

Efforts Toward an Oxa-Conjugate Addition Based Approach to (+)-Neopeltolide Synthesis

by

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DISSERTATION

**A thesis submitted to the Faculty of Science
In partial fulfillment of the requirements
of a Masters of Science in**

CHEMISTRY

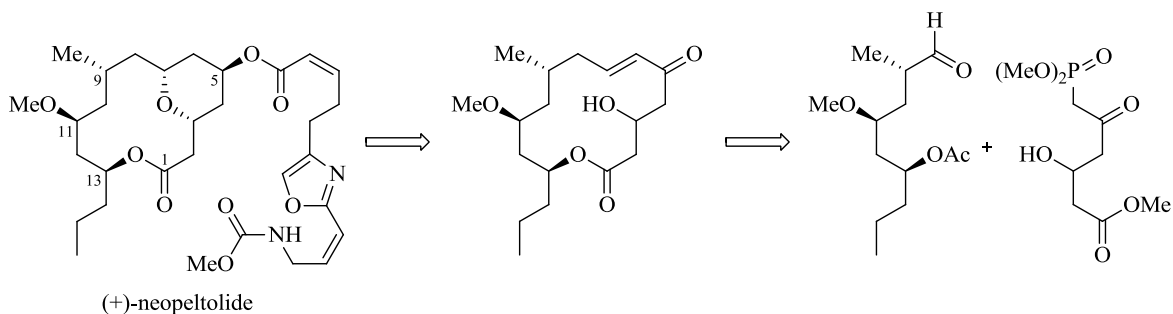
At the University of Ottawa

January 2012

**University of Ottawa
Department of Chemistry
Ottawa, ON, Canada
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Abstract

(+)-Neopeltolide is a highly potent marine polyketide natural product with activity against multiple cancer cell lines *in vitro*. The nanomolar range of antifungal and anticancer cytotoxicity in this tetrahydropyran (THP)-containing polyketide, combined with its limited natural supply, has led to several syntheses. In this study, the feasibility of an oxa-Michael conjugate addition route to *cis*-2,6-THP rings is examined through the efforts toward a total synthesis of the macrocyclic core of (+)-neopeltolide using a highly convergent route. This study is based on the successful preliminary results with a simple 14-member ring model system and the synthesis of the key aldehyde intermediate shown below. The highlighted transformation of this synthesis will be a transannular oxa-conjugate addition to generate the *cis*-2,6-tetrahydropyran ring system. This route also highlights a highly convergent Wittig coupling to generate the full carbon framework of (+)-neopeltolide. One of the key goals of this project is to compare this synthesis with a chemo-enzymatic total synthesis that relies on chemistry catalyzed by polyketide synthase enzymes in the late stage of the synthesis.



I. MARINE-DERIVED MACROLIDE (+)-NEOPELTOLIDE AND ITS DERIVATIVES
**II. TOWARD THE OXA-CONJUGATE ADDITION ROUTE TO THE TOTAL
SYNTHESIS OF (+)-NEOPELTOLIDE**

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Taylor:

Good luck with the
synthesis. Looking forward
to an outstanding yield!

Amy Wright

Acknowledgements

First and foremost I want to thank Chris, my supervisor, role model and associate, for giving me the privilege and opportunity to work with him in his research laboratory at the University of Ottawa. I want to extend my thanks to you for your guidance, expertise, encouragements, eternal optimism and for always having an open door and open mind. Your love for the sciences and to always continue learning is both contagious and motivating. The fact that above your responsibilities as my supervisor, you have always extended invitations into your home and family throughout the years, and that has always been appreciated in ways I've never told. Above all else, you have my deepest thanks for going out on a limb and taking a chance on me as a researcher – when we first met, I did not boast a colorful CV or the best of grades, but you took me into your group regardless. I hope that I have made you proud with my capabilities and research, and that I continue to represent myself in a manner that illustrates the tools and experiences learned from you over these past years.

Of the many instructors that I have had the pleasure of encountering during my academic tenure, I would like to pay special thanks to Professors André Beauchemin and Jeffrey Manthorpe for acting as my dissertation committee, and to Professor Heshel Teitelbaum for acting as the thesis chair. André and Jeff, I truly appreciate what you both contributed to my thesis through your comments and stringent eye for details, and as a direct result, I know it has made for a better overall product. Your gentle grilling during the defence was also appreciated, and made certain that I remained in my calm state throughout the process. Thank you for your involvement in the completion of my degree.

Burkhardt Ingersoll Wilke, I could easily write an entire chapter in this thesis entirely surrounding you, but a paragraph will have to suffice. Burk, I truly wish to thank you from my very core for all that you have taught me in regards to chemistry and to life in general. From the first day I met you and wondered “who the hell is the bear-like figure, and what the hell is he wearing?!” I have learned that I will always have “what the hell?” questions when it comes to you. But I mean that in the nicest of ways. You are the one person I worked with most closely during our shared tenure as grad students, and I am extremely pleased it turned out that way. Your bizarre work hours may not have impressed Chris in any way, but I certainly appreciated them because I always knew that you would be around for someone to talk to/procrastinate with/make sure I didn't blow up and be found dead the following morning. I realize this would cost me dearly, if it wasn't the extreme metal being blared, it was you wanting to learn to play violin – but I can vouch for you that you may not be the most skilled in that capacity, but by god, you sure are persistent in hoping you one day might. I'll always value you as a roommate – I knew I'd always have bulk bags of candy on hand, and a partner for Gran Turismo ... I will always refer to the Mercedes-Benz 300SL as “Burk's car.” To try and sum this up, thank you for always being there if ever I needed, thanks for all the help and knowledge you have provided me, and thank you for being a truly great person - you will always be a friend first, Burk, and a colleague second.

Doctor David Cole Stevens, don't think that because Burk got his paragraph first that I think of you as second rate. You too could have an entire chapter in this thesis as well; however, it would be a pretty intense one, and may be rated NC-17 in some places. Like Burk, I will always

consider you a friend first, and although we never worked together directly per se, I most certainly am fortunate to have had you around the lab for the time I did. On a professional level, you always were willing to take the time to look over any of my work for me, and even better, were always willing to help me with any issues I encountered, or provide advice for improvement. On a personal level, it was great to have someone around who appreciated video games, and you most certainly went above and beyond what I could have ever expected in that regard. All of the SingStar parties have been truly missed by myself ever since you left for Notre Dame, but you will always have “Life on Mars” as a ringtone in my phone, and Phantom Planet’s “California” will be a song for us to duel, and not lame title music. You taught me a lot in your time here – where else am I going to learn that real men do not ride bicycles after the age of seven, or exactly how many squirrels I would need in order to make squirrel brain soup. But in all honesty, just like the Golden Girls would say, thank you for being a friend. I *literally* mean that, and have full intentions of keeping it that way.

I have had the good fortune of working with some very talented individuals during my time in the Boddy Lab. Doctors Ben Lundgren and Meng Wang showed me the dedication a graduate student should put forth when conducting research, but also illustrated the importance of making time for yourself and the things you enjoy, whether it was computer games or beer, wings and horse racing. Doctor Atahualpa Pinto, thank you for your friendship and knowledge in the lab. You were always there to provide a voice of reason when it came to life decisions or events, in addition to your experiences in chemistry, and that always was quietly appreciated. Monica Wirz, you and I brought the uOttawa Boddy Lab to fruition, and we shared a lot of time and experiences together as a result. Thank you for your friendship, and willingness to do whatever you could in order to help me if ever I needed it. You and I have stumbled through these degrees in similar fashion, and despite the fact you are from the dirty ‘Peg, I wish the very best of you now that you are graduated and hope you find your calling whether it is in chemistry or not.

To “the new class,” Mark “Dale” Dornan, P. Hizz, Dr. Lou, Mark Horsman, Kyle Conway and Panos Agryolopolopololousolous. Dale, thank you for your decision on joining the Boddy Lab – you have become a welcomed vehicle to dealing with my moments of angst and of happiness. Much like your hopper, you always seemed to have something we could get up to and I’ll always appreciate that. We may not be part of “The Core Group,” but they don’t know how to shut down The Merc on a regular, so I think we come out on top. Your business savvy ways, and determination in life will take you anywhere you desire, and I only ask that you always keep an open position in your future businesses for me. Pat Rick Hill – I still have no idea of who the hell you actually are, and I don’t think I ever will, but this is probably your best feature! *In Groningen*, you were a man, but here, you are an absolute legend. Thank you for always thinking I have a horrible taste in women, have no sense of style, and most of all, for dealing with my constant joking around with you. Dr. Lou, ¡mucho gusto! Que rajado. Muy Bueno! Before I start adding my entire Spanish repertoire, I want to thank you big Lou for being such a great guy. You have always been there to hear me vent about my drama, and to offer your worldly advice, and I’ve always appreciated that. I can’t wait for you to finish your schooling here, so I can come visit in Costa Rica and put my Spanish to good use – ¡viva el gringo! Horsman, you like asking questions. You are a very bright person; this will take you far in all your endeavors, and I will always appreciate having you in my group so you wouldn’t make an ass of me in big presentations.

You're a great guy, and I wish you all the best in your future. Computer Conway, you are a truly great guy with that "knows a lot about everything" characteristic like Chris. You're a genuine person who has always been willing to talk to about anything, whether it is me needing to work my way out of a computer problem or to discuss subjects of greater seriousness. I wish you all the best in what you decide to do following this degree, and I am certain that you will be truly great at it. Uncle Jesse Katsopolis, you are the most recent graduate student to join the group, and you've fit in well ... in your segregated upstairs lab! In all honesty, you've been a welcomed addition to the group, and I will try my best to forgive you for being a Canucks fan. You've shown great improvements during this first year with us, and I can only see things following this trend – all the best!

And then there were the undergrads. I only am going to recognize those that have meant anything to me, so consider this your award. Nelson Pearce, I am sad that we lost you to Memorial for pharmacy school. I always liked having you around, as you were always extremely positive about everything, but just because of your character. I'm glad you're getting your professional degree in counting, and I hope your future career in monotony is an exciting one! Let's be honest Nelson, you're going to be making more money than anyone else I'm thanking, so you most certainly get a well-deserved last laugh. Am-a-dago Falsetto, you know exactly how I feel about you. I'm glad we received you as a UROP student, and that we were able to keep you around for another two years time. Very little needs to be said to you, so I'll just write key words: Ninja's Night Out (0:23.05); Shild; Poncho; busting dusties; Lions, No Lambs; Ceiling Jumps; Sandy; Nona Maria; Subway; Hakim Gol. It's been a true pleasure these past years, and I wish you the very best in your future (provided you don't die of malnutrition when you get to Toronto). I consider you a good friend, and anticipate many more random adventures in our future. Slim Thug, Young Snoop, Sanjeezy – thank you from the very bottom of my heart for teaching me what a gambling addiction looks like. I'll always marvel at how an incredibly bright person such as yourself can be so foolish with his money, but I also have loved every anxious second I've spent with you in the casino. You have a good head on your shoulders, and whether or not you decide to go to med school after your Ph.D., you'll be successful regardless. I have so many great memories that involve you – many of which I will always have captured as quotes – and I cherish all of them. I'm grateful to have met you, and to be able to call you a friend of mine. Christine (yes, Christine) Achampong – you like boots, uh? Thank you for being so to-the-point with me from day one, and for trying to pretend like you meant it in a nice way. Bringing me to Fashion Week always leaves me feeling like I'm somehow special, and I have you to thank for that. I appreciate you as my friend and for being someone whose opinion I actually can respect (regardless of if I want to accept it or not). I feel bad that we lost you to Toronto for grad school, but I'm secretly happy that you had such a shitty group and experience there that we will get to have you back. Most of all, I should thank you for secretly being madly in love with me, but not making it apparent to the world – it has always been much appreciated. To BigMoe01 – you are without a doubt the friendliest of giants. You have found your place within the group with such ease despite your enormous stature, and we all appreciate how incredibly humbled and genuine you are. Continue being this way and combined you're your intelligence, you will go on to accomplish anything you desire. Finally, Mr. No-Show-Bo! I want to thank you for absolutely nothing. You've been a great source of humor, and I will always cherish the fact you plagiarized the shit out of my thesis. I wish you all the best.

Mrs. Crittall, for better or for worse, I can wholly attribute my current educational status to you with absolute certainty. The perfect 100% grade I received in your grade 12 chemistry course catalyzed the decisions made during my university application process, which ultimately brought me to Ottawa for an undergraduate degree in Biopharmaceutical Sciences with a concentration in Medicinal Chemistry. Subsequently, with nothing better to do, I ended up staying in Ottawa for this graduate degree. I remain uncertain as to whether or not I should ever thank you for this apparent life of chemistry, but regardless of my uncertainties in this career field, it certainly has been a breeze getting to this point thanks to the knowledge I exited your classroom with.

To my family, how can I properly put my thoughts and feelings into words? Mom, Dad, Snork – you have all been a constant source of support for me, in every respect of the term. I cannot thank you all enough for this, and for any of the sacrifices you have made, in order for me to get where I am today. I love you all very much, and wish to make you proud of me and my accomplishments throughout life. For all that you have done for me, I will be endlessly grateful. Spencer – neither of us have ever been one to really express much to each other, but I am infinitely envious of you for doing what makes you happy, regardless of the outcome or payoff. I can only wish the world to you and your talents, so be sure you don't squander them. To my late grandmother, Elsie Elizabeth Spence – you are the most amazing woman I have ever had the pleasure of knowing, and I think of you every single day. I miss you more than any word could ever express, and I hope you are shining down from above with a proud smile. To the remainder of my family, all my aunts, uncles and cousins, I want to thank you all for your support of me during my academic career. I know I seem crazy for being in school for such a long period of time, with potentially more to come, but I can only hope that all of this education will bring me the successes and happiness that you have.

Finally, to say one "Last Word – featuring Tinsel Korey," I would like to express a very necessary migwetch, to Wab Kinew.

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List of Abbreviations

¹ HNMR	Proton Nuclear Magnetic Resonance
¹³ CNMR	Carbon Nuclear Magnetic Resonance
4 Å ms	Four Angström (4 x 10 ⁻¹⁰ m) Molecular Sieves
9-BBN	9-Borabicyclo[3.3.1]nonane
acac	Acetylacetonate
Ar	Argon Gas
AT	Acyltransferase
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Bz	Benzoyl
Brine	Saturated Sodium Chloride Solution
br s	Broad Singlet
CAM	Ceric Ammonium Molybdate Solution
COSY	Correlation (2D-NMR) Spectroscopy
CSA	Camphorsulfonic Acid
d	Doublet
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DH	Dehydratase
dH ₂ O	Distilled Water
DEAD	Diethyl Azodicarboxylate
DET	Diethyl Tartrate
DIAD	Diisopropyl Azodicarboxylate
DIBAL-H	Diisobutylaluminum Hydride
DMAP	4- <i>N,N</i> -Dimethylaminopyridine
DMP	Dess-Martin Periodinane
DMF	<i>N,N</i> -Dimethylformamide
DMMP	Dimethylmethyl Phosphonate
DMSO	Dimethyl Sulfoxide
dr	Diastereomeric Ratio
DTBMP	2,6-Di- <i>tert</i> -butyl-4-methylpyridine
DVDS	1,3-Divinyl-1,1,3,3-tetramethyldisiloxane
EA/EtOAc	Ethyl Acetate
ee	Enantiomeric Excess
EI	Electron Impact
EQ/eq.	Equivalents
Et ₂ O	Diethyl Ether
g	Gram
G-II	Second Generation Grubbs' Catalyst
H	Hydrogen
h	Hour(s)
HCl	Hydrochloric Acid
hex	Hexanes
HG-II	Second Generation Hoveyda-Grubbs' Catalyst
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HPLC	High Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
HSQC	Heteronuclear Single-Quantum Correlation Spectroscopy
Hünig's Base	<i>N,N</i> -diisopropylethylamine
Hz	Hertz
IBX	2-Iodoxybenzoic Acid
IC ₅₀	Half Maximal Inhibitory Concentration
Ipc	Isopinocampheyl
IR	Infrared Spectrum
<i>J</i>	Coupling Constant
KPhos	Potassium Phosphate

KR	Ketoreductase
KS	Ketosynthase
LAH	Lithium Aluminum Hydride
LD ₅₀	Median Lethal Dose
LDA	Lithium Di- <i>tert</i> -butyl Amine
LiDBB	Lithium 4,4'-Di- <i>tert</i> -butylbiphenylide
M	Molar (mol · L ⁻¹)
m	Multiplet
MeOH	Methanol
MES	Mesitylenesulfonate
mg	Milligram
MgSO ₄	Anhydrous Magnesium Sulphate
MHz	Megahertz
MIC	Minimum Inhibitory Concentration
min	Minute
mmol	Millimole
mmu	Milli Mass Unit
MNBA	2-Methyl-6-nitrobenzoic Anhydride
mL	Milliliter
mol	Mole
MTPA	(S)-(+)- α -Methoxy- α -(trifluoromethyl)-phenylacetyl Chloride
MW	Molecular Weight (g · mol ⁻¹)
N ₂	Nitrogen Gas
NaCl	Sodium Chloride
NaHCO ₃	Saturated Sodium Bicarbonate Solution
NaOH	Sodium Hydroxide
nM	Nanomolar (10 ⁻⁹ mol · L ⁻¹)
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
<i>o</i> -DPPB	<i>o</i> -Diphenylphosphinobenzoyl
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
Ph	Phenyl
pH	Power of Hydrogen
PKS	Polyketide Synthase
PLE	Pig Liver Esterase
ppm	Parts Per Million
PPTS	Pyridinium <i>p</i> -Toluenesulfonate
Proton Sponge	1, 8-bis(dimethylamino)naphthalene
q	Quartet
RCM	Ring-Closing Metathesis
R _f	Retention Factor
rt	Ambient Temperature (~22 °C)
s	Singlet
S _N 2	Bimolecular Nucleophilic Substitution
t	Triplet
T	Thiolation Domain (Acyl Carrier Protein)
TE	Thioesterase
TBAI	Tetrabutylammonium Iodide
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBME	<i>tert</i> -Butyl Methyl Ether
TBS	<i>tert</i> -Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1yl)oxyl
TfOH	Triflic Acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
μL	Microliter
°C	Degree Celcius
δ	Chemical Shift

“Chemistry is a class you take in high school or college, where you figure out two plus two is ten, or something.”

- *Dennis Redman*

For my blankies, and in honor of the Nanamobile.

Chapter 1

Synthetic Approaches to the Marine-Derived Natural Product Neopeltolide and Its Derivatives

1.1 Introduction

Mankind has always relied on nature's generosity for basic needs such as shelter, food, clothing, and medicines. After 3.8 billion years of research and development, Earth's failures are fossils, and all that remains is the secret to our survival – truly mother nature knows best.¹ Plants have been the cornerstone of traditional medicine that have been in existence for millenia.² Although traditionally associated with Asian countries, the World Health Organization estimates 65% of the world's population relies on plant-derived medicines for primary healthcare.^{3,4} Unfortunately, the harvesting of natural sources for the isolation of active compounds is not sustainable, especially in the case of slow-growing, endangered, and protected organisms. This is especially true for producing organisms that make only minute amounts of their natural active product. The low abundance of these compounds becomes an even greater concern when factors like climate changes and global population growth put further limits on natural resources.^{5,6} Scientists from diverse backgrounds are keen on recognizing novel approaches to the pharmaceutical development of, and alternative sources for, natural product-derived medicines.

Synthetic chemistry offers a plausible solution to the dwindling supply of natural resources as it circumvents dependency on the producing organism. Additionally, modern chemical synthesis possesses the ability to enrich the diversity of natural products by providing structural analogues that can aid in the elucidation of the pathways responsible for a compound's biosynthesis, and can lead to development of second-generation pharmaceuticals.

As part of an ongoing effort to discover compounds that possess useful therapeutic properties, in 2007 Wright *et al.* reported the isolation of a novel, highly cytotoxic, marine-derived macrolide, neopeltolide (Figure 1.1, **1.1**).⁷ The source of the compound was a deep-water sponge of the family Neopeltidae that was collected off the northern coast of Jamaica. Following a series of complex isolation procedures and exhaustive purification steps, neopeltolide was isolated from the collected sample with a recovery yield of $4.0 \times 10^{-3}\%$ wt/wet wt. Initial biological evaluation revealed neopeltolide was an extremely potent bioactive compound with possible therapeutic applications, but due to the limited supply from the source organism there was not enough material for further biological evaluation. Chemical synthesis has fortunately addressed the supply problem for the initial evaluation of activity and mechanism of action studies.

This chapter reviews the current literature pertaining to the biological evaluation and synthetic efforts of neopeltolide (**1.1**). The initial isolation and identification of neopeltolide will be discussed and followed by both the total and formal synthetic work available up to June 2012.

Finally, the results of several fragment syntheses, structure-activity relationship (SAR), as well as stereostructural-activity relationship (SSAR) studies will be presented.

1.2 Neopeltolide Background

1.2.1 Isolation and Biological Evaluation

In 2007, Wright and co-workers reported the new natural product neopeltolide, isolated from deep-water sponges most closely matching the taxonomic description for the genus *Daedalopelta* and a close relative of *Callipelta*.^{7–10} A 105 g sample of the sponge was collected using a human-occupied submersible, and was extracted exhaustively with ethanol. The crude residue was separated under multiple vacuum-column chromatographic conditions, and neopeltolide eluted cleanly into the third fraction (heptanes:ethyl acetate, 2:3). Further separation of this fraction was accomplished using preparative reverse-phase HPLC, and led to 4.0×10^{-3} % isolated yield from frozen sample weight of pure neopeltolide, as colourless oil.⁷

Despite the minute quantities of neopeltolide obtained, it was possible for Wright's team to perform several biological activity assays. Neopeltolide is a potent antifungal agent toward the *Candida albicans* pathogen (MIC value of 0.625 µg/mL), which severely and adversely affects AIDS and other immunocompromised patients, potentially resulting in death. Neopeltolide (**1.1**) was also found to be a potent inhibitor of tumour cell proliferation *in vitro*. In the cytotoxicity assays to determine effects of **1.1** on the proliferation of the A549 human lung adenocarcinoma, NCI/ADR-RES ovarian sarcoma, and P388 murine leukemia cell lines, results revealed nanomolar concentration IC₅₀ values of 1.2, 5.1, and 0.56 nM respectively (Table 1.1).⁷ It is interesting to note that the multibillion dollar¹¹ anticancer pharmaceutical Taxol® has reported IC₅₀ values of 3.10,¹² 3814,¹³ and 7.7 nM¹⁴ for A549, NCI/ADR-RES, and P388 cell lines, respectively, indicating great potential for neopeltolide.

Table 1.1 – Biological activity comparison of neopeltolide and Taxol®,^{7,12–14}

(+)-neopeltolide				Taxol®	
Antifungal		Antiproliferative		Antiproliferative	
Test Organism	MIC (µg/mL)	Cell Lines	IC ₅₀ (nM)	Cell Lines	IC ₅₀ (nM)
<i>Candida albicans</i>	0.625	A549	1.2	A549	3.10
		NCI/ADR-RES	5.1	NCI/ADR-RES	3814
		P388	0.56	P388	7.7

Neopeltolide also showed strong inhibitory effects in nanomolar concentrations for PANC-1 human pancreatic cancer, and DLD-1 human colorectal adenocarcinoma cell lines; however, only 50% cell death over an extended dose range suggests cytostatic, rather than cytotoxic effects for these cell lines.⁷

1.2.2 Structural Determination

The molecular formula and structure of neopeltolide was proposed by the Wright group on the basis of considerable spectroscopic analysis of the available material (Figure 1.1).⁷ The carbon skeleton was established from analysis of one- and two-dimensional NMR data, where advanced one-dimensional double pulsed field gradient spin echo (DPFGSE) NOE¹⁵ experiments proved instrumental in regions of heavy overlap. It was determined that neopeltolide contains a 14-membered macrolactone bearing a 2,4,6-trisubstituted tetrahydropyran ring, which served as an anchor for an oxazole-containing side chain identical to that of leucascandrolide A (Figure 1.4, 1.2), as was assigned on the basis of comparison to the reported chemical shifts.

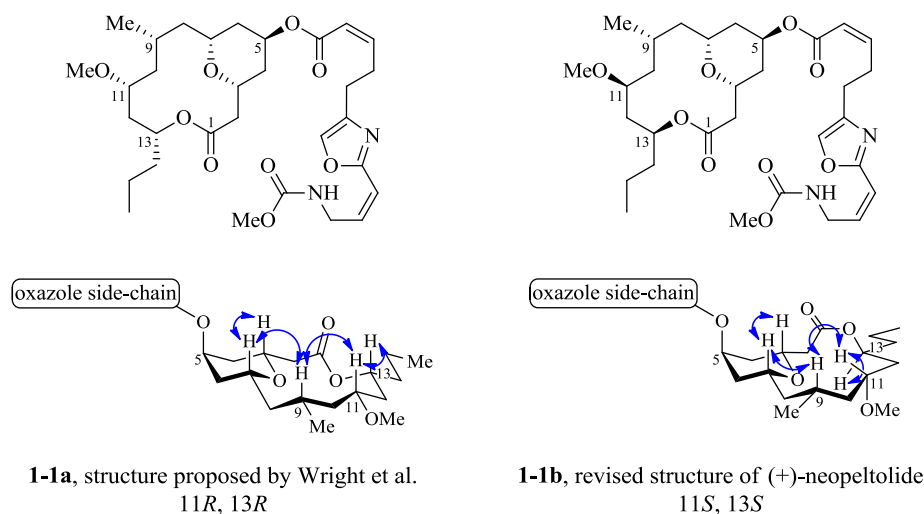


Figure 1.1 – The proposed (**1.1a**) and revised (**1.1b**) structures of neopeltolide. Key NOE interaction data from within neopeltolide's framework used to define the relative stereochemistry by Wright *et al.*,⁷ and structural revision by Scheidt¹⁶ are presented in blue. The oxazole-containing side chain is not included for clarity purposes.

The configuration of neopeltolide's six stereocenters was assigned on the basis of analysis of coupling constants, the 2D-NOESY spectrum, and a series of 1D-DPFGSE NOE experiments.⁷ Diaxial coupling in H3 and H7 were supported by strong interactions observed in the NOESY experiments; however, H5 was assigned as equatorial, and the anchored C5 ester was proposed in the axial position due to small coupling constants and zero enhancements observed with H3 and H7. The relative stereochemistry proposed was best supported by observed NOE enhancements

between H3-H7, H7-H9, H9-H11, and H11-H13, thus assigning all corresponding protons on the same side of the macrolide ring (Figure 1.1). As a result of being an oil, crystallographic studies were not able to facilitate the structural elucidation of neopeltolide.¹⁷

Although the relative configuration of neopeltolide was assigned by the Wright group,⁷ absolute configurations were not possible due to a lack of available material, and would rely upon chemical synthesis, which ultimately would overturn the proposed C11 and C13 assignments.^{12,14} Studies by the Panek group presented an explanation for the strong interactions observed by the NOESY studies, which was used as heavy support for the originally proposed configuration, despite the incorrect configuration.¹⁹ Their hypothesis centered on the region of heavy overlap in the proton spectrum of neopeltolide, which was coupled with NOE enhancements between H7-H9 and H9-H11 to suggest a *syn* relationship.⁷ Youngsaye proposed in his thesis work that the aforementioned NOE enhancements were ambiguous due to the crowded aliphatic region of the C9 methine.¹⁹ Within the buried region of the C9 proton ($\delta = 1.38$ ppm) are overlapping protons from the neighbouring C8 methylene ($\delta = 1.36$ ppm) and C12 methylene groups ($\delta = 1.28$ ppm), respectively (Figure 1.2). Considering the close proximity of these three protons, it was suggested that the initial reported NOE enhancements between H7-H9 and H9-H11 were actually occurring between H7-H8 and H11-H12.¹⁹ Under this alternative interpretation, it concludes that no information existed in relation to the C9 stereochemistry.

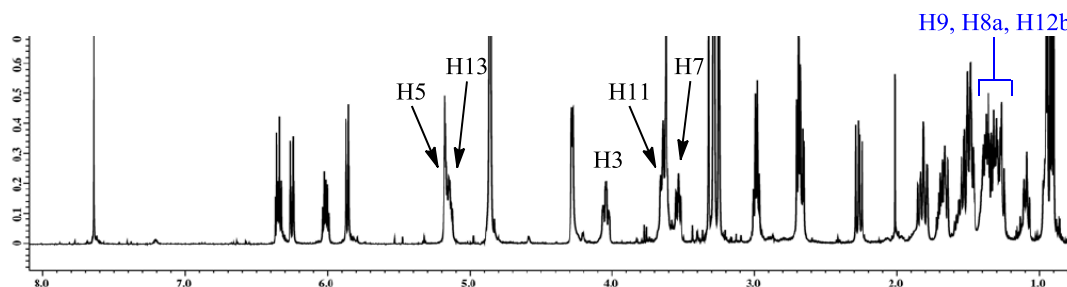


Figure 1.2 – ¹H NMR spectrum of the originally-isolated neopeltolide sample by the Wright group.⁷ 600 MHz CD₃OD. Note the heavy overlap of the C8 proton ($\delta = 1.36$ ppm, m), C9 proton ($\delta = 1.38$ ppm, m), and C12 proton ($\delta = 1.28$ ppm, m) region, as indicated in **blue**.

To elaborate his hypothesis, Youngsaye rationalized that the stereocenters of natural neopeltolide was segregated into three regions based on the spectroscopic analysis and observations: (1) a C11,C13-*syn* segment, (2) a C3,C5-*trans*-C5,C7-*trans* trisubstituted tetrahydropyran, and (3) an “isolated” C9 methyl group.¹⁹ Excluding enantiomeric pairings, there exists four stereoisomers of the three segregated regions, one of which should be the natural isomer of (+)-neopeltolide, and would possess the absolute stereochemistry (Figure 1.3).

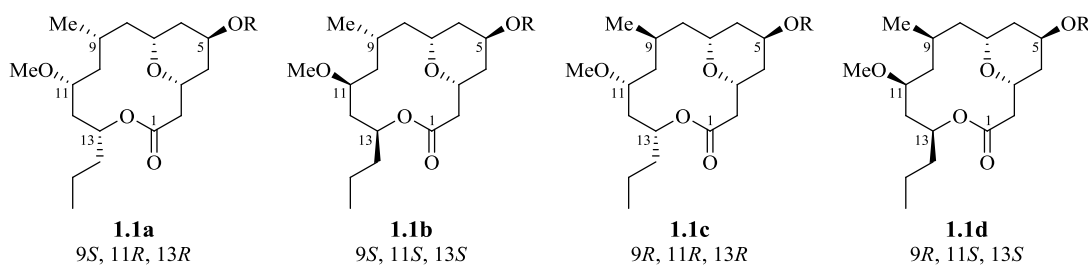


Figure 1.3 – Summary of the four candidate stereoisomers of (+)-neopeltolide based on the three segregated regions of stereocenters based on spectroscopic data, as proposed by Youngsaye.¹⁹ Shown are the four permutations of (3*R*, 5*R*, 7*R*) isomers, and the enantiomeric (3*S*, 5*S*, 7*S*) stereoisomers have been excluded. The oxazole-containing side chain is not included for clarity purposes.

The originally proposed structure of neopeltolide by Wright *et al.*⁷ (**1.1a**) represents one of the four stereoisomers, and the remaining three were prepared synthetically by the Panek group to validate their hypothesis.¹⁹ The successful synthesis of all three stereoisomers (**1.1b**, **1.1c**, **1.1d**) identified isomer **1.1b** as natural (+)-neopeltolide, based on comparison of spectroscopic data.

1.2.3 Mode of Action

Preliminary investigations into the mechanism of action for neopeltolide was done in conjunction with an analog of the structurally homologous leucascandrolide A (**1.2**).^{20–33} Neopeltolide shares several common structural features with leucascandrolide A, including a 2,4,6-trisubstituted tetrahydropyran (THP) subunit, with an identical oxazole-containing, highly unsaturated side chain (Figure 1.4). Thus, one can assume similar biological targets for these two compounds, as neopeltolide may be considered a simplified analog of leucascandrolide A.³⁴

Using flow cytometric methods, Wright *et al.* reported that neopeltolide causes a block of the cell cycle at G₁[†] at doses of 100 nM in the A549 lung adenocarcinoma cell line.⁷ The Kozmin group substantiated this finding in their report of the mechanism by which neopeltolide inhibits cell proliferation.^{23,34} Kozmin suggests that neopeltolide does not act *via* interaction with tubulin or actin, but rather inhibits complex III[‡] of the electron transport chain, inducing apoptosis. Cancerous cells are particularly vulnerable to disruption of oxidative phosphorylation due to an increased dependency on glycolysis, known as the Warburg effect,^{35–37} making neopeltolide a promising lead compound. Although it remains uncertain whether the inhibition of cytochrome *bc*₁ fully accounts for the potent antiproliferative activity of neopeltolide, the results provide a molecular basis for the further experimentation required for complete elucidation.

[†] G₁ Phase: Gap 1 phase of eukaryotic cell-division cycle, between the end of cytokinesis and the start of DNA synthesis.¹⁹⁸

[‡] Complex III is also referred to as cytochrome *bc*₁ complex, or ubiquinol:cytochrome *c* oxido-reductase; it is a transmembrane protein, central to the mitochondrial respiratory electron transport chain by reducing cytochrome *c* (Fe³⁺) into cytochrome *c* (Fe²⁺) *via* ubiquinol.^{23,198}

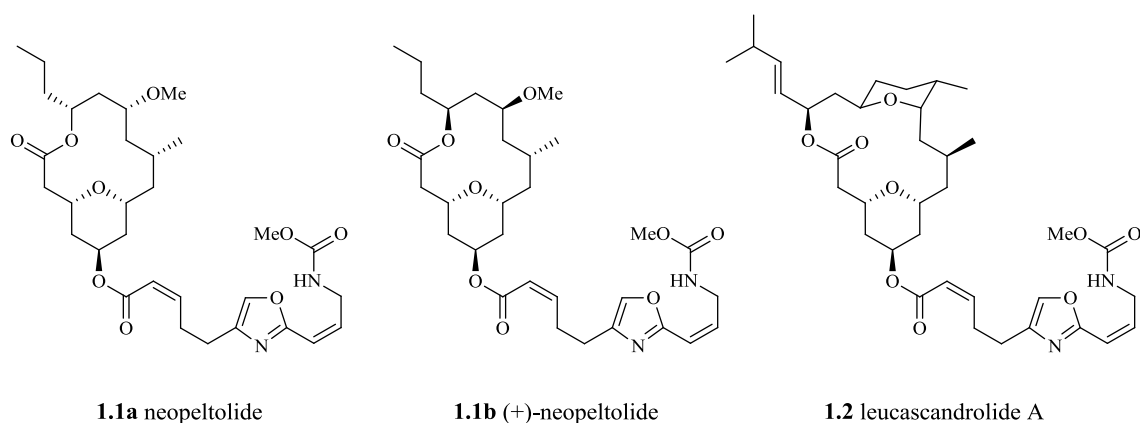


Figure 1.4 – Sponge metabolites: the original structure of neopeltolide (**1.1a**) as reported by Wright *et al.*⁷ the absolute configuration of (+)-neopeltolide (**1.1b**) as reassigned by Panek,¹⁸ and Scheidt;¹⁶ and the structurally similar natural product, leucascandrolide A (**1.2**).³²

Additionally, following hydrolysis of the oxazole-containing side chain ester linkage, further evaluation of leucascandrolide A, and (+)-neopeltolide by extension, demonstrated that the macrocyclic domain is solely responsible for the cytotoxicity.³² Moreover, the oxazole-containing unsaturated side chain was reported responsible for the antifungal properties, suggesting that the bioactivity of neopeltolide functions under the same conditions.

1.3 Early Synthetic Work and Stereochemical Reassignment

Due to its promising biological profile and complex macrolide structure, combined with an extremely limited natural supply, neopeltolide garnered considerable attention from the synthetic community. However, the first two syntheses, one by Panek *et al.*,¹⁸ and the other by Scheidt *et al.*¹⁶ reported spectroscopic discrepancies with the data from natural neopeltolide. As a result, the stereocenters at C11 and C13 had to be revised to the (*S*) configuration. This revision provided the absolute stereochemistry of (+)-neopeltolide and inverted the relative stereochemistry proposed by spectroscopic analysis,⁷ via comparison of prepared diastereomers of neopeltolide.

1.3.1. Panek *et al.* total synthesis (2007)

The initial efforts of Panek *et al.* focused on the synthesis of the original neopeltolide structure proposed by Wright, and they obtained a compound with several spectroscopic discrepancies from the natural product data. In order to identify the absolute configuration of neopeltolide, Panek *et al.* also undertook the synthesis of a set of diastereomers. The Panek route to (+)-neopeltolide relied on coupling the macrocyclic lactone **1.3** and the oxazole side chain **1.4** using a Still-Gennari olefination. The construction of the macrolactone was accomplished with a Yamaguchi esterification, a [4+2]-annulation strategy with an allylsilane was used to install the

tetrahydropyran unit and a ring-opening of an enantio-enriched epoxide to control the C13 stereocenter coupled with a modified Evans-Tishchenko reduction to control the C11 stereocenter was used to generate the key stereochemical centers (Figure 1.5).¹⁸

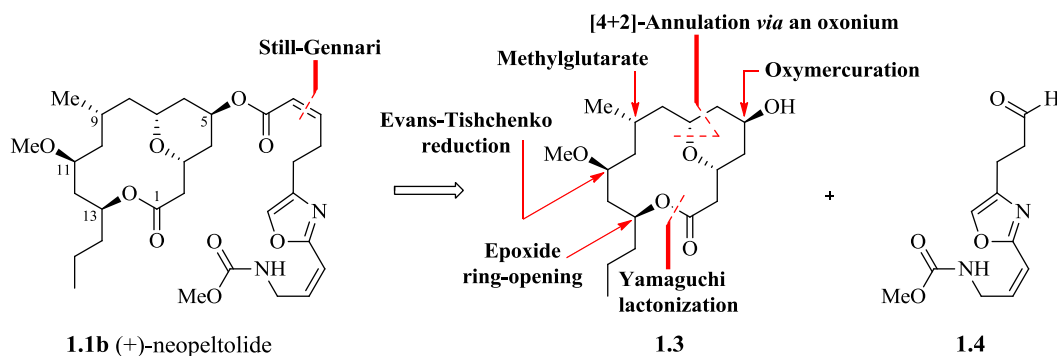
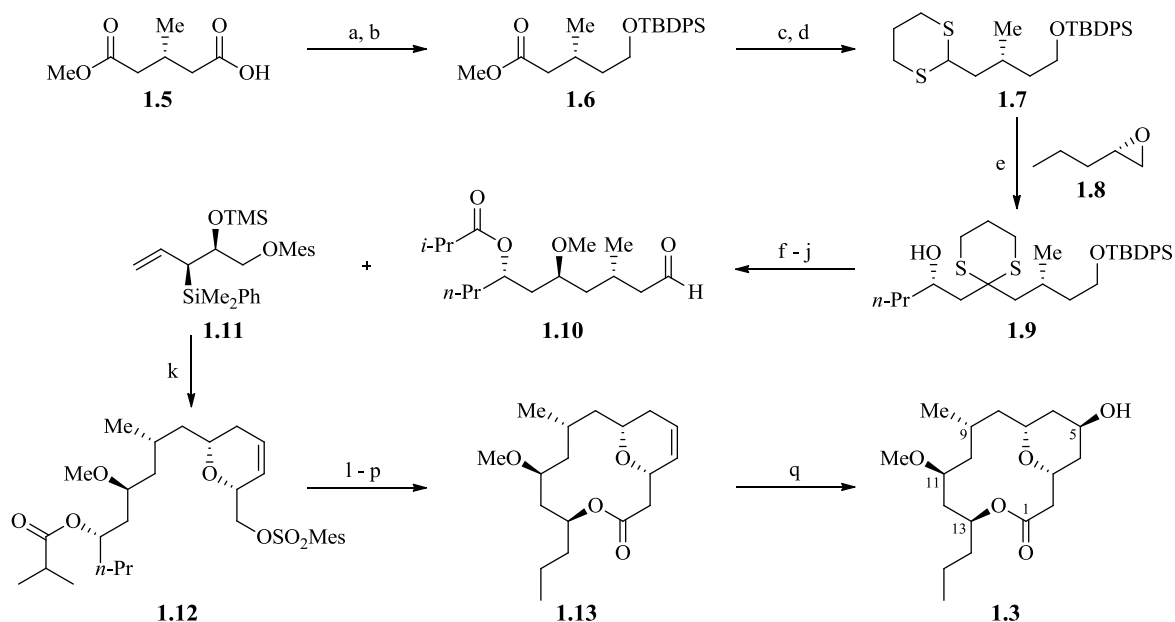


Figure 1.5 – Retrosynthetic analysis for the Panek *et al.* total synthesis of (+)-neopeltolide.

The synthesis of (+)-neopeltolide began with the preparation of the C7-C11 fragment using the commercially available methyl (*R*)-(+)-methylglutarate **1.5** (Scheme 1.1). The chemoselective reduction of the carboxylic acid functionality in **1.5** using borane dimethyl sulfide complex³⁸ provided the primary alcohol, which was subsequently protected as the TBDPS ether **1.6**, and transformed to dithiane **1.7** in two steps (reduction of the ester into an aldehyde and thioacetalization). Coupling of dithiane **1.7** with epoxide **1.8** provided the complete carbon framework for the C7-C16 fragment of (+)-neopeltolide **1.9**. Removal of the dithioketal (CaCO₃/MeI) and stereo-directed reduction of the resulting β -hydroxy ketone with a modified Evans-Tishchenko reduction^{39–41} provided the *anti* Stereochemical relationship (dr = 14:1) between the ester group at C13 and the hydroxyl group at C11. The etherification of the C11 hydroxy group was accomplished with Meerwein's reagent,⁴² which underwent deprotection of the silyl ether and immediate oxidation under Swern conditions^{43,44} to provide aldehyde **1.10**.

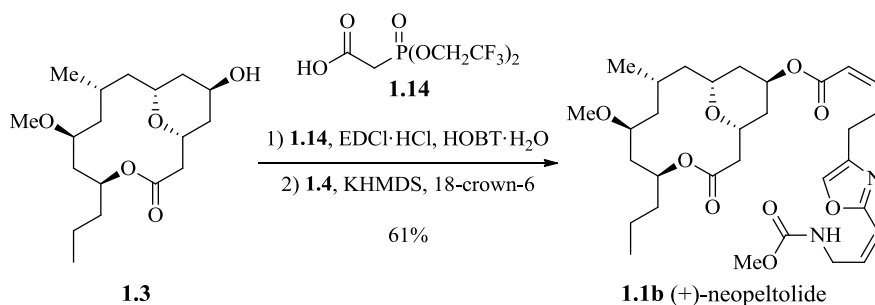
Allylsilane **1.11** was prepared in a six-step synthesis from commercially available 3-propyn-1-ol,²¹ and was coupled to aldehyde **1.10** via a [4+2]-annulation in triflic acid to access *cis*-dihydropyran **1.12** in good yield (75%) and diastereoselectivity (dr = 10:1). The transformation of **1.12** to the macrocyclic lactone **1.13** was accomplished in five steps and required the conversion of the mesylate group into a carboxylic acid. Mesylate **1.12** was treated NaCN to displace the sulfonate group, followed by a first treatment with DIBAL-H in Et₂O to selectively reduce the C13 ester group, and a second treatment with DIBAL-H in DCM to reduce the cyano group to the corresponding aldehyde, which was oxidized through a Pinnick oxidation^{45,46} (NaClO₂) to the desired carboxylic acid. The *seco*-acid intermediate was then transformed into macrolactone **1.13** through a Yamaguchi macrocyclization⁴⁷ in 44% yield. In order to introduce the hydroxyl group at

C5, selective oxymercuration of the pyran olefin yielded the axial C5 alcohol **1.3** as a single stereoisomer.



Scheme 1.1 – Conditions for Panek’s synthesis of the macrocyclic lactone core of (+)-neopeltolide (**1.3**).¹⁸ a) $\text{BH}_3\cdot\text{SMe}_2$, THF, 0°C to rt; TBDPSCl, imidazole, DMF, 0°C to rt, 80% (over 2 steps); c) DIBAL-H, diethyl ether, -78°C ; 1,3-propanedithiol, I_2 , DCM, rt, 85% (over 2 steps); e) $t\text{-BuLi}$, HMPA, THF, **1.8**, -78°C , 68%; f) CaCO_3 , MeI, MeCN/ H_2O , rt, 73%; g) $\text{Zr}(\text{OtBu})_4$, $i\text{PrCHO}$, toluene, -78°C ; h) Me_3OBF_4 , Proton Sponge, 4 Å molecular sieves, DCM, rt, 90% (over 2 steps); i) 49% HF in H_2O , MeCN, rt, 91%; j) $(\text{COCl})_2$, DMSO, DCM, Et_3N , -78°C to rt, 89%; k) TfOH, DCM/benzene (3:1), -78°C , 75% (dr = 10:1); l) NaCN, DMF, 60°C , 84%; m) DIBAL-H, diethyl ether, -78°C , 96%; n) DIBAL-H, DCM, -78°C , 60%; o) NaClO_2 , 2-methyl-2-butene, $\text{NaH}_2\text{PO}_4\cdot\text{H}_2\text{O}$, $t\text{-BuOH}$, H_2O , 85%; p) 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, Et_3N , 44%; q) $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ then NaBH_4 , THF: H_2O (1:1), 63%.

To complete the synthesis of (+)-neopeltolide, a Still-Gennari olefination was used to establish the *cis* enoate of the side chain.²⁵ Acylation of **1.3** with bis-(2,2,2-trifluoroethyl) phosphonoacetic acid (**1.14**)⁴⁸ gave the corresponding phosphoacetate, which was immediately deprotonated with KHMDS at -78°C in THF in the presence of [18]crown-6 ether, and the generated anion was quenched with aldehyde²⁷ **1.4**, providing a mixture of (+)-neopeltolide **1.1b** and the corresponding (*E*)-olefin in a 7:1 mixture (Equation 1.1).



Equation 1.1 – Completion of Panek *et al.* (+)-neopeltolide **1.1b** synthesis.

The first enantioselective total synthesis of (+)-neopeltolide required 19 steps for the longest linear sequence, with an overall yield of 1.3%, starting from the commercially available methyl (*R*)-(+)-3-methylglutarate **1.5**.¹⁸

1.3.2. Scheidt *et al.* total synthesis (2008)

At the beginning of 2008, the syntheses of both neopeltolide **1.1a** and (+)-neopeltolide **1.1b** were reported by the Scheidt group.¹⁶ For this review, only the total synthesis of the absolute configuration natural product **1.1b** will be described, as the strategy and key steps are identical for the two diastereomers.

The synthesis of (+)-neopeltolide was accomplished using an intramolecular Lewis acid-catalyzed cyclization between a dioxinone and an *in situ* generated oxocarbenium ion (intermediate **1.17**), thereby constructing the tetrahydropyran ring and the macrolactone simultaneously. The oxazole side chain was introduced through a Mitsunobu reaction^{49–51} between the hydroxyl group present at C5 position of **1.15** and the carboxylic acid of **1.16**. The synthesis of **1.15** is highly convergent and was achieved from the two compounds **1.18** and **1.19** (Figure 1.6).

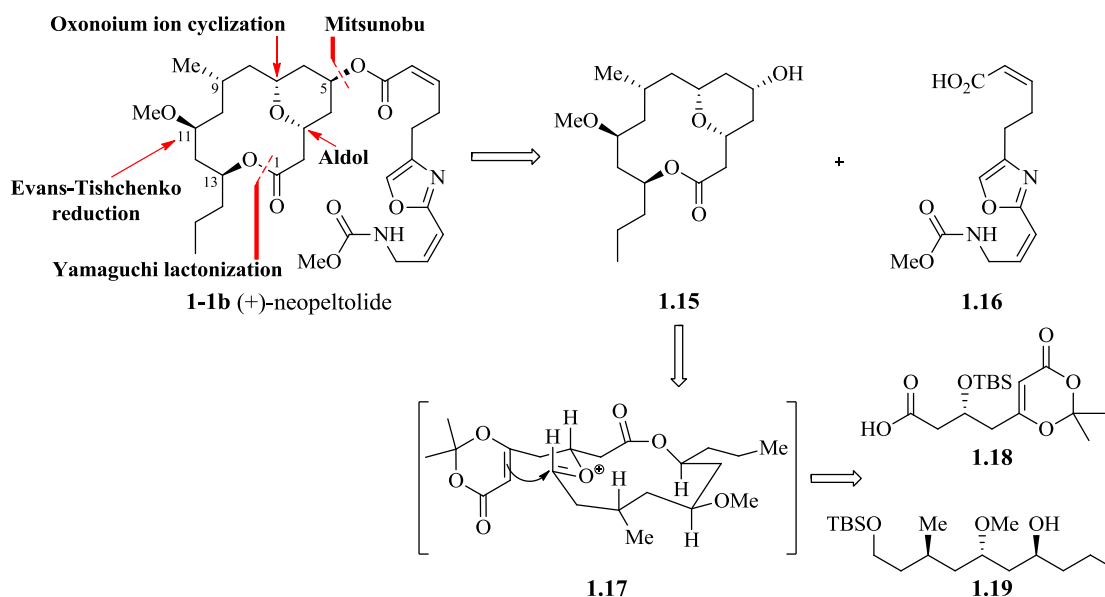
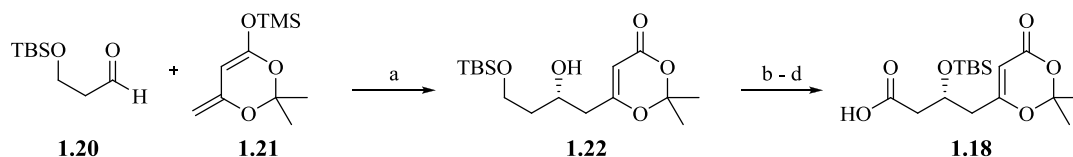


Figure 1.6 – Retrosynthetic analysis for the Scheidt et al. total synthesis of (+)-neopeltolide.

The synthesis of (+)-neopeltolide began with the Ti(IV)-(R)-BINOL-catalyzed aldol reaction between the simple aldehyde **1.20** and dienoxysilane **1.21**,^{52,53} affording the secondary alcohol **1.22** in 63% yield (88% ee).⁵⁴ The protection of the alcohol and subsequent two-step conversion of the primary silyl ether to the carboxylic acid afforded the dioxinone **1.18** (Scheme 1.2).

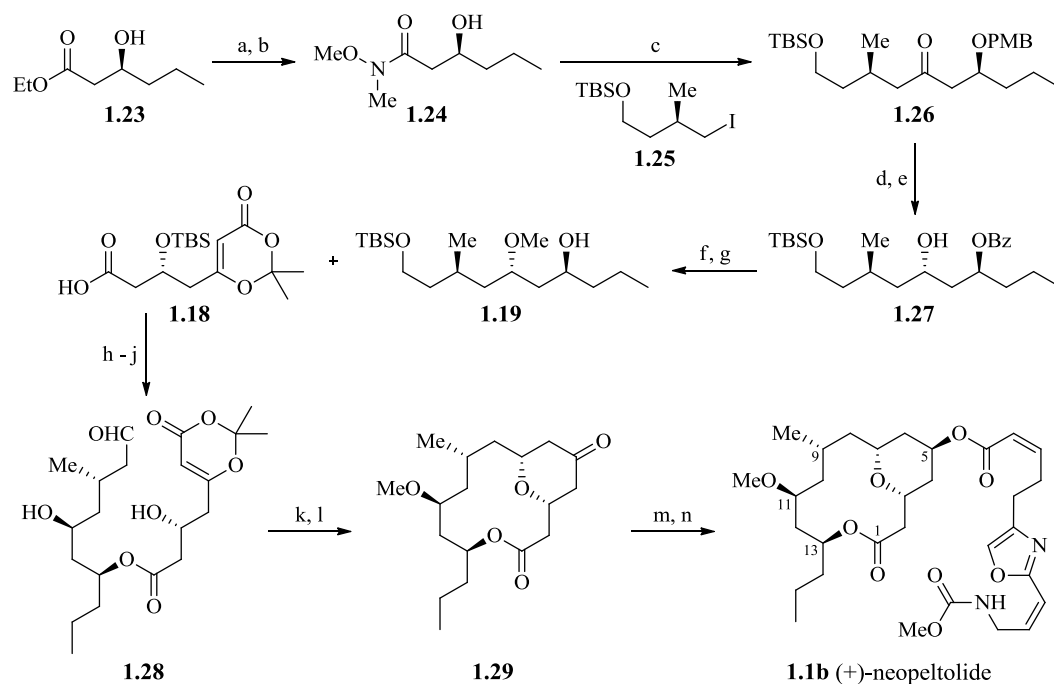


Scheme 1.2 – Conditions for Scheidt's synthesis of the dioxinone fragment **1.18** *en route* to (+)-neopeltolide.¹⁶ a) Ti(*i*PrO)₄, (R)-BINOL, 4 Å ms, DCM, 63% (88% ee); b) TBS-OTf, 2,6-lutidine, DCM; c) PPTS, EtOH; d) PDC, DMF, 73% (over 3 steps).

The synthesis of the alcohol fragment **1.19** began with the two-step conversion of β -hydroxyester **1.23** to Weinreb amide **1.24**.⁵⁵ Its transformation to the extended ketone **1.26** was accomplished *via* the addition of the alkyllithium derived from iodide **1.25**.⁵⁶ The removal of the PMB protecting group of **1.26** by DDQ was followed by an Evans-Tishchenko reduction,³⁹ yielding **1.27** with the desired *anti*-stereochemistry between the hydroxyl group at C11 and the benzoate group at C13. Subsequent methylation of **1.27** and hydrolysis of the benzoate furnished the desired alcohol fragment **1.19** (Scheme 1.3).

The fragment coupling of **1.18** and **1.19** was accomplished using a Yamaguchi esterification,⁴⁷ which was followed by the removal of both silyl ethers and a selective oxidation

(TEMPO)⁵⁷ to generate aldehyde **1.28**. The key step of this synthesis is an intramolecular Prins reaction, which occurred *via* an oxonium species of type **1.17** generated from **1.28** with scandium(III) triflate to yield the fully elaborated 14-membered ring. This single step afforded a tricyclic dioxinone intermediate in modest yield, but with a high degree of complexity. Treatment of the dioxinone with wet DMSO formed the bicyclic ketone **1.29**, which was converted to alcohol **1.15** by a selective NaBH₄ reduction. Completion of the synthesis was accomplished *via* a Mitsunobu reaction with alcohol **1.15** and the known carboxylic acid^{22,25} **1.16**,^{49,51,58} yielding (+)-neopeltolide (Scheme 1.3).



Scheme 1.3 – Conditions for Scheidt's synthesis of the alcohol fragment **1.19**, and completion of (+)-neopeltolide.¹⁶ a) HN(Me)OMe·HCl, *i*PrMgBr, THF; b) PMB-OC(NH)CCl₃, PPTS, cyclohexane/DCM, 68% (over 2 steps); c) **1.25**, *t*-BuLi, pentane/Et₂O, 50%; d) DDQ; e) SmI₂, PhCHO, THF, 0°C, 76% (over 2 steps); f) MeOTf, DTBMP, DCM; g) K₂CO₃, MeOH, 75% (over 2 steps); h) 2,4,6-trichlorobenzoyl chloride, DMAP, THF; i) HF·pyridine, THF; j) TEMPO, PhI(OAc)₂, DCM, 76% (over 3 steps); k) Sc(OTf)₃, CaSO₄, MeCN; l) DMSO, H₂O, 130°C, 21% (over 2 steps); m) NaBH₄, MeOH, 0°C; n) DIAD, Ph₃P, **1.16**, 76% (over 2 steps).

The Scheidt synthesis of (+)-neopeltolide required 15 steps in the longest linear sequence, with an overall yield of 2.3%, starting from the chiral hydroxyester **1.23**.¹⁶ Following the elucidation of the absolute configuration of (+)-neopeltolide *via* this synthesis and the synthesis of Panek *et al.*,¹⁸ the synthetic community was attracted and literature reports began to appear in rapid fashion in 2008.

1.4 Total Syntheses of Neopeltolide

1.4.1 Lee *et al.* total synthesis (2008)

Similar to the synthesis detailed by Scheidt *et al.*, the synthesis of (+)-neopeltolide by Lee utilizes a Mitsunobu reaction between macrocyclic lactone **1.15** and carboxylic acid **1.16** to introduce the oxazole side chain. Key steps to the macrocyclic lactone **1.15** include a Prins reaction of **1.39**, which is obtained following a Yamaguchi esterification of **1.30** and **1.31**, that simultaneously forms the *cis*-tetrahydropyran moiety. An asymmetric crotyl transfer reaction and titanium-mediated methallylation were used to set the stereogenic centers at C11 and C13, and a substrate-directed hydroformylation was used to control the C9 stereochemistry.

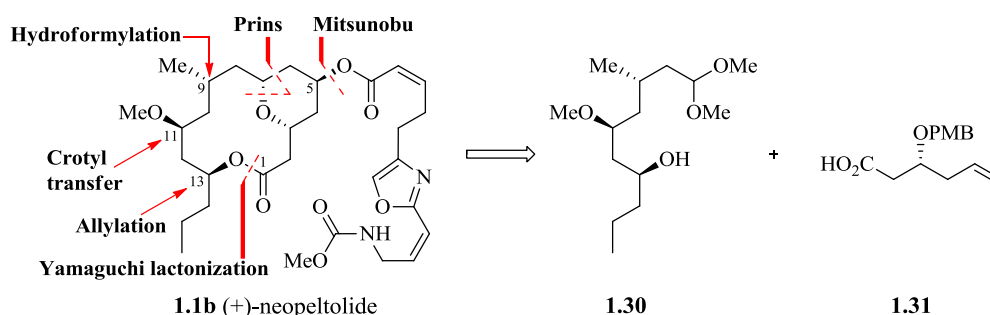
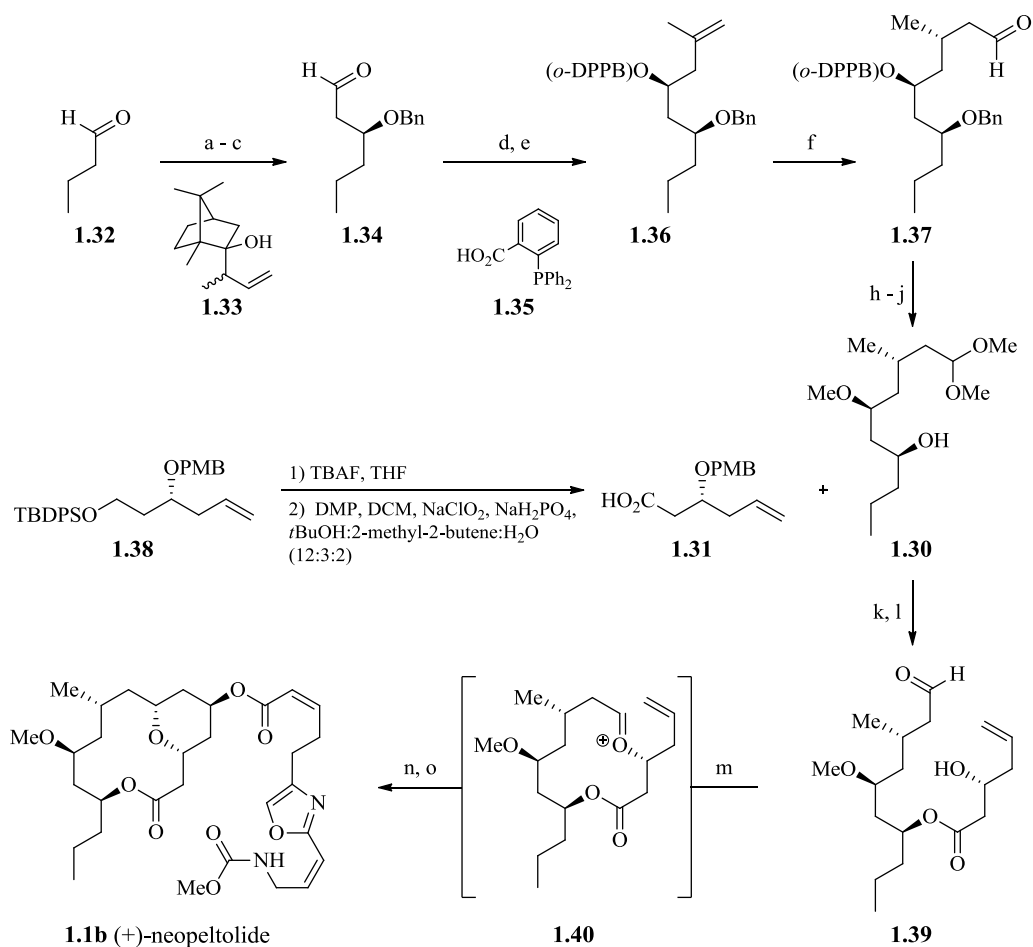


Figure 1.7 – Retrosynthetic analysis for the Lee *et al.* total synthesis of (+)-neopeltolide.

Synthesis began with an asymmetric crotyl transfer reaction of butanal **1.32**,⁵⁹ protection of the C13 alcohol with a benzyl group, and ozonolysis of the double bond, yielding aldehyde **1.34**. A diastereoselective methallylation in the presence of titanium(IV) chloride led to a homoallylic alcohol that was acylated with 2-diphenylphosphinobenzoic acid **1.35** to produce ester **1.36**. The substrate-directed hydroformylation⁶⁰ of **1.36** preferentially yielded the desired aldehyde **1.37** in a 5:1 ratio, which was transformed to the dimethyl acetal **1.30** in four steps (acetalization, saponification, *O*-methylation, and benzyl cleavage). The second fragment, carboxylic acid **1.31**, was prepared from the known olefin **1.38**⁶¹ after removal of the silyl protecting group and subsequent oxidation (Scheme 1.3).

Esterification of the secondary alcohol of **1.30** with **1.31**, following prolonged exposure to DDQ, produced the aldehydic homoallylic alcohol **1.39** in good yield. Substrate **1.39** underwent Prins conditions⁶² efficiently and stereoselectively, to yield the Prins adduct **1.40**, which was subjected to a methanolysis to give the macrocyclic core of (+)-neopeltolide **1.15**. Completion of the synthesis was achieved using a Mitsunobu reaction of **1.15** with known carboxylic acid²⁷ **1.16** (Scheme 1.3).^{49,51,58}



Scheme 1.3 – Conditions for Lee's synthesis of (+)-neopeltolide.⁶³ a) **1.33**, CSA, DCM; b) NaH, BnBr, TBAI, THF/DMF (5:1); c) O₃, DCM, -78°C; Ph₃P, 49% (over 3 steps); d) CH₂C(CH₃)CH₂TMS, TiCl₄, DCM, -78°C; e) **1.35**, DCC, DMAP, DCM, 78% (over 2 steps); f) Rh(CO)₂(acac), P(OPh)₃, 40 bar H₂/CO (1:1), PhMe, 30°C, 65% (dr = 5:1); g) H₂SO₄, HC(OMe)₃, MeOH; h) KOH, EtOH, reflux; i) NaH, MeI, THF, 62% (over 3 steps); j) H₂, Pd/C, MeOH; k) **1.31**, DCC, DMAP, DCM; l) DDQ, pH 7 buffer, DCM, 81% (over 3 steps); m) TESOTf (20 EQ), TMSOAc (30EQ), AcOH, rt, 30 min; n) K₂CO₃, MeOH, 68% (over 2 steps); o) **1.16**, DIAD, Ph₃P, benzene, 79%.

The Lee synthesis of (+)-neopeltolide required 15 steps in the longest linear sequence, with an overall yield of 6.7%, starting from butyraldehyde **1.32**.⁶³

1.4.2 Kozmin *et al.* racemic total synthesis (2008)

In his synthesis, Kozmin expands his previous experience with the structurally homologous leucascandrolide A (Figure 1.4, **1.2**)^{20,22,24} into a rapid and efficient preparation of neopeltolide. In their approach, they applied a Prins desymmetrization of diene **1.41** in order to establish the substituted tetrahydropyran moiety *en route* to the synthesis of racemic neopeltolide (Figure 1.8).

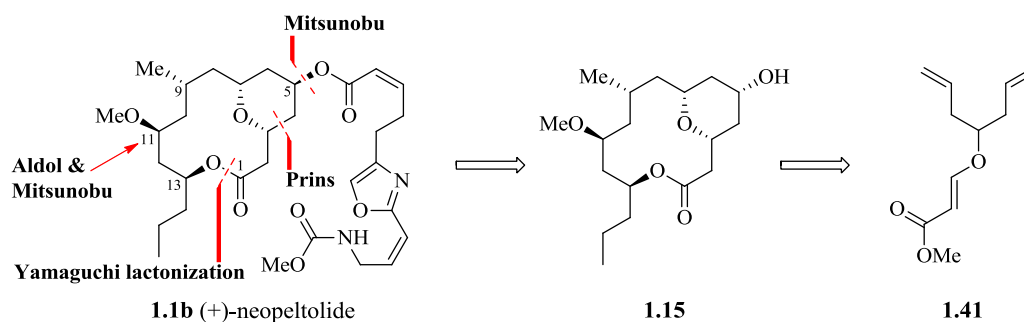
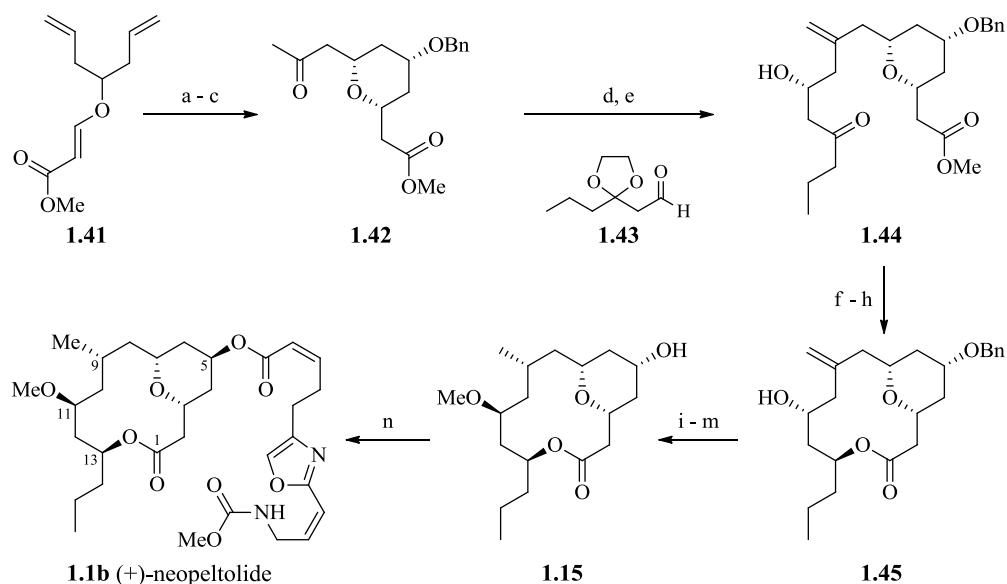


Figure 1.8 – Retrosynthetic analysis for the Kozmin *et al.* racemic total synthesis of (±)-neopeltolide.

The racemic synthesis of neopeltolide began with the Prins desymmetrization of diene **1.41**,²⁴ followed by benzyl protection of the generated hydroxyl group at C5, and a Wacker alkene oxidation⁶⁴ to yield ketone **1.42**. An aldol condensation between a boron-enolate generated from ketone **1.42** and aldehyde **1.43** gave the expected aldol product with excellent diastereoselectivity (dr > 98:2),⁶⁵ which was subjected to Wittig methylenation, followed by acidic removal of the dioxolane to give ketone **1.44**. A 1,3-*syn*-selective reduction of the hydroxyketone **1.44**, followed by saponification of the ester with potassium trimethylsilanolate, gave the diol, which was successfully macrocyclized to **1.45** under Yamaguchi conditions (Scheme 1.4).⁴⁷

After a diastereoselective hydrogenation of the methylene at C9 using palladium on carbon catalyst, an inversion of the C11 alcohol using a Mitsunobu reaction,^{49,51,58} followed by the hydrolysis of the resulting *p*-nitrophenyl benzoate, subsequent methylation of the generated alcohol, and hydrogenolysis of the benzyl ether afforded the macrolactone core of neopeltolide (**1.15**). Completion of the synthesis of (±)-neopeltolide was achieved using a Mitsunobu reaction of **1.15** with known carboxylic acid²² **1.16** (Scheme 1.4).



Scheme 1.4 – Conditions for Kozmin synthesis of (±)-neopeltolide.²³ a) $\text{CF}_3\text{CO}_2\text{H}$, 0°C , aq NH_4OH ; b) $\text{BnOC}(\text{NH})\text{CCl}_3$, TfOH (cat.); c) PdCl_2 , CuCl , H_2O , DMF , O_2 , 64% (over 3 steps); d) **1.43**, Cy_2BCl , Et_3N ; e) Ph_3PMeBr , KHMDs , HCl quench, 75% (over 2 steps); f) Et_2BOMe , NaBH_4 ; g) TMSOK , Et_2O ; h) 2,4,6-trichlorobenzoyl chloride, DMAP , Et_3N , 55% (over 3 steps); i) H_2 , Pd/C (dr = 3:1); j) $p\text{-NO}_2\text{C}_6\text{H}_4\text{CO}_2\text{H}$, PPh_3 , DEAD ; k) K_2CO_3 , MeOH ; l) Me_3OBF_4 , Proton Sponge; m) H_2 , $\text{Pd}(\text{OH})_2$, 40% (over 5 steps); n) **1.15**, DIAD , Ph_3P , benzene, 83%.

The Kozmin synthesis of (±)-neopeltolide required 14 steps in the longest linear sequence, with an overall yield of 8.7%, starting from diene **1.41**.²³

1.4.3 Fuwa *et al.* total synthesis (2008)

Similar to the previous reported syntheses of (+)-neopeltolide, Fuwa utilizes a Mitsunobu reaction^{49–51} between macrocyclic lactone **1.15** and carboxylic acid **1.16** to introduce the oxazole side chain. However, in contrast to the use of the Prins reaction⁶² in previous syntheses, Fuwa envisioned the dihydropyran moiety of **1.46** could be prepared by Suzuki-Miyaura coupling of the alkylborate **1.47** and enol phosphate **1.48**, followed by a RCM of the obtained diene to build **1.46** (Figure 1.9).

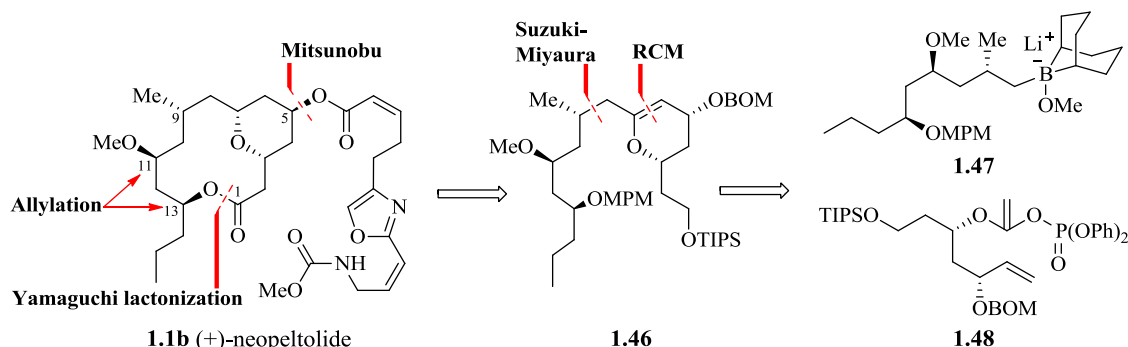
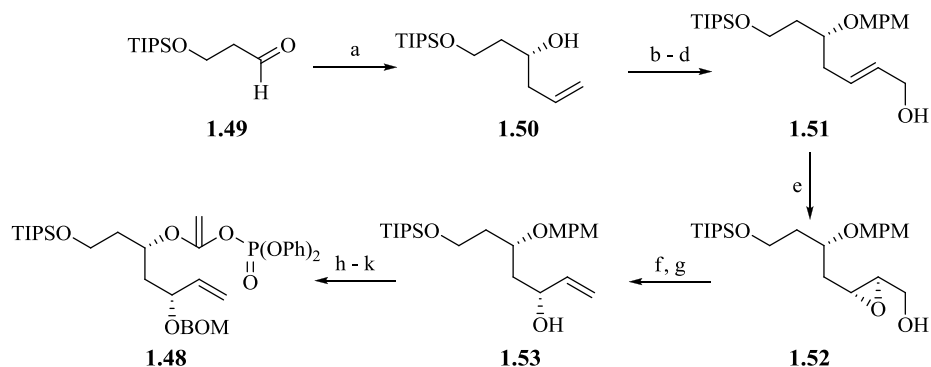


Figure 1.9 – Retrosynthetic analysis for the Fuwa *et al.* total synthesis of (+)-neopeltolide.

The synthesis of the enol phosphate **1.48** began with the asymmetric Brown allylation of aldehyde **1.49**,^{66,67} furnishing alcohol **1.50** in excellent yield (98%). After protection of the hydroxyl group as its MPM ether, followed by olefin cross-metathesis⁶⁸ with methyl acrylate and reduction of the obtained α,β -unsaturated ester, homoallylic alcohol **1.51** was isolated. A Sharpless asymmetric epoxidation delivered epoxide **1.52** in 97% yield as a single diastereomer,^{69,70} which was transformed to the allylic alcohol **1.53** *via* an iodination/reductive ring-opening sequence. Alcohol **1.53** was converted to the enol phosphate **1.48** in four steps. At first, the alcohol was protected as a BOM ether, then the MPM ether was selectively cleaved and subsequently acylated to the corresponding acetate which, after enolization with KHMDS in the presence of $(\text{PhO})_2\text{P}(\text{O})\text{Cl}$ furnished enol phosphate **1.48** (Scheme 1.5).

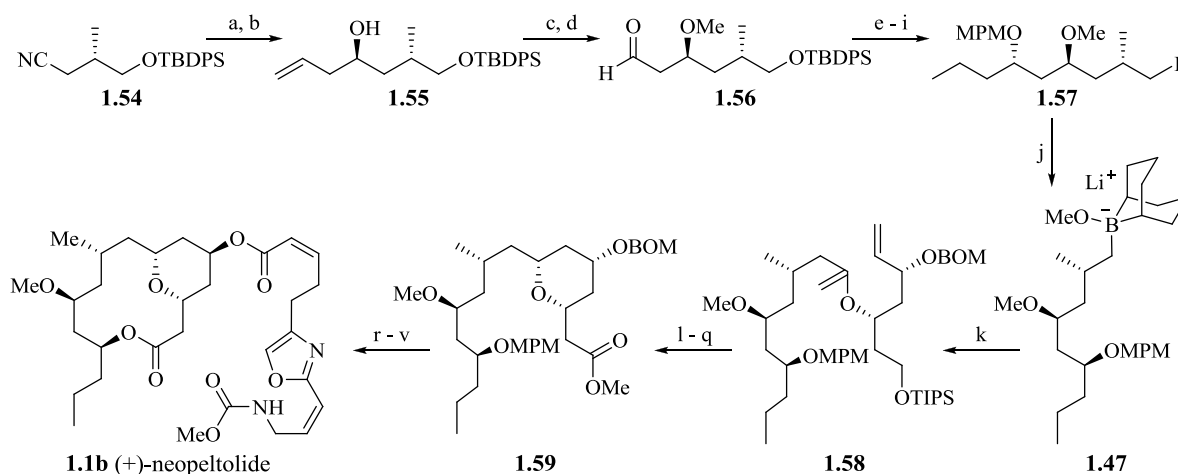


Scheme 1.5 – Conditions for Fuwa's synthesis of the enol phosphate fragment **1.48** *en route* to (+)-neopeltolide.⁷¹ a) (+)- Ipc_2BOMe , allylMgBr , Et_2O , -78°C ; then aq NaOH , H_2O_2 , rt, 98%; b) $\text{MPMOC}(\text{=NH})\text{CCl}_3$, $\text{La}(\text{OTf})_3$, PhMe , rt; c) methyl acrylate, G-II (3 mol%), DCM , 40°C ; d) DIBAL-H , DCM , -78°C , 46% (over 3 steps); e) (-)-DET, $\text{Ti}(\text{OiPr})_4$, $t\text{-BuOH}/\text{H}_2\text{O}$, 4 Å ms, -20°C , 97%; f) I_2 , PPh_3 , imidazole, THF , rt; g) Zn , AcOH , EtOH , rt, 75% (over 2 steps); h) BOMCl , $i\text{Pr}_2\text{Net}$, DCM , rt; i) DDQ , pH 7 buffer, DCM ; j) Ac_2O , Et_3N , DMAP , THF , rt; k) KHMDS , $(\text{PhO})_2\text{POCl}$, $\text{THF}:\text{HMPA}$ (1:1), -78°C , 71% (over 4 steps).

The synthesis of the alkylborate **1.47** commenced with the known nitrile **1.54**.⁷² Following a DIBAL-H reduction, an asymmetric Brown allylation of the obtained aldehyde yielded allylic alcohol **1.55** in 87% as a single diastereomer.^{66,67} The methylation of alcohol **1.55** followed by

ozonolysis of the double bond delivered aldehyde **1.56**, which was subsequently subjected to a final asymmetric Brown allylation and hydrogenation of the obtained homoallylic alcohol to introduce the terminal alkyl chain. Finally, protection of the remaining hydroxyl group as its MPM ether, followed by desilylation and iodination under standard conditions furnished iodide **1.57** in 47% yield (Scheme 1.6).

Completion of the synthesis began with the lithiation of iodide **1.57** with *t*-BuLi in the presence of *B*-MeO-9-BBN to generate the alkylborate **1.47**,^{73,74} which was coupled *in situ*, under Suzuki-Miyaura conditions, with enol phosphate **1.48** to give the acyclic enol ether **1.58**.⁷⁵ The intermolecular Suzuki-Miyaura coupling of **1.47** and **1.48** predominated over the possible intramolecular Heck cyclization^{76,77} of enol phosphate **1.48**.⁷¹ Subsequent RCM of **1.58** led to the cyclic enol ether **1.46** (Figure 1.9), which underwent stereoselective hydrogenation of the double bond to form the *cis*-tetrahydropyran as a single diastereomer. Removal of the TIPS protecting group, and an oxidation/esterification sequence furnished ester **1.59**. Completion of the synthesis was achieved in four steps. Removal of the MPM ether, followed by saponification gave a *seco*-acid,⁷⁸ which was treated under Yamaguchi conditions⁴⁷ to form the macrocyclic core of neopeltolide (**1.15**). A Mitsunobu reaction of **1.15** with known carboxylic acid²² **1.16** provided (+)-neopeltolide (Scheme 1.6).^{49,51,58}



Scheme 1.6 – Conditions for Fuwa's synthesis of the iodide fragment **1.47**, and completion of (+)-neopeltolide.⁷¹ a) DIBAL-H, DCM, -78°C; b) (+)-Ipc₂BOMe, allylMgBr, Et₂O, -78°C; then aq NaOH, H₂O₂, rt, 81% (over 2 steps); c) MeOTf, 2,6-di-*tert*-butylpyridine, DCM, rt; d) O₃, DCM, -78°C; then PPh₃, rt, 74% (over 2 steps); e) (-)-Ipc₂BOMe, allylMgBr, Et₂O, -78°C; then aq NaOH, H₂O₂, rt; f) H₂, Pd/C, EtOH, rt; g) MPMOC(=NH)CCl₃, La(OTf)₃, PhMe, rt; h) TBAF, 50°C; i) I₂, PPh₃, imidazole, THF, rt, 47% (over 5 steps); j) B-MeO-9-BBN, *t*-BuLi, Et₂O:THF (1:1), -78° to rt; k) Cs₂CO₃, Pd(PPh₃)₄ (10 mol%), **1.48**, DMF, rt; l) G-II (10 mol%), PhMe, 70°C, 78% (over 2 steps); m) H₂, Pd/C, EtOAc:MeOH (1:1), rt; n) TBAF, THF, rt; o) SO₃·Pyr., Et₃N, DMSO:DCM (1:1), 0°C; p) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH:H₂O (1:1), rt; q) TMSCHN₂, MeOH:benzene (1:1), 54% (over 7 steps); r) DDQ, pH 7 buffer, DCM; s) TMSOK, rt; t) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, rt; u) H₂, Pd(OH)₂/C, THF:MeOH (1:1), rt; v) **1.16**, DIAD, Ph₃P, benzene, 56% (over 5 steps).

The Fuwa synthesis of (+)-neopeltolide required 25 steps in the longest linear sequence, with an overall yield of 8.3%, starting from the commercially available methyl (*R*)-(-)-3-hydroxy-2-methylpropionate *via* the known nitrile **1.54**.^{71,72} Despite being longer compared to the previously reported syntheses, this approach shows the efficiency of the employed reactions.

1.4.4 Paterson *et al.* total synthesis (2008)

Having achieved success in the synthesis of leucascandrolide A,^{30,33} the Paterson synthesis of (+)-neopeltolide highlights his earlier work. A Mitsunobu reaction was employed to couple the oxazole side-chain and the macrocyclic core of (+)-neopeltolide, which was divided into two fragments that were to be joined through an asymmetric hetero Diels-Alder⁷⁹ that would simultaneously incorporate the tetrahydropyran moiety (Figure 1.10).

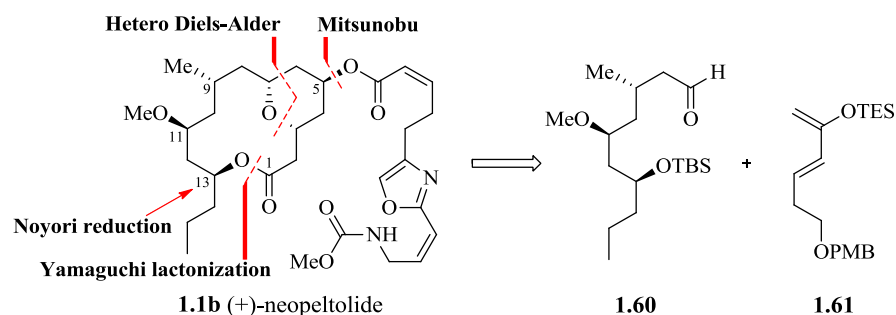
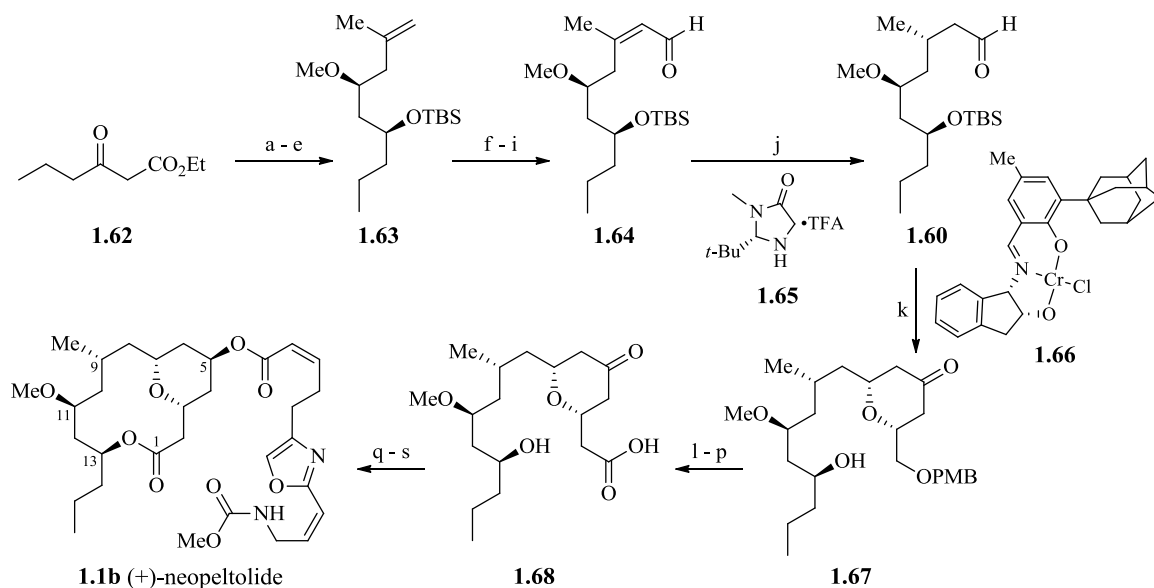


Figure 1.10 – Retrosynthetic analysis for the Paterson *et al.* total synthesis of (+)-neopeltolide.

The synthesis of (+)-neopeltolide began with a Noyori asymmetric hydrogenation of ketoester **1.62**,^{80,81} which was subsequently protected as its silyl ether, reduced to the corresponding aldehyde and underwent a Brown methallation to install the methyl ester in good yield (81%) with high diastereoselectivity (dr = 94:6). Four steps were required for the conversion of **1.63** into its corresponding α,β -unsaturated aldehyde **1.64**, which underwent MacMillan's organocatalytic conjugate reduction⁸² with the trichloroacetic acid salt of imidazolidinone catalyst **1.65** and ethyl Hantzsch ester, obtaining a 3:1 mixture of desired product **1.60**.

A [4+2]-cycloaddition of **1.60** with diene **1.61**, in the presence of catalyst **1.66**, yielded the expected *cis*-tetrahydropyranone **1.67** with complete control of the C3 and C7 stereocenters, and allowed for purification from its C9 epimer. Subsequent deprotection and oxidation steps provided *seco*-acid **1.68**, which underwent macrolactonization under Yamaguchi conditions,⁴⁷ was reduced and coupled to the oxazole side-chain **1.16** with a Mitsunobu reaction,^{49–51} yielded (+)-neopeltolide (Scheme 1.7).



Scheme 1.7 – Conditions for Paterson's synthesis of (+)-neopeltolide.⁸³ a) (S)-BINAP-Ru(II) complex, MeOH, 6 atm H₂, 100°C; b) TBSCl, imidazole, DMF; c) DIBAL-H, DCM, -78°C; d) (-)-Ipc₂BCH₂(Me)C=CH₂, Et₂O, -90°C; e) NaH, MeI, THF, 58% (over 5 steps); f) O₃, DMS, DCM/MeOH; g) trimethyl phosphonoacetate, NaH, THF, reflux, 16 h; h) DIBAL-H, DCM, -78°C; i) DMP, NaHCO₃, 57% (over 4 steps); j) cat. **1.65** (20 mol%), Hantzsch ester (1.2 equiv.), CHCl₃, -30°C, 3 d, 80% (dr = 76:24); k) **1.61** (10 mol%), 4 Å ms, 8 d; then acidified chloroform, 78%; l) DDQ, pH 7 buffer, DCM; m) DMP, NaHCO₃, DCM; n) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH, H₂O; o) TBAF, THF, 88%; p) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 0°C, 1 h; then DMAP, PhMe; q) NaBH₄, MeOH; r) **1.16**, DIAD, Ph₃P, benzene, 42% (over 3 steps).

The Paterson synthesis of (+)-neopeltolide required 18 steps in the longest linear sequence, with an overall yield of 5.8%, starting from ketoester **1.62**.

