over magnesium sulfate, filtered and concentrated. Crude oil was diluted in diethyl ether (5mL), cooled to 0 C and diazomethane was added by pipette until bubbling ceased. Acetic acid was added to quench excess diazomethane.

Solution was then concentrated under vacuum and purified by flash column chromatography (5% EtOAc/Hex) to yield 82.3mg of a clear oil in a varying mixture of unseparable diastereomers ranging from 3:1 to 6:1 favoring **35**. ^{1}H NMR of mixture (600MHz , $CDCl_3$) □ = 5.87 - 5.73 (m, 6 H), 5.56 (td, *J* = 10.0, 16.9 Hz, 3 H), 5.28 (td, *J* = 1.5, 16.9 Hz, 2 H), 5.24 (td, *J* = 1.5, 17.3 Hz, 2 H), 5.20 - 5.14 (m, 3 H), 5.13 (d, *J* = 1.9 Hz, 1 H), 5.08 (d, *J* = 2.3 Hz, 1 H), 5.06 (t, *J* = 2.3 Hz, 1 H), 5.04 (d, *J* = 2.3 Hz, 1 H), 4.96 (dd, *J* = 2.3, 16.9 Hz, 2 H), 4.45 (br. s., 1 H), 4.14 - 4.09 (m, 1 H), 3.63 (s, 3 H), 3.62 (s, 3 H), 3.05 (d, *J* = 10.2 Hz, 1 H), 2.45 (dt, *J* = 2.3, 11.7 Hz, 1 H), 2.06 (dt, *J* = 2.6, 10.9 Hz, 1 H), 1.89 (br. s., 1 H), 1.67 - 1.55 (m, 4 H), 1.15 (s, 3 H), 1.04 (s, 3 H), 0.83 (t, *J* = 7.3 Hz, 3 H), 0.79 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (150MHz , $CDCl_3$) □ = 176.4, 139.2, 137.8, 137.0, 136.6, 117.8, 117.5, 117.3, 116.7, 77.2, 76.8, 75.4, 75.2, 54.3, 54.1, 52.4, 51.5, 51.4, 49.8, 21.8, 20.6, 14.8, 14.5, 12.5, 12.3; IR (film) 3502.1, 2961.16, 1731.76, 1455.99, 1224.58, 997.98, 921.81, 512.00 cm^{-1}; $[\alpha]^{23}_{D}$ = +9.5^{o} (*c* .3, CH_2Cl_2); MS (ESI) calculated for $C_{20}H_{27}NO_5$ $[M+H]^+$: 213.1413 , found: 213.1513.



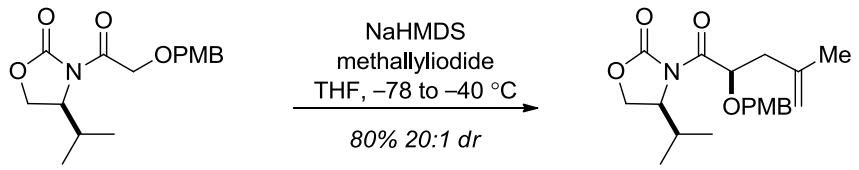
^{1}H NMR (600MHz ,$CDCL_3$) □ = 7.35 (d, *J* = 7.9 Hz, 2 H), 7.29 (t, *J* = 7.5 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 6.27 (td, *J* = 10.2, 16.6 Hz, 1 H), 5.72 (ddd, *J* = 6.4, 10.5, 16.9 Hz, 1 H), 5.19 (d, *J* = 16.9 Hz, 1 H), 5.14 (d, *J* = 10.5 Hz, 1 H), 5.10 (d, *J* = 7.5 Hz, 1 H), 5.08 (s, 1 H), 4.12 (d, *J* = 9.8 Hz, 1 H), 3.69 - 3.63 (m, 4

H), 3.51 (d, *J* = 10.5 Hz, 1 H), 1.02 (s, 1 H); ^{13}C NMR (151MHz ,$CDCL_3$) □ = 176.2, 138.8, 136.4, 136.3, 129.7, 128.1, 126.9, 117.7, 117.4, 77.2, 76.8, 75.3, 54.9, 52.5, 51.8, 14.8; IR (film) 3495.35, 2949.59, 2360.44, 2341.16, 1720.19, 1454.06, 1225.54, 1108.87, 1039.44, 994.125, 922.771, 754.031 cm^{-1}; $[\alpha]^{23}_D$ = $+1.87^o$ (*c* 3.33, CH_2Cl_2); MS (ESI) calculated for $C_{20}H_{27}NO_5$ $[M+Na]^+$: 283.1311, found: 283.1258.

General Procedure for Dianionic Ireland-Claisen Rearrangement:

In a flame dried round-bottom flask equipped with a stirbar, 3.1 equivalents of HMDS was added. THF was added to bring reaction concentration to 0.5M. After cooling to 78 C, 3.0 equivalents of *n*-Butyllithium were added and stirred for 1 hour. Allylic ester was then diluted in THF (1M) and added dropwise by syringe. The reaction was stirred for 2 hours at -78 C, then warmed over two hours to room temperature. After stirring at room temperature for 4-6 hours, the reaction was heated to reflux for 12-16 hours. The reaction was cooled to 0 C in an ice-water bath and treated with 10% aq. HCl to quench any remaining base and acidify the carboxylic acid. With a pH = 2, the reaction was quickly separated and extracted with ethyl acetate three times and washed with brine. The combined organics were dried over anhydrous magnesium sulfate, filtered and concentrated. The resulting crude oil was diluted in diethyl ether (0.1M) and cooled to 0 C. Freshly prepared diazomethane added to the solution until bubbling ceased. Excess diazomethane was quenched with acetic

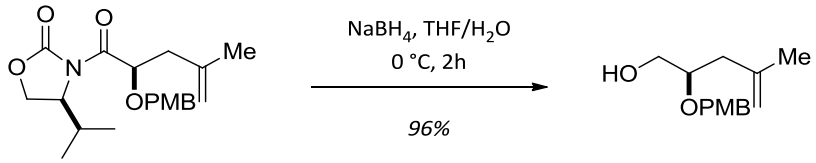
acid. The reaction was then concentrated under vacuum and purified by flash chromatography.



139 **140**

Into a flask equipped with an addition funnel and a low-temperature thermometer was added sodium bis(trimethylsilyl)amide (0.80 M in toluene/THF, 62.6 mL, 50.07 mmol, 1.5 eq) and 250 mL of THF. The solution was cooled to –78 ^{o}C and a solution of glycolate **139** (10.26 g, 33.38 mmol, 1.0 eq) in THF (50 mL) was added slowly via addition funnel to keep the internal temperature below –65 ^{o}C. After stirring for 30 minutes at –78 ^{o}C, methallyl iodide (89.5 wt% in pentane, 33.92 g, 166.91 mmol, 5.0 eq) was added to the reaction mixture dropwise via addition funnel. The solution was allowed to stir for 2 h at –78 ^{o}C, slowly warmed to -45 ^{o}C over 1 h and stirred for an additional 1 h at -45 ^{o}C. The reaction was subsequently quenched by the addition of half-saturated aqueous NH_4Cl, followed by warming to room temperature. The layers were separated and the aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (12.5-17-25% EtOAc/hexanes) provided 9.51 g (80%) of the alkene as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 5.26 (dd, J = 8.4, 3.6 Hz, 1H), 4.80 (s, 2H), 4.44 (AB, J_{AB} = 11.2 Hz, Δv_{AB} = 27.2 Hz, 2H), 4.33 (m, 1H), 4.18 (m,

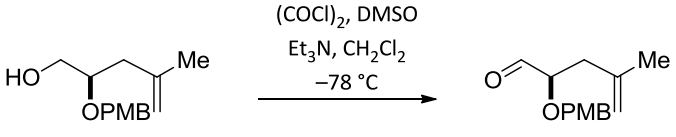
2H), 3.76 (s, 3H), 2.49 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.37 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.25 (m, 1H), 1.75 (s, 3H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 172.8, 159.2, 153.5, 141.0, 129.9, 129.5, 113.6, 113.5, 75.4, 72.3, 63.8, 58.1, 55.1, 41.1, 28.3, 22.3, 17.7, 14.7; IR (film) 3076, 2965, 1779, 1711, 1613, 1514, 1389, 1248 cm^{-1}; $[\alpha]^{23}_D$ = +83.1^o (*c* 4.32, CH_2Cl_2); MS (ESI) calculated for $C_{20}H_{27}NO_5$ $[M+Na]^+$: 384.1788, found: 384.1802.



140

To a stirring solution of oxazolidinone **140** (15.78 g, 43.66 mmol, 1.0 eq) in THF (200 mL) and water (65 mL) was added sodium borohydride (2.48 g, 65.49 mmol, 1.5 eq) at 0 ^{o}C. After 10 min at 0 ^{o}C, the reaction mixture was allowed to stir for an additional 2 h at room temperature. Saturated solution of sodium potassium tartrate (150 mL) was then added, and the resulting mixture was stirred vigorously at room temperature for 15 h. The organic layer was separated and the aqueous layer was further extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (20-25% EtOAc/hexanes) gave 10.05 g (96%) of the desired alcohol as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.80 (s, 1H), 4.76 (s, 1H), 4.52 (AB, J_{AB} = 10.8 Hz, Δv_{AB} = 53.6 Hz, 2H), 3.79 (s, 3H), 3.65 (m, 2H), 3.49 (m, 1H), 2.37 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.17 (dd, *J* = 13.8, 7.0 Hz,

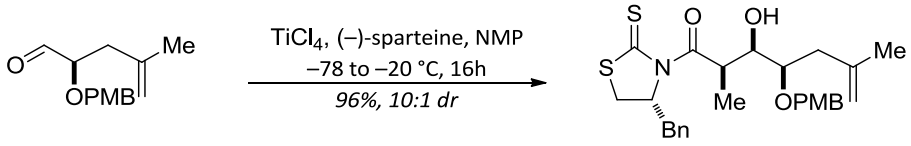
1H), 1.93 (t, *J* = 3.1 Hz, 1H), 1.74 (s, 3H); ^{13}C (100 MHz, CDCl3) δ 159.2, 142.0, 130.3, 129.3, 113.7, 113.0, 77.6, 71.1, 64.1, 55.1, 39.3, 22.7; IR (film) 3409 (br), 3074, 2935, 1613, 1513, 1249, 1036 cm^{-1}; $[\alpha]^{21}_{D}$ = -25.4^{o} (*c* 2.95, CH_2Cl_2); MS (ESI) calculated for $C_{14}H_{20}O_3$ $[M+Na]^+$: 259.1, found: 259.1.



141

A solution of oxalyl chloride (2.0 M in CH_2Cl_2, 20.26 mL, 40.52 mmol, 1.2 eq) in CH_2Cl_2 (250 mL) was cooled to -78 ^{o}C and dimethyl sulfoxide (5.75 mL, 81.05 mmol, 2.4 eq) was added dropwise via syringe. After stirring for 15 min at -78 ^{o}C, a solution of the alcohol (7.98 g, 33.77 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) was added slowly. The resulting solution was stirred for 15 min followed by the dropwise addition of triethylamine (29.41 mL, 168.85 mmol, 5.0 eq). After stirring for another 15 min at -78 ^{o}C, the reaction mixture was warmed to 0 ^{o}C and stirred for an additional 1 h. Water was then added to quench the reaction and the organic layer was separated. The aqueous solution was further extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (12-15% EtOAc/hexanes) gave 7.51 g (95%) of the desired aldehyde **141** as a light yellow oil, which was used in the next reaction: ^{1}H (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 1.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.83 (s, 1H), 4.78 (s, 1H), 4.53 (AB, J_{AB} = 11.6 Hz, Δv_{AB} = 29.6 Hz, 2H), 3.87 (m, 1H), 3.77 (s,

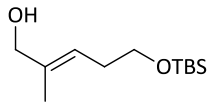
3H), 2.37 (d, *J* = 6.4 Hz, 2H), 1.70 (s, 3H); ^{13}C (100 MHz, CDCl3) δ 203.2, 159.4, 140.3, 129.7, 120.1, 113.9, 113.8, 81.4, 72.2, 55.1, 38.3, 22.6.



141 **118**

A stirring solution of thiazolidinethione propionate **23** (3.92 g, 14.77 mmol, 2.0 eq) in CH_2Cl_2 (35 mL) was cooled in an ice/water bath and $TiCl_4$ (1.70 mL, 15.51 mmol, 2.1 eq) was added slowly via syringe. The resultant dense orange precipitate was stirred for 15 min before (-)-sparteine (3.56 mL, 15.51 mmol, 2.1 eq) was added dropwise, causing the suspension to become a homogeneous dark blue color solution. After stirring for 30 min at 0 ^{o}C, the enolate mixture was cooled to -78 ^{o}C and *N*-methyl-2-pyrrolidinone (3.56 mL, 15.51 mmol, 2.1 eq) was added slowly. The reaction mixture was stirred for 15 min at -78 ^{o}C, and the previously prepared aldehyde **141** (1.72 g, 7.36 mmol, 1.0 eq) was added, as a solution in CH_2Cl_2 (5 mL). After stirring an additional 2 h at -78 ^{o}C, the reaction mixture was allowed to slowly warm to -20 ^{o}C, and stored in a -20 ^{o}C fridge for 12 h. Half-saturated aqueous NH_4Cl solution was added to quench the reaction and the resulting mixture was stirred vigorously while warming up to room temperature. The layers were separated and the aqueous layer was further extracted three times with EtOAc. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (10-15% EtOAc/hexanes) provided 3.54 g (96%) of an

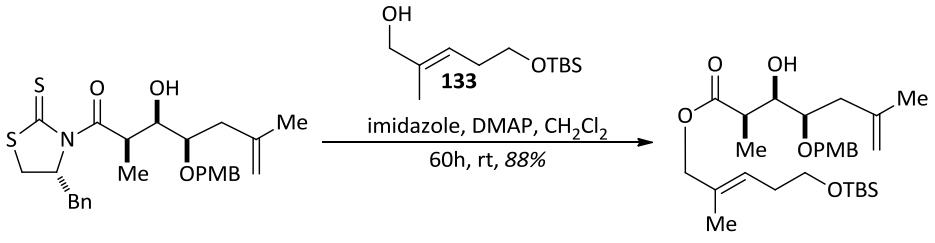
inseparable 10:1 mixture of the desired aldol adduct **118** and another minor diastereomer as a bright yellow color, viscous oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.24 (m, 1H), 7. 21 (d, *J* = 8.4 Hz, 2H), 7.15 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.92 (m, 1H), 4.87 (s, 2H), 4.57 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.41 (AB, J_{AB} = 10.4 Hz, Δv_{AB} = 51.6 Hz, 2H), 3.98 (m, 1H), 3.72 (s, 3H), 3.55 (m, 1H), 3.15 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.06 (dd, *J* = 11.4, 7.0 Hz, 1H), 2.95 (dd, *J* = 13.0, 11.0 Hz, 1H), 2.67 (d, *J* = 11.6 Hz, 1H), 2.37 (dd, *J* = 13.2, 7.0 Hz, 1H), 2.31 (dd, *J* = 13.0, 7.2 Hz, 1H), 2.19 (d, *J* = 5.6 Hz, 1H), 1.78 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 201.0, 176.4, 159.3, 142.2, 136.5, 129.9, 129.6, 129.4, 128.8, 127.0, 113.8, 113.5, 78.1, 73.7, 71.9, 69.2, 55.2, 41.2, 38.6, 36.4, 32.0, 22.7, 13.8; IR (film) 3479 (br), 3028, 2935, 1693, 1513, 1455, 1343, 1252, 1166, 1058 cm^{-1}; $[\alpha]^{24}_{D}$ = -181.5^{o} (*c* 2.75, CH_2Cl_2); MS (ESI) calculated for $C_{27}H_{33}NO_4S_2$ $[M+Na]^{+}$: 522.2, found: 522.3.



133

^{1}H NMR (600MHz ,$CDCl_3$) □ = 5.39 (t, *J* = 6.8 Hz, 1 H), 3.98 (br. s., 2 H), 3.59 (t, *J* = 7.2 Hz, 2 H), 2.25 (q, *J* = 7.2 Hz, 2 H), 1.65 (s, 3 H), 1.45 (br. s., 1 H), 0.87 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 136.6, 122.1, 77.2, 76.8, 68.8, 62.7, 31.4, 25.9, 18.3, 13.8, -5.3; IR (film) 3349.75 (broad), 2929.34, 2857.99, 2361.44, 1472.38, 1386.38, 1361.50, 1255.43, 1097.30, 1006.66,

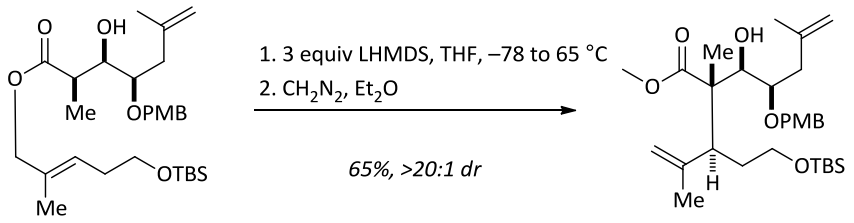
937.25, 835.99, 776.21, 664.39 cm^{-1}; MS (ESI) calculated for $C_{12}H_{26}O_2Si$, $[M+Na]^+$: 253.1600, found: 253.1604.



118 **132**

To a stirring solution of aldol adduct 203 (3.09 g, 6.19 mmol, 1.0 eq) in CH_2Cl_2 (2.5 mL), was added alcohol **133** (1.43 g, 6.19 mmol, 1.0 eq), imidazole (631.9 mg, 9.28 mmol, 1.5 eq) and 4-dimethylaminopyridine (151.2 mg, 1.24 mmol, 0.2 eq) sequentially. The resulting mixture was allowed to stir at room temperature for 60 hours, followed by concentration under reduced pressure. Purification by column chromatography (20% EtOAc/hexanes) provided 2.58 g (80%) of the desired β-hydroxy ester **132** as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.41 (t, *J* = 6.8 Hz, 1H), 4.83 (s, 1H), 4.81 (s, 1H), 4.45 (AB, J_{AB} = 10.4 Hz, Δv_{AB} = 75.2 Hz, 2H), 4.36 (AB, J_{AB} = 12.0 Hz, Δv_{AB} = 35.6 Hz, 2H), 3.78 (s, 3H), 3.68 (ddd, *J* = 8.4, 8.4, 2.2 Hz, 1H), 3.58 (t, *J* = 7.0 Hz, 2H), 3.53 (ddd, *J* = 7.8, 7.8, 2.4 Hz, 1H), 2.72 (dq, *J* = 7.6, 7.2 Hz, 1H), 2.37 (m, 2H), 2.31 (d, *J* = 9.2 Hz, 1H), 2.24 (dt, *J* = 7.2, 6.8 Hz, 2H), 1.73 (s, 3H), 1.61 (s, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 174.7, 159.3, 141.8, 131.6, 130.1, 129.6, 125.9, 113.7, 113.6, 76.9, 73.4, 71.9, 70.0, 62.4, 55.2, 43.1, 38.9, 31.5, 25.9, 22.7, 18.3, 14.1, 13.6, -5.3; IR (film) 3500 (br), 3075, 2931, 2857, 1731, 1613, 1515, 1463,

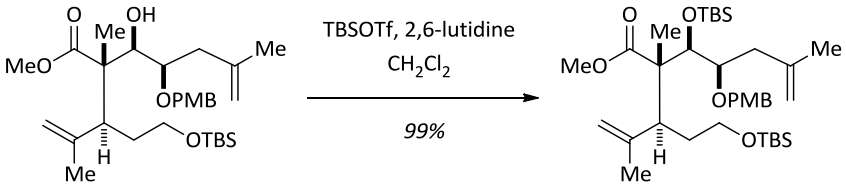
1250, 1173, 1096, 1038 cm^{-1}; $[\alpha]^{25}_D$ = +28.3° (*c* 4.80, CH_2Cl_2); MS (ESI) calculated for $C_{29}H_{48}O_6Si$ $[M+Na]^+$: 543.3, found: 543.4.



132 **142**

A stirring solution of hexamethyldisilazane (11.22 mL, 53.16 mmol, 3.2 eq) in THF (125 mL) was cooled to -78 °C and *n*-BuLi (2.12 M in hexanes, 23.51 mL, 49.84 mmol, 3.0 eq) was added dropwise via syringe. The resulting solution was stirred for 20 min at -78 °C, followed by 30 min at 0 °C, and cooled to -78 °C afterward. Into this freshly prepared lithium hexamethyldisilazide solution, a solution of ester **132** (8.65 g, 16.60 mmol, 1.0 eq) in THF (25 mL) was added dropwise via syringe and stirred at -78 °C for 2 h. The solution was then allowed to slowly warm to room temperature over 2 h, stirred for an additional 6 h, and heated to reflux for another 12 h. After cooling in an ice/water bath, the reaction was quenched by slow addition of 10% HCl solution until the pH value was 2. The layers were separated and the aqueous layer was further extracted three times with EtOAc. The organic layers were combined, washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude acid was dissolved in ether (120 mL) and cooled to 0 °C, into which freshly prepared diazomethane in Et_2O was added slowly via pipette and gas was immediately generated. The reaction mixture was stirred for 10 min at 0 °C,

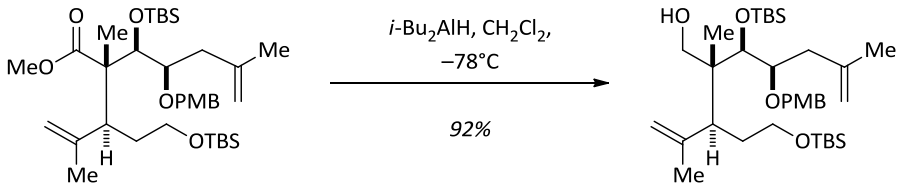
followed by 30 min at room temperature. Excess diazomethane was subsequently quenched by adding acetic acid dropwise into the reaction mixture at 0 ^{o}C until evolution of nitrogen ceased. The reaction mixture was concentrated under vacuum and loaded directly to column. Purification by column chromatography (8-10% EtOAc/hexanes) provided 5.78 g (65%) of the desired methyl ester **142** as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.82 (m, 3H), 4.63 (s, 1H), 4.33 (AB, J_{AB} = 10.4 Hz, Δv_{AB} = 134.0 Hz, 2H), 3.77 (s, 3H), 3.62 (dd, *J* = 9.4, 4.2 Hz, 1H), 3.51 (m, 4H), 3.18 (s, 3H), 3.00 (dd, *J* = 12.0, 2.4 Hz, 1H), 2.54 (dd, *J* = 13.4, 9.4 Hz, 1H), 2.41 (dd, *J* = 13.4, 3.8 Hz, 1H), 1.74 (s, 3H), 1.69 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.56 (m, 1H), 1.08 (s, 3H), 0.86 (s, 9H), 0.012 (s, 3H), 0.007 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 175.8, 159.1, 144.1, 141.9, 129.8, 115.8, 113.6, 113.4, 75.3, 74.3, 71.0, 62.1, 55.1, 51.3, 50.8, 45.1, 38.1, 30.0, 25.9, 22.9, 21.4, 18.2, 15.6, -5.2; IR (film) 3561, 3447, 3076, 2952, 2857, 1734, 1707, 1613, 1515, 1463, 1251, 1100 cm^{-1}; $[\alpha]^{21}_{D}$ = +0.2^{o} (*c* 1.94, CH_2Cl_2); MS (ESI) calculated for $C_{30}H_{50}O_6Si$ $[M+Na]^+$: 557.3275, found: 557.3304.



142

A stirring solution of alcohol **142** (6.87 g, 12.85 mmol, 1.0 eq) and 2,6-lutidine (2.99 mL, 25.70 mmol, 2.0 eq) in CH_2Cl_2 (100 mL) was cooled to -78 ^{o}C, and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.43 mL, 19.28 mmol, 1.5 eq) was added dropwise via syringe. The resultant mixture was stirred at -78 ^{o}C

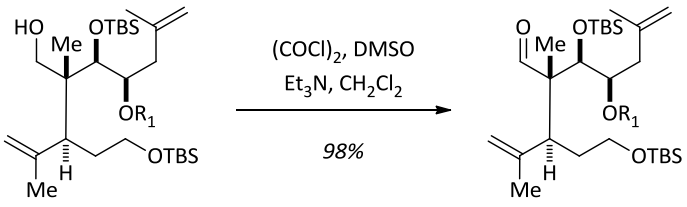
for 30 min, and allowed to warm to room temperature. After stirring an additional 2 h at room temperature, half-saturated NH_4Cl was added to quench the reaction. The layers were separated and the aqueous layer was further extracted three times with CH_2Cl_2. The combined organic layers was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (5% EtOAc/hexanes) yielded 8.24 g (99%) of the TES ether as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.81 (s, 1H), 4.78 (s, 2H), 4.70 (s, 1H), 4.45 (AB, J_{AB} = 10.8 Hz, Δv_{AB} = 37.6 Hz, 2H), 4.04 (d, *J* = 1.6 Hz, 1H), 3.77 (s, 3H), 3.74 (m, 1H), 3.48 (m, 1H), 3.46 (s, 3H), 3.38 (m, 1H), 2.67 (dd, *J* = 10.8, 2.2 Hz, 1H), 2.41 (dd, *J* = 14.0, 8.8 Hz, 1H), 2.22 (dd, *J* = 14.0, 3.6 Hz, 1H), 1.83 (m, 1H), 1.74 (s, 3H), 1.66 (s, 3H), 1.53 (m, 1H), 1.29 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H), 0.00 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 175.6, 158.8, 145.1, 143.1, 131.2, 128.8, 115.9, 113.5, 112.8, 77.5, 76.6, 71.1, 61.8, 55.2, 54.9, 50.9, 46.6, 40.1, 31.0, 26.1, 26.0, 23.0, 21.1, 18.7, 18.3, 15.9, -3.3, -4.3, -5.3; IR (film) 3074, 2952, 2857, 1727, 1614, 1514, 1464, 1250, 1099 cm^{-1}; $[\alpha]^{22}_D$ = +7.0^o (*c* 2.91, CH_2Cl_2); MS (ESI) calculated for $C_{36}H_{64}O_6Si_2$ $[M+Na]^+$: 671.4140, found: 671.4156.



143

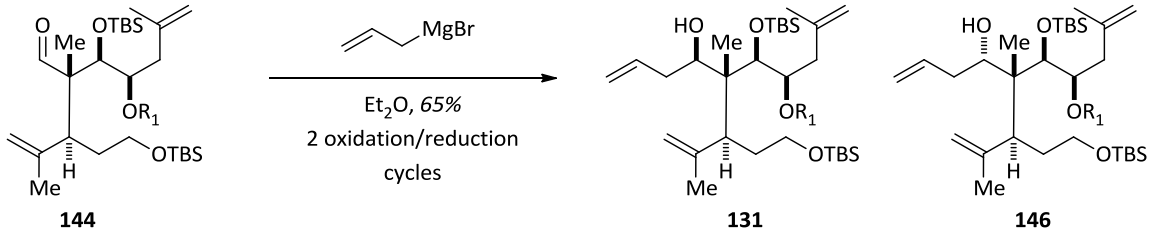
A stirring solution of the methyl ester (7.88 g, 12.15 mmol, 1.0 eq) in CH_2Cl_2 (100 mL) was cooled to -78 ^{o}C, into which *i*-Bu_2AlH (1.0 M in hexanes,

36.45 mL, 36.45 mmol, 3.0 eq) was added dropwise via addition funnel over 1 h. After stirring for an additional 2 h at -78 ^{o}C, MeOH was added to quench the reaction and the mixture was allowed to warm to room temperature. A saturated solution of sodium potassium tartrate (50 mL) was added and the resulting bi-phase mixture was stirred vigorously for 6 h. The organic layer was separated and the aqueous layer was extracted three more times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (12% EtOAc/hexanes) yielded 6.90 g (92%) of the alcohol **143** as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.89 (s, 1H), 4.86 (s, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 4.49 (AB, J_{AB} = 10.4 Hz, Δv_{AB} = 70.8 Hz, 2H), 3.81 (m, 1H), 3.78 (m, 1H), 3.77 (s, 3H), 3.67 (m, 1H), 3.48 (m, 3H), 3.25 (m, 1H), 2.57 (dd, *J* = 11.4, 3.4 Hz, 1H), 2.48 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.40 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.77 (s, 6H), 1.61 (m, 2H), 0.88 (s, 9H), 0.86 (s, 9H), 0.79 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.01 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 159.2, 142.5, 129.9, 129.5, 113.7, 113.6, 78.1, 75.6, 71.0, 67.2, 62.5, 55.2, 45.0, 40.4, 26.2, 26.1, 22.8, 18.8, 18.4, 15.7, -3.3, -3.5, -5.2; IR (film) 3462 (br), 3076, 2963, 2857, 1614, 1515, 1464, 1251, 1076 cm^{-1}; $[\alpha]^{22}_{D}$ = -3.0^{o} (*c* 2.75, CH_2Cl_2); MS (ESI) calculated for $C_{35}H_{64}O_5Si_2$ $[M+Na]^+$: 643.4191, found: 643.4204.



143 **144**

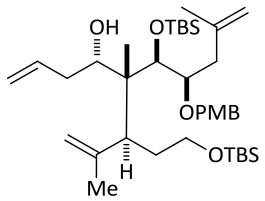
A stirring solution of oxalyl chloride (2.0 M in CH_2Cl_2, 6.53 mL, 13.06 mmol, 1.2 eq) in CH_2Cl_2 (90 mL) was cooled to -78 ^oC and dimethyl sulfoxide (1.85 mL, 26.13 mmol, 2.4 eq) was added dropwise via syringe. After stirring for 15 min at -78 ^oC, alcohol **143** (6.76 g, 10.89 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) was added slowly. The resulting solution was stirred for 15 min followed by dropwise addition of triethylamine (7.59 mL, 54.43 mmol, 5.0 eq). After stirring for another 15 min at -78 ^oC, the reaction mixture was warmed to 0 ^oC and stirred for an additional 1 h. Water was then added to quench the reaction and the organic layer was separated. The aqueous solution was further extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (8% EtOAc/hexanes) gave 6.58 g (98%) of the desired aldehyde **144** as a light yellow oil: ^1H (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 4.78 (m, 3H), 4.74 (s, 1H), 4.34 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 35.0 Hz, 2H), 3.96 (d, J = 2.0 Hz, 1H), 3.77 (s, 3H), 3.58 (m, 1H), 3.49 (m, 2H), 3.08 (dd, J = 11.6, 4.0 Hz, 1H), 2.24 (dd, J = 14.0, 8.4 Hz, 1H), 2.17 (dd, J = 14.2, 4.2 Hz, 1H), 1.70 (s, 3H), 1.64 (m, 2H), 1.56 (s, 3H), 1.05 (s, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H), 0.03 (s, 6H); ^{13}C (100 MHz, CDCl3) δ 205.5, 159.0, 143.4, 142.7, 130.4, 129.1, 115.9, 113.5, 112.8, 78.3, 76.7, 71.5, 61.7, 55.0, 54.4, 43.8, 39.3, 29.8, 26.0, 25.9, 22.8, 20.8, 18.4, 18.3, 13.1, -3.4, -3.9, -5.4.



144 **131** **146**

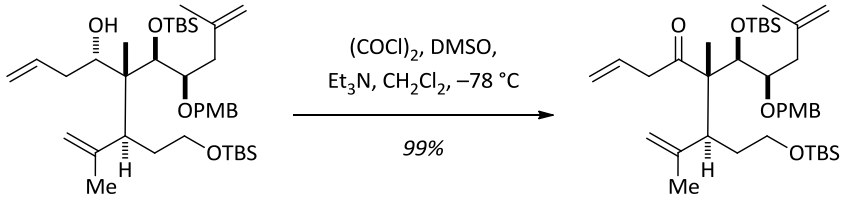
A stirring solution of aldehyde **144** (1.08 g, 1.86 mmol, 1.0 eq) in Et_2O (20 mL) was cooled in an ice/water bath and allyl magnesium bromide (1M solution in Et_2O, 2.80 mL, 2.80 mmol, 1.5 eq) was added dropwise via an addition funnel. After stirring for an additional 2 h at 0 ^oC, the reaction was quenched by the addition of 10% HCl solution until the pH value became 2. The organic layer was separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ solution followed by saturated NaCl solution, dried over $MgSO_4$ and concentration under reduced pressure. Purification by flash chromatography (8% EtOAc/hexanes) and separation of the diastereomers gave a combined 653.0 mg (65%) of the desired triene **131** as a light yellow oil after 2 oxidation reduction sequences (see following experimental): ^1H (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 5.80 (m, 1H), 4.87 (m, 6H), 4.52 (AB, J_{AB} = 10.8 Hz, Δv_{AB} = 17.6 Hz, 2H), 3.91 (s, 1H), 3.79 (m, 2H), 3.77 (s, 3H), 3.46 (m, 2H), 3.36 (m, 1H), 2.79 (d, J = 7.2 Hz, 1H), 2.52 (m, 2H), 2.30 (dd, J = 13.6, 6.0 Hz, 1H), 2.22 (m, 1H), 2.06 (m, 1H), 2.02 (s, 6H), 1.56 (m, 1H), 0.91 (s, 9H), 0.89 (s, 3H), 0.84 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), -0.03 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 159.2, 142.9, 137.8, 129.8, 129.5, 115.5, 114.0, 113.7, 78.1, 75.5, 72.2, 62.4, 55.2, 49.3, 40.9, 36.1, 26.2, 26.0, 22.6, 18.6, 18.3, -3.2, -3.9, -5.4; IR (film) 3437 (br), 3075, 2954,

2929, 2857, 1515, 1471, 1252, 1077 cm^{-1}; $[\alpha]^{20}_D$ = +0.8° (*c* 3.29, CH_2Cl_2); MS (ESI) calculated for $C_{38}H_{68}O_5Si_2$ $[M+Na]^+$: 683.4504, found: 683.4514.



146

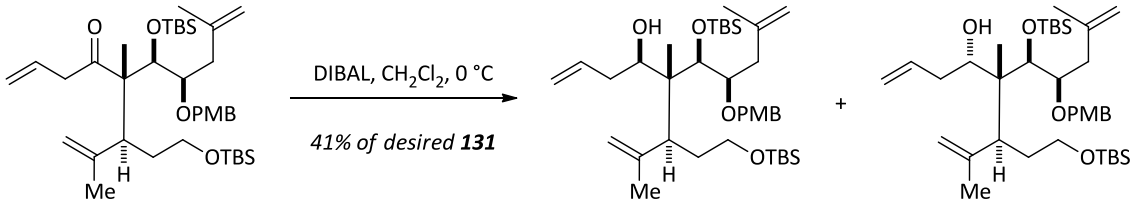
^{1}H NMR (600MHz ,$CDCl_3$) □ = 7.26 (d, *J* = 8.7 Hz, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 5.80 - 5.71 (m, 1 H), 4.91 - 4.82 (m, 4 H), 4.81 (s, 2 H), 4.60 (d, *J* = 10.5 Hz, 1 H), 4.30 (d, *J* = 10.5 Hz, 1 H), 3.81 (s, 1 H), 3.77 (s, 3 H), 3.68 (br. s., 1 H), 3.51 (br. s., 1 H), 3.48 - 3.41 (m, 1 H), 2.80 (d, *J* = 9.8 Hz, 1 H), 2.49 (dd, *J* = 3.2, 13.7 Hz, 1 H), 2.40 (br. s., 1 H), 2.33 (d, *J* = 9.0 Hz, 1 H), 2.27 - 2.18 (m, 1 H), 1.83 (br. s., 3 H), 1.78 - 1.74 (m, 4 H), 1.67 - 1.56 (m, 2 H), 0.89 - 0.84 (m, 18 H), 0.14 (s, 3 H), 0.17 (s, 3 H), 0.01 (s, 6 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 159.0, 142.2, 138.7, 129.9, 129.5, 115.0, 113.9, 113.5, 79.6, 77.2, 77.1, 76.8, 74.0, 70.5, 62.4, 55.2, 55.2, 46.9, 40.9, 37.4, 29.7, 26.3, 26.2, 26.0, 25.9, 22.6, 18.9, 18.4, 16.7, -3.4, -3.7, -5.2, -5.2, -5.4; IR (film) 3508.85 (broad), 3073.98, 2954.41, 1639.20, 1614.13, 1587.13, 1514.81, 1463.71, 1387.53, 1302.68, 1251.58, 1173.48, 1096.33, 894.51, 835.99, 774.88, 676.90 cm^{-1}; $[\alpha]^{20}_D$ = -7.05° (*c* = 7.5, CH_2Cl_2); MS (ESI) calculated for $C_{38}H_{68}O_5Si_2$ $[M+Na]^+$: 683.4504, found: 683.4527.



146 **145**

A stirring solution of oxalyl chloride (0.477 ml, 5.45 mmol, 2 equiv) was cooled to -78 °C in 20ml CH_2Cl_2. DMSO (0.773 ml, 10.89 mmol, 4 equiv) was added by syringe and stirred 20 minutes. Undesired alcohol **146** (1.8 g, 2.72 mmol, 1 equiv) was added as a solution in CH_2Cl_2 (7 mL) and stirred 30 minutes. Triethylamine (1.897 ml, 13.61 mmol, 5 equiv) added and stirred 1 hour at -78 °C. Reaction was quenched with NH_4Cl and warmed to rt. Extracted three times with CH_2Cl_2 (5mL), washed with aqueous sodium bicarbonate, dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography afforded 1.793g of the ketone **145** as a clear viscous oil: ^{1}H NMR (400MHz ,$CDCl_3$) □ = 7.16 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 5.63 (tdd, *J* = 6.7, 10.4, 17.2 Hz, 1 H), 4.86 (dd, *J* = 2.3, 10.2 Hz, 1 H), 4.80 (br. s., 2 H), 4.76 (s, 1 H), 4.69 (s, 1 H), 4.63 (dd, *J* = 1.9, 17.5 Hz, 1 H), 4.36 (d, *J* = 10.2 Hz, 1 H), 4.11 (d, *J* = 10.2 Hz, 1 H), 3.82 (s, 1 H), 3.76 (s, 3 H), 3.57 (t, *J* = 6.3 Hz, 1 H), 3.53 (d, *J* = 6.8 Hz, 1 H), 3.51 - 3.44 (m, 3 H), 3.42 - 3.34 (m, 1 H), 3.02 (t, *J* = 7.8 Hz, 1 H), 2.36 (dd, *J* = 5.7, 14.0 Hz, 1 H), 2.24 (dd, *J* = 6.6, 14.2 Hz, 1 H), 1.73 (s, 3 H), 1.67 - 1.59 (m, 3 H), 1.58 (s, 3 H), 1.10 (s, 3 H), 0.95 (s, 9 H), 0.87 (s, 9 H), 0.22 (s, 3 H), 0.17 (s, 3 H), 0.02 (s, 6 H); ^{13}C (100 MHz, $CDCl_3$) δ 210.87, 158.94, 144.00, 142.60, 133.05, 130.61, 129.40, 117.07, 116.43, 113.42, 113.05, 77.96, 75.65, 71.57, 62.11, 57.87, 55.20, 47.07, 44.97, 40.61, 29.74, 26.52, 26.02,

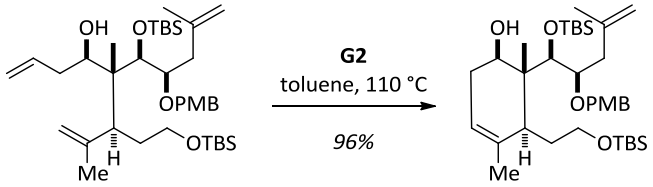
22.87, 20.03, 19.05, 18.40, 16.51, -2.97, -3.74, -5.21; IR (film) 3073.98, 2954.41, 2857.02, 1696.09, 1614.13, 1514.81, 1250.61, 1090.55, 835.99, 775.24 cm^{-1}; $[\alpha]^{20}_{D}$ = -0.11° (*c* 4.05, CH_2Cl_2); MS (ESI) calculated for $C_{38}H_{66}O_5Si_2$, $[M+Na]^+$: 681.4389, found 681.4365.



145 **131** **146**

To a stirring solution of ketone **145** (1146 mg, 1.739 mmol, 1 equiv) dissolved in dichloromethane (Volume: 17.4mL) and cooled to 0 °C with an ice/water bath. The bath was removed, and DIBAL (1 molar solution in hexanes, 1.5mL, 2 equiv) was added quickly and stirred for 45 minutes. Reaction quenched with Rochelle's salt and stirred for 3 hours. Mixture was extracted with dichloromethane (3 x 5 mL), washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (5-10-20% EtOAc/Hexanes) separated the diastereomers and afforded 471.0mg of desired alcohol **131** as a clear oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.80 (m, 1H), 4.87 (m, 6H), 4.52 (AB, J_{AB} = 10.8 Hz, Δv_{AB} = 17.6 Hz, 2H), 3.91 (s, 1H), 3.79 (m, 2H), 3.77 (s, 3H), 3.46 (m, 2H), 3.36 (m, 1H), 2.79 (d, *J* = 7.2 Hz, 1H), 2.52 (m, 2H), 2.30 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.22 (m, 1H), 2.06 (m, 1H), 2.02 (s, 6H), 1.56 (m, 1H), 0.91 (s, 9H), 0.89 (s, 3H), 0.84 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), -0.03 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 159.2, 142.9, 137.8, 129.8, 129.5, 115.5, 114.0, 113.7, 78.1, 75.5, 72.2, 62.4, 55.2,

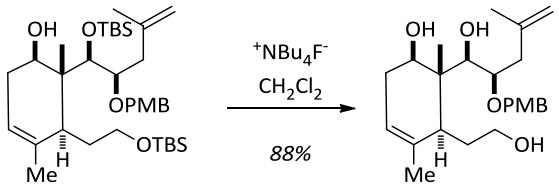
49.3, 40.9, 36.1, 26.2, 26.0, 22.6, 18.6, 18.3, -3.2, -3.9, -5.4; IR (film) 3437 (br), 3075, 2954, 2929, 2857, 1515, 1471, 1252, 1077 cm^{-1}; $[\alpha]^{20}_{D}$ = +0.8^{o} (*c* 3.29, CH_2Cl_2); MS (ESI) calculated for $C_{38}H_{68}O_5Si_2$ $[M+Na]^+$: 683.4504, found: 683.4514.



131 **150**

A stirring solution of triene **131** (3.10 g, 4.69 mmol, 1.0 eq) in toluene (500 mL) was degassed by heating to reflux for 30 min. Grubbs second generation catalyst [$Cl_2(PCy_3)$(IMes)Ru=CHPh] (100.0 mg, 0.12 mmol, 0.025 eq) was added and the solution was stirred at reflux under an argon atmosphere. After 10 min, TLC indicated a complete consumption of starting material and the reaction mixture was allowed to cool to room temperature. After stirring in the air for an additional 2 h, the reaction mixture was concentrated and loaded directly to a silica gel column, and purification by flash chromatography (2-10-15% EtOAc/hexanes) gave 2.80 g (96%) of the desired alcohol 287 as a light brown oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.28 (s, 1H), 4.89 (s, 1H), 4.84 (s, 1H), 4.49 (s, 1H), 4.48 (AB, J_{AB} = 10.4 Hz, Δv_{AB} = 65.2 Hz, 2H), 3.89 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.79 (s, 1H), 3.74 (s, 3H), 3.69 (m, 2H), 3.50 (m, 1H), 2.48 (d, *J* = 12.8 Hz, 1H), 2.37 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.14 (m, 1H), 1.98 (m, 1H), 1.92 (m, 1H), 1.78 (s, 3H), 1.66 (m, 1H), 1.64 (s, 3H), 1.49 (m, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.76 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.03 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 159.2, 142.2, 135.1, 129.4, 129.3, 120.4, 113.8,

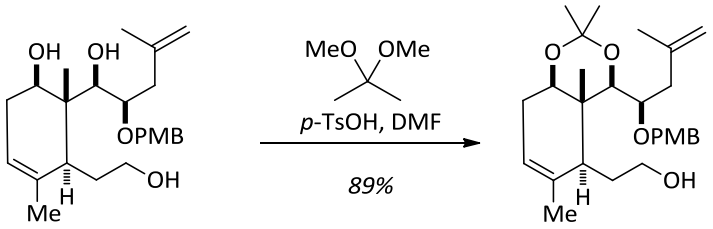
113.6, 76.9, 74.4, 70.4, 68.0, 64.2, 55.1, 46.5, 42.9, 40.0, 32.5, 29.8, 26.0, 25.9, 22.8, 22.3, 18.8, 18.2, 11.8, -3.3, -3.5, -5.27, -5.31; IR (film) 3438 (br), 3076, 2954, 2929, 2856, 1614, 1515, 1252, 1089 cm^{-1}; $[\alpha]^{21}_{D}$ = -1.7° (*c* 2.89, CH_2Cl_2); MS (ESI) calculated for $C_{36}H_{64}O_5Si_2$ $[M+Na]^+$: 655.4191, found: 655.4192.



