LASONOLIDE A: SYNTHETIC EXPLORATIONS

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ABSTRACT

ERIN E. MILNER: Lasonolide A: Synthetic Explorations
(Under the direction of Dr. M. Crimmins)

First isolated in 1984 from the marine sponge *Forcepia trilabis*, lasonolide A was found to inhibit A-549 human lung carcinoma cells and P-388 murine leukemia cell lines among others. This cytotoxic natural product was chosen because of its biological activity and challenging polyketide structure. Interesting structural features include two *cis*-2,6-substituted tetrahydropyran rings integrated into the highly unsaturated macrolide structure, and a quaternary stereogenic center at C22. Construction of the A-ring showcases a novel zinc triflate-mediated asymmetric alkynylzinc addition hetero-Michael reaction, which was developed to selectively form the 2,6-*cis* tetrahydropyran motif. To assemble the B-ring, alternate carbon nucleophiles were explored to displace the *N*-acyl thioimide auxiliary and prepare β-ketonitrile and β-ketoester moieties. Coupling of the three fragments via olefination, esterification, and metathesis strategies is also outlined.

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"What a long, strange trip it has been" -Robert Hunter

"Never, Never, Never Quit" -Winston Churchill

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LIST OF ABBREVIATIONS

Bn = benzyl

DCC = dicylcohexyl carbodiimide

DCE = dichloroethane

DDQ = dichloro-5,6-dicyano-1,4-benzoquinone

DIEA = diisopropylethyl amine

DMAP = 4-dimethylaminopyridine

LiHMDS = lithium hexamethyl disilazide

NME = N-methylephedrine

NMP = N-methylpyrrolidinone

PMB = *p*-methoxybenyl

PPTS = pyridinium para-toluenesulfonate

TBDPS = tert-butyldiphenylsilyl

TBS = tert-butyldimethylsilyl

TES = triethylsilyl

TFA = trifluoroacetic acid

TIPS = triisopropylsilyl

TMS = trimethylsilyl

CHAPTER 1

LASONOLIDES A-G: ISOLATION, STRUCTURAL ELUCIDATION, AND BIOLOGICAL ACTIVITY

1.1 Marine Macrolide Overview

Marine organisms have proven to be a beneficial source of secondary metabolites with unique biological activities and have shown promise as chemotherapeutic agents. Unfortunately, one factor impeding the large-scale isolation of these secondary metabolites for clinical development is their low natural abundance. Current efforts in the synthetic organic chemistry community are focused on generating quantities of material for further therapeutic evaluation, as well as more accurate structural elucidation. Thus, the synthesis of natural products has sparked the development of new and innovative methodologies and retrosynthetic strategies.

1.2 Isolation, Structural Elucidation, and Biological Activity

Lasonolide A (**1-1** originally proposed) was isolated in 1994 by McConnell and coworkers from the shallow water Caribbean marine sponge *Forcepia trilabis*.[1] The red-orange sponge was collected in 1992 by a dive team from the Harbor Branch Oceanographic Institute (HBOI) approximately 100 nautical miles southwest of Sanibel Island, Florida. Due to the abundance of *Forcepia trilabis* in the region, it has been termed "Forcepia-land" by researchers at HBOI.[2] This species of sponge is unusual since it prefers the sandy bottom at a depth of approximately 230 feet.

Extensive solvent partitioning of the bioactive extract allowed for the isolation of pale orange oil (reported $[\alpha]^{20}_{D}$ = +24.1). The extract was discovered to inhibit the *in vitro* proliferation of A-549 human lung adenocarcinoma cell lines (IC_{50} = 40 ng/mL) and inhibit cell adhesion in the EL-4.IL2 cell line (IC_{50} = 19 ng/mL), which is a response correlating to signal transduction activity.[3] In addition, the extract is a potent cytotoxin against P-388 murine leukemia cell lines (IC_{50} = 2 ng/mL). The sponge metabolite responsible for the biological activity was aptly named lasonolide, a term derived from the Philippine word *lason* which translates to poison or toxin. The molecular formula was reported as $C_{41}H_{60}O_9$ based on HRFABMS [$(M + H)^+$ *m/z* 697.4243] and key absorption peaks in the IR spectrum at 1736 and 1690 cm^{-1} indicated a conjugated ester. After employing extensive ^{1}H, ^{13}C, DEPT, HMBC, and ROESY NMR analysis, McConnell and coworkers proposed structure **1-1** (Figure 1.2.1) for the lasonopyran skeleton, with the specific stereochemistry at C28 still unclear.

The lasonopyran skeletal structure **1-2**, common to several related lasonolides, has since been revised based on the total synthesis of lasonolide A by Lee and coworkers (Section 2.1); correcting for the configuration about the C17-C18 and C25-C26 olefins, as well as elucidating the previously unknown stereochemistry at C28. Interesting structural features include two *cis*-2,6-substituted tetrahydropyran rings integrated into the macrolide structure, a quaternary stereogenic center at C22, and a highly unsaturated macrolide.

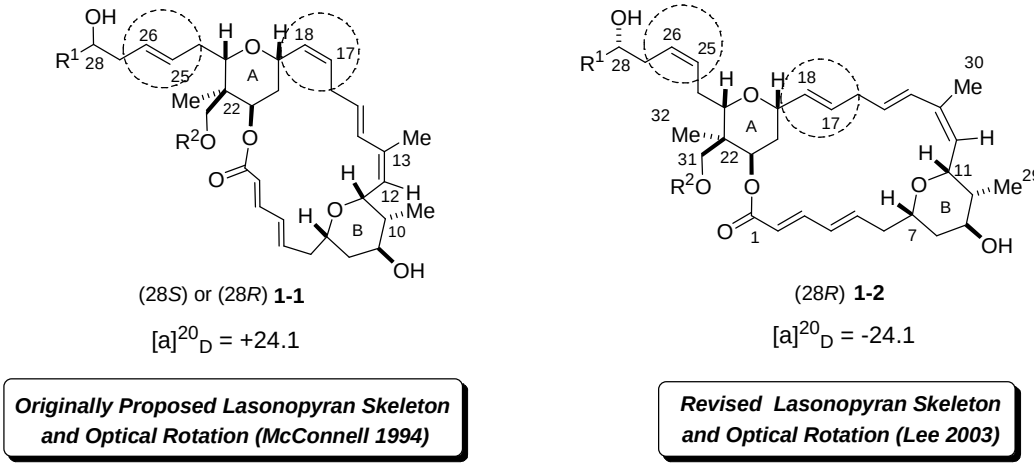
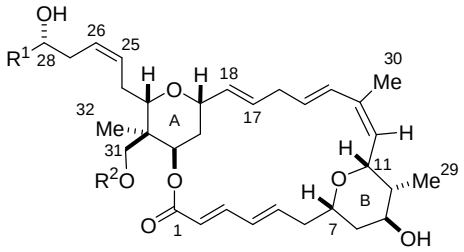


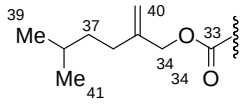
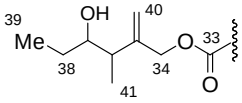
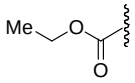
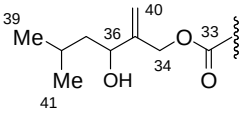
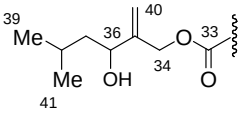
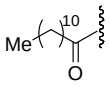
Figure 1.2.1. Originally Proposed and Revised Lasonopyran Skeletons

The related lasonolides A – G (**1-3** – **1-9**), isolated from *Forcepia trilabis*, possess the same C1-C28 polyketide, but exhibit differing side chain moieties (Table 1.2.1.). Interestingly, lasonolide C **1-5** was isolated as a white powder, while lasonolides D – G (**1-6** – **1-9**) were isolated as oils.



Lasonopyran Skeleton **1-2**

Table 1.2.1. Lasonolides A-G (**1-3** – **1-9**)

Lasonolide		R^1	R^2	Lasonolide		R^1	R^2
A	**1-3**		H	D	**1-6**	H	H
B	**1-4**		H	E	**1-7**		H
C	**1-5**		H	F	**1-8**		H
				G	**1-9**		

Despite the structural similarities of the lasonolides, all show significantly reduced toxicity in relation to lasonolide A.[4] The biological activities of lasonolides C-G toward human pancreatic carcinoma (PANC-1), human breast cell lines (NCI/ADR-RES, formally MCF-7/ADR), and human lung carcinoma (A549) are shown in Table 1.2.2. Lasonolide C (**1-5**), the closest structural analogue to lasonolide A (**1-3**), is 4.5-fold less active in the PANC-1 cell line, 2-fold less active in the NCI/ADR-RES line, and 15-fold less active in the A-549 cell line. Hydrolysis to the carboxylic acid (**1-8**) results in a >175-fold reduction in activity compared to lasonolide A (**1-3**).

Although each compound contains identical lasonopyran skeletal structures the cytotoxicity profile varies dramatically, illustrating the biological importance of the side chain moiety.

Table 1.2.2. Bioactivities of Lasonolides A (**1-3**) and C-G (**1-5** – **1-9**)

Compound	***PANC-1 (IC_{50} μM)***	***NCI/ADR-RES (IC_{50} μM)***	***A-549 (IC_{50} μM)***
lasonolide A (**1-3**)	0.089	0.49	0.0086
lasonolide C (**1-5**)	0.38	1.12	0.13
lasonolide D (**1-6**)	4.89	> 9	4.50
lasonolide E (**1-7**)	0.57	> 8	0.31
lasonolide F (**1-8**)	15.6	> 9	> 9
lasonolide G (**1-9**)	> 6	> 6	> 6

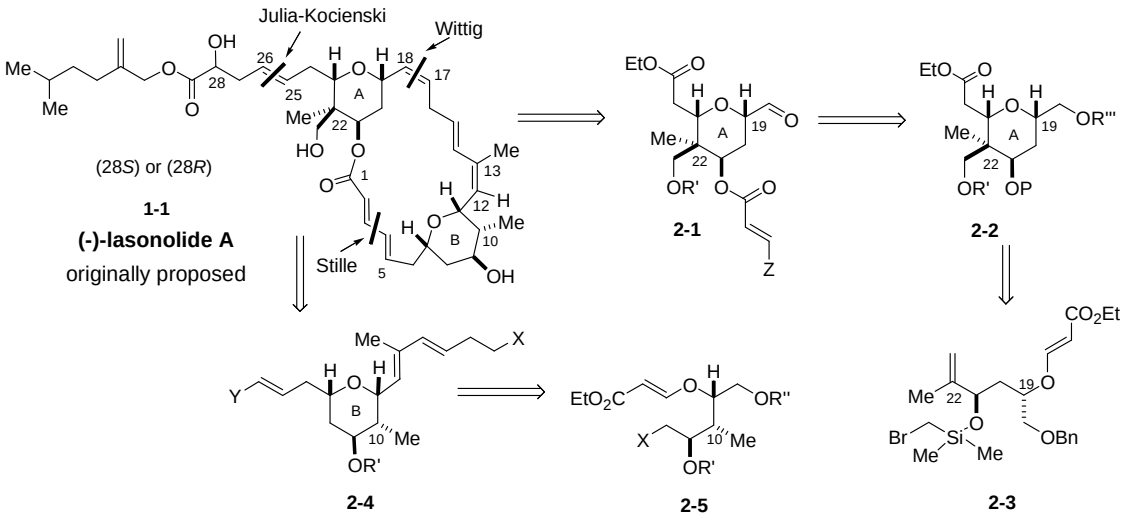
CHAPTER 2

STUDIES DIRECTED TOWARD THE SYNTHESIS OF LASONOLIDE A: LITERATURE REVIEW

2.1 Lee's Total Synthesis and Structural Revision of Lasonolide A[5]

2.1.1 Retrosynthetic Analysis

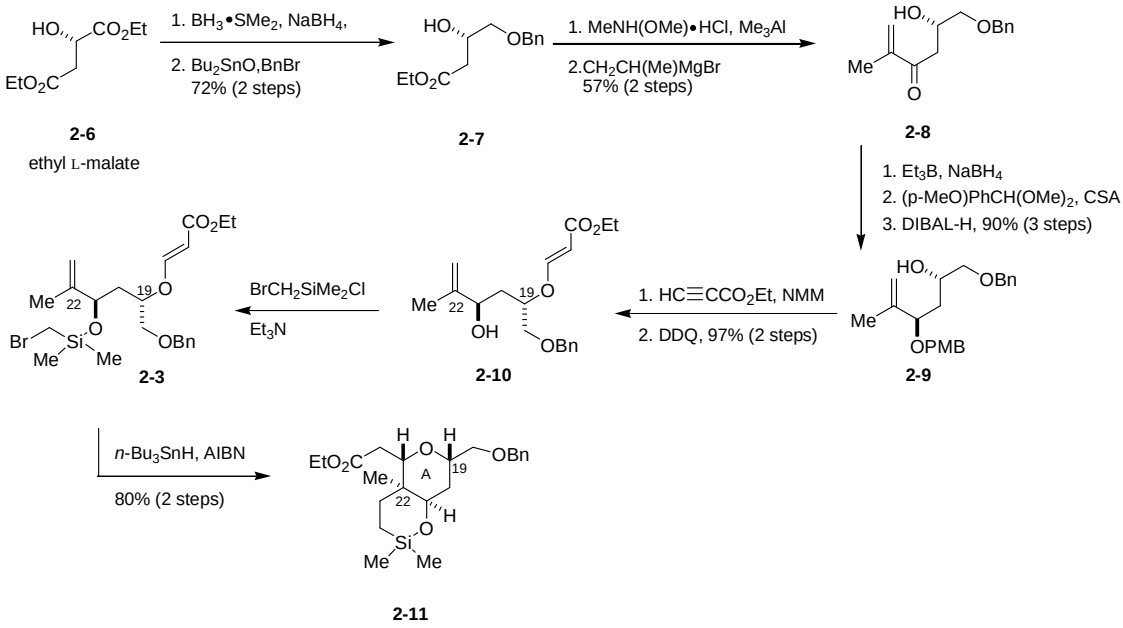
To ascertain the unknown stereochemistry of the C28 hydroxyl group, a strategy was devised whereby the side chain could be coupled with the lasonopyran skeleton towards the end of the synthesis (Scheme 2.1.1). Retrosynthetically, the C17-C18 *cis*-alkene and the C2-C5 diene were envisioned to be accessible using Wittig olefination and Stille-type reaction conditions, respectively. With this strategy, each prepared enantiomer of the side chain could be appended late stage with a Julia-Kocienski protocol to give the *trans*-olefin. The Lee group chose an innovative radical cyclization of the (bromomethyl)silyloxy-substituted β-alkoxyacrylate **2-3** to fashion the quaternary center at C22 of the A-ring, while β-alkoxyacrylate **2-5** was utilized to form tetrahydropyran ring B.



Scheme 2.1.1. Lee's Retrosynthetic Analysis Based on Originally Proposed **1-1**

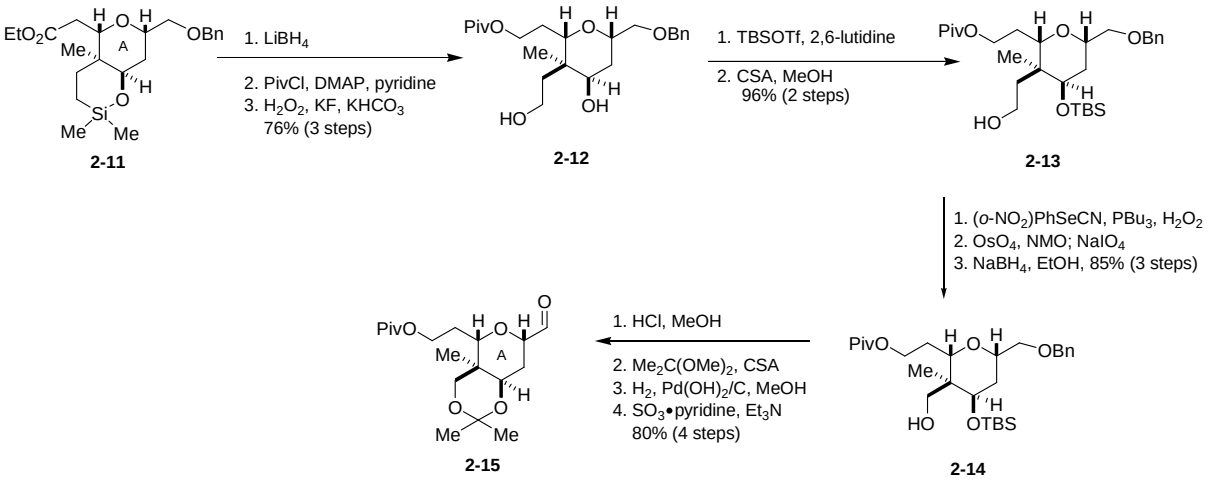
2.1.2 First Generation Synthesis

The assembly of the A-Ring fragment began with commercially available ethyl L-malate **2-6**, which was subjected to reduction and subsequent protection as the benzyl ether (Scheme 2.1.2). Formation of the corresponding Weinreb amide and Grignard addition provided enone **2-8**. A three step sequence afforded alcohol **2-9**, which was subsequently added to ethyl propiolate. Further PMB-deprotection and silylation provided the critical bromomethyl(dimethyl)silyl intermediate **2-3**. Bicyclic product **2-11** was formed as a single diastereomer via a tandem 6-*endo*, 6-*exo* radical cyclization based on conditions developed in the Lee laboratory.[6]



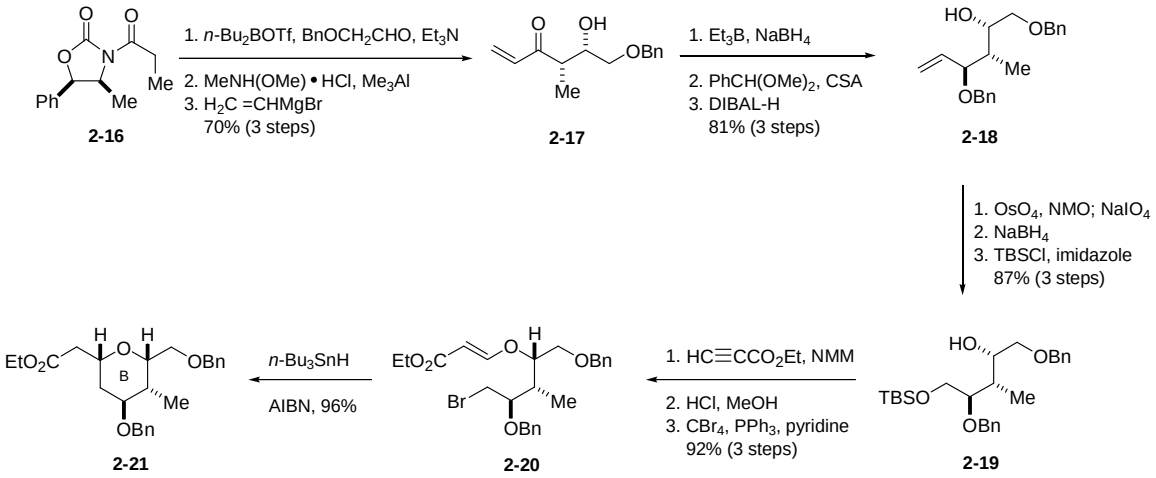
Scheme 2.1.2. Lee's Synthesis of the A-Ring

Reduction of the ester, protection as the pivaloate derivative, and Tomao oxidation allowed for conversion to diol **2-12** (Scheme 2.1.3). The diol was *bis*-TBS protected, followed by removal of the primary silyl ether to provide alcohol **2-13**. Selenoxide elimination, osmium tetroxide dihydroxylation/sodium periodate cleavage, and sodium borohydride reduction sequence was utilized to afford lower homologue **2-14**. Cleavage of the silyl ether and protection of the resultant diol as the acetonide, followed by cleavage of the benzyl ether and subsequent oxidation of the primary alcohol provided aldehyde **2-15**.



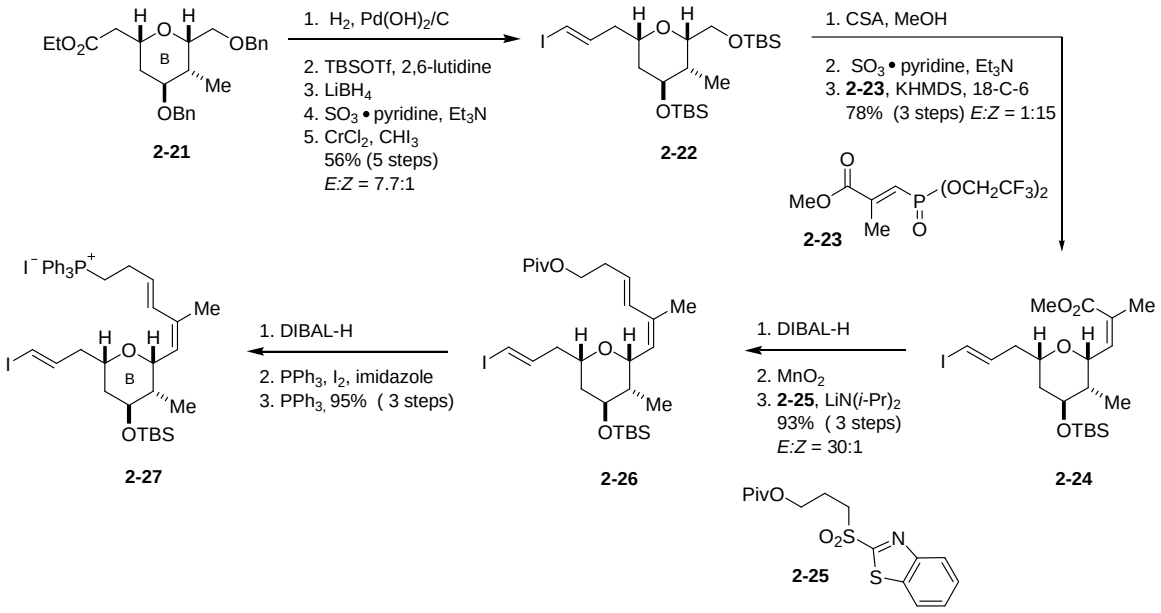
Scheme 2.1.3. Lee's Synthesis of the A-Ring Coupling Partner **2-15**

Towards the preparation of the B-ring fragment, β-hydroxyenone **2-17** was generated via reaction of the *Z*-boron enolate of Evans imide **2-16** and benzyloxyacetaldehyde (Scheme 2.1.4). The imide was converted to the corresponding Weinreb amide, which was reacted with vinyl magnesium bromide to provide enone **2-17**. Chelation controlled reduction of the hydroxyl lactone, benzylidine formation of the resultant diol, and reduction of the benzylidine with DIBAL-H provided olefin **2-18**. Oxidative cleavage of the terminal olefin, reduction of the resultant aldehyde, and protection as its TBS ether afforded alcohol **2-19**. Extension to β-alkoxyacrylate **2-20** was achieved via reaction of the secondary alcohol with ethyl propiolate and 2-step conversion of the primary TBS ether to the corresponding primary bromide. Radical cyclization employing *n*-Bu_3SnH delivered tetrahydropyran **2-21**.



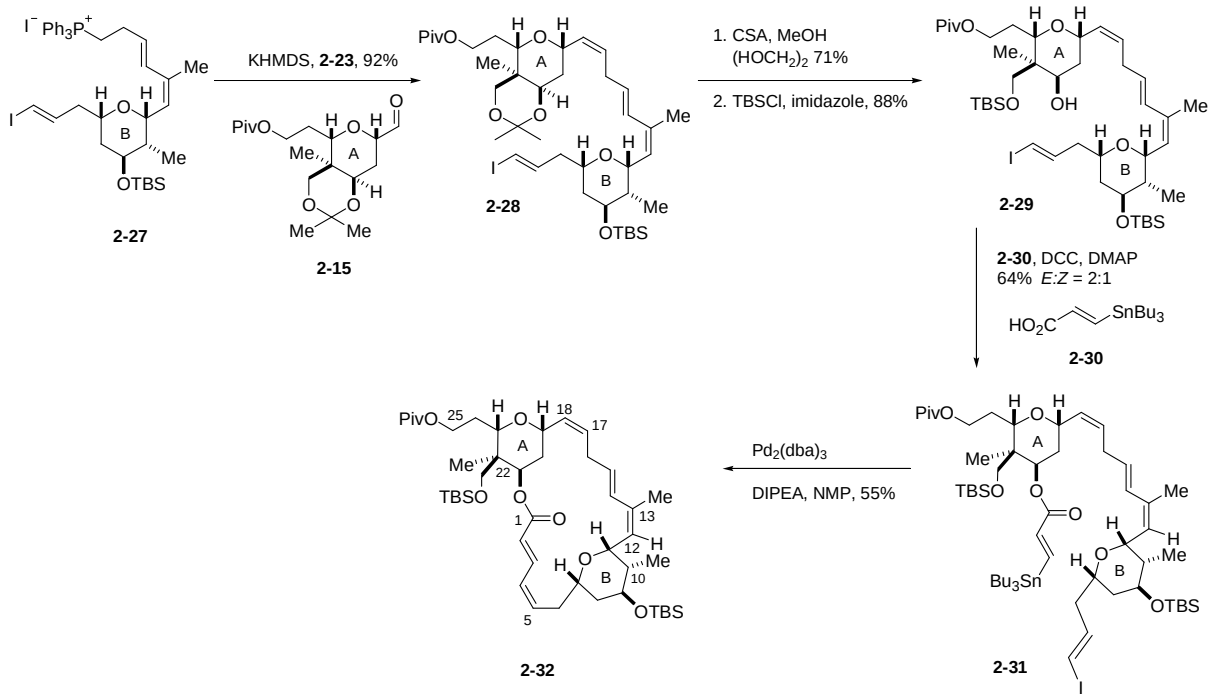
Scheme 2.1.4. Lee's Synthesis of the B-Ring

A five-step sequence involving removal of the benzyl ethers via hydrogenation, protection of the resultant alcohols as the corresponding silyl ethers, reduction of the ester to the aldehyde, and elaboration of the aldehyde via Takai olefination afforded vinyl iodide **2-22** (Scheme 2.1.5). Selective deprotection of the primary TBS ether **2-22** and oxidation to the resultant aldehyde allowed for conversion to trisubstituted olefin **2-24** via the *Z*-selective Still-Gennari olefination protocol. Reduction of the resultant ester produced an allylic alcohol, which was oxidized to the aldehyde. Subsequent Julia-Julia coupling of the aldehyde with sulfone **2-25** provided diene **2-26** with good *E*-selectivity. Phosphonium salt **2-27** was formed through a standard three step sequence.



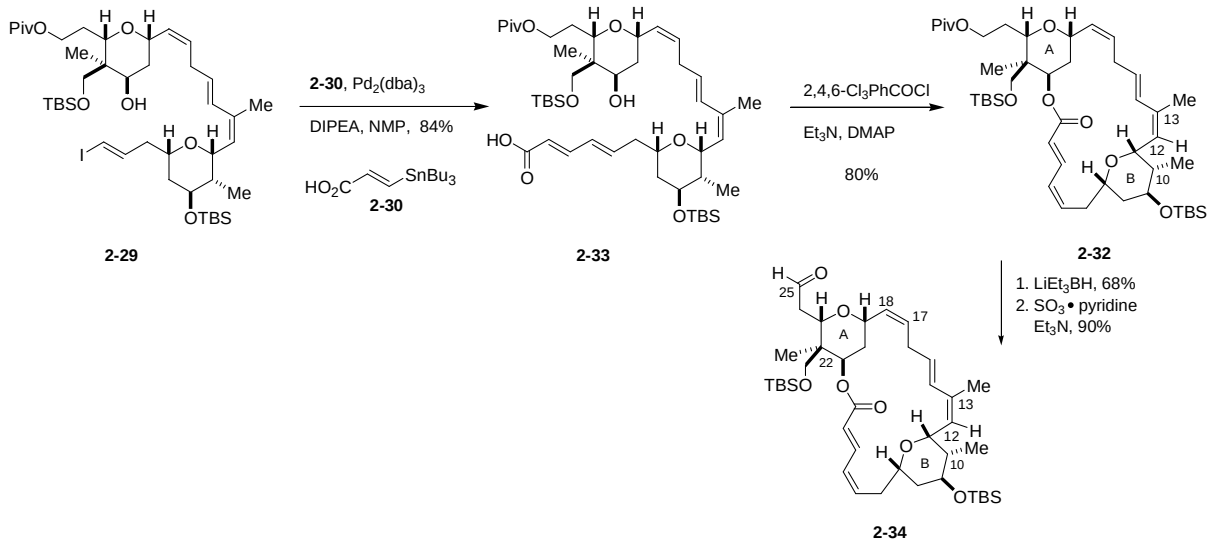
Scheme 2.1.5. Lee's Synthesis of the B-Ring Coupling Partner **2-27**

Wittig olefination of phosphonium salt **2-27** with aldehyde **2-15** was employed to obtain the coupled product solely as the C17-C18 *cis* isomer (Scheme 2.1.6). Hydrolysis of the acetonide and selective protection of the primary alcohol provided unmasked secondary alcohol **2-29**, which underwent an esterification to install the diene. Unfortunately, in the synthesis of unsaturated ester **2-31** a stereorandomization problem resulted in a 2:1 *E:Z* ratio. The desired *E*-olefin (**2-31**) was subjected to an intramolecular Stille coupling to provide macrolactone **2-32**.



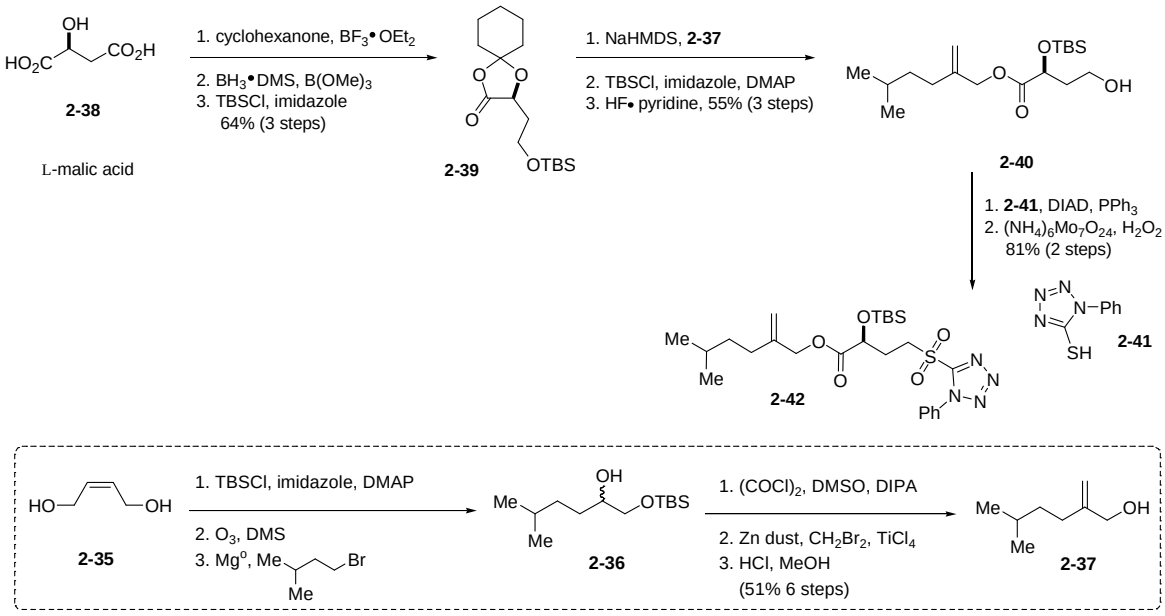
Scheme 2.1.6. Lee's Synthesis of Macrolactone **2-32**

To circumvent the stereorandomization issue encountered, they reversed the order of the key steps to form the macrolactone (Scheme 2.1.7). First, a Stille reaction was performed involving vinyl iodide **2-29** and acid **2-30** to give dienoic acid **2-33**, which underwent intramolecular lactonization under standard Yamaguchi conditions to afford macrolactone **2-32**.[7] The pivaloate was selectively removed by a Super-Hydride reduction followed by oxidation of the alcohol to give aldehyde **2-34**.



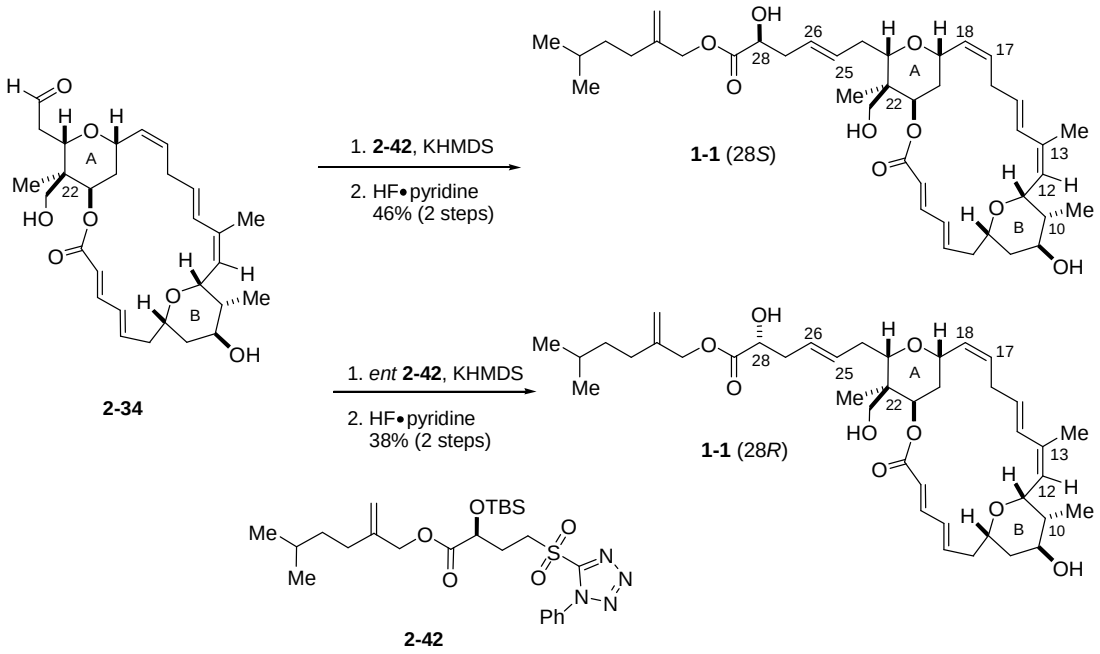
Scheme 2.1.7. Lee's Revised Approach to Macrolactone **2-32**

Commercially available malic acid was used to obtain the stereocenter in the side chain moiety (Scheme 2.1.8). As the configuration at C28 was unknown at the time, both enantiomers were subjected to the same protocol to give both desired configurational isomers: L-malic acid (**2-38**) was utilized to give the *S*-configuration, while D-malic acid was utilized to give the *R*-configuration. Synthesis of *S*-C28 is outlined below. Selective ketal formation followed by borane reduction to the primary alcohol and ensuing protection as the silyl ether provided ketal **2-39**. The sodium alkoxide of **2-37**, made in six steps from commercially available diol **2-35**, opened the lactone of **2-39** to provide the ester. This intermediate was converted to alcohol **2-40** by silylation of the secondary alcohol followed by selective cleavage of the primary alcohol. Mitsunobu reaction with tetrazole derivative **2-41** provided the sulfide, which was oxidized to sulfone **2-42**.



Scheme 2.1.8. Lee's synthesis of Side-Chain Coupling Partner **2-42**

Sulfoxide **2-42**, and its corresponding enantiomer *ent* **2-42**, were coupled with aldehyde **2-34** via a Kocienski-Julia olefination (Scheme 2.1.9).[8] However, it was apparent upon evaluation of the NMR spectra obtained from **1-1** (28*S*) and **1-1** (28*R*) that neither matched that of the natural product.



Scheme 2.1.9. Completion of Lasonolide A (Originally Proposed Structure)

2.1.3 Structural Revision

In light of these results, Lee and coworkers subsequently undertook the synthetic challenge to obtain several stereoisomers of lasonolide A (Scheme 2.1.10). Based on a similar issue encountered in their synthesis of ambruticin, they decided to construct the C17-C18 *trans*-olefin. The NMR spectra of **2-43** (28*S*) and **2-44** (28*R*) were comparable to the natural product, but discrepancies in the vinylic region persisted. Hence they decided to install the C25-C26 *cis*-olefin, leading to structures **1-3** (28*R*) and **2-45** (28*S*). Although the NMR spectrum of **1-3** matched that of the natural product, the optical rotation was opposite the value reported (incorrectly) by McConnell and coworkers (Section 1.2). With the correct structure known, Lee and coworkers constructed enantiomeric **1-3** (*ent* **1-3**), which was identical to the natural product in both NMR data and the optical rotation value reported by McConnell. To

preclude any uncertainty regarding the structure, stereoisomers **2-46** and **2-47** were also constructed, but the NMR spectrums did not match the natural product. The Lee laboratory subjected all of the isomers to a series of biological assays (Section 2.1.4), thereby determining that (-)-lasonolide A is indeed the most biologically active enantiomer (Table 2.1.1). The work of Lee elucidated the correct structure and optical rotation ($[\alpha]^{20}_D$ = -24.1), while the structure (**1-1**) and optical rotation ($[\alpha]^{20}_D$ = +24.1) reported by McConnell and coworkers were found to be in error.

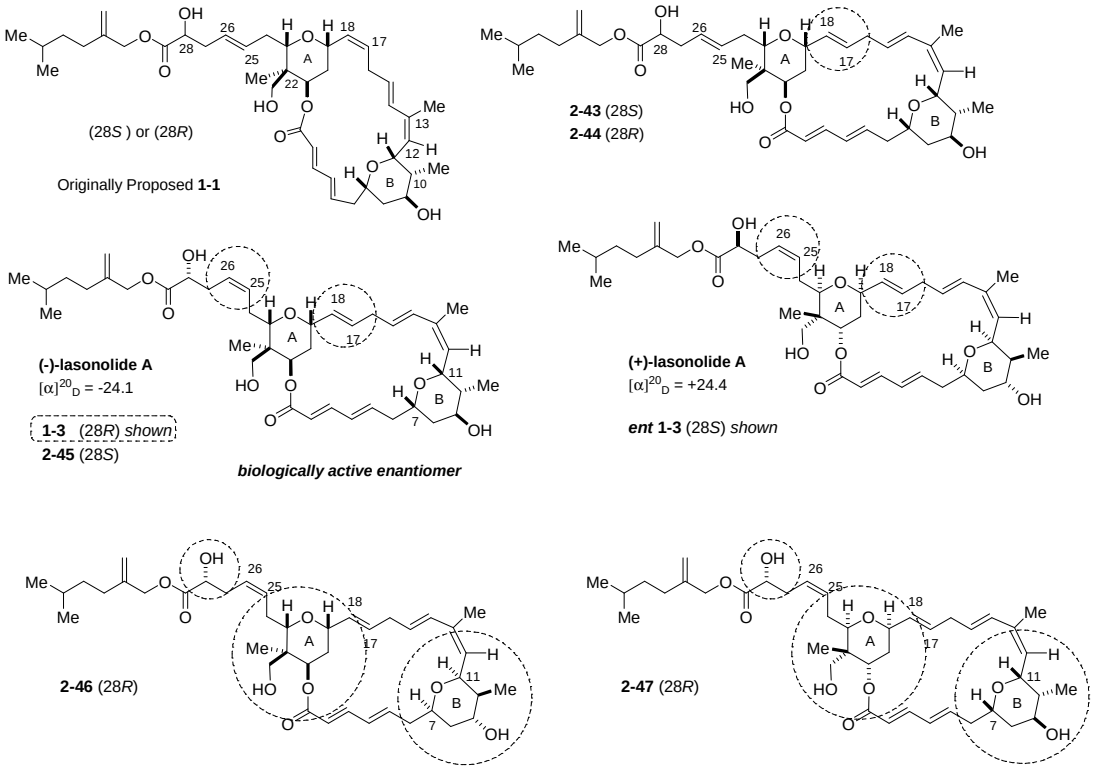


Figure 2.1.1. Lasonolide A: Stereoisomers Prepared by Lee

2.1.4 Biological Evaluation and Synthesis of Lasonolide A Analogues

Lee and coworkers later reported the preparation of four analogs (Figure 2.1.2).[9] In derivative **2-48**, the macrolactone is missing a methyl group at C10. Furthermore, homologue **2-49** was chosen due to the ease of preparation from **2-12**, and side-chain derivatives **1-7** and **2-50** were assembled for a similar reason.

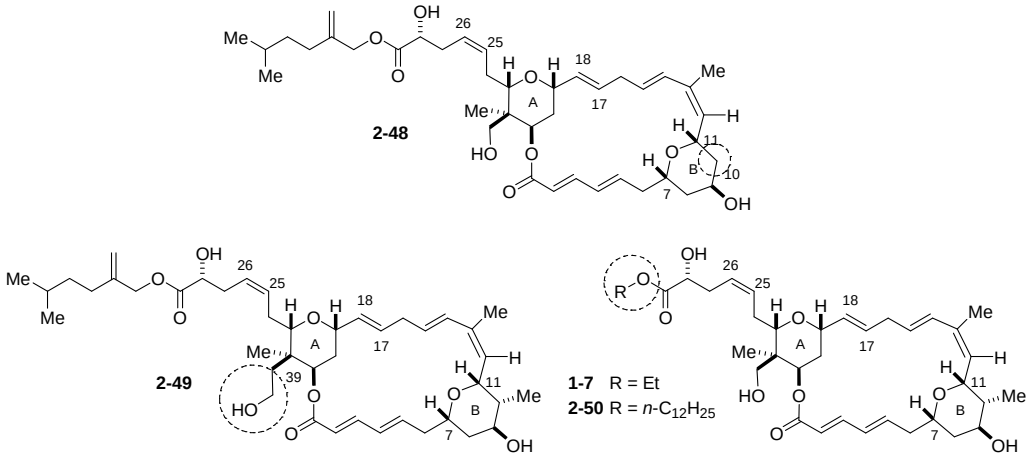


Figure 2.1.2. Synthesis and Evaluation of (-)-Lasonolide A Analogues

The biological activities corresponding to the compounds in Figure 2.1.1 and Figure 2.1.2 toward human lung adenocarcinoma (A-549 and NCI-H460) and colon cancer (HCT-116) are shown in Table 2.1.1. In particular, it was determined that the *R*-configuration at C28 is vital to the activity when compared with its diastereomer **2-45**. The researchers describe the C25-C26 *cis*-olefin as “important,” and the C17-C18 *trans*-olefin as “essential,” while 10-desmethyllasonolide A **2-47** and lasonolide homologue **2-48** exhibit reduced activity when compared to **1-3** (Figure 2.1.2). Furthermore, the A-549 cell line activity of lasonolide E (**1-7**) reported by Wright and

coworkers (IC_{50} = 0.31 μM)[10] differs from the value reported by Lee and coworkers (IC_{50} = 0.007 μM).[11]

Table 2.1.1. Bioactivities for Lasonolide A and Related Compounds

Figure	***Compound***	***A 549***	***HCT-116***	***NCI-H460***
2.1.1	**1-1** (28*S*)	> 10	5	5
	1-3 (28*R*)	0.015	< 0.003	< 0.003
	ent **1-3** (28*S*)	6	3	2
	2-43 (28*S*)	3.2	0.1	0.04
	2-44 (28*R*)	2	0.04	0.02
	2-45 (28*S*)	0.05	0.009	< 0.003
	2-46 (28*R*)	> 10	> 10	> 10
2.1.2	**2-48** (28*R*)	0.100	0.045	0.065
	2-49 (28*R*)	0.800	1.800	1.000
	1-7 (28*R*)	0.007	0.100	0.015
	2-50 (28*R*)	0.390	0.190	0.170

2.2 Kang's Total Synthesis of (+)-Lasonolide A[12]

From a retrosynthetic perspective, Kang and coworkers envisioned three disconnections as shown in Figure 2.2.1. Similar to the Lee laboratory, the C25-C26 olefin would be formed utilizing a Wittig olefination, while the C14-C15 and C17-C18 alkenes would be fashioned via Julia olefination conditions. A Horner-Emmons protocol would install the C2-C3 olefin of the conjugated diene.

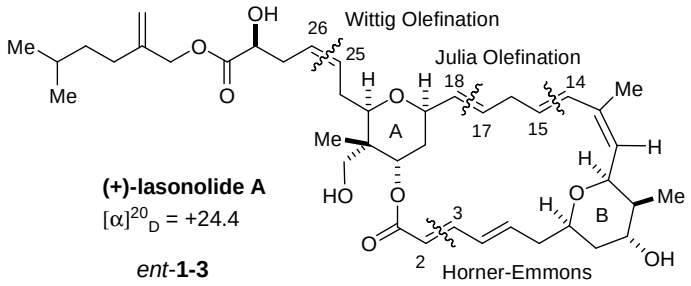
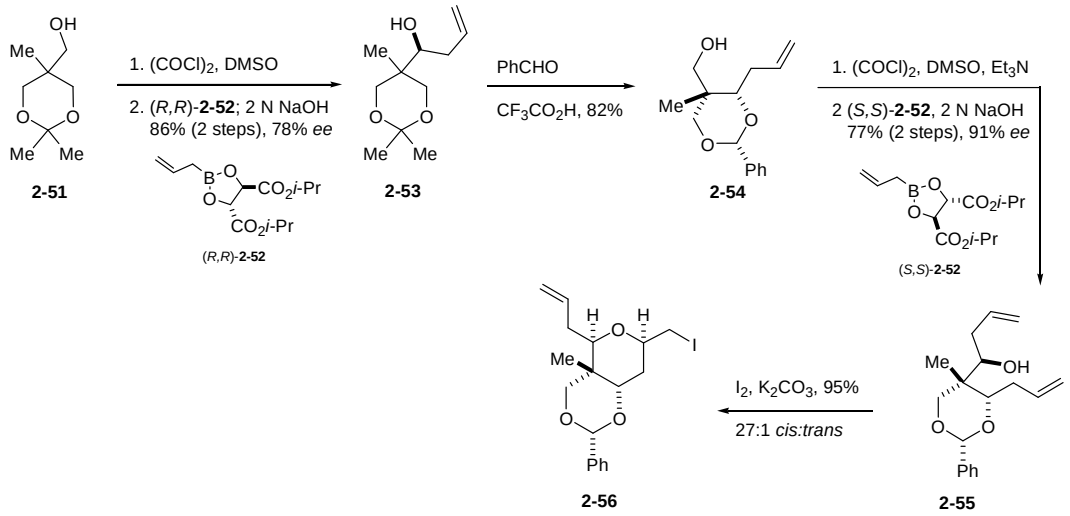


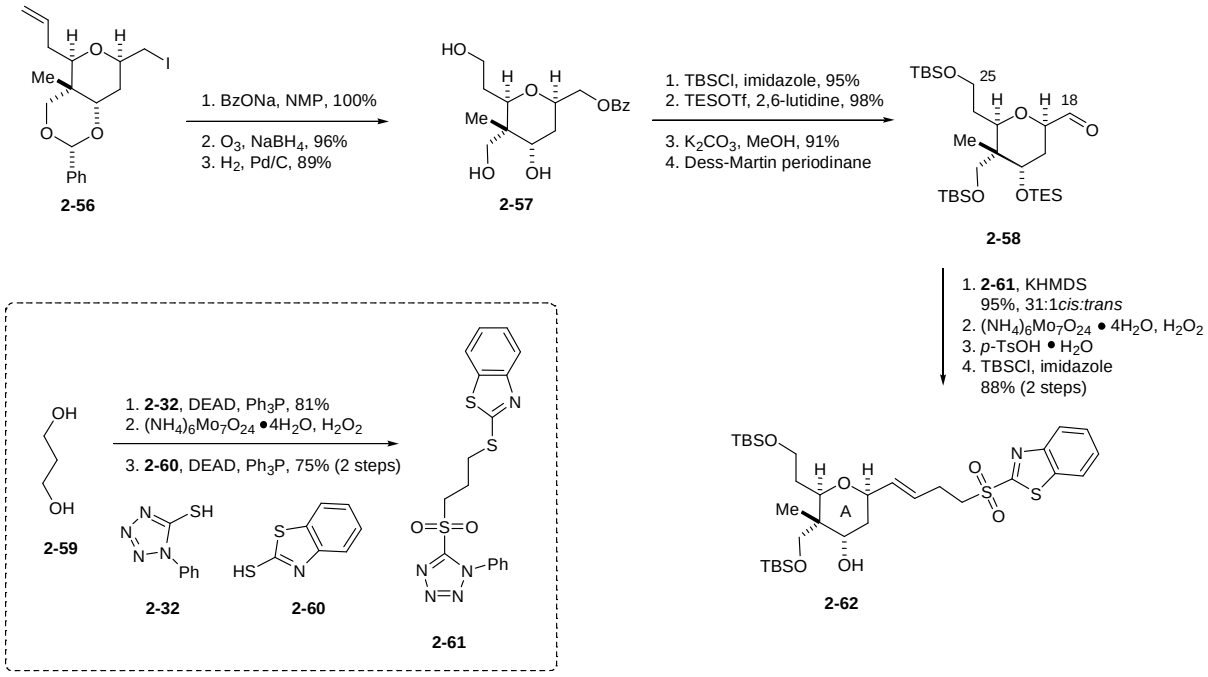
Figure 2.2.1. Kang's Retrosynthetic Analysis of (+)-Lasonolide A

The construction of *cis*-2,6-disubstituted tetrahydropyran ring A began with known alcohol **2-51**,[13] which was oxidized to the aldehyde and reacted with allylboronate (*R,R*)-**2-52** reported by Roush (Scheme 2.1.12).[14] Next, they were able to differentiate between the two hydroxyl methyl groups of the 1,3-dioxane in **2-53** through treatment with benzaldehyde and trifluoroacetic acid. The result was a 5:1 separable mixture of benzylidine **2-54** and its diastereomeric acetal with 82% yield reported after several recycles of the undesired benzylidine diastereomer. Oxidation of primary alcohol **2-54** followed by allylation with (*S,S*)-**2-52** led to homo-allylic alcohol **2-55**. Iodoetherification of **2-55** afforded a 27:1 product ratio in favor of *cis*-2,6-disubstituted tetrahydropyran **2-56** in excellent yield.



Scheme 2.2.1. Kang's Synthesis of A-Ring Fragment **2-56**

The resultant iodide **2-56** was then converted to the benzoate moiety, and ozonolysis with a reductive workup gave the primary alcohol (Scheme 2.2.2). The benzylidine group was cleaved via hydrogenolysis to give triol **2-57**. A selective protection of the two primary alcohols with TBSCl was followed by protection of the secondary alcohol with TESOTf. Further hydrolysis of the benzoate group and oxidation provided aldehyde **2-58** suited for the impending Julia coupling.

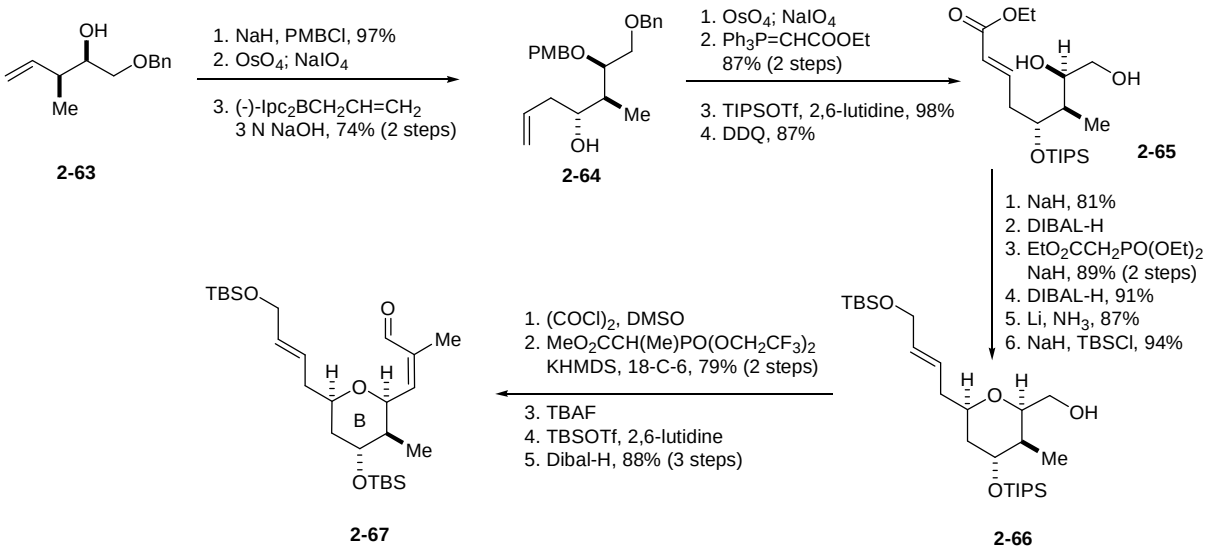


Scheme 2.2.2. Kang's Synthesis of A-Ring Coupling Partner **2-62**

The Julia olefination coupling partner was prepared from the reaction of 1,3-propanediol **2-59** with 1-phenyl-1-H-tetrazole-5-thiol **2-32** using the protocol of Mitsunobu. Oxidation of the sulfide to the sulfone was followed by another Mitsunobu reaction with benzothiazole-2-thiol **2-60** to give thiazolethiol **2-61**, which was coupled with aldehyde **2-59** under Julia-Kocienski conditions to afford the C25-C26 olefin (31:1 *trans:cis*). Oxidation of the sulfide to the sulfone, cleavage of the silyl ether, and selective protection of the primary alcohols provided fragment **2-62**.

The synthesis of *cis*-2,6-disubstituted tetrahydropyran B began with the protection of known alcohol **2-63** (Scheme 2.2.3).[15] Oxidative cleavage of the olefin afforded the aldehyde, which was reacted under asymmetric Brown allylation conditions.[16] Alkene **2-64** was subjected to oxidative cleavage and subsequent conversion to the α,β-unsaturated ester. The secondary alcohol was protected as

the TIPS ether and DDQ was used to remove both the benzyl and *p*-methoxybenzyl moieties to afford diol **2-65**.

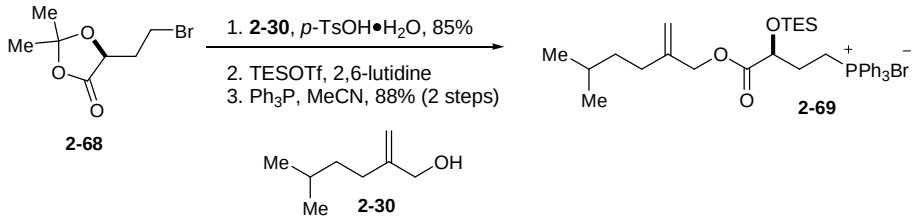


Scheme 2.2.3. Kang's Synthesis of B-Ring Coupling Partner **2-67**

A hydride-mediated intramolecular Michael addition of enoate **2-65** afforded the *cis*-2,6-disubstituted tetrahydropyran as a single diastereomer. Reduction of the ester was followed by homologation to the α,β-unsaturated ester via Horner-Wadsworth-Emmons conditions. Subsequent reduction of the ester and protection as the silyl ether afforded B-ring precurser **2-66**. The primary alcohol was oxidized and converted to the trisubstituted olefin via the Still-Gennari procedure.[17] The secondary alcohol was desilylated and protected as the TBS ether. The methyl ester was subsequently reduced to aldehyde **2-67** in preparation for the Julia-Julia olefination.

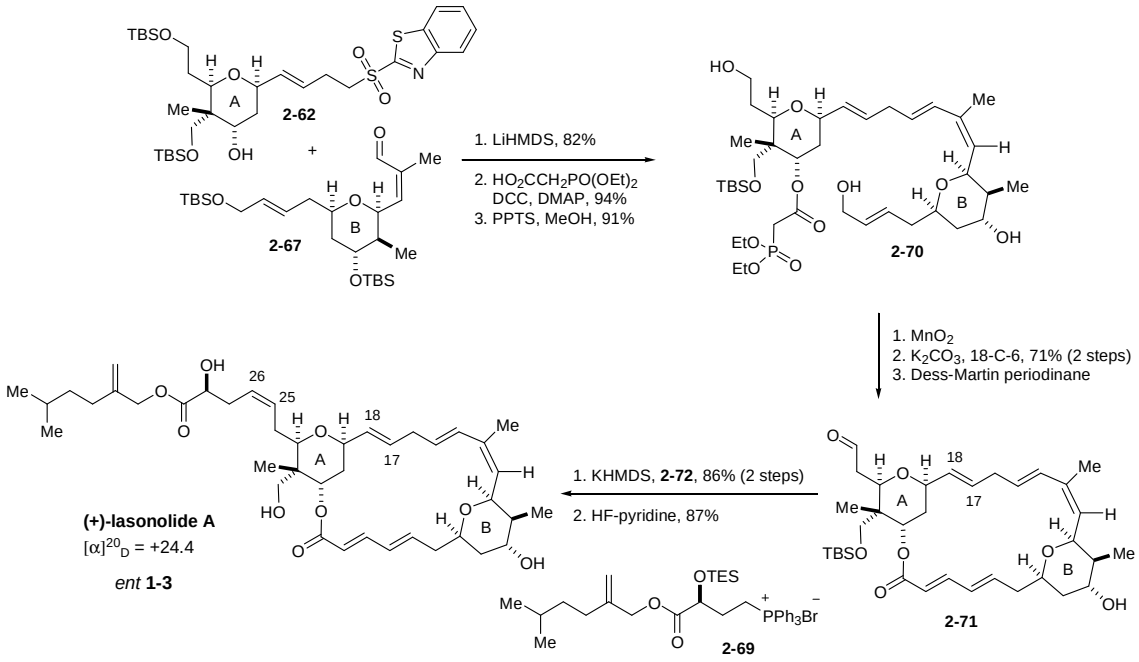
To prepare the side-chain, known acetonide **2-68**[18] was reacted with alcohol **2-30** through an acid-mediated transesterification. The secondary alcohol was protected

as the silyl ether and exposure of the bromide to triphenylphosphine led to phosphonium salt **2-69**.



Scheme 2.2.4. Kang's Synthesis of Side Chain **2-69**

To complete the synthesis, the anion of sulfone **2-62** was reacted with aldehyde **2-67** via a Julia-KoKocienski coupling reaction (Scheme 2.1.14). Formation of the phophonoacetate was followed by deprotection of the allylic alcohol provided Horner-Emmons precursor **2-70**. Selective oxidation of the allylic alcohol with manganese dioxide followed by potassium carbonate mediated cyclization supplied macrolactone **2-71**. The primary alcohol was oxidized to the aldehyde and reacted with phosphonium salt **2-69** via a Wittig olefination. Global deprotection gave (+)-lasonolide A in 26 steps and 7.4% overall yield.



Scheme 2.2.5. Kang's Synthesis (+)-Lasonolide A *ent* **1-3**

2.3 Shishido's Total Synthesis of (+)-Lasonolide A[19]

Shishido and coworkers envisioned lasonolide to arise from a cross metathesis and macrolactonization to form the 20-membered polyene macrolide, while the side chain would be appended using the Wittig conditions reported by the Lee laboratory (Figure 2.3.1).

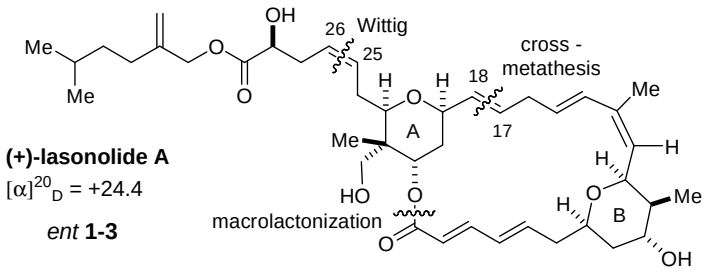
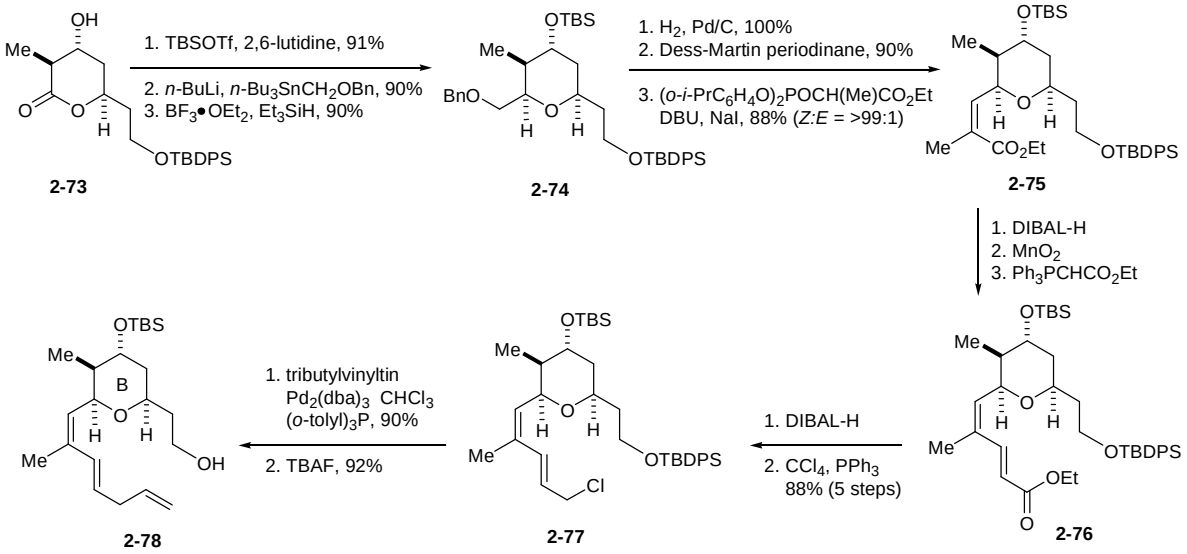


Figure 2.3.1. Shishido's Retrosynthetic Analysis of (+)-Lasonolide A

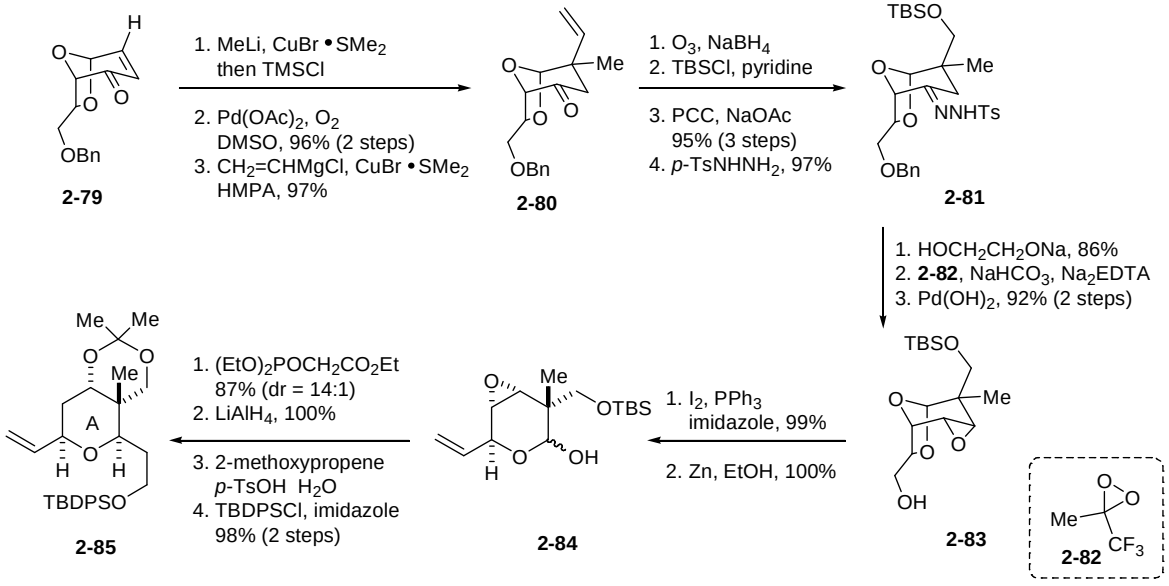
Tetrahydropyran **2-78** was prepared in thirteen steps from lactone **2.73** (Scheme 2.3.1).[20] Following protection of the secondary alcohol as the silyl ether, addition of benzyloxymethyl anion gave the lactol, which was reduced with boron trifluoride etherate and triethylsilane to provide c*is*-2,6-disubstituted tetrahydropyran **2-74** as a single diastereomer.[21] Removal of the benzyl group and subsequent oxidation allowed for homologation to trisubstituted olefin **2-75** with excellent diastereoselectivity. Reduction of the ester, oxidation of the resultant allylic alcohol, and elongation produced conjugated ester **2-76**. Another reduction and installation of the terminal halide set the stage for a Stille coupling to provide skipped triene **2-78** after removal of the primary silyl ether. [22]



Scheme 2.3.1. Shishido's Synthesis of *cis*-2,6-disubstituted Tetrahydropyran B **2-78**

The synthesis of A-ring fragment **2-85** began with known enone **2-79** (Scheme 2.3.2).[23] Conjugate addition with lithium dimethylcuprate, subsequent

oxidation of the silyl enol ether, and copper catalyzed conjugate addition of vinyl magnesium bromide provided ketone **2-80**.[24] Ozonolysis of the terminal alkene with reductive workup gave the corresponding diol, which was selectively protected as the primary silyl ether. Further oxidation of the secondary alcohol and treatment with *p*-toluenesulfonylhydrazine provided hydrazone **2-81**.

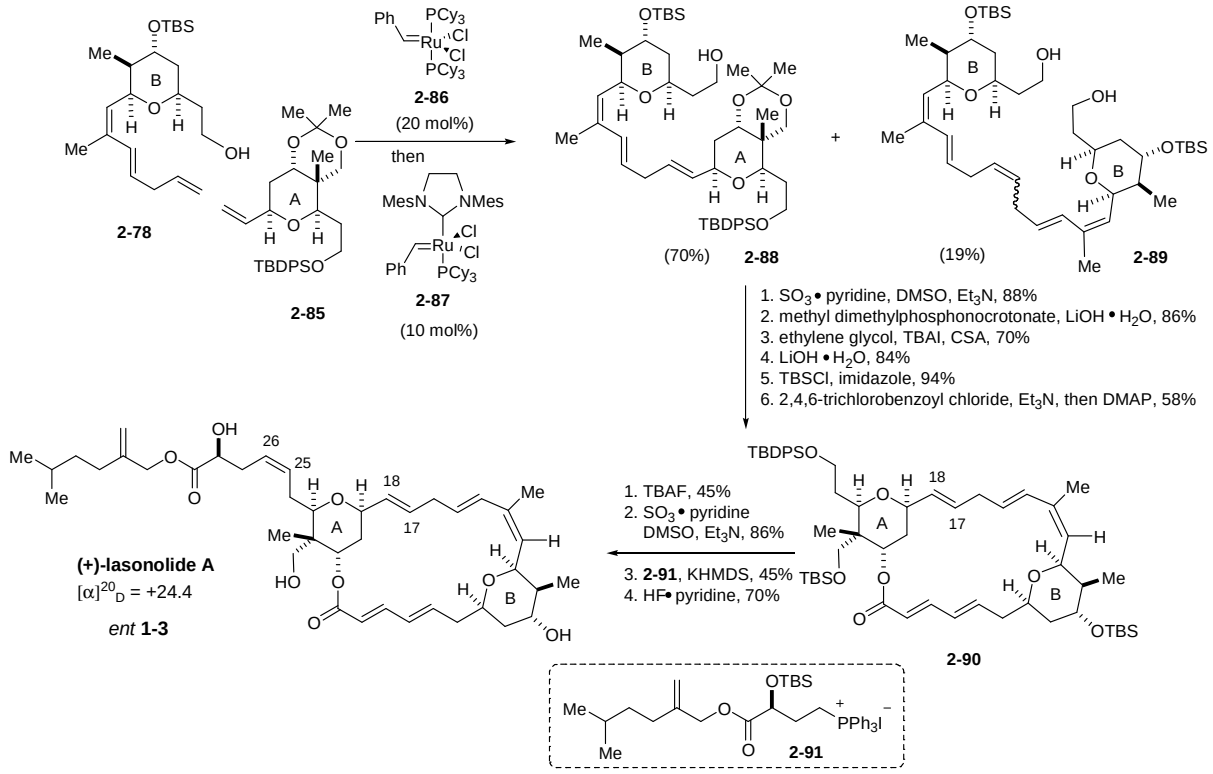


Scheme 2.3.2. Shishido's Synthesis of *cis*-2,6-Disubstituted Tetrahydropyran A **2-85**

A Bamford-Stevens reaction[25] then provided the internal olefin. Epoxidation of alkene **2-81** with methyl(trifluoromethyl)-dioxirane **2-82**, followed by reduction of the benzyl ether provided alcohol **2-83** in 90% *de*. The primary halide was formed and subsequently reduced with an ethanolic zinc suspension to provide hemiacetal **2-84**. Conversion to the α,β-unsaturated ester and subsequent intramolecular Michael addition furnished the *cis*-2,6-disubstituted tetrahydropyran in 14:1 *dr*. Lithium

aluminum hydride reduction of the epoxy-hemiacetal provided a triol, which was selectively protected as the acetonide and corresponding silyl ethers (**2-85**).

The 20-membered macrolide backbone was constructed with a cross metathesis and macrolactonization strategy (Scheme 2.1.18). The cross metathesis between olefins **2-78** and **2-85** was achieved through the use of a mixture of Grubbs first generation (G1) catalyst **2-86** and Grubbs second generation (G2) catalyst **2-87** to provide 70% of triene **2-88** and 19% of homodimer **2-89**.[26] With macrolide precursor **2-88** in hand, the primary alcohol was oxidized and homologation provided the extended diene. Removal of the acetonide gave the diol and hydrolysis afforded the dienoic acid. After protection of the primary alcohol, macrolactone **2-90** was formed under Yamaguchi conditions.[27] Desilylation of both primary alcohols and subsequent oxidation of the least sterically hindered alcohol to the aldehyde set the stage for a Wittig olefination with phosphonium salt **2-91**. Global deprotection concluded the enantiocontrolled total synthesis of (+)-lasonolide A (*ent* **1-3**).



Scheme 2.3.4. Shishido's Synthesis (+)-Lasonolide A *ent* **1-3**

2.4 Beck and Hoffmann's Synthesis of the B-Ring (C1-C16 Segment)[28]

The enantioselective synthesis of the C1-C16 segment of the originally proposed structure of lasonolide A was reported in 1999 by Beck and Hoffmann (Figure 2.4.1).

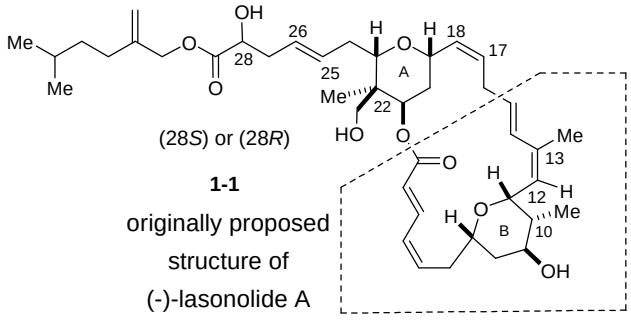
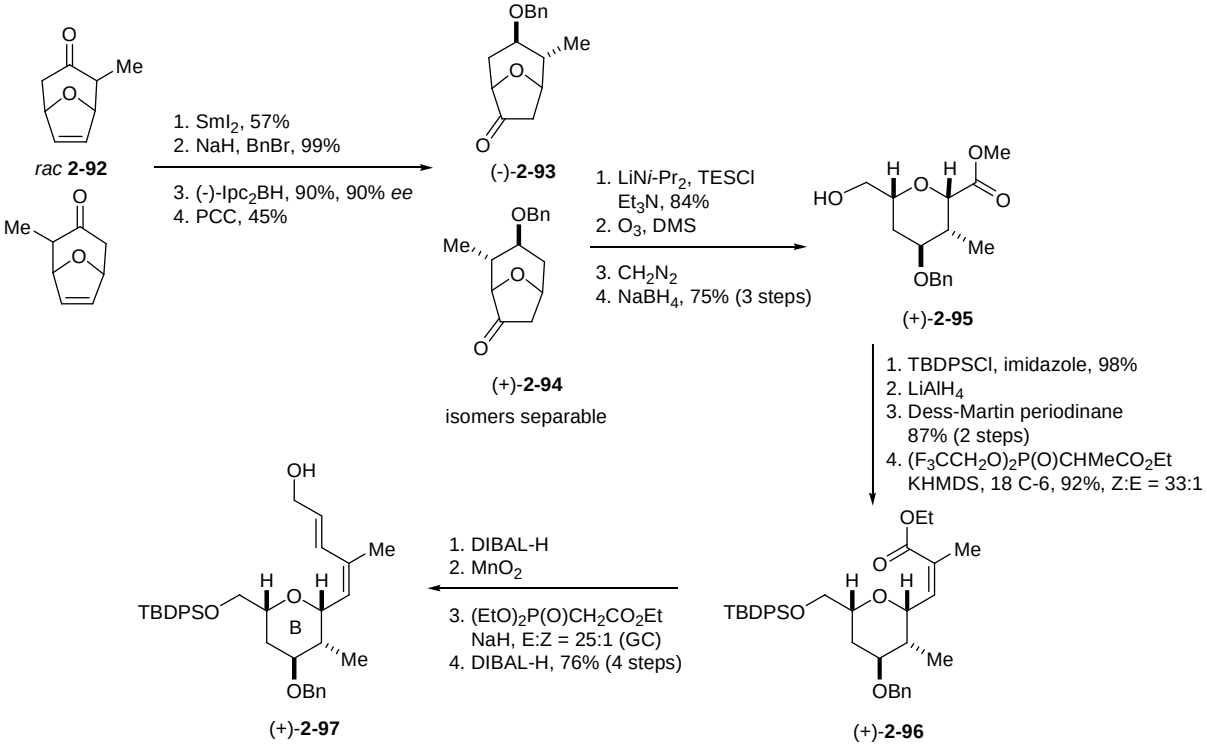


Figure 2.4.1. C11-C16 Segment Targeted by Beck and Hoffmann

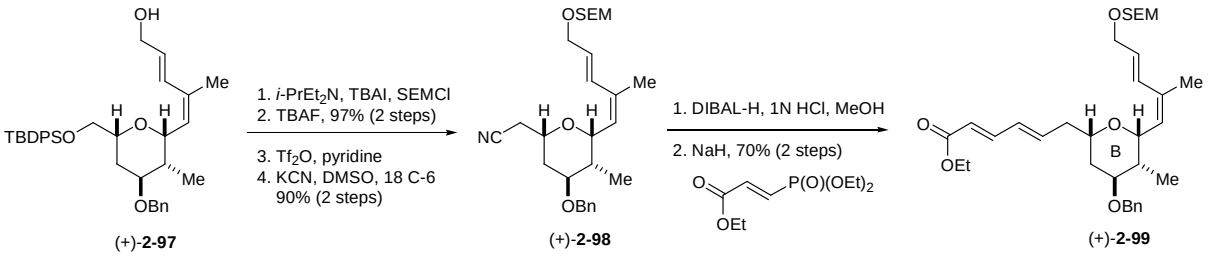
The synthesis of the B-ring fragment began with racemic 2α-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (*rac* **2-92**), which had been previously employed in their synthesis of the C29-C37 segment of spongistatin.[29] A samarium iodide reduction of *rac*-**2-92** afforded the equatorial alcohol, which was protected as the benzyl ether (Scheme 2.4.1). Easily separable regioisomers (-)-**2-93** and desired (+)-**2-94** were obtained after hydroboration of the olefin and oxidation of the resulting secondary alcohol. The authors note that this step provides an opportunity for an "early racemic switch, [which] has been defined as the development in single-enantiomer form of a drug that was first approved as a racemate."[30] The silyl enol ether, formed from ketone (+)-**2-94**, was ozonolyzed and the resulting aldehyde-acid was converted to *cis*-2,6-disubstituted tetrahydropyran **2-95** by esterification of the acid and reduction of the aldehyde.



Scheme 2.4.1. Beck and Hoffmann's Synthesis of B-Ring **2-97**

Protection of the primary alcohol **2-95** as the silyl ether, adjustment of the ester oxidation state to an aldehyde by reduction to the alcohol and reoxidation, and subsequent olefination afforded trisubstituted olefin **2-96** with high *Z*-selectivity. Reduction of the ester, oxidation of the resultant primary alcohol to the aldehyde, further extension utilizing Horner-Wadsworth-Emmons conditions, and subsequent reduction afforded diene **2-97**.

Allylic alcohol **2-97** was protected as the 2-(trimethylsilyl)ethoxymethyl (SEM) ether. Upon selective deprotection of the primary TBDPS ether, the alcohol was converted to the triflate to undergo nucleophillic substitution and deliver nitrile **2-98**. Reduction of nitrile **2-98** and ensuing hydrolysis allowed for conversion to the aldehyde, which was subjected to a (*E,E*)-selective Horner-Wadsworth-Emmons reaction to give B-ring polyene **2-99**.



Scheme 2.4.2. Beck and Hoffmann's Synthesis of B-Ring **2-99**

2.5 Rychnovsky's Synthesis of the A-Ring (C18-C25 Segment)[31]

In order to showcase the 2-oxonia-Cope Prins cascade reported by Dalgard and Rychnovsky,[32] the A-ring (C18-C25 segment) of (-)-lasonolide A was targeted (Figure 2.5.1).

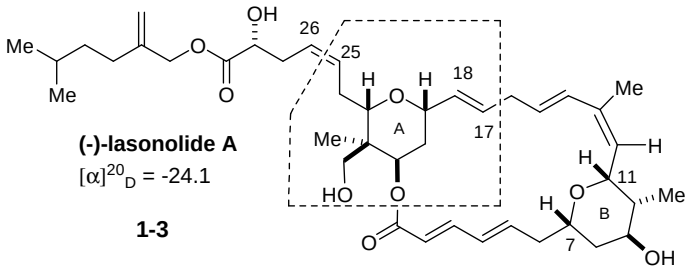
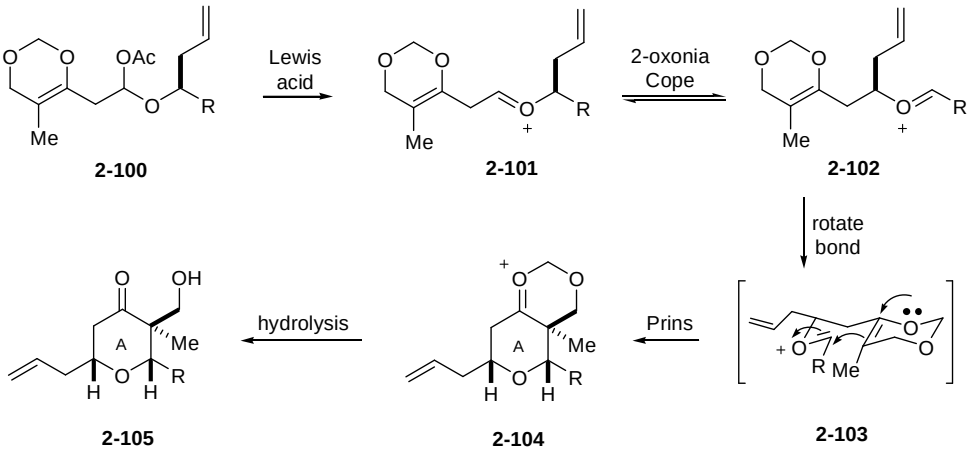


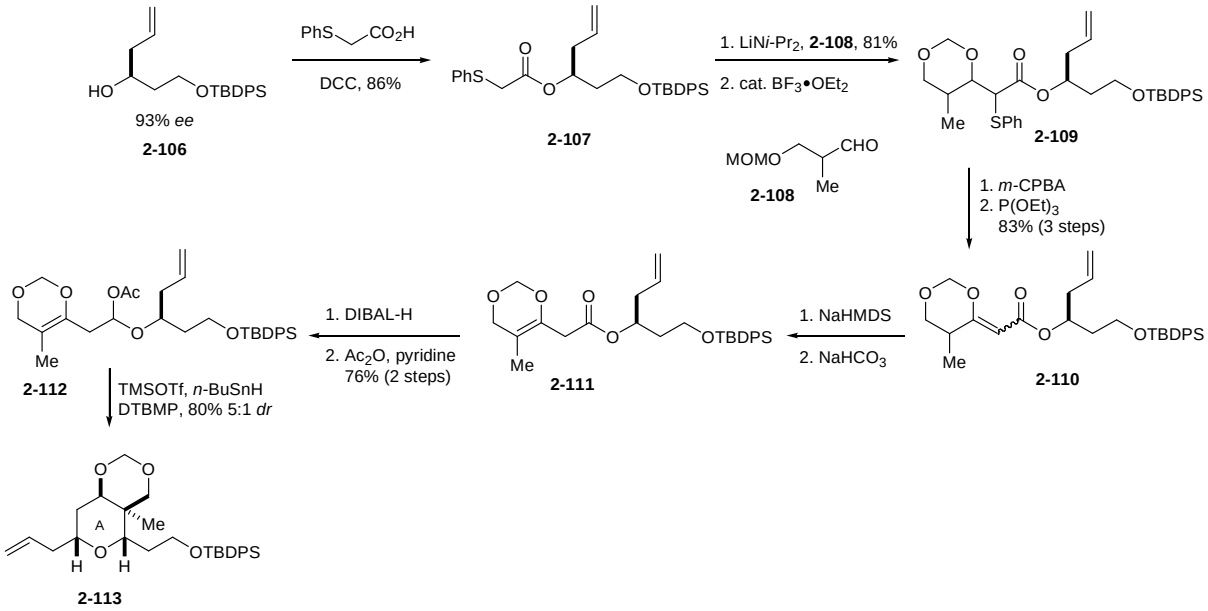
Figure 2.5.1. A-Ring (C18-C25) Segment Targeted by Dalgard and Rychnovsky

The proposed 2-oxonia-Cope Prins cyclization, shown in Scheme 2.5.1, is based on a tandem oxacarbenium ion reaction. Mixed acetal **2-100** could be reacted with a Lewis acid to form oxacarbenium ion **2-101**, allowing for a stereospecific 2-oxonia Cope rearrangement to form oxacarbenium ion **2-102**. The authors propose that upon bond rotation, transition state **2-103** could allow for cyclization of the chair conformer to yield **2-104**. Further hydrolysis would provide *cis*-2,6-disubstituted tetrahydropyrans **2-105**, like that of the A-ring of lasonolide.



Scheme 2.5.1. Proposed Mechanism of the 2-Oxonia-Cope Prins Cyclization

Application of the proposed 2-oxonia-Cope Prins cyclization began with optically active alcohol **2-106** as shown in Scheme 2.5.2. DCC-Mediated esterification led to **2-107**, which upon enolization was subjected to an aldol reaction with aldehyde **2-108**. An *in situ* Lewis acid-mediated cyclization led to 1,3-dioxane **2-109**, which was oxidized to the corresponding sulfoxide and subsequent elimination afforded olefin **2-110**. A 2-step deconjugation followed by reductive acylation afforded mixed acetal **2-112**. Oxacarbenium ion formation and *in situ* hydride reduction supplied *cis*-2,6-disubstituted tetrahydropyran **2-113.**



Scheme 2.5.2. A-Ring (C18-C25) Segment Targeted by Dalgard and Rychnovsky

2.6 Gujar's Synthesis of the A and B-Rings[33]

Gujar and coworkers utilized a different approach and prepared the A and B-rings of lasonolide A from sugar derivatives. The stereochemistry of the C18-C23 A-ring segment corresponds to (-)-lasonolide A, while the C7-C16 B-Ring segment corresponds to (+)-lasonolide A (Figure 2.1.6).

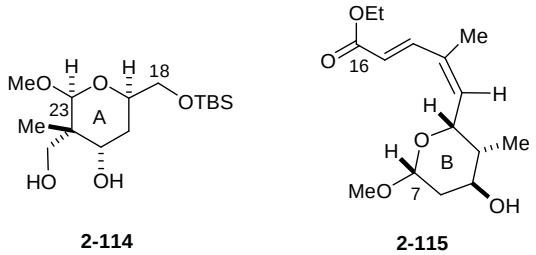
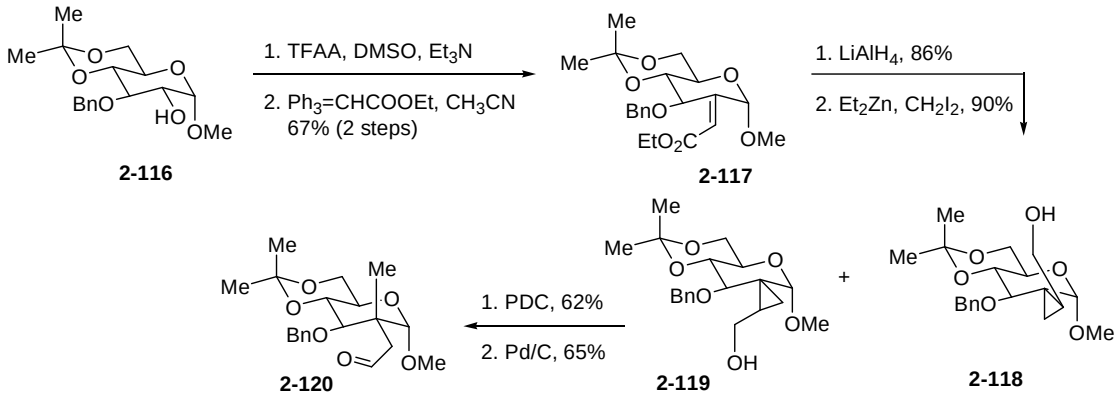


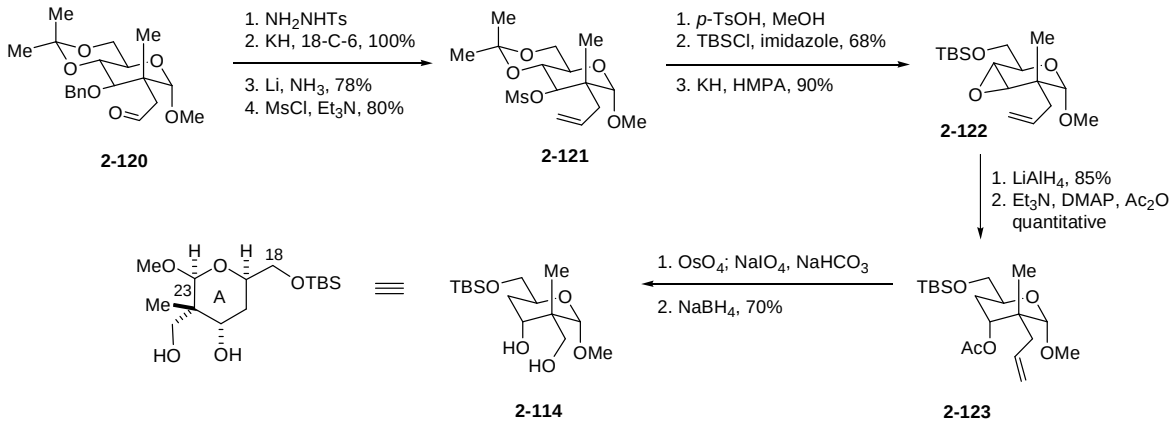
Figure 2.6.1. A-Ring (C18-C23) and B-Ring (C7-C16) Segments Targeted by Gujar and Coworkers

The synthesis of the A-ring (C18-C23) began with known methyl-3-*O*-benzyl-4,6-*O*-isopropylidene-α-D-glucopyranoside **2-116** (Scheme 2.6.1).[34] Oxidation of the secondary alcohol and subsequent two-carbon extension led to unsaturated ester **2-117**. Reduction of the ester was followed by a Simmons-Smith reaction, and the stereoisomeric cyclopropane derivates **2-118** and **2-119** were separated via chromatography. Oxidation of the alcohol was followed by hydrogenation to induce regiocontrolled ring cleavage.



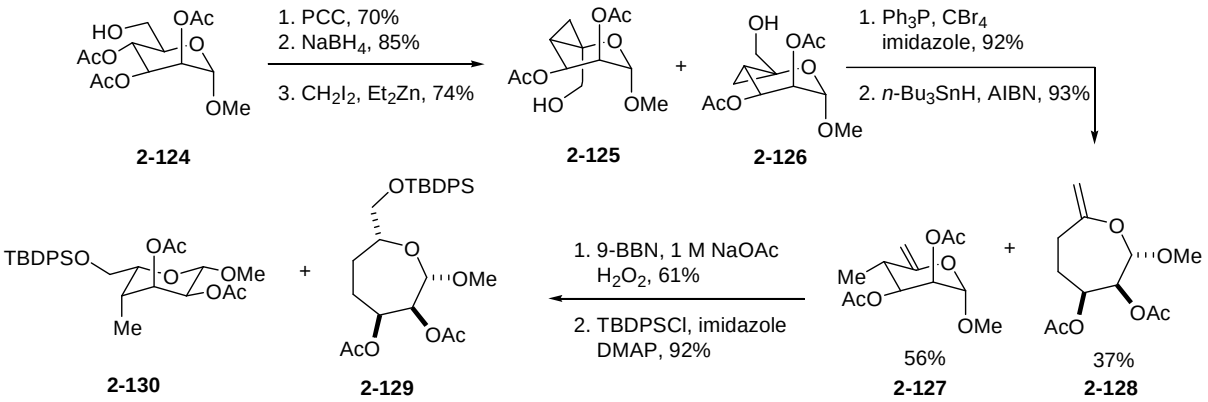
Scheme 2.6.1. A-Ring (C18-C23) Segment Targeted by Gujar and Coworkers

The aldehyde was transformed into the corresponding hydrazone, which was heated under Bamford-Stevens conditions (Scheme 2.6.2). The benzyl group was removed under dissolving metal conditions, and the free alcohol was protected to provide mesylate **2-121**. Acetonide removal followed by primary alcohol protection and elimination delivered epoxide **2-122**. Lithium aluminum hydride regioselectively opened the epoxide, and the resultant alcohol was acylated to supply 3-*O*-acetyl derivative **2-123**. Oxidative cleavage of the olefin was then followed by reduction to afford alcohol **2-114**.



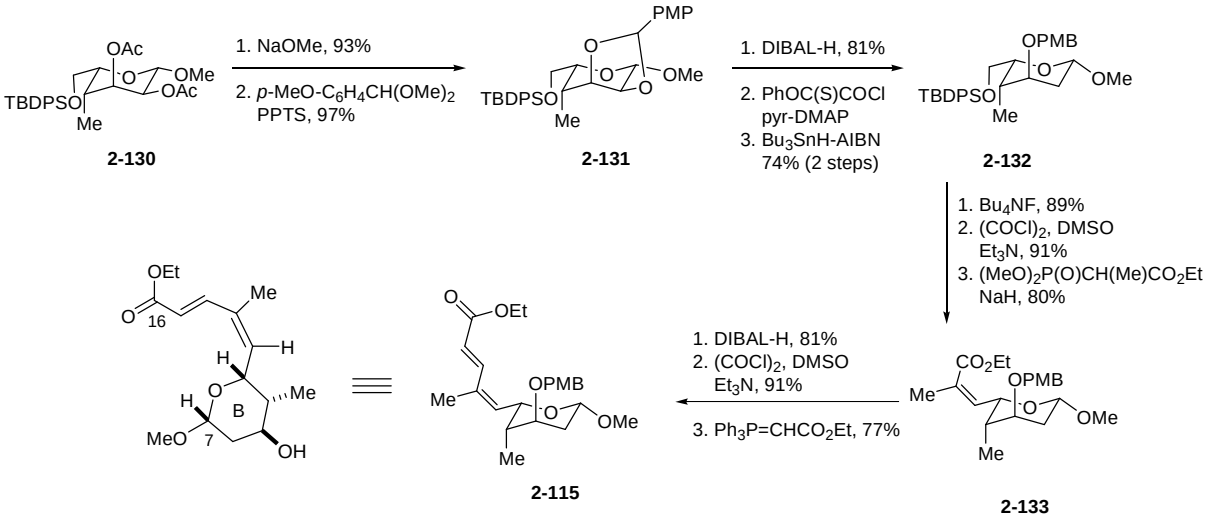
Scheme 2.6.2. A-Ring (C18-C23) Segment Targeted by Gujar and Coworkers

Efforts directed toward the C7-C16 segment began with methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside **2-124** (Scheme 2.6.3). Oxidation and reduction was followed by a Simmons-Smith cyclopropanation to yield a racemic mixture of diastereomers **2-125** and **2-126**, which were separable via chromatography. Cyclopropane **2-126** was converted to the 6-bromo-derivative and the ring was subsequently opened under radical conditions to give both pyranose derivative **2-127** and seven-membered ring **2-128**. The mixture of **2-127** and **2-128** was subjected to hydroboration-oxidation conditions and following silyl protection, ring ethers **2-129** and **2-130** were separated via column chromatography.



Scheme 2.6.3. B-Ring (C7-C16) Segment Targeted by Gujar and Coworkers

With **2-130** in hand, the acetates were removed, followed by treatment of the diol with *p*-anisaldehyde dimethylacetal under acidic conditions to yield PMP-acetal **2-131** (Scheme 2.6.4). Regioselective reduction of the acetal followed by acylation and Barton deoxygenation afforded 2-deoxy pyranoside **2-132**. Silyl deprotection, Swern oxidation, and homologation gave trisubstituted alkene **2-133**. Conversion of the ester to the aldehyde was followed by a second Wittig olefination to afford α,β-unsaturated ester **2-115**.



Scheme 2.6.4. B-Ring (C7-C16) Segment Targeted by Gujar and Coworkers

2.7 Jennings' Synthesis of the B-Ring (C1-C14 Segment)[35]

Jennings and coworkers constructed the B-ring of (-)-lasonolide A through a Molander-Reformatsky samarium iodide-mediated intramolecular aldol reaction (Figure 2.7.1).[36]

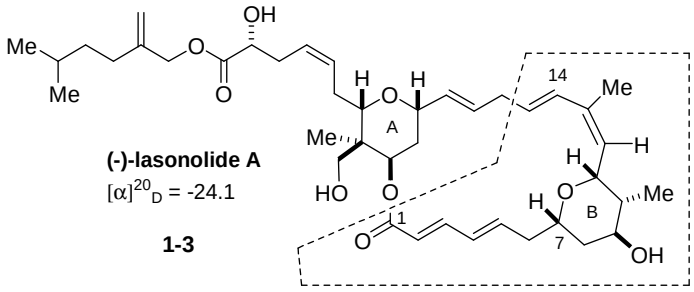
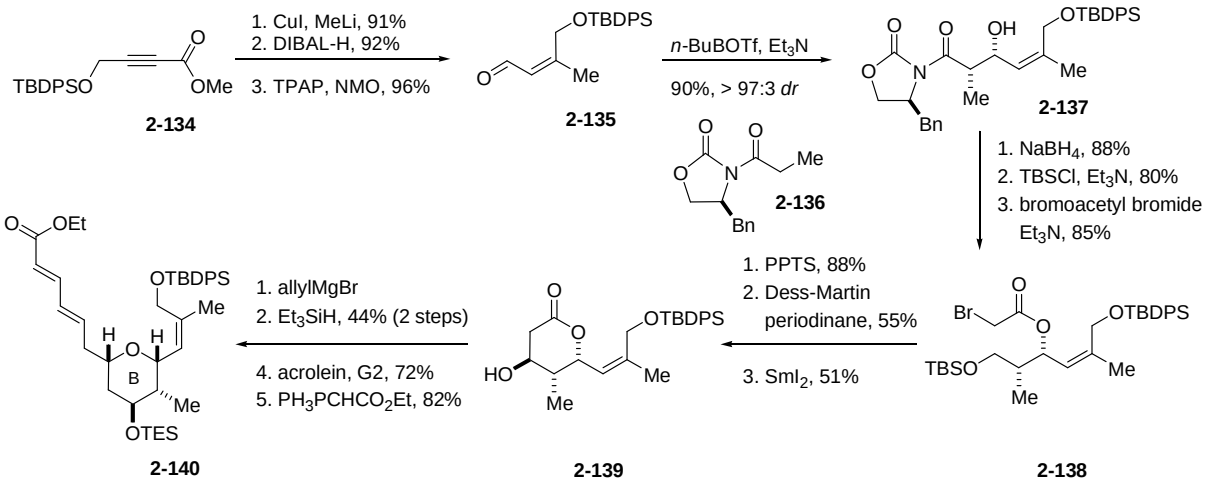


Figure 2.7.1. B-Ring (C1-C14 Segment) Targeted by Jennings and Coworkers

Known α,β-acetylenic ester **2-134** was reacted with lithium dimethylcuprate to form the trisubstituted olefin (Scheme 2.7.1). Reduction of the ester to the alcohol and oxidation led to aldehyde **2-135**. The *Z*-boron enolate of **2-136** was reacted with aldehyde **2-135** utilizing Evans' conditions to provide *syn*-aldol adduct **2-137**. Removal of the chiral auxiliary was followed by selective silylation of the primary alcohol and acylation of the secondary alcohol with bromoacetyl bromide provided bromo-acetate **2-138**. Selective removal of the *t*-butyldimethylsilyl ether and oxidation of the alcohol with Dess-Martin periodinane was followed by an intramolecular Molander-Reformatsky samarium iodide-mediated cyclization to stereoselectively provide lactone **2-139**. Addition of allyl magnesium bromide to lactone **2-139** provided the lactol, which was reduced with triethylsilane to provide

the 2.6-*cis*-tetrahydropyran. Cross-metathesis with acrolein and subsequent extension to diene **2-140** completed the synthesis of the C1-C14 B-ring segment.



Scheme 2.7.1. B-Ring (C1-C14 Segment) Targeted by Jennings and Coworkers

2.8 *Hart's Synthesis of the A and B-Rings*[37]

Hart, Patterson, and Unch have reported their collaborative efforts in synthesizing the A and B-Rings of (+)-lasonolide A (Figure 2.1.8). Their approach involved a cycloetherification reaction of *bis*-homoallylic alcohols in the key step.

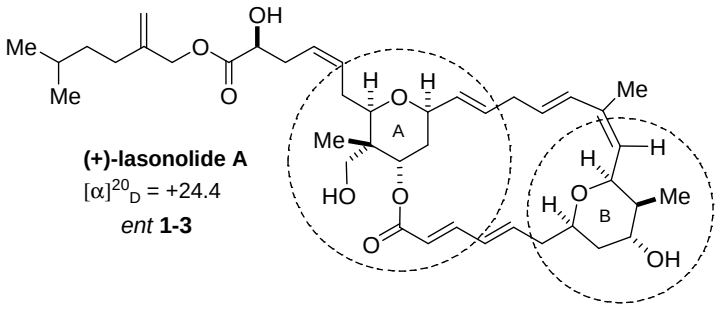
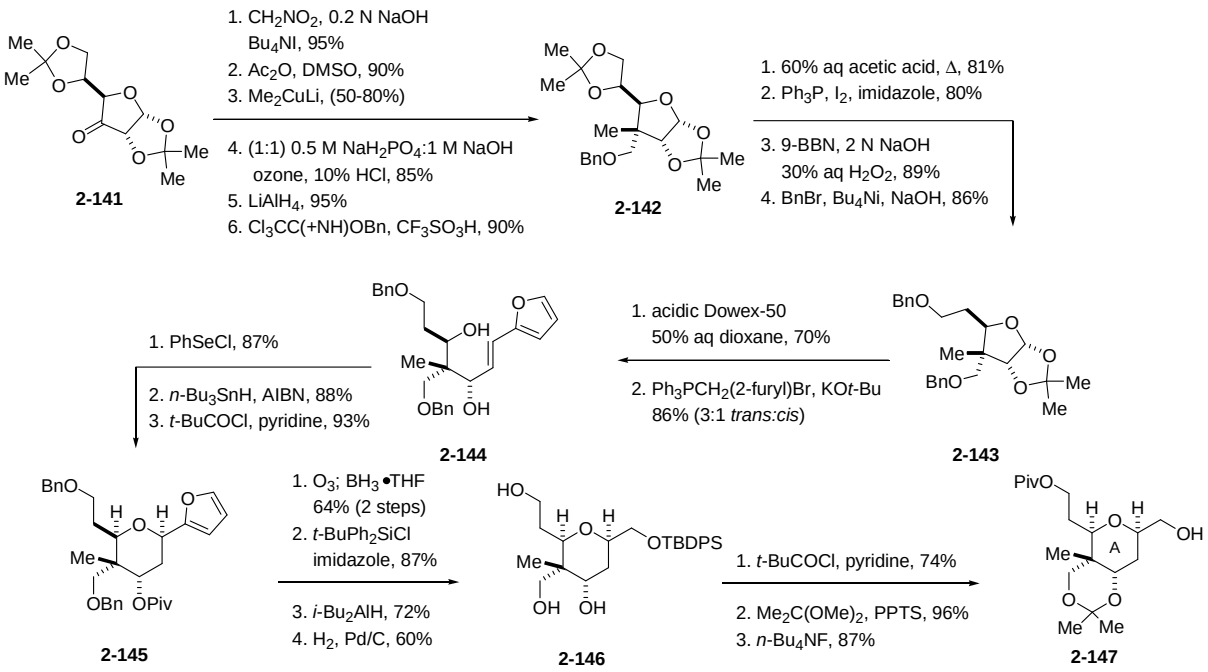


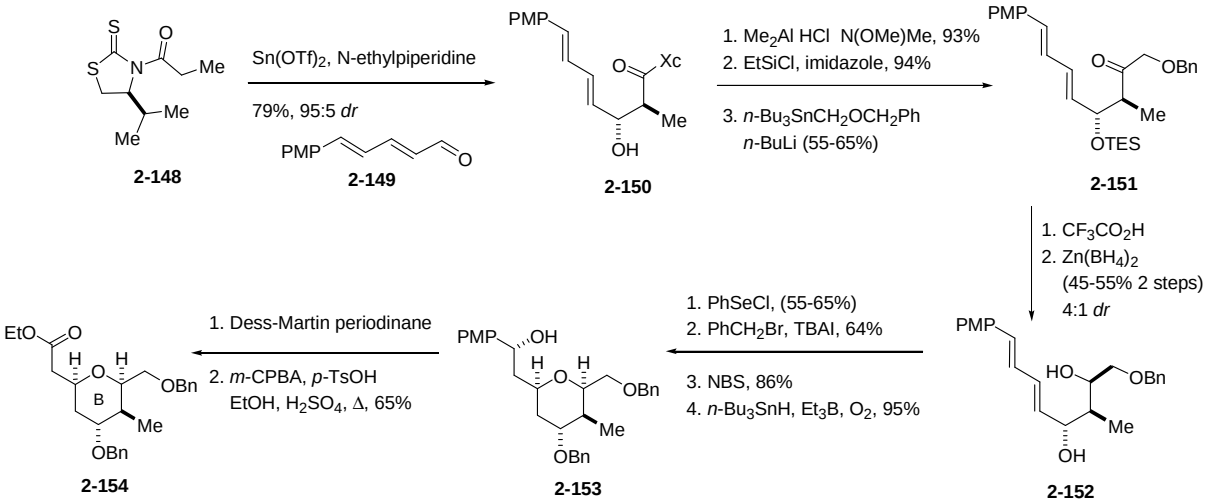
Figure 2.8.1. A and B-Rings of (+)-lasonolide A Targeted by Hart and Coworkers

Commercially available diacetone glucose **2-141** was oxidized and converted to the corresponding nitroalkane. Addition of dimethylcuprate and oxidation to the carboxylic acid with ozone set the stage for a reduction with lithium aluminum hydride. Protection as a benzyl ether then provided **2-142**. Selective hydrolysis and reaction with triphenylphosphine-iodine provided the mono-substituted olefin. Hydroboration-oxidation followed by benzyl protection gave acetonide **2-143**, which underwent hydrolysis and Wittig olefination with (2-furyl)methylidenetriphenyl phosphorane to provide **2-144**. The *trans* olefin proceeded through a three-step sequence involving phenylselenenyl chloride, reduction of the selenide, and protection as the pivaloate to give *cis*-2,6-disubstituted tetrahydropyran **2-145**. Oxidative degradation of the furan via ozonolysis, reduction of the carboxylic acid to the primary alcohol, and silylation set the stage for reduction of the pivaloate and hydrogenolysis to give triol **2-146**. Protection of the primary alcohol as the pivaloate and protection of the diol as the acetonide, followed by deprotection of the silyl ether provided A-ring fragment **2-147**.



