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Biomimetic Total Synthesis of (–)-Arabilin and (±)-Kingianins A, D, F, and H, and An approach to the total synthesis of (±)-Arisugacin A

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Hee Nam Lim

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Hee Nam Lim

We, the dissertation committee for the above candidate for the

Doctor of Philosophy degree, hereby recommend

acceptance of this dissertation.

Kathlyn A. Parker - Advisor
Professor, Department of Chemistry

Isaac Carrico - Chairperson of Defense
Associate Professor, Department of Chemistry

Robert C. Kerber – Third Member
Professor, Department of Chemistry

Yeon-Hee Lim
Associate Principal Scientist at Merck

This dissertation is accepted by the Graduate School

Charles Taber
Interim Dean of the Graduate School

Abstract of the Dissertation

Biomimetic Total Synthesis of (–)-Arabilin and (±)-Kingianins A, D, F, and H, and An approach to the total synthesis of (±)-Arisugacin A

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Chapter 1 demonstrates the total synthesis of (□)-arabilin. (□)-Arabilin is a potent androgen receptor antagonist that was isolated from *Streptomyces* sp. MK756-CF1. We hypothesized that the *enol ether-containing skipped-tetraene* structure of arabilin is formed from a conjugated tetraene system by a thermally allowed, nonenzymatic rearrangement- a [1,7]-hydrogen shift. The feasibility of this transformation was first demonstrated in a model system and subsequently incorporated into the first total synthesis of arablin. The synthesis supports the premise that a [1,7]-hydrogen shift is a nonenzymatic step in the biosynthesis of arabilin.

Chapter 2-4 demonstrate the total synthesis of some members of kingianins. The kingianins, a family of structurally complex polyketides, were isolated from the species Endiandra kingiana. They are reported to have low- to mid-micromolar binding to the antiapoptotic protein Bcl-xL. All of the kingianins share a pentacyclic core, itself believed to be the Diels-Alder dimer of

monomeric bicyclooctadienes. We proposed that, in nature, the Diels-Alder dimerization proceeds by a cation radical-mediated reaction (presumably photo-initiated). In addition, the regioselectivity and stereoselectivity of the Diels-Alder reaction is presumed to result from steric factors in the transition state for cycloaddition. In the synthesis of kingianin A, we used a tether-mediated *intramolecular* reaction to control the regioselectivity of the Diels-Alder reaction and to avoid difficulty during separation. Then kingianin A was prepared by a double homologation method from the endo RCDA diol. We postulated that the isomeric diols in the kingianin series might have usefully different chromatographic behaviors. Indeed, the *intermolecular* RCDA dimerization of the endo and exo bicyclooctadienes afforded separable endo diols that corresponded to kingianins D, F, and H. With the same double-homologation methods, the synthesis of kingianins D and F were completed. Manchand's three-carbon homologation was adapted to prepare kingianin H.

Chapter 5-7 demonstrate the synthetic approach of (±)-Arisugacin A. (±)-Arisugacin A is a potent inhibitor of acetylcholinesterase (Ache). We designed a synthesis based on a polyene cyclization and a Tamao oxidation. Thus, we have studied the catalytic polyene cyclization of the substrates containing vinyl silanes. In addition, we sought the stereoselective synthesis of (E)-vinyl silanes by a relay-ring closing metathesis reaction.

To Yeongah Choi

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List of Abbreviations

α	alpha
[α]	specific rotation
β	beta
γ	gamma
δ	delta
π	pi bond or orbital
π*	antibonding pi orbital
hv	light
σ	sigma
^{o}C	Celcius degree
Å	Angström
Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Aq.	Aqueous
Ar	Aryl
Atm	Atmosphere
br d	Broad doublet
Bn	Benzyl
br s	Broad singlet
bp	Boiling point
Bz	Benzoyl
Calcd	Calculated
CDI	1,1'-Carbonyldiimidazole
CM	Cross metathesis
cm^{-1}	Reciprocal Centimeter
COSY	Homonuclear proton-proton correlated spectroscopy
d	Doublet
dd	Doublet of doublet
dq	Doublet of quartet
dt	Doublet of triplet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DIBAL-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	N,N-Dimethylaminopyridine
DME	Dimethoxyethane

DMF	N,N-Dimethylformamide
DMP	Dess-Martin periodinane
Ea	Activation energy
ee	Enantiomeric excess
EI	Electron-impact
eq.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
g	Gram
G II	Grubbs second generation catalyst
G-H II	Grubbs-Hoveyda second generation catalyst
h	Hour(s)
HMBC	Heteronuclear multiple bond correlation
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexametylphosphoramide
HMQC	Heteronuclear multiple quantum coherence
HRMS	High resolution mass spectrometry
Hz	Hertz
IC_{50}	Concentration for 50% inhibition
Imid.	Imidazole
^{i}Pr	Isopropyl
IR	Infrared spectroscopy
in vacuo	Under vaccum
J	First order coupling constant
K	Kelvin
KHMDS	Potassium 1,1,1,3,3,3-hexamethyldisilazide
L	Liter
LDA	Lithium diisopropylamine
LG	Leaving group
$LiAlH_4$	Lithium aluminium hydride
LiHMDS	Lithium 1,1,1,3,3,3-hexamethyldisilazide
m	Multiplet
m-CPBA	Meta chloro perbenzoic acid
MDR	Multi-drug resistance
Me	Methyl
MEM	Methoxyethoxylmethyl
mg	Milligram

MHz	Mega hertz
min	Minute
mL	Milliliter
mmol	Millimole
mol	Mole
MOM	Methoxymethyl
mp	Melting point
MS	Mass spectroscopy
Ms	Methansulfonyl
m.z	Mass-charge ratio
NaHMDS	Sodium 1,1,1,3,3,3-hexamethyldisilazide
NMO	4-Methylmorpholine N-oxide
NMP	1-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
Ns	p-Nitrobenzenesulfonyl
Ph	Phenyl
PhH	Benzene
Pip	Piperonyl
ppm	Parts per million
Py	Pyridine
q	Quartet
RCM	Ring closing metathesis
RCDA	Radical cation Diels-Alder
Rf	Retention factor
RRCM	Relay Ring Closing metathesis
Rt	Retention time
r.t.	room temperature
s	Singlet
t	Triplet
tq	Triplet of quartet
TBAF	Tetrabutylammonium fluoride
TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
Tf	Trifluoromethane sulfonate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	para-toluenesulfonyl

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List of Schemes

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Publications

• Hee Nam Lim and Kathlyn A. Parker, “Total Synthesis of Kingianin A”, *Org. Lett.* **2013**, *15*, 398-401.
• Hee Nam Lim and Kathlyn A. Parker, “Total Synthesis of the Potent Androgen Receptor Antagonist (−)-Arabilin: A Strategic, Biomimetic [1,7]-Hydrogen Shift”, *J. Am. Chem. Soc*. **2011**, *133*, 20149-20151.

Chapter 1

Total Synthesis of Arabilin

1.1 Introduction

1.1.1 Isolation and structure determination of (-)-arabilin

In 2010, (-)-arabilin (**1**) (Figure 1) was isolated by the Imoto group from Streptomyces sp. MK756-CF1 during a screen for androgen receptor (AR) antagonists.[1] Arabilin competitively blocks binding of dihydrotestosterone (DHT) to the AR with an IC50 of 11 μM and inhibits DHT-induced expression of prostate specific antigen mRNA in LNCaP cells. Arabilin was produced by fermentation in liquid state of pressed wheat (2.4 Kg). The culture was then extracted with ethyl acetate and the extract was submitted to column chromatography. Preparative ODS (octadecasilyl) HPLC gave arabilin (3.3 mg) with its congeners, spectinabilin (3.0 mg) and SNF4435C (6.0 mg). The physicochemical properties are as shown on Table 1-1.[1]

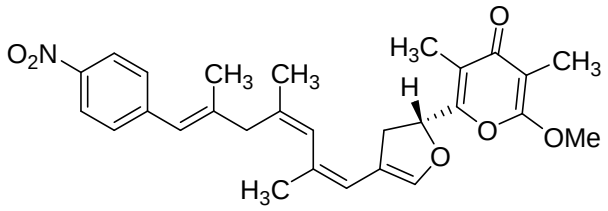


Figure 1-1. Arabilin (**1-1**)

The structure of arabilin was determined by a combination of spectroscopic techniques including HMQC, HMBC, and NOE NMR methods. Although the configuration at C-6 was not determined, we initially assumed this to be (*R*) by analogy to that of its congeners.

[1] Isolation and Structure elucidation of a novel androgen antagonist, arabilin, produced by *Streptomyces* sp. MK756-CF1. Kawamura, T.; Fujimaki, T.; Hamanaka, N.; Torii, K.; Kobayashi, H.; Takahashi, Y.; Igarashi, M.; Kinoshita, N.; Nishimura, Y.; Tashiro, E.; Imoto, M. *J. Antibiot.* **2010**, *63*, 601-605.

Table 1-1. Physicochemical properties of (-)-arabilin

Appearance	Pale yellow powder
Molecular formula	$C_{28}H_{31}NO_6$
Molecular weight	477
HRESI-MS (m/z, Positive)	
calcd	478.2224
Found	478.2215
Optical rotation $[\alpha]_D$	-166.2° (c 0.13, $CHCl_3$, 25 °C)
IR Vmax (cm-1) (KBr)	2956, 2854, 1666, 1597, 1516, 1342
UV vmax (nm)	263 (18400), 315 (sharp, 10300) (MeOH)
TLC (R_F)[a]	0.68
HPLC (Retention time, min)[b]	25.2 (85 % MeOH)
Solubility	
Soluble	$CHCl_3$, MeOH
Insoluble	n-hexane, H_2O

[a]Silica gel TLC (Kieselgel 60F254; Merck); mobile phase, n-hexane-EtOAc (1:2).
[b]Column, SunFire ODS (Waters, 5 mm, 4.6□250mm); mobile phase, aqMeOH; flow

Androgen receptor (AR) is a type of nuclear receptor that plays a critical role in male sexual function. “AR interacts with androgen response element that regulates the target gene transcription related to the prostate cancer”.[2] Thus, androgen receptor antagonists are considered to be potential prostate cancer drugs. Currently, there are two major AR antagonists: steroidal and nonsteroidal compounds. The drawback of the steroidal antagonists is that they don’t usually have selective activity for prostate cancer because they have cross-reactivity with other steroid hormone nuclear receptors.[2] In addition, treatments by nonsteroidal drugs including commercial flutamid and bicalutamide have resulted in resistant cancer cells and induce hormone-refractory prostate cancer.[3] Therefore, the exploration and development of new AR antagonists without side-effect are important in the prostate cancer research.[4]

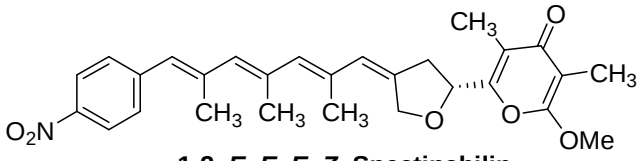
[2] Increase of androgen-induced cell death and androgen receptor transactivation by BRCA1 in prostate cancer cells. Yeh, S.; Hu, Y. C.; Rahman, M.; Lin, H. K.; Hsu, C. L.; Ting, H. J.; Kang, H. Y.; Chang, C. *Proc. Natl. Acad. Sci.* **2000**, *97*, 11256–11261.

[3] The antiandrogen bicalutamide promotes tumor growth in a novel androgen-dependent prostate cancer xenograft model derived from a bicalutamide-treated patient. Yoshida, T. et al. *Cancer Res*. **2005**, *65*, 9611-9616.

[4] Targeting continued androgen receptor signaling in prostate cancer. Massard, C.; Fizazi, K. *Clin.*

1.1.2 Congeners, Bisosynthetic Proposals, and Biomimetic Retrosynthesis

Sepctinabilin (**1-2**) (Figure 1-2) and SNF4435 C (**1-7a**) were isolated with arabilin from the same organism. Spectiinabilin is reported to be a weak inhibitor of Rauscher leukemia virus reverse transcriptase [5] and SNF4435 C is preported to be a potent immunosuppressant. [6]. Spectinabilin has a fully conjugated linear *E*,*E*,*E*,*Z*-tetraene. However, SNF 4435 C (**1-7a**) and 4435 D (**1-7b**) have a bicyclo[4.2.0]octadiene core. The SNF compounds are believed to be derived from *E*,*Z*,*Z*,*Z* or *Z*,*Z*,*Z*,*E*-tetraene **1-5** by thermal conrotatory 8π, disrotatory 6π tandem electrocyclization (Scheme 1-1).[7]



1-2 ***E, E, E, Z*** **Spectinabilin**

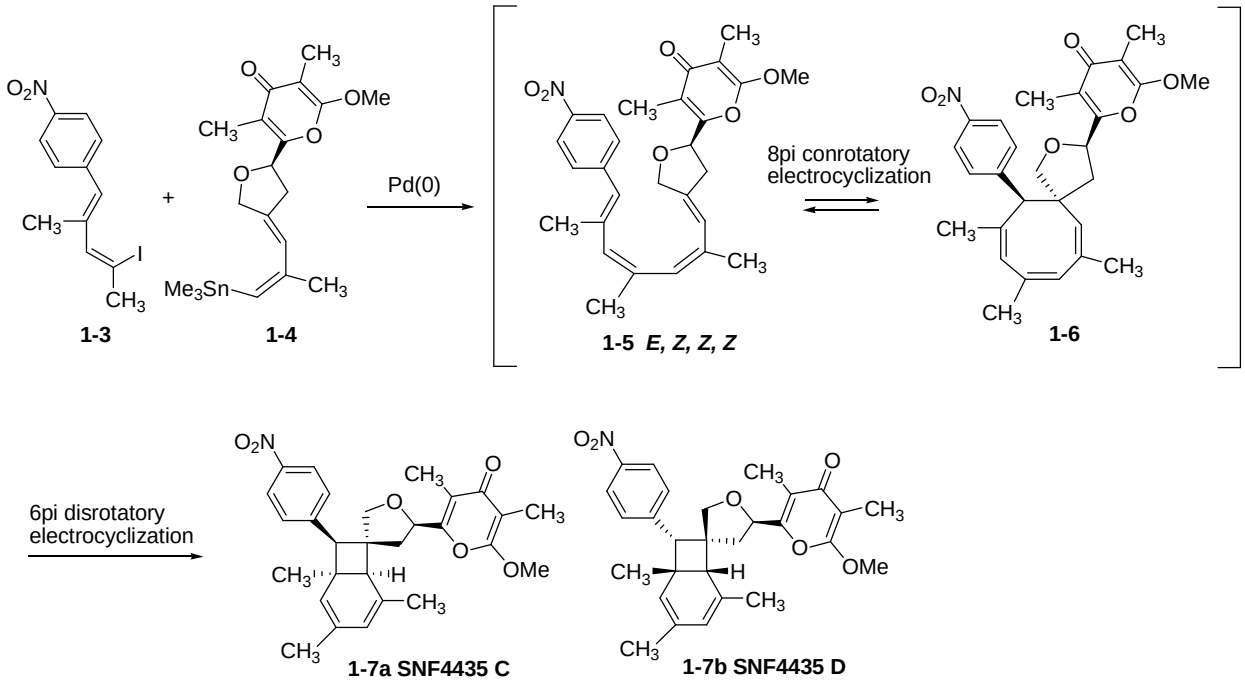
Figure 1-2. Spectinabilin (**1-2**)

Cancer Res. **2011**, *17*, 3876-3883.

[5] Spectinabilin, a new nitro-containing metabolite isolated from Streptomyces spectabilis. Kakinuma, K.; Hanson, C. A.; Rinehart, K. L. Jr. *Tetrahedron*, **1976**, *32*, 217-222.

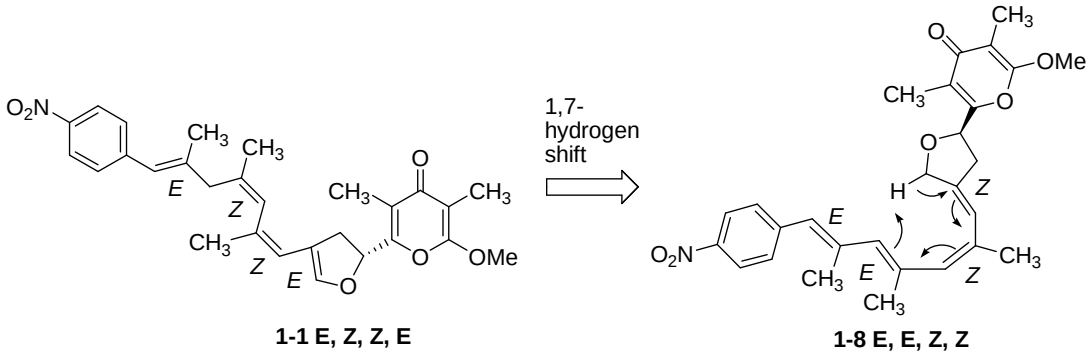
[6] SNF4435C and D, novel immunosuppressants produced by starain of Streptomyces spectanilis. I. Taxonomy, fermentation, isolation and biological activities. Kurosawa, K.; Takahashi, K. Tsuda, E. *J. Antibiot*. **2001**, *54*, 541-547.

[7] (a) Synthetic Studies toward SNF4435 C and SNF4435 D. Beaudry, C. M.; Trauner, D. *Org. Lett*. **2002**, *13*, 2221–2224. (b) Studies on the Biomimetic Synthesis of SNF4435 C and D. Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett*. **2002**, *4*, 3731–3734. (c) “Endo” and “Exo” Bicyclo[4.2.0]-octadiene Isomers from the Electrocyclization of Fully Substituted Tetraene Models for SNF 4435C and D. Control of Stereochemistry by Choice of a Functionalized Substituent. Parker, K. A.; Lim, Y.-H. *Org. Lett*. **2004**, *6*, 161–164.



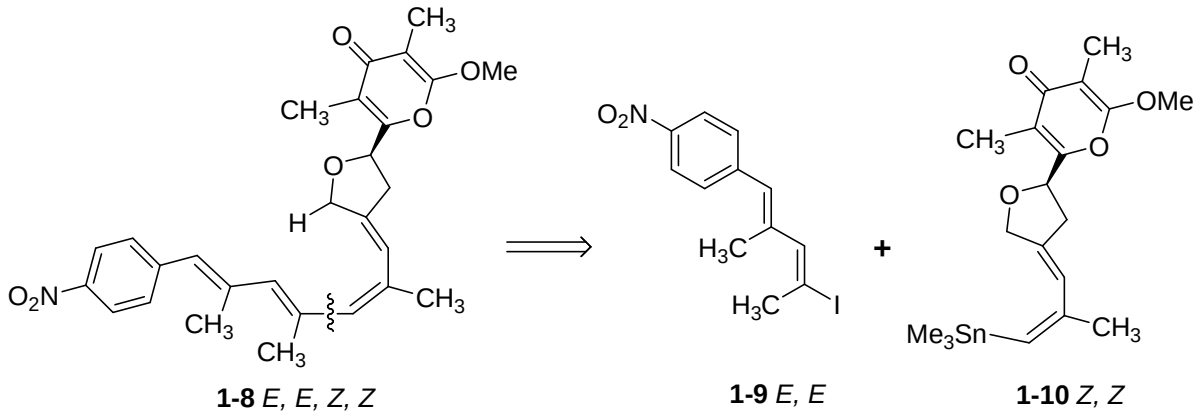
Scheme 1-1. Spectinabilin, SNF4435 C (**1-7a**) and SNF4434 D (**1-7b**)

We were intrigued by the possibility that, in nature, the enol ether-containing, skipped polyene system of arabilin is formed from a conjugated tetraene system by another thermally allowed, non-enzymatic rearrangement - in this case, a [1,7]-hydrogen shift. A thermal, [1,7]-hydrogen shift is, in principle, available to conjugated *E, Z, Z, Z*-tetraene such as **1-5;** however the 8π electrocyclization is facile in this system. Alternatively, arabilin, but not the SNF compounds, could be formed from the *E, E, Z, Z* isomer **1-8**. The helical transition state required for a [1,7]-antarafacial hydrogen shift is available to isomer **1-8**. However, that required for the 8 π electrocyclization is not available to isomer **1-8**. Therefore we considered tetraene **1-8** to be a potential biogenetic and synthetic precursor of arabilin (Scheme 1-2).



Scheme 1-2. Synthetic precursor of arabilin (**1-1**)

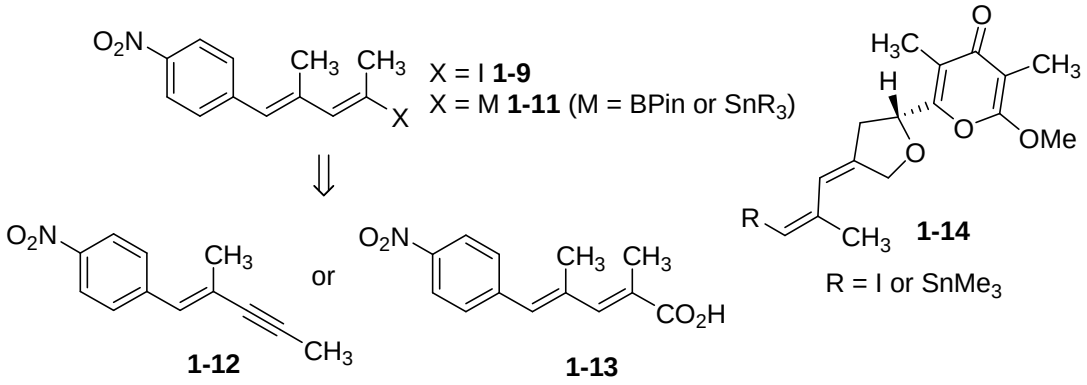
To evaluate our biomimetic synthesis, we needed two pieces: *E,E*-iododiene **1-9** and *Z,Z*-stannyldiene **1-10** containing 2-pyranofuran shown in scheme 1-3. We thought that coupling of the two pieces under palladium catalyst would give intermediate, *E,E,Z,Z* tetraene **1-8** (Scheme 1-3).



1-8 *E, E, Z, Z* **1-9** *E, E* **1-10** *Z, Z*

Scheme 1-3. Retrosynthesis of the key intermediate **1-8**

We initially designed iododiene **9** or its equivalents (metalladienes) **11** in the following ways: (1) from an internal alkyne **12** by hydroboration, hydrozyrconation/iodination, stannylcupration or hydrostannylation or (2) from a carboxylic acid **13** by the decarboxylative iodination (Scheme 1-4). Meanwhile, the synthesis of the other coupling partner, γ-pyrones **14**, is known.[8]



Scheme 1-4. Retrosynthesis of coupling partners **1-9**, **1-11** and **1-14**

[8] The Total Synthesis of (-)-SNF4435 and (+)-SNF4435. Parker, K. A.; Lim, Y. -H. *J. Am. Chem. Soc.* **2004**, *126*, 15968-15969.

1.1.3 [1,7]-Hydrogen shift: theory and stereochemistry

As one of the thermal isomerizations predicted to follow the rules of orbital symmetry, the [1,7]-hydrogen shift has been extensively studied by theory and by experimental for several decades.[9] For example, vitamin D has been prepared by the biomimetic thermal [1,7]-hydrogen shift through a cyclic transition state.[10] The computational study by Panciř[9b] demonstrated that the cyclic transition state of (3Z, 5Z)-1,3,5-heptatriene has a distorted C_{2v} symmetry during the hydrogen migration (Figure 1-3).

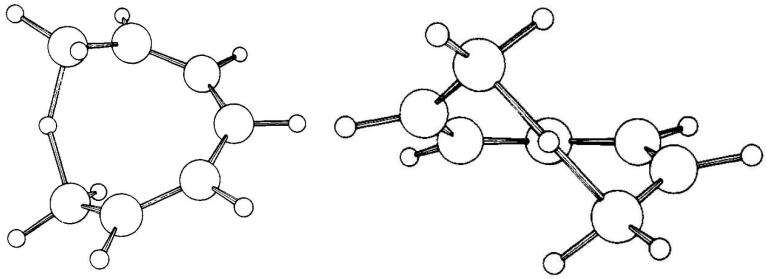
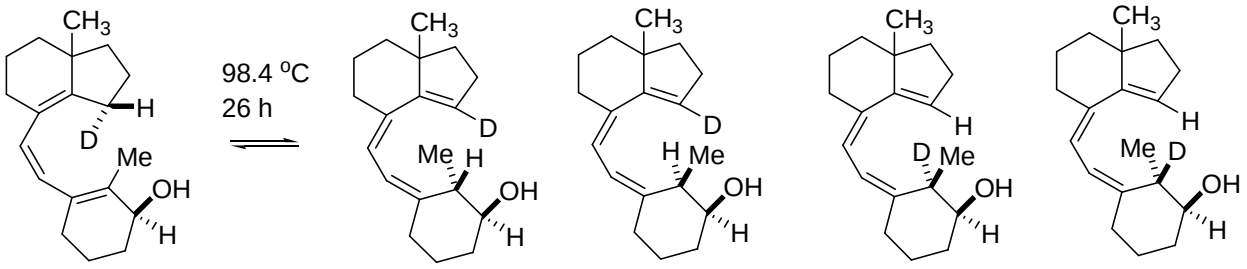


Figure 1-3. ORTEP drawing of the transition structure (C2) of [1,7]-hydrogen shift in 1,3,5-heptatriene from different perspectives

[9] a) Selection Rules for Sigmatropic Reactions. Woodward, R. B.; Hoffman, R. *J. Am. Chem. Soc*. **1965**, *87*, 2511-2513. b) Theoretical Studies of [1,n]-Sigmatropic Rearrangements Involving Hydrogen Transfer in Simple Methyl-Substituted Conjugated Polyenes. Hess, B. A.; Schaad, L. J.; Panciř, J. *J. Am. Chem. Soc*. **1985**, *107*, 149-154. c) Kinetics and Deuterium Kinetic Isotope Effects for the Thermal [1,7] Sigmatropic Rearrangements of *cis,cis*-1,3,5-Octatriene. Baldwin, J. E.; Reddy, P. *J. Am. Chem. Soc*. **1987**, *87*, 8051-8056. d) A Detailed Theoretical Analysis of the 1,7-Sigmatropic Hydrogen Shift: The Möbius Character of the Eight Electron Transition Structure. Jiao, H.; Schleyer, R. *Angew. Chem. Int. Ed. Eng*. **1993**, *32*, 1763-1765.

[10] Remarks on the specificities of the photochemical and thermal transformations in the vitamin D field. Havinga, E.; Schlatmann, M. A. *Tetrahderon* **1961**, *16*, 146-152

The stereochemistry of the [1,7]-H shift has been studied by deuterium labeling experiments with *cis*-isotachysterols by Okamura et al. (Scheme 1-5).[11] The deutrated triene **1-15** under thermal conditions produced only two antarafacial products **1-17** and **1-19** without observation of the suprafacial products **1-16** and **1-18**. This demonstrated that the 1,7-hydrogen migration occurred with facial selectivity; this result is consistent with the Woodward-Hoffmann selection rule.[12]



Scheme 1-5. Deuterium labeling experiment of cis-isotachysterol **1-15**

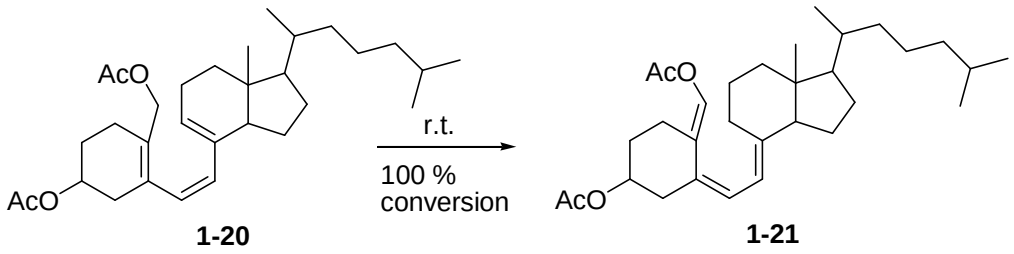
1.1.4 Applications of [1,7]-hydrogen shift to the synthesis of natural products

The substitutent effects on the [1,7]-H shift have been described in the synthesis of vitamin D analogues. The Moriarty and Mazur groups studied the oxo-substituent effect on the equilibrium

[11] a) On the Antarafacial Stereochemistry of the Thermal [1,7]-Sigmatropic Hydrogen Shift. Hoeger, C. A.; Okamura, W. H. *J. Am. Chem. Soc*. **1985**, *107*, 268-270. b) Thermal [1,7]-Sigmatropic Hydrogen Shifts: Stereochemistry, Kinetics, Isotope Effects, and π-Facial Selectivity. Hoeger, C. A.; Jhonston, A. D.; Okamura, W. H. *J. Am. Chem. Soc*. **1987**, *109*, 4690-4698. c) Thermal [1,7]-Sigmatropic Shift of Previtamin D_3 to Vitamin D_3: Synthesis and Study of Pentadeuterio Derivatives. Okamura, W. H.; Elnagar, H. Y.; Ruther, M.; Dobreff, S. *J. Org. Chem*. **1993**, *58*, 600-610.

[12] The Conservation of Orbital Symmetry. Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl*. **1969**, *8*, 781–853.

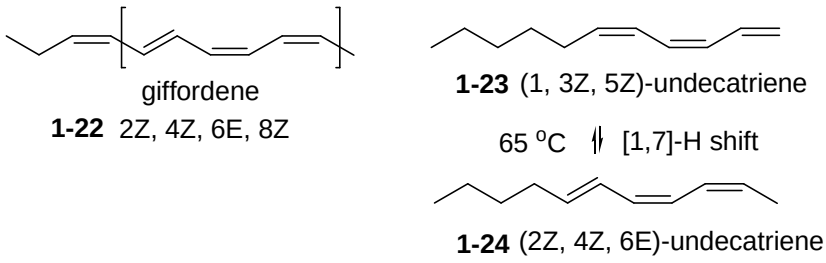
between previtamin D and vitamin D.[13] They observed complete conversion of oxo-substituted previtamin D **1-20** to vitamin D **1-21** (Scheme 1-11), wheres the equilibrium of non-substituted previtamin D has been known to have the ratio of 80:20 (vitamin D: previtamin D).



1-20 **1-21**

Scheme 1-6. Oxo-substituent effect on [1,7]-H shift

In 1994, Boland and coworkers reported the biomimetic synthesis of several polyene natural products using either a nonenzymatic 1,7-hydrogen shift or an 8π-electrocyclization as the key strategy.[14] Giffordene (**1-22**) was isolated along with (1, 3Z, 5Z)-undecatriene (**1-23**) from the brown alga mitchellae. The authors found that triene **21** was in equilibrium with (2Z, 4Z, 6E)-undecatriene (**1-24**) by a [1,7]-H shift under thermal conditions. (Scheme 1-7).



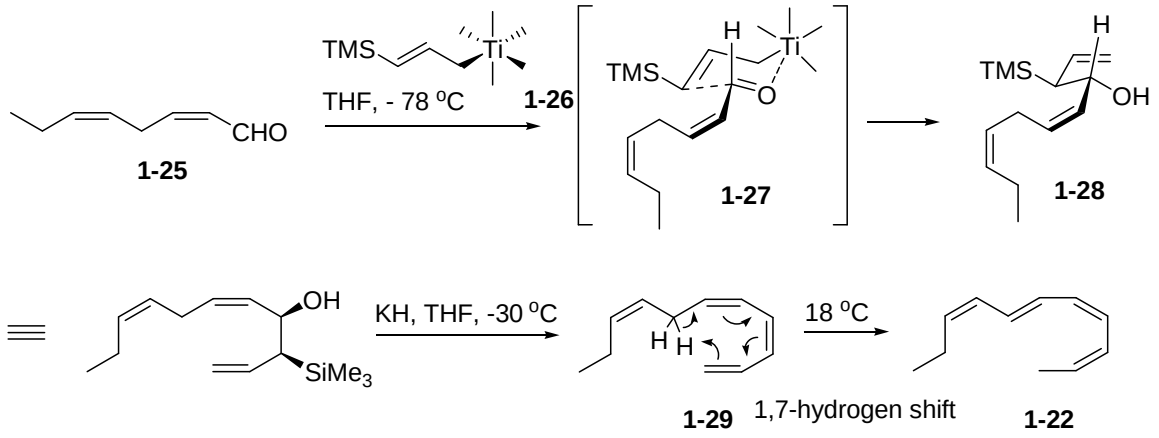
Scheme 1-7. A marine natural product, giffordene (**1-22**)

---

[13] (a) Synthesis of C(19)-Acetoxy Precalciferl$_3$ and Its Converstion into the Vitamin D$_3$ Analogue. Moriarty, R. M.; Paaren, H.; Gilmore, J. *J. Chem. Soc., Chem. Commun*. **1974**, 927. (b) Influence of Fluorine and Oxygen Atoms at C-19 on the Previtamin D-Vitamin D Interconversion. Sialom, B.; Mazur, Y. *J. Org. Chem*. **1980**, *45*, 2201-2204.

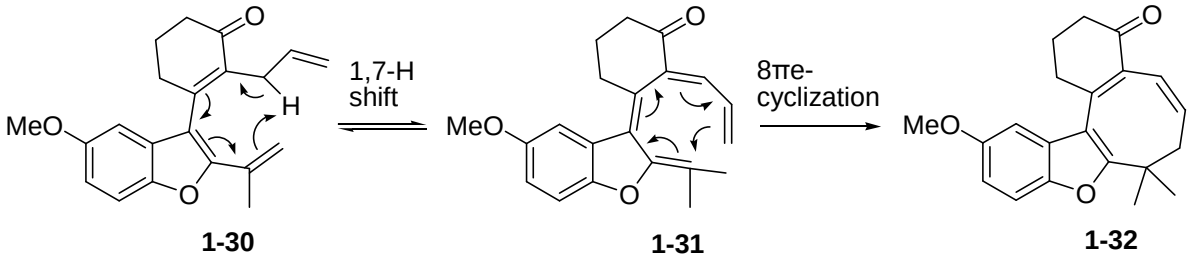
[14] Pericyclic Reactions in Nature: Evidence for a Spontaneous [1,7]-Hydrogen Shift and an 8πe Electrocyclic Ring Closure in the Biosynthesis of Olefinic Hydrocarbons from Marine Brown Algae (phaeophyceae). Pohnert, G.; Boland, W. *Tetrahedron* **1994**, *50*, 10235-10244.

They hypothesized that the conjugated (2Z, 4Z, 6E, 8Z)-tetraene structure of giffordene (**1-22**) would be induced from a skipped (1, 3Z, 5Z, 8Z)-tetraene **1-29** by a thermal [1,7]-H shift. To synthesize the skipped tetraene, they commenced an asymmetric allylation of the aldehyde **23** with Ti-allyl complex **1-26** and obtained a *β*-hydroxysilane **1-28** with high diastereoselectivity (> 90%). Then, the Peterson olefination of the *β*-hydroxysilane at low temperature gave the precursor, (1, 3Z, 5Z, 8Z)-tetraene **1-29**. As expected, the quick isomerization of the skipped tetraene at 18 ^{o}C furnished giffordene (**1-22**) in quantitative yield (Scheme 1-8).



Scheme 1-8. Synthesis of giffordene

In 2004, Flynn and coworkers reported the synthesis of tetracycle **1-32**. They utilized a protocol that includes a tandem [1,7]-H shift of skipped tetraene **1-30** followed by 8π-electrocyclization of the fully conjugated intermediate **1-31** (Scheme 1-9).[15]

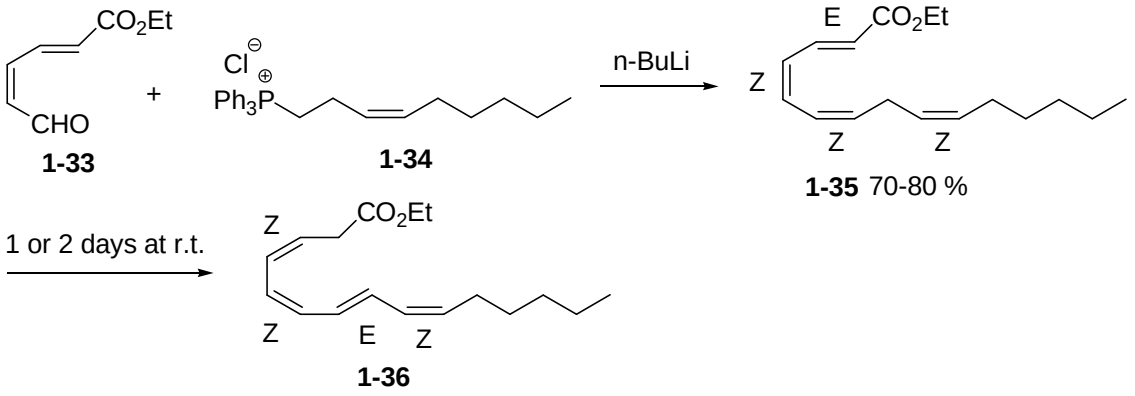


Scheme 1-9. A tandem [1,7]-H shift and 8π-electrocyclization

[15] Multicomponent Coupling Approach to (±)-Frondosin B and a Ring-Expanded Analogue. Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457-460.

1.1.5 Unexpected cases of [1,7]-hydrogen shift

In addition to applications of this novel thermal isomerization to the synthesis of natural products, there have been several examples in which the [1,7]-H shift was unexpectedly observed in polyene systems. For example, in 1980, Rokach and coworkers reported an unexpected isomerization product **1-36** from a skipped (E, Z, Z, Z)-tetraene **1-35** by the [1,7]-H shift during their synthesis of leukotriene (Scheme 1-10).[16]



Scheme 1-10. Unexpected [1,7]-H shift reported in the synthesis of leukotriene

Meanwhile, in the course of a study for the total synthesis of TAN-1085, Suzuki et al. reported the unexpected formation of the silylenol ether by the thermal [1,7]-H shift (Scheme 1-10). They intended to have a thermal retro-[2+2] cycloaddition of cyclobutene **1-37** to get a triene **1-38** which then affords a naphalene **1-39** by way of 6π-electrocyclization followed by aromatization. However, an unexpected enol ether **1-41** was predominantly obtained by the [1,7]-H shift, instead of the desired product, naphthalene **1-39**.[17]

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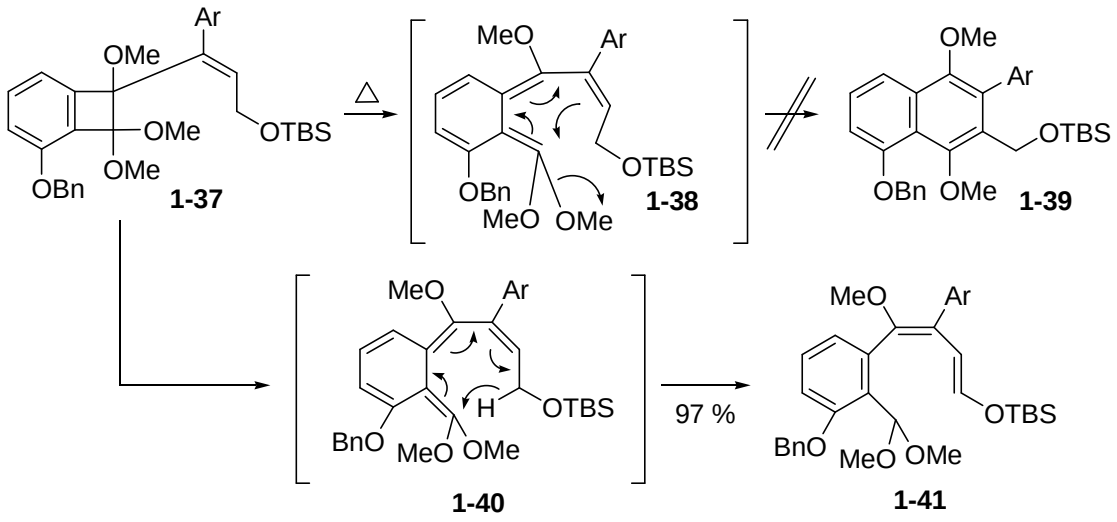
[16] The synthesis of a leukotriene with SRS-like activity. Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J. G.; Larue, M.; Young, R. N.; Masson, P.; Holme, G. *Tetrahedron Lett*. **1980**, *21*, 1485-1488.

[17] Concise Total Synthesis and Structure Assignment of TAN-1085. Ohmori, K.; Mori, K.; Ishikawa, Y.; Tsuruta, H.; Kuwahara, S.; Harada, N.; Suzuki, K. *Angew. Chem. Int. Ed*. **2004**, *43*, 3167-3171.



Scheme 1-11. Enol ether formed by [1,7]-H shift in the synthesis of TAN-1085

Houk and coworkers studied this experimental result by computational. Using a series of DFT calculations, they investigated the substituent effect of the pericyclic reaction pathway. Two model systems (A and B) were examined to describe the transition states and activation energies of both 6π-electrocyclization and [1,7]-H shift. As a result, the preferred [1,7]-hydrogen shift exhibited a lower activation energy than did the thermodynamically favorable 6π-electrocyclization pathway (Figure 1-4).[18]

[18] DFT study of Pericyclic Reaction Cascades in the Synthesis of Antibiotic TAN-1085. Akerling, Z. R.; Norton, J. E.; Houk, K. N. *Org. Lett*. **2004**, *6*, 4273-4275.

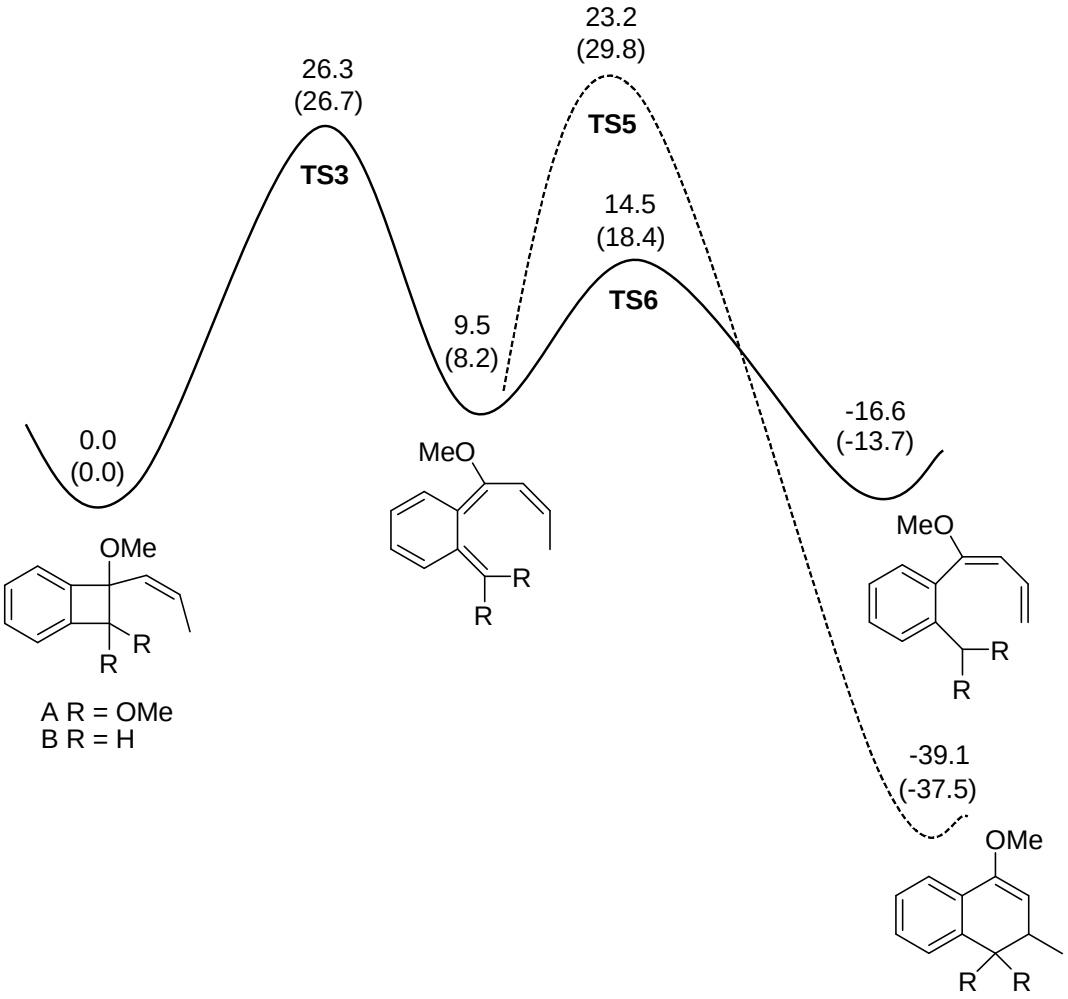


Figure 1-4. Energy diagram for reaction pathways of model systems[21]

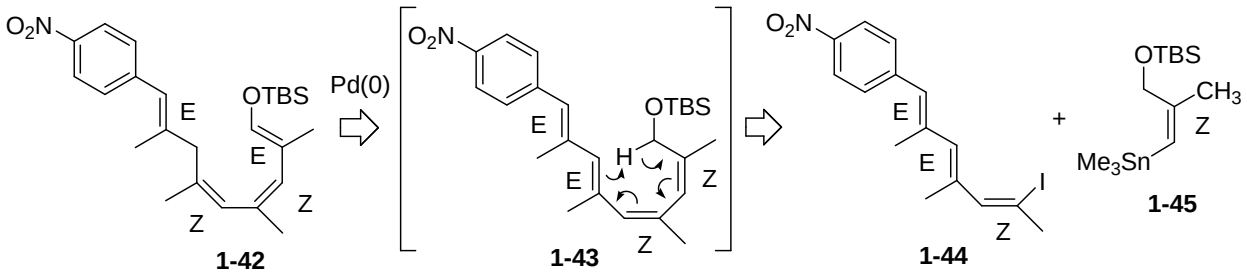
1.2 Result and Discussion

1.2.1 Models for the proposed rearrangement

1.2.1.1 (E, E, Z, Z)-tetraene

Before commencing a multi-step synthesis of the arabilin, we needed to evaluate our premise in a simple and closely related model system. Therefore, we postulated that the intermediate **1-43** would be spontaneously converted to the skipped tetraene **1-42** by a [1,7]-H shift. Thus, the synthesis of the presumed compound **1-43** was designed (Scheme 1-12). The fully conjugated (E,

E, Z, Z)-tetraene **1-43** could be obtained by coupling (E, E, Z)-iodotriene **1-44** and (Z)-vinylstannane **1-45**.



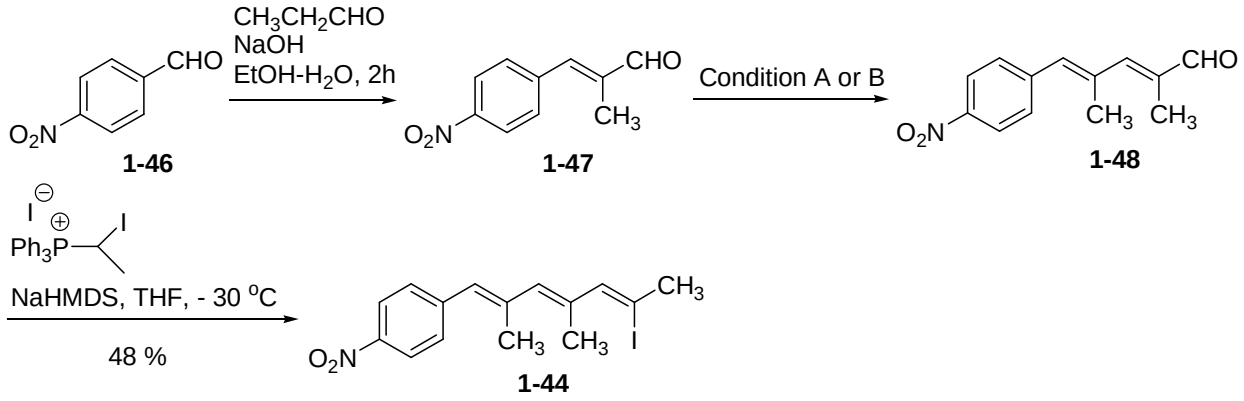
Scheme 1-12. Model compound, the conjugated (E, E, Z, Z)-tetraene **1-43**

1.2.1.1.1 Synthesis of (E, E, Z)-iodotriene **1-44**

First, (E, E, Z)-iodotriene **1-44** was prepared by following standard methods. The aldehyde **1-47** was obtained by condensation between the propionaldehyde and p-nitrobenzaldehyde **1-46**.[19] The aldehyde **1-47** was then homologated by two general conditions A and B (see Scheme 1-13), providing an aldehyde **1-48**. The Stork-Zhao[20] reaction was then applied to afford the iodotriene **1-44** (48 % yield) with excellent Z-selectivity (Scheme 1-13). The geometry of the iodotriene **1-44** was firmly identified by a combination of COSY and NOE nmr experiments (Table 1-2).

[19] Gold-Catalyzed Activation of Epoxides: Application in the Synthesis of Bicyclic Ketals. Balamurugan, R.; Kothapalli, R. B.; Thota, G. K. *Eur. J. Org. Chem.* **2011**, *8*, 1557-1569.

[20] A stereoselective synthesis of (Z)-1-iodo-1-alkenes. Stork, G; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173-2174.



Scheme 1-13. Synthesis of (E, E, Z)-iodotriene **1-44**

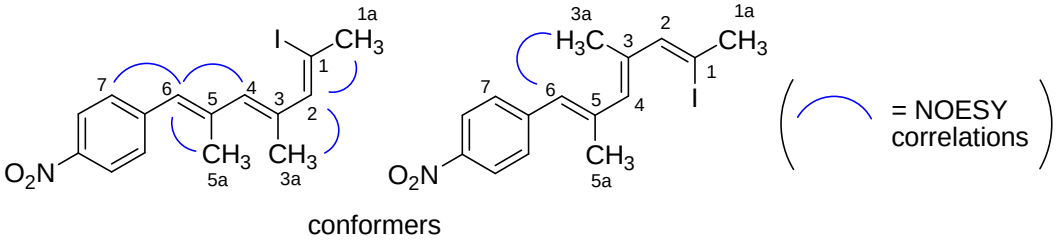


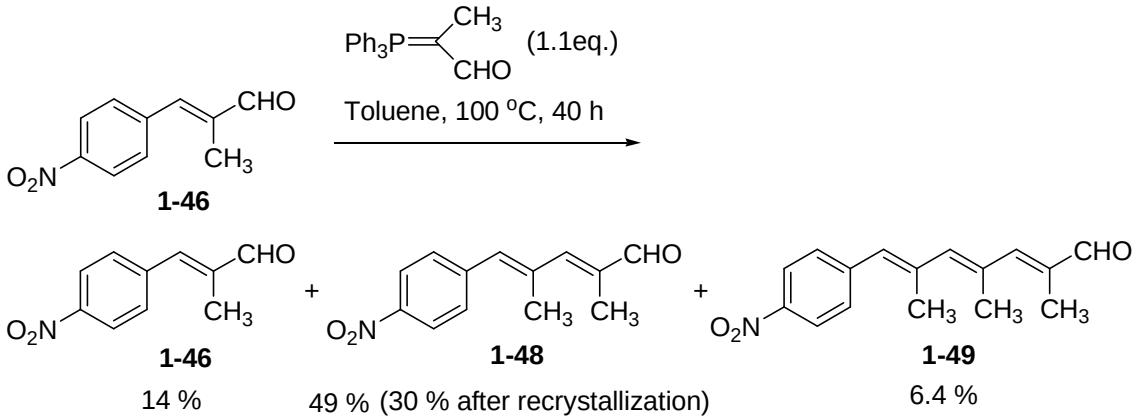
Table 1-2. Difference 1D-NOE chart for compound **1-44**

Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH_3 (3a, 2.01)	CH (2, 6.08), CH (6, 6.48)
CH_3 (1a, 2.61)	CH (2, 6.08)
CH (6, 6.48)	CH_3 (3a, 2.01), CH (4, 6.11), CH (7, 7.44)

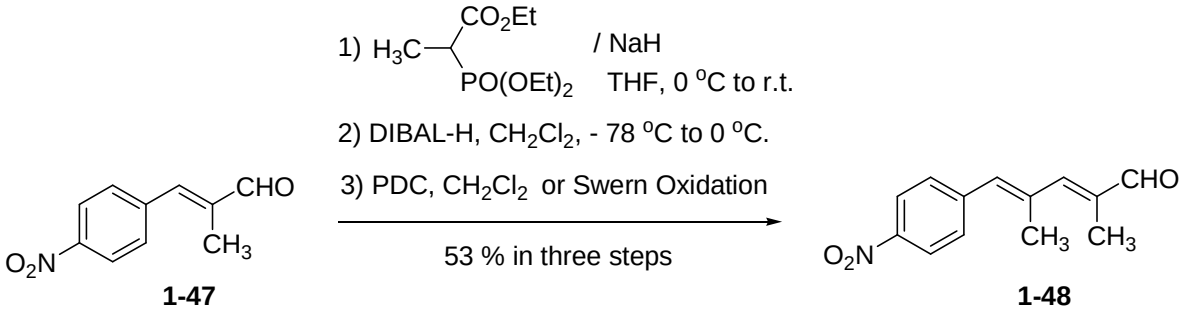
In condition A, the commercially available Wittig reagent was used for homologation. This procedure produced the aldehyde **1-48** from **1-47** in one step. In this experiment, the desired aldehyde **1-48** was produced in 49 % yield (30 % after recrystallization) which accompanied doubly homologated triene **1-49** (6.4 % yield) with unreacted starting material recovered (14 % yield).

In condition B, the aldehyde **1-48** was obtained by the conventional three step sequence; Horner-Wadsworth-Emmons homologation, DIBAL-reduction, and PDC oxidation (Scheme 1-14). The overall yield for three steps was 53 % yield.

Condition A



Condition B

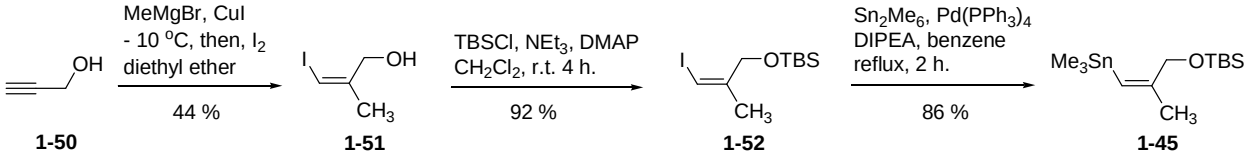


Scheme 1-14. Synthetic conditions A and B for the aldehyde **1-48**

1.2.1.1.2 Synthesis of (Z)-vinylstannane **1-45**

The known (Z)-vinylstannane **1-45** was prepared by the known procedure in three steps..[21] Z-iIdoallylic alcohol **1-51** was prepared by methyl cupration of propargyl alcohol (**1-50**) followed by the addition of iodine. Then, the protection of alcohol **1-51** was followed by the iodine-tin exchange, providing the Z-vinylstannane **1-45** (79 % yield for two steps, Scheme 1-15).

[21] Total synthesis of (+)-jatrophone. Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692-7697.



Scheme 1-15. Synthesis of (Z)-vinylstannane **1-45**

1.2.1.1.3 The coupling reactions between (E, E, Z)-iodotriene and (Z)-vinylstannane

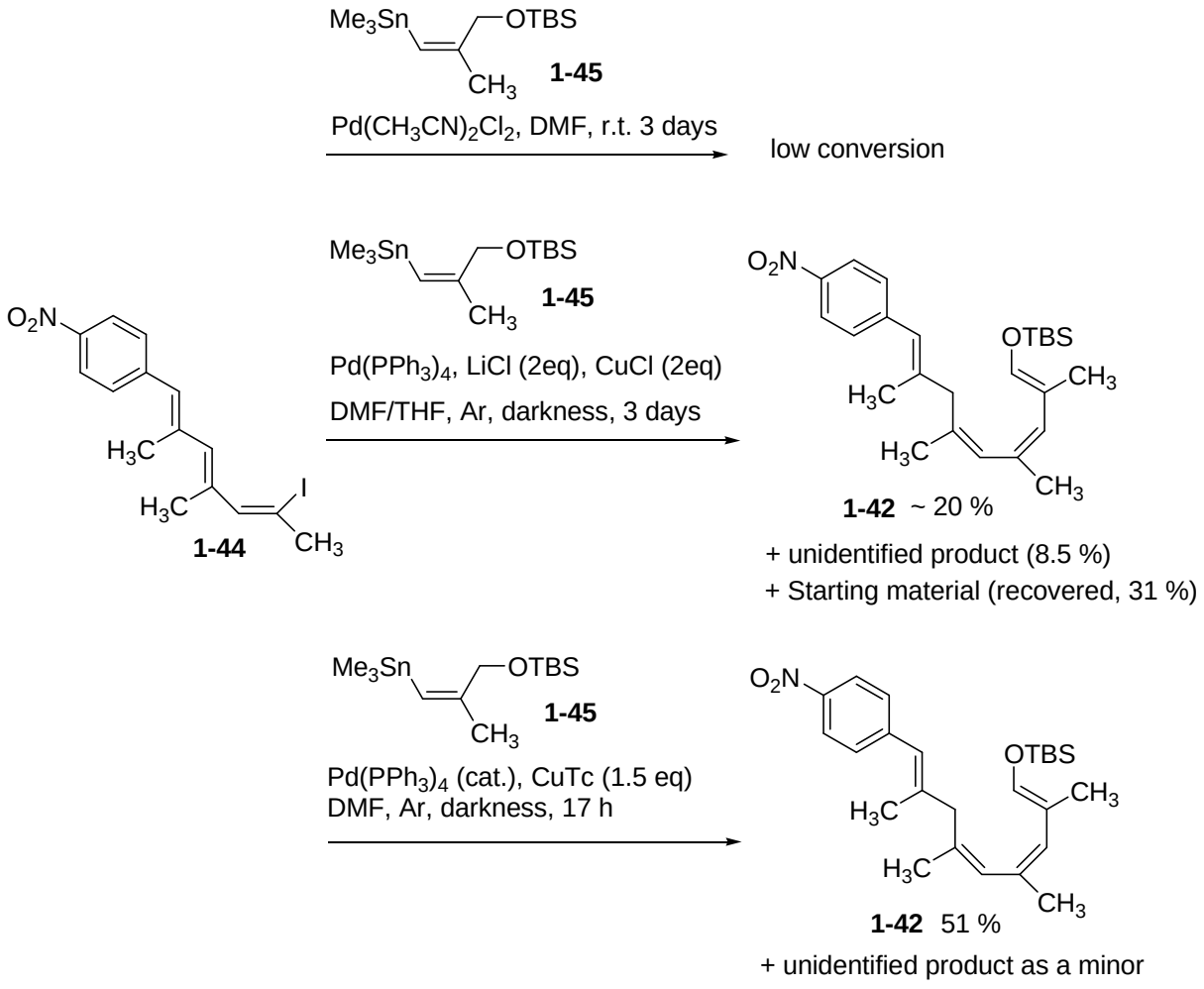
Having prepared the two pieces, we tried to couple the (E, E, Z)-iodotriene **1-44** and (Z)-vinylstannane **1-45**. First, we applied Stille's conditions, $Pd(CH_3CN)_2Cl_2$ in DMF in the dark, but this reaction only showed low conversion.[22] Thus, we next tested the reaction by employing Pd (0) with Li/Cu salts as additives.[23] Monitoring of the coupling reaction by TLC revealed the formation of a yellow product after approximately 2 h and its subsequent disappearance concurrent with the formation of a new colorless product. This result strongly supported our expectation that coupling between (E, E, Z)-iodotriene 1-44 and (Z)-vinylstannane **1-45** followed by [1,7]-H shift smoothly occurs to provide the enol ether **1-42**. Because the yield of coupling reaction was low, we optimized the conditions before proceeding to the synthesis of arabilin. Catalytic Pd(0) with 1.5 eq. CuTC[24] at room temperature gave an acceptable yield of the model

[22] a) Stereospecific Cross-Coupling of Vinyl Halides with Vinyl Tin Reagents Catalyzed by Palladium. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813-817. b) Total synthesis of the cholesterol biosynthesis inhibitor 1233A via a (π-allyl)tricarbonyliron lactone complex. Bates, R. W.; Fernández-Megia, E.; Ley, S. V.; Rück-Braun, K.; Tilbrook, D. M. G. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1917-1925.

[23] a) Synthetic Studies toward GKK1032s, Novel Antibiotic Antitumor Agents: Enantioselective Synthesis of the Fully Elaborated Tricyclic Core via an Intramolecular Diels−Alder Cycloaddition. Asano, M.; Inoue, M.; Watanabe, K.; Abe, H.; Katoh, T. *J. Org. Chem.* **2006**, *71*, 6942-6951. b) Cu-mediated Stille reactions of sterically congested fragments: towards the total synthesis of zoanthamine. Nielsen, T. E.; Quement, S. L.; Juhl M.; Tanner, D. *Tetrahedron* **2005**, *61*, 8013-8024.

[24] a) Copper-Mediated Cross-Coupling of Organostannanes with Organic Iodides at or below

[1,7]-shift product **1-42** (Scheme 1-16). The geometry of the skipped tetraene **1-42** was elucidated by a combination of 2D COSY and 1D NOE nmr experiments (Table 1-3).



Scheme 1-16. Tandem coupling reaction and [1,7]-H shift in a model system

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Room Temperature. Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1996**, *118*, 2748-2749. b) A Synthesis of the Hypocholesterlemic Agent 1233A Via Asymmetric [2+2] Cycloaddition. Dymock, B. W.; Locienski, P. J.; Pons, J. -M. *Synthesis* **1998**, 1665-1661. C) Stereoselective Synthesis of Cyercene A and the Placidenes. Liang, G.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 819–821.

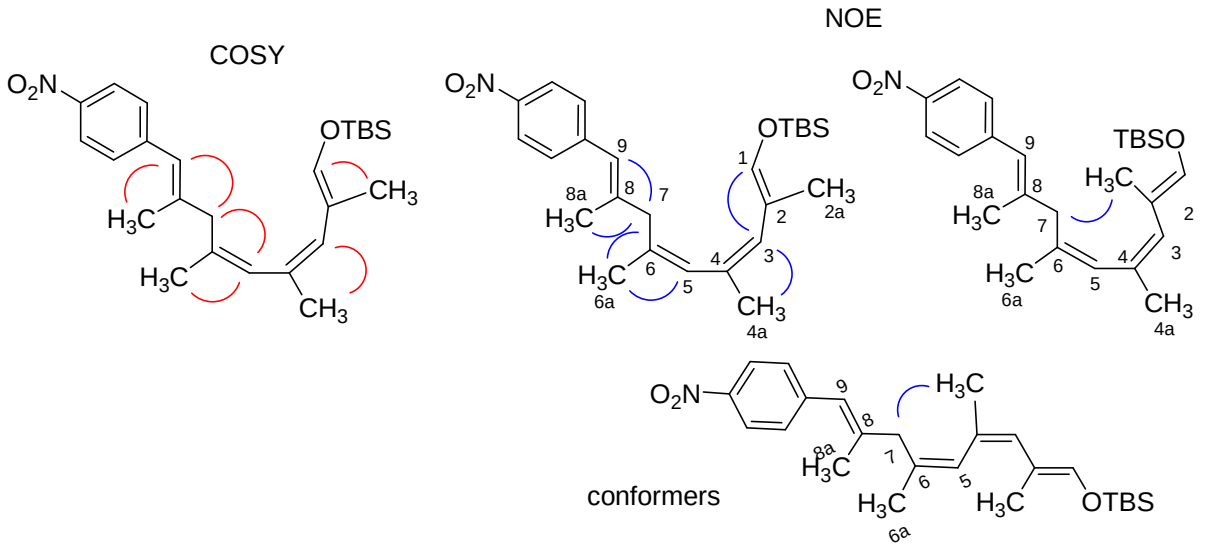


Table 1-3. COSY and difference 1D-NOE chart for compound **1-42**

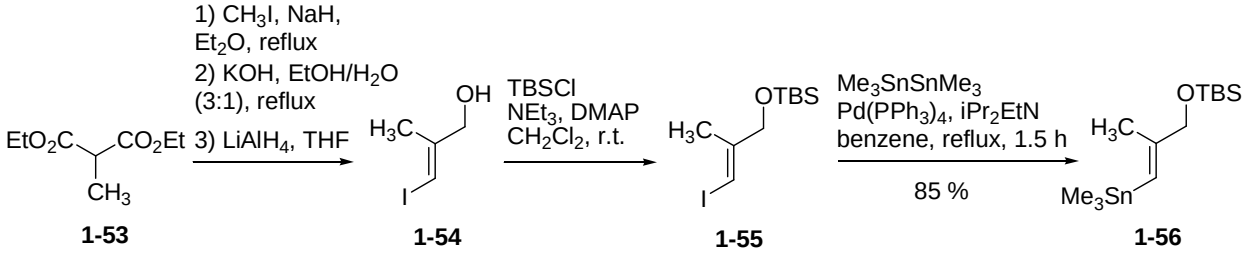
COSY, protons – corresponding CH_3 and CH_2 (C_{number}, ppm)		Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH (9, 6.32)/ CH_3 (8a, 1.82), CH_2 (7, 2.92)	CH (3, 5.70)/ CH_3 (4a, 1.86)	CH_2 (7, 2.92)	CH_3 (2a, 1.70), CH_3 (6a, 1.73), CH_3 (8a, 1.82), CH_3 (4a, 1.86), CH (9, 6.32)
CH (5, 6.06)/ CH_3 (6a, 1.73), CH_2 (7, 2.92)	CH (1, 6.37)/ CH_3 (2a, 1.70)	CH (3, 5.70)	CH_3 (4a, 1.86), CH (1, 6.37)
		CH (5, 6.06)	CH_3 (6a, 1.73)

1.2.1.2 A test of importance of the O-substituent

To demonstrate that the observed [1,7]-H shift is only derived from geometrically restricted tetraene that have the helical transition state, we needed to test geometrical isomers [i.e. (E, E, E, Z)-tetraene] of the fully conjugated (E, E, Z, Z)-tetraene **1-43**. We believed that (E, E, E, Z)-tetraene **1-57** would not undergo [1,7-H]-shift because (E, E, E, Z)-tetraene doesn't have the helical transition state unless there are isomerizations. According to the known procedure,[25] (E)-iodoallylic alcohol **1-54** was prepared in 28 % yield (three steps, lit. yield = 40 %). Then, a

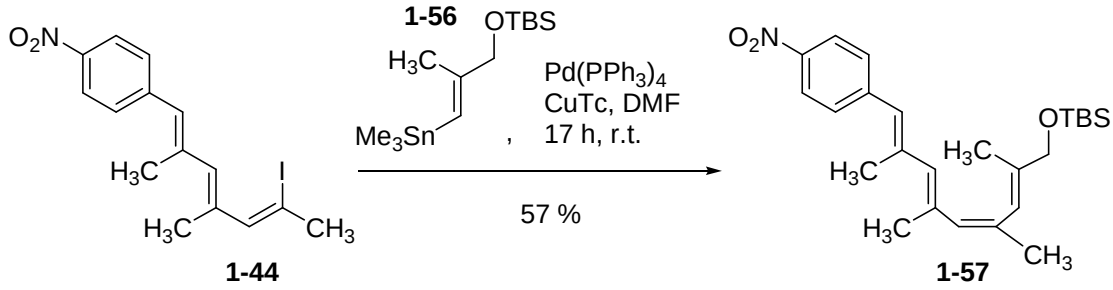
[25] a) Total Synthesis of (+)-Macbecin I. Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47-65. b) Addition of Dichlorocarbene to Diethyl Methylsodiomalonate. Krapcho, A. P. *J. Org. Chem*. **1962**, *27*, 2375.

protection of the alcohol **1-54** with TBS was followed by iodine-tin exchange to afford the requisite (E)-vinylstanne **1-56** (Scheme 1-17).



Scheme 1-17. Synthesis of (E)-vinylstannane **1-56**

Then, we coupled (E, E, Z)-iodotriene **1-44** and (E)-vinylstanne **1-56** under the same conditions used in the synthesis of model compound **1-42**. As expected, the (E, E, E, Z)-tetraene **1-57** was obtained, but no isomerization was observed within the same time span (Scheme 1-18).



Scheme 1-18. Coupling of (E, E, Z)-iodotriene **1-44** and (E)-vinylstannane **1-56**

The stereochemistry of the fully conjugated tetraene **1-57** was identified by 2D COSY and 1D NOE nmr experiments (Table 1-4).

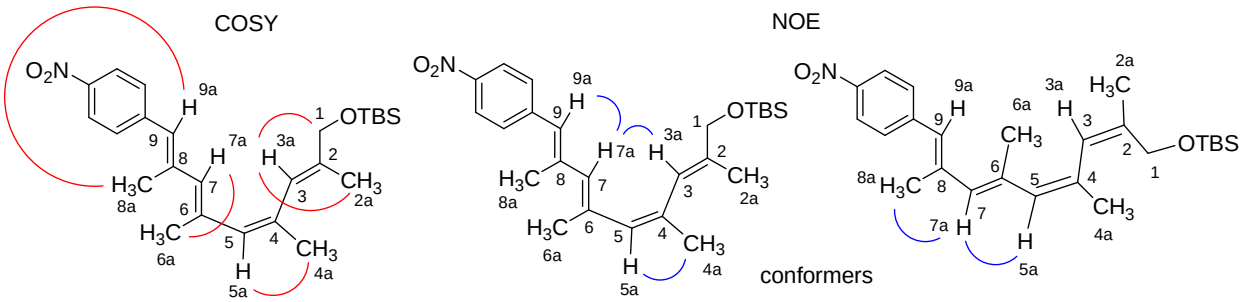


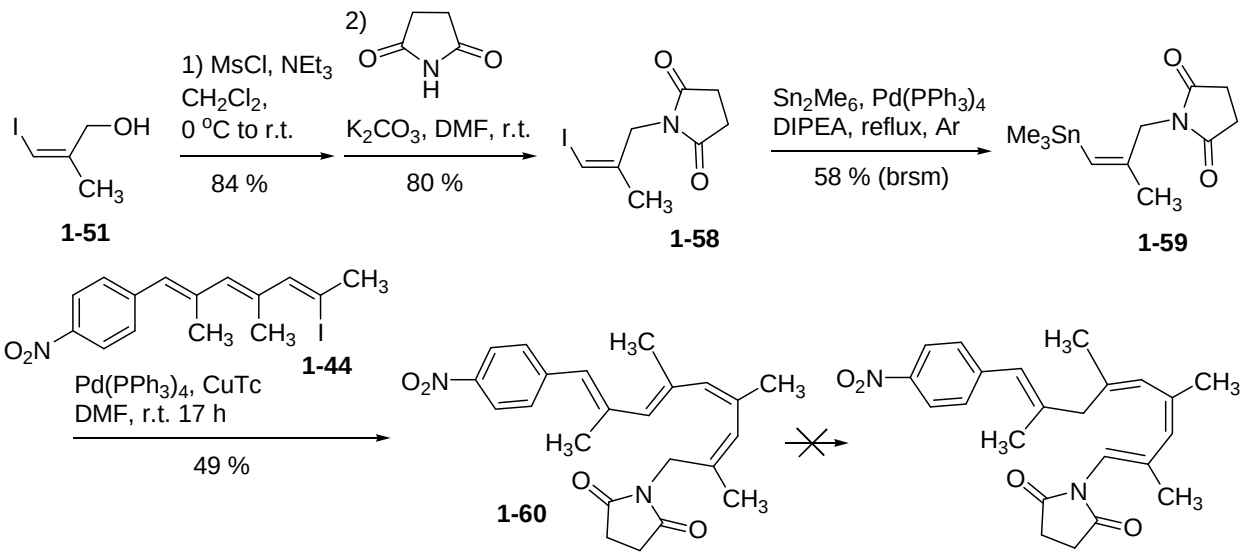
Table 1-4. COSY and difference NOE chart for compound **1-57**

COSY, protons – corresponding CH_3, CH_2, CH (C_{number}, ppm)		Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH (9a, 6.40)/ CH_3 (8a, 2.05)	CH (5a, 5.91)/ CH_3 (4a, 1.92)	CH (7a, 5.99)	CH_3 (8a, 2.05), CH (5a, 5.91), CH (9a, 6.40), CH (3a, 6.18)
CH (7a, 5.99)/ CH_3 (6a, 1.96)	CH (3a, 6.18)/ CH_3 (2a, 1.63), CH_2 (1, 4.06)	CH (5a, 5.91)	CH (7a, 5.99), CH_3 (4a, 1.92)

1.2.1.3 Nitrogen analogs-testing the generality of the heteroatom substituent

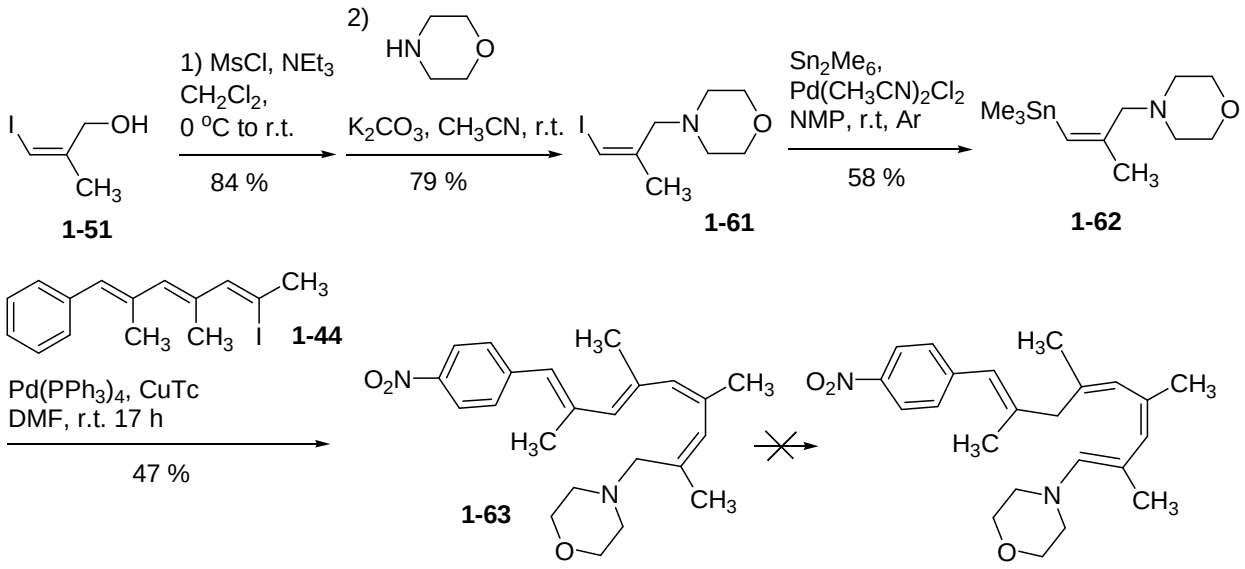
Having confirmed that the model compound **1-42** is a thermodynamically stable product formed by the thermal isomerization, we next wanted to explore the synthetic scope of the [1,7]-H shift as a methodology. Therefore, we examined other heteroatom-containing substrates have been examined.

First, the (Z)-vinylstannane containing succinimide **1-59** was prepared from alcohol **1-51** by three steps: mesylation, displacement by the succinimde, and tin-iodine exchange. Then, we coupled (Z)-vinylstannane **1-59** and (E, E, Z)-iodotriene **1-44** with the catalytic Pd(0)/ CuTC conditions. As a result, the fully conjugated (E, E, Z, Z)-tetraene **1-60** was obtained. However, the skipped tetraene-enamine by [1,7]-H shift was not observed (Scheme 1-19).



Scheme 1-19. Examination of [1,7]-H shift in succinimide-contained tetraene **1-60**

Because we suspected that the two of carbonyls may alter the electronic requirement for the [1,7]-H shift of the substrate, we examined another substrate. The (Z)-vinylstannane **1-62** was prepared by the same reaction sequence described in Scheme 1-18. The (E, E, Z)-iodotriene **1-44** and (Z)-vinylstannane **1-62** were coupled to give the fully conjugated (E, E, E, Z)-tetraene **1-63** (Scheme 1-20). The desired [1,7]-H shift product was not observed.

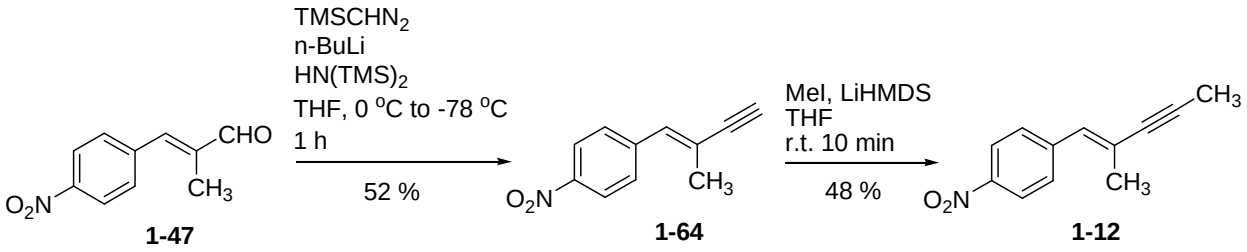


Scheme 1-20. Examination of [1,7]-H shift in morpholine-containing tetraene **63**

1.2.2 Preparation of Key Building Blocks for arabilin

1.2.2.1 Preparation of (E, E)-iododiene

To prepare the (E, E)-iododiene **1-9** or (E, E)-metalladiene **1-11** as originally planned (Scheme 1-4), we needed internal alkyne **1-12**. The alkyne **1-12** was prepared by two steps by a known procedure (Scheme 1-21).[26] Peterson type olefination of the aldehyde **1-47** followed by the expulsion of nitrogen gave the alkyne **1-64**. Then, the methylation at the terminal carbon of alkyne **1-64** furnished the desired alkyne **1-12**.



Scheme 1-21. Preparation of the internal alkyne

1.2.2.1.1 Hydroboration of the internal alkyne **1-12**

Baldwin and coworkers reported that the hydroboration of the internal alkyne **1-12** containing a nitro group was unsuccessful under several conditions with pinacol- and catecholborane..[27] However, because the hydroboration method can give a facile approach to **1-11**, we hoped to find an appropriate condition for the hydoboration.

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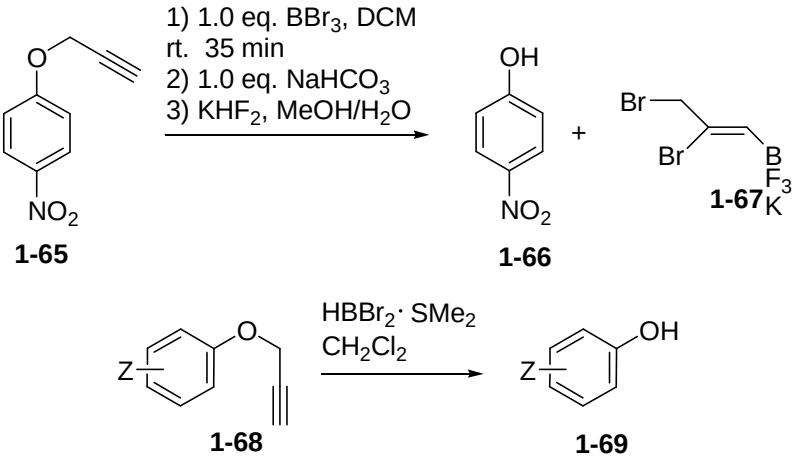
[26] Extension of the Colvin Rearrangement Using Trimethylsilyldiazomethane. A New Synthesis of Alkynes. Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107-108.

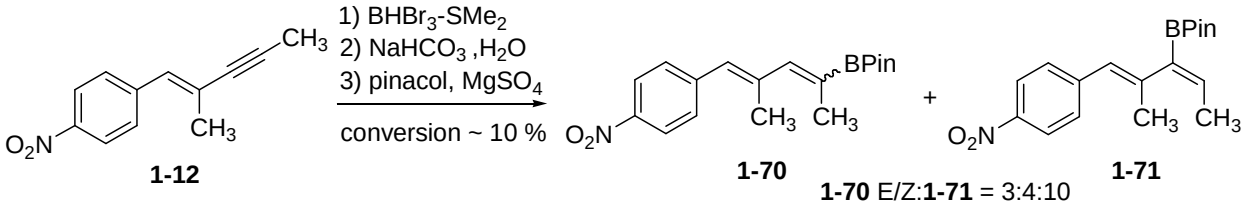
[27] The biomimetic synthesis of SNF4435C and SNF4435D, and the total synthesis of the polyene metabolite aureothin, N-acetyl-aureothanmine and specinabilin. Jacobsen, M. F.; Moses, J. E.; Adlington, R. T.; Baldwin, J. E. *Tetrahedron* **2006**, *62*, 1675-1689.

In 2009, Yao et al. reported the successful cleavage of propargyl ethers containing *p*-nitrobenzene by using boron tribromide or $HBBr_2$-SMe_2 (Scheme 1-22).[28] Here, the nitro group tolerated the hydroboration conditions.



Scheme 1-22. Hydroboration of nitrobenzene-contained substrate as reported by Yao et al

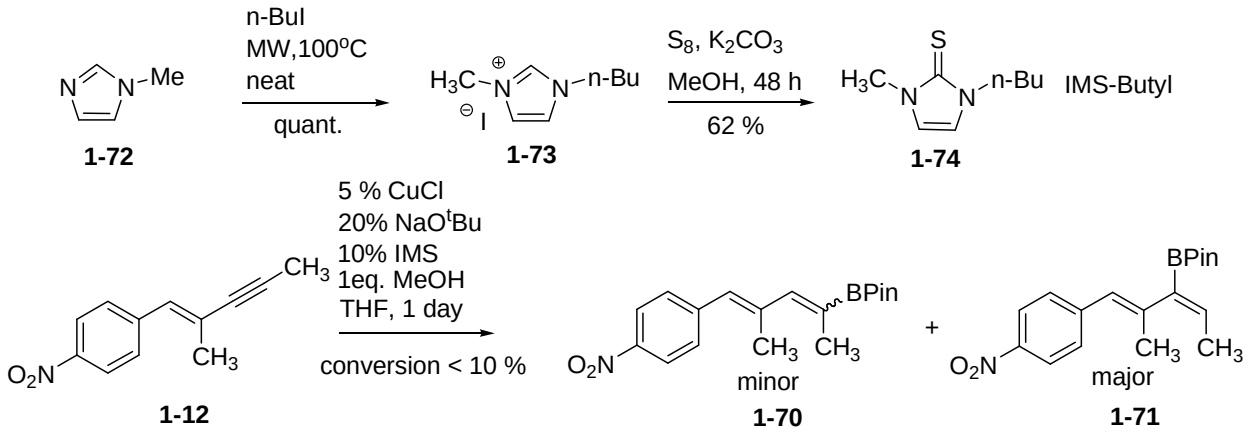
According to this procedure, we anticipated that the alkyne **1-12** was amenable to this condition. However, disappointingly the yield for the desired product was low and the regioselectivity turned out to be very poor (Scheme 1-23).



Scheme 1-23. Hydroboration of the internal alkyne **1-12**

[28] Identification of a Boron-Containing Intermediate in the Boron Tribromide Mediated Aryl propargyl Ether Cleavage Reaction. Yao, M. -L.; Reddy, M. S.; Zeng, W.; Hall, K.; Walfish, I.; Kabalka, G. W. *J. Org. Chem.* **2009**, *74*, 1385-1387.

We next examined another hydroboration procedure with the imidazoline-2-thione ligand-copper(I) complex. [29] The essential ligand in this reaction, IMS-Butyl **1-74** (1,3-dimethylimidazoline-2-thiones), was prepared from the *N*-methylimidazole **1-72**. The reaction of **1-72** with n-BuI in the microwave provided imidazolium salt **1-73**,[30] which was then converted to IMS-butyl **1-74.**[31] The application of these novel reaction conditions to our substrate **1-12** gave a mixture of products **1-70** and **1-71** with low conversion (Scheme 1-24).



Scheme 1-24. Copper-catalyzed hydroboration of the internal alkyne **1-12**

1.2.2.1.2 Hydrozirconation of the internal alkyne **1-12**

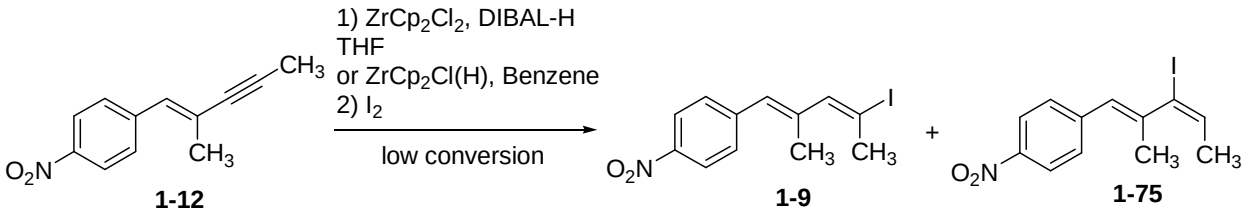
Because the hydroboration of the alkyne **1-12** was not successful, we next turned our attention to hydrozirconation. The internal alkyne **1-12** was treated with in-situ prepared Schwartz

[29] Bis(imidazoline-2-thione)-copper(I) catalyzed regioselective boron addition to internal alkynes. Kim, H. R.; Jung, I. G.; Jang, K. Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun*. **2010**, *46*, 758-760.

[30] An expeditious solvent-free route to ionic liquids using microwaves. Varma, R. S.; Namboodiri, V. V. *Chem. Commun*. **2001**, 643-644.

[31] 1,3-DIMETHYLIMIDAZOLE-2-THIONE. Benac, B. L.; Burgess, E. M.; Arduengo III, A. J. *Org. Synth.* **1986**, *64*, 92.

reagent[32] and trapped with iodine at low temperature. As a result, an inseparable mixture of **1-9** and **1-75** was obtained in 7 % yield. When commercially available Schwartz reagent (Aldrich) was used, the reaction did not work at all (Scheme 1-25).



Scheme 1-25. Hydrozirconation of the internal alkyne **1-12**

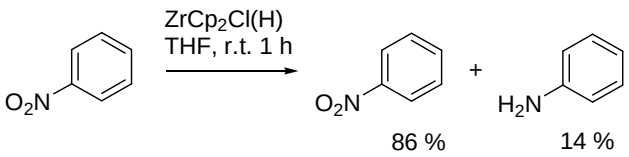
Hydrozirconation has been known to undergo thermodynamic equilibrium to reach the terminally zirconated product from alkynes.[33] Therefore, we tried to vary the reaction conditions by using excess reagent or changing temperature. However, these efforts were not fruitful. These unsuccessful results were presumed to be the result of deactivation of the zirconium reagent by the nitro group or the reduction of the nitro group by the zirconium reagent.[34]

---

[32] A Convenient and Genuine Equivalent to $HZrCp_2Cl$ Generated in Situ from $ZrCp_2Cl_2$-DIBAL-H. Huang, Z.; Negishi, E. *Org. Lett*. **2006**, *8*, 3675-3678.

[33] a) Hydrozirconation. IIII. Stereospecific and Regioselective Functionalization of Alkylacetylenes via Vinylzirconium(IV) intermediates. Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc*. **1975**, *97*, 679-680. b) Stereo- and Regiocontrolled Synthesis of Branched Trissubstituted Conjugated Dienes by Palladium(0)-catalyzed Cross-Coupling Reaction. Panek, J.; Hu, Tao. *J. Org. Chem*. **1997**, *62*, 4912-4913.

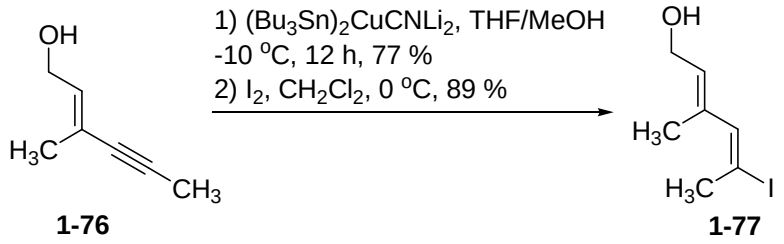
[34] The reduction of nitrobenzene was observed when it was subjected to 1 eq. Schwartz reagent (the ratio of the nitrobenzene and the resulting aniline was identified by crude ^1H nmr).



see: reduction of nitro compounds using $ZrCl_4/NaBH_4$: a novel and efficient conversion of aromatic, aliphatic nitro compounds to primary amines. Chary, K. P.; Ram, S. R.; Iyengar, D. S.

1.2.2.1.3 Stannylcuparation of the internal alkyne **1-12**

Since Piers and coworkers have reported a study for the stereoselective stannylcupration of the acetylenic esters,[35] the mechanistic study[36] and applications of this method have been of great interests to many research groups. For example, Pancrazi and coworkers have reported the regio- and stereoselective synthesis of dienylstannanes and corresponding iodides from the alkynes or conjugated enyne alcohols (Scheme 1-26).[37]



1-76 **1-77**

Scheme 1-26. Stannylcupration of the enyne alcohol **1-76**

Synlett **2000**, 683-685

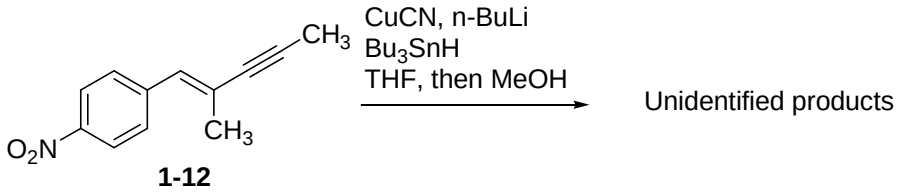
[35] a) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263. b) Piers, E. Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22,* 4905. c) Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 934. d) Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron Lett.* **1985**, *26*, 6265. e) Piers, E.; Chong, J. M. *Can. J. Chem.* **1988**, *66,* 1425. f) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron.* **1989**, *45*, 363. 7) Piers,

E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70,* 2058.

[36] a) Singer, R. D.; Hutzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 4933. b) Cummins, C. H.; Gordon, E. J. *Tetrahedron Lett*. **1994**, *35*, 8133.

[37] a) An Efficient Method in Stannylcupration of a Methyl Substituted Enyne or Alkyne by Kinetic Control Using Methanol. Betzer, J. –F.; Ardisson, J.; Lallemand, J. –Y.; Pancrazi, A. *Tetrahedron Lett*. **1997**, *38*, 2279-2282. b) Regio- and Stereoselectivity in Stannyl- and Silylcupration of Alkyne and Enynes Using Proton Sources. Betzer, J. –F.; Pancrazi, A. *Synlett* **1998**, 1129-1131. c) Water as a Proton Source in Regio- and Chemoselective Stannylcupration of Alkynes and Enynes. Betzer, J. F.; Pancrazi, A. *Synthesis* **1999**, 629-634.

We applied this methodology to the alkyne **1-12** and obtained two the unidentified products. We tried to recrystallize these products for X-ray structure determination, but the resulting crystals were not good enough to derive the requisite diffraction for crystallographic data (Scheme 1-27).

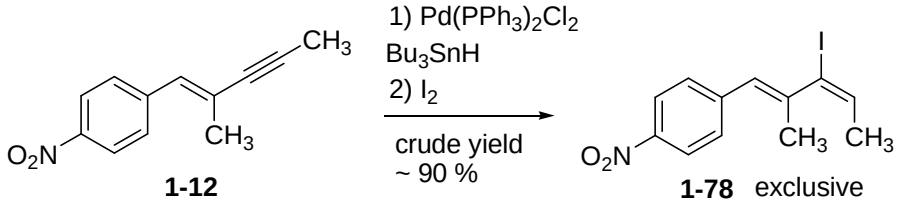


Scheme 1-27. Stannylcupration of the internal alkyne **1-12**

1.2.2.1.4 Hydrostannylation of the internal alkyne **1-12**

Generally, the hydrostannylation ofinternal alkynes gives E-products. The regioselectivity is affected by the catalytic system, functional groups, and steric hindrance in the substrate.[38]

The first hydrostannylation of **1-12** using a catalytic system of Pd(0) with tributyltin hydride followed by quenching with iodine gave exclusively α-iodinated product **1-78**[39] (Scheme 1-28).

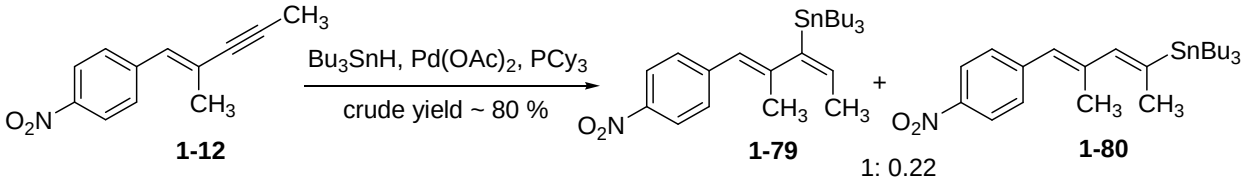


Scheme 1-28. Hydrostannylation of the internal alkyne **1-12**

[38] Metal-Catalyzed Hydrostannylation. Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev*. **2000**, *100*, 3257-3282.

[39] Literature search showed several examples of hydrostannylation of enyne, and the product of hydrostannylation of enyne were α-selective due to steric effect of terminal methyl group. See: a) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768. b) Lautens, M.; Smith, N. D.; Ostrovsky, D. *J. Org. Chem*. **1997**, *62*, 8970. c) Lautens, M.; Mancuso, J. *Org. Lett.* **2000**, *2*, 671.

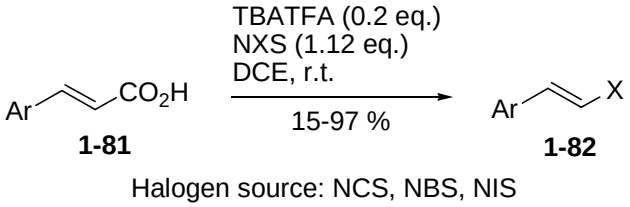
We next tried the hydrostannylation of the alkyne **1-12** with bulky ligand in hexane.[40] These conditions afforded an inseparable mixture of the regioisomeric products **1-79** and **1-80** (Scheme 1-29).



Scheme 1-29. Hydrostannylation of the internal alkyne **1-12** with a bulky ligand

1.2.2.1.5 Microwave-assisted decarboxylative iodination of dienylcarboxylic acid

Roy and coworkers have studied a metal-free catalytic Hunsdiecker reaction of α, β-unsaturated carboxylic acid. [41] In their study, they described a catalytic condition for decarboxylative halogenations of various *α*, *β*-unsaturated carboxylic acids by combining catalytic TBATFA (tetrabutylammonium trifluoroacetate) and stochiometric NXS (*N*-halosuccinimide) (Scheme 1-30).

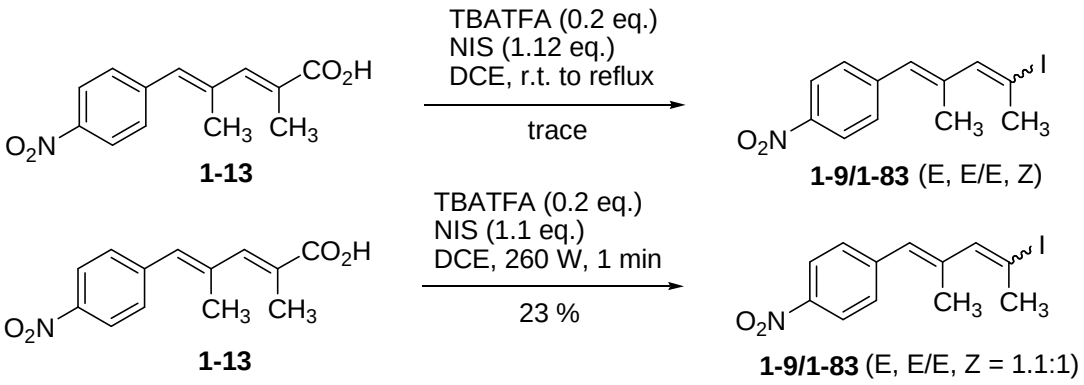


Scheme 1-30. Catalytic Hunsdiecker Reaction of *α*, *β*-Unsaturated Carboxylic Acids

[40] Palladium-catalyzed hydrostannylations of highly hindered acetylenes in hexane. Semmelhack, M. F.; Hooley, R. J. *Tetrahedron Lett.* **2003**, *44*, 5737-5739.

[41] a) Is Metal Necessary in the Hunsdiecker-Borodin Reaction? Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett*. **1998**, *39*, 699-702. b) Catalytic Hunsdiecker Reaction of *α*, *β*-Unsaturated Carboxylic Acids: How efficient Is the Catalyst? Parkash, J.; Roy, S. *J. Org. Chem*. **2002**, *67*, 7861-7864. c) Catalytic Hunsdiecker Reaction and One-Pot Catalytic Hunsdiecker-Heck Strategy: Synthesis of *α*, *β*-Unsaturated Aromatic Halides, *α*-(Dihalomethyl)benzenemethanols, 5-Aryl-2,4-pentadienoic acids, Denoates, and Dienamides. Naskar, D.; Roy, S. *Tetrahedron*, **2000**, *56*, 1369-1377.

So, we applied this method to the known acid **1-13**[42], but the desired product **1-9** was not obtained under thermal conditions. However, when we used microwave reactor (260W) under the same reaction conditions, we got a quite pure mixture of E, E/ E, Z-iododienes **1-9** and **1-83** in 1 min (Scheme 1-31).



Scheme 1-31. Hunsdiecker reaction of the substrate **1-13**

1.2.2.1.6 Synthesis of pure (E, E)-iododiene **1-9**

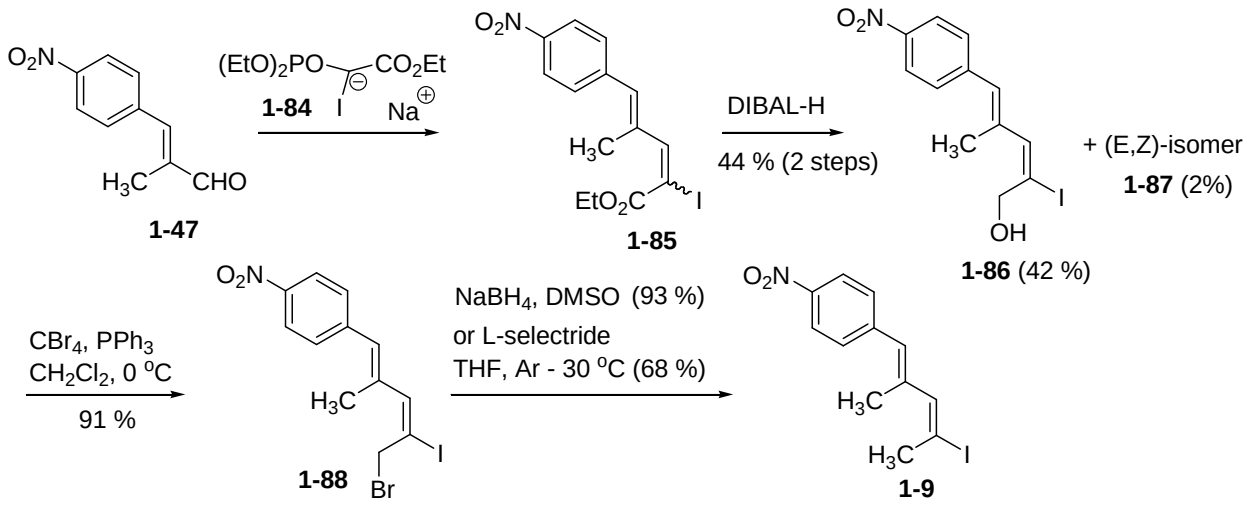
To obtain a geometrically pure form of (E, E)-iododiene **1-9**, we finally examined the Still-Gennari olefination of aldehyde **1-47** with the iodo reagent **1-84**.[43, 44] The olefination at low temperature gave iodoesters **1-85**, and the esters were directly reduced by DIBAL-H to furnish the 2-iodoallylic alcohols in 44 % yield (42% for EE-diene **1-86** and and 2 % for EZ-diene **1-87**,

[42] Interchenar Retrotransfer of Aureothin Intermediates in an Iterative Polyketide Synthase Module. Busch, B.; Ueberschaar, N.; Sugimoto, Y.; Hertweck, C. *J. Am. Chem. Soc*. **2012**, *134*, 12382-12385.

[43] A versatile building block for the synthesis of substituted cyclopropanephosphonic acid esters. Töke, L.; Jászay, Z. M.; Petneházy, I.; Clementis, G.; Vereczkey, G. D.; Kövesdi, I.; Rockenbauer, A.; Kováts, K. *Tetrahedron* **1995**, *51*, 9167-9178.

[44] A one-pot synthesis of (*E*)-α-bromo-α,β-unsaturated esters and their trifluoromethylation: a general and stereoselective route to (*E*)-α-trifluoromethyl-α,β-unsaturated esters. Qing, F. –L.; Zhang, X. *Tetrahedron Lett*. **2001**, *42*, 5929-5931.

two steps). van Tamelen's procedure was adapted for the conversion of allylic alcohol **1-86** to bromide **1-88**.[45] The resulting bromide **1-88** was reduced by either L-selectride (68 %) or sodium borohydride in DMSO[46] (93 %) to afford the desired (E, E)-iododiene **1-9** (Scheme 1-32).



Scheme 1-32. Synthesis of (E, E)-iododiene **1-9**

The stereochemistry of the intermediates **1-86**, **1-88**, and **1-9** was identified by 1D NOE nmr experiments (Table 1-5, 1-6, 1-7).

[45] A General 1,s-Diene Synthesis Involving Overall Allyl Alcohol Coupling with Geometrical and Positional Control. Axelrod, E. H.; Milne, *G.* M.; Tamelen, E. E. V. *J. Am. Chem. Soc.* **1970**, *92*, 2139-2141.

[46] a) Sodium borohydride in dimethyl sulfoxide or sulfolane. Convenient systems for selective reductions of primary, secondary and certain tertiary halides and tosylates. Hutchins, R. O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* **1969**, 3495-3498. b) Reduction of organic halogen compounds by sodium borohydride. Bell, H. M.; Vanderslice, C. W.; Spehar, A. *J. Org. Chem.* **1969**, *34*, 3923.

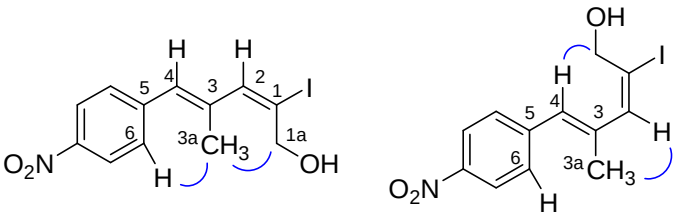


Table 1-5. Difference NOE chart for compound **1-86**

Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH_3 (3a, 2.01)	CH_2 (1a, 4.44), CH (2, 6.96), CH (6, 7.42)
CH_2 (1a, 4.44)	CH_3 (3a, 2.01), CH (4, 6.46)

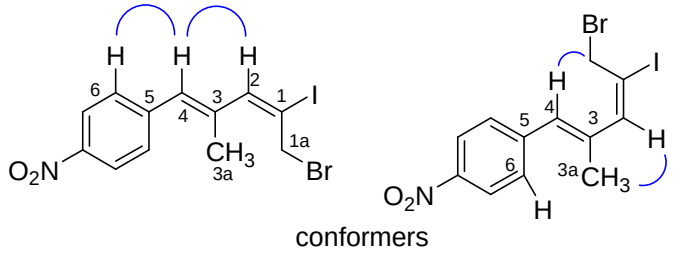


Table 1-6. Difference NOE chart for compound **1-88**

Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH (4, 6.71)	CH_2 (1a, 4.53), CH (2, 6.93), CH (6, 7.46)
CH (2, 6.93)	CH_3 (3a, 2.05), CH (4, 6.71)

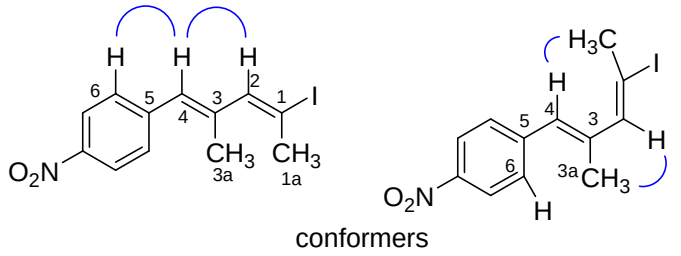
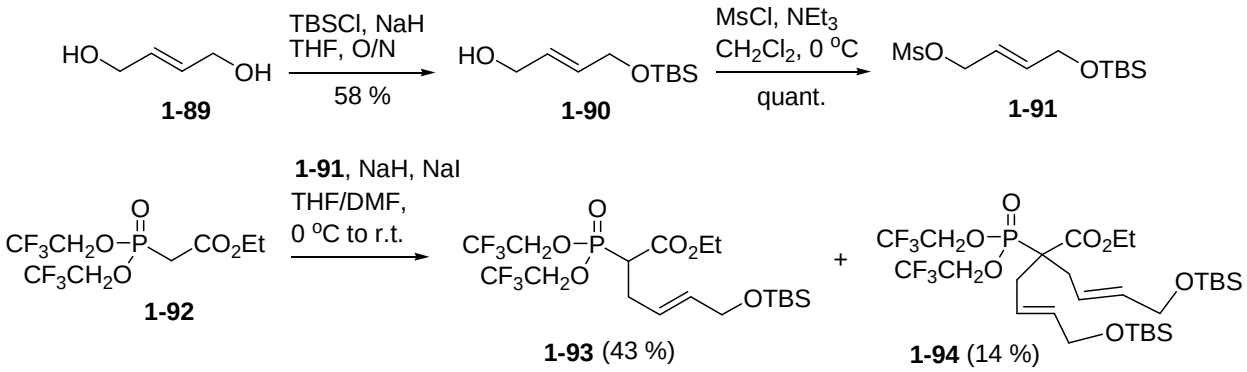


Table 1-7. Difference NOE chart for compound **1-9**

Inverted peak (C_{number}, ppm)	Enhanced peaks (C_{number}, ppm)
CH (4, 6.40)	CH_3 (1a, 2.68), CH (2, 6.81), CH (6, 7.42)
CH (2, 6.81)	CH_3 (3a, 2.01), CH (4, 6.40)

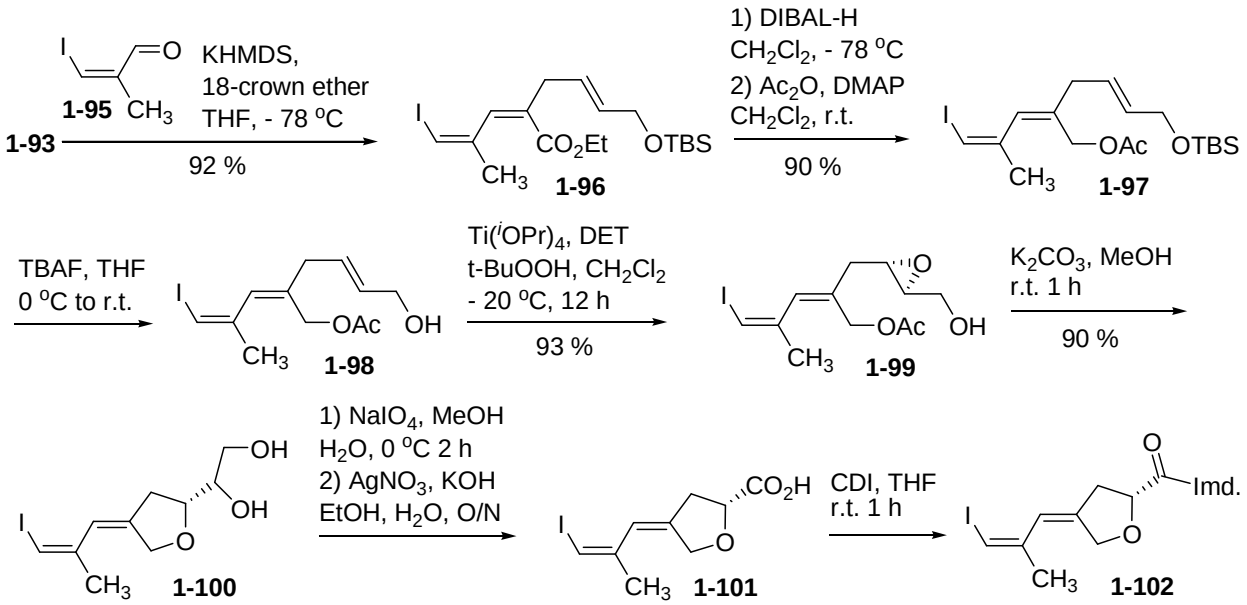
1.2.2.2 Preparation of γ-pyrone **1-10**

The γ-pyrone **1-10** was synthesized according to the known procedure.[8] First, the Wittig reagent **1-93** was prepared by alkylation of the commercial phosphonate **1-92** with the mesylate **1-91** (Scheme 1-33).



Scheme 1-33. The preparation of the Wittig reagent **1-93**

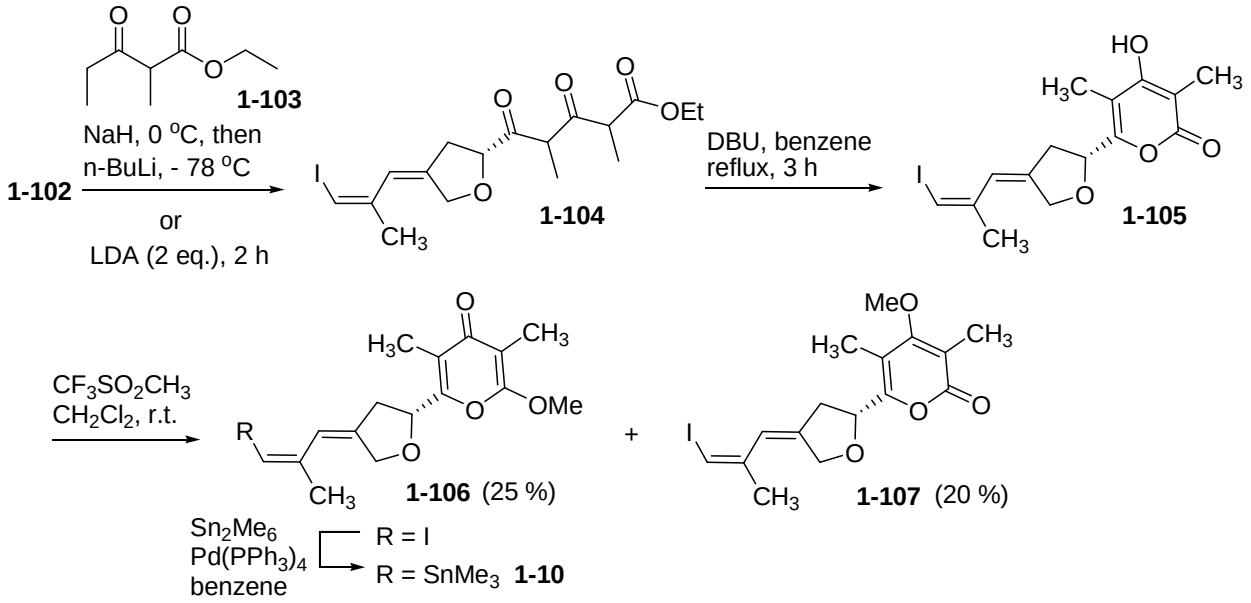
Next, the acyl imidazole **1-102** was prepared by 9-step sequence including Still-Gennari olefination, Sharpless asymmetric epoxidation, and oxidative cleavage of 1,2-diol. The chiral carbon C6 of the γ-pyrone **1-10** was constructed as an enantiomerically pure form (Scheme 1-34).



Scheme 1-34. Preparation of the acyl imidazole **1-102**

The completion of the synthesis of γ-pyrone **1-10** was achieved in 4 steps from the acyl imidazole **1-102**. The β-hydroxy-α-pyrone **1-105** was prepared by the substitution reaction of **1-102** with ketoester **1-103** followed by an intramolecular cyclization of the tricarbonyl **1-104** (Scheme 1-34). This was followed by selective methylation of β-hydroxy-α-pyrone **1-105** and an iodine-tin exchange (Scheme 1-35).

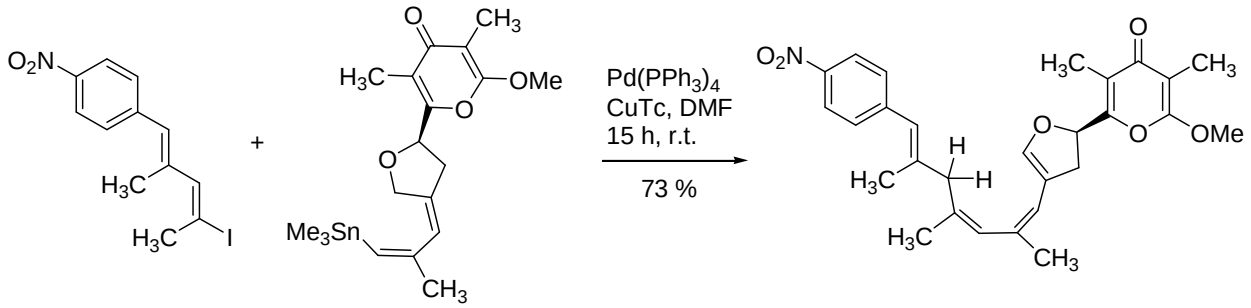
The conditions using LDA to form a dianionic reagent of the ketoester **97** was found to be more consistent and less sensitive than those using sodium hydride followed by butyl lithium.



Scheme 1-35. Preparation of γ-pyrone **1-10**

1.2.3 Coupling of the tin reagent **1-10** with iododiene **1-9** and isolation of arabilin

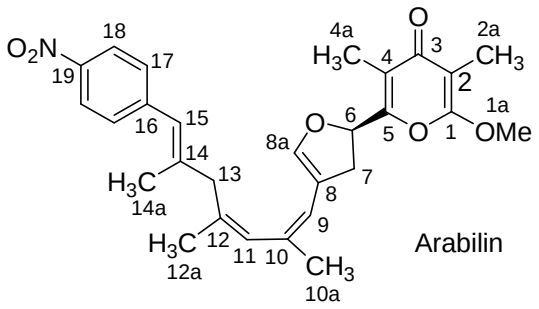
Having pure coupling partners **1-9** and **1-10**, the Pd(0)/Cu(I) catalytic system was applied (Scheme 1-36). Gratifyingly, (-)-arabilin was cleanly obtained with good yield (73 %). The optical rotation of our synthetic material was found to be -139.4 ^{o} (c 0.16, CH_2Cl_2, 20-21 ^{o}C) while that of the natural product is reported to be -166.2 ^{o}. Thus, the calculated enantiomeric excess of the synthetic natural product was approximately 84 %. The correlation of the optical rotation between natural- and synthetic arabilin confirmed the configuration of the C-6 chiral center as (R).



1-9 **1-10** **(-)-arabilin (1-1)**

Scheme 1-36. Synthesis of (-)-arabilin (**1-1**)

The ^{1}H and ^{13}C nmr spectra of synthetic arabilin were compared with those of authentic arabilin in Table 1-8. The chemical shifts as well as coupling constants were consistent with the authentic data.



Arabilin

Table 1-8. ^{1}H, ^{13}C-NMR for arabilin in $CDCl_3$, δ (ppm), *J* (Hertz)

Number	Authentic (^{1}H)	Synthetic (^{1}H)	Authentic (^{13}C)	Synthetic (^{13}C)
1	-	-	162.1	162.1
1a	3.92 (s, 3H)	3.92 (s, 3H)	55.3	55.3
2	-	-	99.9	99.9
2a	1.86 (s, 3H)	1.86 (s, 3H)	6.9	6.9
3	-	-	180.6	180.6
4	-	-	119.6	119.6
4a	2.02 (s, 3H)	2.02 (s, 3H)	9.4	9.4
5	-		154.2	154.3
6	5.59 (dd, *J*=11.01, 7.7 , 1H)	5.59 (dd, *J*=10.8, 7.6, 1H)	77.2	77.2
7	2.85 (dd, *J*=15.2, 7.5 , 1H)	2.85 (dd, *J*=15.2, 8.8, 1H)	35.6	35.7
	3.08 (dd, *J*=15.2, 11.0, 1H)	3.08 (dd, *J*=15.2, 11.2, 1H)		
8	-	-	114.9	114.9
8a	6.48 (s, 1H)	6.48 (s, 1H)	144.4	144.4
9	5.91 (s, 1H)	5.91 (s, 1H)	118.5	118.5
10	-	-	131.7	131.7
10a	1.88 (s, 3H)	1.88 (s, 3H)	25.3	25.2
11	5.99 (s, 1H)	5.99 (s, 1H)	128.6	128.6
12	-	-	134.7	134.7
12a	1.73 (bd, 3H)	1.73 (d, *J*=1.6, 3H)	22.8	22.8
13	2.91 (s, 2 H)	2.90 (s, 2H)	44.2	44.1
14	-	-	141.1	141.1
14a	1.81 (bd, 3 H)	1.81 (d, *J*=0.8, 3H)	18.1	18.1
15	6.32 (s, 1H)	6.32 (s, 1H)	124.9	124.9
16	-	-	145.1	145.1
17	7.35 (d, *J*=8.8, 2H)	7.35 (d, *J* = 8.4, 2H)	129.3	129.3
18	8.17 (d, *J*=8.8, 2H)	8.18 (d, *J* = 8.8, 2H)	123.5	123.5
19	-	-	145.9	145.9

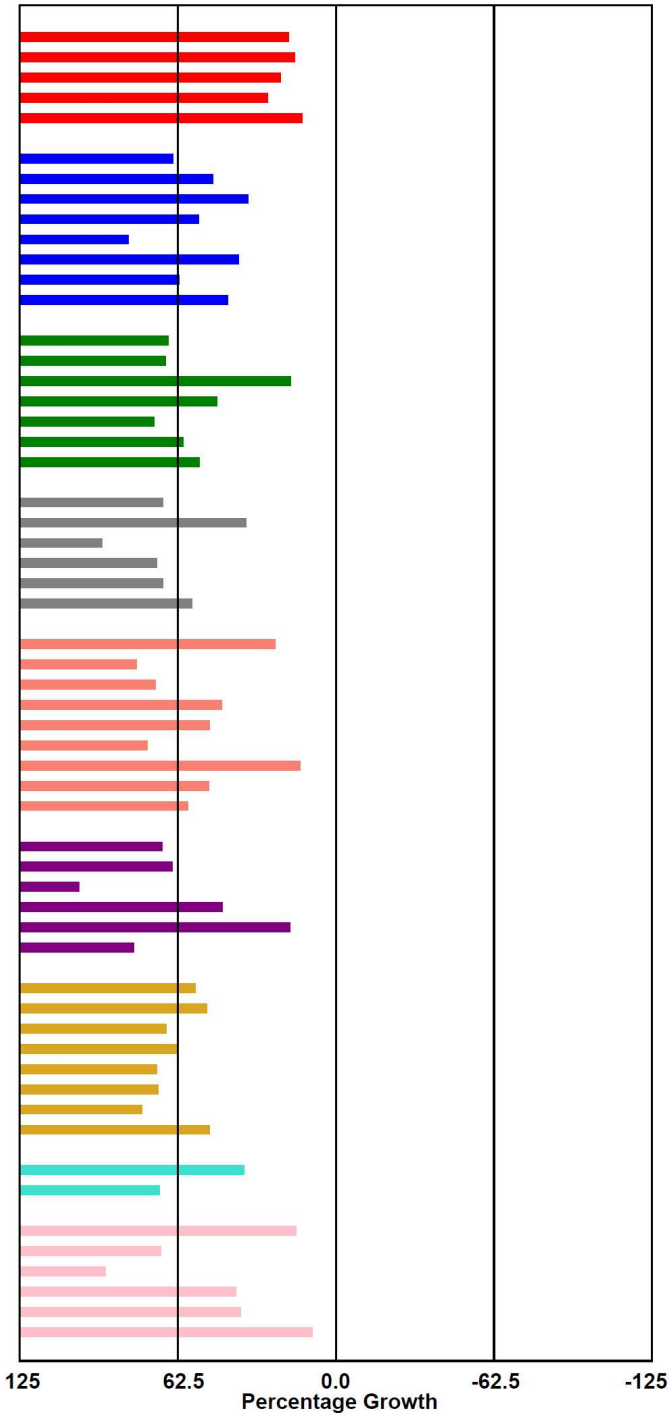
1.2.4 The test result in NCI-60 cell lines

The synthetic arabilin was sent to Dr. Beutler in Nation Cancer Institute (NCI) for further screening in NCI-60 cell line. The resulting data is attached. The first set of data is from a one dose experiment for measuring the relative cell death. As shown in the first two bar graphs, the selective activity against the prostate cancer cell was not observed. The second set of data is from the full dose experiment.

Developmental Therapeutics Program One Dose Bar Graph	NSC: D-761943 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 24, 2011
	Experiment ID: 1110OS52		Report Date: Nov 18, 2011

Panel/Cell Line	Growth Percent
Leukemia	
HL-60(TB)	18.92
K-562	16.58
MOLT-4	22.12
RPMI-8226	27.16
SR	13.70
Non-Small Cell Lung Cancer	
A549/ATCC	64.62
EKVX	48.89
HOP-62	35.11
HOP-92	54.48
NCI-H226	82.46
NCI-H23	38.82
NCI-H460	62.21
NCI-H522	43.06
Colon Cancer	
COLO 205	66.63
HCC-2998	67.71
HCT-116	18.27
HCT-15	47.18
HT29	72.09
KM12	60.61
SW-620	54.28
CNS Cancer	
SF-268	68.78
SF-295	35.91
SF-539	92.63
SNB-19	71.19
SNB-75	68.68
U251	57.21
Melanoma	
LOX IMVI	24.32
MALME-3M	79.10
M14	71.60
MDA-MB-435	45.44
SK-MEL-2	50.16
SK-MEL-28	74.76
SK-MEL-5	14.30
UACC-257	50.61
UACC-62	58.70
Ovarian Cancer	
IGROV1	69.08
OVCAR-3	65.06
OVCAR-5	101.86
OVCAR-8	45.25
NCI/ADR-RES	18.37
SK-OV-3	80.32
Renal Cancer	
786-0	55.84
A498	51.42
ACHN	67.40
CAKI-1	62.75
RXF 393	71.12
SN12C	70.69
TK-10	76.90
UO-31	50.33
Prostate Cancer	
PC-3	36.65
DU-145	69.97
Breast Cancer	
MCF7	15.93
MDA-MB-231/ATCC	69.47
HS 578T	91.51
BT-549	39.80
T-47D	37.93
MDA-MB-468	9.69

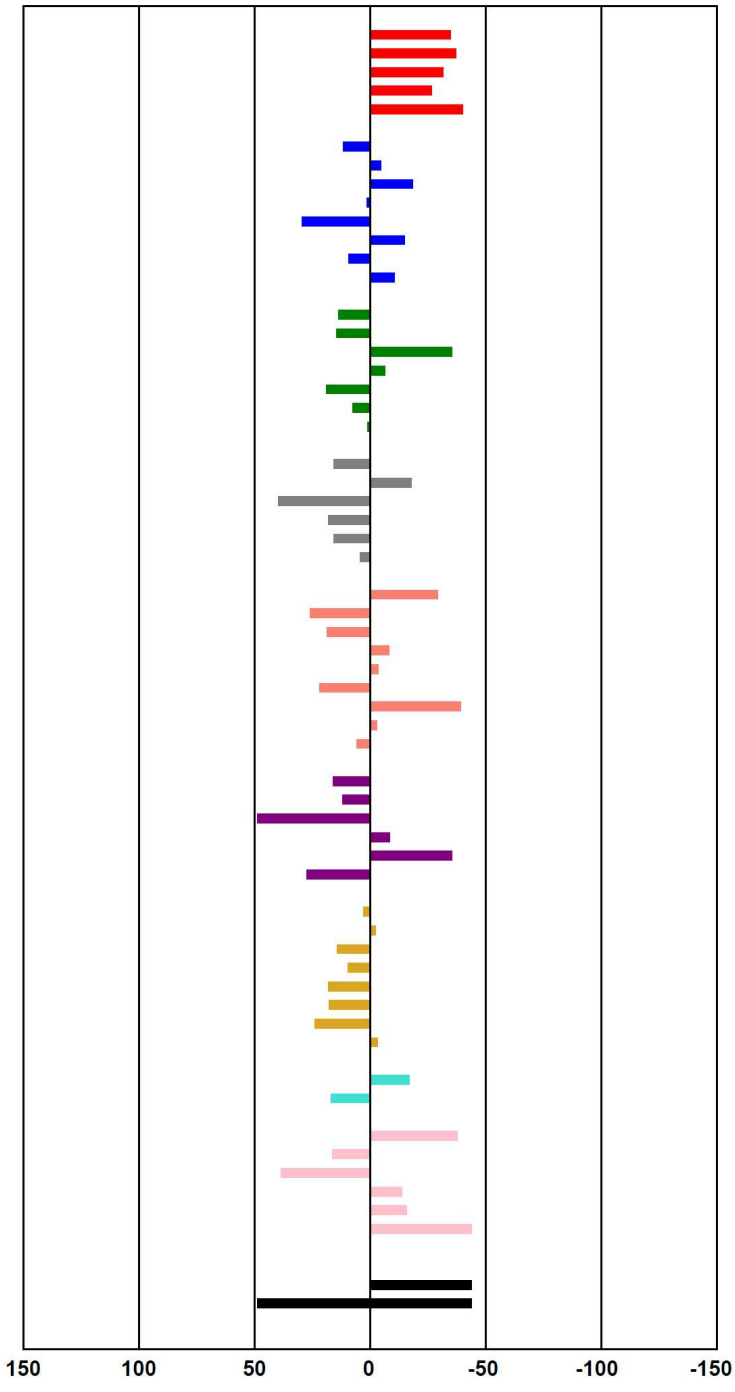
Bar Graph



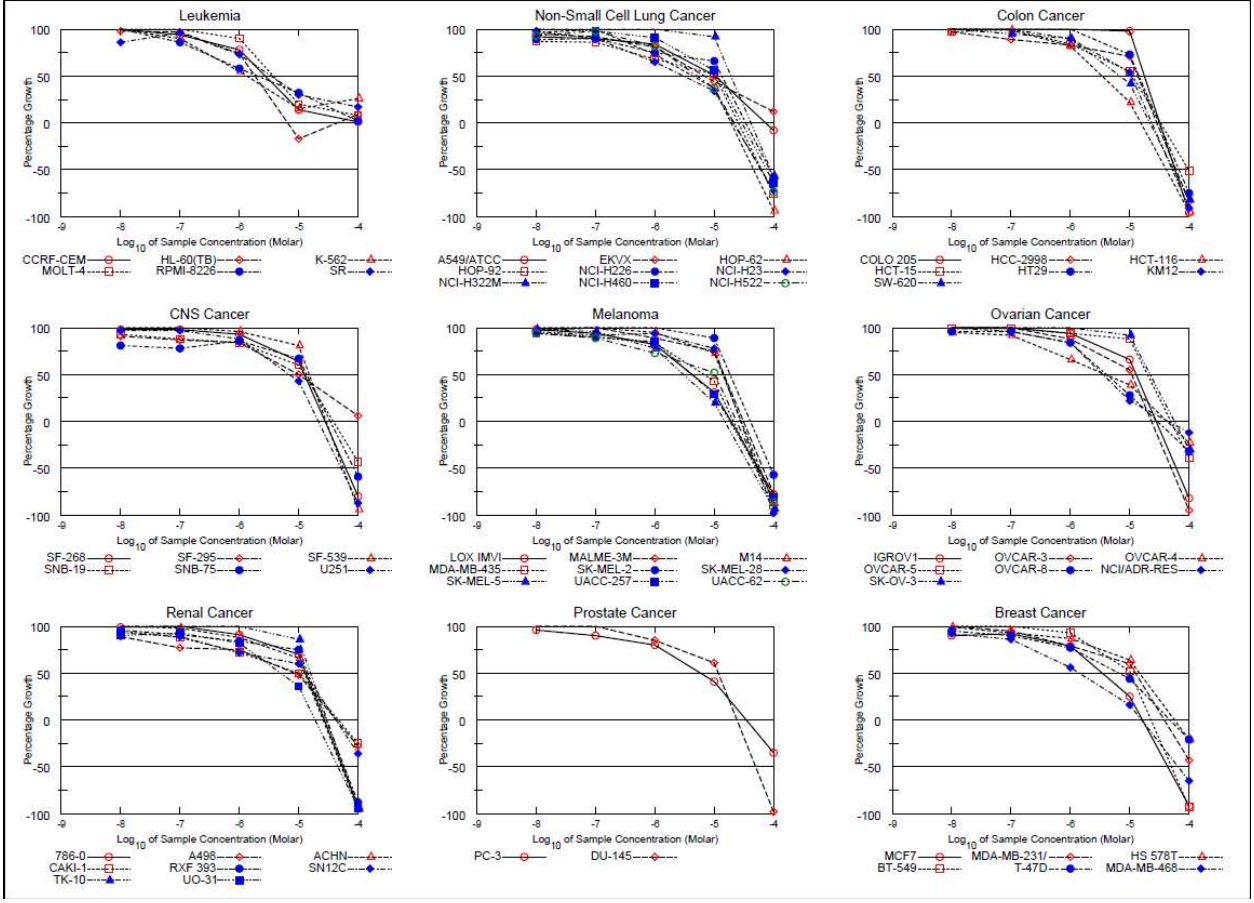
Developmental Therapeutics Program	NSC: D-761943 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 24, 2011
One Dose Mean Graph	Experiment ID: 1110OS52		Report Date: Nov 18, 2011

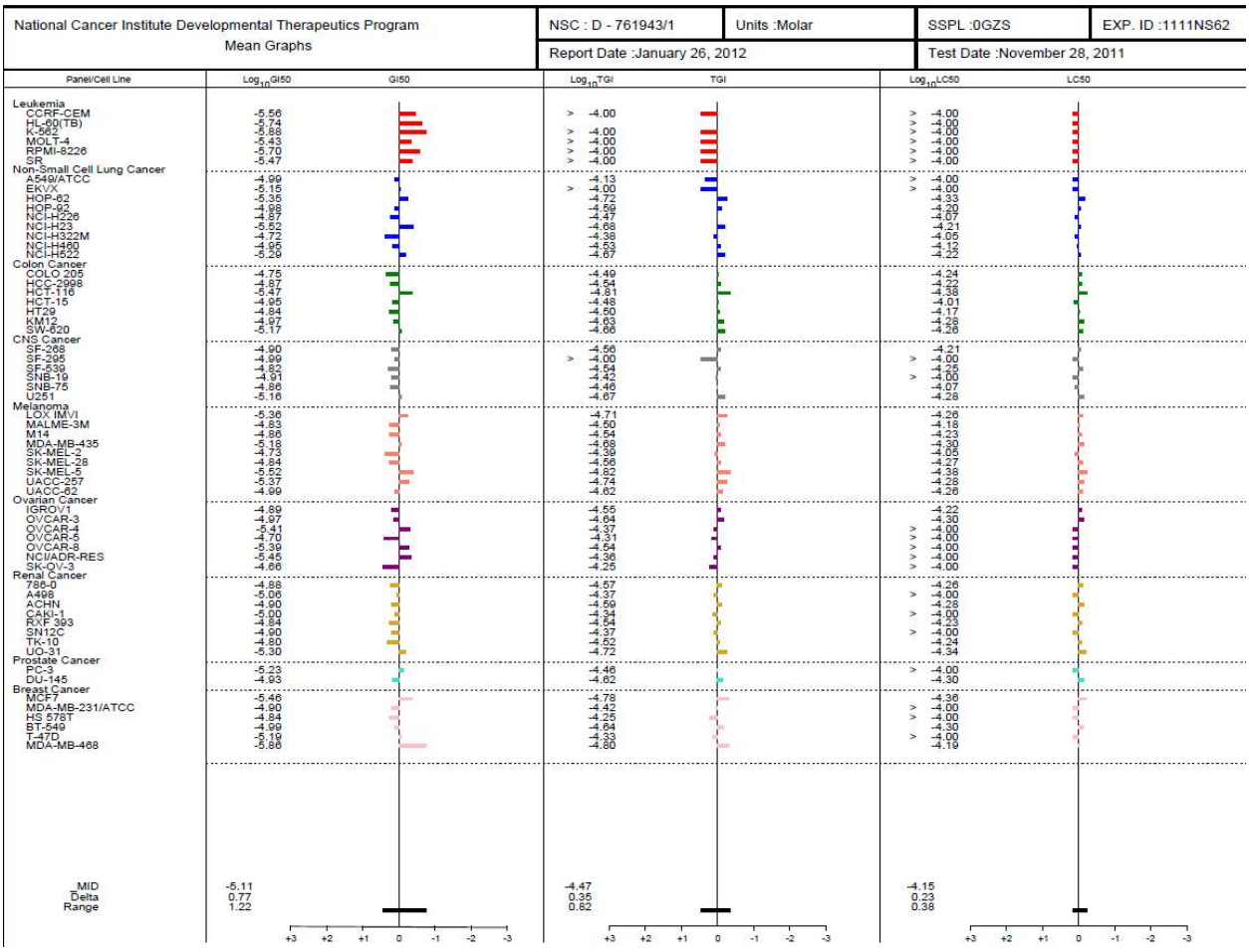
Panel/Cell Line	Growth Percent
Leukemia	
HL-60(TB)	18.92
K-562	16.58
MOLT-4	22.12
RPMI-8226	27.16
SR	13.70
Non-Small Cell Lung Cancer	
A549/ATCC	64.62
EKVX	48.89
HOP-62	35.11
HOP-92	54.48
NCI-H226	82.46
NCI-H23	38.82
NCI-H460	62.21
NCI-H522	43.06
Colon Cancer	
COLO 205	66.63
HCC-2998	67.71
HCT-116	18.27
HCT-15	47.18
HT29	72.09
KM12	60.61
SW-620	54.28
CNS Cancer	
SF-268	68.78
SF-295	35.91
SF-539	92.63
SNB-19	71.19
SNB-75	68.68
U251	57.21
Melanoma	
LOX IMVI	24.32
MALME-3M	79.10
M14	71.60
MDA-MB-435	45.44
SK-MEL-2	50.16
SK-MEL-28	74.76
SK-MEL-5	14.30
UACC-257	50.61
UACC-62	58.70
Ovarian Cancer	
IGROV1	69.08
OVCAR-3	65.06
OVCAR-5	101.86
OVCAR-8	45.25
NCI/ADR-RES	18.37
SK-OV-3	80.32
Renal Cancer	
786-0	55.84
A498	51.42
ACHN	67.40
CAKI-1	62.75
RXF 393	71.12
SN12C	70.69
TK-10	76.90
UO-31	50.33
Prostate Cancer	
PC-3	36.65
DU-145	69.97
Breast Cancer	
MCF7	15.93
MDA-MB-231/ATCC	69.47
HS 578T	91.51
BT-549	39.80
T-47D	37.93
MDA-MB-468	9.69
Mean	53.26
Delta	43.57
Range	92.17

Mean Growth Percent - Growth Percent



National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: D - 761943 / 1	SSPL: 0GZS	EXP. ID: 1111NS62
	Report Date: January 26, 2012	Test Date: November 28, 2011	





1.3 Conclusion

Our total synthesis of (-)-arabilin, the first and to date the only synthesis, requires 15 steps in the longest linear sequence and 19 steps total from commercially available starting materials.

We postulated that the skipped tetraene structure of (-)-arabilin was presumably derived by a thermal isomerization, [1,7]-H shift in this case, from the fully conjugated (E, E, Z, Z)-tetraene structure. Before the total synthesis, we tested a simple model compound closely related to the structure of (-)-arabilin. In a model experiment, we observed [1,7]-H shift at room temperature, giving a desired skipped tetraene **1-42** from the fully conjugated (E, E, Z, Z)-tetraene **1-43**.

This result allowed us to set out on a total synthesis of (-)-arabilin. We needed two coupling partners, (E, E)-iododiene **1-10** and (E, Z)-stannyldiene **1-10**. The significant efforts to prepare (E, E)-iododiene **1-9** were not successful; hydroboration, hydrozirconation, and stannylcupration.

A diastereomeric mixture of (E, E)- and (E, Z)-iododiene was obtained when the Hunsdieker reaction was applied to diene-carboxylic acid **1-13**. Finally, the pure (E, E)-iododiene **1-9** was prepared by a 5-step sequence that included amodified Still-Gennari olefination as a key step. (E, Z)-Stannyldiene **1-10** was obtained by the known procedure. The coupling of **1-9** and **1-10** successfully provided (-)-arabilin (**1-1**) in 73 % yield.

Our synthesis of (-)-arabilin demonstrates the effective use of a [1,7]-hydrogen shift as a key step and supports the premise that this rearrangement is a nonenzymatic step in the biosynthesis of this interesting natural product

1.4 Experimental Section

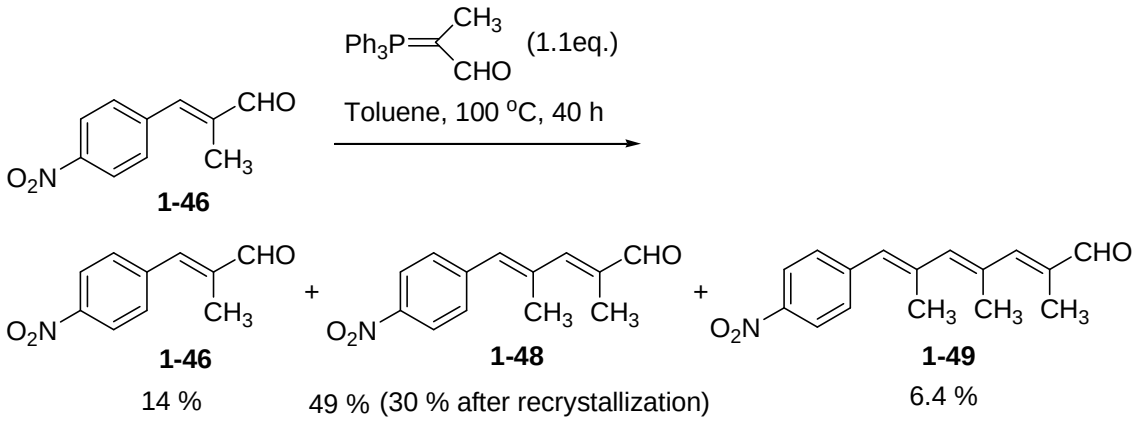
General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. HPLC grade hexane, EtOAc, CH_2Cl_2 and CH_3OH were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol or $KMnO_4$ aq. solution and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for ^1H and 126 MHz for ^{13}C), Varian Inova-400 (400 MHz for ^1H and 100 MHz for ^{13}C), or Gemini-2300 (300 MHz for ^1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-*d*. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and

NOE experiments were measured on a Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

Experimetal Procedure/ Characterization

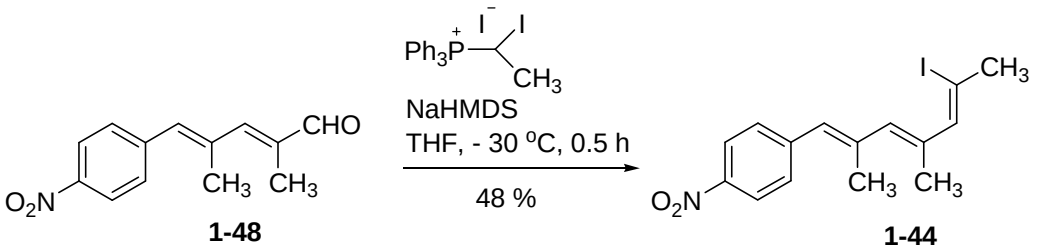


Aldehydes 1-48 and 1-49. To a stirred solution of the aldehyde **1-46** (0.31 g, 1.60 mmol) in toluene (10 mL) was added (triphenylphosphoranylidene)propionaldehyde (0.56 g, 1.76 mmol) under Ar. The reaction mixture was then heated to reflux for 20 h. The solution was cooled and concentrated. The residue was chromatographed (Hex:EtOAc = 5:1) to afford singly homologated aldehyde **1-48** (0.18 g, 49 %) and doubly homologated aldehyde **1-49** (28.0 mg, 6.4 %).

Aldehyde **1-48**: Rf value: 0.25 (Hex:EtOAc = 5:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3 H), 2.24 (s, 3 H), 6.83 (s, 3 H), 6.90 (s, 1 H), 7.50 (d, *J* = 8.5 Hz, 2 H), 8.25 (d, *J* = 8.5 Hz, 2 H), 9.51 (s, 1 H). The data were consistent with literature values.[47]

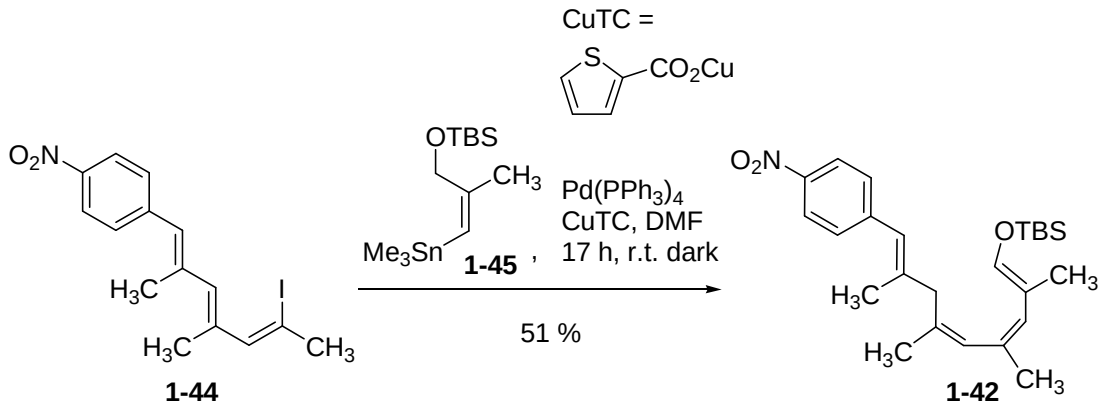
Aldehyde **1-49**: Rf value: 0.30 (Hex:EtOAc = 5:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3 H), 2.12 (s, 3 H), 2.24 (s, 3 H), 6.40 (s, 1 H), 6.58 (s, 1 H), 6.82 (s, 1 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 8.23 (d, *J* = 8.5 Hz, 2 H), 9.46 (s, 1 H).). The data were consistent with literature values.[55]

[47] Biomimetic studies on polyenes. Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Organic Letters* **2002**, *4*, 3731-3734.



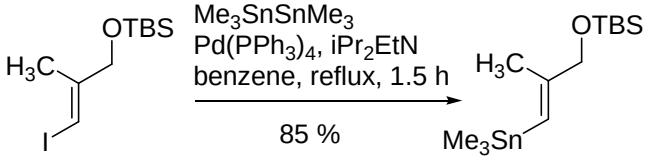
(E, E, Z)-Iodotriene 1-44 In an oven-dried 50 mL round bottom flask was placed ethyltriphenylphosphonium iodide (1.27 g, 2.35 mmol). After the flask was flushed with an Ar streamAn Ar stream for 10 min, dry THF (10 mL) was added. NaHMDS (1.05 mL, 2 M in THF, 2.11 mmol) was added at – 30 ^{o}C, and then the reaction mixture was stirred for 10 min. The solution of the aldehyde **1-48** (0.27 g, 1.17 mmol) in THF (2 mL) was added dropwise to the solution of phosphine ylide at same temperature. After 0.5 h, the mixture was warmed to room temperature and quenched with sat. NH_4Cl aq. solution. The mixture was extracted with ethyl acetate (20 mL X 3), and the combined organic solution was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (Hex:EtOAc = 20:1) to afford the *E, E, Z*-iodotriene **1-44** as yellow oil (0.21 g, 48 %).

Rf value: 0.65 (Hex:EtOAc = 20:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.08 (d, *J* = 1.0 Hz, 3 H), 2.61 (d, *J* = 1.5 Hz, 3 H), 6.08 (s, 1 H), 6.11 (s, 1 H), 6.48 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 2 H), 8.19 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.2, 19.1, 35.0, 98.3, 123.5, 128.1, 129.5, 134.7, 136.6, 138.2, 139.0, 144.6, 145.9.; IR (neat) νmax 1338, 1441, 1514, 1591, 2912 cm^{-1}.; HRMS[ES+] calcd for $C_{15}H_{16}INO_2$ $[M + Na]^+$ 392.0124, found 392.0134.



Enol ether 1-42 To a stirred solution of the *E, E, Z*-iodotriene **1-44** (28.4 mg, 76.9 μmol) and vinyl stannane **1-45**[22] (53.7 mg, 153.8 μmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (13.2 mg, 11.5 μmol) and CuTC[24a] (copper thiophene-2-carboxylate, 21.9 mg, 115.3 μmol). Then, the reaction flask was wrapped with aluminum foil. The reaction mixture was purged by an Ar streamAn Ar stream for 10 min at room temperature and then it was stirred and monitored by tlc. After 2 h, a deep yellow spot, Rf = 0.75 (Hex:EtOAc = 20:1), appeared and after 13 h, this had disappeared while a new spot, Rf = 0.78 (Hex:EtOAc = 20:1), visible under uv light, appeared. The reaction mixture was quenched with water and diethyl ether was added. Then, the suspension was filtered through a short pad of Celite and the Celite was washed with diethyl ether several times. The filtrate was partitioned, and the organic layer was washed with water (5 mL x 3) and brine. Then it was dried over $MgSO_4$, filtered, and concentrated. The crude mixture was subjected to preparative TLC (Hex:EtOAc = 10:1) to afford the enol ether **1-42** (16.7 mg, 51 %) as pale yellow oil.

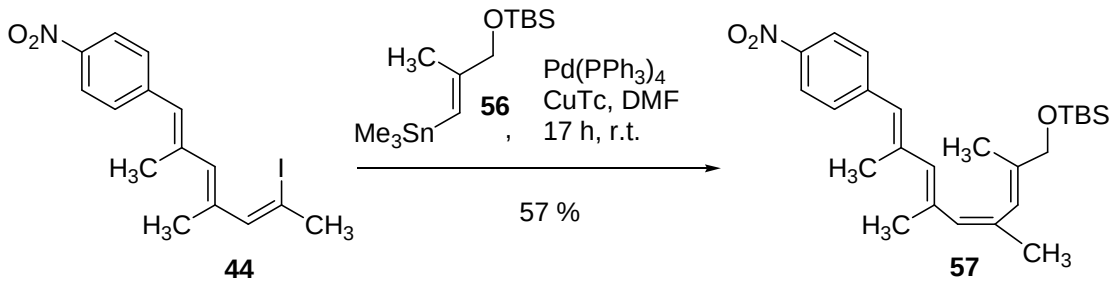
Rf value: 0.75 (Hex:EtOAc = 20:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 0.93 (s, 9 H), 1.70 (d, *J* = 1.2 Hz, 3 H), 1.73 (d, *J* = 1.6 Hz, 3 H), 1.82 (d, *J* = 1.2 Hz, 3 H), 1.86 (s, 3H), 2.92 (s, 2 H), 5.70 (d, *J* = 1.2 Hz, 1H), 6.06 (s, 1 H), 6.32 (s, 1 H), 6.37 (s, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 8.17 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 12.7, 18.2, 18.3, 22.9, 25.6, 44.1, 117.3, 123.5, 124.5, 127.7, 129.3, 129.6, 129.8, 133.0, 141.0, 142.0, 145.5, 145.8.; IR (neat) νmax 1176, 1342, 1518, 1595, 1635 cm^{-1}.; HRMS[ES+] calcd for $C_{25}H_{37}NO_3Si$ $[M + H]^+$ 450.2440, found 450.2447.



1-55 **1-56**

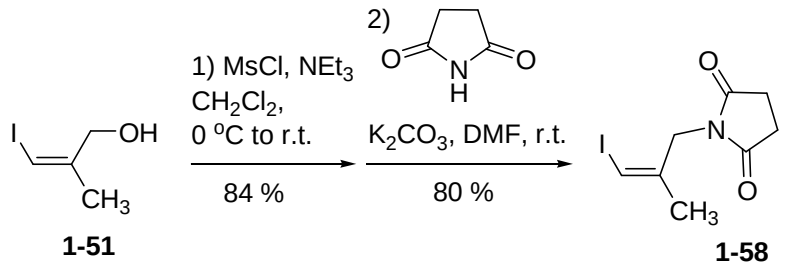
(E)-Vinylstannane 1-56 To a stirred solution of silyl ether **1-55** (39.0 mg, 125 μmol) in benzene (3 mL) was added diisopropylethylamine (6.2 μL, 37.4 μmol), hexamethylditin (31.0 μL, 150 μmol), and $Pd(PPh_3)_4$ (7.2 mg, 6.2 μmol) at room temperature. The reaction mixture was degassed by an Ar streamAn Ar stream for 10 min and stirred at reflux. After 2 h, the mixture was diluted with hexane, filtered through a pad of basic alumina, and concentrated. The crude

mixture was subjected to basic alumina chromatography to afford (E)-vinylstannane **1-56** as colorless oil (37.2 mg, 85 %). The toxic and unstable product was directly used for the next step without characterizations.



(*E, E, Z, E*)-tetraene enol ether 1-57 To a stirred solution of the iodotriene **1-44** (18.6 mg, 50.3 μmol) and vinyl stannane **1-56** (37 mg, 106 μmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (8.6 mg, 7.5 μmol) and CuTC (14.4 mg, 75.4 μmol). Then, the reaction flask was wrapped with aluminum foil. The mixture was degassed by an Ar streamAn Ar stream for 10 min at room temperature, and then allowed to stir for 17 h. The reaction mixture was quenched with water and diethyl ether. Then, the suspension was filtered through a short pad of Celite and washed with diethyl ether several times. The filtrate was partitioned, and the organic layer was washed with water (5 mL x 3), brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by preparative TLC (Hex: EtOAc = 4:1) to afford the tetraene **1-57** (12.3 mg, 57 %) as yellow oil. The product was not subjected to bulb-to-bulb distillation because of the possible thermal isomerizations.

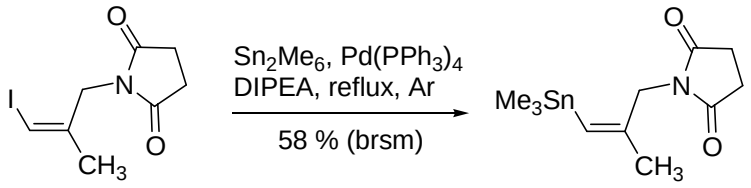
Rf value: 0.75 (Hex:EtOAc = 20:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.067 (s, 6 H, $2CH_3$), 0.905 (s, 9 H, $3CH_3$), 1.63 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3), 2.05 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 5.91 (s, 1 H, CH), 5.99 (s, 1 H, CH), 6.18 (s, 1 H, CH), 6.40 (s, 1 H, CH), 7.41 (d, *J* = 8.5 Hz, 2 H, 2CH), 8.18 (d, *J* = 9.0 Hz, 2 H, 2CH). ^{13}C NMR (126 MHz, $CDCl_3$) δ -5.3, 15.1, 18.4, 18.7, 19.6, 25.9, 68.0, 123.5, 124.3, 127.5, 129.4, 132.4, 133.8, 135.0, 136.0, 137.0, 140.0, 145.0, 145.7.; IR (neat) νmax 1109.4, 1339.8, 1440.7, 1515.9, 1592.4 cm^{-1}.; HRMS[ES+] calcd for $C_{25}H_{37}NO_3Si$ $[M + Na]^+$ 450.2440, found 450.2448.



1-51 **1-58**

N-Alkyl succinimide 1-58 Step 1: To a stirred solution of the alcohol **1-51** (0.39 g, 1.99 mmol) in CH_2Cl_2 (7 mL) was added triethylamine (0.33 mL, 2.39 mmol) and then mesyl chloride (0.17 mL, 2.19 mmol) at 0 ^oC. After 1 h, the reaction mixture was diluted with ethyl ether and washed with cold water, 1 N HCl, water, and sat $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$, filtered, and concentrated (crude yield = 84 %). The crude product was directly used for the next step. Step 2: To a stirred solution of mesylate (50 mg, 0.19 mmol) in DMF (1 mL) was added succinimide and potassium carbonate at room temperature under Ar. After 5 h, the mixture was diluted with ethyl acetate (15 mL) and washed with water (5 mL X 3). The organic solution was dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (Hex:EtOAc = 2:1) to afford the N-alkyl succinimide **1-58** as a colorless oil (42.4 mg, 80 %).

Rf value: 0.50 (Hex:EtOAc = 2:1) ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (d, J = 1.3 Hz, 3 H), 2.75 (s, 4 H), 4.26 (s, 2 H), 6.14 (q, J = 1.3 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7, 28.1, 45.9, 76.9, 140.2, 176.7.; IR (neat) νmax 1174, 1330, 1395, 1419, 1669 cm^{-1}.

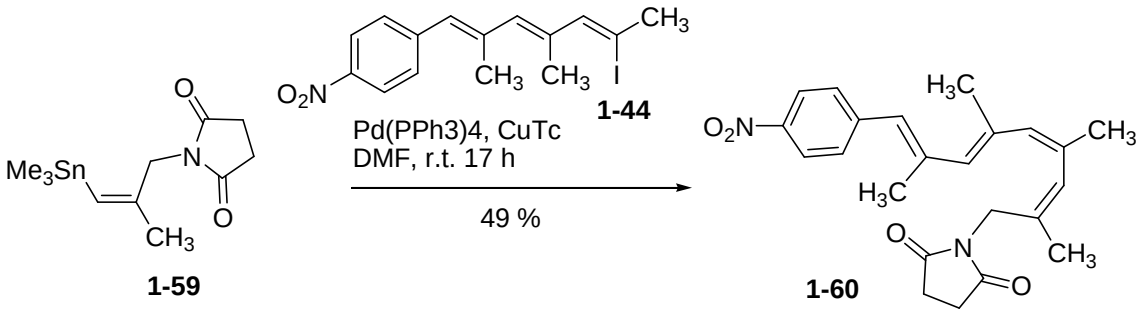


1-58 **1-59**

(Z)-Vinylstannane succinimide 1-59 To a stirred solution of N-alkyl succinimide **1-58** (42.0 mg, 150 μmol) in benzene (3 mL) was added diisopropylethylamine (7.5 μL, 45.1 μmol), hexamethylditin (37.0 μL, 181 μmol), and $Pd(PPh_3)_4$ (8.7 mg, 7.5 μmol) at room temperature. The reaction mixture was degassed by an Ar stream for 10 min and heated to reflux. After 2.5 h,

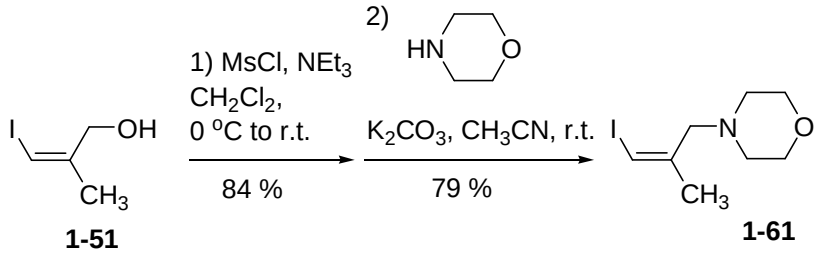
the mixture was diluted with hexane, filtered through a pad of basic alumina, and concentrated. The crude mixture was subjected to basic alumina chromatography to afford (Z)-vinylstannane succinimde **1-59** (colorless oil, 18.0 mg, isolation yield = 38 %, 58 % brsm, 14.4 mg of starting material was recovered).

Rf value: 0.50 (Hex:EtOAc = 2:1) ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.23 (s, 9 H), 1.75 (s, 3 H), 2.72 (s, 4 H), 4.14 (s, 2 H), 5.77 (s, 1 H).



(E, E, Z, Z)-Tetraene succinimide 1-60 To a stirred solution of the iodotriene **1-44** (28.0 mg, 75.9 μmol) and (Z)-vinyl stannane succinimide **1-59** (16.0 mg, 50.6 μmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (8.8 mg, 7.6 μmol) and CuTC (14.5 mg, 75.9 μmol). Then, the reaction flask was wrapped with aluminum foil. The mixture was degassed by an Ar stream for 10 min at room temperature, and then it was allowed to stir for 17 h. The mixture was quenched with water and diethyl ether. Then, the suspension was filtered through a short pad of Celite and washed with diethyl ether several times. The filtrate was partitioned, and the organic solution was washed with water (5 mL x 3) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by preparative TLC (Hex: EtOAc = 3:1) to afford the (E, E, Z, Z)-tetraene succinimide **1-60** (9.8 mg, 49 %) as yellow oil.

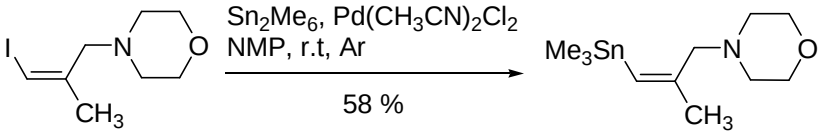
Rf value: 0.35 (Hex:EtOAc = 3:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.9465 (s, 3 H), 1.95 (s, 3 H), 2.05 (s, 3 H), 2.72 (s, 4 H), 4.12 (s, 2 H), 6.01 (br s, 2 H), 6.02 (s, 1 H), 6.44 (s, 1 H), 7.44 (d, *J* = 9.0 Hz, 2 H), 8.19 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.4, 19.5, 20.4, 25.1, 28.1, 40.2, 112.1, 123.5, 127.8, 129.5, 129.8, 133.2, 134.4, 134.5, 136.6, 139.7, 144.9, 145.7, 177.0.; IR (neat) νmax 1338, 1395, 1513, 1592, 1703 cm^{-1}.



1-51 **1-61**

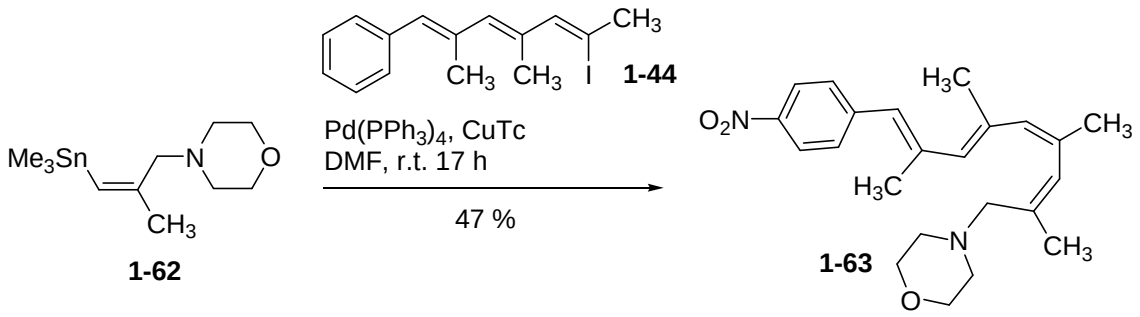
N-Alkyl morpholine 1-61 Step 1: Mesylate was prepared by the same protocol shown in the synthesis of N-alkyl succinimide **1-58**. Step 2: To a stirred solution of the mesylate (0.11 g, 0.43 mmol) in acetonitrile (2 mL) was added the morpholine (56.0 μL, 0.65 mmol) and potassium carbonate (0.12 g, 0.86 mmol). After 5 h, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic solution was then dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 5:1) to afford the N-alkyl morpholine **1-61** (91.2 mg, 79 %) as colorless oil.

Rf value: 0.75 (Hex:EtOAc = 20:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3 H), 2.43 (m, 4 H), 3.09 (s, 2 H), 3.68 (m, 4 H), 6.04 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 53.4, 65.0, 67.0, 143.9.; IR (neat) νmax 1118, 1275, 1453, 2852 cm^{-1}.



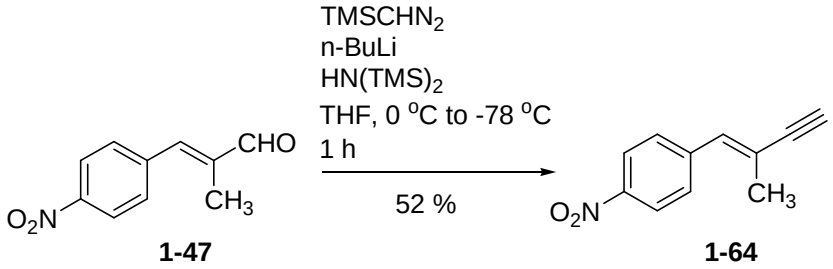
1-61 **1-62**

(Z)-Vinylstannane morpholine 1-62 To a stirred solution of N-alkyl morpholine **1-61** (16.2 mg, 60.6 μmol) and hexamethylditin (39.7 mg, 121 μmol) in NMP (0.4 mL, N-methylpyrrolidone) was added $Pd(CH_3CN)_2Cl_2$ (1.6 mg, 6.1 μmol) at room temperature. After stirring 15 h, the reaction mixture was directly subjected to chromatography on basic alumina (hex: ethyl ether = 10:1) to afford (Z)-vinylstannane morpholine **1-62** (15.1 mg, 58 %) as a colorless oil. The toxic and unstable product was directly used for the next step without characterizations.



(E, E, Z, Z)-tetraene morpholine 1-63 To a stirred solution of the iodotriene **1-44** (38.9 mg, 0.11 mmol) and (Z)-vinyl stannane morpholine **1-62** (22.7 mg, 52.7 μmol) in DMF (1 mL) was added $Pd(PPh_3)_4$ (9.1 mg, 7.9 μmol) and CuTC (15.1 mg, 79.0 μmol). Then, the reaction flask was wrapped with aluminum foil. The mixture was degassed by An Ar stream for 10 min at room temperature, and the mixture was allowed to stir for 18 h. The mixture was quenched with water and diethyl ether. Then, the suspension was filtered through a short pad of Celite and washed with diethyl ether several times. The filtrate was partitioned, and the organic layer was washed with water (5 mL x 3) and brine, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by preparative TLC (Hex: EtOAc = 3:1) to afford the (E, E, Z, Z)-tetraene morpholine **1-63** (8.7 mg, 49 %) as a yellow oil.

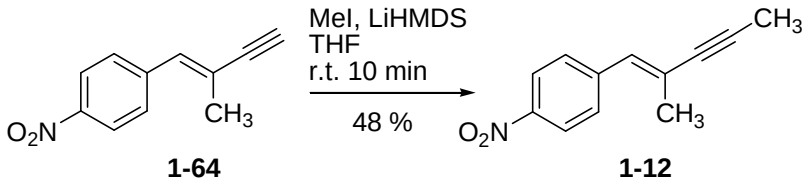
Rf value: 0.40 (Hex:EtOAc = 3:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 3H), 1.86 (s, 3 H), 1.94 (s, 3 H), 2.04 (s, 3 H), 2.33 (m, 4 H), 2.87 (s, 2 H), 3.68 (m, 4 H), 5.91 (s, 1 H), 5.98 (s, 1 H), 6.01 (s, 1 H), 6.37 (s, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 8.18 (d, *J* = 8.0 Hz, 2 H).



Terminal alkyne 1-64 n-BuLi (1.6 M in hexane, 2.25 mL, 3.60 mmol) was added to a stirred solution of $HN(TMS)_2$ (0.82 mL, 3.90 mmol) in THF (20 mL) at 0 °C under Ar. To this mixture was added dropwise $TMSCHN_2$ over 10 min and the aldehyde **1-47** (0.57 g, 3.0 mmol) in THF (5 mL) at -78 °C. After 1 h, the reaction nmixture was quenched with sat. H_4NCl sol'n and

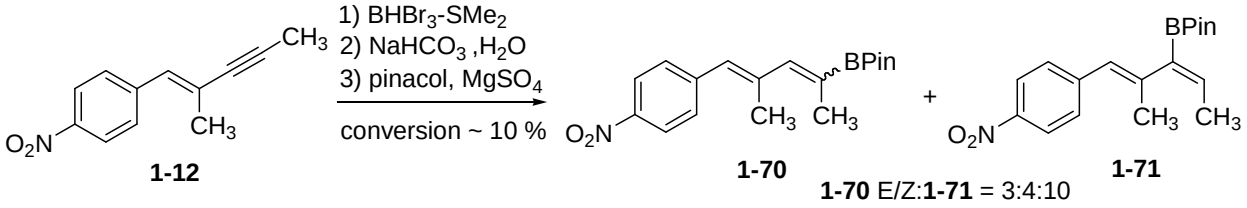
extracted with diethyl ether. The organic solution was then dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 30:1) to give the terminal alkyne **1-64** (0.29 g, 52 %) as a yellow solid.

Rf value: 0.40 (Hex:EtOAc = 20:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (d, *J* = 1.5 Hz, 3 H), 3.09 (s, 1 H), 6.93 (s, 1 H), 7.42 (d, *J* = 9.0 Hz, 2 H), 8.21 (d, *J* = 9.0 Hz, 2 H). IR (neat) νmax 1118.0, 1275.4, 1453.6, 2852.6 cm $^{-1}$.



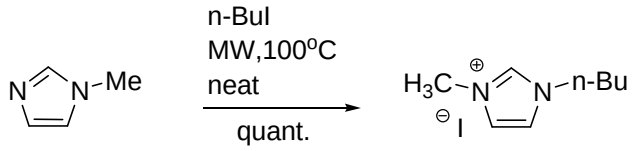
Internal alkyne 1-12 To a stirred solution of the terminal alkyne **1-64** (0.29 g, 1.57 mmol) in THF (5 mL) was added LiHMDS (1.0 M in THF, 1.88 mL) at 0 ^{o}C. After 5 min, MeI (0.20 mL, 3.14 mmol) was added, and, after stirring 10 min, the reaction mixture was quenched with water. The mixture was extracted with ethyl ether, dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 30:1) to give the internal alkyne **1-12** (0.15 g, 48 %) as an orange solid.

Rf value: 0.45 (Hex:EtOAc = 20:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.06 (s, 3 H), 6.75 (s, 1 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 8.18 (d, *J* = 8.5 Hz, 2 H). IR (neat) νmax 1337, 1510, 1592, 2221 cm^{-1}.



Hydroboration: Steps 1 and 2) The internal alkyne **1-12** (20.1 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and flushed with An Ar stream at 0 ^{o}C. To this mixture was added $HBBr_2{\cdot}SMe_2$ (1.0 M in CH_2Cl_2, 0.1 mL), and the mixture was stirred for 5 h at room temperature. The reaction mixture was poured to a mixture of ether (2 mL) and sat. $NaHCO_3$ sol'n at 0 ^{o}C and stirred for 30

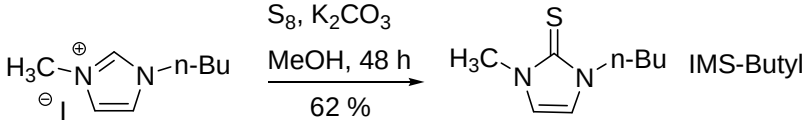
min. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic solution was washed with cold water, dried over $MgSO_4$, concentrated. Step 3) To a crude boronic acid in dry ether (2 mL) was added pinacol (13.0 mg, 0.2 mmol) and $MgSO_4$ (24.1 mg, 0.2 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with diethyl ether, filtered, concentrated, and purified by column chromatography (Hex: EtOAc = 30:1) to give an inseparable mixture of **1-70** and **1-71** (2.9 mg, ~10%). For the ratio of products, see ^{1}H nmr spectrum.



1-72 **1-73**

Imidazolium salt 1-73 A mixture of N-methylimidazole (1.64 g, 20.0 mmol) and n-BuI (4.04 g, 22.0 mmol) was stirred at 240 W (100 ^{o}C) for 1 min. The resulting sticky brown oil was washed with dry diethyl ether and dried under vaccum (~5 torr).

^{1}H NMR (300 MHz, D_2O) δ 0.77 (t, *J* = 7.5 Hz, 3 H), 1.17 (m, 2 H), 1.70 (m, 2 H), 3.74 (s, 3 H), 4.05 (t, *J* = 6.9 Hz, 2 H), 7.28 (s, 1 H), 7.33 (s, 1 H), 8.57 (s, 1 H). The data were consistent with literature values.[48]



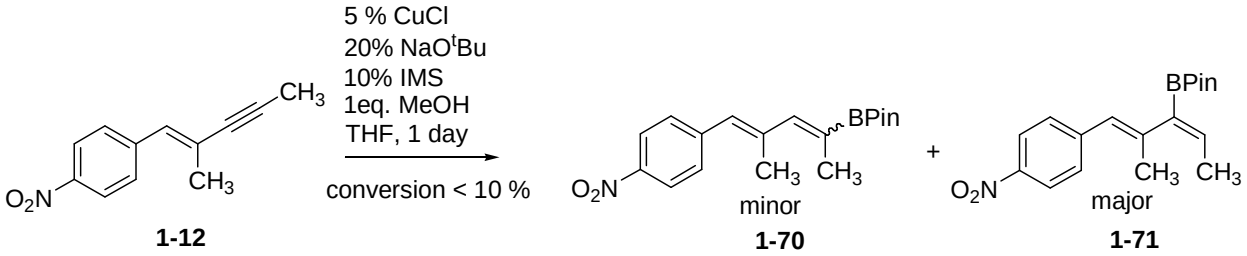
1-73 **1-74**

IMS-Butyl 1-74 The mixture of imidazolium salt **1-73** (4.39 g, 16.5 mmol), sulfur (0.63 g, 19.8 mmol), and K_2CO_3 (2.73 g, 19.8 mmol) in MeOH (30 mL) was stirred overnight. The mixture was concentrated, diluted with ethyl aceate, and washed with water. The organic solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc =

[48] Extended dissolution studies of cellulose in imidazolium based ionic liquids. Vitz, J.; Erdmenger, T.; Haensch, C.; Schubert, U. S. *Green Chem.*, **2009**, *11*, 417-424.

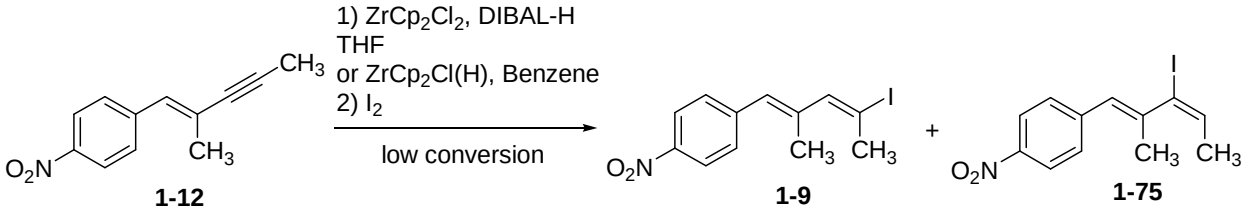
1:1) to give the IMS-Butyl **1-74** (0.15 g, 48 %) as an orange solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.36 (m, 2 H), 1.74 (m, 2 H), 3.60 (s, 3 H), 4.02 (t, *J* = 7.5 Hz, 2 H), 6.66 (d, *J* = 2.7 Hz, 1 H), 6.67 (d, *J* = 2.7 Hz, 1 H). IR (neat) νmax 1234, 1416, 1461, 1568, 2932, 2957 cm^{-1}. The data were consistent with literature values.[30]



1-12 **1-70** **1-71**

Cu-catalyzed hydroboration: In an oven dried two-neck round bottom flask were placed CuCl (0.5 mg, 5.0 μmol), IMS-butyl (1.7 mg, 10.0 μmol), NaO^{t}Bu (1.9 mg, 20.0 μmol) in THF (0.2 mL) under Ar, and the mixture was stirred for 30 min before bis(pinacolato)diboron (27.9 mg, 0.11 mmol) was added. After 10 min, the internal alkyne **12** (20.1 mg, 0.1 mmol) and then MeOH (6.4 μL) were added. Then, the reaction mixture was stirred overnight.

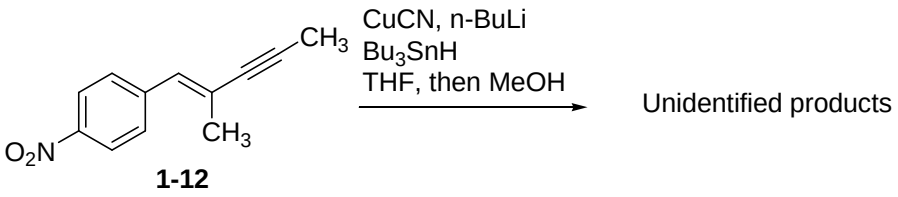


1-12 **1-9** **1-75**

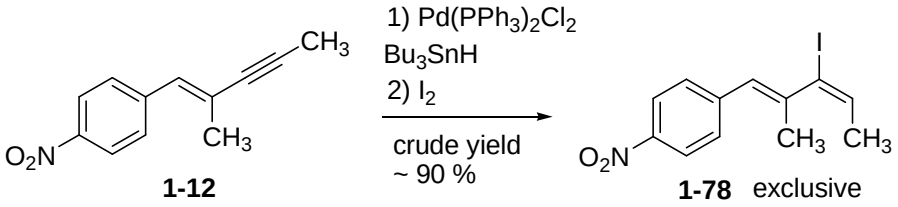
Hydrozirconation: Procedure 1) To a stirred solution of Cp_2ZrCl_2 (77.7 mg, 0.27 mmol) in THF (2 mL) was added DIBAL-H (1.0 M in hexane, 0.27 mL, 0.27 mmol) at 0 ^{o}C under Ar. The resulting suspension was stirred at room temperature for 1.5 h. The internal alkyne **1-12** (48.7 mg, 0.24 mmol) in benzene (2 mL) was added, and the reaction mixture was stirred for 1.5 h. Then, I_2 in benzene (2 mL) was slowly added to the mixture at 0 ^{o}C. After 1 h, the reaction mixture was quenched with sat. $Na_2S_2O_3$ sol'n, and extracted with diethyl ether. The combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The ^{1}H nmr spectrum of the residue showed the regioisomers **1-9** and **1-75** with low conversion.

Procedure 2) $Cp_2ZrCl(H)$ (28.3 mg, 0.11 mmol) was placed in oven-dried 10 mL round bottom

flask, flushed with Ar, and charged with benzene (1 mL). The internal alkyne **12** (20.1 mg, 0.1 mmol) in benzene (1.0 mL) was added and the mixture was stirred overnight. Then, I_2 in benzene (2 mL) was slowly added to the mixture at 0 ^oC. After 1 h, the reaction mixture was quenched with sat. $Na_2S_2O_3$ sol'n and extracted with diethyl ether. The combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The crude ^1H nmr spectrum showed the regioisomers **1-9** and **1-75** with low conversion.



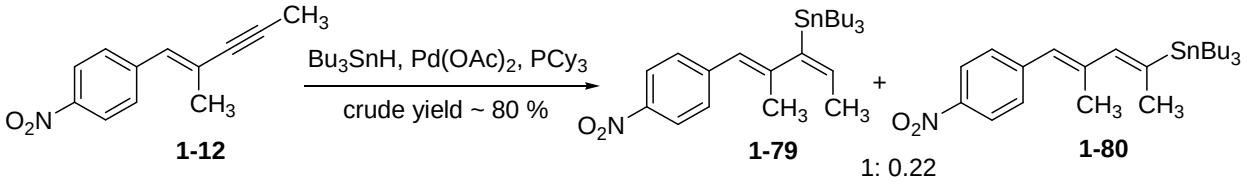
Stannylcupration: To a stirred suspension of CuCN (8.9 mg, 0.1 mmol) in THF (1.5 mL) was added n-BuLi (1.6 M in THF, 0.13 mL, 0.2 mmol) at - 50 ^oC. After stirring for 15 min, tributyltin hydride (53.0 μL, 0.2 mmol) was added, and the resulting bright yellow solution was stirred for 30 min at - 50 ^oC. The internal alkyne **1-12** (20.1 mg, 0.1 mmol) in THF (0.5 mL) was added to the mixture, and the reaction mixture was stirred for 3 h. Then, degassed MeOH (0.38 mL, 10 mmol) was added to the mixture at – 78 ^oC, and the resulting deep red solution was stirred at - 40 ^oC for 30 min. The reaction mixture was quenched with water and extracted with diethyl ether. The combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The yellow crude mixture was subjected to basic alumina column chromatography (pentane: diethyl ether = 50:1) to afford two mysterious products. The structures of these products were not yet determined.



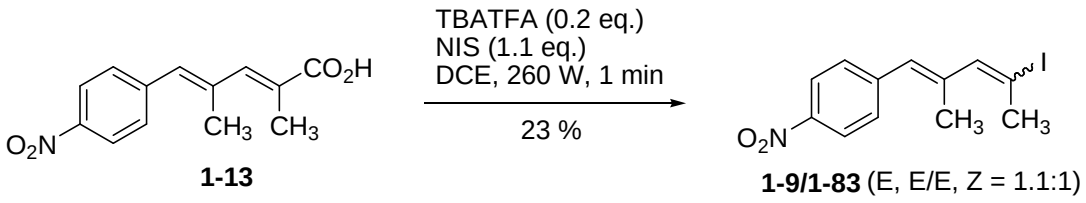
Hydrostannylation 1: To a stirred solution of the internal alkyne **1-12** (20.1 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added $Pd(PPh_3)_4$ (2.8 mg, 4.0 μmol) and tributyltin hydride (79.5 μL, 0.3

mmol) at room temperature. After 10 min, the reaction mixture was quenched with I_2 (63.4 mg, 0.25 mmol) in CH_2Cl_2 (1.5 mL) and then washed with sat. $Na_2S_2O_3$. The organic solution was dried over $MgSO_4$, filtered, and concentrated. The ^1H nmr spectrum of crude product revealed the exclusive formation of iodinated product **1-78**.

Rf value: 0.50 (Hex:EtOAc = 20:1) ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (d, *J* = 6.9 Hz, 3 H), 2.06 (d, *J* = 1.2 Hz, 3 H), 6.29 (q, *J* = 6.9 Hz, 1 H), 6.52 (s, 1 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 8.21 (d, *J* = 8.4 Hz, 2 H).



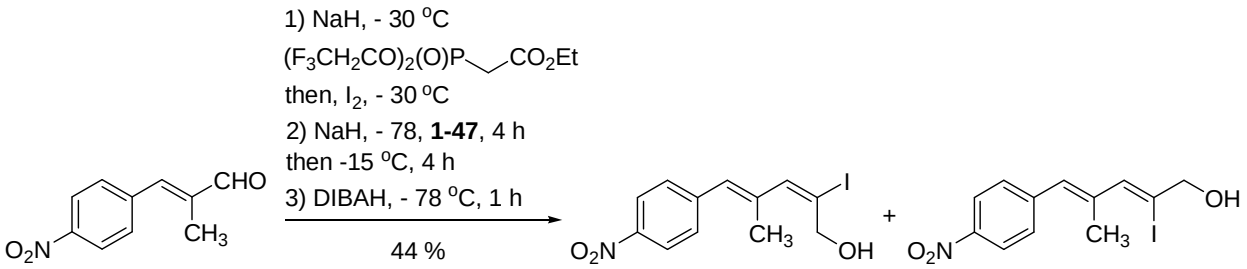
Hydrostannylation 2: To a stirred homogeneous solution of $Pd(OAc)_2$ (0.8 mg, 3.7 μmol) and PCy_3 (2.1 mg, 7.5 μmol) in dry hexane (1 mL) under Ar was slowly added the internal alkyne **1-12** (15.0 mg, 74.5 μmol) at room temperature. Then, tributyltin hydride (39.5 μL, 149 μmol) was slowly added to the reaction mixture. After 1.5 h, the mixture was concentrated under reduced pressure and subjected to column chromatography (1% NEt_3, Hex: EtOAc = 40:1) to afford an inseparable mixture of **1-79** and **1-80**. For the ratio of **1-79** and **1-80**, see ^1H nmr spectrum.



Microwave assisted Hunsdiecker reaction: A mixture of the carboxylic acid **1-13** (50.0 mg, 0.2 mmol), tetrabutylammonium trifluoroacetate (14.3 mg, 40.4 μmol), and N-iodosuccinimide (50.0 mg, 0.22 mmol) in dichloroethane (4 mL) was stirred at 260 W (microwave, the observed temperature was 120 – 150 ^oC) for 1 min. The reaction mixture was washed with water and brine and the resulting organic solution was dried over $MgSO_4$, concentrated and subjected to column chromatography (Hex: EtOAc = 20:1) to afford an inseparable mixture of 9 and 79 (15.1 mg,

23%) as yellow oil. The ratio of **1-9** and **1-83** was calculated from the ^{1}H nmr spectrum.

Rf value: 0.50 (Hex:EtOAc = 20:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ (E, E)-iododiene: 2.01 (s, 3 H), 2.68 (s, 3H), 6.40 (s, 1 H), 6.82 (s, 1 H), 7.41 (d, *J* = 7.5 Hz, 2 H), 8.20 (d, *J* = 7.5 Hz, 2 H). (E, Z)-iododiene: 2.03 (s, 3 H), 2.65 (s, 3 H), 6.17 (s, 1 H), 6.59 (s, 1 H), 7.45 (d, *J* = 7.5 Hz, 2 H), 8.21 (d, *J* = 7.5 Hz, 2 H).



1-47

1-86:**1-87** = >20:1

The ratio was determined by ^{1}H nmr of the crude product.

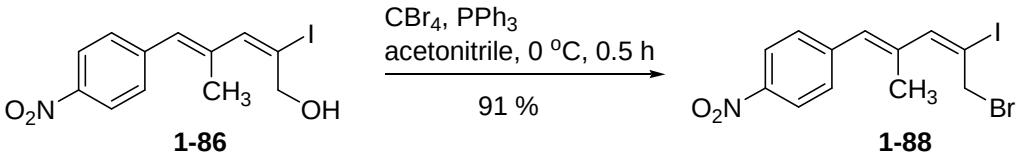
Iododienes 1-86 and 1-87 Ethyl bis(trifluoroethyl)phosphonoacetate (2.0 g, 6.0 mmol) in THF (6 mL) was added dropwise to a slurry of 60 % NaH (0.30 g, 7.5 mmol) in THF (25 mL) – 30 °C under Ar. After 30 min, I_2 (1.53 g, 6.0 mmol) in THF (10 mL) was added to the reaction mixture at – 30 °C. After the addition of iodine, the reaction mixture was briefly warmed to room temperature, and then cooled to – 78 °C. To the stirred mixture at – 78 °C was added 60 % NaH (0.30 g, 7.5 mmol). After the reaction mixture had stirred for 40 min, the aldehyde **1-47** (0.57 g, 3.0 mmol) in THF (5 mL) was added dropwise, and the mixture was stirred for 4 hrs at – 78 °C. Then it was warmed to – 15 °C and stirred for an additional 4 h. Finally it was warmed to r.t. and poured into cold sat. NH_4Cl solution. The mixture was extracted with ethyl acetate (50 mL x 3). The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The concentrate was passed through a short pad of silica gel with 20% EtOAc in hexane until a yellow band came out. The combined yellow fractions were concentrated again. The crude product was directly used for the next step.

To a stirred solution of the crude product in CH_2Cl_2 at – 78 °C was added dropwise DIBAL-H (6.2 mL, 1.0 M in hexane, 6.2 mmol). After 1 h at – 78 °C, the reaction mixture was warmed to room temperature, quenched by MeOH (1 mL) and stirred with Celite for 6 h. The resulting slurry was filtered through a short pad of Celite which was washed several times with CH_2Cl_2.

The combined filtrate was concentrated and subjected to column chromatography (Hex:EtOAc = 3:1) to afford iododiene **1-86** (370 mg, 42 %, yellow powder, mp = 67-69 ^{o}C)/ and the isomeric **1-87** (19 mg, 2 %, yellow powder, 65-66 ^{o}C).

1-86 Rf value: 0.7 (Hex:EtOAc = 2:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.05 (t, *J* = 6.6 Hz, 1 H), 4.44 (d, *J* = 6.6 Hz, 2H), 6.46 (s, 1 H), 6.96 (s, 1 H), 7.42 (d, *J* = 9.0 Hz, 2 H), 8.20 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.3, 66.0, 107.5, 123.6, 129.2, 129.7, 138.3, 143.3, 146.1, 146.4.; IR (neat) νmax 1340, 1513, 1593, 2924, 3382 cm^{-1}. HRMS[ES+] calcd for $C_{12}H_{12}INO_3$ $[M + Na]^+$ 367.9760, found 367.9760.

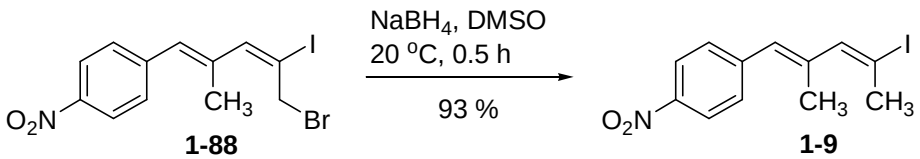
1-87 Rf value: 0.55 (Hex:EtOAc = 2:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 3 H), 2.15 (t, *J* = 5.5 Hz, 1 H), 4.37 (d, *J* = 5.5 Hz, 2H), 6.67 (s, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 8.21 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.1, 72.5, 106.1, 123.6, 129.6, 129.8, 136.8, 139.0, 143.8, 146.3.; IR (neat) νmax 1341, 1514, 1592, 2921, 3374 cm^{-1}. HRMS[ES+] calcd for $C_{12}H_{12}INO_3$ $[M + Na]^+$ 367.9760, found 367.9767.



1-86 **1-88**

Iodobromide 1-88 To a stirred solution of **1-86** (250 mg, 0.72 mmol) and CBr_4 (477 mg, 1.44 mmol) in acetonitrile (5 mL) at 0 ^{o}C was added PPh_3 (340 mg, 1.30 mmol) in portions. After 0.5 h, the reaction mixture was warmed to room temperature, concentrated and subjected to column chromatography (Hex:EtOAc = 50:1 to 20:1) to afford the iodobromide **1-88** (276 mg, 91 %) as a yellow solid (mp = 95-97 ^{o}C).

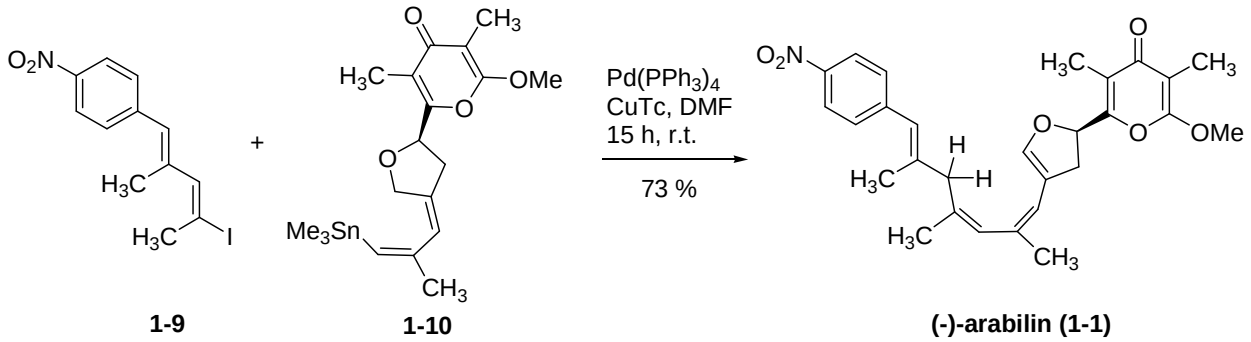
Rf value: 0.4 (Hex:EtOAc = 20:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3 H), 4.53 (s, 2H), 6.71 (s, 1 H), 6.93 (s, 1 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 8.22 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.1, 39.2, 98.9, 123.5, 129.5, 129.8, 138.1, 143.1, 146.6, 148.2.; IR (neat) νmax 1341, 1514, 1594, 2924 cm $^{-1}$.



1-88 **1-9**

(E, E)-Iododiene 1-9 To a stirred slurry of $NaBH_4$ (75.6 mg, 2.0 mmol) in DMSO (5 mL) was added the iodobromide **1-88** (410 mg, 1.0 mmol) in DMSO (4 mL). The reaction mixture was stirred for 30 min at 20 ^oC. The reaction mixture was stirred for 0.5 h and poured into the cold 2N HCl solution (10 mL). The resulting yellow mixture was extracted with diethyl ether (20 mL x 3). The combined organic solution was washed with sat. aq. $NaHCO_3$ solution and with brine. Then it was was dried over $MgSO_4$, filtered, and concentrated. The crude mixture was subjected to flash column chromatography (Hex:EtOAc = 20:1) to afford the E,E-iododiene **1-9** (306 mg, 93 %, mp = 64-66 ^oC).

Rf value: 0.5 (Hex:EtOAc = 20:1) ^1H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3 H), 2.68 (s, 3H), 6.40 (s, 1 H), 6.82 (s, 1 H), 7.41(d, *J* = 7.5 Hz, 2 H), 8.20 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.4, 29.9, 99.2, 123.6, 128.5, 129.6, 138.8, 143.8, 144.3, 146.2.; IR (neat) νmax 1376, 1440, 1515, 1592, 2915 cm^{-1}. HRMS[EI+] calcd for $C_{12}H_{12}INO_2$ $[M]^+$ 328.9913, found 328.9901.



1-9 **1-10** **(-)-arabilin (1-1)**

Synthesis of arabilin (1-1) To a stirred solution of the iododiene **1-9** (43.8 mg, 134 mmol) and vinyl stannane **1-10** (29.4 mg, 66.9 mmol) in DMF (1.35 mL) was added $Pd(PPh_3)_4$ (11.7 mg, 9.9 mmol) and CuTC (19.2 mg, 100 mmol). Then, the reaction flask was wrapped with aluminum foil. The reaction mixture was degassed by Ar stream for 10 min and allowed to stir for 15 h. After completion of the reaction, the suspension was filtered through short pad of Celite. The Celite was washed with ethyl acetate and the combined filtrate was diluted with EtOAc (15 mL), and washed with water (5 mL x 3) and brine. The resulting organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to preparative TLC (Hex: EtOAc = 2:1) to afford the desired arablin **1-1** (23.3 mg, 73 %) as light yellow sticky oil.

Rf value: 0.35 (Hex:EtOAc = 2:1), optical rotation $[\alpha]_D$ = -139.4 (c = 0.33, T = 20 ^oC, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (d, *J*=1.6, 3 H), 1.81 (d, *J*=0.8, 3 H), 1.86 (s, 3 H), 1.88 (s, 3H), 2.02 (s, 3 H), 2.85 (dd, *J* = 15.2 and 8.8 Hz, 1 H), 2.90 (s, 2 H), 3.08 (dd, *J* = 15.2 and 11.2 Hz, 1 H), 3.92 (s, 3 H), 5.59 (dd, *J* = 10.8 and 7.6 Hz, 1 H), 5.91 (s, 1 H), 5.99 (s, 1 H), 6.32 (s, 1 H), 6.48 (s, 1 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 8.18 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 9.4, 18.1, 22.8, 25.2, 35.7, 44.1, 55.3, 77.2, 99.9, 114.9, 118.5, 119.6, 123.5, 124.9, 128.6, 129.3, 131.7, 134.7, 141.1, 144.4, 145.1, 145.9, 154.3, 162.1, 180.6.; IR (neat) νmax 1341, 1464, 1515, 1596, 1667. HRMS[ES+] calcd for $C_{28}H_{31}NO_6$ $[M + H]^+$ 478.2230, found 478.2234.

Chapter 2

Total Synthesis of Kingianin A

2.1. Introduction

2.1.1 Isolation and Structure Determination of the Kingianins

Polyacetates and polypropionates natural products are popular natural source for exploiting drug candidates. Indeed, many molecules including rapamycin, erythromycin, lovastatin, and amphotericin B have been released to the drug market.[49]

In 2010, while screeening new bioactive natural products from Malaysian plants, Litaudon et al. isolated kingianin A (**2-1A,** Figure 2-1) from the tree, *Endiandra kingiana* Gamble.[50] They elucidated the relative stereochemistry of the pentacyclic compound by a combination of nmr techniques including ^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, HMBC experiments and by an X-ray crystal structure.

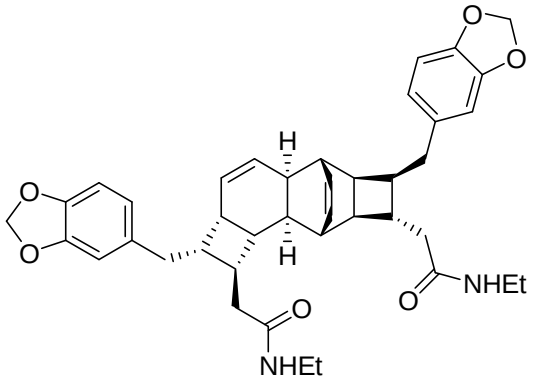


Figure 2-1. Kingianin A (**2-1A**)

In 2011, the same team disclosed the additional 13 members of kingianin family.[51] These compounds were isolated by extraction of the dried bark of E. Kingiana Gamble (1.5 Kg) followed by a series of gradient chromatographies. Further purification was carried out with a

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[49] Polyketide biosynthesis: a millennium review. Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.*, **2001**, *18*, 380–416.