150 **151**

A stirring solution of bis-TBS ether **150** (482.0 mg, 0.76 mmol, 1.0 eq) in THF (10 mL) was cooled in an ice/water bath, into which was added tetrabutyl-ammonium fluoride (1.0 M in THF, 2.28 mL, 2.28 mmol, 3.0 eq) dropwise via syringe. After stirring for 10 min at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 5 h. Half-saturated NH_4Cl solution was subsequently added to quench the reaction and the aqueous layer was further extracted three times with 50% EtOAc/hexanes. The combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (50-75% EtOAc/hexanes) gave 278.1 mg (88%) of the desired triol **151** as a light yellow oil: ^1H (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.22 (s, 1H), 4.87 (s, 1H), 4.81 (s, 1H), 4.50 (AB, J_{AB} = 10.8 Hz, Δv_{AB} = 102.0 Hz, 2H), 4.26 (br, 1H), 3.83 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.74 (m, 1H), 3.73 (s, 3H), 3.64 (m, 2H), 3.48 (m, 1H), 3.07 (br, 2H), 2.50 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.44 (dd, *J* = 12.8, 11.0 Hz, 1H), 2.18 (m, 2H), 1.93 (m, 1H), 1.73 (s, 3H), 1.66 (m, 1H), 1.59 (s, 3H), 1.43 (m, 1H),

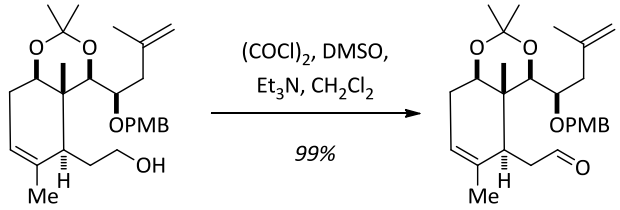
0.70 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.5, 141.8, 135.4, 130.0, 128.3, 119.2, 114.4, 113.8, 74.0, 73.5, 70.1, 67.9, 63.3, 55.1, 45.1, 41.4, 39.0, 30.6, 30.3, 22.6, 21.9, 10.8; IR (film) 3287 (br), 3076, 2913, 1613, 1515, 1442, 1251, 1046 cm^{-1}; $[\alpha]^{20}_D$ = -28.7° (*c* 2.24, CH_2Cl_2); MS (ESI) calculated for $C_{24}H_{36}O_5$ $[M+Na]^+$: 427.2461, found: 427.2465.



151 **152**

Alcohol **151** (275.0 mg, 0.68 mmol, 1.0 eq) was dissolved in 5 mL 2,2-dimethoxypropane and 1 mL DMF, followed by addition of *p*-toluenesulfonic acid (11.7 mg, 0.068 mmol, 0.1 eq). The resulting reaction mixture was stirred at room temperature for 6 h, before saturated $NaHCO_3$ solution was added to quench the reaction. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with 10% HCl solution with vigorous shaking, followed by drying over Na_2SO_4 and concentration under reduced pressure. Purification by flash chromatography (25-30% EtOAc/hexanes) gave 286.5 mg (89%) of the desired alcohol **152** as a light yellow oil: ^{1}H (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.25 (d, *J* = 4.5 Hz, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 4.56 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 140.5 Hz, 2H), 4.06 (t, *J* = 6.5 Hz, 1H), 3.74 (s, 3H), 3.70 (m, 1H), 3.58 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.47 (dt, *J* = 9.0, 8.5 Hz, 1H), 3.38 (s, 1H), 2.51 (d, *J* =

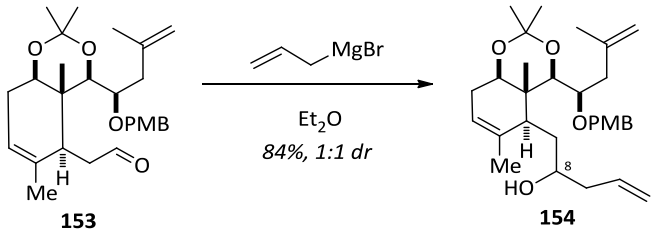
6.5 Hz, 2H), 2.31 (br, 1H), 1.98 (m, 2H), 1.87 (m, 1H), 1.78 (s, 3H), 1.59 (s, 3H), 1.58 (m, 1H), 1.46 (s, 3H), 1.36 (s, 3H), 1.32 (m, 1H), 1.11 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 158.9, 142.4, 135.6, 130.9, 129.4, 119.4, 113.5, 113.3, 99.1, 79.2, 75.2, 74.8, 69.0, 63.3, 55.1, 40.7, 40.6, 37.8, 32.5, 30.0, 27.3, 22.7, 22.5, 19.5, 8.1; IR (film) 3444 (br), 3075, 2989, 2939, 2860, 1613, 1515, 1380, 1250, 1043 cm^{-1}; $[\alpha]^{20}_D$ = -24.4^o (*c* 1.89, CH_2Cl_2); MS (ESI) calculated for $C_{27}H_{40}O_5$ $[M+Na]^+$: 467.2774, found: 467.2780.



152 **153**

A stirring solution of oxalyl chloride (2.0 M in CH_2Cl_2, 1.8 mL, 3.60 mmol, 1.2 eq) in CH_2Cl_2 (25 mL) was cooled to -78 ^{o}C and dimethyl sulfoxide (0.52 mL, 7.20 mmol, 2.4 eq) was added dropwise via syringe. After stirring for 15 min at -78 ^{o}C, alcohol 289 (1.31 g, 2.94 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) was added slowly. The resulting solution was stirred for 15 min followed by dropwise addition of triethylamine (2.67 mL, 15.0 mmol, 5.0 eq). After stirring for another 15 min at -78 ^{o}C, the reaction mixture was allowed to warm to 0 ^{o}C in an ice/water bath and stirred for an additional 1 h. Half-saturated NH_4Cl solution was then added to quench the reaction and the organic layer was separated. The aqueous solution was further extracted three times with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 followed by concentration under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) gave 1.30 g (99%) of

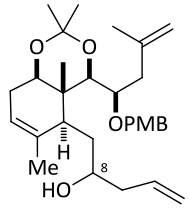
the desired aldehyde **153** as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.2 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.26 (d, *J* = 4.8 Hz, 1H), 4.84 (s, 1H), 4.78 (s, 1H), 4.49 (AB, J_{AB} = 11.8 Hz, Δv_{AB} = 168.0 Hz, 2H), 3.78 (s, 3H), 3.70 (dd, *J* = 7.2, 6.4 Hz, 1H), 3.64 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.44 (s, 1H), 2.51 (m, 4H), 2.24 (dd, *J* = 19.2, 9.2 Hz, 1H), 1.93 (m, 2H), 1.76 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.11 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 201.0, 158.9, 141.9, 134.1, 130.1, 129.6, 119.3, 113.5, 113.3, 99.2, 78.8, 74.4, 73.3, 67.8, 54.8, 44.6, 39.3, 36.9. 36.8, 29.7, 26.9, 21.9, 21.9, 21.7, 19.3, 8.2.



153 **154**

To a flask fitted with a dry ice condenser was added magnesium turnings (214.4 mg, 8.82 mmol, 3.0 eq), Et_2O (25 mL) and a small crystal of iodine. Allyl bromide (0.76 mL, 8.82 mmol, 3.0 eq) was added via syringe at a rate to maintain a gentle reflux of the reaction mixture. After stirring an additional 30 min at room temperature, the reaction mixture was cooled in an ice/water bath. Freshly prepared aldehyde **153** (1.30 g, 2.94 mmol, 1.0 eq) in Et_2O (5 mL) was added dropwise and the reaction mixture was allowed to stir another 1 h at 0 ^{o}C. 10% HCl solution was added at 0 ^{o}C to quench the reaction until the pH value became 2. The organic layer was separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ and saturated NaCl sequentially, followed by drying over

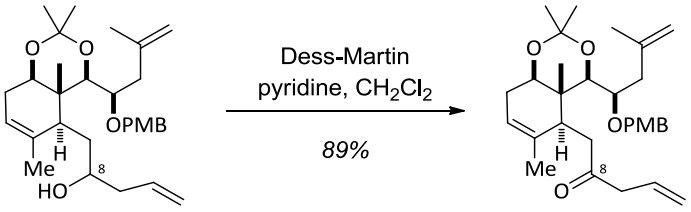
$MgSO_4$ and concentration under reduced pressure. Purification by flash chromatography (10% EtOAc/ hexanes) gave 690.1 mg (49%) of the desired alcohol **154** as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.81 (m, 1H), 5.32 (s, 1H), 5.15 (s, 1H), 5.22 (d, *J* = 5.2 Hz, 1H), 4.85 (s, 1H), 4.81 (s, 1H), 4.57 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 106.2 Hz, 2H), 4.03 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.82 (m, 1H), 3.76 (s, 3H), 3.66 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.45 (s, 1H), 2.60 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.45 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.41 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.07-1.92 (band, 5H), 1.80 (s, 3H), 1.73 (s, 3H), 1.71 (m, 1H), 1.51 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.14 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.8, 142.3, 136.0, 134.8, 131.1, 128.9, 119.9, 118.3, 113.5, 113,4. 98.7, 79.8, 75.3, 74.6, 71.1, 68.2, 55.1, 42.4, 42.0, 41.4, 37.9, 36.3, 30.0, 27.7, 23.8, 22.8, 19.3, 7.9; IR (film) 3460 (br), 3075, 2937, 1515, 1380, 1250 cm^{-1}; $[\alpha]^{20}_D$ = -17.7^o (*c* 2.73, CH_2Cl_2); MS (ESI) calculated for $C_{30}H_{44}O_5$ $[M+Na]^+$: 507.3087, found: 507.3104.



undesired dr

^{1}H NMR (600MHz ,$CDCl_3$) □ = 7.29 (d, *J* = 8.7 Hz, 4 H), 6.84 (d, *J* = 8.7 Hz, 5 H), 5.81 - 5.71 (m, 1 H), 5.28 (d, *J* = 4.9 Hz, 1 H), 5.13 - 5.05 (m, 2 H), 4.80 (d, *J* = 7.5 Hz, 2 H), 4.72 (d, *J* = 11.3 Hz, 2 H), 4.47 (d, *J* = 11.3 Hz, 1 H), 3.92

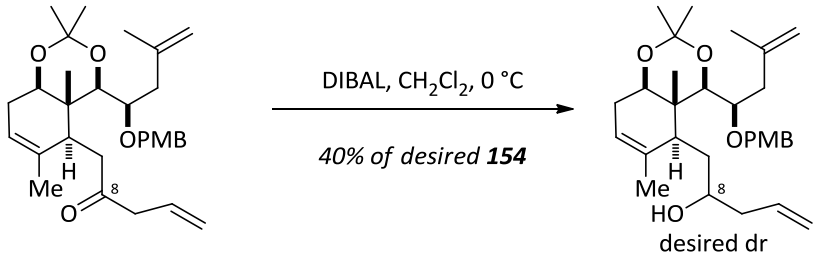
(br. s., 1 H), 3.80 - 3.74 (m, 3 H), 3.66 (dd, *J* = 5.5, 10.4 Hz, 1 H), 3.45 (d, *J* = 1.5 Hz, 1 H), 2.54 - 2.44 (m, 2 H), 2.25 - 2.19 (m, 1 H), 2.16 (d, *J* = 8.7 Hz, 1 H), 2.09 - 1.95 (m, 3 H), 1.94 - 1.86 (m, 1 H), 1.79 (s, 3 H), 1.75 (t, *J* = 1.0 Hz, 1 H), 1.68 - 1.63 (m, 3 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.31 (dd, *J* = 9.4, 15.1 Hz, 1 H), 1.13 (s, 3 H); ^{13}C NMR (150MHz , $CDCl_3$) □ = 158.6, 143.2, 136.4, 134.6, 131.5, 128.6, 119.6, 118.6, 113.5, 112.9, 98.9, 79.2, 77.2, 76.8, 74.9, 70.4, 55.2, 43.8, 40.9, 39.6, 37.8, 37.0, 30.1, 27.6, 23.7, 22.6, 19.6, 14.0, 8.1, 8.1; IR (film) 3509.81, 3073.98, 2938.02, 2857.99, 2360.44, 1643.05, 1314.13, 1586.16, 1514.81, 1456.96, 1379.82, 1301.72, 1249.65, 1202.40, 1172.51, 1119.48, 1038.48, 887.09, 813.81, 736.67, 521.65 cm^{-1}; $[\alpha]^{20}_D$ = -10.06^o (*c* 2.7, CH_2Cl_2); MS (ESI) calculated for $C_{30}H_{44}O_5$ $[M+Na]^+$: 507.3087, found: 507.3105.



undesired dr

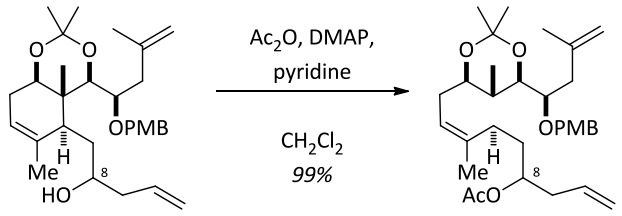
Alcohol (350mg, 0.722 mmol, 1 equiv.) and pyridine (0.292 mL, 3.61 mmol, 5 equiv) were diluted in dichloromethane (Volume: 3.6mL) and stirred at room temperature for 5 minutes. Dess-Martin periodinane (919 mg, 2.166 mmol, 3 equiv) was added and the reaction was stirred for 3 hours. Quenched with 5:1 NaS_2O_3:$NaHCO_3$ and stirred for 1 hour. The aqueous layer was separated and extracted with dichloromethane (x3, 5mL). The organic layers were combined,

dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography purification resulted in 310mg (89%) of the desired ketone.: ^1H NMR (600MHz , $CDCl_3$) □ = 7.26 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 5.87 (tdd, *J* = 7.1, 10.1, 17.1 Hz, 1 H), 5.26 (d, *J* = 4.5 Hz, 1 H), 5.14 (dd, *J* = 1.1, 10.2 Hz, 1 H), 5.10 (dd, *J* = 1.5, 16.9 Hz, 1 H), 4.84 (s, 1 H), 4.79 (s, 1 H), 4.70 (d, *J* = 11.3 Hz, 1 H), 4.22 (d, *J* = 11.3 Hz, 1 H), 3.80 (s, 3 H), 3.77 - 3.73 (m, 1 H), 3.68 (dd, *J* = 5.5, 10.4 Hz, 1 H), 3.47 (d, *J* = 1.5 Hz, 1 H), 3.11 (d, *J* = 7.2 Hz, 2 H), 2.79 (d, *J* = 18.8 Hz, 1 H), 2.68 (d, *J* = 8.7 Hz, 1 H), 2.49 (d, *J* = 6.8 Hz, 2 H), 2.44 (dd, *J* = 9.0, 19.2 Hz, 1 H), 2.02 - 1.95 (m, 1 H), 1.95 - 1.87 (m, 1 H), 1.77 (s, 3 H), 1.48 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 208.1, 158.8, 142.2, 135.1, 131.0, 130.5, 128.8, 119.1, 119.0, 113.6, 113.4, 99.6, 79.3, 77.2, 76.8, 74.9, 74.7, 68.5, 55.2, 48.0, 43.4, 39.6, 37.9, 37.5, 30.0, 27.1, 22.2, 21.5, 19.6, 8.6; IR (film) 3075.96, 2938.02, 1714.41, 1644.02, 1613.16, 1586.16, 1514.81, 1443.46, 1380.78, 1344.14, 1301.72, 1249.65, 1201.43, 1172.51, 1120.44, 1073.19, 915.058, 820.563, 732.817, 520.868 cm^{-1}; $[\alpha]^{20}_D$ = -25.66° (*c* 0.4, CH_2Cl_2); MS (ESI) calculated for $C_{30}H_{42}O_5$: $[M+Na]^+$: 505.2931, found 505.2955.



154

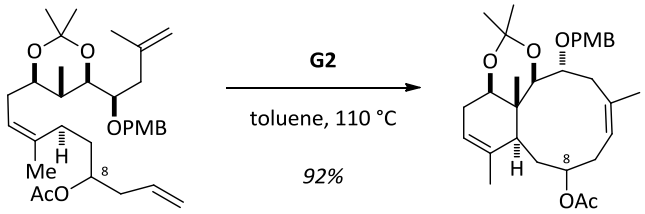
Ketone (300mg, 0.622 mmol, 1 equiv) was diluted in dichloromethane (Volume: 6.26mL) and cooled to 0 °C. DIBAL (1.243 mL, 1.243 mmol, 2 equiv) was added quickly and the reaction was allowed to stir for 1 hour. TLC showed two equal spots signaling the completion of the reaction as the desired diastereomer co-spots on the TLC plate with the starting ketone. Reaction was quenched with Rochelle's salt and stirred at room temperature for 2 hours. The separated aqueous layer was extracted with dichloromethane and the combined organic layers were dried over MgSO4 and concentrated under reduced pressure. Crude material was dry-loaded on to column and purified (10% EtOAc/Hexanes). Efficient separation of diastereomers was possible only by dry-loading column. 121 mg (40%) of desired alcohol **154** was isolated as a clear oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.81 (m, 1H), 5.32 (s, 1H), 5.15 (s, 1H), 5.22 (d, *J* = 5.2 Hz, 1H), 4.85 (s, 1H), 4.81 (s, 1H), 4.57 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 106.2 Hz, 2H), 4.03 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.82 (m, 1H), 3.76 (s, 3H), 3.66 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.45 (s, 1H), 2.60 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.45 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.41 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.07-1.92 (band, 5H), 1.80 (s, 3H), 1.73 (s, 3H), 1.71 (m, 1H), 1.51 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 1.14 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.8, 142.3, 136.0, 134.8, 131.1, 128.9, 119.9, 118.3, 113.5, 113,4. 98.7, 79.8, 75.3, 74.6, 71.1, 68.2, 55.1, 42.4, 42.0, 41.4, 37.9, 36.3, 30.0, 27.7, 23.8, 22.8, 19.3, 7.9; IR (film) 3460 (br), 3075, 2937, 1515, 1380, 1250 cm^{-1}; $[\alpha]^{20}_{D}$ = -17.7^{o} (*c* 2.73, CH_2Cl_2); MS (ESI) calculated for $C_{30}H_{44}O_5$ $[M+Na]^+$: 507.3087, found: 507.3104.



154 **130**

Freshly distilled pyridine (0.35 mL, 4.34 mmol, 3.0 eq) was added to a stirring solution of alcohol **154** (701.0 mg, 1.44 mmol, 1.0 eq) in CH_2Cl_2 (15 mL). The reaction mixture was cooled in an ice/water bath and acetic anhydride (0.27 mL, 2.89 mmol, 2.0 eq) was added dropwise via syringe, followed by the addition of 4-dimethylaminopyridine (17.1 mg, 0.14 mmol, 0.1 eq). After 10 min, the reaction mixture was allowed to warm to room temperature and stirred an additional 3 h. Half-saturated NH_4Cl solution was added to quench the reaction and the layers were separated subsequently. The aqueous layer was further extracted three times with CH_2Cl_2 and the combined organic solution was dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) gave 751 mg (99%) of the desired acetate **130** as a light yellow oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.71 (dddd, *J* = 10.4, 7.6, 2.8, 2.8 Hz, 1H), 5.31 (d, *J* = 4.0 Hz, 1H), 5.22 (m, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 5.00 (d, *J* = 2.8 Hz, 1H), 4.86 (s, 1H), 4.83 (s, 1H), 4.58 (AB, J_{AB} = 11.0 Hz, Δv_{AB} = 114.6 Hz, 2H), 4.06 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.76 (s, 3H), 3.63 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.45 (s, 1H), 2.63 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.47 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.43 (dd, *J* = 9.2, 3.6 Hz, 1H), 2.24 (m, 1H), 2.11 (dd, *J* = 15.2, 10.0 Hz, 1H), 1.98 (s, 3H), 1.97 (m, 1H), 1.91 (m, 1H), 1.85 (m, 1H), 1.84 (s, 3H), 1.72 (s, 3H), 1.65 (dddd, *J* =

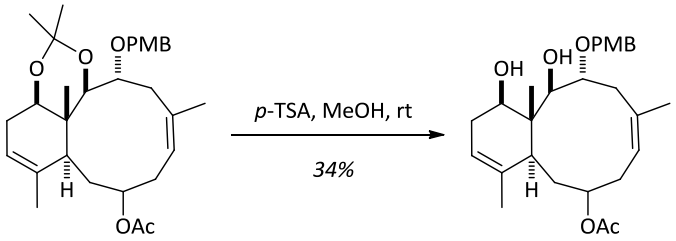
16.0, 8.0, 8.0, 8.0 Hz, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.13 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 170.5, 158.8, 142.2, 135.4, 133.6, 131.1, 128.7, 120.1, 117.6, 113.5, 113.4, 98.8, 79.7, 75.6, 74.5, 73.8, 68.2, 55.1, 41.60, 41.56, 39.2, 37.9, 33.3, 30.0, 27.6, 23.5, 22.7, 21.1, 19.3, 7.9; IR (film) 3077, 2938, 2857, 1735, 1644, 1613, 1514, 1442, 1380, 1247, 1035 cm^{-1}; $[\alpha]^{20}_D$ = -16.7° (*c* 1.61, CH_2Cl_2); MS (ESI) calculated for $C_{32}H_{46}O_6$ $[M+Na]^+$: 549.3193, found: 549.3214.



130 **155**

A solution of triene **130** (47.1 mg, 0.089 mmol, 1.0 eq) in toluene (45 mL) was degassed by heating to reflux for 30 min. Grubbs second generation catalyst $[Cl_2(PCy_3)(IMes)Ru=CHPh]$ (3.8 mg, 0.0045 mmol, 0.05 eq) was added and the solution was stirred at reflux under an argon atmosphere. After 10 min, TLC indicated that all the triene **130** was consumed and the reaction mixture was allowed to cool to room temperature and stirred in the air for an additional 2 h. The reaction mixture was concentrated and then directly loaded to a silica gel column, and purification by flash chromatography (2-10-15% EtOAc/hexanes) gave 39.9 mg (92%) of the desired bicycle **155** as a light brown oil: ^{1}H (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.38 (m, 1H), 5.34 (s, 1H), 5.19 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.56 (AB, J_{AB} = 9.4 Hz, Δv_{AB} = 154.2 Hz, 2H), 3.77 (s, 3H), 3.70 (m, 2H), 3.64 (d, *J* = 6.4 Hz, 1H), 2.35-2.26 (m, 4H), 2.05-1.96

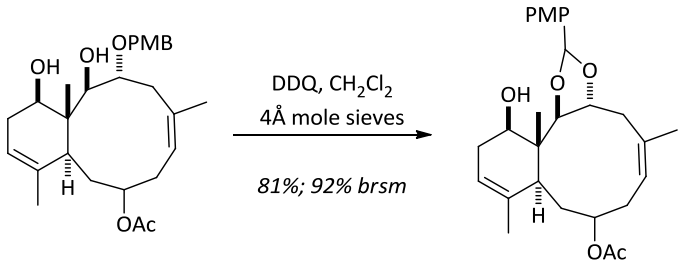
(m, 3H), 2.02 (s, 3H), 1.86 (s, 3H), 1.81 (m, 1H), 1.80 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.23 (m, 1H), 0.98 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 170.2, 159.2, 135.9, 131.1, 129.8, 120.4, 113.7, 98.5, 74.1, 73.5, 73.0, 55.2, 39.9, 30.0, 27.9, 21.2, 19.1, 7.4; IR (film) 3076, 2988, 2936, 2859, 1733, 1613, 1514, 1379, 1249, 1205, 1171, 1029 cm^{-1}; $[\alpha]^{22}_D$ = +13.3^o (*c* 2.32, CH_2Cl_2); MS (ESI) calculated for $C_{30}H_{42}O_6$ $[M+Na]^+$: 521.2815, found: 521.2882.



155 **178**

Bicycle **155** (35mg, 0.07mmol, 1 equiv) in freshly distilled, dry methanol (7.0mL, 0.01M). *P*-toluenesulfonic acid monohydrate (13mg, .07 mmol, 1 equiv) was added and the reaction was allowed to stir for 6 hours at room temperature and monitored by TLC. The reaction was quenched with saturated $NaHCO_3$ (5mL) and a milky mixture formed instantly. Addition of water (5mL) and CH_2Cl_2 formed a clear biphasic mixture. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (x3, 5mL). Combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Flash chromatography afforded 10mg (31%) of the desired diol as a clear oil. 16.1 mg (46%) of the starting material was recovered and could be resubjected. If allowed to react to complete consumption of the bicycle starting material, the major product is the triol product where both the acetonide and the acetate protecting group have

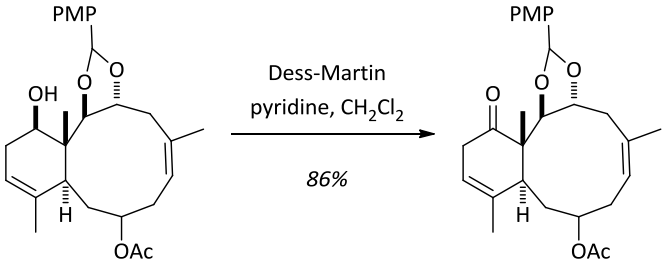
been displaced. ^{1}H NMR (600MHz ,$CDCl_3$) □ = 7.29 (d, *J* = 8.3 Hz, 2 H), 6.89 (d, *J* = 8.3 Hz, 2 H), 5.35 (t, *J* = 8.1 Hz, 1 H), 5.26 (br. s., 1 H), 5.11 (br. s., 1 H), 4.73 (d, *J* = 10.9 Hz, 1 H), 4.54 (d, *J* = 10.9 Hz, 1 H), 4.08 (br. s., 1 H), 3.80 (s, 1 H), 3.78 - 3.78 (m, 1 H), 3.69 (dd, *J* = 4.7, 8.1 Hz, 1 H), 3.35 (br. s., 1 H), 2.65 (br. s., 1 H), 2.34 (br. s., 1 H), 2.31 - 2.23 (m, 1 H), 2.12 (d, *J* = 15.1 Hz, 2 H), 2.02 (s, 4 H), 2.04 - 2.00 (m, 1 H), 1.98 (br. s., 2 H), 1.92 (d, *J* = 10.2 Hz, 1 H), 1.81 (br. s., 3 H), 1.72 (br. s., 4 H), 1.65 (d, *J* = 10.5 Hz, 1 H), 1.46 (d, *J* = 11.3 Hz, 1 H), 1.44 - 1.38 (m, 1 H), 0.94 (s, 3 H); ^{13}C (150MHz, $CDCl_3$) δ 170.08, 159.68, 135.99, 133.86, 129.95, 129.07, 122.50, 119.19, 114.08, 113.71, 81.43, 73.34, 70.72, 55.29, 42.58, 40.17, 39.63, 36.60, 33.99, 29.67, 24.66, 23.32, 23.27, 21.32; IR (film) 3446.17, 2918.73, 2360.44, 1731.76, 1612.20, 1513.85, 1456.96, 1375, 1251.58, 1175.4, 1032.69, 822.49, 539.00, 512.00; $[\alpha]^{20}_{D}$ = -17.7 ° (c=.004, CH_2Cl_2); MS (ESI) calculated for $C_{27}H_{38}O_6$ $[M+Na]^+$: 481.2567, found: 481.2569.



178 **176**

Diol **178** (240 mg, .523 mmol, 1 equiv) was diluted in dichloromethane (5.23 ml) and cooled to 0 °C. DDQ (0.119 g, 0.523 mmol, 1 equiv) added in one portion as a solid and the reaction was allowed to stir for 3 hours. Reaction didn't change by TLC after 3 hours and was quenched with saturated sodium bicarbonate and stirred for 30 minutes. Organic phase was separated and the

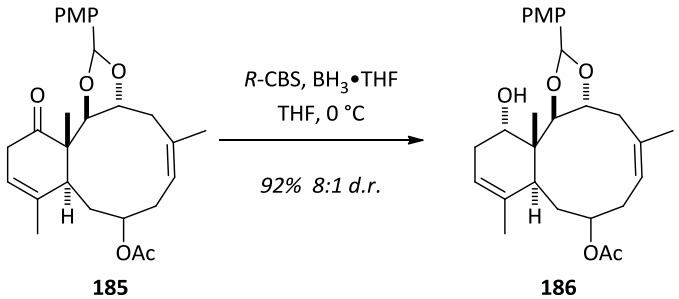
aqueous layer was washed with dichloromethane (x3, 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (30% EtOAc/Hexanes) afforded 194mg (81%) of the desired acetal **176** as a clear oil: ^{1}H NMR (400MHz, $CDCl_3$) □ = 7.37 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 5.80 (s, 1 H), 5.45 (br. s., 1 H), 5.37 (br. s., 1 H), 5.27 (br. s., 1 H), 4.66 (s, 1 H), 3.87 (d, *J* = 7.8 Hz, 1 H), 3.84 - 3.76 (m, 4 H), 3.73 (dd, *J* = 5.2, 10.4 Hz, 1 H), 2.37 (br. s., 3 H), 2.12 (d, *J* = 11.1 Hz, 3 H), 2.05 - 2.00 (m, 4 H), 1.87 (s, 3 H), 1.82 (s, 3 H), 1.77 (d, *J* = 4.6 Hz, 2 H), 1.03 (s, 3 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 170.3, 160.6, 128.3, 128.1, 113.8, 113.8, 103.8, 91.4, 77.2, 76.8, 76.4, 55.3, 53.4, 39.7, 36.6, 31.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 29.0, 28.4, 24.7, 24.6, 23.3, 22.7, 21.3, 14.1, 7.9; IR (film) 3458.71 (broad), 2916.81, 2849.31, 2359.48, 1731.76, 1615.09, 1517.7, 1462.74, 1373.07, 1303.64, 1249.65, 1170.58, 1083.80, 1024.88, 830.20 cm^{-1}; $[\alpha]^{20}_D$ = -5.59° (c= 0.25, CH_2Cl_2); MS (ESI) calculated for $C_{27}H_{36}O_6$: $[M+Na]^+$: 479.2410, found: 479.2414.



176 **185**

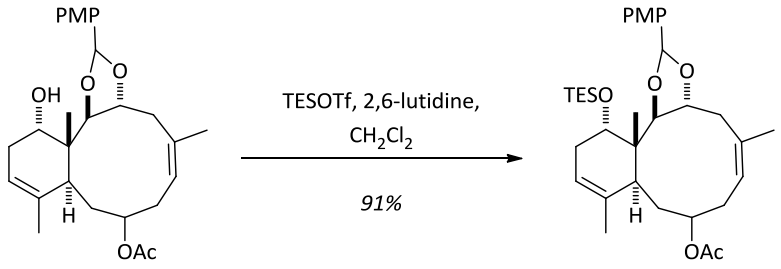
Alcohol **176** (.15 g, 0.329 mmol, 1 equiv) was diluted in dichloromethane (Volume: 3.29 ml). Pyridine (0.133 ml, 1.643 mmol, 5 equiv) added and stirred 5 minutes. Dess-Martin periodinane (0.418 g, 0.986 mmol 3 equiv) added and

reaction stirred for 3 hours. TLC shows no change, though complete consumption is observed by NMR after 3 hours. Reaction quenched with 5:1 NaS_2O_3:$NaHCO_3$ aqueous solution and stirred for 1 hour. Organic layer was separated and the aqueous washed with dichloromethane (x3, 5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (30% EtOAc/Hexanes) purification afforded 283mg (86%) of the ketone **185** as a clear oil: ^{1}H NMR (400MHz ,$CDCl_3$) □ = 7.39 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 5.58 (br. s., 1 H), 5.29 - 5.20 (m, 2 H), 4.22 - 4.17 (m, 1 H), 4.16 (br. s., 1 H), 3.80 (s, 1 H), 3.78 (s, 3 H), 3.09 (d, *J* = 15.3 Hz, 1 H), 2.87 (d, *J* = 14.3 Hz, 1 H), 2.71 (d, *J* = 15.3 Hz, 1 H), 2.59 (d, *J* = 11.1 Hz, 1 H), 2.36 (d, *J* = 6.2 Hz, 3 H), 2.08 - 2.04 (m, 4 H), 2.03 (s, 1 H), 1.90 (s, 3 H), 1.86 (br. s., 4 H), 1.85 - 1.81 (m, 2 H), 1.23 (br. s., 3 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 170.2, 160.4, 138.8, 129.9, 128.3, 128.1, 113.8, 113.7, 113.6, 103.7, 77.2, 76.8, 73.2, 55.3, 51.6, 38.7, 36.6, 35.7, 33.8, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 29.0, 24.7, 22.7, 22.2, 21.3, 14.1; IR (film) 3441.25 (broad), 2924.52, 1732.73, 1614.13, 1515.77, 1375.96, 11247.72, 626.91 cm^{-1}; $[\alpha]^{20}_D$ = -53.15° (c= 0.05, CH_2Cl_2); MS (ESI) calculated for $C_{27}H_{34}O_6$ $[M+Na]^+$: 477.2254, found: 477.2245.



185 **186**

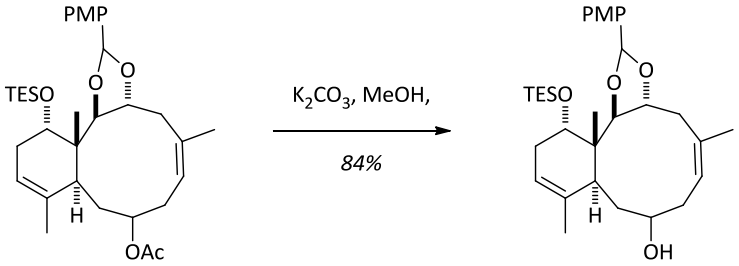
Ketone **185** (55mg, 0.121 mmol, 1 equiv) was diluted in THF (1.2mL, 0.1M). (*R*)-CBS was added and the reaction was cooled to 0 ^{o}C before adding borane-THF complex (1M solution, 0.133mL, 1.1 equiv). The reaction was stirred for 3.5 hours, at which point the starting material had been consumed as observed by TLC. The reaction as quenched with saturated NaHCO3 and diluted with 3mL ethyl acetate. Organic layer was separated and the aqueous was extracted with ethyl acetate (x3, 3mL), dried over MgSO4, concentrated under reduced pressure and purified by flash chromatography (30% EtOAc/Hexanes) to afford 45.3mg (82%) of alcohol **186** as a clear oil: ^{1}H NMR (600MHz , $CDCl_3$) □ = 7.40 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.72 (s, 1 H), 5.39 (br. s., 1 H), 5.33 (d, *J* = 4.5 Hz, 1 H), 5.22 (t, *J* = 8.7 Hz, 1 H), 4.27 (d, *J* = 8.3 Hz, 1 H), 4.22 (d, *J* = 5.6 Hz, 1 H), 4.09 - 4.05 (m, 1 H), 3.79 (s, 3 H), 3.78 - 3.76 (m, 1 H), 2.42 - 2.30 (m, 4 H), 2.14 (d, *J* = 11.7 Hz, 1 H), 2.03 (s, 3 H), 1.88 (d, *J* = 7.2 Hz, 6 H), 1.85 (br. s., 1 H), 1.83 - 1.78 (m, 1 H), 1.66 (br. s., 2 H), 0.89 (s, 3 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 171.1, 170.2, 170.1, 160.5, 160.4, 136.5, 130.4, 128.4, 128.2, 126.9, 119.0, 113.8, 113.7, 103.3, 77.2, 76.8, 74.2, 70.7, 67.5, 60.4, 55.3, 55.3, 51.8, 43.6, 39.4, 36.4, 36.1, 35.3, 34.7, 31.6, 29.6, 29.0, 25.7, 25.3, 24.1, 22.6, 21.6, 21.3, 21.0, 20.7, 18.8, 14.2, 14.1, 13.2, 11.4; IR (film) 3441.25 (broad), 2924.52, 1732.73, 1614.13, 1515.77, 1375.96, 1247.72, 1026.91 cm^{-1}; $[\alpha]^{20}_{D}$ = -12.28° (c= 0.1, CH_2Cl_2); MS (ESI) calculated for $C_{27}H_{36}O_6$ $[M+Na]^+$: 479.2410, found: 479.2413.



186 **187**

Alcohol **186** (40 mg, 0.088 mmol, 1 equiv) was diluted in dichloromethane (Volume: 876 µl) and purged with argon. Freshly distilled 2,6-Lutidine (30.6 µl, 0.263 mmol, 3 equiv) was added by syringe and the reaction was cooled to 0 °C. TESOTf (29.7 µl, 0.131 mmol, 1.5 equiv) was then added dropwise and the reaction stirred for 2 hours at 0 °C. The reaction was complete and quenched with sat. NH_4Cl, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure. Purified by flash chromatography (10-20% EtOAc/Hexanes) resulting in the silyl ether **187** as a clear oil: ^{1}H NMR (600MHz , $CDCl_3$) □ = 7.39 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.68 (s, 1 H), 5.40 (br. s., 1 H), 5.26 - 5.17 (m, 1 H), 4.19 (d, *J* = 6.8 Hz, 1 H), 4.13 (d, *J* = 6.4 Hz, 1 H), 4.05 (br. s., 1 H), 3.79 (s, 3 H), 2.70 (br. s., 1 H), 2.42 - 2.29 (m, 2 H), 2.21 - 2.12 (m, 2 H), 2.03 (s, 3 H), 1.89 (br. s., 1 H), 1.88 (s, 3 H), 1.84 (d, *J* = 3.4 Hz, 1 H), 1.82 (s, 3 H), 1.80 - 1.75 (m, 1 H), 1.21 - 1.13 (m, 1 H), 0.91 - 0.87 (m, 9 H), 0.83 (s, 3 H), 0.53 (d, *J* = 8.3 Hz, 9 H), 0.53 (q, *J* = 1.0 Hz, 6 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 170.2, 160.4, 160.3, 135.5, 130.6, 128.3, 128.2, 113.7, 113.6, 103.2, 77.2, 76.8, 74.6, 71.3, 55.3, 55.3, 44.1, 36.6, 36.1, 35.7, 35.2, 29.9, 25.5, 24.7, 23.3, 21.3, 12.5, 7.0, 6.9, 5.4, 5.2, 5.1, 5.0; IR (film) 3790.4, 3698.80, 2915.84, 2360.44, 2342.12, 1737.55, 1613.16, 1514.81, 1379.82, 1246.75, 1072.05, 1012.45, 668.21, 574.683, 521.65, 505.26 cm^{-1}; $[\alpha]^{20}_D$ = -6.22° (c=

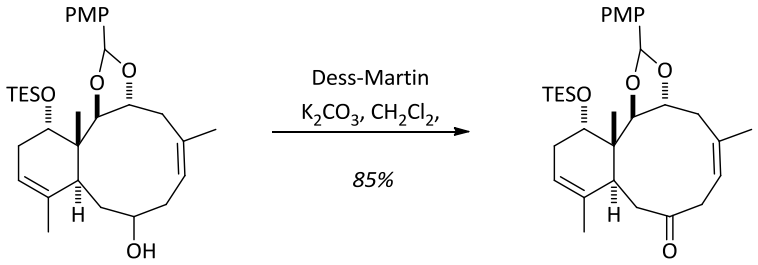
0.25, CH_2Cl_2); MS (ESI) calculated for $C_{33}H_{50}O_6Si$ $[M+Na]^+$: 593.3275, found: 593.3304.



187

Acetate **187** (103mg, 0.180 mmol, 1 equiv) was diluted in MeOH (Volume: 1.8 mL). Potassium carbonate (74.8 mg, 0.541 mmol, 3 equiv) was added and the reaction was left to stir for 4 hours. An additional 3 equiv of potassium carbonate were added and reaction was allowed to stir for 5 more hours. The reaction was quenched with sat. NH_4Cl, diluted with water and ethyl acetate. The organic layer was separated and the aqueous was extracted with EtOAc, dried over $MgSO_4$ and concentrated. Purified by flash chromatography (30%EtOAc/Hexanes) resulting in the alcohol product as a clear oil: ^{1}H NMR (600MHz ,$CDCl_3$) □ = 7.40 (d, *J* = 8.2 Hz, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 5.69 (s, 1 H), 5.32 (t, *J* = 8.2 Hz, 1 H), 5.23 (br. s., 1 H), 4.20 - 4.15 (m, 1 H), 4.06 (br. s., 1 H), 3.79 (s, 3 H), 2.69 (br. s., 1 H), 2.41 (d, *J* = 10.2 Hz, 1 H), 2.34 (s, 1 H), 2.30 - 2.24 (m, 1 H), 2.18 (d, *J* = 17.4 Hz, 1 H), 2.11 (d, *J* = 10.2 Hz, 1 H), 1.90 - 1.83 (m, 5 H), 1.79 (br. s., 3 H), 0.89 (t, *J* = 7.7 Hz, 9 H), 0.83 (s, 3 H), 0.57 - 0.50 (m, 6 H); ^{13}C NMR (150 MHz ,$CDCl_3$) □ = 160.3, 135.7, 130.2, 128.5, 128.5, 128.3, 128.2, 113.7, 113.6, 103.2, 77.2, 76.8, 71.8, 71.3, 55.3, 55.3, 44.1, 36.6, 36.1, 35.4, 30.0, 25.5, 24.7, 23.3, 21.9, 12.4, 7.0, 6.9, 6.8, 5.2, 5.1; IR (film)

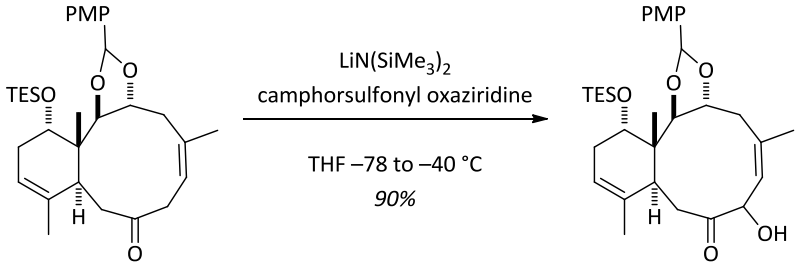
3732.55, 2926.45, 2358.98, 2341.16, 1455.99, 668.214, 581.433, 525.507, 509.115 cm^{-1}; $[\alpha]^{20}_{D}$ = +19.62° (c= 0.3, CH_2Cl_2); MS (ESI) calculated for $C_{31}H_{48}O_5Si$ $[M+Na]^+$: 551.3169, found: 551.3553.



188

Alcohol (10.6mg, 0.020 mmol, 1 equiv) was diluted in dichloromethane (Volume: 200 µl) and buffered with potassium carbonate (13.85 mg, 0.100 mmol, 5 equiv) added and stirred for 2 minutes. Dess-Martin periodinane (25.5 mg, 0.060 mmol, 3 equiv) was added and reaction allowed to stir at room temperature for 3 hours. Reaction was quenched with 5:1 $Na_2S_2O_3$:$NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography purification (15-25% EtOAc/Hexanes) resulted in the ketone **188** as a clear oil: ^{1}H NMR (600MHz ,$CDCl_3$) □ = 7.39 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.71 (s, 1 H), 5.27 (t, *J* = 6.2 Hz, 1 H), 5.21 (d, *J* = 5.3 Hz, 1 H), 4.19 - 4.15 (m, 1 H), 4.14 - 4.08 (m, 1 H), 4.00 (s, 1 H), 3.81 - 3.78 (m, 3 H), 3.45 (dd, *J* = 6.8, 13.6 Hz, 1 H), 2.91 - 2.83 (m, 2 H), 2.80 (d, *J* = 9.4 Hz, 1 H), 2.72 (d, *J* = 15.4 Hz, 1 H), 2.29 (dd, *J* = 5.3, 15.4 Hz, 1 H), 2.21 (d, *J* = 18.1 Hz, 1 H), 1.98 (dd, *J* = 9.4, 16.2 Hz, 1 H), 1.91 (br. s., 1 H), 1.88 - 1.85 (m, 3 H), 1.59 - 1.55 (m, 3 H), 0.89 (t, *J* = 7.9 Hz, 9 H), 0.83 (s, 3 H), 0.53 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 211.7, 160.4, 138.2, 135.1, 130.5, 128.3, 128.1, 119.2, 117.6, 113.7,

113.6, 103.4, 84.2, 79.5, 77.2, 76.8, 71.2, 55.3, 43.4, 42.6, 40.2, 36.4, 36.1, 29.8, 25.5, 24.4, 24.0, 22.4, 12.7, 7.0, 6.9, 5.1, 5.0; IR (film) 2915.84, 2359.48, 2342.12, 1705.73, 1517.70, 1456.96, 1248.68, 1076.08, 668.21, 502.36 cm^{-1}; $[\alpha]^{20}_{D}$ = -6.21° (c= 0.3, CH_2Cl_2); MS (ESI) calculated for $C_{31}H_{46}O_5Si$ $[M+Na]^+$: 549.3013, found: 549.3013.