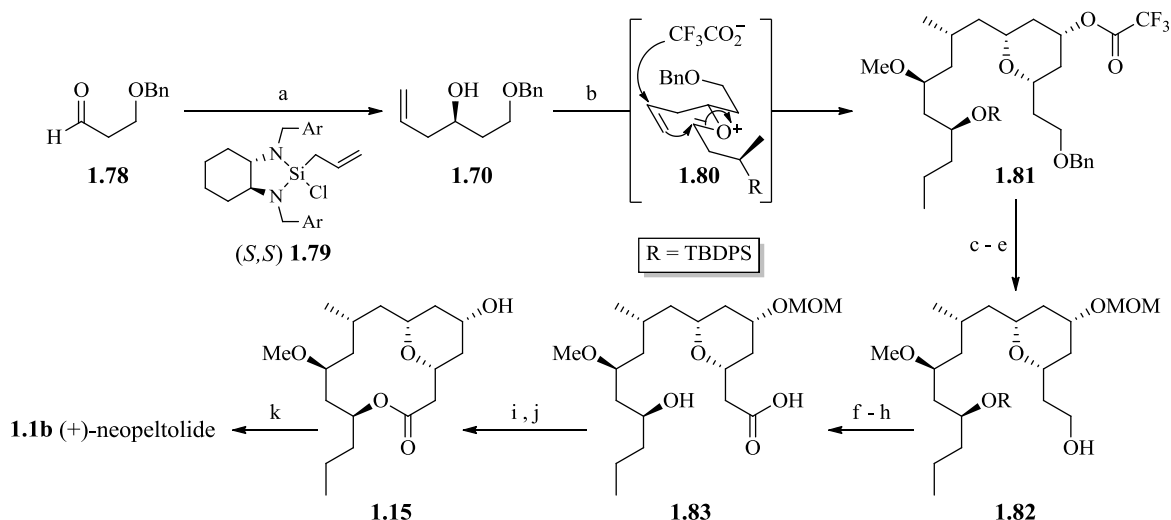
1.4.5 Maier *et al.* Total synthesis (2008)

In early 2008, the Maier group reported a formal synthesis of the macrolactone core of (+)-neopeltolide.⁸⁴ In the following months, the group successfully extended their research to cover the total synthesis, as well as several analogs.⁸⁵ In their synthetic plan, key steps included pyran formation *via* a Prins reaction, introduction of the C9 methyl group using the Feringa-Minnaard reaction,^{86–88} as well as several integrated applications of Leighton allylations (Figure 1.11).^{89–91}



The homoallylic alcohol **1.70** required for the Prins reaction was obtained by allylation of aldehyde **1.78** with Leighton's chiral reagent **1.79**. The Prins reaction between aldehyde **1.70** and homoallylic alcohol **1.70** proceeded *via* oxonium ion **1.80**, with an all equatorial orientation of the substituents, leading to the *cis*-tetrahydropyran of **1.81** in good yield (72%). Few functional group

manipulations (cleavage of trifluoroacetate, MOM protection and debenzylation) led to primary alcohol **1.82**, which was converted to *seco*-acid **1.83** via oxidation and desilylation. Classical Yamaguchi conditions,⁴⁷ and subsequent reduction of the macrolactone provided the necessary precursor **1.15** for Mitsunobu coupling⁵⁸ with **1.16** to complete the synthesis of (+)-neopeltolide (Scheme 1.9).



Scheme 1.9 – Conditions for Maier’s completion of (+)-neopeltolide.⁸⁵ a) (S,S)-**1.79**, DCM, -10°C, 84%; b) **1.69**, TFA, DCM, -5°C, 1 h, 72% (major:minor = 8:1); c) K₂CO₃, MeOH; d) MOMCl, iPr₂NEt, DMF; e) H₂, Pd/C, EtOH, 82% (over 3 steps); f) DMP, DCM; g) NaClO₂, *t*-BuOH:H₂O (1:1); h) TBAF, THF, 93% (over 3 steps); i) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 0°C, 1 h; DMAP, PhMe, rt; j) conc. HCl, MeOH, 80% (over 2 steps); k) **1.16**, DIAD, Ph₃P, benzene, 80%.

The Maier synthesis of (+)-neopeltolide required 18 steps in the longest linear sequence, with an overall yield of 18.7%, starting from commercially available reagents. The synthetic approach to the macrocyclic core of (+)-neopeltolide that was used in this synthesis was the subject of an earlier reported formal synthesis by Maier *et al.* where the longest linear sequence consists of 17 steps providing **1.1b** with an overall yield of 23%.⁸⁴ Synthesis of neopeltolide analogs by the Maier group will be outlined in section 1.6.1 of this chapter.

1.4.6 Roulland *et al.* total synthesis (2009)

In the second to last total synthesis to date, Roulland *et al.* use substrate-controlled diastereoselective reactions to install four of neopeltolide’s six stereocenters, while making use of asymmetric catalysis and reagents for the remaining two, all while minimizing protecting group manipulations.

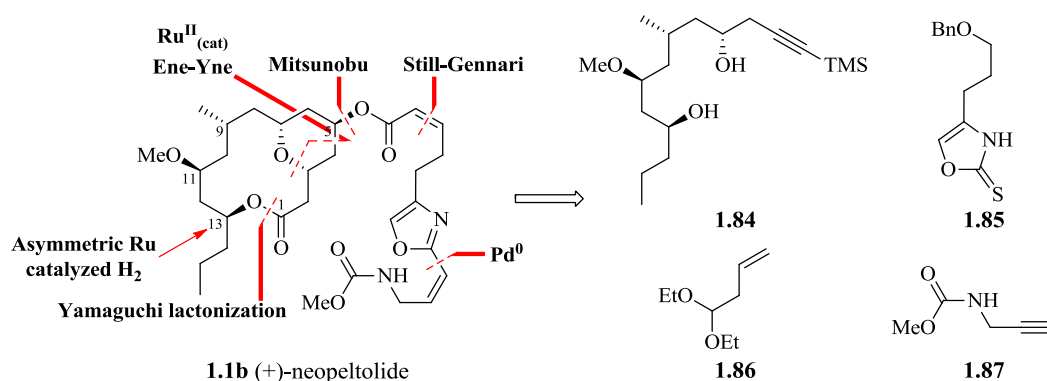
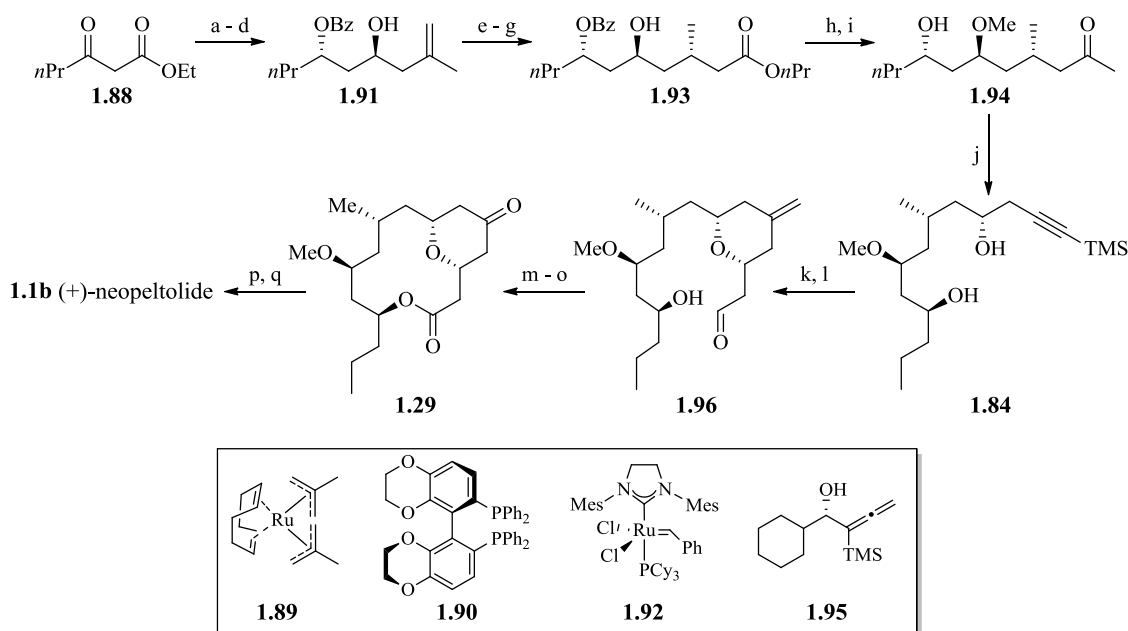


Figure 1.12 – Retrosynthetic analysis for the Roulland *et al.* total synthesis of (+)-neopeltolide.

The synthesis toward neopeltolide began with the ruthenium-catalyzed asymmetric hydrogenation of β -ketoesters developed by Genêt *et al.*,⁹⁴ providing alcohol **1.91** from **1.88** with full stereocontrol of the new C13 alcohol center. Following reduction, the Weinreb⁵⁵ amide was derived from the ethyl ester and subsequently displaced by methylallyl Grignard reagent, and the isolated β -hydroxyketone was subjected to Evans-Tishchenko conditions,³⁹ selectively reducing the ketone to the *anti* 1,3-diol **1.91** as a single diastereomer, while installing the benzoate ester. The free alcohol was reacted with acryloyl chloride, yielding a diene that underwent ring-closing metathesis with second-generation Grubbs catalyst **1.92**.^{95–97} The obtained α,β -unsaturated lactone proved to hydrogenate diastereoselectively under simple Pd/C conditions, leading to an equilibrated mixture of *seco*-acid **1.93** and lactone, which could cleanly be converted to **1.93** under mild acid conditions. Final methylation of the secondary alcohol and global ester reduction by DIBAL-H provided aldehyde **1.94**, while simultaneously removing the benzoyl group inherited from the Evans-Tishchenko step (Scheme 1.10).

The second of two steps involving asymmetric catalysis was used to control the C7 stereocenter during the indium(III)-catalyzed propargylation reaction,⁹⁸ which stereoselectively transferred a trimethylsilylpropynyl group from **1.95** to **1.94**, yielding homopropargylic alcohol **1.84**. Potassium carbonate mediated the deprotection of the alkynyl silicon protecting group, and the ene-yne cross-coupling with 4,4-diethoxy-1-butene⁹⁹ was accomplished using [CpRu(MeCN)₃]PF₆ complex,¹⁰⁰ converting the alkyne system to a *gem*-substituted olefin. One pot treatment of the cross-coupling mixture with LiBF₄·H₂O promoted acetal hydrolysis and subsequent Michael cyclization to yield a single *cis*-tetrahydropyran product **1.96**. The *exo*-methylene function of **1.96** was oxidized to its carboxylic acid, and macrocyclized using classical Yamaguchi macrolactonization conditions⁴⁷ affording *cis*-tetrahydropyrone **1.29** in high yield.

Completion of the synthesis was realized by the reduction of **1.29**, and subsequent Mitsunobu coupling^{49–51} with known carboxylic acid **1.16**, affording (+)-neopeltolide.



Scheme 1.10 – Conditions for Roulland’s synthesis of the macrocyclic core of (+)-neopeltolide.¹⁰¹ a) **1.89** (0.25 mol%), (R)-(+)-SYNPHOS **1.90** (0.26 mol%), H₂, 4 bars, 50°C, EtOH, (>99% ee); b) MeONHMe·HCl, AlMe₃, THF; c) 2-methyl-2-propenyl magnesium chloride, THF, -78°C to rt; d) PhCHO, SmI₂, THF, -10°C to rt, (dr = >99:1) 59% (over 4 steps); e) *i*PrNEt₂, acryloyl chloride, DCM, -10°C; f) **1.92**, DCM, reflux; g) H₂, Pd/C, *n*PrOH, rt; PPTS, 49% (over 3 steps); h) Me₃OBf₄, Proton Sponge, DCM, rt; i) DIBAL-H, PhMe, -78°C, 87% (over 2 steps); j) **1.95**, InBr₃ (1 mol%), DCM, rt, 77%; k) K₂CO₃, MeOH, rt; l) 4,4-diethoxy-1-butene, [CpRu(MeCN)₃]PF₆ (10 mol%), AcOH (10 mol%), acetone; then LiBF₄, MeCN:H₂O (50:1), rt, 47 – 52% (over 2 steps); m) OsO₄, NaIO₄, *t*-BuOH:H₂O (2:1), rt; n) NaClO₂ KH₂PO₄, 2-methyl-2-butene, THF:H₂O (2:1), rt; o) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, rt; DMAP, PhMe, 80°C, 71% (over 3 steps); p) NaBH₄, EtOH, -10°C, 99% (dr = 92:8), q) DIAD, PPh₃, **1.16**, benzene, rt, 75%.

The Roulland synthesis of (+)-neopeltolide required 16 steps in the longest linear sequence, with an overall yield of 6.2%, starting from ketoester **1.88**.

1.4.7 Floreancig *et al.* total synthesis and analogs (2010)

In the last total synthesis of (+)-neopeltolide published to date, attention is directed to a DDQ-mediated cyclization reaction as the key step to install the bicyclic *cis*-tetrahydropyrone **1.104** onto the macrocyclic core of (+)-neopeltolide *via* cyclic substrate **1.97**.

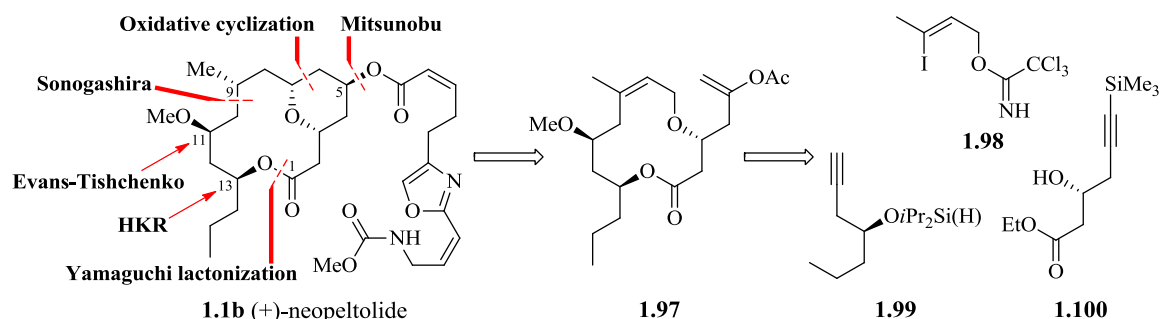
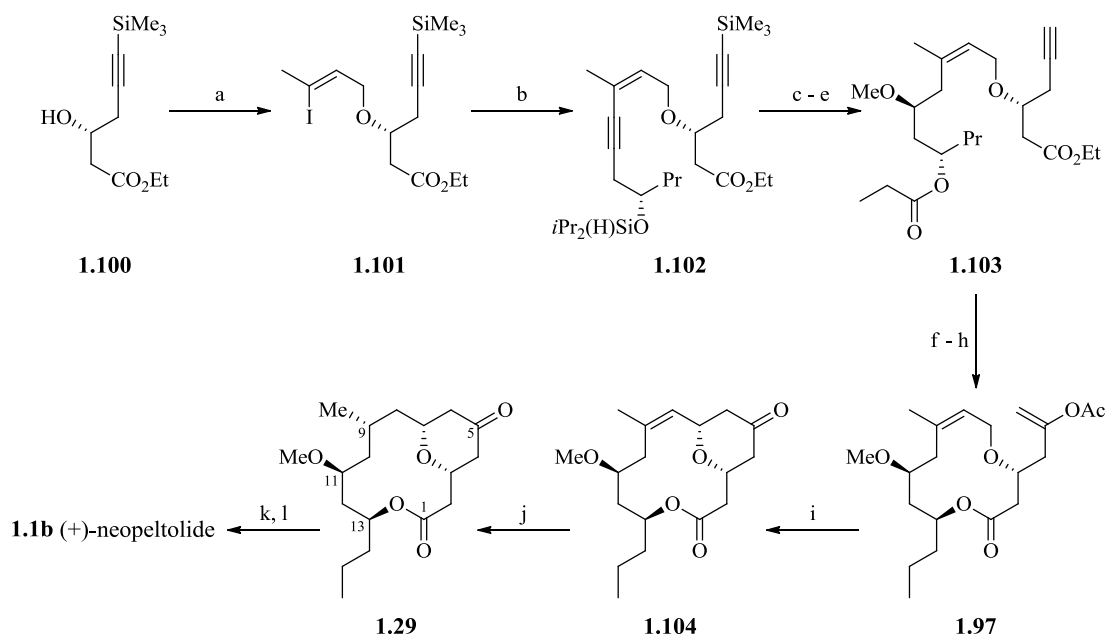


Figure 1.13 – Retrosynthetic analysis for the Floreancig *et al.* total synthesis of (+)-neopeltolide.

The coupling of fragments **1.98** and **1.100** was achieved with catalytic triflic acid, resulting in the isolation of an inseparable 7.3:1 mixture of geometrical isomers of **1.101**. The remaining carbons for the skeleton of the neopeltolide macrolactone core were introduced *via* Sonogashira coupling¹⁰² of **1.101** with alkyne **1.99** in good yield (89%). The regioselective alkyne hydration reaction of **1.102** required that the sequence of intramolecular hydrosilylation and Tamao oxidation¹⁰³ proceed without isomerisation of the resulting β,γ -unsaturated ketone product. The hydrosilylation proceeded smoothly with Pt(DVDS);¹⁰⁴ however, the isopropyl groups of the silyl ether create greater steric congestion than the typically used methyl groups. The steric congestion resulted in unusually harsh Tamao oxidation conditions, which provided the desired isomer in an 11:1 ratio and simultaneously cleaved the alkynylsilane group. Installation of the *anti* 1,3-stereochemical relationship in **1.103** was introduced *via* Evans-Tishchenko conditions,³⁹ allowing methylation of the resulting C11 hydroxyl group using Meerwein's salt.⁴² Simultaneous ester cleavage in **1.103** and exposure to Yamaguchi conditions⁴⁷ provided the 12-member macrolactone, which upon exposure to acetic acid and [(*p*-cymene)RuCl₂]₂ provided cyclization substrate **1.97** in good yield (Scheme 1.11).¹⁰⁵

The key oxidative cyclization of enol acetate **1.97** proceeded slower than previous cyclizations reactions,¹⁰⁶ successfully yielding *cis*-tetrahydropyrone **1.104** with no isolation of 5-*endo*-cyclization product from the reaction.¹⁰⁷ Studies showed that catalytic lithium perchlorate prevents over-oxidation during the conversion, and that optimal conditions were 3 equivalents of DDQ at room temperature, as more DDQ or heating caused severe decomposition, and less DDQ could not fully deplete the starting material.¹⁰⁶ With **1.104** in hand, the C8-C9 alkene was hydrogenated with high facial control using Pd/C, proving that the substrate was conformationally-controlled by steric interactions. Completion of the synthesis was easily accomplished *via* sodium borohydride reduction of the tetrahydropyrone, and subsequent Mitsunobu reaction^{49–51} with known carboxylic acid **1.16**, affording (+)-neopeltolide.



Scheme 1.11 – Conditions for Floreancig’s synthesis of (+)-neopeltolide.¹⁰⁷ a) **1.98**, TfOH, cyclohexane, 77%; b) **1.99**, (Ph₃P)₂PdCl₂, CuI, *i*Pr₂NH; c) [Pt(DVDS)], THF, then H₂O₂, KF, Bu₄NF, KHCO₃, DMF, 40°C; d) SmI₂, EtCHO, THF, -10°C; e) Me₃OBF₄, DCM, Proton Sponge, 42% (over 4 steps); f) LiOH, THF, MeOH, H₂O, 45°C; g) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF; then DMAP, PhMe, 65°C, 71% (over 2 steps); h) HOAc, Na₂CO₃, [{Ru(*p*-cymene)Cl₂]₂, (2-furyl)₃P, 1-decyne, PhMe, 80°C, 82% (5:1 regioisomer mixture); i) DDQ, LiClO₄, 2,6-Cl₂Py, 4 Å ms, (ClCH₂)₂, 65%; j) H₂, Pd/C, EtOH, 74%; k) NaBH₄, MeOH, 0°C; l) **1.16**, DIAD, Ph₃P, benzene, 88% (over 2 steps).

The Floreancig synthesis of (+)-neopeltolide required 14 steps in the longest linear sequence, with an overall yield of 7.8%, starting from 2-butyn-1-ol. The synthetic approach to the macrocyclic core of (+)-neopeltolide that was used synthesis was the subject of a reported formal synthesis by Floreancig *et al.* where the longest linear sequence consists of 12 steps providing **1.29** with an overall yield of 9.3%.¹⁰⁸ Synthesis of neopeltolide analogs by the Floreancig group will be outlined in section 1.6.5 of this chapter.

1.5 Formal Total Syntheses of Neopeltolide

1.5.1 Taylor *et al.* formal synthesis (2008)

The formal synthesis of (+)-neopeltolide by the Taylor group in 2008 closed out a very prolific year of synthesis toward the natural compound. In their approach to the macrocyclic core of neopeltolide, Taylor *et al.* employed a novel intramolecular ether transfer reaction and a radical cyclization for the stereoselective construction of the tetrahydropyran moiety.

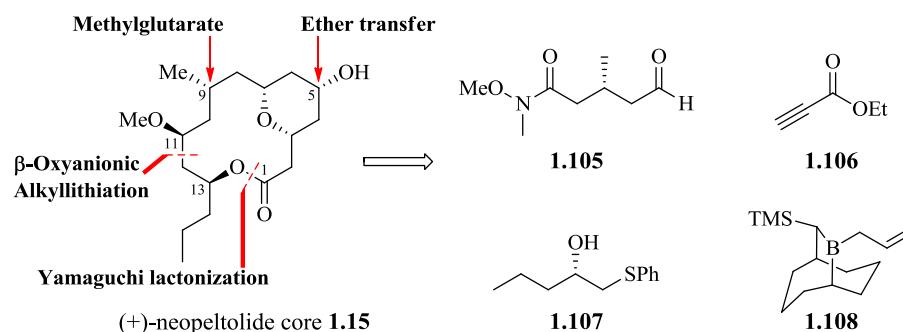
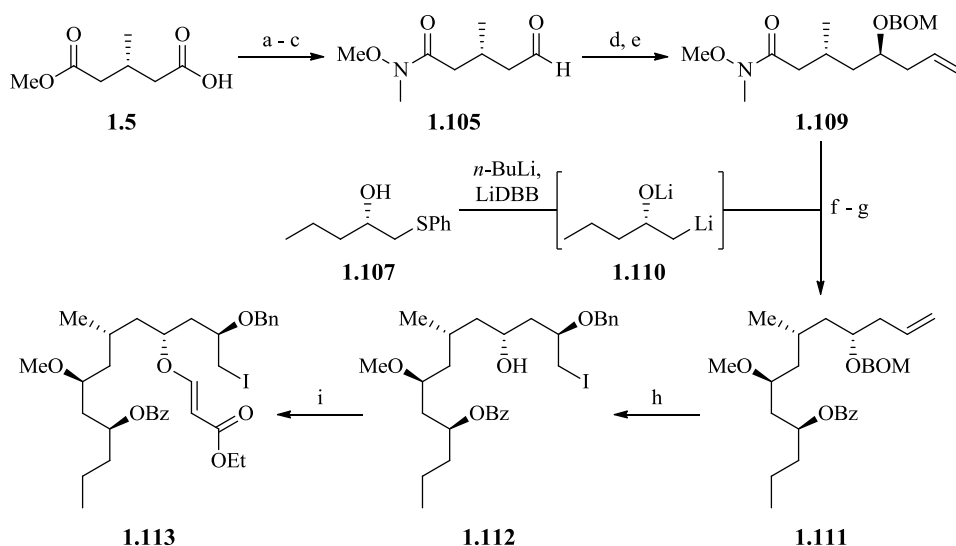


Figure 1.14 – Retrosynthetic analysis for the Taylor *et al.* formal synthesis of (+)-neopeltolide.

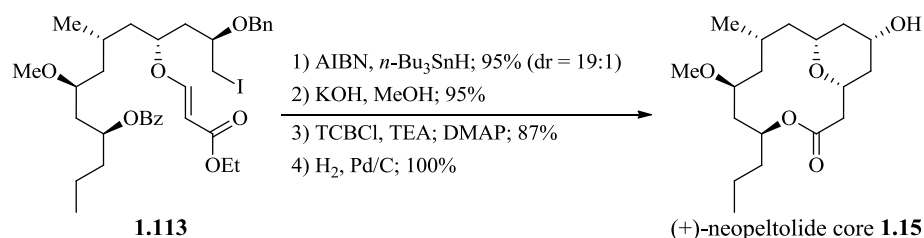
Similar to Panek's approach, synthesis began with methyl (*R*)-(+)-3-methylglutarate **1.5**, which was transformed into the Weinreb amide **1.105** via common chemical treatment.⁵⁵ This compound represents an interesting synthetic intermediate due to its dual electrophilic sites; however, asymmetric allylation at the more electrophilic aldehyde moiety with Soderquist's chiral bicyclodecane-allylborane reagent **1.108**¹⁰⁹ introduced the corresponding homoallylic alcohol, which was subsequently protected as the benzylmethoxymethyl ether **1.109**. Rychnovsky's method¹¹⁰ of reductive lithiation coupling between **1.109** and **1.107** (via dilithio species **1.110**) cleanly produced the β -hydroxy ketone, which, following Evans-Tishchenko introduction of the *anti* 1,3-selectivity and methylation,³⁹ afforded methyl ether **1.111** (Scheme 1.12).

The synthesis of β -alkoxyacrylate **1.113** was completed in two additional steps. The Taylor group ether transfer technology¹¹¹ was used to directly and stereoselectively install the required C5 hydroxyl as a benzyl-protected ether via treatment of **1.111** with iodine monochloride.¹¹¹ Aqueous workup yielded the 1,3-*syn*-diol monoether **1.112** in good yield and excellent stereoselectivity. The completion of the carbon skeleton of the neopeltolide macrolactone core was accomplished with the tributylphosphine-promoted conjugate addition¹¹² of the free alcohol to ethyl propiolate **1.106**, yielding **1.113** as the precursor substrate to the construction of the tetrahydropyran moiety (Scheme 1.12).



Scheme 1.12 – Conditions for Taylor’s synthesis of β -alkoxyacrylate **1.113** *en route* to the macrolide core (+)-neopeltolide **1.15**.¹¹³ a) $\text{BH}_3\cdot\text{SMe}_2$; b) $(\text{OMe})\text{MeNH}_2\text{Cl}$, $i\text{PrMgCl}$; c) DMP, 86% (over 3 steps); d) **1.108**, $\text{BF}_3\cdot\text{OEt}_2$; e) BOMCl, Hünig’s base, 55% (over 2 steps); f) SmI_2 , PhCHO, (dr >20:1); g) Me_3OBF_4 , Proton Sponge, 73% (over 3 steps); h) ICl ; then $\text{Na}_2\text{S}_2\text{O}_3$, 71% (dr >20:1); i) **1.106**, PBu_3 , 98%.

The construction of the tetrahydropyran core was executed through radical cyclization with AIBN and *n*-Bu₃SnH in refluxing toluene,¹¹⁴ followed by exposure to KOH and methanol to saponify the ethyl ester to the corresponding carboxylic acid, while simultaneously cleaving the C13 benzoate ester. Yamaguchi macrolactonization,⁴⁷ and ensuing hydrogenolysis in the presence of Pd/C catalyst removed the C5 benzyl ether and completed the synthesis of the macrocyclic core of (+)-neopeltolide (Equation 1.2).



Equation 1.2 – Completion of Taylor *et al.* (+)-neopeltolide macrolactone core **1.15** synthesis.

The Taylor synthesis of the macrolactone core of (+)-neopeltolide required 14 steps in the longest linear sequence, with an overall yield of 18.9%, starting from methyl (*R*)-(+)-3-methyl glutarate **1.5**.¹¹³

1.5.2 Hong et al. formal synthesis (2009)

The approach taken by Hong *et al.* toward the synthesis of the macrocyclic core of neopeltolide centered around the formation of the *cis*-tetrahydropyran through a tandem allylic

oxidation/oxa-Michael addition of a free alcohol into an α,β -unsaturated aldehyde through promotion by the *gem*-disubstituent effect.¹¹⁵

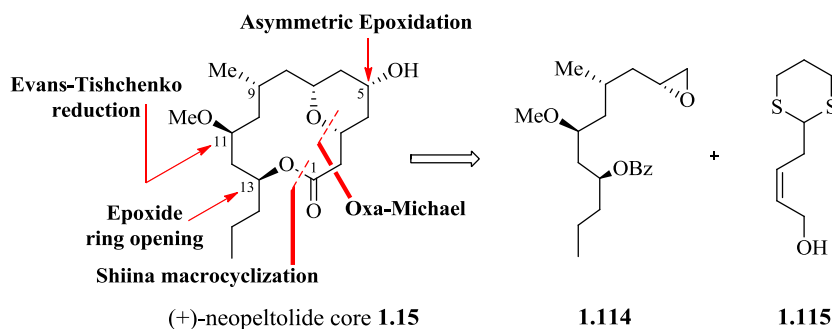
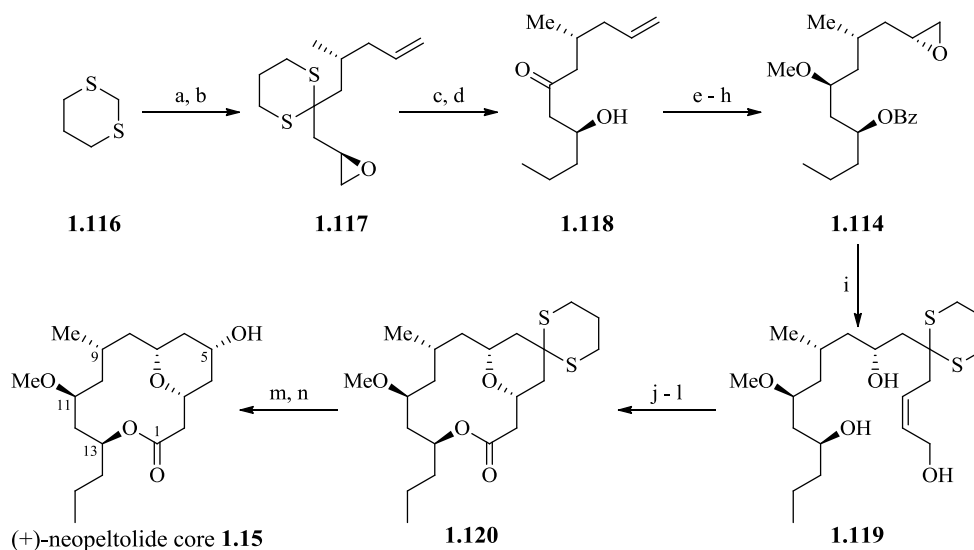


Figure 1.15 – Retrosynthetic analysis for the Hong *et al.* formal synthesis of (+)-neopeltolide.

The synthesis of the macrocyclic core of neopeltolide began with the synthesis of the chiral epoxide **1.114**, which began with the 1,3-dithiane coupling¹¹⁶ of **1.116** with (*R*)-5-iodo-4-methylpentene,¹¹⁷ followed by the ring opening of (*R*)-(-)-epichlorohydrin and simultaneous epoxide formation, afforded **1.117**. Ring opening of epoxide **1.117**, and deprotection of the dithiane group yielded β -hydroxyketone **1.118**, which then underwent Evans-Tishchenko reduction to afford the desired *anti* 1,3-selectivity between C11 and C13. Methylation of the secondary alcohol,¹¹⁸ asymmetric dihydroxylation⁶⁹ and epoxide formation¹¹⁹ prepared the substrate **1.114** for the second dithiane coupling (Scheme 1.13).

Coupling of **1.114** and **1.115**, followed by subsequent deprotection of the benzoyl-protected hydroxy group prepared the carbon skeleton for the key tandem allylic oxidation and oxa-Michael reaction. The tandem sequence of **1.119** (step *j*, Scheme 1.13) installed the *cis*-tetrahydropyran methyl ester with excellent stereoselectivity (*dr* > 20:1), *via* chemoselectivity; it did not require any protection of the three hydroxy groups in **1.119**.¹²⁰ Hydrolysis of the methyl ester, followed by the macrocyclization procedure of Shiina¹²¹ proceeded smoothly to give **1.120**, which was then deprotected of the dithiane and the resulting carbonyl was reduced with sodium borohydride to complete the synthesis of the neopeltolide core (Scheme 1.13)



Scheme 1.13 – Conditions for Hong’s synthesis of the macrolactone core of (+)-neopeltolide **1.15**.¹²⁰ a) *n*BuLi, THF, -78° to -10°C, 1 h; then (*R*)-5-iodo-4-methylpentene, -78°C to -40°C, 4 h; b) *n*BuLi, THF, rt, 5 min; then (*R*)-epichlorohydrin, -78°C, 2 h; then 25°C, 12 h, 66% (over 2 steps); c) EtMgBr, CuI, THF, -40°C to -10°C, 3 h; d) MeI, CaCO₃, MeCN:H₂O (3:1), rt, 14 h, 72% (over 2 steps); e) PhCHO, SmI₂, THF, 0°C, 3 h; f) 1,8-bis(dimethylamino)naphthalene, Me₃O·BF₄, DCM, 0-25°C, 2 h; g) AD mix-β, H₂O:*t*-BuOH (1:1), 0°C, 10 h; h) NaH, *N*-*p*-toluenesulfonylimidazole, THF, 0-25°C, 1 h, 69% (over 4 steps); i) **1.115**, *t*-BuLi, HMPA:THF (1:10), -78°C, 5 min; then **1.114**, -78°C, 3 h, 75%; j) MnO₂, DCM, rt, 3 h; then dimethyltriazolium iodide, MnO₂, DBU, MeOH, 4 Å ms, rt, 21; k) 0.1N LiOH, THF:MeOH (3:1), rt, 1 h; l) 2-methyl-6-nitrobenzoic anhydride iodide, DMAP, DCM, 24 h, 53% (over 3 steps); m) MeI, CaCO₃, MeCN:H₂O (3:1), rt, 30 h; n) NaBH₄, MeOH, 0°C, 1 h, 83% (over 2 steps).

The Hong synthesis of the macrolactone core of (+)-neopeltolide required 16 steps in the longest linear sequence, with an overall yield of 5.2%, starting from commercially available reagents with minimal use of protecting groups.¹²⁰

1.5.3 Yadav *et al.* formal synthesis (2010)

The synthesis by the Yadav group focussed on the success and utility of the Prins reaction, which had previously been employed by Scheidt,¹⁶ Lee,⁶³ and Maier^{84,85} during the installation of the *cis*-tetrahydropyran ring. The Yadav *et al.* approach included synthesis of a C7-C16 aldehyde fragment already containing the C9 methyl stereocenter, and incorporation of the C11 and C13 *anti* 1,3-stereoselectivity *via* an intermolecular Prins-cyclization.⁶²

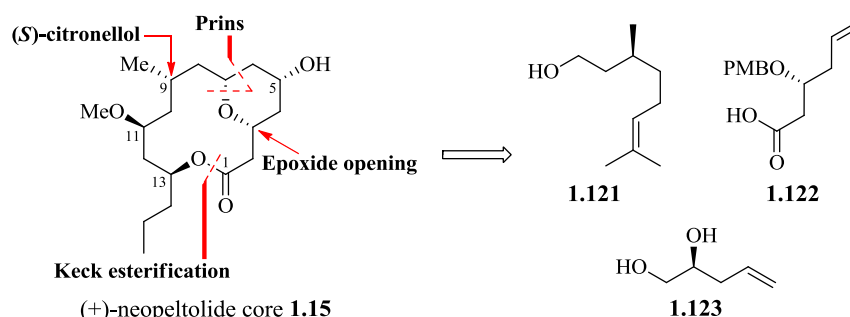
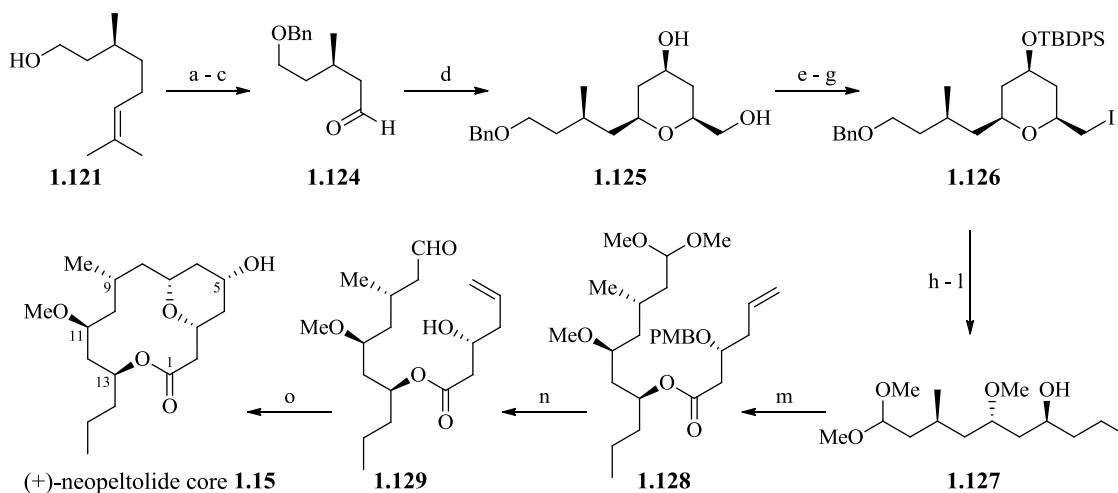


Figure 1.16 – Retrosynthetic analysis for the Yadav *et al.* formal synthesis of (+)-neopeltolide.

Synthesis began with the protection of (S)-citronellol **1.122** with benzyl bromide, which was then oxidized, ozonized, and finally reduced to give the desired aldehyde **1.125**.¹²² An intermolecular Prins reaction between aldehyde **1.125** and diol **1.124** in the presence of TFA, followed by hydrolysis of the resulting trifluoroacetate yielded pyran **1.126**. Tosylation of the primary alcohol, silyl protection of the secondary alcohol, and subsequent treatment of the tosylate with NaI in refluxing acetone gave the corresponding iodo compound **1.127**. Exposure of iodo compound **1.127** to unactivated zinc in refluxing ethanol cleaved the pyran ring, and upon methylation using Meerwein's salt,⁴² one-pot olefin reduction and benzyl deprotection with Raney nickel,¹²³ oxidation, aldehyde protection and silyl deprotection, led to *seco*-acid **1.128** (Scheme 1.14).

The endgame toward the macrocyclic core of (+)-neopeltolide began with the Keck esterification¹²⁴ of the free alcohol of **1.127** and carboxylic acid **1.122** in the presence of DCC and a catalytic amount of DMAP, to give compound **1.128**. The aldehydic homoallylic alcohol **1.129** was realized on treatment of **1.128** with DDQ, which was required for the ring-closing intramolecular Prins cyclization. Compound **1.129** was treated with TESOTf in acetic acid in the presence of TMSOAc and subsequently treated under basic conditions⁶³ to yield the macrocyclic core of (+)-neopeltolide in 66% yield (Scheme 1.14).



Scheme 1.14 – Conditions for Yadav’s synthesis of the macrolactone core of (+)-neopeltolide **1.15**.¹²⁵ a) NaH, BnBr, TBAL, THF, 12 h; b) H₂O₂, PhSeSePh, *t*-BuOOH, MgSO₄, DCM, 27 h; c) O₃, Me₂S, MeOH, 65% (over 3 steps); d) (*S*)-pent-4-ene-1,2-diol, TFA, DCM; then K₂CO₃, MeOH, 3.5 h, 56%; e) TsCl, Et₃N, DCM, 5 h; f) TBDPSCl, DMAP, imidazole, DCM, 3 h; g) NaI, acetone, reflux, 24 h, 84% (over 3 steps); h) Zn, EtOH, reflux, 1 h; i) Me₃OBf₄, Proton Sponge, DCM, 2 d; j) H₂, Raney nickel, EtOH, 6 h; k) DMP, NaHCO₃, DCM, 1 h; l) PTSA, CH(OMe)₃, 6 h, 61% (over 5 steps); m) **1.122**, DCC, DMAP, DCM, 3 h, 92%; n) DDQ, pH 7 buffer, DCM, 36 h, 92%; o) TESOTf, TMSOAc, AcOH; then K₂CO₃, MeOH, 30 min, 66%.

The Yadav synthesis of the macrolactone core of (+)-neopeltolide required 15 steps in the longest linear sequence, with an overall yield of 9.2%, starting from the commercially available (*S*)-Citronellol **1.121**.

1.5.4 Fuwa *et al.* formal synthesis (2010)

The previous synthesis of (+)-neopeltolide by the Fuwa group in 2008 (Section 1.4.3) relied on a Suzuki-Miyaura coupling and RCM strategy. Unfortunately this synthesis required 24 steps in the longest linear sequence, and multiple protection group manipulations and redox steps. Consequently, Fuwa *et al.* designed a more concise synthetic approach to (+)-neopeltolide by minimizing manipulations of oxygen functionalities. Envisaged was that the macrocyclic core of neopeltolide could be accessed *via* a RCM/hydrogenation sequence of diene **1.130** to form the C8-C9 bond, while chemoselectively defining the stereogenic C9 methyl group.

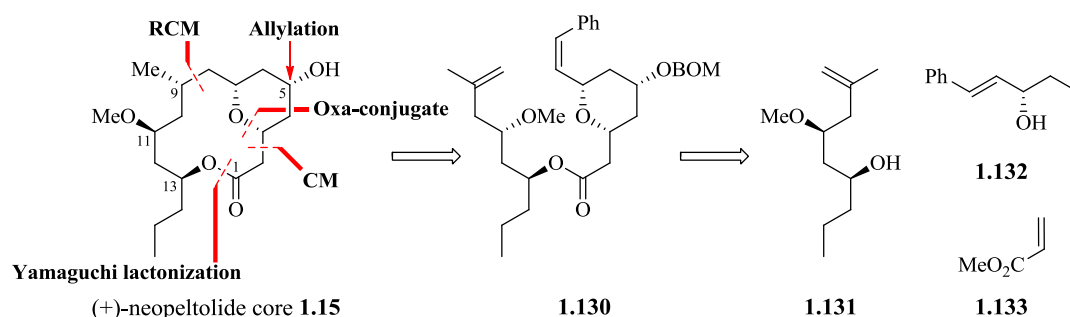
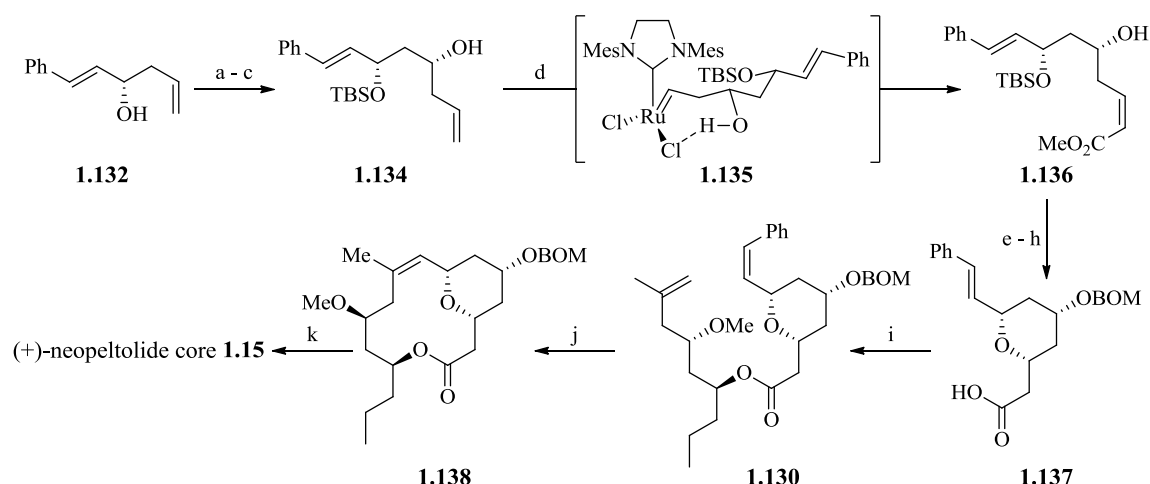


Figure 1.17 – Retrosynthetic analysis for the Fuwa *et al.* formal synthesis of (+)-neopeltolide.

The synthesis commenced with the protection of the known homoallylic alcohol **1.32**,¹²⁶ chemoselective dihydroxylation, subsequent oxidative cleavage, and asymmetric Brown allylation,⁶⁷ yielding homoallylic alcohol **1.134** with good diastereoselectivity (dr = 10:1). Olefin cross metathesis of **1.134** with second generation Grubbs catalyst^{95–97} *via* ruthenium alkylidene intermediate **1.135** occurred smoothly where the hydroxy group at C5 of **1.134** was exploited as a “directing group” to render unfavourable conformation for the competitive RCM.¹²⁷ Methyl acrylate **1.133** was successfully installed in the preparation of **1.136**, followed by subsequent protection of the C5 alcohol as its BOM ether and desilylation, setting the stage for the ensuing intramolecular oxa-Michael conjugate addition. The oxa-conjugate addition was best accomplished by treatment with DBU in refluxing toluene, which afforded the thermodynamically favoured *seco*-acid **1.137**, following ester hydrolysis⁷⁸ (Scheme 1.15).

Esterification of *seco*-acid **1.137** and alcohol **1.131** under classical Yamaguchi conditions⁴⁷ provided the RCM precursor **1.130** in excellent yield (94%). Treatment of **1.130** with second generation Grubbs catalyst in the presence of 1,4-benzoquinone in refluxing toluene macrocyclized the bicyclic **1.138** in 85% yield as the single desired *Z* isomer. Completion of the macrolide synthesis was realized *via* chemoselective hydrogenation from the less hindered face of the molecule^{107,108} to give the macrolactone core of (+)-neopeltolide **1.15** (Scheme 1.15).



Scheme 1.15 – Conditions for Fuwa’s synthesis of the macrolactone core of (+)-neopeltolide **1.15**.¹²⁷ a) TBSCl, imidazole, DMF, rt; b) OsO₄, NaIO₄, 2,6-lutidine, 1,4-dioxane:H₂O (3:1), 0°C; c) (+)-Ipc₂BOMe, allylMgBr, Et₂O, -78°C; then NaOH, H₂O₂, rt, 56% (dr = 10:1); d) G-II (5 mol%), **1.133**, DCM, rt, 82%; e) BOMCl, *i*Pr₂Net, *n*Bu₄NI, 1,2-dichloroethane, 50°C; f) TBAF, AcOH, THF, 35°C; g) DBU, PhMe, 100°C, (dr >20:1); h) TMSOK, Et₂O, rt, 90% (over 4 steps); i) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, rt; then **1.131**, DMAP, PhMe, rt, 94%; j) G-II (30 mol%), 1,4-benzoquinone, PhMe, 100°C, 85%; k) H₂ (0.8MPa), Pd/C, Pd(OH)₂/C, EtOH, rt, 93%.

Improving greatly upon the efficiency of their first synthesis toward (+)-neopeltolide,⁷¹ the Fuwa group has reported a concise formal synthesis of (+)-neopeltolide requiring only 12 steps in the longest linear sequence, with an overall yield of 19.6% from the homoallylic alcohol of commercially available (*E*)-cinnamaldehyde.¹²⁷ To date, this remains as one of the highest yielding, and shortest asymmetric synthesis of (+)-neopeltolide.

1.5.5 She *et al.* formal synthesis (2011)

In their report on (+)-neopeltolide, She *et al.* were inspired by the 2010 Fuwa synthesis¹²⁷ and envisioned the macrolactone core of neopeltolide could be constructed by the fragment assembly of alcohol **1.140** and acid **1.141** *via* intermolecular esterification and a RCM reaction. The tetrahydropyran ring could be realized through key asymmetric transformation steps of palladium-catalyzed intramolecular alkoxyacylation of the diol **1.142**, which can be derived from 1,3-propanediol *via* iridium-catalyzed asymmetric carbonyl allylation (Figure 1.18).

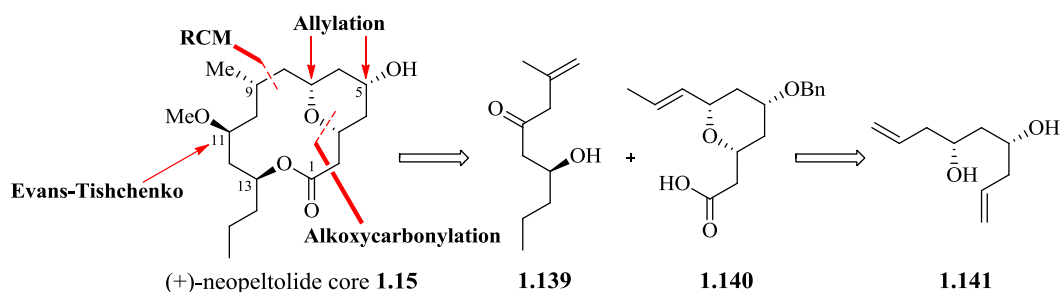
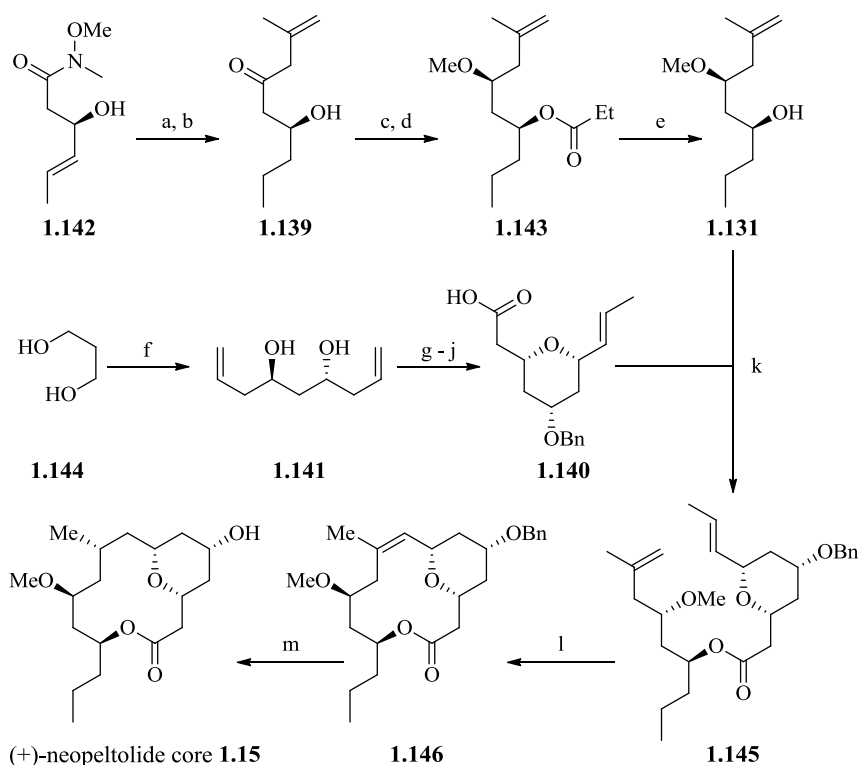


Figure 1.18 – Retrosynthetic analysis for the She *et al.* formal synthesis of (+)-neopeltolide.

The synthesis of alcohol **1.139** began with the Weinreb amide **1.142**, which was prepared according to literature from L-Valinol in several steps.^{128–130} Hydrogenation of **1.142**, followed by Grignard allylation afforded the β -hydroxyketone **1.139**.¹⁰¹ An Evans-Tishchenko reduction³⁹ installed the desired *anti* relationship between C11 and C13, and subsequent methylation of the resulting secondary alcohol with Meerwein's salt yielded **1.143** in excellent yield.⁴² Ester hydrolysis of **1.143** gave alcohol **1.131**, which was to be coupled to fragment **1.140** in later steps (Scheme 1.16).

Synthesis of carboxylic acid fragment **1.140** began with the iridium-catalyzed double asymmetric carbonyl allylation^{131,132} of 1,3-propanediol **1.144**, yielding the C2-symmetric diol **1.141**.¹³² Palladium-catalyzed intramolecular alkoxyacylation¹³³ smoothly installed the tetrahydropyran ring with high stereoselectivity (dr > 20:1), followed by benzyl protection of the free secondary alcohol, isomerisation of the terminal olefin using Grubbs' second generation catalyst,^{95–97} and hydrolysis of the methyl ester to its corresponding acid **1.140**. Intermolecular esterification between alcohol **1.131** and acid **1.140** under Shiina conditions¹³⁴ provided diene **1.145**, and set the RCM. The resulting macrolactone **1.146** underwent a chemoselective hydrogenation in the presence of catalytic Pd/C, simultaneously removing the benzyl ether and completing the formal synthesis of (+)-neopeltolide.



Scheme 1.16 – Conditions for She’s synthesis of the macrocyclic core of (+)-neopeltolide **1.15**.¹³⁵ a) Raney-Ni, H₂, EtOH, 4 h; b) (2-methylallyl)magnesium bromide, THF, -78°C, 3 h, 73% (over 2 steps); c) SmI₂, EtCHO, THF, -10°C, 2 h; d) Me₃BOF₄, Proton Sponge, DCM, 0°C, 6 h, 82% (over 2 steps); e) K₂CO₃, MeOH, 6 h, 87%; f) [Ir(cod)Cl]₂ (5 mol%), (R)-Cl₂MeO-BIPHEP (10 mol%), Cs₂CO₃ (40 mol%), 4-Cl-3-NO₂-BzOH (20 mol%), allylacetate, dioxane (0.2M), 110°C, 3 d, 70%; g) PdCl₂, CuCl₂, CO, MeCN, MeOH, rt, 4 h; h) BnO(NH=C)CCl₃, CF₃SO₃H, DCM, 0°C, 2 h; i) G-II (10 mol%), MeOH, 60°C, 12 h; j) LiOH (1.0 M):THF:MeOH (2:1:1), rt, 58% (over 4 steps); k) MNBA, DMAP, **1.140**, DCM, rt, 3 h, 91%; l) HG-II (20 mol%), PhMe, 80°C, 4 h, 74%; m) Pd/C, H₂, EtOH, rt, 12 h, 72%.

The She synthesis of the macrolactone core of (+)-neopeltolide required 12 steps in the longest linear sequence, with an overall yield of 18%, starting from commercially available L-valinol. In this report on (+)-neopeltolide, a high atom economy with minimized protecting group manipulation makes this efficient pathway a great prospective for offering convenience for further studies.¹³⁵

1.5.6 Raghavan *et al.* formal synthesis (2012)

In the final report on (+)-neopeltolide to date, Raghavan *et al.* envisaged a strategy wherein three of the six stereocenters were introduced *via* organocatalytic and metal complex promoted catalytic asymmetric transformations, and the remaining three were introduced stereoselectively by substrate controlled asymmetric induction. A dihydropyran ring could be realized through a hetero Diels-Alder cyclization,⁷⁹ whereby the natural-stereochemistry addition of the C5 hydroxyl group *via* oxymercuration-demercuration would yield the desired *cis*-tetrahydropyran¹⁸ (Figure 1.19).

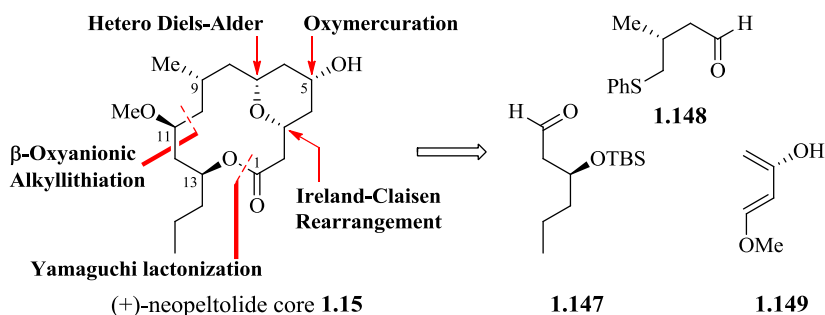
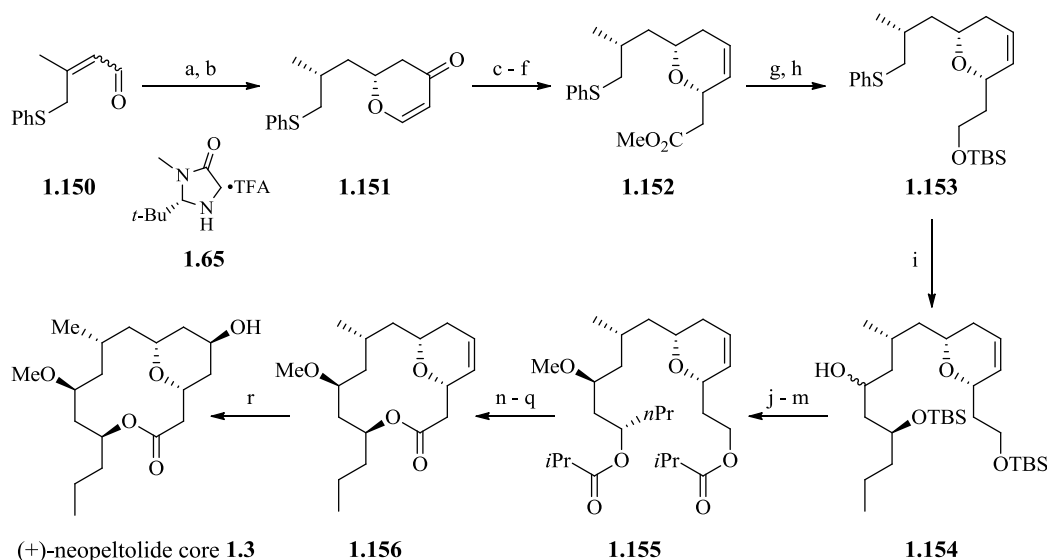


Figure 1.19 – Retrosynthetic analysis for the Raghavan *et al.* formal synthesis of (+)-neopeltolide.

The synthesis commenced with the enantioselective organocatalytic hydride reduction of the mixture of *E/Z* isomers of enal **1.150** using MacMillan's protocol⁸² with the trichloroacetic acid salt of imidazolinone catalyst **1.65** and the ethyl Hantzsch ester, yielding **1.148** in good selectivity.⁸² Pyranone **1.151** was realized *via* hetero Diels-Alder cyclization between **1.148** and **1.149**, in the presence of (*S,S*)-Cr(III)-salen-BF₄⁺ catalyst.¹³⁶ Four steps were required for the conversion of **1.151** into the disubstituted dihydropyran **1.152**, including an Ireland-Claisen rearrangement¹³⁷ of the corresponding silyl ketene acetal, and esterification of the resulting acids using ethereal diazomethane. Lithium aluminum hydride reduction¹³⁸ of the ester yielded its primary alcohol, which was subsequently protected to afford **1.153** under standard conditions (Scheme 1.17).^{138–140}



Scheme 1.17 – Conditions for Raghavan's synthesis of the macrocyclic core of (+)-neopeltolide **1.3**.¹⁴¹ a) cat. **1.65** (20 mol%), Hantzsch ester (1.2 equiv.), DMF, -20°C, 72 h; b) **1.149**, (*S,S*)-Cr(III)-salen-BF₄⁺ (4 mol%), TBME, -30°C, 1 d; then TFA, 2 h, 56% (over 2 steps); c) NaBH₄, CeCl₃·7 H₂O, MeOH, -10°C, 5 min; d) Ac₂O, Et₃N, cat. DMAP, DCM, 0°C, 5 min; e) LDA, TMSCl, THF, -78°C to rt, 16 h; then 2N aq. HCl; f) ethereal CH₂N₂, 82% (over 4 steps); g) LAH, THF, 0°C to rt, 4 h; h) TBSCl, imidazole, DCM, rt, 1 h, 86% (over 2 steps); i) LiDBB, THF, -78°C, 10 min; then **1.147**, -78°C, 30 min, 60%; j) IBX, DMSO, DCM, rt, 2 h; k) TBAF, AcOH, THF, 0°C to rt, 8 h; l) isobutanol, Zr(Ot-Bu)₄, THF, -50°C, 6 h; m) NaH, MeI, THF, 0°C, 1 h, 68% (over 4 steps); n) K₂CO₃, MeOH, rt, 30 min; o) PhI(OAc)₂, TEMPO, DCM, rt, 2 h; p) NaClO₂, *t*-BuOH, cyclohexene, H₂O, rt, 5 h; q) 2,4,6-trichlorobenzoyl chloride, DMAP, THF, toluene, 0°C to 100°C, 36 h, 39% (over 4 steps); r) Hg(OTFA)₂, aq. THF, rt, 1 d; then NaOH, NaBH₄, rt, 1 d, 60%.

Aldehyde **1.147** was synthesized in three steps from *n*-butanol *via* an asymmetric allylation developed by Krische¹⁴² and subsequent silyl protection and ozonolysis, which was coupled to **1.153** in the presence of lithium 4,4'-di-*tert*-butylbiphenylide^{143,144} to afford the epimeric mixture of **1.154** and the full carbon framework of the (+)-neopeltolide core. Four steps, including IBX oxidation,^{145–147} silyl deprotection, a modified Evans-Tishchenko reaction^{39–41} and O-methylation¹⁴⁸ provided diester **1.155**, which contained five of the six stereocenters. The diester was hydrolyzed, and selectively oxidized the primary alcohol using $\text{PhI}(\text{OAc})_2/\text{TEMPO}$ ⁵⁷ to the aldehyde, and to the *seco* acid using Pinnick protocol,⁴⁵ and finally cyclised under classical Yamaguchi conditions⁴⁷ to yield the bicyclic **1.156**. Conversion to the (+)-neopeltolide core **1.3** was accomplished by oxymercuration-demercuration, as originally reported by Panek *et al.*¹⁸

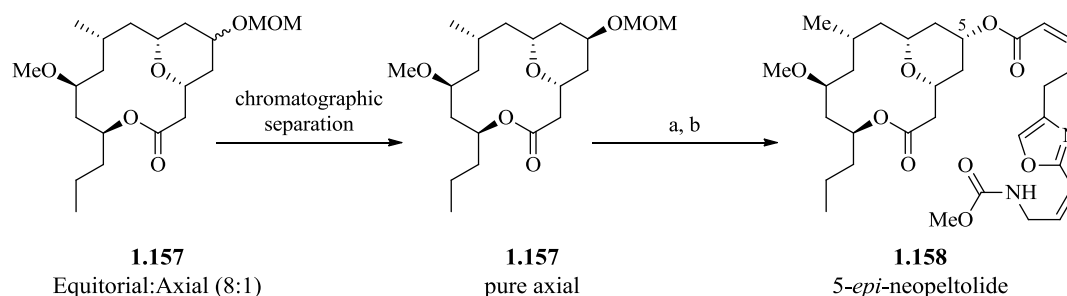
In the final report on (+)-neopeltolide to date, the Raghavan synthesis of the macrolactone core of (+)-neopeltolide required 16 steps in the longest linear sequence, with an overall yield of 3.83%, starting from commercially available starting materials.

1.6 Syntheses of Neopeltolide Analogs and Fragments

1.6.1 Maier *et al.* total synthesis and SAR investigation (2008)

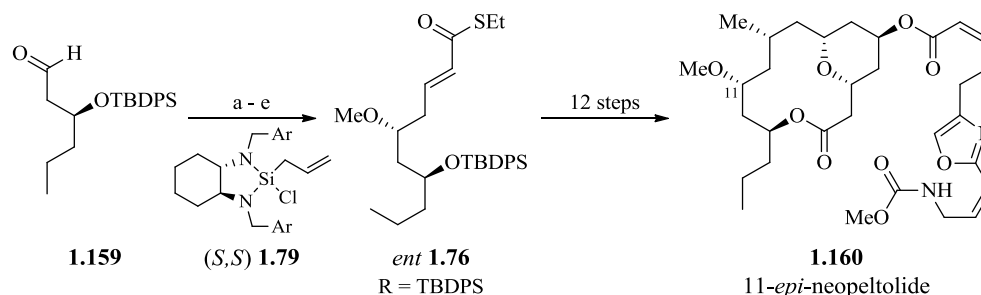
The total synthesis of (+)-neopeltolide by the Maier group was previously outlined in Section 1.4.5,⁸⁵ and herein only outlines the synthetic work toward its analogs. By slight variations in their synthesis, Maier *et al.* hoped to probe the effect of various configurations within the macrolactone core, as well as the distance between the macrolactone and oxazole ring of the side chain.

Initial analog synthesis required very little synthetic work for the Maier group. The analog of 5-*epi*-neopeltolide **1.158** was accessible from the minor diastereomer obtained during the total synthesis (Scheme 1.9). Separation of isomers provided the minor isomer (5-*epi*) with the axial hydroxyl group. Cleavage of the MOM ether and subsequent Mitsunobu coupling with known acid **1.16** provided analog **1.158** (Scheme 1.18).



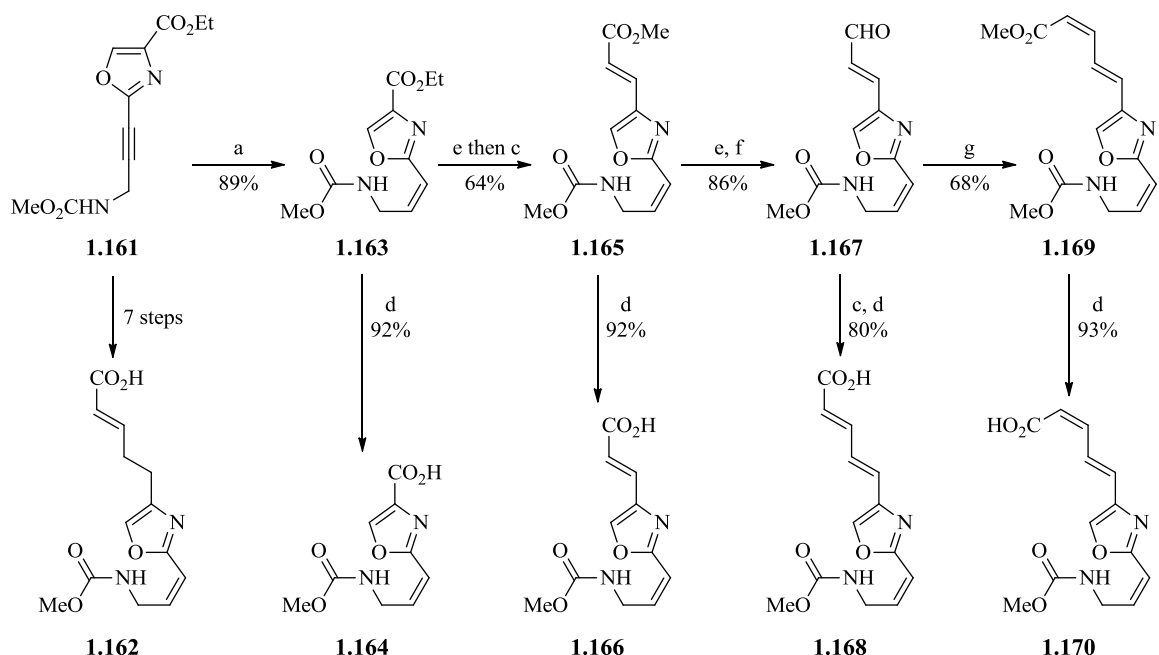
Scheme 1.18 – Conditions for Maier’s synthesis of 5-*epi*-neopeltolide **1.158**.⁸⁵ a) conc. HCl, MeOH; b) Ph₃P, DIAD, **1.16**, PhMe, rt, 1 h, 83% (over 2 steps).

A second analog from the Maier group was accomplished through the exchange of Leighton’s chiral allyating reagent from the (*R,R*)-catalyst in the total and formal syntheses,^{84,85} to the (*S,S*)-catalyst. Consequently, the thioester (*ent* **1.73**) is the enantiomer of the substrate used toward the synthesis of (+)-neopeltolide. Similar synthetic steps were utilized to complete the synthesis of the 11-*epi* analog of neopeltolide.



Scheme 1.19 – Conditions for Maier’s synthesis of 11-*epi*-neopeltolide **1.160**.⁸⁵ a) (*S,S*)-**1.79**, DCM, -10°C; b) Me₃OBf₄, Proton Sponge, DCM; c) OsO₄, NMO; d) NaIO₄, MeOH; e) **1.76** (Scheme 1.8), DCM, reflux, 63% (over 5 steps).

In addition to the macrocyclic diastereomers, Maier *et al.* prepared several side chain analogs to evaluate the possible effects of side chain length upon bioactivity. These alternative side chains were derived from intermediates obtained *en route* to the natural acid substrate **1.16** and vary in their length and olefin geometry. Scheme 1.20 outlines the synthetic work toward the side chain analogs.



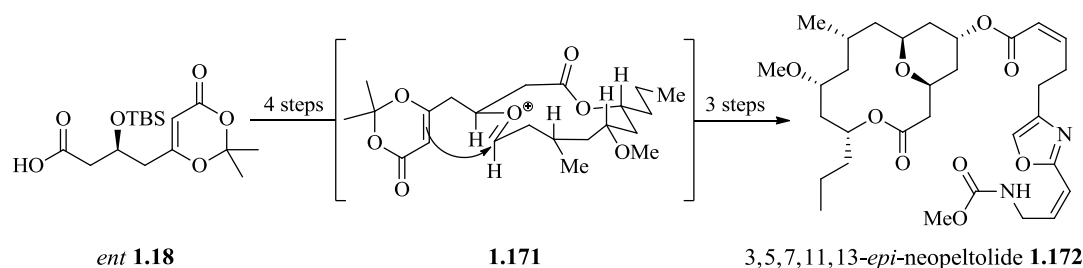
Scheme 1.20 – Conditions for Maier's synthesis of various acid analogs of the (+)-neopeltolide oxazole side chain.⁸⁵ a) H_2 , Lindlar's catalyst, quinoline, EtOAc; b) DIBAL-H, DCM, -80°C ; c) LiOH, THF/ H_2O ; d) $\text{Ph}_3\text{P}=\text{CH}(\text{CO}_2\text{Me})$, DCM, rt; e) DMP, DCM; f) $\text{KN}(\text{SiMe}_3)_2$, 18-crown-6, THF, -80°C .

The neopeltolide analogs that were synthesized by Maier *et al.* were then evaluated for their respective biological activity, and compared to natural (+)-neopeltolide **1.1b**. Testing revealed interesting structure-activity information, particularly that modifications to the natural structure are tolerated to some degree as several IC_{50} values were within the range of (+)-neopeltolide. Trends observed include a more pronounced drop in activity when stereochemical modification of the macrolactone is closer to the side chain. Moreover, it appears that the distance between the lactone and the oxazole ring is relevant, as analog **1.164** is not active. Finally, the configuration of the enoate double bond of the side chain appears more active in the *Z*-isomers by a factor of 10.⁸⁵

1.6.2 Scheidt *et al.* total synthesis and SAR investigation (2009)

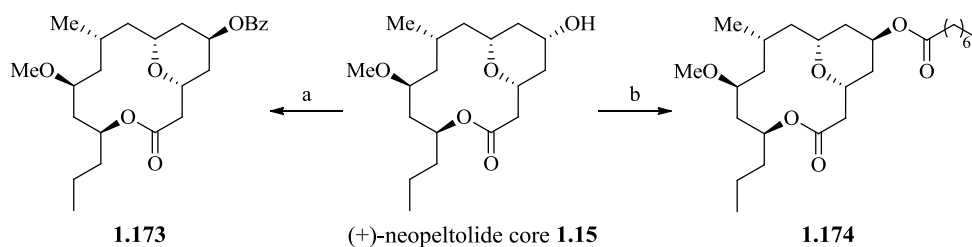
During the research toward their initial total synthesis of (+)-neopeltolide, the Scheidt group observed NMR discrepancies with their synthetic product from the reported data of the natural compound.^{7,16} An initial hypothesis for the discrepancy was that during the scandium triflate-catalyzed macrocyclization step (Scheme 1.3), an oxonia-Cope mechanism^{149–151} could yield the inverted stereochemistry at the C3 and C7 positions within the tetrahydropyran ring. A second hypothesis was that their synthesis had successfully yielded their desired compound but differed in some way from the initially proposed configuration of neopeltolide by the Wright group.⁷

In order to test their hypotheses, the Scheidt group synthesized carboxylic acid (*ent* **1.18**) as the enantiomer of substrate used in their total synthesis¹⁶ by utilizing (*S*)-BINOL for the vinylogous aldol reaction, as opposed to (*R*)-BINOL (Scheme 1.21). This successfully installed the β -hydroxy substituent with the opposite configuration, and the same sequence of synthetic transformations was employed as previously (Scheme 1.3). The scandium(III) triflate-catalyzed cyclization occurred through intermediate **1.171** without epimerization, therefore the stereochemistry of the tetrahydropyran ring was not inverted *via* the oxonia-Cope pathway, suggesting the originally reported configuration of neopeltolide was incorrect. Completion of the analog synthesis was accomplished with ease, and the known carboxylic acid **1.16** was installed, yielding 3,5,7,11,13-*epi*-neopeltolide **1.172** (Scheme 1.21).



Scheme 1.21 – Synthesis of Scheidt *et al.* 3,5,7,11,13-*epi*-neopeltolide **1.172**.¹⁵² Overall yield for the 7 step process is 7% and is indicative of a low-yielding (20%) scandium(III) triflate-catalyzed cyclization step.

Further analog synthesis was accomplished by performing a Mitsunobu coupling reaction^{49–51} of the advanced synthetic intermediate **1.15** with various commercially available carboxylic acid partners (Equation 1.3).



Equation 1.3 – Conditions for Scheidt's synthesis of neopeltolide analogs.¹⁵² a) benzoic acid, DIAD, Ph_3P , benzene, 74%; b) *n*-octanoic acid, DIAD, Ph_3P , benzene, 60%.

The neopeltolide analogs that were synthesized by Scheidt *et al.* were then evaluated for their respective biological activity, and compared to natural (+)-neopeltolide **1.1b**. Diastereomer **1.172** revealed 5-fold less potency than (+)-neopeltolide in the murine P388 cell line. In addition, analogs **1.173** and **1.174** reported loss of the majority of activity,¹⁵² and this result coincides with analog work by Maier *et al.*⁸⁵ that the side chain plays a significant role in the activity of the compound, as both the octanoyl and benzoyl side chains are significantly shorter than the natural side chain. Finally, and most interesting, the group tested the activity of the originally proposed

structure against (+)-neopeltolide and found that the originally proposed structure is 84- to 100-fold less potent than the natural product.¹⁵²

1.6.3 Florence *et al.* synthesis of RCM macrocyclization precursor (2010)

In contrast to the majority of previous syntheses toward neopeltolide establishing all the stereocenters prior to macrocyclization, the Florence group envisaged the use of macrocyclic conformations of suitable precursors to control the introduction of three of the six stereocenters.¹⁵³ Herein describes the stereocontrolled synthesis of **1.175** and studies toward its subsequent RCM macrolactonization (Figure 1.20).

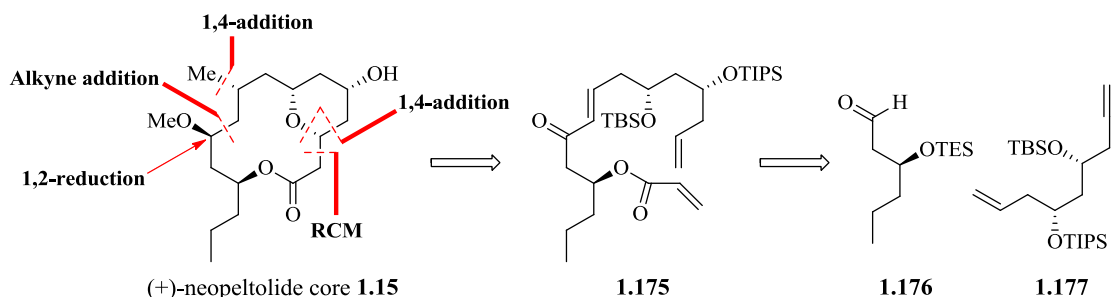
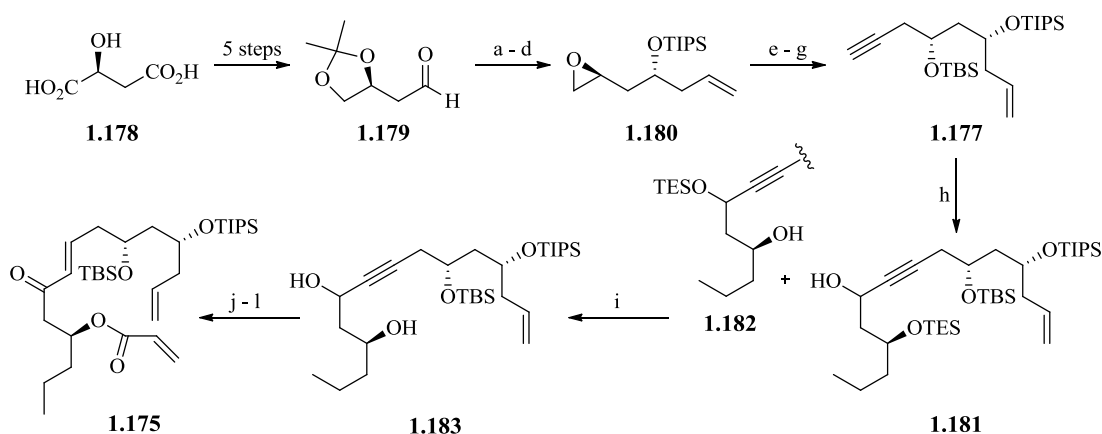


Figure 1.20 – Retrosynthetic analysis for the Florence *et al.* synthesis of a RCM macrocyclization precursor **1.175**.

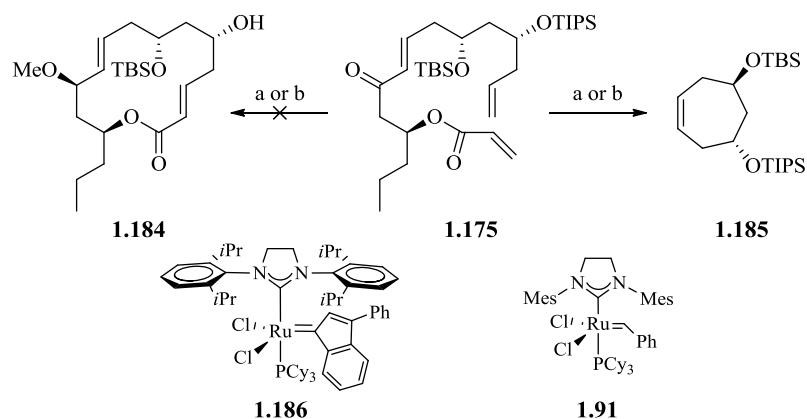
The synthesis of the ring closing metathesis precursor **1.175** started from D-malic acid **1.178**, which was transformed into aldehydic acetonide **1.179** in five steps.^{154–158} Asymmetric Brown allylation,^{66,67} followed by the TIPS protection of the secondary alcohol yielded the corresponding silyl ether. Subsequent TFA-mediated acetonide cleavage and epoxidation of the intermediate diol led to substrate **1.180** in good yield (61%) over the four steps.^{119,159,160} Epoxide **1.180** was opened with the lithium anion of TMS-acetylene during the installation of the alkyne group, which was followed by deprotection of the TMS group using potassium carbonate, and TBS protection of the C7 hydroxy group to provide the C2-C10 fragment **1.177** (Scheme 1.22).

Coupling of fragment **1.176** with aldehyde **1.177**, which was efficiently prepared from racemic 1,2-epoxypentane in several steps,^{153,161–163} was achieved *via* treatment of alkyne **1.177** with *n*-butyllithium and tetramethylethylenediamine (TMEDA), yielding a 1:1 mixture of diastereomers **1.181** at C11, co-isolated with the [1,5]-Brook rearrangement¹⁶⁴ product **1.182**. The mixture of addition products was deprotected of the triethylsilyl ether to provide diol **1.183**, which subsequently underwent reduction of the C9-C10 alkyne with Red-AlTM to selectively yield the *E*-allylic alcohols (*E*:*Z* = 6:1).¹⁶⁵ This was selectively oxidized using manganese dioxide to afford a hydroxy-enone, which was converted to the ring-closing metathesis precursor **1.175** through a Yamaguchi esterification with acrylic acid (Scheme 1.22).⁴⁷



Scheme 1.22 – Conditions for the synthesis of Florence's ring closing metathesis precursor **1.175**.¹⁵³ a) allylMgBr, (+)-Ipc₂BOMe, PhMe, -78°C, 1 h; then NaOH, H₂O₂, 3 h, (dr = 97:3); b) TIPSOTf, 2,6-lutidine, DCM, -20°C, 2 h; c) TFA 50% aq, DCM, rt, 30 min; d) NaH, TrisIm, THF, 0°C to rt, 1.5 h, 61% (over 4 steps); e) TMS-acetylene, *n*BuLi, BF₃·Et₂O, THF, -78°C to -20°C, 1.5 h; f) K₂CO₃, MeOH, rt, 16 h; g) TBSOTf, 2,6-lutidine, DCM, -20°C, 1 h, 81% (over 3 steps); h) *n*BuLi, TMEDA, THF, -78°C, 30 min; then **1.176**, -78°C to -20°C, 2 h, 81%; i) CSA, MeOH:DCM (1:1), 0°C, 30 min, 77%; j) Red-Al™, Et₂O, rt, 1.5 h (*E*:*Z* = 6:1); k) MnO₂, Et₂O, rt, 5 h; l) acrylic acid, 2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP, PhMe, rt, 1 h, 31% (over 3 steps).

The completion of the synthesis was to be accomplished *via* ring-closing metathesis of alkene **1.175**; however, ring closure did not yield the expected macrolactone **1.184**, but to the exclusive formation of the unexpected cycloheptene **1.185** (Equation 1.4). This observation occurred under high dilution conditions with Grubbs' second generation catalyst **1.91**,^{95–97} as well as with Nolan's indenylidene complex **1.186**¹⁶⁶ in comparable yields (70% and 65%, respectively). The exclusive formation of the cycloheptene suggests that either conformational flexibility and the corresponding intermediate carbene complex leads to preferential C3-C7 metathesis directly, or that the transient formation of a 14-membered macrolactone is followed by a transannular metathesis reaction due to conformational constraint.^{95,96,153,167}



Equation 1.4 – Conditions for Florence's ring closing metathesis of precursor **1.175**.¹⁵³ a) G-II **1.91** (5 mol%), DCM, reflux, 16 h, 70%; b) Nolan's indenylidene complex **1.186** (20 mol%), DCM, rt, 4 h, 65%. Ring closing product **1.184** was not observed under either set of conditions.

The progress toward a RCM macrocyclization precursor by Florence *et al.* for the synthesis of (+)-neopeltolide was unsuccessful, and led to the unexpected formation of silylated cycloheptene **1.186** under two different sets of conditions.

1.6.4 Floreancig *et al.* total synthesis and analogs (2010)

The total synthesis of (+)-neopeltolide by the Floreancig group was previously outlined in Section 1.4.7,⁸⁵ and herein outlines the synthetic work done toward several analogs of neopeltolide from common tetrahydropyrone intermediate **1.104**.

The presence of the unsaturation between C8 and C9 of **1.104** creates opportunity for analog synthesis. Simple reduction of the C5 carbonyl group of **1.104** under common conditions, followed by subsequent Mitsunobu coupling⁵⁸ of the known oxazole side chain **1.16** provided dehydroneopeltolide **1.187**. This structure is believed unlikely to differ from (+)-neopeltolide with respect to physical properties or biological activity (Figure 1.21).¹⁰⁷

The subjection of **1.104** to hydrogenation in the presence of Crabtree's catalyst¹⁶⁸ confirmed reagent coordination to the tetrahydropyranyl oxygen to functionalize the alkene from the convex face, albeit with low diastereoselectivity (1.4:1).¹⁰⁷ Simple reduction of the C5 carbonyl group under common conditions, followed by subsequent Mitsunobu coupling⁵⁸ of the known oxazole side chain **1.16** provided 9-*epi*-neopeltolide **1.188** (Figure 1.21).

The C8-C9 alkene of interest also provides opportunity for the introduction of polar groups that could improve physical properties, such as water solubility.¹⁰⁷ Using this foundation of thought, conversion of **1.104** into its corresponding epoxide **1.189** and dihydroxylation product **1.190** were achieved in reasonable yields (Figure 1.21).

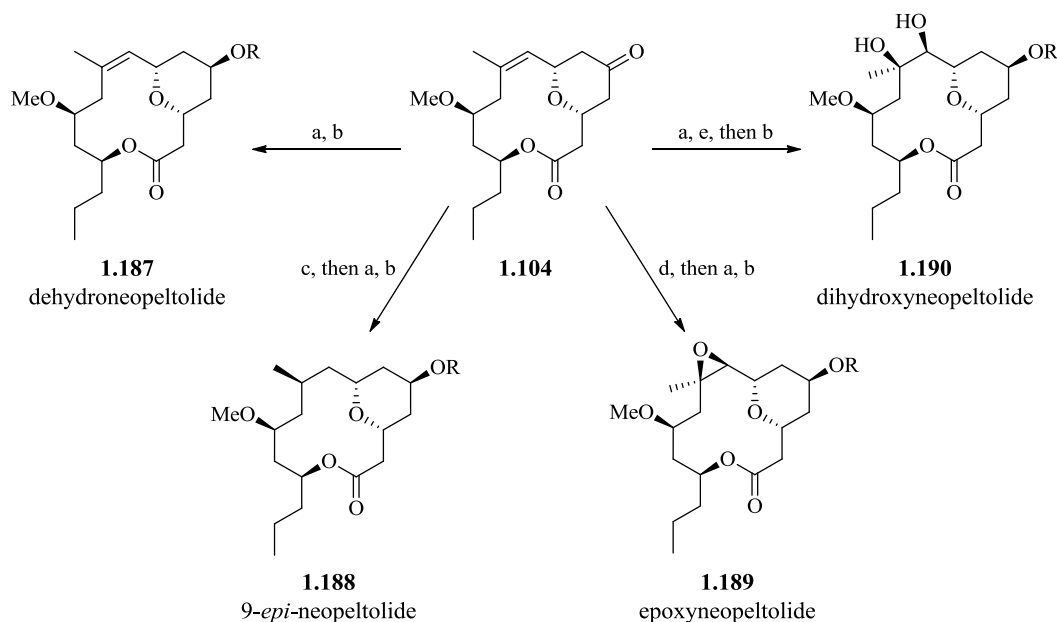


Figure 1.21 – Conditions for Floreancig’s synthesis of neopeltolide analogs.¹⁰⁷ a) NaBH₄, MeOH, 0°C, 84%; 96%; 92%; 84%; b) **1.16**, DIAD, Ph₃P, benzene, 70%; 67%; 50%; 66%; c) (cod)Ir(Py)PCy₃PF₆, H₂, DCM, 54%; d) OsO₄, pyridine, NMO, THF, 75%; e) *m*-CPBA, NaHCO₃, DCM, 55%; R = oxazole side chain.

The common tetrahydropyran intermediate **1.104** of the Floreancig synthesis accommodates the synthesis of various neopeltolide analogs; however, biological activity studies are needed to verify the potential of the chemical alterations.