[50] Kingianin A: A New Natural Pentacyclic Compound from Endiandra kingiana. Leverrier, A.; Dau, M. E. T. H.; Retailleau, P.; Awang, K.; Gueritte, F.; Litaudon, M. *Org. Lett*. **2010**, *12*, 3638-3641.

[51] Pentacyclic Polyketide from Endiandra kingiana as inhibitors of the Bcl/Bak interaction. Leverrier, A.; Awang, K.; Gueritte, F.; Litaudon, M. *Phytochemistry* **2011**, *72*, 1443-1452.

series of chromatography and HPLC techniques, providing kingianin A (8.1 mg), B (3.0 mg), C (28.7 mg), D (1.1 mg), E (19.1 mg), F (41.1 mg), G (2. 8mg), H (3.3 mg), I (2.2 mg), J (7. 8 mg), K (7.4 mg), L (22 mg), M (3. 0 mg), and N (7. 4 mg).

Kingianins A (**2-1A**) - N (**2-1N**) are racemic. They share a complex pentacyclic core but contain different sets of side chains: piperonyl and ethylamide, ethanoic acid, and/or butanoic acid substituents (Figure 2-2).

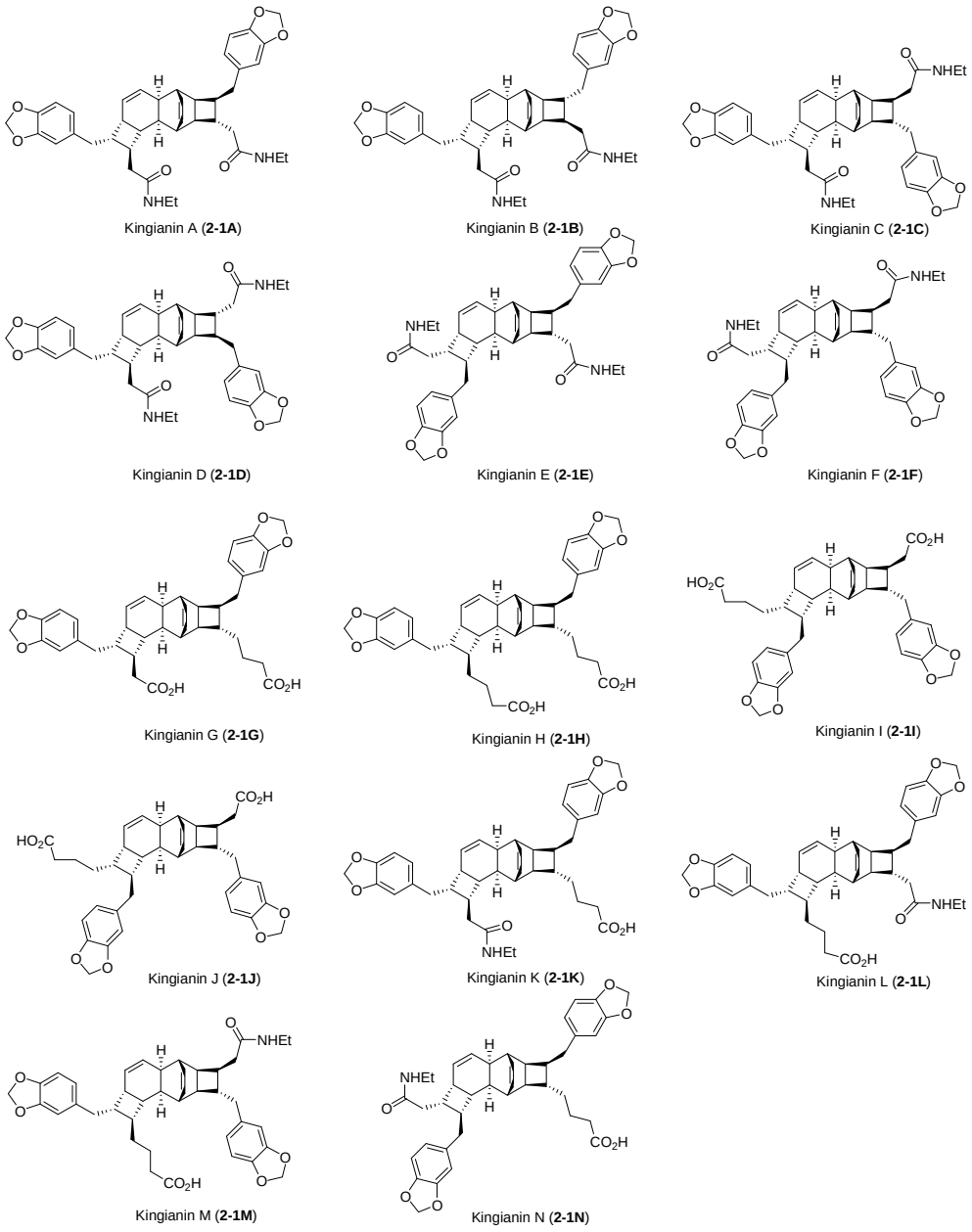


Figure 2-2. Kingianin A (**2-1A**) to N (**2-1N**)

The kingianins inhibit the Bcl-xL protein with low- to mid micromolar binding constants. (Table 2-1).[2] The antiapoptotic Bcl proteins are considered to be valid drug targets for the treatment of cancer, particularly lymphomas, leukemias, and small cell lung cancers.[52] Among the 14 compounds, kingianins G - J showed the highest activity. In each case, both enantiomers are active; the (□)- enantiomer is more active than the (+)-enantiomer.

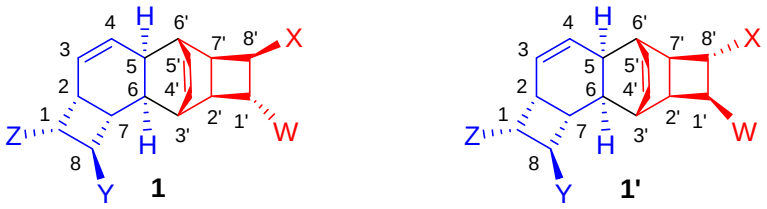
Table 2-1. Bcl-xL binding affinity of kingianin A to N (K_i in μM)[2]

Compound	Bcl-xLKi		
	Racemic mixture	Enantiomer (-)	Enantiomer (+)
Kinganin A	213 ± 53	60 ± 1.5	>300
Kinganin B	>300	n. d.	n. d.
Kinganin C	>300	n. d.	n. d.
Kinganin D	>300	n. d.	n. d.
Kinganin E	>300	n. d.	n. d.
Kinganin F	213 ± 47	n. d.	n. d.
Kinganin G	2 ± 0	1.0 ± 0.2	5 ± 1
Kinganin H	18 ± 7	4.0 ± 0.4	27.0 ± 0.6
Kinganin I	18 ± 3	12.0 ± 1.1	16.0 ± 2.2
Kinganin J	29 ± 6	9.0 ± 0.2	25.0 ± 3.2
Kinganin K	80 ± 36	6.0 ± 0.1	112 ± 15
Kinganin L	36 ± 11	4.0 ± 0.1	71 ± 10
Kinganin M	236 ± 34	n. d.	n. d.
Kinganin N	177 ± 9	n. d.	n. d.

Ki values are the means ± standard deviation from two replicates

[52] Selected recent, informative reviews: (a) Central roles of apoptotic proteins in mitochondrial function. Kilbride, S. M.; *Prehn, J. H.* M**.** *Oncogene*, **2013**, *32*, 2703-2711. (b) Bcl-2 inhibitors: emerging drugs in cancer therapy. Bodur, C.; Basaga, H. *Curr. Med. Chem*. **2012**, *19*, 1804-1820. (c) Inhibitors of the anti-apoptotic Bcl-2 proteins: a patent review. Bajwa, N.; Liao, C.; Nikolovska-Coleska, Z. *Expert Opin. Ther. Pat.* **2012**, *22*, 37-55. (d) Bcl-2 family proteins as therapeutic targets. Czabotar, P. E.; Lessene, G. *Curr. Pharm. Des.* **2010**, *16*, 3132-3148. (e) Navitoclax, Abbott's drug candidate ABT-263, currently in phase II clinical trials for lymphomas, leukemias, and small cell lung carcinoma, inhibits Bcl-x_L and Bcl-2. See http://clinicaltrials.gov/ct2/results/refine?term=navitoclax

On the basis of the stereochemistry of the substituents on the pentacylic core, Litaudon et al divided the kingianins A to N, into two groups (**2-1** and **2-1'**) as shown in Figure 2-3.



A W, Y = $CH_2CONHEt$
X, Z = Pip

B W, Y = $CH_2CONHEt$
X, Z = Pip

C W, Z = Pip
X, Y = $CH_2CONHEt$

D W, Z = Pip
X, Y = $CH_2CONHEt$

E W, Z = $CH_2CONHEt$
X, Y = Pip

F W, Y = Pip
X, Z = $CH_2CONHEt$

G W = $(CH_2)_3CO_2H$
Y = CH_2CO_2H
X, Z = Pip

H W, Y = $(CH_2)_3CO_2H$
X, Z = Pip

I W, Y = Pip
X = CH_2CO_2H
Z = $(CH_2)_3CO_2H$

J W, Y = Pip
X, Z = $(CH_2)_3CO_2H$

K W = $(CH_2)_3CO_2H$
Y = $CH_2CONHEt$
X, Z = Pip

L W = $CH_2CONHEt$
Y = $(CH_2)_3CO_2H$
X, Z = Pip

M W, Z = Pip
X = $CH_2CONHEt$
Y = $((CH_2)_3CO_2H$

N W = $((CH_2)_3CO_2H$
X, Y = Pip
Z = $CH_2CONHEt$

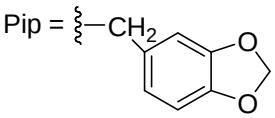
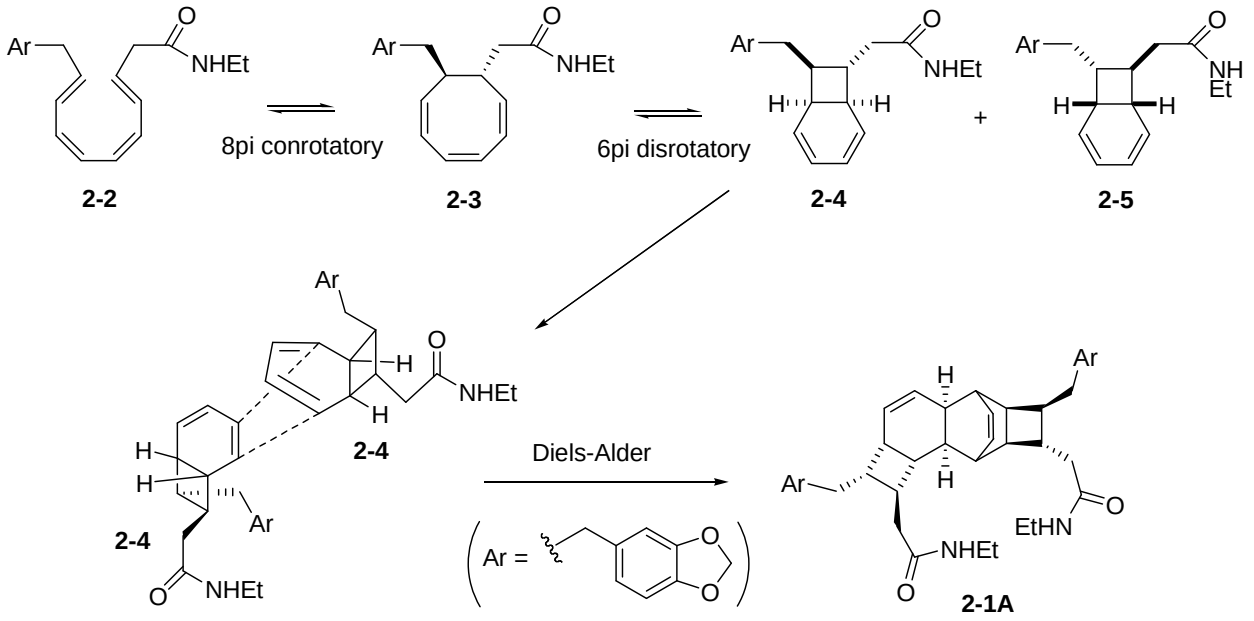
Pip = 

Figure 2-3. Classification of kingianins A-N

2.1.2 Proposed Biosynthesis of Kingianin A and the Biomimetic Study of Moses

Litaudon and Moses groups proposed the biogenesis of kingianin A. The biosynthesis of this molecule is believed to include a tandem conrotatory 8π - disrotatory 6π electrocyclization to form bicycle[4,2,0]octadiene monomers **2-4** and **2-5** followed by Diels-Alder dimerization of **2-4** to afford kingianin A (**2-1A**) as key steps in nature (Scheme 2-1).



Scheme 2-1. Proposed Biosynthesis of Kingianin A

Cursory inspection reveals the relationship of the kingianin structures to the endo Diels Alder dimer of cyclohexadiene. Each of the pseudosymmetric kingianins A - F is, formally at least, a Diels Alder adduct derived from two molecules of the purported biogenetic precursors: the enantiomers of endo[53] amides **2-2** and those of their exo isomers **2-3** (Figure 2-4). The dienophiles (western part of **2-1** and **2-1'**) and dienes (eastern part of **2-1** and **2-1'**) corresponding to kingianins A-F are indicated in Table 2-2.

[53] The endo/exo terminology for the bicyclooctadiene natural products is derived from the relationship of the aryl-substituted sidechain to the cyclohexadiene ring. See "Endo" and "Exo" Bicyclo[4.2.0]-octadiene Isomers from the Electrocyclization of Fully Substituted Tetraene Models for SNF 4435C and D. Control of Stereochemistry by Choice of a Functionalized Substituent. Parker, K. A.; Lim, Y. –H. *Org. Lett.* **2004**, *6*, 161-164.

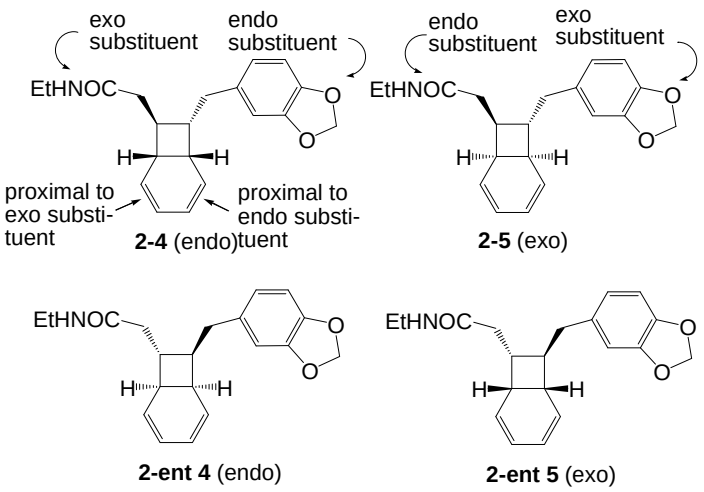


Table 2-2. Derivation of Kingianins A-F from Pre-kingianins **2-4** and their exo isomers **2-5**

Kingianin	Dienophile	Diene
A	**2-4**	**2-4**
B	**2-4**	**2-ent 5**
C	**2-4**	**2-5**
D	**2-4**	**2-ent 4**
E	**2-5**	**2-4**
F	**2-5**	**2-5**

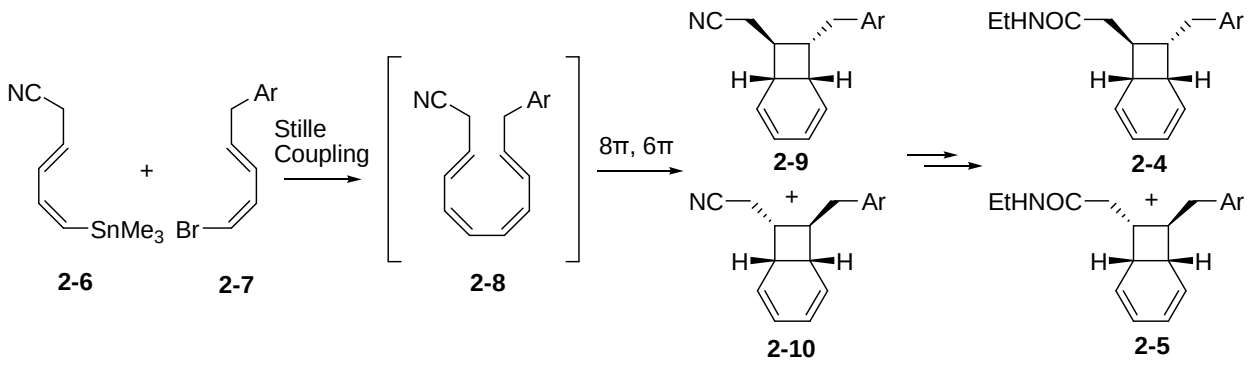
Figure 2-4. Pre-kingianins A - F and its exo isomers

The synthesis of a mixture of the two racemic bicyclooctadienes **2-4** and **2-5** by the classical Stille coupling/electrocyclization cascade method[54,55] and the separation of the two racemic compounds were reported by Moses et al (Scheme 2-2). These authors dubbed isomer **2-4** "pre-kingianin A."[56]

[54] Since its introduction for this purpose (see Synthetic Studies toward SNF4435 C and SNF4435 D. Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221-2224), the Stille coupling/ electrocyclization cascade method has been used consistently to access [4.2.0]-bicyclooctadienes.

[55] Asymmetric Induction in 8π Electrocyclizations. Design of a Removable Chiral Auxiliary. Kim, K.; Lauher, J. W.; Parker, K. A. *Org. Lett.* **2012**, *14*, 138-141 and references therein.

[56] A synthetic approach to kingianin A based on biosynthetic speculation. Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Comm.* **2011**, *47*, 10605-10607.



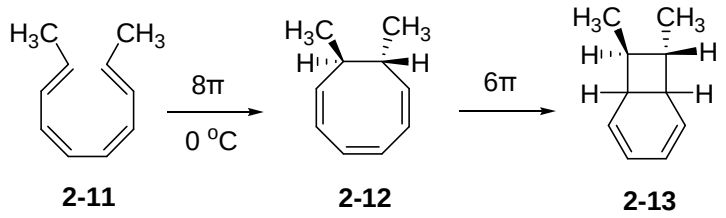
Scheme 2-2. Moses' synthesis of pre-kingianin A[56]

Not surprisingly, Moses and coworkers could not induce cyclohexadiene **2-4** or **2-5** (or a mixture of isomers **2-4** and **2-5**) to provide kingianins under thermal conditions. The Diels Alder dimerization of unactivated cyclohexadienes does not take place at ambient temperatures and therefore does not occur in non-enzymatic transformations in plants. Indeed, Moses et al end their paper with "We believe therefore that the process involved in the proposed dimerisation of pre-kingianin A (**2-4**) into the kingianin A (**2-1A**) in vivo may be subtler than hitherto expected. This is consistent with the chemistry of cyclohexadienes, which do not undergo Diels–Alder dimerisation readily."

2.1.3 Examples of bicyclooctadiene natural products

The conjugated tetraene structure of the certain polyacetate or polypropionate is not stable and undergoes thermal isomerization to form thermodynamically more stable structure. The isomerization depends on the geometry of the substrate. For example, Marvell and Huisgen demonstrated the formation of bicyclcooctadienes from the fully conjugated (E, Z, Z, E)-tetraene by thermal isomerization by way of the thermal 8π, 6π-electrocyclization (Scheme 2-3).[57]

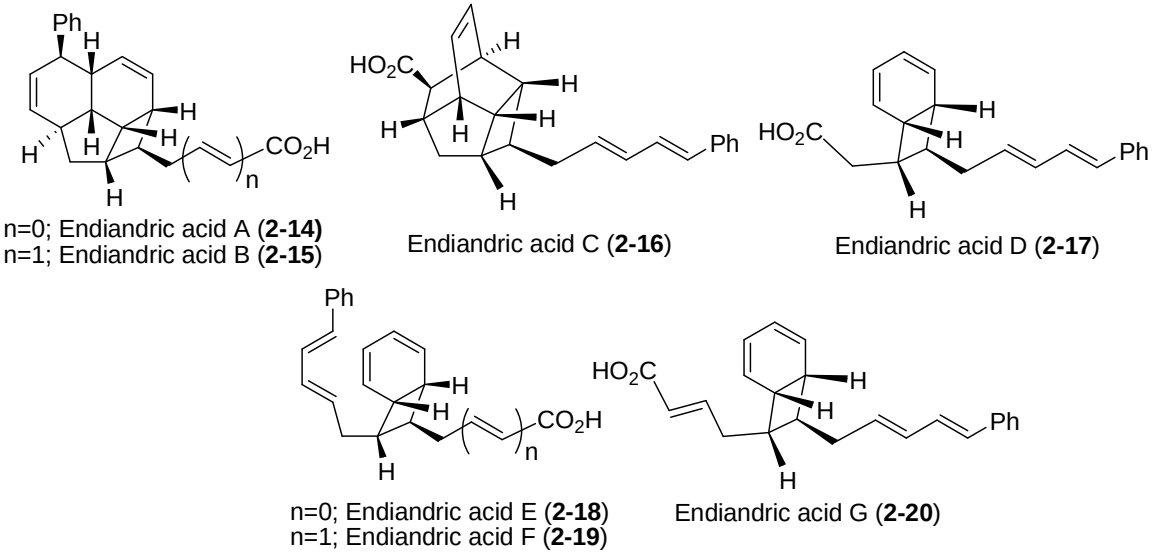
[57] Stereochemistry of formation of cyclooctatrienes via valence isomerization. Marvell, E. N.; Seubert, J. *J. Am. Chem. Soc.* **1967**, *89*, 3377.



2-11 **2-12** **2-13**

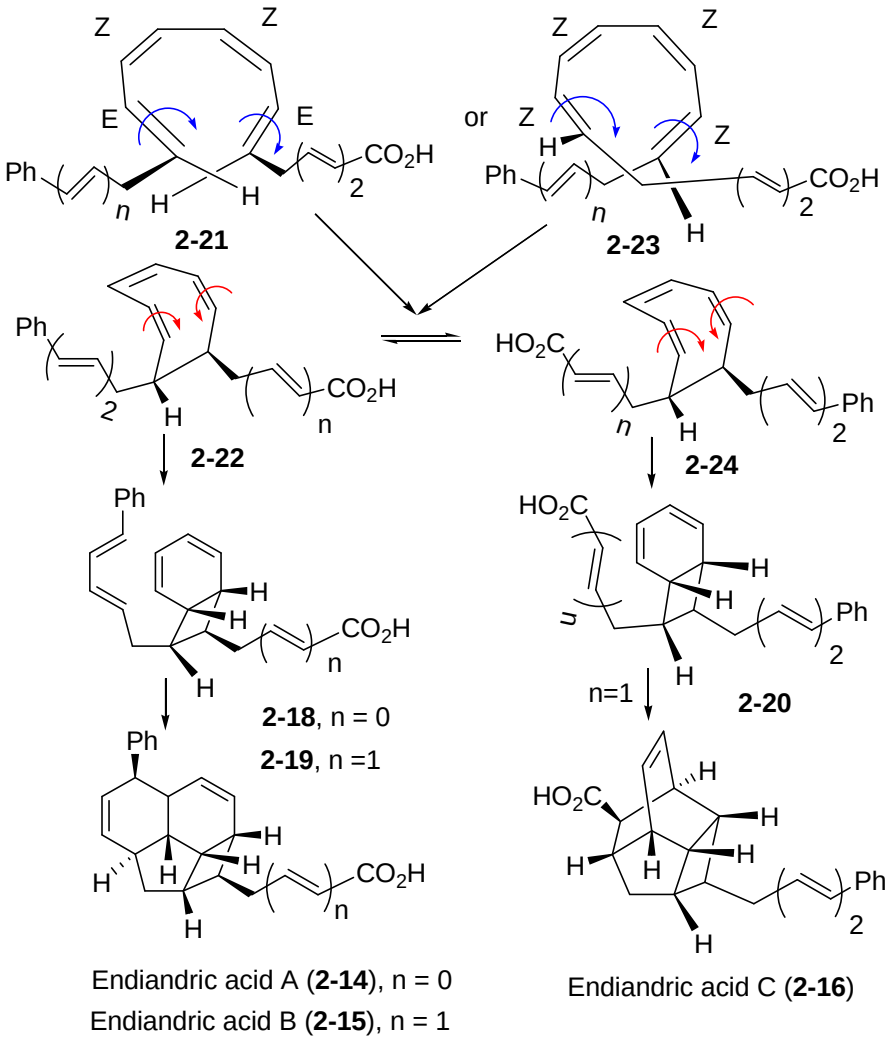
Scheme 2-3. Marvell's study on 8π-6π electrocyclization of (E, Z, Z, E)-tetraene

In 1980, Black and co-workers reported the endiandric acids A-G (Figure 2-5).[58] Analysis of the structures led them to suggest a plausible biosynthetic pathway in which the (E, Z, Z, E)- or (Z, Z, Z, E)-conjugated tetraene **2-21** or **2-23** underwent a tandem 8π, 6π-electrocyclization to afford the bicyclooctadiene cores **2-18**, **19**, and **20**. Then, the intermolecular Diels-Alder reaction between one alkene of the bicyclooctadiene and the diene of the side chain was believed to give endiandric acids A and B. On the other hand, the endiandric acid C was presumed to be derived from the intramolecular Diels-Alder reaction between a diene of bicyclooctadiene and an activated alkene of the side chain (Scheme 2-4).



[58] Postulated electrocyclic reactions leading to endiandric acid and related natural products. Bandaranayake, W. M.; Banfield, J. E.; Black, D. S. C. *J. Chem. Soc., Chem. Commun*. **1980**, 902.

Figure 2-5. Endiandric acids A-G

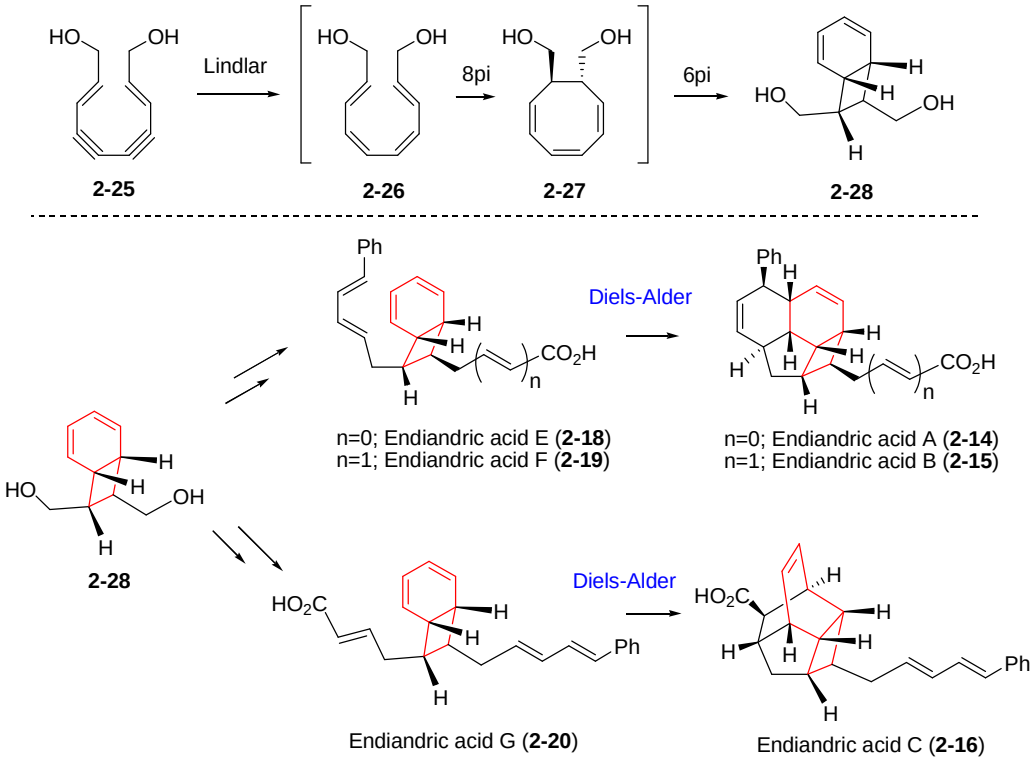


Scheme 2-4. Biosynthetic pathway of the endiandric acids

In 1983, Nicolaou and co-workers reported the chemical synthesis of these molecules.[59] They prepared the bicyclooctadiene **2-28** by an 8π, 6π-electrocyclization strategy. The symmetrical diol **2-25** from oxidative coupling of the commercially available 2-penten-4-yn-1-ol was subjected to semihydrogenation conditions and afforded racemic **2-28** directly. The diol **2-28** was

[59] The endiandric acid cascade. Electrocyclizations in organic synthesis. I. Stepwise, stereocontrolled total synthesis of endiandric acids A and B. Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc*. **1982**, *104*, 5555-5562.

then desymmetrized and functionalized to provide endiandric acids E, F, and G. When heated, each of endiandric acids E, F, and G was smoothly converted to the corresponding tetracyclic endiandric acid A, B, and C by the intramolecular Diels-Alder reaction (Scheme 2-5). This synthetic strategy successfully demonstrated the synthetic pathway that was originally proposed by Black et al.



Scheme 2-5. Nicolaou's synthesis of endiandric acids

Since the total synthesis of the endiandric acids was reported, many related compounds having beautiful architectures have been isolated from nature and synthesized. The syntheses of natural products containing a bicyclooctadiene core are summarized in Scheme 2-8. The total synthesis of SNF 3335C and 4435D was completed by way of a tandem coupling and electrocyclization by Parker[60] and Trauner[61] groups. Meanwhile, Baldwin and co-workers reported the biomimetic

[60] The Total Synthesis of (-)-SNF4435 C and (+)-SNF4435 D. Parker, K. A.; Lim, Y. -H. *J. Am. Chem. Soc*. **2004**, *126*, 15968-15969.

[61] Total Synthesis of (-)-SNF4435 C and (+)-SNF4435 D. Beaudry, C. M.; Trauner, D. *Org. Lett*. **2005**, *7*, 4475-4477.

synthesis of SNF compounds by a palladium-assisted isomerization of a tetraene precursor.[62] The extensive studies on bicyclooctadiene natural products were continued to the synthesis of ocellapyrones A and B [63], elysiapyrones A and B ,[64] shimalactones A and B [65] by the Trauner and Baldwin groups (Figure 2-6).

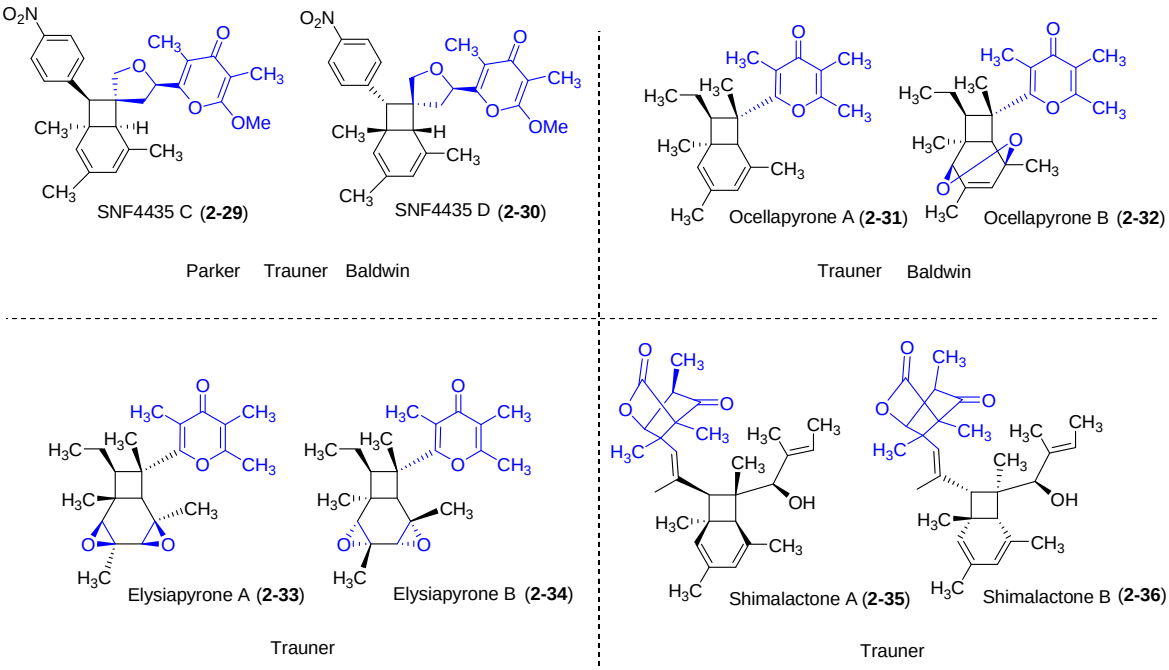


Figure 2-6. Completed synthesis of bicyclooctadiene natural products

[62] The Total Synthesis of Spectinabilin and Its Biomimetic Conversion to SNF4435C and SNF4435D. Mikkel F. J.; John E. M.; Robert M. A.; Baldwin, J. E. *Org. Lett.*, **2005**, *7*, 2473–2476.

[63] (a) Mining the Tetraene Manifold: Total Synthesis of Complex Pyrones from *Placobranchus ocellatus*. Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4602. (b) Total synthesis of cyercene A and the biomimetic synthesis of (±)-9,10-deoxytridachione and (±)-ocellapyrone A. Rodriguez, R.; Adlington, R. M.; Eade, S. J.; Walter, M. W.; Baldwin, J. E.; Moses, J. E. *Tetrahedron* **2007**, 63, 4500-4509.

[64] Biomimetic Synthesis of Elysiapyrones A and B. Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901–2903.

[65] Biomimetic Synthesis of the Shimalactones. Sofiyev, V; Navarro, G.; Trauner, D. *Org. Lett.* **2008**, *10*, 149–152.

2.1.4 Hypothesis and Retrosynthesis

2.1.4.1 Hypothesis

Although the kingianins appear to be Diels Alder dimers, information at the time of their discovery indicated that cyclohexadienes do not undergo Diels Alder dimerizations under thermal conditions. Here, we suggest that the biogenetic Diels Alder reaction proceed by a cation radical-mediated reaction (perhaps initiated photochemically).[66] In support of this premise, we have pursued what we believe to be a biomimetic synthesis of kingianin A. Although the radical cation Diels Alder reaction (RCDA) has been known for 30 years, it has not previously been applied in the synthesis of complex natural product structures. [8c, 67]

The RCDA reaction of pre-kingianin A (**2-4**) is expected to be subject to certain regio- and steroselective influences. We know, for example, that the RCDA reaction prefers to proceed through an endo transition state[68] and we would expect the monomers to approach each other from the less hindered face of each diene. Indeed, each of the naturally occurring kingianins has stereochemistry that is derived from an endo transition state corresponding to this direction of approach.

Furthermore, each of the natural products isolated corresponds to a cycloaddition in which the dienophilic olefinic bond is the one proximal to the exo substituent on the cyclobutane ring (see

---

[66] (a) Accessing the Synthetic Chemistry of Radical Ions. Ischay, M. A.; Yoon, T. P. *Eur. J. Org. Chem.* **2012**, 3359-3372. (b) Visible light photocatalysis of intramolecular radical cation Diels-Alder cycloadditions. Lin, S.; Padilla, C. E.; Ischay, M. A.; Yoon, T. P. *Tetrahedron Lett.* **2012**, *53*, 3073-3076. (c) Radical Cation Diels-Alder Cycloadditions by Visible Light Photocatalysis. Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. *P. J. Am. Chem. Soc.* **2011**, *133*, 19350-19353. (d) Photochemically induced radical-cation Diels-Alder reaction of indole and electron-rich dienes. Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F. *J. Org. Chem.* **1991**, *56*, 1405-1411.

[67] An elegant demonstration of the properties of the RCDA was provided early on by Bauld in a total synthesis of the bicyclic sesquiterpene (-)-β-selinene; see Harirchian, B.; Bauld, N. L. *J. Am. Chem. Soc.* **1989**, 111, 1826-8.

[68] Selectivity profile of the cation radical Diels-Alder reaction. Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1982**, *10*, 2665-2667.

Figure 2-5). Consequently, in all of the kingianins, the C-8 substituent is exo with respect to the adjacent bicyclic system and the C-1 substituent is endo to this system (see Figure 2-3).

We believe that this pathway selection follows from a second steric factor that develops in the endo transition state when the dienophilic olefin is proximal to the endo substitutent Z (see interaction in Figure 2-7).

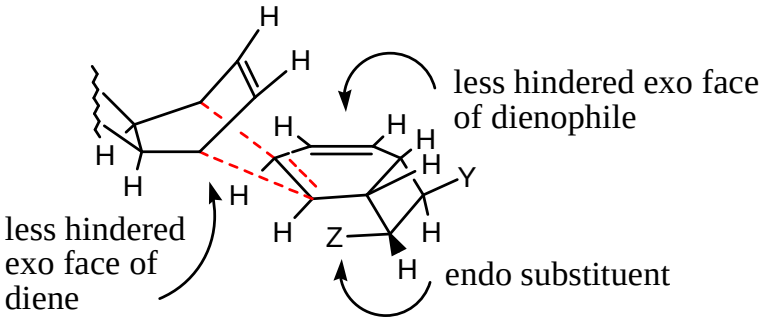


Figure 2-7. Disfavored endo transition state for RCDA (The approach is from the less hindered face of the diene to the less hindered face of the dienophile. The dienophilic olefin is proximal to the endo substituent)

Thus, the cyclobutane ring prevents addition to the dienophile from the endo (hindered) face and the endo substituent prevents addition to the double bond nearer to it from the exo face. Consequently the reaction proceeds through a transition state resembling that shown in Figure 2-8.

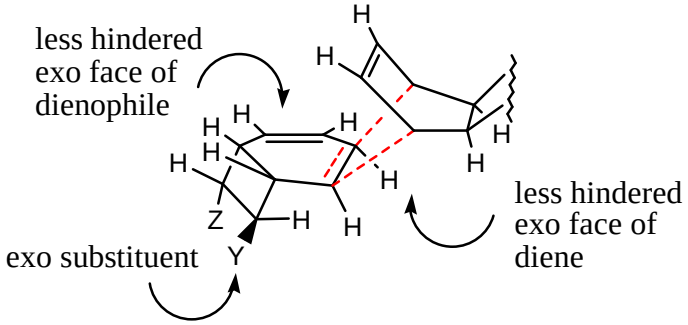
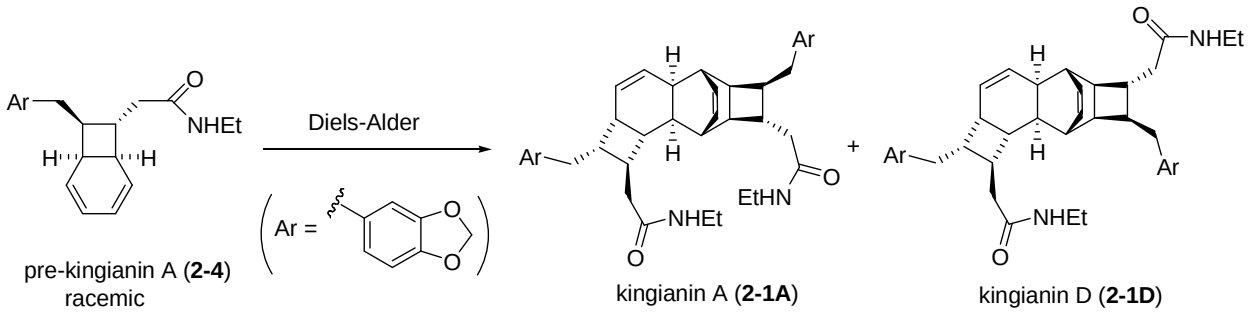


Figure 2-8. Favored endo transition state for RCDA (The approach is from the less hindered face of the diene to the less hindered face of the dienophile. The dienophilic olefin is proximal to the exo substituent.)

Because the RCDA reaction of pre-kingianin A should be subject to the stereochemical limitations described as above, a single enantiomer is expected to undergo the RCDA dimerization to give a single enantiomer of kingianin A. However, racemic pre-kingianin A (**2-4**) should give two products, racemic kingianin A (**2-1A**) and racemic kingianin D (**2-1D**) (Scheme 2-6). Therefore the isolation of kingianin A at the end of the synthesis requires either an asymmetric synthesis of pre-kingianin A (or a synthetic equivalent)[69] or a practical method for the separation of kingianins A and D (or their synthetic equivalents).

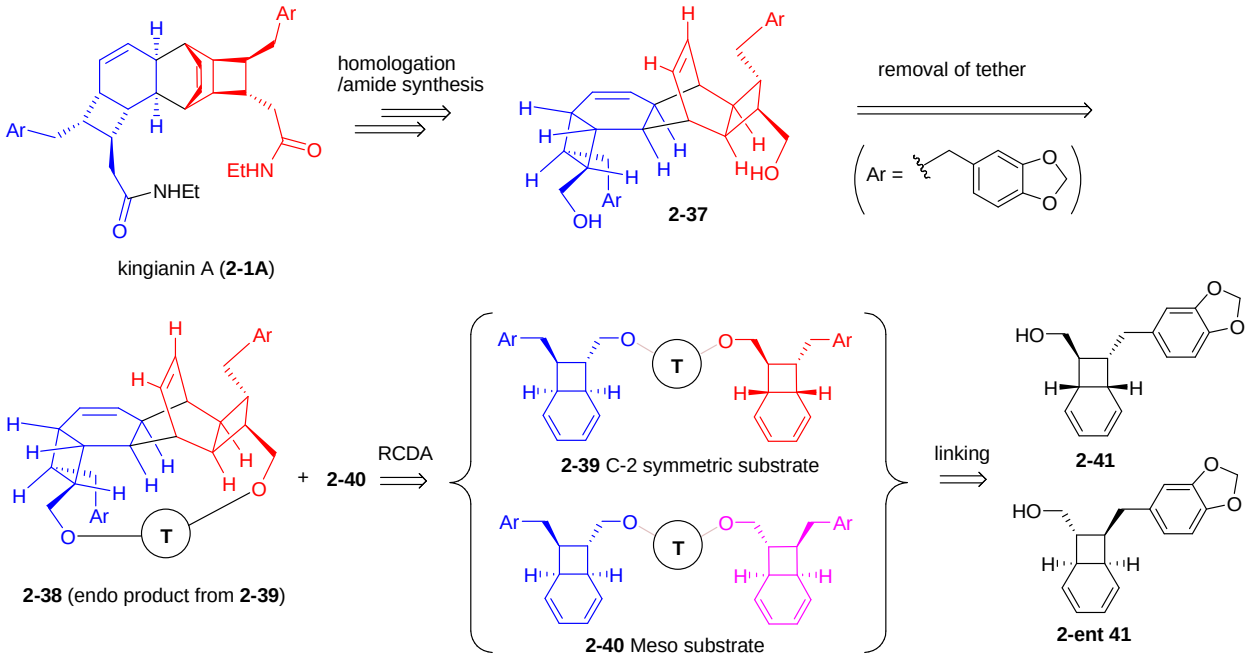


Scheme 2-6. The Diels Alder products of racemic pre-kingianin A (**2-4**)

2.1.4.2 Retrosynthesis

We were aware of the heroic efforts required to separate kingianin A from other kingianins during the isolation procedure.[2] Therefore, as a strategy for obtaining easily separable isomers from the dimerization step, we considered an intramolecular RCDA approach. We imagined linking two molecules of alcohol **2-41** by a removable tether and we hoped that we could find a pair of diastereomers in which the transition state geometry for endo cycloaddition could be reached only by the C-2 symmetric dimer **2-39**. We thought that perhaps the meso dimer **2-40** would be recovered and easily separated from the expected pentacyclic product **2-38** (Scheme 2-7). Removal of the tether will give a key diol **2-37**. Then, the steps for functionalization of diol **2-37** will lead to completion of the total synthesis of kingianin A (**2-1A**).

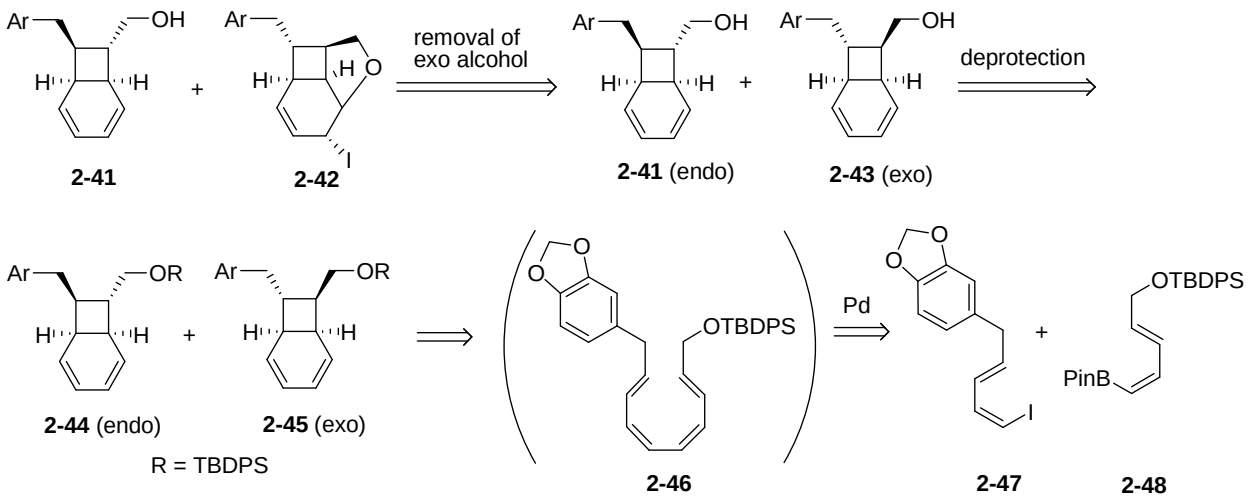
[69] For approaches to the asymmetric synthesis of [4.2.0] bicyclootadienes, see reference 7 and Cleavable Chiral Auxiliaries in (8π, 6π)-Electrocyclizations. Parker, K. A.; Wang, Z. *Org. Lett.* **2006**, *8*, 3553-3556.



Scheme 2-7. Retrosynthesis of kingianin A

To evaluate the tether mediated intramolecular RCDA strategy depicted in Scheme 2-7, we needed a single diastereomeric endo alcohol **2-41**. We decided to use the proven coupling/ tandem electrocyclization method for the bicyclo[4.2.0]octadiene structure of the alcohol **2-41**. Thus, the two partners **2-47** and **2-48** are required. We thought that the coupling of the (E, Z)-iododiene **2-47** and known boronate **2-48**[70] would provide a mixture of the diastereomeric bicyclooctadienes **2-44** and **2-45** through the intermediate **2-46**. Then, deprotection of TBDPS group would give a mixture of endo and exo alcohol **2-41** and **2-43**. If these alcohols were inseparable, selective iodoetherification would remove the exo alcohol **2-43** (Scheme 2-8).

[70] Convergent Synthesis of Fostriecin via Selective Alkene Couplings and Regioselective Asymmetric Dihydroxylation. Robles, O.; McDonald, F. E. *Org. Lett*. **2009**, *11*, 5498-5501.

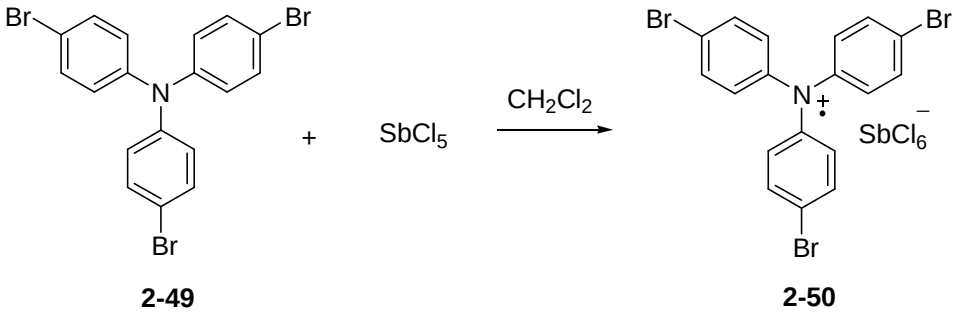


Scheme 2-8. Retrosynthesis of endo alcohol **2-13**

2.2. Result and Discussion

2.2.1 Preparation of the catalyst for the RCDA reaction

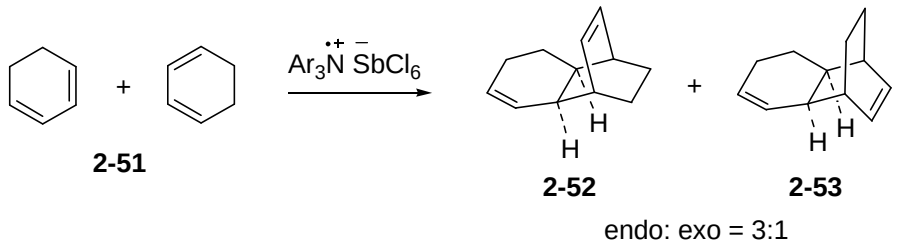
The radical-cation salt, known as Weitz salt, was prepared by the known procedure.[71] The blue needle-like solid **2-50** was isolated by crystallization from dichlorometane/ diethyl ether (Scheme 2-9).



Scheme 2-9. Preparation of the Weitz salt

[71] Cation-radicals: Tris-(p-bromophenyl)ammonium Perchlorate and Hexachloroantimonate. Bell, F. A.; Ledwith, A.; Sherrington, D. C. *J. Chem. Soc*. **1969**, 2719-2720.

To test catalytic activity of the freshly prepared salt, the radical-cation Diels-Alder reaction was tested with the simple cyclohexadiene **2-51** (Scheme 2-10). This successfully resulted in Diels-Alder products, the endo and exo adducts **2-52** and **2-53** (ratio = 3:1, lit.: 5:1).[72]

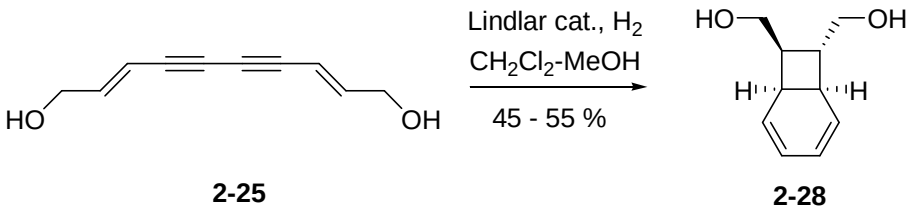


Scheme 2-10. A test RCDA reaction of the cyclohexadiene

2.2.2 Model study for the RCDA reaction of bicyclooctadienes

2.2.2.1 Preparation of a model compound

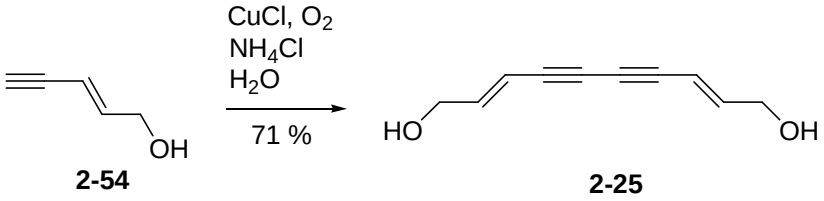
Before commencing preparation of the alcohol **2-41** suggested in Scheme 2-8, we decided to test a simple model compound to see a result of the RCDA reaction of bicyclooctadiene. Symmetric substrates for the 8□, 6□ cascade can give only one stereoisomeric product (as a racemate), making analysis more straightforward. Thus, we planned to have a bicyclooctadiene-diol **2-28** (racemic) as a model compound according to the procedure presented in Nicolaou's endiandric acid synthesis (Scheme 2-11).[15]



Scheme 2-11. Nicolaou's synthesis of the diol **2-28**

[72] The Cation-Radical Catalyzed Diels-Alder Reaction. Bellville, D. J.; Wirth, D. D.; Bauld, N. L. *J. Am. Chem. Soc*. **1981**, *103*, 718-720.

The diol **2-25**[73] was prepared by copper catalyzed oxidative coupling reaction from the commercially available (E)-pent-2-en-4-yn-1-ol[74] (**2-54**) (Scheme 2-12).



Scheme 2-12. Synthesis of the diol **2-25**

The semihydrogenation of the diol **2-25** was conducted with commercial Lindlar catalyst (Aldrich). However, despite the numerous experiments, the desired product **2-28** was not obtained. We note that Nicolaou's paper acknowledges a special catalyst provided by Hoffman-La-Roche.[75] We tested other reductive methods employing P2-Ni[76], activated Zn[77], and Zn-Cu catalysts[78]. However, the diol **2-28** was not cleanly produced, and a mixture of the fully or partially hydrogenated products was observed. Interestingly, the reaction conditions using activated Zn-Cu catalyst gave a selectively reduced alkyne **2-53** as a major product (Scheme 2-

[73] Acetylenic compounds. XIV. The reactions of the readily available ethynyl-ethylenic alcohol, 2-penten-4-yn-1-ol. Heilbron, I. M.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1947**, 1586-1590.

[74] The purchased (E)-pent-2-en-4-yn-1-ol (Alpha, 90 % purity) was used after distillation.

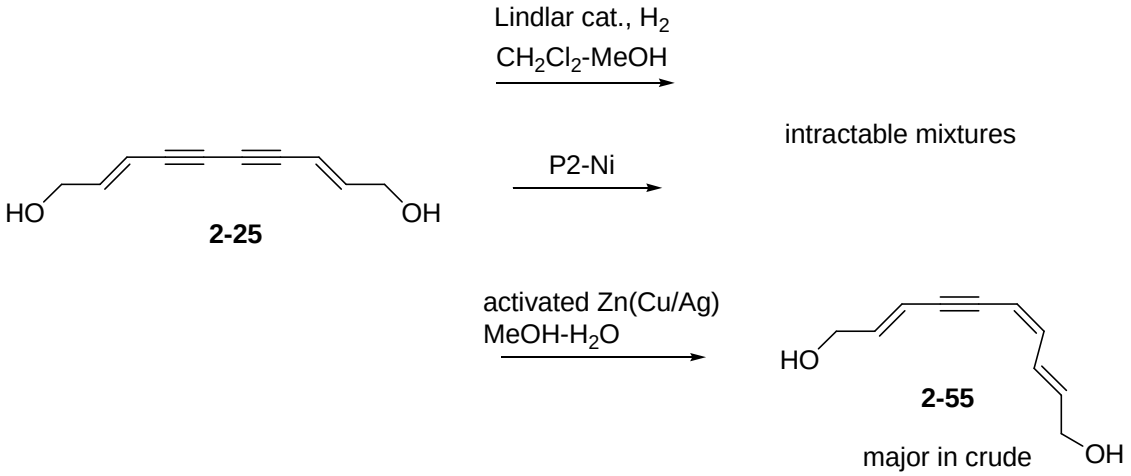
[75] Sharma, G. V. M.; Choudary, B. M.; Sarma, M. R.; Rao, K. K. *J. Org. Chem.* **1989**, *54*, 2997.

[76] The Handy Use of Brown's P2-Ni Catalyst for a Skipped Diyne Deuteration: Application to the Synthesis of a [D4]-Labeled F4t-Neuroprostane. Oger, C.; Bultel-Poncé, V.; Guy, A.; Balas, L.; Rossi, J. -C.; Durand, T.; Galano, J. -M. *Chem. Eur. J.* **2010**, *16*, 13976-13980.

[77] Total Synthesis of the Boron-Containing Ion Carrier Antibiotic Macrodiolide Tartrolon B. Mulzer, J.; Berger, M. **2004**, *6*, 891-898.

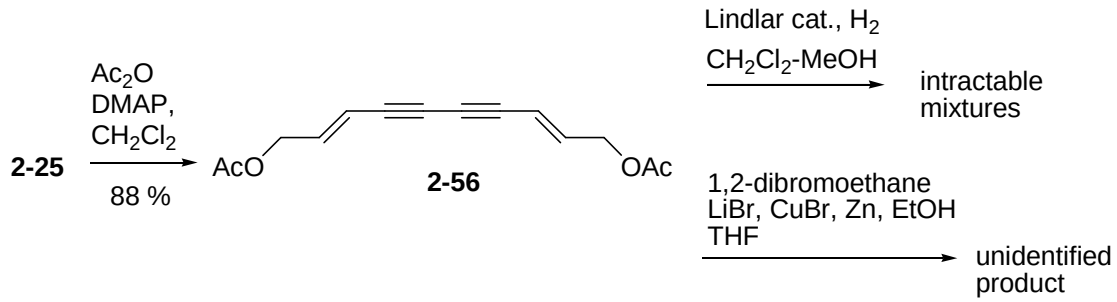
[78] Stereospecific Syntheses and Spectroscopic Properties of Isomeric 2,4,6,8,-Undecatetraenes. New Hydrocarbons from the Marine Brown Alga *Giffordia mitchellae*. Bolad, W.; Schroer, N.; Sieler, C. *Helv. Chim. Acta* 1987, *70*, 1025-1040.

13).



Scheme 2-13. The semihydrogenation conditions of the dicetylene **2-25**

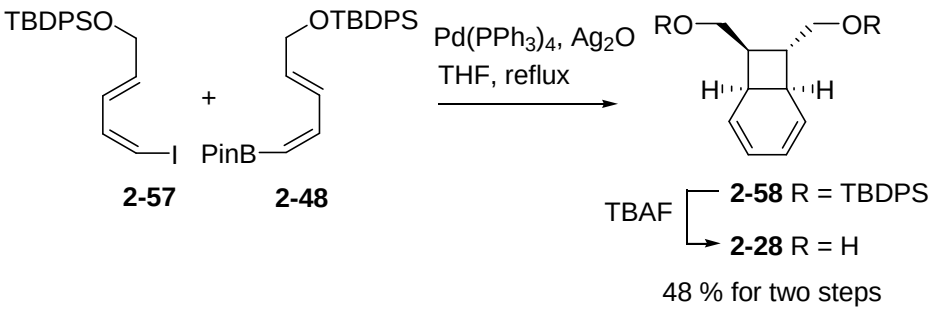
Furthermore, when diacetate **2-56** was subjected to conditions with the Lindlar catalyst or activated Zn-Cu catalyst, the bicyclooctadiene product was not obtained (Scheme 2-14).



Scheme 2-14. The semihydrogenation conditions of the diacetate **2-56**

Thus we resorted to a conventional coupling/ tandem electrocyclization method. We prepared (E, Z)-iododiene **2-57**[79] and (E, Z)-boronate **2-48**[12] by following known procedures. Then, the two components **2-57** and **2-48** were subjected to the Suzuki conditions that were used in O'Doherty's fostriecin synthesis.[31] This coupling gave the bicyclooctadiene compound **2-58**. Then, the TBDPS group was removed to release the diol **2-28** (Scheme 2-15).

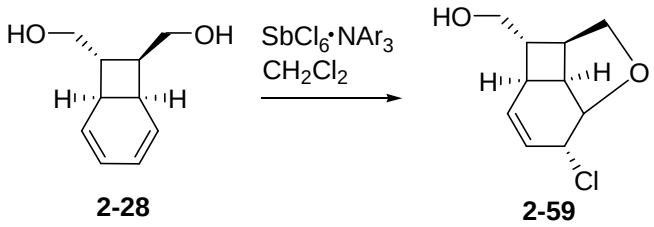
[79] Total Synthesis of Fostriecin: Via a Regio- and Stereoselective Polyene Hydration, Oxidation, and Hydroboration Sequence. Gao, Dong; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752-3755.



Scheme 2-15. Synthesis of the model diol **2-28** by coupling approach

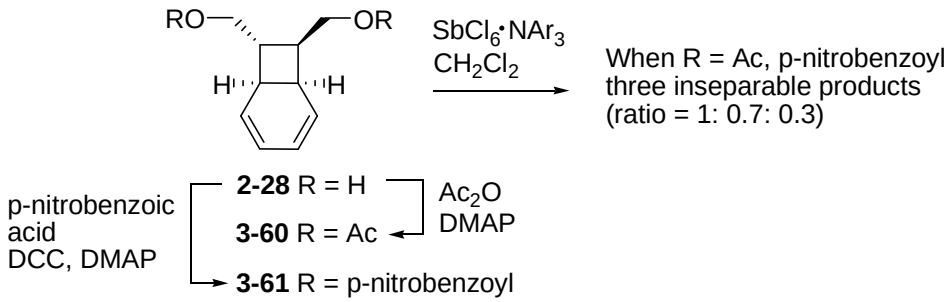
2.2.2.2 Model reactions: the RCDA reaction of the bicyclooctadiene diol

Having the model compound **2-28**, we tested the RCDA reaction. When the diol **2-38** was not protected, no RCDA product was obtained under the given conditions. Instead of dimerization, the chloro ether **2-57** was obtained (Scheme 2-16).



Scheme 2-16. A model RCDA reaction of bicyclooctadiene diol **2-28**

Interestingly, the RCDA reaction of the diacetate **2-60** and dibenzoate **2-61** furnished three major compounds as an inseparable mixture with a ratio of 1: 0.7: 0.3 (Scheme 2-17). We could find that some of characteristic signals observed in ^{1}H nmr of the mixture resembled that of kingianins. This allowed us to have some confidence that the result of RCDA reaction of the bicyclooctadienes probably accords with our hypothesis on stereochemistry of kingianins.



Scheme 2-17. The model RCDA reactions of protected bicyclooctadienes

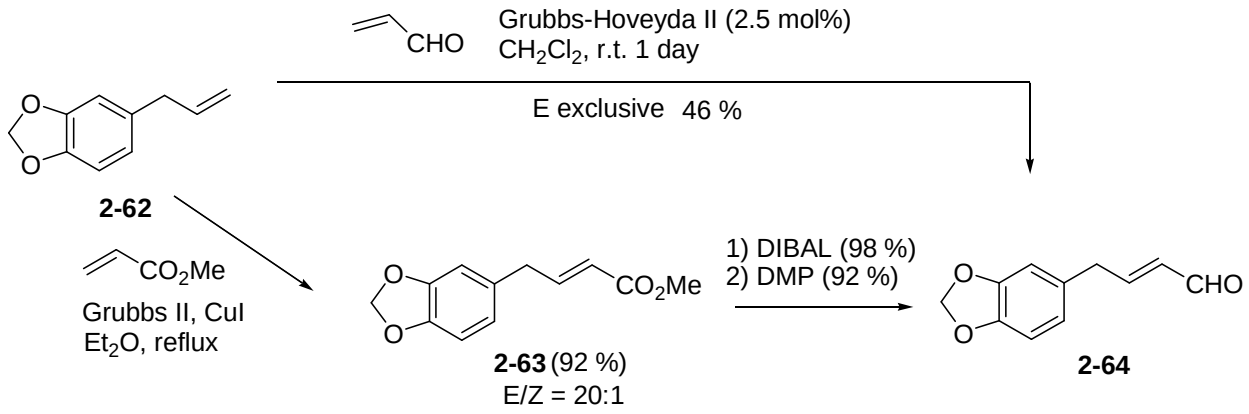
2.2.3 Preparation of (E, Z)-iododiene **2-47**

Having tested model compounds, we set out to synthesize the monomeric endo alcohol **2-41**. As shown in Scheme 2-8, we needed to prepare one of the coupling partners, (E, Z)-iododiene **2-2-47**. We performed a cross-metathesis reaction between the safrole **2-62** and acrolein to produce a homologated aldehyde **2-64**. We thought that Stork-Zhao olefination would be applicable to obtain Z-iodo olefin **2-47** from the aldehyde **2-64**.

Here, we employed two synthetic routes. The aldehyde **2-64** was obtained by adapting the Cossy's one step procedure[80] or as 3-step sequence including the cross metathesis in the presence of catalytic copper[81] (Scheme 2-18).

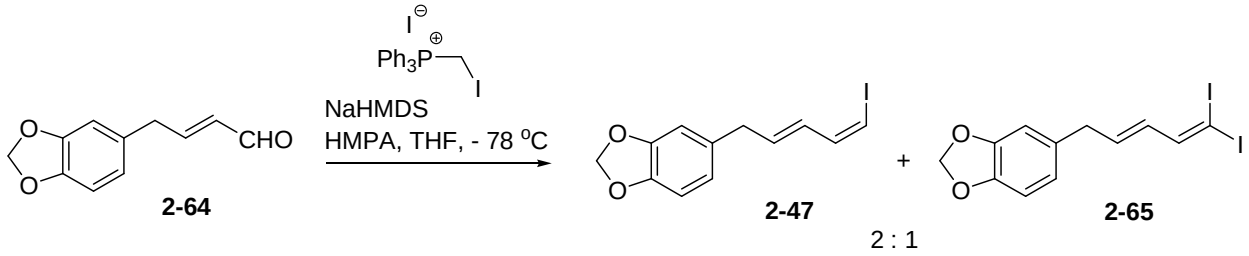
[80] Cross-metathesis reaction. Generation of highly functionalized olefins from unsaturated alcohols. Cossy, J.; BouzBouz, S. Hoveyda, A. H. *J. Organomet. Chem*. **2001**, *624*, 327-332.

[81] Rate Enhanced Olefin Cross-Metathesis Reactions: The Copper Iodide Effect. Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.*, **2011**, *76*, 4697–4702.



Scheme 2-18. Synthesis of the aldehyde via cross metathesis

The aldehyde **2-64** was subjected to the Stork-Zhao conditions, but the resulting product was an inseparable mixture of the desired (E, Z)-iododiene **2-47** and diiododiene **2-65** (Scheme 2-19).



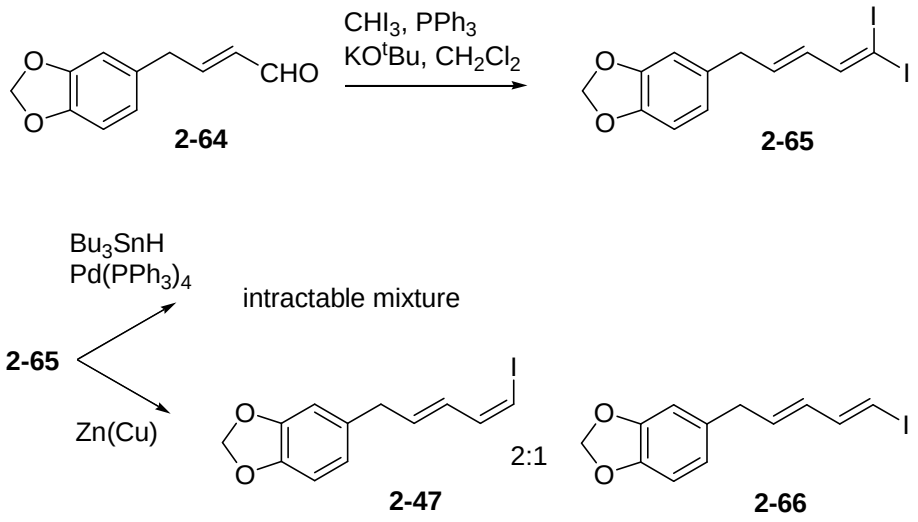
Scheme 2-19. The Stork-Zhao olefination of aldehyde **2-64**

We considered then the selective reduction of diiodide **2-65**. The diiododiene **2-65** was prepared by adapting Charette's procedure.[82] The diiodide **2-65** was subjected to reductive dehalogenation conditions. When tributyltin hydride was used in the presence of catalytic palladium, a complicated mixture was observed. The treatment of excess Zn-Cu couple[83] to the diiodide, on the other hand, provided an inseparable mixture of (E, E)- and (E, Z)-iododienes **2-**

[82] Highly Efficient Two-Step Synthesis of C-sp3-Centered Geminal Diiodides. Cloarec, J. -M.; Charette, A. B. *Org. Lett*. **2004**, *6*, 4731-4734.

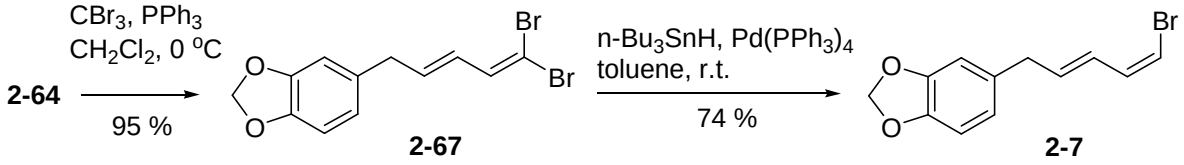
[83] Convergent Total Syntheses of Gambierol and 16-epi-Gambierol and Their Biological Activities. Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 11893-11899.

47 and **2-66** with a ratio of 1:2 (Scheme 2-20).



Scheme 2-20. Synthetic efforts of pure (E, Z)-iododiene

As a surrogate substrate for the iododiene **2-19**, we decided to synthesize the bromodiene **2-5**. Corey-Fuchs homologation of the aldehyde **2-62** followed by the Pd-catalyzed selective debromination of dibromide **2-65** (adapted by Moses et al.) gave the (E, Z)-bromodiene **2-5** (Scheme 2-21).[5]

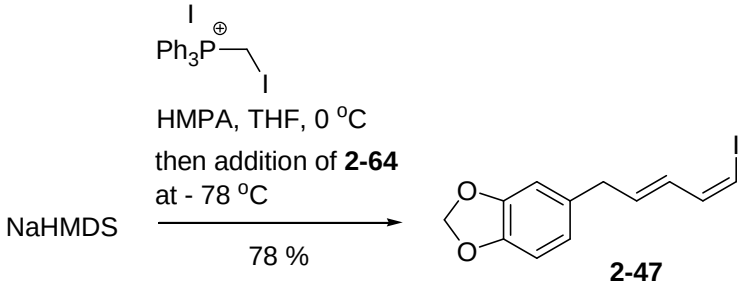


Scheme 2-21. Synthesis of (E, Z)-bromodiene

Meanwhile, the extensive search for the Stork-Zhao procedures allowed us to find a useful paper for the synthesis of pure (E, Z)-iododiene.[84] Menche and coworkers described a solution to avoid the formation of undesired diiodide **2-65**. Following Menche's protocol (the order of the

[84] Stereoselective Total Synthesis of Etnangien and Etnangien Methyl Ester. Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem*. **2010**, *75*, 2429-2444.

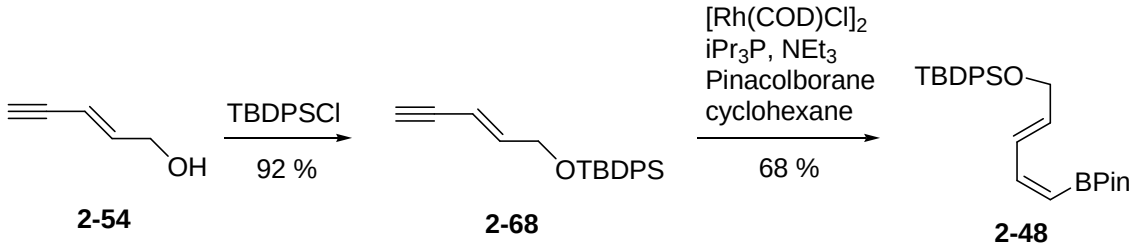
addition of reagents was critical to avoid the formation of the diiodide, see experimental section), we obtained the desired (E, Z)-iododiene **2-47** in good yield (Scheme 2-22).



Scheme 2-22. Synthesis of (E, Z)-iododiene **2-47**

2.2.4 Synthesis of (E, Z)-boronate **2-48**

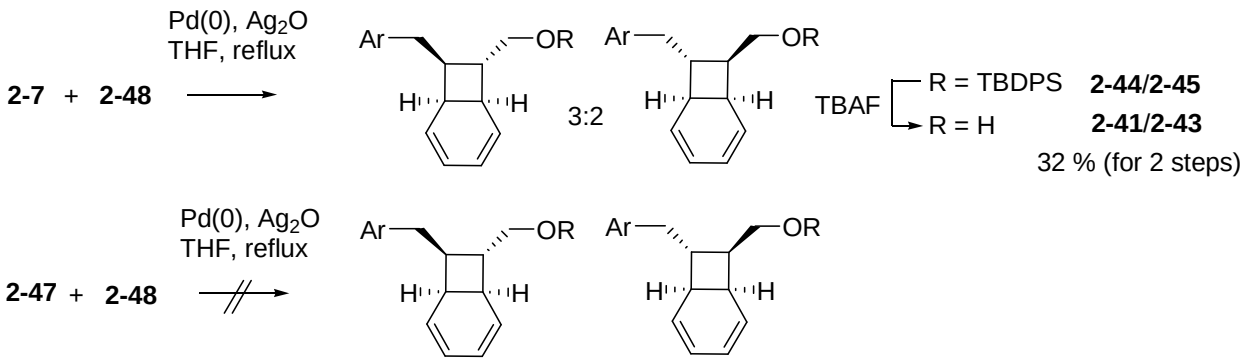
The other coupling partner, (E, Z)-boronate **2-48**, was prepared by the known procedure[12] (Scheme 2-23).



Scheme 2-23. Synthesis of (E, Z)-boronate **2-48**

2.2.5 Synthesis of the endo alcohol **2-41**

Having both coupling partners, we next tested Suzuki reaction. When the (E, Z)-bromodiene **2-7** was used for the coupling in a catalytic Pd/ Ag system,[21] the bicyclooctadienes **2-43** and **2-43** were obtained in 32 % yield (2 steps) after removal of the TBDPS group. However, when (E, Z)-iododiene **2-47** was subjected to the same conditions, no bicyclooctadienes were produced (Scheme 2-24).



Scheme 2-24. Suzuki reaction of bromo- or iododiene and boronate

Because the iododiene **2-47** was not successful in the conditions using silver oxide, we needed to optimize reaction conditions for the Suzuki reaction. After screening the several conditions, we found a superior protocol with $Pd(PPh_3)_4$ and aq. NaOH solution (Scheme 2-25 and Table 2-3). The diol mixture **2-41**/**2-43** was thus available in 80% yield for the coupling/8□, 6□, deprotection sequence.

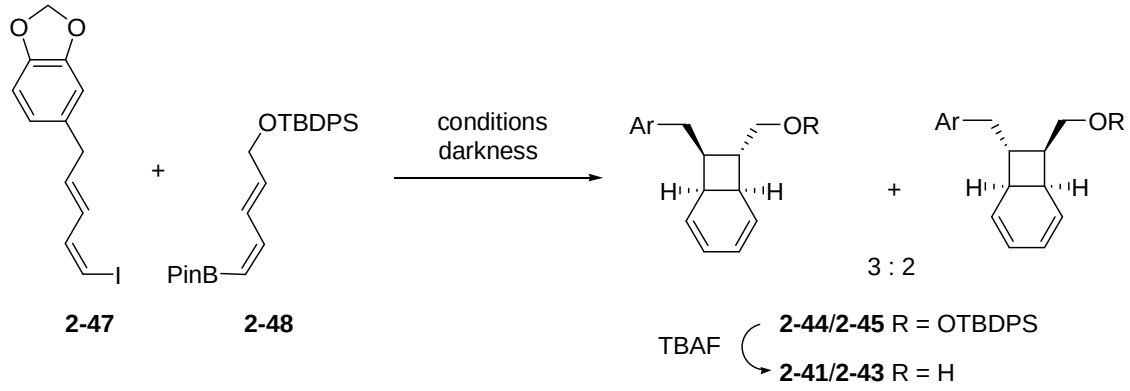
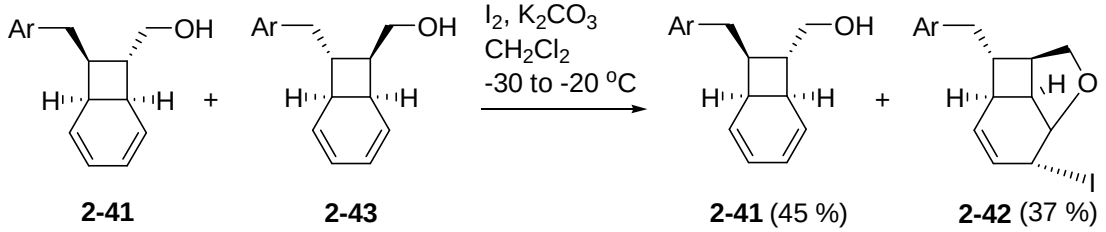


Table 2-3. Conditions for Suzuki reaction	result
$Pd(PPh_3)_4$, Ag_2O, THF, reflux	no coupled product, instead homocoupled product from boronate was obtained as major product
$Pd(PPh_3)_4$, NaOEt, Benzene, EtOH, reflux	no coupled product
$Pd(PPh_3)_2Cl_2$, NEt_3, MeOH, r.t.	sluggish
$Pd(PPh3)_4$, aq. NaOH, THF, reflux, 20 h	clean (80 % for 2 steps)

Scheme 2-25. Screening of the conditions for the Suzuki reaction

When the inseparable mixture of alcohols **2-41** and **2-43** was treated with iodine in the presence of potassium carbonate, only isomer **2-43** underwent iodoetherification.[15] Iodoether **2-42** and alcohol **2-41** were easily separated by chromatography (Scheme 2-26).



Scheme 2-26. Removal of the exo alcohol **2-43** by iodoetherification

2.2.6 Screening of tethers

To examine the planned tether-mediated RCDA reaction, we prepared several dimeric diesters **2-39a-e** and **2-40a-e** from the alcohol **2-41** using succinyl, glutaryl, adipoyl, adamantanedicarboxyl, and adamantanediacetyl acid dichloride (Scheme 2-27 and Table 2-4).

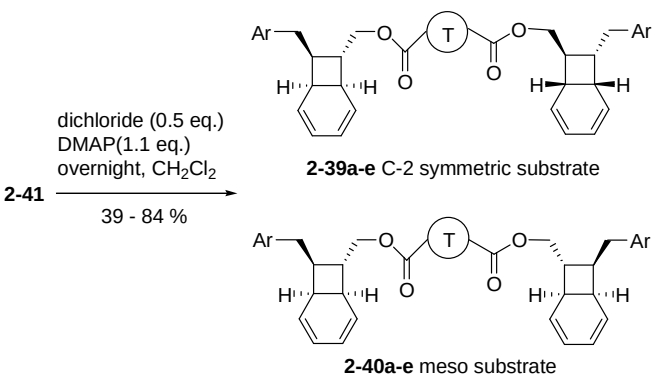
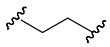
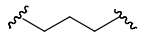
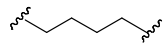
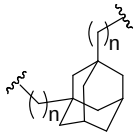


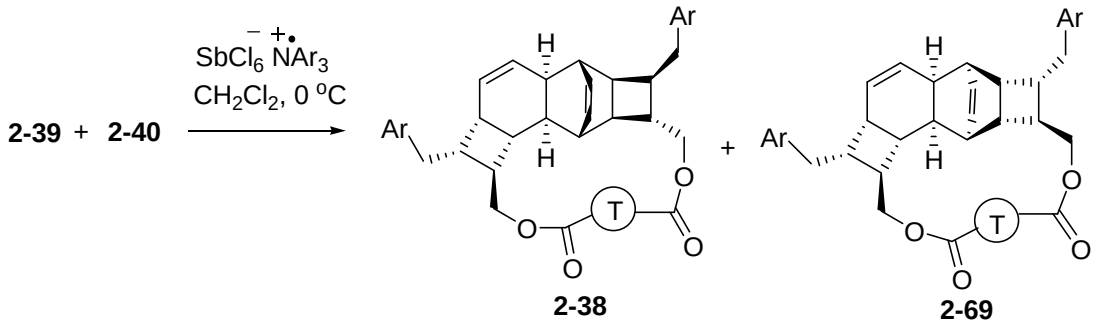
Table 2-4. Screening of Tethers

Tethers			Yield
a		succinyl	72 %
b		glutaryl	84 %
c		adipoyl	75 %
d	 n = 0,1	adamantanedicarboxyl	39 %
e		adamantanediacetyl	62 %

Scheme 2-27. Preparation of diacid-tethered substrates

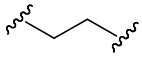
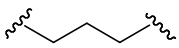
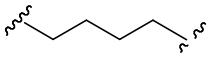
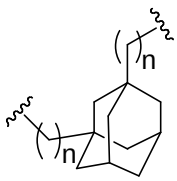
The diacid-tethered substrates were then subjected to the RCDA conditions. Contrary to our expectation, in the case of each diastereomeric pair, both isomers appeared to have undergone the

intramolecular cycloaddition reaction. The results are summarized (Scheme 2-28 and Table 2-5). Of the five conversions studied, the adipic acid-tethered substrate provided the best result in terms of yield and separation of the isomeric products. A slight improvement in yield was obtained when the reaction was carried out in a more dilute solution. Noteworthy in any case was the fact that the product mixture from the adipic acid-tethered substrate consisted of two compounds, formed in approximately equal amounts and easily separated by chromatography.



Scheme 2-28. Dimerization of the diacid-tethered substrates under RCDA conditions

Table 2-5. The RCDA reaction of the C-2 symmetric substrate **2-39** and meso substrate **2-40**

	Tethers			Result	Separation
a			succinyl	mystery (8 %), **2-69a** (12 %)	ok
b			glutaryl	**2-38b** + mystery (19 %), **2-69b** (20 %)	ok
c			adipoyl	**2-38c** (27 %), **2-69c** (30 %)	ok
			M=0.005	**2-38c** (34 %), **2-69c** (39 %)	
d		n = 0	adamantanedicarboxyl	**2-38d** (24 %), **2-69d** (38 %)	difficult
e		n = 1	adamantanediacetyl	**2-38e** (36 %), **2-69e** (39 %)	difficult

[M] = 0,01 unless commented. The structures of the RCDA products from succinyl, glutaryl, adamantanes diesters are not exactly assigned, but determined on the basis of the ^{1}H nmr pattern of RCDA products **2-38c** and **2-69c**.

2.2.7 Structural assignment of the endo RCDA adduct **2-38c**

The more polar of the adipoyl tethered products **2-38c** displayed a ^{1}H NMR spectrum that contained signals consistent with those expected from a compound in the kingianin A series (see Figure 2-12 and Table 2-11). The identity of this product was firmly established as **2-38c** by X-ray crystallography (Figure 2-9).

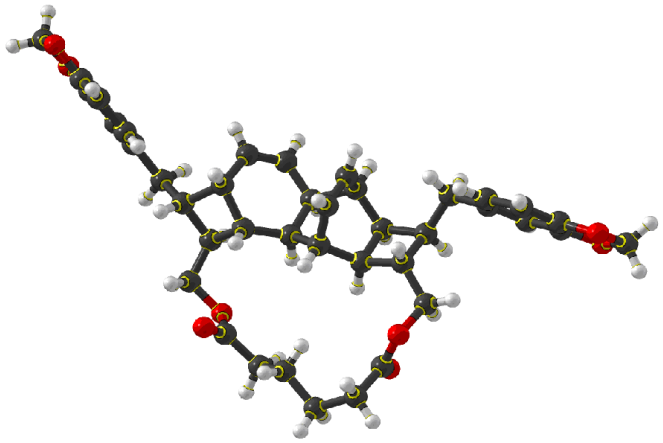


Figure 2-9. X-ray structure of RCDA product **2-10c**

2.2.8 Structural assignment of the exo RCDA adduct **2-67c**

The less polar product **2-69c** had a 1H NMR spectrum that differed in noticeable ways from those of compounds in the kingianin family. Furthermore, the absence of characteristic patterns in the spectrum was not the result of the presence of the tether; removal of the tether gave a diol **2-70**, the NMR spectrum of which differed in important respects from that of kingianin D (see Table 2-10 and 2-11).

A series of nmr experiments (^{1}H, ^{13}C, COSY, NOESY, HSQC, HMBC) allowed us to identify the second RCDA product as **2-70**, the unanticipated but not surprising exo Diels Alder product (Figure 2-10). The correlations shown in 2D-COSY and 2D-NOESY are depicted in Figure 2-11.

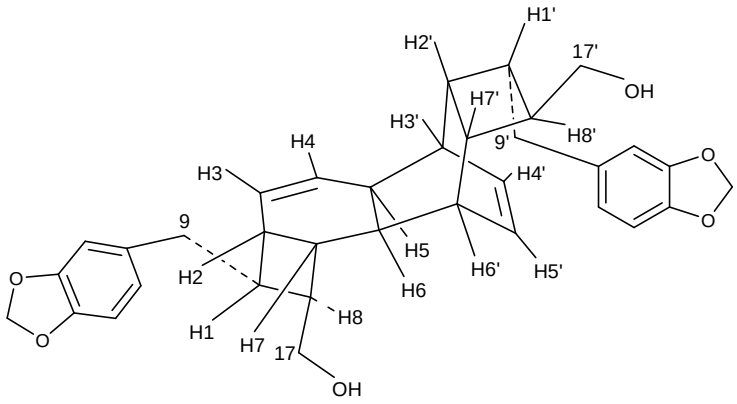


Figure 2-10. The exo RCDA diol **2-70**

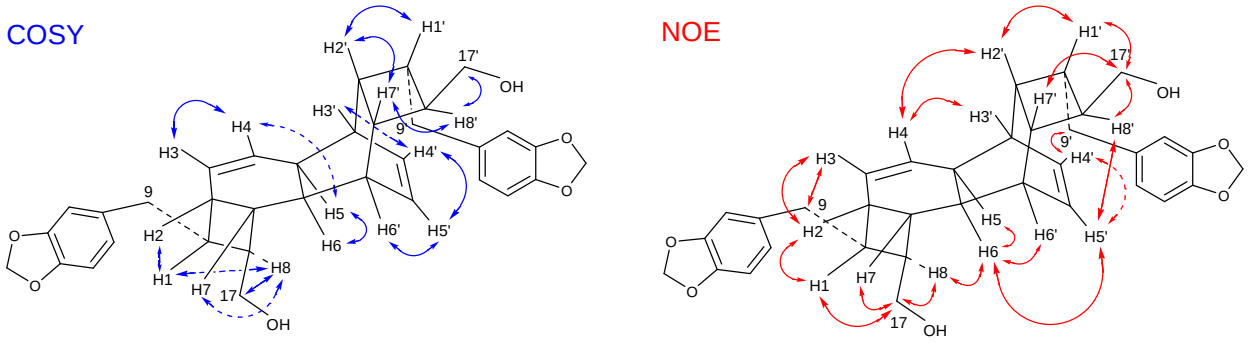


Figure 2-11. 2D-COSY and NOESY correlations of the diol **2-70**

The nmr spectrum of the second RCDA adduct **2-68c** contained overlapping signals for protons at high field. It was not possible to assign peaks for individual protons in this region. Consequently, we converted this diester to the corresponding diol. With the exception of the protons under a 2H signal at 2.70 ppm and a 3H signal at 2.62 ppm, each proton in this diol was represented by an isolated signal with a clear splitting pattern. The 2D nmr spectra of the diol allowed complete assignment of these individual signals. The complete assignment of the pentacyclic core structure is shown in Table 2-8.

The structure of the pentacyclic core in diol **2-70** was confirmed by a combination of COSY (Table 2-6), NOESY (Table 2-7), HMQC (Table 2-8), and HMBC (Table 2-9) nmr experiments. Both the ^{1}H and the ^{13}C nmr spectra indicated that diol **2-70** was derived from an intramolecular Diels Alder adduct. However, comparison of the ^{1}H nmr pattern with those of diol **2-70** and the kingianins suggested that its structure differed from those of these compounds in some

fundamental way. Most impressive was a significant difference in the chemical shifts of the two most downfield olefinic protons; compare the chemical shifts of **2-38c** and **2-70** in Table 2-11.

On the basis of the chemical shifts of the two upfield olefinic signals (5.83 and 5.66, in the same range as H3 and H4 in the kingianins), we assigned the dienophilic western substructure of the pentacyclic core as identical with that in diol **2-38c**. This assumption was well supported by the crosspeaks of H3 (5.83) and H9a and H9b (2.50 and 2.70) in the NOESY. Also, the crosspeaks of H3/H2, H2/H1, H1/H17, H17/H7, H17/H8, H8/H6, and H6/H5 in the NOESY and the crosspeaks of H3/H4, H4/H5, H5/H6, H2/H1, H1/H8, H7/H8, and H8/H17 in the COSY confirmed that the connectivity and relative stereochemistry of the fused [4.2.0]-bicyclooctene ring system in the western sector were the same as those in diol **2-38c**.

With the H9 and H2 protons identified, we could assign the 3H signal at 2.62 ppm to the H9' and H2' protons. The crosspeaks of H9'/H4', H4'/H5', H5'/H8', H8'/H17', H17'/H1', and H1'/H2' in the NOESY and the crosspeaks of H1'/H2', H2'/H7', H7'/H8', H8'/H17', H4'/H5', H4'/H3', and H5'/H6' in the COSY confirmed the connectivity and relative stereochemistry of the fused [4.2.0]-bicyclooctene ring system in the eastern sector.

Next we needed to determine the stereochemistry of the connection of the eastern and western substructures. The crosspeaks of H5/H6 in the NOESY and COSY showed H5 and H6 to be cis. The key crosspeaks of H6/H5' in the NOESY showed that H5/H6 and H4'/H5' are on same face of the pentacycle. Furthermore, the crosspeaks of H4/H3', H4/H2', and H6/H6' in the NOSEY showed that the stereochemical relationship of the eastern and western sectors corresponds to that of an exo Diels Alder product as shown in the COSY and NOE pictures (Figure 2-11).

The exo Diels Alder structure was further supported by HMQC and HMBC assignments. Each carbon in the core pentacyclic structure was assigned to the attached protons by the crosspeaks in the HMQC. Indeed, the examination of the connectivity by HMBC analysis (the crosspeaks of selected carbon atoms and the corresponding protons) are consistent with the suggested structure in the COSY and NOE pictures. The crosspeaks in the HMQC and HMBC spectra are summarized in Tables 2-8 and 2-9, respectively.

The structure determination of diol **2-70** allowed us to identify the second RCDA product as the exo cycloaddition product **2-69c** as shown in Scheme 2-28. Also, the full assignment of the pentacyclic structure of diol **2-70** was presented in Table 2-10.

Table 2-6. Crosspeaks in COSY Spectrum of Diol **2-70**

Proton number (ppm)	
H1 (2.03) ↔ H2 (2.71) and H8 (1.84)	H3 (5.83) ↔ H4 (5.66)
H4 (5.66) ↔ H5 (2.20)	H5 (2.20) ↔ H6 (1.54)
H7 (2.28) ↔ H8 (1.84)	H8 (1.84) ↔ H17 (3.36)
H1’ (2.11) ↔ H2’ (2.60)	H2’ (2.60) ↔ H7’ (2.28)
H3’ (2.44) ↔ H4’ (6.58)	H4’ (6.58) ↔ H5’ (6.38)
H5’ (6.38) ↔ H6’ (2.39)	H7’ (2.28) ↔ H8’ (1.96)
H8’ (1.96) ↔ H17’ (3.27)	

Table 2-7. Crosspeaks in NOESY Spectrum of Diol **2-70**

proton number (ppm)	
H1 (2.03) ↔ H2 (2.71) and H17 (3.36)	H2 (2.71) ↔ H3 (5.83)
H3 (5.83) ↔ H9a and H9b (2.50 and 2.70)	H4 (5.66) ↔ H2’ (2.60) and H3’ (2.44)
H5 (2.20) ↔ H6 (1.54)	H6 (1.54) ↔ H8 (1.84), H5’ (6.38), and H6’ (2.39)
H7 (2.28) ↔ H17 (3.36)	H8 (1.84) ↔ H6 (1.54) and H17 (3.36)
H1’ (2.11) ↔ H2’ (2.60) and H17’ (3.27)	H4’ (6.58) ↔ H5’ (6.38) and H17’ (3.27)
H5’ (6.38) ↔ H8’ (1.96)	H7’ (2.28) ↔ H17’ (3.27)
H8’ (1.96) ↔ H17’ (3.27)	

Table 2-8. Crosspeaks in the HMQC Spectrum of Diol **2-70**

Carbon number (ppm)	Corresponding proton number (ppm)	Carbon number (ppm)	Corresponding proton number (ppm)
C1 (36.9)	H1 (2.03)	C1’ (34.6)	H1’ (2.11)
C2 (34.4)	H2 (2.71)	C2’ (34.3)	H2’ (2.60)
C3 (131.4)	H3 (5.83)	C3’ (42.2)	H3’ (2.44)
C4 (126.3)	H4 (5.66)	C4’ (121.0)	H4’ (6.58)
C5 (33.0)	H5 (2.20)	C5’ (135.3)	H5’ (6.38)
C6 (34.3)	H6 (1.54)	C6’ (36.4)	H6’ (2.39)

C7 (40.7)	H7 (2.28)	C7’ (41.7)	H7’ (2.28)
C8 (48.5)	H8 (1.84)	C8’ (45.3)	H8’ (1.96)
C9 (42.2)	H9 (2.50 and 2.70)	C9’ (35,6)	H9’ (2.62)
C16 (100.7)	H16 (5.89)[a]	C16’ (100.8)	H16’ (5.91)[a]
C17 (64.8)	H17 (3.36)	C17’ (67.1)	H17’ (3.27)

[a] may be interchanged.

Table 2-9. Crosspeaks in the HMBC Spectrum of Diol **2-70**

Carbon (number, ppm)	Corresponding protons (number, ppm)]
C1 (36.9)	H17 (3.36)
C3 (131.4)	H2 (2.71), H5 (2.20)
C4 (126.3)	H1 (2.03), H2 (2.71), H5 (2.20), H7 (2.28)
C5 (33.0)	H4 (5.66), H6 (1.54)
C7 (40.7)	H17 (3.36)
C8 (48.5)	H1 (2.03), H6 (1.54) H7 (2.28), H9 (2.50 and 2.70), H17 (3.36)
C17 (64.8)	H1 (2.03), H7 (2.28)
C1’ (34.6)	H17’ (3.27)
C3’ (42.2)	H4’ (6.58), H5’ (6.38), H6 (1.54)
C6’ (36.4)	H4’ (6.58), H5’ (6.38)
C7’ (41.7)	H17’ (3.27)
C8’ (45.3)	H9’ (2.62), H17’ (3.27)
C17’ (67.1)	H7’ (2.28), H8’ (1.96)

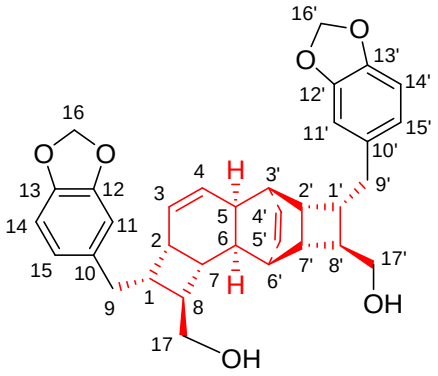


Table 2-10. ^{1}H and ^{13}C-NMR for the pentacylic core of diol **2-70** in $CDCl_3$

Number	^{1}H, δ (ppm), *J* (Hertz)	^{13}C, δ (ppm)
1	2.03 (dd, *J* = 7.9, 1 H)	36.9
2	2.71 (m, 1 H)	34.4
3	5.83 (d, *J* = 10.4, 1 H)	131.4
4	5.66 (ddd, *J* = 10.4, 3.6, and 2.0, 1 H)	126.3
5	2.20 (m, 1 H)	33.0
6	1.54 (dd, *J* = 10.7 and 2.4, 1 H)	34.29
7	2.28 (m, 1 H)	40.7
8	1.84 (m, 1 H)	48.5
9	2.50 (dd, *J* = 14.1 and 8.1, 1 H), 2.70 (dd, *J* = 14.1 and 7.9, 1 H)	35.9
17	3.36 (m, 2 H)	64.8
1’	2.11 (m, 1 H)	34.6
2’	2.60 (m, 1 H)	34.34
3’	2.44 (m, 1 H)	42.2
4’	6.59[a]	121.0
5’	6.38 (t, *J* = 7.2, 1 H)	135.3
6’	2.39 (m, 1 H)	36.4
7’	2.28 (m, 1 H)	41.7
8’	1.96 (quintet, *J* = 6.8, 1 H)	45.3
9’	2.62 (m, 2 H)	35.6
17’	3.24 (dd, *J* = 8.4 and 5.5 Hz, 1 H), 3.29 (dd, *J* = 8.4 and 5.5 Hz, 1 H)	67.1

[a] The signal for the proton at 6.59 ppm lies under that for the aromatic protons.

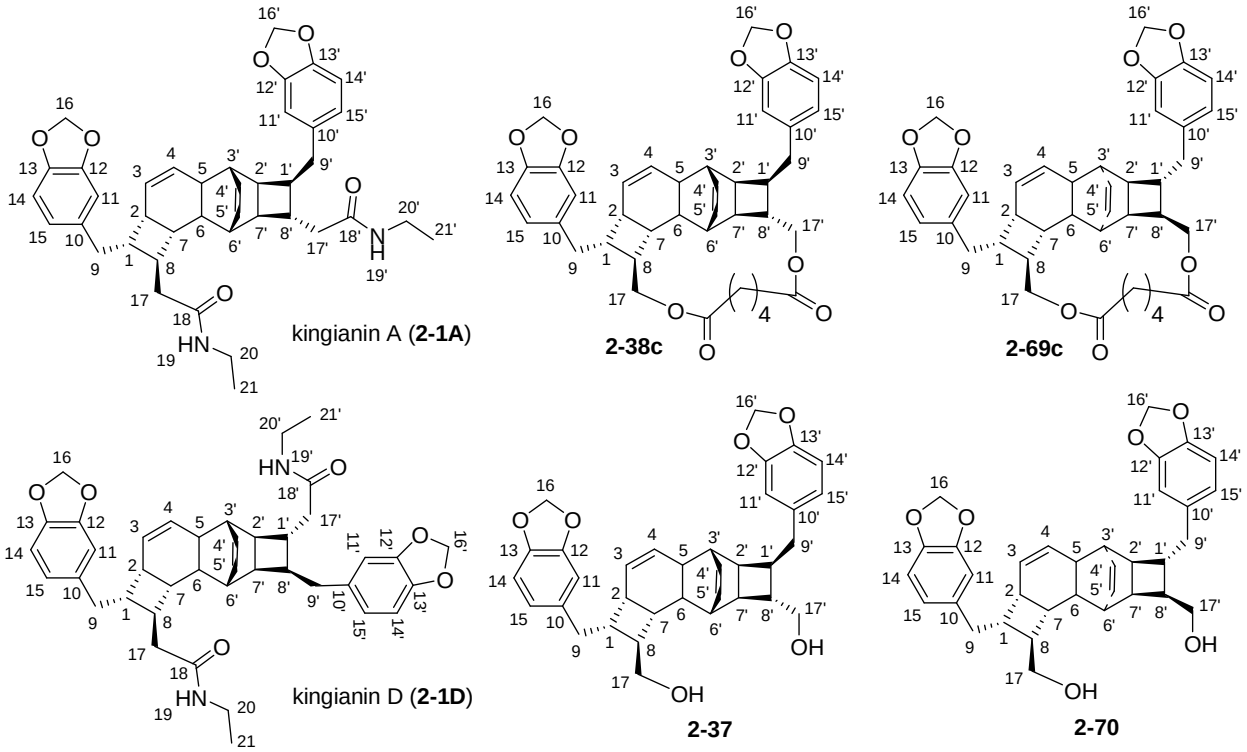


Figure 2-12. Structures of Kingianins A, D and synthetic dimers

Table 2-11. Characteristic ^{1}H-NMR Data for Kingianin A, D, and Synthetic Dimers **2-38c**, **2-69c**, **2-37**, **2-70** in $CDCl_3$ (at 7.26), δ (ppm)

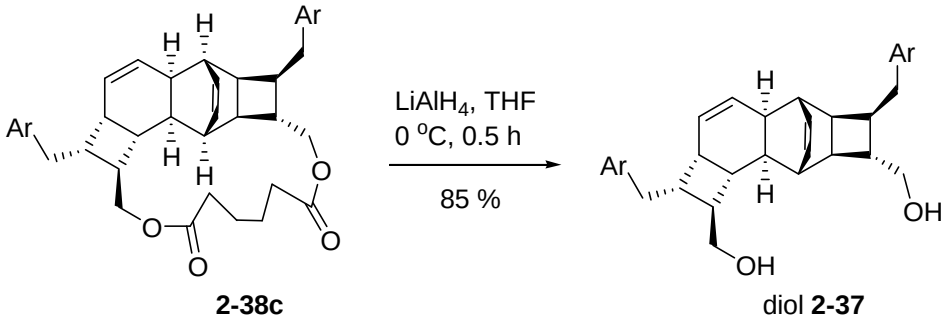
Num.	Kingianin A, δ_H (*J* in Hz)	Kingianin D, δ_H (*J* in Hz)	**2-38c**	**2-37**	**2-69c**	**2-70**
3	5.56 (brd, *J* = 10.4 Hz)	5.56 (brd, *J* = 10.4 Hz)	5.61	5.62	5.84	5.83
4	5.66 (brd, *J* = 10.4 Hz)	5.75 (brd, *J* = 10.4 Hz)	5.75	5.71	5.69	5.66
6	1.70 (brd, *J* = 9.0 Hz)	1.67	1.73	1.72	1.46	1.54
16	5.90[a]	5.90	5.89[a]	5.93[a]	5.92[a]	5.89[a]
4'	6.11 (dd, *J* = 7.1 and	6.29 (dd, *J* = 7.1 and 7.6Hz)	6.16	6.13	6.63	6.59
5'	6.22 (t, *J* = 7.1 Hz)	6.14 (t, *J* = 7.1 Hz)	6.29	6.27	6.36	6.38
16'	5.88[a]	5.90	5.90[a]	5.90[a]	5.92[a]	5.91[a]

[a]Values are interchangeable

2.2.9 Hydrolysis and Double homologation

2.2.9.1 Efforts for one carbon homologation

With some confidence that we had a significant intermediate in hand, we released the diol **2-37** from its tether in diester **2-38c** (Scheme 2-29).



2-38c diol **2-37**

Scheme 2-29. Hydrolysis of the diester **2-38c**

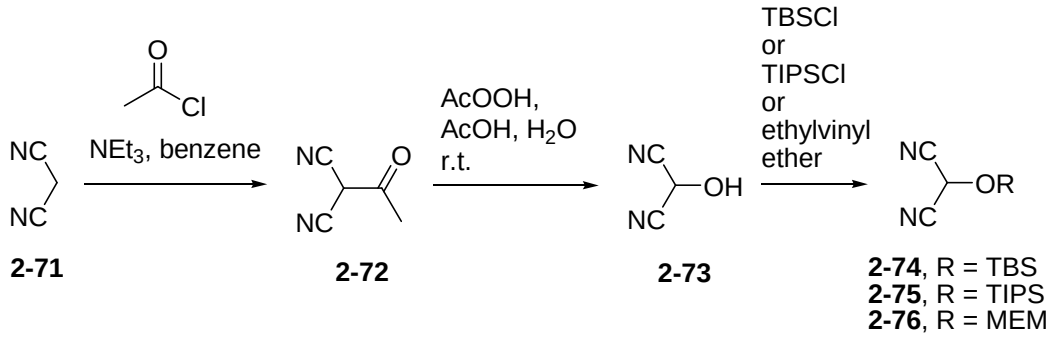
The next job was construction of the ethyl amide functionality from the diol **2-37**. The reagents for one carbon homologation have been extensively studied and most of them are modified Wittig[85] or Peterson[86] olefination reagents. Also, the reaction conditions are harsh in

[85] For Wittig-type olefinations, see (a) Reactions of ketene thioacetals with electrophiles. Homologation of aldehydes. Carey, F. A.; Neergaard, J. R. *J. Org. Chem*. **1971**, *36*, 2731. (b) A one-carbon homologation of carbonyl compounds to carboxylic acids, esters, and amides. Dinizo, S. E.; Freerksen, R. W.; Pabst, W. E.; Watt, D. S. *J. Am. Chem. Soc*. **1977**, *99*, 182-186. (c) Synthetic applications of 2-chloro-1,3-dithiane preparation of ketene dithioacetals. Kruse, C. G.; Broekhof, N. L. J. M.; Wijsman, A.; Van der gen, A. *Tetrahedron Lett*. **1977**, *18*, 885-888. (d) Heteroatom directed photoarylation synthesis of functionalized indolines. Schultz, A. G.; Sha, C. -K. *Tetrahedron*, **1980**, *36*, 1757-1761. (e) α-Substituierte phosphonate-38: 1-dimethylamino-1-cyano-methanphosphonsäurediethylester, ein neues edukt zur darstellung von carbonsäuren, 1-cyanoenaminen und homoenolaten. Costisella, K.; Gross, H. *Tetrahedron* **1982**, *38*, 139-145.

[86] For Peterson-type olefination, see (a) Reactions of ketene thioacetals with electrophiles. Homologation of aldehydes. Carey, F. A.; Neergaard, J. R. *J. Org. Chem*. **1971**, *36*, 2731. (b) Silicon-containing carbanions. II. Ketene thioacetal synthesis via 2-lithio-2-trimethylsilyl-1,3-

some cases and the preparations of the reagents are not trivial. Furthermore, our substrate is potentially exposed to epimerization when the diol **2-37** is oxidized to the dialdehyde.

Thus, we first considered the one carbon homologation with masked acyl cyanides (MACs). We anticipated that we might get a one carbon homologated acyl cyanide by way of an S_N2 reaction between a MAC and the mesylate of diol **2-37**. The known MACs **2-74**, **2-75**, and **2-76**[87] were prepared from malononitrile by the three steps sequence in Scheme 2-30.



Scheme 2-30. The preparation of MAC reagents

Having the MAC reagents, we screened the reaction conditions with a model compound **2-77**. First, we tried the substitution reaction with the MAC **2-74**. As shown in all results, the starting material, the mesylate **2-77**, was recovered and the desilylation of TBS-MAC reagent was observed in several conditions (Scheme 2-31). Changing base and solvent did not affect the reaction.

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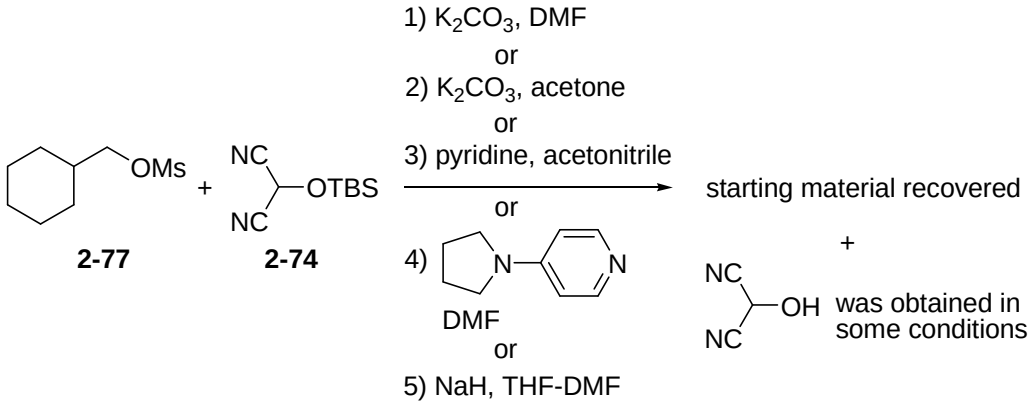
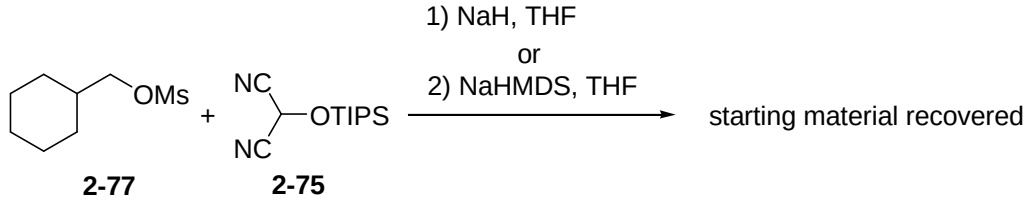
dithiane. Carey, F. A.; Court, A. S. *J. Org. Chem*. **1972**, *37*, 1926. (c) S-Methyl Thiocarboxylates from Aldehydes and Ketones through Ketene Thioacetals. Reductive Nucleophile Thiocarbonylation. Seebach, D.; Burstinghaus, R. *Synthesis* **1975**, 461. (d) [Methoxy(phenylthio)methyl]lithium and [methoxy(phenylthio)(trimethylsilyl)methyl]lithium. Two exceedingly convenient reagents for the facile conversion of aldehydes, ketones, and 3-alkoxy enones into ketene O,S-acetal derivatives. Hackett, S.; Livinghouse, T. *J. Org. Chem*. **1986**, *51*, 879-885. (e) Development of a one-pot method for the homologation of aldehydes to carboxylic acids. McNulty, J; Das, P. *Tetrahedron*, **2009**, *65*, 7794-7800.

[87] A three-step preparation of MAC reagents from malononitrile. Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett*. **2003**, *44*, 73-75



Scheme 2-31. The S_N2 reaction of the mesylate **2-77** with TBS-MAC **2-74**

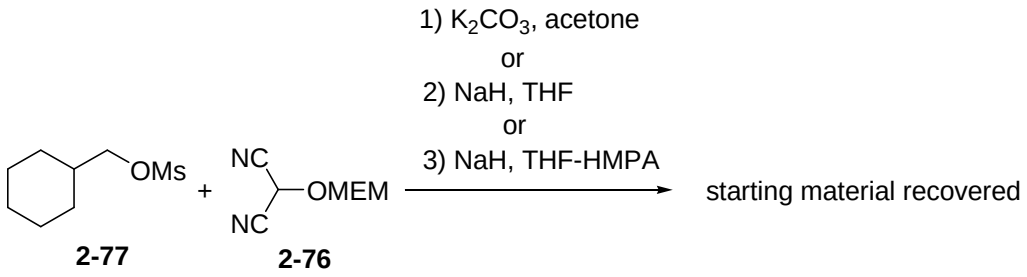
Because the TBS-protected MAC **2-74** was labile in some cases, we tested a more robust TIPS-MAC **2-75**. However, the mesylate **2-77** was recovered in the conditions using strong bases (Scheme 2-32).



Scheme 2-32. The S_N2 reaction of the mesylate **2-77** with TIPS-MAC **2-75**

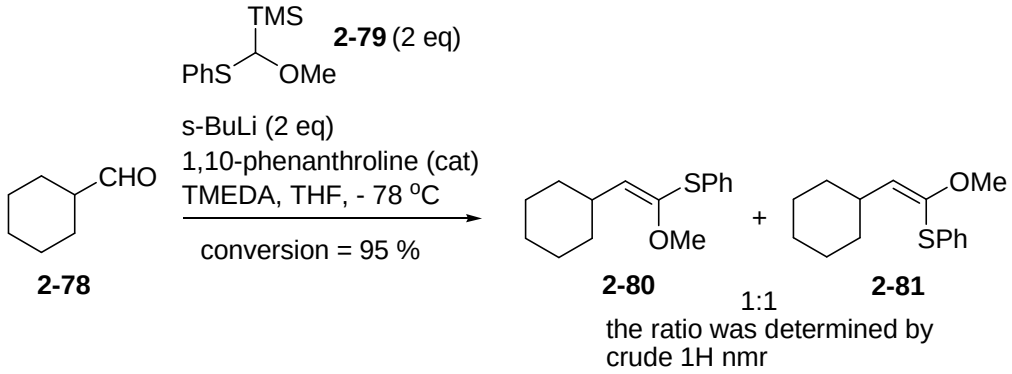
Finally, we examined the MEM-MAC **2-76**. The successful substitution reaction between MEM-MAC and a primary iodide is known.[88] Inspired by this successful reaction, we first adapted the same protocol with potassium carbonate for our substrate. However, only starting material was recovered. Other conditions using strong bases gave the same result (Scheme 2-33).

[88] Development of a New Acyl Anion Equivalent for the Preparation of Masked Activated Esters and Their Use To Prepare a Dipeptide. Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515-4516.



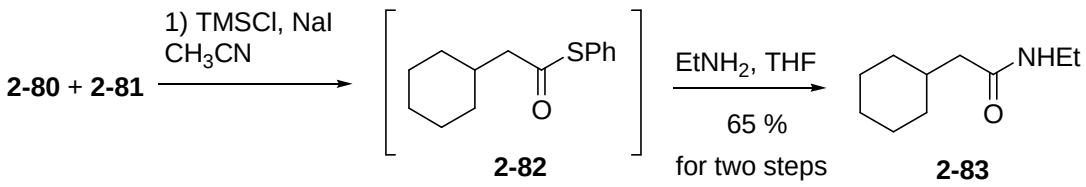
Scheme 2-33. The S_N2 reaction of the mesylate **2-77** with MEM-MAC **2-76**

We next turned our attention to the Peterson olefination type reagent, [methoxy(phenylthio)-(trimethylsilyl)methane **2-79** developed by Livinghouse et al.[38d] This reagent has the advantagesthat the conversion of the intermediate thioester to ethylamide is easy. We first performed a model reaction with cyclohexanecarboxaldehyde **2-78**. The aldehyde **2-78** was subjected to the Livinghouse's conditions to provide an inseparable mixture of (E)-, (Z)-olefins **80** and **81** (Scheme 2-34).



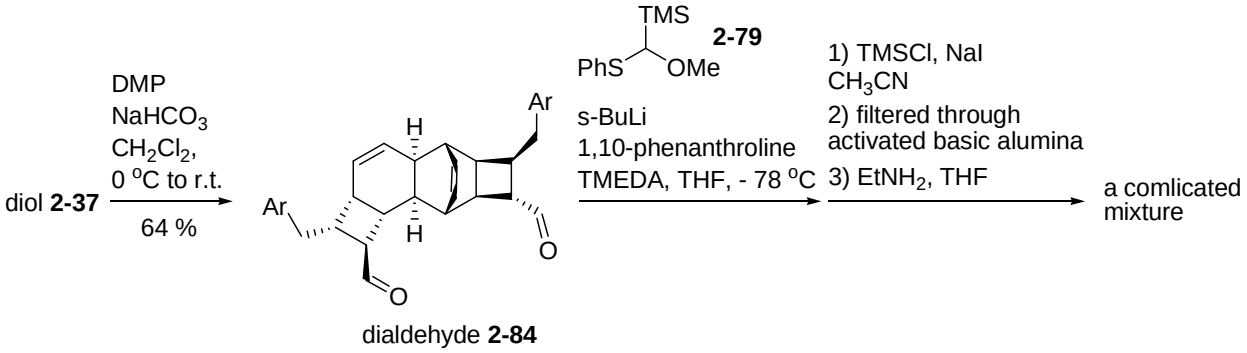
Scheme 2-34. Olefination usting Livinghouse's procedure

The demethylation of using TMSI was followed by the treatment with ethylamine. As a result, the desired one carbon homologated ethyl amide was obtained in 65 % yield (Scheme 2-35).



Scheme 2-35. The demethylation and ethyl amide synthesis

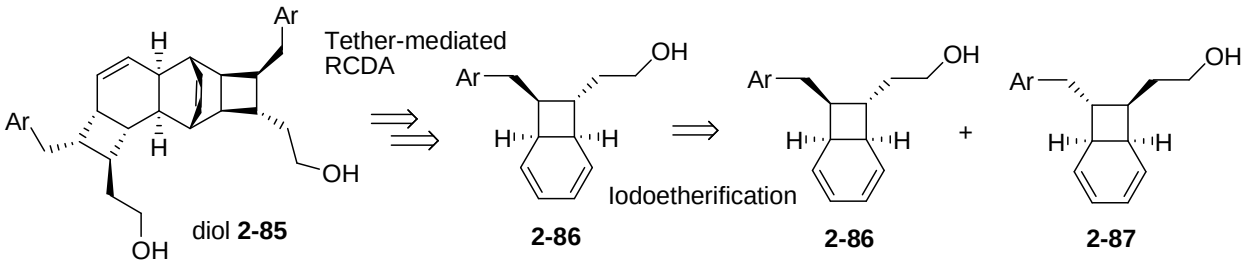
Next, we applied the method to the dialdehyde **2-84** that was oxidized from the diol **2-37**. However, a complicated mixture was obtained (Scheme 2-36).



Scheme 2-36. The application of Livinghouse's procedure to the dialdehyde **2-84**

2.2.9.2 The alternative monomer for the RCDA reaction

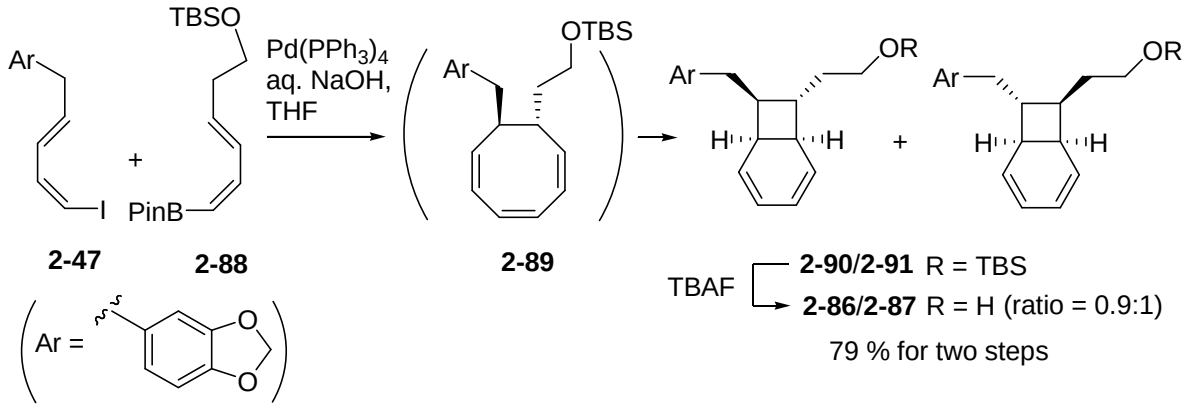
We have been frustrated with one carbon homologation of the diol **2-37**. This led us to consider an alternative route to pre-homologated diol **2-85**. The amide formation from the acid that might be produced by oxidation of the diol **2-85** looked attractive. We thought that the diol **2-85** would be available from endo alcohol **2-86** by a tether-mediated RCDA reaction as in the preparation of the diol **2-37**. Again, the exo alcohol **2-87** would be removed by iodoetherification and chromatography (Scheme 2-37).



Scheme 2-37. An alternative route to pre-homologated diol **2-85**

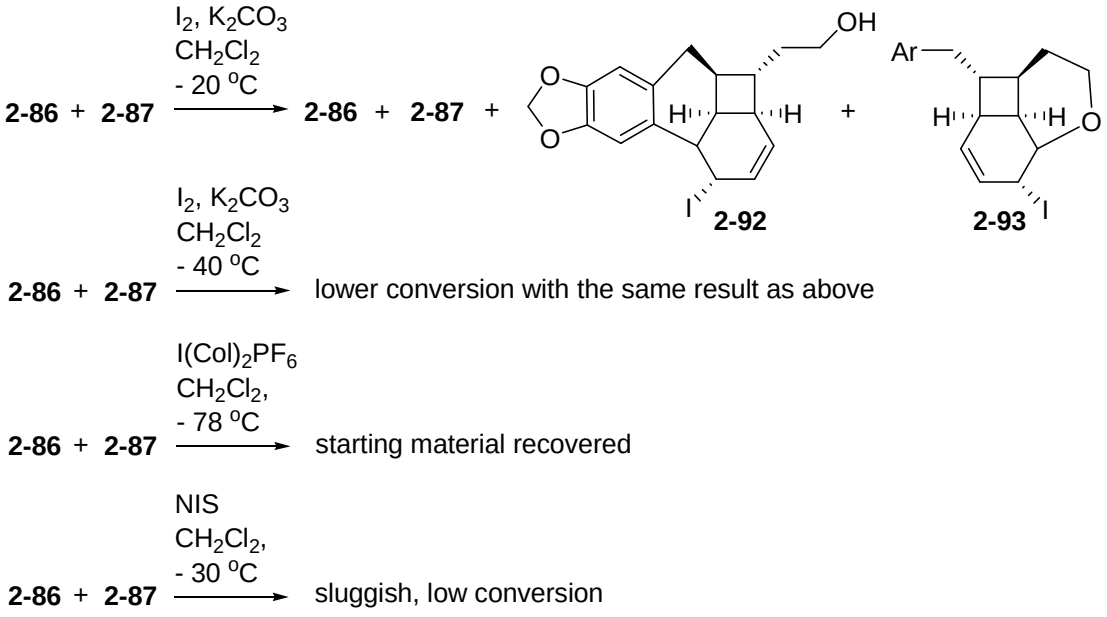
Following a conventional tandem coupling and electrocyclization strategy, we obtained an inseparable mixture of endo- and exo-alcohols **2-86** and **2-87** by adaptation of the procedure that had been successfully applied to the synthesis of the bicyclooctadienes **2-41** and **2-43** (Scheme 2-

38).



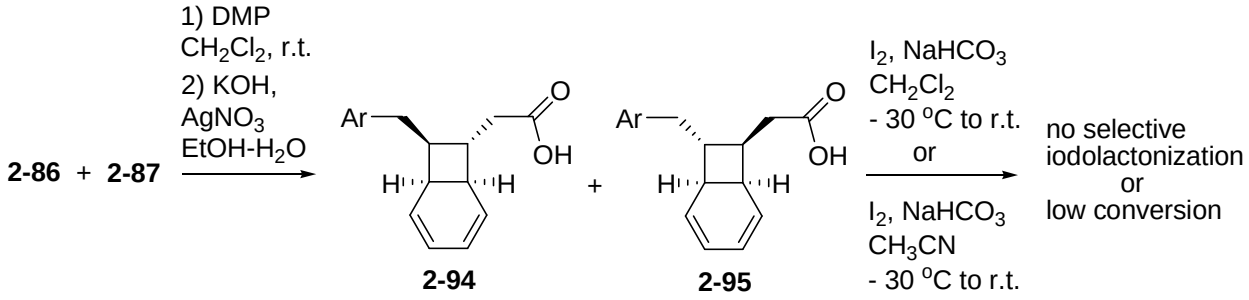
Scheme 2-38. Synthesis of the endo- and exo-alcohols **2-86** and **2-87**

Having a mixture of **2-86** and **2-87**, we next carried out iodoetherification to selectively remove exo isomer **2-87**. However, in contrast to our expectation, the iodoetherifiation did not result in a selective removal. The resulting inseparable mixture contained pentacyclic **2-92** and iodoether **2-93** along with unreacted starting materials. Lowering the temperature or changing the reagent to a hard iodine electrophile did not give a successful result (Scheme 2-39).



Scheme 2-39. Iodoetherification of the endo- and exo-alcohols **2-86** and **2-87**

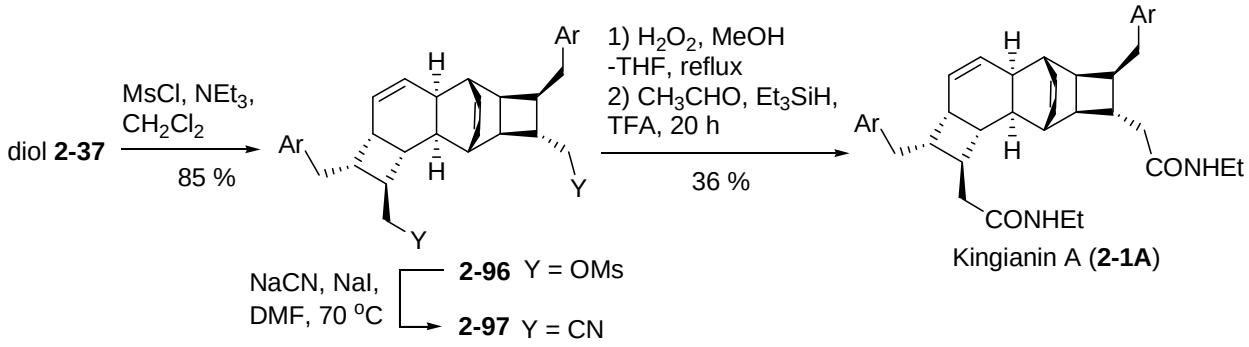
In addition, when we tuned the nucleophilicity of the sidechain functionality by converting the alcohols to carboxylic acids, the selective iodolactonization was not observed (Scheme 2-40).



Scheme 2-40. Iodolactonization of the acids **2-94** and **2-95**

2.2.9.3 Double homologation: completion of the total synthesis of kingianin A

Meanwhile, we performed the double homologation procedure that had been employed by Moses for the synthesis of pre-kingianin A. Mesylation of the diol **2-37** and displacement by cyanide (→ **2-97**) were followed by peroxide-promoted hydrolysis[89] and the reductive N-alkylation procedure of Dube.[90] This 5-step sequence converted diol **2-37** to (±)-kingianin A (**2-1A**) in 26 % yield (Scheme 2-41).



Scheme 2-41. Double homologation: completion of the total synthesis of kingianin A

[89] For a study of effective media for this reaction, see Brinchi, L.; Chiavini, L.; Goracci, L.; Di Profio, P.; Germani, R. *Lett. Org. Chem.* **2009,** *6*, 175-179.

[90] Reductive N-alkylation of amides, carbamates and ureas. Dube, D.; Scholte, A. A. *Tetrahedron Lett*. **1999**, *40*, 2295-2298.

The ^{1}H and ^{13}C nmr spectra of our synthetic kingianin A were compared with those reported for the natural product in Table 2-12 and 2-13. The chemical shifts as well as coupling constants were consistent with the authentic data.

Table 2-12. ^{1}H-NMR for Kingianin A in $CDCl_3$, δ (ppm), mult, (*J* in Hz)[91]

No.	Authentic, δ_c	Synthetic, δ_c	No.	Authentic, δ_c	Synthetic, δ_c
1	2.05 m	2.05 m	1’	2.09 m	2.09 m
2	2.48 m	2.48 m	2’	2.26 m	2.26 m
3	5.56 br d (10.4)	5.57 br d (10.3)	3’	2.41 m	2.42 m
4	5.66 br d (10.4)	5.67 br d (10.3)	4’	6.11 dd (7.1, 7.6)	6.12 t (7.2)
5	2.24 m	2.24 m	5’	6.22 t (7.1)	6.23 t (7.2)
6	1.70 br d (9.0)	1.71 br d (9.0)	6’	2.52 m	2.53 m
7	1.91 m	1.92 m	7’	2.49 m	2.50 m
8	2.02 m	2.03 m	8’	2.28 m	2.28 m
9	2.57/2.46 m	2.57/2.46 m	9’	2.63/2.49 m	2.64/2.50
10	-	-	10’	-	-
11	6.63 d (1.2)	6.63 br s	11’	6.60 br s	6.61 br s
12	-	-	12’	-	-
13	-	-	13’	-	-
14	6.69 d (7.9)	6.70 d (4.1)	14’	6.68 d (7.9)	6.68 d (4.1)
15	6.56 dd (7.9, 1.2)	6.56 br d (8.2)	15’	6.57 br d (7.9)	6.58 br d (9.3)
16	5.90[a] s	5.91[a] s	16’	5.88[a] s	5.89[a] s
17	2.02 m	2.03 m	17’	2.07/1.95 m	2.07/1.96 m
18	-	-	18’	-	-
19	5.30 t (5.7)	5.20[b] t (5.2)	19’	5.25 t (5.7)	5.16[b] t (5.2)
20	3.21 qd (7.2, 5.7)	3.21 qd (7.2, 5.2)	20’	3.21 qd (7.2, 5.7)	3.21 qd (7.2, 5.2)
21	1.09 t (7.2)	1.09[c] t (7.2)	21’	1.09 t (7.2)	1.10[c] t (7.2)

The data for the authentic sample are extracted from the report of the structure assignment.[9]
[a, b, c] Values are interchangeable

[91] Our laboratory uses 7.260 ppm for the chemical shift of $CHCl_3$. All values in the Experimental Section are based on this standard. The Litaudon group uses 7.240 ppm for the chemical shift of $CHCl_3$. Therefore in this Table we have adjusted the values reported by Litaudon et al by adding 0.020 ppm.

Table 2-13. ^{13}C-NMR for Kingianin A in $CDCl_3$, δ (ppm)[92]

Number	Authentic	Synthetic	Number	Authentic	Synthetic
1	43.7	43.7	1’	38.8	38.8
2	33.2	33.2	2’	44.3	44.3
3	124.9	124.9	3’	42.8	42.7
4	132.2	132.3	4’	132.4	132.4
5	38.1	38.0	5’	134.8	134.8
6	37.9	37.9	6’	38.4	38.4
7	42.4	42.40[a]	7’	39.7	39.7
8	42.4	42.42[a]	8’	43.7	43.7
9	35.8	35.8	9’	35.2	35.2
10	135.3	135.2	10’	135.5	135.5
11	108.8	108.79[b]	11’	108.8	108.84[b]
12	147.5	147.5	12’	147.5	147.5
13	145.4	145.4	13’	145.4	145.4
14	108.1	108.1	14’	108.1	108.1
15	121.0	121.00[c]	15’	121.0	121.02[c]
16	100.7	100.7	16’	100.7	100.7
17	41.8	41.8	17’	43.0	43.0
18	171.9	171.9	18’	171.9	171.8
19	-	-	19’	-	-
20	34.3	34.3	20’	34.2	34.2
21	14.9	14.86[d]	21’	14.9	14.91[d]

The data for the authentic sample are extracted from the report of the structure assignment.[9]
[a, b, c, d] Values are interchangeable

[92] Our laboratory uses 77.000 ppm for the chemical shift of $CDCl_3$. All values in the Experimental Section are based on this standard. The Litaudon group uses 77.230 ppm for the chemical shift of $CDCl_3$. Therefore in this Table we have adjusted the values reported by Litaudon et al by subtracting 0.230 ppm.

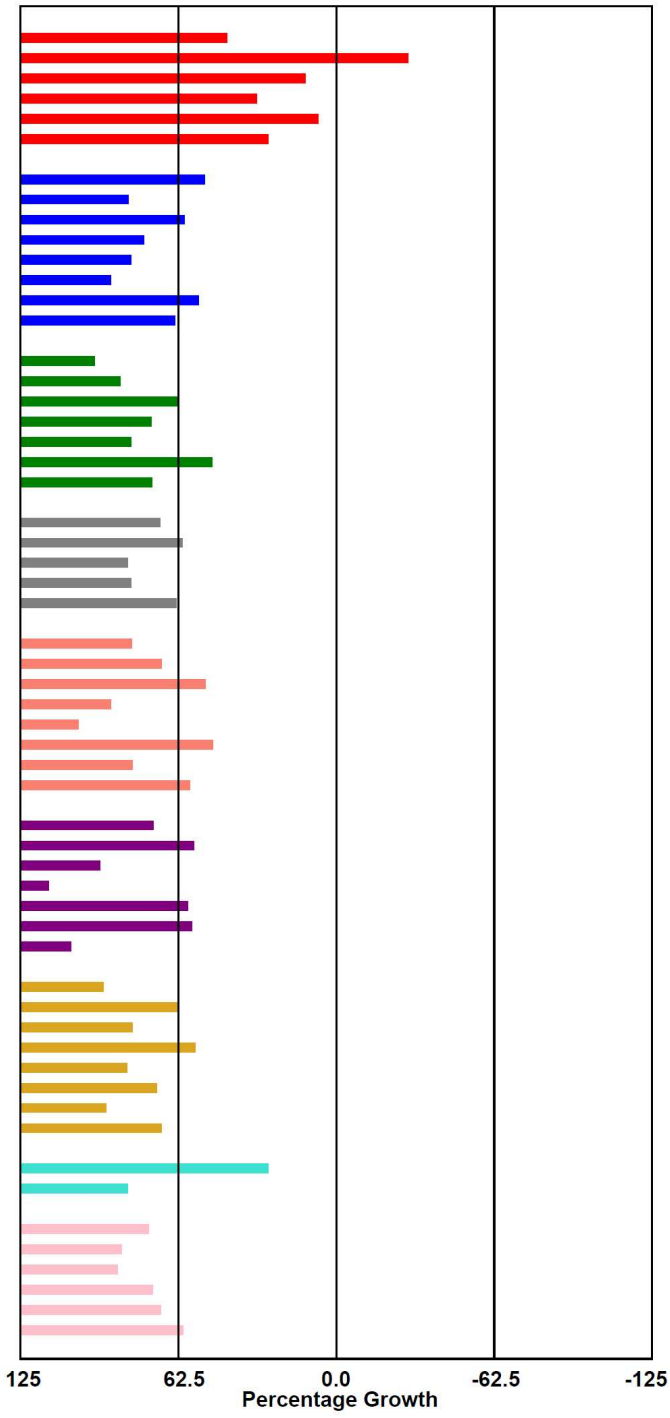
2.2.10 The test result in NCI-60 cell lines

Our synthetic kingianin A was sent to Dr. John Beutler at the National Cancer Institute (NCI) for testing in the NCI-60 cell line screen. The resulting bar graphs are attached. The first graph is for the one dose experiment for measuring the relative cell death. Kingianin A showed a complicated result, demanding the further experiments.

Developmental Therapeutics Program One Dose Bar Graph	NSC: D-768505 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 26, 2012
	Experiment ID: 1211OS83		Report Date: Jan 03, 2013

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	43.55
HL-60(TB)	-28.06
K-562	12.57
MOLT-4	31.71
RPMI-8226	7.39
SR	27.11
Non-Small Cell Lung Cancer	
A549/ATCC	52.29
HOP-62	82.67
HOP-92	60.45
NCI-H226	76.43
NCI-H23	81.44
NCI-H322M	89.58
NCI-H460	54.74
NCI-H522	64.07
Colon Cancer	
COLO 205	96.10
HCC-2998	85.71
HCT-116	62.98
HCT-15	73.57
HT29	81.46
KM12	49.42
SW-620	73.13
CNS Cancer	
SF-268	70.04
SF-295	61.22
SNB-19	82.80
SNB-75	81.42
U251	63.56
Melanoma	
MALME-3M	81.14
M14	69.54
MDA-MB-435	52.05
SK-MEL-2	89.57
SK-MEL-28	102.36
SK-MEL-5	49.23
UACC-257	80.87
UACC-62	58.16
Ovarian Cancer	
IGROV1	72.71
OVCAR-3	56.64
OVCAR-4	93.70
OVCAR-5	114.13
OVCAR-8	59.13
NCI/ADR-RES	57.33
SK-OV-3	105.28
Renal Cancer	
786-0	92.42
A498	62.60
ACHN	81.12
CAKI-1	56.02
RXF 393	83.12
SN12C	71.24
TK-10	91.44
UO-31	69.44
Prostate Cancer	
PC-3	27.19
DU-145	82.78
Breast Cancer	
MCF7	74.48
MDA-MB-231/ATCC	85.37
HS 578T	86.84
BT-549	73.08
T-47D	69.89
MDA-MB-468	60.88

Bar Graph

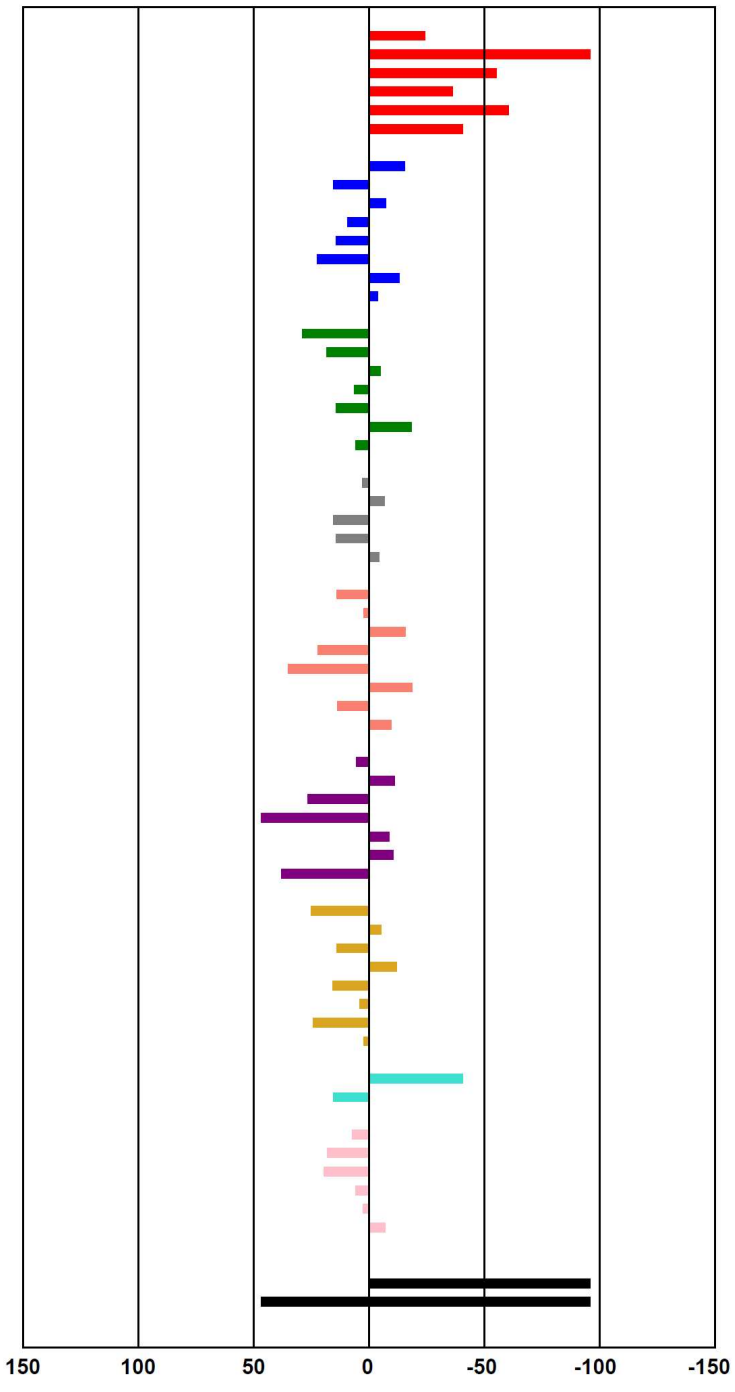


Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-768505 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 26, 2012
Experiment ID: 1211OS83		Report Date: Jan 03, 2013

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	43.55
HL-60(TB)	-28.06
K-562	12.57
MOLT-4	31.71
RPMI-8226	7.39
SR	27.11
Non-Small Cell Lung Cancer	
A549/ATCC	52.29
HOP-62	82.67
HOP-92	60.45
NCI-H226	76.43
NCI-H23	81.44
NCI-H322M	89.58
NCI-H460	54.74
NCI-H522	64.07
Colon Cancer	
COLO 205	96.10
HCC-2998	85.71
HCT-116	62.98
HCT-15	73.57
HT29	81.46
KM12	49.42
SW-620	73.13
CNS Cancer	
SF-268	70.04
SF-295	61.22
SNB-19	82.80
SNB-75	81.42
U251	63.56
Melanoma	
MALME-3M	81.14
M14	69.54
MDA-MB-435	52.05
SK-MEL-2	89.57
SK-MEL-28	102.36
SK-MEL-5	49.23
UACC-257	80.87
UACC-62	58.16
Ovarian Cancer	
IGROV1	72.71
OVCAR-3	56.64
OVCAR-4	93.70
OVCAR-5	114.13
OVCAR-8	59.13
NCI/ADR-RES	57.33
SK-OV-3	105.28
Renal Cancer	
786-0	92.42
A498	62.60
ACHN	81.12
CAKI-1	56.02
RXF 393	83.12
SN12C	71.24
TK-10	91.44
UO-31	69.44
Prostate Cancer	
PC-3	27.19
DU-145	82.78
Breast Cancer	
MCF7	74.48
MDA-MB-231/ATCC	85.37
HS 578T	86.84
BT-549	73.08
T-47D	69.89
MDA-MB-468	60.88
Mean	67.49
Delta	95.55
Range	142.19



2.3 Conclusion

A 12-step synthesis of kingianin A, an inhibitor of the antiapoptotic protein Bcl-$_X$L, is based on a radical cation Diels Alder reaction (RCDA), an approach thought to be biomimetic.

We hypothesized that the stereochemistry of the RCDA reaction of the bicyclooctadienes are derived by two steric factors; 1) the substituents on cyclobutane blocks an approach from sterically hindered faces of both bicyclooctadienes and 2) another steric factor is believed to be built when the diene approaches the dienophile proximal to endo substituent. Also, our concern about the practical synthesis led us to have a tether-mediated intramolecular RCDA strategy.

The presumed monomeric bicycloocatdiene, the endo alcohol **2-41**, was prepared by a tandem coupling and electrocyclization. The selective iodoetherification removed exo alcohol **2-43** successfully. The best tether, adipic acid tether, was found by screening five candidates including succinyl, glutaryl, adipoyl, adamatanedicarboxyl, and adamantanediacetyl groups.

The RCDA reaction of the tethered diesters **2-39c** and **2-40c** gave two pentacyclic dimers in contrast with our expectation that only C-2 symmetric substrate would form dimer. Each of the dimers was identified by X-ray structure determination and a series of nmr experiments, respectively. As a result, we found that one was endo RCDA product **2-38c** from the C-2 symmetric diester and the other was exo RCDA product **2-69c** from the meso diester.

After hydrolysis of the diester **2-38c**, we focused on one carbon homologation to form ethyl amide. Despite our efforts, the one carbon homologation was not easily achieved. At last, we adapted the double homologation method that was used in the synthesis of pre-kingianin A by Moses group. This double homologation successfully afforded the kingianin A.

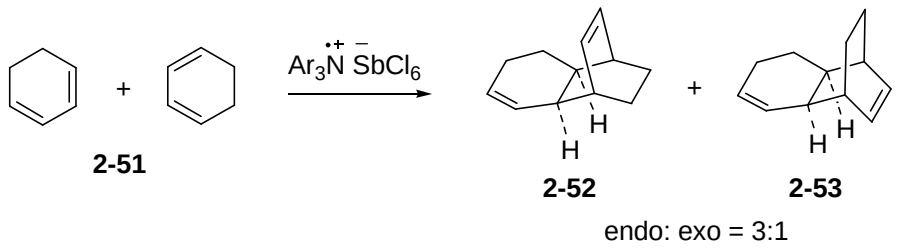
2.4 Experimental Section

General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. HPLC grade hexane, EtOAc, CH_2Cl_2 and CH_3OH were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol or $KMnO_4$ aq. solution and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for ^1H and 126 MHz for ^{13}C), Varian Inova-400 (400 MHz for ^1H and 100 MHz for ^{13}C), or Gemini-2300 (300 MHz for ^1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-*d*. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on a Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

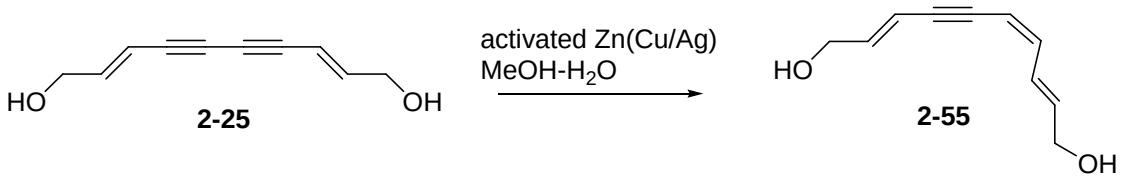
Experimental Procedure/ Characterization



2-51 **2-52** **2-53**

endo: exo = 3:1

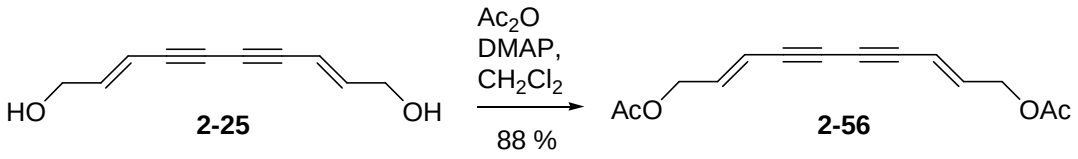
Dimers 2-52 and 2-53 To a stirred solution of 1,3-cyclohexene **2-51** (95.0 μL, 1.0 mmol) in CH_2Cl_2 (3.3 mL) was added aminium salt (40.8 mg, 0.05 mmol) at 0 ^oC. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with NH_4Cl and brine. The organic solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hexane) to afford an inseparable mixture of the dimers **2-52** and **2-53** (38.2 mg, 48 %) as colorless oil. For the ratio, see a spectrum.



2-25 **2-55**

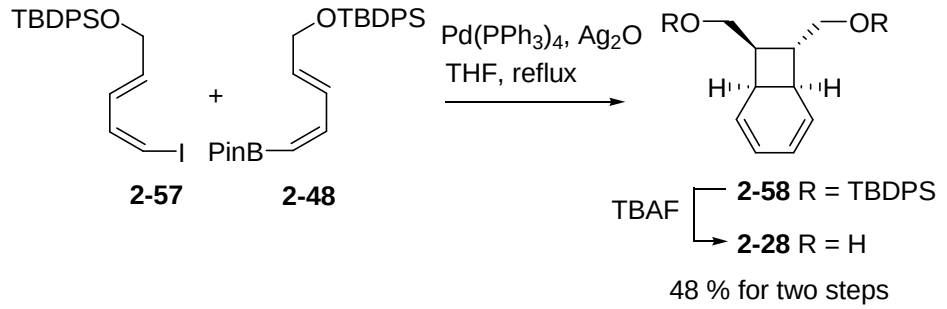
(1E, 3Z, 7E)-nona-1,3,7-triene-5-yne-1,9-diol (2-55) To a stirred suspension of activated Zn(Cu/Ag) (2 g) in H_2O (10 mL)-MeOH (10 mL) was added diyne **2-25** (0.10 g, 0.62 mmol) at r.t. under Ar. The mixture was wrapped with aluminum foil and stirred for 1 day. The small portion of the reaction mixture was taken and worked up. The crude ^1H nmr of the reaction mixture showed a major product as a partially reduced product **2-55**.

Rf value: 0.50 (Hex: EtOAc = 1:1) ^1H NMR (600 MHz, $CDCl_3$) δ 4.26 (m, 4 H), 5.58 (d, *J* = 10.8 Hz, 1 H), 5.95 (d, *J* = 16.2 Hz, 1 H), 6.02 (dt, *J* = 15.0 and 6.0 Hz, 1 H), 6.28 (dt, *J* = 16.2 and 4.8 Hz, 1 H), 6.40 (t, *J* = 10.8 Hz, 1 H), 6.78 (dd, *J* = 15.0 and 11.4 Hz, 1 H).



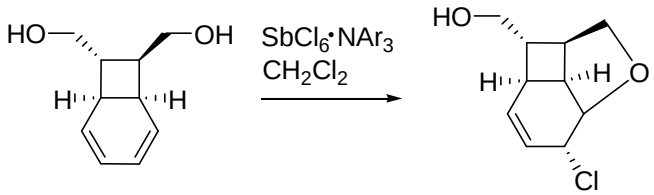
Diacetate 2-56 To a stirred solution of the diyne **2-25** (0.19 g, 1.18 mmol) in CH_2Cl_2 (15 mL) was added DMAP (28.8 mg, 0.24 mmol) and acetic anhydride (0.33 mL, 3.54 mmol) at r.t. The reaction mixture was stirred for 2 h and quenched with sat. $NaHCO_3$ sol'n. The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 3:1) to afford diacetate **2-56** as yellow solid.

Rf value: 0.40 (Hex:EtOAc = 3:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 6 H), 4.62 (d, *J* = 5,7 Hz, 4 H), 5.82 (d, *J* = 15.6 Hz, 2 H), 6.31 (dt, *J* = 15.6 and 5.7 Hz, 2 H). IR (neat) νmax 1266, 1382, 1740, 3047.



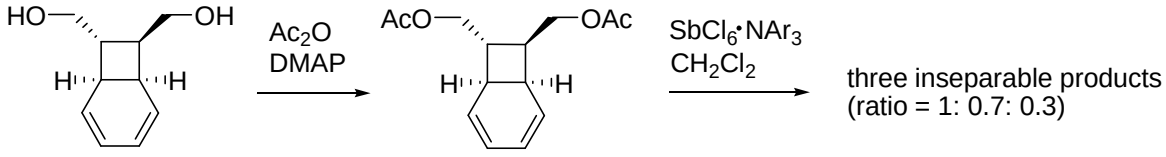
Bicyclooctadiene diol 2-28 1) Suzuki coupling: To a stirred solution of the iododiene **2-57** (2.0 g, 4.6 mmol) and $Pd(PPh_3)_4$ (1.3 g, 1.2 mmol) in THF (50 mL) was added boronate **2-48** (3.0 g, 6.9 mmol) and Ag_2O (2.67 g, 11.5 mmol) at r.t. Then, the reaction mixture was heated to reflux under darkness. After 12 h, the mixture was cooled to room temperature, filtered, concentrated. The concentrate was passed through a short pad of silica gel and washed with 5% EtOAc in hexane until desired band was completely eluted. The yellow fractions were combined. The crude product was directly used for the next step. 2) Deprotection of TBDPS group: To a stirred solution of the crude product in THF (20 mL) was slowly added tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 12.4 mL, 12.4 mmol) at r.t. After 2 h, the mixture was quenched with sat NH_4Cl and partitioned. The aqueous layer was extracted with diethyl ether. The combined organic solution was dried over $MgSO_4$, concentrated, purified by column chromatography (Hex:

EtOAc = 1:2) to afford bicyclooctadiene diol **2-28** (0.37 g, 48 % for two steps) as yellow oil.
Rf value: 0.2 (Hex:EtOAc = 1:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (m, 3 H), 3.14 (m, 1 H), 3.72 (dd, *J* = 10.0 and 3.2 Hz, 2 H), 3.78 (d, *J* = 7.2 Hz, 2 H), 5.51 (dd, *J* = 10.0 and 4.0 Hz, 1 H), 5.59 (dd, *J* = 9.6 and 4.0 Hz, 1 H), 5.71 (dd, *J* = 9.6 and 5.2 Hz, 1 H), 5.86 (ddd, *J* = 9.6, 5.2, and 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4, 32.9, 51.1, 52.5, 62.5, 65.2, 122.2, 124.2, 125.5, 126.1.



2-28 **2-59**

Chloro ether 2-59 To a stirred solution of the diol **2-28** (20.0 mg, 0.12 mmol) in CH_2Cl_2 was added the catalyst (4.9 mg, 6.0 μmol) at 0 °C under Ar. Because no reaction was observed by monitoring TLC, more catalyst was added in portions until the starting material was completely consumed. The reaction mixture was then quenched with triethylamine, filtered, concentrated. The crude ^{1}H nmr spectrum indicated the presence of chloro ether **2-59** although it was contaminated.
Rf value: 0.6 (CH_2Cl_2:MeOH = 10:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (m, 1 H), 1.97 (br s, 1 H), 2.64 (br s, 1 H), 2.73 (br s, 1 H), 3.11 (br s, 1 H), 3.62 (d, *J* = 8.4 Hz, 1 H), 3.82 (d, *J* = 8.2 Hz, 1 H), 3.89 (m, 2 H), 4.65 (d, J = 3.2 Hz, 1 H), 5.90 (m, 2 H).



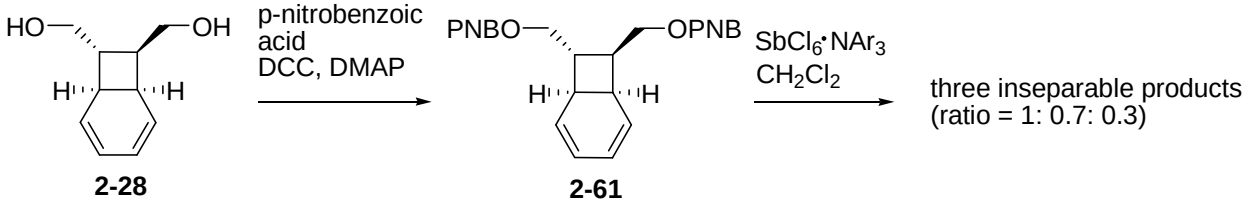
2-28 **2-60**

RCDA reaction of the diacetate 2-60 1) Acetylation: To a stirred solution of the diol **2-28** (38.0 mg, 0.23 mmol) in CH_2Cl_2 was added DMAP (5.6 mg, 45.7 μmol) and Ac_2O (65.0 μL, 0.69 mmol) at r.t. After 1.5 h, the reaction mixture was quenched with sat. $NaHCO_3$ sol'n and portioned. The aqueous layer was then extracted with CH_2Cl_2, and combined organic solution

was dried over MgSO4, concentrated, and purified by column chromatography (Hex: EtOAc = 15:1) to afford bicyclooctadiene diacetate **2-60** (50.4 mg, 88 %) as colorless oil.

2-60 Rf value: 0.5 (Hex:EtOAc = 10:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3 H), 2.05 (s, 3 H), 2.65 (m, 1 H), 2.75-2.89 (, 2 H), 3.20 (m, 1 H), 4.06 (d, *J* = 6.0 Hz, 2 H), 4.23 (dd, *J* = 7.2 and 3.2 Hz, 2 H), 5.51 (dd, *J* = 10.0 and 4.0 Hz, 1 H), 5.57 (dd, *J* = 9.6 and 5.6 Hz, 1 H), 5.71 (dd, *J* = 9.6 and 5.6 Hz, 1 H), 5.88 (ddd, *J* = 9.6, 5.2, and 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.898, 20.920, 32.8, 33.1, 44.6, 47.1, 64.5, 66.1, 122,3, 124.5, 124.7, 126.0, 170.9, 171.0.

2) RCDA reaction: To a stirred solution of the diacetate **2-60** (20 mg, 79.9 μmol) in CH_2Cl_2 (0.7 mL) was added the catalyst (3.2 mg, 3.9 μmol) at 0 ^{o}C. After 1 h, 5 mol % of catalyst (3.2 mg, 3.9 μmol) was added, and the resulting blue solution was stirred overnight. Then, the reaction mixture was diluted with CH_2Cl_2, washed with NH_4Cl, H_2O, and brine. The organic solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 3:1) to afford a mixture of unidentified three products (9.5 mg, 48 %) as sticky colorless oil. For the ratio and intrinsic peaks of three products, see spectrum.

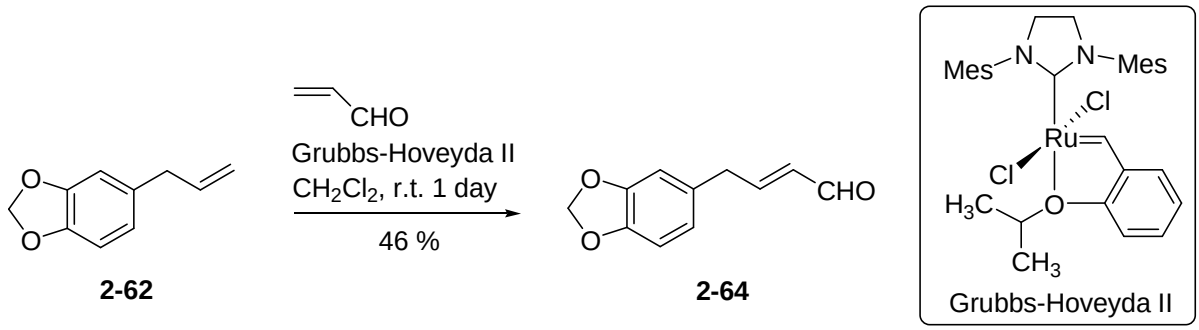


RCDA reaction of the di-p-nitrobenzoate 2-61 1) Esterification: To a stirred solution of the diol **2-38** (10 mg, 60.1 μmol), DCC (62.0 mg, 300 μmol), DMAP (0.7 mg, 6.0 μmol) in CH_2Cl_2 (1.0 mL) was added p-nitrobenzoic acid (50.2 mg, 300 μmol) at r.t. After stirring 1.5 h, the reaction mixture was quenched with sat $NaHCO_3$ sol'n and partitioned. The aqueous layer was extracted with CH_2Cl_2, and the combined organic solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 4:1 to 2:1) to afford di-p-nitrobenzoate **2-61** (20.7 mg, 74 %) as yellow solid.

2-61 Rf value: 0.8 (Hex:EtOAc = 2:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (m, 2 H), 3.13 (m, 1 H), 3.37 (m, 1 H), 4.42 (d, *J* = 5.6 Hz, 2 H), 4.58 (dd, *J* = 11.2 and 8.0 Hz, 1 H), 4.64 (dd, *J* = 11.2 and 8.0 Hz, 2 H), 5.64 (m, 2 H), 5.78 (dd, *J* = 9.6 and 5.6 Hz, 1 H), 5.96 (ddd, *J* = 9.6, 5.6,

and 1.6 Hz, 1 H).

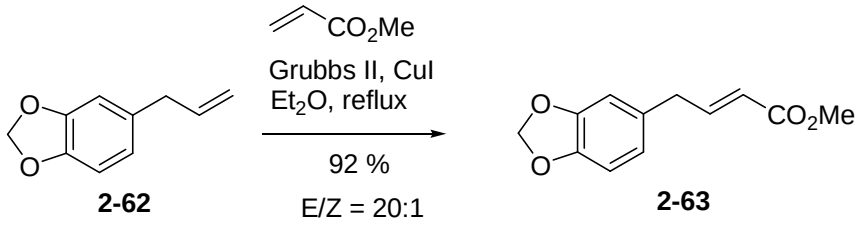
2) RCDA reaction of di-p-nitrobenzoate **2-61** To a stirred solution of the di-p-nitrobenzoate **2-61** (20.5 mg, 44.1 μmol) in CH_2Cl_2 (0.88 mL) was added the catalyst (1.8 mg, 2.2 μmol) at 0 ^oC. After 5 h, 10 mol % of catalyst (3.6 mg, 4.4 μmol) was added, and the resulting blue solution was stirred for days. Then, the reaction mixture was diluted with CH_2Cl_2, washed with NH_4Cl, H_2O, and brine. The organic solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 3:1) to afford a mixture of unidentified three products (13.2 mg, 64 %) as sticky yello oil. For the ratio and intrinsic peaks of three products, see spectrum.



2-62 **2-64**

Aldehyde 2-64 The metathesis procedure described by Cossy et al was adapted.[32] In an oven-dried 50 mL round bottom flask was placed safrole **2-62** (0.88 g, 5.4 mmol) and acrolein (1.07 mL, 19.3 mmol) in dry CH_2Cl_2 (25 mL) under Ar. The Grubbs-Hoveyda second generation catalyst (85 mg, 0.14 mmol) was added, and then the mixture was stirred for 1 day. The resulting black solution was concentrated and directly subjected to silica gel column chromatography (Hex:EtOAc = 5:1) to afford aldehyde **2-64** as yellow oil (0.47 g, 46 %).

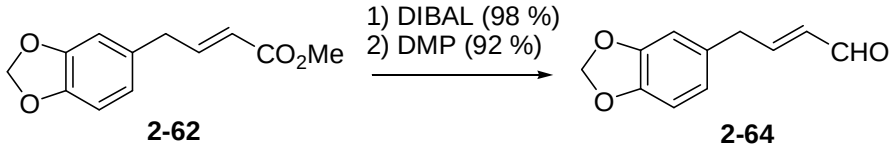
Rf value: 0.3 (Hex:EtOAc = 5:1) ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (dd, *J* = 6.6, 1.5 Hz, 2 H), 5.95 (s, 2 H), 6.09 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1 H), 6.62 – 6.79 (m, 3 H), 6.92 (dt, *J* = 15.6 and 6.6 Hz, 1 H), 9.53 (d, *J* = 7.8 Hz, 1 H). The data are in consistent with the literature values.[9]



2-62 **2-63**

Methyl ester 61 Safrole **2-62** (3.00 g, 18.72 mmol), methyl acrylate (5.06 mL, 56.2 mmol), Grubbs II catalyst (0.31 g, 0.37 mmol), and CuI (0.11 g, 0.56 mmol) were placed in dry diethyl ether (187.0 mL) in a flame-dried 500 mL round bottom under Ar. The mixture was heated to reflux for 2 h. Then, the reaction mixture was filtered, concentrated, and purified by column chromatography (Hex:EtOAc = 8:1) to afford methyl ester **2-63** as yellow oil

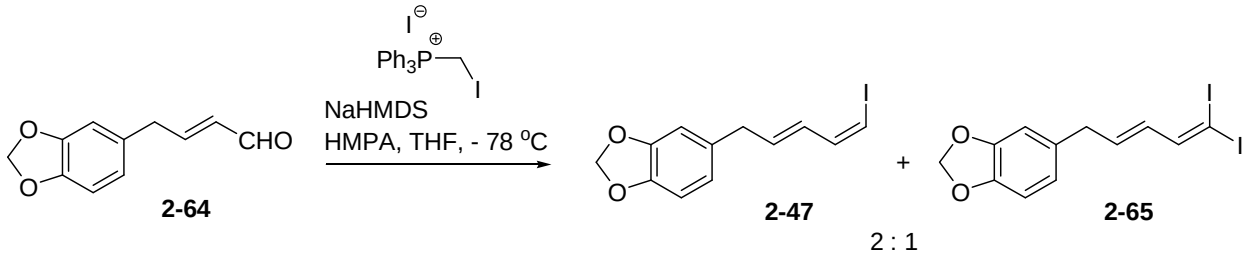
Rf value: 0.5 (Hex:EtOAc = 5:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (d, *J* = 6.6 Hz, 2 H), 3.71 (s, 3 H), 5.80 (d, *J* = 15.3 Hz, 1 H), 5.93 (s, 2 H), 6.60 – 6.76 (m, 3 H), 7.06 (dt, *J* = 15.3 and 6.6 Hz, 1 H). The data are in consistent with the literature values.[9]



2-62 **2-64**

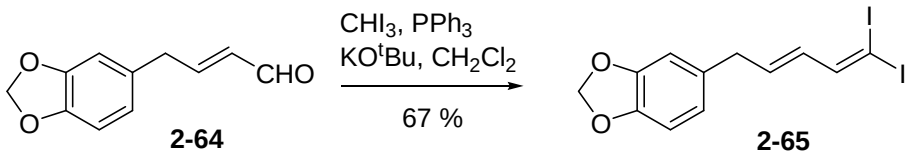
The aldehyde 2-64 1) DIBAL-reduction: To a stirred solution of the ester **2-62** (3.90 g, 17.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise DIBAL-H (1.0 M in hexane, 40.7 mL, 40.7 mmol) at -78 ^{o}C under Ar. After 30 min, the mixture was quenched with MeOH (5 mL), sat. sodium potassium tartrate sol'n, and diluted with diethyl ether (100 mL). The mixture was further stirred for 2 h at room temperature and partitioned. The aqueous layer was extracted with diethyl ether, and the combined organic layer was dried over $MgSO_4$, concentrated. The crude mixture was subjected to silica gel column chromatography (Hex: EtOAc = 3:1) to afford a corresponding allylic alcohol (3.3 g, 98 %) as colorless oil. This known alcohol was directly used for the next step without characterization. 2) Oxidation: To a stirred solution of the alcohol (2.60 g, 13.52 mmol) in CH_2Cl_2 (27.0 mL) was added Dess-Martin periodinane (DMP, 6.88 g, 16.22 mmol) at 0 ^{o}C. The reaction mixture was warmed to r.t. and stirred for 1 h. Then, the reaction mixture was quenched with sat. $NaHCO_3$ sol'n and extracted with CH_2Cl_2. The organic solution was washed with water, brine, dried over $MgSO_4$, concentrated, and purified by column

chromatography (Hex: EtOAc = 3:1) to afford the aldehyde **2-64** (2.37 g, 92 %).



Iododiene 2-47 and diiododiene 2-65 To a stirred suspension of the methyl iodophosphonium salt (0.17 g, 0.32 mmol) in THF (2 mL) was added NaHMDS (2.0 M in THF, 0.14 mL, 0.29 mmol) at r.t. After 15 min, the clear solution was cooled to – 78 °C. The aldehyde **2-64** (50.0 mg, 0.27 mmol) in HMPA (0.5 mL) was slowly added to the solution. After stirring for 1 h, the reaction mixture was quenched with sat. NH_4Cl sol'n, and extracted with ethyl ether. The organic solution was then dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 20:1) to afford an inseparable mixture of the iododiene **2-47** and diiododiene **2-65** (44.3 mg) as yellow oil. The ratio was calculated from the ^1H nmr spectrum.

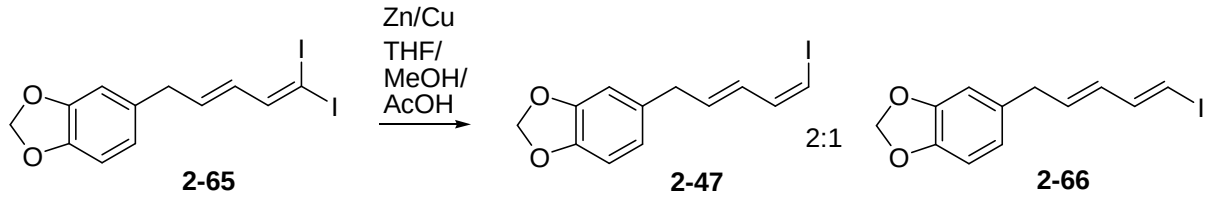
^1H NMR (300 MHz, $CDCl_3$) (E, Z)-iododiene **2-47** δ 3.39 (d, *J* = 7.5 Hz, 2 H), 5.93 (s, 2 H), 6.07 (dt, *J* = 15.0 and 7.5 Hz, 1 H), 6.18 (d, *J* = 8.0 Hz, 1 H), 6.29 (ddd, *J* = 15.0, 10.0, 1.5 Hz), 6.64 - 6.76 (m, 4 H); diiododiene **2-65** δ 3.33 (d, *J* = 7.0 Hz, 2 H), 5.90-5.95 (dd, *J* = 15.5 and 9.5 Hz, 1 H), 5.93 (s, 2 H), 6.05 (dt, *J* = 15.5 and 7.0 Hz, 1 H), 6.63 (d, *J* = 8.5 Hz, 1 H), 6.66 (s, 1 H), 6.75 (d, 8.0 Hz, 1 H), 7.48 (d, *J* = 9.5 Hz, 1 H).



Diiododiene 2-65 To a stirred solution of CHI_3 (0.25 g, 0.63 mmol) and PPh_3 (0.17 g, 0.63 mmol) in toluene (2.1 mL) was added KO^tBu (70.8 mg, 0.63 mmol) in portions over 20 min at -20 °C. The resulting viscous mixture was stirred for 20 min. Then, a solution of the aldehyde **2-64** (60.0 mg, 0.32 mmol) in toluene (1 mL) was added dropwise to the reaction mixture. After 20 min, the reaction mixture was quenched with water and extracted ethyl ether. The organic

solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 50:1) to afford a diiododiene **2-65** (93.0 mg, 67 %) as light yellow oil.

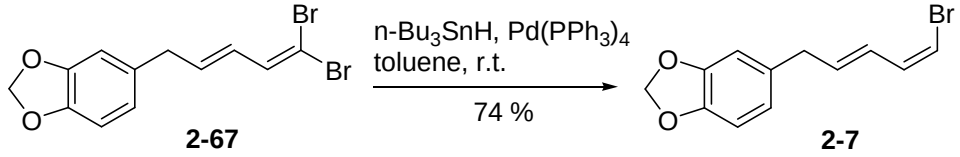
Rf value: 0.7 (Hex:EtOAc = 10:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (d, *J* = 7.0 Hz, 2 H), 5.90-5.95 (dd, *J* = 15.5 and 9.5 Hz, 1 H), 5.93 (s, 2 H), 6.05 (dt, *J* = 15.5 and 7.0 Hz, 1 H), 6.63 (d, *J* = 8.5 Hz, 1 H), 6.66 (s, 1 H), 6.75 (d, 8.0 Hz, 1 H), 7.48 (d, *J* = 9.5 Hz, 1 H).



2-65 **2-47** **2-66**

Zn(Cu) mediated reductive deiodination: To a stirred solution of diiododiene **2-65** (50.0 mg, 0.11 mmol) in THF (4 mL)-MeOH (2.5 mL)-AcOH (0.4 mL) was added Zn-Cu (200 mg) at r.t. After stirring 1 h, the reaction mixture was filtered through a pad of Celite. The filtrate was washed with sat. $NaHCO_3$ sol'n and partitioned. The aqueous layer was extracted with ethyl ether and the combined organic solution was dried over $MgSO_4$ and concentrated. The crude ^{1}H nmr data showed a mixture of (E, Z)-iododiene **2-47** and (E, E)-iododiene **2-66**.

Rf value: 0.7 (Hex:EtOAc = 10:1) ^{1}H NMR (500 MHz, $CDCl_3$) (E, Z)-iododiene **2-47** δ 3.39 (d, *J* = 7.5 Hz, 2 H), 5.93 (s, 2 H), 6.07 (dt, *J* = 15.0 and 7.5 Hz, 1 H), 6.18 (d, *J* = 8.0 Hz, 1 H), 6.29 (ddd, *J* = 15.0, 10.0, 1.5 Hz), 6.64 - 6.76 (m, 4 H); (E, E)-iododiene **2-66** δ 3.62 (d, *J* = 7.0 Hz, 2 H), 5.83 (dt, *J* = 15.0 and 7.0 Hz, 1 H), 5.93 (s, 2 H), 6.00 (dd, *J* = 15.5 and 11.0 Hz, 1 H), 6.18 (d, *J* = 7.5 Hz, 1 H), 6.61 – 6.76 (m, 3 H), 7.01 (dd, *J* = 15.0 and 11.0 Hz, 1 H).

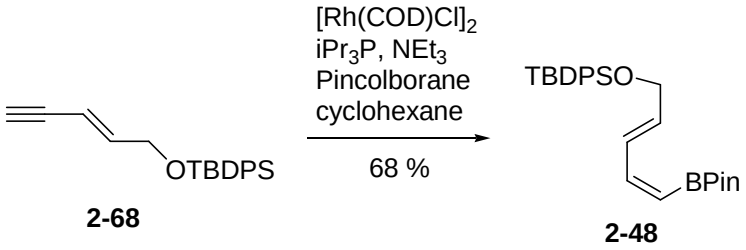


2-67 **2-7**

(E, Z)-bromodiene **2-7** To a stirred solution of the dibromide **2-67**[5] (0.20 g, 0.58 mmol) and $Pd(PPh_3)_4$ (26.7 mg, 23.1 μmol) in toluene (5 mL) was slowly added tributyltin hydride (0.16 mL, 0.61 mmol) at r.t. under Ar. After 1 h, the reaction mixture was quenched with sat. $NaHCO_3$ sol'n and partitioned. The aqueous solution was extracted with diethyl ether. The combined organic

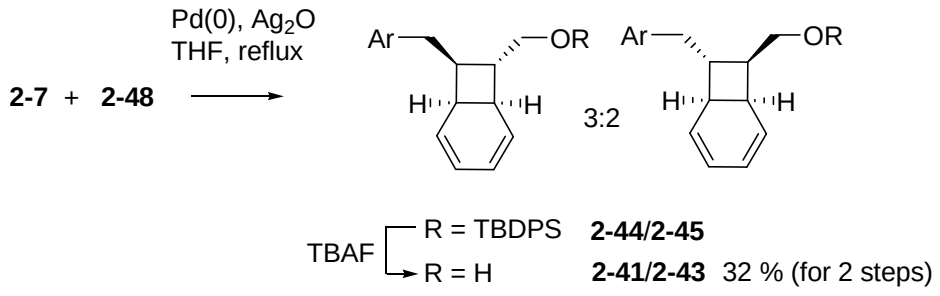
solution was then dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 50:1) to afford a (E, Z)-bromodiene **2-7** (0.11 g, 74 %) as yellow oil.

Rf value: 0.7 (Hex:EtOAc = 10:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (d, *J* = 7.2 Hz, 2 H), 5.93 (s, 2 H), 6.00 (dt, *J* = 15.2 and 6.8 Hz, 1 H), 6.09 (d, *J* = 6.8 Hz, 1 H), 6.45 (ddd, *J* = 15.2, 10.4 and 1.2 Hz, 1 H), 6.59 – 6.76 (m, 4 H). The data are consistent with the literature values.[9]



(E, Z)-boronate 2-48 To a stirred solution of cyclooctadiene rodium chloride dimer (134.6 mg, 0.27 mmol) in cyclohexane (50 mL) was added triethylamine (12.6 mL, 91.0 mmol), triisopropyl pholsphine (0.21 mL, 0.17 mmol),and pinacolborane (2.64 mL, 18.2 mmol) at r.t. under Ar. The mixture was stirred for 30 min until the enyne **2-68** (7.0 g, 21.8 mmol) was added. After 5 h, the reaction mixture was quenched with MeOH (5 mL) and concentrated. The concentrate was directly subjected to silica gel chromatography (Hex: EtOAc = 50:1 to 30:1, 1% triethylamine) to afford the (E, Z)-boronate **2-48** (6.48 g, 72 %) as yellow oil.

Rf value: 0.5 (Hex:EtOAc = 20:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 12 H), 3.40 (d, *J* = 6.5 Hz, 2 H), 5.31 (d, *J* = 12.5 Hz, 1 H), 5.90 – 5.96 (m, 1 H), 5.92 (s, 2 H), 6.65 – 6.90 (m, 3 H), 6.87 (m, 2 H). The data are consistent with the literature values.[12]

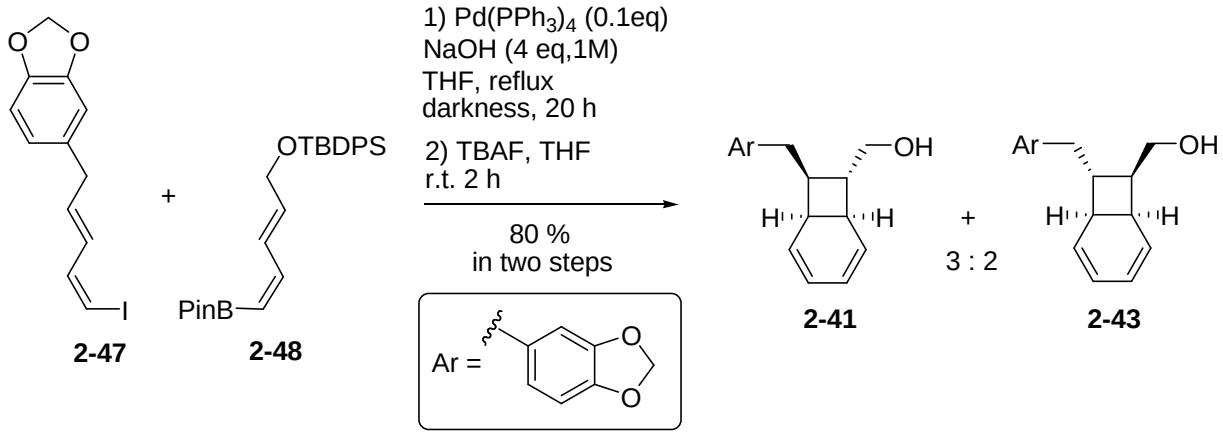


Endo- and exo alcohols 2-41 and 2-43 from the boromodiene 2-7 and boronate 2-48

1) Suzuki coupling: To a stirred suspension of Ag_2O (2.83 g, 12.2 mmol) and boronate **2-48** (3.16

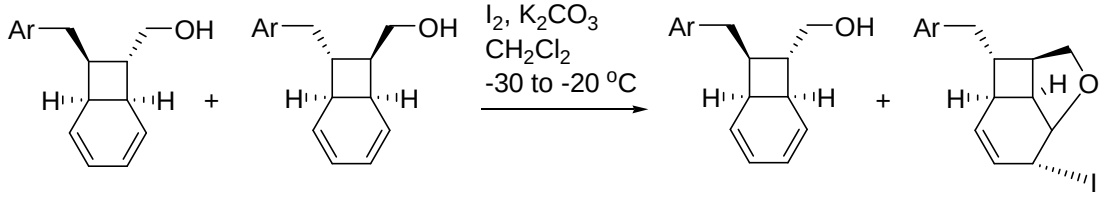
g, 7.30 mmol) in THF (50 mL) was added a solution of the bromide **2-7** (1.30 g, 4.87 mmol) and $Pd(PPh_3)_4$ (1.41 g, 0.25 mmol) in THF (11 mL) at r.t. The mixture was then heated to reflux and stirred overnight. The resulting black solution was filtered, concentrated. The concentrate was passed through a short pad of silica gel and washed with 5% EtOAc in hexane until desired band was completely eluted. The yellow fractions were combined. The crude product was directly used for the next step. 2) Deprotection of the TBDPS group: To a stirred solution of **2-44** and **2-45** in THF (30 mL) was added the tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 14.6 mL, 14.6 mmol) at r.t. After 3 h, the reaction mixture was concentrated, diluted with ethyl acetate, washed with water and brine. The organic solution was dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex: EtOAc = 5:1) to afford a mixture of endo- and exo alcohols **2-41** and **2-43** (0.42 g, 32 %) as yellow oil.

2-41/**2-43** Rf value: 0.4/0.38 (Hex:EtOAc = 3:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 - 2.88 (m, 5 H), 3.20 - 3.25 (m, 1 H), 3.33 (dd, *J* = 11.0 and 6.1 Hz, 0.6 H), 3.39 (dd, *J* = 11.0 and 5.6 Hz, 0.6 H), 3.57 (dd, *J* = 10.9 and 5.7 Hz, 0.4 H), 3.71 (dd, *J* = 10.9 and 8.4 Hz, 0.4 H), 5.43 (dd, *J* = 9.6 and 5.5 Hz, 0.4 H), 5.57 - 5.64 (m, 2 H), 5.72 (dd, *J* = 9.8 and 5.4 Hz, 0.6 H), 5.84 (ddd, J = 9.6, 5.5, and 1.5 Hz, 0.4 H), 5.90 - 5.93 (m, 0.6 H), 5.913 (s, 1.2 H), 5.915 (s, 0.8 H), 6.60 - 6.72 (m, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.5, 32.9, 34.5, 36.1, 36.2, 41.6, 48.3, 50.4, 51.7, 53.6, 63.3, 65.3, 100.8 (two), 108.15, 108.22, 108.9, 109.0, 121.2, 121.4, 121.5, 121.8, 124.3, 124.4, 125.3, 126.2, 126.7, 127.1, 134.3, 134.8, 145.7, 145.8, 147.57, 147.62. IR (neat) νmax 1247, 1488, 1502, 2917, 3355. (endo/exo = 3:2; the ratio was determined from the ^{1}H nmr data)



Endo- and exo alcohols 2-41 and 2-43 from the iododiene 2-47 and boronate 2-48

1) Suzuki coupling: To a stirred solution of (*E,Z*)-iododiene **2-47** (3.39 g, 10.8 mmol) in THF (200 mL) was added $Pd(PPh_3)_4$ (1.25 g, 1.08 mmol) and the mixture was stirred for 5 min at r.t. The pinacolboronate **2-48** (7.00 g, 16.2 mmol) in THF (5 mL) and aq. NaOH solution (43.2 mL, 1 M, 43.2 mmol) were added to the mixture. Then, the reaction mixture was heated to reflux under darkness. After 20 h, the mixture was cooled to room temperature and partitioned. The aqueous layer was extracted with diethyl ether (30 mL X 3) and the combined organic solution was dried over $MgSO_4$, and concentrated. The concentrate was passed through a short pad of silica gel and washed with 10% EtOAc in hexane until desired band was completely eluted. The yellow fractions were combined. The crude product was directly used for the next step. 2) Deprotection of the TBDPS group: To a stirred solution of crude product in THF (50 mL) was added TBAF (32.4 mL, 1 M in THF, 32.4 mmol) under Ar. The reaction mixture was stirred for 2 h and diluted with sat. NH_4Cl solution (50 mL). The resulting mixture was extracted with ethyl acetate (50 mL X 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. Then, the crude mixture was subjected to column chromatography (Hex:EtOAc = 6:1 to 4:1) to afford 2.33 g, (80 %) of a mixture of alcohols **2-41** and **2-43** as light yellow oil. The data are identical with them reported on page 54.



2-41 **2-43** **2-41** (45 %) **2-42** (37 %)

Alcohol 2-41 and Iodoether 2-43 To a stirred solution of the mixture of diastereomeric alcohols **2-41** and **2-43** (200 mg, 0.74 mmol) and potassium carbonate (82 mg, 0.59 mmol) in CH_2Cl_2 (10 mL) was quickly added iodine (75.1 mg, 0.30 mmol) at – 30 ^oC under Ar. After 30 min, the reaction mixture was warmed to – 20 ^oC and stirred for 2.5 h. Then, the mixture was quenched with sat. $Na_2S_2O_3$ solution and partitioned. The organic solution was washed with sat. $Na_2S_2O_3$ solution again and the combined aqueous solution was extracted with CH_2Cl_2 (10 mL X 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. Then, the residue was subjected to column chromatography (Hex:EtOAc = 10:1 to 5:1) to afford the alcohol **2-41** (108 mg, 45 %) as light yellow oil and the iodoether **2-42** (86.8 mg, 37 %) as

light yellow solid (mp = 76 -78 ^{o}C).

2-41 Rf value: 0.4 (Hex:EtOAc = 3:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 1 H), 2.57 (m, 1 H), 2.70 - 2.88 (m, 4 H), 3.18 - 3.20 (m, 1 H), 3.31 - 3.38 (m, 2 H), 5.57 -5.63 (m, 2 H), 5.72 (dd, *J* = 9.2 and 5.3 Hz, 1 H), 5.89 - 5.93 (m, 1 H), 5.91 (s, 2 H), 6.63 - 6.72 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 34.5, 36.2, 48.3, 53.6, 65.3, 100.8, 108.2, 108.9, 121.2, 121.8, 124.3, 126.2, 126.7, 134.8, 145.7, 147.6.; IR (neat) νmax 1247, 1488, 1502, 3353. HRMS[ES+] calcd for $C_{17}H_{18}O_3Na$ $[M + Na]^+$ 293.1154, found 293.1153.

2-42 Rf value: 0.8 (Hex:EtOAc = 3:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (m, 1 H), 2.57 - 2.60 (m, 1 H), 2.61 - 2.65 (m, 1 H), 2.74 (d, *J* = 8.2 Hz, 2 H), 3.28 (dd, *J* = 14.3 and 8.2 Hz, 1 H), 3.55 (dd, J = 9.3 and 4.6 Hz, 1 H), 3.78 (d, *J* = 9.3 Hz, 1 H), 4.31 (dd, *J* = 5.8 and 1.9 Hz, 1 H), 4.92 (dd, *J* = 5.8 and 1.9 Hz, 1 H), 5.42 (dd, J = 9.9 and 4.3 Hz, 1 H), 5.87 (m, 1 H), 5.92 (s, 2 H), 6.58 - 6.72 (m, 3 H).^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 32.6, 32.7, 41.5, 42.6, 48.0, 73.6, 80.4, 100.8, 108.1, 108.9, 121.4, 125.4, 129.7, 133.4, 145.8, 147.6.; IR (neat) νmax 1246, 1442, 1488, 1503, 1607, 1634, 2892. HRMS [EI+] calcd for $C_{17}H_{17}IO_3$ $[M]^+$ 396.0222, found 396.0214.

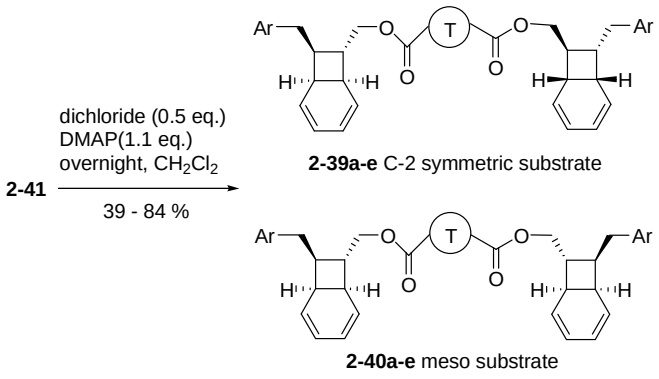
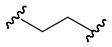
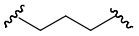
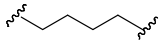
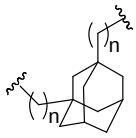


Table 2-4. Screening of Tethers

	Tethers		Yield
a		succinyl	72 %
b		glutaryl	84 %
c		adipoyl	75 %
d	 n = 0,1	adamantanedicarboxyl	39 %
e		adamantanediacetyl	62 %

Tethered diesters 2-39a-e and 2-40a-e Representative procedure: To a stirred solution of the alcohol **2-13** (1 eq) and DMAP (1.1 eq) in CH_2Cl_2 (0.1 M) was added dropwise diacyl chloride (0.5 eq) at 0 ^{o}C under Ar; in case of **2-39d-e** and **2-40d-e**, pyridine (3 eq) was additionally used. The reaction mixture was warmed to r.t. and stirred overnight. Then, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water. The organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 10:1) to afford a mixture of the diesters **2-39a-e** and **2-40a-e**.

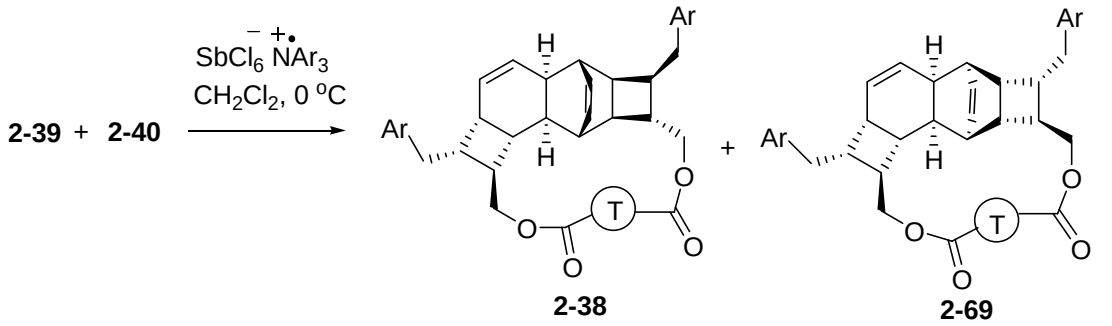
2-39a and 2-40a (colorless oil) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 4 H), 2.64 - 2.86 (m, 8 H), 3.19 (m, 2 H), 3.85 (d, *J* = 5.4 Hz, 4 H), 5.58 (m, 4 H), 5.73 (m, 2 H), 5.87 – 5.02 (m, 2 H), 5.91 (s, 4 H), 6.60 – 6.72 (m, 6 H).

2-39b and 2-40b (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (quint, *J* = 7.5 Hz, 2 H), 2.30 (t, *J* = 7.5 Hz, 4 H), 2.64 - 2.87 (m, 10 H), 3.19 (m, 2 H), 3.83 (m, 4 H), 5.58 (m, 4 H), 5.71 (m, 2 H), 5.90 - 5.92 (m, 2 H), 5.91 (s, 4 H), 6.61 - 6.71 (m, 6 H).

2-39c and 2-40c (colorless oil) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (m, 4 H), 2.26 (m, 4 H), 2.64 - 2.88 (m, 10 H), 3.19 (m, 2 H), 2.82 - 3.83 (m, 4 H), 5.55 - 5.59 (m, 4 H), 5.71 (dd, *J* = 9.5 and 5.6 Hz, 2 H), 5.89 - 5.93 (m, 2 H), 5.91 (s, 4 H), 6.60 - 6.72 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ. 24.4, 33.6, 33.8, 34.7, 36.0, 48.1, 49.8, 66.3, 100.8, 108.2, 108.9, 121.2, 122.0, 124.4, 126.0, 126.3, 134.5, 145.7, 147.6, 173.2. IR (neat) νmax 1248, 1488, 1503, 1731, 2932. HRMS[ES+] calcd for $C_{40}H_{43}O_8Na$ $[M + H]^+$ 651.2940, found 651.2934.

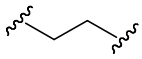
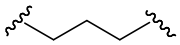
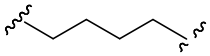
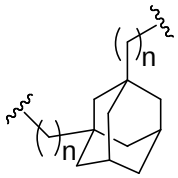
2-39d and 2-40d (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (br s, 2 H), 1.82 (m, 8 H), 1.98 (s, 2 H), 2.14 (br s, 2 H), 2.64 – 2.88 (m, 10 H), 3.19 (m, 2 H), 3.77 – 3.85 (m, 4 H), 5.58 (m, 4 H), 5.72 (m, 2 H), 5.88 – 5.92 (m, 2 H), 5.91 (s, 2 H), 6.61 – 6.72 (m, 6 H). IR (neat) νmax 1248, 1443, 1488, 1502, 1723.

2-39e and 2-40e (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (br s, 2 H), 1.47 (br s, 2 H), 1.49 (br s, 2 H), 1.56 – 1.59 (m, 6 H), 2.04 (br s, 6 H), 2.57 – 2.89 (m, 10 H), 3.19 (m, 2 H), 3.81 (m, 4 H), 5.58 (m, 4 H), 5.71 (m, 2 H), 5.90 – 5.92 (m, 2 H), 5.91 (s, 4 H), 6.60 – 6.71 (m, 6 H). IR (neat) νmax 1248, 1443, 1488, 1502, 1728.



2-38 Endo RCDA product from **2-39**

2-69 Exo RCDA product from **2-40**

	Tethers			Result	Separation
a			succinyl	mystery (8 %), **2-69a** (12 %)	ok
b			glutaryl	**2-38b** + mystery (19 %), **2-69b** (20 %)	ok
c			adipoyl	**2-38c** (27 %), **2-69c** (30 %)	ok
			M=0.005	**2-38c** (34 %), **2-69c** (39 %)	
d		n = 0	adamantanedicarboxyl	**2-38d** (24 %), **2-69d** (38 %)	difficult
e		n = 1	adamantanediacetyl	**2-38e** (36 %), **2-69e** (39 %)	difficult

[M] = 0,01 unless commented. The structures of the RCDA products from succinyl, glutaryl, adamantanes diesters are not exactly assigned, but determined on the basis of the ^{1}H nmr pattern of RCDA products **2-38c** and **2-69c**.

Intramolecular RCDA reaction of 2-39 and 2-40 Representative procedure: To a stirred solution of **2-39** and **2-40** (1 eq) in CH_2Cl_2 (M = 0.01) added $SbCl_6 \cdot N(p\text{-}BrPh)_3$ (0.05 eq) in ice-bath. The resulting deep blue solution was stirred for 2 h at 0 ^{o}C and quenched with wet NEt_3. After concentration of the reaction mixture, column chromatography (Hex:EtOAc = 7:1 to 5:1) afforded dimeric products **2-38** and **2-69**.

Succinyl tether: Mystery (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (m, 1 H), 1.72 (d, *J* = 8.0 Hz, 1 H), 1.78 (t, *J* = 9.5 Hz, 1 H), 2.28 (m, 1 H), 2.42 (m, 3 H), 2.54 (s, 1 H), 2.67 – 2.85 (m, 5 H), 2.97 (d, *J* = 14.5 Hz, 1 H), 3.13 (d, *J* = 12.0 Hz, 1 H), 3.19 (m, 1 H), 3.85 (d, *J* = 5.5 Hz, 1 H), 4.60 (dd, *J* = 12.0 and 3.5 Hz, 1 H), 5.57 (m, 1 H), 5.73 (dd, *J* = 10.0 and 2.5 Hz, 1 H), 5.89 – 5.92 (m, 1 H), 5.91 (s, 2 H), 6.03 (m, 1 H), 6.60 – 6.71 (m, 6 H). **2-69a** (colorless oil) ^{1}H NMR

(500 MHz, $CDCl_3$) δ 1.60 (m, 1 H), 1.75 (m, 1 H), 1.96 (m, 1 H), 2.12 (m, 2 H), 2.24 – 2.47 (m, 7 H), 2.53 – 2.84 (m, 7 H), 2.97 (m, 1 H), 3.33 (dd, *J* = 10.0 and 6.0 Hz, 1 H), 4.07 (dd, *J* = 10.5 and 4.0 Hz, 1 H), 4.17 (dd, *J* = 11.0 and 8.5 Hz, 1 H), 4.45 (t, *J* = 12.0 Hz, 1 H), 5.75 (m, 2 H), 5.89 (s, 2 H), 5.91 (s, 2 H), 6.30 (t, *J* = 7.5 Hz, 1 H), 6.49 – 6.70 (m, 7 H).