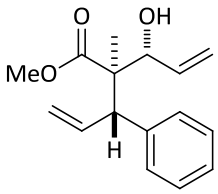


188 **175**

A freshly prepared 1M LHMDS solution (37.0 µl, 0.037 mmol, 3 equiv) was added to a flame dried vial and cooled to -78 °C. Ketone **188** (6.5mg, 0.012 mmol) was diluted in THF (247 µl) and added dropwise to the base. Instantly, the reaction became a bright yellow color. After 30 minutes, dried (+)-camphorsulfonyl oxaziridine (14.15 mg, 0.062 mmol) was diluted in THF (Ratio: 1.000, Volume: 50 µl) and added quickly to the reaction at -78 °C. After 30 minutes, the reaction was warmed to -40 °C and stirred for 3 hours at which point the starting material had been consumed. Saturated NH_4Cl was added to quench the reaction and the organic layer was separated. The aqueous layer was extracted with ethyl acetate repeatedly (x5, 1mL), dried over MgSO4, and concentrated under reduced pressure. Flash chromatography purification (5-10-20% EtOAc/Hexanes) afforded the hydroxyketone **175** as a clear oil: ^{1}H NMR (400MHz , $CDCl_3$) □ = 7.40 (d, *J* = 8.5 Hz, 2 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 6.89 (d,

J = 8.8 Hz, 2 H), 5.71 (s, 1 H), 5.68 (s, 0 H), 5.31 (t, *J* = 6.8 Hz, 1 H), 5.21 (d, *J* = 5.2 Hz, 1 H), 5.00 (d, *J* = 6.5 Hz, 1 H), 4.33 (d, *J* = 9.1 Hz, 1 H), 4.30 (d, *J* = 8.2 Hz, 1 H), 4.14 (dd, *J* = 4.7, 8.6 Hz, 1 H), 4.00 (br. s., 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.78 (d, *J* = 6.5 Hz, 1 H), 2.99 (d, *J* = 15.0 Hz, 1 H), 2.85 (d, *J* = 14.3 Hz, 1 H), 2.73 (d, *J* = 10.8 Hz, 1 H), 2.55 (dd, *J* = 4.6, 15.3 Hz, 2 H), 2.33 (dt, *J* = 2.1, 7.4 Hz, 1 H), 2.22 (br. s., 1 H), 2.20 - 2.10 (m, 2 H), 1.95 - 1.91 (m, 1 H), 1.89 (br. s., 3 H), 1.87 (s, 3 H), 1.51 (br. s., 3 H), 0.90 (t, *J* = 7.8 Hz, 20 H), 0.84 (s, 3 H), 0.54 (q, *J* = 8.2 Hz, 6 H); ^{13}C NMR (150MHz ,$CDCl_3$) □ = 160.5, 135.2, 128.2, 127.2, 125.0, 118.4, 113.7, 103.6, 84.6, 72.9, 72.2, 71.3, 55.4, 53.4, 44.1, 44.0, 43.9, 43.6, 38.9, 37.7, 33.2, 32.2, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 29.1, 26.4, 24.7, 23.4, 23.4, 23.3, 23.2, 22.7, 22.6; IR (film) 3496.31, 2921.63, 2851.24, 1709.59, 1516.54, 1455.03, 1248.68, 1074.16, 739.57 cm^{-1}; $[\alpha]^{23}_{D}$ = 28.88° (c= 0.015, CH_2Cl_2); MS (ESI) calculated for $C_{31}H_{46}O_6Si$: 542.3064, found: 542.3205.

X-Ray Analysis of alcohol 37



37

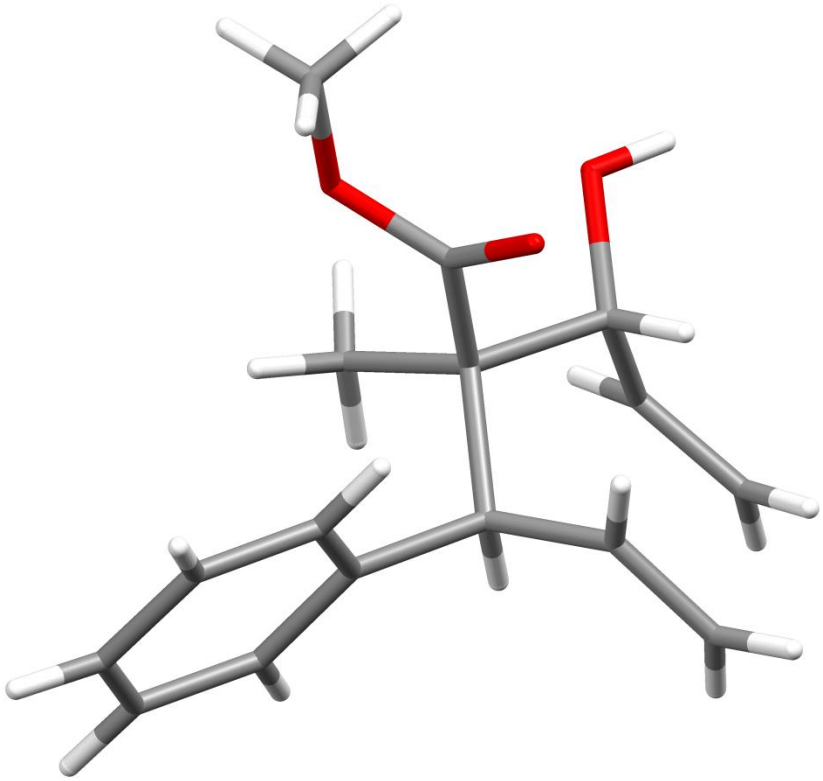


Table 1. Crystal data and structure refinement for c07324.

Identification code	c07324	
Empirical formula	C_{16} H_{20} O_3	
Formula weight	260.32	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 7.6566(4) Å	□= 90°.
	b = 7.0967(4) Å	□= 97.297(2)°.
	c = 13.3256(8) Å	□ = 90°.
Volume	718.20(7) $Å^3$	
Z	2	
Density (calculated)	1.204 Mg/m^3	
Absorption coefficient	0.658 mm^{-1}	
F(000)	280	
Crystal size	0.30 x 0.30 x 0.25 mm^3	
Theta range for data collection	3.34 to 69.96°.	
Index ranges	-9<=h<=9, -8<=k<=8, -16<=l<=16	
Reflections collected	7963	
Independent reflections	2612 [R(int) = 0.0116]	
Completeness to theta = 69.96°	98.8 %	
Absorption correction	Numerical	
Max. and min. transmission	0.8527 and 0.8270	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2612 / 1 / 253	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0731	
R indices (all data)	R1 = 0.0277, wR2 = 0.0731	
Absolute structure parameter	-0.01(14)	
Extinction coefficient	0.0066(12)	
Largest diff. peak and hole	0.211 and -0.160 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for c07324. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8467(1)	3994(1)	6014(1)	23(1)
C(2)	5027(2)	3683(3)	5632(1)	33(1)
O(3)	6089(1)	2288(1)	6234(1)	24(1)
C(4)	7821(2)	2606(2)	6351(1)	18(1)
C(5)	8892(2)	1050(2)	6947(1)	17(1)
C(6)	7710(2)	-527(2)	7282(1)	21(1)
C(7)	10126(2)	261(2)	6202(1)	18(1)
C(8)	11161(2)	-1443(2)	6607(1)	24(1)
C(9)	12886(2)	-1467(2)	6866(1)	29(1)
O(10)	9002(1)	-212(2)	5295(1)	25(1)
C(11)	10030(2)	1900(2)	7914(1)	18(1)
C(12)	11396(2)	3335(2)	7689(1)	21(1)
C(13)	13104(2)	3153(2)	7979(1)	26(1)
C(14)	8865(2)	2688(2)	8665(1)	20(1)
C(15)	8053(2)	4455(2)	8528(1)	23(1)
C(16)	6978(2)	5136(2)	9216(1)	28(1)
C(17)	6693(2)	4058(2)	10053(1)	31(1)
C(18)	7514(2)	2313(2)	10208(1)	30(1)
C(19)	8596(2)	1641(2)	9521(1)	25(1)

Table 3. Bond lengths [Å] and angles [°] for c07324.

O(1)-C(4)	1.2134(15)
C(2)-O(3)	1.4558(16)
O(3)-C(4)	1.3343(14)
C(4)-C(5)	1.5354(16)
C(5)-C(6)	1.5405(16)
C(5)-C(7)	1.5592(16)
C(5)-C(11)	1.5799(15)
C(7)-O(10)	1.4313(14)
C(7)-C(8)	1.5077(17)
C(8)-C(9)	1.3228(19)
C(11)-C(12)	1.5165(16)
C(11)-C(14)	1.5297(16)
C(12)-C(13)	1.3222(18)
C(14)-C(19)	1.3983(18)
C(14)-C(15)	1.4014(18)
C(15)-C(16)	1.3943(19)
C(16)-C(17)	1.392(2)
C(17)-C(18)	1.392(2)
C(18)-C(19)	1.3944(19)
C(4)-O(3)-C(2)	115.24(10)
O(1)-C(4)-O(3)	122.66(11)
O(1)-C(4)-C(5)	123.99(11)
O(3)-C(4)-C(5)	113.35(10)
C(4)-C(5)-C(6)	112.18(9)
C(4)-C(5)-C(7)	104.83(9)
C(6)-C(5)-C(7)	110.47(9)
C(4)-C(5)-C(11)	110.50(9)
C(6)-C(5)-C(11)	108.93(9)
C(7)-C(5)-C(11)	109.87(9)
O(10)-C(7)-C(8)	110.25(10)
O(10)-C(7)-C(5)	105.88(9)
C(8)-C(7)-C(5)	113.18(10)
C(9)-C(8)-C(7)	124.44(12)
C(12)-C(11)-C(14)	110.96(10)

C(12)-C(11)-C(5)	114.73(9)
C(14)-C(11)-C(5)	111.46(9)
C(13)-C(12)-C(11)	123.90(11)
C(19)-C(14)-C(15)	118.25(11)
C(19)-C(14)-C(11)	119.90(11)
C(15)-C(14)-C(11)	121.84(11)
C(16)-C(15)-C(14)	120.86(12)
C(17)-C(16)-C(15)	120.16(13)
C(16)-C(17)-C(18)	119.64(12)
C(17)-C(18)-C(19)	120.05(13)
C(18)-C(19)-C(14)	121.02(13)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for c07324. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	24(1)	23(1)	22(1)	5(1)	5(1)	1(1)
C(2)	23(1)	47(1)	29(1)	12(1)	2(1)	12(1)
O(3)	16(1)	33(1)	23(1)	6(1)	3(1)	4(1)
C(4)	19(1)	22(1)	15(1)	-1(1)	4(1)	3(1)
C(5)	16(1)	17(1)	19(1)	1(1)	2(1)	-1(1)
C(6)	18(1)	20(1)	24(1)	1(1)	3(1)	-3(1)
C(7)	16(1)	19(1)	20(1)	-1(1)	3(1)	-2(1)
C(8)	26(1)	19(1)	28(1)	0(1)	9(1)	2(1)
C(9)	27(1)	30(1)	29(1)	0(1)	4(1)	10(1)
O(10)	20(1)	33(1)	21(1)	-7(1)	4(1)	0(1)
C(11)	17(1)	17(1)	18(1)	2(1)	0(1)	1(1)
C(12)	23(1)	20(1)	20(1)	0(1)	3(1)	-3(1)
C(13)	23(1)	27(1)	30(1)	0(1)	3(1)	-4(1)
C(14)	16(1)	23(1)	19(1)	-2(1)	-1(1)	-2(1)
C(15)	23(1)	22(1)	22(1)	-2(1)	0(1)	-1(1)
C(16)	23(1)	27(1)	31(1)	-10(1)	0(1)	1(1)
C(17)	24(1)	44(1)	26(1)	-14(1)	7(1)	-5(1)
C(18)	31(1)	40(1)	20(1)	-2(1)	7(1)	-6(1)
C(19)	24(1)	28(1)	23(1)	1(1)	2(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)
for c07324.

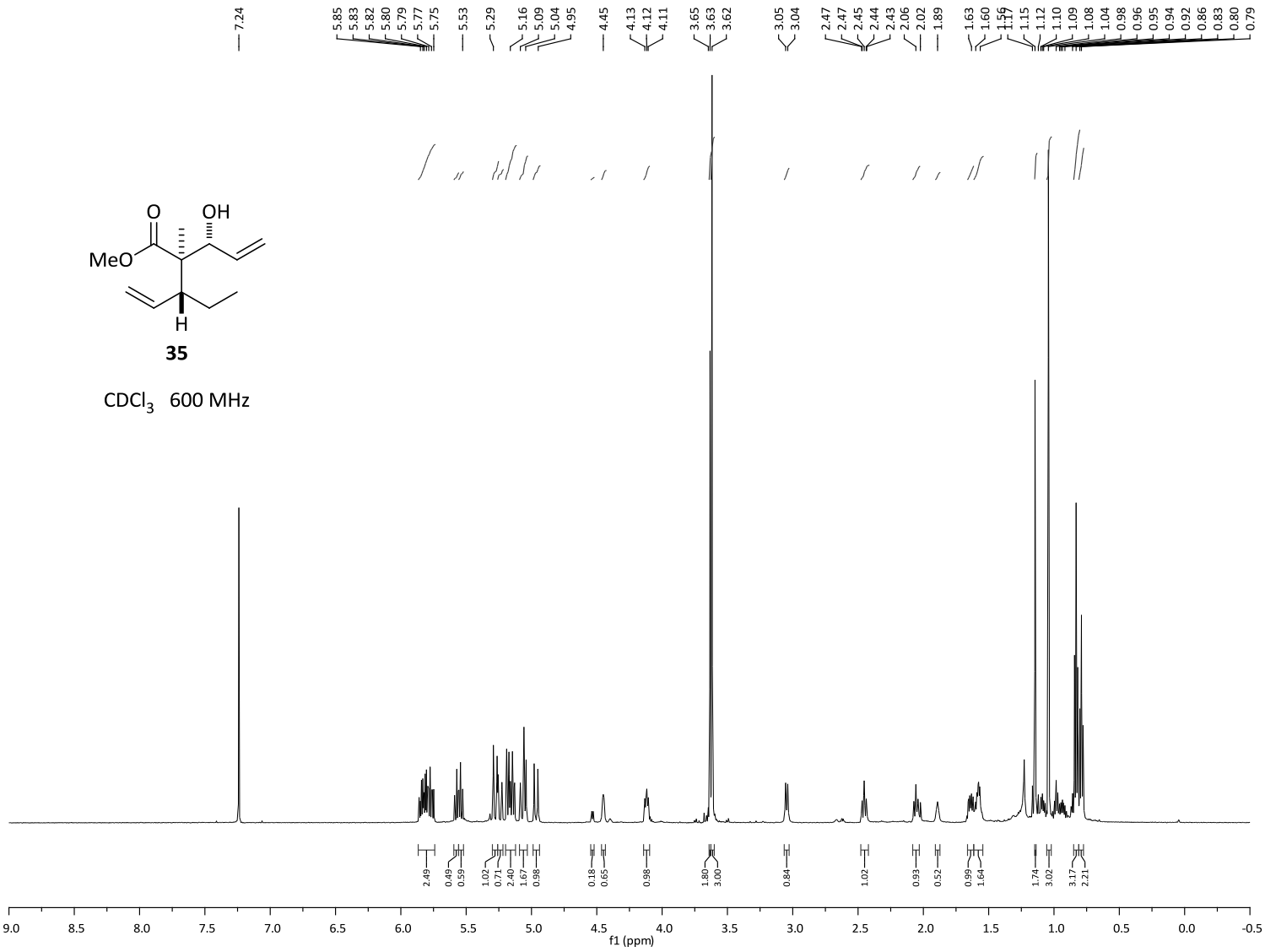
	x	y	z	U(eq)
H(2A)	5430(20)	3780(20)	4971(13)	25(4)
H(2B)	3820(30)	3260(30)	5558(15)	45(5)
H(2C)	5150(30)	4890(30)	5976(16)	44(5)
H(6A)	8450(20)	-1380(30)	7737(13)	25(4)
H(6B)	7140(20)	-1190(30)	6690(13)	31(4)
H(6C)	6780(20)	-20(20)	7611(11)	21(3)
H(7)	10943(19)	1210(20)	6079(11)	16(3)
H(8)	10480(20)	-2560(30)	6627(13)	32(4)
H(9A)	13500(20)	-2650(30)	7141(13)	33(4)
H(9B)	13610(20)	-400(30)	6804(13)	34(4)
H(10)	9620(30)	-450(30)	4873(16)	34(5)
H(11)	10679(19)	840(20)	8252(11)	17(3)
H(12)	10970(20)	4440(30)	7320(14)	34(5)
H(13A)	13590(30)	2010(30)	8296(15)	44(5)
H(13B)	13930(20)	4130(30)	7847(13)	29(4)
H(15)	8230(20)	5170(20)	7962(13)	25(4)
H(16)	6500(20)	6360(30)	9119(13)	33(4)
H(17)	5920(20)	4540(30)	10511(13)	30(4)
H(18)	7310(20)	1550(30)	10791(15)	42(5)
H(19)	9150(20)	440(30)	9636(12)	28(4)

Table 6. Torsion angles [°] for c07324.

C(2)-O(3)-C(4)-O(1)	2.63(16)
C(2)-O(3)-C(4)-C(5)	-177.24(11)
O(1)-C(4)-C(5)-C(6)	179.69(11)
O(3)-C(4)-C(5)-C(6)	-0.45(13)
O(1)-C(4)-C(5)-C(7)	-60.40(14)
O(3)-C(4)-C(5)-C(7)	119.46(10)
O(1)-C(4)-C(5)-C(11)	57.92(14)
O(3)-C(4)-C(5)-C(11)	-122.22(10)
C(4)-C(5)-C(7)-O(10)	-52.77(11)
C(6)-C(5)-C(7)-O(10)	68.27(12)
C(11)-C(5)-C(7)-O(10)	-171.52(9)
C(4)-C(5)-C(7)-C(8)	-173.65(10)
C(6)-C(5)-C(7)-C(8)	-52.61(13)
C(11)-C(5)-C(7)-C(8)	67.60(12)
O(10)-C(7)-C(8)-C(9)	129.80(13)
C(5)-C(7)-C(8)-C(9)	-111.82(14)
C(4)-C(5)-C(11)-C(12)	-62.31(13)
C(6)-C(5)-C(11)-C(12)	174.03(10)
C(7)-C(5)-C(11)-C(12)	52.88(13)
C(4)-C(5)-C(11)-C(14)	64.86(12)
C(6)-C(5)-C(11)-C(14)	-58.80(12)
C(7)-C(5)-C(11)-C(14)	-179.95(9)
C(14)-C(11)-C(12)-C(13)	111.35(14)
C(5)-C(11)-C(12)-C(13)	-121.22(13)
C(12)-C(11)-C(14)-C(19)	-129.60(12)
C(5)-C(11)-C(14)-C(19)	101.20(12)
C(12)-C(11)-C(14)-C(15)	49.98(14)
C(5)-C(11)-C(14)-C(15)	-79.22(13)
C(19)-C(14)-C(15)-C(16)	-1.22(17)
C(11)-C(14)-C(15)-C(16)	179.20(11)
C(14)-C(15)-C(16)-C(17)	-0.16(18)
C(15)-C(16)-C(17)-C(18)	1.2(2)
C(16)-C(17)-C(18)-C(19)	-0.9(2)
C(17)-C(18)-C(19)-C(14)	-0.56(19)

C(15)-C(14)-C(19)-C(18)	1.58(18)
C(11)-C(14)-C(19)-C(18)	-178.83(11)

Spectra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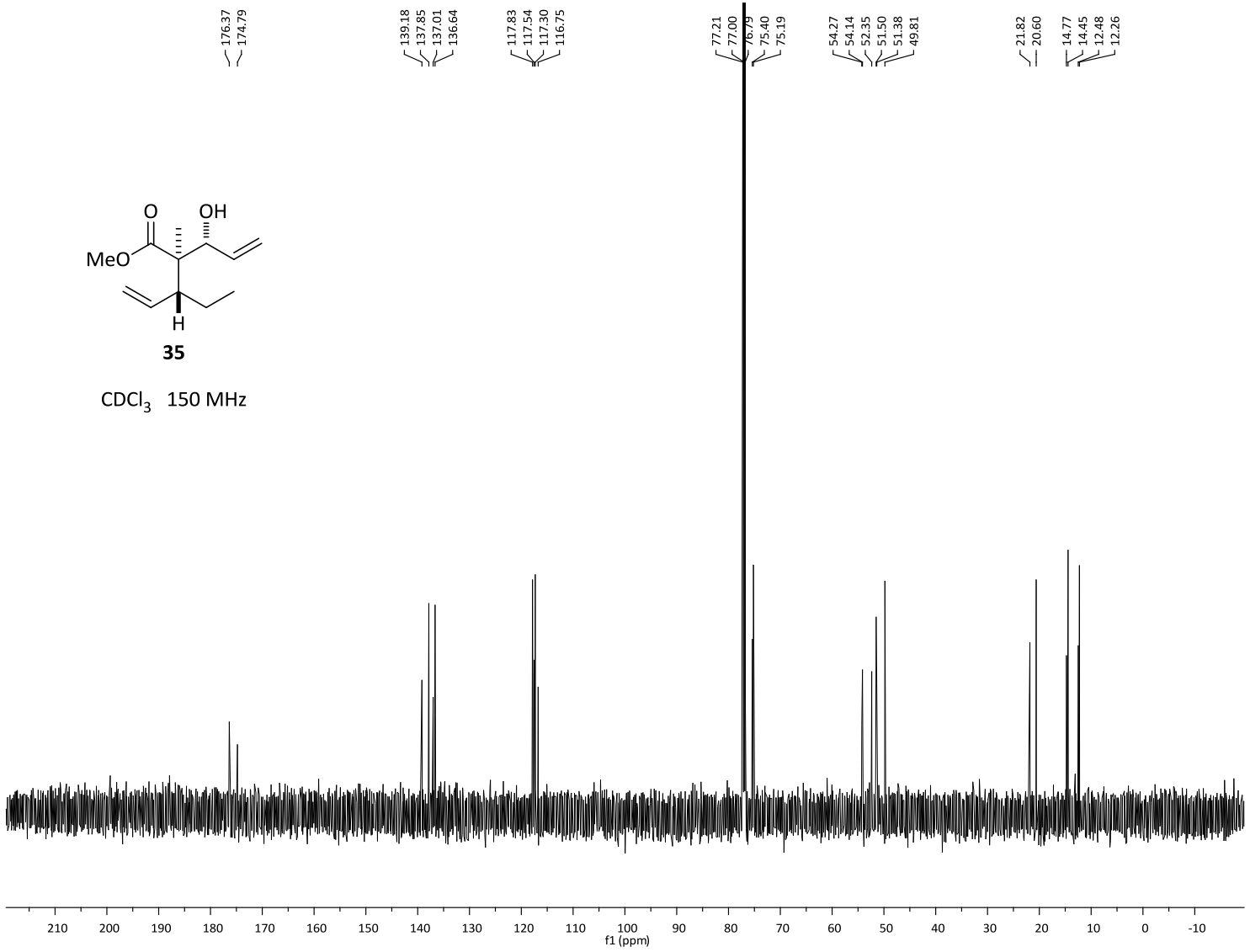
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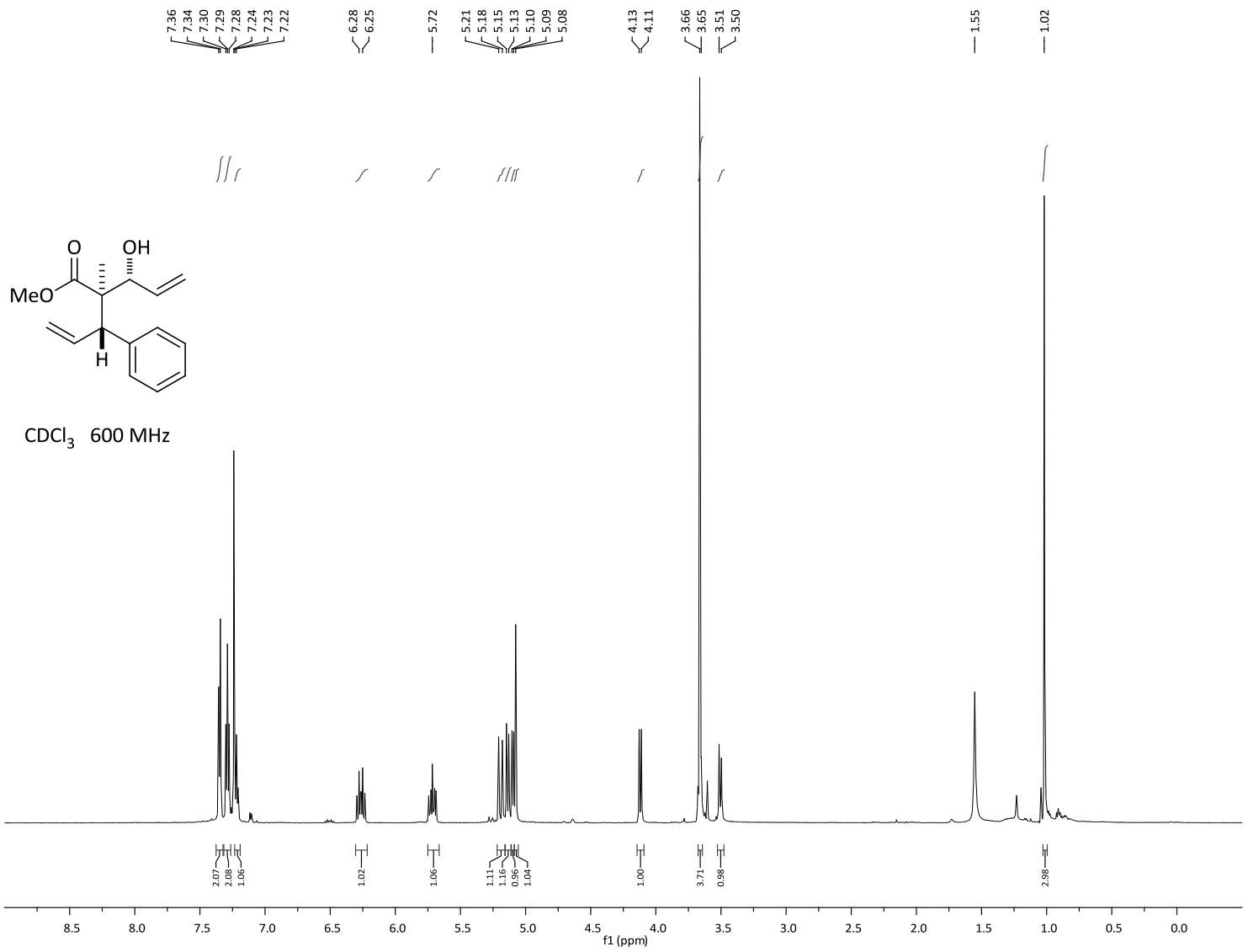
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7.0
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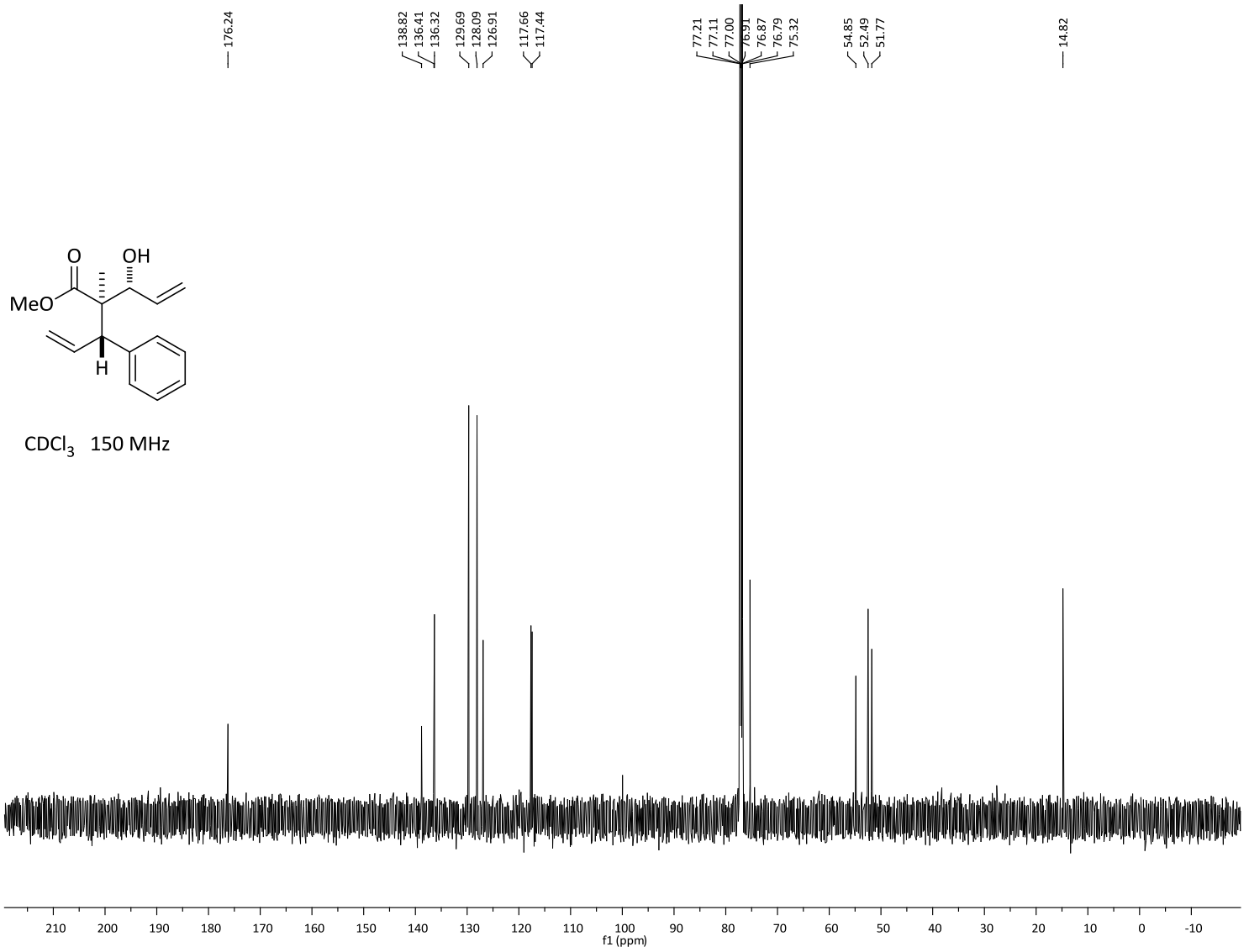
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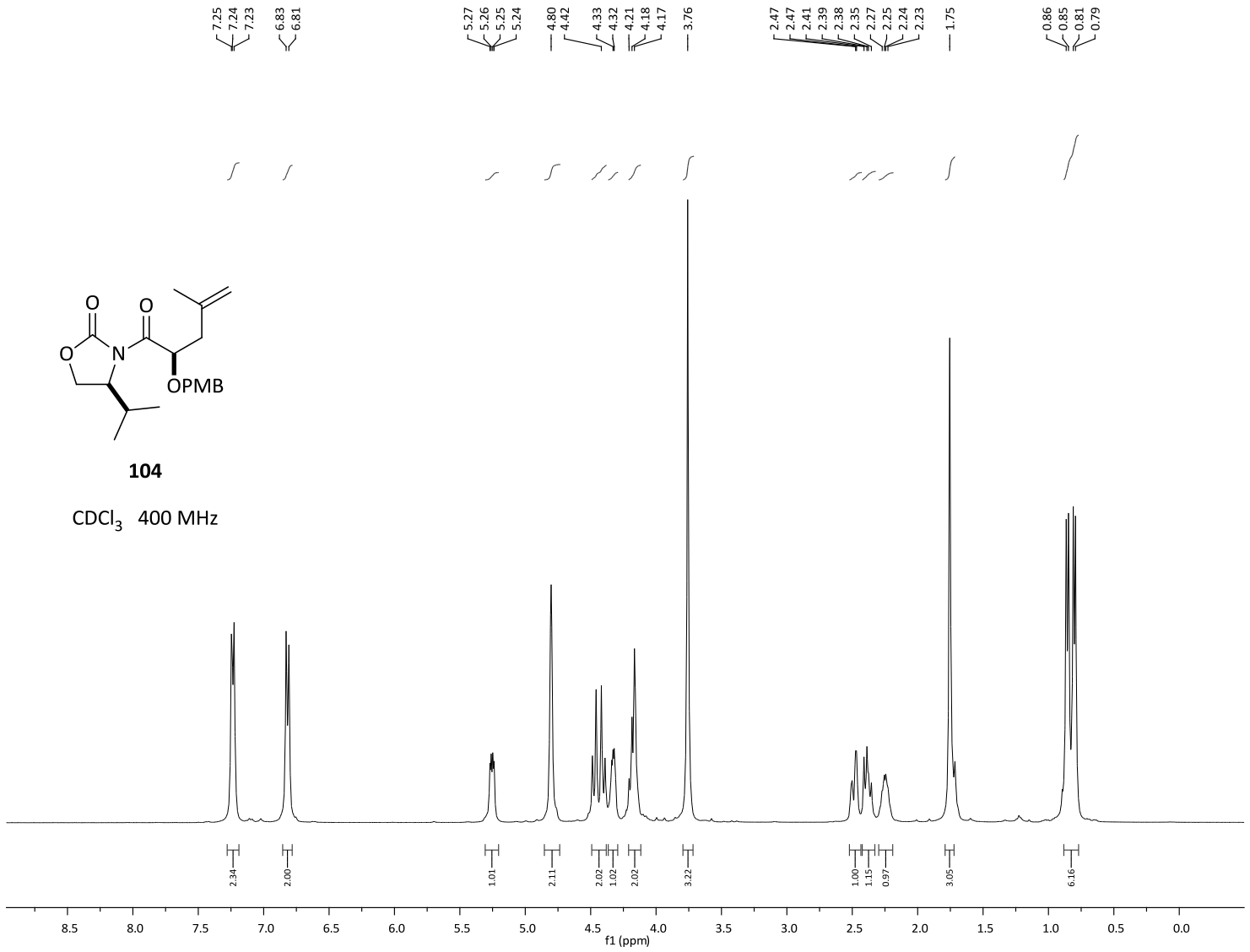
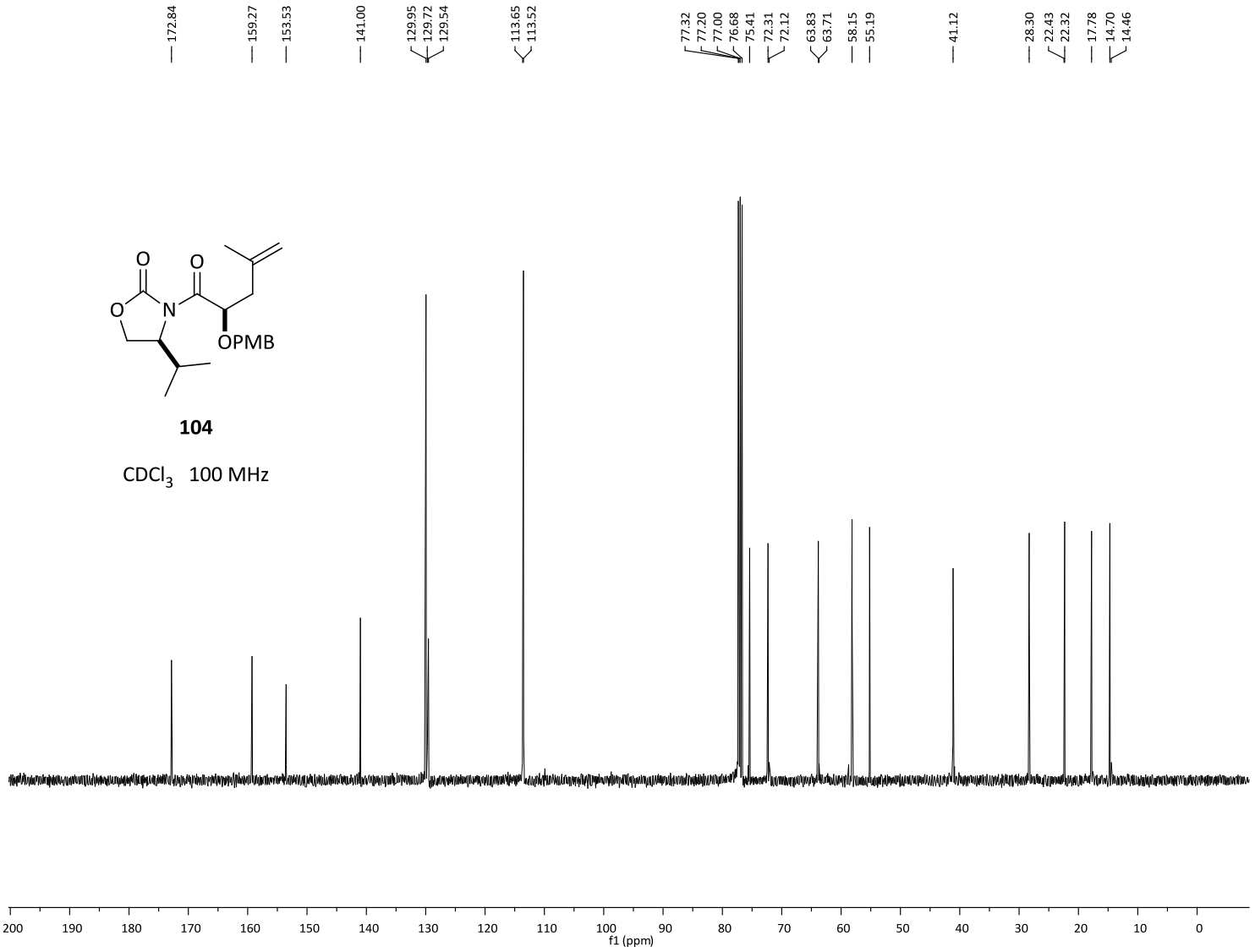
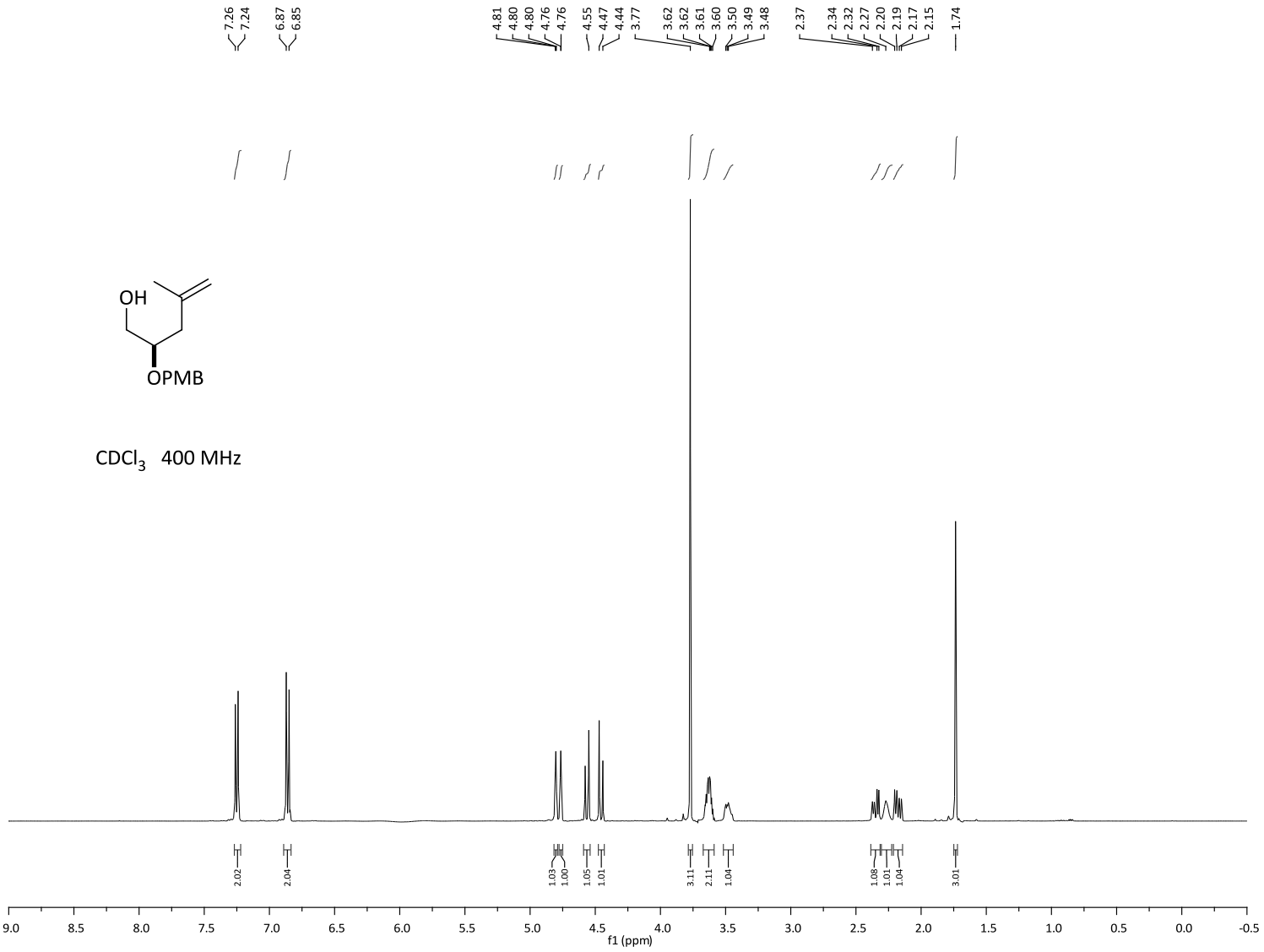
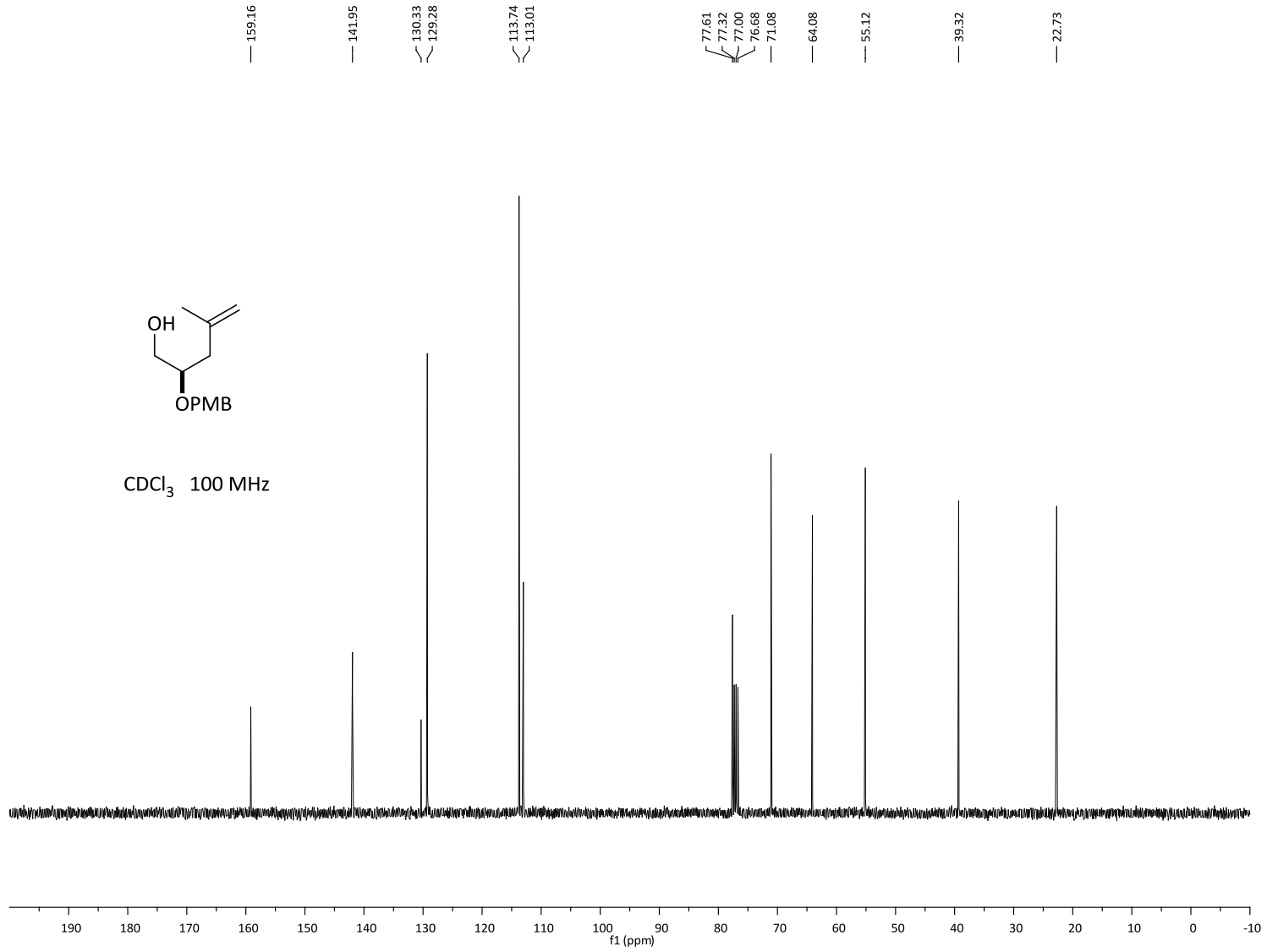
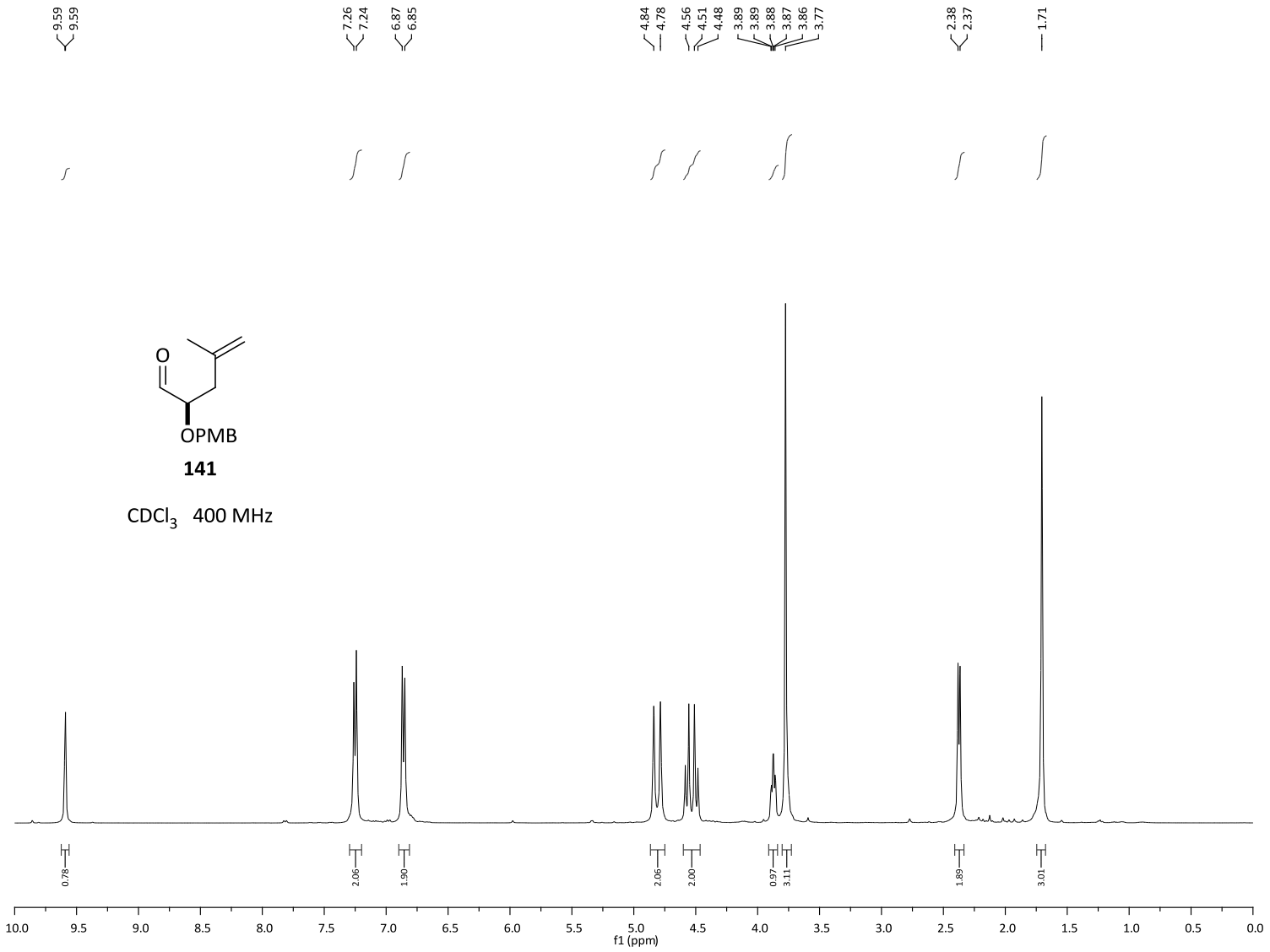
117.66
117.44
77.21
77.11
77.00
76.91
76.87
76.79
75.32
54.85
52.49
51.77
14.82
O
OH
MeO
H
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