1.6.5 Jennings *et al.* formal synthesis of (–)-neopeltolide (2010)

The Jennings group has previously shown that the obvious synthesis of the unnatural and enantiomeric structure of a compound can prove instrumental in SAR studies, revealing greater activity than the natural product itself.¹⁶⁹ Consequently, a total synthesis of the macrocyclic core of the unnatural (–)-neopeltolide **1.3c** was performed for the undertaking of more comprehensive *in vitro* biological screening. The Retrosynthetic analysis of **1.3c** followed Panek’s initial disconnection of the side chain,¹⁸ in that it could be introduced *via* a two-step Still-Gennari olefination¹⁷⁰ that doesn’t require the inversion of the C5 stereocenter. As their key step, the *cis*-tetrahydropyran ring would emerge from a stereoselective reduction of an endocyclic oxocarbenium cation mediated by the treatment of an appropriate hemiketal with a Lewis acid. This hemiketal would be derived from a nucleophilic addition of an allyl Grignard to the MOM ether of δ -lactone **1.191** (Figure 1.22).¹⁷¹

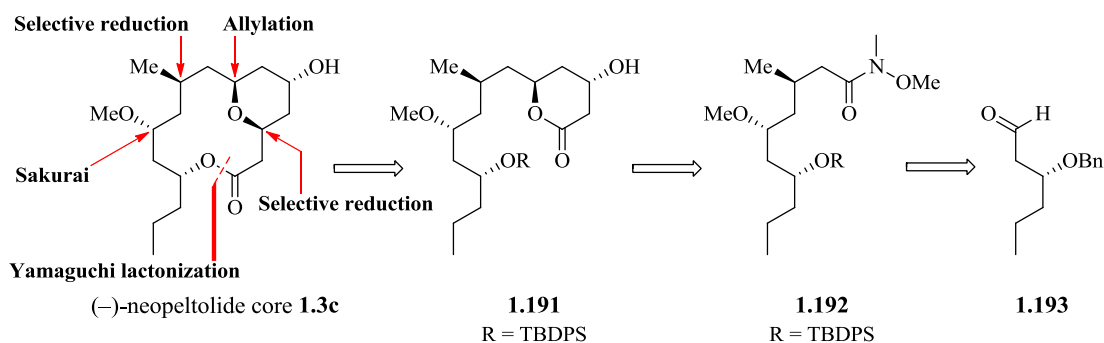
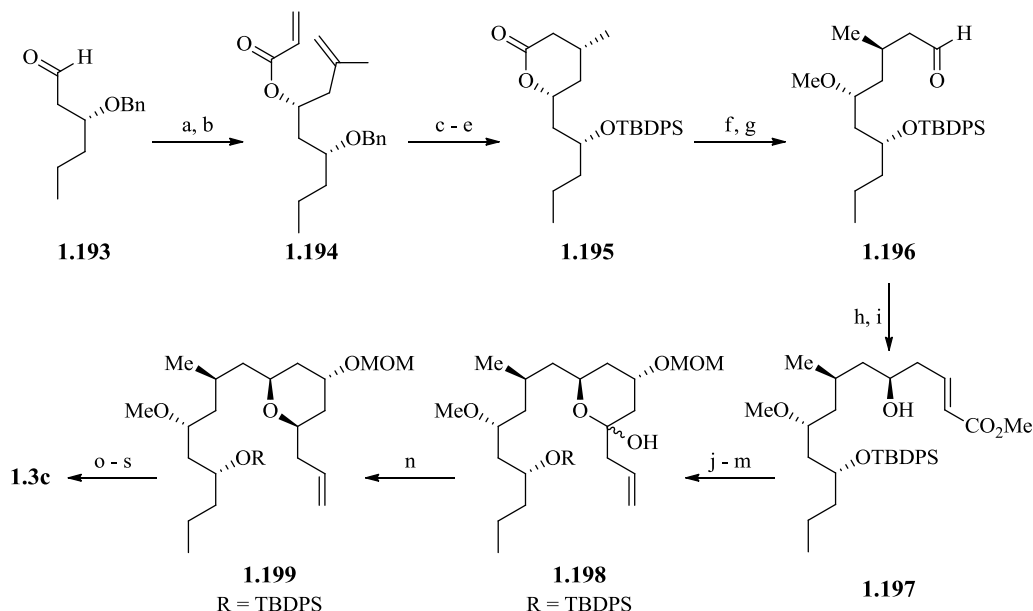


Figure 1.22 – Retrosynthetic analysis for the Jennings *et al.* synthesis of the macrocyclic core of (-)-neopeltolide.

Synthesis began with the three step conversion of butyraldehyde to aldehyde **1.193** via asymmetric Brown allylation^{66,67} to provide its corresponding homoallylic alcohol, which subsequently was benzyl protected and underwent ozonolysis.⁶³ A diastereoselective methallylation of **1.193** in the presence of titanium(IV) chloride¹⁷² provided its corresponding homoallylic alcohol, and converted into ester **1.194** with subsequent treatment with acryloyl chloride and Hünig's base. Ring-closing metathesis of ester **1.194** provided an α,β -unsaturated lactenone, which was diastereoselectively reduced with simultaneous removal of the benzyl ether by means of a Pd/C hydrogenation. The secondary alcohol was reprotected as a TBDPS ether to afford lactone **1.195** in 91% over the three steps. Conversion of lactone **1.195** into the Weinreb amide **1.192** under transamidation conditions,⁵⁵ and immediately treated with Meerwein's salt to provide the methoxy ether and prevent relactonization.⁴² Removal of the amide moiety via DIBAL reduction furnished aldehyde **1.196** in excellent yield, and was elongated again under asymmetric Brown allylation conditions.^{66,67} The alkene of the resulting homoallylic alcohol underwent diastereoselective cross metathesis with methyl acrylate and Grubbs' second generation catalyst^{95–97} to yield the *E*- α,β -unsaturated ester **1.197**.¹⁷³ The Evans' protocol for the diastereoselective synthesis of 1,3-*syn*-diols^{174,175} was employed on substrate **1.197** to provide the *syn*-benzilidine acetal with excellent stereoselectivity (dr > 20:1), and upon reductive deprotection of the acetal with Pearlman's catalyst,¹⁷⁶ was subsequently transformed to β -hydroxy lactone **1.191** with acidic reaction conditions. MOM-protection of the free alcohol yielded the desired δ -lactone, and treatment with excess allylmagnesium bromide in kinetic conditions provided the hemiketal intermediate **1.198**, which was directly treated with TFA and stereoselectively reduced, via the corresponding oxocarbenium cation, to the *cis*-tetrahydropyran subunit **1.199** (dr > 20:1). This result was consistent with previous observations by the Jennings group,^{177–183} and based on Woerpel's models,^{148,184} and **1.199** was assumed to arise from a reactive conformer that places the C5 alkyl side chain in the pseudoequatorial position and the C3 MOM-protected alcohol in the axial position (Scheme 1.23).

Completion of the synthesis of (–)-neopeltolide began with the ozonolysis of the terminal alkene of **1.199**, followed by reductive workup with triphenyl phosphine to its corresponding aldehydic intermediate. A Lindgren-Kraus-Pinnick oxidation^{45,185–187} converted the aldehyde to the carboxylic acid, and TBAF-mediated cleavage of the silyl ether protecting group provided the *seco*-acid precursor for Yamaguchi macrolactonization.⁴⁷ Yamaguchi esterification proceeded in 83% yield, and final deprotection of the MOM acetal was accomplished using Maier's conditions to provide the macrocyclic core of (–)-neopeltolide **1.3c** (Scheme 1.23).^{18,84}



Scheme 1.23 – Conditions for Jennings' synthesis of the macrocyclic core of (–)-neopeltolide.¹⁷¹ a) TiCl_4 , $\text{CH}_2\text{C}(\text{CH}_3)\text{CH}_2\text{TMS}$, DCM, (dr = 10:1); acryloyl chloride, Hünig's base, DCM, 84% (over 2 steps); c) G-II, PhMe; d) H_2 , Pd/C, EtOH; e) TBDPSCl, imidazole, DMF, 91% (over 3 steps); f) $\text{MeO}(\text{NH})\text{Me}\cdot\text{HCl}$, Me_3Al , DCM; g) Me_3OBF_4 , Proton Sponge, DCM; h) DIBAL-H, DCM, 52% (over 3 steps); i) (+)-Ipc₂Ballyl, Et₂O, NaOH, H₂O₂, (dr = 6:1); j) G-II, benzene, methyl acrylate, 76% (over 2 steps); k) PhCHO, KOrBu, THF, (dr = 20:1); l) H_2 , Pd(OH)₂, HOAc; m) MOMCl, DIPEA; n) allylMgBr, Et₂O, 54% (over 4 steps); o) TFA, Et₃SiH, 72% (dr = 20:1); p) O₃, DCM, MeOH; q) 2-methylbutene, NaClO₂, NaH₂PO₄, *t*-BuOH; r) TBAF, THF; s) 2,4,6-trichlorobenzoyl chloride, THF, DMAP, PhMe; t) HCl, MeOH, 49% (over 5 steps).

The Jennings synthesis of (–)-neopeltolide required 19 steps in the longest linear sequence, with an overall yield of 5.6%, starting from known aldehyde **1.193**. Unfortunately, biological activity studies were not reported for (–)-neopeltolide.

1.6.6 Oestreich *et al.* synthesis of C7-C16 fragment (2010)

The Oestreich group proposed a synthetic approach to the C7-C16 fragment of (+)-neopeltolide based on previous experience with enantioselective conjugate silyl transfer,^{188–191} and wanted to merge this into the Feringa-Minnaard installation of the C9 methyl substituent.^{87,88,192} The C7-C16 fragment of (+)-neopeltolide is a key piece of the carbon skeleton, as it possesses four

of the six stereogenic centers. Their design was to build aldehydic fragment **1.60**, which is common to the Paterson⁸³ and Maier^{84,85} syntheses, from the known ester **1.200**.^{83–85,193}

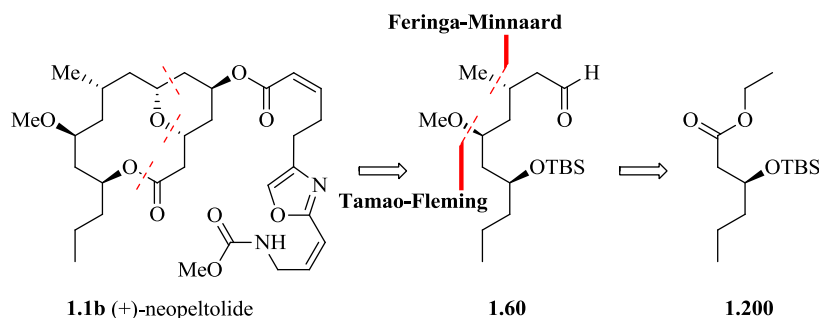
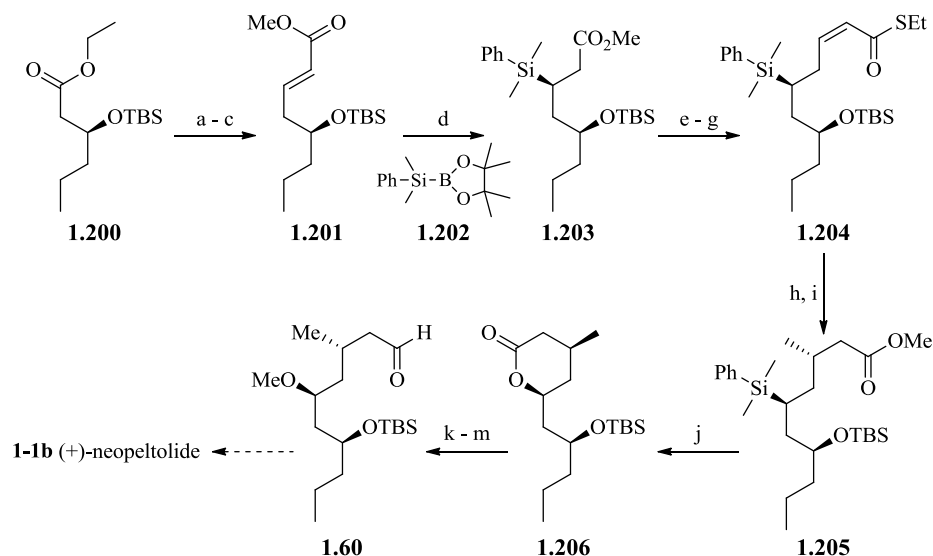


Figure 1.23 – Retrosynthetic analysis for the Oestreich *et al.* synthesis of the C7-C16 fragment of (+)-neopeltolide.

Synthesis of the C7-C16 fragment began with ester **1.200**, which was obtained from 3-hydroxy hexanoic acid ethyl ester *via* a known process.¹⁹³ The α,β -unsaturated ester **1.201** was derived from **1.200** *via* a three-step process involving DIBAL-H reduction, Swern oxidation,^{43,44} and Still-Gennari olefination,¹⁷⁰ which was subsequently treated with (*R*)-BINAP to afford ester **1.203** from ruthenium-catalyzed conjugate addition of silyl boronic acid **1.202**. An additional three-step homologation afforded α,β -unsaturated thioester **1.204** in good yield (60%) and excellent selectivity (*E:Z* > 95:5), which underwent Feringa-Minnaard *anti*-selective methylation⁸⁶ to yield the fully elaborated carbon framework as a single diastereomer **1.205**.^{87,88,192} Following thio-to-oxo transesterification, a Tamao-Fleming^{103,194,195} oxidation allowed selective oxidative degradation to form lactone **1.206**. Its opening to the corresponding Weinreb amide was followed by formation of the methyl ether at C11 with Meerwein's reagent,¹⁹⁶ and subsequent reduction of the ester to complete the synthesis of the C7-C16 aldehydic fragment **1.60** of (+)-neopeltolide.



Scheme 1.24 – Conditions for Oestreich’s synthesis of the C7-C16 fragment of (+)-neopeltolide.¹⁹⁷ a) DIBAL-H, THF, -78°C; b) DMSO, CO(Cl)₂, DCM, -78°C; then Et₃N; c) (CF₃CH₂O)₂P(O)CH₂CO₂H, 18-crown-6, KHMDs, THF, -78°C, 61% (over 3 steps); d) [Rh(cod)₂OTf] (5 mol%), (R)-BINAP (10 mol%), 1,4-dioxane:H₂O (10:1); then Et₃N, **1.202**, 45°C, 55% (dr > 95:5); e) DIBAL-H, THF, -78°C; f) DMSO, CO(Cl)₂, DCM, -78°C; then Et₃N; g) Ph₃P(CH)₂C(O)SEt, DCM, reflux, 3 d, (*E*:*Z* > 95:5), 60% (over 3 steps); h) CuBr·SMe₂ (5 mol%), (*S,R*)-Josiphos **1.77** (6 mol%), *t*-BuOMe, rt, 30 min; then MeMgBr, **1.204**, *t*-BuOMe, -78°C, 6 h, (dr > 95:5); i) NaOMe, MeOH, 89% (over 2 steps); j) KBr, NaOAc, HOAc, peracetic acid (40% w/w), 10 h, 75%; k) Me(MeO)NH·HCl, THF, *i*PrMgCl, -15°C, 1 h; l) Me₃OBF₄, Proton Sponge, 3 Å ms, 3 h; m) DIBAL-H, THF, -78°C, 68% (over 3 steps).

The Oestreich synthesis of a C7-C16 fragment of (+)-neopeltolide required 13 steps in the longest linear sequence, with an overall yield of 9.1%, starting from known ester **1.200**.

1.7 General Evaluation

After presenting the complete synthetic work directed toward neopeltolide, the following short discussion underscores the key aspects of neopeltolide chemistry and highlight some of the novel methodology involved (Table 1.2).

1.7.1 C9 Methyl Installation

There are a limited number of strategies for the stereoselective installation of a methyl group. Consequently, the introduction of the C9 (*R*)-methyl substituent in the syntheses of (+)-neopeltolide relied on two options. The first option was to include a pre-configured methyl group from a chiral pool as is seen with Panek’s (and others) use of methyl (*R*)-(+)-methylglutarate. The second option relied on diastereoselective reduction of an alkene, which encompasses the Feringa-Minnaard diastereoselective methylation utilized by the Maier syntheses^{84,85} and C7-C16 fragment construction of Oestreich.¹⁹⁷ An unsaturated C8-C9 bond within the native configuration of the trisubstituted macrocyclic olefin intermediate of Floreancig’s synthesis enabled highly

chemoselective hydrogenation to install the required C9 methyl group stereochemistry (also see Roulland, Fuwa 2010, and She syntheses).

1.7.2 1,3-Anti Selectivity of C11 and C13

The *anti* relationship between C11 and C13 of (+)-neopeltolide was predominantly installed *via* an Evans-Tishchenko reaction. This reaction is ideal as it sets the 1,3-*anti* relationship from a β -hydroxy ketone while protecting the β -hydroxy group as an ester. Alternative approaches to the required selectivity were accomplished through multiple iterations of asymmetric allylation processes, utilizing asymmetric allyl borane reagents developed by both Brown^{66,67} or Leighton.^{89–91}

1.7.3 Tetrahydropyran Formation

The incorporation of the tetrahydropyran moiety proved most variable in the syntheses of (+)-neopeltolide, with a total of six distinctly different approaches being utilized. The strongest trend observed was the utilization of oxonium ion cyclization. The Prins reaction was most favourable, being implemented by seven of the presented reports (Panek, Scheidt, Lee, Kozmin, Maier, Floreancig, and Yadav). One unanimous trend with respect to the formation of the THP ring is that it is done on an open-chain precursor, prior to macrocyclization.

1.7.4 Macrolactonization

The macrocyclization of (+)-neopeltolide has proven to be a late-stage transformation, and has employed common esterification processes with high levels of success. The Yamaguchi macrolactonization is the most heavily utilized process toward the cyclization of the (+)-neopeltolide core. The advantages of the Yamaguchi macrolactonization over other existing methods are its operational simplicity, its mild conditions, high reaction rate and lack of by-products. To a lesser extent, oxonium ion cyclizations including the Prins reaction were successfully used to macrocyclize the core of (+)-neopeltolide (Lee, Scheidt and Yadav syntheses) with high levels of success. Finally, the implementation of RCM by Fuwa *et al.* in their 2010 synthesis, and the formal synthesis by She *et al.* provided a C8-C9 unsaturation that allowed for the penultimate chemoselective hydrogenation, affording the C9 stereocenter and (+)-neopeltolide core in high yield.

1.7.5 Oxazole Side-Chain Installation

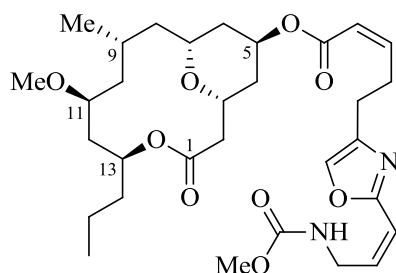
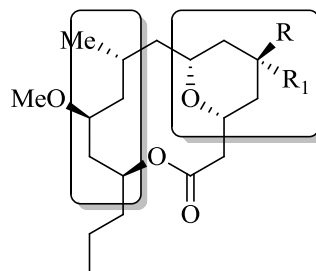
Mitsunobu reaction conditions seem to be the most favourable, and implemented route, toward the installation of the oxazole-containing side chain of (+)-neopeltolide. Of the published reports, eight of the nine total syntheses implemented this route, while only the synthesis of Panek *et al.* used an alternative, which was a decision based on their previous work in the total synthesis of leucascandrolide A.²¹ It is interesting to note that all total syntheses of (+)-neopeltolide employed the use of pre-existing synthetic routes toward the construction of the oxazole side-chain that were proven successful for leucascandrolide A.^{20–33} This observation shows that the focus of the (+)-neopeltolide studies was on the macrolide core itself, and also that the previous route to the required side-chain is a highly efficient process.

1.8 Conclusions and Prospects

Neopeltolide is a lead compound with unique and potent bioactivity, which holds great promise as an antifungal and anticancer agent that rivals paclitaxel. The bioactive potential and combined structural complexity of (+)-neopeltolide has led to seventeen syntheses (nine total syntheses, eight formal syntheses), in addition to several reports on SAR studies and fragments construction, since its discovery by the Wright group in 2007. The most efficient routes to (+)-neopeltolide include the total synthesis of Maier *et al.* (19% over 18 steps), and the 2010 formal synthesis of Fuwa *et al.* (20% over 12 steps). As short and economical solutions to the macrocyclic core of (+)-neopeltolide have been established, biological evaluation through *in vitro* studies can help to conclusively identify its mode of action. The biosynthesis of (+)-neopeltolide remains unknown and future research is required to elucidate its origin and the potential origin of structurally homologous compounds.

Table 1.2 – Summary of the various strategies that have been employed en route to (+)-neopeltolide by both the total and formal syntheses, based on work available up to June 2012.

Legend	
Fl	Floreancig ^{107,108}
F08	Fuwa (2008) ⁷¹
F10	Fuwa (2010) ¹²⁷
H	Hong ¹²⁰
K	Kozmin ²³
Lee	Lee ⁶³
M	Maier ^{84,85}
P	Paterson ⁸³
Pk	Panek ¹⁸
R	Raghavan ¹⁴¹
Ro	Roulland ¹⁰¹
S	Scheidt ^{16,152}
She	She ¹³⁵
T	Taylor ¹¹³
Y	Yadav ¹²⁵

**1.1b** (+)-neopeltolide**1.3** R = OH, R₁ = H**1.15** R = H, R₁ = OH

C9

Diastereoselective Reduction

Fl, F10, K, M, Lee, P, R, Ro, She

Pre-configured Chiral Pool

F08, H, Pk, S, T, Y

C11

Evans-Tishchenko

Fl, H, Pk, R, Ro, S, She, T

Asymmetric Allylation

F08, Lee, M, P

Pre-configured Chiral Pool

F10, Y

Asymmetric Aldol

K

C13

Asymmetric Reduction

K, Lee, Ro, S

Pre-configured Chiral Pool

F10, H, T, She

Asymmetric Allylation

F08, M, P, R

Epoxide-Opening

Fl, Pk

Tetrahydropyran Formation

Oxonium Ion Cyclization

Fl, K, Lee, M, Pk, S, Y

Oxa-Conjugate Addition

F10, H, Ro

Hetero Diels-Alder

P, R

Radical Cyclization

T

Ring-Closing Metathesis

F08

Alkoxyacylation

She

Macrocyclization

Yamaguchi Reaction

Fl, F08, K, M, P, Pk, R, Ro, T

Oxonium Ion Cyclization

Lee, S, Y

Ring-Closing Metathesis

F10, She

Side-Chain Installation

Mitsunobu Reaction

Fl, F08, K, Lee, M, P, Ro, S

Still-Gennari Reaction

Pk

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Chapter 2

Towards an Oxa-Conjugate Addition Route to the Total Synthesis of (+)-Neopeltolide

2.1 Introduction

The substantial attention of the synthetic community and their efforts directed toward (+)-neopeltolide (Figure 2.1), as outlined in chapter 1, have solved the acute supply problem and provided sufficient material for further biological evaluation of this promising anticancer agent.^{1–21} Unfortunately, total synthesis is unlikely to provide a permanent solution to the supply problem faced by (+)-neopeltolide, especially if this promising anticancer agent becomes a successful clinical therapeutic. In order to address the ongoing supply needs for (+)-neopeltolide and to push the state-of-the-art in combining biosynthesis with synthetic chemistry, we have focused on the exploration of a synthetic route based on biosynthetically accessible functional groups to this polyketide. If successful, this route will enable the design of a *de novo* biosynthetic pathway for (+)-neopeltolide production even though no biosynthetic mechanism for tetrahydropyran synthesis has been biochemically characterized.

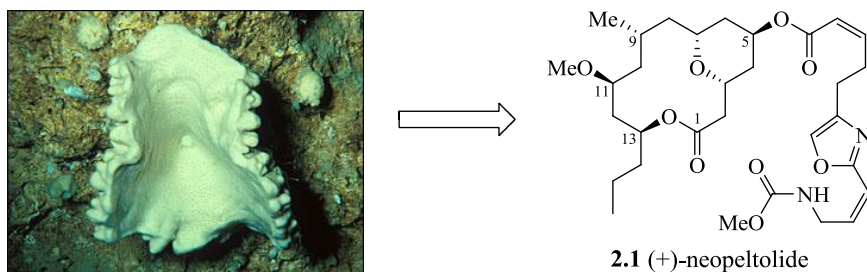


Figure 2.1 – (+)-Neopeltolide is a marine (sponge) derived polyketide natural product with potent anticancer activity. There is currently limited natural supply of this compound, limiting its development as a pharmaceutical agent.

2.2 Project Background

2.2.1 (+)-Neopeltolide: A Polyketide Natural Product

Neopeltolide is a member of the polyketide family of natural products. This diverse class of natural products is based on acetate or propionate subunits. Polyketide natural products display a vast range of potent biological activities, and has led to the development of numerous important clinical agents (Figure 2.2).^{22–24} Each acetate or propionate subunit is incorporated through successive decarboxylative Claisen condensations of thioester-enzyme tethered intermediates bound to a large enzyme complex that contains multiple catalytic domains known as a polyketide synthase (PKS).²⁵

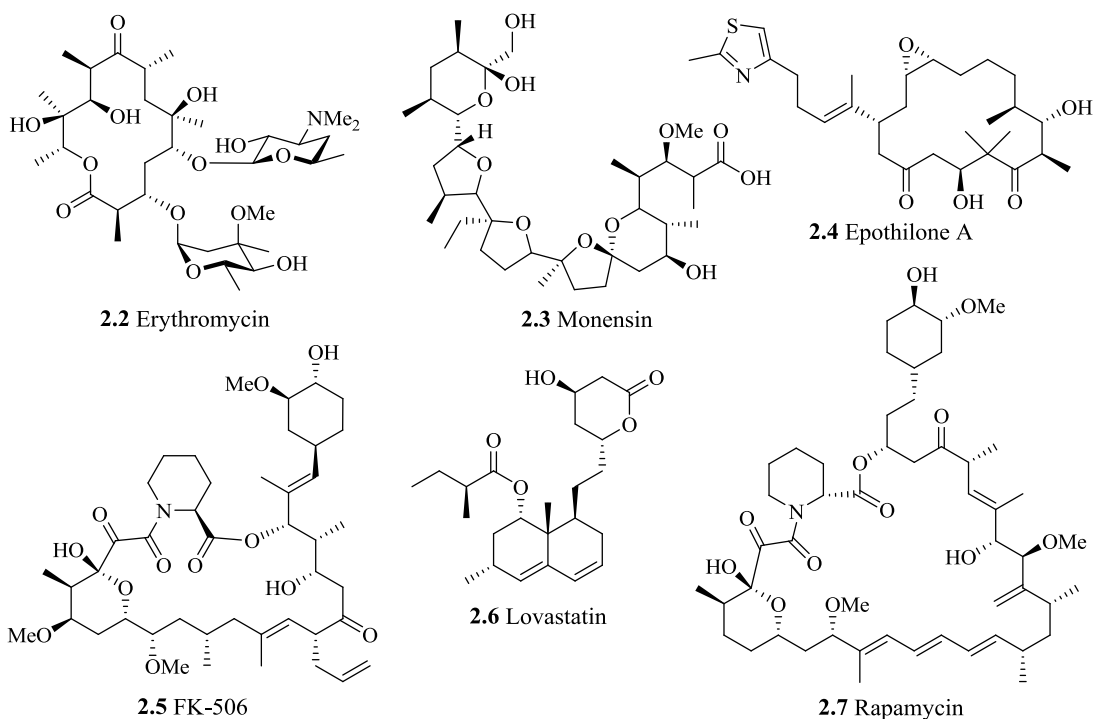


Figure 2.2 – Selected examples of medicinally important polyketide compounds. Erythromycin **2.2** acts as an antibiotic by binding to the 50s subunit of the 70s bacterial ribosome complex.²⁶ Monensin **2.3** is a potent antibiotic that binds tightly to monovalent cations.²⁷ The epothilone family (epothilone A **2.4** is shown) displays potent anticancer activity through stabilization of microtubules.²⁸ FK-506 **2.5** and rapamycin **2.7** are important immunosuppressants. Lovastatin **2.6** is a blockbuster cholesterol-lowering drug.²⁹

While much is known about the biosynthetic mechanisms responsible for the formation of the carbon backbone and the control of the oxygenation levels of polyketides,²⁵ very little is known about how some functional groups, such as tetrahydropyrans, are constructed. In the biosynthesis of (+)-neopeltolide, the best working hypothesis proposes that the tetrahydropyran functionality is generated by a catalytic domain similar to the well-characterized dehydratase (DH) domain (Figure 2.3). As can be seen in module 6, a postulated redundant-DH domain is likely present with the first DH domain catalyzing elimination of the β -hydroxyl group to generate the α,β -unsaturated thioester. The second DH domain is then thought to catalyze the intramolecular addition of the ζ -hydroxyl group, forming the tetrahydropyran functionality. While the elucidation of the pederin biosynthesis provides genetic evidence to support this hypothesis,³⁰ there remains no biochemical or chemical support for this mechanism.

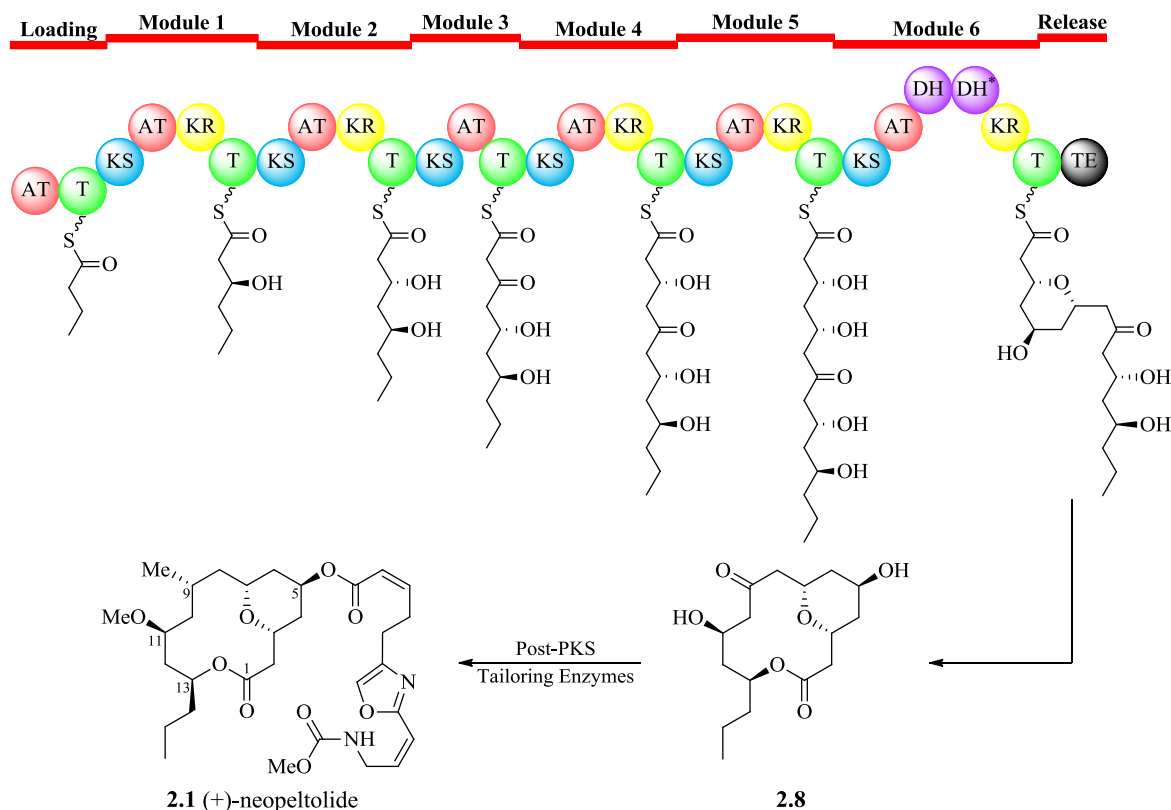


Figure 2.3 – Postulated biosynthetic pathway for the formation of the macrocyclic core of (+)-neopeltolide **2.1**. A redundant dehydratase (DH*) domain is likely responsible for the formation of the transannular tetrahydropyran ring system.

2.2.2 Polyketide Synthase Engineering

Over the past 15 years, it has become increasingly clear that modular polyketide synthase pathways, such as the one postulated in the biosynthesis of neopeltolide, are highly amenable to being re-engineered. Substantial work in the literature has shown that groups of catalytic domains can be added or removed from these biosynthetic pathways leading to predictable changes in the polyketide product.^{31–34} An outstanding example of this flexibility can be seen in the work from Kosan Bioscience, where 14 different groups of polyketide synthase catalytic domains were recombined in a *de novo* fashion to generate upward of 70 designer polyketide products.^{32,33} The flexibility and amenability of these polyketide synthases to *de novo* design enables researchers to build new biosynthetic pathways to produce complex molecules through bacterial fermentation.

Application of the *de novo* pathway design to (+)-neopeltolide production is highly appealing as it would enable rapid and scalable production of the natural product *via* bacterial fermentation. However, because the mechanism for tetrahydropyran (THP) formation in polyketides is poorly characterized, it has not been possible to engineer *de novo* pathways to produce this functional group. In order to overcome this limitation, we are investigating a chemical

method for THP formation from functional groups easily accessible through *de novo* polyketide synthase pathway design, namely alcohols, olefins and carbonyls. For example, if a (+)-neopeltolide precursor such as **2.9** (Figure 2.4), which is easily accessible through *de novo* pathway engineering, can be chemically converted into (+)-neopeltolide **2.1**, then a fermentation route for reliable, sustainable production of this natural product can be established.

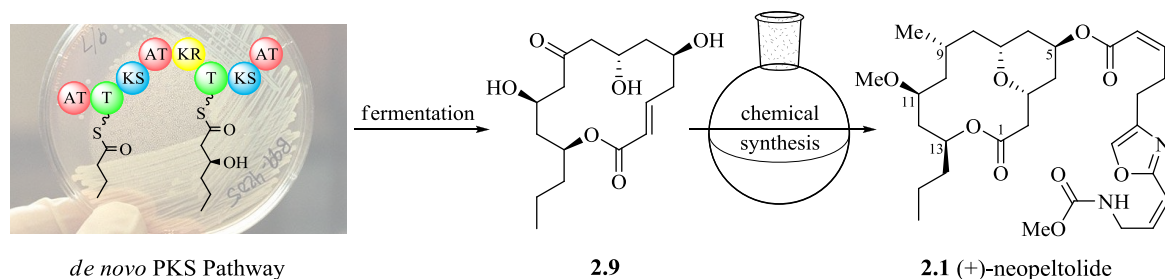


Figure 2.4 – A combined biosynthetic-synthetic approach to solve the limited supply problem for (+)-neopeltolide.

The immediate goal of this project has thus been to establish an oxa-conjugate addition route to the total synthesis of (+)-neopeltolide that takes advantage of biosynthetically accessible functional groups. Longer term goals include the development of a *de novo* biosynthetic pathway to access the THP precursor and to interface the chemical synthesis of the transannular THP ring with the fermentation based production of the precursor *via* a chemoenzymatic synthesis.

2.2.3 Transannular Oxa-Conjugate Addition in (+)-Neopeltolide Synthesis

The chemistry which fulfills the requirement of synthesizing the THP of neopeltolide from functional groups easily accessible by *de novo* engineered polyketide synthase systems is a transannular oxa-conjugate addition (Figure 2.4). A number of oxa-conjugate addition approaches have been used in the synthesis of the neopeltolide THP (Table 2.1); however, none of these approaches have been transannular oxa-conjugate additions.

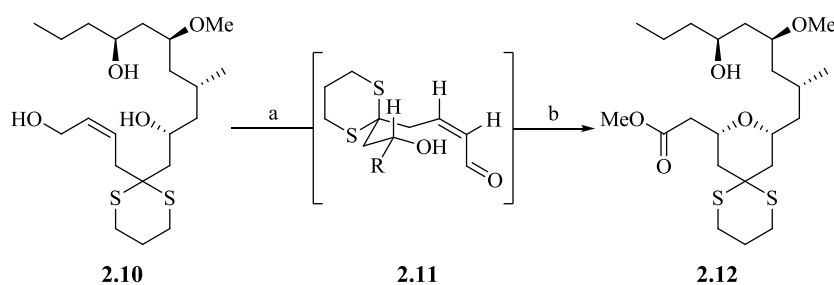
The first study to utilize an oxa-conjugate addition *en route* to (+)-neopeltolide was the formal synthesis by the Hong group in 2009.¹⁶ In their report, a tandem allylic oxidation/oxa-conjugate reaction was used in good yield. Following the oxidation of the primary alcohol **2.10**, the 1,3-diaxial interaction of the C6 α,β -unsaturated carbonyl group and the C4 dithiane was much greater than that of the C6 proton. Thus, the *cis*-tetrahydropyran of **2.12** was selectively formed through the lower-energy intermediate conformation **2.11** with greater than 20:1 diastereoselection (Figure 2.5).¹⁶

In the same year, Roulland *et al.* reported a formal synthesis of (+)-neopeltolide that implemented an ene-yne coupling/Michael addition sequence. This novel approach was successful

with moderate yields, providing the desired *cis*-tetrahydropyran **2.15** in a fully diastereoselective manner (Figure 2.5).⁹

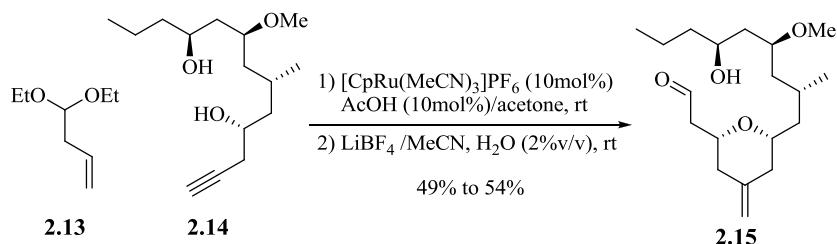
The final example of an oxa-conjugate addition route to the *cis*-tetrahydropyran ring system of (+)-neopeltolide was reported in 2010 with the Fuwa group's published synthesis of the natural product.^{14,17} They report that the intramolecular oxa-conjugate addition of **2.16** was best accomplished by treatment with DBU in refluxing toluene, yielding the thermodynamically favored^{35–37} 2,6-*cis*-tetrahydropyran with greater than 20:1 diastereoselectivity.¹⁴

Hong (2009)¹⁶



a) MnO_2 , DCM, rt, 3 h; b) triazolium iodide, MnO_2 , DBU, MeOH, rt, 21 h, 78% (over 2 steps)

Roulland (2009)⁹



Fuwa (2010)¹⁴

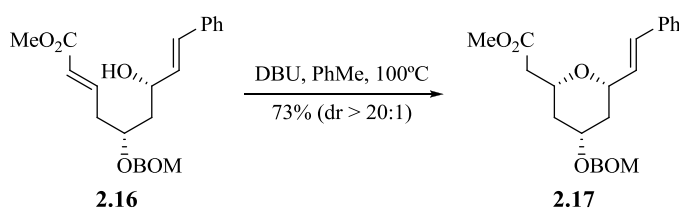


Figure 2.5 – Oxa-conjugate Michael addition strategies used to access the THP ring of (+)-neopeltolide.

Oxa-conjugate addition based routes clearly have proven effective in the diastereoselective formation of the 2,6-*cis*-tetrahydropyran ring system of (+)-neopeltolide. However, it is important to note that all of these examples have been performed on linear substrates. The conformational strain of the macrolactone ring system and its impact on the highly reversible oxa-conjugate addition has not been evaluated.

2.3.1 (+)-Neopeltolide Model System

In order to address the impact of the macrocyclic ring system on an oxa-conjugate addition approach to neopeltolide a model 14-membered macrolactone system with a ζ -hydroxy- α,β -unsaturated lactone system was synthesized and evaluated for the transannular oxa-conjugate addition reaction. This work was carried out by Burkhardt Wilke, a Ph.D. student in the Boddy lab.

Accessing the key α,β -unsaturated ester precursor **2.19** was envisaged via two plausible routes. In the first, ring-closing metathesis with acrylate **2.20** was based on literature precedence,^{38,39} and is supported by Kang's synthesis of the α,β -unsaturated carbonyl-containing narbonolide,⁴⁰ a macrolactone of the same size. Alternatively, classical Yamaguchi lactonization⁴¹ of **2.21** would readily provide the desired precursor, as confirmed by its heavily employed use in published syntheses of (+)-neopeltolide (Figure 2.6).^{1,2,7–12,17,20} Both synthetic precursors would be readily accessed from 1,7-heptanediol via a series of oxidations and allyl-elongations.

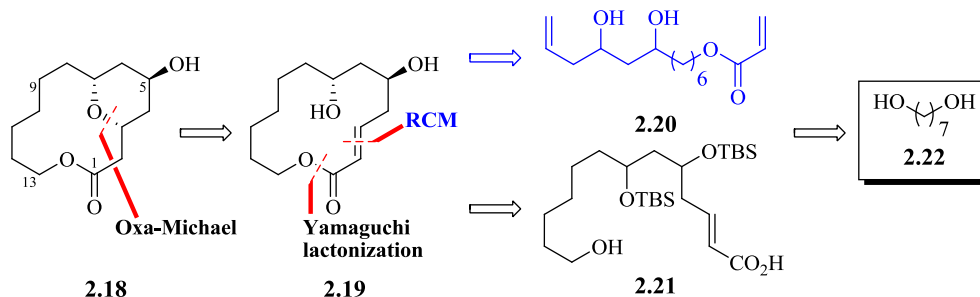


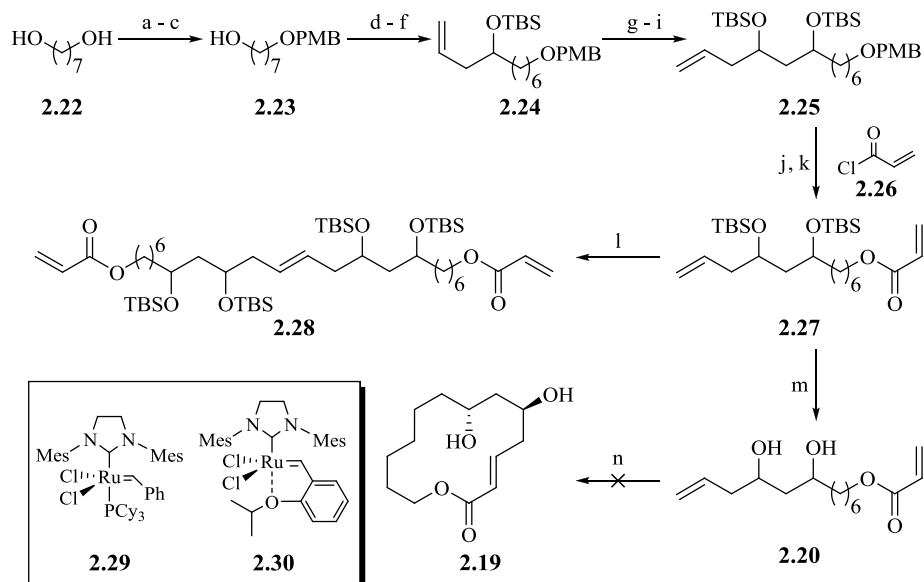
Figure 2.6 – Retrosynthetic analysis for the synthesis of a model system for the macrocyclic core of (+)-neopeltolide.

Synthesis of the oxa-Michael conjugate addition model system began with a three-step monofunctionalization of diol **2.22** via unpublished monoprotection conditions. The PMB-protected diol **2.23** was oxidized to its corresponding aldehyde using Parikh-Doering conditions,⁴² allylated under Grignard conditions^{43–45} and protected as its silyl ether **2.24**. Sharpless dihydroxylation and lead tetraacetate cleavage oxidized **2.24**,^{46–49} which was followed by the same allylation and protection steps. Subsequent treatment of **2.25** with DDQ and deprotection of the PMB ether yielded its primary alcohol, which underwent addition with acryloyl chloride to yield the ring-closing precursor **2.26**.

The ring-closing metathesis was evaluated under various conditions and two different metathesis catalysts **2.29** and **2.30** (Scheme 2.1). The second-generation Grubbs catalyst **2.29** lead exclusively to the dimerization of precursor **2.27**, which can be rationalized by the greater activity of the electron-rich terminal alkene in comparison to the electron-deficient acrylate in cross

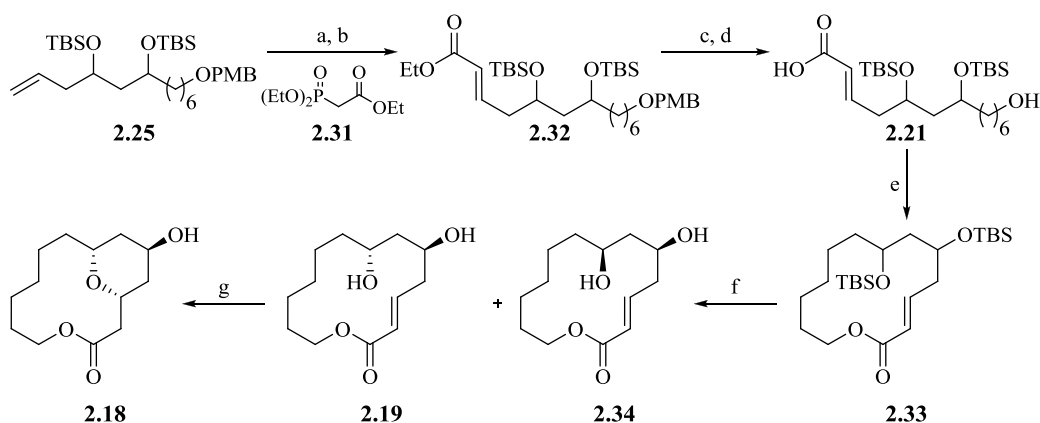
metathesis reactions. Use of the second-generation Hoveyda-Grubbs catalyst **2.30** resulted in uncharacterized decomposition of the starting material with no evidence of dimerization.

Reports of the steric bulk near the catalytic center contributing greatly to the success of similar reactions^{50,51} prompted the removal of both silyl ether protecting groups with TBAF to afford the dihydroxy intermediate **2.20** in excellent yield. Treatment with Grubbs' second-generation catalyst yielded the corresponding dimer product, albeit in very low yields. The use of second-generation Hoveyda-Grubbs catalyst consumed the starting material and gave no discernible dimerization; however, also failed to yield the expected macrolactone **2.19** (Scheme 2.1).



Scheme 2.1 – Conditions for Wilke's ring-closing metathesis approach to the model system of (+)-neopeltolide. a) Et₃N, TBSCl, hexanes:MeCN (3:1), rt, 2 d; b) *n*BuLi, PMBBBr, THF, 6 h; c) TsOH, MeOH, rt, 12 h, 50% (over 3 steps); d) SO₃·pyr, DMSO, DCM, Et₃N, 0 °C; e) allylMgBr, THF, 0 °C; f) TBSCl, imidazole, DMF, 48% (over 3 steps); g) K₂CO₃, K₃Fe(CN)₆, K₂OsO₇·(H₂O)₂ (in 15% NaOH w/w), *t*-BuOH:H₂O (1:1), 14 h; then Pb(OAc)₄, DCM; h) allylMgBr, THF, 0 °C; i) TBSCl, imidazole, DMF, 68% (over 3 steps); j) DDQ, DCM:deionizedH₂O (9:1), 0 °C; k) Et₃N, acryloyl chloride **2.26**, DMF (10 mol%), DCM, rt, 12 h, 74% (over 2 steps); l) G-II **2.29**, PhMe, reflux, 5 d; m) TBAF (1.0 M), THF, rt, 12 h, 92%; n) G-II **2.29**, GH-II **2.30**, PhMe, reflux, various conditions.

The unsuccessful ring-closing metathesis encouraged the alternative Yamaguchi approach to yield the desired α,β -unsaturated macrolactone **2.19** (Scheme 2.2). Conversion of the alkene intermediate **2.25** to its corresponding ester **2.32** was accomplished *via* Sharpless dihydroxylation^{46–49} and subsequent cleavage with lead tetraacetate, followed by Horner-Wadsworth-Emmons reaction between the aldehydic intermediate and phosphonate **2.31**.^{52–57} Saponification and PMB-deprotection of the α,β -unsaturated ethyl ester **2.32** yielded hydroxy acid **2.21**, which underwent Yamaguchi macrocyclization⁴¹ to provide macrolactone **2.33** in 75% yield.



Scheme 2.2 – Conditions for Wilke’s model system of (+)-neopeltolide. a) K_2CO_3 , $K_3Fe(CN)_6$, $K_2OsO_7 \cdot (H_2O)_2$ (in 15% NaOH w/w), t -BuOH:H₂O (1:1), 14 h; then $Pb(OAc)_4$, DCM; b) triethylphosphonoacetate **2.31**, KOH, THF, rt, 1 h, 30% (over 2 steps); c) DDQ, DCM:deionizedH₂O (9:1), 0 °C; d) LiOH (1.0 M), EtOH, rt, 14 h, 54% (over 2 steps); e) 2,4,6-trichlorobenzoyl chloride, Hünig’s base, benzene, rt, 14 h; then DMAP, rt, 2 h, 75%; f) HF, MeCN, 85%; g) DBU, d_6 -benzene, reflux.

With the macrocycle **2.33** in hand it was possible to evaluate the impact of the macrolactone ring on oxa-conjugate addition based THP-formation. The silyl protecting group was easily removed under standard conditions affording the *syn* and *anti* diols **2.19** and **2.34**, respectively. The diols could easily be distinguished using Rychnovsky’s method following conversions to their corresponding acetonides.⁵⁸ Numerous conditions were investigated to convert the *syn* diol into the THP **2.18** unsuccessfully. The THP product was only observed after prolonged heating in d_6 -benzene in the presence of DBU. The successful formation of the transannular tetrahydropyran suggests that this may be a viable synthetic route to neopeltolide; however, the forcing conditions required to access this framework indicate that this process is substantially more difficult than in the corresponding linear systems (Figure 2.5).^{9,16} However the stability of the THP in the natural product neopeltolide indicates that the retro-oxa-conjugate addition is not a kinetically favorable process. This suggests that it may be possible to use an oxa-conjugate addition approach to access the natural product.

2.3 Results and Discussion

2.3.2 Strategy Toward (+)-Neopeltolide

Based on our and previously reported data^{9,14,16} supporting the feasibility of an oxa-conjugate addition approach to neopeltolide, we commenced a total synthesis.

2.3.2.1 Retrosynthetic Analysis

The initial disconnection analysis for our synthesis of (+)-neopeltolide was heavily based on the total synthesis published by Panek *et al.*,¹² and conclusions from the model system. The biomimetic synthesis once again hinged upon the key oxa-conjugate conjugate addition incorporation of the tetrahydropyran moiety into the already cyclized macrolactone. Based on the challenges seen in our RCM route to the macrolactone, this approach was abandoned in favor of the well-documented Yamaguchi macrocyclization. The linear substrate **2.38** was envisioned to arise from the cross-metathesis precursor **2.39**, which could be obtained from sequential asymmetric allylations of **2.40**. The aldehyde **2.40** was envisioned from umpolung addition and setting of the *anti*-1,3-stereoselectivity via Evans-Tishchenko reduction. Key aldehydic intermediate **2.41** would be prepared from commercially available reagents using documented procedures (Figure 2.7).

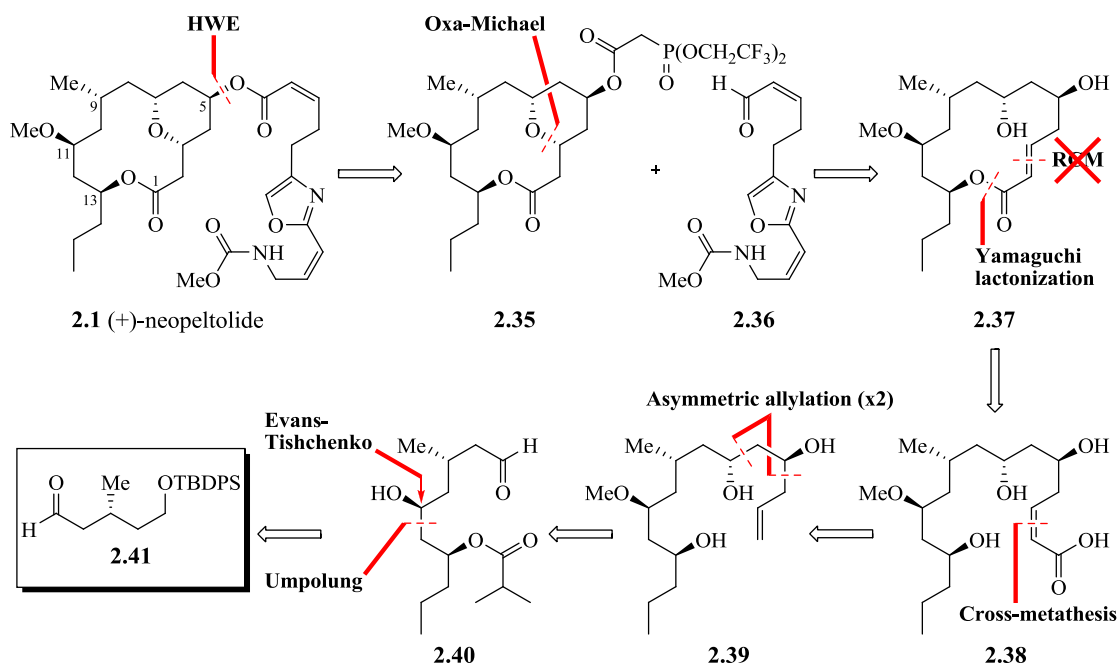


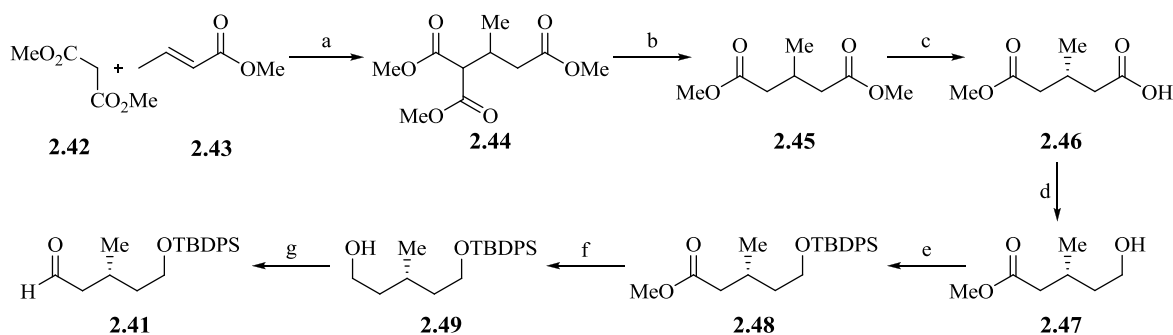
Figure 2.7 – Retrosynthetic analysis for the biomimetic synthesis of (+)-neopeltolide via a key oxa-Michael addition installation of the tetrahydropyran moiety following macrocyclization. The RCM approach to macrocyclization was abandoned due to challenges faced in the (+)-neopeltolide model system.

Herein I report my progress toward the synthesis outlined in Figure 2.7, and the conclusions made to date.

2.3.2.2 Key Intermediate Synthesis

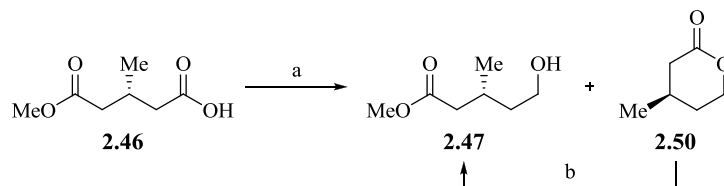
The synthesis of the key aldehydic intermediate began with the 1,4-addition of dimethylmalonate **2.42** to methylcrotonate **2.43**,⁵⁹ furnishing triester **2.44** in excellent yield. Krapcho decarboxylation^{60–62} yielded methyl 3-methylglutarate **2.45**, which subsequently

underwent a desymmetrization process *via* pig liver esterase at pH 7 to afford 94% of acid **2.46**^{63–69} in excellent enantiomeric purity (see Equation 2.2).⁷⁰ Selective reduction of the acid moiety using borane dimethyl sulfide⁷¹ afforded hydroxy ester **2.47** in good yield, which was immediately protected as its TBDPS silyl ether **2.48**.⁷² Hydride reduction of the monoester, and subsequent PCC oxidation furnished key aldehydic intermediate **2.41** in good overall yield (47% over 7 steps).^{73–75}



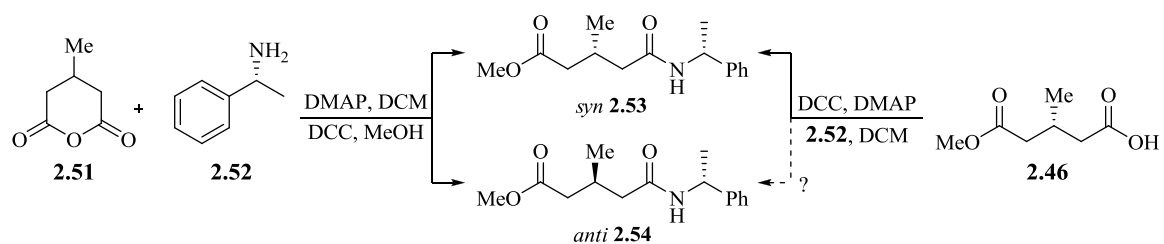
Scheme 2.3 – Conditions for the synthesis of key aldehydic intermediate **2.41** *en route* to (+)-neopeltolide. a) NaOMe, MeOH (2.05 M), reflux, 3 h, 90%; b) DMSO, H₂O, NaCl, reflux, 1 d, 85%; c) KPhos buffer (0.1 M), MeOH (10% v/v), pig liver esterase, NaOH, 94% (ee > 95:5); d) BH₃·Me₂S (1.7 M), THF, -78 °C to rt, 84%; e) TBDPSCl, imidazole, DMF, 95%; f) LAH, Et₂O, 0 °C, 98%; g) PCC, DCM, 84%.

During the aforementioned selective reduction of the acid substrate **2.46** using borane dimethyl sulfide, lactone side-product **2.50** was observed, as had been previously reported (Equation 2.1).^{20,66–68} The preferential reactivity of BH₃·Me₂S toward acids versus ester moieties provided excellent, and nearly exclusive reduction to the desired hydroxy ester **2.47** as was evident *via* ¹HNMR analysis of the reaction mixture; however, following alcoholic workup conditions, mixtures of a major side-product contaminant was as high as 50%. Workup conditions employed a quench of the borate esters with alcoholic solution (methanol or water), followed by dilution in EtOAc and separation of the organic layer using saturated sodium chloride solution. Subsequent re-conversion of lactone **2.50** into the open-chain alcohol **2.47** was accomplished in low yields due to the high volatility of the lactone, and was abandoned as a feasible, scalable option. Alterations were made to the initial workup that resulted in a dramatic increase in the desired hydroxy ester product selectivity. Following alcoholic quench of the reduction, the crude product was evaporated to dryness and the resulting white residue was then diluted in EtOAc and separated under typical workup. This procedural change minimized the formation of lactone side-product *via* the readily available 6-*exo* trig intramolecular cyclization, resulting in a greater than 20:1 ratio of desired alcohol **2.47** product.



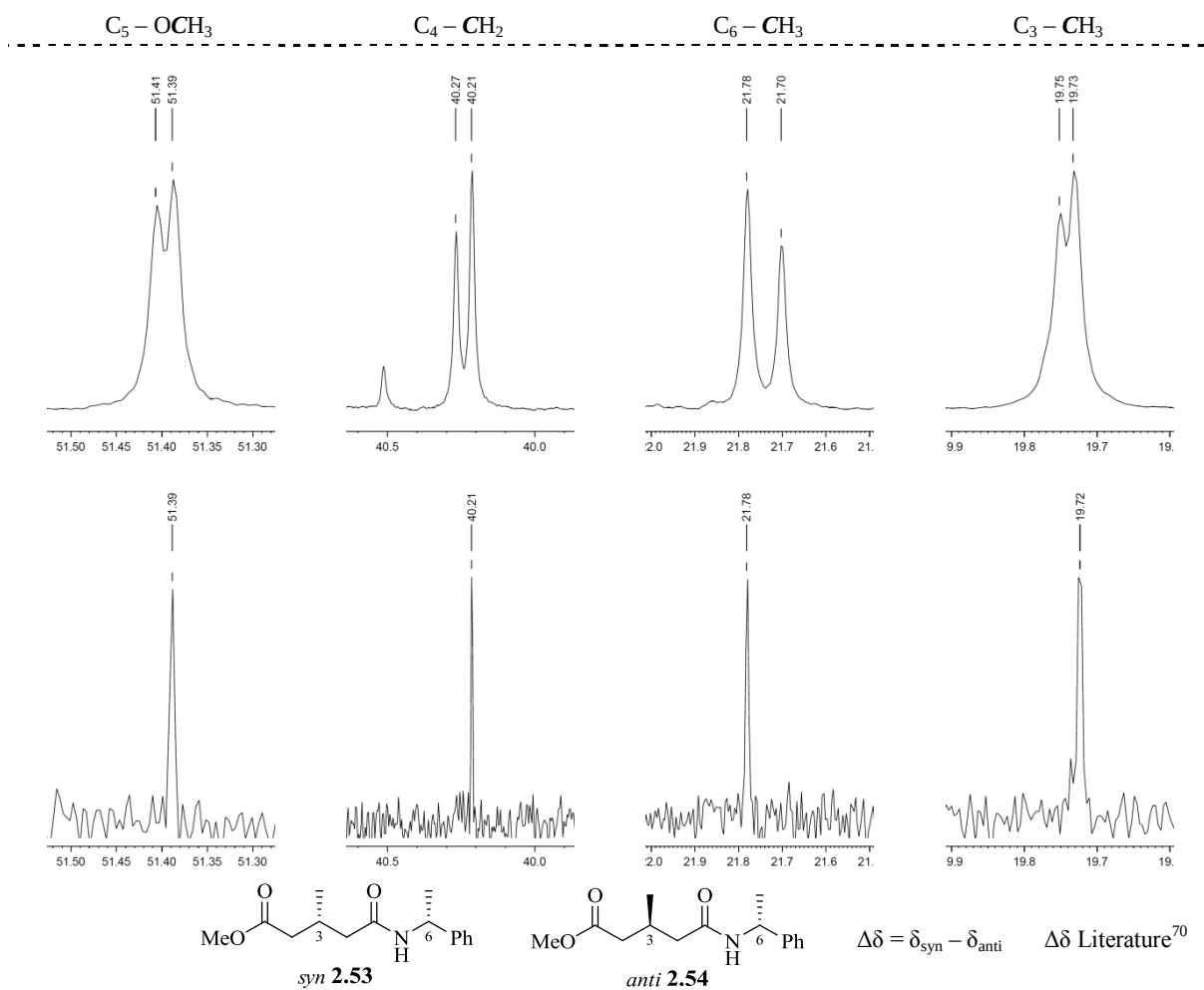
Equation 2.1 – Conditions for the selective reduction of monoester **2.46**.^{12,20,66–68,71} a) $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (1.7 M), THF, -78°C to rt, 84% (**2.47**:**2.50** > 20:1); b) NaOMe, MeOH, 16%.

The desymmetrization process using pig liver esterase is well-documented; however, the formation of diastereomers during stereoselective allylation of a product derived from precursor **2.46** led us to question the selectivity of this enzyme (*vide infra*). Consequently, the success of the stereoselective installation of the C9 methyl center, and subsequent determination of enantiomeric purity, was evaluated using two complementary NMR-based methods. The first technique was developed by Hoyer *et al.*, and employs (*R*)- α -methylbenzylamine **2.52** as a chiral auxiliary for ^{13}C NMR analysis based on anisotropic shielding effects (Equation 2.2).⁷⁰ The opening of 3-methylglutaric anhydride **2.51**, and coupling with **2.52** afforded diastereomeric amides *syn* **2.53** and *anti* **2.54** in a mixture that favored the *syn* product. Acid precursor **2.46** was treated with EDC, DMAP and (*R*)- α -methylbenzylamine generating the amide product and analyzed spectroscopically, which showed high diastereoselectivity for the *syn* amide product (greater than 95:5 ratio, Table 2.1). This result confirms the expected absolute configuration for the C9 methyl group and supports a high enantiomeric excess for acid **2.46** (> 95 % ee). Detailed analysis revealed that some of the ^{13}C signals are concentration-dependent, and that the data reported by Hoyer shows some discrepancies with the data we collected. Hoyer reports that β -methyl groups such as the C3 methyl in **2.53** and **2.54** appear further downfield in *syn* substrates in comparison to their *anti* counterparts.⁷⁰ However, as clearly indicated by the spectral comparison for C3- CH_3 , and supported by their relative intensities, the *syn* diastereomer is further upfield than its *anti* counterpart. Moreover, the $\Delta\delta$ value is over twice the relative value as that which was reported by Hoyer. Investigation into the role of sample concentration and conformation on spectroscopic data is currently ongoing.



Equation 2.2 – Conditions and general outline used for the NMR-based establishment of enantiomeric purity of acid **2.46** using (*R*)- α -methylbenzylamine **2.52** as a chiral auxiliary.⁷⁰

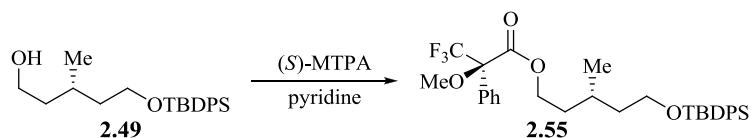
Table 2.1 – ¹³CNMR spectroscopic comparison of regions of interest for the diastereomeric excess analysis using Hoyer's method.⁷⁰ The top spectrum represents the diastereomeric mixture of *syn* **2.53** and *anti* **2.54**, while the bottom trace represents evaluated precursor **2.46** (Scheme 2.3). Spectroscopic analysis clearly indicates the exclusive formation of the *syn* diastereomer, and suggests an enantiomeric purity > 95% of **2.46**.



	δ_{syn}	δ_{anti}	$\Delta\delta = \delta_{\text{syn}} - \delta_{\text{anti}}$	$\Delta\delta$ Literature ⁷⁰
C ₃ –CH ₃	19.7237	19.7518	$\Delta\delta = -0.0281$	+0.013
C ₆ –CH ₃	21.7816	21.7028	$\Delta\delta = +0.0788$	n.d.*
C ₄ –CH ₂	40.2149	40.2688	$\Delta\delta = -0.0539$	n.d.*
C ₅ –OCH ₃	51.3887	51.4069	$\Delta\delta = -0.0182$	-0.015

* – not determined

Mosher's analysis^{76–80} of alcoholic precursor **2.49** provided additional support for the success of the enzymatic hydrolysis and determination of enantiomeric purity. The conversion of alcohol **2.49** to its corresponding (*R*)-Mosher ester **2.55** via acylation with (*S*)-MTPA allowed ¹HNMR analysis of the chemical shift separation between diastereomeric MTPA-methoxy peaks, corroborating an enantiomeric excess in greater than 95:5 ratio.⁷⁶ The success of this procedure relies on the complete derivatization of the alcohol to MTPA-ester **2.55**, so that the diastereomeric purity is truly reflective of the enantiomeric purity of **2.49**, and is sensitive enough to detect 1% of minor alcohol enantiomer (Equation 2.3).⁷⁶



Equation 2.3 – Conditions for Mosher's analysis of enantiomeric purity to determine the success of the enzymatic hydrolysis installation of the C9 methyl substituent.^{76–80}

The coupled success of both NMR-based methods of enantiopurity evaluation suggests high levels of enantiomeric enrichment are obtained from the enzymatic hydrolysis (ee > 95%), providing a stereoselective installation of the C9 methyl substituent.

2.3.2.3 Fragment Coupling Methodology

The stereoselective completion of aldehydic intermediate **2.41** provided an outlet for various fragment coupling transformations (Figure 2.8).

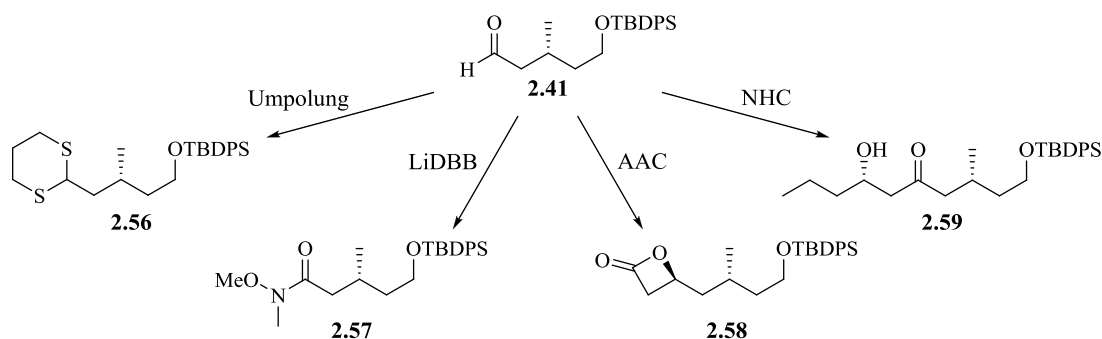
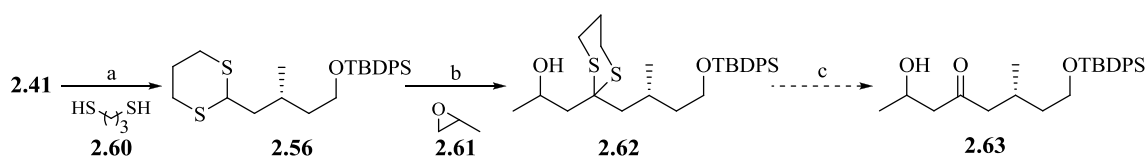


Figure 2.8 – Summary of synthetic transformations of aldehydic intermediate **2.41** studied *en route* to the installation of the required *anti* 1,3-stereoselectivity between C11–C13, and the completion of the C7–C16 fragment of (+)-neopeltolide.

Our initial attempts at elongation of intermediate **2.41** were based on the successful carbonyl umpolung chemistry employed by the Panek group *en route* to their total synthesis of (+)-neopeltolide.¹² The iodine-catalyzed dithioacetalization of aldehyde **2.41** furnished its corresponding dithiane intermediate, which is set for umpolung coupling with pentylene oxide to provide the complete carbon framework of the C7–C16 fragment of (+)-neopeltolide.⁸¹ The term

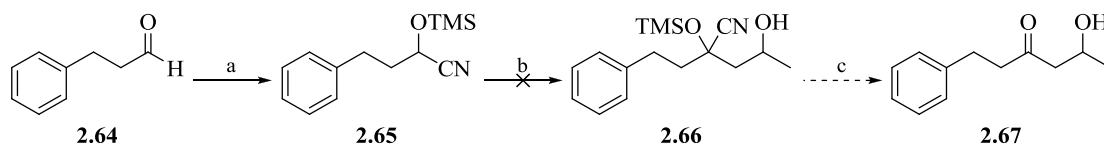
“umpolung” has been used when describing the inversion of reactivity that occurs when a typically electrophilic carbonyl group is transformed into a nucleophile.^{81–86}

Panek *et al.* reports the successful synthesis of dithiane **2.56** in greater than 85% yield;¹² however, the reproducibility of this transformation was not possible in our hands, providing yields ranging from 27–72%. Episodes of higher-yielding conversions allowed for investigation into the viability of the this route *via* the umpolung coupling of racemic propylene oxide.⁸⁷ The coupling of the nucleophilic dithiane with epoxide **2.61** afforded β -hydroxy intermediate **2.62** in low yields. Similar couplings have proven unexpectedly difficult in literature.^{85,88} Preliminary attempts to remove the dithiane protecting group and yield the β -hydroxy ketone **2.63** showed apparent success in accordance to ¹HNMR, but were not quantified.⁸⁹ This ketone intermediate would be the appropriate precursor for an Evans-Tishchenko treatment to install the *anti* 1,3-stereoselectivity of the C7-C16 fragment; however, the variability of yields in this route proved too inefficient for application to our total synthesis.



Scheme 2.4 – Conditions for the dithiane transformation of aldehydic intermediate **2.41** using umpolung chemistry *en route* to the installation of the required *anti* 1,3-stereoselectivity between C11-C13, and the completion of the C7-C16 fragment of (+)-neopeltolide.¹² a) 1,3-propanedithiol **2.60**, I₂, DCM, rt, variable yields (27 – 72%); b) *n*BuLi, THF, -65 °C, 3 h; then, **2.61**, DMPU, THF, 22%; c) I₂, H₂O, acetone, NaHCO₃.

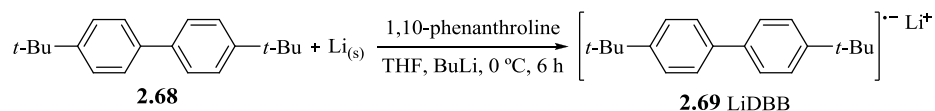
Ultimately, the inconsistent yields obtained during dithioacetalization of aldehyde **2.41** prompted investigation into alternative conditions for an umpolung addition with its corresponding epoxide.⁸¹ The canonical cyanide-type umpolung conditions were employed in an attempt to yield a Benzoin condensation-type coupling between the masked acyl anion equivalent and the corresponding epoxide (Scheme 2.5).^{81–86,90} A quantitative, solvent-free method afforded cyanohydrin **2.65**,⁸⁵ which subsequently was treated with umpolung conditions in attempts to couple to propylene oxide. Unfortunately none of the expected alcohol product **2.66** was obtained and only a complex uncharacterized product was obtained. Based on this result we halted the umpolung chemistry approach.



Scheme 2.5 – Alternate conditions for an umpolung addition model for the installation of required *anti* 1,3-stereoselectivity between C11-C13, and the completion of the C7-C16 fragment of (+)-neopeltolide. a) TMSCN, Et₃N (10 mol%), rt, 100%; b) *n*BuLi, THF, -65 °C, 3 h; then, **2.61**, DMPU, THF; c) TBAF, THF.

The formal synthesis of (+)-neopeltolide by the Taylor group employed Rychnovsky's method of reductive lithiation coupling⁹¹ between a Weinreb amide⁹² and thio-ether species to provide the complete carbon framework for their C7-C16 fragment.²⁰ Based on these successes, reductive lithiation coupling became an alternative route toward the completion of the C7-C16 fragment and studies were initiated.

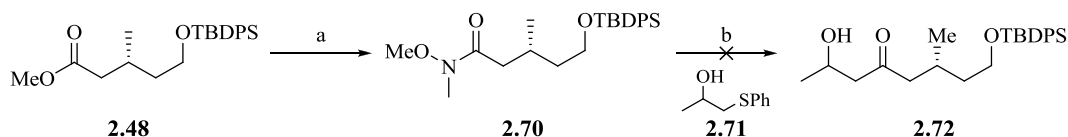
The preparation of the radical reagent lithium 4,4'-di-*tert*-butylbiphenylidene (LiDBB) proved deceptively difficult at the outset, despite the straight-forward scheme presented below (Equation 2.4). The reagent 1,10-phenanthroline was used as an indicator, and competently *indicated* the initial failures incurred. According to literature,²⁰ the conversion sequence of **2.68** to **2.69** would yield a wintergreen liquid upon completion; unfortunately, a dark red, clumpy product was continually obtained.⁹³ Attempts to correct this problem began with small procedural adjustments. The size of the elemental lithium being used was questioned and diligent preparation of lithium shavings were used to no apparent change in productivity. In accordance with a colleague, rubber septa used during radical chemistry could interfere with reactivity due to the monomer, plasticizer, or unreacted polymer present in the septa. As a result, a glass stopper was used in place; unfortunately, this did not provide the expected product. Surprisingly, it was concluded that the formation of lithium nitride (Li₃N)⁹³ was readily afforded under the “inert” atmosphere of N₂, and consequently was corrected by the simple exchange for argon gas.



Equation 2.4 – Synthesis of lithium 4,4'-di-*tert*-butylbiphenylidene (LiDBB) for reductive lithiation via Rychnovsky's procedure.^{91,94}

It was envisaged that the reductive lithiation coupling between **2.70** and **2.71** would afford the β -hydroxy ketone **2.72**, completing the carbon framework for the C7-C16 fragment. Synthesis began with the efficient preparation of amide **2.70**^{92,95} and thio-ether **2.71**²⁰ according to literature. In similar fashion to the umpolung chemistry studies, racemic propylene oxide was used for the synthesis of the thio-ether species **2.71** in order to test the viability of this synthetic route. Successful conversion would necessitate kinetic resolution^{96,97} of pentylene oxide and its

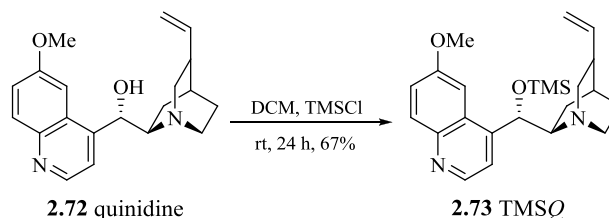
subsequent treatment with thiophenol²⁰ to provide the required number of carbons for (+)-neopeltolide. The corresponding substrate (analogous to **2.72**) obtained from the stereopure reagent could then introduce the desired *anti* 1,3-selectivity between C11-C13 via an Evans-Tishchenko reaction to yield intermediate **2.40**, and undergo subsequent elongation (see Figure 2.7).



Scheme 2.6 – Conditions for the reductive lithiation of a Weinreb amide approach *en route* to the installation of the required *anti* 1,3-stereoselectivity between C11-C13, and the completion of the C7-C16 fragment of (+)-neopeltolide.^{20,91,94} a) Me(MeO)NH·HCl, *i*PrMgCl, THF, 72%; b) **2.71**, 1,10-phenanthroline, *n*BuLi, LiDBB, THF:hexanes (1:1), -78 °C, 1 h; then, **2.70**, THF, -78 °C, 2 d.

Multiple coupling attempts between Weinreb amide **2.70** and thio-ether **2.71** employing various procedural modifications did not lead to formation of the desired hydroxyl-ketone product. In accordance with the seminal publication on the use of LiDBB,⁹⁸ its dependence on temperature is the most crucial variable to control. Success is best obtained at temperatures consistently at, or below -78 °C, as anion trapping drops dramatically as the temperature rises. In addition, the stability of the lithium reagent is lost at temperatures above -50 °C. Due to not having the equipment required to maintain this temperature for the two day reaction, this route was thus also abandoned.

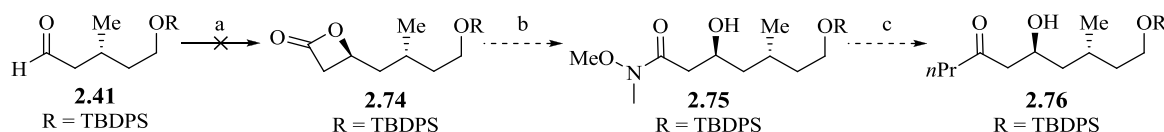
The enantioselective synthesis of (–)-pironetin by the Nelson group⁹⁹ successfully extended the Wynberg ketene-aldehyde cycloaddition to a structurally diverse aldehyde.^{100–103} Nelson reports an alkaloid-catalyzed acyl halide-aldehyde cyclocondensation (AAC) to afford an enantioenriched β -lactone using a cinchona catalyst available from commercial reagents.¹⁰⁴ High enantio- and diastereoselectivity in the asymmetric synthesis suggested the AAC reaction was a tempting alternative toward the completion of the C7-C16 fragment of (+)-neopeltolide.



Equation 2.5 – Synthesis of the trimethylsilyl-quinidine (TMSQ) catalyst **2.73** for cinchona alkaloid-catalyzed acyl halide-aldehyde cycloaddition reaction.^{104,105}

The preparation of the trimethylsilyl quinidine (TMSQ) catalyst simply required the silyl protection of commercially available quinidine (Equation 2.5).¹⁰⁴ It was envisaged that following

the conversion of acetyl chloride into its corresponding ketene, TMSQ catalyst would bind to it with its chiral tertiary amine and impose a facial bias through the corresponding ammonium enolate.¹⁰⁴ Subsequent [2+2] cycloaddition would yield optically enriched β -lactone **2.74**, which would be opened as its corresponding Weinreb amide **2.75** under standard protocol.⁹⁵ Exchange of the amide for the required *n*-propyl chain would afford **2.76**, and provide the full carbon framework for the C7-C16 fragment of (+)-neopeltolide.



Scheme 2.7 – Conditions and outline for the AAC transformation of aldehydic intermediate **2.41**, *en route* to the installation of the required *anti* 1,3-stereoselectivity between C11-C13, and the completion of the C7-C16 fragment of (+)-neopeltolide. a) **2.73** (10 mol%), LiClO₄, *i*PrNEt, -78 °C; b) Me(MeO)NH·HCl, *i*PrMgCl, THF; c) *n*PrMgCl, Et₂O; then HCl.

Difficulties were faced during the initial cycloaddition step, prohibiting further elaboration of the proposed synthetic route (Scheme 2.7). Although the route was abandoned, it is believed after further considerations that ketene formation was not realized under the set conditions. Future investigation warrants modifications to the proposed conditions using substrate **2.41** and a model system using commercial ketene and aldehyde reagents.

We then recognized that an umpolung approach where a carbonyl is directly added to an epoxide is a highly efficient route to the important C7-C16 fragment of (+)-neopeltolide. We therefore further investigated alternatives to the dithiane and cyanohydrin conditions that we had previously investigated. *N*-heterocyclic carbenes are well-documented for the generation of acyl anion equivalents.^{106–109} These nucleophiles are well-known to couple with a variety of electrophiles, providing many different functional group products, however, there is no precedence for direct coupling between an aldehyde and an epoxide. To investigate the viability of this synthetic approach, a series of reactions were tested under varying conditions (including NHC catalyst, catalyst loading, base, and temperature).

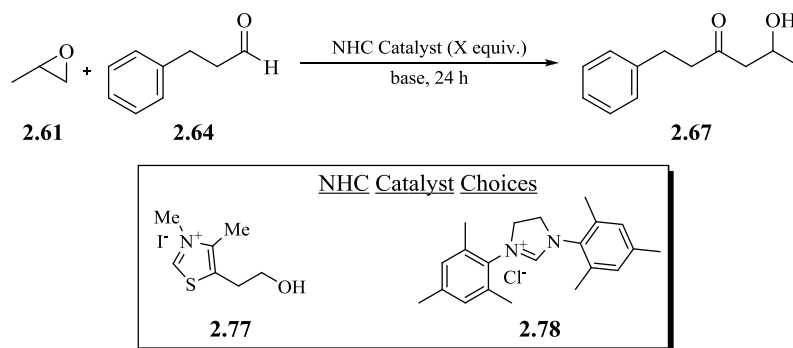
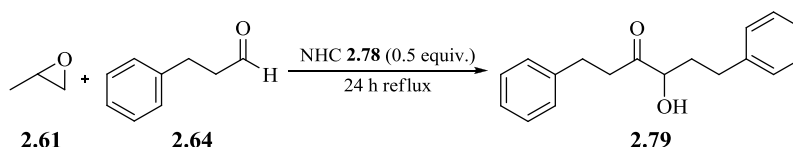


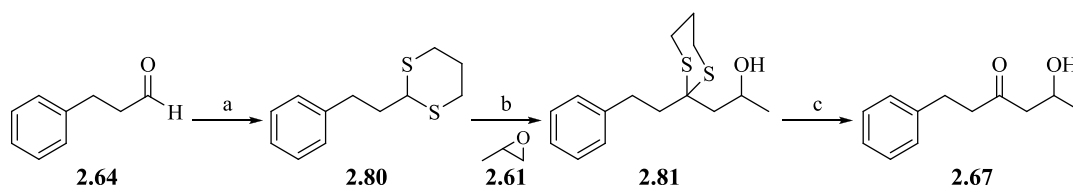
Figure 2.9 – General outline for the *N*-heterocyclic carbene mediated direct-addition of propylene oxide into an aldehydic precursor. Two NHC catalysts – 5-(2-Hydroxyethyl)-3,4-dimethylthiazolium iodide **2.77**, and 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride **2.78** – were employed during this study under various sets of conditions.

The employment of both thiazolium and imidazolium reagents **2.77** and **2.78** ranging in concentrations from catalytic (10 mol%) to stoichiometric (1.0 equiv.), temperatures ranging from 0 °C to refluxing (120 °C), various bases (Et₃N, NaHMDS, K₂CO₃) and solvents (DCM, DMF, 1,4-dioxane, toluene, propylene oxide **2.61**) consistently resulted in a tar residue. Surprisingly, one experiment yielded a crude NMR with peaks of apparent interest. Upon purification, it was realized that a Benzoin cross-coupling product **2.79** had been isolated. This result suggested that the employed conditions remained too non-nucleophilic enough to effectively activate the system for the opening of the epoxide. However, subsequent trials and manipulation of conditions could not yield the desired product **2.67**.



Equation 2.6 – Conditions for unexpected Benzoin cross-coupling product isolated during the *N*-heterocyclic carbene mediated direct-addition of propylene oxide into an aldehydic precursor studies.

In order to efficiently monitor this study, an authentic standard was required for spectroscopic comparison that could identify crude products with similar peaks of interest. An efficient dithiane masking of hydrocinnamaldehyde successfully inverted the polarity of the electrophilic aldehyde, allowing subsequent coupling with epoxide **2.61**. The carbonyl was deprotected using solid iodine and sodium bicarbonate in an acetone:water (6:1) solution. With the standard in hand, quick spectroscopic analysis was possible to determine potential efficacy of the studied experiments. Following multiple combinations of transformation conditions, successful coupling using the NHC approach were not realized, and the study was suspended.



Scheme 2.8 – Conditions for the synthesis of an authentic standard **2.67** for the *N*-heterocyclic carbene mediated addition of epoxide studies, for the synthesis of the C7-C16 fragment of (+)-neopeltolide. a) $\text{BF}_3 \cdot \text{OEt}_2$, 1,3-propanedithiol, DCM, quantitative; b) $n\text{BuLi}$ (1.6 M in THF), THF; then, **2.61**, DMPU, THF, 97%; c) I_2 , NaHCO_3 , acetone:water (6:1, 0.1 M), 48%.

While development of an NHC catalyzed coupling of aldehydes to epoxides would provide a powerful alternative to the aldol reaction in the construction of β -hydroxy ketones, the limited electrophilicity of the epoxide, and limited nucleophilicity of the acyl anion intermediate, coupled with the high electrophilicity of the aldehyde starting material made this reaction scheme incompatible with the desired cross-coupling chemistry. Future investigation into this novel coupling approach would necessitate activation of the epoxide to increase its electrophilicity, and to promote the intermolecular coupling.

2.3.3 Convergent Synthetic Strategy Toward (+)-Neopeltolide

The difficulties faced during the attempted linear elongation process of the C7-C16 fragment of (+)-neopeltolide prompted a retrosynthetic re-evaluation. As a linear synthesis sees the overall yield drop quickly with each additional reaction step required, the obvious solution was to utilize a more convergent strategy. A convergent synthesis is most beneficial in its application to complex molecule total synthesis, allowing the use of multiple fragment couplings from independent syntheses. Although a convergent synthesis is a deviation from our original approach which tracks with the linear nature of the biosynthesis of neopeltolide, it does not dramatically alter the project goals of testing the feasibility of THP formation from PKS accessible functional groups.

Kinetic and thermodynamically controlled oxa-conjugate additions have proven to be effective transformations for pyran synthesis. In the total synthesis of apicularen A, a transannular dihydropyrone **2.83** was assembled *via* reversible acid-catalyzed addition into an α,β -unsaturated ketone.^{110–112} Though the conditions are arguably non-natural, Rizzacasa was looking to generate the thermodynamically stable product from a mixture of diastereomers at the C13 hydroxyl group. This equilibrium goes through an oxonium ring opening sequence, and represents their optimized conditions (Figure 2.10).

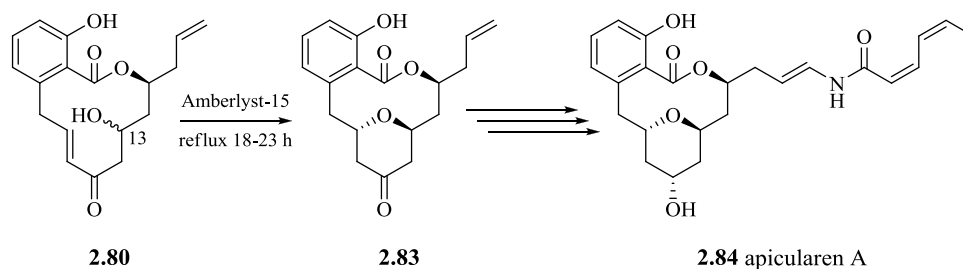


Figure 2.10 – Thermodynamic oxa-Michael addition in the total synthesis of apicularen A by Rizzacasa *et al.*^{110,111}

The successes of the tetrahydropyran installation in apicularen A, combined with the knowledge that *cis*-2,6-disubstituted tetrahydropyrans are thermodynamically favored,^{35–37} inspired a new retrosynthetic analysis (Figure 2.11).