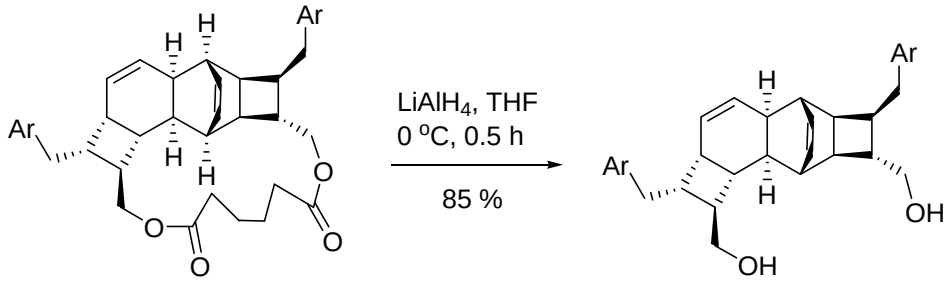
Glutaryl tether: 2-38b (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (d, *J* = 10.5 Hz, 1 H), 1.94 – 2.70 (m, 22 H), 3.20 (dd, *J* = 10.5 and 5.0 Hz, 1 H), 3.30 (dd, *J* = 10.5 and 6.0 Hz, 1 H), 4.61 (t, *J* = 10.5 Hz, 1 H), 4.71 (t, *J* = 11.0 Hz, 1 H), 5.62 (d, *J* = 10.0 Hz, 1 H), 5.72 (d, *J* = 10.0 Hz, 1 H), 5.90 (s, 4 H), 6.11 (t, *J* = 8.0 Hz, 1 H), 6.30 (t, *J* = 8.0 Hz, 1 H), 6.51 – 6.69 (m, 6 H). **2-69b** (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, *J* = 7.0 Hz, 1 H), 1.61 (m, 1 H), 1.76 (m, 1 H), 1.83 (t, *J* = 9.0 Hz, 1 H), 1.95 (m, 2 H), 2.14 (m, 3 H), 2.26 – 2.55 (m, 11 H), 2.68 – 2.88 (m, 4 H), 3.14 (d, *J* = 11.5 Hz, 1 H), 3.20 (dd, *J* = 10.5 and 5.5 Hz, 1 H), 4.77 (t, *J* = 10.5 Hz, 1 H), 4.68 (dd, *J* = 11.5 and 2.0 Hz, 1 H), 5.70 (m, 1 H), 5.83 (br d, *J* = 10.0 Hz, 1 H), 5.89 (s, 2 H), 5.92 (s, 2 H), 6.29 (t, *J* = 8.0 Hz, 1 H), 6.49 – 6.72 (m, 7 H)

Adipoyl tether: 2-38c (white solid, mp = 164 - 165 ^{o}C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 – 1.82 (4 H), 1.73 (d, *J* = 7.8 Hz, 1 H), 1.93 – 2.65 (m, 19 H), 3.44 (dd, *J* = 10.8 and 5.9 Hz, 1 H), 3.54 (dd, *J* = 10.8 and 4.9 Hz, 1 H), 3.96 (t, *J* = 10.8 Hz, 1 H), 4.36 (t, *J* = 10.8 Hz, 1 H), 5.61 (br d, *J* = 10.2 Hz, 1 H), 5.75 (br d, *J* = 10.2 Hz, 1 H), 5.89 (s, 2 H), 5.90 (s, 2 H), 6.16 (t, *J* = 7.3 Hz, 1 H), 6.29 (t, *J* = 7.3 Hz, 1 H), 6.52 – 6.69 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 25.7, 32.6, 34.5, 35.1, 35.5, 36.6, 38.1, 38.7, 38.8, 39.6, 40.16, 40.21, 40.7, 41.1 (two), 43.1, 44.0, 67.0, 69.0, 100.71, 100.73, 108.1, 108.2, 108.7, 108.8, 120.98, 121.03, 124.9, 131.8, 132.0, 134.5, 135.1, 135.3, 145.5, 145.7, 147.5, 147.6, 173.4, 174.1.; IR (neat) νmax 1244, 1488, 1502, 1728, 2922. HRMS[ES+] calcd for $C_{40}H_{42}O_8Na$ $[M + Na]^+$ 673.2777, found 673.2764. **2-69c** (colorless oil) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (dd, *J* = 10.8 and 3.0 Hz, 1 H), 1.60 – 2.71 (m, 23 H), 3.17 (d, *J* = 11.0 Hz, 1 H), 3.25 (dd, *J* = 10.2 and 4.9 Hz, 1 H), 3.96 (t, *J* = 10.9 Hz, 1 H), 4.61 (dd, *J* = 11.8 and 2.4 Hz, 1 H), 5.69 (ddd, *J* = 10.2, 4.4, and 2.1 Hz, 1 H), 5.84 (br d, *J* = 10.2 Hz, 1 H), 5.89 (s, 2 H), 5.92 (d, *J* = 2.3 Hz, 2 H), 6.36 (t, *J* = 7.2 Hz, 1 H), 6.49 – 6.73 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.6, 32.5, 33.6, 33.7, 34.0 (two), 34.9, 35.2, 35.56, 35.58, 36.0, 36.7, 37.0, 41.0, 41.1, 41.7, 46.4, 61.5, 67.9, 100.68, 100.74, 108.1, 108.2, 108.7, 108.9, 120.9, 121.1, 126.4, 131.1, 134.5 (two), 135.1, 136.5, 145.5, 145.6, 147.5, 147.6, 173.5, 173.7.; IR

(neat) νmax 1247, 1488, 1503, 1729, 2931. HRMS[ES+] calcd for $C_{40}H_{42}O_8Na$ $[M + Na]^+$ 673.2777, found 673.2777.

Adamantanedicarboxyl tether: 2-38d (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 – 2.66 (m, 30 H), 3.54 (dd, *J* = 10.5 and 7.0 Hz, 1 H), 3.65 (t, *J* = 11.0 Hz, 1 H), 3.75 (dd, *J* = 11.5 and 5.0 Hz, 1 H), 4.51 (t, *J* = 11.0 Hz, 1 H), 5.63 (br d, *J* = 13.5 Hz, 1 H), 5.75 (br d, *J* = 13.5 Hz, 1 H), 5.90 (s, 4 H), 6.19 (t, *J* = 7.0 Hz, 1 H), 6.36 (t, *J* = 7.0 Hz, 1 H), 6.51 – 6.69 (m, 6 H). **2-69d** (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59 – 2.68 (m, 30 H), 3.54 – 3.74 (m, 3 H), 4.08 (m, 1 H), 5.78 (m, 2 H), 5.90 (s, 2 H), 5.91 (d, *J* = 3.5 Hz, 2 H), 6.38 (t, *J* = 7.5 Hz, 1 H), 6.50 – 6.70 (m, 7 H).

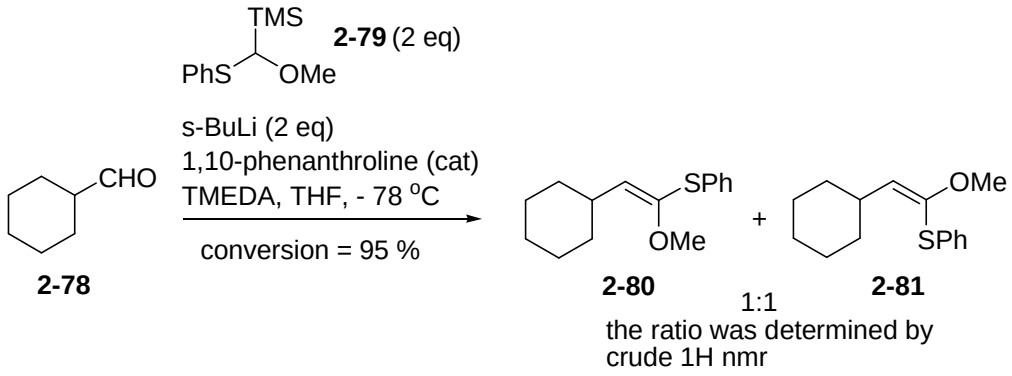
Adamantanediacetyl tether: 2-38e (colorless oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 – 1.61 (m, 12 H), 1.78 (d, *J* = 13.0 Hz, 1 H), 2.00 – 2.64 (m, 21 H), 3.18 (dd, *J* = 11.5 and 4.5 Hz, 1 H), 3.43 (dd, *J* = 10.5 and 5.0 Hz, 1 H), 3.82 (t, *J* = 10.5 Hz, 1 H), 4.38 (t, *J* = 11.5 Hz, 1 H), 5.60 (br d, *J* = 10.5 Hz, 1 H), 5.74 (m, 1 H), 5.90 (s, 2 H), 5.90 (s, 2 H), 6.16 (t, *J* = 7.0 Hz, 1 H), 6.26 (t, *J* = 7.0 Hz, 1 H), 6.51 – 6.69 (m, 6 H). **2-69e** (colorless oil) 1.40 – 1.66 (m, 12 H), 1.76 (t, J = 10.5 Hz, 1 H), 1.92 (t, J = 9.0 Hz, 2 H), 2.00 – 2.69 (m, 19 H), 3.20 (m, 2 H), 4.06 (dd, *J* = 13.5 and 6.5 Hz, 1 H), 4.38 (d, *J* = 10.0 Hz, 1 H), 5.69 (m, 1 H), 5.83 (br d, *J* = 9.5 Hz, 1 H), 5.89 (s, 2 H), 5.91 (d, 2.0 Hz, 1 H), 6.35 (t, *J* = 7.5 Hz, 1 H), 6.50 – 6.71 (m, 7 H).



2-38c diol **2-37**

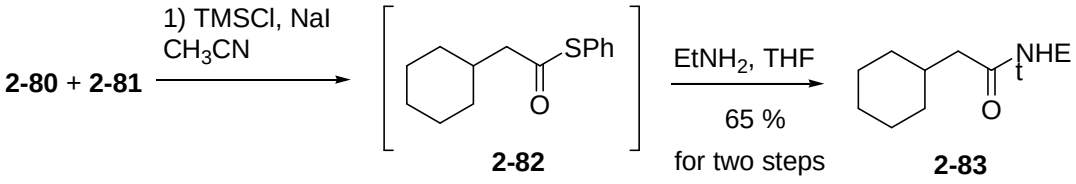
Diol 2-37 To a stirred solution of the diester **2-38c** (34.0 mg, 52.0 μmol) in THF (2 mL) was added $LiAlH_4$ (15.8 mg, 0.42 mmol) at 0 °C. Then, the reaction mixture was stirred for 30 min at this temperature and quenched with water (0.2 mL). Aqueous NaOH solution (1M, 2 mL) was added to the mixture and the mixture was stirred for additional 1 h. The slurry was then diluted

with water and extracted with ethyl acetate (10 mL X 3). The organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 1:1) to afford diol **2-37** (24.6 mg, 87 %) as colorless sticky oil.
Rf value: 0.4 (Hex:EtOAc = 1:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, *J* = 9.0 Hz, 1 H), 1.78 – 1.85 (m, 1H), 1.92 – 2.00 (m, 2 H), 2.16 – 2.68 (m, 12 H), 3.31 – 3.38 (m, 4 H), 5.62 (br d, *J* = 10.4 Hz, 1 H), 5.71 (br d, *J* = 10.3 Hz, 1 H), 5.8998 (s, 2 H), 5.9040 (s, 2 H), 6.13 (t, *J* = 7.3 Hz, 1 H), 6.27 (t, *J* = 7.3 Hz, 1 H), 6.56 – 6.72 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.7, 35.3, 36.2, 38.0, 38.3, 38.6, 38.7, 39.5, 40.7 (two), 41.1, 42.7, 44.0, 47.7, 65.2, 67.0, 100.7 (two), 108.2 (two), 108.8, 108.9, 121.0, 121.1, 125.3, 132.0, 132.1, 135.0, 135.1, 135.4, 145.57, 145.60, 147.59, 147.63.; IR (neat) νmax 1246, 1441, 1488, 1502, 2912, 3346. HRMS[ES+] calcd for $C_{34}H_{36}O_6Na$ $[M + Na]^+$ 563.2410, found 563.2403.



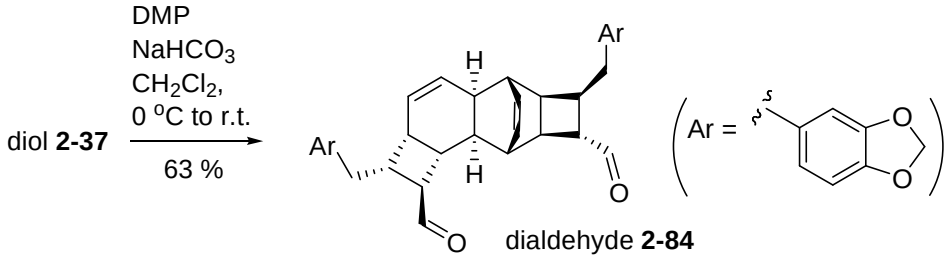
(E)- and (Z)-olefins 2-80 and 2-81 To a stirred solution of the silylated O, S-acetal **2-79** (54.3 mg, 0.2 mmol), 1,10-phenanthroline (0.8 mg, 4.4 μmol), and tetramethylethylenediamine (TMEDA, 24.8 mg, 0.2 mmol) in THF (1 mL) was added dropwise sec-BuLi (0.15 mL, 0.2 mmol) at – 78 °C under Ar. After 2.5 h, a solution of the aldehyde **2-78** (11.3 mg, 101 μmol) in THF (0.2 mL) was added to the mixture. The reaction mixture was stirred for 1 h, quenched with water, extracted with diethyl ether. The organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 1:1) to afford an inseparable mixture of (E)-, (Z)-olefins **2-80** and **2-81** with unreacted excess O, S-acetal (21mg). The ^{1}H nmr showed the > 95 % conversion.
Rf value: 0.7 (Hex:EtOAc = 20:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 – 1.81 (m, 20 H), 2.60 (m, 2 H), 3.61 (s, 3 H), 3.64 (s, 3 H), 5.19 (d, J = 9.0 Hz, 1 H), 5.34 (d, J = 9.3 Hz, 1 H), 7.21 – 7.38

(m, 8 H), 7.58 (m, 2 H).



Ethyl amide 2-83 1) Demethylation: To a stirred solution of the olefins **2-80** and **2-81** (21 mg) and NaI (31.1 mg, 0.21 mmol) in CH_3CN (1 mL) was added TMSCl at r.t. under Ar. After 5 min, the reaction mixture was filtered through activated alumina, and concentrated. The residue was directly used for the next step. 2) Amide formation: To a stirred solution of the residue in THF (0.5 mL) was added ethyl amine (2.0 M in THF, excess) at r.t. The reaction mixture was stirred overnight. After concentration, the crude products were subjected to column chromatography (Hex:EtOAc = 1:1) to afford ethyl amide **2-83** (7.3 mg, 65 %) as yellow solid.

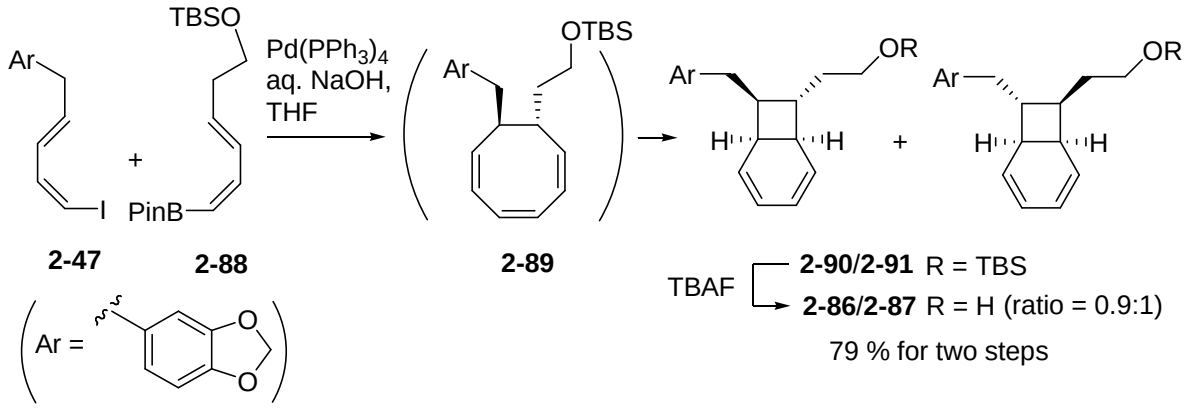
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (m, 3 H), 1.13 (t, *J* = 5.8 Hz, 3 H), 1.25 (m, 3 H), 1.63 – 1.76 (m, 5 H), 2.01 (d, *J* = 5.6 Hz, 2 H), 3.28 (dq, J = 5.8 and 1.1 Hz, 2 H), 5.41 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 26.1, 26.2, 33.1, 34.3, 35.4, 45.0, 172.3.; IR (neat) νmax 1249, 1438, 1477, 1579, 1644, 3281.



Dialdehyde 2-84 To a stirred solution of the diol **2-37** (4.5 mg, 8.3 µmol) and $NaHCO_3$ (3.5 mg, 41.5 µmol) in CH_2Cl_2 was added DMP (12.3 mg, 29.0 µmol) at 0 °C. The reaction mixture was warmed to r.t. and stirred for 2 h. Then, the mixture was quenched with water and partitioned. The aqueous layer was extracted with CH_2Cl_2, and the combined organic solution was washed with brine, dried over $MgSO_4$, concentrated. The concentrate was subjected to column chromatography (Hex:EtOAc = 1:1) to afford the dialdehyde **2-84** (2.8 mg, 63 %) as

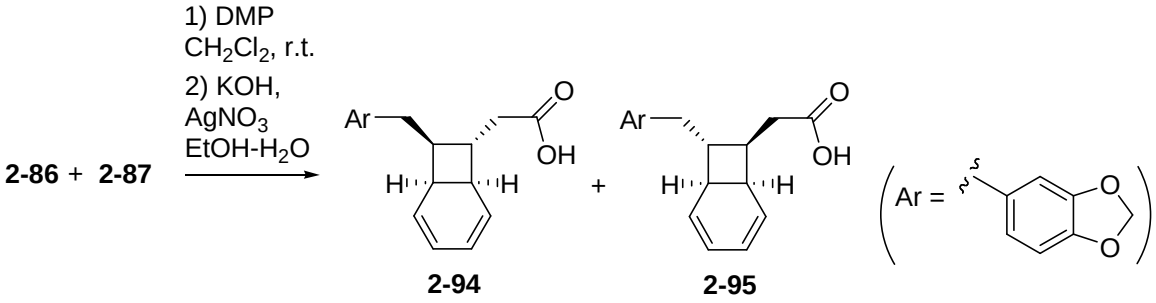
colorless oil.

Rf value: 0.6 (Hex:EtOAc = 2:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, *J* = 9.0 Hz, 1 H), 2.33 – 2.93 (m, 16 H), 5.65 (d, *J* = 10.5 Hz, 1 H), 5.76 (dd, *J* = 10.5 and 2.5 Hz, 1 H), 5.90 (s, 2 H), 5.91 (s, 2 H), 6.16 (t, *J* = 7.4 Hz, 1 H), 6.32 (t, *J* = 7.4 Hz, 1 H), 6.54 – 6.71 (m, 6 H), 9.33 (m, 2 H).



Endo and Exo Alcohols 2-86 and 2-87 1) Suzuki coupling: To a stirred solution of (*E*,*Z*)-iododiene **2-47** (0.36 g, 1.16 mmol) in THF (35 mL) was added $Pd(PPh_3)_4$ (0.13 g, 0.12 mmol) and the mixture was stirred for 5 min at r.t. The pinacolboronate **2-88** (0.56 g, 1.74 mmol) in THF (3 mL) and aq. NaOH solution (4.60 mL, 1 M, 4.60 mmol) were added to the mixture. Then, the reaction mixture was heated to reflux under darkness. After 20 h, the mixture was cooled to room temperature and partitioned. The aqueous layer was extracted with diethyl ether (20 mL X 3) and the combined organic solution was dried over $MgSO_4$, and concentrated. The concentrate was passed through a short pad of silica gel and washed with 5% EtOAc in hexane until desired band was completely eluted. The yellow fractions were combined. The crude product was directly used for the next step. 2) Deprotection of the TBDPS group: To a stirred solution of crude product in THF (10 mL) was added TBAF (2.32 mL, 1 M in THF, 2.32 mmol) under Ar. The reaction mixture was stirred for 3 h and diluted with sat. NH_4Cl solution (50 mL). The resulting mixture was extracted with ethyl acetate (10 mL X 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. Then, the crude mixture was subjected to column chromatography (Hex:EtOAc = 5:1 to 3:1) to afford 0.27 g, (79 %) of a mixture of alcohols **2-86** and **2-87** as light yellow oil.

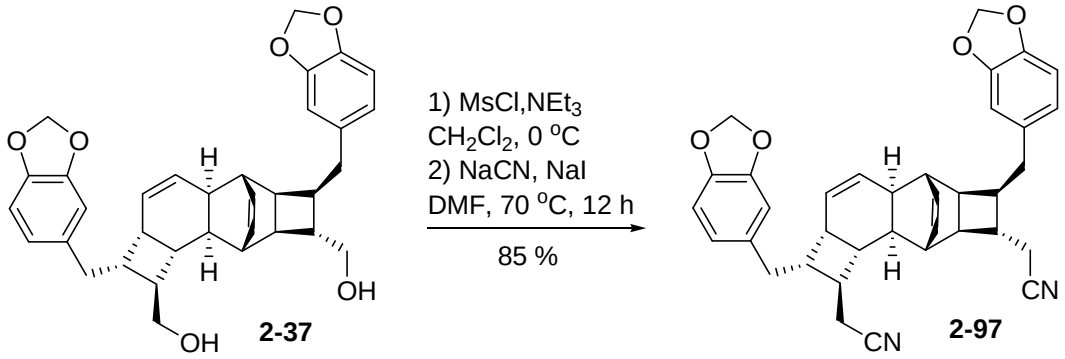
Rf value: 0.3 (Hex:EtOAc = 3:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (m, 1.9 H), 1.65 (m, 1 H), 1.84 (m, 0.9 H), 2.38 – 2.88 (m, 9.5 H), 3.17 (m, 1.9 H), 3.44 (t, *J* = 6.8 Hz, 1.8 H), 3.52 (t, *J* = 6.8 Hz, 2 H), 5.33 (dd, *J* = 9.5 and 4.6 Hz, 1 H), 5.52 – 5.62 (m, 3.7 H), 5.70 (dd, *J* = 10.0 Hz and 5.9 Hz, 0.9 H), 5.83 (m, 1 H), 5.88 (m, 1 H), 5.91 (s, 3.8 H), 6.59 – 6.72 (m, 5.7 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 33.9, 34.8, 36.2, 36.6, 36.8, 38.8, 41.7, 46.9, 18.5, 52.1, 53.4, 61.5, 61.7, 100.7 (two), 108.0, 108.1, 108.9, 109.1, 121.2, 121.3, 121.4, 121.7, 124.16, 124.21, 126.1, 126.5, 126.7, 127.1, 164.6, 135.0, 145.5, 145.6, 147.46, 147.53.; IR (neat) νmax 1039, 1246, 1442, 1488, 1502, 3353.



Acids 2-94 and 2-95 1) DMP oxidation: To a stirred solution of the alcohols **2-86** and **2-87** (30.0 mg, 0.11 mmol) in CH_2Cl_2 (1.0 mL) was added DMP (67.1 mg, 0.16 mmol) at r.t. After 1 h, the mixture was concentrated and subjected to silica gel chromatography (Hex: EtOAc = 5:1) to afford a mixture of the aldehydes (26.6 mg, 89 %). The products were directly used for the next step without characterization. 2) Ag_2O-Oxidation: To a stirred solution of the aldehydes (26.6 mg, 89.2 μmol) and $AgNO_3$ (48.4 mg, 285 μmol) in EtOH (0.4 mL)-H_2O (0.14 mL) was added a solution of KOH (42.0 mg, 0.75 mmol) in H_2O (0.1 mL) at 0 ^{o}C and the mixture was warmed to r.t. After 10 min, the mixture was filtered through a pad of Celite and washed with water. The filtrate was concentrated to remove the EtOH and the remaining aqueous solution was acidified with 2N HCl. The resulting suspension was extracted with EtOAc. The organic solution was dried over $MgSO_4$ and concentrated to afford the acids **2-94** and **2-95** (23.1 mg, 82 %) as sticky colorless oil.

Rf value: 0.2 (Hex:EtOAc = 3:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (m, 0.85 H), 2.25 – 2.34 (m, 1.85 H), 2.52 – 2.89 (m, 10.25 H), 3.22 (m, 1.85 H), 5.37 (dd, *J* = 9.5 and 5.4 Hz, 1 H), 5.49 – 5.64 (m, 3.7 H), 5.70 (dd, *J* = 9.5 Hz and 5.4 Hz, 0.85 H), 5.84 – 5.91 (m, 5.55 H), 6.58 – 6.71(m,

5.5 H).



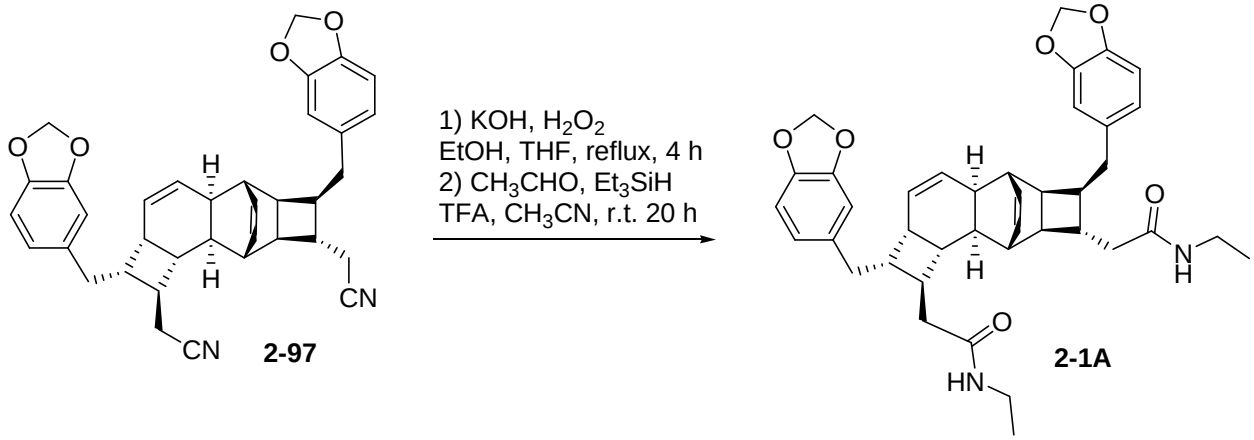
Dinitrile 2-97 Step 1: To a stirred solution of the diol **2-37** (12.0 mg, 22.0 μmol) in CH_2Cl_2 (1 mL) was added triethylamine (49.6 μL, 352 μmol) and methanesulfonyl chloride (13.6 μL, 176 μmol) at 0 ^oC under Ar. After 30 min, the reaction mixture was diluted with diethyl ether (15 mL) and the resulting mixture was washed with water, 5 % HCl, and sat. $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$, and concentrated. The crude product was directly used for the next step.

2-96 Rf value: 0.6 (Hex:EtOAc = 1:1) ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (d, *J* = 9.0 Hz, 1 H), 1.95 – 2.67 (m, 15 H), 2.88 (s, 3 H), 2.89 (s, 3 H), 3.82 – 3.95 (m, 4 H), 5.61 (br d, *J* = 10.4 Hz, 1 H), 5.72 (br d, *J* = 10.4 Hz, 1 H), 5.90 (s, 2 H), 5.91 (s, 2 H), 6.12 (t, *J* = 7.3 Hz, 1 H), 6.28 (t, *J* = 7.3 Hz, 1 H), 6.54 – 6.70 (m, 6 H).

Step 2: To a stirred solution of the dimesylate in DMF (1 mL) was added sodium iodide (1.6 mg, 11 μmol) and sodium cyanide (4.3 mg, 88 μmol) at r.t. Then, the solution was heated to 70 ^oC and stirred for 12 h. Then it was diluted with ethyl acetate (20 mL) and washed with water (10 mL X 3). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (Hex:EtOAc = 4:1) to afford dinitrile **2-97** (10.4 mg, 85 % in two steps, white solid, mp = 178 - 179 ^oC).

2-97 Rf value: 0.3 (Hex:EtOAc = 5:1) ^1H NMR (500 MHz, $CDCl_3$) δ 1.78 (d, *J* = 9.0 Hz, 1 H), 1.83 – 1.89 (m, 1 H), 1.99 – 2.67 (m, 18 H), 5.61 (br d, *J* = 10.4 Hz, 1 H), 5.71 (br d, J = 10.4 HZ, 1 H), 5.91 (s, 2 H), 5.92 (s, 2 H), 6.13 (t, *J* = 7.3 Hz, 1 H), 6.29 (t, J = 7.3 Hz, 1 H), 6.54 – 6.71 (m, 6 H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.7, 22.6, 33.3, 34.7, 35.6, 37.3, 37.6, 37.8, 38.1, 39.2, 40.5, 41.2, 41.9, 42.7, 42.8, 43.3, 100.8 (two), 108.25, 108.27, 108.68, 108.74, 118.6, 118.9, 121.0 (two), 124.8, 131.9, 132.0, 133.9, 134.2, 135.4, 145.7, 145.8, 147.6, 147.7.; IR (neat) νmax

1246, 1442, 1488, 1502, 2242, 2919. HRMS[ES+] calcd for $C_{36}H_{34}N_2O_4Na$ $[M + Na]^+$ 581.2416, found 581.2421.



Kingianin A (2-1A) Step 1: To a stirred solution of dinitrile **2-97** (10.0 mg, 17.9 μmol) in EtOH-THF (1.5 mL - 0.5 mL) was added aq. NaOH sol'n (0.05 mL, 7 M) and dropwise H_2O_2 sol'n (0.6 mL, 35 % in water) at 0 ^oC. Then, the mixture was warmed to room temperature, stirred for 30 min, and heated to reflux. After stirring for additional 4 h, the reaction mixture was diluted with brine and extracted with CH_2Cl_2 (15 mL X 5). The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used for the next step.

Step 2: The residue from step 1 was placed in 3 mL vial and flushed with Ar for 10 min. To the well stirred solution of the crude product in CH_3CN (1.0 mL) was added acetaldehyde (6.0 μL, 107 μmol), triethylsilane (17.2 μL, 107 μmol), and trifluoroacetic acid (10.2 μL, 89.0 μmol) in that order at r.t. Then, the vial was capped and sealed with parafilm. After stirring 20 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ sol'n and brine, dried over Na_2SO_4, and concentrated. The residue was subjected to preparative TLC (CH_2Cl_2:acetone = 7:1) to afford Kingianin A (4.2 mg, 36 %, white solid, recrystallized from MeOH-Hexane, mp = 74 - 78 ^oC, decomp. 212-215 ^oC, lit[1]. 78 - 82 ^oC).

Rf value: 0.3 (CH_2Cl_2:acetone = 7:1). For ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$), see Table 2-12 and 2-13. IR (neat) νmax 1039, 1246, 1442, 1488, 1503, 1555, 1641, 2924, 3292.

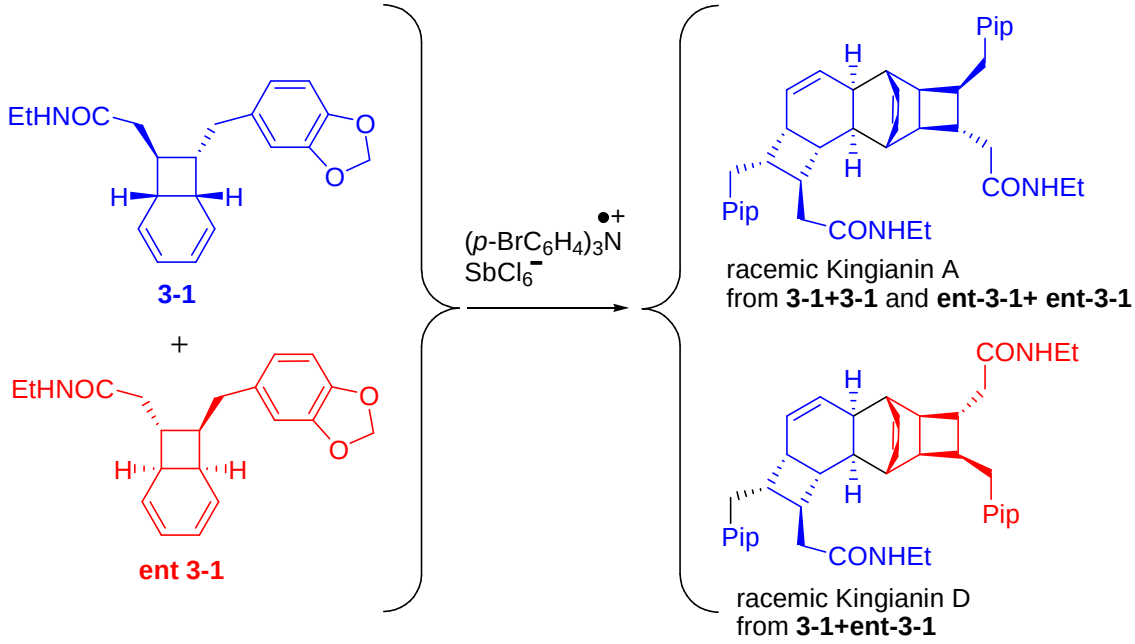
Chapter 3

Study for asymmetric synthesis of kingianin A

3.1 Introduction

3.1.1 Hypothesis for synthesizing enantiomerically pure bicyclooctadienes

The kingianin natural products, e.g. kingianin A (**3-1A**) and kingianin D (**3-1D**), are all reported to be racemic.[93] This is in accordance with our belief that the kingianins are the products of a dimerization event, perhaps a radical cation Diels-Alder (RCDA) reaction of racemic pre-kingianins (see Scheme 3-1). The pre-kingianins, like their relatives the racemic SNF4435 C and D, are believed to be formed in a non-enzymatic 8π, 6π-electrocyclic cascade in which asymmetry is not controlled.



Scheme 3-1. The dimerization of the racemic pre-kingianin A by RCDA reaction

The enantioselective synthesis of kingianins is an attractive goal because the (□)-kingianins

[93] (a) Kingianin A: A New Natural Pentacyclic Compound from Endiandra kingiana. Leverrier, A.; Dau, M. E. T. H.; Retailleau, P.; Awang, K.; Gueritte, F.; Litaudon, M. *Org. Lett*. **2010**, *12*, 3638-3641. (b) Pentacylcic Polyketide from Endiandra kingiana as inhibitors of the Bcl/Bak interaction. Leverrier, A.; Awang, K.; Gueritte, F.; Litaudon, M. *Phytochemistry* **2011**, *72*, 1443-1452.

bind more tightly to their target, the antiapoptotic BcL-xL protein, than do the (+)-enantiomers (Table 3-1).

Table 3-1. Bcl-xL binding affinity of Kingianin A to N (Ki in μM)[1b]

Compound	Bcl-xLKi		
	Racemic mixture	Enantiomer (-)	Enantiomer (+)
Kinganin A	213 ± 53	60 ± 1.5	>300
Kinganin B	>300	n. d.	n. d.
Kinganin C	>300	n. d.	n. d.
Kinganin D	>300	n. d.	n. d.
Kinganin E	>300	n. d.	n. d.
Kinganin F	213 ± 47	n. d.	n. d.
Kinganin G	2 ± 0	1.0 ± 0.2	5 ± 1
Kinganin H	18 ± 7	4.0 ± 0.4	27.0 ± 0.6
Kinganin I	18 ± 3	12.0 ± 1.1	16.0 ± 2.2
Kinganin J	29 ± 6	9.0 ± 0.2	25.0 ± 3.2
Kinganin K	80 ± 36	6.0 ± 0.1	112 ± 15
Kinganin L	36 ± 11	4.0 ± 0.1	71 ± 10
Kinganin M	236 ± 34	n. d.	n. d.
Kinganin N	177 ± 9	n. d.	n. d.

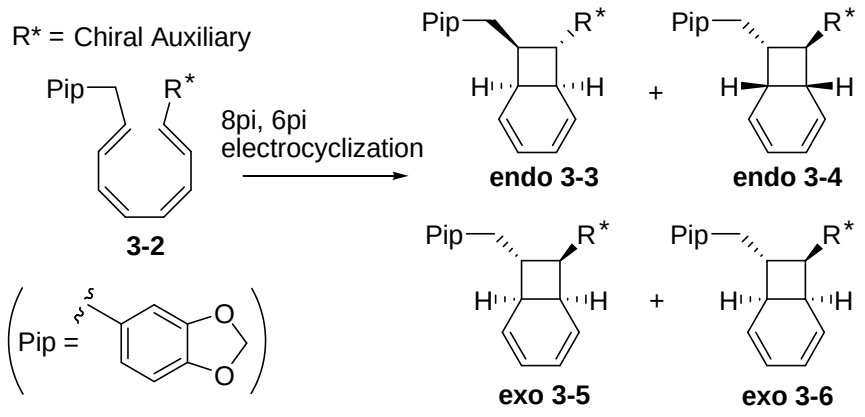
Ki values are the means ± standard deviation from two replicates

A kingianin that is the adduct of two identical monomers can, of course, be obtained from a synthesis that prepares a mixture of diastereomers and then relies on chromatographies, including one that employs a chiral column. On the other hand, this type of dimer might be approached by subjecting a single enantiomer of the pre-kingianin to the RCDA conditions.

Although no studies on an asymmetric synthesis of a pre-kingianin have been reported, the literature on asymmetric induction in the preparation of intermediates for SNF analog synthesis is relevant. The SNF system is more easily studied than the kingianin system because, in this case, the 8π, 6π-cascade gives only the endo bicyclooctadiene.[94]

[94] (a) The Total Synthesis of (-)-SNF4435 and (+)-SNF4435. Parker, K. A.; Lim, Y. -H. *J. Am. Chem. Soc.* **2004**, *126*, 15968-15969. (b) "Endo" and "Exo" Bicyclo[4.2.0]-octadiene Isomers from the Electrocyclization of Fully Substituted Tetraene Models for SNF 4435C and D. Control of Stereochemistry by Choice of a Functionalized Substituent. Parker, K. A.; Lim, Y.-H. *Org.*

First, the diastereoselective induction of pre-kingianin A or synthetic equivalent looks viable by adding chiral auxilliary to the tetraene precursor. In principle, the 8π, 6π-electrocyclization of a conjugated tetraene yields four stereoisomers.[95] Thus, it can be considered practical only when the endo selectivity predominates the exo or four diasteromers are easily separable (Scheme 3-2).



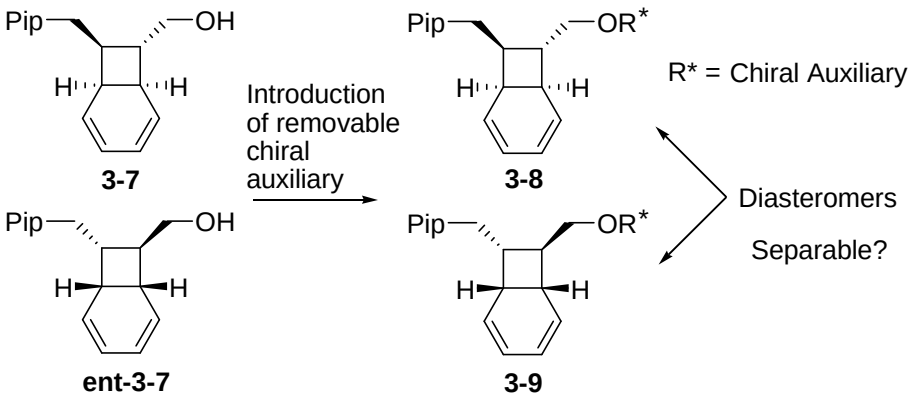
Scheme 3-2. Four diastereomeric bicyclooctadienes incorporating chiral auxiliary

Second, the practical separation of the racemic alcohol **3-7**, a synthetic precursor for the tether-mediated intramolecular RCDA reaction in the synthesis of kingianin A,[96] is possible by introducing removable chiral functionality on the alcohol (Scheme 3-3). Therefore, the success of this approach is dependent on separation of the resulting diastereomers **3-8** and **3-9**.

Lett. **2004**, *6*, 161–164.

[95] The endo/exo selectivity for the synthesis of pre-kingianin A was reported to be 1:1. See A synthetic approach to kingianin A based on biosynthetic speculation. Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Comm.* **2011**, *47*, 10605-10607.

[96] Total Synthesis of Kingianin A. Lim, H. N.; Parker, K. A. Org. Lett. **2013**, *15*, 398-401.

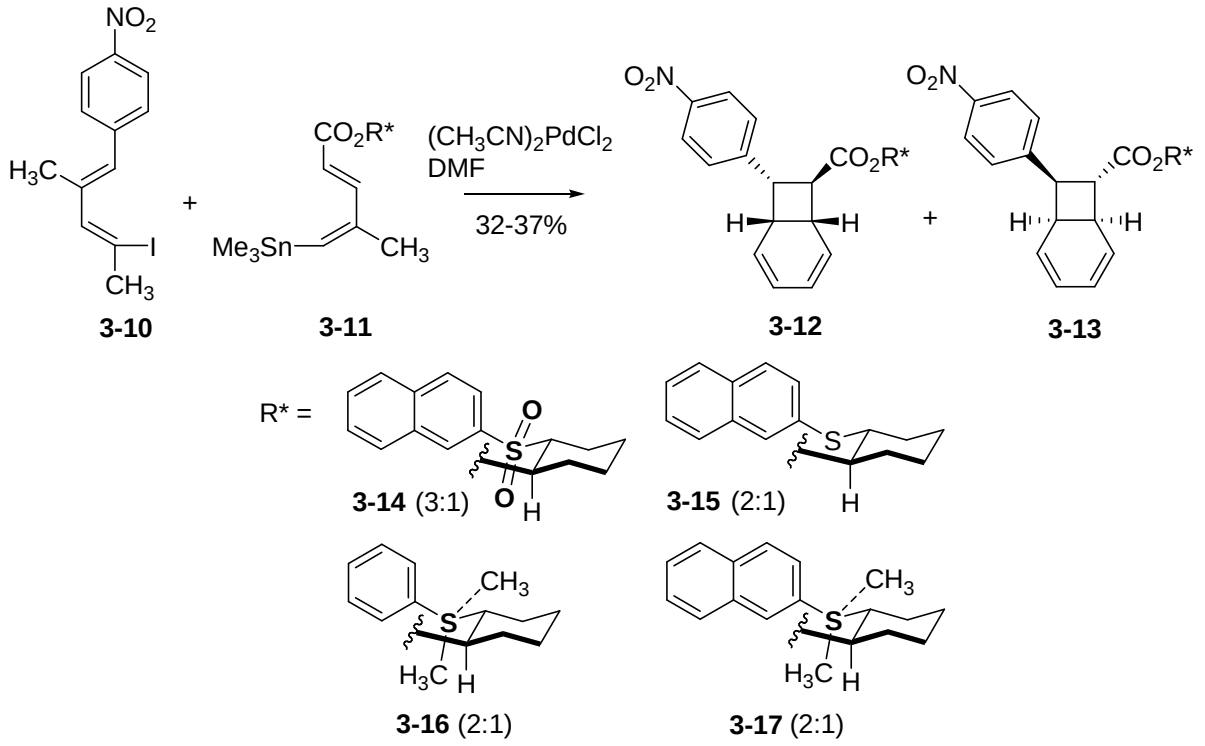


Scheme 3-3. Separation of the racemic alcohols by introducing cleavable chiral auxiliary

3.1.2 Examples for the asymmetric synthesis of bicyclooctadienes

Although there are many interesting natural products bearing bicyclooctadienes, there have not been many systematic studies on the asymmetric synthesis of bicyclooctadienes. Meanwhile, the asymmetric synthesis of the bicyclooctadienes using chiral auxiliaries have been studied by Parker group. In 2006, Wang and Parker studied diastereoselective synthesis of the backbones of chiral SNF analogues by using Corey-Sarakinos chiral sulfone auxiliaries.[97] Herein, they showed the successful separation of endo diastereomeric bicyclooctadienes although the diastereomeric ratio was modest to low (Scheme 3-4).

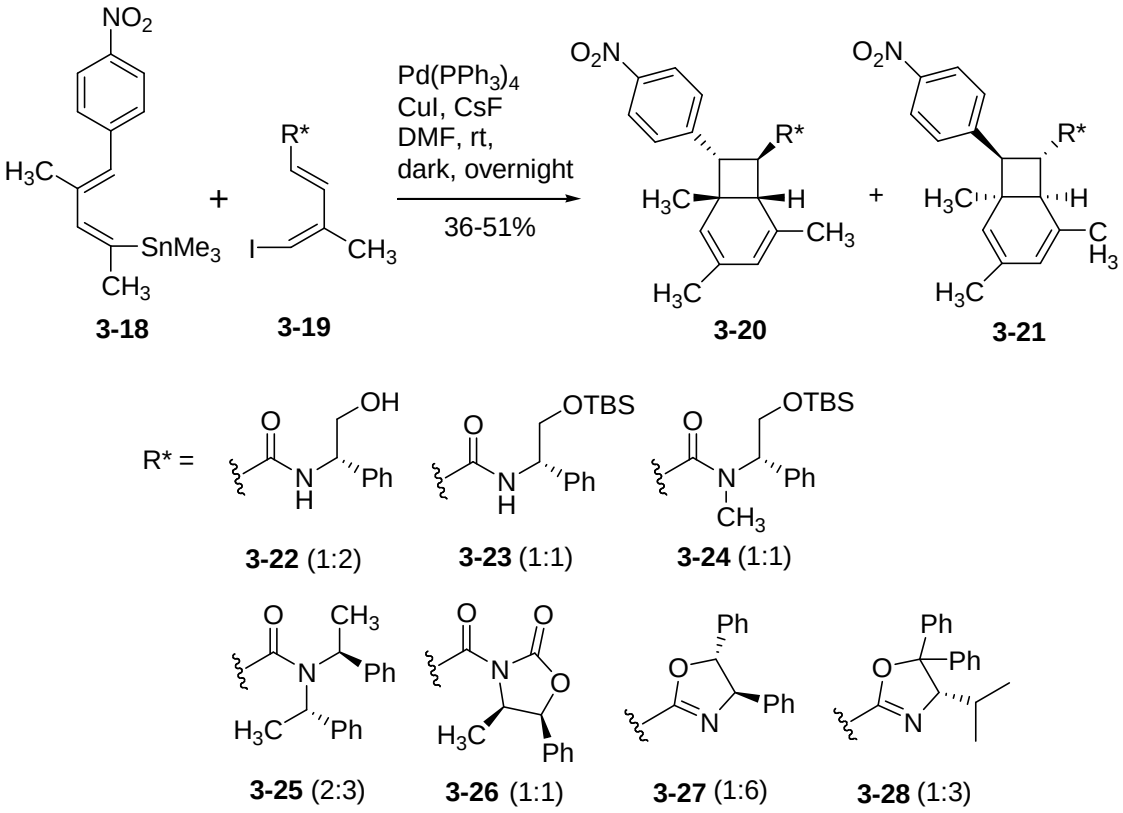
[97] Cleavable Chiral Auxiliaries in 8π (8π, 6π) Electrocyclizations. Parker, K. A.; Wang, Z. *Org. Lett*. **2006**, *8*, 3553-3556.



Scheme 3-4. Study for the diastereoselective synthesis of bicyclooctadienes using Corey-Sarakinos chiral sulfone auxiliaries

This initial study was extended. In 2012, Kim and Parker reported the research results for asymmetric induction in 8π electrocyclizations. They screened the candidates to provide the higher diastereoselectivity. Among the studied, the C-2 symmetric 2,3-diphenyloxazoline moiety was turned out to give the highest selectivity, presumably derived by the difference of steric hindrance in the transition states of 8π-electrocyclization. Interestingly, the (S)-phenylglycinol as a chiral auxiliary showed exceptional tlc behaviors[98] for the two of endo diastereomers, providing clean separation of the diastereomers (Scheme 3-5).

[98] For the chromatographic properties of phenylglycinol-derived amides, see Helmchen, G.; Nill, G. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 65. (b) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 63. (C) Helmchen, G.; Volter, H.; Schuhle, W. *Tetrahedron Lett* **1977**, 1417. (d) Helmchen, G.; Sauber, K.; Ott, R. *Tetrahedron Lett* **1972**, 3873.

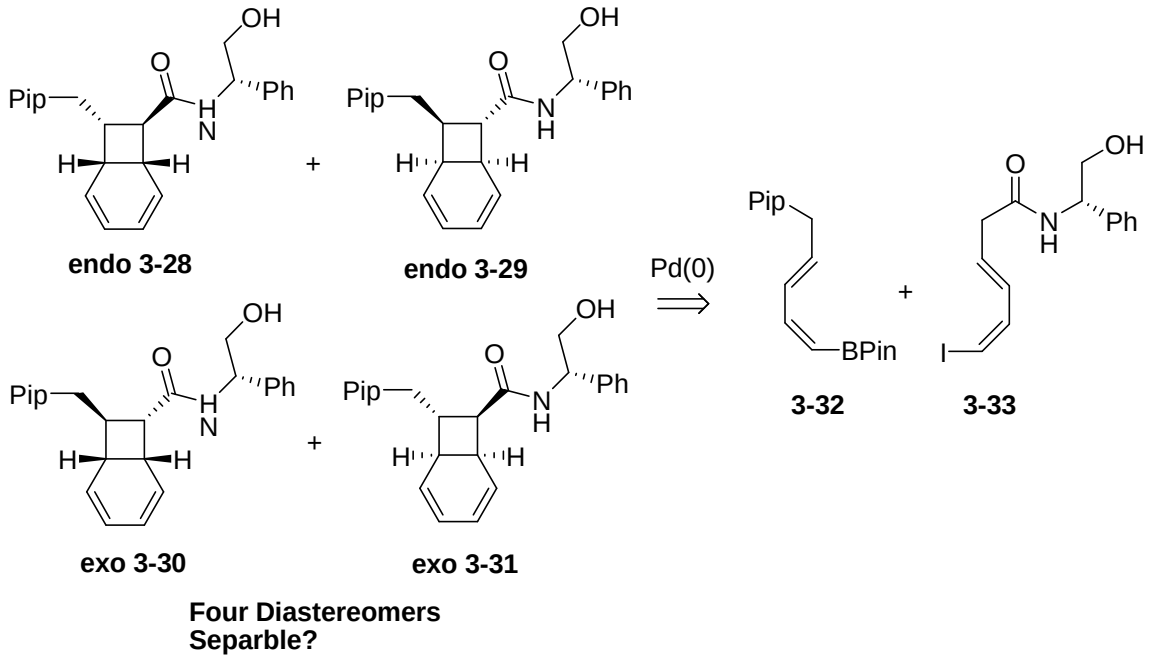


Scheme 3-5. Chiral auxiliaries for the asymmetric synthesis of bicyclooctadienes

3.2 Result and Discussion

3.2.1 Phenylglycinol-derived bicyclootadienes

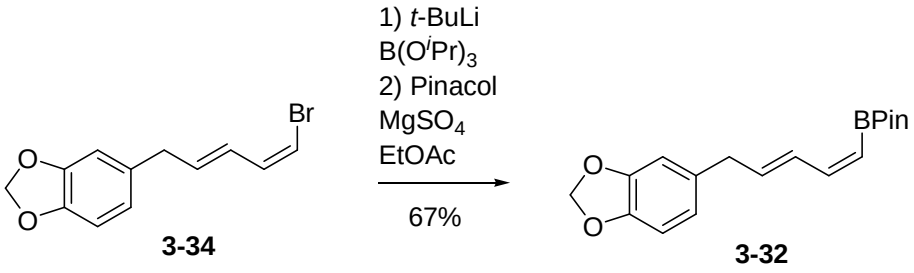
Our first idea was adapting an appropriate chiral auxiliary that is able to resolve four diastereomers by silica gel chromatography. In doing so, we could provide scalable procedure of the chiral bicyclooctadiene that can be utilized for the RCDA reaction. We planned to do Suzuki coupling and use (S)-glycinol as the chiral auxiliary (Scheme 3-6).



Scheme 3-6. Plan to separate single diastereomer using (S)-phenylglycinol

3.2.1.1 Preparation of pinacolboronate **3-32**

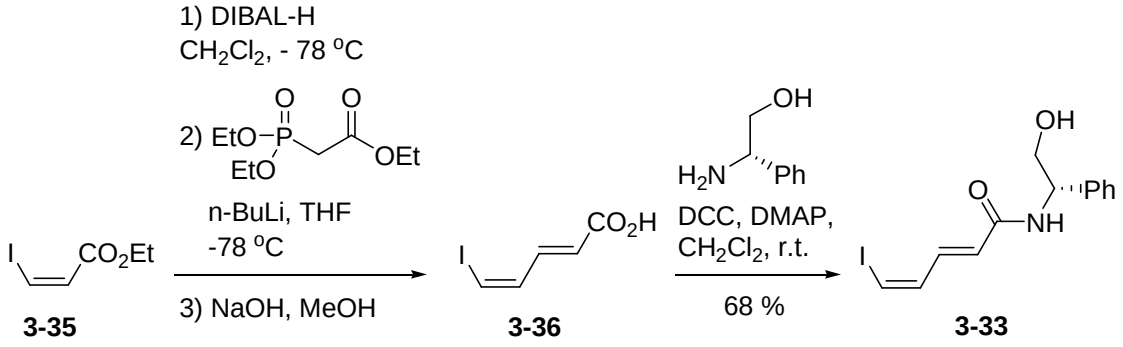
The left building block **3-32** was prepared from the known (E, Z)-bromodiene **3-34**. The two step sequence gave the pinacolboronate **3-32** in 67 % yield (Scheme 3-7).



Scheme 3-7. Synthesis of pinacolboronate **3-32**

3.2.1.2 Preparation of (E, Z)-iododiene **3-33**

The right building block **3-33** was prepared by a four step sequence from the commercially available iodoester **3-35**. The DIBAL reduction of the ethyl ester **3-35** was followed by a Horner-Wardworth-Emmons homologation and hydrolysis to afford the known acid **3-36**.[99] The resulting acid **3-36** was converted to the amide **3-33** by DCC coupling reaction (Scheme 3-8).

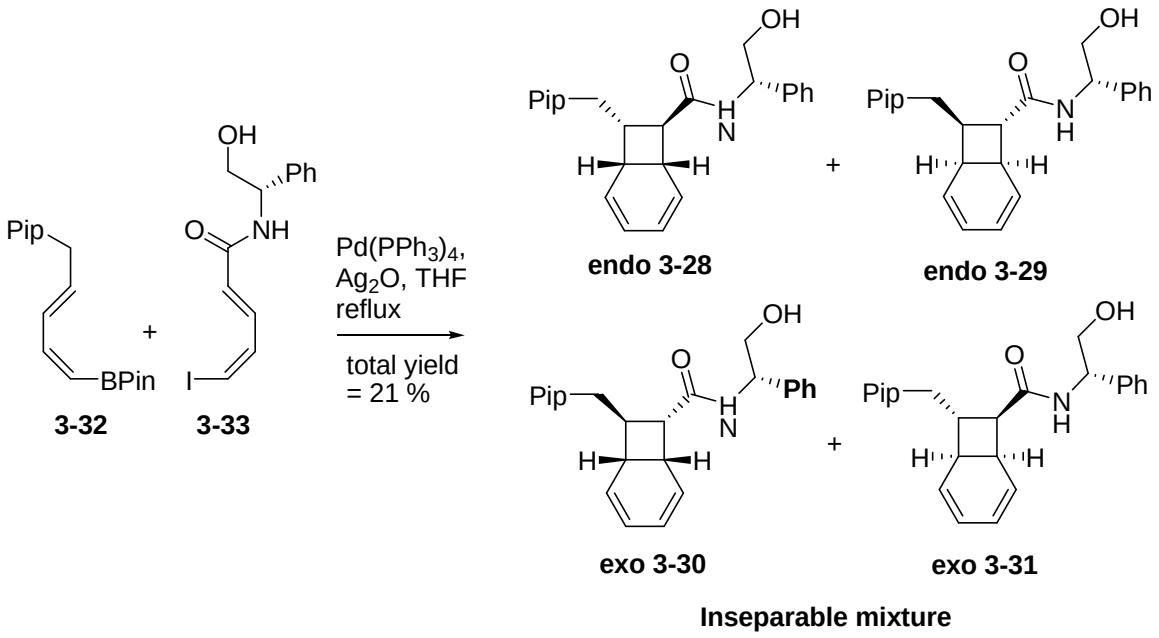


Scheme 3-8. Preparation of (E, Z)-iododiene **3-33**

[99] Stereocontrolled synthesis of polyenoic acids by a Heck-Sonogashira reaction: easy access to 9,10-didehydro retinoic acids. Abarbri, M.; Thibonnet, J.; Parrain, J. –L.; Duchene, A. *Tetrahedron Lett.* **2002**, *43*, 4703-4705.

3.2.1.3 Coupling of pinacolboronate **3-32** and (E, Z)-iododiene **3-33**

Having prepared both coupling partners, we next examined Suzuki reaction. The crude products were separated by silica gel chromatography. As a result, only two major spots were isolated and any single diastereomer was not cleanly separated. However, the ^{1}H nmr spectra corresponding to each of two spots showed a mixture of unidentified cyclooctadiene compounds; it is presumed that each spot is one pair between four diastereomers shown below (Scheme 3-9).

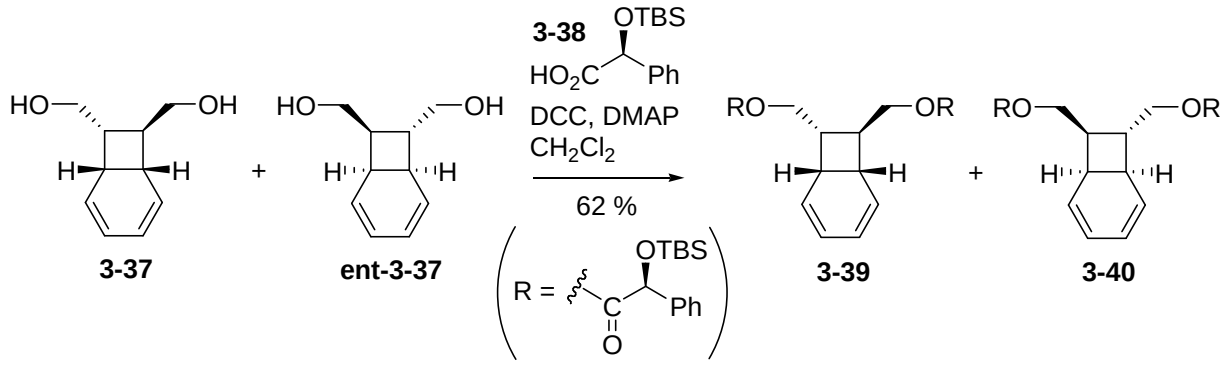


Scheme 3-9. Suzuki coupling of **3-32** and **3-33**

3.3.2 Experiments for resolving enantiomers using chiral mandelic acid

Frustrated by the unsuccessful separation of the four diastereomers formed by electrocyclization, we next considered the resolution of a racemic bicyclooctadiene. The chiral mandelic acids or their derivatives have been studied as substrates for resolving the racemic alcohols.[100] Although the exemplified alcohols are mostly secondary alcohols, we decided to look at the possibility of the application for the primary alcohols.

As a simple model compound, we utilized the racemic diol **3-37**. Using the TBS-protected (S)-mandelic acid, we prepared dimandelates **3-39** and **3-40**. However, the mixture of **3-39** and **3-40** was not separable (Scheme 3-10). Furthermore, an attempt to effect the tetrabutylammonium fluoride mediated deprotection of the TBS group was frustrated, producing the hydrolyzed products **3-37** and **ent-3-37**.

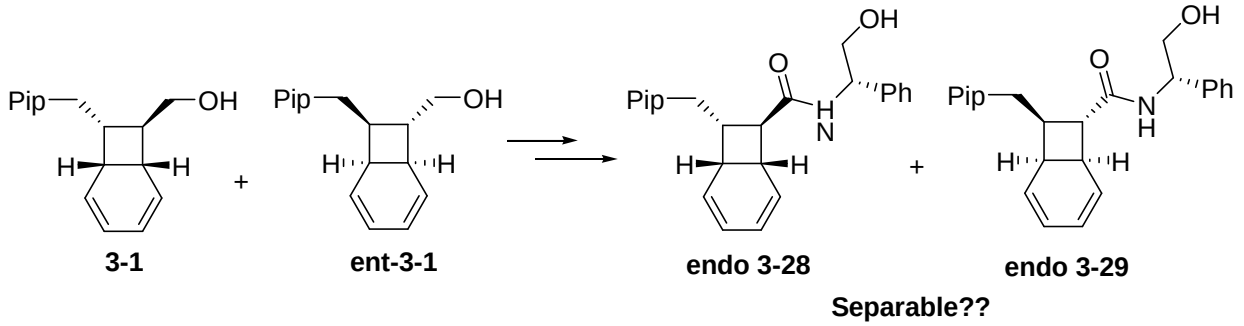


Scheme 3-10. Synthesis of the dimandelates to examine the resolution

[100] (a) Resolution of Chiral Alcohols with Mandelic Acid. Whitesell, J. K.; Reynolds, D. J. Org. Chem. 1983, 48, 3548-3551. (b) An experimental/theoretical approach to determine the optical purity and the absolute configuration of endo- and exo-norborn-5-en-2-ol using mandelate derivatives. Pisano, P. L.; Sarotti, A. M.; Pellegrinet, S. C. *Tetrahedron Lett*. **2009**, *50*, 6121-6125. (c) Synthesis of Both Enantiomers of ω-Trifluorononatic Acid, a New Analogue of Nonactin Monomers. Takai, K.; Hanadate, T.; Oi, S.; Yamada, T.; Kuwahara, S.; Kiyota, H. *Synthesis* **2011**, 3741-3748.

3.3.3 Resolution of the endo diol using (S)-phenylglycinol

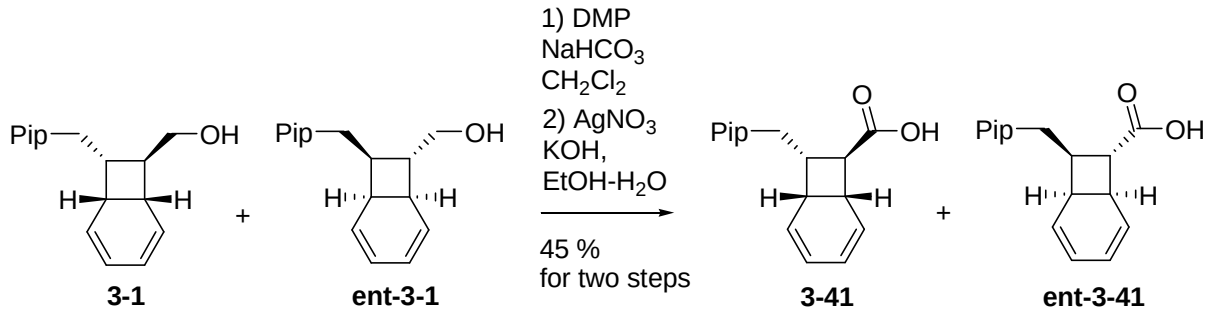
Previously, we prepared endo bicyclooctadiene **3-1** (rac) by a way of iodoetherification to remove exo bicyclooctadiene from an inseparable mixture of endo and exo bicyclooctadienes.[101] We anticipated that the introduction of an amide bearing (S)-phenylglycinol to the endo bicyclooctadiene **3-1** may give a separation of two diastereomers **3-28** and **3-29** (Scheme 3-11).



Scheme 3-11. Plan for resolving endo rac-bicyclooctadiene **3-1**

3.3.3.1 Synthesis of the carboxylic acid and amide from the endo rac-bicyclooctadiene **3-1**

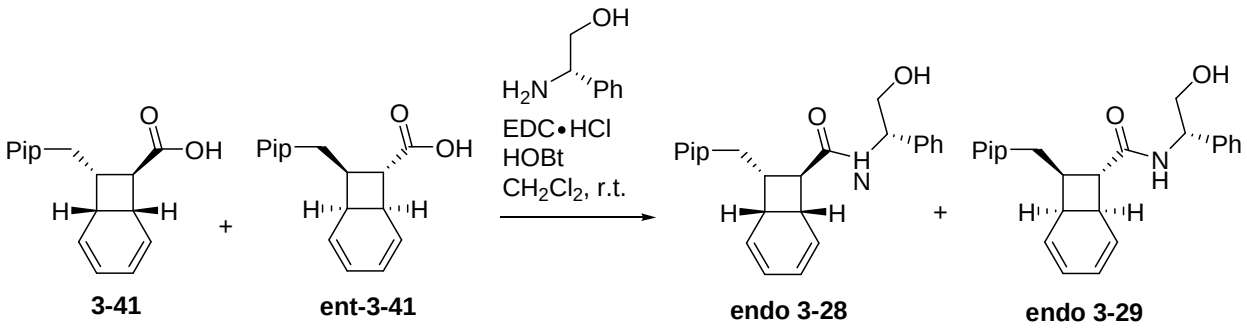
In order to have an amide functionality, we decided to use a conventional peptide synthesis method between the acid and (S)-phenylglycinol. Thus, we prepared the acid **3-41** by consecutive oxidations (Scheme 3-12). The isolated acid did not contain any epimerized product.



Scheme 3-12. Synthesis of carboxylic acid **3-41**

[101] Total Synthesis of Kingianin A. Lim, H. N.; Parker, K. A. *Org. Lett*. **2013**, *15*, 398-401.

We next examined the EDC-assisted coupling reaction. The coupling reaction between the acid **3-41** and (S)-phenylglycinol surprisingly resulted in two separable compounds. The ^{1}H nmr pattern of them resembled each other (Scheme 3-13).



Scheme 3-13. EDC coupling reaction between the acid **3-41** and (S)-phenylglycinol

3.3 Conclusion

The asymmetric synthesis of bicyclooctadiene compounds is limited due to their random nature in 8π, 6π-electrocyclization. Thus, the asymmetric synthesis of them have been approached by chiral auxiliaries. In some cases, the separation of the resulting diastereomers of bicyclooctadiens were successful. In particular, (S)-phenylglycinol-derived bicyclooctadienes showed significant difference of Rf values between diastereomers.

In order to prepare an enantiomerically pure bicyclooctadiene structure for the asymmetric synthesis of kingianin A, we explored the possibility of separation using (S)-phenylglycinol. In the first experiment, we wanted to see the possibility of separation for the four diastereomers which are formed by a tandem couling and electrocyclization between boronate **3-32** and iododiene **3-33**. However, we could not separate any single diastereomer cleanly from the mixture.

In the second experiment using (S)-phenylglycinol, we prepared the rac-acid **3-41**. The acid **3-40** was converted to two diastereomers bearing (S)-phenylglycinol, endo **3-28** and **endo 3-29**. Surprisingly, these isomers were separable by silica gel chromatography. Although the absolute stereochemistry has not been determined yet, each of them is presumably a precursor for the synthesis of (+)- or (-)-kingianin A.

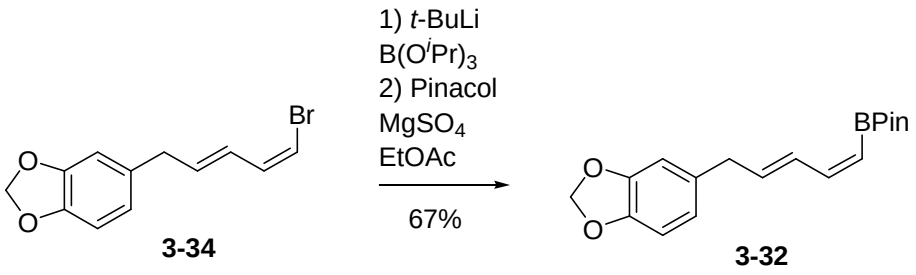
3.4 Experimental Section

General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. HPLC grade hexane, EtOAc, CH_2Cl_2 and CH_3OH were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol or $KMnO_4$ aq. solution and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for ^{1}H and 126 MHz for ^{13}C), Varian Inova-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C), or Gemini-2300 (300 MHz for ^{1}H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-*d*. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on a Varian Inova-600 spectrometer.

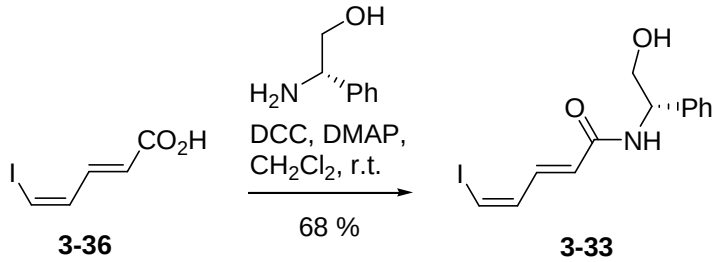
Experimetal Procedure/ Characterization



3-34 **3-32**

Boronate 3-32 Step 1: To a stirred solution of (E, Z)-bromodiene **3-34** (0.27 g, 1.0 mmol) in diethyl ether (5 mL) was added dropwise tert-BuLi (1.6 M in pentane, 0.75 mL, 1.2 mmol) at – 78 ^{o}C under Ar. After the mixture was stirred for 1 h, triisopropylborate (0.27 mL, 1.2 mmol) was added. The reaction mixture was then warmed to r.t., stirred for additional 3 h, and quenched with water. The mixture was extracted with ethyl acetate and organic solution was dried over $MgSO_4$, concentrated. The residue was directly used for the next step. Step 2: A mixture of the crude product, pinacol (0.15 g, 1.3 mmol), and $MgSO_4$ (0.8 g) in EtOAc (4 mL) was stirred overnight. The resulting mixture was filtered, concentrated, and subjected to silica gel chromatography (Hex:EtOAc = 40:1 to 20:1) to afford the boronate **3-32** (0.21 g, 67 %) as yellow oil.

Rf value: 0.6 (Hex:EtOAc = 20:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 12 H), 3.40 (d, *J* = 6.5 Hz, 2 H), 5.31 (d, *J* = 12.5 Hz, 1 H), 5.90 – 5.96 (m, 1 H), 5.92 (s, 2 H), 6.45 – 6.92 (5 H).

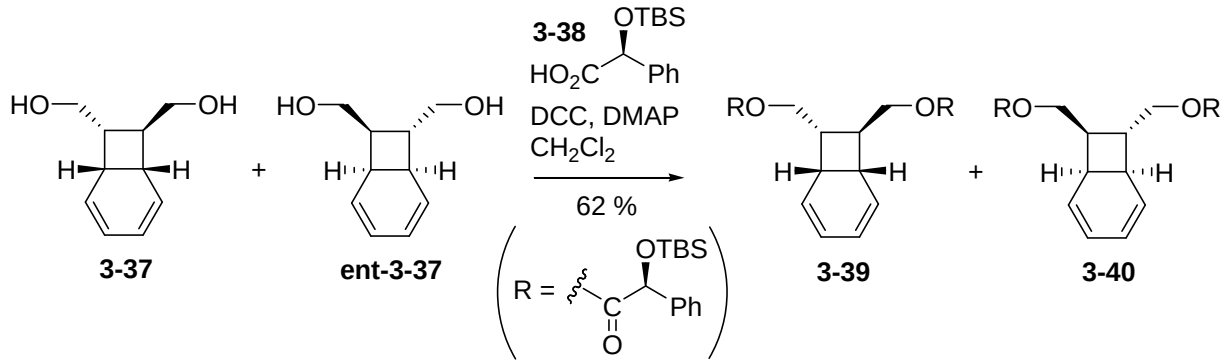


3-36 **3-33**

(E, Z)-Iododiene 3-33 To a stirred solution of the acid **3-36** (0.54 g, 2.41 mmol), DMAP (59 mg, 0.48 mmol), and (S)-phenylglycinol (0.40 g, 2.89 mmol) in CH_2Cl_2 (5 mL) was added N,N'-dicyclohexylcarboimide (DCC, 0.55 g, 2.65 mmol) at 0 ^{o}C. The reaction mixture was warmed to r.t. and stirred for 30 min. The resulting suspension was filtered, diluted with diethyl ether, and washed with water. The organic solution was dried over $MgSO_4$, concentrated, subjected to silica gel chromatography (Hex:EtOAc = 1:1) to afford the (E, Z)-iododiene **3-33** (0.56 g, 68 %) as

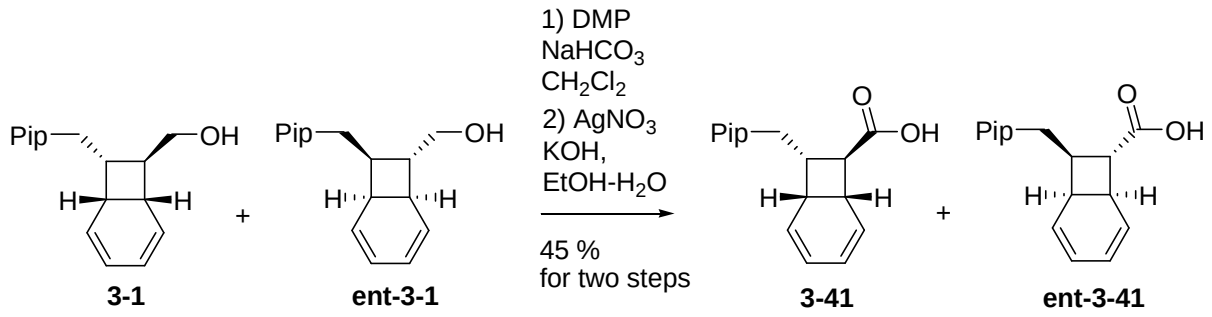
colorless solid.

Rf value: 0.6 (Hex:EtOAc = 20:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (br s, 1 H), 3.91 (d, J = 4.8 Hz), 5.13 (m, 1 H), 6.18 (d, *J* = 14.8 Hz), 6.56 (d, J = 6.8 Hz, 1 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 6.85 (dd, *J* = 10.4 and 8.0 Hz), 7.27 – 7.40 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 66.4, 91.1, 126.7, 127.7, 127.9, 128.9, 136.5, 138.7, 140.4, 165.9.; IR (neat) νmax 1306, 1537, 1614, 1650, 3280.



Dimandelates 3-39 and 3-40 To a stirred solution of the diol **3-37** (20.0 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added TBS-mandelic acid **3-38** (96.1 mg, 0.36 mmol), DMAP (1.5 mg, 12 μmol), and DCC (74.5 mg, 0.36 mmol) in order at 0 ^{o}C. The reaction mixture was stirred overnight and quenched with sat. $NaHCO_3$ sol'n. The organic solution was dried over $MgSO_4$, concentrated, subjected to silica gel chromatography (Hex:EtOAc = 30:1) to afford the inseparable mixture of dimandelates **3-39** and **3-40** (0.47 g, 62 %) as colorless oil.

Rf value: 0.6 (Hex:EtOAc = 10:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 12 H), 0.10 (s, 12 H), 0.91 (s, 36 H), 2.42 – 2.52 (m, 3 H), 2.57 – 2.70 (m, 3 H), 2.92 (m, 2 H), 3.83 – 4.19 (m, 8 H), 5.14 (dd, *J* = 10.5 and 4.5 Hz, 1 H), 5.17 (s, 2 H), 5.20 (d, *J* = 2.0 Hz, 2 H), 5.30 – 5.35 (m, 3 H), 5.57 – 5.62 (m, 2 H), 5.72 (dd, *J* = 9.0 and 5.5 Hz, 1 H), 5.78 (dd, *J* = 9.0 and 4.5 Hz, 1 H), 7.24 – 7.46 (m, 20 H).; IR (neat) νmax 1131, 1253, 1471, 1733, 1756.



Acid 3-41 Step 1: To a stirred solution of the alcohol **3-1** (30 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) was added $NaHCO_3$ (28.0 mg, 0.33 mmol) and DMP (94.1 mg, 0.22 mmol) at 0 ^oC. After the reaction mixture was stirred for 1 h at r.t., it was quenched with water, extracted with diethyl ether. The organic solution was The organic solution was dried over $MgSO_4$, concentrated, subjected to silica gel chromatography (Hex:EtOAc = 10:1) to afford the aldehyde as colorless oil. The aldehyde was directly used for the next step without characterization. Step 2: To a stirred solution of $AgNO_3$ (50.9 mg, 0.30 mmol) in H_2O (0.15 mL) was added a solution of the aldehyde in EtOH (0.4 mL) and KOH (44.2 mg, 0.79 mmol) in H_2O at 0 ^oC. The reaction mixture was warmed to r.t. and stirred for 30 min. The reaction mixture was filtered and washed with water. The filtrate was concentrated until the remaining ethanol was evaporated. The resulting aqueous solution was treated with 2N HCl until the pH became 3. Then, the resulting suspension was extracted with CH_2Cl_2 and the organic solution was dried over $MgSO_4$, concentrated.

Rf value: 0.4 (Hex:EtOAc = 5:1) ^1H NMR (500 MHz, $CDCl_3$) δ 2.84 (dd, *J* = 14.4 and 6.8 Hz, 1 H), 2.90 (dd, *J* = 14.4 and 9.0 Hz, 1 H), 3.12 – 3.21 (m, 3 H), 3.31 (m, 1 H), 5.60 – 5.65 (m, 2 H), 5.79 (dd, *J* = 9.5 and 5.5 Hz, 1 H), 5.91 (s, 2 H), 5.96 (dd, *J* = 9.8 and 5.5 Hz, 1 H), 6.62 – 6.72 (m, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.7, 34.7, 35.9, 47.5, 52.1, 100.8, 108.2, 108.8, 121.2, 123.1, 124.7, 124.9, 125.7, 133.7, 145.7, 147.6, 179.1.; IR (neat) νmax 1246, 1443, 1489, 1502, 1698, 2920.

Chapter 4

Total synthesis of kingianins D, F, H, and J

4.1 Introduction

4.1.1 Structures of kingianin A, D, F, H, and J

The kingianins (e.g. kingianins A (**4-1A**), D (**4-1D**), F (**4-1F**), H (**4-1H**), and J (**4-1J**) Figure 1) are newly discovered racemic natural products from *Endiandra kingiana* Gamble; they are reported to be inhibitors of the anti-apoptotic protein Bcl-xL.[102] Like the endiandric acids which are isolated from another *Endiandra* species,[103] the kingianins are thought to be the products of non-enzymatic cascades that proceed through bicyclooctadienes.

While the last step in the biosynthesis of the endiandric acids is believed to be an intramolecular Diels Alder reaction, that in the biosynthesis of the kingianins appears to be an ***inter***molecular Diels Alder dimerization. For example, kingianin A is the dimer of two enantiomerically identical molecules of pre-kingianin A (**4-2**) and kingianin D is the dimer of two enantiomeric molecules of pre-kingianin A as suggested in Figure 4-1. On the other hand, kingianin F is the dimer of two enantiomerically identical molecules of the exo isomer of pre-kinginan A (**4-3**).

A biomimetic approach to the kingianins is appealing but it has not been without its disappointments. Attempts by Moses et al. to prepare kingianin A by a thermal Diels Alder dimerization of the presumed biogenetic precursor **4-2** were frustrated by the stability of the monomeric bicyclooctadiene structure with respect to the desired conversion.[104]

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[102] (a) Pentacylcic Polyketide from Endiandra kingiana as inhibitors of the Bcl/Bak interaction. Leverrier, A.; Awang, K.; Gueritte, F.; Litaudon, M. *Phytochemistry* **2011**, *72*, 1443-1452. (b) Kingianin A: A New Natural Pentacyclic Compound from Endiandra kingiana. Leverrier, A.; Dau, M. E. T. H.; Retailleau, P.; Awang, K.; Gueritte, F.; Litaudon, M. *Org. Lett*. **2010**, *12*, 3638-3641.

[103] Postulated electrocyclic reactions leading to endiandric acid and related natural products. Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *J. Chem. Soc., Chem. Commun*. **1980**, *19*, 902-903.

[104] However, the authors did see interconversion of monomers **4-2** and **4-3**; see A synthetic approach to kingianin A based on biosynthetic speculation. Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun*. **2011**, *47*, 10605-10607.

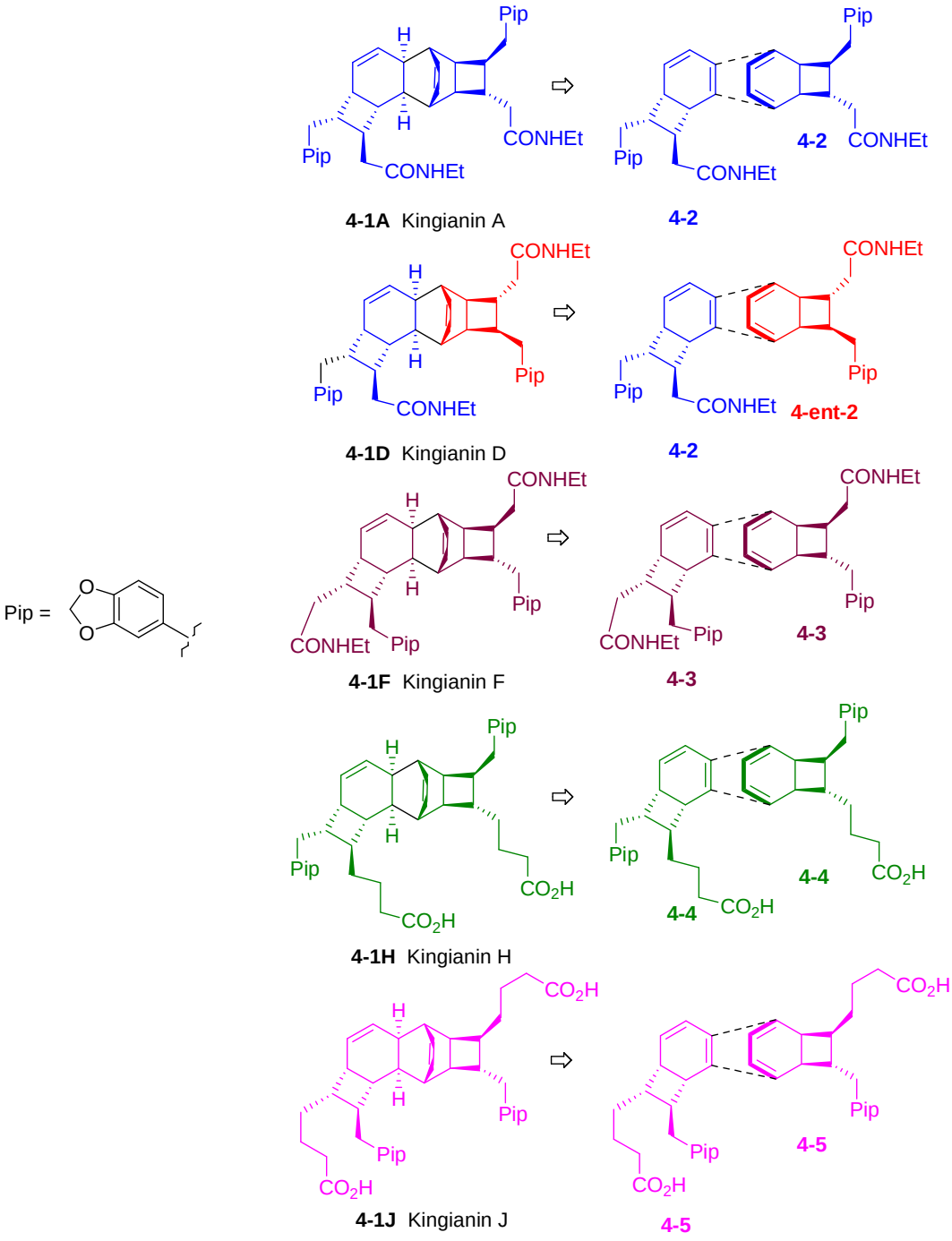
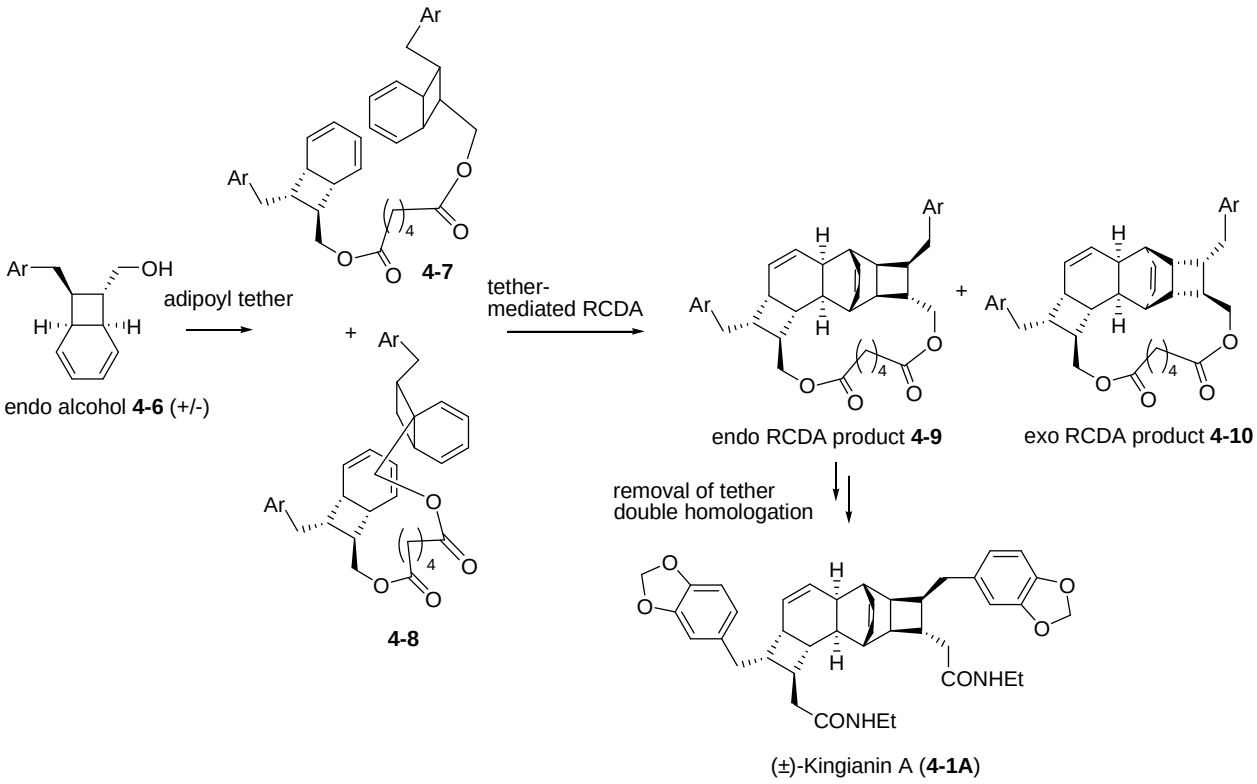


Figure 4-1. Kingianins A, D, F, and H and their corresponding monomers

We recognized that radical cation catalysis overcomes the reticence of cyclohexadienes to

undergo the Diels Alder dimerization reaction.[105] Furthermore, we postulated that the biosynthesis of the kingianins proceeds through a radical cation-mediated reaction, perhaps initiated by a photochemical event.[106] Pursuing this idea, we examined the bicyclooctadiene dimerization under radical cation initiating conditions. Our substrate was designed to control regiochemistry and stereochemistry in the cycloaddition of two bicyclooctadienes by linking them with a tether. This approach, applied to a mixture of the dimeric C-2 symmetric **4-7** and meso **4-8** precursors, yielded two pentacyclic isomers. One **4-9**, derived from the C-2 symmetric linked dimer (the endo Diels Alder product) was converted to kingianin A. The structure of the second Diels Alder product **4-10** (exo product, from the meso linked dimer) did not correspond to that of any of the naturally occurring kingianins (Scheme 4-1).



Scheme 4-1. Total synthesis of kingianin A

[105] The Cation-Radical Catalyzed Diels-Alder Reaction. Bellville, D. J.; Wirth, D. W.; Bauld, N. L. *J. Am. Chem. Soc.* **1981**, *103*, 718-720.

[106] Total Synthesis of Kingianin A. Lim, H. N.; Parker, K. A. *Org. Lett.* **2013**, *15*, 398-401.

4.1.2 Hypothesis

The intramolecular experiment established the radical cation Diels Alder (RCDA) strategy as an entry to the kingianins and it provided an element of regiocontrol to this key reaction. However, the ***inter***molecular RCDA has the potential to provide a stereodivergent synthesis,[107] affording up to four[108] pentacyclic scaffolds, three of which correspond to naturally occurring kingianins (A, D, and F and their homologs).

As we have noted previously, a regio- and stereodivergent scheme can be considered practical only if the components of the final products or the components of an intermediate are readily separable.[5] Despite the description of sequential silica gel and HPLC chromatographies required for the separation of the natural products,[1a] we were encouraged to pursue the divergent intermolecular approach by the observation that diol **4-11** and its exo stereoisomer **4-12** (Figure 4-2) had slightly different R_f values on tlc. We postulated that regio- and stereoisomeric diols in the kingianin series might have usefully different chromatographic behaviors.

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[107] During the preparation of a manuscript describing this work, the synthesis of kingianins A, D, and F by a sequence that used the intermolecular RCDA reaction appeared. This work focused primarily on testing the biomimetic premise and it relies on preparative HPLC for the isolation of the individual kingianins. Yields for the recovered kingianins from the HPLC experiment were not reported. See Drew, S. L.; Lawrence, A. L. Sherburn, M. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 4221-4224.

[108] The number of possible regio- and stereoisomers from an unsymmetrical bicyclooctadiene such as **4-2** is limited by the preference for an endo transition state and steric factors; see reference 5 for a discussion.

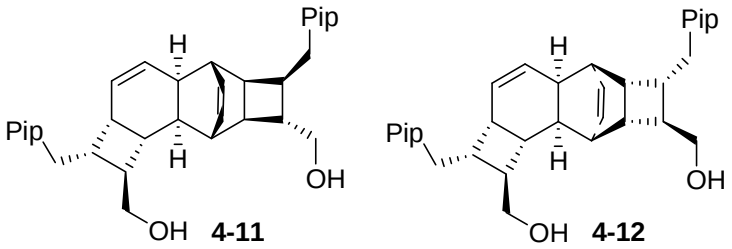
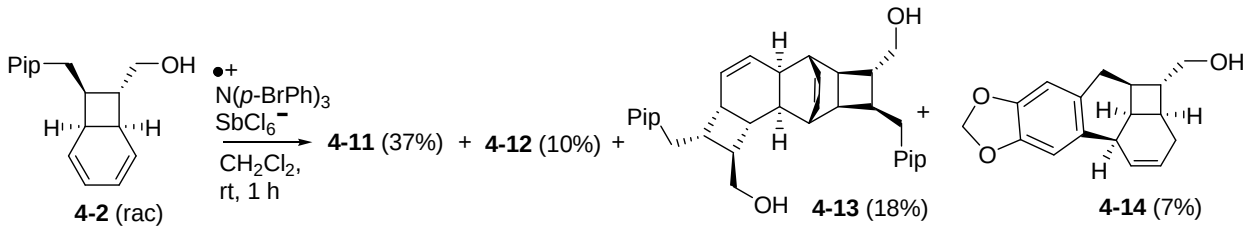


Figure 4-2. Endo diol **4-11** and exo diol **4-12**, obtained from a tether mediated RCDA reaction of the bicyclooctadiene **4-2**

4.2 Result and Discussion

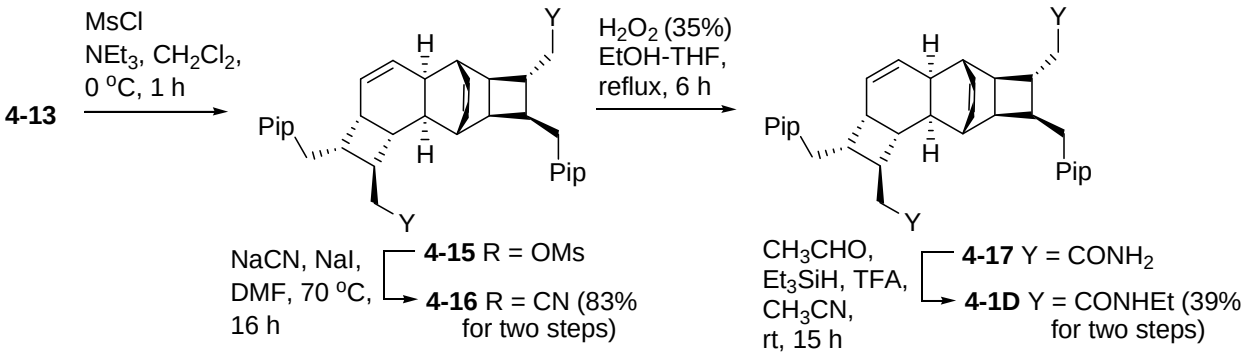
4.2.1 RCDA reaction of endo alcohol **4-2** and synthesis of kingianin D

Indeed, when endo cyclooctadienol **4-2** was subjected to RCDA conditions, a mixture of four separable compounds was obtained (Scheme 4-2). Known endo diol **4-11** (37%), known exo diol **4-6** (10%), a new endo dimeric diol **4-13** (18%, corresponding in structure to kingianin D) and alcohol **4-14** (7%, a non-Diels Alder product) were easily isolated by preparative tlc.



Scheme 4-2. Intermolecular RCDA dimerization of racemic endo bicyclooctadiene **4-2**

Diol **4-13** was converted to kingianin D in 32% yield (Scheme 4-3) by the 4-step sequence employed previously in the synthesis of kingianin A.[5]



Scheme 4-3. Synthesis of kingianin D

The ^{1}H and ^{13}C nmr spectra of synthetic kingianin D were compared with those of authentic arabilin in Tables 4-1 and 4-2. The chemical shifts as well as the coupling constants are consistent with the authentic data.

Table 4-1. ^{1}H-NMR for Kingianin D in $CDCl_3$, δ (ppm), mult, (*J* in Hz)[109]

No.	Authentic, δ_c	Synthetic, δ_c	No.	Authentic, δ_c	Synthetic, δ_c
1	2.02	2.02 m	1’	2.28	2.28 m
2	2.50	2.50 m	2’	2.50	2.50 m
3	5.56 br d (10.4)	5.55 br d (10.3)	3’	2.37	2.37 m
4	5.75 br d (10.4)	5.75 br d (10.3)	4’	6.29 dd (7.1, 7.6)	6.29 t (7.2)
5	2.27	2.27 m	5’	6.14 t (7.1)	6.1041 t (7.2)
6	1.67 br d (9.0)	1.66 br d (9.0)	6’	2.61	2.61 m
7	1.91	1.90 m	7’	2.27	2.27 m
8	1.99	1.99 m	8’	2.07	2.08 m
9	2.59/2.47	2.59/2.48 m	9’	2.66/2.53	2.66/2.53
10	-	-	10’	-	-
11	6.63	6.63 br s	11’	6.60	6.59 br s
12	-	-	12’	-	-
13	-	-	13’	-	-
14	6.69	6.69 d (2.2)	14’	6.68	6.68 d (2.2)
15	6.58	6.58 br d (8.2)	15’	6.56	6.55 br d (8.0)
16	5.90[a]	5.90[a] s	16’	5.90[a] s	5.90[a] s
17	2.02/1.97	2.02/1.98 m	17’	2.09/1.97	2.09/1.98 m
18	-	-	18’	-	-
19	5.10 t (5.7)	5.15[b] br s	19’	5.14 t (5.7)	5.19 br s
20	3.18 qd (7.2, 5.7)	3.18 qd (7.3, 5.2)	20’	3.23 qd (7.2, 5.7)	3.23 quintet (7.3)
21	1.06 t (7.2)	1.05[c] t (7.3)	21’	1.10 t (7.2)	1.10[c] t (7.3)

The data for the authentic sample are extracted from the report of the structure assignment.[3]
[a, b, c] Values are interchangeable

[109] Our laboratory uses 7.260 ppm for the chemical shift of $CHCl_3$. All values in the Experimental Section are based on this standard. The Litaudon group uses 7.240 ppm for the chemical shift of $CHCl_3$. Therefore in this Table we have adjusted the values reported by Litaudon et al by adding 0.020 ppm.

Table 4-2. ^{13}C-NMR for Kingianin D in $CDCl_3$, δ (ppm)[110]

Number	Authentic	Synthetic	Number	Authentic	Synthetic
1	43.5	43.4	1’	43.9	43.8
2	33.7	33.6	2’	40.9	40.8
3	124.4	124.3	3’	41.5	41.4
4	132.5	132.5	4’	133.1	133.0
5	37.2	37.1	5’	134.7	134.7
6	39.2	39.1	6’	40.3	40.2
7	42.2	42.2	7’	43.5	43.4
8	42.9	42.8	8’	39.6	39.5
9	35.9	35.8	9’	35.4	35.4
10	135.2	135.2	10’	135.6	135.5
11	108.9	108.85[a]	11’	108.8	108.76[a]
12	147.6	147.5	12’	147.5	147.4
13	145.6	145.43	13’	145.5	145.35
14	108.1	108.06[b]	14’	108.1	108.09[b]
15	121.1	121.1	15’	121.0	121.0
16	100.7	100.66[c]	16’	100.8	100.71[c]
17	41.8	41.7	17’	43.2	43.1
18	171.8	171.8[d]	18’	171.8	171.9[d]
19	-	-	19’	-	-
20	34.2	34.2	20’	34.3	34.3
21	14.9	14.82	21’	15.0	14.92

The data for the authentic sample are extracted from the report of the structure assignment.[3]

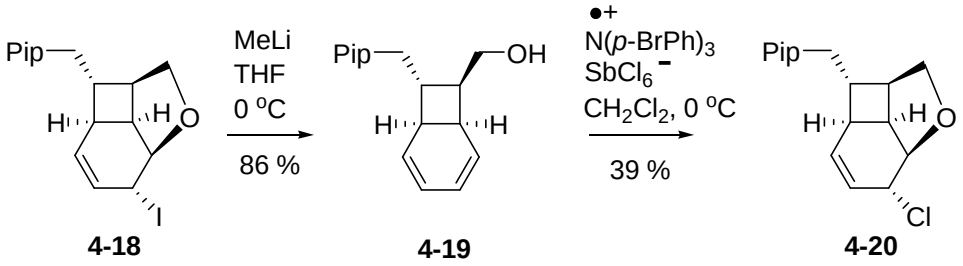
[a, b, c, d] Values are interchangeable

[110] Our laboratory uses 77.000 ppm for the chemical shift of $CDCl_3$. All values in the Experimental Section are based on this standard. The Litaudon group uses 77.230 ppm for the chemical shift of $CDCl_3$. Therefore in this Table we have adjusted the values reported by Litaudon et al by subtracting 0.230 ppm.

4.2.2 RCDA reaction of exo alcohol **4-19** and synthesis of kingianin F

4.2.2.1 Preparation of exo alcohol **4-19** and RCDA reaction

Having completed the syntheses of kingianins A and D from endo monomer **4-2**, we undertook the synthesis of kingianin F from the exo monomer **4-19**. This compound was prepared from the known ether **4-18** by reductive elimination initiated by methyllithium (Scheme 4-4).[111] However, it proved to be an unsatisfactory substrate in the RCDA reaction. When exo monomer **4-19** was subjected to the RCDA conditions, chloroether **4-20** was the only product isolated.

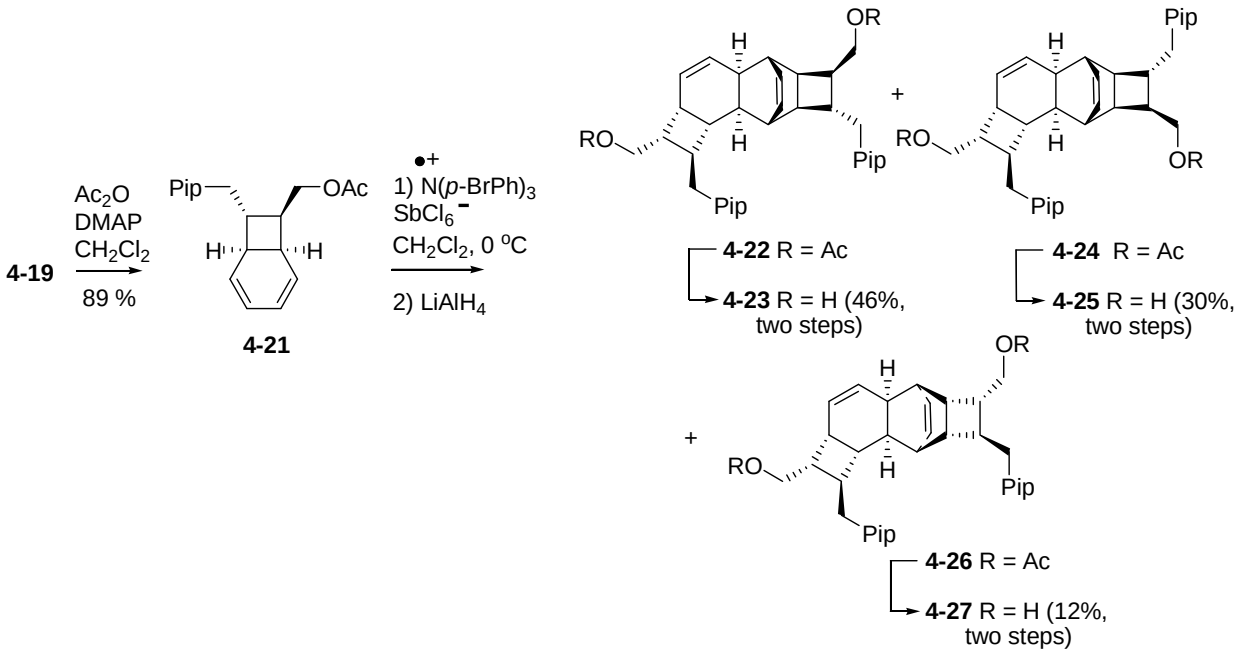


4-18 **4-19** **4-20**

Scheme 4-4. Preparation of exo substrate **4-19** and its RCDA reaction

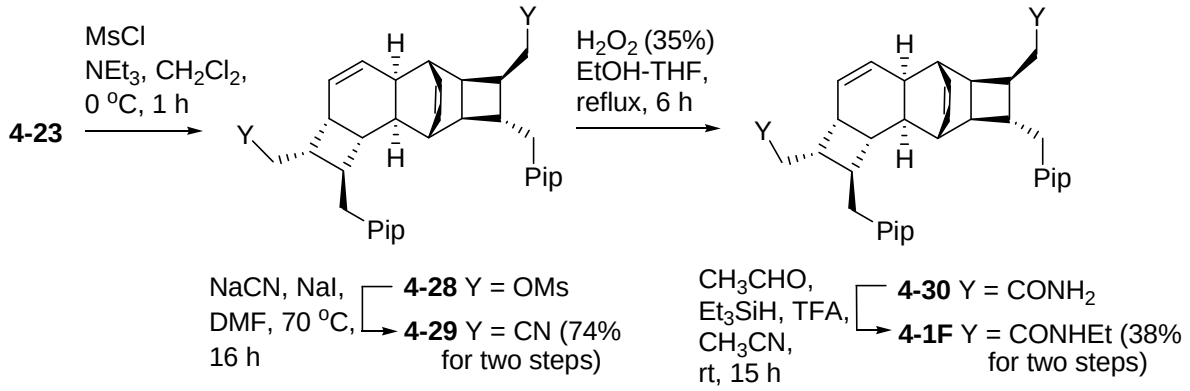
Therefore, the RCDA reaction was applied to acetate **4-21** (from alcohol **4-19**, Scheme 4-5). This reaction gave a mixture of two major products, **4-22** and **4-24**, both derived from endo transition states, and a minor product **4-26**, derived from an exo transition state. These diacetates appeared to be inseparable; however, removal of the acetyl groups gave a mixture of three diols, **4-23**, **4-25**, and **4-27**, that were readily separated by preparative tlc.

[111] When zinc-mediated reductive conditions were applied, 24 % of the alcohol **4-19** was isolated.



Scheme 4-5. Preparation of exo substrate **4-21** and its RCDA reaction

Diol **4-23** was then converted to kingianin F (Scheme 4-6) by the 4-step homologation/modification sequence used in the syntheses of kingianins A and D.



Scheme 4-6. Synthesis of kingianin F

The ^{1}H and ^{13}C nmr spectra of synthetic kingianin F were compared with those of authentic arabilin in Tables 4-3 and 4-4. The chemical shifts as well as coupling constants were consistent with the authentic data.

Table 4-3. ^{1}H-NMR for Kingianin F in pyridine-d_5, δ (ppm), mult, (*J* in Hz)

No.	Authentic, δ_c	Synthetic, δ_c	No.	Authentic, δ_c	Synthetic, δ_c
1	2.54	2.54 m	1’	2.11	2.11 m
2	2.61	2.60 m	2’	2.22	2.22 m
3	5.82 br d (10.4)	5.82 br d (10.3)	3’	2.16	2.15 m
4	5.66 br d (10.4)	5.66 br d (10.3)	4’	5.91 dd (7.1, 7.6)	5.90 t (7.3)
5	2.12	2.11 m	5’	6.15 t (7.1)	6.14 t (7.3)
6	1.39	1.38 br d (9.1)	6’	2.62	2.61 m
7	1.81	1.80 t (7.9)	7’	2.47	2.47 m
8	1.91	1.90 m	8’	2.83	2.83 m
9	2.72/2.62	2.71 dd (13.2, 6.5)/2.63 m	9’	2.86/2.66	2.86/2.65 m
10	-	-	10’	-	-
11	6.85	6.85 br s	11’	6.91	6.91 d (7.7)
12	-	-	12’	-	-
13	-	-	13’	-	-
14	6.91	6.90 br s	14’	6.96	6.96 d (7.9)
15	6.70	6.70 br d (7.8)	15’	6.79	6.79 br d (7.7)
16	5.98[a]	5.98[a] d (2.9)	16’	5.95[a]	5.95[a] d (10.9)
17	2.40/2.27	2.40 dd (14.2, 8.8)/2.26 dd (14.2, 6.5)	17’	2.50/2.34	2.50 m/2.33 dd (14.3, 8.0)
18	-	-	18’	-	-
19	8.21 t (5.7)	8.28 t (5.2)	19’	8.21 t (5.7)	8.28 t (5.2)
20	3.45 qd (7.2, 5.7)	3.45 qd (7.2, 5.2)	20’	3.45 qd (7.2, 5.7)	3.45 qd (7.2, 5.2)
21	1.14 t (7.2)	1.1353[b] t (7.2)	21’	1.14 t (7.2)	1.1392[b] t (7.2)

The data for the authentic sample are extracted from the report of the structure assignment. [a, b] Values are interchangeable

Table 4-4. ^{13}C-NMR for Kingianin F in pyridine-d_5, δ (ppm)

Number	Authentic	Synthetic	Number	Authentic	Synthetic
1	39.8	39.74	1’	44.7	44.7
2	33.9	33.8	2’	45.0	44.9
3	126.4	126.4	3’	43.7	43.7
4	132.7	132.7	4’	133.3	133.3
5	38.9	38.86[a]	5’	135.4	135.4
6	38.9	38.89[a]	6’	39.4	39.4
7	42.3	42.3	7’	40.2	40.1
8	48.0	48.0	8’	39.7	39.7
9	41.0	41.0	9’	42.6	42.6
10	135.6	135.5	10’	136.2	136.3
11	110.4	110.4	11’	110.0	110.0
12	148.5	148.5	12’	148.5	148.5
13	146.6	146.6	13’	146.6	146.6
14	108.9	108.9	14’	109.0	109.0
15	122.7	122.4[b]	15’	122.7	122.7[b]
16	101.7	101.7	16’	101.7	101.7
17	38.3	38.3	17’	37.5	37.5
18	172.5	172.6	18’	172.8	172.8
19	-	-	19’	-	-
20	34.8	34.8	20’	34.7	34.8
21	15.7	15.7[c]	21’	15.7	15.8[c]

[a, b, c] The data for the authentic sample are extracted from the report of the structure assignment. Values are interchangeable

4.2.2.2 Structural Assignment of dimer **4-25**

The structure of the endo diol **4-25** was firmly identified by X-ray crystallography (Figure 4-3). The stereochemistry of the piperonyl and methyl alcohol sidechains on both cyclobutanerings were shown to be as assigned by the nmr data.

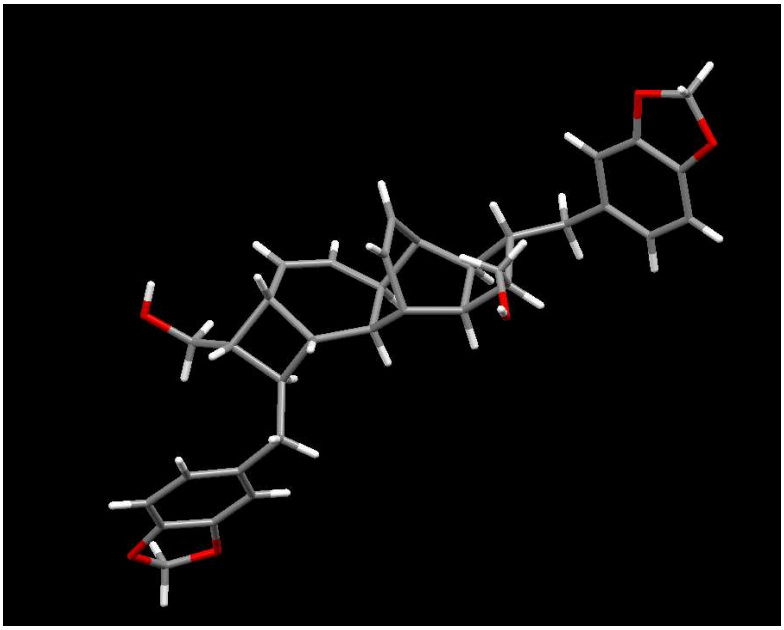


Figure 4-3. X-ray crystal structure of Diol **4-25**

4.2.2.2 Structural Assignment of dimer **4-27**

In addition, the structure of exo diol **4-27** was firmly established as the exo RCDA product by a combination of COSY, NOESY, HMQC, and HMBC nmr experiments (see Tables 4-5, 4-6, 4-7, 4-8). The key correlations in the COSY and NOESY are depicted in Figure 4-4.

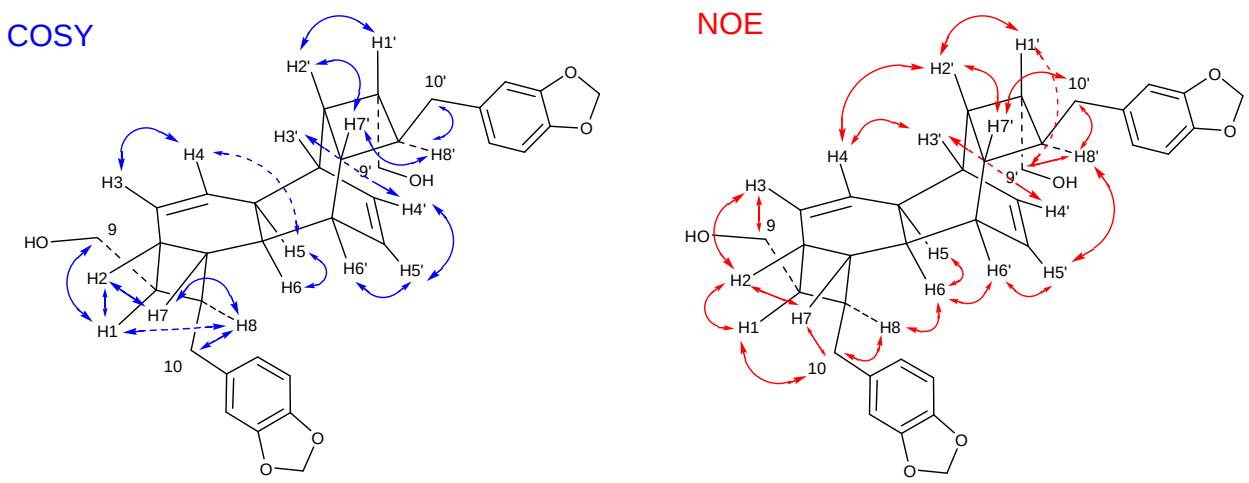


Figure 4-4. COSY and NOE correlations in diol **4-27**

On the basis of the chemical shifts of the two more upfield olefinic signals (5.81 and 5.63, in the same range as H3 and H4 in the kingianins), we assigned the dienophilic western substructure of the pentacyclic core as being identical to that in diols **4-23** and **4-25**. This assumption was well supported by the crosspeaks of H3 (5.81) and H9 (3.28 and 3.46) in the NOESY. Also, the crosspeaks of H3/H2, H2/H1, H1/H10, H10/H7, H10/H8, H8/H6, and H6/H5 in the NOESY and the crosspeaks of H3/H4, H4/H5, H5/H6, H2/H1, H2/H7, H1/H8, H1/H9, H7/H8, and H8/H10 in the COSY confirmed that the connectivity and relative stereochemistry of the fused [4.2.0]-bicyclooctene ring system in the western sector were the same as those in diols **4-23** and **4-25**.

With the H9 and H2 protons identified, we could assign the 2H signal at 3.32/ 3.50 ppm to the H9’ protons and the 1H signal at 2.60 ppm to the H2’ proton. The crosspeaks of H9’/H1’, H1’/H2’, H2’/H7’, H7’/H10’, H10’/H8’, H3’/H4’, H5’/H6’, H5’/H8’ and H8’/H9’ in the NOESY and the crosspeaks of H1’/H2’, H2’/H7’, H7’/H8’, H8’/H10’, H4’/H5’, H4’/H3’, and H5’/H6’ in the COSY confirmed the connectivity and relative stereochemistry of the fused [4.2.0]-bicyclooctene ring system in the eastern sector.

Next we needed to determine the stereochemistry of the connection of the eastern and western substructures. The key crosspeaks of H4/H2’ in the NOESY showed that the stereochemical relationship of the eastern and western sectors corresponds to that of an exo Diels Alder product (Figure 4-4).

The exo Diels Alder structure was further supported by HMQC and HMBC assignments. Each carbon in the core pentacyclic structure was assigned to the attached protons by the crosspeaks in the HMQC. Indeed, the examination of the connectivity by HMBC analysis (the crosspeaks of selected carbon atoms and the corresponding protons) are consistent with the suggested structure in the COSY and NOE pictures. The full assignment for the pentacyclic structure of the diol **4-27** is summarized in Table 4-9.

Table 4-5. Crosspeaks in COSY Spectrum of Diol **4-27**

Proton number (ppm)	
H1 (2.14) ↔ H2 (2.76), H8 (1.83), H9 (3.28/ 3.46)	H2 (2.76) ↔ H7 (1.92)
H3 (5.81) ↔ H4 (5.63)	H4 (5.63) ↔ H5 (2.10)
H5 (2.10) ↔ H6 (1.29)	H7 (1.92) ↔ H8 (1.83)
H8 (1.83) ↔ H10 (2.49/ 2.68)	H1’ (2.21) ↔ H2’ (2.60), H9’ (3.32/ 3.50)
H2’ (2.60) ↔ H7’ (2.12)	H3’ (2.44) ↔ H4’ (6.41)
H4’ (6.41) ↔ H5’ (6.24)	H5’ (6.24) ↔ H6’ (2.24)
H7’ (2.28) ↔ H8’ (1.89)	H8’ (1.89) ↔ H10’ (2.47/ 2.65)

Table 4-6. Crosspeaks in NOESY Spectrum of Diol **4-27**

proton number (ppm)	
H1 (2.14) ↔ H2 (2.76), H10 (2.49/ 2.65)	H2 (2.71) ↔ H3 (5.81), H7 (1.92)
H3 (5.83) ↔ H9 (3.28/ 3.46)	H4 (5.66) ↔ H2’ (2.60), H3’ (2.44)
H5 (2.10) ↔ H6 (1.29)	H6 (1.54) ↔ H8 (1.83), H6’ (2.24)
H7 (1.92) ↔ H10 (2.49/ 2.65)	H8 (1.83) ↔ H10 (2.49/ 2.65)
H1’ (2.21) ↔ H2’ (2.60), H9’ (3.32/ 3.50)	H2’ (6.58) ↔ H7’ (2.12)
H3’ (2.44) ↔ H4’ (6.41)	H5’ (6.24) ↔ H6’ (2.24), H8’ (1.89)
H7’ (2.28) ↔ H10’ (2.47/ 2.65)	H8’ (1.89) ↔ H9’ (3.32/ 3.50), H10’ (2.47/ 2.65)

Table 4-7. Crosspeaks in the HMQC Spectrum of Diol **4-27**

Carbon number (ppm)	Corresponding proton number (ppm)	Carbon number (ppm)	Corresponding proton number (ppm)

C1 (44.2)	H1 (2.14)	C1’ (44.8)	H1’ (2.21)
C2 (33.2)	H2 (2.76)	C2’ (32.0)	H2’ (2.60)
C3 (126.0)	H3 (5.81)	C3’ (36.1)	H3’ (2.44)
C4 (131.5)	H4 (5.63)	C4’ (135.5)	H4’ (6.41)
C5 (32.9)	H5 (2.10)	C5’ (135.0)	H5’ (6.24)
C6 (33.7)	H6 (1.29)	C6’ (42.0)	H6’ (2.24)
C7 (40.3)	H7 (1.92)	C7’ (37.6)	H7’ (2.12)
C8 (45.6)	H8 (1.83)	C8’ (43.1)	H8’ (1.89)
C9 (62.8)	H9 (3.28/ 3.46)	C9’ (62.9)	H9’ (3.32/ 3.50)
C10 (40.5)	H10 (2.49/ 2.68)	C10’ (42.4)	H10’ (2.47/ 2.65)
C17 (100.8)	H17 (5.91)	C17’ (100.8)	H17’ (5.92)

Table 4-8. Crosspeaks in the HMBC Spectrum of Diol **4-27**

Carbon (number, ppm)	Corresponding protons (number, ppm)]
C1 (44.2)	H7 (1.92)
C2 (33.2)	H4 (5.63), H7 (1.92), H9 (3.28/ 3.46)
C3 (126.0)	H1 (2.14), H7 (1.92)
C5 (32.9)	H3 (5.81)
C7 (40.3)	H10 (2.49/ 2.68)
C8 (45.6)	H6 (1.29), H7 (1.92), H9’ (3.32/ 3.50)
C9 (62.8)	H1 (2.14), H8 (1.83)
C10 (40.5)	H7 (1.92)
C1’ (44.8)	H10’ (2.47/ 2.65)
C2’ (32.0)	H6 (1.29), H9’ (3.32/ 3.50)
C3’ (36.1)	H4’ (6.41), H5’ (6.24)
C6’ (42.0)	H4’ (6.41), H5’ (6.24)
C7’ (37.6)	H6 (1.29), H10’ (2.47/ 2.65)
C8’ (43.1)	H10’ (2.47/ 2.65)
C9’ (62.9)	H1’ (2.21), H8’ (1.89)
C10’ (42.2)	H1’ (2.21)

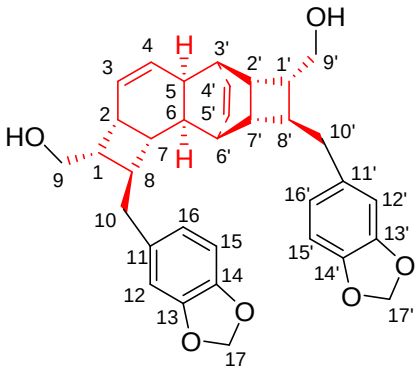


Table 4-9. ^{1}H and ^{13}C-NMR for the pentacylic core of diol **4-27** in $CDCl_3$

Number	^{1}H, δ (ppm), *J* (Hertz)	^{13}C, δ (ppm)
1	2.14 (m, 1 H)	44.2
2	2.76 (br t, *J* = 6.9 Hz, 1 H)	33.2
3	5.81 (br d, *J* = 10.4 Hz, 1 H)	126.0
4	5.63 (br d, *J* = 10.4 Hz, 1 H)	131.5
5	2.10 (m, 1 H)	32.9
6	1.29 (dd, *J* = 10.9 and 2.4 Hz, 1 H)	33.7
7	1.92 (m, 1 H)	40.3
8	1.83 (m, 1 H)	45.6
9	3.28 (dd, *J* = 10.9 and 5.7 Hz, 1H), 3.46 (dd, *J* = 10.9 and 8.8 Hz, 1 H)	62.8
10	2.49 (m, 1 H), 2.68 (br d, *J* = 6.6 Hz, 1 H)	40.5
1’	2.21 (dd, *J* = 9.6 and 8.0 Hz, 1 H)	44.8
2’	2.60 (br td, *J* = 9.5 and 2.7 Hz, 1 H)	32.0
3’	2.44 (m, 1 H)	36.1
4’	6.41 (t, *J* = 7.3 Hz, 1 H)	135.5
5’	6.24 (t, *J* = 7.3 Hz, 1 H)	135.0
6’	2.24 (m, 1 H)	42.0
7’	2.12 (m, 1 H)	37.6
8’	1.89 (m, 1 H)	43.1
9’	3.32 (dd, *J* = 10.6 and 7.7 Hz, 1 H) 3.50 (dd, *J* = 10.6 and 7.9 Hz, 1 H)	62.9
10’	2.47 (m, 1 H), 2.65 (br d, *J* = 6.5, 1 H)	42.4

4.2.3 Synthesis of kingianin H

Of the pseudosymmetric kingianins (i.e. those that are constructed from two identical or enantiomeric monomers, A-F, H, and J), kingianin H is reported to be the most active in the Bcl-xL inhibition assay.[1a] We considered therefore the synthesis of kingianin H from diol **4-10** which was in hand.

Conversion of diol **4-10** (previously converted to kingianin A) to kingianin H requires lengthening of the two hydroxymethyl sidechains. Short sequences that effect 3-carbon homologations are relatively rare. An attractive plan was the transition metal-catalyzed conversion of primary iodides to 3-carbon homologated esters by the Ni(0)-catalyzed "formal conjugate addition" described by Manchand et al.[112,113] Accordingly, we prepared diiodide **4-31** and applied the chain-lengthening procedure, obtaining diester **4-32** in 70% yield. Hydrolysis then provided kingianin H (**4-1H**, Scheme 4-7).

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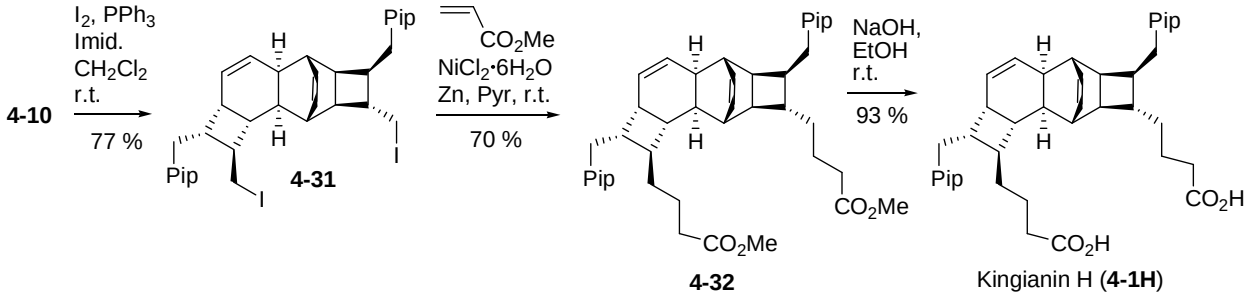
[112] (a) Nickel-Mediated Conjugate Addition. Elaboration of Calcitriol from Ergocalciferol. Manchand, P. S.; Yiannikouros, G. P.; Belica, P. S.; Madan, P. *J. Org. Chem*. **1995**, *60*, 6574-81. (b) Process Control Limits from a Laboratory Study on the Ni(0)-Mediated Coupling of Ethyl Acrylate with a C-22 Steroidal Iodide: A Case Study on the Role of Experimental Design in Highly Developed Processes. Van Arnum, S. D.; Moffet, H.; Carpenter, B. K. *Org. Process Res. Dev*. **2004**, *8*, 769-776.

[113] (a) For a related reaction see Cobalt-Catalyzed Reductive Coupling of Saturated Alkyl Halides with Activated Alkenes. Shukla, P.; Hsu, Y.-C.; Cheng, C.-H. *J. Org. Chem*. **2006**, *71*, 655-658. (b) For related transformations and a discussion of mechanism, see Nickel-Catalyzed Reductive Conjugate Addition to Enones via Allylnickel Intermediates. Shrestha, R.; Dorn, S. C. M.; Weix, D. J. *J. Am. Chem. Soc*. **2013**, *135*, 751-762 and Reductive Conjugate Addition of Haloalkanes to Enones To Form Silyl Enol Ethers. Shrestha, R.; Weix, D. J. *Org. Lett*. **2011**, *13*, 2766-2769.



Scheme 4-7. Synthesis of Kingianin H

The ^{1}H and ^{13}C nmr spectra of synthetic kingianin H are compared with those reported for the natural product in Tables 4-10 and 4-11. The chemical shifts as well as coupling constants are consistent with the authentic data.

Table 4-10. ^{1}H-NMR for Kingianin H in $CDCl_3$, δ (ppm), mult, (*J* in Hz)[8]

No.	Authentic, δ_c	Synthetic, δ_c	No.	Authentic, δ_c	Synthetic, δ_c
1	2.00	2.02 m	1’	1.64	1.65 m
2	2.47	2.48 m	2’	2.12	2.12 m
3	5.58 br d (10.4)	5.57 br d (10.5)	3’	2.39	2.41 m
4	5.67 br d (10.4)	5.66 br d (10.5)	4’	6.07 dd (7.1, 7.6)	6.07 t (7.3)
5	2.21	2.23 m	5’	6.23 t (7.1)	6.21 t (7.3)
6	1.68	1.69 br d (10.9)	6’	2.52	2.52 m
7	1.83	1.82 t (9.1)	7’	2.46	2.48 m
8	1.59	1.60 m	8’	2.19	2.28 m
9	2.57/2.43	2.57/2.46 m	9’	2.63/2.49	2.64/2.50 m
10	-	-	10’	-	-
11	6.62	6.63 d (1.2)	11’	6.60	6.61 d (1.2)
12	-	-	12’	-	-
13	-	-	13’	-	-
14	6.67	6.68 d (7.9)	14’	6.68	6.69 d (7.9)
15	6.56	6.58 dd (8.1, 1.3)	15’	6.55	6.56 dd (8.0, 1.3)
16	5.89[a]	5.89[a] s	16’	5.89[a]	5.90[a] s
17	1.26	1.26 m	17’	1.17/1.22 m	1.18/1.24 m
18	1.57/1.28	1.58/1.28 m	18’	1.36/1.49	1.37/1.50 m
19	2.20	2.21 m	19’	2.24	2.25 m
20	-	-	20’	-	-
21	-	-	21’	-	-

The data for the authentic sample are extracted from the report of the structure assignment.[1a]

[a] Values are interchangeable

Table 4-11. ^{13}C-NMR for Kingianin H in $CDCl_3$, δ (ppm)[9]

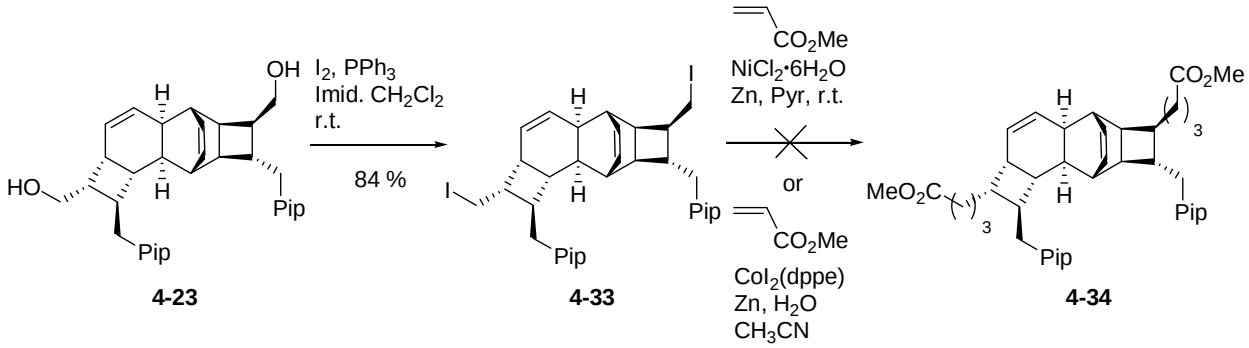
Number	Authentic	Synthetic	Number	Authentic	Synthetic
1	43.3	43.2	1’	42.0	41.8
2	32.7	32.7	2’	44.4	44.3
3	125.4	125.4	3’	43.6	43.4
4	132.0	132.0	4’	132.2	132.2
5	38.3	38.2	5’	134.9	134.9
6	39.6	39.2	6’	38.7	38.6
7	42.0	42.3	7’	39.7	39.4
8	45.4	45.2	8’	43.9	43.9
9	36.3	36.2	9’	35.5	35.5
10	135.4	135.4	10’	135.8	135.8
11	108.8	108.78[a]	11’	108.8	108.83[a]
12	147.5	147.40[b]	12’	147.5	147.44[b]
13	145.4	145.32[c]	13’	145.4	145.34[c]
14	108.1	108.0	14’	108.1	108.0
15	121.0	120.9[d]	15’	121.0	121.0[d]
16	100.7	100.6	16’	100.7	100.6
17	34.6	34.2	17’	36.0	36.0
18	22.7	22.5	18’	22.8	22.7
19	35.0	34.5	19’	34.7	34.4
20	ND	180.0[e]	20’	ND	180.2[e]
21	-	-	21’	-	-

The data for the authentic sample are extracted from the report of the structure assignment.[1a]
[a, b, c, d, e] Values are interchangeable

4.2.4 Synthesis of kingianin J

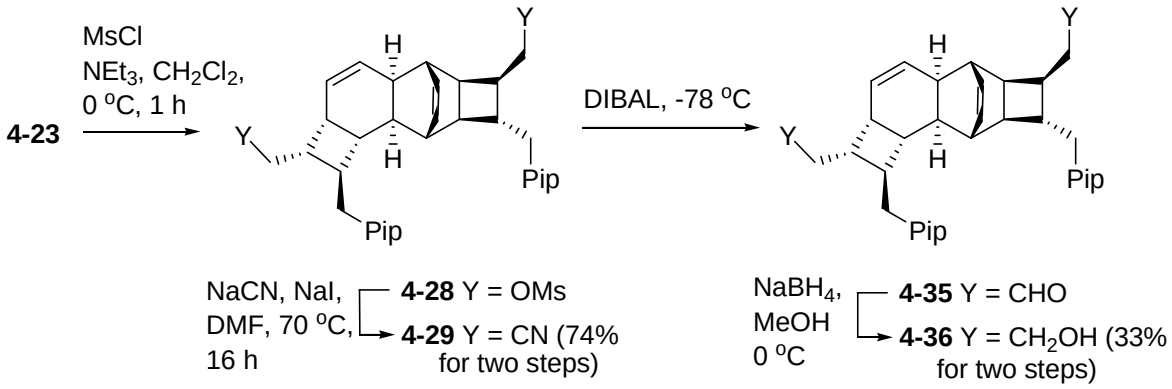
Of the pseudosymmetric kingianins (i.e. those that are constructed from two identical or enantiomeric monomers, A-F, H, and J), kingianin J is reported to be the second most active in the Bcl-xL inhibition assay. Diol **4-23** is a potential precursor for the synthesis of kingianin J.

By analogy to the successful synthesis of kingianin H, we initially planned a 3-carbon homologation of the diiodide **4-33** to afford diester **4-34**. However, the Ni(0)-catalyzed reaction produced intractable mixture. Furthermore, when the Co(0)-mediated homologation[12a] was attempted, we obtained a complicated mixture. In both cases, the ^{1}H nmr spectrum showed that the olefinic proton of the western cyclohexene had disappeared, indicating the participation of that olefin in the reaction (Scheme 4-8).



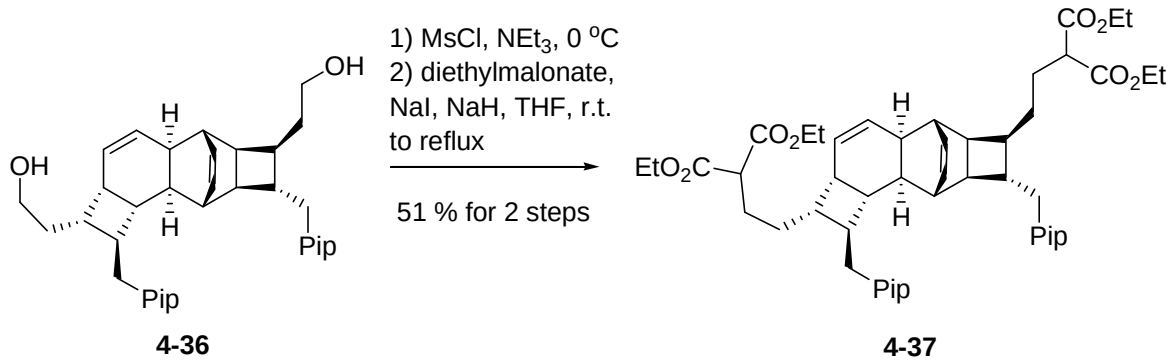
Scheme 4-8. 3-Carbon homologations of the diiodide **4-33**

This result led us to use a conventional homologation method. First, the one carbon homologated alcohol **4-35** was obtained by the four step sequence involving mesylation, cyanide displacement, and then partial DIBAL reduction of the dinitrile **4-29** followed by $NaBH_4$ mediated reduction of the aldehyde **4-35** (Scheme 4-9).



Scheme 4-9. Synthesis of one carbon homologated alcohol **4-36**

The diol **4-36** was then converted to dimalonate **4-37** (Scheme 4-10).



Scheme 4-10. Synthesis of dimalonate **4-36**

The completion of the synthesis of kingianin J from this dimalonate **4-37** is underway.

4.3 Conclusion

In summary, the intermolecular RCDA procedure, applied to the individual pre-kingianin structures **4-2** and **4-19** gave key intermediates for kingianin synthesis. As expected,[114] the intermolecular RCDA reaction has a preference for an endo transition state in the RCDA reaction but this is not overwhelming. In both cases, the addition of the (+)-enantiomer to the (–)-

[114] Selectivity profile of the cation radical Diels-Alder reaction. Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1982**, *104*, 2665-2667.

enantiomer gives an exo Diels Alder adduct as a minor product. Like the intramolecular case examined previously, both intermolecular RCDA reactions (Schemes 4-2 and 4-5) demonstrated additional regio- and stereoselective effects consistent with the structures of the isolated natural products. Thus, the C-5,6 double bond (proximal to the exo substituent on the cyclobutane ring) acts as the dienophile. It is attacked from the less hindered face by the diene component which reacts from its less hindered face.

Three of the major RCDA products were elaborated to three additional members of the kingianin family. The total syntheses of kingianins D, F, and H entailed 10, 13, and 9 steps respectively from commercially available materials. None of the schemes required preparative HPLC separation of intermediates or products. These short syntheses appear to be scalable.

4.4 Experimental Section

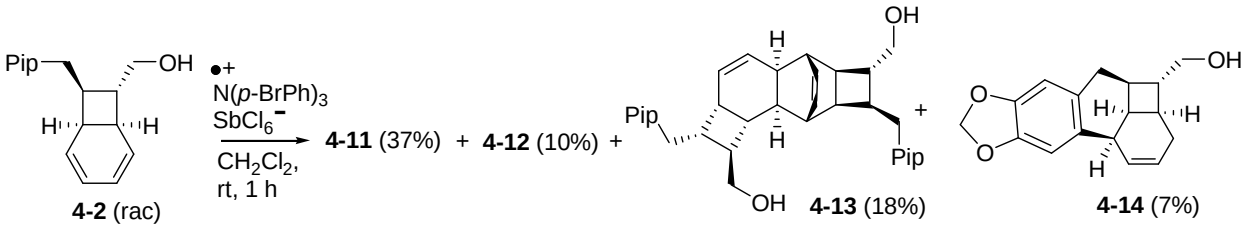
General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. HPLC grade hexane, EtOAc, CH_2Cl_2 and CH_3OH were used in chromatography. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl under argon. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol or $KMnO_4$ aq. solution and then heating. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å, 230-400 mesh, surface area 500-600 m^2/g, bulk density 0.4 g/mL, pH range 6.5-7.5).

Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with Bruker Avance III-400 (400 MHz for ^1H and 100 MHz for ^{13}C) and

Bruker Avance III-500 spectrometer (500 MHz for ^{1}H and 126 MHz for ^{13}C). Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.260 ppm for chloroform-*d* and to the singlets at 8.74, 7.58, 7.22 ppm for pyridine-*d*5. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-*d* set at 77.000 ppm and the triplets for pyridine-*d*5 set at 150.35, 135.91, 123.87 ppm. The COSY, NOESY, HMQC, and HMBC spectra were recorded with Bruker Avance III-500 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer (ESI) and a Micromass 70-VSE spectrometer (EI) by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

Experimental Procedure/ Characterization

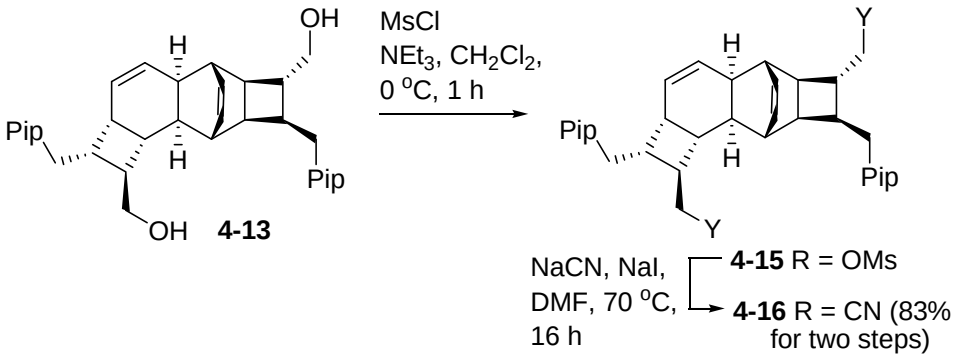


Diol 4-13 and 4-14 To a stirred solution of the endo bicyclooctadienol **4-2** (100 mg, 0.37 mmol) in dry CH_2Cl_2 (2 mL) was added $SbCl_6 \cdot N(p\text{-}BrPh)_3$ (15.1 mg, 0.019 mmol) at room temperature. The resulting deep blue solution was stirred for 1 h and quenched with wet NEt_3. After concentration of the reaction mixture, the residue was subjected to preparative TLC (hexane: Et_2O: CH_2Cl_2: MeOH = 1: 1: 1: 0.02). Diols **4-11** (37 mg, 37 %), **4-12** (10 mg, 10 %), **4-13** (18 mg, 18 %), and alcohol **4-14** (7 mg, 7 %) were isolated.

Diol **4-13** Rf value: 0.5 (Hex:EtOAc = 1:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (d, *J* = 8.9 Hz, 1 H), 1.81 (m, 1 H), 1.95 (m, 1 H), 2.15 (m, 1 H), 2.22-2.36 (m, 3 H), 2.41-2.69 (m, 9 H), 3.30-3.40 (m, 4 H), 5.61 (br d, *J* = 10.3 Hz, 1 H), 5.68 (ddd, *J* = 10.4, 3.7 and 1.9 Hz, 1 H), 5.90 (s, 4 H), 6.11 (t, *J* = 7.3 Hz, 1 H), 6.32 (t, *J* = 7.3 Hz, 1 H), 6.55-6.71 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 35.5, 36.2, 37.2, 38.1, 39.2, 39.6, 40.2, 40.3, 40.6, 41.2, 41.4, 44.7, 48.2, 65.0, 67.0, 100.7229, 100.7431, 108.2 (two), 108.8082, 108.8443, 120.9838, 121.0175, 124.8, 132.2, 133.1, 134.4, 135.0, 135.5, 145.5, 145.6, 147.5673, 147.6179.; IR (neat) νmax 1039, 1246, 1441,

1448, 1502, 2915, 3373 cm^{-1}. HRMS[ES+] calcd for $C_{34}H_{36}O_6Na$ $[M + Na]^+$ 563.2410, found 563.2417.

Alcohol **4-14** Rf value: 0.7 (Hex:EtOAc = 1:1) ^1H NMR (500 MHz, $CDCl_3$) δ 1.76 (m, 1 H), 1.93 (ddd, *J* = 16.7, 6.6 and 1.7 Hz, 1 H), 2.13 (m, 1 H), 2.24 (m, 1 H), 2.43 (dd, *J* = 14.2 and 9.7 Hz, 1 H), 2.50 (m, 1 H), 2.61 (dd, *J* = 17.7 and 9.7 Hz, 1 H), 2.71 (dd, *J* = 14.4 and 8.0 Hz, 1 H), 3.26 (m, 1 H), 3.72 (d, *J* = 7.0 Hz, 2 H), 5.67 (dt, *J* = 9.9 and 2.5 Hz, 1 H), 5.89 (s, 2 H), 5.97 (m, 1 H), 6.60 (s, 1 H), 6.69 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.0, 31.6, 32.0, 32.6, 33.2, 37.1, 49.4, 66.9, 100.5, 108.3, 108.5, 128.5, 131.6, 131.7, 135.1, 145.5, 145.7.; IR (neat) νmax 1039, 1233, 1481, 1501, 2921, 3356 cm^{-1}. HRMS[EI+] calcd for $C_{17}H_{18}O_3$ $[M]^+$ 270.1256, found 270.1249.



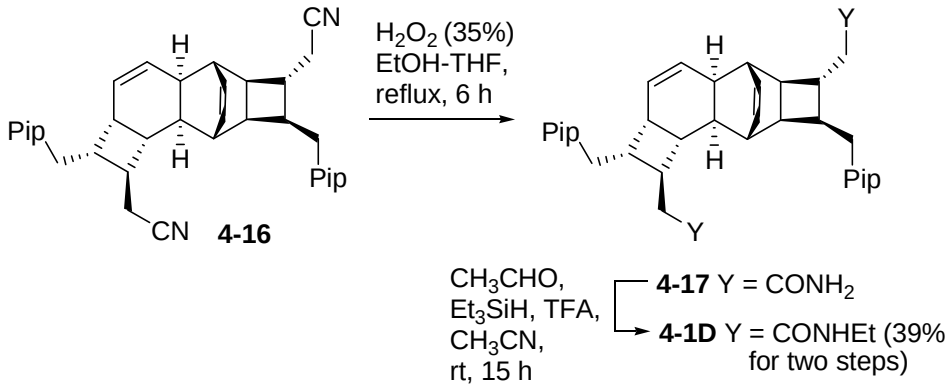
Dinitrile 4-16 Step 1: To a stirred solution of the diol **4-13** (18.0 mg, 33.3 μmol) in CH_2Cl_2 (1 mL) was added triethylamine (27.9 μL, 200 μmol) and methanesulfonyl chloride (7.70 μL, 99.8 μmol) at 0 °C under Ar. After 30 min, the reaction mixture was diluted with diethyl ether (20 mL) and the resulting mixture was washed with water, 5 % HCl, and sat. $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$, and concentrated. The crude product was directly used for the next step.

Dimesylate **4-15** Rf value: 0.6 (Hex:EtOAc = 1:1) ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, *J* = 9.1 Hz, 1 H), 1.97 (m, 1 H), 2.04-2.60 (m, 15 H), 2.85 (s, 3 H), 2.87 (s, 3 H), 3.79-3.94 (m, 4 H), 5.60 (br d, *J* = 10.3 Hz, 1 H), 5.79 (ddd, *J* = 10.3, 3.8 and 1.9 Hz, 1 H), 5.9012 (s, 2 H), 5.9023 (s, 2 H), 6.11 (t, *J* = 7.3 Hz, 1 H), 6.34 (t, *J* = 7.3 Hz, 1 H), 6.53-6.70 (m, 6 H).

Step 2: To a stirred solution of the dimesylate **4-15** in DMF (1 mL) was added sodium iodide (2.5 mg, 17 μmol) and sodium cyanide (13.0 mg, 270 μmol) at r.t. Then, the solution was heated to

70 °C and stirred for 12 h. Then it was diluted with ethyl acetate (20 mL) and washed with water (10 mL X 3). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (Hex:EtOAc = 4:1) to afford dinitrile **4-16** (15.4 mg, 83 % for two steps, colorless liquid).

Dinitrile **4-16** Rf value: 0.25 (Hex:EtOAc = 5:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (d, *J* = 9.0 Hz, 1 H), 1.84 (m, 1 H), 1.95-2.07 (m, 5 H), 2.12-2.21 (m, 2 H), 2.31-2.39 (m, 3 H), 2.44 (dd, *J* = 14.0 and 8.5 Hz, 1 H), 2.50-2.69 (m, 7 H), 5.61 (br d, *J* = 10.3 Hz, 1 H), 5.79 (ddd, *J* = 10.3, 3.9 and 2.0 Hz, 1 H), 5.91 (s, 4 H), 6.12 (t, *J* = 7.3 Hz, 1 H), 6.36 (t, *J* = 7.3 Hz, 1 H), 6.52-6.71 (m, 6 H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.7, 22.8, 33.6, 34.9, 35.5, 36.7, 38.0, 38.9, 39.6, 40.3, 40.9013, 40.9611, 41.0403, 41.5, 42.4, 43.6, 100.7848, 100.8054, 108.3 (two), 108.6, 108.7, 118.5, 119.0, 120.9515, 120.9952, 124.3, 132.1, 133.3, 133.8, 134.2, 134.4, 145.7, 145.8, 147.6, 147.7.; IR (neat) νmax 1246, 1442, 1488, 1502, 2245, 2917 cm^{-1}. HRMS[ES+] calcd for $C_{36}H_{35}N_2O_4$ $[M + H]^+$ 559.2597, found 559.2609.



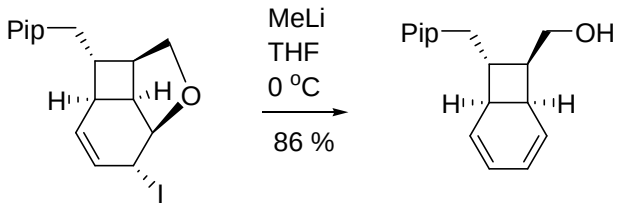
Kingianin D (1D)

Step 1: To a stirred solution of dinitrile **11** (13.0 mg, 23.2 μmol) in EtOH-THF (2.5 mL/0.5 mL) was added aq. NaOH sol'n (0.05 mL, 7 M) and dropwise H_2O_2 sol'n (0.6 mL, 35 % in water) at 0 °C. Then, the mixture was warmed to room temperature, stirred for 30 min, and heated to reflux. After stirring for an additional 4 h, the reaction mixture was diluted with brine and extracted with CH_2Cl_2 (15 mL X 5). The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used for the next step.

Step 2: The residue from step 1 was placed in a 3 mL-vial and flushed with Ar for 10 min. To the stirred clear solution of the crude product in CH_3CN (1.5 mL) was added acetaldehyde (7.7 μL,

139 μmol), triethylsilane (22.2 μL, 139 μmol), and trifluoroacetic acid (9.8 μL, 128 μmol) in that order at r.t. Then, the vial was capped and sealed with parafilm. After stirring for 15 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ sol'n and brine, dried over Na_2SO_4, and concentrated. The residue was subjected to preparative TLC (hexane: EtOAc = 1:2) to afford Kingianin D (5.9 mg, 39 %, white solid, mp = 86-91 ^oC, lit[1a]; mp not reported).

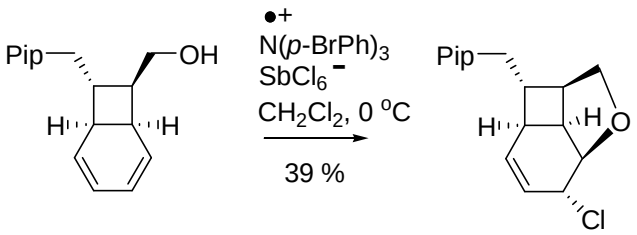
Rf value: 0.2 (hexane: EtOAc = 1:2). For ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$), see Tables 4-1 and 4-2. IR (neat) νmax 1040, 1246, 1442, 1488, 1503, 1555, 1639, 2924, 3287 cm^{-1}.



4-18 **4-19**

Exo alcohol 4-19 To a stirred solution of iodo ether **4-18** (92.0 mg, 0.232 mmol) in THF (5 mL) was added MeLi (1.6 M in THF, 0.24 mL, 1.2 mmol) at 0 ^oC under Ar. After 10 min, the reaction mixture was quenched with sat. NH_4Cl sol'n and then extracted with diethyl ether (10 mL X 3). The combined organic solution was washed with sat. $Na_2S_2O_3$ solution, brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 5:1) to afford the exo alcohol **4-19** (66 mg, 86 %) as colorless oil.

Rf value: 0.3 (Hex:EtOAc = 4:1) ^1H NMR (500 MHz, $CDCl_3$) δ 2.55-2.75 (m, 5 H), 3.23 (m, 1 H), 3.57 (dd, *J* = 10.8 and 5.7 Hz, 1 H), 3.71 (dd, *J* = 10.8 and 8.4 Hz, 1 H), 5.44 (dd, *J* = 9.6 and 5.4 Hz, 1 H), 5.59 (dd, *J* = 9.8 and 3.8 Hz, 1 H), 5.62 (dd, *J* = 9.7 and 5.4 Hz, 1 H), 5.85 (ddd, *J* = 9.8, 5.5 and 1.6 Hz, 1 H), 5.92 (s, 2 H), 6.61 (dd, *J* = 7.9 and 1.6 Hz, 1H), 6.65 (d, *J* = 1.6 Hz, 1 H), 6.72 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.5, 36.1, 41.6, 50.4, 51.7, 63.3, 100.8, 108.2, 109.1, 121.4, 121.5, 124.4, 125.3, 127.2, 134.3, 145.8, 147.6.; IR (neat) νmax 1040, 1246, 1442, 1488, 1502, 2916, 3356 cm^{-1}. HRMS[ES+] calcd for $C_{17}H_{18}O_3Cl$ $[M + Na]^+$ 293.1154, found 293.1150.

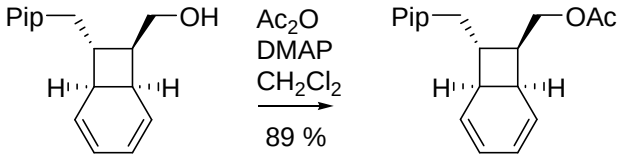


4-19 **4-20**

Chloro ether 4-20

To a stirred solution of alcohol **4-19** (7.0 mg, 25.9 μmol) in CH_2Cl_2 (1.0 mL) was added $SbCl_6 \cdot N(p\text{-}BrPh)_3$ (1.1 mg, 1.3 μmol) at room temperature. After 1 min, the reaction mixture became yellow in color. To ensure complete conversion, more catalyst (29.6 mg, 36.3 μmol) was added in portions until a blue color was maintained. The deep blue solution was stirred for 1 h and quenched with wet NEt_3. After concentration of the reaction mixture, the residue was subjected to column chromatography (Hex:EtOAc = 20:1 to 10:1) to afford chloro ether **4-20** (3.1 mg, 39 %, colorless oil).

Rf value: 0.8 (Hex:EtOAc = 5:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (m, 1 H), 2.54 (m, 1 H), 2.62 (dt, *J* = 6.4 and 3.8 Hz, 1 H), 2.74 (d, *J* = 6.6 Hz, 2 H), 3.10 (m, 1 H), 3.53 (dd, *J* = 7.4 and 3.7 Hz, 1 H), 3.68 (d, *J* = 7.4 Hz, 1 H), 4.09 (dd, *J* = 4.8 and 1.7 Hz, 1 H), 4.62 (dd, *J* = 4.6 and 1.8 Hz, 1H), 5.62 (dd, *J* = 8.0 and 3.4 Hz, 1 H), 5.82 (m, 1 H), 5.92 (s, 2 H), 6.60 (dd, *J* = 6.3 and 1.2 Hz, 1H), 6.63 (d, *J* = 1.2 Hz, 1 H), 6.72 (d, *J* = 6.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 32.9, 41.4, 41.8, 47.5, 50.3, 73.1, 78.9, 100.8, 108.2, 108.9, 121.4, 122.3, 131.9, 133.4, 145.9, 147.6. IR (neat) νmax 1248, 1440, 1489, 1504, 2920 cm^{-1}. HRMS[EI+] calcd for $C_{17}H_{17}O_3Cl$ $[M]^+$ 304.0866, found 304.0869.

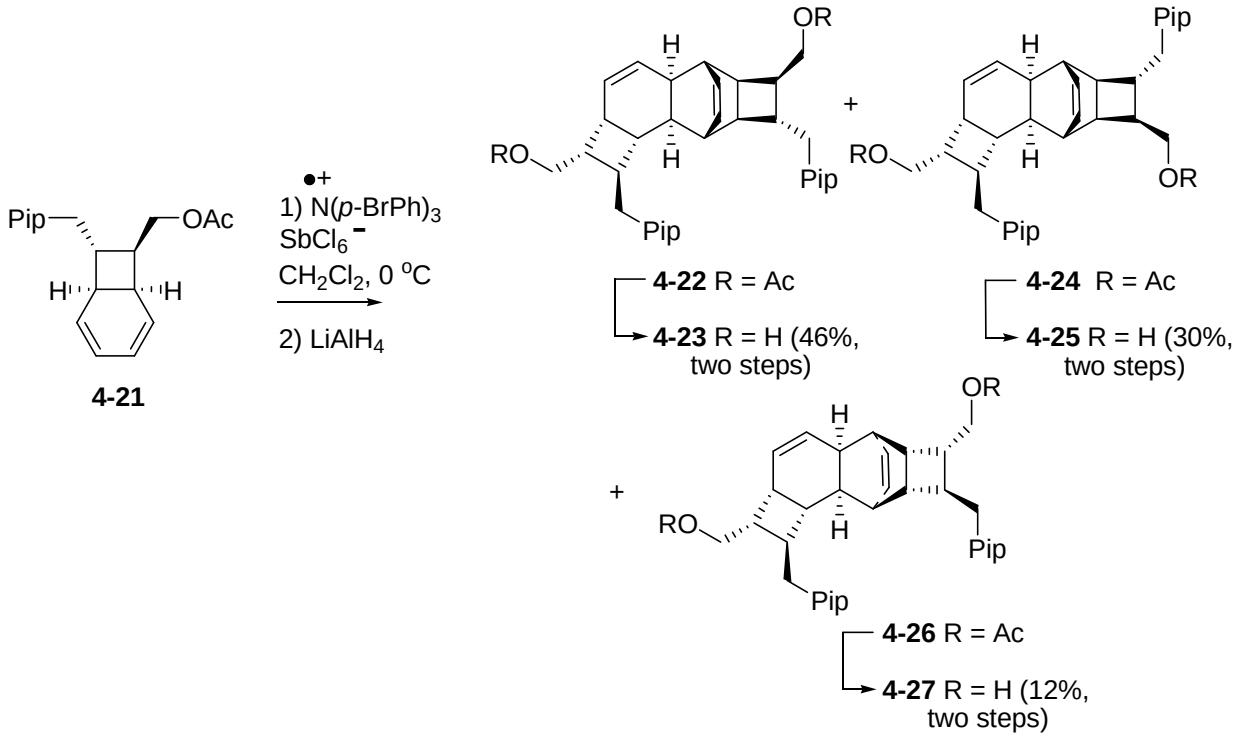


4-19 **4-21**

Aetate 4-21 To a stirred solution of exo alcohol **4-19** (114 mg, 0.422 mmol) and DMAP (10.3 mg, 0.0843 mmol) in CH_2Cl_2 (2 mL) was added acetic anhydride (59.7 μL, 0.632 mmol) at room temperature. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with sat.

$NaHCO_3$ sol'n, and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 5:1) to afford the acetate **4-21** (117 mg, 89 %) as a colorless oil.

Rf value: 0.6 (Hex:EtOAc = 5:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3 H), 2.56-2.80 (m, 5 H), 3.23 (m, 1 H), 4.04 (dd, *J* = 11.0 and 6.4 Hz, 1 H), 4.13 (dd, *J* = 11.0 and 9.1 Hz, 1 H), 5.38 (dd, *J* = 9.6 and 5.4 Hz), 5.50 (dd, *J* = 9.9 and 3.7 Hz, 1 H), 5.61 (dd, *J* = 9.7 and 5.5 Hz, 1 H), 5.84 (ddd, *J* = 9.8, 5.5 and 1.6 Hz, 1 H), 5.92 (s, 2 H), 6.60 (dd, *J* = 7.9 and 1.6 Hz, 1H), 6.64 (d, *J* = 1.6 Hz), 6.71 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0, 32.7, 36.2, 41.4, 47.7, 50.4, 64.7, 100.8, 108.1, 109.1, 121.4, 121.6, 124.6, 124.8, 126.8, 134.1, 145.8, 147.5, 171.0.; IR (neat) νmax 1239, 1364, 1442, 1489, 1502, 1738, 2917 cm^{-1}. HRMS[ES+] calcd for $C_{19}H_{20}O_4Na$ $[M + Na]^+$ 335.1259, found 335.1253.



Diols 4-23, 4-25, and 4-27

Step 1: To a stirred solution of acetates **4-21** (115 mg, 0.369 mmol) in CH_2Cl_2 (2 mL) was added $SbCl_6 \cdot N(p\text{-}BrPh)_3$ (9.0 mg, 0.011 mmol) at 0 °C. The resulting deep blue solution was stirred for 1 h and quenched with wet NEt_3. After concentration of the reaction mixture, the residue was

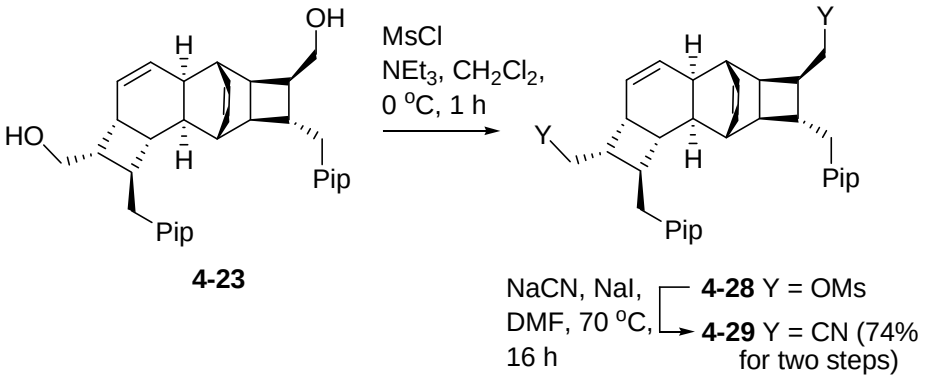
subjected to column chromatography. The fractions containing an inseparable mixture of diacetates were combined and concentrated. The crude product mixture was directly used for the next step.

Step 2: To a stirred solution of the diacetates in dry THF (3 mL) was added lithium aluminum hydride (56 mg, 1.5 mmol) at 0 ^{o}C under Ar. After 1 h, the reaction mixture was quenched with water and with sat. NaOH solution. After stirring for an additional 2 h, the mixture was extracted with diethyl ether (10 X 5 mL). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to preparative TLC (hexane: Et_2O: CH_2Cl_2: MeOH = 1: 1: 1: 0.04) to afford the diols **4-23** (52.9 mg, 46 %, colorless oil), **4-25** (34.5 mg, 30 %, white solid, mp = 179-181 ^{o}C), **4-27** (13.8 mg, 12 %, colorless oil).

Diol **4-23** Rf value: 0.4 (hexane: Et_2O: CH_2Cl_2: MeOH = 1: 1: 1: 0.04) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, *J* = 8.9 Hz, 1 H), 1.79 (m, 1 H), 1.87-1.94 (m, 2 H), 2.00 (m, 1 H), 2.12-2.28 (m, 4 H), 2.44-2.70 (m, 7 H), 3.24 (dd, *J* = 10.9 and 5.6 Hz, 1 H), 3.31 (dd, *J* = 10.6 and 7.3 Hz, 1 H), 3.40 (dd, *J* = 10.9 and 8.3 Hz, 1 H), 3.52 (dd, *J* = 10.6 and 8.2 Hz, 1 H), 5.56 (br d, *J* = 10.4 Hz, 1 H), 5.64 (br d, *J* = 10.4 Hz, 1 H), 5,92 (m, 4 H), 6.00 (t, *J* = 7.3 Hz, 1 H), 6.10 (t, *J* = 7.3 Hz, 1 H), 6.56-6.74 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 37.3, 38.0 (two), 38.2, 40.8, 41.5117, 41.5410, 42.2, 42.5, 43.6, 44.1, 44.2, 44.7, 62.5, 63.0, 100.8 (two), 108.1 (two), 109.0, 109.2, 121.2, 121.4, 124.9, 131.9, 132.1, 134.5, 134.7, 134.8, 145.6, 145.7, 147.5, 147.5.; IR (neat) νmax 1040, 1243, 1441, 1488, 1502, 2919, 3354 cm^{-1}. HRMS[ES+] calcd for $C_{34}H_{37}O_6$ $[M + H]^+$ 541.2590, found 541.2578.

Diol **4-25** Rf value: 0.55 (hexane: Et_2O: CH_2Cl_2: MeOH = 1: 1: 1: 0.04) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, *J* = 9.1 Hz, 1 H), 1.78 (m, 1 H), 1.86-1.93 (m, 2 H), 1.99 (m, 1 H), 2.13-2.27 (m, 3 H), 2.35-2.56 (m, 6 H), 2.63-2.68 (m, 2 H), 3.25 (dd, *J* = 10.9 and 5.6 Hz, 1 H), 3.34 (dd, *J* = 10.6 and 7.4 Hz, 1 H), 3.41 (dd, *J* = 10.9 and 8.3 Hz, 1 H), 3.55 (dd, *J* = 10.6 and 8.0 Hz, 1 H), 5.55 (br d, *J* = 10.3 Hz, 1 H), 5.67 (ddd, *J* = 10.3, 3.8 and 1.9 Hz, 1 H), 5,91 (d, *J* = 1.4 Hz, 2 H), 5.92 (d, *J* = 1.4 Hz, 2 H), 5.98 (t, *J* = 7.3 Hz, 1 H), 6.17 (t, *J* = 7.3 Hz, 1 H), 6.55-6.72 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 36.9, 38.3, 39.6, 40.0, 40.7, 41.2, 41.6, 42.1615, 42.2499, 42.3, 43.8, 44.4, 45.3, 62.7, 63.0, 100.7, 100.8, 108.1, 108.2, 108.9, 109.2, 121.2, 121.4, 124.5, 132.2, 132.9, 134.2, 134.4, 134.7, 145.6, 145.7, 147.5, 147.5.; IR (neat) νmax 1040, 1245, 1441, 1488, 1502, 2918, 3356 cm^{-1}. HRMS[ES+] calcd for $C_{34}H_{37}O_6$ $[M + H]^+$ 541.2590, found 541.2582.

Diol **4-27** Rf value: 0.35 (hexane: Et_2O: CH_2Cl_2: MeOH = 1: 1: 1: 0.04) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (dd, *J* = 10.9 and 2.4 Hz, 1 H), 1.83 (m, 1 H), 1.89 (m, 1 H), 1.92 (m, 1 H), 2.10 (m, 1 H), 2.12 (m, 1 H), 2.14 (m, 1 H), 2.21 (dd, *J* = 9.6 and 8.0 Hz, 1 H), 2.24 (m, 1 H), 2.44 (m, 1 H), 2.47 (m, 1 H), 2.49 (m, 1 H), 2.60 (br td, *J* = 9.5 and 2.7 Hz, 1 H), 2.65 (br d, *J* = 6.5, 1 H), 2.68 (br d, *J* = 6.6 Hz, 1 H), 2.76 (br t, *J* = 6.9 Hz, 1 H), 3.28 (dd, *J* = 10.9 and 5.7 Hz, 1H), 3.32 (dd, *J* = 10.6 and 7.7 Hz, 1 H), 3.46 (dd, *J* = 10.9 and 8.8 Hz, 1 H), 3.50 (dd, *J* = 10.6 and 7.9 Hz, 1 H), 5.63 (br d, *J* = 10.4 Hz, 1 H), 5.81 (br d, *J* = 10.4 Hz, 1 H), 5.91 (s, 2 H), 5.92 (s, 2 H), 6.24 (t, *J* = 7.3 Hz, 1 H), 6.41 (t, *J* = 7.3 Hz, 1 H), 6.55-6.72 (m, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.0, 32.9, 33.2, 33.7, 36.1, 37.6, 40.3, 40.5, 42.0, 42.4, 43.1, 44.2, 44.8, 45.6, 62.8, 62.9, 100.8 (two), 108.1 (two), 108.9, 109.2, 121.2, 121.5, 126.0, 131.5, 134.2, 134.8, 135.0, 135.5, 145.6565, 145.7234, 147.5, 147.6.; IR (neat) νmax 1040, 1244, 1441, 1488, 1502, 2917, 3351 cm^{-1}. HRMS[ES+] calcd for $C_{34}H_{37}O_6$ $[M + H]^+$ 541.2590, found 541.2585.



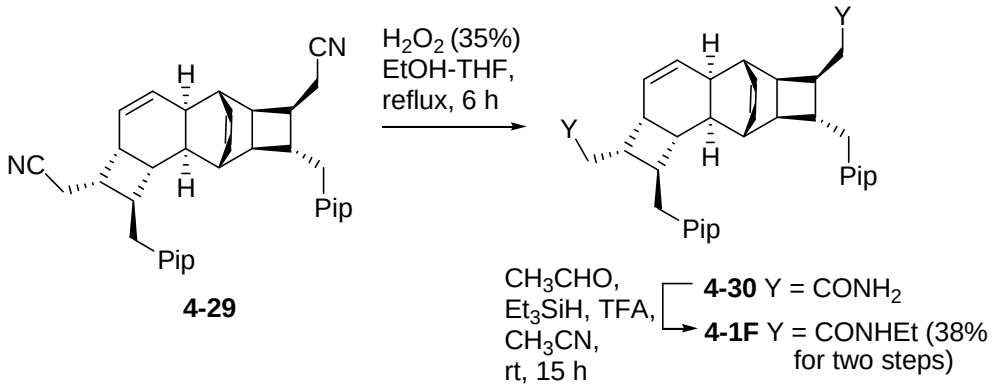
Dinitrile 4-29 Step 1: To a stirred solution of the diol **4-23** (16.5 mg, 30.5 μmol) in CH_2Cl_2 (0.5 mL) was added triethylamine (25.5 μL, 183 μmol) and methanesulfonyl chloride (7.1 μL, 91.5 μmol) at 0 °C under Ar. After 30 min, the reaction mixture was diluted with diethyl ether (20 mL) and the resulting mixture was washed with water, 5 % HCl, and sat. $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$, and concentrated. The crude product was directly used for the next step.

Dimesylate **4-28** Rf value: 0.7 (Hex:EtOAc = 1:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, *J* = 9.1 Hz, 1 H), 1.77 (m, 1 H), 1.91 (m, 2H), 2.13-2.24 (m, 4 H), 2.43-2.67 (m, 8 H), 2.89 (s, 3 H), 2.90 (s, 3 H), 3.74 (dd, *J* = 9.8 and 5.6 Hz, 1 H), 3.80 (dd, *J* = 9.7 and 6.4 Hz, 1 H), 3.97 (t, *J* = 9.7 Hz,

1 H), 4.17 (t, *J* = 9.1 Hz, 1 H), 5.55 (br d, *J* = 10.4 Hz, 1 H), 5.67 (br d, *J* = 10.4 Hz, 1 H), 5,93 (m, 4 H), 6.04 (t, *J* = 7.2 Hz, 1 H), 6.14 (t, *J* = 7.2 Hz, 1 H), 6.54-6.74 (m, 6 H).

Step 2: To a stirred solution of the dimesylate **23** in DMF (1 mL) was added sodium iodide (2.3 mg, 15 μmol) and sodium cyanide (12.0 mg, 244 μmol) at r.t. The resulting suspension was heated to 70 ^{o}C and stirred for 16 h. Then it was diluted with ethyl acetate (20 mL) and washed with water (10 mL X 3). The organic layer was then washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (Hex:EtOAc = 4:1) to afford dinitrile **4-29** (12.6 mg, 74 % in two steps, colorless liquid).

Dinitrile **4-29** Rf value: 0.7 (Hex:EtOAc = 2:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, *J* = 9.1 Hz, 1 H), 1.75 (m, 1 H), 1.82-1.99 (m, 4 H), 2.04-2.22 (m, 5 H), 2.29-2.42 (m, 2 H), 2.52-2.71 (m, 7 H), 5.55 (br d, *J* = 10.3 Hz, 1 H), 5.72 (ddd, *J* = 10.3, 3.4 and 2.1 Hz, 1 H), 5.94 (m, 4 H), 6.07 (t, *J* = 7.2 Hz, 1 H), 6.36 (t, *J* = 7.2 Hz, 1 H), 6.55-6.74 (m, 6 H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 16.9, 17.8, 31.9, 37.5, 37.6 (two), 37.8, 37.9, 38.0, 39.9, 41.2, 41.3, 42.5, 43.6, 43.9, 47.1, 100.8, 100.9, 108.2021, 108.2421, 108.8, 109.1, 119.0, 119.4, 121.2, 121.5, 123.5, 133.0, 133.3, 133.5, 133.7, 134.0, 145.8, 145.9, 147.5799, 147.6499.; IR (neat) νmax 1039, 1240, 1441, 1488, 1502, 2242, 2920 cm^{-1}. HRMS[ES+] calcd for $C_{36}H_{35}N_2O_4$ $[M + H]^+$ 559.2597, found 559.2591.



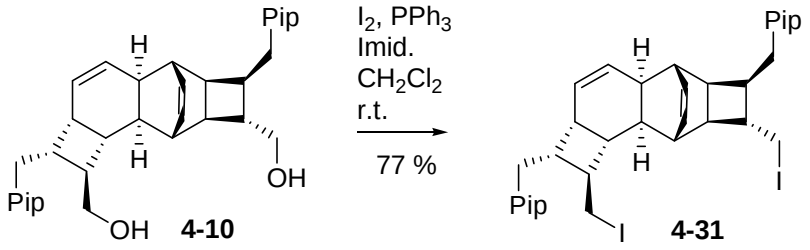
Kingianin F (4-1F)

Step 1: To a stirred solution of dinitrile **4-29** (14.1 mg, 25.2 μmol) in EtOH-THF (2.5 mL - 0.5 mL) was added aq. NaOH sol'n (0.05 mL, 7 M) and dropwise H_2O_2 sol'n (0.6 mL, 35 % in water) at 0 ^{o}C. Then, the mixture was warmed to room temperature, stirred for 30 min, and heated to reflux. After 3 h, the same amount of NaOH and H_2O_2 sol'n was added to the mixture.

After stirring for additional 3 h, the reaction mixture was diluted with brine and extracted with CH_2Cl_2 (15 mL X 5). The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used for the next step.

Step 2: The residue from step 1 was placed in 3 mL vial and flushed with Ar for 10 min. To the stirred clear solution of the crude product in CH_3CN (1.5 mL) was added acetaldehyde (8.4 μL, 151 μmol), triethylsilane (24.3 μL, 151 μmol), and trifluoroacetic acid (10.6 μL, 139 μmol) in that order at r.t. Then, the vial was capped and sealed with parafilm. After stirring 15 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ sol'n and brine, dried over Na_2SO_4, and concentrated. The residue was subjected to preparative TLC (hexane: EtOAc = 1:2) to afford Kingianin F (6.2 mg, 38 %, white solid, mp = 86-91 ^oC, lit[1a]. 90-95 ^oC).

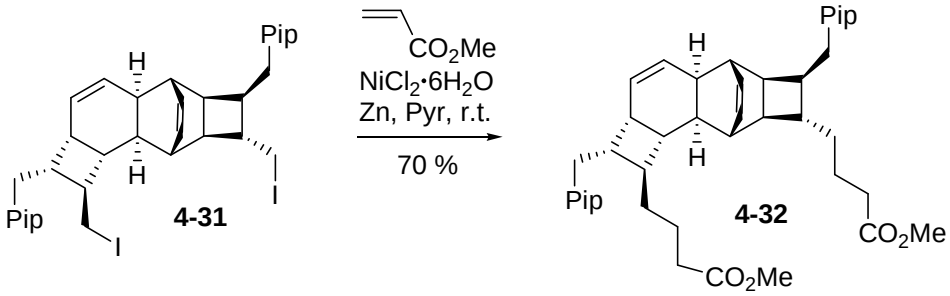
Rf value: 0.2 (hexane: EtOAc = 1:2). For ^1H NMR (500 MHz, pyridine-d_5) and ^{13}C NMR (126 MHz, pyridine-d_5), see Tables 4-3 and 4-4 in the supporting information. IR (neat) νmax 1039, 1244, 1441, 1488, 1502, 1548, 1641, 2922, 3292 cm^{-1}.



Diiodide 4-31 To a stirred solution of triphenylphosphine (58 mg, 0.22 mmol) and imidazole (25 mg, 0.37 mmol) in CH_2Cl_2 (1.5 mL) was added iodine (56 mg, 0.22 mmol) at 0 ^oC under Ar. The mixture was stirred for 20 min and treated dropwise with a solution of the diol **4-10** (20 mg, 0.037 mmol) in CH_2Cl_2 (0.5 mL). Then, the mixture was warmed to room temperature for 1 h. The resulting suspension was filtered. The filtrate was diluted with ethyl ether (10 mL) and washed twice with sat. $Na_2S_2O_3$ solution. The combined aqueous solution was extracted with CH_2Cl_2 (5 mL X 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 20:1) to afford the diiodide **4-31** (21.7 mg, 77 %) as a colorless oil.

Rf value: 0.5 (Hex:EtOAc = 10:1) ^1H NMR (500 MHz, $CDCl_3$) δ 1.83-1.92 (m, 2 H), 1.99 (d, *J* = 8.9 Hz, 1 H), 2.07-2.27 (m, 5 H), 2.49 (m, 2 H), 2.56-2.67 (m, 6 H), 2.93-3.03 (m, 4 H), 5.59 (br

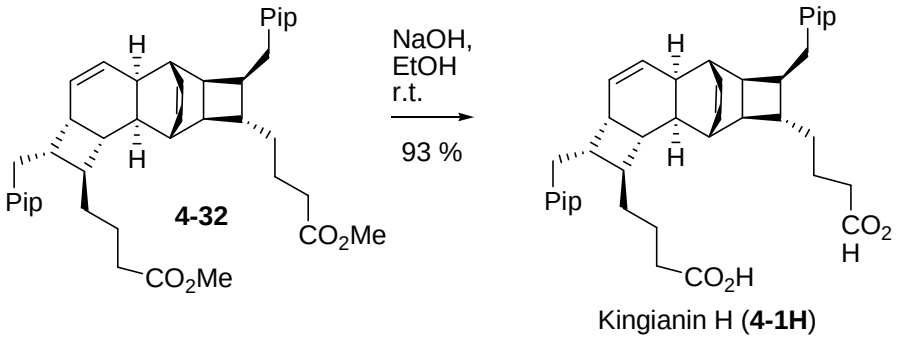
d, *J* = 10.4 Hz, 1 H), 5.68 (ddd, *J* = 10.4, 3.1 and 2.0 Hz, 1 H), 5.91 (s, 2 H), 5.92 (s, 2 H), 6.11 (t, *J* = 7.3 Hz, 1 H), 6.23 (t, *J* = 7.3 Hz, 1 H), 6.56-6.72 (m, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.6, 13.5, 32.1, 34.8, 35.5, 37.5783, 37.6140, 38.1, 38.2, 42.2, 43.5, 44.6, 45.2, 45.3, 45.8, 46.8, 100.7 (two), 108.1, 108.2, 108.7, 108.8, 120.9641, 120.9749, 125.1, 132.1, 132.3, 134.4, 134.8291, 134.8485, 145.5, 145.6, 147.5 (two).; IR (neat) νmax 938, 1039, 1247, 1442, 1488, 1501, 2919 cm^{-1}.



Diester 4-32 The procedure of Manchand et al was adapted.[8a] A mixture of $NiCl_2 \cdot 6H_2O$ (32.8 mg, 138 μmol), Zn (45.1 mg, 690 μmol), and methyl acrylate (57.5 μL, 634 μmol) in pyridine (0.5 mL) was stirred at 60 ^{o}C for 30 min under Ar. The resulting reddish brown heterogeneous suspension was cooled to room temperature and treated with a solution of diiodide **4-31** (21.0 mg, 27.6 μmol) in pyridine (0.5 mL). After 4 h, the reaction mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was diluted with EtOAc (15 mL) and washed with 5 % HCl (10 mL X 2). The organic solution was then washed with sat. $NaHCO_3$ sol'n, brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 5:1) to afford the diesters **4-32** (13.1 mg, 70 %) as a colorless oil.

Rf value: 0.5 (Hex:EtOAc = 1:2) ^{1}H NMR (MHz, $CDCl_3$) δ 1.12-1.71 (m, 11 H), 1.79 (m, 1 H), 2.00 (m, 1 H), 2.11 (m, 1 H), 2.16-2.25 (m, 6 H), 2.33 (m, 1 H), 2.45-2.66 (m, 7 H), 3.65 (s, 3 H), 3.66 (m, 3 H), 5.56 (br d, *J* = 10.4 Hz, 1 H), 5.64 (ddd, *J* = 10.4, 3.0 and 2.0 Hz, 1 H), 5.89 (s, 2 H), 5.91 (s, 2 H), 6.06 (t, *J* = 7.3 Hz, 1 H), 6.20 (t, *J* = 7.3 Hz, 1 H), 6.55-6.70 (m, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.7, 23.2, 32.6, 34.1, 34.5, 34.7, 35.5, 36.1506, 36.2386, 38.2, 38.5, 39.1, 39.3, 41.7, 42.6, 43.3525, 43.4203, 43.9, 44.4, 45.1, 51.4048, 51.4349, 100.6 (two), 108.0 (two), 108.7575, 108.8181, 120.9, 121.0, 125.4, 132.0, 132.2, 134.8, 135.4, 135.8, 145.3009, 145.3130, 147.3997, 147.4370, 174.1, 174.2. IR (neat) νmax 1246, 1440, 1488, 1503, 1737,

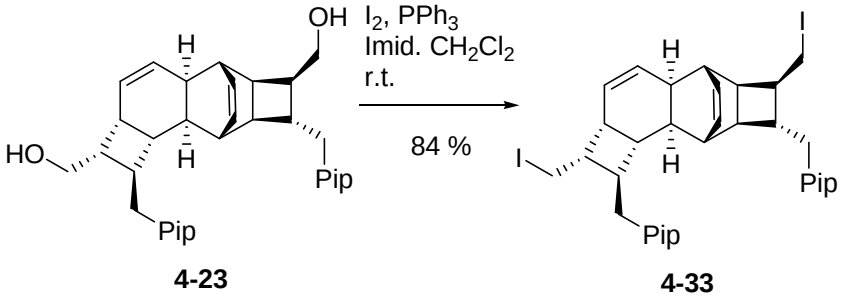
2914 cm^{-1}. HRMS[ES+] calcd for $C_{42}H_{49}O_8$ $[M + H]^+$ 681.3427, found 681.3425.



Kingianin H (1H)

To a stirred solution of diester **4-32** (12.5 mg, 18.3 μmmol) in EtOH-H_2O (2 mL/0.2 mL) was added NaOH (7.30 mg, 180 μmol) at room temperature. The mixture was stirred overnight and concentrated. The residue was dissolved in water and acidified with 1 N aq. HCl solution. The resulting mixture was extracted with CH_2Cl_2 (20 mL X 3). The combined organic solution was then washed with water, and brine, dried over $MgSO_4$, and concentrated to afford the kingianin H (11.2 mg, 93 %, white solid, m.p = 59-63 ^oC, lit[1a]; mp not reported).

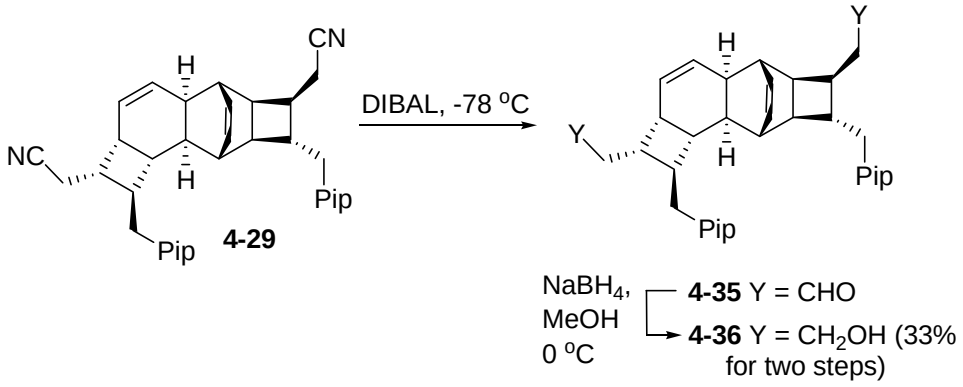
Rf value: 0.5 (Hex:EtOAc = 5:1) ^1H NMR (400 MHz, $CDCl_3$) δ. ^{13}C NMR (100 MHz, $CDCl_3$) δ. see Tables 4-5 and 4-6. IR (neat) νmax 924, 1039, 1186, 1245, 1442, 1488, 1503, 1704, 2913 cm^{-1}.



Diiodide 4-33 To a stirred solution of triphenylphosphine (72 mg, 0.28 mmol) and imidazole (19 mg, 0.28 mmol) in CH_2Cl_2 (1.0 mL) was added iodine (63 mg, 0.28 mmol) at 0 ^oC under Ar. The mixture was stirred for 20 min and treated dropwise with a solution of the diol **4-23** (15.0 mg, 27.7 μmol) in CH_2Cl_2 (0.5 mL). Then, the mixture was warmed to room temperature for 1 h.

The resulting suspension was filtered. The filtrate was diluted with ethyl ether (10 mL) and washed twice with sat. $Na_2S_2O_3$ solution. The combined aqueous solution was extracted with CH_2Cl_2 (5 mL X 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex:EtOAc = 20:1) to afford the diiodide **4-33** (17.9 mg, 85 %) as a colorless oil.

Rf value: 0.5 (Hex:EtOAc = 10:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (d, *J* = 9,0 Hz, 1 H), 1.68 (m, 1 H), 1.80-1.87 (m, 2 H), 2.03-2.24 (m, 4 H), 2.46-2.59 (m, 5 H), 2.64 (dd, *J* = 12.9 and 6.9 Hz, 1 H), 2.70 (dd, *J* = 13.7 and 6.8 Hz, 1 H), 2.76-2.81 (m, 3 H), 2.95 (dd, *J* = 9.1 and 6.9 Hz, 1 H), 3.11 (t, *J* = 9.1 Hz), 5.69 (br d, *J* = 11.7 Hz, 1 H), 5.72 (br d, *J* = 11.7 Hz, 1 H), 5.93 (s, 2 H), 5.95 (s, 2 H), 6.00 (t, *J* = 7.2 Hz, 1 H), 6.12 (t, *J* = 7.2 Hz, 1 H), 6.55-6.73 (m, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 6.9, 7.1, 33.0, 37.1, 37.8718, 37.9093, 39.7, 40.1, 40.2, 42.0, 42.3, 45.0920, 45.1396, 45.2, 48.5, 100.7593, 100.8013, 108.1, 108.2, 108.9, 109.0, 121.3, 121.4, 123.1, 132.5, 133.0, 134.0, 134.3, 134.4, 145.7, 145.8, 147.5, 147.6.; IR (neat) νmax 733, 1040, 1242, 1441, 1487, 1501, 2920 cm^{-1}.

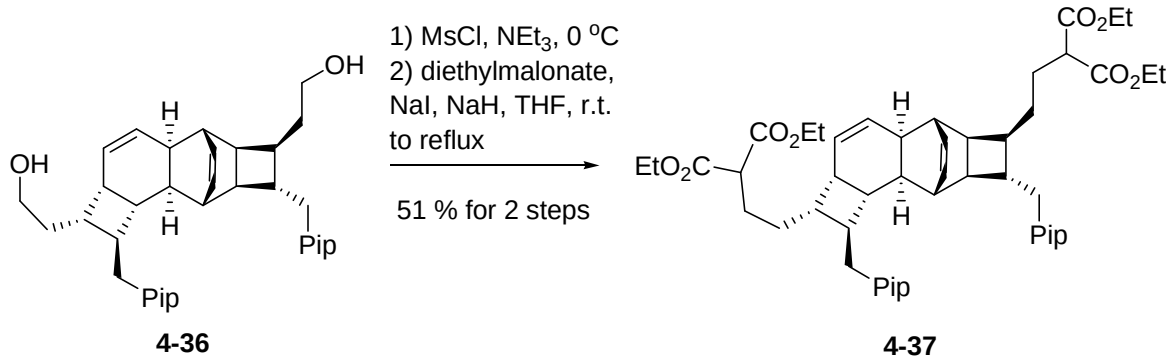


Diol 4-36 Step 1: To a stirred solution of the dinitrile **4-29** (17.8 mg, 31.9 μmol) in CH_2Cl_2 (1.5 mL) was added dropwise DIBAL (1.0 M in hexane, 70.0 μL, 70.0 μmol) at – 78 °C. The mixture was stirred for 4 h at the same temperature, quenched with sat. NH_4Cl sol'n, treated with 10 % potassium sodium tartrate. The resulting mixture was stirred for 1 h and extracted with CH_2Cl_2 (5 mL X 5). The organic solution was dried over $MgSO_4$, concentrated, and directly used for the next step.

Step 2: To a stirred solution the dialdehyde **4-35** in MeOH (1.0 mL) was slowly added $NaBH_4$ (3.6 mg, 95.6 μmol) at 0 °C. The mixture was stirred for 30 min and quenched with sat. NH_4Cl

sol'n, extracted with ethyl acetate (5 mL x 3). The combined organic solution was then dried over $MgSO_4$, concentrated, and subjected to silica gel column chromatography (Hex: EtOAc = 2:1) to afford the diol **4-36** (6.1 mg, 33 %) as colorless oil.

Rf value: 0.6 (Hex:EtOAc = 1:1) ^{1}H NMR (MHz, $CDCl_3$) δ 1.30 (m, 1 H), 1.42 (m, 1 H), 1.49-1.62 (m, 3 H), 1.72 (m, 1 H), 1.80-1.87 (m, 3 H), 2.04-2.12 (m, 4 H), 2.7 (m, 2 H), 2.50 (m, 1 H), 2.56 (m, 4 H), 3.33 (m, 2 H), 3.47 (m, 2 H), 5.53 (br d, *J* = 10.4 Hz, 1 H), 5.62 (br d, *J* = 10.4 Hz, 1 H), 5.92 (s, 2 H), 5.94 (s, 2 H), 5.97 (t, *J* = 6.8 Hz, 1 H), 6.11 (t, *J* = 6.8 Hz, 1 H), 6.55-6.74 (m, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.3, 32.9, 33.4, 38.0, 38.2, 38.6 (two), 38.9, 39.0, 41.0, 42.0, 42.6, 42.7, 43.8, 44.3, 47.2, 61.8, 61.9, 100.7, (two), 108.0 (two), 109.0, 109.3, 121.2, 121.5, 125.3, 131.9951, 132.0289, 134.6, 134.8, 135.1, 145.5, 145.6, 147.4 (two). IR (neat) νmax 1040, 1243, 1441, 1488, 1502, 2917, 3347 cm^{-1}.



4-36 **4-37**

Dimalonate **4-37** Step 1: To a stirred solution of the diol **4-36** (6.1 mg, 10.7 μmol) in CH_2Cl_2 (1.0 mL) was added triethylamine (9.0 μL, 64 μmol) and methanesulfonyl chloride (2.5 μL, 32 μmol) at 0 °C under Ar. After 30 min, the reaction mixture was diluted with diethyl ether (10 mL) and the resulting mixture was washed with water, 5 % HCl, and sat. $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$, and concentrated. The crude product was directly used for the next step.

Step 2: To a stirred solution of NaH (60% dispersion in oil, 7.70 mg, 193 μmol) in THF (3.0 mL)-DMF (0.3 mL) was added diethylmalonate (32.5 μL, 214 μmol) at r.t. After 30 min, the mixture was treated with mesylate in THF (0.2 mL) and NaI (0.8 mg, 5.4 μmol). The reaction mixture was then heated to reflux and stirred for 18 h. The resulting mixture was cooled to r.t., quenched with sat. NH4Cl so'n, and extracted with diethyl ether (10 mL X 3). The combined

organic solution was dried over $MgSO_4$, concentrated, and subjected to silica gel column chromatography (Hex: EtOAc = 5:1) to afford the dimesylate **4-37** (4.7 mg, 51 %) as colorless oil.

Rf value: 0.5 (Hex:EtOAc = 5:1) ^{1}H NMR (MHz, $CDCl_3$) δ 1.24 (m, 17 H), 1.54 (m, 1 H), 1.61-1.83 (m, 7 H), 1.95-1.2.08 (m, 4 H), 2.36 (m, 2 H), 2.52 (m, 5 H), 3.18 (m, 2 H), 4.17 (m, 8 H), 5.50 (br d, *J* = 10.4 Hz, 1 H), 5.59 (br d, *J* = 10.4 Hz, 1 H), 5.91-5.94 (m, 5 H), 6.03 (t, *J* = 7.2 Hz, 1 H), 6.52-6.73 (m, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0590 (two), 14.0842 (two), 27.2, 27.4, 27.5, 28.0, 32.1, 38.0505, 38.0845, 38.3, 38.9, 40.9, 41.7, 42.0, 42.2, 42.5, 42.7, 43.6, 44.0, 47.2, 52.1, 52.2, 61.2 (four), 100.7, (two), 108.0 (two), 109.0, 109.2, 121.2, 121.5, 124.9, 131.9, 132.1, 134.6, 134.8, 135.1, 145.4528, 145.5236, 147.4 (two), 169.4, 169.5 (two), 169.5. IR (neat) νmax 1036, 1146, 1324, 1375, 1463, 1742, 2922 cm^{-1}.

Chapter 5

Arisugacin A; Background and Retrosynthesis

5.1 Introduction: Bioactivity and Structure of (±)-Arisugacin A

(±)-Arisugacin A (**5-1**), a microbial metabolite, was isolated together with Territrem B and C, from the culture broth of *Penicillium* sp. FO-4295 in 1995.[115] These natural products are potent inhibitors of acetylcholine esterase (AChE). Inhibition of the AChe has been used as one of the clinical treatments of Alzheimer's disease (AD).[2] The therapeutic role of AChE inhibitors is to maintain the concentration of the acetylcholine, a neurotransmitter which is involved in the memory process.

In particular, high selectivity against AChE was observed in case of (±)-Arisugacin A, while tacrine (an AD drug approved by the FDA) displayed no selectivity[2] that causes the overdose. To date, only a few drugs including tacrine,[116] donpezil,[117] rivastigmine and galantimine[118] have been approved for the treatment of AD. As a highly selective and potent AD drug, (±)-arisugacin A is an intriguing synthetic target.

(±)-Arisugacin A has a tetracyclic skeleton in which four continuous stereogenic centers and a 2-aryl-α-pyrone are incorporated. The construction of two angular tertiary alcohols and two angular methyl groups at the ring junctures of the ABC ring system is considered to be synthetically challenging. The structures of arisugacin A and its congeners are depicted in Figure 5-1 and Table 5-1.

---

[115] Arisugacin, a Novel and Selective Inhibiotr of Acetylcholinesterase from Penicillium sp. FO-4259. Omura, S.; Kuno, F. Otoguro, K.; Sunazuka, T.; Shiomi, K.; Masuma, R.; Iwai, Y. *J. Antibit*. **1995**, 48, 745.

[116] Tacrine. Davis, K. L.; Powchik, P. *Lancet* **1995**, *345*, 625-630.

[117] Donepezil. Bryson, P.; Benfield, P. Donepezil, *Drugs Aging* **1997**, *10*, 234-239.

[118] Review of the acetylcholinesterase inhibitor galanthamine. Sramek, J. J.; Frackiewicz, E. J.; Cutler, N. R. Review of the acetylcholinesterase inhibitor galanthamine, *Expert Opin. Investg. Drugs* **2000**, *9*, 2393-3402.