Scheme 2.8.2. A-Ring of (+)-lasonolide A Targeted by Hart and Coworkers

The synthesis of the B-ring was initiated with the scandium triflate enolate of thiazolidinethione **2-148**. Reaction of *E,E*-5-(4-methoxyphenyl)penta-2,4-dienal **2-149** with the enolate of **2-148** gave *syn*-aldol adduct **2-150**.[38] Displacement of the auxiliary with Weinreb's amide, silylation of the secondary alcohol, and treatment with benzyloxymethyllithium afforded ketone **2-151**. Removal of the silyl ether and reduction with zinc borohydride[39] provided diol **2-152** as a 4:1 mixture of diastereomers and treatment with phenylselenyl chloride initiated cyclization to the *cis*-2,6-disubstituted tetrahydropyran.[40] Etherification of the secondary alcohol was followed by formation of diastereoselective bromohydrins. Finally, oxidation with Dess-Martin periodinane was followed by Bayer-Villiger reaction to give the desired B-ring fragment.



Scheme 2.8.3. B-Ring of (+)-lasonolide A Targeted by Hart and Coworkers

CHAPTER 3

STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF (-)-LASONOLIDE A

3.1 Retrosynthetic Analysis

When lasonolide A was first examined in the laboratory of M. T. Crimmins, (+)-lasonolide A (*ent* **1-3**) was presumed to be the biologically active natural product. As shown in Figure 3.1.1, projected disconnections partition the molecule into three components: two substituted tetrahydropyran segments (C1-C14 and C15-C25) and the side-chain extending from C26-C35. The macrolide could be assembled using a Julia olefination to install the *trans* C14-C15 alkene, a Stille-type protocol to form the C3-C4 bond, and a Yamaguchi lactonization. The side chain would be appended utilizing a Wittig olefination to form the *cis* geometry of the C25-C26 alkene. This strategy provided several options for constructing the molecule from the key fragments.

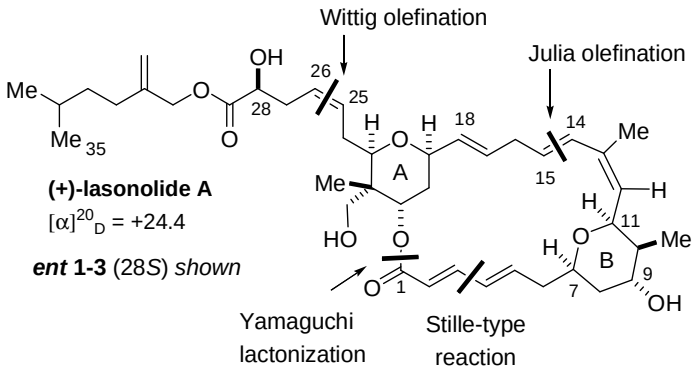
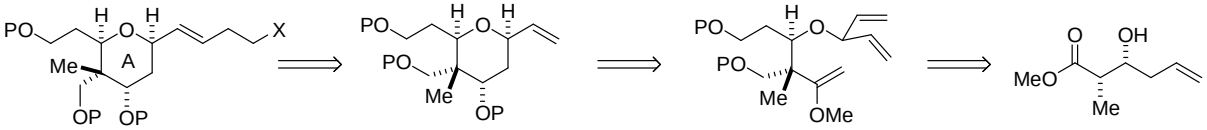


Figure 3.1.1. Preliminary Disconnections to Construct (+)-Lasonolide A

3.2 *A-Ring: Synthesis of the C15-C25 Segment*

The preliminary retrosynthesis of the C15-C25 fragment of (+)-lasonolide A (Scheme 3.2.1) was based on the ring closing metathesis of intermediate **3-3**, which would be prepared from aldol adduct **3-4**.[41]



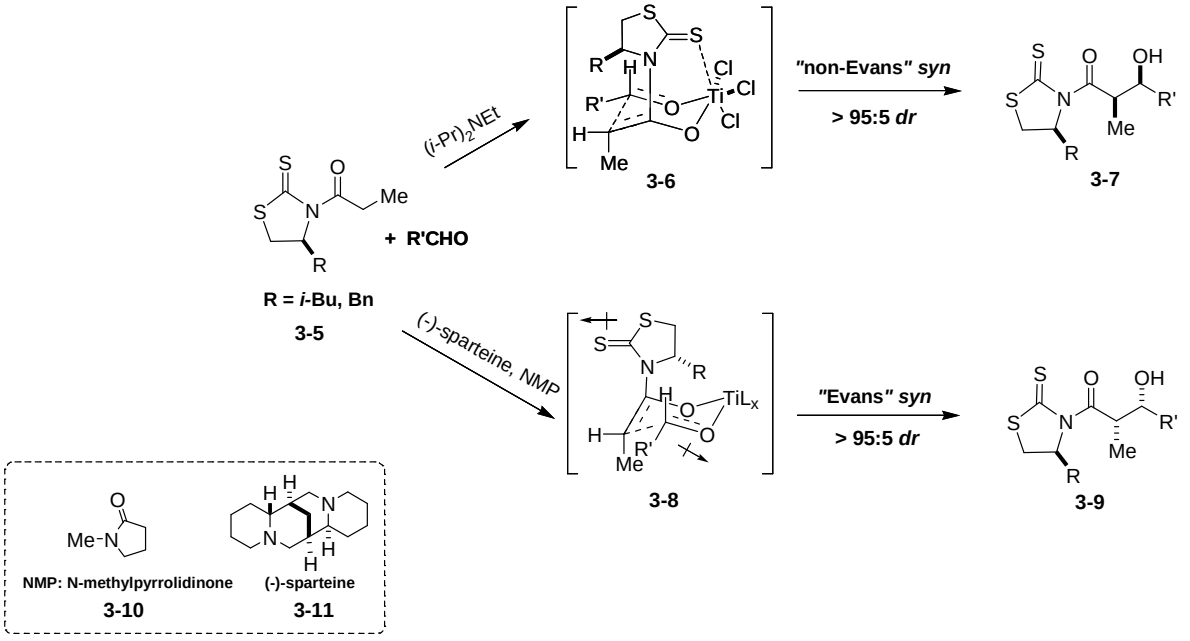
3-1 **3-2** **3-3** **3-4**

Scheme 3.2.1. Retrosynthetic Analysis of C15-C25 Segment of (+)-Lasonolide A

3.2.1 Frater-Seebach Alkylation via Syn Aldol Intermediate

The formation of aldol adduct **3-4** was based on previous studies in the Crimmins laboratory.[42] As shown in Scheme 3.2.2, *N*-acyl thiazolidinethione **3-5** allows access to either Evans or non-Evans *syn* aldol products by altering the stoichiometry of the base. When employing one equivalent of amine base, it is believed that non-Evans

syn aldol product **3-7** is formed via transition state **3-6**, wherein the sulfur atom of the thiazolidinethione is chelated to the titanium atom. In this highly rigid arrangement, the chlorotitanium enolate forms a new C-C bond with the aldehyde opposite to the large R group of the chiral auxiliary.

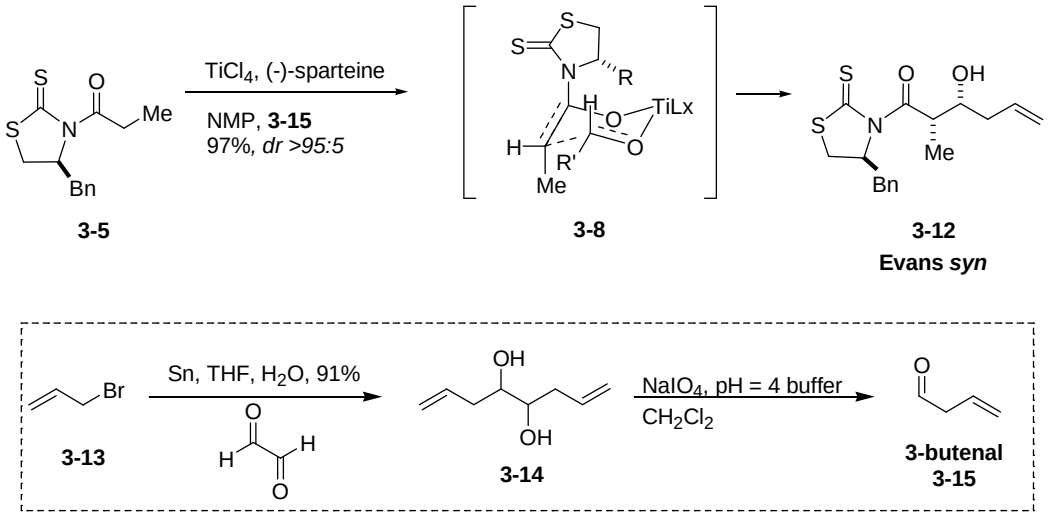


Scheme 3.2.2. Asymmetric Aldol Addition of Thiazolidinethione Propionate

On the other hand, by employing one equivalent each of amine base and an unreactive coordinating ligand such as N-methylpyrrolidinone (NMP, **3-10**), dipole-minimized transition state **3-8** predominates. N-Methylpyrrolidinone coordinates to the metal center and occupies the open coordination sites available on titanium, which leads to Evans *syn* aldol adduct **3-9**.

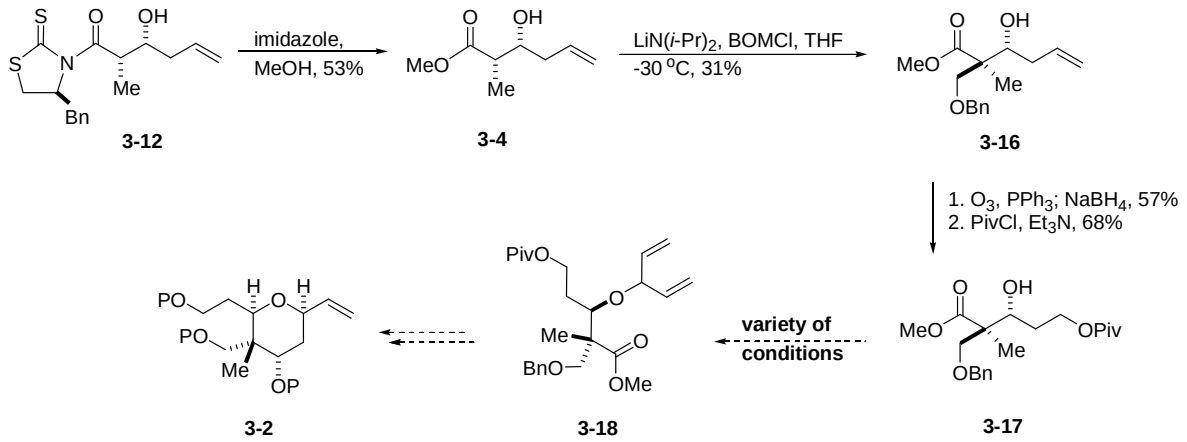
Based on these earlier studies, a previous graduate student, M. Stanton, began the synthesis of the C15-C25 fragment of (+)-lasonolide A with the installation of the C21-C22 propionate subunit via an Evans *syn* aldol reaction (Scheme 3.2.2). The

chlorotitanium enolate of acyl thiazolidinethione **3-5** was treated with aldehyde **3-15** (prepared in two steps from allyl bromide) providing *syn* aldol product **3-12** in excellent yield and diastereoselectivity.



Scheme 3.2.2. Evans *syn* Aldol Involving 3-butenal

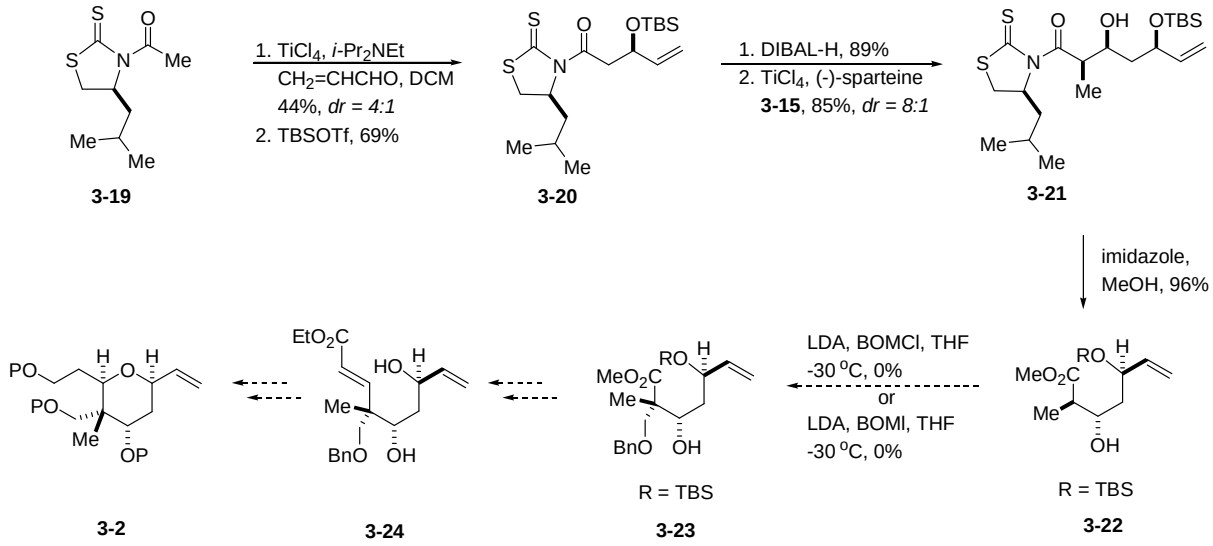
After exchange of the *N*-acyl thioimide for the corresponding methyl ester,[43] the quaternary center was installed through a Frater-Seebach alkylation[44] (Scheme 3.2.3). Benzyl ether **3-16** was obtained in modest yield as a single diastereomer using a chelation controlled alkylation with the lithium enolate of ester **3-4** and benzyloxymethyl chloride (BOMCl = $BnOCH_2Cl$). Ozonolysis of the alkene followed by reductive workup and protection of the resultant alcohol provided **3-17**. The ring closing metathesis strategy was reliant on divinyl carbinol **3-18**, which would be transformed to tetrahydropyran **3-2**. Numerous conditions were tested by Stanton, but protection of the secondary alcohol to provide divinyl carbinol **3-18** was not achieved.[45]



Scheme 3.2.3. Divinyl Carbinol Approach

3.2.2 Iterative Aldol Approach

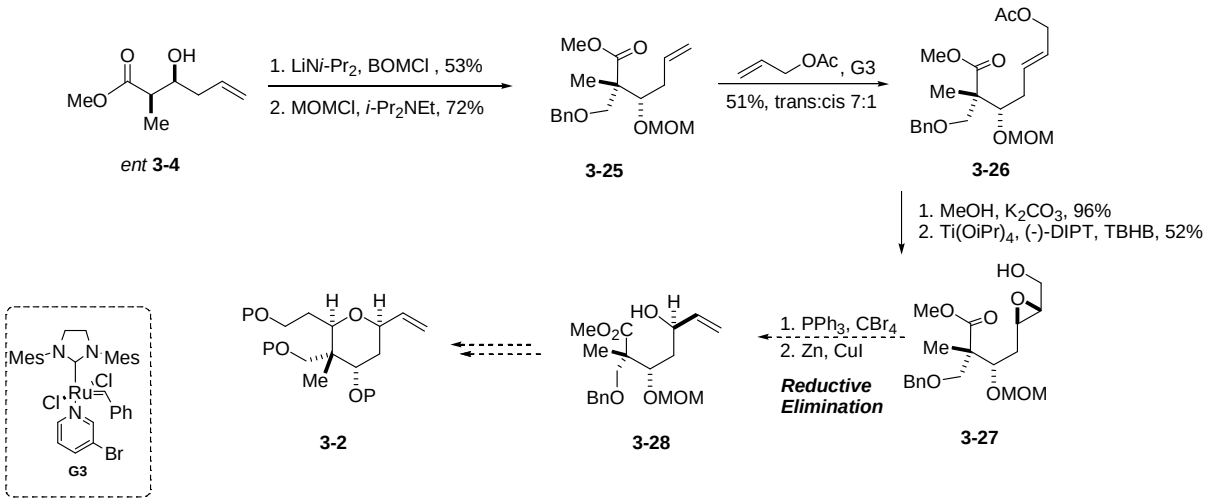
A second approach for the construction of tetrahydropyran **3-2** involved an asymmetric intramolecular Michael reaction of α,β-unsaturated ester **3-24**. As shown in Scheme 3.2.4, the chlorotitanium enolate of thiazolidinethione acetate **3-19** was reacted with acrolein to afford the desired diastereomer in modest yield and stereoselectivity. After protection of the secondary alcohol and reduction of the *N*-acyl thioimide to the aldehyde, a propionate aldol was utilized to form **3-21**. Exchange of the *N*-acyl thioimide for the corresponding methyl ester set the stage for a chelation-controlled stereoselective alkylation with the lithium enolate of ester **3-22**. However, the alkylation failed despite investigating a variety of conditions.



Scheme 3.2.4. Iterative Asymmetric Aldol Approach

3.2.3 Reductive Elimination Approach

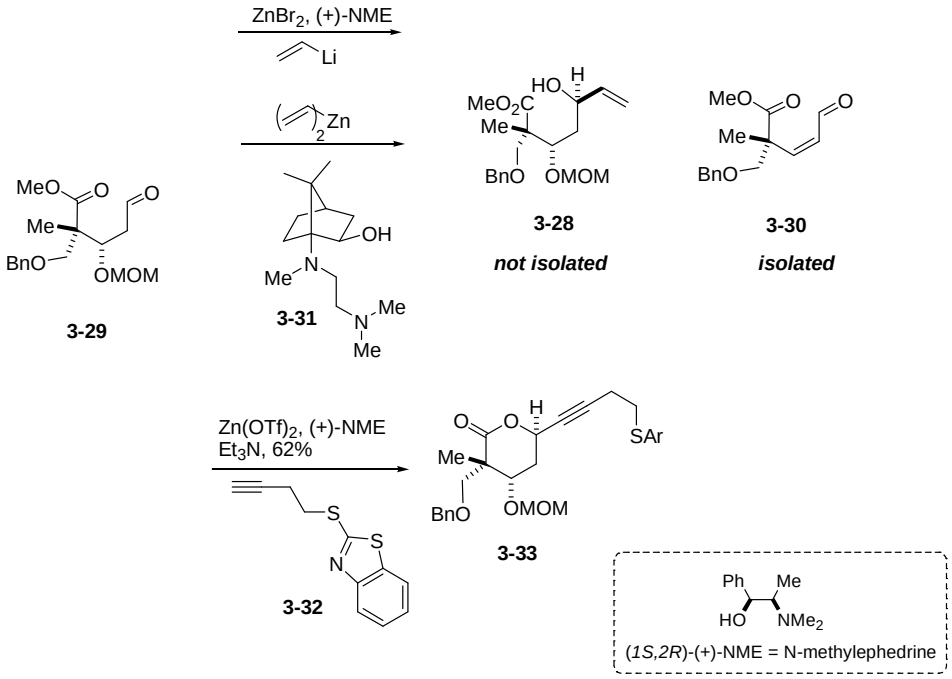
As shown in Scheme 3.2.5, the enantiomer of **3-4** was subjected to the same Frater-Seebach conditions utilized to form benzyl ether **3-16** and subsequently protected to yield intermediate **3-25**. After exploring numerous cross-metathesis conditions involving allyl acetate, the desired *trans* olefin was prepared using Grubbs' third generation catalyst. Removal of the acetate group was followed by epoxidation under Sharpless conditions.[46] However, further attempts to form the alkyl bromide and trigger reductive elimination led to poor results.



Scheme 3.2.5. Reductive Elimination Investigation

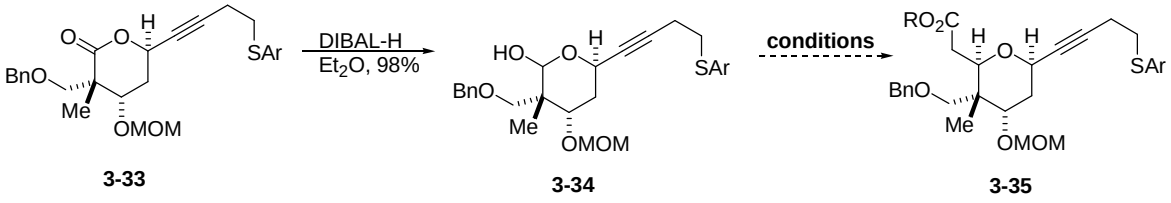
3.2.4 Organozinc Approach

In an attempt to successfully obtain allylic alcohol **3-28**, alkene **3-25** was subjected to ozonolysis conditions. The resultant aldehyde **3-29** was treated with various organozinc reagents to give the corresponding vinyl alcohol with high stereoselectivity. Unfortunately, employing zinc bromide and vinyllithium in the presence of (+)-NME led to elimination product **3-30**, as did divinyl zinc following the Oppolzer's protocol.[47] After a literature search for a mild alternative, the asymmetric acetylene addition reported by Carreira was tested.[48] Fortunately, alcohol formation followed by *in situ* cyclization to the corresponding lactone **3-33** occurred in 62% yield as a single diastereomer. The installed alkyne would be employed as an olefin surrogate and could be later reduced to the desired *trans* alkene.



Scheme 3.2.6. Employing Organozinc Reagents

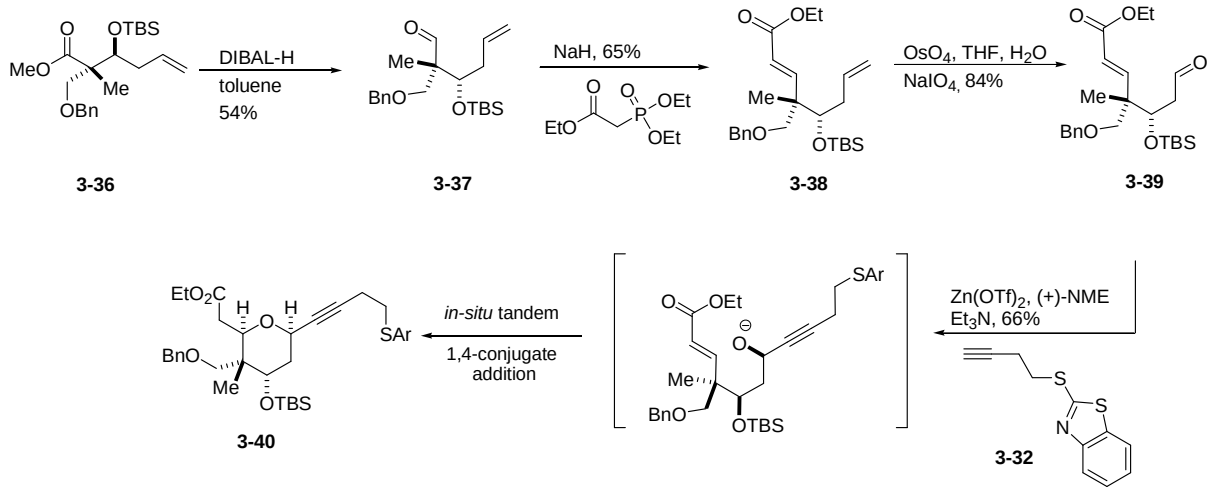
Lactone **3-33** was reduced to provide hemi-acetal **3-34**, which was subjected to a variety conditions in an effort to execute a diastereoselective addition to the oxacarbenium ion to yield 2,6-*cis* tetrahydropyran **3.35**. However, these attempts never came to fruition.



Scheme 3.2.7. Conversion to 2,6-*cis* Tetrahydropyran **3.35**

3.2.5 Tandem Zinc Acetylide Addition 1,4-Conjugate Addition

Based on the successful chelation controlled alkylation with the lithium enolate of ester **3-4**, which provided benzyl ether **3-16** (Scheme 3.2.3), the enantiomer of **3-16** was synthesized and protected to yield silyl ether **3-36**. As shown in Scheme 3.2.8, the methyl ester was reduced to aldehyde **3-37** and converted to the α,β-unsaturated ester via a Horner-Wadsworth-Emmons olefination. Oxidative cleavage of the terminal alkene then delivered aldehyde **3-39**, which was subjected to a zinc triflate-mediated asymmetric alkynylzinc addition. It was discovered that heating the reaction initiated an *in situ* 1,4-conjugate addition, which gave 2,6-*cis* tetrahydropyran **3-40**. Upon a literature review, this appears to be the first example of a zinc acetylene addition tandem 1,4-conjugate addition and this sequence will be discussed further in section 3.2.6.



Scheme 3.2.8. Zinc Acetylene Addition Tandem 1,4-conjugate Addition

3.2.6 Completion of the C15-C25 Segment of (-)-lasonolide A

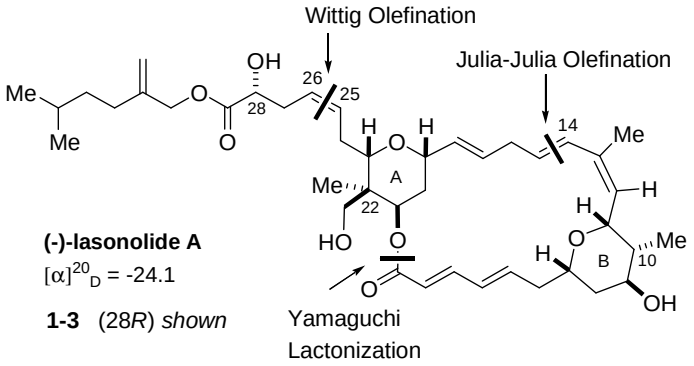


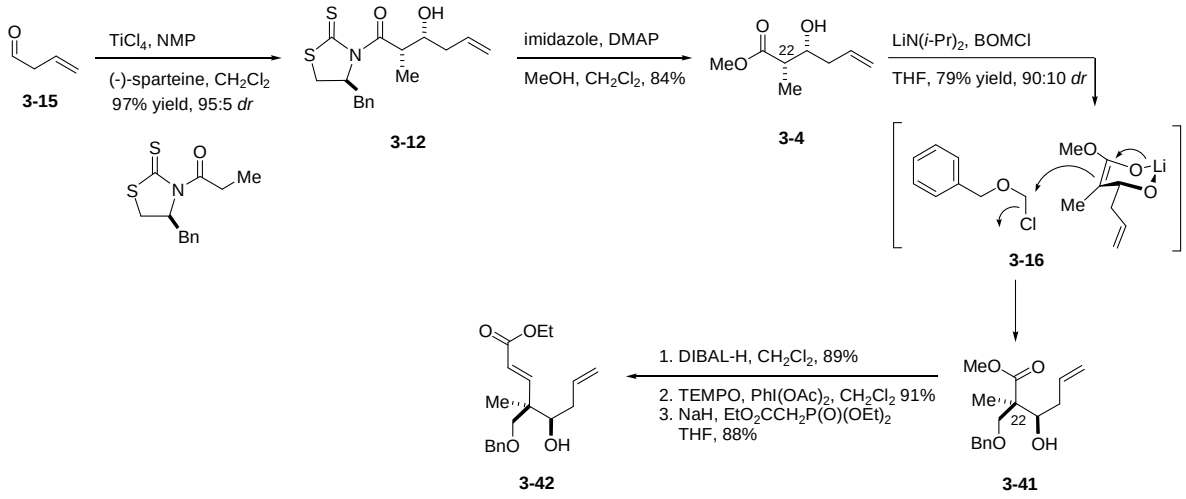
Figure 3.2.1. (-)-Lasonolide A: Projected Disconnections

As discussed in Chapter 2 (Section 2.1), Lee and coworkers determined that (-)-lasonolide A (Figure 3.2.1) is indeed the biologically active enantiomer. Armed with this information, it was necessary to construct the C15-C25 segment of (-)-lasonolide A while optimizing the reaction sequence.

Aldehyde **3-15** was treated with the chlorotitanium enolate of acyl thiazolidinethione **3-5** to afford Evans *syn* aldol product **3-12** in excellent yield and diastereoselectivity (Scheme 3.2.9). At this point, exchange of the *N*-acyl thioimide for the corresponding methyl ester was optimized. Methyl ester **3-4** is volatile and co-elutes with the *N*-acyl thioimide by-product of the reaction, therefore isolation in high yield is problematic. Originally, copious amounts of methanol were used for the esterification, which was difficult to remove *in vacuo* due to the volatility of methyl ester **3-4**. By using dichloromethane as the solvent and only twenty equivalents each of methanol and imidazole, and additional catalytic dimethylaminopyridine (DMAP)

to aid the esterification, removal of methanol *in vacuo* was no longer an issue. The additive effect of these simple alterations resulted in a yield increase of at least 30%.

Attention was then directed towards the installation of the quaternary center. Benzyl ether **3-41** was obtained in excellent selectivity using a chelation-controlled Frater-Seebach alkylation with benzyloxymethyl chloride (BOMCl = $BnOCH_2Cl$). Commercially available BOMCl and material generated in the laboratory are contaminated with large quantities of benzyl alcohol. The yield of this reaction is dependent upon successful separation of BOMCl from benzyl alcohol via careful distillation. This precaution in conjunction with exceptionally pure methyl ester increases the yield to nearly 80%. Methyl ester **3-41** was reduced to the diol and selective oxidation[49] of the primary alcohol to the corresponding the aldehyde was followed by conversion to α,β-unsaturated ester **3-42** via a Horner-Wadsworth-Emmons protocol.



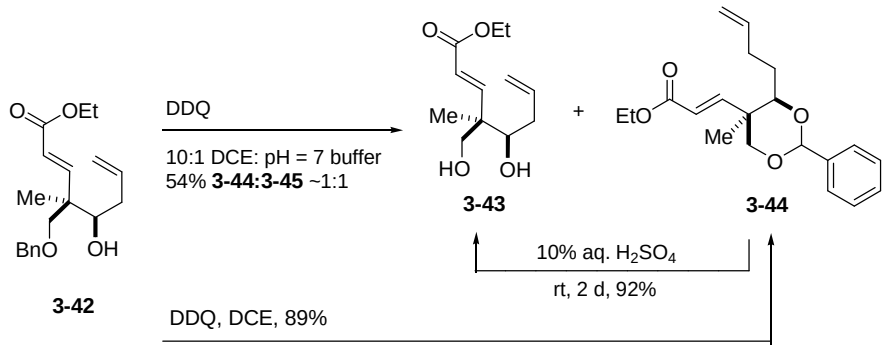
Scheme 3.2.9. Formation of α,β-Unsaturated Ester **3-42** via Evans *Syn:* Aldol Adduct **3-12**

At this juncture, it was necessary to remove the benzyl group from intermediate **3-42**. As will be discussed in Section 3.5, late-stage removal of the benzyl group proved quite difficult. Hydrogenation conditions employed to remove the benzyl moieties led to olefin reduction, while dissolving metal conditions, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and Lewis acids resulted in decomposition. Therefore, it was deemed necessary to remove the benzyl groups early in the synthetic route.

Debenzylation of **3-42** required some experimentation. Using a wealth of Lewis acids including Me_3SiBr, Me_3SiI, Me_2BBr, BCl_3, BBr_3, $FeCl_3$, and CrO_3/AcOH among others resulted in decomposition and/or low mass recovery of the starting material, while treatment with boron trifluoride etherate did not affect the benzyl ether. Furthermore, hydrogenation conditions employing Raney Nickel, Pd/C, and $Pd(OH)_2$ with a variety of solvents provided the alkane via reduction of the terminal olefin.

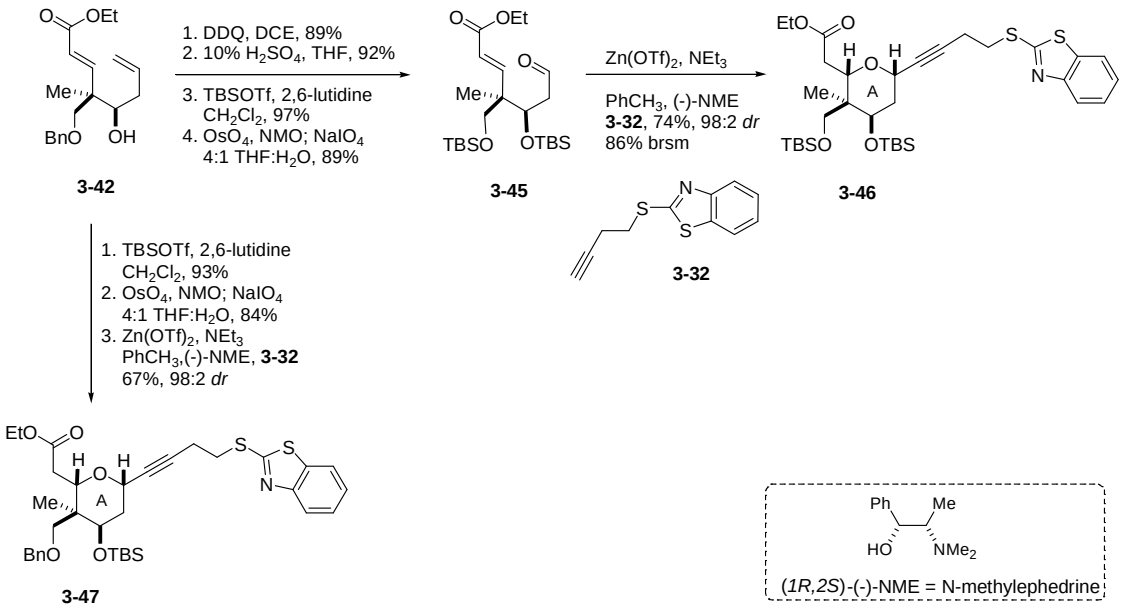
The use of DDQ led to an interesting result (Scheme 3.2.10). After dissolving benzyl ether **3-42** in dichloroethane (DCE) and aqueous buffer, the addition of DDQ afforded a mixture of desired diol **3-43** and the corresponding benzylidene acetal **3-44** even if the secondary alcohol was protected as the silyl ether (TES or TBS). Varying reaction conditions, e.g. solvent ratio, temperature, equivalents, did not favor diol **3-43**. In fact, the addition of buffer consistently led to poor mass recovery. However, it was found that the benzylidene acetal could be removed via acid hydrolysis in high yield. Based on these results, intermediate **3-41** was subjected to DDQ in dry DCE to yield benzylidene acetal **3-44** in good yield. Subsequent acid-

catalyzed hydrolysis provided desired diol **3-43** in excellent yield based on recovery of acetal **3-44**.



Scheme 3.2.10. Benzyl Ether **3-42** DDQ Experiment

As shown in Scheme 3.2.11, this sequence was successfully applied and followed by protection of the resultant diol. Oxidative cleavage of the terminal alkene delivered aldehyde **3-45**, which was subjected to the asymmetric alkynylzinc tandem 1,4-conjugate addition. For comparison purposes, the original route is also illustrated. Alcohol **3-42** was protected as the silyl ether, followed by oxidative cleavage and asymmetric alkynylzinc addition tandem 1,4-conjugate addition to yield 2,6-*cis*-tetrahydropyran **3-47**.

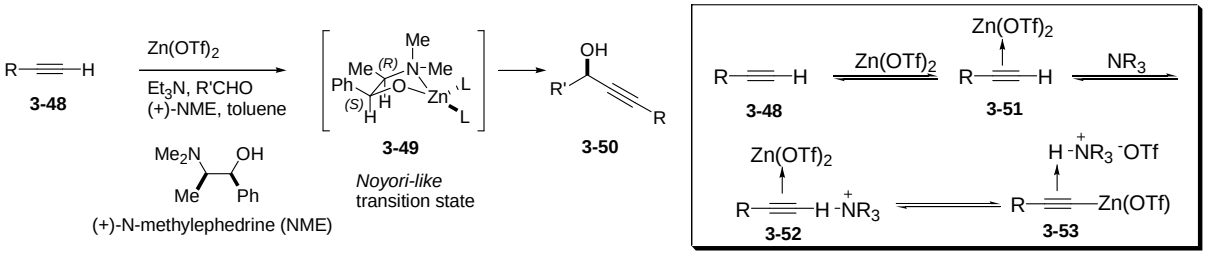


Scheme 3.2.11. Revised Synthesis of 2,6-*cis* Tetrahydropyran **3-46**

The yield of the zinc triflate-mediated asymmetric alkynylzinc addition is dependent on a variety of factors. First, the zinc triflate purchased from Aldrich chemical company gave inconsistent results, while material obtained from Strem was reliable. It was necessary to dry this reagent under vacuum (0.2 mm Hg) at 110 ^{o}C overnight; *N*-methylephedrine must also be dried under vacuum, but not heated. In addition, it was determined that performing the reaction under dilute conditions led to poor conversion and using the previously described drying precautions increased the reliability and yield of this reaction.

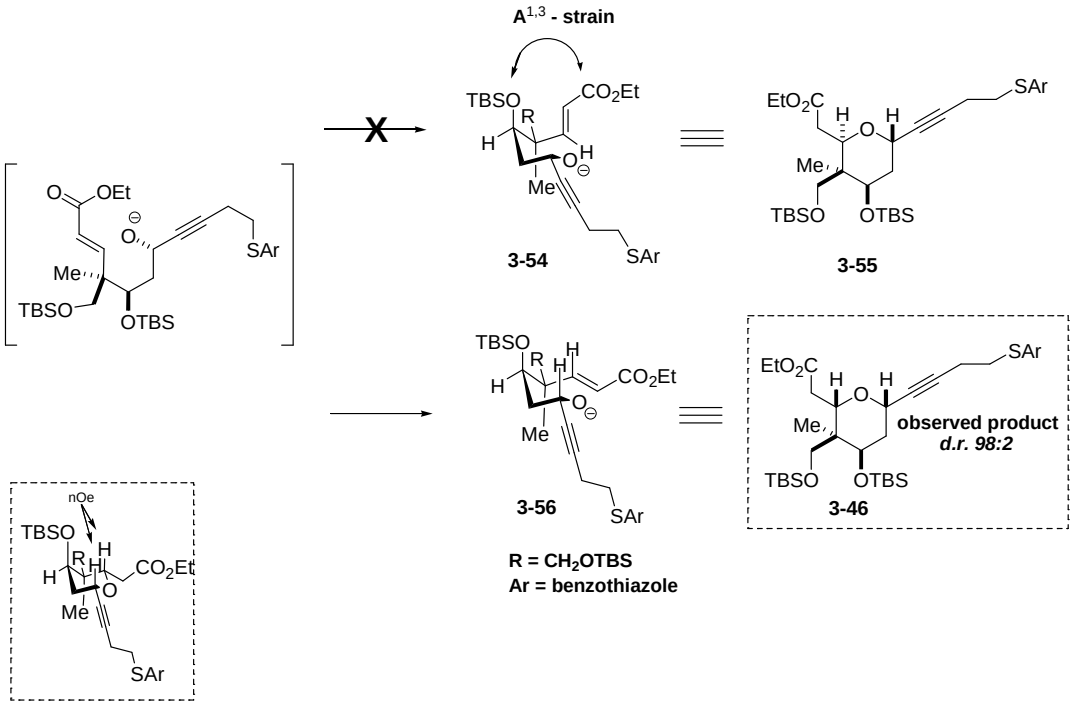
While the mechanism of the reaction remains unclear, it is hypothesized that coordination of the metal with the alkyne generates species **3-51**, which increases the acidity of the terminal alkyne (Scheme 3.2.12).[50] This coordination allows for a weak amine base, such as triethylamine, to deprotonate the terminal alkyne and form the *sp*-hybridized anion, producing zinc acetylide **3-53**. In the presence of

optically pure *N*-methylephedrine, chiral propargylic alcohols species **3-50** are isolated in high enantiomeric excess (92-98%).



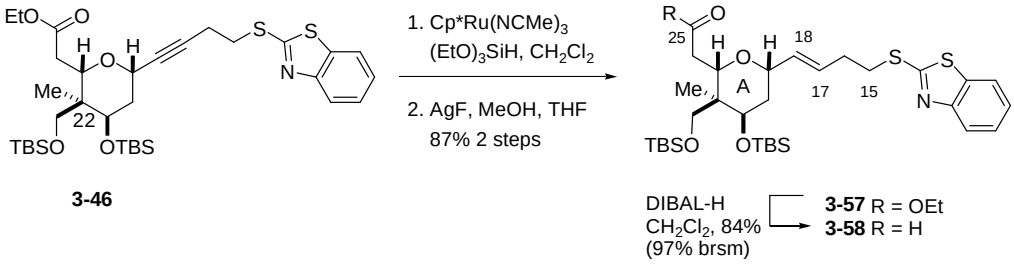
Scheme 3.2.12. Mechanistic Hypothesis of the Alkynyzinc Addition Proposed by Carreira

The rationale for the observed selectivity involving the formation of 2,6-*cis* tetrahydropyran **3-46** is shown in Scheme 3.2.13. Upon asymmetric alkynylzinc addition, a number of puckered conformations may be adopted *en route* to 1,4-conjugate addition. Two chair conformations can be visualized, where a diaxial interaction exists in conformer **3-54** involving the bulky *t*-butyldimethylsilyl ether and the α,β-unsaturated ester. In conformer **3-56**, this nonbonding interaction is minimized, leading to the observed 2,6-*cis* tetrahydropyran **3-46**. A combination of COSY and NOESY NMR analysis confirmed the stereochemistry of the isolated product.



Scheme 3.2.13. Rational for Selectivity Observed in the Formation of 2,6-*cis* Tetrahydropyran **3-46**

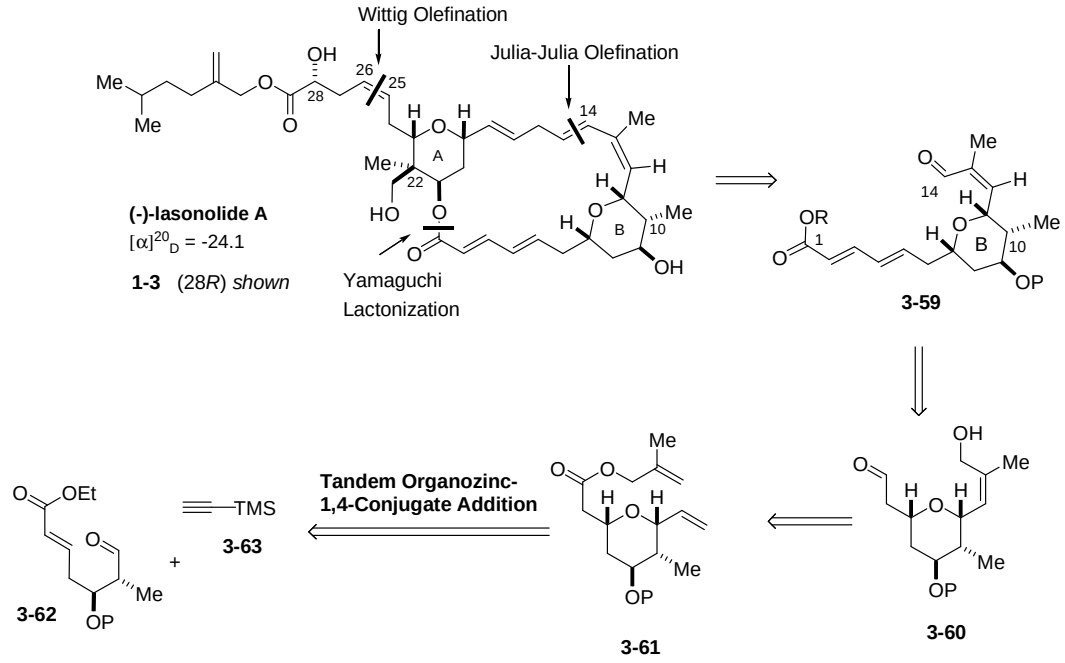
A *trans*-hydrometalation[51] and subsequent protodemetalation[52] was used to achieve a two-step net *trans* reduction of alkyne **3-46** to olefin **3-57** (Scheme 3.2.14). The ester was reduced to the corresponding aldehyde **3-58**, which completed the C15-C25 segment of (-)-lasonolide A.



Scheme 3.2.14. Installation of the C17-C18 *trans* olefin

3.3 B Ring: Synthesis of the C1-C14 Segment

On the basis of the success of the tandem alkynylzinc-hetero 1,4-conjugate addition utilized to construct the A-ring, the strategy was to be similarly applied to the synthesis of the C1-C14 B-ring segment **3-59** of (-)-lasonolide A (Scheme 3.3.1). Pivotal intermediate **3-60** could be formed via reduction of the ring-closing metathesis (RCM) product obtained from **3-61**.

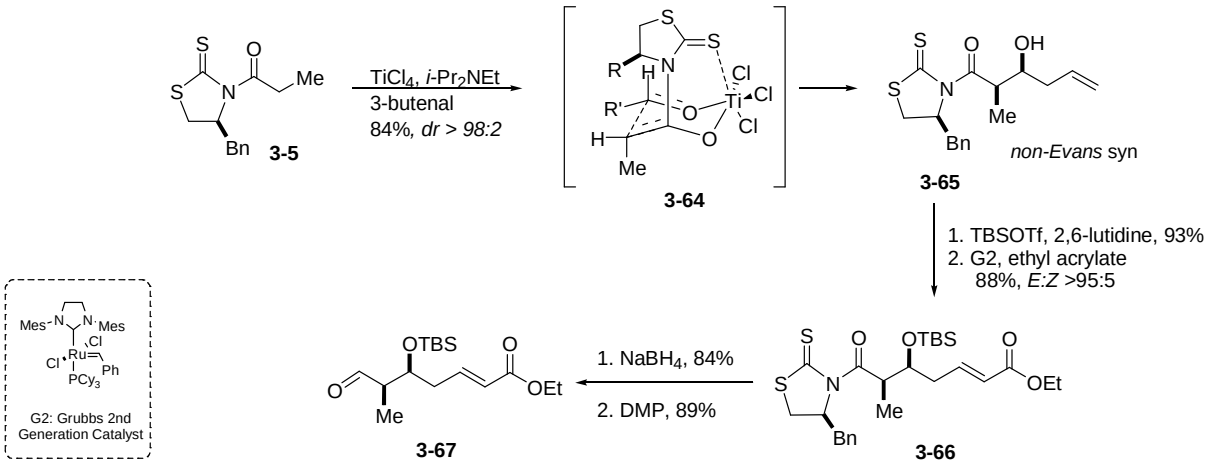


Scheme 3.3.1. Retrosynthetic Analysis of C1-C14 Segment of (-)-lasonolide A

3.3.1 Exploiting the Non-Evans Syn Aldol

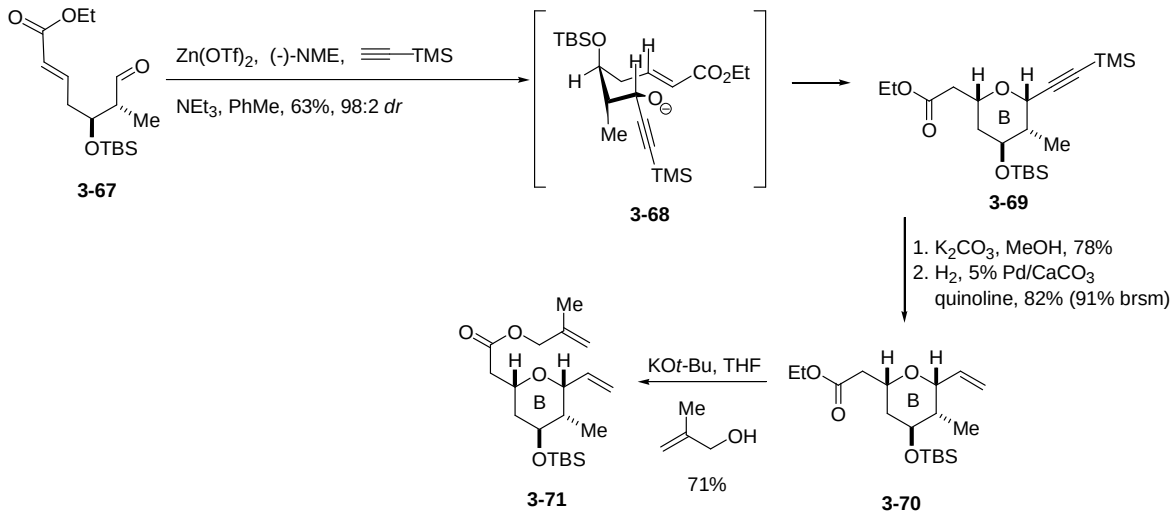
The construction of ester **3-62** began with formation of non-Evans *syn* aldol adduct **3-65**, which was obtained via chelated transition state **3-64**.[53] Protection as

the silyl ether was followed by cross-metathesis to provide α,β-unsaturated ester **3-66**. A reduction-oxidation sequence was used to acquire aldehyde **3-67** and allow the ester to remain intact.



Scheme 3.3.2. Synthesis of Aldehyde 3-67 via *Non-Evans syn* Aldol

Requisite aldehyde **3-67** was subjected to an asymmetric zinc-mediated alkyne addition to yield 2,6-*cis*-tetrahydropyran **3-69** presumably through transition state **3.68** (Scheme 3.3.3). Pyran **3-69** was elaborated to metathesis precursor **3-71** via a three-step sequence. Deprotection of the acetylene was readily achieved under standard conditions and the terminal olefin was obtained through hydrogenation of the alkyne in the presence of Lindlar's catalyst. Numerous conditions were used to instigate transesterification with methallyl alcohol, but potassium *t*-butoxide conferred the cleanest reaction.

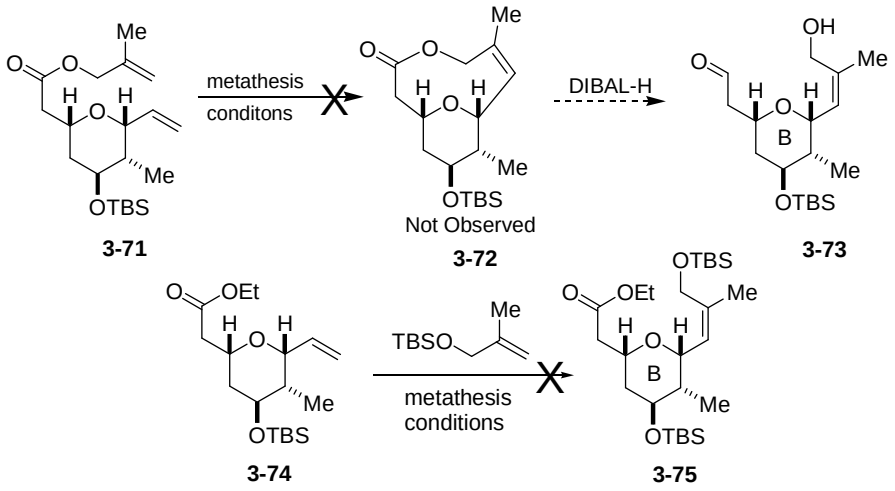


Scheme 3.3.3. Synthesis of Diene **3-71** via Zinc-mediated Alkyne Addition

3.3.2 Installation of the C12-C13 Trisubstituted Olefin

3.3.2.1. Ring Closing Metathesis Approach

Efforts to obtain the nine-membered ring closing metathesis product **3-72** led only to dimerization of the terminal olefin (Scheme 3.3.4). Further attempts to form the trisubstituted olefin via cross-metathesis also led to dimerization of **3-71** at the terminal olefin.



Scheme 3.3.4. Metathesis Reactions Involving Diene **3-71**

3.3.2.2. Nozaki Hiyama Kishi Reaction

Since lactone **3-72** was never isolated, a new strategy was devised for the addition of an organochromium compound to aldehyde **3-67** which could directly install the trisubstituted olefin. These reaction conditions were originally described by Nozaki and Hiyama as a method for vinylic C-C bond formation, while Kishi later found that nickel salts exhibit a catalytic effect on the formation the C-Cr bond.[54]

Trisubstituted vinyl iodide **3-76** was prepared via Grignard addition to propargyl alcohol and subsequent protection of the resulting allylic alcohol. The alkenylchromium reagent was prepared from protected vinyl iodide **3-76** by reduction with chromium(II) chloride under nickel catalysis (Scheme 3.3.5). This reaction proved problematic. Since the reaction is known to be particularly solvent-dependent, numerous attempts were made to increase the yield by varying reaction conditions as highlighted in Table 3.3.1. In addition, use of ligand **3-79,** constructed following Kishi's procedure,[55] resulted in the wrong diastereomer (confirmed by

Mosher ester analysis and NMR after conversion to the pyran under Michael conditions). This was not surprising, since previous examples of vinyl additions involving this ligand and α-methyl-substituted aldehydes have not been reported.

Probing whether substrate control could result in higher steric bias towards the desired diastereomer, the reaction was allowed to proceed without ligand **3-79**. As shown in Table 3.3.1, the yields increased, but no stereoselectivitiy was observed.

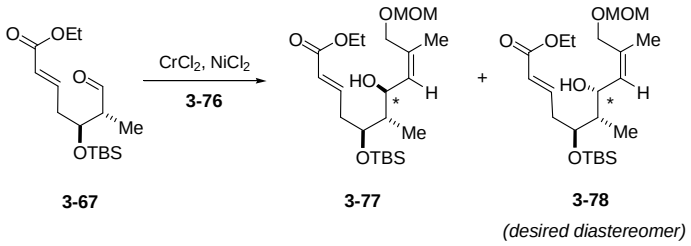
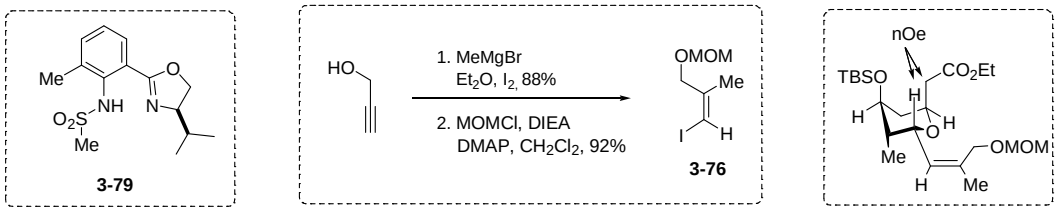


Table 3.3.1. Organochromium Addition

Ligand	Solvent	Yield	Selectivity 3-77:3-78
3-79	DMSO	56%	2:1
3-79	THF	45%	2.5:1
3-79	DMF	30%	1.3:1
3-79	EtCN	33%	2.4:1
3-79	THF:EtCN (6:4)	44%	2.2:1
3-79	THF:DMF:*t*-BuPy (6:3:1)	N.R.	
none	DMSO	62%	1.2:1
none	THF	41%	~1:1
none	THF:DMF:*t*-BuPy (6:3:1)	73%	~1:1

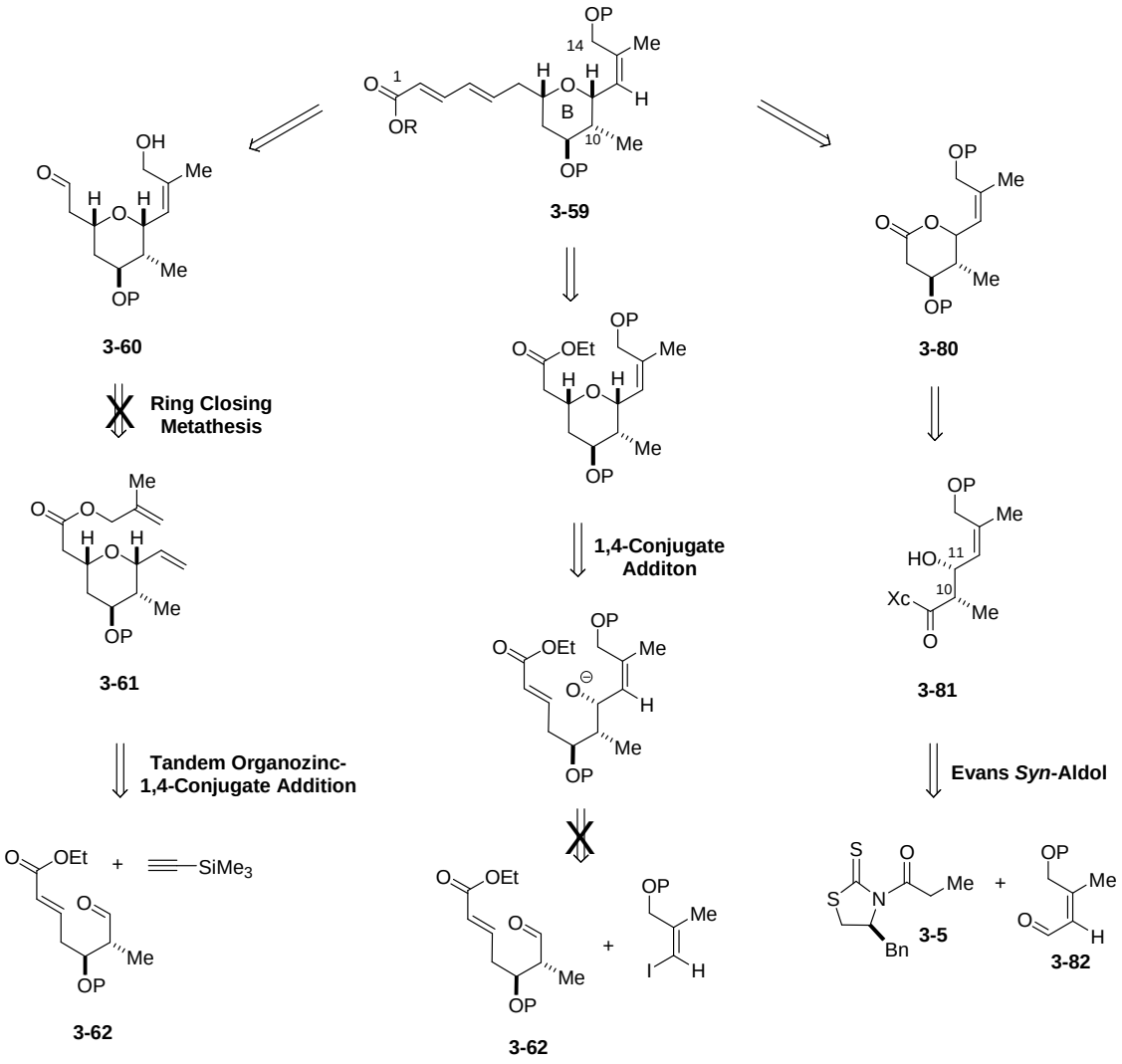


Scheme 3.3.5. Organochromium Addition Involving Aldehyde **3-67**

3.3.3 Revised Approach to the C1-C14 Segment

After additional attempts to install the trisubstituted olefin via stereoselective addition to aldehyde **3-62,** or addition to the corresponding Weinreb amide surrogate, it was apparent the route should be abandoned. An alternate route to

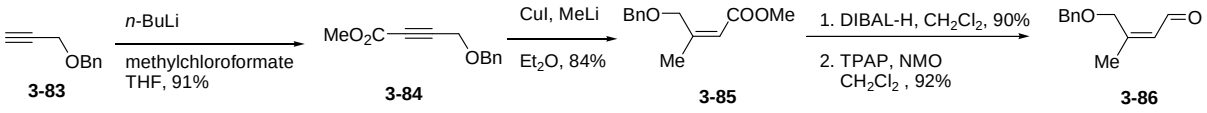
tetrahydropyran B was investigated that relied on an Evans *syn* aldol involving vinylic aldehyde **3-82** (Scheme 3.3.6). A boron-mediated 1,3-*syn* reduction would then be used to install the oxygenated stereocenter at C9.



Scheme 3.3.6. Revised Retrosynthetic Analysis *en route* to C1-C14 Segment **3-59**

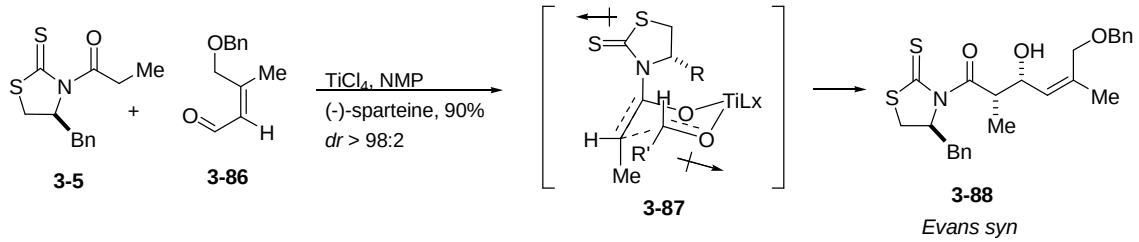
3.3.4 Evans Syn Aldol Involving a *Vinylic Aldehyde*

Aldehyde **3-86** was prepared in three steps from benzyl propargyl ether (Scheme 3.3.7). Upon carbomethoxylation, the corresponding α,β-acetylenic ester **3-84** was treated with a Gilman reagent to form the trisubstituted α,β-unsaturated ester **3-85**.[56] Reduction of the ester moiety was followed by oxidation to yield trisubstituted α,β-unsaturated aldehyde **3-86**.



Scheme 3.3.7. Preparation of Aldehyde **3-86**

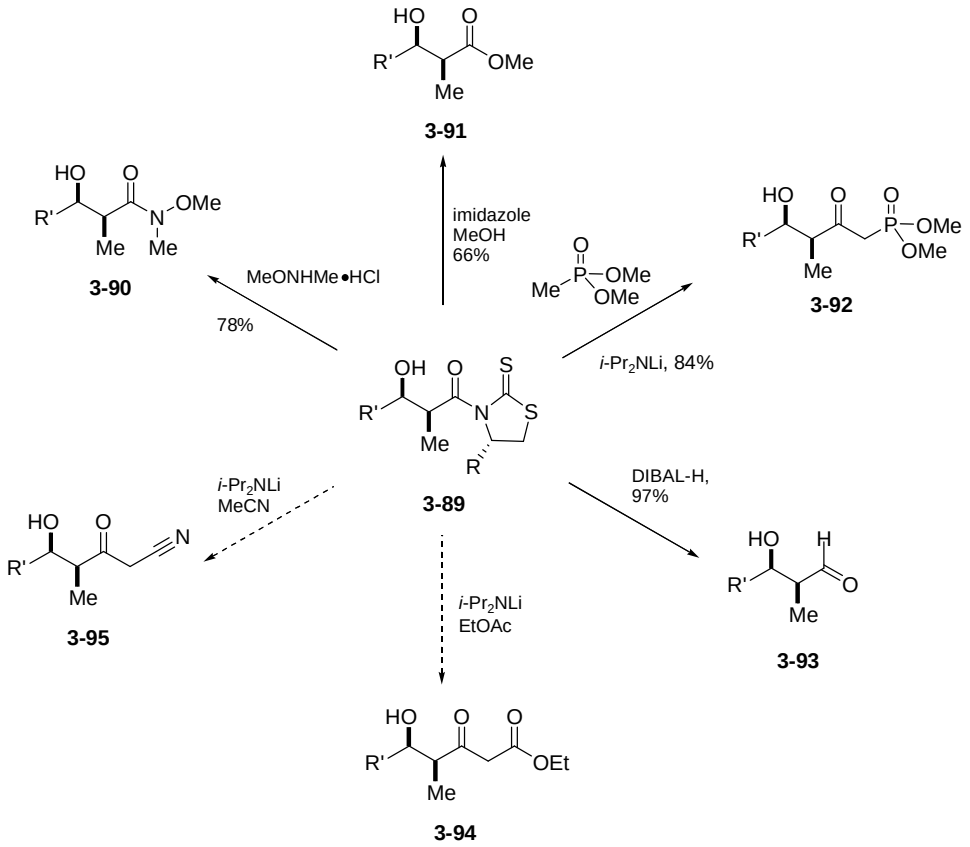
Aldehyde **3-86** was added to the chlorotitanium enolate of *N*-acyl thioimide **3-5** to form Evans *syn* aldol adduct **3-88** in 90% yield and 98:2 diastereoselectivity (Scheme 3.3.7). At this point aldol adduct **3-88** required a two-carbon homologation in order to complete the carbon framework of lactone **3-80** (Scheme 3.3.5).



Scheme 3.3.7. Evans *syn* Aldol Adduct **3-88** via *N*-thioimide **3-5**

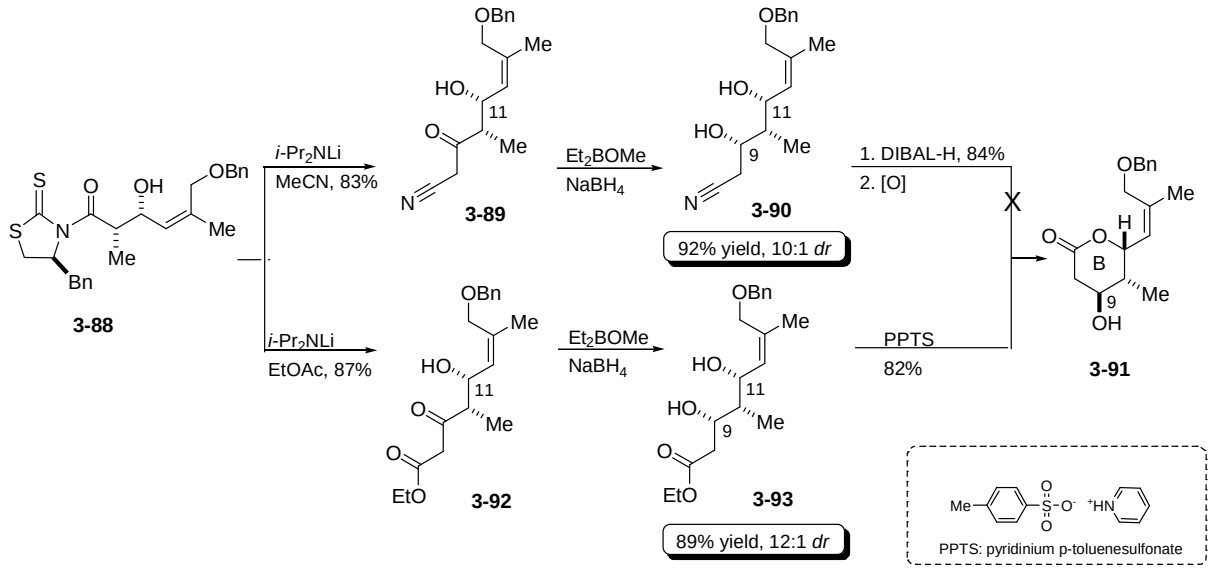
3.3.5 Extending the Versatility of the Thiazolidinethione Auxiliary

The *N*-acyl thioimide auxiliary, unlike traditional oxazolidinone variants, is easily removed from aldol adducts via nucleophillic addition to provide a variety of functional groups as shown in Scheme 3.3.8.[57] For example, Weinreb amide derivative **3-90** and ester **3-91** are formed in moderate yield, while DIBAL-H reduction affords aldehyde **3-93** in high yield. After it was discovered methyl phosphonate could directly displace the auxiliary to form β-ketophosphonate **3-92**, alternate carbon nucleophiles were explored to prepare homologated products, particularly β-ketonitrile **3-95** and β-ketoester **3-94**, for the construction of lactone **3-80**.



Scheme 3.3.8. Displacement of the N-thioimide Auxiliary

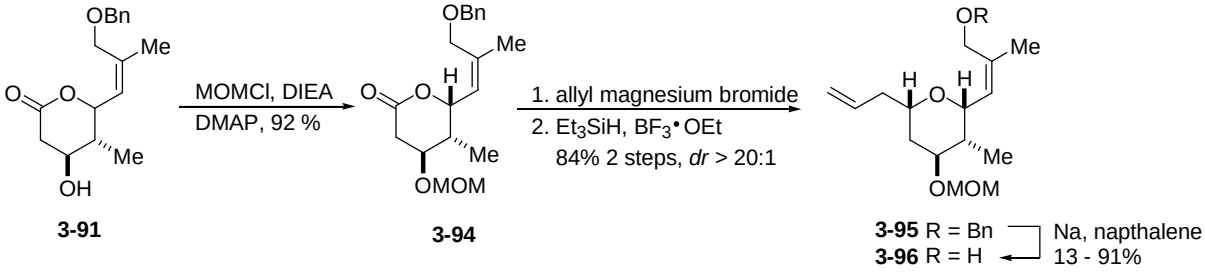
After some experimentation, *N*-acyl thioimide aldol adduct **3-88** was treated with lithiated acetonitrile to give the β-ketonitrile **3-89** (Scheme 3.3.9). Reduction of β-ketonitrile **3-89** set the stereochemistry at C9. Nitrile **3-90** was then reduced, followed by *in situ* formation of the hemiacetal. However, all attempts at selective oxidization to lactone **3-91** in the presence of the secondary alcohol failed with this substrate. A more direct route was explored; where the lithium enolate of ethyl acetate was utilized as a nucleophile in the displacement of *N*-acyl thioimide aldol adduct **3-88**. Reduction of β-ketoester **3-93** set the stereochemistry at C9, and subsequent exposure to PPTS in refluxing benzene afforded lactone **3-91**.



Scheme 3.3.9. Displacement of the *N*-Thioimide Auxiliary

Alcohol **3-91** was protected to give **3-94**, which was treated with allylmagnesium bromide to give the corresponding hemiketal (Scheme 3.3.10). Further reduction with triethylsilane and boron trifluoride etherate furnished *cis*-

substituted pyran **3-95** in 84% yield and >20:1 diastereoselectivity.[58] A variety of protocols were employed to remove the benzyl group including Lewis acids and DDQ, but only dissolving metal conditions cleanly provided allylic alcohol **3-96**, albeit in widely varying yields.

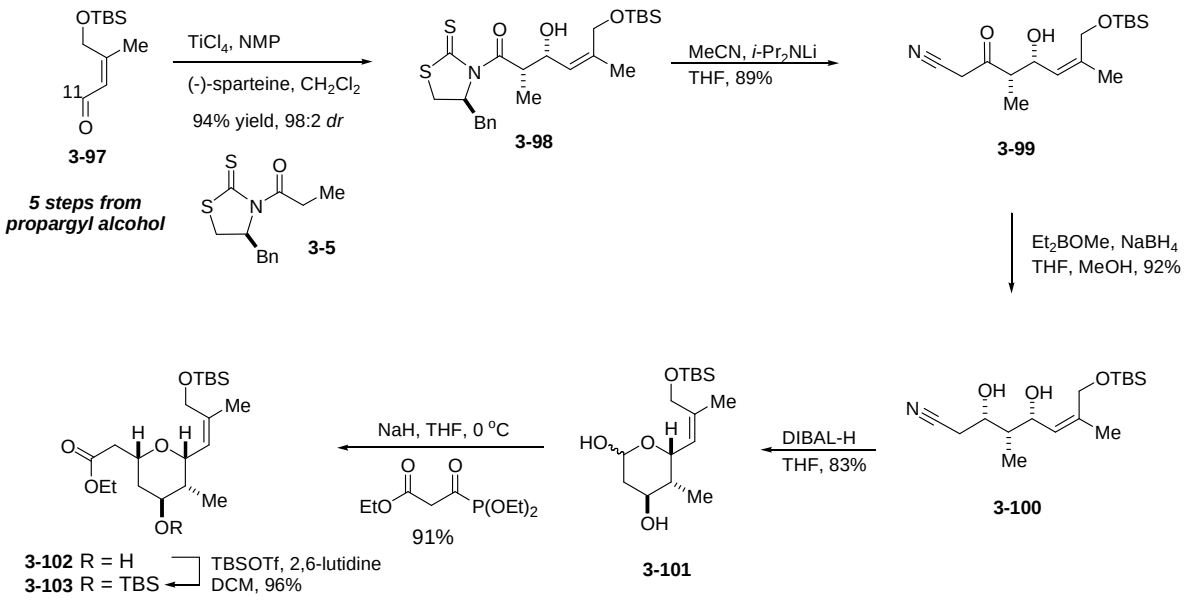


Scheme 3.3.10. 2,6-*cis*-tetrahydropyran **3-95** via Nucleophillic Addition to Lactone

After the synthesis of 2,6-*cis*-tetrahydropyran **3-95** (Scheme 3.3.10), Jennings and coworkers published their work on the C1-C14 segment of (-)-lasonolide A (section 2.1.7). Because the nucleophillic addition to lactone **3-94** was similar to the protocol employed by Jennings and coworkers, and the benzyl deprotection was unreliable, an alternate synthesis from Jennings was pursued (Scheme 3.3.11).

Based upon previous success, aldehyde **3-97** was added to the chlorotitanium enolate of *N*-acyl thioimide **3-5** to form Evans *syn* aldol adduct **3-98** in good yield and excellent selectivity. The thioimide auxiliary was displaced with lithiated acetonitrile, and further 1,3-*syn* reduction of β-ketonitrile **3-99** set the stereochemistry at C9. Nitrile **3-100** was reduced, followed by *in situ* formation of the hemiacetal. A Horner-Wadsworth-Emmons olefination and *in situ* 1,4-conjugate addition furnished 2,6-*cis*-tetrahydropyran **3-102** as one diastereomer as detected by

^{1}H and ^{13}C NMR.[59] Protection of the secondary alcohol as the silyl ether supplied **3-103.**



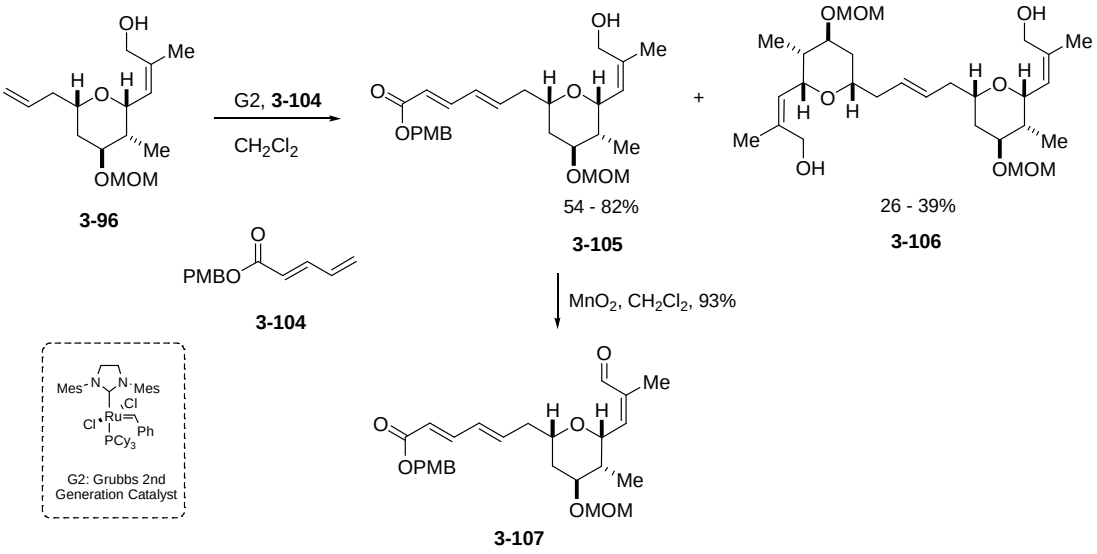
Scheme 3.3.11. 2,6-*cis*-tetrahydropyran **3-101** via Horner-Wadsworth-Emmons Protocol

3.3.6 Installation of the C2-C5 Diene

Two strategies were explored to install the C2-C5 diene based on homologation of **3-96** or **3-102**. The first involved a cross-metathesis and the other involved a Horner-Wadsorth-Emmons protocol.

3.3.6.1. Cross-Metathesis Approach

A cross-metathesis utilizing Grubbs' second generation catalyst and diene **3-104** was utilized to achieve extension of **3.96**.[60] In addition, varying amounts of dimer **3-106** were also isolated, and successfully recycled[61] to provide additional **3-105**. A mild allylic oxidation with manganese dioxide gave aldehyde **3-107**.

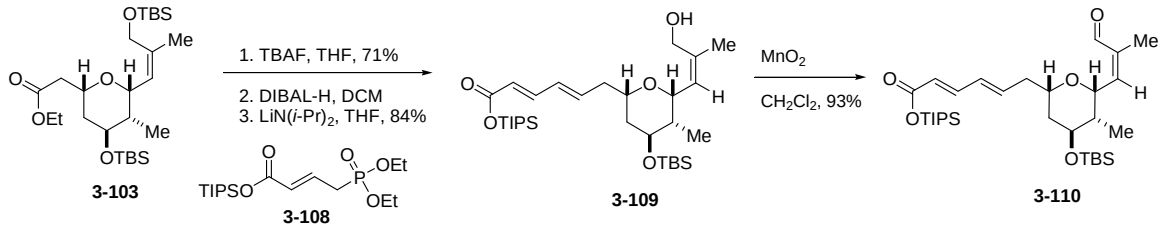


Scheme 3.3.12. Homologation to Diene via Cross-Metathesis

3.3.6.2. Horner-Wadsworth-Emmons Approach

To extend ester **3-102**, a Horner-Wadsorth-Emmons protocol utilizing phosphonocrotonate **3-108** was employed.[62] The allylic alcohol was deprotected using tetrabutylammonium fluoride (TBAF) at 0 ^{o}C, and the ester was reduced to the corresponding aldehyde by careful addition of diisobutylaluminum hydride. The

aldehyde was immediately subjected to the lithium anion of phosphonate **3-108**[63] to provide the C1-C14 segment **3-110** after oxidation with manganese dioxide.

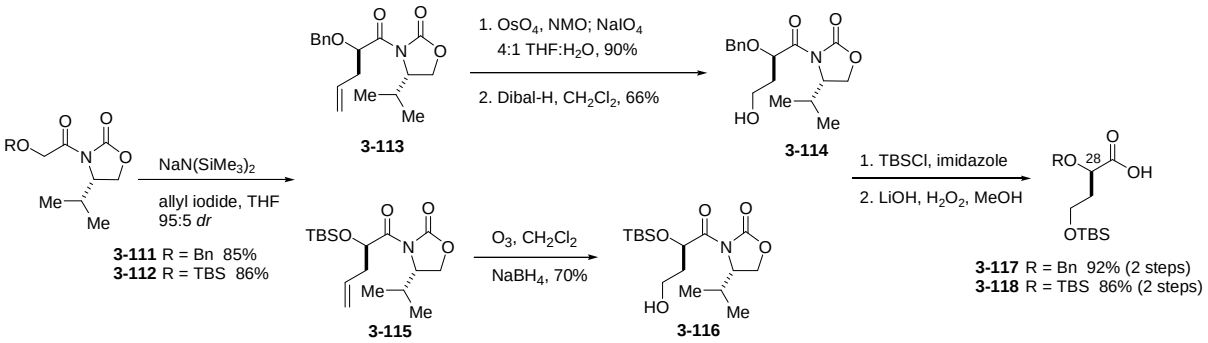


Scheme 3.3.13. Homologation to Diene via Horner-Wadsworth-Emmons Protocol

3.4 Side Chain: Synthesis of the C26-C35 Segment

3.4.1 Glycolate Alkylation Approach

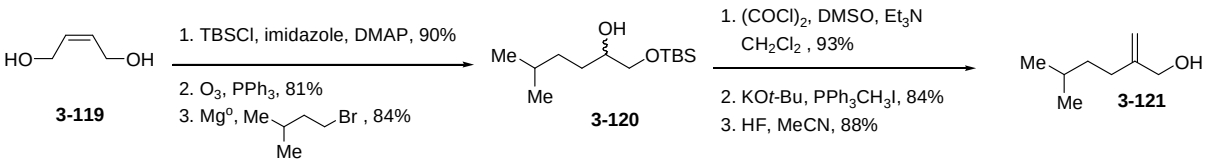
The C28 stereogenic center present in the side chain was installed via asymmetric alkylation of the sodium enolate of glycolate **3-111** (R = Bn) or glycolate **3-112** (R = TBS) with allyl iodide to stereoselectively provide **3-113** or **3-115**, respectively (Scheme 3.4.1).[64] The side chain synthesis was initiated with benzyl glycolate **3-111**, but after troublesome late-stage benzyl deprotection (section 3.5), it was deemed necessary to reconstruct the side chain beginning with silyl glycolate **3-112**.



Scheme 3.4.1. Glycolate Alkylation to Install the C28 Stereocenter

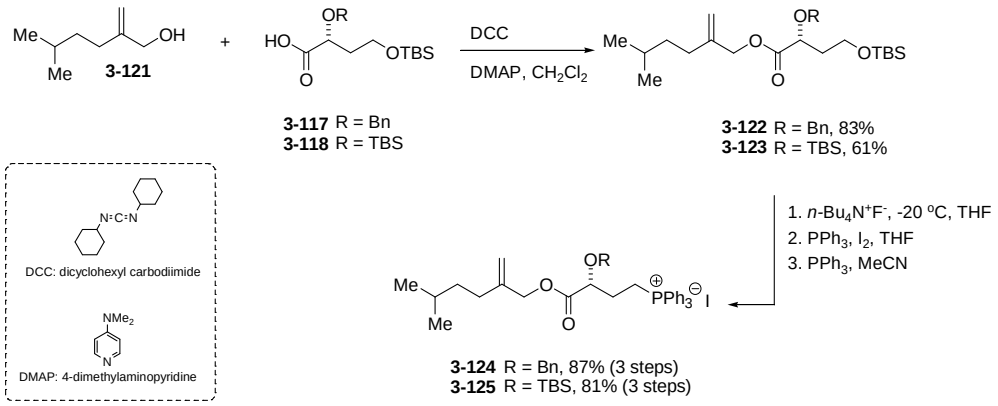
Glycolate alkylation product **3-113** was subjected to a two-step oxidative cleavage sequence and subsequent reduction to yield primary alcohol **3-114**, while product **3-115** was subjected to ozonolysis and *in situ* reduction to yield the corresponding alcohol. Alcohols **3-114** and **3-116** were protected as the *t*-butyldimethylsilyl ether and hydrolyzed to yield acids **3-117** and **3-118**, respectively.

Following a protocol similar to Lee, alcohol **3-121** was assembled in six steps from 2-butenediol **3-119**. *Bis*-silyl protection, ozonolysis, and Grignard addition provided racemic alcohol **3-120**. Swern oxidation of alcohol **3-120** to the ketone followed by a methylene Wittig reaction furnished the 1,1-disubstituted olefin. Desilylation with hydrofluoric acid in acetonitrile supplied alcohol **3-121** necessary for the side chain esterification.



Scheme 3.4.2. Construction of alcohol **3-121**

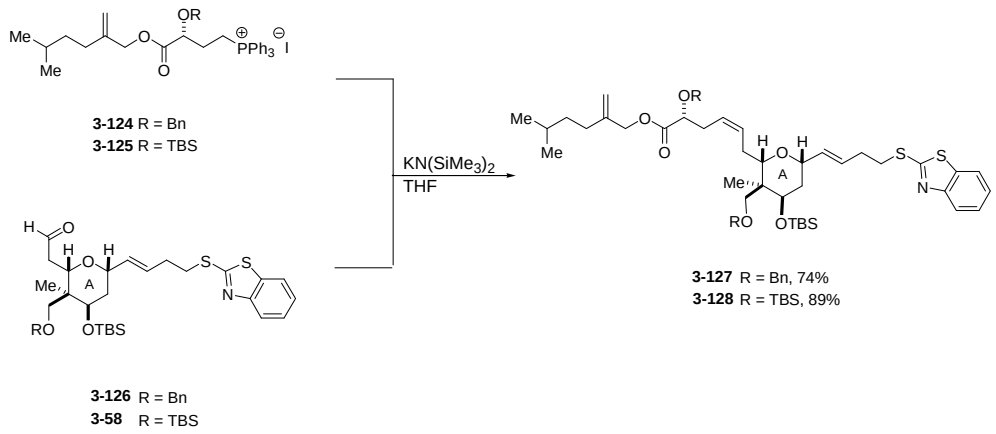
A DCC-mediated coupling of alcohol **3-121** with acids **3-117** and **3-118** afforded esters **3-122** and **3-123**, respectively (Scheme 3.4.3). The primary alcohols were liberated, converted to the corresponding iodide, and subsequently to their phosphonium salts **3-124** and **3-125**.



Scheme 3.4.3. Assembly of the Phosphonium Salt of the Side Chain

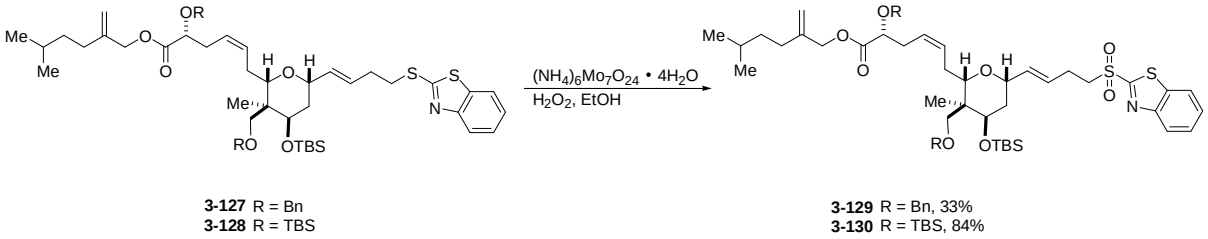
3.5 Coupling Strategies

A variety of substrates were utilized in an effort to construct the carbon backbone of (-)-lasonolide A. The initial approach involved the coupling of benzyl-protected phosphonium salt **3-124** and benzyl-protected aldehyde **3-126** using a standard Wittig olefination protocol to provide coupled product **3-127** (Scheme 3.5.1).



Scheme 3.5.1. Wittig Olefination: Coupling the A-Ring and the Side-Chain

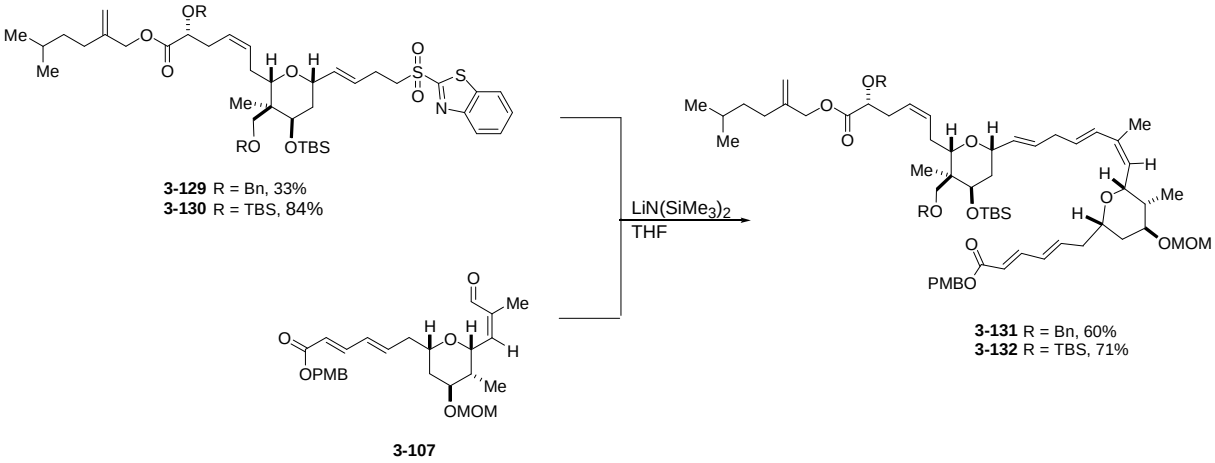
Oxidation of sulfide **3-127** to sulfone **3-129** (Scheme 3.5.2) allowed for Julia olefination[65] with PMB-protected aldehyde **3-107** providing intermediate **3-131** (Scheme 3.5.3).



Scheme 3.5.2. Oxidation of the Sulfide to the Sulfone

Substrate **3-131** was treated with HF-pyridine to deprotect the secondary TBS ether and trifluoroacetic acid to liberate the PMB-protected acid, and subjected to Yamaguchi macrolactonization conditions.[66] Disappointingly, the resulting NMR spectra showed impurities despite purification via HPLC. Regardless, the material generated was subjected to hydrogenation conditions (H_2/Pd-C, THF), dissolving metal reduction (Na/NH_3, LDBB), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),

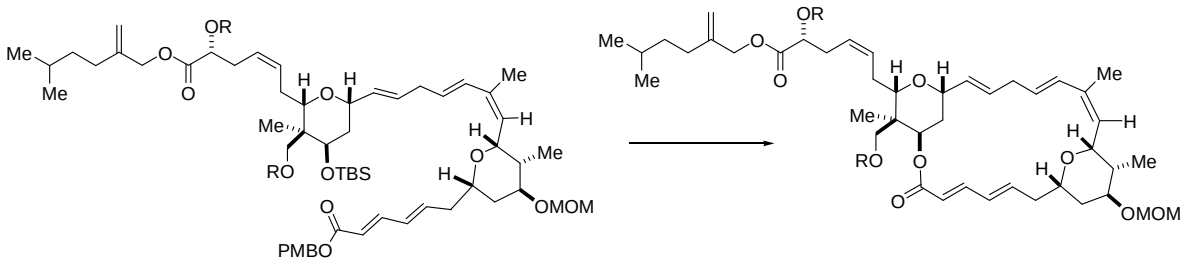
and Lewis acids (BCl_3, $SnCl_4$, $BF_3{\cdot}OEt_2$). Unfortunately, all attempts at late-state benzyl-deprotection of **3-133** did not result in the isolation of (-)-lasonolide A. After this disappointing result, it was necessary to construct the segments using different protecting groups, such as silyl ethers, that did not require such a rigorous late-stage deprotection.



Scheme 3.5.3. Julia Olefination: Appending the B-Ring

Thus, after reconstructing the silyl-protected fragments, the anion of TBS-protected phosphonium salt **3-125** was reacted with TBS-protected aldehyde **3-58** to provide coupled intermediate **3-128** (Scheme 3.5.1). Oxidation of sulfide **3-128** provided sulfone **3-130** (Scheme 3.5.2). Julia olefination with aldehyde **3-107** afforded polyene **3-132** (Scheme 3.5.3). Unfortunately, liberation of the PMB-protected acid from this substrate with trifluoroacetic acid suffered from poor results and did not lead to the successful isolation of the desired macrolactone **3-134** (Scheme 3.5.4). Numerous attempts involving a variety of deprotection conditions

exhausted supplies of **3-132**, and prompted further reconsideration of the final deprotection strategy of the macrolactone precursor.

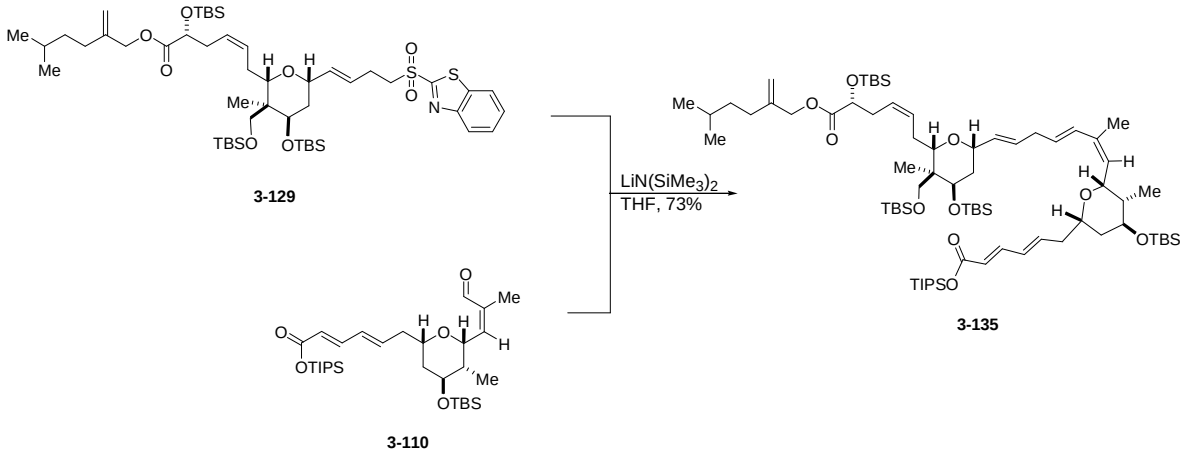


3-131 R = Bn
3-132 R = TBS

3-133 R = Bn
3-134 R = TBS

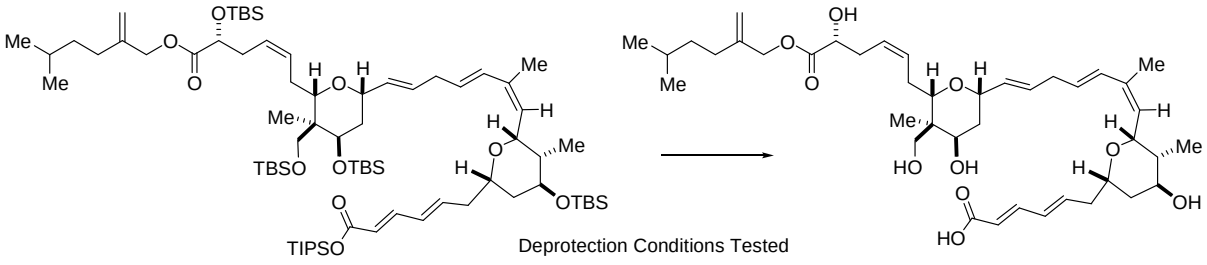
Scheme 3.5.4. Late-Stage Deprotection-Macrolactonization Strategy with PMB-Protected Acid

Since deprotection of the PMB-protected acid proved problematic, it was reasoned that a TIPS-protected acid would offer a wider range of deprotection conditions to test. Therefore, intermediate **3-129** was prepared once more and coupled with aldehyde **3-110** to afford silyl protected intermediate **3-135** (Scheme 3.5.5). However, another challenge was encountered during the ensuing deprotection-macrolactonization sequence.



Scheme 3.5.5. Julia Olefination: Appending the Silyl-Protected B-Ring

Previous attempts at deprotection and macrolactonization at a scale necessary for detection by ^{1}H NMR quickly consumed material, therefore a different tactic had to be utilized to minimize fast consumption of precious intermediate **3-135**. Experiments were performed on μg – mg scale, and analyzed by mass spectrometry (Scheme 3.5.6).



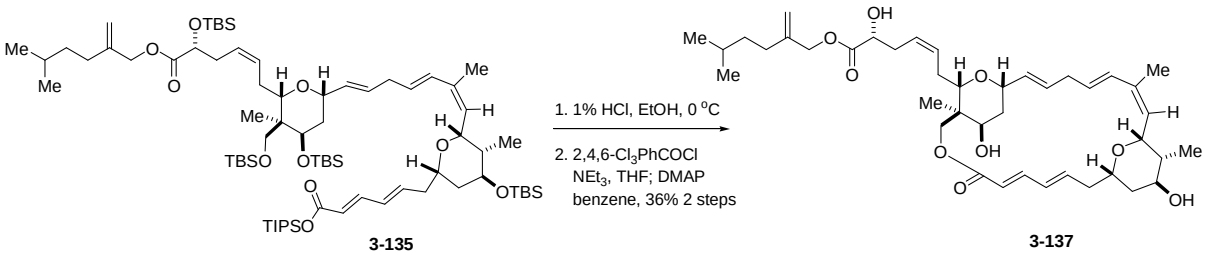
Deprotection Conditions Tested

Fluoride Sources	Acidic Conditons
HF/pyridine, THF	1% HCl, EtOH
HF/MeCN	1% H_2SO_4, EtOH
TBAF	TsOH
H_2SiF_6, MeCN	CSA
TAS-F, DMF	PPTS
	TFA

Scheme 3.5.6. Late-Stage Deprotection-Macrolactonization Strategy with TBS-Protected Acid

Deprotection strategies involving fluoride sources led to decomposition, while experiments involving acid sources led to varied results. In each case, the liberation of the acid moiety occurred based on the mass spectra results. Using 1% HCl in EtOH resulted in full deprotection, while reactions involving PPTS, CSA, and TsOH resulted in products with various silyl groups remaining intact. Each of the products isolated were subjected to Yamaguchi macrolactonization conditions.

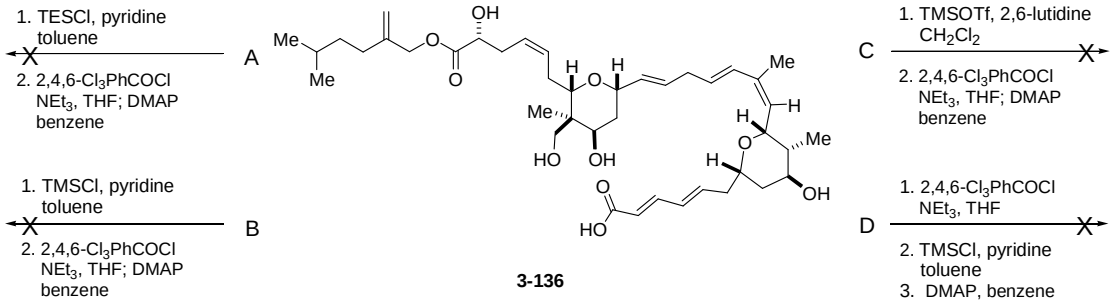
Based on promising mass spectral results of the products isolated from the Yamaguchi macrolactonization, increasing quantities of **3-135** were subjected to 1% HCl in EtOH and subsequent macrolactonization. After purification via HPLC, the ^{1}H NMR spectra of the isolated product was similar to the natural product, but unfortunately there were discrepancies from 2.5 – 4.0 ppm. Based on ^{1}H NMR and mass spectra, the isolated product could be **3-137**, resulting from macrolactonization with the less-hindered primary alcohol.



3-135 **3-137**

Scheme 3.5.6. Macrolactonization Efforts

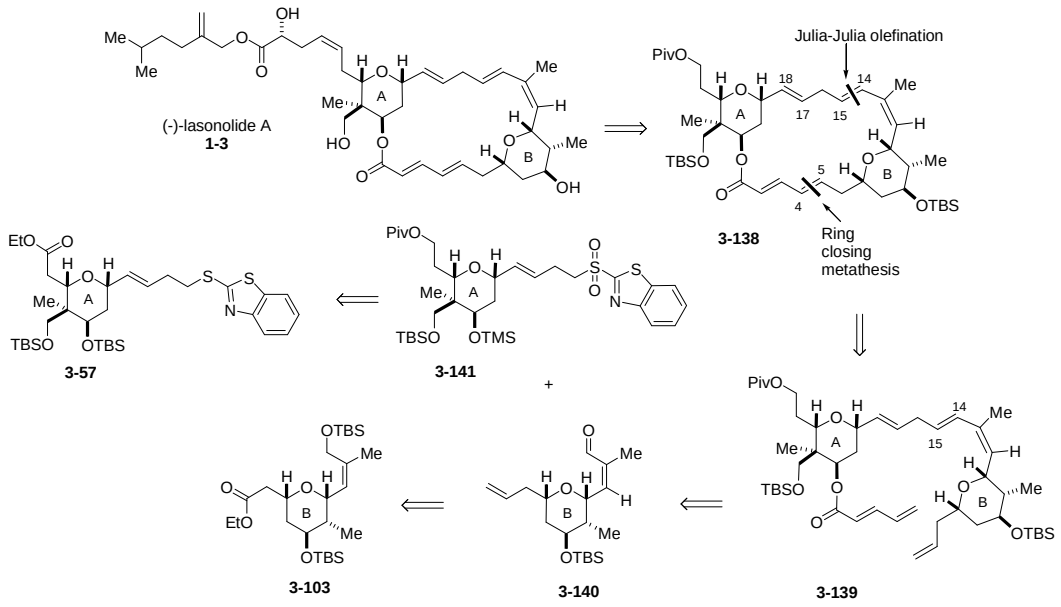
In an effort to inhibit cyclization leading to **3-137**, attempts were made to selectively protect the primary alcohol of intermediate **3-136** (Scheme 3.5.7, A - C). The material was subjected to various silylation conditions (TESCl, TMSCl, TMSOTf) and subsequent Yamaguchi macrolactonization. However, the desired products were never isolated.



Scheme 3.5.7. Efforts Directed Toward Selective Protection of the Primary Alcohol

Another strategy (Scheme 3.5.7, D) involved formation of the mixed anhydride prior to silyl protection. After formation of the mixed anhydride, the reaction medium was filtered, concentrated *in vacuo*, and subjected to TMSCl/pyridine. The intermediate was dissolved in benzene and added via syringe pump to a solution of DMAP in benzene. Regrettably, the desired product was not isolated.

Based upon these unsatisfactory results, a new approach was considered to intercept macrolactone **3-138** and avoid a deprotection-macrolactonization sequence. The pivotal step would entail the ring-closing-metathesis (RCM) macrocyclization of polyene **3-139** to install the C4-C5 *trans* alkene (Scheme 3.5.8).[67]



Scheme 3.5.8. RCM-Macrocyclization Retrosynthetic Approach

Necessary aldehyde **3-140** was constructed from intermediate **3-103** in a four-step sequence involving reduction of the ester to the aldehyde with DIBAL-H, followed by a methylene Wittig to install the terminal olefin. Deprotection of the allylic alcohol with TBAF and oxidation with manganese dioxide provided aldehyde **3-140** for the Julia olefination.

In order to construct polyene **3-139** from tetrahydropyran **3-57**, the ester was reduced to the primary alcohol and protected as the pivaloate. Oxidation to the sulfone was achieved under standard conditions with ammonium heptamolybdate. A *bis*-TBS silyl deprotection was performed followed by selective protection of the primary alcohol with TBSCl and protection of the secondary alcohol with TMSOTf to provide intermediate **3-141**, which was reacted with aldehyde **3-140** utilizing NaHMDS.

The selective deprotection of the secondary TMS ether in the presence of the primary TBS ether utilizing acidic conditions (0.5M HCl, THF) or treatment with a fluoride source (H_2SiF_6, MeCN) proved problematic. In each instance, the diol resulted from concomitant liberation of the primary alcohol. After protecting the primary alcohol with TBSCl, the secondary alcohol was subjected to DCC-mediated esterification conditions to supply ring-closing-metathesis (RCM) macrocyclization precursor **3-139**. Preliminary experiments involving polyene **3-139** were performed in an effort to find suitable ring-closing-metathesis (RCM) macrocyclization reaction conditions. In particular, both Grubb's first and second generation ruthenium catalyst were employed in dichloromethane at ambient temperature and under reflux, but desired macrolide **3-138** was not isolated.