2.3.3.1 Retrosynthetic Analysis

The key disconnection for the current synthetic strategy toward (+)-neopeltolide remains hinged upon an oxa-Michael conjugate addition incorporation of the THP ring into the already closed macrolactone system. Unlike previous macrolactone systems, however, the α,β -unsaturation is not conjugated to the ester carbonyl, but within the system that will produce a 4-ketopyran containing compound analogous to Rizzacasa's apicularen A.^{110,111} Convergence of aldehydic fragment **2.88** and phosphonate **2.87** via a Horner-Wadsworth-Emmons reaction completes the carbon framework for (+)-neopeltolide.^{52–57} Aldehydic fragment **2.88** is readily available from the previously synthesized intermediate **2.41** through a series of asymmetric allylation reactions, while phosphonate **2.87** can be accessed from commercially available dimethyl-1,3-acetonedicarboxylate **2.89** (Figure 2.11). There exists additional benefit to this synthetic route in that the 6-*endo* trig addition into the α,β -unsaturated ketone system is favored far greater than the 6-*exo* trig addition into the α,β -unsaturated ester system of the original synthetic route.¹¹³ The revised route should prove substantially faster and efficient in this new chemical environment for the transannular oxa-conjugate addition, and rely solely on the conformational strain of the macrolactone.

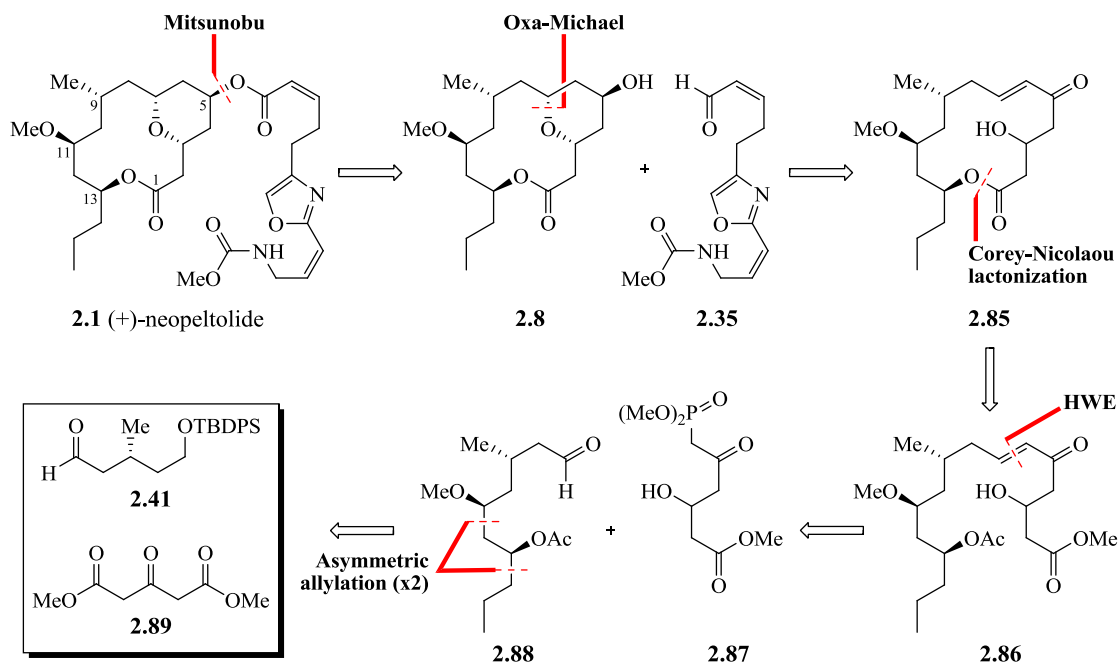
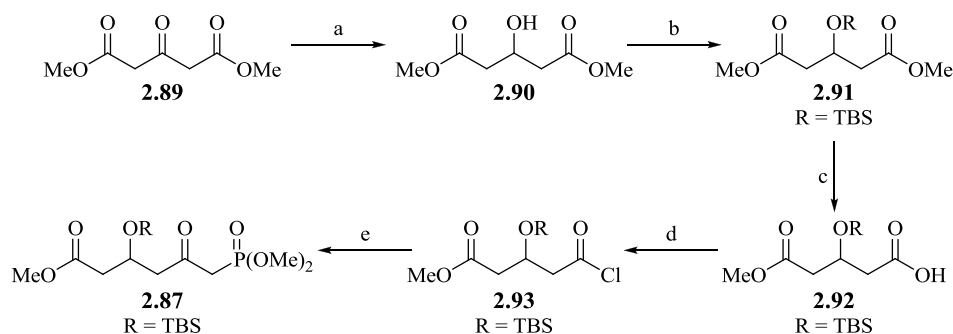


Figure 2.11 – Retrosynthetic analysis for the convergent synthesis of (+)-neopeltolide via a key oxa-Michael addition installation of the tetrahydropyran moiety following macrocyclization.

Herein reports the progress toward the synthesis outlined in Figure 2.11 and the conclusions made to date.

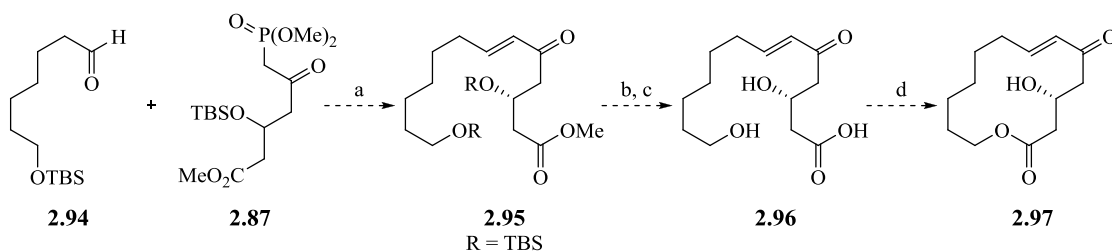
2.3.3.2 C1-C6 Fragment Synthesis

Synthesis of the C1-C6 phosphonate fragment began with the selective reduction of the commercially available dimethyl-1,3-acetonedicarboxylate **2.89** using sodium borohydride, to afford the meso intermediate **2.90** in good yield. Protection of the free alcohol to its corresponding TBDPS silyl ether⁷² allowed hydrolysis to proceed smoothly, affording the stable monoester intermediate **2.92**. Transformation to the acid chloride and subsequent addition of DMMP completed the synthesis of the C1-C6 phosphonate fragment in an un-optimized 39% over two steps (Scheme 2.9).



Scheme 2.9 – Conditions for the synthesis of the C1-C6 fragment of (+)-neopeltolide. a) NaBH_4 , MeOH, 0 °C, 70%; b) TBSCl, imidazole, DMF, rt, 12 h, 79%; c) NaOH (1.0 M), MeOH:H₂O (2:1), rt, 24 h, 86%; d) $(\text{COCl})_2$, DMF (10 mol%), PhMe, -78 °C to rt, quantitative; e) $n\text{BuLi}$, DMMP, THF, -78 °C; then **2.93**, -78 °C to -50 °C, 39%.

The successful isolation of phosphonate **2.87** prompted preliminary investigation into the viability of the proposed Horner-Wadsworth-Emmons reaction. The analysis of the crude material of this preliminary study suggested formation of the HWE product under standard conditions,^{52–57} albeit in low yield. Studies toward the optimization of this reaction are ongoing.



Scheme 2.10 – Proposed conditions and synthetic outline to test the viability, and optimization of the HWE reaction. a) LiCl, 4 Å ms, Hünig's base, **2.87**, MeCN, rt; then **2.94**, 24 h; b) TBAF, THF, rt; c) LiOH (1.0 M), EtOH, rt, 14 h; d) 2,2'-dipyridyl disulfide, PPh₃, benzene, rt; then benzene reflux, 12 h.

Completion of the proposed synthetic route of Scheme 2.10 will provide sound evidence for the optimal conditions required for the synthesis of (+)-neopeltolide, and will also act as an alternative route to the (+)-neopeltolide model system (*vide supra*).

2.3.3.3 C7-C16 Fragment Synthesis

Synthesis of the C7-C16 aldehydic intermediate **2.88** began with the asymmetric allylation of **2.41** using Brown's conditions,^{114,115} and the subsequent methylation of the corresponding homoallylic alcohol.¹¹⁶ Multiple trials of this allylation process consistently afforded only a modest 40% yield, but provides high stereoselectivity as established *via* spectroscopic analysis (Figure 2.12).

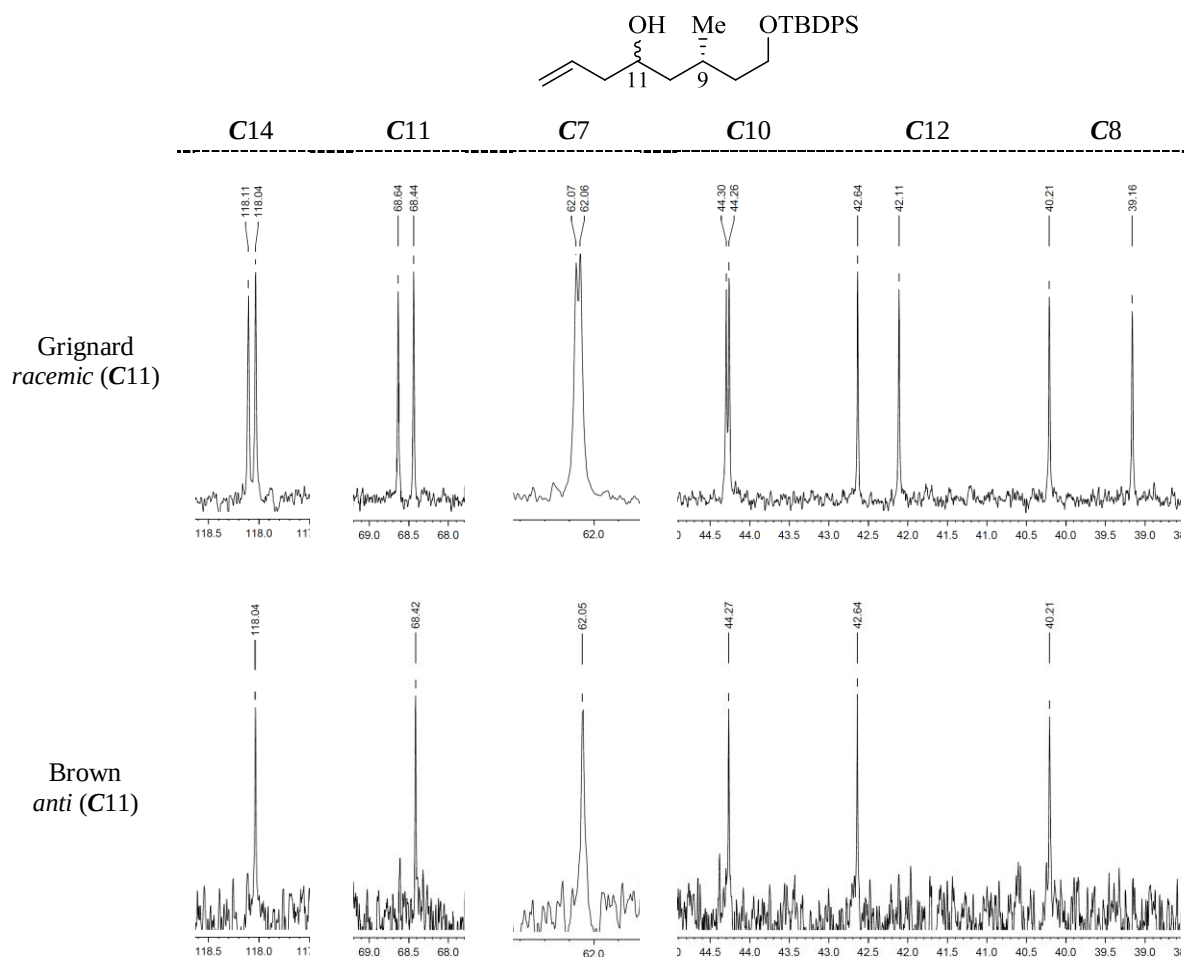


Figure 2.12 – Spectroscopic comparison of select carbon peaks highlighting the stereoselectivity of the Brown allylation, as contrasted against the racemic Grignard allylation procedure. ^{13}C NMR data shows exclusive formation of the 1,3-*anti* relationship between C9-C11 via the asymmetric Brown allylation,^{114,115} suggesting a diastereomeric ratio > 95:5 in **2.98**.

The consistently low yielding Brown allylation prompted investigation into alternative asymmetric procedures and reagents. A well-established route employs the use of Leighton's reagent^{117–119} and requires much milder conditions compared to the stringent procedure of Brown (Equation 2.7).^{114,115} Unfortunately, the preliminary testing of Leighton's reagent and procedure did not prove superior to the results obtained via Brown's conditions. In fact, poorer yields were obtained, which combined with qualitative comparisons of diastereomeric ratios (Figure 2.13) suggests Leighton's conditions were less selective with precursor **2.41** *en route* to the synthesis of the C7-C16 fragment of (+)-neopeltolide.



Equation 2.7 – Alternative stereoselective allylation conditions for the synthesis of homoallylic alcohol **2.98**.^{117–119}

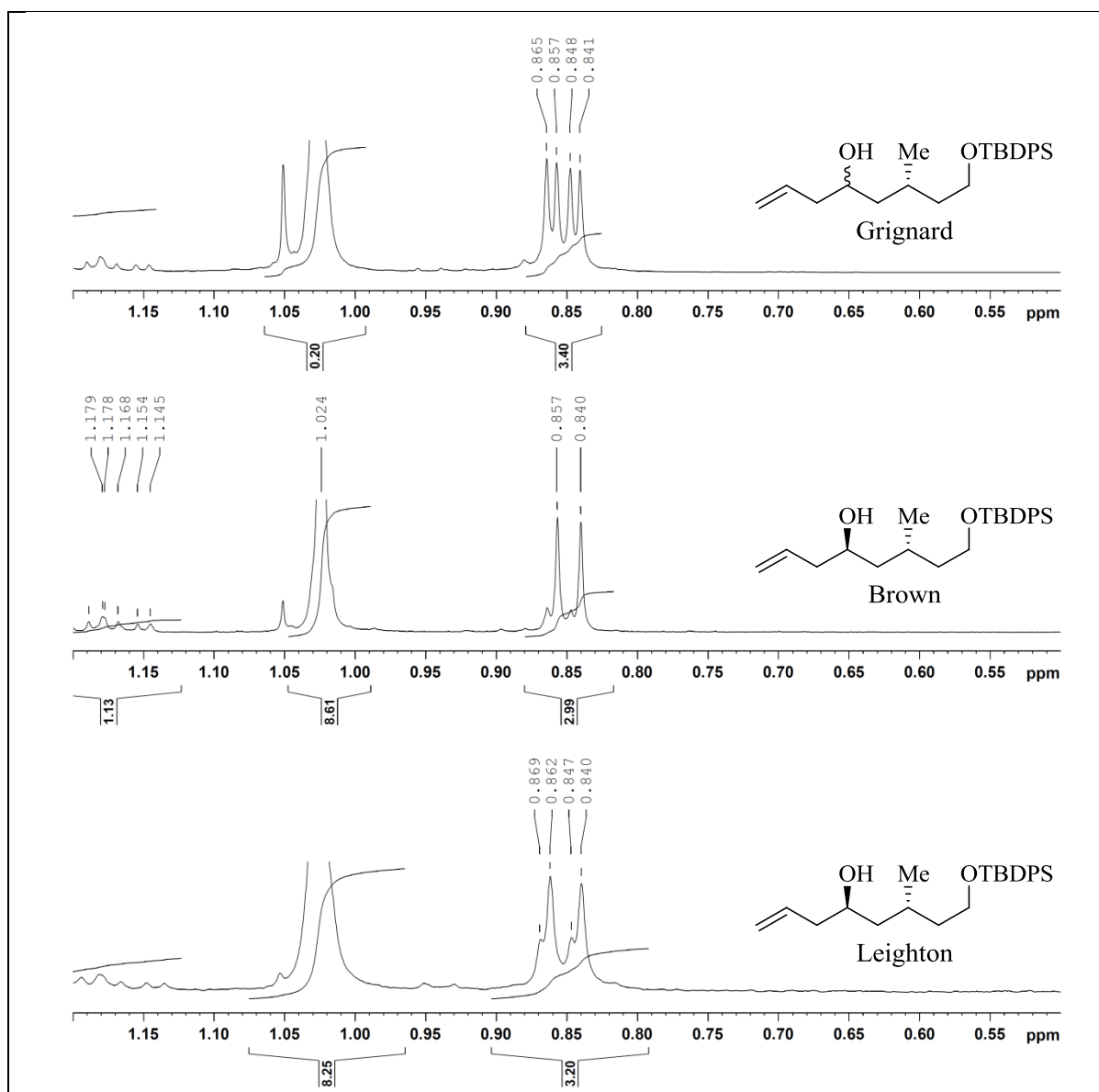
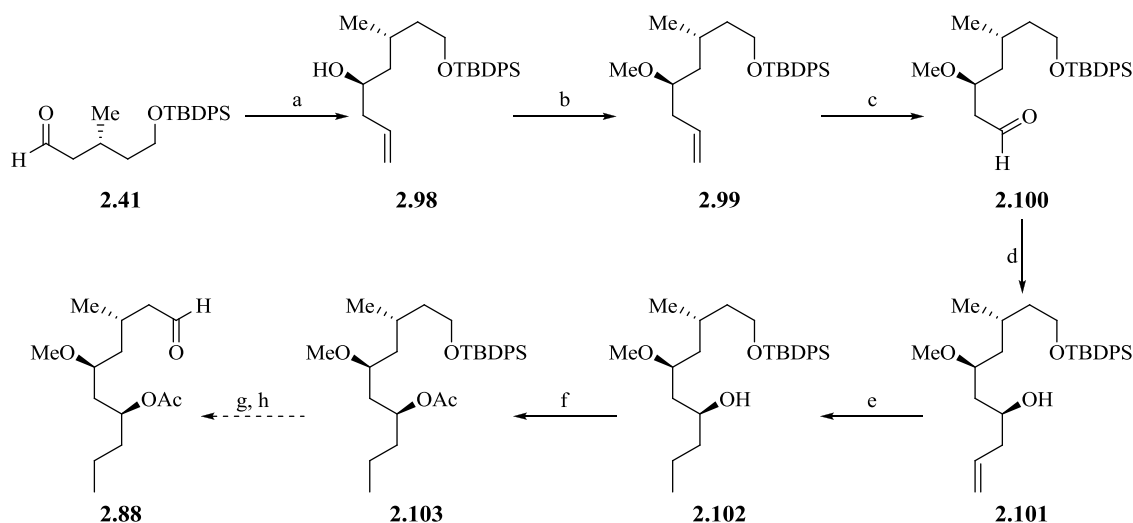


Figure 2.13 – Spectroscopic comparison of C9 methyl peak that highlights the stereoselectivity of the Brown and Leighton asymmetric allylations methods.^{114,115,117–119}



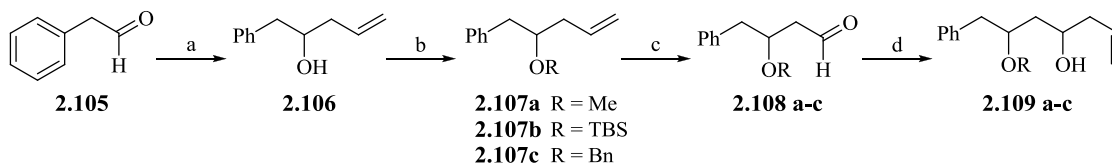
Scheme 2.11 – Conditions and outline for the synthesis of the C7-C16 fragment **2.88** via a stereoselective allylation approach from aldehydic intermediate **2.41**. a) (+)-Ipc₂BAllyl, Et₂O, -100 °C to -78 °C; then NaOH, H₂O₂, reflux, 1 h, 40%; b) MeI, NaH, THF, 1 d, 93%; c) K₂CO₃, K₃Fe(CN)₆, K₂OsO₇·(H₂O)₂, *t*-BuOH:H₂O (1:1), rt, 12 h; then Pb(OAc)₄, DCM, 30 Min, 94%; d) TiCl₄, allyltrimethylsilane, DCM, -78 °C, 1 h, 78%^{*}; e) H₂, Pd/C, EtOH, 76%; f) acetic anhydride, Et₃N, DCM, DMAP (5 mol%), 92% (crude); g) TBAF, THF, rt; h) K₂CO₃, K₃Fe(CN)₆, K₂OsO₇·(H₂O)₂, *t*-BuOH:H₂O (1:1), rt; then Pb(OAc)₄, DCM. ^{*}Yield represents initial studies, where diastereomeric mixtures were obtained.

The terminal alkene of **2.99** underwent Sharpless dihydroxylation,^{46–49} followed by lead tetraacetate cleavage to yield **2.100** in excellent yield over two steps. This β -alkoxy aldehyde was envisioned to undergo an asymmetric Sakurai allylation process to yield the desired *anti* 1,3-stereoselective relationship^{120–128} whilst completing the carbon framework for the C7-C16 fragment of (+)-neopeltolide. Unfortunately, the aforementioned (Section 2.3) formation of diastereomers during this allylation process was realized. This result was surprising and was initially believed to be the result of substrate resolution during the enzymatic hydrolysis during aldehyde **2.41** synthesis (Scheme 2.3). Continuation of the proposed synthetic route via hydrogenation and subsequent acetyl protection of the homoallylic alcohol tested its feasibility, but these preliminary studies were retired due to an inadequate supply of material.

Upon reaching the Sakurai reaction with new material that had undergone NMR-based evaluation of its enantiomeric purity,⁷⁰ circumvention of the previous selectivity challenge was expected. Once again, however, reaction selectivity was a problem and diastereomeric ratios of approximately 3:1 were consistently observed. Literature does not corroborate this observation, and triggered the establishment of a model system to evaluate the effect of various conditions and β -substituents on the Sakurai reaction selectivity.

2.3.3.4 Anti 1,3-Stereoselective Sakurai Model

The unexpected results observed during the synthesis of the C7-C16 fragment of (+)-neopeltolide necessitated the development of a model system for the Sakurai reaction. The model system required a substrate that is comparable to that of the aldehydic intermediate **2.100** of the C7-C16 fragment, and would easily allow systematic evaluation of several modifications. Phenylacetaldehyde **2.105** was chosen as the precursor material for the model system due to its comparable bulk, low cost, high stability and general ease of chemical manipulation.



Scheme 2.12 – Conditions for the synthesis of Sakurai allylation model system standard precursors with varying β -position protecting groups. a) allylMgBr, Et₂O, 75%; b) *condition set a*: MeI, NaH, THF, 100%; *condition set b*: TBSCl, imidazole, DMF, 96%; *condition set c*: BnBr, NaH, DMF, 87%; c) K₂CO₃, K₃Fe(CN)₆, K₂OsO₇·(H₂O)₂, *t*-BuOH:H₂O (1:1), rt, 12 h; then Pb(OAc)₄, DCM, 30 Min, 58% (**2.108a**), 53% (**2.108b**), 44% (**2.108c**); d) allylMgBr, Et₂O.

Synthesis of the Sakurai allylation model system began with a non-selective Grignard allylation of phenylacetaldehyde **2.105**, yielding large quantities of homoallylic alcohol **2.106**.^{43–45} Three protecting groups were subsequently affixed to evaluate the effect that the β -substituent has on the selectivity of the reaction – the required methyl ether **2.107a**, a non-coordinating silyl ether **2.107b**, and a benzyl ether **2.107c** which has shown success in literature Sakurai reports¹²⁹ (Scheme 2.12). Sharpless dihydroxylation^{46–49} of the terminal alkene, and subsequent lead tetraacetate cleavage provided the corresponding aldehyde products **2.108a-c**. A second non-selective Grignard allylation of aldehydes **2.108a-c** afforded authentic standards for spectroscopic analysis of the Sakurai study (Table 2.2).

Table 2.2 – Summary of the stereoselective Sakurai allylation model system *via* precursors with varying β -position substituents under multiple Lewis acid concentrations. Averages of yields (reported as percentages) and diastereomeric ratios (*syn:anti*) are presented relative to 1,4-dimethoxybenzene (0.25eq) as an internal ^1H NMR standard. Model system studies remain ongoing.

	2.108a R = Me 2.108b R = TBS 2.108c R = Bn	2.109a R = Me 2.109b R = TBS 2.109c R = Bn	
	2.109a (–OMe)	2.109b (–OTBS)	2.109c (–OBn)
0.150 equiv.	9.0 ± 0.7 (9:2)	8 ± 0.7 (1:1)	-
0.250 equiv.	25 ± 11 (9:1)	12 ± 4.2 (1:1)	-
0.375 equiv.	22 ± 4.9 (8:3)	-	-
0.500 equiv.	47 ± 13 (6:1)	7 ± 0.7 (1:1)	62
0.650 equiv.	55 ± 2.1 (9:2)	18 ± 6.1 (3:2)	-
0.750 equiv.	77 ± 21 (5:2)	24 ± 9.3 (2:1)	59
1.000 equiv.	73 ± 8.7 (1:1)	35 ± 7.2 (2:1)	15

Based on the initial results of the Sakurai model system, it was envisaged that a 0.65 equivalent of the Lewis acid, titanium(IV) tetrachloride would yield adequate amounts of product with the desired stereoselectivity when applied to the (+)-neopeltolide precursor. Unexpectedly, the diastereomeric ratio remained approximately 1:1 between *syn* and *anti* products, challenging the well-established preference for β -alkoxy aldehydes to afford good level of 1,3-*anti*-diastereoselection under the Cram-chelation model *via* a half-chair transition state (Figure 2.14). Potential causes of this result could be that the β -methoxy substituent is either not chelating with the TiCl_4 due to strain, or perhaps is in competition with the silyl ether. In the event that it does not participate in chelation, the Felkin-Anh product (1,3-*syn*) is favored. If competition exists between the silyl ether, the 1,3-*syn* product is again favored due to the pseudo-*trans*-decalin conformation of the chelated transition state. Finally, perhaps the methyl ether does not provide great enough dipole interactions to induce the polar model of Cram and Reetz, which orients itself preferentially for *anti* nucleophilic attack.^{130,131} These preliminary results warrant continued investigation using the outlined model system, in order to help determine the lack of diastereoselection.

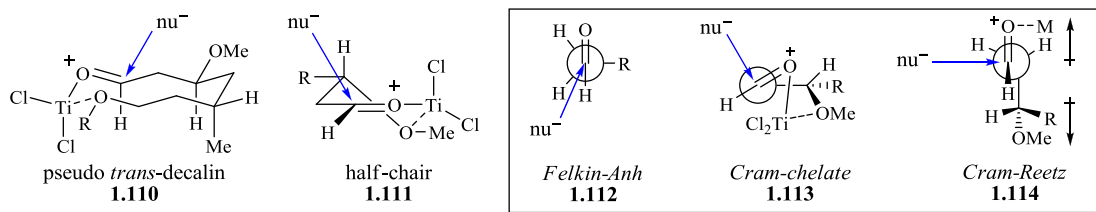
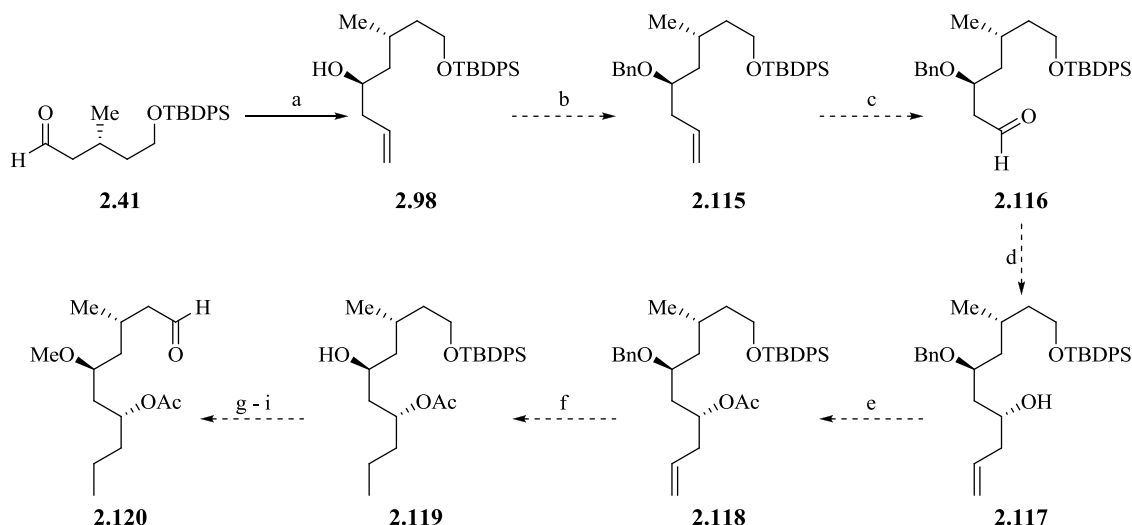


Figure 2.14 – Potential conformations of the β -methoxy (+)-neopeltolide substrate during Sakurai allylation. Competitive chelation with the silyl ether could adopt a pseudo *trans*-decalin conformation **1.110** that would afford 1,3-*syn* diastereoselection. The desired 1,3-*anti* diastereoselective product would yield from a half-chair transition state **1.111** via the Cram-chelate model **1.113**.

2.4 Future Work and Prospects

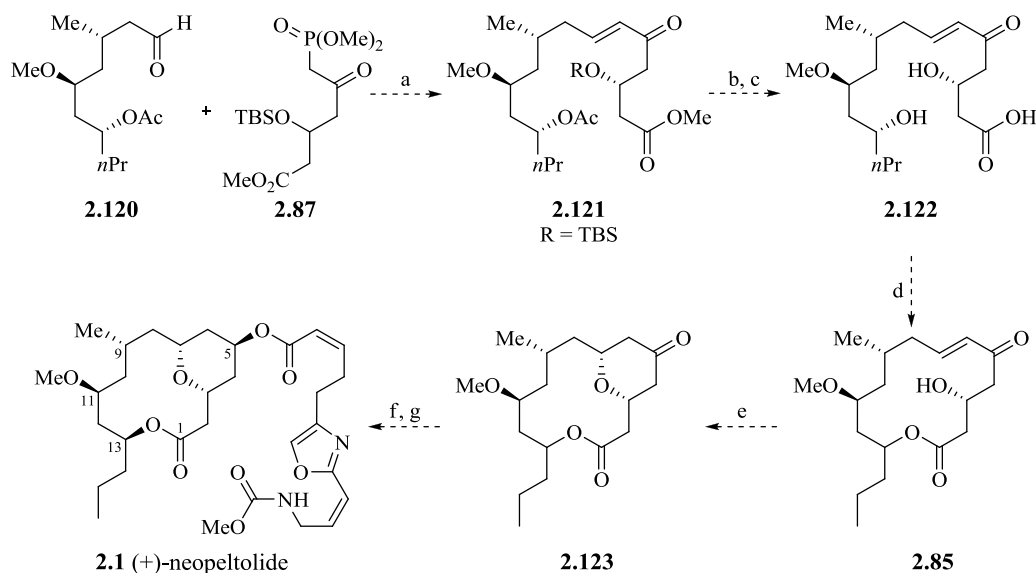
The unexpected results of the asymmetric Sakurai allylation process have deterred the forward progress of the total synthesis of (+)-neopeltolide. Regrettably, the model system has not successfully yielded conclusive evidence to date concerning ideal conditions and β -substituent for high diastereoselectivity. However, based on extrapolation of the preliminary results and predominantly through literature precedence, we believe a route based on iterative asymmetric allylation outlined in Scheme 2.13 will enable us to rapidly access the required building block in high diastereopurity.



Scheme 2.13 – Conditions and outline toward the projected synthesis of the C7-C16 fragment of (+)-neopeltolide. a) (+)-Ipc₂Ballyl, Et₂O, -100 °C to -78 °C; then NaOH, H₂O₂, reflux, 1 h, 40%; b) BnBr, NaH, DMF; c) K₂CO₃, K₃Fe(CN)₆, K₂OsO₇·(H₂O)₂, *t*-BuOH:H₂O (1:1), rt, 12 h; then Pb(OAc)₄, DCM, 30 Min; d) TiCl₄, allyltrimethyl silane, DCM; e) acetic anhydride, Et₃N, DCM, DMAP (5 mol%); f) H₂, Pd/C, EtOH; g) MeI, NaH, THF; h) TBAF, THF, rt, 12 h; i) PCC, DCM.

The future synthetic approach to the completion of the C7-C16 fragment of (+)-neopeltolide will begin with an asymmetric Brown allylation once again. Subsequent benzyl protection of the resulting homoallylic alcohol will provide the conformational requirements

needed in order to yield a successfully diastereoselective Sakurai allylation (Scheme 2.13, step *d*). With substrate **2.117** in hand, acetylation of the homoallylic alcohol, followed by a one-step hydrogenation of the terminal alkene and cleavage of the benzyl ether will afford **2.119**. The completion of the fragment will be accomplished with deprotection of the silyl ether, and subsequent oxidation of the resulting primary alcohol to the aldehyde **2.120**.



Scheme 2.14 – General conditions and outline for projected future work and synthetic completion of (+)-neopeltolide via an oxa-Michael conjugate addition installation of the tetrahydropyran moiety following macrocyclization. a) LiCl, 4 Å ms, MeCN, **2.87**, Hünig's base; then **2.120**, rt; b) LiOH (1.0 M), EtOH, rt; c) TBAF, THF, rt; d) 2,2'-dipyridyl disulfide, PPh₃, benzene, rt; then benzene reflux; e) DBU, PhMe, reflux; f) NaBH₄, EtOH, 0 °C; g) DIAD, PPh₃, **2.35**, benzene, rt.

Our proposed synthesis of (+)-neopeltolide will conclude with the Horner-Wadworth-Emmons coupling of aldehydic fragment **2.120** and its corresponding phosphonate **2.87** to afford the complete carbon skeleton.^{56,132} Deprotection of the silyl ether and saponification will afford acid **2.122**, which will be macrocyclized under Corey-Nicolaou lactonization conditions.^{133,134} With substrate **2.85** in hand, the viability of an oxa-conjugate addition will be evaluated in the penultimate step to the macrocyclic core of (+)-neopeltolide. Selective reduction with sodium borohydride, and Mitsunobu coupling of the known acid **2.35** would complete the total synthesis of (+)-neopeltolide. The results of this project will provide synthetic support to the ability of tetrahydropyran formation of PKS-like substrates, thus, allowing *de novo* synthesis to elucidate the biosynthetic origins of tetrahydropyran ring moieties in nature.

2.5 References

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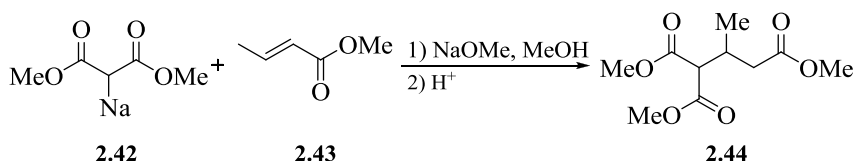
2.6 Supporting Information

2.7.1 General Procedures

All reactions were carried out using oven-dried glassware under an inert atmosphere (nitrogen, or argon) with dry solvents under anhydrous conditions, unless otherwise noted. Anhydrous solutions of tetrahydrofuran (THF), diethyl ether (Et₂O), and dichloromethane DCM were obtained from an anhydrous solvent delivery system. Yields refer to chromatographically and spectroscopically (¹HNMR) homogenous materials, unless otherwise stated. Reagents were commercially purchased at the highest quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 Mm Silicycle silica gel plates (60F-254) using UV light as a visualizing agent and an aqueous solution of ceric ammonium molybdate (CAM), and heat as a developing agent. Silica gel (230 – 400 mesh) obtained from the University of Ottawa Science Store was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 Mm Silicycle silica gel plates (60F-254). NMR spectra were recorded on Bruker Avance 300 or 400 instruments and calibrated using residual undeuterated solvent (CDCl₃: δ H = 7.26 ppm, δ C = 77.0 ppm) as an internal reference. Data are reported as follows: chemical shift (multiplicity abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad) *J* = coupling constant (Hz), integration, peak assignment. Infrared (IR) spectra were recorded on an ABB Bomen MB Series Arid-Zone™ Infrared Spectrometer. High-resolution mass spectra (HRMS) were recorded by positive ion electrospray on Kratos Analytical Concept 11A mass spectrometer with an electron beam of 70 eV (Ottawa-Carleton Mass Spectrometry Centre).

2.7.2 Experimental Procedures and Physical Data of Compounds

All the experimental procedures are representative, and arranged to reflect the synthetic procedures shown in the schemes.



Trimethyl-2-methylpropane-1,1,3-tricarboxylate (2.44). A mixture of sodium methyl malonate (6.34 g, 48.0 mmol, 1.0 equiv.) and methyl crotonate (4.0 g, 48.0 mmol, 1.0 equiv.) was added dropwise to a round bottom flask charged with 20.0 mL of a 2.05 M solution of sodium methoxide

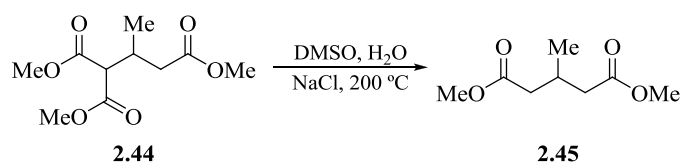
in methanol so as to maintain solvent reflux. The reaction stirred at 100 °C under N₂ for 3 h, until completion by TLC (silica gel, 40% EA:hex). Methanol was removed by rapid distillation at 110 °C, and the mixture was cooled to 0 °C in an ice bath and 30 mL of ether was added, precipitating the sodium salt of **2.44**. To this, 8.2 mL of 5 M HCl cooled to 0 °C was added and extracted with ether. Extraction with brine (3 × 50 mL) until neutral, followed by evaporation of the dried (MgSO₄) organic extracts yielded 10.04 g (43.2 mmol, 90.1%) of **2.44** as clear, colorless oil.

R_f = 0.38 (silica gel, 40% EA:hex).

¹HNMR (400 M Hz, CDCl₃): δ = 1.02 (d, J = 6.9 Hz, 3H, -CH₃), 2.28 (dd, J = 16.0, 8.4 Hz, 1H, -CHH-), 2.50 (dd, J = 15.9, 5.1 Hz, 1H, -CHH-), 2.65 – 2.76 (m, 1H, -CH-), 3.41 (d, J = 7.2 Hz, 1H, -CH-), 3.64 (s, 3H, -OCH₃), 3.69 (s, 3H, -OCH₃), 3.70 (s, 3H, -OCH₃) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 17.5, 30.2, 38.4, 41.1, 51.6, 52.5, 55.9, 166.9, 168.8, 172.5 ppm.

NMR spectra consistent with those previously reported within literature data.⁶⁸



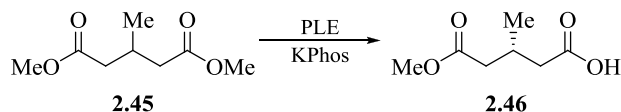
Dimethyl-3-methylglutarate (2.45). To **2.44** (7.70 g, 33.0 mmol, 1.0 equiv.), DMSO (36.0 mL), water (1.2 mL), and finely ground NaCl (3.82 g, 66.0 mmol, 2.0 equiv.) were stirred under an N₂ atmosphere. The reaction refluxed for 24 h at 210 °C in a sand bath until completion by TLC (silica gel, 10% EA:hex), upon which the mixture was cooled to rt and poured over a liter of ice water. Extraction with ether and brine (3 × 75 mL), followed by evaporation of the dried (MgSO₄) organic extracts yielded 4.90 g (28.1 mmol, 85.2%) of **2.45** as clear, pale yellow oil.

R_f = 0.25 (silica gel, 10% EA:hex).

¹HNMR (400 M Hz, CDCl₃): δ = 0.99 (d, J = 6.6 Hz, 3H, -CH₃), 2.22 (dd, J = 15.1, 7.5 Hz, 2H, -CH₂-), 2.33 – 2.55 (m, 3H, -CH-, -CH₂-), 3.65 (s, 6H, 2 × -OCH₃) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 19.9, 27.4, 40.6, 51.5, 172.8 ppm.

NMR spectra consistent with those previously reported within literature data.^{68,135,136}



Methyl-(R)-(+)-3-methylglutarate (2.46). A rapidly stirred solution of **2.47** (0.96 mL, 5.83 mmol, 1 equiv.) in 0.1 M KPhos buffer (30 mL) plus methanol (3 mL) at 0 °C was neutralized to pH 7

with 0.5 M aqueous NaOH by using a **SevenEasy** Mettler Toledo pH-meter. Esterase from hog liver, PLE, (15 mg, 400 units) was then added and the pH of the solution was maintained at 7. The hydrolysis proceeded until 1 equivalent (11.6 mL, 1 equiv.) of base had been consumed, at which point it stopped. The resulting solution was washed with ether (2 × 30 mL) to remove unreacted diester then acidified to pH < 2.5 with concentrated HCl, using Fisher Scientific Company Alkacid® Test Ribbon. Extraction with ether (3 × 70 mL) followed by evaporation of the dried (MgSO₄) ether extracts to yield 860.0 mg (5.37 mmol, 94% yield) of **2.46** as a clear colorless oil.

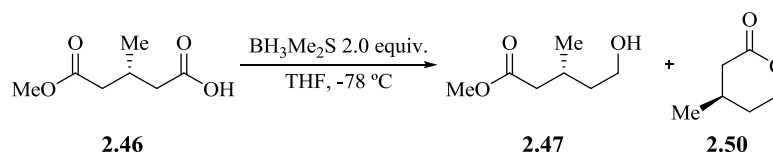
(105)

R_f = 0.18 (silica gel, 20% EA:hex).

¹HNMR (400 M Hz, CDCl₃): δ = 1.04 (d, J = 6.6 Hz, 3H, -CH₃), 2.21 – 2.51 (m, 5H, -CH-, 2 × -CH₂-), 3.66 (s, 3H, -OCH₃), 10.68 (br s, 1H, -CO₂H) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 19.9, 27.2, 40.4, 40.5, 51.6, 172.8, 178.3 ppm.

NMR spectra consistent with those previously reported within literature data.^{68,136–139}



(3R)-5-Hydroxy-3-methylpentanoic acid methyl ester (2.47). To **2.46** (1.0 g, 6.24 mmol, 1 equiv.) was added dry THF (25 mL) stirring under N₂ at -78°C, and BH₃ Me₂S (0.5 mL, 12.48 mmol, 2 equiv.) was added dropwise *via* syringe. The mixture was then allowed to warm to room temperature and stirred further for 4 h under N₂. Reaction mixture is checked by NMR showing progression, and upon complete conversion of **2.47** was quenched by carefully adding 0.5 mL of alcohol (H₂O or methanol), and evaporated to dryness. The resulting white residue was diluted in EtOAc and extraction with brine (2 × 20 ml), followed by the drying of the organic layer with MgSO₄, filtered and concentrated to dryness yielded 721.0 mg (5.00 mmol, 84%) as a mixture (**2.47**:**2.50** > 20:1) of clear, colorless oil.

R_f = 0.36 (silica gel, 20% EA:hex).

¹HNMR (400 M Hz, CDCl₃): δ = 0.93 (d, J = 6.5 Hz, 3H, -CH₃), 1.35 – 1.61 (m, 2H, -CH₂-), 2.04 – 2.39 (m, 3H, -CH-, -CH₂-), 3.63 (s, 3H, -OCH₃), 3.74 – 3.84 (m, 2H, -CH₂-) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 19.7, 27.3, 38.0, 41.5, 51.3, 61.1, 173.5 ppm.

NMR spectra consistent with those previously reported within literature data.^{68,140}



(3R)-5-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-5-methyl ester pentanoic acid (2.48). To **2.47** (2.96 g, 20.5 mmol, 1 equiv.) dissolved in anhydrous DMF (27 mL) under N₂, affording a 0.8 M overall solution, was added TBDPSCl (6.33 mL, 26.7 mmol, 1.3 equiv.). Imidazole (4.19 g, 61.5 mmol, 3.0 equiv.) was added to a rapidly stirring solution, and left to stir for 24 h, at which point it stopped. The reaction mixture was diluted in ethyl acetate and washed with saturated ammonium chloride to remove unreacted imidazole. The organic layers were then washed with an increasing gradient concentration of brine, followed by evaporation of the dried (MgSO₄) organic layers. Purification *via* flash chromatography (2% EA:hex) separated unreacted ester and silanol from product, yielding 7.50 g (19.5 mmol, 95% yield) of **2.48** as clear, colorless oil.

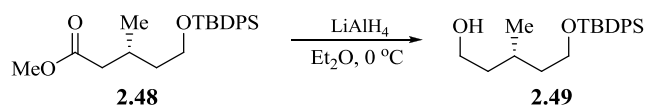
R_f = 0.37 (silica gel, 10% EA:hex).

IR (NaCl): ν_{max} = 3074, 2930, 1736, 1474 cm⁻¹.

¹HNMR (400 M Hz, CDCl₃): δ = 0.89 (d, J = 6.4 Hz, 3H, -CH₃), 1.02 (s, 9H, O-TBDPS *t*-Bu), 1.39 – 1.63 (m, 2H, -CH₂-), 2.05 – 2.34 (m, 3H, -CH-, -CH₂-), , 3.63 (s, 3H, -OCH₃), 3.67 (t, J = 6.4 Hz, 2H, -CH₂-), 7.32 – 7.42 (m, 6H, -CH- Ph), 7.64 (dd, J = 1.6, 7.8 Hz, 4H, -CH- Ph) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 19.1, 19.8, 26.7, 27.6, 39.3, 41.6, 51.4, 62.1, 127.7, 129.8, 134.1, 135.7, 173.7 ppm.

HRMS (EI): Calculated for C₁₉H₂₃O₃Si (M – *t*-Bu) 327.1417, Observed 327.1424 (Δ = -0.7 mmu).



(3S)-5-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-pentan-1-ol (2.49). To **2.48** (3.90 g, 10.1 mmol, 1.0 equiv.) was added anhydrous diethyl ether to yield an overall concentration of 0.1 M, and placed under N₂ in an ice bath with vigorous stirring. LAH (268.3 mg, 7.07 mmol, 0.7 equiv.) was added to constantly stirring, cold solution and let stir for 2 – 5 h while checking reaction progress *via* TLC (silica gel, 20% EA:hex). Upon completion, the reaction was quenched using modified Fieser conditions with 40 μ L filtered, distilled water per mmol LAH, and letting stir for 10 Min.^{74,75} Continue quench by adding 40 μ L of 15% w/w NaOH per mmol LAH to precipitate aluminum salt. Finalize with second aliquot of filtered, distilled water. Wash with saturated ammonium chloride (1 $\times$ 30 mL), and brine (2 $\times$ 30 mL). Rinse flask with Et₂O, and evaporate

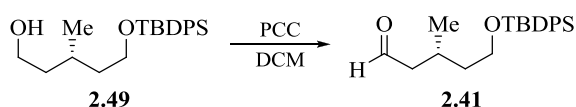
dried (MgSO₄) ether layers. Purify with flash chromatography (10% EA:hex), and concentrate *in vacuo* yielding 3.35 (9.40 mmol, 93% yield) of **2.49** as clear, colorless oil.

R_f = 0.22 (silica gel, 20% EA:hex).

¹HNMR (400 M Hz, CDCl₃): δ = 0.86 (d, J = 6.7 Hz, 3H, -CH₃-), 1.05 (s, 9H, O-TBDPS *t*-Bu), 1.29 – 1.47 (m, 2H, -CH₂-), 1.55 – 1.61 (m, 2H, -CH₂-), 1.68 – 1.82 (m, 1H, -CH-), 3.57 – 3.78 (m, 4H, 2 × -CH₂-), 7.33 – 7.45 (m, 6H, -CH- Ph), 7.64 – 7.70 (m, 4H, -CH- Ph) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 19.2, 19.8, 26.4, 26.9, 39.6, 39.9, 61.1, 62.1, 127.6, 129.6, 134.0, 135.6 ppm.

NMR spectra consistent with those previously reported within literature data.¹⁴¹



(3S)-5-(tert-Butyl-diphenyl-silanyloxy)-3-methyl-pentanoate (2.41). To a round bottom flask charged with **2.49** (2.45 g, 6.9 mmol, 1.0 equiv.) dissolved in DCM (70.0 mL), was added PCC (1.94 g, 9.0 mmol, 1.3 equiv.) and silica gel (3.88 g). The reaction was allowed to stir under N₂ at rt for 2 – 5 h, checking reaction by TLC (silica gel, 10% EA:hex). Upon completion, DCM was evaporated, yielding a dark brown powder. To a pre-equilibrated column (silica gel, 2% EA:hex), flash purification was performed, yielding 2.05 g (5.8 mmol, 84%) of **2.41** as clear, colorless oil.

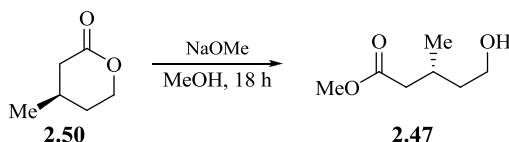
R_f = 0.29 (silica gel, 10% EA:hex).

IR (NaCl): $\nu_{\max}$ = 3070, 2960, 2858, 2705, 1724 cm⁻¹.

¹HNMR (400 M Hz, CDCl₃): δ = 0.91 (d, J = 6.5 Hz, 3H, -CH₃), 1.03 (s, 9H, O-TBDPS *t*-Bu), 1.42 – 1.62 (m, 2H, -CH₂-), 2.14 – 2.41 (m, 3H, -CH-, -CH₂-), 3.68 (t, J = 6.3 Hz, 2H, -CH₂-), 7.33 – 7.44 (m, 6H, -CH- Ph), 7.61 – 7.67 (m, 4H, -CH- Ph), 9.70 (t, J = 2.2 Hz, 1H, -CHO) ppm.

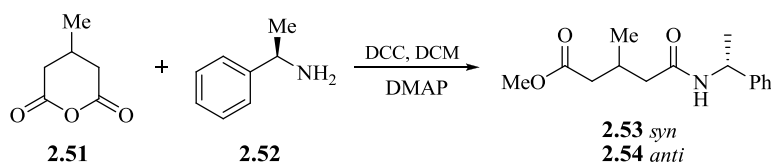
¹³CNMR (75 M Hz, CDCl₃): δ = 19.2, 20.0, 39.2, 50.8, 61.5, 127.6, 129.6, 133.8, 135.5, 202.9 ppm.

HRMS (EI): Calculated for C₁₈H₂₁O₂Si (M – *t*-Bu) 297.1311, Observed 297.1329 (Δ = -1.8 mmu).



(3R)-5-Hydroxy-3-methylpentanoic acid methyl ester (2.47). To lactone **2.50** (1.07 g, 9.37 mmol, 1.0 equiv.) in dry methanol (10.0 mL) was added NaOMe (253 mg, 4.69 mmol, 0.5 equiv.) to afford an overall solution of 0.5 M. Upon addition of NaOMe/MeOH, the solution immediately

turned pale yellow. The solution was stirred at rt for 1 d, after which the methanol was removed *in vacuo*, yielding 220 mg (1.52 mmol, 16%) of **2.47** with consistent physical and spectral data (*vide supra*).

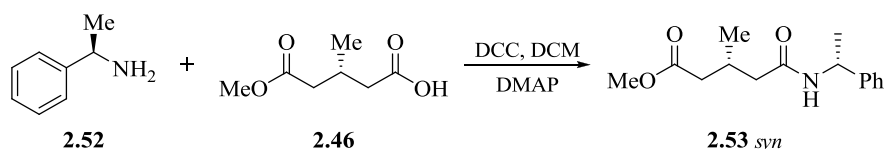


(R/S)-Methyl 3-methyl-5-oxo-5-((R)-1-phenylethylamino)pentanoate (2.53/2.54). In a flame-dried flask, 3-Methylglutaric anhydride (101.2 mg, 0.79 mmol, 1.0 equiv.), 1-(*R*)-phenylethylamine (101 μ L, 0.79 mmol, 1.0 equiv.), and DMAP (100 mg, 0.82 mmol, 1.03 equiv.) were dissolved in 2 mL of anhydrous DCM and stirred for 1 h under N₂ atmosphere. At this point, DCC (163 mg, 0.79 mmol, 1.0 equiv.) was added as one portion, followed by the addition of 1 mL of dry MeOH after several minutes. The reaction mixture was left to stir for 24 h, then filtered through a plug of silica. The solution was washed with 5% HCl (2 $\times$ 2 mL) and saturated NaHCO₃ (2 mL), dried over MgSO₄ and concentrated to yield compounds **2.53** and **2.54** as a mixture with a 2:1 ratio. The crude material was of sufficient purity for spectroscopic analysis, and was not purified. The NMR resonances were easy to distinguish because of the difference in relative intensity.⁷⁰

¹H NMR (300 M Hz, CDCl₃): δ = 0.95 (d, *J* = 6.6 Hz, 3H, -CH₃, *anti*), 0.97 (d, *J* = 6.6 Hz, 3H, -CH₃, *syn*), 1.43 (d, *J* = 7.0 Hz, 3H, -CH₃), 1.99 – 2.48 (m, 5H, 2 $\times$ -CH₂-, -CH-), 3.60 (s, 3H, -OCH₃, *syn*), 3.62 (s, 3H, -OCH₃, *anti*), 5.08 (p, *J* = 7.2 Hz, 1H, -CH-), 6.18 (br, 1H, -NH), 7.17 – 7.32 (m, 5H, -CH- Ph) ppm.

¹³C NMR (75 M Hz, CDCl₃): δ = 19.7 (*syn*), 19.8, 21.7 (*syn*), 21.8, 28.1 (*syn*), 28.6, 40.2 (*syn*), 40.3, 42.9 (*syn*), 43.0, 48.5, 48.6 (*syn*), 51.39 (*syn*), 51.40, 126.0 (*syn*), 126.1, 127.2, 128.6, 143.2, 143.3 (*syn*), 170.7, 173.1 ppm.

NMR spectra consistent with those previously reported within literature data.⁷⁰

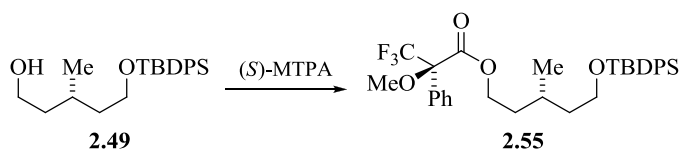


(R)-Methyl 3-methyl-5-oxo-5-((R)-1-phenylethylamino)pentanoate (2.53). In a flask charged with DCC (26.4 mg, 0.13 mmol, 1.0 equiv.), DMAP (1.6 mg, 0.01 mmol, 0.1 equiv.) and 0.2 mL of anhydrous DCM was added **2.46** (20.5 mg, 0.13 mmol, 1.0 equiv.) in 0.1 mL anhydrous DCM. The flask was rinsed with an addition 0.1 mL of DCM and added to the reaction mixture, forming a thick white precipitate instantaneously. After the mixture was stirred for 5 min, (*R*)- α -

methylbenzylamine (15.9 μ L, 0.13 mmol, 1.0 equiv.) was added neat and the reaction stirred for 2 h, then filtered through a plug of silica. The solution was dried over MgSO_4 and concentrated to yield **2.53** as crude material that was of sufficient purity for spectroscopic analysis.⁷⁰

^1H NMR (400 M Hz, CDCl_3): δ = 1.00 (d, J = 6.9 Hz, 3H, $-\text{CH}_3$, syn), 1.47 (d, J = 7.0 Hz, 3H, $-\text{CH}_3$), 2.08 (dd, J = 13.9, 7.0 Hz, 1H, $-\text{CH}-$), 2.18 – 2.47 (m, 4H, $2 \times -\text{CH}_2-$), 3.61 (s, “0.09H,” $-\text{OCH}_3$, anti), 3.64 (s, 3H, $-\text{OCH}_3$, syn), 5.12 (p, J = 7.3 Hz, 1H, $-\text{CH}-$), 5.87 (br, 1H, $-\text{NH}$), 7.26 – 7.36 (m, 5H, $-\text{CH}-\text{Ph}$) ppm.

^{13}C NMR (100 M Hz, CDCl_3): δ = 19.9, 21.8, 28.3, 40.2, 43.1, 48.7, 51.5, 125.7, 126.1, 126.8, 127.3, 128.5, 128.7, 143.3, 170.6, 173.1 ppm. ^{13}C NMR comparison of the crude **2.53** with **2.53/2.54** suggests ee > 95% purity, as based on the relative methoxy integrations.

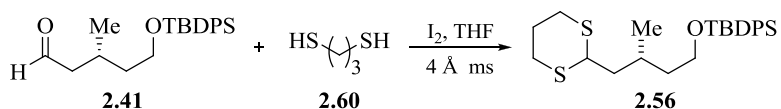


3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 5-(TBDPS)-3-methyl-pentyl ester (**2.55**).

To a dry round bottom flask containing a Teflon magnetic stir bar under N_2 atmosphere, **2.49** (17 mg, 0.048 mmol, 1.0 equiv.) was dissolved in pyridine (0.4 mL), yielding an overall solution concentration of 0.1 M. The mixture was placed in an ice bath and cooled to 0 $^\circ\text{C}$, upon which (S)-MTPA chloride (13.6 μ L, 0.072 mmol, 1.5 equiv.) was added. The reaction was brought to rt and allowed to stir under N_2 for 2 – 4 h, checking reaction by TLC (silica gel, 10% EA:hex). Upon completion, the mixture was quenched in water (10 mL), and washed in Et_2O (3×20 mL). The combined organic layers were washed with sat. NaHCO_3 (3×30 mL), and brine (3×50 mL), followed by evaporation of the dried (MgSO_4) organic layers, to yield clear, colorless oil as the crude ester product.

R_f = 0.63 (silica gel, 10% EA:hex).

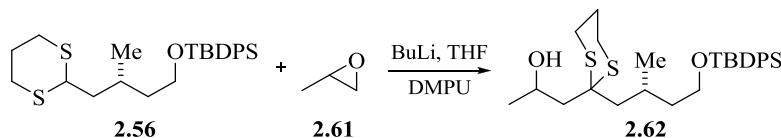
^1H NMR (400 M Hz, CDCl_3): δ = 0.84 (d, J = 6.4 Hz, 3H, $-\text{CH}_3$), 1.00 (s, 9H, O-TBDPS *t*-Bu), 1.16 – 1.77 (m, 5H, $-\text{CH}-$, $2 \times -\text{CH}_2-$), 3.51 (s, 3H, $-\text{OCH}_3$), 3.57 – 3.69 (m, 2H, $-\text{CH}_2-$), 4.25 – 4.36 (m, 2H, $-\text{CH}_2-$), 7.30 – 7.67 (m, 15H, $3 \times \text{Ph}$) ppm. ^1H NMR analysis of the crude material suggest ee > 95% purity, as based on the relative methoxy integrations.



(R)-(4-(1,3-Dithian-2-yl)-3-methylbutoxy)(tert-butyl)diphenylsilane (2.56). To a dried round bottom flask containing a Teflon stir bar and charged with activated 4 Å molecular sieves, purified **2.41** (640.0 mg, 1.81 mmol, 1.0 equiv.), and 1,3-propanedithiol **2.60** (255 µL, 2.53 mmol, 1.4 equiv.) were dissolved in anhydrous THF (3.6 mL), yielding an overall solution concentration of 0.5 M. Catalytic iodine (46 mg, 0.18 mmol, 0.1 equiv.) was added, and the reaction was allowed to stir under N₂ at rt for 2 h, checking reaction by TLC (silica gel, 10% EA:hex). Upon completion, THF was evaporated from the crude product, yielding a pale yellow powder. To a pre-equilibrated column (silica gel, 8% EA:hex), flash purification was performed, yielding 582 mg (1.31 mmol, 72%) of crude **2.56** as clear, colorless oil.

R_f = 0.44 (silica gel, 10% EA:hex).

¹HNMR (400 M Hz, CDCl₃): δ = 0.85 (d, *J* = 6.9 Hz, 3H, -CH₃), 1.03 (s, 9H, O-TBDPS *t*-Bu), 1.30 – 1.41 (m, 2H, -CH₂-), 1.46 – 1.64 (m, 2H, -CH₂-), 1.64 – 1.74 (m, 1H, -CH-), 1.80 – 1.90 (m, 1 h, -CHH-), 1.92 – 2.02 (m, 1H, -CHH-), 2.56 – 2.91 (m, 4H, 2 × -CH₂-), 3.62 – 3.74 (m, 2H, -CH₂-), 4.06 (dd, *J* = 8.4 Hz, 1H, -CH-), 7.33 – 7.43 (m, 6H, -CH- Ph), 7.62 – 7.69 (m, 4H, -CH- Ph) ppm.

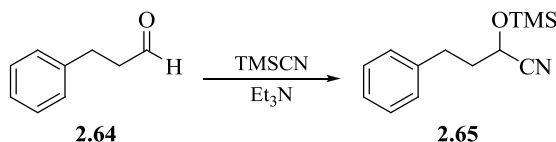


1-(2-((R)-4-(tert-butyldiphenylsilyloxy)-2-methylbutyl)-1,3-dithian-2-yl)propan-2-ol (2.62). To a solution of **2.56** (200 mg, 0.45 mmol, 1.0 equiv.) in THF (2.3 mL) stirred at -65 °C (EtOH-dry ice bath) was added *n*BuLi (1.6 M, in hexanes, 0.400 mL, 1.00 mmol, 2.2 equiv.) under N₂. After completion of the addition, the mixture was stirred between temperatures of -40 °C and -20 °C for 3 h. The bath temperature was re-cooled to -65 °C, and a solution of **2.61** (35 µL, 0.50 mmol, 1.1 equiv.) in THF (0.8 mL) and DMPU (0.34 mL, 2.82 mmol, 6.2 equiv.) was then introduced. The stirring continued at -40 °C, checking reaction by TLC (silica gel, 20% EtOAc:hex). Upon completion, the mixture was partitioned between H₂O and DCM, and the phases were separated. The combined organic layers were dried (MgSO₄) and concentrated to afford 50 mg (0.1 mmol, 22%) of crude **2.62** as clear, colorless oil.

R_f = 0.11 (silica gel, 20% EA:hex)

¹HNMR (400 M Hz, CDCl₃): δ = 0.83 (dd, *J* = 6.7, 1.6 Hz, 3H, -CH₃-), 1.03 (s, 9H, O-TBDPS *t*-Bu), 1.24 (d, *J* = 6.0 Hz, 3H, -CH₃-), 1.36 – 1.42 (m, 2H, -CH₂-), 1.55 (buried m, 1H, -CH-), 1.81 – 1.88 (m, 2H, -CH₂-), 2.39 – 2.51 (m, 4H, 2 × -CH₂-), 2.58 – 2.73 (m, 4H, 2 × -CH₂-), 3.59 – 3.76

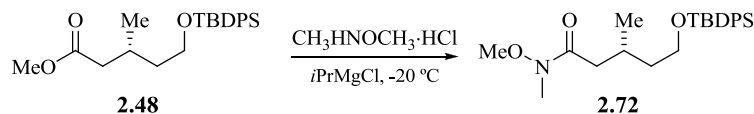
(m, 2H, $-CH_2-$), 3.77 – 3.87 (m, 1H, $-CH-$), 4.12 (br s, 1H, $-OH$), 7.34 – 7.42 (m, 6H, $-CH-$ Ph), 7.63 – 7.66 (m, 4H, $-CH-$ Ph) ppm.



4-phenyl-2-(trimethylsilyloxy)butanenitrile (2.65). In a round bottom flask were placed phenylacetaldehyde (0.400 mL, 3.02 mmol, 1.0 equiv.) and Et_3N (0.05 mL, 12 mol%) and the mixture was stirred at rt. TMSCN (0.444 mL, 3.32 mmol, 1.1 equiv.) was slowly added at rt, and the reaction was stirred for 30 Min, and checked by TLC (silica gel, 10%). Upon completion, the Et_3N was evaporated under vacuum, giving **2.65** quantitatively as crude material that was pure enough for spectroscopic analysis.

$R_f = 0.50$ (silica gel, 10% EA:hex)

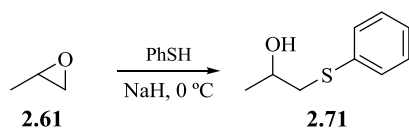
$^1\text{H NMR}$ (400 M Hz, CDCl_3): $\delta = 0.19$ (s, 9H, O-TMS $-CH_3$ x3), 2.07 – 2.11 (m, 1H, $-CHH-$), 2.11 (buried dt, $J = 6.8, 1.6$ Hz, 1H, $-CHH-$), 2.78 (t, $J = 7.9$ Hz, 2H, $-CH_2-$), 4.35 (t, $J = 6.6$ Hz, 2H, $-CH_2-$), 7.15 – 7.23 (m, 3H, $-CH-$ Ph), 7.26 – 7.32 (m, 2H, $-CH-$ Ph) ppm.



(R)-5-(tert-butyldiphenylsilyloxy)-N-methoxy-N-3-dimethylpentanamide (2.72). In a round bottom flask, **2.48** (1.00 g, 2.6 mmol, 1.0 equiv.) and $\text{Me(MeO)NH}\cdot\text{HCl}$ (0.406 g, 4.2 mmol, 1.6 equiv.) were slurried in THF (5.0 mL) and cooled to -20 $^\circ\text{C}$ under N_2 . A solution of $i\text{PrMgCl}$ in THF (4.0 mL, 2.0 M in THF) was added over 15 min maintaining the temperature below -5 $^\circ\text{C}$. The mixture stirred for 20 min at -10 $^\circ\text{C}$ and quenched with 20 wt% aqueous NH_4Cl . The mixture was diluted in Et_2O and extracted with brine, dried (MgSO_4) and concentrated to yield 770 mg (1.86 mmol, 72%) of crude **2.72** that was pure enough for spectroscopic analysis.

$R_f = 0.12$ (silica gel, 10%)

$^1\text{H NMR}$ (400 M Hz, CDCl_3): $\delta = 0.90$ (d, $J = 6.7$ Hz, 3H, $-CH_3-$), 1.02 (s, 9H, O-TBDPS $t\text{-Bu}$), 1.41 – 1.49 (m, 1H, $-CH-$), 1.60 – 1.68 (m, 1H, $-CHH-$), 2.20 – 2.27 (m, 2H, $-CHH-$), 2.38 (dd, $J = 14.9, 4.9$ Hz, 1H, $-CH-$), 3.15 (s, 3H, $-NCH_3$), 3.61 (s, 3H, $-OCH_3$), 3.67 (dt, $J = 6.7, 2.4$ Hz, 2H, $-CH_2-$), 7.33 – 7.41 (m, 6H, $-CH-$ Ph), 7.63 – 7.66 (m, 4H, $-CH-$ Ph) ppm.

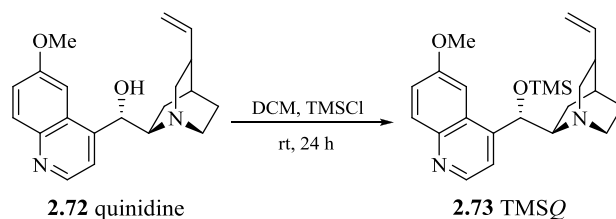


1-(phenylthio)propan-2-ol (2.71). NaH (0.231 g, 9.64 mmol, 1.3 equiv.) was suspended in dry THF (20 mL) and cooled to 0 °C. PhSH (0.76 mL, 7.42 mmol, 1.0 equiv.) was then carefully added dropwise and stirred for 30 Min, upon which dropwise addition of **2.61** (1.0 mL, 9.64 mmol, 1.3 equiv.) and stirred for 4 h while brought to rt. The reaction was re-cooled to 0 °C and quenched with MeOH until no more gas evolution was observed. The mixture was separated with NH₄Cl solution and washed with EtOAc. Combined organic layers were dried (MgSO₄), filtered and concentrated to yield 1.21 g (7.2 mmol, 75%) of crude **2.71** as a yellow oil.

R_f = 0.15 (silica gel, 10%)

¹HNMR (400 M Hz, CDCl₃): δ = 1.25 (d, J = 6.2 Hz, 3H, -CH₃-), 2.10 (br s, 1H, -OH), 2.82 (dd, J = 13.8, 8.7 Hz, 1H, -CHH-), 3.10 (dd, J = 13.9, 3.7 Hz, 1H, -CHH-), 3.83 (m, 1H, -CH-), 7.20 (tt, J = 6.5, 1.3 Hz, 1H, -CH- Ph), 7.28 (tt, 7.0, 2.0 Hz, 2H, -CH- Ph), 7.36 – 7.38 (m, 2H, -CH- Ph) ppm.

¹HNMR spectrum consistent with literature data.²⁰

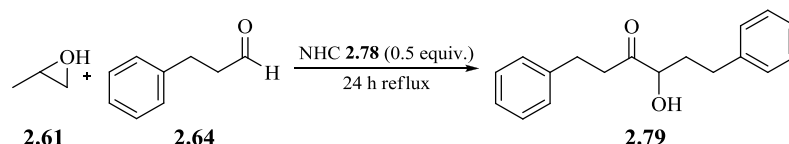


9-Trimethylsilylquinidine (2.73). To a solution of **2.72** (0.5 g, 3.08 mmol, 1.0 equiv.) in DCM (5 mL) was added trimethylsilylchloride (0.20 mL, 3.08 mmol, 1.0 equiv.). The resulting solution was stirred at rt for 24 h, and was then partitioned between 5 mL DCM and 10 mL of aqueous NaHCO₃. The layers were separated, the aqueous with DCM (3x2 mL), and the combined organic layers were dried (MgSO₄), filtered and concentrated. Purify with flash chromatography (3% MeOH:DCM), and concentrate *in vacuo* yielding 0.83 g (2.1 mmol, 67%) of **2.73** as clear, colorless oil.

¹HNMR (400 M Hz, CDCl₃): δ = 0.04 (s, 9H, O-TMS -CH₃ x3), 1.42 (m, 1H, -CH-), 1.47 (apparent d, J = 9.2 Hz, 2H, -CH₂-), 1.72 (m, 1H, -CH-), 2.10 (m, 1H, -CHH-), 2.21 (apparent d, J = 7.0 Hz, 1H, -CHH-), 2.69 – 2.98 (m, 4H, 2 × -CH₂-), 3.34 (m, 1H, -CH-), 3.92 (s, 3H, -CH₃), 5.06 (d, J = 14.3 Hz, 2H, -CH₂-), 5.64 (m, 1H, -CH-), 6.06 (apparent p, J = 8.1 Hz, 1H, -CH-), 7.14 (m,

1H, -CH- Ph), 7.35 (dd, $J = 9.3, 2.4$ Hz, 1H, -CH- Ph), 7.50 (m, 1H, -CH- Ph), 8.01 (d, $J = 9.2$ Hz, 1H, -CH- pyr), 8.72 (d, $J = 3.3$ Hz, 1H, -CH- pyr) ppm.

¹HNMR spectrum consistent with literature data.¹⁰⁴

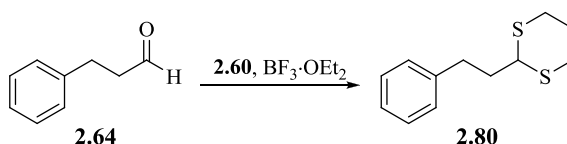


4-hydroxy-1,6-diphenylhexan-3-one (2.79). To a stirring solution of hydrocinnamaldehyde (30 μ L, 0.234 mmol, 1.0 equiv.) in propylene oxide (2.72 mL, 200 equiv.), imidazolium salt **2.78** (40 μ g, 0.117 mmol, 0.5 equiv.) was added and allowed to dissolve under N₂. Potassium carbonate (162 μ g, 1.17 mmol, 5.0 equiv.) was added, and the resulting solution was brought to reflux (60 °C) for 24 h. The mixture was allowed to cool to rt, diluted with EtOAc, and washed with brine. Purification of the crude residue (silica gel, 2% EA:hex) afforded Benzoin cross-coupling product **2.79**.

R_f = 0.15 (silica gel, 10%)

¹H NMR (400 M Hz, CDCl₃): δ = 1.75 (dddd, *J* = 13.7, 9.3, 9.3, 5.3 Hz, 1H, -CHH-), 2.07 (dddd, *J* = 13.8, 9.6, 3.6, 3.6 Hz, 1H, -CHH-), 2.23 – 2.50 (m, 1H, -OH), 2.61 – 2.79 (m, 4H, 2 × -CH₂-), 2.84 – 2.95 (m, 2H, -CH₂-), 4.10 (dd, *J* = 8.3, 3.6 Hz, 1H, -CH-), 7.12 – 7.20 (m, 6H, -CH- Ph), 7.24 – 7.29 (m, 4H, -CH- Ph) ppm.

¹H NMR spectrum consistent with predicted data calculated using Advanced Chemistry Development, Inc. (ACD/Labs) Software V11.01 (© 1994-2012 ACD/Labs).

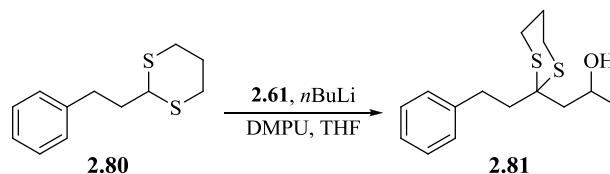


2-phenethyl-1,3-dithiane (2.80). To a solution of **2.64** (1.0 mL, 7.4 mmol, 1.0 equiv.) and **2.60** (1.12 mL, 11.2 mmol, 1.5 equiv.) in DCM (8.0 mL) to afford an overall concentration of 1.0 M, BF₃·OEt₂ (1.84 mL, 14.9 mmol, 2.1 equiv.) was added and the reaction was stirred at rt for 18 h. Upon completion, the solution was poured into 10% NaHCO₃ (15 mL) and the layers were separated, and the aqueous phase was back-washed with DCM (2 × 5 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated yield 1.49 mg (6.7 mmol, 90%) of crude **2.80** that was pure enough for spectroscopic analysis.

R_f = 0.47 (silica gel, 10%)

¹HNMR (400 M Hz, CDCl₃): δ = 1.81 – 1.92 (m, 1H, -CHH-), 2.03 – 2.14 (m, 3H, -CHH-, -CH₂-), 2.80 – 2.85 (m, 6H, 3 $\times$ -CH₂-), 3.97 (t, J = 7.0 Hz, 1H, -CH-), 7.16 – 7.20 (m, 3H, -CH- Ph), 7.26 – 7.29 (m, 2H, -CH- Ph) ppm.

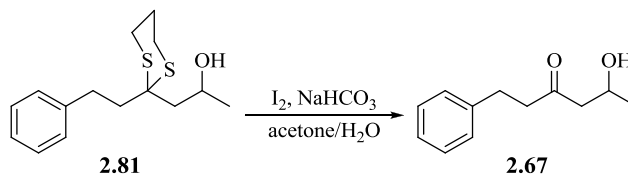
¹HNMR spectrum consistent with literature data.^{142–144}



1-(2-phenethyl-1,3-dithian-2-yl)propan-2-ol (2.81). To a solution of **2.80** (3.40 g, 15.1 mmol, 1.0 equiv.) in THF (40 mL) stirred at -65 °C was added *n*BuLi (1.6 M, in hexanes, 12.7 mL, 31.7 mmol, 2.1 equiv.) under N₂. The mixture undergoes color change (clear > white > yellow > orange > amber) during slow addition of *n*BuLi. After completion of the addition, the mixture was stirred between temperatures of -40 °C and -20 °C for 3 h. The bath temperature was re-cooled to -65 °C, and a solution of **2.61** (1.06 mL, 15.1 mmol, 1.1 equiv.) in THF (20 mL) and DMPU (11.3 mL, 93.1 mmol, 6.2 equiv.) was then introduced. The stirring continued at -40 °C, checking reaction by TLC (silica gel, 10% EtOAc:hex). Upon completion, the mixture was partitioned between H₂O and DCM, and the phases were separated. The combined organic layers were dried (MgSO₄) and concentrated to afford 4.14 g (14.7 mmol, 97%) of crude **2.81** as clear, pale yellow oil.

R_f = 0.18 (silica gel, 10% EA:hex)

¹HNMR (400 M Hz, CDCl₃): δ = 1.19 (d, J = 6.3 Hz, 3H, -CH₃), 1.89 – 1.98 (m, 2H, -CH₂-), 1.99 – 2.07 (m, 1H, -CHH-), 2.17 (ddd, J = 14.2, 12.3, 5.1 Hz, 1H, -CHH-), 2.29 (ddd, J = 14.2, 12.3, 5.1 Hz, 1H, -CHH-), 2.35 (dd, J = 15.3, 9.4 Hz, 1H, -CHH-), 2.68 – 2.76 (m, 1H, -CHH-), 2.78 – 2.86 (m, 3H, 3 $\times$ -CHH-), 2.89 – 2.95 (m, 1H, -CHH-), 3.00 (dd, J = 14.3, 9.5, 3.3 Hz, 1H, -CHH-), 3.40 (br s, 1H, -OH), 4.16 – 4.23 (m, 1H, -CH-), 7.16 – 7.20 (m, 3H, -CH- Ph), 7.26 – 7.30 (m, 2H, -CH- Ph) ppm.



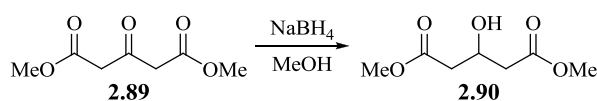
5-hydroxy-1-phenylhexan-3-one (2.67). In a round bottom flask, solid I₂ (11.2 g, 44.1 mmol, 3.0 equiv.) was added in three portions over 5 min to a mixture of **2.81** (4.14 g, 14.7 mmol, 1.0 equiv.) and powdered NaHCO₃ (8.02 g, 95.6 mmol, 6.5 equiv.) in acetone (150 mL) and water (25 mL) stirred in an ice-bath. The reaction was stirred for 15 min and diluted in Et₂O (30 mL) and washed with aq. Na₂S₂O₃ to quench the iodine. The phases were separated and the combined organic

phases were washed with brine, dried (MgSO₄) and concentrated to afford 1.37 g (7.04, 48%) of crude **2.67** as clear, colorless oil.

R_f = 0.12 (silica gel, 20% EA:hex)

¹HNMR (400 M Hz, CDCl₃): δ = 1.15 (d, J = 6.3 Hz, 3H, -CH₃), 2.48 (dd, J = 17.6, 8.6 Hz, 1H, -CHH-), 2.56 (dd, J = 17.7, 3.4 Hz, 1H, -CHH-), 2.74 (t, J = 7.6 Hz, 2H, -CH₂-), 2.89 (t, J = 7.5 Hz, 2H, -CH₂-), 2.99 (d, J = 3.2 Hz, 1H, -CHH-), 4.20 (m, 1H, -CH-), 7.15 – 7.20 (m, 3H, -CH- Ph), 7.24 – 7.29 (m, 2H, -CH- Ph) ppm.

¹HNMR spectrum consistent with predicted data calculated using Advanced Chemistry Development, Inc. (ACD/Labs) Software V11.01 (© 1994-2012 ACD/Labs).



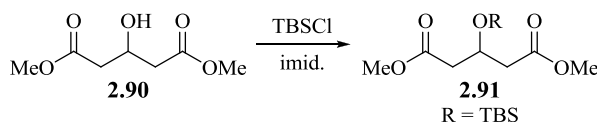
Dimethyl-3-hydroxypentanedioate (2.90). A stirred solution **2.89** (10.0 g, 57.4 mmol, 1.0eq) in methanol (60 mL), was cooled using an ice bath, and sodium borohydride (1.1 g, 28.7 mmol, 2.0 equiv.) was slowly added in small portions. The clear solution gradually turned clear and yellow in color. Upon completion, the reaction mixture was evaporated to dryness and the residue was diluted in EtOAc (50 mL) and washed with brine. The aqueous phase was separated and extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was sufficiently pure for use in the following step, yielding **2.90** in 7.1 g (40.2 mmol, 70%) as clear, colorless oil.

R_f = 0.28 (silica gel, 20% EA:hex).

¹HNMR (400 M Hz, CDCl₃): δ = 2.54 (d, J = 6.0 Hz, 4H, 2 × -CH₂), 3.35 (d, J = 4.1 Hz, 1H, -OH), 3.70 (s, 6H, 2 × -OCH₃), 4.44 (dp, J = 4.0, 6.1 Hz, 1H, -CH-) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 40.4, 51.9, 64.7, 172.2 ppm.

NMR spectra consistent with those previously reported within literature data.¹⁴⁵



Dimethyl-3-(tert-butyldimethylsilyloxy)pentanedioate (2.91). To **2.90** (1.75 g, 9.9 mmol, 1.0 equiv.) dissolved in anhydrous DMF (7.5 mL) under N₂, affording a 0.8 M overall solution, was added TBSCl (1.5 g, 13.8 mmol, 1.4 equiv.). Imidazole (2.0 g, 29.4 mmol, 3.0 equiv.) was added to a rapidly stirring solution, and left to stir for 12 h, at which point it stopped. The reaction mixture was quenched with saturated ammonium chloride, and diluted in ethyl acetate. The

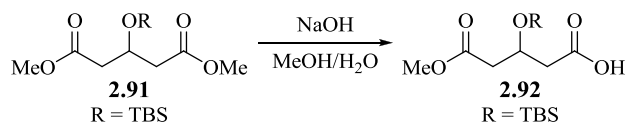
organic layers were then washed with water and an increasing gradient concentration of brine, followed by evaporation of the dried (MgSO_4) organic layers. Purification via flash chromatography (5% EA:hex) yielded 2.3 g (8.0 mmol, 70% yield) of **2.91** as clear, colorless oil.

$R_f = 0.27$ (silica gel, 10% EA:hex).

$^1\text{H NMR}$ (300 M Hz, CDCl_3): $\delta = 0.04$ (s, 6H, $\text{Si}(\text{CH}_3)_2$), 0.82 (s, 9H, *t*-Bu), 2.54 (d, $J = 6.2$ Hz, 4H, $2 \times \text{CH}_2$), 3.65 (s, 6H, $2 \times \text{OCH}_3$), 4.53 (p, $J = 6.2$ Hz, 1H, CH) ppm.

$^{13}\text{C NMR}$ (100 M Hz, CDCl_3): $\delta = -5.0, 17.9, 25.6, 42.4, 51.6, 66.3, 171.4$ ppm.

NMR spectra consistent with those previously reported within literature data.¹⁴⁶



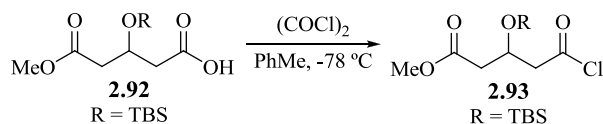
3-(tert-butylidimethylsilyloxy)-5-methoxy-5-oxopentanoic acid (2.92). To **2.91** (2.0 g, 6.89 mmol, 1.0 equiv.) in MeOH:H₂O (24 mL:12 mL) was added NaOH (7.7 mL, 1.0 M) and left to stir at rt for 1 d. Upon completion, the mixture was quenched with saturated NH_4Cl , diluted in EtOAc (50 mL) and extracted (3x10 mL). The aqueous layer was acidified and re-extracted with EtOAc (30 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated to afford 1.63 g (5.91 mmol, 86%) of crude **2.92** as clear, colorless oil.

$R_f = 0.20$ (silica gel, 20% EA:hex).

$^1\text{H NMR}$ (300 M Hz, CDCl_3): $\delta = 0.06$ (m, 3H, $-\text{CH}_3$), 0.83 (s, 9H, O-TBS *t*-Bu), 2.53 – 2.65 (m, 4H, $2 \times -\text{CH}_2-$), 3.66 (s, 3H, $-\text{OCH}_3$), 4.53 (p, $J = 6.0$ Hz, 1H, $-\text{CH}-$), 10.65 (br s, 1H, $-\text{CO}_2\text{H}$) ppm.

$^{13}\text{C NMR}$ (100 M Hz, CDCl_3): $\delta = -5.0, 17.9, 25.6, 41.9, 42.1, 51.7, 66.1, 171.3, 175.5$ ppm.

NMR spectra consistent with those previously reported within literature data.¹⁴⁷

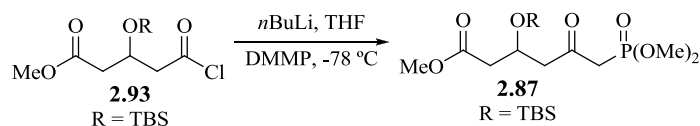


Methyl-3-(tert-butylidimethylsilyloxy)-5-chloro-5-oxopentanoate (2.93). A stirring solution of **2.92** (150 mg, 0.54 mmol, 1 equiv.) in freshly distilled toluene and catalytic DMF (5 μL , 10 mol%) under N_2 atmosphere was cooled to -78°C . To this mixture, slow-addition of oxalyl chloride was introduced and allowed to warm to rt over 30 min. Upon disappearance of starting material according to TLC (silica gel, 20% EA:hex), the mixture was concentrated *in vacuo* to afford a quantitative yield of **2.93** as clear, yellow oil. The crude residue was placed on a vacuum pump for 30 min and was immediately used in the subsequent step.

¹HNMR (400 M Hz, CDCl₃): δ = 0.07 (d, *J* = 8.4 Hz, 6H, Si(CH₃)₂), 0.83 (s, 9H, O-TBS *t*-Bu), 2.54 (dd, *J* = 3.5, 6.1 Hz, 2H, -CH₂-), 3.09 (dd, *J* = 7.2, 16.2 Hz, 1H, -CHH-), 3.17 (dd, *J* = 4.8, 16.2 Hz, 1H, -CHH-), 3.67 (s, 3H, -OCH₃), 4.53 – 4.59 (m, 1H, -CH-) ppm.

¹³CNMR (75 M Hz, CDCl₃): δ = -5.0, -4.9, 17.9, 25.6, 41.6, 51.7, 54.4, 65.8, 170.7, 171.3 ppm.

HRMS (EI): Calculated for C₁₂H₂₃O₄Si (M – Cl) 259.1365, Observed 259.1331 (Δ = 3.4 mmu).

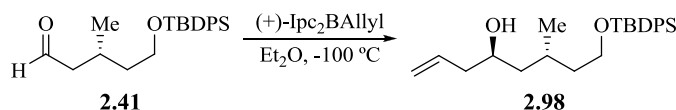


Methyl-3-(*tert*-butyldimethylsilyloxy)-6-(dimethoxyphosphoryl)-5-oxohexanoate (2.87). To a stirring solution of *n*BuLi (0.26 mL of 2.2 M in THF, 0.52 mmol, 2.2 equiv.) in THF (1 mL) at -78 °C, was added dimethyl methylphosphonate (60 μL, 0.52 mmol, 2.2 equiv.) over 10 Min. The resulting mixture was stirred for 1 h, maintaining a temperature between -50 and -30 °C, upon which the mixture was re-cooled to -78 °C and the freshly prepared **2.93** (70 μg, 0.24 mmol, 1.0 equiv.) was introduced slowly. The solution changed from a white/yellow opaque solution to a clear bright red, and upon completion was quenched with HCl (1 mL). The mixture was diluted in EtOAc, washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the crude residue *via* flash chromatography (3% MeOH:DCM) yielded 35 mg (0.09 mmol, 39% yield) of **2.87** as clear, colorless oil.

