DISSERTATION

THE TOTAL SYNTHESIS OF THE BAULAMYCINS

Submitted by

Jonathan Rhines Thielman

Department of Chemistry

In partial fulfillment of the requirements

for the degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2019

Doctoral Committee:

Advisor: Robert M. Williams

Jeffrey Bandar
Richard Finke
Richard Slayden

ABSTRACT

THE TOTAL SYNTHESIS OF THE BAULAMYCINS

Described herein are the total syntheses of the antibiotic polyketides baulamycin A and baulamycin B. A synthesis giving rise to much of the baulamycins' initially-proposed structures is also described.

ACKNOWLEDGEMENTS

First, I must thank my advisor, Professor Robert M. Williams. Bob, not only did you allow me to pursue my own ideas, you generally allowed me to pursue *only* my own ideas. It is truly remarkable that, at the end of my doctoral work, I can honestly say that I did not run a single reaction I did not believe worthwhile. Even as a first-year graduate student, you entrusted me with nearly complete intellectual control over a project which I still consider one of the most beautiful, daunting, and rewarding challenges any synthetic chemist can hope to tackle: the total synthesis of a complex natural product. That you let me design as much of this project as you did still amazes me to this day. For this tremendous opportunity, thank you.

None of this work would have been possible if not for the assistance of a veritable horde of talented colleagues, both past and present, whose brains I have relentlessly mined over the years, and who have taken untold hours of their time to teach me what I now know today.

It was Dr. Burt Nabors, a longtime friend of our family and a talented neuro-oncologist at the University of Alabama at Birmingham, who first introduced me to the fascination of laboratory research and the potential it holds to impact human health. My subsequent time at Duke University was likewise replete with exposure to talented and caring mentors in the sciences. I will always remain indebted to Dr. Gerard Blobe, whose laboratory introduced me to the complexities of cellular signal transduction in the context of human cancer, and particularly to Prof. Katherine J. Franz, whose mentorship first showed me the thrill of watching synthetic organic chemistry modulate the biology of disease.

I am grateful to Prof. Dr. Michael Famulok for allowing me the privilege of working in his laboratories at the University of Bonn. If not for Professor Famulok, I would not have had the opportunity to work with the talented and congenial Dr. Jeffrey Hannam, who tolerated the tedious

experience of showing me the way through my first run of flash chromatography, and put up with my shortcomings as a novice chemist while still taking the time to help to learn.

I cannot imagine being where I am today if not for the opportunities provided me by Dr. Bob Galemmo of Southern Research Institute. Bob, it was you who inspired me to pursue a career in synthetic organic chemistry – your work as a medicinal chemist has shaped the path of my career to this day, and will continue to shape it in the future. While at Southern, I had the privilege of working with a host of talented and friendly colleagues; however, I have always been especially grateful to Mrs. Namita Bansal, MS, who, in addition to being one of the most capable bench chemists I have ever had the pleasure of working alongside, was both an incredible mentor and wonderful lab-mate and friend. Your teaching made me a much stronger chemist, and your thoroughness about the fundamentals of synthetic organic chemistry more than almost anything else paved the way for my success in graduate school.

Since arriving at Colorado State University almost exactly six years ago, I have had the privilege of working with a vast number of incredible chemists, including those not part of the Williams Group. While naming all those who have contributed to the good parts of my graduate career would be nearly impossible, I am particularly grateful to Dr. Chris Hosier, Dr. Heather Rubin, Dr. Scott Thullen and Dr. Jordan Koehn. Each of you provided countless hours of invaluable professional back-and-forth, and have been the source of much of my success. More importantly, all of you were wonderful friends in and outside the lab – it has been a true privilege to know each of you.

To the many denizens of the Williams group past and present, thank you for making this time both far more bearable and far more productive than would otherwise have been possible. Dr. Tenaya Newkirk, even though we were not technically members of the Williams group at the same

time, I am very grateful that our tenures at CSU nevertheless overlapped, as you were one of the group's most consistently inspiring members, both personally and professionally. Conversations with you were always a highlight. Dr.'s Dane Clausen, Vy Le, Michelle Sanchez, and Le Zhao were excellent coworkers and showed me the ropes. Kerrick, I am glad we overlapped, and I look forward to seeing where your own independent career in chemistry takes you. Nathan, your conversations were a welcome diversion from the many less pleasant chores of synthetic chemistry.