EXPERIMENTAL

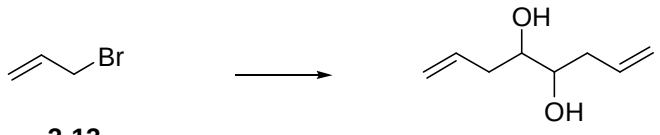
A. Materials and Methods

Infrared (IR) spectra were obtained using a JASCO FT/IR 460-plus. Proton and carbon nuclear magnetic resonance (^{1}H, ^{13}C NMR, COSY, NOESY) spectra were obtained on the following instruments: Bruker model DRX 300 (^{1}H at 300 MHz; ^{13}C at 75 MHz), Bruker model DRX 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz), and Bruker model DRX 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Chemical shifts are reported in ppm with internal references for ^{1}H NMR: $CHCl_3$ (7.26), C_6D_6 (7.15), CD_3OD (3.31) and deuterated solvent shifts for ^{13}C NMR $CHCl_3$ (77.0), C_6D_6 (128.06), CD_3OD (49.00). Multiplicities are reported as (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. Unresolved, overlapping resonances are reported as “band”. Coupling constants (*J*) are given in Hertz. Optical rotations were determined using a JASCO P-1010 polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) with nano-electrospray ionization. Thin layer chromatography (TLC) was conducted on silica gel 60 F_{254} TLC plates purchased from EMD Chemicals, Inc. Flash chromatography was performed using silica gel (60 Å, 40 to 63 μm) purchased from Sorbent Technologies, Inc. Diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene (PhMe) were dried by passing through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines and

benzene were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Anhydrous *N*,*N*-dimethylformamide (DMF) and *N*-methylpyrrolidinone (NMP) were purchased from Aldrich chemical company in 1L Sure/Seal^{TM} bottles. Titanium (IV) chloride was stored in a Schlenk flask under argon. Pivaloyl chloride was distilled and stored over 4Å molecular sieves. Titanium (IV) isopropoxide was distilled under reduced pressure and stored in a dark desiccator. Dess-Martin periodinane was prepared according to literature procedures and stored at -20 ºC. Zinc triflate $(ZnOTf)_2$ was purchased from Strem chemical company and dried in the reaction vessel for 12 h under vacuum (0.2 mmHg). The reaction vessel was placed in a 110 ^{o}C oil bath during the drying process. *N*-methylephedrine (NME) was dried for 12 h under vacuum (0.2 mmHg). All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were performed in flasks flame dried under vacuum, cooled under a positive flow of argon, and conducted under an argon atmosphere.

B: Experimental

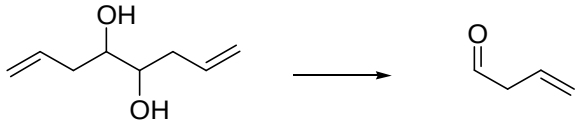
B-1. A-ring: C15-C25 Segment of (-)-lasonolide A:



3-13 **3-14**

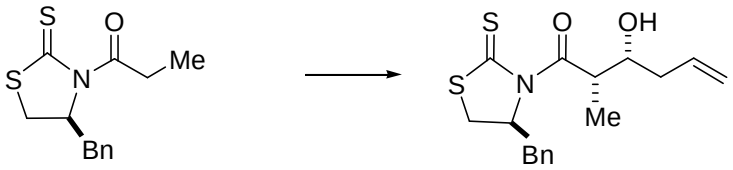
THF (130 mL), DI water (130 mL), allyl bromide (624 mmol, 54 mL), and 40% aqueous glyoxal (260 mmol, 30 mL) were added to a three-neck round-bottomed flask fitted with a mechanical stirrer and reflux condenser. Granular tin metal (624

mmol, 74g) was added in three portions. The suspension was stirred under ultrasonic irradiation (few ice cubes added to sonicator) for 2 h. The THF was removed *in vacuo* and 25% aq. KOH was added (60 mL). Solid NaCl and diethyl ether (350 mL) were added and the mixture was allowed to stir vigorously for 1 h. The thick suspension was filtered through celite using a large Buchner funnel under vacuum (aspirator). The filter pad was rinsed with excess Et_2O, and the combined ether washes were concentrated *in vacuo*. The residue was purified by gradient flash column chromatography, by eluting with 15%-25%-45% EtOAc/hexanes, to afford 31.75g (86%) of diol **3-14** as translucent, viscous oil.



3-14 **3-15**

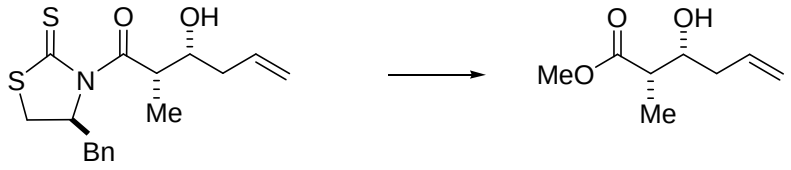
Diol **3-14** (77.01 mmol, 10.94 g) was dissolved in CH_2Cl_2 (40 mL) and pH = 4 buffer (40 mL). The flask was fitted with a mechanical stirrer and cooled in an ice bath. Sodium periodate (92.41 mmol, 20 g) was added and the suspension was stirred for 2 h. Aqueous 1:1 $Na_2S_2O_3$:$NaHCO_3$ was added and the mixture was stirred for 10 min. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x 10 mL). The combined organic extracts were washed with brine (2x) and dried over Na_2SO_4 with a septum and positive flow of argon. The flask was cooled to -78 ℃ awaiting transfer to the reaction vessel describ ed in the following procedure.



3-5 **3-12**

A stirring solution of (S)-4-benzyl-3-propionyl-1,3-thiazolidine-2-thione **3-5** (13.62 g, 51.34 mmol) in CH_2Cl_2 (350 mL) was cooled in an ice bath. $TiCl_4$ (5.91 mL, 53.9 mmol) was added at once, turning the solution a yellow-orange hue. After stirring the mixture for 20 min, (-)-sparteine (11.8 mL, 51.34 mmol) was added at once converting the solution to a purple-brown hue. After stirring the mixture for 20 min, *N*-methyl-2-pyrrolidinone (NMP) (5.0 mL, 51.34 mmol) was added dropwise. After stirring the mixture for 20 min the solution was cooled to -78 ℃ and pre-cooled 3-butenal **3-15** was added as a solution in CH_2Cl_2. The homogeneous reaction mixture was stirred at -78 ℃ for 4 h, and then warmed in a n ice bath. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously while warming to room temperature. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 16.68 g (97%) of aldol **3-12** as a bright-yellow colored, viscous oil. ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.32 (dd, *J* = 9.11, 5.72 Hz, 2H), 7.30-7.23 (m, 4H), 5.77 (dd, *J* = 17.10, 10.14 Hz, 1H), 5.32 (ddd, *J* = 10.80, 7.06, 3.91 Hz, 1H), 5.12 (dd, *J* = 14.11, 5.67 Hz, 2H), 4.48 (dd, *J* = 6.82, 3.48 Hz, 1H), 4.01-3.95 (m, 1H), 3.37 (dd, *J* = 11.45, 7.04 Hz, 1H), 3.19 (dd, *J* = 13.18, 3.83 Hz, 1H), 3.02 (dd, *J* = 13.17, 10.54 Hz, 1H), 2.88 (d, *J* = 11.53 Hz, 1H), 2.27 (t, *J* = 7.48 Hz, 1H), 2.25-2.17 (m, 1H),

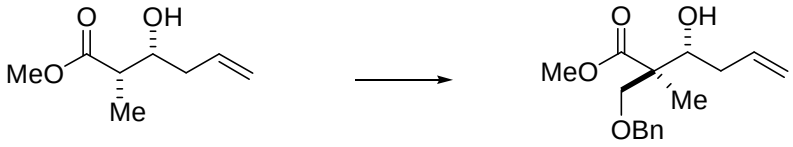
1.21 (m, 12H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 201.131, 177.893, 173.045, 136.248, 134.095, 129.346, 128.836, 127.189, 118.144, 95.242, 77.177, 77.126, 76.968, 76.923, 76.669, 71.459, 68.680, 42.617, 38.771, 36.651, 31.977, 29.616, 14.056, 10.626; IR (film) 3442.94, 2926.01, 1689.64, 1494.83, 1454.33, 1361.74, 1342.46, 1261.45, 1192.01, 1165, 1136.07, 1029.99, 918.12, 744.52, 702.09 cm^{-1}; MS calculated for $C_{17}H_{21}NO_2S_2$ $[M + Na]^+$: 358.1, found 358.3; $[\alpha]^{24}_D$ = +151.6 ^{o} (*c* 1.55, CH_2Cl_2).



3-12 **3-4**

Aldol product **3-12** (16.68 g, 49.79 mmol) was diluted in CH_2Cl_2 (200 ml), treated with MeOH (31 mL, 770 mmol), imidazole (52.5 g, 770 mmol), and 4-dimethylaminopyridine (DMAP) (0.6 g, 4.9 mmol) before stirring for 18 h. The crude reaction mixture was evaporated *in vacuo* and the residue was mixed with hexanes, whereupon the (S)-4-(phenylmethyl)-2-thiazolidinethione precipitated as a white solid (after seeding). The solid was filtered off and washed with additional hexanes. The combined hexanes solution was washed several times with ice cold 2.5M aqueous sodium hydroxide to remove any remaining (S)-4-(phenylmethyl)-2-thiazolidinethione. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash column chromatography, eluting with 25% EtOAc/hexanes, to afford 6.56 g (84%) of methyl ester **3-4** as pale-yellow colored, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ

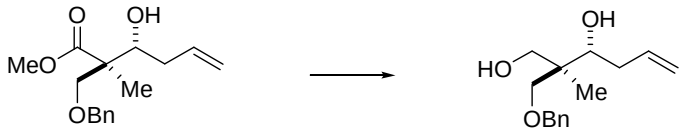
ppm 5.84-5.74 (m, 1H), 5.16-5.07 (m, 2H), 3.98-3.91 (m, 1H), 3.68 (s, 3H), 2.59-2.51 (m, 1H), 2.28-2.15 (m, 2H), 1.19 (t, *J* = 8.85 Hz, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 176.280, 134.355, 118.057, 77.253, 77.000, 76.745, 70.918, 51.816, 43.643, 38.489, 10.822; IR (film) 2953.02, 2953.02, 2922.16, 2922.16, 2852.72, 1697.36, 1672.28, 1454.33, 1261.45, 1165, 1136.07, 1029.99, 918.12, 746.45, 702.09 cm^{-1}; MS calculated for $C_8H_{14}O_3$ $[M + H]^+$: 159.09, found 159.0; $[\alpha]^{24}_D$ = +5.4 ^{o} (*c* 0.9, CH_2Cl_2).



3-4 **3-41**

In a 3-neck round-bottomed flask, a solution of diisopropylamine (18.3 mL, 130.8 mmol) in THF (40 mL) was cooled to -78 ℃. A 2.5M s olution of *n*-butyllithium (43.6 mL, 109 mmol) was added via addition funnel. Upon complete addition, the solution was stirred for 20 min. A solution of methyl ester **3-4** (8.57 g, 54.5 mmol) in THF (100 mL) was pre-cooled to -78 ℃ and added via can nula. The reaction vessel was placed in a pre-cooled (-20 ℃) *cryocool* instrument for 20 min, then re-cooled to -78 ℃. Freshly distilled (0.2 mmHg, 80 ℃ oil bath, gl ass-wool insulated short-path, distillate collected over anhydrous $CaCl_2$ spheres at ~60 ℃) benzyloxymethyl chloride (BOMCl) (30 mL, 218 mmol) was added via addition funnel. The reaction vessel was place in a precooled (-30 ℃) *cryocool* instrument and the mixture was stirred under an argon-filled balloon for 48 h. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously while warming to room

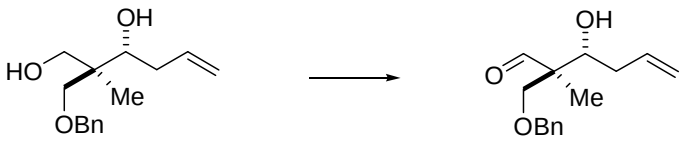
temperature. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25%-40% EtOAc/hexanes, to afford 12.08 g (79%) of **3-41** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.35 (tt, *J* = 12.78, 5.36 Hz, 3H), 7.31-7.27 (m, 3H), 5.93-5.83 (m, 1H), 5.11 (ddd, *J* = 16.72, 8.29, 2.31 Hz, 2H), 4.52-4.49 (m, 2H), 3.92 (dd, *J* = 10.06, 2.77 Hz, 1H), 3.62 (dd, *J* = 9.05, 4.32 Hz, 1H), 3.72-3.69 (m, 3H), 3.68 (d, *J* = 5.38 Hz, 1H), 2.28-2.21 (m, 1H), 2.14-2.06 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 175.705, 175.689, 137.775, 137.761, 135.430, 128.480, 128.461, 128.331, 128.314, 127.669, 127.653, 127.513, 127.496, 126.884, 117.143, 117.119, 77.254, 76.999, 76.746, 73.718, 73.692, 73.523, 73.502, 73.427, 73.403, 51.985, 51.971, 51.956, 51.280, 51.262, 36.800, 16.691, 16.676; IR (film) 3512.37, 2949.16, 2918.3, 2866.22, 1728.22, 1716.65, 1641.42, 1454.33, 1361.74, 1234.44, 1138, 1097.5, 1072.42, 1028.06, 991.41, 914.26, 736.81, 698.23 cm^{-1}; MS calculated for $C_{16}H_{22}O_4$ $[M + Na]^+$: 301.15, found 301.1; $[\alpha]^{24}_D$ = +3.0 ^{o} (*c* 1.51, CH_2Cl_2).



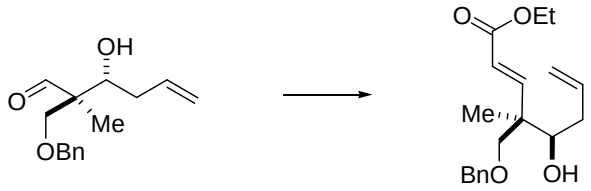
3-41

A solution of ester **3-41** (12.08 g, 43.6 mmol) in CH_2Cl_2 (400 mL) was cooled to -78 ℃. A solution of *i*-Bu_2AlH (1 M in hexanes, 175 mL, 175 mmol) was added dropwise via addition funnel and the mixture was stirred for 3 h after addition was complete. A saturated solution of sodium potassium tartrate (200 mL) was added and the mixture was warmed to room temperature. Water (100 mL) and CH_2Cl_2 (100 mL) were added and the mixture was stirred vigorously for 1 h. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 25%-40% EtOAc/hexanes, to afford 9.61 g (88%) of the diol as opaque, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.40-7.32 (m, 3H), 7.33-7.27 (m, 3H), 5.88 (dddd, *J* = 16.73, 10.64, 8.10, 5.93 Hz, 1H), 5.18-5.12 (m, 2H), 4.70 (s, 1H), 4.51 (q, *J* = 12.08 Hz, 2H), 3.89 (td, *J* = 10.61, 2.72 Hz, 1H), 3.74 (dd, *J* = 11.08, 6.14 Hz, 1H), 3.65 (dd, *J* = 11.08, 4.18 Hz, 1H), 3.51-3.46 (m, 2H), 2.80 (d, *J* = 4.11 Hz, 1H), 2.52 (t, *J* = 8.50 Hz, 1H), 2.29 (ddd, *J* = 13.89, 3.96, 1.85 Hz, 1H), 2.17-2.08 (m, 1H), 0.81 (s, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 137.893, 135.977, 128.519, 128.438, 127.759, 127.595, 127.550, 126.942, 117.742, 77.253, 77.000, 76.745, 75.725, 73.557, 73.536, 68.164, 42.611, 36.085, 15.454; IR (film) 3377.36, 3361.93, 3064.89, 3030.17, 2962.66, 2929.87, 2914.44, 2875.86, 1639.49, 1454.33, 1417.68, 1361.74, 1207.44, 1095.57, 1076.28, 1039.63, 1028.06, 991.41, 912.33, 736.81,

698.23 cm^{-1}; MS calculated for $C_{15}H_{22}O_3$ $[M + Na]^+$: 273.33, found 273.3; $[\alpha]^{24}_D$ = +2.36 ^{o} (*c* 2.18, CH_2Cl_2).



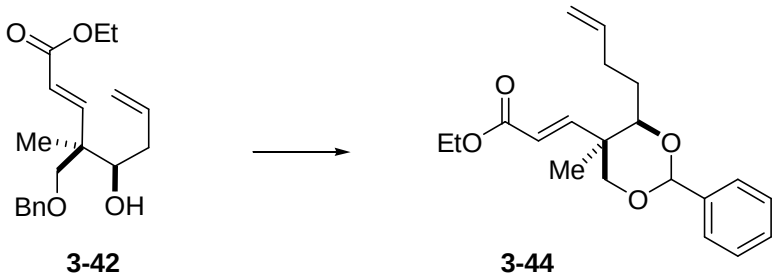
The diol (1.47 g, 5.87 mmol) was dissolved in CH_2Cl_2 (20 mL) and DI water (2 mL). $PhI(OAc)_2$ and TEMPO were added and the solution was stirred at room temperature for 30 min. Aqueous 1:1 $Na_2S_2O_3$:$NaHCO_3$ was added and the mixture was stirred for 10 min. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x 10 mL). The organic extracts were concentrated *in vacuo* and the residue was purified by gradient flash column chromatography, eluting with hexanes-5%-15% EtOAc/hexanes, to afford 1.21 g (83%) of the aldehyde as an opaque, viscous oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.72 (s, 1H), 7.38-7.26 (m, 7H), 5.86 (dddd, *J* = 20.89, 9.53, 7.77, 6.16 Hz, 1H), 5.18-5.09 (m, 2H), 4.50 (d, *J* = 5.87 Hz, 2H), 4.04 (dd, *J* = 10.19, 2.76 Hz, 1H), 3.69-3.61 (m, 1H), 3.59 (d, *J* = 9.40 Hz, 1H), 2.68 (d, *J* = 0.59 Hz, 1H), 2.28 (dtdd, *J* = 7.47, 4.19, 2.78, 1.40 Hz, 1H), 2.19-2.07 (m, 2H), 1.07 (d, *J* = 7.91 Hz, 4H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 205.511, 137.380, 134.960, 128.469, 127.901, 127.625, 118.086, 77.317, 76.999, 76.682, 73.660, 72.928, 72.283, 54.019, 36.455, 13.242; IR (film) 3438.46, 2859.92, 1725.01, 1641.13, 1496.49, 1306.54, 1096.33, 997.232, 738.603, 699.069 cm^{-1}; MS calculated for $C_{15}H_{22}O_3$ $[M + Na]^+$: 271.14, found 271.2; $[\alpha]^{24}_D$ = +9.06 ^{o} (*c* 0.675, CH_2Cl_2).



3-42

A solution of sodium hydride (60% suspension in mineral oil, 0.23 g, 9.6 mmol) in THF (20 mL) was treated with ethyl (diethylphosphono)acetate (1.81 mL, 9.6 mmol) and the mixture was stirred for 20 min at room temperature. The aldehyde (0.93 g, 3.2 mmol) in THF (5 mL + 5 mL rinse) was added to the reaction vessel via cannula. The solution was stirred for 2 h at room temperature. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with hexanes-5%-15% EtOAc/hexanes, to afford 0.956 g (94%) of **3-42** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *$CDCl_3$)* δ ppm 7.36-7.21 (m, 6H), 5.06 (dd, *J* = 11.96, 5.93 Hz, 2H), 7.08 (d, *J* = 16.25 Hz, 1H), 5.88-5.75 (m, 2H), 4.49 (dd, *J* = 17.82, 5.74 Hz, 2H), 4.14 (q, *J* = 7.12 Hz, 2H), 3.70-3.61 (m, 1H), 3.53 (d, *J* = 8.95 Hz, 1H), 3.37 (t, *J* = 11.36 Hz, 1H), 2.74 (d, *J* = 3.73 Hz, 1H), 2.21 (ddd, *J* = 6.05, 5.09, 2.54 Hz, 1H), 2.02-1.92 (m, 1H), 1.30-1.19 (m, 4H), 1.05 (m, 4H); ^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm 166.415, 150.543, 137.540, 135.666, 128.390, 127.759, 127.566, 121.389, 117.386, 77.254, 77.000, 76.745, 76.149, 75.590, 73.590, 60.298, 45.117, 36.772, 18.790, 14.199; IR (film) 3437.15, 2978.09, 2929.87, 2856.58, 1716.65, 1651.07, 1454.33, 1367.53, 1309.67, 1269.16, 1184.29,

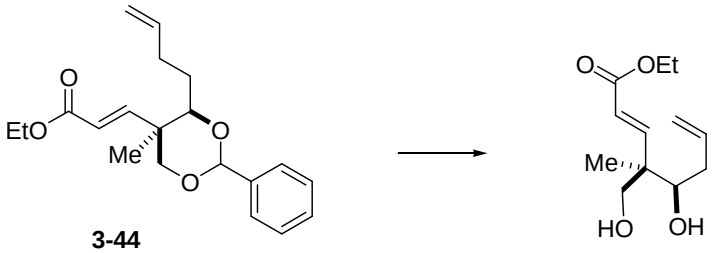
1095.57, 993.34, 910.4, 866.04, 736.81, 698.23 cm^{-1}; MS calculated for $C_{19}H_{26}O_4$ [M + H]$^+$: 319.18, found 319.3; $[\alpha]^{24}_D$ = +17.45 ^{o} (*c* 2.95, CH_2Cl_2).



3-42 **3-44**

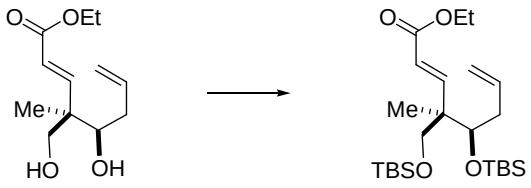
A solution of benzyl ether **3-42** (0.956 g, 3.0 mmol) in freshly distilled dichloroethane (30 mL) was treated with DDQ (3.41g, 15.0 mmol) and the mixture was stirred vigorously at 40 ℃ for 18 h. Aqueous 1:1 $Na_2S_2O_3$:$NaHCO_3$ was added and the mixture was stirred for 20 min. The biphasic red-colored mixture was filtered through a pad of celite, rinsing with excess CH_2Cl_2. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 10%-25%-40% EtOAc/hexanes, to afford 0.873 g (92%) of benzylidine acetal **3-44** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *$CDCl_3$)* δ ppm 7.54-7.45 (m, 2H), 7.36 (dd, *J* = 15.23, 7.33 Hz, 2H), 7.18 (d, *J* = 16.27 Hz, 1H), 5.97 (d, *J* = 16.29 Hz, 1H), 5.87 (dt, *J* = 16.52, 8.25 Hz, 3H), 5.56 (s, 1H), 5.14-5.05 (m, 3H), 4.20 (dd, *J* = 13.42, 6.72 Hz, 3H), 3.90 (d, *J* = 11.18 Hz, 1H), 3.77-3.65 (m, 5H), 3.59 (d, *J* = 9.59 Hz, 1H), 3.20 (s, 1H), 2.30-2.13 (m, 3H), 2.09-1.97 (m, 1H), 1.28 (dd, *J* = 15.38, 8.54 Hz, 7H), 1.04-0.94 (m, 6H), 0.89 (s, 11H), 0.06 (d, *J* = 2.61 Hz, 13H); ^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm 166.372, 150.609, 150.188, 149.844, 138.052, 138.030,

135.772, 134.932, 134.881, 128.804, 128.157, 126.082, 126.061, 121.548, 121.383, 121.143, 117.190, 116.696, 102.001, 101.964, 84.947, 84.899, 77.254, 77.000, 76.745, 76.592, 76.304, 70.267, 60.300, 60.248, 51.464, 45.335, 39.204, 39.171, 36.951, 34.715, 29.632, 25.723, 25.638, 18.189, 18.086, 17.910, 17.839, 14.222, 14.197, 0.959, -5.700, -5.745; IR (film) 2929.87, 2906.73, 2883.58, 2856.58, 1712.79, 1699.29, 1643.35, 1462.04, 1392.61, 1365.6, 1311.59, 1269.16, 1184.29, 1101.35, 1072.42, 1033.85, 995.27, 914.26, 837.11, 779.24, 736.81, 698.23, 671.23 cm^{-1}; MS calculated for $C_{19}H_{24}O_4$ $[M + Na]^+$: 339.17, found 339.2; $[\alpha]^{24}_D$ = +9.38 ^{o} (*c* 0.7, CH_2Cl_2).



Benzylidine acetal **3-44** (0.873 g, 2.76 mmol) was dissolved in 4:1 THF:10% aqueous H_2SO_4 (50 mL total) and the mixture was stirred for 48 h at room temperature. Saturated $NaHCO_3$ and EtOAc were added, the layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 25%-40%-60% EtOAc/hexanes, to afford 0.616 g (98 %) of diol **3-43** as a white powder. Efforts to recrystalize the solid were unsuccessful. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.16 (dd, *J* = 16.27, 10.28 Hz, 1H), 5.86-5.75 (m, 1H), 5.90 (td, *J* =

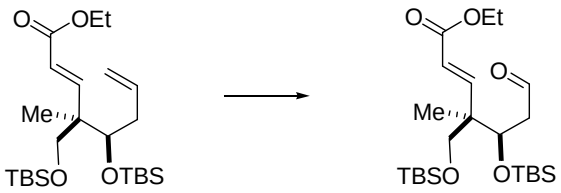
16.27, 4.58 Hz, 1H), 5.18-5.11 (m, 2H), 4.23-4.14 (m, 1H), 3.69 (ddd, *J* = 20.68, 10.42, 7.60 Hz, 2H), 3.62 (t, *J* = 8.34 Hz, 1H), 3.74 (d, *J* = 11.63 Hz, 2H), 2.98 (d, *J* = 0.92 Hz, 1H), 2.74 (s, 1H), 2.30 (ddd, *J* = 14.01, 3.45, 1.54 Hz, 1H), 2.05-1.96 (m, 1H), 1.28 (dd, *J* = 9.11, 5.15 Hz, 2H), 1.24 (t, *J* = 3.43 Hz, 1H), 1.05 (t, *J* = 5.20 Hz, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 166.953, 166.570, 150.389, 150.063, 134.972, 134.922, 121.846, 121.435, 118.694, 118.644, 101.025, 77.254, 77.000, 76.745, 76.061, 76.038, 69.667, 69.627, 60.464, 60.392, 51.586, 45.451, 45.436, 37.073, 31.211, 29.643, 27.068, 18.352, 18.291, 14.204, 14.139; IR (film) 3415.31, 3076.87, 2923.56, 2852.2, 1704.76, 1645.95, 1435.74, 1369.21, 1314.25, 1198.54, 1098.26, 1034.62, 992.196, 914.093, 865.882, 722.211, 588.182, 530.328 cm^{-1}; MS calculated for $C_{12}H_{20}O_4$ $[M + H]^+$: 229.14, found 229.1; $[\alpha]^{24}_D$ = +10.35 ^{o} (*c* 1.9, CH_2Cl_2).



3-43

A solution of diol **3-43** (0.6 g, 1.74 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 ℃. To the stirring solution was added 2,6-lutidine (0.3 mL, 2.4 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (0.6 mL, 2.4 mmol). After 1 h saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10% EtOAc/hexanes, to afford 0.771 g (97 %) of

the *bis*-silyl ether as a viscous oil. ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.14 (t, *J* = 9.39 Hz, 1H), 5.88-5.79 (m, 1H), 5.82-5.77 (m, 2H), 5.00 (dd, *J* = 20.29, 4.97 Hz, 2H), 4.22-4.16 (m, 2H), 3.85-3.80 (m, 1H), 3.54 (d, *J* = 9.63 Hz, 1H), 3.39 (d, *J* = 9.61 Hz, 1H), 2.37-2.29 (m, 1H), 2.19-2.11 (m, 1H), 1.32-1.25 (m, 4H), 1.01 (s, 3H), 0.87 (dd, *J* = 13.28, 4.56 Hz, 19H), 0.07-0.03 (m, 6H), 0.02 (t, *J* = 3.31 Hz, 6H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 166.759, 152.893, 136.469, 120.935, 116.331, 77.254, 76.999, 76.746, 74.658, 67.649, 60.045, 47.951, 38.408, 26.035, 25.882, 25.853, 18.239, 17.583, 14.259, -3.528, -4.445, -5.424, -5.532; IR (film) 3426.89, 2955.38, 2857.02, 2360.44, 1721.16, 1645.95, 14782.38, 1363.43, 1307.5, 1256.4, 1182.15, 1089.58, 1004.73, 910.236, 836.955, 775.224, 668.214, 546.72, 522.615 cm^{-1}; MS calculated for $C_{24}H_{48}O_4Si_2$ $[M + Na]^+$: 479.3, found 479.4; $[\alpha]^{24}_D$ = +1.85 ^{o} (*c* 0.907, CH_2Cl_2).



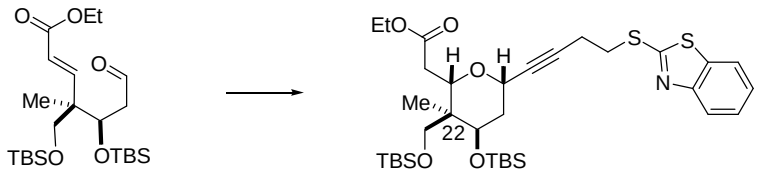
3-45

The *bis*-silyl ether (0.21 g, 0.42 mmol) was dissolved in 4:1 THF:H_2O (5 mL total volume). *N*-methylmorpholine oxide (NMO) (52 mg, 0.44 mmol) and osmium tetroxide (0.26 mL of 20 mg/mL solution in H_2O, 0.021 mmol) were added and the solution was stirred for 5 h. To this solution was added sodium periodate (0.27 g, 1.26 mmol) and the reaction mixture was stirred for an additional 2 h. Aqueous 1:1 $Na_2S_2O_3$:$NaHCO_3$ was added and the mixture was stirred for 20 min. The mixture was partitioned through the addition of EtOAc. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts

were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-60% EtOAc/hexanes, to afford 0.174 g (90%) of aldehyde **3-45** as an opaque oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 9.77 (s, 1H), 7.08 (d, *J* = 16.22 Hz, 1H), 5.85 (dd, *J* = 16.25, 9.19 Hz, 1H), 4.39 (t, *J* = 5.05 Hz, 1H), 4.19 (q, *J* = 7.10 Hz, 2H), 3.58 (d, *J* = 9.78 Hz, 1H), 3.39 (d, *J* = 9.80 Hz, 1H), 2.64 (dd, *J* = 17.00, 4.83 Hz, 1H), 2.50 (ddd, *J* = 17.01, 5.29, 2.51 Hz, 1H), 1.26 (td, *J* = 14.88, 6.17 Hz, 5H), 1.01-0.92 (m, 4H), 0.89 (dd sext., *J* = 19.69, 13.47, 5.05 Hz, 21H), 0.09 (s, 3H), 0.03 (t, *J* = 7.43 Hz, 9H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 201.312, 166.412, 151.172, 121.989, 101.051, 77.401, 77.382, 77.356, 77.253, 77.091, 77.000, 76.817, 76.745, 69.897, 67.146, 60.275, 48.442, 47.500, 25.985, 25.866, 25.836, 25.773, 18.237, 18.118, 17.325, 14.224, -4.194, -4.726, -5.447, -5.564; IR (film) 3852.11, 3434.6, 2957.3, 2857.99, 2089.49, 1646.91, 1472.38, 1362.46, 1308.46, 1257.36, 1184.08, 1092.48, 835.99, 776.208, 553.47, 525.507, 513.936 cm^{-1}; MS calculated for $C_{23}H_{46}O_5Si_2$ [M + H]$^+$: 459.39, found 459.4; $[\alpha]^{24}_D$ = +1.77 ^{o} (*c* 1.75, CH_2Cl_2).

3-32

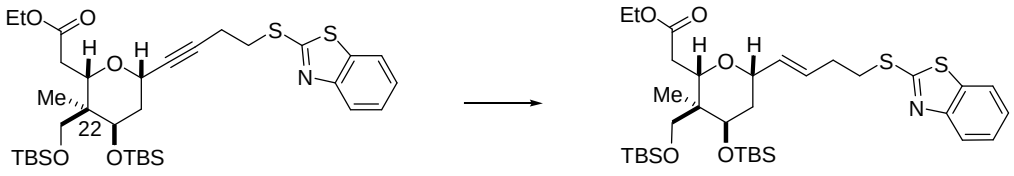
A solution of 3-butyne-1-ol (0.76 mL, 10.0 mmol) in THF (100 mL) was charged with PPh_3, (2.89 g, 11.0 mmol), diethylazodicarboxylate (DEAD) (1.81 mL, 11.0 mmol), and 2-mercaptobenzothiazole (1.84 g, 11.0 mmol). The resulting mixture was stirred for 12 h at room temperature. Saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10% EtOAc/hexanes, to afford 1.6 g (72 %) of thioether **3-32** as a clear, viscous oil. ^1H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.87 (d, *J* = 8.12 Hz, 1H), 7.75 (d, *J* = 7.94 Hz, 1H), 7.41 (t, *J* = 7.43 Hz, 1H), 7.29 (t, *J* = 7.60 Hz, 1H), 3.52 (t, *J* = 7.15 Hz, 2H), 2.79 (dt, *J* = 7.14, 2.51 Hz, 2H), 2.08 (t, *J* = 3.31 Hz, 1H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm ppm 95.949, 83.321, 65.462, 56.238, 54.502, 51.751, 51.191, 12.047, 7.514, 7.260, 7.005, 0.363, -37.756, -50.253; IR (film) 3905.15, 3294.79, 3060.48, 2929.34, 2118.42, 1685.48, 1560.13, 1458.89, 1427.07, 1322.93, 1309.43, 1282.43, 1238.08, 1159.01, 1126.22, 1077.05, 1019.19, 996.053, 935.306, 905.415, 851.418, 755.959, 726.068, 704.855, 642.179 cm^{-1}; MS calculated for $C_{11}H_9NS_2$ $[M + H]^+$: 220.02, found 220.0.



3-45 **3-46**

N-methylephedrine (NME) was dried for 12 h under vacuum (0.2 mmHg). Zinc triflate $(ZnOTf)_2$ (0.34g, 0.93 mmol) was pre-weighed (based on theoretical yield of aldehyde **3-45**) and dried in the reaction vessel for 12 h under vacuum (0.2 mmHg). The reaction vessel was placed in a 110 ^{o}C oil bath during the drying process. It is beneficial to use a conical-shaped flask for this reaction due to issues with the suspension. The reaction vessel was cooled under argon and (-)-NME (0.18 g, 1.01 mmol) (weighed in glove box) was added under positive argon flow. Toluene (2 mL) and Et_3N (0.14 mL, 1.01 mmol) were added and the suspension was stirred for 2 h at room temperature. Acetylene **3-32** (0.5 mL of 2M solution in toluene, 1.01 mmol) was added and the suspension was stirred for 1 h. Aldehyde (0.174 g, 0.378 mmol) **3-45** in toluene (1 mL + 1 mL rinse) was added via cannula. If excess solvent was need to transfer the aldehyde, then the solvent level was marked on the side of the flask, and a positive flow of argon with an outlet needle was used to reduce the solvent level. The reaction medium was heated to reflux for 8 h, and then cooled to ambient temperature. Saturated NH_4Cl and EtOAc were added, the layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-25%-40% EtOAc/hexanes, to afford 0.189 g (74 %) of pyran **3-46** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.86 (d, *J* = 7.96 Hz, 1H), 7.75 (d, *J* = 7.91 Hz, 1H), 7.41 (t, *J* = 7.33 Hz, 1H), 7.29 (t, *J* = 7.86 Hz, 1H), 4.62 (d, *J* = 6.74 Hz, 1H), 4.17 (td, *J* = 11.63, 6.19 Hz, 2H), 3.73 (s, 1H), 3.72-3.65 (m, 1H), 3.49 (dd, *J* = 12.55, 7.05 Hz, 2H), 3.46-3.40 (m, 1H), 3.39-3.32

(m, 1H), 2.78 (d, *J* = 4.25 Hz, 2H), 2.72-2.58 (m, 1H), 2.50-2.40 (m, 1H), 1.99 (s, 1H), 1.75-1.67 (m, 1H), 1.32-1.23 (m, 5H), 0.97 (t, *J* = 7.89 Hz, 2H), 0.94-0.82 (m, 22H), 0.05 (m, 13H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 172.439, 172.117, 166.377, 153.486, 135.546, 135.536, 126.284, 126.255, 124.497, 124.475, 121.810, 121.204, 108.406, 101.322, 82.557, 82.407, 81.891, 81.661, 77.521, 77.424, 77.411, 77.385, 77.327, 77.267, 77.149, 77.132, 77.013, 76.928, 76.908, 76.888, 76.861, 76.832, 76.672, 76.643, 76.584, 75.143, 72.091, 71.989, 71.876, 71.656, 71.635, 67.387, 65.627, 65.601, 63.213, 61.602, 60.717, 60.689, 60.575, 42.478, 41.855, 37.198, 36.860, 35.992, 35.155, 35.139, 32.548, 32.499, 32.320, 29.963, 26.218, 26.150, 26.124, 26.018, 20.464, 20.419, 20.353, 18.557, 18.543, 18.376, 16.272, 16.254, 14.540, 14.484, 7.276, 5.266, -3.551, -4.051, -4.730, -4.837, -5.179, -5.207, -5.292, -5.359; IR (film) 2954.41, 2928.38, 2856.06, 2359.48, 1737.55, 1651.73, 1558.2, 1539.88, 1507.1, 1462.74, 1428.03, 1361.5, 1298.82, 1254.47, 1185.04, 1081.87, 1052.94, 1004.73, 957.484, 888.059, 835.99, 812.849, 774.279, 755.959, 669.178 cm^{-1}; MS calculated for $C_{34}H_{55}NO_5S_2Si_2$ [M + Na]$^+$: 700.31, found 700.3; $[\alpha]^{24}_D$ = -7.52 ^{o} (*c* 0.75, CH_2Cl_2).

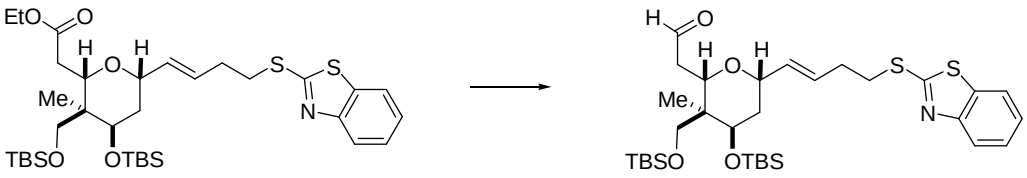


3-46 **3-57**

A solution of alkyne **3-46** (66.1 mg, 0.98 mmol) in CH_2Cl_2 (0.3M; 0.5 mL) and freshly distilled triethoxy silane (9 μL, 0.12 mmol) was cooled to 0 ^{o}C. [Cp*Ru(NCMe)$_3$]PF$_6$ (2.5 mg, 0.005 mmol) was added under positive argon flow. The suspension was

immediately warmed to ambient temperature and the mixture was stirred for 1 h. The reaction mixture was diluted in Et_2O and filtered through fluorisil (eluting with excess Et_2O). The Et_2O was removed *in vacuo* and the residue was dissolved in THF (1 mL). A suspension of AgF in MeOH (0.0126g in 0.1 ml) was added at once and the mixture was stirred (shielded from light) for 3 h. The dark reaction mixture was filtered through fluorisil and concentrated *in vacuo*. The residue was purified via The residue was purified by gradient flash column chromatography, eluting with 10%-25%-40% EtOAc/hexanes to afford 0.542 g (87 %) of olefin **3-57** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.86 (d, *J* = 7.90 Hz, 1H), 7.75 (d, *J* = 7.90 Hz, 1H), 7.41 (d, *J* = 7.27 Hz, 1H), 7.28 (dd, *J* = 13.96, 5.63 Hz, 2H), 5.66 (s, 1H), 5.60 (d, *J* = 5.24 Hz, 1H), 4.30-4.21 (m, 2H), 4.15 (dd, *J* = 6.70, 3.78 Hz, 2H), 3.88-3.78 (m, 1H), 3.70 (s, 1H), 3.46 (d, *J* = 9.79 Hz, 1H), 3.43-3.34 (m, 3H), 2.72-2.59 (m, 1H), 2.60-2.50 (m, 2H), 2.35 (d, *J* = 10.36 Hz, 1H), 1.70 (s, 1H), 1.46 (s, 1H), 1.24 (dd, *J* = 13.86, 6.79 Hz, 5H), 1.05-0.80 (m, 26H), 0.04 (dd, *J* = 16.71, 10.03 Hz, 14H); ^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm 172.531, 166.938, 153.306, 135.183, 133.418, 127.718, 125.976, 124.113, 121.470, 120.900, 77.254, 77.151, 77.000, 76.913, 76.746, 74.600, 72.293, 71.939, 67.284, 60.194, 41.633, 36.914, 35.882, 32.910, 32.140, 25.955, 25.873, 18.274, 18.129, 14.278, 6.984, 5.033, -4.335, -4.990, -5.476, -5.611; IR (film) 3444.24, 3059.51, 2954.41, 2929.34, 2884.02, 2857.02, 2738.42, 2709.5, 2360.44, 2341.16, 2125.17, 1735.62, 1644.98, 1559.17, 1462.74, 1428.03, 1389.46, 1644.98, 1559.17, 1462.74, 1428.03, 1389.46, 1361.5, 1337.39, 1299.79, 1256.4, 1186.97, 1079.94, 1051.98, 1004.73, 995.089, 961.341, 938.199, 923.736, 835.026, 812.849, 775.244, 938.199, 923.736, 835.026, 812.849, 775.244,

755.959 cm^{-1}; MS calculated for $C_{34}H_{57}NO_5S_2Si_2$ $[M + Na]^+$: 702.32, found 702.4; $[\alpha]^{24}_D$ = -11.7 ^{o} (*c* 0.55, CH_2Cl_2).

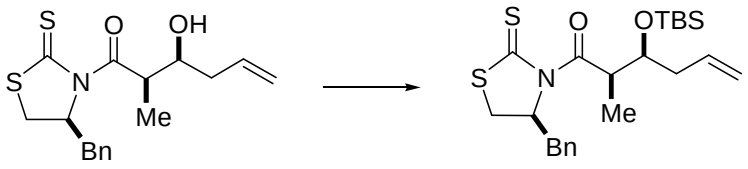


3-57 **3-58**

Ester **3-57** (20.5 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to -78 ^oC. DIBAL-H (1.0M in hexanes, 0.13 mL, 0.13 mmol) was added at once. The reaction was closely monitored by TLC and was complete in within 20 min. A saturated solution of sodium potassium tartrate (10 mL) was added and the mixture was warmed to room temperature. Water (5 mL) and CH_2Cl_2 (5 mL) were added and the mixture was stirred vigorously for 1 h. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Chromatography, eluting with 15% EtOAc/hexanes, to afford 15.1 mg (84 %) of **3-58** as a clear, viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.73 (d, *J* = 1.52 Hz, 1H), 7.84 (d, *J* = 8.08 Hz, 1H), 7.72 (d, *J* = 7.60 Hz, 1H), 7.38 (s, 1H), 7.26 (s, 1H), 5.71-5.60 (m, 1H), 5.59-5.50 (m, 1H), 4.27 (s, 2H), 3.67 (s, 1H), 3.43 (s, 1H), 3.35 (dd, *J* = 16.16, 8.70 Hz, 3H), 2.52 (d, *J* = 7.07 Hz, 3H), 2.46-2.36 (m, 1H), 1.75-1.65 (m, 1H), 1.47-1.39 (m, 1H), 1.23 (s, 2H), 0.90-0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 202.912, 166.913, 153.277, 135.167, 133.106, 128.310, 127.952, 125.988, 124.130, 121.464, 120.914, 77.701, 77.654, 77.620, 77.577, 77.542, 77.500, 77.317, 77.190, 77.129, 76.999, 76.682, 76.554, 72.003,

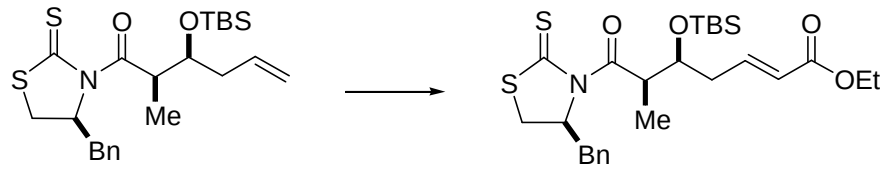
67.281, 65.854, 45.132, 41.571, 35.878, 32.821, 32.149, 29.695, 26.001, 25.935, 25.854, 22.012, 21.594, 18.260, 18.118, 16.031, 15.281, 15.261, 14.292, 6.578, -4.335, -5.016, -5.508, -5.626, -11.434; IR (film) 3435.56, 2953.45, 2928.38, 2856.06, 2712.39, 1728.87, 1651.73, 1360.53, 1308.46, 1255.43, 1407.78, 1388.5, 1360.53, 1308.46, 1255.43, 1077.05, 1019.19, 994.125, 961.341, 938.199, 904.451, 835.026, 813.81, 775.244, 755.959, 726.068, 702.926, 667.25, 563.112 cm^{-1}; MS calculated for $C_{32}H_{53}NO_4S_2Si_2$ $[M + Na]^+$: 658.30, found 658.3; $[\alpha]^{24}_D$ = -4.22 ^{o} (*c* 1.6, CH_2Cl_2).

B-2. B-ring: C1-C14 Segment of (-)-lasonolide A:



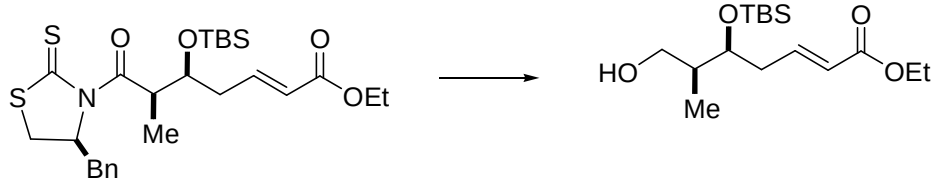
3-65

A solution of alcohol **3-65** (0.167 g, 0.5 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 ℃. To the stirring solution was added 2,6-lutidine (0.17 mL, 0.65 mmol).and *t*-butyldimethylsilyl trifluoromethanesulfonate (76 μL, 0.65 mmol). After 1 h saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-25% EtOAc/hexanes, to afford 0.209 g (93 %) of the silyl ether as a viscous, yellow oil. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.30-7.23 (m, 4H), 7.32 (dd, *J* = 9.11, 5.72 Hz, 2H), 5.77 (dd, *J* = 17.10, 10.14 Hz, 1H), 5.32 (ddd, *J* = 10.80, 7.06, 3.91 Hz, 1H), 5.12 (dd, *J* = 14.11, 5.67 Hz, 2H), 4.48 (dd, *J* = 6.82, 3.48 Hz, 1H), 4.01-3.95 (m, 1H), 3.37 (dd, *J* = 11.45, 7.04 Hz, 1H), 3.19 (dd, *J* = 13.18, 3.83 Hz, 1H), 3.02 (dd, *J* = 13.17, 10.54 Hz, 1H), 2.88 (d, *J* = 11.53 Hz, 1H), 2.27 (t, *J* = 7.48 Hz, 1H), 2.25-2.17 (m, 1H), 1.21 (m, 12H), 0.99-0.85 (m, 9H), 0.06 (m 6H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 201.131, 177.893, 173.045, 136.248, 134.095, 129.346, 128.836, 127.189, 118.144, 95.242, 77.177, 77.126, 76.968, 76.923, 76.669, 71.459, 68.680, 42.617, 38.771, 36.651, 31.977, 29.616, 14.056, 10.626, -5.0, -5.1; IR (film) 3442.94, 2926.01, 1689.64, 1494.83, 1454.33, 1361.74, 1342.46, 1261.45, 1192.01, 1165, 1136.07, 1029.99, 918.12, 744.52, 702.09 cm^{-1}; MS calculated for $C_{23}H_{35}NO_2S_2Si$ $[M + Na]^+$: 472.19, found 472.2; $[\alpha]^{24}_D$ = +139.2 ^{o} (*c* 0.98, CH_2Cl_2).



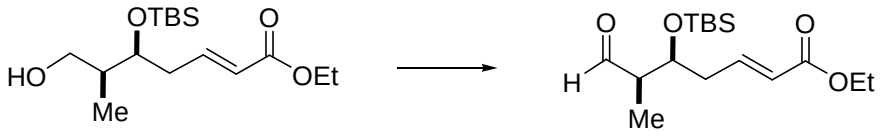
3-66

A solution of the aldol adduct (0.21 g, 0.46 mmol) in CH_2Cl_2 (5 mL) and freshly distilled methyl acrylate (0.13 mL, 1.4 mmol) were degassed with argon for 30 min. Grubbs 2nd generation catalyst (39 mg, 0.046 mmol) was weighed in the glovebox and placed into a dry vial. Under positive flow of argon, the vial was inverted and the contents were added to the reaction vessel. The reaction mixture was allowed to stir under an atmosphere of argon for 8 h and then open to air for 12 h. The reaction medium was concentrated *in vacuo*. The residue was mixed with silica gel and hexanes, concentrated *in vacuo* and loaded onto the column as a powder. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-15% EtOAc/hexanes, to afford 0.205 g (88%, *E:Z* >95:5) of **3-66** as a viscous, yellow oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.40-7.23 (m, 12H), 6.95 (d, *J* = 15.62 Hz, 1H), 5.83 (d, *J* = 15.62 Hz, 1H), 5.30-5.18 (m, 1H), 4.58-4.47 (m, 1H), 4.13 (q, *J* = 7.17 Hz, 3H), 3.72 (d, *J* = 5.59 Hz, 4H), 3.39-3.30 (m, 1H), 3.28-3.19 (m, 1H), 3.09-2.96 (m, 1H), 2.88 (d, *J* = 11.65 Hz, 1H), 2.53-2.43 (m, 2H), 1.31-1.20 (m, 8H), 0.93-0.83 (m, 9H), 0.06 (m 6H); MS calculated for $C_{26}H_{39}NO_4S_2Si$ [M + Na]$^+$: 544.21, found 544.2.



3-66

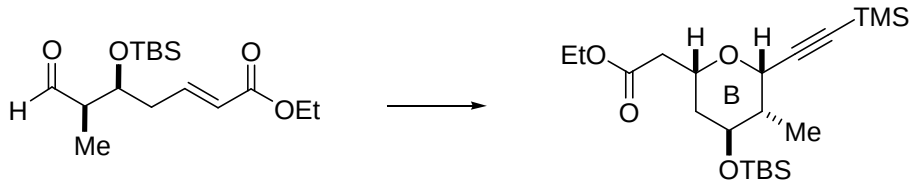
A solution of **3-66** (0.781 g, 1.5 mmol) in THF (2 mL) and MeOH (5 mL) was cooled to 0 ℃. $NaBH_4$ (85 mg, 2.25 mmol) was added under positive argon flow. After 1 h saturated $NaHCO_3$ solution was slowly added and the mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-25% EtOAc/hexanes, to afford 0.403 g (84 %) of the primary alcohol as a viscous, opaque oil. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 6.99-6.85 (m, 1H), 7.40-7.16 (m, 5H), 5.86 (d, *J* = 15.64 Hz, 1H), 4.45 (t, *J* = 7.22 Hz, 1H), 3.92 (d, *J* = 3.13 Hz, 1H), 3.72 (s, 3H), 3.68-3.45 (m, 3H), 3.32 (dd, *J* = 11.18, 6.82 Hz, 1H), 3.00 (dd, *J* = 7.20, 3.30 Hz, 2H), 2.40 (t, *J* = 7.03 Hz, 2H), 2.34 (s, 1H), 1.96-1.83 (m, 1H), 0.90-0.81 (m, 14H), 0.06 (m, 7H); MS calculated for $C_9H_{16}O_4$ $[M + Na]^+$: 211.10, found 211.1.



3-67

To a solution of the alcohol (0.196 g, 0.613 mmol) and 6 mL CH_2Cl_2 at room temperature was added Dess-Martin periodinane (0.390 g, 0.920 mmol). The solution was allowed to stir for 1 h. After the addition of a 1:1 aqueous solution of $Na_2S_2O_3$:$NaHCO_3$ the organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 15%-25% EtOAc/hexanes, to afford 0.173 g (89 %) of aldehyde **3-67** as a viscous, opaque oil. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 9.72 (s,

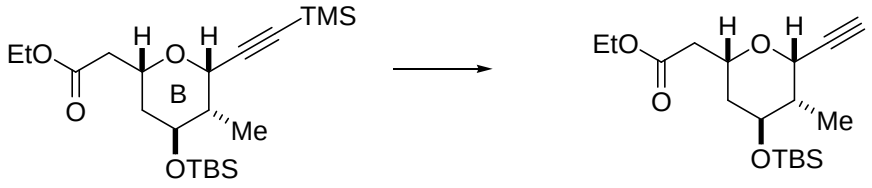
1H), 6.94-6.80 (m, 1H), 5.85 (d, *J* = 15.62 Hz, 1H), 4.33-4.07 (m, 4H), 2.42 (tdd, *J* = 16.44, 7.47, 5.20 Hz, 3H), 1.33-1.17 (m, 5H), 1.09 (t, *J* = 7.63 Hz, 4H), 0.99-0.80 (m, 12H), 0.05 (dd, *J* = 11.71, 8.29 Hz, 7H).



3-67 **3-69**

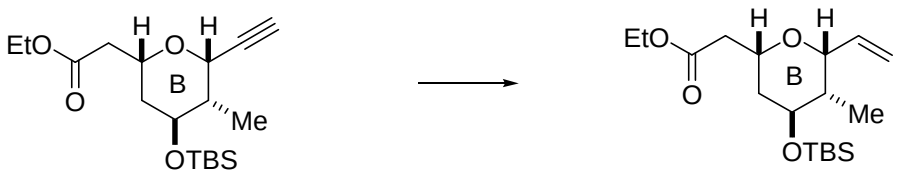
N-Methylephedrine (NME) was dried for 12 h under vacuum (0.2 mmHg). Zinc triflate $Zn(OTf)_2$ (0.113g, 0.31 mmol) was pre-weighed (based on theoretical yield of aldehyde **3-44**) and dried in the reaction vessel for 12 h under vacuum (0.2 mmHg). The reaction vessel was placed in a 110 ^{o}C oil bath during the drying process. It is beneficial to use a conical-shaped flask for this reaction due to issues with the suspension. The reaction vessel was cooled under argon and (-)-NME (0.061 g, 0.34 mmol) was added under positive argon flow. Toluene (2 mL) and Et_3N (47 μL, 0.34 mmol) were added and the suspension was stirred for 2 h at room temperature. Trimethylsilyl acetylene (0.1 mL, 0.71 mmol) was obtained from an ampoule (opened immediately prior to use) and added and the suspension was stirred for 1 h. Aldehyde **3-67** (45 mg, 0.142 mmol) in toluene (0.2 mL + 0.2 mL rinse) was added via cannula. If excess solvent was need to transfer the aldehyde, then the solvent level was marked on the side of the flask, and a positive flow of argon with an outlet needle was used to reduce the solvent level. The reaction medium was heated to reflux for 8 h, and then cooled to ambient temperature. Saturated NH_4Cl and EtOAc were added, the layers were separated and the aqueous solution was extracted with

EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-25%-40% EtOAc/hexanes, to afford 37 mg (63 %) of pyran **3-69** as a clear oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 4.51 (d, *J* = 5.12 Hz, 1H), 4.13 (dd, *J* = 7.16, 4.97 Hz, 4H), 2.49 (d, *J* = 7.62 Hz, 1H), 2.42 (d, *J* = 5.53 Hz, 1H), 1.91-1.82 (m, 1H), 1.74-1.60 (m, 2H), 1.31-1.18 (m, 13H), 0.94 (dd, *J* = 6.66, 4.78 Hz, 4H), 0.90-0.78 (m, 18H), 0.21-0.08 (m, 17H), 0.03 (dd, *J* = 11.71, 8.29 Hz, 9H).



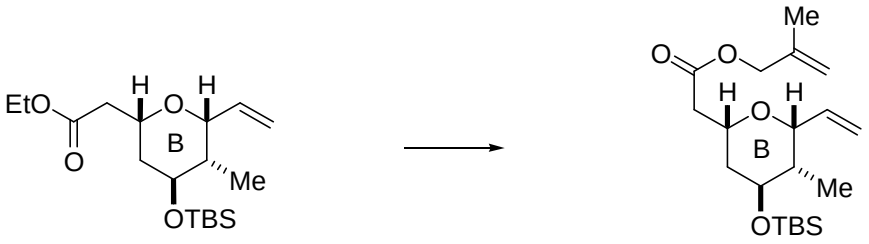
3-69

To a solution of pyran **3-69** (0.08 g, 0.19 mmol) in EtOH (200 proof, 2.7 mL) was added K_2CO_3 (0.11 g, 0.7 mmol). The mixture was allowed to stir at room temperature for 12 h. Saturated NH_4Cl and EtOAc were added, the layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15% EtOAc/hexanes, to afford 43 mg (78 %) of the terminal alkyne as a clear oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 4.74 (t, *J* = 2.44 Hz, 2H), 4.58-4.52 (m, 1H), 4.42-4.31 (m, 1H), 4.26-4.12 (m, 2H), 3.85 (d, *J* = 2.89 Hz, 2H), 2.67-2.51 (m, 3H), 2.45-2.30 (m, 6H), 1.06 (d, *J* = 7.22 Hz, 6H), 0.89-0.83 (m, 9H), 0.03 (m, 6H).



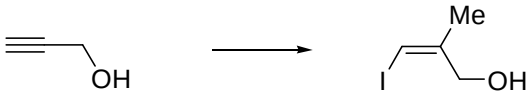
3-70

A solution of the terminal alkyne (0.0165 g, 0.055 mmol), EtOAc (3 mL), and quinoline (~1 μL, 0.0135 mmol) was evacuated under vacuum and backfilled with hydrogen 3x with the aid of a 3-way stop-cock and hydrogen-filled balloon. Lindlar's catalyst (5% Pd on $CaCO_3$ modified with lead salts, 11 mg, 0.005 mmol Pd) was added and the reaction medium was stirred under a balloon filled with hydrogen for 12 h. The reaction vessel was opened to air for 1 h. The suspension was filtered through celite and concentrated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15% EtOAc/hexanes, to afford 13 mg (82 %) of terminal olefin # as a clear oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 5.71 (m, 1H), 5.17 (td, *J* = 17.33, 1.94 Hz, 2H), 5.10-5.03 (m, 1H), 4.44 (dd, *J* = 4.51, 2.18 Hz, 1H), 3.86-3.81 (m, 1H), 3.65 (d, *J* = 4.25 Hz, 3H), 2.56 (dd, *J* = 14.83, 7.29 Hz, 1H), 2.37 (dd, *J* = 14.83, 6.05 Hz, 1H), 1.64-1.50 (m, 3H), 1.44-1.37 (m, 1H), 1.30-1.19 (m, 8H), 0.85 (m, 9H), 0.03 (m, 6H).



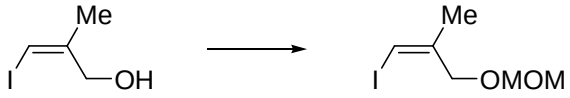
3-70 **3-71**

A solution of terminal olefin **3-70** (44 mg, 0.153 mmol) in THF (2 mL) and freshly distilled methallyl alcohol (50 μL, 0.306 mmol) was cooled to 0 ℃. KO *t*-Bu (0.3 mL of 1M solution in THF, 0.275 mmol) was added. After 4 h saturated $NaHCO_3$ solution was slowly added and the mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10% EtOAc/hexanes, to afford 38 mg (71 %) of **3-71** as a viscous, opaque oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 5.82-5.67 (m, 1H), 5.25-5.22 (m, 1H), 5.19-5.16 (m, 1H), 5.12-5.10 (m, 1H), 5.08-5.06 (m, 1H), 4.99 (s, 1H), 4.93-4.90 (m, 1H), 4.52 (d, *J* = 4.45 Hz, 2H), 4.50-4.46 (m, 1H), 4.32-4.22 (m, 1H), 3.89-3.86 (m, 1H), 2.67-2.58 (m, 1H), 2.49-2.40 (m, 1H), 1.75 (d, *J* = 0.42 Hz, 3H), 0.08-0.04 (m, 7H), 0.92-0.88 (m, 9H), 0.86 (d, *J* = 7.18 Hz, 3H).



Copper iodide (0.191 g, 3.0 mmol) was added to a round-bottomed flask and was gently stirred under positive argon flow for 15 min. Et_2O (90 mL) was added, followed by propargyl alcohol (1.74 mL, 30.0 mmol). The suspension was cooled to -20 ℃ using a recrystallization dish wrapped in gla ss-wool and tin foil (use of a

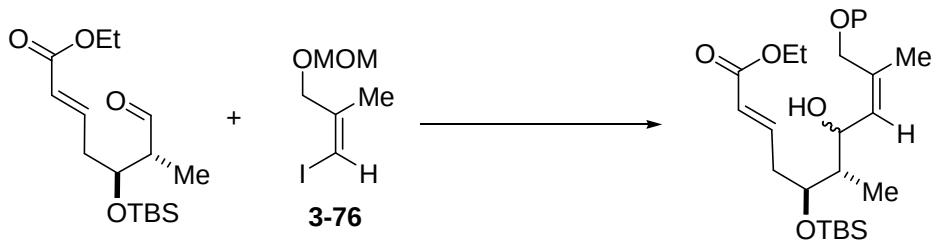
Dewer complicated stirring). Methylmagnesium bromide (25 mL of 3M solution in Et_2O, 75.0 mmol) was dissolved in Et_2O and added via syring pump 4 mL/h. The reaction medium changed from a suspension to a yellow solution. The reaction mixture was allowed to slowly warm to room temperature while stirring overnight. A suspension of I_2 (23g, 9.0 mmol) in Et_2O (90 mL) was allowed to stir overnight at room temperature shielded from light. After ~12 h, the original I_2/Et_2O suspension had become a homogeneous solution. The reaction medium was cooled to 0 ℃ and a solution of I_2 in Et_2O was added slowly via cannula. The reaction was complete in 8 h. Saturated NH_4Cl, and Et_2O were added, the layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 5.15 g (88 %) of the vinyl iodide as a clear oil. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 4.56 (s, 1H), 3.73 (td, *J* = 3.63, 1.81 Hz, 2H), 3.21 (s, 1H), 3.09 (d, *J* = 1.47 Hz, 2H).



3-76

A solution of vinyl iodide (5.5 g, 28.0 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 ℃. *N,N*-diisopropylethylamine (DIEA) (20 mL, 113.0 mmol), MOMCl (8.5 mL, 113.0 mmol), and 4-dimethylaminopyridine (DMAP) (0.34 g, 2.8 mmol) were added. The reaction mixture was stirred for 12 h at room temperature. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were

separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 5.76 g (87%) of protected vinyl iodide **3-76** as a viscous oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 6.03 (dd, *J* = 1.54, 0.78 Hz, 1H), 4.63-4.60 (m, 2H), 4.14 (d, *J* = 8.38 Hz, 2H), 3.39-3.36 (m, 3H), 1.91 (dd, *J* = 6.83, 1.54 Hz, 3H).

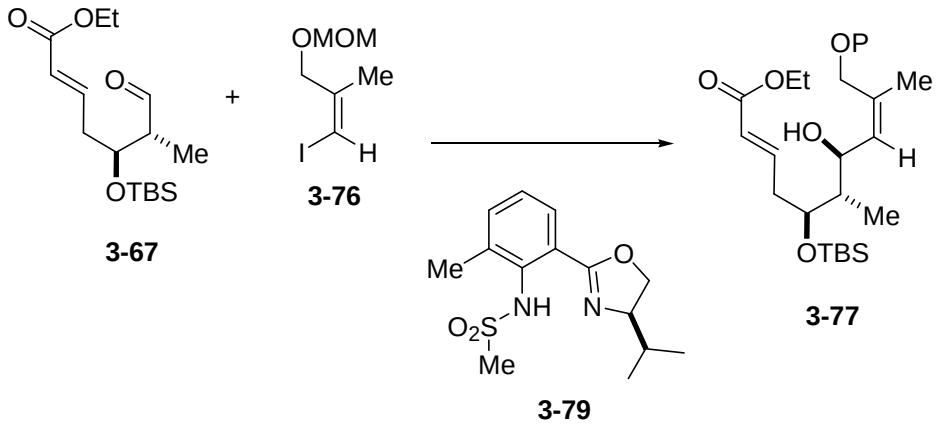


3-67 **3-76** **3-77/3-78**

$CrCl_2$ (0.368 g, 3.0 mmol) and $NiCl_2$ (77 mg, 0.06 mmol) purchased from Strem chemical company were opened and weighed into a flame-dried vial in the glovebox. Upon removal from the glovebox with a septum present, the vial was purged with argon and served as the reaction vessel. THF (4 mL) was added resulting in a thick suspension, DMF (3 mL) was added yielding a bright blue solution, and *t*-BuPy (1 mL) was added resulting in a bright green solution, whereupon the mixture was

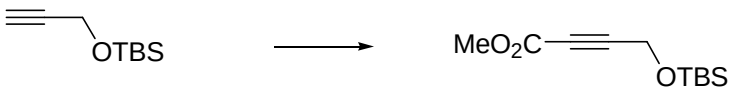
stirred for 15 min.[1] Aldehyde **3-67** (0.159 g, 0.5 mmol) was added in THF (1.5 mL), followed by vinyl iodide **3-76** (0.63 mL of 2M solution in THF, 1.25 mmol). The reaction mixture was stirred for 12 h at room temperature. 1.0M aqueous ethylenediamine was added, creating a purple aqueous layer, and the resulting mixture was stirred vigorously for 20 min. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with 10% aqueous HCl, $NaHSO_4$, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 0.156 g (73%, 1.5:1 *dr*) of racemic alcohols **3-77** and **3-78** as translucent, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.95-6.81 (m, 1H), 5.85 (d, *J* = 15.64 Hz, 1H), 5.55 (d, *J* = 8.42 Hz, 1H), 4.67-4.58 (m, 2H), 4.49 (dd, *J* = 8.46, 4.47 Hz, 1H), 4.20 (td, *J* = 16.18, 7.01 Hz, 3H), 3.42-3.36 (m, 4H), 3.97 (d, *J* = 11.64 Hz, 1H), 3.90 (d, *J* = 3.29 Hz, 1H), 2.49-2.40 (m, 2H), 1.81 (d, *J* = 1.21 Hz, 3H), 1.63-1.52 (m, 1H), 1.29 (t, *J* = 7.14 Hz, 3H), 0.98 (d, *J* = 6.90 Hz, 3H), 0.92-0.86 (m, 10H), 0.06 (d, *J* = 7.65 Hz, 6H).

[1] Stamos, D.; Sheng, C.; Chen, S.; Kishi, Y. *Tetrahdron Lett*. **1997**, *38*, 6355.

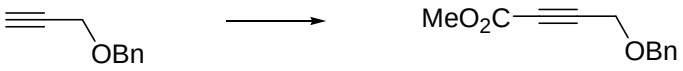


Dry benzene (5 mL) was added to ligand **3-79** (0.444 g, 1.5 mmol) and the solution was concentrated *in vacuo*. This was repeated two additional times, after which the residue was dissolved in THF (1 mL). Triethylamine (0.21 mL, 1.5 mmol) was added and the mixture was stirred for 5 min. Chromium (II) chloride (0.184 g, 1.5 mmol) and nickel (II) chloride (0.13 g, 1.0 mmol) purchased from Strem chemical company were added and the suspension was stirred for 1 h. Aldehyde **3-67** (0.159 g, 0.5 mmol) was added in THF (1 mL), followed by vinyl iodide **3-76** (0.5 mL of 2M solution in THF, 1.0 mmol). The reaction mixture was stirred for 12 h at room temperature. 1.0M aqueous ethylenediamine was added and the resulting mixture was stirred vigorously (purple aqueous layer). The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with 10% aqueous HCl, $NaHSO_4$, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 96 mg (45%, 2.5:1 *dr*) of alcohol **3-77** as translucent, viscous oil. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 6.96-6.82 (m, 1H), 5.92-5.78 (m, 1H), 5.42-5.33 (m, 1H), 4.66-4.53 (m, 2H), 4.16 (d, *J* = 7.02 Hz, 3H), 3.35 (s, 3H), 2.53-2.32 (m, 3H), 1.78 (s,

4H), 1.54 (s, 4H), 1.25 (dd, *J* = 13.05, 5.59 Hz, 5H), 0.86 (d, *J* = 9.57 Hz, 9H), 0.70 (d, *J* = 6.95 Hz, 2H), 0.06 (t, *J* = 11.52 Hz, 6H).

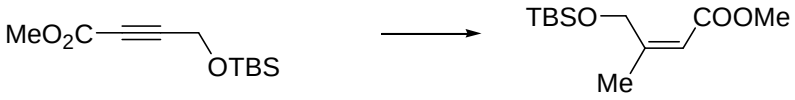


TBS-protected propargylic ether (25.55 g, 150 mmol) was dissolved in THF (500 mL) and cooled to -78 ℃. *n*-Butyllithium (2.5M in hexanes, 80 mL, 200 mmol) was added dropwise via addition funnel. The mixture was stirred for 1 h upon complete addition while gradually warming to -60 ℃. Methylchloroform ate (15.5 mL, 200 mmol) was added via addition funnel and the reaction mixture was gradually warmed to 0 ℃ over 2 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with Et_2O (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10% EtOAc/hexanes, to afford 31.12 g (91 %) of the alkyne # as a viscous, translucent oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 4.36 (d, *J* = 19.80 Hz, 2H), 3.73-3.63 (m, 3H), 0.81 (d, *J* = 8.22 Hz, 9H), 0.05 (d, *J* = 5.84 Hz, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 153.421, 85.841, 77.255, 77.000, 76.744, 76.186, 52.394, 51.114, 25.477, 17.976, -5.492; IR (film) 3423.65, 2954.95, 2929.87, 2887.44, 2858.51, 2241.28, 1716.65, 1463.97, 1435.04, 1409.96, 1361.74, 1255.66, 1107.14, 1056.99, 1028.06, 1006.84, 939.33, 839.03, 815.89, 781.17, 752.24 cm^{-1}; MS calculated for $C_{11}H_{20}O_3Si$ $[M + Na]^+$: 251.12, found 251.1.



3-83 **3-84**

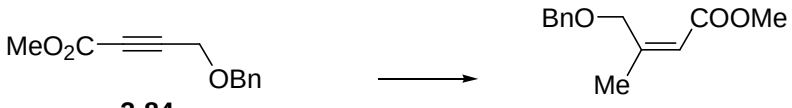
^{1}H NMR (500 MHz, $CDCl_3$) ppm 7.36 (m, 5H), 4.60 (s, 2H), 4.26 (s, 2H), 3.80-3.73 (m, 3H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 153.017, 136.407, 128.051, 128.002, 127.907, 127.655, 127.621, 127.159, 83.244, 77.543, 71.526, 56.233, 52.258; IR (film) 3868.33, 3727.73, 3660.23, 3413.39, 3088.44, 3064.33, 3031.55, 2953.45, 2862.81, 2359.48, 2340.19, 2237.99, 2071.17, 1959.32, 1874.37, 1719.23, 1659.45, 1606.41, 1548.56, 1496.49, 1453.1, 1435.74, 1353.78, 1256.4, 1154.19, 1096.33, 1058.73, 1027.87, 941.092, 858.168, 817.67, 750.174, 699.069, 668.214 cm^{-1}; MS calculated for $C_{12}H_{12}O_3$ $[M + Na]^+$: 227.08, found 227.0.



Copper iodide (15.24 g, 80.0 mmol) suspended in Et_2O (500 mL) and cooled to 0 ℃. [2] Methyl lithium (1.6M in Et_2O, 100 mL, 160.0 mmol) was added and the yellow-colored mixture was stirred for 45 min at 0 ℃. The reaction vessel was placed in a Dewer and the mixture was cooled to -78 ℃. Pre-cooled (-78 ℃) alkyne (33.3 mL of a 2M solution in Et_2O, 66.6 mmol) was transferred to the reaction mixture via cannula and the solution was allowed to stir for 3-4 h at -78 ℃. Acetic acid (10 mL) was added and the reaction mixture was warmed to 0 ℃. Half-saturated $NaHCO_3$ solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with Et_2O (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and

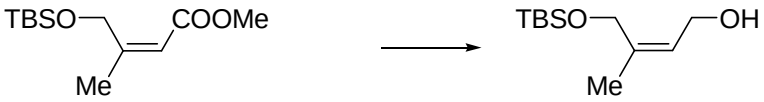
[2] Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 14.32 g (88%) of the vinyl ester as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.96 (s, 1H), 4.07 (s, 2H), 3.65 (d, *J* = 1.90 Hz, 3H), 2.01 (s, 3H), 0.91-0.83 (m, 12H), 0.04 (d, *J* = 1.56 Hz, 8H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 112.694, 66.854, 50.671, 25.695, 15.243, -5.627,; IR (film) 2953.02, 2929.87, 2897.08, 2885.51, 2856.58, 1720.5, 1662.64, 1471.69, 1463.97, 1435.04, 1388.75, 1377.17, 1361.74, 1321.24, 1251.8, 1224.8, 1155.36, 1112.93, 1066.64, 1039.63, 1006.84, 839.03, 815.89, 777.31, 738.74, 669.3 cm^{-1}; MS calculated for $C_{12}H_{24}O_5Si$ $[M + H]^+$: 245.13, found 245.1.

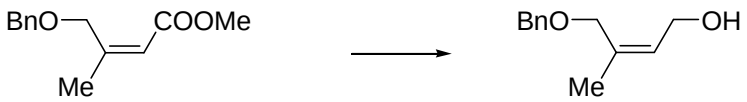


3-84 **3-85**

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.27 (m, 5H), 5.69 (s, 1H), 4.58 (s, 2H), 4.44 (d, *J* = 6.21 Hz, 2H), 3.58 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 166.300, 157.274, 137.993, 130.011, 128.394, 128.319, 128.292, 128.232, 127.673, 127.528, 127.512, 126.313, 116.702, 77.254, 77.000, 76.745, 73.822, 72.549, 69.135, 50.962, 21.598; IR (film) 2951.52, 2862.81, 2359.48, 2340.19, 2237.99, 2071.17, 1959.32, 1874.37, 1719.23, 1657.52, 1606.41, 1548.56, 1496.49, 1443.46, 1368.25, 1260.25, 1153.22, 1099.23, 738.603, 698.105 cm^{-1};MS calculated for $C_{13}H_{16}O_3$ $[M + H]^+$:221.09, found 221.1.

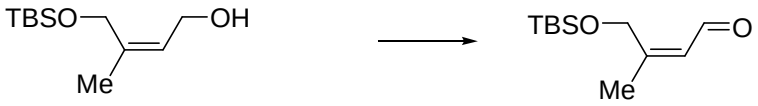


The vinyl ester (16.71 g, 68.37 mmol) was dissolved in CH_2Cl_2 (500 mL) and cooled to -78 ^oC. DIBAL-H (1.0M in hexanes, 171 mL, 171 mmol) was added at once. The reaction was monitored by TLC and was complete in within 3 h. A saturated solution of sodium potassium tartrate (200 mL) was added and the mixture was warmed to room temperature. Water (100 mL) and CH_2Cl_2 (100 mL) were added and the mixture was stirred vigorously for 1 h. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Chromatography, eluting with 15% EtOAc/hexanes, to afford 12.43 g (84 %) of the alcohol as a clear, viscous oil. ^1H NMR (500 MHz, *CDCl*$_3$) δ ppm 5.61 (t, *J* = 5.93 Hz, 1H), 4.13 (d, *J* = 6.30 Hz, 3H), 3.98 (s, 2H), 2.38-2.11 (m, 1H), 1.59 (s, 3H), 0.87 (s, 12H), 0.04 (d, *J* = 6.37 Hz, 8H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 122.783, 77.233, 76.978, 76.723, 67.654, 58.742, 25.792, 25.750, 18.247, 13.325, -5.481, -5.503; IR (film) 3338.78, 2954.95, 2927.94, 2885.51, 2856.58, 1471.69, 1462.04, 1442.75, 1406.11, 1388.75, 1361.74, 1251.8, 1188.15, 1111, 1076.28, 1004.91, 960.55, 837.11, 813.96, 775.38, 667.37 cm^{-1}; MS calculated for $C_{12}H_{24}O_2Si$ $[M + H]^+$: 217.15, found 217.2.



3-85

^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 7.22 (m, 5H), 5.61-5.51 (m, 1H), 4.39 (s, 2H), 4.02 (dd, *J* = 7.07, 0.94 Hz, 2H), 3.93 (s, 2H), 1.73 (dd, *J* = 2.40, 1.03 Hz, 3H), 1.54 (t, *J* = 7.43 Hz, 1H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 139.231, 138.292, 128.367, 127.796, 127.612, 121.479, 77.253, 77.000, 76.745, 72.376, 68.077, 66.185, 13.886; IR (film) 3397.96, 3087.48, 3063.37, 2917.77, 2859.92, 2360.44, 1813.72, 1722.12, 1678.73, 1604.48, 1548.56, 1495.53, 1454.06, 1363.43, 1328.71, 1269.9, 1205.29, 1069.33, 1026.91, 943.02, 844.669, 738.603, 698.105 cm^{-1}; MS calculated for $C_{12}H_{15}O_2$ $[M + H]^+$:193.08, found 193.1.

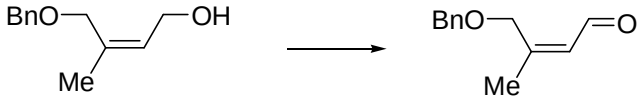


3-97

A solution of the alcohol (5.41 g, 25 mmol) in CH_2Cl_2 (100 mL) and cooled to 0 ^{o}C. 4-Methyl-morpholine-*N*-oxide (NMO) (5.6 g, 50 mmol) and tetrapropylammonium perruthenate (TPAP)[3] (0.44 g, 1.25 mmol) were added at once. The reaction mixture was stirred for 1 h depending on scale. The black solution was partially concentrated *in vacuo*, silica gel was added, and then the mixture was fully concentrated to yield a gray powder. The powder was purified by chromatography, eluting with 15% EtOAc/hexanes, to afford 4.77 g (89 %) of aldehyde **3-97** as a clear, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 10.00 (t, *J* = 9.52 Hz, 1H), 6.13 (dd, *J* = 8.17, 1.28 Hz, 1H), 4.11 (d, *J* = 0.93 Hz, 2H), 4.09-4.00 (m, 1H), 2.11-1.88 (m, 6H), 1.21-1.15 (m, 2H), 0.87-0.81 (m, 9H), 0.01 (m, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 191.028, 161.415, 124.054, 77.318, 77.000, 76.681, 66.564, 60.255, 25.709,

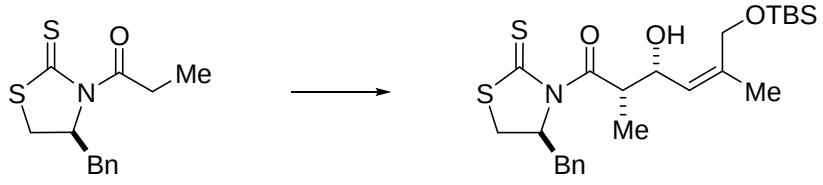
[3] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

25.659, 25.579, 20.915, 18.211, 14.087, 13.935, -5.542, -5.598; IR (film) 2954.95, 2929.87, 2885.51, 2856.58, 1732.08, 1681.93, 1651.07, 1471.69, 1444.68, 1408.04, 1361.74,1315.45, 1253.73, 1222.87, 1165, 1120.64, 1006.84, 939.33, 839.03, 815.89, 779.24, 669.3 cm^{-1}; MS calculated for $C_{12}H_{22}O_2Si$ $[M + H]^+$: 215.12, found 215.1.



3-86

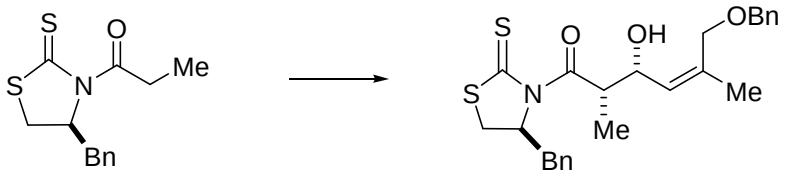
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 9.32 (s, 1H), 7.46-7.22 (m, 5H), 4.53-4.38 (m, 3H), 4.20 (d, *J* = 5.56 Hz, 2H), 1.59 (dd, *J* = 6.83, 1.54 Hz, 4H); IR (film) 3354.57, 3030.59, 2854.13, 1691.27, 1496.49, 1454.06, 1364.39, 1328.71, 1266.04, 1203.36, 1113.69, 1073.19, 1026.91, 835.99, 739.567, 699.069 cm^{-1}.



3-5 **3-98**

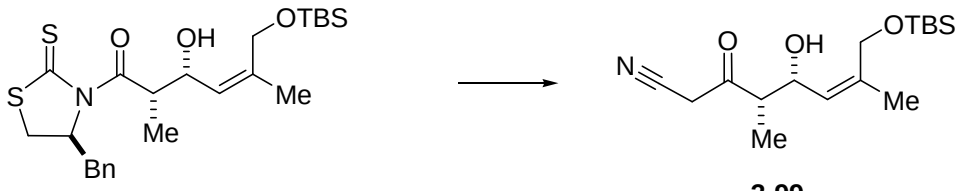
A stirring solution of (S)-4-benzyl-3-propionyl-1,3-thiazolidine-2-thione **3-5** (2.12 g, 8.0 mmol) in CH_2Cl_2 (80 mL) was cooled in an ice bath. $TiCl_4$ (0.92 mL, 8.4 mmol) was added at once, turning the solution a yellow-orange hue. After stirring the mixture for 20 min, (-)-sparteine (1.85 mL, 8.0 mmol) was added at once converting the solution to a purple-brown hue. After stirring the mixture for 20 min, *N*-methyl-2-pyrrolidinone (NMP) (0.77 mL, 8.0 mmol) was added, dropwise. After stirring the mixture for 20 min the solution was cooled to -78 °C and pre-cooled aldehyde **3-97** (1.78 g, 8.0 mmol) in CH_2Cl_2 (10 mL) was added. The homogeneous reaction mixture was stirred at -78 ℃ for 3 h, and then war med in an ice bath. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously while warming to room temperature. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 3.607 g (94%) of aldol **3-98** as a bright-yellow colored, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.36-7.30 (m, 2H), 7.30-7.24 (m, 5H), 5.51 (dd, *J* = 8.87, 1.40 Hz, 1H), 5.12 (ddd, *J* = 10.64, 6.85, 3.83 Hz, 1H), 4.69-4.63 (m, 1H), 4.50 (dd, *J* = 12.92, 6.27 Hz, 1H), 3.99 (s, 2H), 3.41 (dd, *J* = 11.34, 7.02 Hz, 1H), 3.24 (dd, *J* = 13.21, 3.72 Hz, 1H), 3.04 (dd, *J* = 13.18, 10.72 Hz, 1H), 2.87 (d, *J* = 11.33 Hz, 1H), 2.09 (d, *J* = 3.19 Hz, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.33 (t, *J* = 5.56 Hz, 3H), 0.87-0.81 (m, 9H), 0.01 (m, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 201.171, 177.343, 139.169, 136.510, 129.414, 128.893, 127.186, 123.203, 77.254, 77.154, 77.000, 76.861, 76.835, 76.746, 70.055, 69.227, 67.555, 45.038, 36.630,

32.402, 25.891, 25.867, 18.329, 14.046, 12.201, -5.358, -5.394; IR (film) 2953.02, 2927.94, 2854.65, 1697.36, 1454.33, 1361.74, 1342.46, 1263.37, 1190.08, 1165, 1114.86, 1029.99, 837.11, 777.31, 702.09 cm^{-1}; MS calculated for $C_{24}H_{37}NO_3S_2Si$ $[M + Na]^+$: 502.198, found 502.2; $[\alpha]^{24}_D$ = +113.3 ^{o} (*c* 0.82, CH_2Cl_2).



3-5 **3-88**

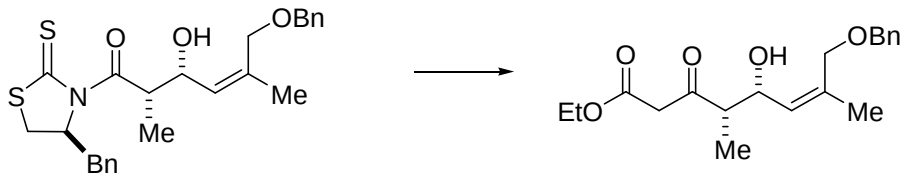
^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.39-7.21 (m, 10H), 5.47 (d, *J* = 8.64 Hz, 1H), 5.18 (s, 1H), 4.63 (dd, *J* = 8.57, 5.77 Hz, 1H), 4.57-4.50 (m, 1H), 4.49 (d, *J* = 3.47 Hz, 2H), 4.08 (d, *J* = 11.60 Hz, 1H), 3.98 (d, *J* = 11.66 Hz, 1H), 3.28 (dd, *J* = 11.35, 7.02 Hz, 1H), 3.21 (dd, *J* = 13.16, 3.73 Hz, 1H), 3.01 (dd, *J* = 13.17, 10.61 Hz, 1H), 2.84 (d, *J* = 11.48 Hz, 1H), 1.81 (s, 3H), 1.30 (d, *J* = 6.74 Hz, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 201.195, 177.030, 137.947, 136.673, 136.366, 129.319, 129.080, 128.932, 128.793, 128.543, 128.426, 128.324, 128.237, 127.623, 127.092, 77.256, 77.000, 76.746, 72.408, 69.543, 68.976, 68.918, 44.777, 36.539, 32.320, 21.915, 12.175; IR (film) 3416.28, 3027.69, 2927.41, 2360.44, 1693.19, 1603.52, 1495.53, 1454.06, 1343.18, 1291.11, 1263.15, 1192.76, 1164,79, 1137.8, 1028.84, 901.558, 740.531, 700.033 cm^{-1}; MS calculated for $C_{25}H_{29}NO_3S_2$ $[M + H]^+$:456.16, found 456.3; $[\alpha]^{24}_D$ = +110.7 ^{o} (*c* 1.82, CH_2Cl_2).



3-98 **3-99**

In a 3-neck round-bottomed flask, a solution of diisopropylamine (3.1 mL, 22 mmol) in THF (15 mL) was cooled to -78 ℃. A 2.5M solutio n was of *n*-butyllithium (8.34 mL, 20.84 mmol) was added via addition funnel. Upon complete addition, the solution was stirred for 30 min. Freshly distilled MeCN (1.1 mL, 20.84 mmol) was added and the mixture was stirred for 15 min. A solution of aldol adduct **3-98** (2.5 g, 5.2 mmol) in THF (20 mL) was pre-cooled to -78 ℃ a nd added to the solution via cannula. The reaction mixture was stirred at -78 ℃ for 1 h. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously while warming to room temperature. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25%-40% EtOAc/hexanes, to afford 1.28 g (85%) of β–ketonitrile **3-99** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.43 (d, *J* = 9.18 Hz, 1H), 4.66 (dd, *J* = 9.20, 5.08 Hz, 1H), 4.02 (d, *J* = 15.40 Hz, 2H), 3.75-3.55 (m, 2H), 2.99-2.88 (m, 1H), 1.98 (s, 1H), 1.64 (s, 3H), 1.11 (dd, *J* = 13.24, 7.02 Hz, 3H), 0.94-0.84 (m, 10H), 0.06 (m, 7H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 200.220, 140.418, 121.645, 113.874, 77.317, 77.000, 76.682, 69.002, 67.152, 50.877, 32.789, 25.833, 18.309, 13.835, 11.340, -5.411, -5.439; IR (film) 3423.65, 2954.95, 2929.87, 2856.58, 1724.36, 1463.97, 1388.75, 1361.74, 1303.88, 1253.73, 1114.86, 1076.28, 1006.84, 937.4,

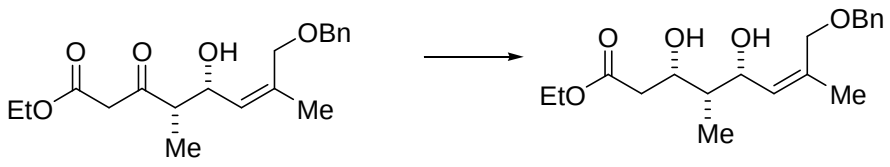
837.11, 777.31, 667.37 cm^{-1}; MS calculated for $C_{16}H_{29}NO_3Si$ $[M + Na]^+$: 334.19, found 334.2; $[\alpha]^{24}_D$ = +23.8 ^{o} (*c* 0.79, CH_2Cl_2).



3-88 **3-92**

In a 3-neck round-bottomed flask, a solution of diisopropylamine (8.21 mL, 58.6 mmol) in THF (40 mL) was cooled to -78 ℃. A 2.5M s olution was of *n*-butyllithium (21.33 mL, 58.6 mmol) was added via addition funnel. Upon complete addition, the solution was stirred for 30 min. Freshly distilled EtOAc (5.2 mL, 53.4 mmol) was added dropwise and the mixture was stirred for 15 min. A solution of aldol adduct **3-88** (3.04 g, 6.65 mmol) in THF (20 mL) was pre-cooled to -78 ℃ and added via cannula. The reaction vessel was stirred at -78 ℃ for ~90 min. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously while warming to room temperature. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25%-40% EtOAc/hexanes, to afford 0.923 g (91%) of β̃-ketoester **3-92** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.38-7.26 (m, 5H), 5.44 (d, *J* = 8.58 Hz, 1H), 4.67 (dd, *J* = 8.54, 4.60 Hz, 1H), 4.51-4.45 (m, 2H), 4.18 (dq, *J* = 7.15, 3.19 Hz, 2H), 4.12-4.06 (m, 1H), 3.96 (dd, *J* = 11.62, 4.22 Hz, 1H), 3.49 (s, 2H), 2.82 (dq, *J* = 7.07, 4.64 Hz, 1H), 1.82 (s, 3H), 1.27 (dt, *J* = 7.13, 3.84 Hz, 3H), 1.15 (t, *J* = 6.59 Hz, 3H);

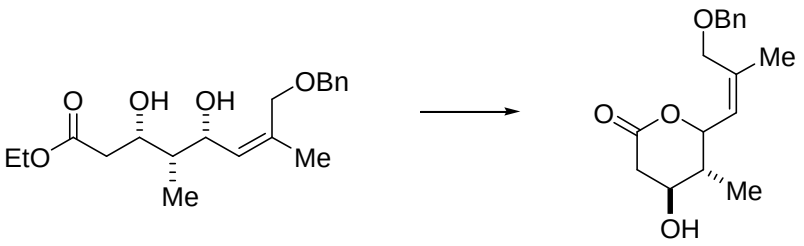
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 205.847, 167.041, 137.658, 136.200, 128.717, 128.691, 128.330, 128.121, 128.078, 128.045, 127.994, 127.483, 127.451, 127.391, 127.365, 127.004, 77.214, 76.958, 76.703, 72.090, 68.580, 68.518, 67.855, 60.969, 51.435, 48.852, 21.741, 13.907, 13.794, 10.938; IR (film) 3437.49, 3087.48, 3063.37, 3030.59, 2979.48, 2934.16, 2875.34, 2247.63, 1956.43, 1878.33, 1740.44, 1710.55, 1645.95, 1496.49, 1454.06, 1407.78, 1368.25, 1311.36, 1263.15, 1156.12, 1093.44, 1071.26, 1017.27, 844.669, 807.063, 740.531, 700.033, 652.786, 618.074, 560.22, 521.65, 504.294 cm^{-1}; MS calculated for $C_{19}H_{26}O_5$ $[M + H]^+$: 335.18, found 335.2; $[\alpha]^{24}_D$ = +13.73^o (*c* 3.49, CH_2Cl_2).



3-92 **3-93**

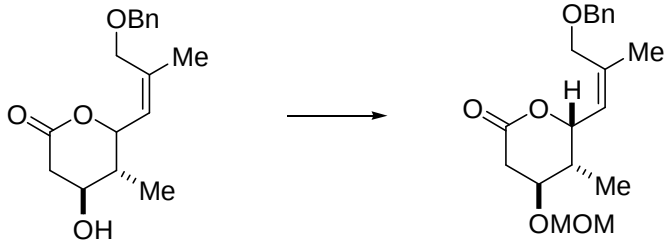
A solution of β̃-ketoester **3-92** (0.4429 g, 1.32 mmol) in THF (10 mL) and MeOH (3 mL) was cooled to -78 ℃. Et$_2$BOMe (2 mL of 1M solution, 2.0 mmol) was added via syringe and the solution was stirred for 15 min before adding $NaBH_4$ (0.1 g, 2.64 mmol) under positive argon flow. The reaction vessel was stirred at -78 ℃ for ~3 h. A solution of pH = 7 buffer and 30% aqueous H_2O_2 (1:1; 2.5 mL) was added slowly and the mixture was stirred for 30 min while warming to ambient temperature. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with sodium sulfite to remove peroxides (checked with starch paper), brine, dried over Na_2SO_4, filtered, and

evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 25%-40% EtOAc/hexanes, to afford 0.351 g (79%) of diol **3-93** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.39-7.24 (m, 5H), 5.51 (d, *J* = 8.47 Hz, 1H), 4.56 (dd, *J* = 8.22, 3.86 Hz, 1H), 4.50 (q, *J* = 11.83 Hz, 3H), 4.22 (d, *J* = 9.23 Hz, 1H), 4.16 (q, *J* = 7.11 Hz, 2H), 4.02 (dd, *J* = 27.72, 11.21 Hz, 2H), 3.50 (s, 1H), 2.71-2.60 (m, 1H), 2.56 (dd, *J* = 16.07, 9.65 Hz, 1H), 2.31 (dd, *J* = 16.15, 3.00 Hz, 1H), 1.83 (d, *J* = 8.75 Hz, 4H), 1.31-1.21 (m, 6H), 1.00 (d, *J* = 6.94 Hz, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 172.883, 137.807, 135.414, 130.869, 128.463, 128.439, 127.855, 127.802, 77.253, 77.000, 76.745, 72.566, 71.659, 70.868, 69.114, 60.681, 42.699, 39.421, 29.681, 22.446, 14.172, 6.429; IR (film) 3436.53, 2921.63, 1731.76, 1454.06, 1374.03, 1261.22, 1180.22, 1095.37, 1026.91, 739.576, 699.069 cm^{-1}; MS calculated for $C_{19}H_{28}O_5$ $[M + H]^+$: 337.19, found 337.2; $[\alpha]^{24}_D$ = +1.59 ^{o} (*c* 5.6, CH_2Cl_2).



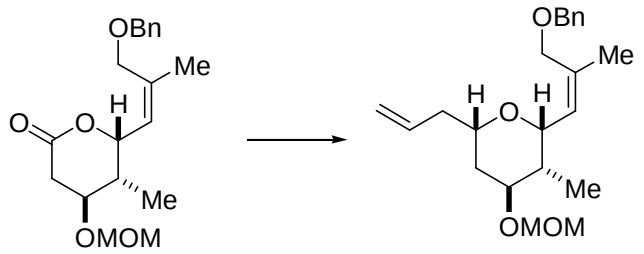
3-93 **3-91**

To a solution of diol **3-93** (0.2889 g, 0.859 mmol) in dry benzene (10 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (0.022 g, 0.0859 mmol). The solution was heated to reflux for 1 h (color changes from opaque to light yellow). After cooling to ambient temperature, half-saturated $NaHCO_3$ solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 40%-60% EtOAc/hexanes, to afford 0.204 g (82%) of lactone **3-91** as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.39-7.32 (m, 2H), 5.48 (s, 1H), 4.52 (d, *J* = 11.73 Hz, 1H), 4.44 (d, *J* = 11.72 Hz, 1H), 4.10 (d, *J* = 11.91 Hz, 1H), 3.97 (d, *J* = 11.92 Hz, 1H), 2.80 (dd, *J* = 18.37, 5.62 Hz, 1H), 2.48 (dd, *J* = 18.33, 3.49 Hz, 1H), 1.90-1.84 (m, 2H), 1.57 (s, 1H), 0.95 (d, *J* = 7.19 Hz, 1H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 137.980, 128.482, 127.968, 127.858, 124.283, 77.253, 77.116, 77.000, 76.870, 76.849, 76.745, 76.607, 76.569, 76.519, 76.500, 74.554, 72.327, 68.800, 68.389, 39.112, 35.784, 21.918, 10.703; IR (film) 3428.81, 2923.56, 2854.13, 1716.34, 1454.06, 1363.43, 1245.79, 1061.62, 983.518, 737.639, 699.069, 609.396 cm^{-1}; MS calculated for $C_{17}H_{22}O_4$ $[M + Na]^+$: 313.15, found 313.1; $[\alpha]^{24}_D$ = +26.6 ^{o} (*c* 0.29, CH_2Cl_2).



3-91 **3-94**

Lactone **3-91** (35 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 ℃. *N,N*-diisopropylethylamine (DIEA) (84 μL, 0.48 mmol), MOMCl (46 μL, 0.6 mmol), and 4-dimethylaminopyridine (DMAP) (~2 mg, 0.012 mmol) were added. The reaction mixture was stirred for 12 h at room temperature. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 37 mg (92%) of protected lactone **3-94** as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.39-7.31 (m, 4H), 7.32-7.27 (m, 1H), 5.50 (d, *J* = 8.83 Hz, 1H), 5.44 (dd, *J* = 8.99, 2.86 Hz, 1H), 4.63-4.59 (m, 2H), 4.48 (q, *J* = 11.88 Hz, 2H), 4.07 (d, *J* = 11.98 Hz, 1H), 3.98 (d, *J* = 11.99 Hz, 1H), 3.84 (dd, *J* = 9.09, 4.40 Hz, 1H), 3.33 (s, 3H), 2.80 (dd, *J* = 18.28, 5.64 Hz, 1H), 2.60 (dd, *J* = 18.22, 3.40 Hz, 1H), 2.04 (dt, *J* = 7.73, 7.47, 3.77 Hz, 1H), 1.87 (s, 3H), 0.97 (t, *J* = 7.87 Hz, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 137.974, 137.861, 128.385, 128.348, 128.309, 127.862, 127.754, 127.724, 127.672, 127.653, 127.606, 124.197, 124.114, 95.001, 77.211, 76.956, 76.703, 74.632, 72.198, 72.077, 68.624, 68.357, 68.076, 38.852, 35.712, 33.821, 29.606, 21.788, 21.750, 10.834, 10.635, 0.934; IR (film) 2924.52, 1738.51, 1496.49, 1454.06, 1363.43, 1260.25, 1234.22, 1149.37, 1036.55, 917.95, 801.278, 740.531, 699.069, 559.255 cm^{-1}; MS calculated for $C_{19}H_{26}O_5$ $[M + H]^+$: 335.24, found 335.2; $[\alpha]^{24}_D$ = +10.58 ^{o} (*c* 0.91, CH_2Cl_2).

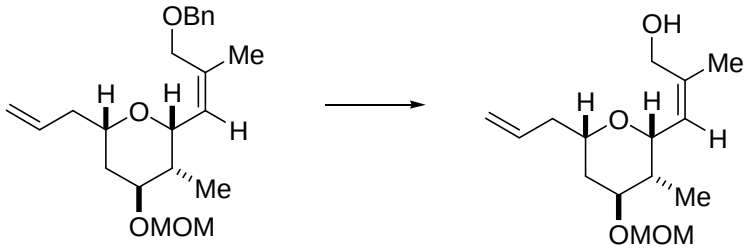


3-94 **3-95**

A solution of lactone **3-94** (0.1024 g, 0.306 mmol) in THF (2 mL) was cooled to -78 ℃. [4] Allyl magnesium bromide (0.92 mL of 1.0M solution in Et_2O, 0.92 mmol) and the reaction mixture was stirred for 5 min while monitoring via TLC. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously while warming to ambient temperature. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Dry benzene was added to the residue and the solution was evaporated *in vacuo*. This was repeated three times before attaching the flask to the vacuum-pump manifold (0.2 mmHg) for 30 min. The residue was admixed with a solution of Et_3SiH (0.27 mL, 1.7 mmol) in CH_2Cl_2 (0.3 mL) and MeCN (0.7 mL). The resulting solution was cooled to -78 ℃ and treated with $SnCl_4$ (1.0M in CH_2Cl_2, 0.19 mL, 0.19 mmol) and gradually warmed to -20 °C over 90 min. Water was added and the resulting mixture was stirred vigorously while warming to ambient temperature. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 93 mg (84%) of pyran **3-95** as a viscous oil. ^{1}H NMR

[4] Paquette, L. *J. Am. Chem. Soc.* **2000**, *122*, 619.

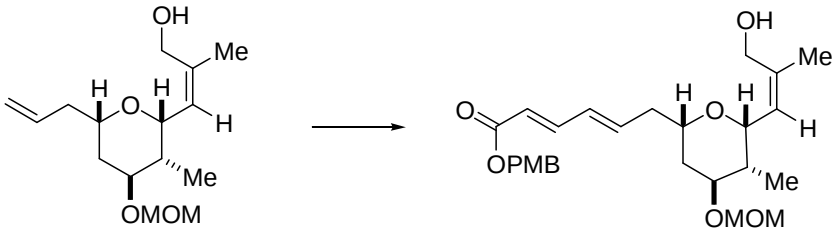
(500 MHz, *CDCl*$_3$) δ ppm 7.40-7.22 (m, 5H), 5.86-5.76 (m, 1H), 5.50-5.45 (m, 1H), 5.11-4.99 (m, 3H), 4.60-4.42 (m, 6H), 4.06 (d, *J* = 13.78 Hz, 4H), 3.71 (s, 3H), 3.29 (s, 7H), 2.34-2.26 (m, 2H), 2.20-2.13 (m, 2H), 1.83 (s, 6H), 1.55 (s, 13H), 0.95 (d, *J* = 7.12 Hz, 8H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 167.735, 138.450, 134.885, 134.402, 132.451, 130.860, 128.853, 128.827, 128.790, 128.337, 127.701, 127.530, 127.473, 116.579, 101.061, 77.505, 77.253, 77.103, 77.000, 76.745, 76.604, 76.559, 76.537, 76.522, 76.499, 76.477, 76.458, 76.430, 76.395, 76.366, 76.347, 76.333, 76.317, 76.299, 76.256, 76.214, 76.192, 75.800, 75.716, 71.766, 71.732, 70.900, 70.815, 68.698, 68.152, 40.572, 40.515, 38.735, 33.580, 31.926, 30.363, 29.701, 29.663, 29.365, 28.926, 25.807, 25.764, 23.749, 22.984, 22.692, 21.287, 18.009, 14.117, 14.048, 11.171, 10.960, 1.018, -4.844, -4.944; IR (film) 3073.98, 3026.73, 2973.7, 2928.38, 2873.42, 1728.87, 1639.2, 1496.49, 1454.06, 1435.74, 1367.28, 1269.9, 1202.4, 1070.3, 1047.16, 997.017, 913.129, 737.639, 697.141 cm^{-1}; MS calculated for $C_{22}H_{32}O_4$ $[M + H]^+$: 361.32, found 361.3; $[\alpha]^{24}_D$ = +18.9 ^{o} (*c* 0.3, CH_2Cl_2).