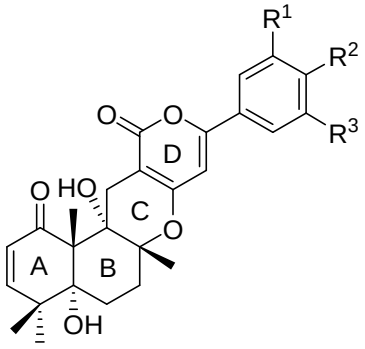


Table 5-1. Arisugacin A and its congeners

	R^1	R^2	R^3
Arusugacin A (**5-1**)	H	OMe	OMe
Arusugacin B (**5-2**)	H	OMe	H
Territrem A (**5-3**)	-OCH_2O-		OMe
Territrem B (**5-4**)	OMe	OMe	OMe
Territrem C (**5-5**)	OMe	OH	OMe

Figure 5-1. (±)-Arisugacin A (**5-1**) and its congeners

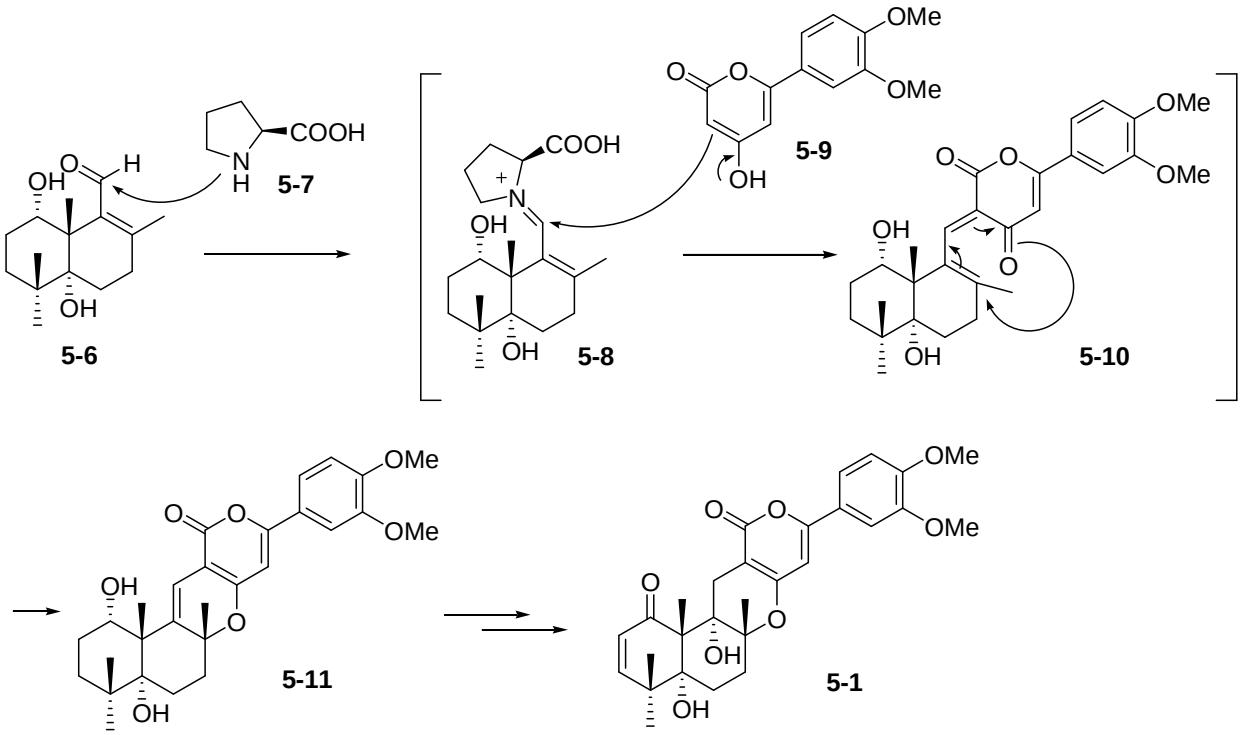
5.2 Previous Syntheses

5.2.1 Omura's synthesis

In 2002, Omura and coworkers reported the first total synthesis of arisugacin A. They employed an enantiomerically pure α, β-unsaturated aldehyde **5-6**[119] bearing an angular tert-alcohol, which reacted with *α*-pyrone **5-9** in the presence of L-proline, to afford a diene **10** by eliminating proline. Then, diene **5-10** underwent a 6π-electrocyclization, providing tetracylic structure **5-11**. The tetracycle **5-11** was converted to (±)-Arisugacin A (**5-1**) by the additional steps including the stereoselective introduction of the other tertiary alcohol. Finally, (±)-Arisugacin A (**5-1**) was achieved in 6.8 % overall yield from the aldehyde **5-6**. (Scheme 5-1).[120]

[119] Total Synthesis of Forskolin - Part I. Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett*. **1996**, *37*, 1015-1018.

[120] The First Total Synthesis of (±)-Arisugacin A, a Potent, Orally Bioavailable Inhibitor of Acetylcholinesterase. Sunazuka, T; Handa, M; Nagai, K.; Shirahata, T.; Harigaya, Y.; Otoguro, K; Kuwajima, I.; Omura, S. *Org. Lett.* **2002**, *4*, 367-369.



Scheme 5-1. Omura's synthesis

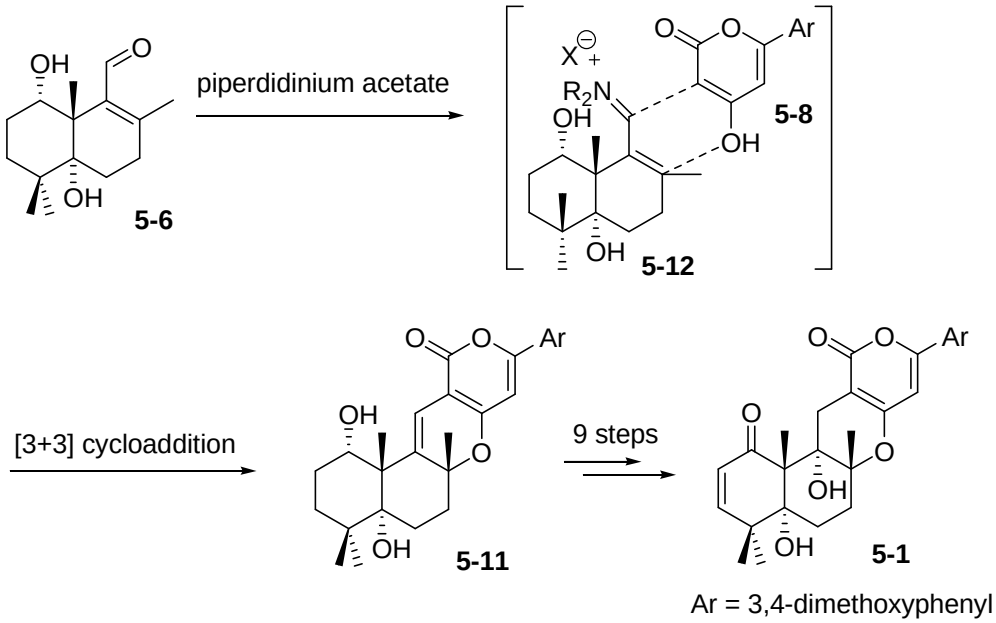
5.2.2 Hsung's synthesis

In 2003, Hsung and coworkers have completed the total synthesis of (±)-Arisugacin A. Their synthesis also featured [3+3] cycloaddition as a key reaction to construct the ABCD ring backbone in one pot.[121] Previously, they illustrated the study about coupling reaction between iminium salt and α-pyrone by way of [3+3]-cycloaddition reaction as an approache to arisugacin backbone.[122]

[121] A Concise Stereoselective Route to the Pentacyclic Frameworks of Arisugacin A and Territrem B. Zehnder, L. R.; Hsung, R. P.; Wang, J.; Golding, G. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 3876.

[122] The total synthesis of (±)-arisugacin A. Hsung, R. P.; Cole, K. P. Zehnder, L.R.; Wang, J. Wei, L, -L.; Yang, X. -F. Coverdane, H. A. *Tetrahedron*, **2003**, *59*, 311.

The [3+3] cycloaddition between iminium salt **5-12** and 2-aryl-4-hydroxypyrone **5-8** produced the key intermediate **5-11**, containing the ABCD ring system The total synthesis (Scheme 5-2). The total synthesis completed in 10 steps from the aldehyde **5-6**.



Scheme 5-2. Hsung's synthesis

5.2.3 Jung's approach

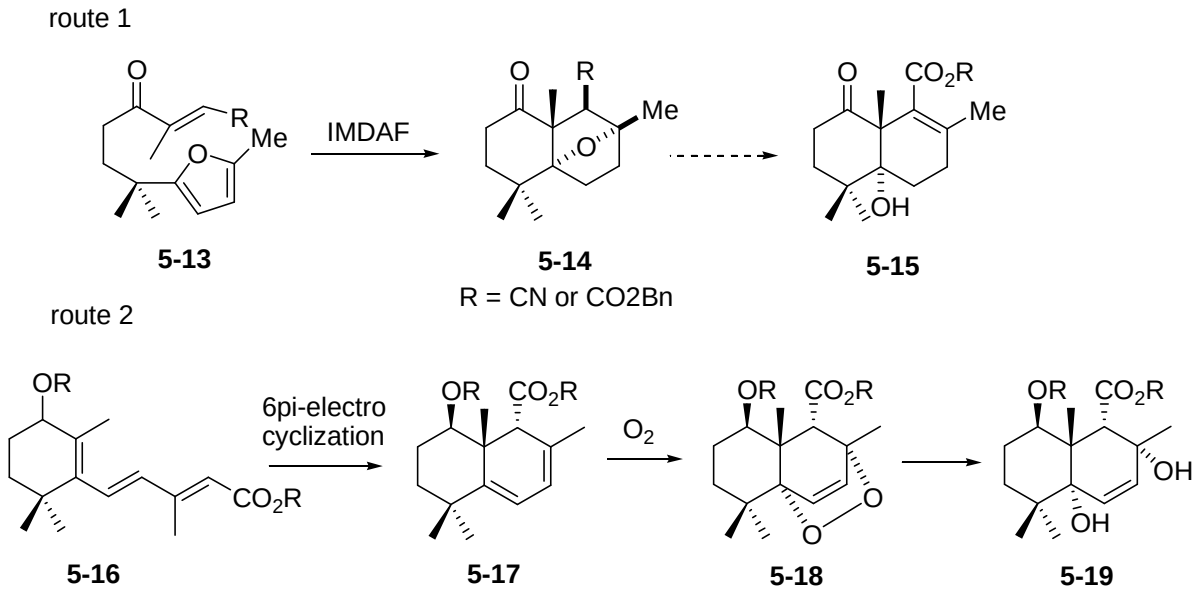
In 2005, Jung and Min disclosed the synthesis of oxatricyclic compounds by a route based on the intramolecular Diels-Alder reaction of a furan (IMDAF). Here, they claimed that the resulting Diels-Alder product would be investigated for the elaboration of arisugacin A.[123]

In 2007, the authors described their synthetic approaches to the AB ring system of arisugacin A (Scheme 5-3).[124] They introduced two synthetic routes to the highly oxidized trans-decalin: 1) IMDAF reaction of the substrate **5-13** and 2) 6π-electrocyclization of the triene **5-16** followed by

[123] Intramolecular Diels-Alder Reaction of Optically Active Allenic ketones: Chirality Transfer in the Preparation of Substituted Oxa-Bridged Octalones. Jung, M. E.; Min, S. -J. *J. Am. Chem. Soc*. **2005**, *127*, 10834-10835.

[124] Approaches to the synthesis of arisugacin A. Jung, M. E.; Min, S. -J. *Tetrahedron*, **2007**, 63, 3682-3701.

cycloaddition between the diene **5-17** and singlet oxygen. By the second approach, they installed the angular tert-alcohols.



Scheme 5-3. Jung's approach

5.3 Our retrosynthesis of arisugacin A

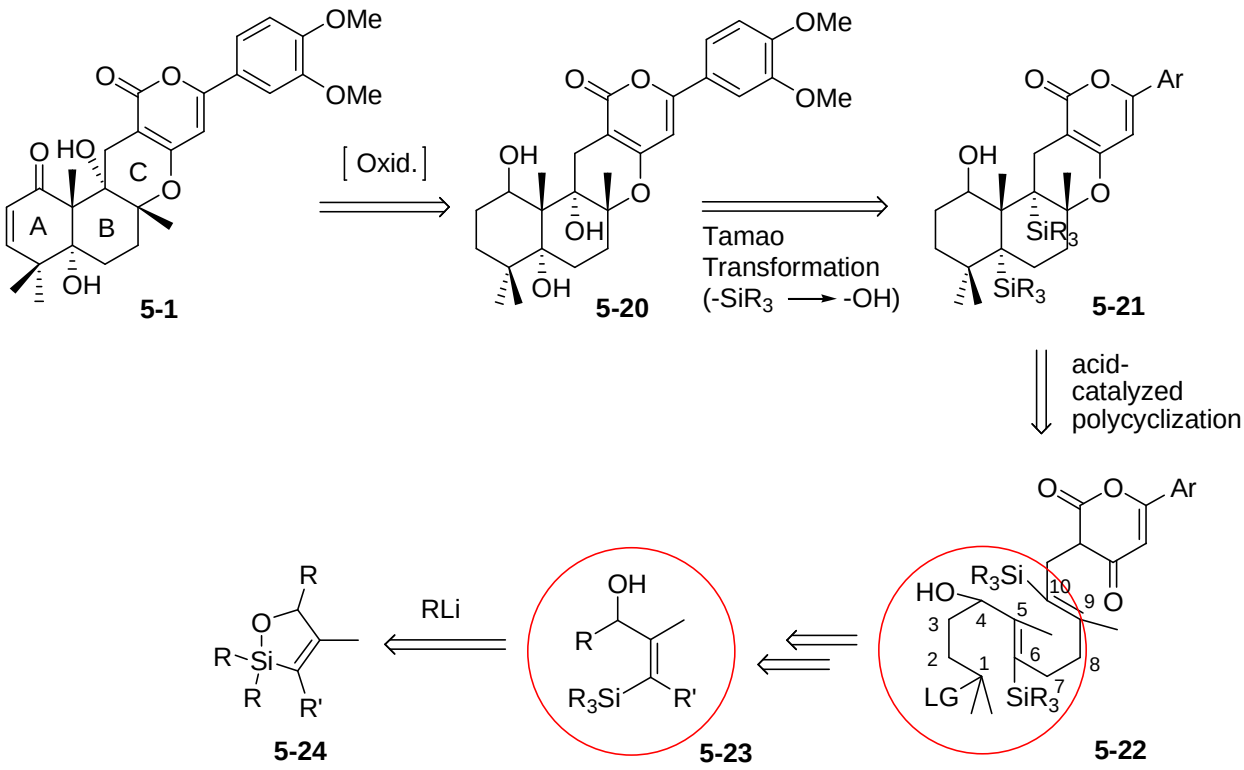
We envisaged that the preparation of polyolefin **5-22** containing tetrasubstitued vinyl silanes followed by the cyclization under acid catalysis would give the ring system **5-21** of (±)-Arisugacin A. If the cyclization of the **5-22** is successful, two *tert*-silyl groups of the tetracycle **5-21** could be transformed into tert-alcohols by the Tamao transformation.[125]

We thought that tetrasubstituted (*Z*)-vinyl silane allylic alcohol **5-23** would be an important precursor for the synthesis of the polyene **5-22**. This alcohol might be achieved by the ring opening of oxasilol **5-24** (Scheme 5-4).

In this proposed synthesis, the key reactions are in three parts. First, the efficient and scalable synthesis of the key starting material **5-23** is required. Second, the conditions for the cyclization

[125] Synthetic Stitching with Silicon: Geminal Alkylation-Hydroxylation of Alkynyl Carbonyl Compounds. Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942-13944. See references therein.

of the substrate **5-22** bearing secondary allylic alcohol and silyl groups should be explored. Third, the Tamao oxidation of the angular silyl groups is not trivial. Thus, the many conditions for that transformation should be screened.



Scheme 5-4. Retrosythesis of Arisugacin A

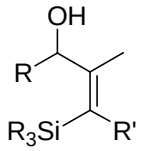
Chapter 6

Arisugacin A; Synthetic study of oxasilacycles

6.1 Introduction

6.1.1 Vinylsilanes

In chapter 5, we designed the total synthesis of arisugacin A. In the retrosynthetic scheme, the vinylsilane **6-1** was a key starting material.



6-1

Figure 6-1. Vinlysilane

Vinylsilanes have played an important role in organic synthesis because of their synthetic utilities, low cost, low toxicity, ease of handling, and simplicity of byproduct removal.[126] The preparation of vinylsilanes, including *β*-(*E*) vinylsilanes[127], *β*-(*Z)* vinylsilanes[128], and *α*-vinylsilanes,[1b] has depended on the metal-catalyzed hydrosilylation of terminal alkynes.

---

[126] (a) Ojima, I; Li, Z.; Zhu, J. In *the Chemistry of Organiosilicon Compounds*; Rappoport, Z.; Apeloig, Y., Eds.; John Wiley & Sons: Great Britain. 1998; Vol. 2, pp 1687-1792. (b) Alkyne Hydrosilylation Catalyzed by a Cationic Rutheniumn Complex: Efficient and General Trans Addition. Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644-17655.

[127] (a) Organolanthanide-Catalyzed Cyclization/Silylation of Nitrogen-Containing Enynes. Molander, G. A. Corrette, C. P. *J. Org. Chem*. **1999**, *64*, 9697. (b) Highly Stereoselective Hydrocarbation of Terminal Alkynes *via* Pt-Catalyzed Hydrosilylation/Pd-Catalyzed Cross-Coupling Reactions. Denmark, S. E.; Wang, Z. *Org. Lett*. **2001**, *3*, 1073. (c) Metal-Catalyzed Hydrosilylation of Alkenes and Alkynes Using Dimethyl(pyridyl)silane. Itami, K.; Mitsudo, K.; Nishino, A.; Yoshida, J. *J. Org. Chem*. **2002**, *67*, 2645.

[128] (a) Ojima, I. Kumagai, M. *Organomet. Chem*. 1974, *66*, C14-C16. (b) Exclusive formation of *cis*-PhCH:CH($SiEt_3$) by addition of triethylsilane to phenylacetylene catalyzed by ruthenium complex $[(Me_2CH)_3P]_2RuHCl(CO)$. Esteruelas, M. A.; Herrero, J.; Oro, L. A. *Organometallics* **1993**, *12*, 2377. (c) Lewis Acid Catalyzed *trans*-Allylsilylation of Unactivated Alkynes.

In particular, the synthesis of (*Z*)-vinylsilane allylic alcohols has been reported by several methods: platinum-catalyzed addition of trimethylsilane to prop-1-ynyl pivalate followed by reduction of carbonyl group[129]; 1,4-O to sp^2-C silyl rearrangement from allylic silyl ether[130]; the tin(IV) chloride-promoted coupling reaction followed by elimination of thiolate by DBU[131] with "reverse Brook" rearrangement.[132] Although many methods have been developed for (Z)-vinylsilane allylic alcohols, few synthetic methods have been reported for the preparation of *tetrasubstituted* (*Z*)-vinylsilanes.

6.1.2 Retrosynthesis of an Oxasilole Containing a Tetrasubstituted Olefin

6.1.2.1 Previous synthesis of trisubstituted (Z)-vinylsilane using RRCM strategy

In the Parker group's continuing efforts on the synthesis of discodermolide, Xie et al. reported that relay ring closing metathesis (RRCM) provided the dihydrooxasiline **6-3** in 92 % yield (Scheme 6-1).[133] Note that (*Z*)-vinylsilane **6-4** was then obtained *via* ring closing (RRCM)/ ring opening strategy.

Yoshikawa, E.; Gevorgyan, V.; Asao, N.; Sudo, T.; Yamamoto, Y. *J. Am. Chem. Soc*. **1997**, *119*, 6781. (d) Highly Stereoselective and Efficient Hydrosilylation of Terminal Alkynes Catalyzed by $[RuCl_2(p\text{-cymene})]_2$. Na, Y.; Chang, S. *Org. Lett*. **2000**, *2*, 1887.

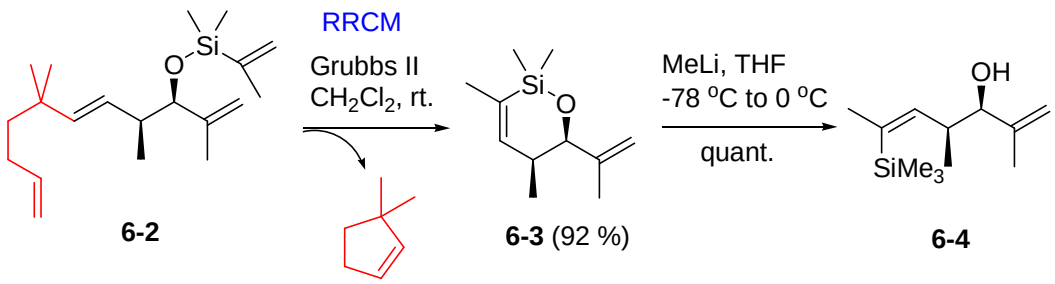
[129] Synthetic routes to halomethyl vinylsilanes. Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc*. **1974**, *96*, 3684.

[130] A new stereoselective synthesis of (*Z*)-vinylsilane allylic alcohols. Kim, K. D.; Magriotis, P. A. *Tetrahedron Lett.* **1990**, *31*, 6137.

[131] Copper(I) *tert*-Butoxide-Promoted 1,4 C^{sp2}-to-O Silyl Migration: Generation of Vinyl Copper Equivalents and Their Stereospecific Cross-Coupling with Allylic, Aryl, and Vinylic Halides. Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem*. **2002**, *67*, 8450.

[132] Brook, A. G.; Bassindale, A. R. *In Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Essay 9, Molecular Rearrangements of Organosilicon Compounds.

[133] A Relay Ring-Closing Metathesis Synthesis of Dihydrooxasilines, Precursors of (Z)-Iodo Olefins. Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett.* **2008**, *10*, 5345-5348.

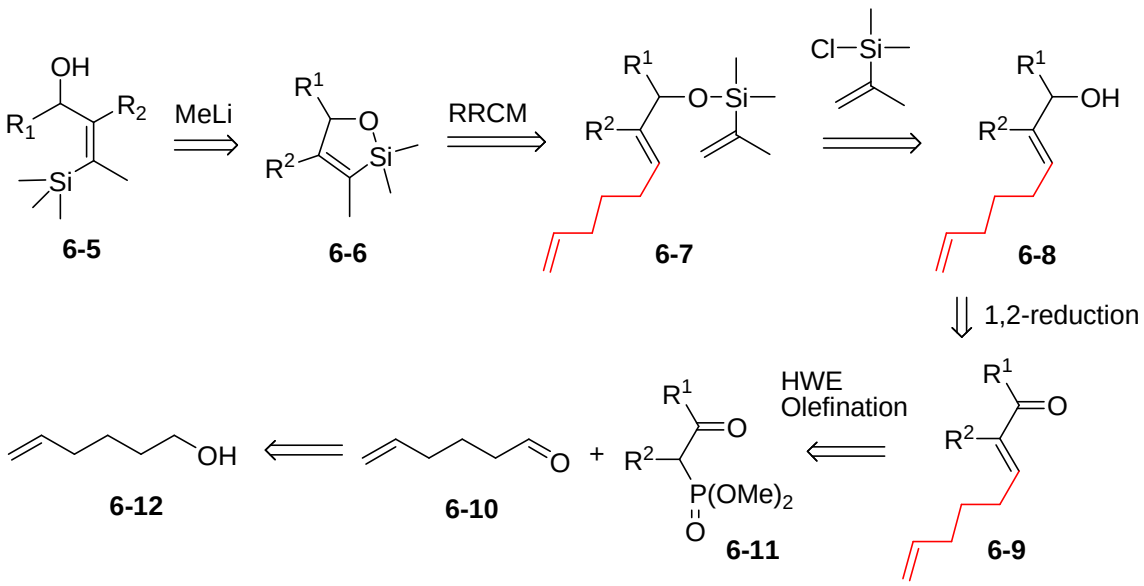


Scheme 6-1. Synthesis of vinylsilane by relay ring closing metathesis

6.1.2.2 Retrosynthesis of tetrasubstituted (*Z*)-vinylsilane allylic alcohol

Our first goal then was to develop an efficient synthetic route to the tetrasubstituted (*Z*)-vinylsilane allylic alcohol. We planned to prepare a model compound **6-5** by way of the ring closing/ring opening strategy that was used in Scheme 6-1.

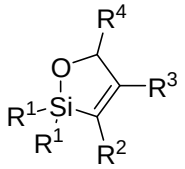
We envisaged that the use of the RRCM procedure would yield the oxasilole **6-6** from silyl ether **6-7**. The 3-step sequence form 5-hexen-1-ol **6-12** (oxidation of **6-12**, Horner-Wadsworth-Emmons (HWE) olefination using a phosphonate **6-11**, and the 1,2-selective reduction of the ketone **6-9**) was expected to give allylic alcohol **6-8**. The O-silylation of the alcohol **6-8** should give silyl ether **6-7**.



Scheme 6-2. Retrosythesis of tetrasubstituted (*Z*)-vinylsilane allylic alcohol

6.1.3 Synthetic examples of oxasiloles

Oxasiloles containing a tetrasubstituted olefin **6-13** (Figure 6-2) have served as masked allylic alcohol derivatives [134] and been widely used as valuable synthetic intermediates in many transformations such as oxidations, cross-couplings, and cycloadditions.[135] As for the preparation of oxasiloles containing a tetra-substituted olefins, three procedures have been developed so far.



6-13

Figure 6-2. Oxasiloles

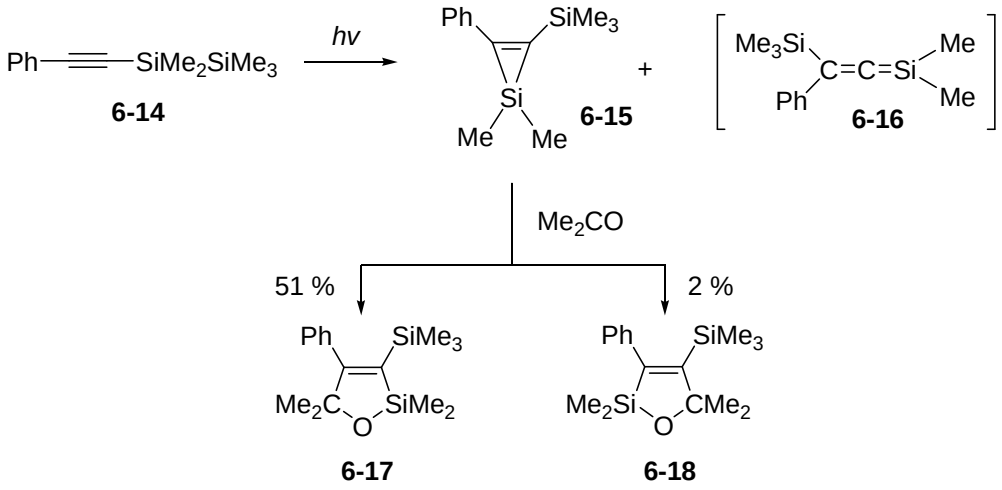
In 1977, the Ishikawa group reported the synthesis of 3-trimethylsilyl-4-phenyl oxasilole.[136] In their communication, they described the synthesis of 1-silacyclopropene **6-15** by UV irradiation of (pentamethyldisilanyl)phenylacetylene (**6-14**). Then, the insertion of activated acetone into 1-silacyclopropene **6-15** provided oxasiloles **6-17** and **6-18** (Scheme 6-3).

---

[134] (a) Silacyclopropenes. 2. Two-atom insertion reactions of 1,1-dimethyl-2,3-bis(trimethylsilyl)silirene. Seyferth, D.; Vick, S.C.; Shannon, M. L. *Organometallics* **1984**, *3*, 1897-1905. (b) Nickel-catalyzed preparation of stereodefined allylic alcohols using silicon-tethered ynals. Lozanov, M.; Montgomery, J. *Tetrahedron Lett.* **2001**, *42*, 3259-3261.

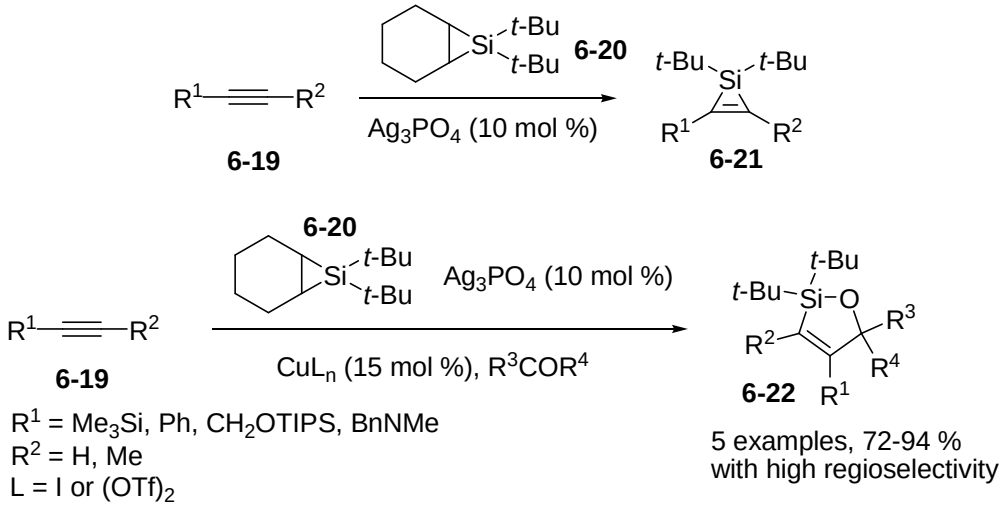
[135] (a) Development of Reactions of Silacyclopropanes as New Methods for Stereoselective Organic Synthesis. Franz, A. K.; Woerpel, K. A. *Acc. Chem. Res.* **2000**, *33*, 813. (b) Intramolecular Diels−Alder Reactions of Siloxacyclopentene Constrained Trienes. Halvorsen, G. T.; Roush, W. R. *Org. Lett.* **2007**, *9*, 2243.

[136] Photolysis of Organopolysilanes. Formation and Reactions of Substituted 1-Silacyclopropene and 1-Sila-1,2-propadiene. Ishikawa, M.; Fuchikami, T.; Kumada, M. *J. Am. Chem. Soc.* **1977**, *99*, 245-247.



Scheme 6-3. Ishikawa's synthesis of oxasilioles

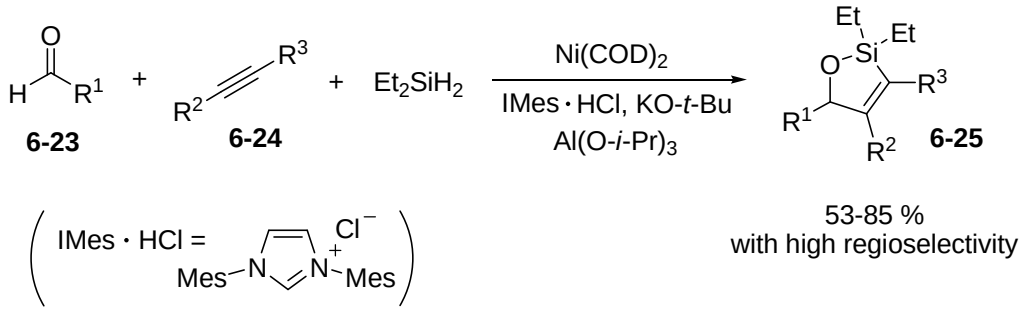
In 2004**,** Clark and Woerpel disclosed the silver catalyzed synthesis of oxasilacyclopropenes **6-21** from the functionalized alkynes **6-19**. This highly reactive species **6-21** was not easy to isolate. Thus, they developed a one pot reaction in which the in-situ prepared oxasilacyclopropenes reacted with the carbonyl-containing substrate under copper catalyst, producing the oxasilacyclopentenes **6-22** in high yields with high regioselectivity (Scheme 6-4).[137]



Scheme 6-4. Woerpel's synthesis of oxasiloles

[137] Formation and Utility of Oxasilacyclopentenes Derived from Functionalized Alkynes. Clark, T. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9522-9523.

In 2008, Baxter and Montgomery reported the nickel-catalyzed dehydrogenative cyclocondensation of aldehydes **6-23**, alkynes **6-24**, and diethylsilane to provide oxisiloles **6-25** in a one-step process.[138] This method provided highly functionalized oxisiloles with high regioselectivity (Scheme 6-5).



Scheme 6-5. Montgomery's synthesis of oxasiloles

6.1.4 Relay Ring Closing Metathesis

The ring closing metathesis (RCM) reaction has been used as a powerful tool not only for the synthesis of small carbocycles but also for medium- to macro- carbocycles for several decades. Because of the air-stability and commercial availability of ruthenium alkylidene catalysts including Grubbs catalyst I and its derivatives **6-26**, **6-27**, **6-28** and etc (Figure 6-3), the RCM reaction has been utilized by many synthetic chemists.[139]

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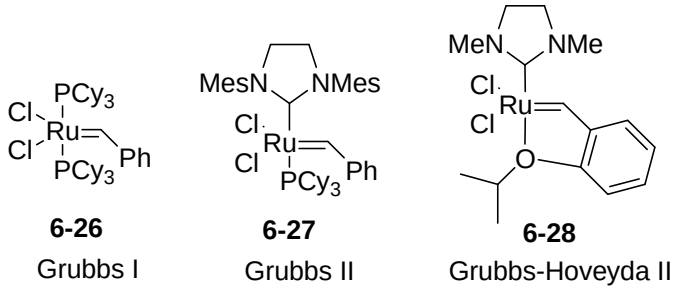
[138] Dehydrogenative Cyclocondensation of Aldehydes, Alkynes, and Dialkylsilanes. Baxter, R. D.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 9662-9663.

[139] Recent reviews, references herein: (a) Metal-Mediated Synthesis of Medium-Sized Rings. Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3008. (b) Microtubule-Stabilizing Marine Metabolite Laulimalide and Its Derivatives: Synthetic Approaches and Antitumor Activity. Mulzer, J.; Öhler, E. *Chem. Rev.* **2003**, *103*, 3753–3786. (c) Synthesis of Oxygen- and Nitrogen-Containing



6-26 Grubbs I

6-27 Grubbs II

6-28 Grubbs-Hoveyda II

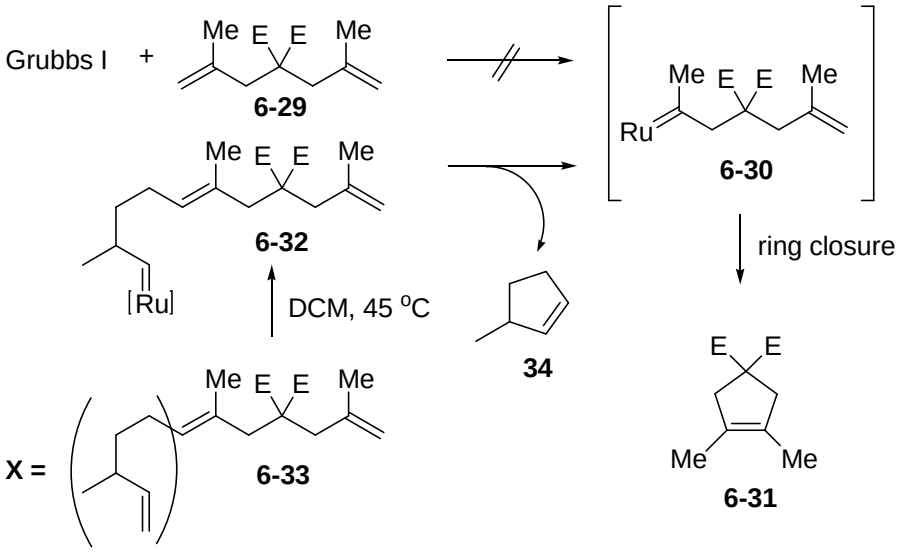
Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl

Figure 6-3. Representative ruthenium alkylidene catalysts

Despite numerous uses of RCM reaction in many laboratories, the application is sometimes limited when alkenes of the substrates are sterically hindered or electronically deactivated. For example, the RCM reaction of the substrate **6-29** was not successful. In 2004, Hoye et al. reported a solution for these problems.[140] In this report, a new concept "relay ring closing metathesis (RRCM)" was introduced as a complementary strategy for the RCM reaction of unactivated alkenes. The relay moiety (X) in the substrate **6-33** overcame the reactivity problem caused by the inertness of the substrate **6-29**. Due to the relay moiety, the RCM reaction of the substrate **6-33** with Grubbs 1st generation successfully gave a cyclized product **6-31** (Scheme 6-6).

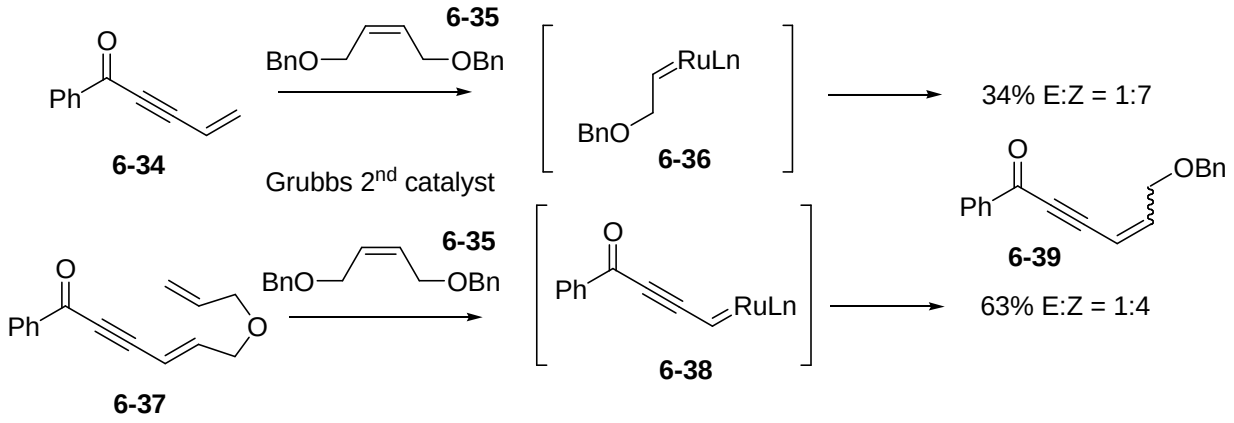
Heterocycles by Ring-Closing Metathesis. Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199-2238. (d) Total Synthesis of Ingenol. Kuwajima, I; Tanino, K. *Chem. Rev.* **2005**, *105*, 4661–4670. (e) Total Synthesis of Natural 8- and 9-Membered Lactones: Recent Advancements in Medium-Sized Ring Formation. Shiina, I. *Chem. Rev.* **2007**, *107*, 239–273.

[140] Relay Ring-Closing Metathesis (RRCM): A Strategy for Directing Metal Movement Throughout Olefin Metathesis Sequences. Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc*. **2004**, *126*, 10210.



Scheme 6-6. Hoye's development of RRCM reaction

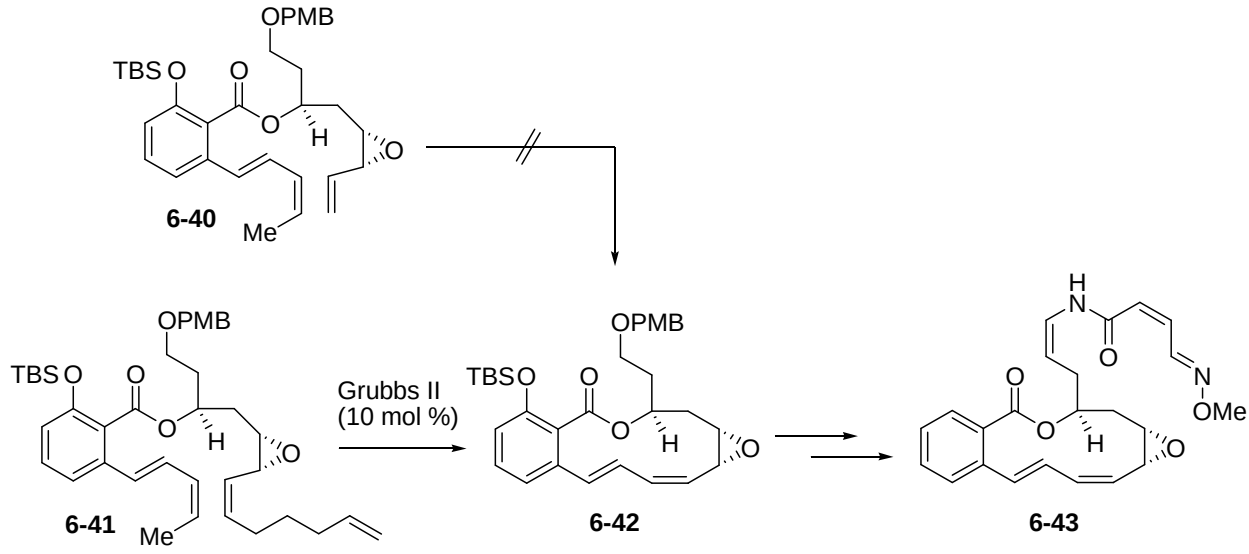
In 2004, Hansen and Lee reported the (Z)-selective synthesis of substituted enynes **6-39** using cross metathesis.[141] This method was conceptually very similar to Hoye's RRCM. They introduced an allyl ether moiety as "a catalyst delivery vehicle" in order to provide the alkynyl alkylidene **6-38**. This method improved the efficiency of cross metathesis between enyne **6-34** and Z-olefin **6-35** (Scheme 6-7).



Scheme 6-7. Lee's RRCM

[141] Efficient and *Z*-Selective Cross-Metathesis of Conjugated Enynes. Hansen, E.; Lee, D. *Org. Lett.* **2004**, *6*, 2035-2038.

In 2005, the Porco group disclosed the total synthesis of the salicylate enamide oximidine III **6-43** using RRCM in the key macro-cyclization step. The RRCM reaction was applied to obtain a 12-membered cyclic *E*/*Z* diene **6-42**. Because of the inertness of electronically unactivated epoxy alkene under Grubbs catalysts, they appended the relay moiety on the terminus of the epoxy alkene **6-40**. By screening the conditions for RRCM, the best result was given when they used a cis-epoxy alkene **6-41** in the presence of 10 mol % Grubbs II catalyst at 50 ^{o}C in 1,2-dichloroethane (Scheme 6-8).[142]



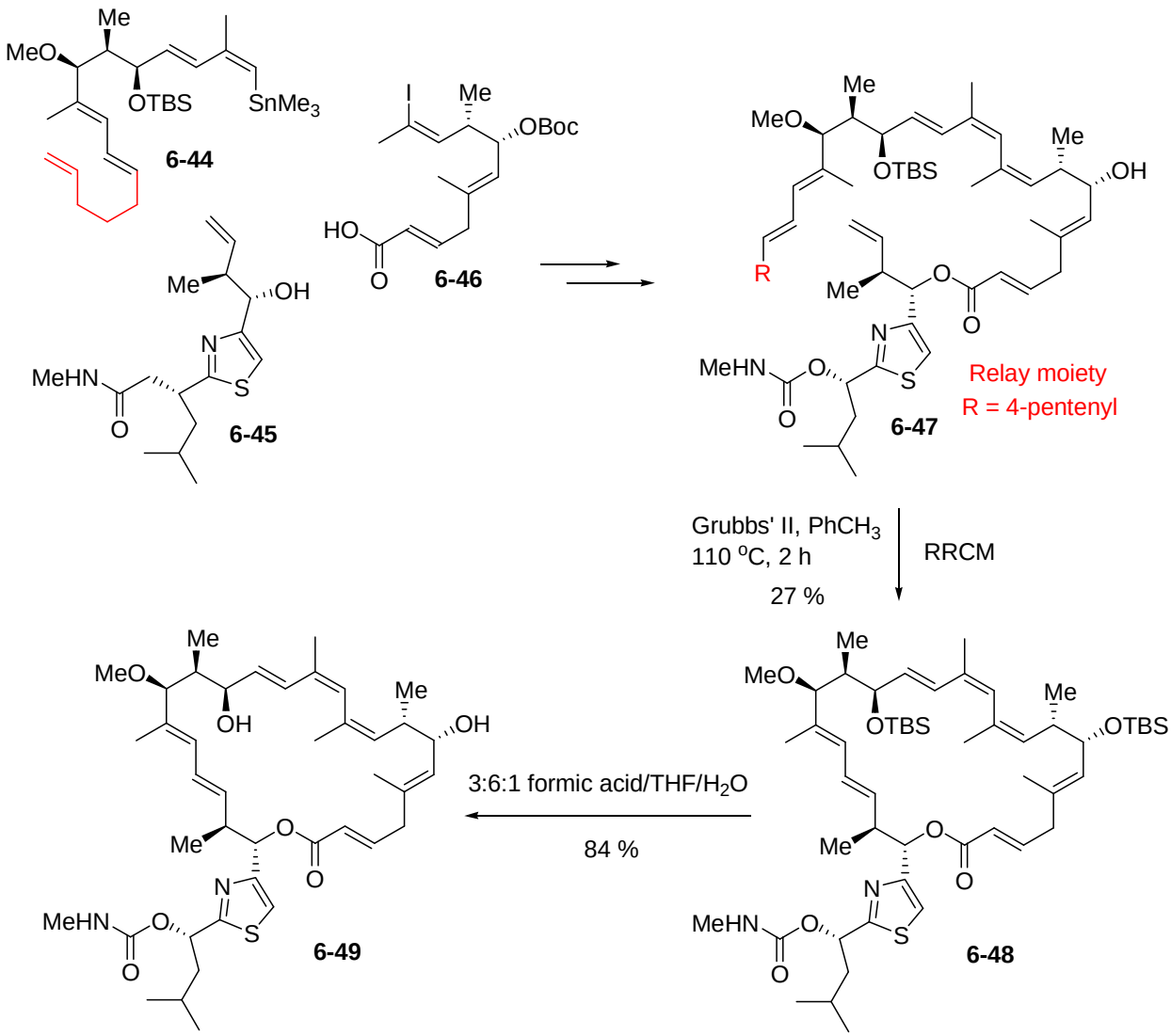
Scheme 6-8. Porco's synthesis of oximidine III

In 2007, Trauner et al. reported the total synthesis of (–)-Archazolid B using the RRCM strategy in the key macrocyclization step.[143] The three building blocks (stannane **6-44**, thiazole **6-45**, and iodide **6-46**) were combined to provide the substrate **6-47** before the RRCM stage (northestern part of scheme 6-9). The RRCM reaction of the subtrate **6-47** with Grubbs's 2nd

[142] Total Synthesis of the Salicylate Enamide Macrolide Oximidine III: Application of Relay Ring-Closing Metathesis. Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, Jr., J. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1912-1915.

[143] Total Synthesis of (-)-Archazolid B. Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960-8961.

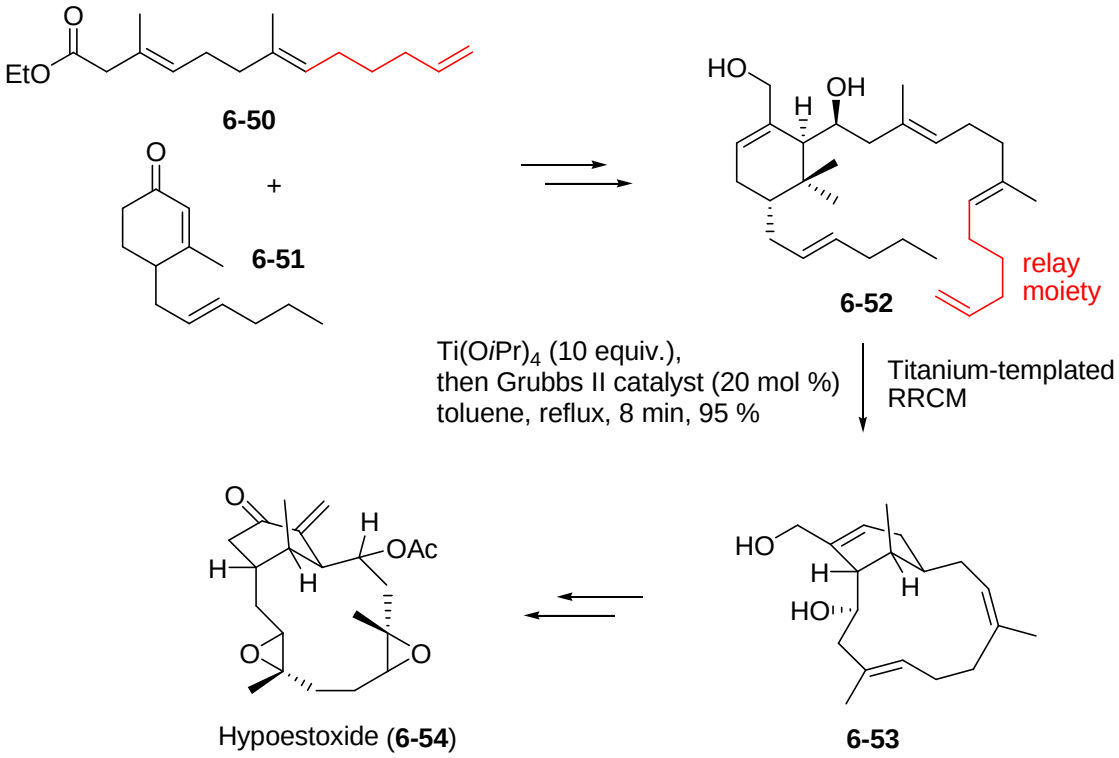
generation catalyst gave the macrolactone in 27 % yield. The careful deprotection of the TBS groups by treatment with aqueous formic acid provided alcohol (–)-Archzolid B (**52**) in 84 % yield (Scheme 4-10).



Scheme 6-9. Trauner's synthesis of (–)-Archzolid B

In 2008, the Njardarson group reported the first total synthesis of hypoestoxide (**6-57)**. This natural compound was reported to have promising anticancer, antimalarial, and anti-inflammatory activities. The titanium-templated RRCM macro-cyclization was the key step in the synthesis. The use of titanium isopropoxide blocks the coordination of diols in the substrate

6-52 to the Grubbs catalyst. As a result, the RRCM reaction of the relay substrate **6-52** provided the macrocycle **6-53** in excellent yield (Scheme 6-10).[144]



Scheme 6-10. Njardarson's synthesis of hypoestoxide

In 2012, Lee and Parker reported the formal synthesis of (–)-englerin A.[145] Starting from the naturally abundant geraniol, their synthesis featured stereoselective ring opening of the epoxide **6-54**, a relay ene-yne-ene metathesis of **6-55**, and oxymercuration of **6-57** as key steps. In the RRCM step, they found that the Stewart-Grubbs catalyst was superior to other catalysts (Scheme 6-11).

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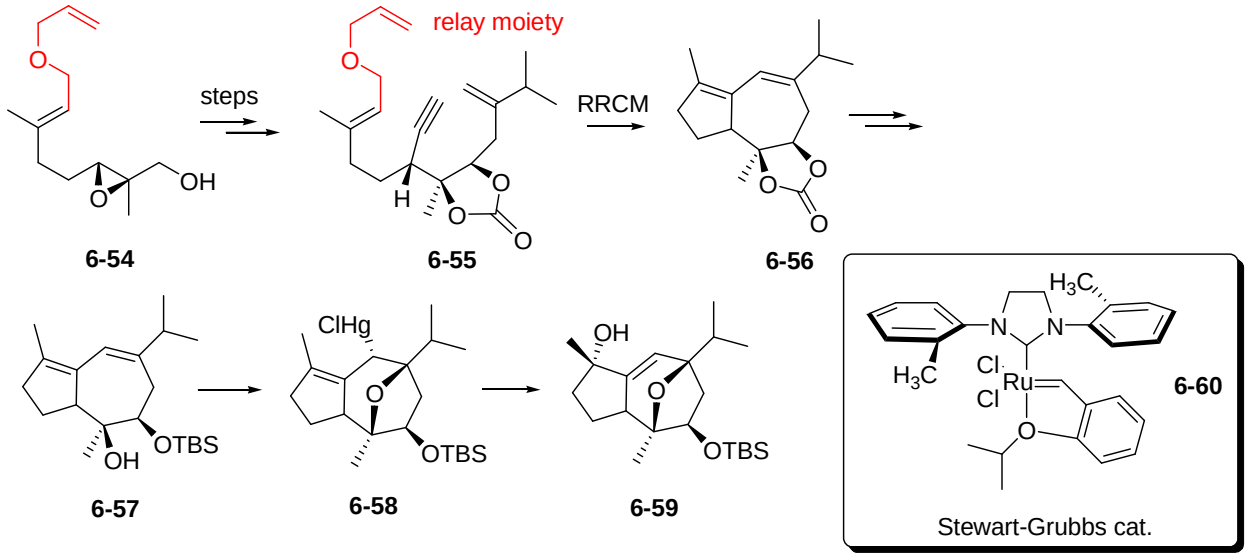
[144] An Efficient Substrate-Controlled Approach Toward Hypoestoxide, a Member of a Family of Diterpenoid Natural Products With an Inside-Out [9,3,1]Bicyclic Core. McGrath, N. A.; Lee, C. A.; Araki, H.; Brichacek, M.; Njardarson, J. T. *Angew. Chem. Int. Ed.* **2008**, *47*, 9450-9453.

[145] A Formal Synthesis of (–)-Englerin A by Relay Ring Closing Metathesis and Transannular therification. Lee, J; Parker, K. A. *Org. Lett.* **2012**, *14*, 2682-2685.



Scheme 6-11. Lee and Parker's formal synthesis of (–)-englerin A

6.2 Result and Discussion

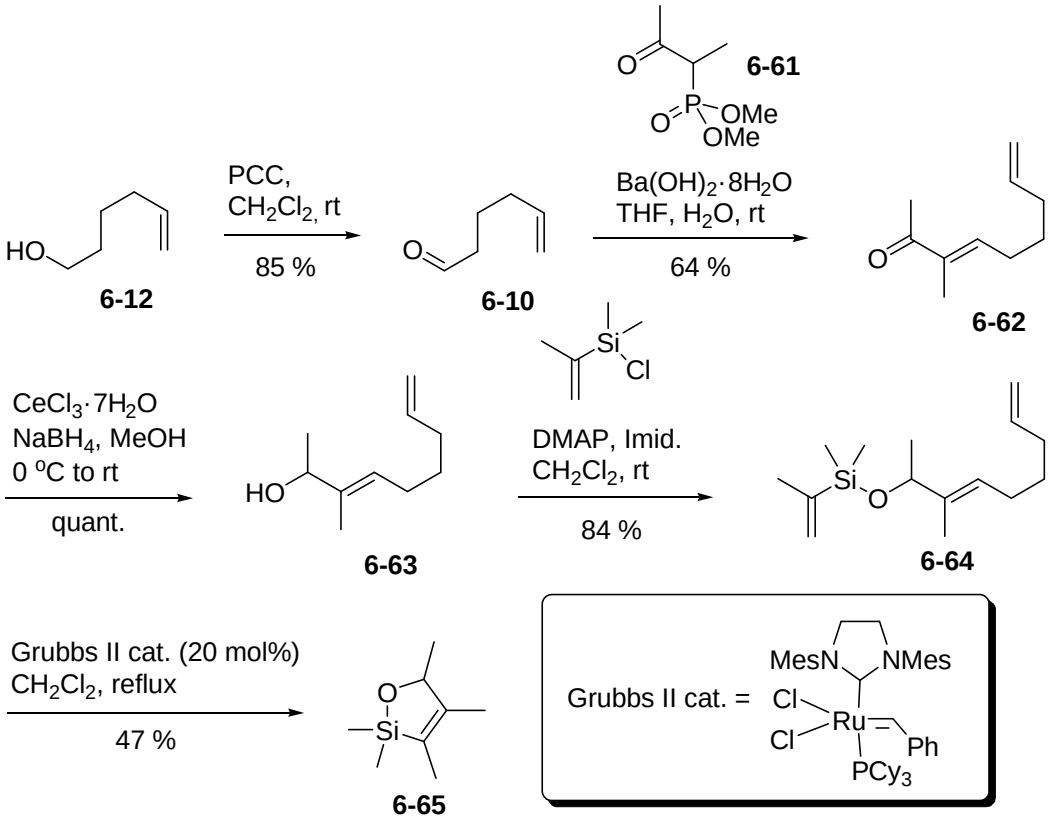
6.2.1 Oxasilole Synthesis

First, the model reaction was performed to look into the feasibility of the RRCM in the synthesis of oxasiloles (Scheme 4-13). We commenced PCC oxidation of 5-hexene-1-ol (**6-12**).[146] The resulting aldehyde **6-10** was treated with the known phosphonate **6-61**[147] in the presence of $Ba(OH)_2 \cdot 8H_2O$ to furnish an enone **6-62** in 64 % yield by way of the Horner-

[146] Combination of RCM and the Pauson-Khand Reaction: One-Step Synthesis of Tricyclic Structures. Rosillo, M; Arnáiz, E.; Abdi, D.; Urgoiti, J. -B., Domínguez, G.; Castells, J. P. *Eur. J. Org. Chem*. **2008**, *23*, 3917-3927.

[147] Biosynthesis of Tetronasin: Part 4, Preparation of Deuterium Labelled C19-C26, C17-C26, C11-C26, and C3-C26 Polyketide Fragments as Putative Biosynthetic Precursors of the Ionophore Antibiotic Tetronasin (ICI 139603). Boons, G. -J.; Clase, A.; Lennon, I. C.; Ley, S. V.; Staunton, J. *Tetrahedron*, **1995**, *51*, 5417-5419.

Wadsworth-Emmons olefination.[148] Lanthanide-assisted selective 1,2-reduction[149] of the enone **6-62** followed by silylation of (E)-allylic alcohol **6-63** with chloro dimethylisopropenylsilane gave a silyl ether **6-64** in 84 % yield. We tested the reaction conditions for RRCM with Grubbs' II catalyst and found that the result was dependent upon the temperature and amount of catalyst. In the first attempt, 10 mol % of catalyst was used at room temperature; although the product was detected on TLC, the reaction was not complete after 1 day Therefore, modified conditions were applied (refluxing temperature and increased catalyst loading). As a result, the oxasilole **6-65** was obtained in 47 % yield after column chromatography. However, because the product **6-65** was very volatile and unstable; careful handling was required.

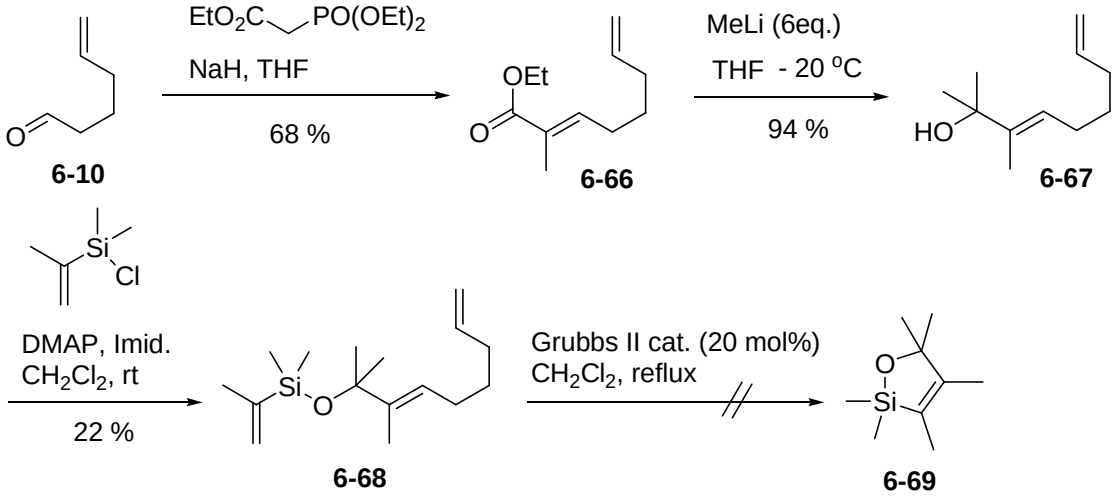


Scheme 6-12. Synthesis of the oxailole **6-65** using RRCM

[148] Total Synthesis of Bistramide A. Lowe, J. T.; Wrona, I. E.; Panek, J. S. *Org. Lett*. **2007**, *9*, 327-330.

[149] Lanthanides in Organic Chemistry. 1. Selective 1,2 Reductions of Conjugated Ketones. Luche, J. -L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

To look at the generality of this method for the synthesis of oxasiloles, another model substrate was examined (Scheme 4-14). The Horner-Wadsworth-Emmons olefination of the aldehyde **6-10** was adapted to give α, β-unsaturated ester **6-66**. Addition of MeLi to the ester **6-66** afforded tert-alcohol **6-67**. The silyation of the alcohol **6-67** showed 100 % conversion, but the 69 % of silyl ether was hydrolyzed during silica gel chromatography. The isolated silyl ether **6-68** was subjected to the Grubbs II catalyst. However, the desired oxasilole **6-69** was not obtained; instead a complicated mixture was recovered.



Scheme 6-13. Examination of the sterically hindered substrate **6-68**

6.2.2 Expansion to the Medium-Sized Rings

6.2.2.1 Study for the synthesis of oxasiline

With the successful application of RRCM to the preparation of oxasilole **6-65**, we moved to expand this chemistry to larger ring formation. First, we decided to apply RRCM conditions to get a 6-membered oxasilacycle (oxasiline). The precursor **6-74** for testing RRCM was prepared by following procedures (Scheme 6-14). The sec-allylic alcohol **6-70** was obtained in 78 % yield by the treatment of aldehyde **6-10** with isopropenylmagnesium bromide in THF at 0 °C. Then, according to the known procedure,[150] alcohol **6-10** was treated with excess thionyl chloride to

[150] The Synthesis and Cyclization of 4-(trans,trans-7,12-Dimethyl-3,7,11-tridecatrienyl)-3-

produce the allylic chloride **6-71**[151] in 69 % yield. Substitution with CuCN without solvent at room temperature gave a β, γ-unsaturated nitrile **6-72** in 14 % yield;[152] a better conversion was obtained with sodium cyanide in DMSO (73 % yield).[153] The nitrile **6-72** was then converted to a *sec*-homoallylic alchol **6-73** (28 % for two steps) by employing diisobutylaluminum hydride (DIBAL-H) reduction followed by mild acidic hydrolysis and subsequent treatment with methyllithium.[154] This low yielding synthesis of the alcohol **6-73** from the chloride **6-71** was able to be improved by one step titanium-mediated allylation[155] of the chloride **6-71** (Scheme 6-15). The silylation of the alcohol **6-73** gave a silyl ether **6-74** in 81 % yield.

Having the key substrate **6-74** in hand, we next evaluated the RRCM reaction. Two catalysts were tested to get an oxasiline **6-77**. First, the Grubbs' II catalyst (15 mol %) was used in dichloromethane at room temperature; however only the relay group was removed to give the compound **6-76** in 22 % yield. Second, when the Grubbs-Hoveyda II catalyst[156] (30 mol %) was

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methyl-2-cyclohexen-1-ol and of Its Allylic Isomer. Parker, K. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 2556-2559.

[151] The synthesis of D,L-15-acetoxypallescensin-A: an intramolecular oxidative free-radical approach. Zoretic, P.A.; Ming, W. *Syn. Commun.* **1996**, *24*, 2783-2796.

[152] On the Mechanism and Kinetics of Radical Reaction of Epoxyketones and Epoxynitriles Induced by Titanocene Chloride. Mateos, A. –F.; Teijón, P. H.; Burón, L. M.; Clemente, R. R.; González, R. R. J. Org. Chem. 2007, 72, 9973-9982.

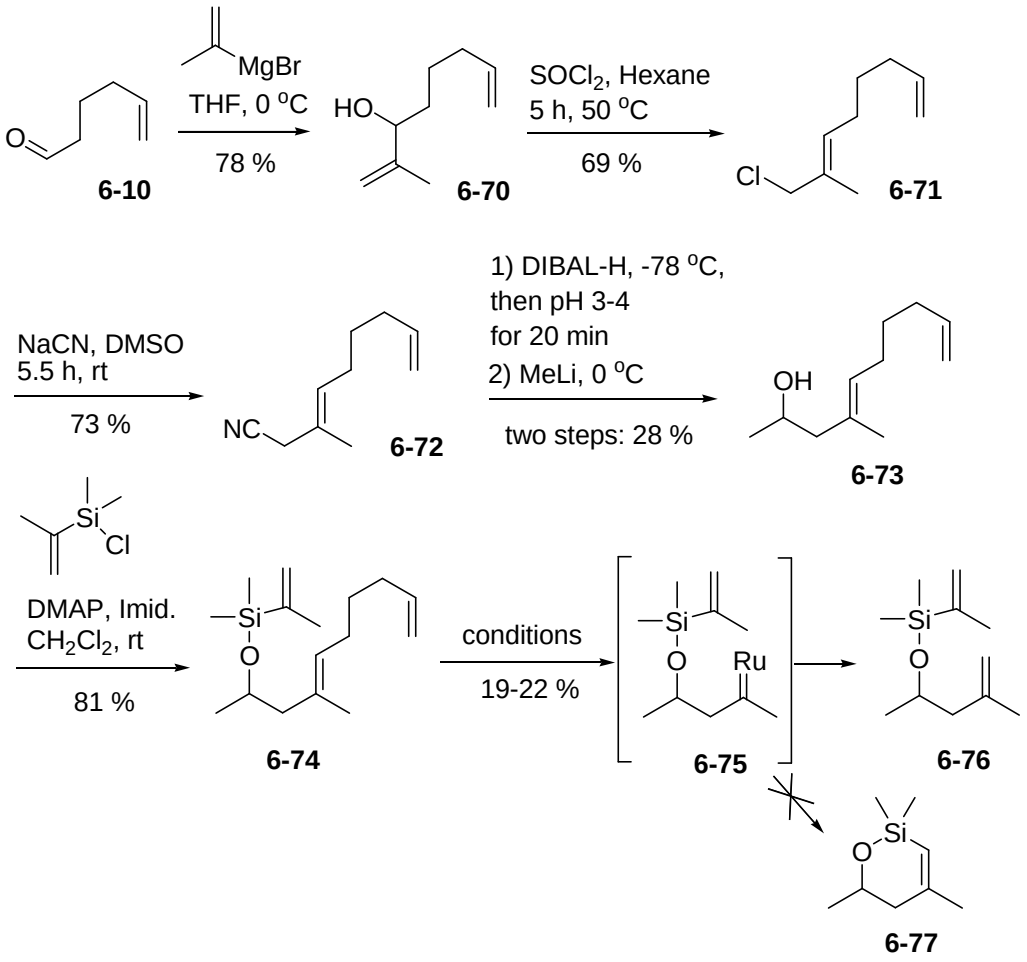
[153] Stereoselective Routes to the C10-C19 Fragment of FK-506. Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2776-2786.

[154] Novel Stererocontrolled Approach to syn- and anti-Oxepene-Cyclogeranyl trans-Fused Polycyclic Systems: Asymmetric Total Synthesis of (-)-Aplysistatin, (+)-Palisadin A, (+)-Palisadin B, (+)-12-Hydroxy-Palisadin B, and the AB Ring System of Adociasulfate-2 and Toxicol A. Couladouros, E. A.; Vidali, V. P. *Chem. Eur. J.* **2004**, *10*, 3822-3835.

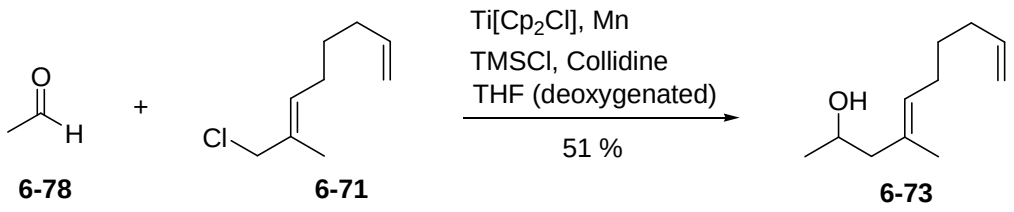
[155] Estévez, R.: Justicia, J.; Bazdi, B.;Fuentes, N.; Paradas, M.; Lazarte, D. C.; Ruiz, G. M.; Robles L,: Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. Ti-Catalyzed Barbier-Type Allylations and Related Reactions. *Chem. Eur. J.* **2009**, *15*, 2774-2791.

[156] Conformations of N-Heterocyclic Carbene Ligands in Ruthenium Complexes Relevant to Olefin Metathesis. Stewart, I. C.; Benitez, D.; O'Leary, D. J.; Tkatchouk, E.; Day, M. W.;

used in refluxing dichloroethane; these conditions also afforded the compound **6-76** (19 %). Presumably, the intermolecular reaction between the ruthenium alkylidene **6-75** and external ligand, styrene in this case, appeared to be faster than the intramolecular metathesis reaction.



Scheme 6-14. The RRCM reaction of silyl ether **6-74** toward oxasiline **6-77**



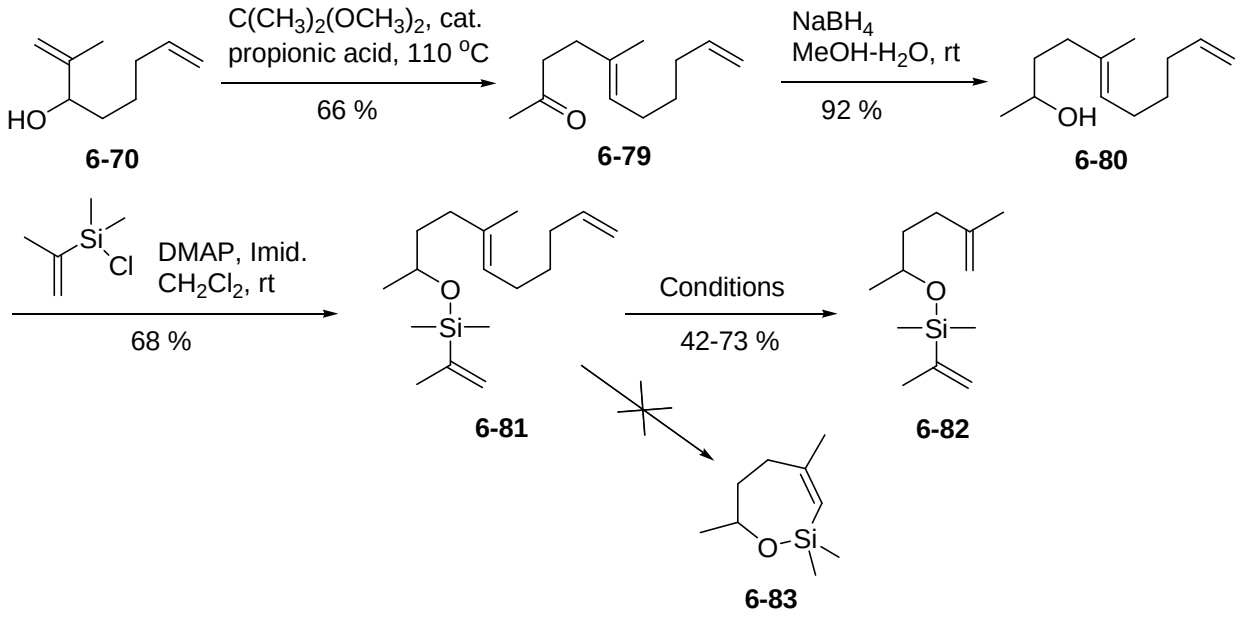
Scheme 6-15. The improved approach to sec-homoallylic alcohol **6-73**

Goddard III, W. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1931-1938.

6.2.2.2 Study for the synthesis of oxasilepine

We next prepared a relay substrate **6-81** to test RRCM conditions for the synthesis of the 7-membered oxasilacycle **6-83** (oxasilepine). The γ, δ-unsaturated ketone **6-79** was obtained in 66 % yield with the starting material recovered (21 %) by Claisen rearrangement of the alcohol **6-70**.[157] The sec-alcohol **6-80** was obtained by sodium borohydride reduction.[158] Silyl protection of the alcohol **6-80** gave a silyl ether **6-81** in 68 % yield.

Having synthesized the substrate **6-81**, we examined the reaction conditions by varying the temperature, solvent, and catalyst. However, no cyclized product **6-83** was obtained and the diene **6-82** was isolated (Scheme 6-16). The screened conditions are summarized in Table 6-1.



Scheme 6-16. The RRCM reaction of silyl ether **6-81** toward oxasilepine **6-83**

[157] Über die Reaktion von tertiären Vinylcarbinolen mit Isopropenyläther Eine neue Methode zur Herstellung von γ, δ-ungesättigten Ketonen. Saucy, G.; Marbet, R. *Helv. Chim. Acta.* **1967**, *7*, 2091.

[158] A New, Simple Synthesis of ***N***-Tosyl Pyrrolidines and Piperidines**.** Marcotullio,M. C.; Campagna' V; Sternativo' S.; Costantino' F.; Curini, M. *Synthesis* **2006**, 2760.

Table 6-1. Screened conditions for RRCM reaction of the silyl ether **6-81**

Cat.	Solvent	Temp.	Time (h)	Result **6-82**
G II (10 mol %)	CH_2Cl_2	reflux	2 h	46 %
G II (20 mol %)	DCE	reflux	3 h	71 %
H-G II	DCE	55 ^oC	2 h	52 %
Stewart-Grubbs	Benzene	50 ^oC	2.5 h	73 %

G II = Grubbs II, H-G II = Hoveyda-Grubbs II

6.3 Conclusion

The tetrasubstituted (*Z*)-vinylsilane allylic alcohol is potentially a key starting material for the synthesis of arisugacin A. In order to obtain this compound, we decided to use ring closing/ring opening strategy that was developed by Parker.

In this chapter, we have studied the RRCM reactions of some silyl ethers for the synthesis of oxasilacycles including an oxasilole, oxasiline, and oxasilepine that are all precursors of tetrasubstituted (*Z*)-vinylsilane allylic alcohols.

Oxasilole **6-65** was obtained in five steps from commercially available 5-hexen-1-ol. The RRCM reaction gave a moderate yield (47%) which may be improved by optimization of reaction conditions. Furthermore, the model product **6-65** was volatile and unstable.[159] Thus, use of a silyl chloride that contain longer alkyl chains or aromatics is expected to solve the synthetic problems.

In case of oxasiline and oxasilepine, the RRCM reactions appeared to be limited. Although we varied the reaction conditions, the ring closure of the silyl ethers was not observed. Instead of the cyclized products, the diene compounds **6-76** and **6-82** were obtained. The optimization for the synthesis of oxasiline and oxasilepine is needed.

[159] The oxasilole **6-65** was decomposed after 1 week at - 20 ^oC.

6.4 Experimental Section

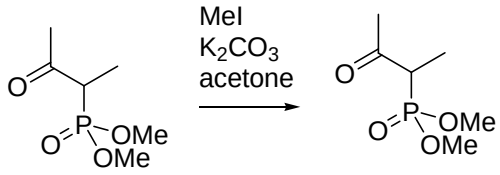
General Information

Reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Acros Organics. Unless otherwise noted, solid reagents were used without further purification. All air- and moisture sensitive reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware. All moisture sensitive solution and anhydrous solvents were transferred *via* standard syringe and cannula techniques. Concentration of solutions was accomplished with a Buchi rotary evaporator evacuated by a water aspirator. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas.

All experiments were monitored by thin layer chromatography (TLC) performed on Whatman 250μm layer aluminum silica gel plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with a 10 % solution of phosphomolybdenic acid (PMA) in ethanol and the heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

Infrared spectra were recorded with a Galaxy Series FT-IR 3000 infrared spectrophotometer. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), Varian Inova-400 (400 MHz for ^1H), Varian Inova-300 (300 MHz for 1H, 75 MHz for 13C) spectrometer. Chemical shifts for proton NMR are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR are reported in ppm with the centerline of the triplet for chloroform-d set at 77.0 ppm. The following abbreviations are used in the experimental section for the description of ^1H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), quintet (q), multiplet (m), doublet of doublets (dd), doublet of quartets (dq), and broad singlet (bs). Coupling constants, *J*, are reported in Herz (Hz).

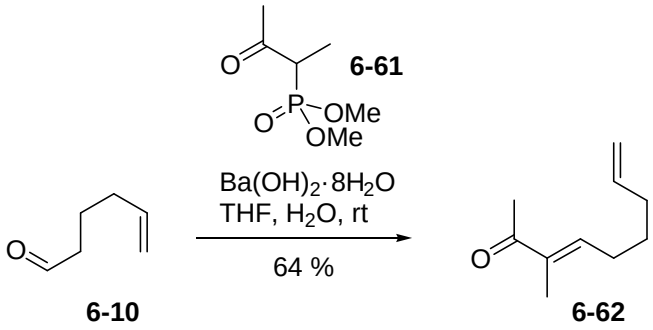
Experimental procedures/ Characterization



6-61

Phosphonate 6-61 Iodomethane (1.56 g, 11 mmol) was added to a stirred solution of dimethyl (2-oxopropyl)phosphonate (1.66 g, 10 mmol) and potassium carbonate (1.80, 13 mmol) in acetone (20 mL) at 0℃. The reaction mixture was stirred at 0℃ for 1 h, and then gradually warmed up to rt. After 16 h, saturated aqueous NH_4Cl solution (30 mL) was poured into the reaction mixture and the mixture was extracted with ethyl acetate (50 × 3 mL). The organic solution was dried over $MgSO_4$ and filtered. The crude product was concentrated *in vacuo* and chromatographed on silica gel (Acetone: Hex = 1:1) to afford phosphonate **6-61** (1.23 g) in 68% yield (pale yellow oil, Lit. yield = 71%).

^{1}H NMR (300MHz, $CDCl_3$): 1.36 (dd, *J* = 18.0 and 7.2 Hz, 3 H), 2.33 (s, 3H), 3.23 (dq, *J* = 25.5 and 7.2 Hz, 1 H), 3.77 (d, *J* = 10.2 Hz, 3 H), 3.78 (d, *J* = 9.6 Hz, 3H). The data were in consistent with literature values.[23]

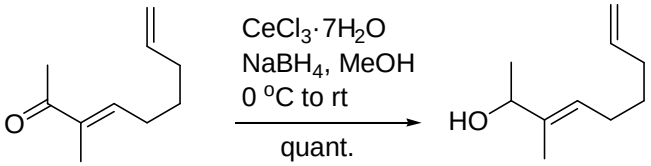


6-10 **6-62**

***α, β*-Unsaturated ketone 6-62.** To a stirred solution of $Ba(OH)_2 \cdot 8H_2O$ (3.94 g, 12.5 mmol) in THF (10 mL) was added phophonate **6-61** (0.90 g, 5 mmol) at room temperature. The solution of aldehyde **6-10** (0.28 g, 2.5 mmol) in THF/H_2O (10 mL/1 mL) was added over dropwise to the pre-mixed solution for 0.5 h. After 0.5 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed by saturated sodium bicarbonate and then extracted with CH_2Cl_2 (20 mL X 3). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was

subjected to silica gel column chromatography (Hex: EtOAc = 25:1) to give *α*, *β*-Unsaturated ketone **6-62** (0.24 g, 64 %) as colorless oil.

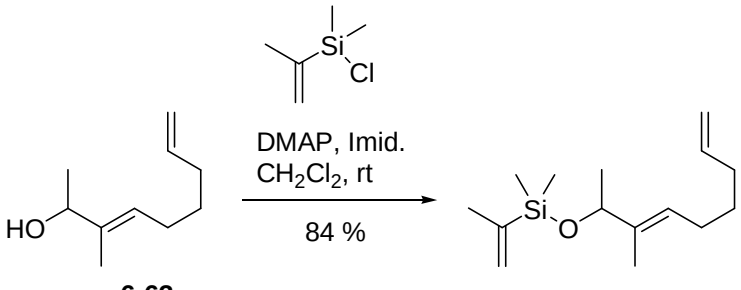
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59-6.65 (m, 1 H), 5.74-5.87 (m, 1 H), 4.96-5.06 (m, 2 H), 2.30 (s, 3 H), 2.21-2.29 (m, 2 H), 2.06-2.13 (m, 2 H), 1.75-1.77 (m, 3 H), 1.52-1.64 (m, 2 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 25.4, 27.8, 28.4, 33.3, 115.1, 137.8, 138.0, 143.3, 199.9.; IR (neat) νmax 2927, 1669, 1641, 1436 cm^{-1}.



6-62 **6-63**

sec-Alcohol 6-63 The *α*, *β*-unsaturated ketone **6-62** (0.20 g, 1.3 mmol) was dissolved in a solution of $CeCl_3·7H_2O$ (0.48 g, 1.3 mmol) in MeOH (3.25 mL). Then, $NaBH_4$ (0.049 g, 1.3 mmol) was slowly added to the solution at 0 ℃. After 10 min, NH_4Cl (2 mL) was added to the reaction mixture and stirred for 5 min. The resulting mixture was extracted with Et_2O (20 × 2 mL), dried over $MgSO_4$ and filtered. The organic solution was concentrated and used without further purification.

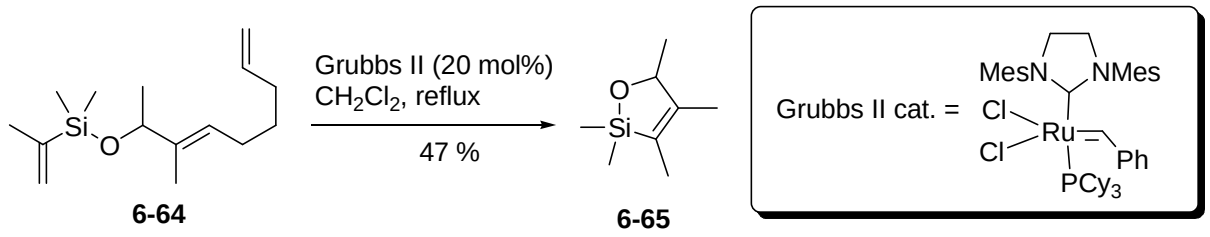
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.6 Hz, 3H), 1.45 (quintet, *J* = 7.5 Hz, 2H), 1.62 (d, *J* = 1.5 Hz, 3 H), 1.99-2.09 (m, 4H), 4.20 (q, *J* = 6.6 Hz, 1 H), 4.92-5.04 (m, 2 H), 5.40 (ddt, *J* = 6.6, 6.6, and 1.2 Hz, 1 H), 5.80 (ddt, *J* = 17.1, 6.6, and 6.6 Hz, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 21.6, 26.9, 28.7, 33.3, 73.4, 114.5, 124.8, 138.7, 138.8.; IR (neat) νmax 3351, 2974, 2926, 2856, 1640 cm^{-1}.



6-63 **6-64**

Silyl ether 6-64 To a stirred solution of dichlorodimethylsilane (0.56 g, 4.4 mmol) in THF (5 mL) was added the propen-2-yl magnesium bromide (0.5 M in THF, 13.2 mL, 6.6 mmol) by cannula at -78 ^{o}C under Ar. The resulting mixture was stirred at -78 ℃ for 0.5 h and then warmed up to r.t. over 2 h. The resulting mixture was transferred to a pre-mixed solution of **6-63** (0.17 g, 1.1 mmol), DMAP (0.067 g, 0.55 mmol) and imidazole (0.37 g, 5.5 mmol) in CH_2Cl_2 (10 mL) at r.t. and the reaction mixture was stirred overnight. The reaction mixture was quenched by NH_4Cl (30 mL), and extracted with Et_2O (30 × 2 mL). The combined organic solution was washed by sat. aqueous $NaHCO_3$ solution and brine. The separate organic layers were dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 50: 1) to afford silyl ether **6-64** (0.23 g, 84%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.3 Hz, 3 H), 1.43 (quintet, *J* = 7.5 Hz, 2 H), 1.57 (m, 3 H), 1.82 (m, 3 H), 1.95-2.08 (m, 4 H), 4.15 (q, *J* = 6.3 Hz, 1 H), 4.92-5.04 (m, 2 H), 5.28-5.35 (m, 2 H), 5.88-5.62 (m, 1 H), 5.74-5.88 (m, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.3, -2.0, 11.3, 21.9, 23.1, 26.9, 28.7, 33.4, 74.1, 114.4, 124.0, 126.1, 138.6, 138.9, 146.5.; IR (neat) νmax 2958, 2929, 1641, 1447 cm^{-1}.

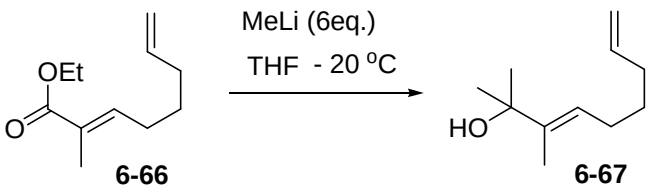


6-64 **6-65**

Oxasilole 6-65 In an oven-dried 250 mL round-bottom flask, silyl ether **6-64** (0.13 g, 0.51 mmol) was placed, and dry CH_2Cl_2 (103 mL) was added by a syringe under Ar. To a resulting solution was added Grubbs II catalyst (0.087 g, 0.10 mmol). The reaction mixture was then refluxed and stirred for 1.5 h. After the reaction mixture was cooled down to r.t., it was concentrated in an ice bath, filtered through a short pad of silica gel (rinsing with Et_2O), and concentrated. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 50: 1) to afford oxasilole **6-65** (0.038 g, 47%) as a colorless oil.

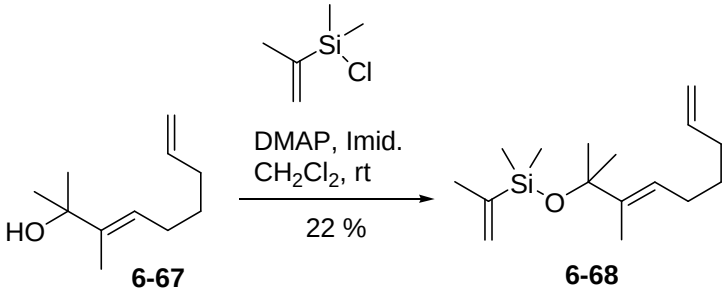
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 3 H), 0.20 (s, 3 H), 1.25 (d, *J* = 6.6 Hz, 3 H), 1.64-1.65 (m, 1 H), 1.65 (s, 3 H), 1.69 (s, 3 H).4.55 (q, *J* = 6.6 Hz, 1 H); IR (neat) νmax 2958, 2921, 2851,

1732, 1462, 1376, 1258 cm^{-1}.



tert-Alcohol 6-67 To a stirred solution of the ester 6-66 (0.36 g, 2.0 mmol) was added MeLi (1.6 M in diethyl ether, 7.5 mL, 12.0 mmol) at – 20 °C under Ar. After the reaction mixture was stirred for 1 h, it was quenched with sat. NH_4Cl sol'n. The aqueous solution was extracted with ethyl acetate and the organic solution was drided over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 10: 1) to afford the tert-alcohol **6-67** (0.32 g, 84%) as colorless oil.

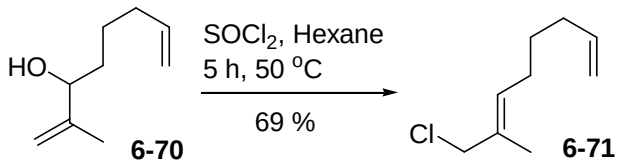
^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 6 H), 1.46 (m, 2 H), 1.66 (q, *J* = 0.9 Hz, 3 H), 2.04 (m, 4 H), 4.92 – 5.04 (m, 2 H), 5.48 (tq, *J* = 7.2 and 0.9 Hz, 1 H), 5.81 (m, 1 H).; IR (neat) νmax 1136, 1371, 1458, 1640, 3373 cm^{-1}.



Silyl ether 6-68 To a stirred solution of dichloromethylsilane (0.77 mL, 6.32 mmol) in THF (10 mL) was added dropwise the propen-2-yl magnesium bromide (0.5 M in THF, 18.9 mL, 9.48 mmol) at – 78 °C. The reaction mixture was warmed to r.t. over 2 h. The resulting mixture was transferred to a pre-mixed solution of **6-67** (0.27 g, 1.58 mmol), DMAP (0.097 g, 0.79 mmol) and imidazole (0.54 g, 7.9 mmol) in CH_2Cl_2 (10 mL) at r.t. and the reaction mixture was stirred overnight. The reaction mixture was quenched by NH_4Cl (30 mL), and extracted with Et_2O (30 × 2 mL). The combined organic solution was washed by sat. aqueous $NaHCO_3$ solution and brine. The separate organic layers were dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 50: 1) to afford silyl ether **6-68** (95.2 mg,

22 %) as colorless oil with starting material (0.18 g, 69 %) recovered.

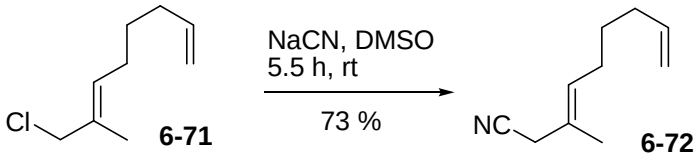
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 6 H), 1.33 (s, 6 H), 1.40 – 1.50 (m, 2 H), 1.63 (q, *J* = 1.2 Hz, 3 H), 1.84 (t, *J* = 1.5 Hz, 3 H), 1.97 – 2.10 (m, 4 H), 4.92 – 5.04 (m, 2 H), 5.34 – 5.53 (m, 2 H), 5.54 (m, 1 H), 5.82 (m, 1 H).



6-70 **6-71**

Allyl chloride 6-71 To a stirred solution of 2-Methylocta-1,7-dien-3-ol (**6-70**) (0.70 g, 5 mmol) in dry hexane was added excess $SOCl_2$ (1.30 mL, 18.06 mmol) at 50 ℃ under Ar. After 5 h, the reaction was cooled down, and the residue of $SOCl_2$ was evaporated. The crude mixture was diluted with hexane (30 mL) and washed with water (10 mL), sat. aqueous $NaHCO_3$ solution (10 mL) and brine. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hexane) to afford allyl chloride **6-71** (0.55 g, 68 %) as a colorless oil.

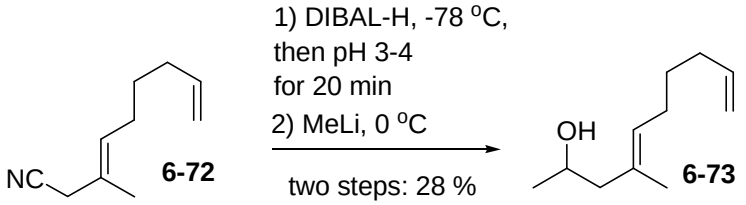
^{1}H NMR (300MHz, $CDCl_3$): 5.73-5.87 (m, 1 H), 5.50-5.55 (m, 1 H), 4.95-5.05 (m, 2 H), 4.02 (d, *J* = 0.9 Hz, 2 H), 2.01-2.10 (m, 4 H), 1.72-1.73 (m, 2 H), 1.464 (q, *J* = 7.5 Hz, 2 H). The data were in consistent with literature values.[26]



6-71 **6-72**

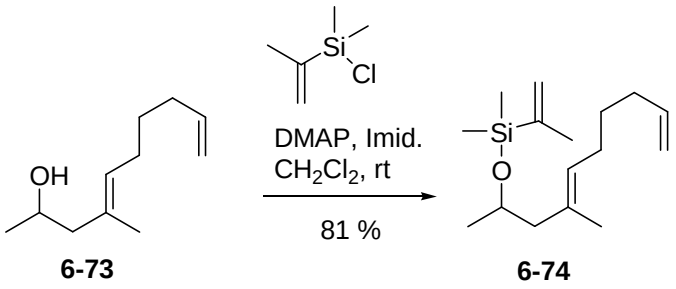
β, γ-Unsaturated nitrile 6-72 To a stirred solution of allyl chloride **6-71** (0.32 g, 2.0 mmol) in DMSO was added sodium cyanide (0.12 g, 2.4 mmol) at r.t. under Ar. After 4 h, the reaction mixture was diluted with water (10 mL) and extracted with Et_2O (20 X 3 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 15: 1) to afford the β, γ-unsaturated nitrile **6-72** (0.26 g, 73 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (q, *J* = 7.5 Hz, 2 H), 1.72 (s, 3 H), 2.02-2.09 (m, 4 H), 3.02 (s, 2 H), 4.94-5.04 (m, 2 H), 5.45-5.51 (m, 1 H), 5.73-5.86 (m, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 27.1, 27.3, 28.3, 33.1, 114.7, 117.8, 124.2, 129.5, 138.4.; IR (neat) νmax 2938, 2248, 1640, 1437 cm^{-1}.



sec-Homoallylic alchol **6-73** 1) To a flame-dried 50 mL round-bottom flask β, γ-Unsaturated nitrile **6-72** (0.15 g, 1.0 mmol) was placed, and CH_2Cl_2 (5 mL) was added under Ar. The resulting solution was stirred at -78 °C for 0.5 h. Then, diisobutylalumium hydride (DIBAL-H) (1. 0 M in Hexane, 1.1 mL, 1.1 mmol) was added dropwise. After 0.5 h, the reaction was quenched by MeOH (0.2 mL) and poured in a mixture of EtOAc/sat. NH_4Cl sol'n (2.5/2.5 mL). The mixture was treated with 10 % potassium sodium tartrate and stirred for 1 h. The mixture was extracted with EtOAc (10 X 3 mL). The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude aldehyde was directly used for the next step without further purifications. 2) To a stirred solution of the aldehyde in THF (5 mL) was added dropwise methyl lithium (1.6 M in Et_2O, 0.94 mL, 1.5 mmol) at 0 °C under Ar. After 0.5 h, the reaction mixture was diluted with Et_2O (20 mL) and quencehd with sat. aqueous NH_4Cl sol'n. The ethereal layer was dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to silica gel column chromatography (Hexane: EtOAc = 10: 1) to afford sec-homoallylic alchol **6-73** (47.0 mg, 28 % two steps) as a colorless oil.

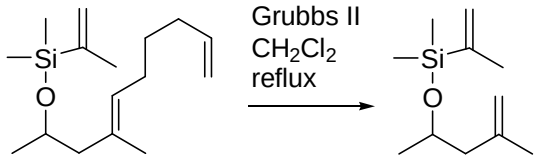
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.0 Hz, 3 H), 1.44 (q, *J* = 7.5 Hz, 2 H), 1.62 (d, *J* = 0.6 Hz, 3 H), 1.75 (bs, 1 H), 1.99-2.09 (m, 5 H), 2.12-2.18 (dd, *J* = 13.0, 4.2 Hz, 1 H), 3.81-3.92 (m, 1 H), 4.92-5.03 (m, 2 H), 5.21-5.26 (m, 1 H), 5.73-5.87 (m, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 22.7, 27.4, 28.9, 33.4, 49.8, 64.7, 114.5, 128.4, 132.2, 138.7.; IR (neat) νmax 3398, 2925, 1664, 1640, 1458 cm^{-1}.



6-73 **6-74**

Silyl ether 6-74 To a stirred solution of dichlorodimethylsilane (0.12 g, 0.96 mmol) in THF (5 mL) was added propen-2-yl magnesium bromide (0.5 M, 2.88 mL, 1.44 mmol) at – 78 ^{o}C by cannula. The resulting mixture was stirred at – 78 ^{o}C for 0.5 h and then warmed up to r.t. over 2 h. The resulting mixture was transferred to a pre-mixed solution of **6-73** (0.041 g, 0.24 mmol), DMAP (0.015 g, 0.012 mmol) and imidazole (0.082 g, 1.2 mmol) in CH_2Cl_2 (2 mL) at r.t. by cannular. After 2 h, the reaction mixture was quenched by sat. NH_4Cl sol'n (5 mL) and extracted with diethyl ether (20 X 3 mL). The combined organic solution was washed by sat. $NaHCO_3$ sol'n and brine. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 50: 1) to afford the silyl ether **6-74** (0.23 g, 81 %) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.171 (s, 3 H), 0.174 (s, 3 H), 1.10 (d, *J* = 6 Hz, 3 H), 1.43 (q, *J* = 7.5 Hz, 2 H), 1.58-1.59 (m, 3 H), 1.83-1.84 (m, 3 H), 1.95-2.09 (m, 5 H), 2.16-2.23 (dd, *J* = 13.0, 6.0 Hz), 3.84-3.95 (m, 1 H), 4.91-5.02 (m, 2 H), 5.13-5.18 (m, 1 H), 5.35-5.39 (m, 1 H), 5.60-5.63 (m, 1 H), 5.74-5.88 (m, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.1, -2.0, 16.5, 22.0, 23.3, 27.4, 28.9, 33.4, 50.1, 67.6, 114.3, 126.3, 127.2, 132.4, 138.9, 146.4.

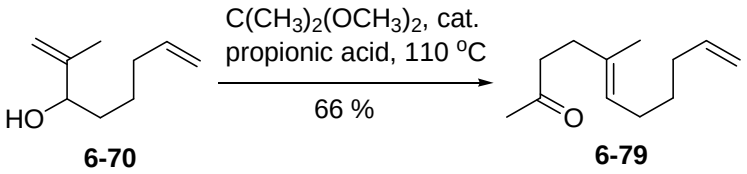


6-74 **6-76**

Diene 6-76 The silyl ether **6-74** (20.0 mg, 0.075 mmol) was placed in an oven-dried 50 mL round-bottom flask, and dry CH_2Cl_2 (7.5 mL) was added by a syringe under Ar. To a resulting

solution was rapidly added Grubbs II catalyst (12.7 mg, 0.015 mmol). The reaction mixture was then refluxed and stirred for 1 h. After the reaction mixture was cooled to r.t., it was concentrated in an ice bath, filtered through a short pad of silica gel (rinsing with Et_2O). The filtrate was carefully concentrated and subjected to silica gel column chromatography (Hex: EtOAc = 100: 1) to afford the diene **6-76** (2.82 mg, 19%) as a colorless oil.

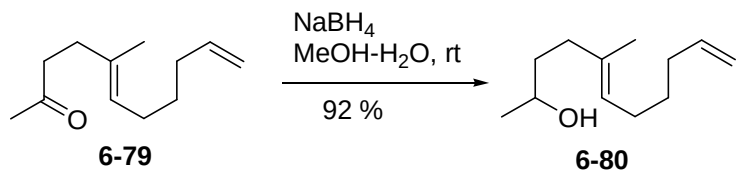
^{1}H NMR (600MHz, $CDCl_3$): 0.184 (s, 3 H), 0.188 (s, 3 H), 1.13 (d, *J* = 6 Hz, 3 H), 1.72 (s, 3 H), 1.85 (s, 3 H), 2.21-2.25 (dd, *J* = 13.5 and 6.6 Hz, 2 H), 3.91-3.97 (m, 1 H), 4.70-4.76 (m, 2 H), 5.37 (m, 1 H), 5.62 (m, 1 H).



6-70 **6-79**

γ, δ-Unsaturated ketone 6-79 A solution of the alcohol **6-70** (0.28 g, 2.0 mmol), dimethoxypropane (1.04 g, 10.0 mmol) and propanoic acid (7.4 μL, 0.10 mmol) was stirred at 110 °C. After 1 day, 5 eq. dimethoxypropane (1.04 g, 10 mmol) was added to the reaction mixture, and the mixture was stirred for additional 1 day. The reaction mixture was then cooled to r.t. and quenched with ice-cold 2 M HCl. The aqueous layer was extracted with EtOAc (10 X 3 mL). The organic solution was dried over $MgSO_4$, concentrated, and subjected to silica gel column chromatography (hexane: EtOAc = 30:1) to give γ, δ-unsaturated ketone **6-79** (0.24 g, 66 %) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$): 1.39 (q, *J* = 7.2 Hz, 2 H), 1.57 (s, 3 H), 1.95-2.02 (m, 4 H), 2.12 (s, 3 H), 2.23 (t, *J* = 7.6 Hz, 2 H), 2.50 (t, *J* = 7.6 Hz, 2 H), 4.90-4.00 (m, 2 H), 5.09-5.12 (m, 1 H), 5.73-5.83 (m, 1 H).; IR (CH_2Cl_2): 2925, 1718, 1640, 1439, 1358cm^{-1}.

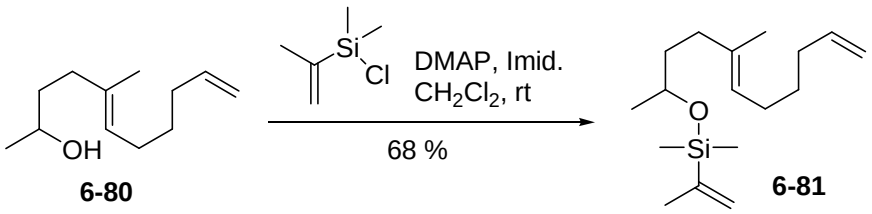


6-79 **6-80**

sec-Alcohol 6-80 To a stirred solution of the ketone **6-79** (0.54 g, 3 mmol) in EtOH (5 mL) was

added dropwise a solution of $NaBH_4$ (0.57 g, 1.5 mmol) in H_2O (3 mL) for 0.5 h. After 2 h, the reaction was quenched with 1 N HCl and extracted with EtOAc (20 X 3 mL). The extracts were washed with sat. $NaHCO_3$ solution. The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to silica gel column chromatography (hex: EtOAc = 10: 1) to afford sec-alcohol **6-80** (0.50 g, 92 %) as a colorless oil.

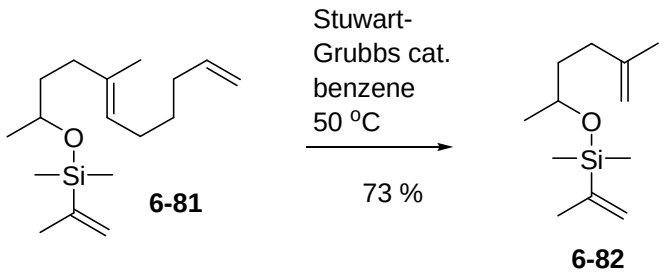
^{1}H NMR (300MHz, $CDCl_3$): 1.19 (d, *J* = 6.6 Hz, 3 H), 1.42, (q, *J* = 7.5 Hz, 2 H), 1.51-1.59 (m, 2 H), 1.61 (d, *J* = 0.9 Hz, 3 H), 1.96-2.10 (m, 6 H), 3.74-3.84 (m, 1 H), 4.92-5.03 (m, 2 H), 5.15-5.21 (m, 1 H), 5.74-5.88 (m, 1 H).; IR (neat) νmax 3353, 2967, 1640, 1454 cm^{-1}.



6-80 **6-81**

Silyl ether 6-81 To a stirred solution of dichlorodimethylsilane (1.03 g, 8 mmol) in THF (10 mL) was added propen-2-yl magnesium bromide (0.5 M, 24.0 mL, 12 mmol) at – 78 ^oC under Ar by cannula. The reaction mixture was stirred at -78 ^oC for 0.5 h and then warmed to r.t. over 2 h. The resulting mixture was transferred to a pre-mixed solution of the alcohol **6-80** (0.36 g, 2 mmol), DMAP (0.12 g, 1 mmol) and imidazole (0.68 g, 10 mmol) in CH_2Cl_2 (20 mL) at r.t. by cannula. After 1 h, the reaction mixture was quenched by sat. NH_4Cl sol'n (10 mL) and extracted with diethyl ether (20 X 3 mL). The combined organic solution was washed by sat. $NaHCO_3$ sol'n, brine, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 100: 1) to afford the silyl ether **6-81** (0.38 g, 68 %) as colorless oil.

^{1}H NMR (300MHz, $CDCl_3$): 0.19 (s, 6 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.42 (q, *J* = 7.2 Hz, 2 H), 1.46-1.63 (m, 2 H), 1.58 (m, 3 H), 1.85 (t, *J* = 1.5 Hz, 3 H), 1.93-2.08 (m, 6 H), 3.70-3.80 (m, 1 H), 4.92-5.03 (m, 1 H), 5.04-5.14 (m, 1 H), 5.36-5.38 (m, 1 H), 5.60-5.63 (m, 1 H), 5.75-5.89 (m, 1 H).



6-81 **6-82**

Diene 6-82 To a stirred solution of the Stuart-Grubbs catalyst (6.1 mg, 11.0 µmol) in dry benzene (30.6 mL) was added a solution of silyl ether **6-81** (30.0 mg, 0.11 mmol) in dry benzene (5 mL) by cannula over 0.5 h at 50 ℃. After 2.5 h, the reaction mixture was cooled to r.t. and concentrated. The concentrate was filtered through a short pad of silica gel (rinsing with Et_2O), and concentrated again. The residue was subjected to silica gel column chromatography (Hex: EtOAc = 100: 1) to afford silyl ether **6-82** (17.1 mg, 73%) as a colorless oil.

^{1}H NMR (300MHz, $CDCl_3$): 5.62 (m, 1 H), 5.37 (m, 1 H), 4.67-4.69 (m, 2 H), 3.75-3.81 (m, 1 H), 1.97-2.08 (m, 2 H), 1.85 (s, 3 H), 1.72 (s, 3 H), 1.46-1.69 (m, 2 H), 1.1.15 (d, *J* = 6.3 Hz, 3 H), 0.190 (s, 6 H).

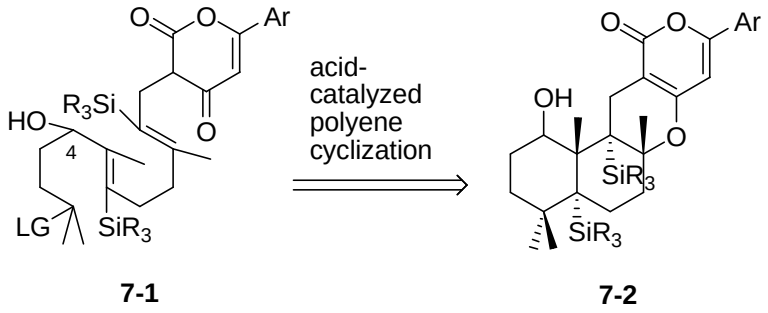
Chapter 7

Arisugacin A; Synthetic Study of Polyolefin cyclization

7.1 Introduction

7.1.1 Synthetic issues posed by the polyolefin cyclization

Previously we designed the retrosynthesis of arisugacin A on the basis of acid-catalyzed polyene cyclization as a key reaction. The potential polyene precursor **7-1** contains a vinyl silane and vinyl silane allyl alcohol (Scheme 7-1). Although the acid catalyzed polyolefin cyclization is now considered as a versatile methodology for the synthesis of multi-fused carbocycles containing angular substituents, our substrate has some anticipated difficulties for its application. First, the incorporation of two vinyl silane moieties in one molecule is not trivial; there has not been any report related to this structure. Second, the acidic conditions in the presence of allyl alchol at C4 might be risky because the allyl alchol is a good leaving group. Third, there's a possibility that the silyl group after the first cyclization might be eliminated to give an olefin. Thus, exploration of appropriate conditions is needed for the successful polyene cyclization of the substrate **7-1**.



7-1 **7-2**

Scheme 7-1. A key polyene cyclization in our retrosynthesis

7.1.2 Examples of polyene cyclization

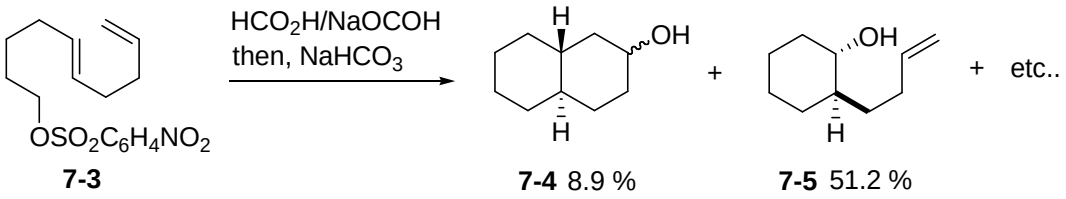
7.1.2.1 Johnson's study

Since the first demonstration of the cationic cyclization of polyolefin by the Johnson group, many chemists have adapted this tandem cyclization protocol to prepare multi-fused carbocycles, especially steroidal natural products.[160] Because of the construction of angular methyl groups

[160] A Case Study in Biomimetic Total Synthesis: Polyolefin Carbocyclization to Terpenes and

and convenient synthesis in one-pot, Johnson's research on natural product syntheses and methodology development for polyene cyclization has been of huge interest and for several decades.

In 1963 and 1964, Johnson et al. reported a series of studies regarding the cationic cyclization of trans-5,9-decadienyl *p*-nitrobenzenesulfonate (**7-3**). The solvolysis of primary p-nosylate **7-3** gave the trans-decalin **7-4** in 8.9% yield (Scheme 7-2).[161]



Scheme 7-2. Solvolysis of diene nosylate

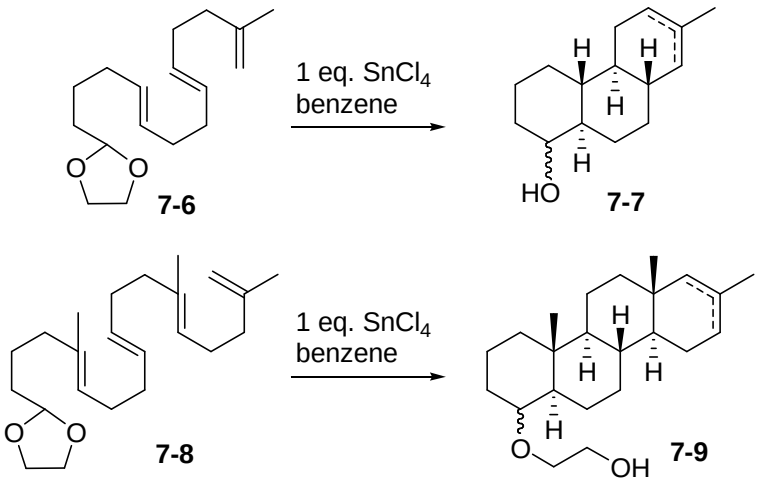
The stereochemistry was studied by Stork and Eschenmoser.[162] The Stork-Eschenmoser hypothesis was concerned with the formation of trans/cis-decalins from the 1, (E)- or (Z)-5, 9-trienes under acid catalyst. Their hypothesis was that the (*Z*)-5-olefin would give cis-decalin while (*E*)-5-olefin would give trans-decalin. Their hypothesis was consistent with Johnson's experimental results.

Steroids. Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730-4756.

[161] Cationic Cyclizations Involving Olefinic Bonds. II. Solvolysis of 5-Hexenyl and *trans*-5,9-Decadienyl *p*-Nitrobenzenesulfonates. Johnson, W. S.; Bailey, D. M.; Owyang, R.; Russell, A. B.; Jaques, B.; Crandall, J. K. J. *J. Am. Chem. Soc.*, **1964**, *86*, 1959–1966.

[162] (a) The Stereochemistry of Polyene Cyclization. Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Triterpenes. CXC. A stereochemical interpretation of the biogenetic isoprene rule of the triterpenes. Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta*. **1955**, *38*, 1890.

They also introduced acetals as initiating groups. They carried out acid catalyzed cyclization using $SnCl_4$ to obtain stereoselective tricyclic **7-7** (87 %) and tetracyclic product **7-9** (30 %) from triene **7-6** and tetraene **7-8**, respectively (scheme 7-3).[163]



Scheme 7-3. $SnCl_4$-catalyzed polyene cyclization

The use of acetylene as a terminating group and of allylic alcohols as initiating groups allowed the synthesis of a number of bicycles, tricycles, and tetracycles. The functionality in the products depended on the nucleophile that was available to capture the terminal vinyl cation.[164]

For example, when nitroalkane was used as a trapping nucleophile, an oxime ether **7-11** was produced byaddition of nitroalkane to the terminal cation followed by rearrangement (Scheme 7-4). Treatment of the resulting oxime ether **7-11** with $LiAlH_4$ gave the diol **7-12**. The catalytic

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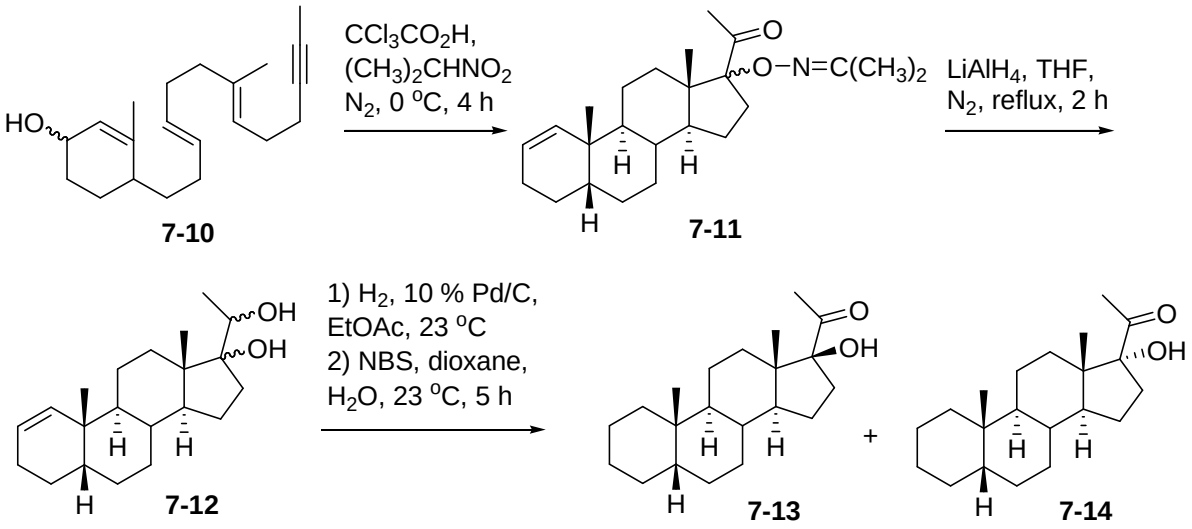
[163] (a) Stereospecific Tricyclization of a Polyolefinic Acetal. Johnson, W. S.; Kinnel, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 3861-3862. (b) The Nonenzymic, Biogenetic-Like Cyclization of a Tetraenic Acetal. Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5277-5279.

[164] (a) Acetylenic Bond Participation in Biogenetic-Like Olefinic Cyclizations. I. Formation of Five-Membered Rings in Model Systems. Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Myers, R. F.; Bryson, T. A.; Miles, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 4330-4332. (b) Acetylenic Bond Participation in Biogenetic-Like Olefinic Cyclizations. II. Synthesis of *dl*-Progesterone. Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332-4334.

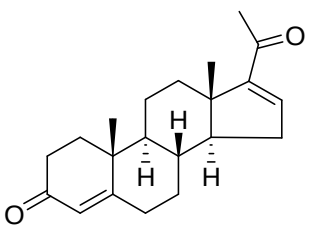
hydrogenation of the double bond was followed by oxidation of the sec-alcohol, providing epimeric products **7-13** and **7-14**.[165]



Scheme 7-4. Synthesis of the 17-Hydroxy-5*β*-pregnan-20-one

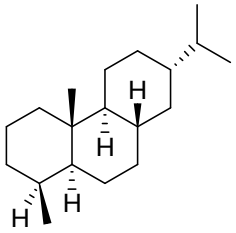
Polyeolefin carbocyclization in the Johnson group had been well-studied; it had resulted in many significant approaches to steroidal natural products. In particular, modifications of the terminating groups (propargylsilane, trimethylsilylacetylene), initiating groups, a cation-stabilizing functional group (e.g fluorine atom) and chiral auxiliaries had been extensively studied. Representative examples of synthesized terpenoids (*dl*-16,17-dehydroprogesterone, *dl*-fichtelite, *dl*-progesterone, 5*β*-D-homoandrostan-17-one, corticoids, euphol, tirucallol, *β*-amyrin, sophoradiol, *dl*-dammarenediol) are presented in Figure 7-1.

[165] Acetylenic Bond Participation in Biogenetic-Like Olefinic Cyclizations in Nitroalkane Solvents. Synthesis of the 17-Hydroxy-5*β*-pregnan-20-one System. Morton, D. R.; Gravestock, M. B.; Parry, R. J.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 4417-4418.



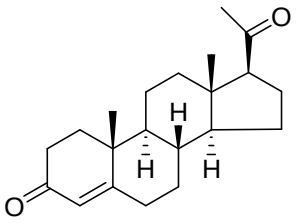
dl-16,17-dehydroprogesterone

(**7-15**)



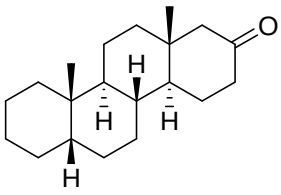
dl-fichtelite

(**7-16**)



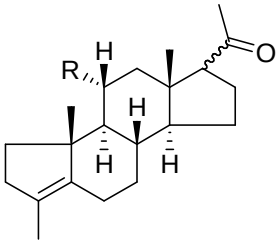
dl-progesterone

(**7-17**)



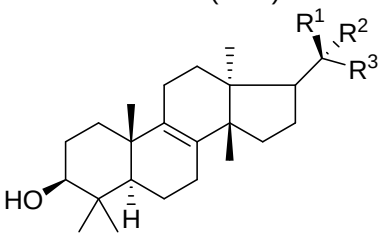
5*β*-D-homoandrostan-17-one

(**7-18**)



corticoids

(**7-19**)

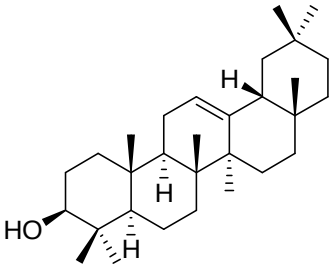


R^1 = H, R^2 = CH_3,
R_3 = $(CH_2)_2CH=C(CH_3)_2$

euphol (**7-20**)

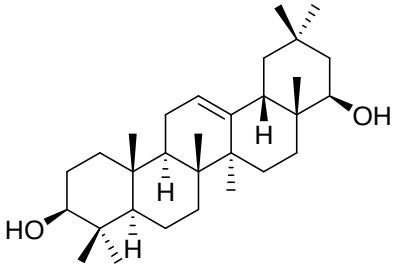
R^1 = CH3, R^2 = H,
R_3 = $(CH_2)_2CH=C(CH_3)_2$

tirucallol (**7-21**)



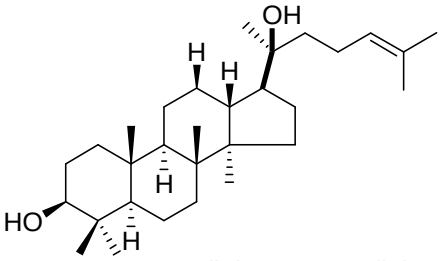
β-amyrin

(**7-22**)



sophoradiol

(**7-23**)



dl-dammarenediol

(**7-24**)

Figure 7-1. Synthesized terpenoids by Jhonson et al.

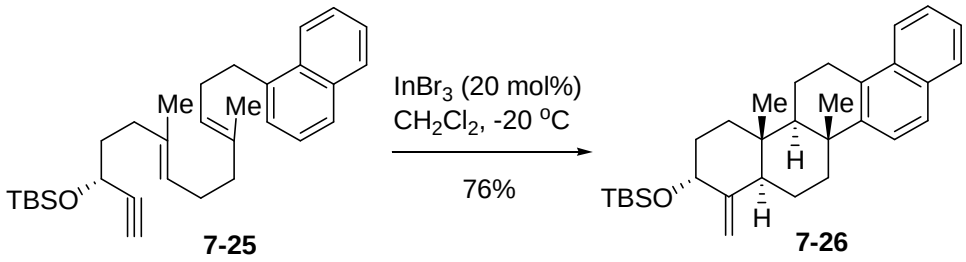
7.1.2.2 Corey's study

The Corey group have studied the polyolefin cyclization to synthesize many polycyclic natural products. In particular, they have used a chiral epoxide as the initiating group to induce enantioselective synthesis in many examples.[166]

In 2011, Surendra and Corey reported the indium(III)-catalyzed cationic cyclization of chiral polyene substrates containing a terminal acetylene as the initiating group.[167] The resulting allyl alcohol structure **7-26** is expected to be used for further transformation into many related natural products (Scheme 7-5).

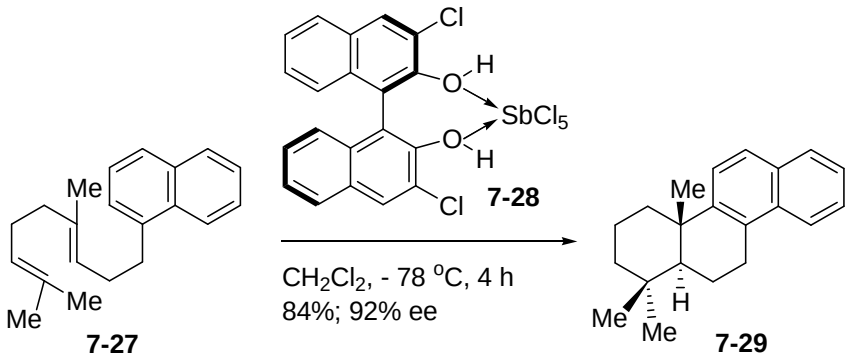
[166] (a) Enantioselective Total Synthesis of Oleanolic Acd, Erythrodiol, β-Amyrin, and Other Pentacyclic Triterpenes from a Common Intermediate. Corey, E. J.; Lee, J. *J. Am. Chem. Soc*. **1993**, *115*, 8873-8874. (b) A New Strategy for Stereocontrol of Cation-Olefin Cyclization. The First Chemical Emulation of the A/B-trans-9,10-syn-Folding Pathway of Steroid Biosynthesis from 2,3-Oxidosqualene. Corey, E. J.; Wood Jr, H. B. *J. Am. Chem. Soc*. **1996**, *118*, 11982-11983. (c) A Simple Enantioselective Synthesis of the Biologically Active Tetracyclic Marine Sesterterpene Scalarenedial. Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc*. **1997,** *119*, 9927-9928. (d) An Exceptionally Short and Simple Enantioselective Total Synthesis of Pentacyclic Triterpenes of the β-Amyrin Family. Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 9999-10003. (e) Simple Enantioselective Approach to Synthetic Limonoids. Behenna, D. C.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 6720–6721. (f) Rapid and Enantioselective Synthetic Approaches to Germanicol and Other Pentacyclic Triterpenes. Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869. (g) A Short Enantioselective Total Synthesis of the Fundamental Pentacyclic Triterpene Lupeol. Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928–13929.

[167] A Powerful New Construction of Complex Chiral Polycycles by an Indium(III)-Catalyzed Cationic Cascade. Surendra, K.; Qiu, W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724-9726.



Scheme 7-5. Indium(III)-catalyzed cationic cyclization

Most recently, Surendra and Corey disclosed enantioselective proton-initiated cationic cyclization of polyene substrates by using stoichiometric chiral BINOL and antimony pentachloride. The BINOL-antimony complex **7-28** provided a chiral environment that limited the approach of polyolefin to the proton source. The resulting products displayed high yield and high enantioselectivity (Scheme 7-6).[168]

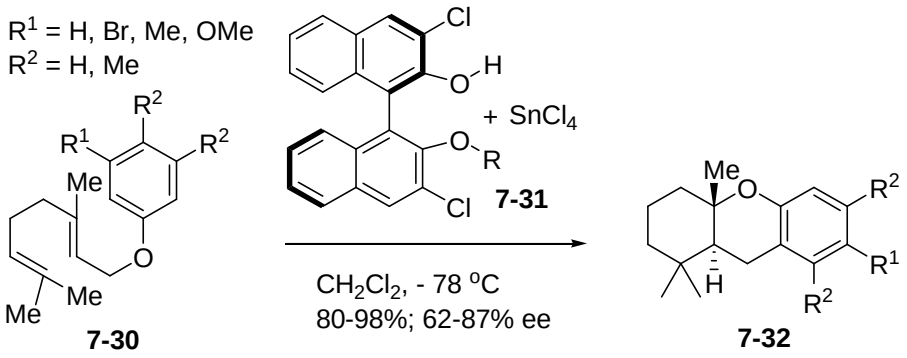


Scheme 7-6. Enantioselective proton-initiated cationic cyclization

[168] Highly Enantioselective Proton-Initiated Polycyclization of Polyenes. Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992-11994.

7.1.2.3 Other approaches to polyoefin cyclization

In 1999, Yamamoto group reported the enantioselective cyclization of polyprenoids using a chiral system by a combination of a Lewis acid and a chiral Bronsted acid (LBA).[169] Interestingly, the LBA catalysis of the aryl ether **7-30** provided an abnormal products **7-31** which presumably formed by Claisen rearrangement followed by the cationic cyclization (Scheme 7-7).

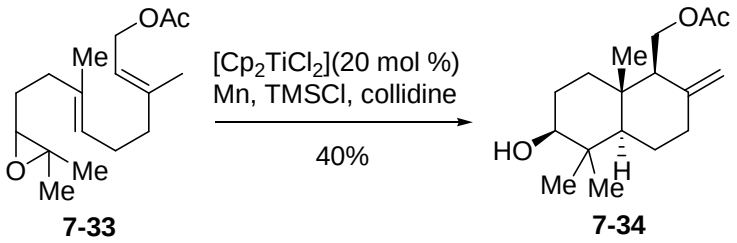


Scheme 7-7. Yamamoto's LBA catalysis

In 2004, Oltra group reported the titiocene-mediated polyolefin cyclization as an approach to terpenoids.[170] The radical opening of epoxide **7-33** was followed by a free radical chain reaction, providing trans-decalin **7-34** (Scheme 7-8).

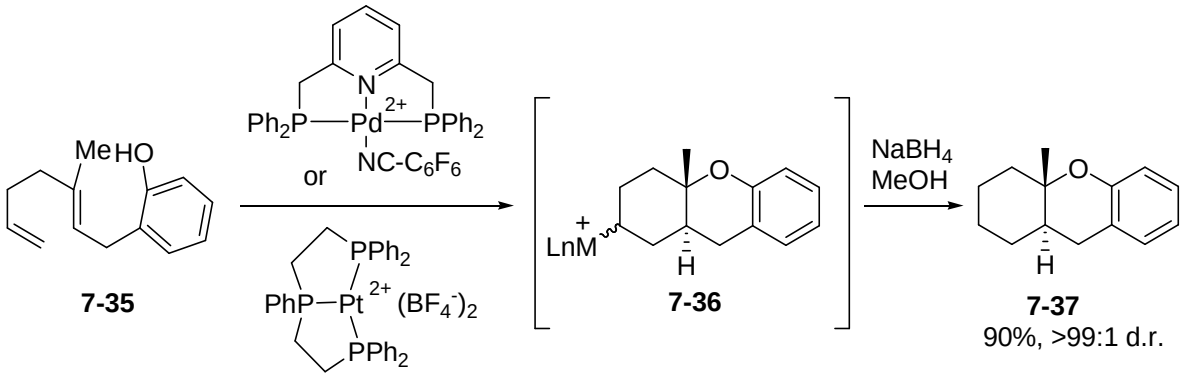
[169] The First Enantioselective Biomimetic Cyclization of Polyprenoids. Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc*. **1999**, *121*, 4906-4907.

[170] Titanocence-Catalyzed Cascade Cyclization of Epoxypolyprenes: Straightforward Synthesis of Terpoenoids by Free-Radical Chemistry. Justicia, J.; Rosales, A.; Bunuel, E.; Oller-Lopez, J. L.; Valdivia, M. V.; Hadour, A.; Otra, J. E.; Barrero, A.; Cardenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778-1788.



Scheme 7-8. Oltra's Ti-mediated radical cyclization

In the same year, Koh and Gagne reported the Pd(II)- or Pt(II)-mediated polycyclization of 1,5-diene **7-35**.[171] They demonstrated that this cyclization undergoes the cationic reaction pathway by isolating the Pd-intermediate **7-36** (Scheme 7-9).



Scheme 7-9. Gagne's Pd(II)- or Pt(II)-mediated cyclization

In 2009, Michele group disclosed the gold-catalyzed cyclization of 1,5-enynes **7-38**. The highly reactive interaction between the alkyne and metal induced the isomerization of 1,5-enynes and *in situ* 6-endo-dig oxycyclization (Scheme 7-10).[172]

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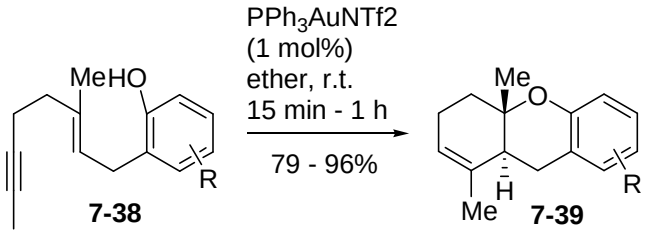
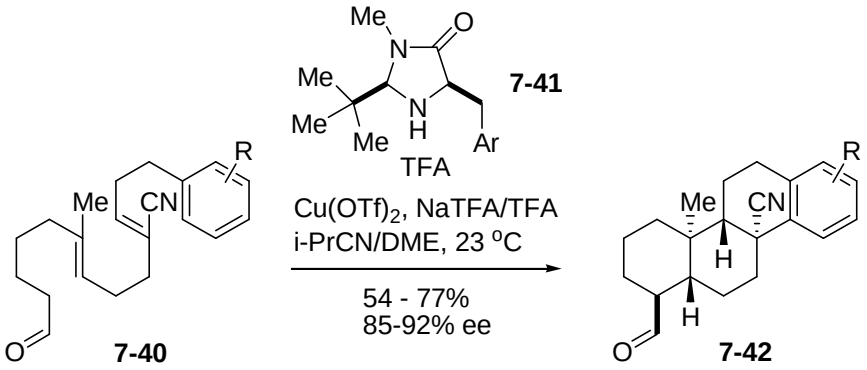
[171] Pd^{II}- and Pt^{II}-Mediated Polycyclization Reaction of 1,5- and 1,6-Dienes: Evidence in Support of Carbocation Intermediates. Koh, J. W.; Gagne, M. R. *Angew. Chem. Int. Ed*. **2004**, *43*, 3459-3461.

[172] Mimicking Polyolefin Carbocyclization Reactions: Gold-Catalyzed Intramolecular Phenoxycyclization of 1,5-Enynes. Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett*. **2009**, *11*,



Scheme 7-10. Michelet's gold-catalyzed cyclization

In 2010, Rendler and MacMillan reported the application of organo-SOMO (singly occupied molecular orbital) catalysis to the polyene cyclization.[173] They demonstrated that the α-imino radical intermediate of **7-40** upon metal oxidant initiated cyclization and the use of chiral imidazolidinone induced enantioselective reaction (Scheme 7-11).



Scheme 7-11. MacMillan's SOMO-cyclization

The Jacobsen group communicated the development of enantioselective cationic cyclization using thiourea **7-44**.[174] Under HCl condition, the hydroxyl lactam was first converted to a

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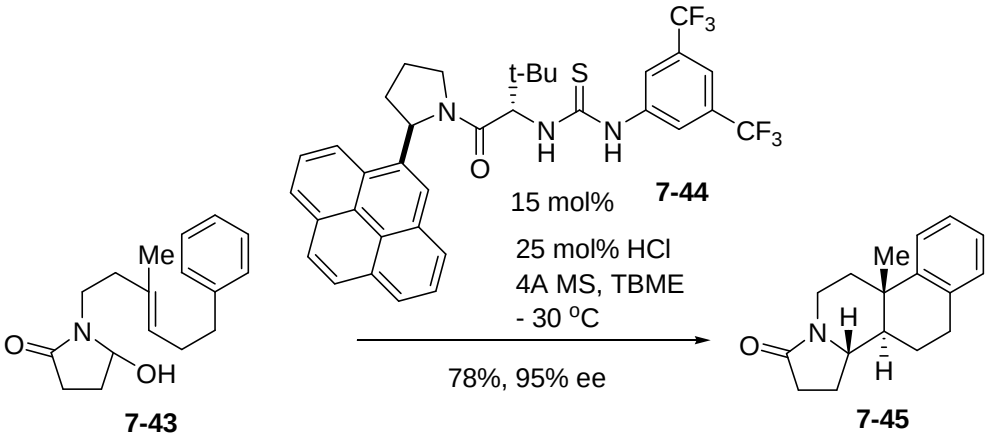
2888-2891.

[173] Enantioselective Polyene Cyclization via Organo-SOMO Catalysis. Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027-5029.

[174] Enantioselective Thiourea-Catalyzed Cationic Polycyclizations. Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030-5032.

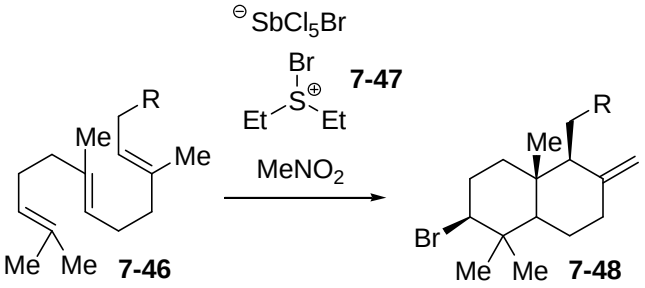
chlorolactam. The hydrogen bond-mediated ionization of the chlorolactam by the chiral thiourea was presumed to give a key complex that is stabilized by cation-π intereaction (Scheme 7-12).



Scheme 7-12. Jacobsen's thiourea-catalyzed polyene cyclization

The Snyder group has studied bromonium-induced polyene cyclizations.[175] They developed an easy preparation of bromodiethylsulfonium bromopentachloroantimonate (BDSB) catatlyst **7-47** as a stable solid. By screening conditions, they successfully induced cyclization of polyprenoidal compounds (Scheme 7-13).

[175] (a) $Et_2SBr{\cdot}SbCl_5Br$: An Effective Reagent for Direct Bromination-Induced Polyene Cyclizations. Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed*. **2009**, *48*, 7899-7903. (b) Simple Reagents for Direct Halonium-Induced Polyene Cyclization. Snyder, S. A.; Treitler, D. S.; Brucks, A. *J. Am. Chem. Soc*. **2010**, *132*, 14303-14314. (c) A two-step mimic for direct, asymmetric bromonium- and chloronium-induced polyene cyclizations. Snyder, S. A.; Treitler, D.; Schall, A. *Tetrahedron* **2010**, *66*, 4796-4804.



Scheme 7-13. Snyder's bromonium-induced polyene cyclization

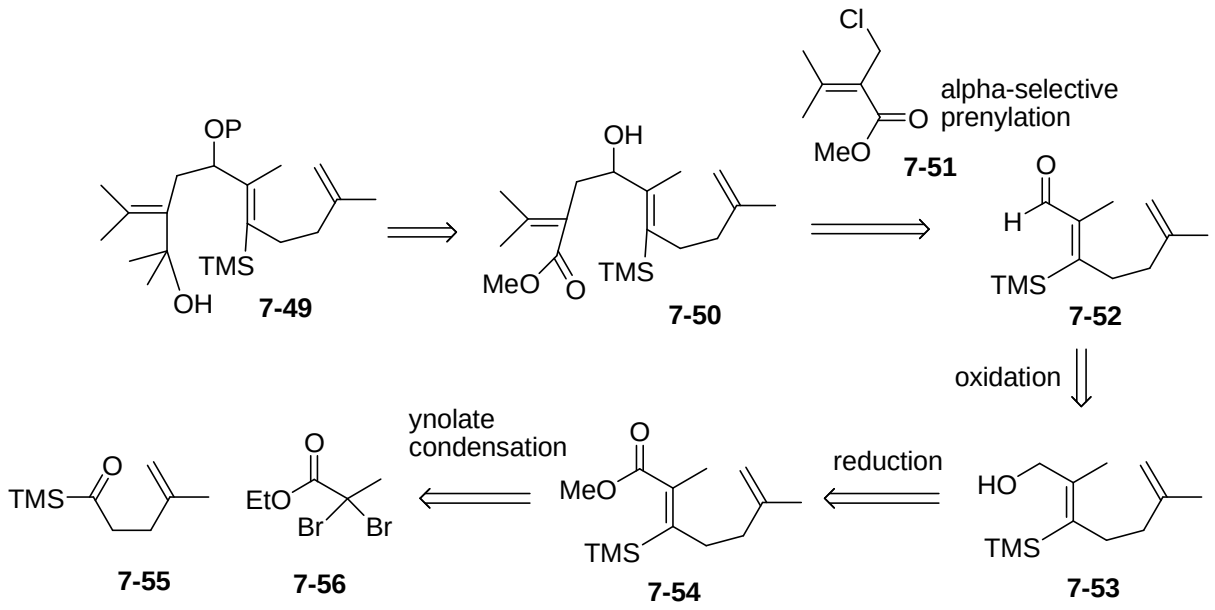
7.2 Result and Discussion

7.2.1 Model compound 1

As a model compound that is closely related structure of arisugacin A, we first considered the triene compound **7-49**. We designed the model compound **7-49** having tetramethylallyl cation precursor which had been shown to be a better initiating group than an epoxide.[176] We hoped that the secondary alcohol **7-50** is prepared by the α-selective prenylation of aldehyde **7-52** using prenyl chloride **7-51**. The aldehyde **7-52** was thought to be given by reduction and oxidation sequence of (*Z*)-α,β-unsaturated ester **7-54** bearing TMS group at β-carbon. The ester **7-54** was presumed to be provided by ynolate condensation[177] between acyl silane **7-55** and 2,2-dibromoester **7-56** (Scheme 7-14).

[176] Johonson, W. S.; Fish, P. V. The Tetramethylallyl Cation as a Surrogate for the Epoxide Function as an Initiator of Biomimetic Polyene Pentacyclizations. Total Synthesis of Sophoradiol. *Tetrahedron Lett*. **1994**, *35*, 1469-1472.

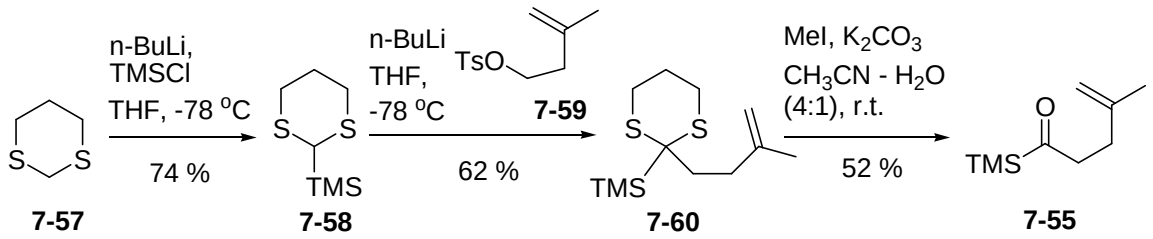
[177] Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. The First General Method for *Z*-Selective Olefination of Acylsilanes via Ynolate Anions Providing Multisubstitued Allenes. *J. Am. Chem. Soc.* **2002**, *124*, 6840-6841.



Scheme 7-14. Retrosynthesis of a model compound **7-49**

7.2.1.1 Synthesis of acyl silane **7-55**

The acylsilane **7-55** was prepared as shown below (Scheme 7-15). The introduction of TMS group to 1,3-dithiane followed by alkylation gave a masked ketone **7-60** (46 % for two steps). The hydrolysis[178] of **7-60** using methyl iodide and potassium carbonate provided the acyl silane **7-55**.

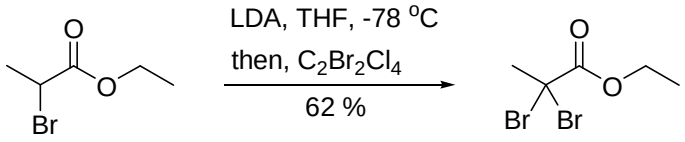


Scheme 7-15. Synthesis of acyl silane **7-55**

[178] A synthesis of multisubstituted vinylsilanes via ynolates: stereoselective formation of β-silyl-β-lactones fllowed by decarboxylation. Shindo, M.; Matsumoto, K.; Shishido, K. *Chem. Commun*. **2005**, 2477-2479.

7.2.1.2 Synthesis of ethyl 2,2-dibromopropionate (**7-56**)

On the basis of the known procedure,[179] we prepared the ethyl 2,2-dibromopropionate (**7-56**) from ethyl 2-bromopropionate (**7-61**) (Scheme 7-16).



7-61 **7-56**

Scheme 7-16. Synthesis of the 2,2'-dibromoester **7-56**

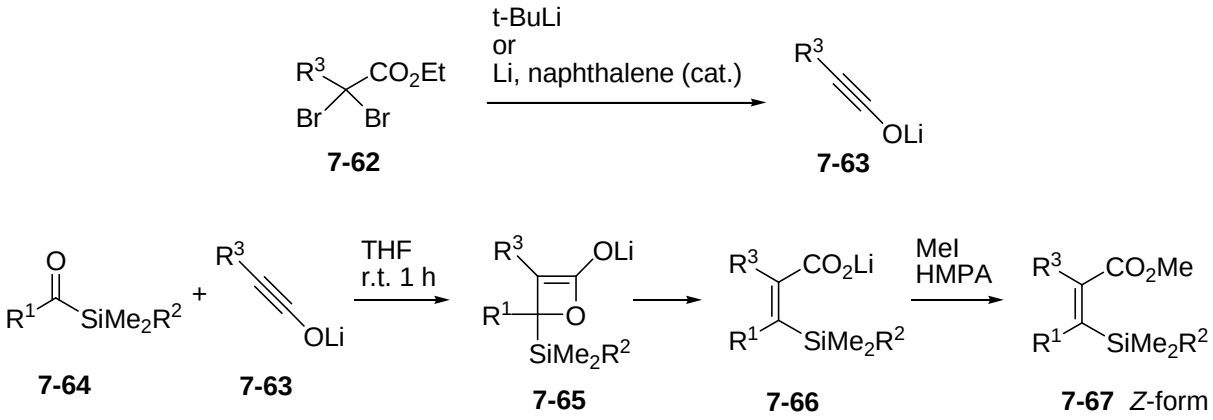
7.2.1.3 Synthesis of the ester **7-54**

Although the Wittig reaction has been one of the most popular reactions for (*E*)- or (*Z*)-stereoselective olefination, most of examples for synthesizing tri- or tetrasubstituted silyl alkene have been shown low stereoselectivity.[180] In 2002, Shindo et al. reported the *Z*-selective olefination of acylsilanes by using ynolate chemistry (Scheme 7-17).[21] They generated ynolate anion **7-63** by reducing 2,2'-dibromo ethyl ester **7-62** with t-BuLi or Li/Naphthalene. The ynolate solution was then treated with the acylsilanes **7-64** to produce *Z*-selective tetrasubstituted olefins **7-68**. The reaction was shown to proceed through the β-lactone enolate intermediate **7-66**. The authors reasoned that the stereochemistry is by the interaction between a σ-bonding orbital of the breaking C-O bond and vacant orbitals on silicon in the electrocyclic ring opening step of the β-lactone enolate **7-66**.[54]

---

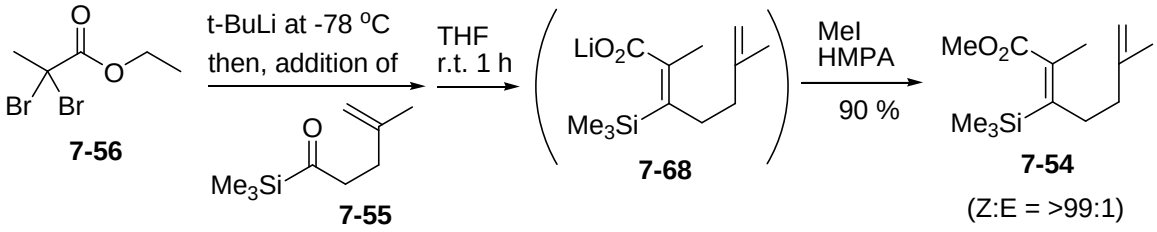
[179] Generation of ynolate and Z-selective olefination of acylsilanes: (Z)-2-methyl-3-trimethylsilyl-2-butenoic acid. Shindo, M.; Matsumoto, K.; Shishido, K. Organic Syntheses, **2007**, *84*, 11.

[180] The First General Method for (Z)-Selective Olefination of Acylsilanes via Ynolate Anions Providing Multisubstituted Alkenes. Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840-6841 and see the references therein.



Scheme 7-17. Shindo's procedure for the synthesis of *Z*-selective olefination of acylsilane

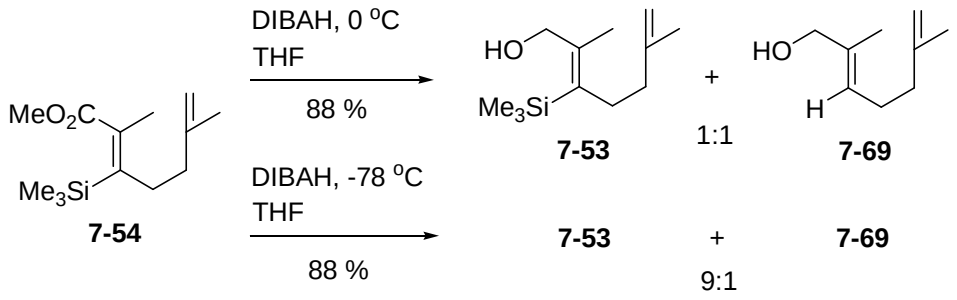
Having two substrates **7-55** and **7-56** in hand, we performed a condensation reaction. The application of Shindo's procedure provided the *Z*-tetrasubstituted olefin **7-54** containing TMS group at β-carbon (Scheme 7-18).



Scheme 7-18. Synthesis of *Z*-olefin tetrasubstrituted olefin **7-54**

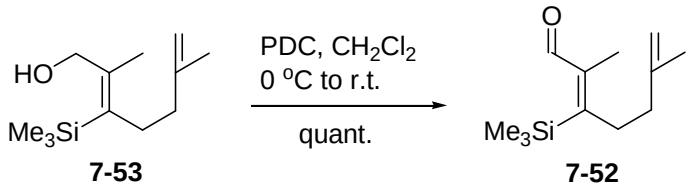
7.2.1.4 Synthesis of the aldehyde **7-52**

In order to get the aldehyde **48**, the reduction of **7-54** was followed by an oxidation of **7-53** as planned. When DIBAL-H was added to the reaction mixture at 0 °C, a mixture of **7-53** and desilylated product **7-69** was obtained with 1:1 ratio. However, when the reaction temperature was decreased to – 78 °C, the ratio of the two compounds was increased to 9:1 (Scheme 7-19). Careful separation gave the clean product **7-53**.



Scheme 7-19. Synthesis of Z-allylic alcohol **7-53**

The oxidation of *Z*-allylic alchol **7-53** was found to undergo isomerization during the oxidation. For example, the oxidation using manganese (IV) oxide[181] afforded a mixture of (E)- and (Z)-isomers. Thus, we next tested a neutral PDC oxidation, which gave a pure α, β-unsaturated aldehyde **7-52** (Scheme 7-20).



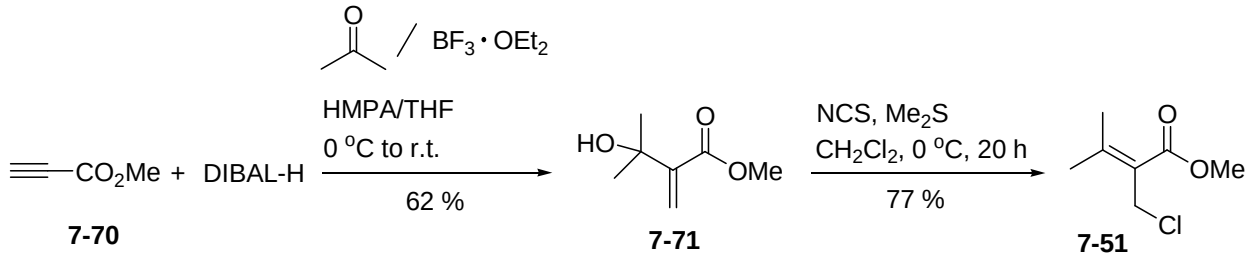
Scheme 7-20. Synthesis of the aldehyde **7-52**

7.2.1.5 Synthesis of the prenyl chloride **7-51**

The prenyl chloride 7-51 was prepared by following the known procedure.[182] In situ coupling of the [α-(methoxycarbonyl)vinyl]aluminum reagent with acetone in the presence of $BF_3 \cdot Et_2O$ gave the tert-alcohol **7-71** in 62 % yield. The tert-alcohol reacted with *N*-chlorosuccinimide in the presence of SMe_2 to afford the S_N2' reaction product, prenyl chloride **7-51** in 77 % yield (Scheme 7-21).

[181] Uniting Anion Relay Chemistry with Pd-Mediated Cross Coupling: Design, Synthesis and Evaluation of Bifunctional Aryl and Vinyl Silane Linchpins. Smith III, A. B.; Kim, W. –S.; Tong, R. *Org. Lett*. **2010**, *12*, 588-591.

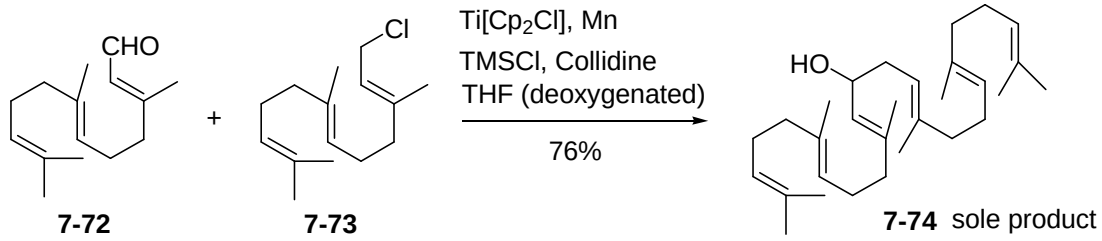
[182] Efficient Synthesis of Methyl 2-(*tert*-Butyl)acrylate and Analogous Esters. Kündig, E. P.; Xu, L. –H. *Helv. Chim. Acta*. **1994**, *77*, 1480.



Scheme 7-21. Synthesis of prenyl chloride **7-71**

7.2.1.6 Examinations for α-prenylation of the aldehyde **7-52**

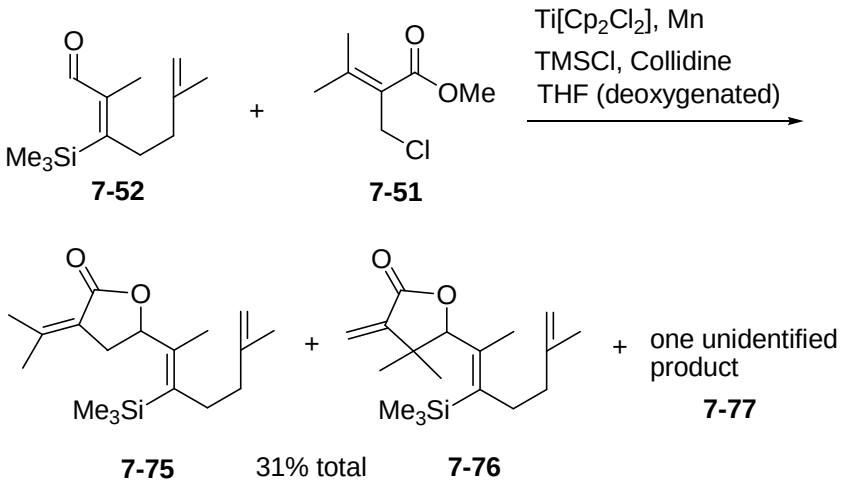
In 2009, the Oltra group reported the stereoselective α-prenylation reaction between aldehydes and a series of prenyl chlorides by Ti-catalysis.[183] Among the many examples, the most intriguing one was the selectively prenylated alcohol **7-74** derived from the farnesal **7-72** and farnesyl chloride **7-73** (Scheme 7-22).



Scheme 7-22. Oltra's α-selective prenylation

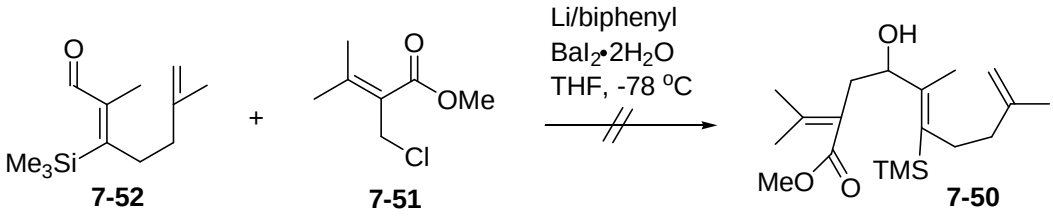
Following Oltra's procedure, we examined coupling reaction between allyl chloride **7-51** and aldehyde **7-52**. However, in contrast to our expectation, the resulting products turned out to be an inseparable 2:1 mixture of lactones **7-75**, **7-76**, and one unidentified product **7-77** (Scheme 7-23). The ratio of lactones **7-75** and **7-76** was determined by the integration of each methine proton.

[183] Ti-Catalyzed Barbier-Type Allylations and Related Reactions. Estévez, R.: Justicia, J.; Bazdi, B.;Fuentes, N.; Paradas, M.; Lazarte, D. C.; Ruiz, G. M.; Robles L,: Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Chem. Eur. J.* **2009**, *15*, 2774-2791.



Scheme 7-23. Ti-mediated Barbier reaction between aldehyde **7-52** and prenyl chloride **7-51**

Because the selective α-prenylation using Ti-catalyst was unsuccessful, Yamamoto's α-prenylation procedure[184] was next examined. However, the prenylated product **7-50** was not obtained and the aldehyde **7-52** was recovered (Scheme 7-24).

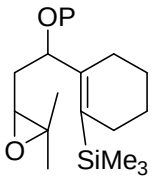


Scheme 7-24. Model reaction using Yamamoto's protocol

7.2.2 Model compound 2

[184] Allylbarium in organic synthesis: unprecedented α-selective and stereospecific allylation of carbonyl compounds. Yanagisawa, A; Habaue, S; Yamamoto, H. *J. Am. Chem. Soc*. **1991**, *113*, 8955-8956.

Because of the difficulty for the scalable synthesis of the aldehyde **7-52** and difficulty to induce α-prenylation product using the prenyl chloride **7-51**, we planned to prepare a new model **7-78** to quickly test cationic cyclization of the substrate containing vinylsilane allyl alcohol moiety (Figure 7-2).

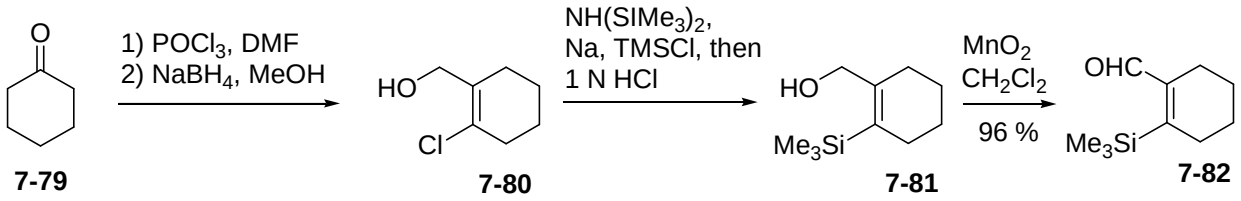


7-78

Figure 7-2. A new model compound

7.2.2.1 Preparation of the epoxide **7-78**

The α,β-unsaturated aldehyde **7-82** was prepared from the known alcohol[185] in gram scale (scheme 7-25).



7-79 **7-80** **7-81** **7-82**

Scheme 7-25. 4-Step synthesis of the aldehyde **7-82**

Next, we tried Ti-mediated Barbier reaction of the aldehyde **7-82** and prenyl bromide by adapting Oltra's protocol.[24] As a result, the isomeric α-prenylated alcohol **83** and γ-prenylated alcohol **84** were isolated in 50 and 29 % yield, respectively (Scheme 7-26).

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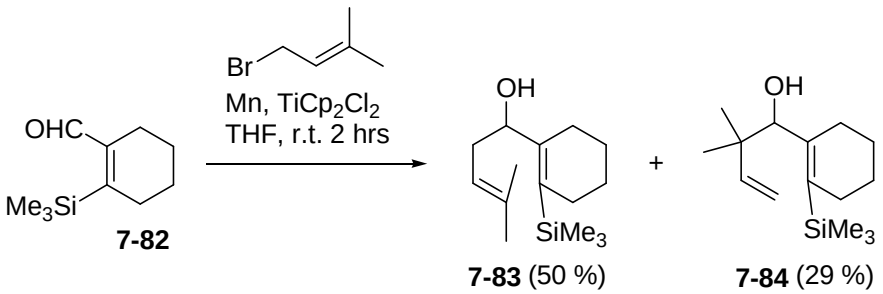
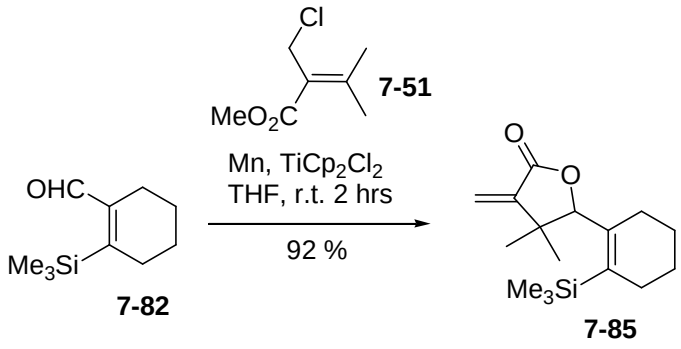
[185] Highly Regio- and Diastereoselective One-Pot Synthesis of Silyl Epoxy Alcohols and Vinylsilanes by Direct Hydroxy-Epoxidation. Adam, W.; Richter, M. J. *J. Org. Chem*. **1994**, *59*, 3341-3346.



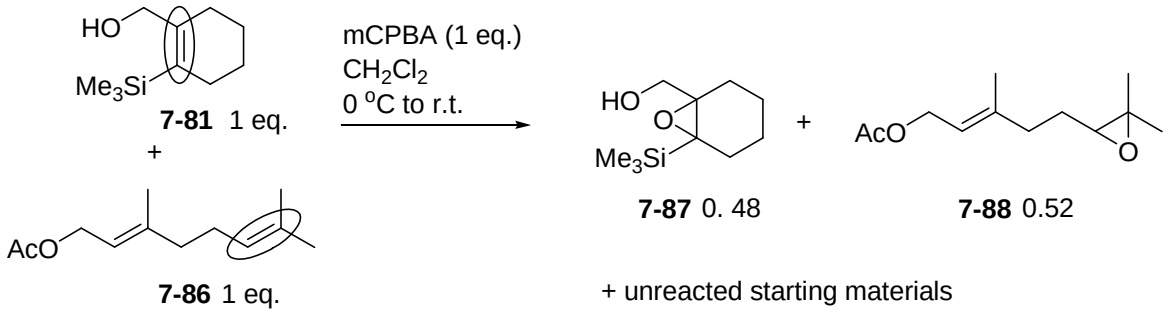
Scheme 7-26. The Ti-mediated prenylation of the model aldehyde **7-82**

However, the coupling reaction of prenyl chloride **7-51** and the aldehyde **7-82** under the same conditions only produced γ-prenylation product **7-85** (Scheme 7-27).



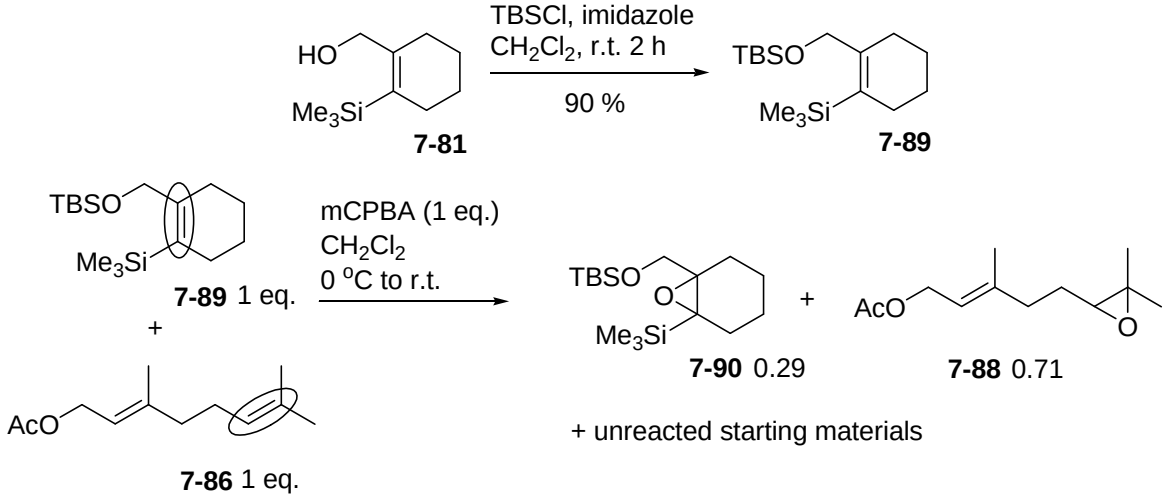
Scheme 7-27. The Ti-mediated coupling reaction of the aldehyde **7-82** and prenyl chloride **7-51**

The selective epoxidation for the alcohol **7-83** and its derivatives was examined by a series of cross-reactivity experiments. When two substrates **7-81** and **7-86** were subjected to m-CPBA, the tetrasubstituted olefin of **7-81** and the terminal trisubstituted olefin of **7-86** almost equally reacted, generating corresponding epoxides **7-87** and **7-88** (Scheme 7-28).



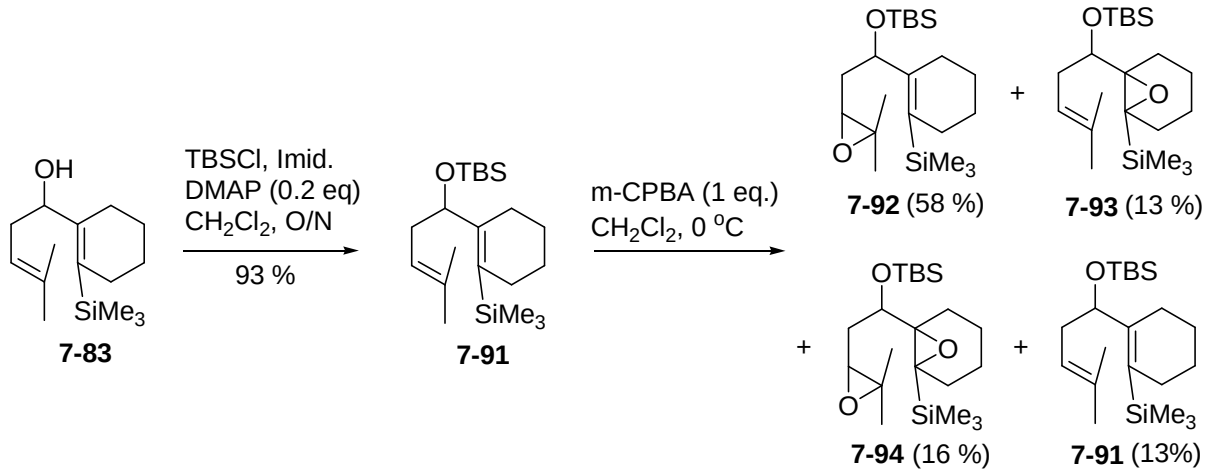
Scheme 7-28. Relative reactivity for the oxidation of the alcohol **7-81**

When the silyl ether **7-89** was subjected to the same oxidation conditions, the ratio was considerably changed, presumably due to steric hindrance (Scheme 7-29).



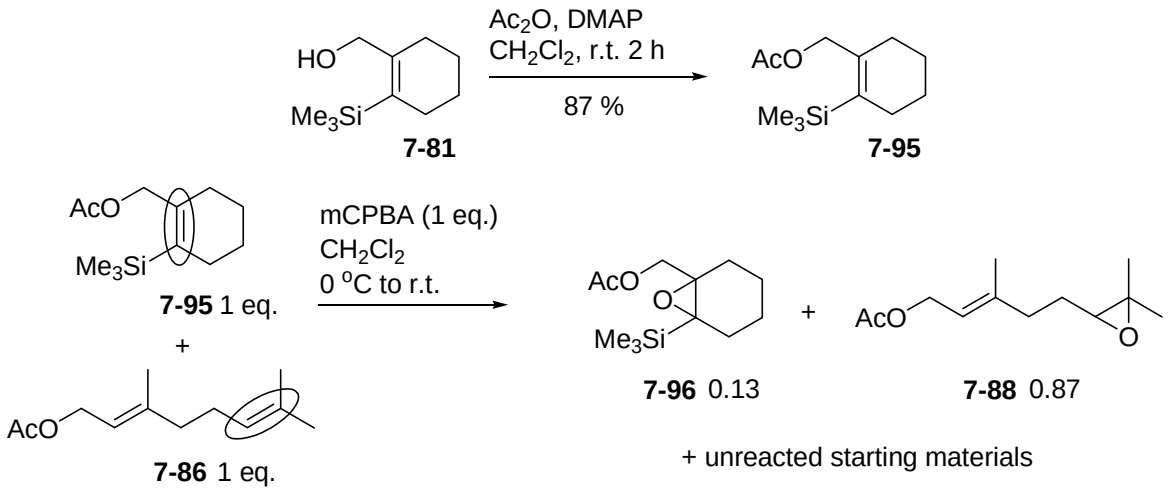
Scheme 7-29. Relative reactivity for the oxidation of the silyl ether **7-89**

This preliminary result led us to prepare the TBS-protected alcohol **7-91**. The ratio of the resulting epoxidized products in ^{1}H nmr was 0.58 (**7-92**): 0.13 (**7-93**): 0.16 (**7-94**). Although the selective formation of monoepoxide **93** is achieved, the difficulty of separation did not allow us to use the substrate **7-91** (Scheme 7-30).



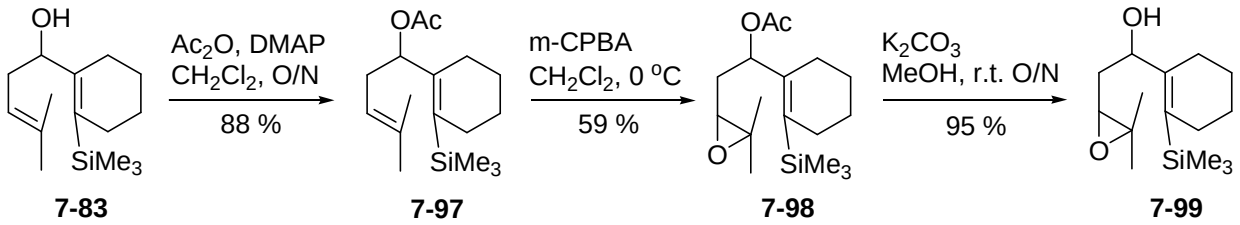
Scheme 7-30. Selective epoxidation of the silyl ether **7-91**

We needed to find another protecting group that is able to give the selectivity and easiness of separation. Therefore, the acetate **7-95** was examined for the selective epoxidation. As a result, the epoxidation of trisubstituted olefin of **7-86** was even more selective than deactivated tetrasubstituted olefin of **7-95** (Scheme 7-31).



Scheme 7-31. Relative reactivity for the oxidation of the acetate **7-95**

The α-prenylated alcohol **7-83** was acetylated and oxidized with m-CPBA (m-chloro perbenzoic acid) to afford the epoxy acetate **7-98**. The acetyl group of the epoxide was removed by potassium carbonate, affording the epoxy alcohol **7-99** (Scheme 7-32).

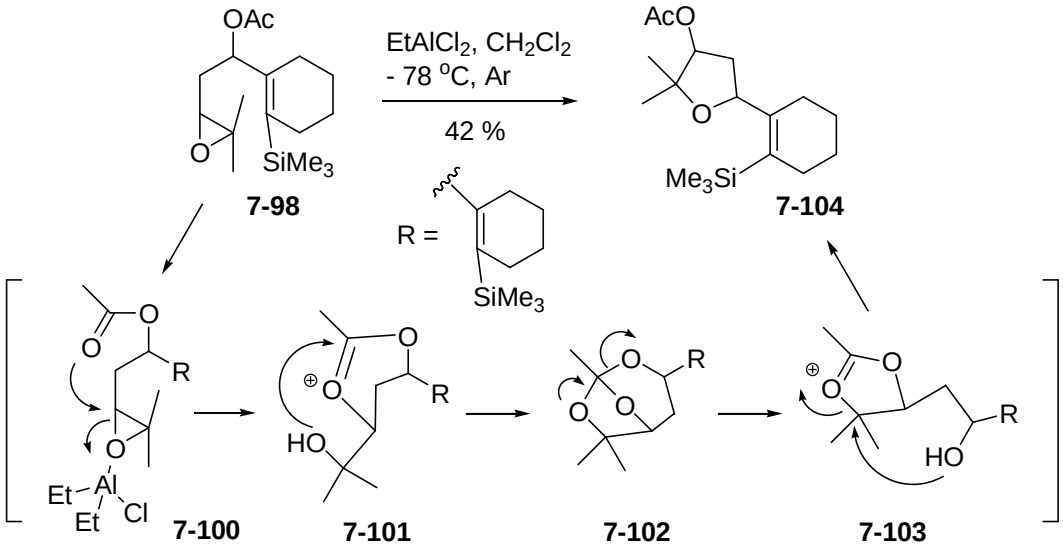


Scheme 7-32. Synthesis of epoxy alcohol **7-99**

7.2.2.2 Examination for the cationic cyclization of the epoxy acetate **7-98**

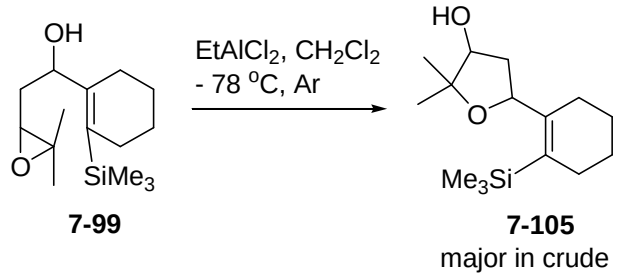
Having a model epoxide **7-98**, we examined acid-catalyzed cationic cyclization. First, the epoxide **7-98** was subjected to ethylaluminumdichloride at – 78 °C. In contrast to our expectation, the cyclized product was not obtained and an unexpected product, tetrahydrofuran **7-104**, was isolated. The addition of the acetate to the carbocation followed by rearrangements was presumed to occur in this substrate (Scheme 7-33). The mechanism for this reaction was previously demonstrated by Giner et al.[186]

[186] Mechanistic Studies of the Biomimetic Epoxy Ester-Orthoester and Orthoester-Cyclic Ether Rearrangements. Giner, J. –L.; Li, X.; Mullins, J. J. *J. Org. Chem*. **2003**, *68*, 10079-10086.



Scheme 7-33. $EtAlCl_2$-catalyzed formation of 2-acetoxyfuran **7-104**

Not surprisingly, the acid-catalyzed cyclization of the hydroxy epoxide **7-99** also produced the furan **7-105**, which was identified by crude ^1H nmr experiment (Scheme 7-34).

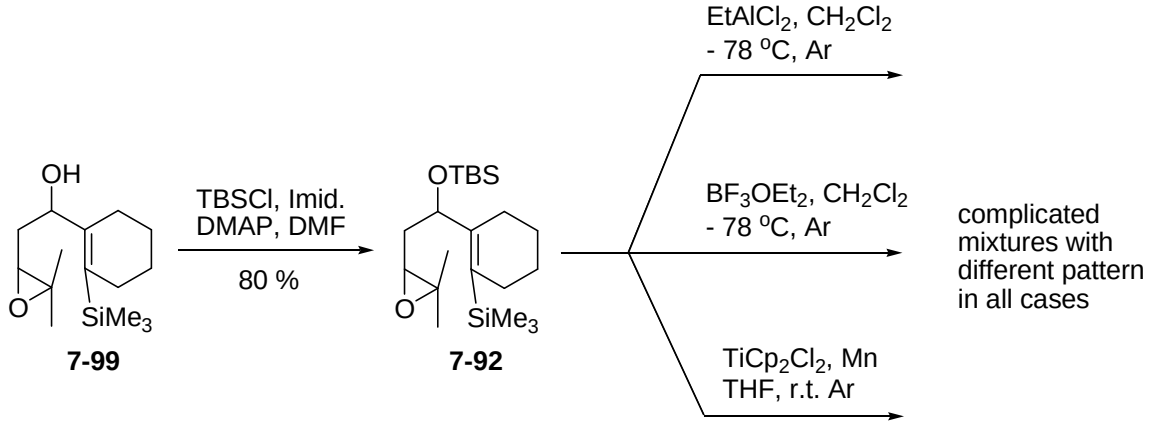


Scheme 7-34. $EtAlCl_2$-catalyzed synthesis of 2-hydroxyfuran **7-105**

7.2.2.3 Examination for the cationic cyclization of TBS-protected substrate

Because both carbonyl group of epoxide **7-98** and hydroxyl group of epoxide **7-99** participated in the reaction under acid-catalyzed conditions, we needed to protect alcohol with non-reactive group. Thus, we protected the hydroxyl epoxide **7-99** with t-butyldimethylsilyl (TBS) group and examined several conditions for cationic cyclization (Scheme 7-35). However, the conditions including Lewis acids and Ti-mediated radical reaction resulted in production of complex

mixtures. The interpretation of the resulting products did not show any evidence that is able to explain the existence of the cyclized products (Scheme 7-34).



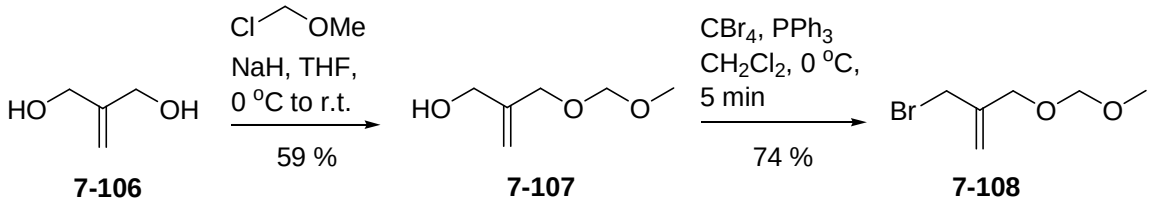
Scheme 7-35. Examinations for the catalytic cyclization of the silyl ether **7-95**

7.2.3 Model compound 3

The polyolefin cyclization of epoxides containing allylic alcohol was frustrated by the participation of the oxo-functionality under acidic conditions. In addition, the interpretation of the products formed from a diastereomeric mixture **7-91** was not easy. Thus, we sought for alternative substrates that are not only able to give simpler stereochemical results, but also to guarantee short-steps synthesis.

For example, we decided to use an allylic alcohol or MOM-ether as the initiating group. The allyl halides were prepared by the known procedures. First, a monoprotected alcohol **7-107** was prepared in 59 % yield by treating 2-methylene-1,3-propandiol with 1 eq. of sodium hydride and chloromethoxymethane. Next, MOM-protected alcohol **7-107** was brominated by treating carbon tetrabromide and triphenylphosphine, giving the allyl bromide **7-108** in 74 % yield[187] (Scheme 7-36).

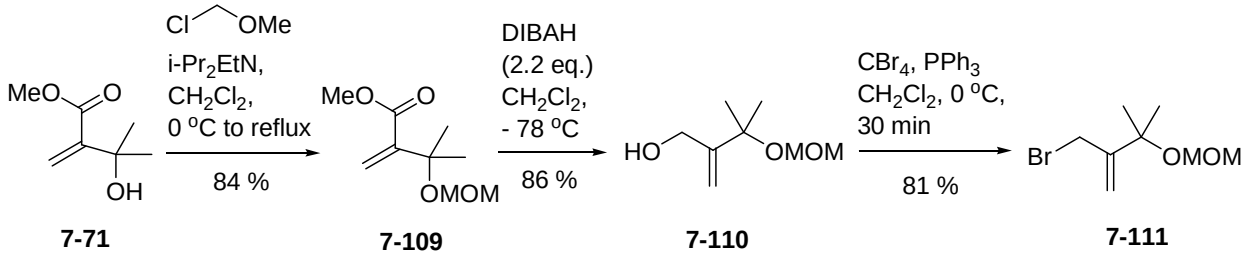
[187] Total Syntheses of Natural Tubelactomicins B, D, and E: Establishment of Their Stereochemistries. Sawamura, K.; Yoshida, K.; Suzuki, A.; Motozaki, T.; Kozawa, I.; Hayamizu, T.; Munakata, R.; Takao, K. –I.; Tadano, K. –I. *J. Org. Chem.* **2007**, *62*, 6143-6148.



7-106 **7-107** **7-108**

Scheme 7-36. Synthesis of MOM-protected allylic bromide **7-108**

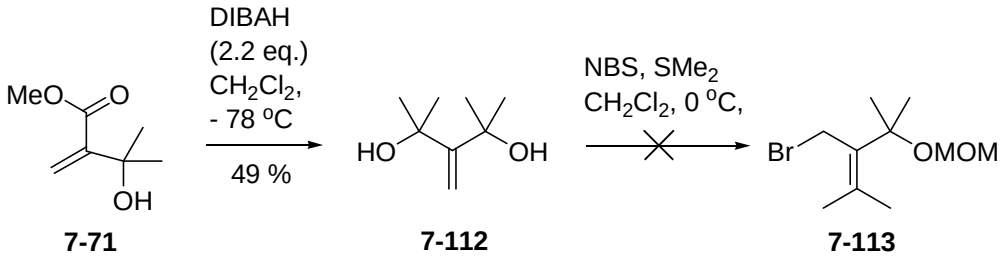
Second, the bromide **7-111** was prepared from tert-alcohol **7-110** (Scheme 7-37). MOM-protection of the alcohol **7-71** followed by DIBAH reduction of the ester **7-109** gave the allyl alcohol **7-110** (72 % for 2 steps).



7-71 **7-109** **7-110** **7-111**

Scheme 7-37. Synthesis of MOM-protected allylic bromide **7-111**

Third, the synthesis of the bromide **7-113** was attempted. The reduction of the methyl ester **7-71** with DIBAL-H provided di-tert-alcohol 7-112 in 49 % yield. However, the bromination procedure using NBS/SMe_2 gave a complicated mixture, discouraging the use of attractive bromide **7-113** (Scheme 7-38).

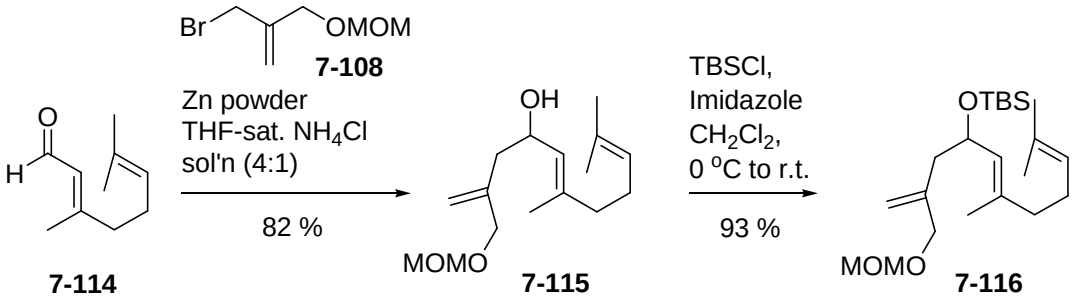


7-71 **7-112** **7-113**

Scheme 7-38. Attempt to synthesize the allyl bromide **7-113**

7.2.3.1 Synthesis of a model compound using geranialdehyde

Although the backbone of a Barbier adduct derived from the geranial is different from the previous model compounds, the easy access to the Barbier adduct is attractive. The zinc-mediated Barbier reaction of the geranial **7-114** with allyl bromide **7-108** was performed by adapting Handy's protocol.[188] This Barbier reaction in THF-saturated aqueous NH_4Cl solution with excess zinc powder (2.5 eq.) furnished the alcohol **7-115** in 82 % yield. Then, the resulting secondary allyl alcohol **7-115** was protected by a TBS group (Scheme 7-39).



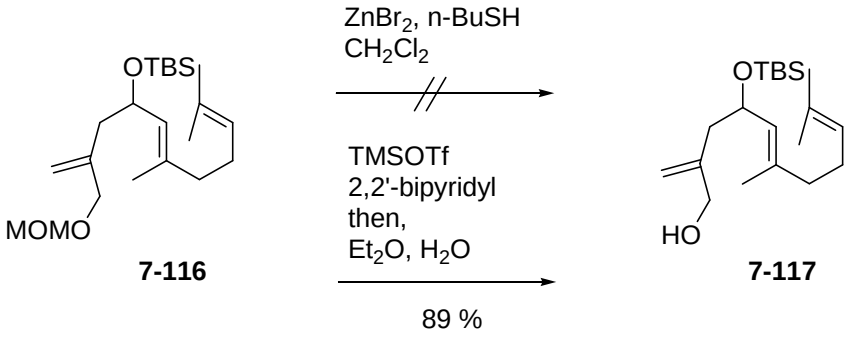
Scheme 7-39. Synthesis of sily ether **7-116** from the geranialdehyde

We next tried MOM-deprotection of the silyl ether **7-116**. The conditions using zinc bromide with n-butanethiol in dichloromethane[189] provided a complicated mixture. When a non-acidic condition with TMSOTf and 2,2'-bipyridyl was applied,[190] we obtained the deprotected alcohol **7-117** (Scheme 7-40).

[188] Regioselective Barbier reactions of 2-bromomethylcyclohexenone. Manchanayakage, R.; Handy, S. T. *Tetrahedron Lett*. **2007**, *48*, 3819-3822.

[189] A facile method for the rapid and selective deprotection of methoxymethyl (MOM) ethers. Han, J. H.; Kwon, Y. E.; Sohn, J. H.; Ryu, D. H. *Tetrahedron* **2010**, *66*, 1673-1677.

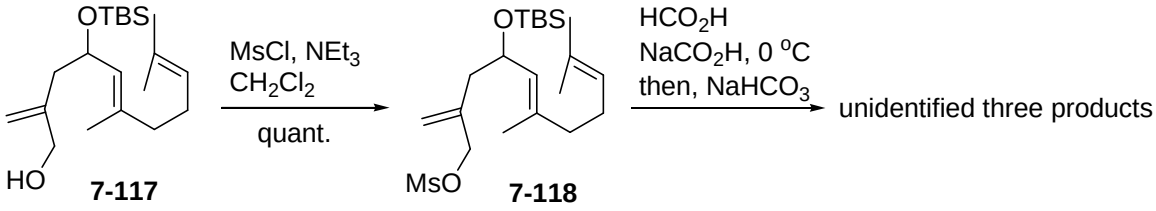
[190] Remarkable effect of 2,2′-bipyridyl: mild and highly chemoselective deprotection of methoxymethyl (MOM) ethers in combination with TMSOTf (TESOTf)–2,2′-bipyridyl. Fujioka, H; Kubo, O.; Senami, K.; Minamitsujia, Y; Maegawa, T. *Chem. Commun*. **2009**, 4429-4431.



Scheme 7-40. MOM-deprotection of the silyl ether **7-116**

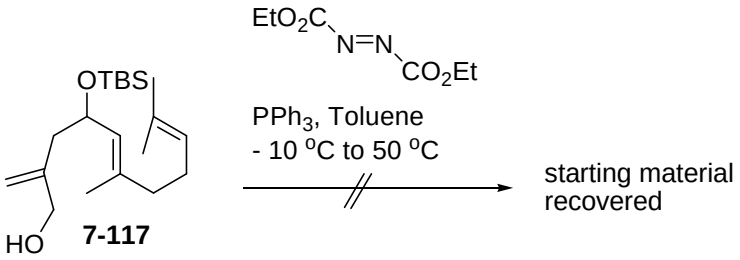
7.2.3.2 Test of the polyene cyclization of the allyl alcohol **7-117**

We anticipated that the mesylate of allylic alchol **7-117** could be cyclized by solvolysis. By adapting Johnson's conditions[2] using formic acid as a solvent to initiate and terminate the reaction, we examined the formolysis of the mesylate **7-118**. The allylic alcohol **7-117** was treated with mesyl chloride to successfully provide the mesylate **7-118** in quantitative yield. Then, the mesylate **7-118** was treated with 97 % formic acid with sodium formate, which resulted in three major products (Scheme 7-41). The exact structure of these products are not yet determined.



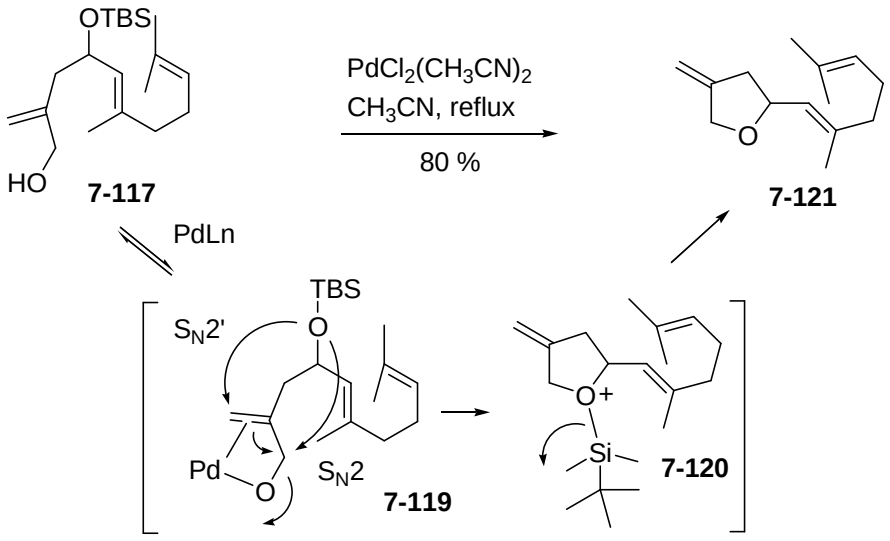
Scheme 7-41. Formolysis of the mesylate **7-118**

Next, we applied the Mitsunobu reaction to the allyl alcohol **7-117**. The application of the Mitsunobu reaction to polyolefin cyclization have not been explored. We hoped that the allylic alcohol is would be activated to give an allyl cationic species under the Mitsunobu conditions. However, the cyclized products were not observed and the starting material was recovered (Scheme 7-42).



Scheme 7-42. Mitsunobu reaction of the allyl alcohol **7-117**

Pd(II)-catalyzed activation of allylic alcohols to π-allyl complex has been reported for the application to the intramolecular carbocyclization.[191] We anticipated that Pd catalyst could initiate the reaction by activating the allylic alcohol, which would induce a tandem Heck-type cyclization. The allylic alcohol **7-117** was subjected to the catalytic $PdCl_2(CH_3CN)_2$ in refluxing acetonitrile. Interestingly, the resulting product was the 5-methylene-hydrofuran **7-121**. The alcohol of π-complex was presumed to be substituted with oxygen of the silyl ether via S_N2 or S_N2' pathway (Scheme 7-43).



Scheme 7-43. Pd-catalyzed activation of allylic alcohol

[191] Direct Syntheses of Polyfused Ring Systems by Intramolecular Tandem Palladium-Ene/Heck Insertion Reactions. Oppolzer, W.; DeVita, R. J. *J. Org. Chem.* **1991**, *56*, 6256-6257.

7.3 Conclusion

In the retrosynthesis of previous chapter 5, we designated the key intermediate for acid-catalyzed polyolefin cyclization. The key substrate **7-1** has an allyl alcohol and vinyl silane in its structure. We thought that the acid-catalyzed cyclization of the substrate **7-1** would not be trivial in view of the reactivity of functional groups. Thus, we sought to find optimized reaction conditions.

We have discussed the polyene cyclization of several model compounds that are related to the key intermediate.

First, we wanted to have a model compound **7-49** that contains tetramethylallyl cation precursor as the good initiating group. Although the synthesis of the aldehyde **7-52** was completed, the α-selective prenylation of the aldehyde **7-52** was not achieved. Therefore, we could not test acid-catalyzed polycyclization reaction.

Second, we prepared simpler model compounds by using the known aldehyde **7-82**. The α-selective prenylated alcohol **7-83** was converted to epoxy ethers **7-87** and **7-95**. Then, we examined acid-catalyzed epoxide opening followed by carbocyclization of epoxy ether **7-87**. However, the acetyl group of **7-87** participated in the reaction, which resulted in the production of the 2-acetoxyfuran **7-104**. In case of polycyclization of the epoxy silyl ether **7-95**, a complicated mixture was obtained. The difficulty for the interpretation of the resulting inseparable mixture didn't allow us to claim that we got cyclized products.

In the third model compounds, we decided to use allyl alcohols as initiating groups. Thus, we planned to prepare three allyl bromides which would be used for Barbier reactions. Also, we chose geranial as an easily accessible starting material. The model alcohol **7-117** was prepared by a 3-step sequence from the geranial. Then, we applied several conditions including formolysis, Mitsnobu reaction, and Pd(II)-catalyzed tandem cyclization. However, a product of cationic polyene cylization was not isolated in any case.

Although we have not been able to induce model substrates to carbocyclization products, we have figured out reactivity of our model compounds. The systematic examination using transition metal complex or organo catalysts upon protected substrate of the model alcohols should be investigated.

7.4 Experimental Section

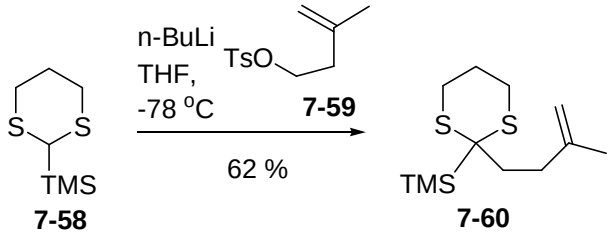
General Information

Reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Acros Organics. Unless otherwise noted, solid reagents were used without further purification. All air- and moisture sensitive reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware. All moisture sensitive solution and anhydrous solvents were transferred *via* standard syringe and cannula techniques. Concentration of solutions was accomplished with a Buchi rotary evaporator evacuated by a water aspirator. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas.

All experiments were monitored by thin layer chromatography (TLC) performed on Whatman 250μm layer aluminum silica gel plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with a 10 % solution of phosphomolybdenic acid (PMA) in ethanol and the heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

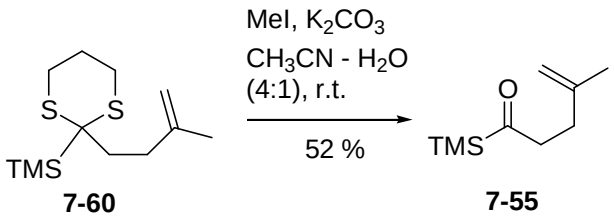
Infrared spectra were recorded with a Galaxy Series FT-IR 3000 infrared spectrophotometer. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), Varian Inova-400 (400 MHz for ^1H), Varian Inova-300 (300 MHz for 1H, 75 MHz for 13C) spectrometer. Chemical shifts for proton NMR are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR are reported in ppm with the centerline of the triplet for chloroform-d set at 77.0 ppm. The following abbreviations are used in the experimental section for the description of ^1H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), quintet (q), multiplet (m), doublet of doublets (dd), doublet of quartets (dq), and broad singlet (bs). Coupling constants, *J*, are reported in Herz (Hz).

Experimental Procedure/ Characterization



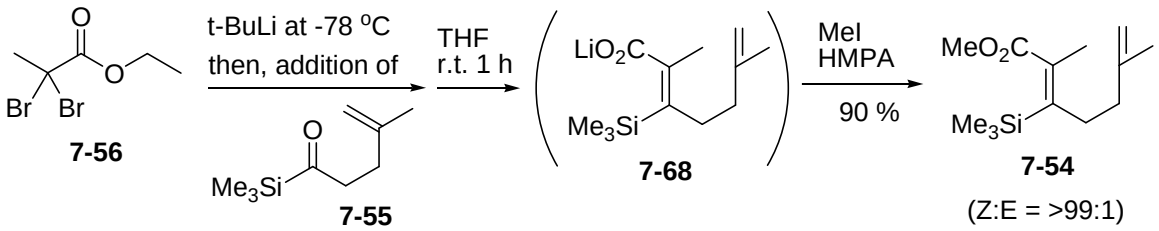
Thiane 7-60 To a stirred solution of 2-trimethylsilyl-1,3-dithiane (**7-58**, 0.43 g, 2.25 mmol) in THF (4 mL) was added n-BuLi (1.48 mL, 2.36 mmol) at -78 °C under Ar. After 30 min, a solution of the tosylate **7-59** (0.57 g, 2.36 mmol) in THF was added to the mixture. The reaction mixture was slowly warmed to r.t and stirred overnight. Then, the mixture was quenched with sat. NH_4Cl sol'n, extracted with diethyl ether. The organic solution was dried over MgSO4, concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 50:1) to afford the thiane **7-60** (0.36 g, 62 %) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9 H), 1.78 (s, 3 H), 1.82 – 1.98 (m, 2 H), 2.01 – 2.10 (m, 2 H), 2.16 – 2.22 (m, 2 H), 2.31 – 2.37 (m, 2 H), 2.42 – 2.49 (m, 2 H), 3.05 (m, 2 H), 4.737 (s, 1 H), 4.741 (s, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.5, 22.8, 23.3, 25.1, 32.5, 35.9, 38.5, 109.9, 145.9.; IR (neat) νmax 1248, 1422, 1450, 1647, 2921 cm^{-1}.