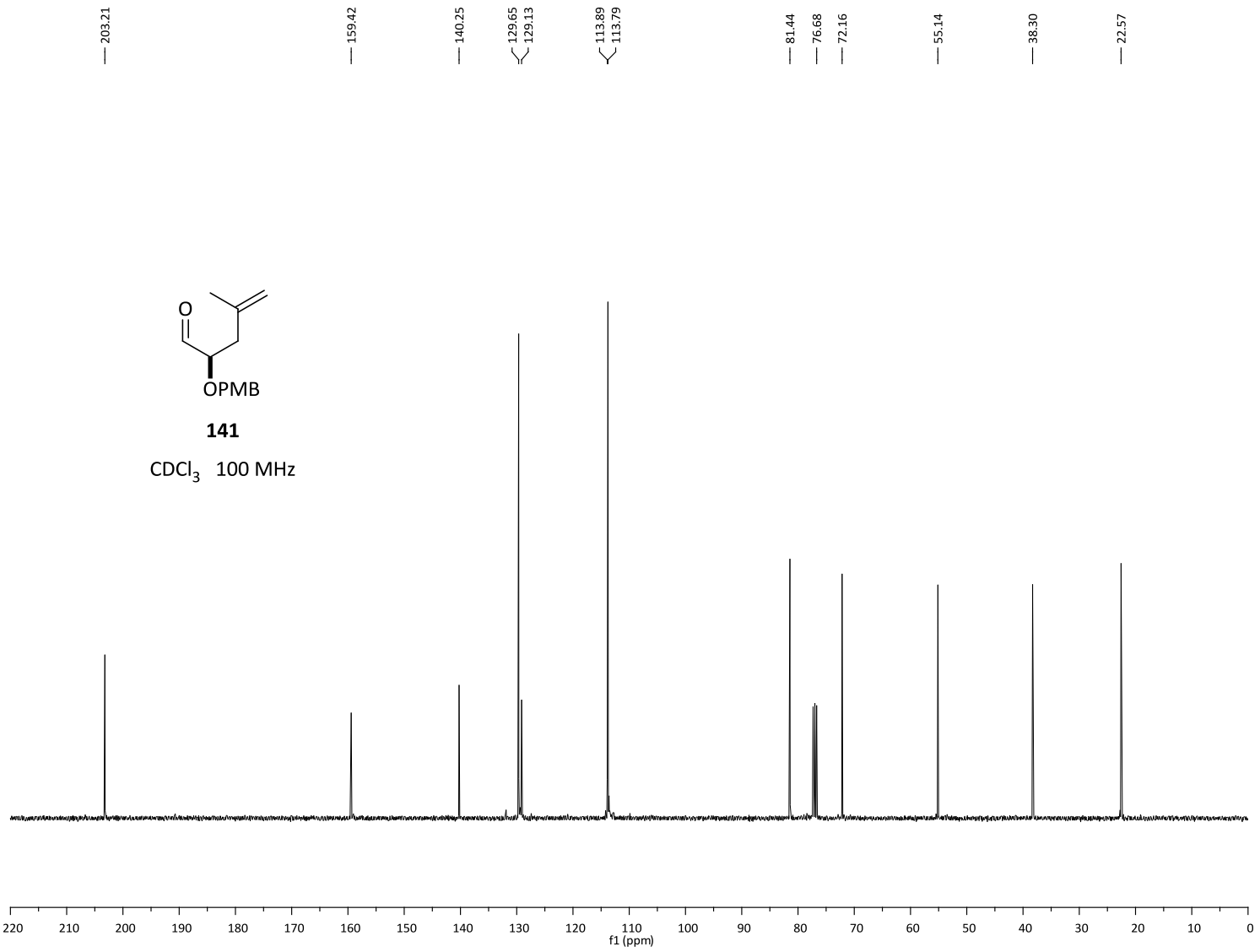

7.25
7.24
7.23
6.83
6.81
5.27
5.26
5.25
5.24
4.80
4.42
4.33
4.32
4.21
4.18
4.17
3.76
2.47
2.47
2.41
2.39
2.38
2.35
2.27
2.25
2.24
2.23
1.75
0.86
0.85
0.81
0.79
O
O
O
N
OPMB
104
CDCl3 400 MHz
2.34
2.00
1.01
2.11
2.02
1.02
2.02
3.22
1.00
1.15
0.97
3.05
6.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

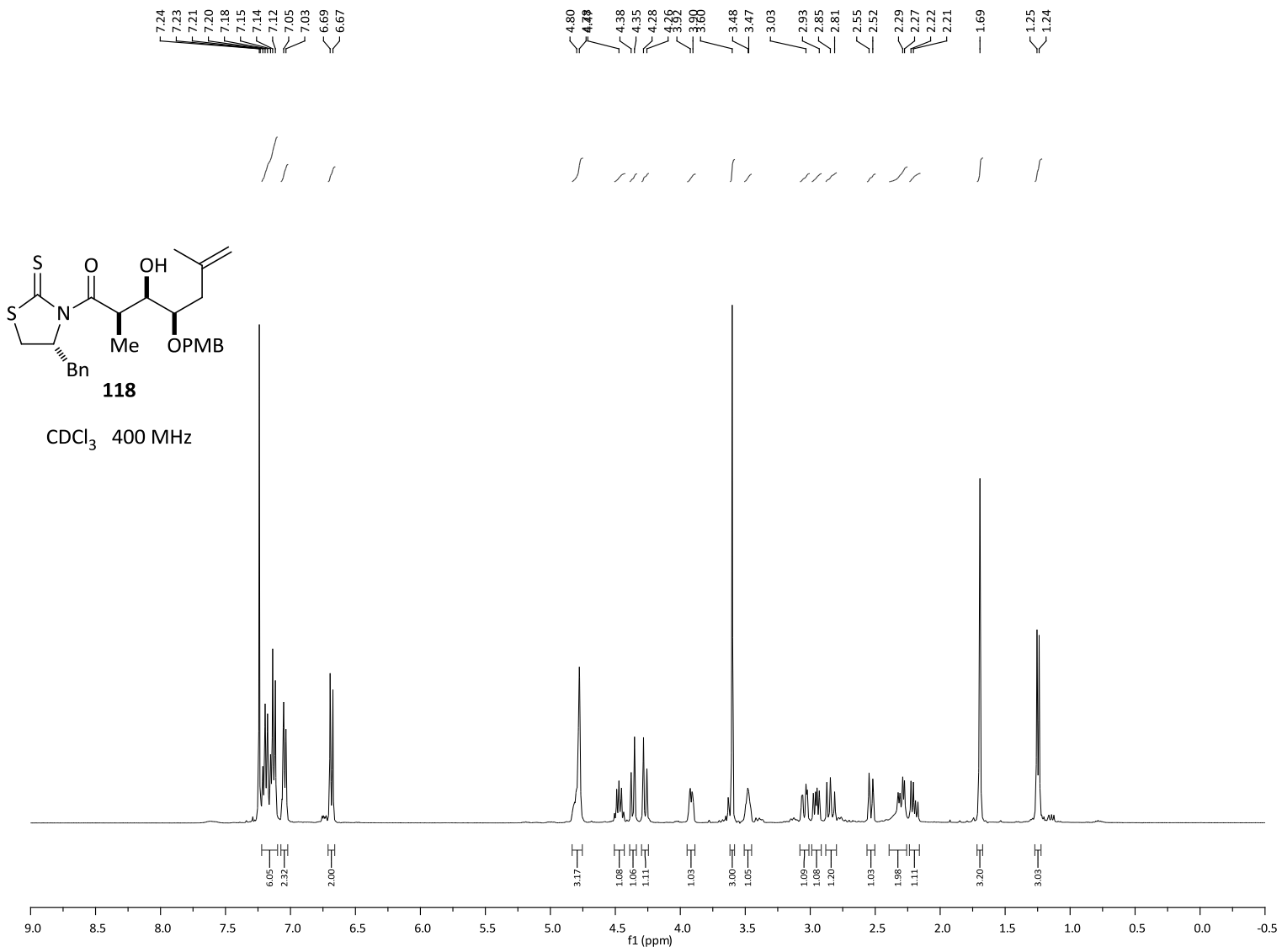

172.84
159.27
153.53
141.00
129.95
129.72
129.54
113.65
113.52
77.32
77.20
77.00
76.68
75.41
72.31
72.12
63.83
63.71
58.15
55.19
41.12
28.30
22.43
22.32
17.78
14.70
14.46
O
O
O
N
OPMB
104
CDCl3 100 MHz
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

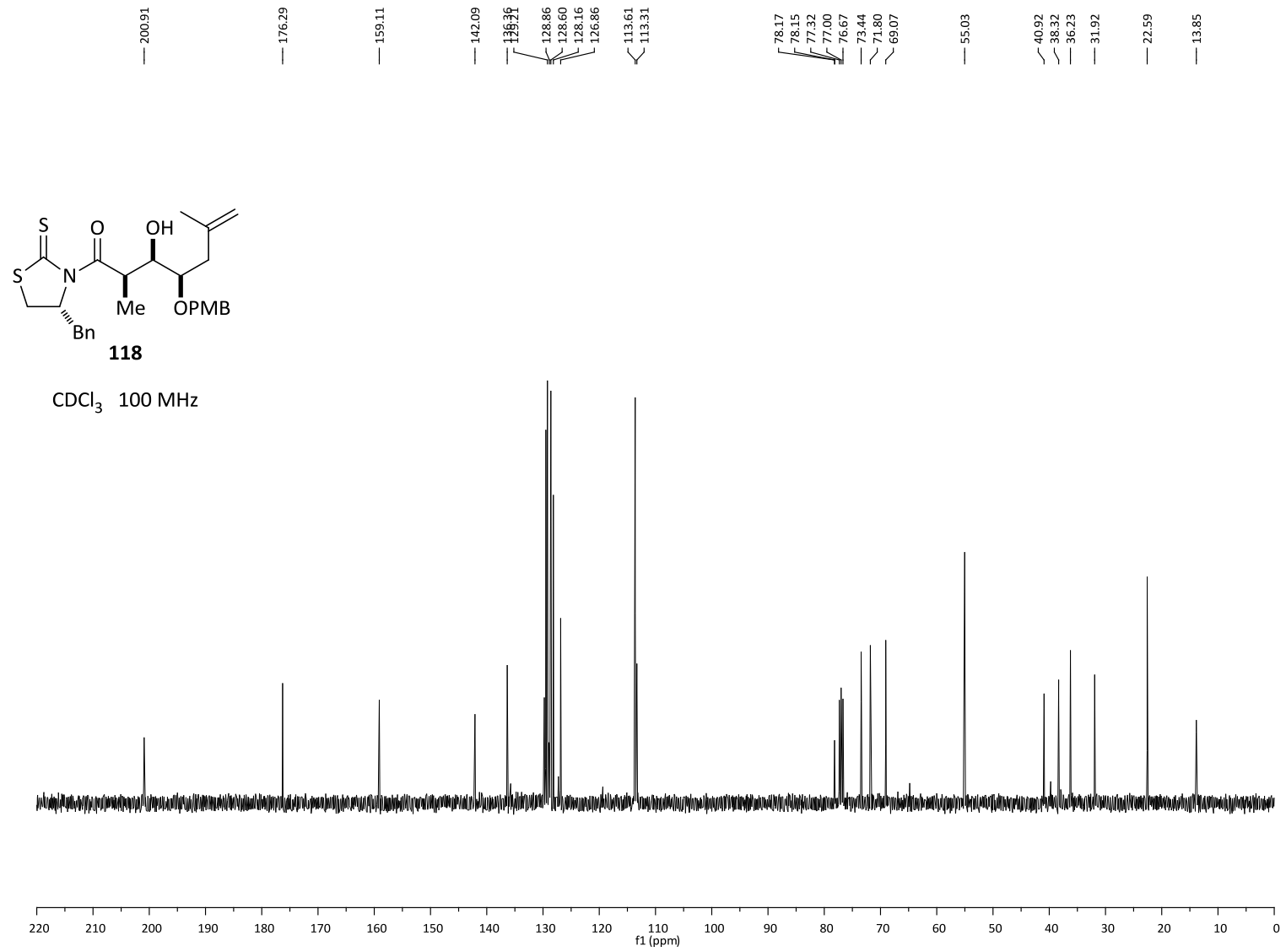

7.26
7.24
6.87
6.85
4.81
4.80
4.80
4.76
4.76
4.55
4.47
4.44
3.77
3.62
3.62
3.61
3.60
3.50
3.49
3.48
2.37
2.34
2.32
2.27
2.20
2.19
2.17
2.15
1.74
OH
OPMB
CDCl3 400 MHz
2.02
2.04
1.03
1.00
1.05
1.01
3.11
2.11
1.04
1.08
1.01
1.04
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

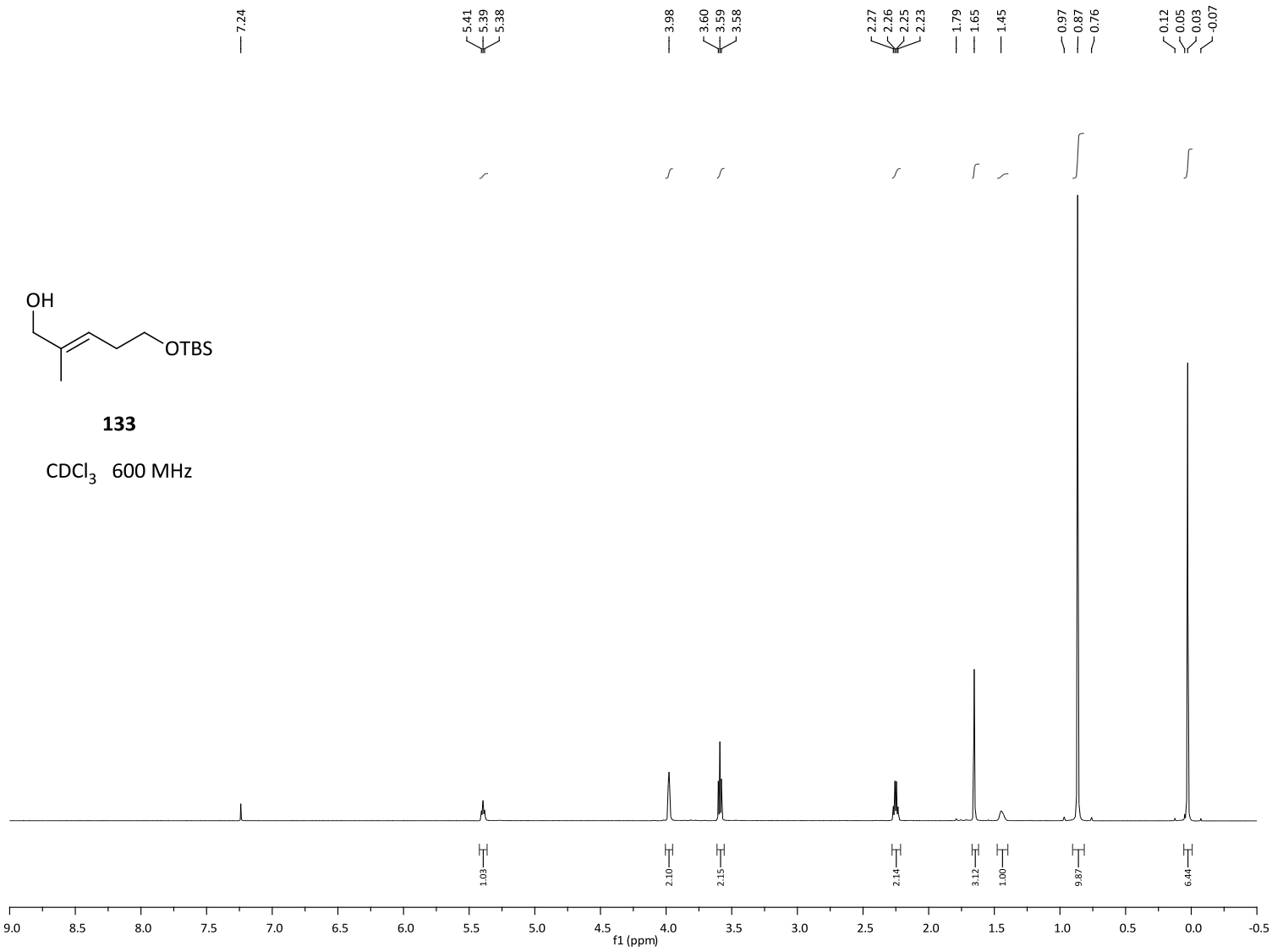

159.16
141.95
130.33
129.28
113.74
113.01
77.61
77.32
77.00
76.68
71.08
64.08
55.12
39.32
22.73
OH
OPMB
CDCl3 100 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

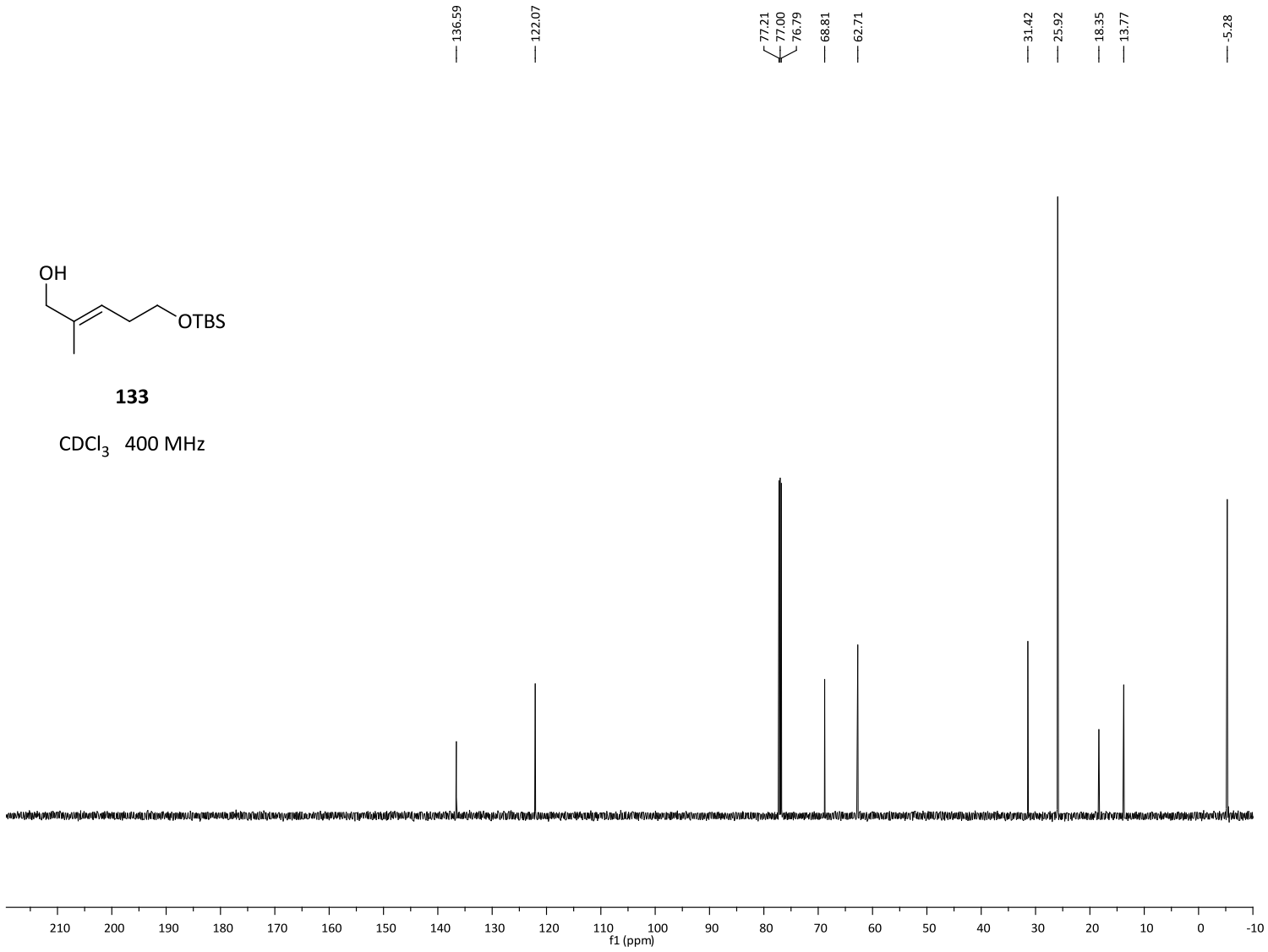

9.59
9.59
7.26
7.24
6.87
6.85
4.84
4.78
4.56
4.51
4.48
3.89
3.89
3.88
3.87
3.86
3.77
2.38
2.37
1.71
O
OPMB
141
CDCl3 400 MHz
0.78
2.06
1.90
2.06
2.00
0.97
3.11
1.89
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

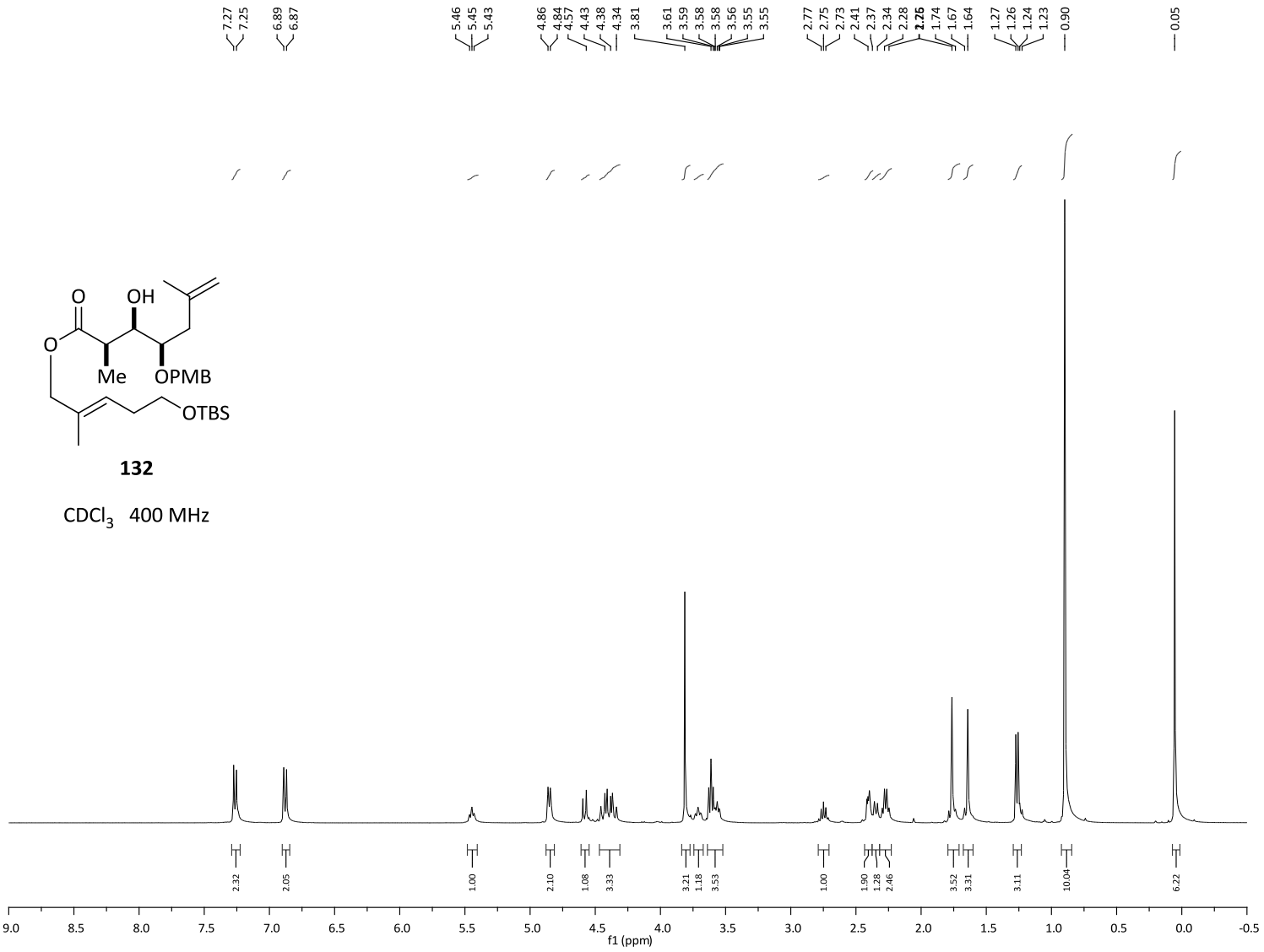

203.21
159.42
140.25
129.65
129.13
113.89
113.79
81.44
76.68
72.16
55.14
38.30
22.57
O
OPMB
141
CDCl3 100 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

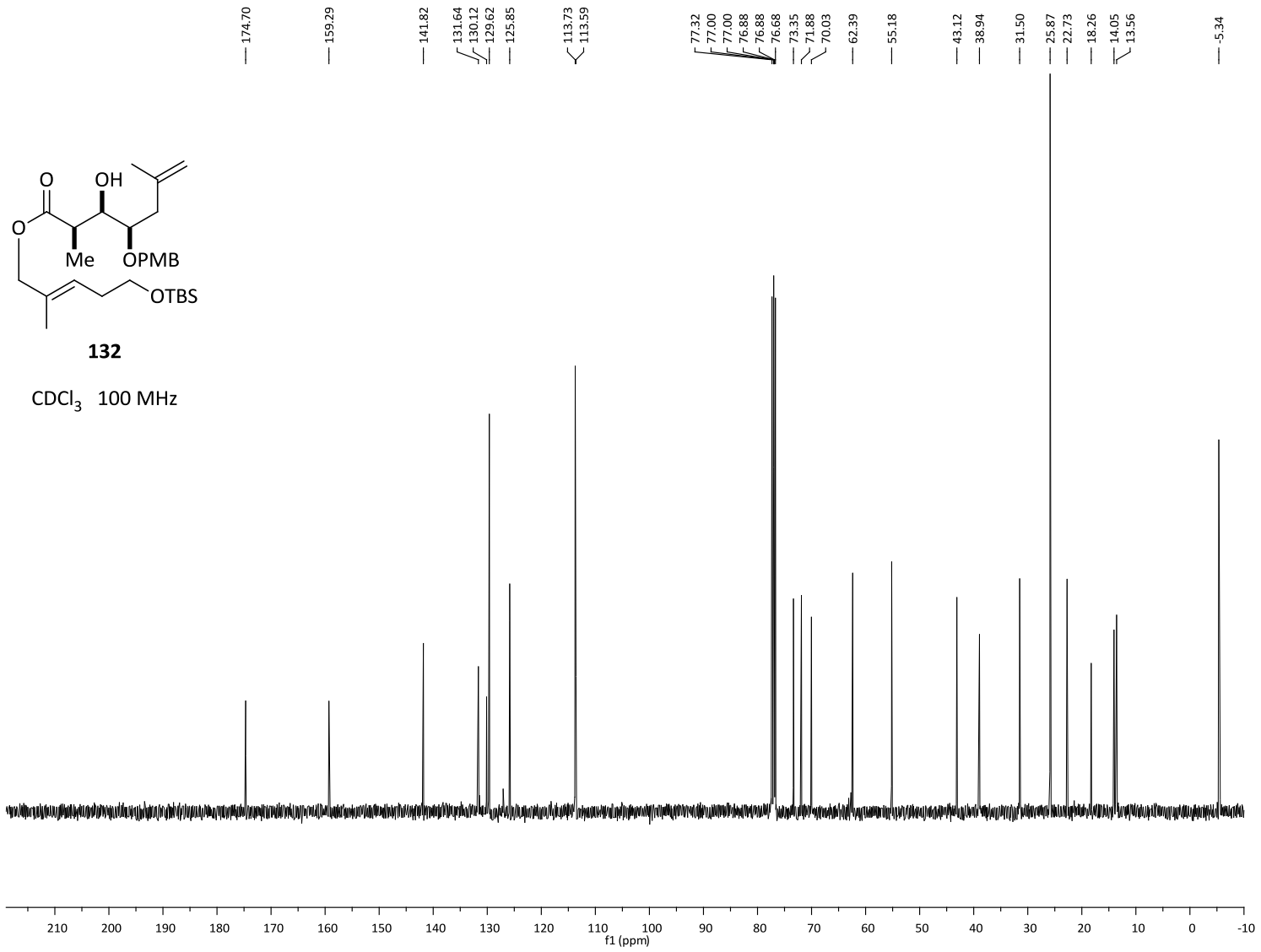

7.24
7.23
7.21
7.20
7.18
7.15
7.14
7.12
7.05
7.03
6.69
6.67
4.80
4.38
4.35
4.28
4.26
3.92
3.90
3.60
3.48
3.47
3.03
2.93
2.85
2.81
2.55
2.52
2.29
2.27
2.22
2.21
1.69
1.25
1.24
S
O
OH
S
N
Me
OPMB
Bn
118
CDCl3 400 MHz
6.05
2.32
2.00
3.17
1.08
1.06
1.11
1.03
3.00
1.05
1.09
1.08
1.20
1.03
1.98
1.11
3.20
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

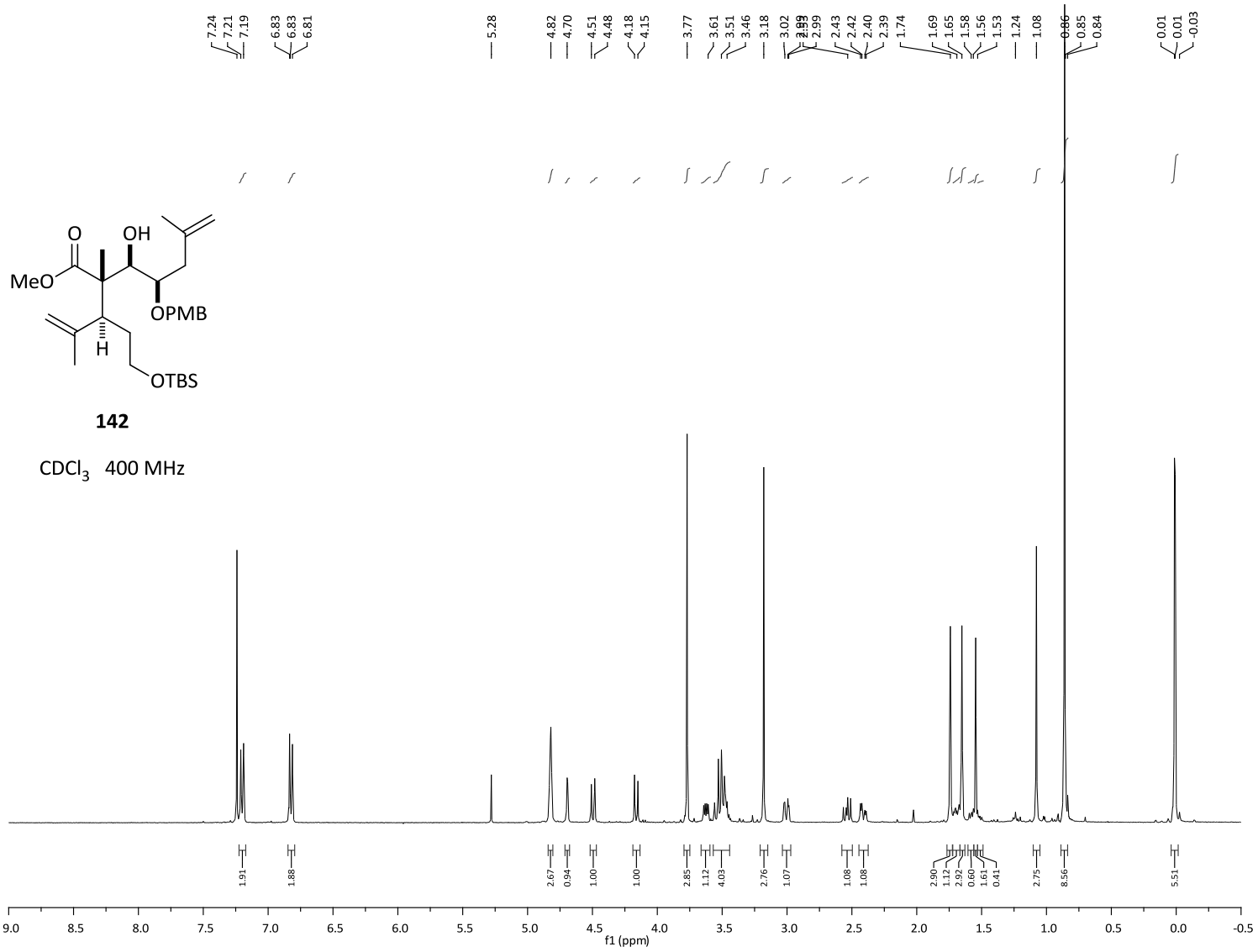

200.91
176.29
159.11
142.09
136.36
129.21
128.86
128.60
128.16
126.86
113.61
113.31
78.17
78.15
77.32
77.00
76.67
73.44
71.80
69.07
55.03
40.92
38.32
36.23
31.92
22.59
13.85
S
O
OH
S
N
Me
OPMB
Bn
118
CDCl3 100 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

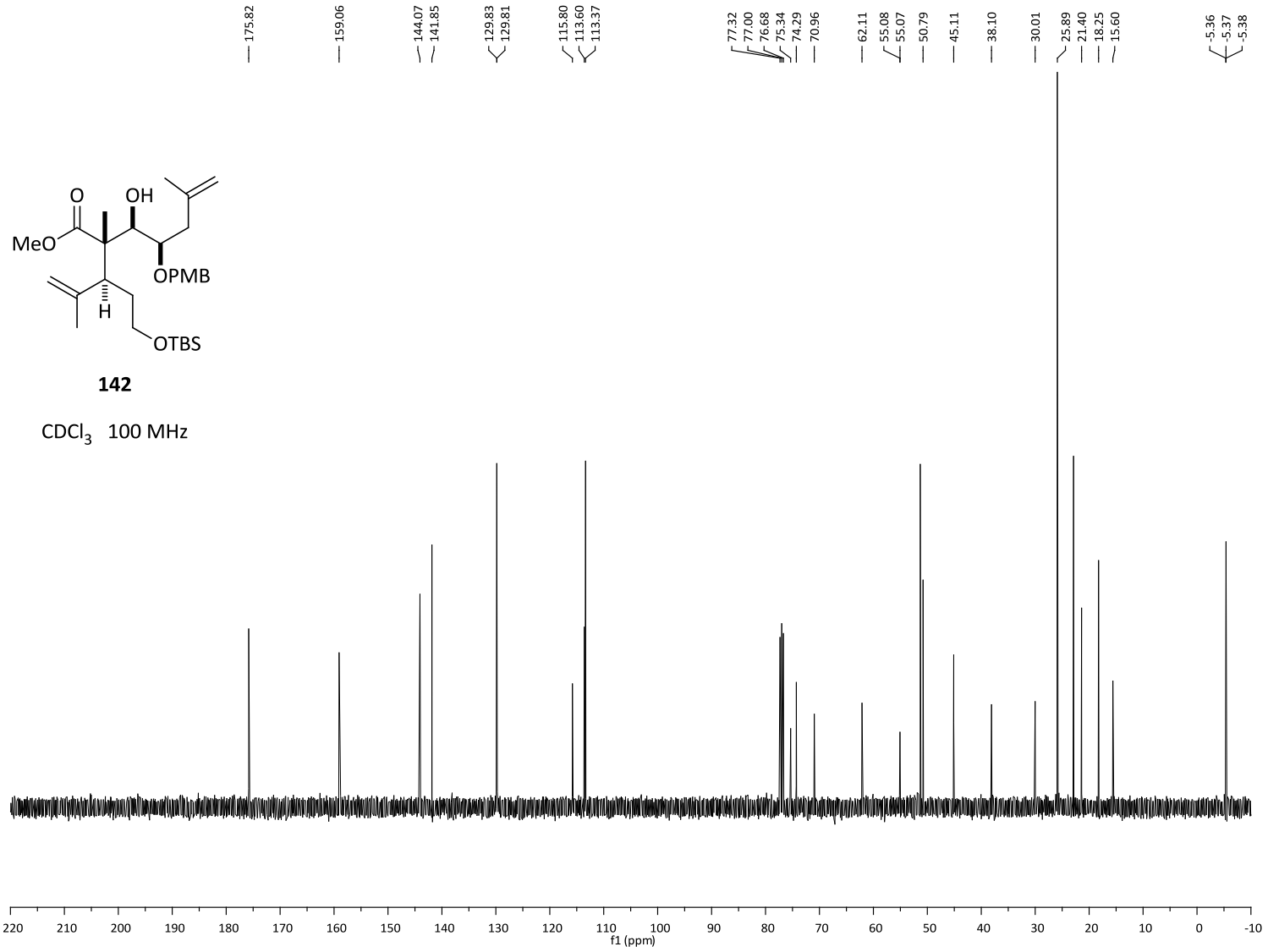

7.24
5.41
5.39
5.38
3.98
3.60
3.59
3.58
2.27
2.26
2.25
2.23
1.79
1.65
1.45
0.97
0.87
0.76
0.12
0.05
0.03
-0.07
OH
OTBS
133
CDCl3 600 MHz
1.03
2.10
2.15
2.14
3.12
1.00
9.87
6.44
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

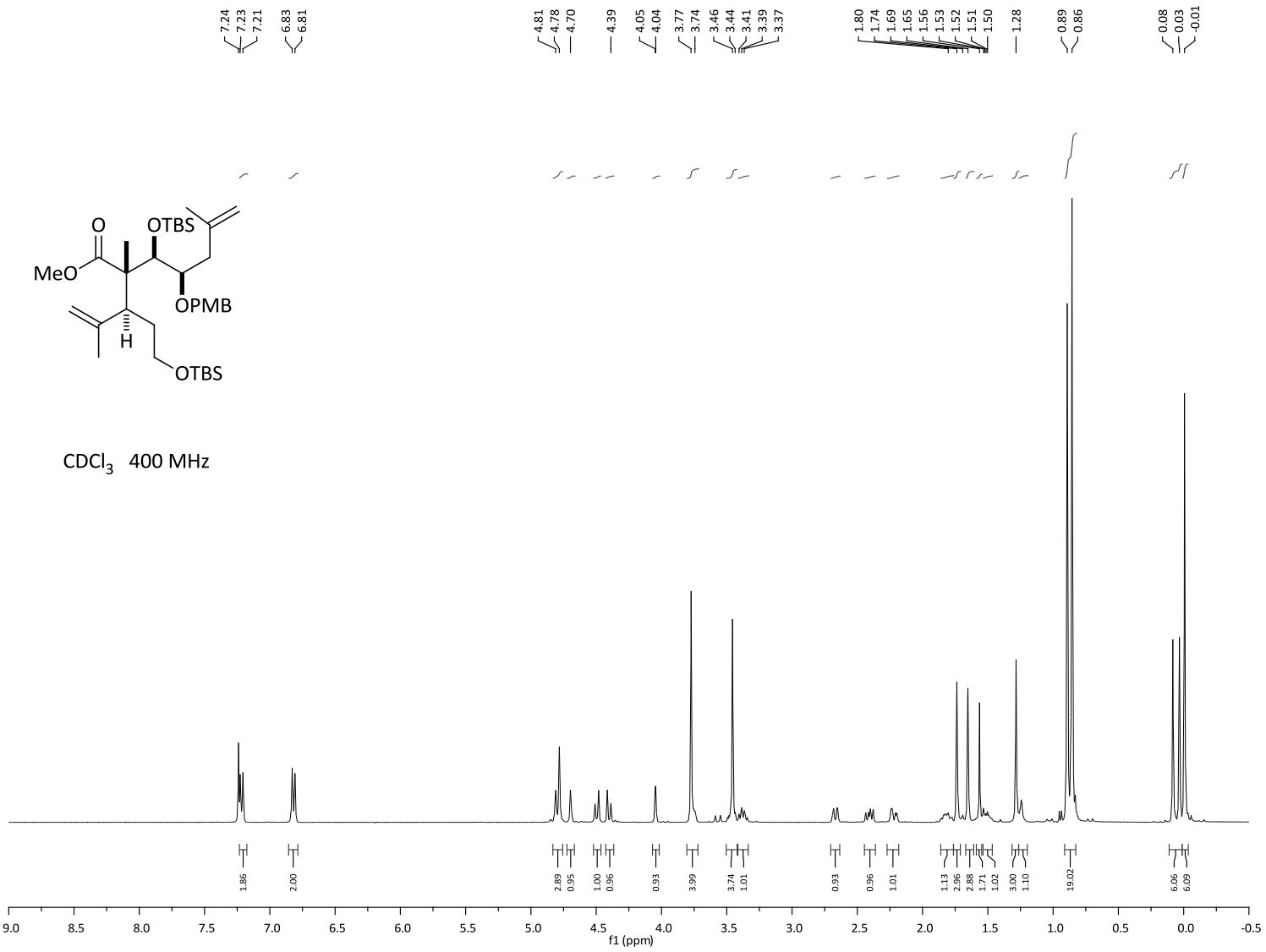

136.59
122.07
77.21
77.00
76.79
68.81
62.71
31.42
25.92
18.35
13.77
-5.28
OH
OTBS
133
CDCl3 400 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