3-95 **3-96**

To a solution of napthalene (0.613 g, 4.78 mmol) in THF (8 mL) was added sodium metal (washed in hexanes, 0.1 g, 4.35 mmol). The flask was subjected to sonication for 2 h. A solution of benzyl ether **3-95** (72 mg, 0.2 mmol) in THF (2 mL) was cooled

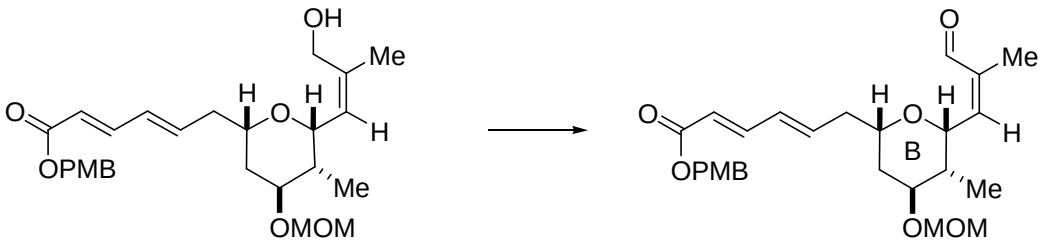
to 0 ℃. The preformed sodium naphthalene solution was added in 1 mL portions until the green color was sustained in the reaction mixture. The reaction was complete in 30 min. Water was added and the resulting mixture was stirred vigorously while warming to ambient temperature. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-15%-25% EtOAc/hexanes, to afford 49 mg (91%) of allylic alcohol **3-96** as a viscous oil. It should be noted that the yields of this reaction varied from 13% to 91%. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.87-5.76 (m, 1H), 5.39-5.32 (m, 1H), 5.12-5.03 (m, 1H), 4.76-4.69 (m, 1H), 4.34-4.26 (m, 1H), 4.26-4.18 (m, 1H), 3.98-3.87 (m, 1H), 3.86-3.81 (m, 1H), 3.52-3.45 (m, 1H), 2.33-2.14 (m, 3H), 2.07-1.97 (m, 2H), 1.83 (s, 2H), 1.39-1.03 (m, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 139.586, 134.678, 130.008, 129.724, 127.011, 117.105, 96.113, 71.979, 71.231, 70.641, 62.515, 40.632, 39.901, 37.097, 33.624, 31.929, 31.904, 30.035, 29.766, 29.701, 29.660, 29.523, 29.364, 29.326, 29.238, 29.208, 29.115, 27.221, 27.165, 25.786, 25.518, 22.723, 22.694, 22.390, 18.032, 14.120, 11.207, 1.019. IR (film) 2927.41, 2856.06, 1726.94, 1462.74, 1259.29, 1078.98, 800.314 cm^{-1}; MS calculated for $C_{15}H_{26}O_4$ $[M + Na]^+$: 302.18, found 302.2; $[\alpha]^{24}_D$ = +29.1 ^{o} (*c* 0.19, CH_2Cl_2).



3-96 **3-105**

A solution of pyran **3-96** (30 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) and freshly prepared diene (0.33 mL of 1M solution in CH_2Cl_2, 0.33 mmol) were degassed with argon for 30 min. Grubbs 2nd generation catalyst (9 mg, 0.011 mmol) was weighed in the glovebox and placed into a dry vial. Under positive flow of argon, the vial was inverted and the contents were added to the reaction vessel. The reaction mixture was allowed to stir under an atmosphere of argon for 8 h and then open to air for 12 h. The reaction medium was concentrated *in vacuo*. The residue was mixed with silica gel and hexanes, concentrated *in vacuo* and loaded onto the column as a powder. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-15% EtOAc/hexanes, to afford 42 mg (81% based on recycled **3-96** dimer) of the homologated pyran **3-105** as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.30-7.24 (m, 2H), 7.24-7.18 (m, 1H), 6.39 (m, 1H), 6.30-6.20 (m, 2H), 5.88 (m, 1H), 5.54 (d, *J* = 16.92 Hz, 1H), 5.08 (s, 2H), 4.78-4.73 (m, 1H), 4.04 (s, 2H), 3.97-3.89 (m, 1H), 3.88-3.83 (m, 1H), 3.73 (d, *J* = 10.62 Hz, 3H), 2.44-2.36 (m, 1H), 2.36-2.27 (m, 1H), 1.70 (s, 3H), 1.59 (s, 10H), 1.28 (d, *J* = 15.44 Hz, 9H), 1.10 (d, *J* = 7.47 Hz, 22H), 0.97-0.87 (m, 15H), 0.06 (d, *J* = 6.96 Hz, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 166.827, 159.788, 145.167, 140.140, 134.883, 130.270, 128.303, 125.863, 122.171, 114.095, 71.589, 71.463, 70.733, 68.360, 66.219, 55.416, 39.637, 39.603, 33.900, 29.697, 25.810, 25.753, 17.998, 17.818, 14.116, 12.009,

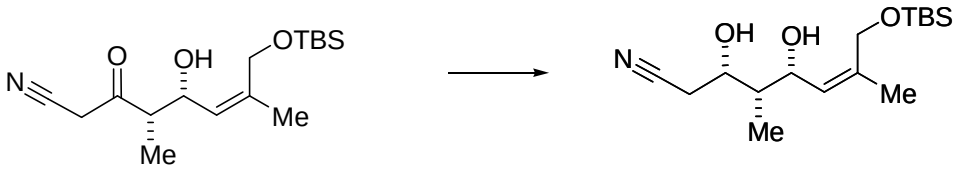
11.266; IR (film) 3359.39, 2925.48, 2854.13, 1733.69, 1653.66, 1633.41, 1463.71, 1428.99, 1376.93, 1256.4, 1077.05, 1004.73, 835.99, 776.208, 741.496 cm^{-1}; MS calculated for $C_{27}H_{40}O_7$ $[M + Na]^+$: 508.28, found 508.3; $[\alpha]^{24}_D$ = +9.4° (*c* 1.2, CH_2Cl_2).



3-105 **3-107**

To a solution of allylic alcohol **3-105** (20 mg, 0.042 mmol) in CH_2Cl_2 (0.5 mL) was added 85% MnO_2 (82 mg, 0.84 mmol). The reaction mixture was stirred at ambient temperature 12 h then filtered through celite rinsing with excess CH_2Cl_2. The filtrate was concentrated *in vacuo*. The residue was mixed with silica gel and hexanes, concentrated *in vacuo* and loaded onto the column as a powder. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-15% EtOAc/hexanes, to afford 19 mg (93%) of aldehyde **3-107** as a viscous oil. ^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm 9.43 (s, 1H), 7.30-7.24 (m, 2H), 7.24-7.18 (m, 1H), 6.39 (m, 1H), 6.30-6.20 (m, 2H), 5.88 (m, 1H), 5.54 (d, *J* = 16.92 Hz, 1H), 5.08 (s, 2H), 4.78-4.73 (m, 1H), 4.04 (s, 2H), 3.97-3.89 (m, 1H), 3.88-3.83 (m, 1H), 3.73 (d, *J* = 10.62 Hz, 3H), 2.44-2.36 (m, 1H), 2.36-2.27 (m, 1H), 1.70 (s, 3H), 1.59 (s, 10H), 1.28 (d, *J* = 15.44 Hz, 9H), 1.10 (d, *J* = 7.47 Hz, 22H), 0.97-0.87 (m, 15H), 0.06 (d, *J* = 6.96 Hz, 6H); ^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm 195.221, 166.827, 159.788, 145.167, 140.140, 134.883, 130.270, 128.303, 125.863, 137.866, 130.515, 122.171, 114.095,

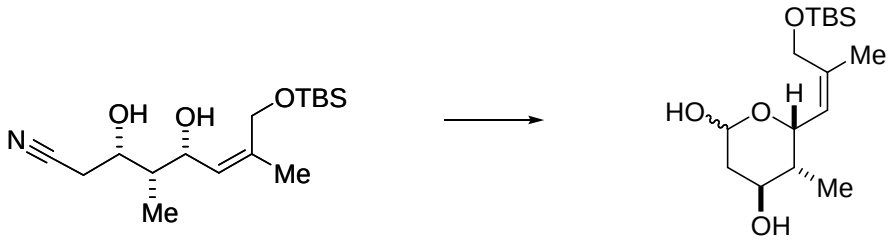
71.589, 71.463, 70.733, 68.360, 66.219, 55.416, 39.637, 39.603, 33.900, 29.697, 25.810, 25.753, 22.640, 17.998, 17.818, 14.116, 12.009, 11.266; IR (film) 3073.98, 3026.73, 2973.7, 2928.38, 2873.42, 1728.87, 1639.2, 1496.49, 1454.06, 1435.74, 1367.28, 1269.9, 1202.4, 1070.3, 1047.16, 997.017, 913.129, 737.639 cm^{-1}; MS calculated for $C_{26}H_{34}O_7$ $[M + Na]^+$: 490.23, found 490.2; $[\alpha]^{24}_D$ = +19.2 ^{o} (*c* 0.21, CH_2Cl_2).



3-99 **3-100**

β–ketonitrile **3-99** (1.28 g, 4.44 mmol) was dissolved in THF (30 mL) and MeOH (9 mL) before cooling to -78 ℃. Et_2BOMe (26.7 mL of 1M solution, 6.66 mmol) was added via syringe and the solution was stirred for 15 min before adding $NaBH_4$ (0.553 g, 8.88 mmol) under positive argon flow. The reaction vessel was stirred at -78 ℃ for 3 h. A solution of pH = 7 buffer and 30% aqueous H_2O_2 (1:1; 5 mL) was added slowly and the mixture was stirred for 30 min while warming to ambient temperature. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with sodium sulfite to remove peroxides (checked with starch paper), brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 25%-40% EtOAc/hexanes, to afford 1.182 g (92%) of diol **3-100** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm 5.56 (d, *J* =

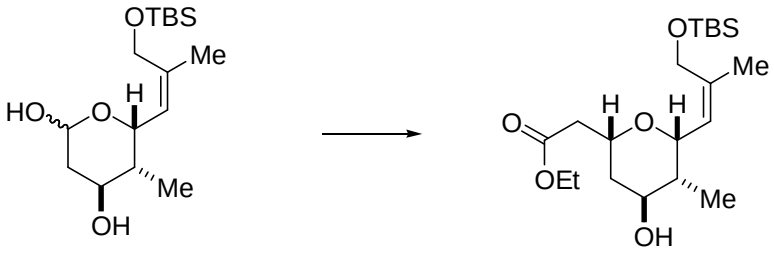
8.45 Hz, 1H), 4.65 (d, *J* = 8.32 Hz, 1H), 4.21 (d, *J* = 6.57 Hz, 1H), 3.97 (s, 2H), 3.41 (d, *J* = 10.73 Hz, 1H), 2.59 (dd, *J* = 16.78, 6.95 Hz, 1H), 2.45 (dd, *J* = 16.68, 6.83 Hz, 1H), 1.59 (d, *J* = 15.26 Hz, 5H), 1.74 (s, 1H), 1.83-1.76 (m, 1H), 1.72-1.65 (m, 1H), 0.98 (t, *J* = 7.86 Hz, 3H), 0.87 (s, 12H), 0.03 (s, 7H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 200.287, 128.955, 128.886, 128.217, 77.254, 76.999, 76.745, 68.894, 67.149, 50.920, 32.726, 25.781, 25.755, 18.245, 13.756, 11.255, 0.913, -5.464, -5.497; IR (film) cm^{-1}; MS calculated for $C_{16}H_{31}NO_3Si$ [M + Na]$^+$: 336.21, found 336.2; $[\alpha]^{24}_D$ = -12.9 ^{o} (*c* 1.91, CH_2Cl_2).



3-100 **3-101**

Nitrile **3-100** (0.5617 g, 1.94 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to -78 ^{o}C. DIBAL-H (1.0M in hexanes, 6.8 mL, 6.8 mmol) was added at once. The reaction mixture was stirred at -78 ^{o}C for 2 h, and then placed in an ice bath for 1 h.

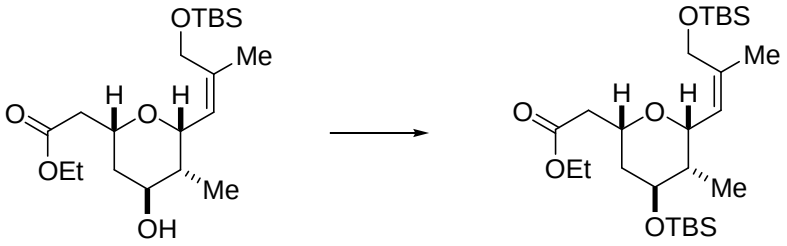
Aqueous citric acid (1M, 20 mL) was added very slowly and the mixture was warmed to room temperature. A saturated solution of sodium potassium tartrate (20 mL) was added. Water (20 mL) and CH_2Cl_2 (20 mL) were added and the mixture was stirred vigorously for 1 h. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2x100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Chromatography, eluting with 50% EtOAc/hexanes, to afford 0.316 g (83 %) of hemiacetal **3-101** as a clear, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.45 (t, *J* = 9.02 Hz, 2H), 5.16-4.98 (m, 2H), 4.57-4.50 (m, 1H), 4.06 (ddd, *J* = 21.48, 12.41, 7.16 Hz, 3H), 3.92 (s, 4H), 2.59-2.48 (m, 1H), 2.43 (d, *J* = 6.11 Hz, 1H), 1.73-1.46 (m, 12H), 1.15 (t, *J* = 6.99 Hz, 2H), 0.93-0.73 (m, 29H), 0.021 (m, 14H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 137.212, 124.229, 121.894, 117.805, 92.230, 77.319, 76.999, 76.680, 71.093, 70.696, 70.257, 67.480, 67.311, 62.433, 60.231, 41.542, 38.580, 30.832, 25.631, 23.272, 20.710, 18.072, 18.052, 13.868, 13.666, 13.633, 13.518, 11.010, 10.815, 5.924, -5.605; IR (film) cm^{-1}; MS calculated for $C_{16}H_{32}O_4Si$ [M + Na]$^+$: 339.21, found 339.2; $[\alpha]^{24}_D$ = +8.53 ^{o} (*c* 3.8, CH_2Cl_2).



3-101 **3-102**

A mixture of sodium hydride (60% suspension in mineral oil, 0.112 g, 2.82 mmol) in THF (5 mL) was cooled to 0 ^{o}C and treated with ethyl (diethylphosphono)acetate

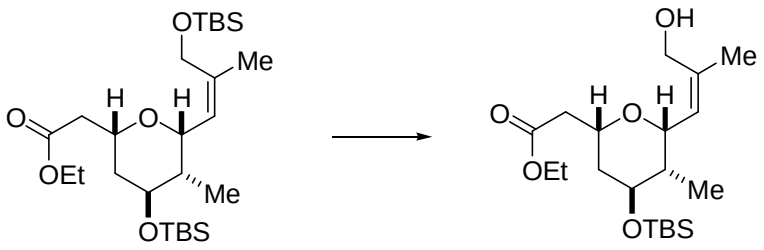
(0.54 mL, 2.82 mmol) and the mixture was stirred for 20 min. A precooled (0 ^{o}C) solution of hemi-acetal **3-101** (0.2779 g, 0.88 mmol) in THF (5 mL) was added to the reaction vessel via cannula. The solution was stirred for 12 h while warming to room temperature. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with hexanes-5%-15% EtOAc/hexanes, to afford 0.31 g (91%) of pyran **3-102** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.57 (d, *J* = 8.58 Hz, 1H), 4.67 (dd, *J* = 8.51, 2.37 Hz, 1H), 4.21 (dd, *J* = 9.21, 4.45 Hz, 1H), 4.01 (d, *J* = 5.28 Hz, 2H), 3.75 (s, 1H), 2.62 (dd, *J* = 16.73, 7.15 Hz, 1H), 2.48 (dd, *J* = 16.72, 6.61 Hz, 1H), 2.34 (d, *J* = 2.68 Hz, 1H), 1.71 (ddd, *J* = 9.35, 6.77, 4.16 Hz, 1H), 1.64 (s, 3H), 1.24 (qd, *J* = 8.34, 7.19 Hz, 2H), 1.06-0.96 (m, 3H), 0.94-0.78 (m, 11H), 0.08 (d, *J* = 18.22 Hz, 7H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 138.250, 123.749, 117.871, 77.318, 77.000, 76.681, 71.992, 71.357, 67.308, 41.418, 29.619, 25.829, 23.413, 18.311, 13.781, 5.603, -5.401; IR (film) 3418.21, 2954.41, 2928.38, 2857.02, 2710.46, 2252.45, 1721.16, 1644.02, 1471.42, 1462.74, 1422.24, 1389.46, 1361.5, 1255.43, 1189.9, 1110.8, 1072.23, 1005.7, 971.947, 939.163, 837.919, 814.775, 777.172, 668.214, 552.506, 537.078, 522.615, 507.187 cm^{-1}; MS calculated for $C_{20}H_{38}O_5Si$ $[M + Na]^+$: 409.25, found 409.4; $[\alpha]^{24}_D$ = 0.64 ^{o} (*c* 3.46, CH_2Cl_2).



3-102 **3-103**

A solution of pyran **3-102** (0.1692 g, 0.653 mmol) in CH_2Cl_2 (6 mL) was cooled to 0 ℃. To the stirring solution was added 2,6-lutidine (0.15 mL, 1.3 mmol).and *t*-butyldimethylsilyl trifluoromethanesulfonate (0.3 mL, 1.3 mmol). After 1 h saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10% EtOAc/hexanes, to afford 0.32 g (98 %) of *bis*-silyl ether **3-103** as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.45 (dd, *J* = 8.99, 1.38 Hz, 1H), 4.66 (dd, *J* = 9.04, 2.85 Hz, 1H), 3.97 (s, 2H), 3.89-3.82 (m, 1H), 2.77 (dd, *J* = 16.81, 6.09 Hz, 1H), 2.59 (dd, *J* = 16.78, 4.00 Hz, 1H), 1.85-1.73 (m, 2H), 1.62 (s, 3H), 1.55 (s, 3H), 0.98-0.83 (m, 18H), 0.13 (d, *J* = 7.84 Hz, 4H), 0.04 (m, 12H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 134.844, 125.400, 118.641, 77.253, 77.140, 77.122, 77.000, 76.863, 76.746, 76.591, 70.438, 68.577, 67.445, 45.267, 25.879, 25.849, 25.795, 25.772, 24.110, 20.991, 18.279, 18.042, 17.978, 14.005, 13.983, 10.792, -3.812, -4.466, -4.490, -4.557, -4.580, -4.793, -5.355, -5.375; IR (film) 3944.68, 3757.62, 3437.49, 3053.73, 2985.27, 2956.34, 2930.31, 2857.02, 2685.39, 2521.47, 2410.58, 2348.8887, 2305.48, 1731.76, 1643.05, 1550.49, 1471.4442, 1462.74, 1422.24, 1377.89, 1265.07, 1161.9, 1076.08, 1052.94, 1006.66, 984.482, 939.163, 895.773, 837.919, 741.44496, 705.819, 554.434 cm^{-1};

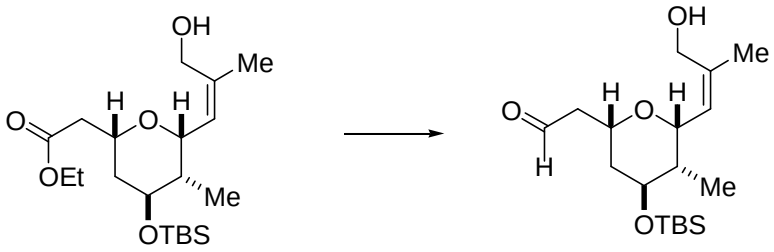
MS calculated for $C_{26}H_{52}O_5Si_2$ [M + Na]$^+$: 523.34, found 523.4; $[\alpha]^{24}_D$ = +34.2 ^{o} (*c* 1.28, CH_2Cl_2).



3-103

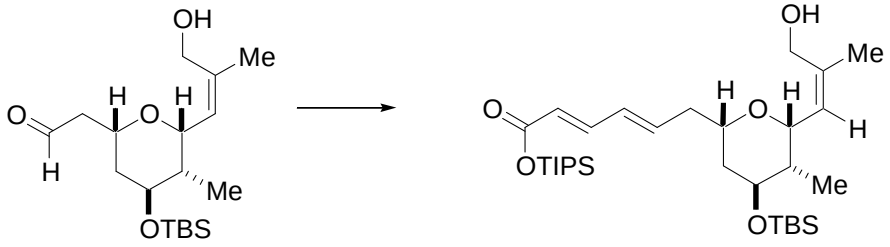
A solution of the *bis*-silyl ether **3-103** (0.2 g, 0.4 mmol) in CH_2Cl_2 (4 mL) was cooled to -10 ℃. To the stirring solution was added *t*-butylammonium fluoride (TBAF) (0.44 mL of 1M solution in THF, 0.44 mmol). The reaction was closely monitored by TLC. In ~40 min the primary silyl group was removed. Saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-40% EtOAc/hexanes, to afford 0.11 g (71 %) of the allylic alcohol as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.66 (dd, *J* = 8.35, 1.23 Hz, 1H), 4.59 (dd, *J* = 8.28, 5.05 Hz, 1H), 4.14-4.08 (m, 3H), 4.06 (s, 2H), 3.68 (dt, *J* = 9.52, 4.48 Hz, 1H), 2.56 (dd, *J* = 15.02, 8.16 Hz, 1H), 2.42 (dd, *J* = 15.02, 5.20 Hz, 1H), 1.90 (ddd, *J* = 12.64, 4.35, 2.81 Hz, 1H), 1.83-1.74 (m, 1H), 1.70 (s, 3H), 1.27-1.21 (m, 4H), 0.85 (m, 13H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 171.445, 141.924, 120.034, 77.254, 77.000, 76.746, 72.558, 70.179, 68.214, 66.717, 60.460, 41.358, 41.248, 40.188, 25.787, 18.011, 14.193, 13.043, -4.177, -4.731; IR (film) 2955.38, 2929.34, 2857.02, 2222.56, 1736.58, 1462.74, 1371.14, 1322.93, 1301.72, 1255.43, 1213.01,

1161.9, 1081.87, 1044.26, 985.447, 937.235, 919.879, 906.379, 836.955, 775.244, 736.674, 702.926, 666.285, 579.504, 538.042, 520.686 cm^{-1}; MS calculated for $C_{20}H_{38}O_5Si$ $[M + Na]^+$: 409.25, found 409.3; $[\alpha]^{24}_D$ = +29.5 ^{o} (*c* 4.65, CH_2Cl_2).



A solution of the ester (96 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was cooled to -78 ^{o}C. DIBAL-H (1.0M in hexanes, 0.75 mL, 0.75 mmol) was added at once. The reaction was monitored by TLC and was complete in within 20 min. A saturated solution of sodium potassium tartrate (10 mL) was added and the mixture was warmed to room temperature. Water (5 mL) and CH_2Cl_2 (5 mL) were added and the mixture was stirred vigorously for 1 h. The layers were separated and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Chromatography, eluting with 15% EtOAc/hexanes, to afford 79 mg (82 %) of the aldehyde as a clear, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 9.72 (s, 1H), 5.47 (dd, *J* = 7.84, 1.34 Hz, 1H), 4.78 (dd, *J* = 7.79, 2.29 Hz, 1H), 4.43-4.32 (m, 1H), 4.01 (s, 3H), 3.86 (d, *J* = 2.76 Hz, 1H), 2.61-2.51 (m, 1H), 2.46 (dd, *J* = 4.79, 2.00 Hz, 1H), 1.74-1.52 (m, 11H), 1.33-1.16 (m, 11H), 0.95-0.78 (m, 9H), 0.06 (m, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 201.611, 136.903, 124.600, 77.253, 77.000, 76.848, 76.745, 71.598, 70.495, 68.256, 68.029, 49.628, 39.408, 34.073, 29.690, 25.756, 18.009, 14.109, 11.215, -

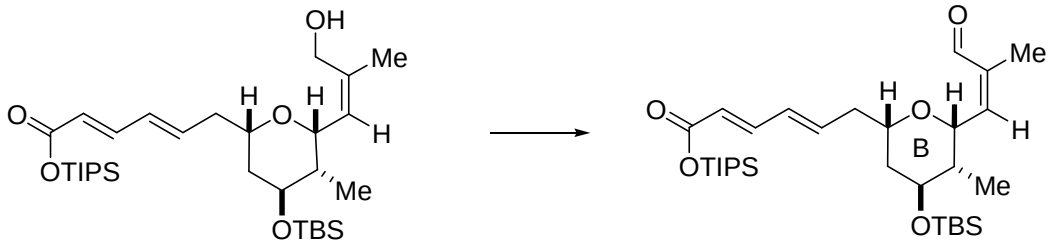
4.890, -4.933; IR (film) 3073.98, 3026.73, 2973.7, 2928.38, 2973.42, 1728.87, 1639.2, 1496.49, 1454.06, 1435.74, 1367.28, 1269.9, 1202.4, 1070.3, 1047.16, 997.017, 913.129, 737.639, 697.141 cm^{-1}; MS calculated for $C_{18}H_{34}O_4Si$ $[M + Na]^+$: 365.22, found 365.2; $[\alpha]^{24}_D$ = +18.5 ^{o} (*c* 0.7, CH_2Cl_2).



3-109

A solution of phosphonate **3-108** (0.97 mL of 1M solution in THF, 0.97 mmol) and THF (1 mL) were cooled to -78 ^{o}C. Lithium bis(trimethylsilyl)amide (LiHMDS) (0.97 mL of 1M solution in THF, 0.97 mmol) was added and the yellow solution was stirred for 1 h. The aldehyde (0.2779 g, 0.88 mmol) in THF (1.4 mL) was added to the reaction vessel via cannula. The solution was stirred for 2 h while warming to 0 ^{o}C. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with hexanes-5%-15% EtOAc/hexanes, to afford 0.121 g (89%) of polyene **3-109** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm 7.26-7.20 (m, 1H), 6.30-6.20 (m, 2H), 6.20-6.13 (m, 1H), 5.86-5.78 (m, 1H), 5.56-5.49 (m, 1H), 4.78-4.73 (m, 1H), 4.04 (s, 2H), 3.97-3.89 (m, 1H), 3.88-3.83 (m, 1H), 2.44-2.36 (m, 1H), 2.36-2.27 (m, 1H), 1.70 (s, 3H), 1.59 (s, 10H), 1.28 (d, *J*

= 15.44 Hz, 9H), 1.10 (d, *J* = 7.47 Hz, 22H), 0.97-0.87 (m, 15H), 0.06 (d, *J* = 6.96 Hz, 6H); ^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 166.883, 145.193, 140.140, 136.700, 130.271, 124.972, 121.500, 77.407, 77.253, 77.000, 76.874, 76.745, 76.597, 76.558, 76.541, 76.519, 71.589, 71.463, 70.733, 68.360, 39.637, 39.603, 33.900, 29.697, 25.810, 25.753, 17.998, 17.818, 14.116, 12.009, 11.266, -4.868, -4.915; IR (film) 3417.24, 2926.45, 2856.06, 2348.87, 2127.1, 1642.09, 1462.74, 1377.89, 1264.11, 1170.58, 1079.94, 883.238, 835.99, 740.531, 663.393, 597.825, 530.328 cm^{-1}; MS calculated for $C_{31}H_{58}O_5Si_2$ [M + Na]$^+$: 589.38, found 589.4; $[\alpha]^{24}_D$ = +11.3 ^{o} (*c* 0.865, CH_2Cl_2).

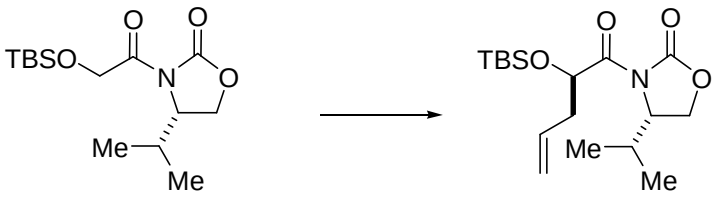


3-109 **3-110**

To a solution of polyene **3-109** (30 mg, 0.052 mmol) in CH_2Cl_2 (1 mL) was added 85% MnO_2 (110 mg, 1.04 mmol). The reaction mixture was stirred at ambient temperature 12 h and then filtered through celite. The celite was washed with excess CH_2Cl_2. The combined filtrates were concentrated *in vacuo*. The residue was mixed

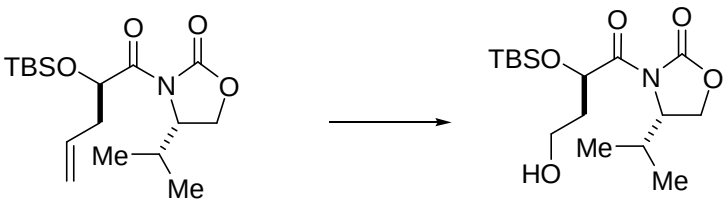
with silica gel and hexanes, concentrated *in vacuo* and loaded onto the column as a powder. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-15% EtOAc/hexanes, to afford 26 mg (90%) of the homologated pyran **3-110** as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 9.42 (s, 1H), 7.27-7.18 (m, 1H), 6.45 (d, *J* = 6.88 Hz, 1H), 6.24 (dd, *J* = 14.98, 11.04 Hz, 1H), 6.18-6.10 (m, 1H), 5.84-5.79 (m, 1H), 4.96 (d, *J* = 6.57 Hz, 1H), 3.94 (td, *J* = 10.28, 5.23 Hz, 1H), 3.87 (s, 1H), 2.40 (td, *J* = 13.85, 6.79 Hz, 1H), 2.36-2.28 (m, 1H), 1.75 (s, 3H), 1.08 (d, *J* = 7.48 Hz, 21H), 0.95-0.88 (m, 14H), 0.06 (d, *J* = 7.58 Hz, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 194.751, 166.782, 153.436, 144.949, 139.574, 137.866, 130.515, 121.778, 77.253, 77.000, 76.745, 72.496, 71.584, 70.397, 39.464, 39.258, 33.749, 31.575, 25.772, 25.731, 22.640, 17.980, 17.807, 14.102, 12.010, 11.386, 9.659, -4.851, -4.951; IR (film) 3434.6, 2927.41, 2866.67, 2359.48, 2341.16, 2089.49, 1692.23, 1644.02, 1463.71, 1257.36, 1142.62, 1062.59, 1000.87, 835.026, 668.214, 551.542 cm^{-1}; MS calculated for $C_{31}H_{56}O_5Si_2$ [M + Na]$^+$: 587.37, found 587.4; $[\alpha]^{24}_D$ = +25.1 ^{o} (*c* 0.39, CH_2Cl_2).

B-3. Side-Chain: C26-C35 Segment of (-)-lasonolide A:



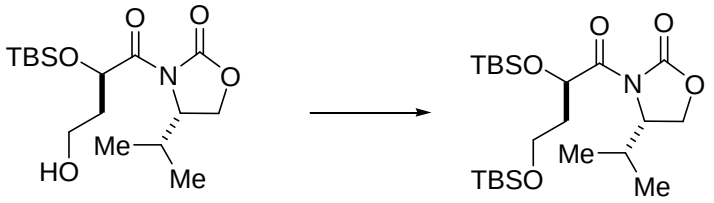
3-112 **3-115**

A flask containing a solution of freshly prepared sodium bis(trimethylsilyl)amide (NaHMDS) (12.0 mL, 8.97 mmol; 0.75 M in toluene/THF) and 30 mL THF was cooled to -78 ºC under an argon atmosphere. A solution of glycolate **3-112** (1.80 g, 5.98 mmol) in 30 mL THF was added dropwise over 20 min and the solution was stirred at -78 ºC for 45 min. Freshly distilled allyl iodide (1.6 mL, 17.3 mmol) was added and the resulting mixture was stirred for 30 min. The reaction mixture was quenched using saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave 1.76 g (86%) of the desired alkylation product **3-115** as a single diastereomer (judged by NMR analysis). ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.92-5.74 (m, 1H), 5.35 (dd, *J* = 7.21, 3.97 Hz, 1H), 5.06 (dd, *J* = 20.41, 4.95 Hz, 2H), 4.45 (td, *J* = 8.49, 3.57 Hz, 1H), 4.28 (t, *J* = 8.87 Hz, 1H), 4.17 (dd, *J* = 9.16, 3.38 Hz, 1H), 2.59-2.46 (m, 1H), 2.35 (td, *J* = 14.78, 7.49 Hz, 1H), 2.25 (dtd, *J* = 13.88, 6.94, 4.02 Hz, 1H), 0.90-0.77 (m, 15H), 0.06 (t, *J* = 9.60 Hz, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 173.413, 153.561, 133.337, 118.035, 77.318, 77.000, 76.681, 70.944, 58.111, 39.900, 28.164, 25.670, 25.582, 18.245, -4.936, -4.995, -5.203, -5.256; IR (film) 3078.8, 2959.23, 29.30.31, 2885.95, 2857.95, 2391.3, 1784.94, 1716.34, 1642.09, 1487.81, 1472.38, 1389.46, 1362.46, 1247.72, 1116.58, 970.983, 812.849, 663.393, 476.331, 431.977 cm^{-1}; MS calculated for $C_{17}H_{31}NO_4Si$ $[M + Na]^+$: 364.20, found 364.2; $[\alpha]^{24}_D$ = +5.4 ^{o} (*c* 2.3, CH_2Cl_2).



3-115 **3-116**

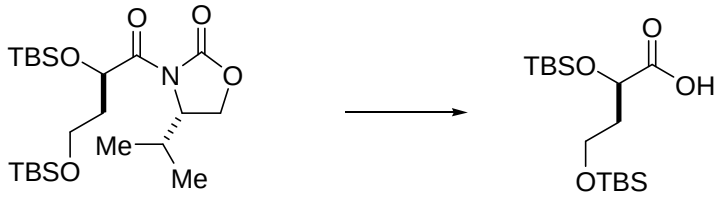
To a two-neck round-bottom flask fitted with a bubbler and a drying tube were added CH_2Cl_2 (50 mL) and the olefin **3-115** (1.435 g, 4.2 mmol). The solution was treated with ozone for 1 h at −78 ^oC then allowed to warm to room temperature. Then $NaBH_4$ (1.59g, 42 mmol) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was washed with water (2.30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 1.02 g (70%) of primary alcohol **3-116**, which was used directly in the next reaction.



3-116

A solution of alcohol **3-116** (1.02 g, 3.0 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 ℃. To the stirring solution was added 2,6-lutidine (0.4 mL, 3.6 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (0.82 mL, 3.6 mmol). After 1 h saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10% EtOAc/hexanes, to afford 1.11 g (81 %) of the

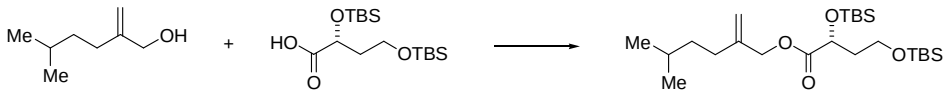
bis-silyl ether as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.35 (dd, *J* = 7.21, 3.97 Hz, 1H), 4.45 (td, *J* = 8.49, 3.57 Hz, 1H), 4.28 (t, *J* = 8.87 Hz, 1H), 4.17 (dd, *J* = 9.16, 3.38 Hz, 1H), 3.21-3.34 (m, 1H), 2.59-2.46 (m, 1H), 2.35 (td, *J* = 14.78, 7.49 Hz, 1H), 2.25 (dtd, *J* = 13.88, 6.94, 4.02 Hz, 1H), 0.90-0.77 (m, 15H), 0.06 (t, *J* = 9.60 Hz, 6H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 173.413, 153.561, 77.318, 77.000, 76.681, 70.944, 58.111, 55.822, 39.583, 28.164, 25.670, 25.582, 18.245, -4.936, -4.995, -5.203, -5.256; IR (film) 2955, 2876, 1780, 1715, 1454, 1389, 1350, 1211, 1136, 1103, 1015, 972, 733, 700 cm^{-1}; MS calculated for $C_{22}H_{45}NO_5Si_2$ [M + Na]$^{+}$:491.28 , found + 491.3; $[\alpha]^{24}_{D}$ = -43.4 ^{o} (*c* 0.99, CH_2Cl_2).



3-118

A solution of the *bis*-silyl ether (0.44 g, 1.0 mmol) in THF (10 mL) at 0 ^{o}C was treated with LiOH-H_2O (3.0 mL, 6.0 mmol) and hydrogen peroxide (30% in H_2O, 2 mL). The resultant suspension was stirred at ambient temperature for 2 h and treated with water (10 mL). The resulting solution was diluted with Et_2O (5 mL) and washed with saturated $Na_2S_2O_3$ (15 mL) solution. The organic phase was washed with 25% aqueous NaOH several times. The aqueous phase was then treated with 10% H_2SO_4 and extracted with Et_2O (10 mL x2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*, affording 0.302g (93 %) of acid **3-118**. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.87 (s, 1H), 5.22

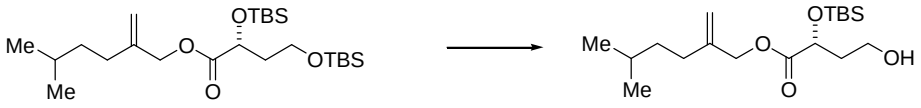
(m,1H), 3.81-3.68 (m, 2H), 1.33 (m, 2H), 0.92-0.83 (m, 18H), 0.8-0.04 (m, 12H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 176.50, 72.97, 58.66, 36.17, 27.74, 25.91, 25.73, 22.47, 18.29, 18.26, -4.882, -5.327, -5.365, -5.462; IR (film) 3445, 2955, 2876, 1456, 1414, 1364, 1238, 1096, 1007, 741 cm^{-1}; MS calculated for $C_{16}H_{36}O_4Si_2$ $[M + Na]^+$: 380.22, found 380.2; $[\alpha]^{24}_D$ = -4.49 ^{o} (*c* 2.4, CH_2Cl_2).



3-121 **3-118** **3-122**

A solution of the alcohol **3-121** (0.6 g, 1.9 mmol) and acid **3-118** (0.696 g, 2.0 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 ^{o}C. dicyclohexyl carbodiimide (DCC) (0.5 g, 2.0 mmol), and 4-dimethylaminopyridine (DMAP) (0.6 g, 2.0 mmol) were added and the flask was removed from the ice bath. After 4 days, the resulting solution was diluted with ether (20 mL) and washed with saturated NH_4Cl (25 mL) solution. The aqueous phase was extracted with ether (20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 10%-25%-40% EtOAc/hexanes, to afford 0.334 g (61 %) of ester **3-122**. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.02 (s, 1H), 4.93 (s, 1H), 4.56 (s, 2H), 4.43-4.38 (m, 1H), 3.81-3.68 (m, 2H), 2.06 (m, 2H), 1.97-1.82 (m, 2H), 1.60-1.50 (m, 1H), 1.33 (m, 2H), 0.92-0.83 (m, 18H), 0.8-0.04 (m, 12H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 173.742,

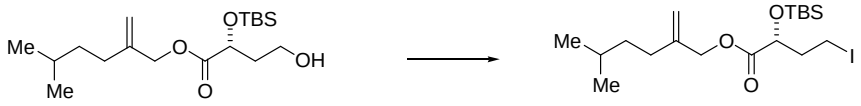
144.127, 112.158, 68.872, 67.056, 65.850, 58.641, 38.218, 36.644, 31.076, 27.774, 25.913, 25.735, 22.479, 18.295, 18.263, -4.882, -5.327, -5.365, -5.462; IR (film) 2955.38, 2929.34, 2857.02, 1756.83, 1471.42, 1361.5, 1255.43, 1138.76, 1097.3, 1005.7, 836.955, 778.136, 523.579, 512.972, 503.33 cm^{-1}; MS calculated for $C_{24}H_{50}O_4Si_2$ $[M + Na]^+$: 481.32, found 481.3; $[\alpha]^{24}_D$ = +9.6 ^{o} (*c* 0.54, CH_2Cl_2).



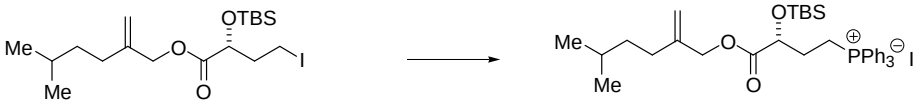
3-122

A solution of the *bis*-silyl ether **3-123** (0.2 g, 0.4 mmol) in CH_2Cl_2 (4 mL) was cooled to -10 ℃. To the stirring solution was added *t*-butylammonium fluoride (TBAF) (0.44 mL of 1M solution in THF, 0.44 mmol). The reaction was closely monitored by TLC. In 40 min the primary silyl group was removed. Saturated $NaHCO_3$ solution was added and the mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-40% EtOAc/hexanes, to afford 0.11 g (71 %) of the primary alcohol as a viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 5.02 (d, *J* = 0.6 Hz, 1H), 4.95 (d, *J* = 0.6 Hz, 1H), 4.62 (s, 2H), 4.47 (dd, *J* = 6.6, 4.8 Hz, 1H), 3.79 (q, *J* = 5.5 Hz, 2H), 2.09-1.98 (m, 5H), 1.55 (td, *J* = 13.30, 6.66 Hz, 1H), 1.37-1.30 (m, 2H), 0.92 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.11 (s, 3H), 0.08 (s, 3H).; ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 173.3, 143.9, 112.5, 70.7, 67.3, 59.5, 36.9, 36.6, 31.0, 27.8, 25.7, 22.5, 18.2, -5.0, -5.6; IR (film) 3436.53, 3030,59, 2923.56, 2854.13, 1716.34, 1496.49, 1454.06,

1363.43, 1245.79, 1096.33, 1061.62, 1026.91, 1009.55, 983.518, 802.242, 737.639, 699.069, 609.396 cm^{-1}; MS calculated for $C_{18}H_{36}O_4Si$ $[M + Na]^+$: 367.24, found 367.2; $[\alpha]^{24}_D$ = +29.8 ^{o} (*c* 0.4, CH_2Cl_2).



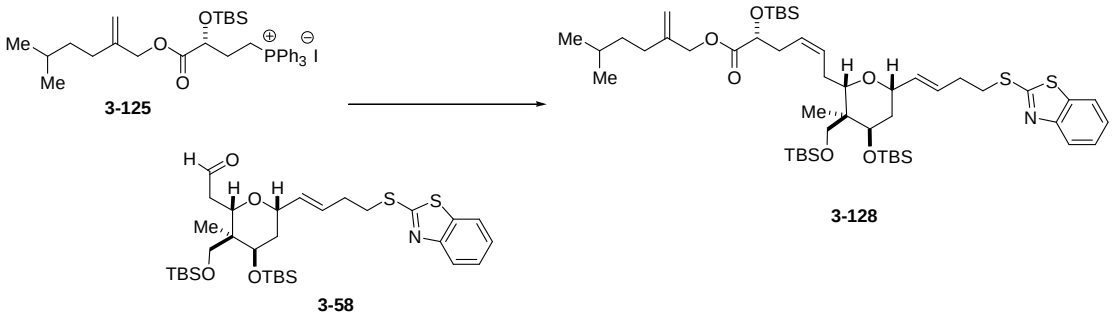
A solution of the primary alcohol (0.135 g, 0.39 mmol) in THF (10 mL) was cooled to 0 ^{o}C. Ph_3P (0.154 g, 0.59 mmol), imidazole (0.080 g, 1.18 mmol), and I_2 (0.149 g, 0.59 mmol) were added. After 2 h, the resulting solution was diluted with ether (20 mL) and washed with saturated $Na_2S_2O_3$ (15 mL) solution. The aqueous phase was extracted with ether (20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 10%-25%-40% EtOAc/hexanes, to afford 0.1 g (81 %) of the iodide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.95 (d, 1H, *J* = 0.7 Hz), 4.57 (s, 2H), 4.30 (dd, 1H, *J* = 7.8, 4.3 Hz), 3.33-3.19 (m, 2H), 2.32-2.13 (m, 2H), 2.06 (t, 2H, *J* = 8.0 Hz), 1.62-1.48 (m, 1H), 1.38-1.28 (m, 2H), 0.91 (s, 9H), 0.90 (d, 6H, *J* = 6.7 Hz), 0.11 (s, 6H). ^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm ; IR (film) 3359.39, 2925.48, 2854.13, 1733.69, 1653.66, 1633.41, 1463.71, 1428.99, 1376.93, 1256.4, 1077.05, 1004.73, 835.99, 776.208, 741.496 cm^{-1}; MS calculated for $C_{18}H_{35}IO_3Si$ $[M + Na]^+$: 486.14, found 486.1; $[\alpha]^{24}_D$ = +31.8 ^{o} (*c* 0.67, CH_2Cl_2).



3-125

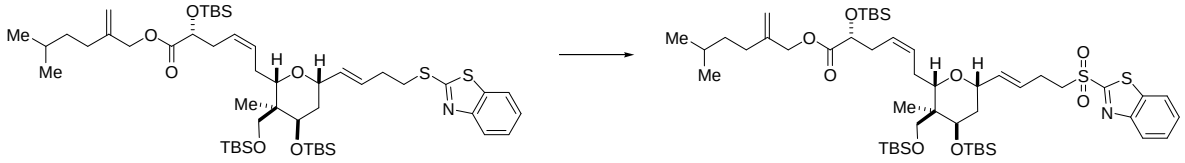
To a solution of the iodide (0.934 g, 0.3219 mmol) in CH_3CN (6 mL) was added Ph_3P (0.17 g, 0.65 mmol). The resulting solution was stirred for 12 h under reflux. The solvent was removed *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 10%-25%-40% EtOAc/hexanes, to afford 0.182 g (79%) of phosphonium salt **3-125** ^{1}H NMR (400 MHz, *CDCl$_3$*): δ ppm 7.88-7.21 (m, 15H), 4.83 (s, 1H), 4.77 (s, 1H), 4.57 (t, 1H, *J* = 5.4 Hz), 4.44 (s, 2H), 3.85-3.68 (m, 1H), 3.37-3.20 (m, 1H), 2.05-1.92 (m, 1H), 1.92-1.77 (m, 3H), 1.43-1.30 (m, 1H), 1.20-1.04 (m, 2H), 0.74 (s, 9H), 0.72 (d, 6H, *J* = 6.8 Hz), 0.01 (s, 3H), 0.002 (s,3H). ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 171.4, 143.3, 135.2, 135.2, 133.3, 133.2, 130.6, 130.4, 117.8, 116.6, 112.3, 70.2, 67.3, 36.2, 30.7, 27.4, 25.5, 22.2, 17.8, -5.0, -5.1; IR (film) 3423.03, 3051.8, 2955.38, 2931.27, 2858.95, 2311.27, 1970.89, 1902.43, 1825.29, 1749.12, 1651.73, 1616.06, 1588.09, 1484.92, 1470.46, 1437.67, 1391.39, 1364.39, 1338.36, 1267, 1190.83, 1162.87, 1111.76, 1027.87, 997.017, 949.77, 856.239, 822.491, 792.6, 727.032, 702.926, 612.288, 541.899 cm^{-1}; MS calculated for $C_{36}H_{50}O_3PSi$ $[M + Na]^+$: 621.23, found 621.2; $[\alpha]^{24}_D$ = +10.5 ^{o} (*c* 0.44, CH_2Cl_2).

B-4. Coupling Silyl-Protected Segments of (-)-lasonolide A:



A solution of phosphonium salt **3-125** (88.6 mg, 0.12 mmol) in THF (1 mL) was cooled to -78 ^{o}C. Potassium bis(trimethylsilyl)amide (KHMDS) (0.25 mL of 0.5M solution in toluene, 0.12 mmol) was added and the yellow solution was stirred for 15 min. A solution of aldehyde **3-58** (21.5 mg, 0.036 mmol) in THF (2 mL + 1 mL rinse) was added to the reaction vessel via cannula. The solution was stirred for 12 h while warming to ambient temperature. Half-saturated NH_4Cl solution was added and the resulting mixture was stirred vigorously. The layers were separated and the aqueous solution was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with hexanes-5%-15%-60% EtOAc/hexanes, to afford 25.4 mg (74%) of **3-128** as an opaque, viscous oil. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.88-7.84 (m, 1H), 7.77-7.73 (m, 1H), 7.43-7.38 (m, 1H), 7.32-7.27 (m, 1H), 5.72-5.57 (m, 3H), 5.49-5.40 (m, 1H), 5.01 (s, 1H), 4.95-4.91 (m, 1H), 4.55 (s, 2H), 4.27-4.18 (m, 2H), 3.82-3.76 (m, 1H), 3.64-3.59 (m, 1H), 3.50-3.46 (m, 1H), 3.39 (s, 2H), 2.05 (s, 3H), 2.28-2.20 (m, 1H), 2.49-2.41

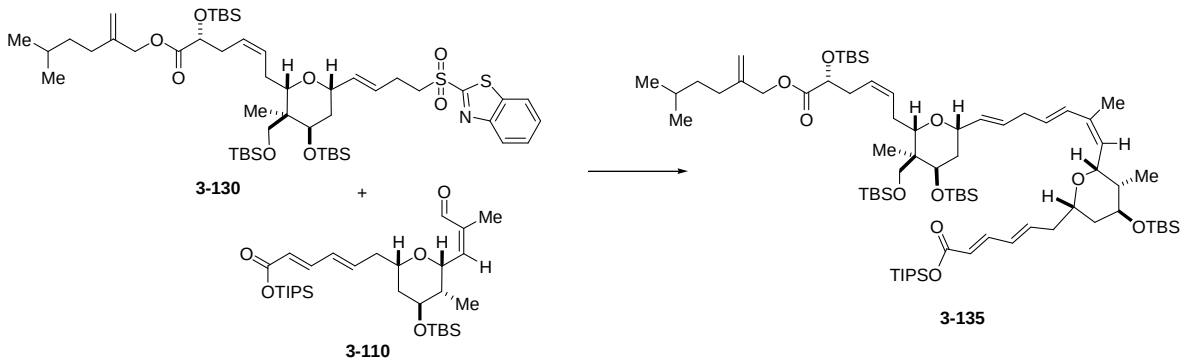
(m, 1H), 2.59-2.52 (m, 2H), 0.05 (dd, *J* = 18.09, 7.58 Hz, 17H), 0.89 (s, 37H), 1.25 (s, 22H), 0.94 (d, *J* = 7.74 Hz, 3H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 196.897, 172.945, 166.983, 153.332, 144.078, 135.200, 133.905, 130.748, 127.308, 125.974, 124.583, 124.108, 121.484, 120.898, 112.123, 77.254, 77.137, 77.123, 77.000, 76.910, 76.746, 72.244, 71.872, 71.213, 66.994, 66.538, 42.269, 36.623, 35.925, 33.555, 32.953, 32.192, 31.928, 31.068, 30.036, 29.701, 29.660, 29.363, 28.446, 27.765, 26.058, 26.029, 25.922, 25.751, 22.693, 22.501, 18.333, 18.286, 18.158, 14.894, 14.119, 7.030, 5.101, -4.368, -4.887, -4.972, -5.172, -5.249, -5.472; IR (film) 3359.39, 2925.48, 2854.13, 1733.69, 1653.66, 1633.41, 1463.71, 1428.99, 1376.93, 1256.4, 1077.05, 1004.73, 835.99, 776.208, 741.496 cm^{-1}; MS calculated for $C_{50}H_{87}NO_6S_2Si_3$ [M + Na]$^+$: 968.53, found 968.5; [α]$^{24}_D$ = -4.3 ^{o} (*c* 0.76, CH_2Cl_2).



3-128 **3-130**

A solution of sulfide **3-128** (4.66 mg, 0.005 mmol) in ethanol (1 mL) at 0 ^{o}C was treated with ammonium molybdate tetrahydrate (2 mg, 0.001 mmol) in hydrogen peroxide (30% in H_2O, 6 μL) (mixed in small, conical flask and transferred via micro-syringe). The resultant suspension was stirred at ambient temperature for 8 h and treated with water (10 mL). The resulting solution was diluted with ether (5 mL) and washed with saturated $Na_2S_2O_3$ (15 mL) solution. The aqueous phase was extracted with ether (10 mL x2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient

flash column chromatography, eluting with 10%-25%-40% EtOAc/hexanes, to afford 3.8 mg (78 %) of sulfone **3-130**. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 8.22 (d, *J* = 8.14 Hz, 1H), 8.02 (d, *J* = 8.02 Hz, 1H), 7.62 (td, *J* = 15.13, 7.35 Hz, 2H), 5.42 (dd, *J* = 17.63, 7.45 Hz, 1H), 5.63-5.53 (m, 3H), 5.00 (s, 1H), 4.92 (s, 1H), 4.54 (s, 2H), 4.22 (t, *J* = 6.14 Hz, 1H), 4.12 (d, *J* = 11.68 Hz, 1H), 3.76 (d, *J* = 10.83 Hz, 1H), 3.58 (dd, *J* = 16.51, 8.44 Hz, 4H), 3.45 (d, *J* = 9.40 Hz, 1H), 3.35-3.30 (m, 1H), 2.64-2.58 (m, 2H), 2.53-2.38 (m, 2H), 2.27 (s, 1H), 2.21 (dd, *J* = 15.13, 7.19 Hz, 1H), 2.07-2.01 (m, 3H), 1.25 (s, 4H), 0.88 (d, *J* = 4.69 Hz, 38H), 0.84 (d, *J* = 4.06 Hz, 4H), 0.03 (m, 19H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 196.897, 172.909, 165.699, 152.734, 144.058, 136.791, 134.593, 130.622, 128.009, 127.642, 125.515, 124.656, 124.624, 122.309, 112.134, 77.253, 77.131, 77.000, 76.878, 76.745, 72.201, 71.512, 71.471, 71.065, 67.001, 66.454, 54.094, 42.230, 36.609, 35.762, 33.513, 31.924, 31.053, 29.695, 29.656, 29.359, 28.377, 27.758, 26.038, 26.009, 25.896, 25.733, 25.308, 22.689, 22.495, 18.338, 18.315, 18.271, 18.133, 14.861, 14.773, 14.116, 7.010, 5.069, 1.015, -4.401, -4.901, -4.979, -5.194, -5.264, -5.352, -5.490; IR (film) 3854.04, 3751.83, 3430.74, 2955.38, 2927.41, 2857.02, 1730.8, 1646.91, 1462.74, 1430.92, 1389.46, 1361.5, 1646.91, 1462.74, 1430.92, 1389.46, 1361.5, 1250.61, 1231.33, 1154.19, 1120.44, 960.377, 835.99, 775.244, 590.111, 523.579 cm^{-1}; MS calculated for CHO [M + Na]$^{+}$: 1000.51, found 1000.6; $[\alpha]^{24}_{D}$ = -16.2 ^{o} (*c* 0.12, CH_2Cl_2).

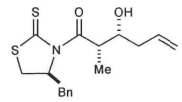


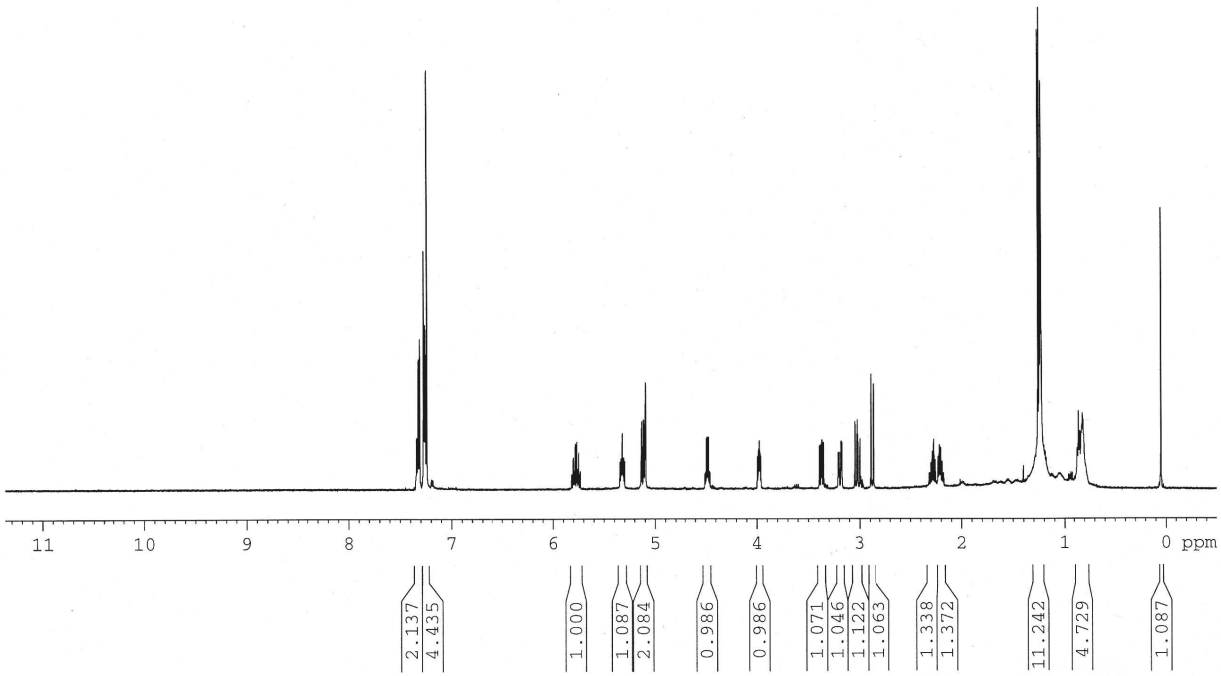
Lithium bis(trimethylsilyl)amide (LiHMDS) (1M in THF, 11 μL, 0.011 mmol) was added dropwise to a solution of sulfone **3-130** (8.7 mg, 0.009 mmol) in dry THF (1 mL) at –78 ^{o}C. Immediately, a solution of aldehyde **3-110** (5.0 mg, 0.009 mmol) in dry THF (0.5 mL + 0.5 mL rinse) was added slowly via micro-syringe. The reaction mixture was stirred for 12 h at -20 ^{o}C. The resulting mixture was partitioned between water (10 mL) and Et_2O (10 mL), and the aqueous phase was extracted with Et_2O (10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by gradient flash column chromatography, eluting with 5%-10%-25% EtOAc/hexanes, to afford 12.1 mg (89 %) of **3-135**. ^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.25-7.18 (m, 2H), 6.26-6.11 (m, 2H), 6.09-6.03 (m, 1H), 5.83-5.77 (m, 1H), 5.70-5.57 (m, 3H), 5.53-5.49 (m, 1H), 5.49-5.47 (m, 1H), 5.44-5.40 (m, 1H), 5.15-5.10 (m, 1H), 5.05-5.00 (m, 1H), 4.97-4.91 (m, 1H), 4.83-4.78 (m, 1H), 4.60-4.53 (m, 2H), 4.27-4.16 (m, 2H), 3.95-3.88 (m, 1H), 3.86-3.82 (m, 1H), 3.80-3.77 (m, 1H), 3.64-3.58 (m, 1H), 3.50-3.45 (m, 1H), 3.39-3.33 (m, 1H), 2.85-2.79 (m, 2H), 2.52-2.36 (m, 3H), 2.33-2.22 (m, 2H), 2.04 (s, 3H), 1.75 (s, 2H), 1.70-1.66 (m, 1H), 0.09-0.01 (m, 15H), 0.89 (t, *J* = 5.66 Hz, 29H), 1.09 (d, *J* = 7.46 Hz, 12H), 1.25 (s, 5H), 1.33 (m, 5H); ^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 171.152, 145.241, 144.075, 140.296, 135.233, 132.197, 130.842, 130.220, 129.772,

128.333, 126.768, 124.488, 121.475, 112.137, 72.247, 71.875, 71.598, 70.835, 67.004, 60.407, 42.282, 39.900, 39.706, 36.623, 31.073, 29.713, 27.774, 26.071, 25.941, 25.776, 25.759, 22.519, 21.072, 17.843, 14.215, 12.029, 11.325, 7.049, 1.039, -4.343, -4.855, -4.888, -4.950, -5.169, -5.235, -5.457; IR (film) 3853.08, 3837.65, 3801.01, 3749.9, 3734.48, 3710.37, 3688.19, 3674.69, 3647.7, 3565.74, 2959.23, 2924.52, 2853.17, 2390.33, 2348.87, 1731.76, 1668.12, 1557.24, 1539.88, 1507.1, 1456.96, 1376.93, 1261.22, 1094.4, 1018.23, 826.989, 800.314, 741.496, 703.89, 663.393, 581.433, 512.972 cm^{-1}; MS calculated for $C_{74}H_{138}O_{10}Si_5$ $[M + Na]^+$: 1349.91, found 1349.9; $[\alpha]^{24}_D$ = -18.6 ^{o} (*c* 0.2, CH_2Cl_2).

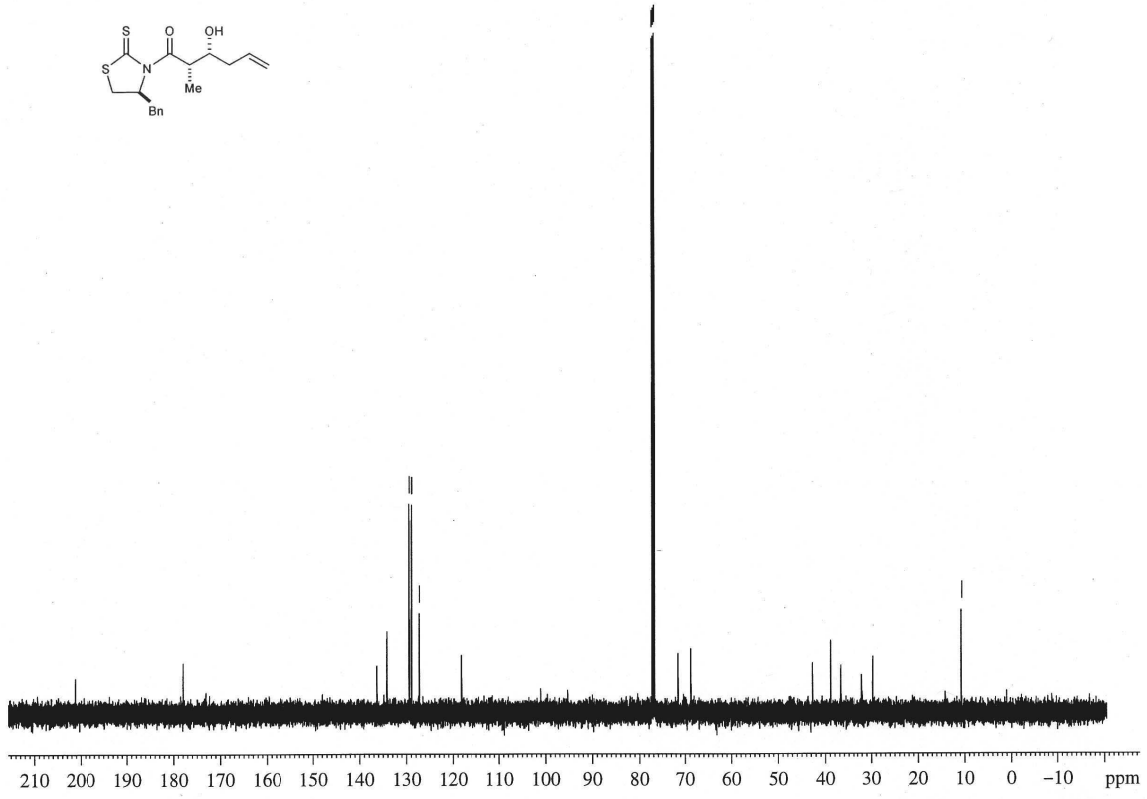
APPENDIX

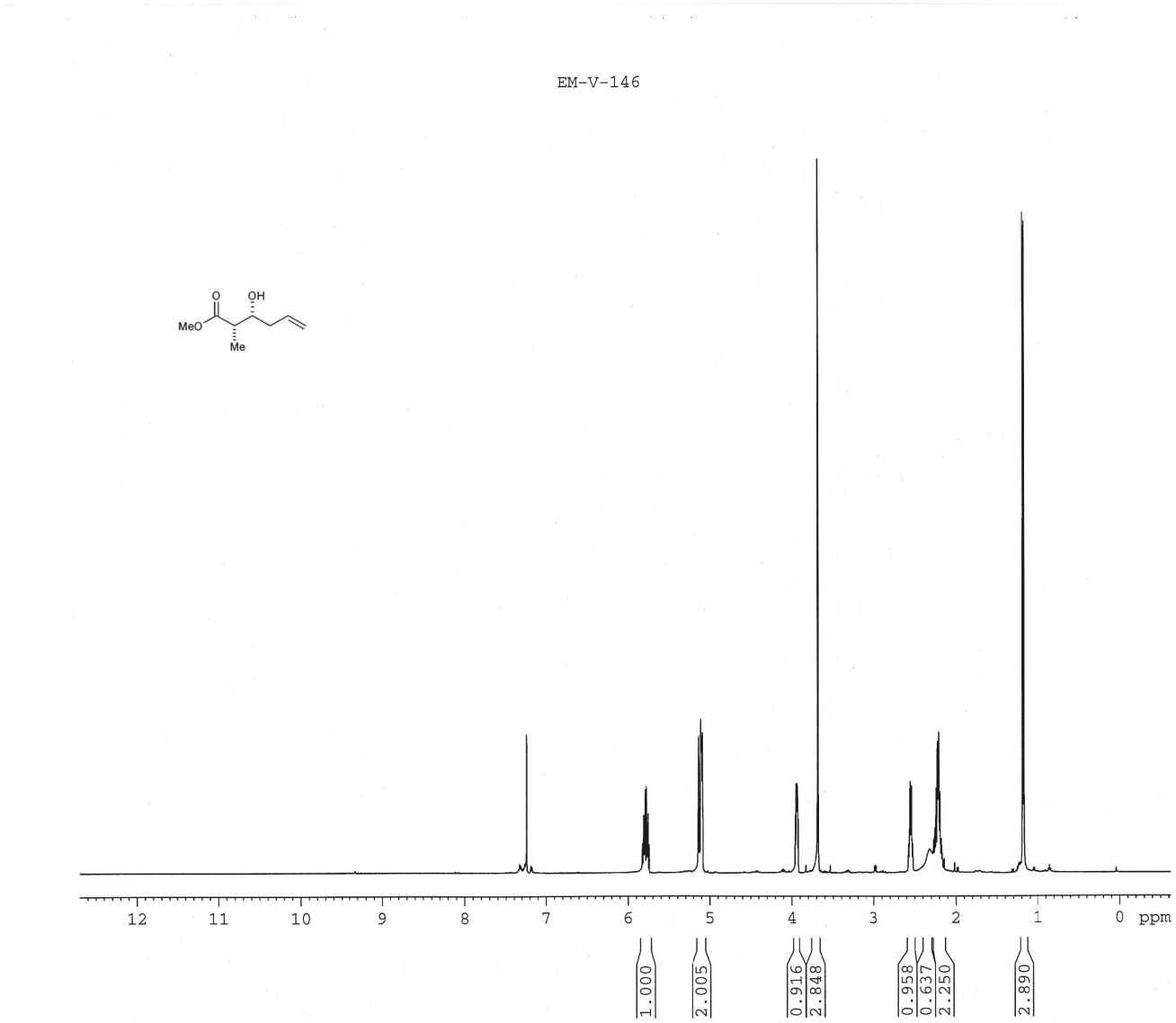
EM-II-145

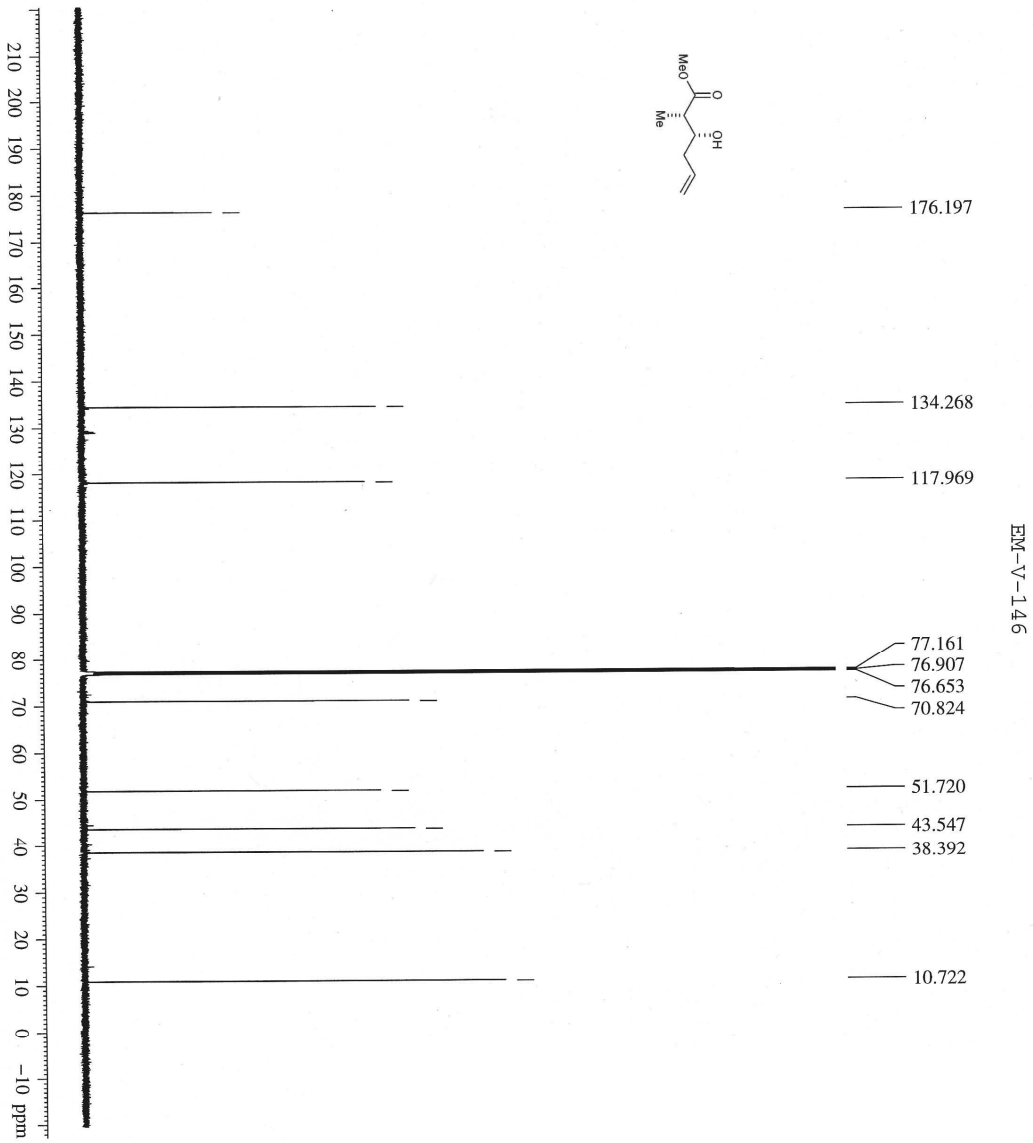

S
O
OH
S
N
Me
Bn

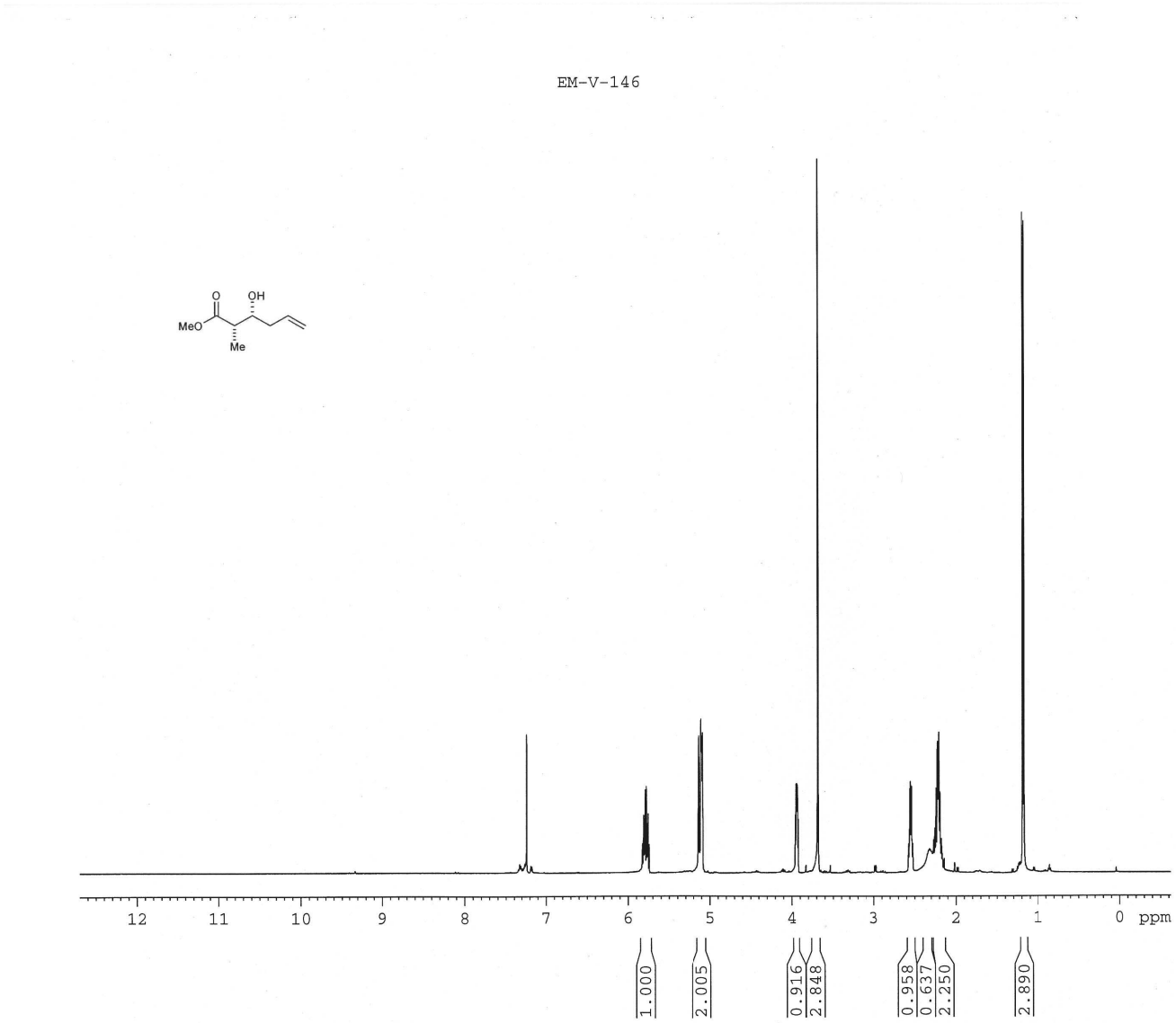

11
10
9
8
7
6
5
4
3
2
1
0 ppm
2.137
4.435
1.000
1.087
2.084
0.986
0.986
1.071
1.046
1.122
1.063
1.338
1.372
11.242
4.729
1.087

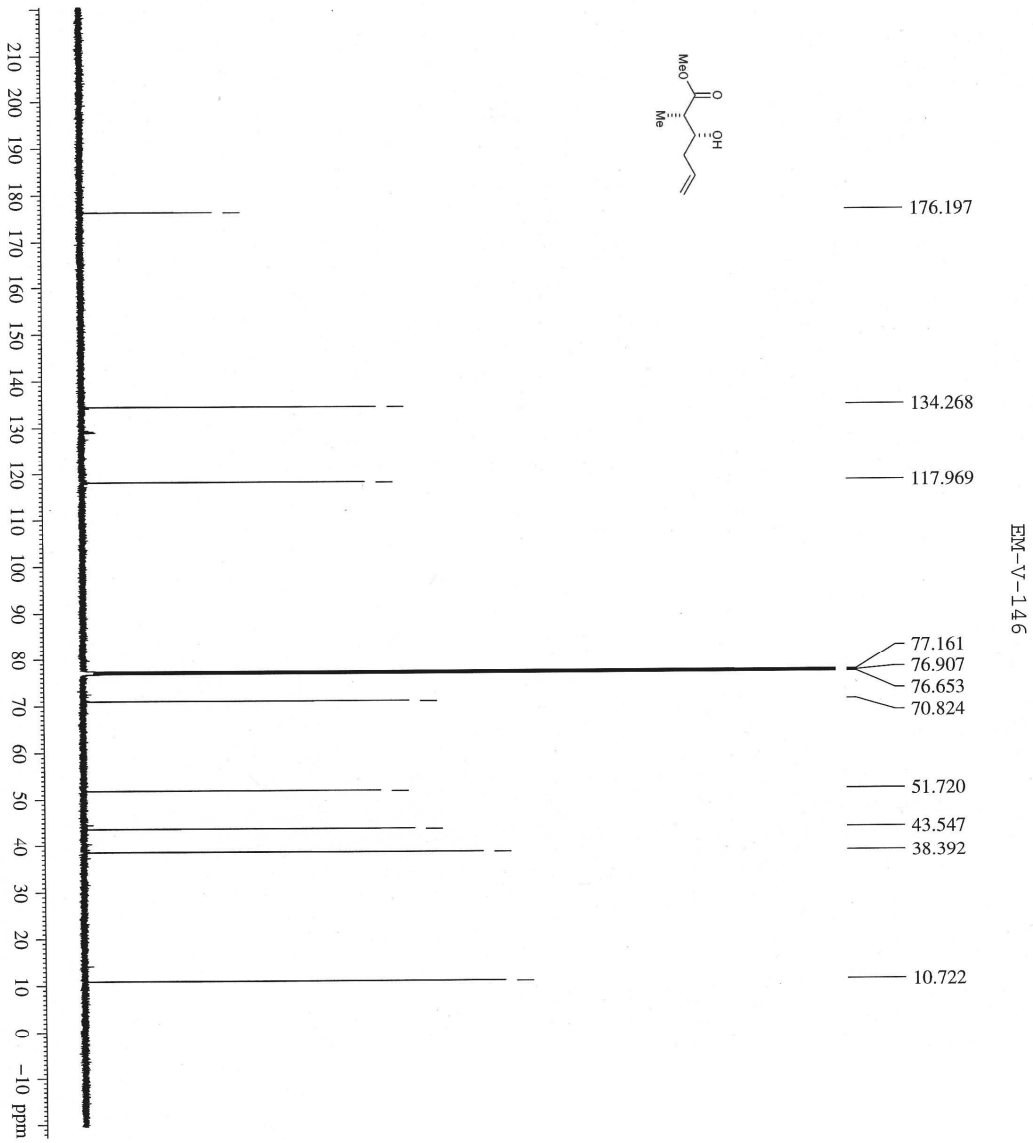
EM-II-145

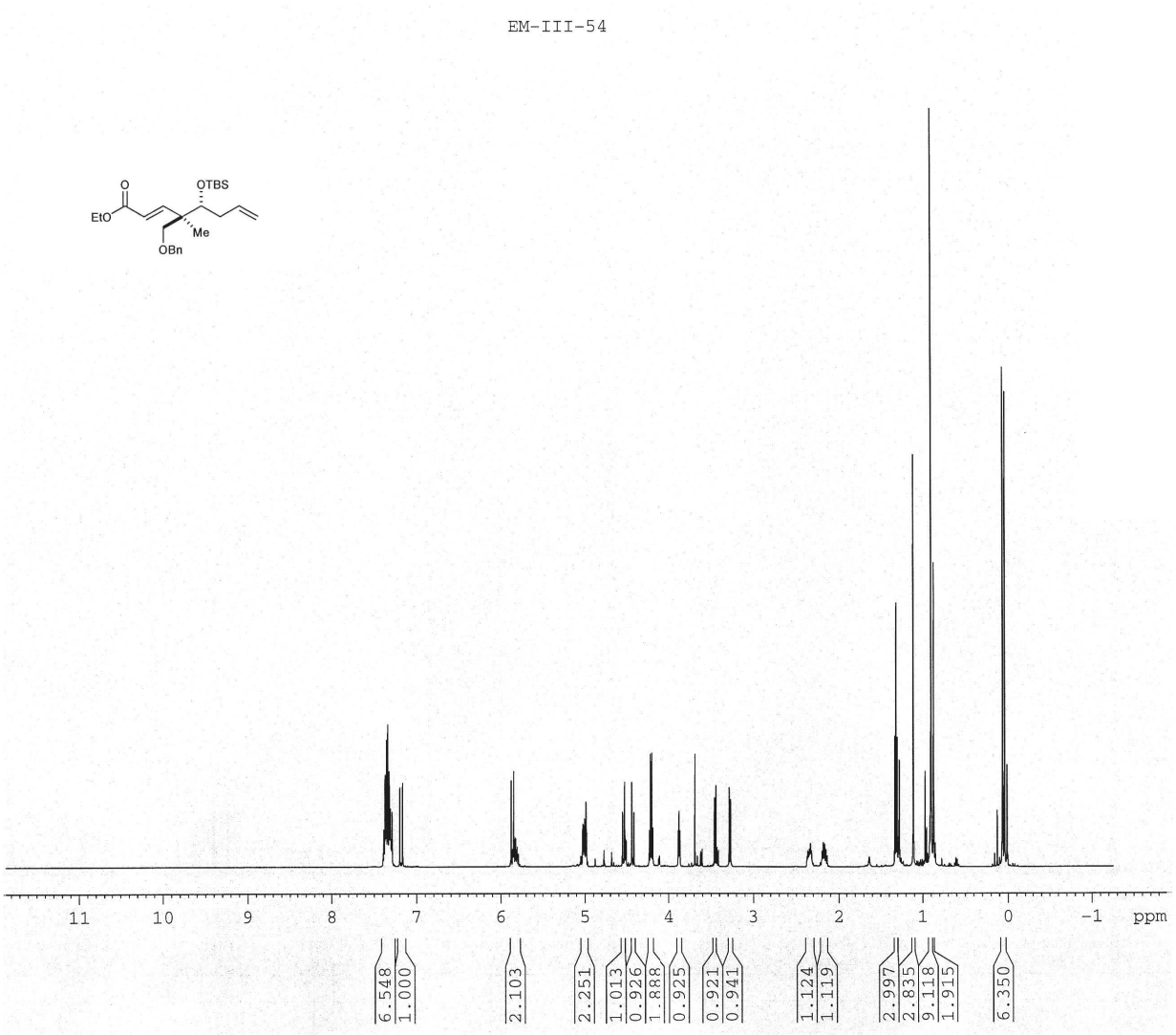

S
O
OH
S
N
Me
Bn
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

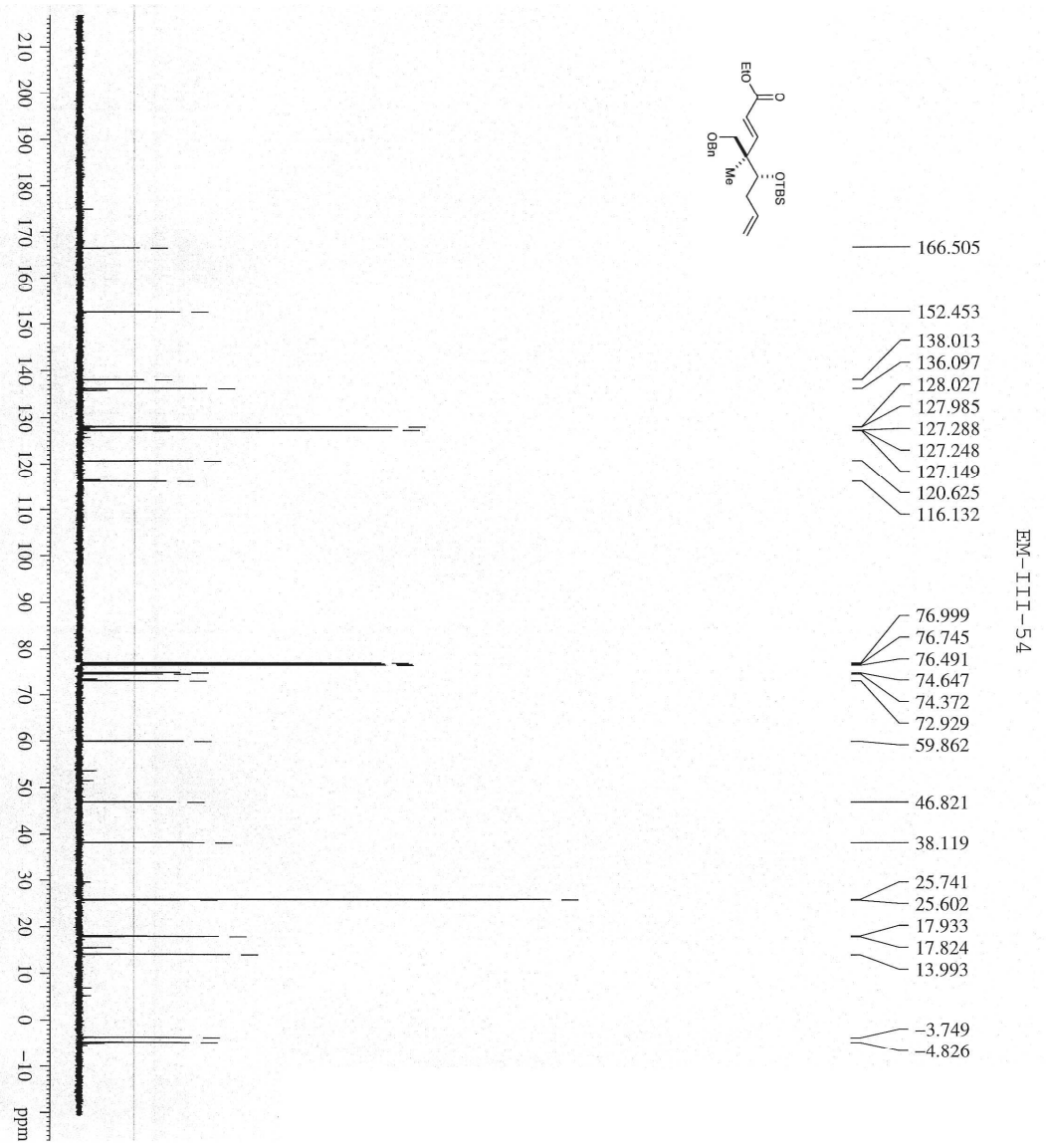

EM-V-146
O
OH
MeO
Me
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
2.005
0.916
2.848
0.958
0.637
2.250
2.890

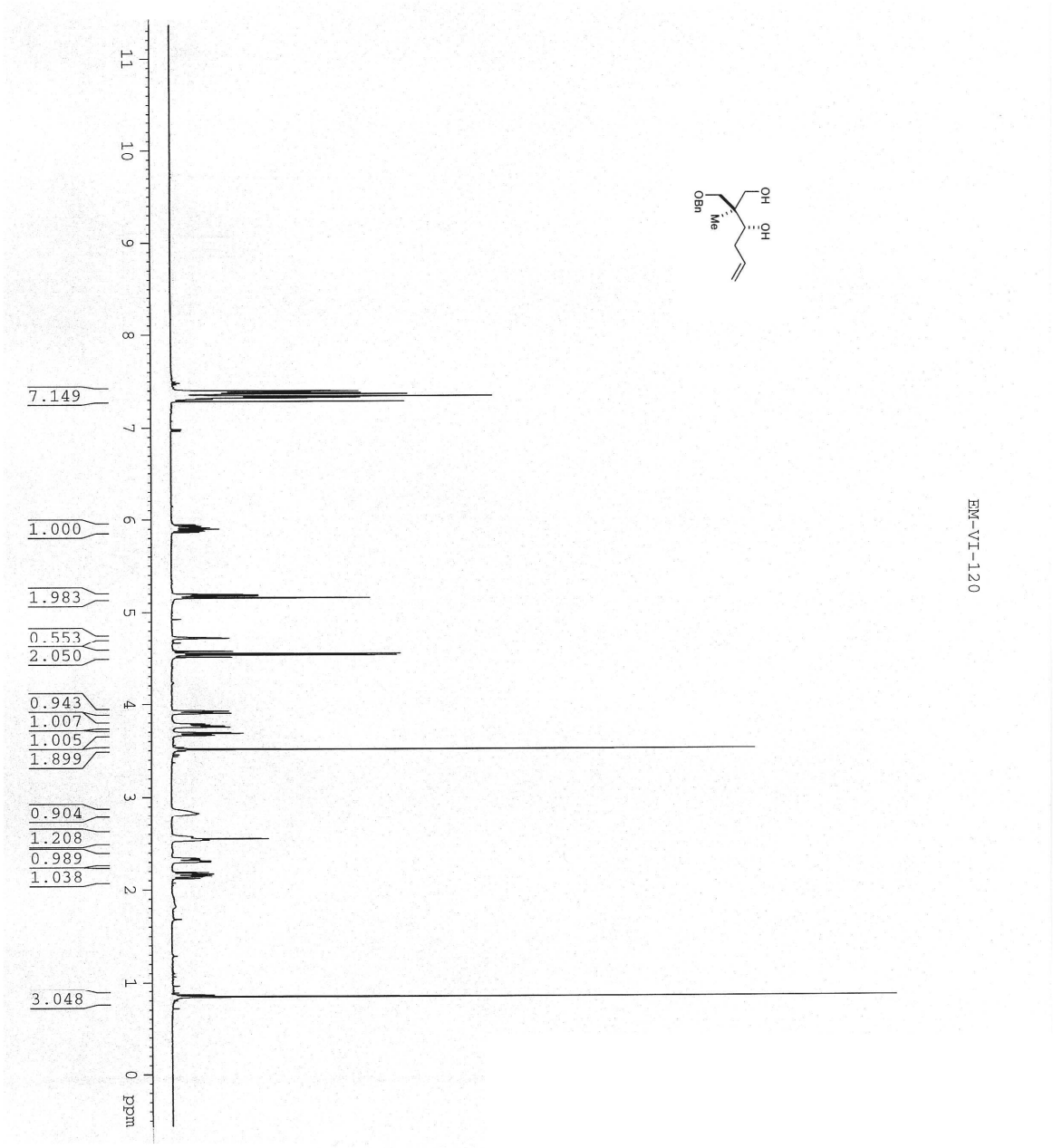

MeO
O
Me
OH
176.197
134.268
117.969
77.161
76.907
76.653
70.824
51.720
43.547
38.392
10.722
EM-V-146
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

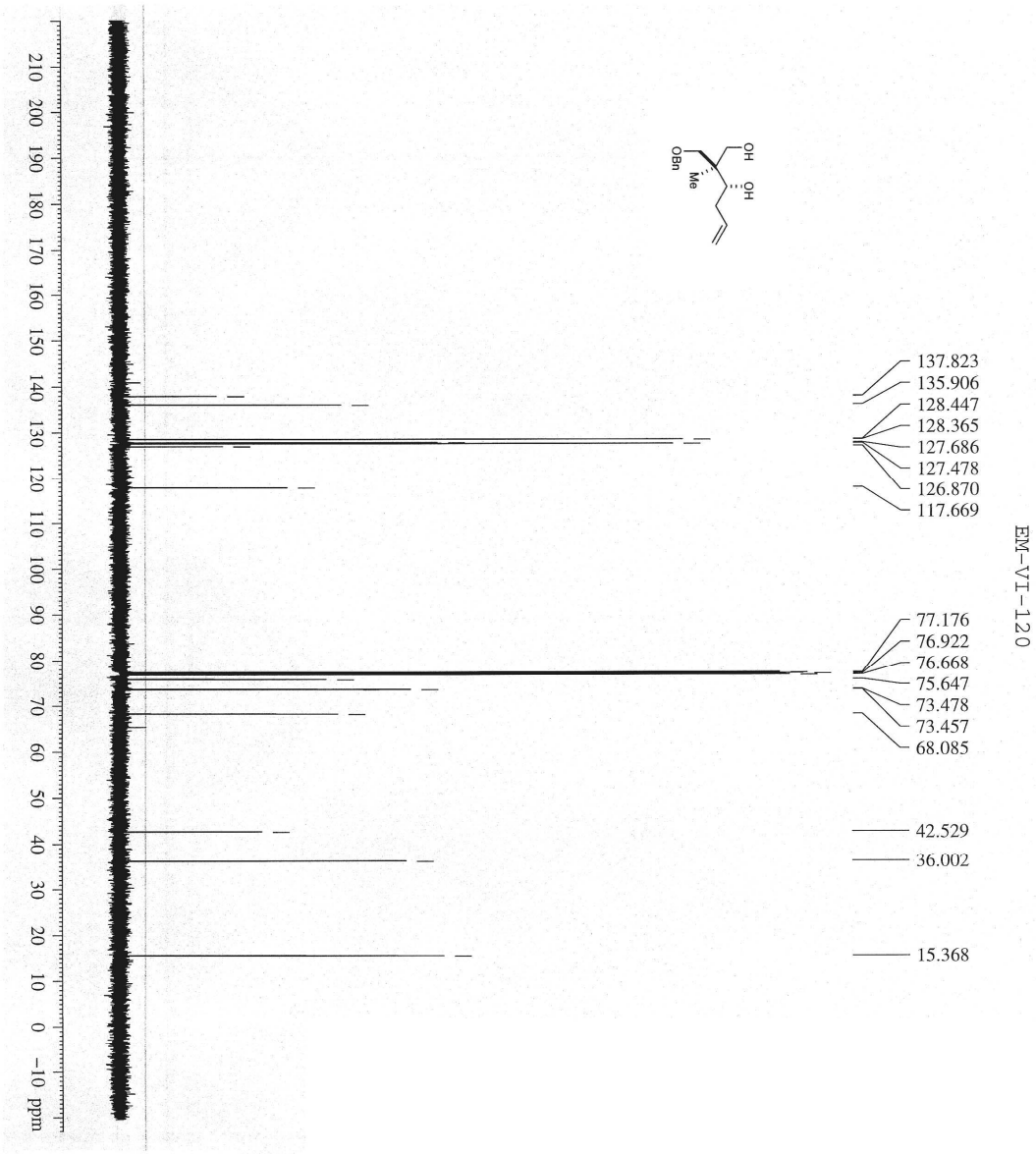

EM-V-146
O
OH
MeO
Me
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
2.005
0.916
2.848
0.958
0.637
2.250
2.890

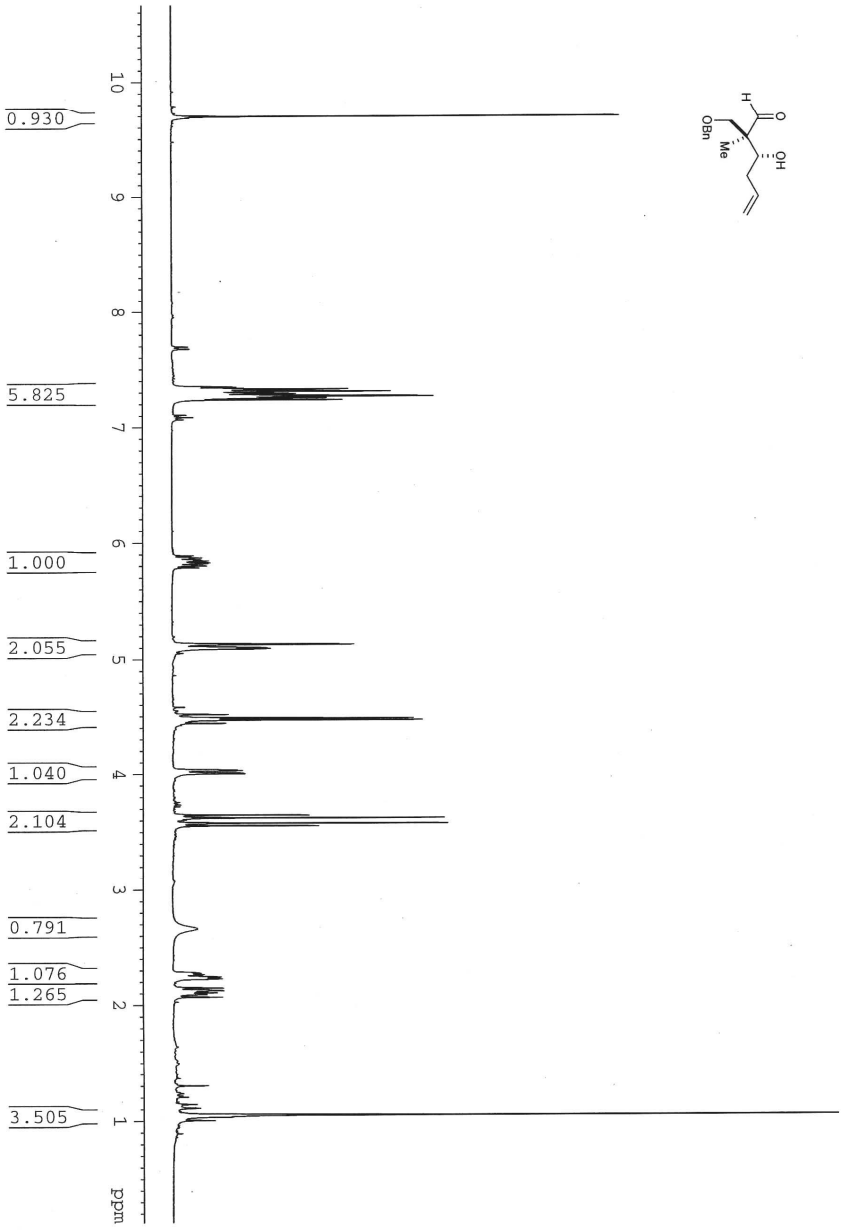

MeO
O
Me
OH
176.197
134.268
117.969
77.161
76.907
76.653
70.824
51.720
43.547
38.392
10.722
EM-V-146
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm


EM-III-54
O
OTBS
EtO
Me
OBn
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
6.548
1.000
2.103
2.251
1.013
0.926
1.888
0.925
0.921
0.941
1.124
1.119
2.997
2.835
9.118
1.915
6.350

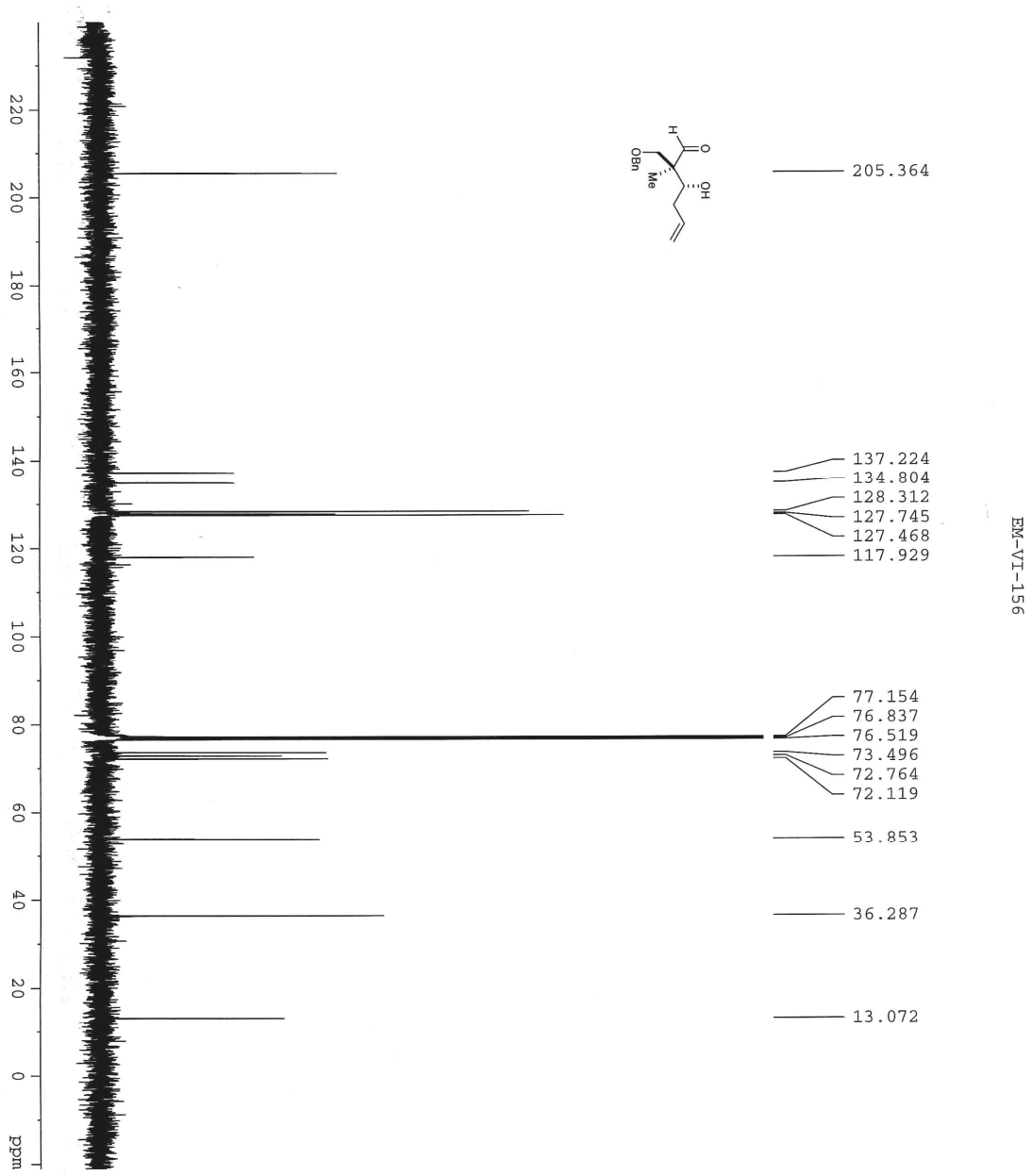

EtO
O
OBn
Me
OTBS
166.505
152.453
138.013
136.097
128.027
127.985
127.288
127.248
127.149
120.625
116.132
76.999
76.745
76.491
74.647
74.372
72.929
59.862
46.821
38.119
25.741
25.602
17.933
17.824
13.993
−3.749
−4.826
EM-III-54
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