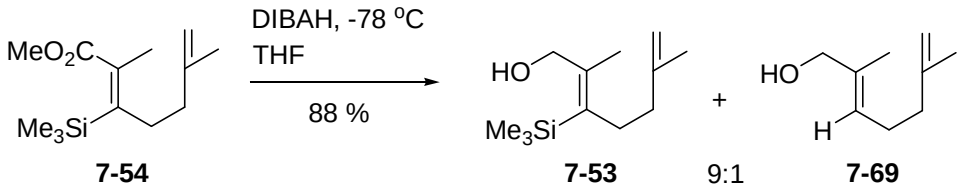
Acylsilane 7-55 To a stirred solution of dithiane 7-60 (1.64 g, 6.28 mmol) in CH_3CN (20 mL)/H_2O (5 mL) was added potassium carbonate (2.51 g, 25.1 mmol) and MeI (3.92 mL, 62.8 mmol) at r.t. under Ar. The resulting mixture was stirred vigorously for 3 days. Then, the mixture was diluted with water and extracted with ethyl acetate. The combined organic solution was dried over MgSO4, concentrated. The residue was subjected to silica gel column

chromatography (Hex:EtOAc = 50:1) to afford the acylsilane **7-55** (0.33 g, 52 %) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9 H), 1.72 (s, 3 H), 2.22 (t, *J* = 7.2 Hz, 2 H), 2.74 (m, 2 H), 4.63 (m, 1 H), 4.70 (m, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.1, 22.7, 29.8, 46.5, 109.8, 144.8, 247.2.; IR (neat) νmax 1248, 1374, 1417, 1451, 1647 cm^{-1}.



Methyl ester 7-54 To a stirred solution of ethyl 2,2-dibromopropionate **7-55** (0.40 g, 1.55 mmol) in THF (10 mL) was slowly added t-BuLi (3.88 mL, 6.20 mmol) at – 78 °C under Ar. The resulting yellow solution was stirred for 3 h at – 78 °C and allowed to warm to r.t. A solution of acylsilane **7-55** (0.22 g, 1.29 mmol) in THF (3 mL) was added to the mixture. After 1.5 h, MeI (0.80 mL, 12.90 mmol) in HMPA (3 mL) was added to the mixture and the reaction mixture was stirred overnight. Then, the reaction mixture was quenched with sat. NH_4Cl sol'n and extracted with ethyl acetate. The organic solution was dried over MgSO4, concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 20:1) to afford the methyl ester **7-54** (0.28 g, 90 %) as colorless oil.

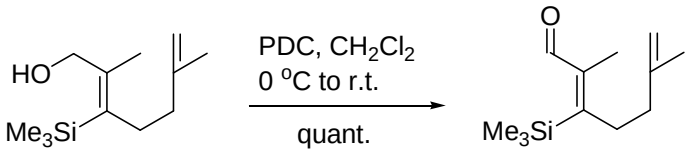
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 1.76 (s, 3 H), 1.93 (m, 2 H), 1.95 (s, 3 H), 2.38 (m, 2 H), 3.72 (s, 3 H), 4.72 (s, 1 H), 4.73 (s, 1 H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.4, 15.5, 22.4, 31.9, 36.8, 51.5, 110.1, 137.3, 145.4, 153.3, 170.1.; IR (neat) νmax 1072, 1196, 1277, 1458, 1717 cm^{-1}.



Allyl alcohol 7-53 To a stirred solution of the ester **7-54** (0.28 g, 1.16 mmol) in THF (8 mL) was added DIBAL-H (3.48 mL, 3.48 mmol) at – 78 °C under Ar. The reaction mixture was

slowly warmed to 0 ^{o}C for 2 h. The reaction mixture was quenched with water, diluted with 10 % potassium sodium tartarate solution and diethyl ether. The suspension was stirred for 1 h and partitioned. The aqueous solution was extracted with diethyl ether. The combined organic solution was dried over MgSO4, concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 5:1) to afford the allyl alcohol **7-53** (0.20 g, 80 %) as colorless oil.

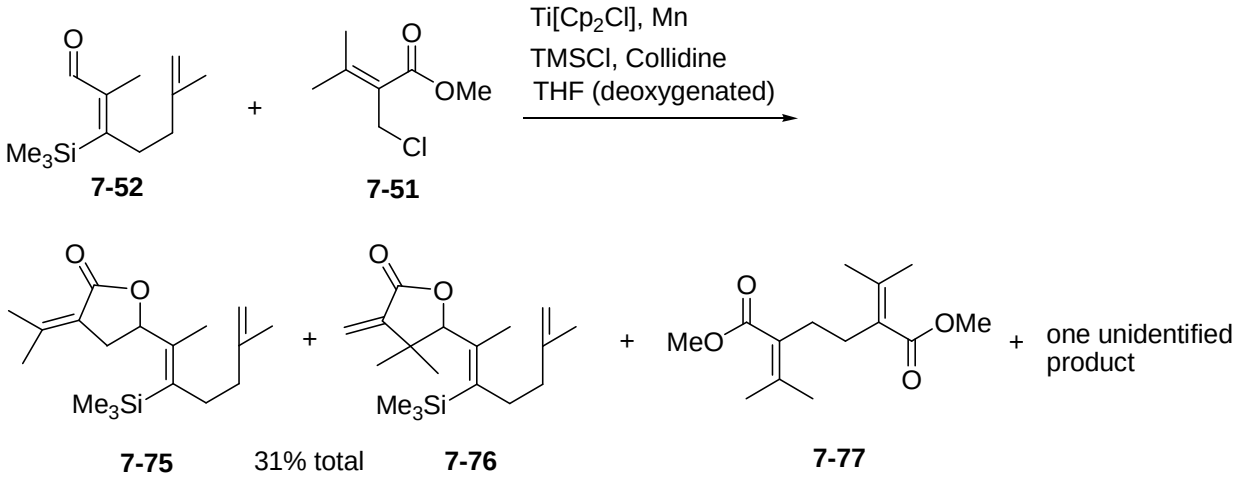
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 1.75 (s, 3 H), 1.84 (s, 3 H), 1.90 (m, 2 H), 2.32 (m, 2 H), 4.14 (s, 2 H), 4.70 (m, 2 H).



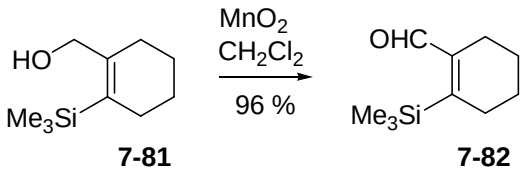
7-53 **7-52**

Aldehyde 7-52 To a stirred solution of allyl alchol **7-53** (26.2 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added pyridinium dichlormate (PDC, 70 mg, 0.18 mmol) at 0 ^{o}C. The reaction mixture was warmed to r.t. and stirred for 3 h. The resulting suspension was concentrated and diluted with cold ethyl ether. The mixture was filtered through a pad of Celite and the filtrate was concentrated (**7-52**, 25.9 mg, quant.). The residue was directly used for the next step without further purification because ^{1}H nmr of that was quite clean.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 9 H), 1.77 (s, 3 H), 1.83 (s, 3 H), 1.96 (m, 2 H), 2.53 (m, 2 H), 4.73 (m, 1 H), 4.75 (m, 1 H), 9.94 (s, 1 H).

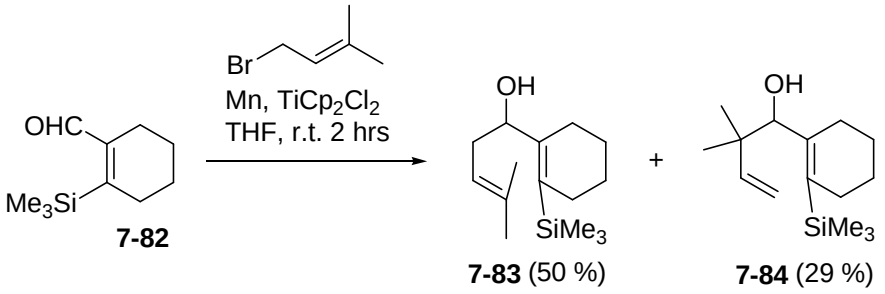


Ti-mediated α-selective prenylation of the aldehyde 7-52 A mixture of $Ti[Cp_2Cl_2]$ (6.1 mg, 24.7 μmol), Mn (54.2 mg, 0.98 mmol), collidine (0.11 mL, 0.86 mmol), and TMSCl (62.0 μL, 0.49 mmol) in THF (3 mL) was stirred for 30 min at r.t. Then, a solution of the aldehyde **7-52** (25.9 mg, 0.12 mmol) and prenylchloride **7-51** (40.0 mg, 0.25 mmol) in THF (1 mL) was added slowly to the premixed lime-green solution over 50 min. After 11 h, the reaction mixture was quenched with 2 N HCl sol'n and stirred for 30 min. The resulting suspension was filtered and the filtrate was extracted with diethyl ether. The organic solution was dried over $MgSO_4$, concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 10:1) to afford the inseparable mixture of **7-75**, **7-76**, and one unidentified product **7-77**. For the ratio of **7-75** and **7-76**, see spectrum.



Aldehyde 7-82 To a stirred solution of the alcohol **7-81** (0.50 g, 2.72 mmol) in CH_2Cl_2 (30 mL) was added MnO_2 (2.36 g, 27.2 mmol) at r.t. After 16 h, 5 equiv. of MnO_2 (1.18 g, 13.6 mmol) was added and the mixture was stirred for 6 h. The resulting mixture was filtered and the filtarate was concentrated to give the aldehyde **7-82** (0.48 g, 96 %) as colorless oil.

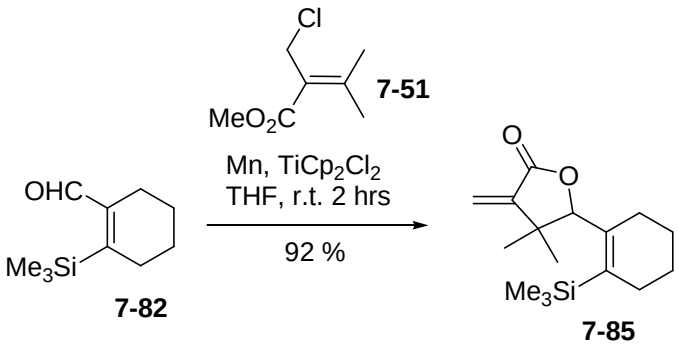
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9 H), 1.60 (m, 4 H), 2.24 (m, 2 H), 2.36 (m, 2 H), 9.89 (s, 1 H).; IR (neat) νmax 1206, 1252, 1430, 1675, 2935 cm^{-1}.



α-Prenylated alcohol 7-83 and γ-prenylated alcohol 7-84 A mixture of $TiCp_2Cl_2$ (0.50 g, 2.2 mmol) and Mn (0.49 g, 8.0 mmol) in THF (20 mL) was stirred for 30 min at r.t. under Ar. Then, a solution of the aldehyde **7-82** (0.18 g, 1.0 mmol) and prenyl bromide (0.29 g, 2.0 mmol) in THF (4 mL) was slowly added to the pre-mixed solution over 1.5 h by syringe pump. After 2 h, the reaction mixture was quenched with sat. $NaHCO_3$ and filtered. The filtrate was extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 20:1) to afford the alcohols **7-83** (0.13 g, 50 %) and **7-84** (81.7 mg, 29 %) as colorless oil.

Alcohol **7-83**: ^{1}H NMR (300 MHz, $CDCl_3$) 0.12 (s, 9 H), 1.44 (d, *J* = 2.4 Hz, 1 H), 1.43 – 1.52 (m, 2 H), 1.65 (s, 3 H), 1.67 (m, 2 H), 1.72 (s, 3 H), 1.92 – 2.15 (m, 4 H), 2.27 (m, 1 H), 2.43 (m, 1 H), 4.35 (m, 1 H), 5.09 (m, 1 H).

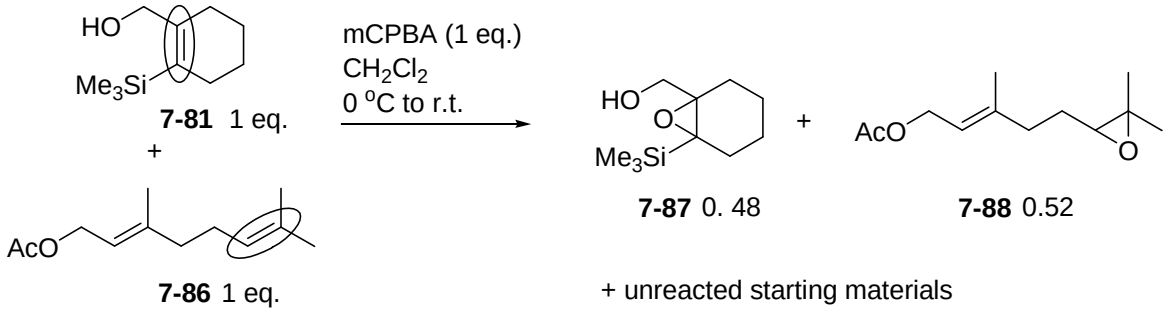
Alcohol **7-84**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 1.04 (s, 3 H), 1.11 (s, 3 H), 1.32 (m, 2 H), 1.45 (d, *J* = 2.7 Hz, 1 H), 1.70 (m, 2 H), 1.90 – 2.19 (m, 4 H), 4.16 (d, *J* = 4.0 Hz, 1 H), 5.02 (s, 1 H), 5.06 (d, *J* = 6.0 Hz, 1 H), 6.09 (dd, J = 18.0 and 10.5 Hz, 1 H).



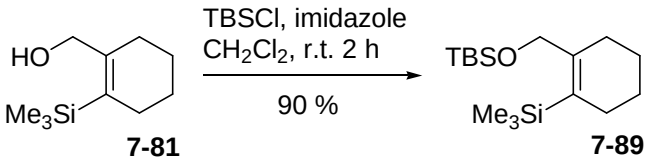
Lactone 7-85 A mixture of $TiCp_2Cl_2$ (0.16 g, 0.66 mmol) and Mn (0.13 g, 2.4 mmol) in THF

(10 mL) was stirred for 30 min at r.t. under Ar. Then, a solution of the aldehyde **7-82** (54.7 mg, 0.3 mmol) and prenyl chloride **7-51** (72.9 mg, 0.45 mmol) in THF (3 mL) was slowly added to the pre-mixed solution over 1.5 h by syringe pump. After 30 min, the reaction mixture was quenched with sat. $NaHCO_3$ and filtered. The filtrate was extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 30:1) to afford the lactone **7-85** (76.6 mg, 92 %) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 9 H), 1.16 (s, 3 H), 1.26 (s, 3 H), 1.46 – 1.64 (m, 4 H), 1.80 – 2.12 (m, 4 H), 4.98 (s, 1 H), 5.43 (s, 1 H), 6.13 (s, 1 H).

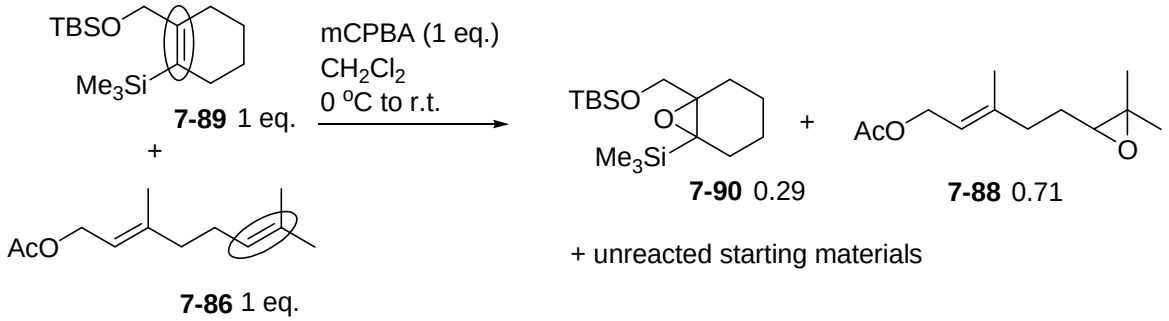


Cross experiment 1 To a stirred solution of the alcohol **7-81** (18.4 mg, 0.1 mmol) and geranyl aceate **7-86** (19.6 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was added m-CPBA (22.3 mg, 0.1 mmol) at 0 °C. The reaction mixture was warmed to r.t. and stirred overnight. Then, the mixture was quenched with sat. $NaHCO_3$ sol'n and extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. For the ratio of both epoxides **7-87** and **7-88**, see spectrum.

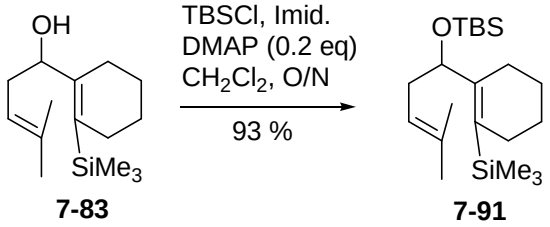


Silyl ether 7-89 To a stirred solution of the alcohol **7-81** (18.4 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added imidazole (10.2 mg, 0.15 mmol) and TBSCl (22.6 mg, 0.15 mmol) at r.t. After 2.5 h, the reaction mixture was concentrated and subjected to silica gel column chromatography (Hex:EtOAc = 50:1) to afford the silyl ether **7-89** (27.0 mg, 90 %) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.11 (s, 9 H), 0.91 (s, 9 H), 1.54 (m, 4 H), 2.08 (m, 4 H), 4.10 (s, 2 H).

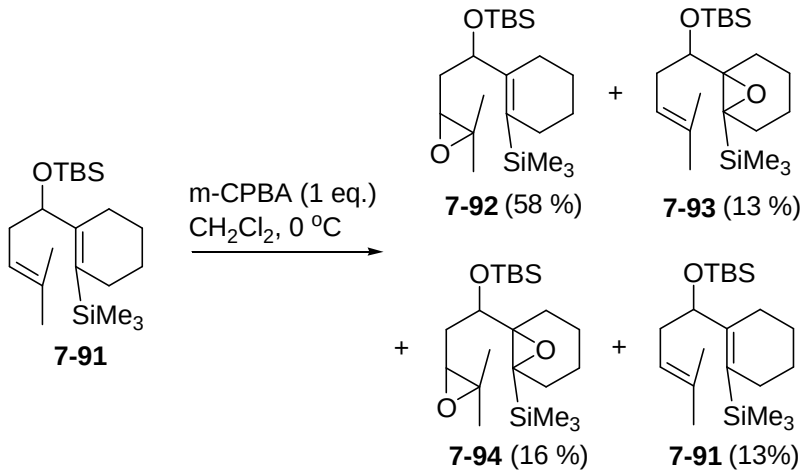


Cross experiment 2 To a stirred solution of the silyl ether **7-89** (27.0 mg, 90.4 µmol) and geranyl aceate **7-86** (17.7 mg, 90.4 µmol) in CH_2Cl_2 (1.0 mL) was added m-CPBA (20.3 mg, 90.4 µmol) at 0 °C. The reaction mixture was warmed to r.t. and stirred overnight. Then, the mixture was quenched with sat. $NaHCO_3$ sol'n and extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. For the ratio of both epoxides **7-90** and **7-88**, see spectrum.

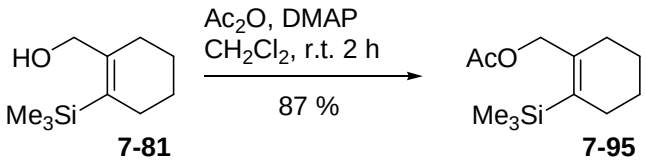


Silyl ether 7-91 To a stirred solution of the alcohol **7-83** (11.0 mg, 43.5 µmol) in CH_2Cl_2 (0.5 mL) was added imidazole (4.4 mg, 65.2 µmol) and TBSCl (9.8 mg, 65.2 µmol) at r.t. After 1 d, the reaction mixture was concentrated and subjected to silica gel column chromatography (Hex:EtOAc = 50:1) to afford the silyl ether **7-91** (14.8 mg, 93 %) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3 H), 0.02 (s, 3 H), 0.11 (s, 9 H), 0.87 (s, 9 H), 1.49 – 1.58 (m, 4 H), 1.60 (s, 3 H), 1.69 (s, 3 H), 1.95 – 2.02 (m, 4 H), 2.92 (m, 2 H), 4.37 (dd, *J* = 8.4 and 4.5 Hz, 1 H), 5.10 (m, 1 H).

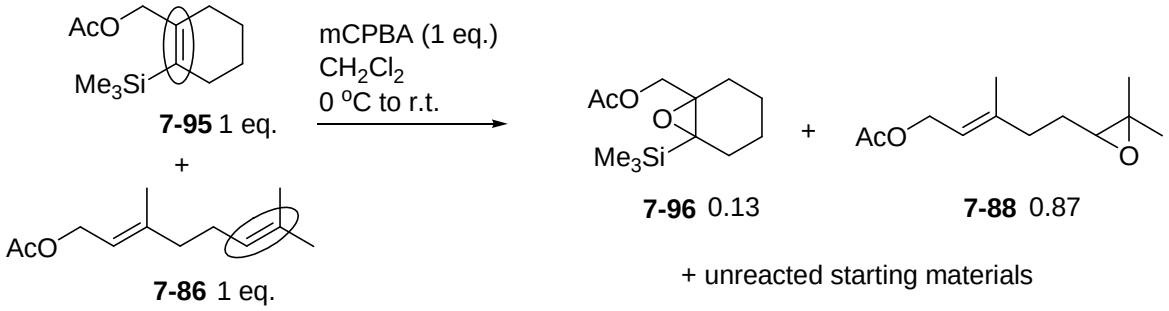


Epoxidation of the silyl ether 7-91 To a stirred solution of the silyl ether **7-91** (7.0 mg, 19.0 µmol) in CH_2Cl_2 (1.0 mL) was added m-CPBA (3.3 mg, 19.0 µmol) at - 40 °C. The reaction mixture was slowly warmed to r.t. over 3 h. Then, the mixture was quenched with sat. $NaHCO_3$ sol'n and extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. For the ratio of epoxides **7-92**, **93**, and **94**, see spectrum.

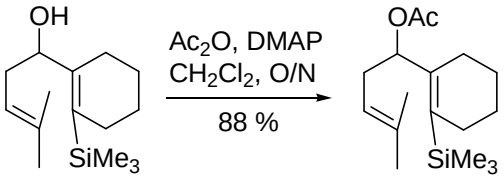


Acetate 7-95 To a stirred solution of the alcohol **7-81** (36.8 mg, 0.2 mmol) in CH_2Cl_2 (1.0 mL) was added DMAP (4.9 mg, 40.0 µmol) and acetic anhydride (28.0 µL, 0.3 mmol) at r.t. and the mixture was stirred for 2 h. Then, the reaction mixture was quenched with sat. $NaHCO_3$ Sol'n, extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 40:1 to 20:1) to afford the acetate **7-95** (39.4 mg, 87 %) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 1.51 – 1.65 (m, 4 H), 2.01 – 2.10 (m, 4 H), 2.07 (s, 3 H), 4.52 (s, 2 H).

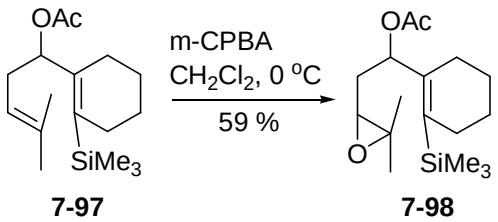


Cross experiment 3 To a stirred solution of the acetate **7-95**(15.0 mg, 66.2 µmol) and geranyl aceate **7-86** (13.0 mg, 66.2 µmol) in CH_2Cl_2 (1.0 mL) was added m-CPBA (14.8 mg, 66.2 µmol) at 0 °C. The reaction mixture was warmed to r.t. and stirred for 2 h. Then, the mixture was quenched with sat. $NaHCO_3$ sol'n and extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. For the ratio of both epoxides **7-96** and **7-88**, see spectrum.



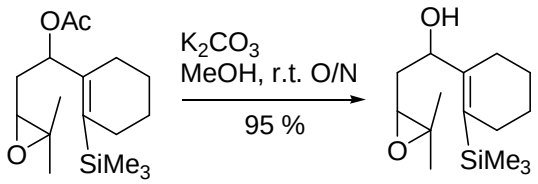
Acetate 7-97 To a stirred solution of the alcohol **7-83** (25.2 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added DMAP (2.4 mg, 20.0 µmol) and acetic anhydride (14.1 µL, 0.15 mmol) at r.t. and the mixture was stirred overnight. Then, the reaction mixture was quenched with sat. $NaHCO_3$ Sol'n, extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 30:1) to afford the acetate **7-97** (23.0 mg, 78 %) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 9 H), 1.46 – 1.60 (m, 4 H), 1.63 (s, 3 H), 1.68 (s, 3 H), 2.01 (s, 3 H), 2.07 – 2.18 (m, 5 H), 2.52 (m, 1 H), 4.99 (m, 1 H), 5.50 (t, *J* = 7.5 Hz, 1 H).



Epoxy acetate 7-98 To a stirred solution of the acetate **7-97** (83.0 mg, 0.28 mmol) in CH_2Cl_2 (2.0 mL) was added m-CPBA (69.4 mg, 0.31 mmol) at 0 ^oC. The reaction mixture was slowly warmed to r.t. and stirred overnight. Then, the mixture was quenched with sat. $NaHCO_3$ sol'n and extracted with ethyl acetate. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 20:1 to 10:1) to afford the epoxy acetate **7-98** (51.8 mg, 59 %) as an inseparable cis- and trans-diastereomers.

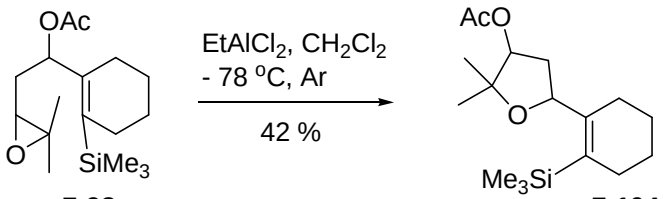
^1H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 0.18 (s, 4.5 H), 1.26 (s, 1.5 H), 1.27 (s, 3 H), 1.29 (s, 4.5 H), 1.49 – 1.61 (m, 4.5 H), 1.76 – 2.17 (m, 10.5 H), 2.70 (dd, *J* = 7.0 and 4.5 Hz, 0.5 H), 2.57 (t, *J* = 6.5 Hz, 1H), 5.73 (dd, *J* = 8.5 and 4.5 Hz, 1 H), 5.82 (dd, *J* = 8.0 and 6.0 Hz, 0.5 H).



7-98 **7-99**

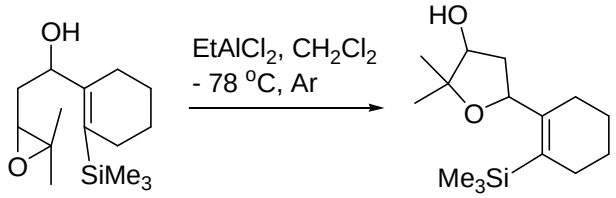
Epoxy alcohol 7-99 To a stirred solution of the epoxy acetate **7-98** (41.7 mg, 0.13 mmol) in MeOH (1.0 mL) was added potassium carbonate (18.5 mg, 0.13 mmol) at r.t. After 15 h, the reaction mixture was quenched with sat. NH_4Cl sol'n and extracted with ethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 5:1) to afford the epoxy alcohol **7-99** (34.2 mg, 95 %) as colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 1.28 (s, 3 H), 1.33 (s, 3 H), 1.39 (d, *J* = 2.1 Hz, 1 H), 1.42 – 1.73 (m, 5 H), 1.93 – 2.09 (m, 4 H), 2.26 (m, 1 H), 2.91 (dd, *J* = 7.2 and 4.5 Hz, 1 H), 4.64 (m, 1 H).



7-98 **7-104**

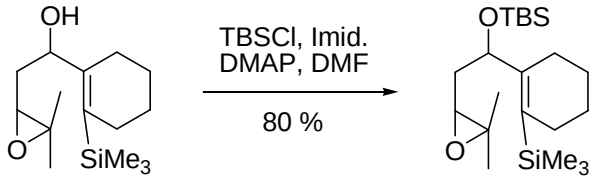
2-Acetoxylfuran 7-104 To a stirred solution of the epoxy acetate **7-98** (14.0 mg, 45.0 µmol) in CH_2Cl_2 (3 mL) was added ethylaluminum dichloride (0.9 M in heptane, 0.10 mL, 90.0 µmol) at – 78 °C. After 2 h, the reaction mixture was quenched with wet triethylamine and diluted with water. The resulting mixture was extracted with diethyl ether. The organic solution was was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 30:1 to 10:1) to afford the 2-acetoxyfuran **7-104** (5.8 mg, 42 %) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 1.23 (s, 3 H), 1.24 (s, 3 H), 1.46 (m, 1 H), 1.54 – 1.67 (m, 4 H), 1.86 (ddd, *J* = 13.8, 8.4, and 4.2 Hz, 1 H), 1.97 – 2.02 (m, 1 H), 2.07 (m, 1 H), 2.08 (s, 3 H), 2.26 (m, 1 H), 2.39 (dt, *J* = 13.6 and 7.2 Hz, 1 H), 4.71 (t, *J* = 7.8 Hz, 1 H), 5.03 (dd, *J* = 7.2 and 4.2 Hz, 1 H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.5, 21.0, 21.1, 22.4, 22.5, 23.3, 25.2, 29.7, 36.7, 77.8, 79.7, 81.7, 136.0, 145.2, 170.6.; IR (neat) νmax 1044, 1248, 1373, 1613, 1741 cm^{-1}.



7-99 **7-105**
major in crude

2-Hydroxyfuran 7-105 To a stirred solution of the epoxy alcohol **7-99** (5.4 mg, 20.1 µmol) in CH_2Cl_2 (1.5 mL) was added ethylaluminum dichloride (0.9 M in heptane, 44.6 mL, 40.2 µmol) at – 78 °C under Ar. After 1 h, the reaction mixture was quenched with wet triethylamine and diluted with water. The resulting mixture was extracted with CH_2Cl_2. The organic solution was was dried over $MgSO_4$ and concentrated. The ^{1}H nmr of the crude product was obtained without silica gel chromatography. As a result, the same pattern of the nmr spectrum indicated the

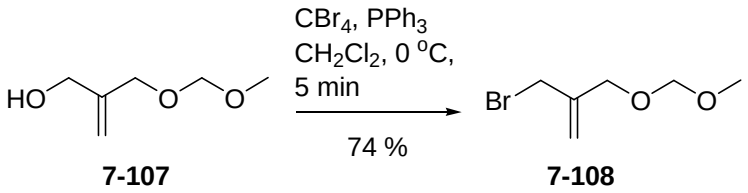
presence of the 2-hydroxyfuran **7-105** as a major product. See spectrum.



7-99 **7-92**

Silyl ether 7-92 To a stirred solution of the epoxy alcohol **7-99** (10.0 mg, 37.2 µmol) in DMF (1.0 mL) was added imidazole (5.1 mg, 74.4 µmol) and TBSCl (8.4 mg, 55.8 µmol) at r.t. under Ar. After 12 h, the reaction mixture was diluted with water and extracted with ethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 30:1) to afford the silyl ether **7-92** (13.5 mg, 95 %) as an inseparable mixture of cis- and trans-diastereomers.

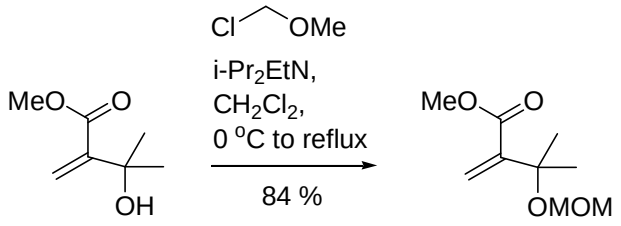
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 1.5 H), 0.06 (s, 1.5 H), 0.08 (s, 1.5 H), 0.11 (s, 1.5 H), 0.148 (s, 4.5 H), 0.153 (s, 4.5 H), 0.88 (s, 4.5 H), 0.89 (s, 4.5 H), 1.26 (s, 1.5 H), 1.27 (s, 1.5 H), 1.29 (s, 1.5 H), 1.31 (s, 1.5 H), 1.36 – 1.68 (m, 5 H), 1.78 – 2.13 (m, 4 H), 2.27 (m, 1 H), 2.76 (t, *J* = 5.4 Hz, 0.5 H), 2.87 (dd, *J* = 6.9 and 4.8 Hz, 0.5 H), 4.64 (m, 1 H).



7-107 **7-108**

Allyl bromide 7-108 To a stirred solution of allyl alcohol **7-107** (0.34 g, 2.56 mmol) in CH_2Cl_2 (12 mL) was added CBr_4 (1.03 g, 3.09 mmol) and PPh_3 (0.88 g, 3.35 mmol) at 0 °C under Ar. After 5 min, the reaction mixture was concentrated and subjected to silica gel column chromatography (Hex:EtOAc = 20:1) to afford the allyl bromide **7-108** (0.37 g, 74 %) as colorless oil.

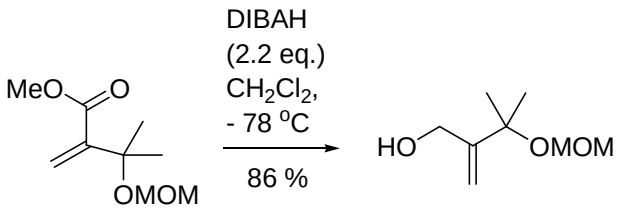
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (s, 3 H), 4.04 (s, 2 H), 4.19 (s, 2 H), 4.66 (s, 2 H), 5.25 (s, 1 H), 5.34 (s, 1 H).



7-71 **7-109**

Methyl ester 7-109 To a stirred solution of tert-alcohol **7-71** (0.47 g, 3.26 mmol) in CH_2Cl_2 (8.0 mL) was added diisopropylethylamine (1.08 mL, 6.52 mmol) and MOMCl (0.37 mL, 4.89 mmol) at 0 °C under Ar. The reaction mixture was heated to reflux and stirred for 40 h. Then, the mixture was cooled to r.t., quenched with sat. NH_4Cl sol'n, and extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 10:1) to afford the MOM-ether **7-109** (0.51 g, 84 %) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 6 H), 3.36 (s, 3 H), 3.75 (s, 3 H), 4.67 (s, 2 H), 5.77 (d, *J* = 0.9 Hz, 1 H), 6.09 (d, *J* = 0.9 Hz, 1 H).

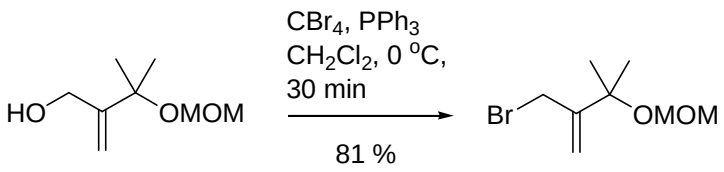


7-109 **7-110**

Allyl alcohol 7-110 To a stirred solution of MOM-ether **7-109** (0.42 g, 2.21 mmol) in CH_2Cl_2 (20 mL) was added DIBAL-H (1.0 M in hexane, 4.64 mL, 4.64 mmol) at – 78 °C under Ar. After 20 min, the reaction mixture was quenched with MeOH and diluted with 10 % potassium sodium tartarate sol'n and diethyl ether (50 mL). The mixture was stirred for 1 h and partitioned. The aqueous solution was extracted with diethyl ether. The combined organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 1:1) to afford the allyl alcohol **7-110** (0.25 g, 86 %) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 6 H), 3.37 (s, 3 H), 4.19 (s, 2 H), 4.62 (s, 2 H), 5.18 (s, 1

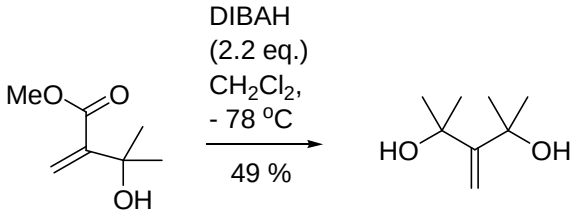
H), 5.28 (s, 1 H).; IR (neat) νmax 1036, 1144, 1401, 1464, 1646, 3414 cm^{-1}.



7-110 **7-111**

Allyl bromide 7-111 To a stirred solution of allyl alcohol **7-110** (80.1 mg, 0.50 mmol) in CH_2Cl_2 (4.0 mL) was added CBr_4 (0.20 g, 0.60 mmol) and PPh_3 (0.17 g, 0.65 mmol) at 0 °C under Ar. After 20 min, the reaction mixture was concentrated and subjected to silica gel column chromatography (Hex:EtOAc = 20:1) to afford the allyl bromide **7-111** (90.7 mg, 81 %) as colorless oil.

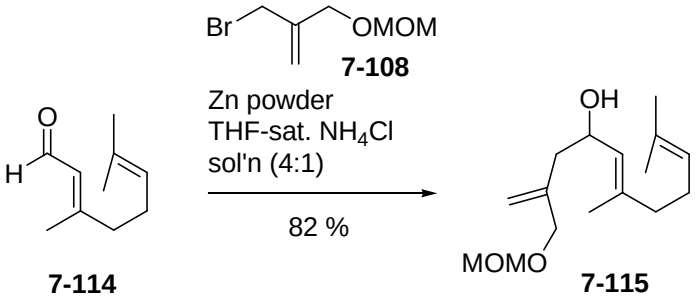
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 6 H), 3.37 (s, 3 H), 4.06 (s, 2 H), 4.59 (s, 2 H), 5.40 (s, 1 H), 5.51 (s, 1 H).



7-71 **7-112**

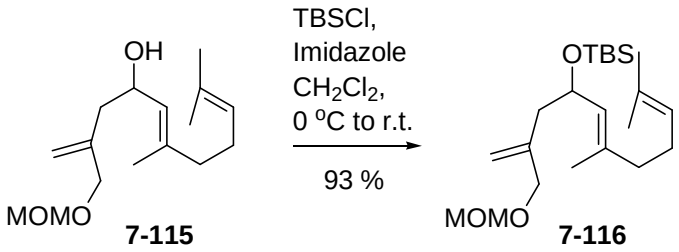
Diol 7-112 To a stirred solution of the tert-alcohol **7-71** (40.0 mg, 0.28 mmol) in diethyl ether (1.0 mL) was added MeLi (1.6 M in diethyl ether, 0.61 mL, 0.97 mmol) at 0 °C under Ar. The reaction mixture was slowly warmed to r.t. over 2 h and quenched with sat. NH_4Cl sol'n. The mixture was extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 5:1) to afford the diol **7-112** (19.5 mg, 49 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 6 H), 3.33 (s, 1 H), 4.90 (s, 1 H).



Allyl alcohol 7-115 A mixture of (E)-geranialdehyde **7-114** (0.12 g, 0.78 mmol), allyl bromide **7-108** (0.23 g, 1.17 mmol), and Zn (0.13 g, 1.95 mmol) in THF (0.8 mL)/ sat. NH4Cl sol'n (0.4 mL) was stirred for 30 min. The reaction mixture was filtered and the filtrate was extracted with diethyl ether. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 5:1) to afford the allyl alcohol **7-115** (0.17 g, 82 %) as colorless oil.

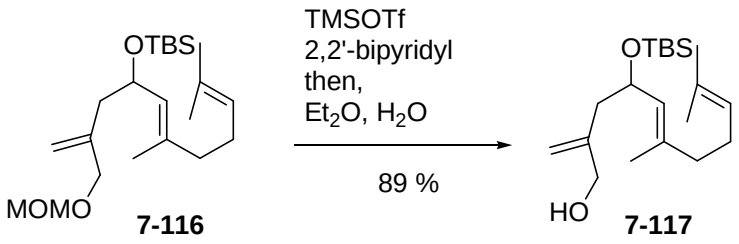
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3 H), 1.67 (d, *J* = 1.2 Hz, 3 H), 1.69 (d, *J* = 1.2 Hz, 3 H), 1.98 – 2.10 (m, 4 H), 2.29 (dd, *J* = 6.0 and 0.9 Hz, 2 H), 3.39 (s, 3 H), 4.04 (s, 2 H), 4.52 (dt, *J* = 8.7 and 6.6 Hz, 1 H), 4.66 (d, *J* = 0.6 Hz, 2 H), 5.04 – 5.22 (m, 4 H).



Silyl ether 7-116 To a stirred solution of the allyl alcohol **7-115** (0.17 g, 0.63 mmol) in CH_2Cl_2 (5 mL) was added imidazole (0.13 g, 1.90 mmol) and TBSCl (0.14 g, 0.95 mmol) at 0 °C. The reaction mixture was warmed to r.t. and stirred overnight. Then, the mixture was diluted with CH_2Cl_2 and washed with water and brine. The organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 50:1) to afford the silyl ether **7-116** (0.23 g, 93 %) as colorless oil.

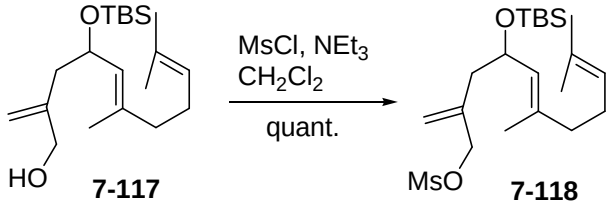
^{1}H NMR (300 MHz, $CDCl_3$) δ - 0.003 (s, 3 H), - 0.007 (s, 3 H), 0.85 (s, 9 H), 1.60 (s, 3 H), 1.61 (d, *J* = 1.5 Hz, 3 H), 1.67 (d, *J* = 0.9 Hz, 3 H), 1.95 – 2.12 (m, 3 H), 2.16 (d, *J* = 5.4 Hz, 1 H),

2.25 (dd, *J* = 13.8 and 7.2 Hz, 1 H), 3.37 (s, 3 H), 4.01 (s, 2 H), 4.48 (m, 1 H), 4.64 (s, 2 H), 4.93 (m, 1 H), 5.05 – 5.15 (m, 3 H).



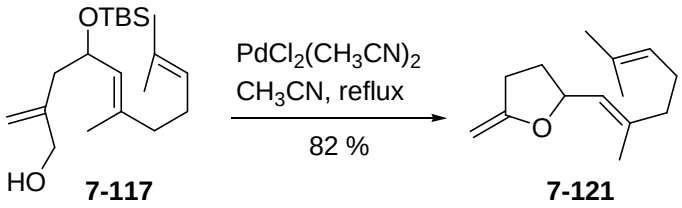
Allyl alcohol 7-117 To a stirred solution of the silyl ether **7-116** (76.5 mg, 0.2 mmol) and bioyridiyl (93.7 mg, 0.6 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise TMSOTf (72.0 µL, 0.4 mmol) at 0 ^oC. The reaction mixture was warmed to r.t. and stirred for 30 min. Then, the reaction mixture was treated with water (3 mL)/diethyl ether (3 mL) and stirred overnight. The resulting bilayer was partitioned and the aqueous layer was extracted with diethyl ether. The combined organic solution was washed with sat. $NaHCO_3$ sol'n, brine, dried over $MgSO_4$, and concentrated. The residue was subjected to silica gel column chromatography (Hex:EtOAc = 10:1) to afford the allyl alchol **7-117** (60.5 mg, 89 %) as colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.60 (s, 3 H), 1.62 (d, *J* = 1.2 Hz, 3 H), 1.70 (d, *J* = 0.9 Hz, 3 H), 1.97 – 2.09 (m , 4 H), 2.28 (d, *J* = 5.7 Hz, 2 H), 4.07 (s, 2 H), 4.53 (dt, J = 8.4 and 5.4 Hz, 1 H), 4.85 (m, 1 H), 5.05 – 5.18 (m, 4 H).



Mesylate 7-118 To a stirred solution of the allyl alchol **7-117** (38.3 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added triethylamine (31.4 µL, 0.22 mmol) and MsCl (13.1 µL, 0.17 mmol) at 0 ^oC. The reaction mixture was warmed to r.t. and stirred overnight. The reaction mixture was diluted with diethyl ether and washed with water, 1N HCl, and sat. $NaHCO_3$ sol'n. The organic solution was dried over $MgSO_4$, and concentrated.

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.003 (s, 3 H), 0.015 (s, 3 H), 0.86 (s, 9 H), 1.60 (s, 3 H), 1.63 (s, 3 H), 1.67 (s, 3 H), 1.99 (t, *J* = 7.8 Hz, 2 H), 2.08 (m, 2 H), 2.22 (dd, *J* = 13.8 and 4.8 Hz, 1 H), 2.27 (dd, *J* = 13.8 and 7.2 Hz, 1 H), 3.01 (s, 3 H), 4.51 (m , 1 H), 4.71 (s, 2 H), 5.07 (t, *J* = 6.6 Hz, 1 H), 5.09 (s, 1 H), 5.13 (d, *J* = 8.4 Hz, 1 H), 5.23 (s, 1 H).

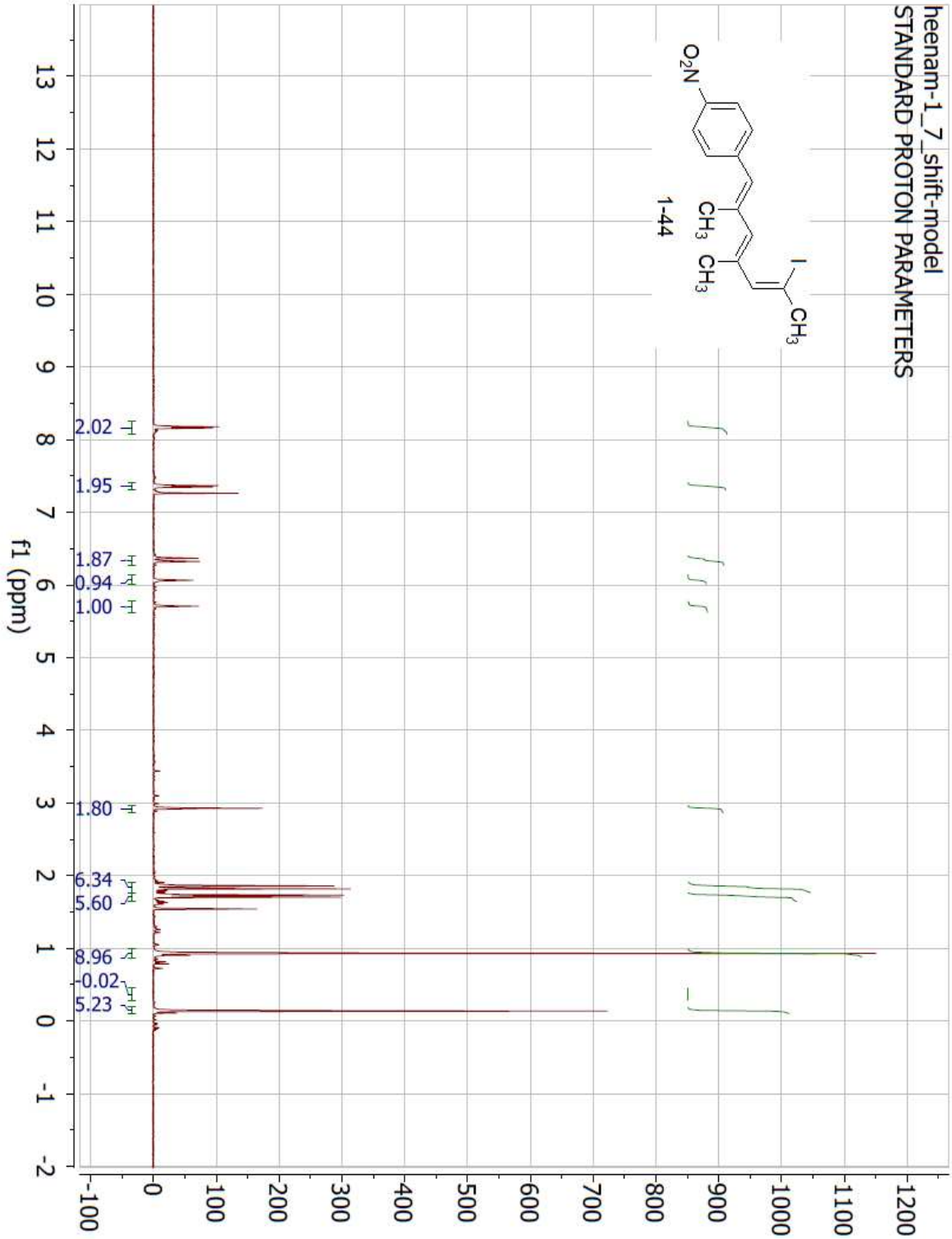


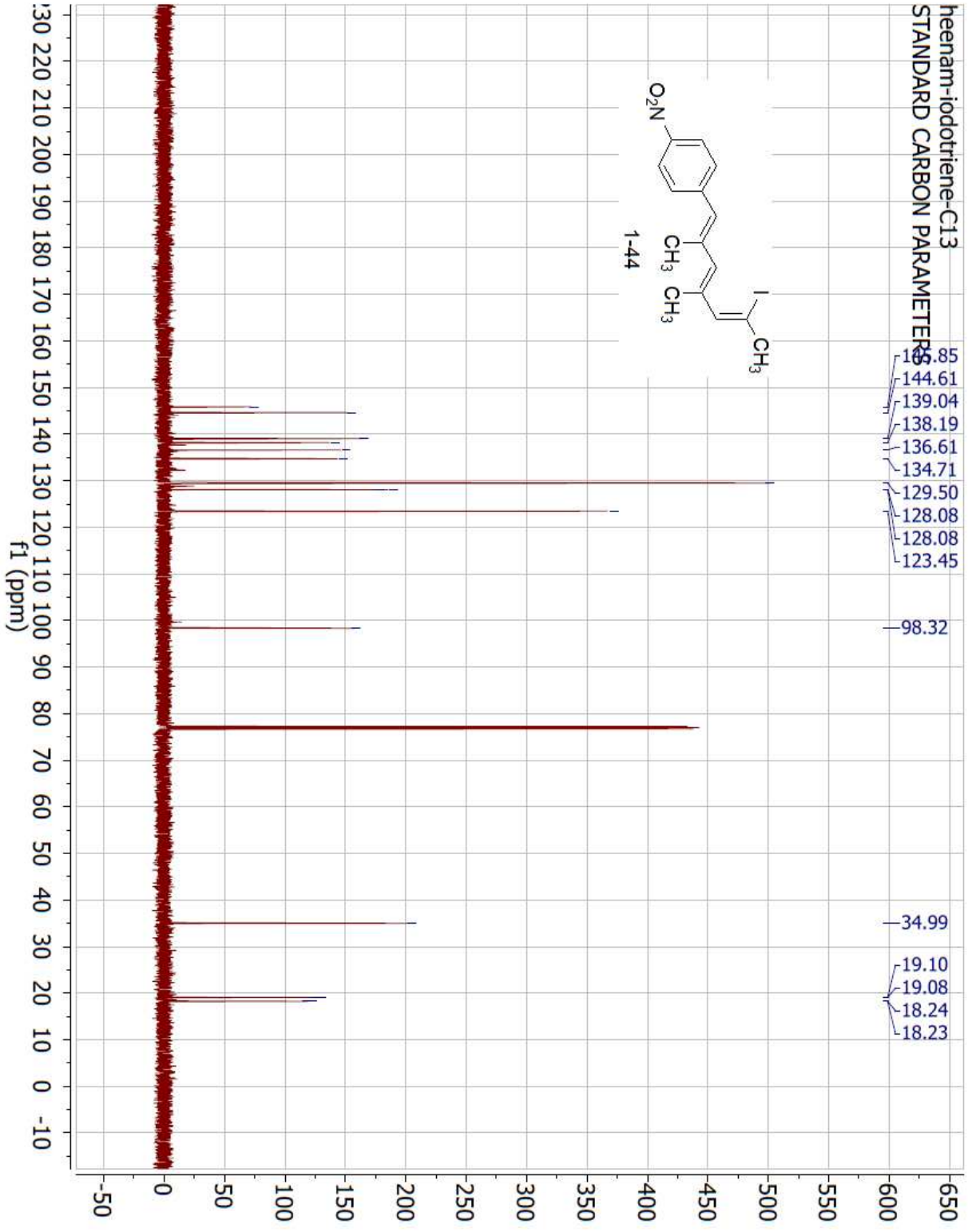
7-117 **7-121**

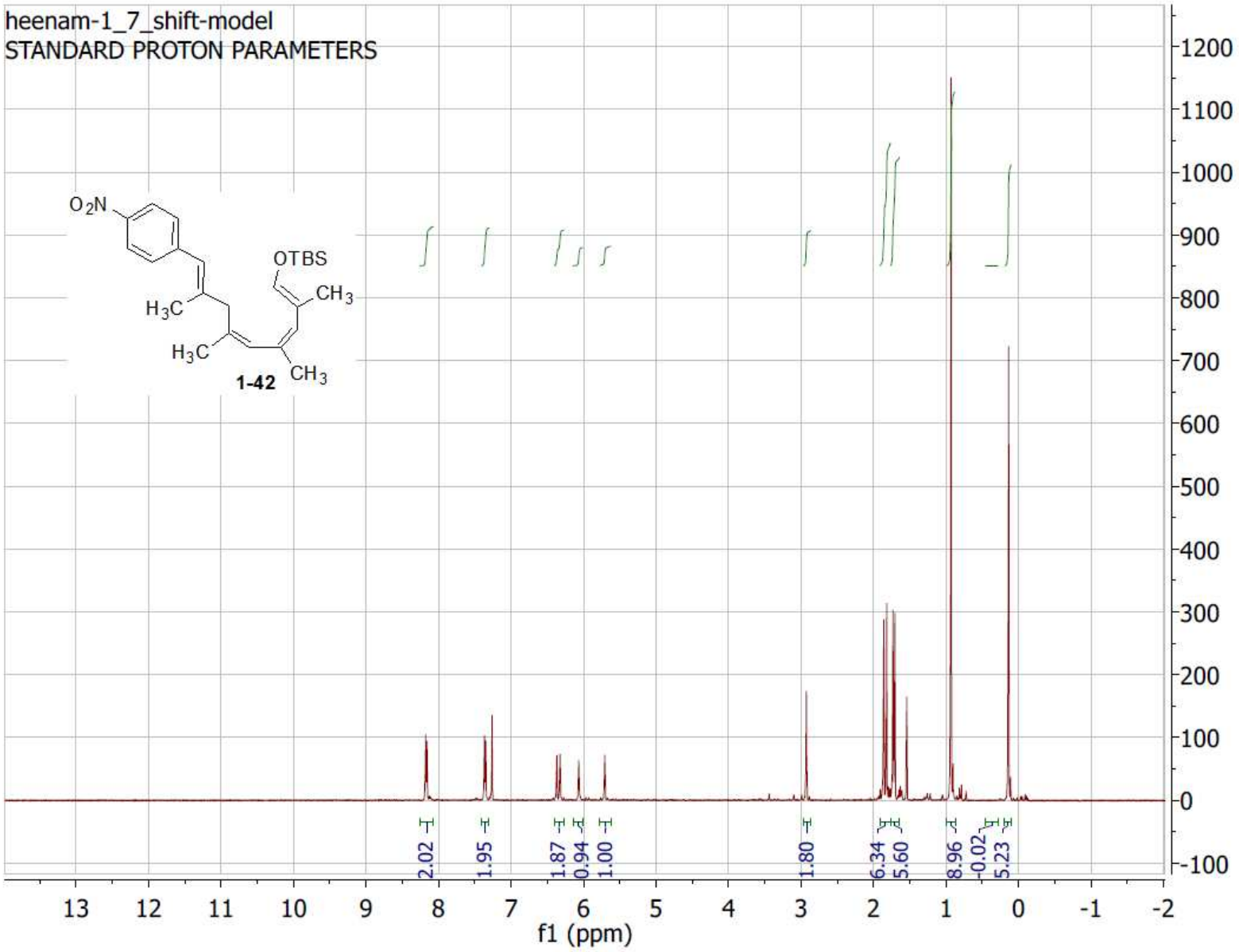
Furan 7-121 To a stirred solution of the allyl alcohol **7-117** (14.7 mg, 43.4 µmol) in CH_3CN (2 mL) was added $PdCl_2(CH_3CN)_2$ (1.1 mg, 4.3 µmol) at r.t. under Ar. After 1 h, the reaction mixture was heated to reflux for 1 h. Then, the mixture was concentrated and subjected to silica gel column chromatography (Hex:EtOAc = 20:1) to afford the furan **7-121** (7.3 mg, 82 %) as colorless oil.

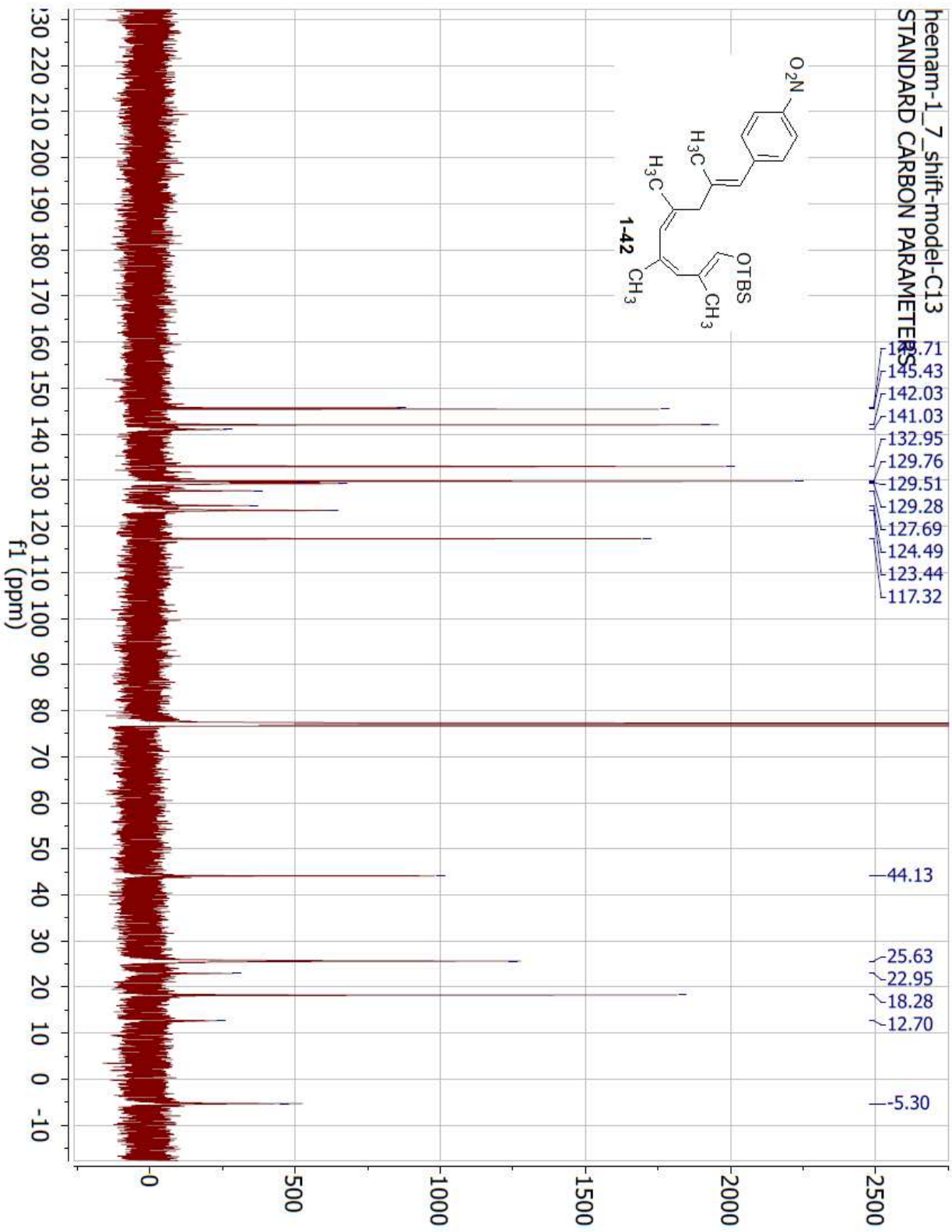
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 3 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 2.01 – 2.13 (m, 4 H), 2.28 (m, 1 H), 2.65 (dd, *J* = 15.0 and 5.5 Hz, 1 H), 4.23 (dd, *J* = 13.0 and 1.5 Hz, 1 H), 4.41 (d, J = 13.0 Hz, 1 H), 4.62 (m, 1 H), 4.90 (s, 1 H), 4.98 (s, 1 H), 5.09 (m, 1 H), 5.26 (d, *J* = 8.5 Hz, 1 H).; IR (neat) νmax 1050, 1323, 1377, 1431, 1667 cm^{-1}.

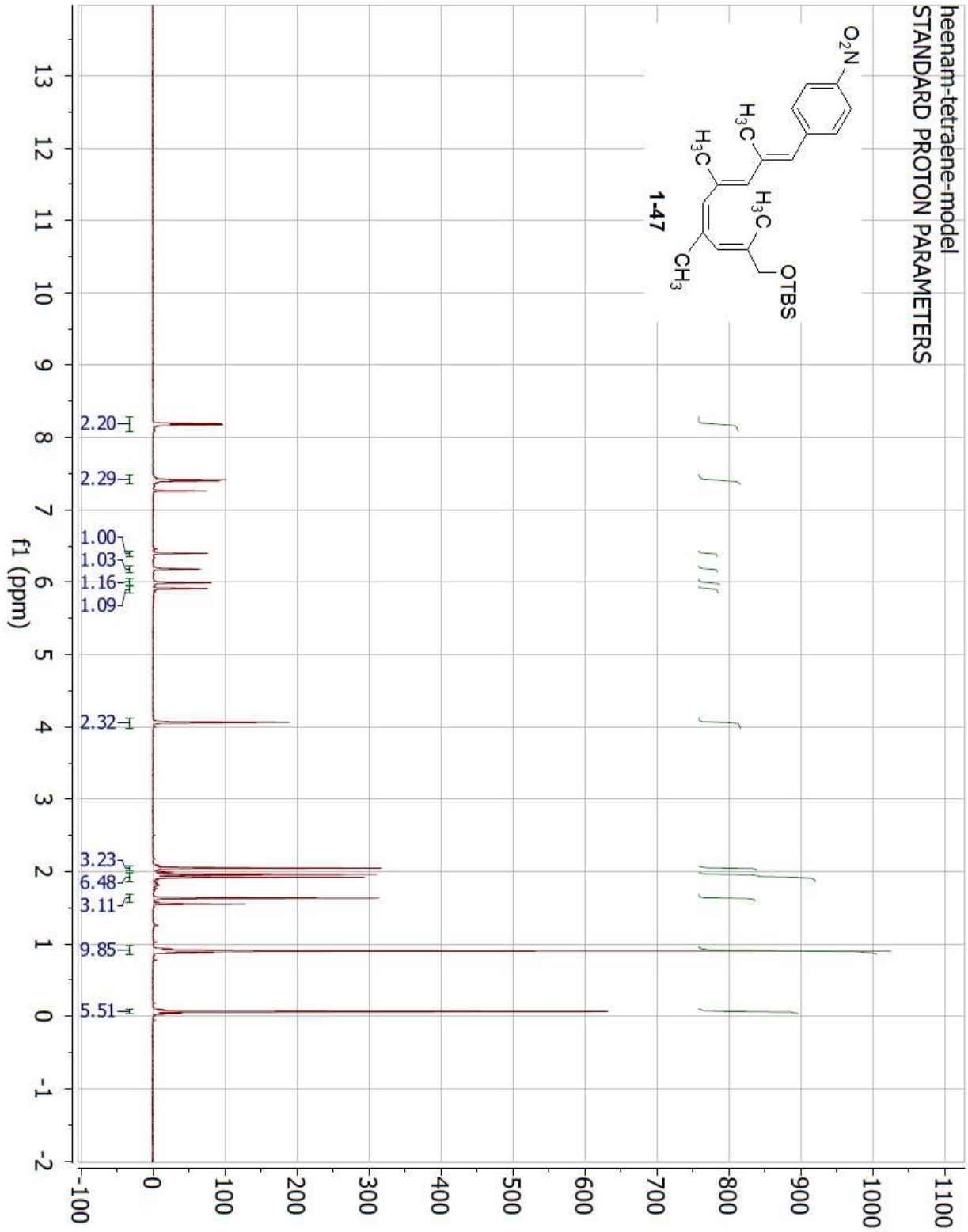
Appendix

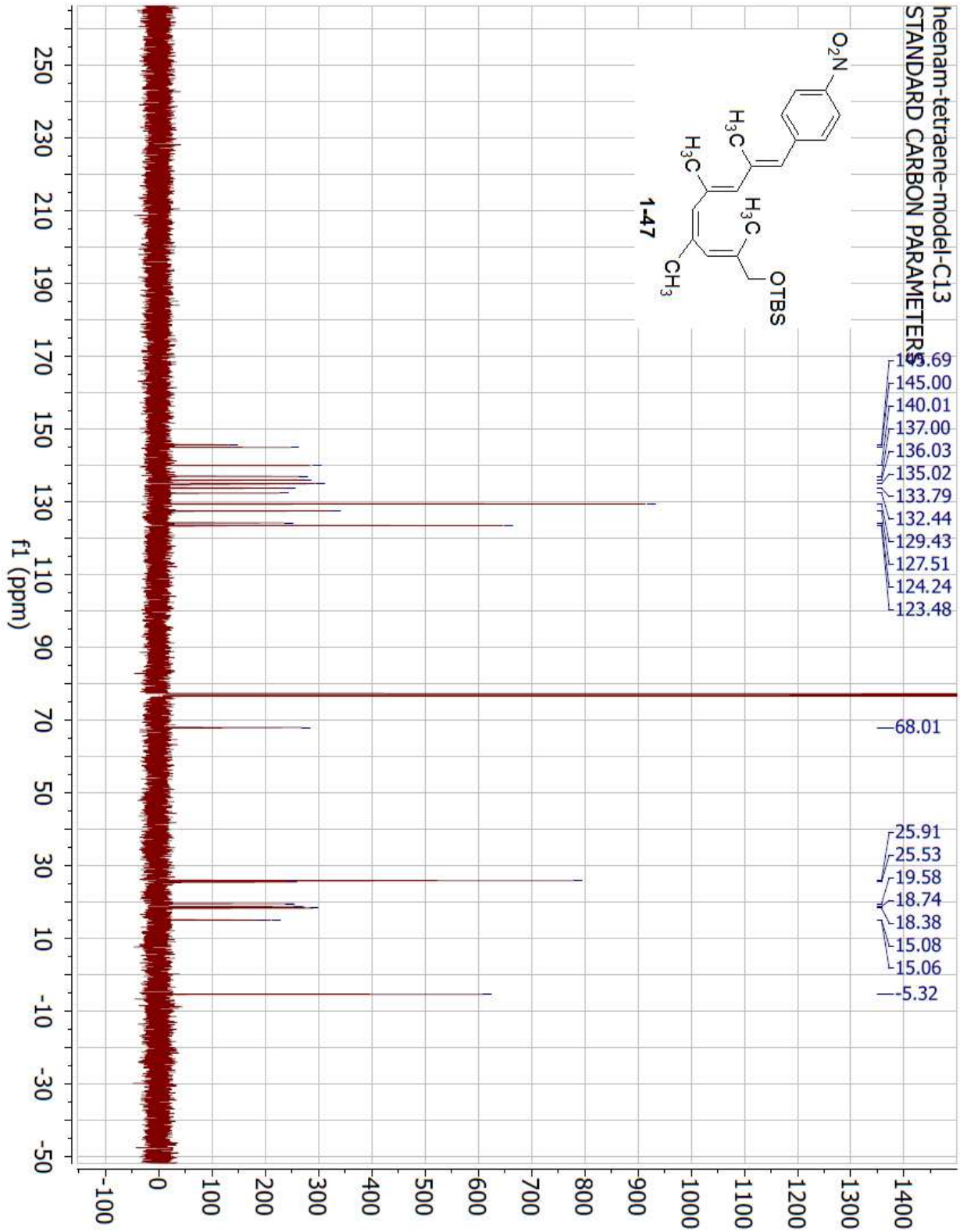

heenam-1_7_shift-model
STANDARD PROTON PARAMETERS
O2N
CH3
CH3
I
CH3
1-44
2.02
1.95
1.87
0.94
1.00
1.80
6.34
5.60
8.96
-0.02
5.23
f1 (ppm)

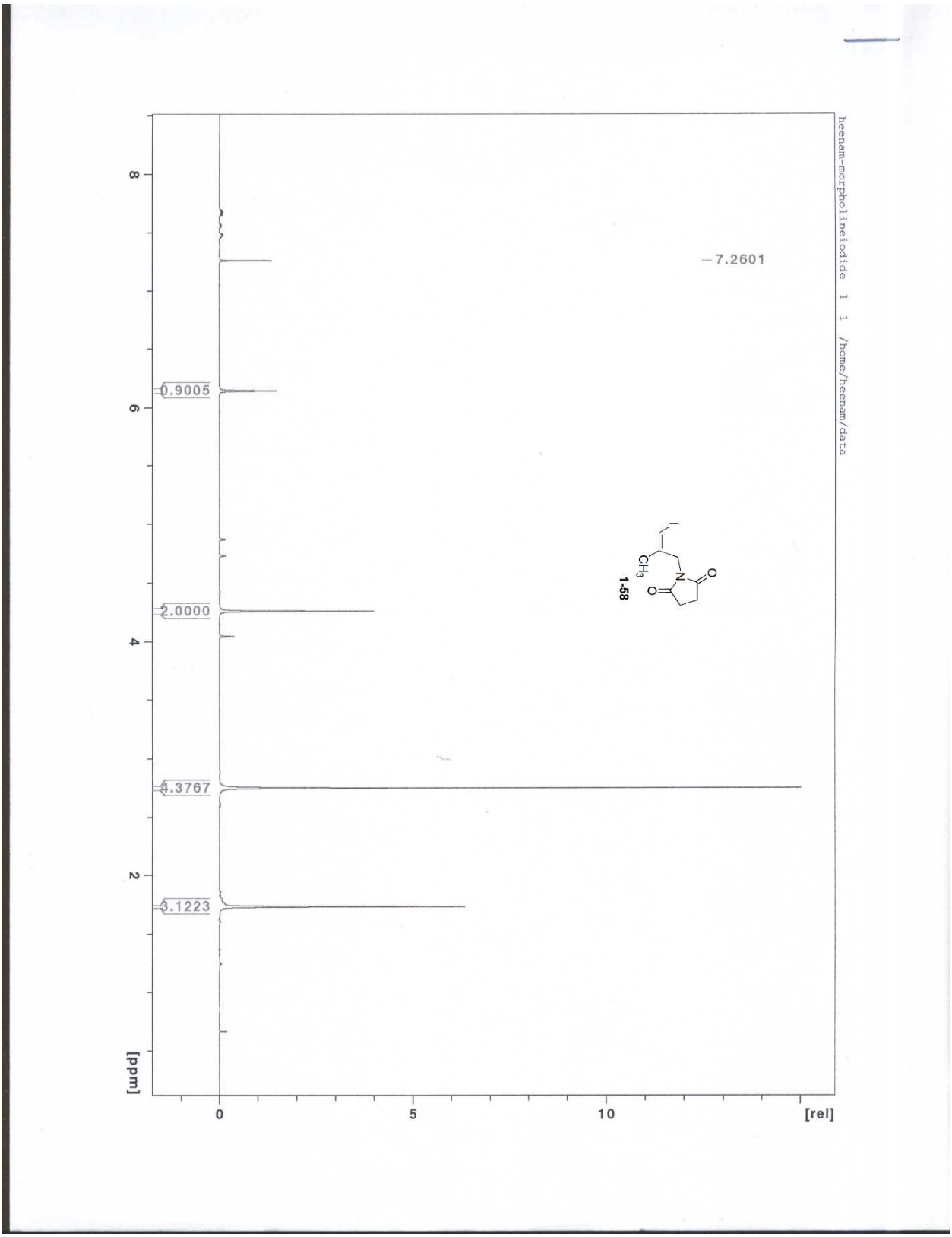

heenam-iodotriene-C13
STANDARD CARBON PARAMETERS
1-44
O_2N
CH_3
CH_3
I
CH_3
146.85
144.61
139.04
138.19
136.61
134.71
129.50
128.08
128.08
123.45
98.32
34.99
19.10
19.08
18.24
18.23
f1 (ppm)


heenam-1_7_shift-model
STANDARD PROTON PARAMETERS
O2N
OTBS
H3C
CH3
H3C
CH3
1-42
2.02
1.95
1.87
0.94
1.00
1.80
6.34
5.60
8.96
-0.02
5.23
f1 (ppm)


heenam-1_7_shift-model-C13
STANDARD CARBON PARAMETERS
1-42
O2N
H3C
H3C
CH3
OTBS
CH3
145.71
145.43
142.03
141.03
132.95
129.76
129.51
129.28
127.69
124.49
123.44
117.32
44.13
25.63
22.95
18.28
12.70
-5.30
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
0
500
1000
1500
2000
2500


heenam-tetraene-model
STANDARD PROTON PARAMETERS
1-47
O_2N
H_3C
H_3C
H_3C
CH_3
OTBS
2.20
2.29
1.00
1.03
1.16
1.09
2.32
3.23
6.48
3.11
9.85
5.51
f1 (ppm)


heenam-tetraene-model-C13
STANDARD CARBON PARAMETERS
1-47
O_2N
H_3C
H_3C
H_3C
CH_3
OTBS
145.00
140.01
137.00
136.03
135.02
133.79
132.44
129.43
127.51
124.24
123.48
68.01
25.91
25.53
19.58
18.74
18.38
15.08
15.06
-5.32
f1 (ppm)


heenam-morpholineiodide 1 1 /home/heenam/data
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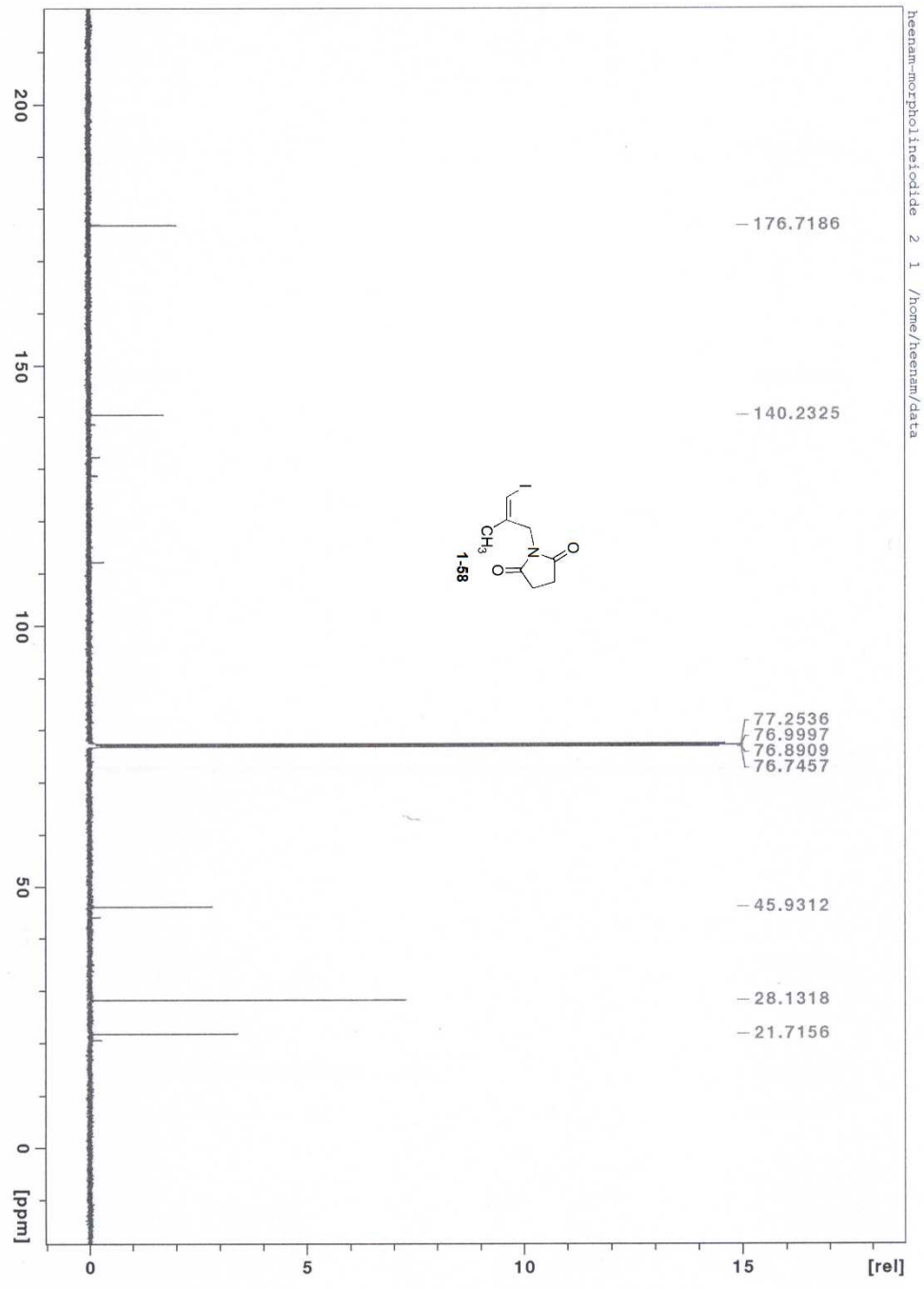
0.9005
2.0000
4.3767
3.1223
1-58
[ppm]
[rel]


heenam-morpholineiodide 2 1 /home/heenam/data
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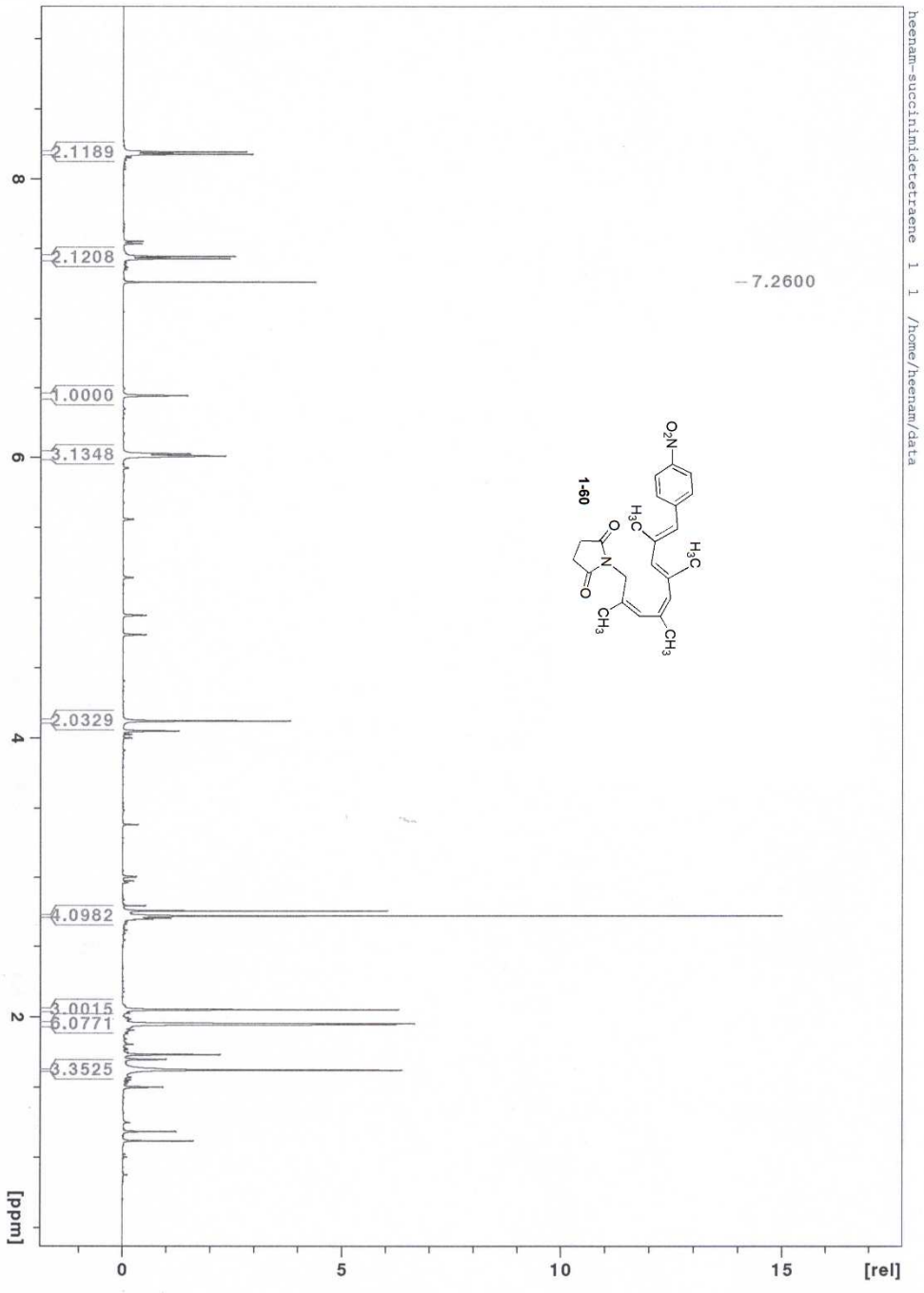
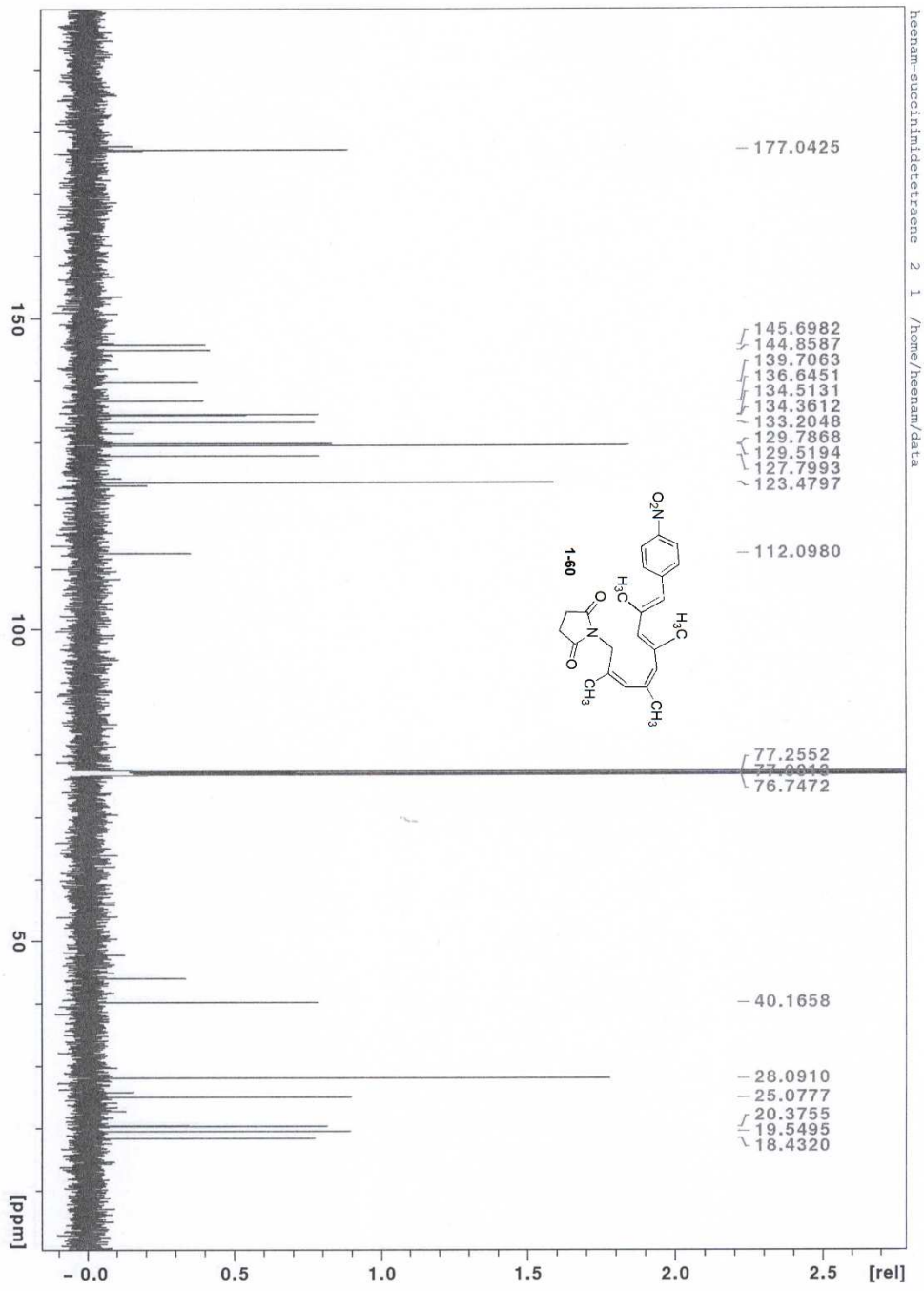
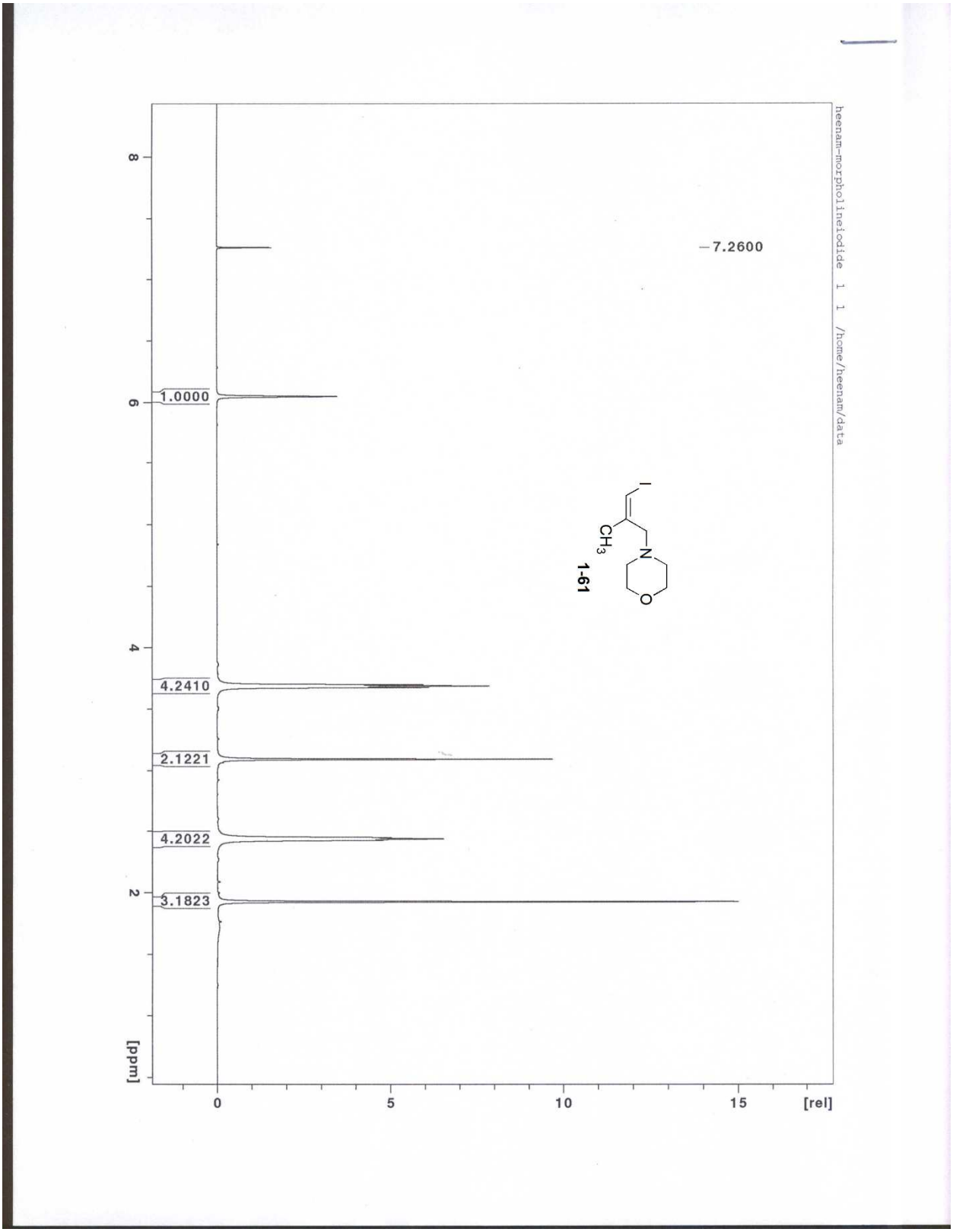
140.2325
77.2536
76.9997
76.8909
76.7457
45.9312
28.1318
21.7156
1-58
200
150
100
50
0
[ppm]
0
5
10
15
[rel]


heenam-succinimidetetraene 1 1 /home/heenam/data
2.1189
2.1208
1.0000
3.1348
2.0329
4.0982
3.0015
6.0771
3.3525
7.2600
1-60
O2N
H3C
H3C
CH3
CH3
O
N
O
[ppm]
[rel]
0
5
10
15
2
4
6
8


heenam-succinimidetetraene 2 1 /home/heenam/data
177.0425
145.6982
144.8587
139.7063
136.6451
134.5131
134.3612
133.2048
129.7868
129.5194
127.7993
123.4797
112.0980
77.2552
77.0013
76.7472
40.1658
28.0910
25.0777
20.3755
19.5495
18.4320
1-60
O2N
H3C
H3C
CH3
CH3
O
N
O
150
100
50
[ppm]
0.0
0.5
1.0
1.5
2.0
2.5
[rel]


heenam-morpholineiodide 1 1 /home/heenam/data
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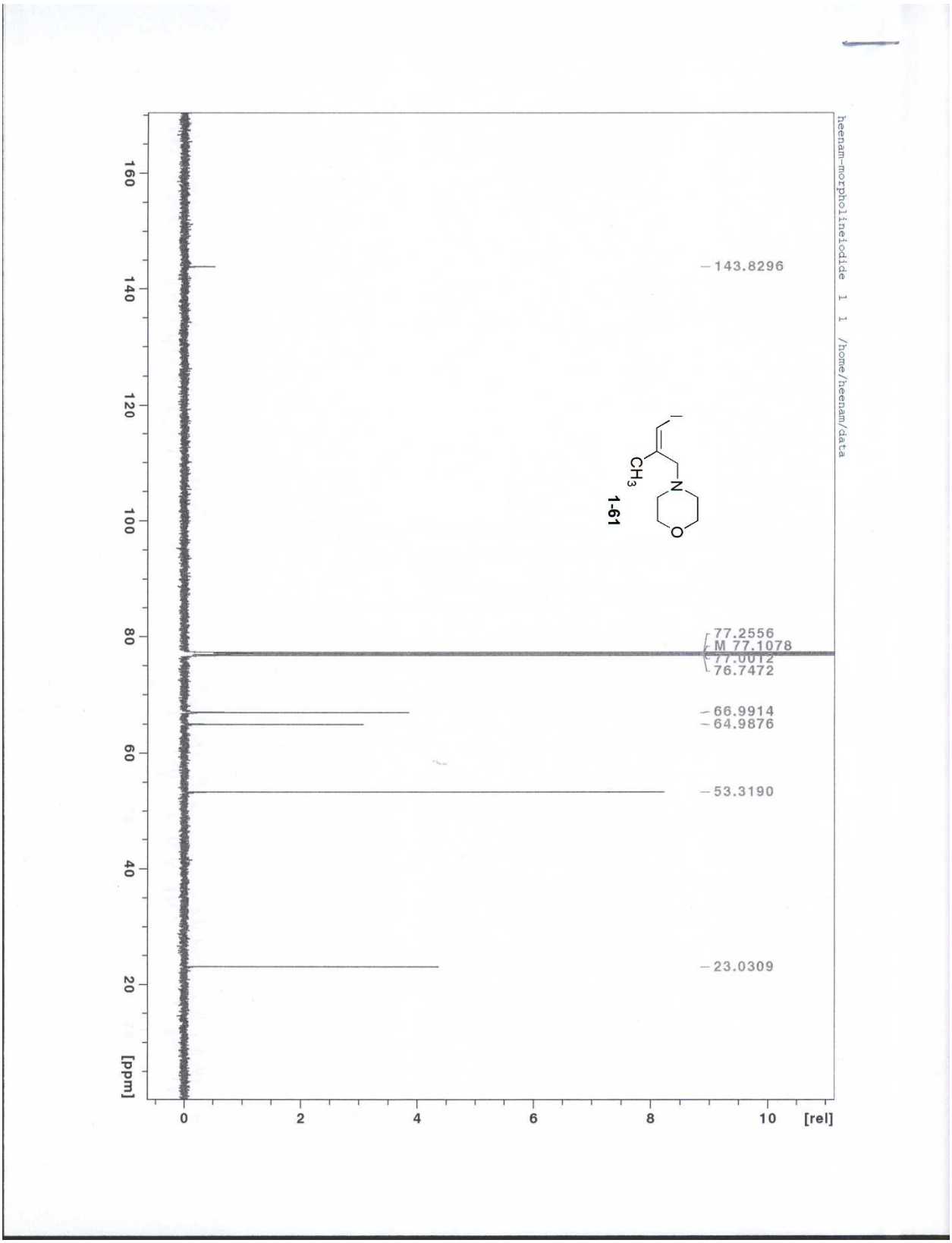
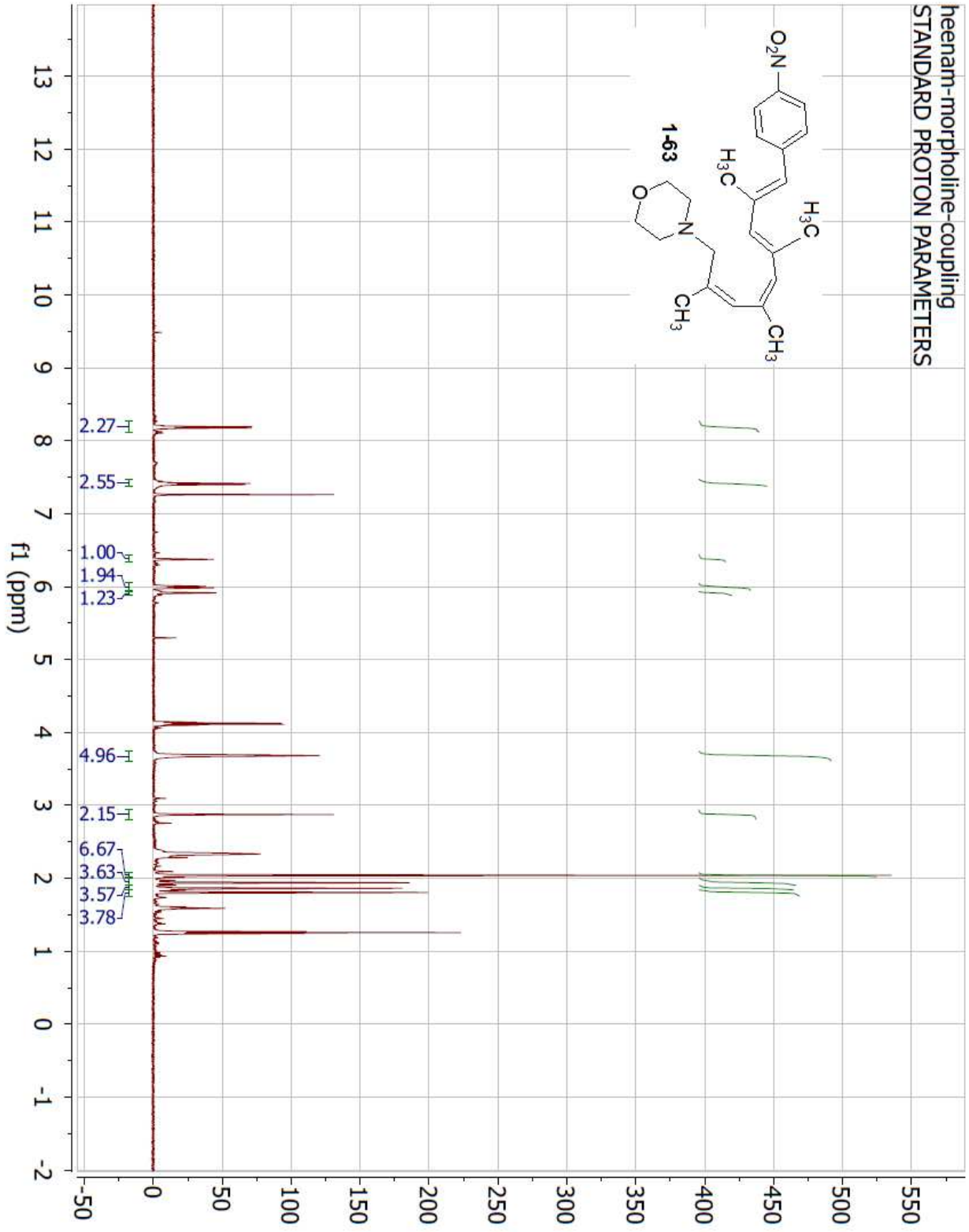
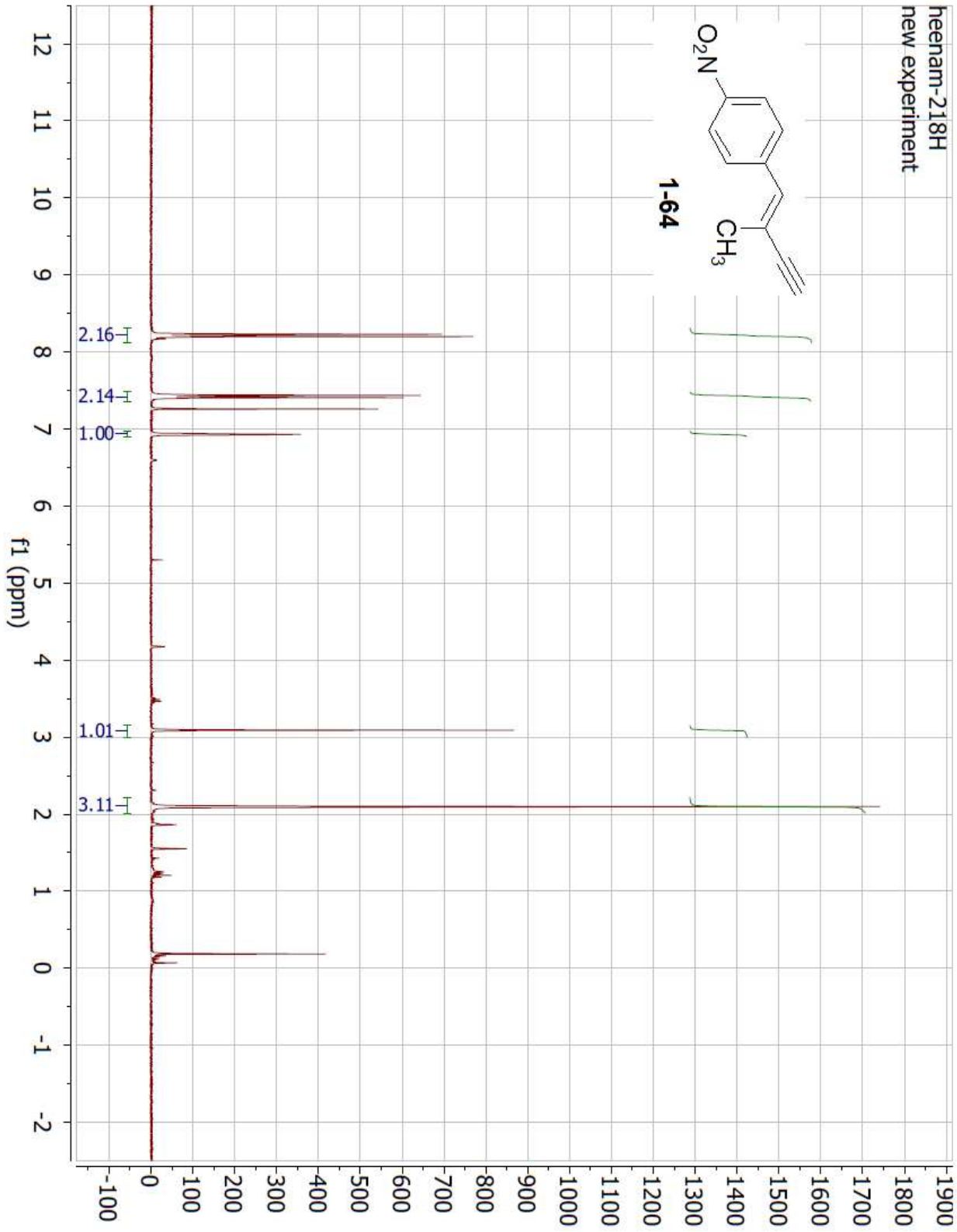
1.0000
4.2410
2.1221
4.2022
3.1823
8
6
4
2
[ppm]
0
5
10
15
[rel]
I
CH3
N
O
1-61


heenam-morpholineiodide 1 1 /home/heenam/data
143.8296
77.2556
M 77.1078
77.0012
76.7472
66.9914
64.9876
53.3190
23.0309
1-61
[ppm]
[rel]

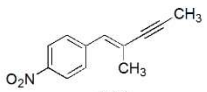

heenam-morpholine-coupling
STANDARD PROTON PARAMETERS
1-63
O2N
H3C
H3C
CH3
CH3
N
O
2.27
2.55
1.00
1.94
1.23
4.96
2.15
6.67
3.63
3.57
3.78
f1 (ppm)


heenam-218H
new experiment
O_2N
CH_3
1-64
2.16
2.14
1.00
1.01
3.11
f1 (ppm)

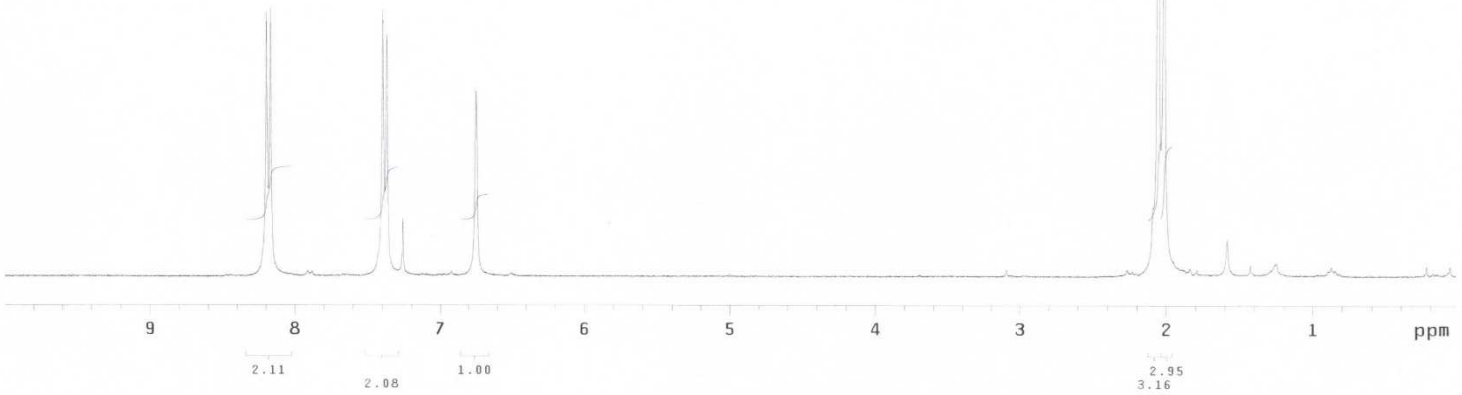
new experiment

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
20 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec



1-12

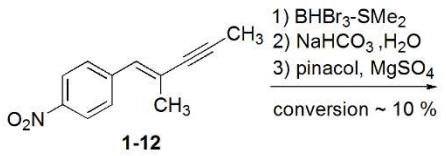


STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-600 "inv601"

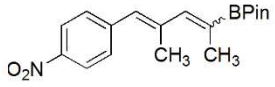
Relax. delay 1.000 sec
Pulse 61.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
23 repetitions
OBSERVE H1, 599.7178142 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 11 sec



1-12

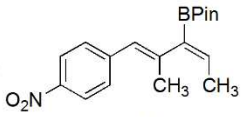
1) $BHBr_3$-SMe_2
2) $NaHCO_3$, H_2O
3) pinacol, $MgSO_4$

conversion ~ 10 %



1-70

+



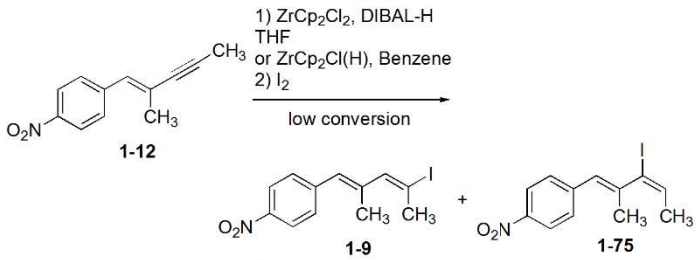
1-71

1-70 E/Z:**1-71** = 3:4:10

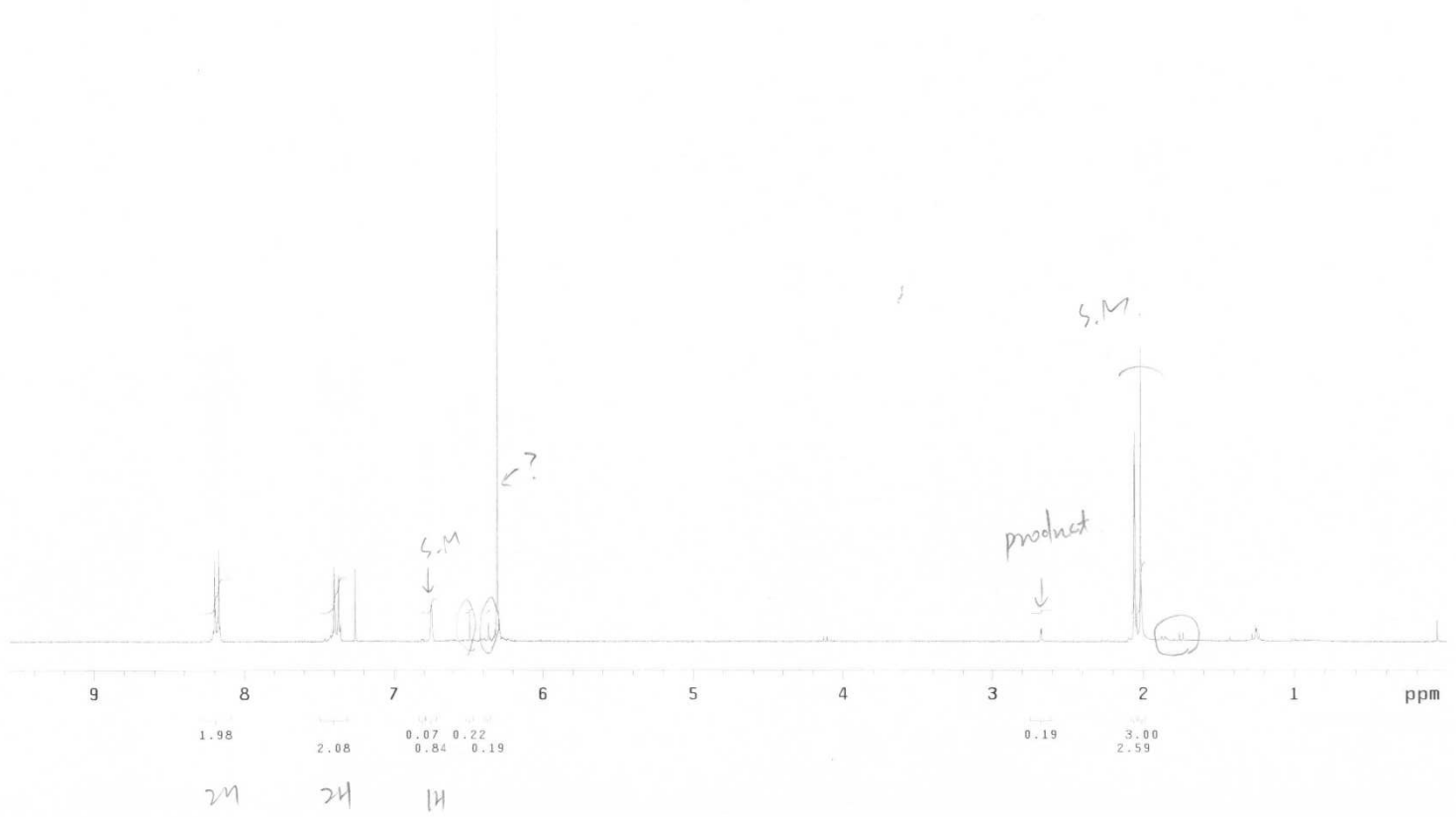
new experiment

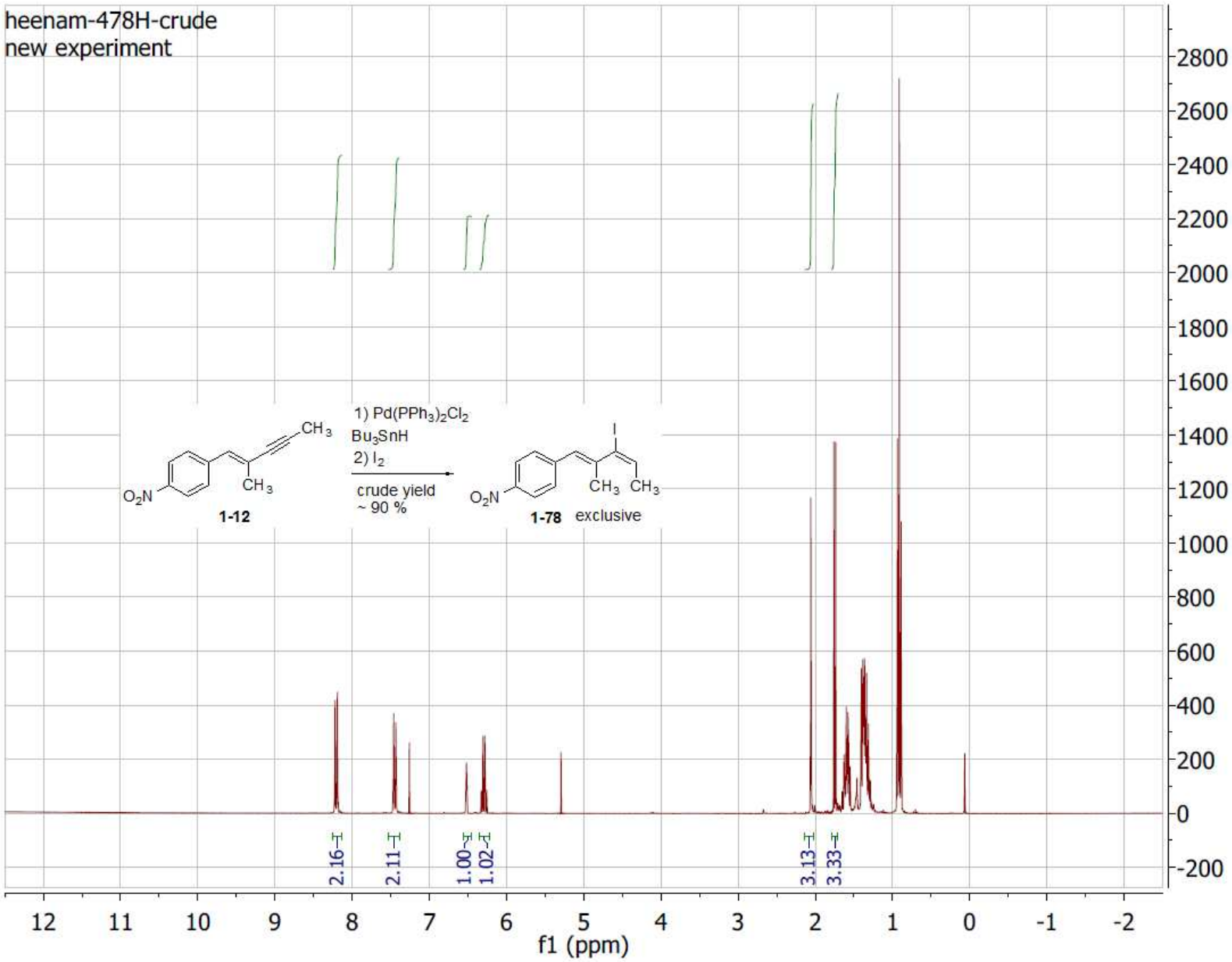
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

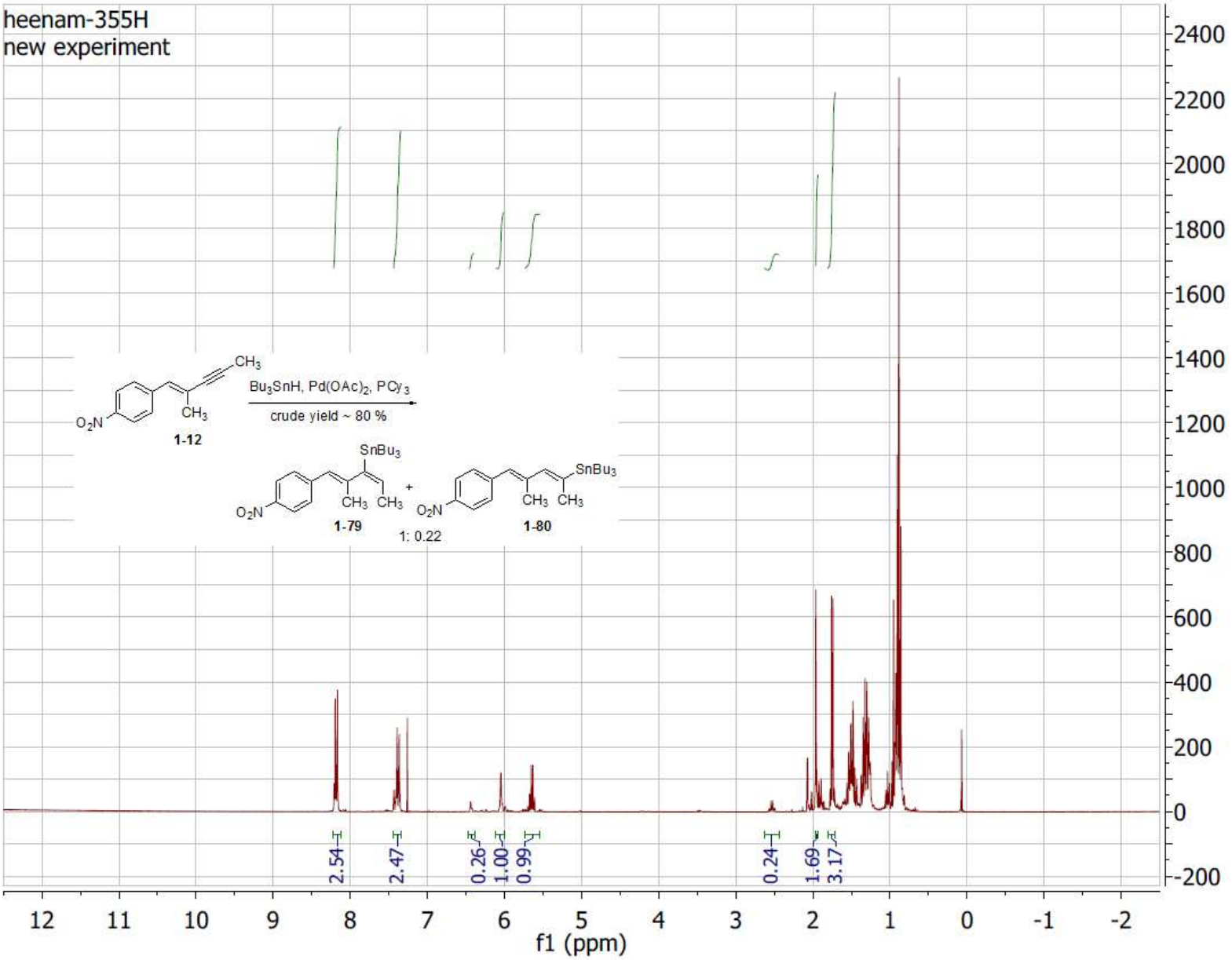
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
13 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 9 min, 16 sec

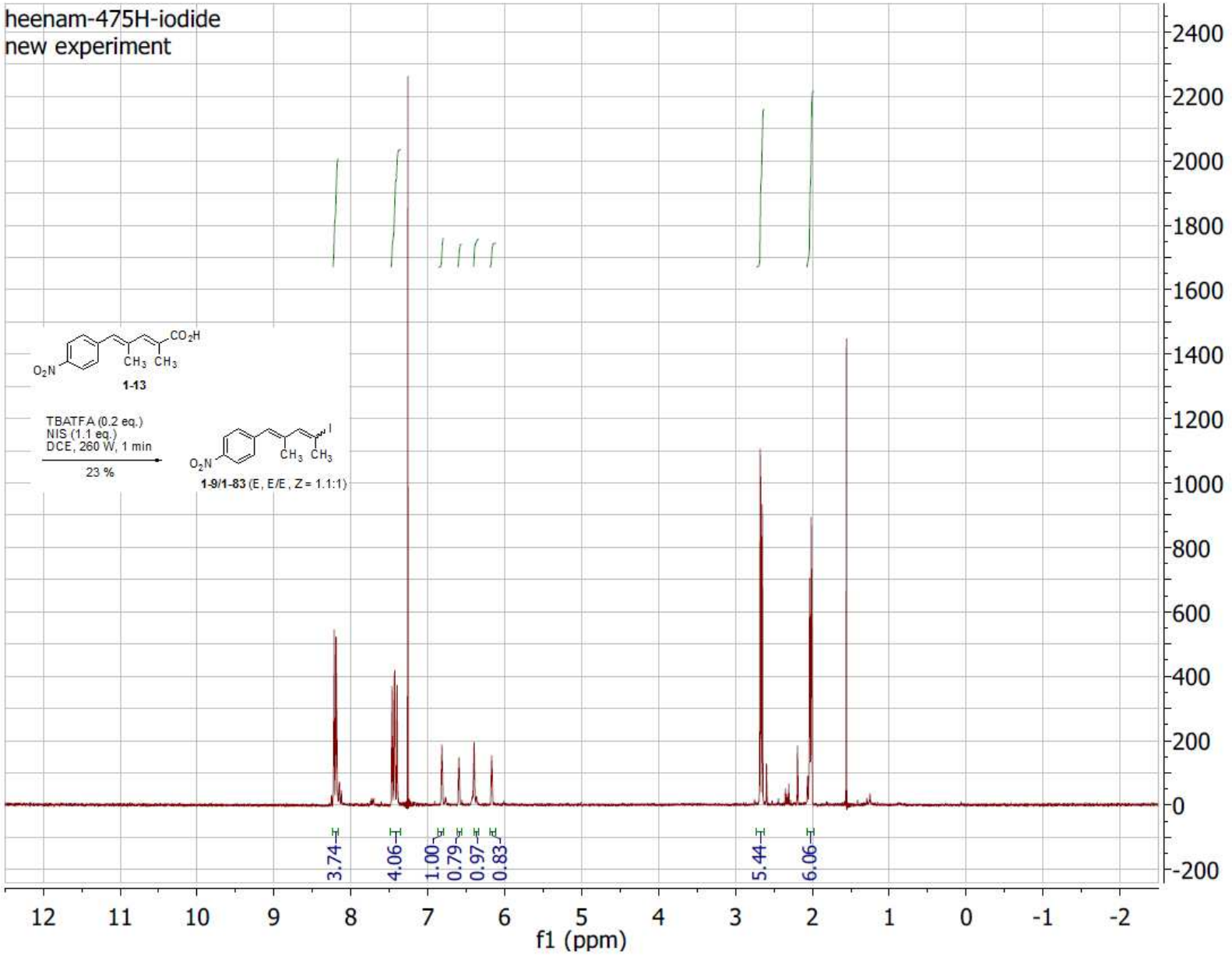


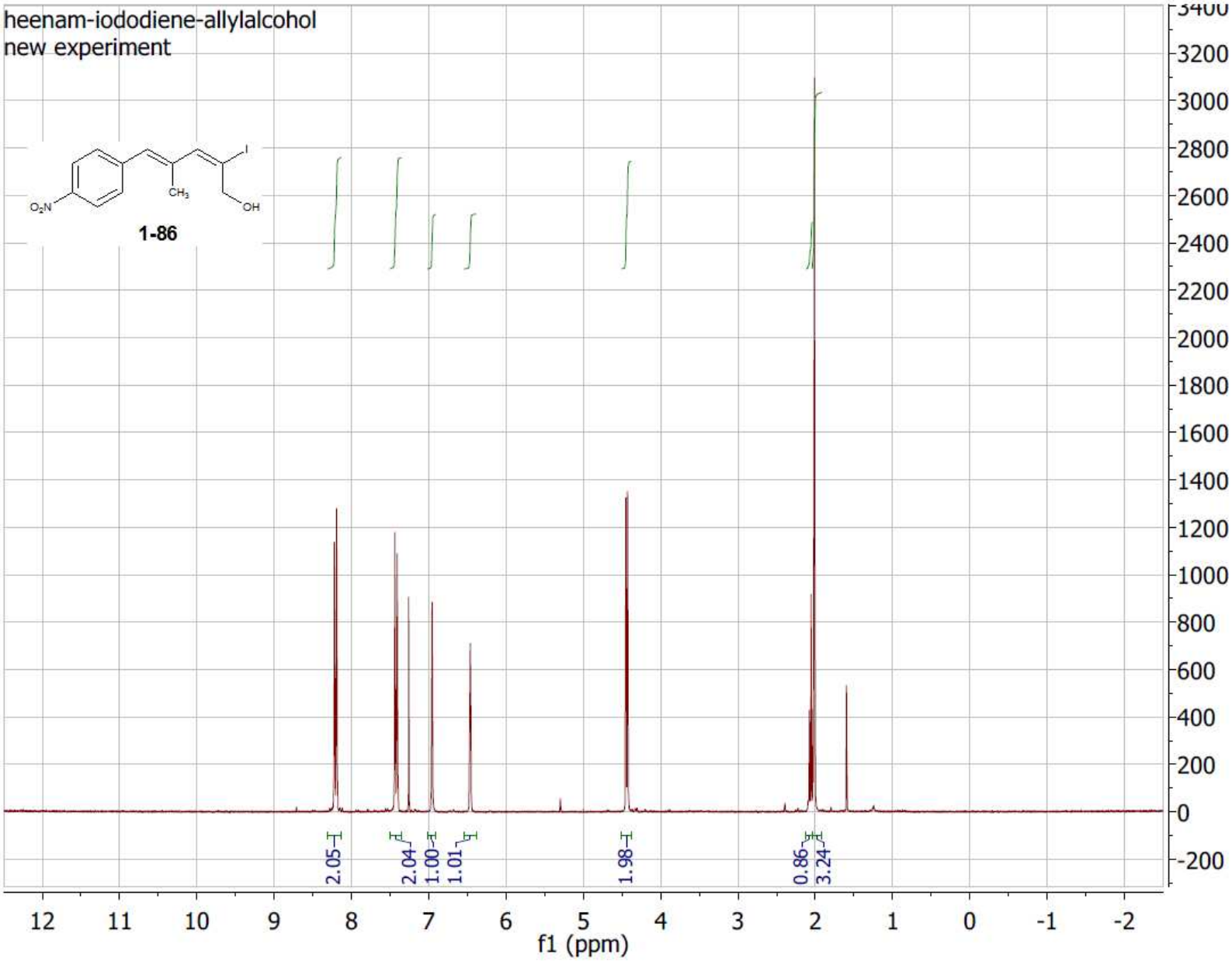
1-12 **1-9** **1-75**

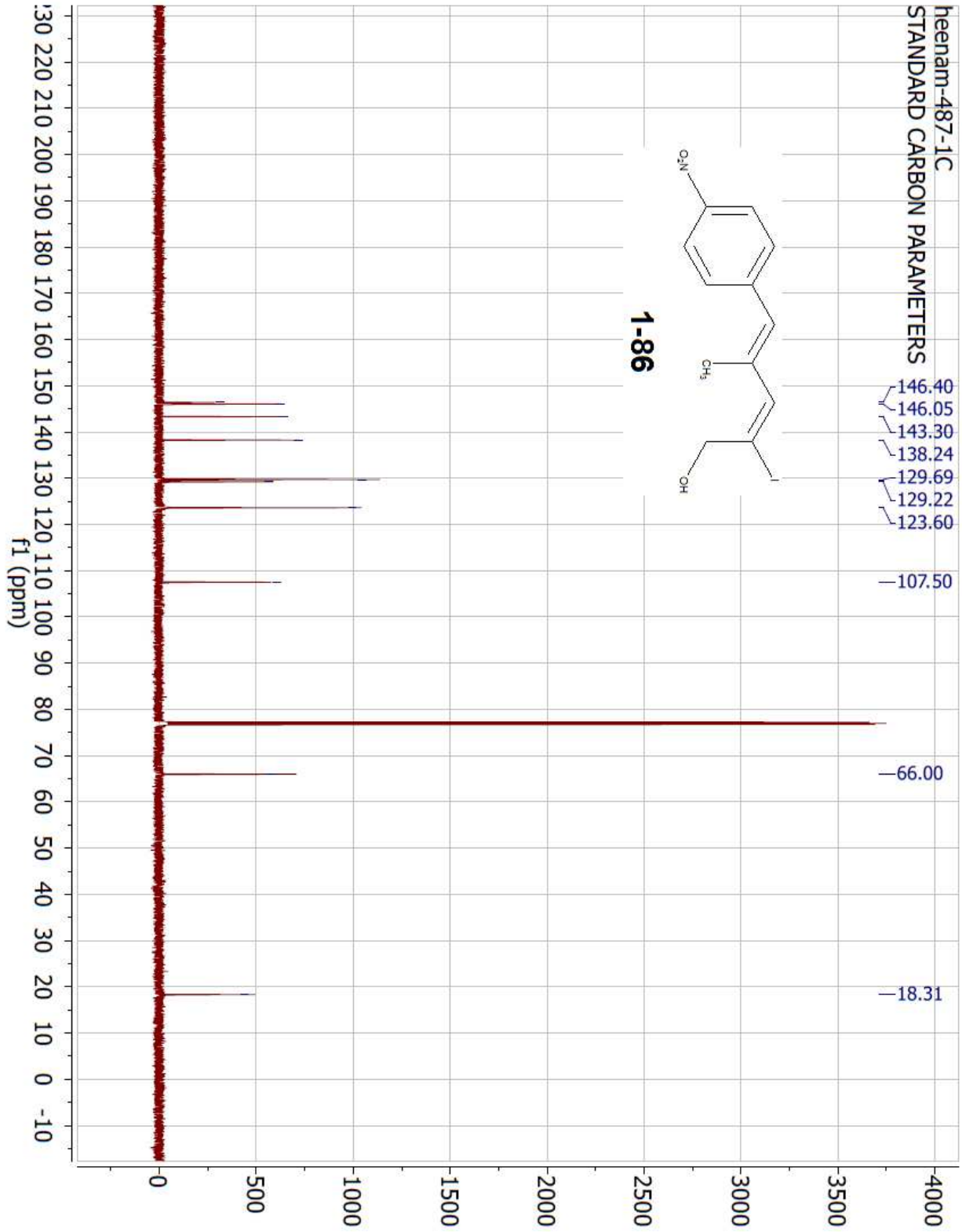


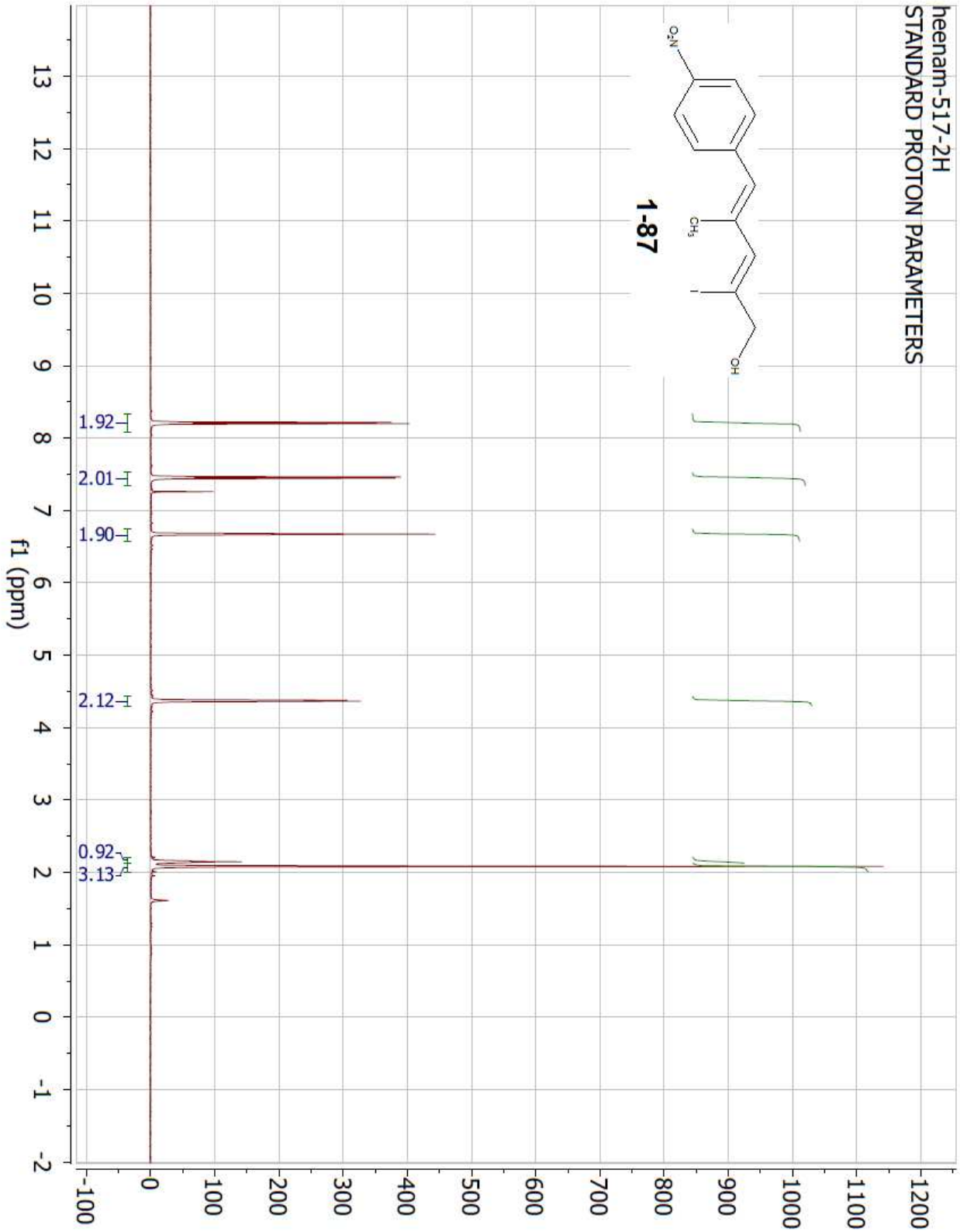

heenam-478H-crude
new experiment
1) Pd(PPh3)2Cl2
Bu3SnH
2) I2
crude yield
~ 90 %
1-12
1-78 exclusive
2.16
2.11
1.00
1.02
3.13
3.33
f1 (ppm)

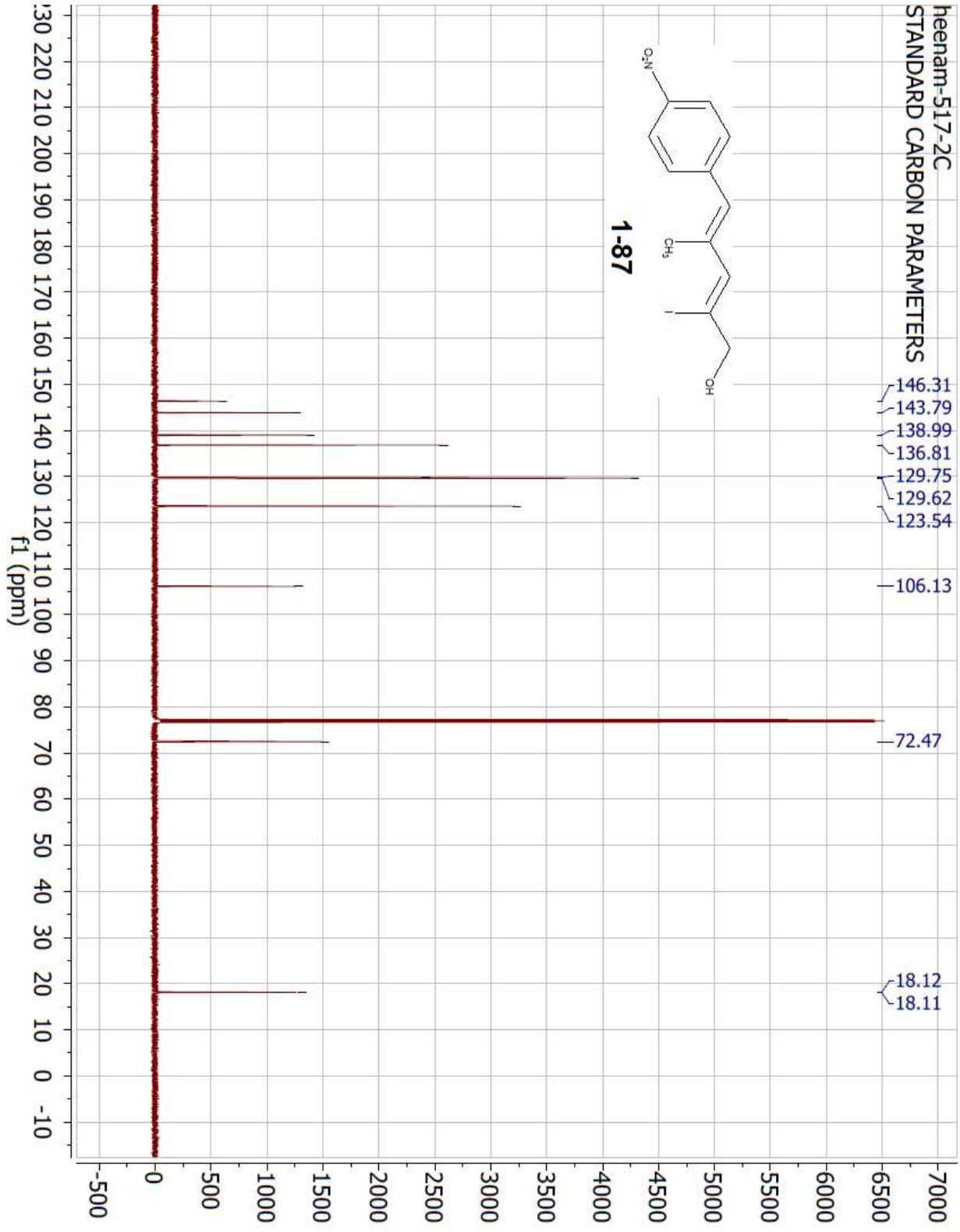

heenam-355H
new experiment
Bu3SnH, Pd(OAc)2, PCy3
crude yield ~ 80 %
1-12
1-79
1-80
1: 0.22
2.54
2.47
0.26
1.00
0.99
0.24
1.69
3.17
f1 (ppm)


heenam-475H-iodide
new experiment
1-13
TBATFA (0.2 eq.)
NIS (1.1 eq.)
DCE, 260 W, 1 min
23 %
1-9/1-83 (E, E/E, Z = 1.1:1)
3.74
4.06
1.00
0.79
0.97
0.83
5.44
6.06
f1 (ppm)


heenam-iododiene-allylalcohol
new experiment
1-86
2.05
2.04
1.00
1.01
1.98
0.86
3.24
f1 (ppm)


heenam-487-1C
STANDARD CARBON PARAMETERS
1-86
146.40
146.05
143.30
138.24
129.69
129.22
123.60
107.50
66.00
18.31
f1 (ppm)


heenam-517-2H
STANDARD PROTON PARAMETERS
1-87
1.92
2.01
1.90
2.12
0.92
3.13
f1 (ppm)


heenam-517-2C
STANDARD CARBON PARAMETERS
1-87
146.31
143.79
138.99
136.81
129.75
129.62
123.54
106.13
72.47
18.12
18.11
f1 (ppm)

STANDARD PROTON PARAMETERS

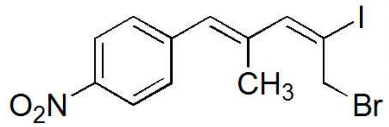
Data Collected on:
inv500-inova500
Archive directory:
/export/home/heenam/vnmrsys/data
Sample directory:

File: PROTON

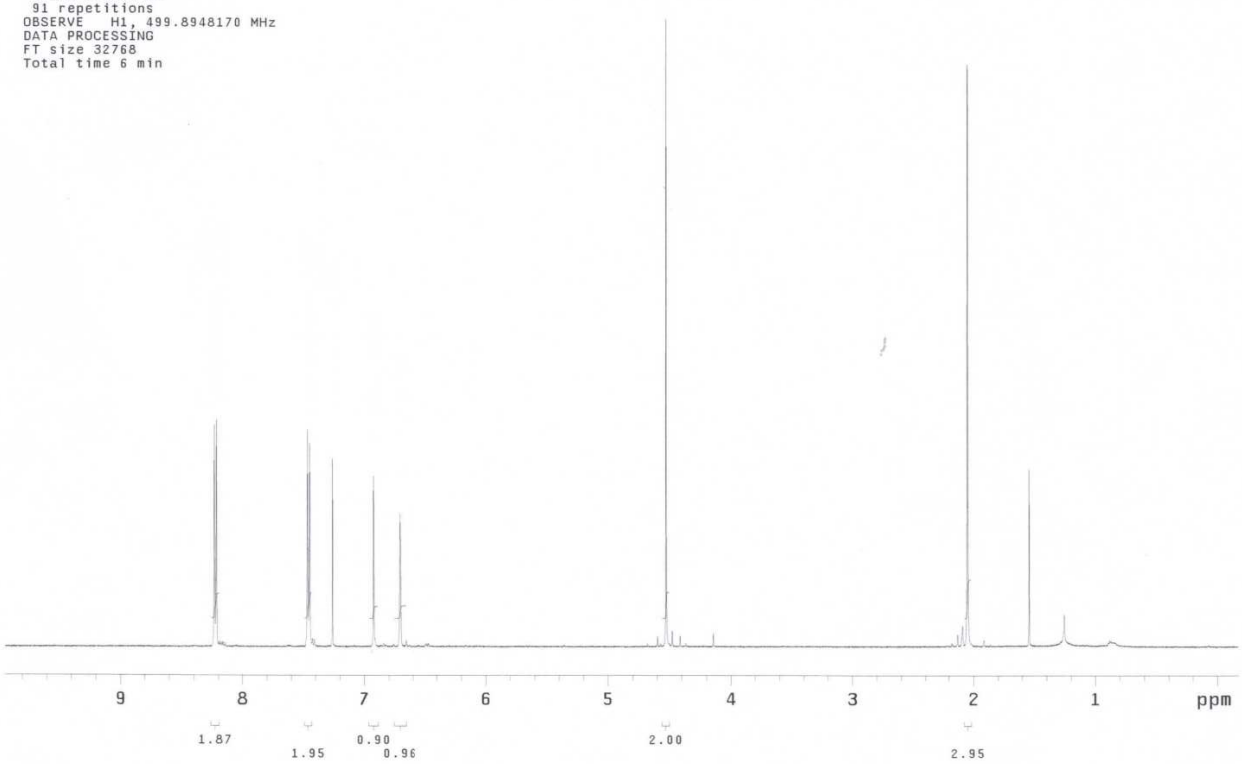
Pulse Sequence: s2pul
Solvent: CDCl3

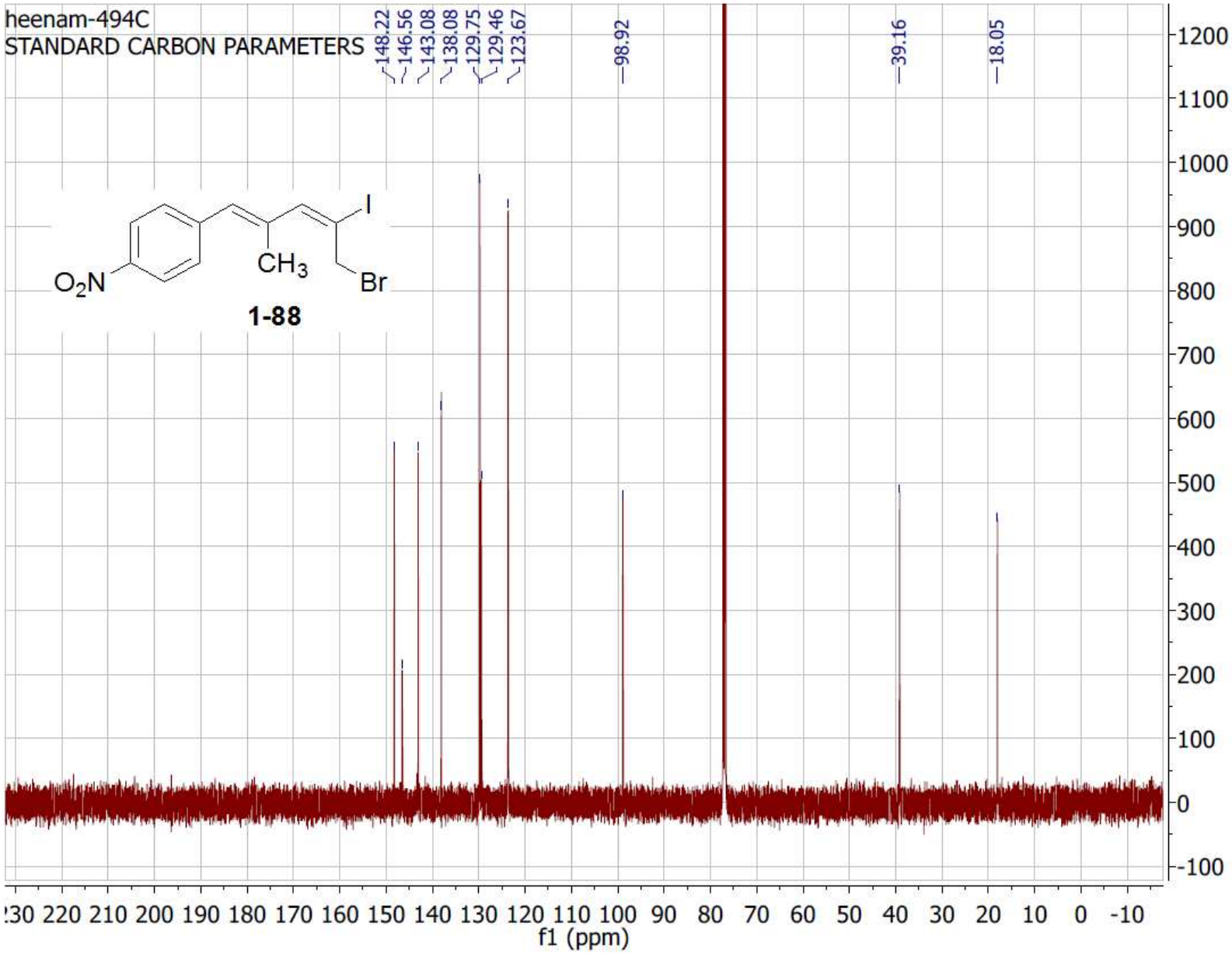
Temp. 25.0 C / 298.1 K

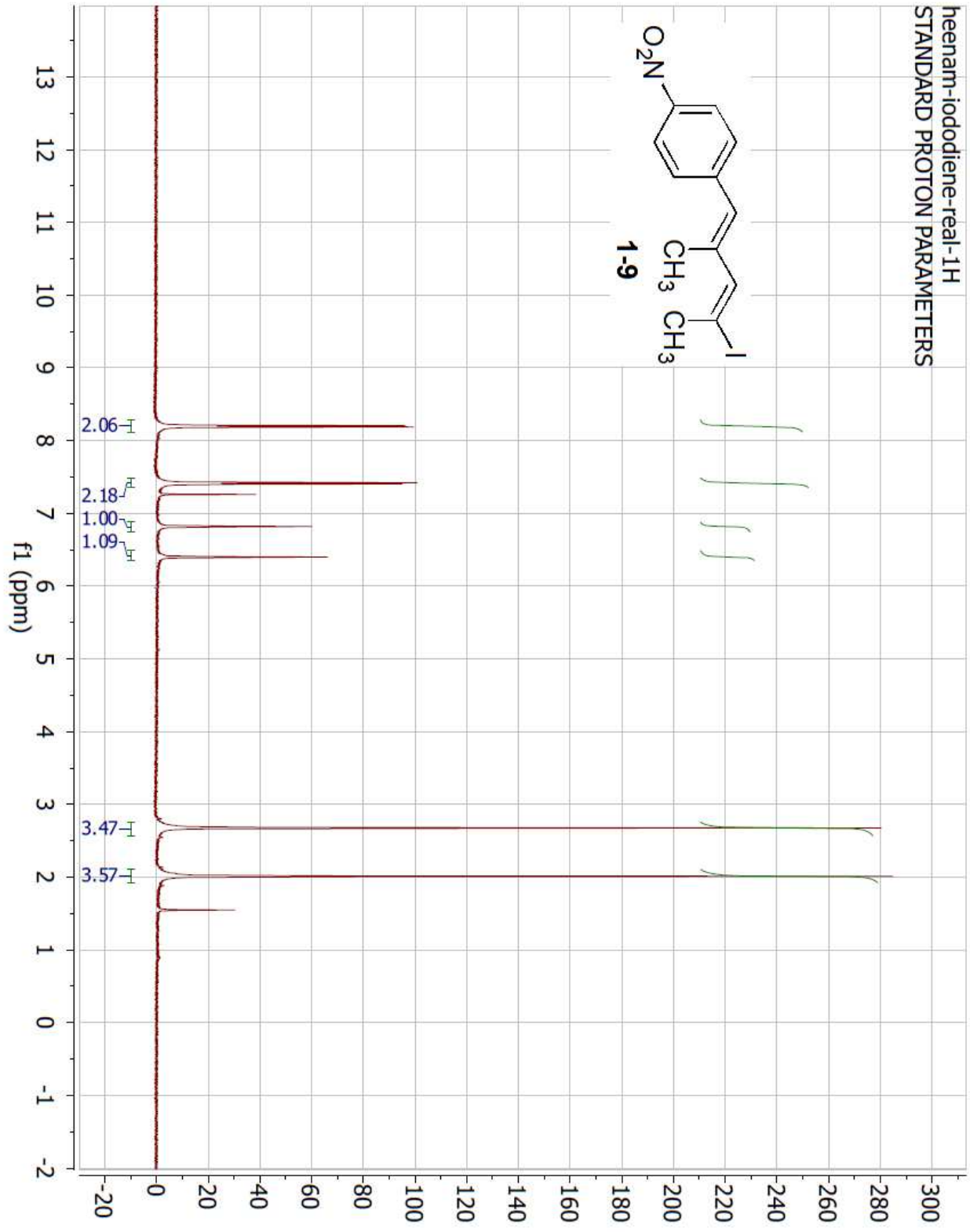
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7998.4 Hz
91 repetitions
OBSERVE H1, 499.8948170 MHz
DATA PROCESSING
FT size 32768
Total time 6 min

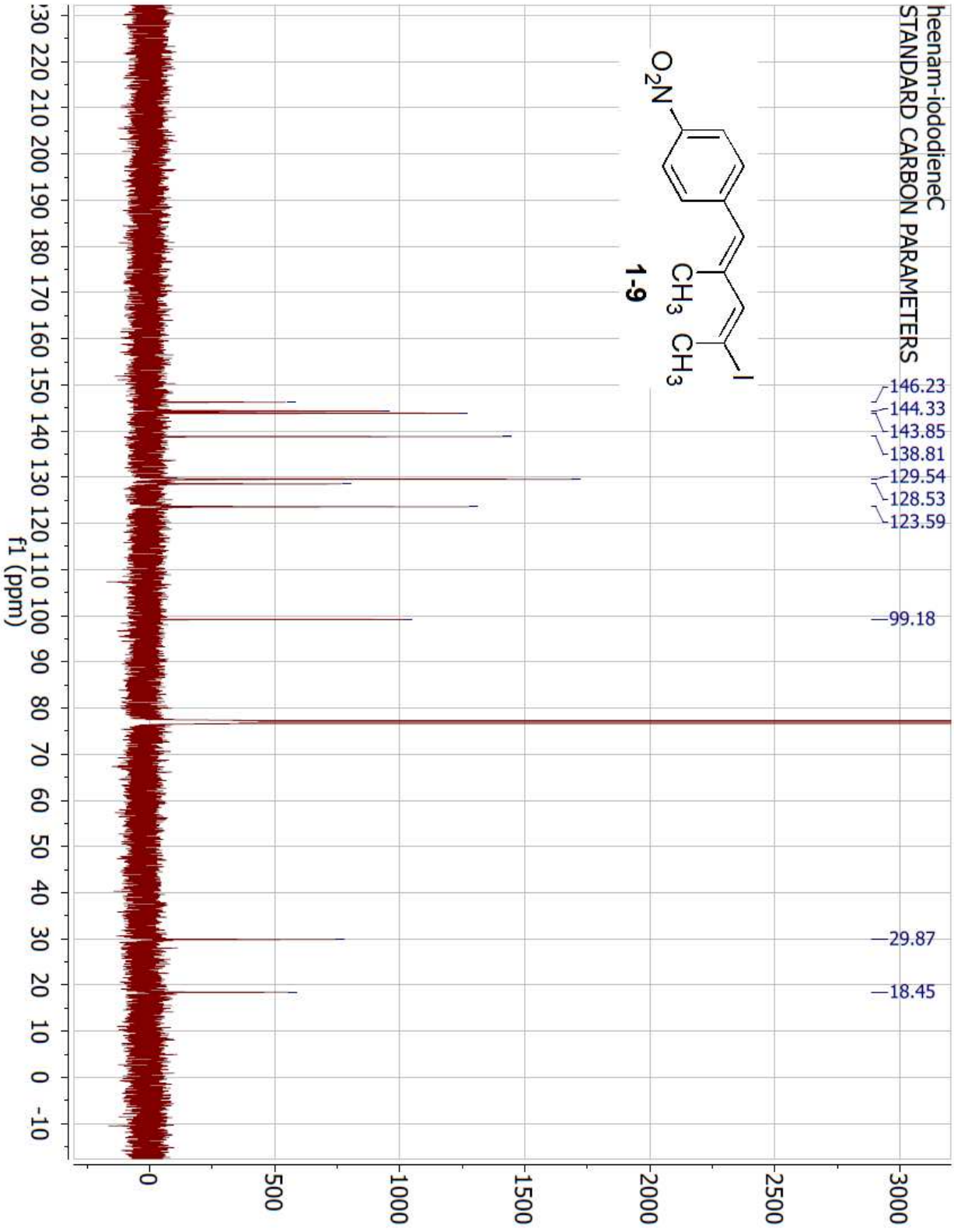


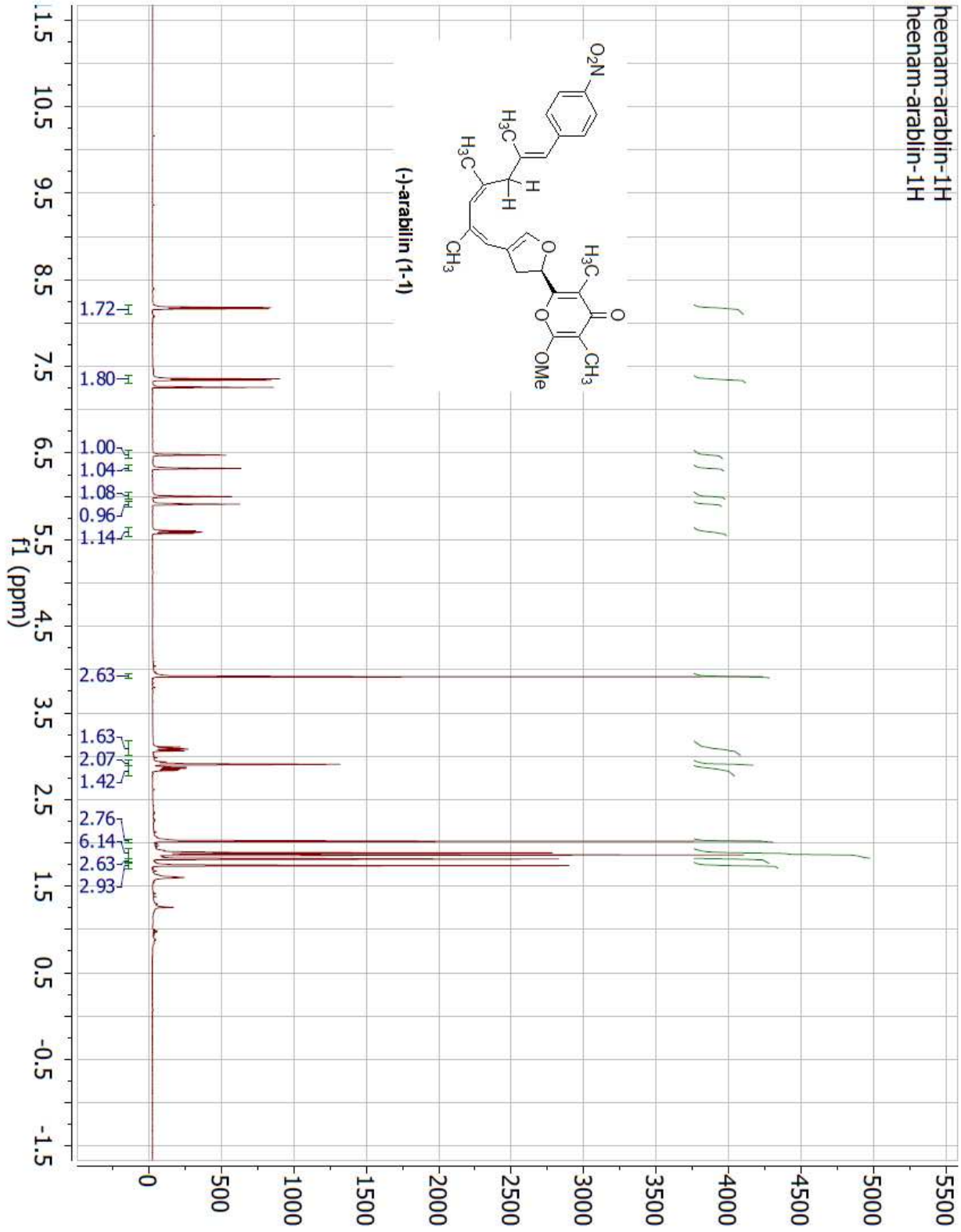
1-88

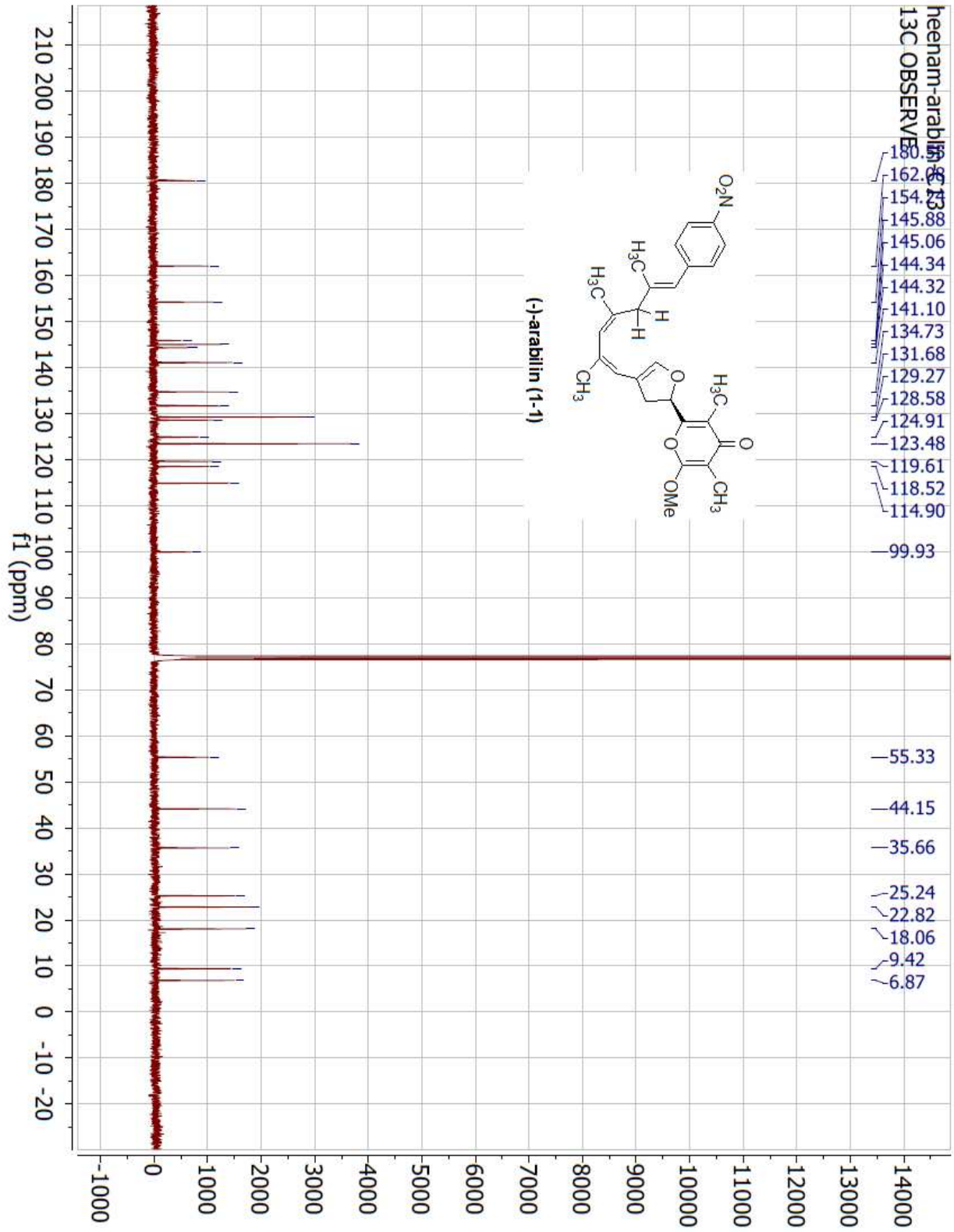


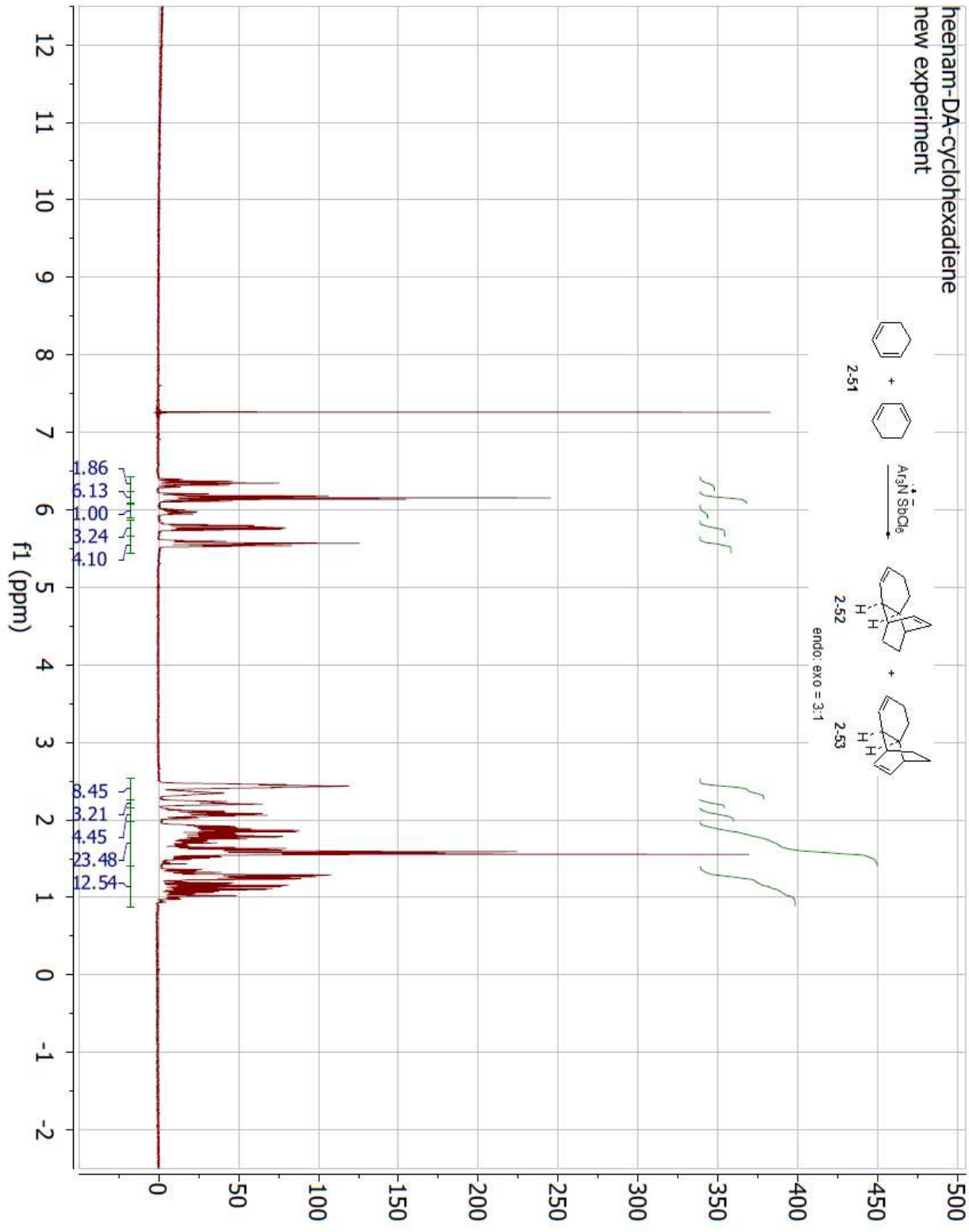

heenam-494C
STANDARD CARBON PARAMETERS
148.22
146.56
143.08
138.08
129.75
129.46
123.67
98.92
39.16
18.05
I
CH3
O2N
Br
1-88
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

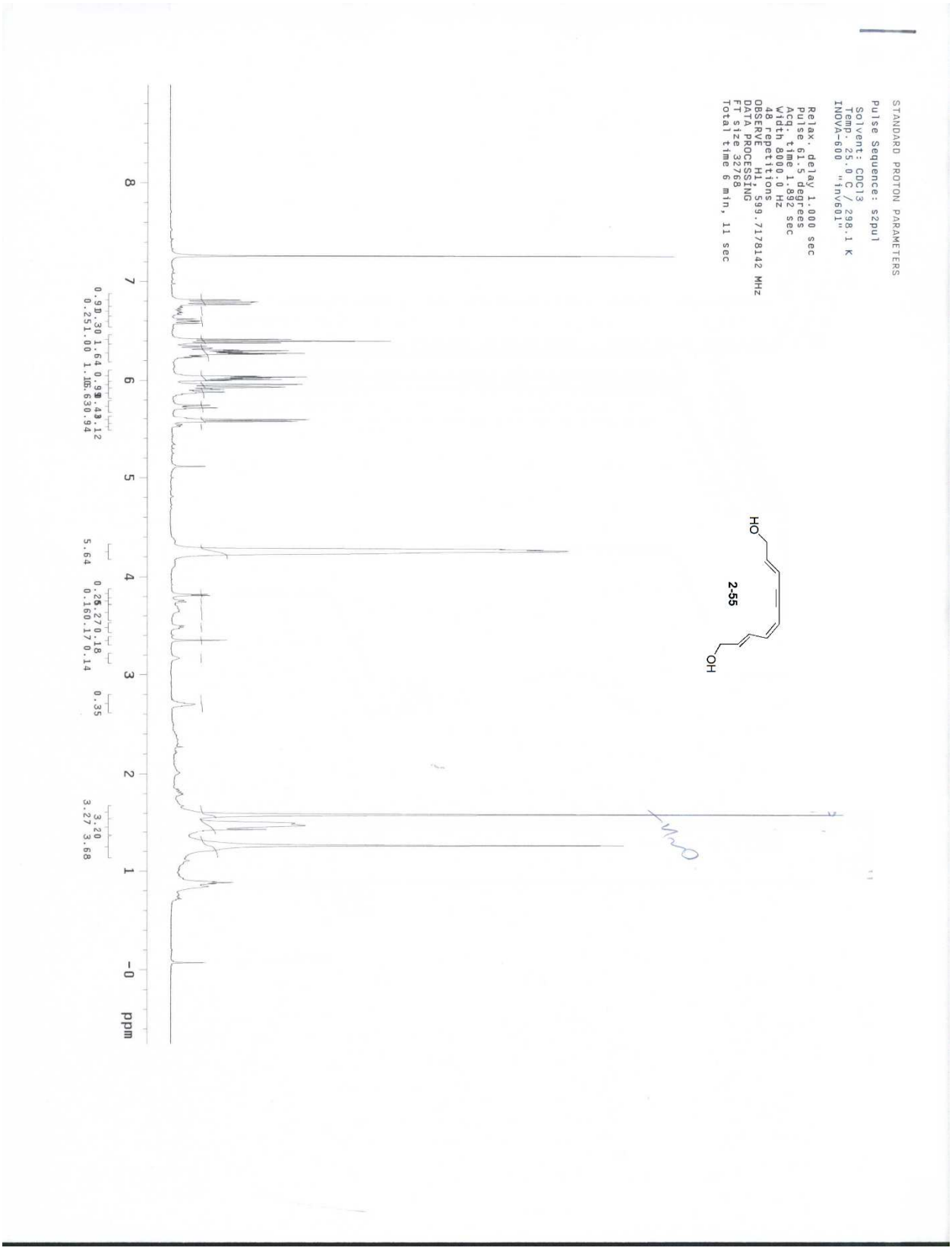

heenam-iododiene-real-1H
STANDARD PROTON PARAMETERS
O2N
CH3
CH3
I
1-9
2.06
2.18
1.00
1.09
3.47
3.57
f1 (ppm)

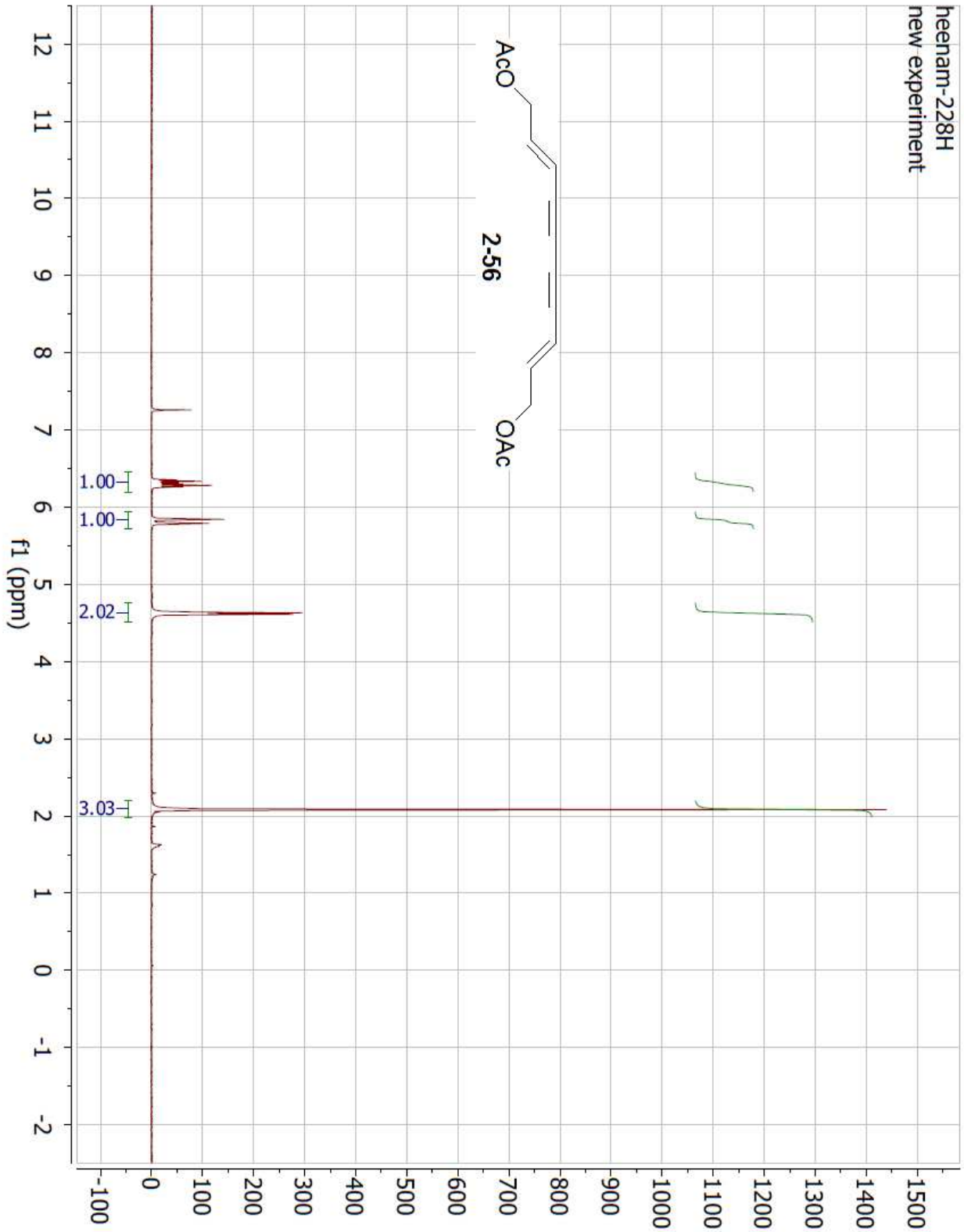

heenam-iododieneC
STANDARD CARBON PARAMETERS
O_2N
CH_3 CH_3
I
1-9
146.23
144.33
143.85
138.81
129.54
128.53
123.59
99.18
29.87
18.45
f1 (ppm)

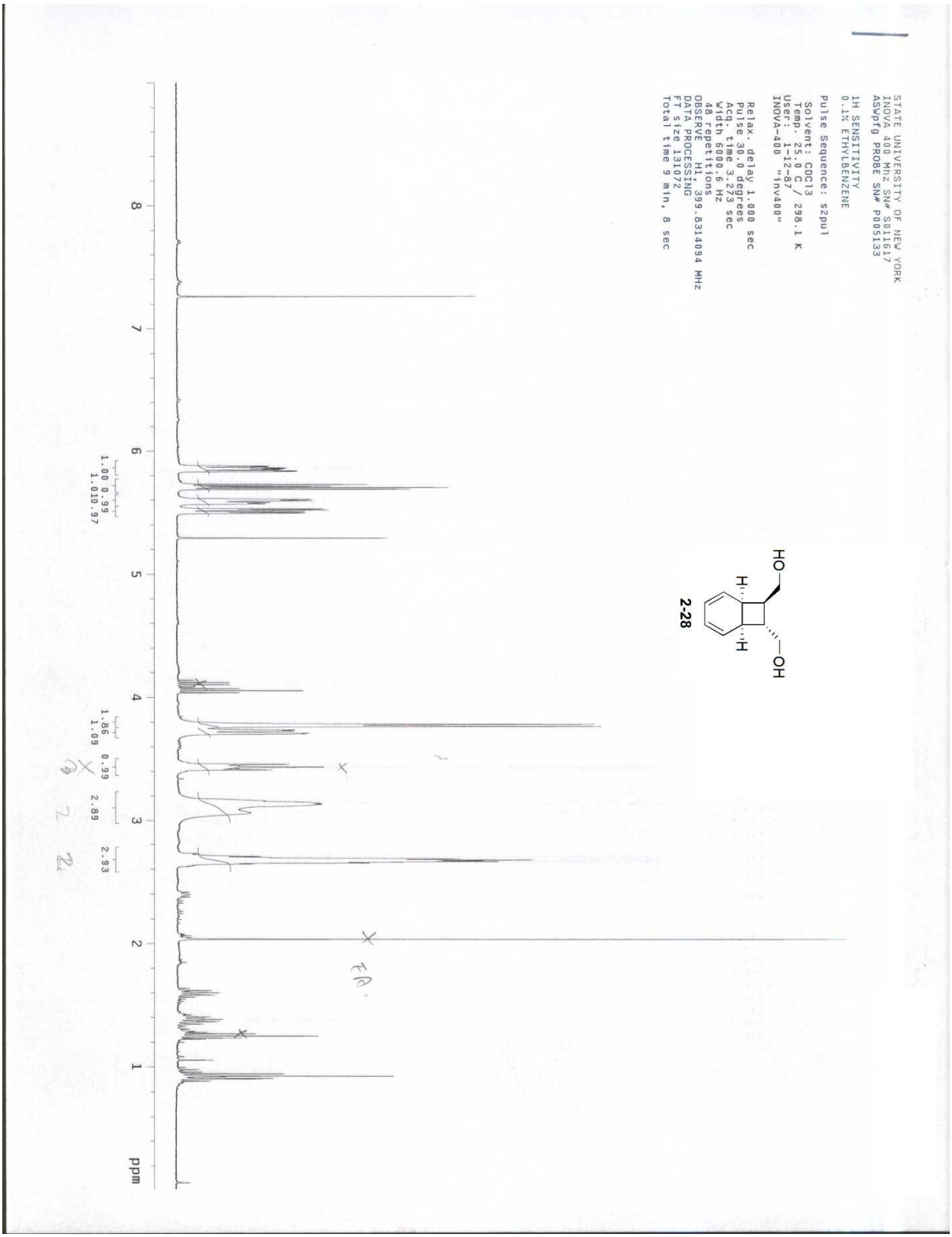

heenam-arablin-1H
heenam-arablin-1H
(-)-arabilin (1-1)
1.72
1.80
1.00
1.04
1.08
0.96
1.14
2.63
1.63
2.07
1.42
2.76
6.14
2.63
2.93
f1 (ppm)


heenam-arabilin 13C
13C OBSERVED
180.58
162.88
154.52
145.88
145.06
144.34
144.32
141.10
134.73
131.68
129.27
128.58
124.91
123.48
119.61
118.52
114.90
99.93
55.33
44.15
35.66
25.24
22.82
18.06
9.42
6.87
(-)-arabilin (1-1)
O2N
H3C
H3C
H
H
CH3
O
H3C
O
O
OMe
CH3
f1 (ppm)


heenam-DA-cyclohexadiene
new experiment
2-51
2-52
2-53
endo: exo = 3:1
1.86
6.13
1.00
3.24
4.10
8.45
3.21
4.45
23.48
12.54
f1 (ppm)


STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-600 "inv601"
Relax. delay 1.000 sec
Pulse 61.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 599.7178142 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 11 sec
HO
2-55
OH
8
7
6
5
4
3
2
1
-0
ppm
0.90 1.30 1.64 0.99 1.43 1.12
0.25 1.00 1.15 5.63 0.94
5.64
0.28 5.27 0.18
0.16 0.17 0.14
0.35
3.20
3.27 3.68

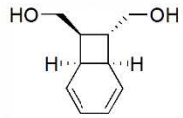

heenam-228H
new experiment
AcO
2-56
OAc
1.00
1.00
2.02
3.03
f1 (ppm)


STATE UNIVERSITY OF NEW YORK
INOVA 400 MHz SN# 501617
ASWPG PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-12-87
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.273 sec
Width 6000.6 Hz
48 repetitions
OBSERVE H1, 399.8314094 MHz
DATA PROCESSING
FT size 131072
Total time 9 min, 8 sec
HO
OH
H
H
2-28
8
7
6
5
4
3
2
1
ppm
1.00 0.99
1.01 0.97
1.86
1.09
0.99
2.89
2.93

13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "inv400"

Relax. delay 1.000 sec
Pulse 82.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
126 repetitions
OBSERVE C13, 100.5376902 MHz
DECOUPLE H1, 399.8364198 MHz
Power 49 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 hr, 50 min, 24 sec



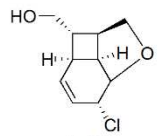
2-28

STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133

1H SENSITIVITY
0.1% ETHYLBENZENE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-12-87
INOVA-400 "inv400"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.273 sec
Width 6000.6 Hz
60 repetitions
OBSERVE H1, 399.8314119 MHz
DATA PROCESSING
FT size 131072
Total time 9 min, 8 sec



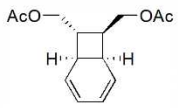
2-59

STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133

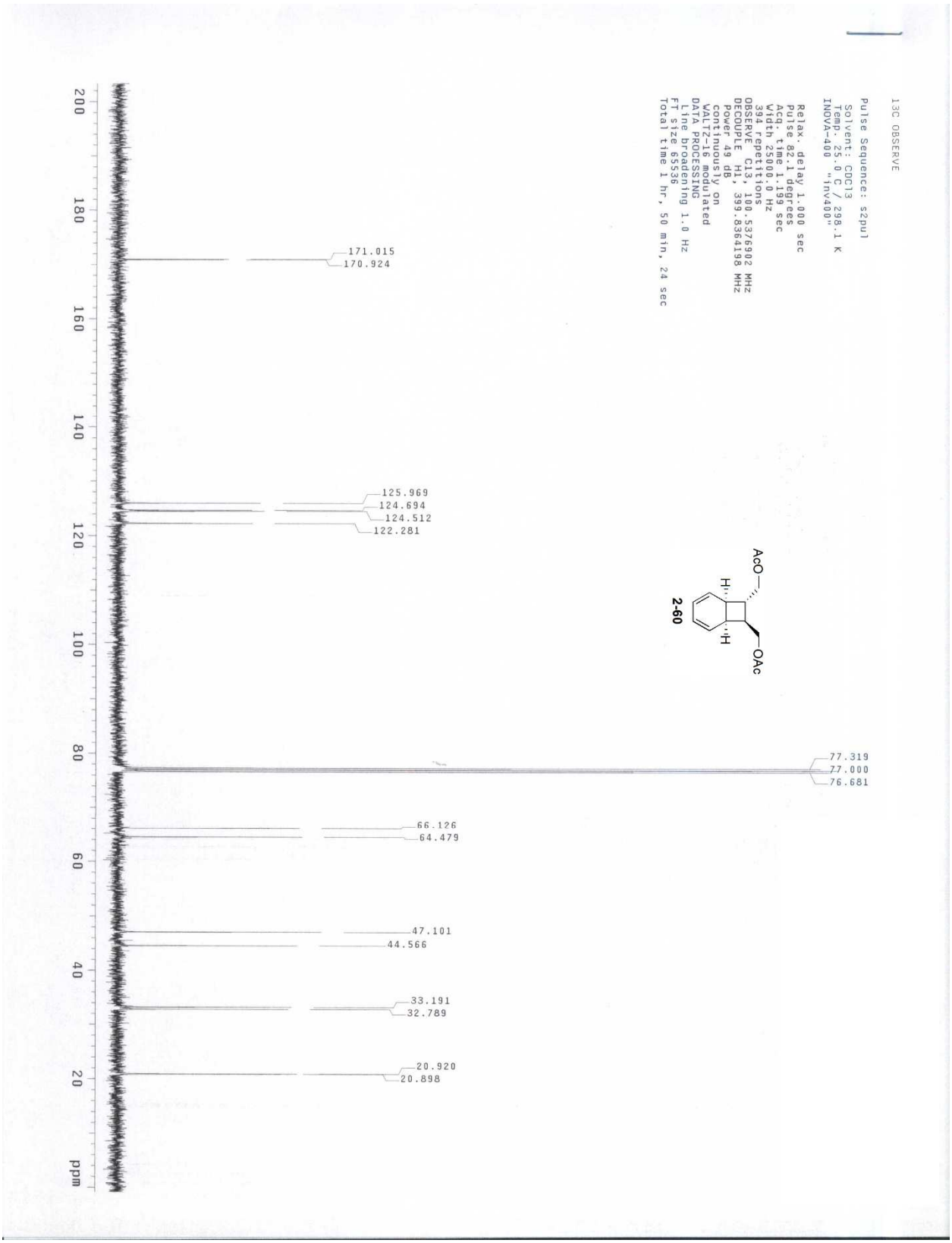
1H SENSITIVITY
0.1% ETHYLBENZENE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-12-87
INOVA-400 "inv400"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.273 sec
Width 6000.6 Hz
50 repetitions
OBSERVE H1, 399.8314109 MHz
DATA PROCESSING
FT size 131072
Total time 9 min, 59 sec



2-60


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 82.1 degrees
Acq. time 1.199 sec
Width 25010.0 Hz
39 repetitions
OBSERVE C13, 100.5376902 MHz
DECOUPLE H1, 399.8364198 MHz
Power 49 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 hr, 50 min, 24 sec
171.015
170.924
125.969
124.694
124.512
122.281
77.319
77.000
76.681
66.126
64.479
47.101
44.566
33.191
32.789
20.920
20.898
AcO
H
H
OAc
2-60
200
180
160
140
120
100
80
60
40
20
ppm

STANDARD PROTON PARAMETERS

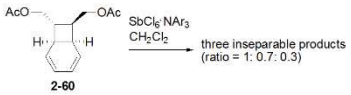
Data Collected on:
inv500-inova500
Archive directory:
/export/home/heenam/vnmrsys/data
Sample directory:

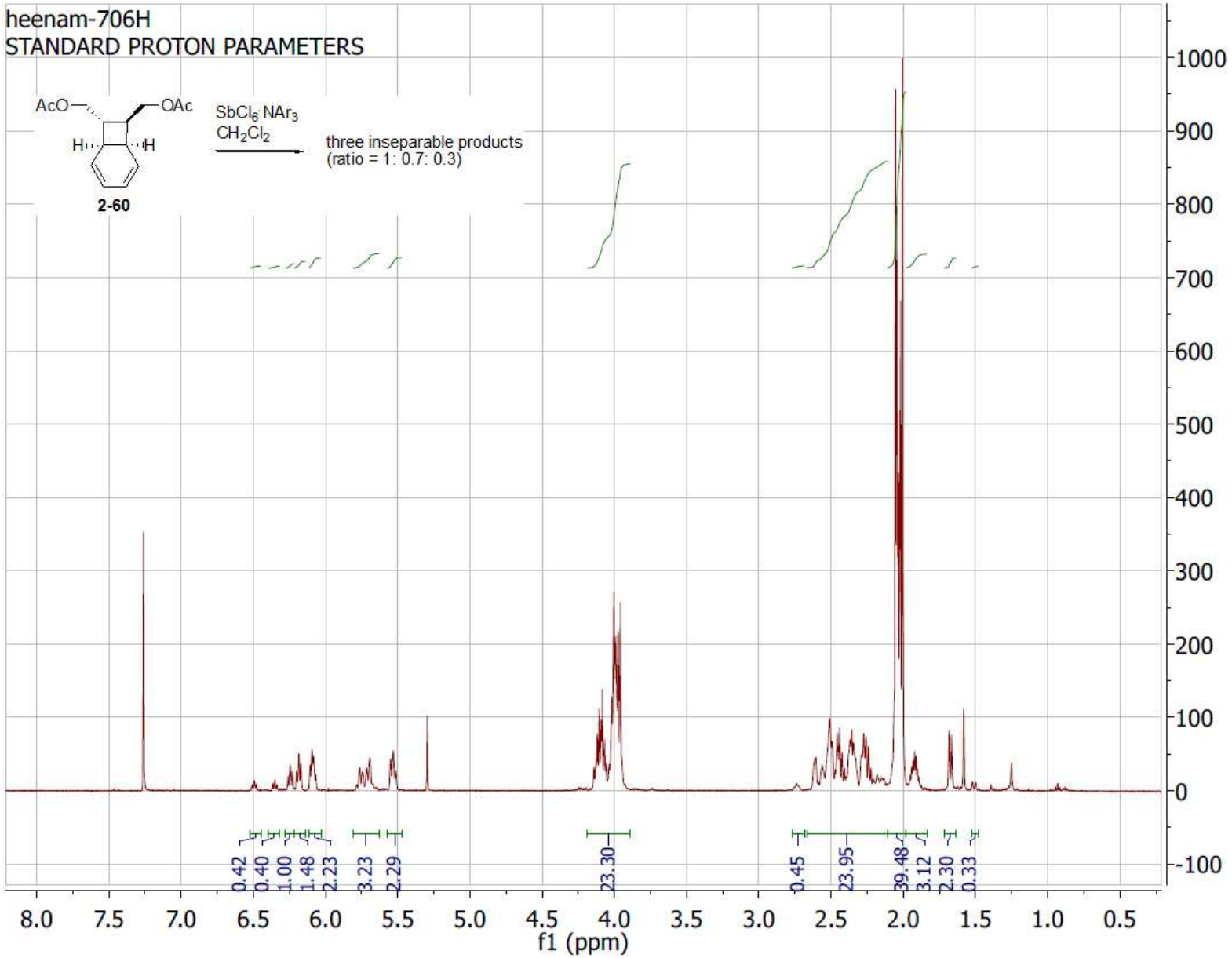
File: PROTON

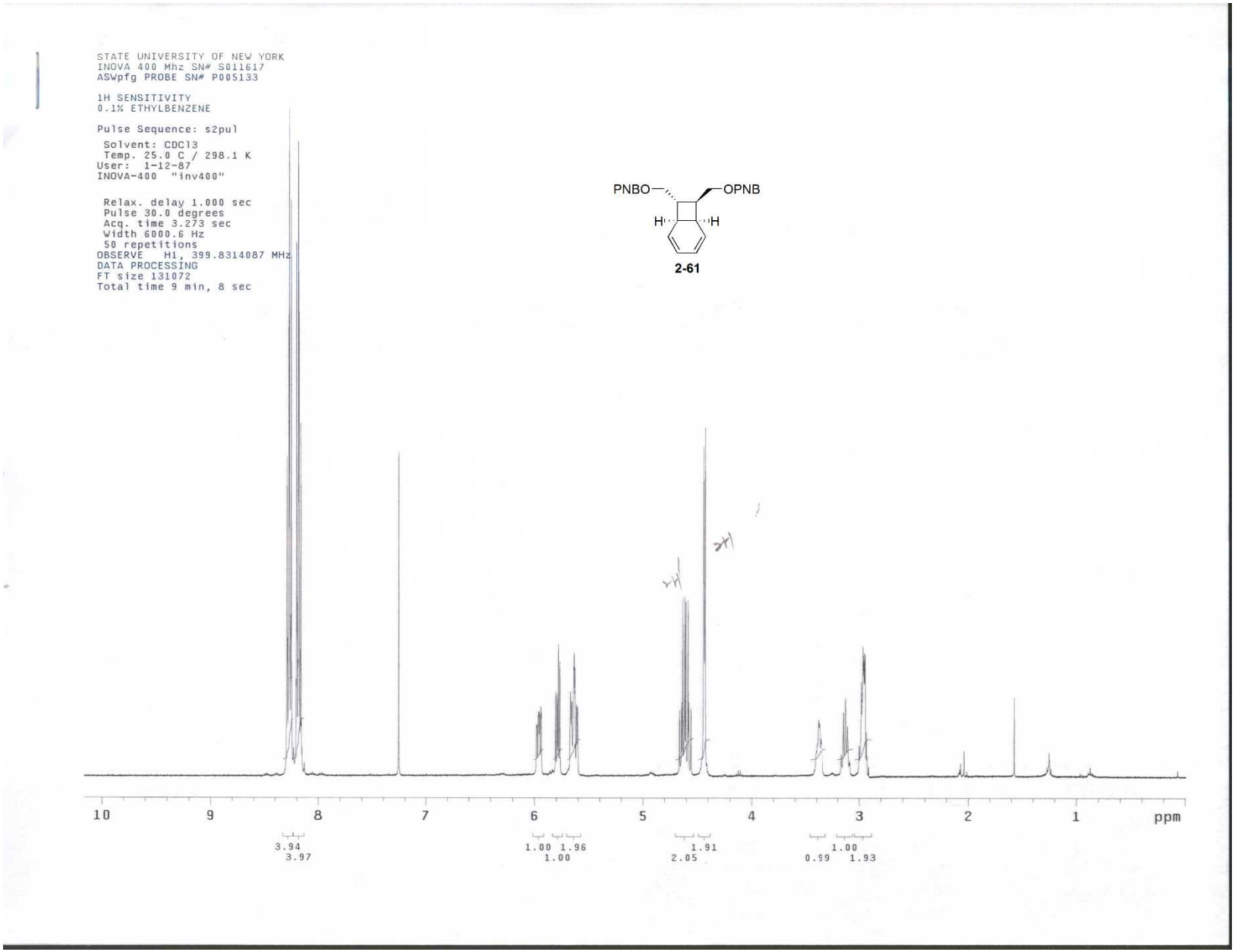
Pulse Sequence: s2pul
Solvent: CDCl3

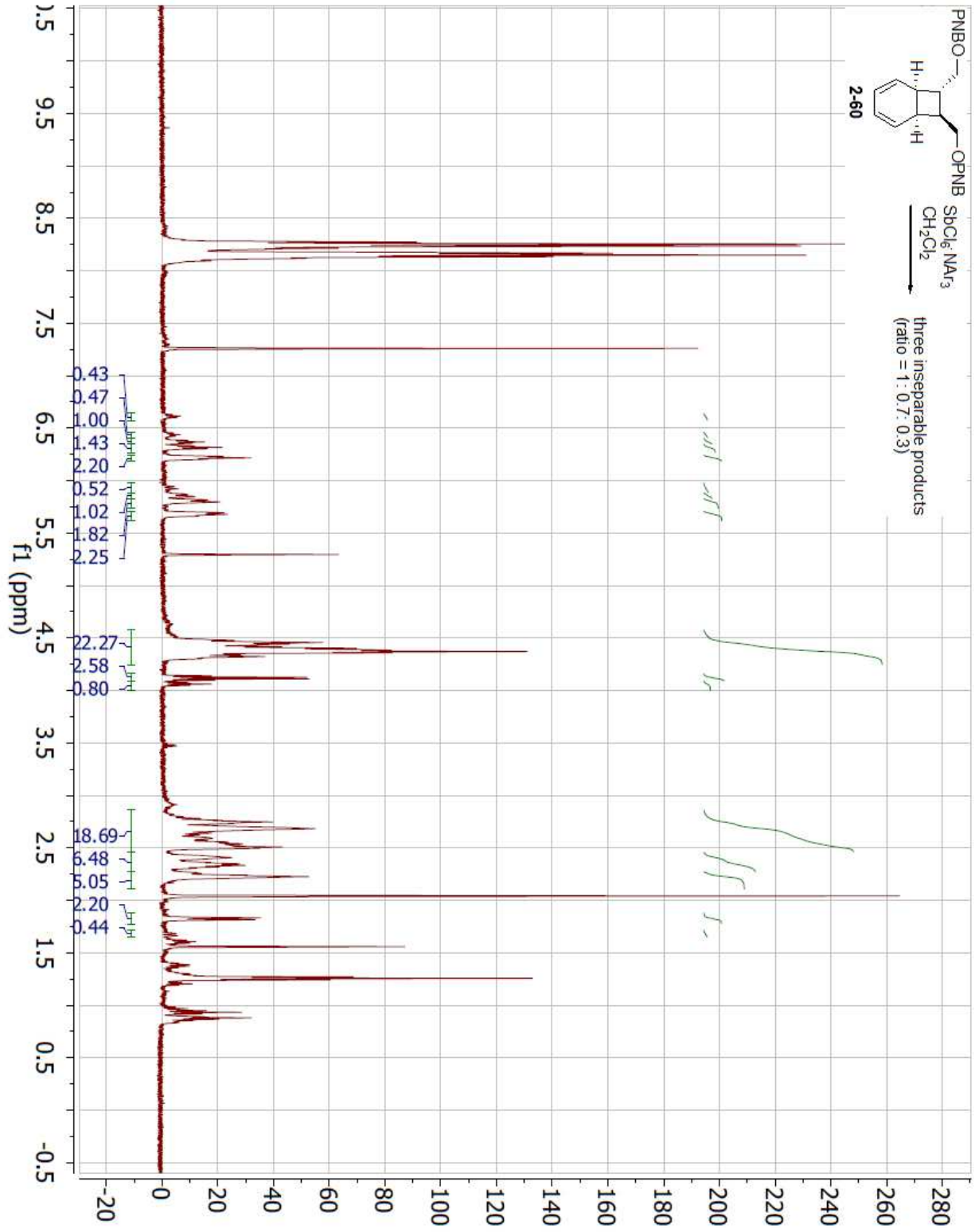
Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7998.4 Hz
192 repetitions
OBSERVE H1, 499.8948175 MHz
DATA PROCESSING
FT size 32768
Total time 12 min




heenam-706H
STANDARD PROTON PARAMETERS
AcO
OAc
H
H
2-60
SbCl6 NAr3
CH2Cl2
three inseparable products
(ratio = 1: 0.7: 0.3)
0.42
0.40
1.00
1.48
2.23
3.23
2.29
23.30
0.45
23.95
39.48
3.12
2.30
0.33
f1 (ppm)