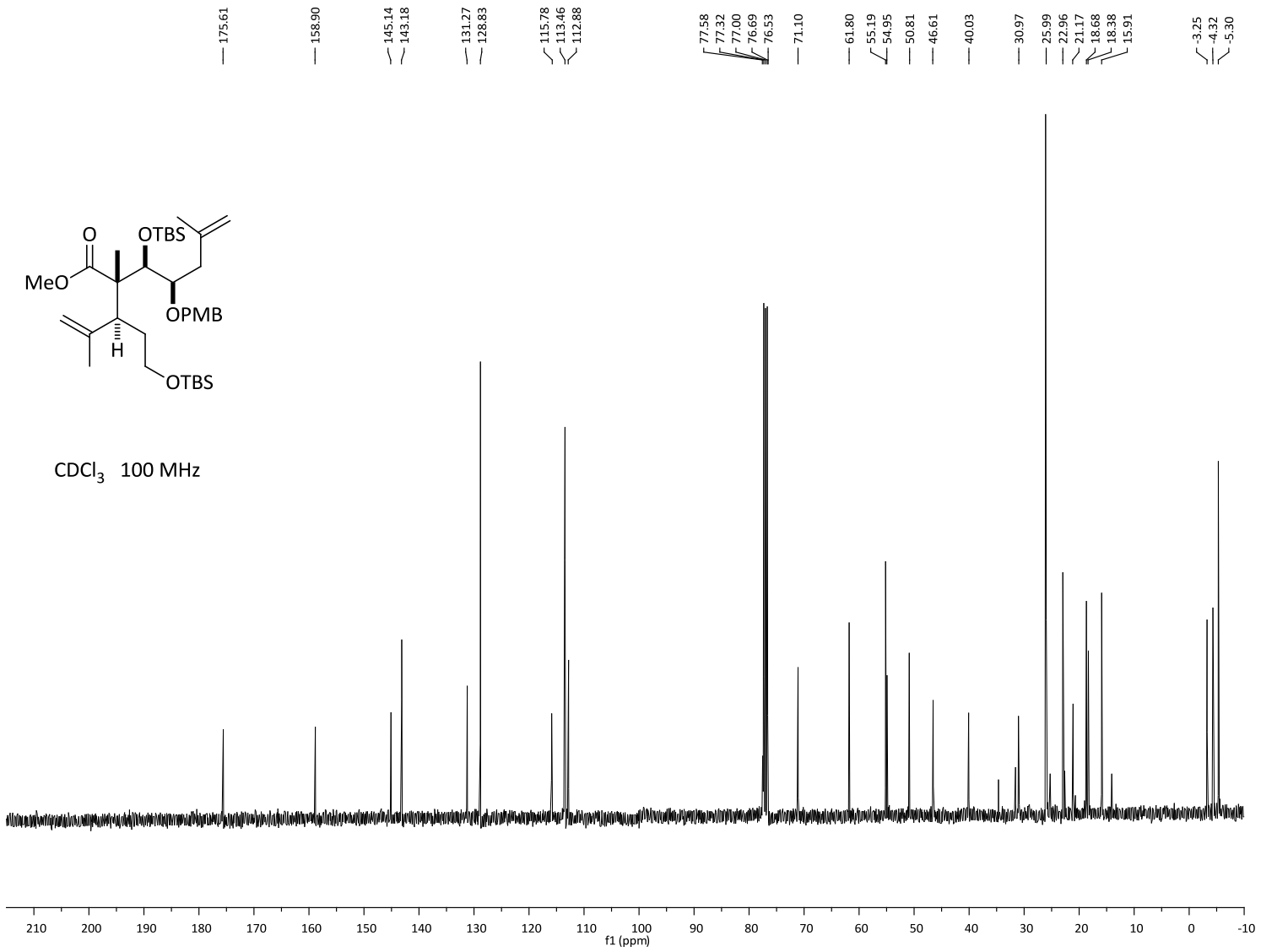

7.27
7.25
6.89
6.87
5.46
5.45
5.43
4.86
4.84
4.57
4.43
4.38
4.34
3.81
3.61
3.59
3.58
3.58
3.56
3.55
3.55
2.77
2.75
2.73
2.41
2.37
2.34
2.28
2.26
1.74
1.67
1.64
1.27
1.26
1.24
1.23
0.90
0.05
O
OH
O
Me
OPMB
OTBS
132
CDCl3 400 MHz
2.32
2.05
1.00
2.10
1.08
3.33
3.21
1.18
3.53
1.00
1.90
1.28
2.46
3.52
3.31
3.11
10.04
6.22
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

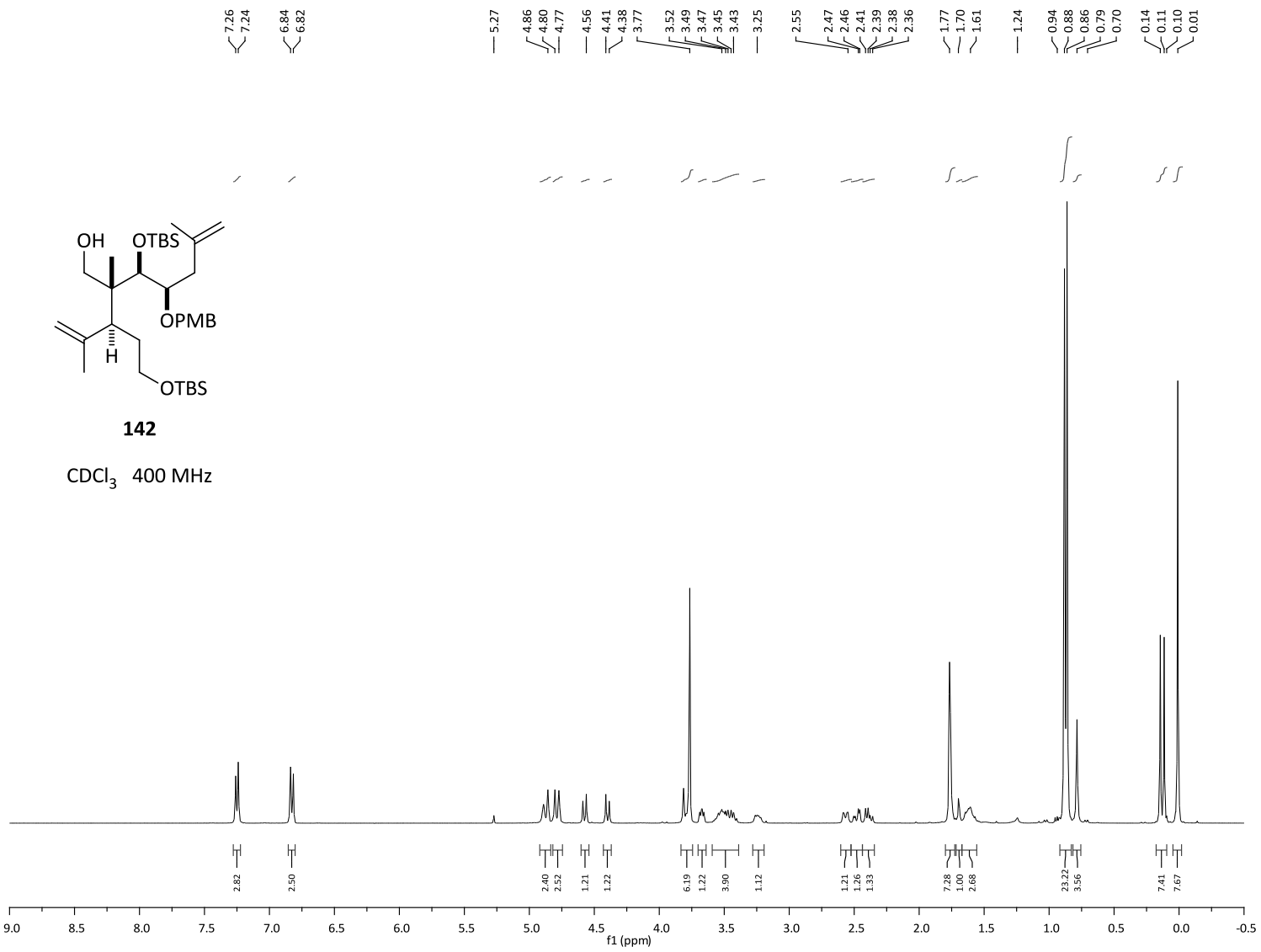

174.70
159.29
141.82
131.64
130.12
129.62
125.85
113.73
113.59
77.32
77.00
77.00
76.88
76.88
76.68
73.35
71.88
70.03
62.39
55.18
43.12
38.94
31.50
25.87
22.73
18.26
14.05
13.56
-5.34
O
OH
O
Me
OPMB
OTBS
132
CDCl3 100 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

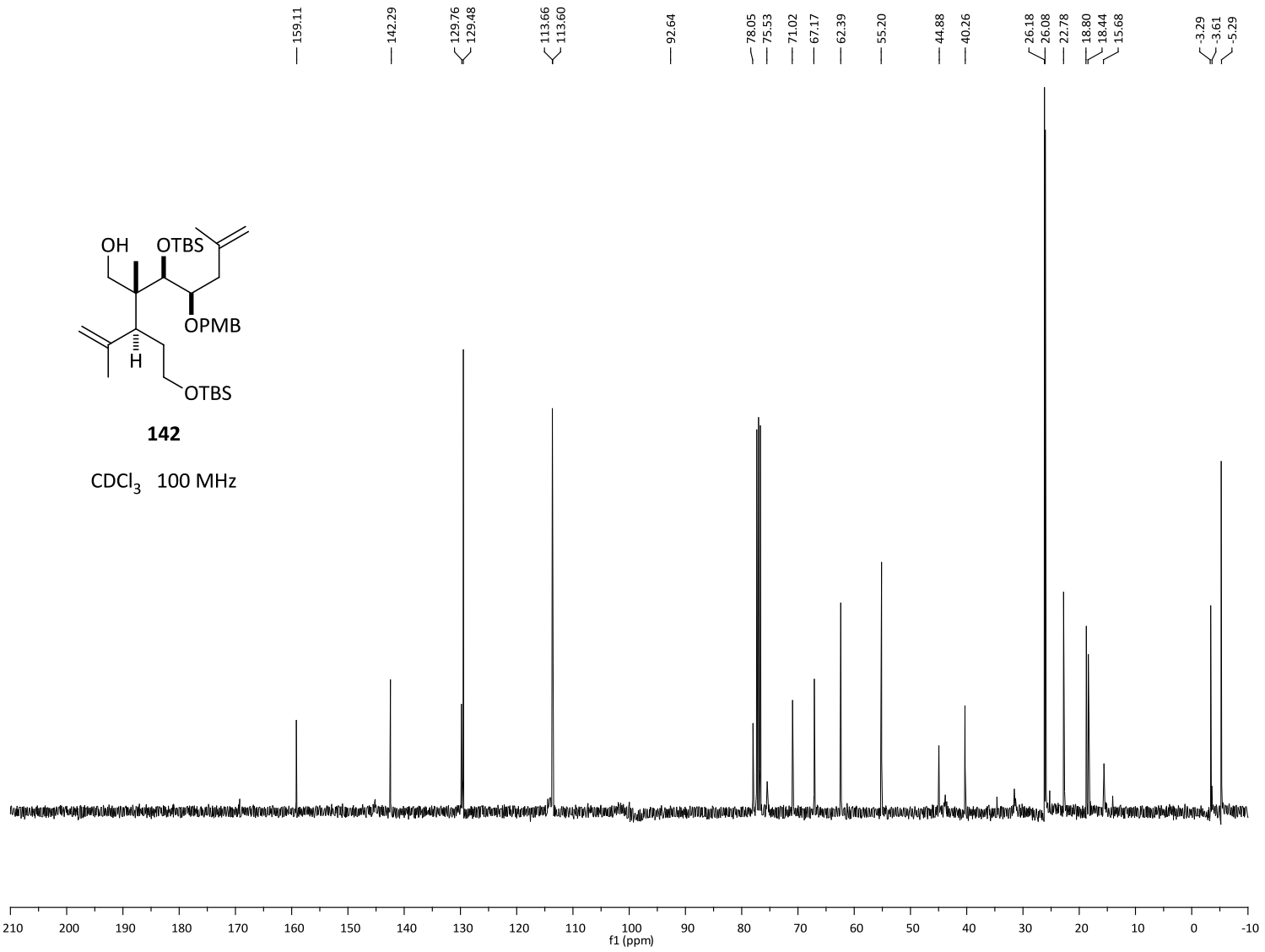

O
OH
MeO
OPMB
H
OTBS
142
CDCl3 400 MHz
f1 (ppm)

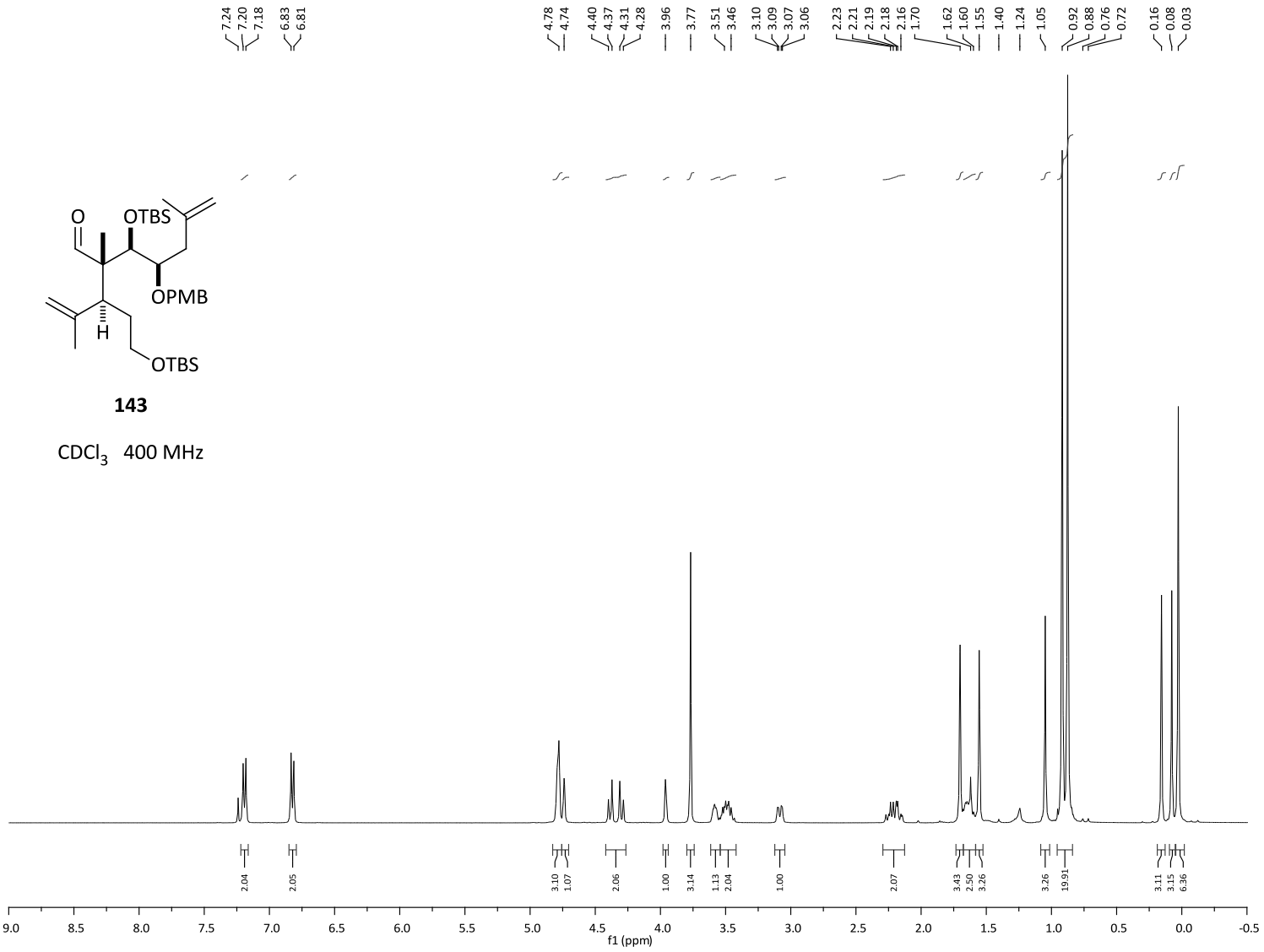

175.82
159.06
144.07
141.85
129.83
129.81
115.80
113.60
113.37
77.32
77.00
76.68
75.34
74.29
70.96
62.11
55.08
55.07
50.79
45.11
38.10
30.01
25.89
21.40
18.25
15.60
-5.36
-5.37
-5.38
O
OH
MeO
OPMB
H
OTBS
142
CDCl3 100 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

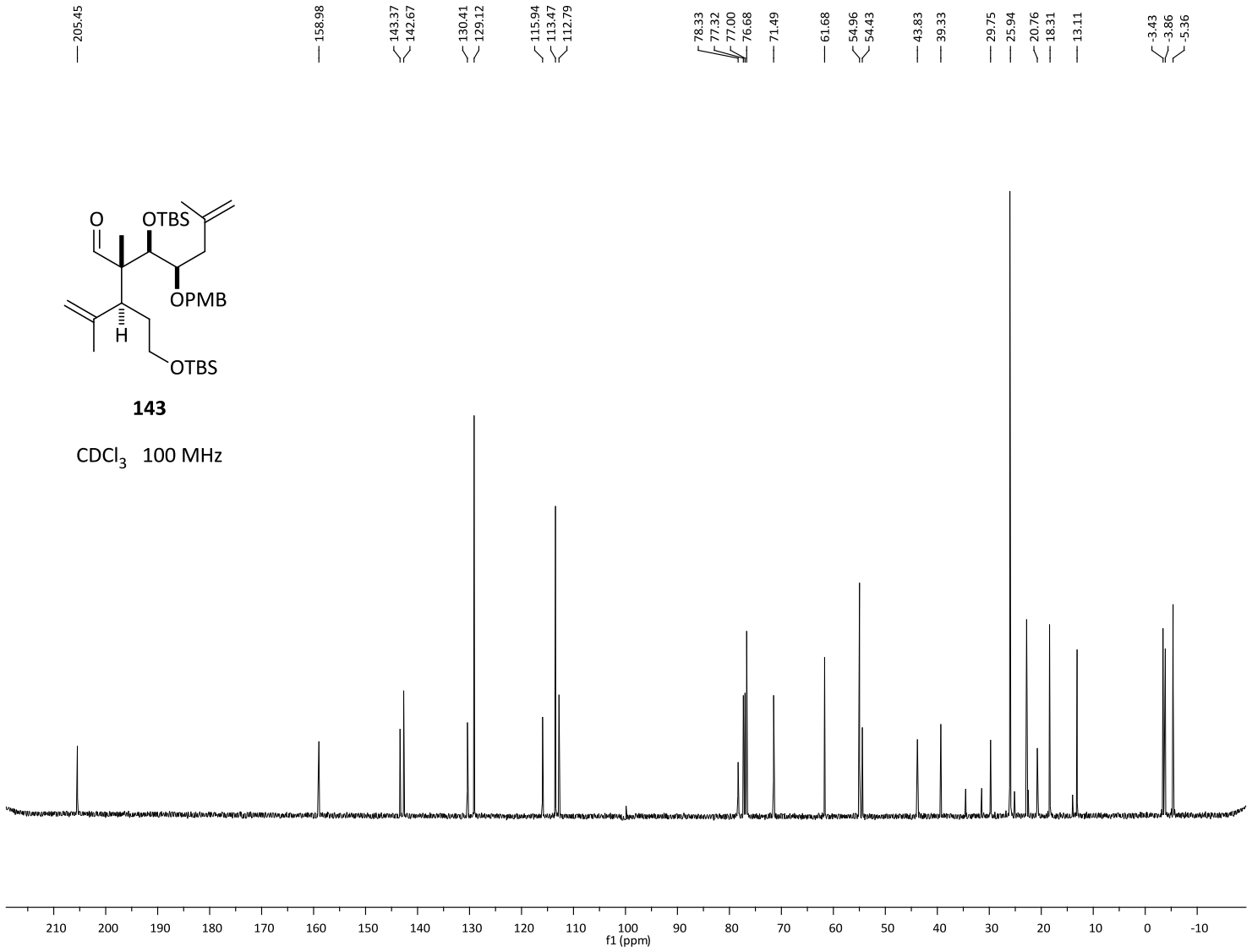

7.24
7.23
7.21
6.83
6.81
4.81
4.78
4.70
4.39
4.05
4.04
3.77
3.74
3.46
3.44
3.41
3.39
3.37
1.80
1.74
1.69
1.65
1.56
1.53
1.52
1.51
1.50
1.28
0.89
0.86
0.08
0.03
-0.01
O
OTBS
MeO
OPMB
H
OTBS
CDCl3 400 MHz
1.86
2.00
2.89
0.95
1.00
0.96
0.93
3.99
3.74
1.01
0.93
0.96
1.01
1.13
2.96
2.88
1.71
1.02
3.00
1.10
19.02
6.06
6.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

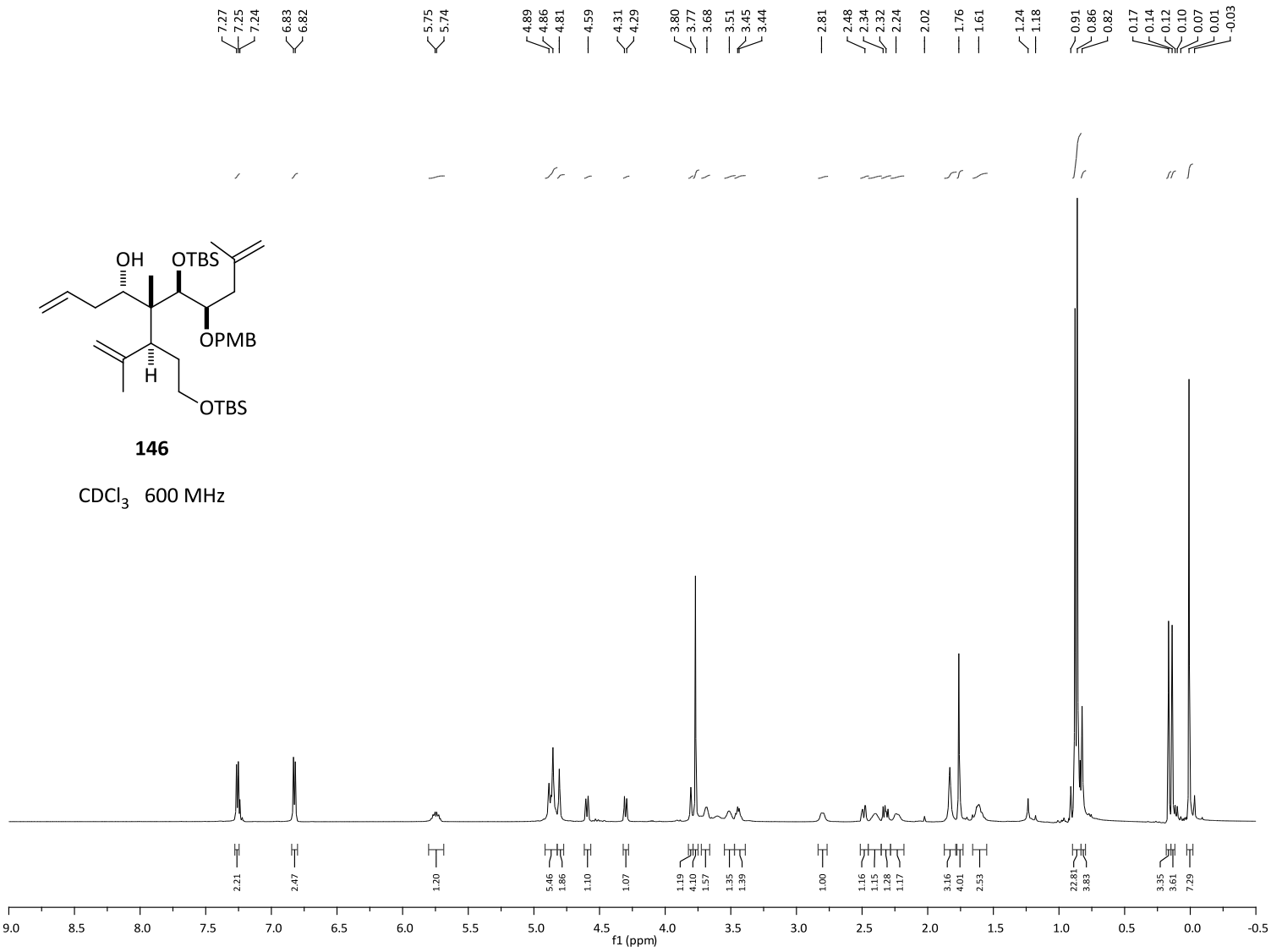

175.61
158.90
145.14
143.18
131.27
128.83
115.78
113.46
112.88
77.58
77.32
77.00
76.69
76.53
71.10
61.80
55.19
54.95
50.81
46.61
40.03
30.97
25.99
22.96
21.17
18.68
18.38
15.91
-3.25
-4.32
-5.30
O
OTBS
MeO
OPMB
H
OTBS
CDCl3 100 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

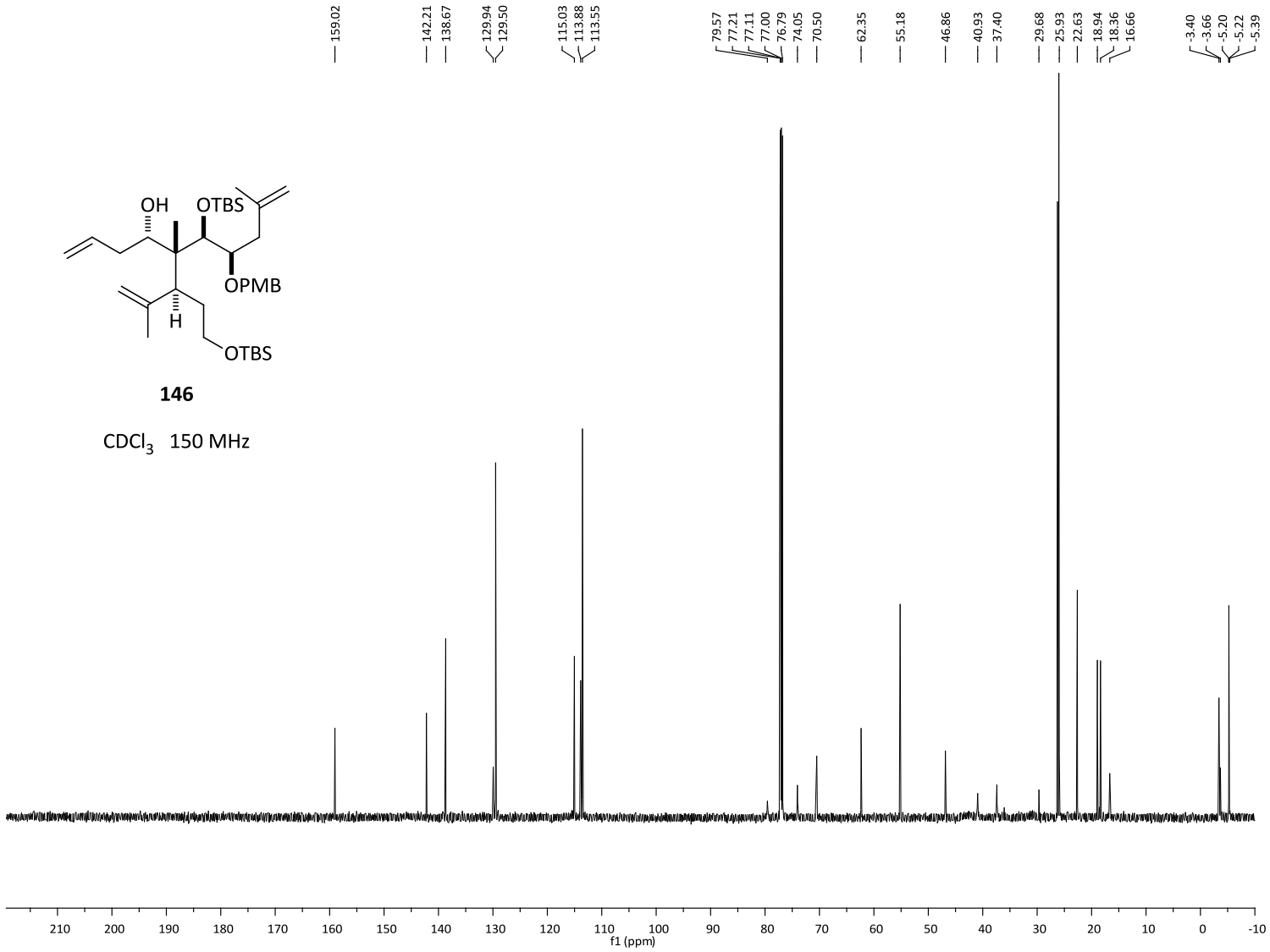

OH
OTBS
OPMB
H
OTBS
142
CDCl3 400 MHz
f1 (ppm)

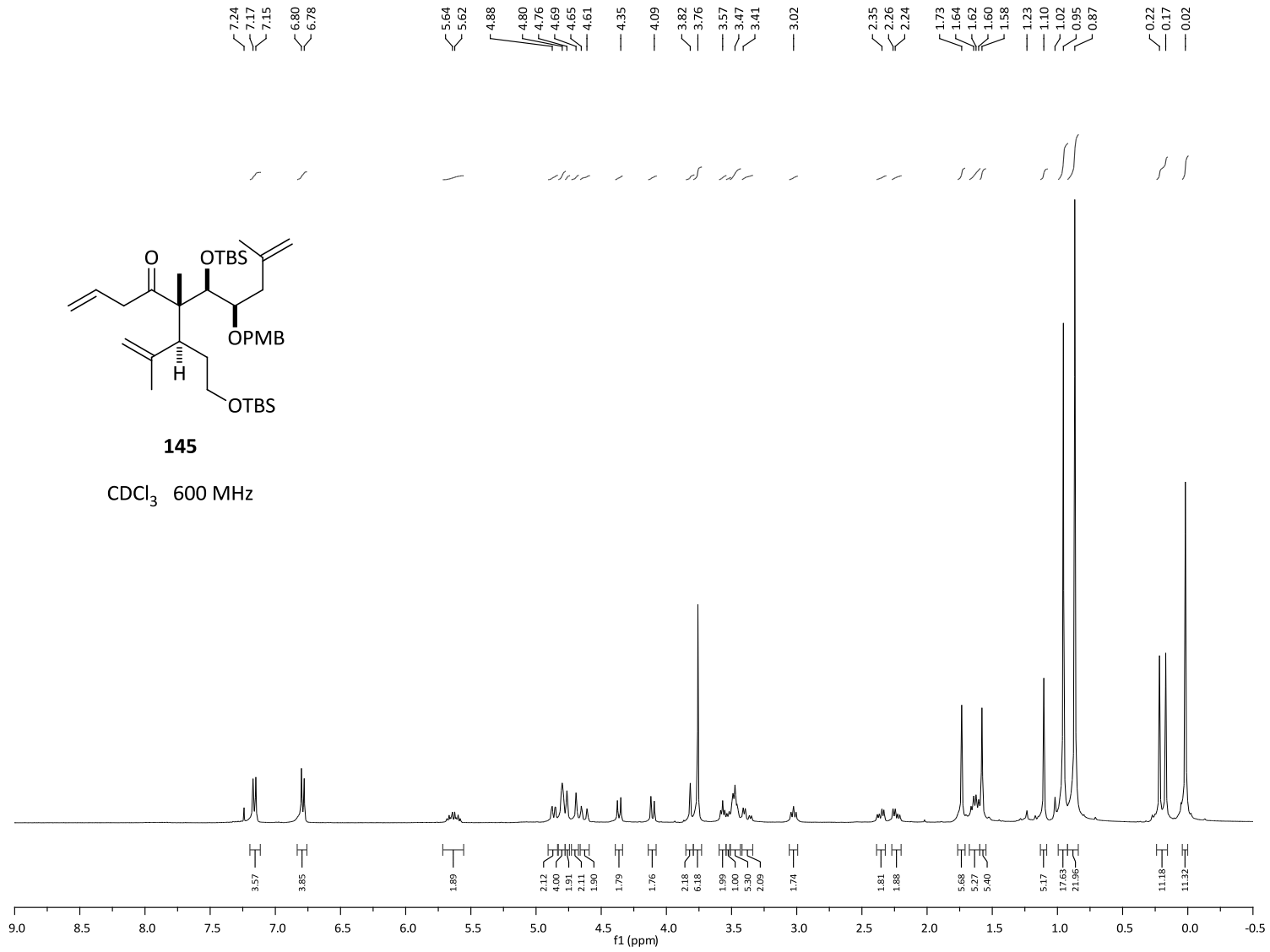

159.11
142.29
129.76
129.48
113.66
113.60
92.64
78.05
75.53
71.02
67.17
62.39
55.20
44.88
40.26
26.18
26.08
22.78
18.80
18.44
15.68
-3.29
-3.61
-5.29
OH
OTBS
OPMB
H
OTBS
142
CDCl3 100 MHz
f1 (ppm)

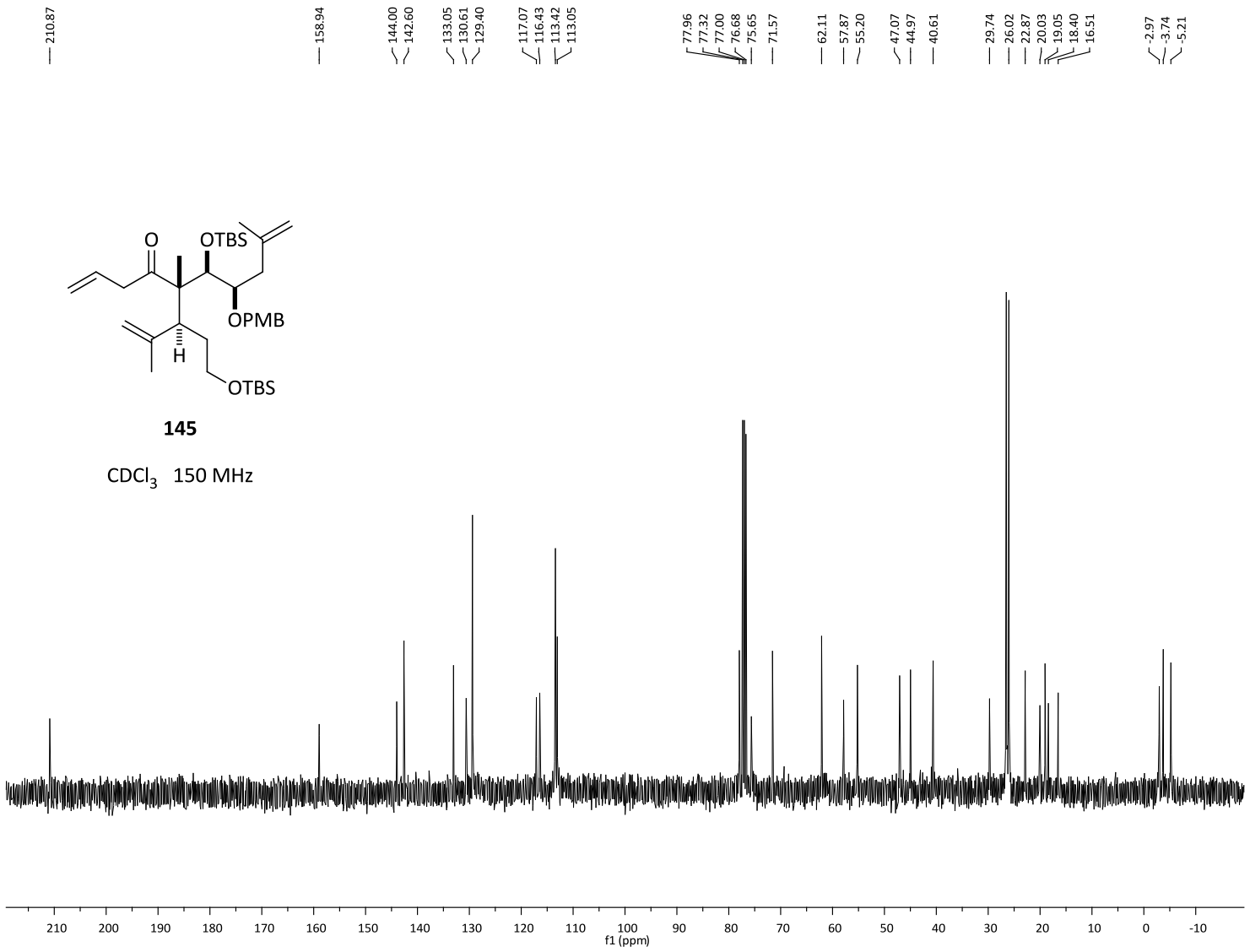

O
OTBS
OPMB
H
OTBS
143
CDCl3 400 MHz
f1 (ppm)

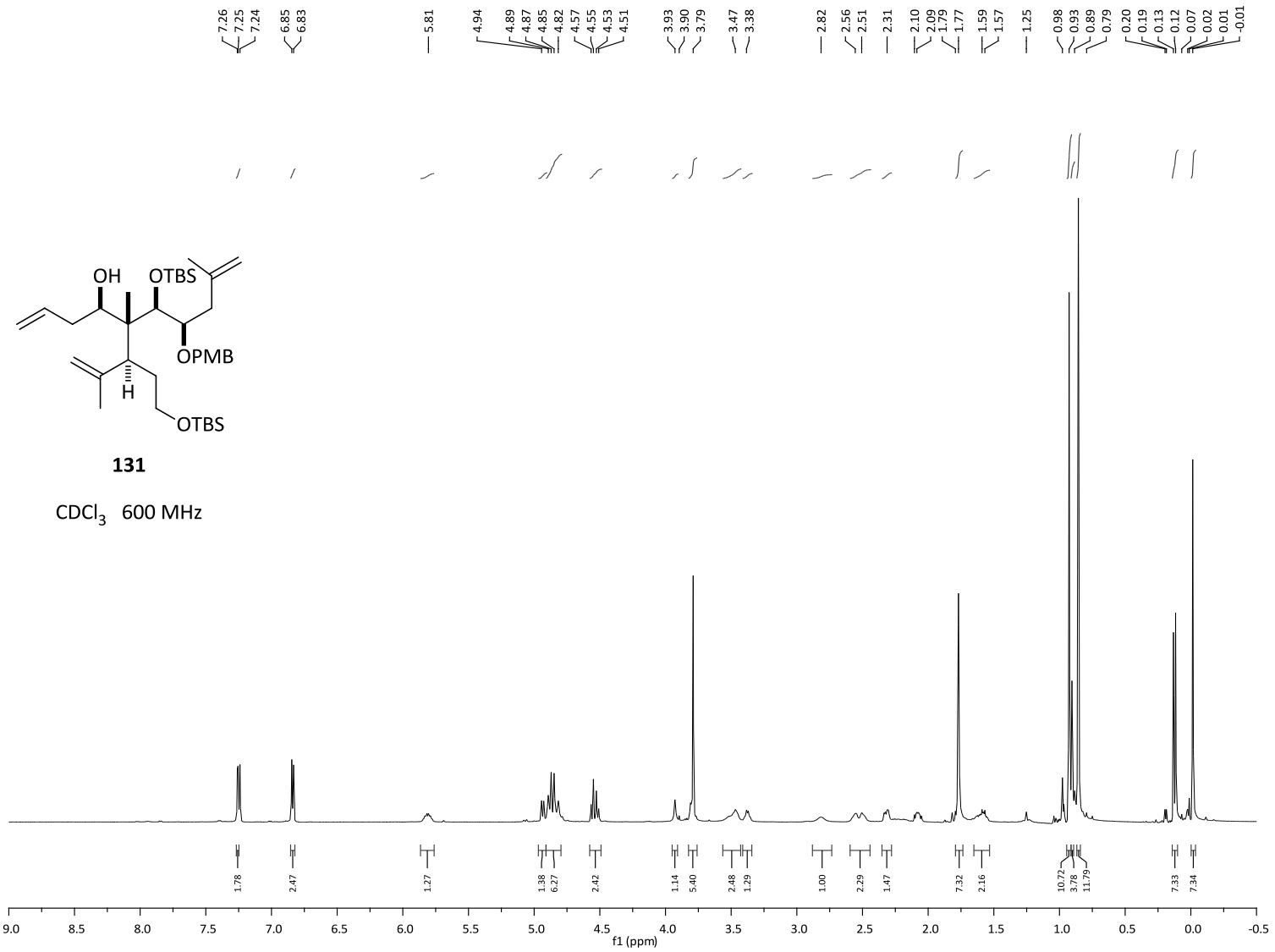

205.45
158.98
143.37
142.67
130.41
129.12
115.94
113.47
112.79
78.33
77.32
77.00
76.68
71.49
61.68
54.96
54.43
43.83
39.33
29.75
25.94
20.76
18.31
13.11
-3.43
-3.86
-5.36
O
OTBS
OPMB
H
OTBS
143
CDCl3 100 MHz
f1 (ppm)

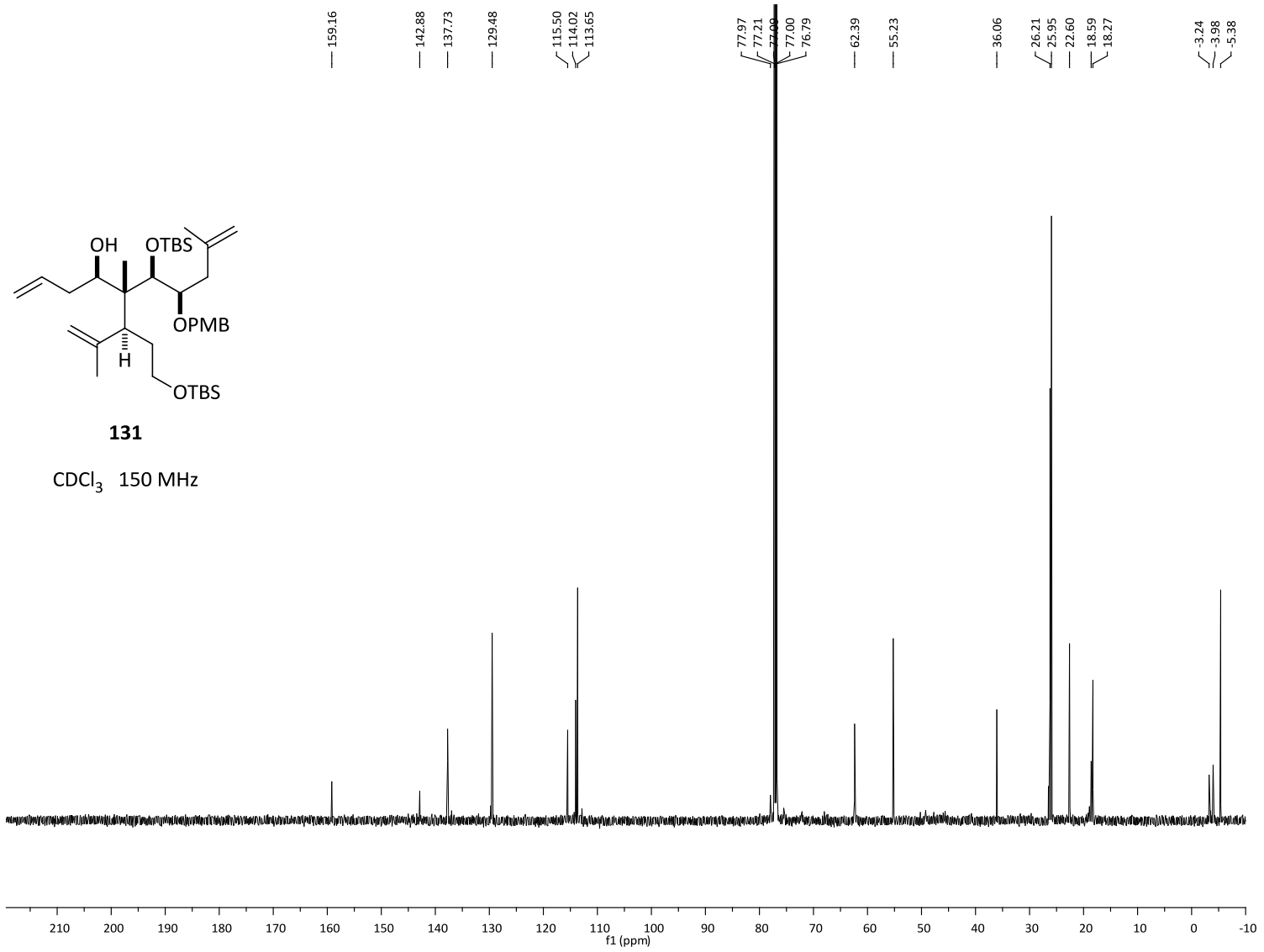

OH
OTBS
OPMB
H
OTBS
146
CDCl3 600 MHz
f1 (ppm)


159.02
142.21
138.67
129.94
129.50
115.03
113.88
113.55
79.57
77.21
77.11
77.00
76.79
74.05
70.50
62.35
55.18
46.86
40.93
37.40
29.68
25.93
22.63
18.94
18.36
16.66
-3.40
-3.66
-5.20
-5.22
-5.39
OH
OTBS
OPMB
H
OTBS
146
CDCl3 150 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.24
7.17
7.15
6.80
6.78
5.64
5.62
4.88
4.80
4.76
4.69
4.65
4.61
4.35
4.09
3.82
3.76
3.57
3.47
3.41
3.02
2.35
2.26
2.24
1.73
1.64
1.62
1.60
1.58
1.23
1.10
1.02
0.95
0.87
0.22
0.17
0.02
O
OTBS
OPMB
H
OTBS
145
CDCl3 600 MHz
3.57
3.85
1.89
2.12
4.00
1.91
2.11
1.90
1.79
1.76
2.18
6.18
1.99
1.00
5.30
2.09
1.74
1.81
1.88
5.68
5.27
5.40
5.17
17.63
21.96
11.18
11.32
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