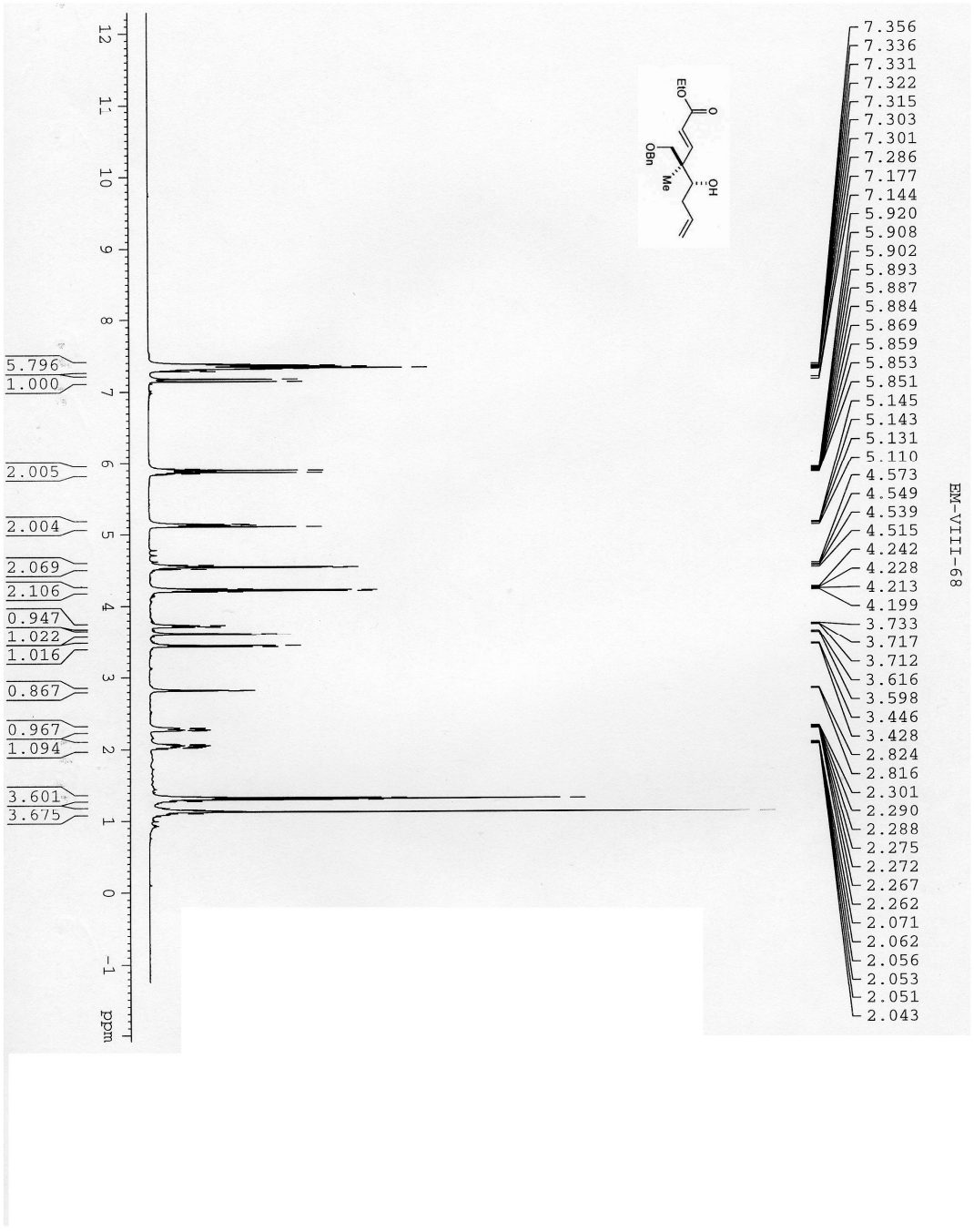

EM-VI-120
OH
OH
Me
OBn
7.149
1.000
1.983
0.553
2.050
0.943
1.007
1.005
1.899
0.904
1.208
0.989
1.038
3.048
ppm

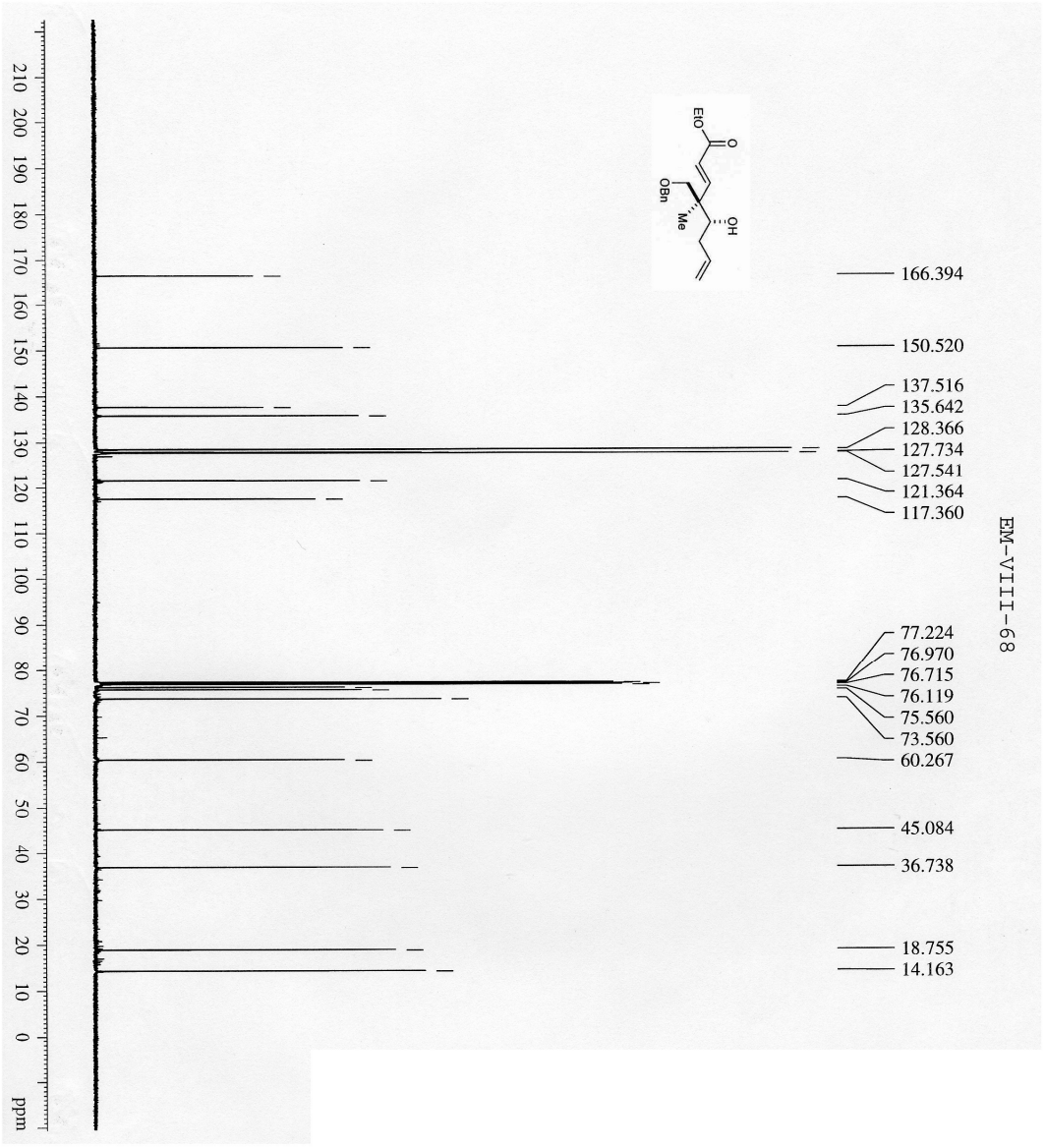

OH
OH
OBn
Me
137.823
135.906
128.447
128.365
127.686
127.478
126.870
117.669
77.176
76.922
76.668
75.647
73.478
73.457
68.085
42.529
36.002
15.368
EM-VI-120
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

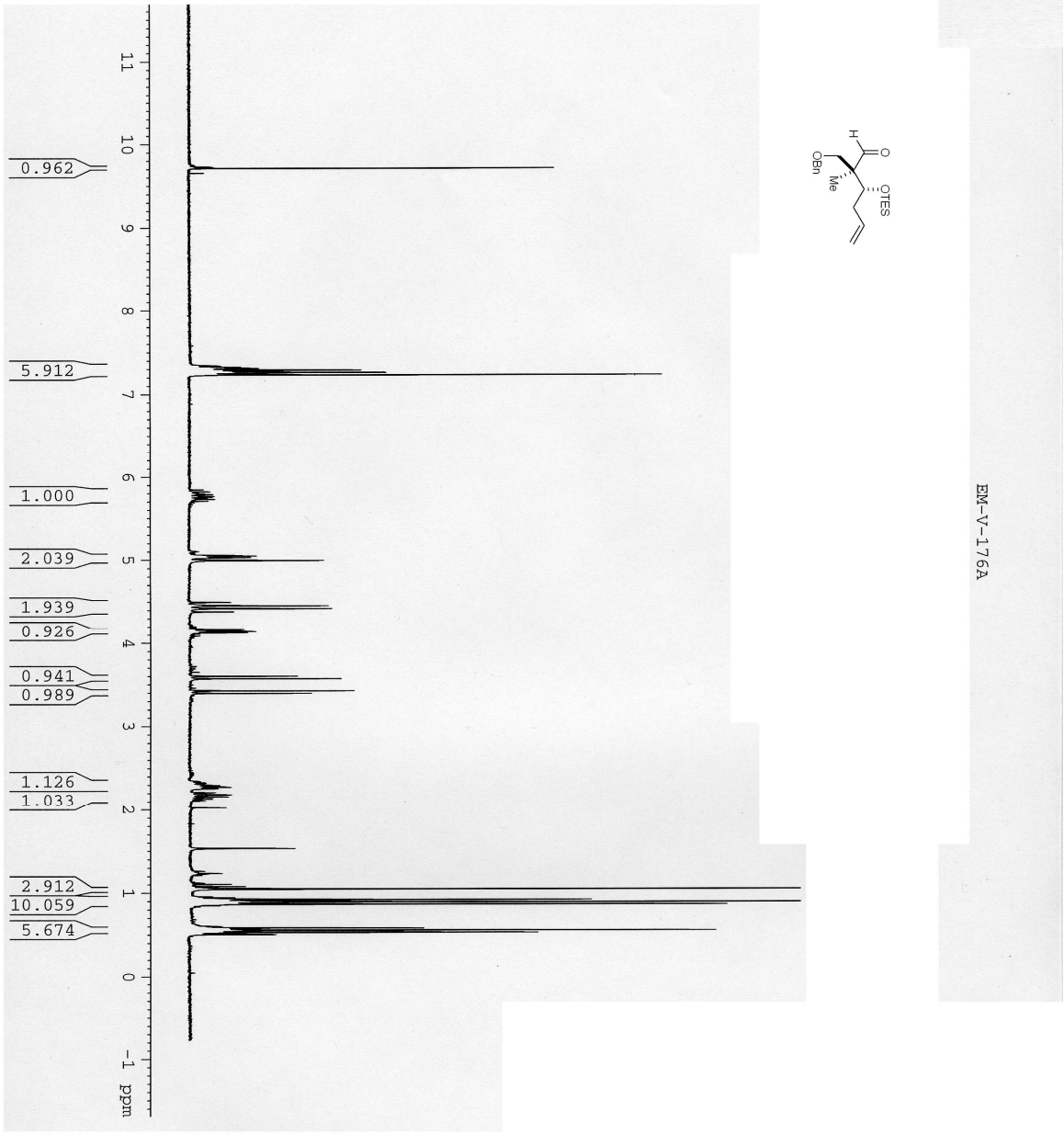

0.930
5.825
1.000
2.055
2.234
1.040
2.104
0.791
1.076
1.265
3.505
10
9
8
7
6
5
4
3
2
1
ppm
H
O
OH
Me
OBn

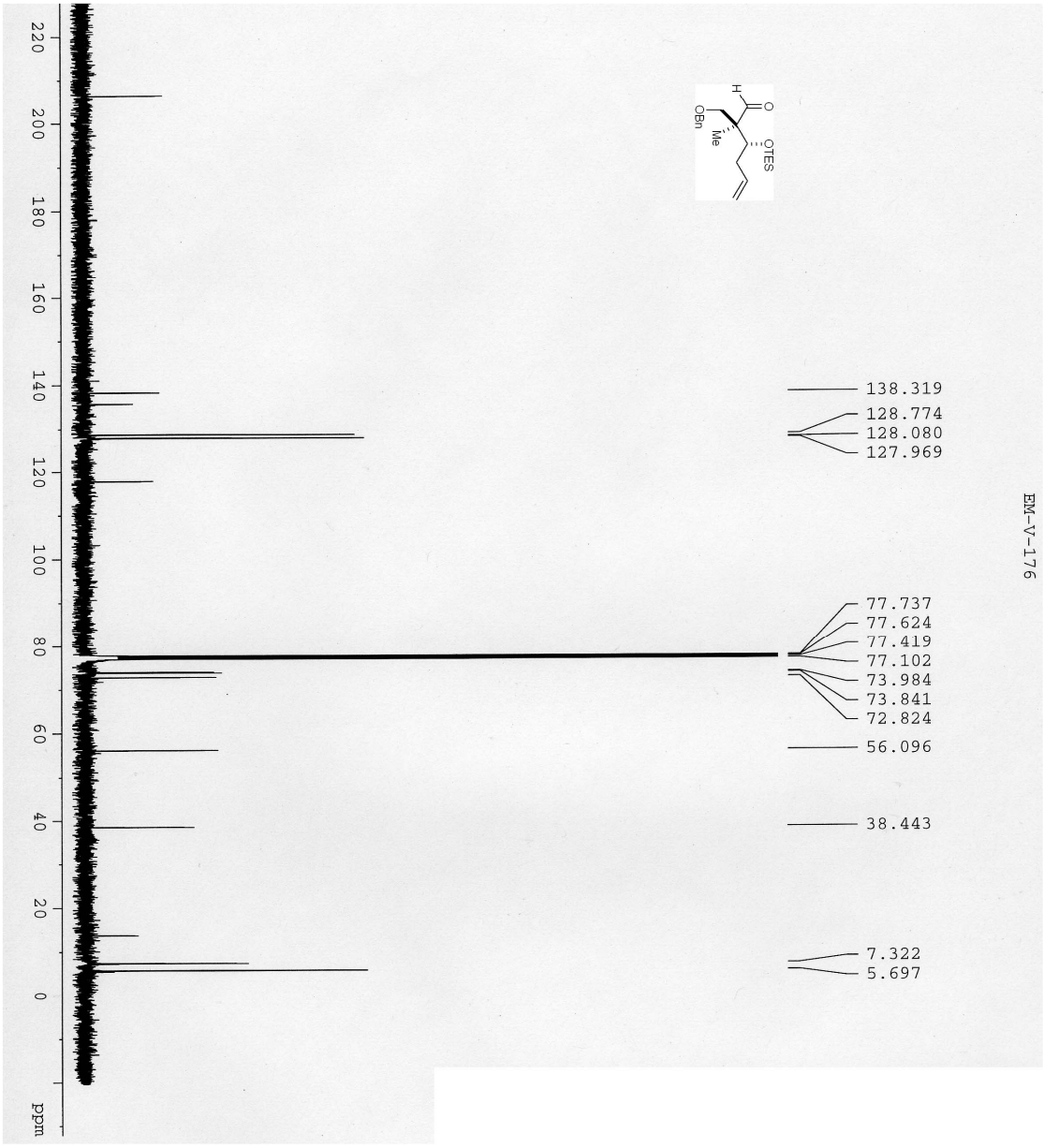
EM-VI-156

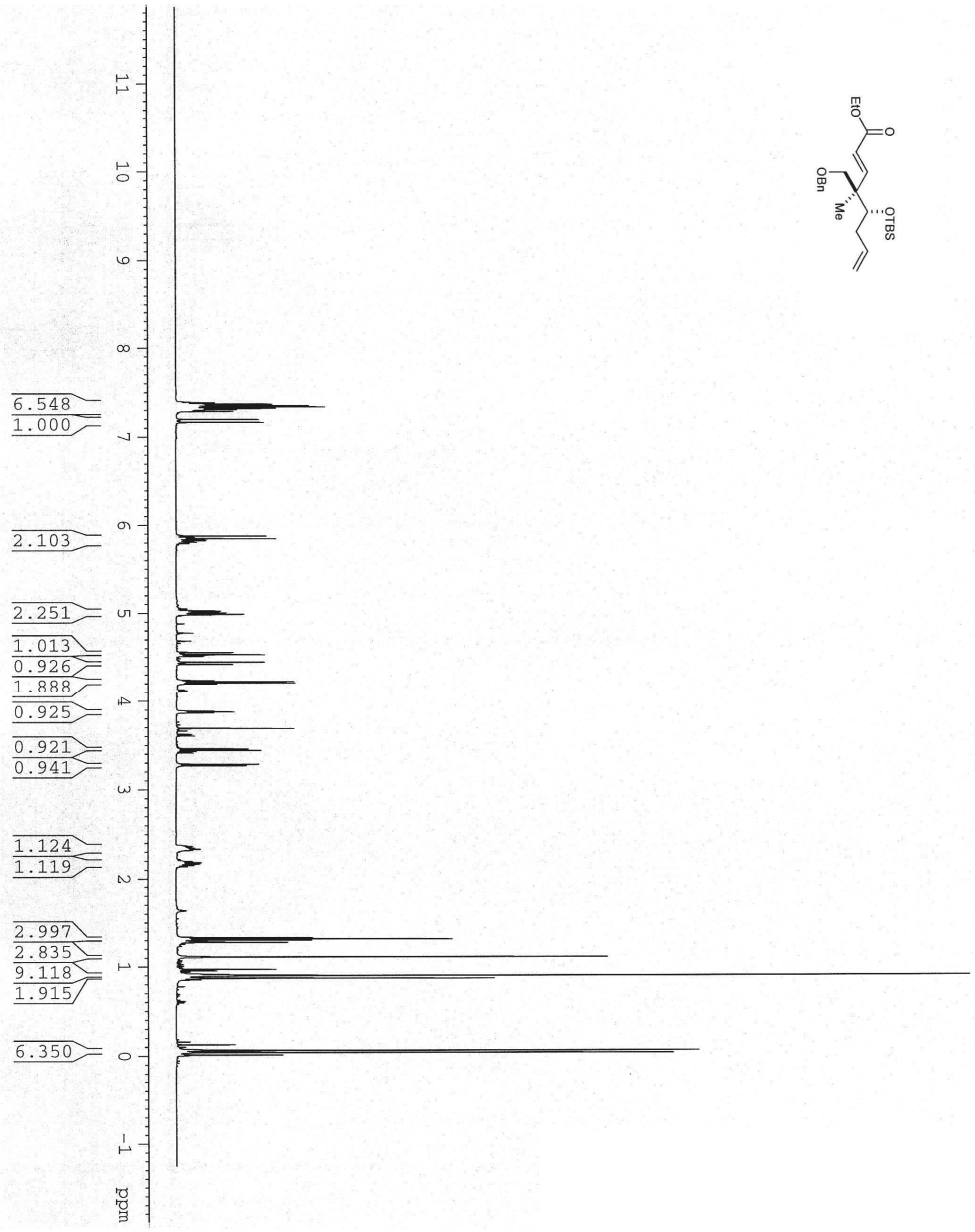

205.364
137.224
134.804
128.312
127.745
127.468
117.929
77.154
76.837
76.519
73.496
72.764
72.119
53.853
36.287
13.072
ppm
EM-VI-156

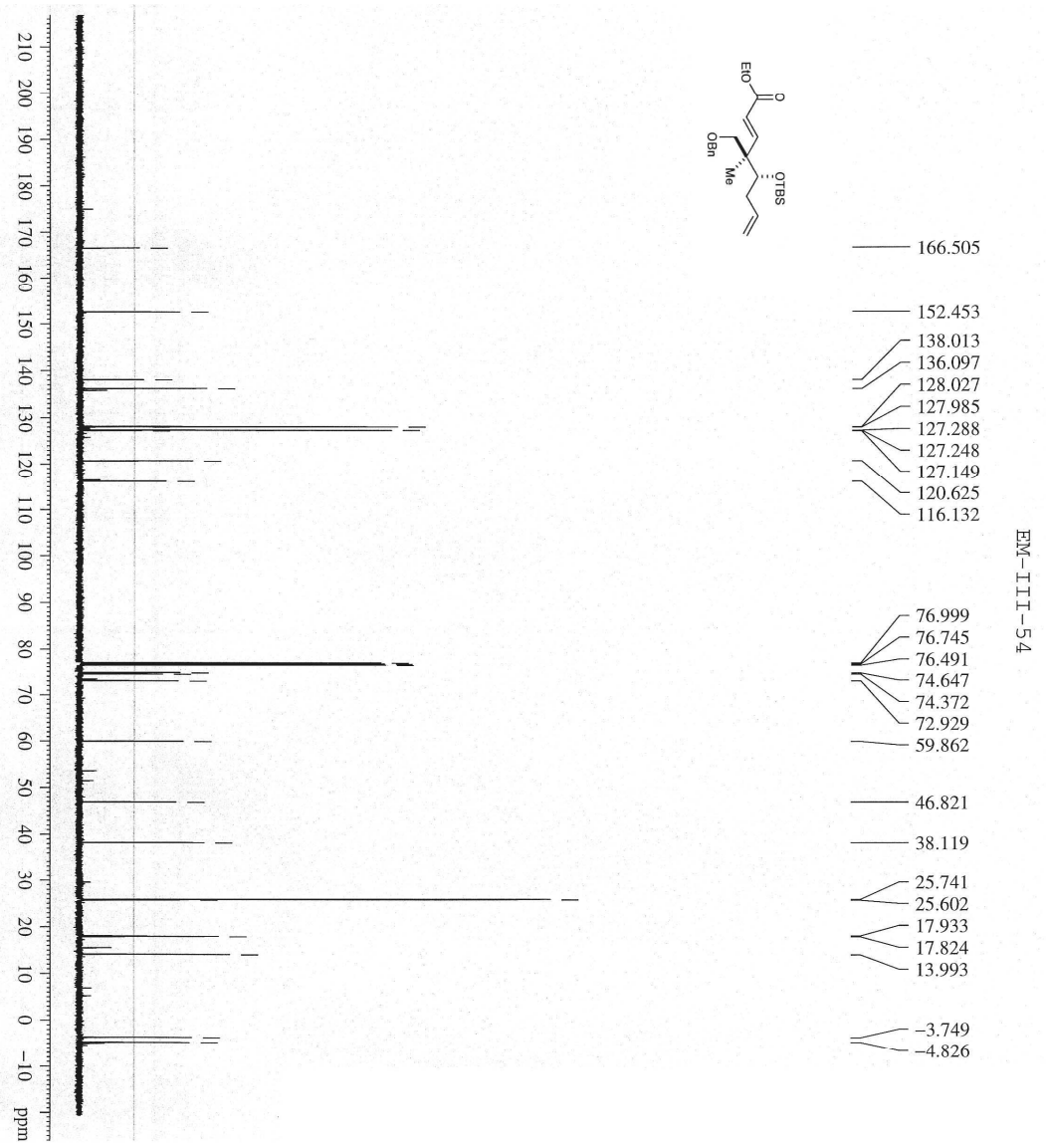

EtO
O
OBn
Me
OH
7.356
7.336
7.331
7.322
7.315
7.303
7.301
7.286
7.177
7.144
5.920
5.908
5.902
5.893
5.887
5.884
5.869
5.859
5.853
5.851
5.145
5.143
5.131
5.110
4.573
4.549
4.539
4.515
4.242
4.228
4.213
4.199
3.733
3.717
3.712
3.616
3.598
3.446
3.428
2.824
2.816
2.301
2.290
2.288
2.275
2.272
2.267
2.262
2.071
2.062
2.056
2.053
2.051
2.043
EM-VIII-68
5.796
1.000
2.005
2.004
2.069
2.106
0.947
1.022
1.016
0.867
0.967
1.094
3.601
3.675
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm

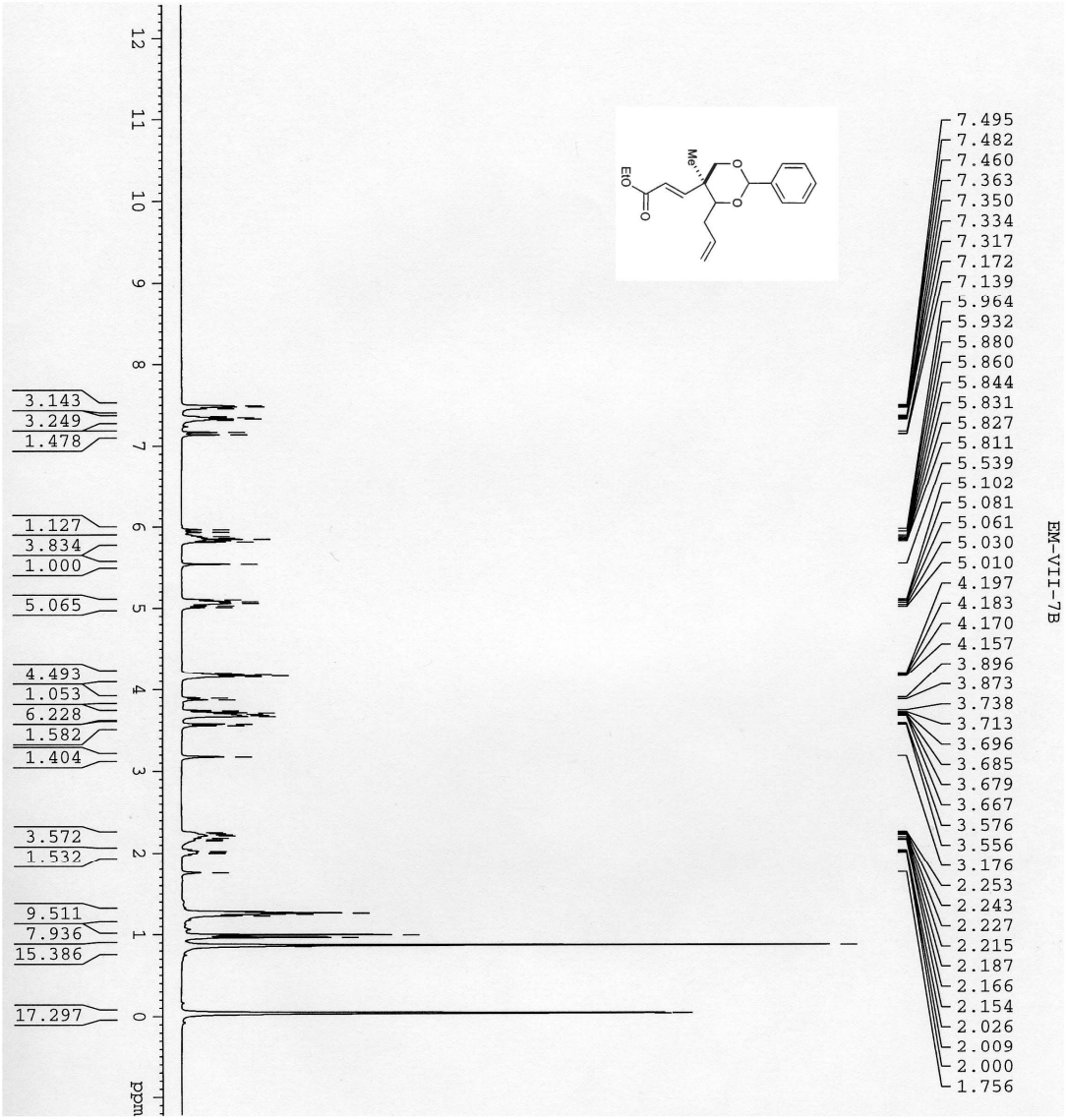

EtO
O
OBn
Me
OH
166.394
150.520
137.516
135.642
128.366
127.734
127.541
121.364
117.360
77.224
76.970
76.715
76.119
75.560
73.560
60.267
45.084
36.738
18.755
14.163
EM-VIII-68
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

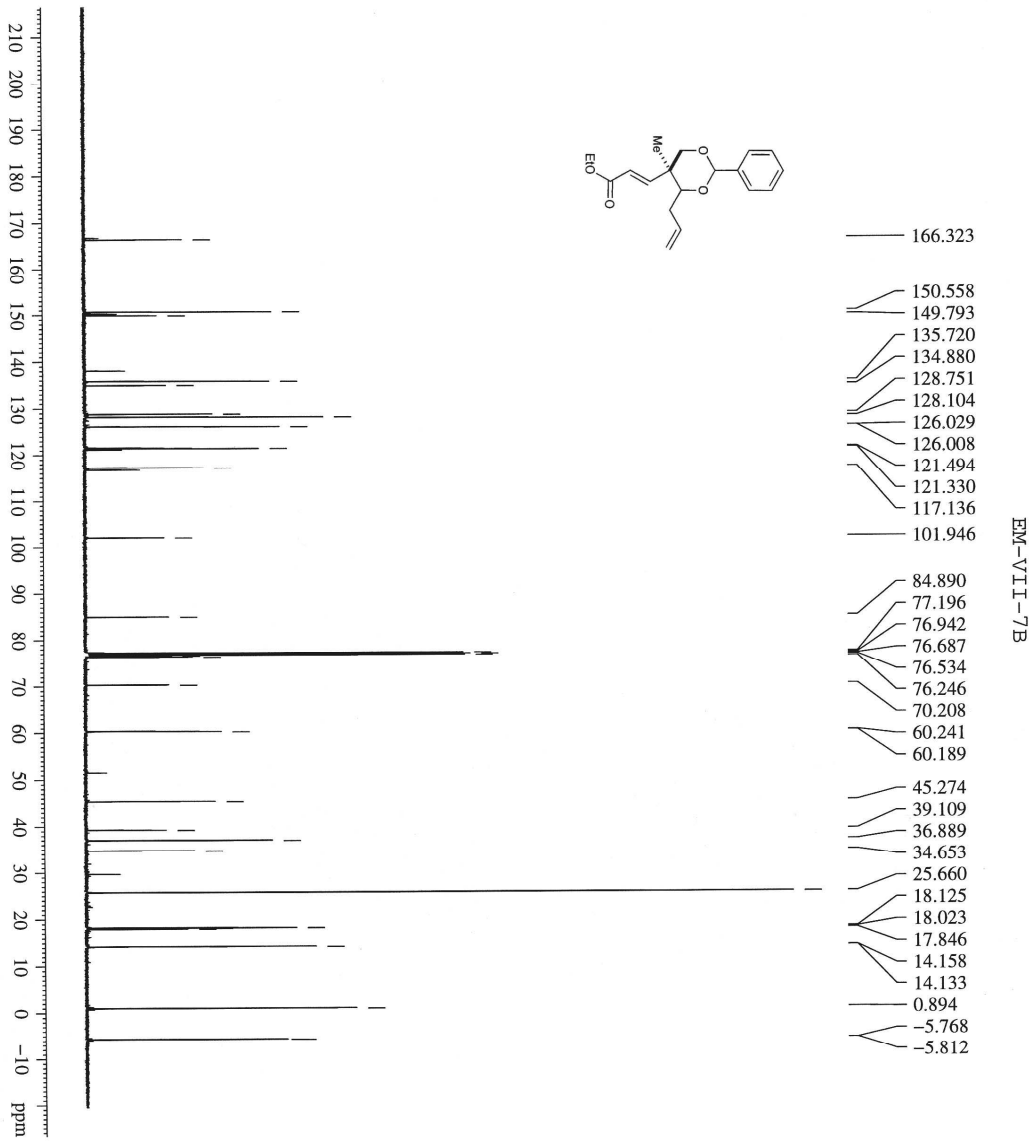

EM-V-176A
OTES
Me
OBn
H
O
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
0.962
5.912
1.000
2.039
1.939
0.926
0.941
0.989
1.126
1.033
2.912
10.059
5.674


138.319
128.774
128.080
127.969
77.737
77.624
77.419
77.102
73.984
73.841
72.824
56.096
38.443
7.322
5.697
EM-V-176
ppm

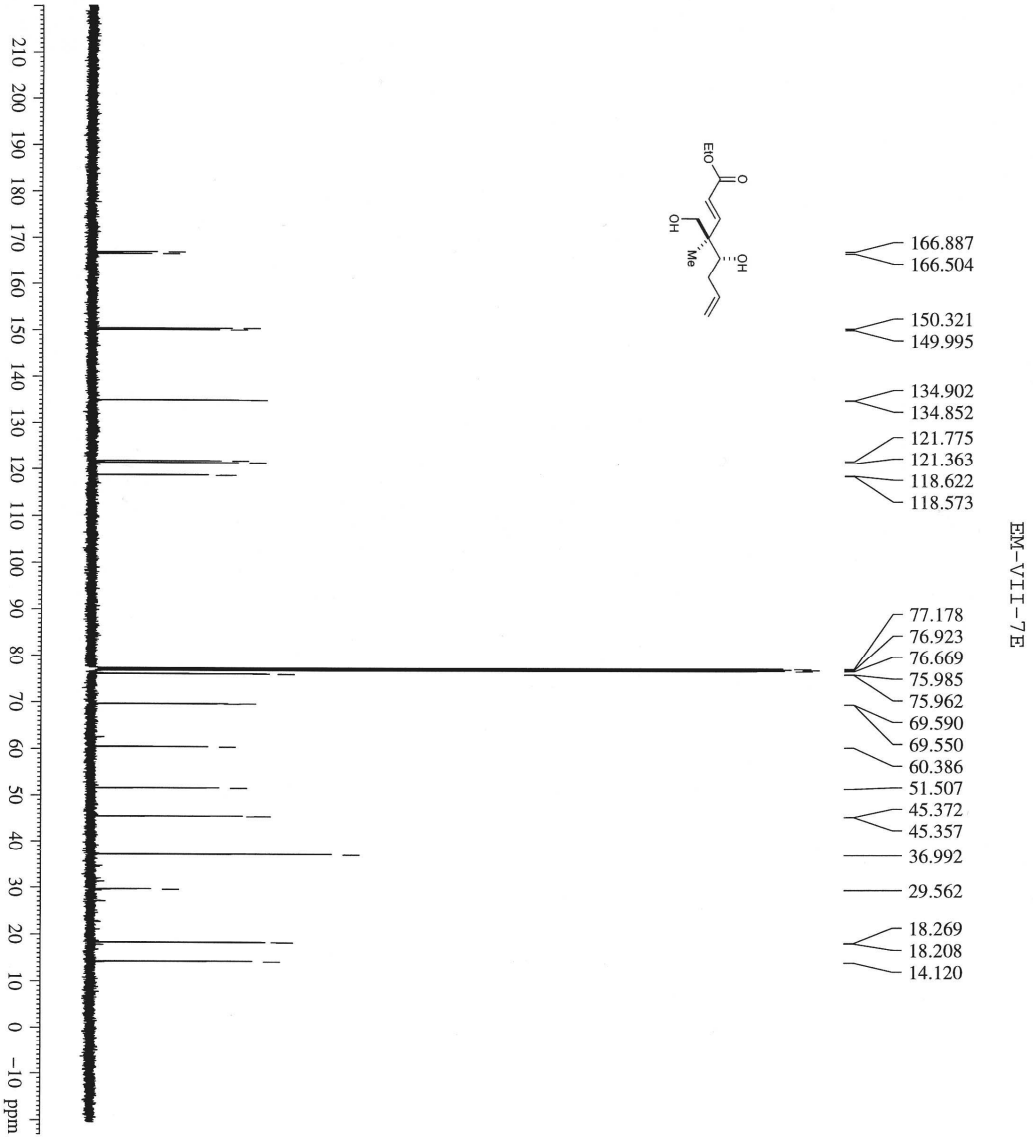

EtO
O
OBn
Me
OTBS
EM-III-54
6.548
1.000
2.103
2.251
1.013
0.926
1.888
0.925
0.921
0.941
1.124
1.119
2.997
2.835
9.118
1.915
6.350
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


EtO
O
OBn
Me
OTBS
166.505
152.453
138.013
136.097
128.027
127.985
127.288
127.248
127.149
120.625
116.132
76.999
76.745
76.491
74.647
74.372
72.929
59.862
46.821
38.119
25.741
25.602
17.933
17.824
13.993
−3.749
−4.826
EM-III-54
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

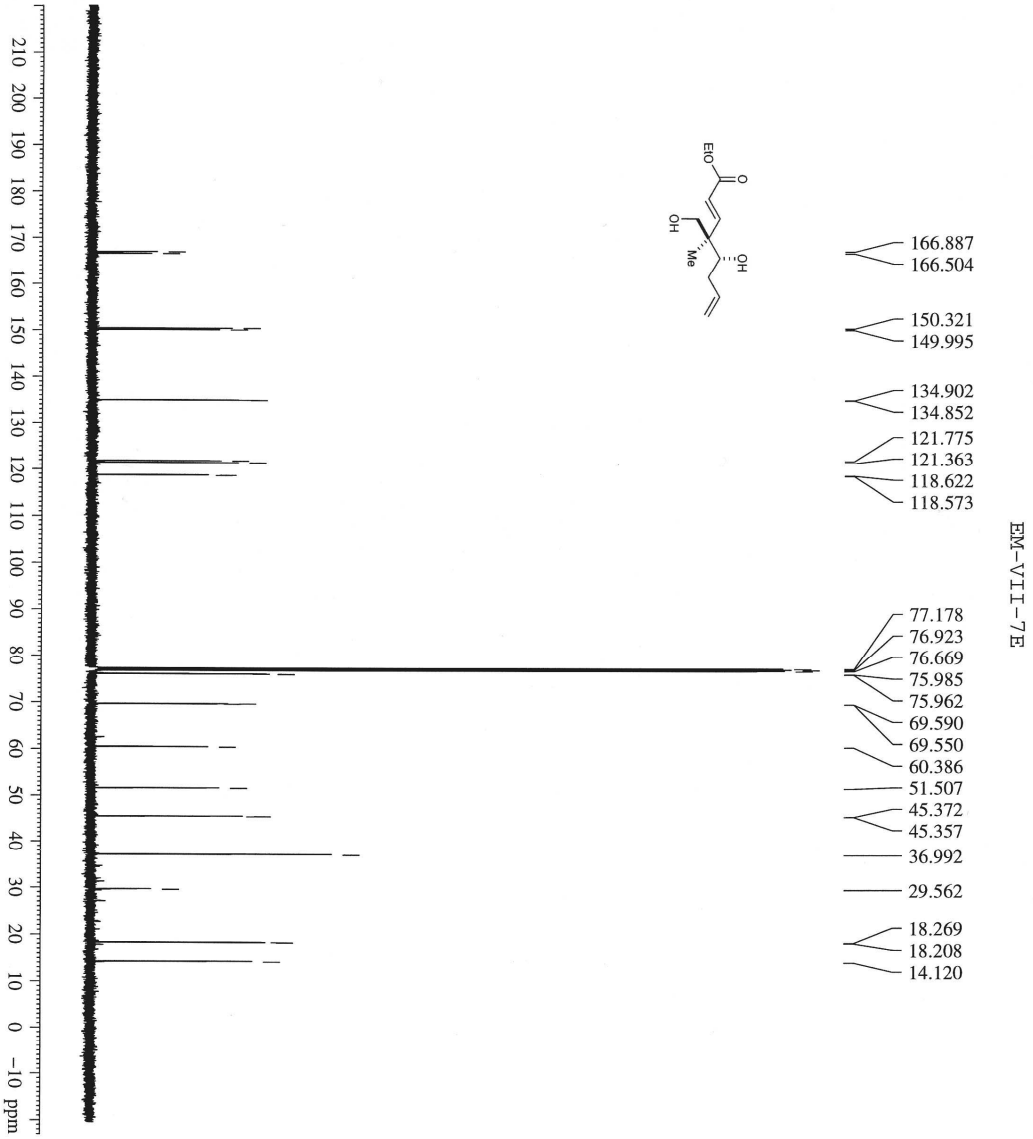

EM-VII-7B
7.495
7.482
7.460
7.363
7.350
7.334
7.317
7.172
7.139
5.964
5.932
5.880
5.860
5.844
5.831
5.827
5.811
5.539
5.102
5.081
5.061
5.030
5.010
4.197
4.183
4.170
4.157
3.896
3.873
3.738
3.713
3.696
3.685
3.679
3.667
3.576
3.556
3.176
2.253
2.243
2.227
2.215
2.187
2.166
2.154
2.026
2.009
2.000
1.756
3.143
3.249
1.478
1.127
3.834
1.000
5.065
4.493
1.053
6.228
1.582
1.404
3.572
1.532
9.511
7.936
15.386
17.297
ppm
Me
EtO
O
O

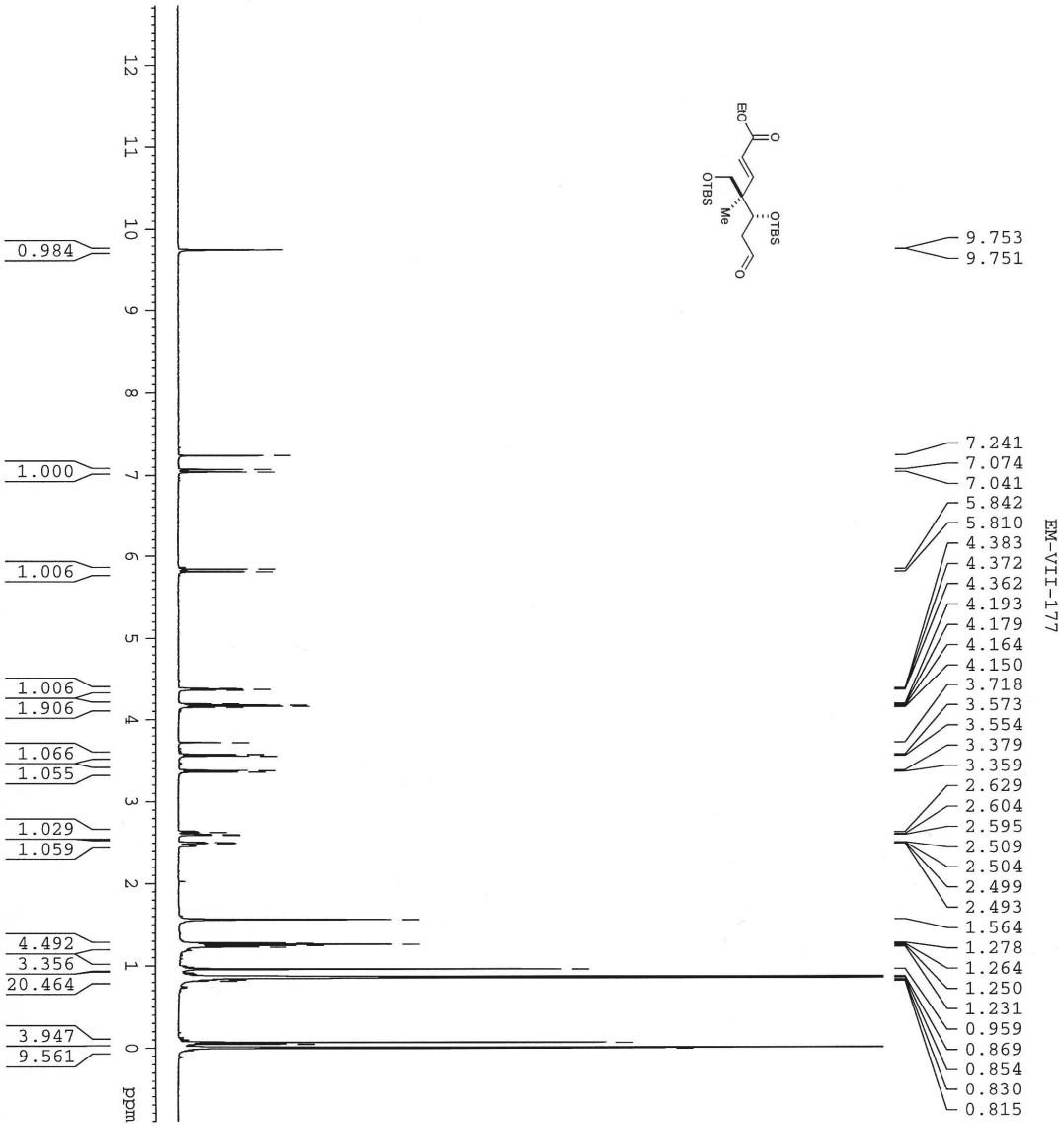

EM-VII-7B
166.323
150.558
149.793
135.720
134.880
128.751
128.104
126.029
126.008
121.494
121.330
117.136
101.946
84.890
77.196
76.942
76.687
76.534
76.246
70.208
60.241
60.189
45.274
39.109
36.889
34.653
25.660
18.125
18.023
17.846
14.158
14.133
0.894
−5.768
−5.812
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

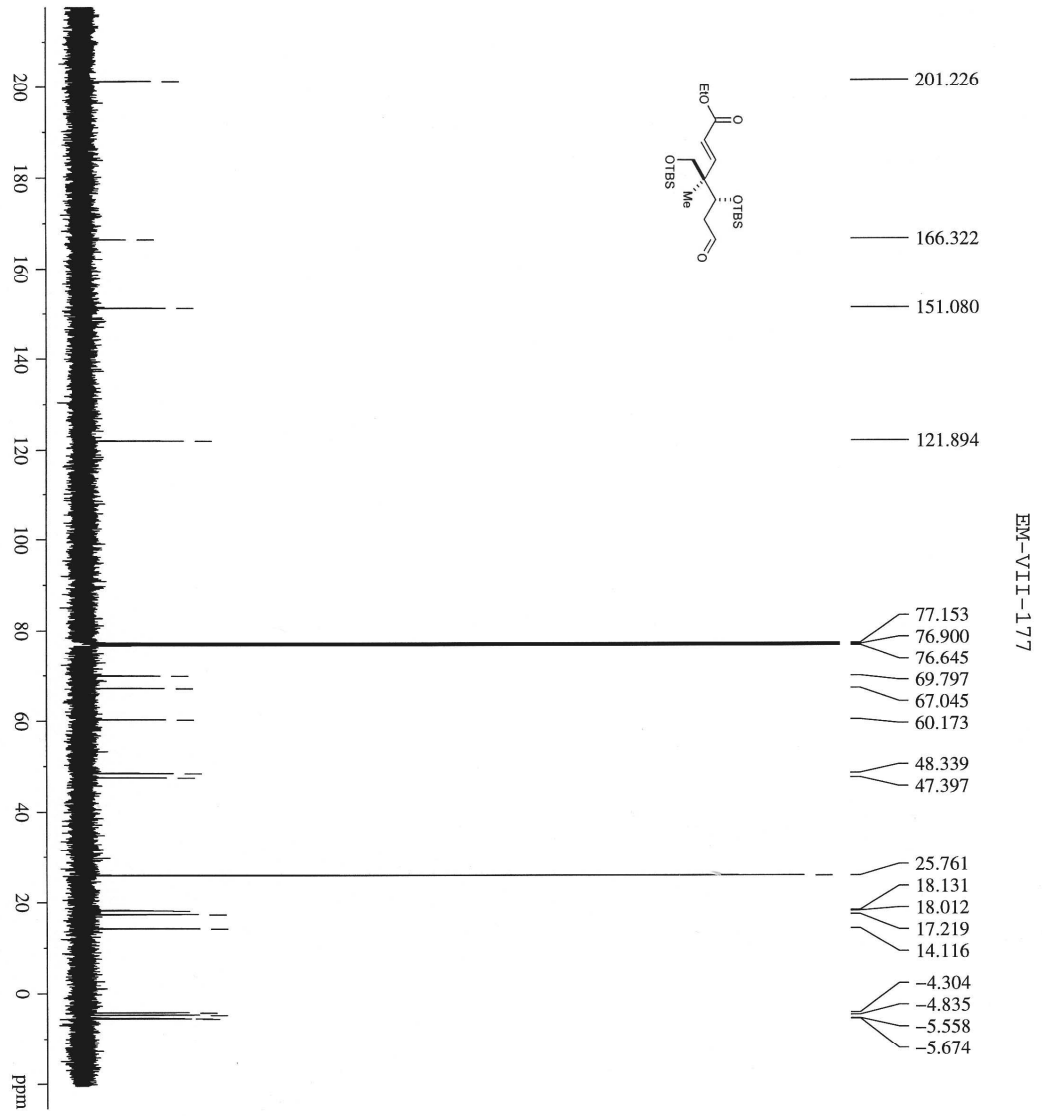
EtO
O
OH
Me
OH
EM-VII-7E
0.941
1.080
1.036
1.963
0.993
0.155
3.700
1.158
1.000
1.369
2.999
3.091
12
11
10
9
8
7
6
5
4
3
2
1
ppm


EtO
O
OH
Me
OH
166.887
166.504
150.321
149.995
134.902
134.852
121.775
121.363
118.622
118.573
77.178
76.923
76.669
75.985
75.962
69.590
69.550
60.386
51.507
45.372
45.357
36.992
29.562
18.269
18.208
14.120
EM-VII-7E
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

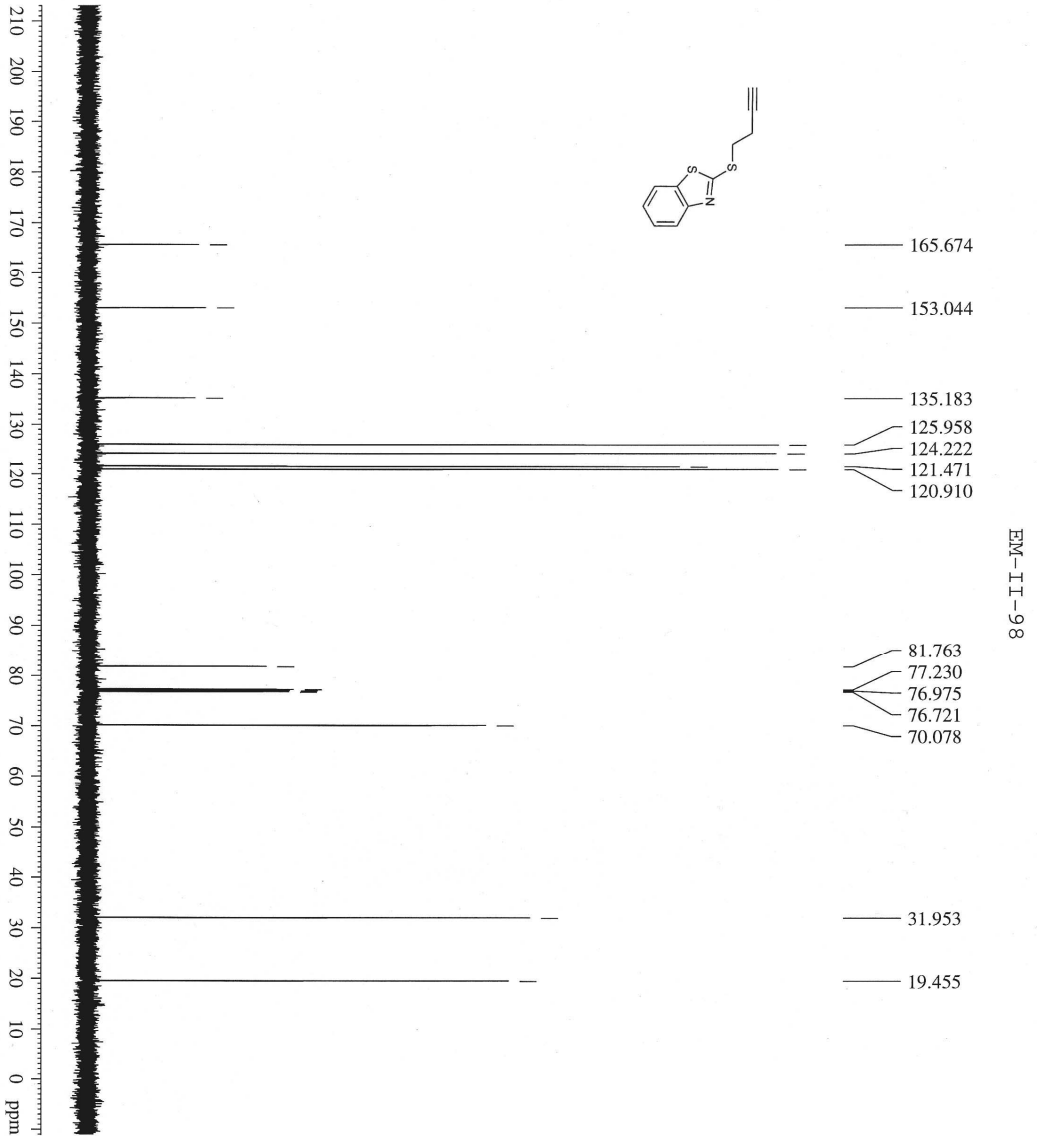
EtO
O
OH
Me
OH
EM-VII-7E
0.941
1.080
1.036
1.963
0.993
0.155
3.700
1.158
1.000
1.369
2.999
3.091
12
11
10
9
8
7
6
5
4
3
2
1
ppm


EtO
O
OH
Me
OH
166.887
166.504
150.321
149.995
134.902
134.852
121.775
121.363
118.622
118.573
77.178
76.923
76.669
75.985
75.962
69.590
69.550
60.386
51.507
45.372
45.357
36.992
29.562
18.269
18.208
14.120
EM-VII-7E
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

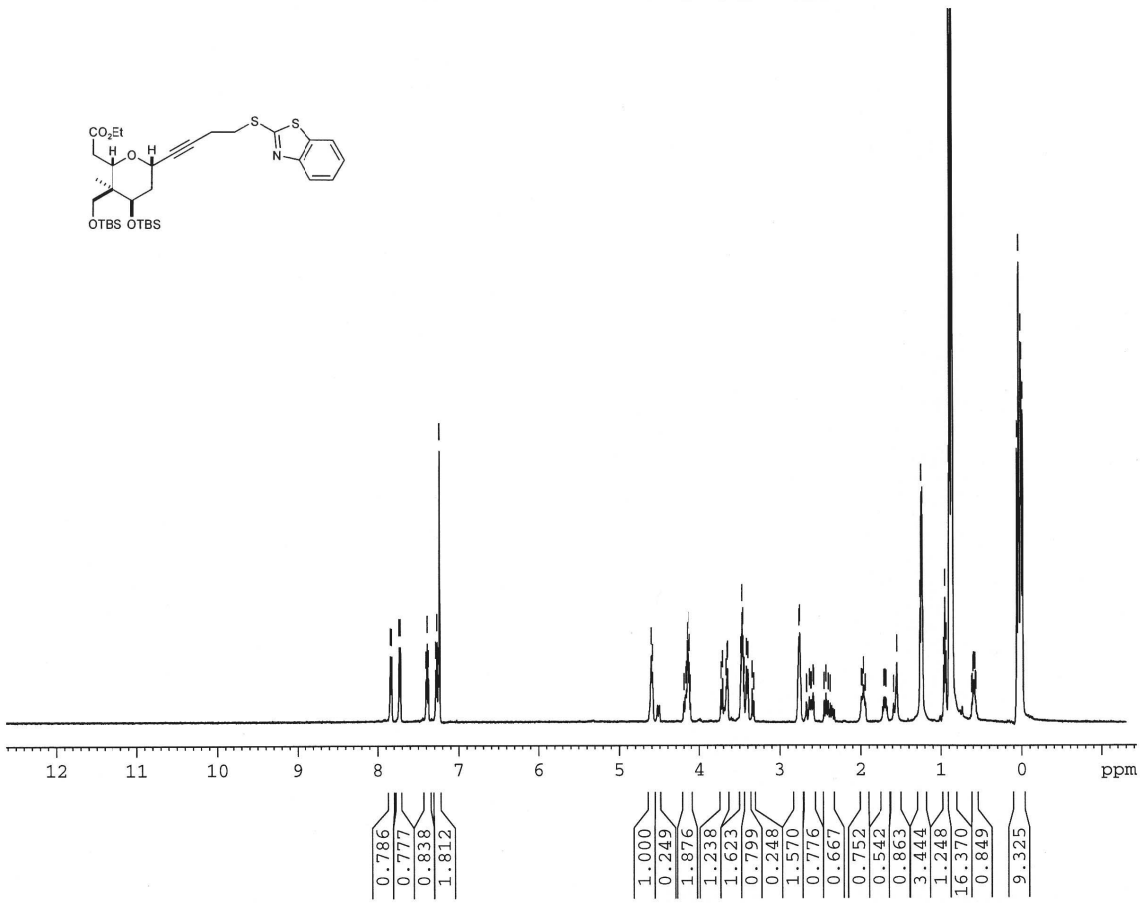

EtO
O
OTBS
Me
OTBS
O
9.753
9.751
7.241
7.074
7.041
5.842
5.810
4.383
4.372
4.362
4.193
4.179
4.164
4.150
3.718
3.573
3.554
3.379
3.359
2.629
2.604
2.595
2.509
2.504
2.499
2.493
1.564
1.278
1.264
1.250
1.231
0.959
0.869
0.854
0.830
0.815
0.984
1.000
1.006
1.006
1.906
1.066
1.055
1.029
1.059
4.492
3.356
20.464
3.947
9.561
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
EM-VII-177

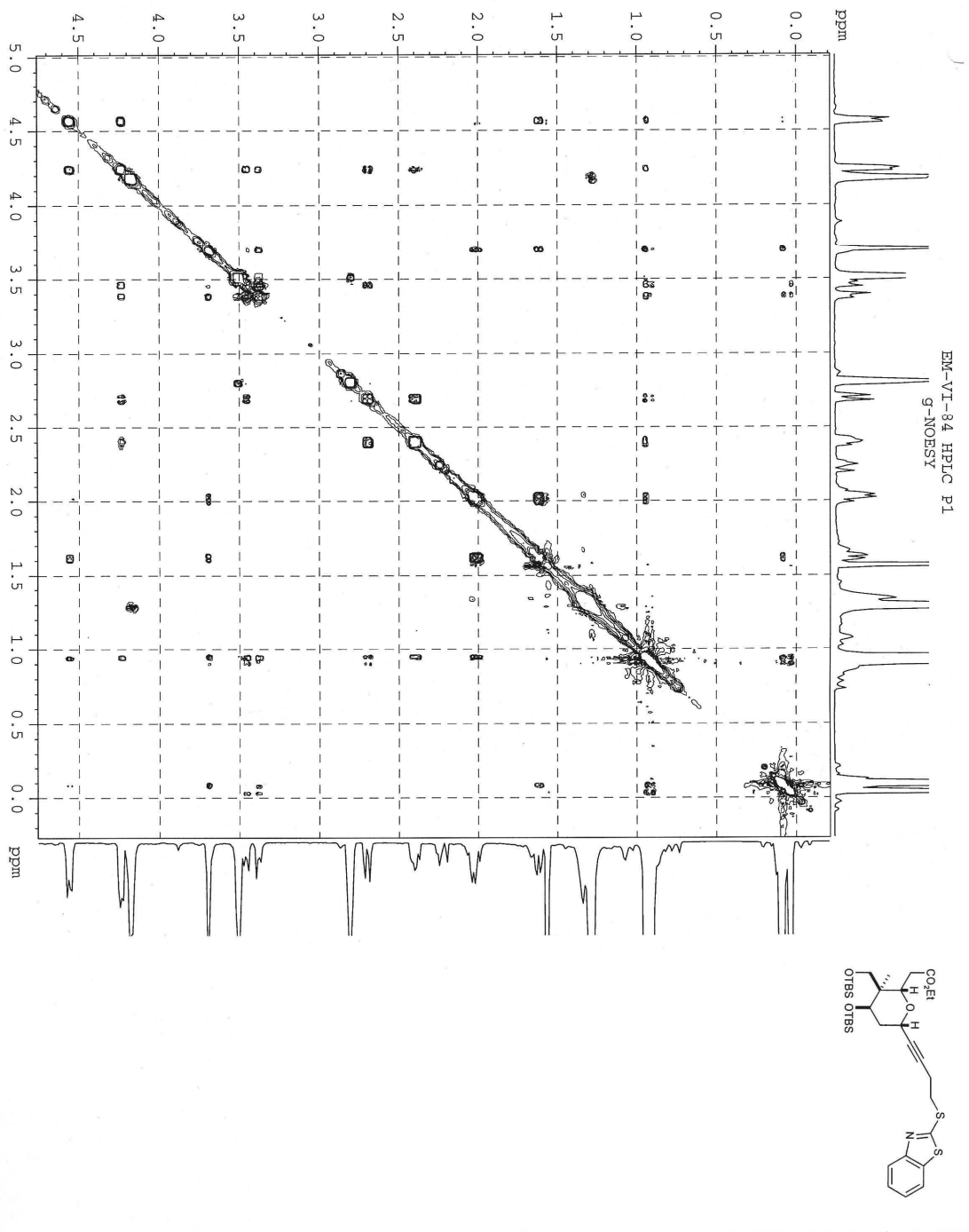

EM-VII-177
201.226
166.322
151.080
121.894
77.153
76.900
76.645
69.797
67.045
60.173
48.339
47.397
25.761
18.131
18.012
17.219
14.116
−4.304
−4.835
−5.558
−5.674
EtO
OTBS
Me
OTBS
O
O
200
180
160
140
120
100
80
60
40
20
0
ppm

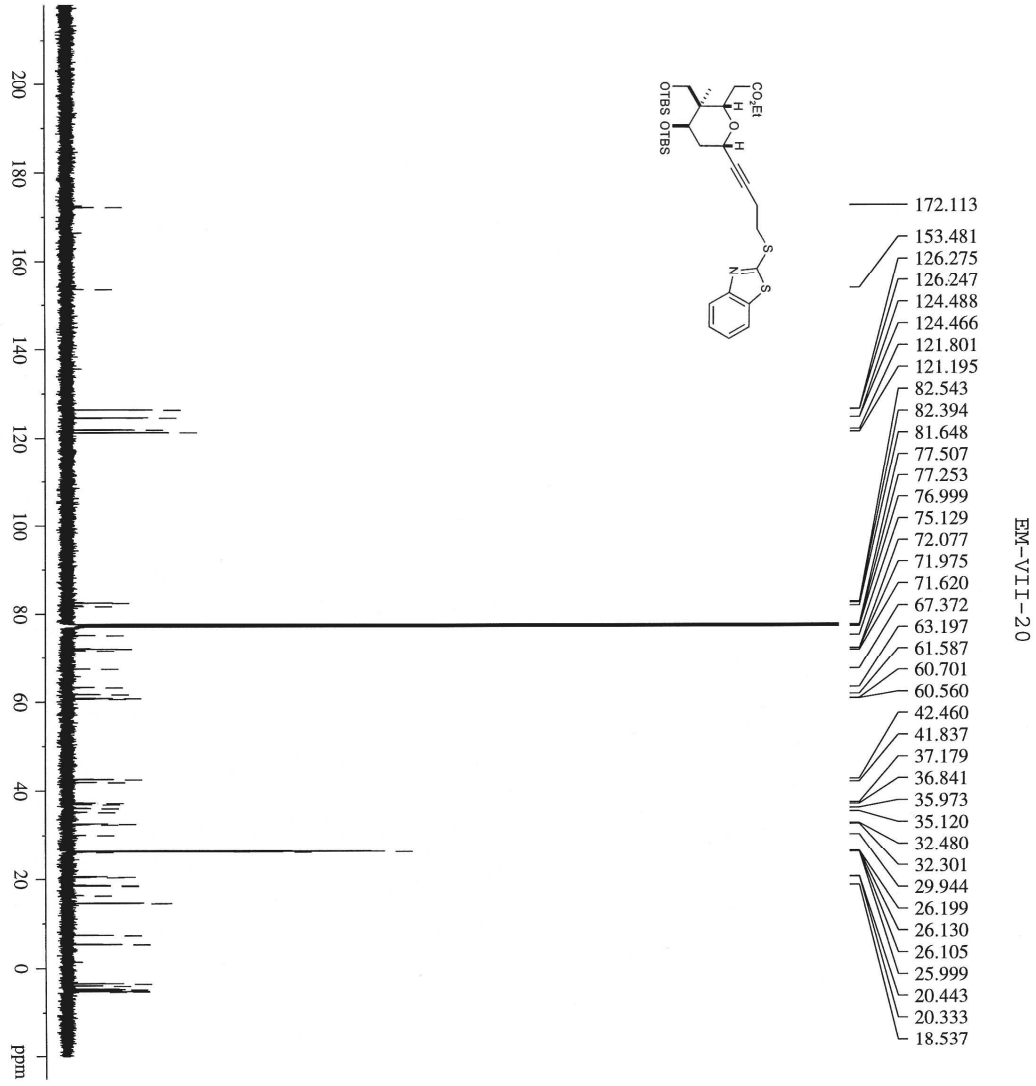
1.110
1.081
1.142
1.165
2.326
2.315
1.000
11
10
9
8
7
6
5
4
3
2
1
ppm
EM-II-98

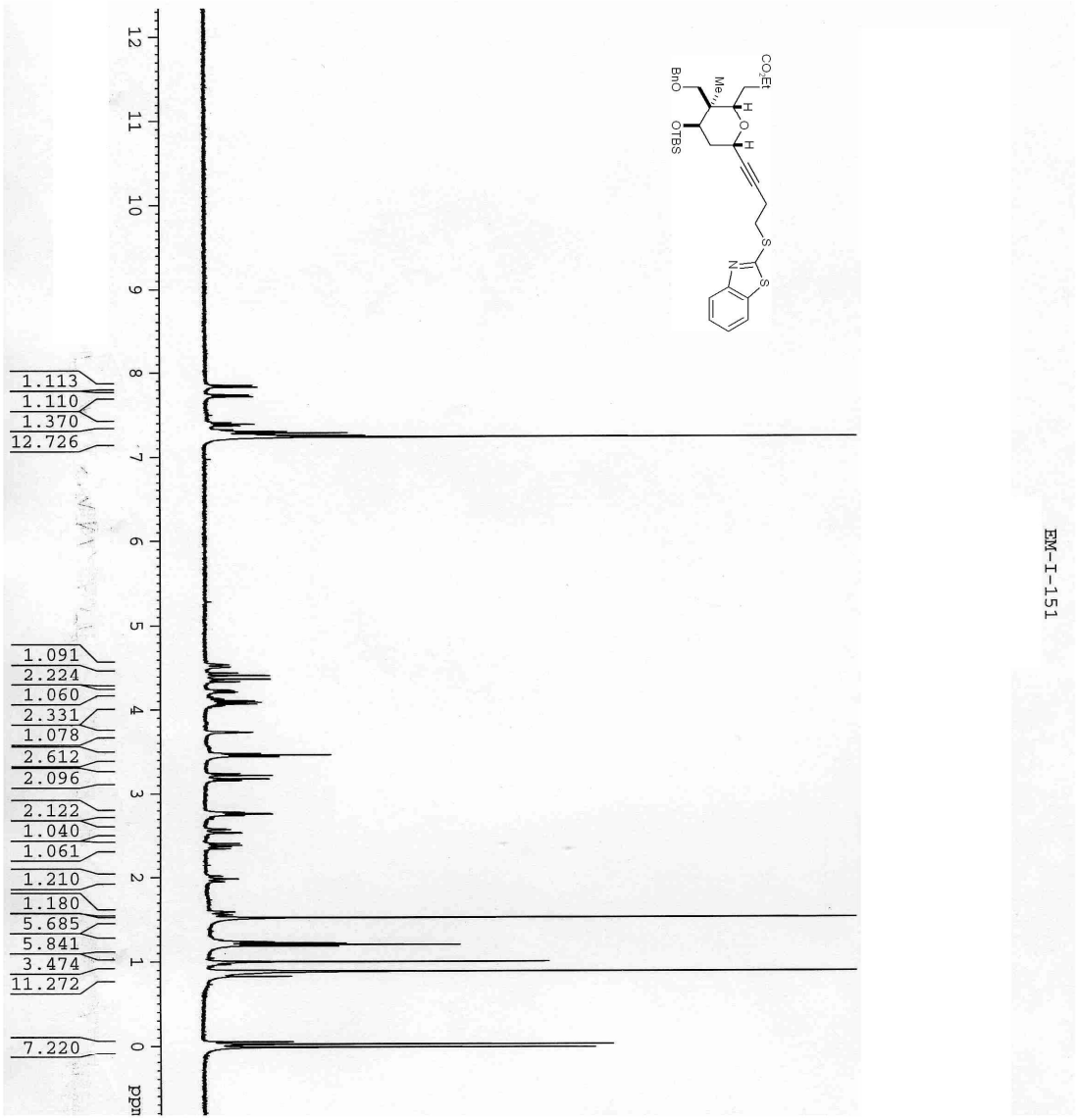

165.674
153.044
135.183
125.958
124.222
121.471
120.910
81.763
77.230
76.975
76.721
70.078
31.953
19.455
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
EM-II-98

EM-VII-20


CO2Et
H
O
H
S
S
N
OTBS OTBS
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.786
0.777
0.838
1.812
1.000
0.249
1.876
1.238
1.623
0.799
0.248
1.570
0.776
0.667
0.752
0.542
0.863
3.444
1.248
16.370
0.849
9.325

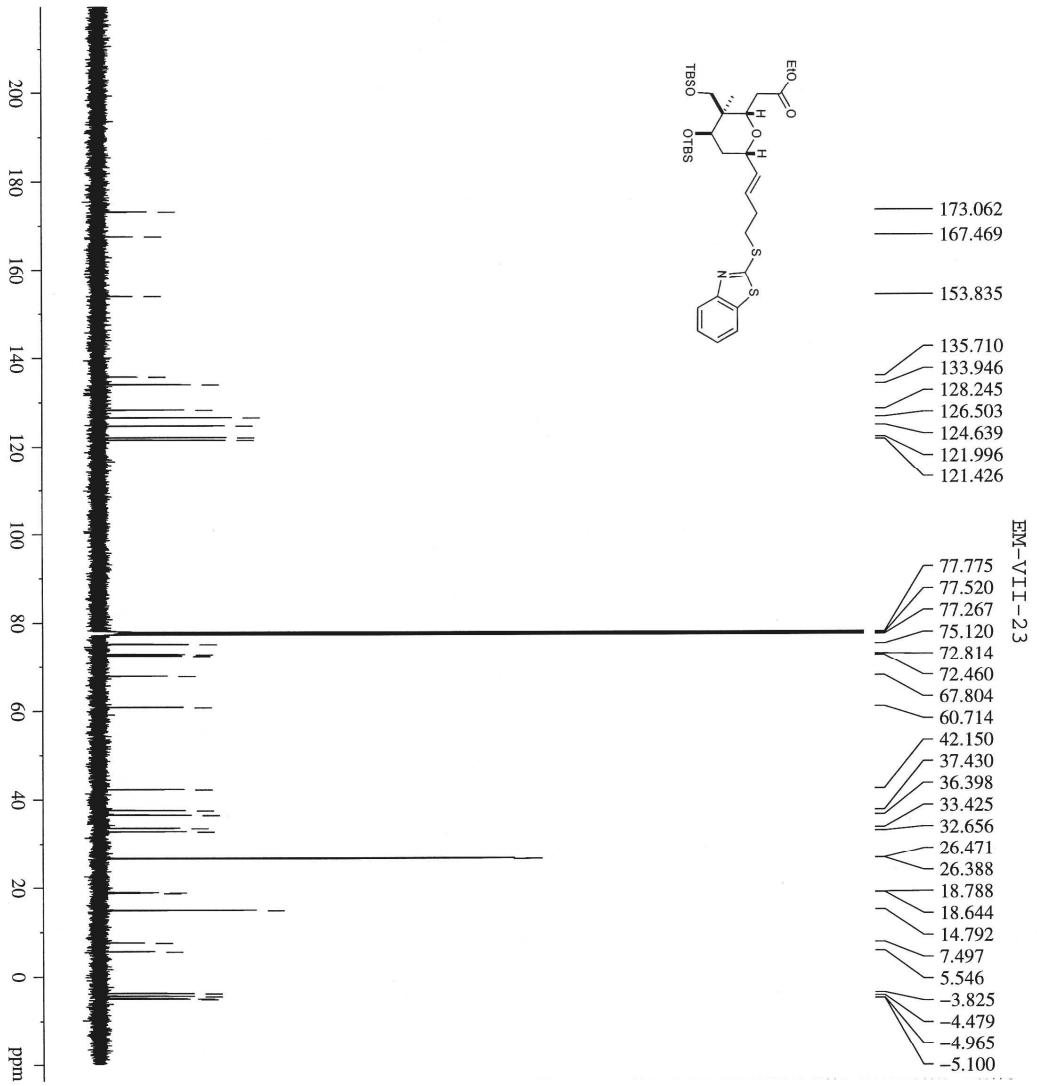

EM-VI-84 HPLC P1
g-NOESY
ppm
ppm
CO2Et
OTBS OTBS
N
S
S

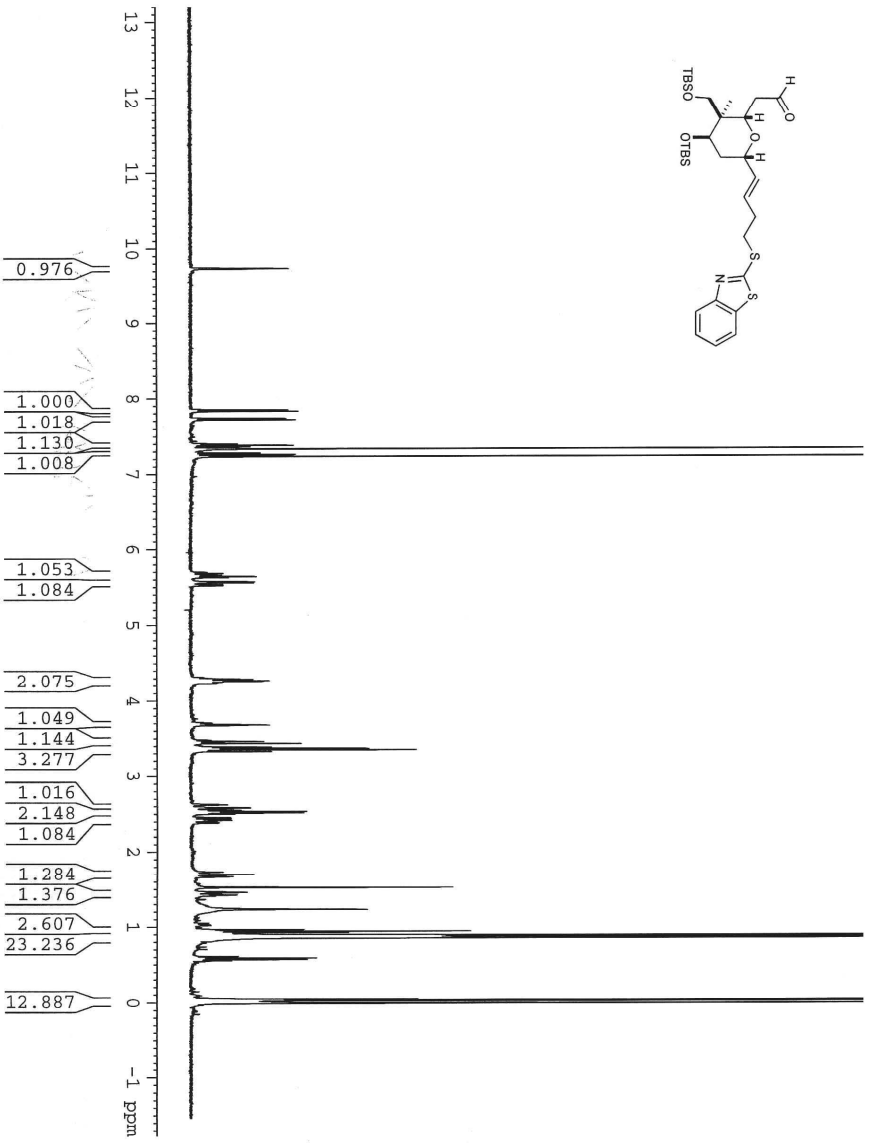

200
180
160
140
120
100
80
60
40
20
0
ppm
OTBS OTBS
CO2Et
H
O
H
S
N
S
172.113
153.481
126.275
126.247
124.488
124.466
121.801
121.195
82.543
82.394
81.648
77.507
77.253
76.999
75.129
72.077
71.975
71.620
67.372
63.197
61.587
60.701
60.560
42.460
41.837
37.179
36.841
35.973
35.120
32.480
32.301
29.944
26.199
26.130
26.105
25.999
20.443
20.333
18.537
EM-VII-20


EM-I-151
CO2Et
Me
H
O
H
BnO
OTBS
S
N
S
1.113
1.110
1.370
12.726
1.091
2.224
1.060
2.331
1.078
2.612
2.096
2.122
1.040
1.061
1.210
1.180
5.685
5.841
3.474
11.272
7.220
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

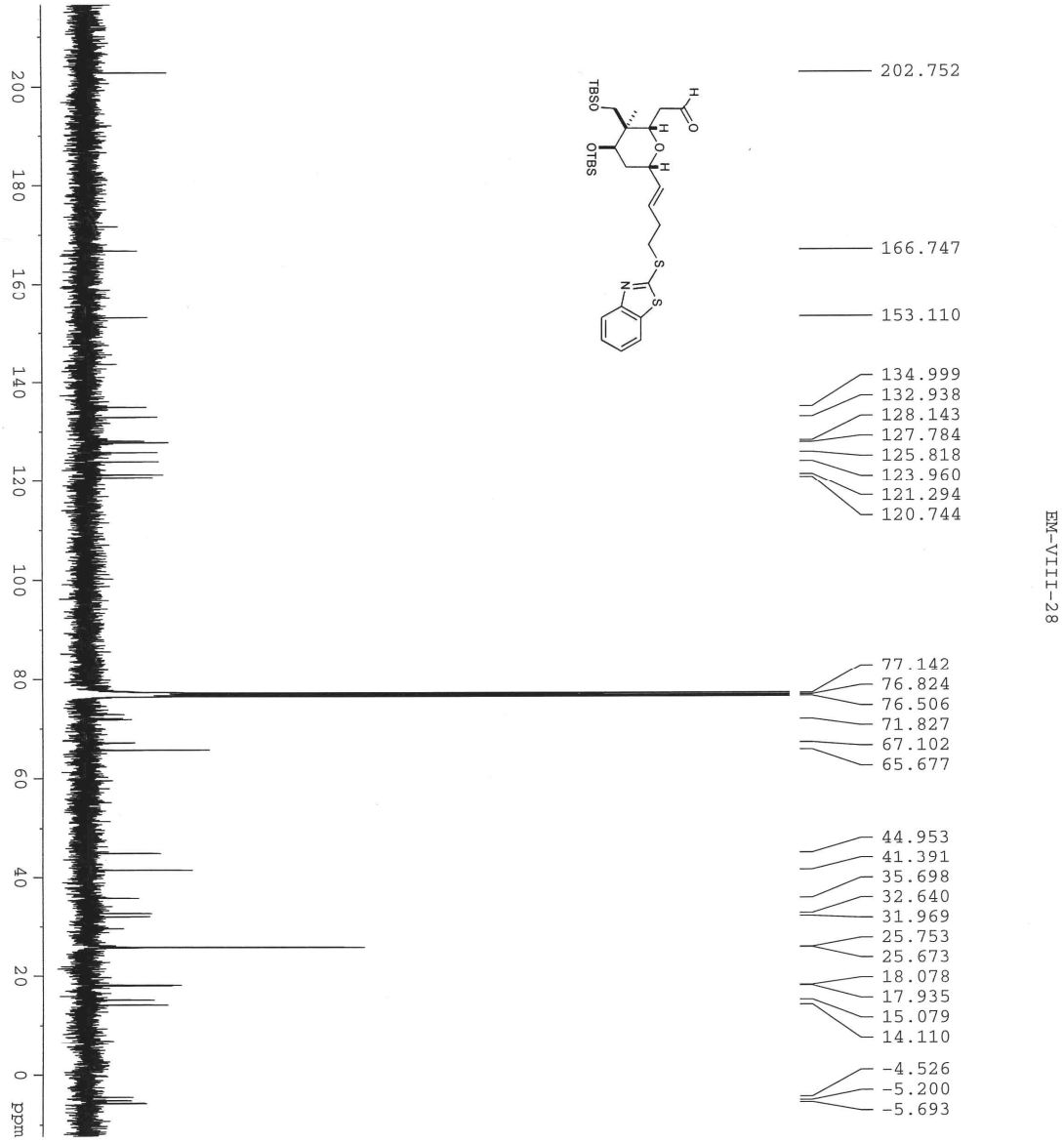
EtO
O
TBSO
OTBS
H
O
H
S
N
S
1.000
0.992
1.085
1.963
1.102
0.963
2.306
2.000
0.331
0.973
1.397
3.050
1.081
1.954
0.935
1.154
1.035
4.460
25.065
13.383
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm

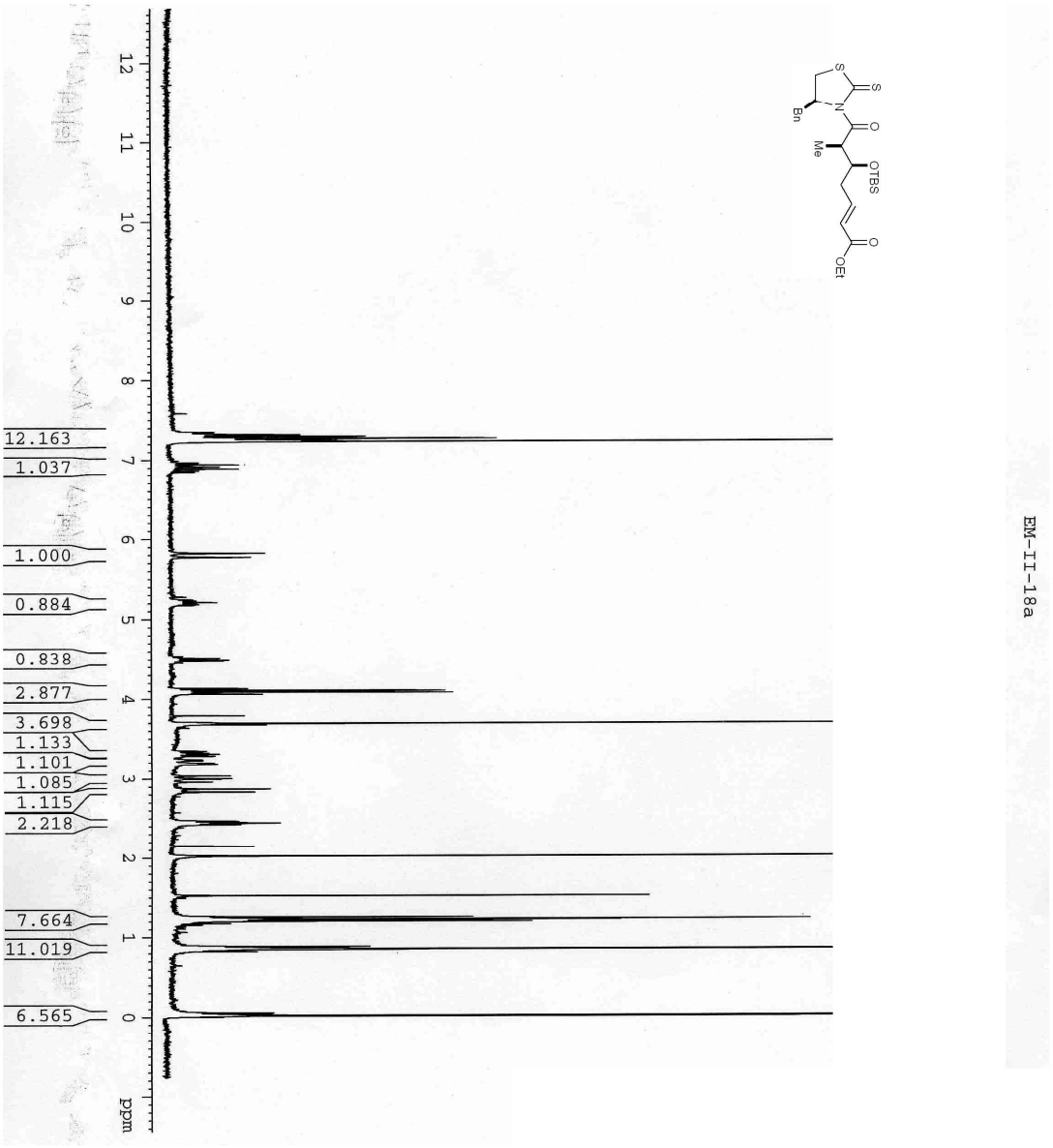
EM-VII-23


EtO
O
TBSO
OTBS
H
O
H
S
N
S
173.062
167.469
153.835
135.710
133.946
128.245
126.503
124.639
121.996
121.426
77.775
77.520
77.267
75.120
72.814
72.460
67.804
60.714
42.150
37.430
36.398
33.425
32.656
26.471
26.388
18.788
18.644
14.792
7.497
5.546
−3.825
−4.479
−4.965
−5.100
EM-VII-23
200
180
160
140
120
100
80
60
40
20
0
ppm

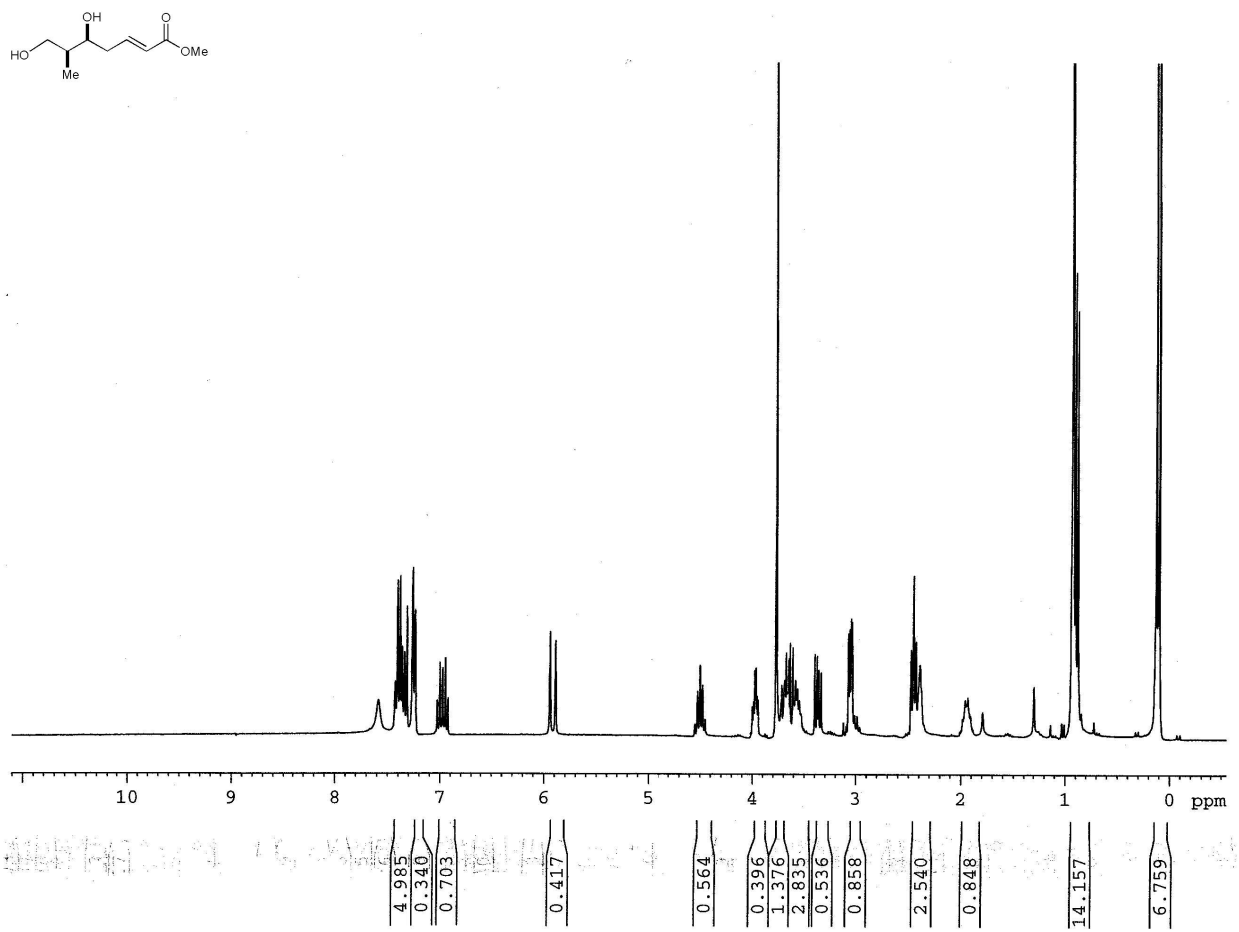

TBSO
OTBS
H
O
H
O
S
N
S
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1 ppm
0.976
1.000
1.018
1.130
1.008
1.053
1.084
2.075
1.049
1.144
3.277
1.016
2.148
1.084
1.284
1.376
2.607
23.236
12.887

EM-VII-37B

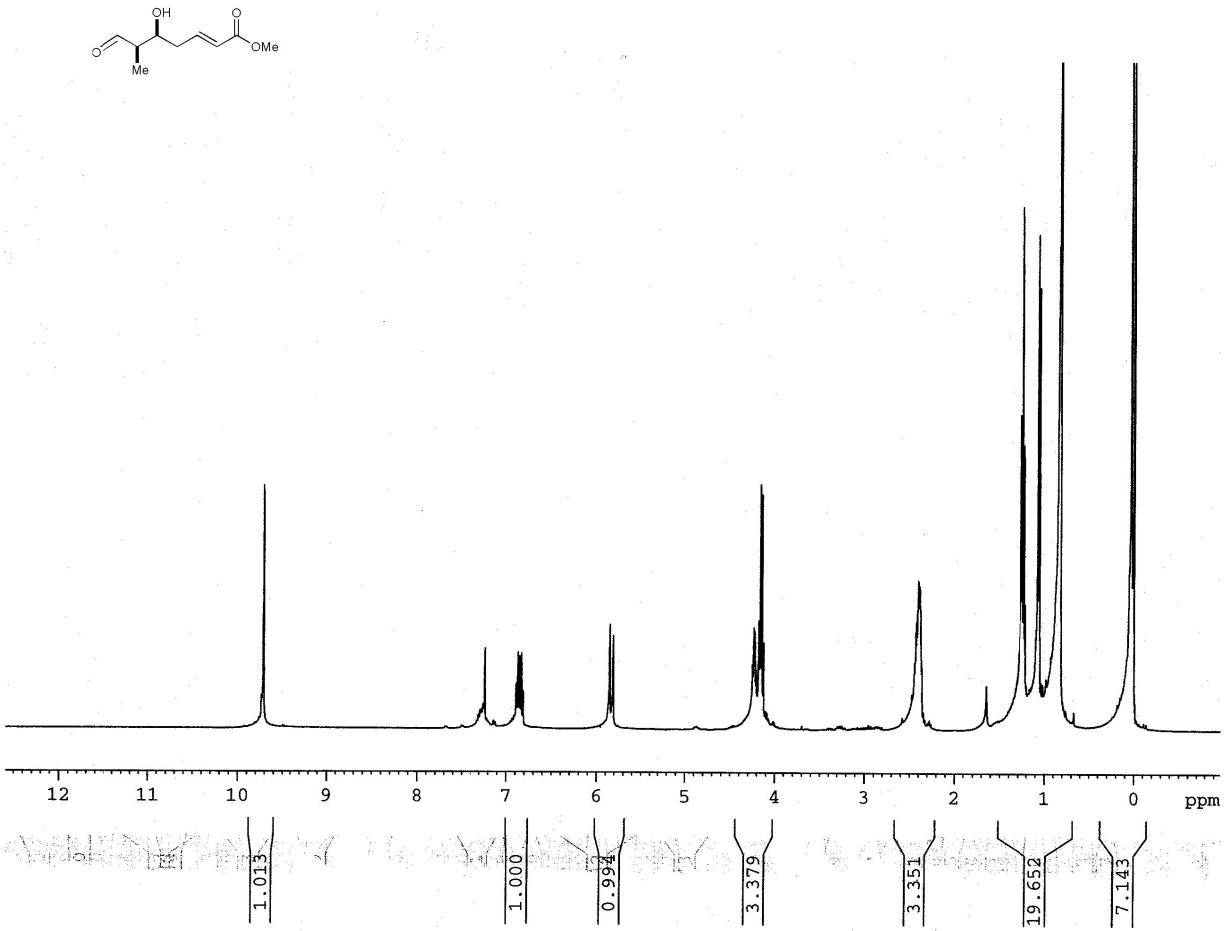

202.752
166.747
153.110
134.999
132.938
128.143
127.784
125.818
123.960
121.294
120.744
77.142
76.824
76.506
71.827
67.102
65.677
44.953
41.391
35.698
32.640
31.969
25.753
25.673
18.078
17.935
15.079
14.110
-4.526
-5.200
-5.693
TBSO
OTBS
H
O
H
O
H
S
N
S
200
180
160
140
120
100
80
60
40
20
0
ppm
EM-VIII-28


12.163
1.037
1.000
0.884
0.838
2.877
3.698
1.133
1.101
1.085
1.115
2.218
7.664
11.019
6.565
ppm
EM-II-18a

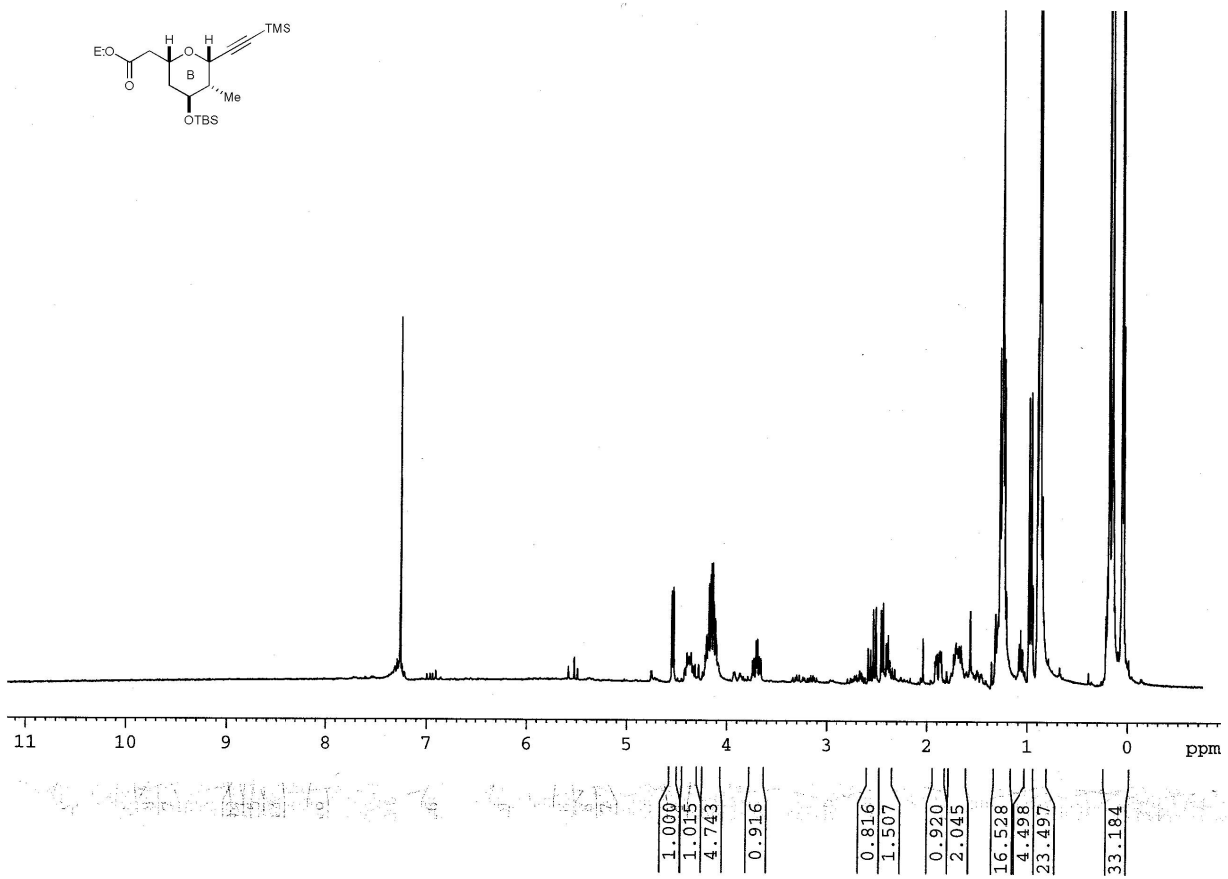
EM-II-61

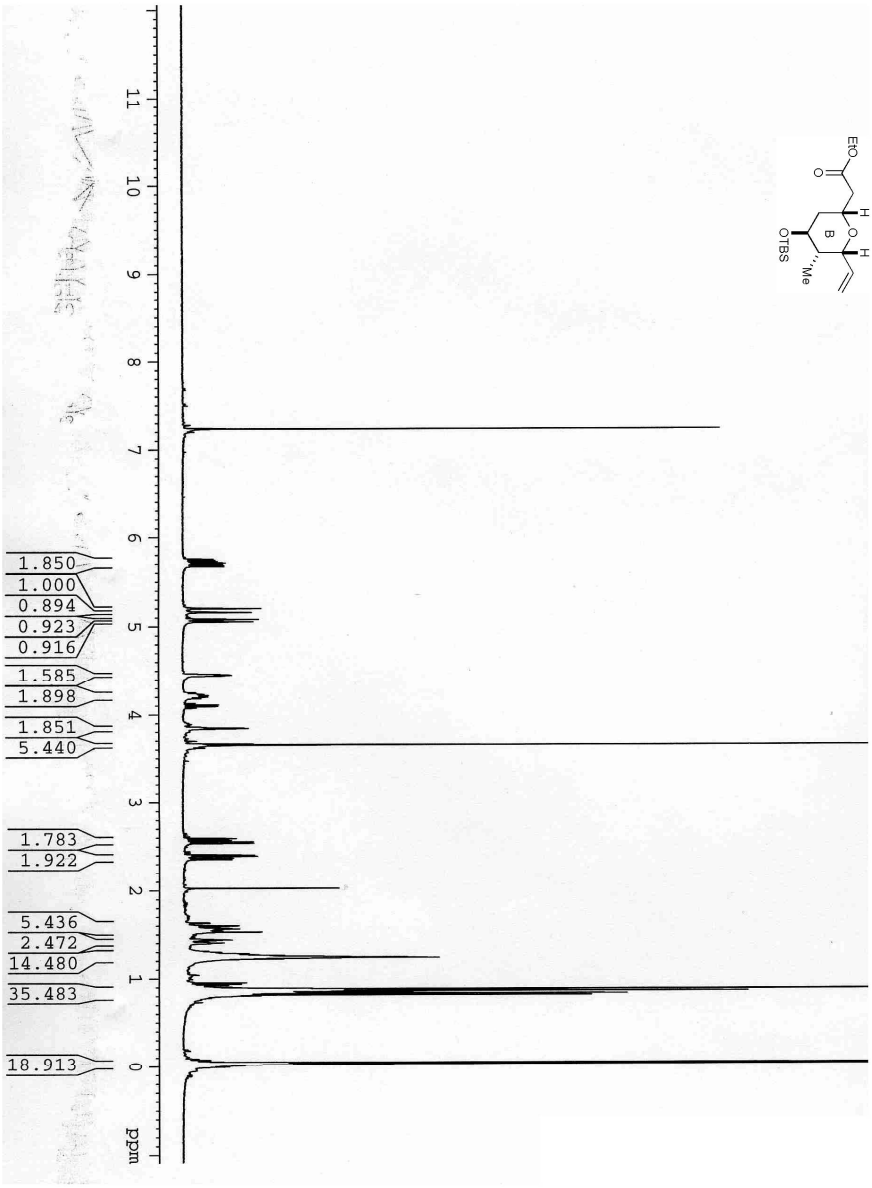

OH
O
HO
OMe
Me
10
9
8
7
6
5
4
3
2
1
0
ppm
4.985
0.340
0.703
0.417
0.564
0.396
1.376
2.835
0.536
0.858
2.540
0.848
14.157
6.759

EM-II-71

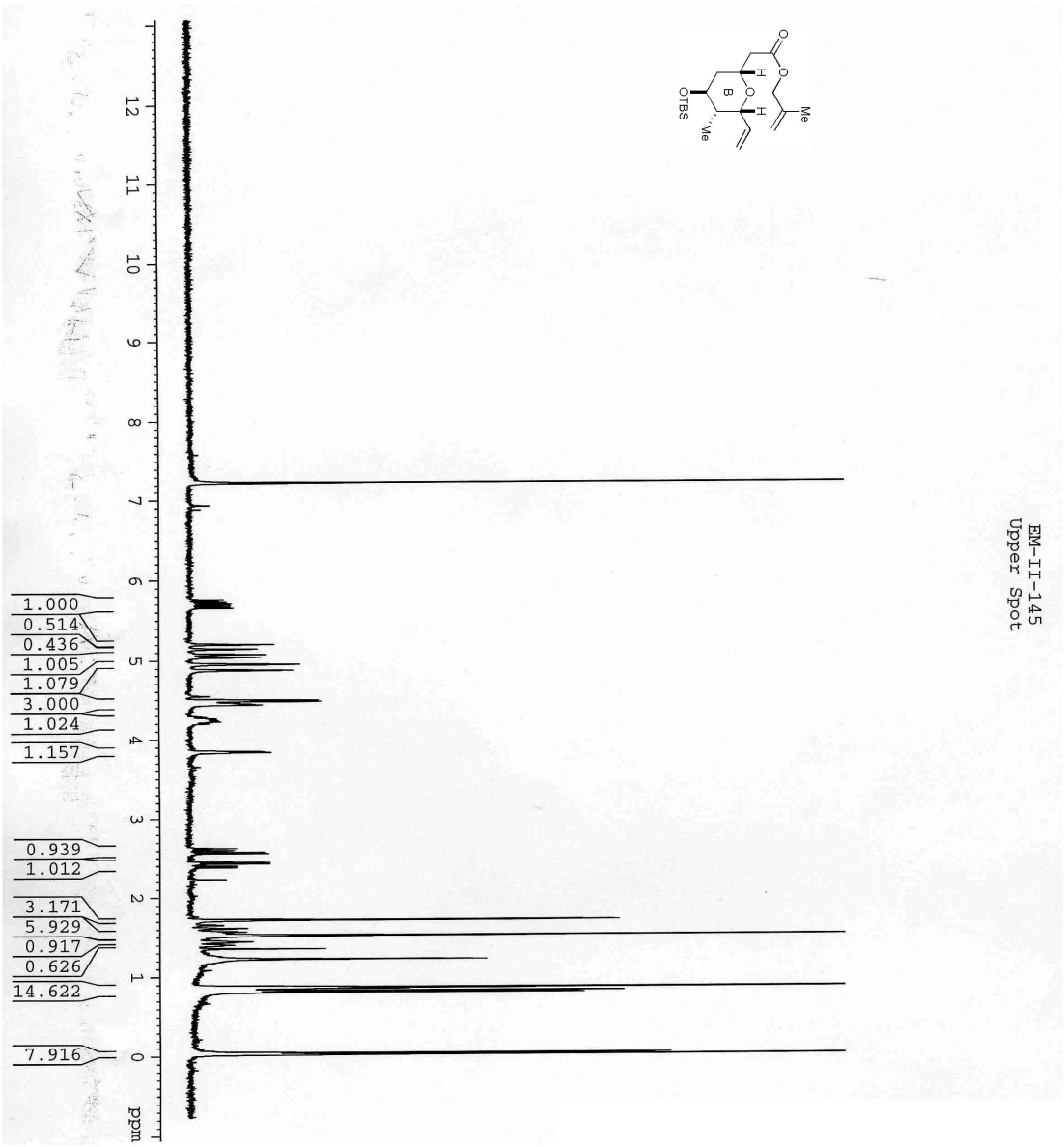

OH
O
O
OMe
Me
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.013
1.000
0.994
3.379
3.351
19.652
7.143