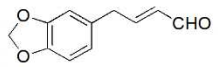

STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-12-87
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.273 sec
Width 6000.6 Hz
50 repetitions
OBSERVE H1, 399.8314087 MHz
DATA PROCESSING
FT size 131072
Total time 9 min, 8 sec
PNBO
OPNB
H
H
2-61
10
9
8
7
6
5
4
3
2
1
ppm
3.94
3.97
1.00
1.00
1.96
1.91
2.05
1.00
0.99
1.93


PNBO
OPNB
H
H
2-60
SbCl6 NAr3
CH2Cl2
three inseparable products
(ratio = 1: 0.7: 0.3)
0.43
0.47
1.00
1.43
2.20
0.52
1.02
1.82
2.25
22.27
2.58
0.80
18.69
6.48
5.05
2.20
0.44
f1 (ppm)

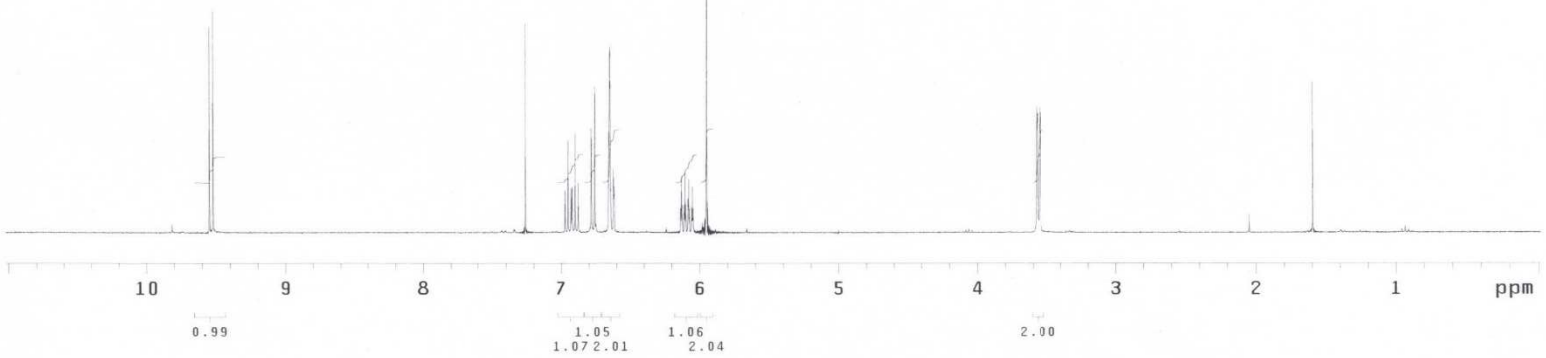
new experiment

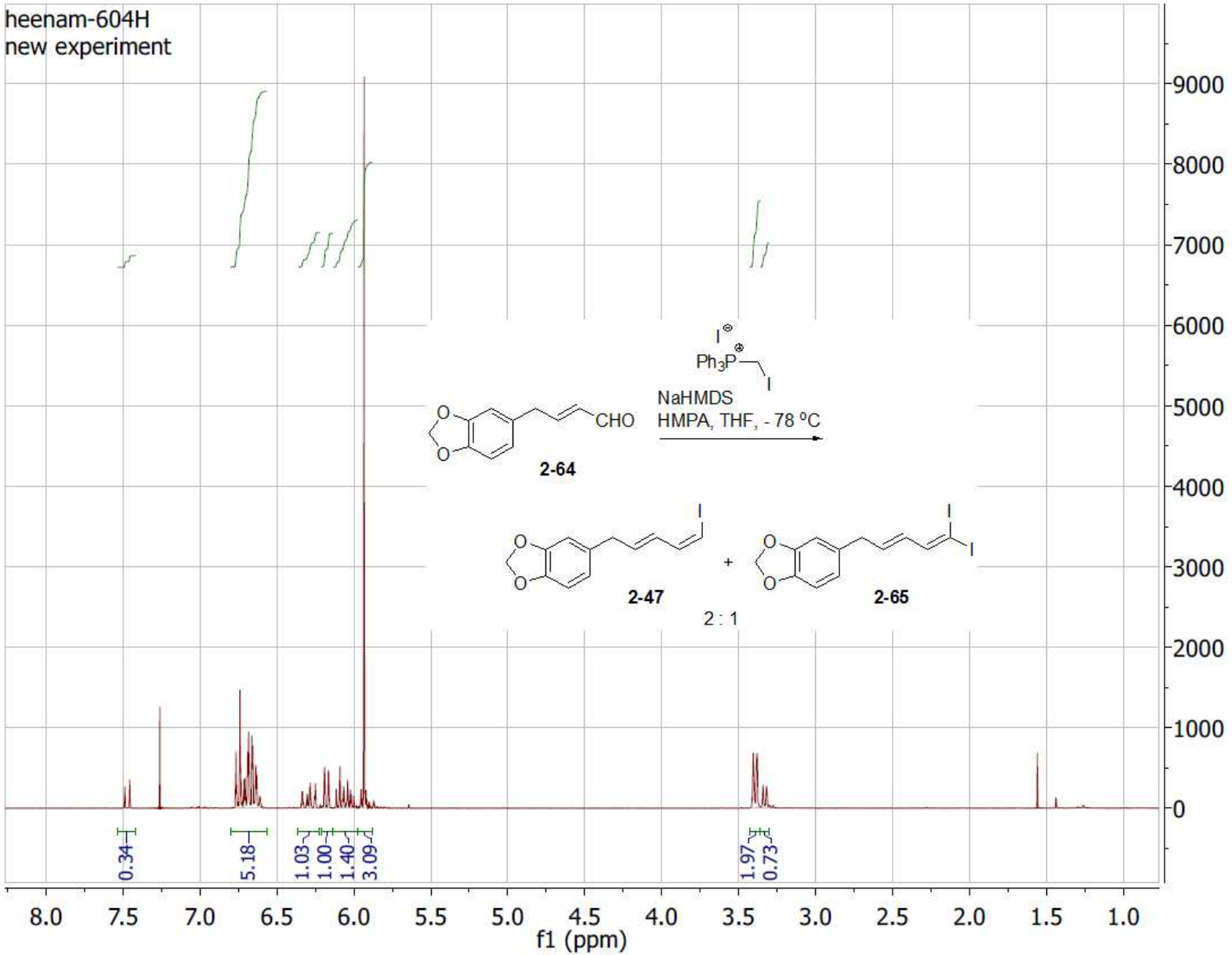
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

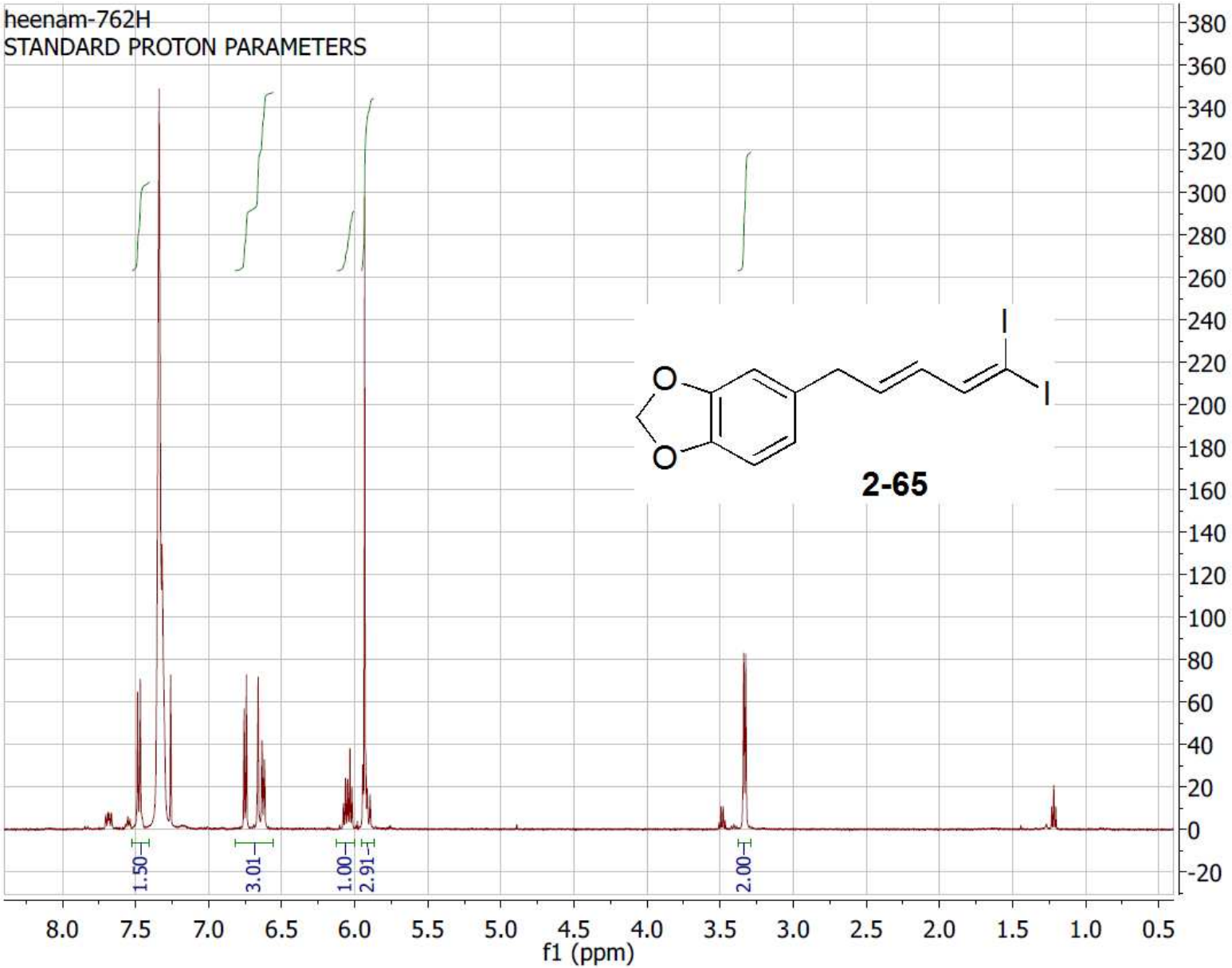
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
28 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 9 min, 16 sec

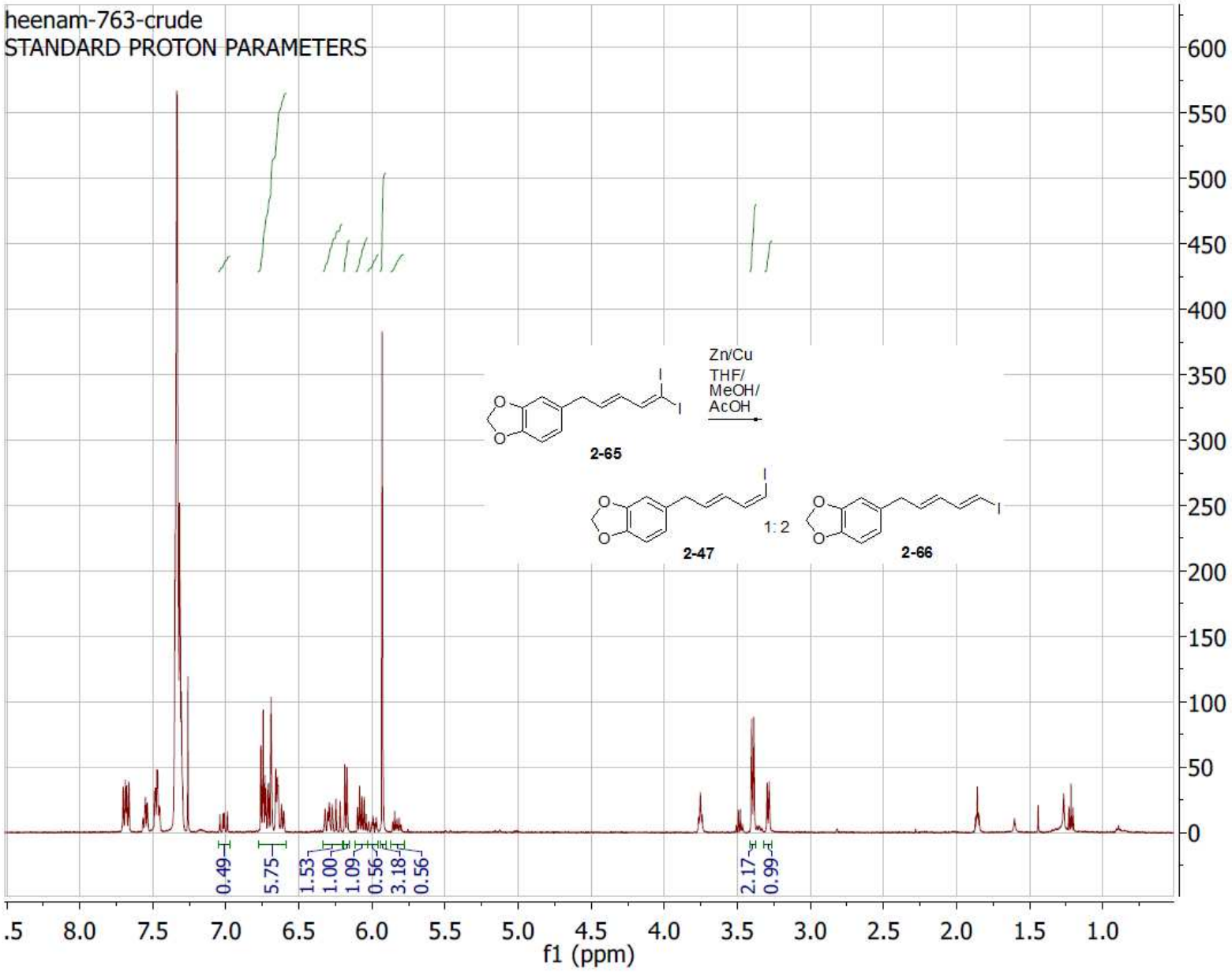


2-64




heenam-604H
new experiment
NaHMDS
HMPA, THF, - 78 °C
CHO
2-64
2-47
2-65
2 : 1
0.34
5.18
1.03
1.00
1.40
3.09
1.97
0.73
f1 (ppm)


heenam-762H
STANDARD PROTON PARAMETERS
2-65
1.50
3.01
1.00
2.91
2.00
f1 (ppm)


heenam-763-crude
STANDARD PROTON PARAMETERS
Zn/Cu
THF/
MeOH/
AcOH
2-65
2-47
1:2
2-66
0.49
5.75
1.53
1.00
1.09
0.56
3.18
0.56
2.17
0.99
f1 (ppm)

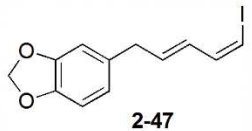
STANDARD PROTON PARAMETERS

Data Collected on:
inv500-inova500
Archive directory:
/export/home/heenam/vnmrsys/data
Sample directory:

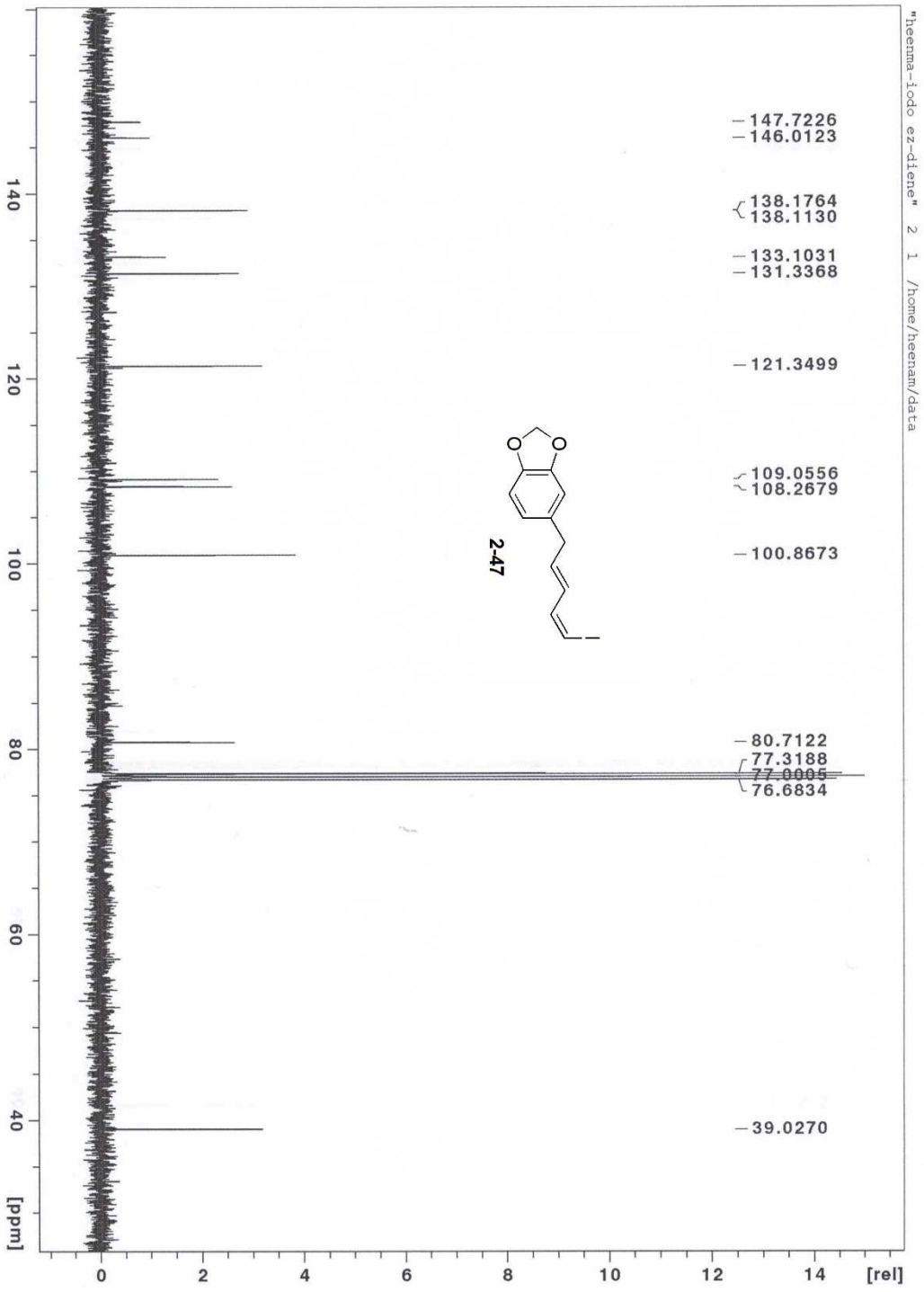
File: PROTON

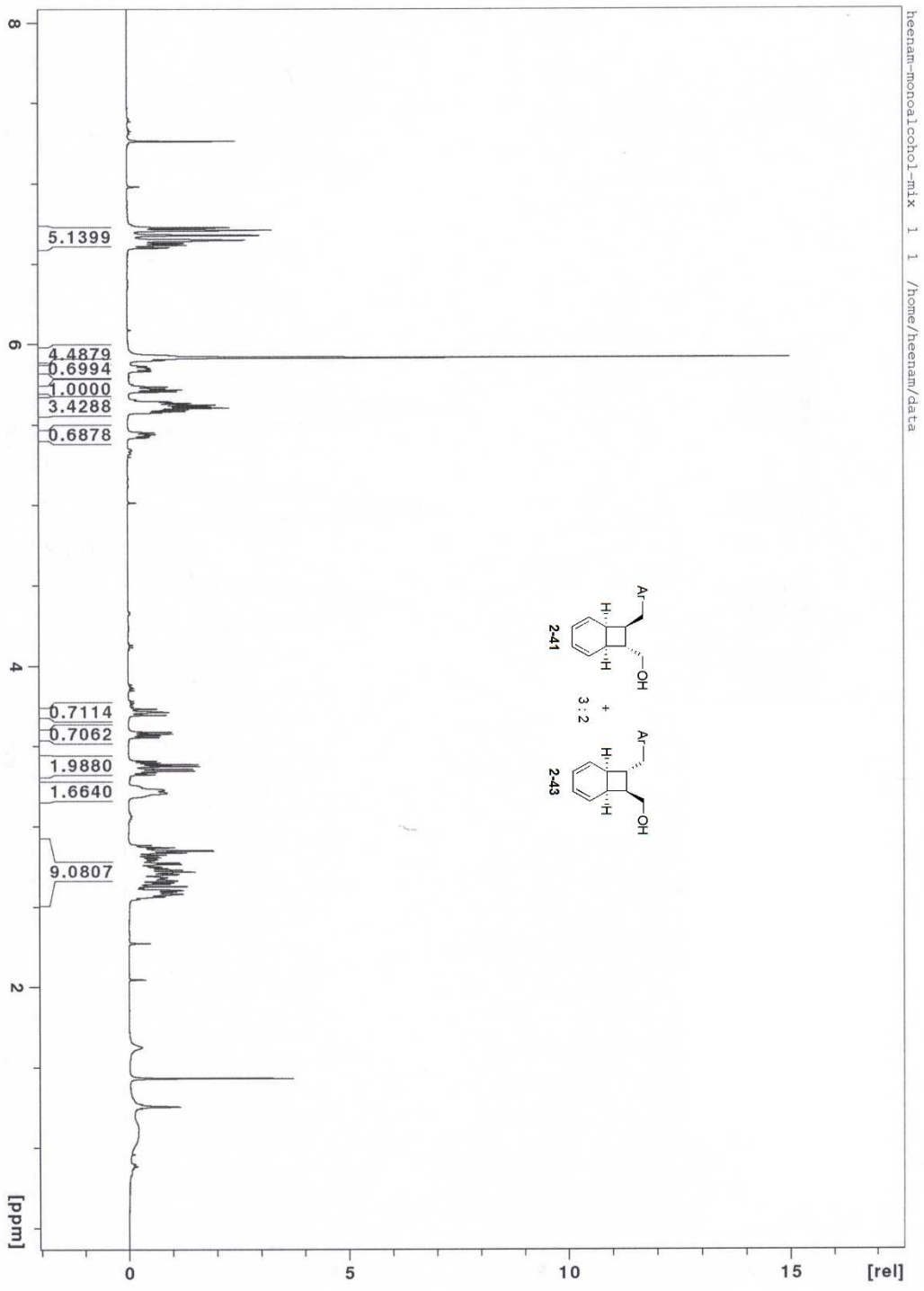
Pulse Sequence: s2pul
Solvent: CDCl3

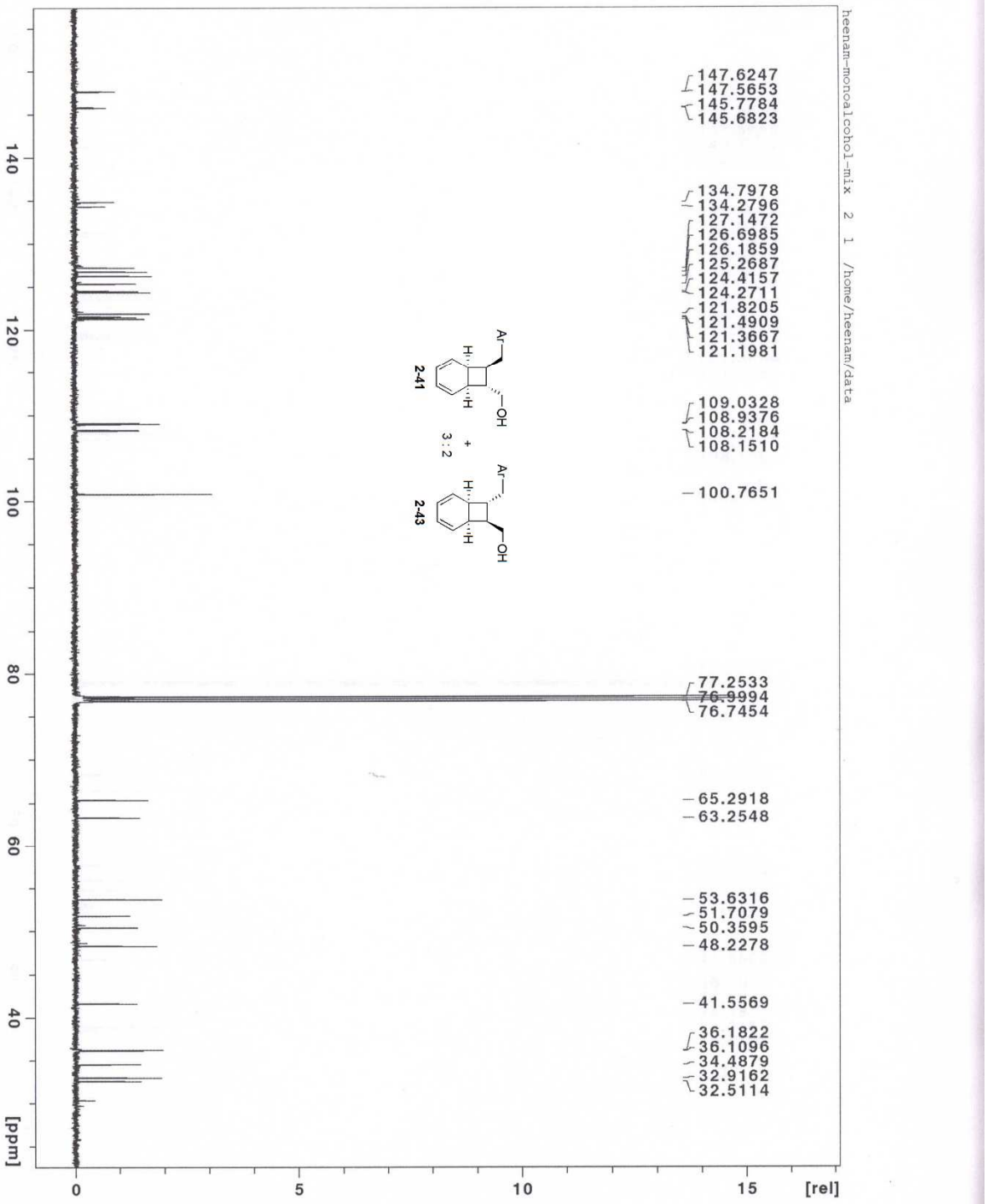
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7998.4 Hz
81 repetitions
OBSERVE H1, 499.8948170 MHz
DATA PROCESSING
FT size 32768
Total time 6 min

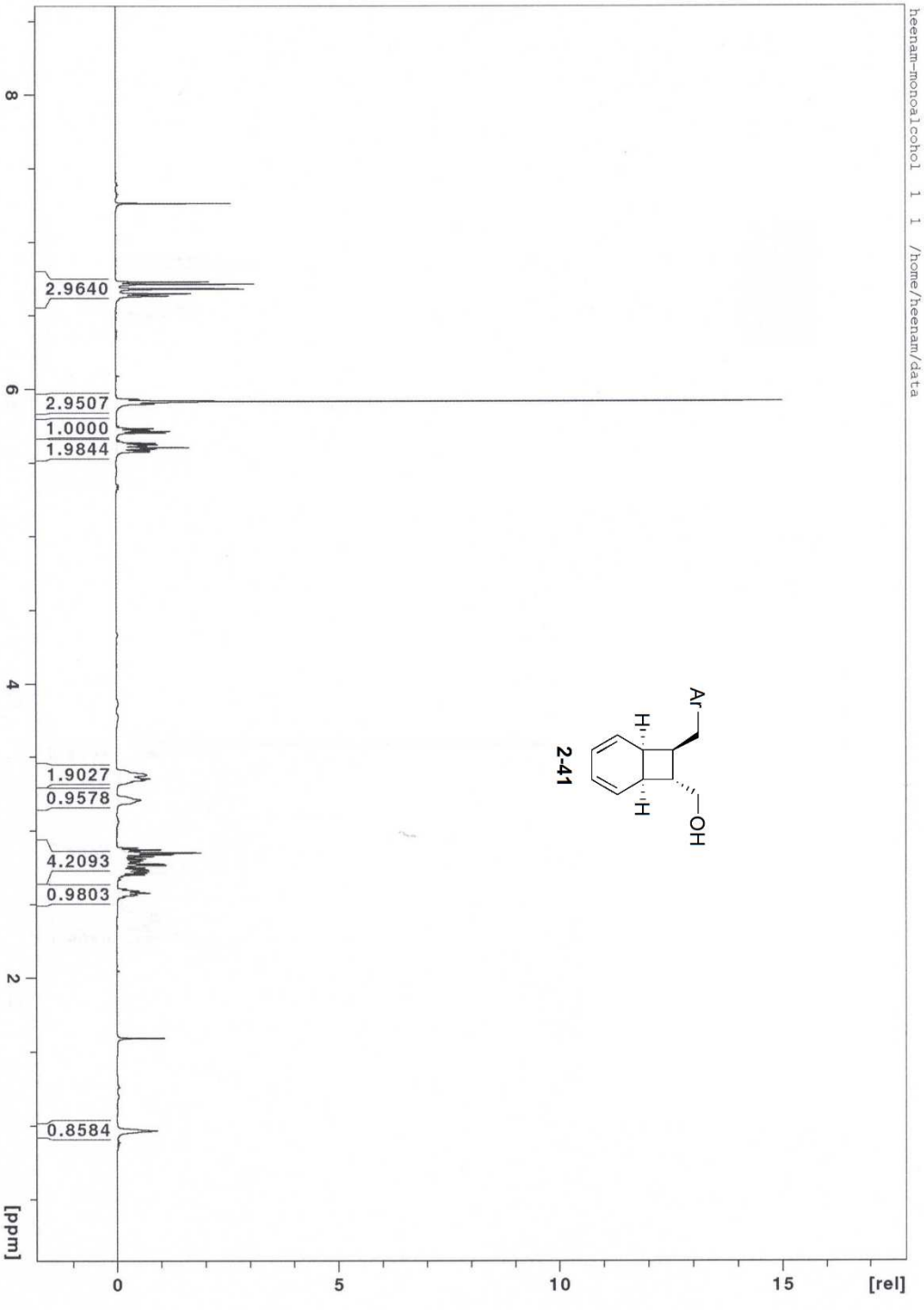


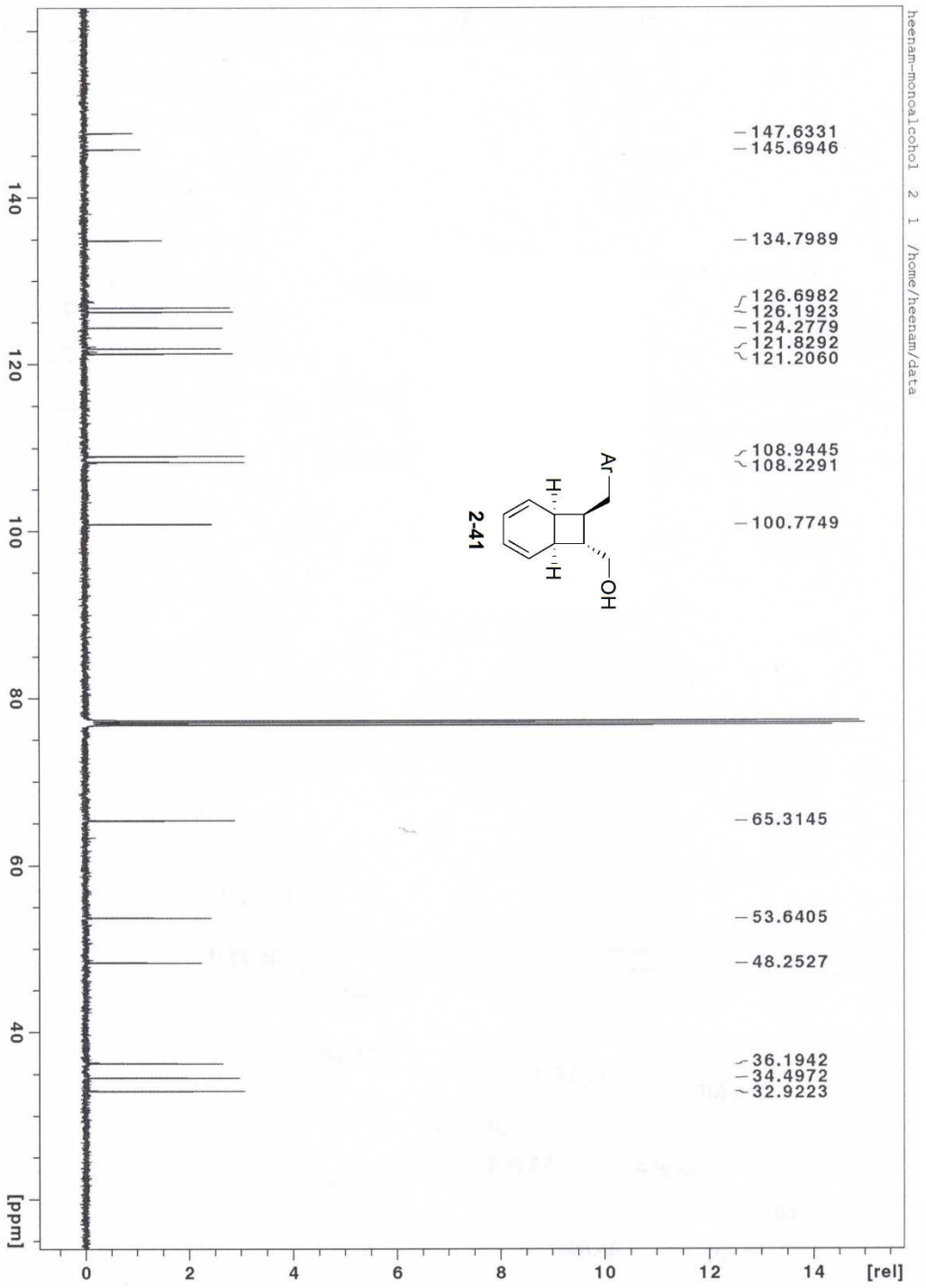
2-47

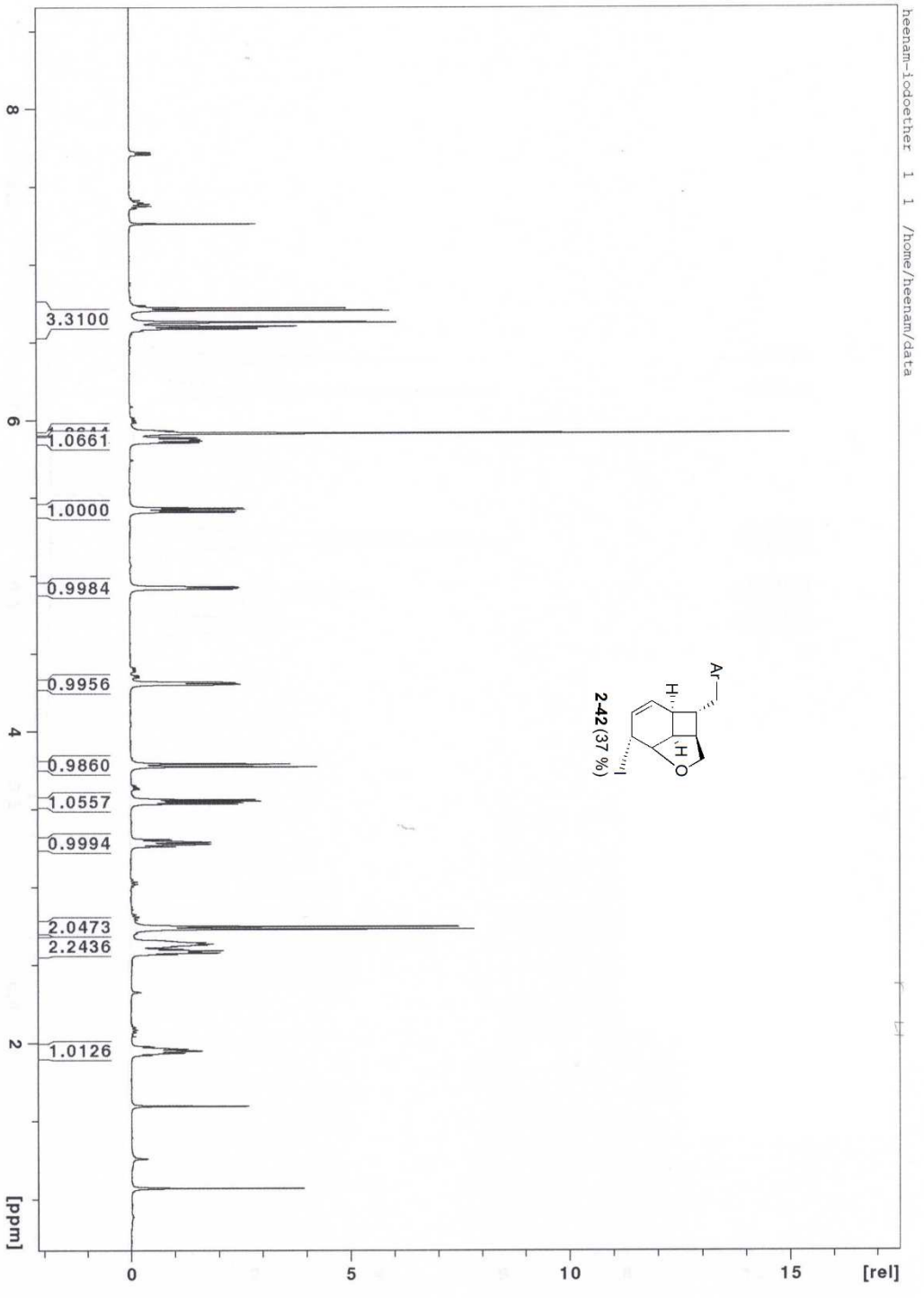

"beenma-iodo ez-diene" 2 1 /home/beenam/data
147.7226
146.0123
138.1764
138.1130
133.1031
131.3368
121.3499
109.0556
108.2679
100.8673
80.7122
77.3188
77.0005
76.6834
39.0270
2-47
140
120
100
80
60
40
[ppm]
0
2
4
6
8
10
12
14
[rel]

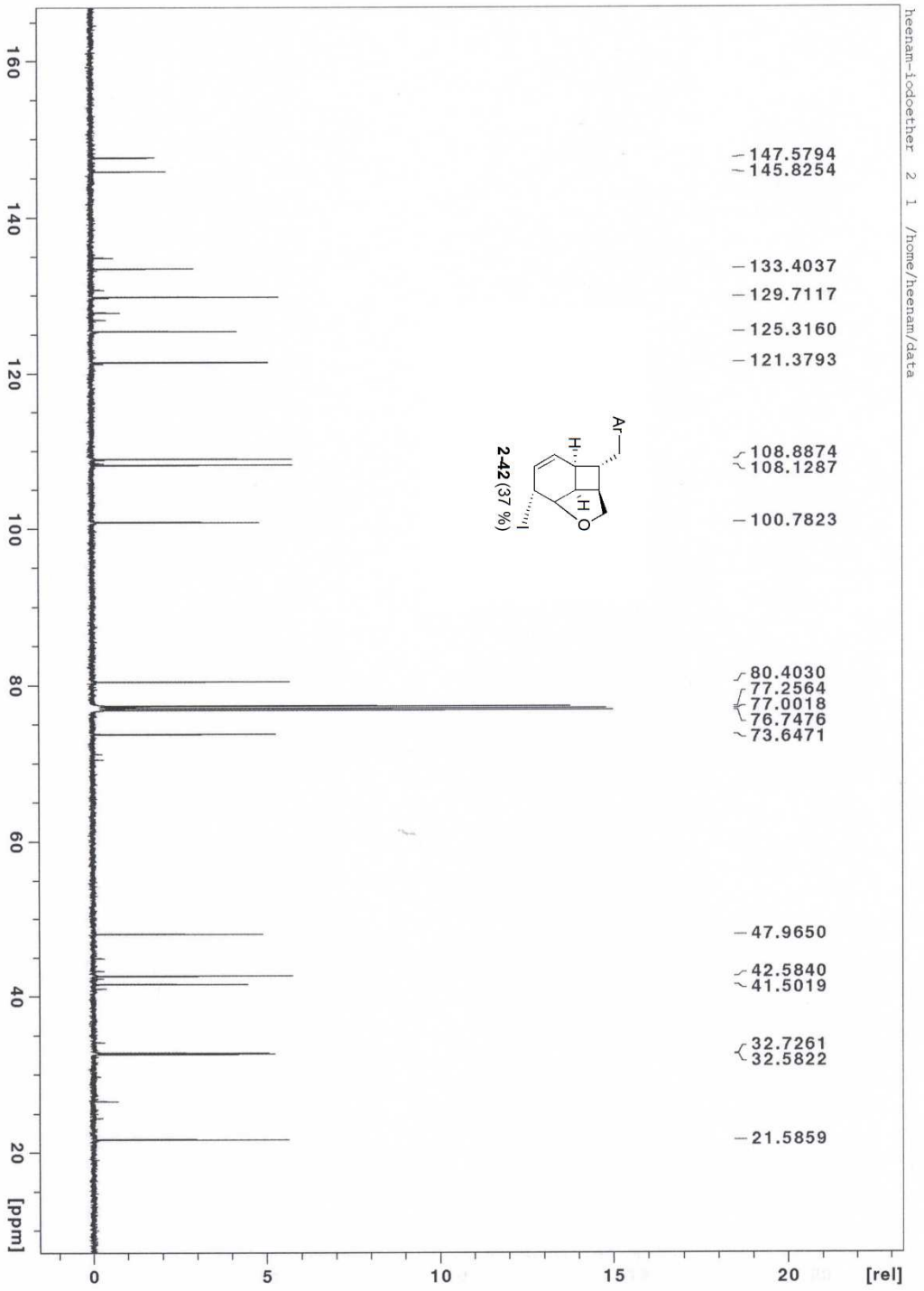

heenam-monoalcohol-mix 1 1 /home/heenam/data
5.1399
4.4879
0.6994
1.0000
3.4288
0.6878
0.7114
0.7062
1.9880
1.6640
9.0807
[ppm]
[rel]
2-41
3 : 2
2-43
Ar
OH


heenam-monoalcohol-mix 2 1 /home/heenam/data
147.6247
147.5653
145.7784
145.6823
134.7978
134.2796
127.1472
126.6985
126.1859
125.2687
124.4157
124.2711
121.8205
121.4909
121.3667
121.1981
109.0328
108.9376
108.2184
108.1510
100.7651
77.2533
76.9994
76.7454
65.2918
63.2548
53.6316
51.7079
50.3595
48.2278
41.5569
36.1822
36.1096
34.4879
32.9162
32.5114
Ar
OH
H
2-41
3 : 2
+
2-43
[ppm]
[rel]
0
5
10
15
40
60
80
100
120
140


heenam-monoalcohol 1 1 /home/heenam/data
2.9640
2.9507
1.0000
1.9844
1.9027
0.9578
4.2093
0.9803
0.8584
[ppm]
[rel]
Ar
H
H
OH
2-41


heenam-monoalcohol 2 1 /home/heenam/data
147.6331
145.6946
134.7989
126.6982
126.1923
124.2779
121.8292
121.2060
108.9445
108.2291
100.7749
65.3145
53.6405
48.2527
36.1942
34.4972
32.9223
Ar
H
H
OH
2-41
[ppm]
[rel]

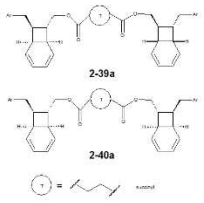

heenam-iodoether 1 1 /home/heenam/data
3.3100
1.0661
1.0000
0.9984
0.9956
0.9860
1.0557
0.9994
2.0473
2.2436
1.0126
[ppm]
[rel]
Ar
H
H
O
2-42 (37 %)


heenam-iodoether 2 1 /home/heenam/data
147.5794
145.8254
133.4037
129.7117
125.3160
121.3793
108.8874
108.1287
100.7823
80.4030
77.2564
77.0018
76.7476
73.6471
47.9650
42.5840
41.5019
32.7261
32.5822
21.5859
2-42 (37 %)
Ar
H
H
O
I
160
140
120
100
80
60
40
20
[ppm]
0
5
10
15
20
[rel]

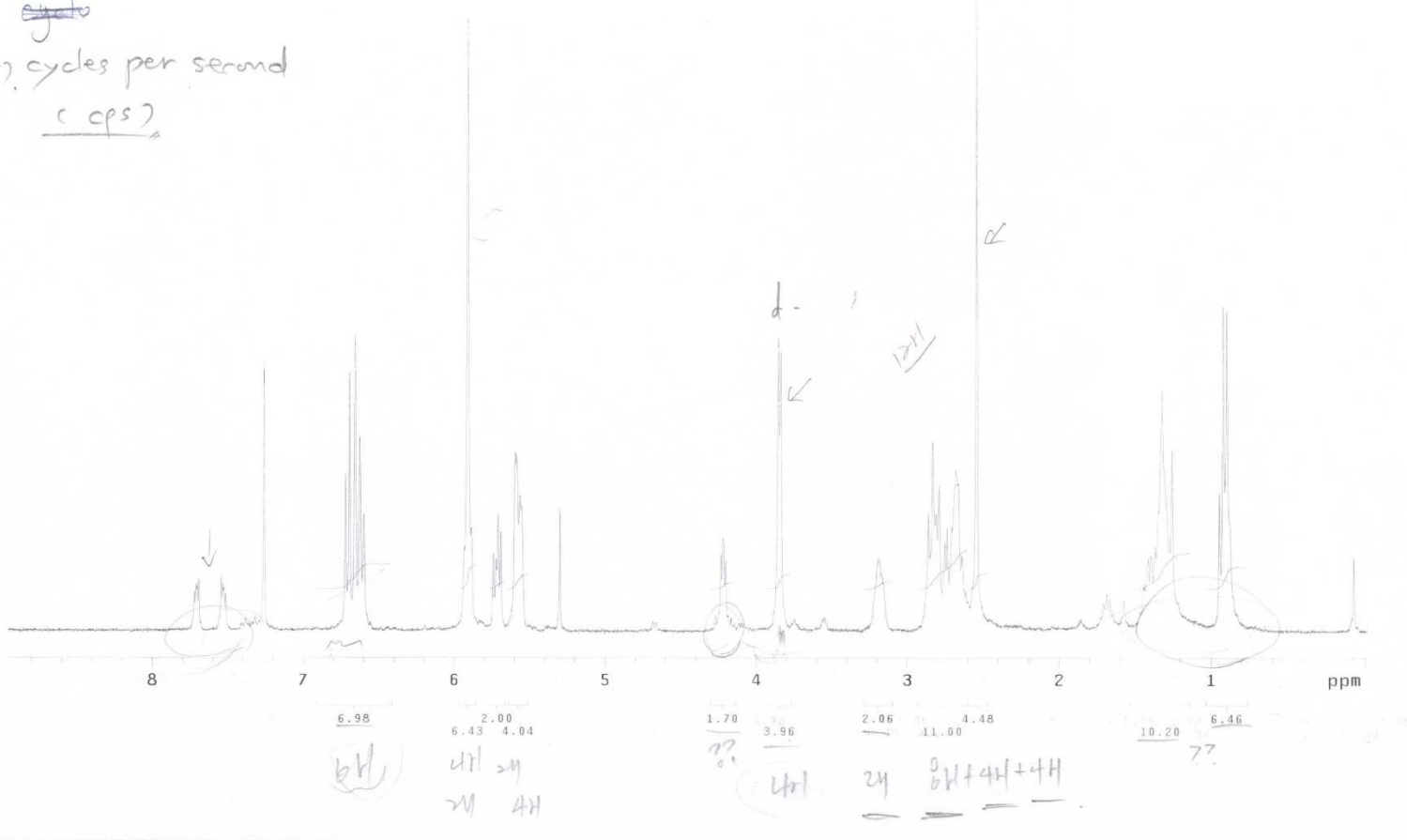
new experiment

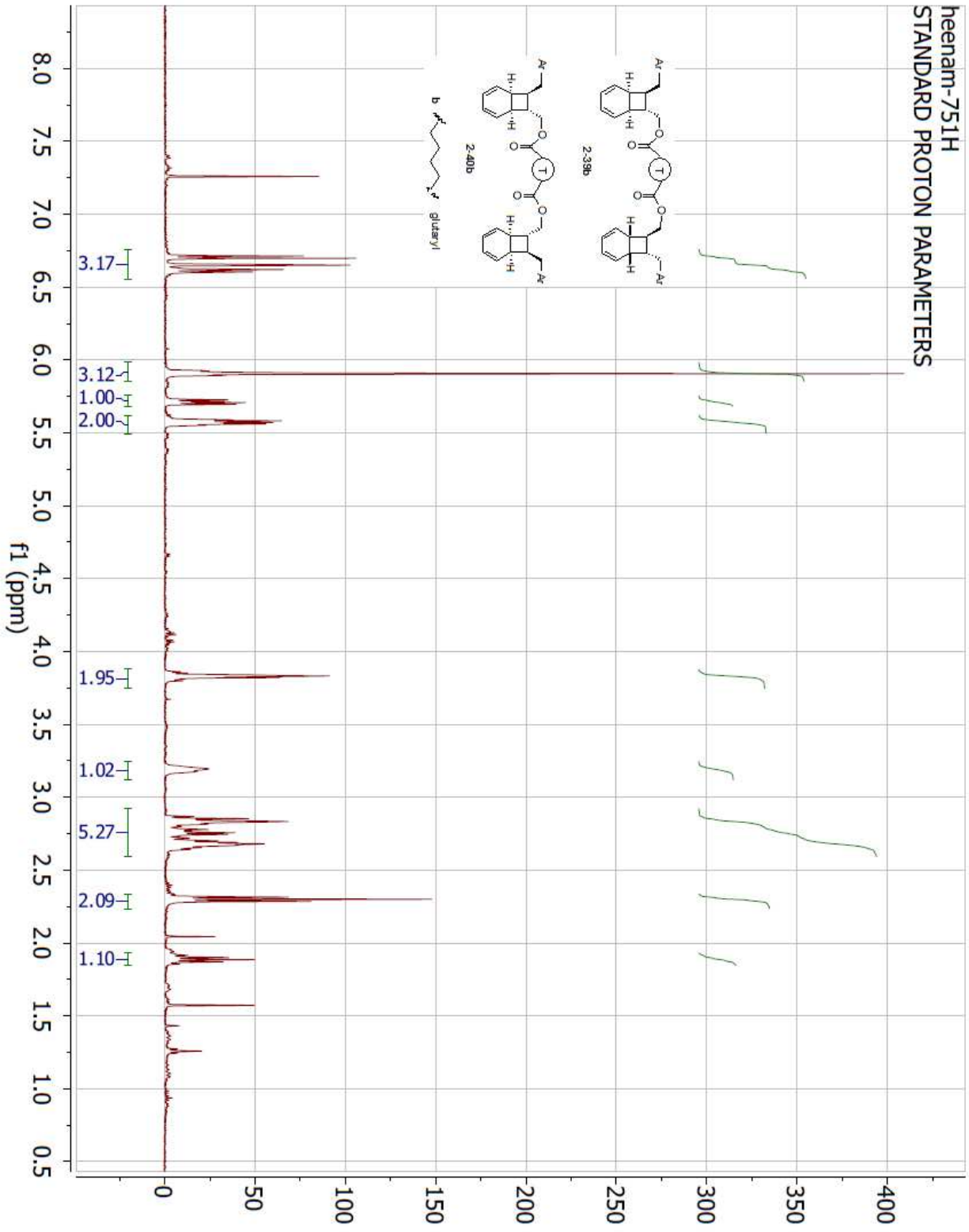
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

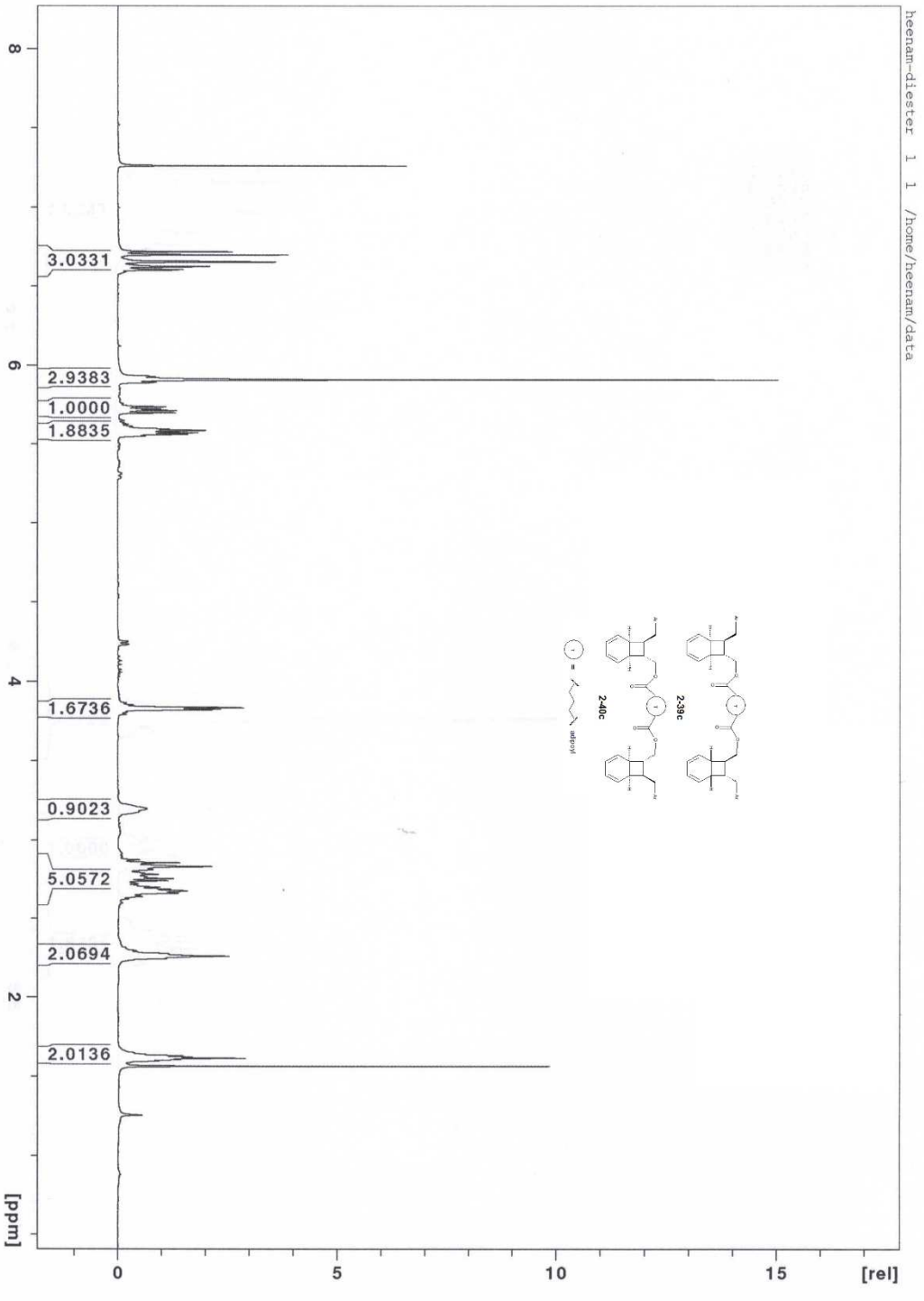
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
41 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec

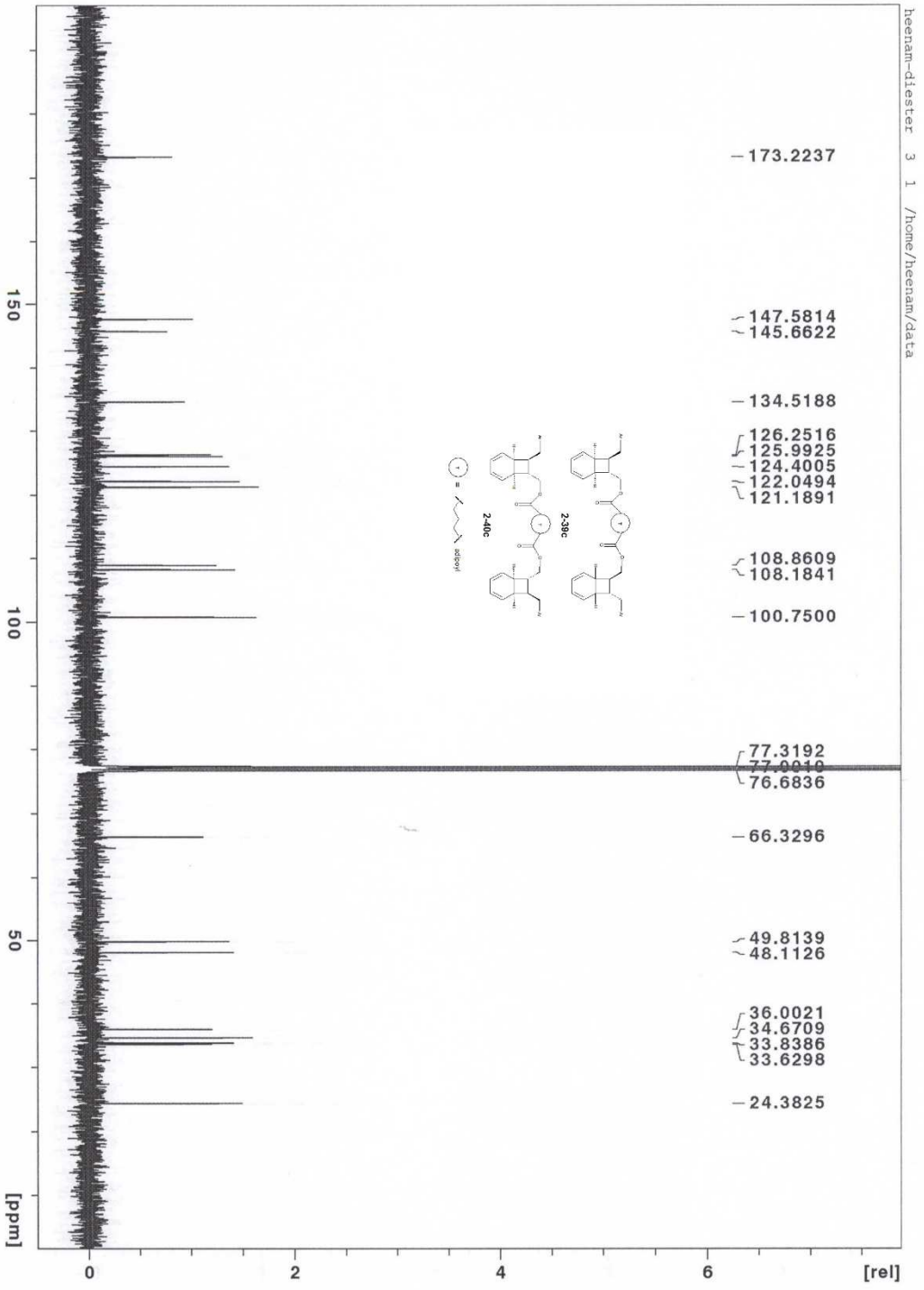


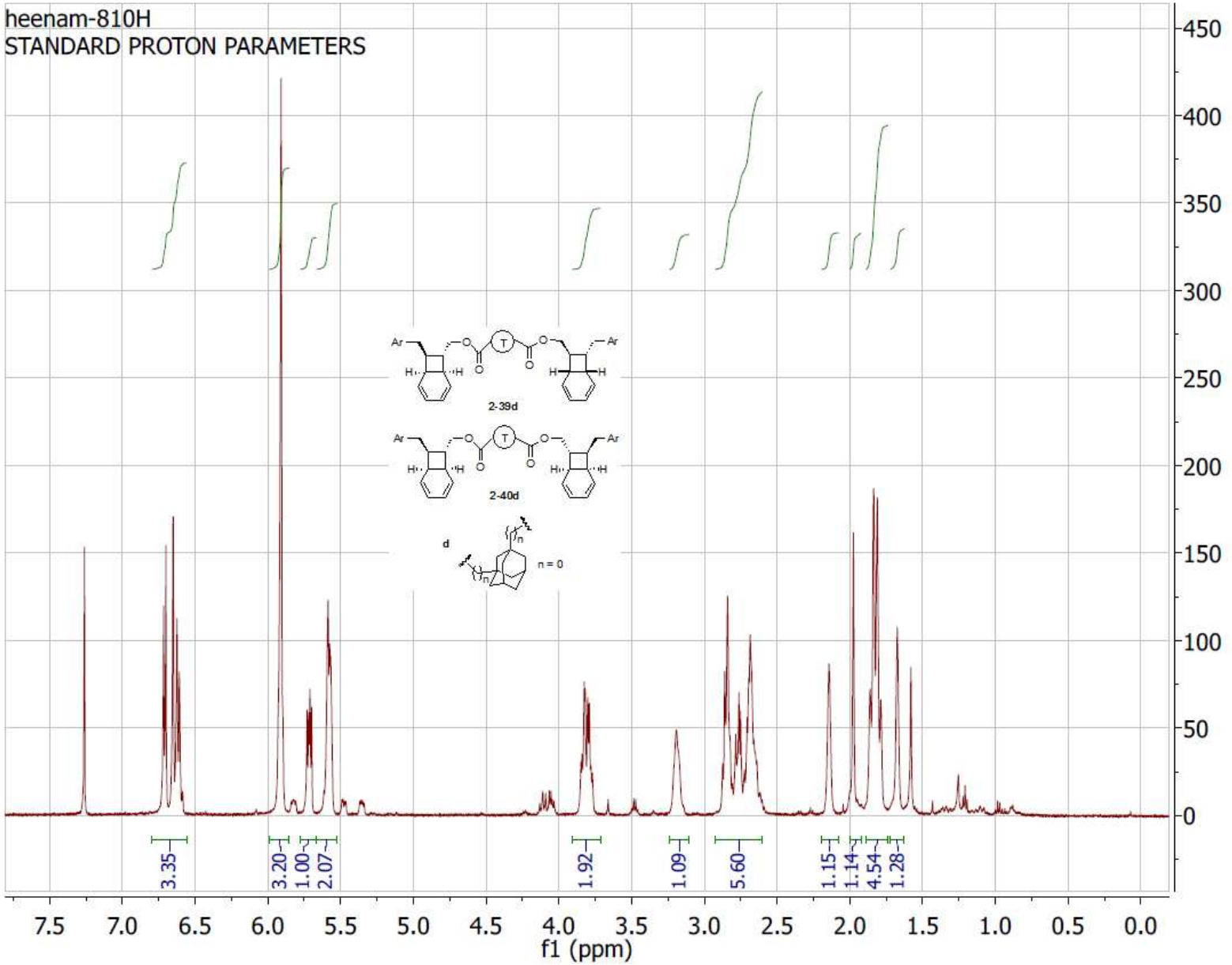
~~Hertz~~
→ cycles per second
(cps)

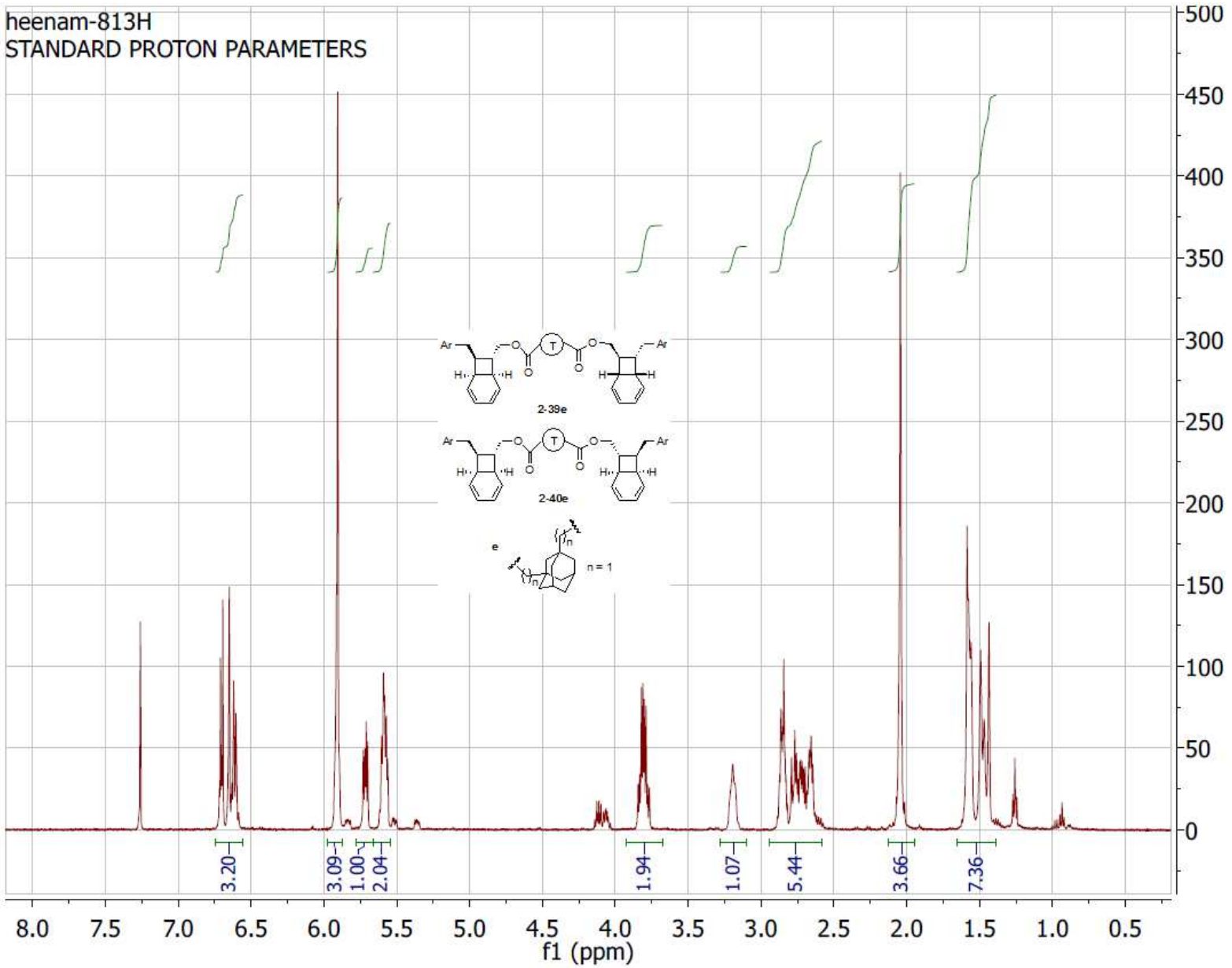


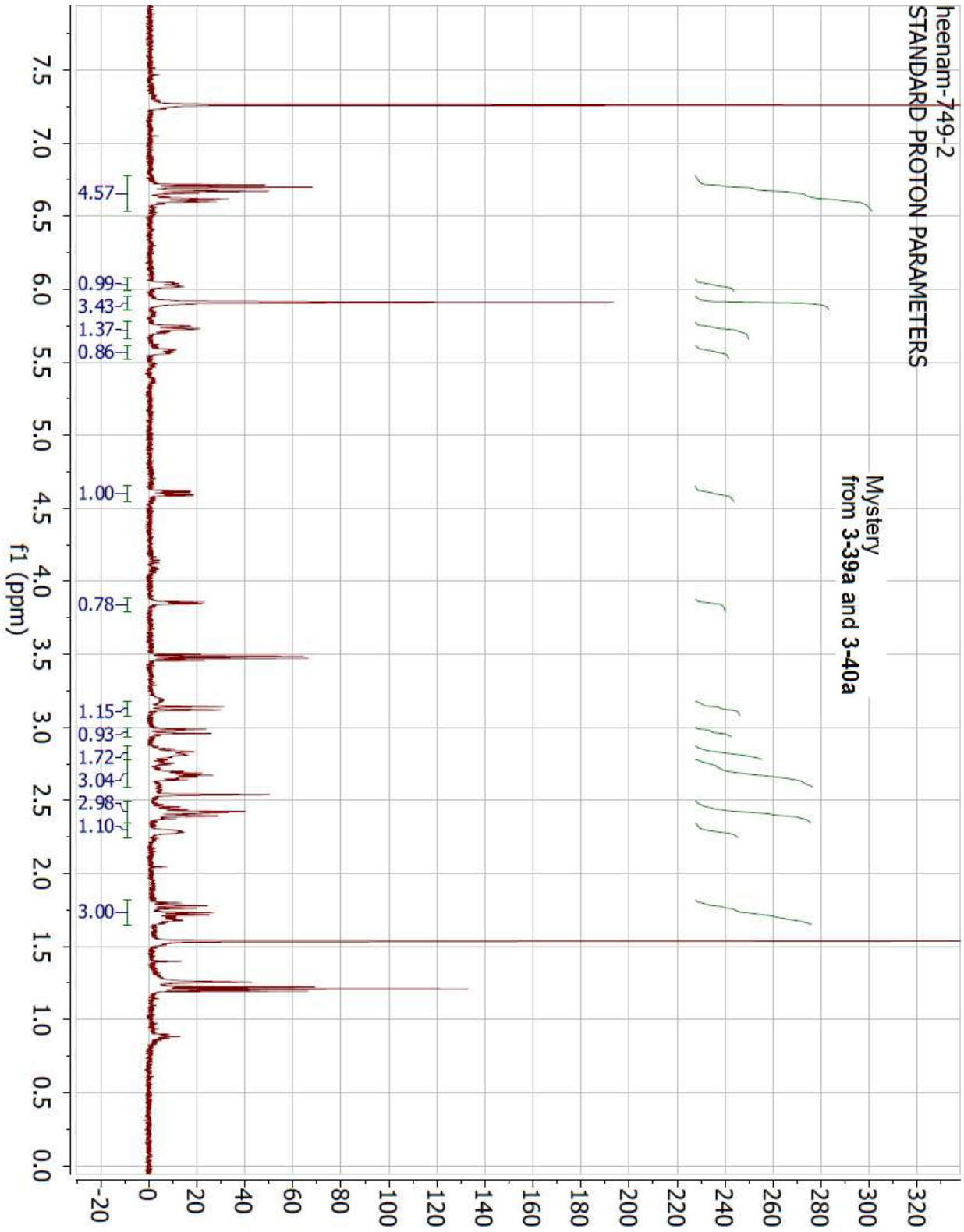

heenam-751H
STANDARD PROTON PARAMETERS
2-38b
2-40b
glutaryl
3.17
3.12
1.00
2.00
1.95
1.02
5.27
2.09
1.10
f1 (ppm)

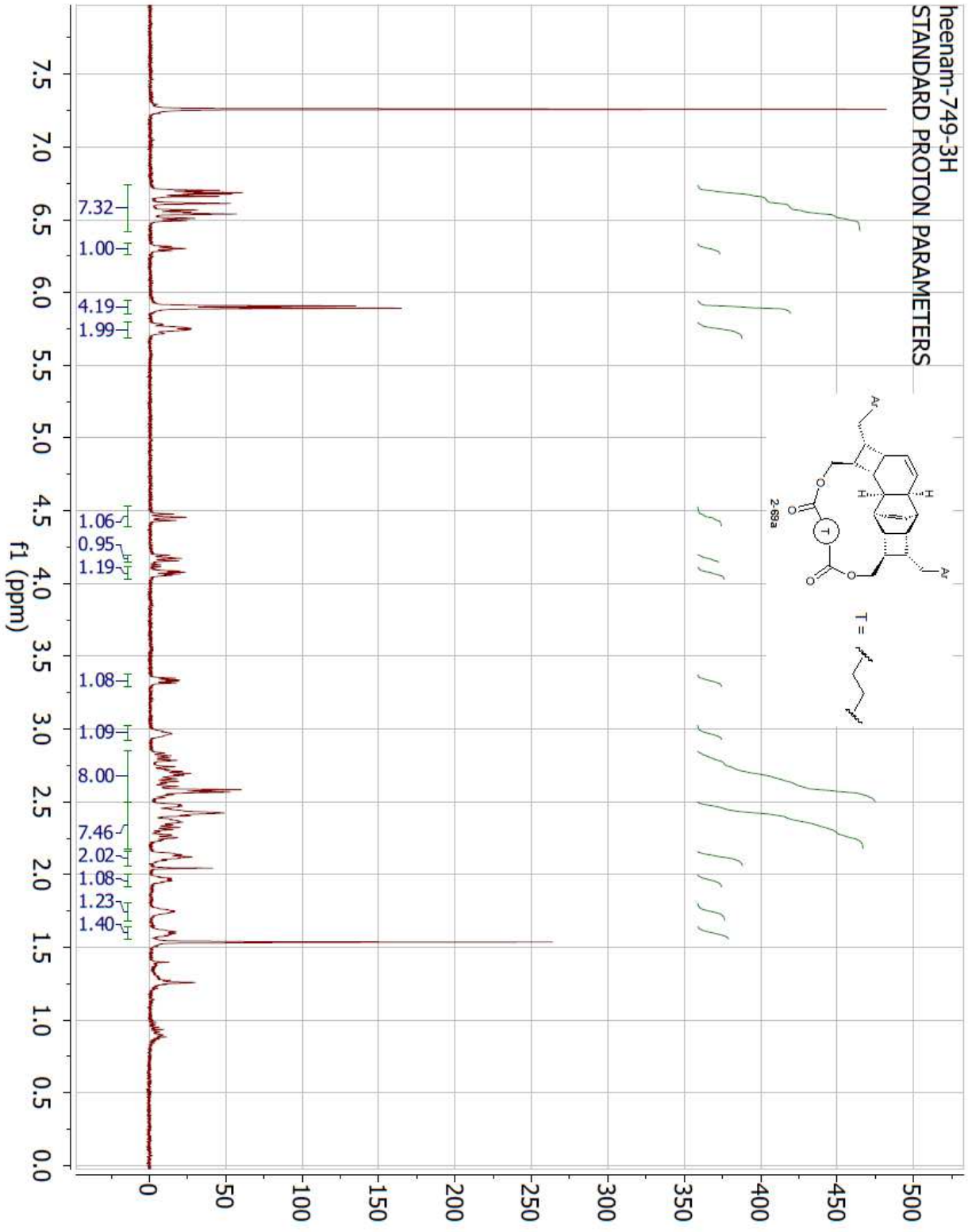

heenam-diester 1 1 /home/heenam/data
3.0331
2.9383
1.0000
1.8835
1.6736
0.9023
5.0572
2.0694
2.0136
8
6
4
2
[ppm]
0
5
10
15
[rel]
2-40c
2-39c

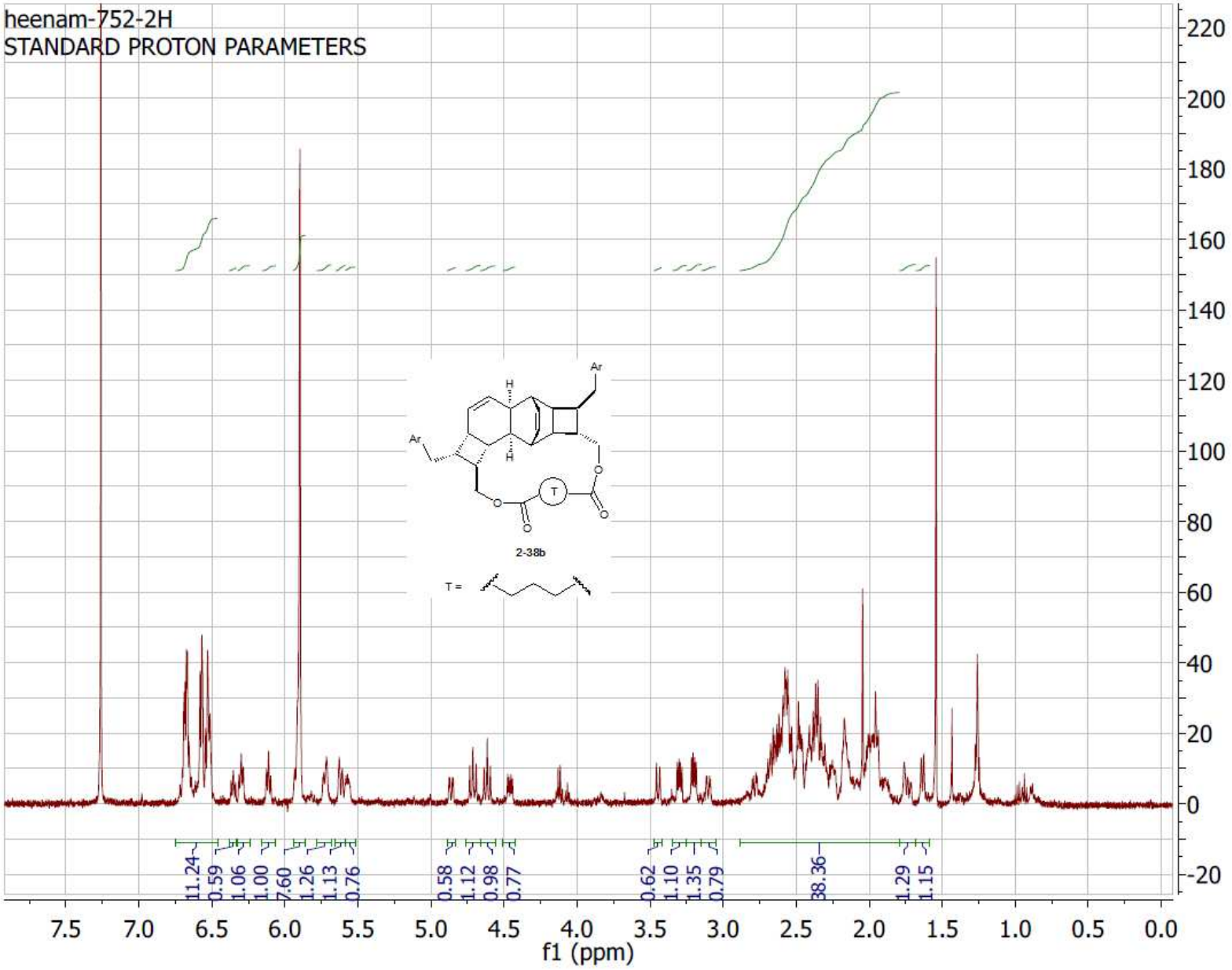

heenam-diester 3 1 /home/heenam/data
173.2237
147.5814
145.6622
134.5188
126.2516
125.9925
124.4005
122.0494
121.1891
108.8609
108.1841
100.7500
77.3192
77.0010
76.6836
66.3296
49.8139
48.1126
36.0021
34.6709
33.8386
33.6298
24.3825
2-40c
2-38c
allyl
150
100
50
[ppm]
0
2
4
6
[rel]

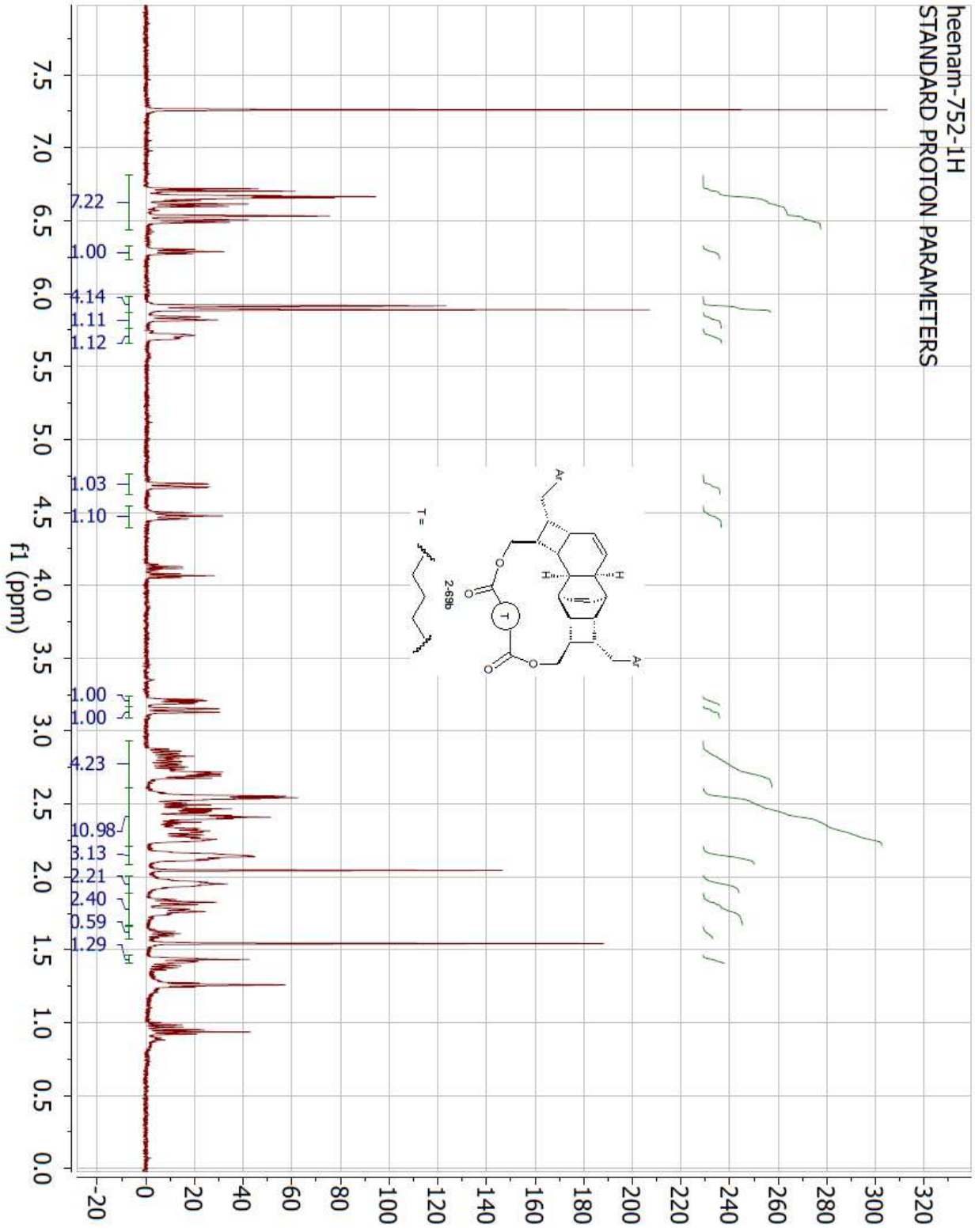

heenam-810H
STANDARD PROTON PARAMETERS
2-39d
2-40d
n = 0
3.35
3.20
1.00
2.07
1.92
1.09
5.60
1.15
1.14
4.54
1.28
f1 (ppm)

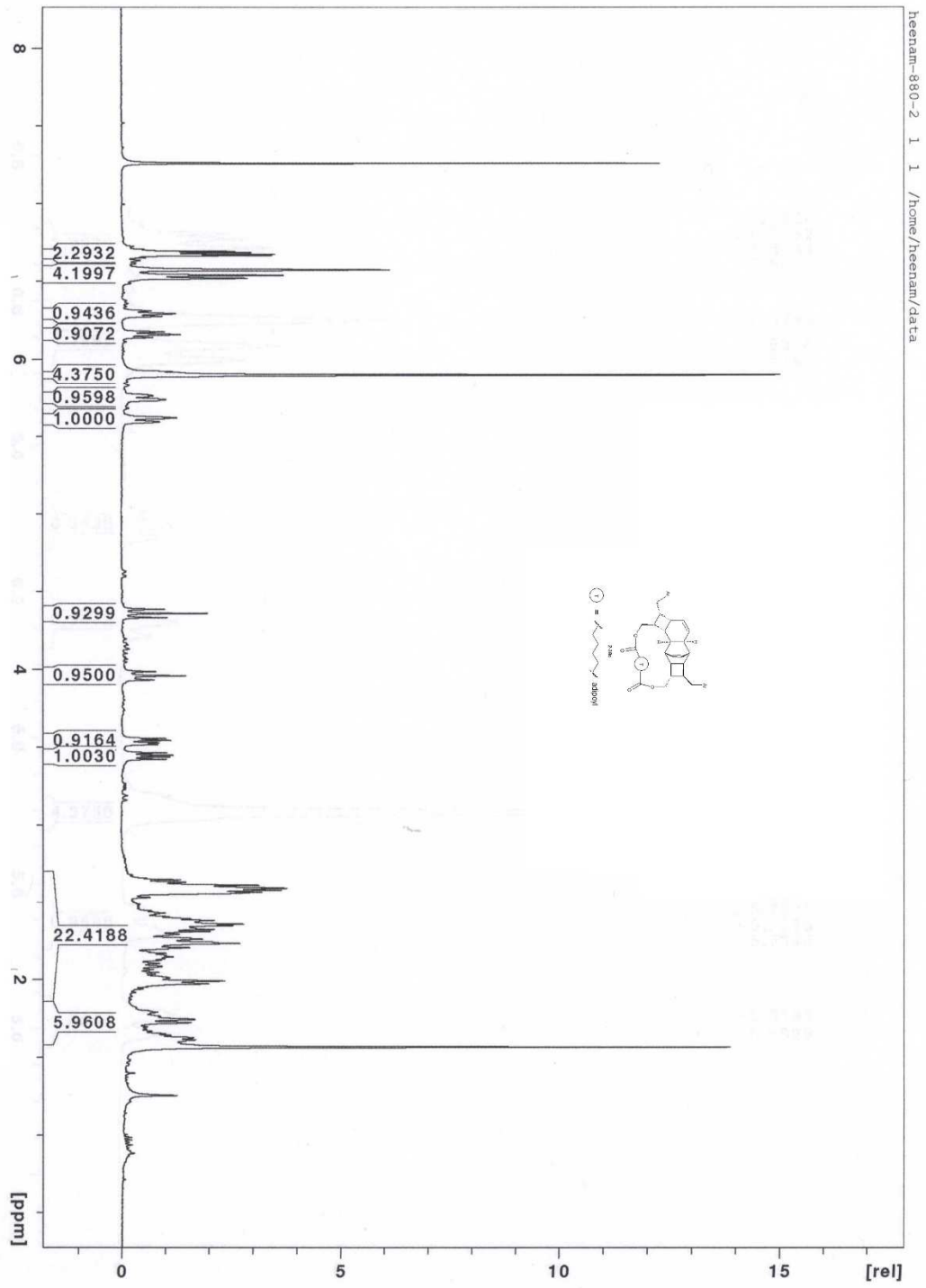

heenam-813H
STANDARD PROTON PARAMETERS
2-39e
2-40e
n = 1
3.20
3.09
1.00
2.04
1.94
1.07
5.44
3.66
7.36
f1 (ppm)

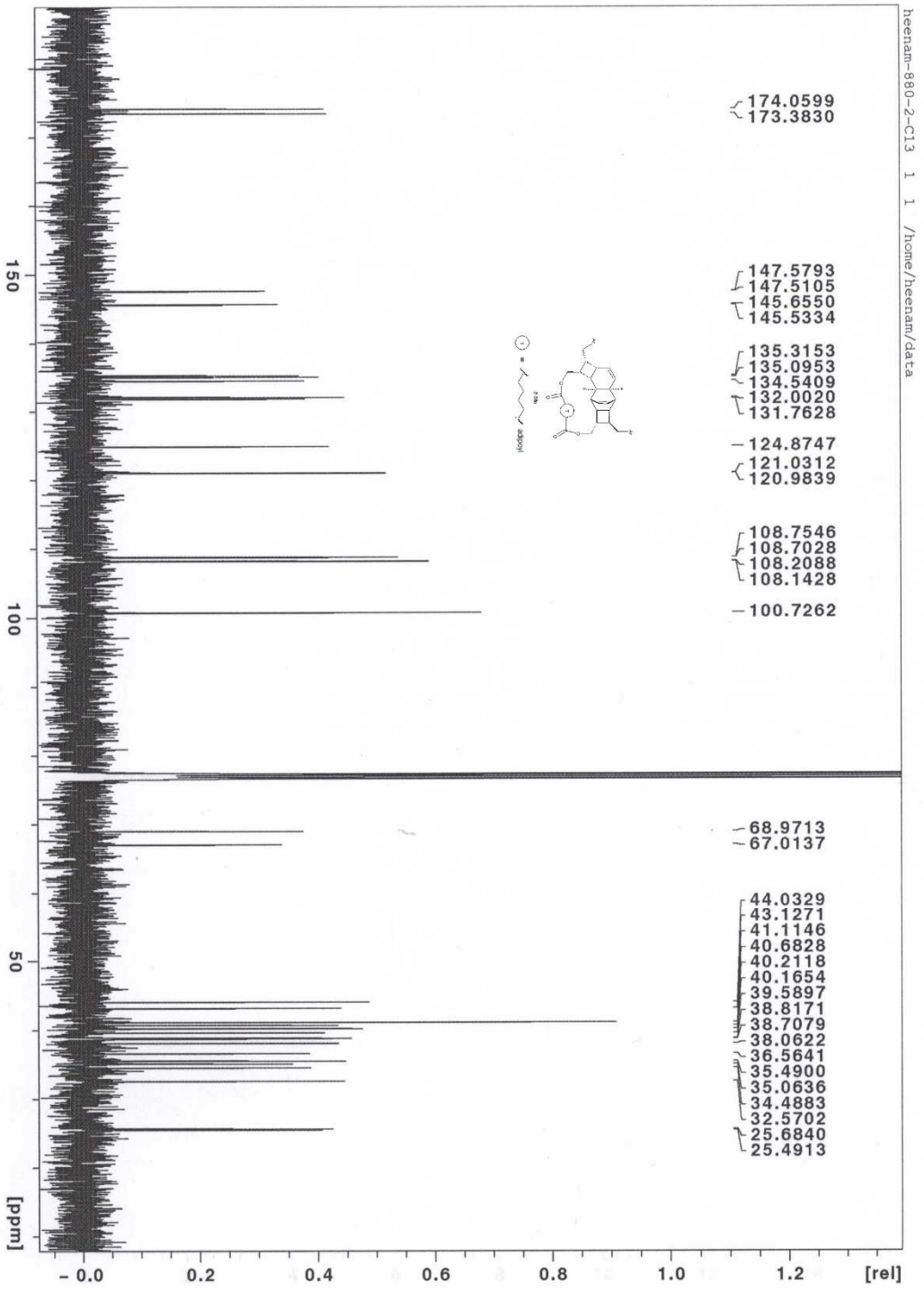

heenam-749-2
STANDARD PROTON PARAMETERS
Mystery
from 3-39a and 3-40a
4.57
0.99
3.43
1.37
0.86
1.00
0.78
1.15
0.93
1.72
3.04
2.98
1.10
3.00
f1 (ppm)

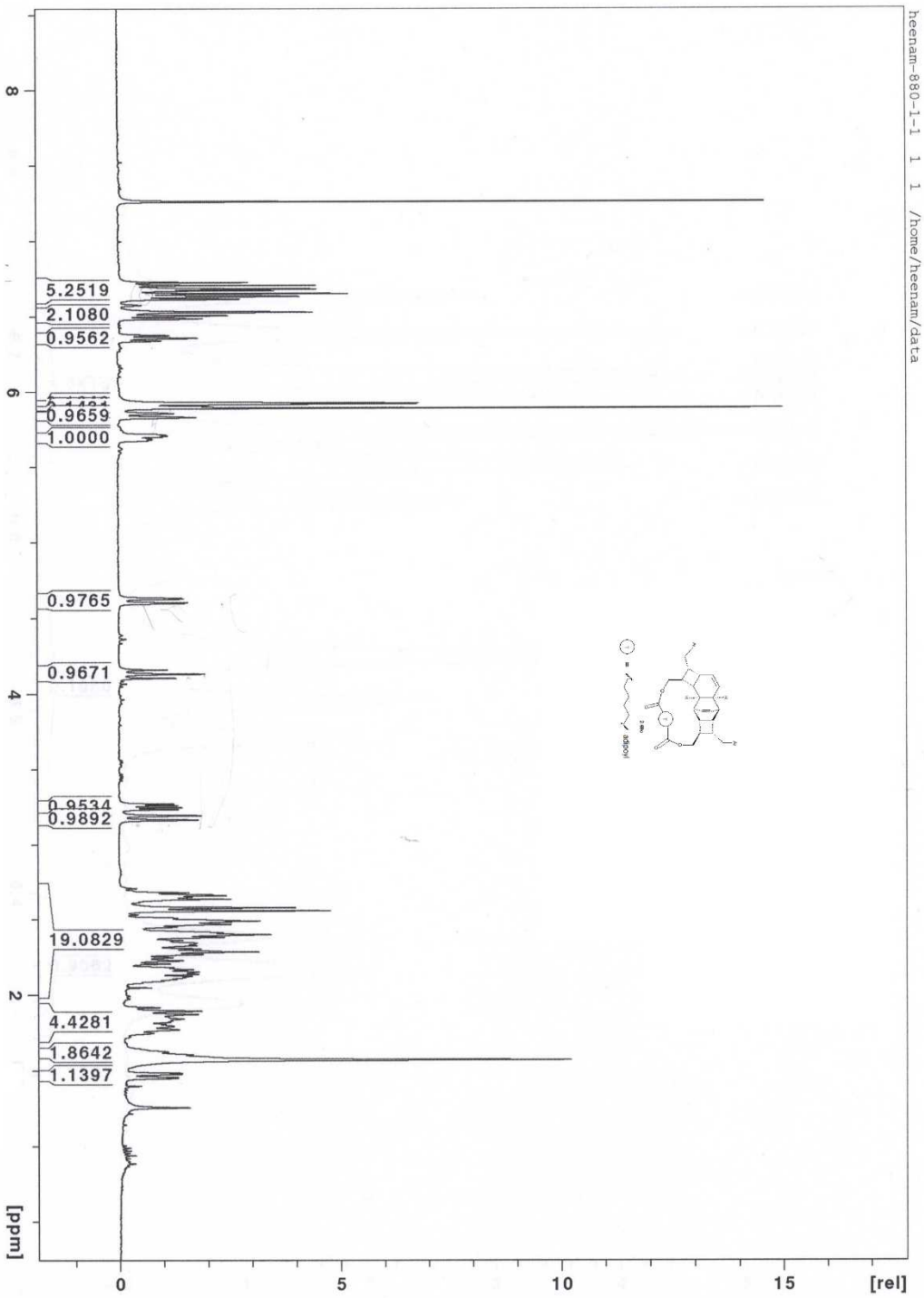

heenam-749-3H
STANDARD PROTON PARAMETERS
2-69a
T =
7.32
1.00
4.19
1.99
1.06
0.95
1.19
1.08
1.09
8.00
7.46
2.02
1.08
1.23
1.40
f1 (ppm)

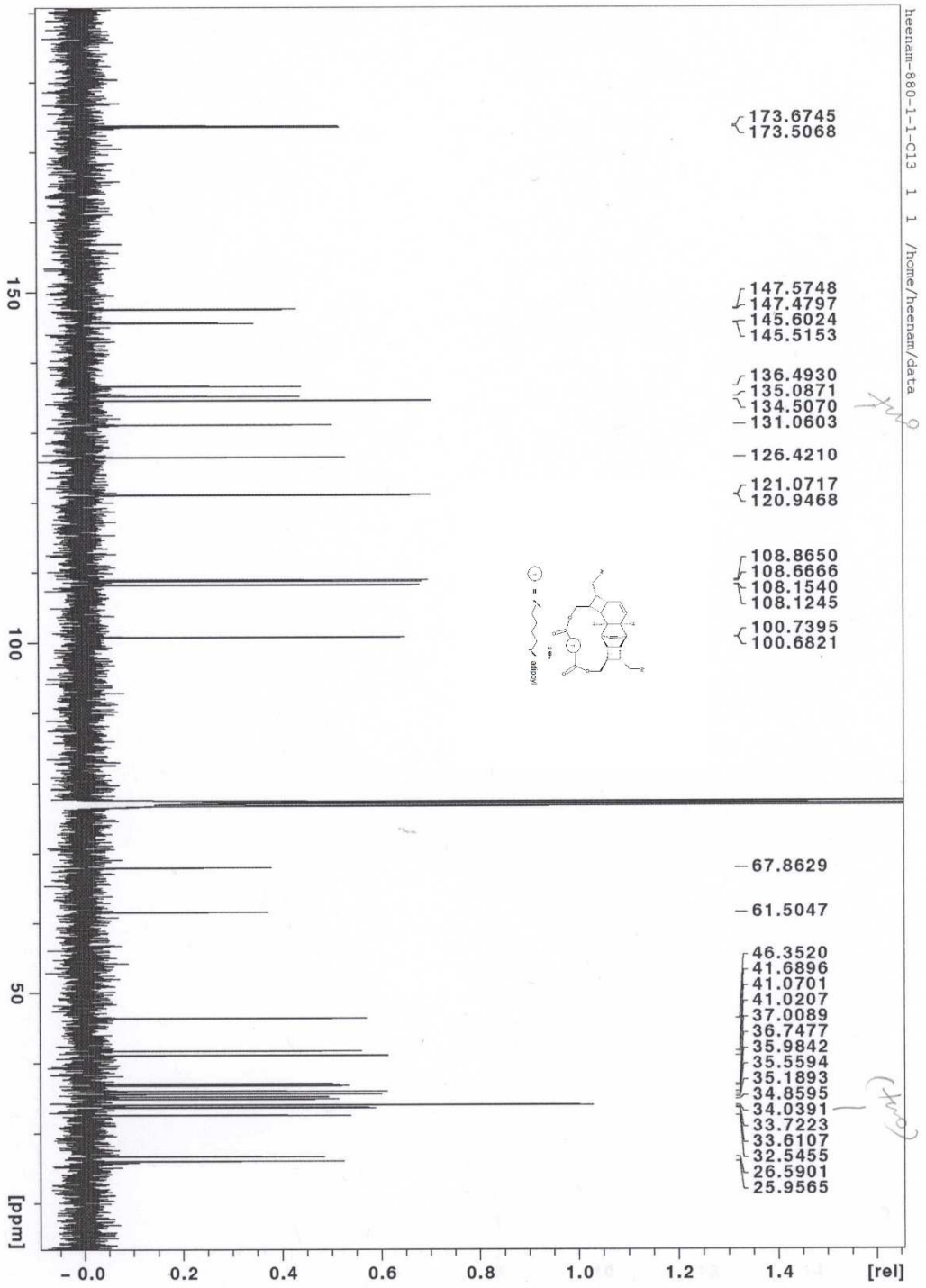

heenam-752-2H
STANDARD PROTON PARAMETERS
Ar
H
H
Ar
O
O
T
O
O
2-38b
T =
11.24
0.59
1.06
1.00
7.60
1.26
1.13
0.76
0.58
1.12
0.98
0.77
0.62
1.10
1.35
0.79
38.36
1.29
1.15
f1 (ppm)

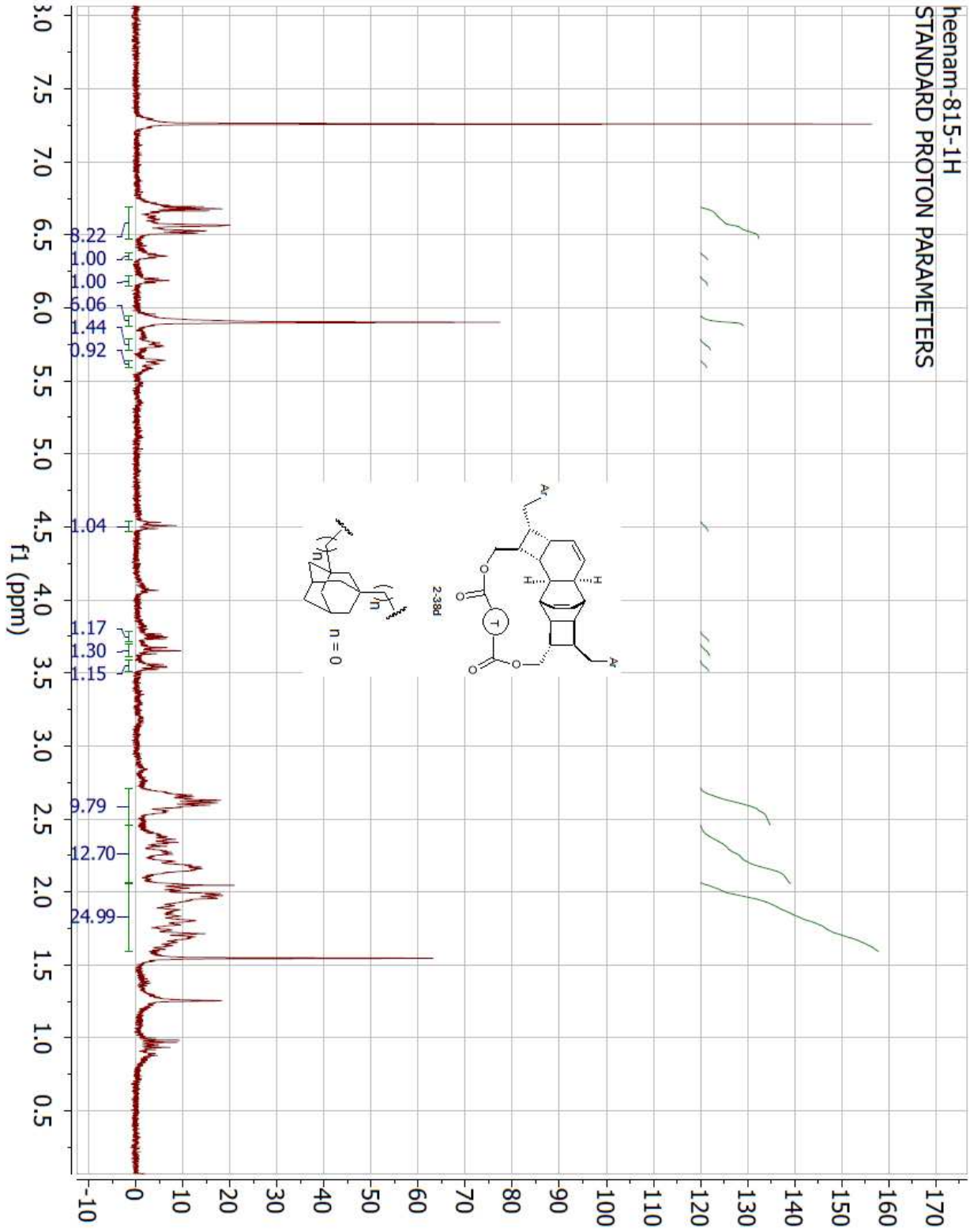

heenam-752-1H
STANDARD PROTON PARAMETERS
7.22
1.00
4.14
1.11
1.12
1.03
1.10
1.00
1.00
4.23
10.98
3.13
2.21
2.40
0.59
1.29
f1 (ppm)
T =
2-69b
Ar
Ar
H
H
O
O
O
O
T

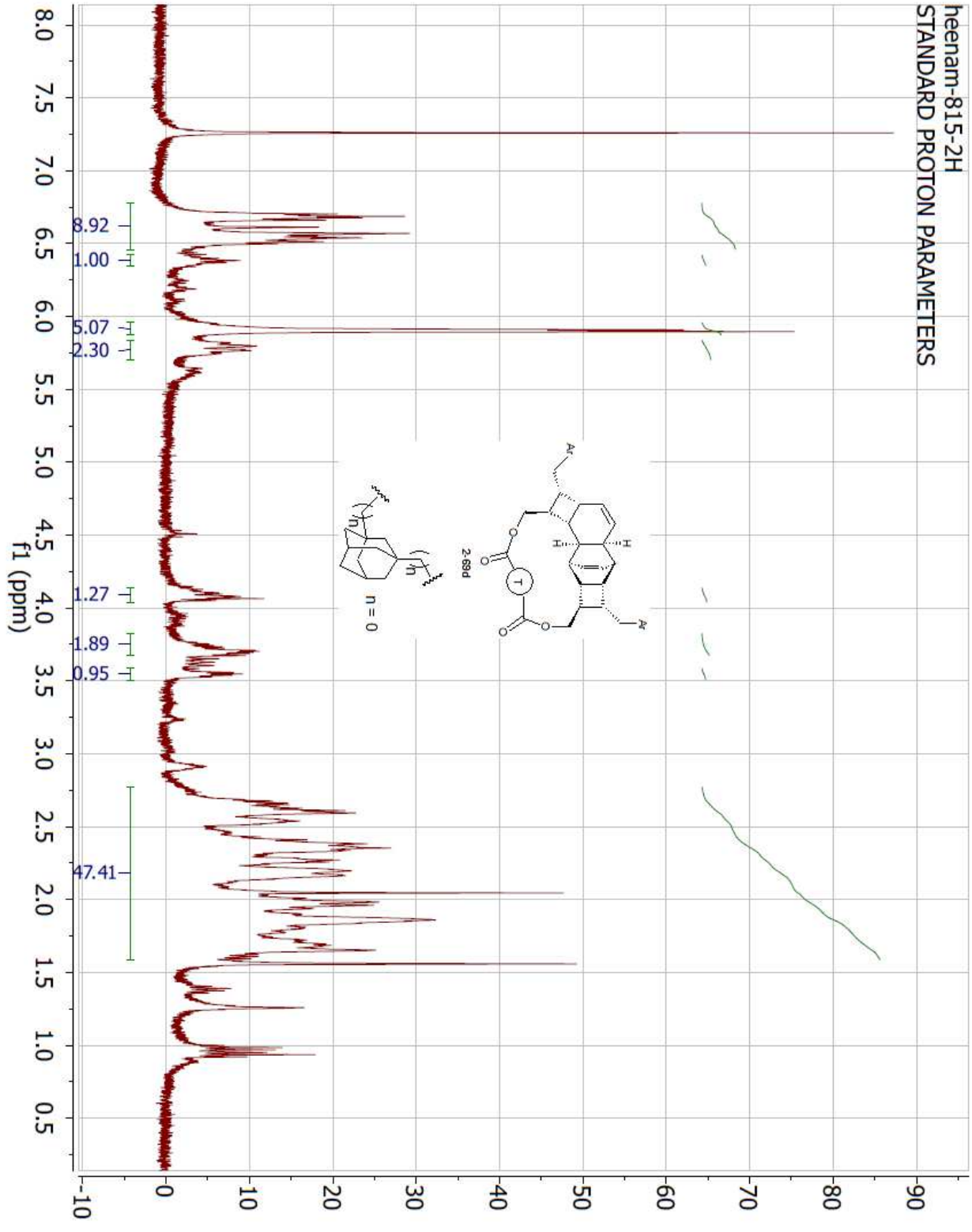

heenam-880-2 1 1 /home/heenam/data
2.2932
4.1997
0.9436
0.9072
4.3750
0.9598
1.0000
0.9299
0.9500
0.9164
1.0030
22.4188
5.9608
8
6
4
2
[ppm]
0
5
10
15
[rel]

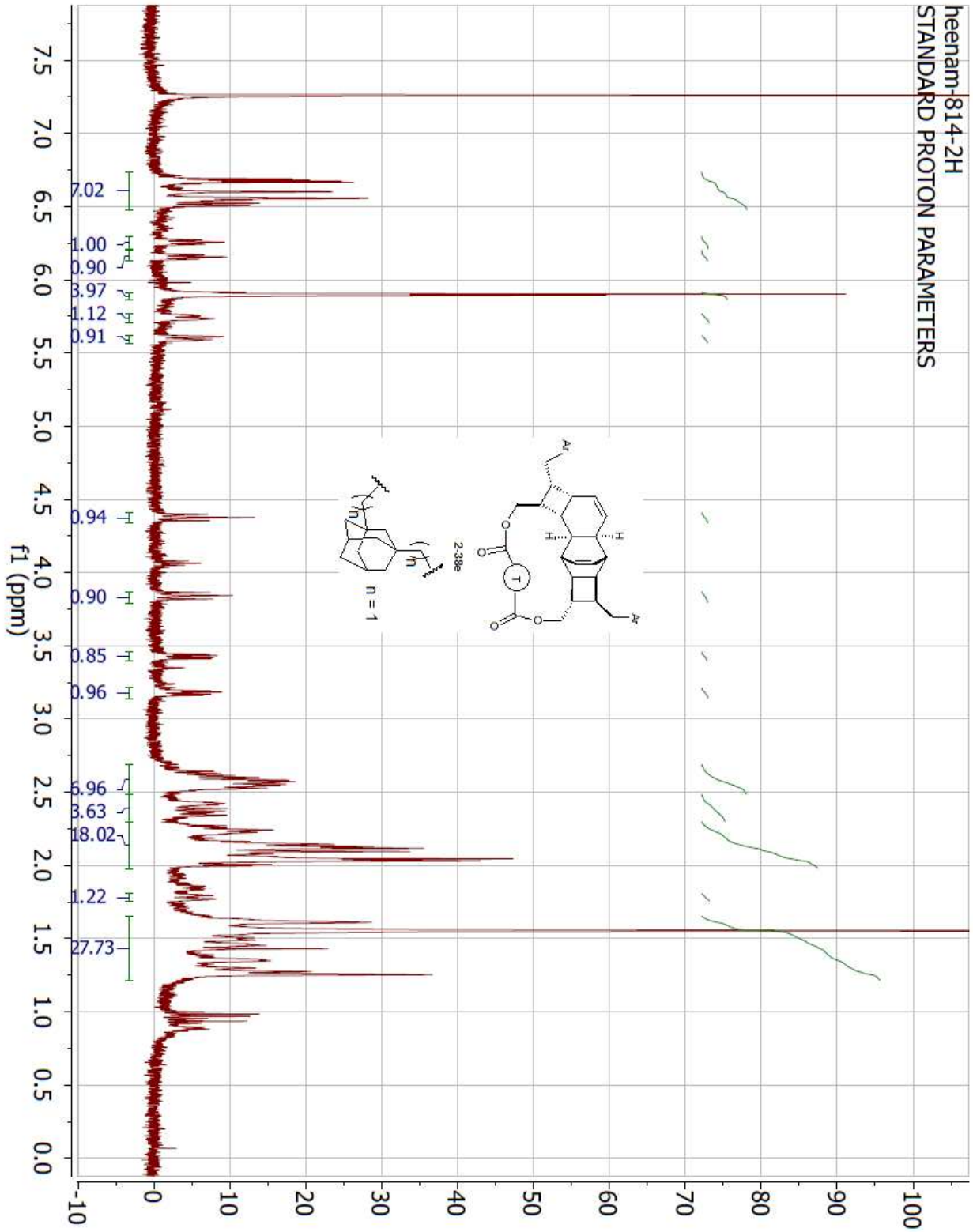

heenam-880-2-C13 1 1 /home/heenam/data
174.0599
173.3830
147.5793
147.5105
145.6550
145.5334
135.3153
135.0953
134.5409
132.0020
131.7628
124.8747
121.0312
120.9839
108.7546
108.7028
108.2088
108.1428
100.7262
68.9713
67.0137
44.0329
43.1271
41.1146
40.6828
40.2118
40.1654
39.5897
38.8171
38.7079
38.0622
36.5641
35.4900
35.0636
34.4883
32.5702
25.6840
25.4913
150
100
50
[ppm]
0.0
0.2
0.4
0.6
0.8
1.0
1.2
[rel]

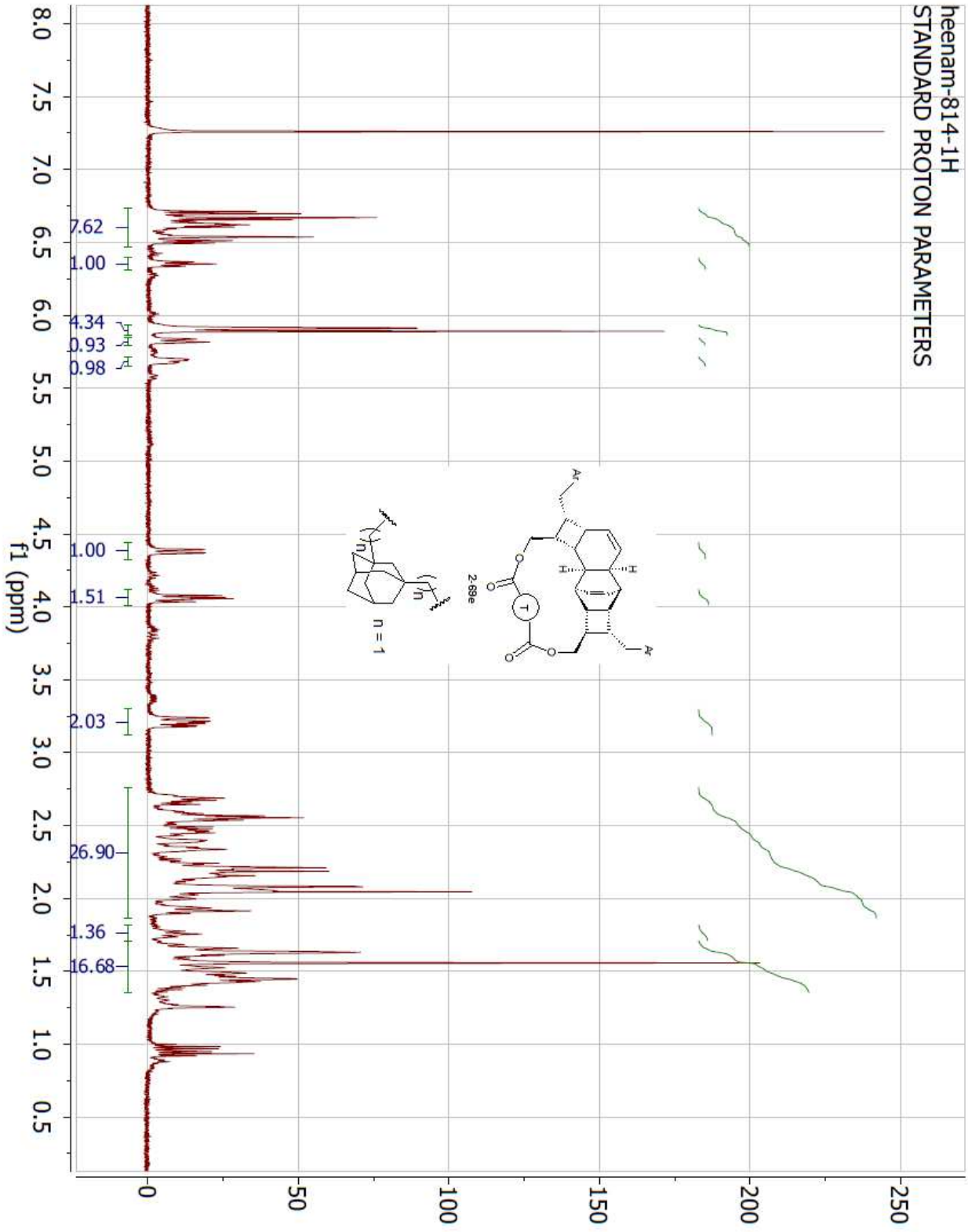

heenam-880-1-1 1 1 /home/heenam/data
5.2519
2.1080
0.9562
0.9659
1.0000
0.9765
0.9671
0.9534
0.9892
19.0829
4.4281
1.8642
1.1397
[ppm]
[rel]
0
5
10
15
2
4
6
8

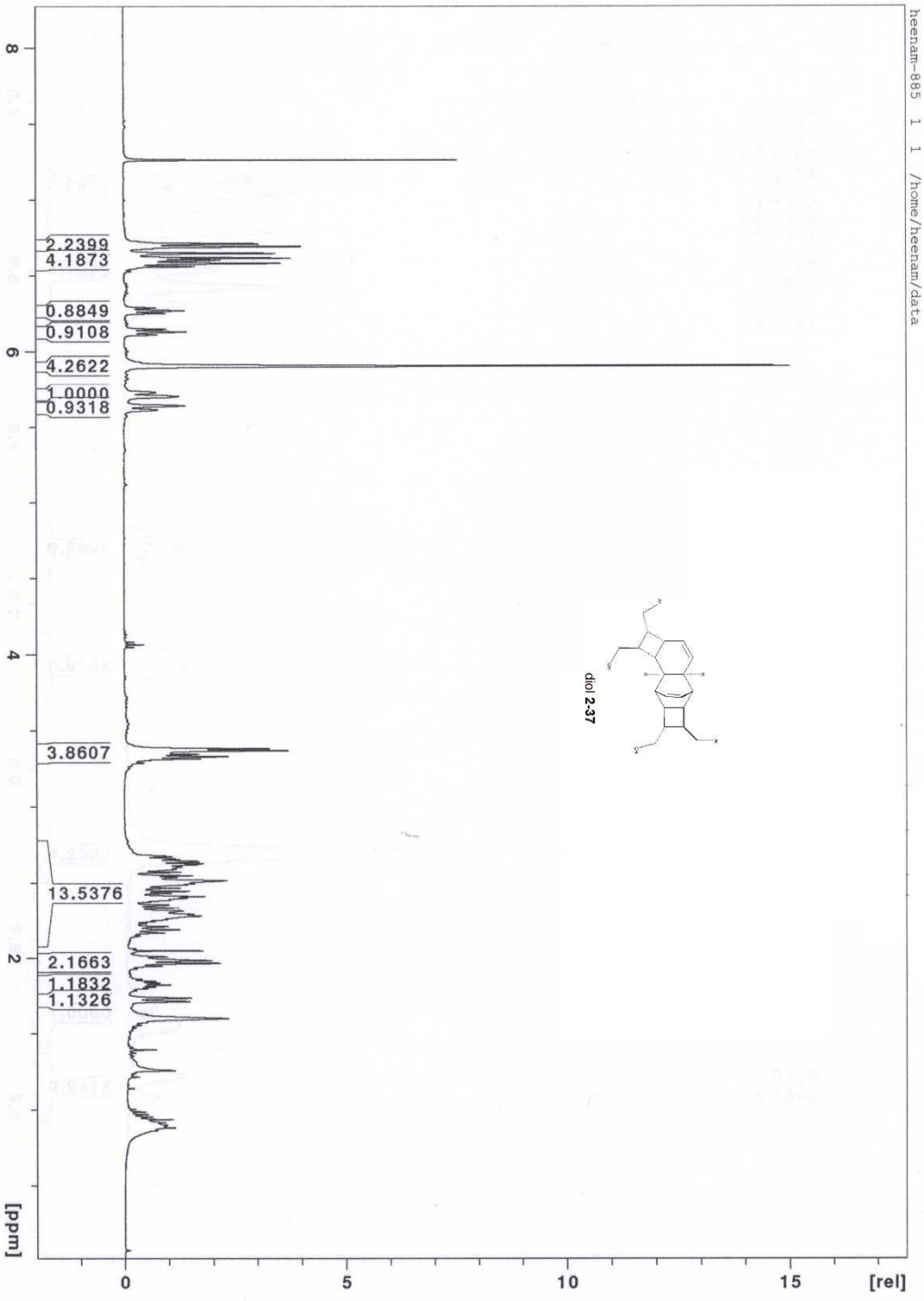

heenam-880-1-1-C13 1 1 /home/heenam/data
173.6745
173.5068
147.5748
147.4797
145.6024
145.5153
136.4930
135.0871
134.5070
131.0603
126.4210
121.0717
120.9468
108.8650
108.6666
108.1540
108.1245
100.7395
100.6821
67.8629
61.5047
46.3520
41.6896
41.0701
41.0207
37.0089
36.7477
35.9842
35.5594
35.1893
34.8595
34.0391
33.7223
33.6107
32.5455
26.5901
25.9565
150
100
50
[ppm]
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
[rel]

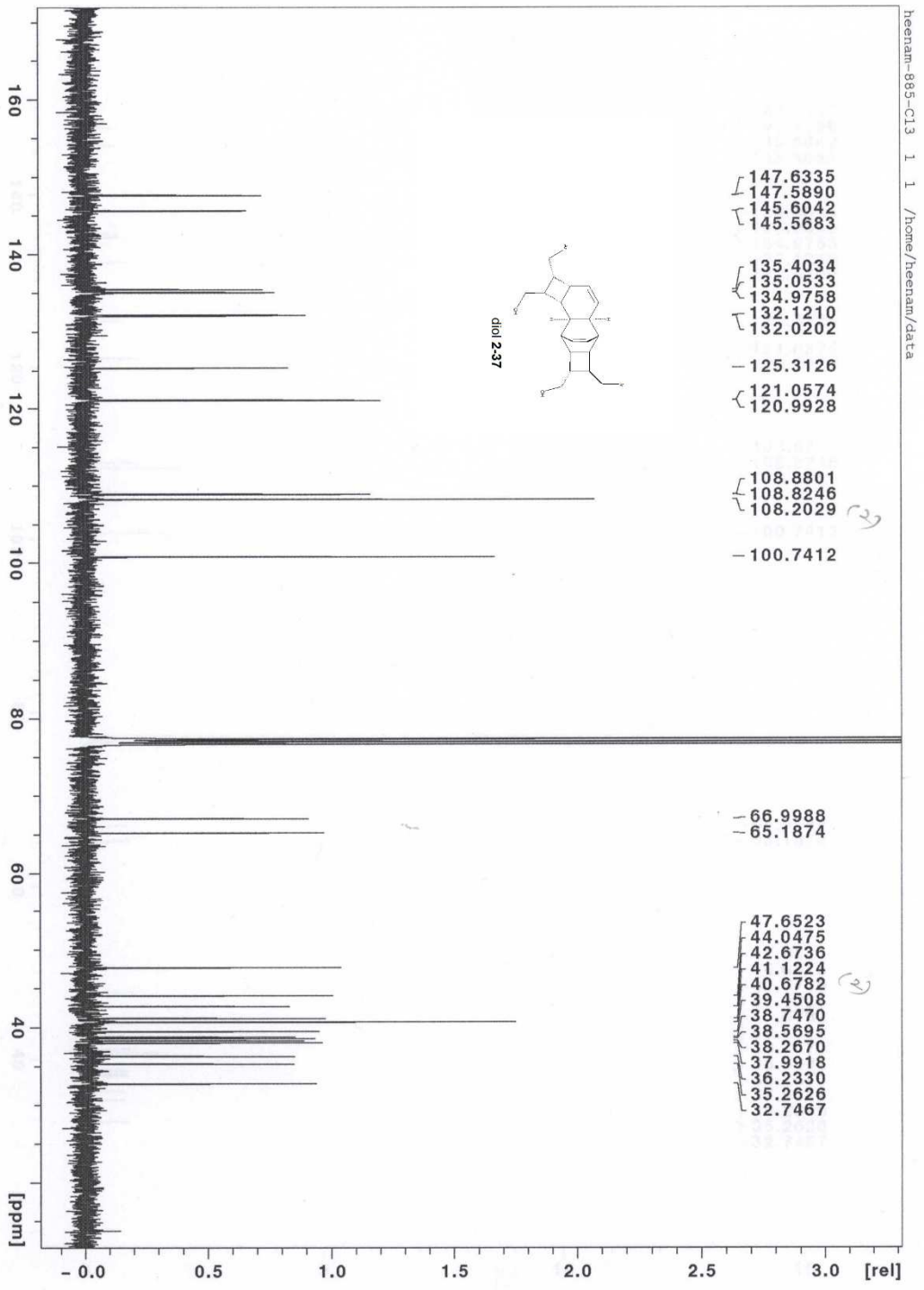

heenam-815-1H
STANDARD PROTON PARAMETERS
8.22
1.00
1.00
6.06
1.44
0.92
1.04
1.17
1.30
1.15
9.79
12.70
24.99
f1 (ppm)
n = 0
2-38d

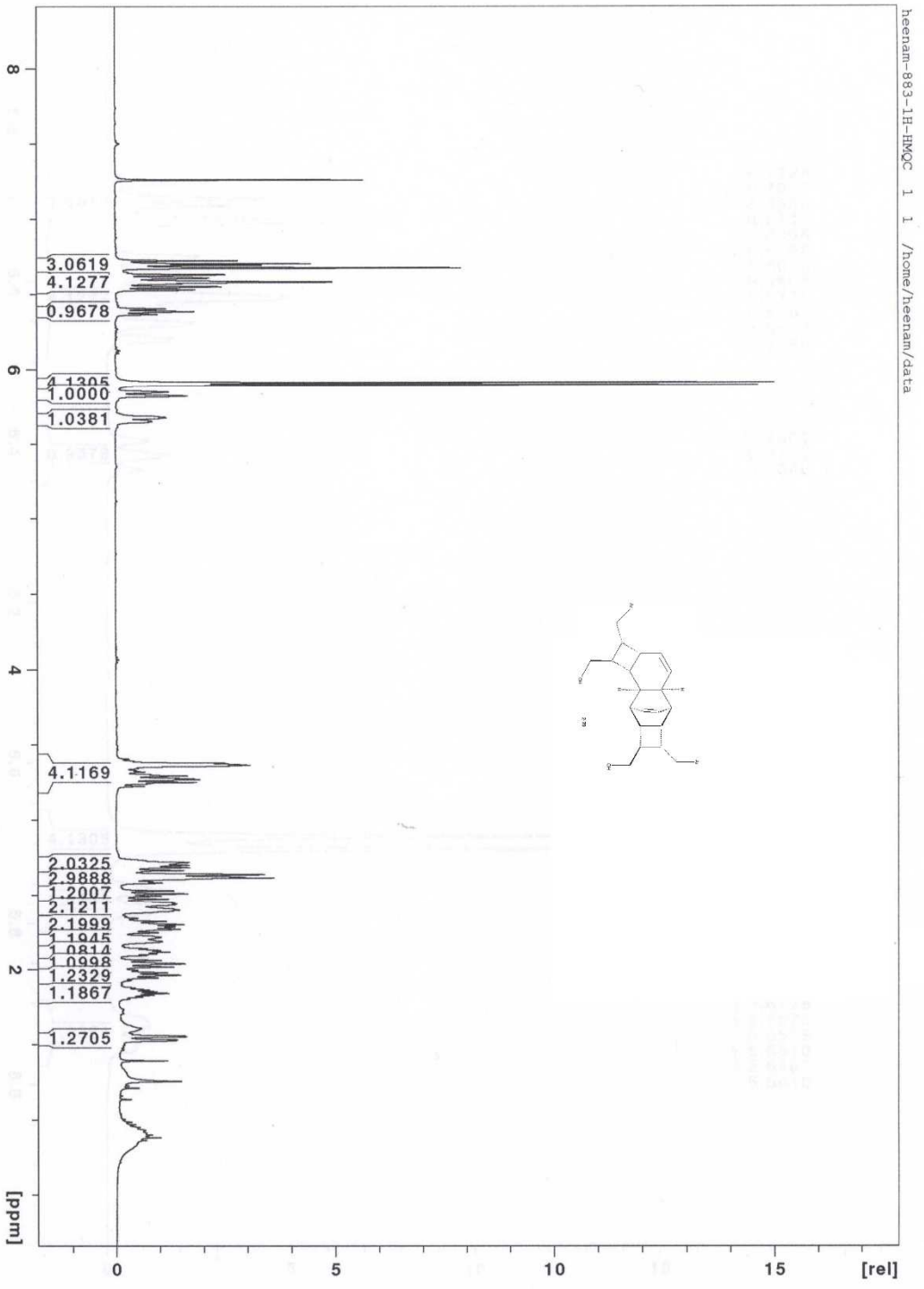

heenam-815-2H
STANDARD PROTON PARAMETERS
8.92
1.00
5.07
2.30
1.27
1.89
0.95
47.41
f1 (ppm)
n = 0
2-69d

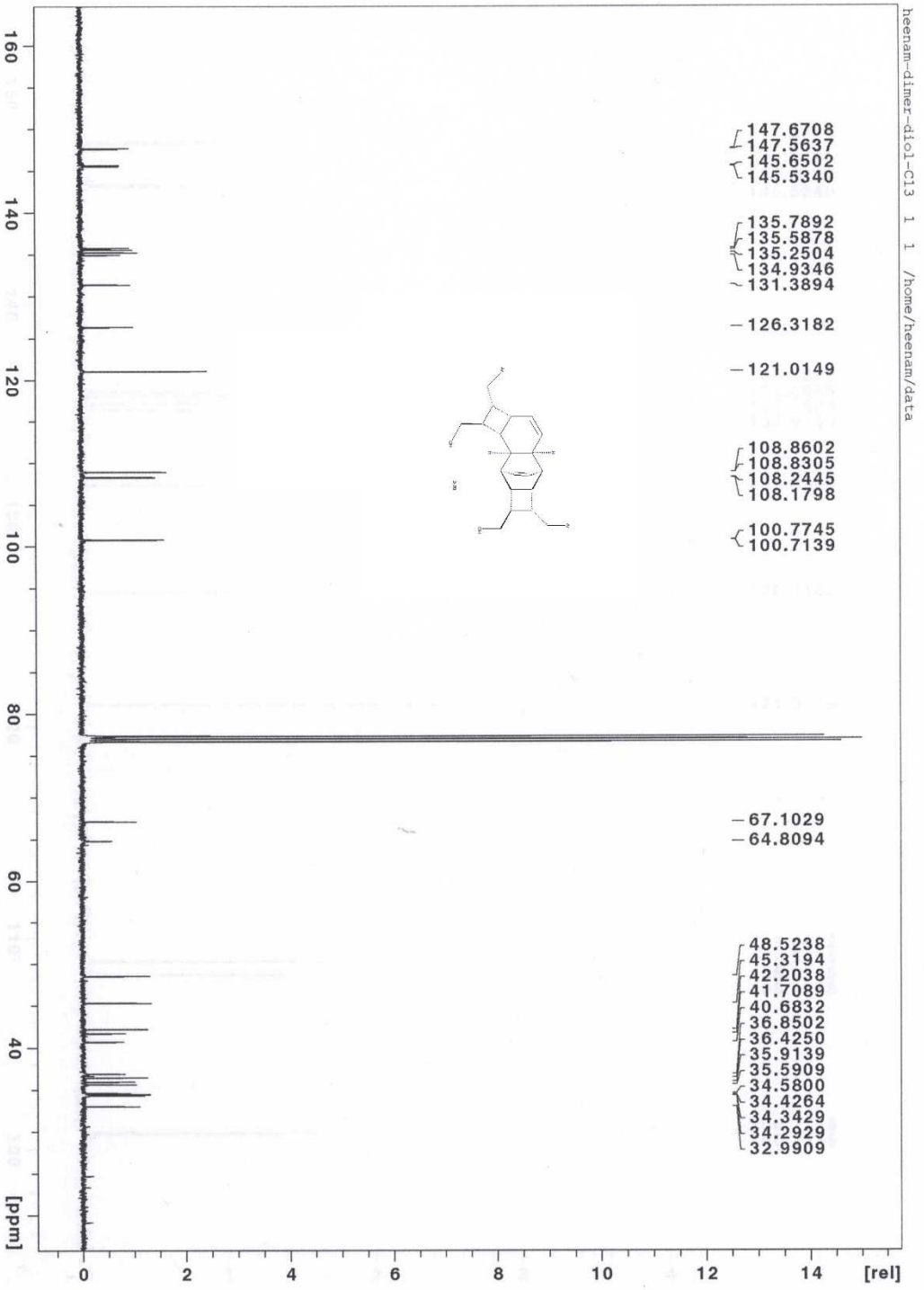

heenam-814-2H
STANDARD PROTON PARAMETERS
f1 (ppm)
7.02
1.00
0.90
3.97
1.12
0.91
0.94
0.90
0.85
0.96
6.96
3.63
18.02
1.22
27.73
n = 1
2-38e

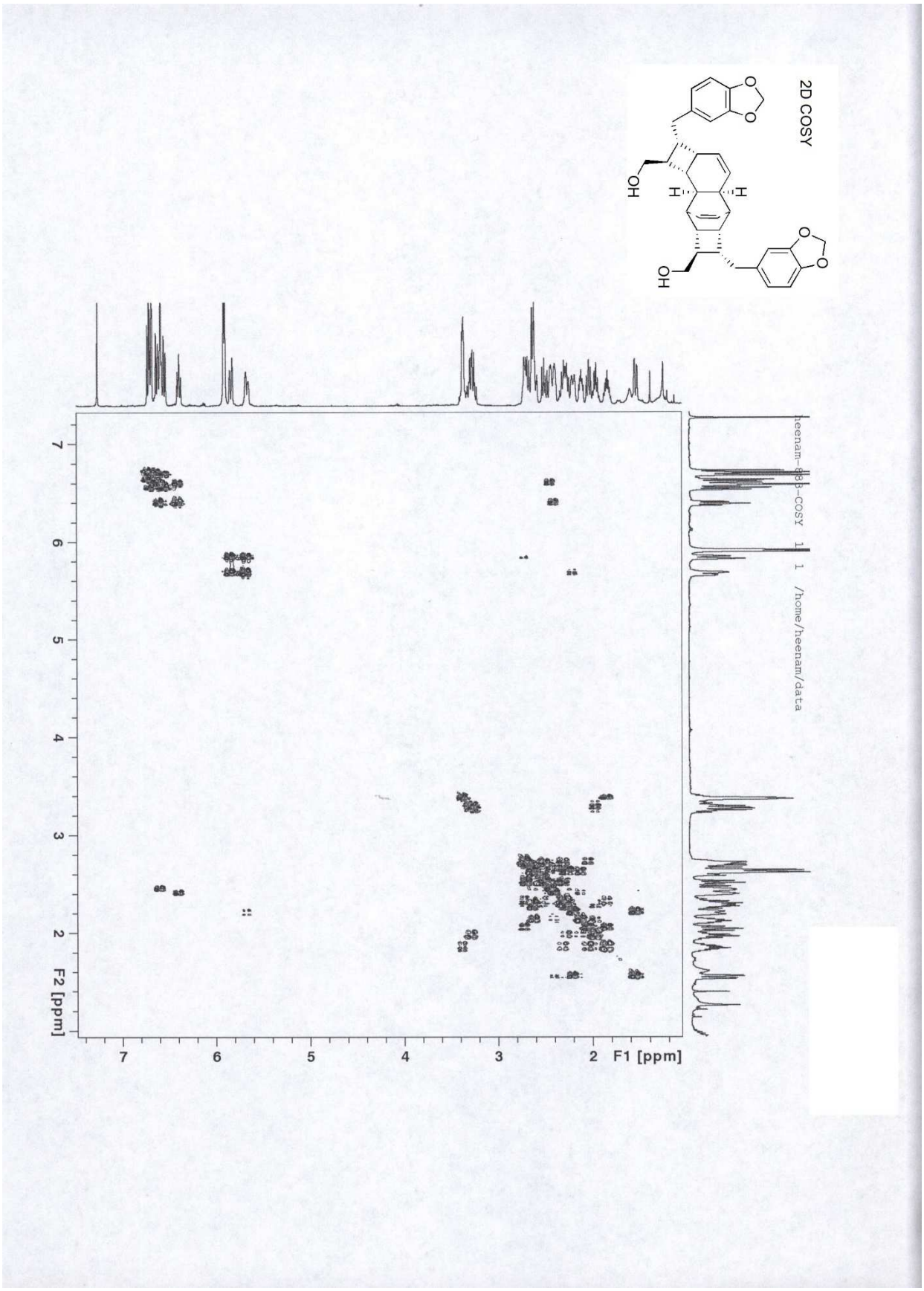

heenam-814-1H
STANDARD PROTON PARAMETERS
f1 (ppm)
7.62
1.00
4.34
0.93
0.98
1.00
1.51
2.03
26.90
1.36
16.68
n = 1
2-69e

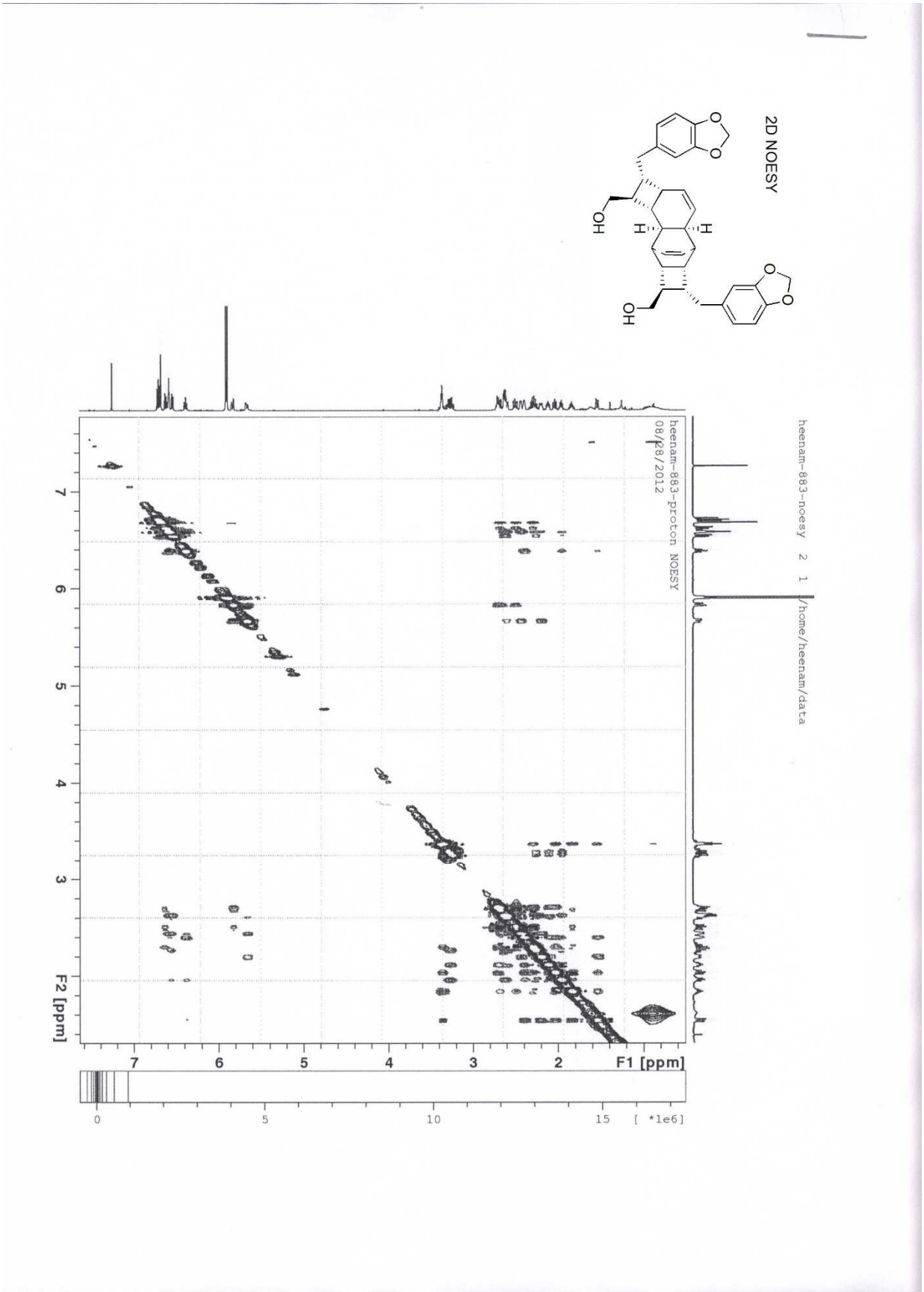

heenam-885 1 1 /home/heenam/data
2.2399
4.1873
0.8849
0.9108
4.2622
1.0000
0.9318
3.8607
13.5376
2.1663
1.1832
1.1326
diol 2-37
8
6
4
2
[ppm]
0
5
10
15
[rel]

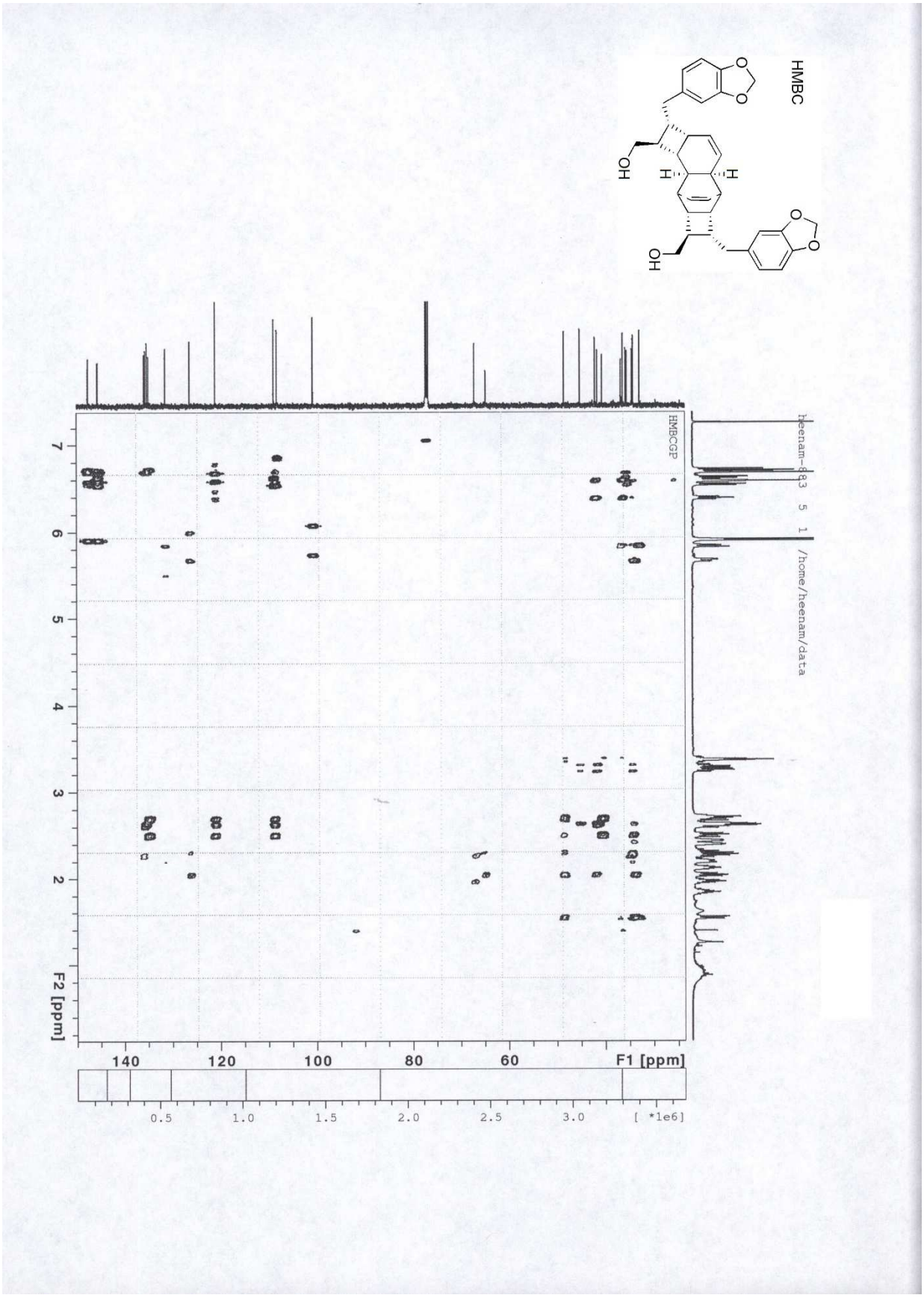

heenam-885-C13 1 1 /home/heenam/data
147.6335
147.5890
145.6042
145.5683
135.4034
135.0533
134.9758
132.1210
132.0202
125.3126
121.0574
120.9928
108.8801
108.8246
108.2029
100.7412
66.9988
65.1874
47.6523
44.0475
42.6736
41.1224
40.6782
39.4508
38.7470
38.5695
38.2670
37.9918
36.2330
35.2626
32.7467
diol 2-37
[ppm]
[rel]

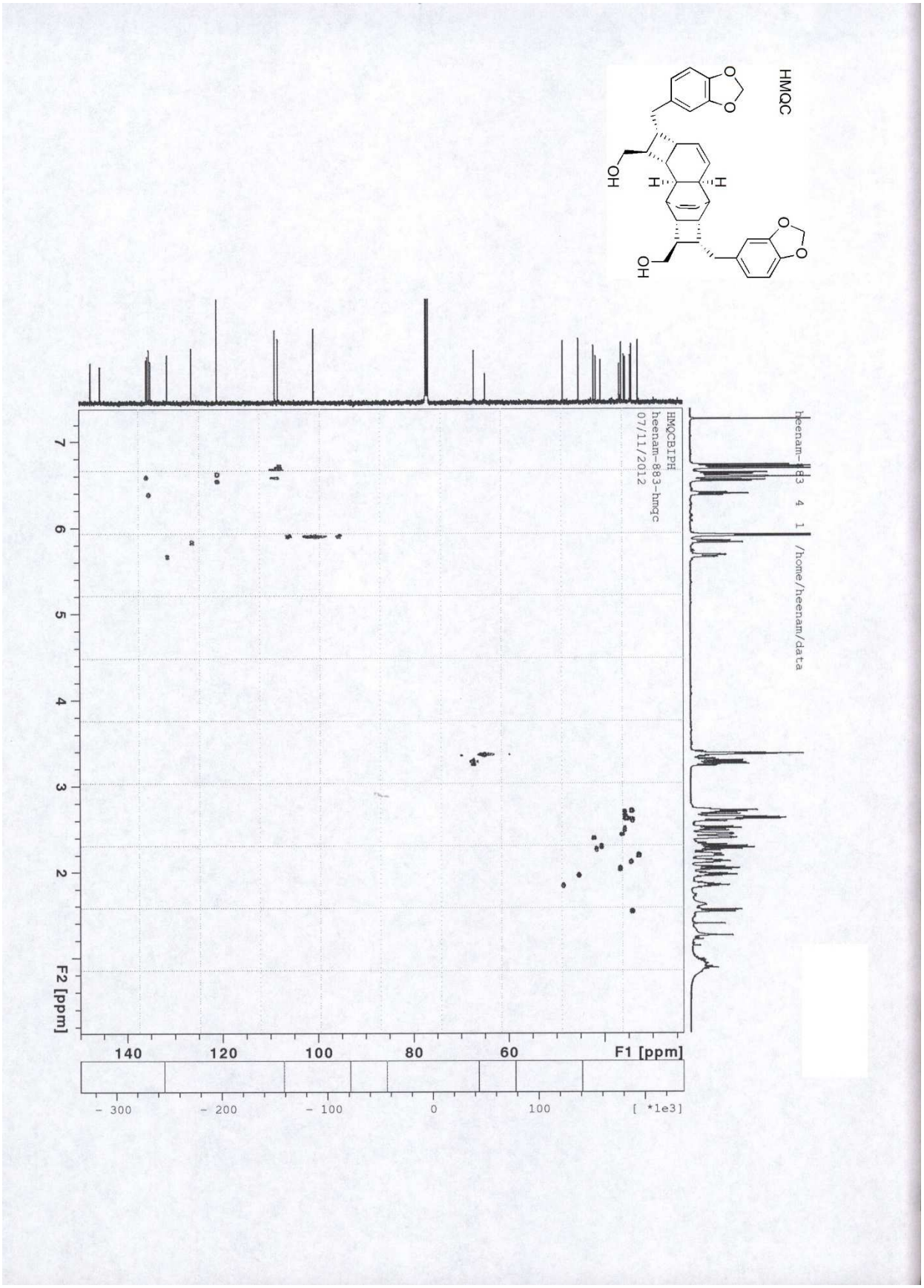

heenam-883-1H-HMQC 1 1 /home/heenam/data
3.0619
4.1277
0.9678
4.1305
1.0000
1.0381
4.1169
2.0325
2.9888
1.2007
2.1211
2.1999
1.1945
1.0814
1.0998
1.2329
1.1867
1.2705
[ppm]
[rel]

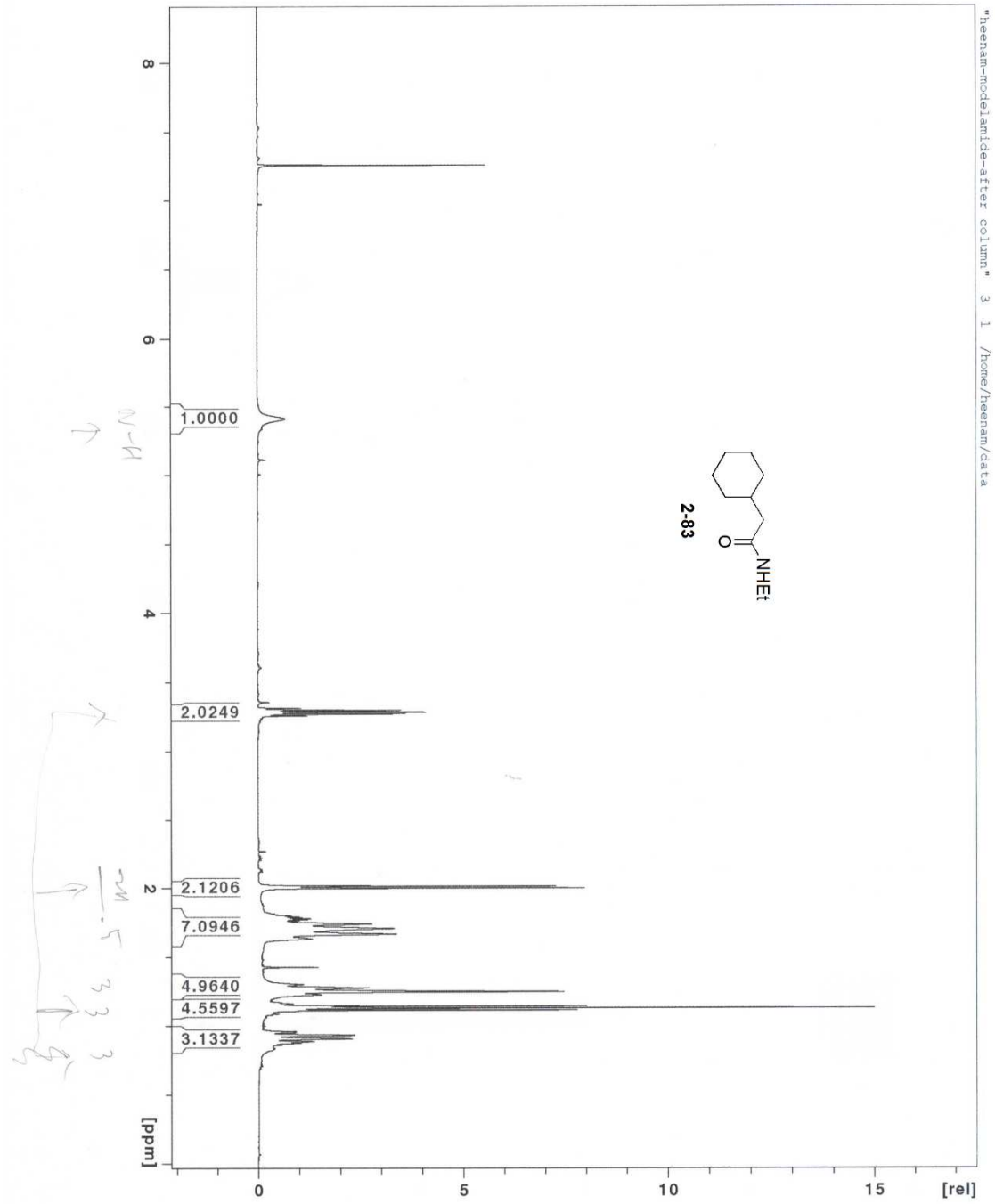

heenam-dimer-diol-C13 1 1 /home/heenam/data
147.6708
147.5637
145.6502
145.5340
135.7892
135.5878
135.2504
134.9346
131.3894
126.3182
121.0149
108.8602
108.8305
108.2445
108.1798
100.7745
100.7139
67.1029
64.8094
48.5238
45.3194
42.2038
41.7089
40.6832
36.8502
36.4250
35.9139
35.5909
34.5800
34.4264
34.3429
34.2929
32.9909
[ppm]
[rel]

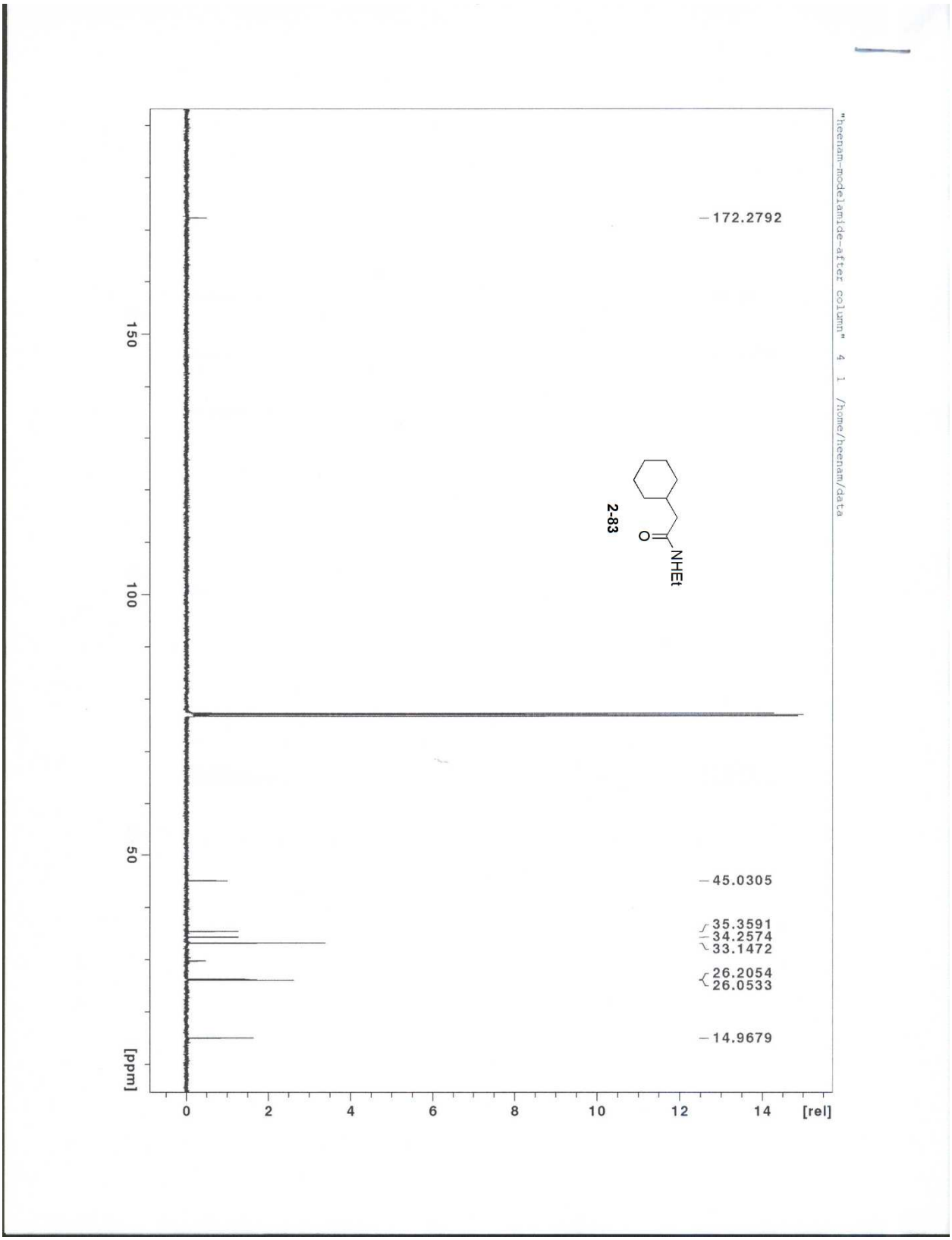

2D COSY
OH
H
H
O
O
O
O
OH
heenam-BB-COSY 1 1 /home/heenam/data
F2 [ppm]
F1 [ppm]
7
6
5
4
3
2

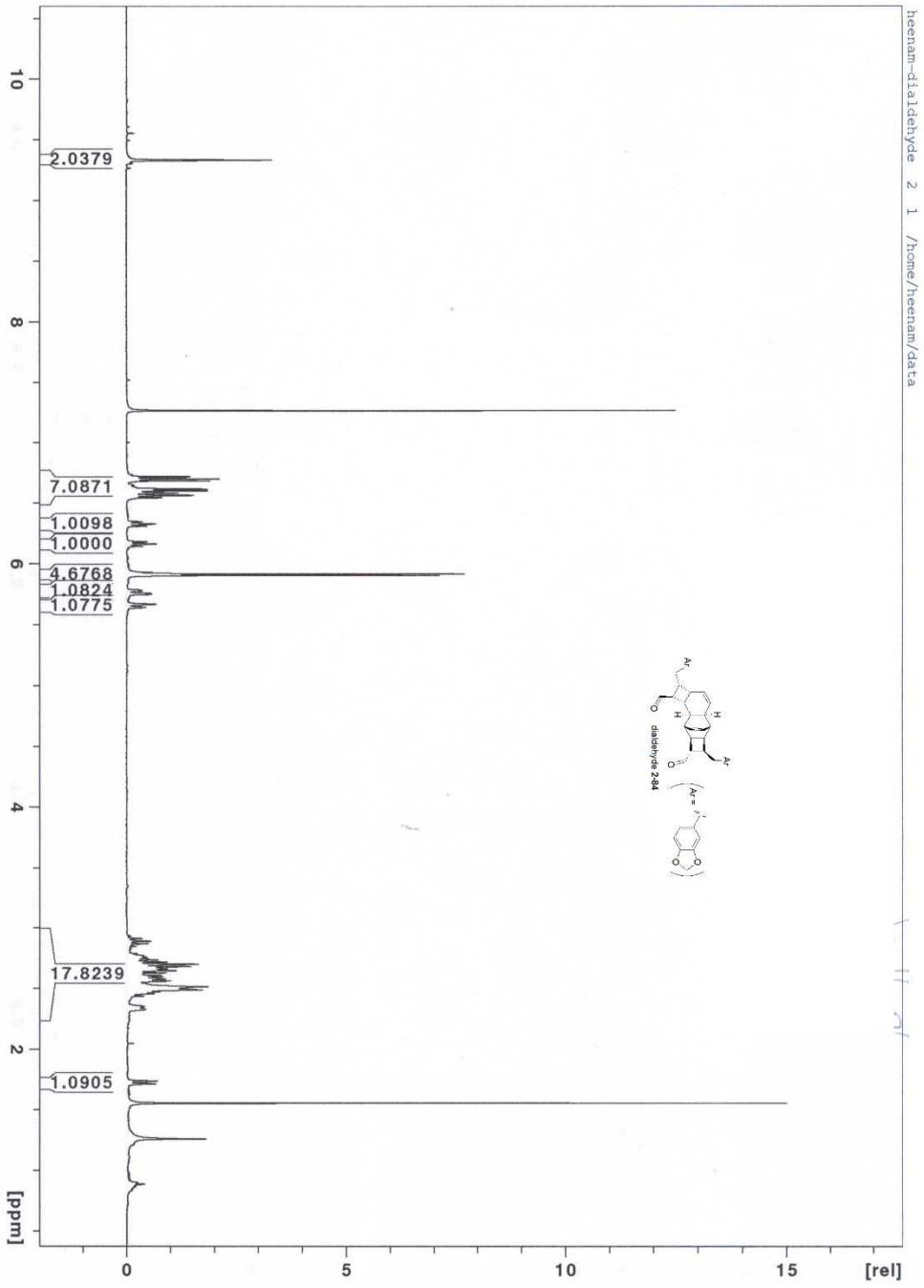

2D NOESY
heenam-883-noesy 2 1 /home/heenam/data
heenam-883-proton NOESY
08/28/2012
F2 [ppm]
F1 [ppm]
7
6
5
4
3
2
0
5
10
15
[*1e6]

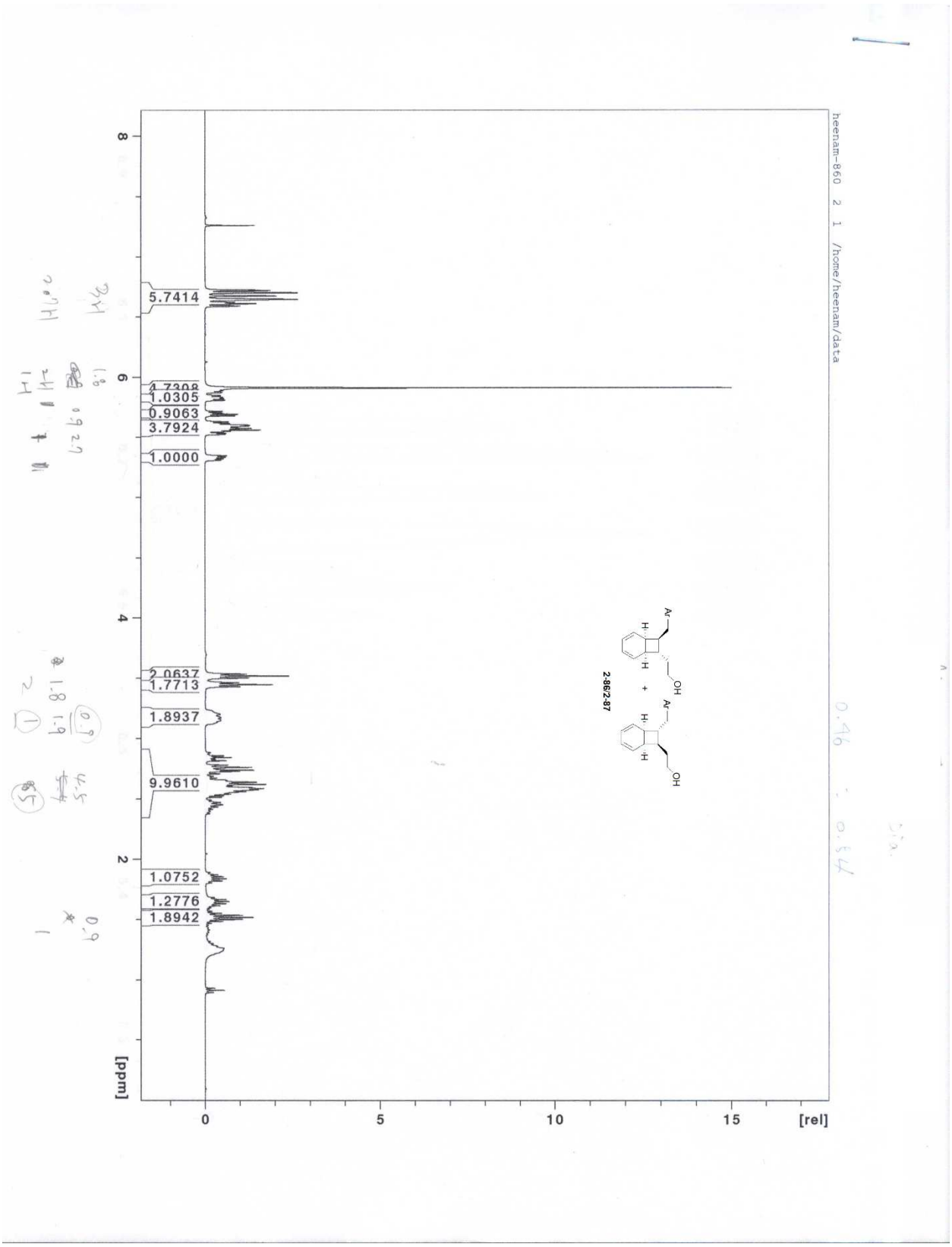

HMBC
HO
H
H
HO
O
O
O
O
HMBCGP
heenam-83 5 1
/home/heenam/data
F2 [ppm]
F1 [ppm]
140
120
100
80
60
0.5
1.0
1.5
2.0
2.5
3.0
[*1e6]

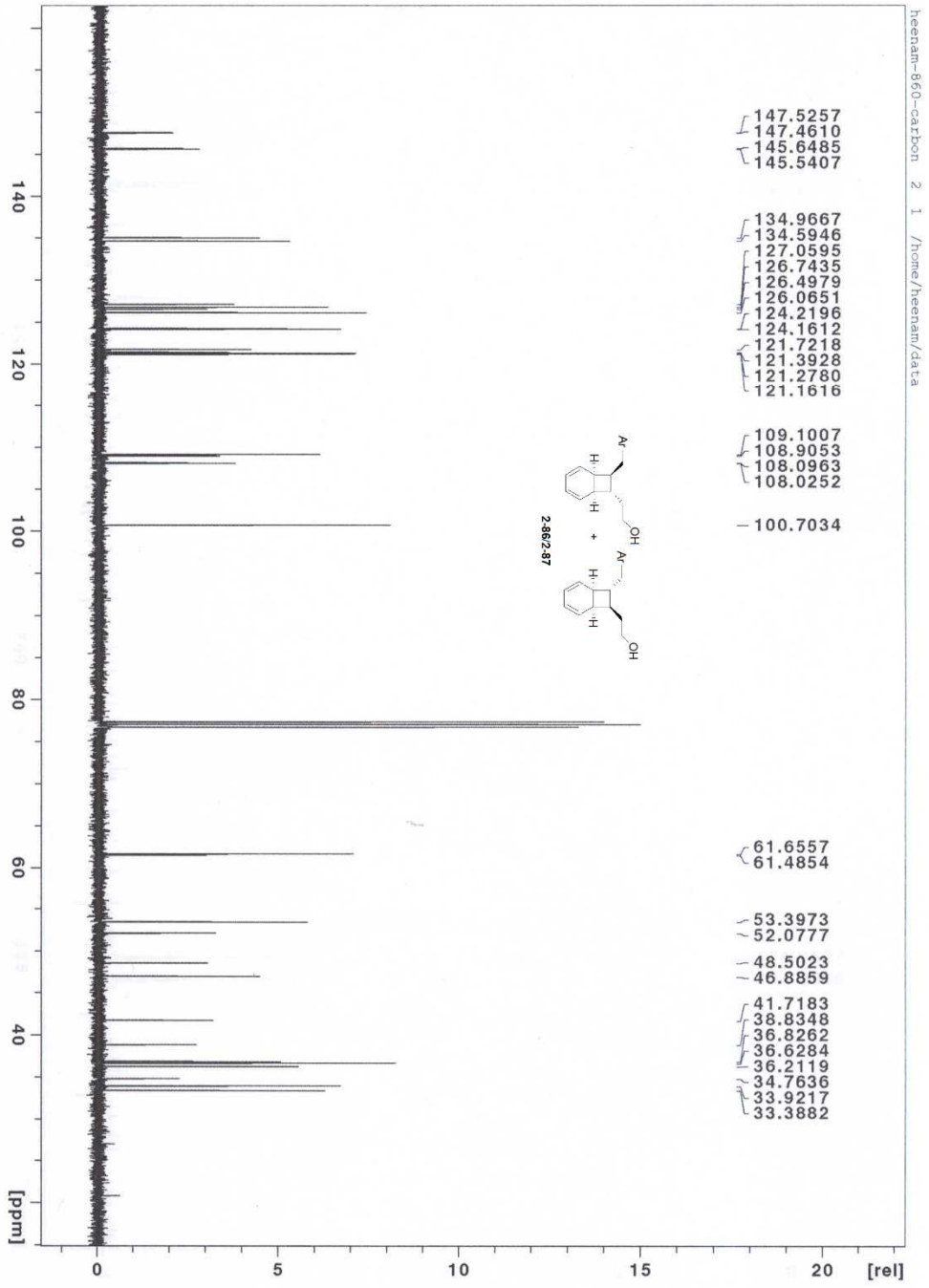

HMQC
OH
H
H
OH
HMQCBIPH
heenam-883-hmqc
07/11/2012
heenam-883 4 1 /home/heenam/data
F2 [ppm]
F1 [ppm]
140
120
100
80
60
- 300
- 200
- 100
0
100
[*1e3]

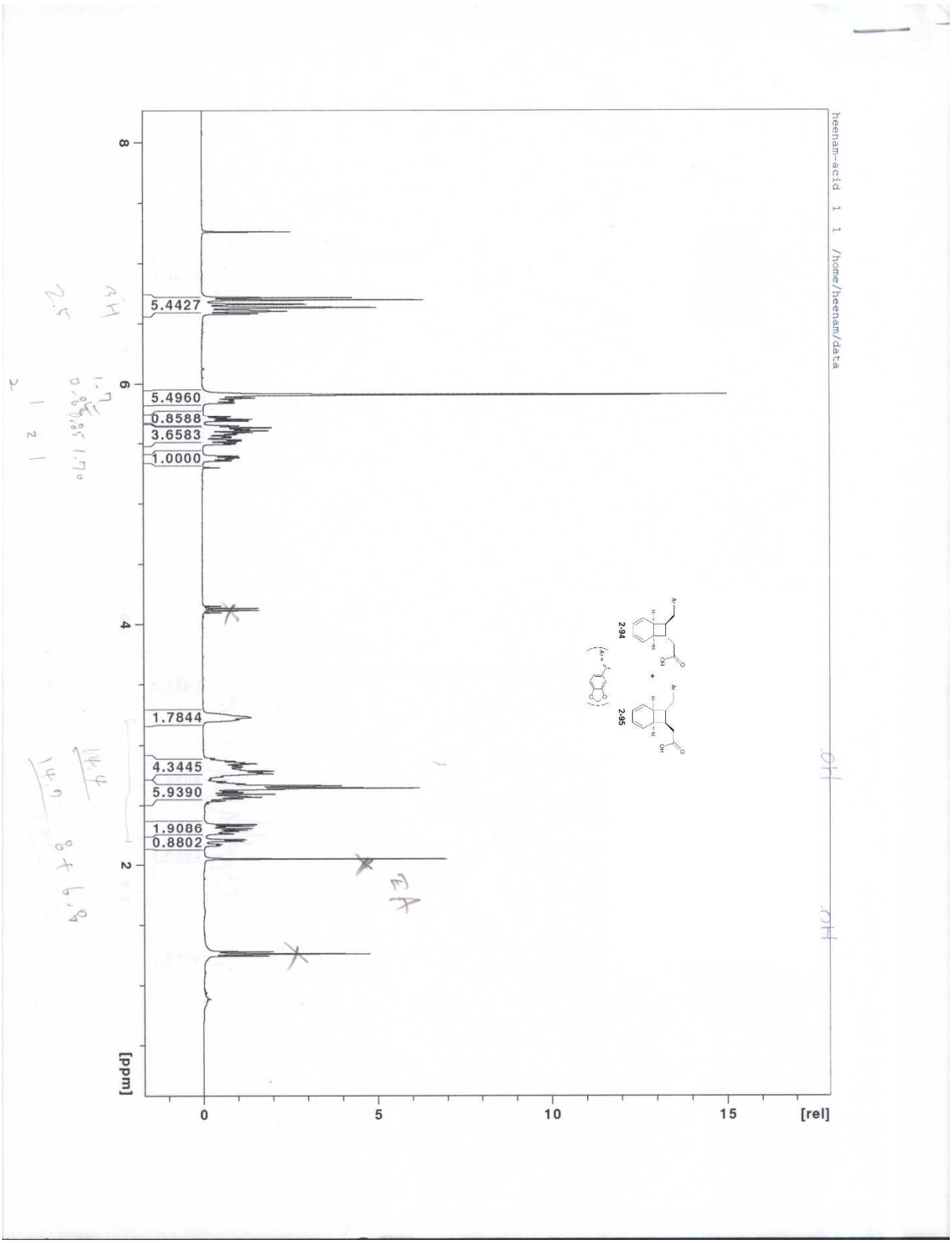

"heenam-modelamide-after column" 3 1 /home/heenam/data
2-83
NHEt
O
1.0000
2.0249
2.1206
7.0946
4.9640
4.5597
3.1337
8
6
4
2
[ppm]
0
5
10
15
[rel]

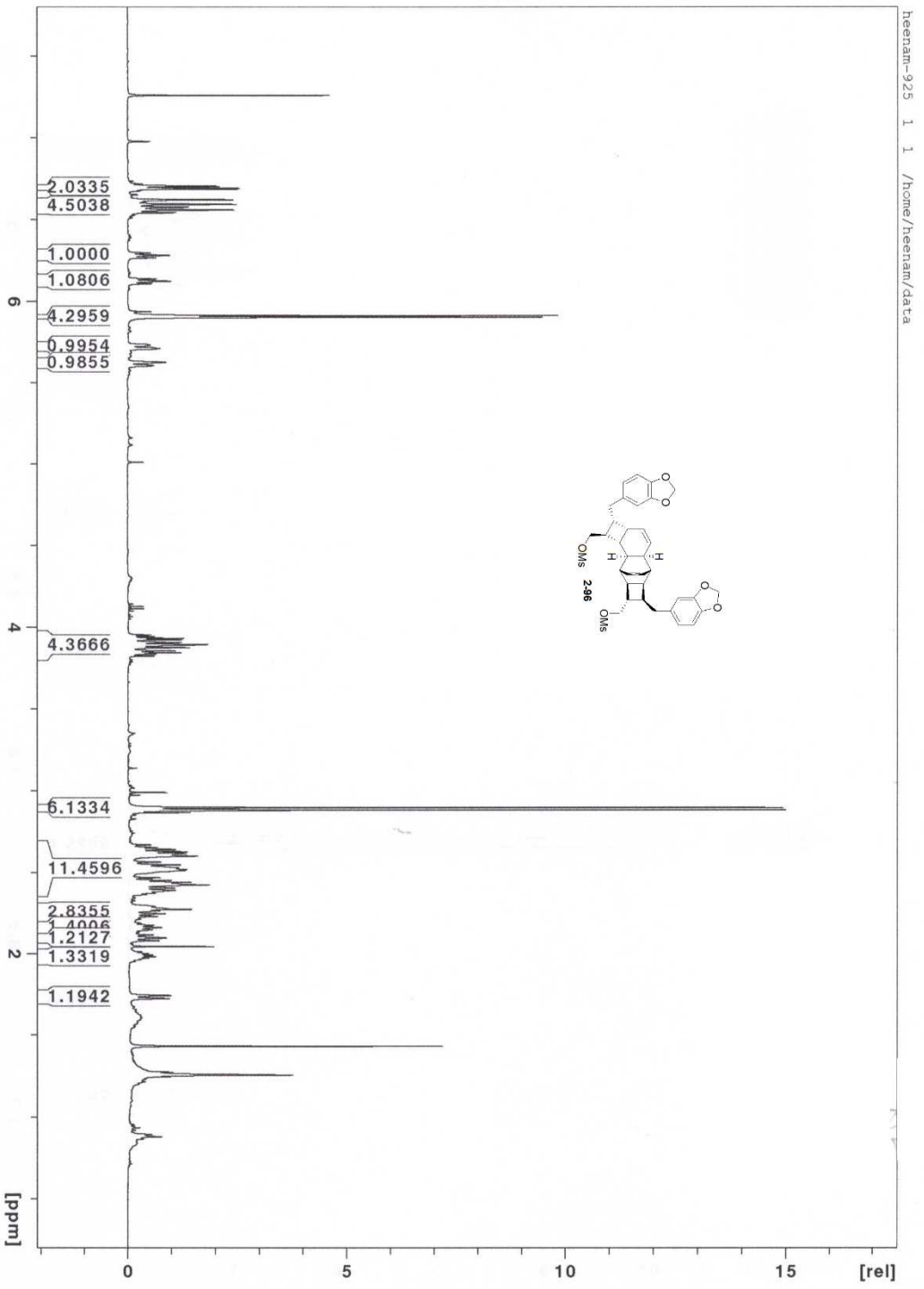

"heenam-modelamide-after column" 4 1 /home/heenam/data
172.2792
45.0305
35.3591
34.2574
33.1472
26.2054
26.0533
14.9679
2-83
NHEt
O
150
100
50
[ppm]
0
2
4
6
8
10
12
14
[rel]

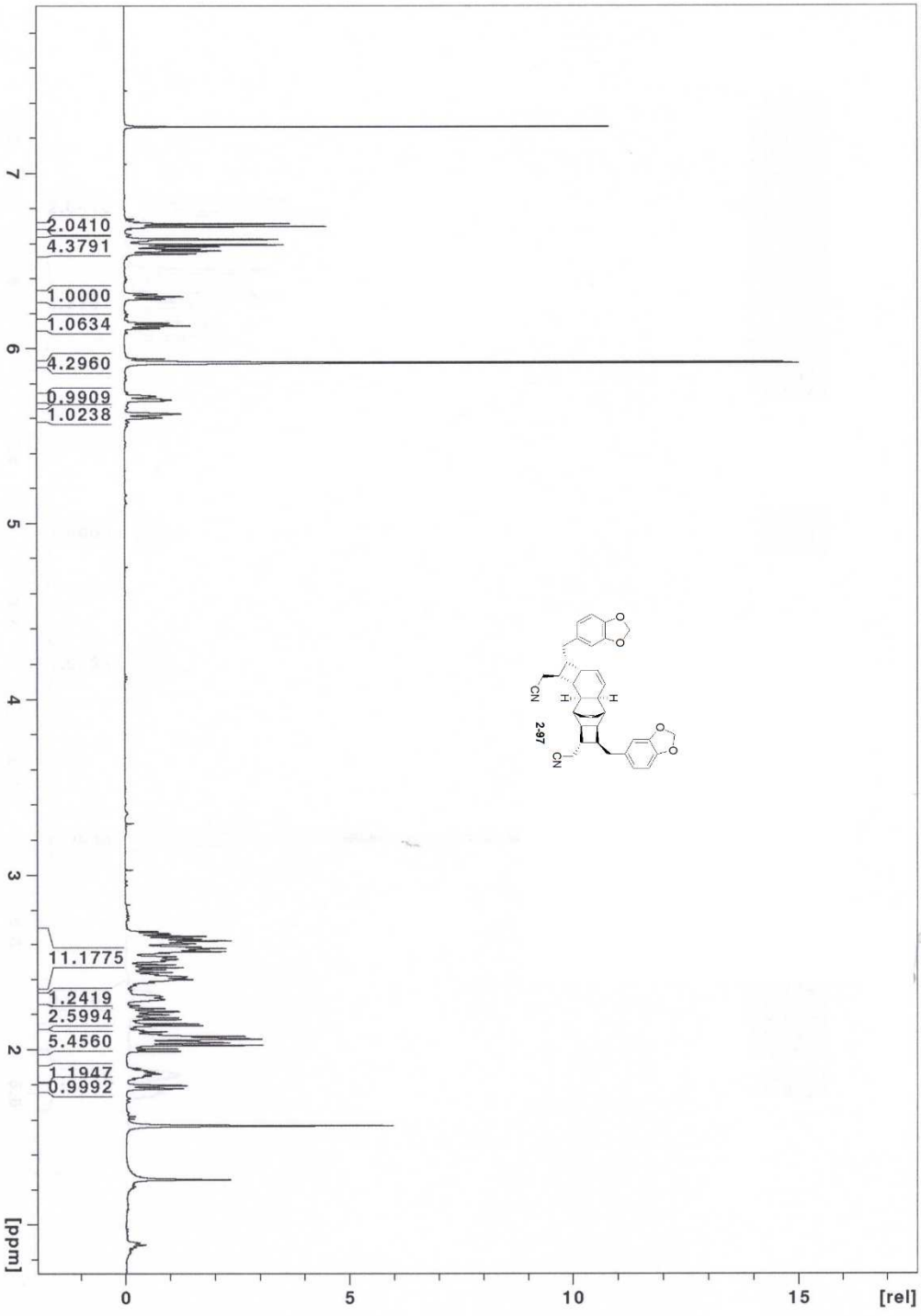

heenam-dialdehyde 2 1 /home/heenam/data
2.0379
7.0871
1.0098
1.0000
4.6768
1.0824
1.0775
17.8239
1.0905
10
8
6
4
2
[ppm]
0
5
10
15
[rel]
dialdehyde 2-94

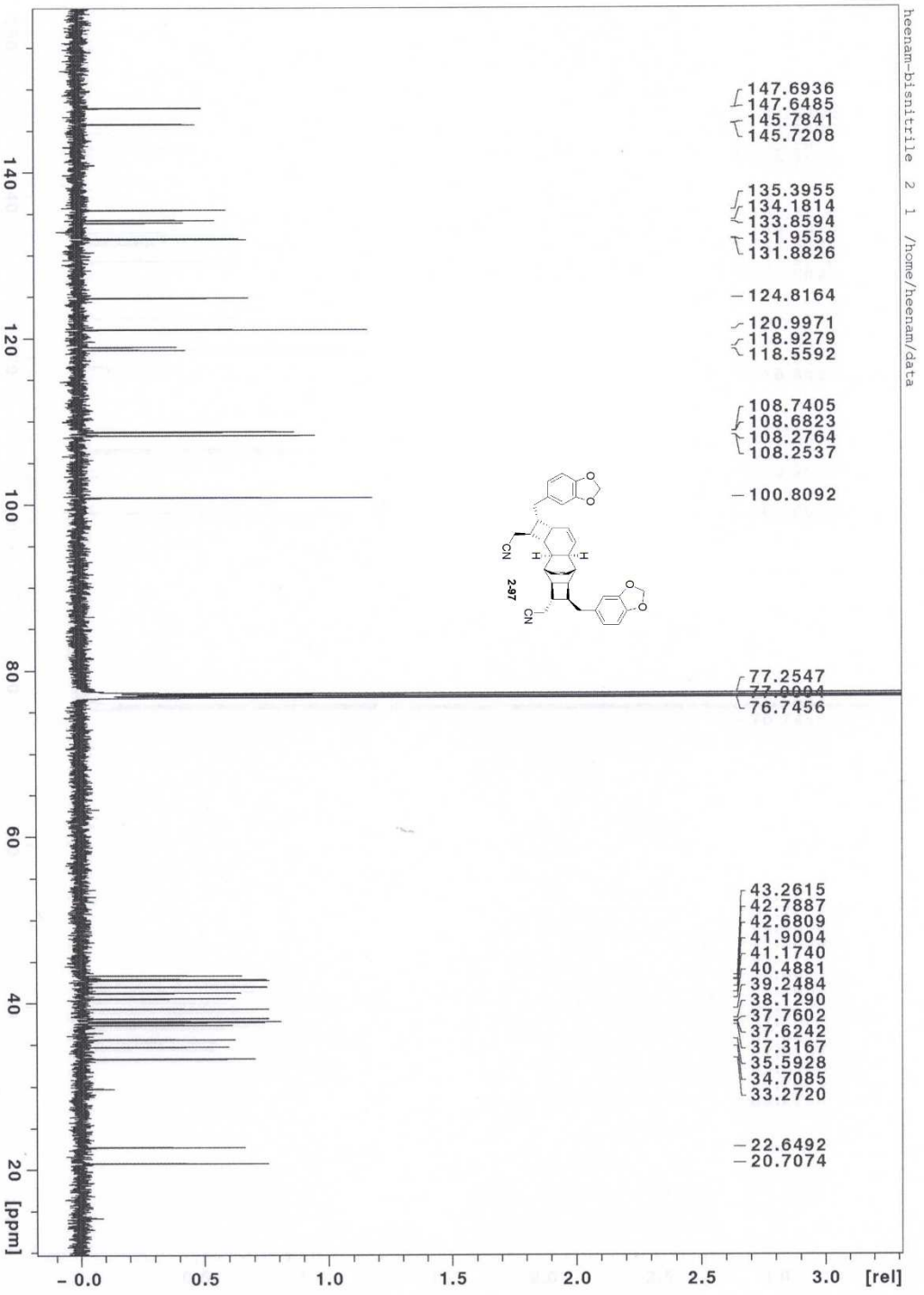

heenam-860 2 1 /home/heenam/data
5.7414
1.7308
1.0305
0.9063
3.7924
1.0000
2.0637
1.7713
1.8937
9.9610
1.0752
1.2776
1.8942
[ppm]
0
5
10
15
[rel]
2-86/2-87
Ar
OH
H
+

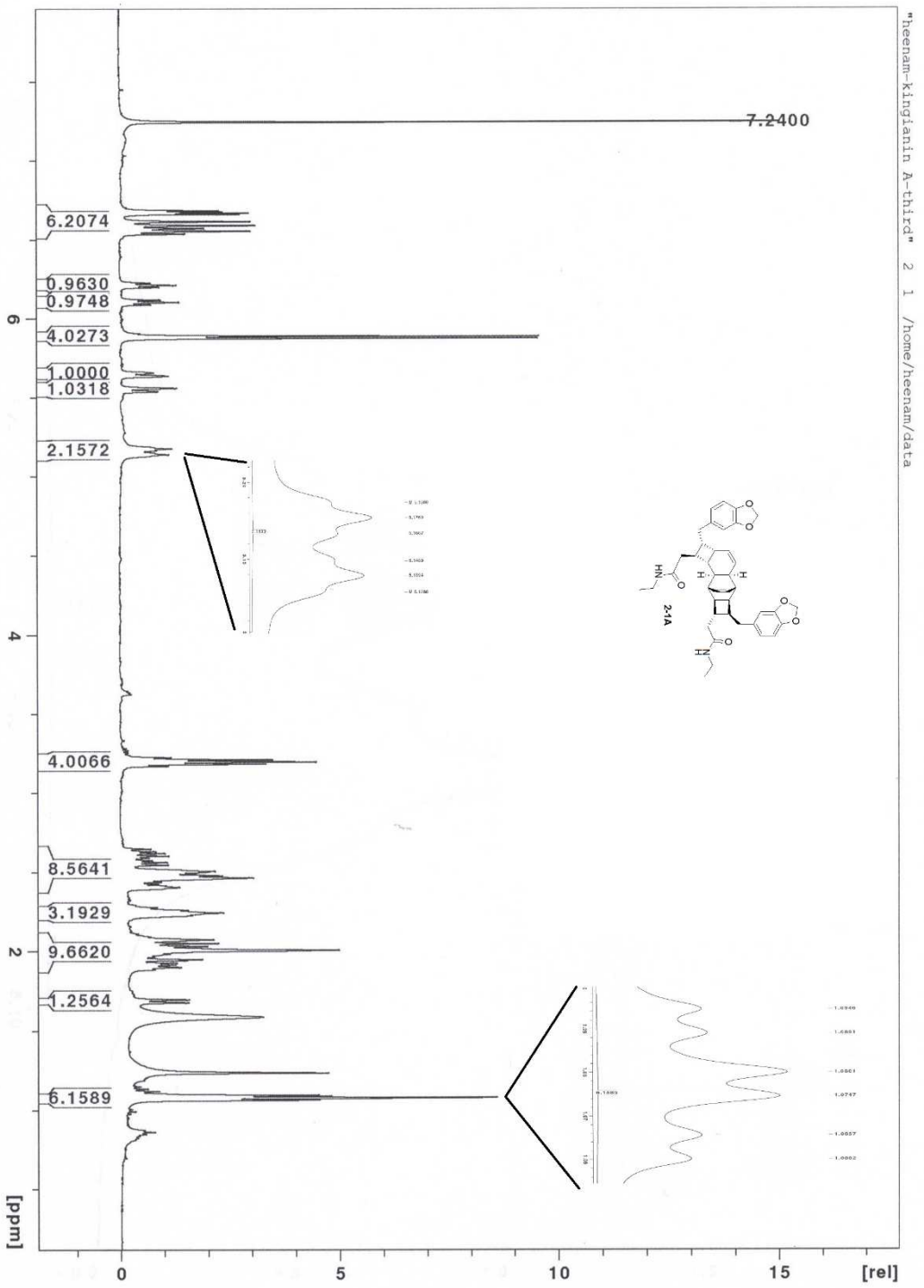

heenam-860-carbon 2 1 /home/heenam/data
147.5257
147.4610
145.6485
145.5407
134.9667
134.5946
127.0595
126.7435
126.4979
126.0651
124.2196
124.1612
121.7218
121.3928
121.2780
121.1616
109.1007
108.9053
108.0963
108.0252
100.7034
61.6557
61.4854
53.3973
52.0777
48.5023
46.8859
41.7183
38.8348
36.8262
36.6284
36.2119
34.7636
33.9217
33.3882
2-862-87
Ar
OH
[ppm]
[rel]
0
5
10
15
20
40
60
80
100
120
140

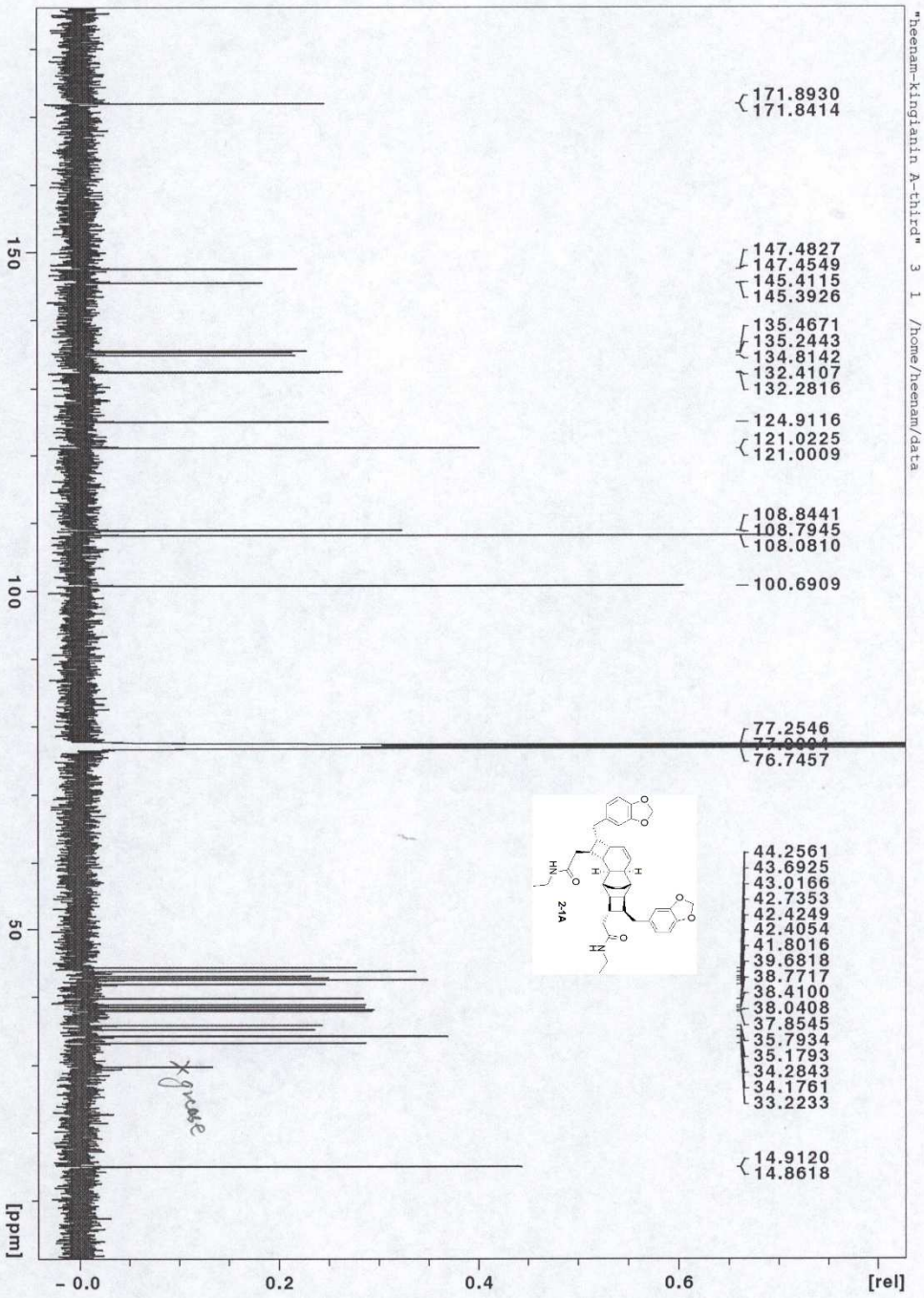

heenam-acid 1 1 /home/heenam/data
5.4427
5.4960
0.8588
3.6583
1.0000
1.7844
4.3445
5.9390
1.9086
0.8802
[ppm]
[rel]
0
5
10
15
2
4
6
8
2.94
2.95


heenam-925 1 1 /home/heenam/data
2.0335
4.5038
1.0000
1.0806
4.2959
0.9954
0.9855
4.3666
6.1334
11.4596
2.8355
1.4006
1.2127
1.3319
1.1942
OMs
2-96
OMs
6
4
2
[ppm]
0
5
10
15
[rel]


heenam-bisnitrile 1 1 /home/heenam/data
2.0410
4.3791
1.0000
1.0634
4.2960
0.9909
1.0238
11.1775
1.2419
2.5994
5.4560
1.1947
0.9992
[ppm]
[rel]
CN
H
H
2-97
CN


heenam-bisnitrile 2 1 /home/heenam/data
147.6936
147.6485
145.7841
145.7208
135.3955
134.1814
133.8594
131.9558
131.8826
124.8164
120.9971
118.9279
118.5592
108.7405
108.6823
108.2764
108.2537
100.8092
77.2547
77.0004
76.7456
43.2615
42.7887
42.6809
41.9004
41.1740
40.4881
39.2484
38.1290
37.7602
37.6242
37.3167
35.5928
34.7085
33.2720
22.6492
20.7074
CN
CN
H
H
297
140
120
100
80
60
40
20
[ppm]
0.0
0.5
1.0
1.5
2.0
2.5
3.0
[rel]