R_f = 0.25 (silica gel, 5% MeOH:DCM).

¹HNMR (400 M Hz, CDCl₃): δ = 0.07 (d, *J* = 10.1 Hz, 6H, 2 × O-TBS -CH₃), 0.84 (s, 9H, O-TBS *t*-Bu), 2.53 (dq, *J* = 6.2, 15.6 Hz, 2H, -CH₂-), 2.89 (dd, *J* = 2.3, 5.9 Hz, 2H, -CH₂-), 3.10 (d, *J* = 22.7 Hz, 2H, -CH₂-), 3.77 (m, 9H, 3x -OCH₃), 4.54 (p, *J* = 5.9 Hz, 1H, -CH-) ppm.

¹HNMR spectra consistent with those previously reported within literature data.¹⁴⁸



(4*R*,6*R*)-8-(*tert*-Butyldiphenylsilyloxy)-6-methyloct-1-en-4-ol (2.98). Two reaction flasks are prepared. In the first, **2.41** (1.689 g, 4.76 mmol, 1.0 equiv.) is dissolved in anhydrous ether (6 mL) and cooled to -100 °C while stirring under Ar atmosphere. In the second flask, (+)-Ipc₂Allyl Borane (5.0 mL of 1.0 M in pentane, 5.0 mmol, 1.05 equiv.) is transferred *via* a dry glass syringe from its ampule to the flask, and cooled to -100 °C while stirring under Ar atmosphere. The first flask is cannulated into the second, with anhydrous ether (4 mL) rinse. The reaction mixture is

slowly brought to $-78\text{ }^{\circ}\text{C}$, and the progress checked *via* TLC (silica gel, 10% EA:hex). Upon completion, the reaction is quenched with MeOH and allowed to stir for 20 Min. Addition of 15% NaOH (2 mL) induced a pale yellow color from the clear mixture, and was allowed to stir for 10 Min, followed by the addition of 30% aqueous H_2O_2 (4 mL), which induced an opaque white solution and exotherm. The reaction mixture was refluxed for 1 h, upon which the mixture was diluted in ether (40 mL) and washed with brine ($3 \times 50\text{ mL}$). The ether layer was dried with MgSO_4 filtered and concentrated *in vacuo*. Purification *via* flash chromatography (2% EA:hex) yielded 0.718 g (1.8 mmol, 40%) of **2.98** as clear, colorless oil.

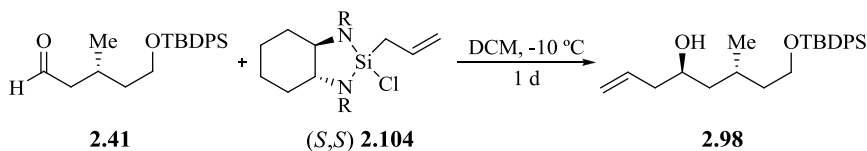
$R_f = 0.23$ (silica gel, 10% EA:hex).

IR (NaCl): $\nu_{\text{max}} = 3409, 3071, 2922, 2857, 1641, 1472\text{ cm}^{-1}$.

^1H NMR (400 M Hz, CDCl_3): $\delta = 0.85$ (d, $J = 6.8\text{ Hz}$, 3H, $-\text{CH}_3$), 1.02 (s, 9H, O-TBDPS *t*-Bu), 1.18 (ddd, $J = 3.8, 9.2, 13.8\text{ Hz}$, 1H, $-\text{CH}-$), 1.32 – 1.47 (m, 3H, $-\text{CHH}-$, $-\text{CH}_2-$), 1.54 – 1.64 (m, 2H, $-\text{CHH}-$), 1.76 – 1.86 (m, 1H, $-\text{OH}$), 2.07 – 2.14 (m, 1H, $-\text{CHH}-$), 2.20 – 2.27 (m, 1H, $-\text{CHH}-$), 3.64 – 3.73 (m, 3H, $-\text{CH}$, $-\text{CH}_2-$), 5.07 – 5.12 (m, 2H, $-\text{CH}_2$), 5.75 – 5.85 (m, 1H, $-\text{CH}-$), 7.34 – 7.43 (m, 6H, $-\text{CH}-\text{Ph}$), 7.64 – 7.66 (m, 4H, $-\text{CH}-\text{Ph}$) ppm.

^{13}C NMR (100 M Hz, CDCl_3): $\delta = 19.2, 19.5, 26.2, 26.9, 40.2, 42.6, 44.3, 62.1, 68.4, 118.0, 127.6, 129.5, 134.1, 134.9, 135.6\text{ ppm}$.

HRMS (EI): Calculated for $\text{C}_{21}\text{H}_{27}\text{O}_2\text{Si}$ (M – *t*-Bu) 339.1780, Observed 339.1797 ($\Delta = -1.7\text{ mmu}$).



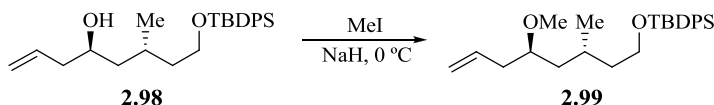
(4*R*,6*R*)-8-(*tert*-Butyldiphenylsilyloxy)-6-methyloct-1-en-4-ol (2.98). To a cooled ($-10\text{ }^{\circ}\text{C}$) solution of (S,S) **2.104** (0.203 g, 0.367 mmol, 1.0 equiv.) in DCM (3.75 mL, 0.2 M) was added **2.41** (0.130 g, 0.367 mmol, 1.0 equiv.). The reaction mixture was left to stir for 48 h at this temperature. Upon completion, 1 N HCl (1.0 mL) and EtOAc (2.0 mL) were added and the mixture was vigorously stirred at rt for 15 min. The layers were separated and the aqueous layer was further extracted with EtOAc ($3 \times 10\text{ mL}$), and the combined organic layers were diluted with hexane, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification *via* flash chromatography (2% EA:hex) yielded 37.1 mg (0.093 mmol, 25%) of **2.98** as clear, colorless oil.¹¹⁸

$R_f = 0.23$ (silica gel, 10% EA:hex).

^1H NMR (400 M Hz, CDCl_3): $\delta = 0.85$ (d, $J = 6.8\text{ Hz}$, 3H, $-\text{CH}_3$), 1.02 (s, 9H, O-TBDPS *t*-Bu), 1.18 (ddd, $J = 3.8, 9.2, 13.8\text{ Hz}$, 1H, $-\text{CH}-$), 1.32 – 1.47 (m, 3H, $-\text{CHH}-$, $-\text{CH}_2-$), 1.54 – 1.64 (m,

2H, -CHH-), 1.76 – 1.86 (m, 1H, -OH), 2.07 – 2.14 (m, 1H, -CHH-), 2.20 – 2.27 (m, 1H, -CHH-) 3.64 – 3.73 (m, 3H, -CH, -CH₂-), 5.07 – 5.12 (m, 2H, -CH₂-), 5.75 – 5.85 (m, 1H, -CH-), 7.34 – 7.43 (m, 6H, -CH- Ph), 7.64 – 7.66 (m, 4H, -CH- Ph) ppm.

¹HNMR spectra consistent with that previously obtained.



tert-Butyl((3*R*,5*R*)-5-methoxy-3-methyloct-7-enyloxy)diphenylsilane (2.99). To a 0 °C solution of 60% NaH (122.3 mg, 3.06 mmol, 2.0 equiv.) in anhydrous THF (5.0 mL) was added **2.98** (606.2 mg, 1.52 mmol, 1.0 equiv.) dropwise followed by addition of iodomethane (120 μL, 1.9 mmol, 1.25 equiv.). The reaction mixture was brought to rt and left to stir under N₂ atmosphere for 24 h while checking reaction progress *via* TLC (silica gel, 10% EA:hex). Upon completion, the reaction was cooled to 0 °C and diluted with 2.5 mL of H₂O. The aqueous layer was extracted twice with 5 mL of EtOAc. The combined organic layers were washed with brine (3 × 10 mL), dried with MgSO₄, filtered and concentrated *in vacuo*. Purification through a plug of silica (100% EtOAc) yielded 589.8 mg (1.44 mmol, 93%) of **2.99** as clear, colorless oil.

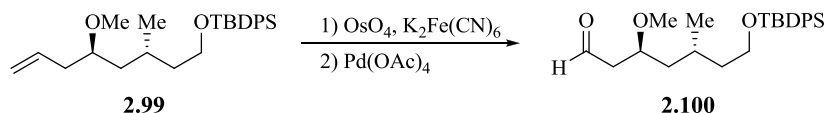
R_f = 0.51 (silica gel, 10% EA:hex).

IR (NaCl): $\nu_{\max}$ = 2953, 2856, 1456, 1452, 1371 cm⁻¹.

¹HNMR (400 M Hz, CDCl₃): δ = 0.82 (d, *J* = 6.7 Hz, 3H, -CH₃), 1.02 (s, 9H, O-TBDPS *t*-Bu), 1.15 (ddd, *J* = 4.4, 8.8, 14.1 Hz, 2H, -CH₂-), 1.30 – 1.40 (m, 2H, -CH₂-), 1.46 (ddd, *J* = 5.2, 8.6, 14.0 Hz, 1H, -CH-), 1.55 – 1.63 (m, 1H, -CH-), 1.71 – 1.82 (m, 1H, -CH-), 2.16 – 2.29 (m, 2H, -CH₂-), 3.22 – 3.29 (m, 1H, -CH-), 3.30 (s, 3H, -OCH₃), 3.62 – 3.72 (m, 2H, -CH₂-), 5.01 – 5.07 (m, 2H, -CH₂-), 5.77 (ddt, *J* = 7.0, 7.0, 10.2 Hz, 1H, -CH-), 7.33 – 7.42 (m, 6H, -CH- Ph), 7.65 (dd, *J* = 1.5, 7.8 Hz, 4H, -CH- Ph) ppm.

¹³CNMR (100 M Hz, CDCl₃): δ = 19.2, 19.7, 26.2, 26.9, 38.1, 40.2, 41.6, 56.4, 62.1, 78.3, 116.9, 127.6, 129.5, 134.1, 134.9, 135.6 ppm.

HRMS (EI): Calculated for C₂₂H₂₉O₂Si (M – *t*-Bu) 353.1937, Observed 353.1907 (Δ = 3.0 mmu).



(3*S*,5*R*)-7-(tert-butylidiphenylsilyloxy)-3-methoxy-5-methylheptanal (2.100). To **2.99** (0.200 g, 0.487 mmol, 1.0 equiv.) in *t*-BuOH:H₂O (1:1, 3.5 mL:3.5 mL) at rt was added potassium carbonate

(0.202 g, 1.461 mmol, 3.0 equiv.), followed by potassium ferricyanide (0.481 g, 1.461 mmol, 3.0 equiv.). Lastly, a solution of potassium osmate (VI) dihydrate (18 mg, 0.049 mmol, 0.1 equiv.) in 15% NaOH (0.2 mL) was added to the reaction and allowed to stir overnight under N₂ atmosphere. Upon completion *via* TLC (10% EA:hex), the mixture was diluted in 0.5 mL water, and extracted with EtOAc (3 × 10 mL), washed with brine (3 × 30 mL) and dried over MgSO₄, filtered and concentrated to dryness *in vacuo*. The crude product was diluted in anhydrous DCM (2 mL) followed by addition of lead tetraacetate (0.260 g, 0.584 mmol, 1.2 equiv.). The reaction was stirred vigorously for 1 h, concentrated to remove 75% of the DCM, and loaded directly on a pre-equilibrated column to be purified by flash chromatography (2% EA:hex), yielding **2.100** in 189.2 mg (0.459 mmol, 94%, 2 steps) as a clear, colorless oil.

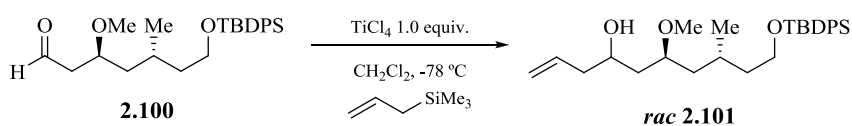
R_f = 0.31 (silica gel, 10% EA:hex).

IR (NaCl): $\nu_{\max}$ = 3071, 2961, 1725 cm⁻¹.

¹H NMR (400 M Hz, CDCl₃): δ = 0.86 (d, *J* = 6.6 Hz, 3H, -CH₃), 1.02 (s, 9H, O-TBDPS *t*-Bu), 1.18 (ddd, *J* = 5.0, 8.4, 13.8 Hz, 1H, -CHH-), 1.31 – 1.40 (m, 1H, -CHH-), 1.55 – 1.64 (m, 2H, -CH₂-), 1.73 – 1.84 (m, 1H, -CH-), 2.49 (ddd, *J* = 2.0, 5.2, 16.2 Hz, 1H, -CHH-), 2.57 (ddd, *J* = 2.6, 6.6, 16.2 Hz, 1H, -CHH-), 3.30 (s, 3H, -OCH₃), 3.62 – 3.78 (m, 3H, -CH-, -CH₂-), 7.33 – 7.43 (m, 6H, -CH- Ph), 7.64 (dd, *J* = 1.6, 7.9 Hz, 4H, -CH- Ph), 9.78 (dd, *J* = 2.0, 2.5 Hz, 1H, -CHO) ppm.

¹³C NMR (100 M Hz, CDCl₃): δ = 19.2, 19.7, 26.1, 26.9, 39.9, 42.1, 48.3, 56.8, 61.9, 74.4, 127.6, 129.6, 134.0, 135.6, 201.6 ppm.

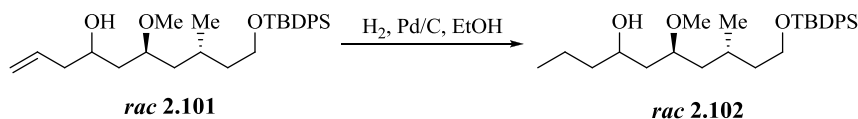
HRMS (EI): Calculated for C₂₀H₂₃O₂Si (M – (*t*-Bu + MeOH)) 323.1467, Observed 323.1491 (Δ = - 2.4 mmu).



(6*S*,8*R*)-10-(*tert*-butyldiphenylsilyloxy)-6-methoxy-8-methyldec-1-en-4-ol (2.101). To a stirred solution of **2.100** (60.0 mg, 0.145 mmol, 1.0 equiv.) in CH₂Cl₂ (1.5 mL) was added, at -78 °C, TiCl₄ (20 μL, 0.145 mmol, 1.0 equiv.). After 10 min, trimethylallylsilane (30 μL, 0.175 mmol, 1.2 equiv.) was added dropwise and stirring was continued at -78 °C for at least 30 min. Upon complete consumption of aldehyde, the mixture was quenched with NH₄Cl aq. and the temperature was allowed to warm to rt. The aqueous phase was separated and extracted with CH₂Cl₂ (3 × 4 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by flash chromatography (5% EA:hex) to give 51.2 mg of **2.101** (0.112 mmol, 78%) as clear, colorless oil.

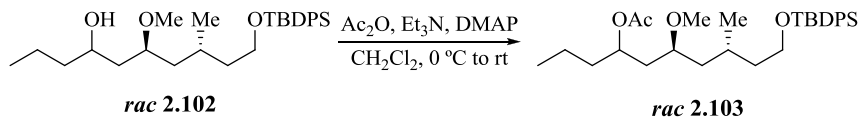
$R_f = 0.16$ (silica gel, 10% EA:hex).

$^1\text{H NMR}$ (400M Hz, CDCl_3): $\delta = 0.85$ (dd, $J = 2.5, 6.5$ Hz, 3H, $-\text{CH}_3$), 1.02 (s, 9H, O-TBDPS *t*-Bu), 1.13 – 1.38 (m, 6H, $3 \times -\text{CH}_2-$), 1.62 – 1.76 (m, 2H, $-\text{CH}_2-$), 2.15 – 2.24 (m, 2H, $-\text{CH}_2-$), 3.30 – 3.36 (m, 3H, $-\text{OCH}_3$), 3.51 – 3.56 (m, 1H, $-\text{OH}$), 3.63 – 3.72 (m, 2H, $-\text{CH}_2-$), 3.74 – 3.97 (m, 1H, $-\text{CH}-$), 5.04 – 5.11 (m, 2H, $-\text{CH}_2-$), 5.74 – 5.86 (m, 1H, $-\text{CH}-$), 7.34 – 7.43 (m, 6H, $-\text{CH}-\text{Ph}$), 7.63 – 7.66 (m, 4H, $-\text{CH}-\text{Ph}$) ppm.



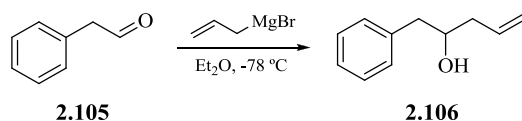
(6*S*,8*R*)-10-(*tert*-butyldiphenylsilyloxy)-6-methoxy-8-methyldecan-4-ol (2.102). Hydrogen gas was bubbled through a stirring solution of **2.101** (49.7 mg, 0.109 mmol, 1.0 equiv.) and Pd/C (1.2 mg, 0.011 mmol, 0.1 equiv.) in EtOH (0.4 mL, 0.3 M) at rt for 1 d. Upon completion, the mixture was diluted with EtOAc (2 mL) and washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford 38.0 mg of *crude* **2.102** (0.083 mmol, 77%) as colorless oil.

$^1\text{H NMR}$ (400M Hz, CDCl_3) clearly indicated the disappearance of the unsaturation peaks between 5.0 and 6.0 ppm. The silyl protecting group clearly indicated its *tert*-butyl peak [$\delta = 1.02$ (s, 9H), ppm], and the aromatic region integrated for the ten protons of the, [$\delta = 7.34 - 7.43$ (m, 6H), 7.61 – 7.71 (m, 4H) ppm].



(6*S*,8*R*)-10-(*tert*-butyldiphenylsilyloxy)-6-methoxy-8-methyldecan-4-yl acetate (2.103). A solution of **2.102** (38.0 mg, 0.083 mmol, 1.0 equiv.), Et_3N (24 μL , 0.174 mmol, 2.1 equiv.) and cat. DMAP (1.0 mg, 0.008 mmol, 0.05 equiv.) in DCM (0.4 mL) was treated with Ac_2O (12 μL , 0.125 mmol, 1.5 equiv.) at rt for 6 h, quenched by MeOH (0.5 mL) and diluted with EtOAc (5 mL). The organic layer was washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford 38.0 mg of *crude* **2.103** (0.076 mmol, 92%) as colorless oil.

$^1\text{H NMR}$ (400M Hz, CDCl_3) clearly indicated the emergence of the acetate peak [$\delta = 2.00$ (s, 3H) ppm], and shifting of neighboring peaks downfield. The silyl protecting group clearly indicated its *tert*-butyl peak [$\delta = 1.02$ (s, 9H), ppm], and the aromatic region integrated for the ten protons of the, [$\delta = 7.34 - 7.43$ (m, 6H), 7.61 – 7.71 (m, 4H) ppm].



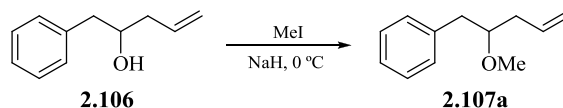
1-Phenylpent-4-en-2-ol (2.106). Phenylacetaldehyde **2.105** (4.00 g, 33.3 mmol, 1.0 equiv.) in anhydrous ethyl ether (110 mL) under argon atmosphere at 0 °C was added allyl magnesium bromide (1 M solution in Et₂O, 12.8 mL, 73.3 mmol, 2.2 equiv.) dropwise over 5 minutes. The reaction was stirred for 1 h, quenched with saturated NH₄Cl (20 mL). The organic layers were then washed with brine (3 × 50 mL), followed by evaporation of the dried (MgSO₄) organic layers *in vacuo*. Purification *via* flash chromatography (5% EA:hex) yielded 4.04g (24.9 mmol, 75%) of **2.106** as a clear, pale yellow oil.

R_f = 0.38 (silica gel, 20% EA:hex).

¹HNMR (300M Hz, CDCl₃): δ = 1.65 (d, J = 3.6 Hz, 1H, -OH), 2.15 – 2.38 (m, 2H, -CH₂-), 2.71 (dd, J = 7.9, 13.6 Hz, 1H, -CHH-), 2.81 (dd, J = 5.0, 13.6 Hz, 1H, -CHH-), 3.83 – 3.92 (m, 1H, -CH-), 5.11 – 5.18 (m, 2H, -CH₂-), 5.79 – 5.92 (m, 1H, -CH-), 7.19 – 7.34 (m, 5H, -CH- Ph) ppm.

¹³CNMR (100M Hz, CDCl₃): δ = 41.2, 43.3, 71.7, 118.2, 126.5, 128.6, 129.4, 134.7, 138.4 ppm.

NMR spectra consistent with those previously reported within literature data.¹⁴⁹



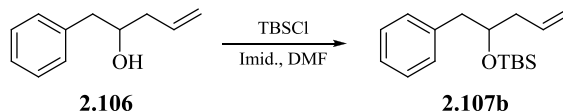
(2-Methoxypent-4-enyl)benzene (2.107a). To a 0 °C solution of 60% NaH (1.0 g, 12.4 mmol, 2.0 equiv.) in anhydrous THF (20.5 mL) was added **2.106** (1.0 g, 6.16 mmol, 1.0 equiv.) dropwise followed by addition of iodomethane (0.52 mL, 8.06 mmol, 1.3 equiv.). The reaction mixture was brought to rt and left to stir under N₂ atmosphere for 24 h while checking reaction progress *via* TLC (silica gel, 10% EA:hex). Upon completion, the reaction was cooled to 0 °C and diluted with 5 mL of H₂O. The aqueous layer was extracted twice with 30 mL of EtOAc. The combined organic layers were washed with brine (3 × 30 mL), dried with MgSO₄, filtered and concentrated *in vacuo*. Purification through a plug of silica (100% EtOAc) yielded 1.083 g (6.14 mmol, 100%) of **2.107a** as clear, yellow oil.

R_f = 0.51 (silica gel, 10% EA:hex).

¹HNMR (400M Hz, CDCl₃): δ = 2.17 – 2.30 (m, 2H, -CH₂-), 2.72 (dd, J = 6.3, 13.8 Hz, 1H, -CHH-), 2.81 (dd, J = 6.3, 13.8 Hz, 1H, -CHH-), 3.31 (s, 3H, -OCH₃), 3.43 (p, J = 6.0 Hz, 1H, -CH-), 5.04 – 5.09 (m, 2H, -CH₂-), 5.79 – 5.89 (m, 1H, -CH-), 7.17 – 7.29 (m, 5H, -CH- Ph) ppm.

¹³CNMR (100M Hz, CDCl₃): δ = 37.6, 39.9, 57.0, 81.8, 117.2, 126.1, 128.3, 129.5, 134.8, 139.0 ppm.

HRMS (EI): Calculated for C₁₁H₁₃ (M – OMe) 145.1017, Observed 145.1017 (Δ = 0.0mmu).

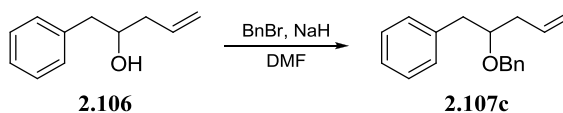


tert-Butyldimethyl(1-phenylpent-4-en-2-yloxy)silane (2.107b). To **2.106** (1.0 g, 6.16 mmol, 1 equiv.) dissolved in anhydrous DMF (7.5 mL) under N₂, affording a 0.8M overall solution, was added TBSCl (1.2 g, 7.7 mmol, 1.25 equiv.). Imidazole (1.1 g, 15.5 mmol, 2.50 equiv.) was added to a rapidly stirring solution, and left to stir for 24 h, at which point it stopped. The reaction mixture was quenched with saturated ammonium chloride, and diluted in ethyl acetate. The organic layers were then washed with water and an increasing gradient concentration of brine, followed by evaporation of the dried (MgSO₄) organic layers. Purification *via* flash chromatography (2% EA:hex) yielded 1.64 (5.9 mmol, 96% yield) of **2.107b** as clear, colorless oil. R_f = 0.72 (silica gel, 10% EA:hex).

¹HNMR (400M Hz, CDCl₃): δ = -0.26 (s, 3H, SiCH₃), -0.08 (s, 3H, SiCH₃), 0.82 (s, 9H, *t*-Bu), 2.15 – 2.27 (m, 2H, -CH₂-), 2.65 (dd, *J* = 7.2, 13.4 Hz, 1H, -CHH-), 2.74 (dd, *J* = 5.5, 13.4 Hz, 1H, -CHH-), 3.83 – 3.89 (m, 1H, -CH-), 5.00 – 5.06 (m, 2H, -CH₂), 5.85 (dddd, *J* = 7.1, 7.1, 10.4, 17.0 Hz, 1H, -CH-), 7.14 – 7.26 (m, 5H, -CH- Ph) ppm.

¹³CNMR (100M Hz, CDCl₃): δ = -5.1, -4.7, 14.1, 18.1, 25.9, 31.6, 41.7, 43.5, 73.5, 117.1, 126.0, 128.1, 129.8, 135.1, 139.3 ppm.

HRMS (EI): Calculated for C₁₃H₁₉OSi (M – *t*-Bu) 219.1205, Observed 219.1182 (Δ = 2.3 mmu).



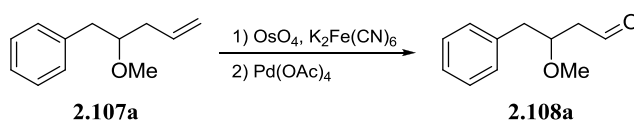
(2-(Benzyloxy)pent-4-enyl)benzene (2.107c). To **2.106** (2.0 g, 12.3 mmol, 1.0 equiv.) dissolved in anhydrous DMF (120 mL) under N₂ and cooled to 0 °C, affording a 0.1 M overall solution, was added NaH (2.0 g, 49.3 mmol, 4.0 equiv.). The solution was stirred for 30 minutes, whereupon benzyl bromide (4.4 mL, 37.0 mmol, 3.0 equiv.) was added to a rapidly stirring solution, and brought to rt over 2 h. The reaction mixture was quenched with MeOH, and diluted in Et₂O and poured into H₂O. The organic layers were then separated with brine, followed by evaporation of the dried (MgSO₄) organic layers. Purification *via* flash chromatography (5% EA:hex) yielded 1.89 g (10.7 mmol, 87% yield) of **2.107c** as clear, colorless oil.

$R_f = 0.72$ (silica gel, 10% EA:hex).

$^1\text{H NMR}$ (400M Hz, CDCl_3): $\delta = 2.28 - 2.32$ (m, 2H, $-\text{CH}_2-$), 2.82 (dq, $J = 7.0, 13.7$ Hz, 2H, $-\text{CH}_2-$), 3.65 (p, $J = 5.8$ Hz, 1H, $-\text{CH}-$), 4.40, 4.50 (ABq, $J = 11.6$ Hz, 2H, $-\text{CH}_2-$), 5.06 – 5.11 (m, 2H, $-\text{CH}_2-$), 5.88 (m, 1H, $-\text{CH}-$), 7.18 – 7.22 (m, 5H, $-\text{CH}-\text{Ph}$), 7.26 – 7.30 (m, 5H, $-\text{CH}-\text{Ph}$) ppm.

$^{13}\text{C NMR}$ (100M Hz, CDCl_3): $\delta = 39.8, 40.4, 40.7, 40.6, 42.0, 42.2, 67.6, 70.6, 71.4, 71.9, 78.0, 81.0, 117.3, 117.7, 126.3, 126.4, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 129.5, 129.6, 134.9, 134.9, 137.6, 138.0, 138.1, 138.5$ ppm.

HRMS (EI): Calculated for $\text{C}_{11}\text{H}_{13}\text{O}^+$ ($\text{M} - \text{C}_7\text{H}_7$) $^+$ 161.0966, Observed 161.0983 ($\Delta = 1.7$ mmu).



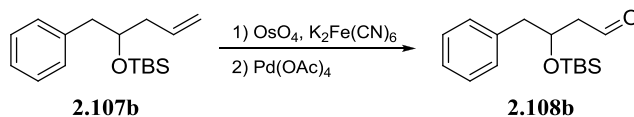
3-Methoxy-4-phenylbutanal (2.108a). To **2.107a** (379.0 mg, 2.15 mmol, 1.0 equiv.) in *t*-BuOH:H₂O (1:1, 12 mL:12 mL) at rt was added potassium carbonate (892 mg, 6.45 mmol, 3.0 equiv.), followed by potassium ferricyanide (2.12 g, 6.45 mmol, 3.0 equiv.). Lastly, a solution of potassium osmate (VI) dihydrate (35 mg, 0.095 mmol, 0.04 equiv.) in 15% NaOH (0.4 mL) was added to the reaction and allowed to stir overnight under N₂ atmosphere. Upon completion via TLC (10% EA:hex), the mixture was diluted in 1.0 mL water, and extracted with EtOAc (3 × 10 mL), washed with brine (3 × 30 mL) and dried over MgSO₄, filtered and concentrated to dryness *in vacuo*. The crude product was diluted in anhydrous DCM (7 mL) followed by addition of lead tetraacetate (1.15 g, 2.58 mmol, 1.2 equiv.). The reaction was stirred vigorously for 1 h, concentrated to remove 75% of the DCM, and loaded directly on a pre-equilibrated column to be purified by flash chromatography (2% EA:hex), yielding **2.108a** in 221.0 mg (1.24 mmol, 58%, 2 steps) as a clear, pale yellow oil.

$R_f = 0.31$ (silica gel, 10% EA:hex).

$^1\text{H NMR}$ (300M Hz, CDCl_3): $\delta = 2.46$ (ddd, $J = 1.7, 4.7, 16.5$ Hz, 1H, $-\text{CHH}-$), 2.55 (ddd, $J = 2.4, 7.4, 16.5$ Hz, 1H, $-\text{CHH}-$), 2.73 (dd, $J = 7.0, 13.6$ Hz, 1H, $-\text{CHH}-$), 2.98 (dd, $J = 5.6, 13.6$ Hz, 1H, $-\text{CHH}-$), 3.37 (s, 3H, $-\text{OCH}_3$), 3.89 – 3.97 (m, 1H, $-\text{CH}-$), 7.16 – 7.31 (m, 5H, $-\text{CH}-\text{Ph}$), 9.72 (dd, $J = 1.7, 2.4$ Hz, 1H, $-\text{CHO}$) ppm.

$^{13}\text{C NMR}$ (75M Hz, CDCl_3): $\delta = 39.9, 47.6, 57.2, 77.5, 126.6, 128.5, 129.5, 137.4, 201.2$ ppm.

HRMS (EI): Calculated for $\text{C}_{11}\text{H}_{11}\text{O}$ ($\text{M} - \text{OMe}$) 147.0810, Observed 147.0804 ($\Delta = 0.6$ mmu).



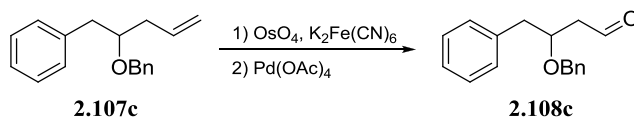
3-(*tert*-Butyldimethylsilyloxy)-4-phenylbutanal (2.108b). To **2.107b** (431.0 mg, 1.56 mmol, 1.0 equiv.) in *t*-BuOH:H₂O (1:1, 10 mL:10 mL) at rt was added potassium carbonate (650.0 mg, 4.68 mmol, 3.0 equiv.), followed by potassium ferricyanide (1.54 g, 4.68 mmol, 3.0 equiv.). Lastly, a solution of potassium osmate (VI) dihydrate (25 mg, 0.068 mmol, 0.04 equiv.) in 15% NaOH (0.3 mL) was added to the reaction and allowed to stir overnight under N₂ atmosphere. Upon completion via TLC (10% EA:hex), the mixture was diluted in 1.0 mL water, and extracted with EtOAc (3 × 10 mL), washed with brine (3 × 30 mL) and dried over MgSO₄, filtered and concentrated to dryness *in vacuo*. The crude product was diluted in anhydrous DCM (6.5 mL) followed by addition of lead tetraacetate (850.0 mg, 1.87 mmol, 1.2 equiv.). The reaction was stirred vigorously for 1 h, concentrated to remove 75% of the DCM, and loaded directly on a pre-equilibrated column to be purified by flash chromatography (2% EA:hex), yielding **2.108b** in 230.5 mg (0.83 mmol, 53%, 2 steps) as a clear, colorless oil.

R_f = 0.31 (silica gel, 10% EA:hex).

¹H NMR (400M Hz, CDCl₃): δ = -0.12 (s, 3H, SiCH₃), -0.01 (s, 3H, SiCH₃), 0.84 (s, 9H, *t*-Bu), 2.49 (dd, *J* = 2.4, 5.7 Hz, 2H, -CH₂-), 2.76 (dd, *J* = 6.7, 13.4 Hz, 1H, -CHH-), 2.85 (dd, *J* = 6.3, 13.4 Hz, 1H, -CHH-), 4.36 (p, *J* = 6.2 Hz, 1H, -CH-), 7.14 – 7.29 (m, 5H, -CH- Ph), 9.76 (t, *J* = 2.3 Hz, 1H, CHO) ppm.

¹³C NMR (100M Hz, CDCl₃): δ = -4.9, -4.8, 18.0, 25.8, 44.5, 50.4, 69.6, 126.6, 128.4, 129.7, 137.8, 201.9 ppm.

HRMS (EI): Calculated for C₁₂H₁₇O₂Si (M – *t*-Bu) 221.0998, Observed 221.0993 (Δ = 0.5 mmu).



3-(Benzyloxy)-4-phenylbutanal (2.108c). To **2.107c** (1.0 g, 5.67 mmol, 1.0 equiv.) in *t*-BuOH:H₂O (1:1, 25 mL:25 mL) at rt was added potassium carbonate (2.4 g, 17.0 mmol, 3.0 equiv.), followed by potassium ferricyanide (5.6 g, 17.0 mmol, 3.0 equiv.). Lastly, a solution of potassium osmate (VI) dihydrate (10 mg, 0.2 mmol, 0.04 equiv.) in 15% NaOH (0.5 mL) was added to the reaction and allowed to stir overnight under N₂ atmosphere. Upon completion via TLC (10% EA:hex), the mixture was diluted in 5.0 mL water, and extracted with EtOAc (3 × 10 mL), washed with brine (3 × 30 mL) and dried over MgSO₄, filtered and concentrated to dryness *in vacuo*. The crude product was diluted in anhydrous DCM (20 mL) followed by addition of lead

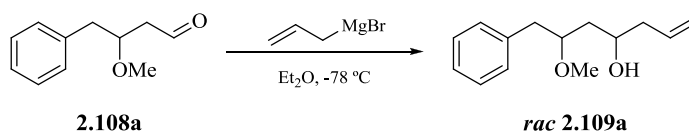
tetraacetate (3.14 g, 7.08 mmol, 1.2 equiv.). The reaction was stirred vigorously for 1 h, concentrated to remove 75% of the DCM, and loaded directly on a pre-equilibrated column to be purified by flash chromatography (2% EA:hex), yielding 439.7 mg of **2.108c** (2.50 mmol, 44%, 2 steps) as a clear, colorless oil.

R_f = 0.22 (silica gel, 10% EA:hex).

$^1\text{H NMR}$ (400M Hz, CDCl_3): δ = 2.50 (ddd, J = 1.7, 4.5, 16.7 Hz, 1H, -CHH-), 2.63 (ddd, J = 2.5, 7.8, 16.7 Hz, 1H, -CHH-), 2.80 (dd, J = 7.0, 13.6 Hz, 1H, -CHH-), 3.02 (dd, J = 6.1, 13.5 Hz, 1H, -CHH-), 4.13 – 4.19 (m, 1H, -CH-), 4.52 (d, J = 5.4 Hz, 2H, -CH₂-), 7.17 – 7.22 (m, 4H, -CH- Ph), 7.26 – 7.34 (m, 6H, -CH- Ph), 9.70 (dd, J = 1.6, 2.5 Hz, 1H, -CHO) ppm.

$^{13}\text{C NMR}$ (100M Hz, CDCl_3): δ = 40.6, 48.0, 71.7, 75.5, 126.6, 127.8, 127.9, 128.4, 128.6, 129.6, 137.6, 137.9, 201.3 ppm.

HRMS (EI): Calculated for $\text{C}_{10}\text{H}_{11}\text{O}_2^+$ ($M - \text{C}_7\text{H}_7$)⁺ 163.0759, Observed 163.0759 (Δ = 0.0 mmu).



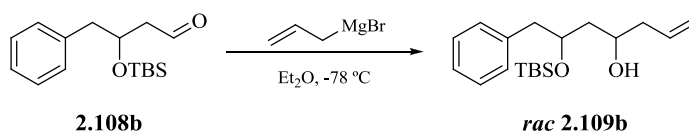
6-Methoxy-7-phenylhept-1-en-4-ol (2.109a). To a stirred solution of **2.108a** (150.0 mg, 0.84 mmol, 1.0 equiv.) in anhydrous ethyl ether (3 mL) under argon atmosphere at 0 °C was added allyl magnesium bromide (1.0 M solution in Et_2O , 0.345 mL, 2.02 mmol, 2.4 equiv.) dropwise over 5 min. The reaction was stirred for 1 h, quenched with saturated NH_4Cl (5 mL). The organic layers were then washed with brine (3×10 mL), followed by evaporation of the dried (MgSO_4) organic layers *in vacuo*. Purification *via* flash chromatography (5% EA:hex) yielded **2.109a** as clear, colorless oil.

R_f = 0.12 (silica gel, 10% EA:hex).

$^1\text{H NMR}$ (400M Hz, CDCl_3): δ = 1.48 – 1.65 (m, 4H, $2 \times$ -CH₂-), 2.11 – 2.20 (m, 4H, $2 \times$ -CH₂-), 2.65 – 2.73 (m, 2H, $2 \times$ -CHH-), 2.91 – 3.00 (m, 2H, $2 \times$ -CHH-), 3.36 (s, 3H, -CH₃), 3.40 (s, 3H, -CH₃), 3.55 – 3.65 (m, 2H, $2 \times$ -OH), 3.70 – 3.81 (m, 2H, $2 \times$ -CH-), 3.95 (ddt, J = 3.1, 8.9, 6.1 Hz, 1H, -CH-), 5.00 – 5.09 (m, 4H, $2 \times$ -CH₂-), 5.70 – 5.84 (m, 2H, $2 \times$ -CH-), 7.15 – 7.23 (m, 6H, -CH- Ph), 7.24 – 7.31 (m, 4H, -CH- Ph) ppm.

$^{13}\text{C NMR}$ (100M Hz, CDCl_3): δ = 39.2, 39.7, 39.9, 39.9, 42.0, 42.2, 56.8, 57.3, 67.7, 70.9, 80.2, 83.4, 117.2, 117.7, 126.2, 126.3, 128.3, 128.4, 129.4, 129.5, 134.8, 134.6, 137.9, 138.4 ppm.

HRMS (EI): Calculated for $\text{C}_7\text{H}_{13}\text{O}_2$ ($M - \text{C}_7\text{H}_7$) 129.0916, Observed 129.0912 (Δ = 0.4 mmu)



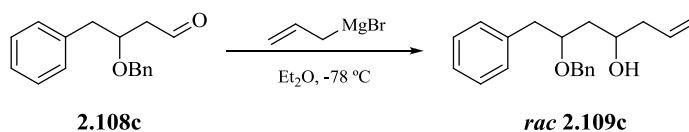
6-(tert-Butyldimethylsilyloxy)-7-phenylhept-1-en-4-ol (2.109b). To a stirred solution of **2.108b** (100.0 mg, 0.36 mmol, 1.0 equiv.) in anhydrous ethyl ether (1.2 mL) under argon atmosphere at 0 °C was added allyl magnesium bromide (1.0 M solution in Et₂O, 0.150 mL, 0.86 mmol, 2.4 equiv.) dropwise over 5 min. The reaction was stirred for 1 h, quenched with saturated NH₄Cl (3 mL). The organic layers were then washed with brine (3 × 5 mL), followed by evaporation of the dried (MgSO₄) organic layers *in vacuo*. Purification *via* flash chromatography (5% EA:hex) yielded **2.109b** as clear, colorless oil.

R_f = 0.23 (silica gel, 10% EA:hex).

¹HNMR (400M Hz, CDCl₃): δ = -0.16 (s, 3H, -CH₃), 0.00 (s, 3H, -CH₃), 0.03 (s, 3H, -CH₃), 0.08 (s, 3H, -CH₃), 0.87 (s, 9H, *t*-Bu), 0.89 (s, 9H, *t*-Bu), 1.50 – 1.63 (m, 4H, 2 × -CH₂-), 2.08 – 2.26 (m, 4H, 2 × -CH₂-), 2.76 – 2.93 (m, 4H, 2 × -CH₂-), 3.37 (d, *J* = 1.7 Hz, 1H, -OH), 3.74 – 3.80 (m, 1H, -OH), 4.03 – 4.13 (m, 2H, 2 × -CH-), 4.16 – 4.21 (m, 1H, -CH-), 5.01 – 5.10 (m, 4H, 2 × -CH₂-), 5.70 – 5.85 (m, 2H, 2 × -CH-), 7.112 – 7.28 (m, 10H, -CH- Ph) ppm.

¹³CNMR (100M Hz, CDCl₃): δ = -5.1, -4.9, -4.7, -4.37 18.0, 18.0, 25.9, 40.8, 42.1, 42.4, 42.5, 43.0, 44.9, 67.7, 69.8, 73.1, 74.0, 76.7, 77.1, 77.4, 117.4, 117.6, 126.3, 126.3, 128.3, 128.4, 128.8, 128.9, 129.6, 129.6, 134.8, 134.9, 138.3, 138.6 ppm.

HRMS (EI): Calculated for C₁₅H₂₃O₂Si (M – *t*-Bu) 263.1467, Observed 263.1364 (Δ = 10.3 mmu)



6-(Benzyloxy)-7-phenylhept-1-en-4-ol (2.109c). To a stirred solution of **2.108c** (170.0 mg, 0.668 mmol, 1.0 equiv.) in anhydrous ethyl ether (2.0 mL) under argon atmosphere at 0 °C was added allyl magnesium bromide (1.0 M solution in Et₂O, 0.275 mL, 1.604 mmol, 2.4 equiv.) dropwise over 5 min. The reaction was stirred for 1 h, quenched with saturated NH₄Cl (5 mL). The organic layers were then washed with brine (3 × 10 mL), followed by evaporation of the dried (MgSO₄) organic layers *in vacuo*. Purification *via* flash chromatography (5% EA:hex) yielded **2.109c** as clear, colorless oil.

R_f = 0.19 (silica gel, 10% EA:hex).

¹HNMR (400M Hz, CDCl₃): δ = 1.59 – 1.63 (m, 4H, 2 × -CH₂-), 2.09 – 2.18 (m, 4H, 2 × -CH₂-), 2.77 (dq, *J* = 1.8, 6.7 Hz, 2H, 2 × -CHH-), 2.98 – 3.04 (m, 2H, 2 × -CHH-), 3.74 – 3.80 (m, 1H, -

CH-), 3.82 – 3.89 (m, 1H, -CH-), 3.90 – 3.99 (m, 2H, 2 × -CH-), 4.43 – 4.63 (m, 4H, 2 × -CH₂-), 5.00 – 5.07 (m, 4H, 2 × -CH₂), 5.69 – 5.81 (m, 2H, 2 × -CH-), 7.17 – 7.23 (m, 8H, -CH- Ph), 7.25 – 7.35 (m, 12H, -CH- Ph) ppm.

¹³CNMR (100M Hz, CDCl₃): δ = 39.2, 39.7, 39.9, 39.9, 42.0, 42.2, 56.8, 57.3, 67.7, 70.9, 80.2, 83.4, 117.2, 117.7, 126.2, 126.3, 128.3, 128.4, 129.4, 129.5, 134.8, 134.6, 137.9, 138.4 ppm.

HRMS (EI): Calculated for C₇H₁₃O₂ (M – C₇H₇) 129.0916, Observed 129.0912 (Δ = 0.4 mmu)

2.7.3 Spectral Data of Compounds (¹HNMR, ¹³CNMR, COSY, HSQC, HMQC)

NMR spectra were recorded on Bruker Avance 300 Hz or 400 Hz instruments, and calibrated using residual undeuterated solvent (CDCl₃: δ H = 7.26 ppm, δ C = 77.0 ppm) as an internal reference. All the spectra are arranged to reflect the synthetic procedures shown in the schemes.

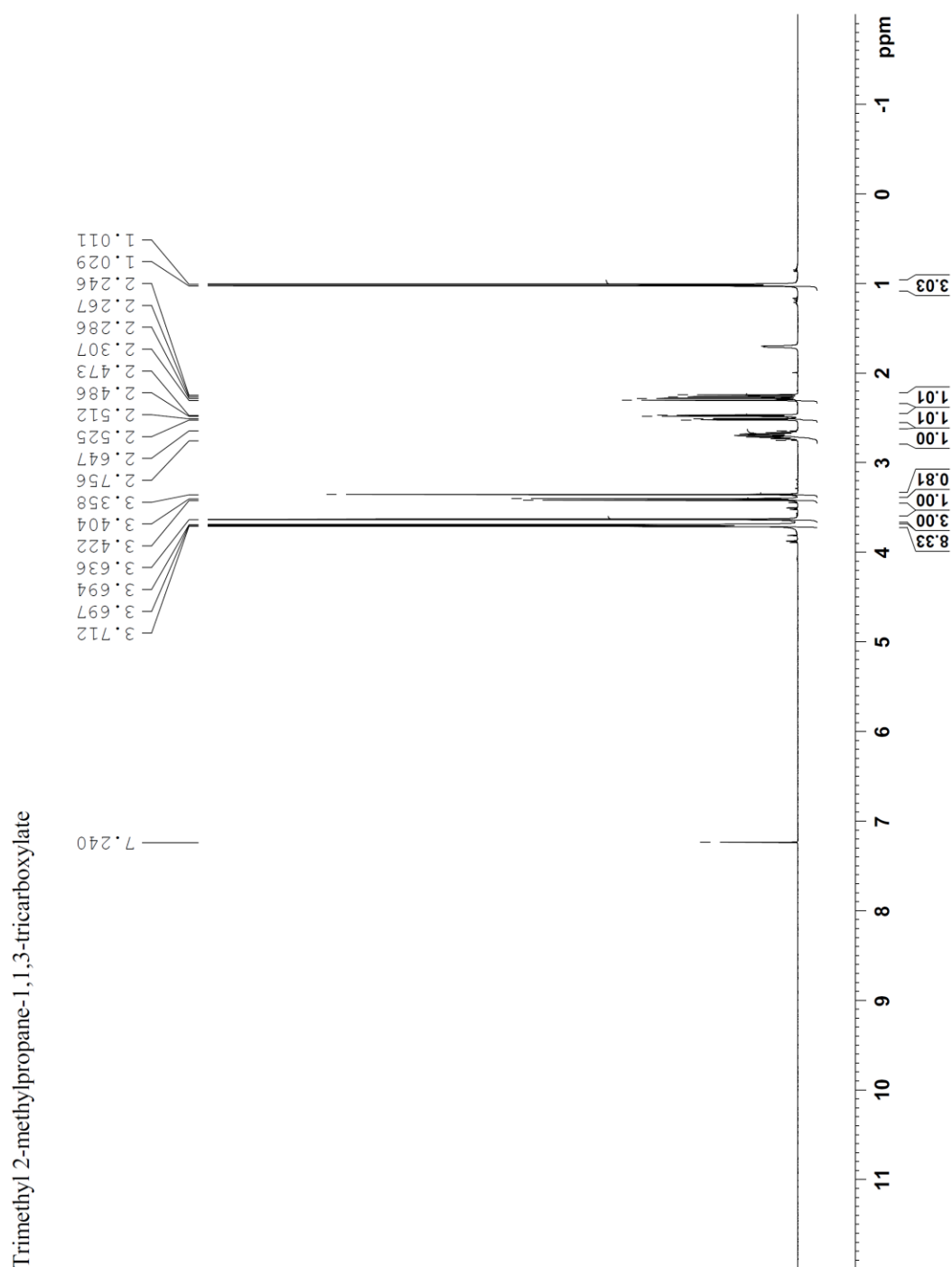


Figure 2.15 – ^1H NMR of trimethyl-2-methylpropane-1,1,3-tricarboxylate (**2.44**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

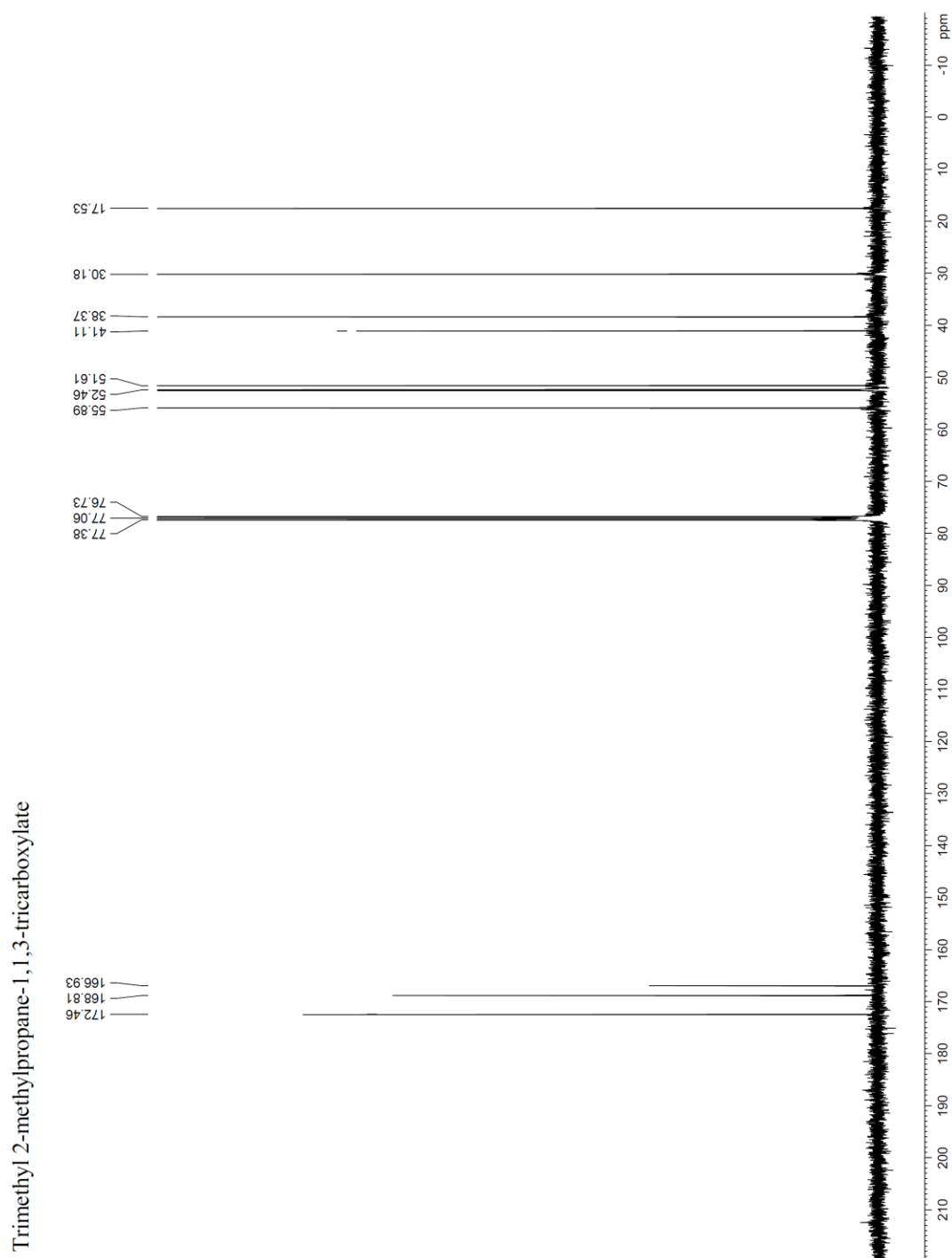


Figure 2.16 – ¹³CNMR of trimethyl-2-methylpropane-1,1,3-tricarboxylate (**2.44**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl₃.

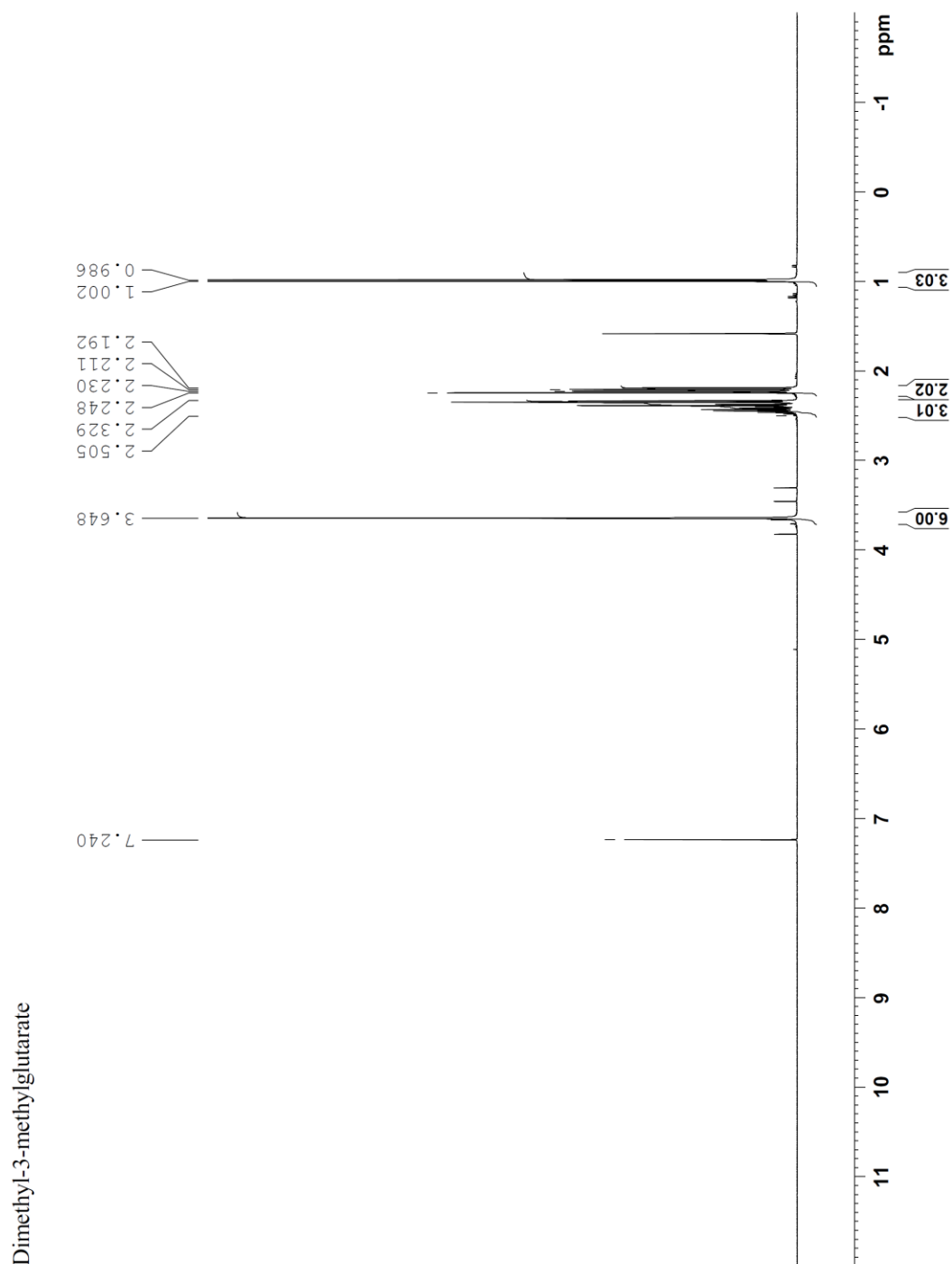


Figure 2.17 – ^1H NMR of dimethyl-3-methylglutarate (**2.45**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

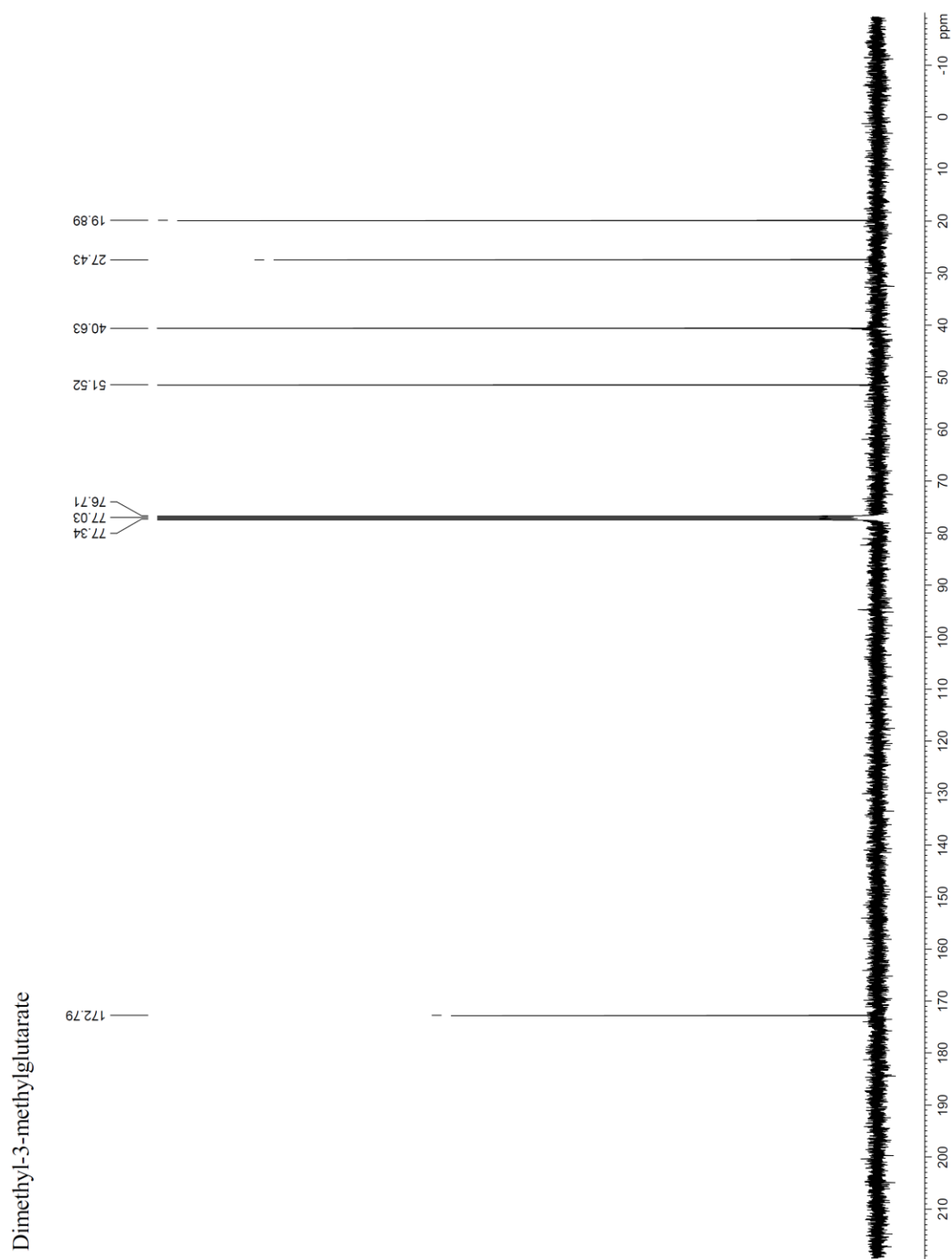


Figure 2.18 – ¹³CNMR of dimethyl-3-methylglutarate (2.45), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl₃.

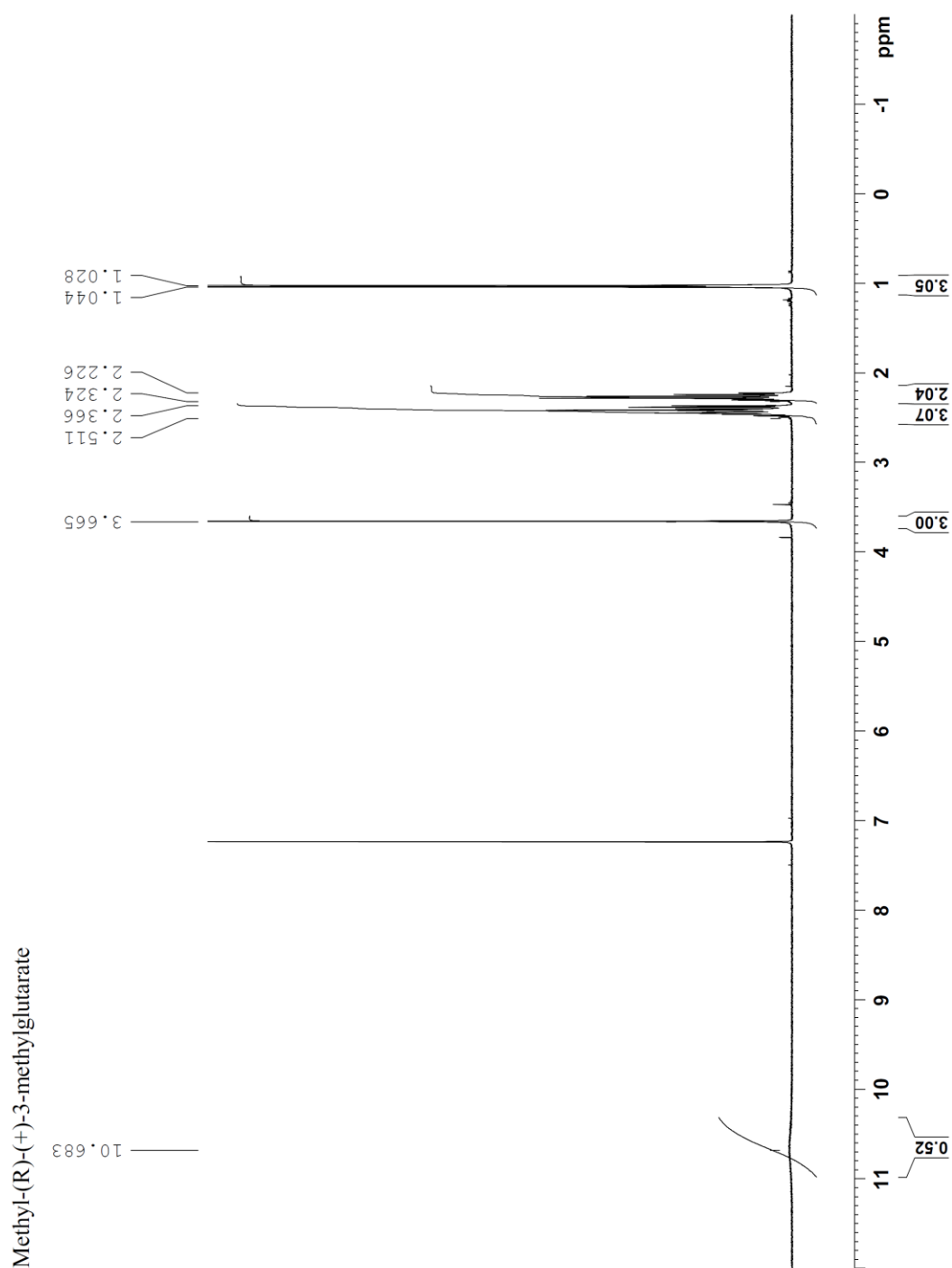


Figure 2.19 – ¹H NMR of methyl-(R)-(+)-3-methylglutarate (2.46), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl₃.

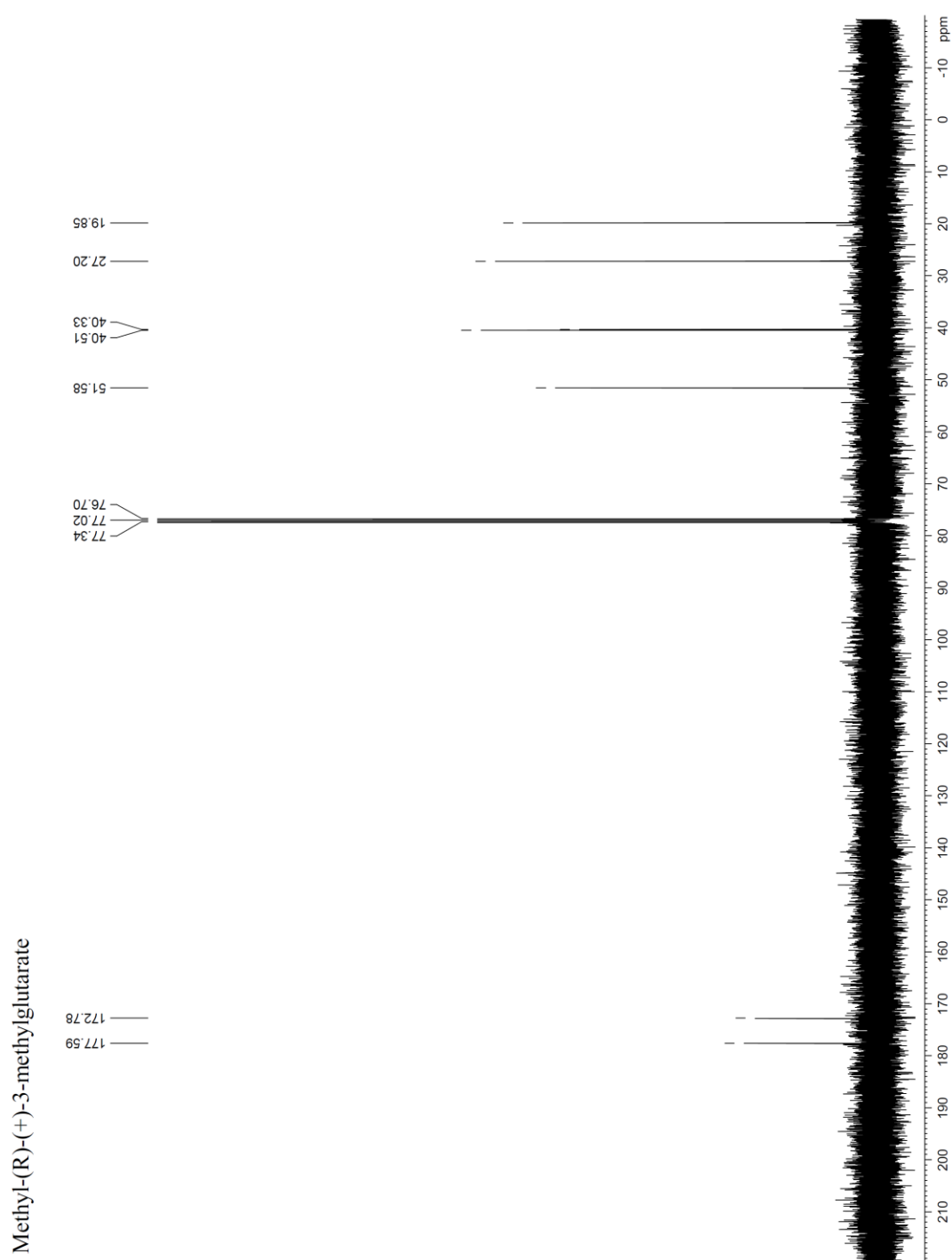


Figure 2.20 – ^{13}C NMR of methyl-(R)-(+)-3-methylglutarate (**2.46**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

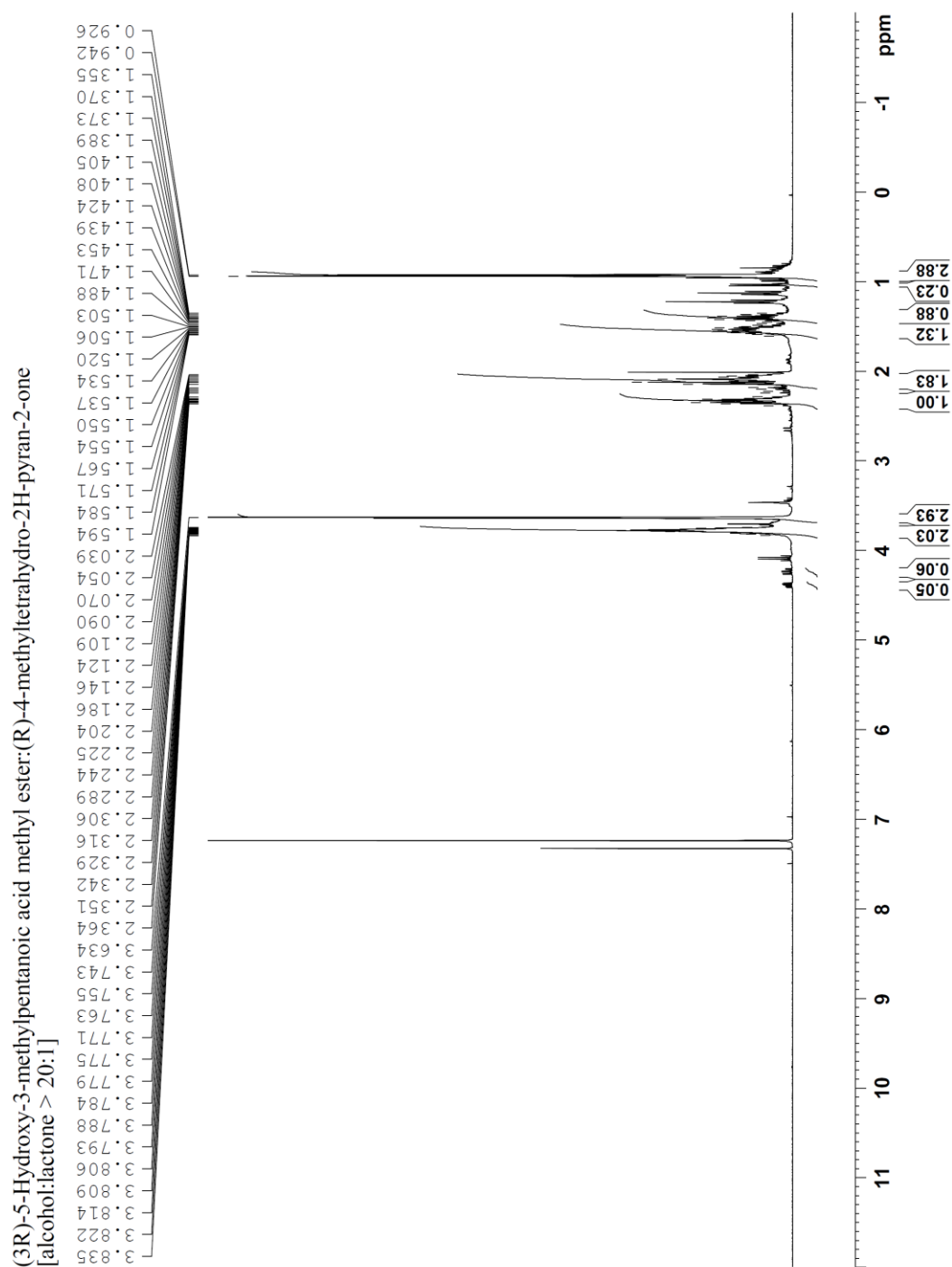


Figure 2.21 – ^1H NMR of crude mixture of (3R)-5-hydroxy-3-methylpentanoic acid methyl ester (**2.47**) and (R)-4-methyltetrahydro-2H-pyran-2-one (**2.50**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

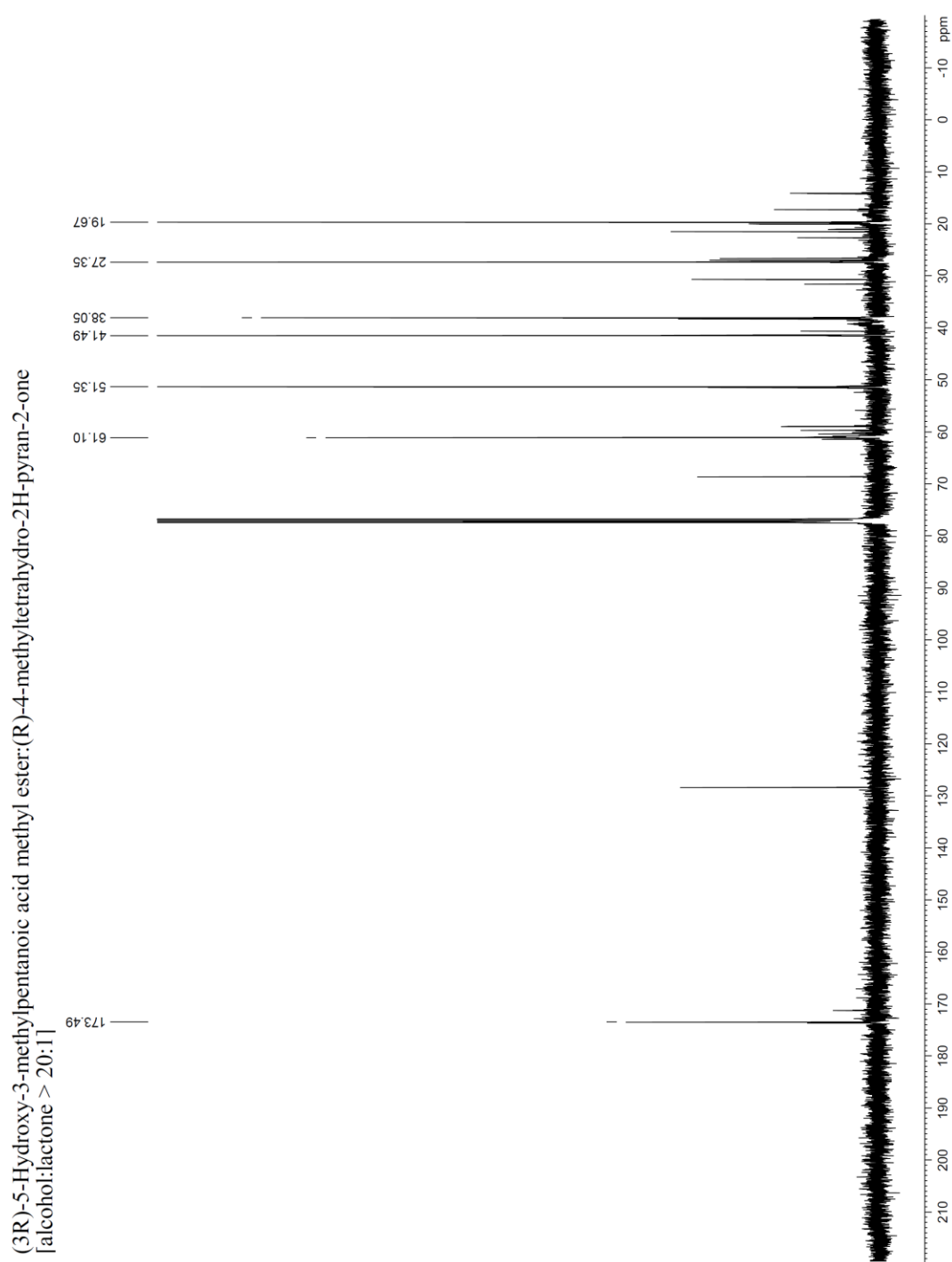


Figure 2.22 – ^{13}C NMR of crude mixture of (3R)-5-hydroxy-3-methylpentanoic acid methyl ester (**2.47**) and (R)-4-methyltetrahydro-2H-pyran-2-one (**2.50**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

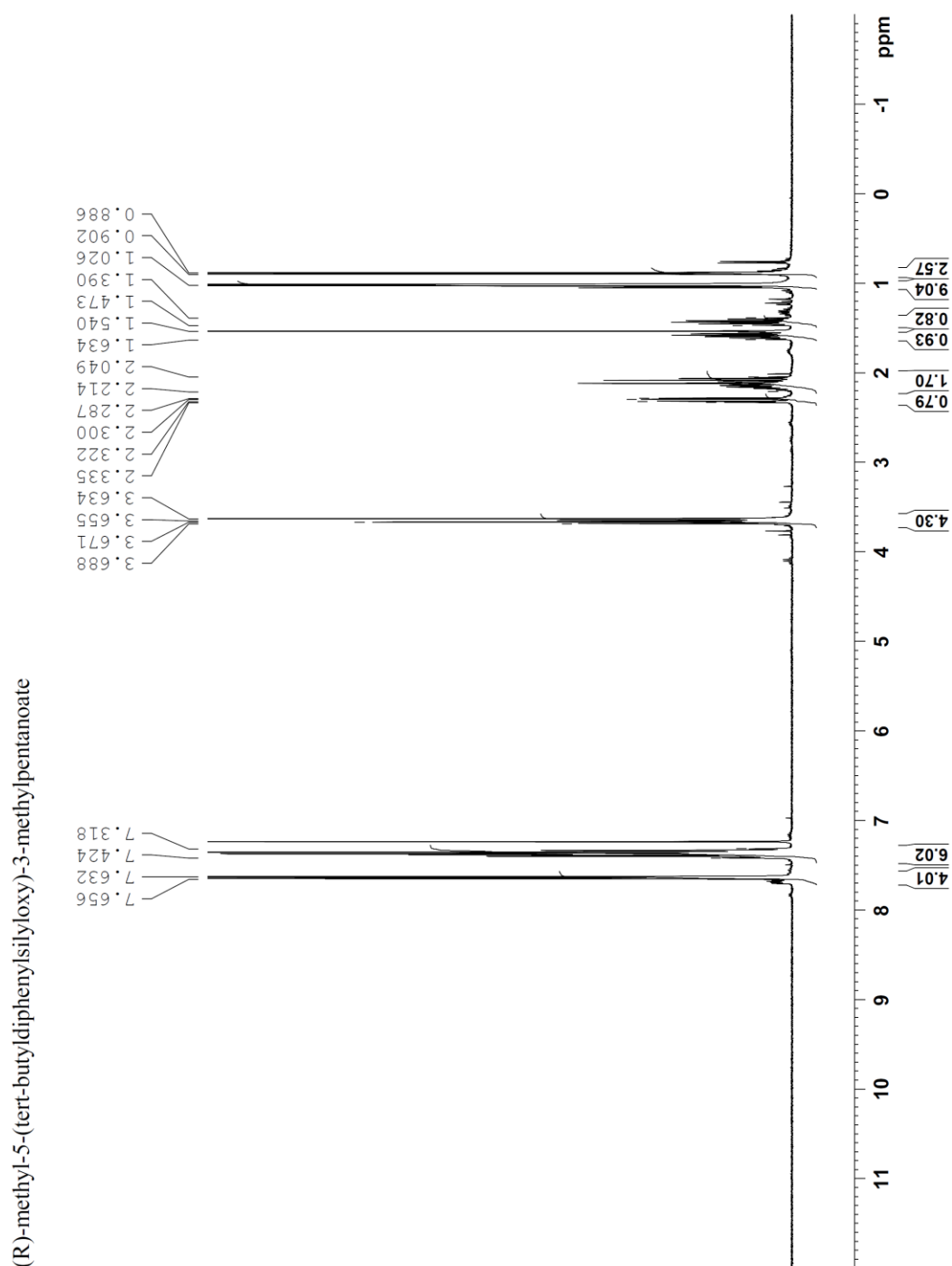


Figure 2.23 – ^1H NMR of (R)-methyl-5-(TBDPS)-3-methylpentanoate (**2.48**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

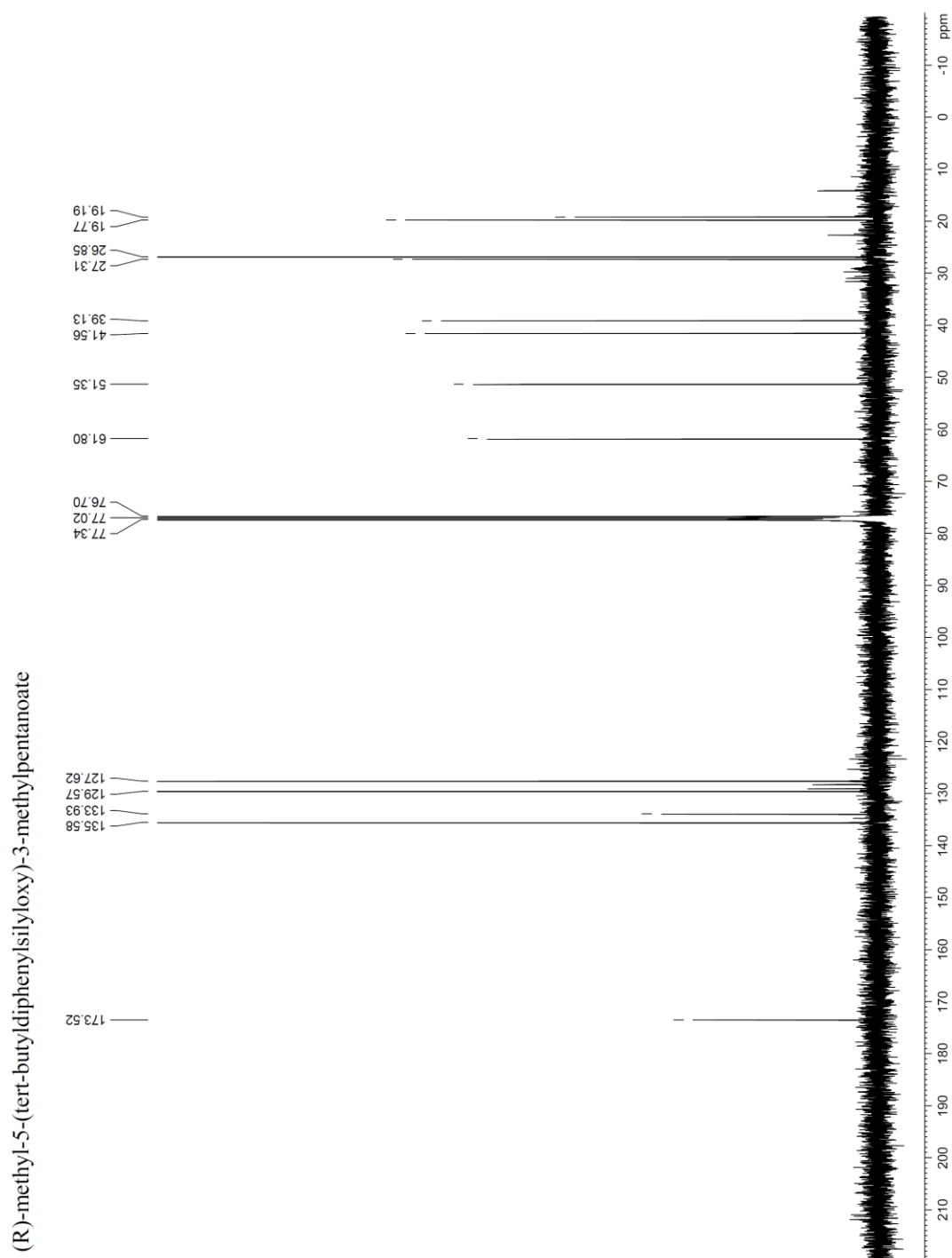


Figure 2.24 – ^{13}C NMR of (R)-methyl-5-(TBDPS)-3-methylpentanoate (**2.48**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

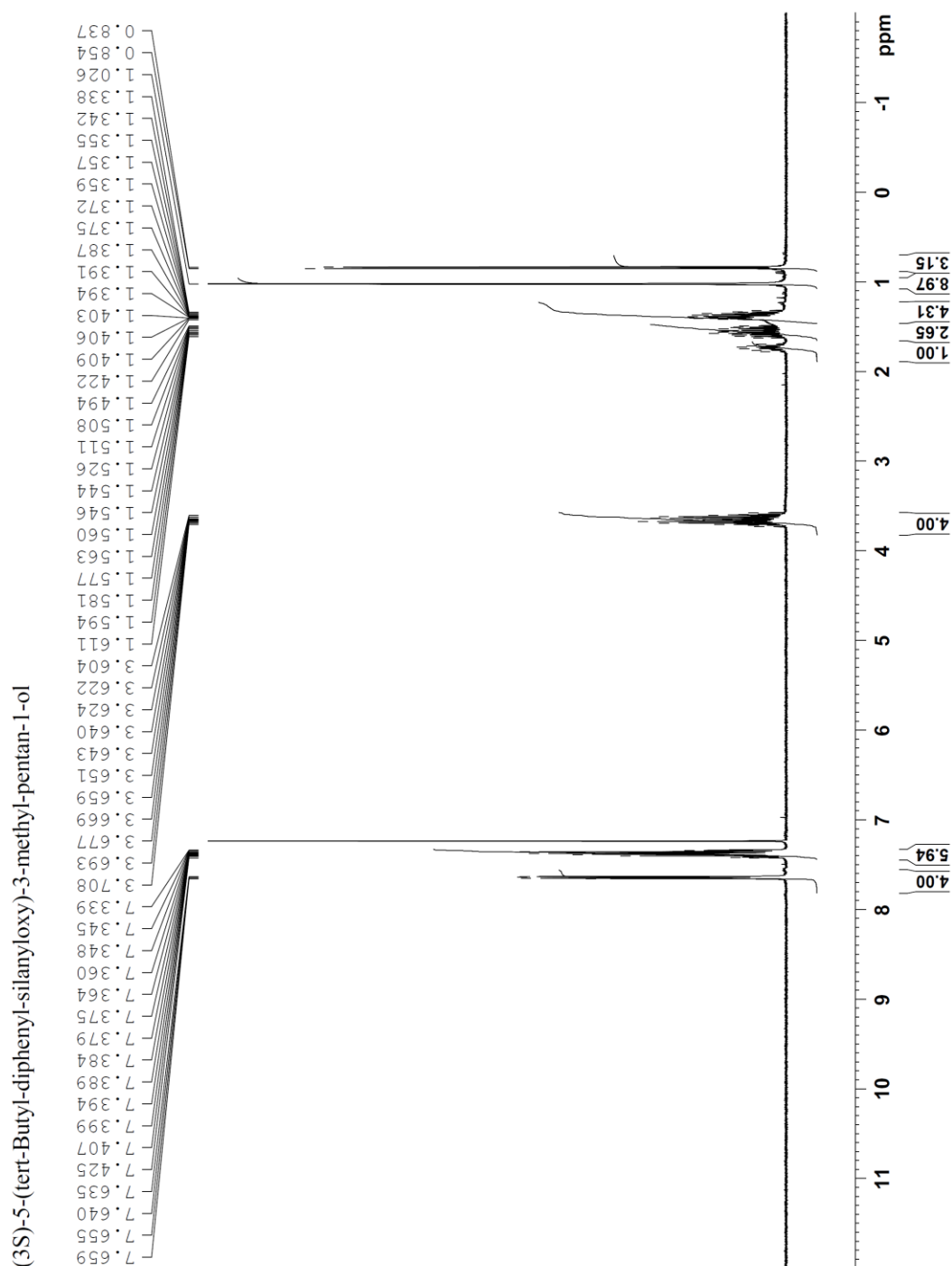


Figure 2.25 – ^1H NMR of (3S)-5-(TBDPS)-3-methyl-pentan-1-ol (2.49), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

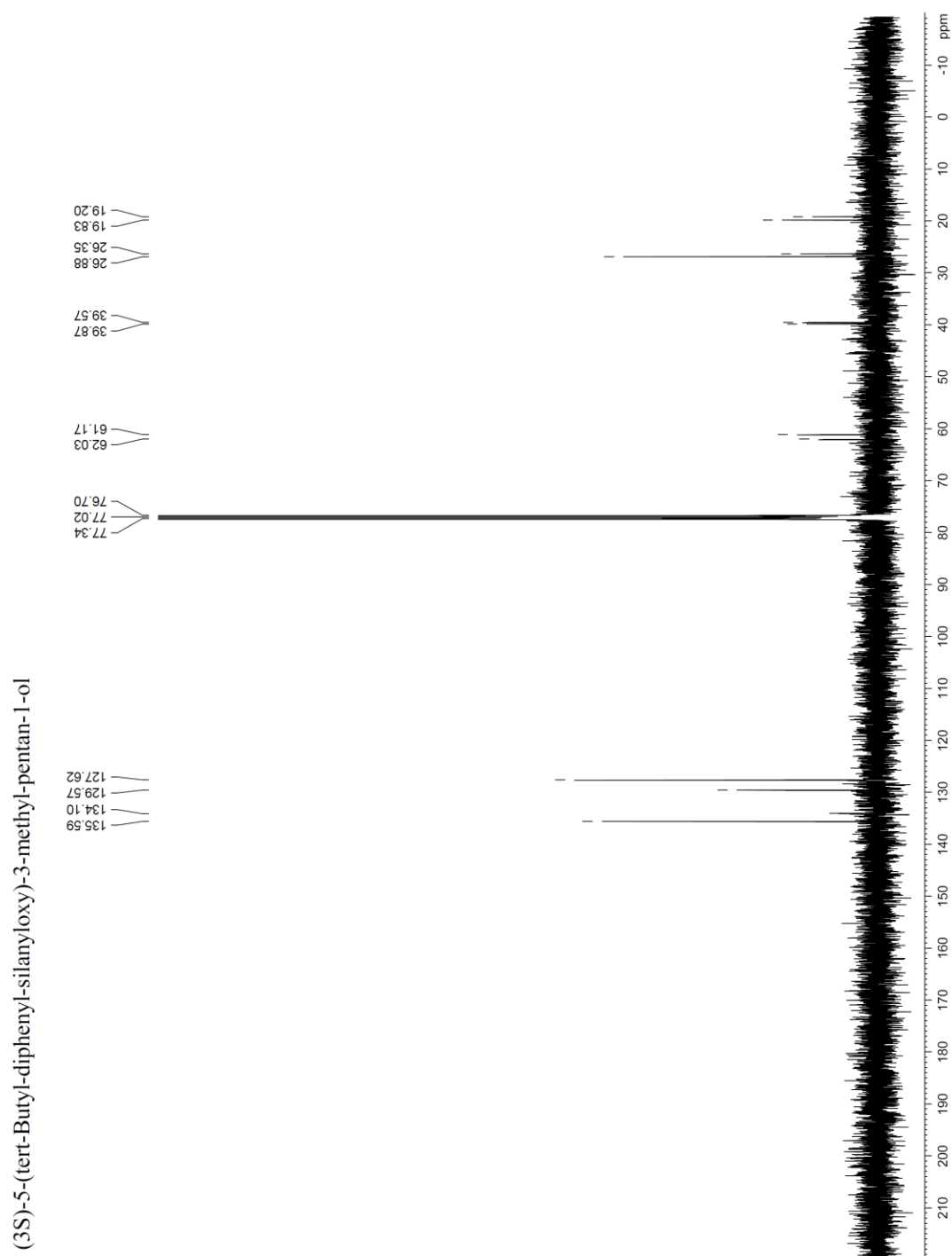


Figure 2.26 – ^{13}C NMR of (3S)-5-(TBDPS)-3-methyl-pentan-1-ol (**2.49**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

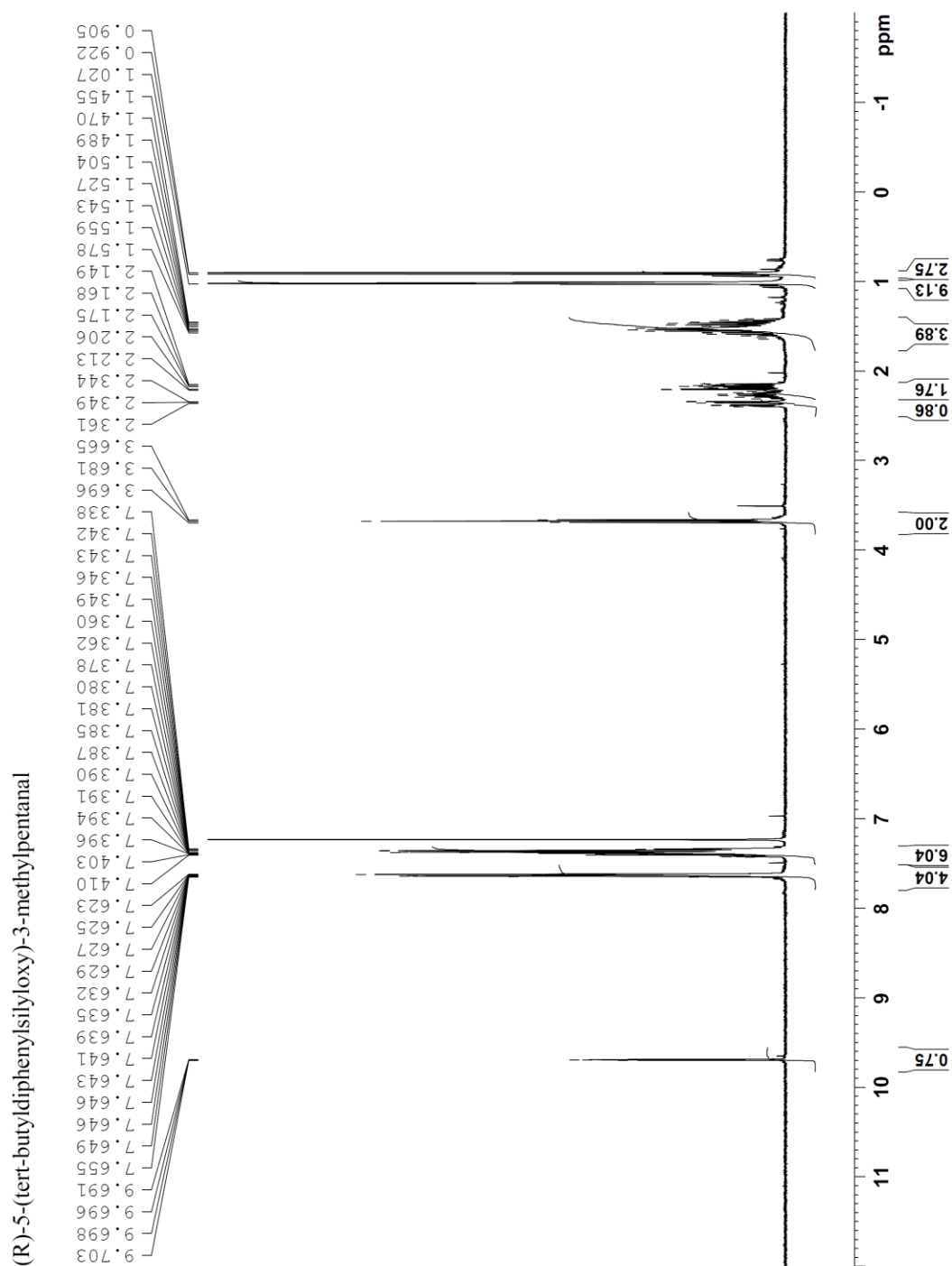


Figure 2.27 – ^1H NMR of (R)-5-(TBDPS)-3-methylpentanal (**2.41**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

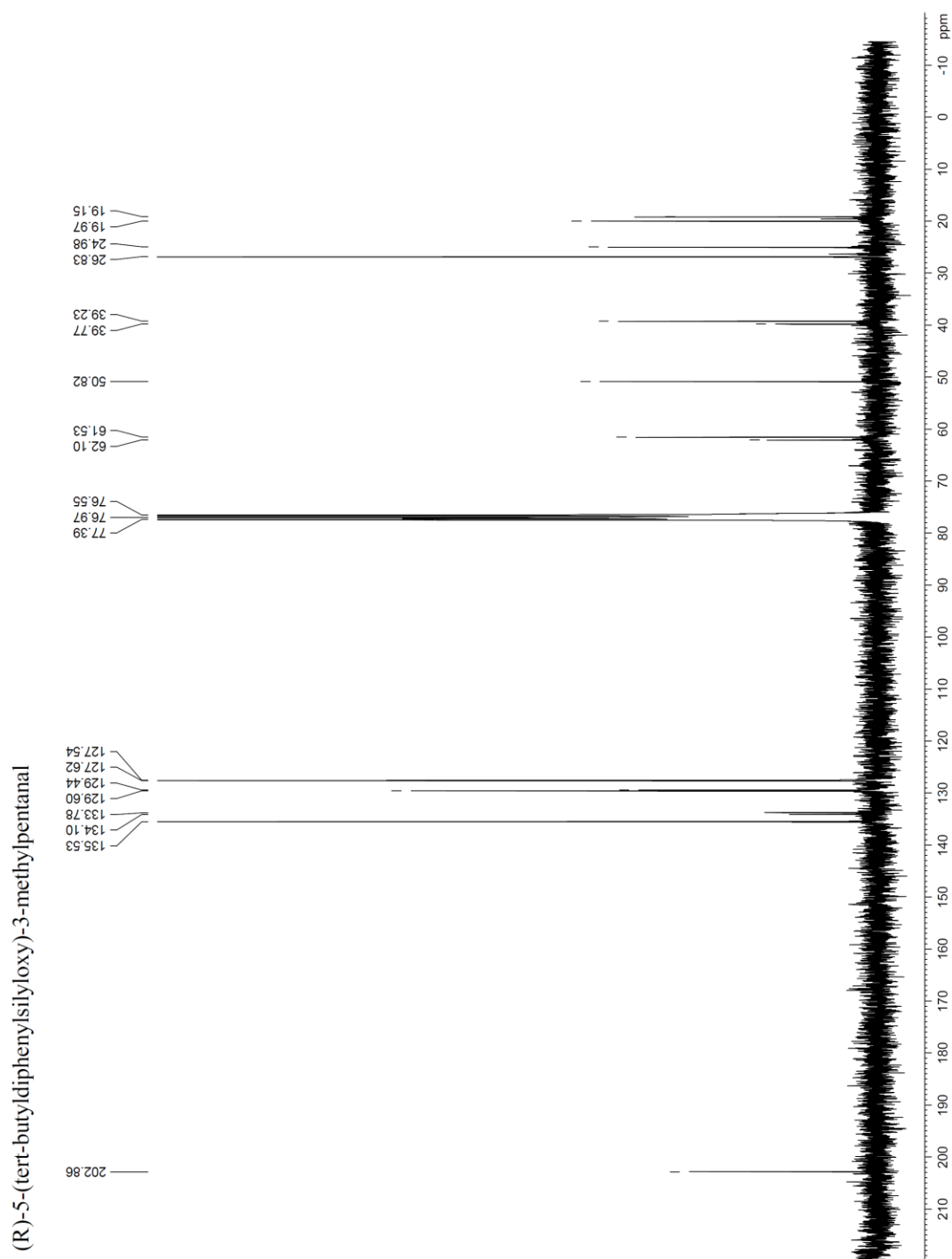


Figure 2.28 – ^{13}C NMR of (R)-5-(TBDPS)-3-methylpentanal (**2.41**), as measured on a Bruker AVANCE 300 spectrophotometer at 75 MHz, calibrated to the residual proton resonance of CDCl_3 .