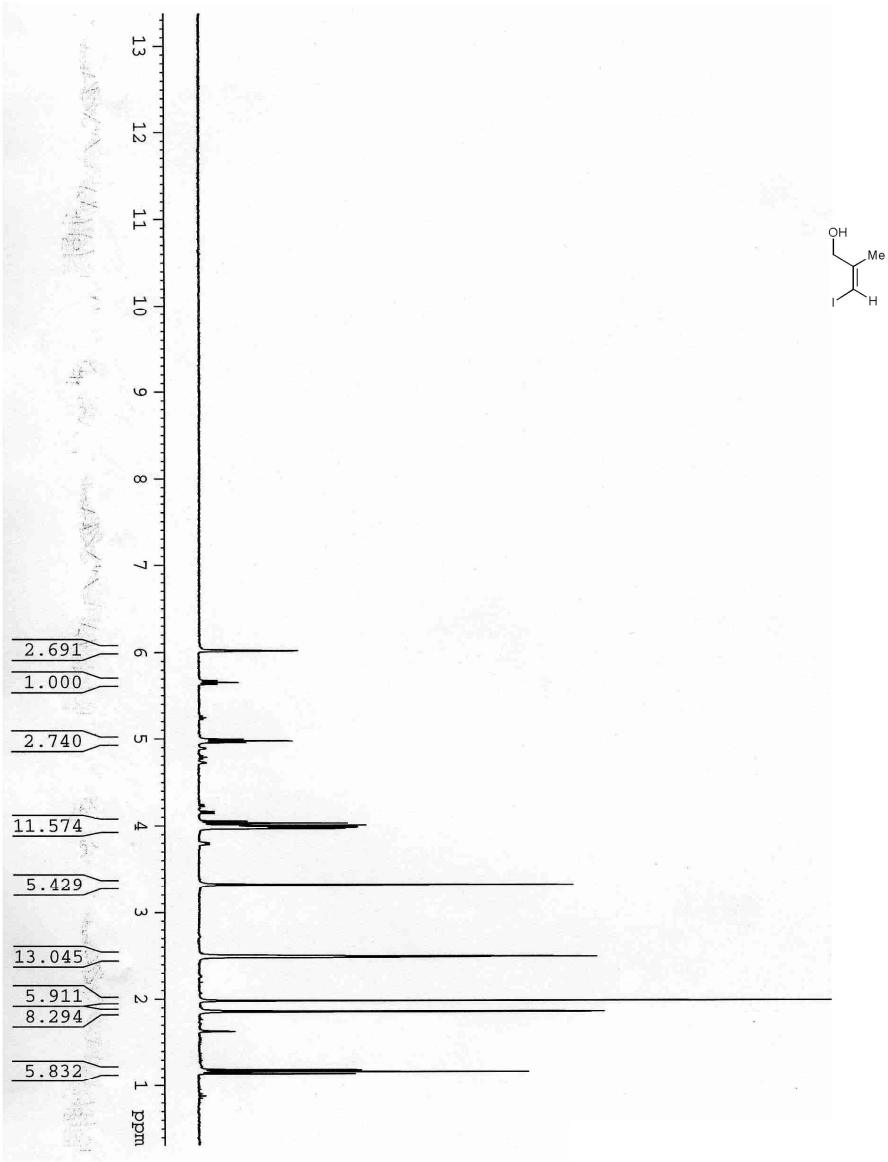
EM-II-136
Lower Spot

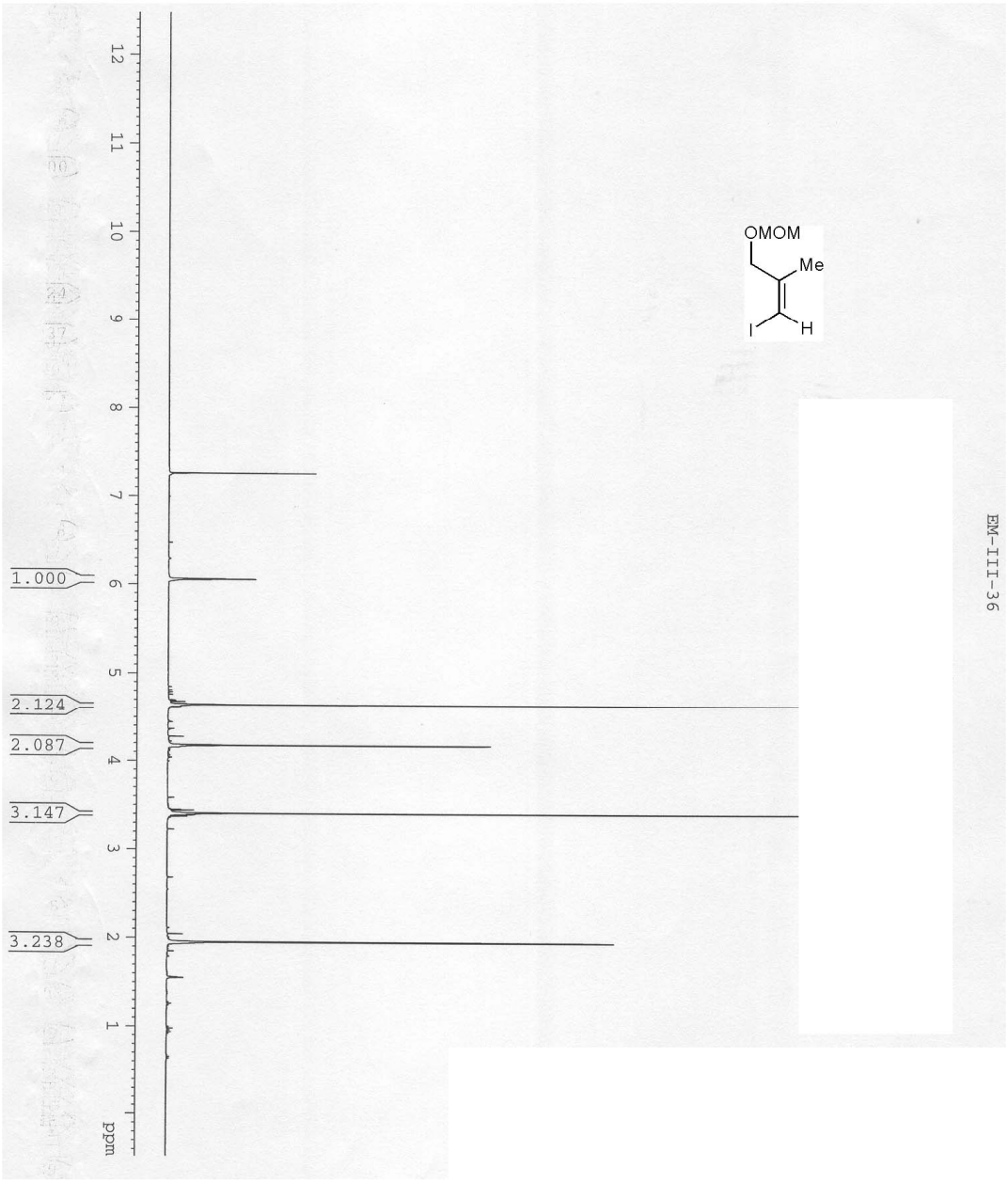


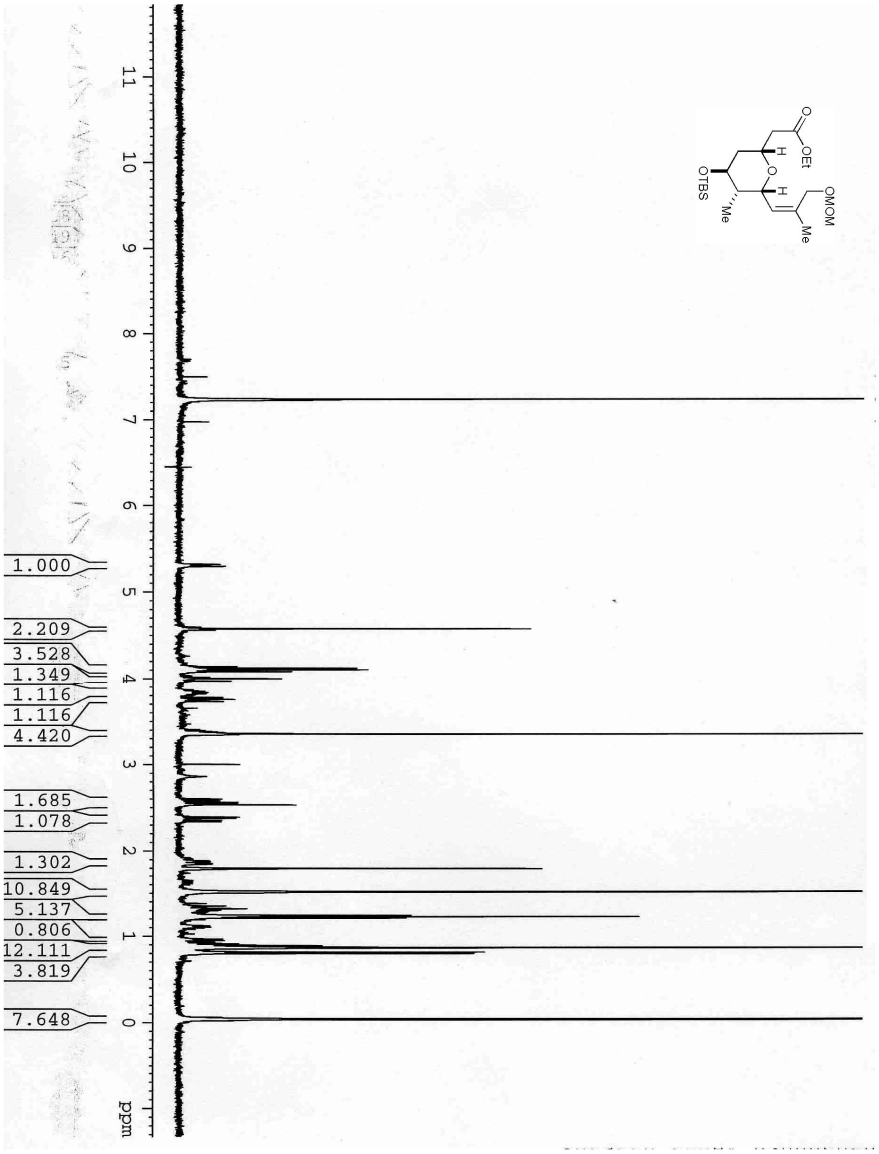

EtO
O
H
O
H
B
OTBS
Me
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.850
1.000
0.894
0.923
0.916
1.585
1.898
1.851
5.440
1.783
1.922
5.436
2.472
14.480
35.483
18.913

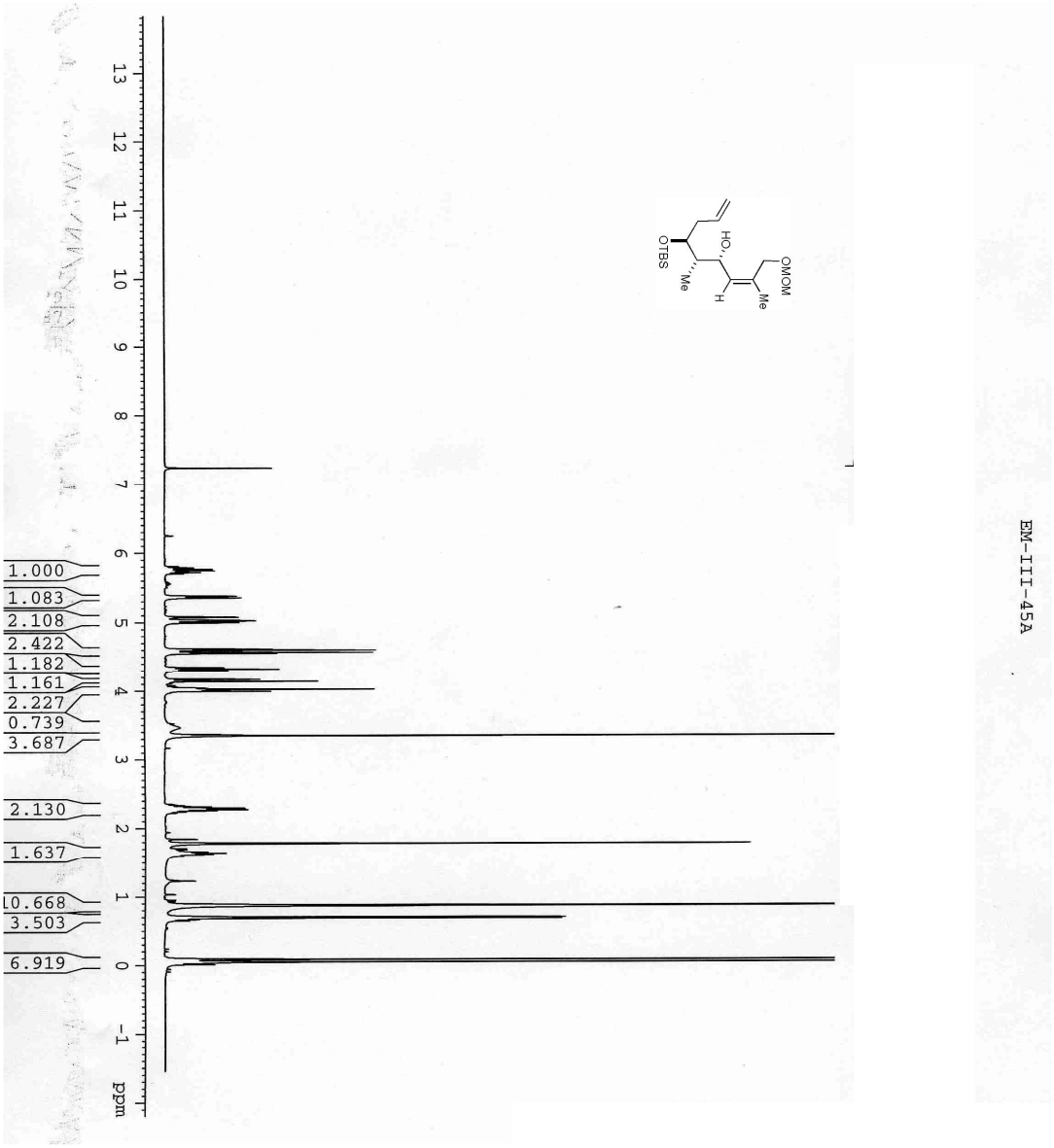
EM-II-131


EM-II-145
Upper Spot
1.000
0.514
0.436
1.005
1.079
3.000
1.024
1.157
0.939
1.012
3.171
5.929
0.917
0.626
14.622
7.916
ppm
OTBS
Me
Me
H
O
H
B

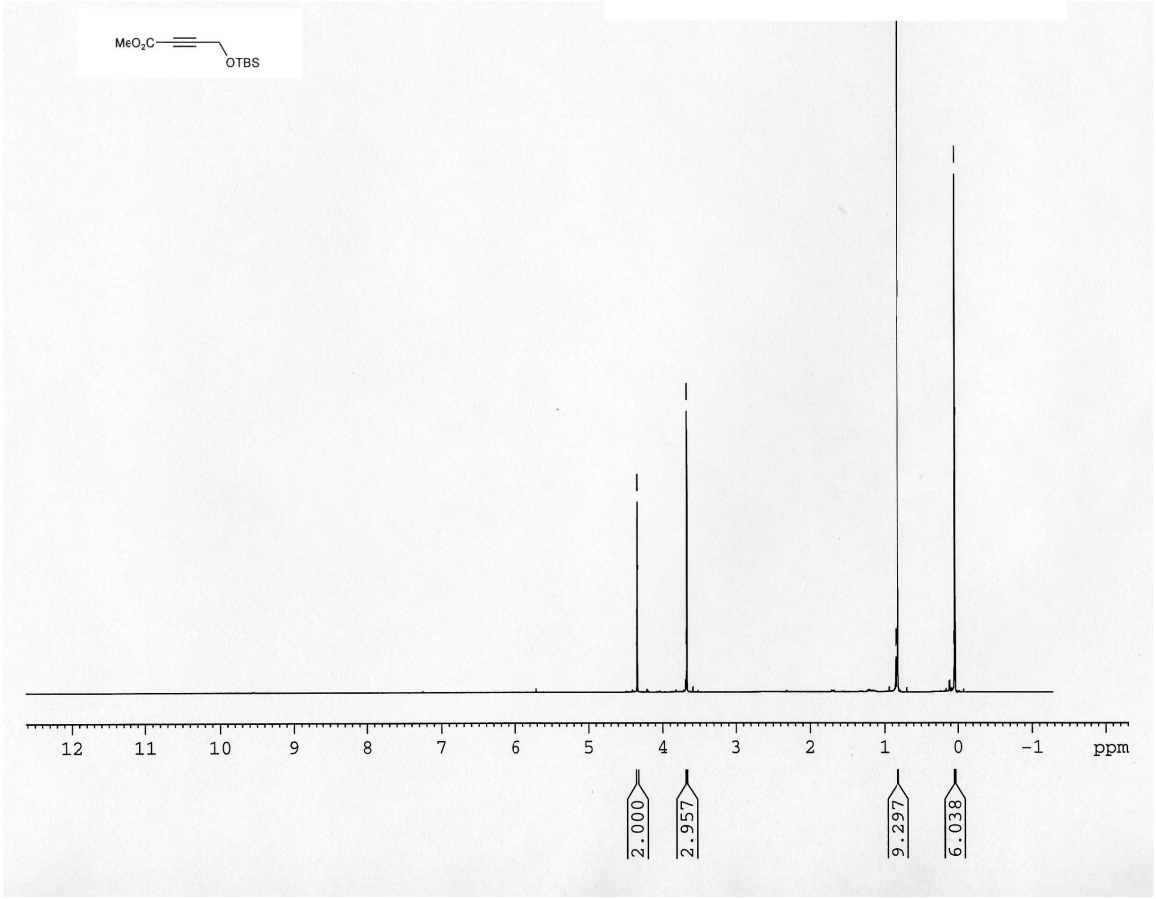

OH
Me
I
H
2.691
1.000
2.740
11.574
5.429
13.045
5.911
8.294
5.832
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
EM-II-164-B


OMOM
Me
I
H
EM-III-36
1.000
2.124
2.087
3.147
3.238
12
11
10
9
8
7
6
5
4
3
2
1
ppm

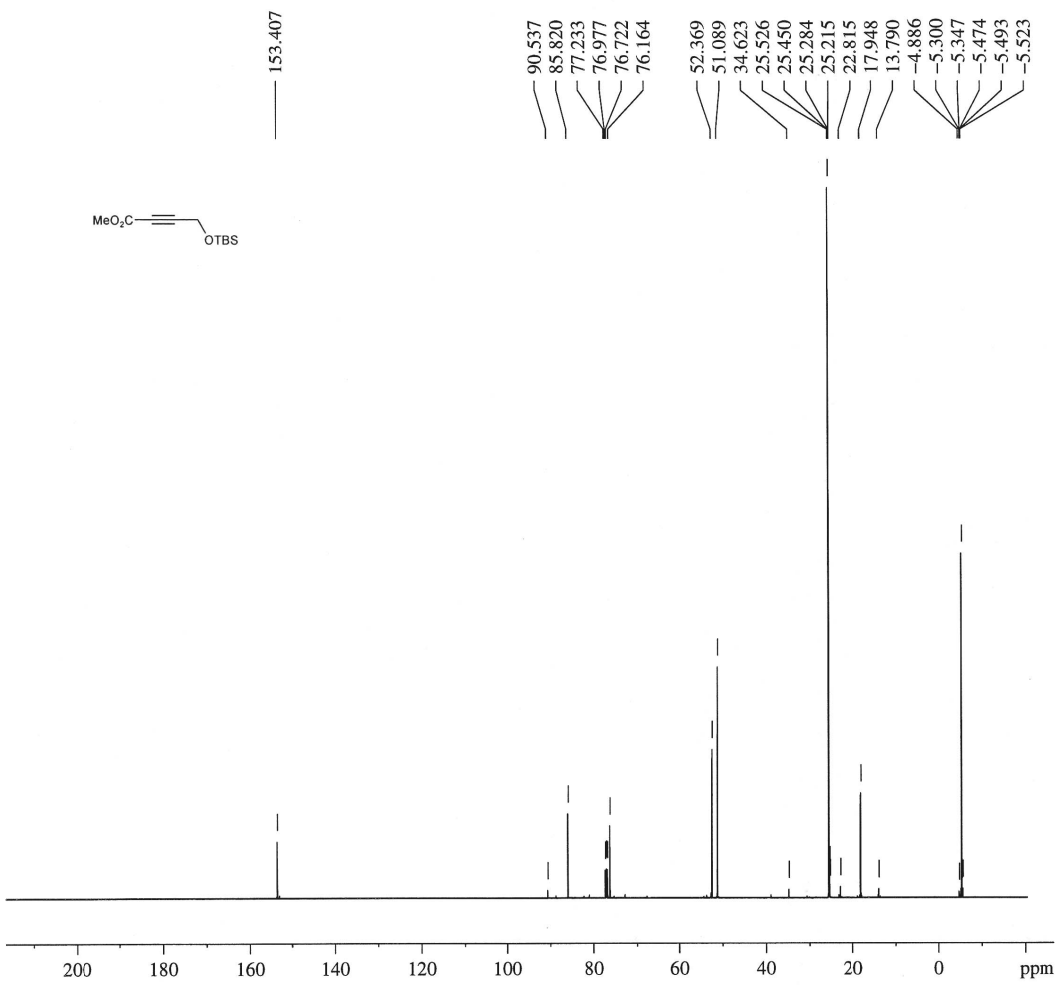

OEt
OTBS
OMOM
Me
Me
1.000
2.209
3.528
1.349
1.116
1.116
4.420
1.685
1.078
1.302
10.849
5.137
0.806
12.111
3.819
7.648
ppm
EM-III-42


EM-III-45A
OTBS
Me
HO
H
Me
OMOM
1.000
1.083
2.108
2.422
1.182
1.161
2.227
0.739
3.687
2.130
1.637
0.668
3.503
6.919
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

EM-VII-136



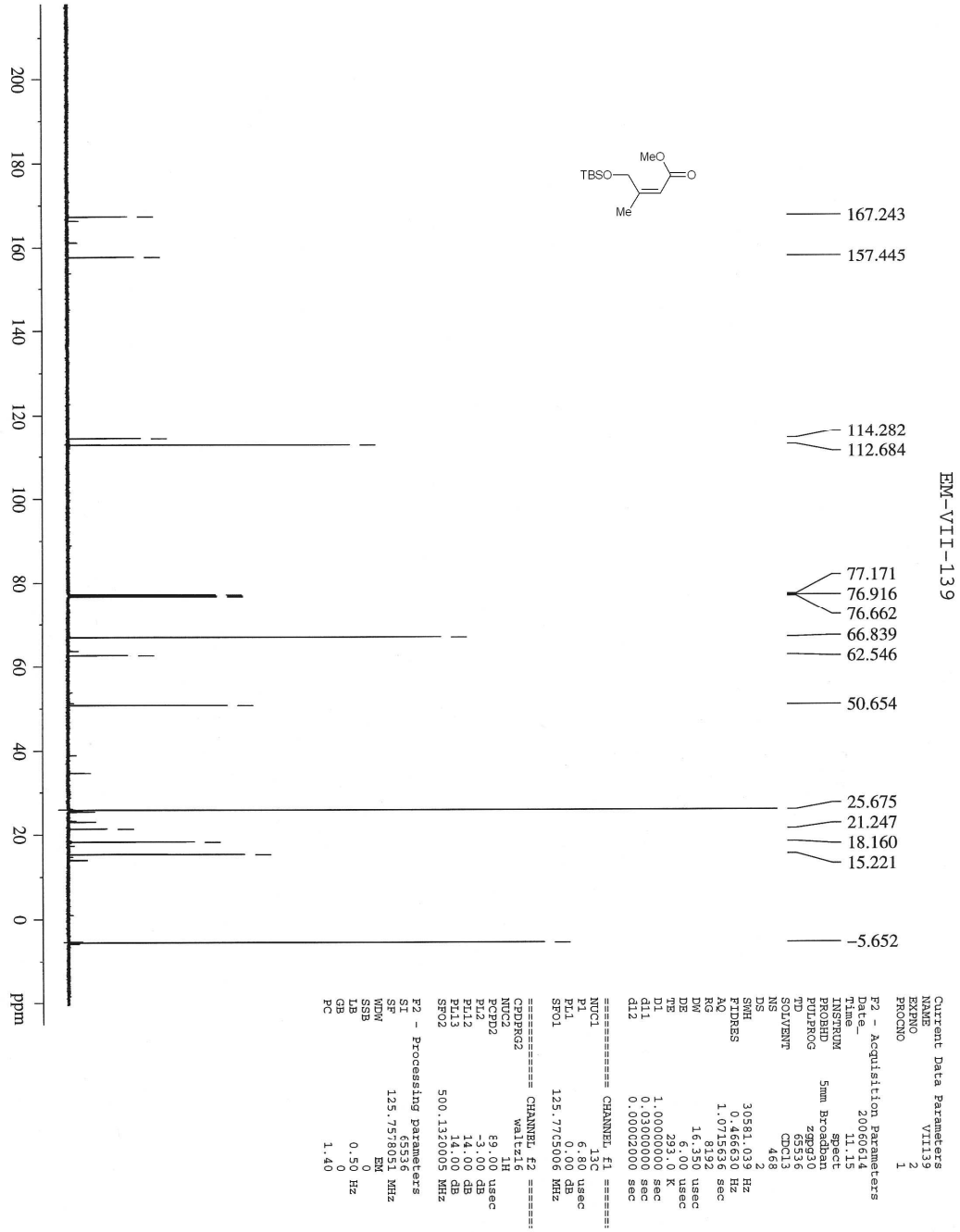
EM-VII-136




```
Current Data Parameters
NAME                  VII136
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20060614
Time                  10.10
INSTRUM               spect
PROBHD      5mm Broadban
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     746
DS                       2
SWH             30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                    4096
DW                 16.350 usec
DE                  6.00 usec
TE                 293.0 K
D1              1.00000000 sec
d11             0.03000000 sec
d12             0.00002000 sec

============ CHANNEL f1 =======
NUC1                  13C
P1                   6.80 usec
PL1                  0.00 dB
SFO1         125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                  1H
PCPD2               89.00 usec
PL2                 -3.00 dB
PL12                14.00 dB
PL13                14.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                   65536
SF           125.7578051 MHz
WDW                     EM
SSB                      0
LB                    0.50 Hz
GB                       0
PC                    1.40
```

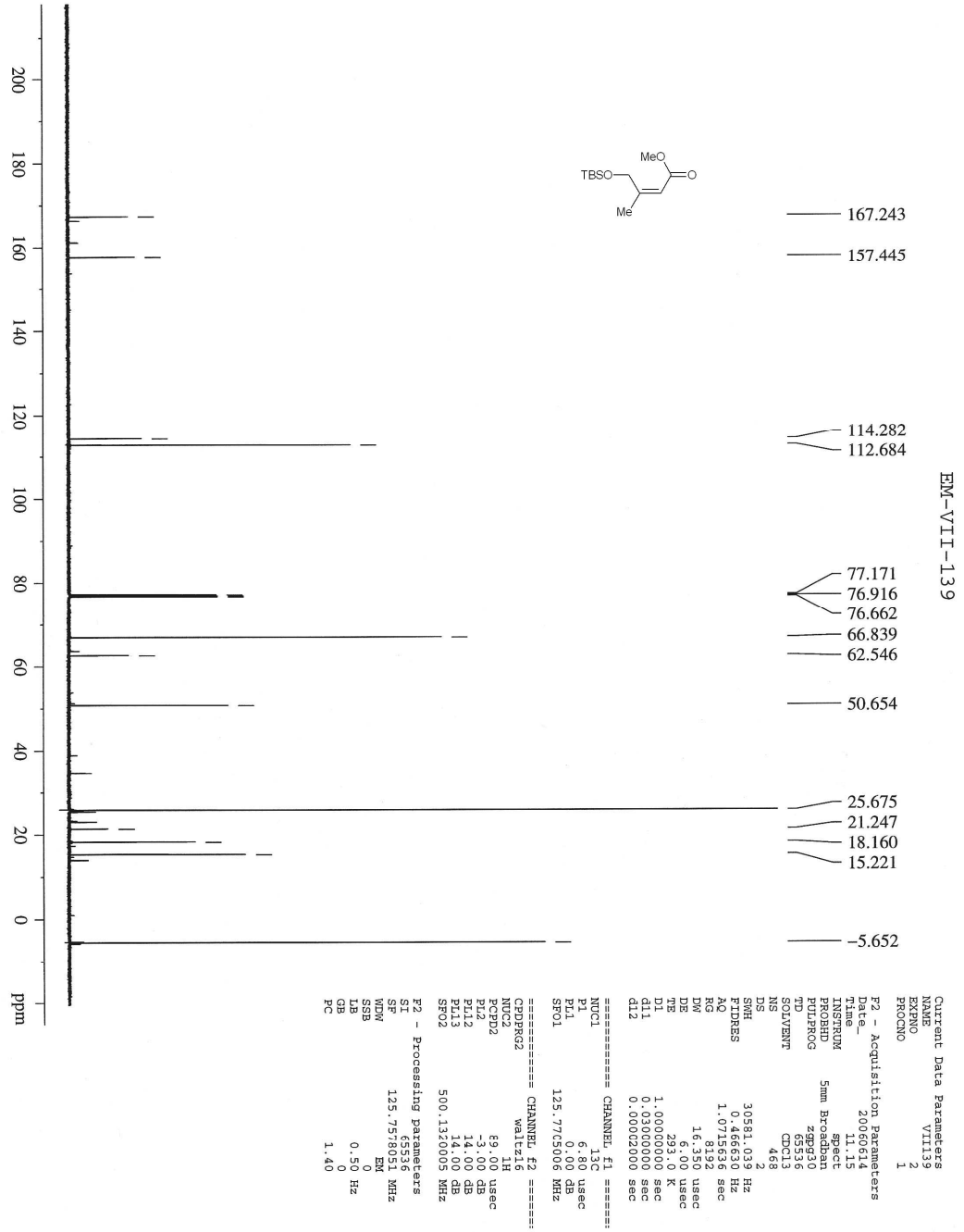
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
0.188
0.380
2.076
3.122
0.582
3.032
0.575
11.793
7.560
Me
TBSO
O
MeO

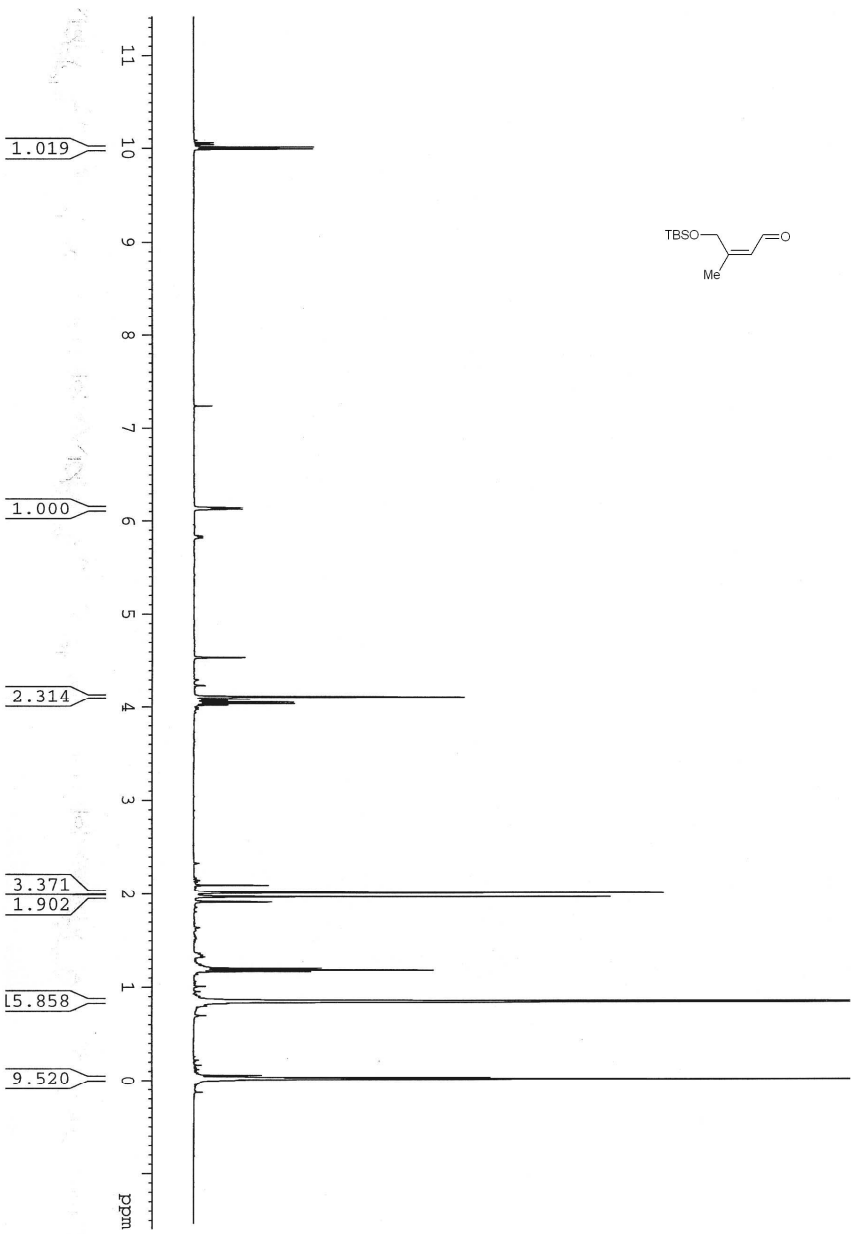
EM-VII-139


EM-VII-139
MeO
TBSO
O
Me
167.243
157.445
114.282
112.684
77.171
76.916
76.662
66.839
62.546
50.654
25.675
21.247
18.160
15.221
-5.652
ppm
200
180
160
140
120
100
80
60
40
20
0
Current Data Parameters
NAME VII139
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060114
Time 11.15
INSTRUM spect
PROBHD 5mm Broadband
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 468
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 8192
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.77575006 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40

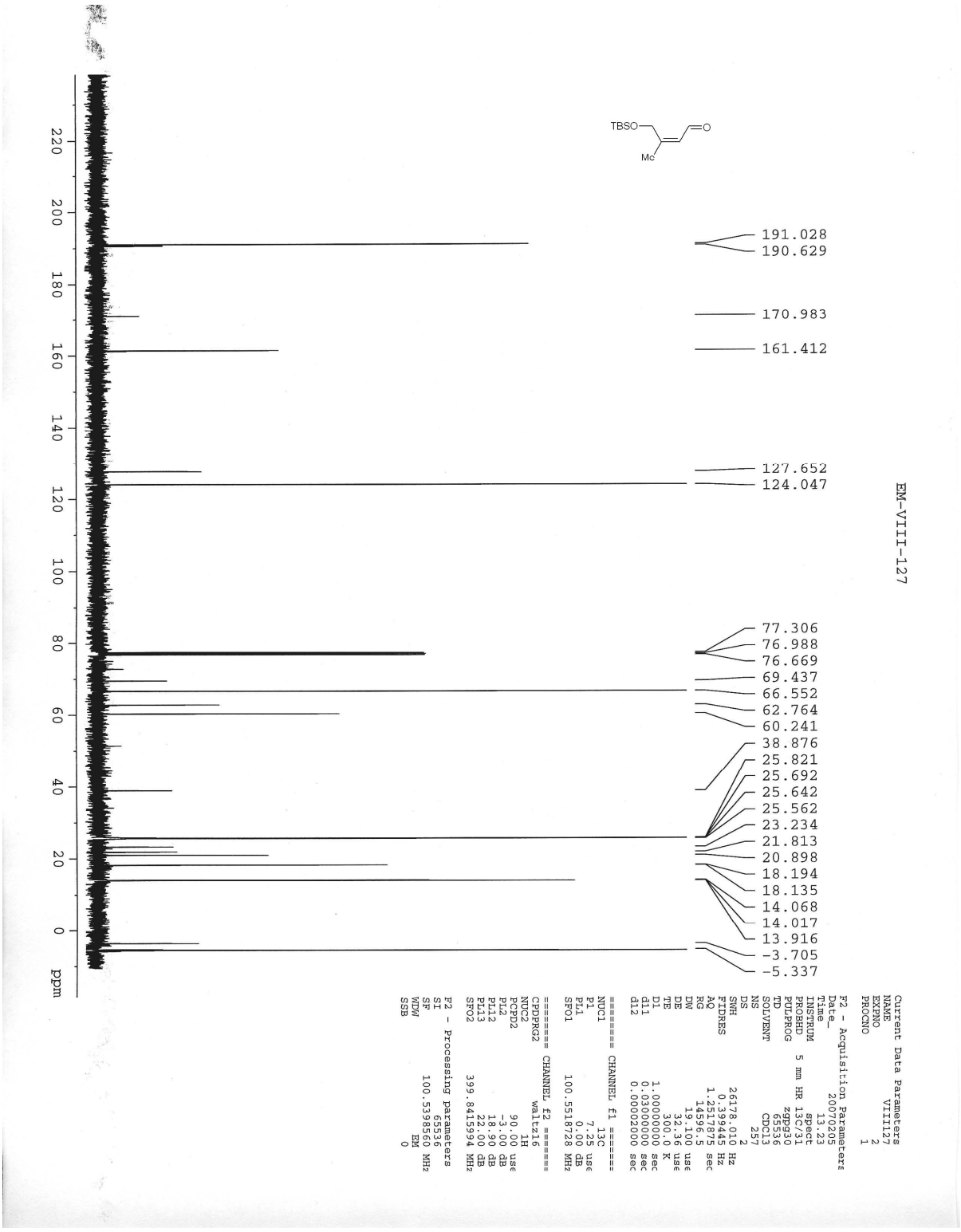
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
0.188
0.380
2.076
3.122
0.582
3.032
0.575
11.793
7.560
Me
TBSO
O
MeO

EM-VII-139

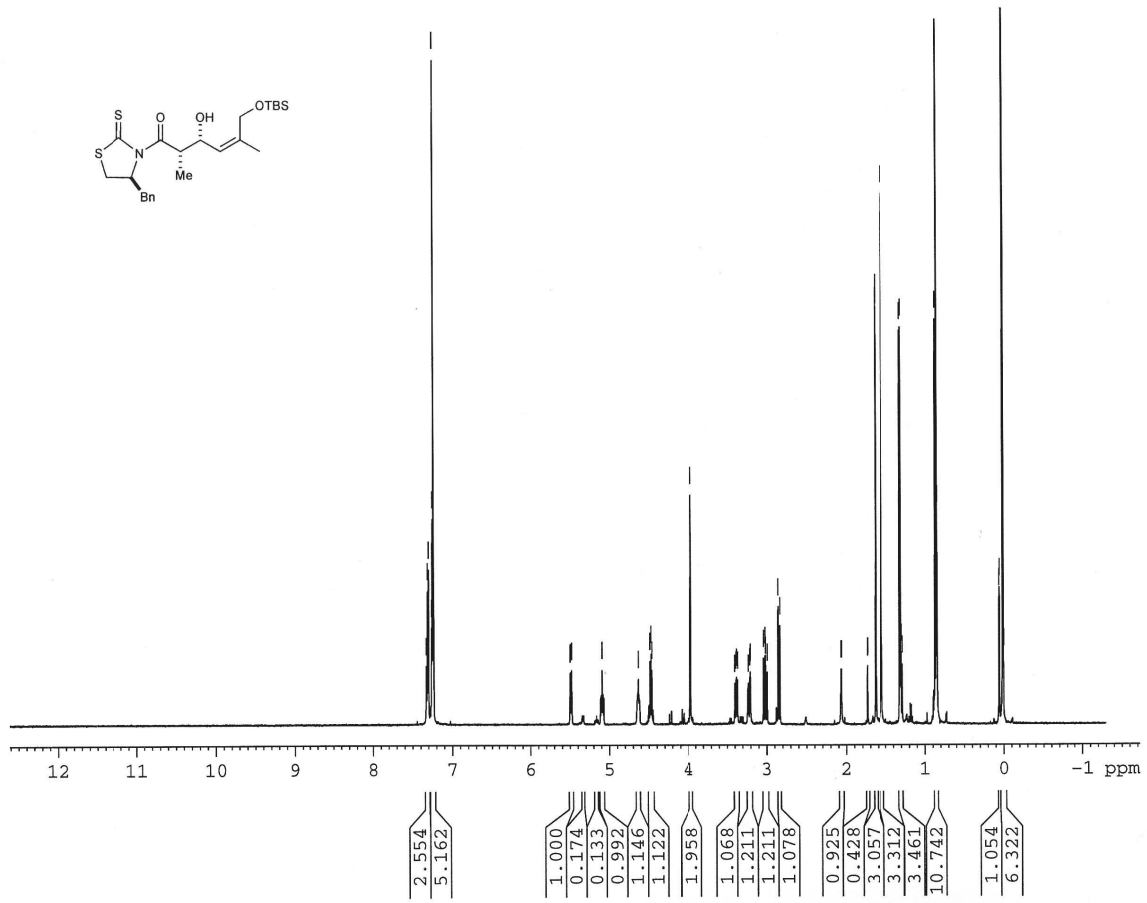

EM-VII-139
MeO
TBSO
O
Me
167.243
157.445
114.282
112.684
77.171
76.916
76.662
66.839
62.546
50.654
25.675
21.247
18.160
15.221
-5.652
200
180
160
140
120
100
80
60
40
20
0
ppm
Current Data Parameters
NAME VII139
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060114
Time 11.15
INSTRUM spect
PROBHD 5mm Broadband
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 468
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 8192
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.77C5006 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40

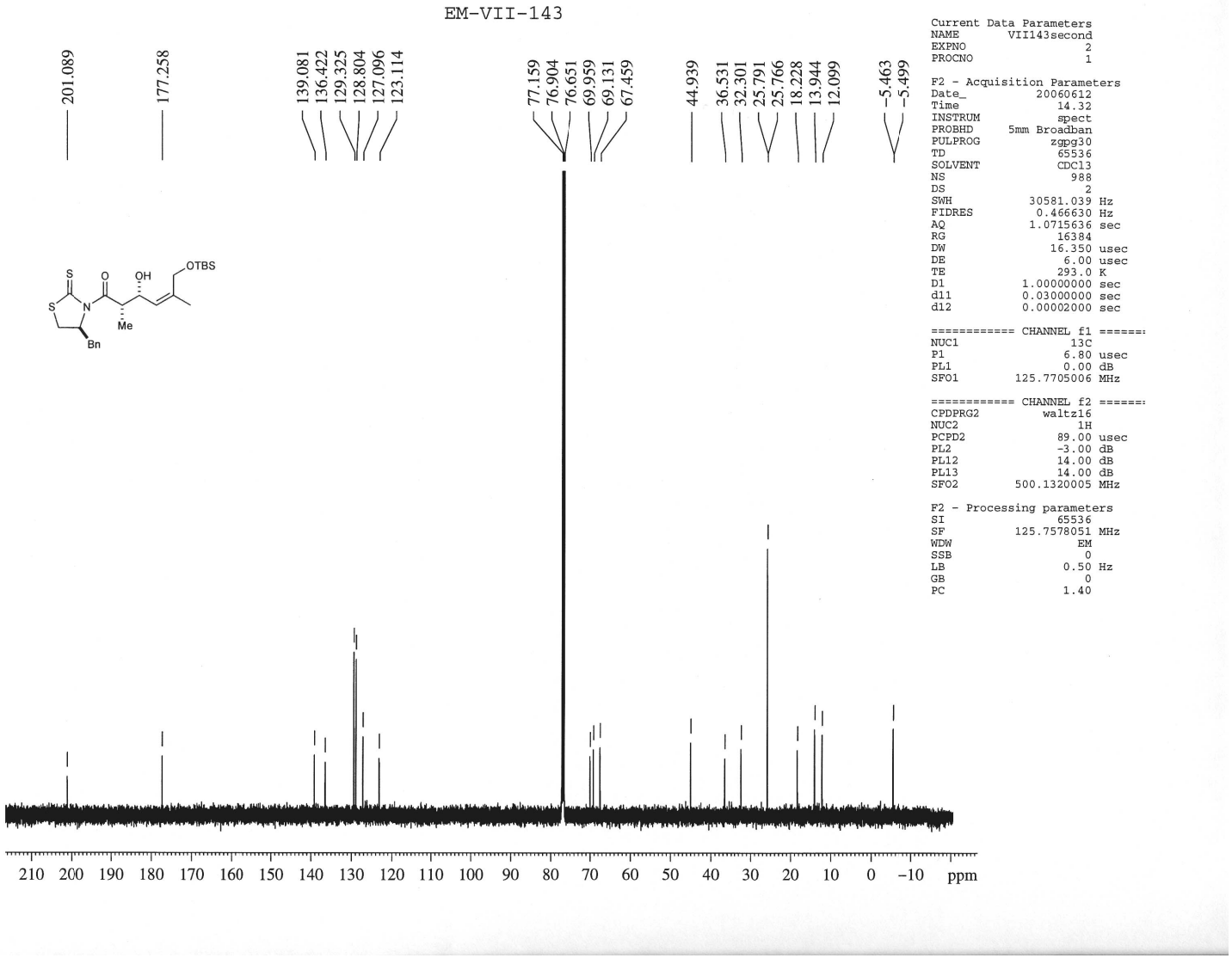


EM-VIII-127

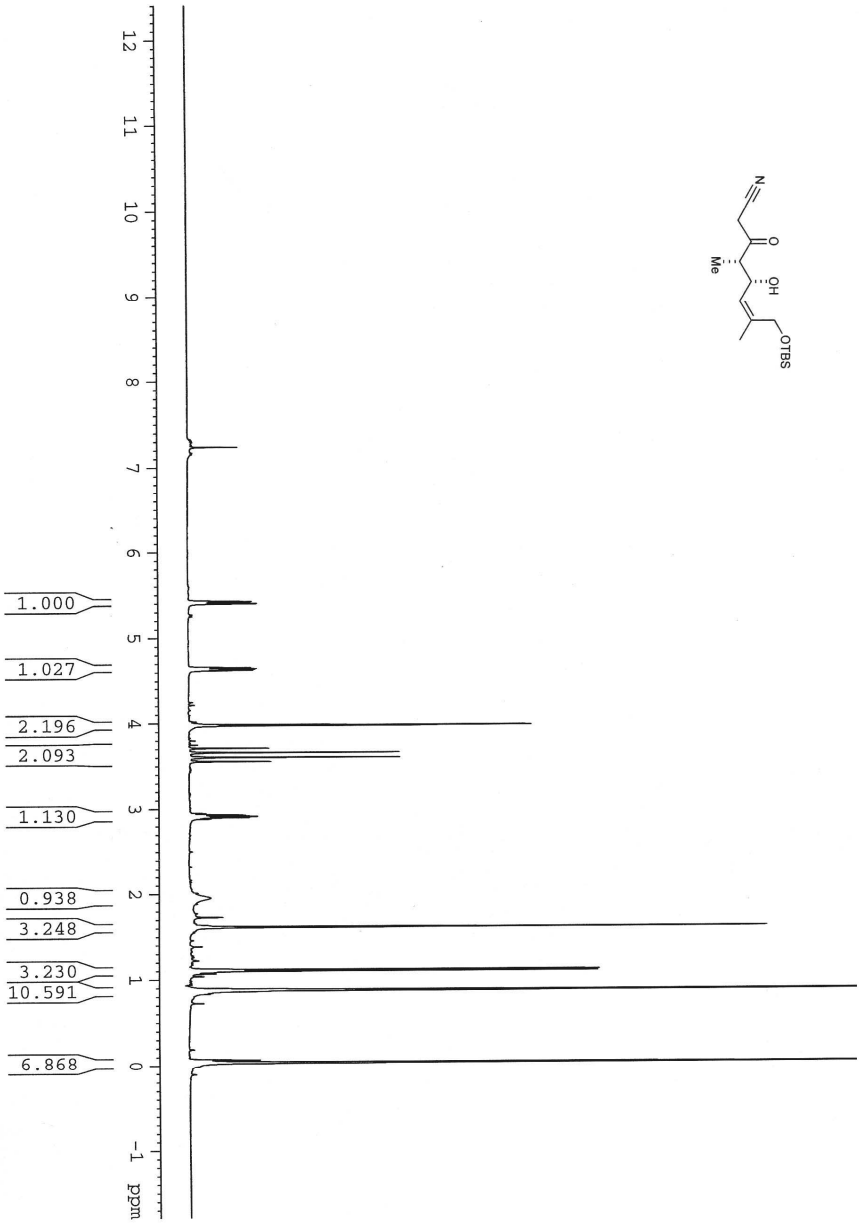

TBSO
Me
O
191.028
190.629
170.983
161.412
127.652
124.047
77.306
76.988
76.669
69.437
66.552
62.764
60.241
38.876
25.821
25.692
25.642
25.562
23.234
21.813
20.898
18.194
18.135
14.068
14.017
13.916
-3.705
-5.337
220
200
180
160
140
120
100
80
60
40
20
0
ppm
EM-VIII-127
Current Data Parameters
NAME VIII127
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070205
Time 13.23
INSTRUM spect
PROBHD 5 mm HR 13C/31
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 257
DS 2
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2517875 sec
RG 14596.5
DW 19.100 use
DE 32.36 use
TE 300.0 K
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.25 use
PL1 0.00 dB
SFO1 100.5518728 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 use
PL2 13.00 dB
PL12 18.50 dB
PL13 22.00 dB
SFO2 399.8415994 MHz
F2 - Processing parameters
SI 65536
SF 100.5398560 MHz
WDW EM
SSB 0

EM-VII-143

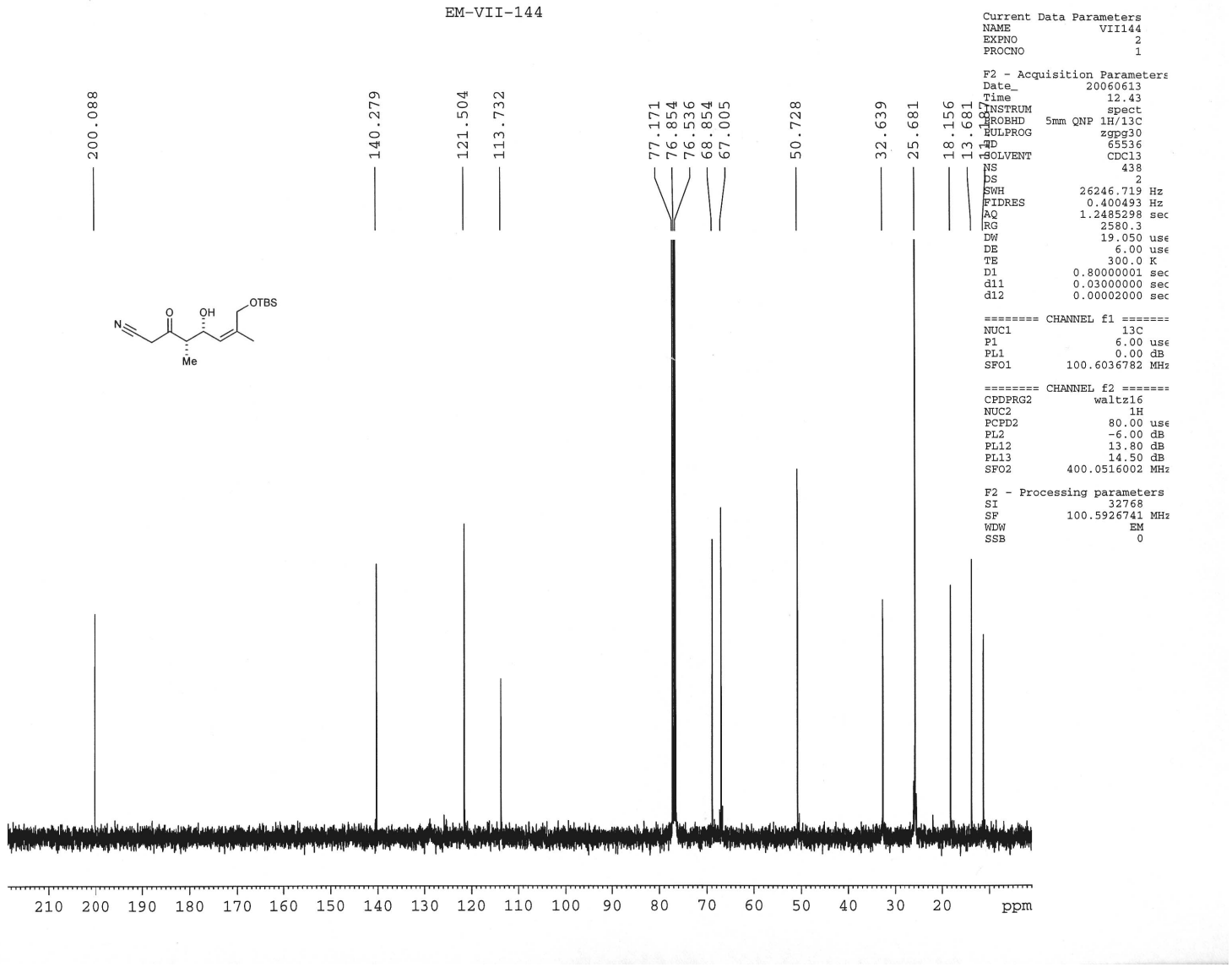

S
O
OH
OTBS
S
N
Me
Bn
12
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm
2.554
5.162
1.000
0.174
0.133
0.992
1.146
1.122
1.958
1.068
1.211
1.211
1.078
0.925
0.428
3.057
3.312
3.461
10.742
1.054
6.322

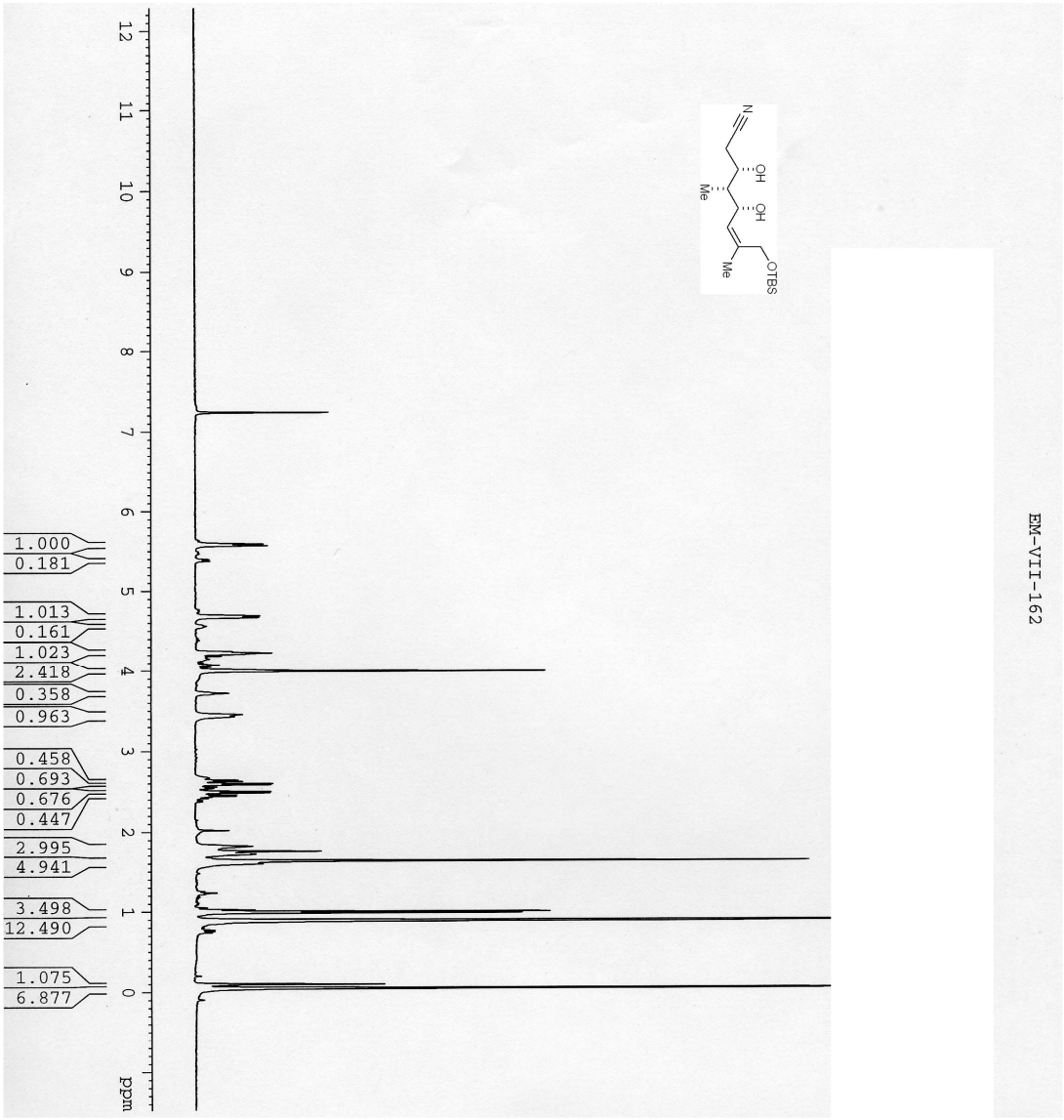


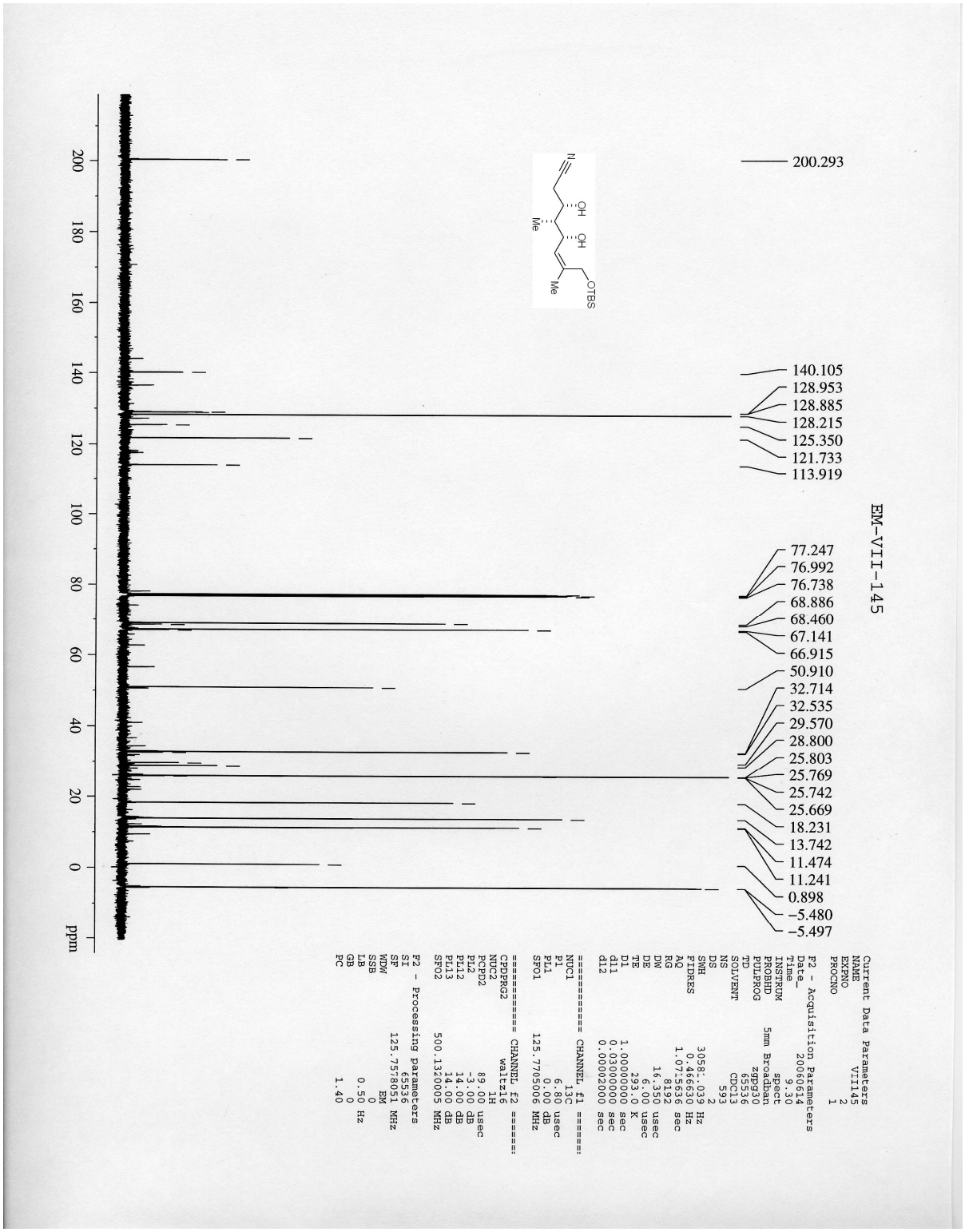

```
Current Data Parameters
NAME          VII143second
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20060612
Time                 14.32
INSTRUM              spect
PROBHD     5mm Broadban
PULPROG          zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    988
DS                      2
SWH           30581.039 Hz
FIDRES        0.466630 Hz
AQ            1.0715636 sec
RG                  16384
DW               16.350 usec
DE                6.00 usec
TE                293.0 K
D1            1.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

============ CHANNEL f1 =======
NUC1                 13C
P1                  6.80 usec
PL1                 0.00 dB
SFO1         125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2          waltz16
NUC2                 1H
PCPD2              89.00 usec
PL2                -3.00 dB
PL12               14.00 dB
PL13               14.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                  65536
SF           125.7578051 MHz
WDW                  EM
SSB                   0
LB                 0.50 Hz
GB                    0
PC                 1.40
```

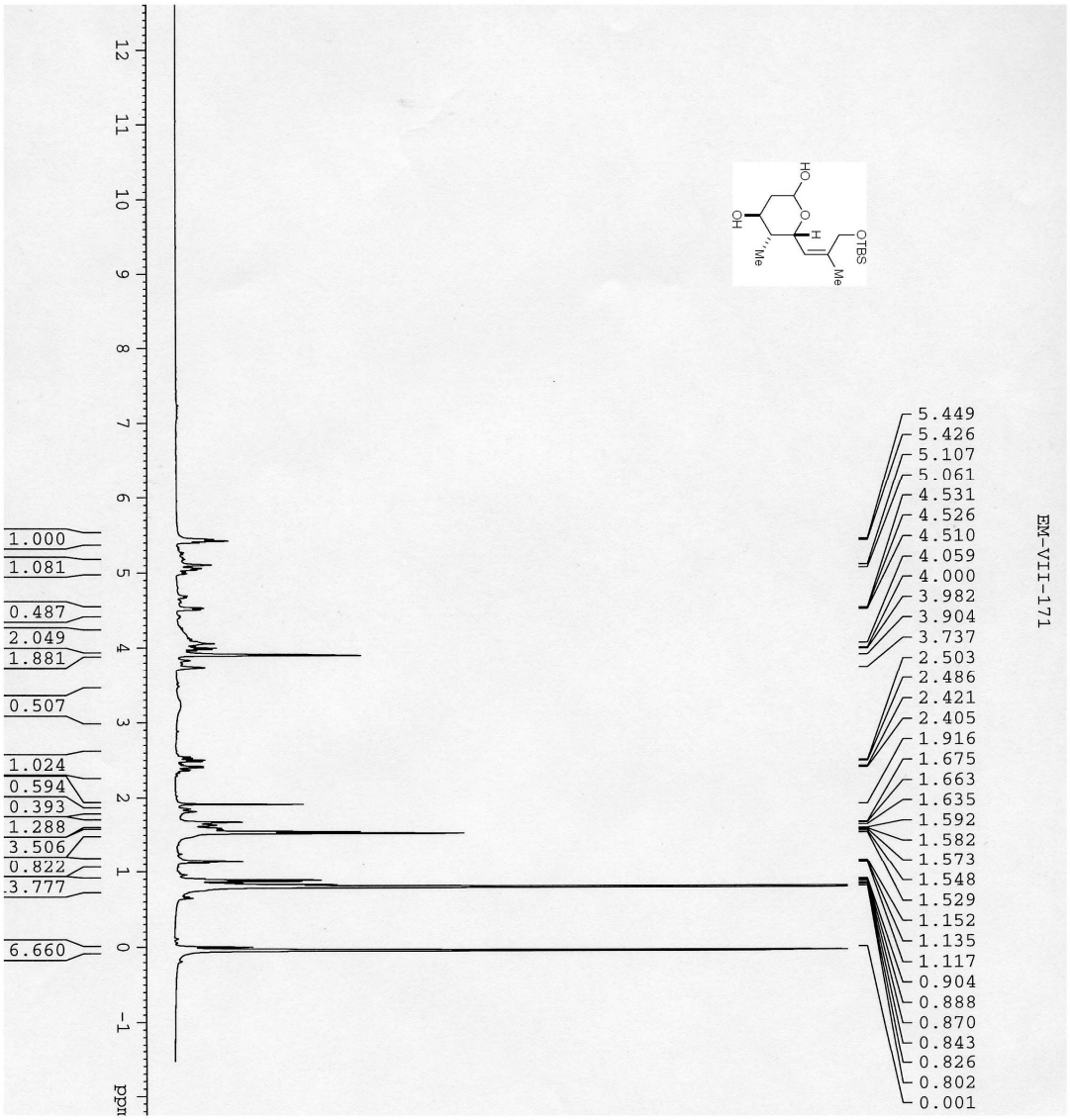

N
O
Me
OH
OTBS
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
1.000
1.027
2.196
2.093
1.130
0.938
3.248
3.230
10.591
6.868

EM-VII-144

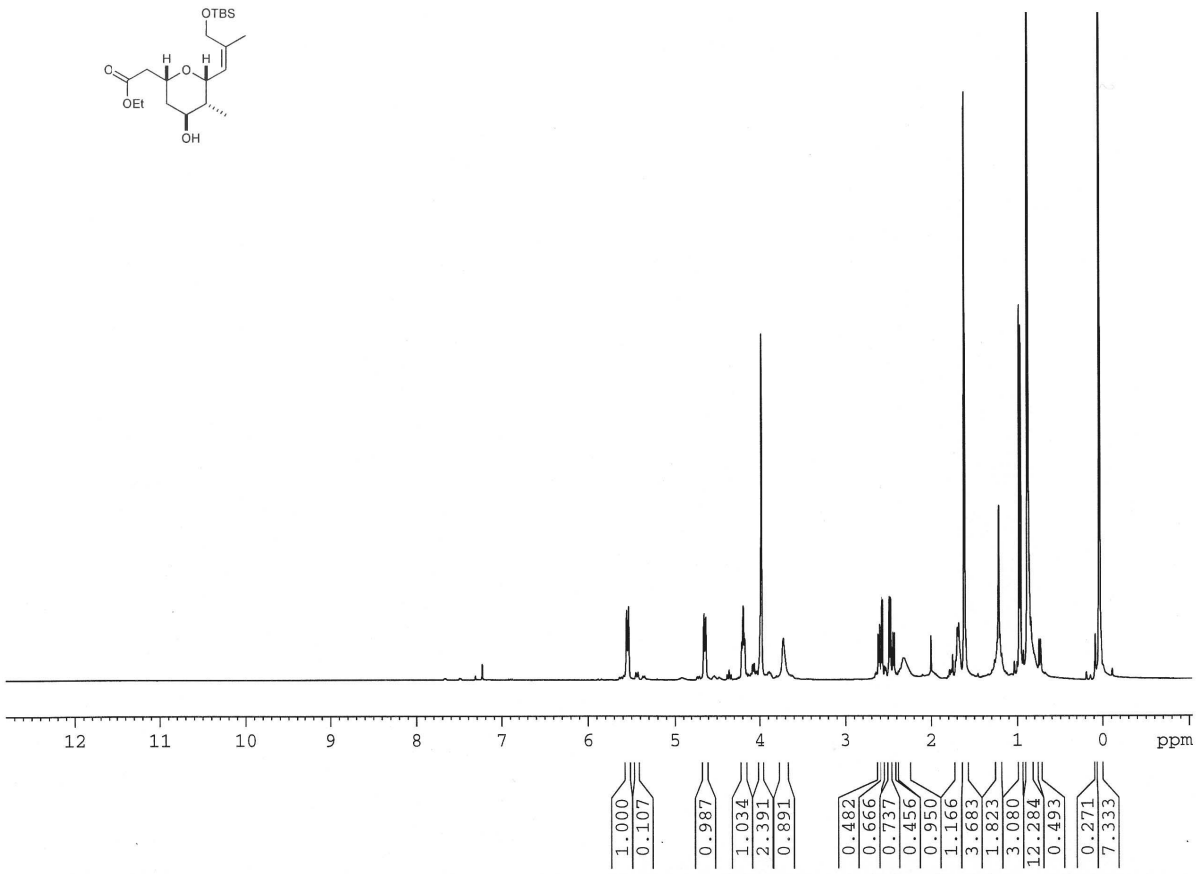

EM-VII-144
200.088
140.279
121.504
113.732
77.171
76.854
76.536
68.854
67.005
50.728
32.639
25.681
18.156
13.681
-4.187
OTBS
OH
O
N
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm
Current Data Parameters
NAME VII144
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060613
Time 12.43
INSTRUM spect
PROBHD 5mm QNP 1H/13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 438
DS 2
SWH 26246.719 Hz
FIDRES 0.400493 Hz
AQ 1.2485298 sec
RG 2580.3
DW 19.050 use
DE 6.00 use
TE 300.0 K
D1 0.80000001 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 =======
NUC1 13C
P1 6.00 use
PL1 0.00 dB
SFO1 100.6036782 MHz
======== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 use
PL2 -6.00 dB
PL12 13.80 dB
PL13 14.50 dB
SFO2 400.0516002 MHz
F2 - Processing parameters
SI 32768
SF 100.5926741 MHz
WDW EM
SSB 0

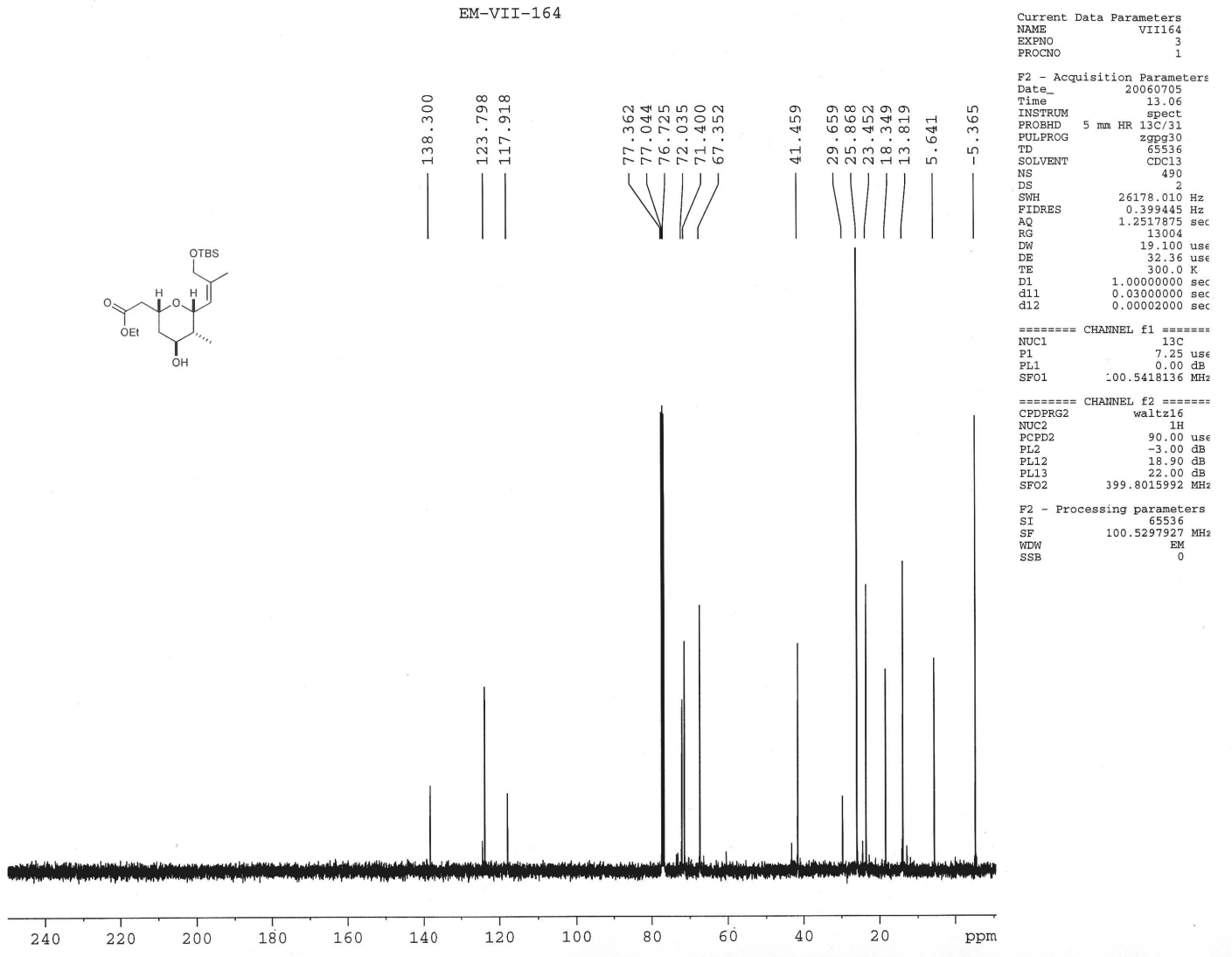

EM-VII-162
N
OH
OH
Me
Me
OTBS
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
0.181
1.013
0.161
1.023
2.418
0.358
0.963
0.458
0.693
0.676
0.447
2.995
4.941
3.498
12.490
1.075
6.877


EM-VII-145
200.293
140.105
128.953
128.885
128.215
125.350
121.733
113.919
77.247
76.992
76.738
68.886
68.460
67.141
66.915
50.910
32.714
32.535
29.570
28.800
25.803
25.769
25.742
25.669
18.231
13.742
11.474
11.241
0.898
−5.480
−5.497
OH
OH
Me
Me
OTBS
200
180
160
140
120
100
80
60
40
20
0
ppm
Current Data Parameters
NAME VII145
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060614
Time 9.30
INSTRUM spect
PROBHD 5mm Broadban
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 593
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 8192
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
======== CHANNEL f2 ========
GPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40


EM-VII-171
5.449
5.426
5.107
5.061
4.531
4.526
4.510
4.059
4.000
3.982
3.904
3.737
2.503
2.486
2.421
2.405
1.916
1.675
1.663
1.635
1.592
1.582
1.573
1.548
1.529
1.152
1.135
1.117
0.904
0.888
0.870
0.843
0.826
0.802
0.001
1.000
1.081
0.487
2.049
1.881
0.507
1.024
0.594
0.393
1.288
3.506
0.822
3.777
6.660
ppm

EM-VII-164


OTBS
H
H
O
O
OEt
OH
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
0.107
0.987
1.034
2.391
0.891
0.482
0.666
0.737
0.456
0.950
1.166
3.683
1.823
3.080
12.284
0.493
0.271
7.333



Current Data Parameters
NAME VII164
EXPNO 3
PROCNO 1

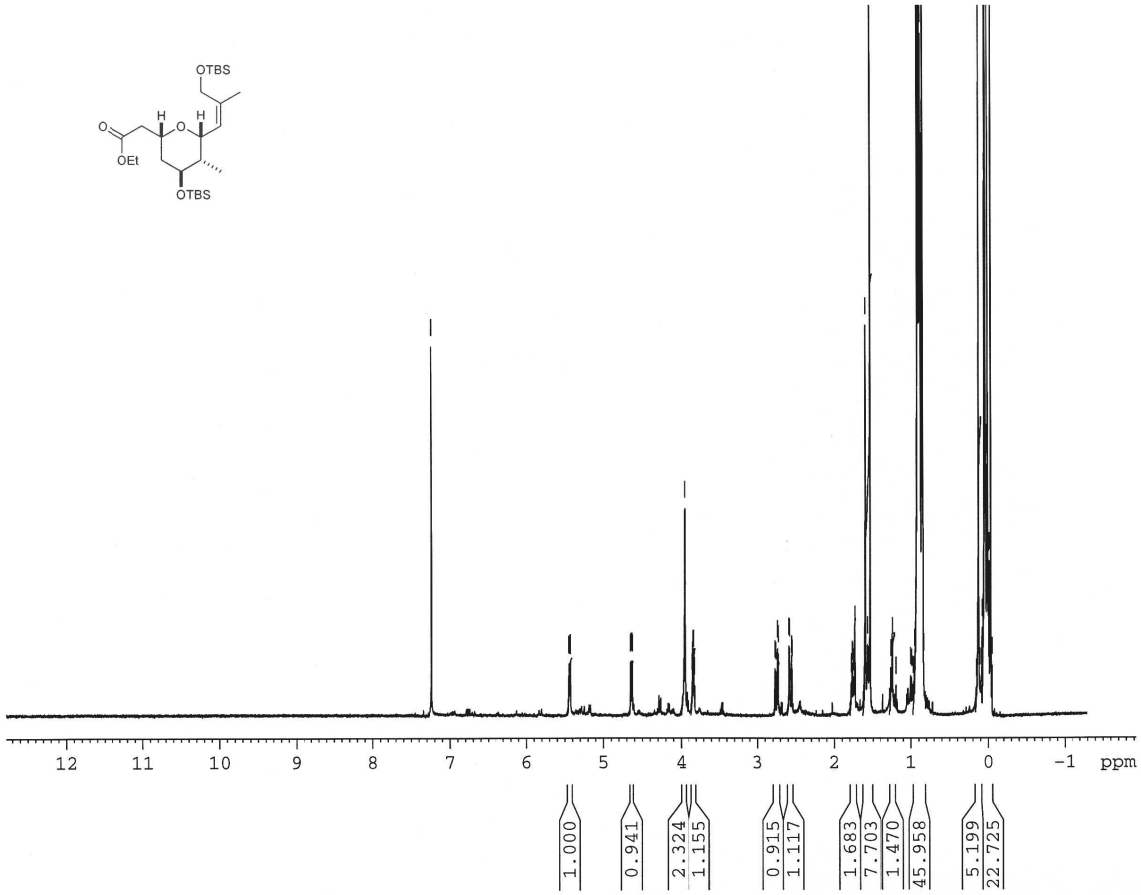
F2 - Acquisition Parameters
Date_ 20060705
Time 13.06
INSTRUM spect
PROBHD 5 mm HR 13C/31
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 490
DS 2
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2517875 sec
RG 13004
DW 19.100 use
DE 32.36 use
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

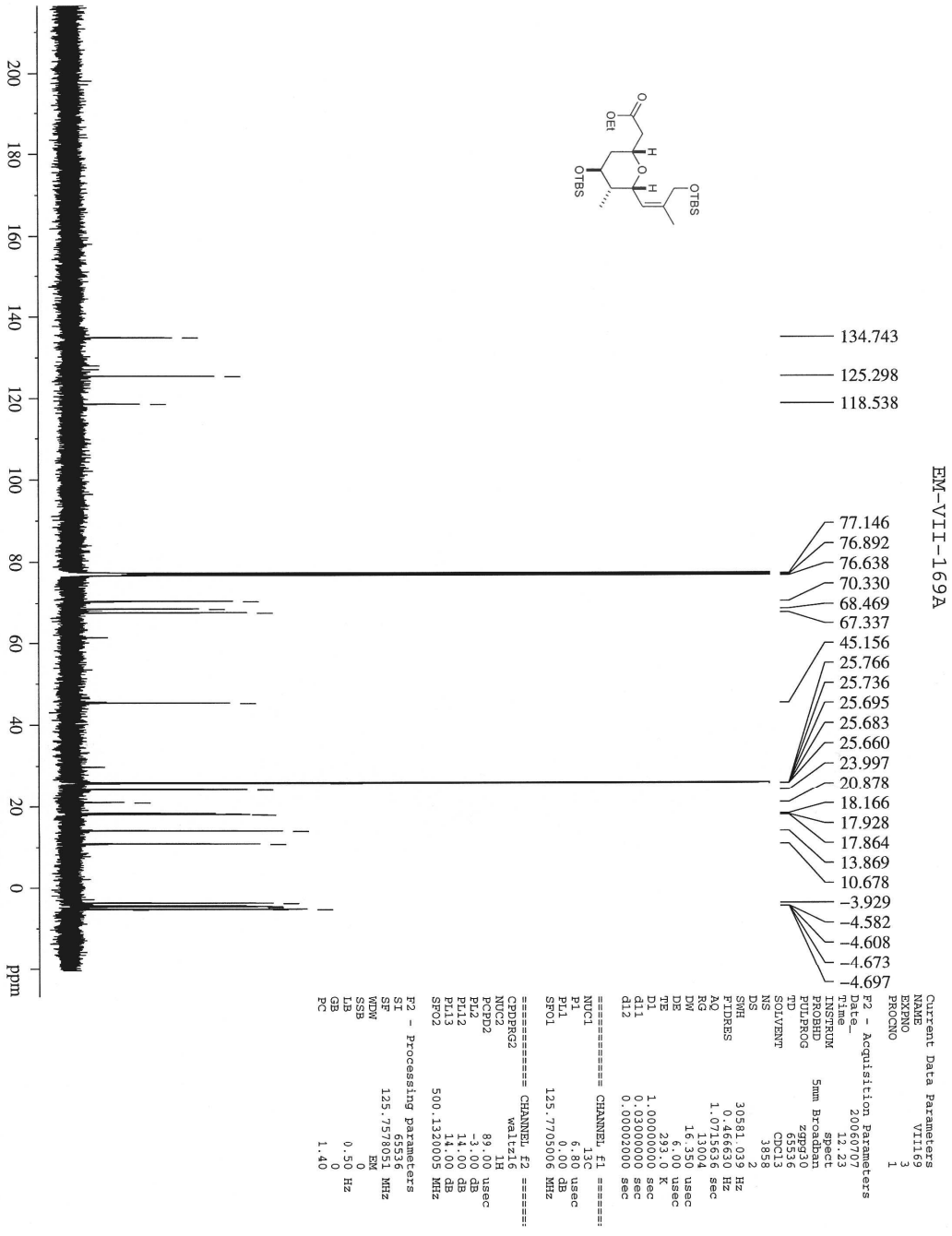
======== CHANNEL f1 =======
NUC1 13C
P1 7.25 use
PL1 0.00 dB
SFO1 100.5418136 MHz

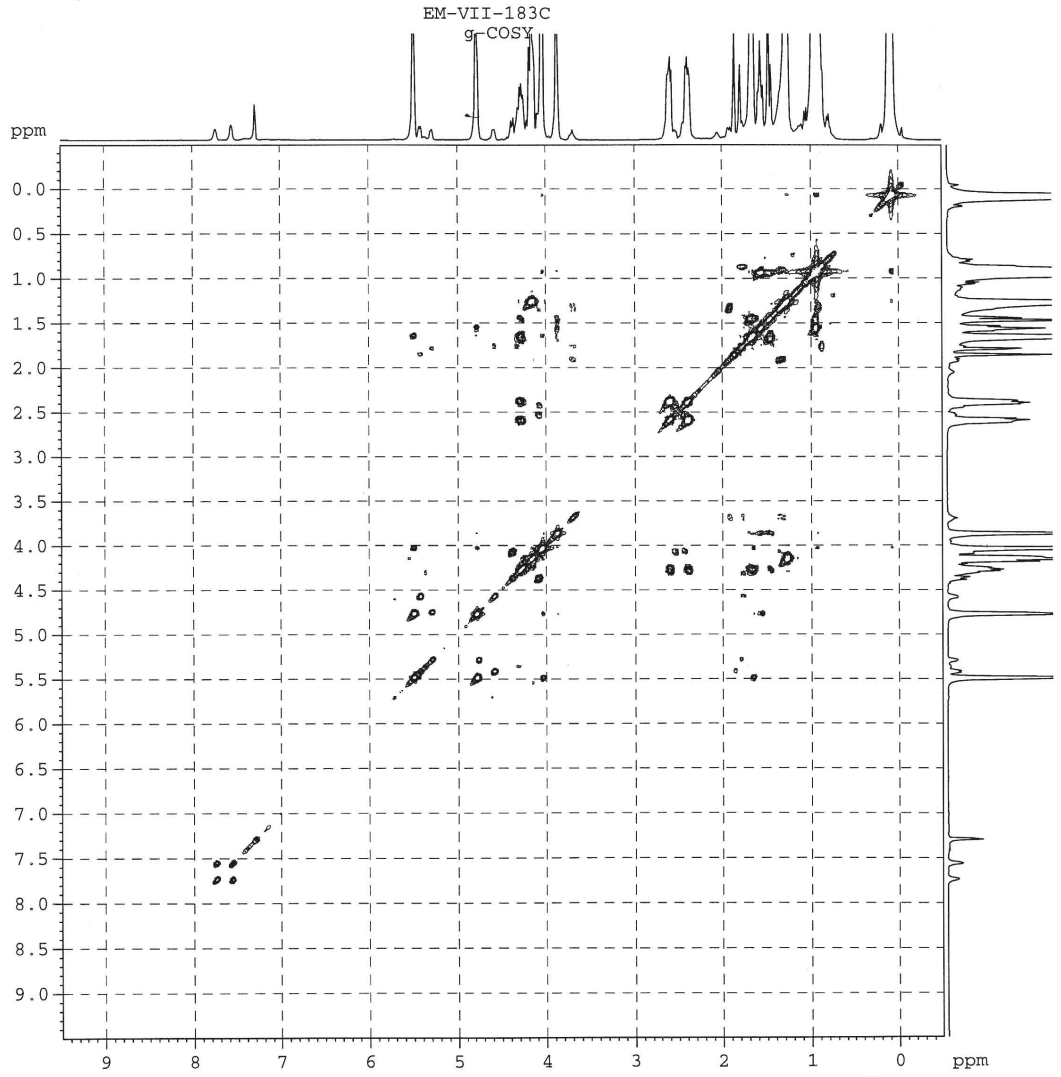
======== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 use
PL2 -3.00 dB
PL12 18.90 dB
PL13 22.00 dB
SFO2 399.8015992 MHz

F2 - Processing parameters
SI 65536
SF 100.5297927 MHz
WDW EM
SSB 0

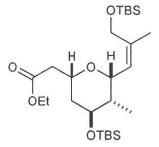
EM-VII-169A


OTBS
H
H
O
O
OEt
OTBS
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.000
0.941
2.324
1.155
0.915
1.117
1.683
7.703
1.470
45.958
5.199
22.725

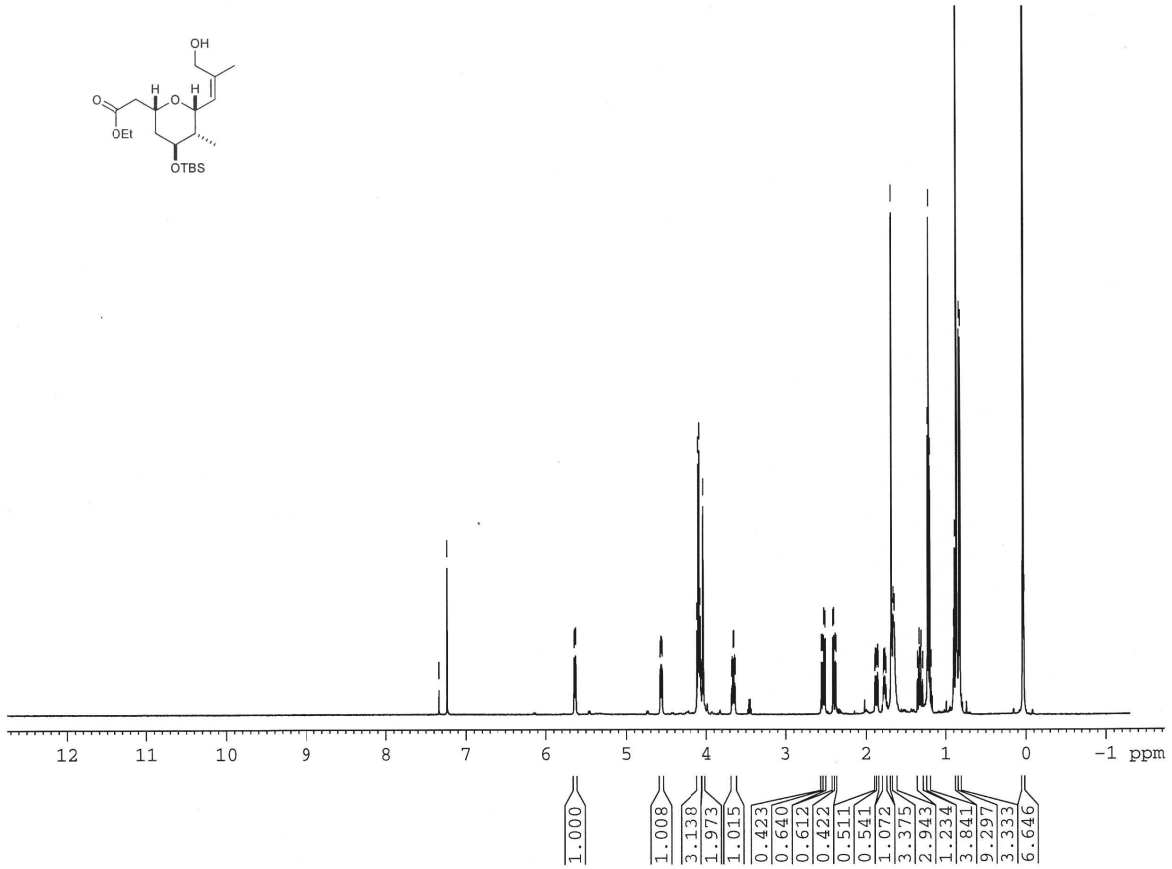

EM-VII-169A
134.743
125.298
118.538
77.146
76.892
76.638
70.330
68.469
67.337
45.156
25.766
25.736
25.695
25.683
25.660
23.997
20.878
18.166
17.928
17.864
13.869
10.678
-3.929
-4.582
-4.608
-4.673
-4.697
OEt
OTBS
OTBS
200
180
160
140
120
100
80
60
40
20
0
ppm
Current Data Parameters
NAME VII169
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060707
Time 12.23
INSTRUM spect
PROBHD 5mm Broadban
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1858
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 13004
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
======== CHANNEL f1 ======
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
======== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40

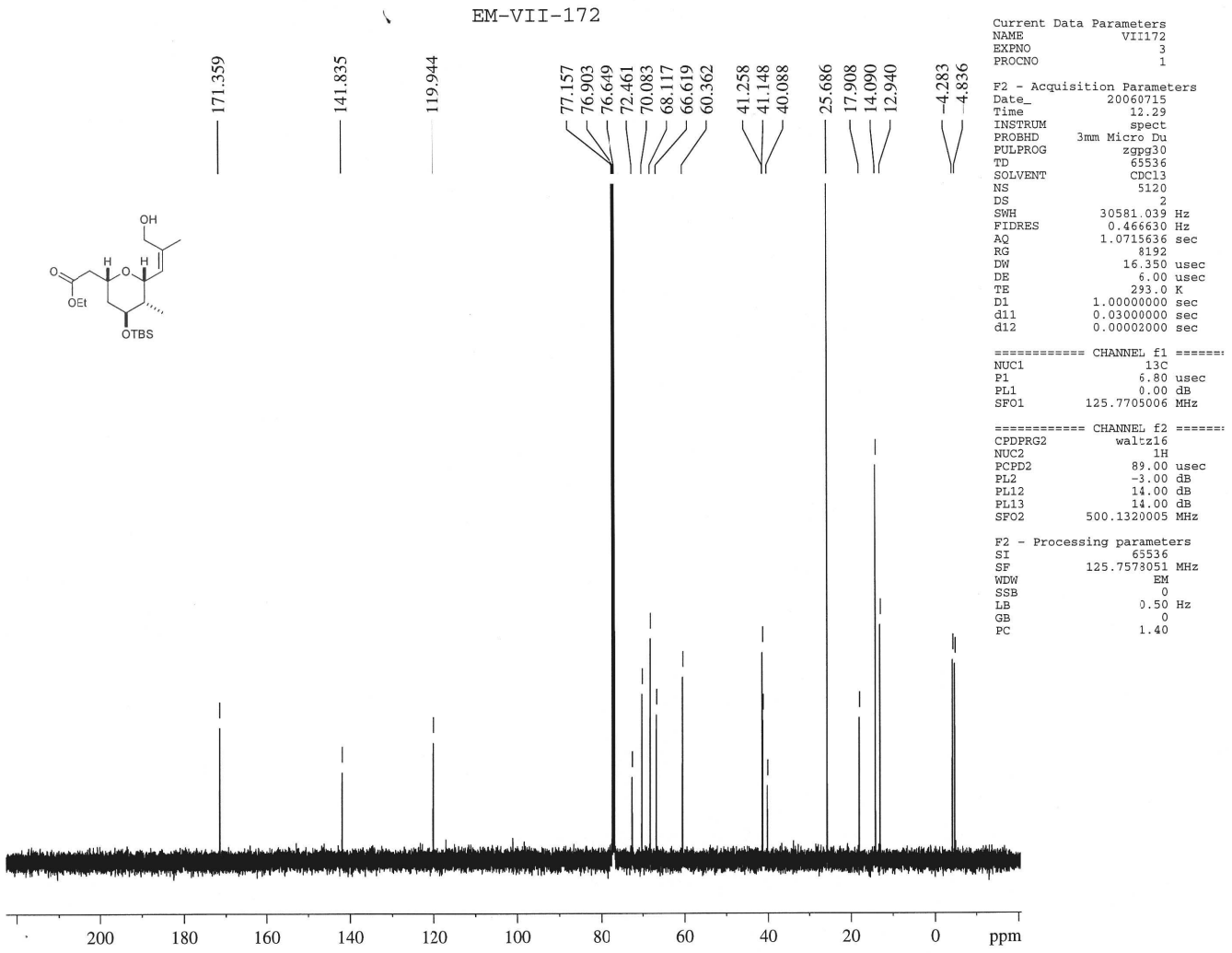



```
Current Data Parameters
NAME                  VII183
EXPNO                      4
PROCNO                     1

F2 - Acquisition Parameters
Date_              20060729
Time                  11.13
INSTRUM               spect
PROBHD      5mm Broadban
PULPROG             cosygs
TD                    2048
SOLVENT               CDCl3
NS                      40
DS                       2
SWH                5000.000 Hz
FIDRES             2.441406 Hz
AQ                 0.2048500 sec
RG                     322.5
DW                   100.000 usec
DE                     6.00 usec
TE                    300.0 K
d0                 0.00000300 sec
D1                 1.50000000 sec
d13                0.00000300 sec
D16                0.00050000 sec
IN0                0.00020000 sec

============ CHANNEL f1 ====
NUC1                      1H
P0                      8.35 usec
P1                      8.35 usec
PL1                    -3.00 dB
SFO1           500.1322506 MHz

============ GRADIENT CHANNE
P16                  1000.00 usec

F1 - Acquisition parameters
ND0                       1
TD                      196
SFO1           500.1323 MHz
FIDRES         25.510204 Hz
SW                  9.997 ppm

F2 - Processing parameters
SI                     1024
SF           500.1300000 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.40

F1 - Processing parameters
```

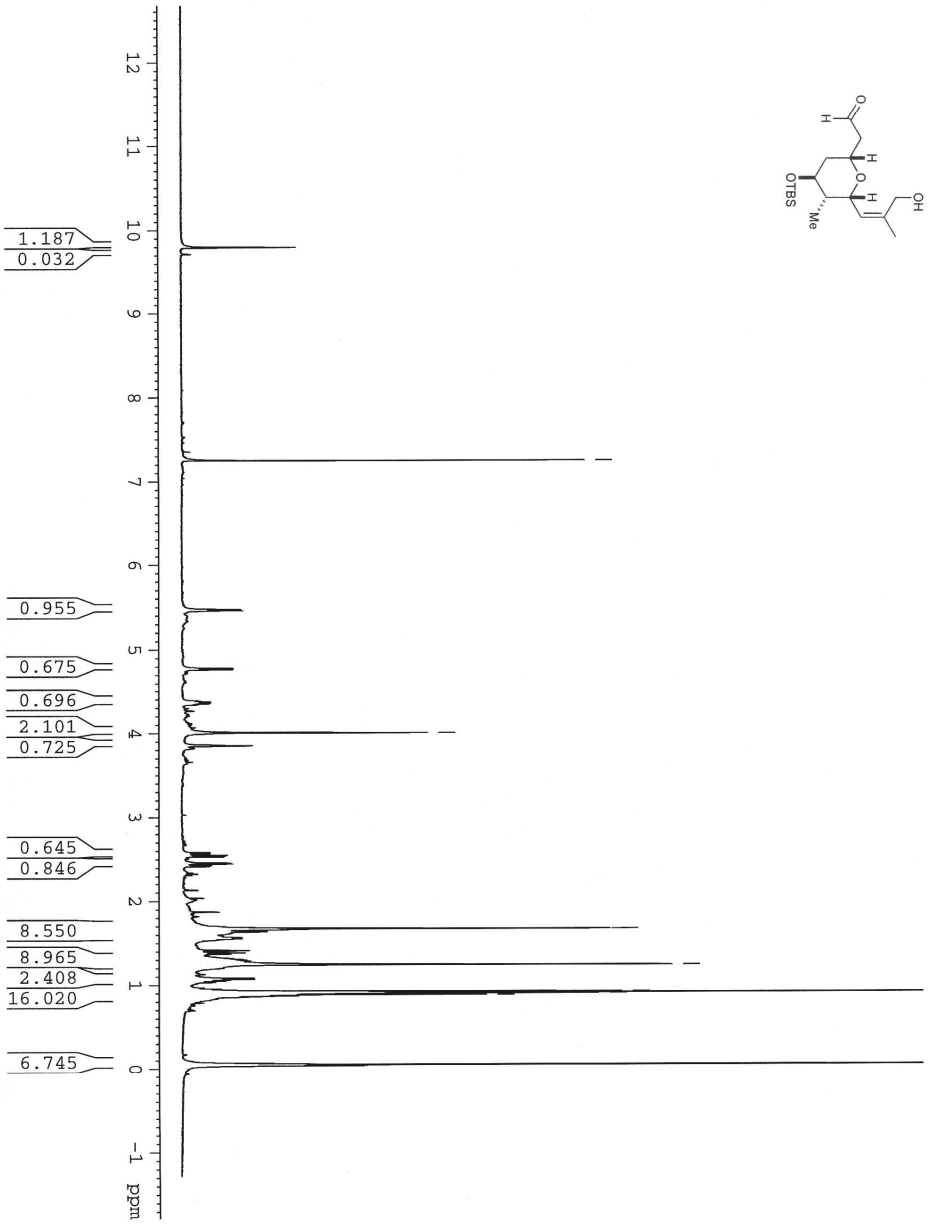


EM-VII-172

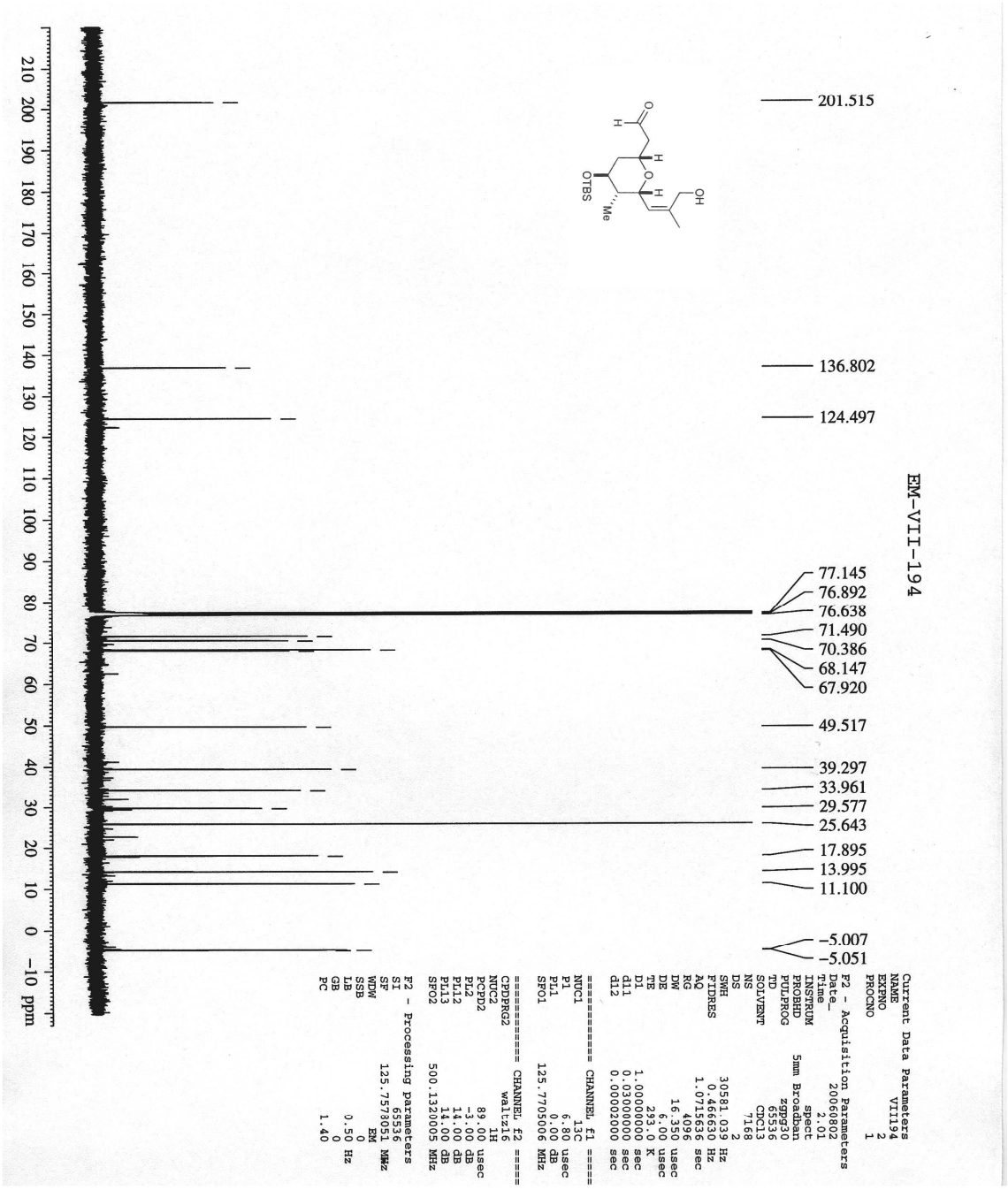

OH
H
O
H
O
OEt
OTBS
12
11
10
9
8
7
6
5
4
3
2
1
0
−1 ppm
1.000
1.008
3.138
1.973
1.015
0.423
0.640
0.612
0.422
0.511
0.541
1.072
3.375
2.943
1.234
3.841
9.297
3.333
6.646