"heenam-kingianin A-third" 2 1 /home/heenam/data
7.2400
6.2074
0.9630
0.9748
4.0273
1.0000
1.0318
2.1572
4.0066
8.5641
3.1929
9.6620
1.2564
6.1589
2-1A
[ppm]
[rel]
0
5
10
15
2
4
6


"heenam-kinglanin A-third" 3 1 /home/heenam/data
171.8930
171.8414
147.4827
147.4549
145.4115
145.3926
135.4671
135.2443
134.8142
132.4107
132.2816
124.9116
121.0225
121.0009
108.8441
108.7945
108.0810
100.6909
77.2546
76.7457
44.2561
43.6925
43.0166
42.7353
42.4249
42.4054
41.8016
39.6818
38.7717
38.4100
38.0408
37.8545
35.7934
35.1793
34.2843
34.1761
33.2233
14.9120
14.8618
2-1A
grease
150
100
50
[ppm]
0.0
0.2
0.4
0.6
[rel]

STANDARD PROTON PARAMETERS

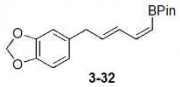
Data Collected on:
inv500-inova500
Archive directory:
/export/home/heenam/vnmrsys/data
Sample directory:

File: PROTON

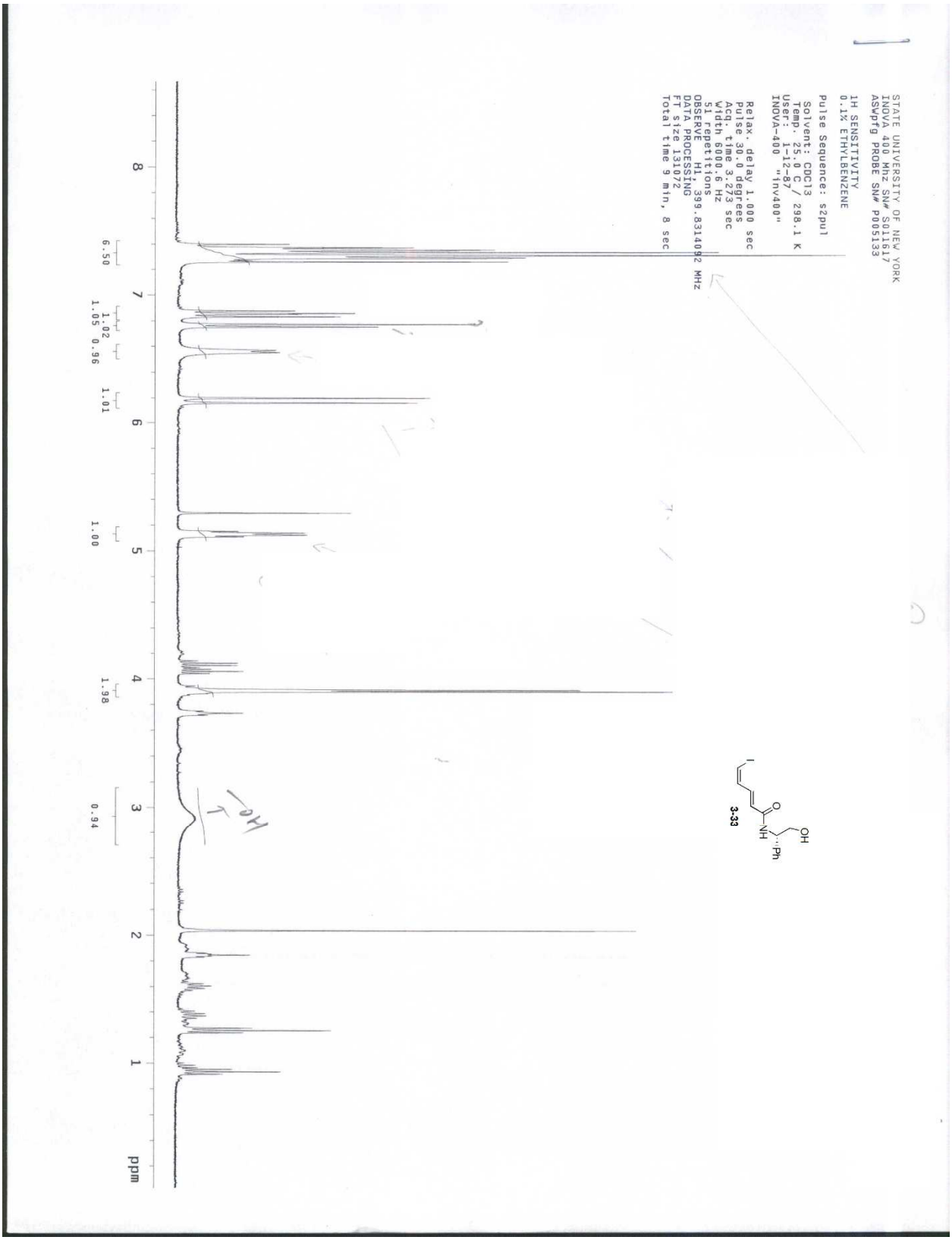
Pulse Sequence: s2pul
Solvent: CDCl3

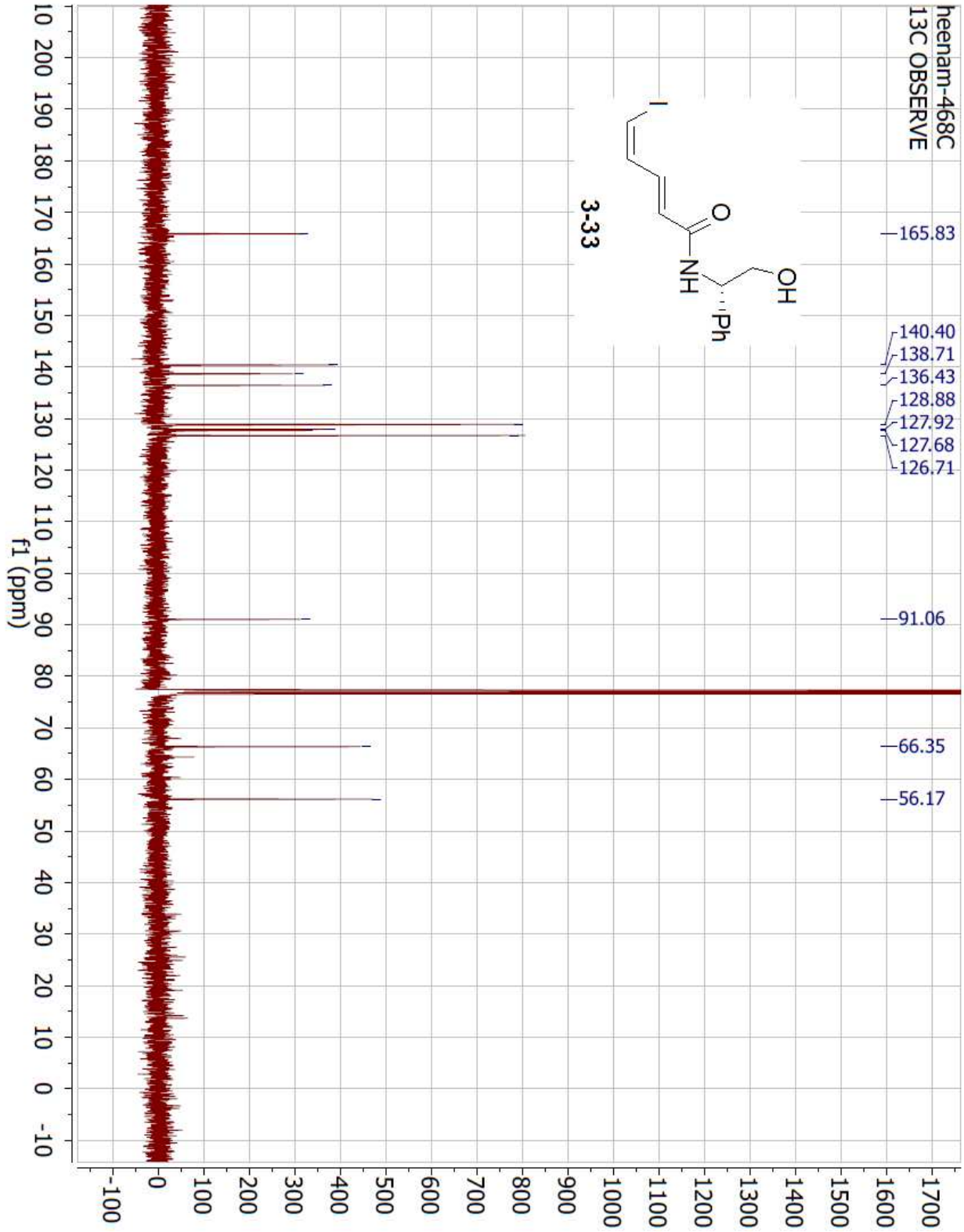
Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7998.4 Hz
33 repetitions
OBSERVE H1, 499.8948175 MHz
DATA PROCESSING
FT size 32768
Total time 6 min



3-32


STATE UNIVERSITY OF NEW YORK
INOVA 400 MHz SN# S01617
ASWPFG PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-12-87
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.273 sec
Width 6000.6 Hz
51 repetitions
OBSERVE H1, 399.8314092 MHz
DATA PROCESSING
FT size 131072
Total time 9 min, 8 sec
3-33
OH
NH
Ph
8
7
6
5
4
3
2
1
ppm
6.50
1.02
1.05
0.96
1.01
1.00
1.98
0.94


heenam-468C
13C OBSERVE
3-33
I
O
NH
OH
Ph
165.83
140.40
138.71
136.43
128.88
127.92
127.68
126.71
91.06
66.35
56.17
f1 (ppm)

STANDARD PROTON PARAMETERS

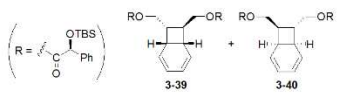
Data Collected on:
inv500-inova500
Archive directory:
/export/home/heenam/vnmrsys/data
Sample directory:

File: PROTON

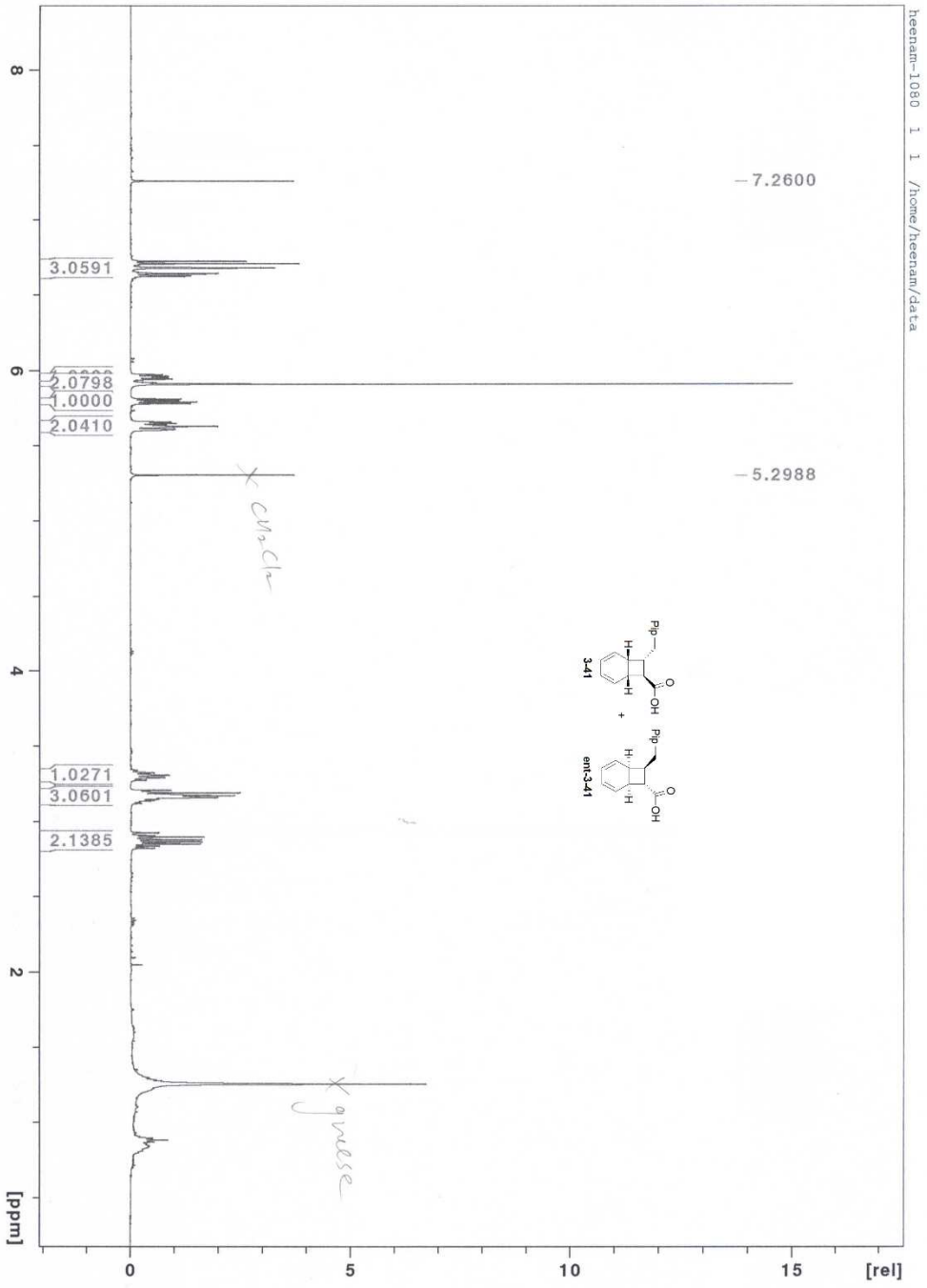
Pulse Sequence: s2pul
Solvent: CDCl3

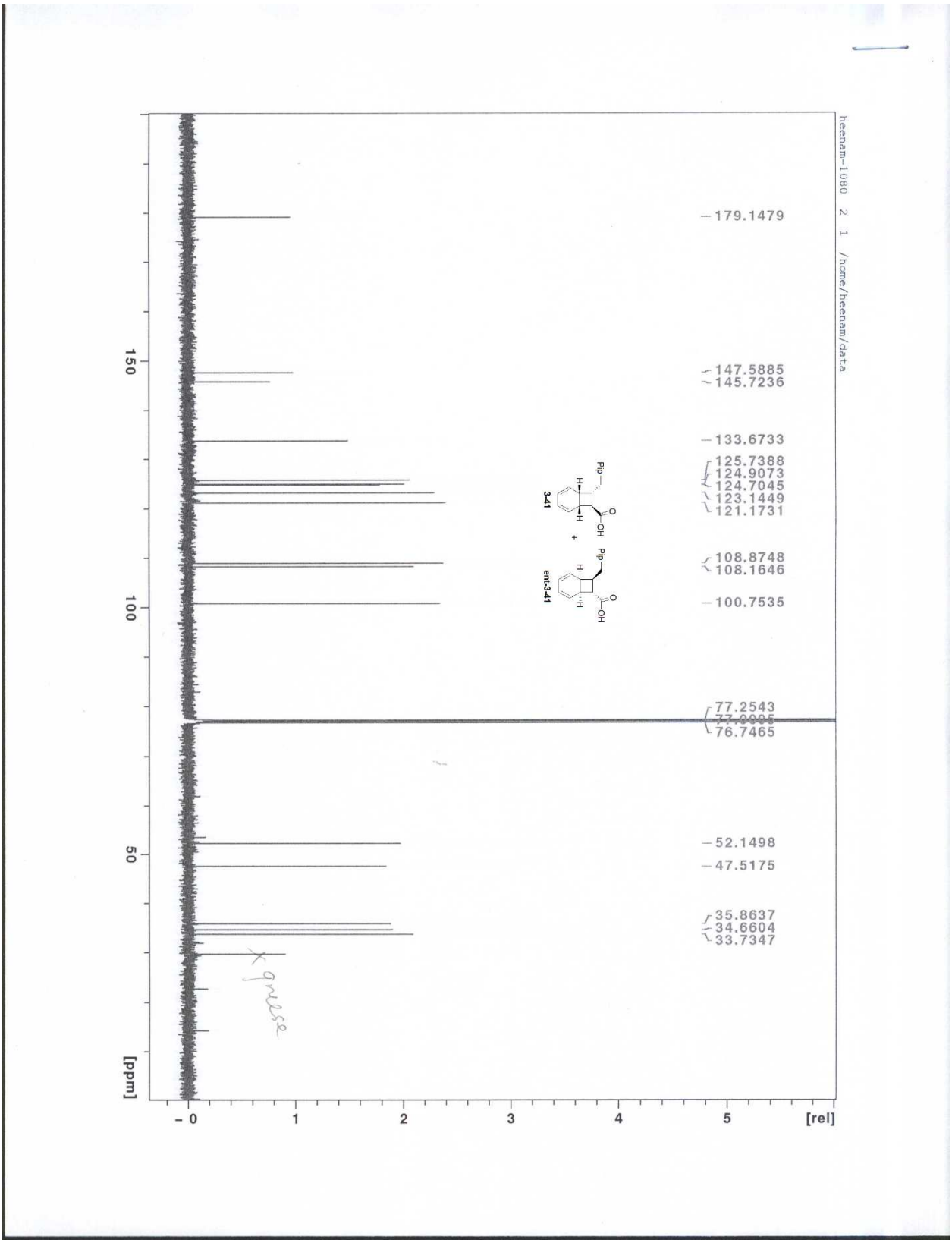
Temp. 25.0 C / 298.1 K

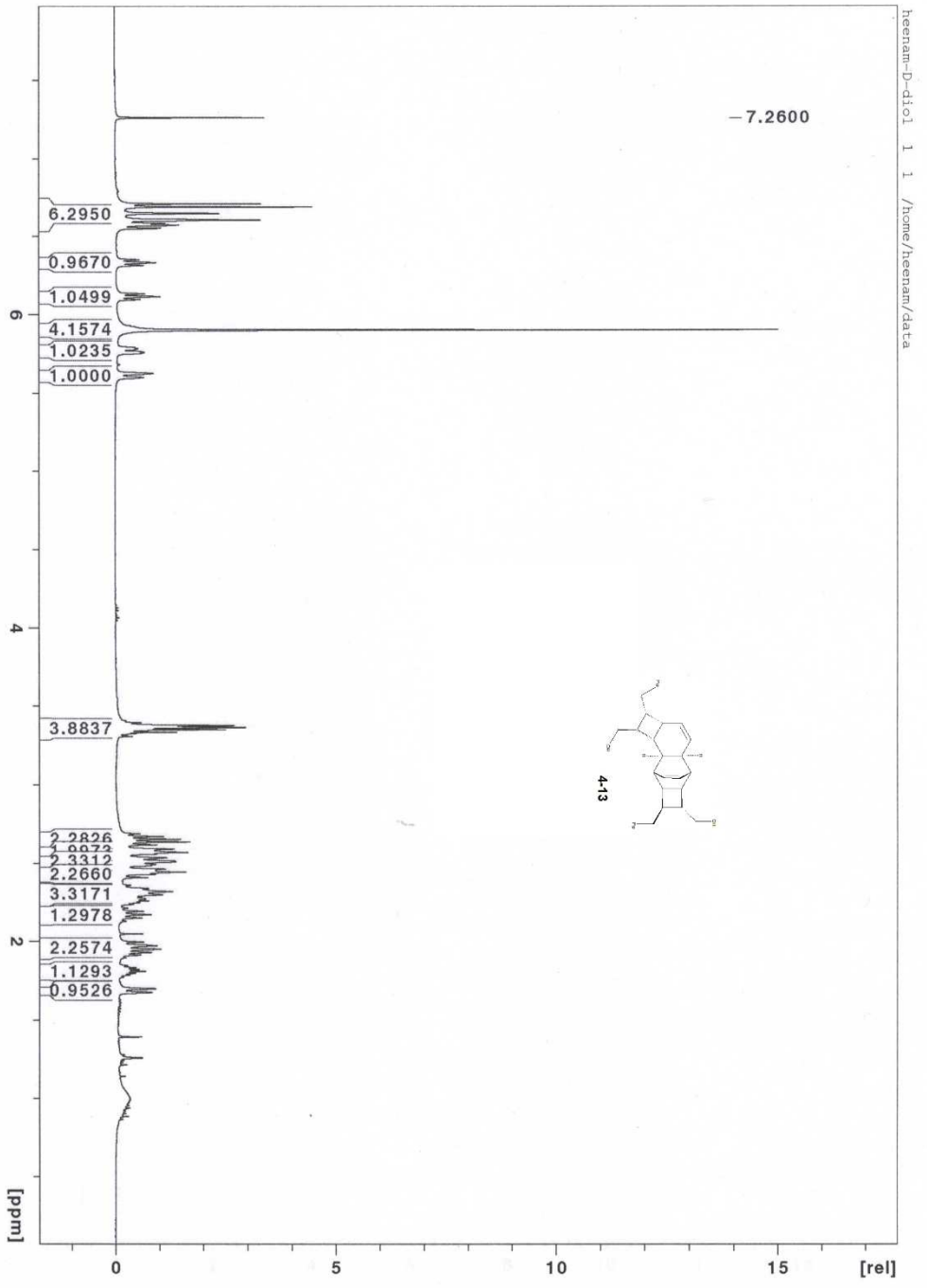
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7998.4 Hz
160 repetitions
OBSERVE H1, 499.8948150 MHz
DATA PROCESSING
FT size 32768
Total time 12 min

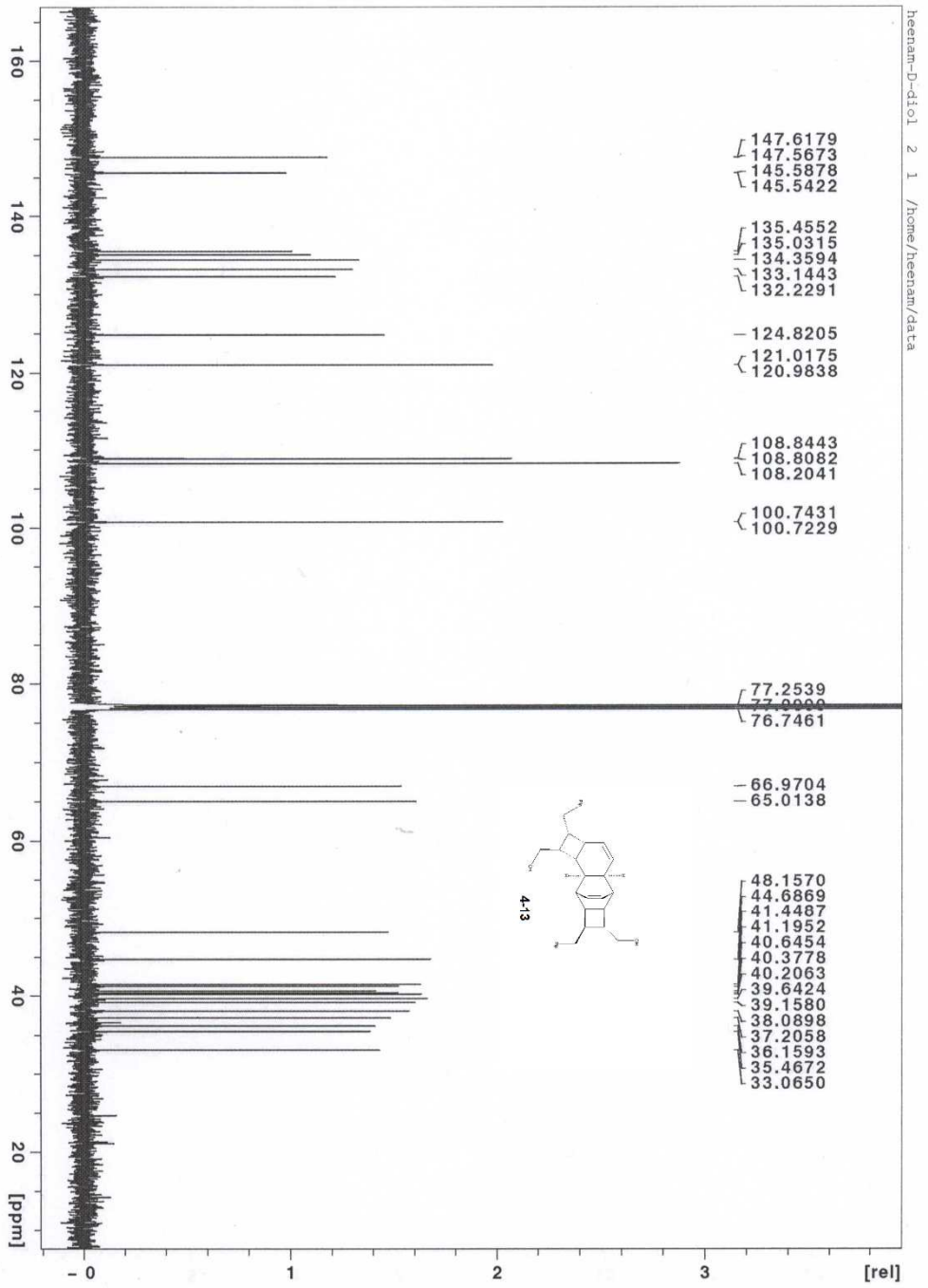


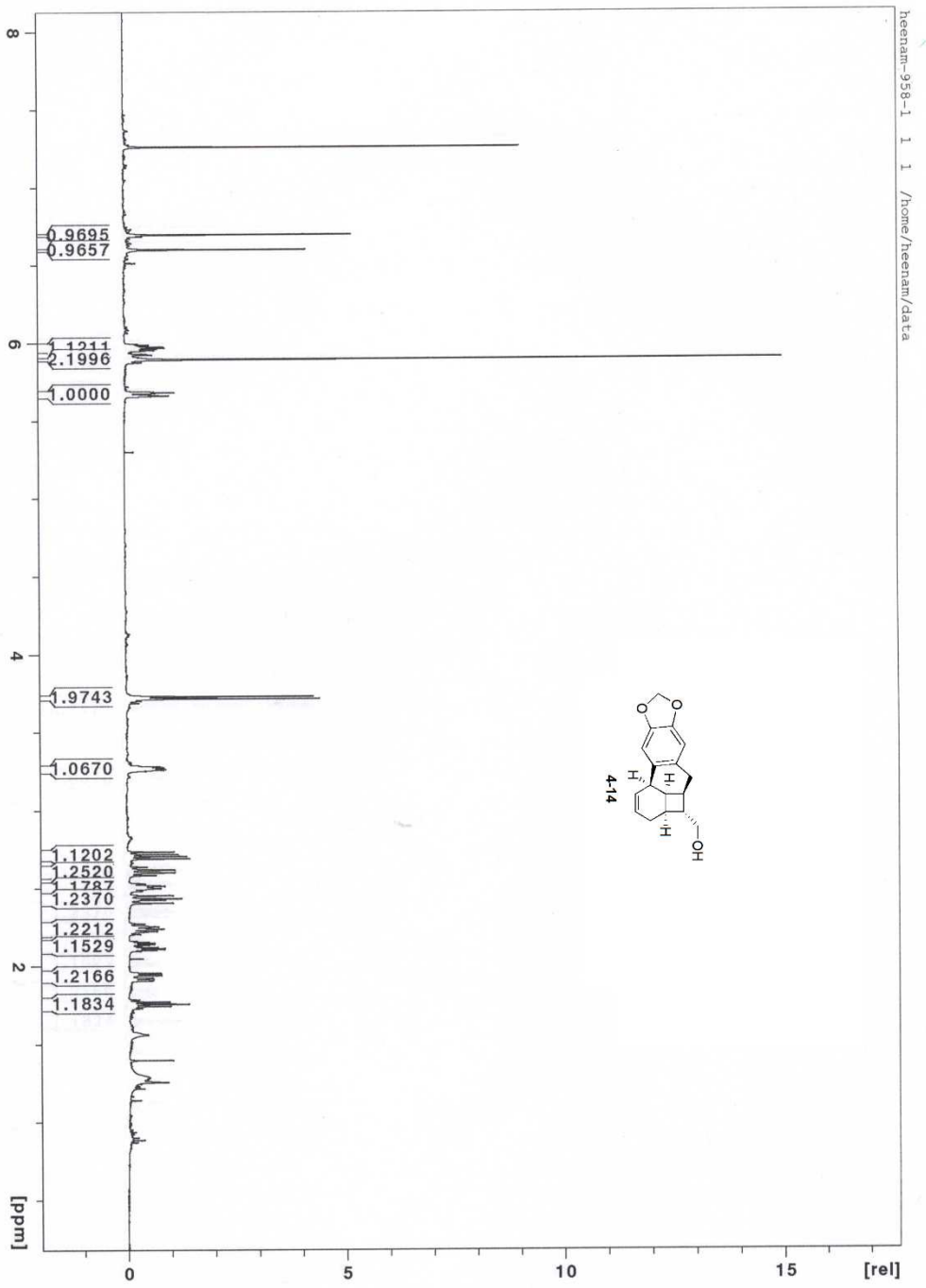
3-39 + 3-40

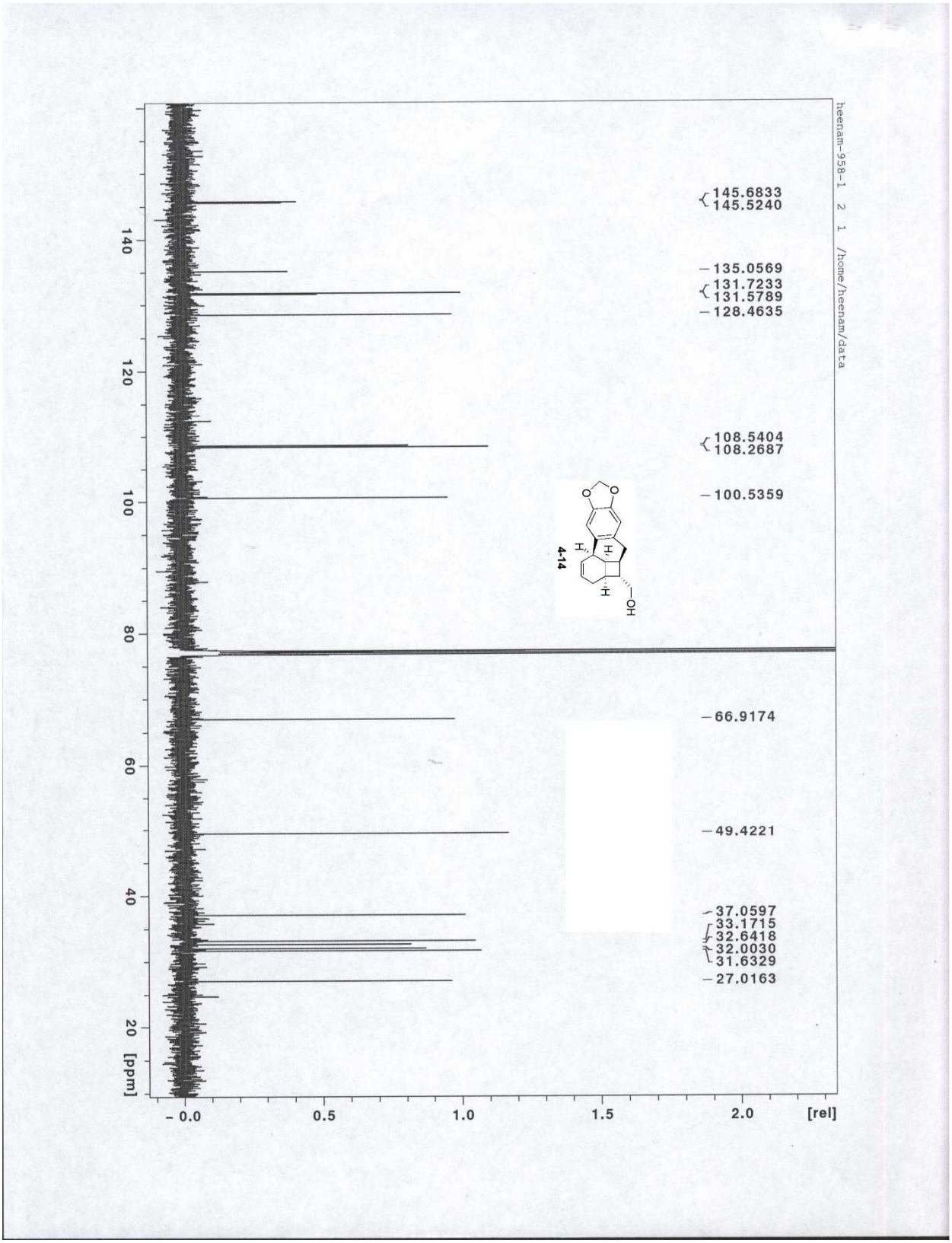

heenam-1080 1 1 /home/heenam/data
7.2600
5.2988
3.0591
2.0798
1.0000
2.0410
1.0271
3.0601
2.1385
CH2Cl2
grease
3-41
ent-3-41
Ph
OH
[ppm]
[rel]
0
5
10
15
2
4
6
8

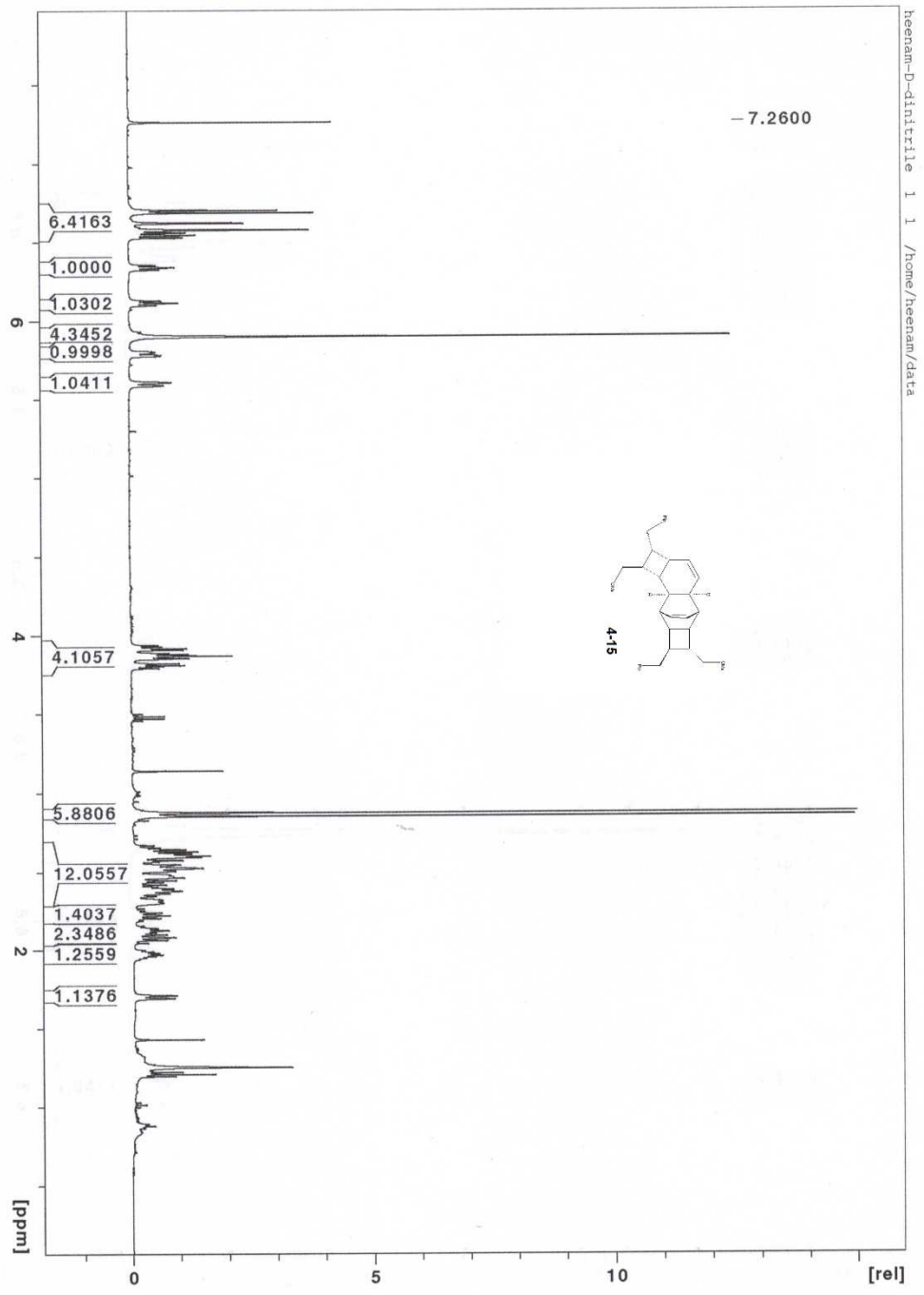

heenam-1080 2 1 /home/heenam/data
179.1479
147.5885
145.7236
133.6733
125.7388
124.9073
124.7045
123.1449
121.1731
108.8748
108.1646
100.7535
77.2543
76.7465
52.1498
47.5175
35.8637
34.6604
33.7347
3-41
ent-3-41
Pip
OH
150
100
50
[ppm]
0
1
2
3
4
5
[rel]

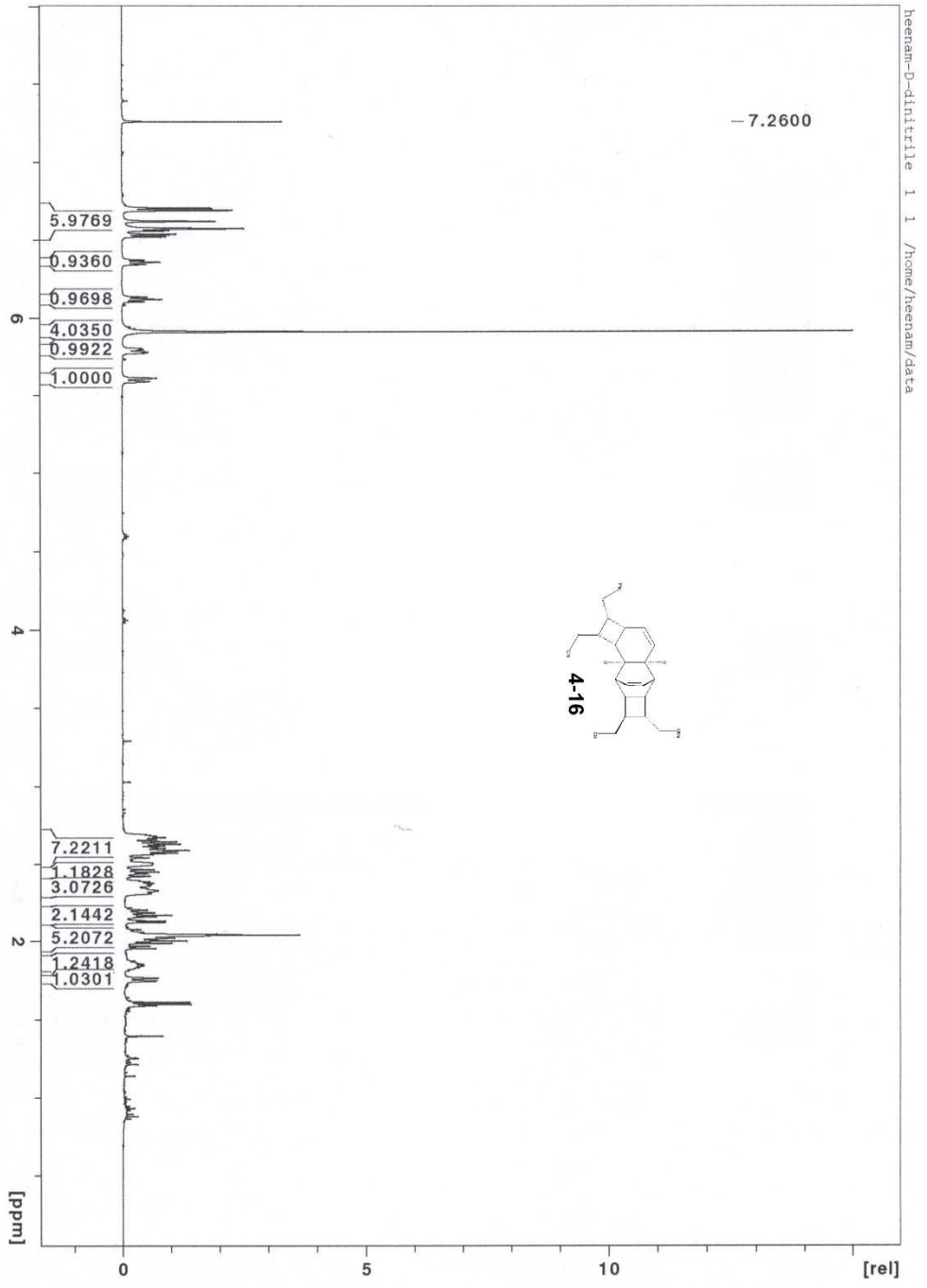

heenam-D-diol 1 1 /home/heenam/data
7.2600
6.2950
0.9670
1.0499
4.1574
1.0235
1.0000
3.8837
2.2826
2.3312
2.2660
3.3171
1.2978
2.2574
1.1293
0.9526
4-13
6
4
2
[ppm]
0
5
10
15
[rel]

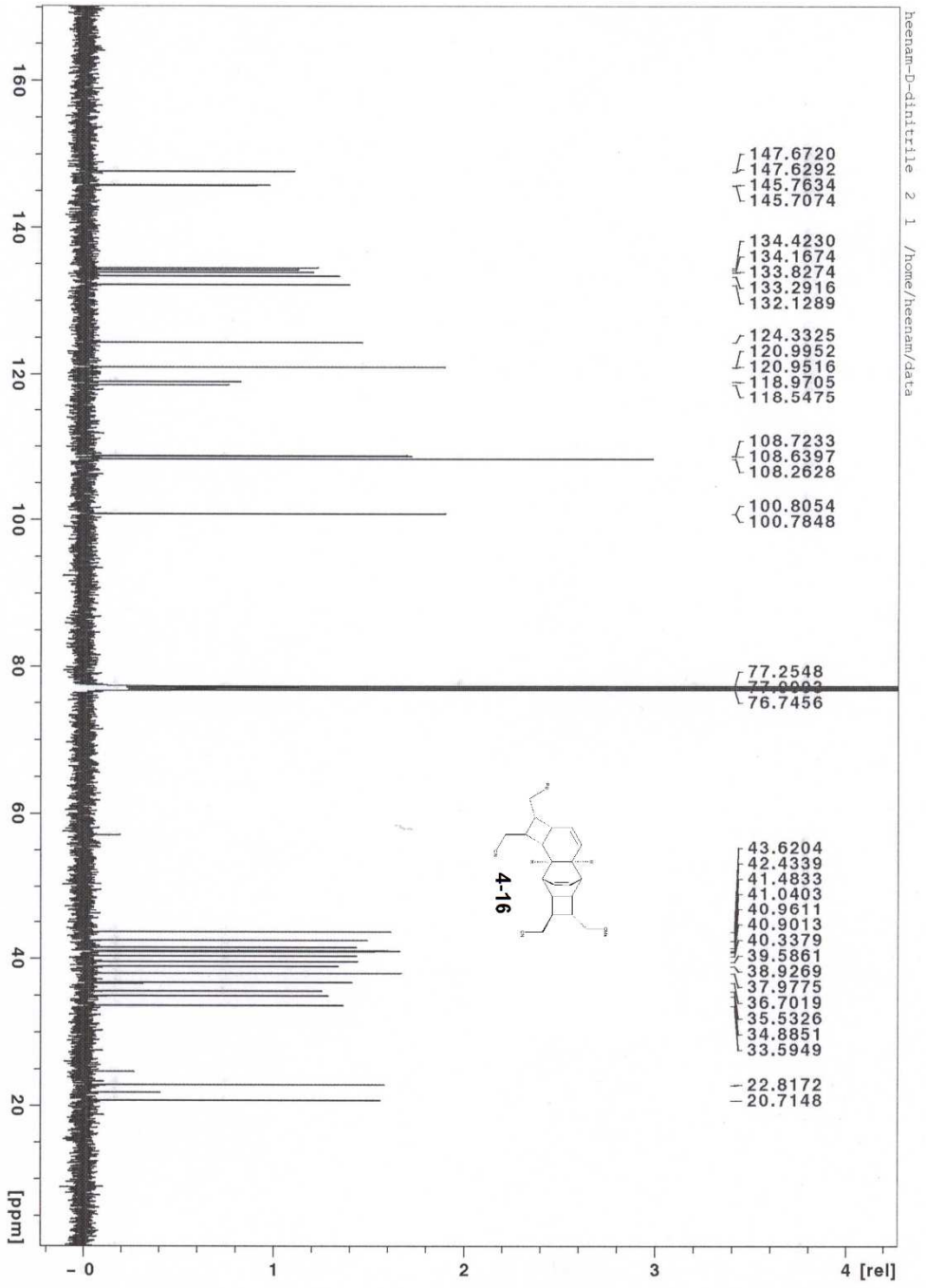

heenam-D-diol 2 1 /home/heenam/data
147.6179
147.5673
145.5878
145.5422
135.4552
135.0315
134.3594
133.1443
132.2291
124.8205
121.0175
120.9838
108.8443
108.8082
108.2041
100.7431
100.7229
77.2539
76.7461
66.9704
65.0138
48.1570
44.6869
41.4487
41.1952
40.6454
40.3778
40.2063
39.6424
39.1580
38.0898
37.2058
36.1593
35.4672
33.0650
4-13
160
140
120
100
80
60
40
20
[ppm]
0
1
2
3
[rel]

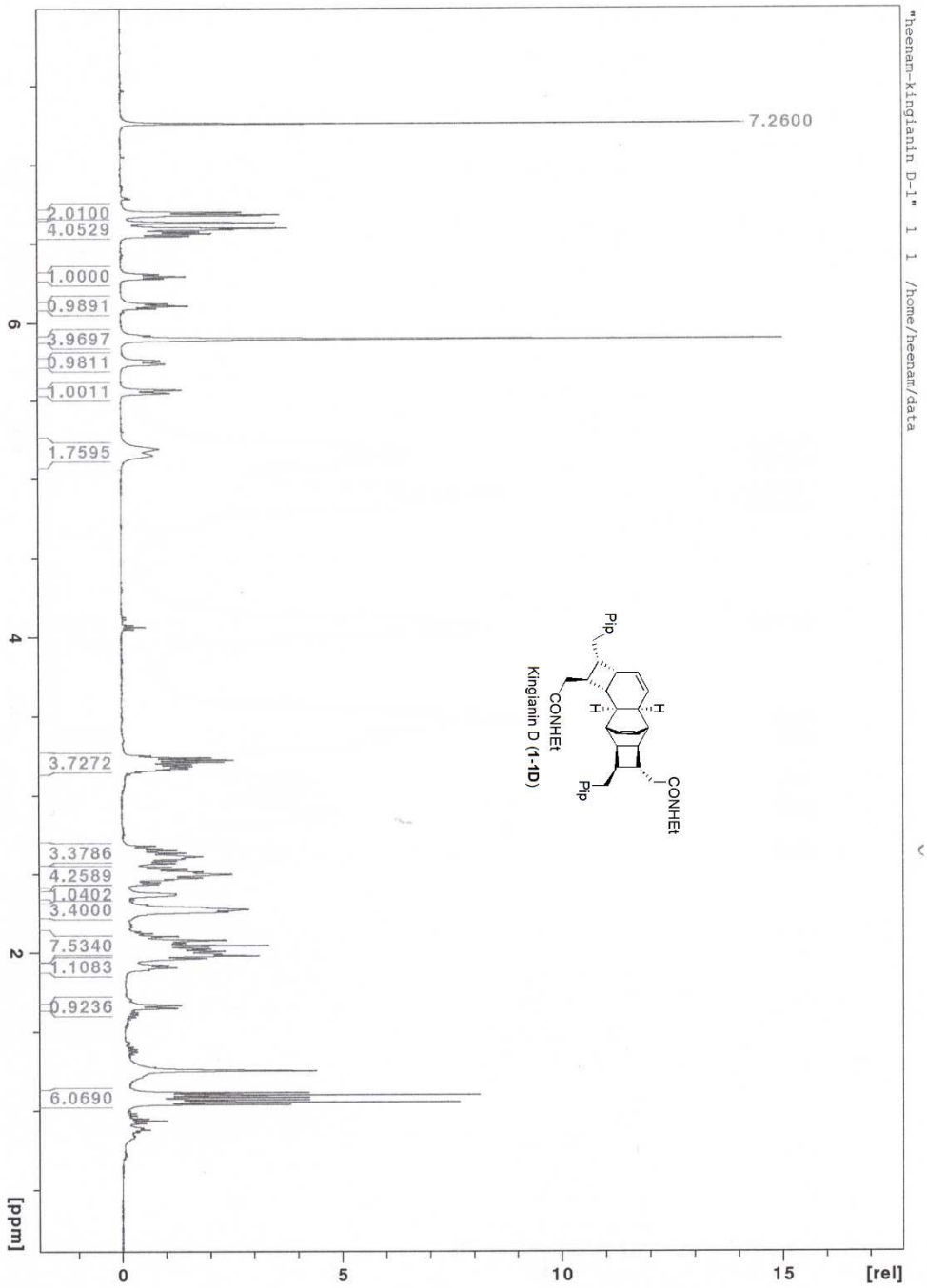

heenam-958-1 1 1 /home/heenam/data
0.9695
0.9657
1.1211
2.1996
1.0000
1.9743
1.0670
1.1202
1.2520
1.1787
1.2370
1.2212
1.1529
1.2166
1.1834
8
6
4
2
[ppm]
0
5
10
15
[rel]
4-14

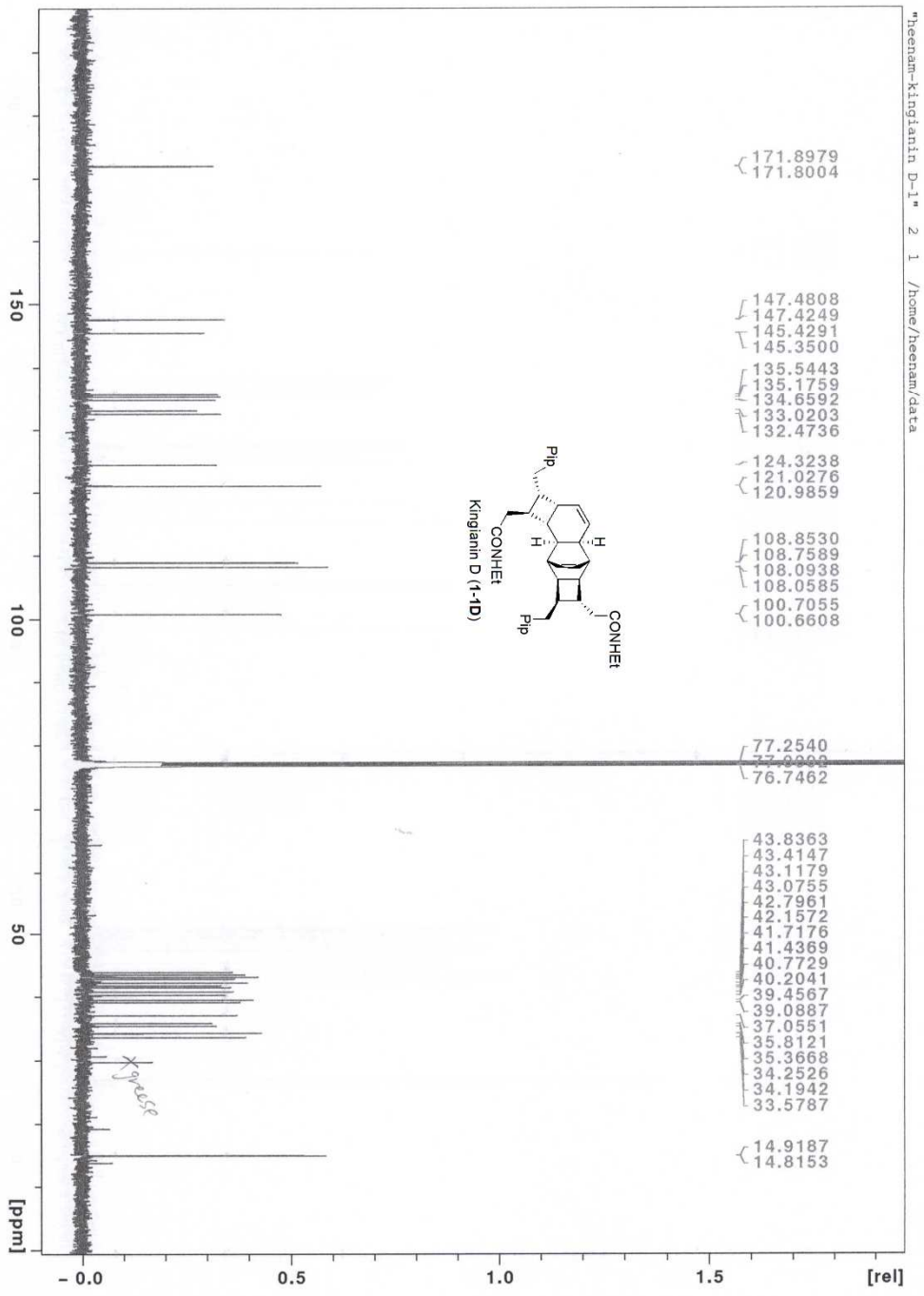

heenam-958-1 2 1 /home/heenam/data
145.6833
145.5240
135.0569
131.7233
131.5789
128.4635
108.5404
108.2687
100.5359
66.9174
49.4221
37.0597
33.1715
32.6418
32.0030
31.6329
27.0163
4-14
OH
140
120
100
80
60
40
20 [ppm]
0.0
0.5
1.0
1.5
2.0
[rel]

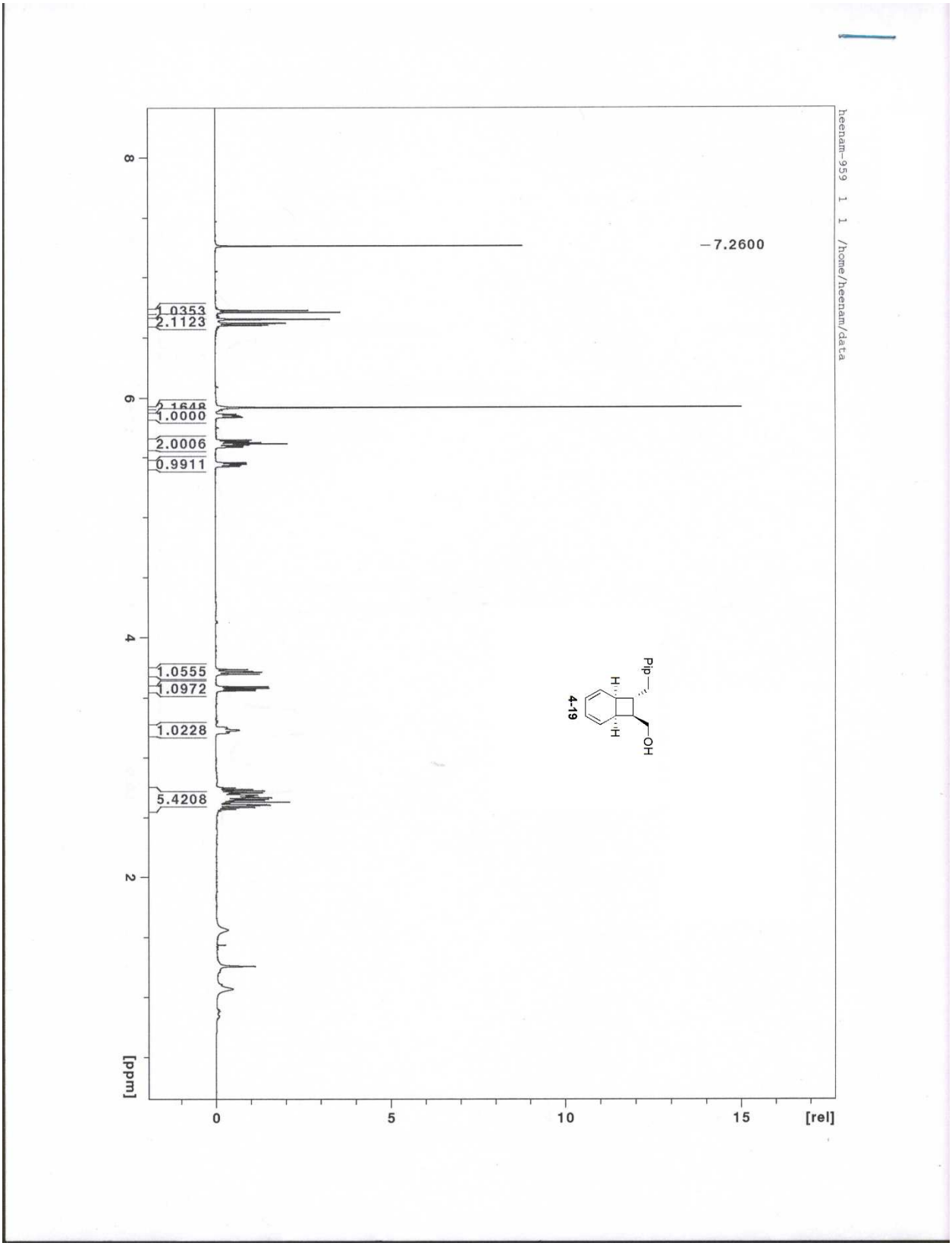

heenam-D-dinitrile 1 1 /home/heenam/data
7.2600
6.4163
1.0000
1.0302
4.3452
0.9998
1.0411
4.1057
5.8806
12.0557
1.4037
2.3486
1.2559
1.1376
4-15
6
4
2
[ppm]
0
5
10
[rel]

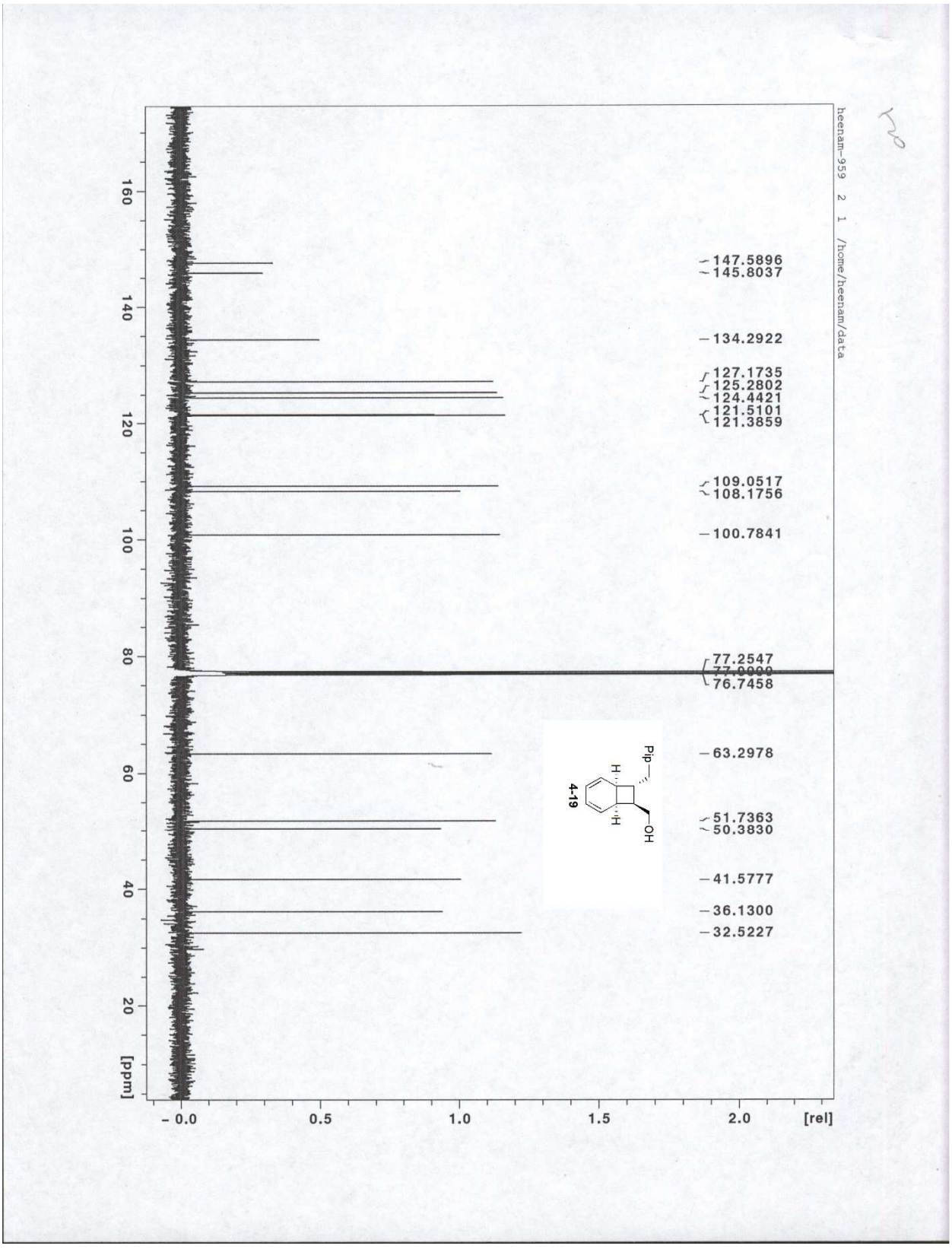

heenam-D-dinitrile 1 1 /home/heenam/data
7.2600
5.9769
0.9360
0.9698
4.0350
0.9922
1.0000
7.2211
1.1828
3.0726
2.1442
5.2072
1.2418
1.0301
6
4
2
[ppm]
0
5
10
[rel]
4-16

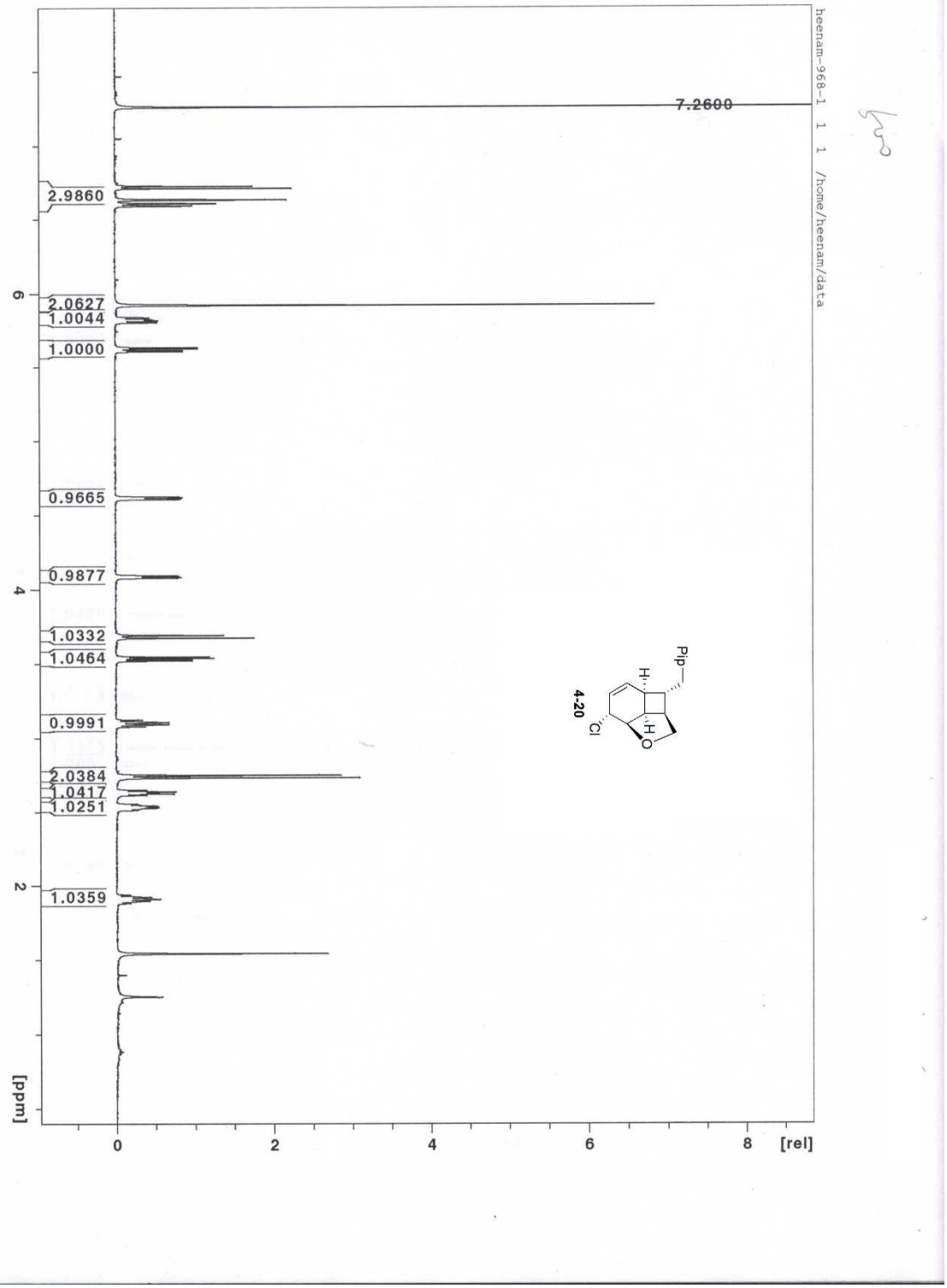

heenam-D-dinitrile 2 1 /home/heenam/data
147.6720
147.6292
145.7634
145.7074
134.4230
134.1674
133.8274
133.2916
132.1289
124.3325
120.9952
120.9516
118.9705
118.5475
108.7233
108.6397
108.2628
100.8054
100.7848
77.2548
76.7456
43.6204
42.4339
41.4833
41.0403
40.9611
40.9013
40.3379
39.5861
38.9269
37.9775
36.7019
35.5326
34.8851
33.5949
22.8172
20.7148
4-16
[ppm]
160
140
120
100
80
60
40
20
0
1
2
3
4 [rel]

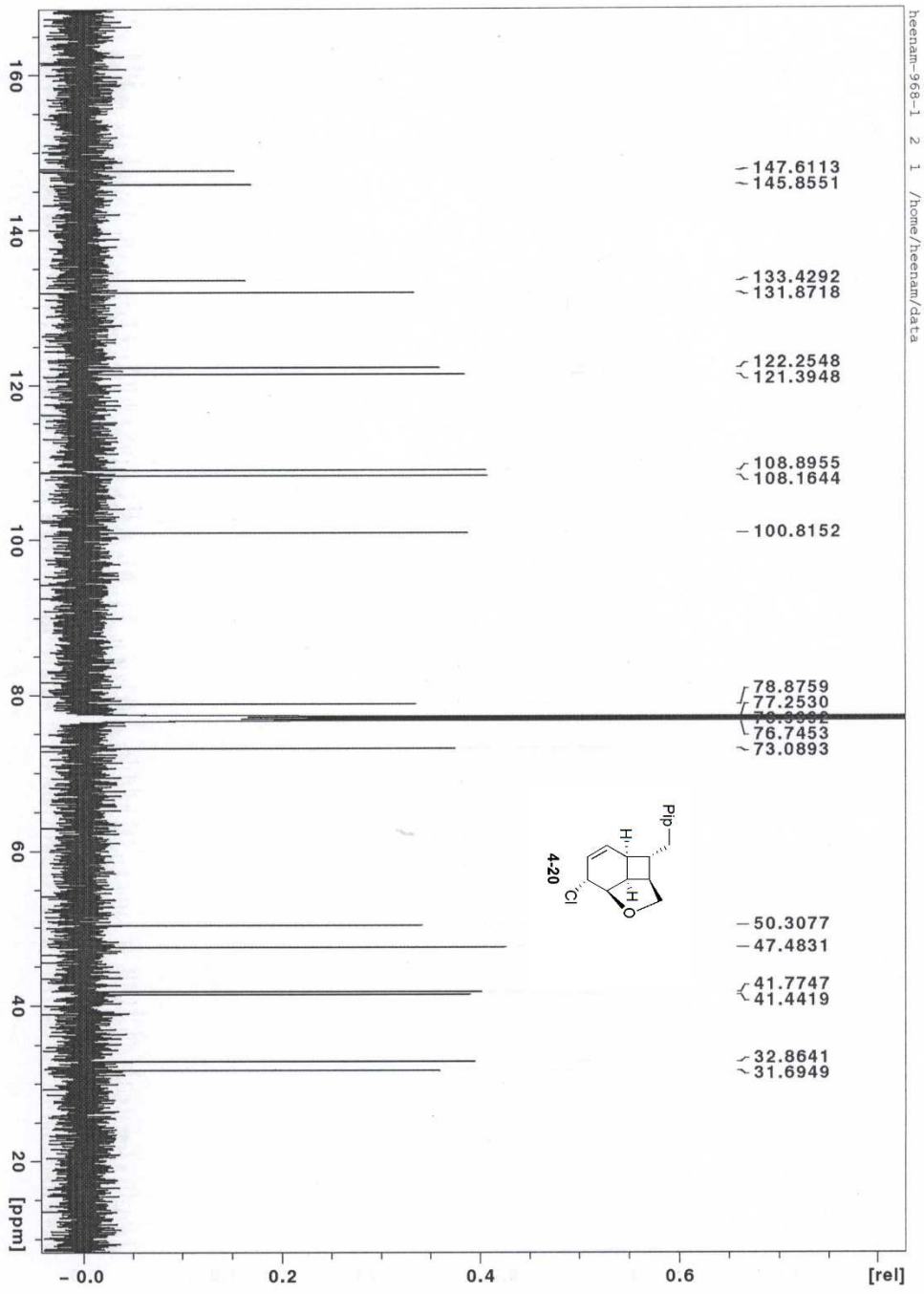

"heenam-kinglanin D-1" 1 1 /home/heenam/data
7.2600
2.0100
4.0529
1.0000
0.9891
3.9697
0.9811
1.0011
1.7595
3.7272
3.3786
4.2589
1.0402
3.4000
7.5340
1.1083
0.9236
6.0690
[ppm]
[rel]
Pip
CONHEt
H
H
Pip
CONHEt
Kinglanin D (1-1D)

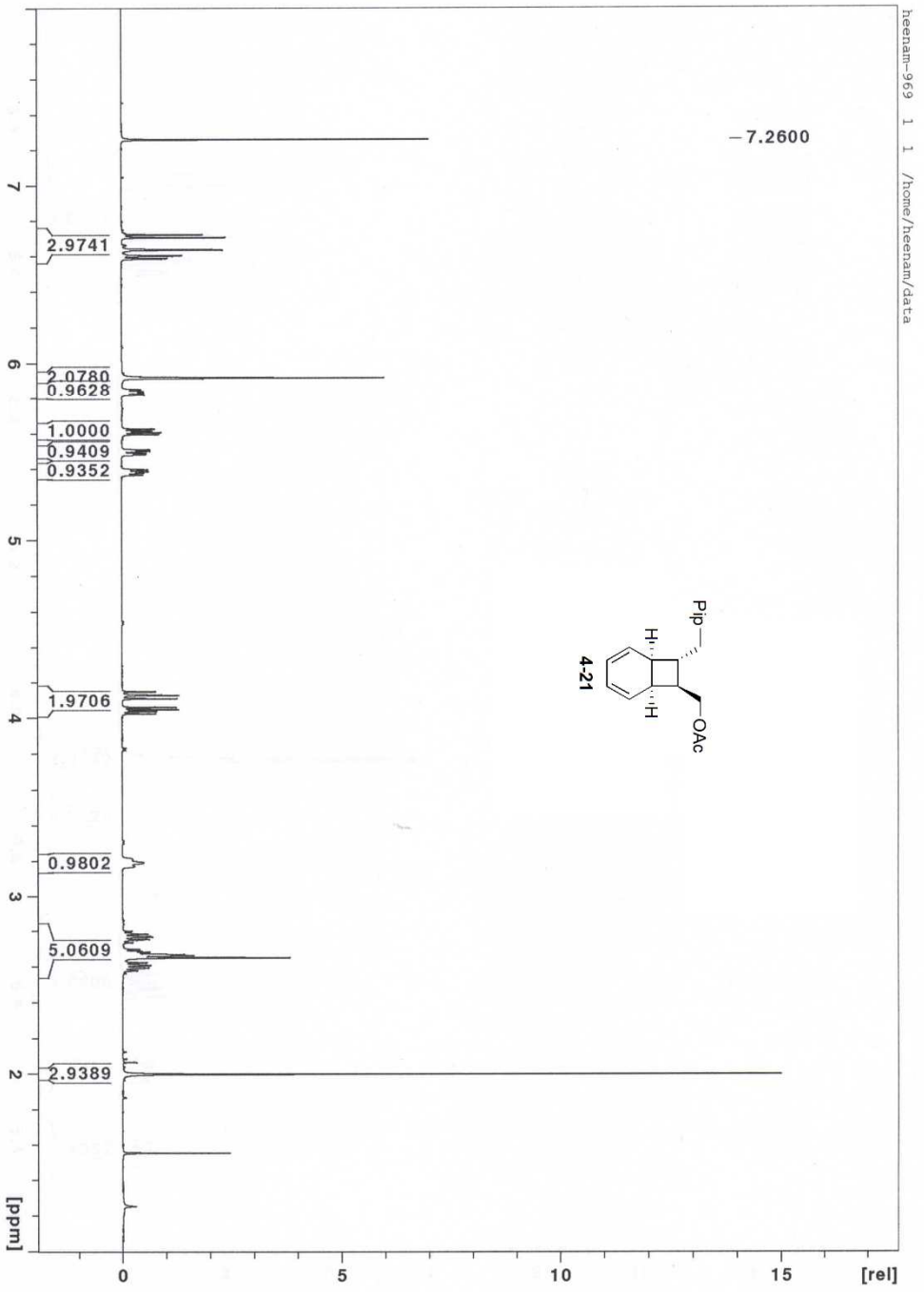

"heenam-kinglianin D-1" 2 1 /home/heenam/data
171.8979
171.8004
147.4808
147.4249
145.4291
145.3500
135.5443
135.1759
134.6592
133.0203
132.4736
124.3238
121.0276
120.9859
108.8530
108.7589
108.0938
108.0585
100.7055
100.6608
77.2540
76.7462
43.8363
43.4147
43.1179
43.0755
42.7961
42.1572
41.7176
41.4369
40.7729
40.2041
39.4567
39.0887
37.0551
35.8121
35.3668
34.2526
34.1942
33.5787
14.9187
14.8153
Kinglianin D (1-1D)
CONHEt
Pip
H
H
Pip
CONHEt
150
100
50
[ppm]
- 0.0
0.5
1.0
1.5
[rel]

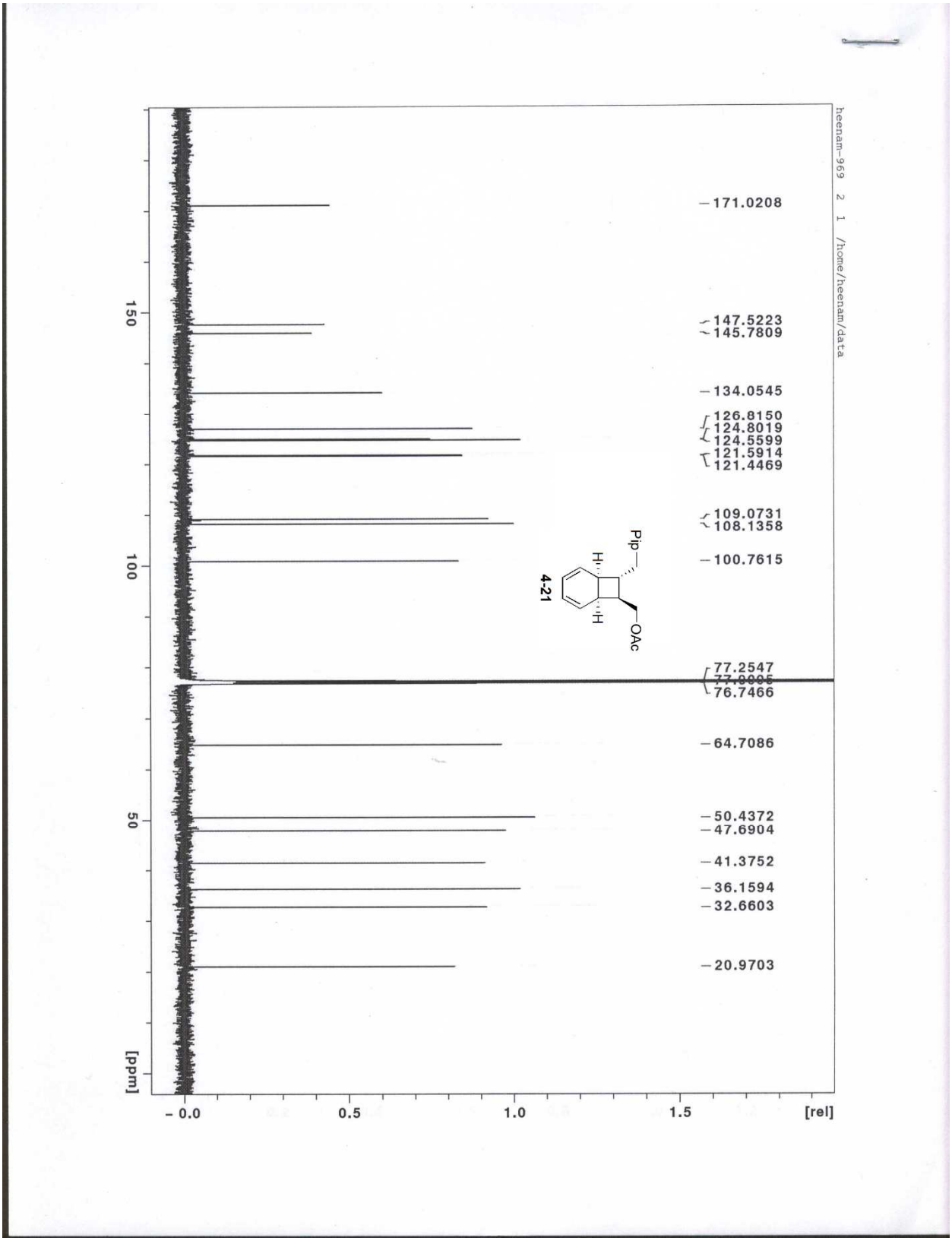

heenam-959 1 1 /home/heenam/data
7.2600
1.0353
2.1123
1.0000
2.0006
0.9911
1.0555
1.0972
1.0228
5.4208
Pip
H
H
OH
4-19
8
6
4
2
[ppm]
0
5
10
15
[rel]

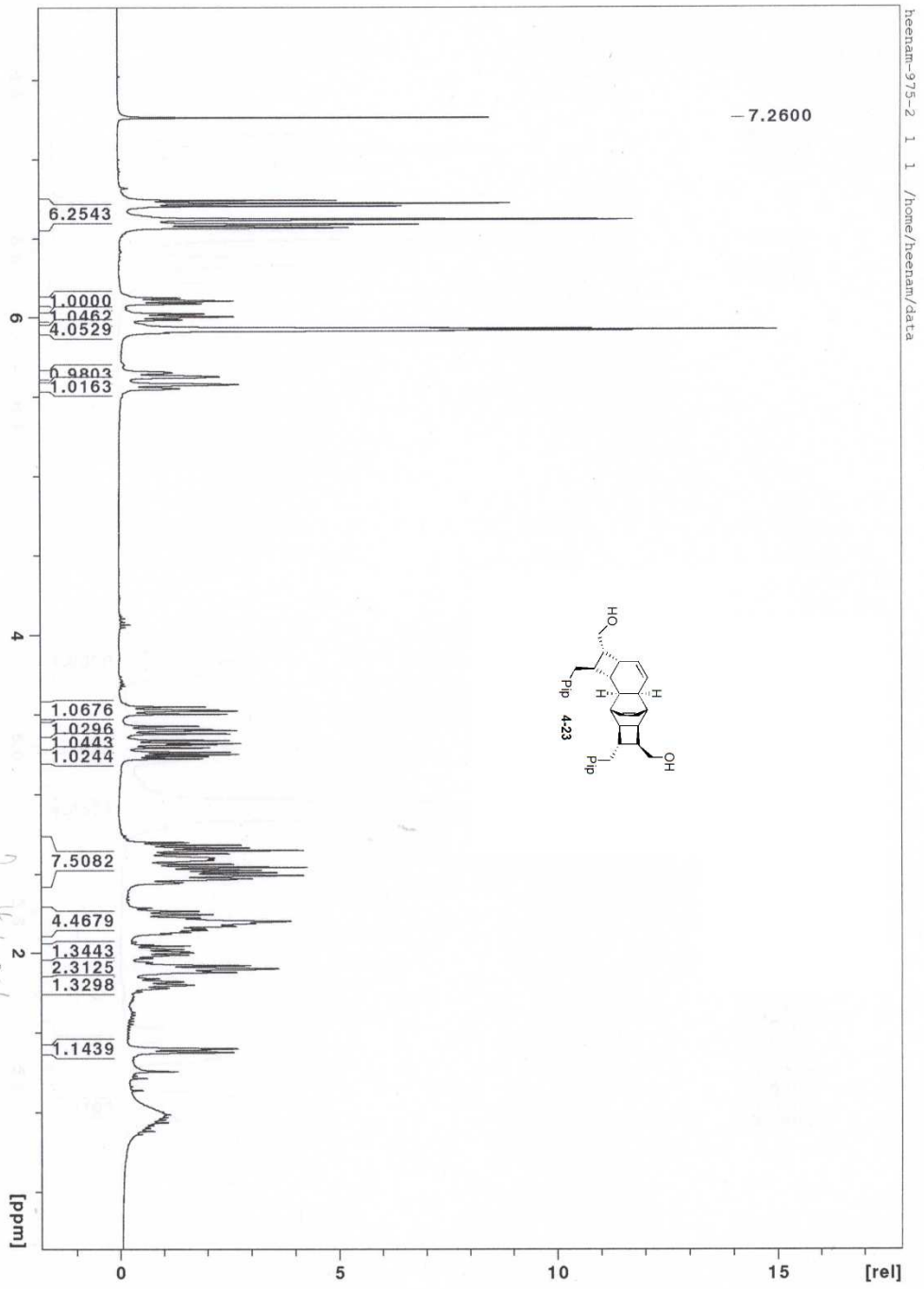

heenam-959 2 1 /home/heenam/data
147.5896
145.8037
134.2922
127.1735
125.2802
124.4421
121.5101
121.3859
109.0517
108.1756
100.7841
77.2547
77.0000
76.7458
63.2978
51.7363
50.3830
41.5777
36.1300
32.5227
Pip
H
H
OH
4-19
160
140
120
100
80
60
40
20
[ppm]
0.0
0.5
1.0
1.5
2.0
[rel]

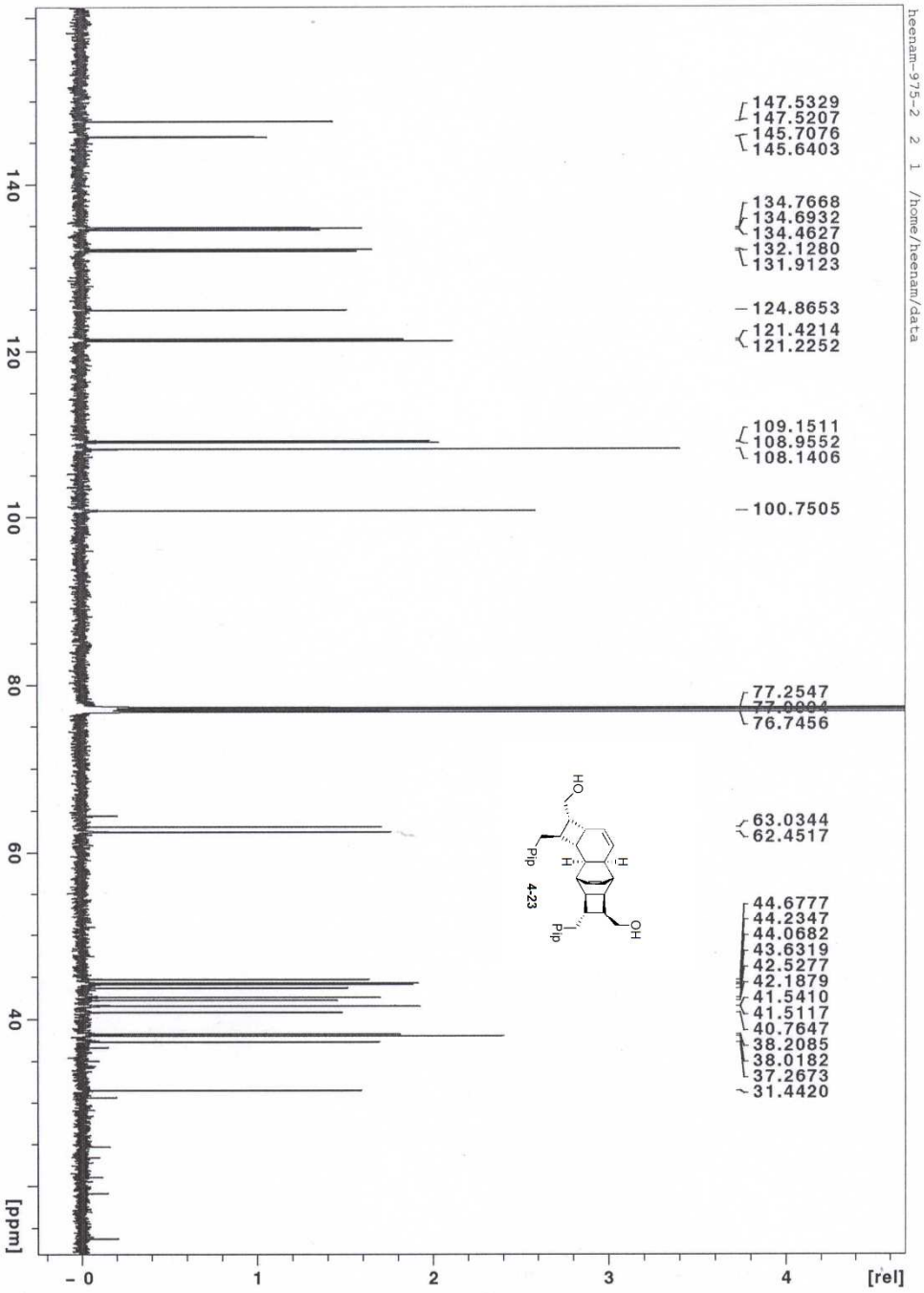

heenam-968-1 1 1 /home/heenam/data
7.2600
2.9860
2.0627
1.0044
1.0000
0.9665
0.9877
1.0332
1.0464
0.9991
2.0384
1.0417
1.0251
1.0359
[ppm]
[rel]
4-20
Pip
H
H
Cl
O

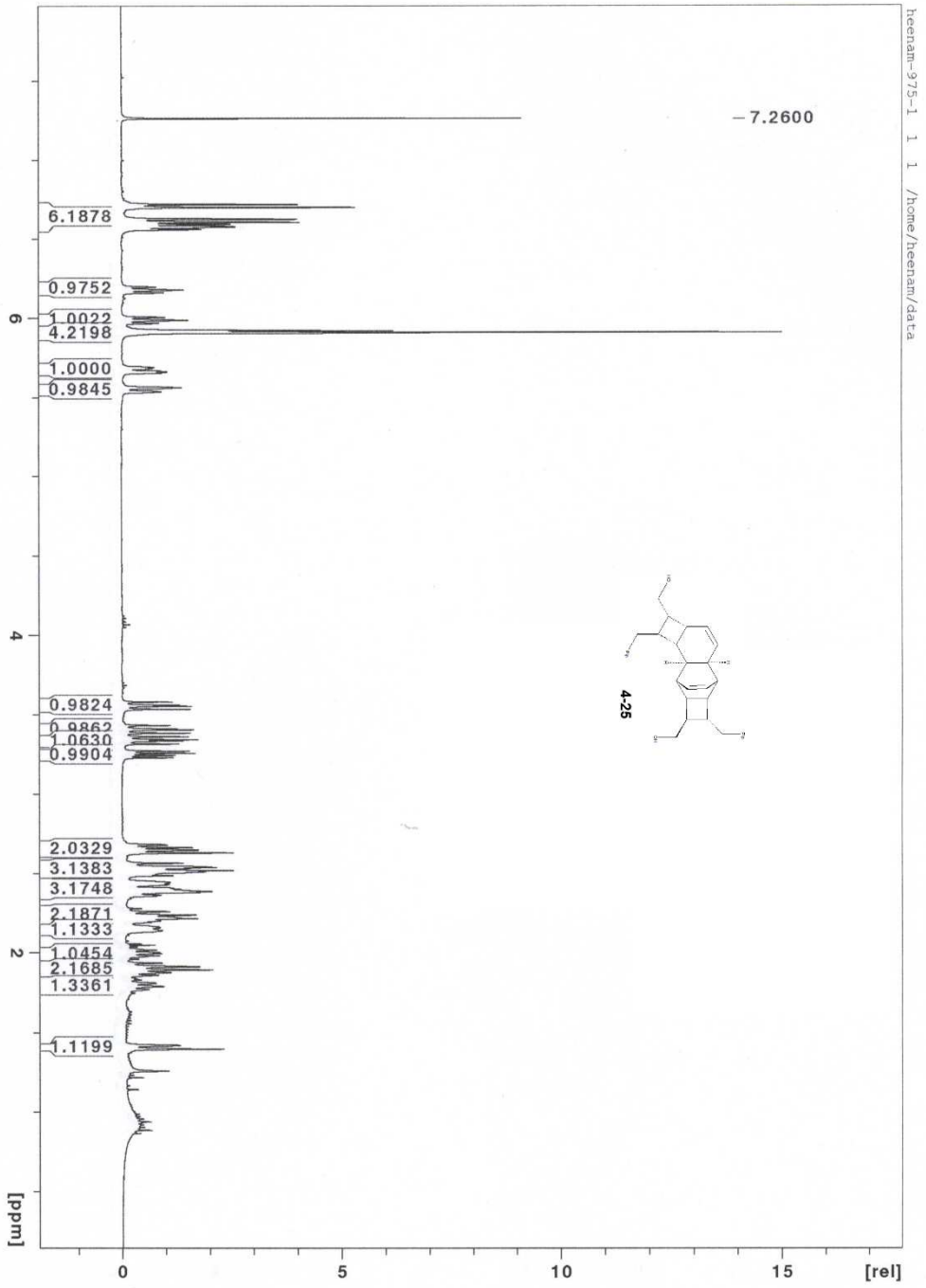

heenam-968-1 2 1 /home/heenam/data
147.6113
145.8551
133.4292
131.8718
122.2548
121.3948
108.8955
108.1644
100.8152
78.8759
77.2530
76.7453
73.0893
50.3077
47.4831
41.7747
41.4419
32.8641
31.6949
Pip
H
H
O
Cl
4-20
160
140
120
100
80
60
40
20
[ppm]
0.0
0.2
0.4
0.6
[rel]

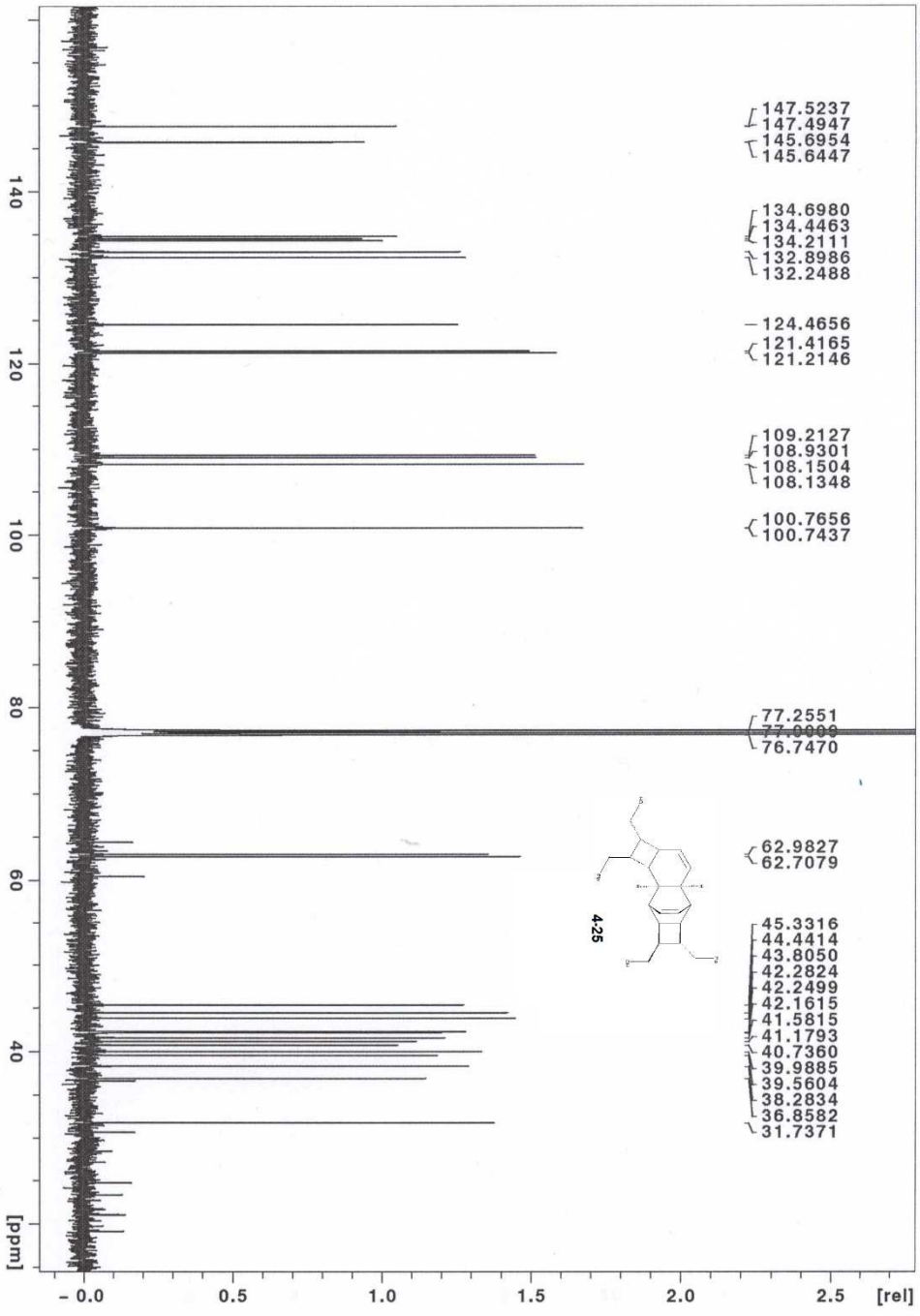

heenam-969 1 1 /home/heenam/data
7.2600
2.9741
2.0780
0.9628
1.0000
0.9409
0.9352
1.9706
0.9802
5.0609
2.9389
[ppm]
[rel]
Pip
H
H
OAc
4-21

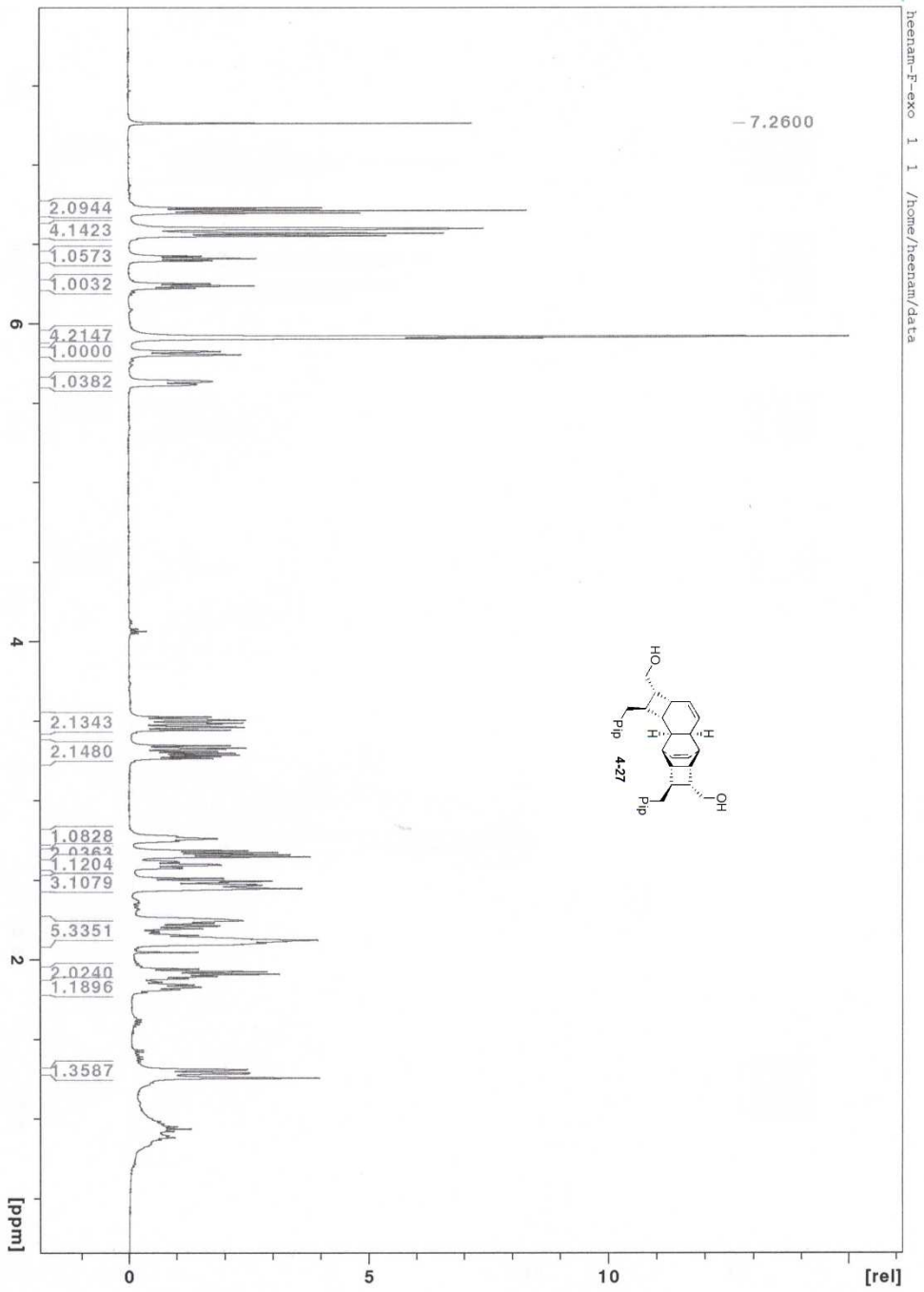

heenam-969 2 1 /home/heenam/data
171.0208
147.5223
145.7809
134.0545
126.8150
124.8019
124.5599
121.5914
121.4469
109.0731
108.1358
100.7615
77.2547
77.0005
76.7466
64.7086
50.4372
47.6904
41.3752
36.1594
32.6603
20.9703
Pip
H
H
OAc
4-21
150
100
50
[ppm]
0.0
0.5
1.0
1.5
[rel]

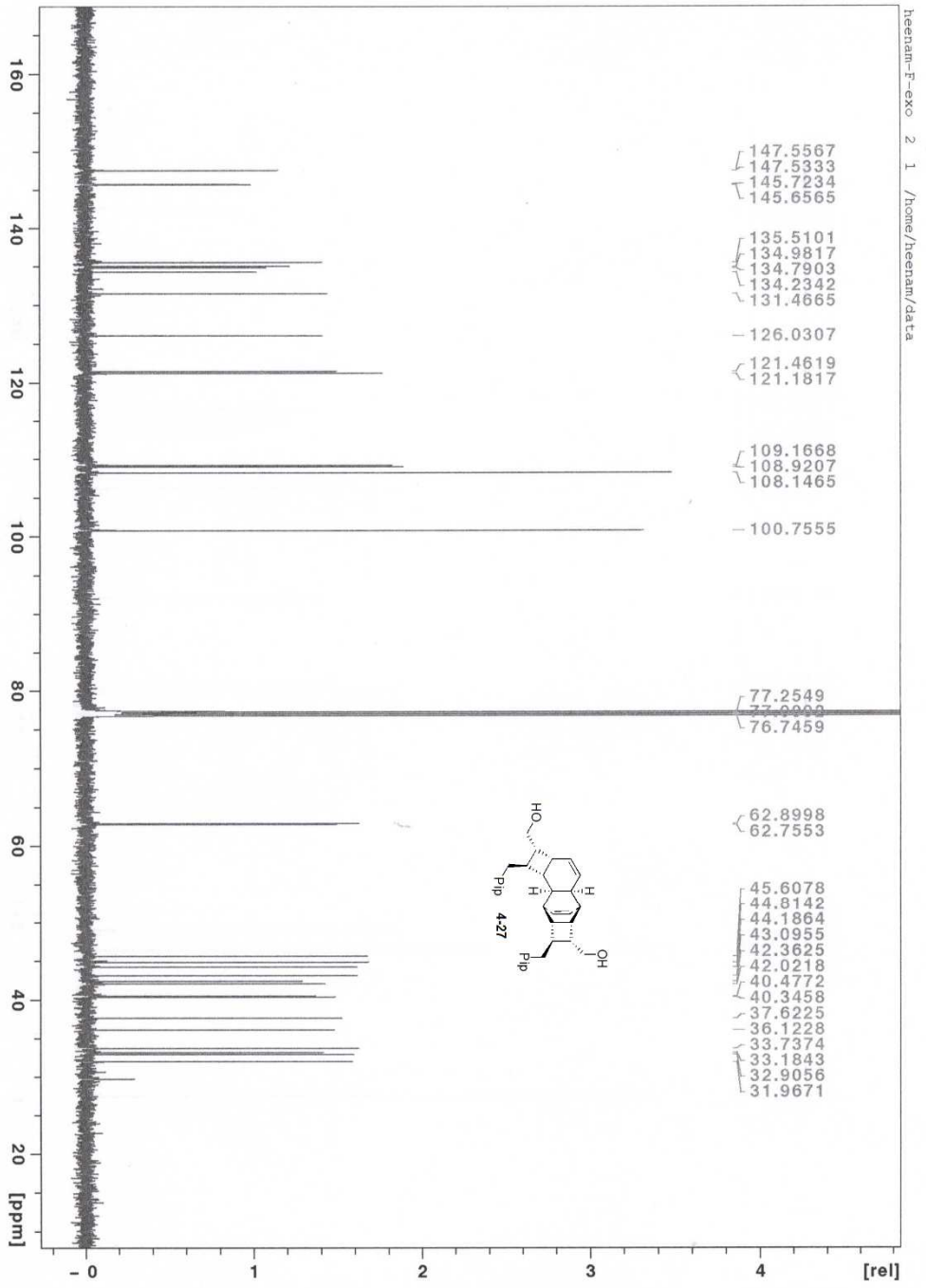

heenam-975-2 1 1 /home/heenam/data
7.2600
6.2543
1.0000
1.0462
4.0529
0.9803
1.0163
1.0676
1.0296
1.0443
1.0244
7.5082
4.4679
1.3443
2.3125
1.3298
1.1439
HO
Pip
H
H
OH
Pip
4-23
6
4
2
[ppm]
0
5
10
15
[rel]

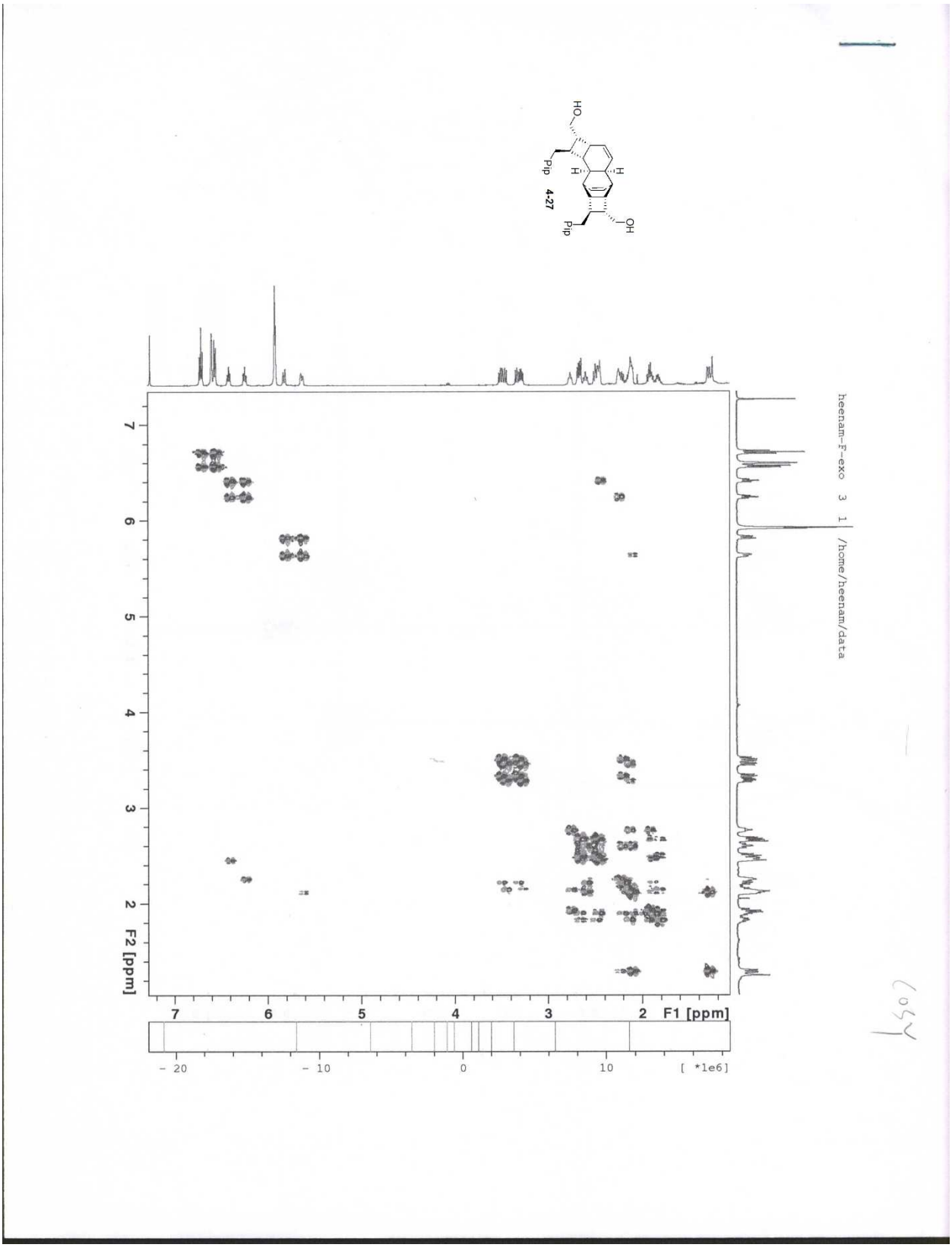

heenam-975-2 2 1 /home/heenam/data
147.5329
147.5207
145.7076
145.6403
134.7668
134.6932
134.4627
132.1280
131.9123
124.8653
121.4214
121.2252
109.1511
108.9552
108.1406
100.7505
77.2547
76.7456
63.0344
62.4517
44.6777
44.2347
44.0682
43.6319
42.5277
42.1879
41.5410
41.5117
40.7647
38.2085
38.0182
37.2673
31.4420
HO
Pip
H
H
4-23
Pip
OH
[ppm]
[rel]

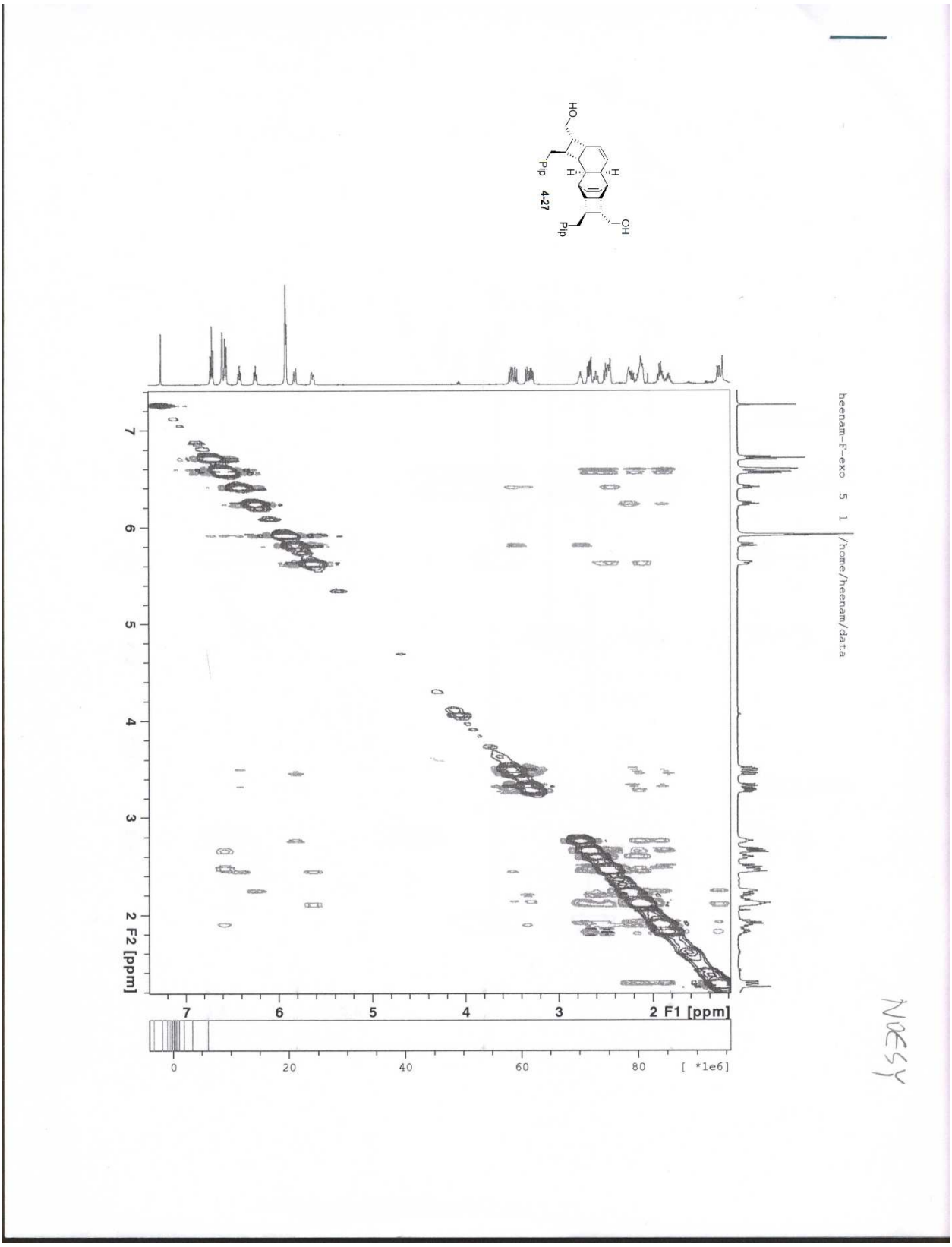

heenam-975-1 1 1 /home/heenam/data
7.2600
6.1878
0.9752
1.0022
4.2198
1.0000
0.9845
0.9824
0.9862
1.0630
0.9904
2.0329
3.1383
3.1748
2.1871
1.1333
1.0454
2.1685
1.3361
1.1199
4-25
[ppm]
[rel]
0
5
10
15
2
4
6

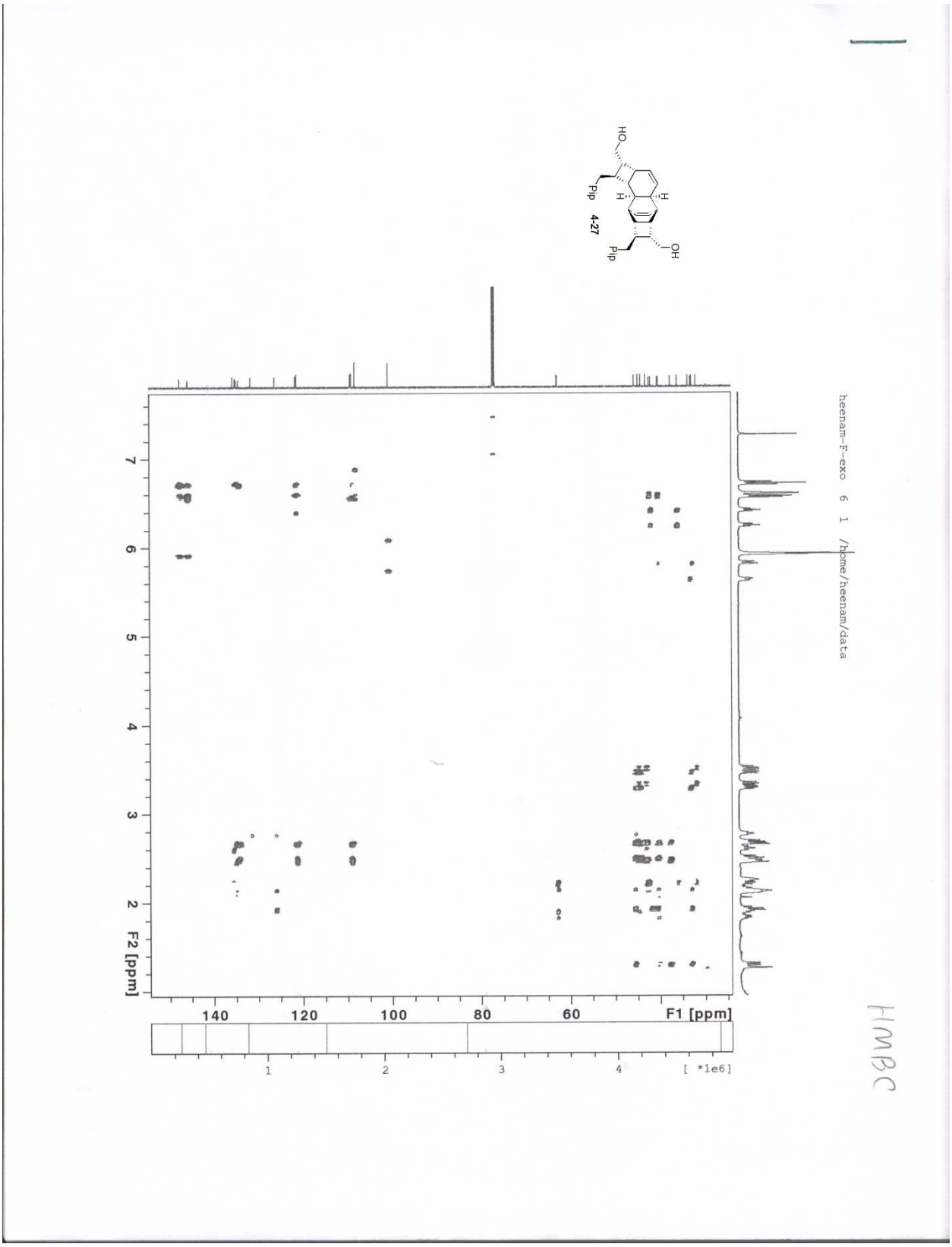

heenam-375-1 4 1 /home/heenam/data
147.5237
147.4947
145.6954
145.6447
134.6980
134.4463
134.2111
132.8986
132.2488
124.4656
121.4165
121.2146
109.2127
108.9301
108.1504
108.1348
100.7656
100.7437
77.2551
77.0000
76.7470
62.9827
62.7079
45.3316
44.4414
43.8050
42.2824
42.2499
42.1615
41.5815
41.1793
40.7360
39.9885
39.5604
38.2834
36.8582
31.7371
4-25
[ppm]
140
120
100
80
60
40
0.0
0.5
1.0
1.5
2.0
2.5
[rel]

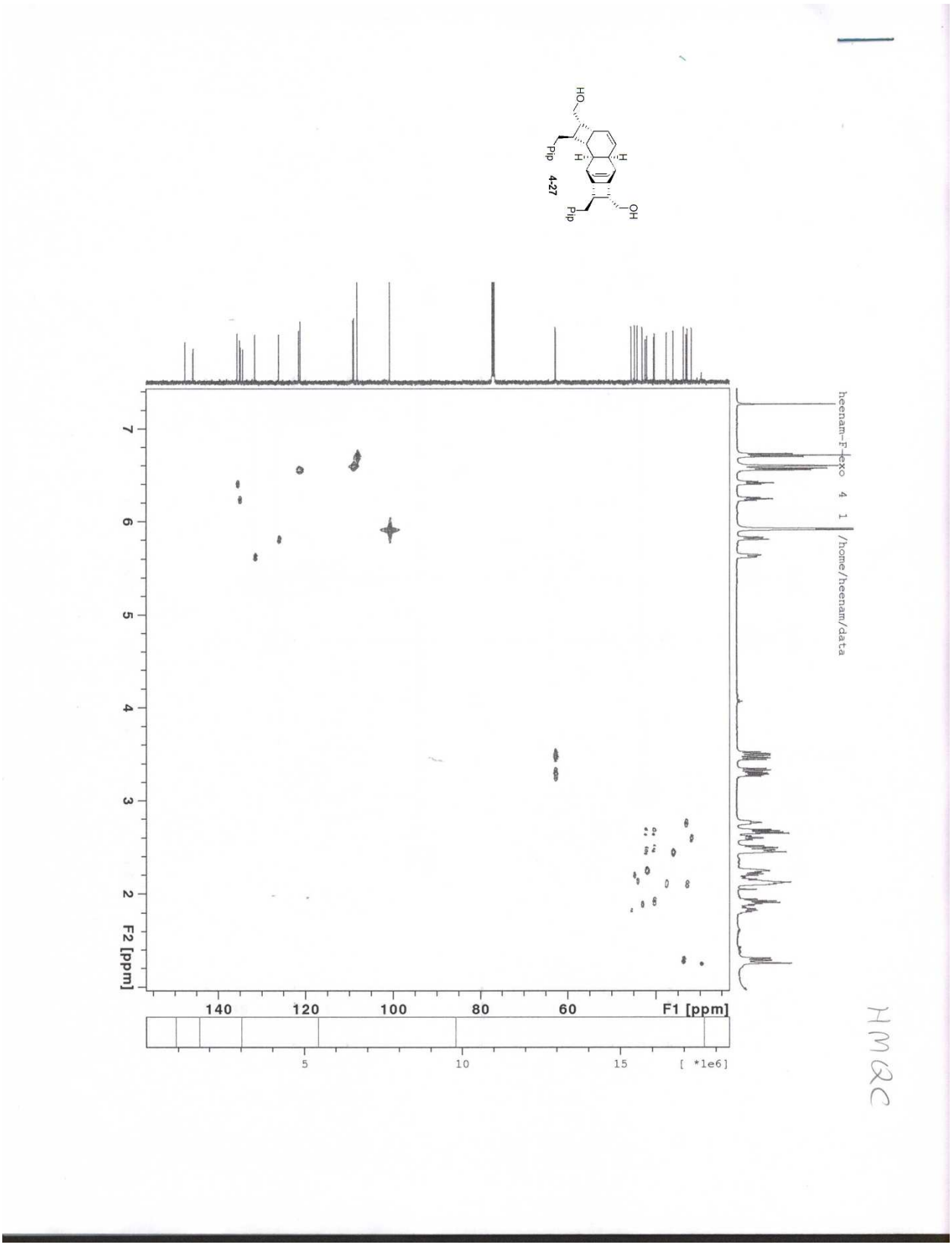

heenam-F-exo 1 1 /home/heenam/data
7.2600
2.0944
4.1423
1.0573
1.0032
4.2147
1.0000
1.0382
2.1343
2.1480
1.0828
1.1204
3.1079
5.3351
2.0240
1.1896
1.3587
HO
Pip
H
H
Pip
OH
4-27
[ppm]
[rel]
0
5
10
2
4
6

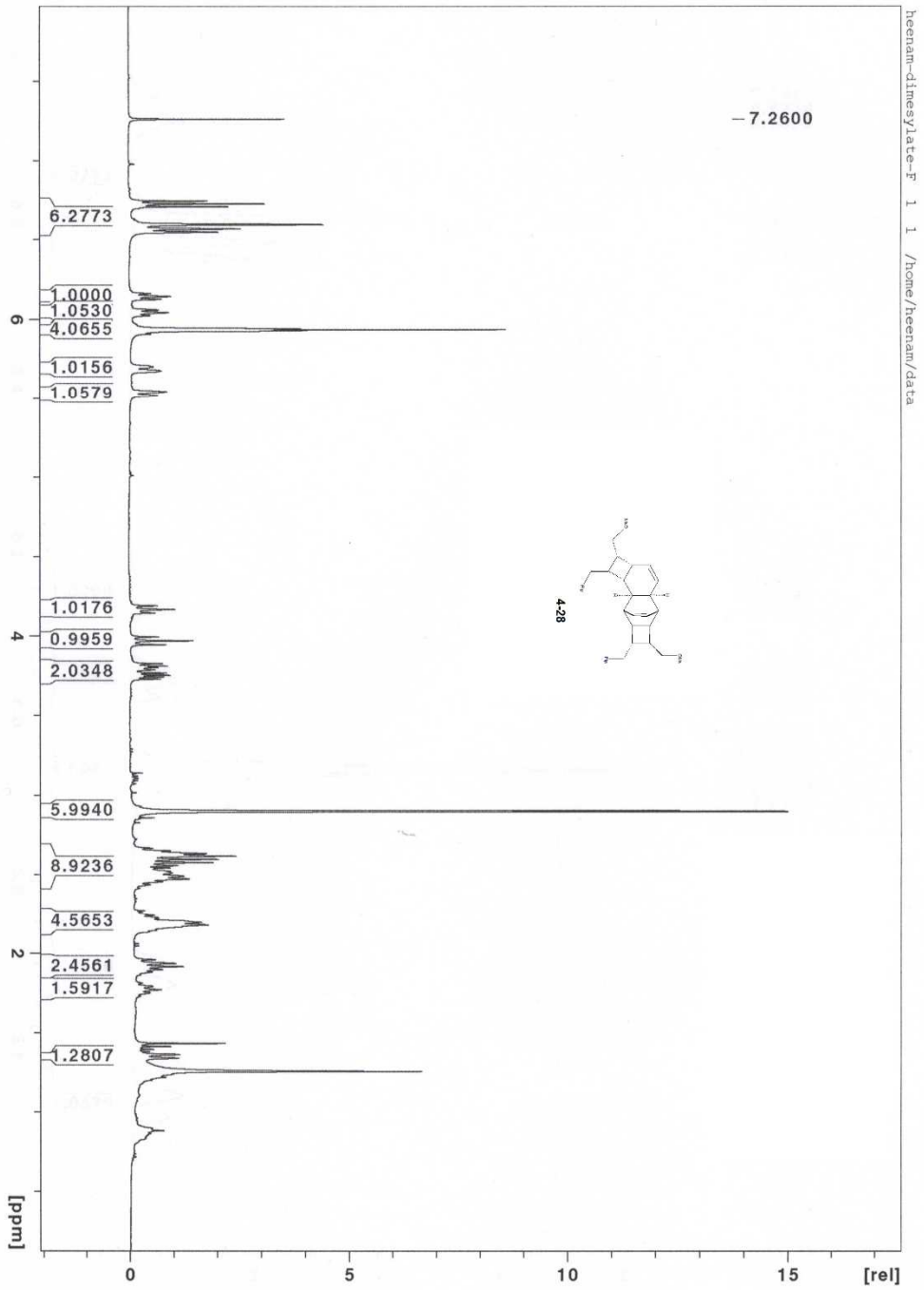

heenam-F-exo 2 1 /home/heenam/data
147.5567
147.5333
145.7234
145.6565
135.5101
134.9817
134.7903
134.2342
131.4665
126.0307
121.4619
121.1817
109.1668
108.9207
108.1465
100.7555
77.2549
76.7459
62.8998
62.7553
45.6078
44.8142
44.1864
43.0955
42.3625
42.0218
40.4772
40.3458
37.6225
36.1228
33.7374
33.1843
32.9056
31.9671
HO
Pip
H
H
4-27
Pip
OH
160
140
120
100
80
60
40
20
[ppm]
0
1
2
3
4
[rel]

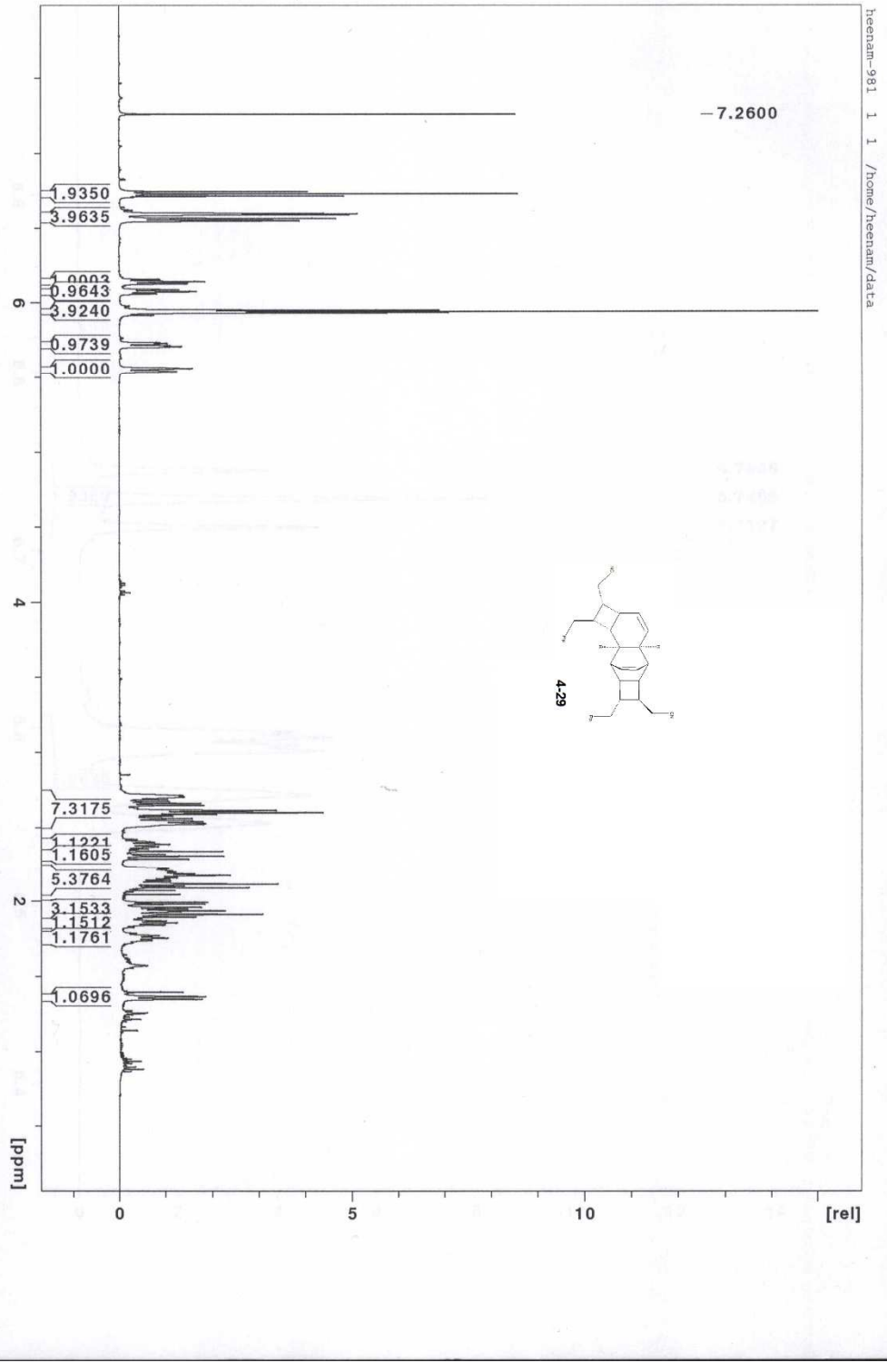

HO
Pip
4-27
Pip
OH
heenam-F-exo 3 1 /home/heenam/data
F2 [ppm]
F1 [ppm]
7
6
5
4
3
2
- 20
- 10
0
10
[*1e6]

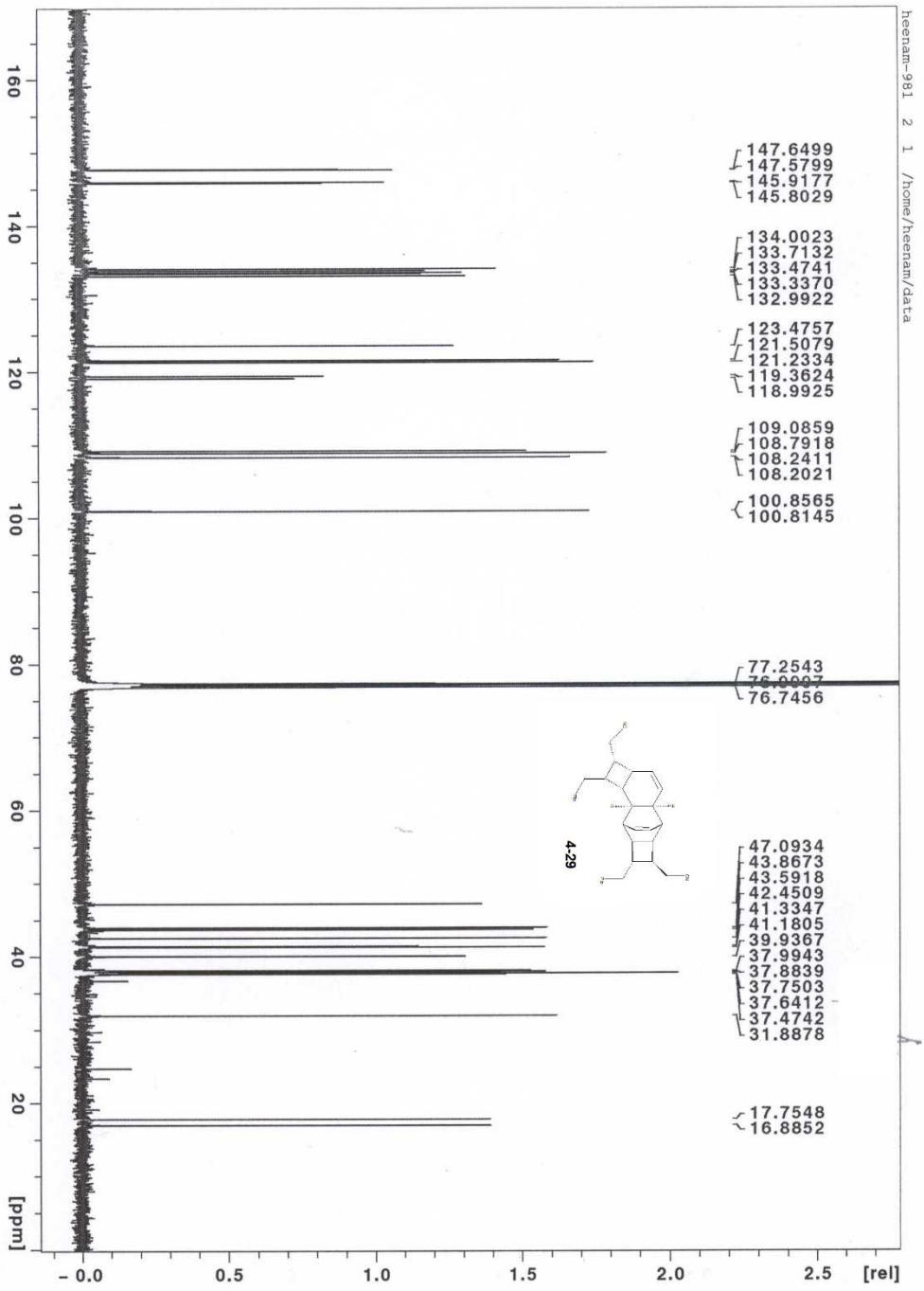

HO
Pip
H
H
4-27
Pip
OH
heenam-F-exo 5 1
/home/heenam/data
2 F2 [ppm]
7
6
5
4
3
2 F1 [ppm]
0
20
40
60
80
[*1e6]
NOESY

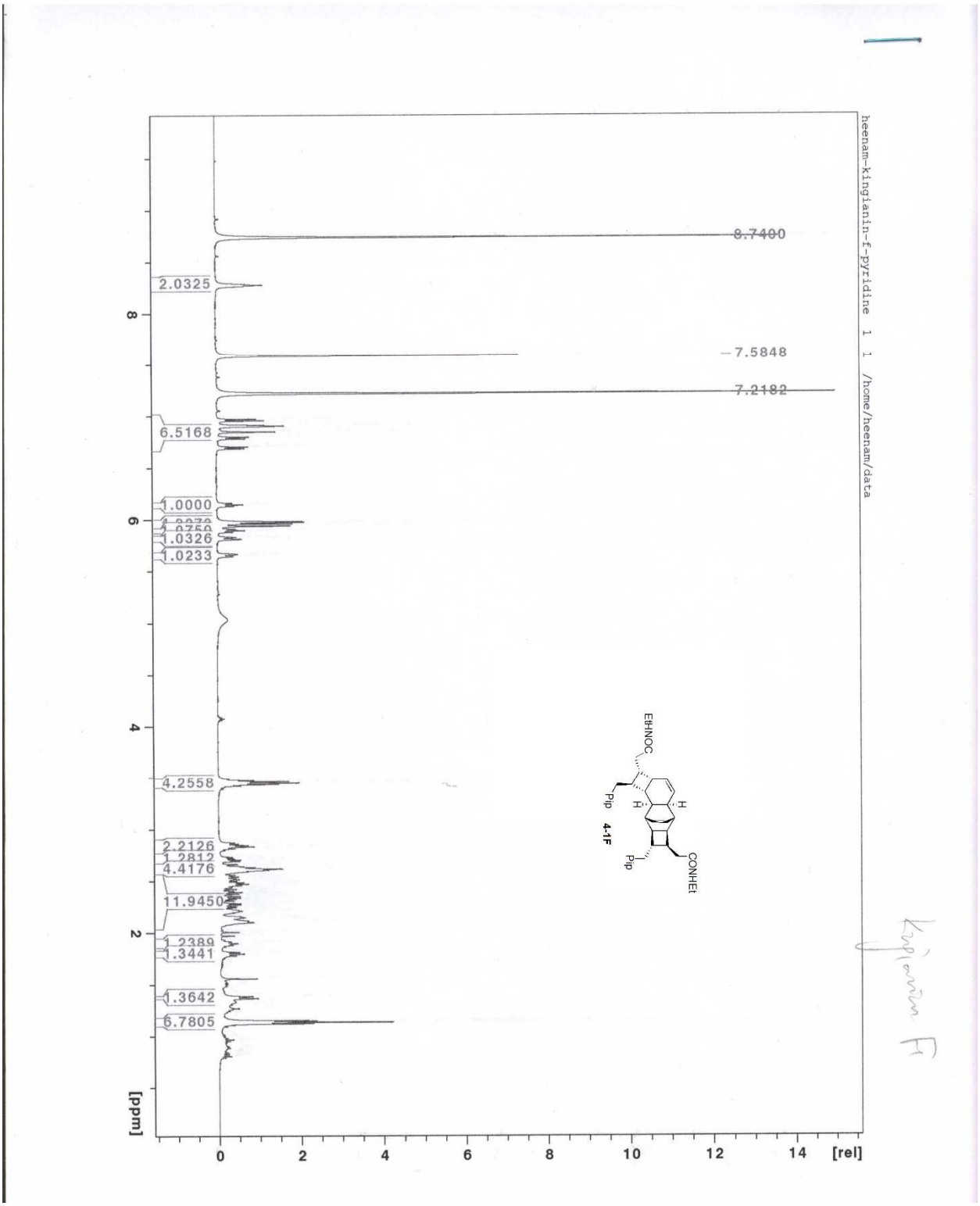

HO
Pip
H
H
4-27
OH
Pip
heenam-F-exo 6 1 /home/heenam/data
F2 [ppm]
F1 [ppm]
140
120
100
80
60
1
2
3
4
[*1e6]
HMBC

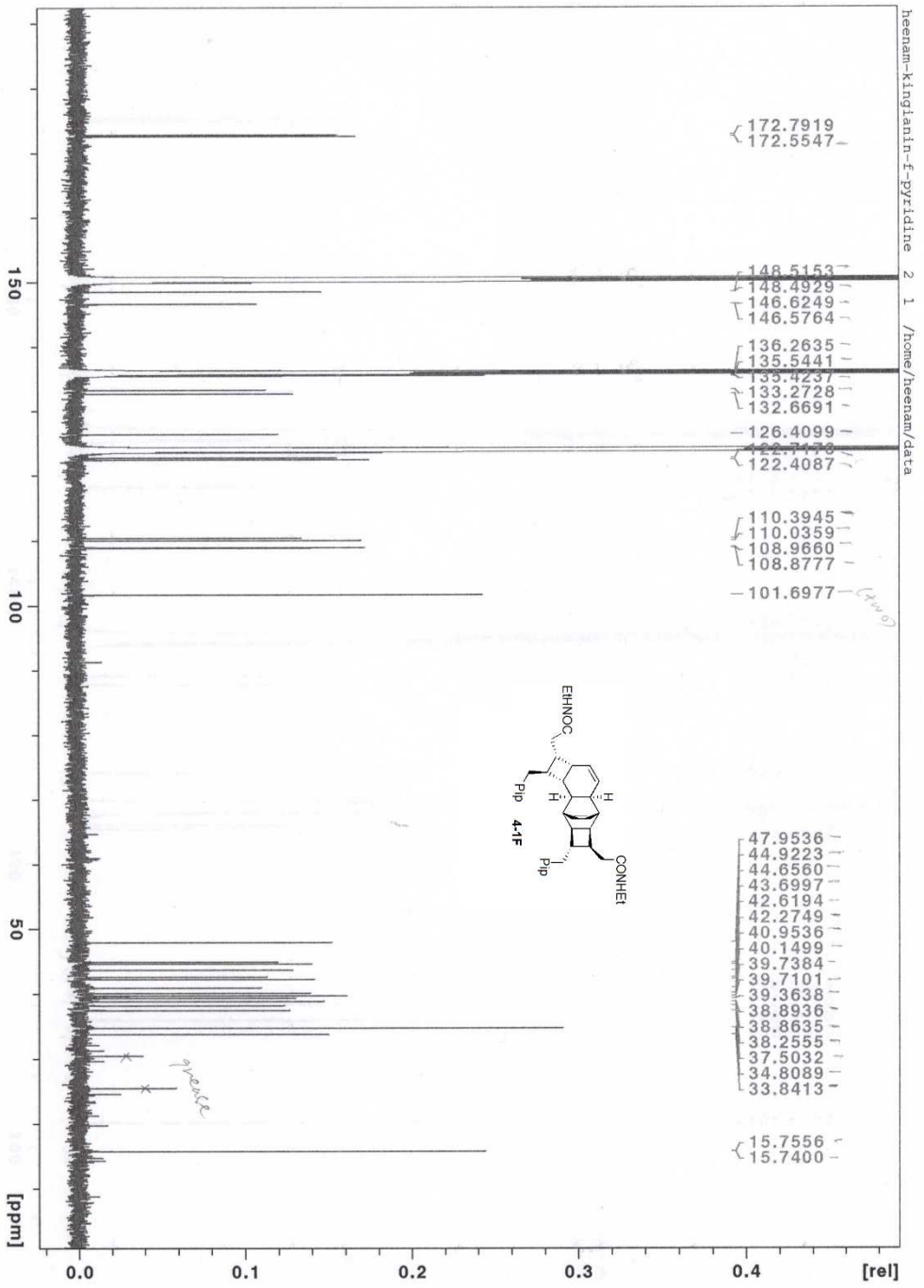

HO
Pip
H
H
Pip
OH
4-27
heenam-F_exo 4 1
/home/heenam/data
F2 [ppm]
F1 [ppm]
140
120
100
80
60
7
6
5
4
3
2
5
10
15
[*1e6]
HMQC

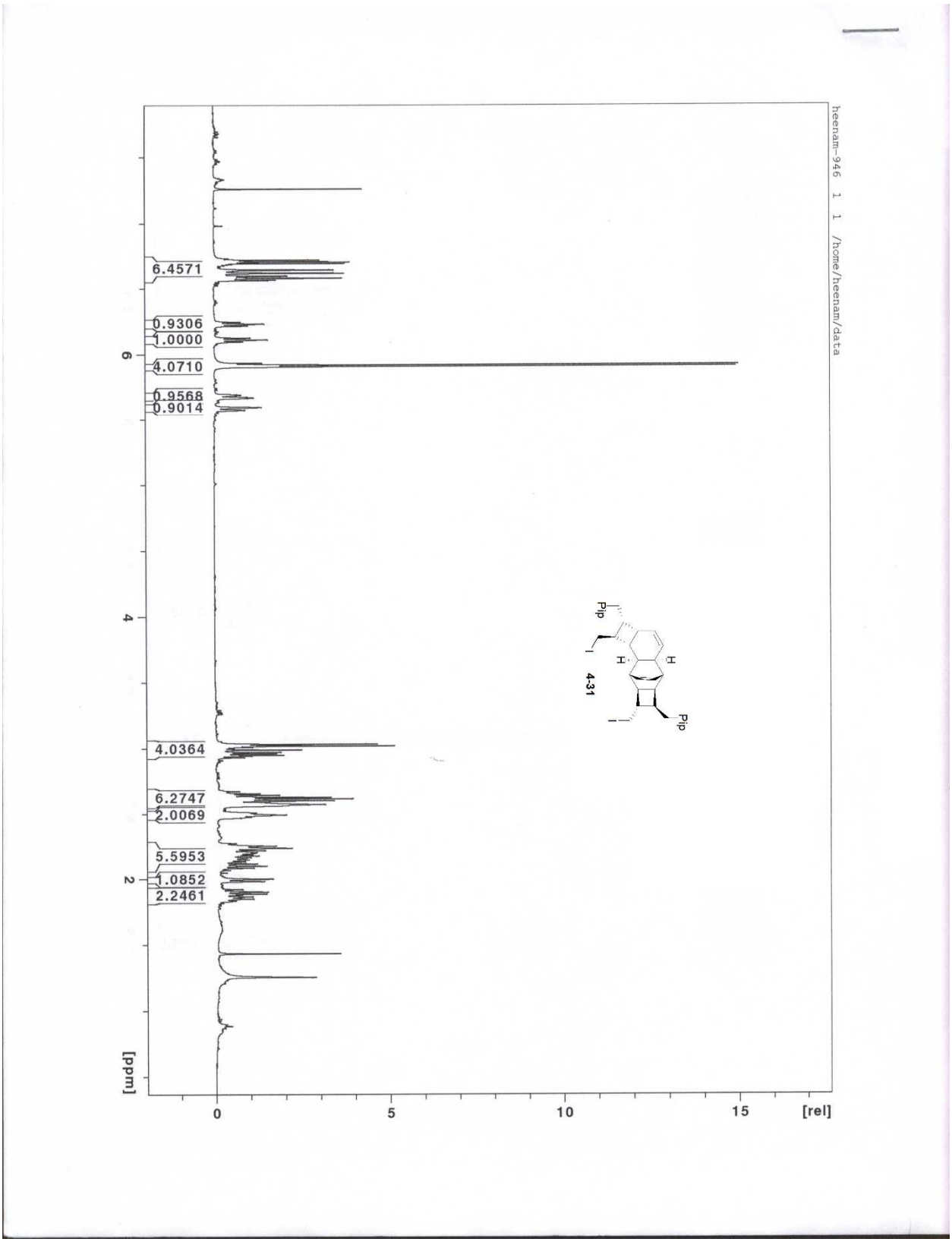

heenam-dimesylate-F 1 1 /home/heenam/data
7.2600
6.2773
1.0000
1.0530
4.0655
1.0156
1.0579
1.0176
0.9959
2.0348
5.9940
8.9236
4.5653
2.4561
1.5917
1.2807
4-28
6
4
2
[ppm]
0
5
10
15
[rel]

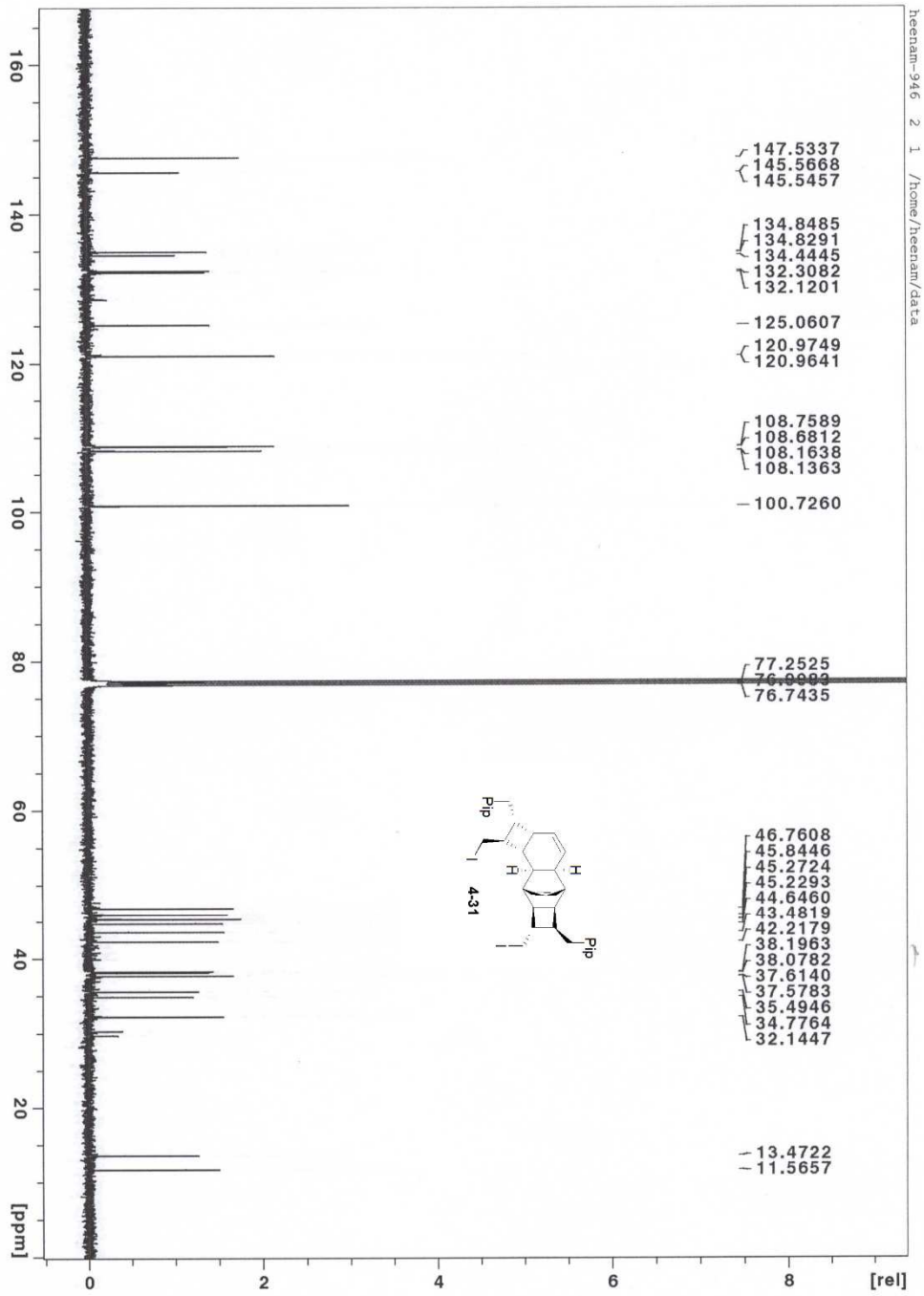

heenam-981 1 1 /home/heenam/data
7.2600
1.9350
3.9635
1.0003
0.9643
3.9240
0.9739
1.0000
7.3175
1.1221
1.1605
5.3764
3.1533
1.1512
1.1761
1.0696
4-29
[ppm]
[rel]
0
5
10
2
4
6

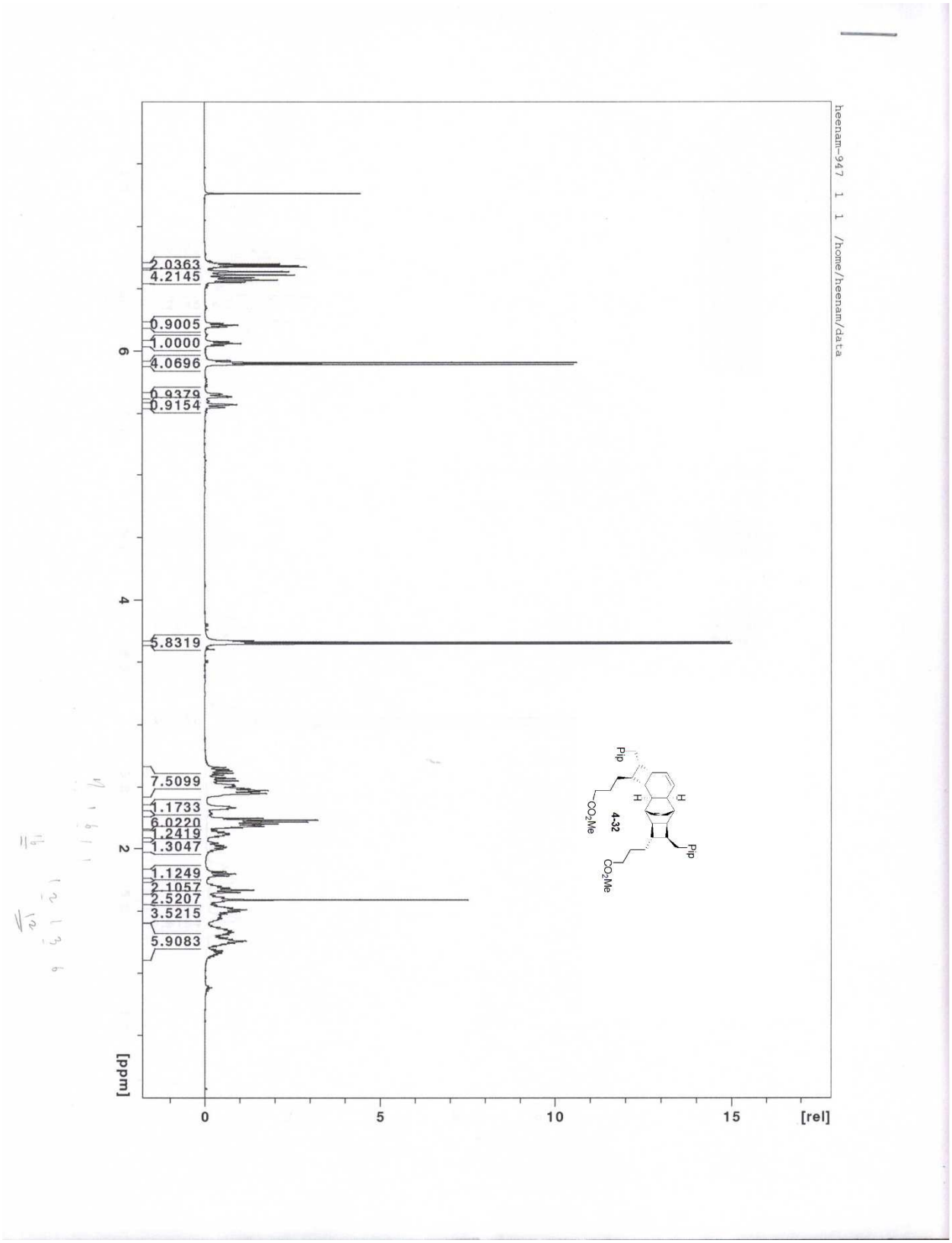

heenam-981 2 1 /home/heenam/data
147.6499
147.5799
145.9177
145.8029
134.0023
133.7132
133.4741
133.3370
132.9922
123.4757
121.5079
121.2334
119.3624
118.9925
109.0859
108.7918
108.2411
108.2021
100.8565
100.8145
77.2543
76.7456
47.0934
43.8673
43.5918
42.4509
41.3347
41.1805
39.9367
37.9943
37.8839
37.7503
37.6412
37.4742
31.8878
17.7548
16.8852
4-29
[ppm]
[rel]

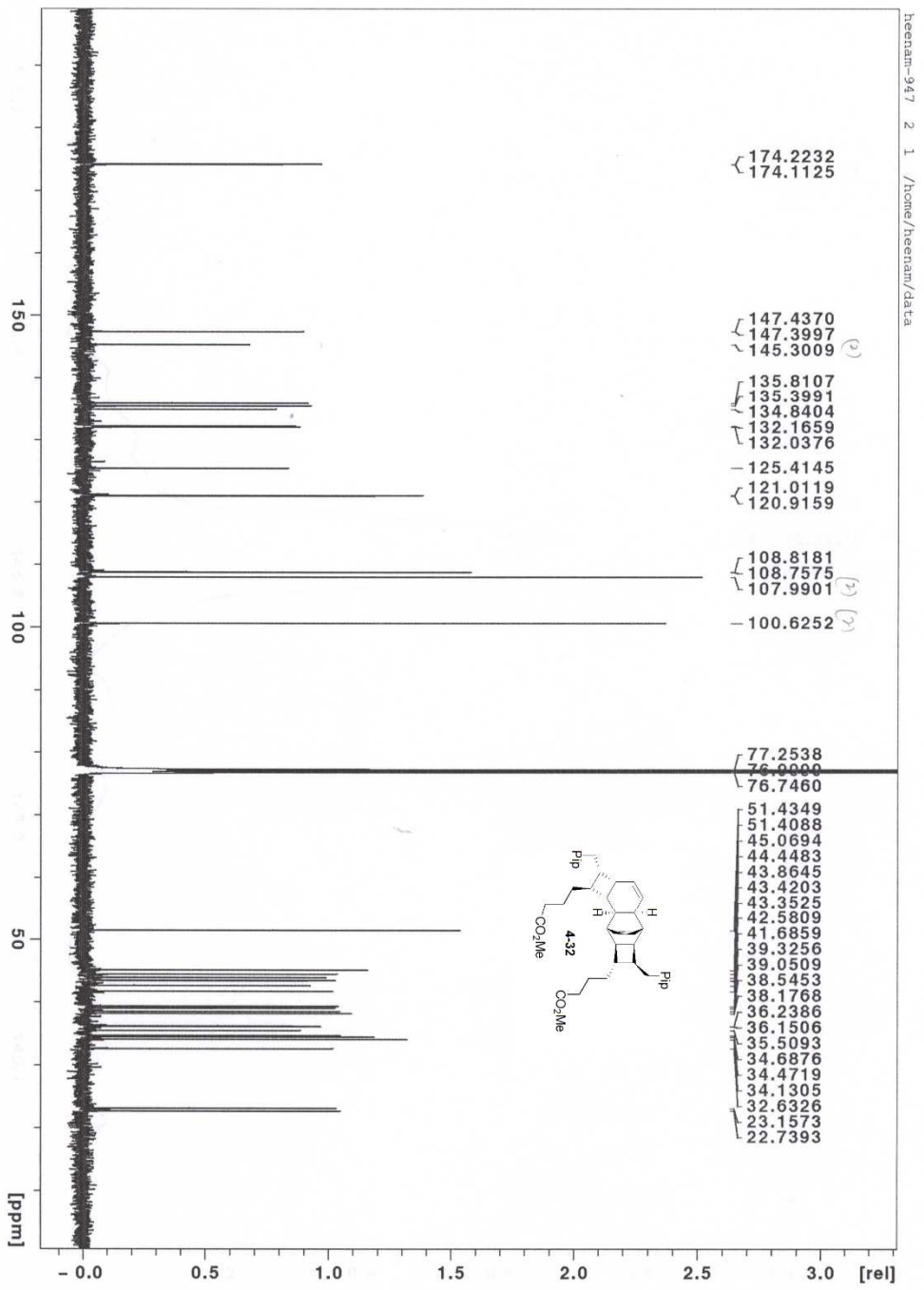

heenam-kinglanin-f-pyridine 1 1 /home/heenam/data
8.7400
7.5848
7.2182
2.0325
6.5168
1.0000
1.0326
1.0233
4.2558
2.2126
1.2812
4.4176
11.9450
1.3441
1.3642
6.7805
[ppm]
[rel]
EtHNOC
Pip
H
H
Pip
CONHEt
4-1F

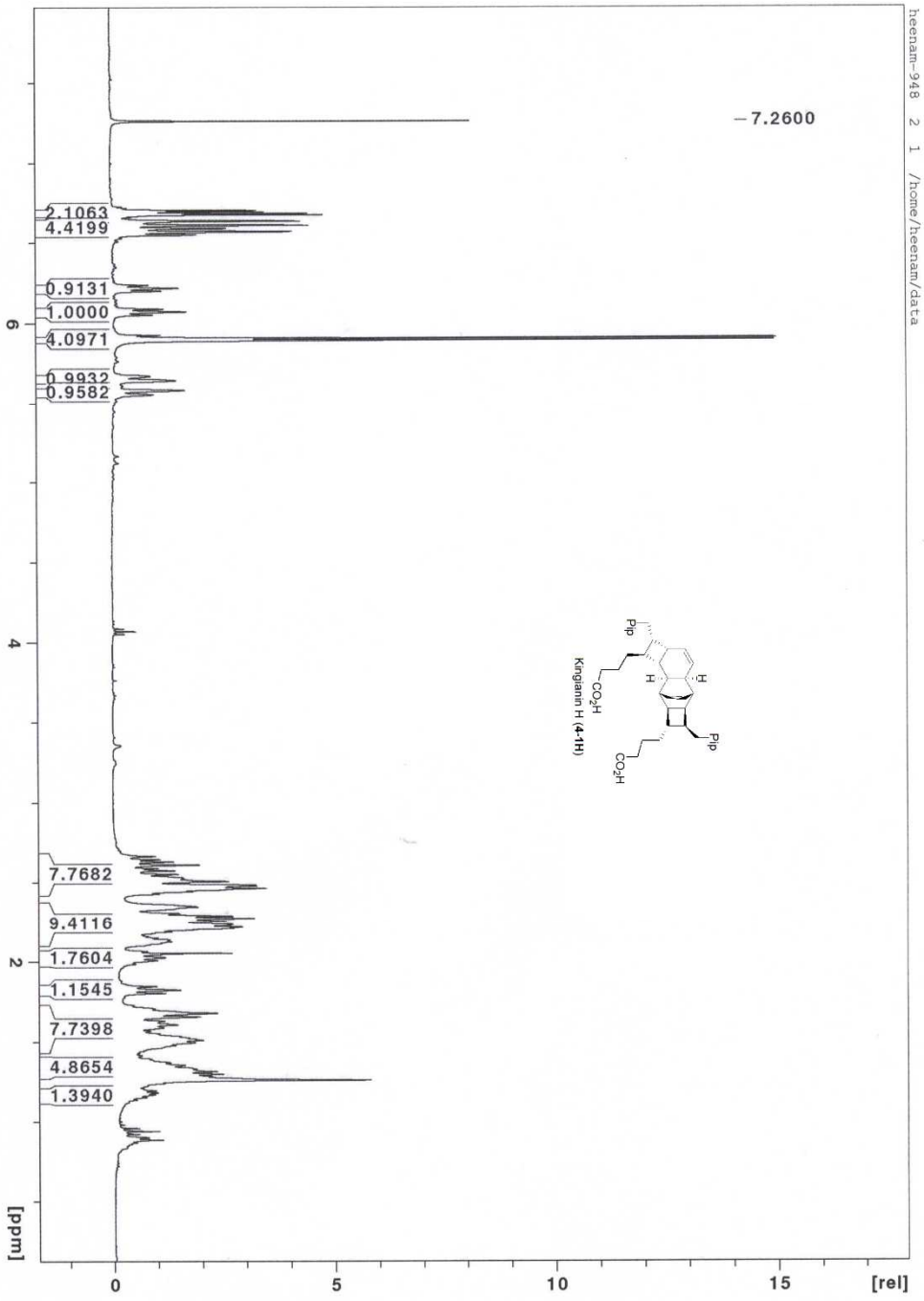

heenam-kinglanin-f-pyridine 2 1 /home/heenam/data
172.7919
172.5547
148.5153
148.4929
146.6249
146.5764
136.2635
135.5441
135.4237
133.2728
132.6691
126.4099
122.4087
110.3945
110.0359
108.9660
108.8777
101.6977
47.9536
44.9223
44.6560
43.6997
42.6194
42.2749
40.9536
40.1499
39.7384
39.7101
39.3638
38.8936
38.8635
38.2555
37.5032
34.8089
33.8413
15.7556
15.7400
EtHNOC
Pip
H
H
Pip
CONHEt
4-1F
150
100
50
[ppm]
0.0
0.1
0.2
0.3
0.4
[rel]

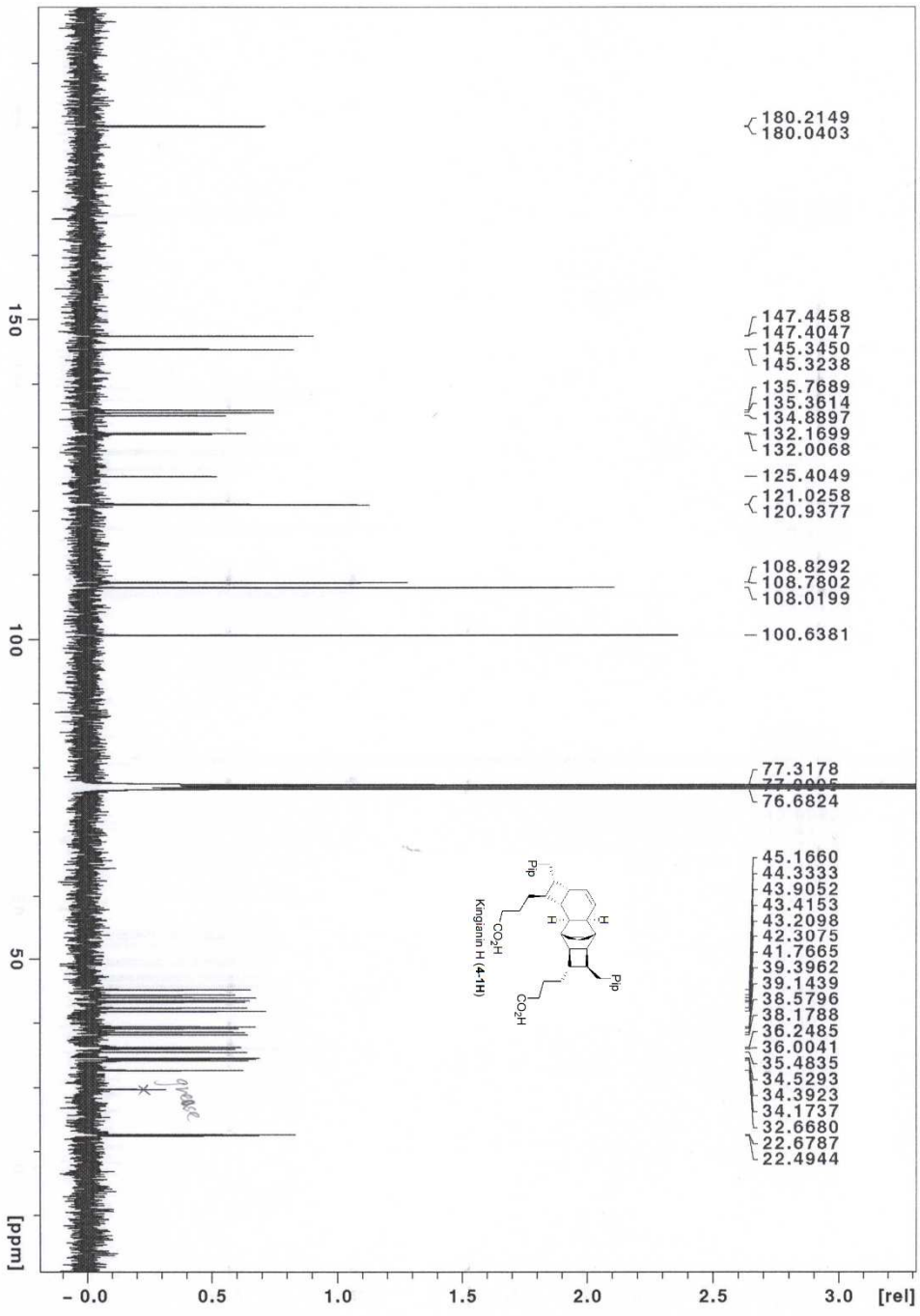

heenam-946 1 1 /home/heenam/data
6.4571
0.9306
1.0000
4.0710
0.9568
0.9014
4.0364
6.2747
2.0069
5.5953
1.0852
2.2461
6
4
2
[ppm]
0
5
10
15
[rel]
Pip
H
H
4-31
Pip

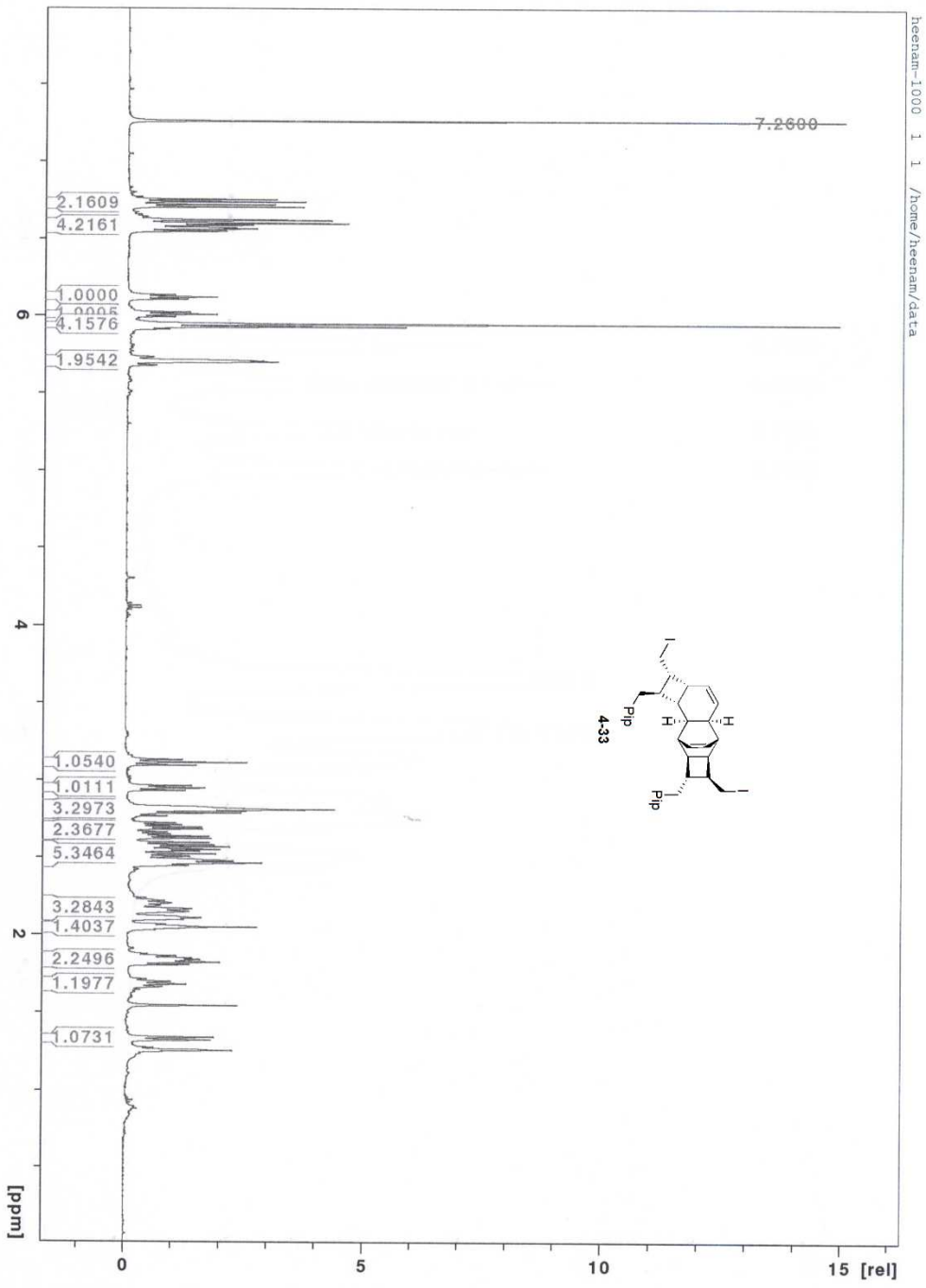

heenam-946 2 1 /home/heenam/data
147.5337
145.5668
145.5457
134.8485
134.8291
134.4445
132.3082
132.1201
125.0607
120.9749
120.9641
108.7589
108.6812
108.1638
108.1363
100.7260
77.2525
76.7435
46.7608
45.8446
45.2724
45.2293
44.6460
43.4819
42.2179
38.1963
38.0782
37.6140
37.5783
35.4946
34.7764
32.1447
13.4722
11.5657
Pip
H
H
Pip
4-31
160
140
120
100
80
60
40
20
[ppm]
0
2
4
6
8
[rel]

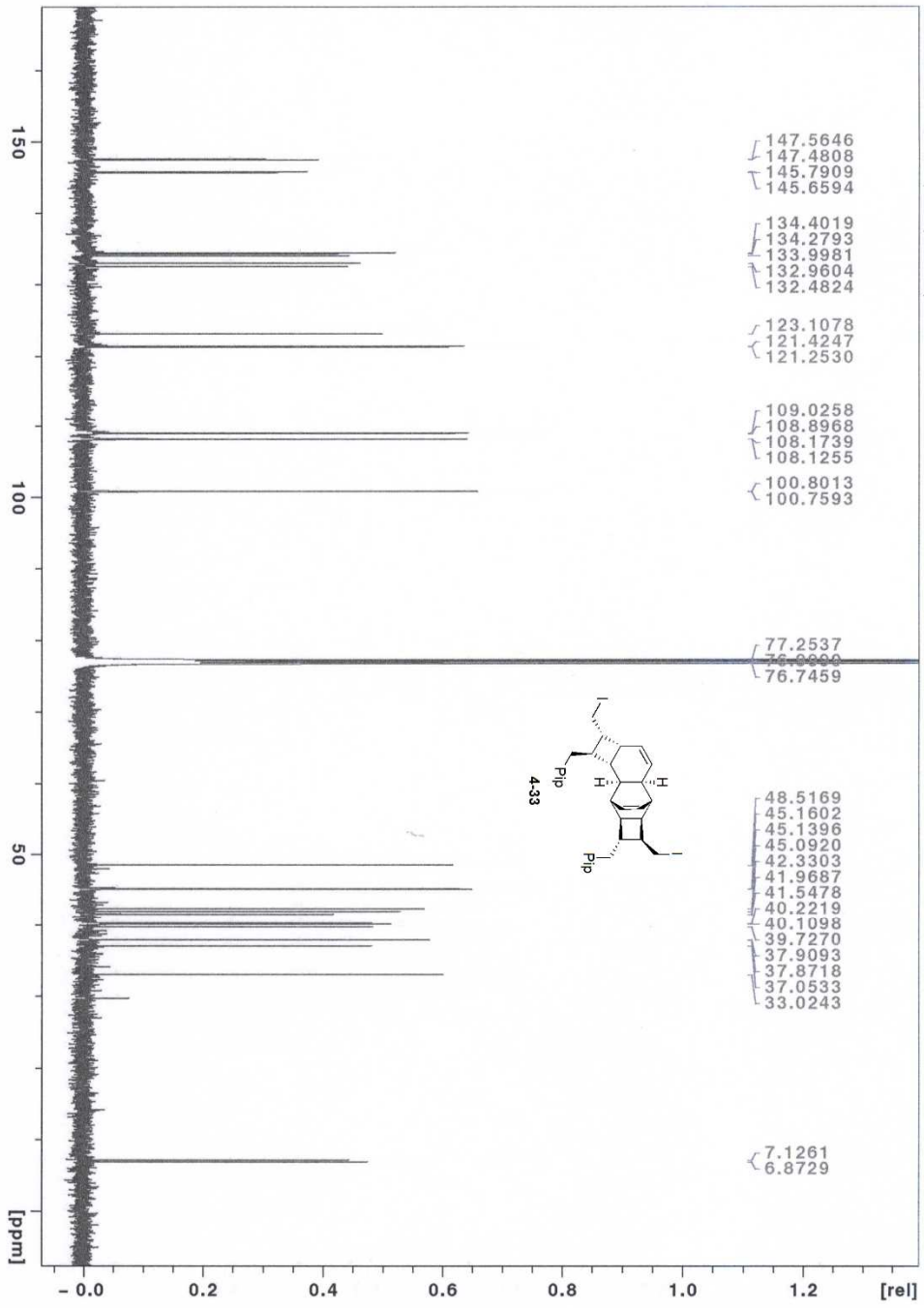

heenam-947 1 1 /home/heenam/data
2.0363
4.2145
0.9005
1.0000
4.0696
0.9379
0.9154
5.8319
7.5099
1.1733
6.0220
1.2419
1.3047
1.1249
2.1057
2.5207
3.5215
5.9083
6
4
2
[ppm]
0
5
10
15
[rel]
Pip
H
H
CO2Me
4-32
Pip
CO2Me

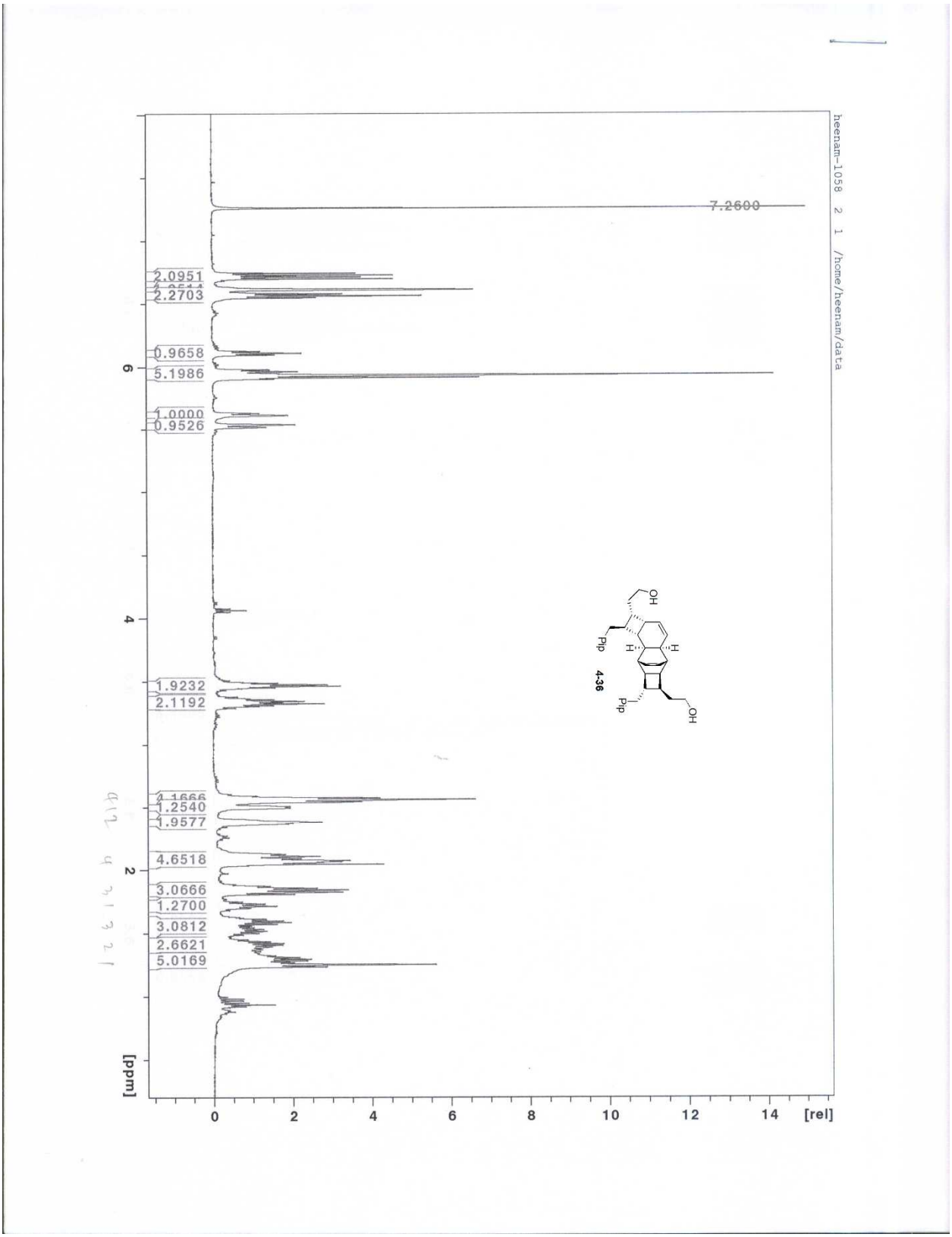

heenam-947 2 1 /home/heenam/data
174.2232
174.1125
147.4370
147.3997
145.3009
135.8107
135.3991
134.8404
132.1659
132.0376
125.4145
121.0119
120.9159
108.8181
108.7575
107.9901
100.6252
77.2538
76.7460
51.4349
51.4088
45.0694
44.4483
43.8645
43.4203
43.3525
42.5809
41.6859
39.3256
39.0509
38.5453
38.1768
36.2386
36.1506
35.5093
34.6876
34.4719
34.1305
32.6326
23.1573
22.7393
Pip
H
H
CO2Me
4-32
Pip
CO2Me
150
100
50
[ppm]
0.0
0.5
1.0
1.5
2.0
2.5
3.0
[rel]

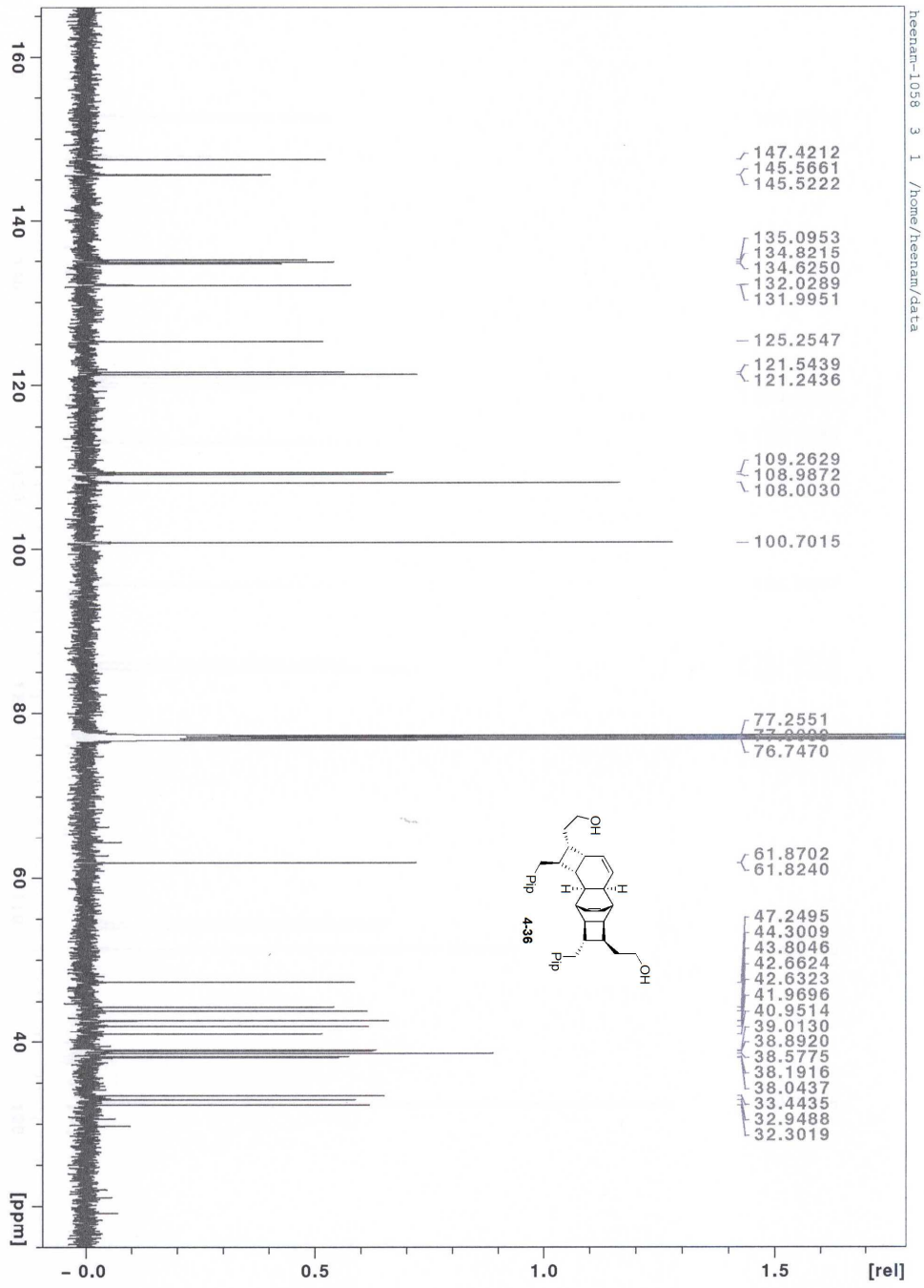

heenam-948 2 1 /home/heenam/data
7.2600
2.1063
4.4199
0.9131
1.0000
4.0971
0.9932
0.9582
7.7682
9.4116
1.7604
1.1545
7.7398
4.8654
1.3940
Kingianin H (4-1H)
[ppm]
[rel]
0
5
10
15
2
4
6

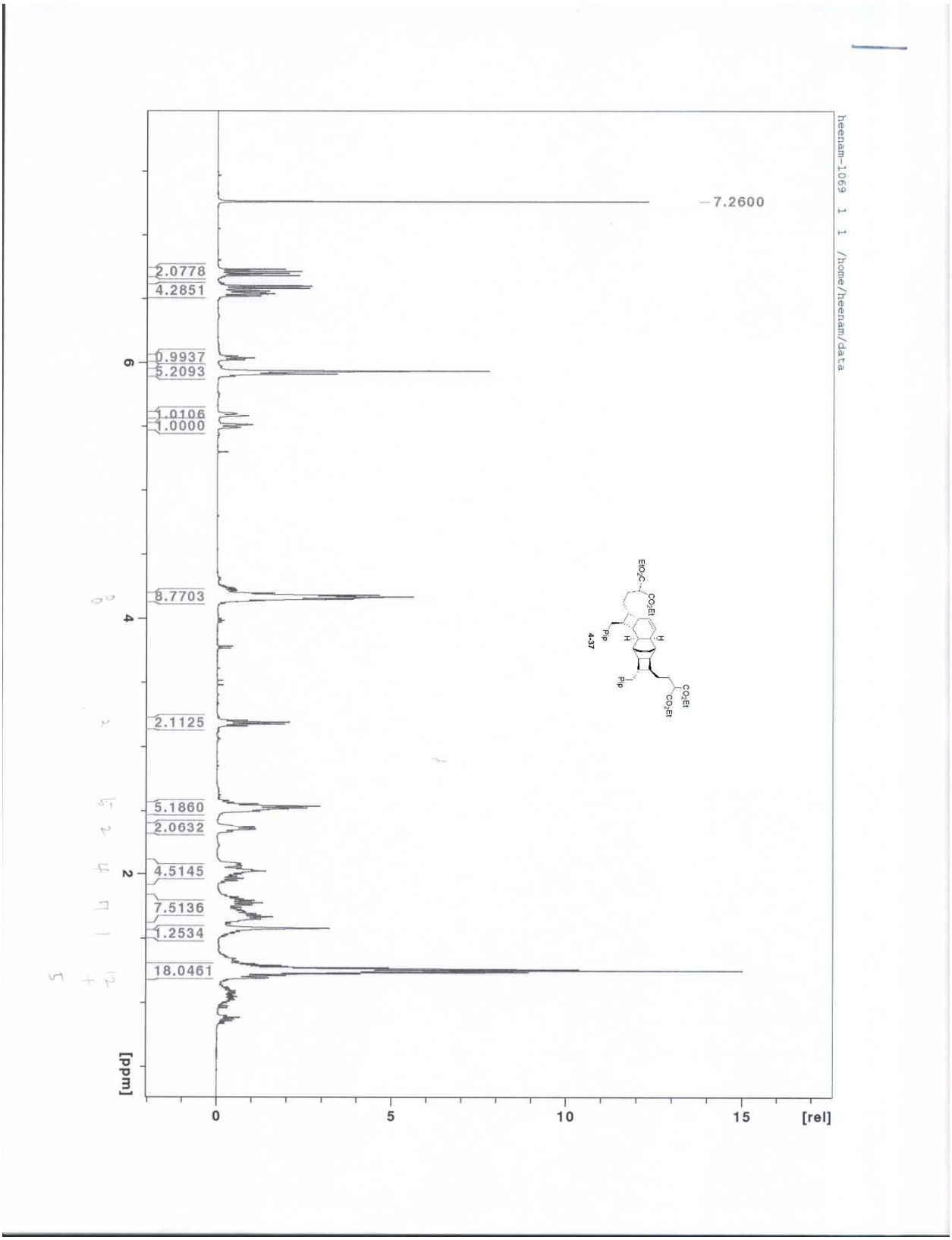

heenam-948 3 1 /home/heenam/data
180.2149
180.0403
147.4458
147.4047
145.3450
145.3238
135.7689
135.3614
134.8897
132.1699
132.0068
125.4049
121.0258
120.9377
108.8292
108.7802
108.0199
100.6381
77.3178
76.6824
45.1660
44.3333
43.9052
43.4153
43.2098
42.3075
41.7665
39.3962
39.1439
38.5796
38.1788
36.2485
36.0041
35.4835
34.5293
34.3923
34.1737
32.6680
22.6787
22.4944
Kingianin H (4-1H)
Pip
Pip
CO2H
CO2H
H
H
150
100
50
[ppm]
0.0
0.5
1.0
1.5
2.0
2.5
3.0
[rel]

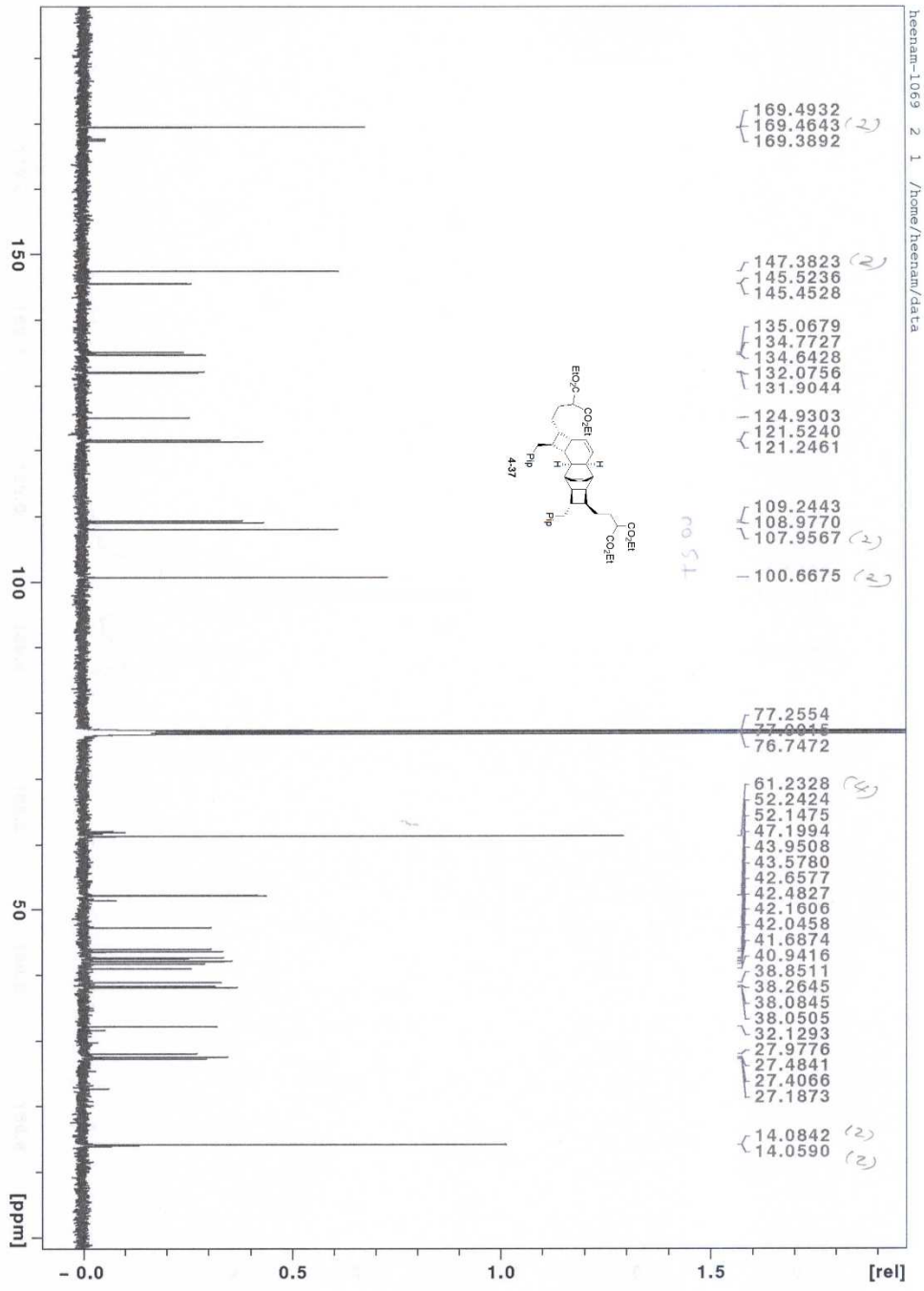

heenam-1000 1 1 /home/heenam/data
7.2600
2.1609
4.2161
1.0000
4.1576
1.9542
1.0540
1.0111
3.2973
2.3677
5.3464
3.2843
1.4037
2.2496
1.1977
1.0731
6
4
2
[ppm]
0
5
10
15 [rel]
I
Pip
H
H
4-33
Pip
I


heenam-1000 2 1 /home/heenam/data
147.5646
147.4808
145.7909
145.6594
134.4019
134.2793
133.9981
132.9604
132.4824
123.1078
121.4247
121.2530
109.0258
108.8968
108.1739
108.1255
100.8013
100.7593
77.2537
76.7459
48.5169
45.1602
45.1396
45.0920
42.3303
41.9687
41.5478
40.2219
40.1098
39.7270
37.9093
37.8718
37.0533
33.0243
7.1261
6.8729
4-33
Pip
Pip
150
100
50
[ppm]
- 0.0
0.2
0.4
0.6
0.8
1.0
1.2
[rel]


heenam-1058 2 1 /home/heenam/data
7.2600
2.0951
2.2703
0.9658
5.1986
1.0000
0.9526
1.9232
2.1192
4.1666
1.2540
1.9577
4.6518
3.0666
1.2700
3.0812
2.6621
5.0169
[ppm]
[rel]
OH
Pip
H
H
Pip
OH
4-36


heenam-1058 3 1 /home/heenam/data
147.4212
145.5661
145.5222
135.0953
134.8215
134.6250
132.0289
131.9951
125.2547
121.5439
121.2436
109.2629
108.9872
108.0030
100.7015
77.2551
76.7470
61.8702
61.8240
47.2495
44.3009
43.8046
42.6624
42.6323
41.9696
40.9514
39.0130
38.8920
38.5775
38.1916
38.0437
33.4435
32.9488
32.3019
OH
Pip
H
H
Pip
OH
4-36
160
140
120
100
80
60
40
[ppm]
0.0
0.5
1.0
1.5
[rel]

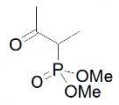

heenam-1069 1 1 /home/heenam/data
7.2600
2.0778
4.2851
0.9937
5.2093
1.0106
1.0000
8.7703
2.1125
5.1860
2.0632
4.5145
7.5136
1.2534
18.0461
[ppm]
[rel]
4-37


heenam-1069 2 1 /home/heenam/data
169.4932
169.4643 (2)
169.3892
147.3823 (2)
145.5236
145.4528
135.0679
134.7727
134.6428
132.0756
131.9044
124.9303
121.5240
121.2461
109.2443
108.9770
107.9567 (2)
100.6675 (2)
77.2554
76.7472
61.2328 (4)
52.2424
52.1475
47.1994
43.9508
43.5780
42.6577
42.4827
42.1606
42.0458
41.6874
40.9416
38.8511
38.2645
38.0845
38.0505
32.1293
27.9776
27.4841
27.4066
27.1873
14.0842 (2)
14.0590 (2)
4-37
150
100
50
[ppm]
0.0
0.5
1.0
1.5
[rel]