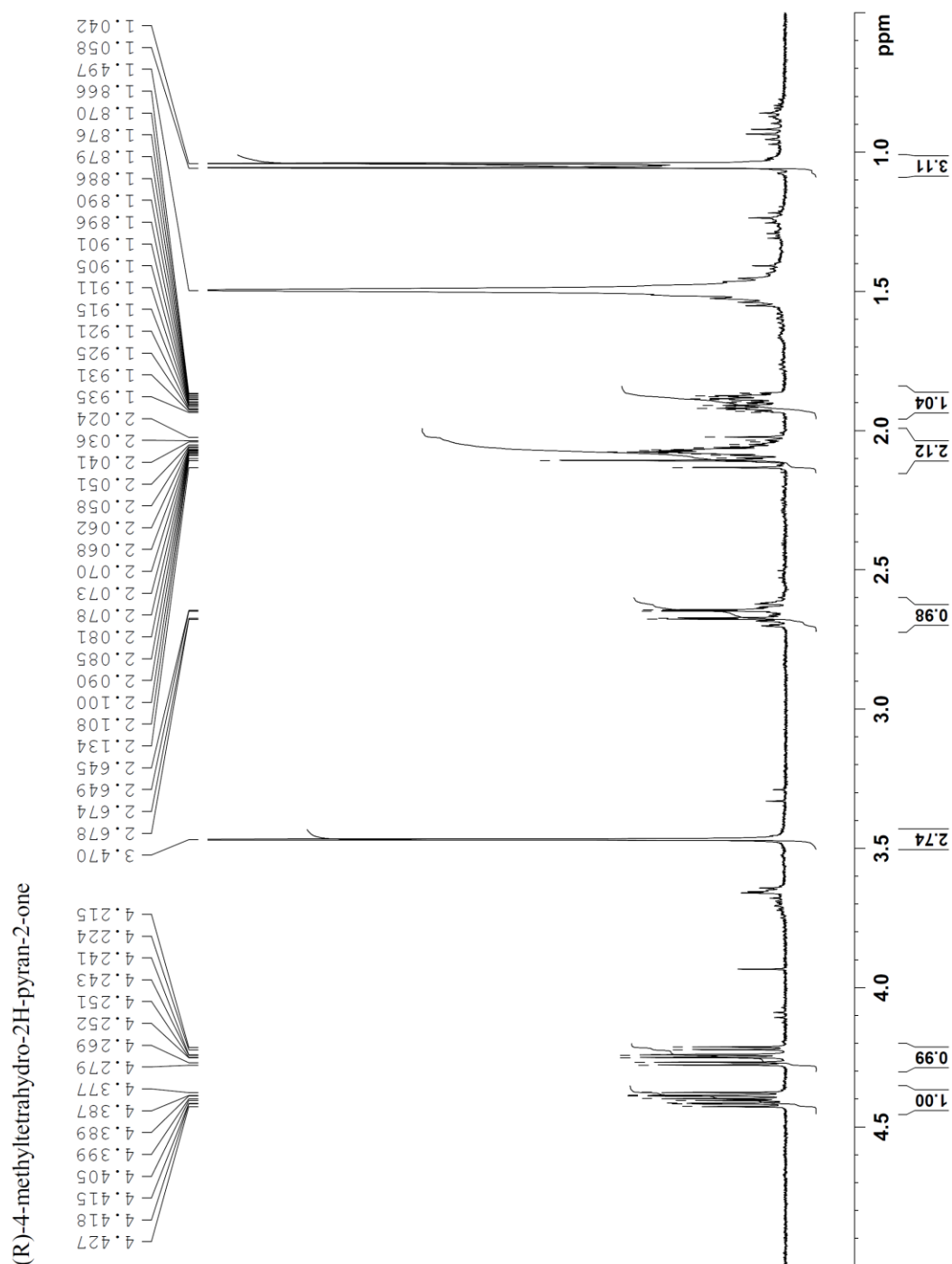


Figure 2.29 – ^1H NMR zoom of (*R*)-4-methyltetrahydro-2H-pyran-2-one (**2.50**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

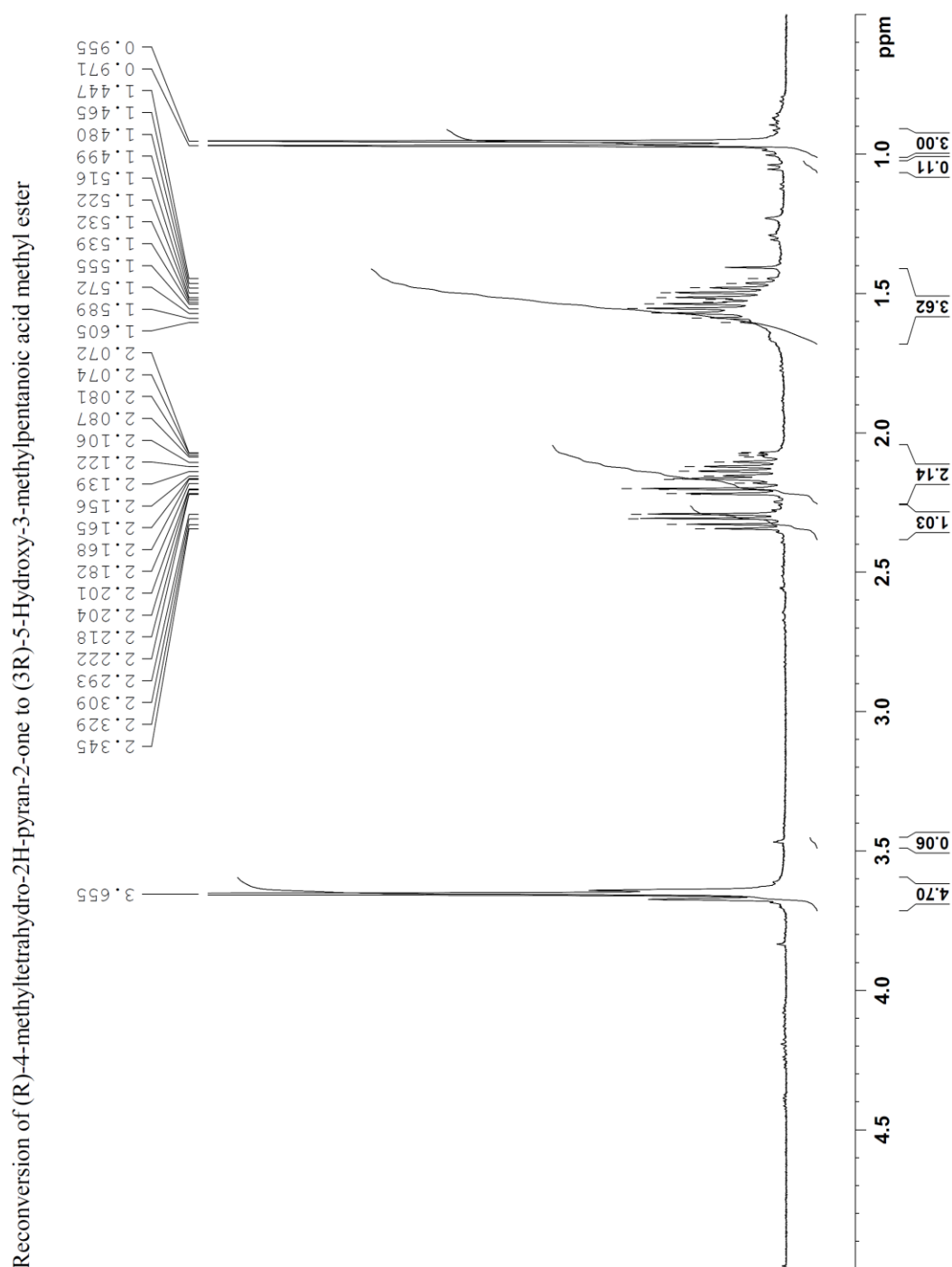


Figure 2.30 – ^1H NMR region of interest for the reconversion of (R)-4-methyltetrahydro-2H-pyran-2-one (**2.50**) into (3R)-5-hydroxy-3-methylpentanoic acid methyl ester (**2.47**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

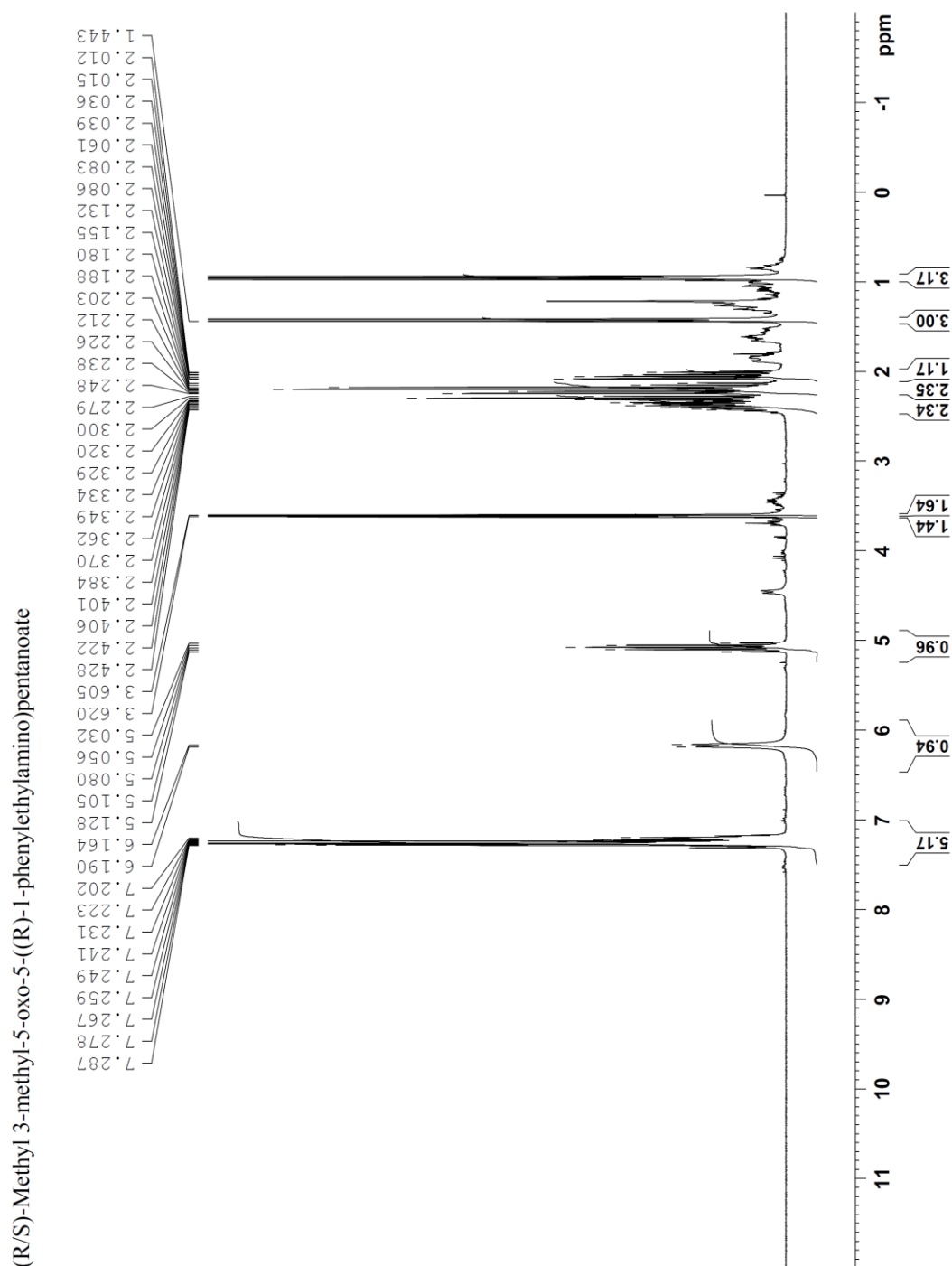


Figure 2.31 – ^1H NMR of 2:1 mixture (*syn:anti*) of $[R-(R^*,R^*)]$ - and $[S-(R^*,S^*)]$ -methyl-3-methyl-5-[(1-phenylethyl)amino]-5-oxopentanoates **2.53** (*syn*) and **2.54** (*anti*), as measured on a Bruker AVANCE 300 spectrophotometer at 300 MHz, calibrated to the residual proton resonance of CDCl_3 .

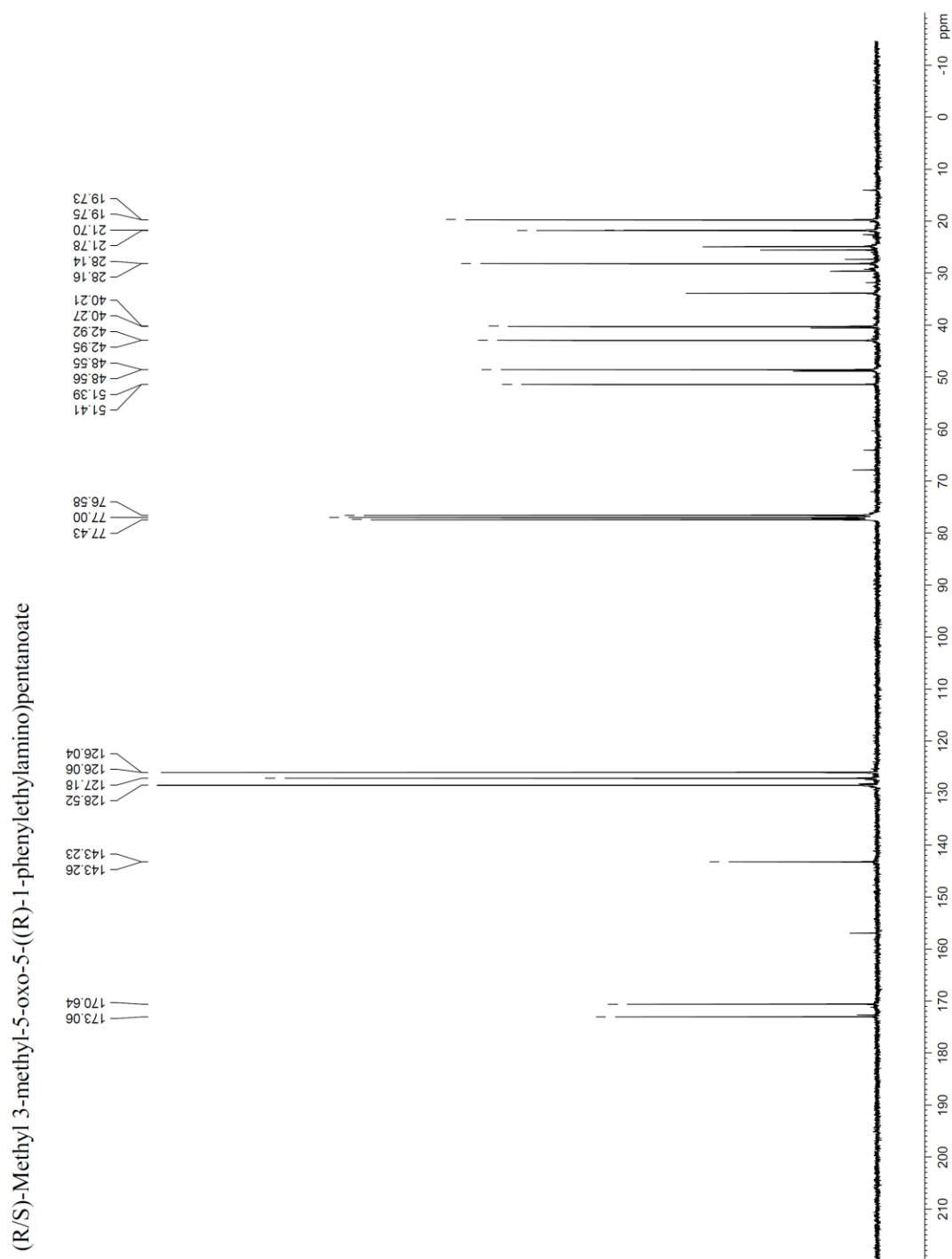


Figure 2.32 – ^{13}C NMR of 2:1 mixture (*syn:anti*) of [*R*-(*R*^{*},*R*^{*})]- and [*S*-(*R*^{*},*S*^{*})]-methyl-3-methyl-5-[(1-phenylethyl)amino]-5-oxopentanoates **2.53** (*syn*) and **2.54** (*anti*), as measured on a Bruker AVANCE 300 spectrophotometer at 75 MHz, calibrated to the residual proton resonance of CDCl_3 .

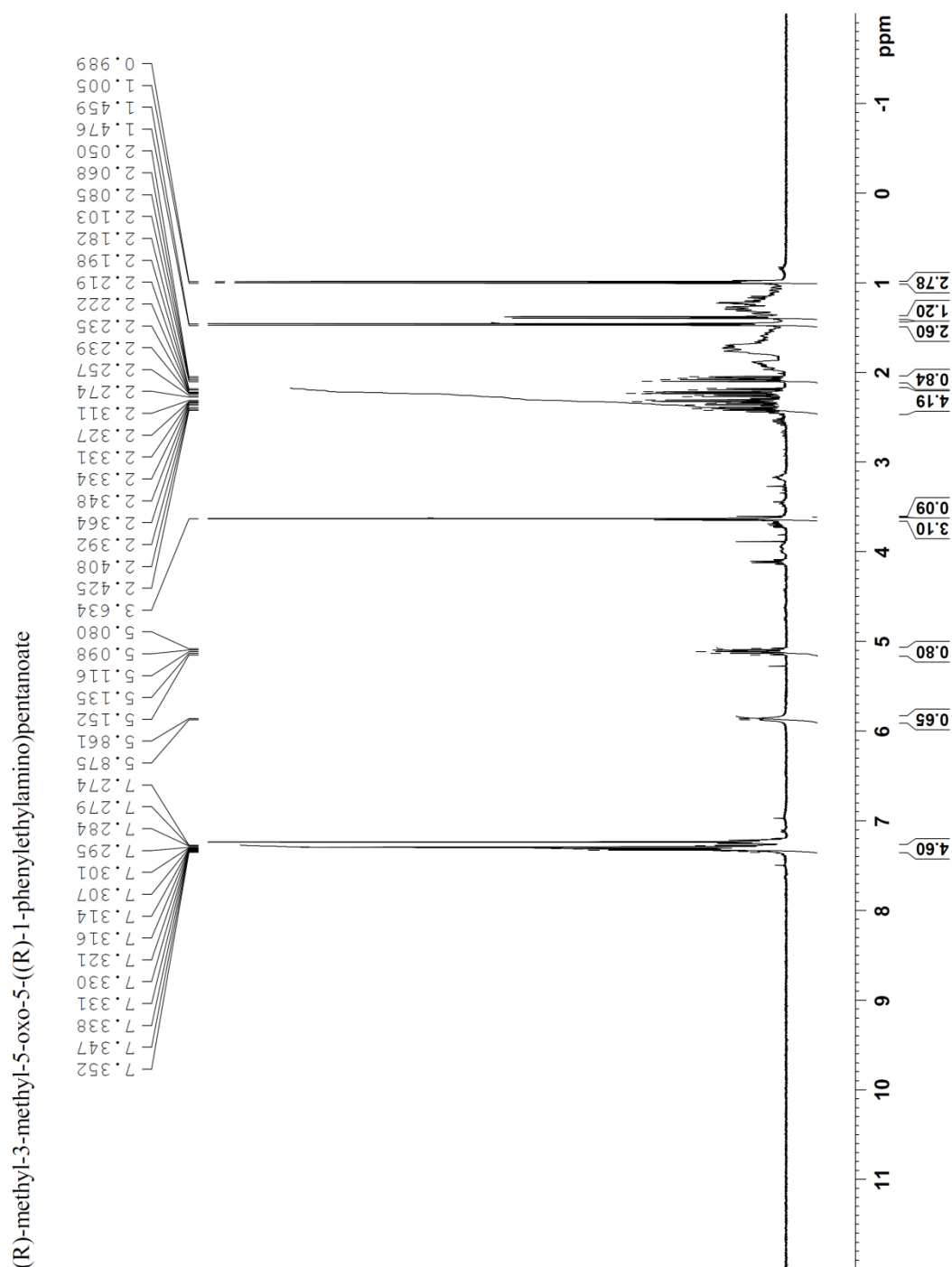


Figure 2.33 – ^1H NMR of (R)-methyl-3-methyl-5-oxo-5-((R)-1-phenylethylamino)pentanoate **2.53** (syn) from acid precursor **2.46**, as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

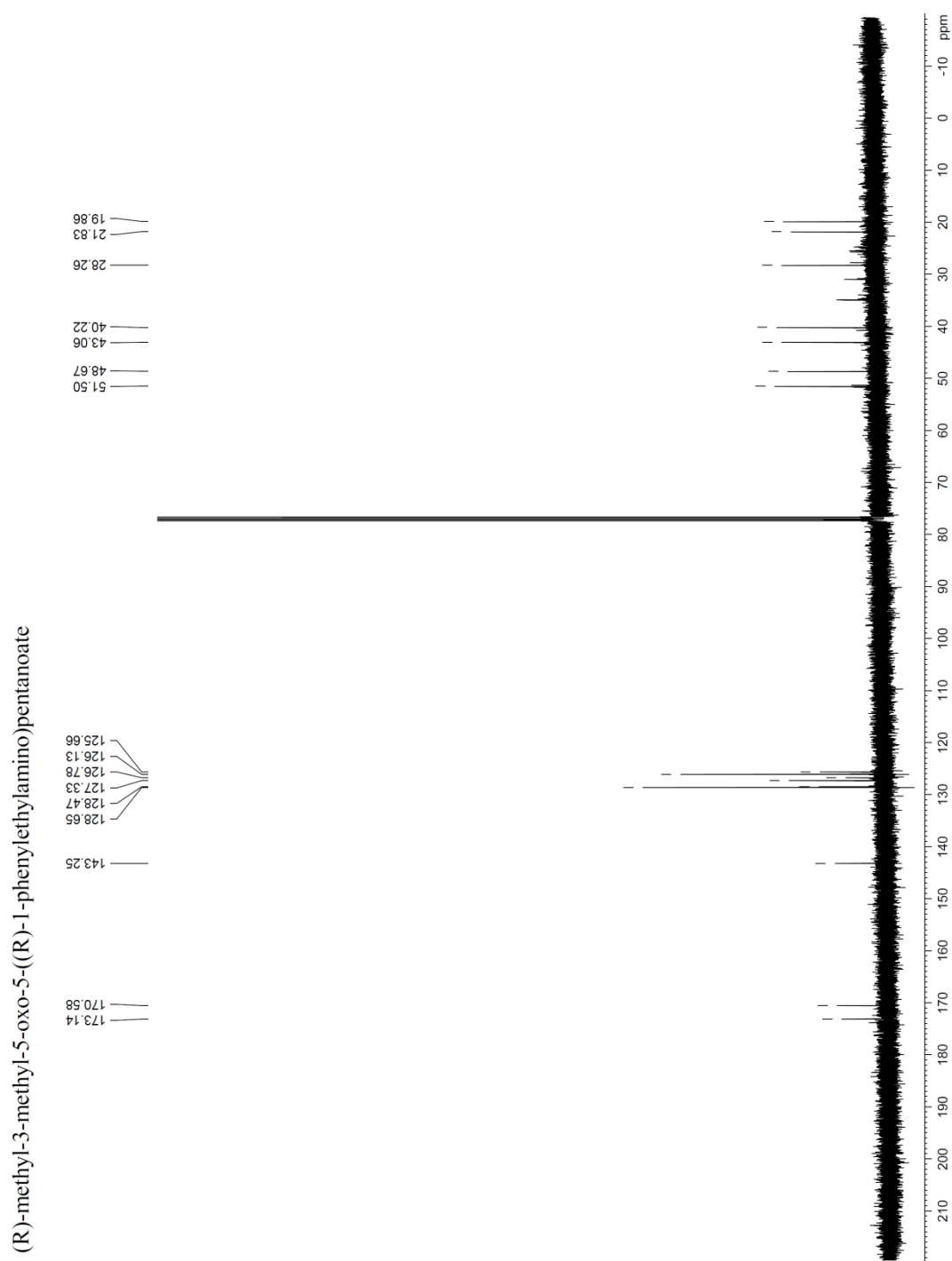


Figure 2.34 – ^{13}C NMR of (R)-methyl-3-methyl-5-oxo-5-((R)-1-phenylethylamino)pentanoate **2.53** (*syn*) from acid precursor **2.46**, as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

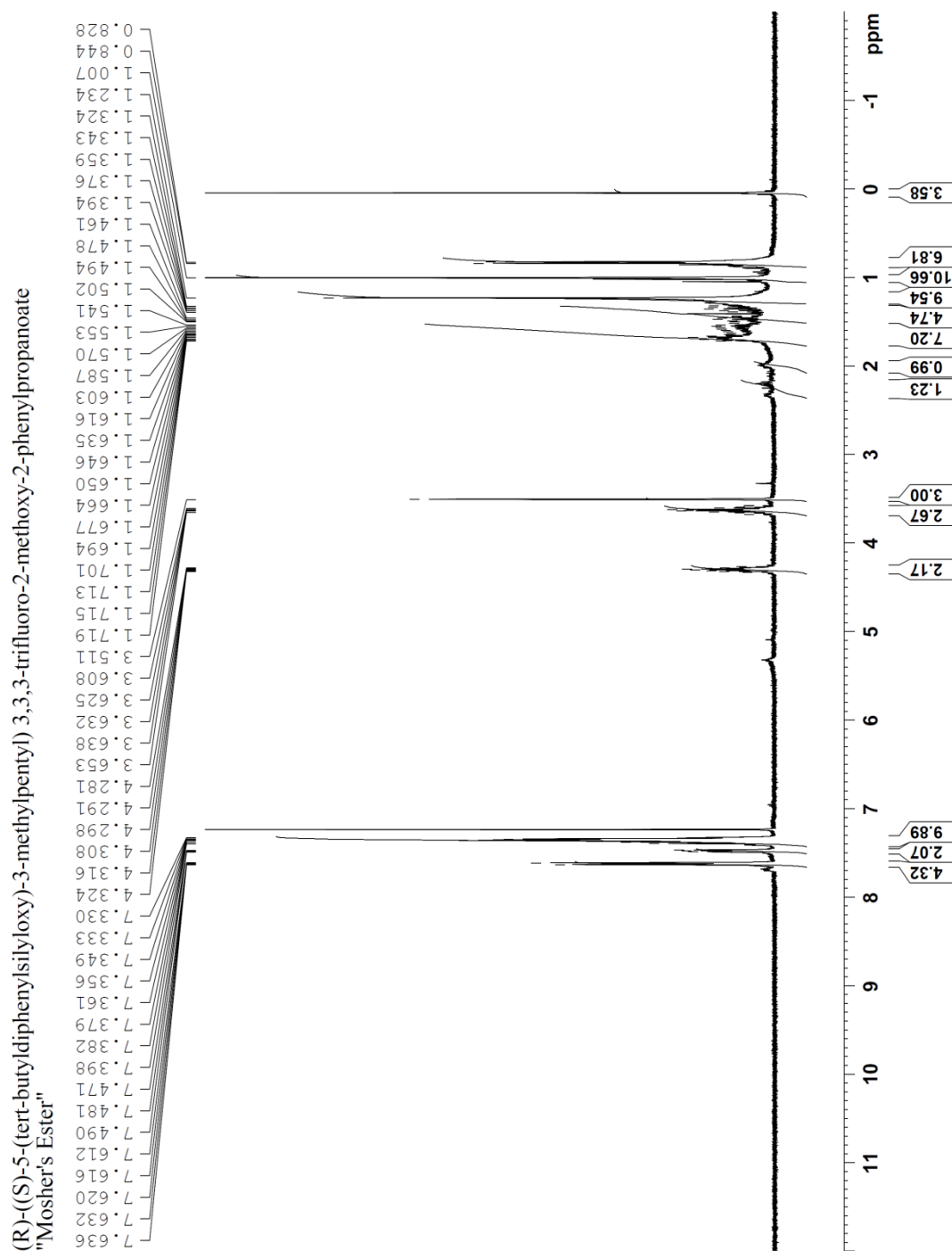


Figure 2.35 – ^1H NMR of crude 3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid 5-(TBDPS)-3-methylpentyl ester **2.55** (Mosher's ester), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

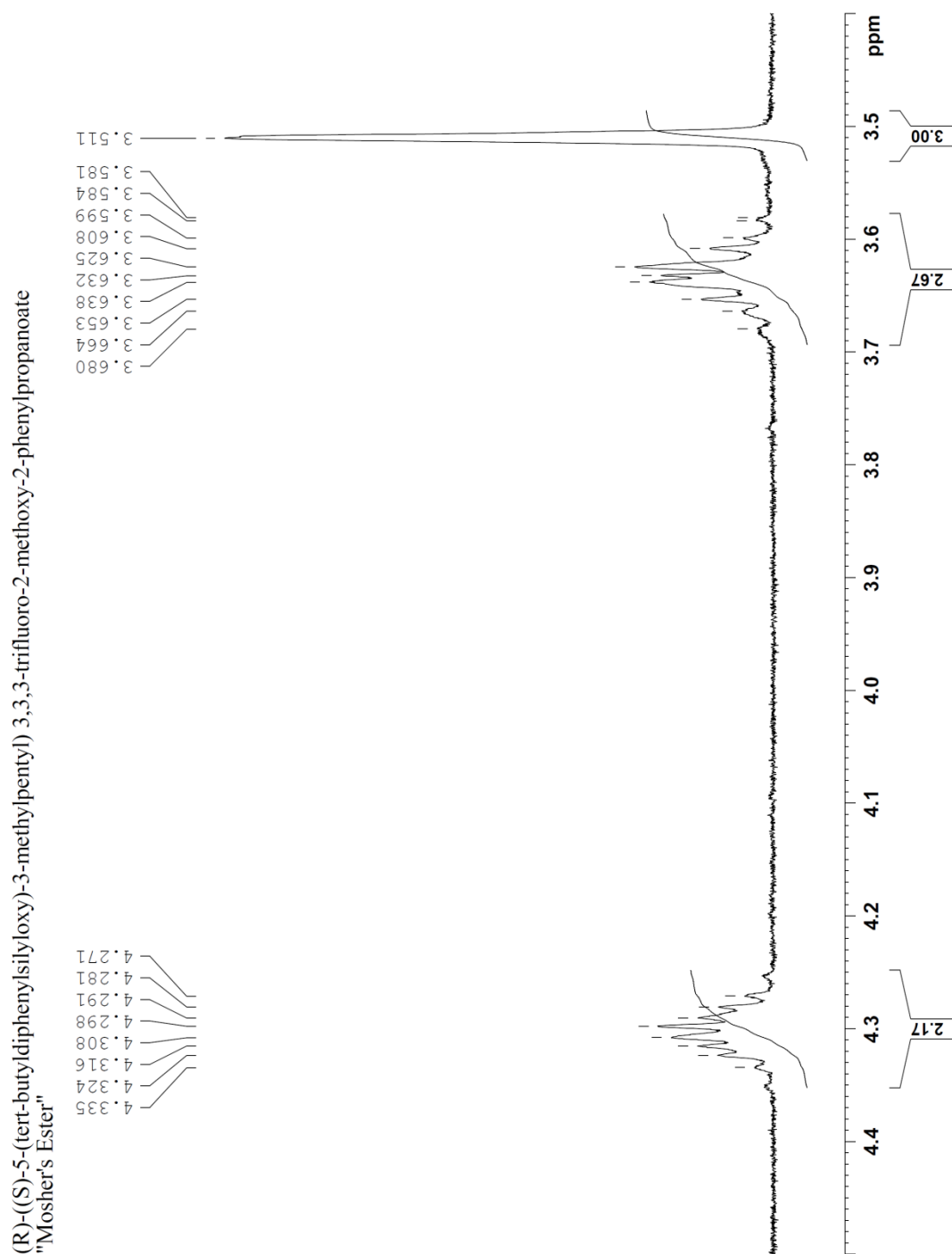


Figure 2.36 – ^1H NMR zoom of region of interest of crude 3,3,3-trifluoro-2-methoxy-2-phenyl-propionic acid 5-(TBDPS)-3-methylpentyl ester **2.55** (Mosher's ester), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

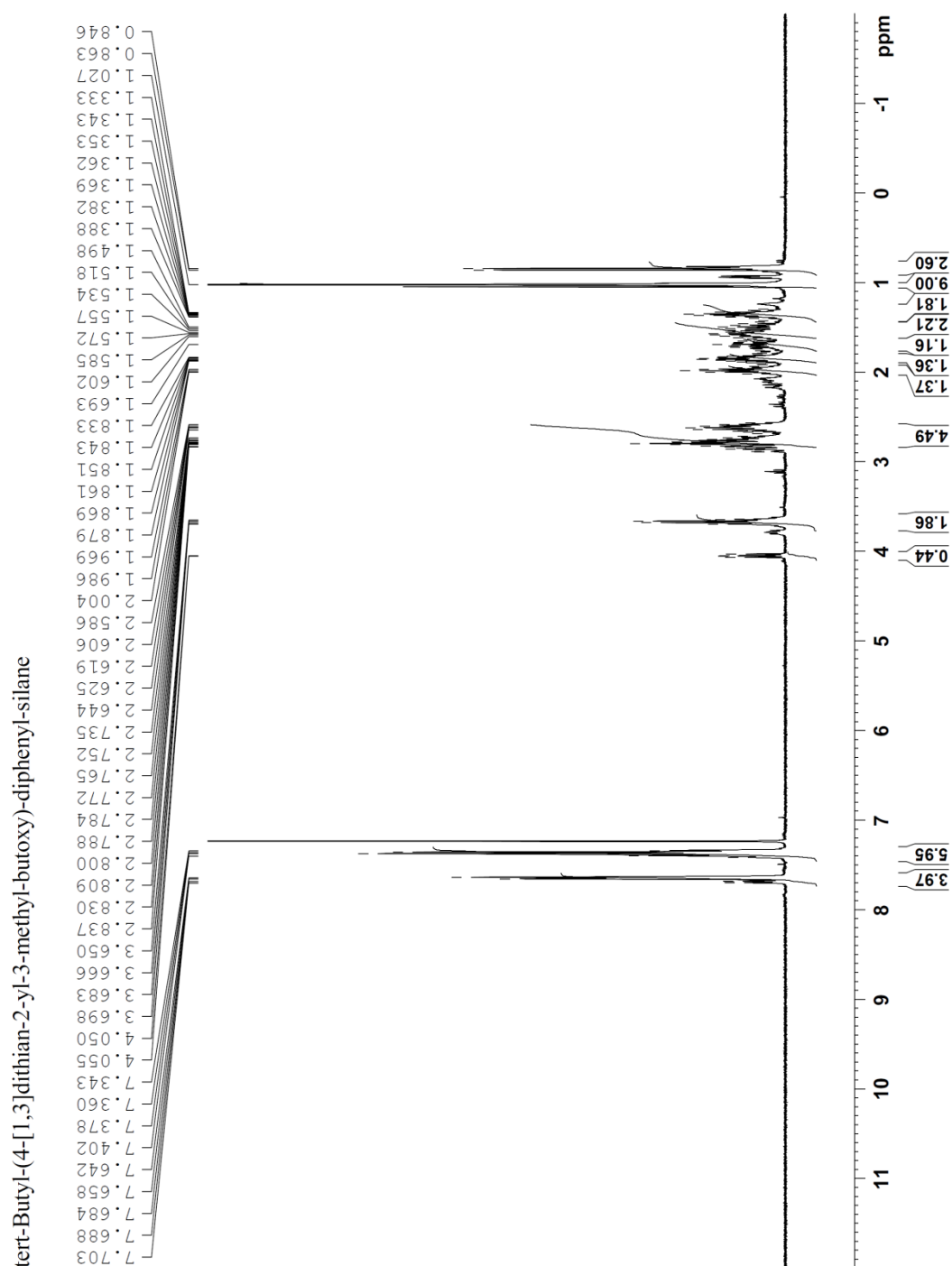


Figure 2.37 – ¹H NMR of crude *tert*-butyl-(4-[1,3]dithiane-2-yl-3-methyl-butoxy)-diphenyl-silane (**2.56**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl₃.



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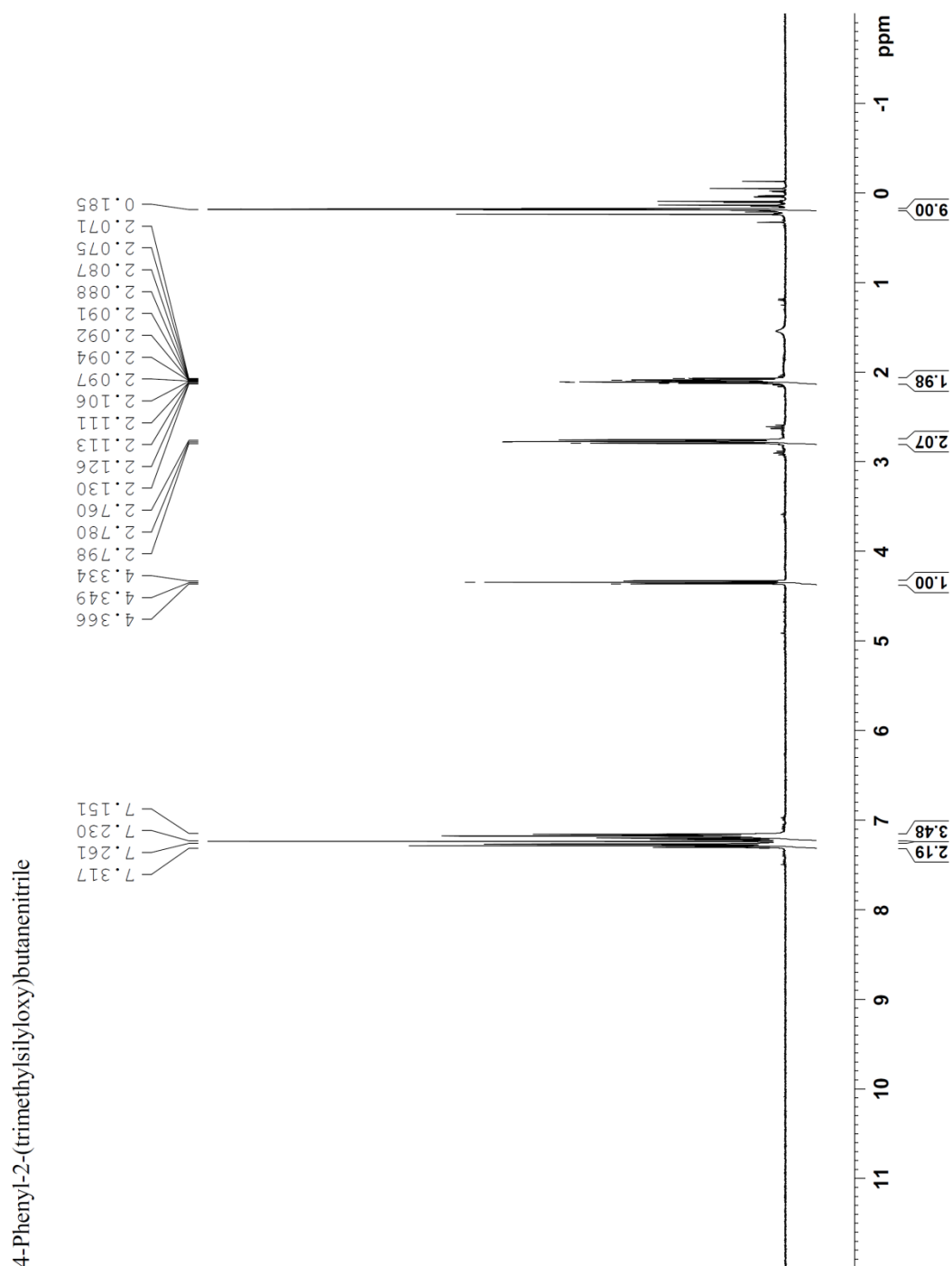


Figure 2.39 – ^1H NMR of crude 4-phenyl-2-(trimethylsilyloxy)butanenitrile (**2.65**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

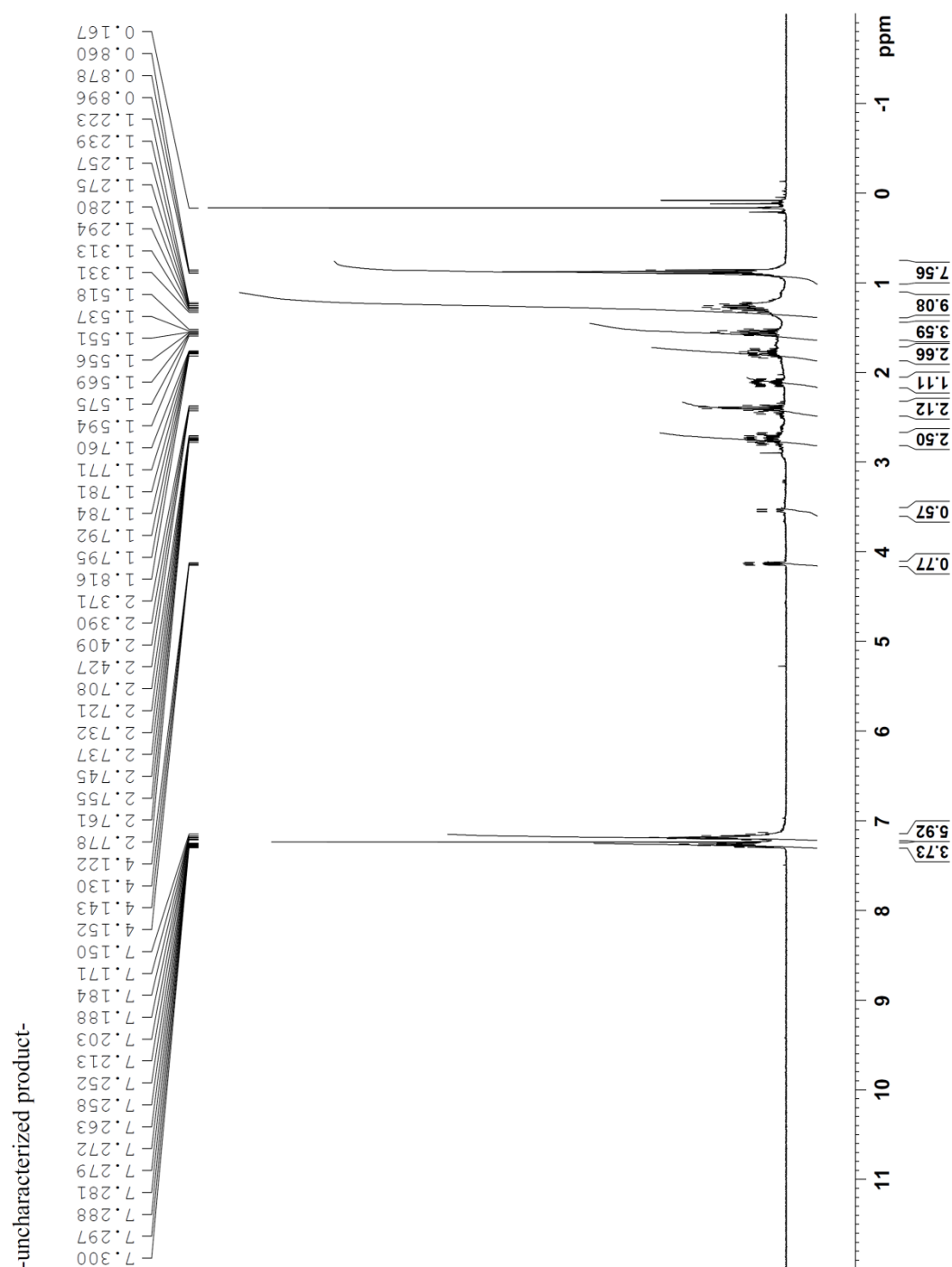


Figure 2.40 – ^1H NMR of crude uncharacterized product obtained during cyano-umpolung addition (expected product **2.66**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

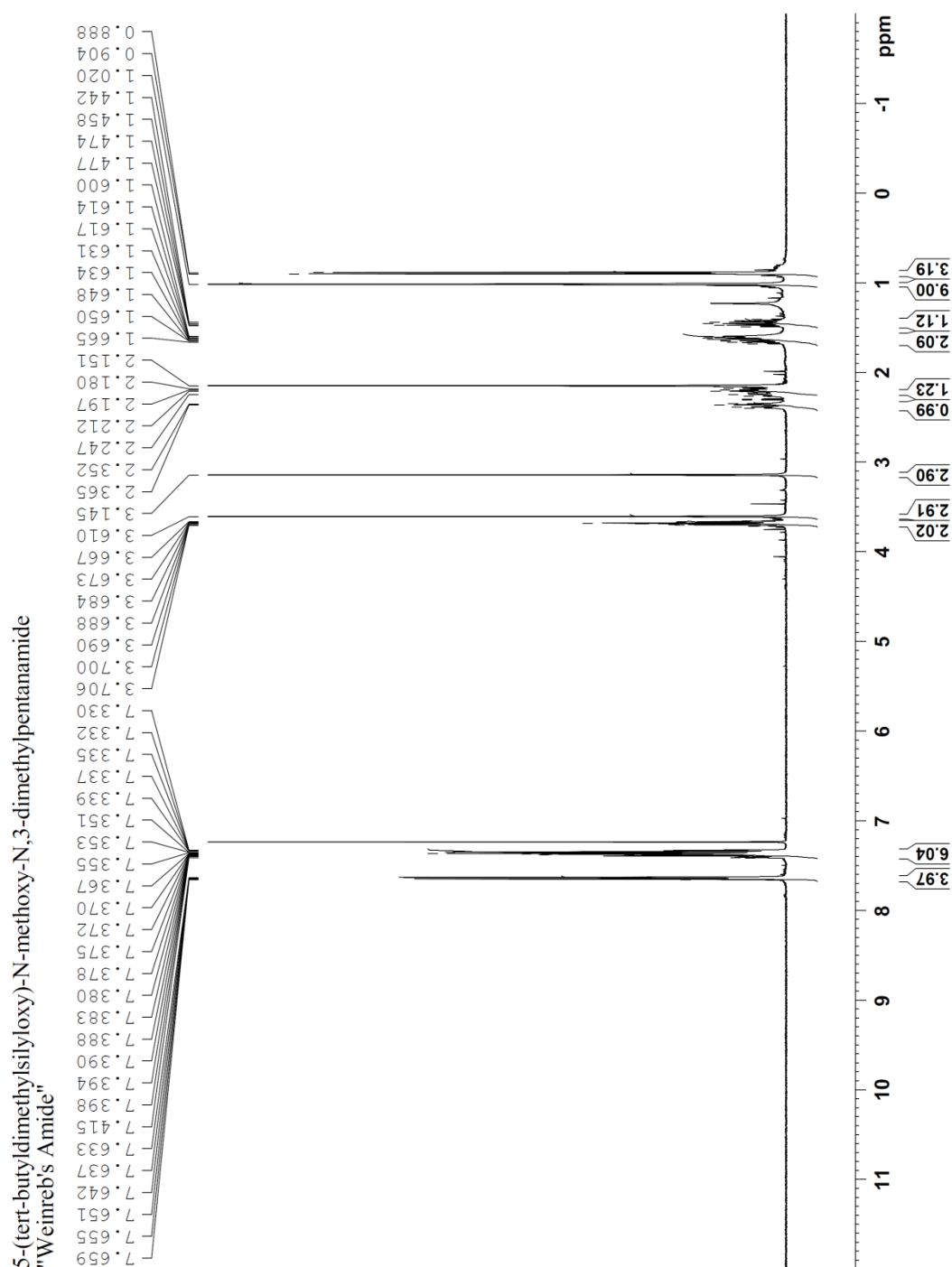


Figure 2.41 – ^1H NMR of crude 5-(TBDPS)-*N*-methoxy-*N*,3-dimethylpentanamide (2.70) “Weinreb’s amide,” as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

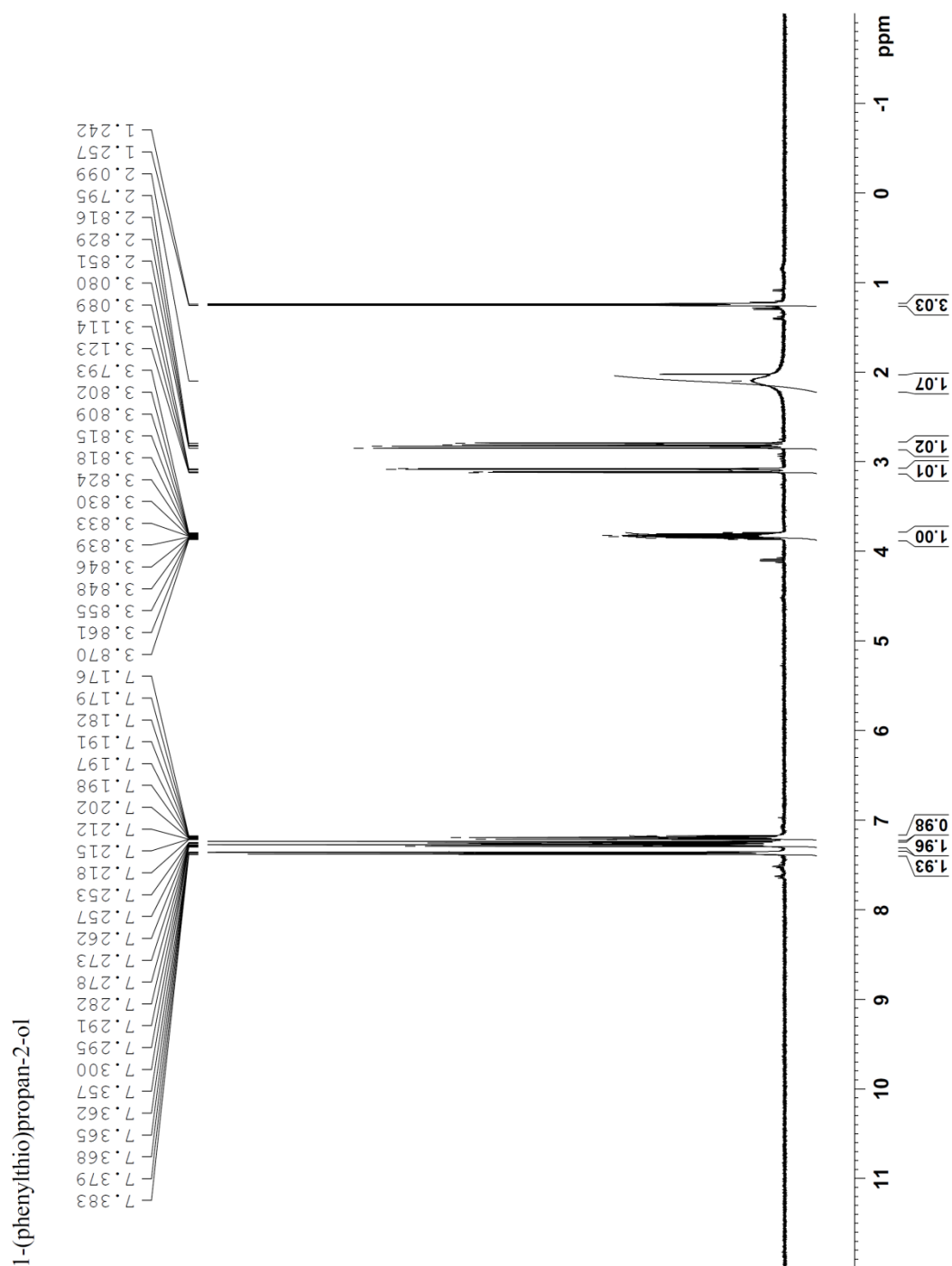


Figure 2.42 – ¹H NMR of 1-(phenylthio)propan-2-ol (**2.71**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl₃.

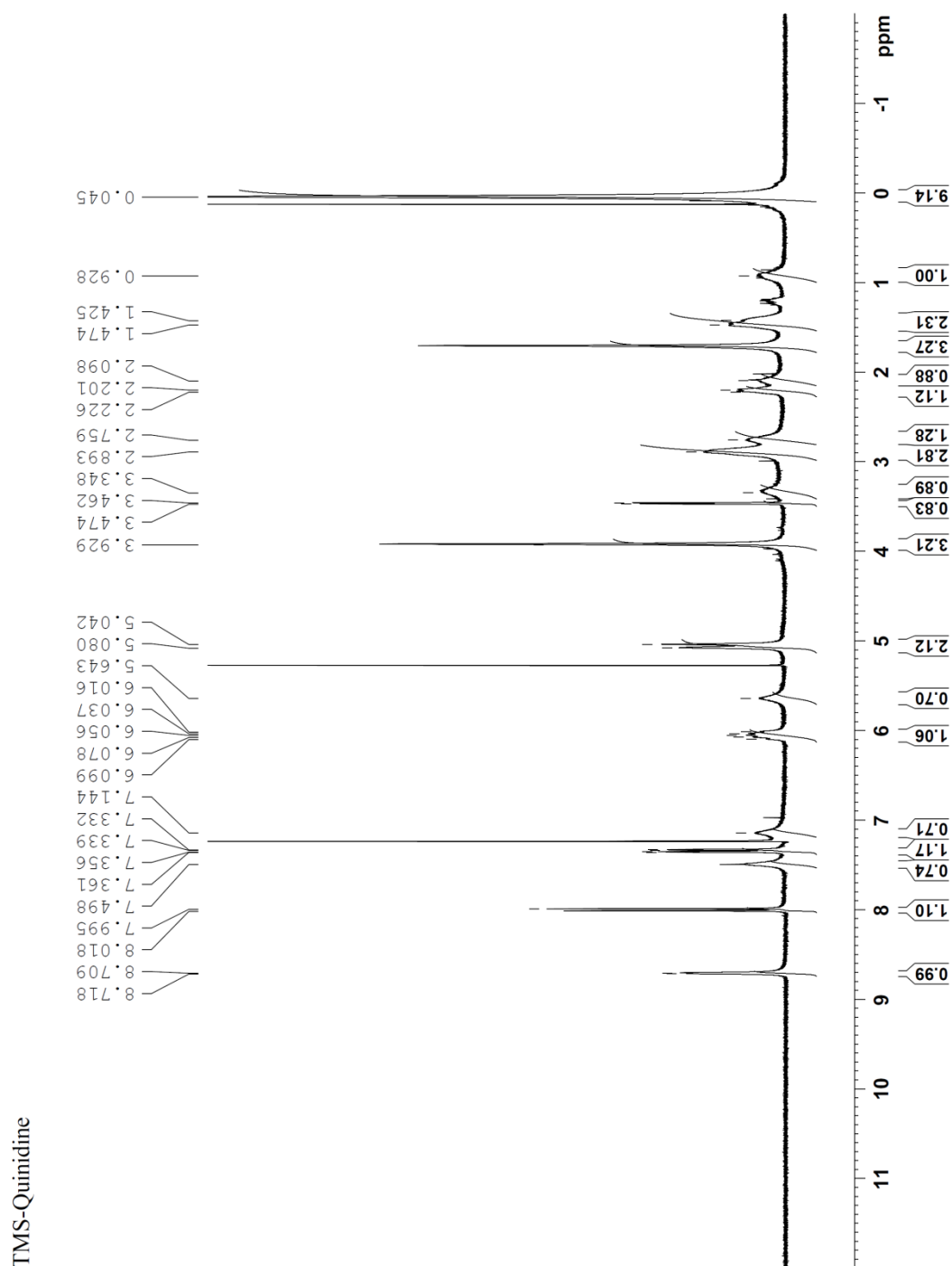


Figure 2.43 – ^1H NMR of crude trimethylsilyl quinidine (**2.73**) TMSQ catalyst, as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .



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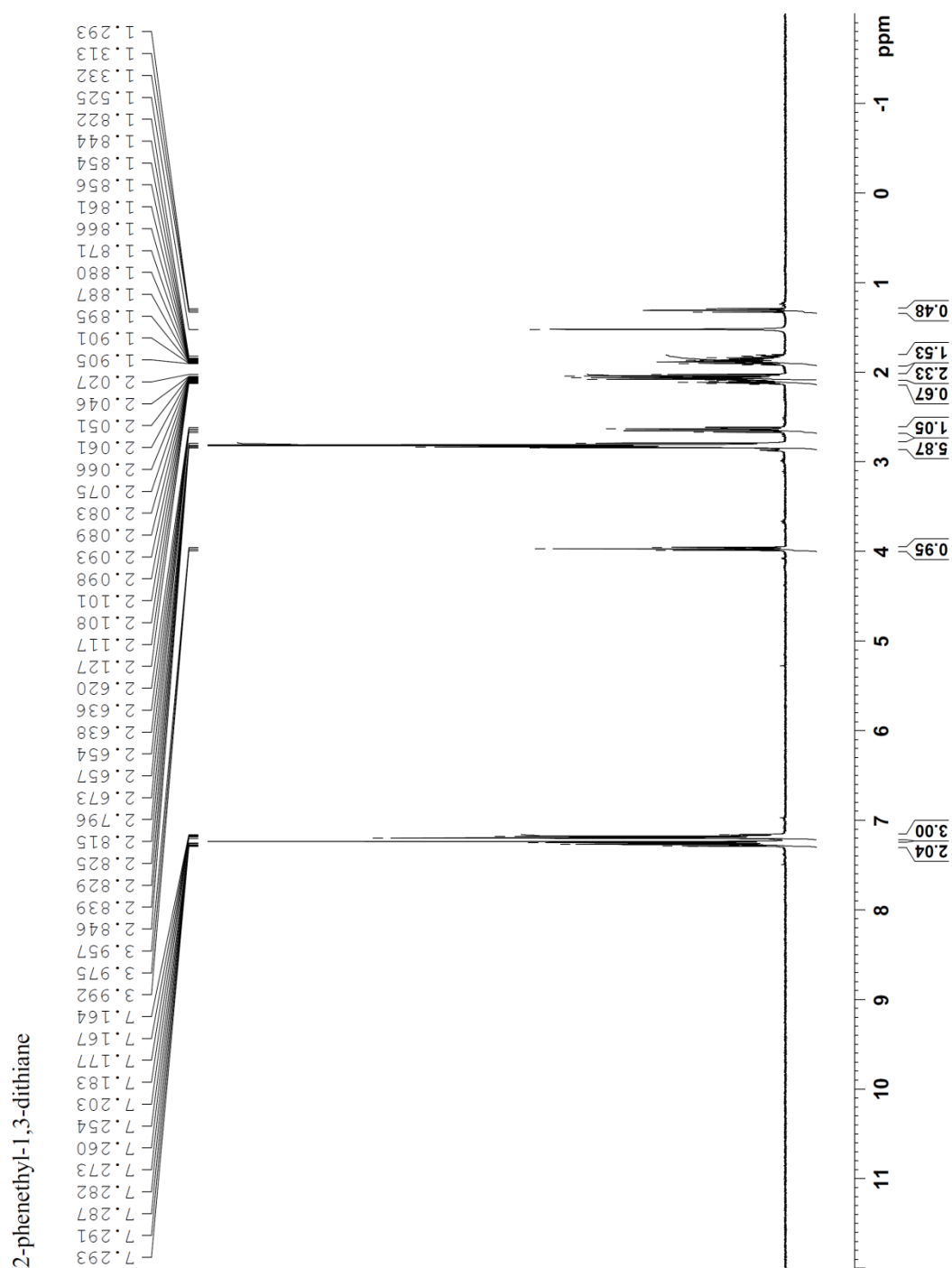


Figure 2.45 – ^1H NMR of dithiane (**2.80**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

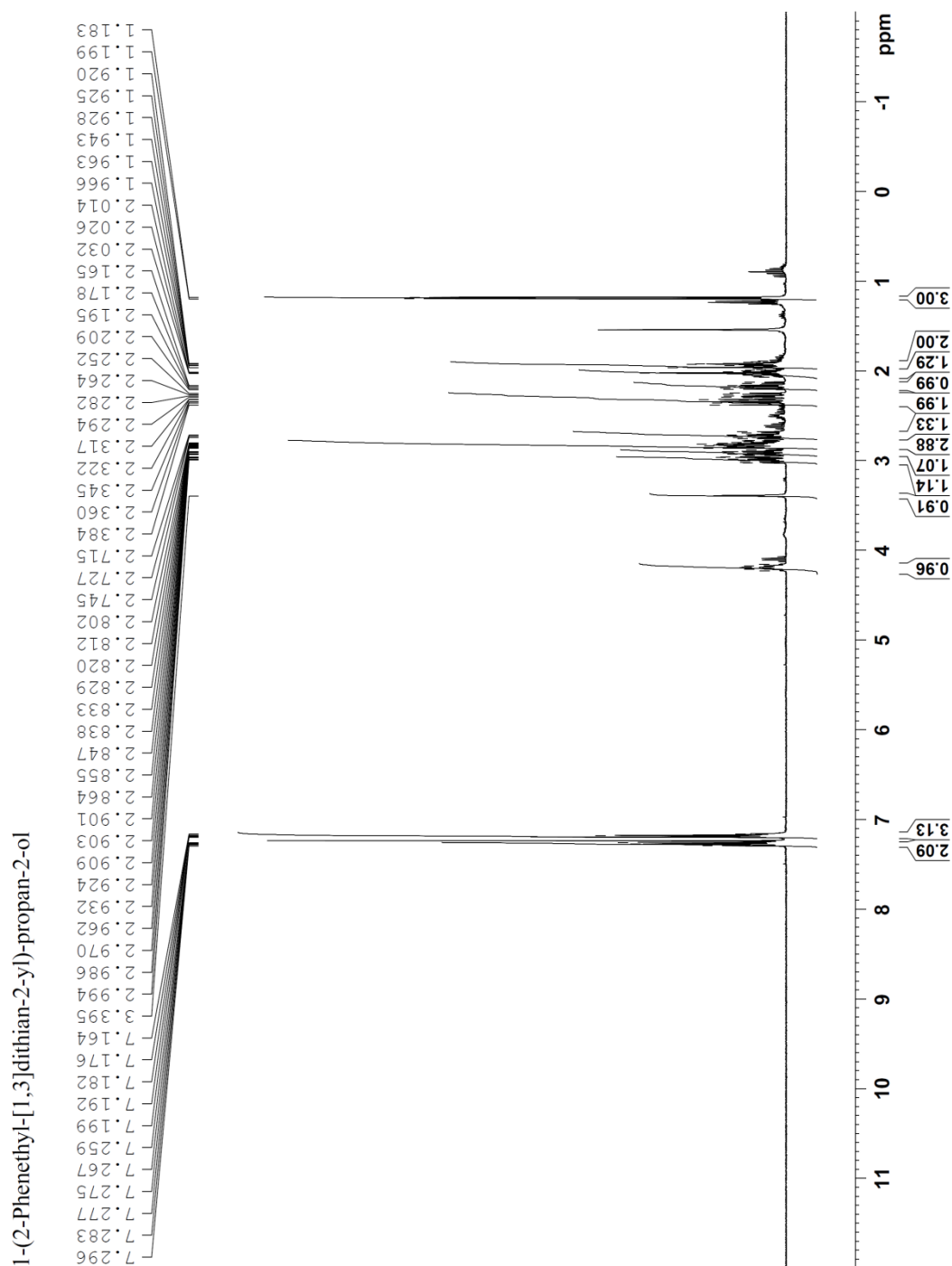


Figure 2.46 – ¹H NMR of crude 1-(2-phenethyl-[1,3]dithiane-2-yl)propan-2-ol (**2.81**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl₃.

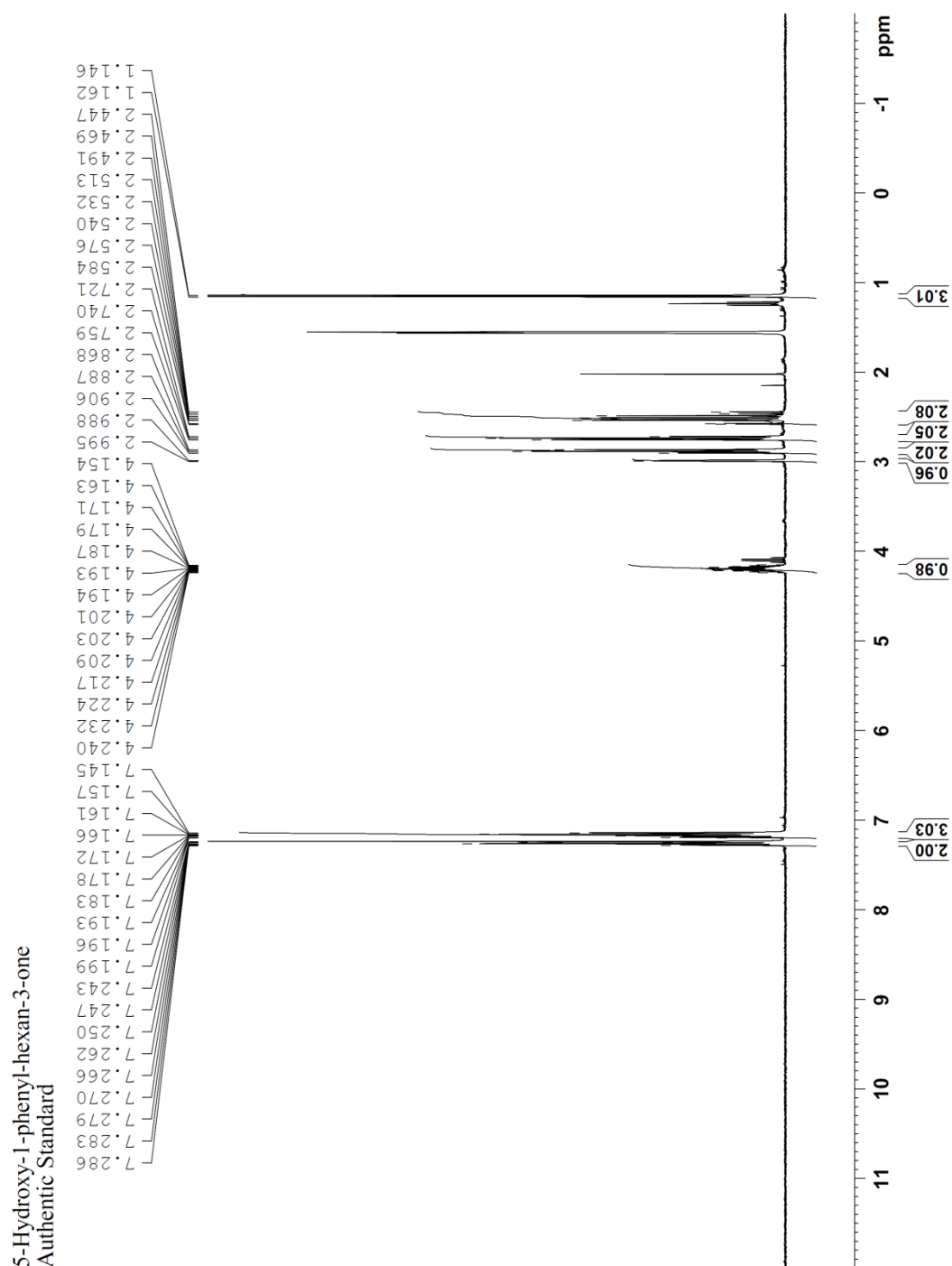


Figure 2.47 – ^1H NMR of the authentic standard (**2.67**) used during fragment coupling studies, as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

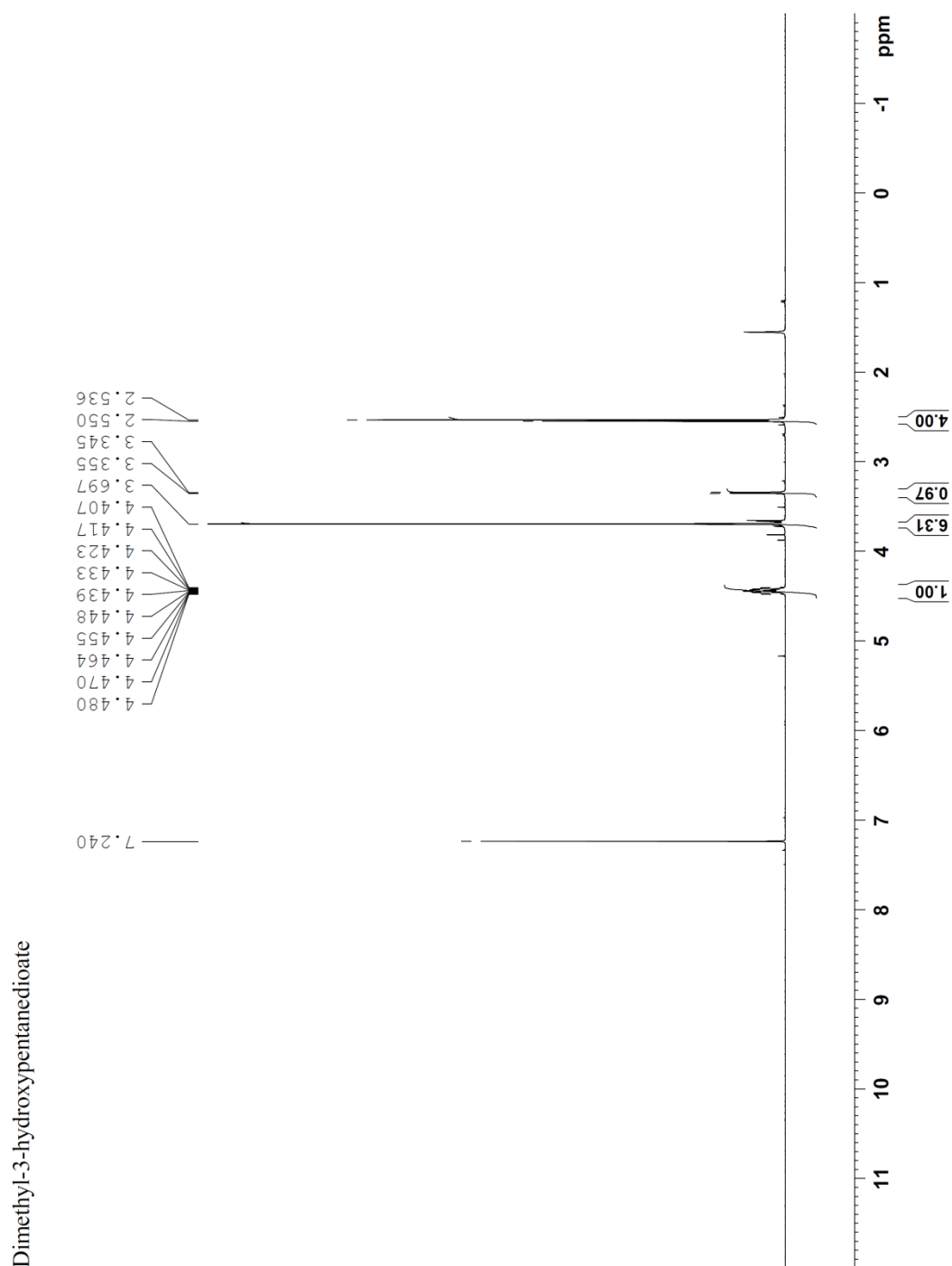


Figure 2.48 – ^1H NMR of dimethyl-3-hydroxypentanedioate (**2.90**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

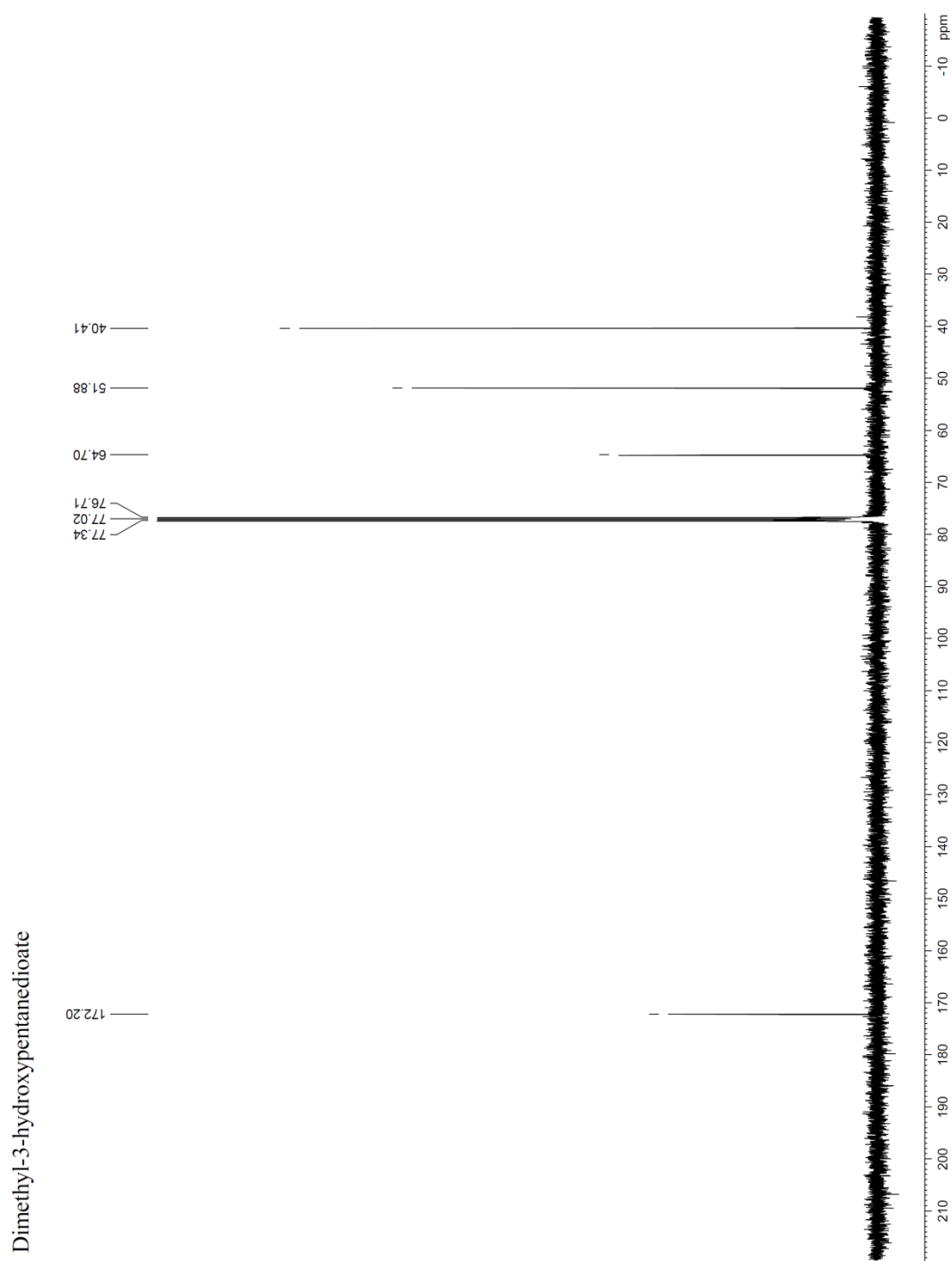


Figure 2.49 – ^{13}C NMR of dimethyl-3-hydroxypentanedioate (**2.90**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

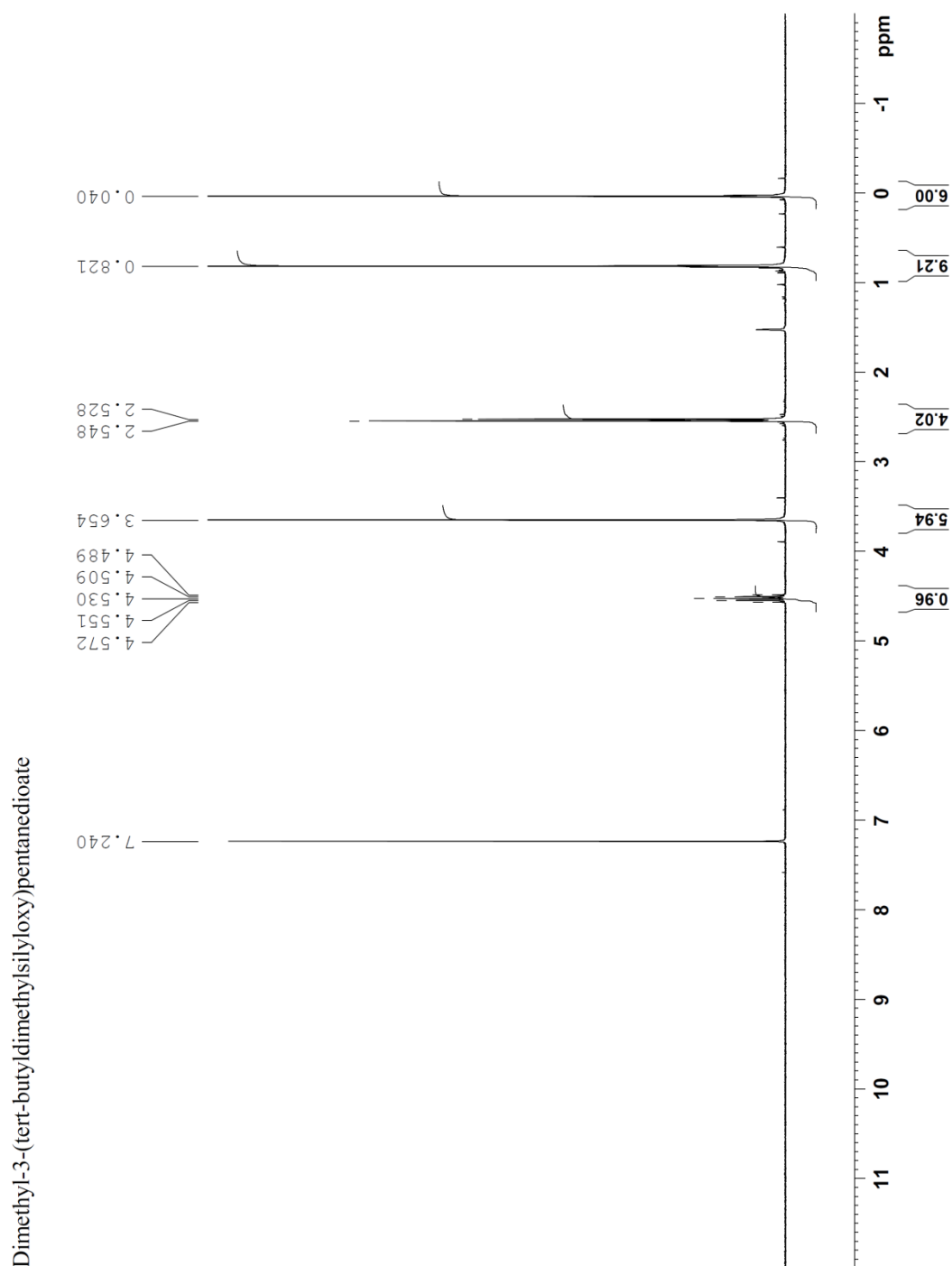


Figure 2.50 – ^1H NMR of dimethyl-3-(TBS)-pentandioate (**2.91**), as measured on a Bruker AVANCE 300 spectrophotometer at 300 MHz, calibrated to the residual proton resonance of CDCl_3 .