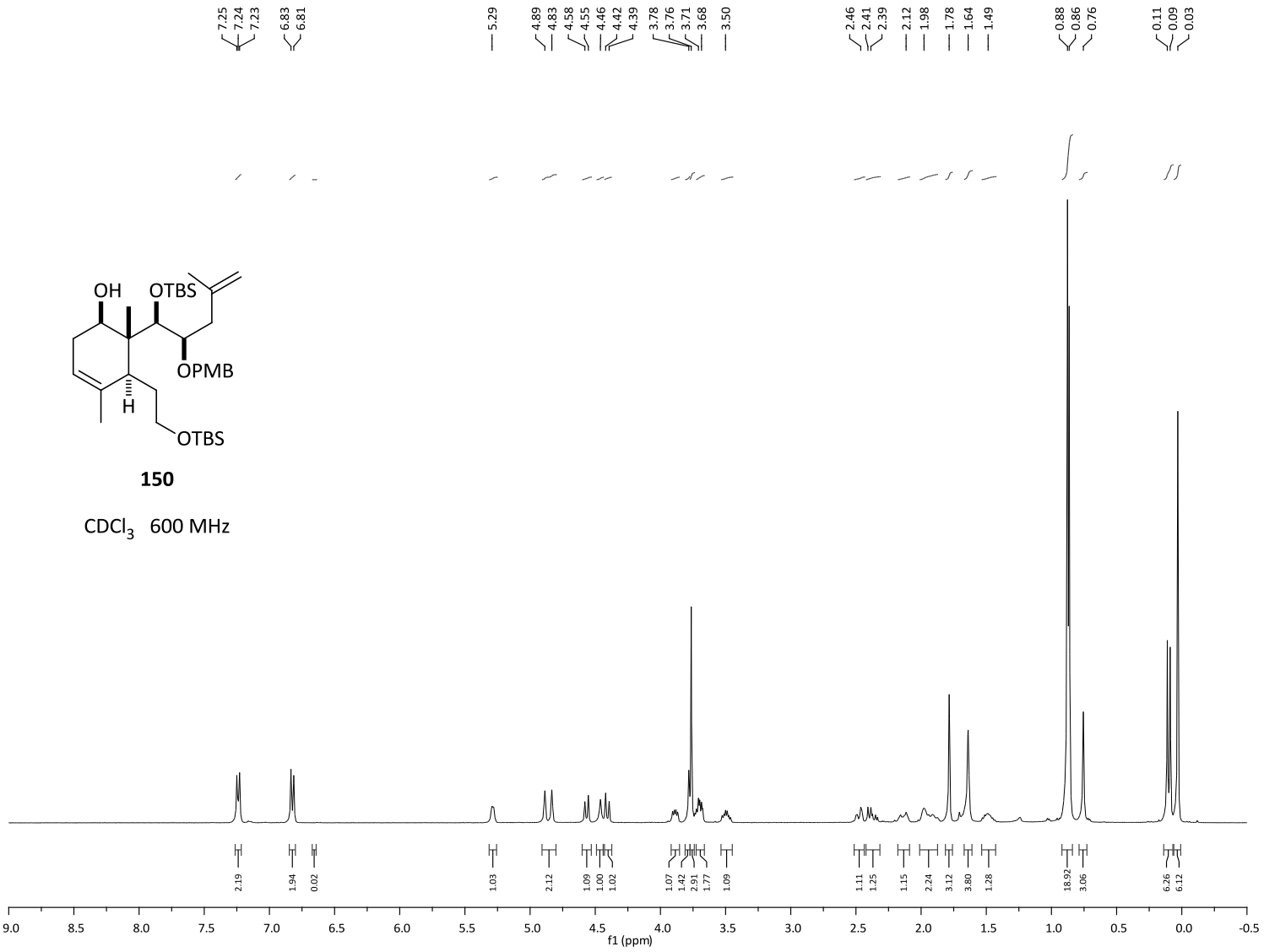

210.87
158.94
144.00
142.60
133.05
130.61
129.40
117.07
116.43
113.42
113.05
77.96
77.32
77.00
76.68
75.65
71.57
62.11
57.87
55.20
47.07
44.97
40.61
29.74
26.02
22.87
20.03
19.05
18.40
16.51
-2.97
-3.74
-5.21
O
OTBS
OPMB
H
OTBS
145
CDCl3 150 MHz
f1 (ppm)

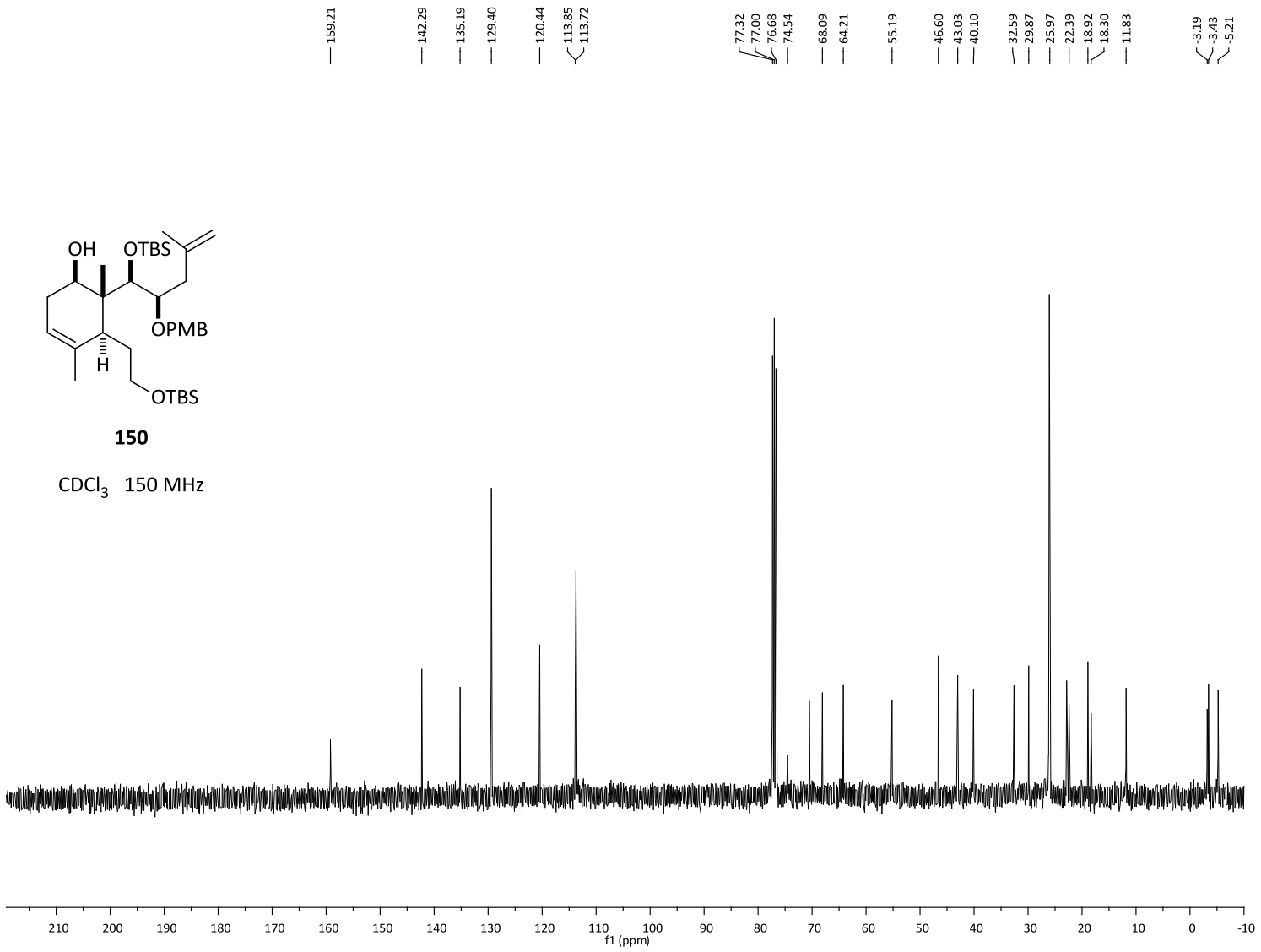

OH
OTBS
OPMB
H
OTBS
131
CDCl3 600 MHz
f1 (ppm)

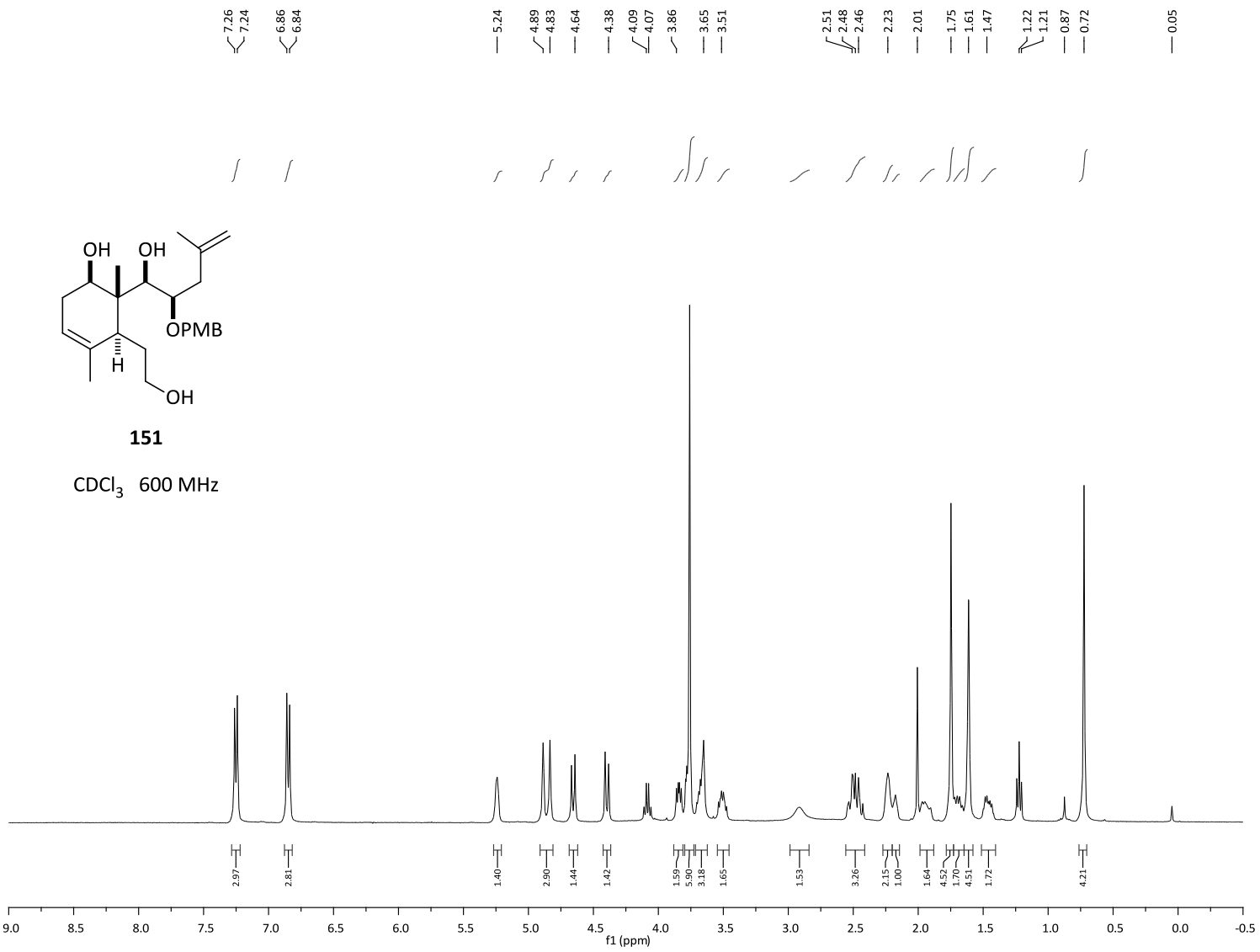


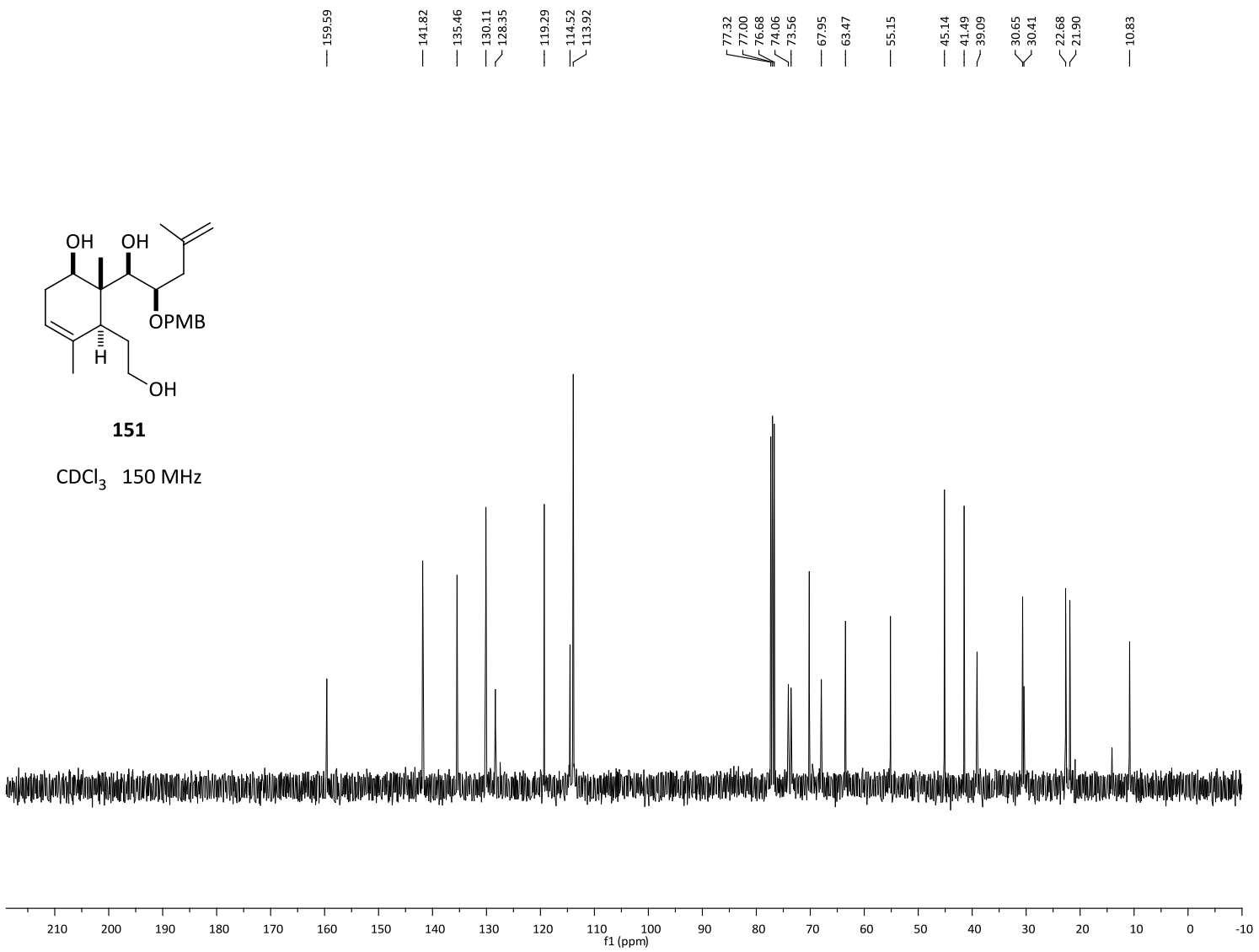
131

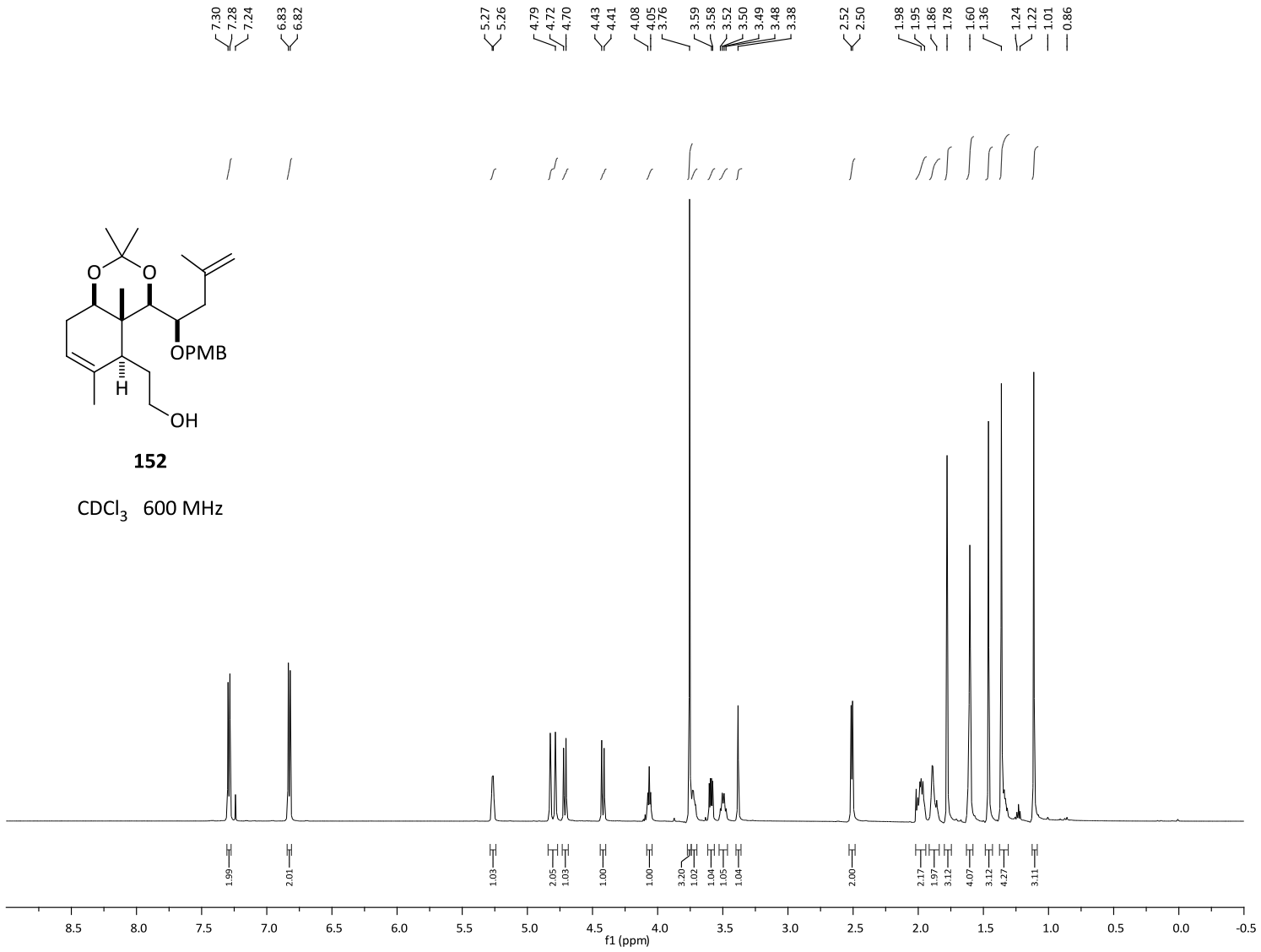
$CDCl_3$ 150 MHz

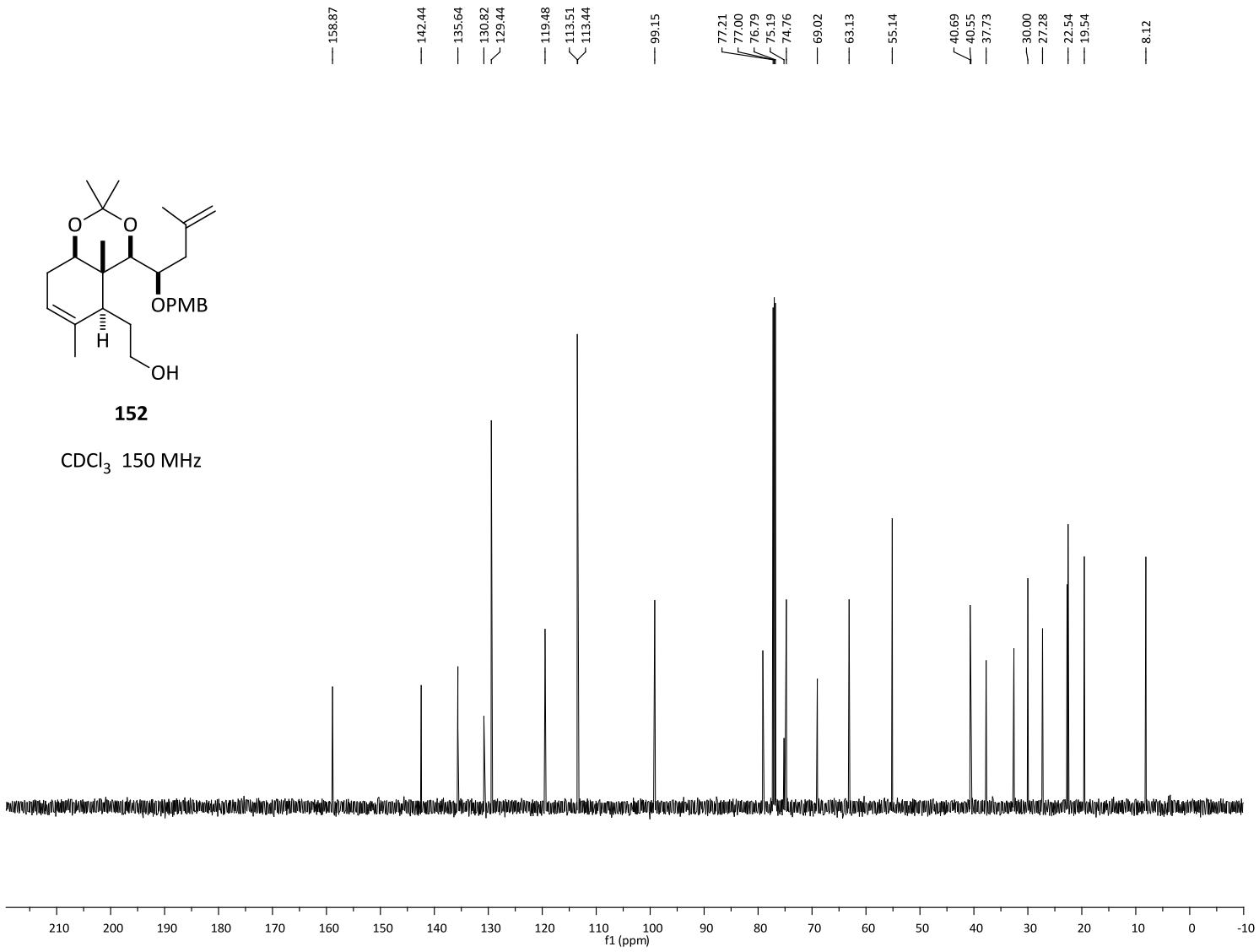

7.25
7.24
7.23
6.83
6.81
5.29
4.89
4.83
4.58
4.55
4.46
4.42
4.39
3.78
3.76
3.71
3.68
3.50
2.46
2.41
2.39
2.12
1.98
1.78
1.64
1.49
0.88
0.86
0.76
0.11
0.09
0.03
OH
OTBS
OPMB
H
OTBS
150
CDCl3 600 MHz
2.19
1.94
0.02
1.03
2.12
1.09
1.00
1.02
1.07
1.42
2.91
1.77
1.09
1.11
1.25
1.15
2.24
3.12
3.80
1.28
18.92
3.06
6.26
6.12
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

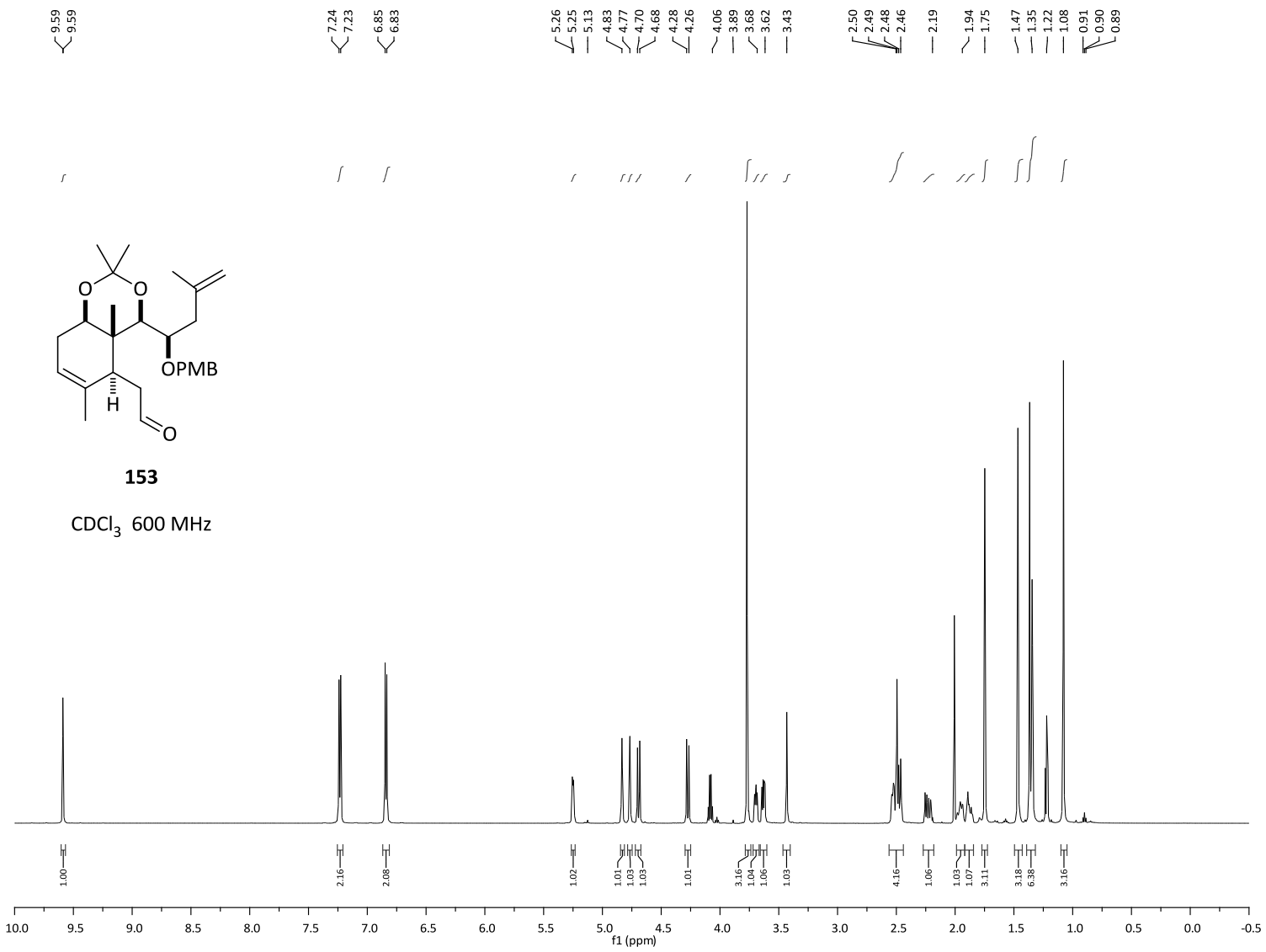

159.21
142.29
135.19
129.40
120.44
113.85
113.72
77.32
77.00
76.68
74.54
68.09
64.21
55.19
46.60
43.03
40.10
32.59
29.87
25.97
22.39
18.92
18.30
11.83
-3.19
-3.43
-5.21
OH
OTBS
OPMB
H
OTBS
150
CDCl3 150 MHz
f1 (ppm)

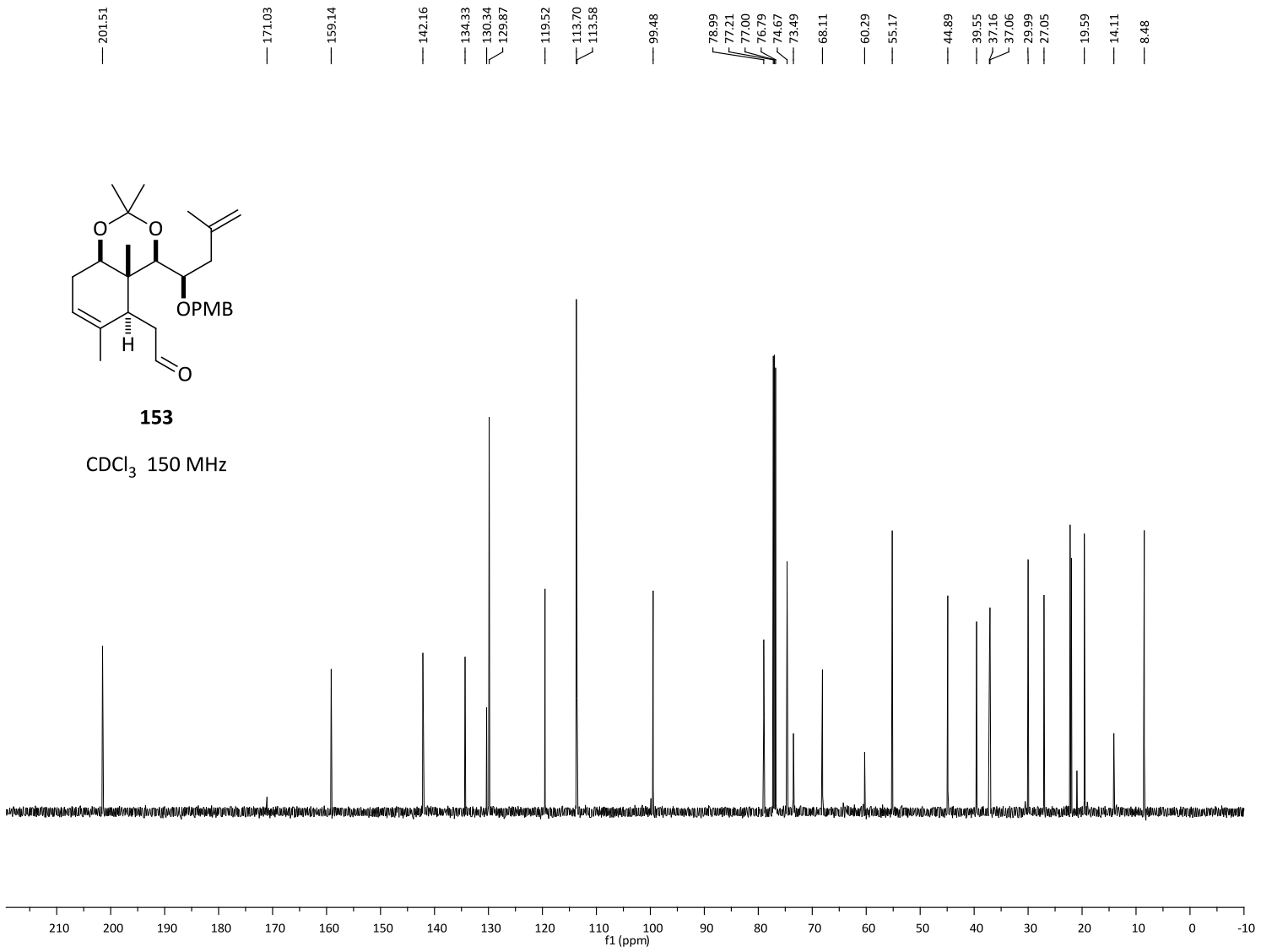

7.26
7.24
6.86
6.84
5.24
4.89
4.83
4.64
4.38
4.09
4.07
3.86
3.65
3.51
2.51
2.48
2.46
2.23
2.01
1.75
1.61
1.47
1.22
1.21
0.87
0.72
0.05
OH
OH
OPMB
H
OH
151
CDCl3 600 MHz
2.97
2.81
1.40
2.90
1.44
1.42
1.59
5.90
3.18
1.65
1.53
3.26
2.15
1.00
1.64
4.52
1.70
4.51
1.72
4.21
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

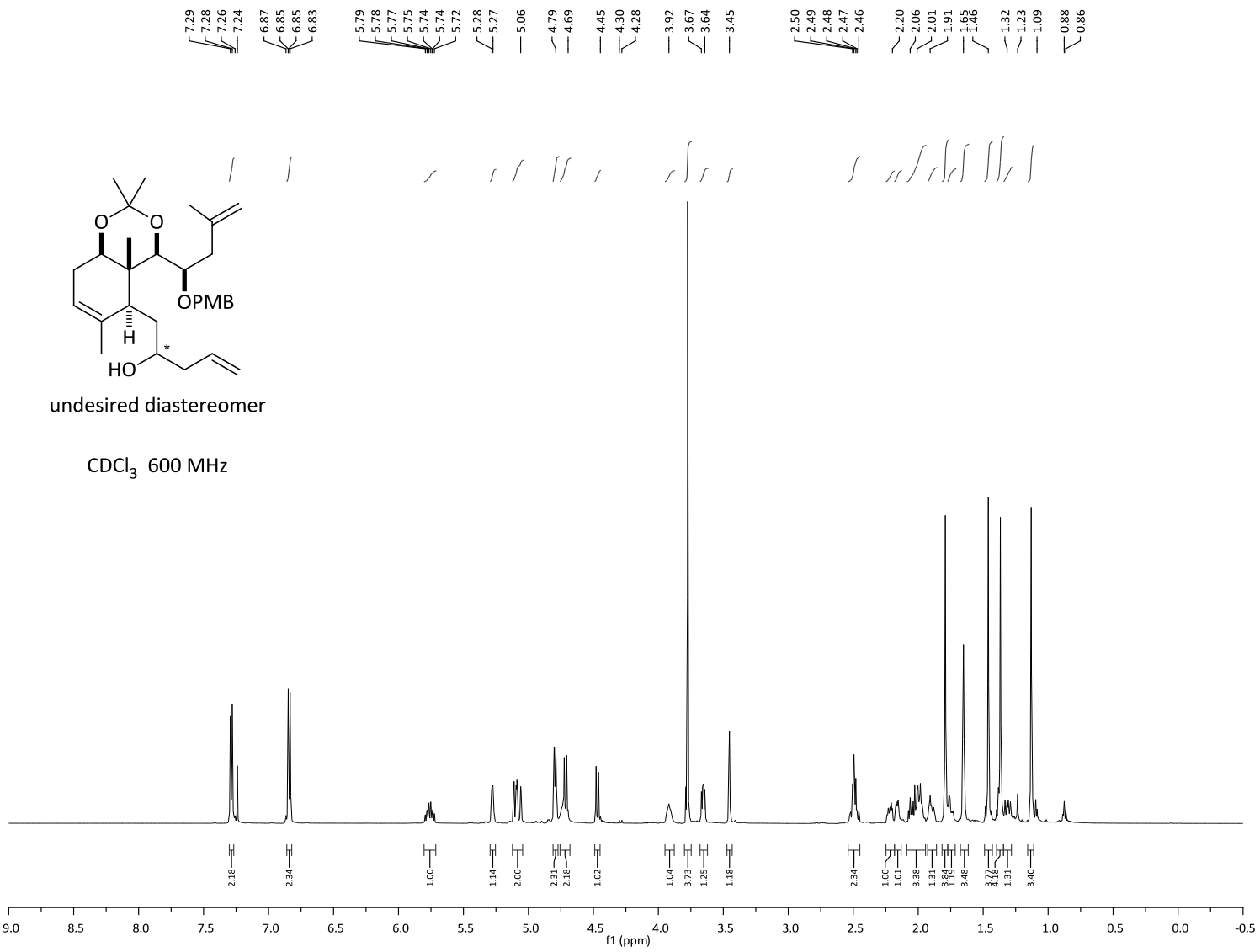

159.59
141.82
135.46
130.11
128.35
119.29
114.52
113.92
77.32
77.00
76.68
74.06
73.56
67.95
63.47
55.15
45.14
41.49
39.09
30.65
30.41
22.68
21.90
10.83
OH
OH
OPMB
H
OH
151
CDCl3 150 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

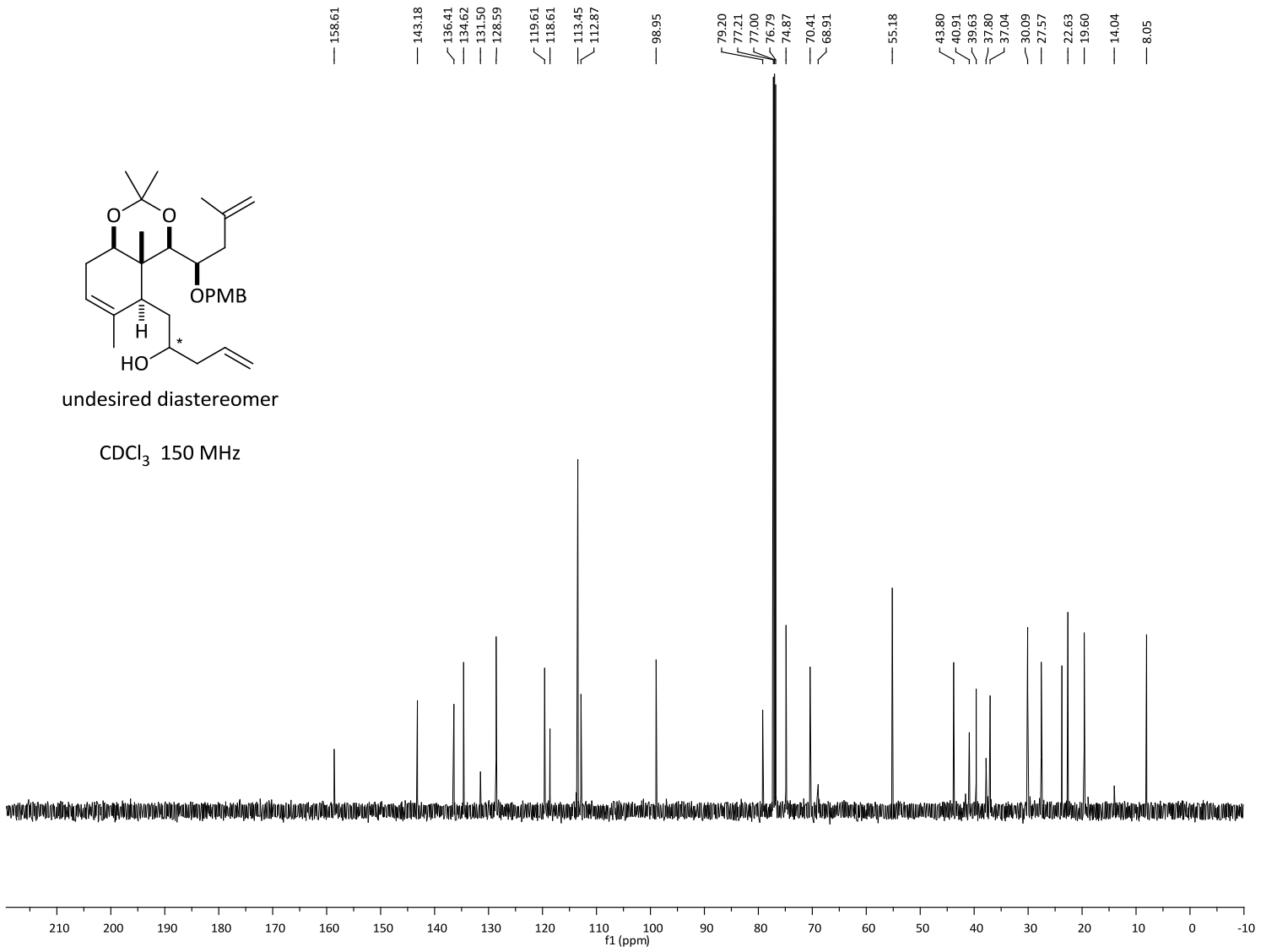

7.30
7.28
7.24
6.83
6.82
5.27
5.26
4.79
4.72
4.70
4.43
4.41
4.08
4.05
3.76
3.59
3.58
3.52
3.50
3.49
3.48
3.38
2.52
2.50
1.98
1.95
1.86
1.78
1.60
1.36
1.24
1.22
1.01
0.86
O
O
OPMB
H
OH
152
CDCl3 600 MHz
1.99
2.01
1.03
2.05
1.03
1.00
1.00
3.20
1.02
1.04
1.05
1.04
2.00
2.17
1.97
3.12
4.07
3.12
4.27
3.11
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

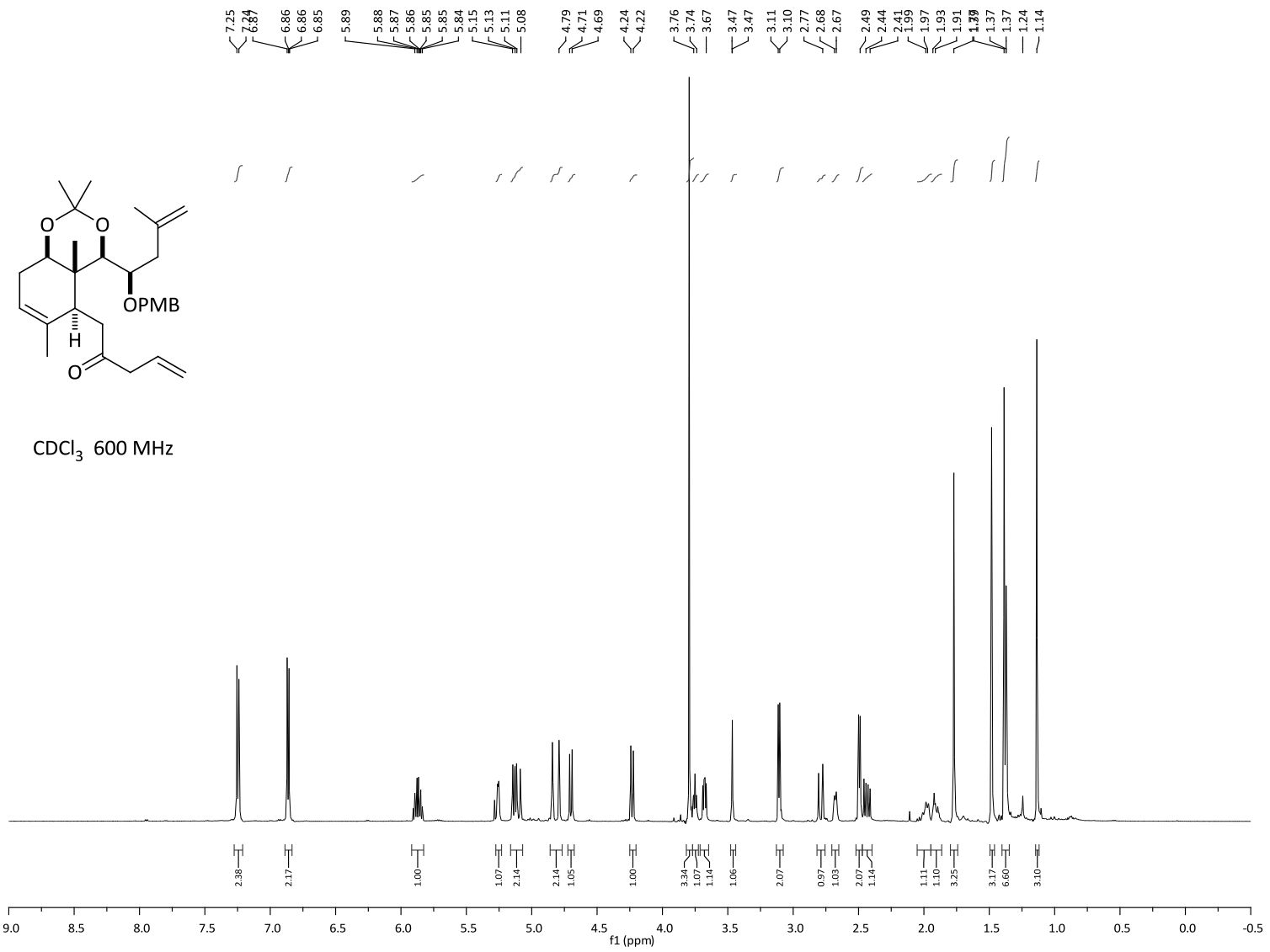

158.87
142.44
135.64
130.82
129.44
119.48
113.51
113.44
99.15
77.21
77.00
76.79
75.19
74.76
69.02
63.13
55.14
40.69
40.55
37.73
30.00
27.28
22.54
19.54
8.12
O
O
OPMB
H
OH
152
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

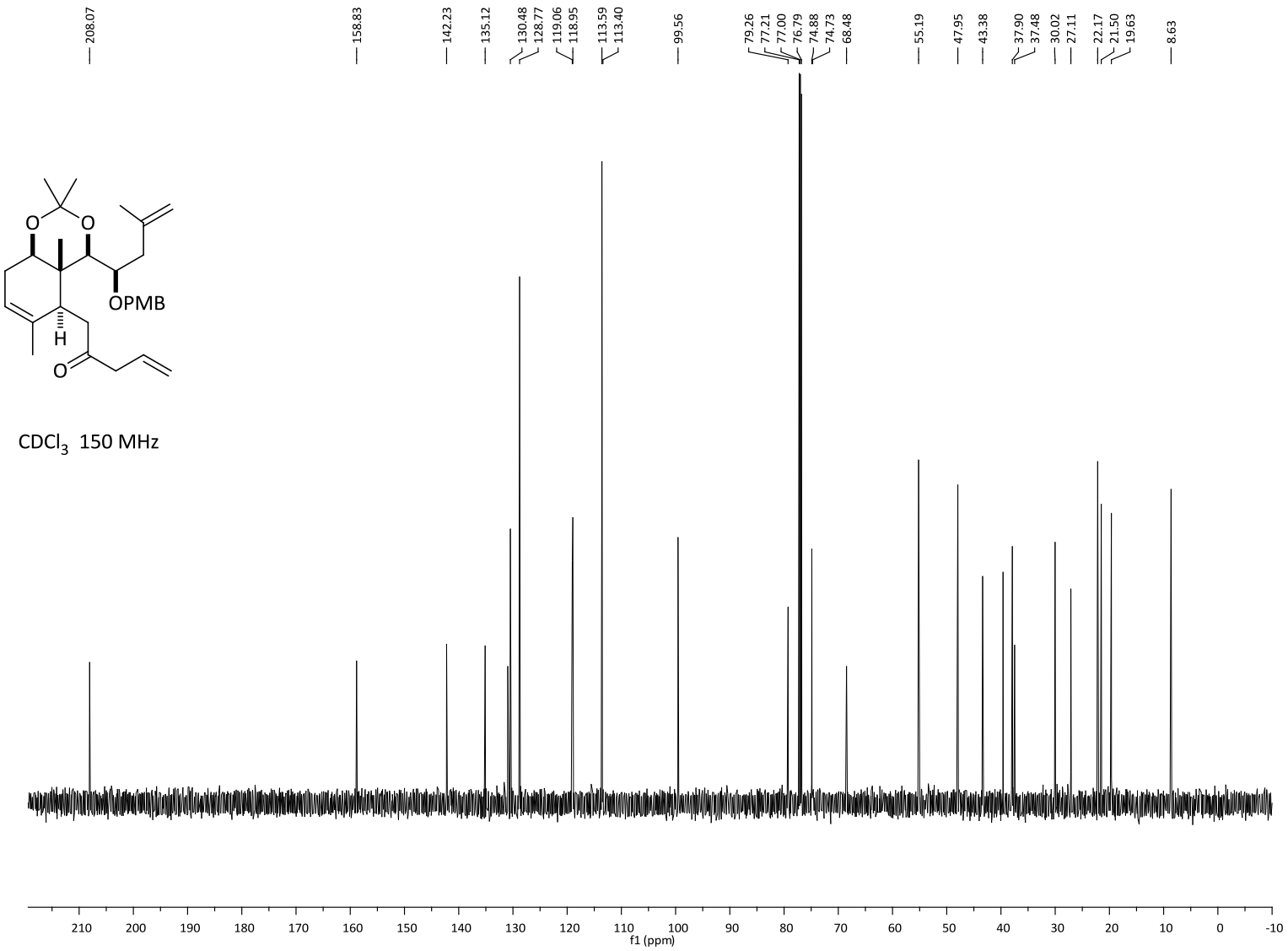

9.59
9.59
7.24
7.23
6.85
6.83
5.26
5.25
5.13
4.83
4.77
4.70
4.68
4.28
4.26
4.06
3.89
3.68
3.62
3.43
2.50
2.49
2.48
2.46
2.19
1.94
1.75
1.47
1.35
1.22
1.08
0.91
0.90
0.89
OPMB
H
O
O
O
153
CDCl3 600 MHz
1.00
2.16
2.08
1.02
1.01
1.03
1.03
1.01
3.16
1.04
1.06
1.03
4.16
1.06
1.03
1.07
3.11
3.18
6.38
3.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