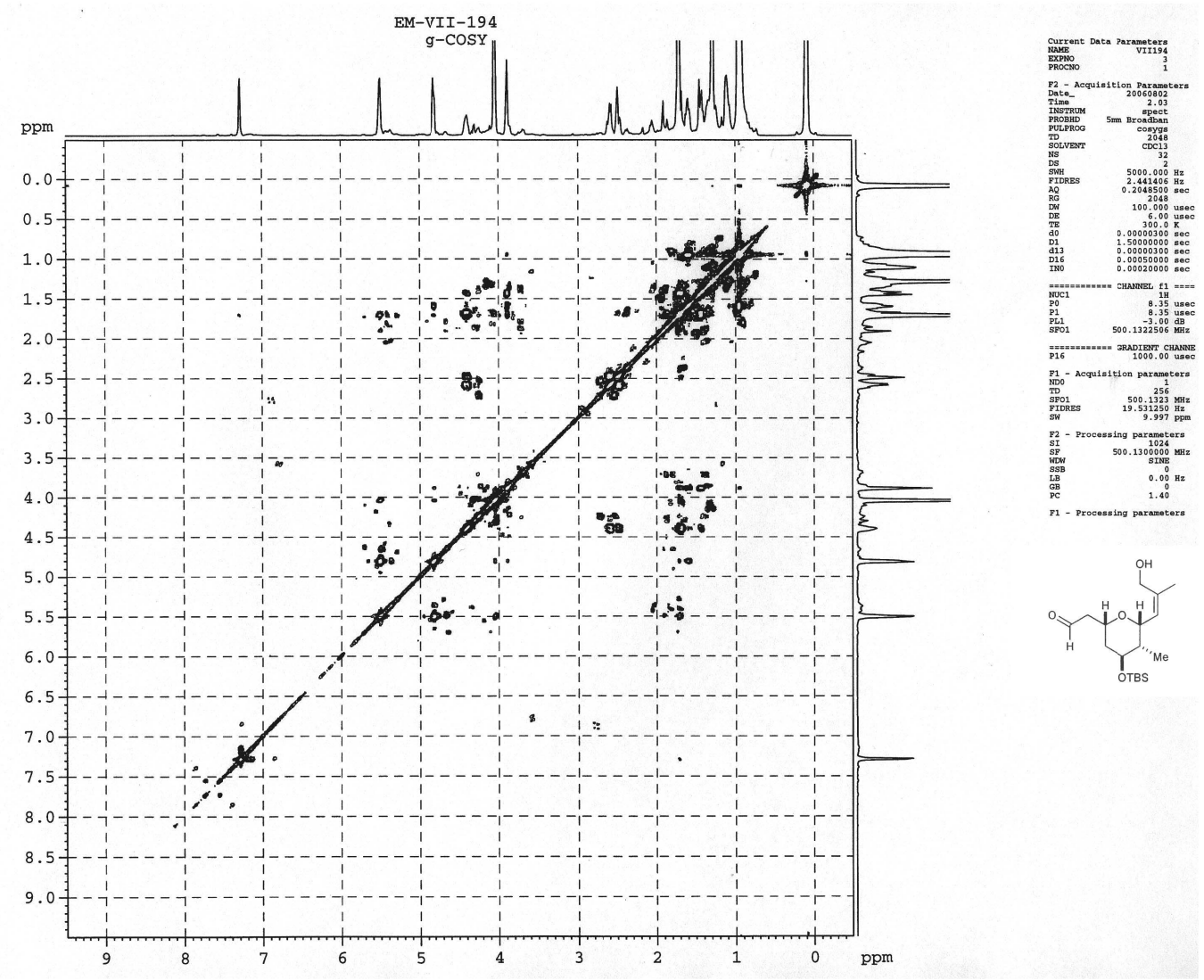



```
Current Data Parameters
NAME                  VII172
EXPNO                      3
PROCNO                     1

F2 - Acquisition Parameters
Date_              20060715
Time                  12.29
INSTRUM               spect
PROBHD      3mm Micro Du
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    5120
DS                       2
SWH             30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                    8192
DW                 16.350 usec
DE                  6.00 usec
TE                  293.0 K
D1              1.00000000 sec
d11             0.03000000 sec
d12             0.00002000 sec

============ CHANNEL f1 =======
NUC1                  13C
P1                   6.80 usec
PL1                  0.00 dB
SFO1          125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                  1H
PCPD2               89.00 usec
PL2                 -3.00 dB
PL12                14.00 dB
PL13                14.00 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                   65536
SF            125.7573051 MHz
WDW                    EM
SSB                     0
LB                   0.50 Hz
GB                      0
PC                   1.40
```

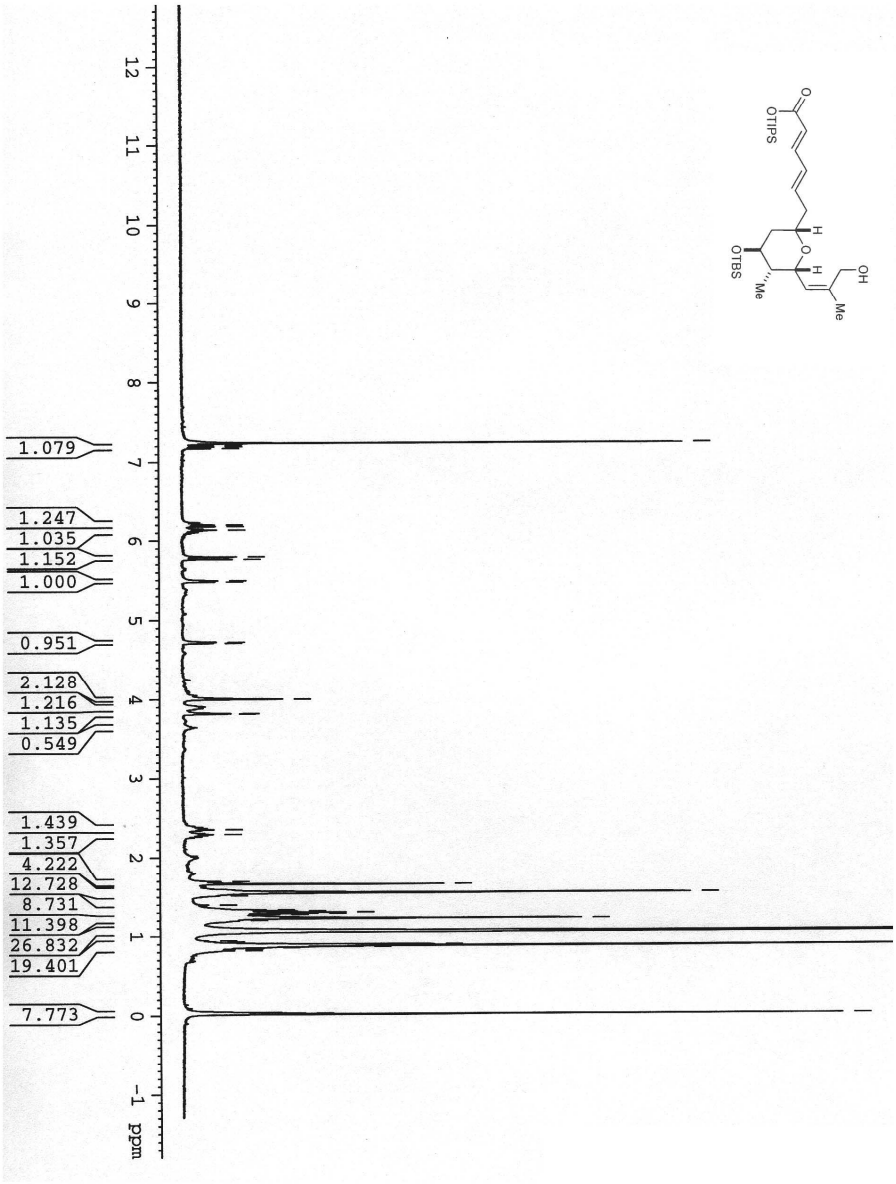

1.187
0.032
0.955
0.675
0.696
2.101
0.725
0.645
0.846
8.550
8.965
2.408
16.020
6.745
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
O
H
H
O
H
OH
OTBS
Me

EM-VII-194

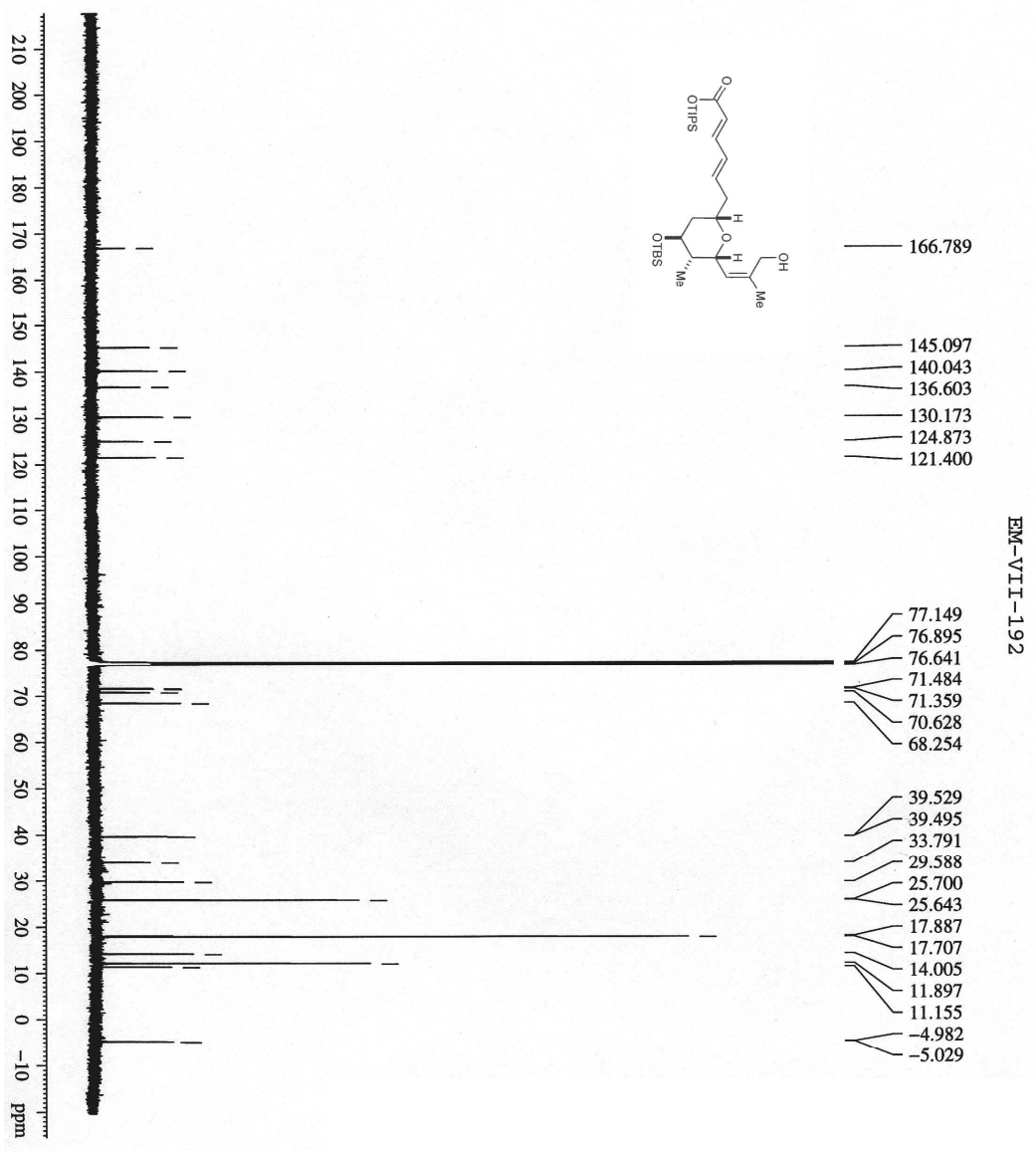

EM-VII-194
201.515
136.802
124.497
77.145
76.892
76.638
71.490
70.386
68.147
67.920
49.517
39.297
33.961
29.577
25.643
17.895
13.995
11.100
-5.007
-5.051
OTBS
Me
OH
Current Data Parameters
NAME VII194
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060802
Time 2.01
INSTRUM spect
PROBHD 5mm Broadban
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 768
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.071936 sec
RG 4096
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7573051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

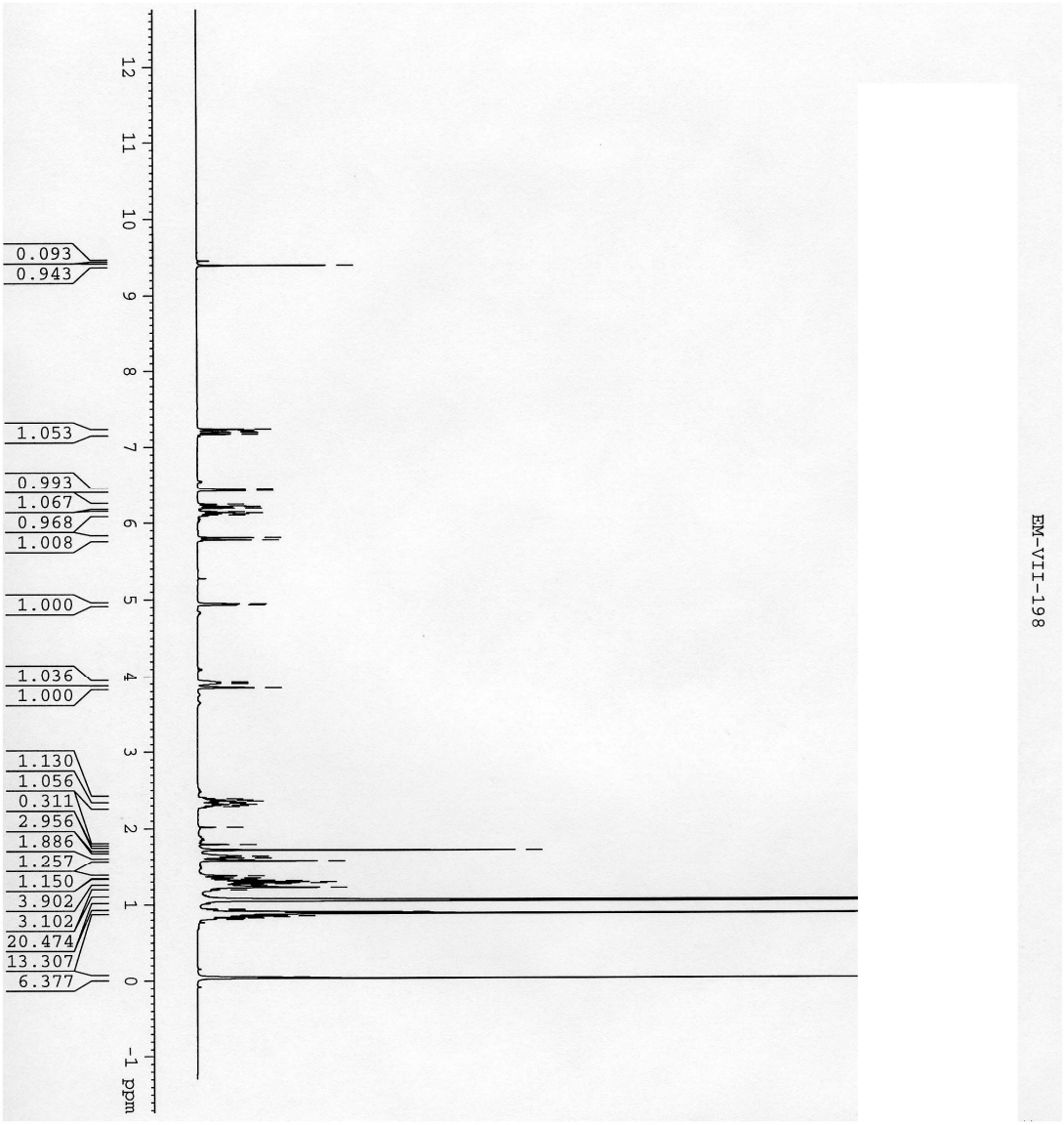


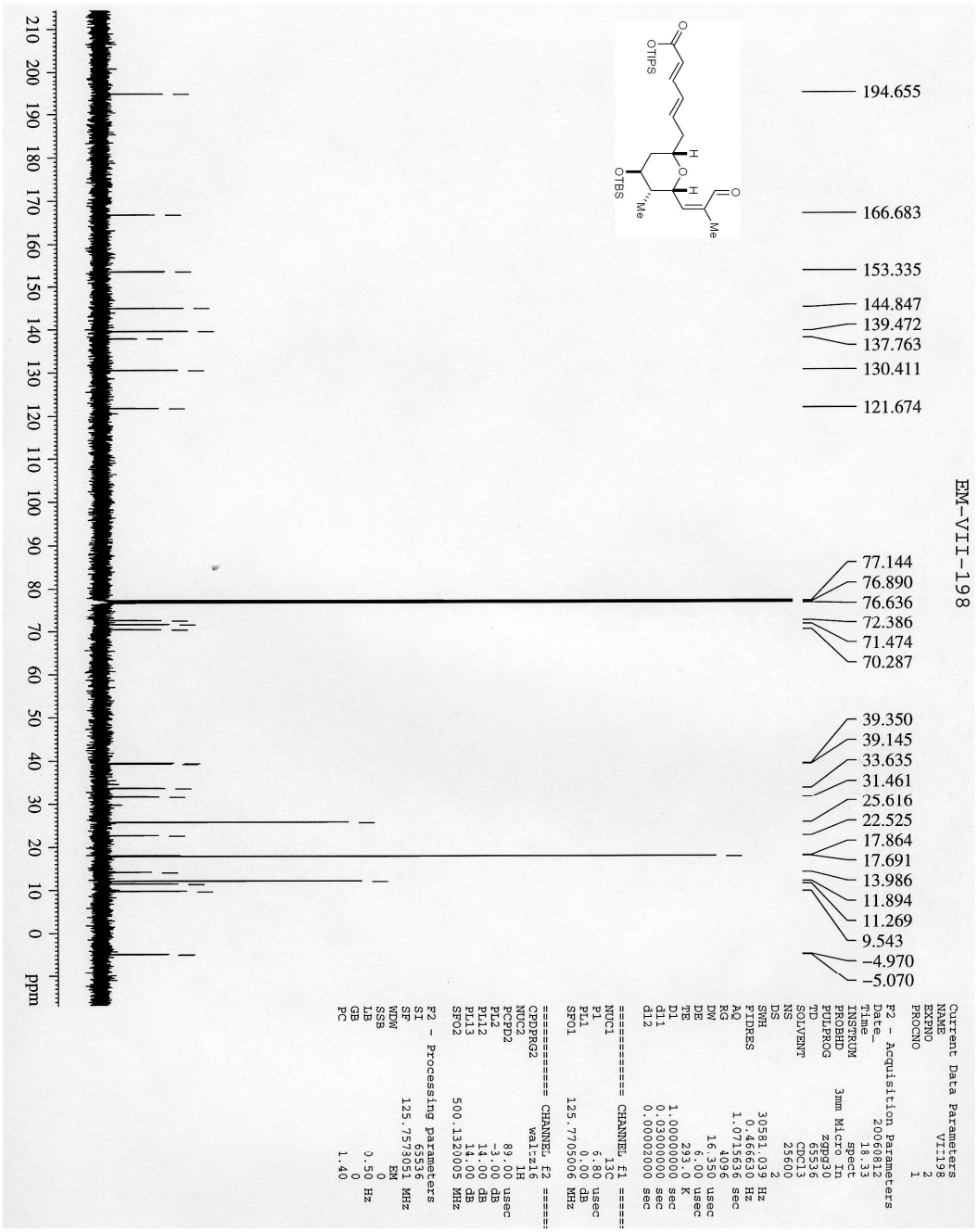

```
Current Data Parameters
NAME                   VII194
EXPNO                       3
PROCNO                      1

F2 - Acquisition Parameters
Date_               20060802
Time                    2.03
INSTRUM                spect
PROBHD      5mm Broadban
PULPROG              cosygs
TD                      2048
SOLVENT                CDCl3
NS                        32
DS                         2
SWH                5000.000 Hz
FIDRES             2.441406 Hz
AQ                 0.2048500 sec
RG                      2048
DW                  100.000 usec
DE                    6.00 usec
TE                   300.0 K
d0                0.00000300 sec
D1                1.50000000 sec
d13               0.00000300 sec
D16               0.00050000 sec
IN0               0.00020000 sec

============ CHANNEL f1 ====
NUC1                       1H
P0                    8.35 usec
P1                    8.35 usec
PL1                  -3.00 dB
SFO1          500.1322506 MHz

============ GRADIENT CHANNE
P16                1000.00 usec

F1 - Acquisition parameters
ND0                        1
TD                       256
SFO1          500.1323 MHz
FIDRES       19.531250 Hz
SW                 9.997 ppm

F2 - Processing parameters
SI                      1024
SF            500.1300000 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.40

F1 - Processing parameters
```


OTIPS
OTBS
Me
OH
Me
1.079
1.247
1.035
1.152
1.000
0.951
2.128
1.216
1.135
0.549
1.439
1.357
4.222
12.728
8.731
11.398
26.832
19.401
7.773
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

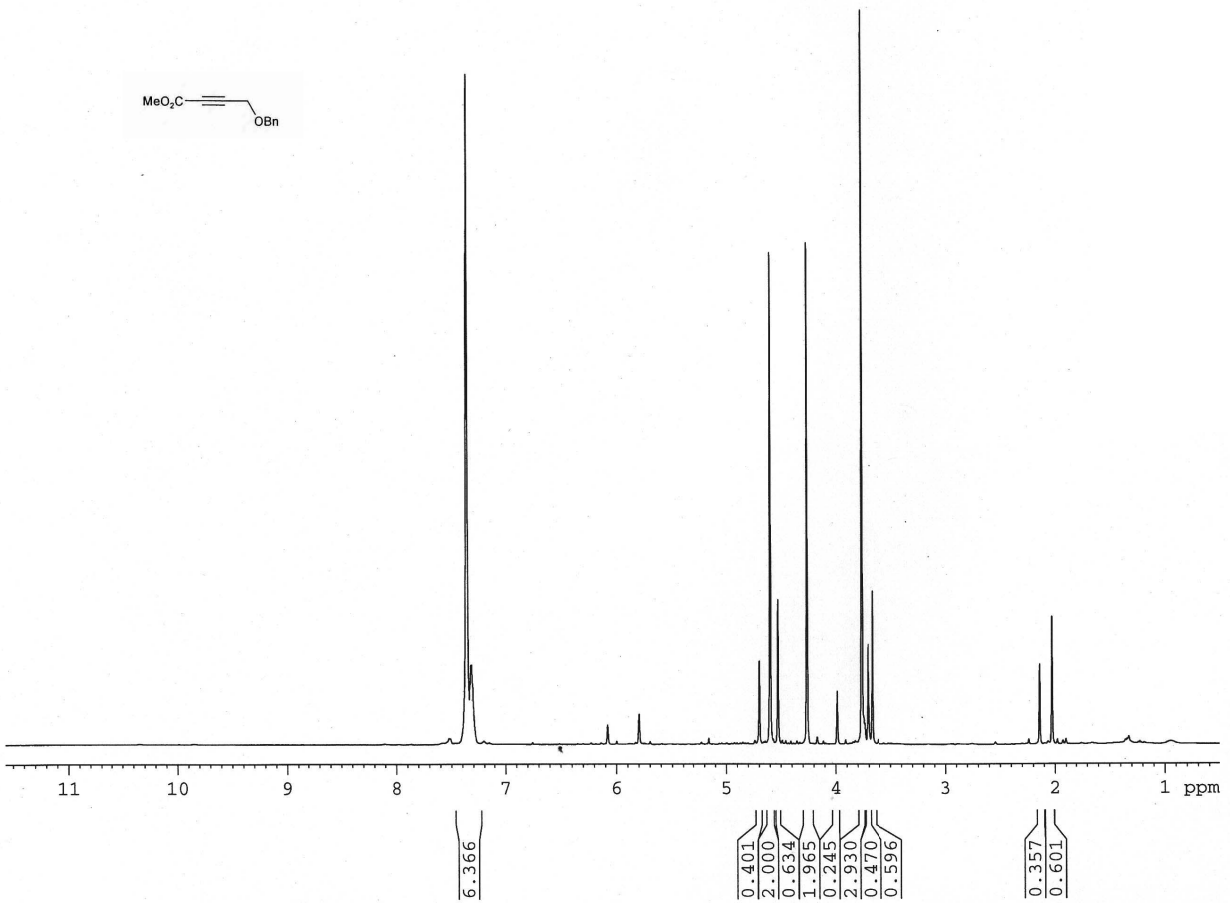
EM-VII-192

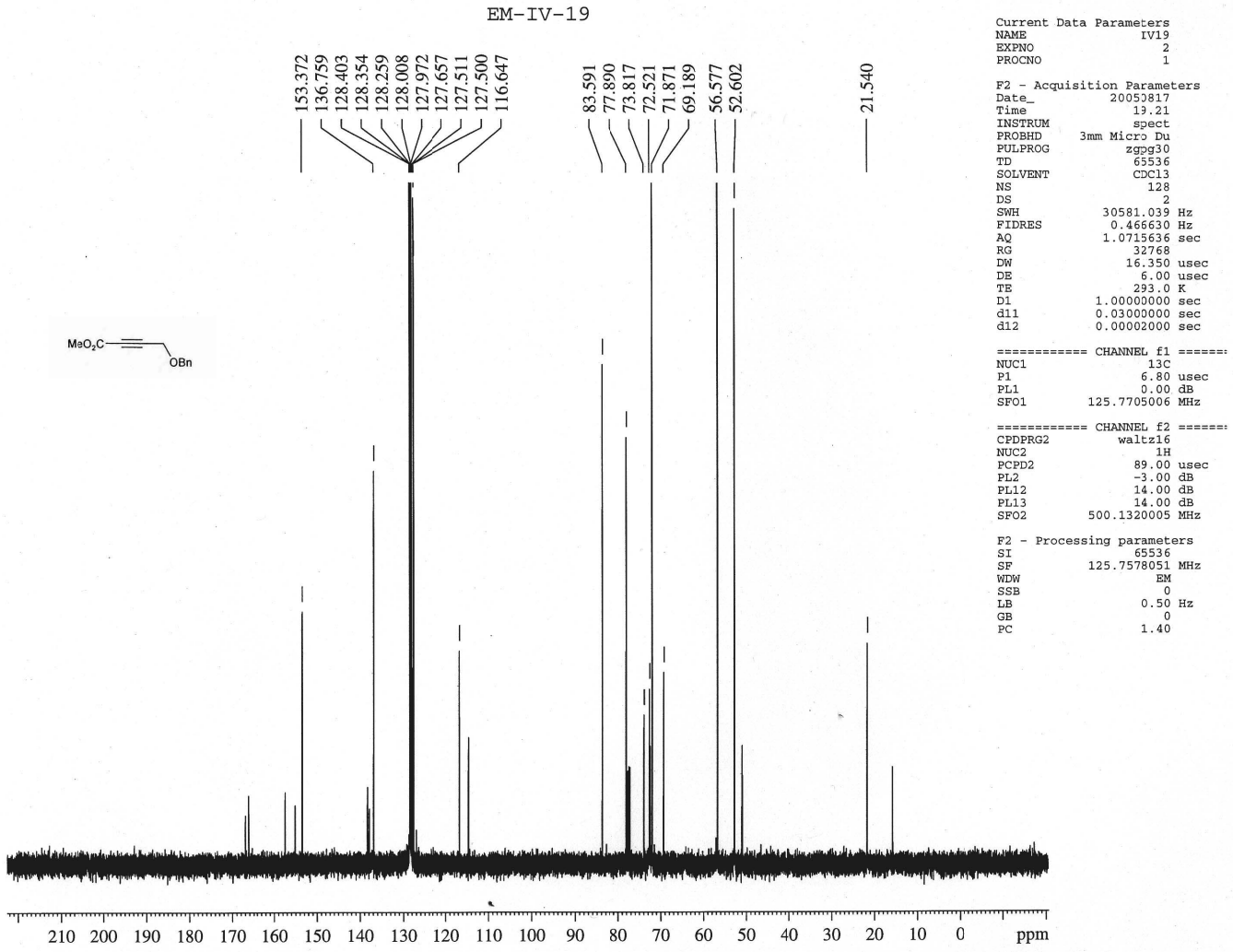

EM-VII-192
166.789
145.097
140.043
136.603
130.173
124.873
121.400
77.149
76.895
76.641
71.484
71.359
70.628
68.254
39.529
39.495
33.791
29.588
25.700
25.643
17.887
17.707
14.005
11.897
11.155
-4.982
-5.029
OTIPS
OTBS
OH
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm


0.093
0.943
1.053
0.993
1.067
0.968
1.008
1.000
1.036
1.000
1.130
1.056
0.311
2.956
1.886
1.257
1.150
3.902
3.102
20.474
13.307
6.377
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
EM-VII-198

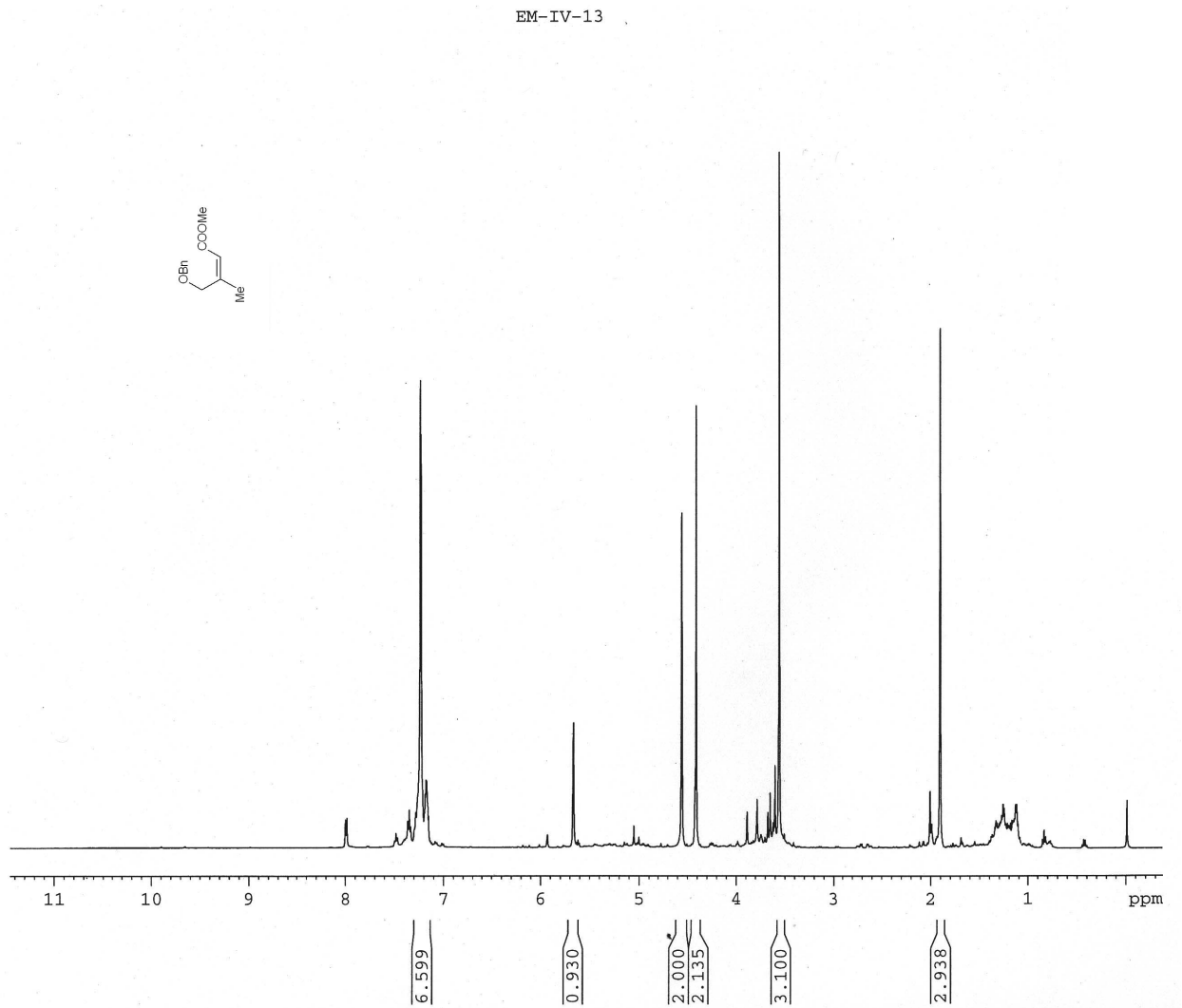

EM-VII-198
194.655
166.683
153.335
144.847
139.472
137.763
130.411
121.674
77.144
76.890
76.636
72.386
71.474
70.287
39.350
39.145
33.635
31.461
25.616
22.525
17.864
17.691
13.986
11.894
11.269
9.543
-4.970
-5.070
OTIPS
OTBS
Me
Me
Current Data Parameters
NAME VI-198
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060812
Time 18.33
INSTRUM spect
PROBHD 3mm Micro in
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2560
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 4096
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7573051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

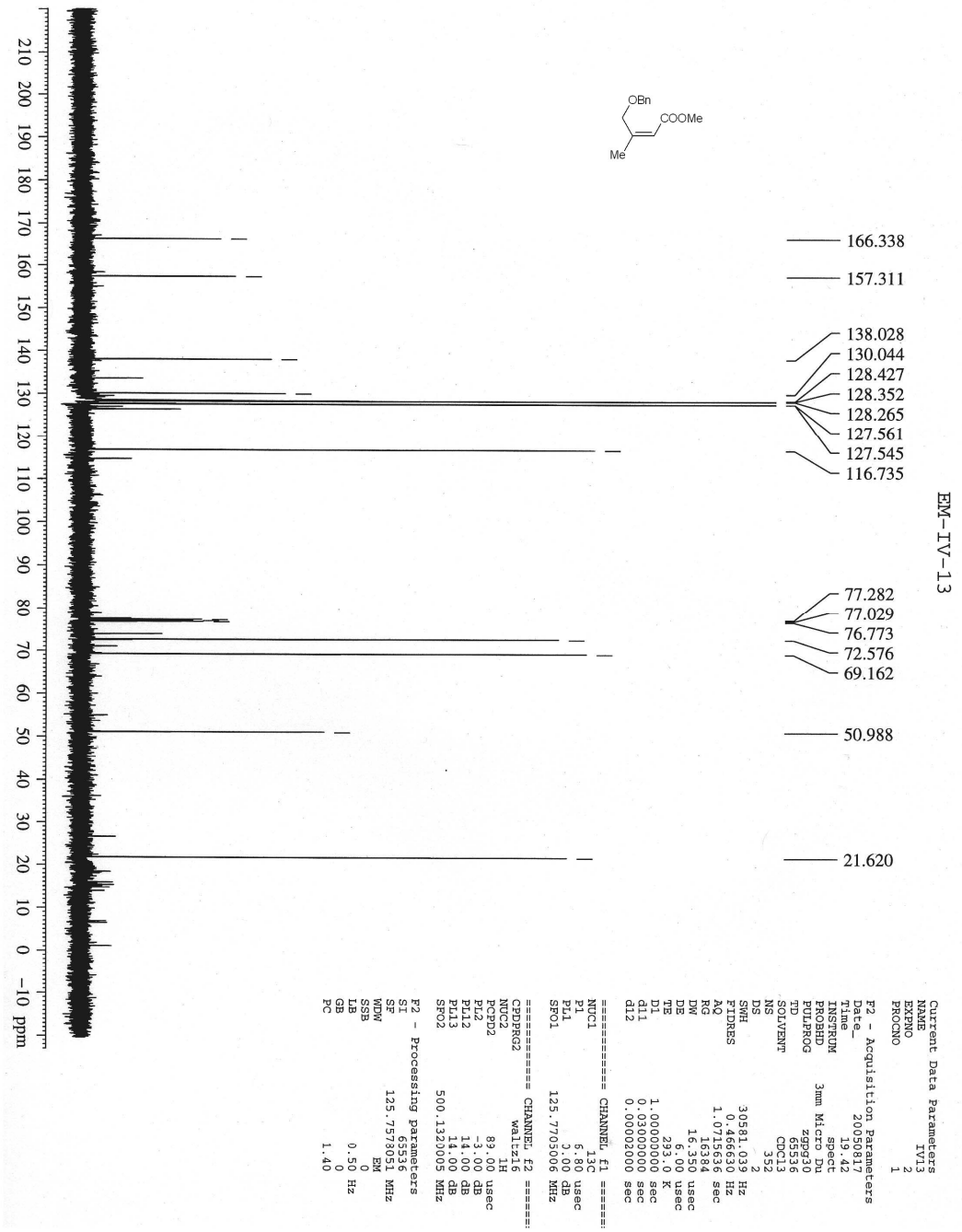
EM-IV-19

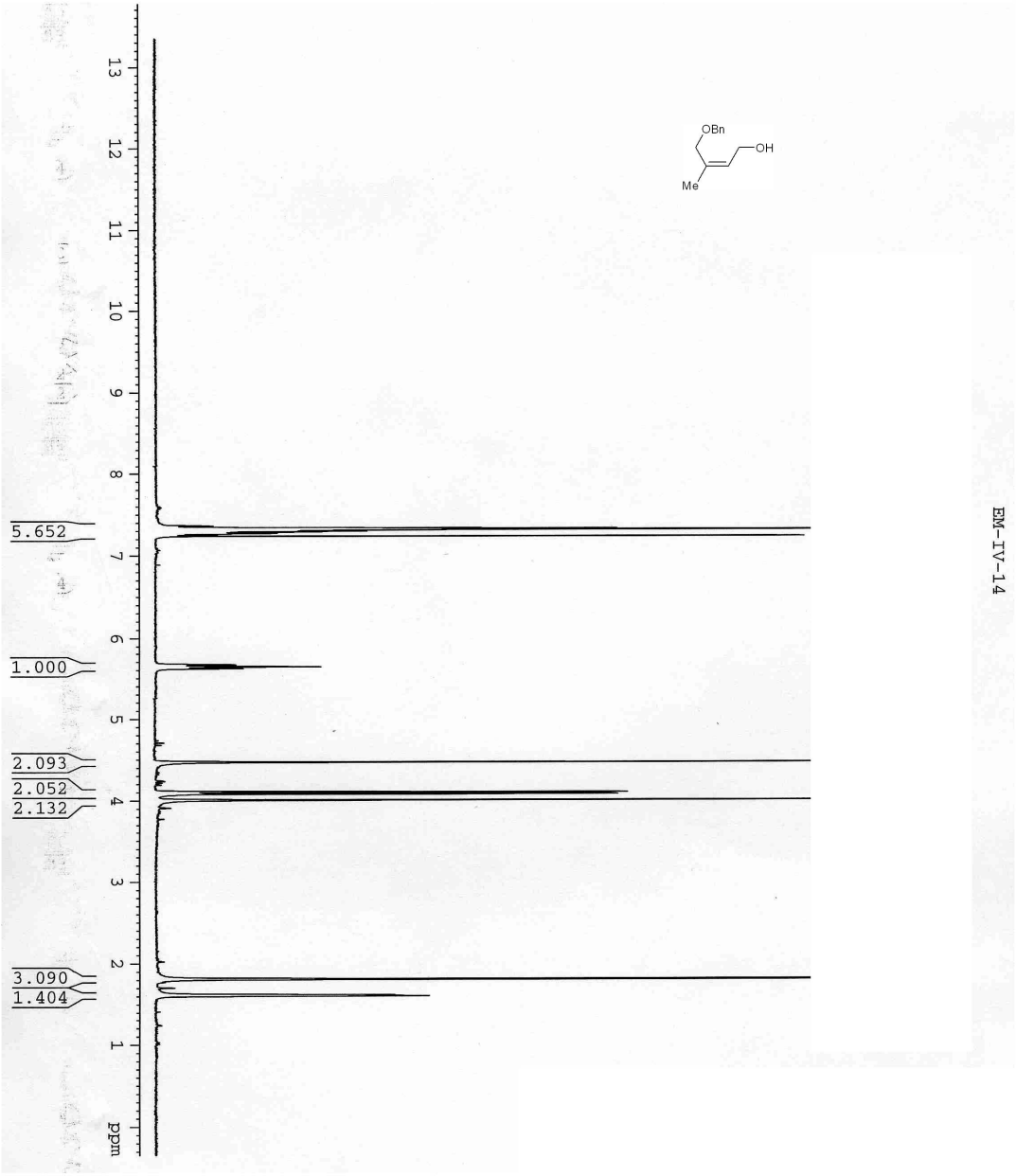

MeO2C
OBn
11
10
9
8
7
6
5
4
3
2
1 ppm
6.366
0.401
2.000
0.634
1.965
0.245
2.930
0.470
0.596
0.357
0.601

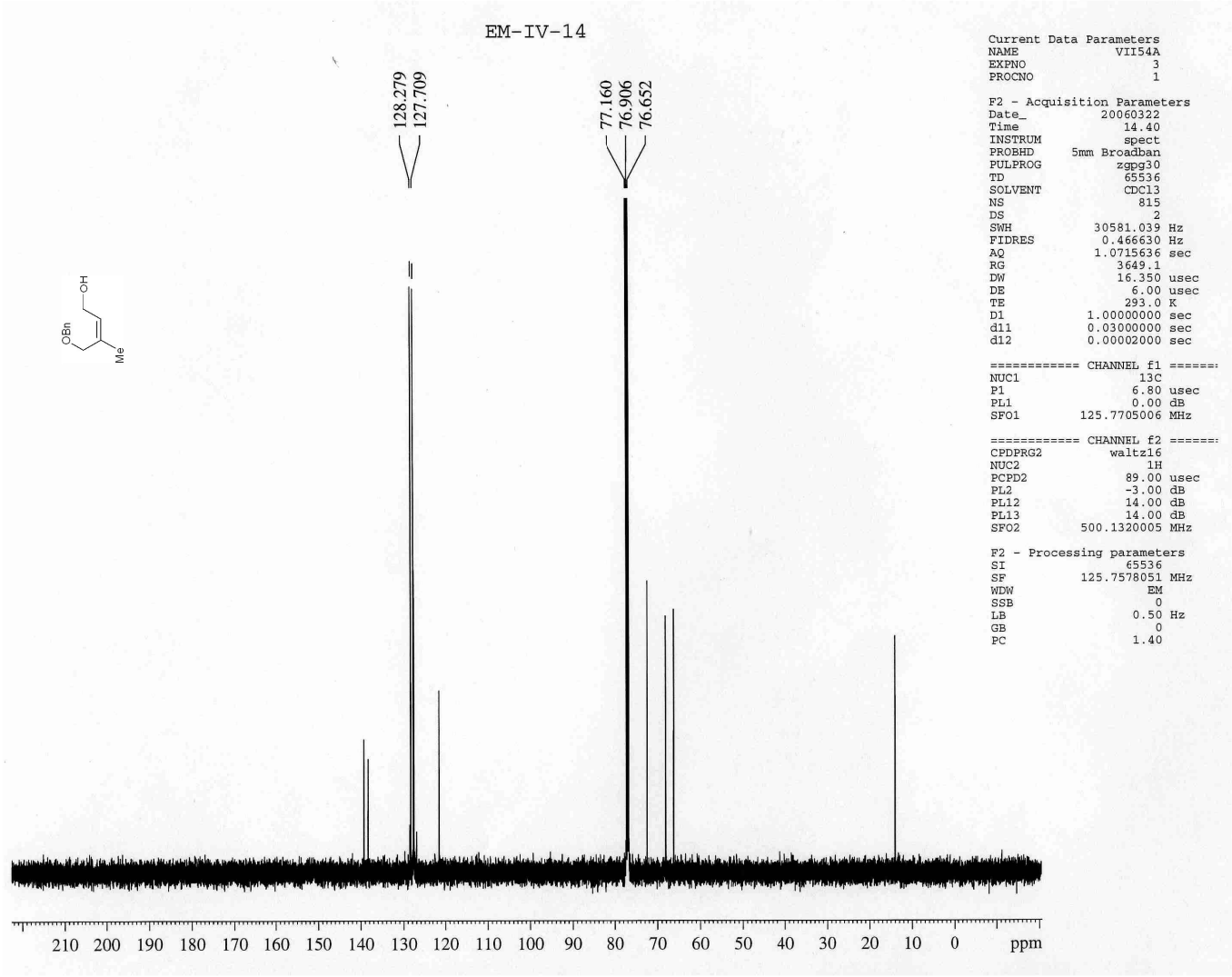


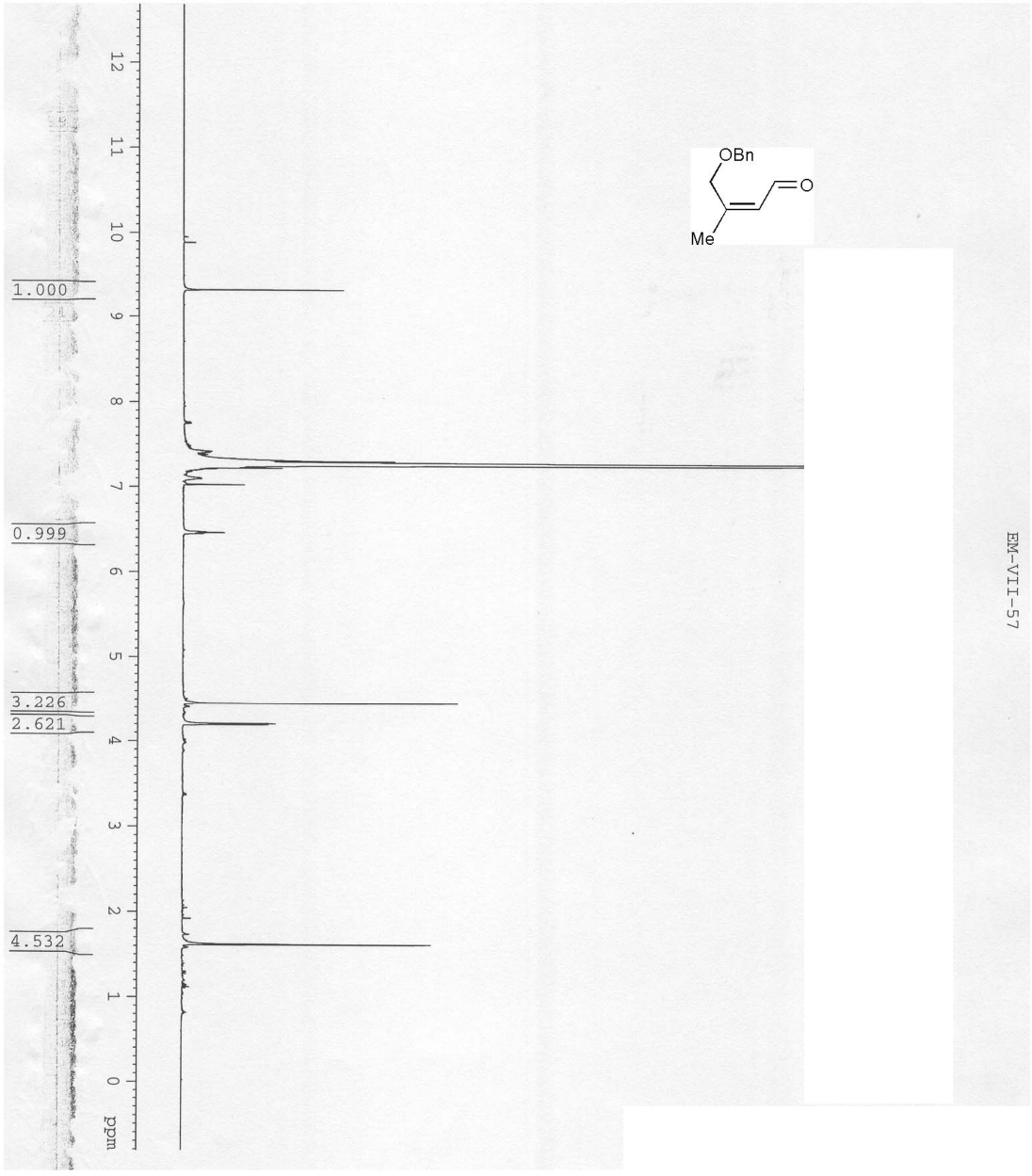

```
Current Data Parameters
NAME                  IV19
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20050817
Time                 19.21
INSTRUM              spect
PROBHD     3mm Micro Du
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    128
DS                      2
SWH            30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                  32768
DW                16.350 usec
DE                 6.00 usec
TE                293.0 K
D1            1.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

============ CHANNEL f1 =======
NUC1                 13C
P1                  6.80 usec
PL1                 0.00 dB
SF01         125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2          waltz16
NUC2                 1H
PCPD2              89.00 usec
PL2                -3.00 dB
PL12               14.00 dB
PL13               14.00 dB
SF02         500.1320005 MHz

F2 - Processing parameters
SI                  65536
SF           125.7578051 MHz
WDW                  EM
SSB                   0
LB                 0.50 Hz
GB                    0
PC                 1.40
```

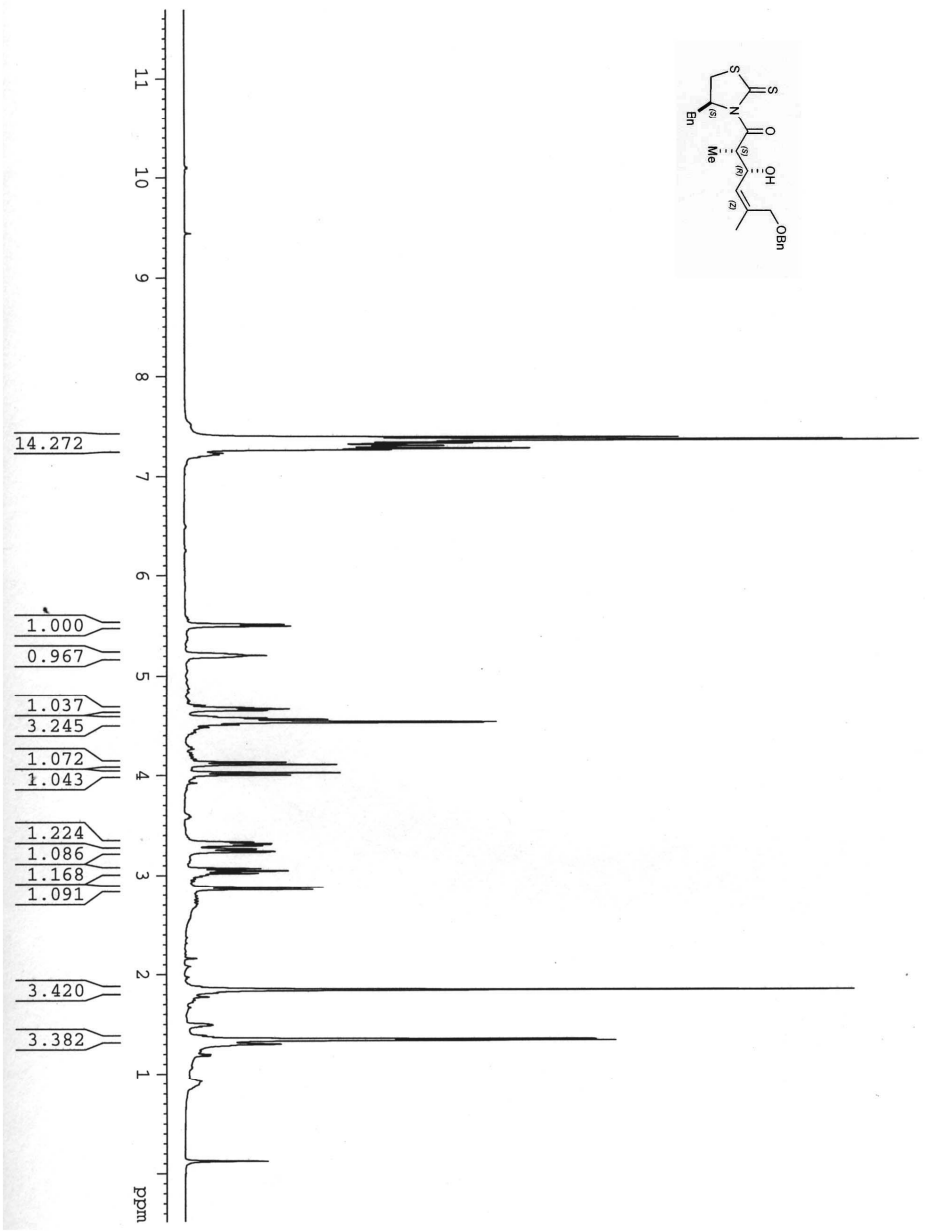

EM-IV-13
OBn
COOMe
Me
11
10
9
8
7
6
5
4
3
2
1
ppm
6.599
0.930
2.000
2.135
3.100
2.938


OBn
COOMe
Me
EM-IV-13
166.338
157.311
138.028
130.044
128.427
128.352
128.265
127.561
127.545
116.735
77.282
77.029
76.773
72.576
69.162
50.988
21.620
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm
Current Data Parameters
NAME IV13
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050817
Time 19.42
INSTRUM spect
PROBHD 3mm Micro Du
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 352
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 16384
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
====== CHANNEL f1 ======
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
====== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 13.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7573051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40

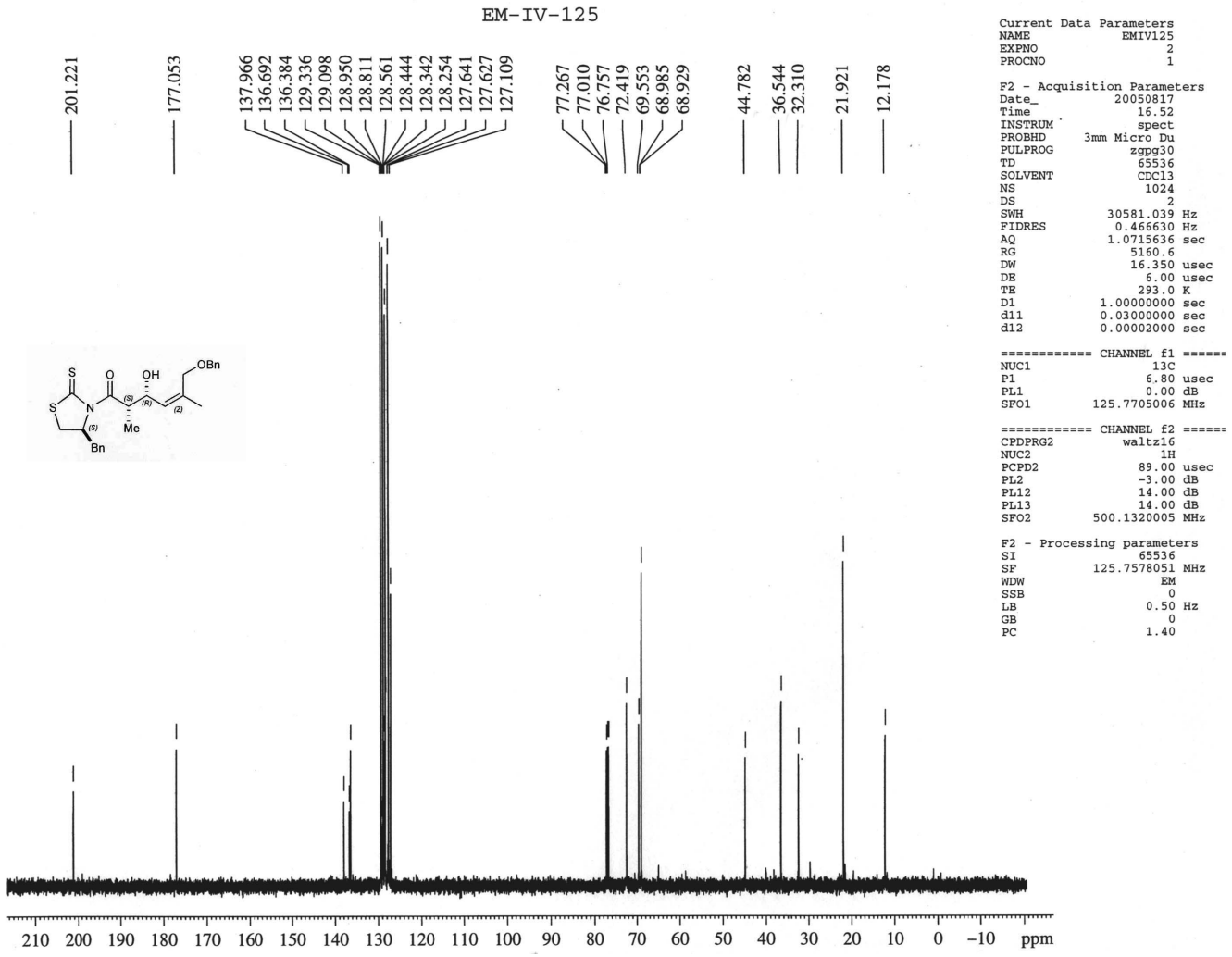

OBn
OH
Me
5.652
1.000
2.093
2.052
2.132
3.090
1.404
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
EM-IV-14


EM-IV-14
128.279
127.709
77.160
76.906
76.652
OH
OBn
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Current Data Parameters
NAME VII54A
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060322
Time 14.40
INSTRUM spect
PROBHD 5mm Broadban
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 815
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 3649.1
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40

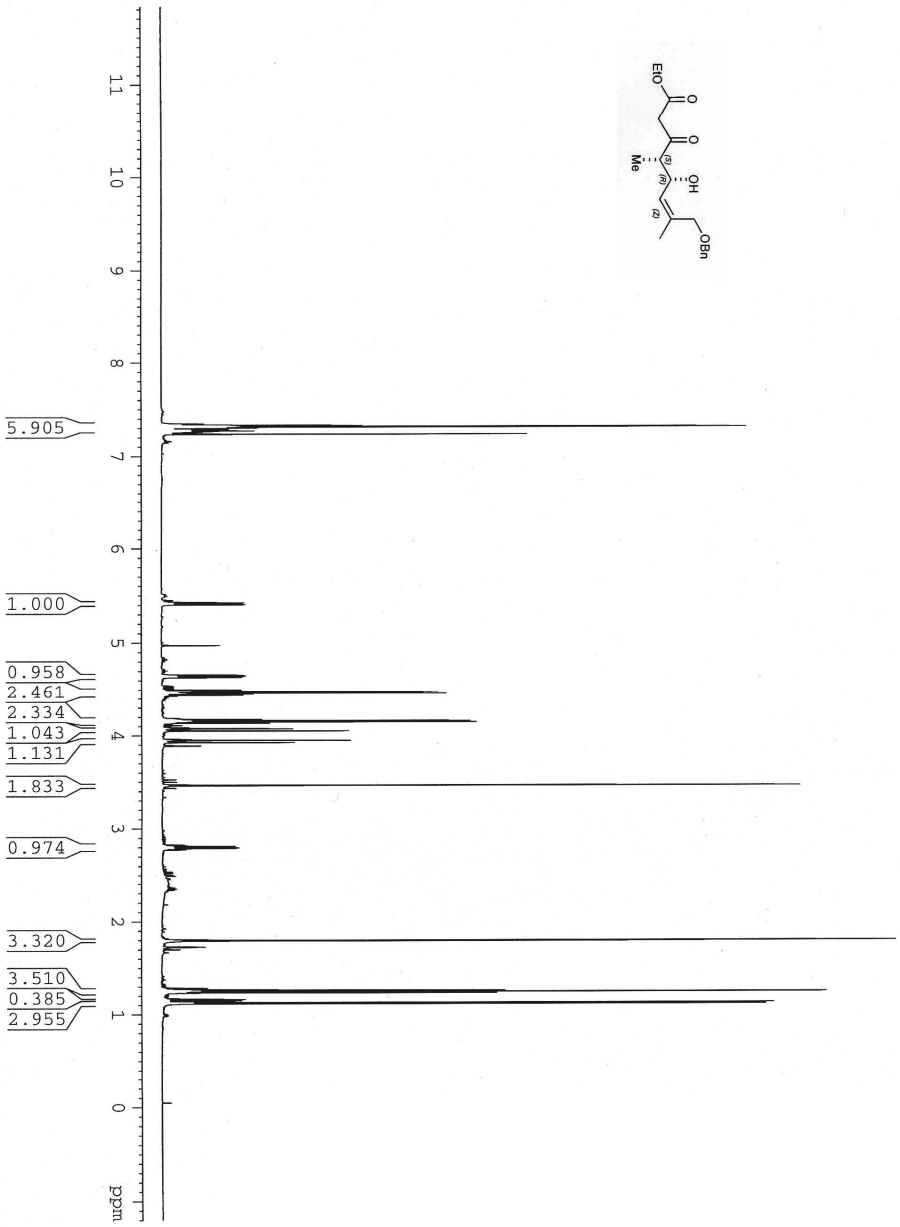

OBn
O
Me
1.000
0.999
3.226
2.621
4.532
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
EM-VII-57


14.272
1.000
0.967
1.037
3.245
1.072
1.043
1.224
1.086
1.168
1.091
3.420
3.382
ppm
11
10
9
8
7
6
5
4
3
2
1
S
S
N
O
OH
OBn
Me
En
(S)
(S)
(R)
(Z)

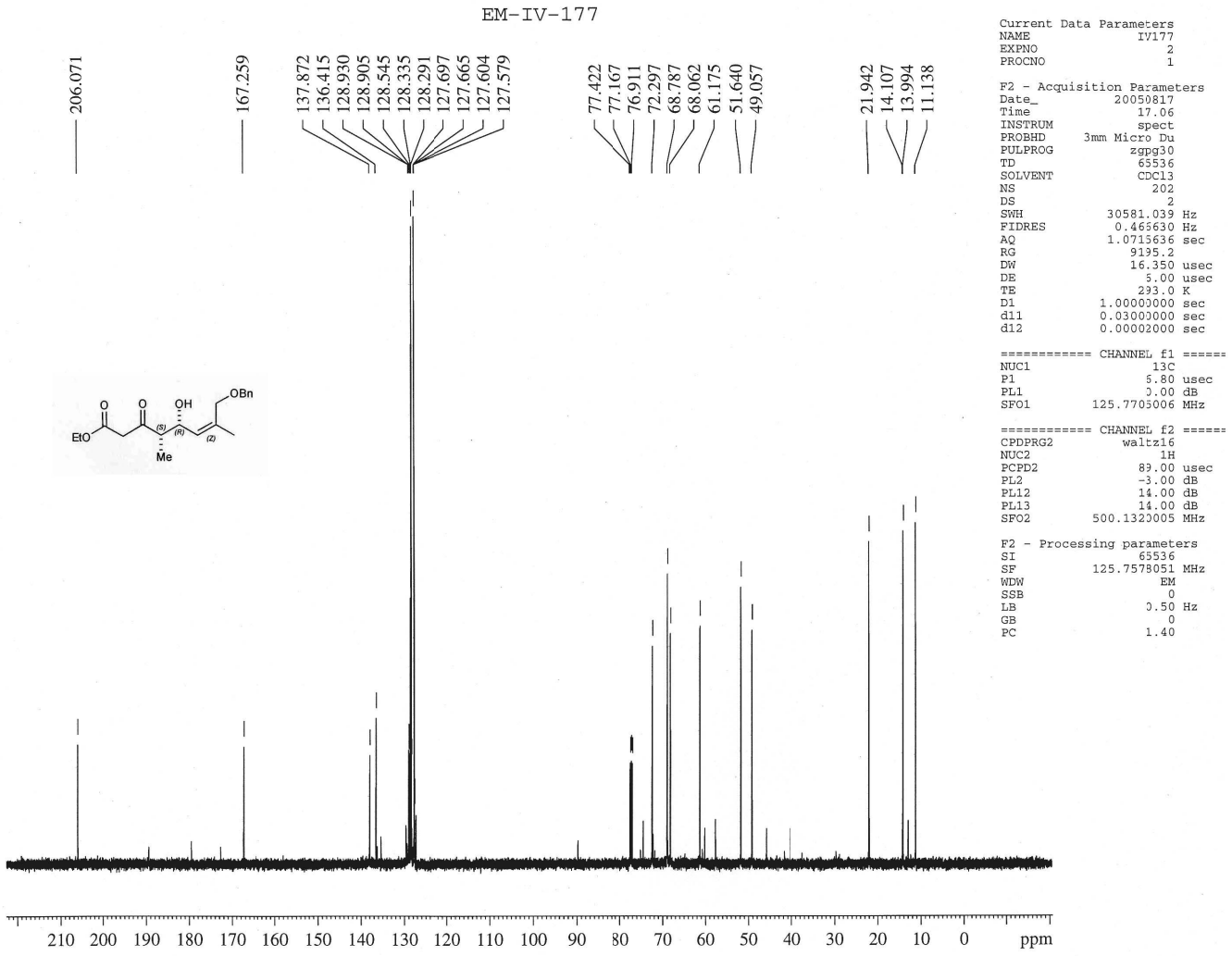
EM-IV-125




```
Current Data Parameters
NAME                  EMIV125
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_                20050817
Time                    16.52
INSTRUM                 spect
PROBHD       3mm Micro Du
PULPROG                zgpg30
TD                      65536
SOLVENT                 CDCl3
NS                       1024
DS                          2
SWH                30581.039 Hz
FIDRES             0.465630 Hz
AQ                 1.0715636 sec
RG                    5150.6
DW                    16.350 usec
DE                     5.00 usec
TE                     293.0 K
D1                1.00000000 sec
d11               0.03000000 sec
d12               0.00002000 sec

============ CHANNEL f1 ======
NUC1                     13C
P1                      6.80 usec
PL1                     0.00 dB
SFO1             125.7705006 MHz

============ CHANNEL f2 ======
CPDPRG2              waltz16
NUC2                     1H
PCPD2                 89.00 usec
PL2                   -3.00 dB
PL12                  14.00 dB
PL13                  14.00 dB
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                      65536
SF               125.7578051 MHz
WDW                        EM
SSB                         0
LB                     0.50 Hz
GB                          0
PC                     1.40
```


5.905
1.000
0.958
2.461
2.334
1.043
1.131
1.833
0.974
3.320
3.510
0.385
2.955
11
10
9
8
7
6
5
4
3
2
1
0
ppm
EtO
O
O
Me
OH
OBn

EM-IV-177

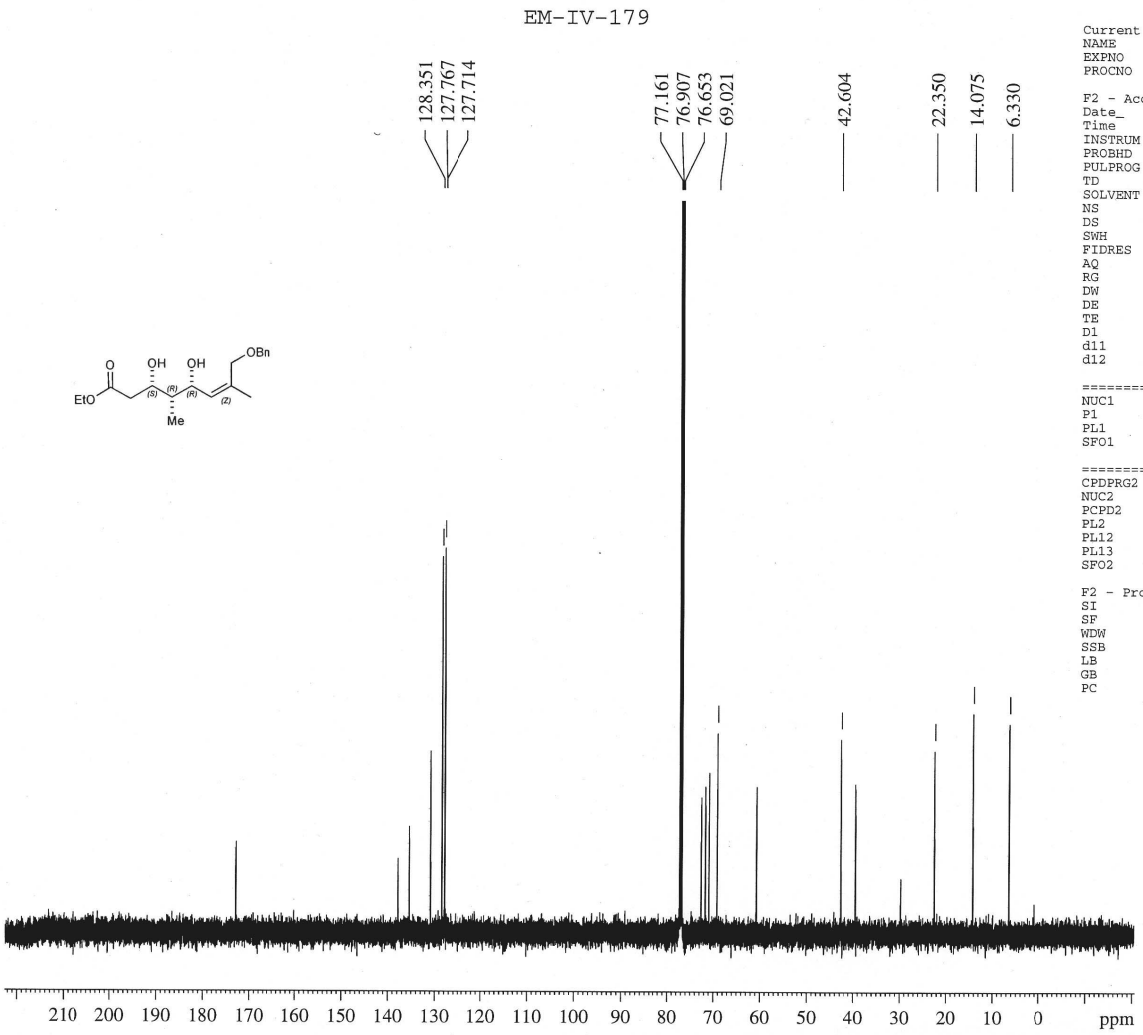



```
Current Data Parameters
NAME                  IV177
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20050817
Time                  17.06
INSTRUM               spect
PROBHD      3mm Micro Du
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      202
DS                        2
SWH             30581.039 Hz
FIDRES          0.465630 Hz
AQ              1.0715636 sec
RG                 9195.2
DW                16.350 usec
DE                 5.00 usec
TE                293.0 K
D1             1.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

============ CHANNEL f1 ======
NUC1                  13C
P1                 5.80 usec
PL1                0.00 dB
SFO1         125.7705006 MHz

============ CHANNEL f2 ======
CPDPRG2           waltz16
NUC2                  1H
PCPD2             89.00 usec
PL2               -3.00 dB
PL12              14.00 dB
PL13              14.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                    65536
SF           125.7578051 MHz
WDW                   EM
SSB                    0
LB                 0.50 Hz
GB                     0
PC                 1.40
```

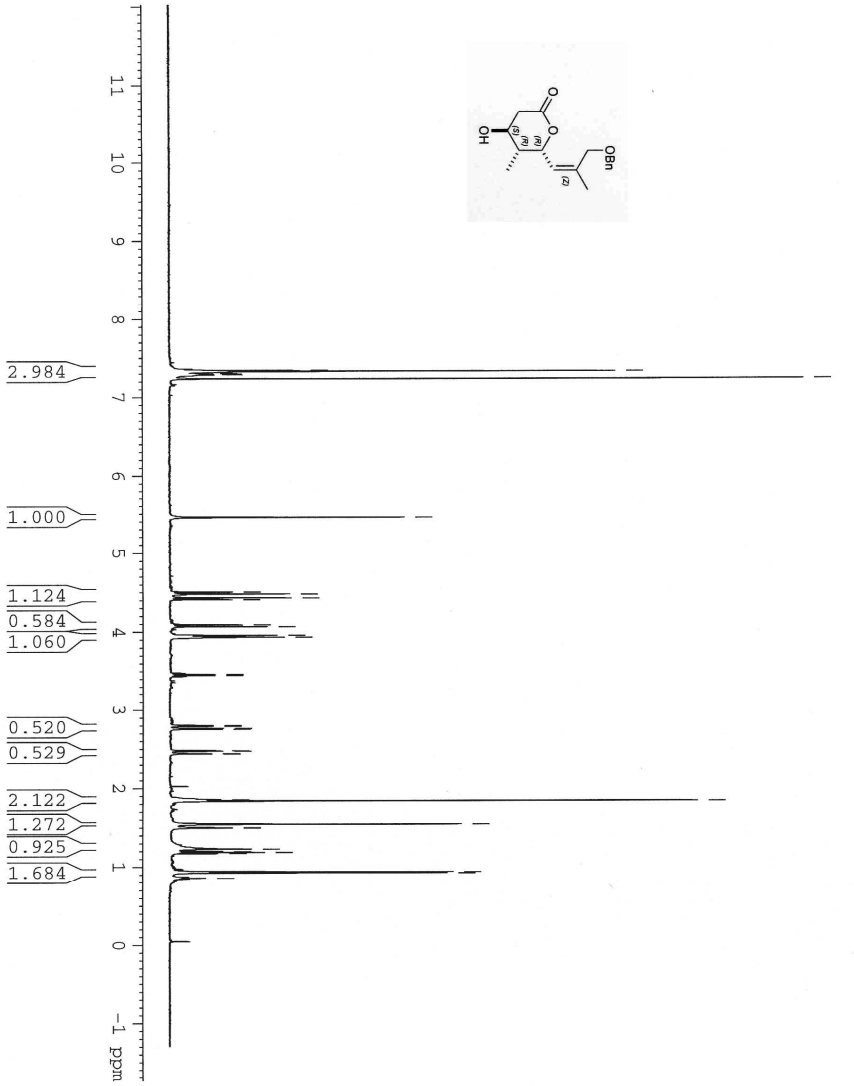
EtO
O
OH
OH
Me
OBn
7.102
0.045
1.000
1.007
2.494
1.054
2.435
1.199
1.198
0.801
0.720
1.211
1.093
3.578
5.879
3.151
0.378
11
10
9
8
7
6
5
4
3
2
1
0 ppm

EM-IV-179

EM-IV-179

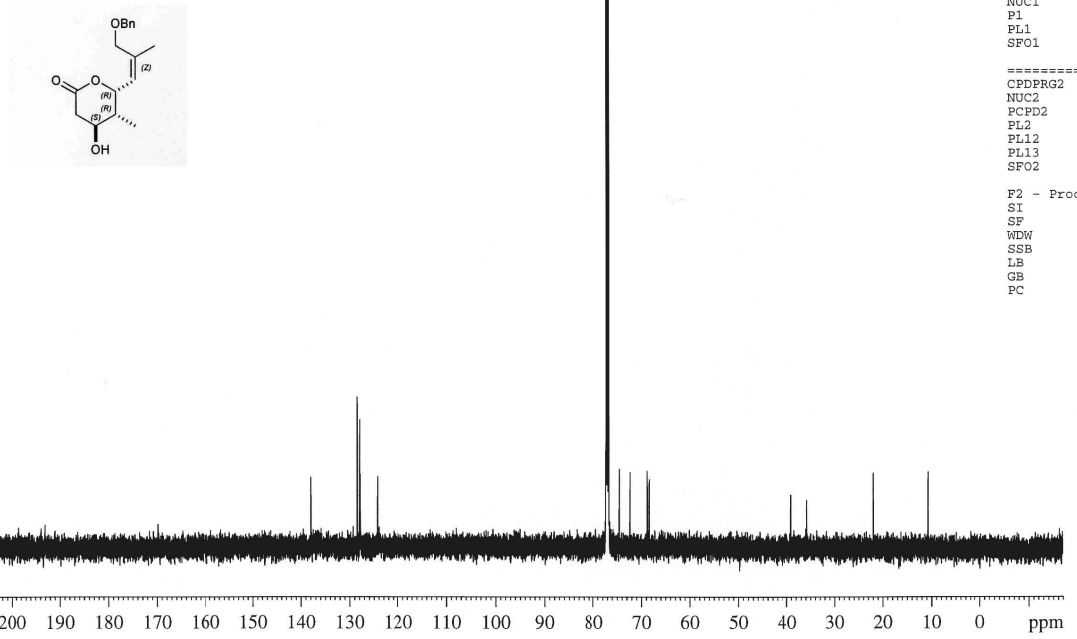



```
Current Data Parameters
NAME                  IV179
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20050817
Time                  18.30
INSTRUM               spect
PROBHD      3mm Micro Du
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  2048
DS                     2
SWH           30581.039 Hz
FIDRES         0.466630 Hz
AQ             1.0715636 sec
RG               14596.5
DW                16.350 usec
DE                 6.00 usec
TE                293.0 K
D1             1.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

============ CHANNEL f1 =======
NUC1                 13C
P1                  6.80 usec
PL1                 0.00 dB
SFO1         125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2          waltz16
NUC2                 1H
PCPD2              89.00 usec
PL2                -3.00 dB
PL12               14.00 dB
PL13               14.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 65536
SF           125.7578051 MHz
WDW                   EM
SSB                    0
LB                  0.50 Hz
GB                     0
PC                  1.40
```

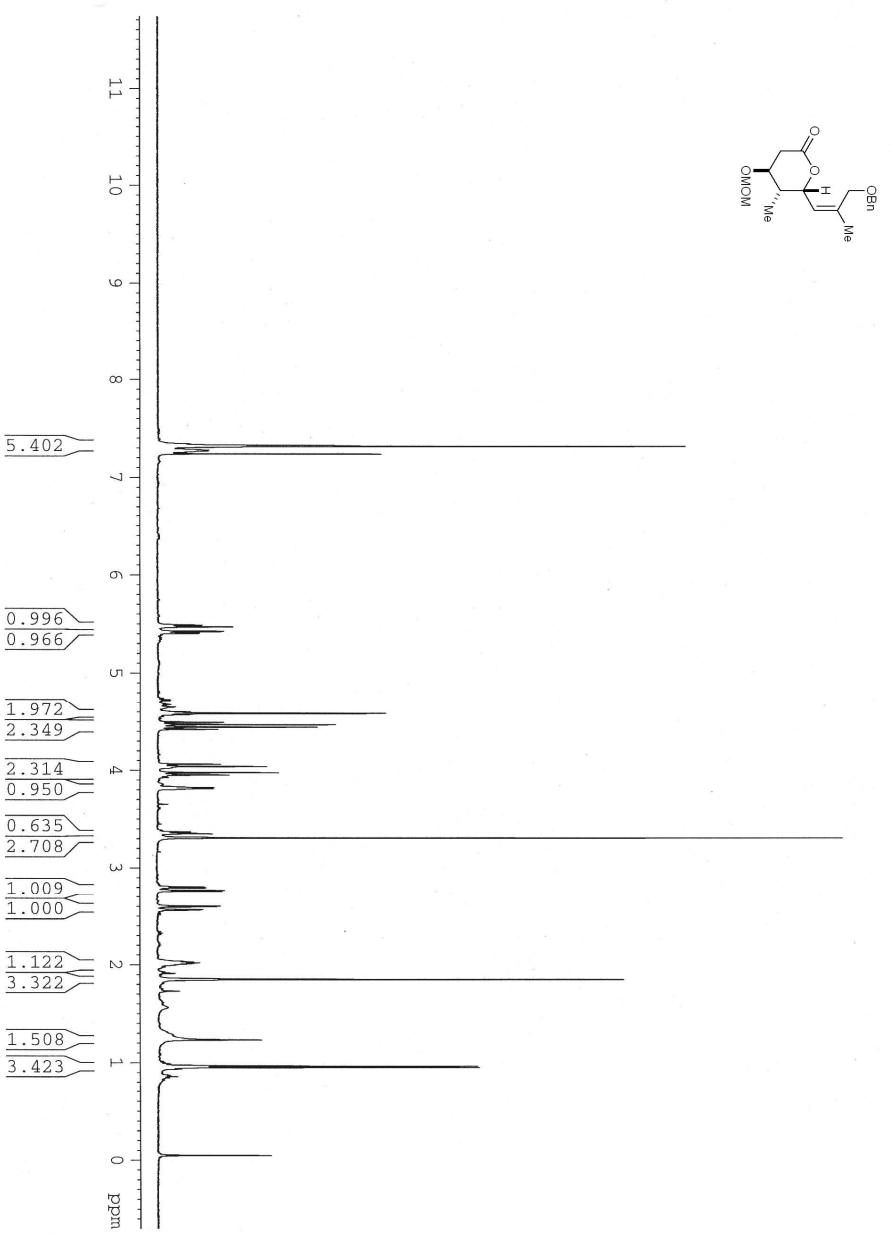

2.984
1.000
1.124
0.584
1.060
0.520
0.529
2.122
1.272
0.925
1.684
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm
OH
OBn

EM-VII-54A

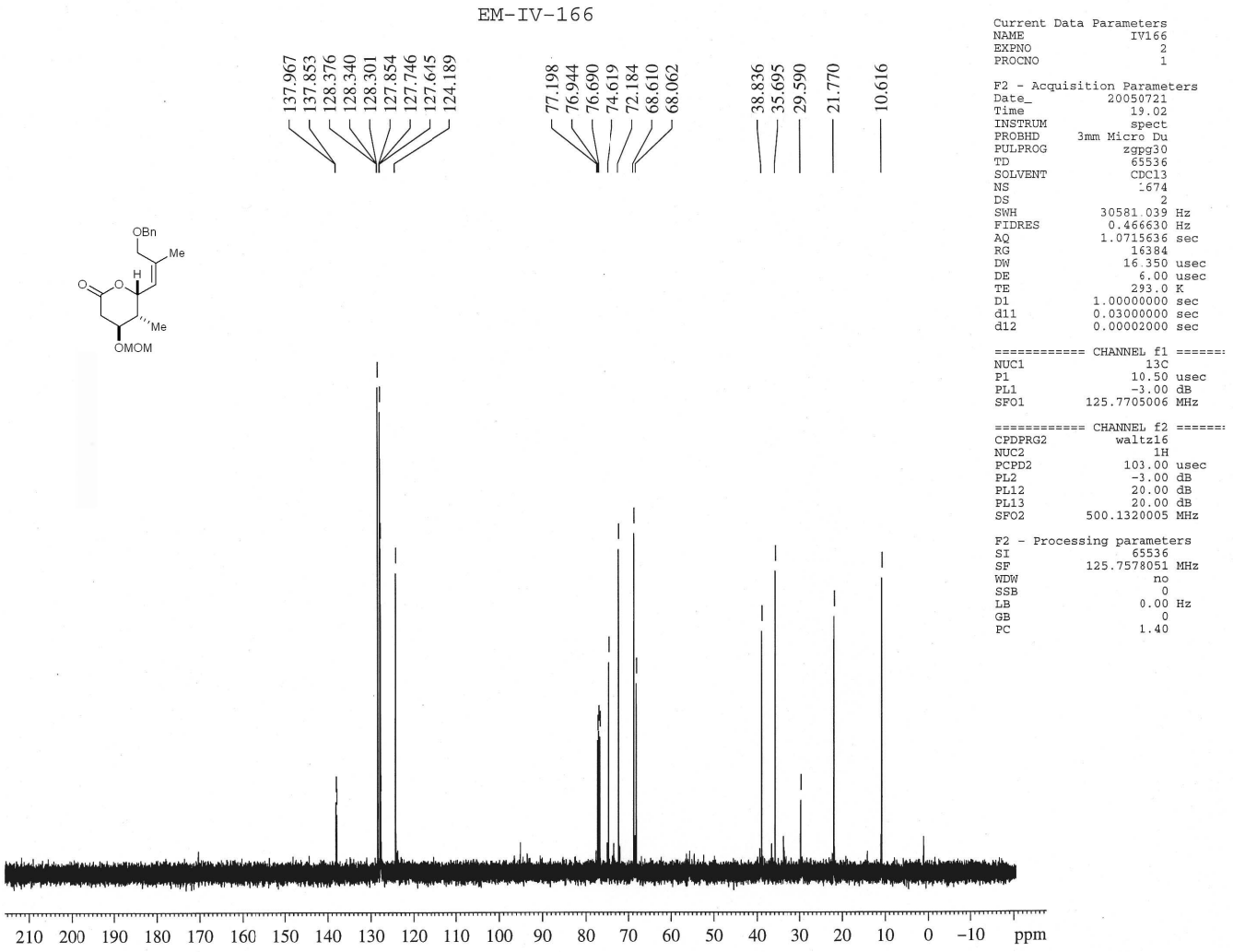
EM-VII-54A



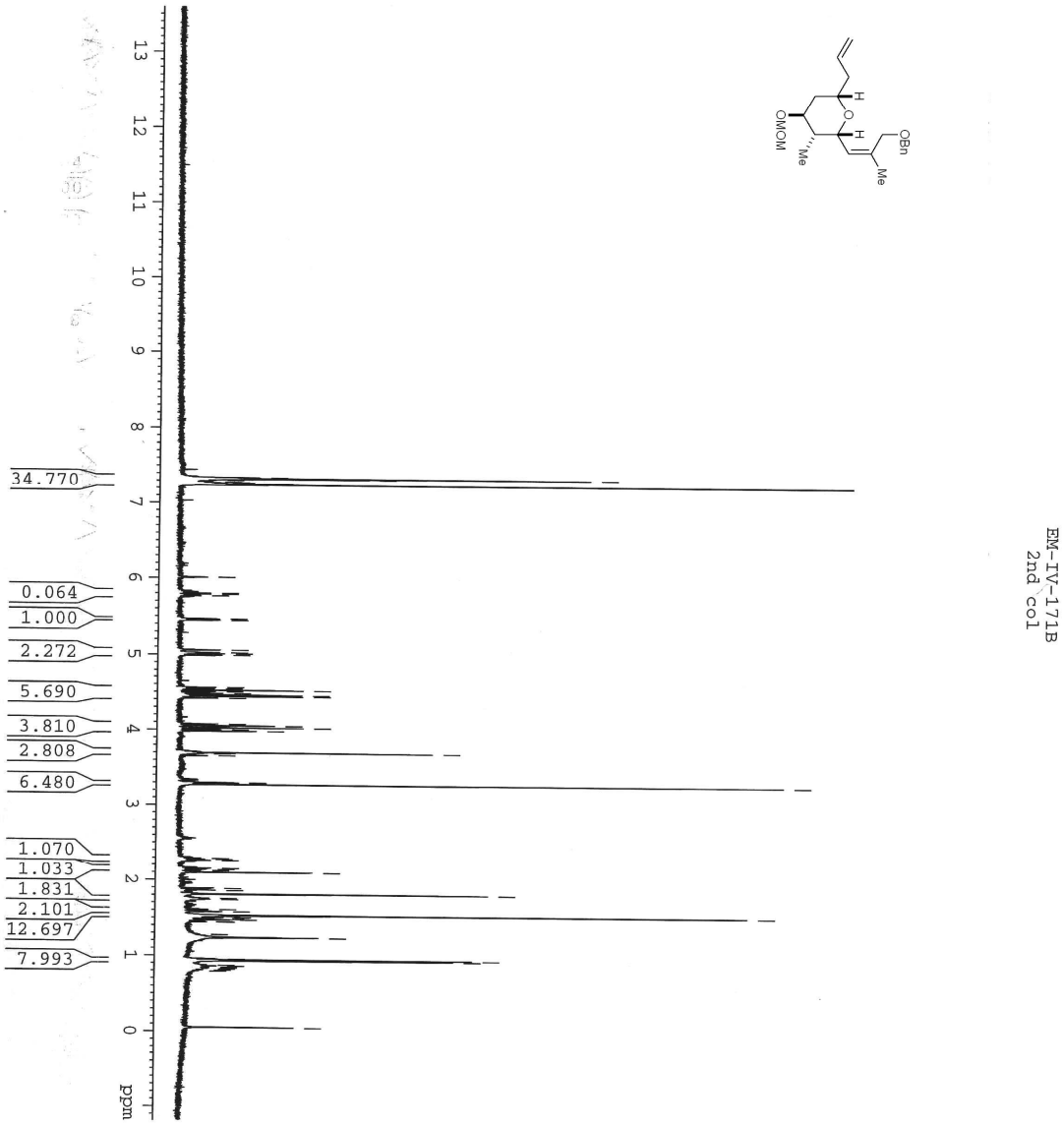

```
Current Data Parameters
NAME                  VII54A
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20060322
Time                  14.11
INSTRUM               spect
PROBHD      5mm Broadban
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  2648
DS                     2
SWH            30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                  4096
DW                16.350 usec
DE                 6.00 usec
TE                293.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

============ CHANNEL f1 =======
NUC1                  13C
P1                   6.80 usec
PL1                  0.00 dB
SFO1         125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                  1H
PCPD2               89.00 usec
PL2                 -3.00 dB
PL12                14.00 dB
PL13                14.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 65536
SF           125.7578051 MHz
WDW                   EM
SSB                    0
LB                  0.50 Hz
GB                     0
PC                  1.40
```


5.402
0.996
0.966
1.972
2.349
2.314
0.950
0.635
2.708
1.009
1.000
1.122
3.322
1.508
3.423
ppm
OMOM
Me
H
Me
OBn

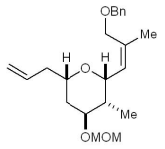
EM-IV-166




```
Current Data Parameters
NAME                  IV166
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20050721
Time                  19.02
INSTRUM               spect
PROBHD      3mm Micro Du
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     674
DS                       2
SWH             30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                   16384
DW                16.350 usec
DE                 6.00 usec
TE                 293.0 K
D1             1.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

============ CHANNEL f1 =======
NUC1                  13C
P1                 10.50 usec
PL1                -3.00 dB
SFO1         125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                  1H
PCPD2             103.00 usec
PL2                -3.00 dB
PL12               20.00 dB
PL13               20.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                   65536
SF           125.7578051 MHz
WDW                     no
SSB                      0
LB                  0.00 Hz
GB                       0
PC                    1.40
```

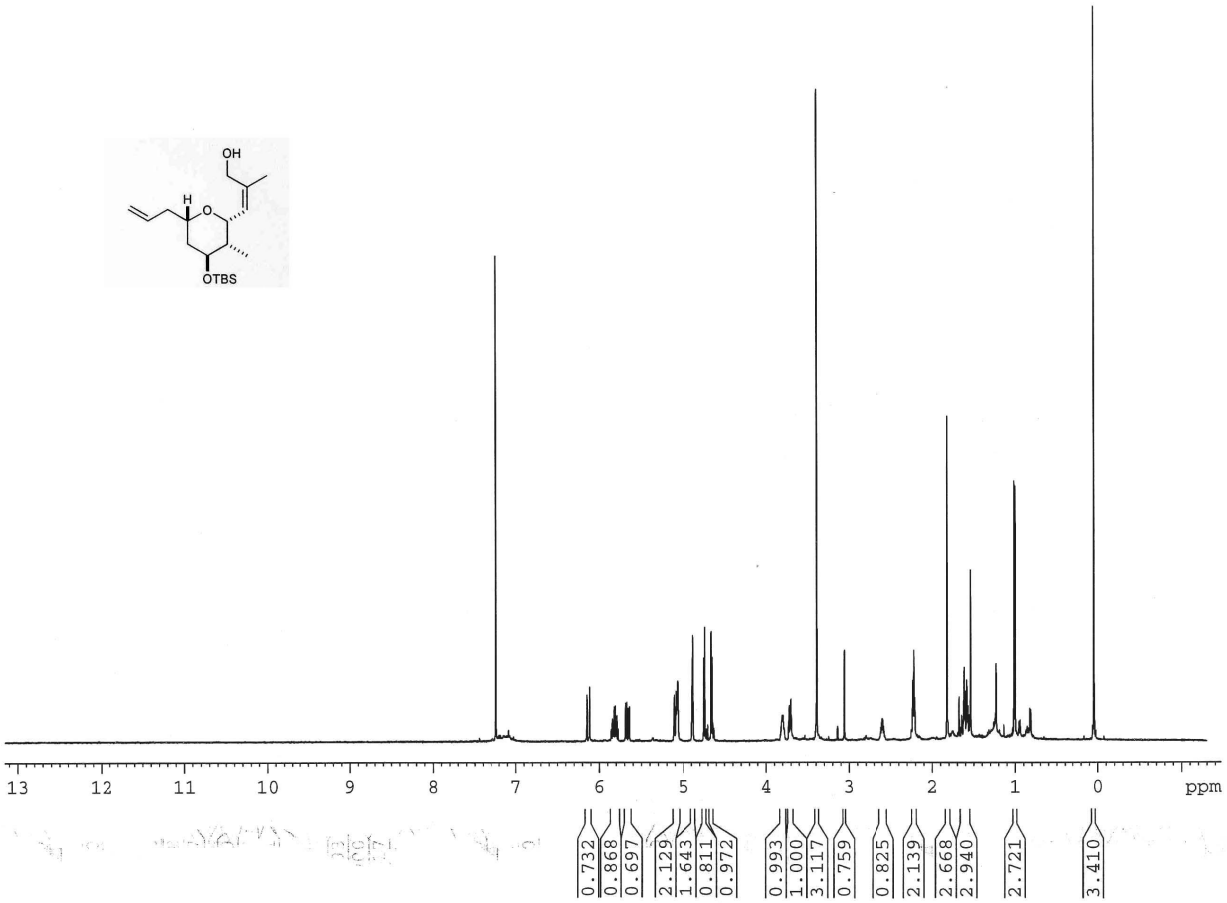

EM-IV-171B
2nd col
34.770
0.064
1.000
2.272
5.690
3.810
2.808
6.480
1.070
1.033
1.831
2.101
12.697
7.993
ppm
OMOM
Me
OBn
Me

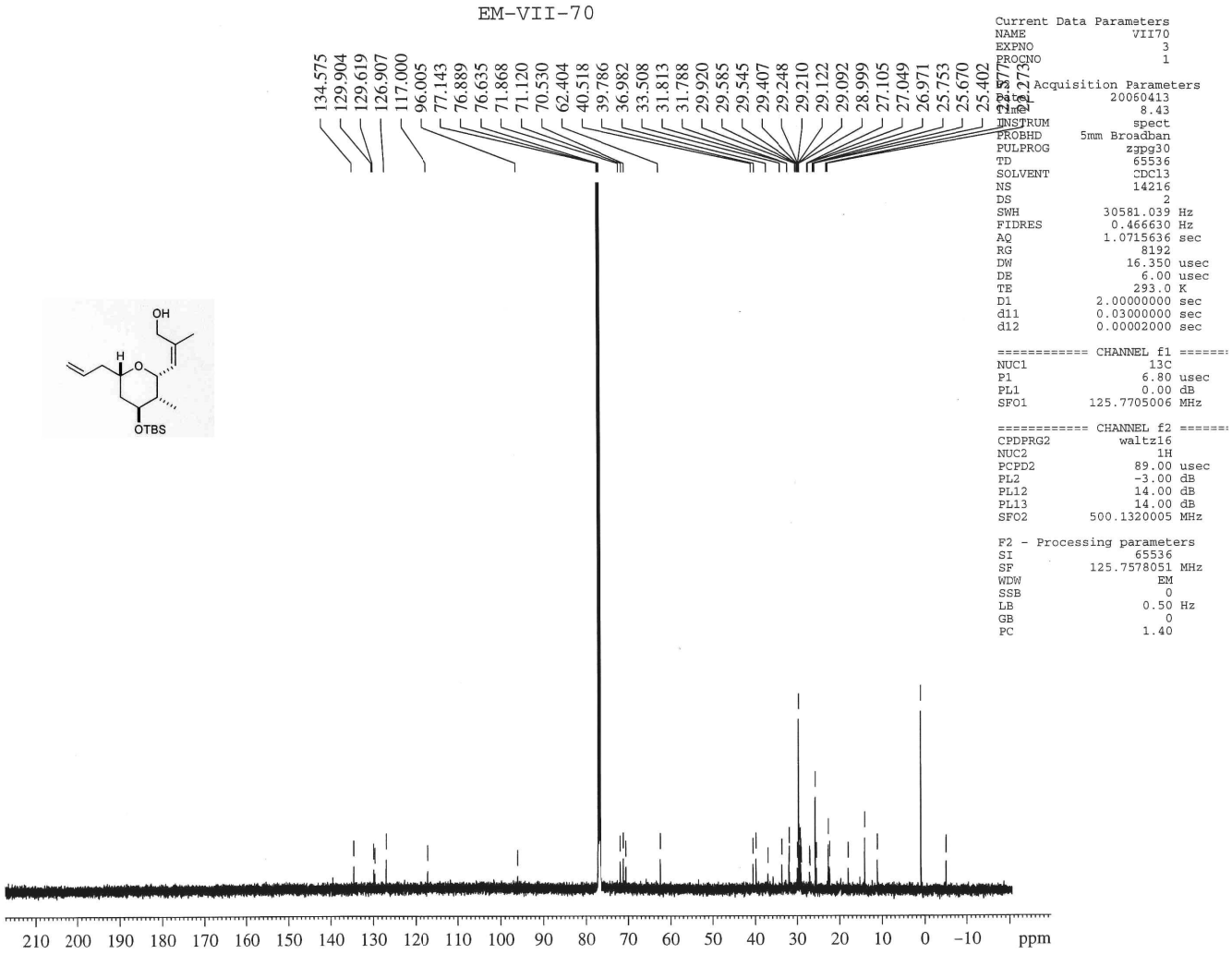
EM-VII-55

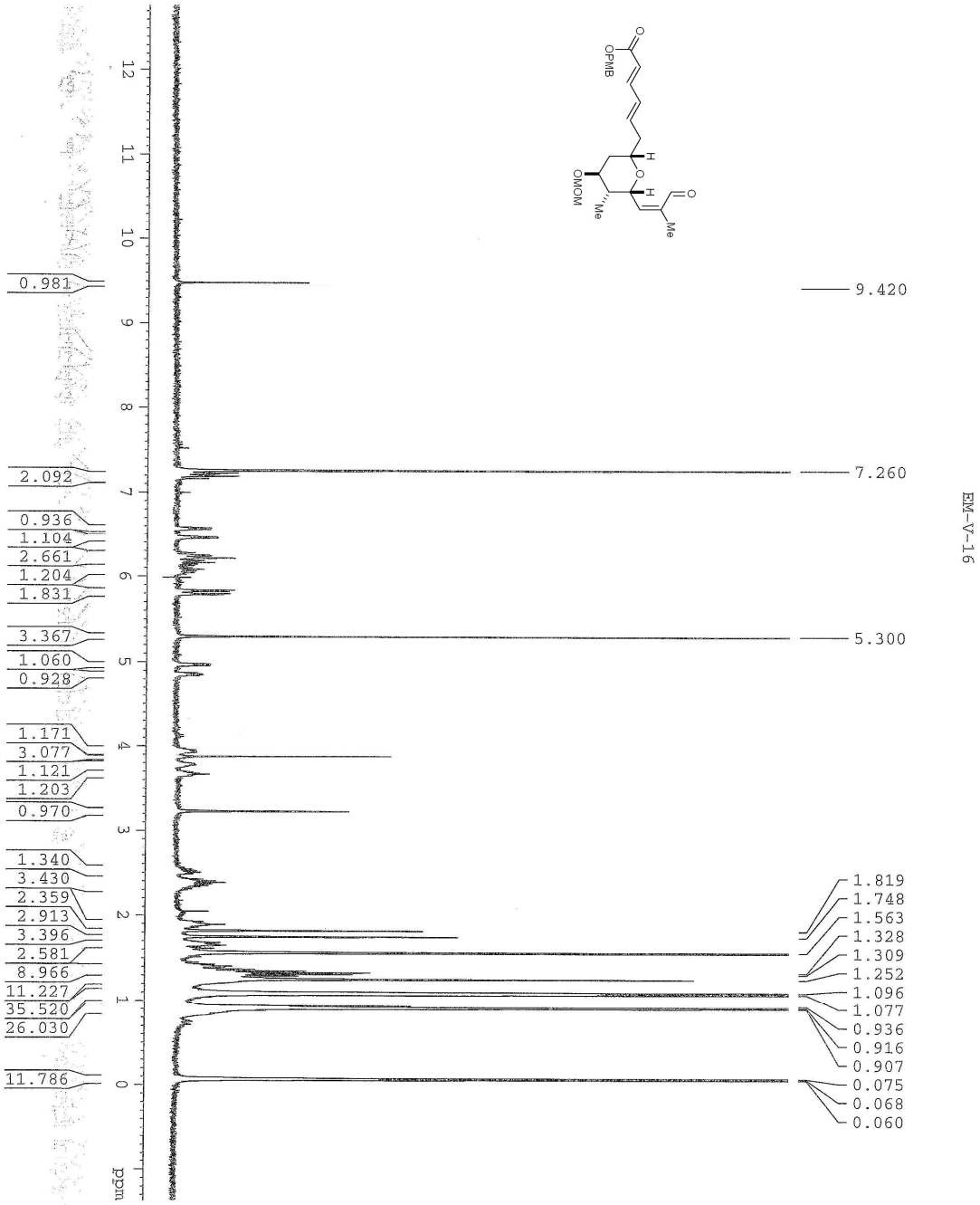


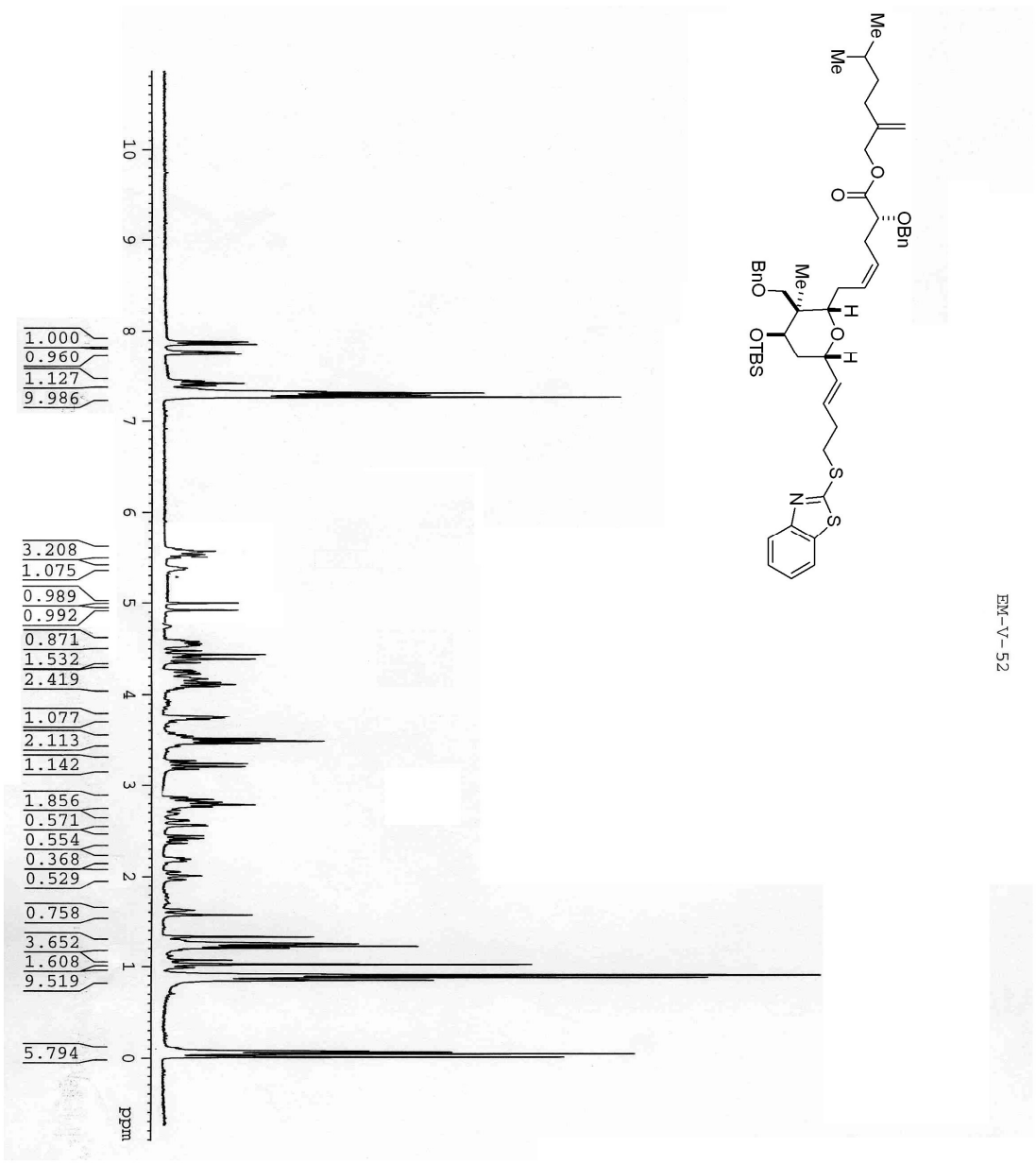

```
Current Data Parameters
NAME                  VII55
EXPNO                     4
PROCNO                    1

F2 - Acquisition Parameters
Date_              20060328
Time                   8.15
INSTRUM               spect
PROBHD      5mm Broadban
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     6164
DS                        2
SWH              30581.039 Hz
FIDRES           0.466630 Hz
AQ               1.0715636 sec
RG                     4096
DW                16.350 usec
DE                 6.00 usec
TE                 293.0 K
D1             1.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

============ CHANNEL f1 =======
NUC1                    13C
P1                   6.80 usec
PL1                  0.00 dB
SFO1          125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2            waltz16
NUC2                    1H
PCPD2               89.00 usec
PL2                 -3.00 dB
PL12                14.00 dB
PL13                14.00 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                    65536
SF            125.7578051 MHz
WDW                      EM
SSB                       0
LB                   0.50 Hz
GB                        0
PC                    1.40
```