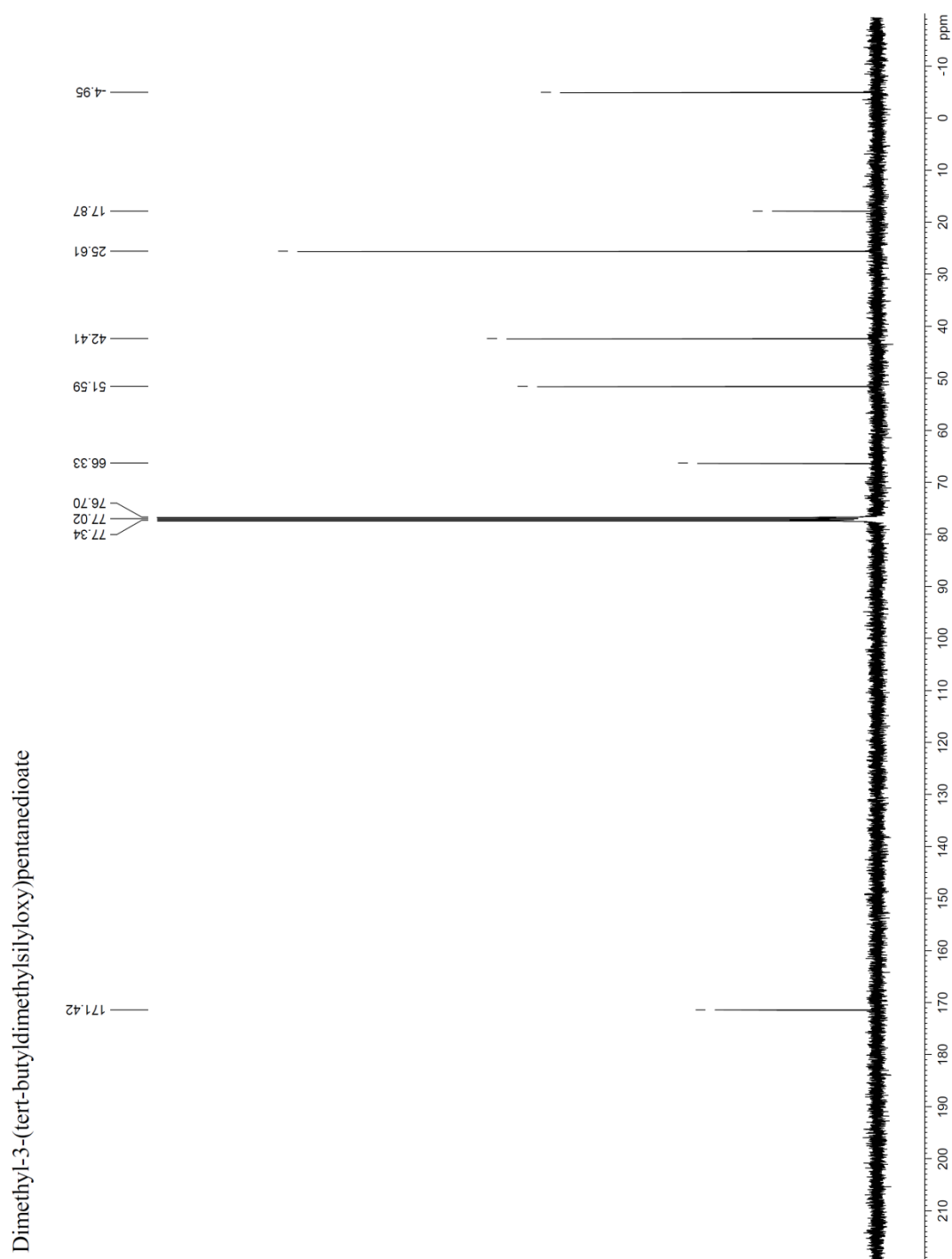


Figure 2.51 – ^{13}C NMR of dimethyl-3-(TBS)-pentandioate (**2.91**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

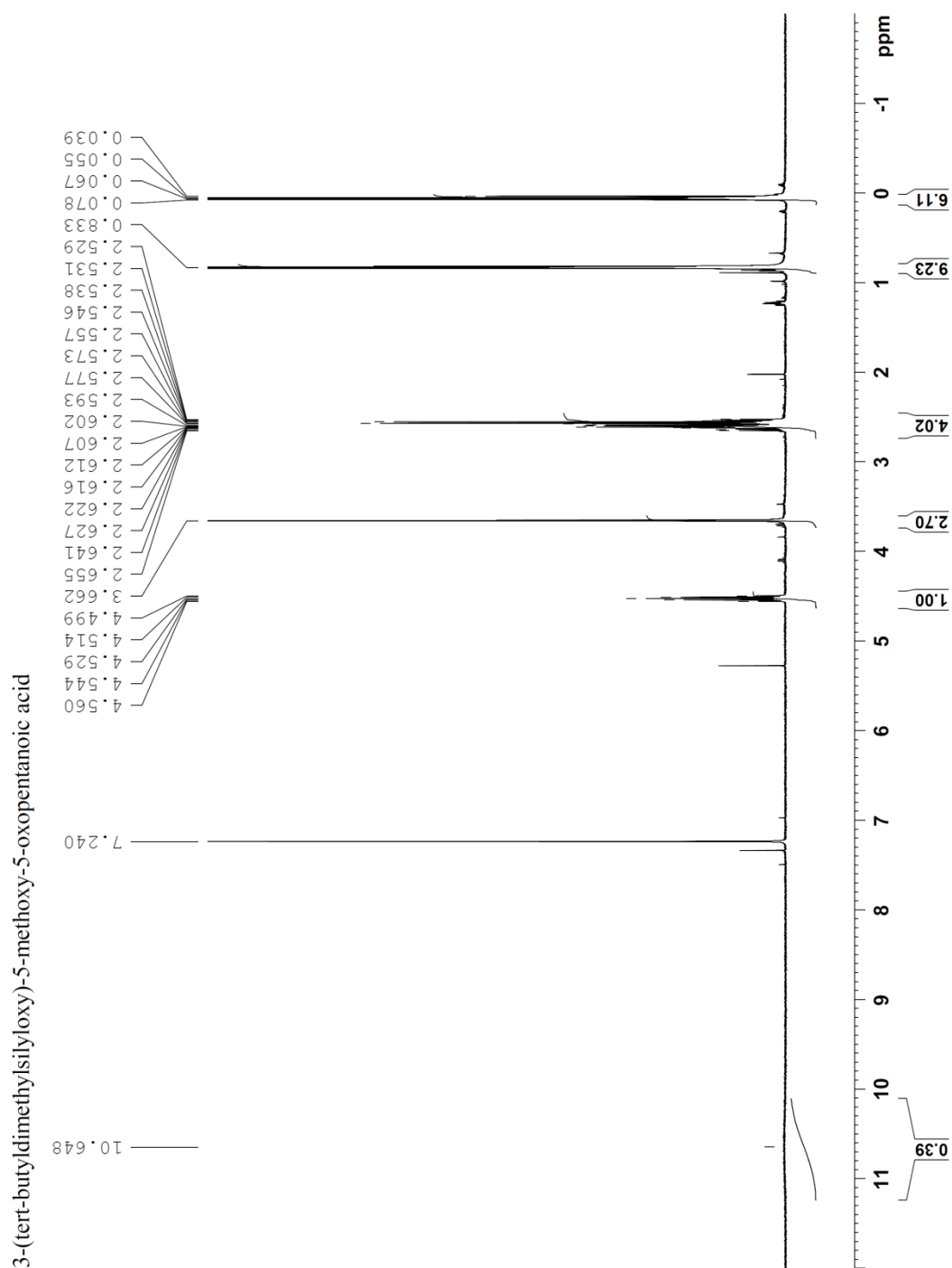


Figure 2.52 – ^1H NMR of 3-(TBS)-5-methoxy-5-oxopentanoic acid (**2.92**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

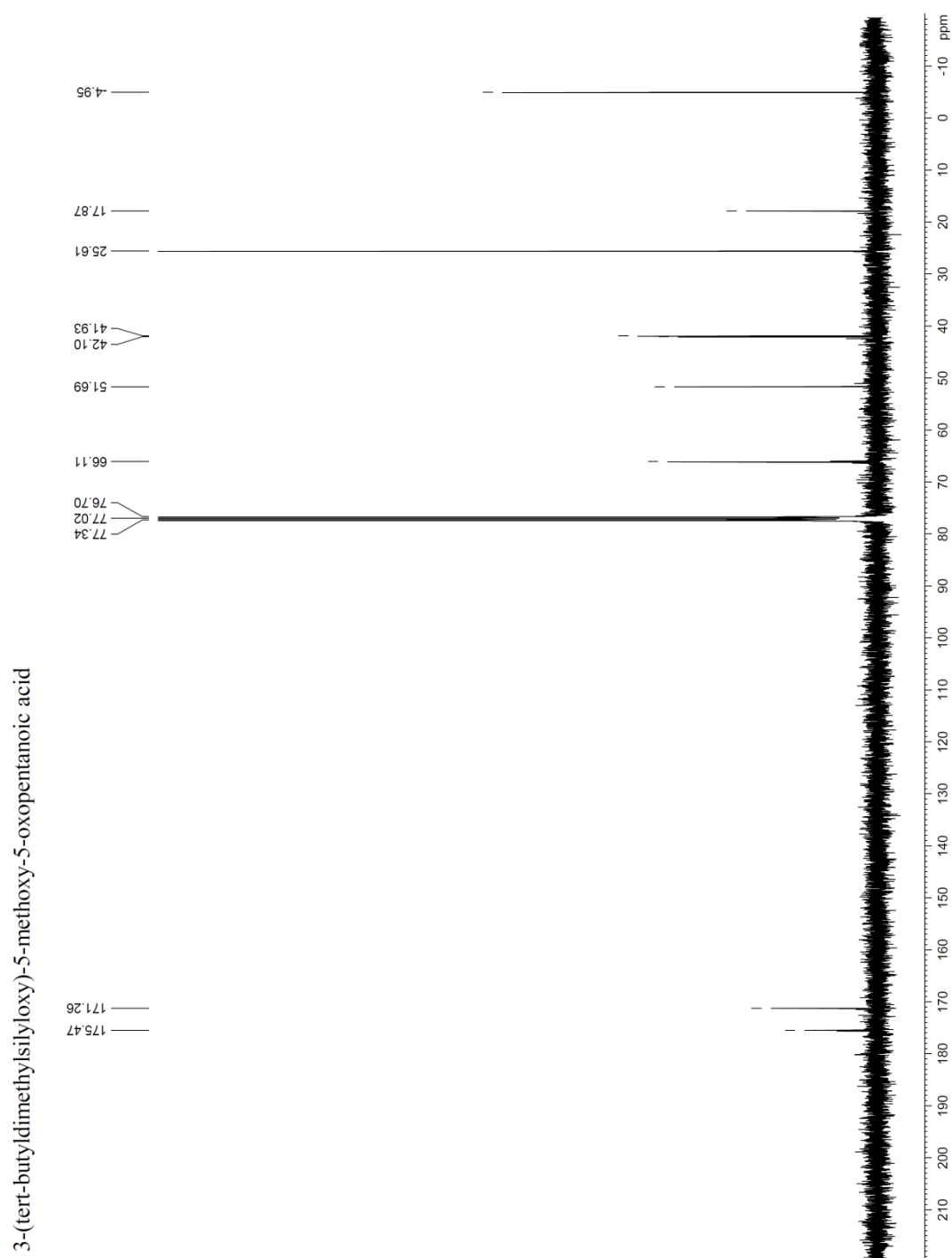


Figure 2.53 – ^{13}C NMR of 3-(TBS)-5-methoxy-5-oxopentanoic acid (**2.92**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

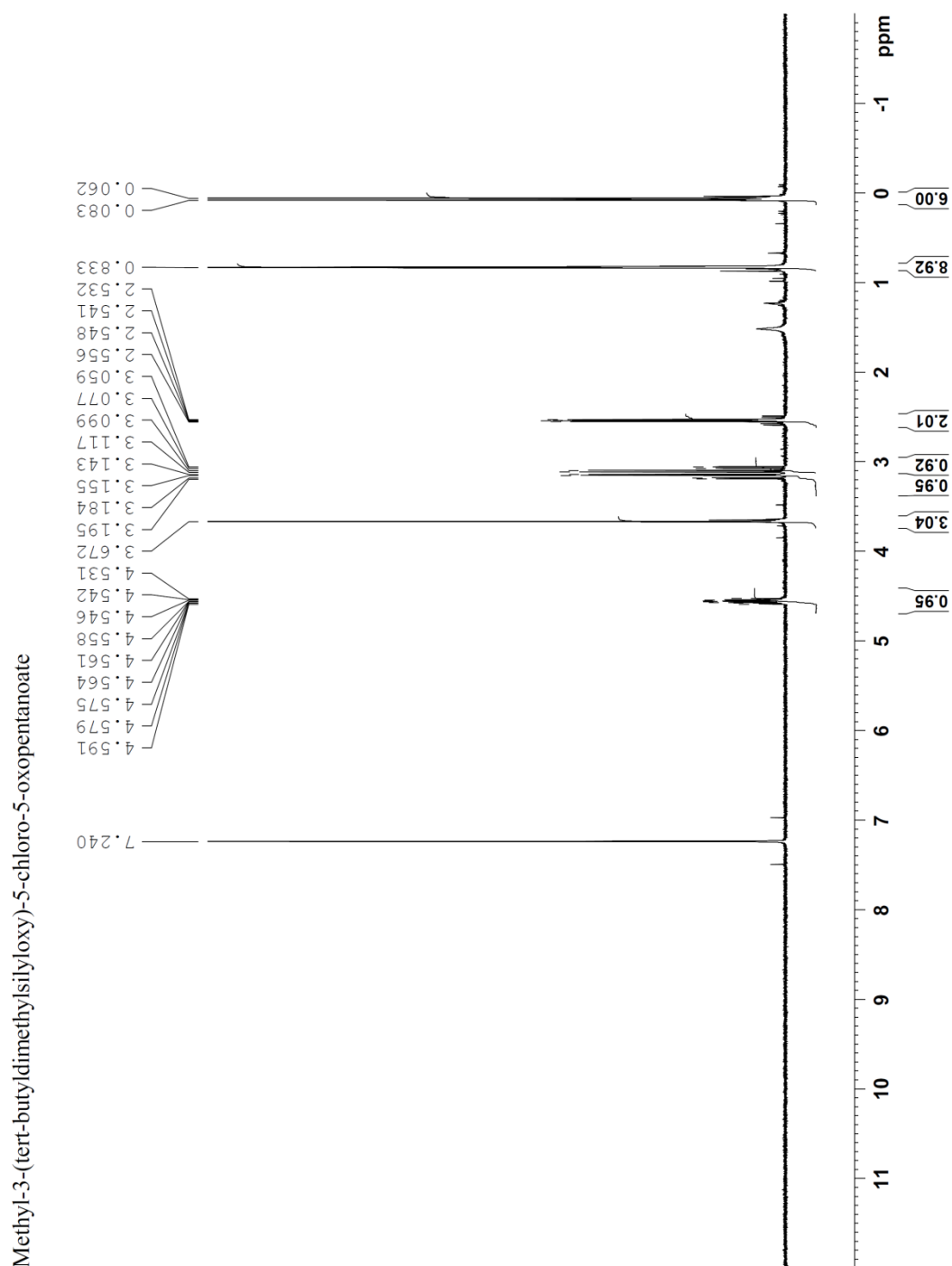


Figure 2.54 – ^1H NMR of methyl-3-(TBS)-5-chloro-5-oxopentanoate (**2.93**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

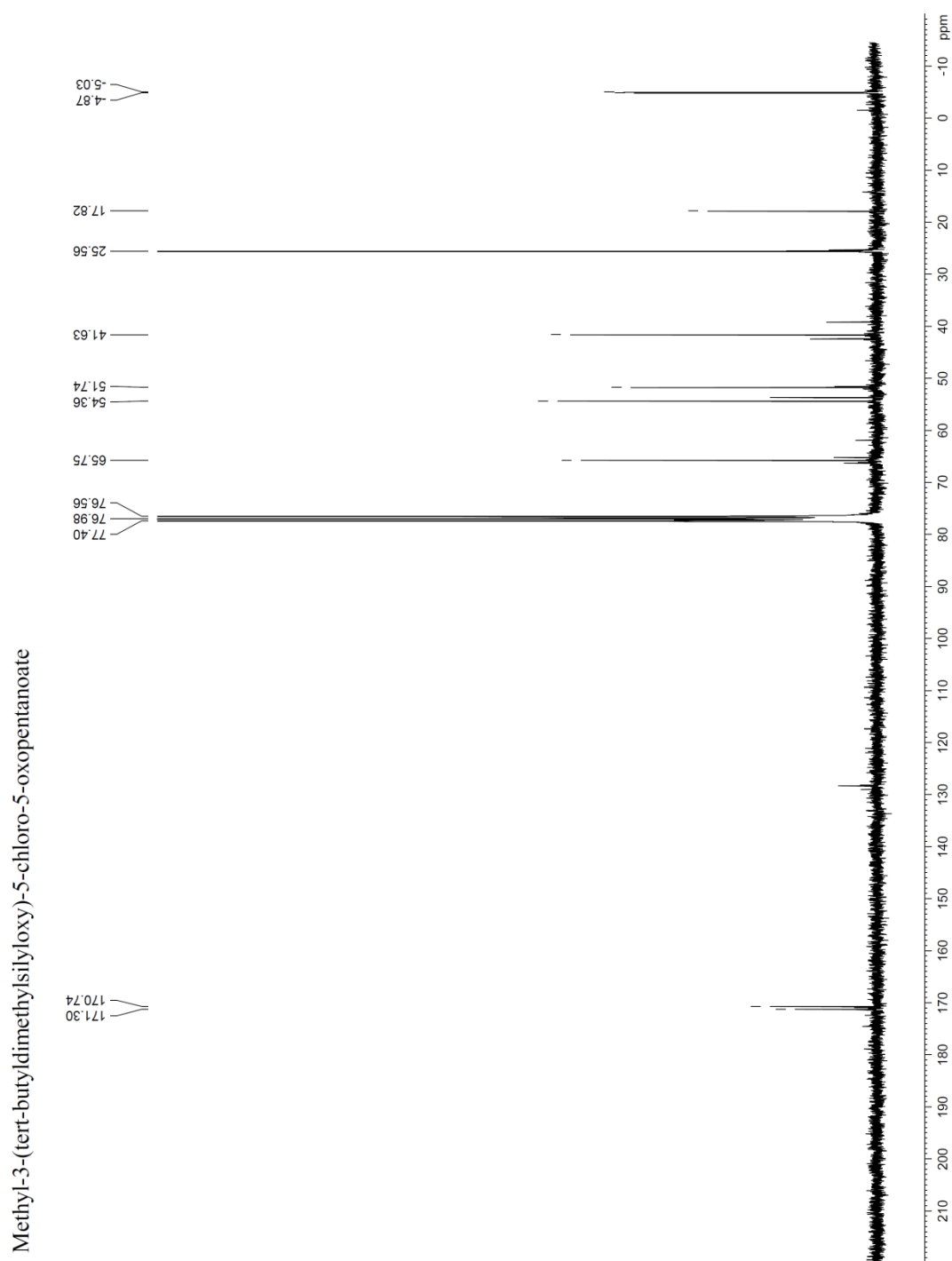


Figure 2.55 – ¹³CNMR of methyl-3-(TBS)-5-chloro-5-oxopentanoate (**2.93**), as measured on a Bruker AVANCE 300 spectrophotometer at 75 MHz, calibrated to the residual proton resonance of CDCl₃.

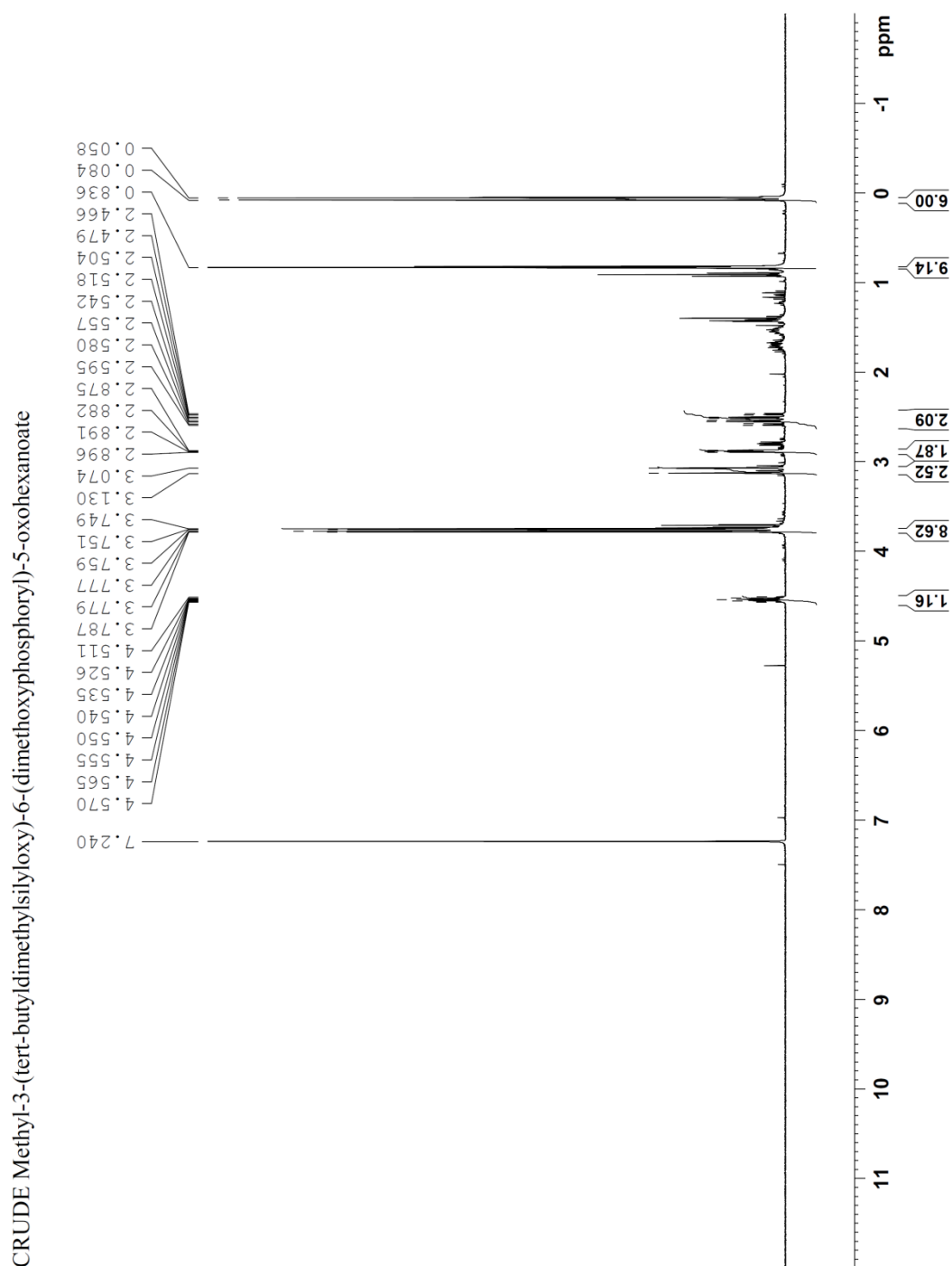
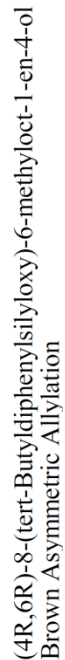


Figure 2.56 – ^1H NMR of methyl-3-(TBS)-6-(dimethoxyphosphoryl)-5-oxohexanoate (**2.87**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .



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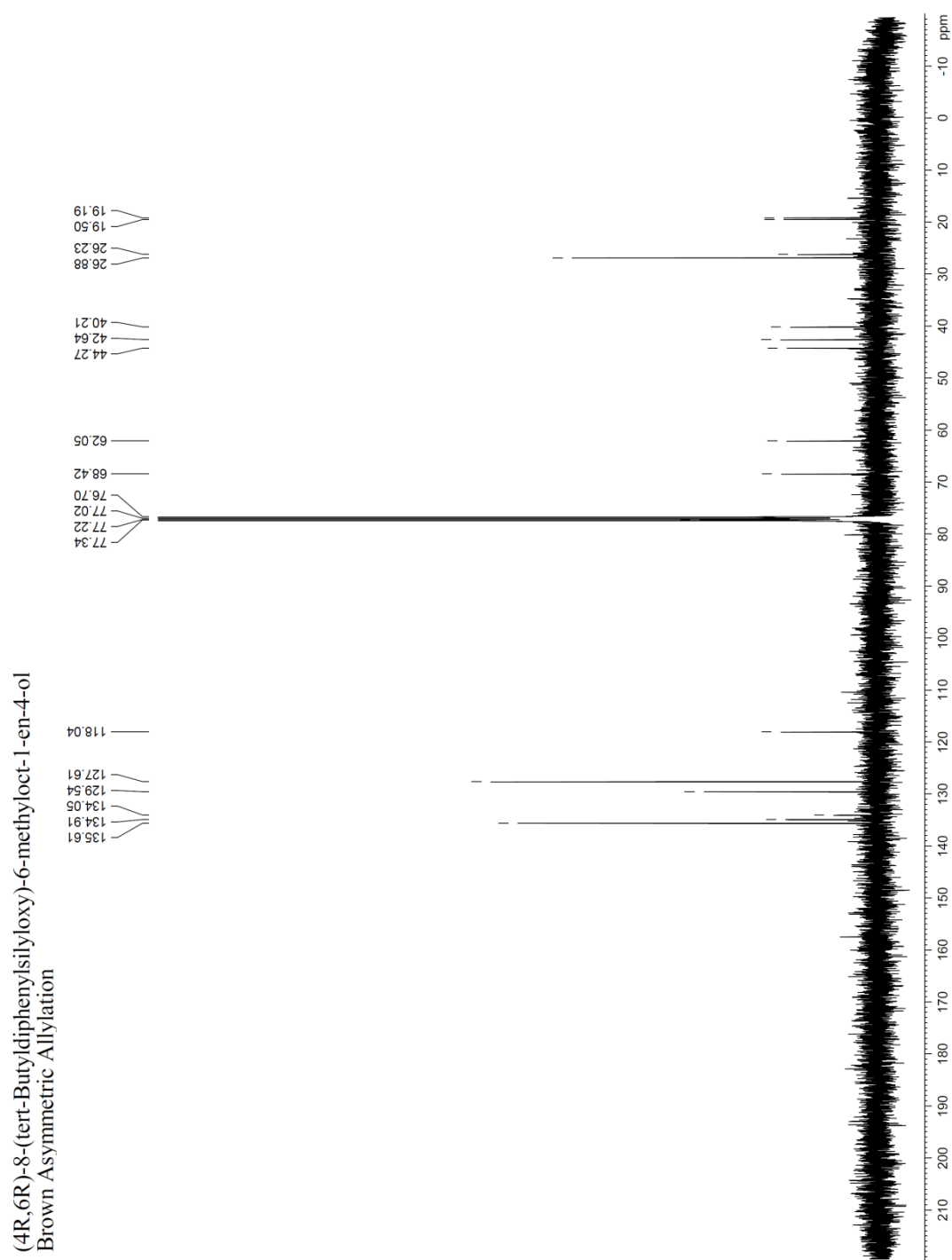


Figure 2.58 – ^{13}C NMR of (4*R*,6*R*)-8-(TBDPS)-6-methyloct-1-en-4-ol (**2.98**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

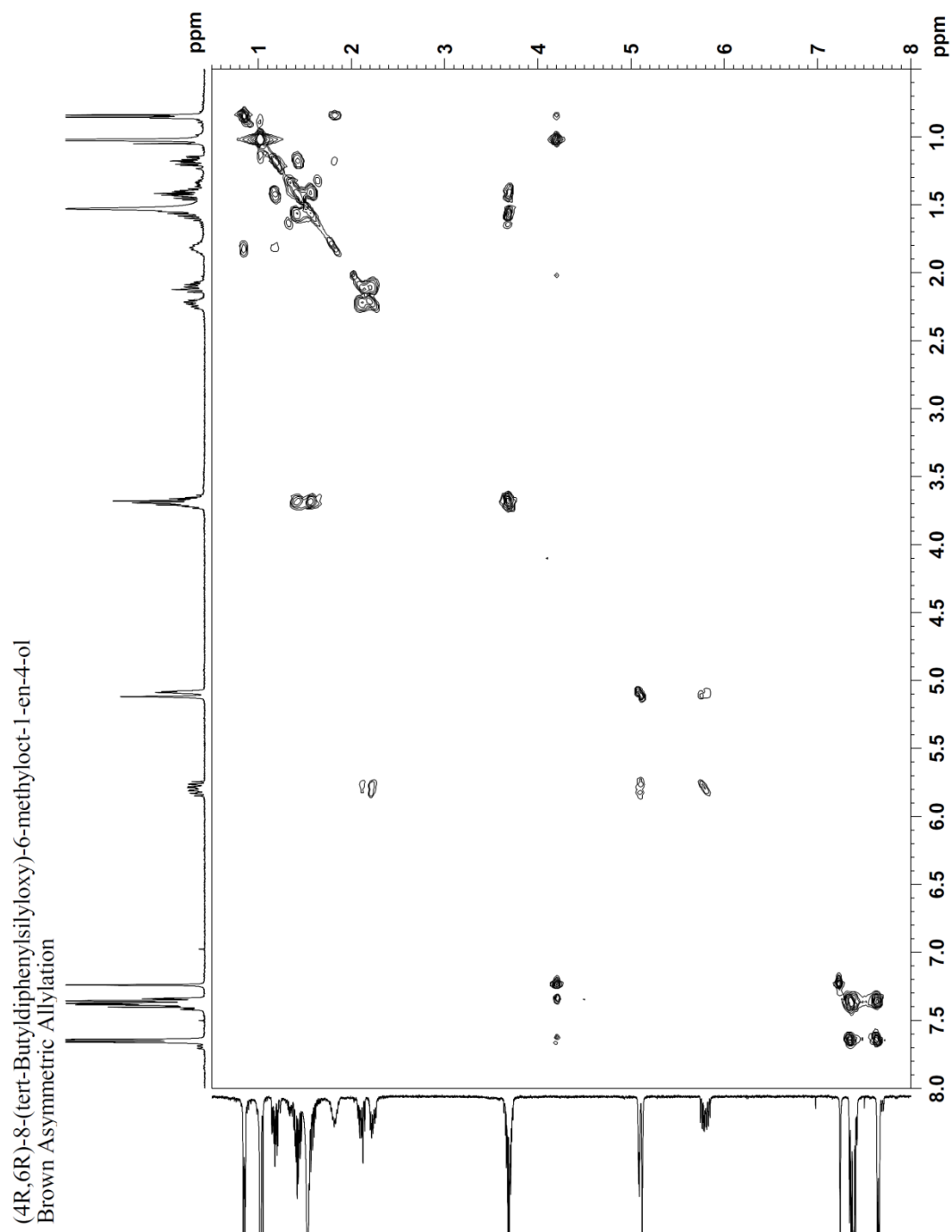


Figure 2.59 – COSY of (4R,6R)-8-(TBDPS)-6-methyloct-1-en-4-ol (**2.98**), as measured on a Bruker AVANCE 400 spectrophotometer, calibrated to the residual proton resonance of CDCl_3 .

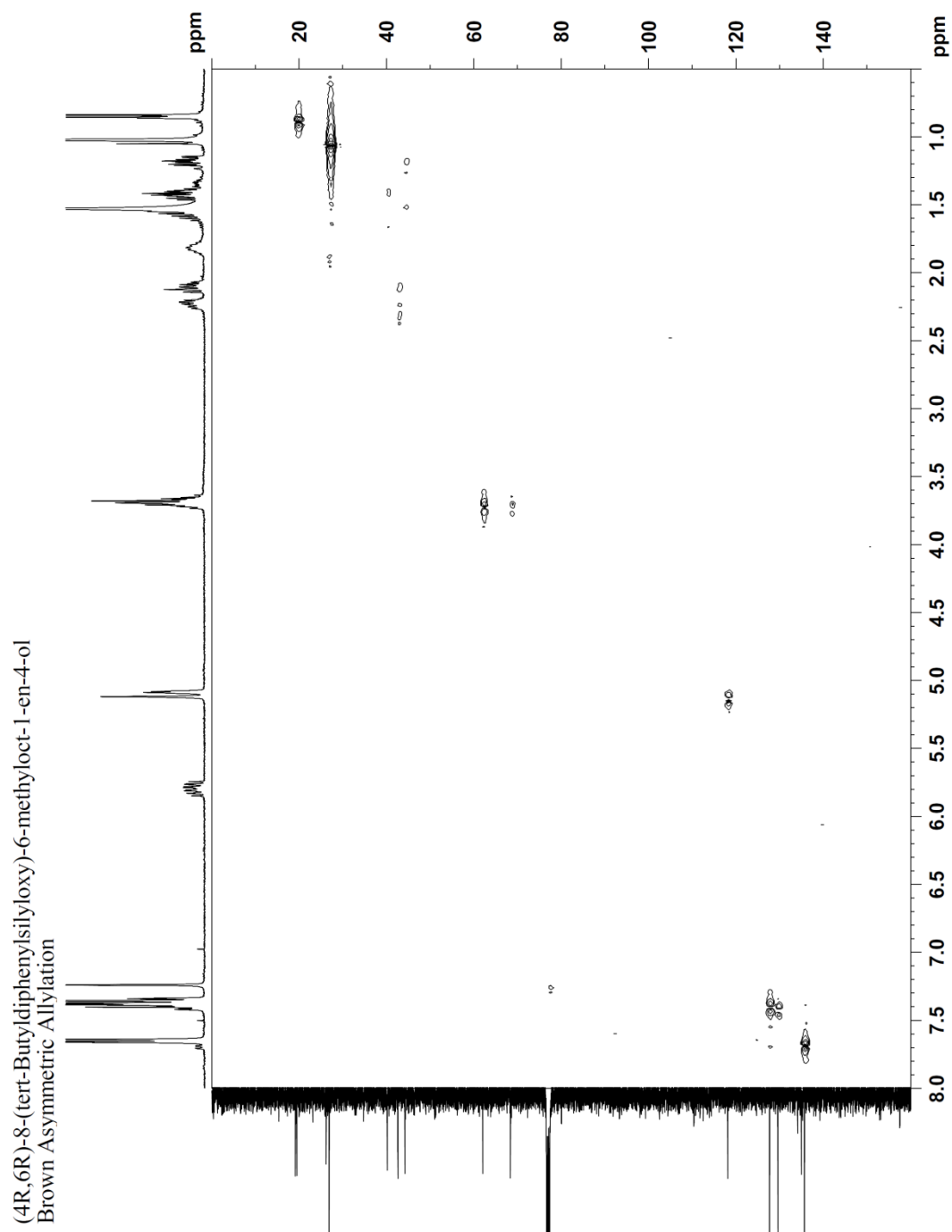


Figure 2.60 – HSQC of (4*R*,6*R*)-8-(TBDPS)-6-methyloct-1-en-4-ol (**2.98**), as measured on a Bruker AVANCE 400 spectrophotometer, calibrated to the residual proton resonance of CDCl₃.

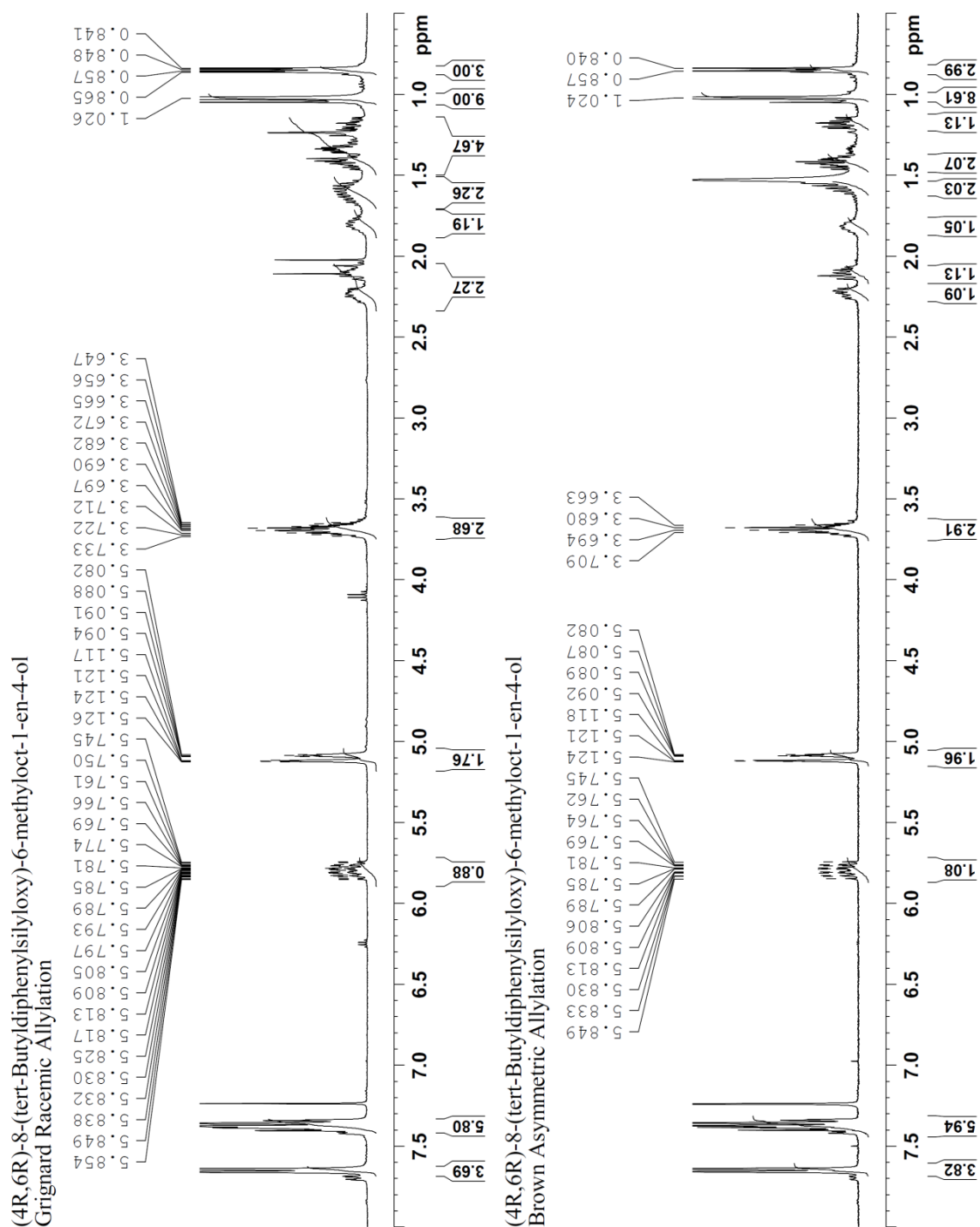


Figure 2.61 – Comparative ^1H NMR of homoallylic alcohol **2.98**, as prepared by racemic Grignard and asymmetric Brown protocols. Both spectra were measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

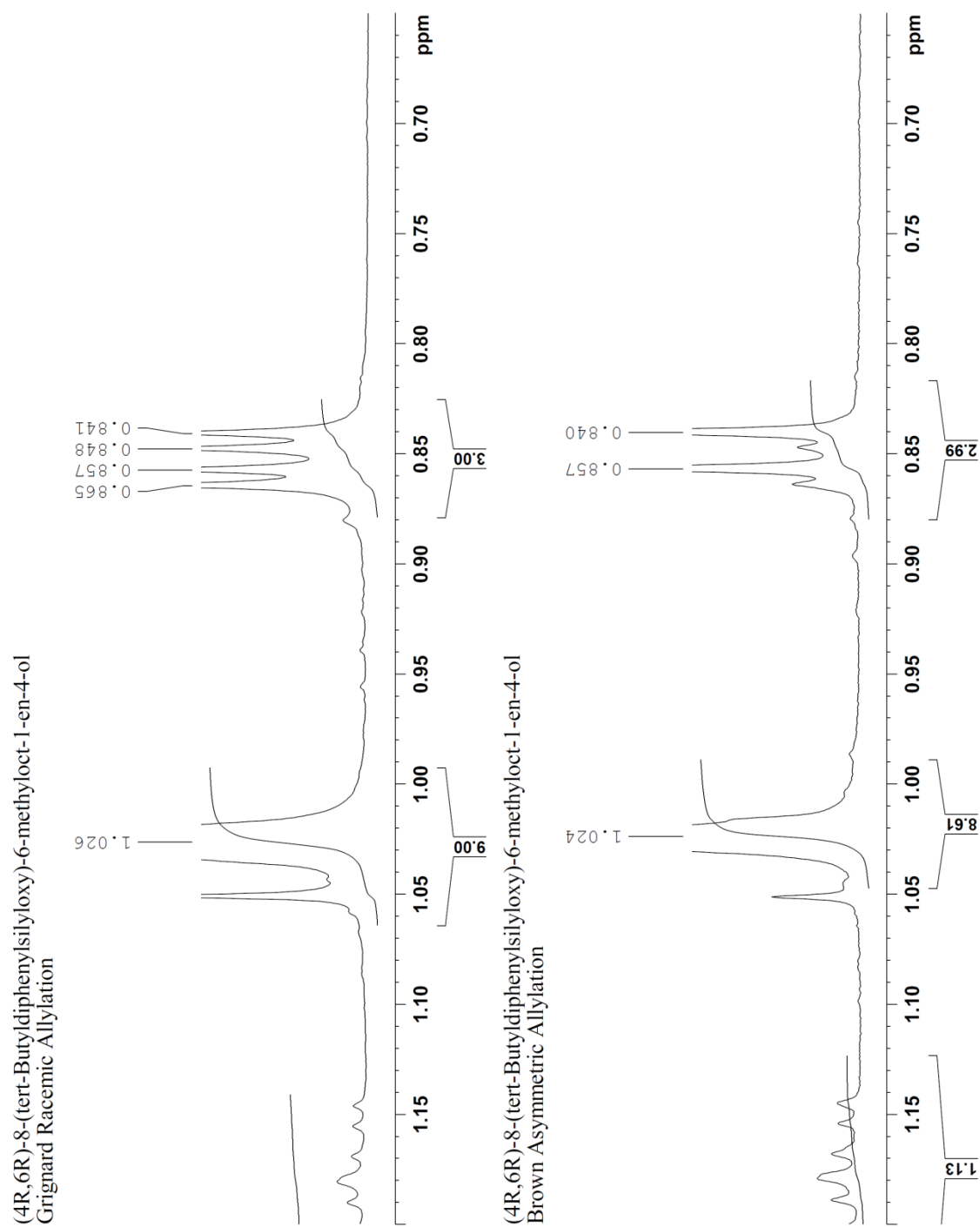


Figure 2.62 – Comparative ¹H NMR zoom of homoallylic alcohol **2.98**, as prepared by racemic Grignard and asymmetric Brown protocols. Both spectra were measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl₃.

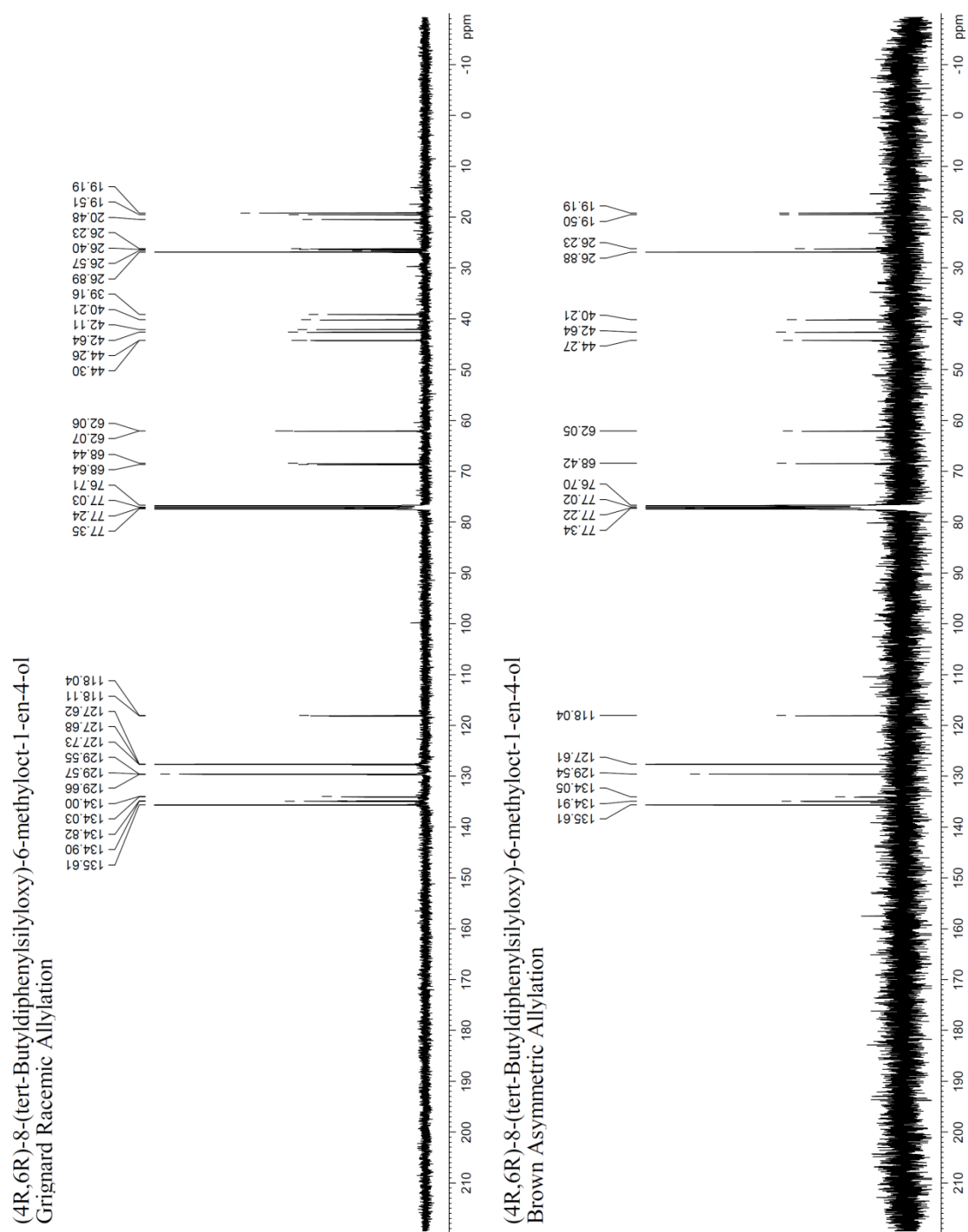
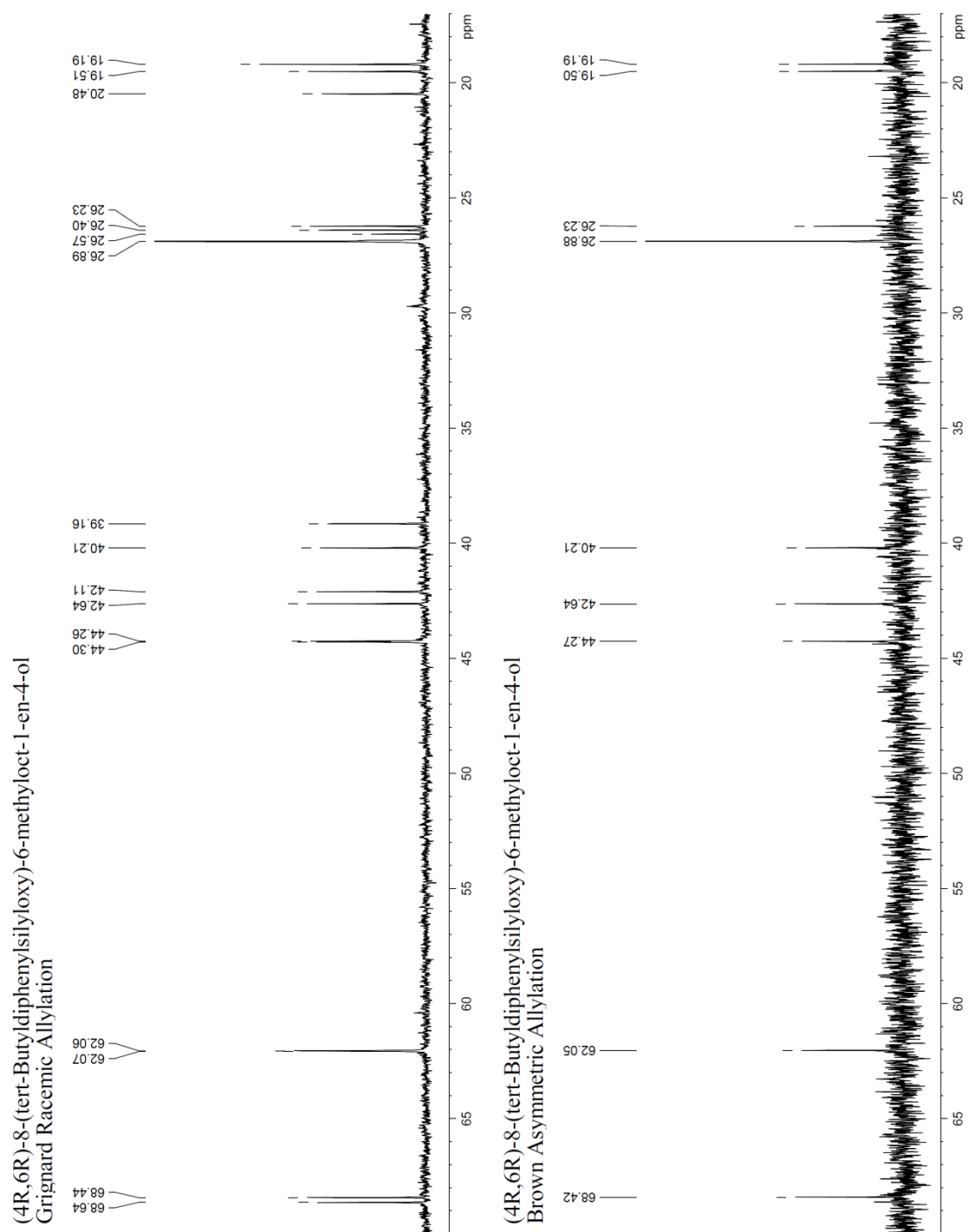


Figure 2.63 – Comparative ^{13}C NMR of homoallylic alcohol **2.98**, as prepared by racemic Grignard and asymmetric Brown protocols. Both spectra were measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .



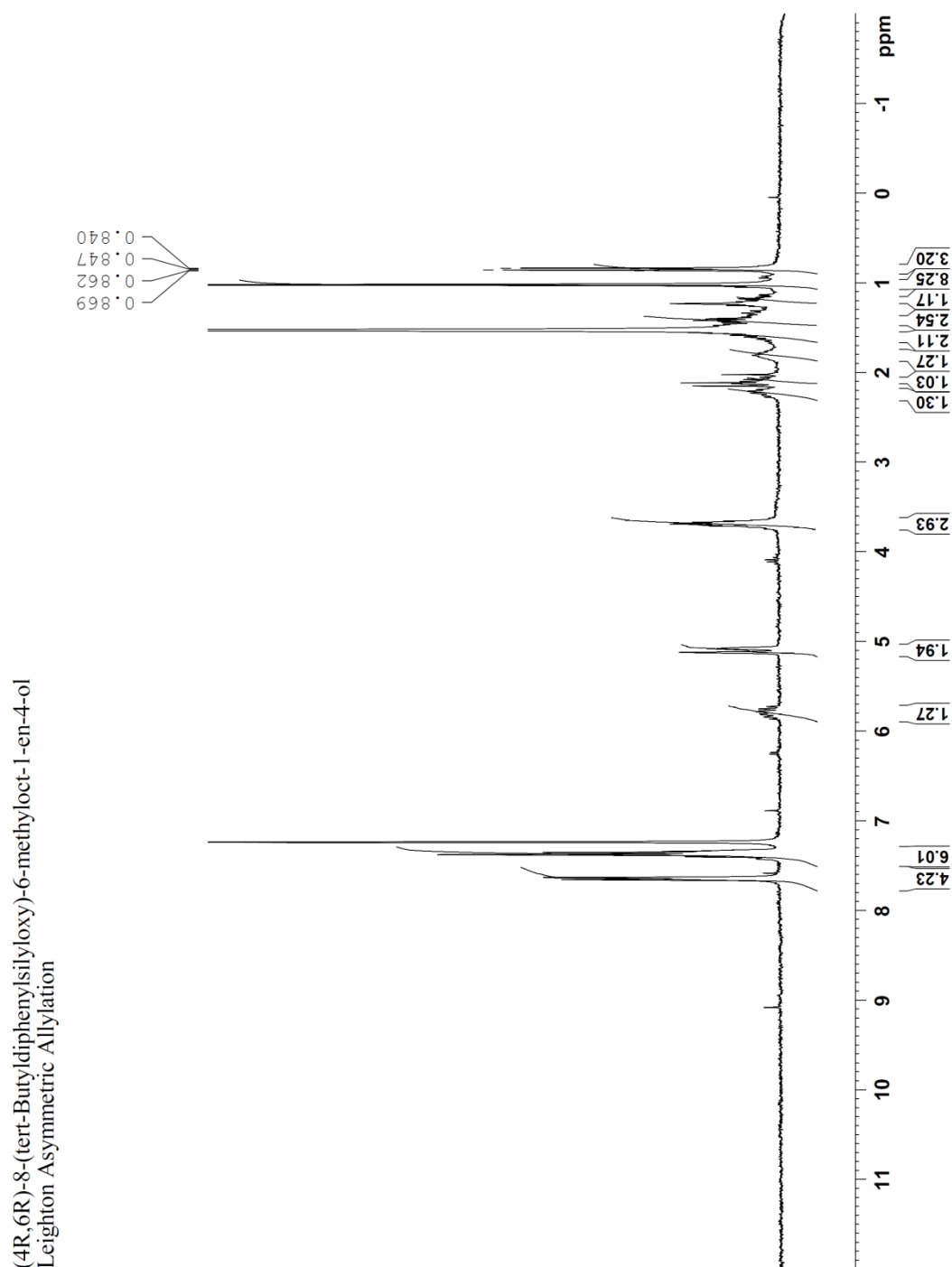


Figure 2.65 – ^1H NMR of (4*R*,6*R*)-8-(TBDPS)-6-methyloct-1-en-4-ol (**2.98**), as prepared by Leighton's protocol and measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

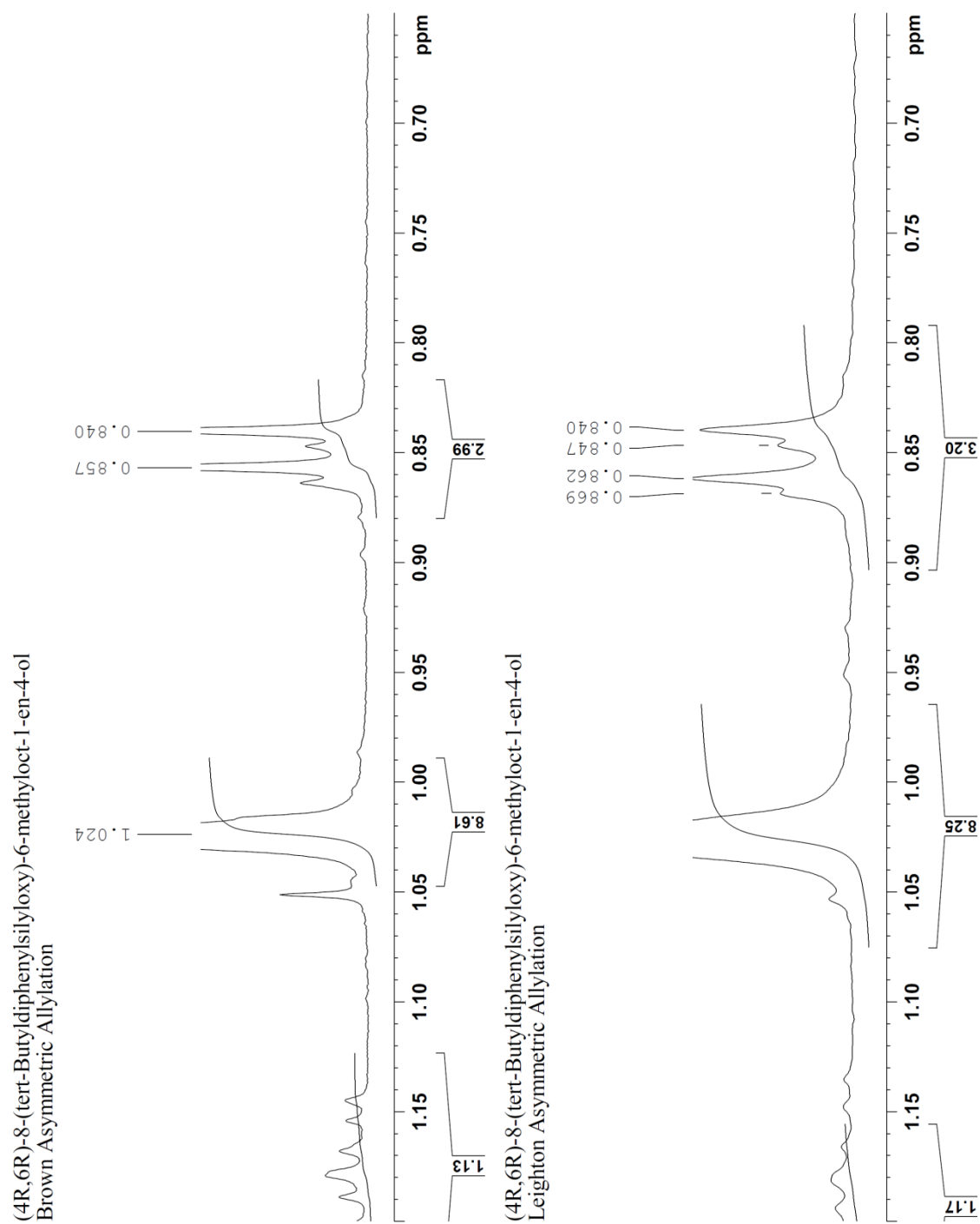


Figure 2.66 – Comparative ^1H NMR zoom of homoallylic alcohol **2.98**, as prepared by asymmetric Brown and Leighton protocols. Both spectra were measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

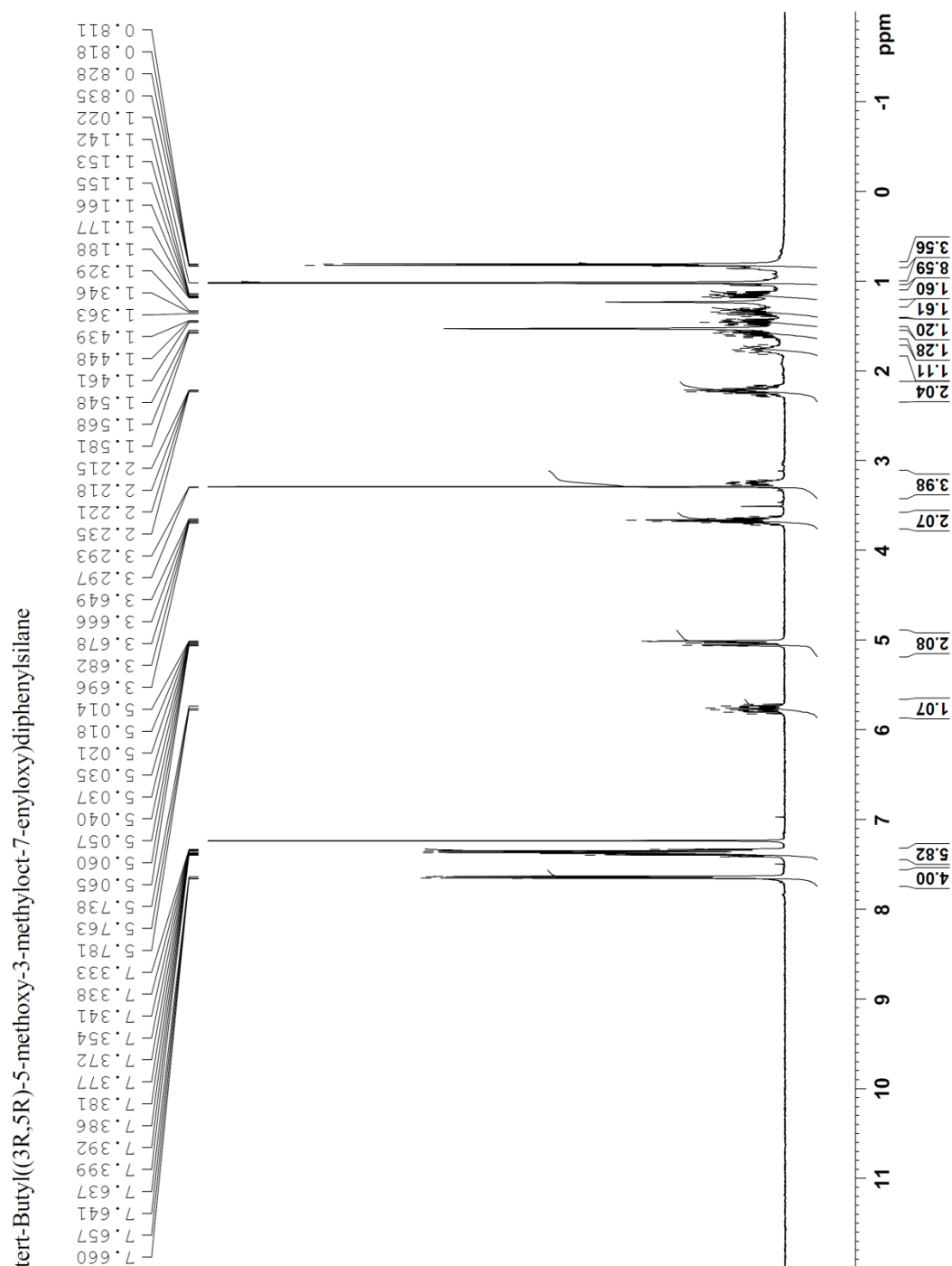


Figure 2.67 – ¹H NMR of *tert*-butyl((3R,5R)-5-methoxy-3-methyloct-7-enyloxy)diphenylsilane (2.99), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl₃.

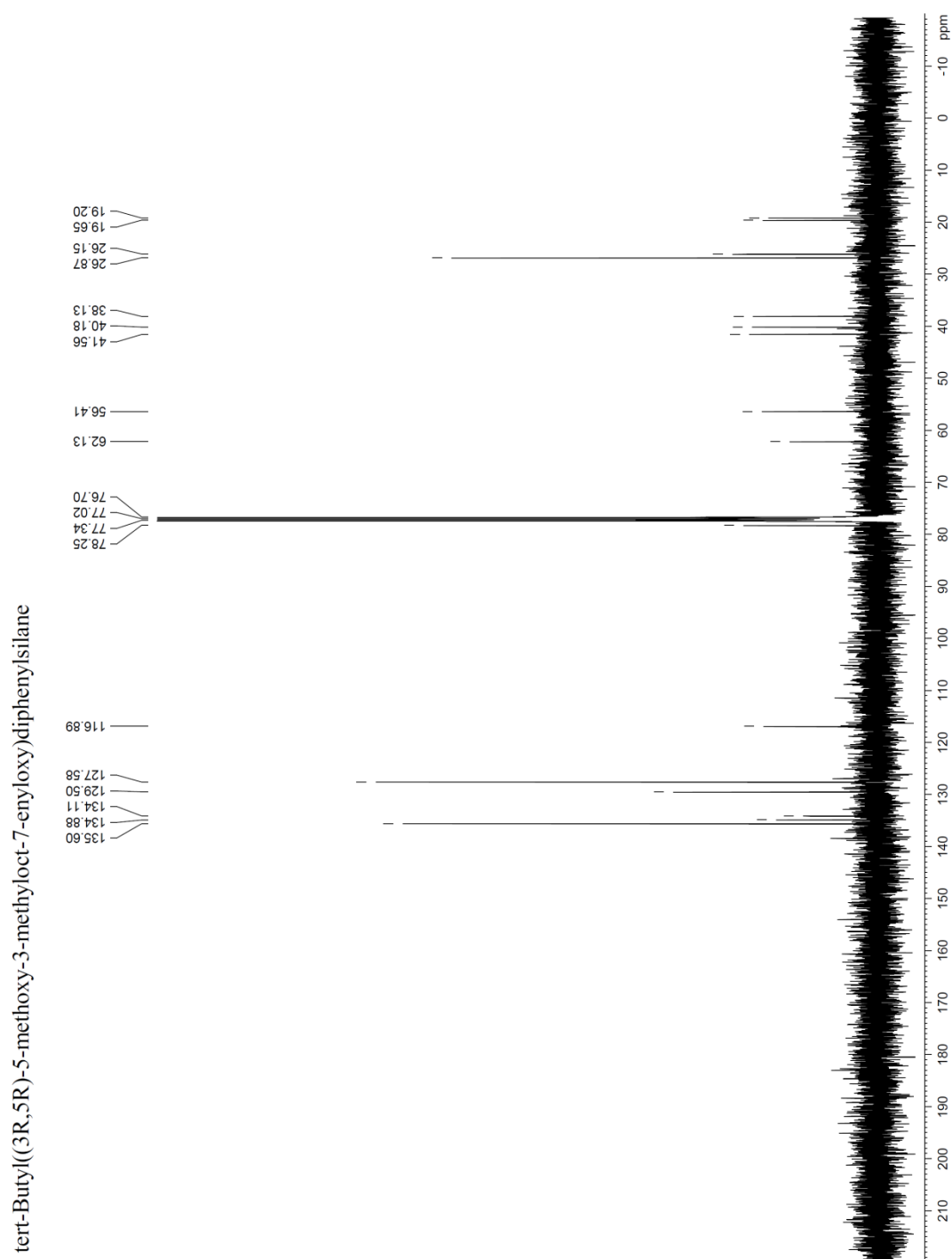


Figure 2.68 – ^{13}C NMR of *tert*-butyl((3*R*,5*R*)-5-methoxy-3-methyloct-7-enyloxy)diphenylsilane (**2.99**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

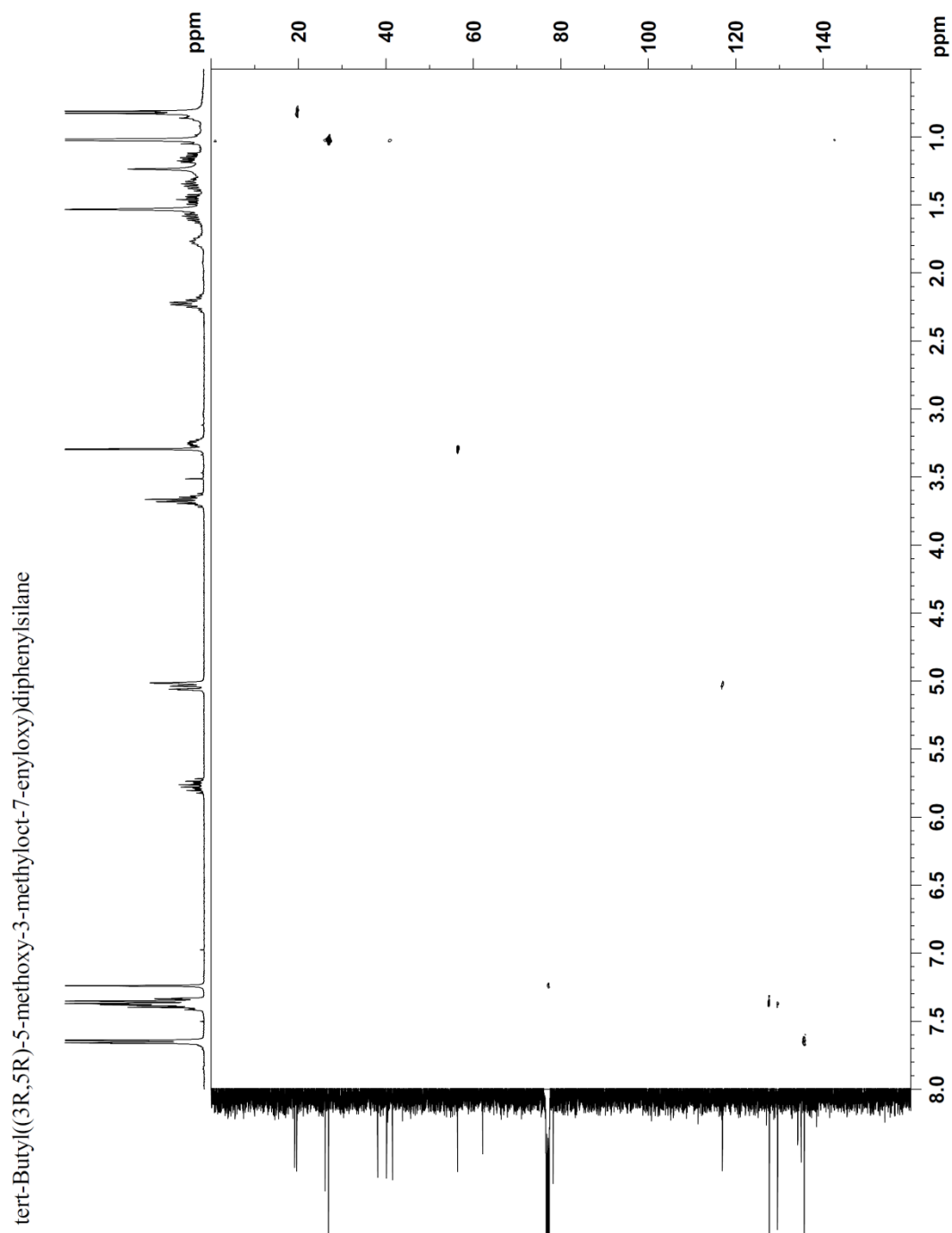


Figure 2.69 – HMQC of *tert*-butyl((3R,5R)-5-methoxy-3-methyloct-7-enyloxy)diphenylsilane (**2.99**), as measured on a Bruker AVANCE 400 spectrophotometer, calibrated to the residual proton resonance of CDCl_3 .

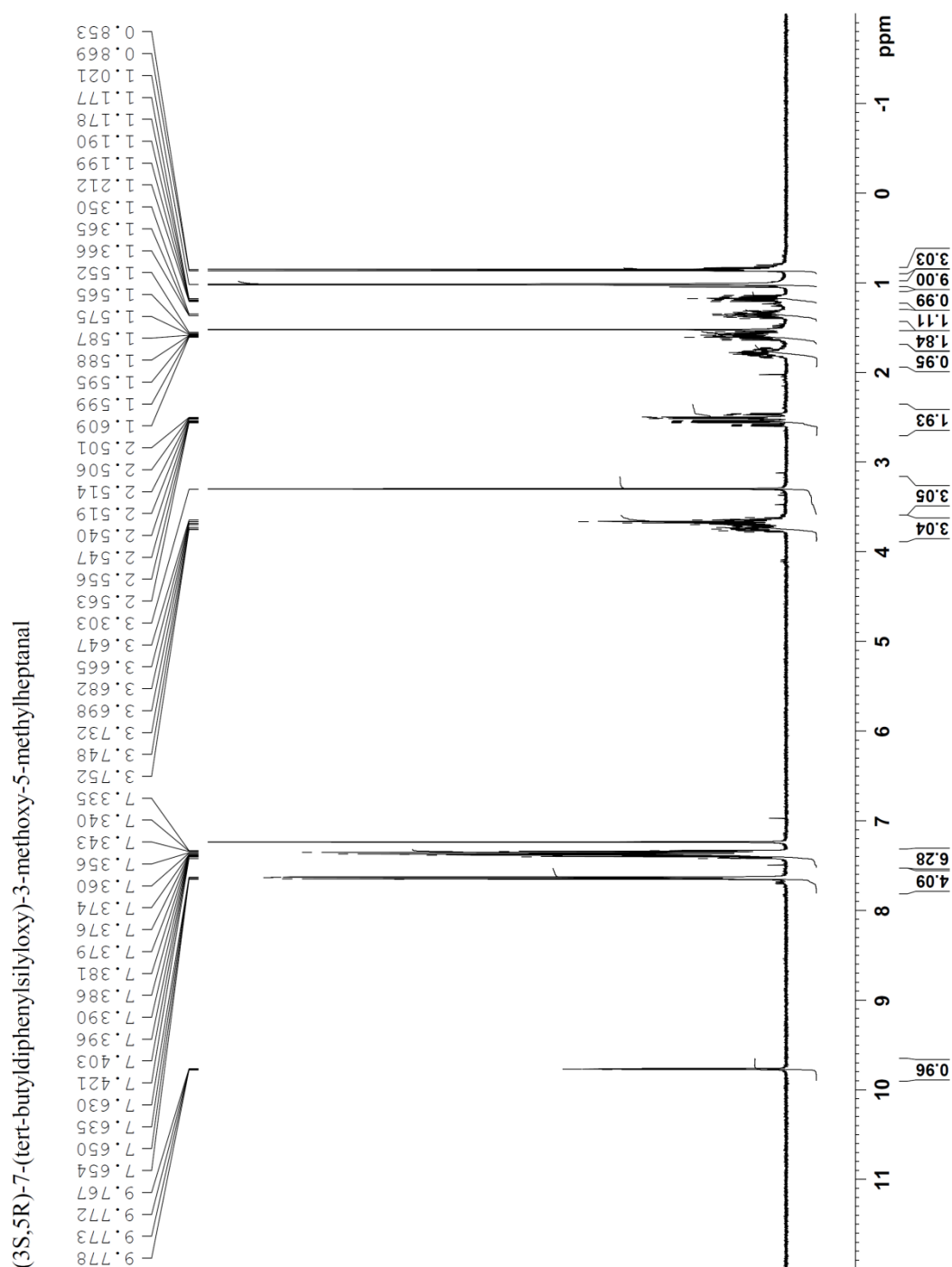


Figure 2.70 – ^1H NMR of (3S,5R)-7-(TBDPS)-3-methoxy-5-methylheptanal (**2.100**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

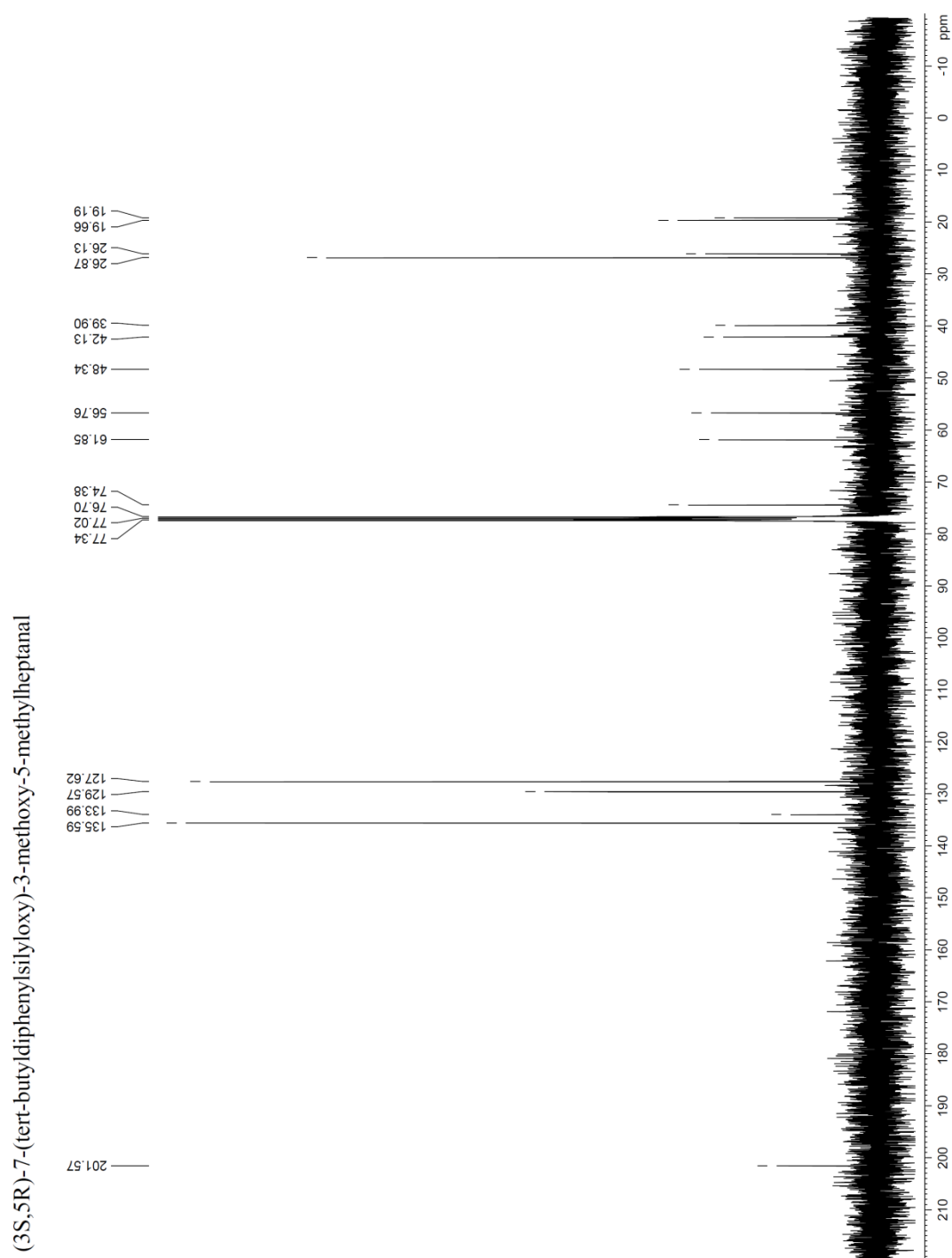


Figure 2.71 – ^{13}C NMR of (3S,5R)-7-(TBDPS)-3-methoxy-5-methylheptanal (**2.100**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

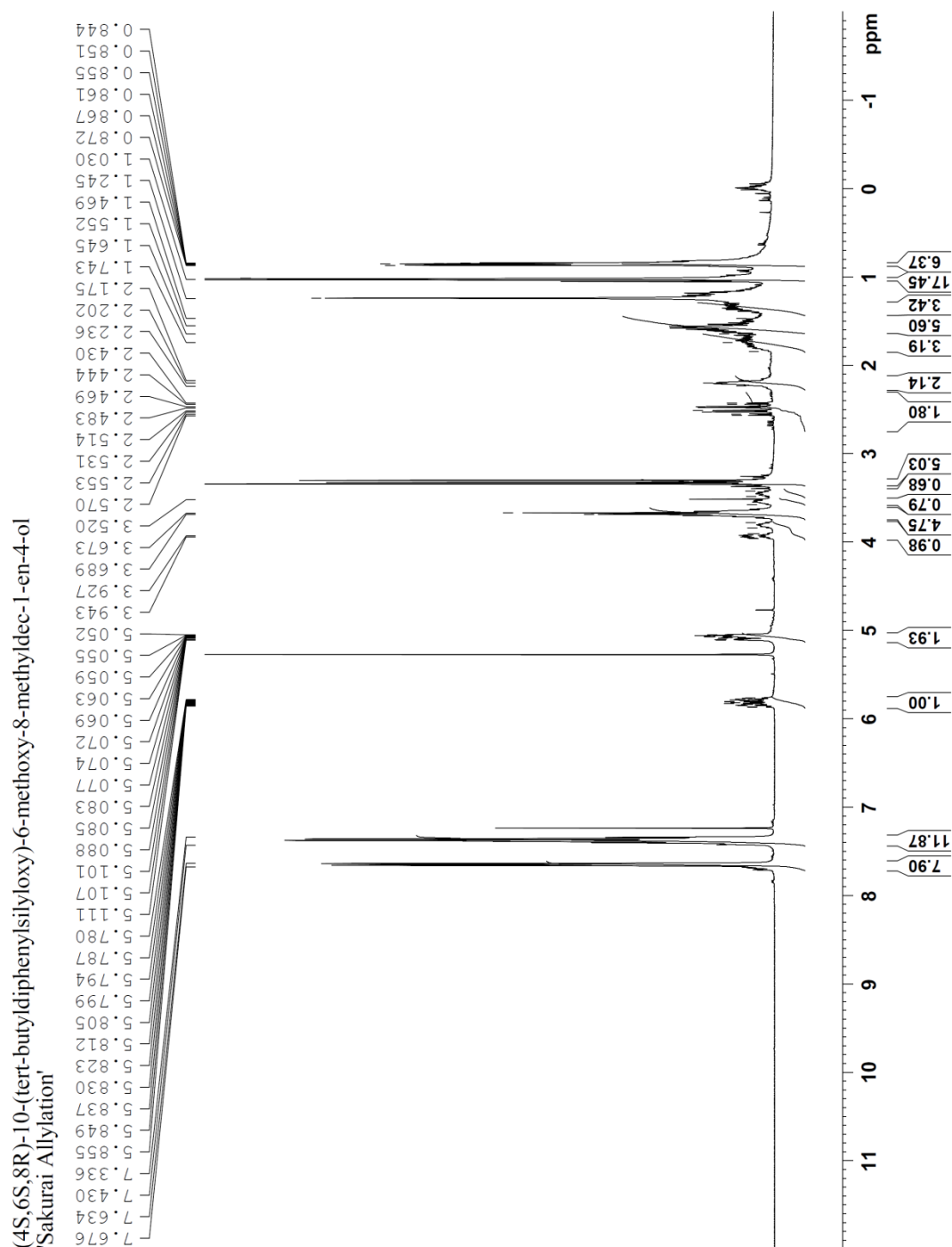


Figure 2.72 – ^1H NMR of crude (4S,6S,8R)-10-(TBDPS)-6-methoxy-8-methyldec-1-en-4-ol (**2.101**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

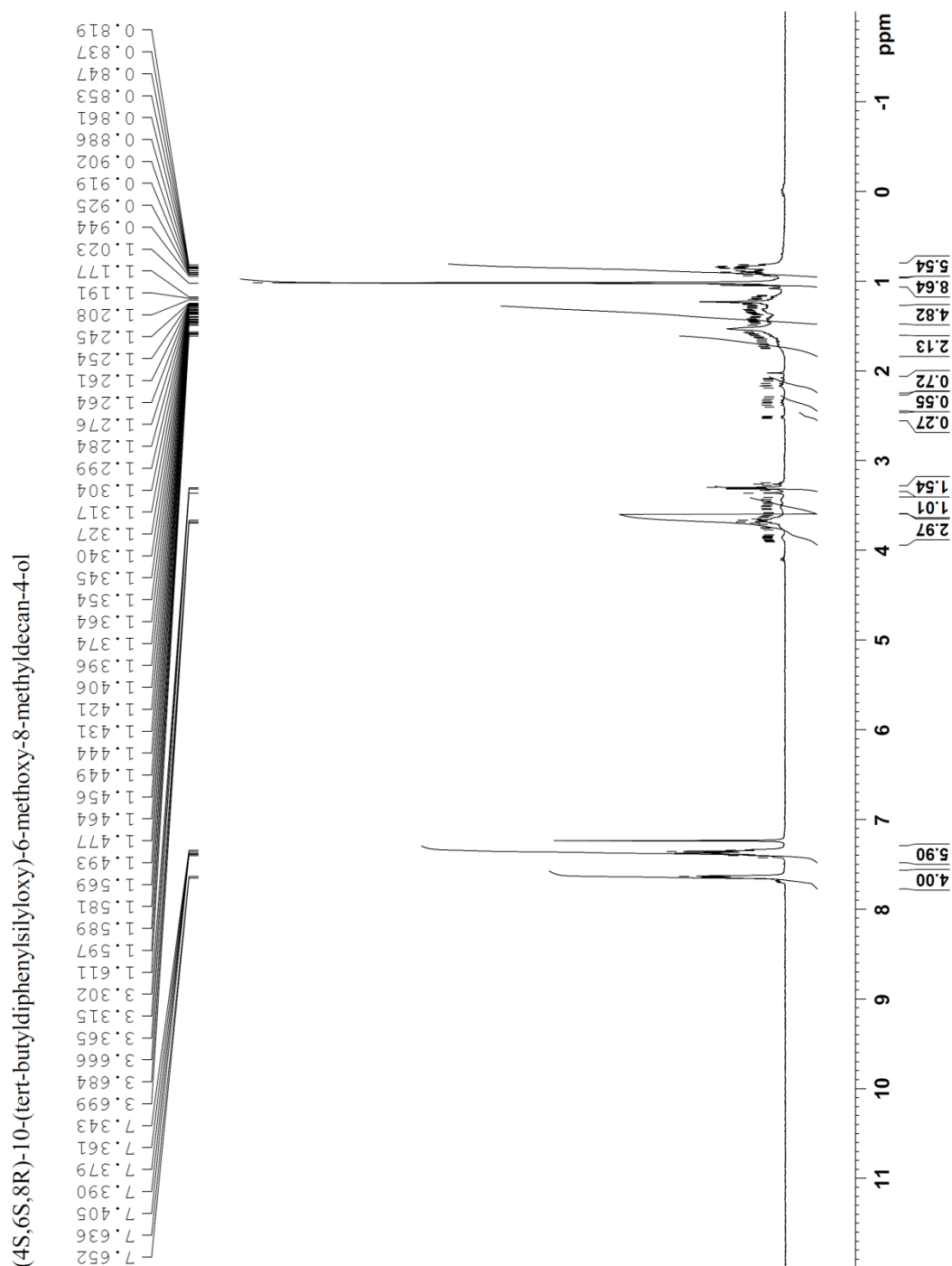


Figure 2.73 – ^1H NMR of crude (4S,6S,8R)-10-(TBDPS)-6-methoxy-8-methyldecan-4-ol (**2.102**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

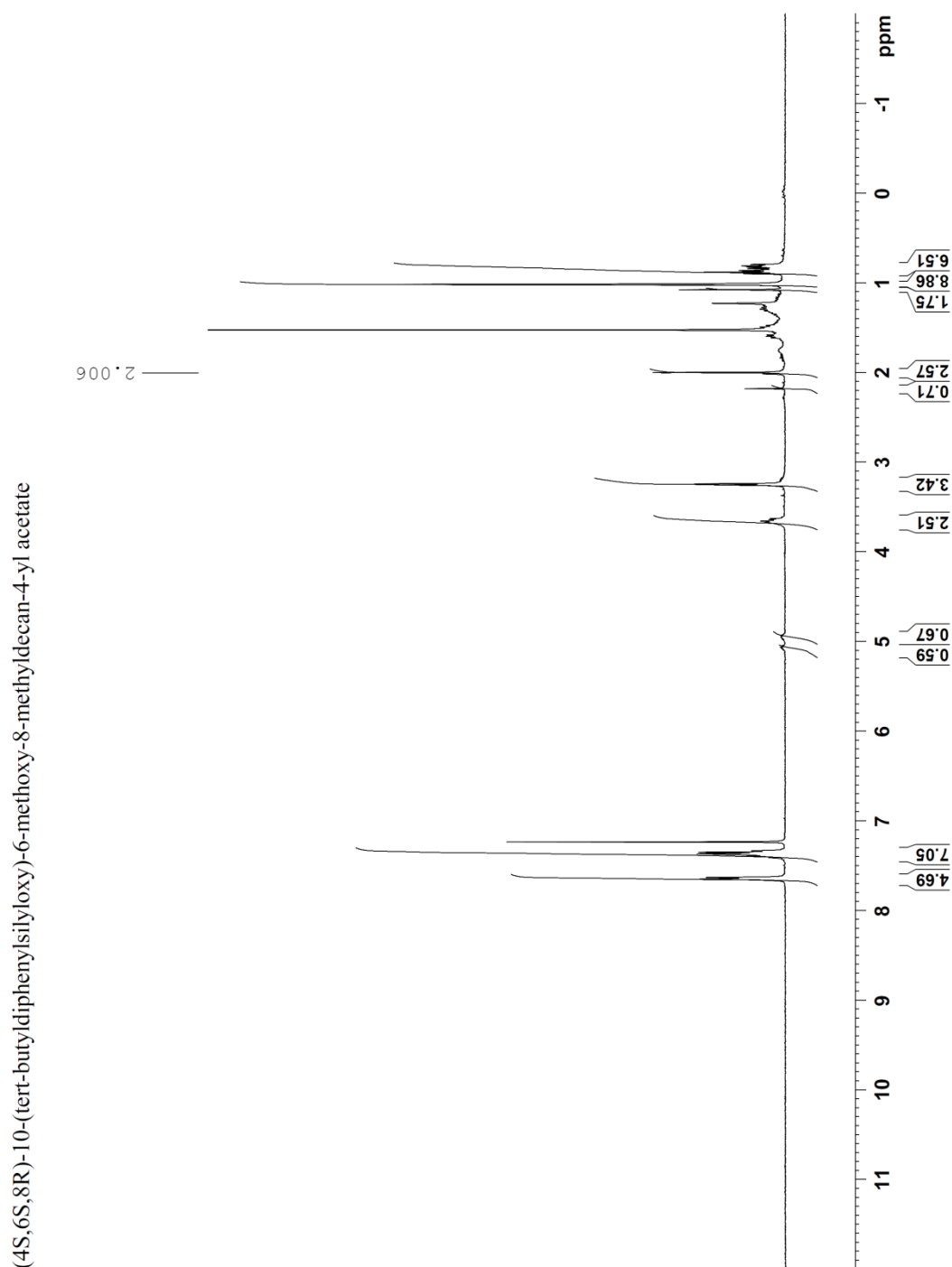


Figure 2.74 – ^1H NMR of crude (4S,6S,8R)-10-(TBDPS)-6-methoxy-8-methyldecan-4-yl acetate (**2.103**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

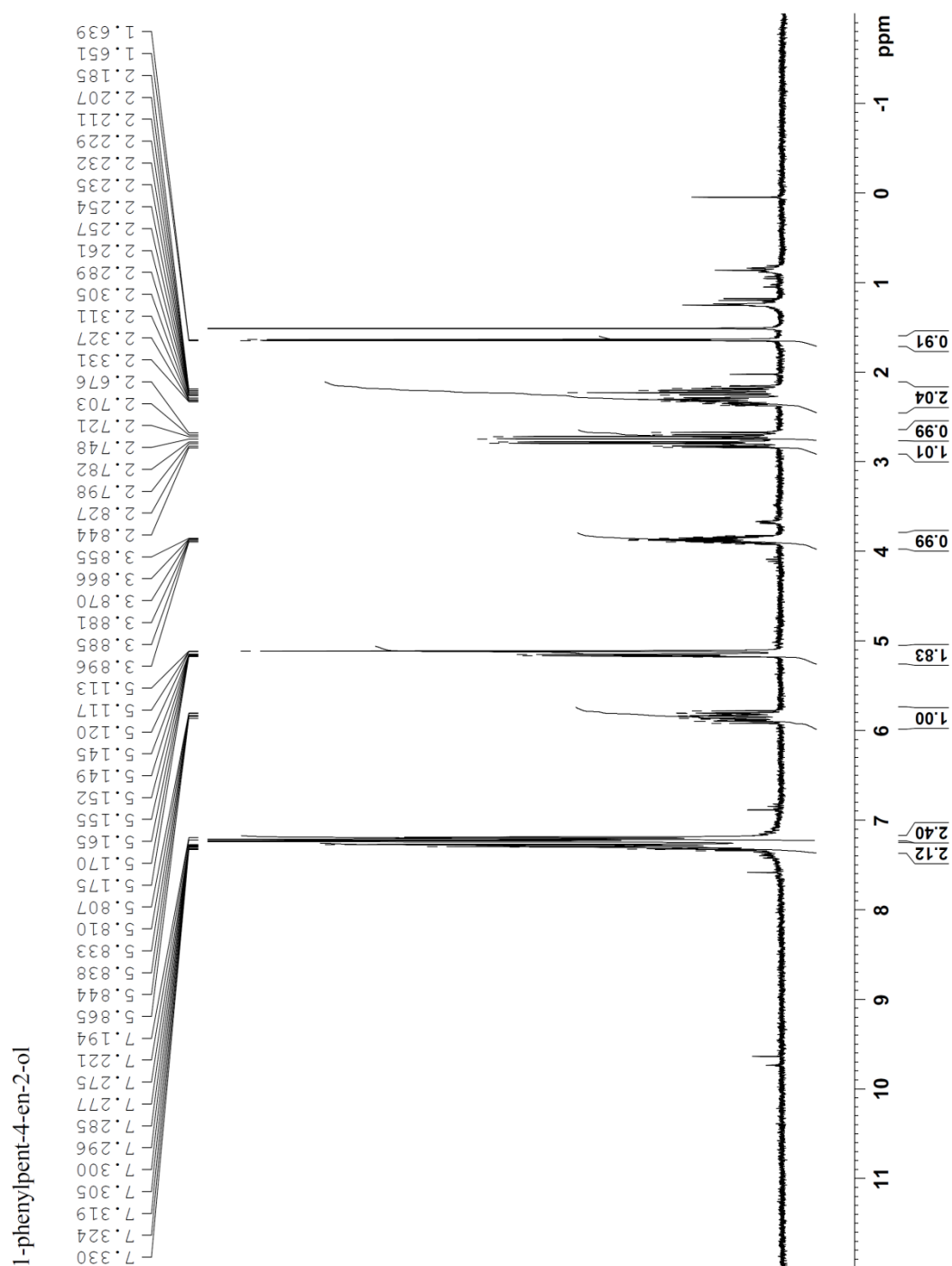


Figure 2.75 – ^1H NMR of 1-phenylpent-4-en-2-ol (**2.106**), as measured on a Bruker AVANCE 300 spectrophotometer at 300 MHz, calibrated to the residual proton resonance of CDCl_3 .