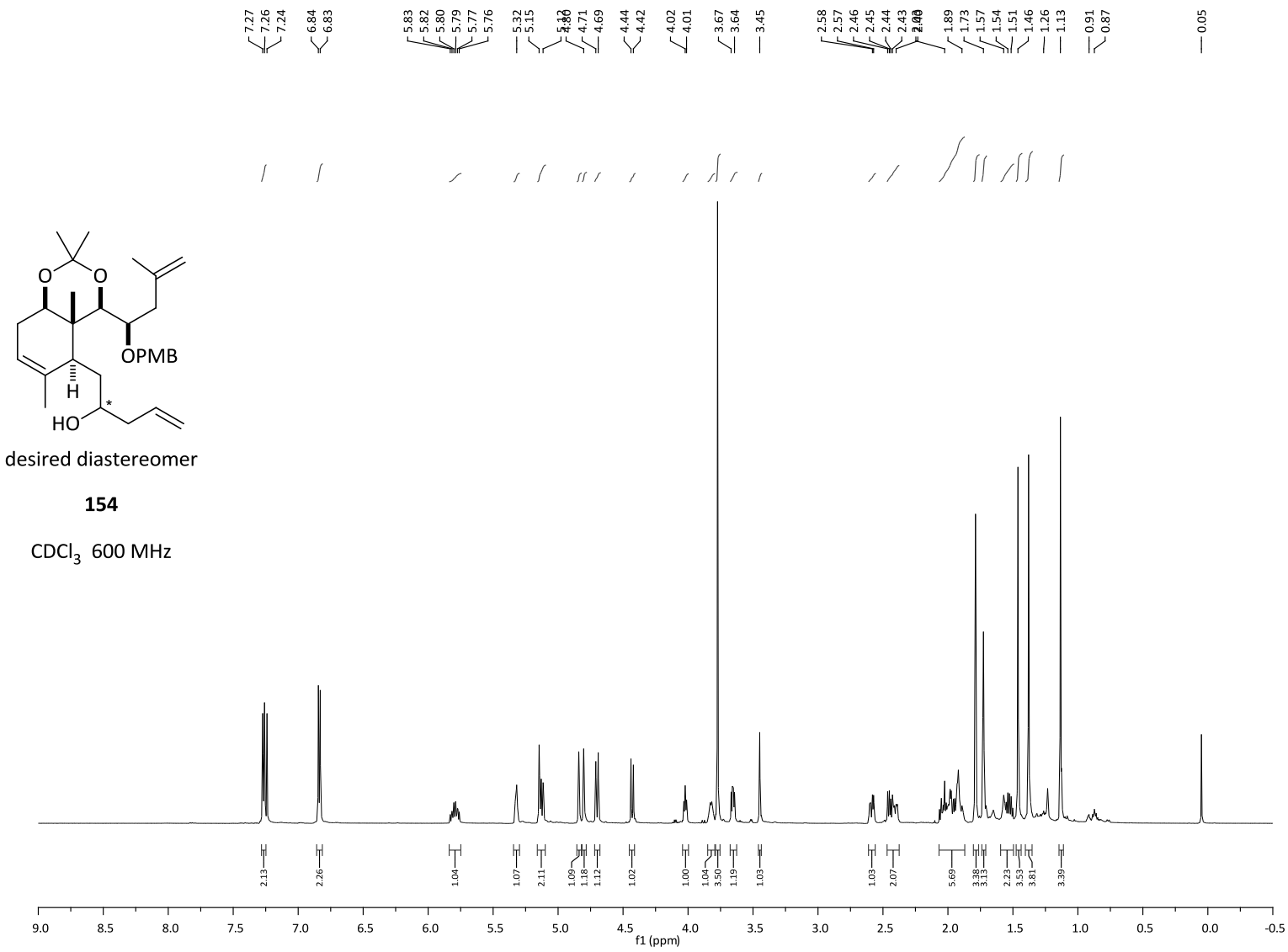

201.51
171.03
159.14
142.16
134.33
130.34
129.87
119.52
113.70
113.58
99.48
78.99
77.21
77.00
76.79
74.67
73.49
68.11
60.29
55.17
44.89
39.55
37.16
37.06
29.99
27.05
19.59
14.11
8.48
O
O
OPMB
H
O
153
CDCl3 150 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

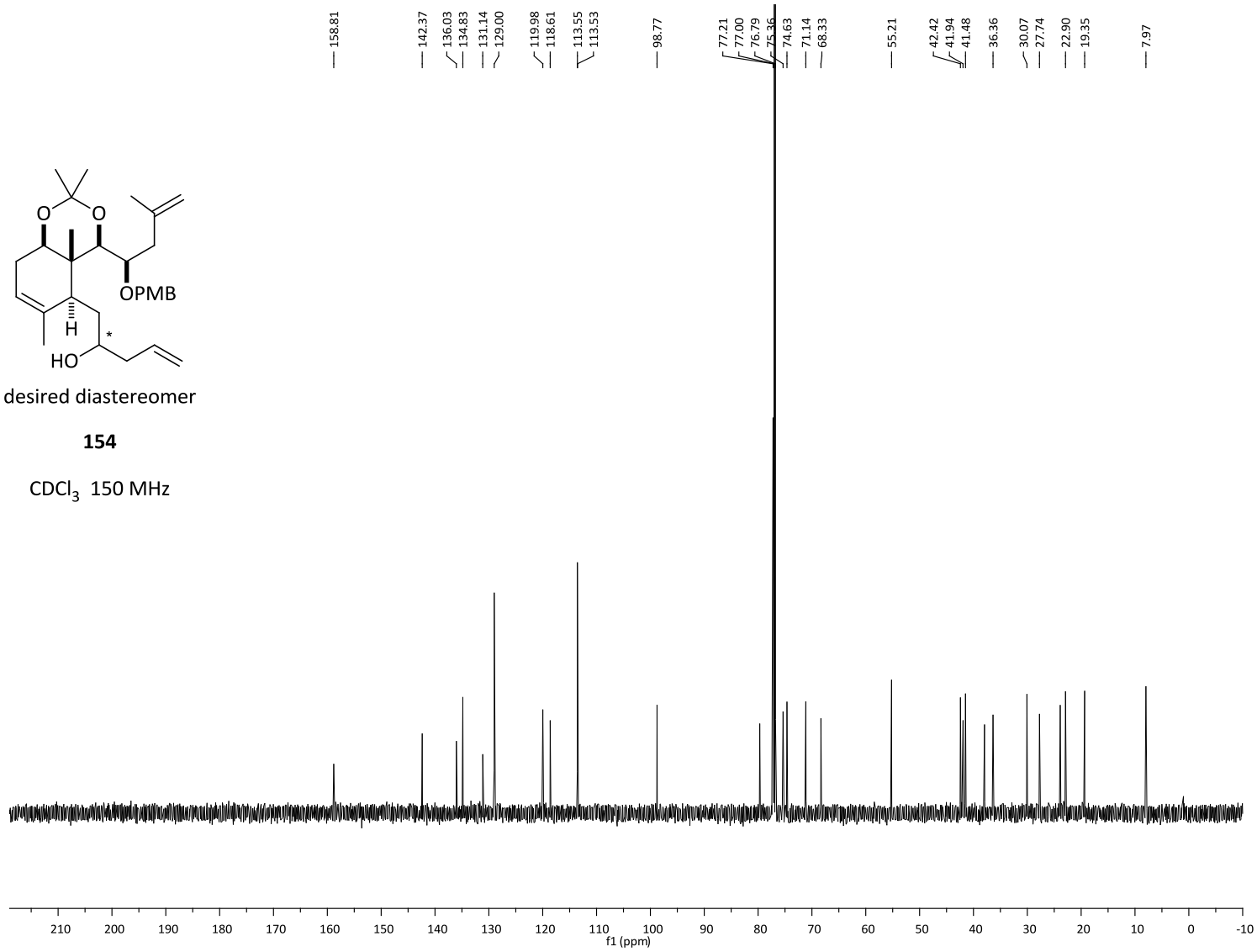

7.29
7.28
7.26
7.24
6.87
6.85
6.85
6.83
5.79
5.78
5.77
5.75
5.74
5.74
5.72
5.28
5.27
5.06
4.79
4.69
4.45
4.30
4.28
3.92
3.67
3.64
3.45
2.50
2.49
2.48
2.47
2.46
2.20
2.06
2.01
1.91
1.65
1.46
1.32
1.23
1.09
0.88
0.86
O
O
OPMB
H
*
HO
undesired diastereomer
CDCl3 600 MHz
2.18
2.34
1.00
1.14
2.00
2.31
2.18
1.02
1.04
3.73
1.25
1.18
2.34
1.00
1.01
3.38
1.31
1.83
1.83
3.48
3.77
4.18
1.31
3.40
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


158.61
143.18
136.41
134.62
131.50
128.59
119.61
118.61
113.45
112.87
98.95
79.20
77.21
77.00
76.79
74.87
70.41
68.91
55.18
43.80
40.91
39.63
37.80
37.04
30.09
27.57
22.63
19.60
14.04
8.05
O
O
OPMB
H
*
HO
undesired diastereomer
CDCl3 150 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OPMB
H
O
O
O
CDCl3 600 MHz
f1 (ppm)


208.07
158.83
142.23
135.12
130.48
128.77
119.06
118.95
113.59
113.40
99.56
79.26
77.21
77.00
76.79
74.88
74.73
68.48
55.19
47.95
43.38
37.90
37.48
30.02
27.11
22.17
21.50
19.63
8.63
O
O
OPMB
H
O
CDCl3 150 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

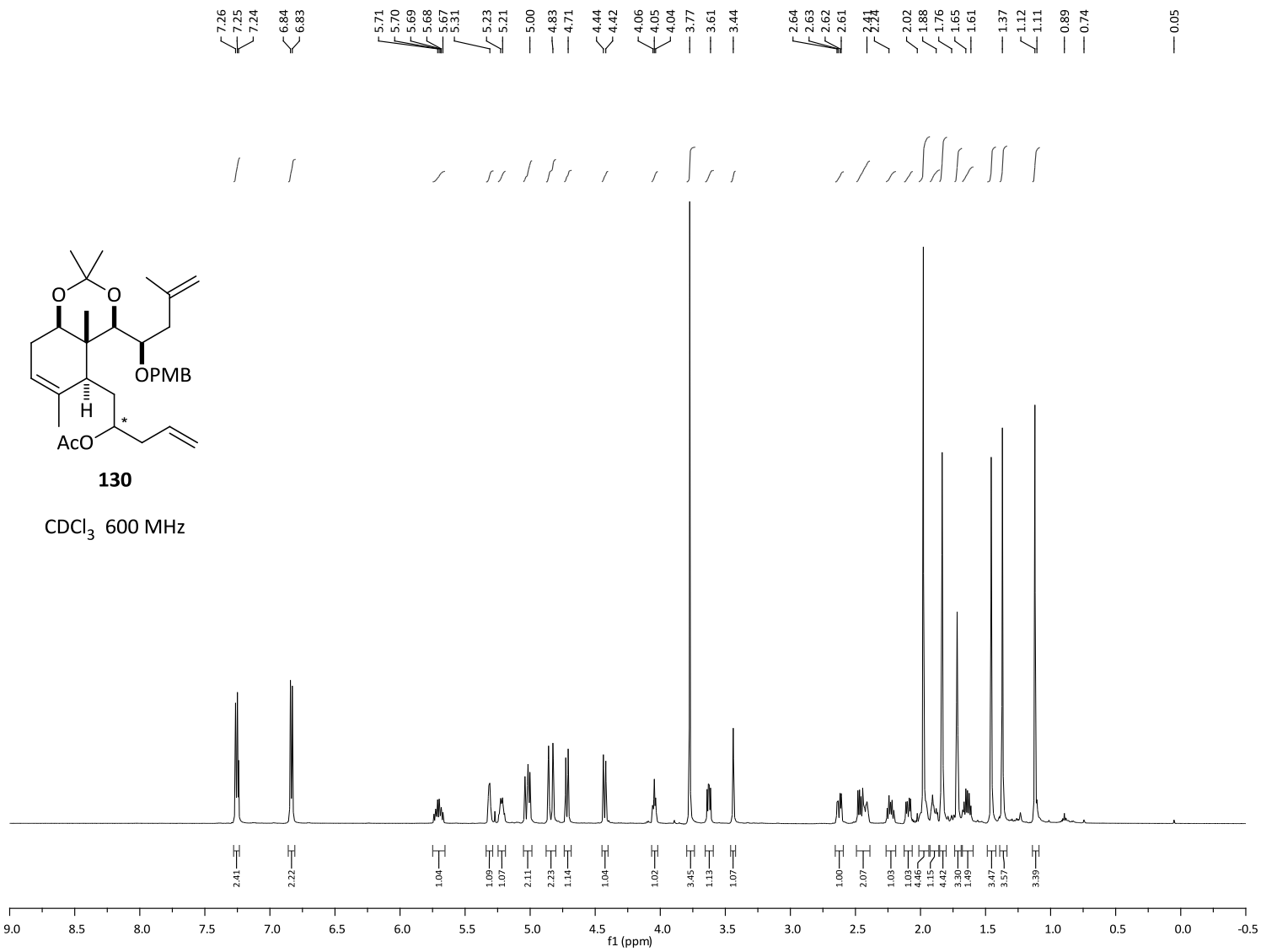

7.27
7.26
7.24
6.84
6.83
5.83
5.82
5.80
5.79
5.77
5.76
5.32
5.15
4.71
4.69
4.44
4.42
4.02
4.01
3.67
3.64
3.45
2.58
2.57
2.46
2.45
2.44
2.43
1.89
1.73
1.57
1.54
1.51
1.46
1.26
1.13
0.91
0.87
0.05
O
O
OPMB
H
HO
*
desired diastereomer
154
CDCl3 600 MHz
2.13
2.26
1.04
1.07
2.11
1.09
1.18
1.12
1.02
1.00
1.04
3.50
1.19
1.03
1.03
2.07
5.69
3.38
3.13
2.23
3.53
3.81
3.39
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

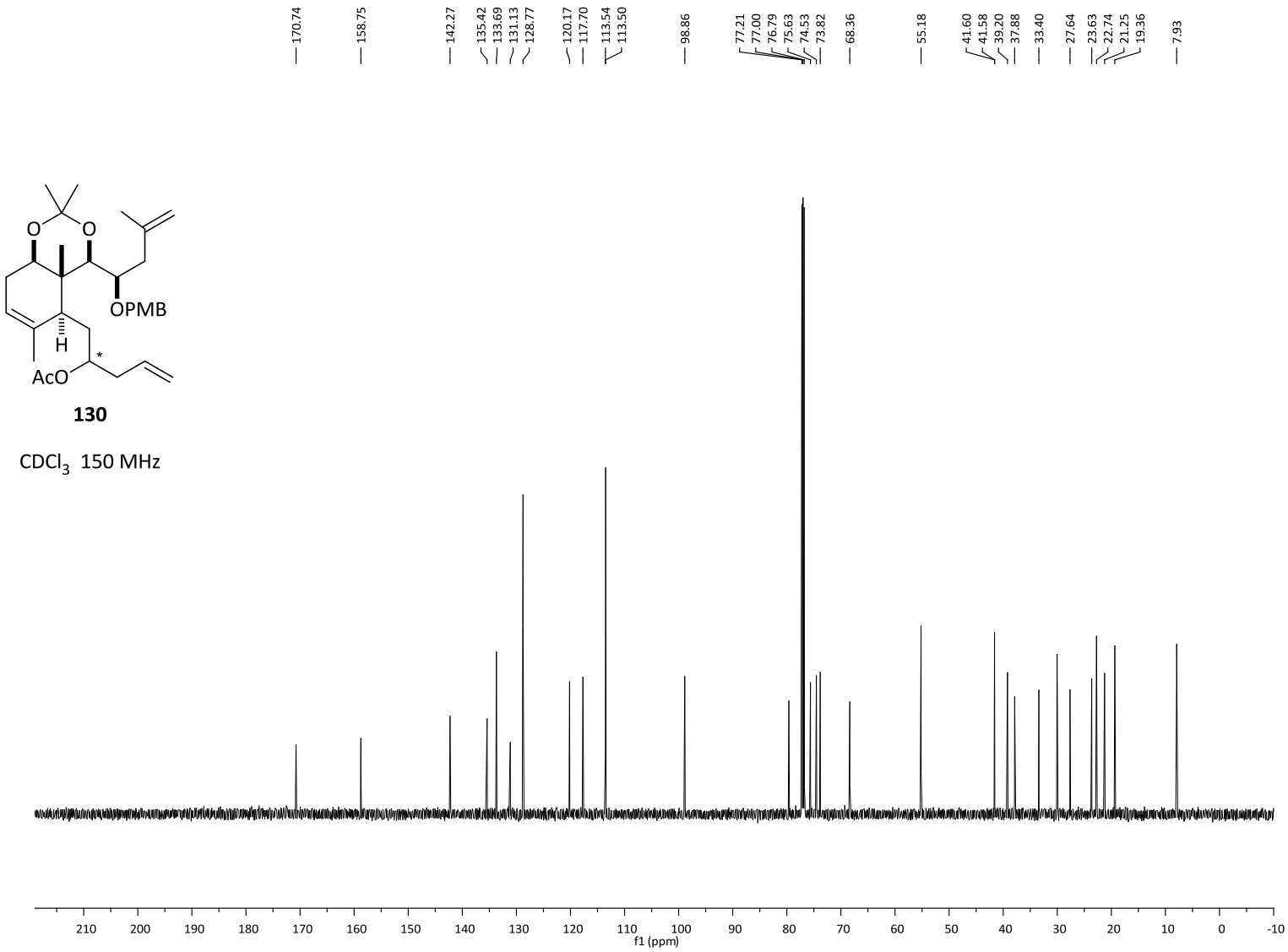


desired diastereomer

154

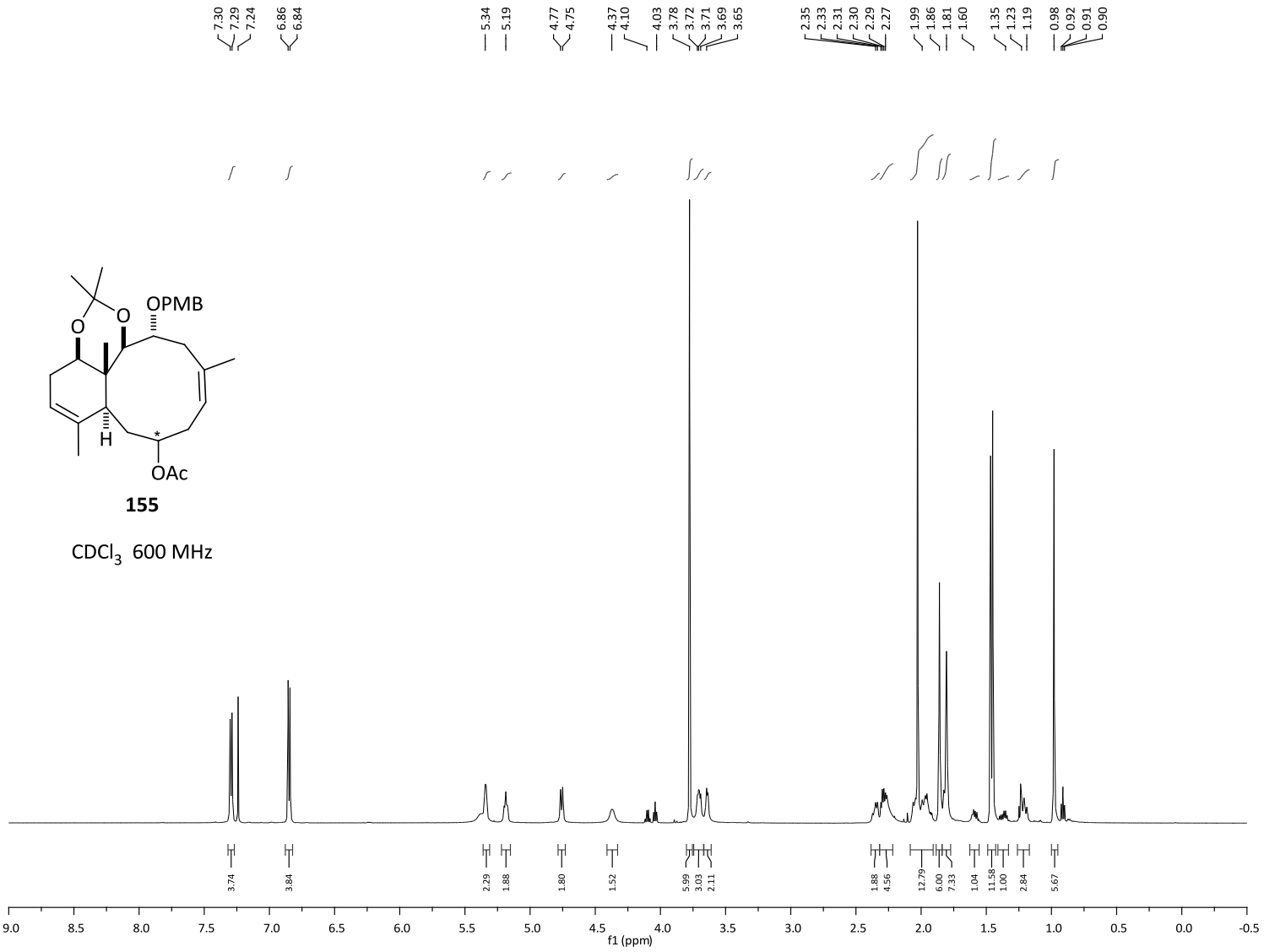
$CDCl_3$ 150 MHz

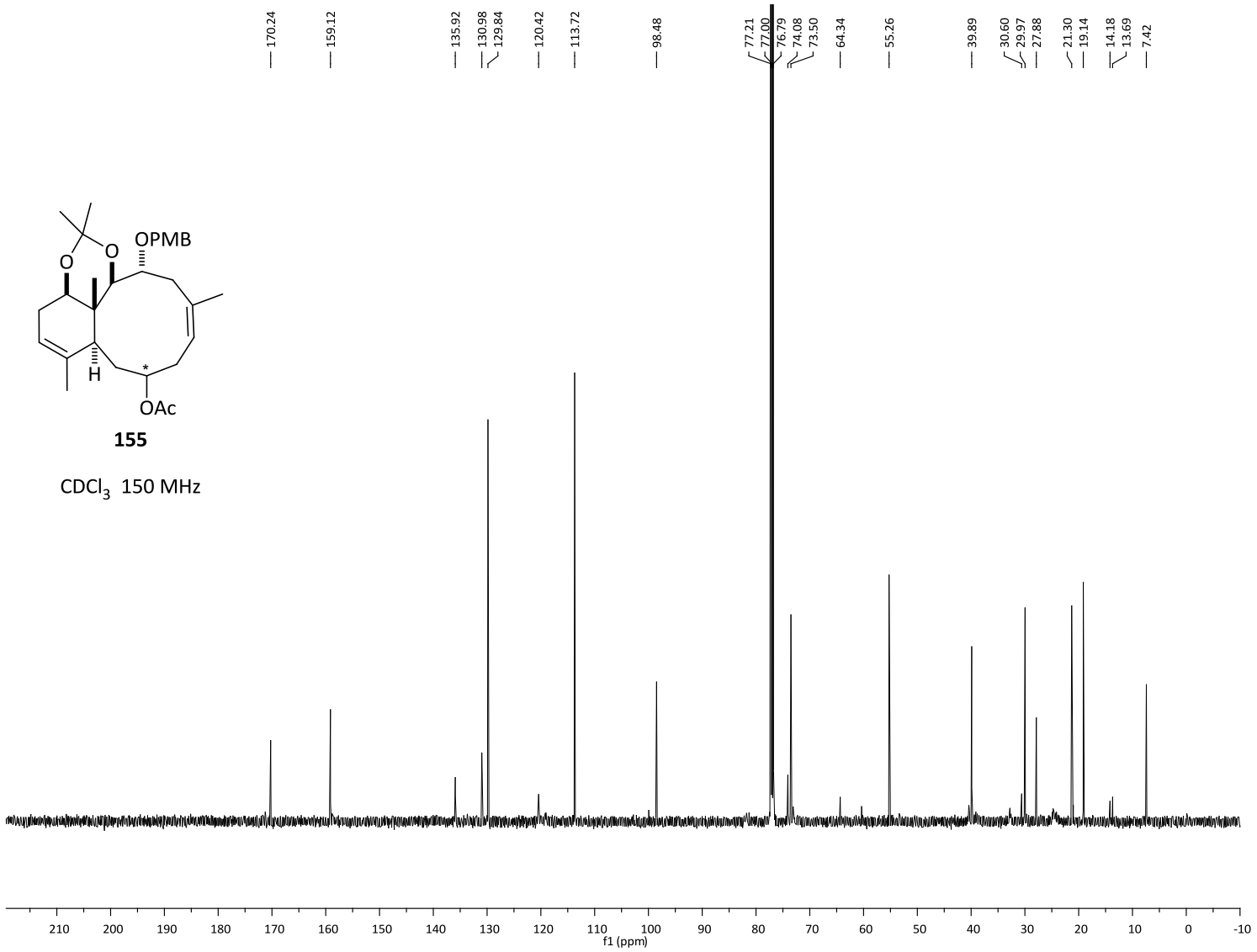

7.26
7.25
7.24
6.84
6.83
5.71
5.70
5.69
5.68
5.67
5.31
5.23
5.21
5.00
4.83
4.71
4.44
4.42
4.06
4.05
4.04
3.77
3.61
3.44
2.64
2.63
2.62
2.61
2.41
2.24
2.02
1.88
1.76
1.65
1.61
1.37
1.12
1.11
0.89
0.74
0.05
O
O
OPMB
H
*
AcO
130
CDCl3 600 MHz
2.41
2.22
1.04
1.09
1.07
2.11
2.23
1.14
1.04
1.02
3.45
1.13
1.07
1.00
2.07
1.03
1.03
4.46
1.15
4.42
3.30
1.49
3.47
3.57
3.39
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

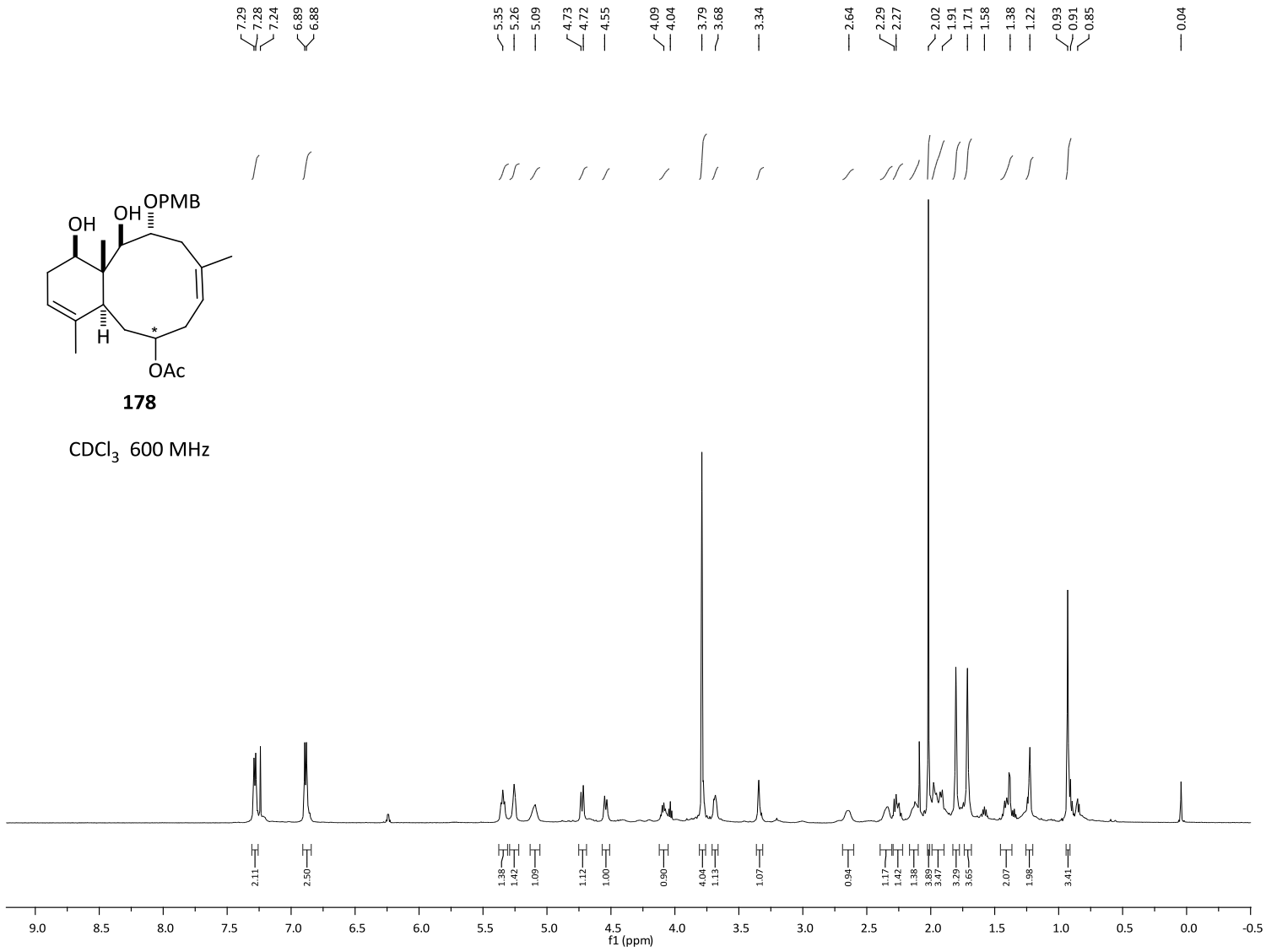


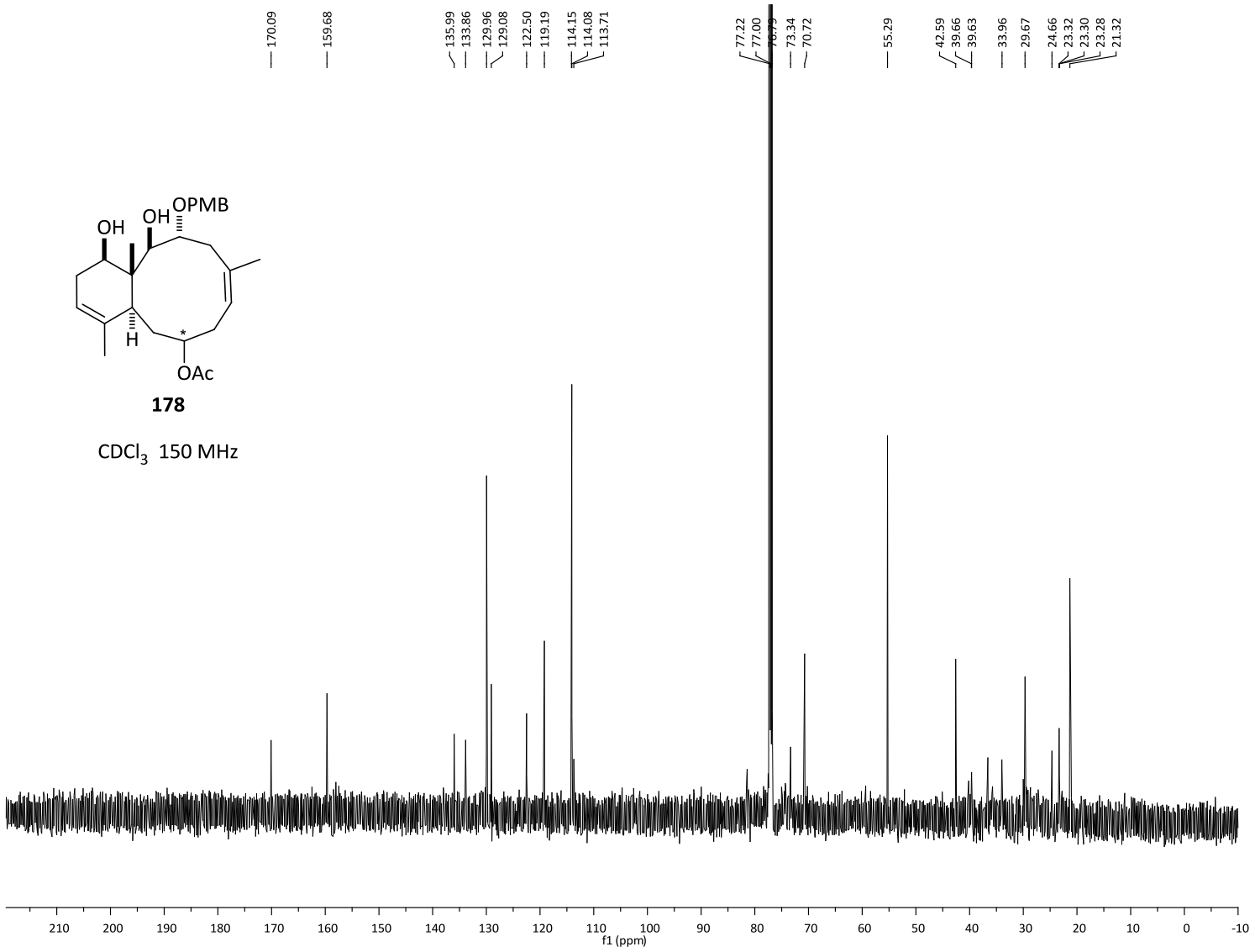
130

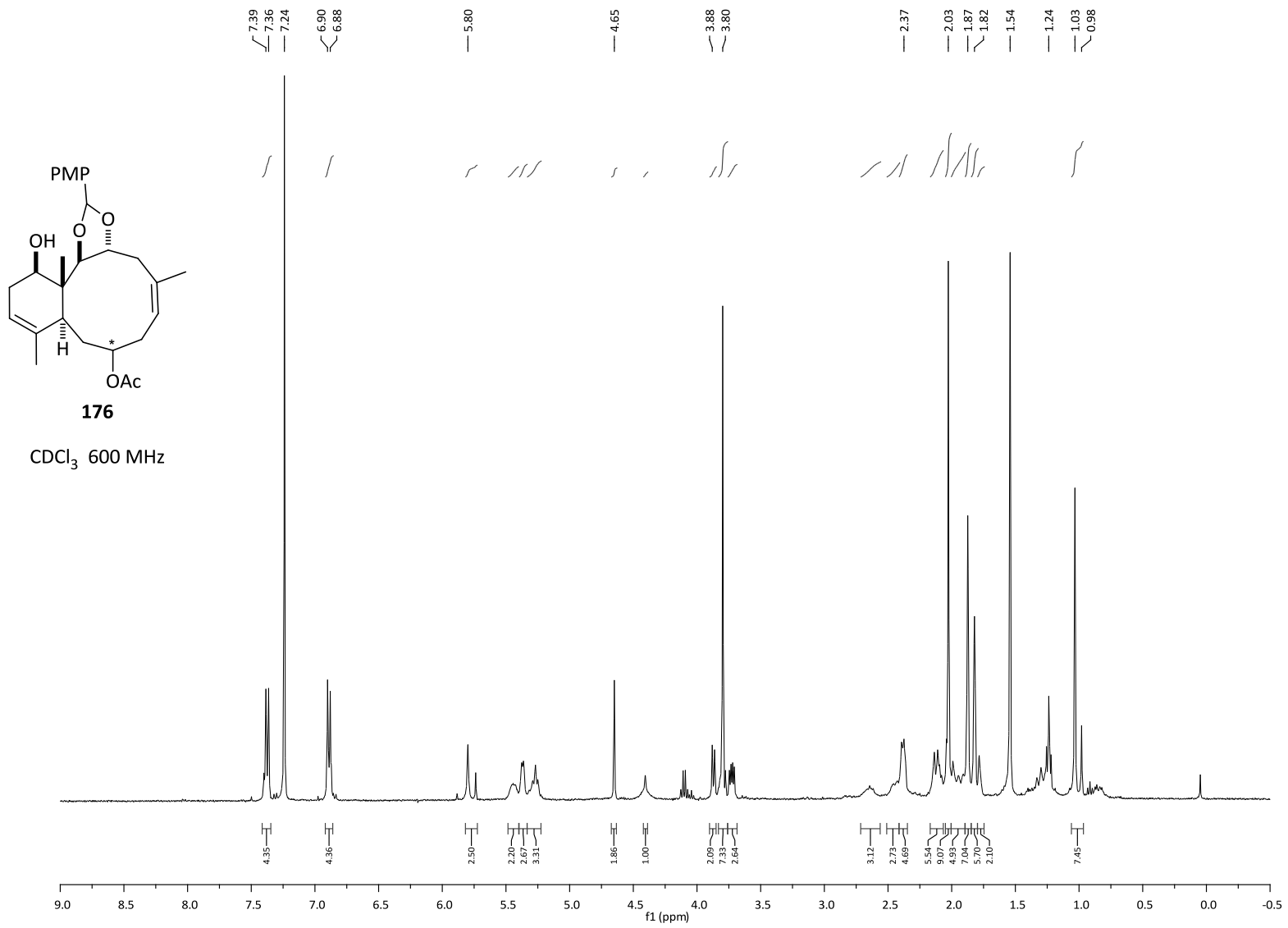
$CDCl_3$ 150 MHz

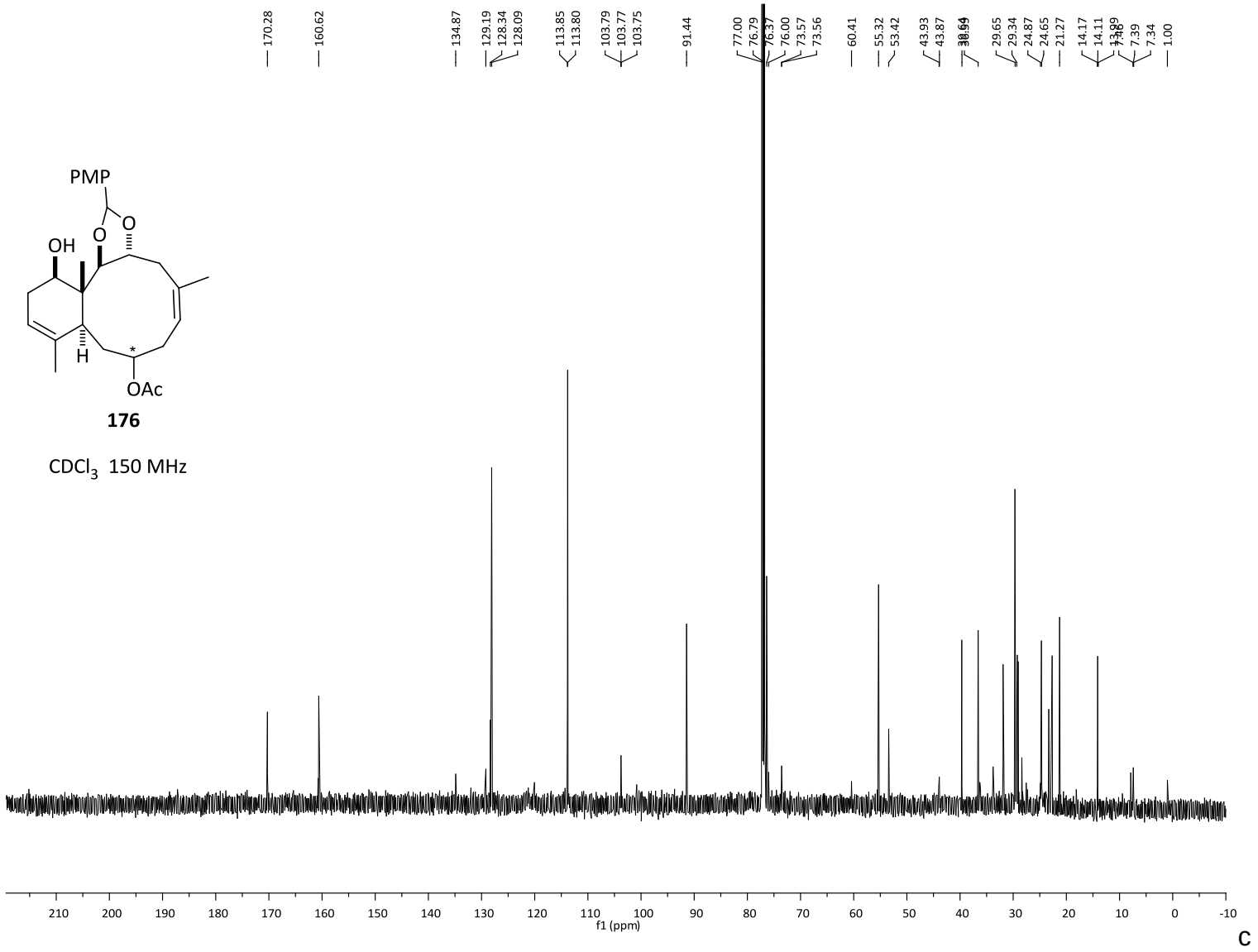

7.30
7.29
7.24
6.86
6.84
5.34
5.19
4.77
4.75
4.37
4.10
4.03
3.78
3.72
3.71
3.69
3.65
2.35
2.33
2.31
2.30
2.29
2.27
1.99
1.86
1.81
1.60
1.35
1.23
1.19
0.98
0.92
0.91
0.90
OPMB
O
O
H
*
OAc
155
CDCl3 600 MHz
3.74
3.84
2.29
1.88
1.80
1.52
5.99
3.03
2.11
1.88
4.56
12.79
6.00
7.33
1.04
11.58
1.00
2.84
5.67
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

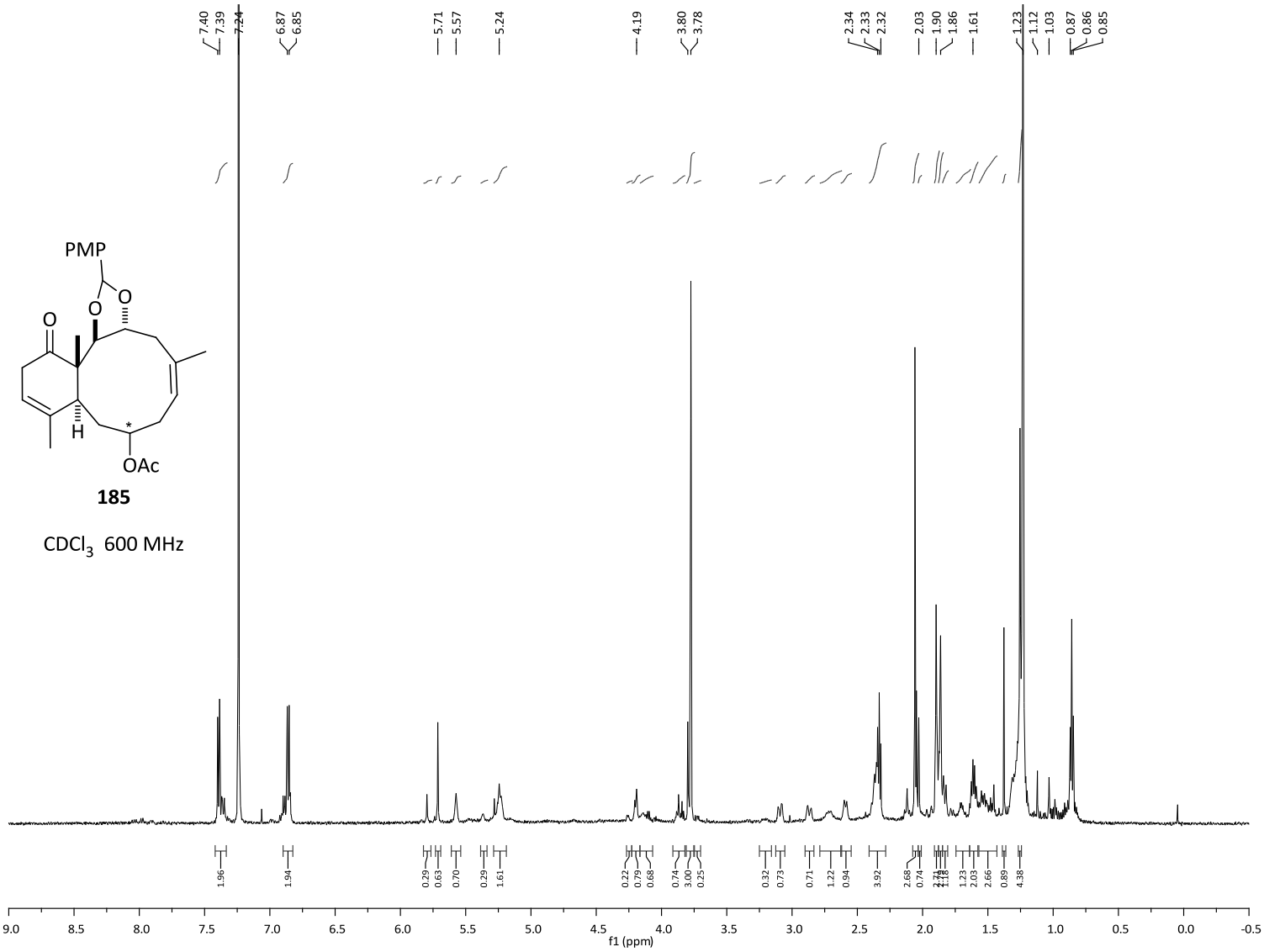

170.24
159.12
135.92
130.98
129.84
120.42
113.72
98.48
77.21
77.00
76.79
74.08
73.50
64.34
55.26
39.89
30.60
29.97
27.88
21.30
19.14
14.18
13.69
7.42
OPMB
O
O
H
*
OAc
155
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