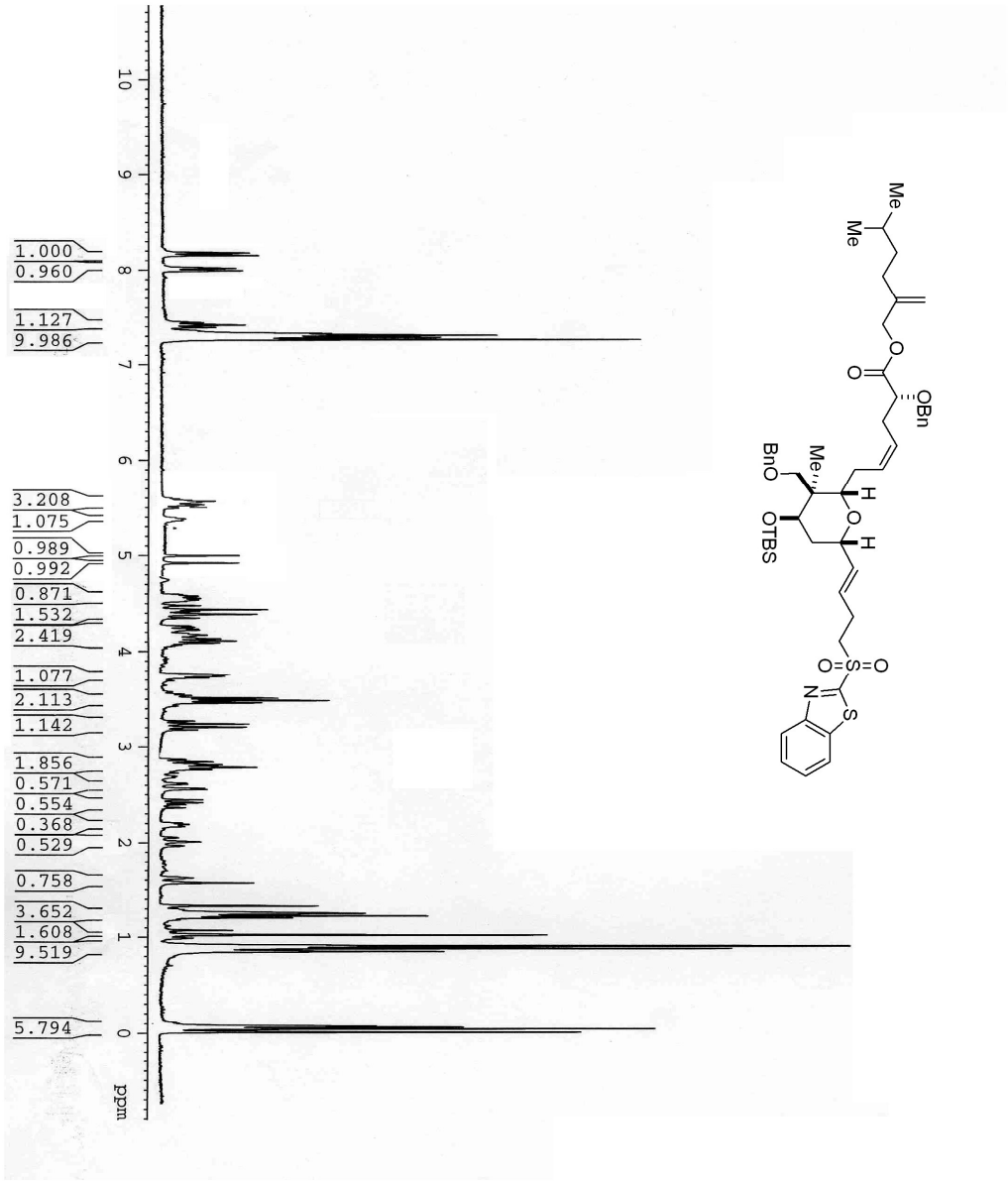
EM-V-14B


OH
H
O
OTBS
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.732
0.868
0.697
2.129
1.643
0.811
0.972
0.993
1.000
3.117
0.759
0.825
2.139
2.668
2.940
2.721
3.410


EM-VII-70
134.575
129.904
129.619
126.907
117.000
96.005
77.143
76.889
76.635
71.868
71.120
70.530
62.404
40.518
39.786
36.982
33.508
31.813
31.788
29.920
29.585
29.545
29.407
29.248
29.210
29.122
29.092
28.999
27.105
27.049
26.971
25.753
25.670
25.402
18.273
OH
H
O
OTBS
Current Data Parameters
NAME VII70
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050413
Time 8.43
INSTRUM spect
PROBHD 5mm Broadban
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 14216
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 8192
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
========== CHANNEL f1 =======
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
========== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

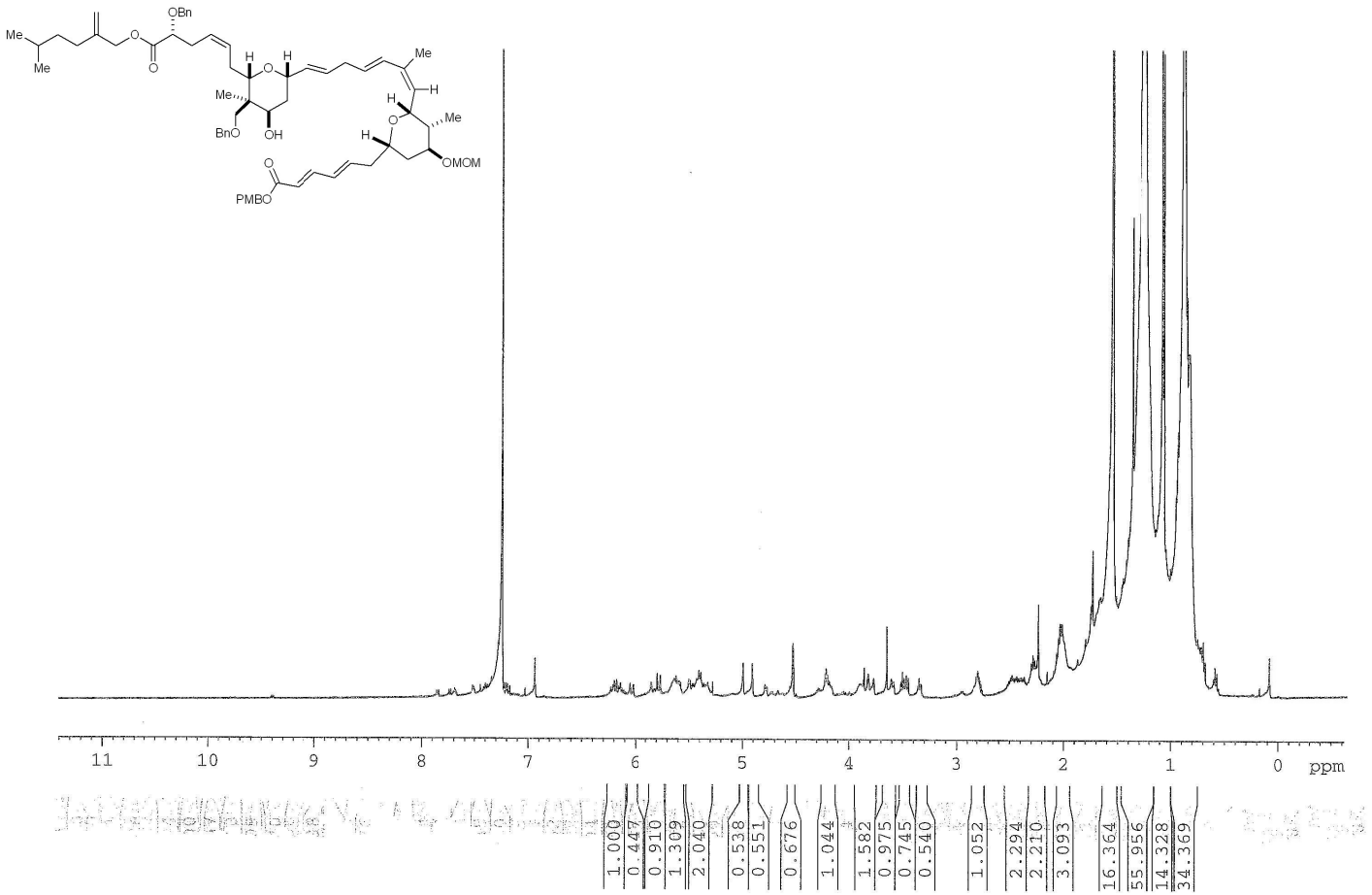

OPMB
OMOM
Me
Me
0.981
2.092
0.936
1.104
2.661
1.204
1.831
3.367
1.060
0.928
1.171
3.077
1.121
1.203
0.970
1.340
3.430
2.359
2.913
3.396
2.581
8.966
11.227
35.520
26.030
11.786
9.420
7.260
5.300
1.819
1.748
1.563
1.328
1.309
1.252
1.096
1.077
0.936
0.916
0.907
0.075
0.068
0.060
ppm
EM-V-16


Me
Me
O
O
OBn
Me
BnO
H
O
H
OTBS
S
N
S
EM-V-52
1.000
0.960
1.127
9.986
3.208
1.075
0.989
0.992
0.871
1.532
2.419
1.077
2.113
1.142
1.856
0.571
0.554
0.368
0.529
0.758
3.652
1.608
9.519
5.794
10
9
8
7
6
5
4
3
2
1
0
ppm


1.000
0.960
1.127
9.986
3.208
1.075
0.989
0.992
0.871
1.532
2.419
1.077
2.113
1.142
1.856
0.571
0.554
0.368
0.529
0.758
3.652
1.608
9.519
5.794
ppm
Me
Me
OBn
BnO
Me
OTBS
H
O
H
O=S=O
N
S
EM-V-53

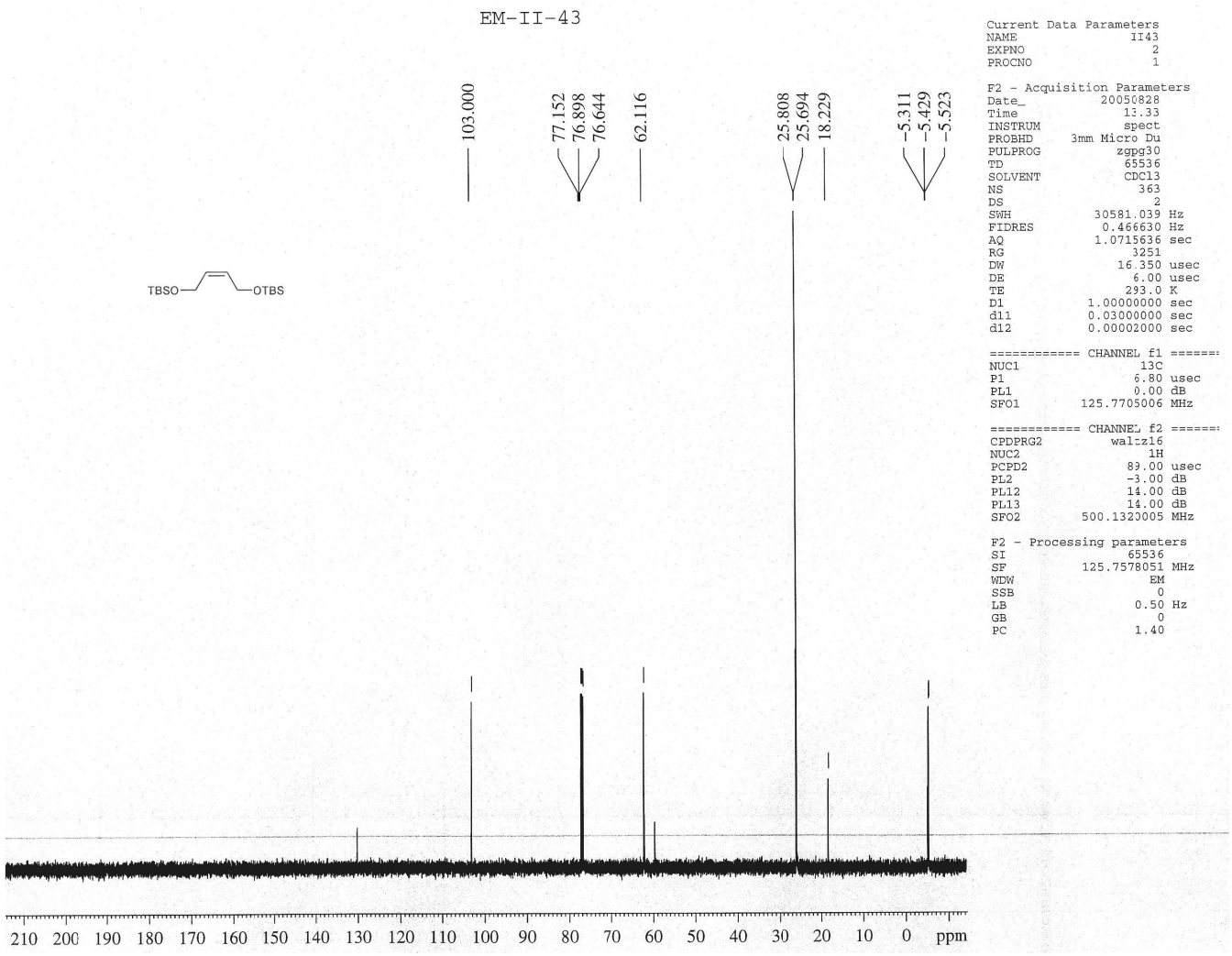
13.251
1.000
0.481
0.499
1.530
1.723
0.530
0.521
0.377
1.008
1.259
6.477
0.484
0.964
0.810
0.745
0.499
2.899
3.399
13.581
28.846
36.712
11.374
37.781
16.290
ppm
Me
Me
OBn
BnO
OTBS
PMBO
OMOM

EM-V-55


OBn
Me
Me
O
O
H
O
H
Me
Me
H
H
O
Me
BnO
OH
H
OMOM
O
PMBO
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
0.447
0.910
1.309
2.040
0.538
0.551
0.676
1.044
1.582
0.975
0.745
0.540
1.052
2.294
2.210
3.093
16.364
55.956
14.328
34.369

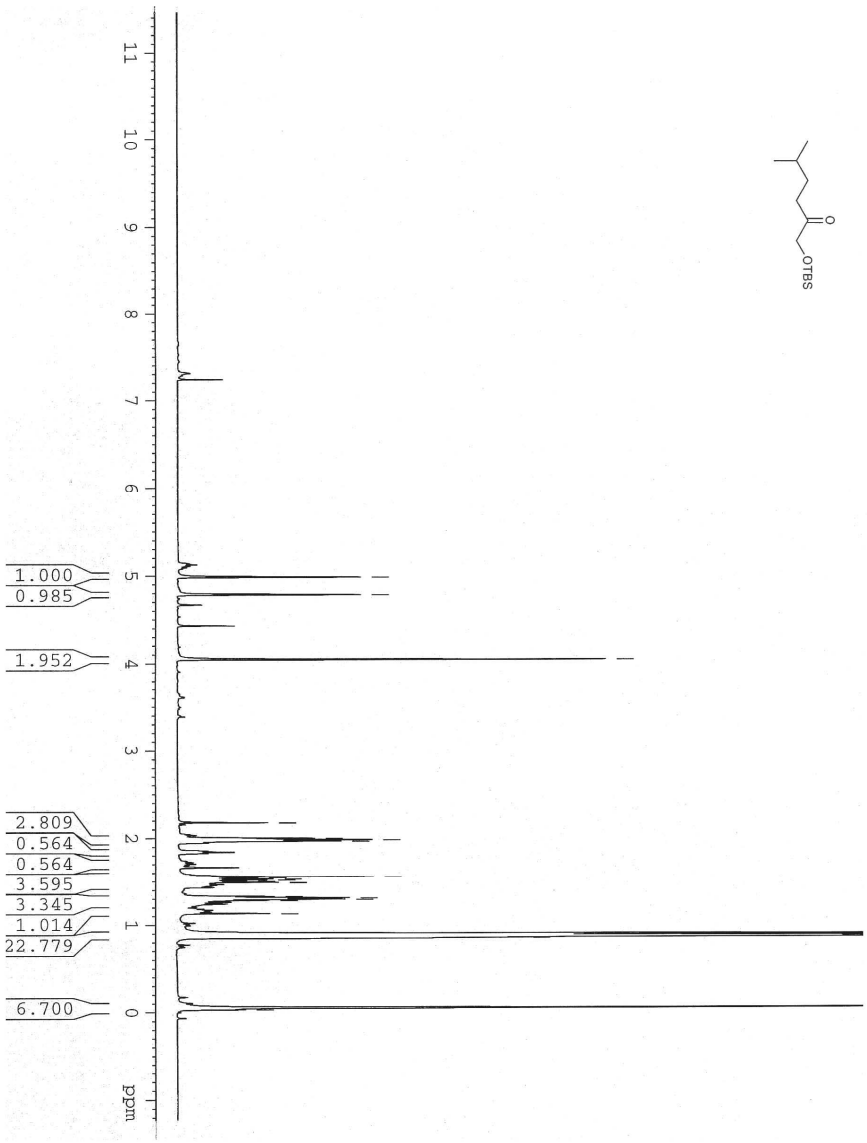
TBSO
OTBS
0.187
0.722
0.212
0.386
2.000
11.978
7.564
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

EM-II-43


EM-II-43
103.000
77.152
76.898
76.644
62.116
25.808
25.694
18.229
-5.311
-5.429
-5.523
TBSO
OTBS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Current Data Parameters
NAME II43
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050828
Time 13.33
INSTRUM spect
PROBHD 3mm Micro Du
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 363
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 3251
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40

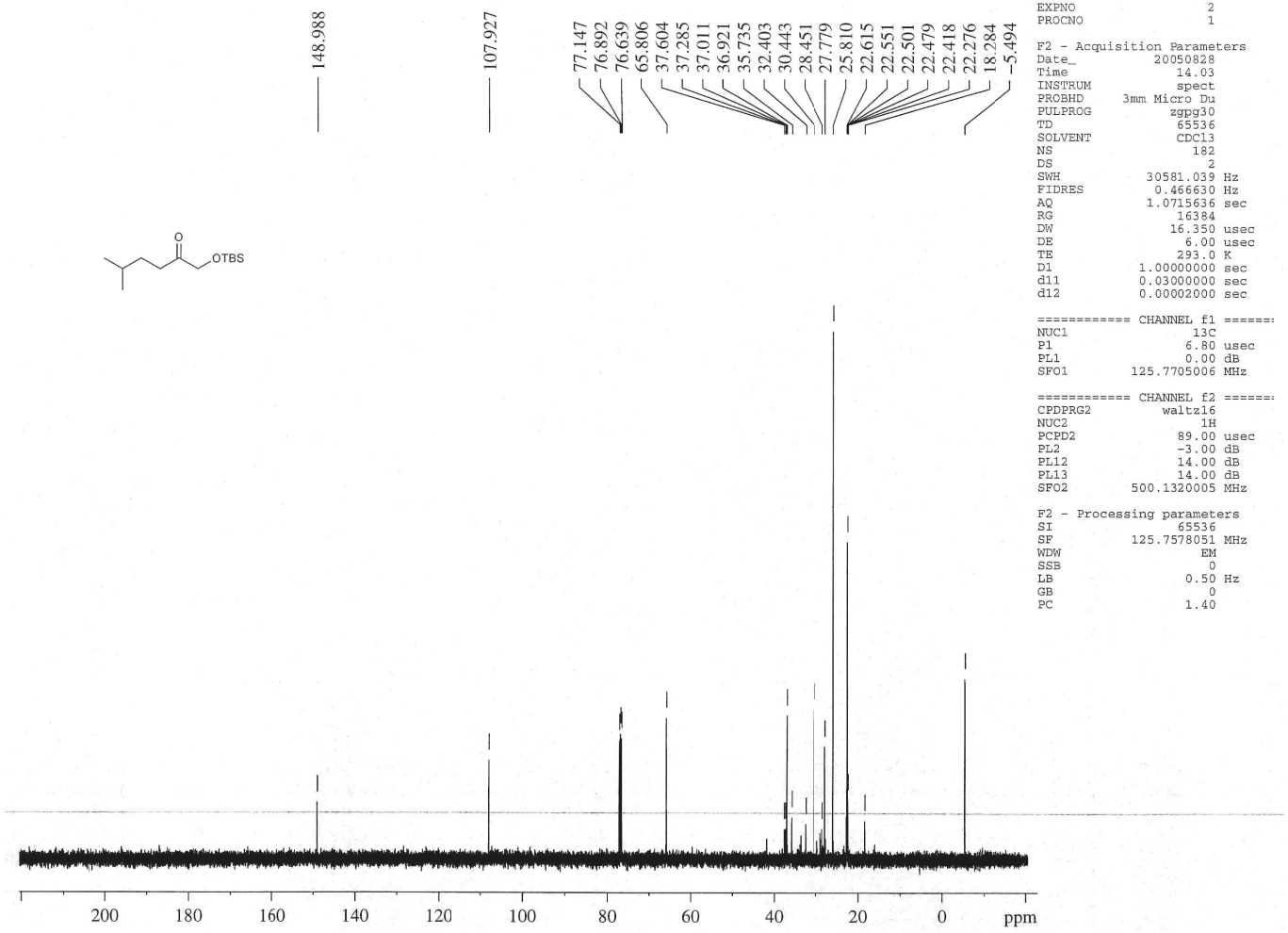
OH
OTBS
2.000
1.038
0.859
1.054
3.175
1.179
16.047
6.211
11
10
9
8
7
6
5
4
3
2
1
0
ppm

EM-V-19

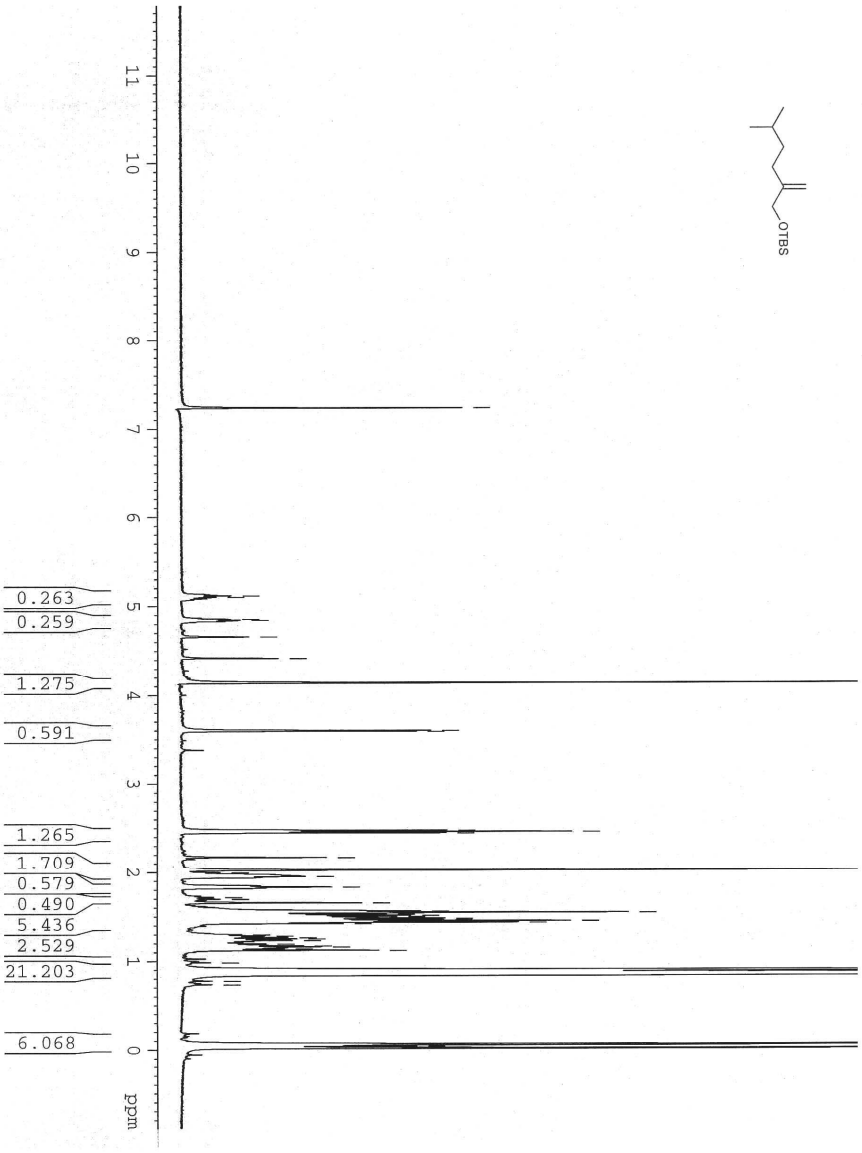

OTBS
1.000
0.985
1.952
2.809
0.564
0.564
3.595
3.345
1.014
22.779
6.700
ppm

EM-V-73

EM-V-73

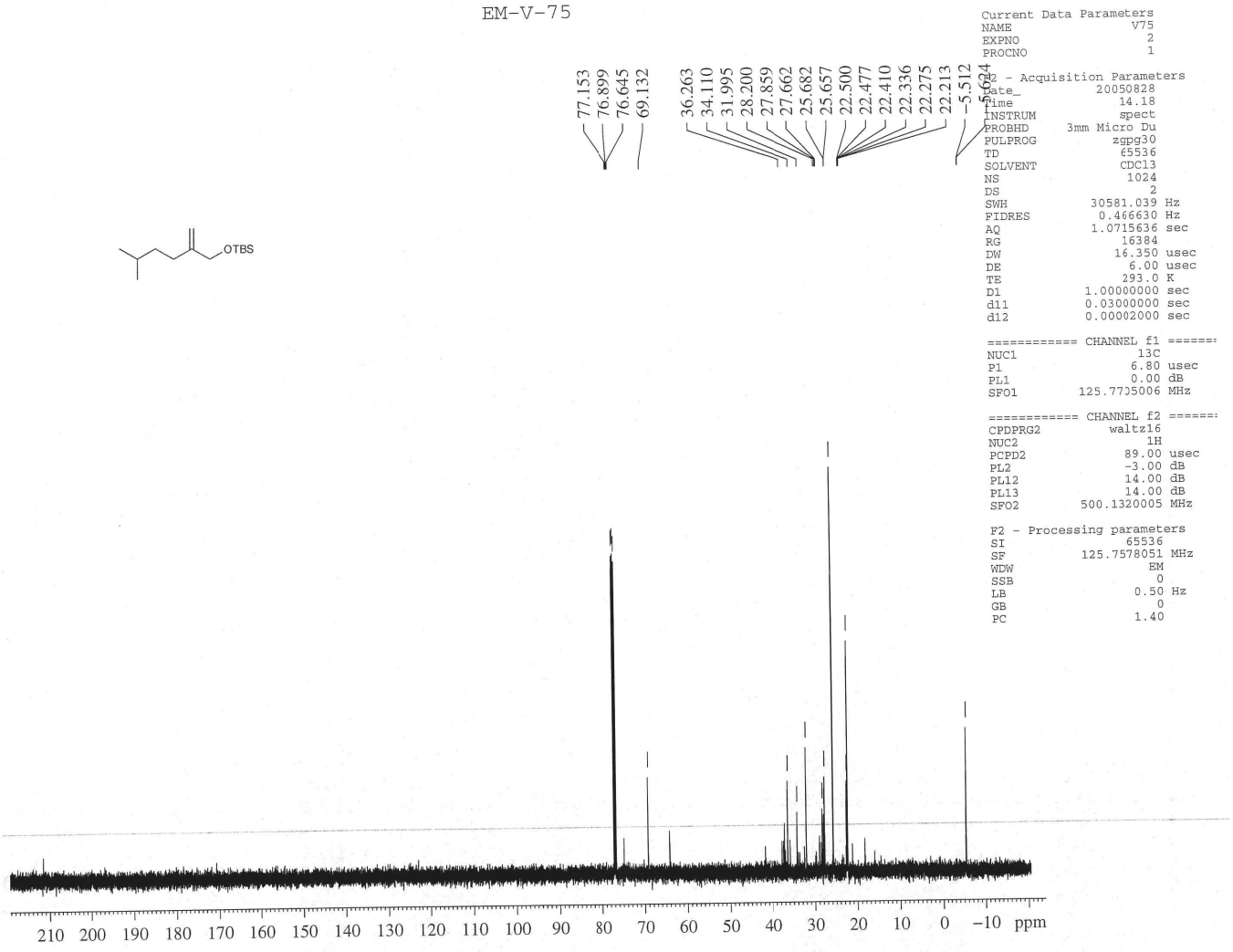



```
Current Data Parameters
NAME                   V73
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20050828
Time                 14.03
INSTRUM              spect
PROBHD     3mm Micro Du
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    182
DS                      2
SWH              30581.039 Hz
FIDRES               0.466630 Hz
AQ                1.0715636 sec
RG                    16384
DW                   16.350 usec
DE                    6.00 usec
TE                   293.0 K
D1                1.00000000 sec
d11               0.03000000 sec
d12               0.00002000 sec

============ CHANNEL f1 =======
NUC1                    13C
P1                     6.80 usec
PL1                    0.00 dB
SFO1           125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2              waltz16
NUC2                    1H
PCPD2                 89.00 usec
PL2                   -3.00 dB
PL12                  14.00 dB
PL13                  14.00 dB
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                    65536
SF             125.7578051 MHz
WDW                     EM
SSB                      0
LB                    0.50 Hz
GB                       0
PC                    1.40
```


OTBS
0.263
0.259
1.275
0.591
1.265
1.709
0.579
0.490
5.436
2.529
21.203
6.068
11
10
9
8
7
6
5
4
3
2
1
0
ppm

EM-V-75

EM-V-75



Current Data Parameters

NAME	V75
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20050828
Time	14.18
INSTRUM	spect
PROBHD	3mm Micro Du
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	2
SWH	30581.039 Hz
FIDRES	0.466630 Hz
AQ	1.0715636 sec
RG	16384
DW	16.350 usec
DE	6.00 usec
TE	293.0 K
D1	1.00000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 =======

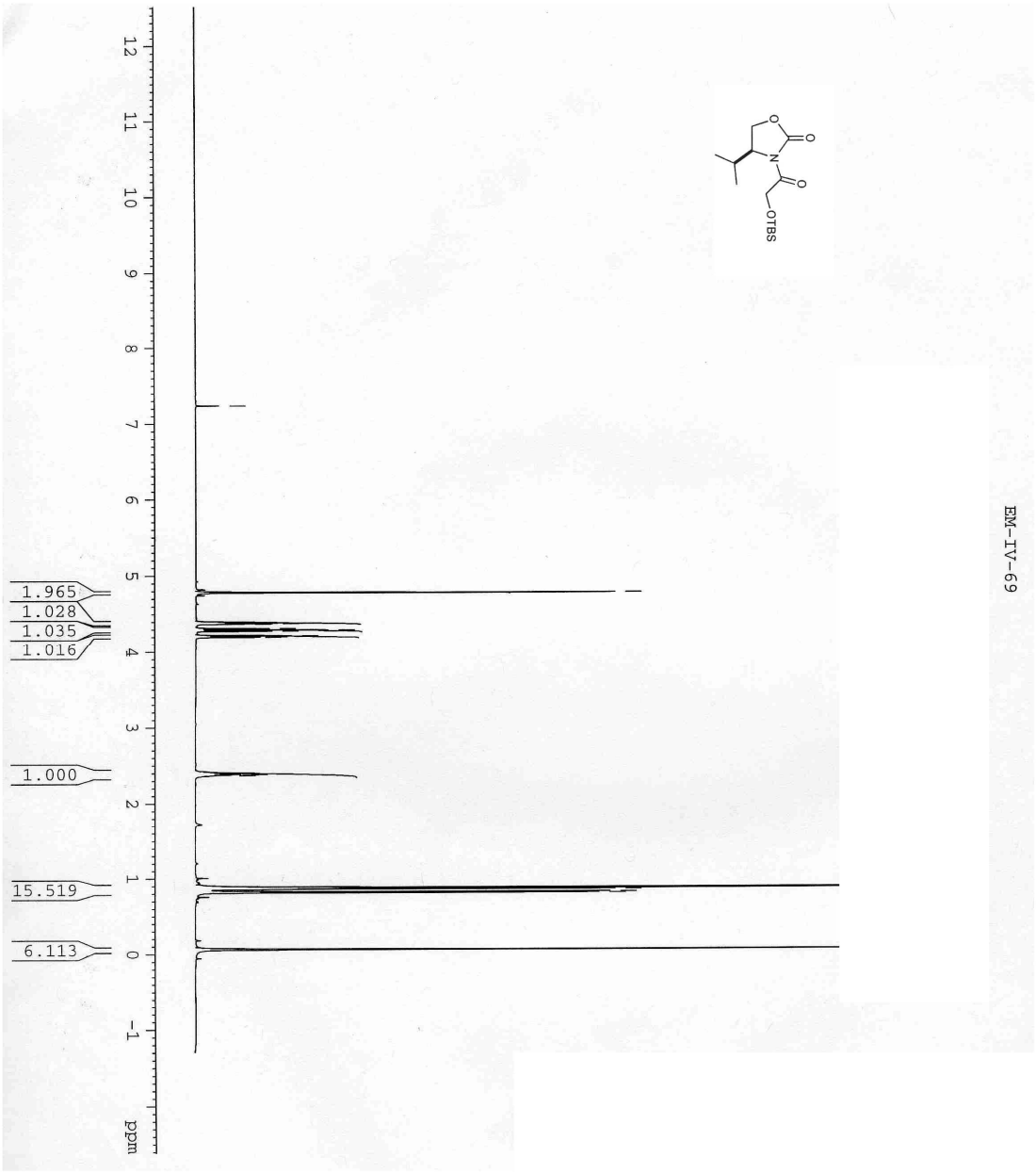
NUC1	13C
P1	6.80 usec
PL1	0.00 dB
SFO1	125.7735006 MHz

========== CHANNEL f2 =======

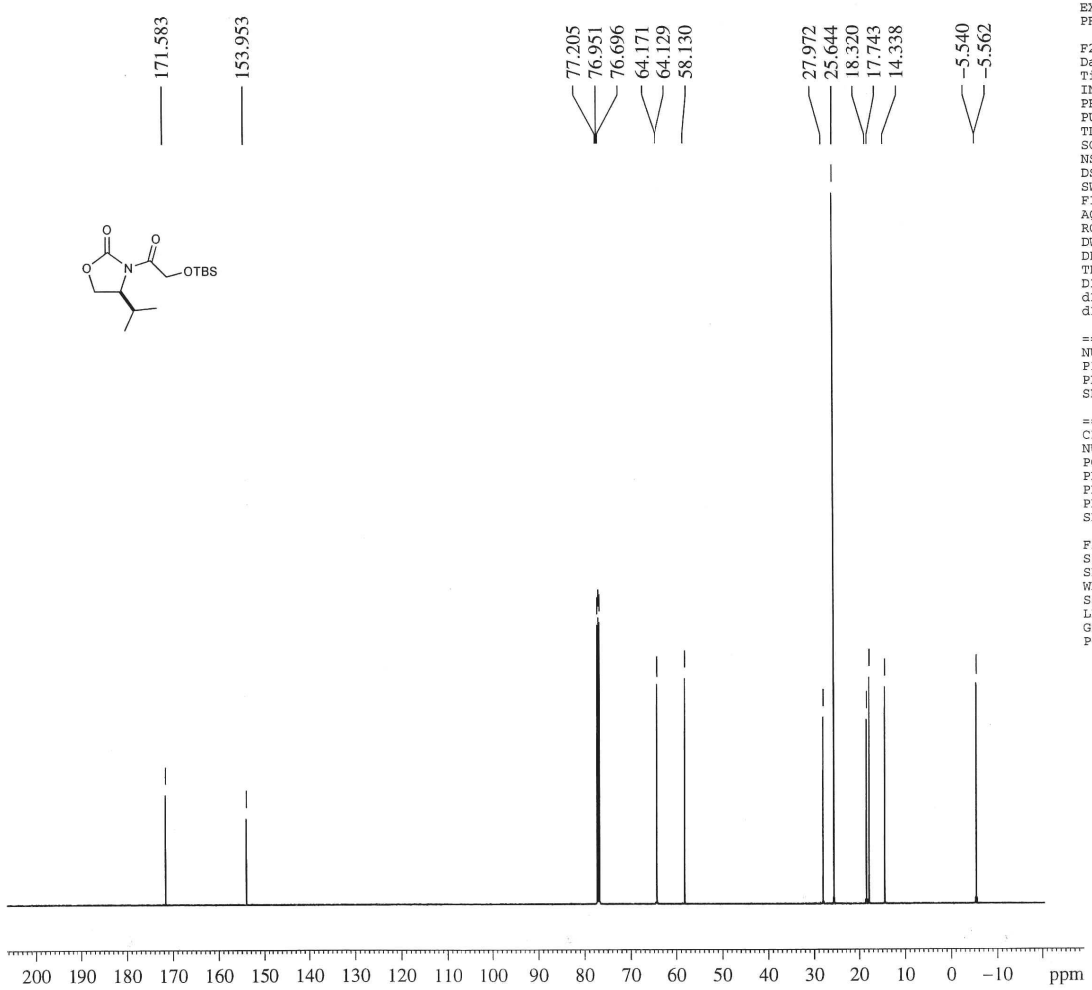
CPDPRG2	waltz16
NUC2	1H
PCPD2	89.00 usec
PL2	-3.00 dB
PL12	14.00 dB
PL13	14.00 dB
SFO2	500.1320005 MHz

F2 - Processing parameters

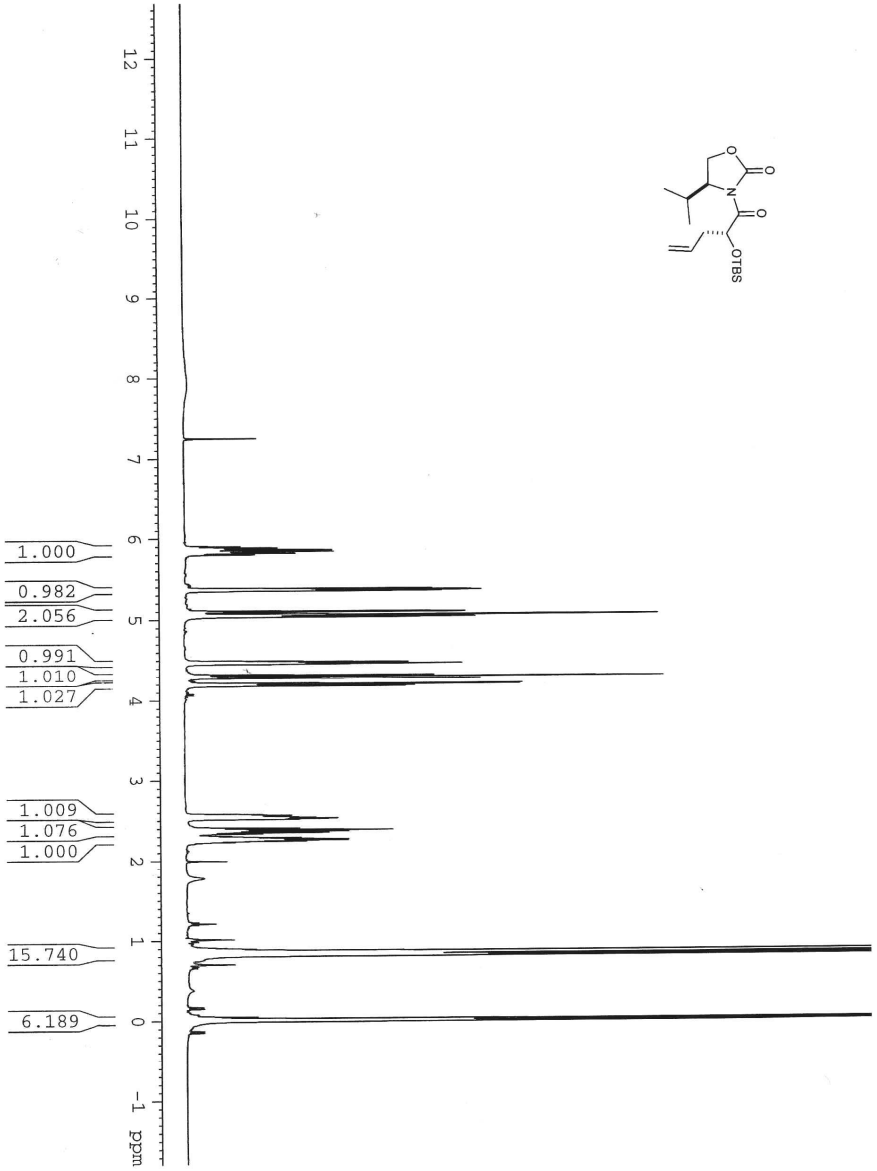
SI	65536
SF	125.7578051 MHz
WDW	EM
SSB	0
LB	0.50 Hz
GB	0
PC	1.40


EM-IV-69
OTBS
1.965
1.028
1.035
1.016
1.000
15.519
6.113
ppm

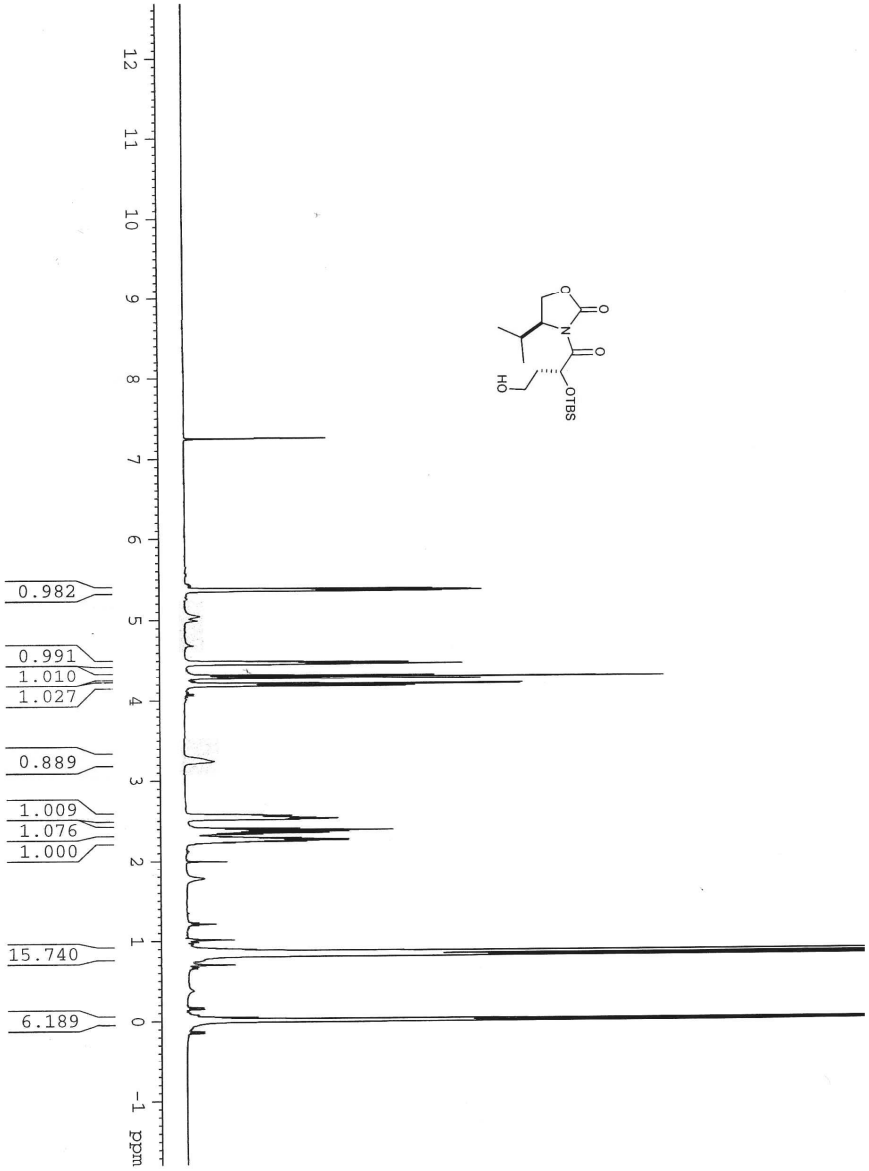
EM-IV-69

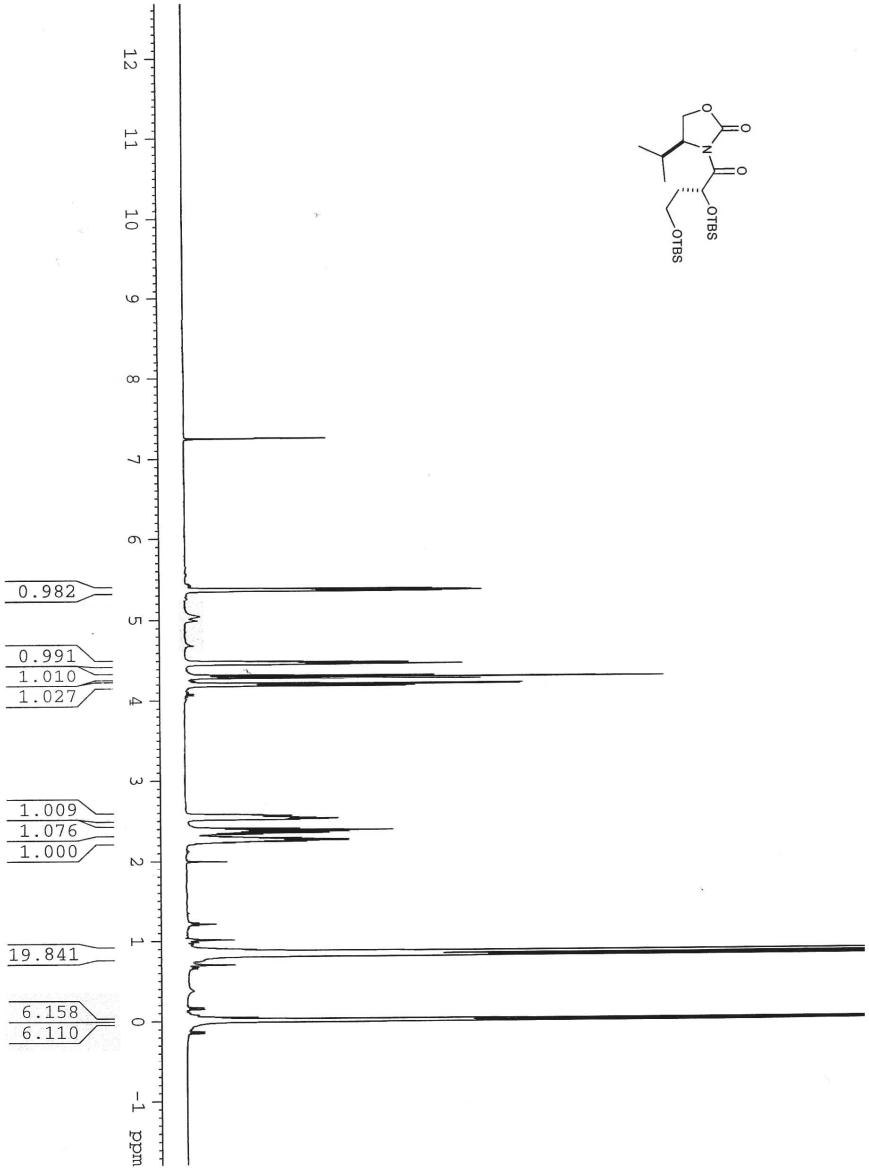


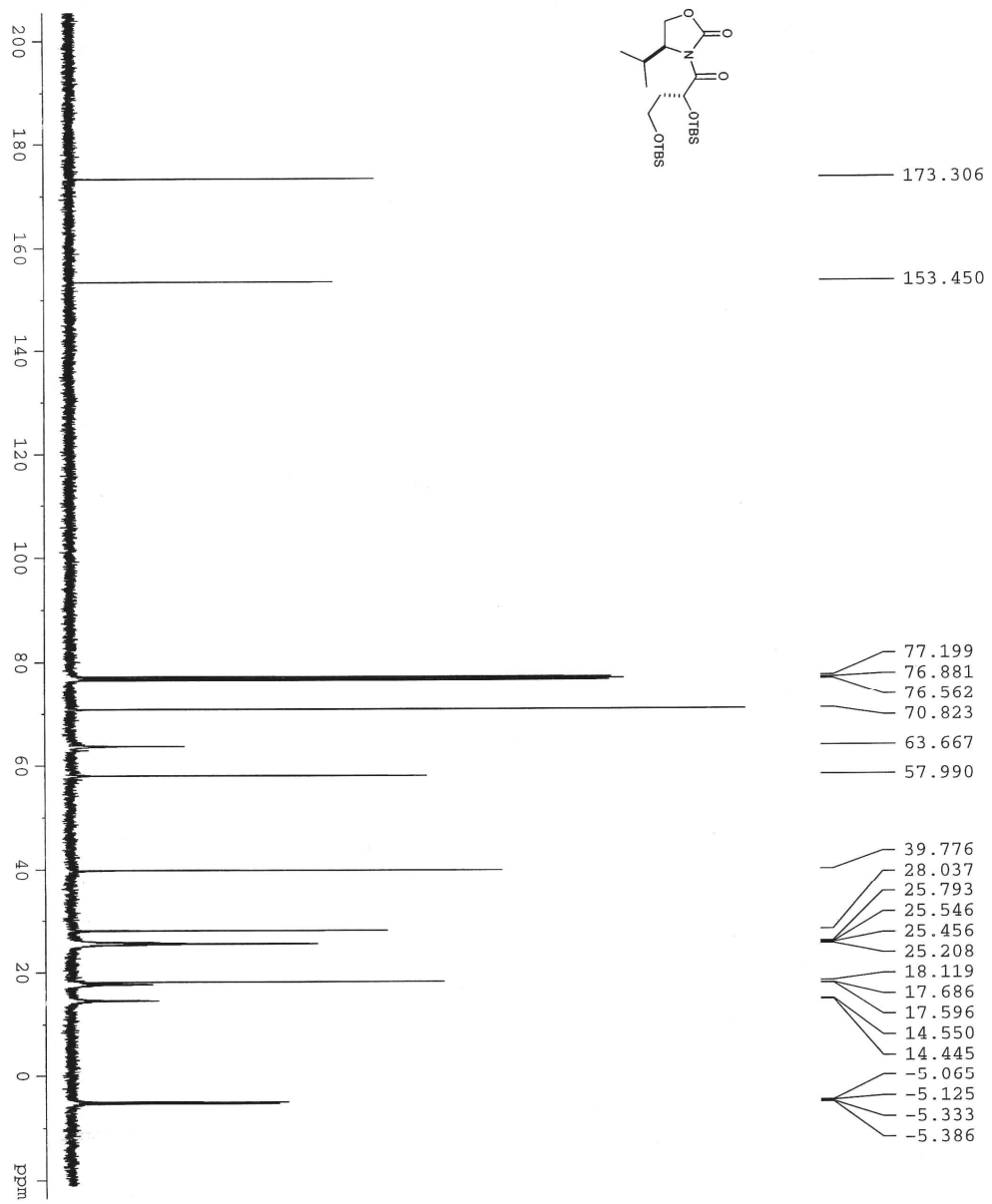

```
Current Data Parameters
NAME                  IV69
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_              20061103
Time                  14.48
INSTRUM               spect
PROBHD      5mm Broadban
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   4801
DS                      2
SWH             30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                14596.5
DW                 16.350 usec
DE                  6.00 usec
TE                293.0 K
D1              1.00000000 sec
d11             0.03000000 sec
d12             0.00002000 sec

============ CHANNEL f1 =======
NUC1                  13C
P1                   6.80 usec
PL1                  0.00 dB
SFO1          125.7735006 MHz

============ CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                  1H
PCPD2               89.00 usec
PL2                 -3.00 dB
PL12                14.00 dB
PL13                14.00 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                  65536
SF            125.7578051 MHz
WDW                   EM
SSB                    0
LB                  0.50 Hz
GB                     0
PC                  1.40
```


OTBS
1.000
0.982
2.056
0.991
1.010
1.027
1.009
1.076
1.000
15.740
6.189
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

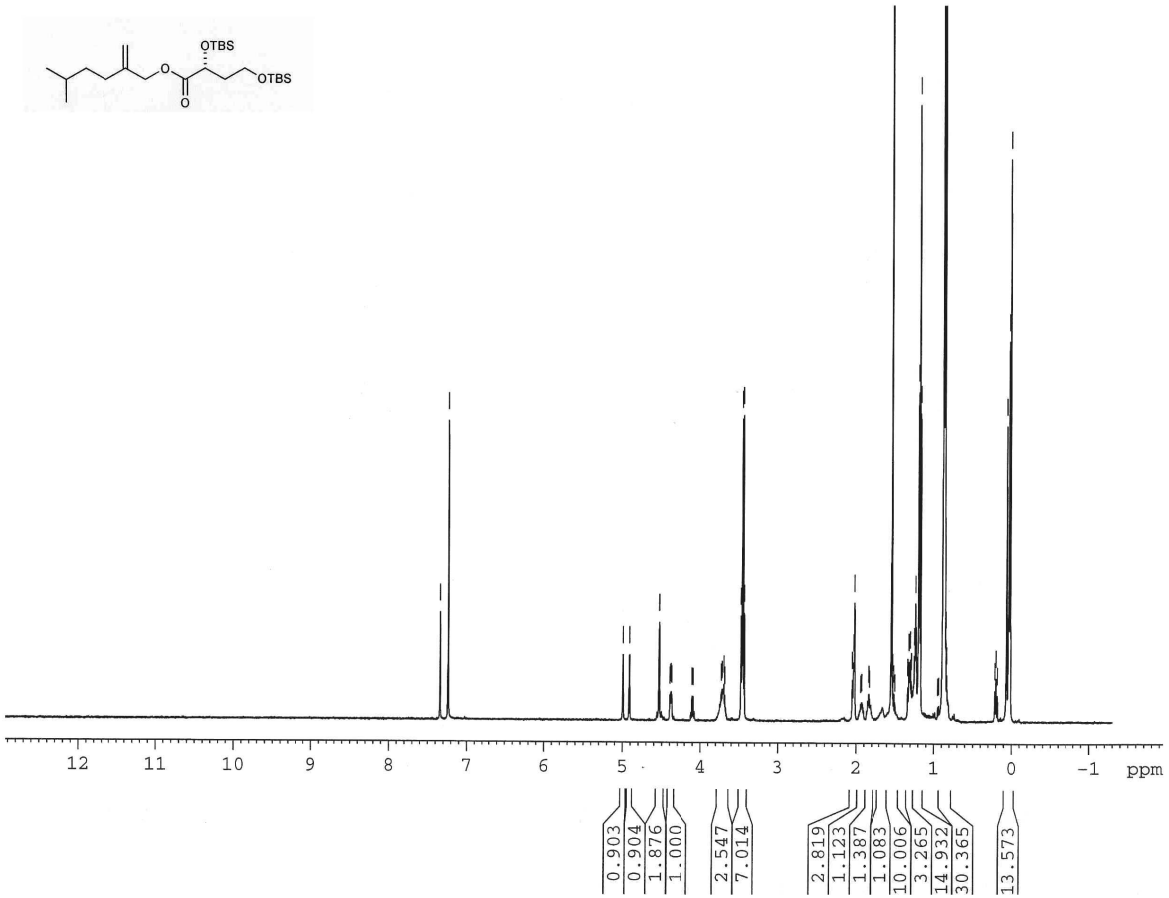
EM-VIII-60

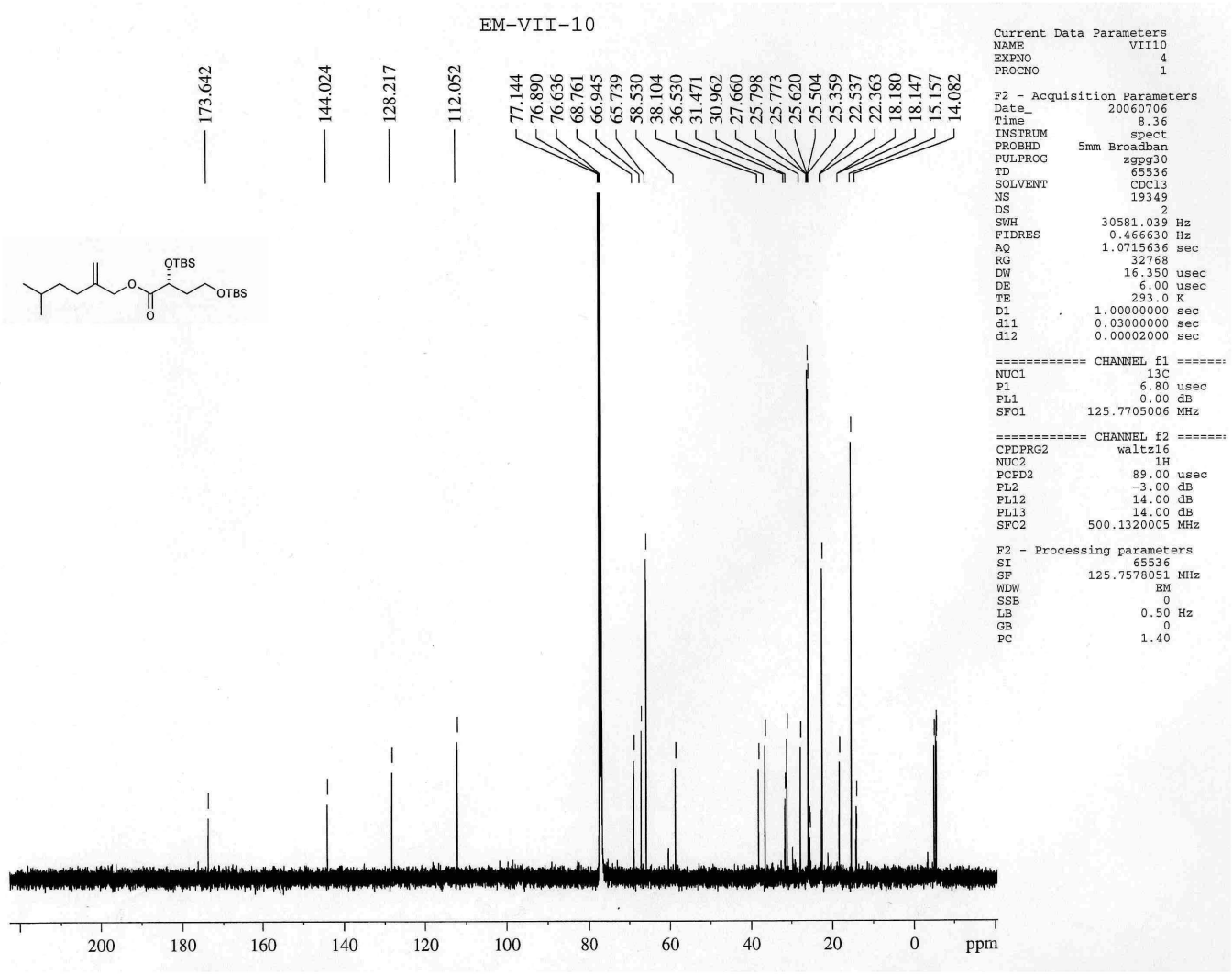

0.982
0.991
1.010
1.027
0.889
1.009
1.076
1.000
15.740
6.189
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
O
O
N
O
O
HO
OTBS

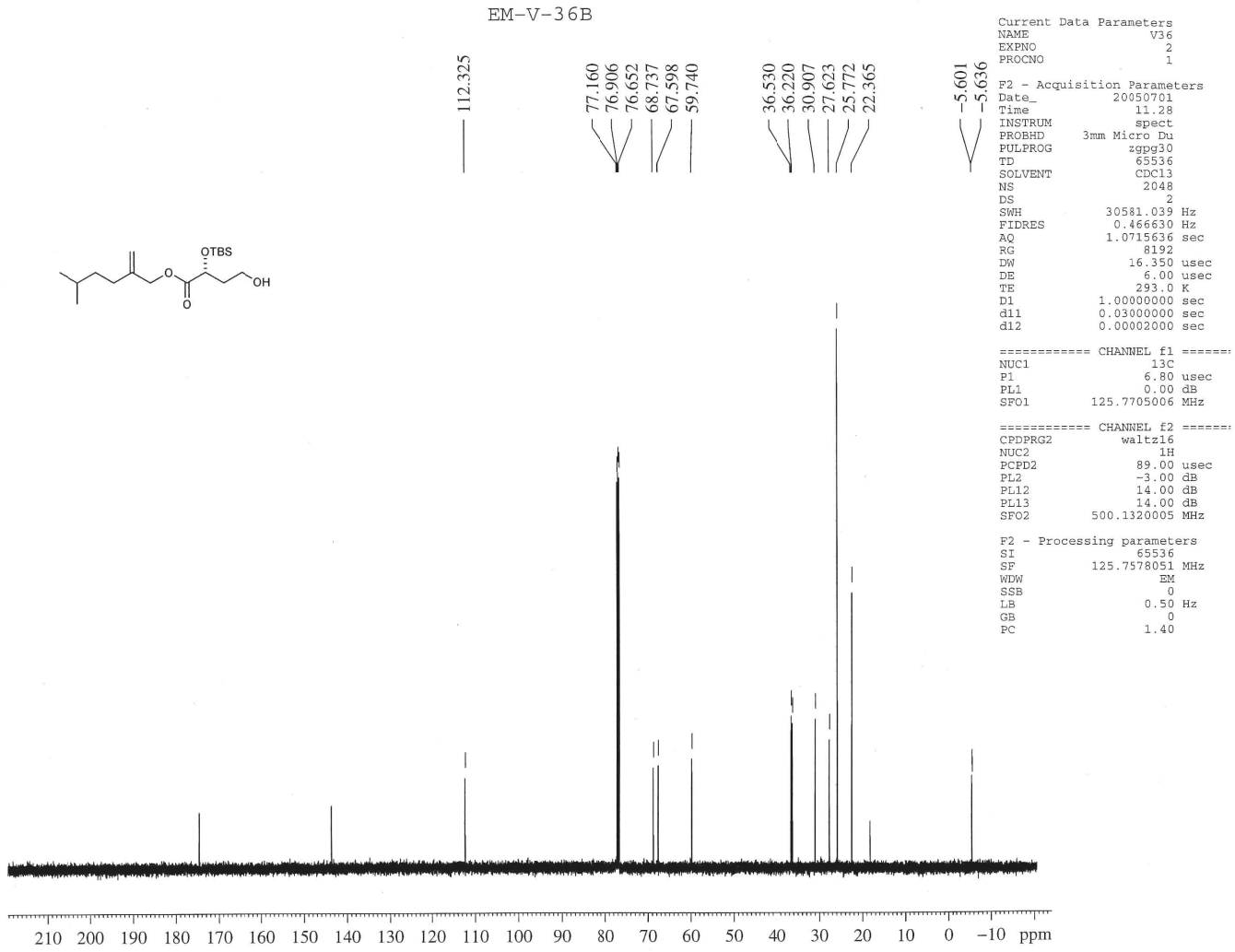

0.982
0.991
1.010
1.027
1.009
1.076
1.000
19.841
6.158
6.110
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
OTBS
OTBS


OTBS
OTBS
173.306
153.450
77.199
76.881
76.562
70.823
63.667
57.990
39.776
28.037
25.793
25.546
25.456
25.208
18.119
17.686
17.596
14.550
14.445
-5.065
-5.125
-5.333
-5.386
200
180
160
140
120
100
80
60
40
20
0
ppm

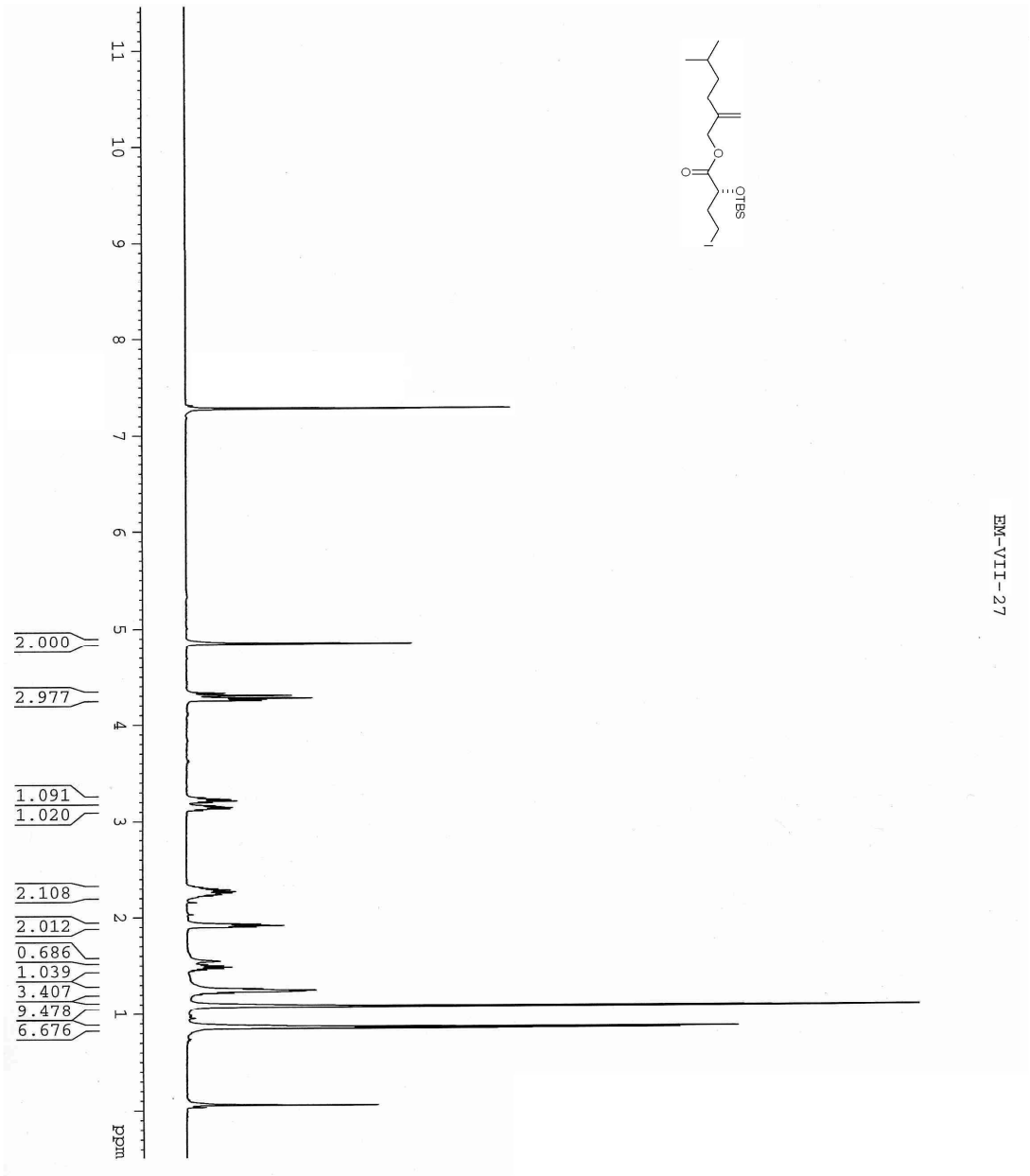
EM-VII-10


OTBS
OTBS
O
O
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
0.903
0.904
1.876
1.000
2.547
7.014
2.819
1.123
1.387
1.083
10.006
3.265
14.932
30.365
13.573

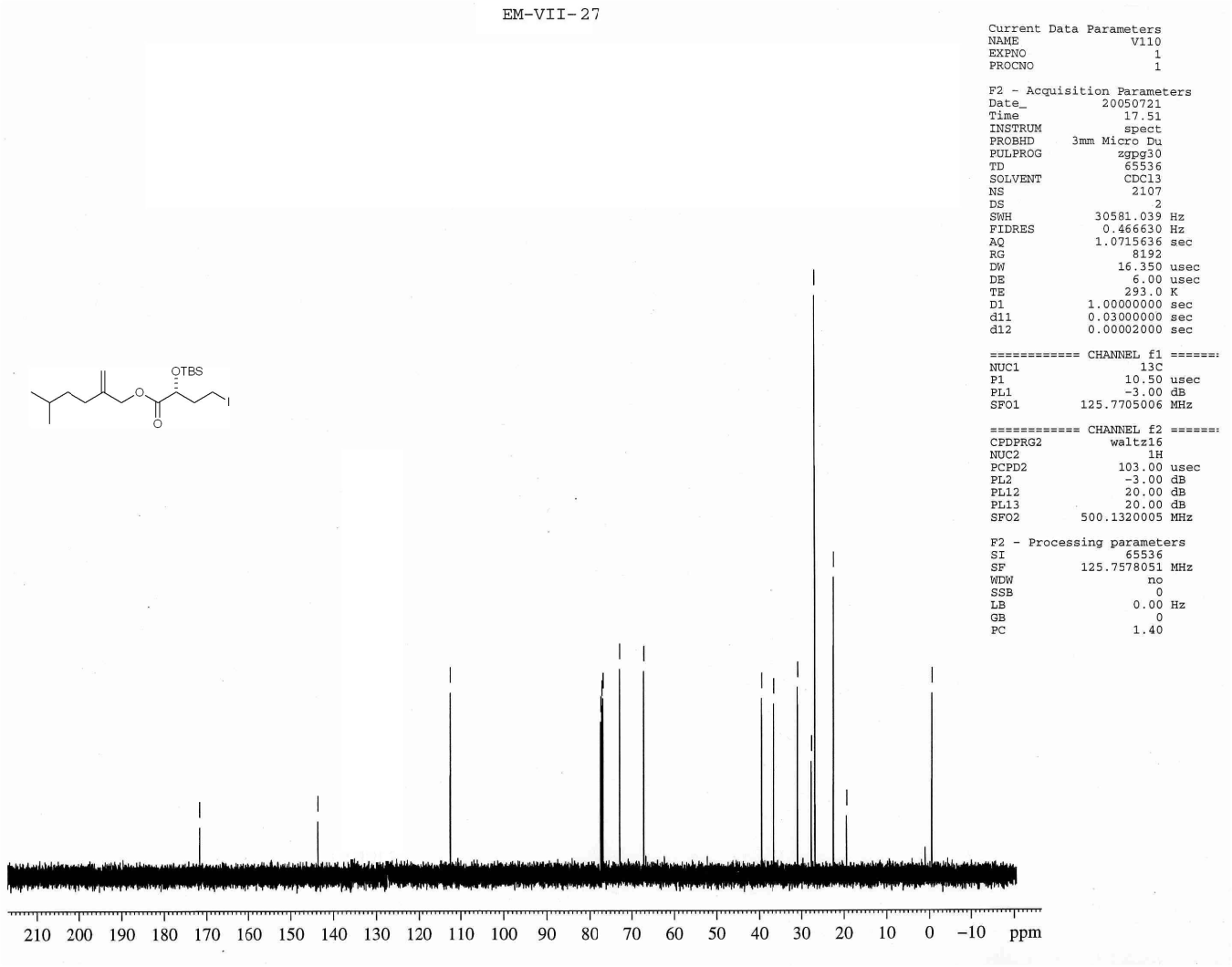

EM-VII-10
173.642
144.024
128.217
112.052
77.144
76.890
76.636
68.761
66.945
65.739
58.530
38.104
36.530
31.471
30.962
27.660
25.798
25.773
25.620
25.504
25.359
22.537
22.363
18.180
18.147
15.157
14.082
OTBS
OTBS
O
O
200
180
160
140
120
100
80
60
40
20
0
ppm
Current Data Parameters
NAME VII10
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060706
Time 8.36
INSTRUM spect
PROBHD 5mm Broadban
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 19349
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 32768
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40



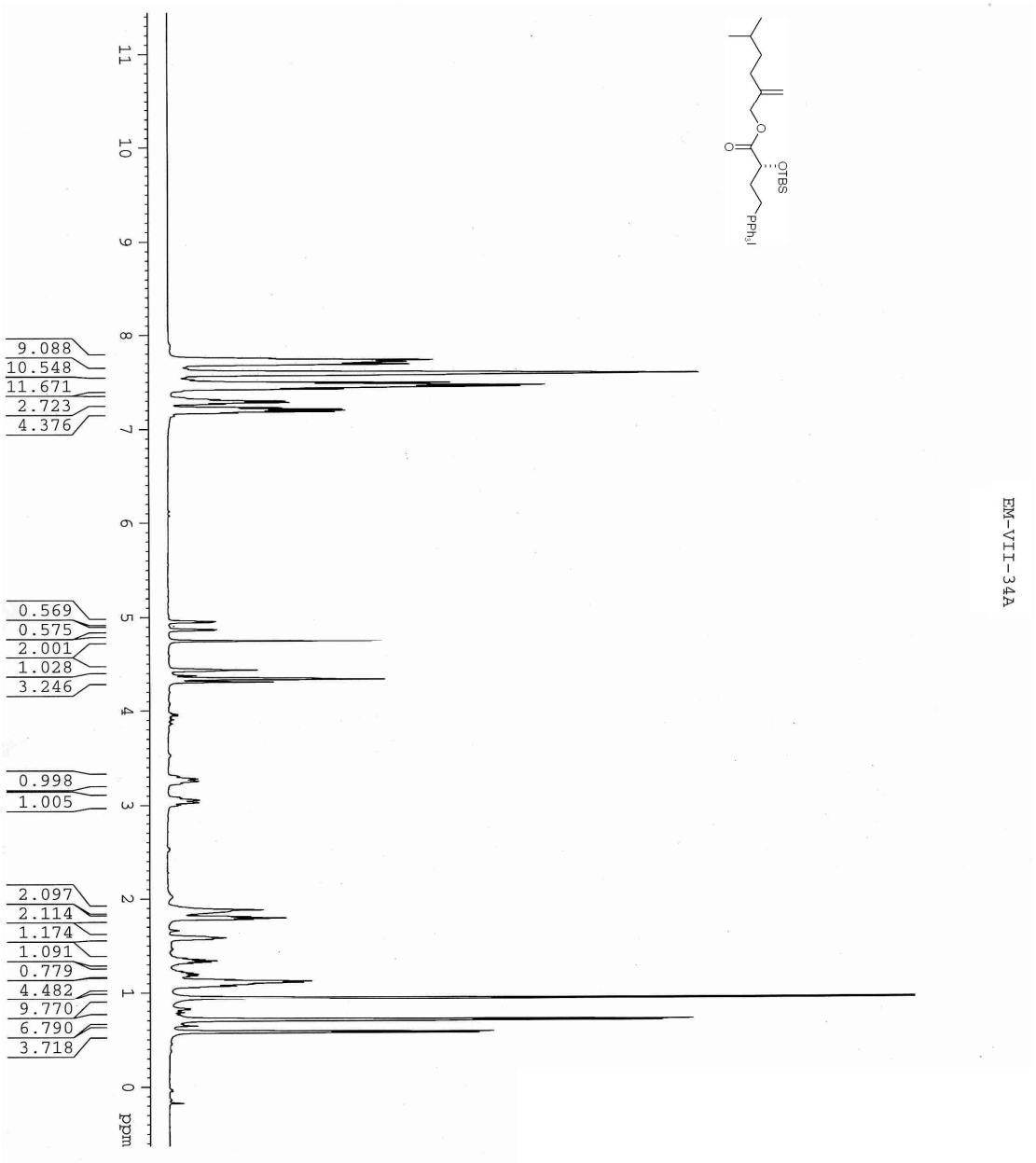

```
Current Data Parameters
NAME                  V36
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20050701
Time                11.28
INSTRUM             spect
PROBHD      3mm Micro Du
PULPROG           zgpg30
TD                 65536
SOLVENT            CDC13
NS                  2048
DS                     2
SWH            30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                  8192
DW                16.350 usec
DE                 6.00 usec
TE                293.0 K
D1             1.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

============ CHANNEL f1 =======
NUC1                  13C
P1                   6.80 usec
PL1                  0.00 dB
SF01         125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                  1H
PCPD2               89.00 usec
PL2                 -3.00 dB
PL12                14.00 dB
PL13                14.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 65536
SF           125.7578051 MHz
WDW                   EM
SSB                    0
LB                  0.50 Hz
GB                     0
PC                  1.40
```


EM-VII-27
OTBS
I
2.000
2.977
1.091
1.020
2.108
2.012
0.686
1.039
3.407
9.478
6.676
ppm

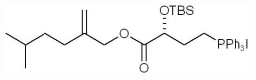
EM-VII-27

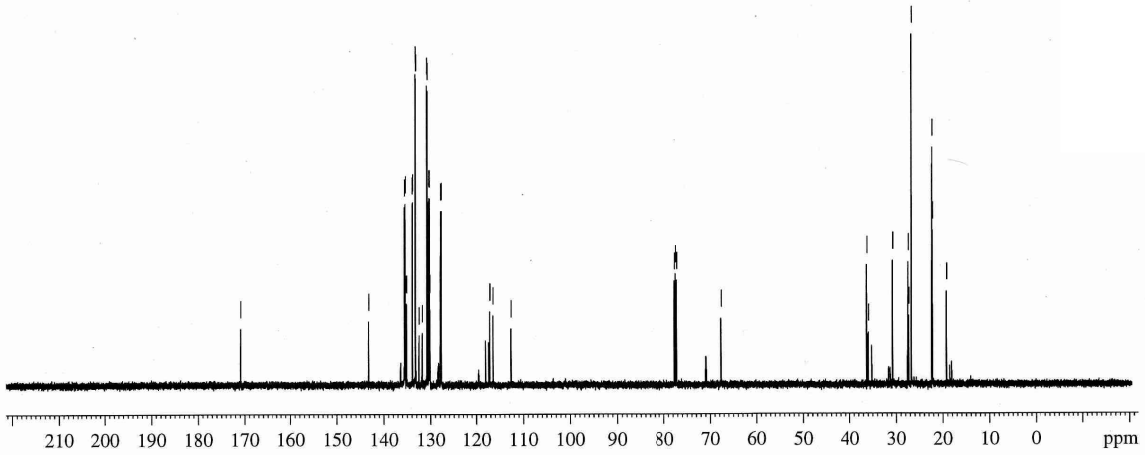


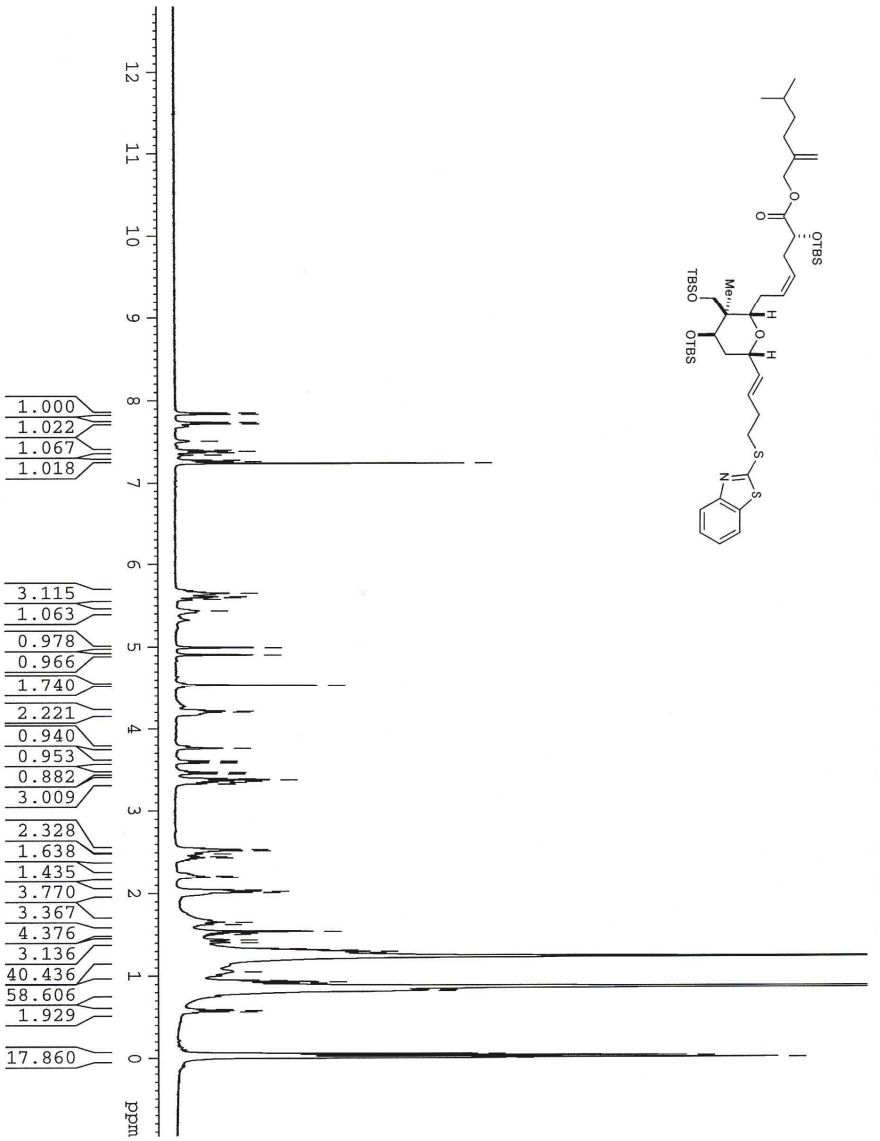

```
Current Data Parameters
NAME                   V110
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_               20050721
Time                   17.51
INSTRUM                spect
PROBHD      3mm Micro Du
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     2107
DS                        2
SWH             30581.039 Hz
FIDRES          0.466630 Hz
AQ              1.0715636 sec
RG                     8192
DW                16.350 usec
DE                 6.00 usec
TE                 293.0 K
D1              1.00000000 sec
d11             0.03000000 sec
d12             0.00002000 sec

============ CHANNEL f1 =======
NUC1                     13C
P1                   10.50 usec
PL1                  -3.00 dB
SFO1          125.7705006 MHz

============ CHANNEL f2 =======
CPDPRG2             waltz16
NUC2                     1H
PCPD2               103.00 usec
PL2                  -3.00 dB
PL12                 20.00 dB
PL13                 20.00 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                    65536
SF            125.7578051 MHz
WDW                      no
SSB                       0
LB                    0.00 Hz
GB                        0
PC                     1.40
```


EM-VII-34A
OTBS
PPh3I
9.088
10.548
11.671
2.723
4.376
0.569
0.575
2.001
1.028
3.246
0.998
1.005
2.097
2.114
1.174
1.091
0.779
4.482
9.770
6.790
3.718
ppm

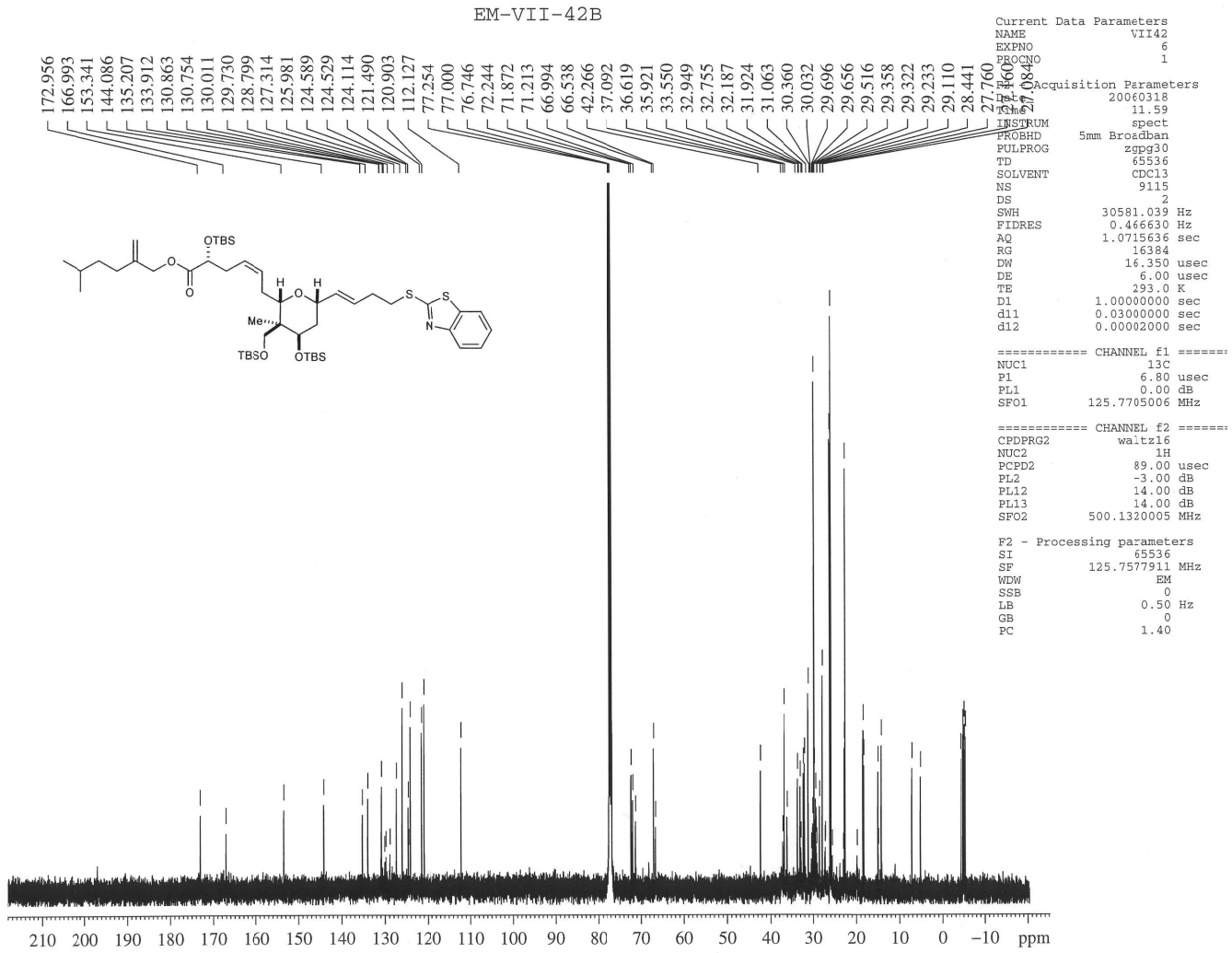
EM-VII-34A


OTBS
O
O
PPh3I


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


1.000
1.022
1.067
1.018
3.115
1.063
0.978
0.966
1.740
2.221
0.940
0.953
0.882
3.009
2.328
1.638
1.435
3.770
3.367
4.376
3.136
40.436
58.606
1.929
17.860
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
OTBS
TBSO
OTBS
Me
O
O
H
H
N
S
S

EM-VII-42B



Current Data Parameters

NAME	VII42
EXPNO	6
PROCNO	1

F2 - Acquisition Parameters

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Time	11.59
INSTRUM	spect
PROBHD	5mm Broadban
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	9115
DS	2
SWH	30581.039 Hz
FIDRES	0.466630 Hz
AQ	1.0715636 sec
RG	16384
DW	16.350 usec
DE	6.00 usec
TE	293.0 K
D1	1.00000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 =======

NUC1	13C
P1	6.80 usec
PL1	0.00 dB
SFO1	125.7705006 MHz

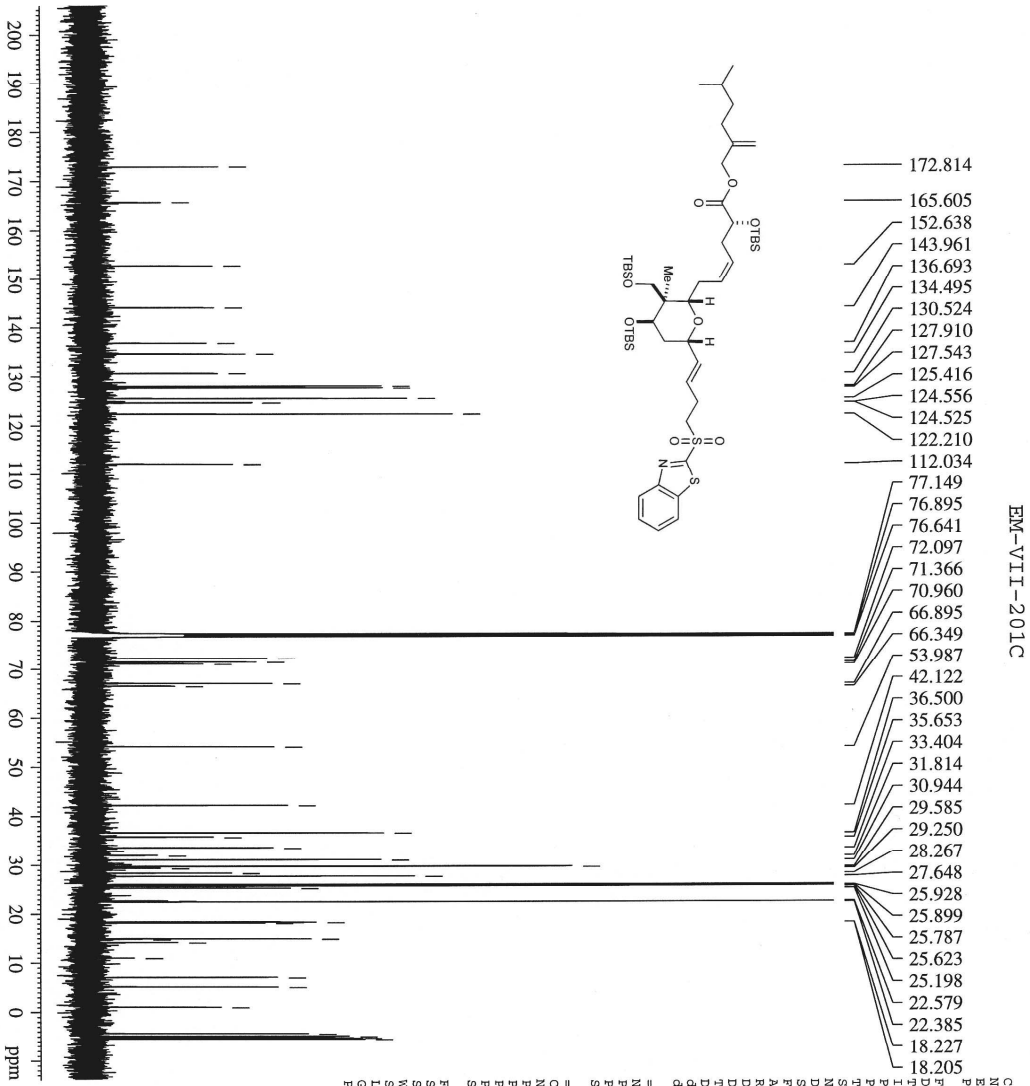
========== CHANNEL f2 =======

CPDPRG2	waltz16
NUC2	1H
PCPD2	89.00 usec
PL2	-3.00 dB
PL12	14.00 dB
PL13	14.00 dB
SFO2	500.1320005 MHz

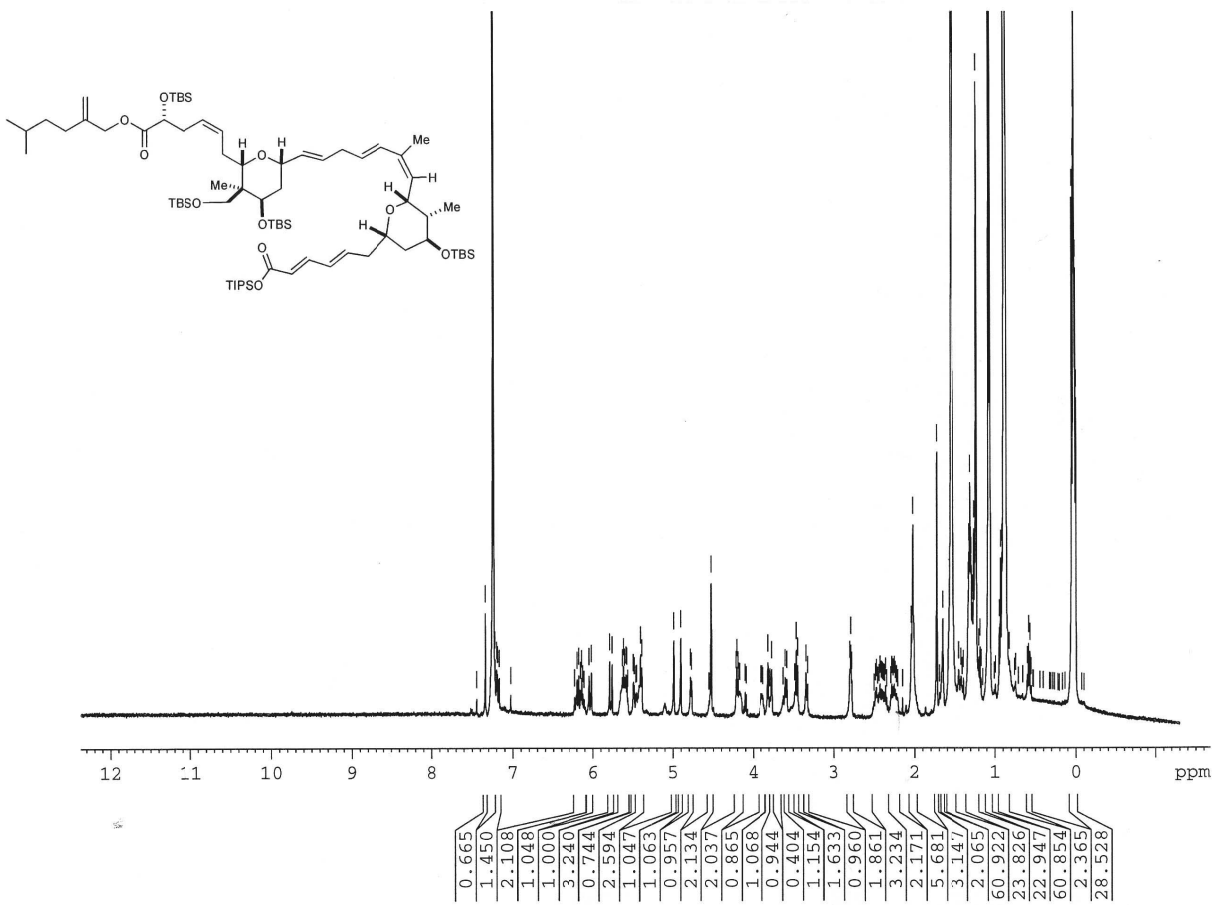
F2 - Processing parameters

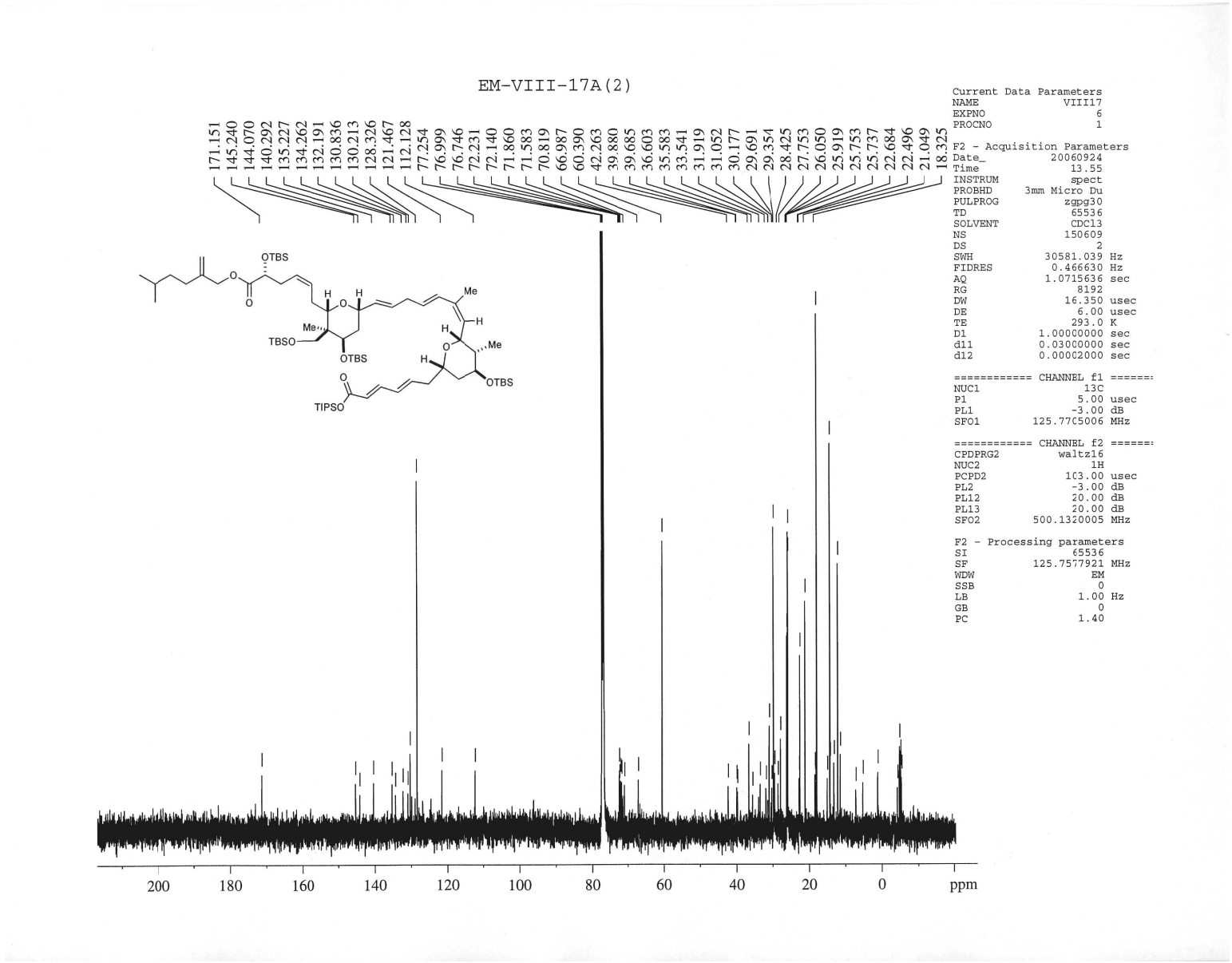
SI	65536
SF	125.7577911 MHz
WDW	EM
SSB	0
LB	0.50 Hz
GB	0
PC	1.40

EM-VII-201
OTBS
TBSO
OTBS
Me
1.000
0.977
2.165
0.389
0.516
3.401
1.197
1.407
1.176
2.333
1.278
1.260
1.160
3.592
1.169
1.171
2.314
2.332
0.741
1.040
2.729
1.030
6.968
5.332
5.367
4.980
43.771
19.826
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


EM-VII-201C
172.814
165.605
152.638
143.961
136.693
134.495
130.524
127.910
127.543
125.416
124.556
124.525
122.210
112.034
77.149
76.895
76.641
72.097
71.366
70.960
66.895
66.349
53.987
42.122
36.500
35.653
33.404
31.814
30.944
29.585
29.250
28.267
27.648
25.928
25.899
25.787
25.623
25.198
22.579
22.385
18.227
18.205
OTBS
TBSO
OTBS
Me
H
O
H
O
O
O
O
S
N
S
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Current Data Parameters
NAME VII201
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060818
Time 20.48
INSTRUM spect
PROBHD 3mm Micro Du
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 38490
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 16384
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
============ CHANNEL f1 ======
NUC1 13C
P1 6.80 usec
PL1 0.00 dB
SFO1 125.7705006 MHz
============ CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 89.00 usec
PL2 -3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7578051 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 1.40

EM-VIII-17A(2)


OTBS
O
O
H
H
O
Me
H
Me
TBSO
OTBS
H
O
Me
H
OTBS
O
TIPSO
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.665
1.450
2.108
1.048
1.000
3.240
0.744
2.594
1.047
1.063
0.957
2.134
2.037
0.865
1.068
0.944
0.404
1.154
1.633
0.960
1.861
3.234
2.171
5.681
3.147
2.065
60.922
23.826
22.947
60.854
2.365
28.528


EM-VIII-17A(2)
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145.240
144.070
140.292
135.227
134.262
132.191
130.836
130.213
128.326
121.467
112.128
77.254
76.999
76.746
72.231
72.140
71.860
71.583
70.819
66.987
60.390
42.263
39.880
39.685
36.603
35.583
33.541
31.919
31.052
30.177
29.691
29.354
28.425
27.753
26.050
25.919
25.753
25.737
22.684
22.496
21.049
18.325
OTBS
TBSO
OTBS
OTBS
TIPSO
Me
Me
Me
H
H
H
H
H
O
O
O
O
200
180
160
140
120
100
80
60
40
20
0
ppm
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NAME VIII17
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PROCNO 1
F2 - Acquisition Parameters
Date_ 20060924
Time 13.55
INSTRUM spect
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 150609
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 8192
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 5.00 usec
PL1 -3.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 103.00 usec
PL2 -3.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577921 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

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