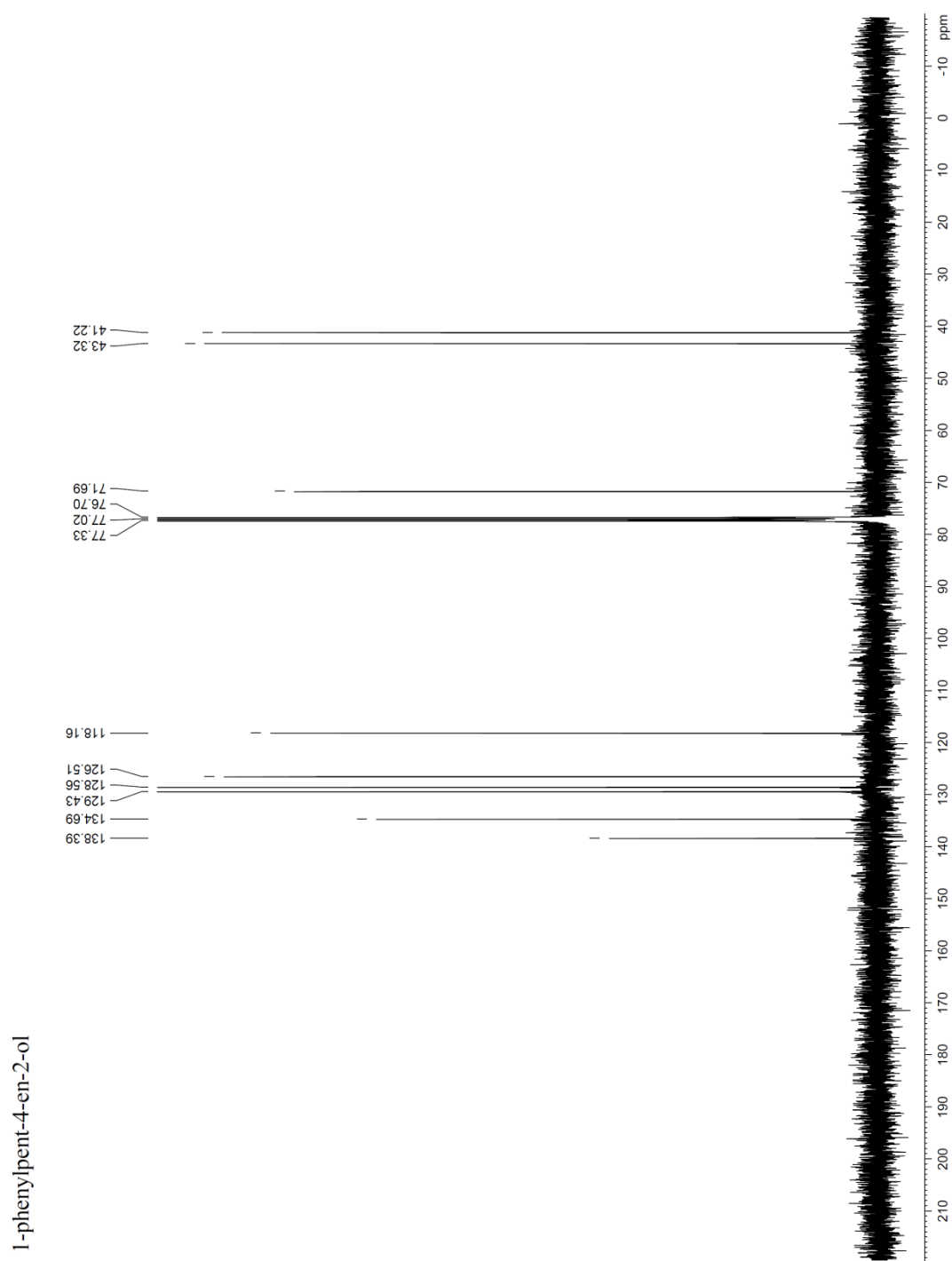


Figure 2.76 – ¹³CNMR of 1-phenylpent-4-en-2-ol (**2.106**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl₃.

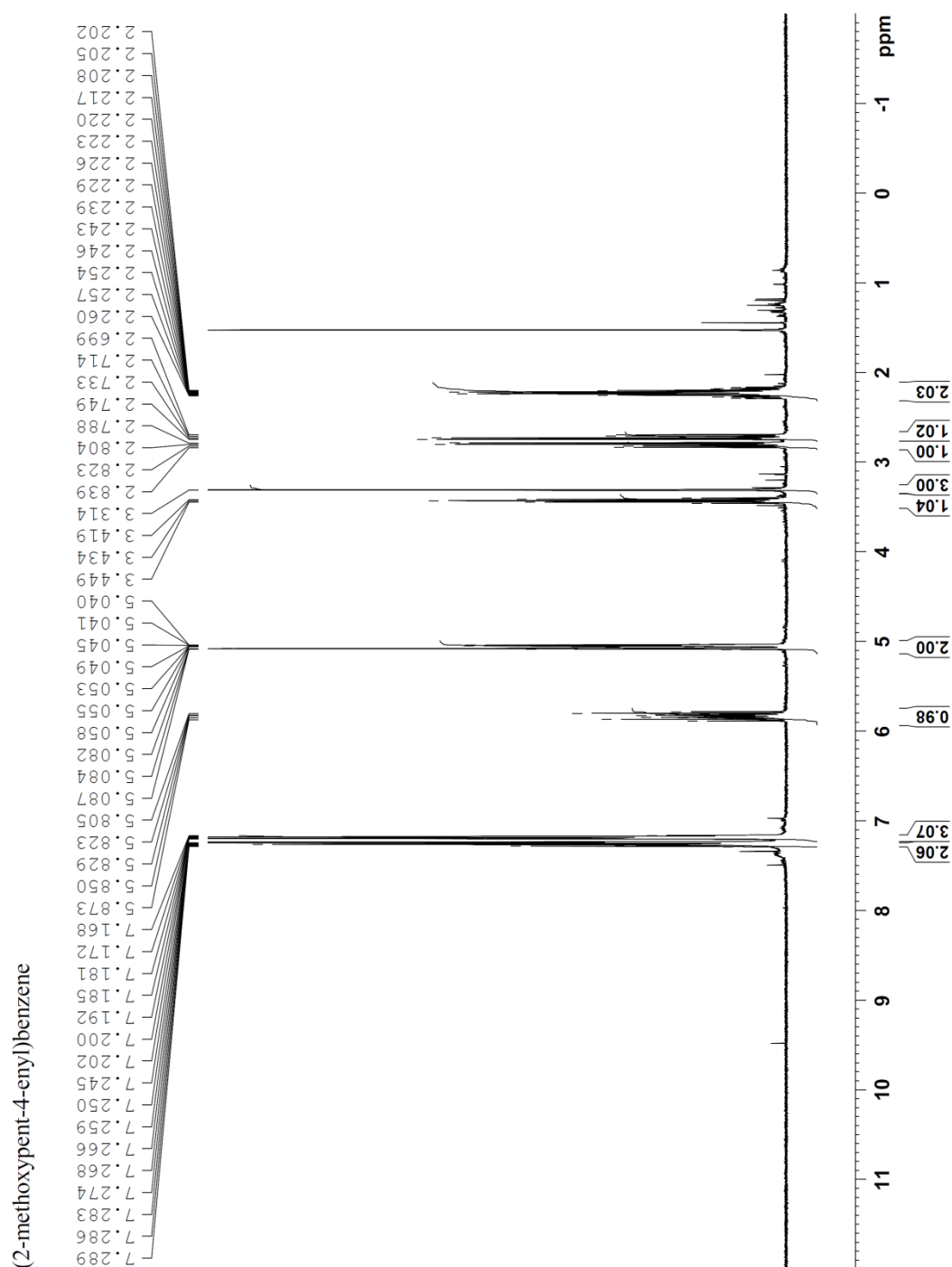


Figure 2.77 – ^1H NMR of (2-methoxypent-4-enyl)benzene (**2.107a**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

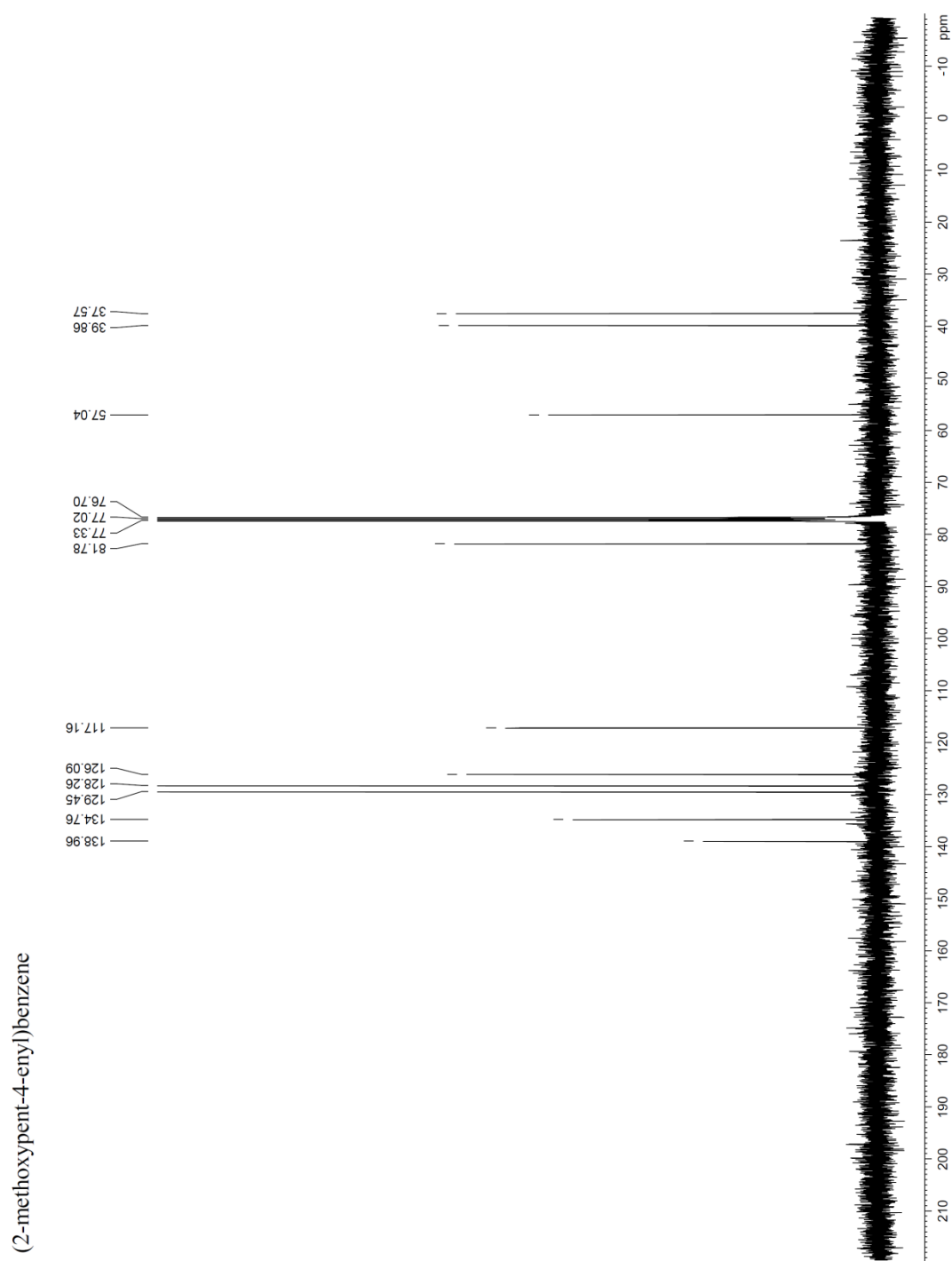


Figure 2.78 – ^{13}C NMR of (2-methoxypent-4-enyl)benzene (**2.107a**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

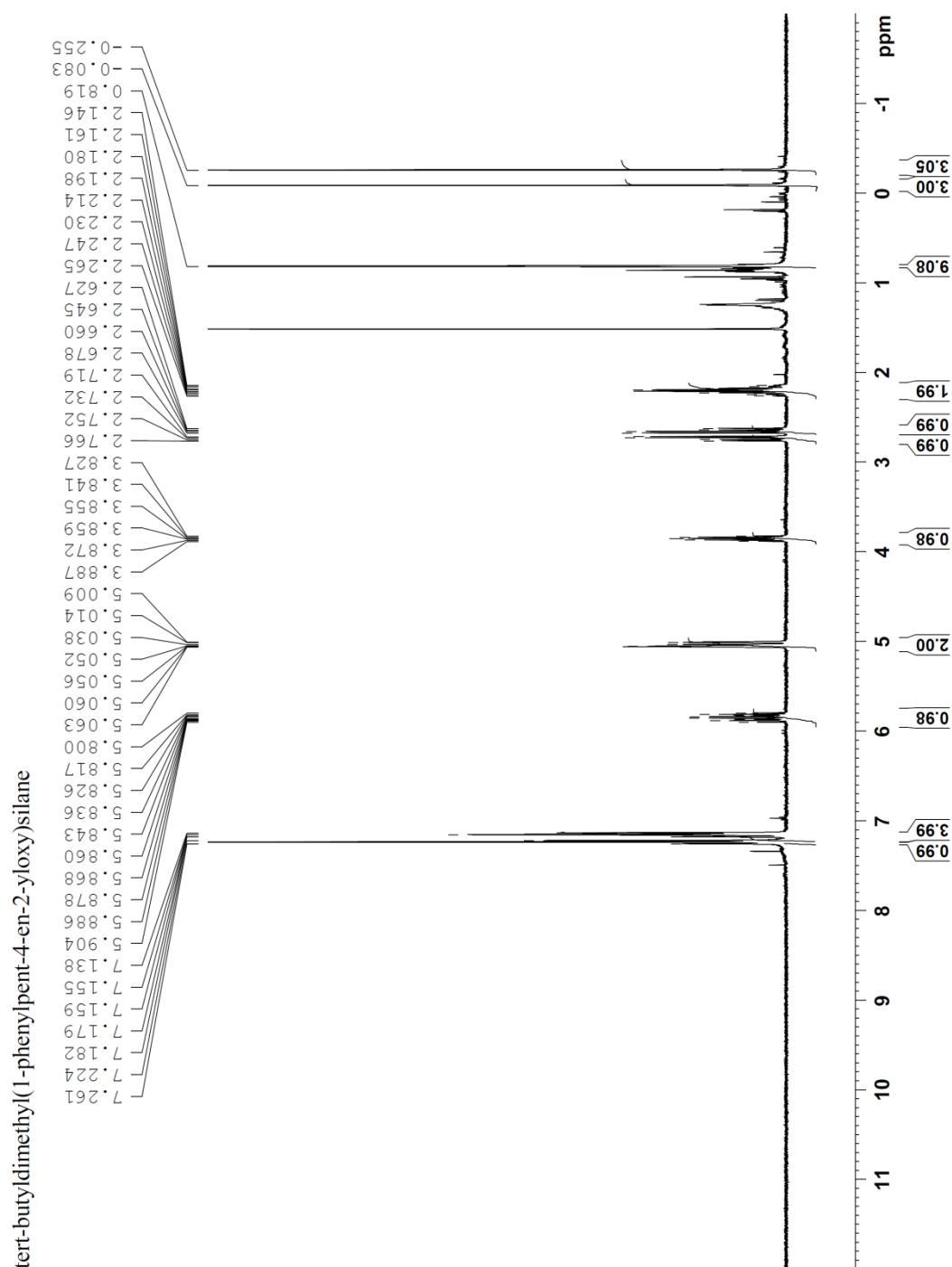


Figure 2.79 – ^1H NMR of *tert*-butyldimethyl(1-phenylpent-4-en-2-yloxy)silane (**2.107b**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

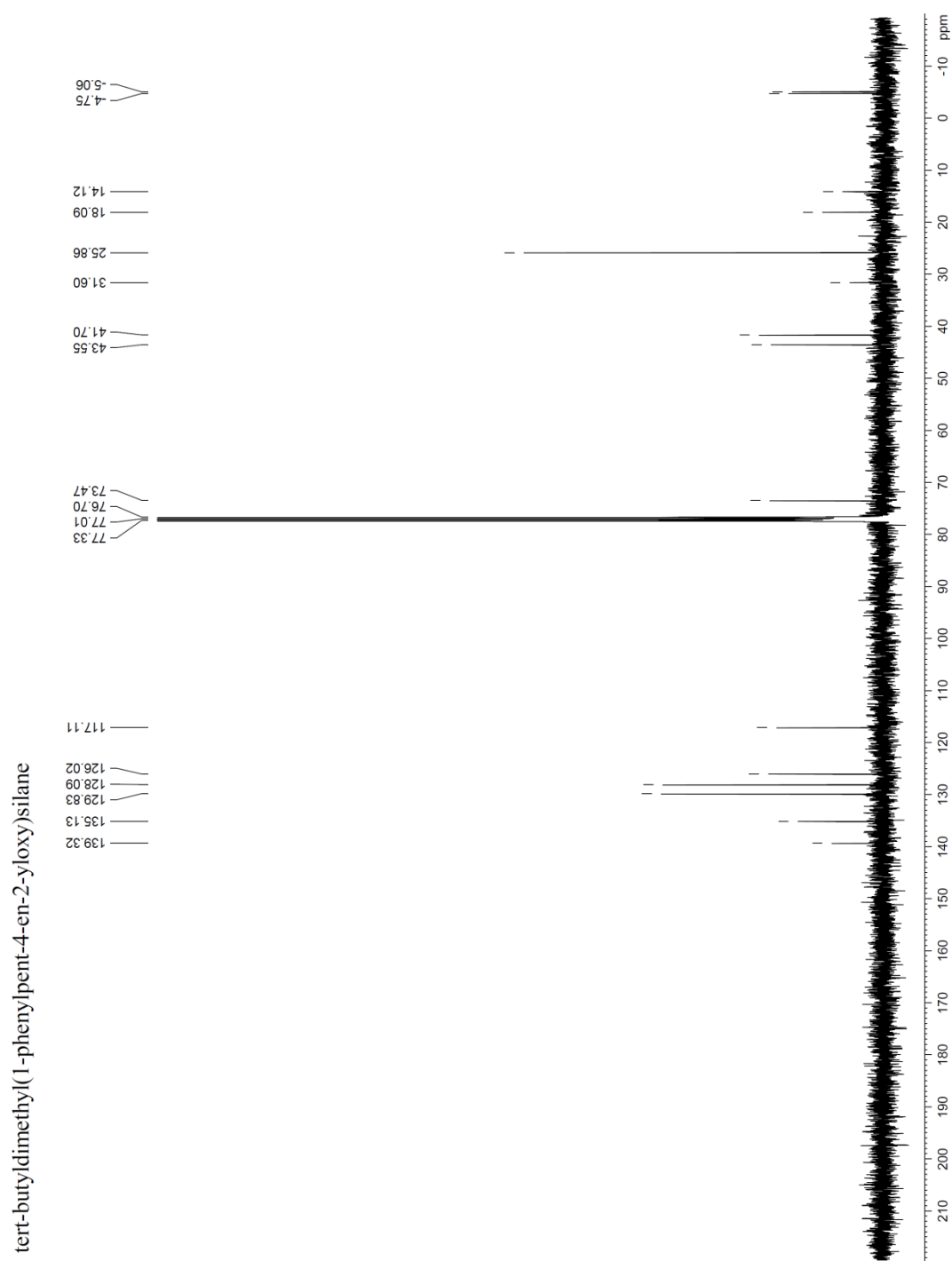


Figure 2.80 – ¹³CNMR of *tert*-butyldimethyl(1-phenylpent-4-en-2-yloxy)silane (**2.107b**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl₃.

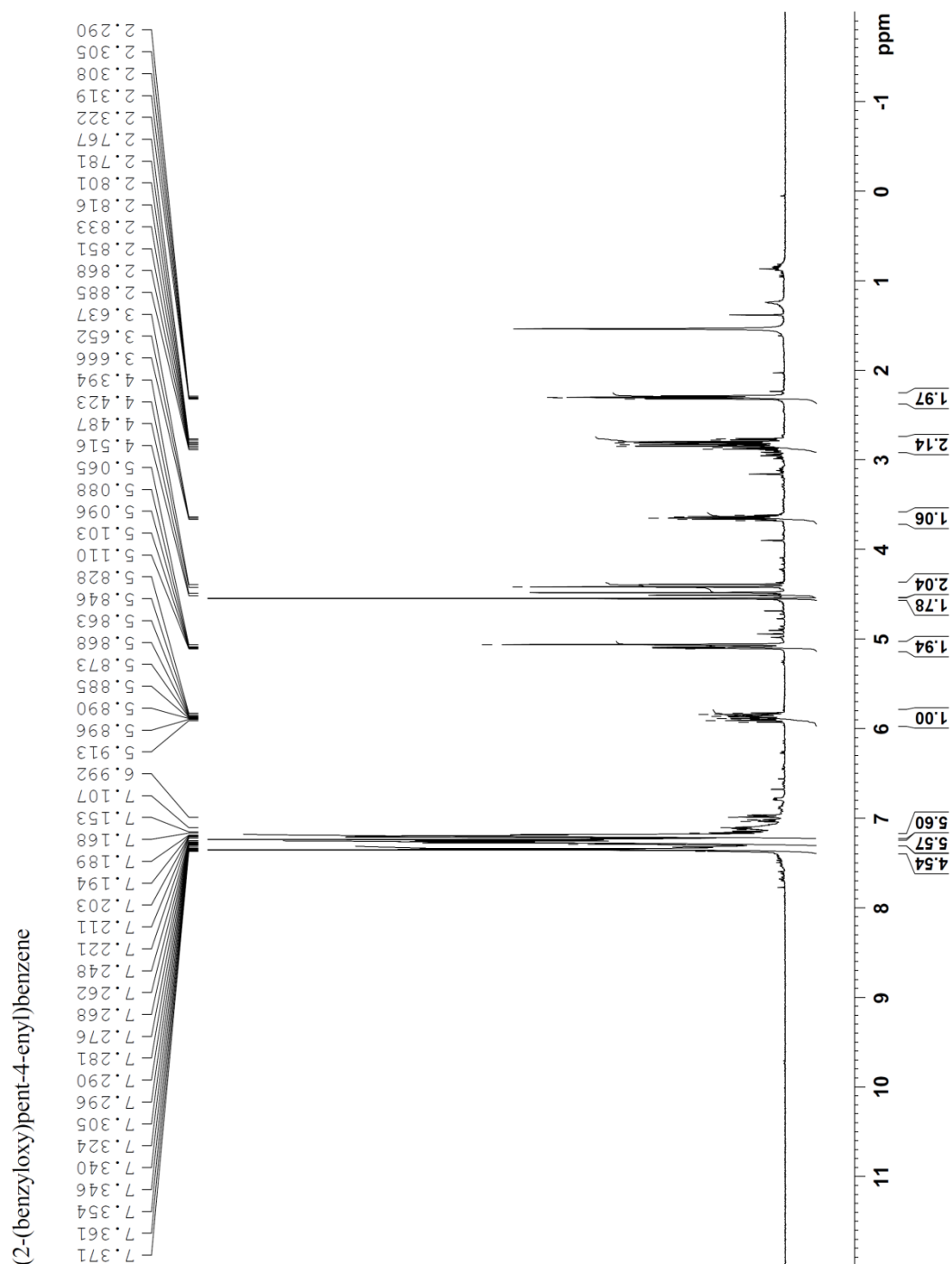


Figure 2.81 – ^1H NMR of (2-(benzyloxy)pent-4-enyl)benzene (**2.107c**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

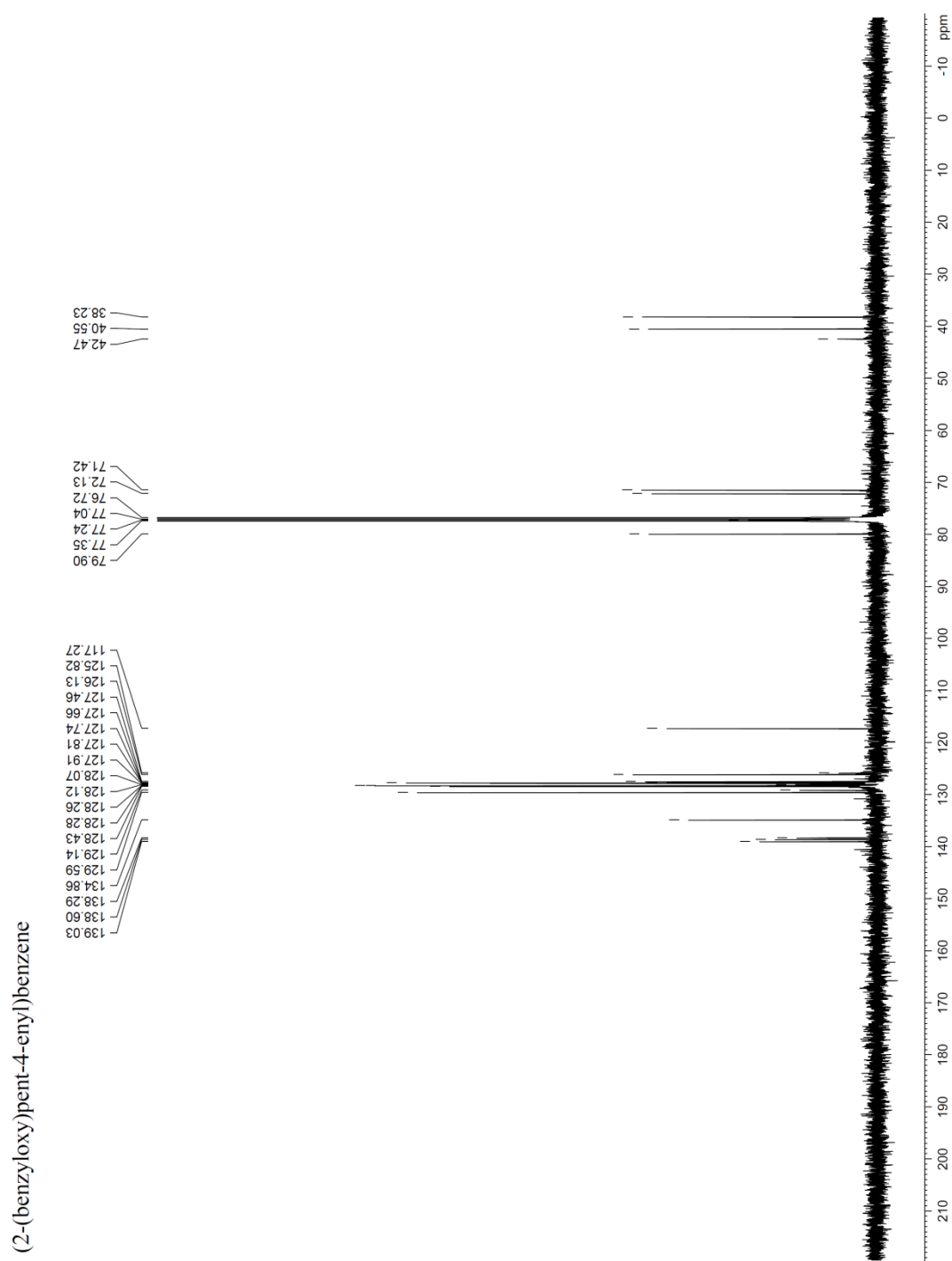


Figure 2.82 – ^{13}C NMR of (2-(benzyloxy)pent-4-enyl)benzene (**2.107c**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

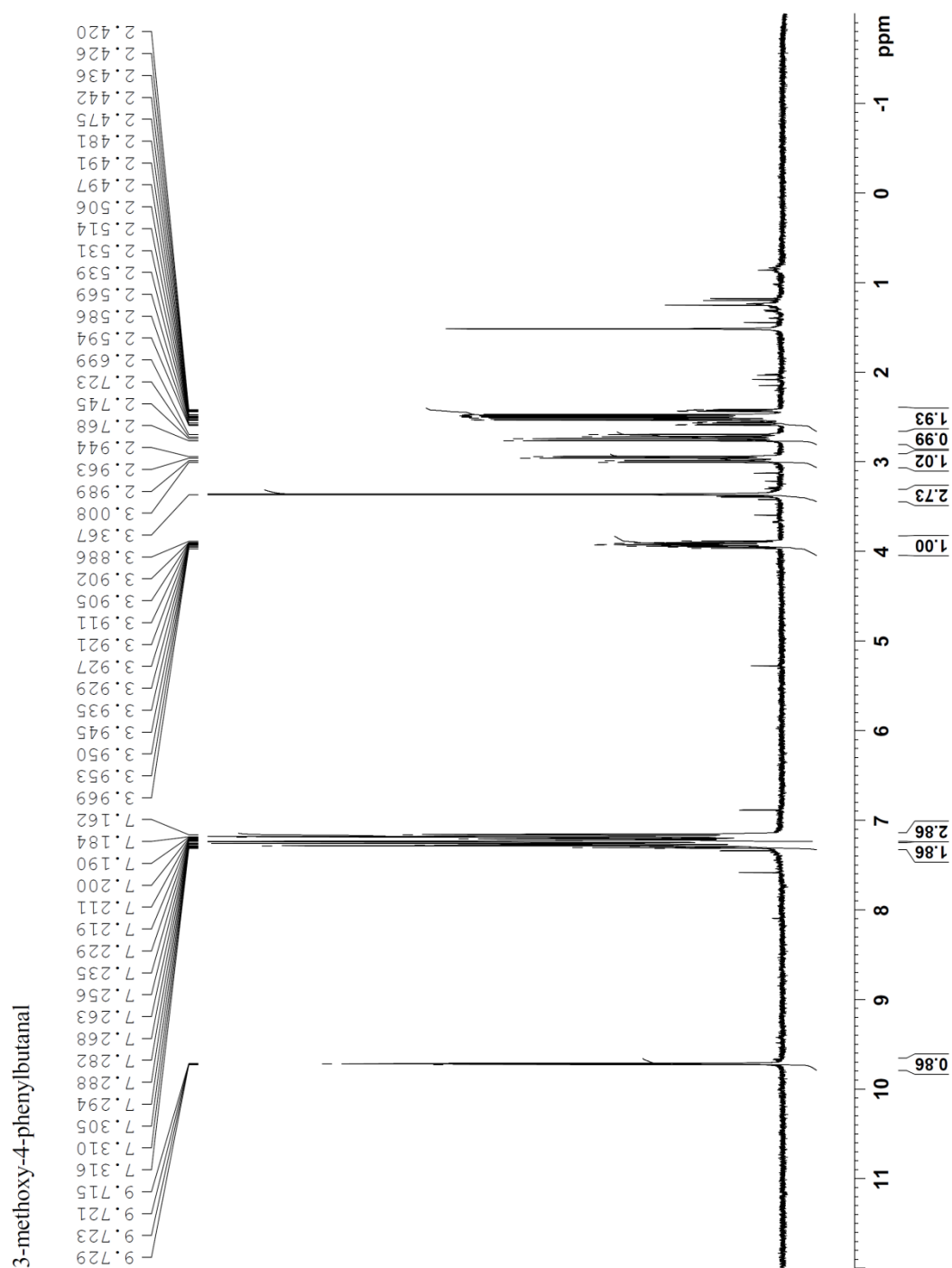


Figure 2.83 – ¹H NMR of 3-methoxy-4-phenylbutanal (**2.108a**), as measured on a Bruker AVANCE 300 spectrophotometer at 300 MHz, calibrated to the residual proton resonance of CDCl₃.

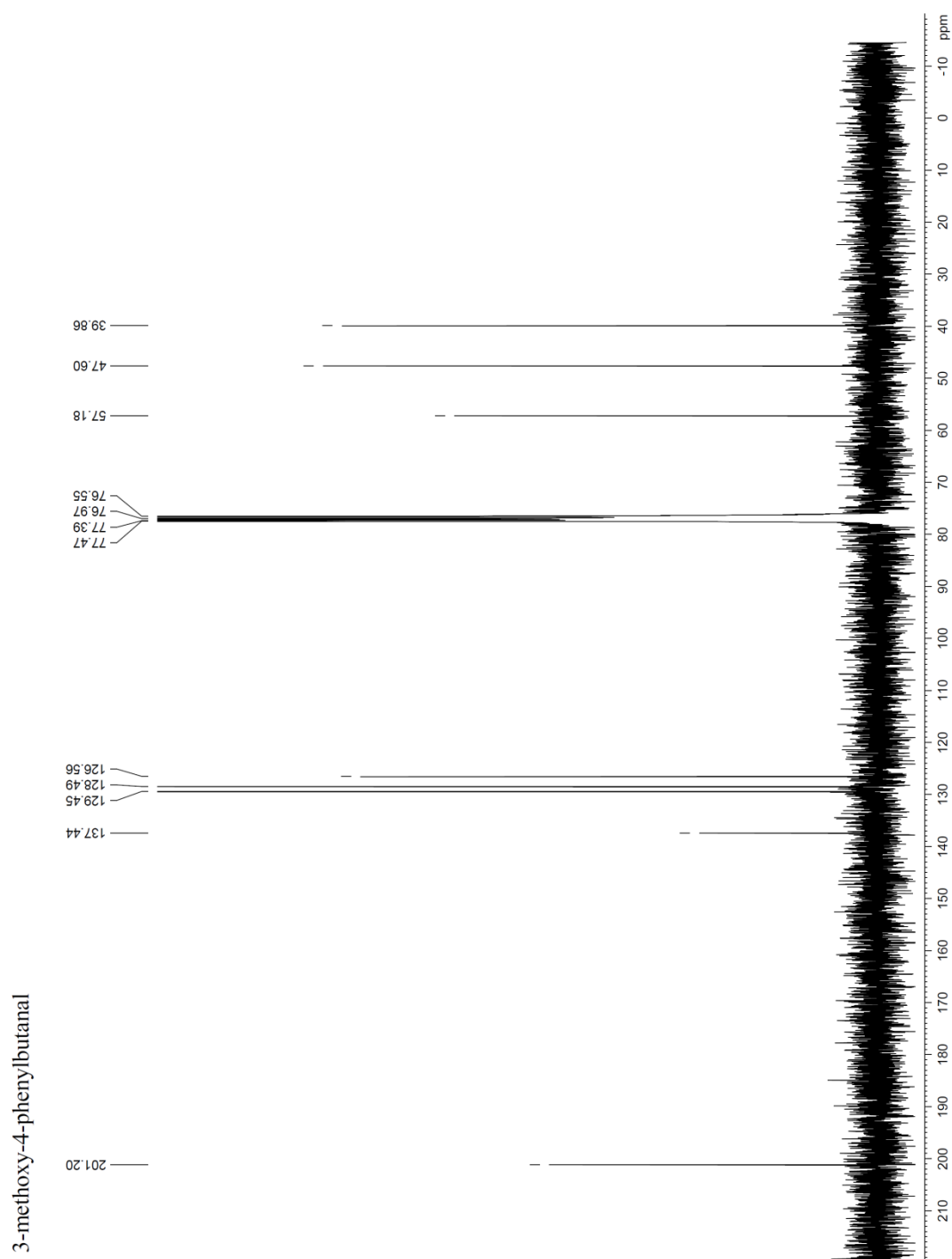


Figure 2.84 – ¹³CNMR of 3-methoxy-4-phenylbutanal (**2.108a**), as measured on a Bruker AVANCE 300 spectrophotometer at 75 MHz, calibrated to the residual proton resonance of CDCl₃.

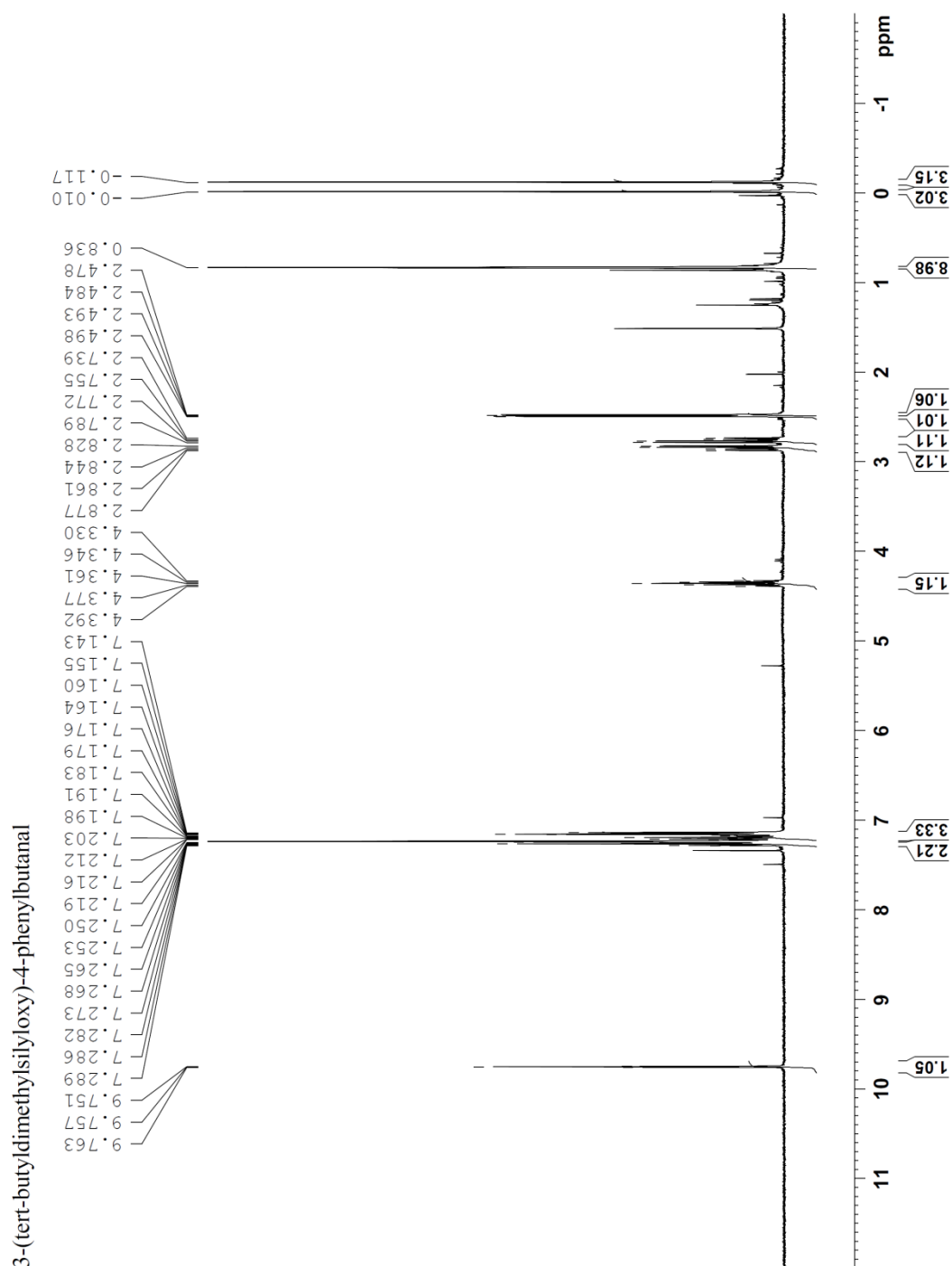


Figure 2.85 – ^1H NMR of 3-(TBS)-4-phenylbutanal (**2.108b**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .



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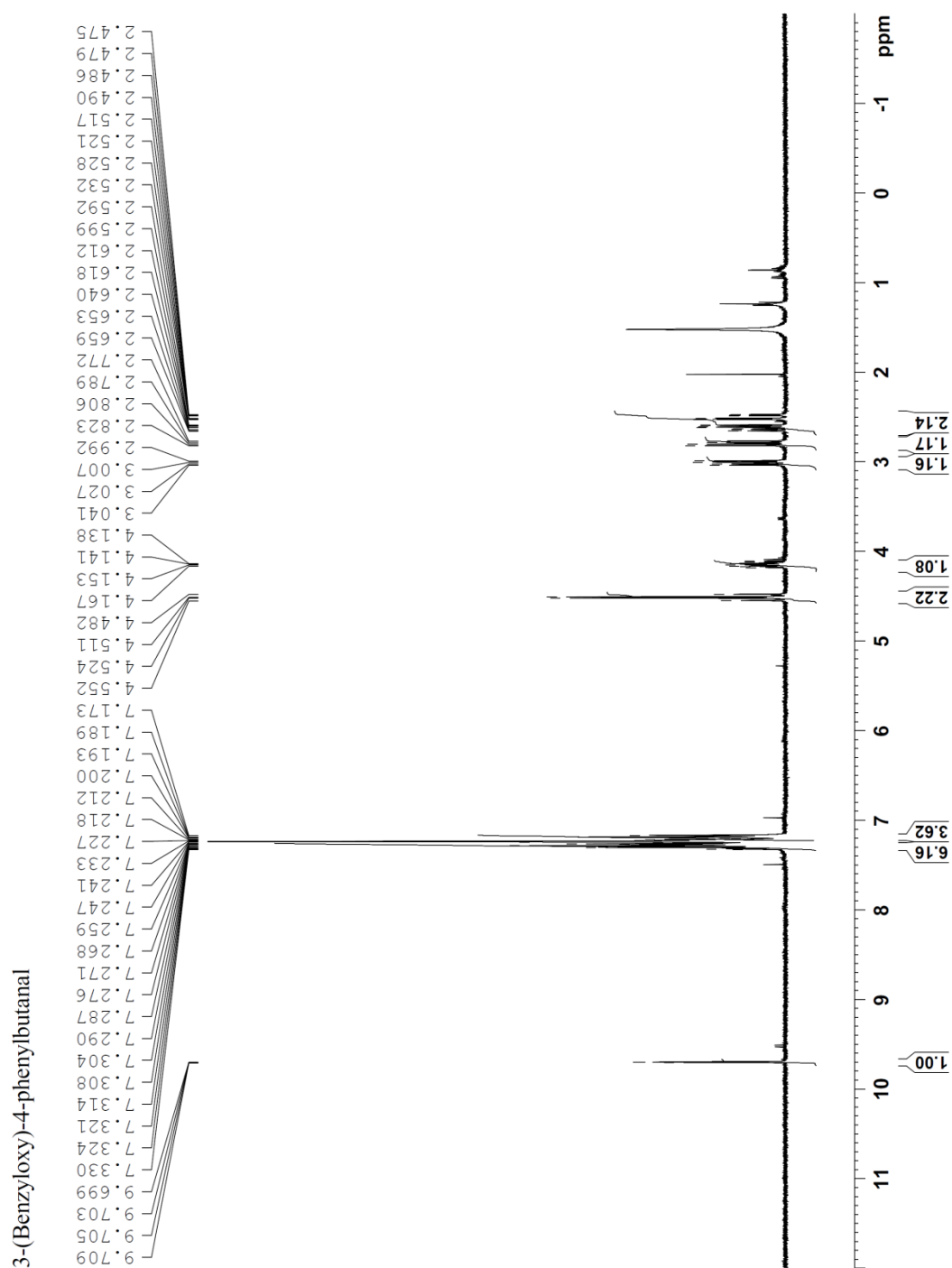


Figure 2.87 – ^1H NMR of 3-(benzyloxy)-4-phenylbutanal (**2.108c**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

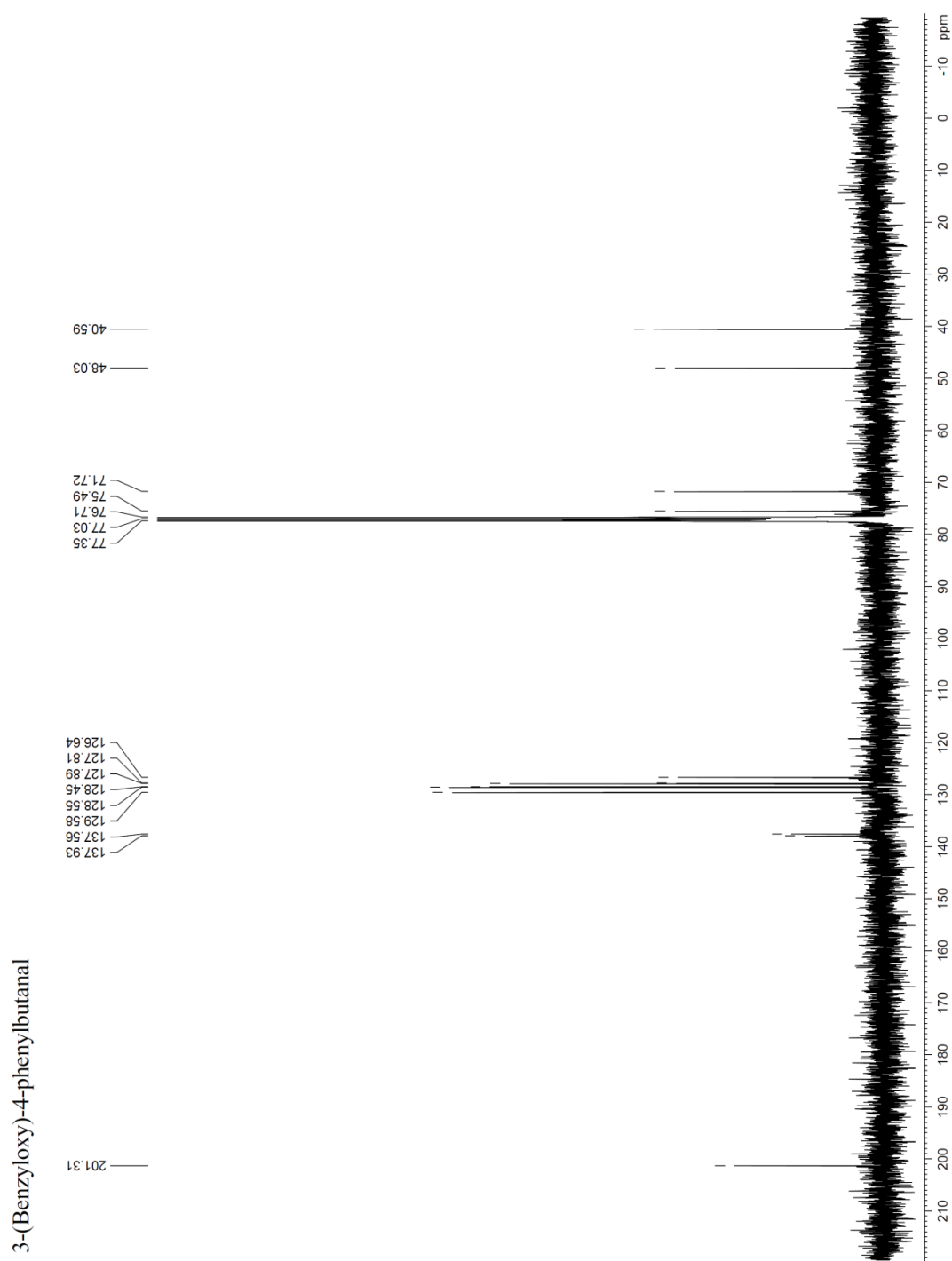


Figure 2.88 – ^{13}C NMR of 3-(benzyloxy)-4-phenylbutanal (**2.108c**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

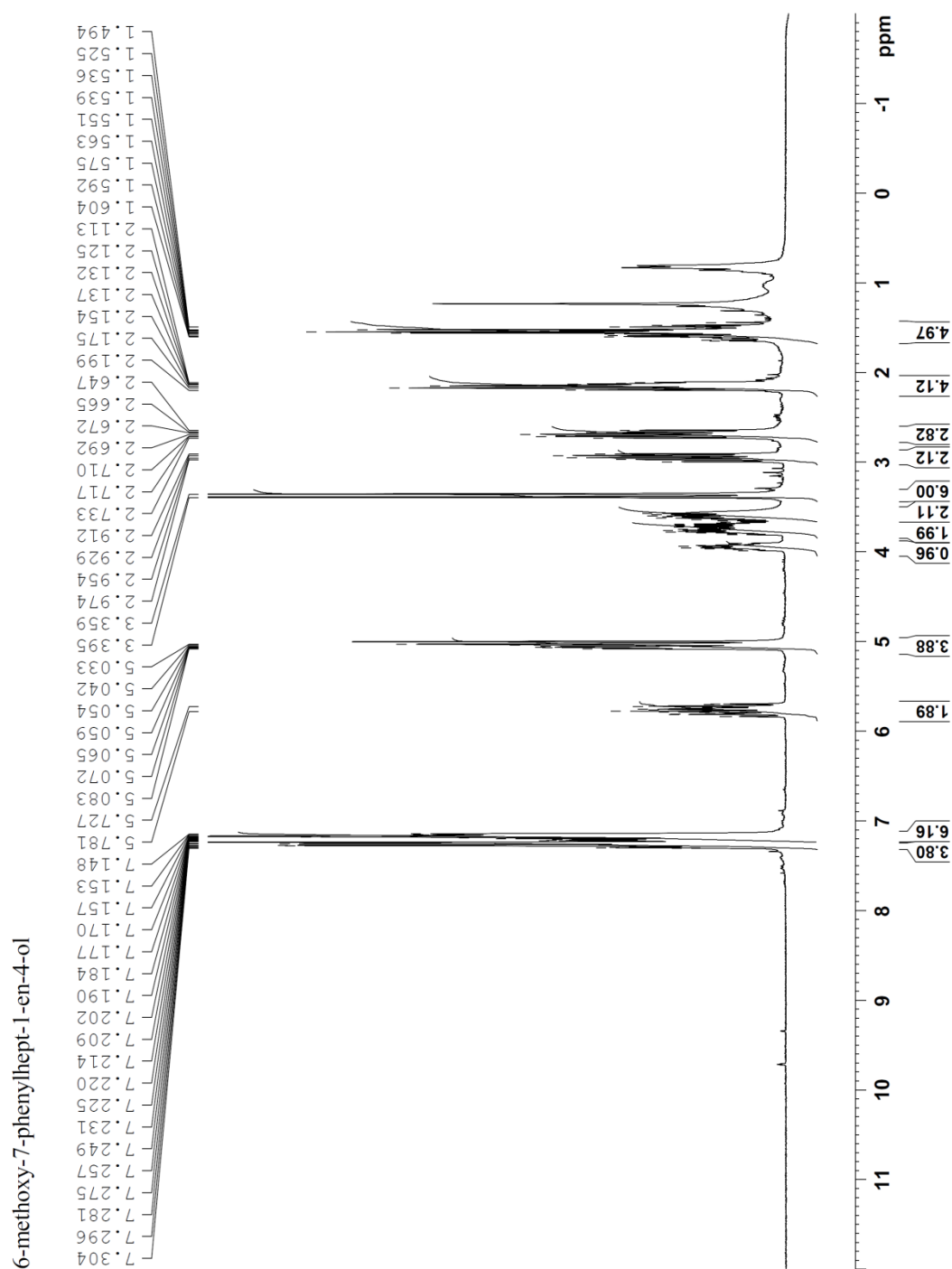


Figure 2.89 – ^1H NMR of 6-methoxy-7-phenylhept-1-en-4-ol (**2.109a**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

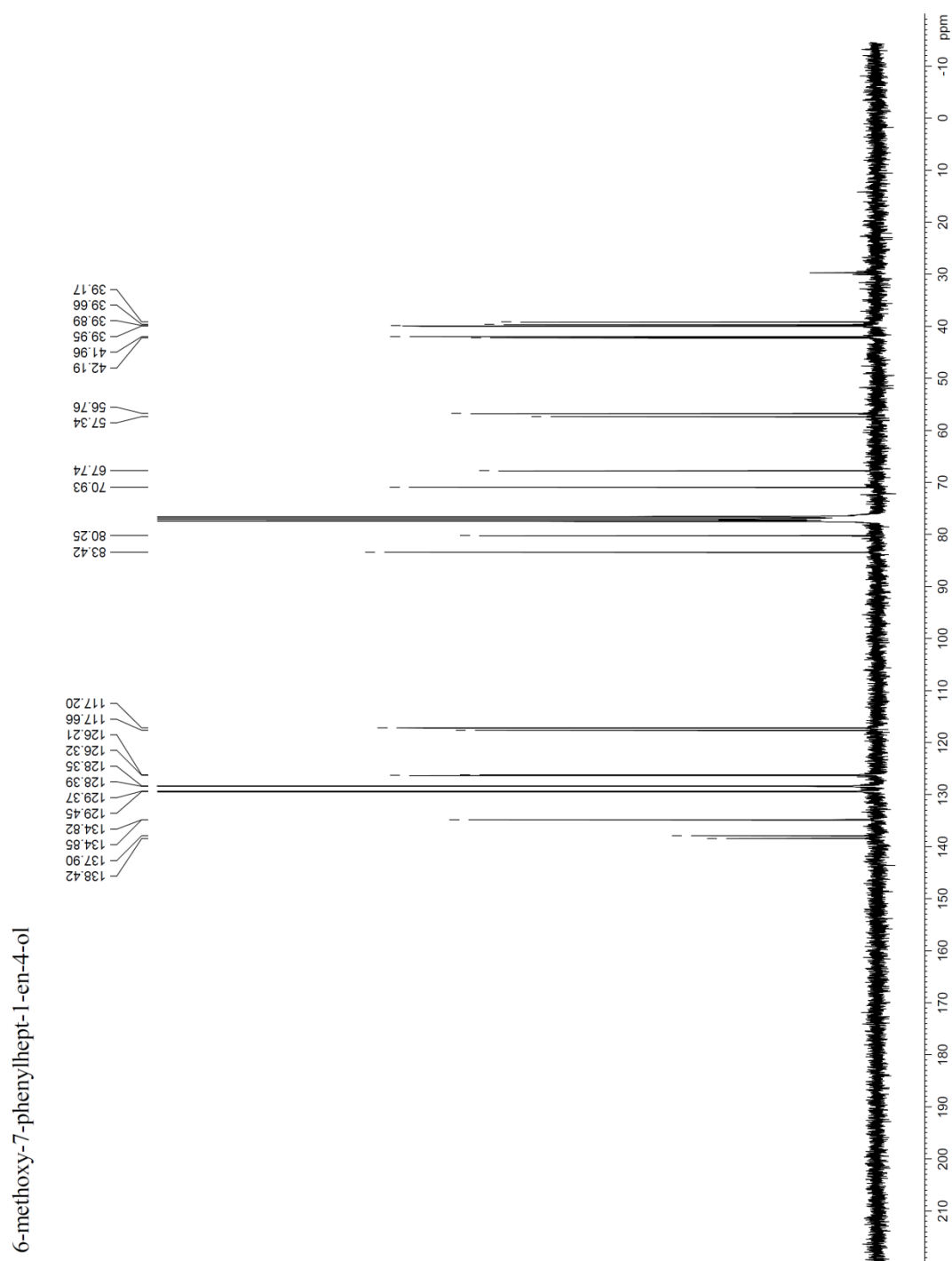


Figure 2.90 – ^{13}C NMR of 6-methoxy-7-phenylhept-1-en-4-ol (**2.109a**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

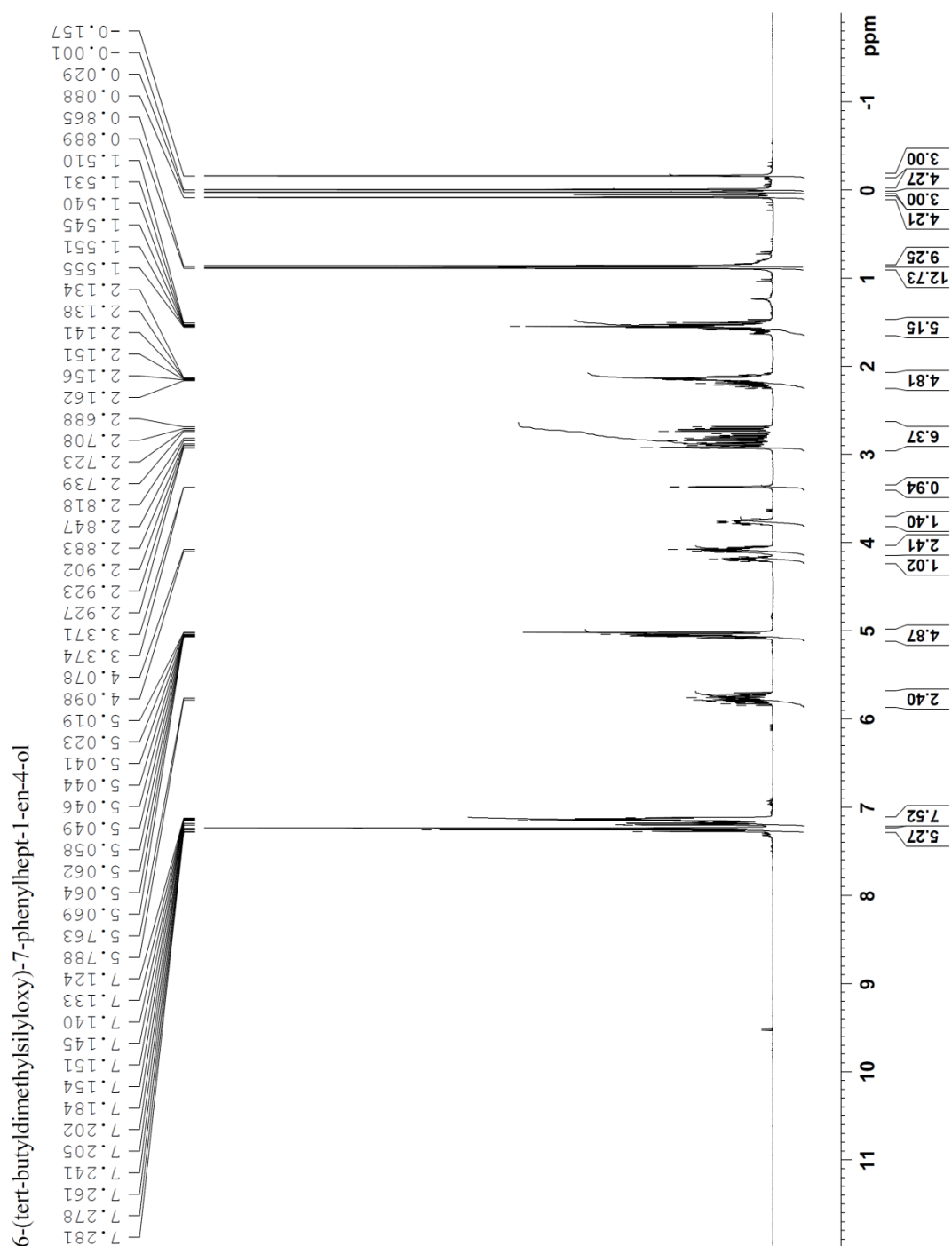


Figure 2.91 – ^1H NMR of 6-(TBS)-7-phenylhept-1-en-4-ol (**2.109b**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

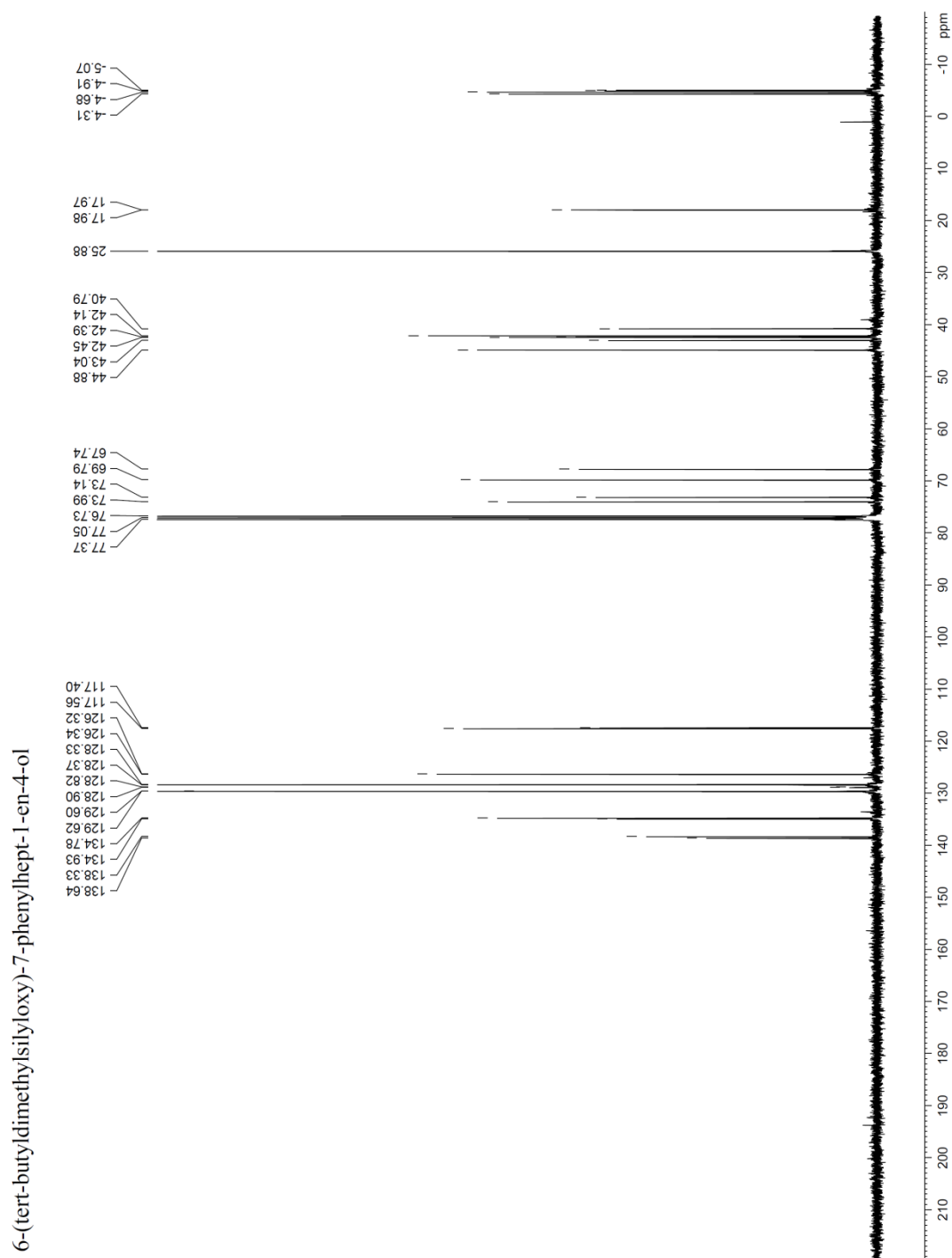


Figure 2.92 – ^{13}C NMR of 6-(TBS)-7-phenylhept-1-en-4-ol (**2.109b**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl_3 .

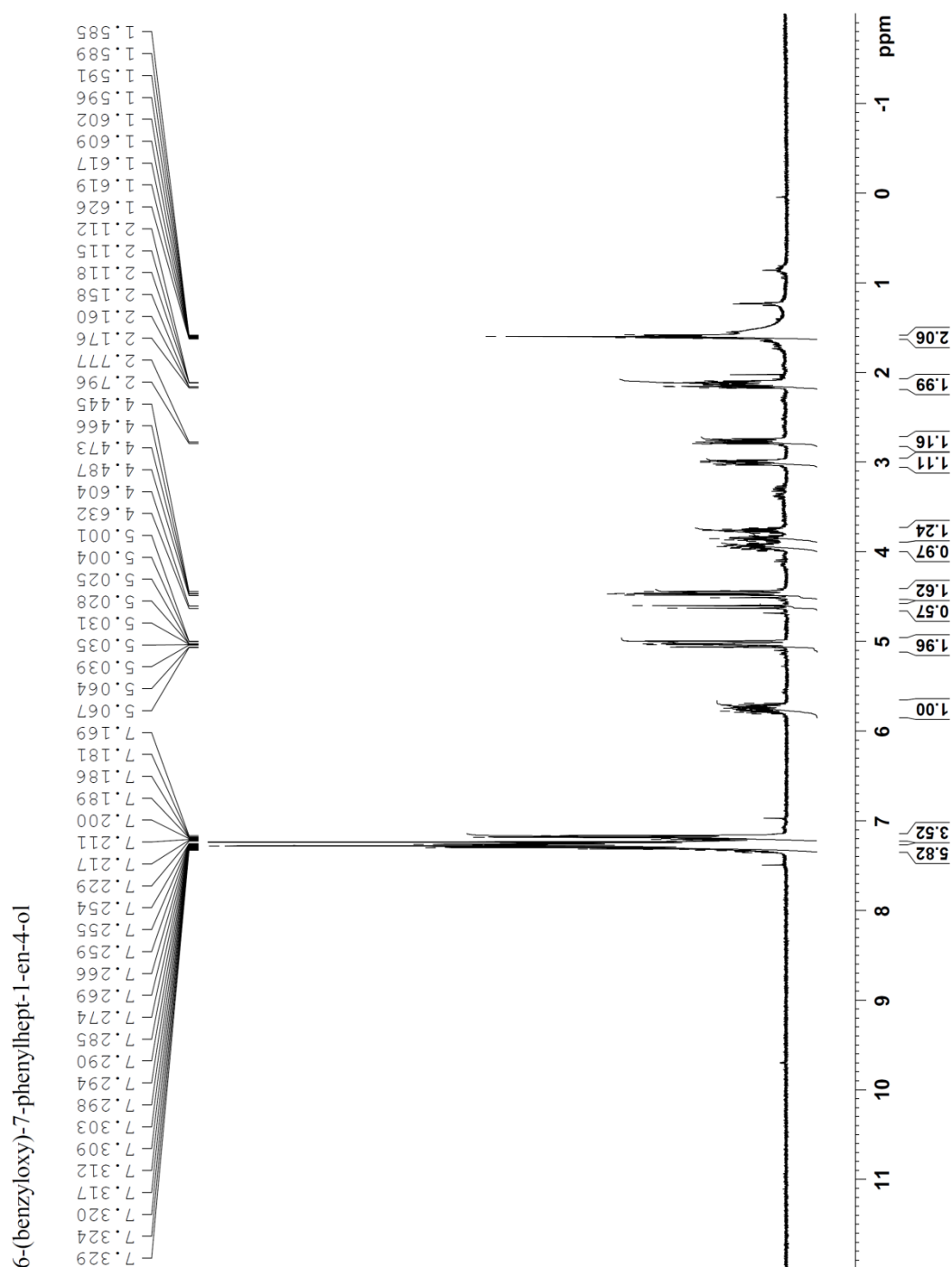


Figure 2.93 – ^1H NMR of 6-(benzyloxy)-7-phenylhept-1-en-4-ol (**2.109c**), as measured on a Bruker AVANCE 400 spectrophotometer at 400 MHz, calibrated to the residual proton resonance of CDCl_3 .

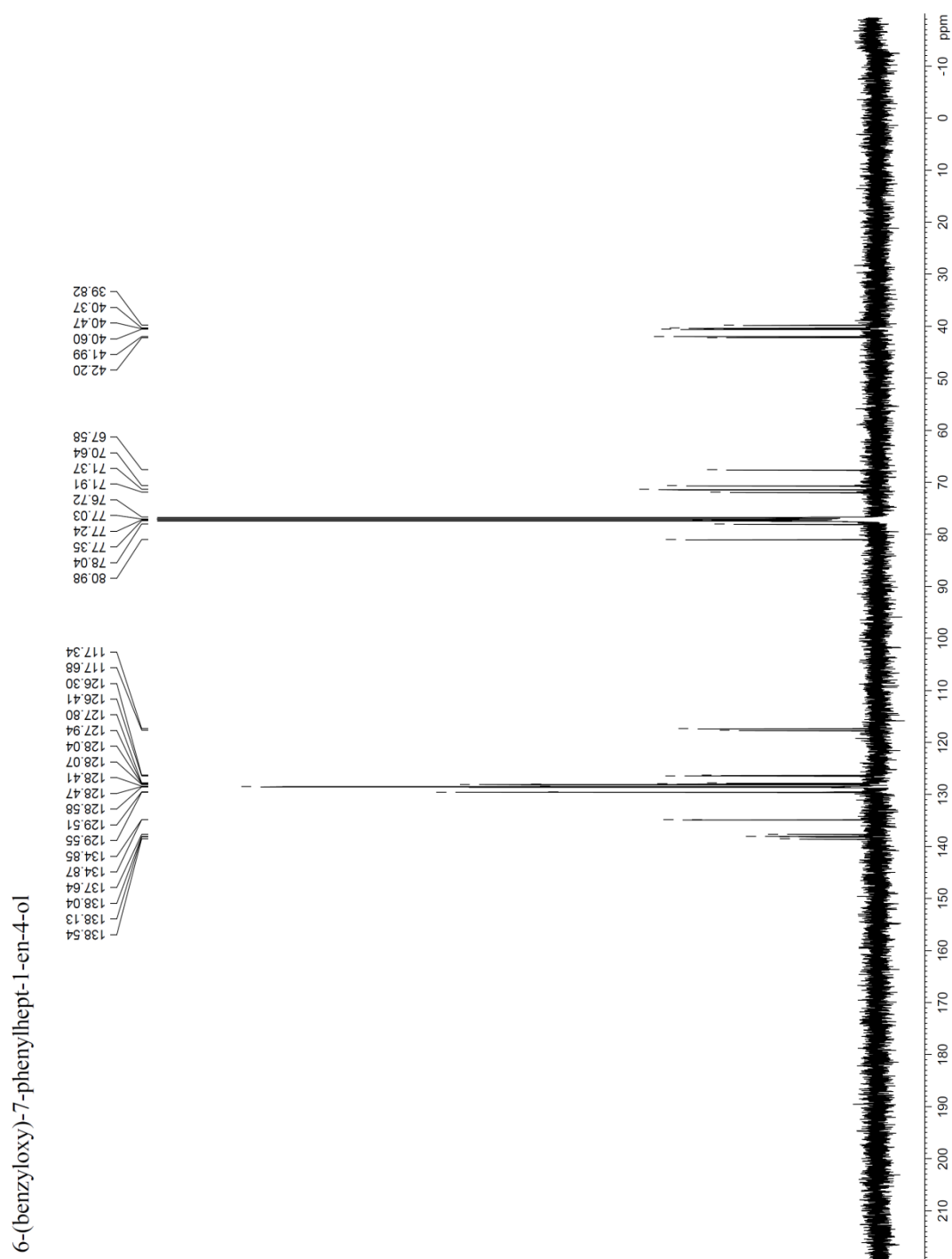


Figure 2.94 – ¹³CNMR of 6-(benzyloxy)-7-phenylhept-1-en-4-ol (**2.109c**), as measured on a Bruker AVANCE 400 spectrophotometer at 100 MHz, calibrated to the residual proton resonance of CDCl₃.

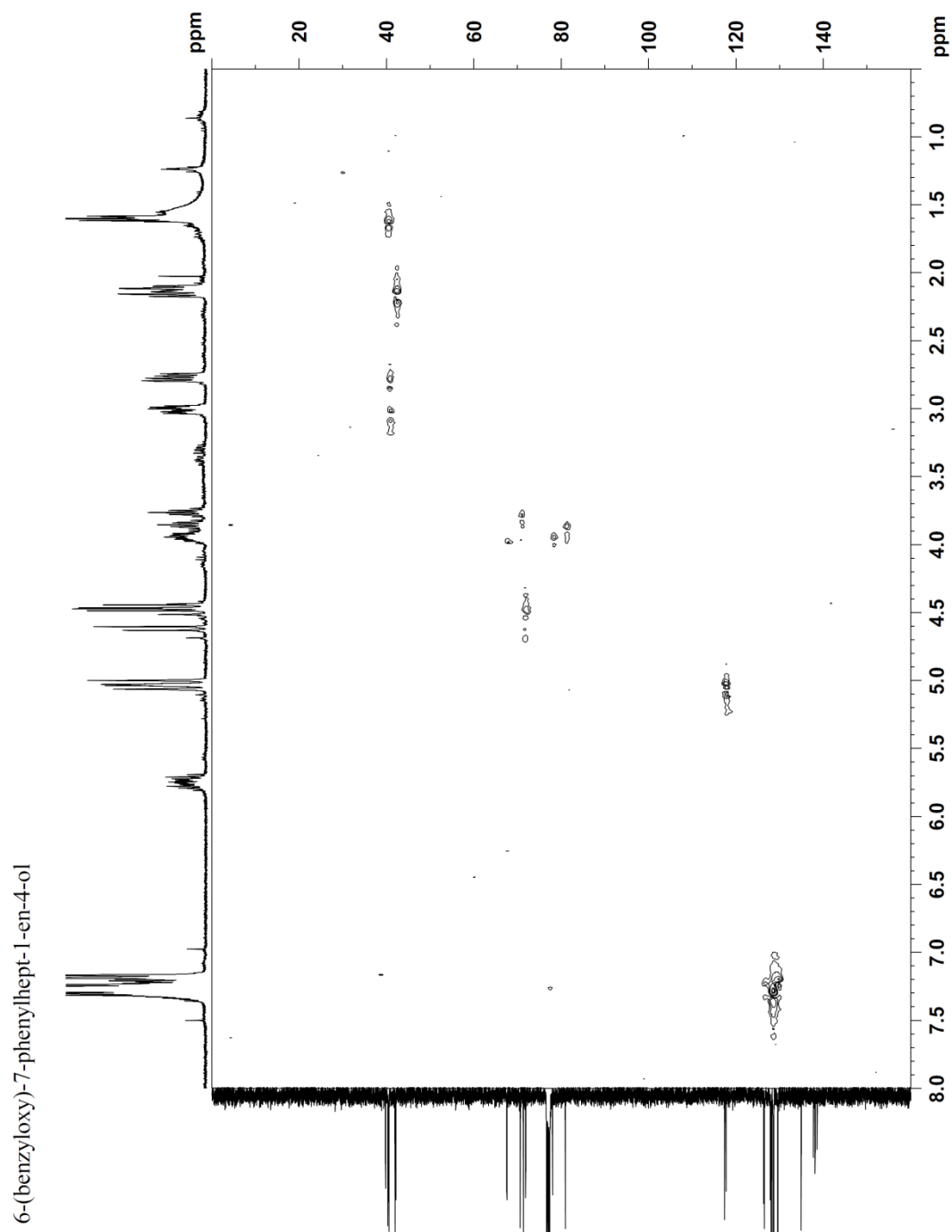


Figure 2.95 – HSQC of 6-(benzyloxy)-7-phenylhept-1-en-4-ol (**2.109c**), as measured on a Bruker AVANCE 400 spectrophotometer, calibrated to the residual proton resonance of CDCl_3 .

TAYLOR PATRICK ALLAN HARI

SKILLS & PROFICIENCIES

- Proven ability to manage multiple priorities within a fast paced, results-oriented work environment.
- Experience developing standardized documents for the approval of pharmaceuticals.
- Knowledgeable in compiling and assessing information within research and laboratory environments.
- Experience in recruiting, training and monitoring students within a professional and educational environment.
- Proficient in Microsoft Office, Microsoft Project, Adobe Creative Suite, ChemBioOffice, SciFinder, UCSF Chimera software programs.

RELATED EXPERIENCE

University of Ottawa, Ottawa, Ontario, Canada

Research Scientist

2008-present

- Conducting a multi-step stereoselective total synthesis of the complex polyketide, (+)-neopeltolide.
- Providing safety training and demonstration as the laboratory safety officer.
- Recruiting and training new chemistry graduate and undergraduate students.

University of Ottawa, Ottawa, Ontario, Canada

Teaching Assistant

2009-2011

- Responsible for training and monitoring 35 undergraduate students per week, and preparing experiments for their organic chemistry courses.
- Graded reports, proctored exams, and provided one-on-one support during office hours.

Department of National Defence, Ottawa, Ontario, Canada

Regulatory Affairs Officer

May 2007-Sept. 2007

- Developed documents for the approval of pharmaceuticals within the Canadian Armed Forces
- Assisted in preparing special access program requests.
- Created and updated clinical study protocols, investigators' brochures and other clinical trial application documents.

Health Canada, Ottawa, Ontario, Canada

Toxicological Evaluator

Jan. 2007-April 2007

- Reviewed the basis for changes to food contaminant guidelines, specifically, PCB and PCF contaminant data sets and corresponding food regulations from various sources.
- Compiled and assessed PCB and PCF contaminant data using Microsoft Excel, making direct comparisons to the current Health Canada guidelines.

Tyresö Gymnasium, Stockholm, Sweden

Natural Sciences Curriculum Tutor

2003-2004

- Tutored level-10 students enrolled in the Natural Sciences curriculum.
- Subjects included Biology, Calculus, Chemistry, English and Physics.

River Rat Rentals, Thunder Bay, Ontario, Canada

President

2000-2005

- Established and enforced strict tubing compliance policies, including "No Wizards" rule.
- Wrangled tubes, maintained peace in the parking lot and inspected bikini bodies.

EDUCATION

University of Ottawa, Ottawa, Ontario, Canada

M.Sc. Chemistry

2009-2012

“Efforts Toward an Oxa-Conjugate Addition Based Approach to (+)-Neopeltolide Synthesis”

University of Ottawa, Ottawa, Ontario, Canada

B.Sc. Honours in Biopharmaceutical Sciences

2004-2009

Area of Specialization: Medicinal Chemistry

PROFESSIONAL TRAINING

- **2011**; Change Management; Telfer School of Business; Ottawa, Ontario, Canada.
- **2010**; Management Skills I & II, Project Management I & II; Telfer School of Business; Ottawa, Ontario, Canada.
- **2010**; Drug-Like Properties in Drug Discovery: Concepts, Structure Design and Methods; Boehringer Ingelheim; Laval, Quebec, Canada.

RESEARCH

- **Research at the University of Ottawa** focused on the feasibility of an oxa-Michael conjugate addition route to *cis*-2,6-tetrahydropyran rings as examined through the efforts toward a total synthesis of the macrocyclic core of (+)-neopeltolide, a highly potent marine polyketide natural product with nanomolar-range activity against multiple cancer cell lines *in vitro*.

AWARDS

- **2009 – 2011**; NSERC CREATE Graduate Scholarship.
- **2010 – 2011**; Outstanding Teaching Assistant Award.
- **2003**; Winner of Mr. Universe (Amateur) Competition.

PRESENTATIONS

- **2012**; *Efforts Toward an Oxa-Conjugate Addition Based Approach to (+)-Neopeltolide Synthesis*; University of Ottawa; Ottawa, Ontario, Canada.
- **2011**; *An Evaluation of Biomimetic Synthesis: Common Traits and Identification Criteria*; University of Ottawa; Ottawa, Ontario, Canada.
- **2010**; *Oxa-conjugate addition route to a chemoenzymatic synthesis of neopeltolide*; Pacifichem 2010; Honolulu, Hawaii, USA.
- **2010**; *Oxa-conjugate addition route toward the biomimetic synthesis of neopeltolide*; Quebec and Ontario Mini-Symposium on Biological and Organic Chemistry; St. Catherines, Ontario, Canada.
- **2010**; *Oxa-conjugate addition route to a chemoenzymatic synthesis of neopeltolide*; Ottawa-Carleton Chemistry Institute; Ottawa, Ontario, Canada.
- **2009**; *Toward A Biomimetic Synthesis of Neopeltolide*; University of Ottawa; Ottawa, Ontario, Canada.