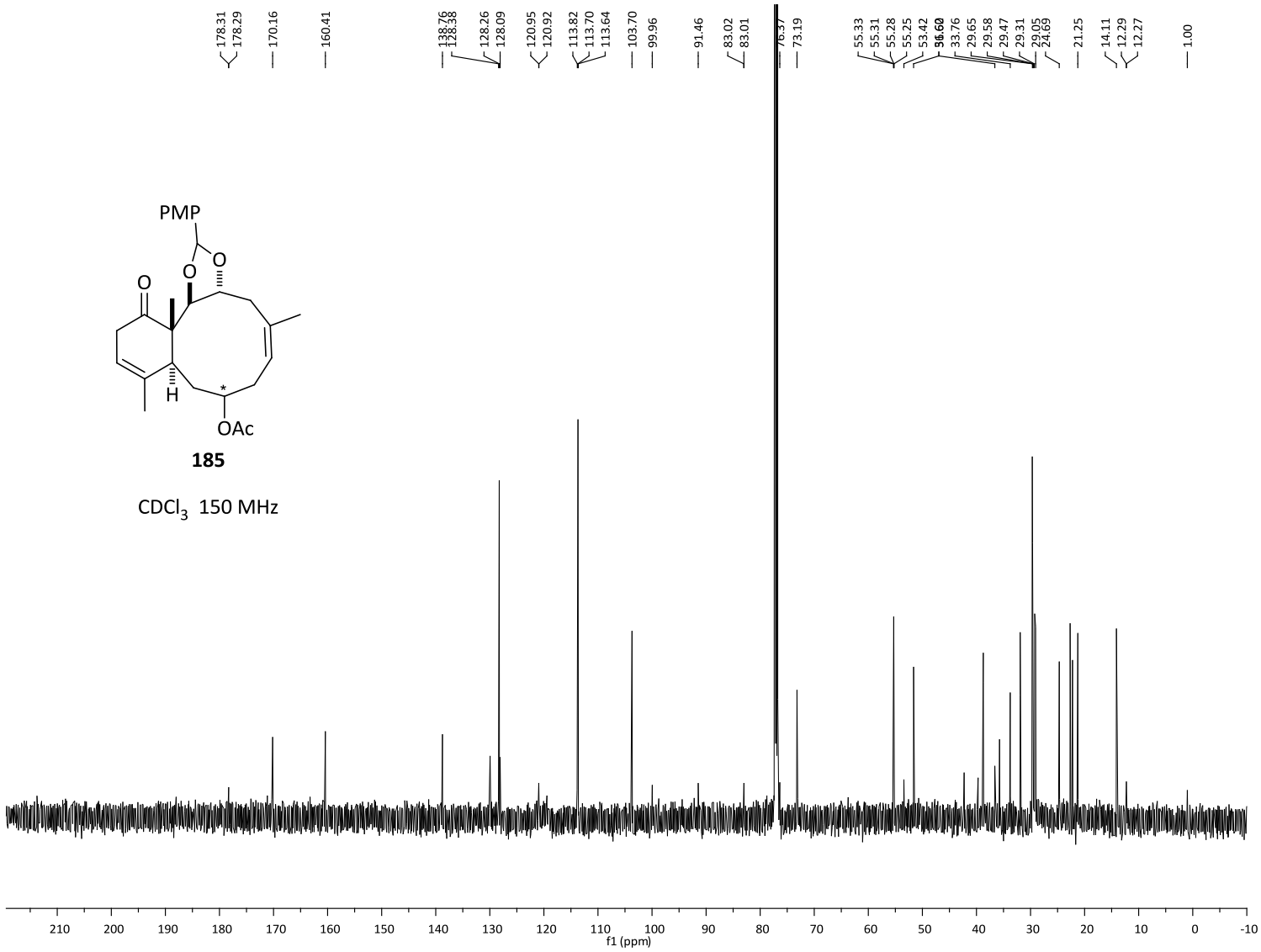

OH
OH
OPMB
H
OAc
178
CDCl3 600 MHz
f1 (ppm)

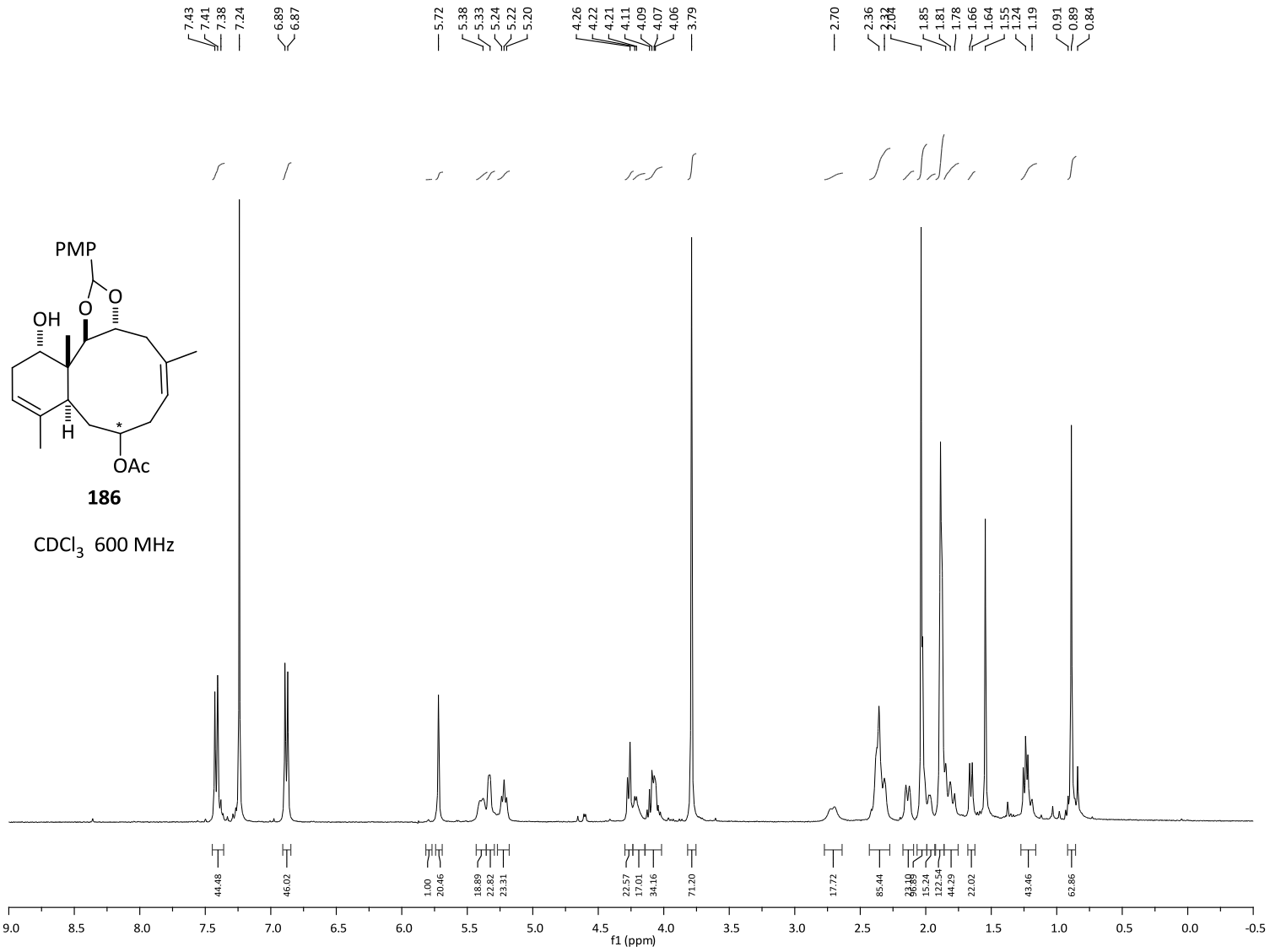

170.09
159.68
135.99
133.86
129.96
129.08
122.50
119.19
114.15
114.08
113.71
77.22
77.00
76.79
73.34
70.72
55.29
42.59
39.66
39.63
33.96
29.67
24.66
23.32
23.30
23.28
21.32
OH
OH
OPMB
H
*
OAc
178
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

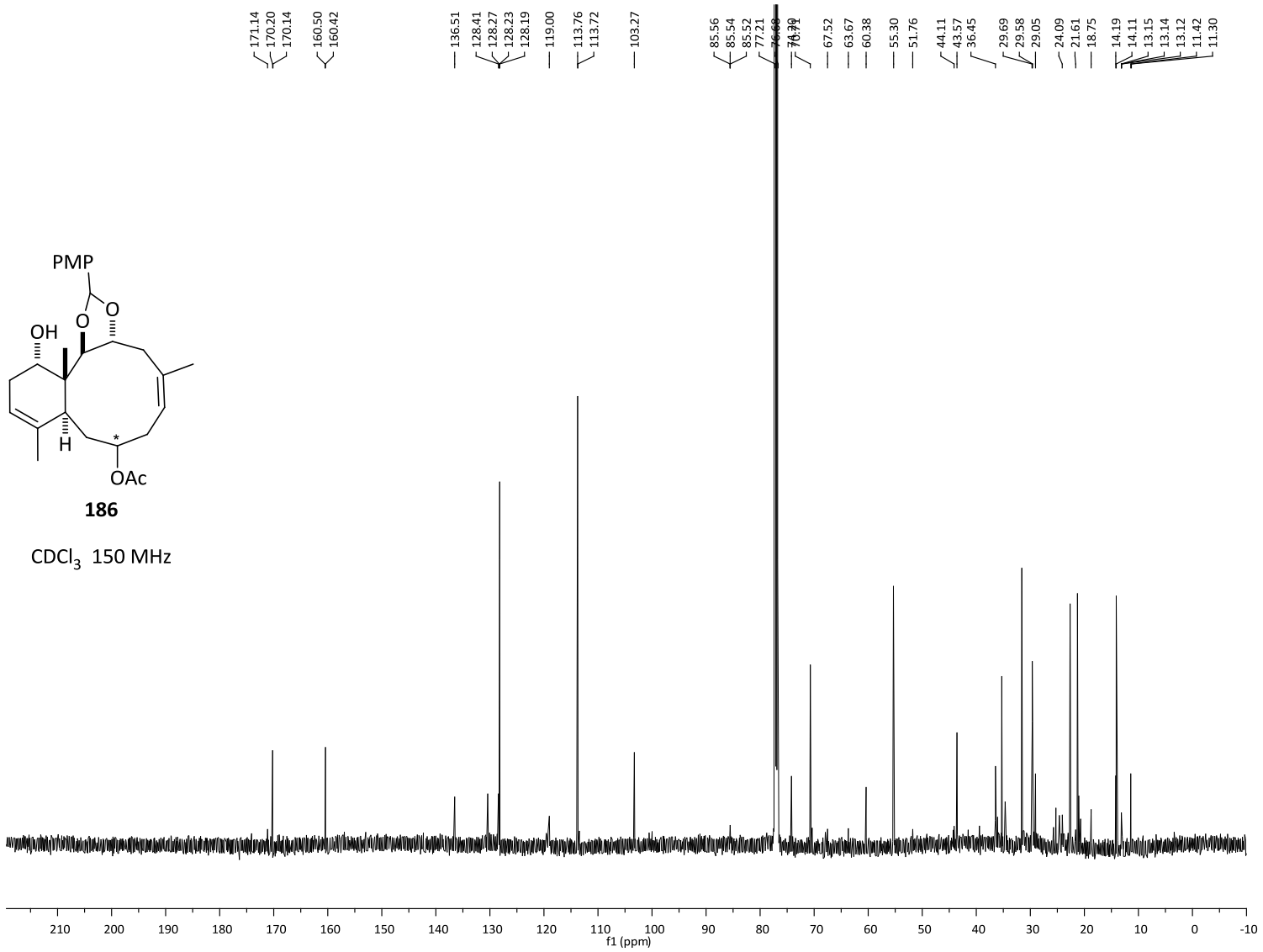

PMP
O
O
OH
H
*
OAc
176
CDCl3 600 MHz
7.39
7.36
7.24
6.90
6.88
5.80
4.65
3.88
3.80
2.37
2.03
1.87
1.82
1.54
1.24
1.03
0.98
f1 (ppm)

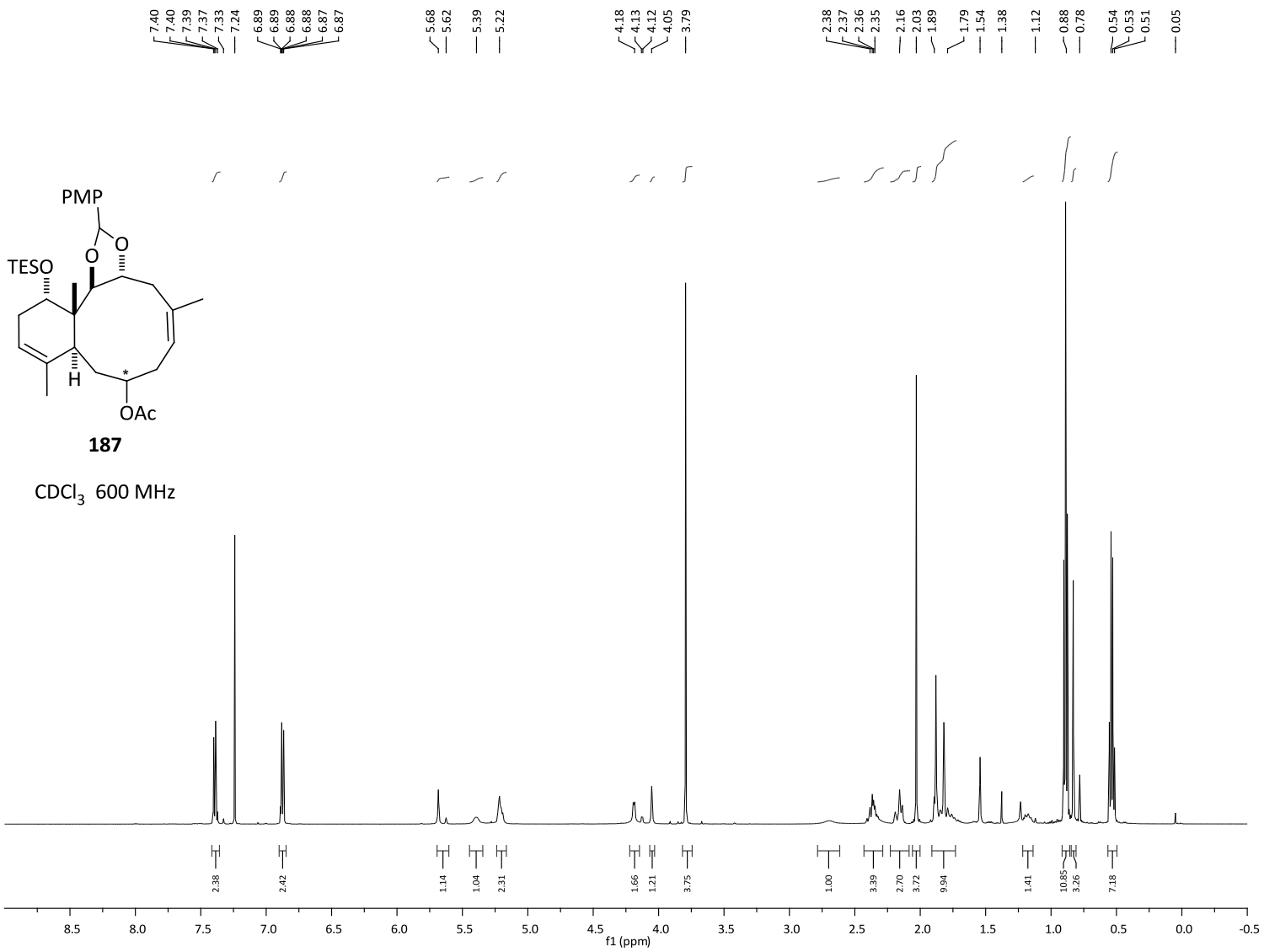

PMP
O
O
OH
H
*
OAc
176
CDCl3 150 MHz
170.28
160.62
134.87
129.19
128.34
128.09
113.85
113.80
103.79
103.77
103.75
91.44
77.00
76.79
76.37
76.00
73.57
73.56
60.41
55.32
53.42
43.93
43.87
29.65
29.34
24.87
24.65
21.27
14.17
14.11
7.39
7.34
1.00
f1 (ppm)

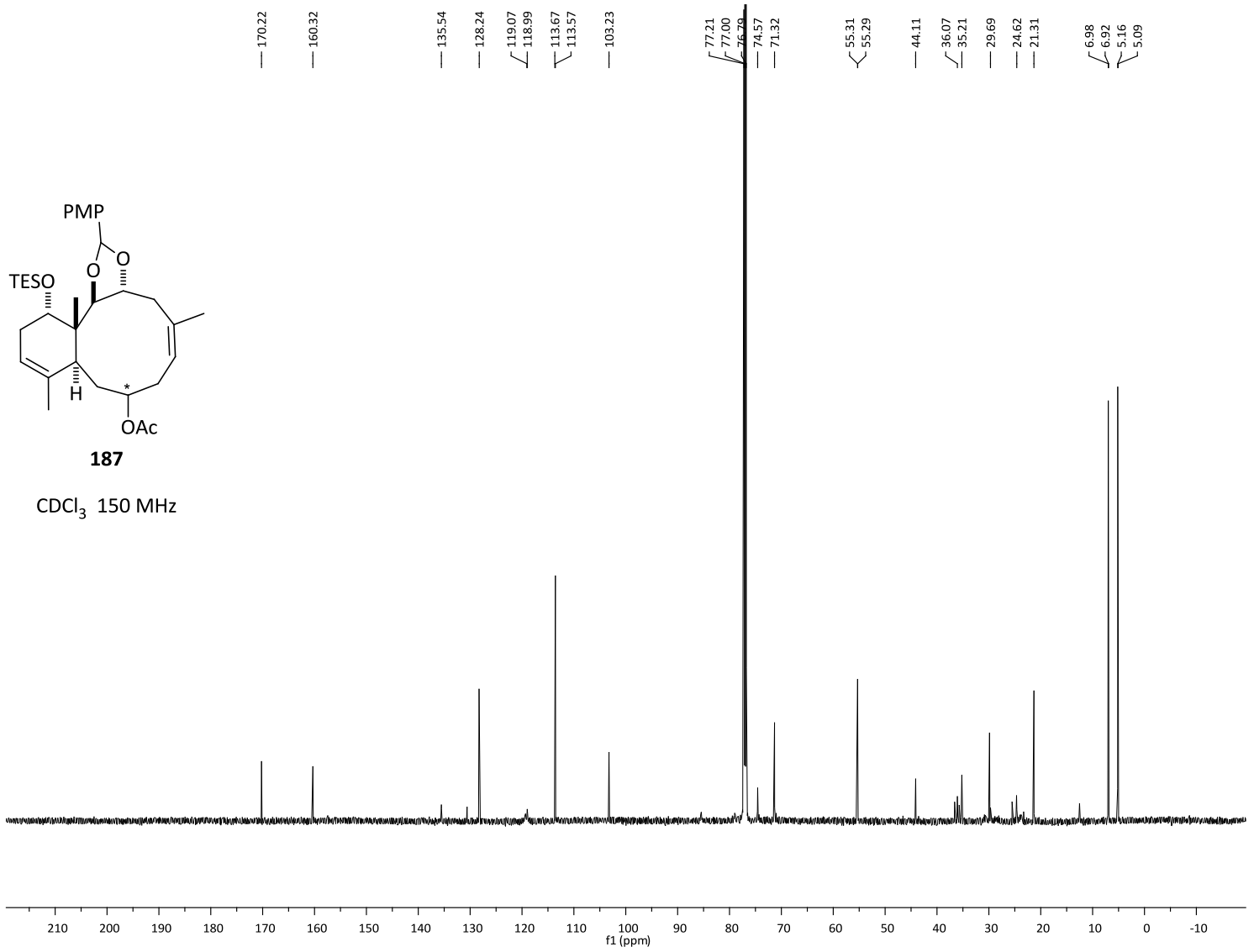

PMP
O
O
O
H
*
OAc
185
CDCl3 600 MHz
7.40
7.39
7.24
6.87
6.85
5.71
5.57
5.24
4.19
3.80
3.78
2.34
2.33
2.32
2.03
1.90
1.86
1.61
1.23
1.12
1.03
0.87
0.86
0.85
f1 (ppm)


178.31
178.29
170.16
160.41
138.76
138.38
128.26
128.09
120.95
120.92
113.82
113.70
113.64
103.70
99.96
91.46
83.02
83.01
76.37
73.19
55.33
55.31
55.28
55.25
53.42
33.76
29.65
29.58
29.47
29.31
24.69
21.25
14.11
12.29
12.27
1.00
PMP
O
O
O
H
*
OAc
185
CDCl3 150 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

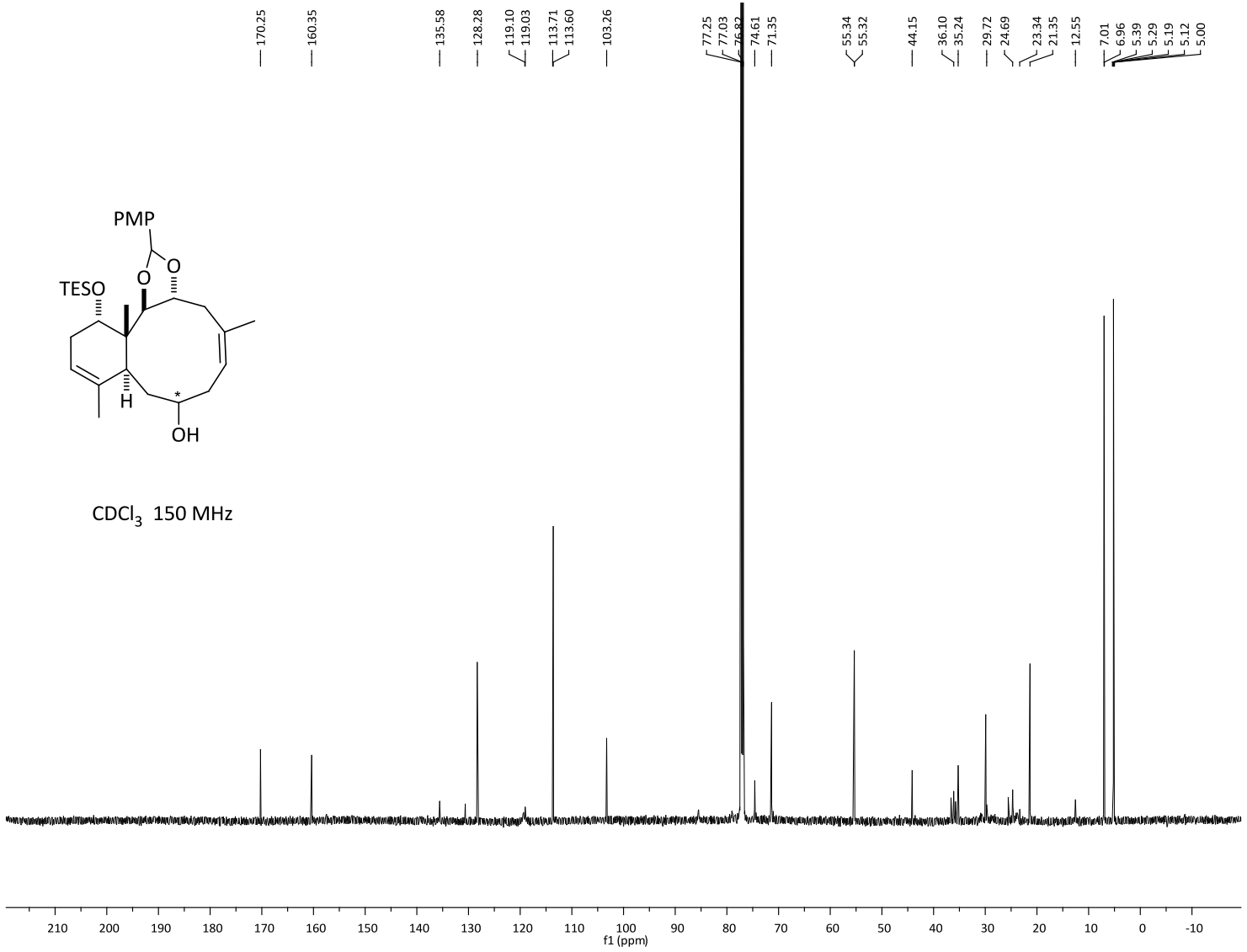

PMP
O
O
OH
H
*
OAc
186
CDCl3 600 MHz
7.43
7.41
7.38
7.24
6.89
6.87
5.72
5.38
5.33
5.24
5.22
5.20
4.26
4.22
4.21
4.11
4.09
4.07
4.06
3.79
2.70
2.36
2.32
2.04
1.85
1.81
1.78
1.66
1.64
1.55
1.24
1.19
0.91
0.89
0.84
44.48
46.02
1.00
20.46
18.89
22.82
23.31
22.57
17.01
34.16
71.20
17.72
85.44
96.89
15.24
122.54
44.29
22.02
43.46
62.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

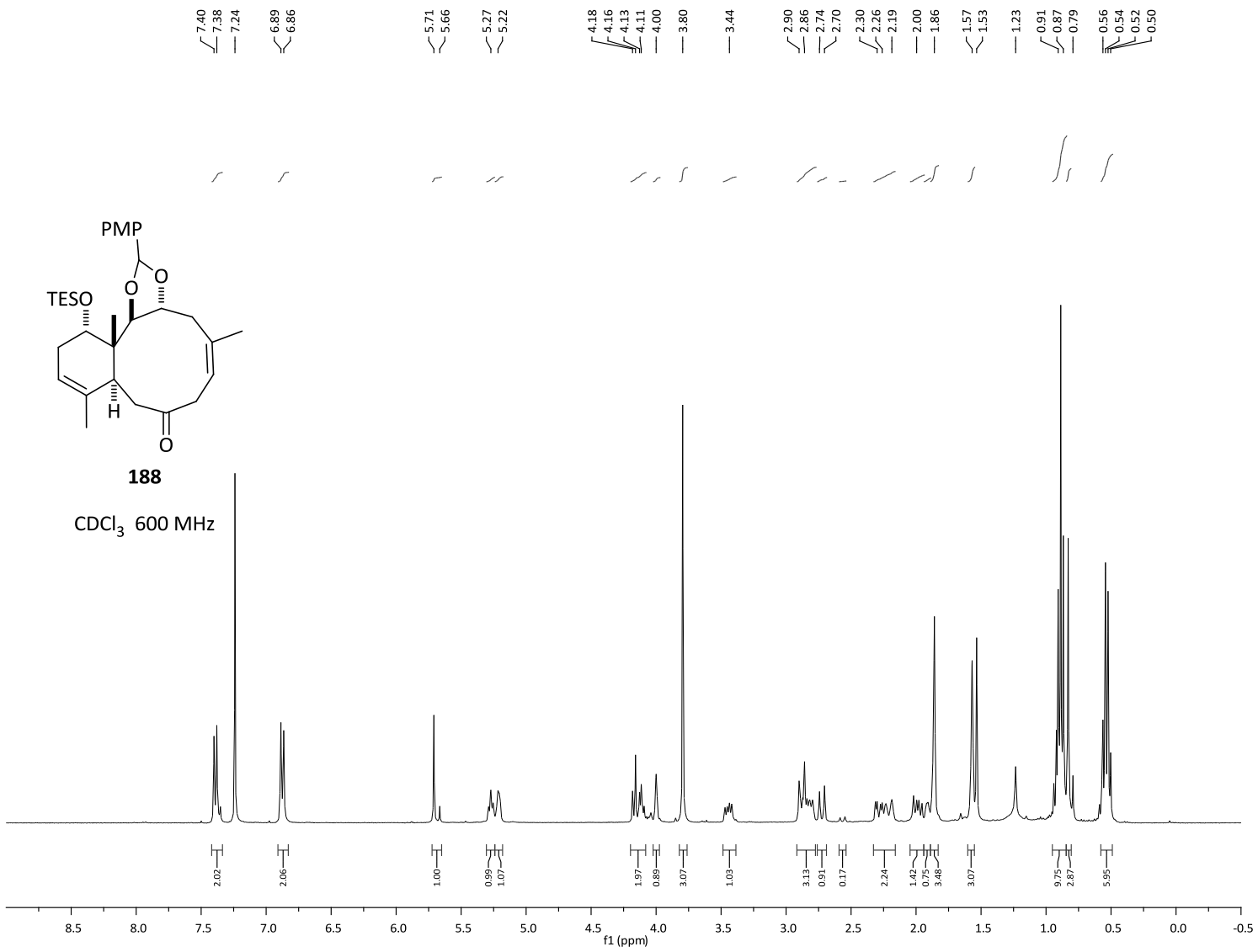

171.14
170.20
170.14
160.50
160.42
136.51
128.41
128.27
128.23
128.19
119.00
113.76
113.72
103.27
85.56
85.54
85.52
77.21
76.68
70.30
70.21
67.52
63.67
60.38
55.30
51.76
44.11
43.57
36.45
29.69
29.58
29.05
24.09
21.61
18.75
14.19
14.11
13.15
13.14
13.12
11.42
11.30
PMP
O
O
OH
H
OAc
186
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

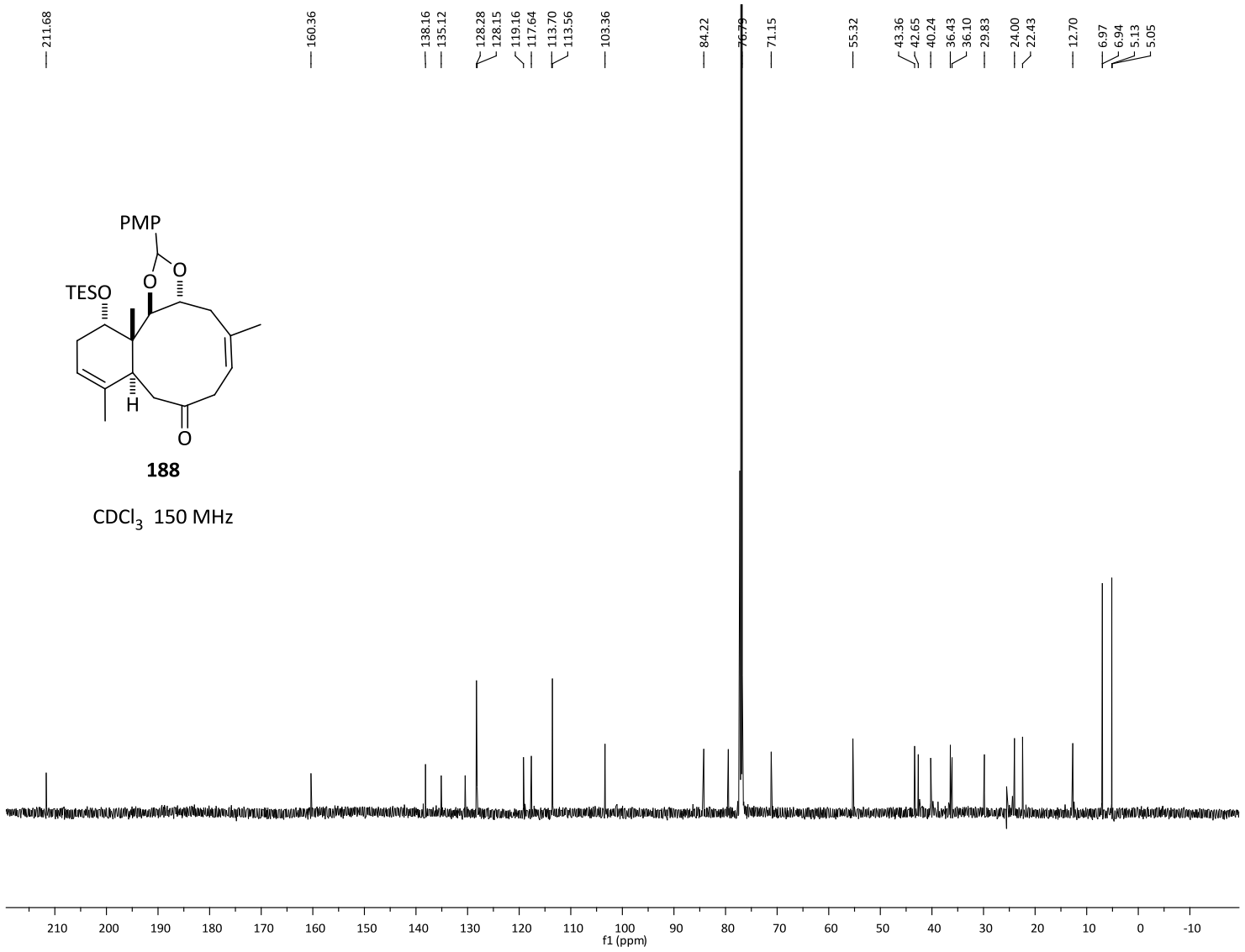

7.40
7.40
7.39
7.37
7.33
7.24
6.89
6.89
6.88
6.88
6.87
6.87
5.68
5.62
5.39
5.22
4.18
4.13
4.12
4.05
3.79
2.38
2.37
2.36
2.35
2.16
2.03
1.89
1.79
1.54
1.38
1.12
0.88
0.78
0.54
0.53
0.51
0.05
PMP
O
O
TESO
H
*
OAc
187
CDCl3 600 MHz
2.38
2.42
1.14
1.04
2.31
1.66
1.21
3.75
1.00
3.39
2.70
3.72
9.94
1.41
10.85
3.26
7.18
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


170.22
160.32
135.54
128.24
119.07
118.99
113.67
113.57
103.23
77.21
77.00
76.79
74.57
71.32
55.31
55.29
44.11
36.07
35.21
29.69
24.62
21.31
6.98
6.92
5.16
5.09
PMP
O
O
TESO
H
*
OAc
187
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

7.40
7.40
7.39
7.37
7.33
7.24
6.89
6.89
6.88
6.88
6.87
6.87
5.68
5.62
5.39
5.22
4.18
4.13
4.12
4.05
3.79
2.38
2.37
2.36
2.35
2.16
2.03
1.89
1.79
1.54
1.38
1.12
0.88
0.78
0.54
0.53
0.51
0.05
PMP
O
O
TESO
H
*
OH
CDCl3 600 MHz
12.63
12.87
4.67
1.00
4.83
12.28
8.26
6.07
19.71
16.88
14.00
19.56
23.18
4.56
17.20
9.71
7.47
59.62
17.13
3.44
38.46
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

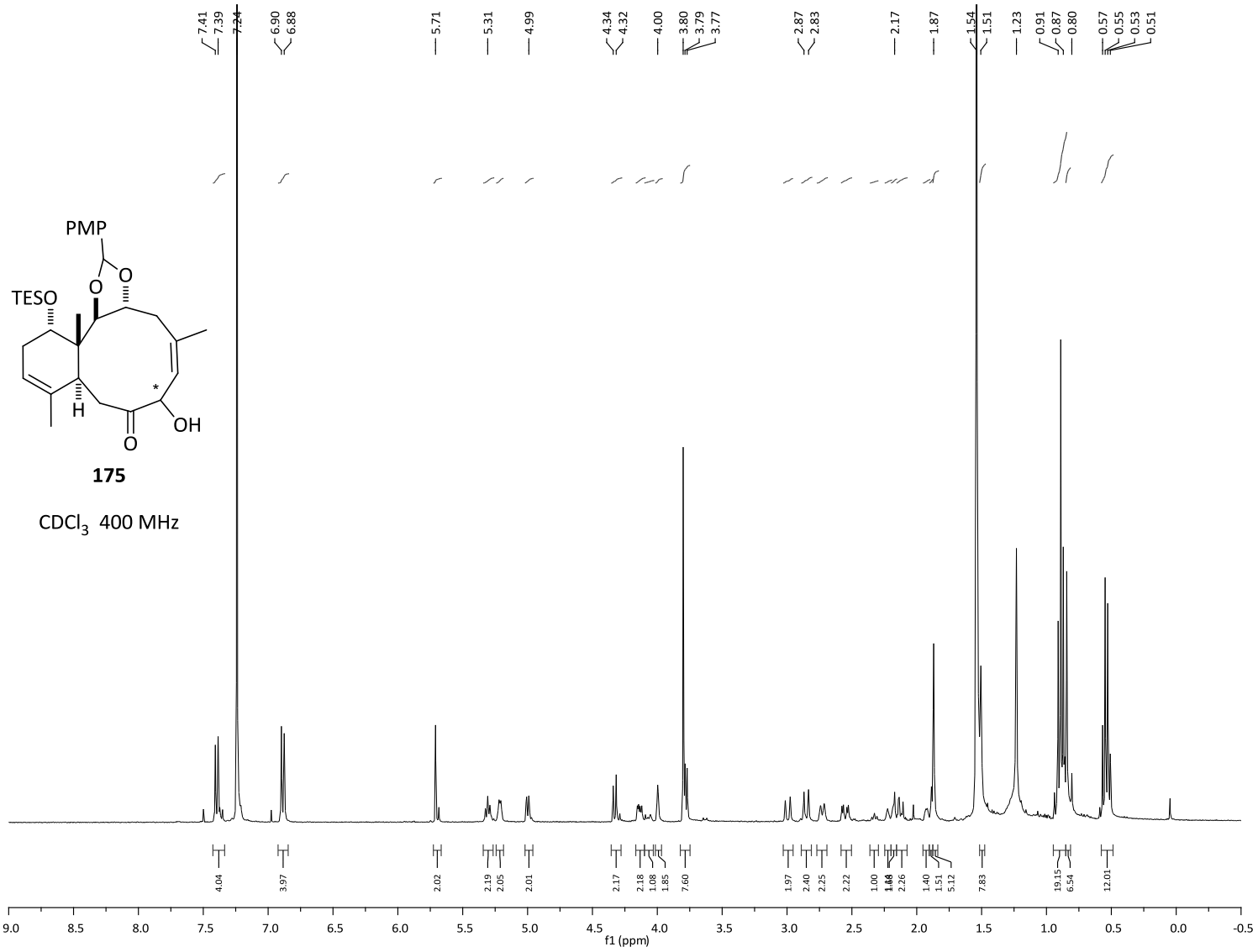

170.25
160.35
135.58
128.28
119.10
119.03
113.71
113.60
103.26
77.25
77.03
76.82
74.61
71.35
55.34
55.32
44.15
36.10
35.24
29.72
24.69
23.34
21.35
12.55
7.01
6.96
5.39
5.29
5.19
5.12
5.00
PMP
O
O
TESO
H
*
OH
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

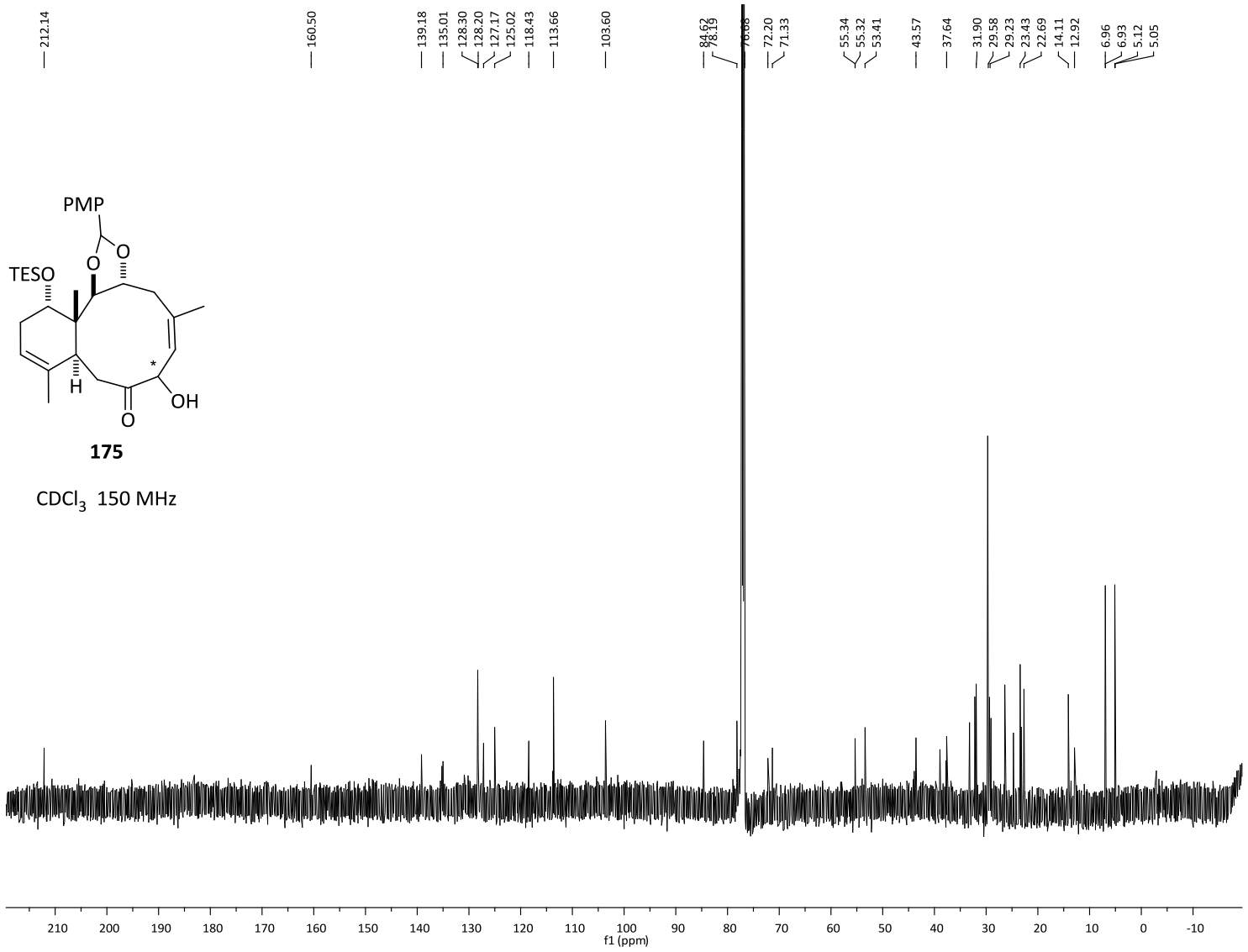

7.40
7.38
7.24
6.89
6.86
5.71
5.66
5.27
5.22
4.18
4.16
4.13
4.11
4.00
3.80
3.44
2.90
2.86
2.74
2.70
2.30
2.26
2.19
2.00
1.86
1.57
1.53
1.23
0.91
0.87
0.79
0.56
0.54
0.52
0.50
PMP
O
O
TESO
H
O
188
CDCl3 600 MHz
2.02
2.06
1.00
0.99
1.07
1.97
0.89
3.07
1.03
3.13
0.91
0.17
2.24
1.42
0.75
3.48
3.07
9.75
2.87
5.95
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



188

$CDCl_3$ 150 MHz


PMP
O
O
TESO
H
*
OH
O
175
CDCl3 400 MHz
7.41
7.39
7.24
6.90
6.88
5.71
5.31
4.99
4.34
4.32
4.00
3.80
3.79
3.77
2.87
2.83
2.17
1.87
1.54
1.51
1.23
0.91
0.87
0.80
0.57
0.55
0.53
0.51
4.04
3.97
2.02
2.19
2.05
2.01
2.17
2.18
1.08
1.85
7.60
1.97
2.40
2.25
2.22
1.00
2.26
1.40
1.51
5.12
7.83
19.15
6.54
12.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


212.14
160.50
139.18
135.01
128.30
128.20
127.17
125.02
118.43
113.66
103.60
84.62
78.19
78.08
72.20
71.33
55.34
55.32
53.41
43.57
37.64
31.90
29.58
29.23
23.43
22.69
14.11
12.92
6.96
6.93
5.12
5.05
PMP
O
O
TESO
H
*
OH
O
175
CDCl3 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

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