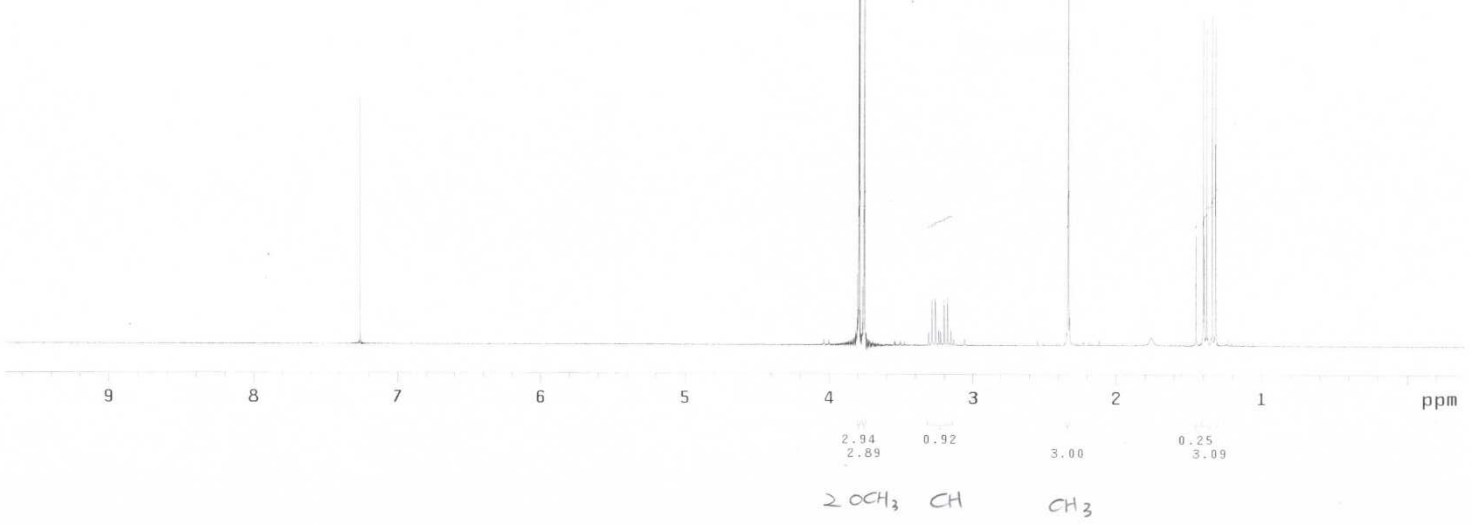
new experiment

expl s2pul

SAMPLE		DEC. & VT	
date	Mar 3 2009	dfrq	300.074
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.074	dm	nnn
tn	H1	dmm	c
at	1.998	dmf	200
np	17984	temp	25.0
sw	4500.5	PROCESSING	
fb	2600	wtfile	
bs	16	proc	ft
tpwr	50	fn	not used
pw	1.0		
d1	1.000	werr	
tof	0	wexp	
nt	64	wbs	
ct	64	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-116.9		
wp	3033.8		
vs	172		
sc	0		
wc	250		
hzmm	12.14		
is	96.28		
rfl	749.5		
rfp	0		
th	21		
ins	3.000		
nm	ph		



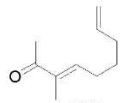
6-61



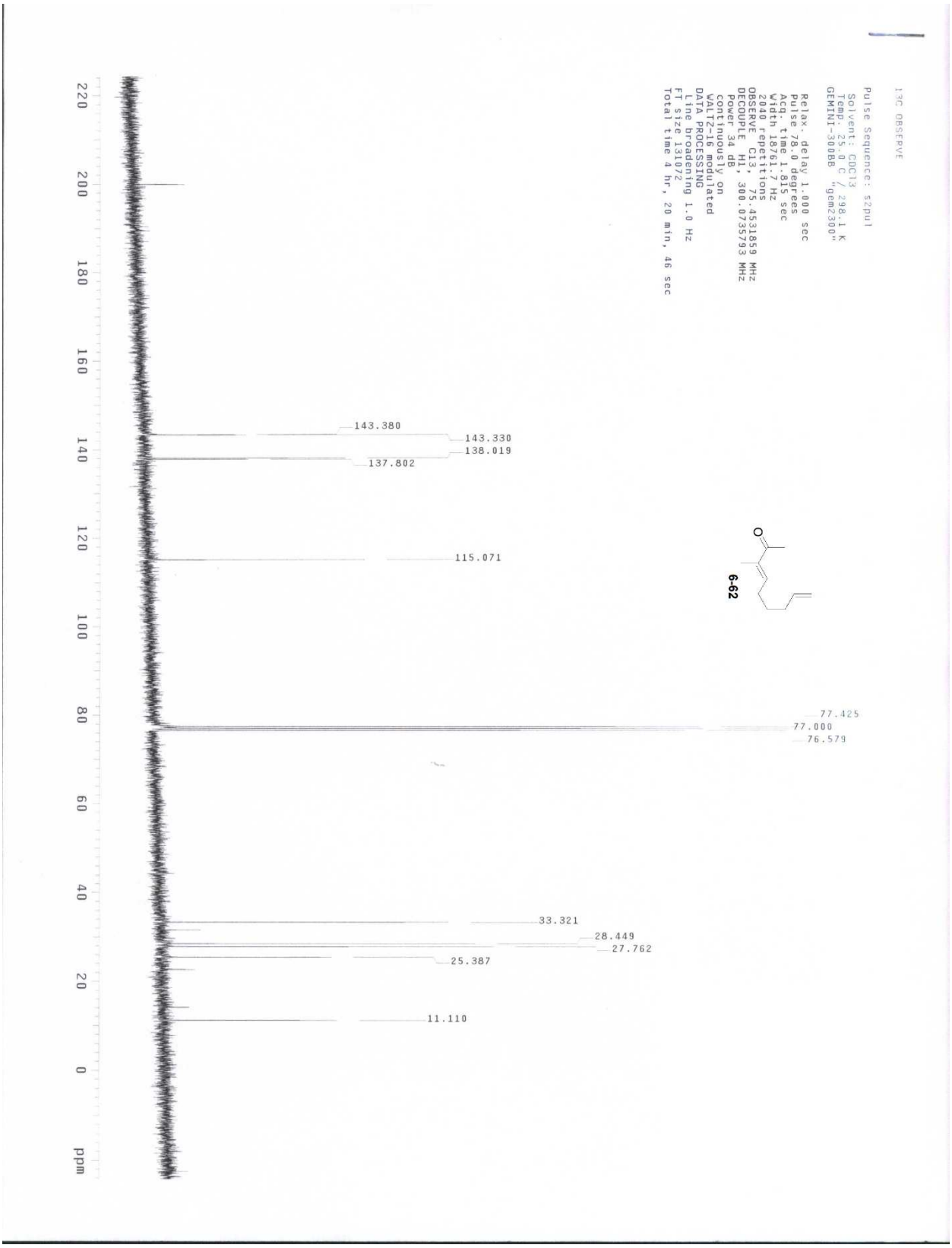
new experiment

expl s2pul

SAMPLE		DEC. & VT	
date	Mar 27 2009	dfrq	300.074
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.074	dm	nnn
tn	H1	dmm	c
at	1.998	dmf	200
np	17984	temp	25.0
sw	4500.5	PROCESSING	
fb	2600	wtfile	
bs	16	proc	ft
tpwr	50	fn	not used
pw	1.0		
d1	1.000	werr	
tof	0	wexp	
nt	16	wbs	
ct	16	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-122.4		
wp	3163.7		
vs	173		
sc	0		
wc	250		
hzmm	12.65		
is	182.45		
rfl	2927.8		
rfp	2178.5		
th	2		
ins	1.000		
nm	ph		



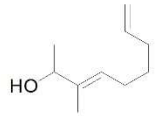
6-62


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp: 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 78.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
2048 repetitions
OBSERVE C13, 75.4531859 MHz
DECOUPLE H1, 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 4 hr, 20 min, 46 sec
143.380
143.330
138.019
137.802
115.071
77.425
77.000
76.579
33.321
28.449
27.762
25.387
11.110
6-62
220
200
180
160
140
120
100
80
60
40
20
0
ppm

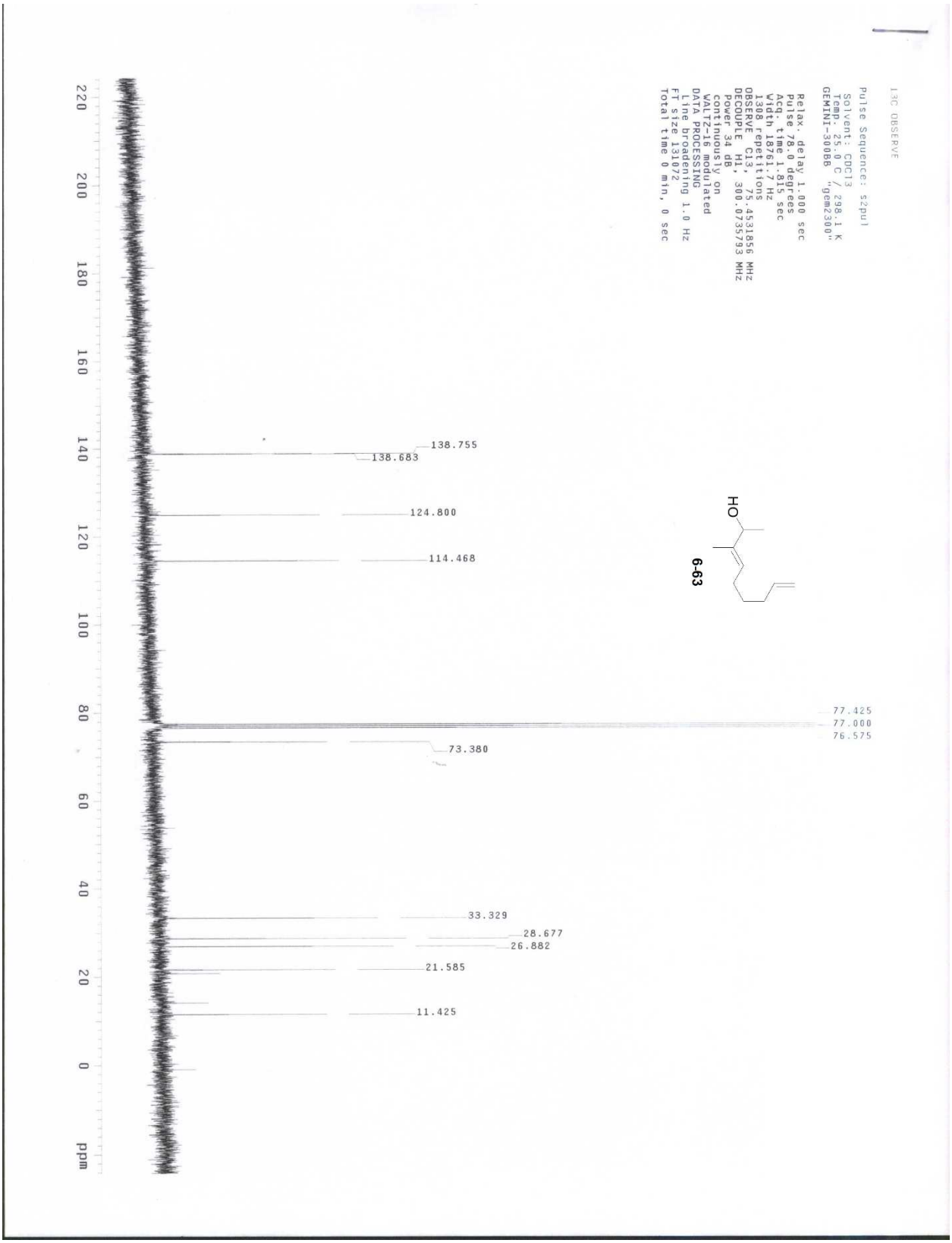
new experiment

expl s2pul

SAMPLE		DEC. & VT	
date	Mar 31 2009	dfrq	300.074
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.074	dm	nnn
tn	H1	dmm	c
at	1.998	dmf	200
np	17984	temp	25.0
sw	4500.5	PROCESSING	
fb	2600	wtfile	
bs	16	proc	ft
tpwr	50	fn	not used
pw	1.0		
d1	1.000	werr	
tof	0	wexp	
nt	64	wbs	
ct	64	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-69.4		
wp	3134.1		
vs	163		
sc	0		
wc	250		
hzmm	12.54		
is	145.86		
rfl	749.3		
rfp	0		
th	4		
ins	1.000		
nm	ph		



6-63

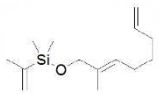

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 78.0 degrees
Acq. time 1.761 sec
Width 18761.7 Hz
1308 repetitions
OBSERVE C13, 75.4531856 MHz
DECOUPLE 'H1', 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 0 min, 0 sec
138.755
138.683
124.800
114.468
77.425
77.000
76.575
73.380
33.329
28.677
26.882
21.585
11.425
HO
6-63
220
200
180
160
140
120
100
80
60
40
20
0
ppm

new experiment

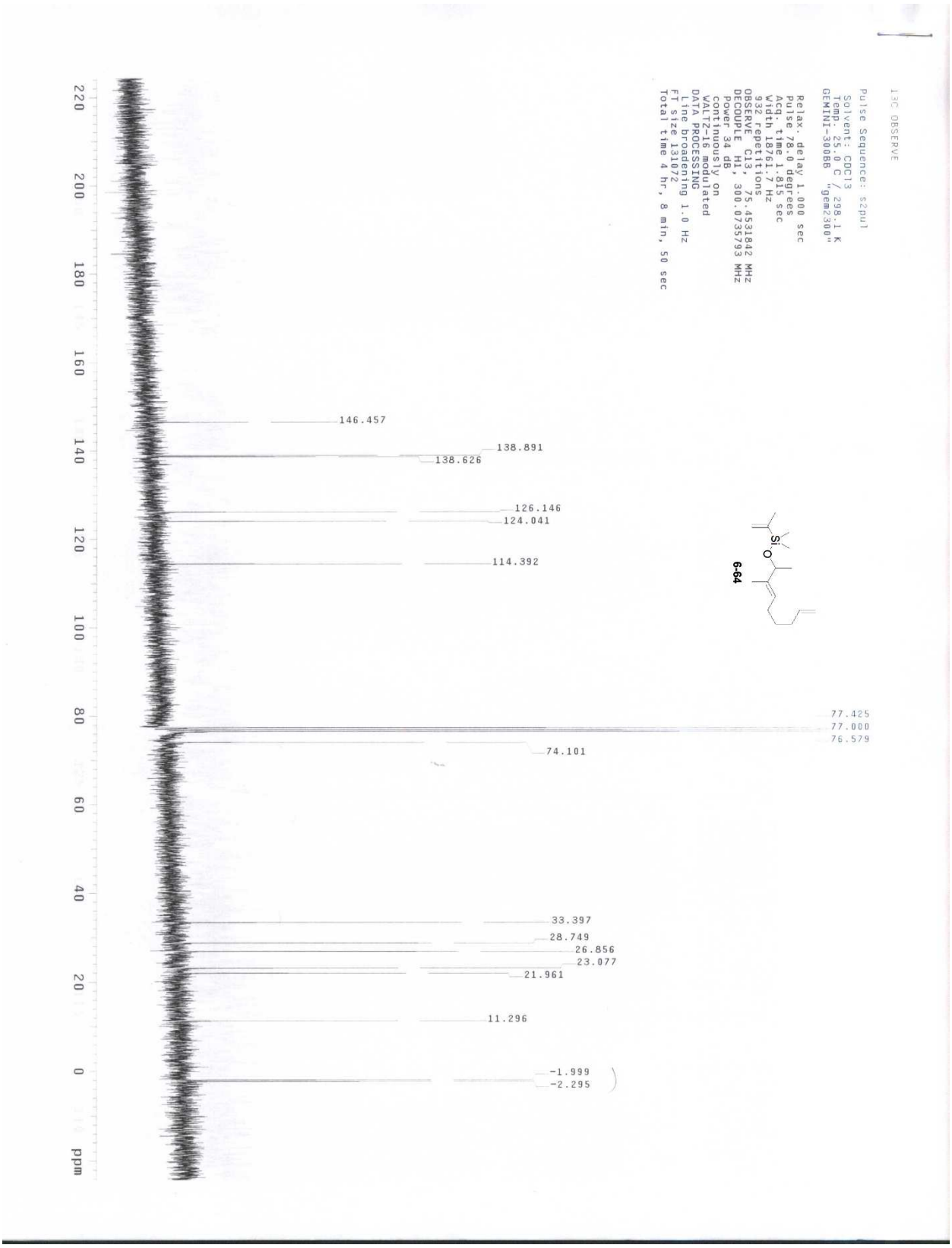
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 58 sec



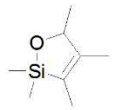
6-64


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 78.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
932 repetitions
OBSERVE C13, 75.4531842 MHz
DECOUPLE H1, 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 4 hr, 8 min, 50 sec
146.457
138.891
138.626
126.146
124.041
114.392
77.425
77.000
76.579
74.101
33.397
28.749
26.856
23.077
21.961
11.296
-1.999
-2.295
ppm
Si
O
6-64

new experiment

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec



6-65

X MC

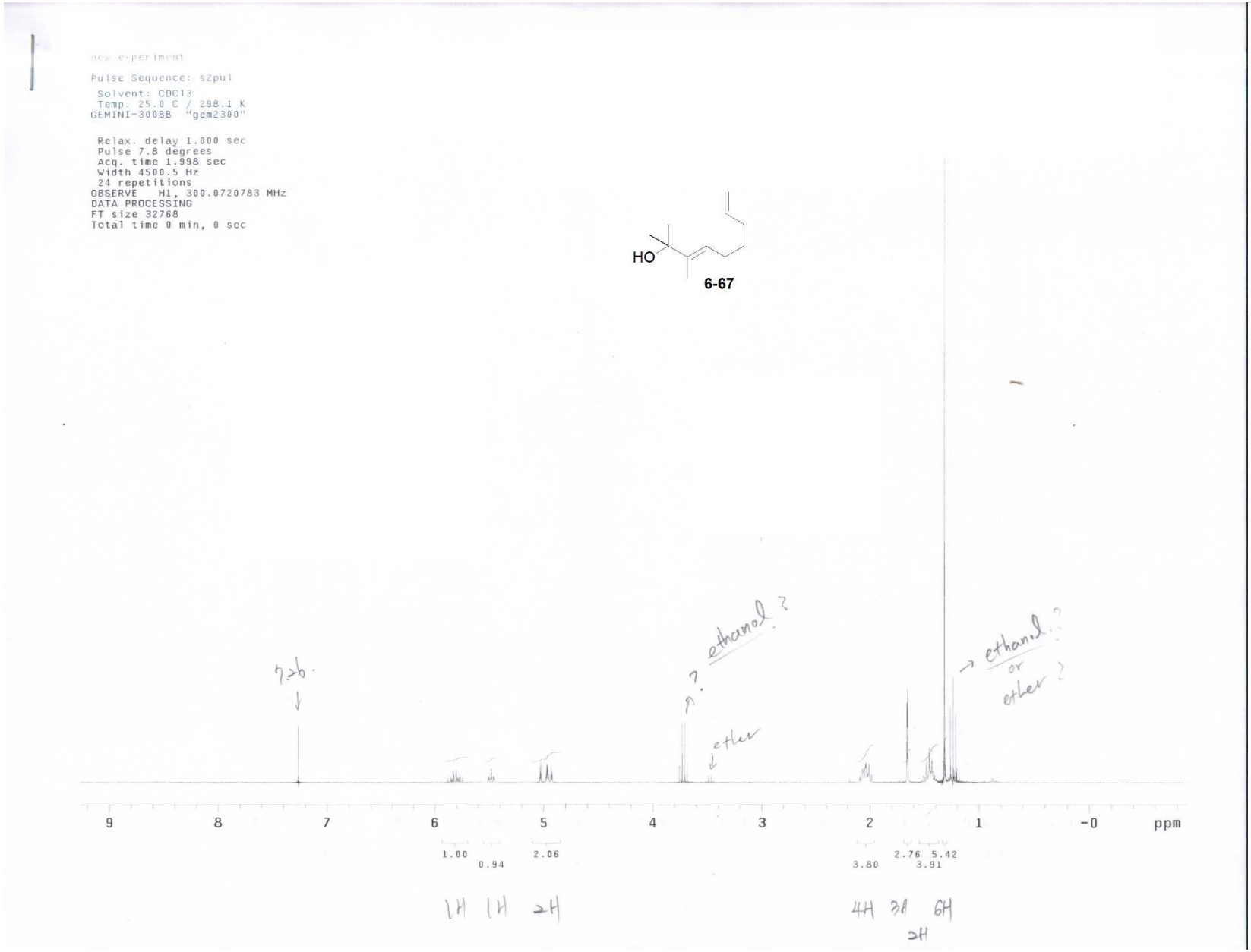
10 9 8 7 6 5 4 3 2 1 -0 ppm

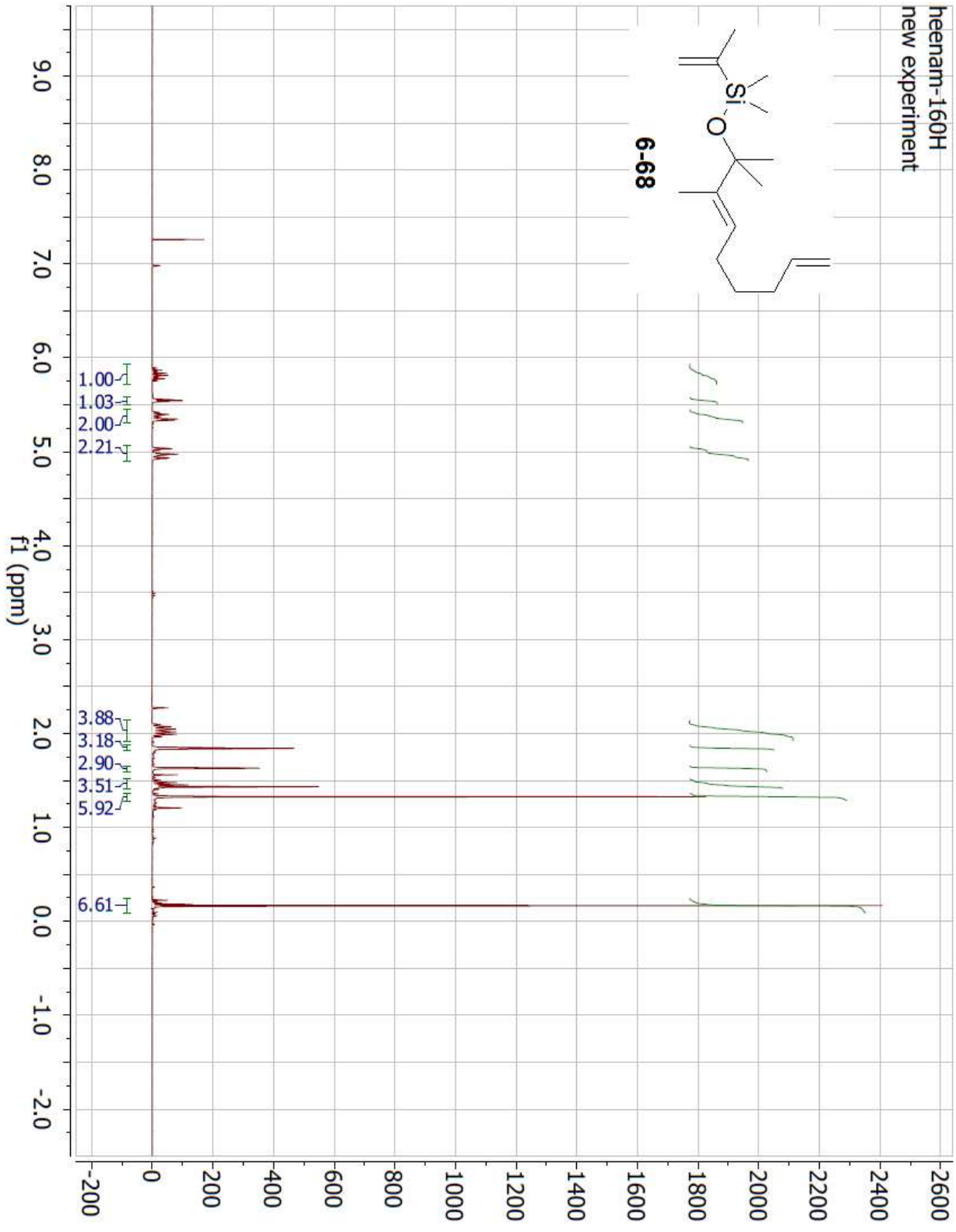
1.00

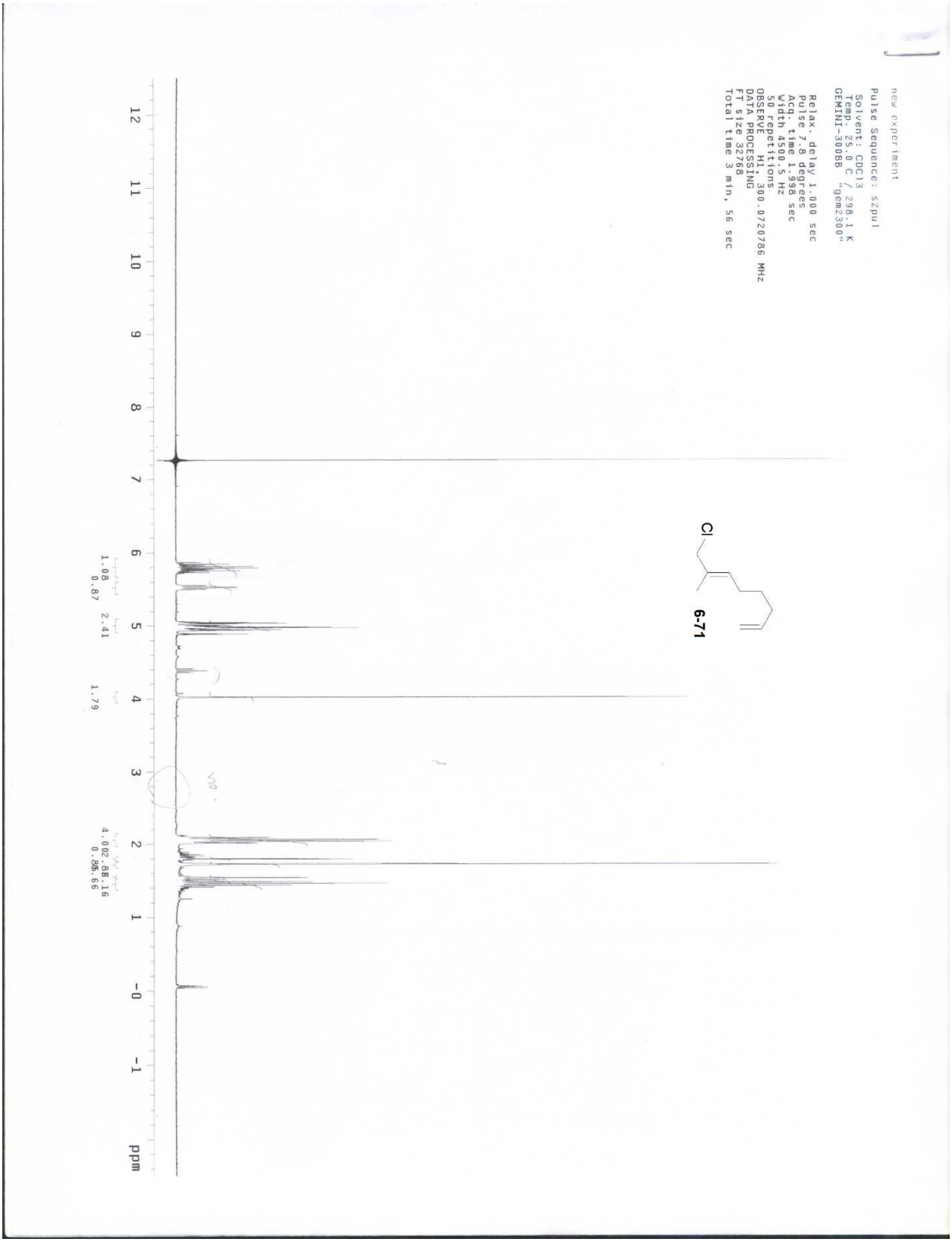
3.32 2.31
3.17 1.70

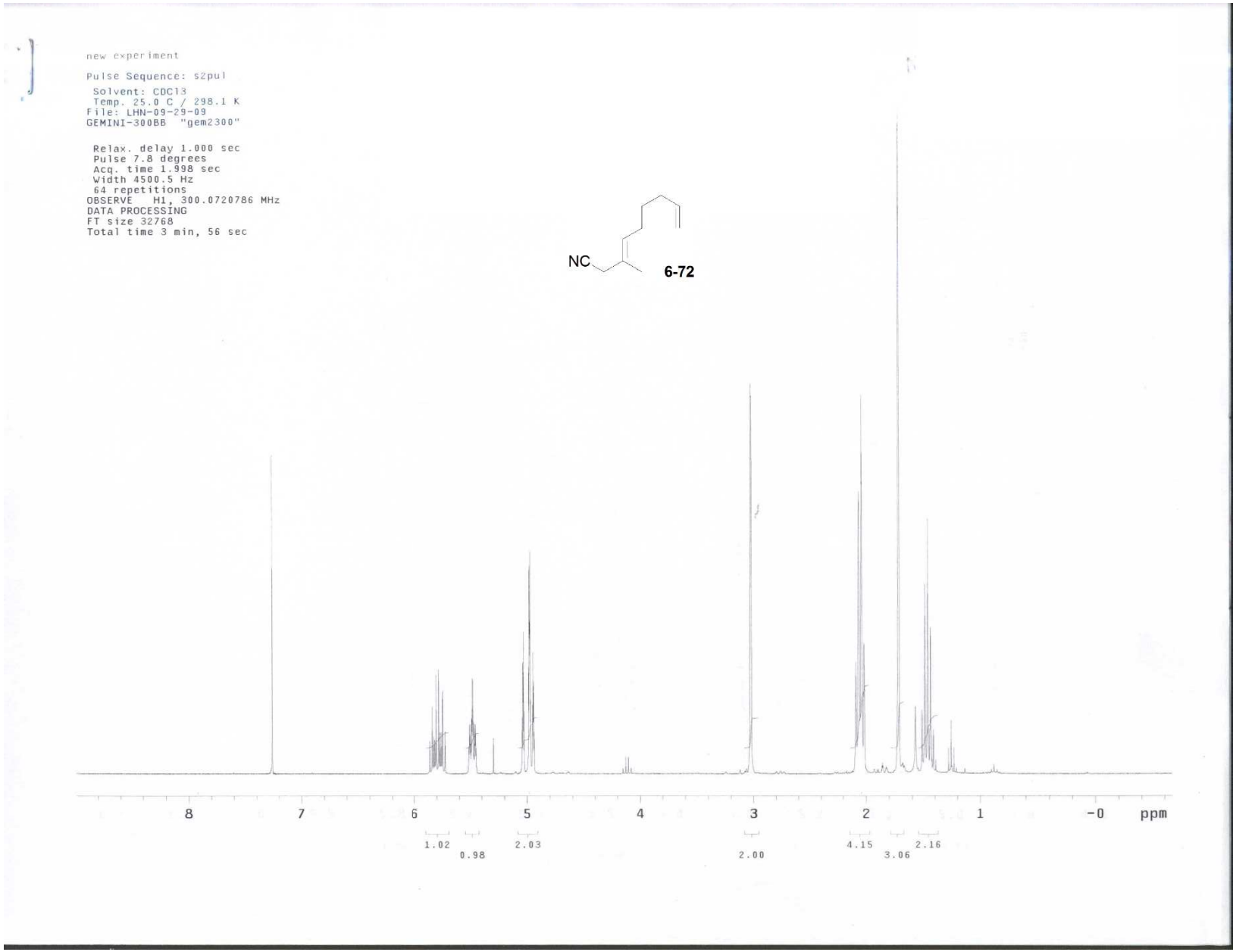
3H

3.01
2.98


new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
24 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
HO
6-67
ethanol ?
ether
ethanol ? or ether ?
9
8
7
6
5
4
3
2
1
-0
ppm
1.00
0.94
2.06
3.80
2.76
5.42
3.91


heenam-160H
new experiment
6-68
Si
O
1.00
1.03
2.00
2.21
3.88
3.18
2.90
3.51
5.92
6.61
f1 (ppm)

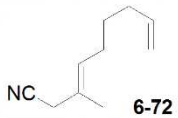

new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
50 repetitions
OBSERVE H1 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 56 sec
Cl
6-71
1.08
0.87
2.41
1.79
4.02
2.88
2.16
0.85
5.66
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm


new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: LHN-09-29-09
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 56 sec
NC
6-72
8
7
6
5
4
3
2
1
-0
ppm
1.02
0.98
2.03
2.00
4.15
3.06
2.16

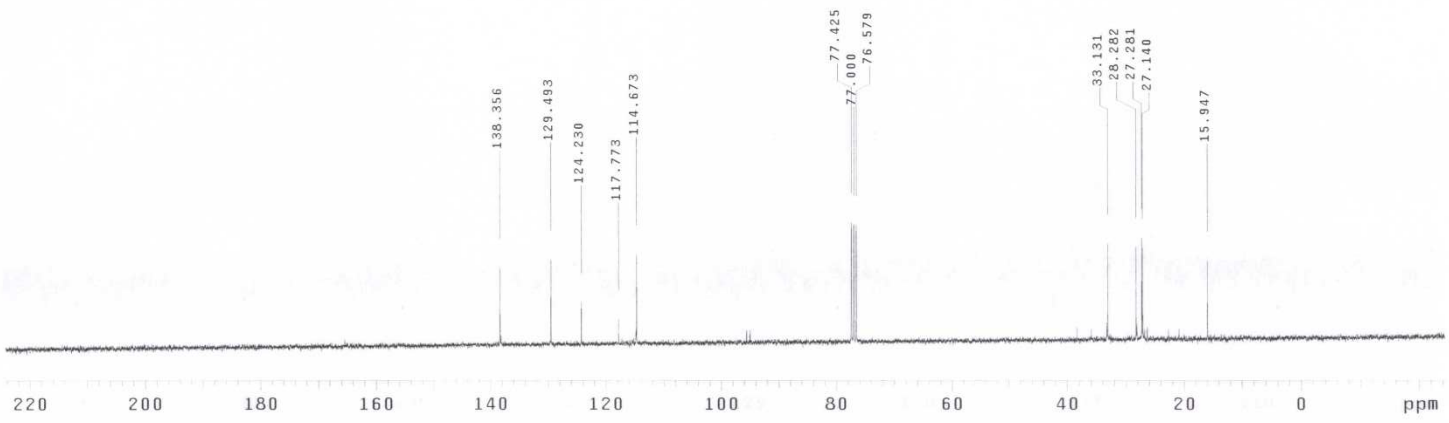
13C OBSERVE

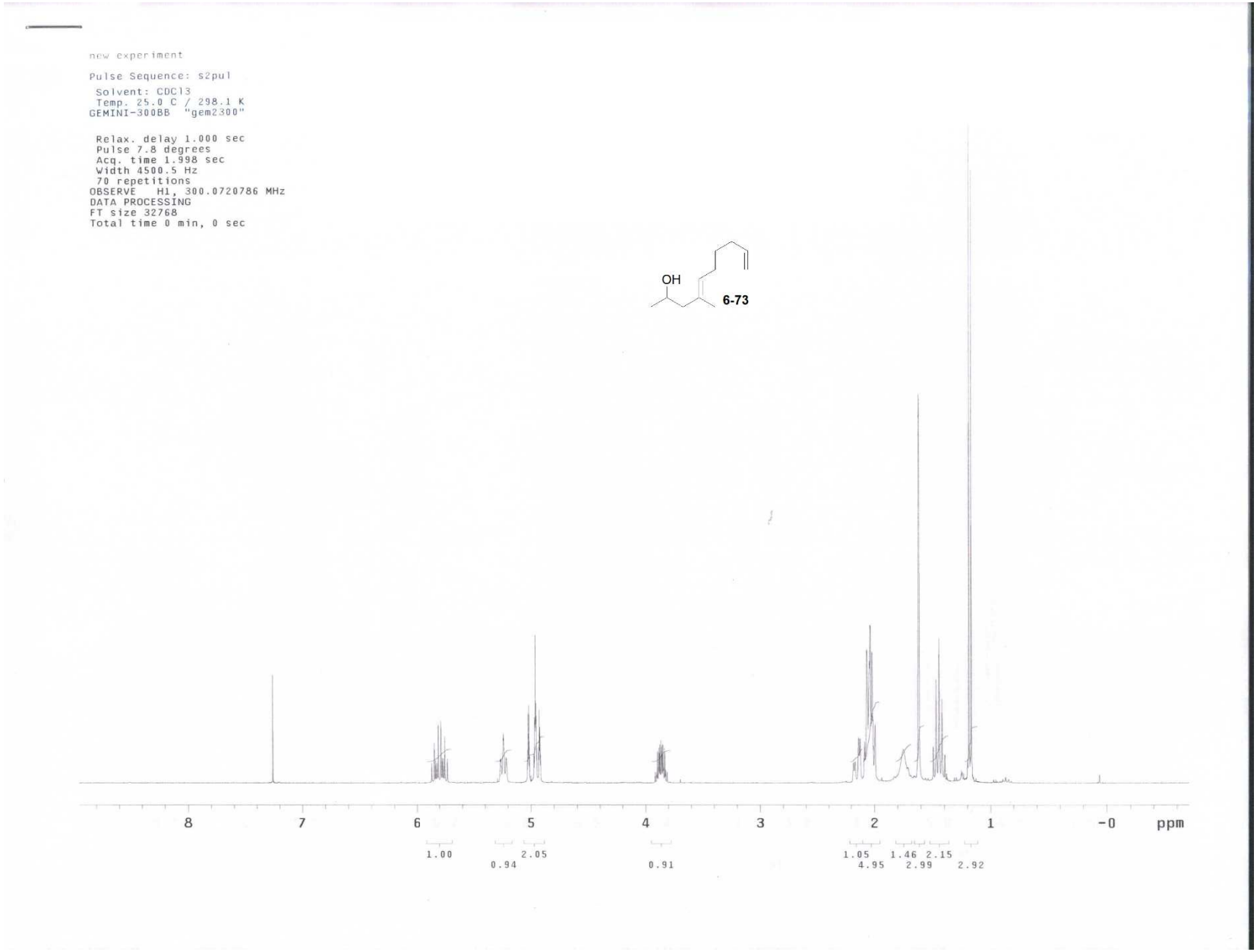
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

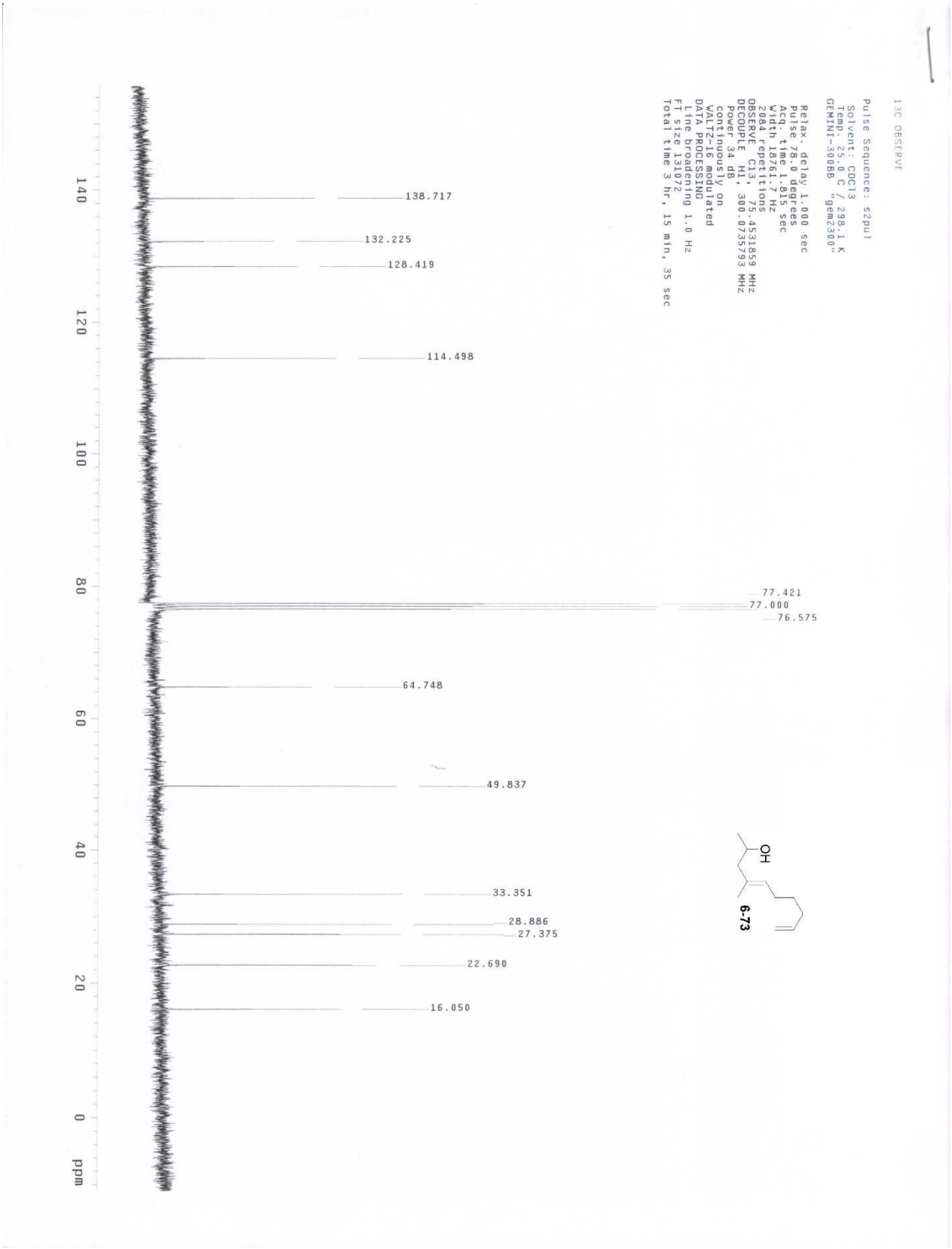
Relax. delay 1.000 sec
Pulse 78.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1180 repetitions
OBSERVE C13, 75.4531896 MHz
DECOUPLE H1, 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 4 hr, 8 min, 50 sec



6-72




new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
70 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
OH
6-73
8
7
6
5
4
3
2
1
-0
ppm
1.00
0.94
2.05
0.91
1.05
4.95
1.46
2.99
2.15
2.92

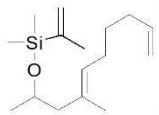

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp: 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 78.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
2084 repetitions
OBSERVE C13, 75.4531859 MHz
DECOUPLE H1, 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 15 min, 35 sec
138.717
132.225
128.419
114.498
77.421
77.000
76.575
64.748
49.837
33.351
28.886
27.375
22.690
16.050
140
120
100
80
60
40
20
0
ppm
OH
6-73

new experiment

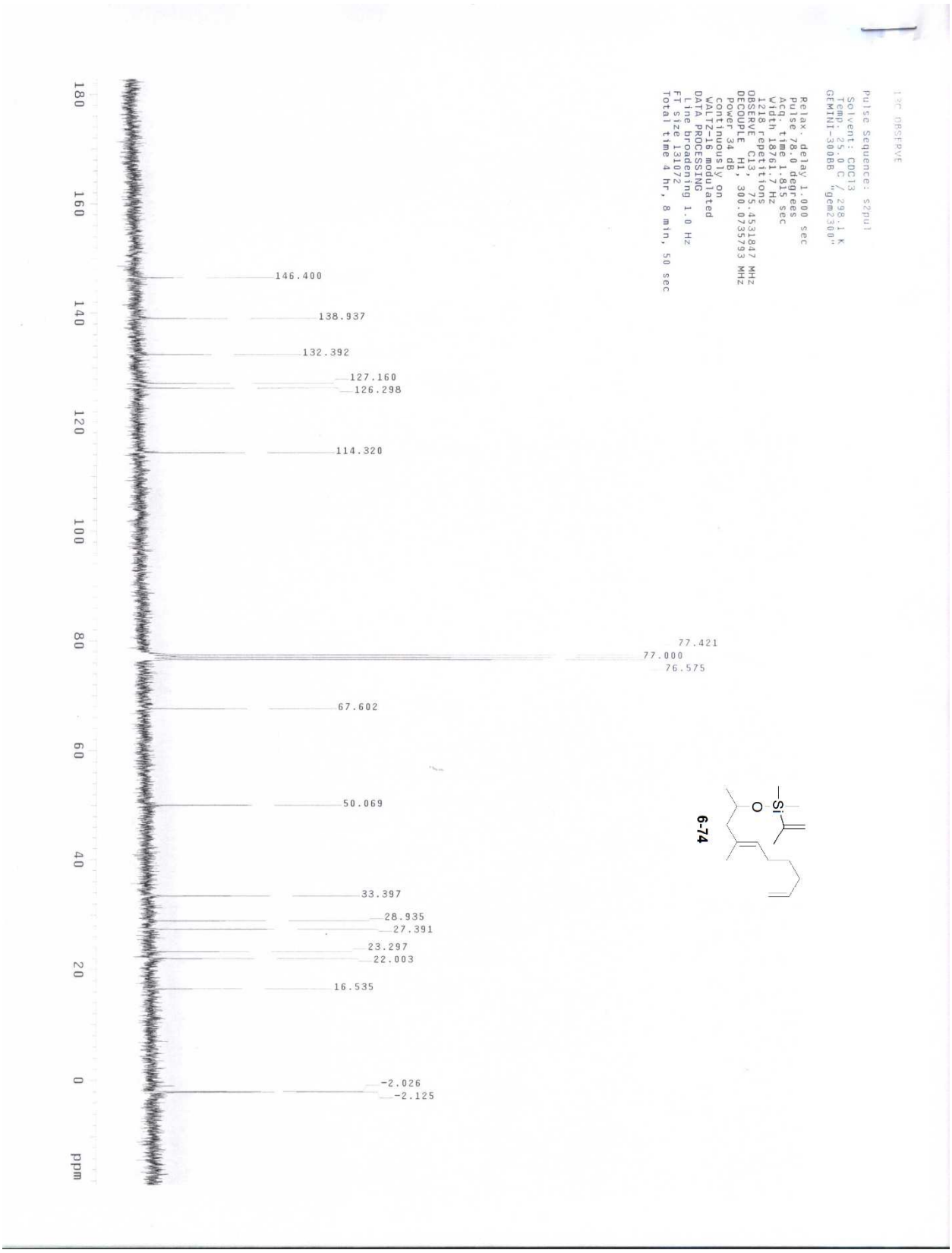
Pulse Sequence: s2pul

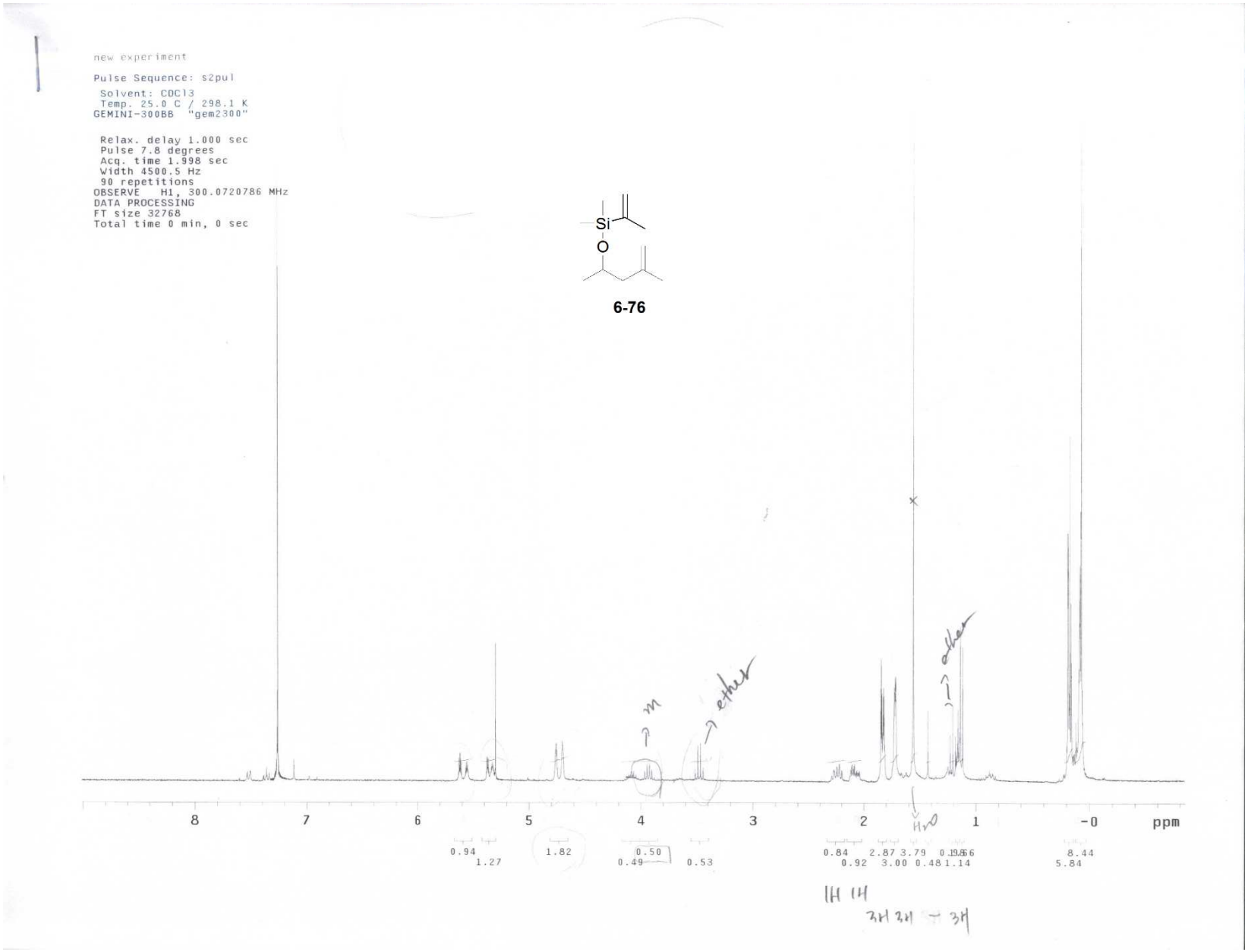
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
44 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 19 sec



6-74


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 78.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1218 repetitions
OBSERVE C13, 75.4531847 MHz
DECOUPLE H1, 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
line broadening 1.0 Hz
FT size 131072
Total time 4 hr, 8 min, 50 sec
146.400
138.937
132.392
127.160
126.298
114.320
77.421
77.000
76.575
67.602
50.069
33.397
28.935
27.391
23.297
22.003
16.535
-2.026
-2.125
ppm
6-74


new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
90 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
Si
O
6-76
m
ether
ether
H2O
8
7
6
5
4
3
2
1
-0
ppm
0.94
1.27
1.82
0.50
0.49
0.53
0.84
0.92
2.87
3.00
3.79
0.48
1.14
8.44
5.84
1H 1H
3H 3H = 3H

STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133

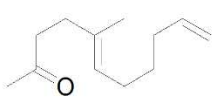
1H SENSITIVITY
0.1% ETHYLBENZENE

Pulse Sequence: s2pul

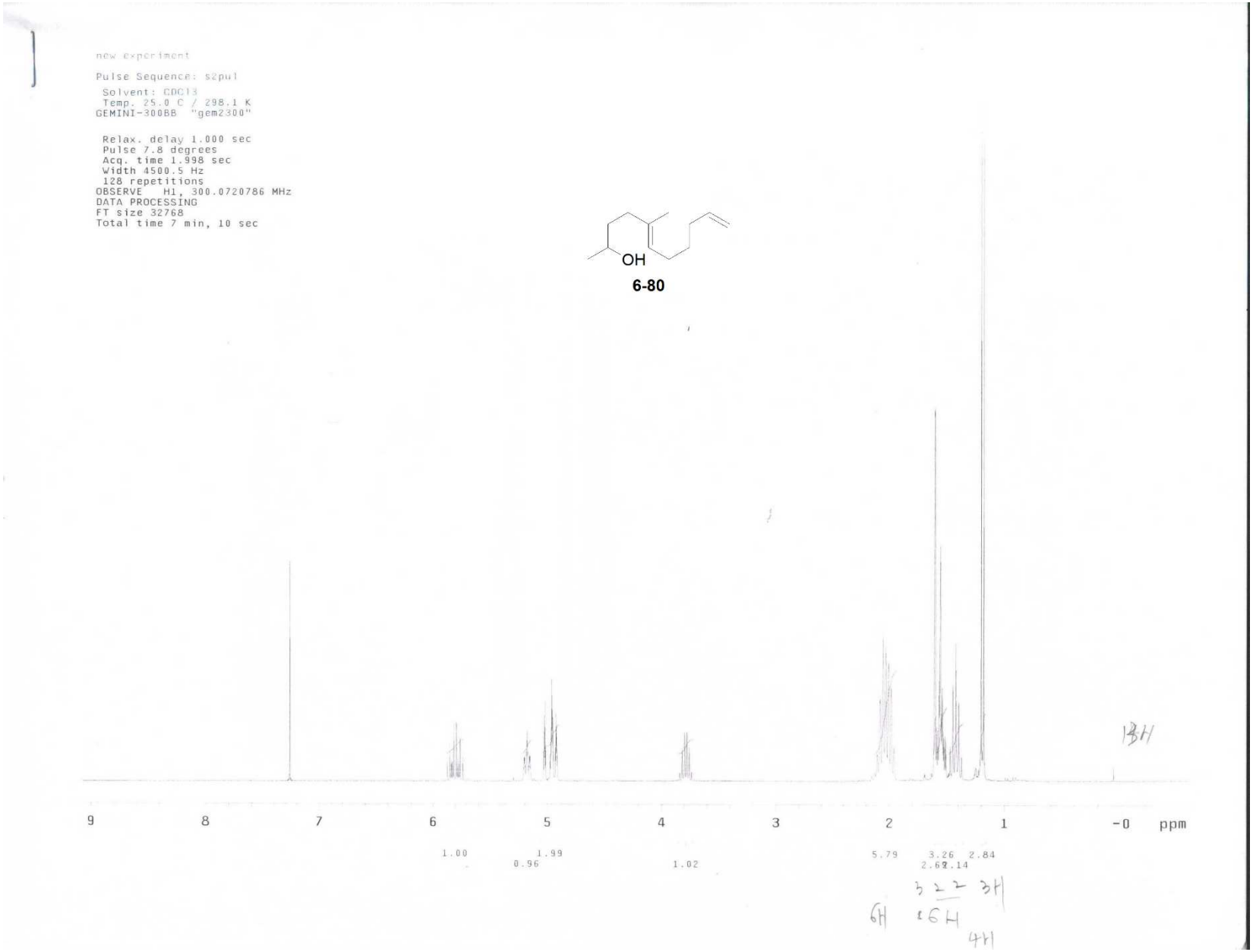
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-12-87
INOVA-400 "inv400"

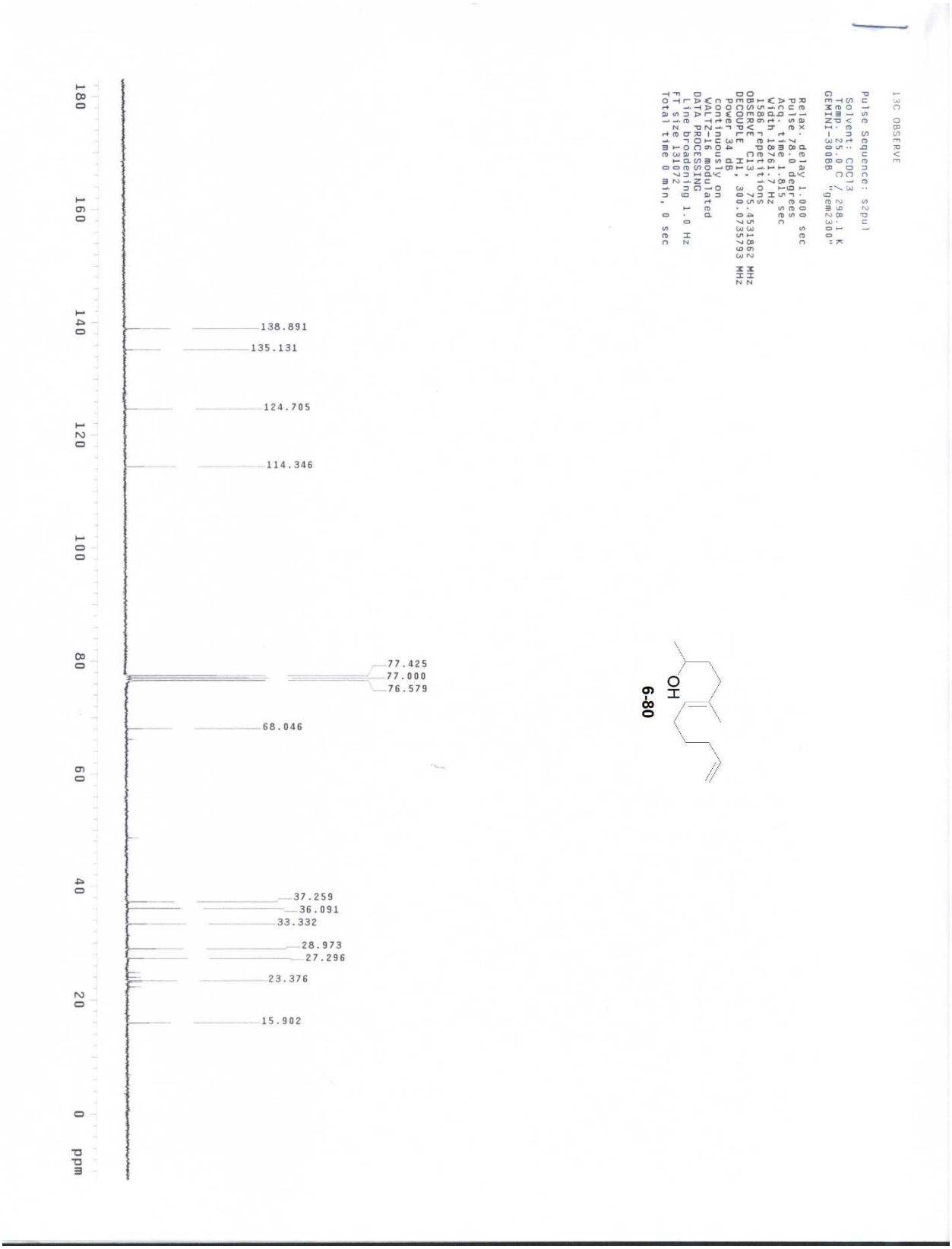
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.273 sec
Width 6000.6 Hz
32 repetitions
OBSERVE H1, 399.8314203 MHz
DATA PROCESSING
FT size 131072
Total time 2 min, 17 sec

at 400 MHz



6-79


new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
128 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 7 min, 10 sec
OH
6-80
9
8
7
6
5
4
3
2
1
-0
ppm
1.00
0.96
1.99
1.02
5.79
3.26
2.84
2.62
2.14
13H

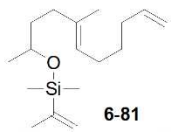

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp: 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 78.0 degrees
Acq. time 1.363 sec
Width 18761.7 Hz
1536 repetitions
OBSERVE C13, 75.4531862 MHz
DECOUPLE H1, 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 0 min, 0 sec
OH
6-80
138.891
135.131
124.705
114.346
77.425
77.000
76.579
68.046
37.259
36.091
33.332
28.973
27.296
23.376
15.902
180
160
140
120
100
80
60
40
20
0
ppm

new experiment

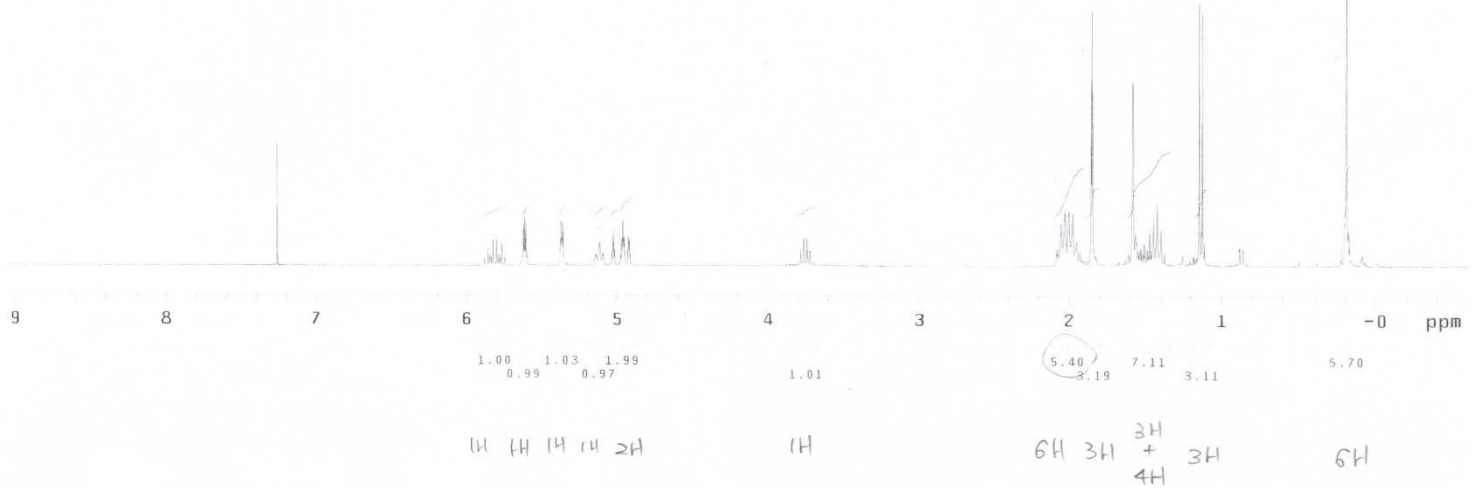
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec



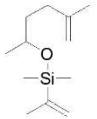
6-81



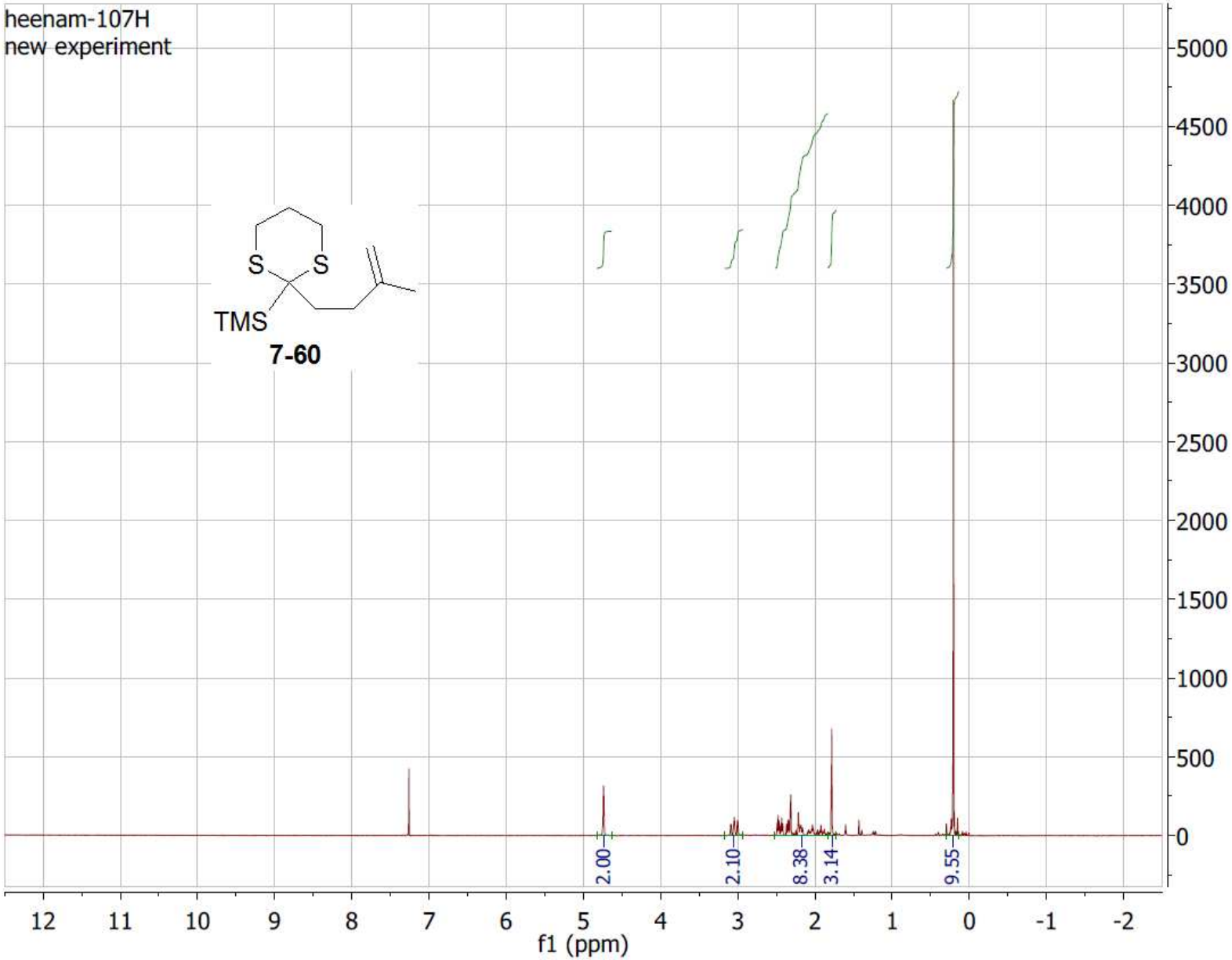
new experiment

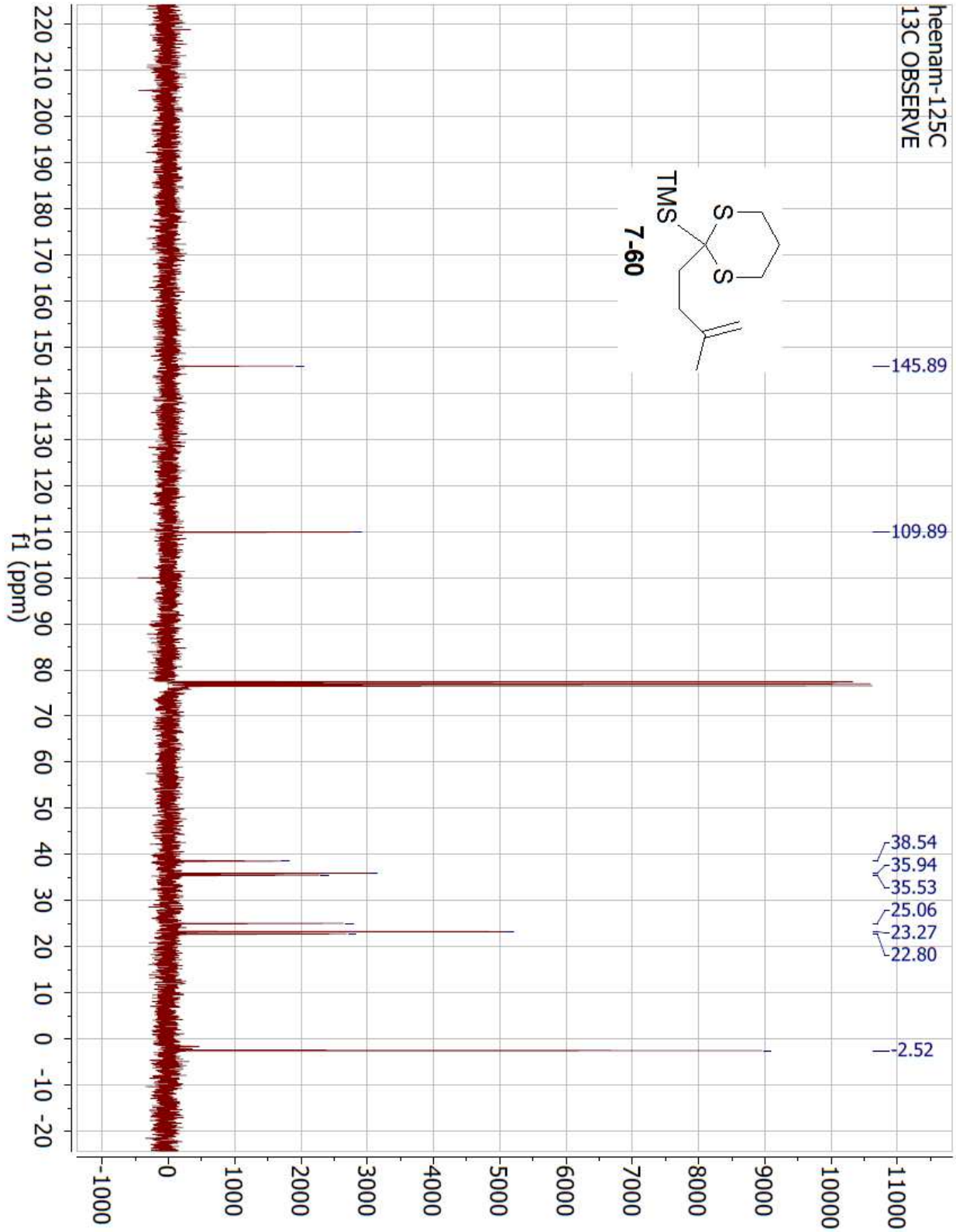
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 58 sec



6-82

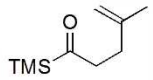

heenam-107H
new experiment
S
S
TMS
7-60
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
2.00
2.10
8.38
3.14
9.55
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


heenam-125C
13C OBSERVE
TMS
7-60
S
S
145.89
109.89
38.54
35.94
35.53
25.06
23.27
22.80
2.52
f1 (ppm)

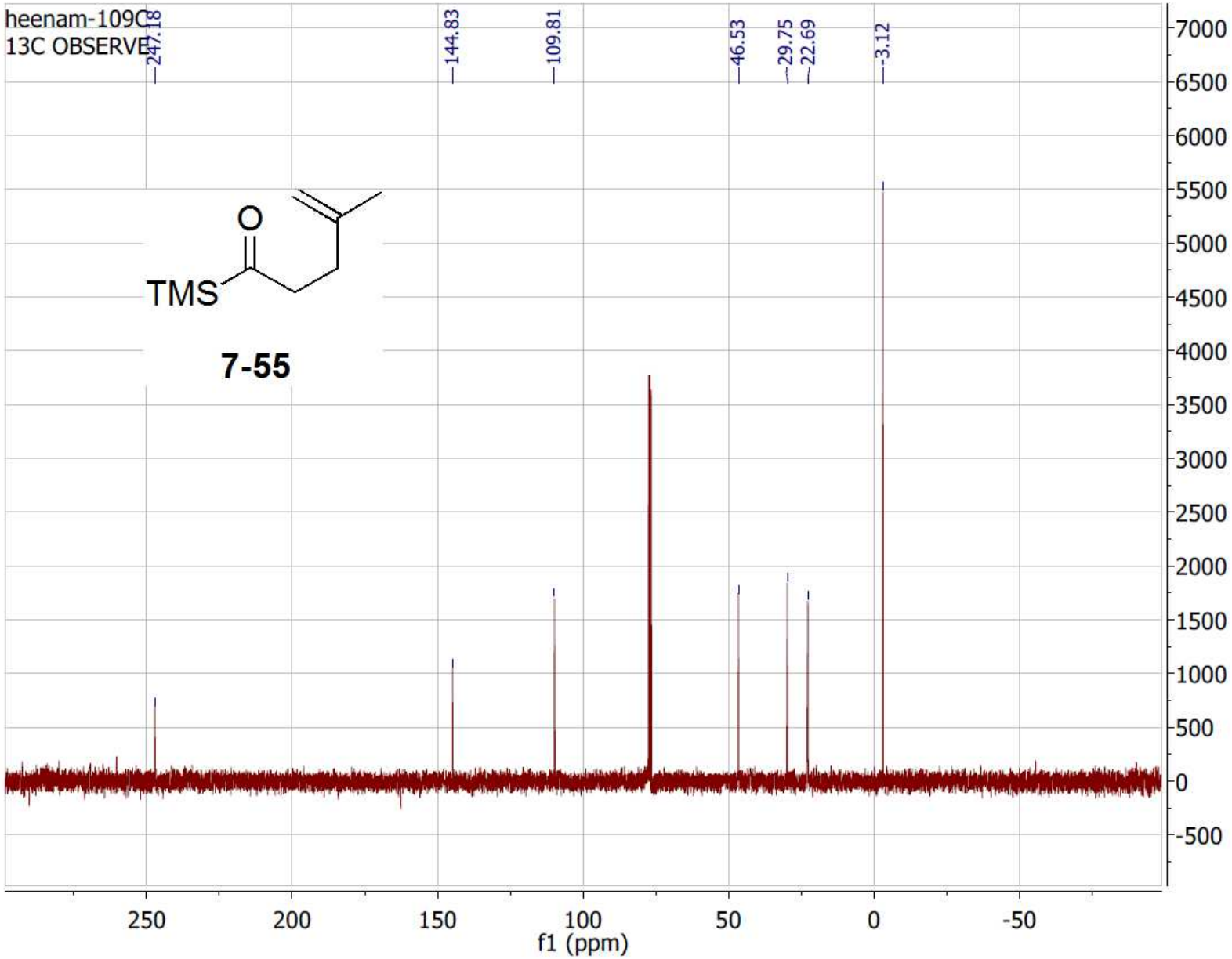
new experiment

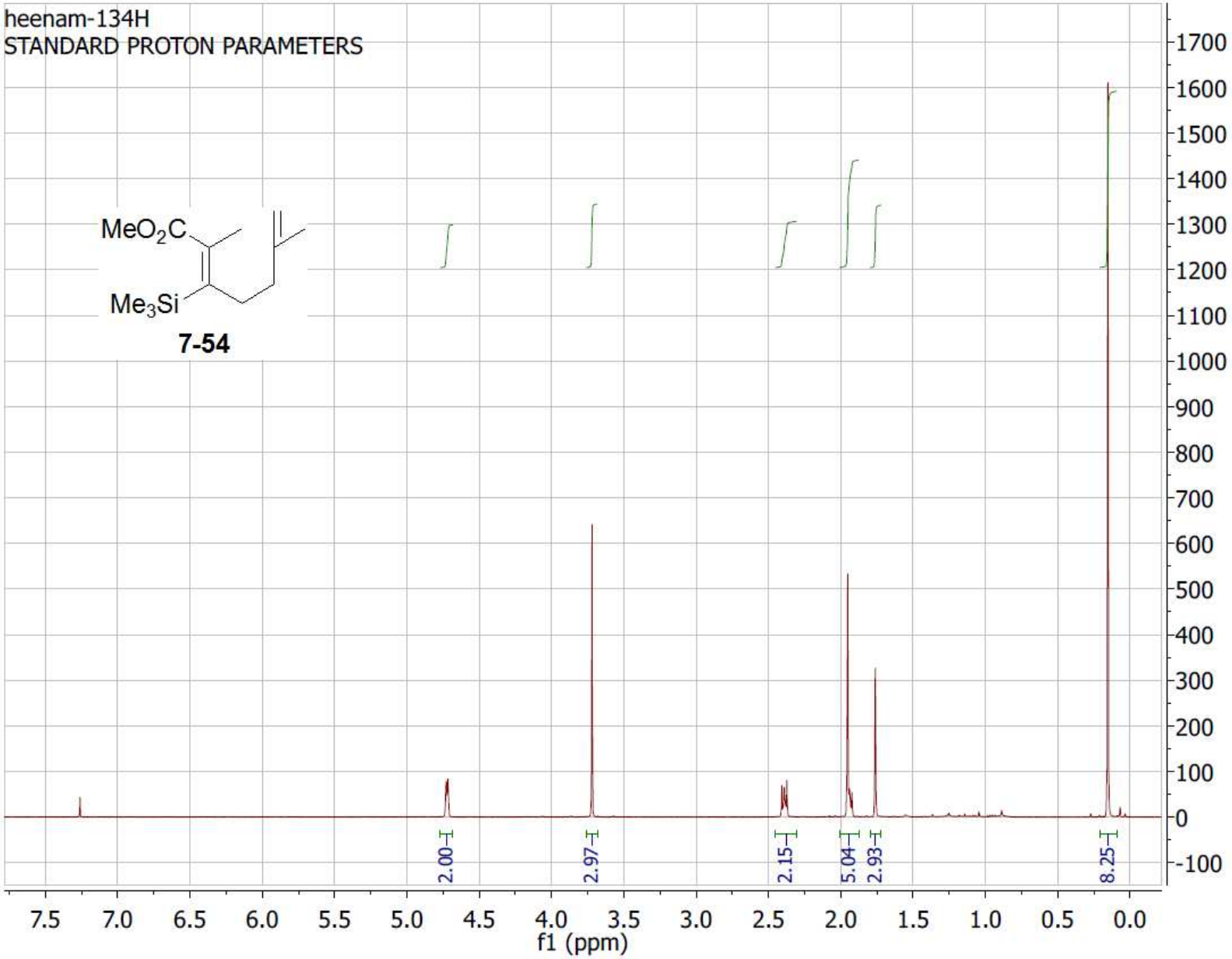
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

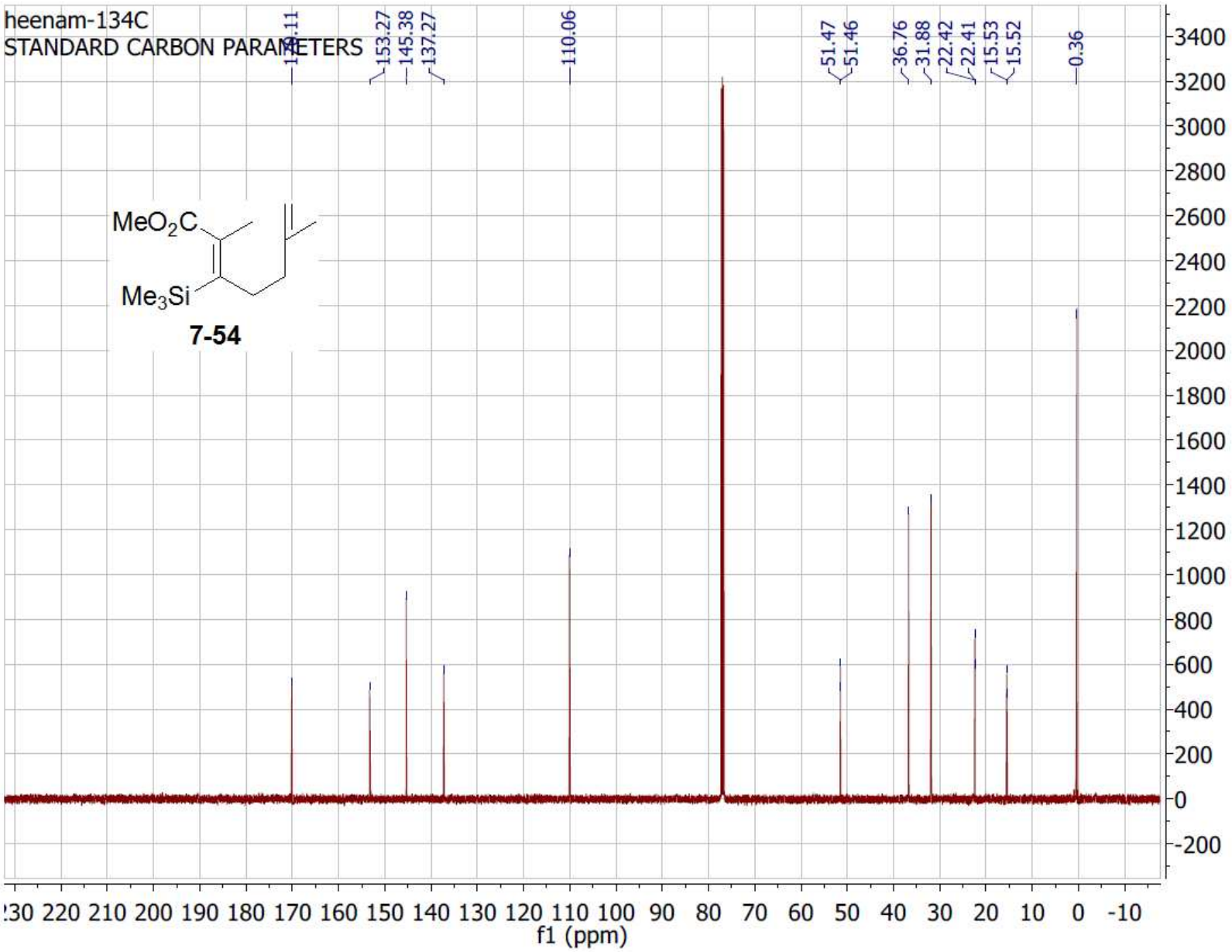
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec

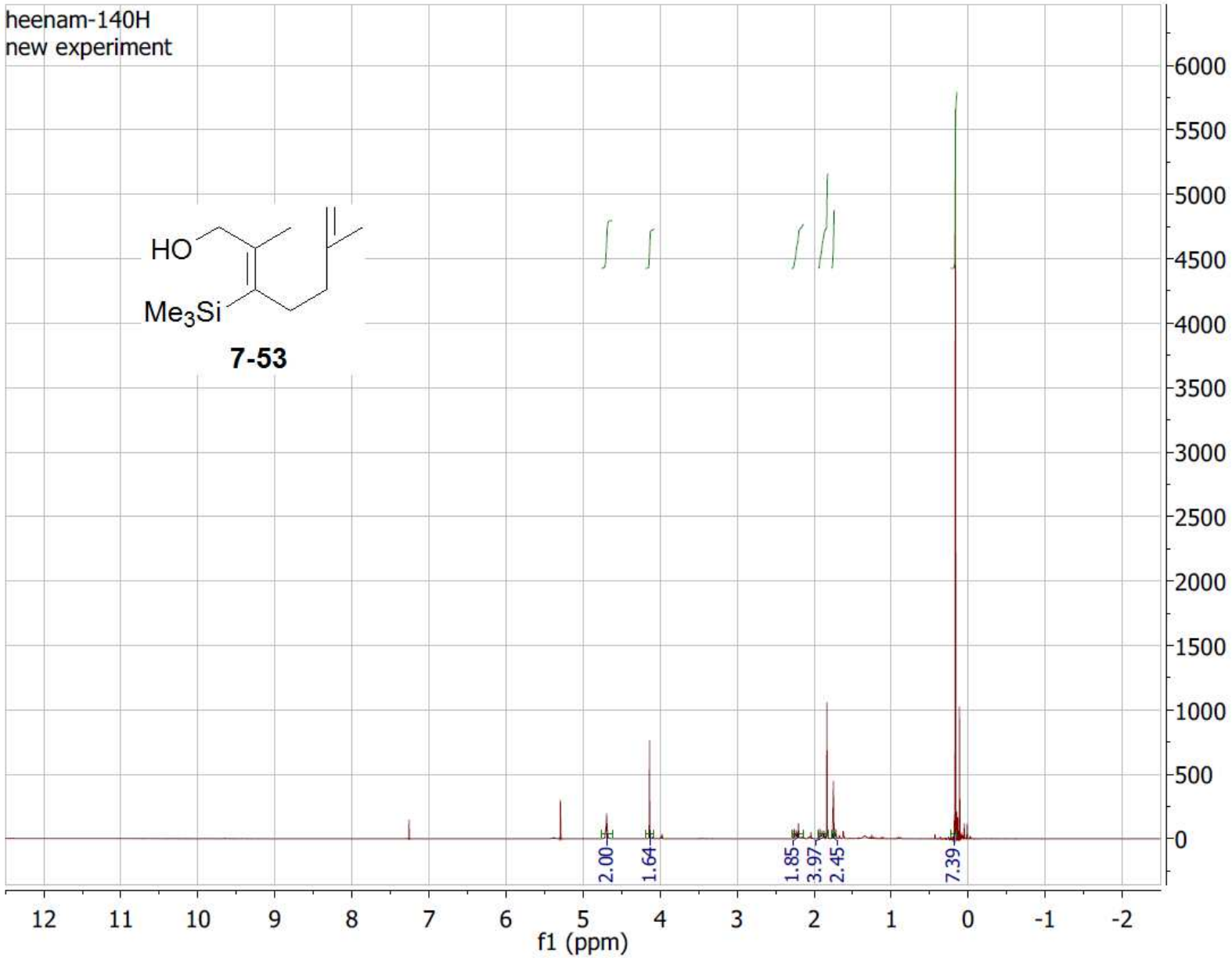


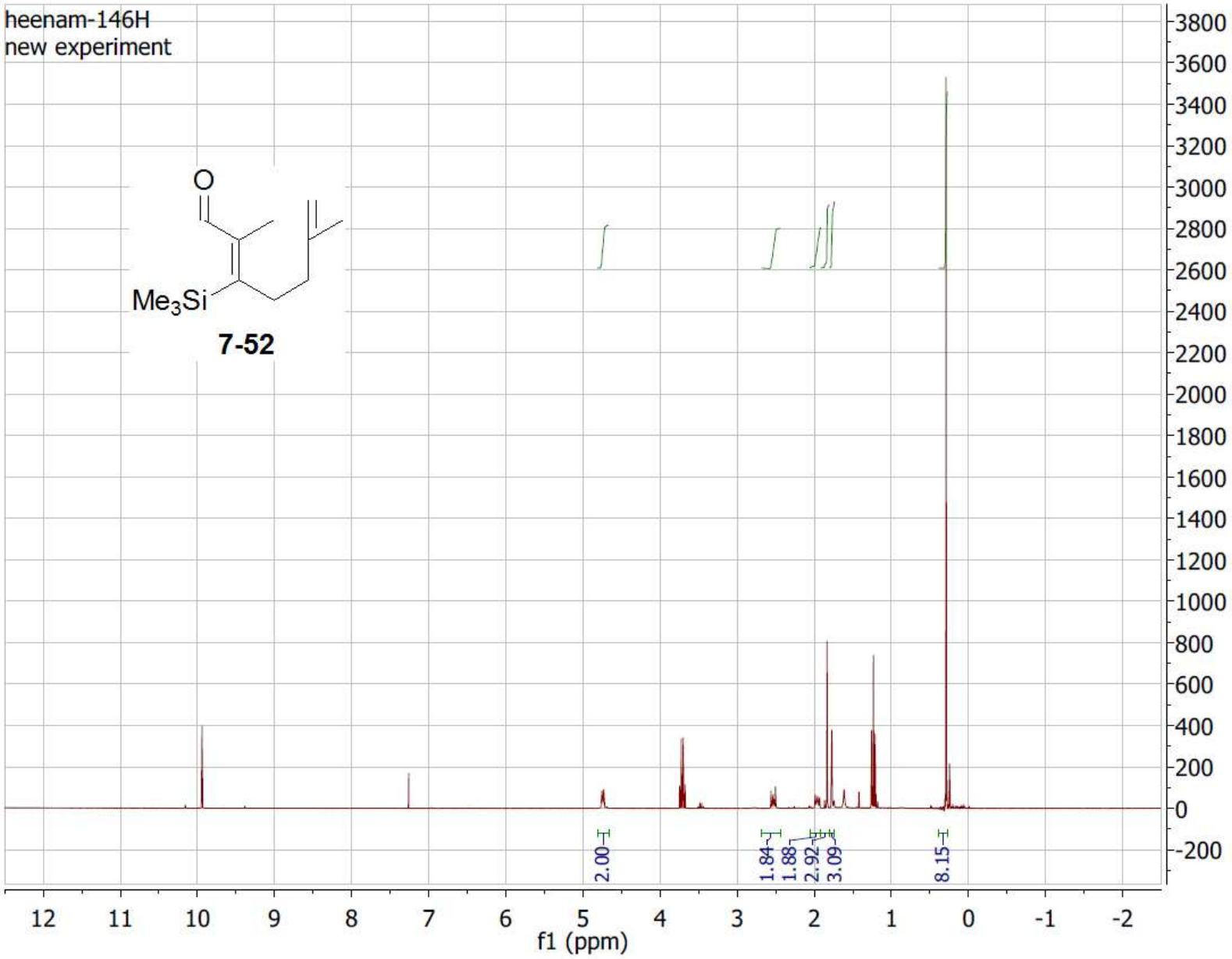
7-55

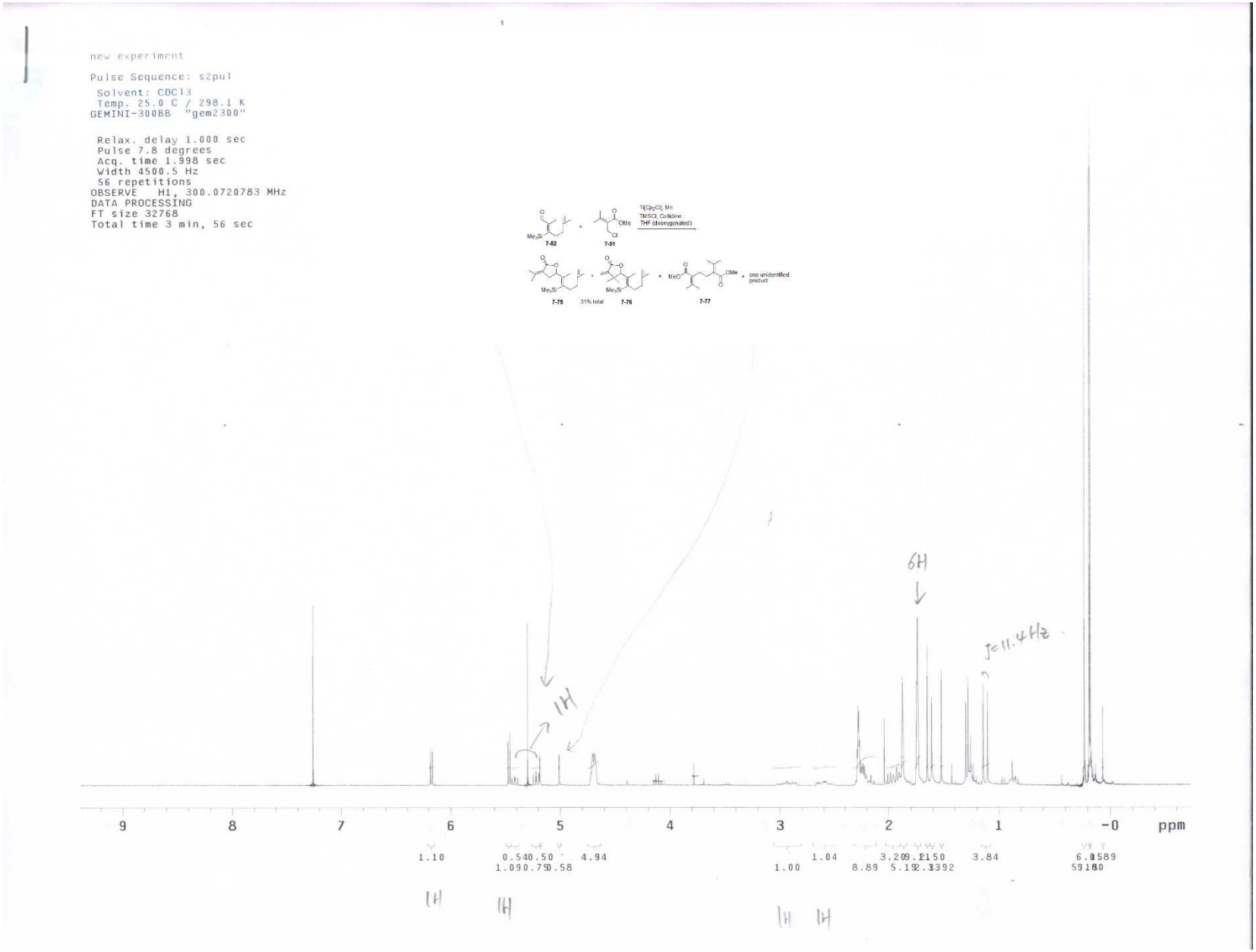

heenam-109C
13C OBSERVE
247.18
144.83
109.81
46.53
29.75
22.69
3.12
O
TMS
7-55
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
250
200
150
100
50
0
-50
f1 (ppm)

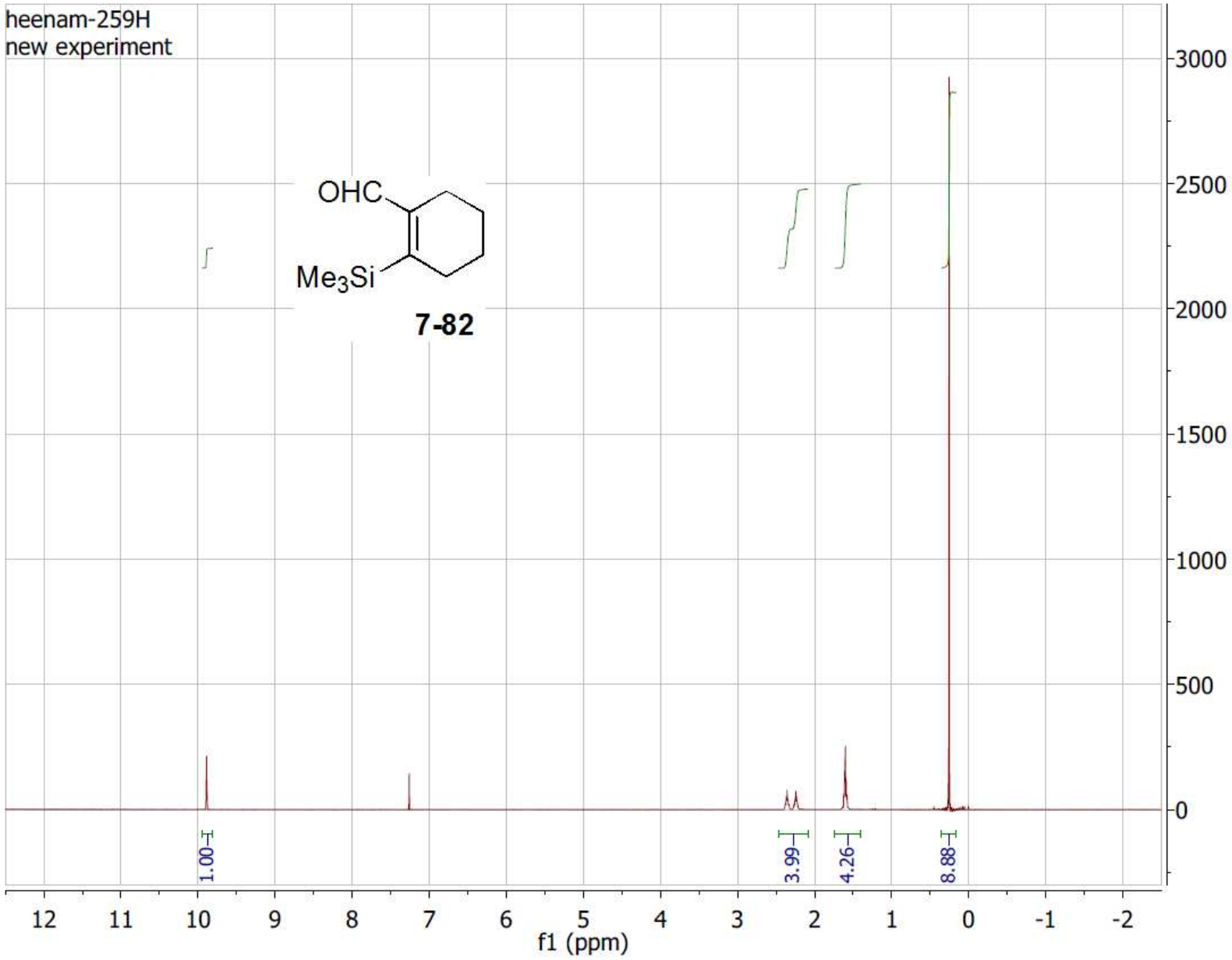

heenam-134H
STANDARD PROTON PARAMETERS
MeO2C
Me3Si
7-54
2.00
2.97
2.15
5.04
2.93
8.25
f1 (ppm)

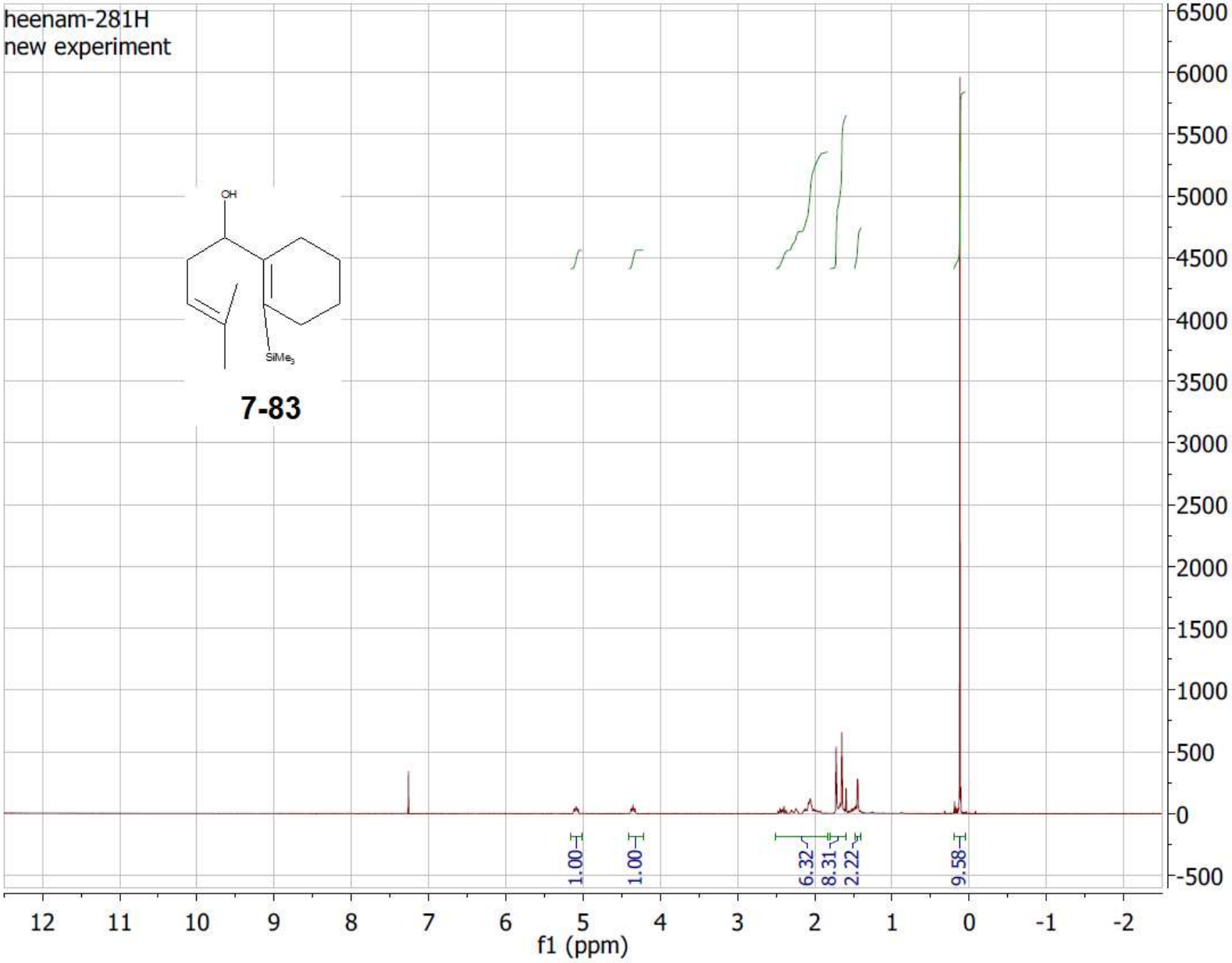

heenam-134C
STANDARD CARBON PARAMETERS
170.11
153.27
145.38
137.27
110.06
51.47
51.46
36.76
31.88
22.42
22.41
15.53
15.52
0.36
MeO2C
Me3Si
7-54
f1 (ppm)

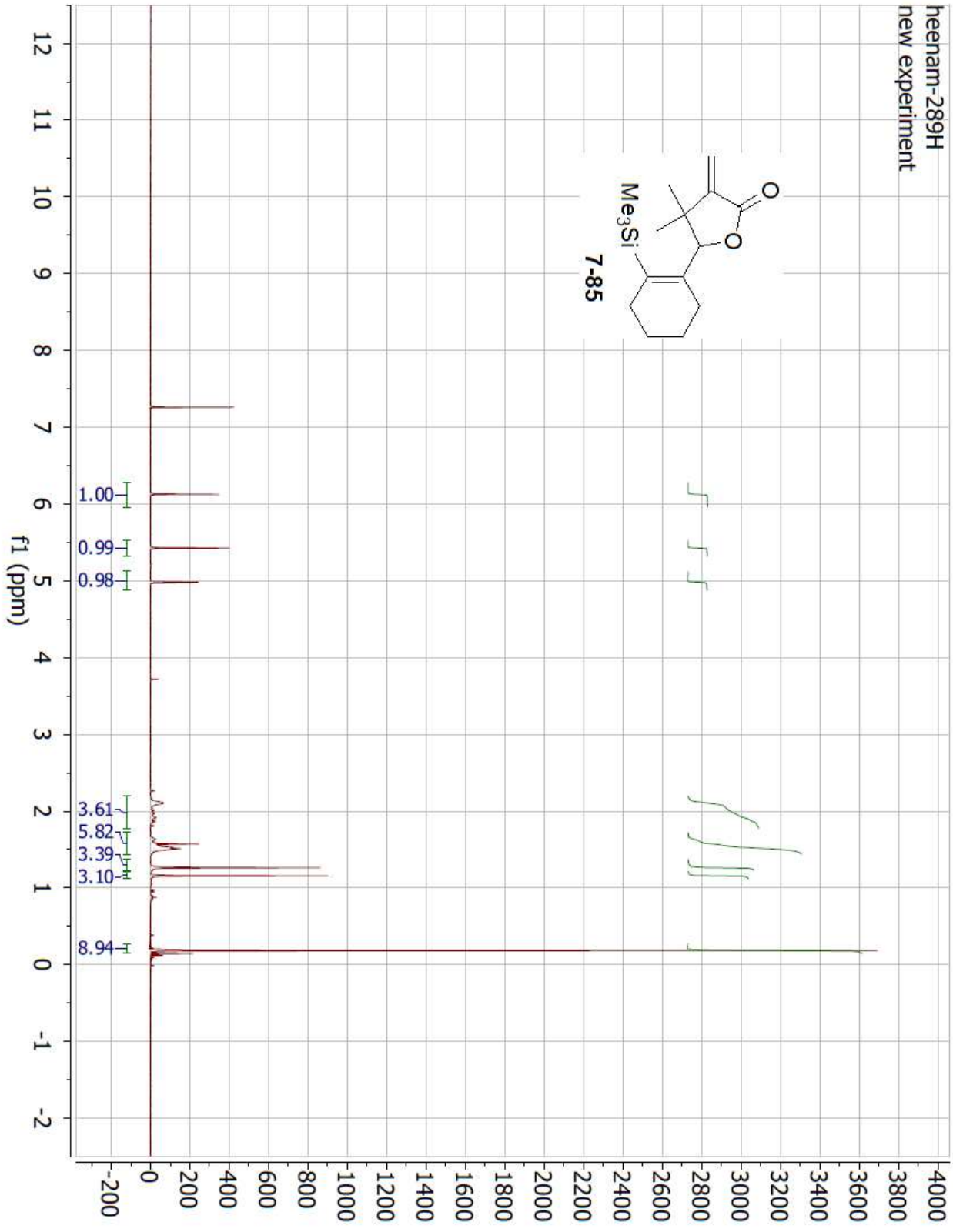

heenam-140H
new experiment
HO
Me3Si
7-53
2.00
1.64
1.85
3.97
2.45
7.39
f1 (ppm)

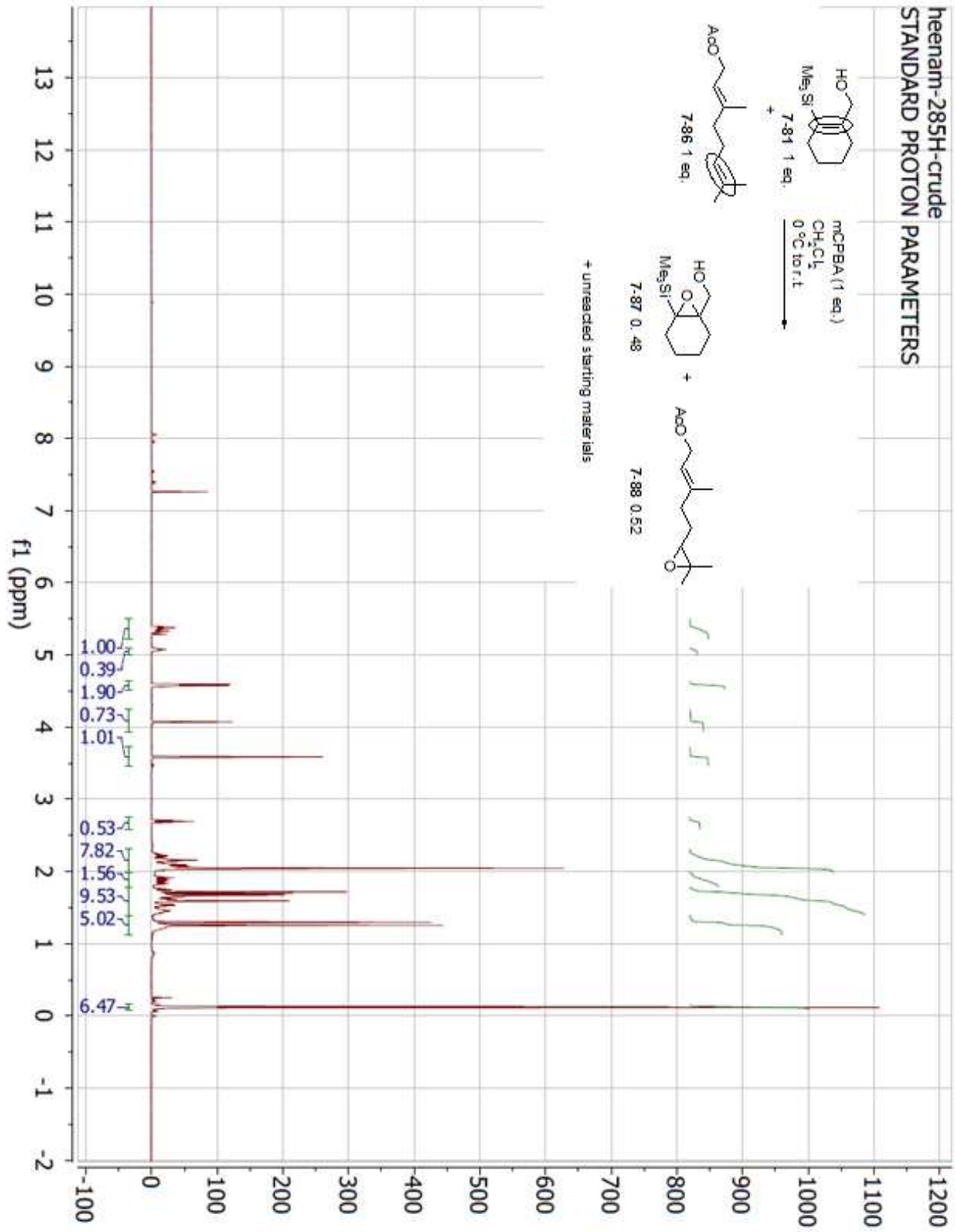

heenam-146H
new experiment
O
Me3Si
7-52
2.00
1.84
1.88
2.92
3.09
8.15
f1 (ppm)

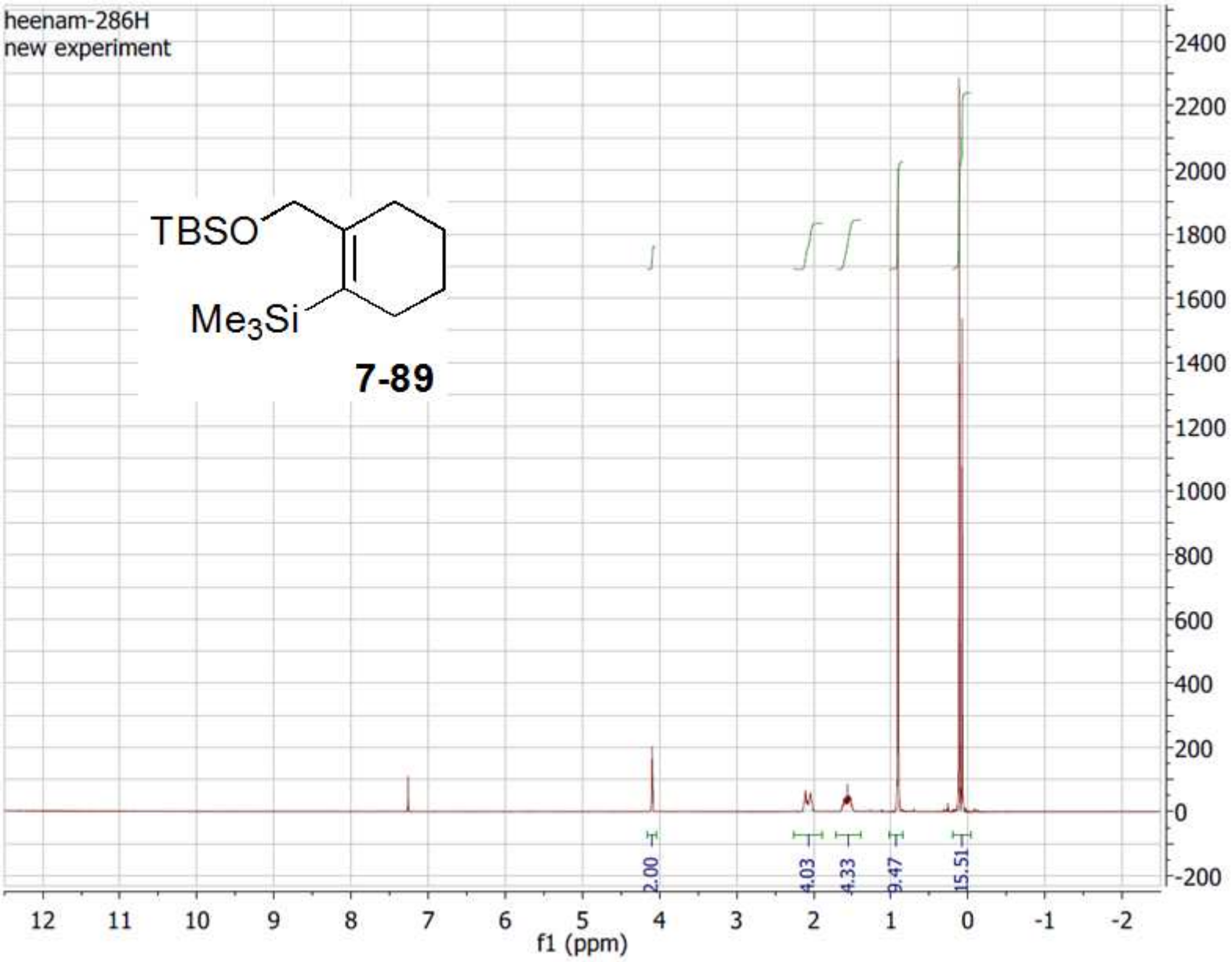

new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
56 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 56 sec
Ti(OiPr)Cl3, Mn
TMSCl, Collidine
THF (deoxygenated)
7-52
7-51
7-75
31% total
7-76
7-77
one unidentified product
6H
1H
J=11.4Hz
9
8
7
6
5
4
3
2
1
-0
ppm
1.10
0.54
0.50
4.94
1.09
0.75
0.58
1.00
1.04
3.20
9.21
1.50
3.84
8.89
5.19
2.13
2.92
6.01
5.89
5.91
1.80
1H
1H
1H
1H

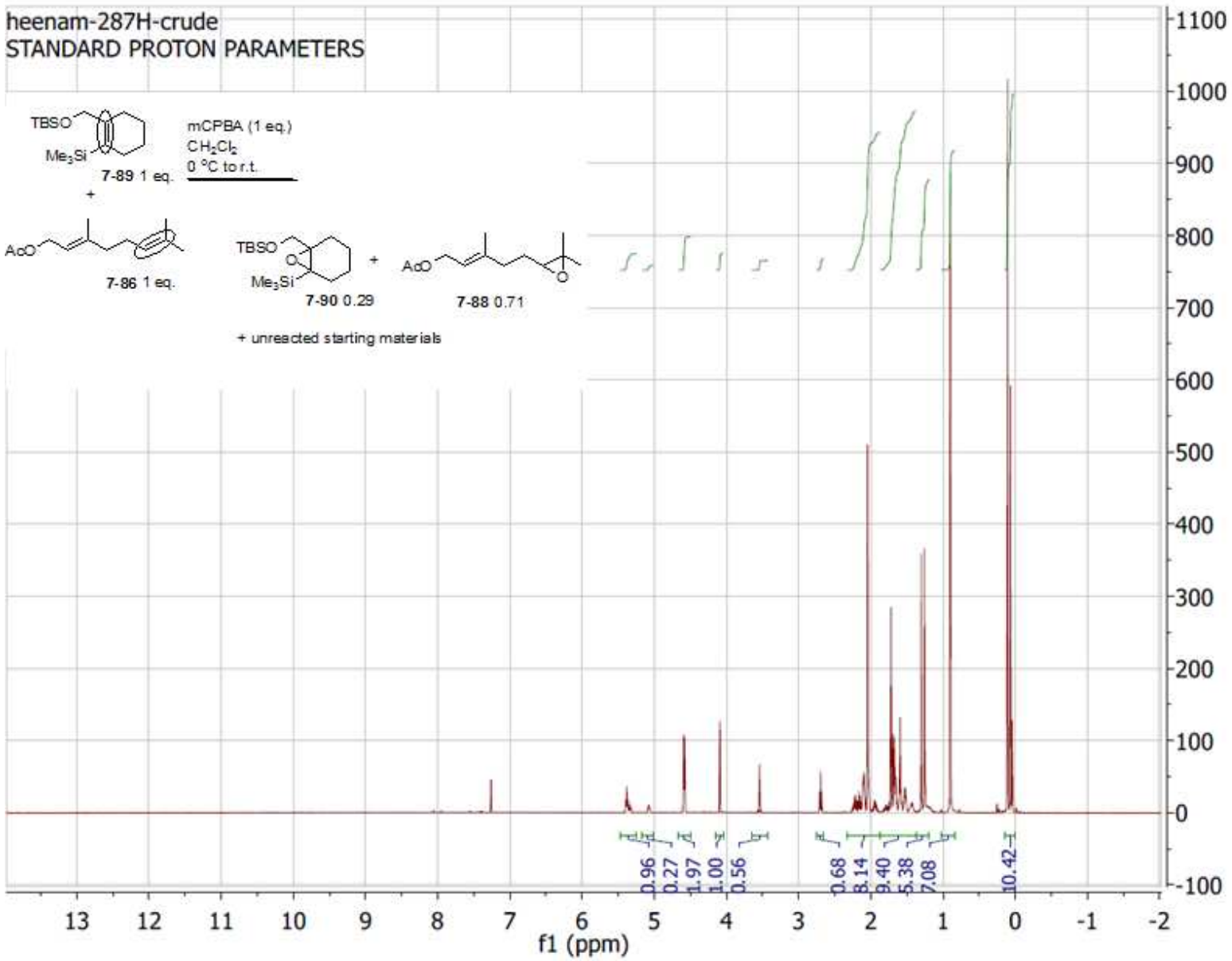

heenam-259H
new experiment
OHC
Me3Si
7-82
3000
2500
2000
1500
1000
500
0
1.00
3.99
4.26
8.88
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


heenam-281H
new experiment
OH
SiMe3
7-83
1.00
1.00
6.32
8.31
2.22
9.58
f1 (ppm)


heenam-289H
new experiment
O
O
Me3Si
7-85
1.00
0.99
0.98
3.61
5.82
3.39
3.10
8.94
f1 (ppm)


heenam-285H-crude
STANDARD PROTON PARAMETERS
HO
Me3Si
7-81 1 eq.
+
AcO
7-86 1 eq.
mCPBA (1 eq.)
CH2Cl2
0 °C to r.t
HO
O
Me3Si
7-87 0. 48
+
AcO
O
7-88 0.52
+ unreacted starting materials
1.00
0.39
1.90
0.73
1.01
0.53
7.82
1.56
9.53
5.02
6.47
f1 (ppm)


heenam-286H
new experiment
TBSO
Me3Si
7-89
2.00
4.03
4.33
9.47
15.51
f1 (ppm)

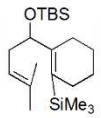

heenam-287H-crude
STANDARD PROTON PARAMETERS
TBSO
Me3Si
7-89 1 eq.
mCPBA (1 eq.)
CH2Cl2
0 °C to r.t.
+
AcO
7-86 1 eq.
TBSO
Me3Si
7-90 0.29
+
AcO
7-88 0.71
+ unreacted starting materials
0.96
0.27
1.97
1.00
0.56
0.68
8.14
9.40
5.38
7.08
10.42
f1 (ppm)

new experiment

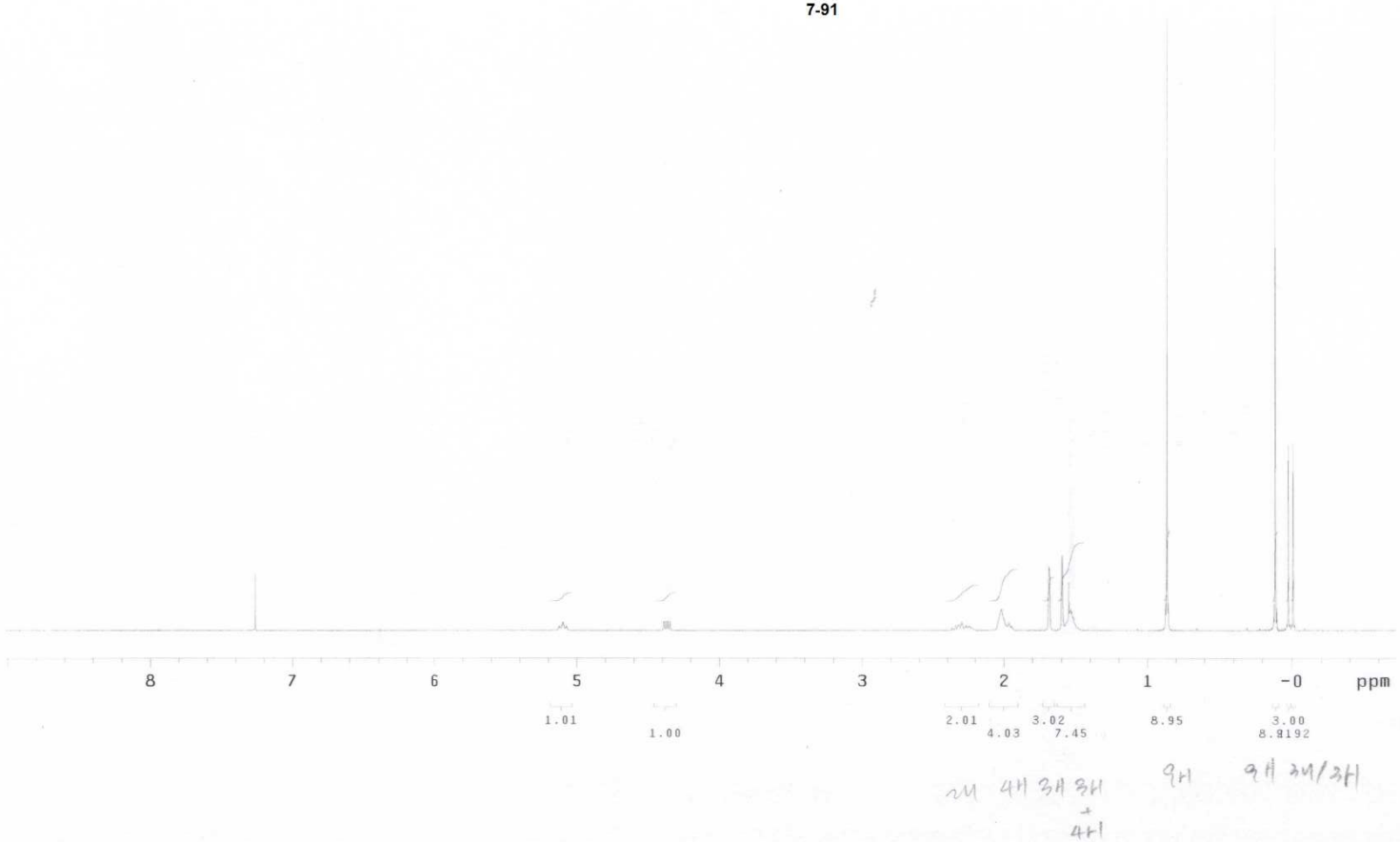
Pulse Sequence: s2pul

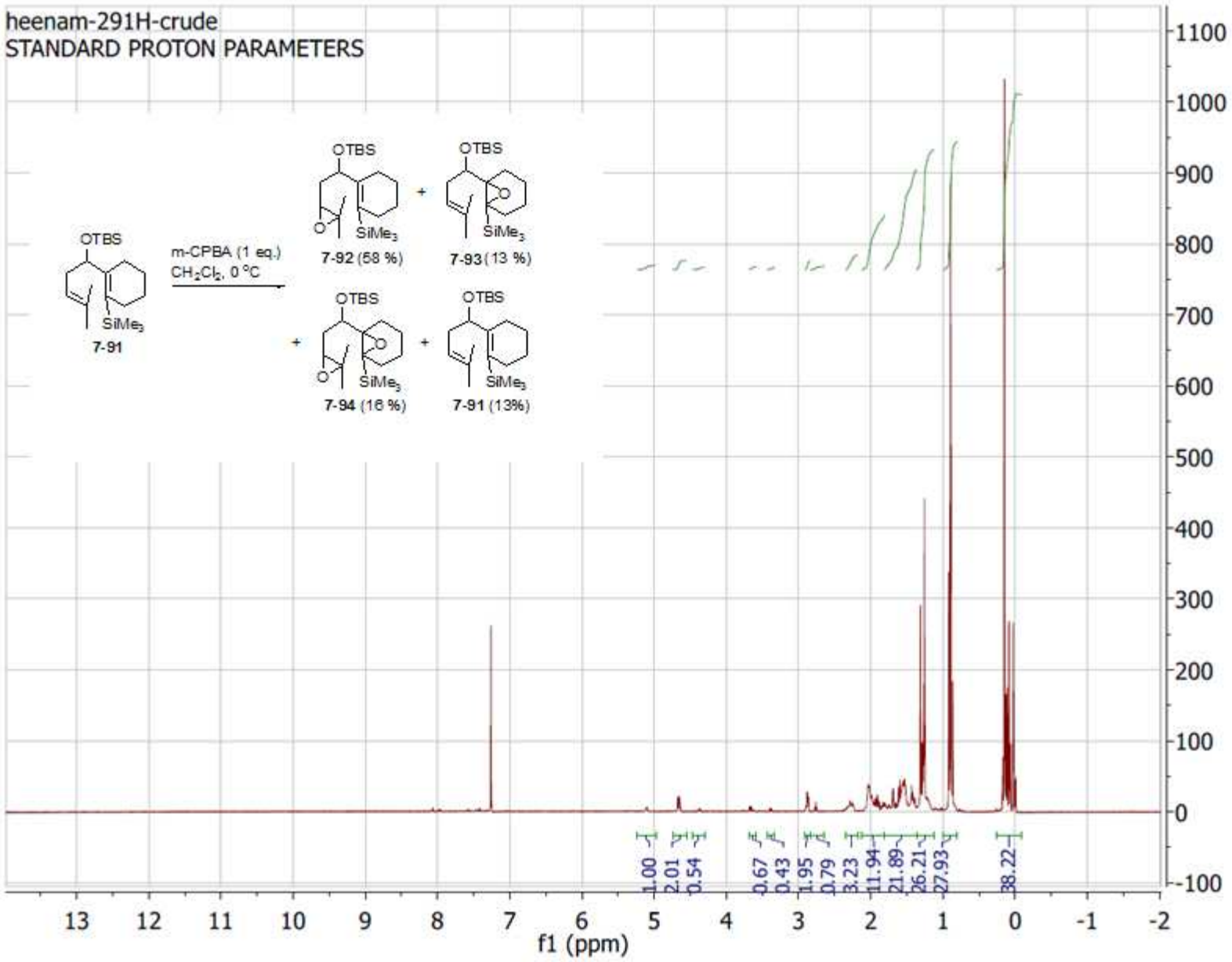
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

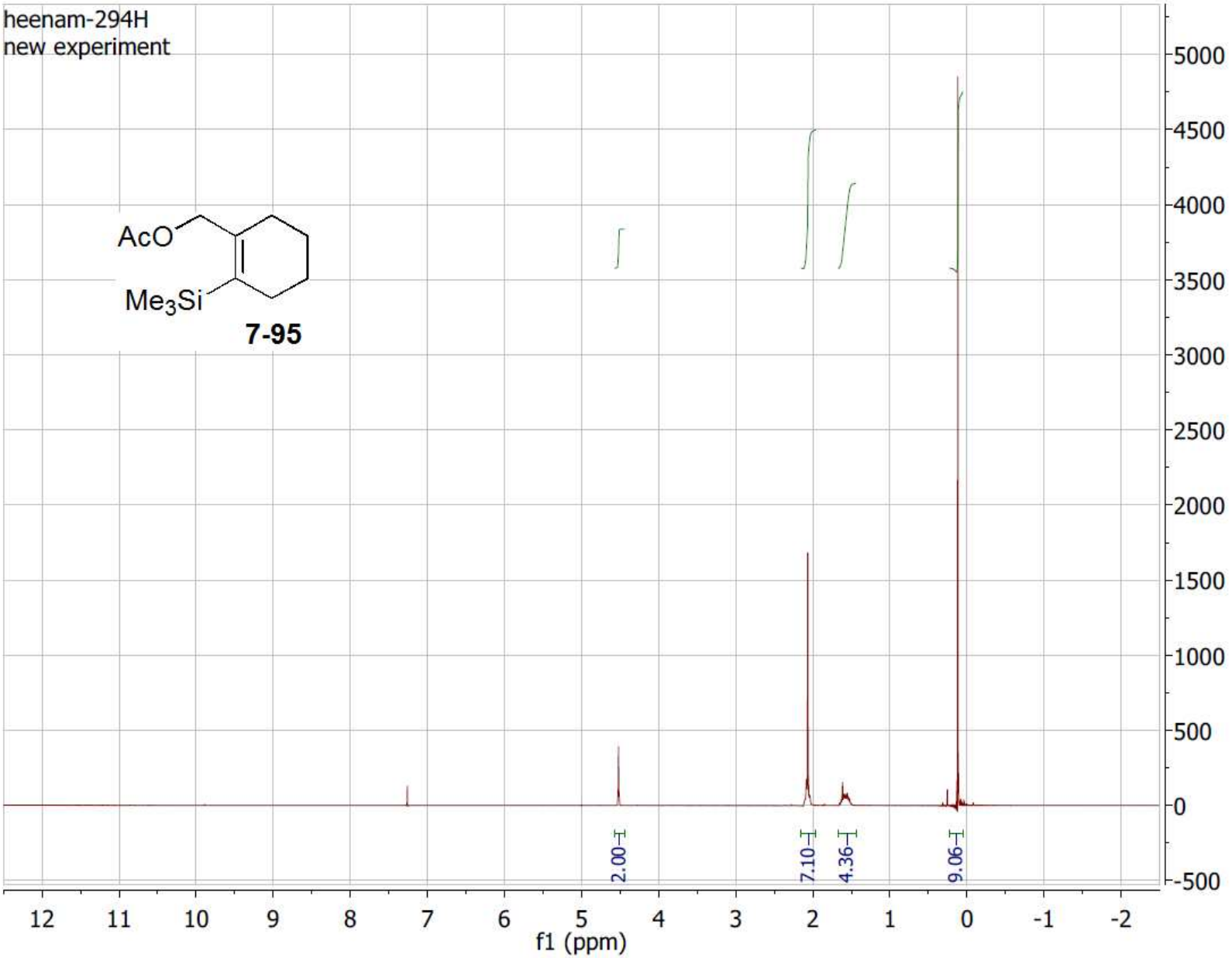
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
15 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec

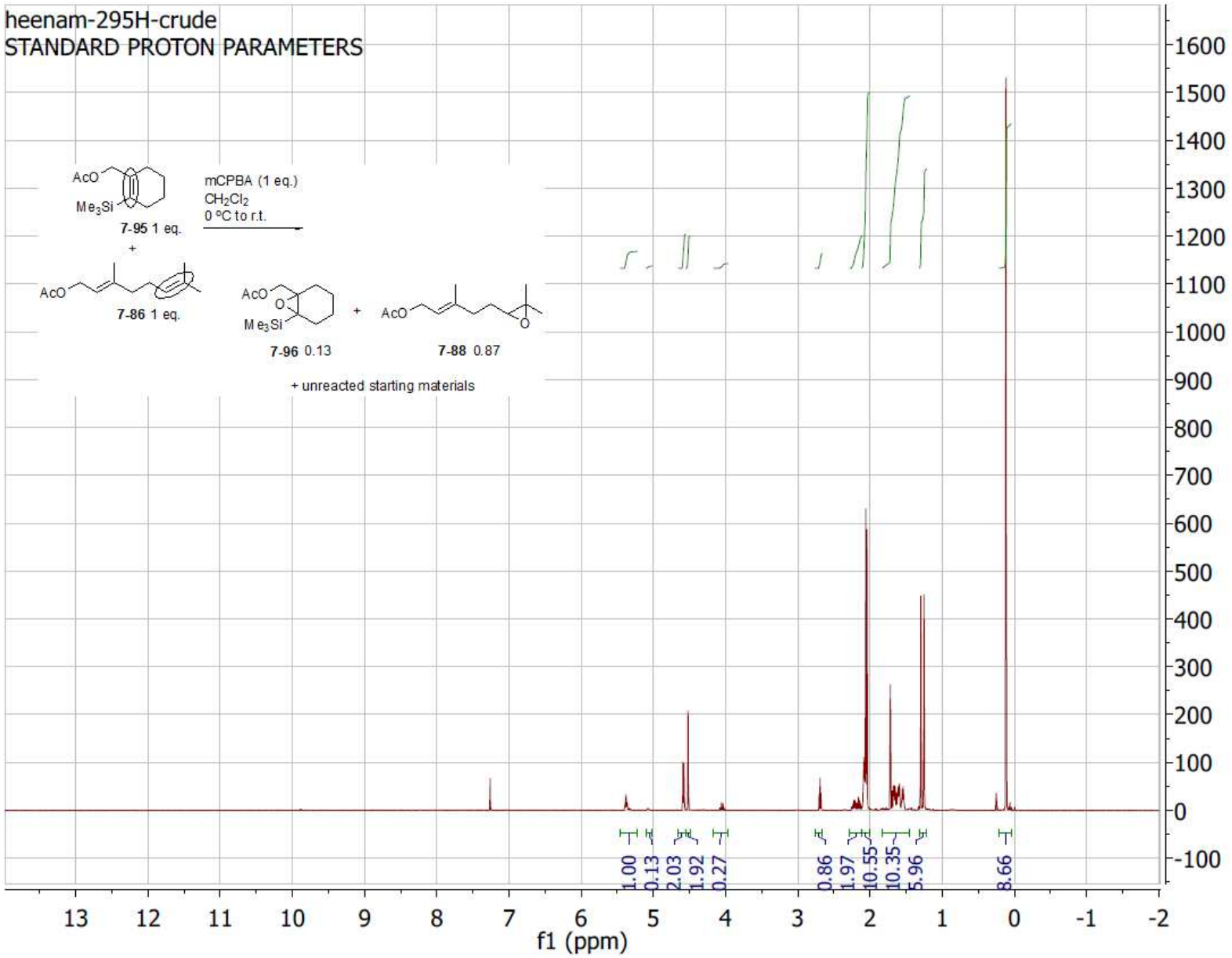


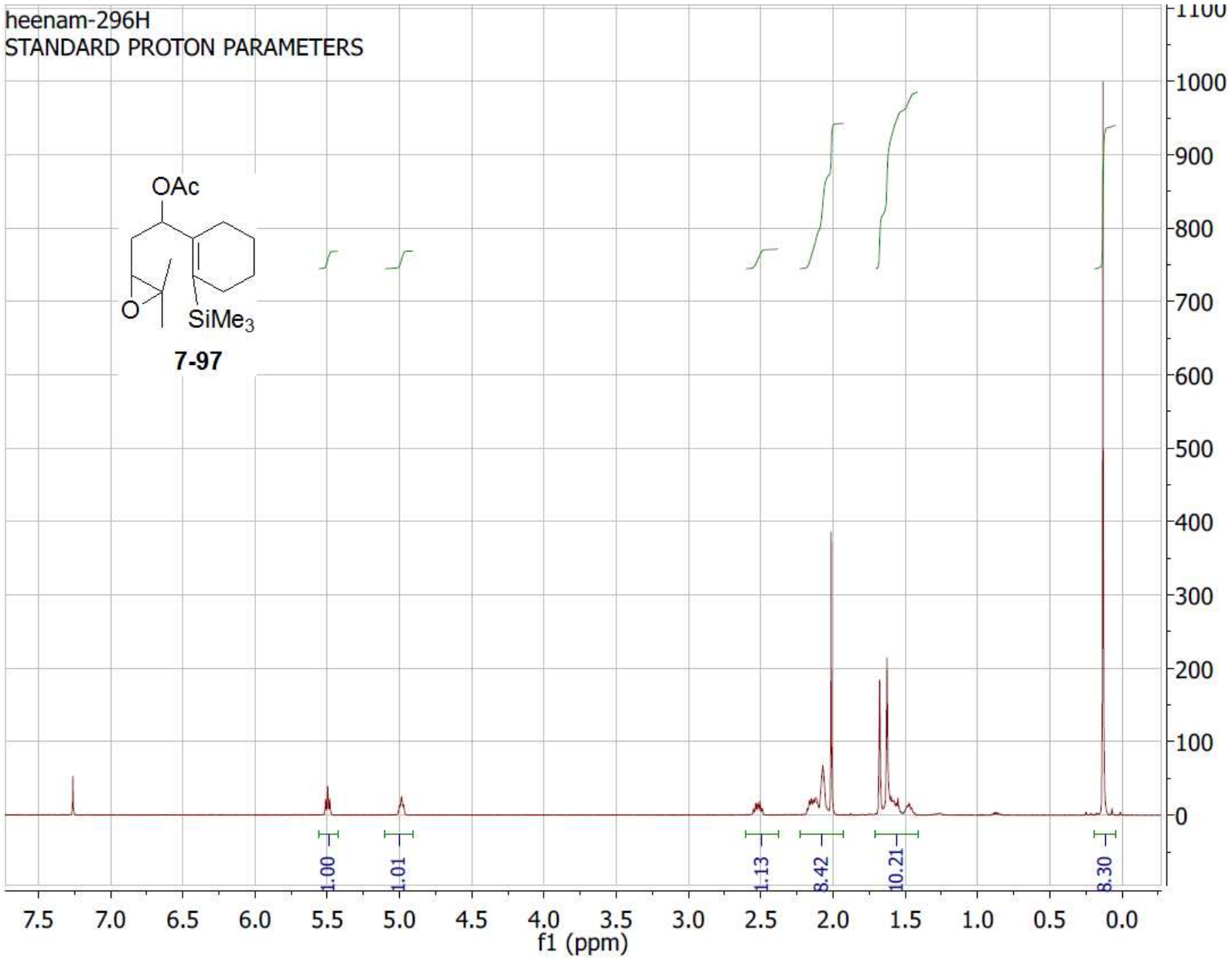
7-91

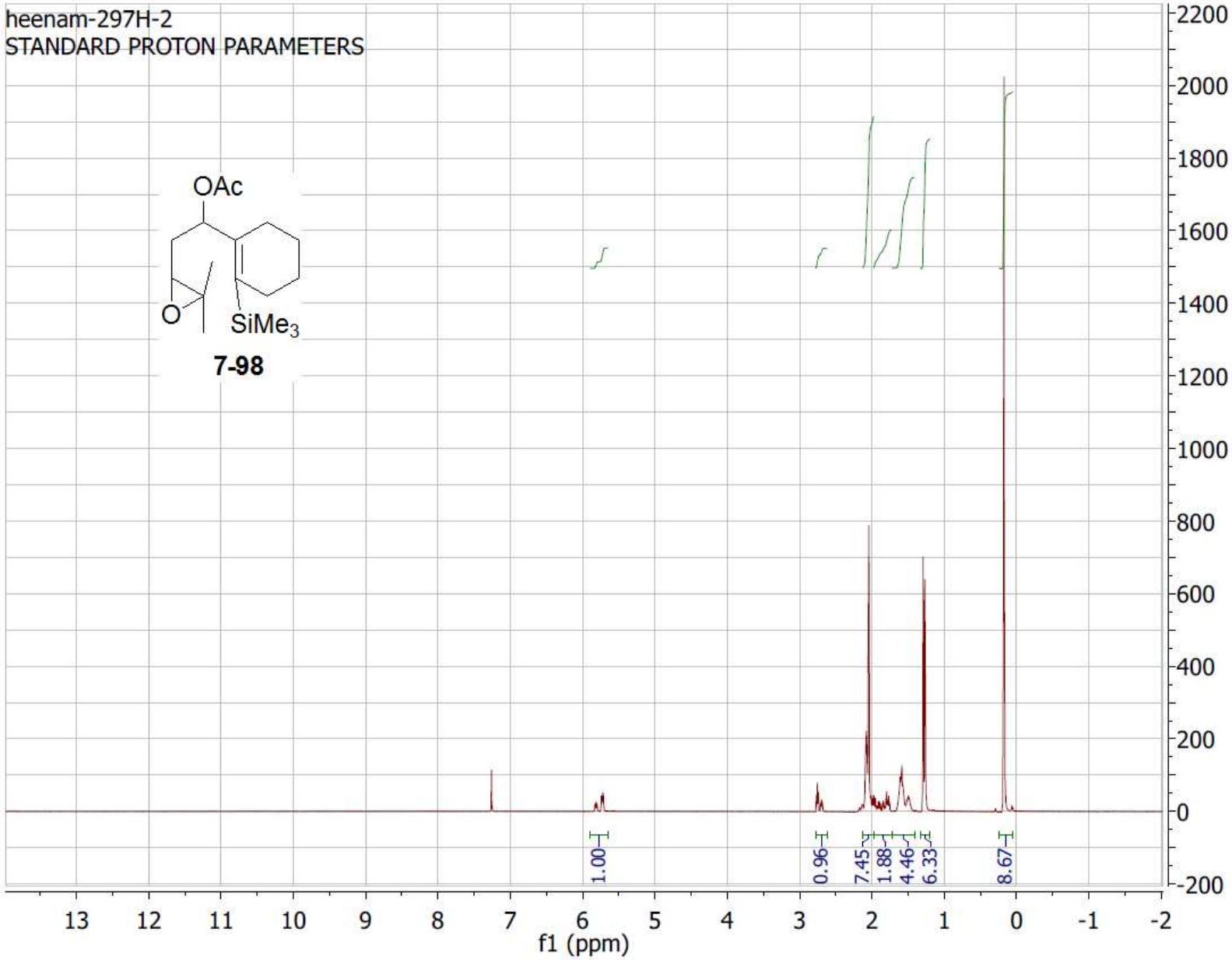


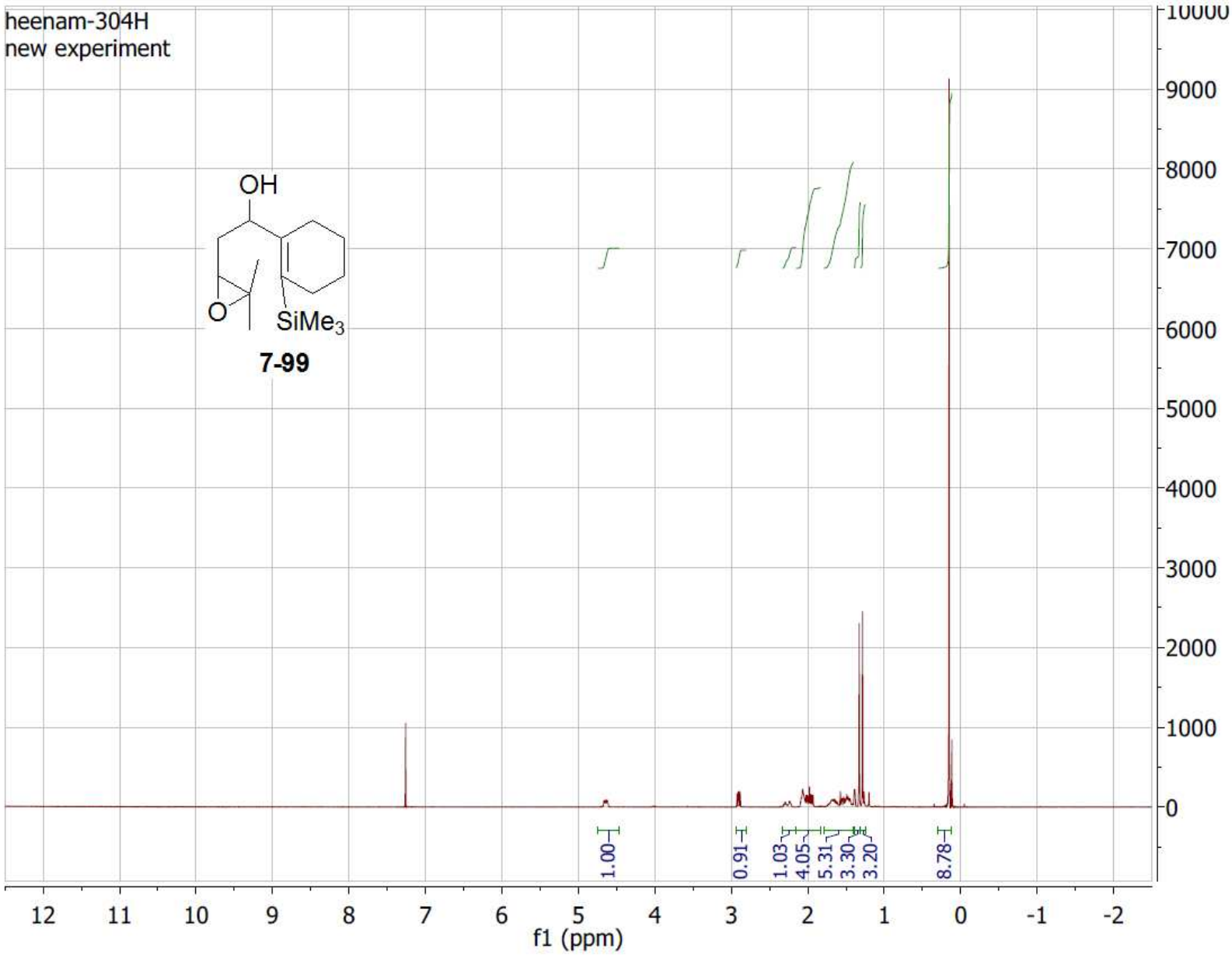

heenam-291H-crude
STANDARD PROTON PARAMETERS
OTBS
SiMe3
7-91
m-CPBA (1 eq.)
CH2Cl2, 0 °C
7-92 (58 %)
7-93 (13 %)
7-94 (16 %)
7-91 (13%)
1.00
2.01
0.54
0.67
0.43
1.95
0.79
3.23
11.94
21.89
26.21
27.93
38.22
f1 (ppm)


heenam-294H
new experiment
AcO
Me3Si
7-95
2.00
7.10
4.36
9.06
f1 (ppm)


heenam-295H-crude
STANDARD PROTON PARAMETERS
AcO
Me3Si
7-95 1 eq.
+
AcO
7-86 1 eq.
mCPBA (1 eq.)
CH2Cl2
0 °C to r.t.
AcO
O
Me3Si
7-96 0.13
+
AcO
O
7-88 0.87
+ unreacted starting materials
1.00
0.13
2.03
1.92
0.27
0.86
1.97
10.55
10.35
5.96
8.66
f1 (ppm)


heenam-296H
STANDARD PROTON PARAMETERS
OAc
O
SiMe3
7-97
1.00
1.01
1.13
8.42
10.21
8.30
f1 (ppm)


heenam-297H-2
STANDARD PROTON PARAMETERS
OAc
O
SiMe3
7-98
1.00
0.96
7.45
1.88
4.46
6.33
8.67
f1 (ppm)

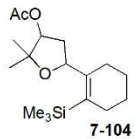

heenam-304H
new experiment
OH
O
SiMe3
7-99
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.00
0.91
1.03
4.05
5.31
3.30
3.20
8.78
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

STANDARD PROTON PARAMETERS

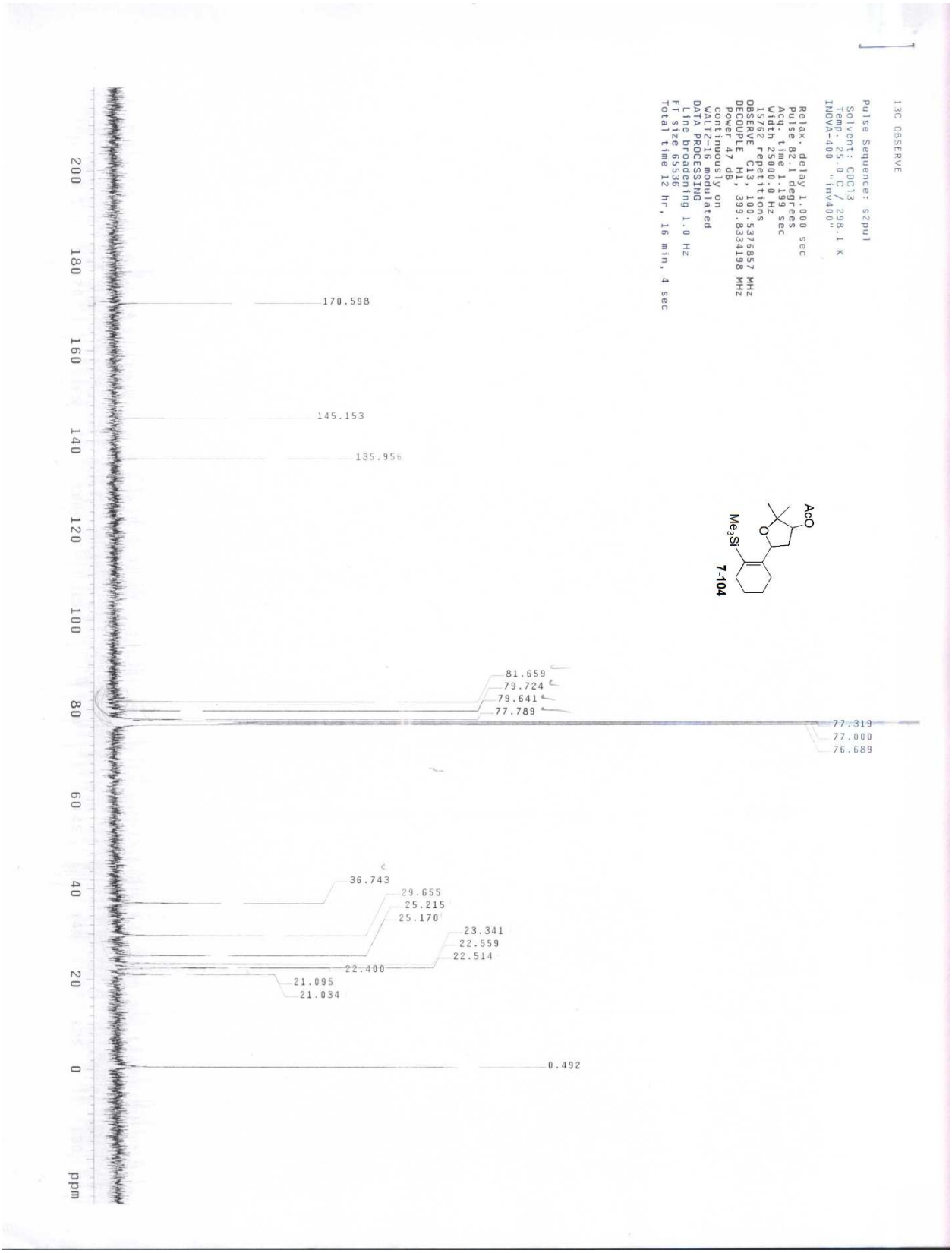
Pulse Sequence: s2pul

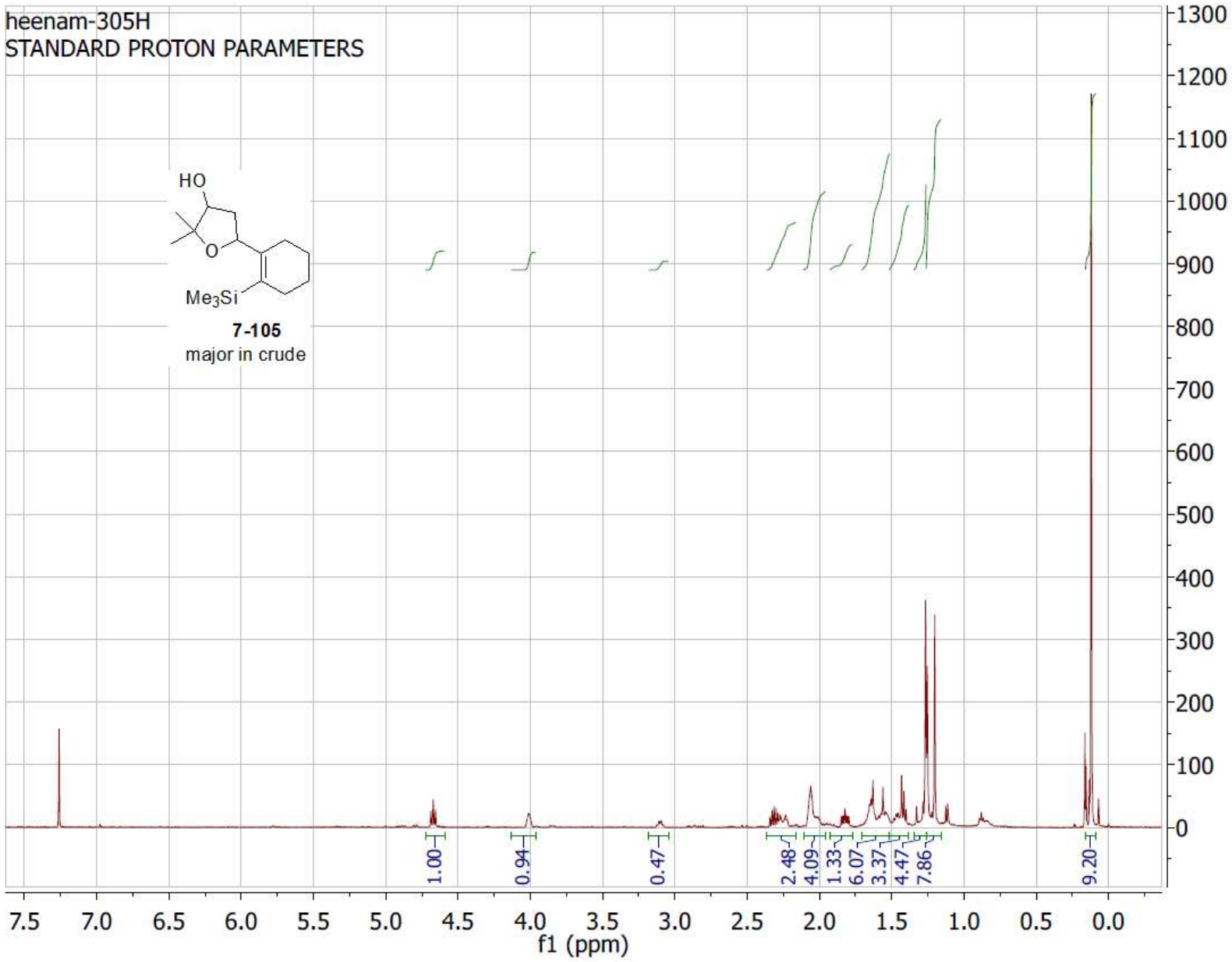
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-600 "inv601"

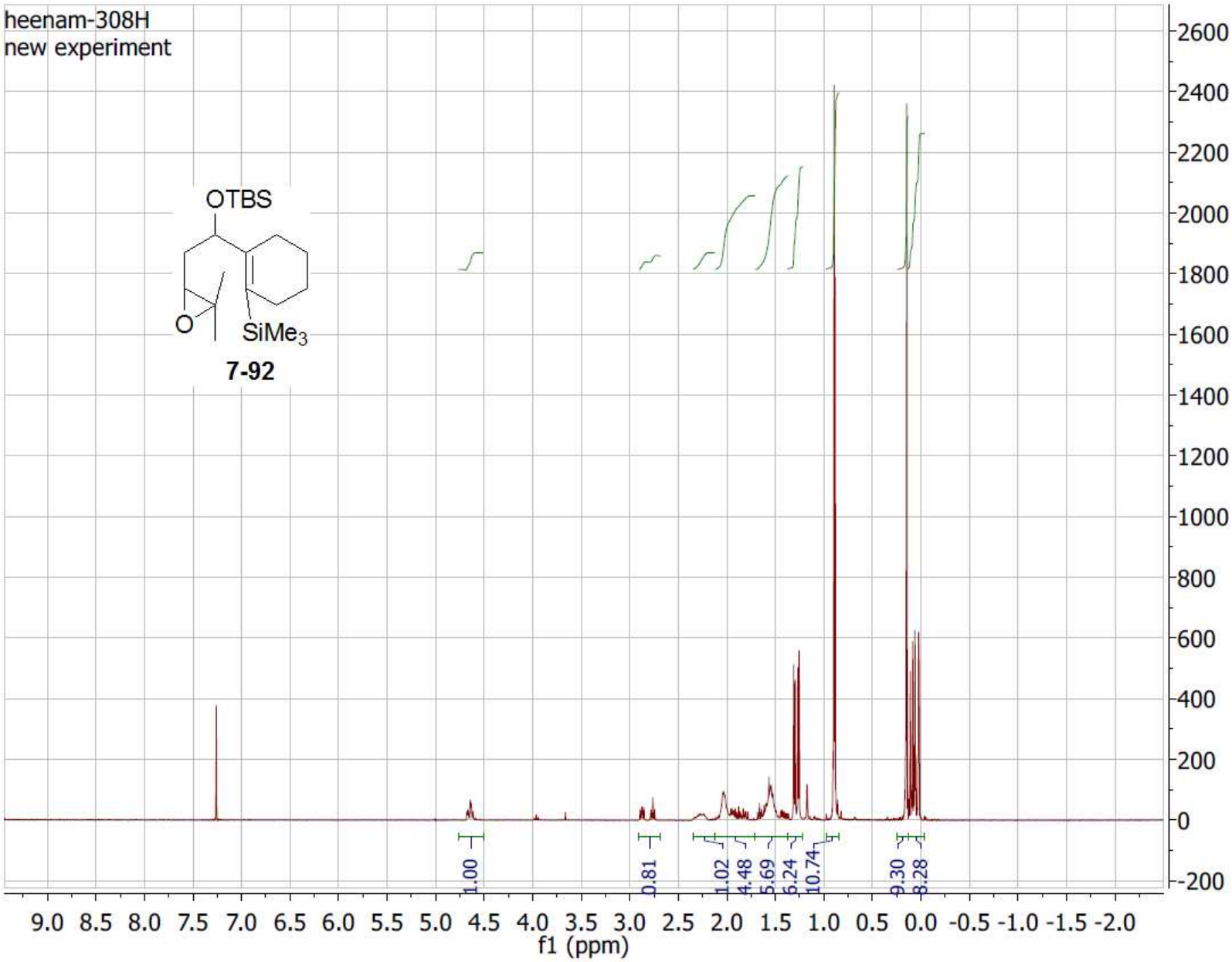
Relax. delay 1.000 sec
Pulse 61.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
24 repetitions
OBSERVE H1, 599.7178132 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 11 sec

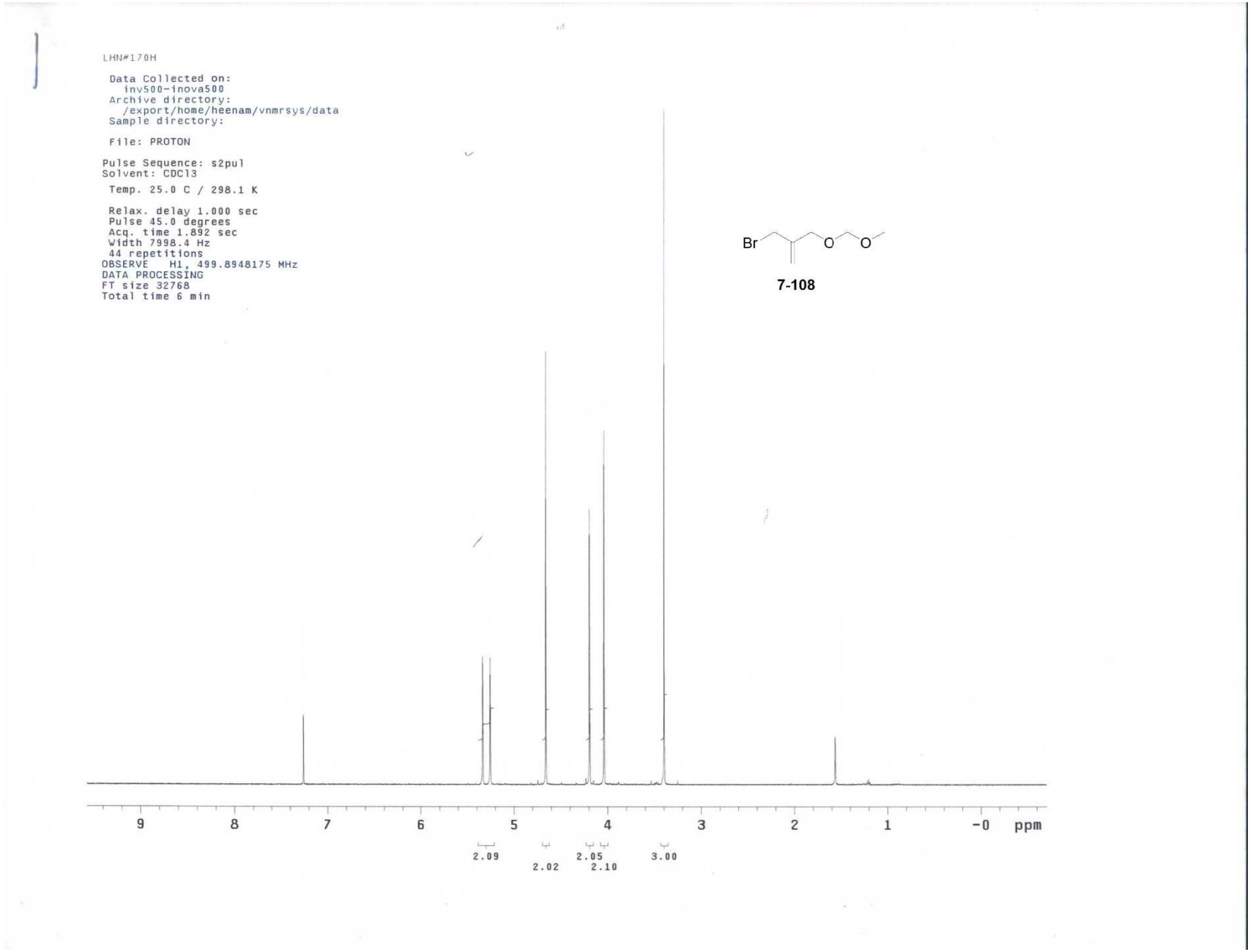


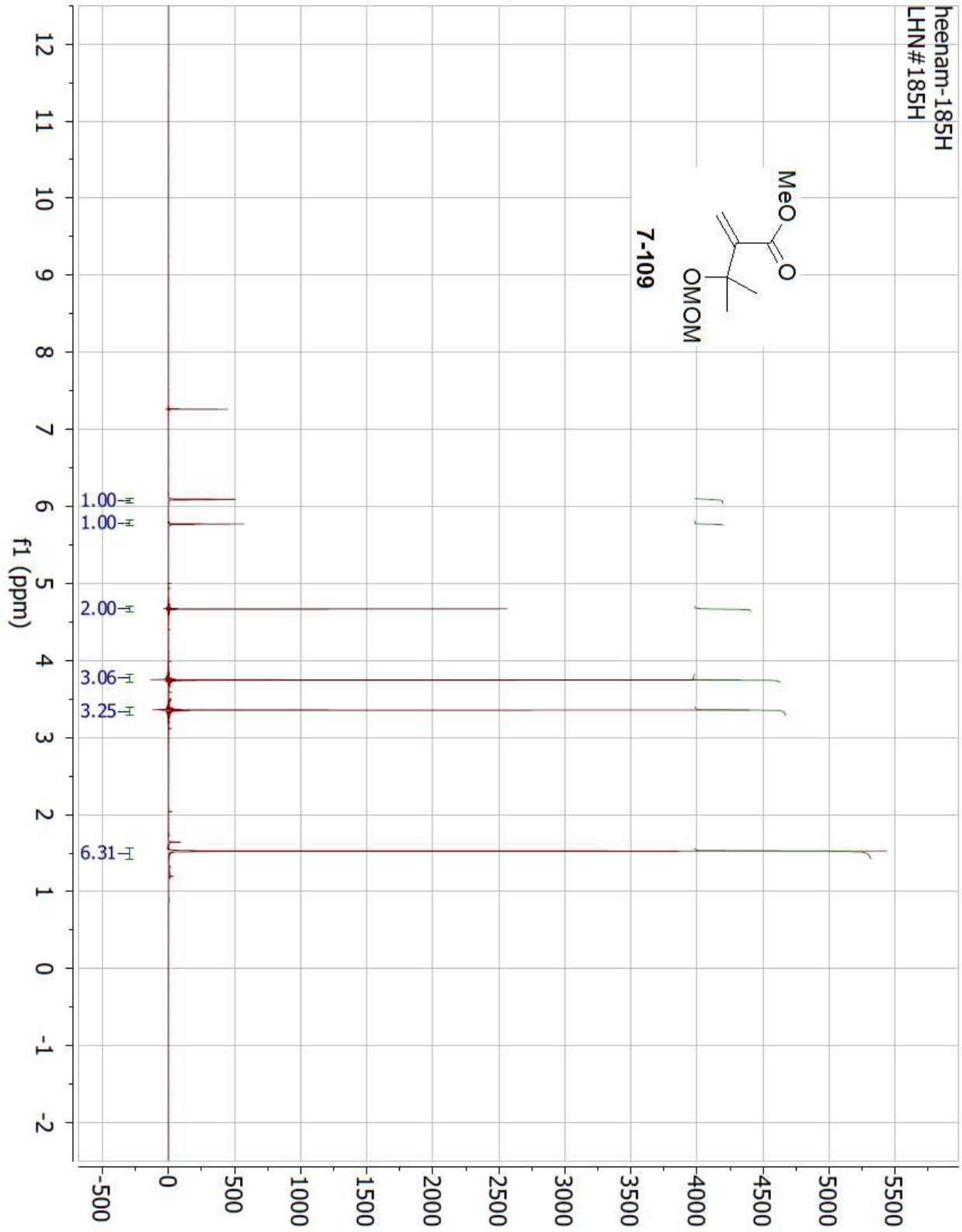
7-104

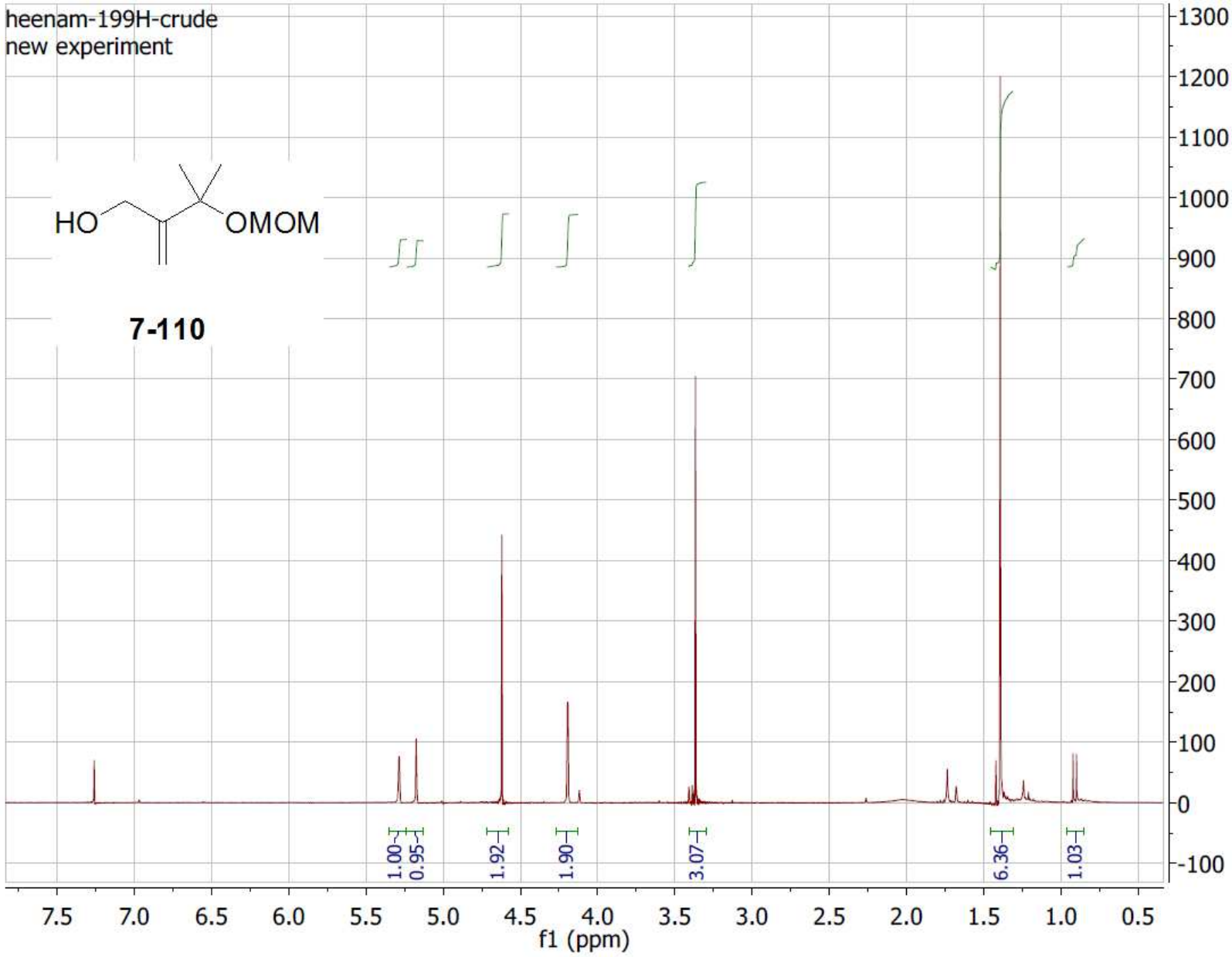

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 82.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
1572 repetitions
OBSERVE C13, 100.5376857 MHz
DECOUPLE H1, 399.8334198 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 12 hr, 16 min, 4 sec
AcO
Me3Si
7-104
170.598
145.153
135.956
81.659
79.724
79.641
77.789
77.319
77.000
76.689
36.743
29.655
25.215
25.170
23.341
22.559
22.514
22.400
21.095
21.034
0.492
200
180
160
140
120
100
80
60
40
20
0
ppm

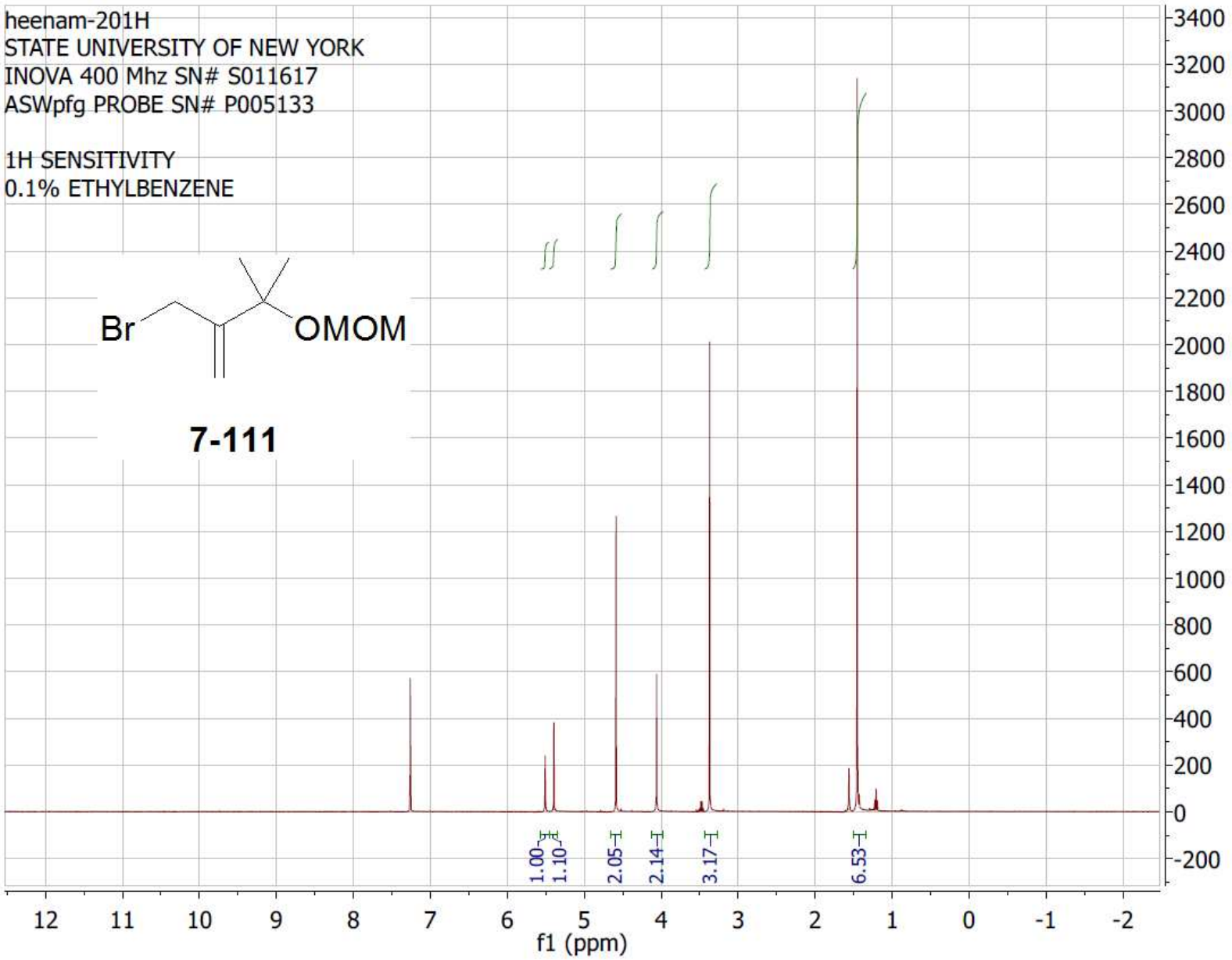

heenam-305H
STANDARD PROTON PARAMETERS
HO
O
Me3Si
7-105
major in crude
1.00
0.94
0.47
2.48
4.09
1.33
6.07
3.37
4.47
7.86
9.20
f1 (ppm)


heenam-308H
new experiment
OTBS
O
SiMe3
7-92
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
1.00
0.81
1.02
4.48
5.69
6.24
10.74
9.30
8.28
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)


LHN#170H
Data Collected on:
inv500-inova500
Archive directory:
/export/home/heenam/vnmrsys/data
Sample directory:
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 7998.4 Hz
44 repetitions
OBSERVE H1, 499.8948175 MHz
DATA PROCESSING
FT size 32768
Total time 6 min
Br
O
O
7-108
9
8
7
6
5
4
3
2
1
-0
ppm
2.09
2.02
2.05
2.10
3.00

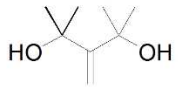

heenam-185H
LHN#185H
7-109
MeO
O
OMOM
1.00
1.00
2.00
3.06
3.25
6.31
f1 (ppm)


heenam-199H-crude
new experiment
HO
OMOM
7-110
1.00
0.95
1.92
1.90
3.07
6.36
1.03
f1 (ppm)

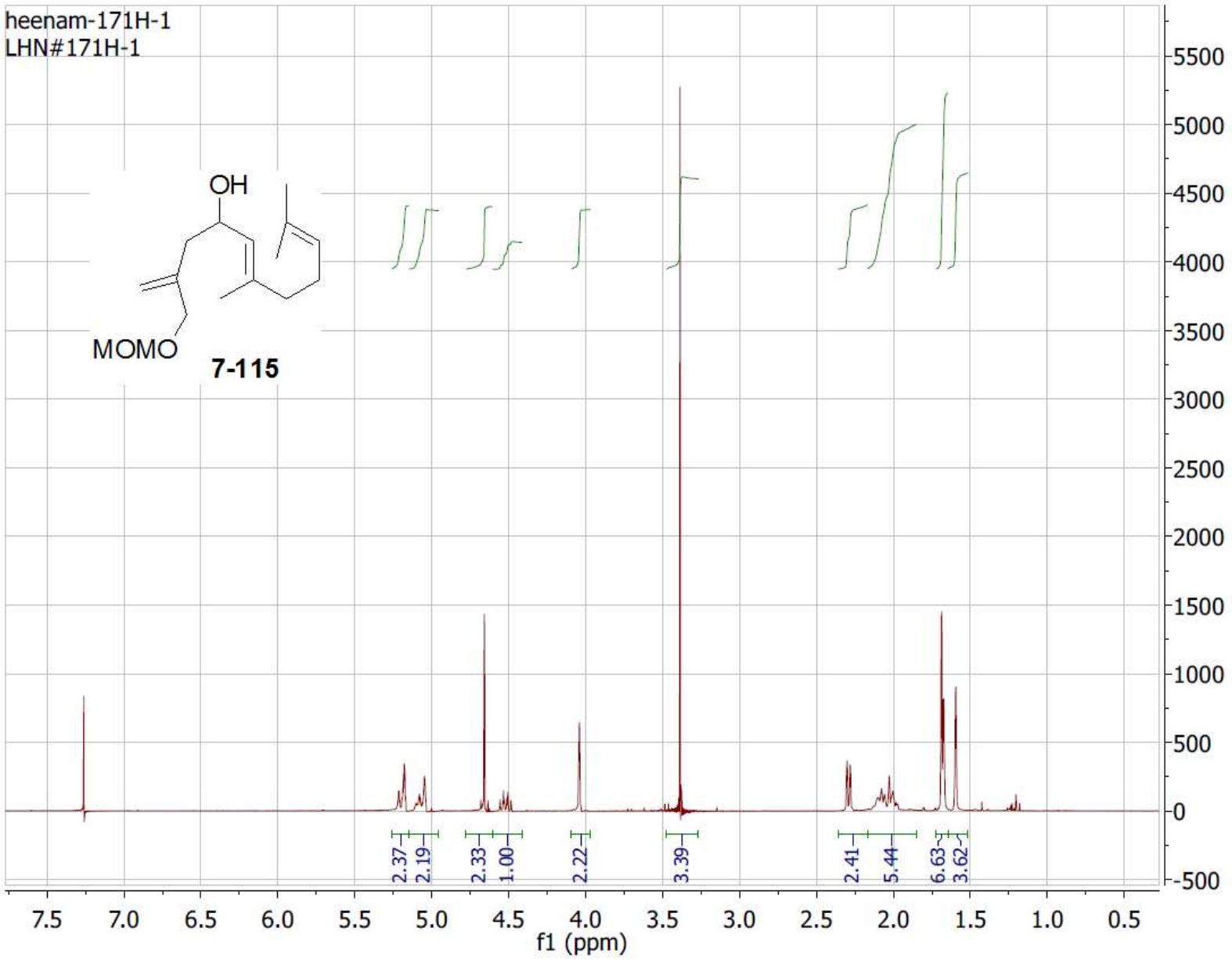

heenam-201H
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Br
OMOM
7-111
1.00
1.10
2.05
2.14
3.17
6.53
f1 (ppm)

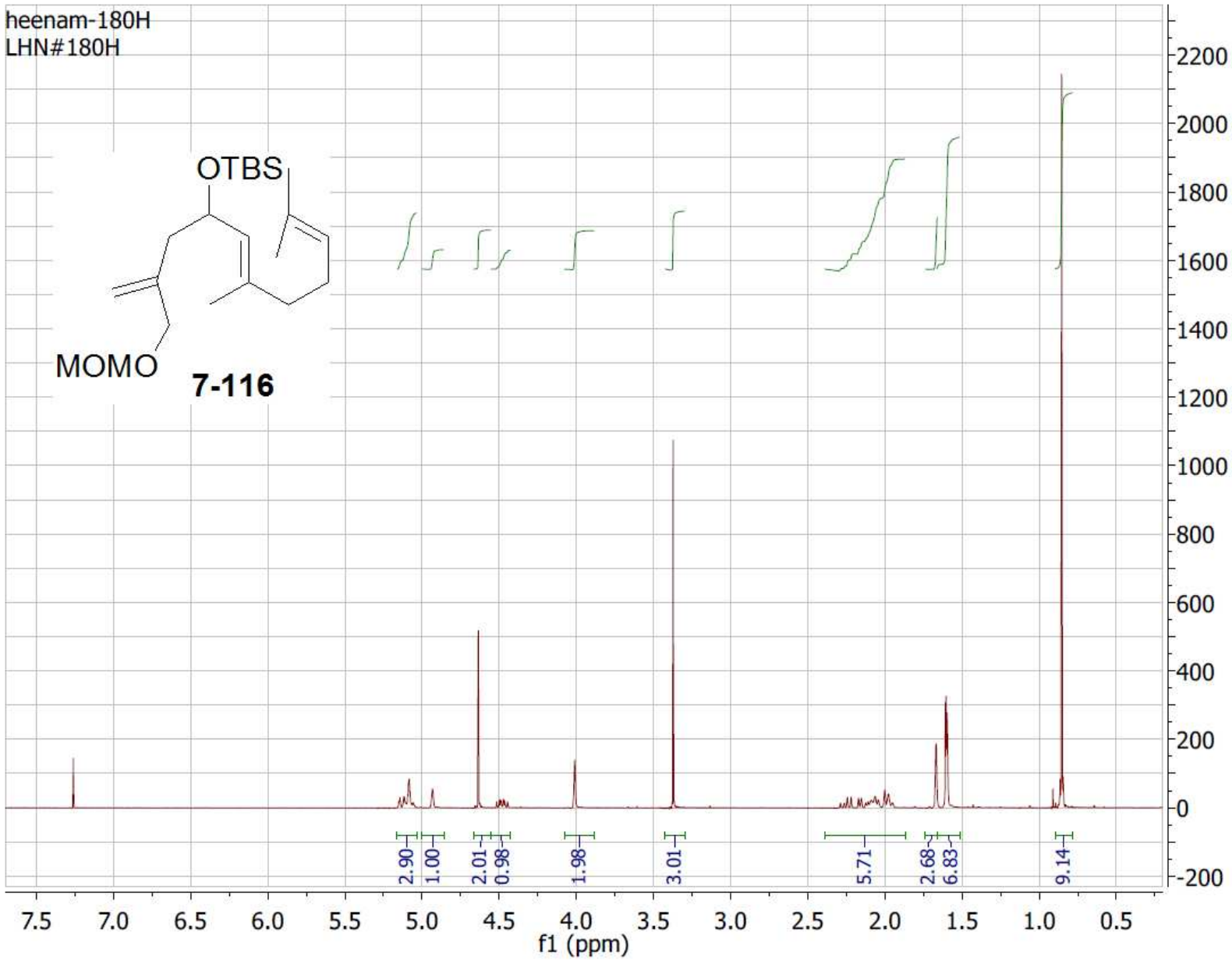
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

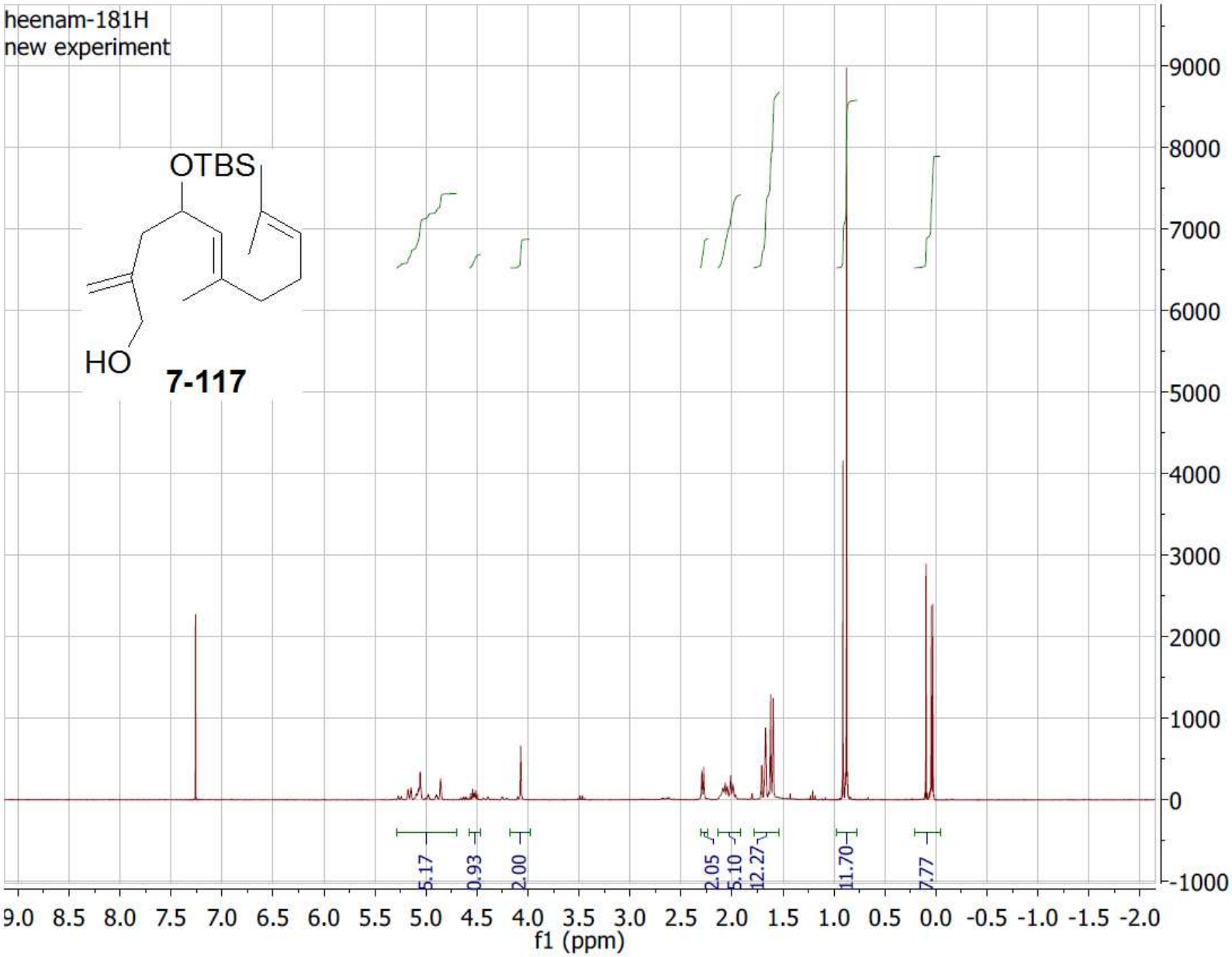
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
12 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 9 sec

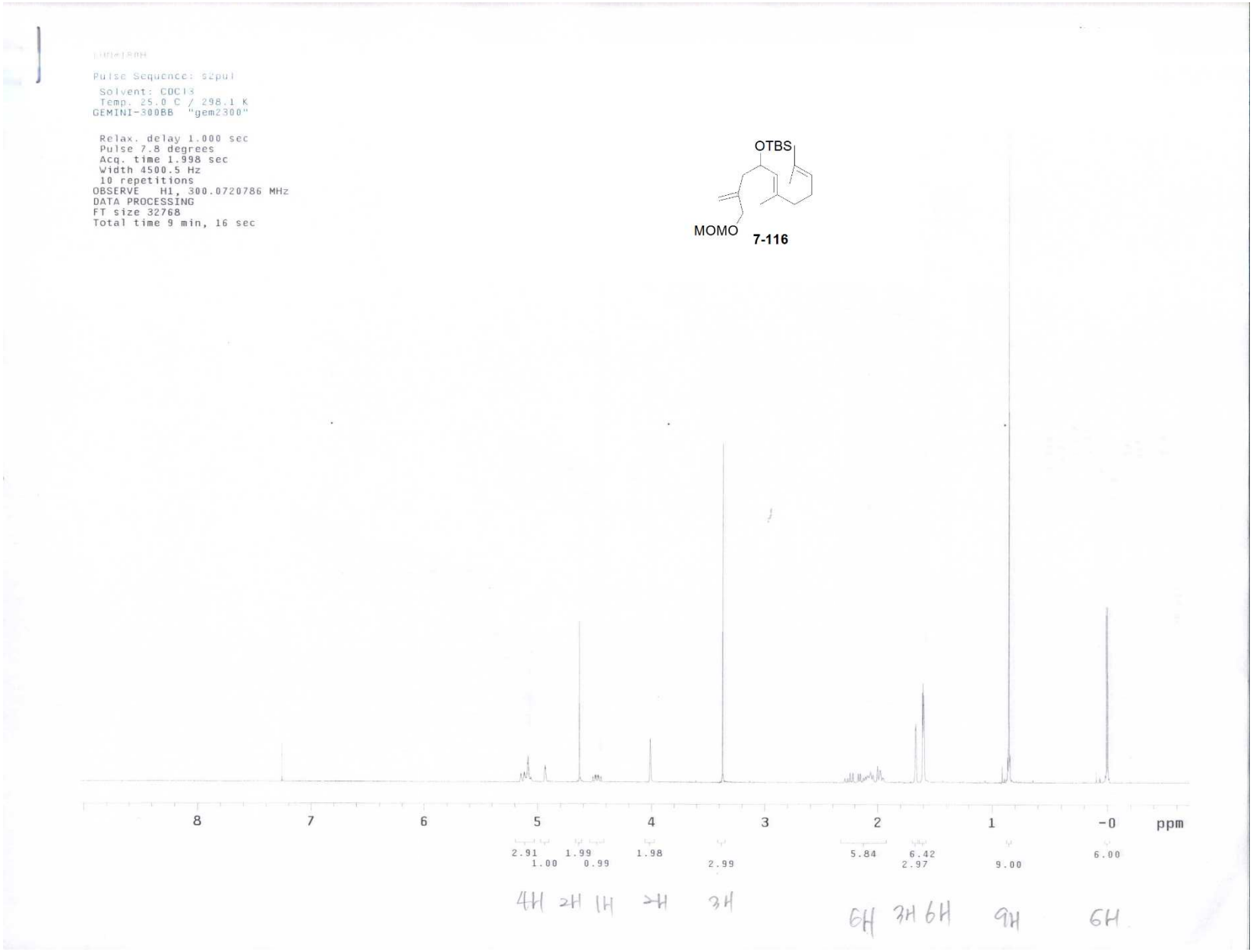


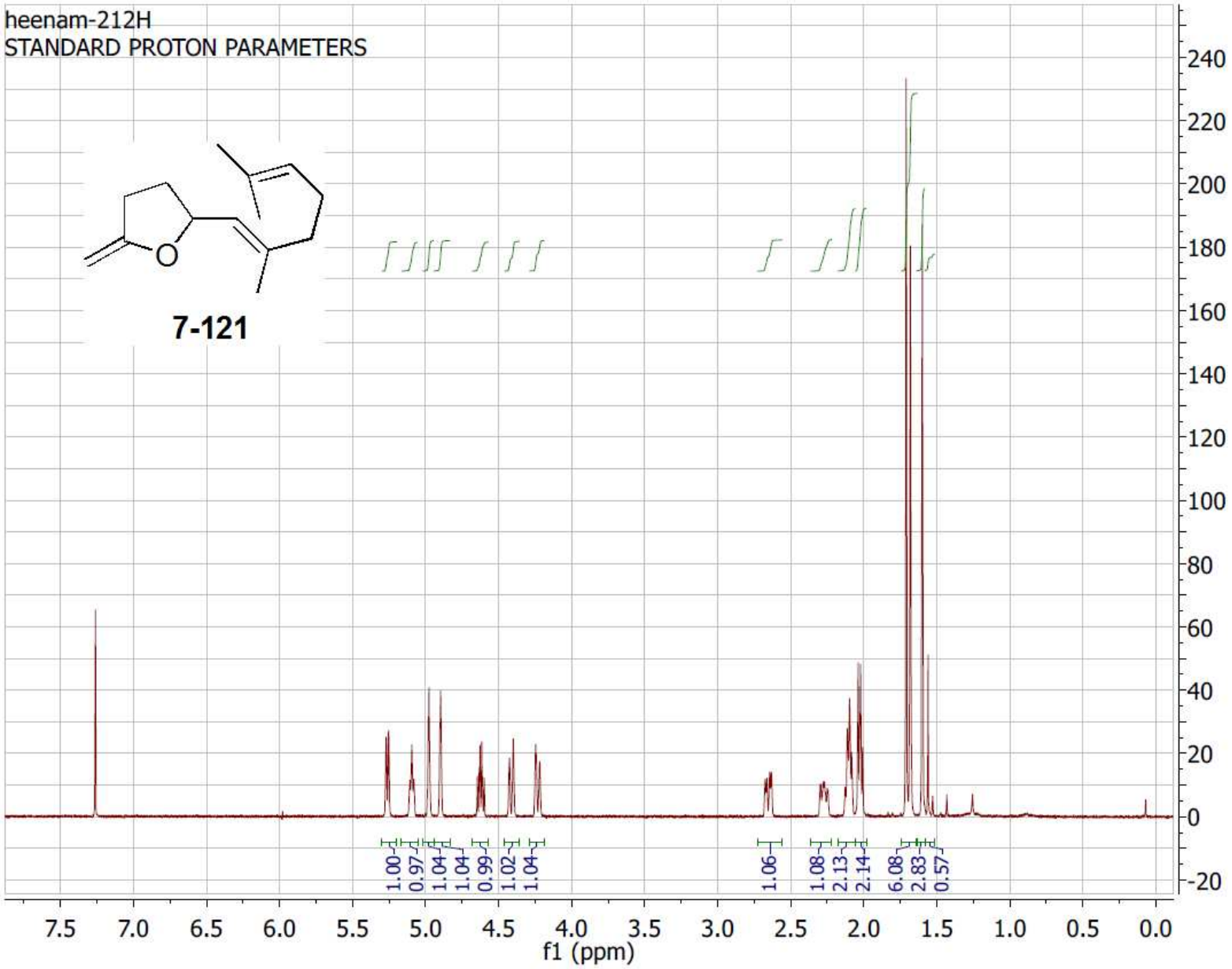
7-112


heenam-171H-1
LHN#171H-1
OH
MOMO
7-115
2.37
2.19
2.33
1.00
2.22
3.39
2.41
5.44
6.63
3.62
f1 (ppm)


heenam-180H
LHN#180H
OTBS
MOMO
7-116
2.90
1.00
2.01
0.98
1.98
3.01
5.71
2.68
6.83
9.14
f1 (ppm)


heenam-181H
new experiment
OTBS
HO
7-117
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
5.17
0.93
2.00
2.05
5.10
12.27
11.70
7.77
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)


Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
10 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 9 min, 16 sec
OTBS
MOMO
7-116
8
7
6
5
4
3
2
1
-0
ppm
2.91
1.00
1.99
0.99
1.98
2.99
5.84
6.42
2.97
9.00
6.00
4H 2H 1H 2H 3H
6H 3H 6H 9H 6H


heenam-212H
STANDARD PROTON PARAMETERS
7-121
1.00
0.97
1.04
1.04
0.99
1.02
1.04
1.06
1.08
2.13
2.14
6.08
2.83
0.57
f1 (ppm)