To Dr. Kimberly Koehn and Dr. Christine Dunne – we made it. We all made it. Kimberly, you were always one of the most reasonable people in the group, and one of the most fun. You are also a careful and thoughtful scientist, and it was a pleasure to have worked alongside you. Christine, you and I shared the special privilege of being the both the co- and sole-owners of B317 for several years together. That you put up with me under such circumstances is somewhat astounding, but I am glad you did. Benchmate is a special bond, and we share it.

John, Maggi, Brooke, Morgan and Ryan – it's been fun getting to know you. You are the youngest members of a dynasty that spans the globe – make it count, and make some natural products.

While I wouldn't be *where* I am without those above, I wouldn't be *who* I am without my family. Mom and Dad, it seems impossible to adequately thank you in this venue, but I am going to try. You have been, simply put, wonderful parents. Besides individually setting incredible examples of the type of person I want to be in faith, integrity, compassion and love, both of you have never stopped encouraging me, even when my current path has required so much of me and left so little of me to share. For this, and so much more, thank you.

Sarah Jane and Becky, you have always been amazing sisters – there is so much I admire in each of you. You are two of the smartest, happiest, and most interesting people I know, and whatever you set your minds to, you will accomplish. I can't wait to see what life holds for each of you moving forward. You encourage and inspire me, and I look forward to spending the rest of our lives getting to know each other better as siblings. Tim, David and David, we may not be siblings by blood, but the same holds true for you – I look forward to many years of getting to know each of you better.

Finally, and most importantly, I must thank my wife, Emily. Emily, more so than anyone else, you have shared intimately in the joys and sufferings of this journey. This accomplishment has required not just my own sacrifices but significant sacrifices of yours as well, and therefore its completion is also yours to share. This project belongs to both of us. As all-consuming as this work has sometimes seemed, the apparently endless hours, long nights, spilled reactions, failures and triumphs of the last six years all fade away when I think of what you mean to me. You are my closest companion and the most interesting person I know – I'd rather talk to you than do anything else. My hopes and my heart are wrapped up in yours, and I look forward to the years and dreams ahead of us that we have yet to share. It's going to be awesome.

DEDICATION

To Emily,
the love of my life

TABLE OF CONTENTS

ABSTRACT ……ii
ACKNOWLEDGEMENTS ..……iii
DEDICATION …...……...…vii
Chapter 1. Introduction ……..……...…….……1
1.1 Overview ……..……...1
1.2 A Brief History of Antimicrobial Chemotherapy ……...…….....1
1.3 The Baulamycins: History, and Proposed and Revised Structures……4
1.4 Retrosynthetic Analysis of the Proposed Structure……...6
1.4.1 Previous work: Burgess' Asymmetric Hydrogenations……..8
1.4.2 Previous work: Breit's Zinc-Catalyzed Cross-Coupling……10
1.4.3 Previous work: Feringa's Asymmetric Conjugate Addition…….12
1.4.4 Previous work: Negishi's Zirconium-Catalyzed Carboalumination……..13
1.4.5 Summary of Previous Approaches to Deoxypropionates……..14
Chapter 2. Partial Synthesis of the Proposed Structures of Baulamycins A and B……...16
2.1 Overview of Synthetic Strategy……..……16
2.2 Synthesis of the Right-Hand Side……..…….18
2.3 Synthesis of the Left-Hand Side……..……...43
2.4 Attempted Aldol Coupling of Left- and Right-Hand Sides……..……..60
2.5 Revised Retrosynthetic Analysis……..……..68
Chapter 3. Structural Revision of the Baulamycins……...74
Chapter 4. Total Synthesis of the Revised Structures of Baulamycins A and B……88
4.1 Overview of Synthetic Strategy……..88
4.2 Synthesis of the Right-Hand Side……...89
4.3 Synthesis of the Left-Hand Side…….94
4.4 Coupling and Formal Hydration of Coupled Scaffold……96
4.5 Synthesis of Baulamycin A……...109
4.6 Synthesis of Baulamycin B……...112
Chapter 5. Detailed Descriptions of Experimental Work…….114
5.1 General Considerations……114
5.2 Experimental Procedures……..116
References……172
Appendix I: Spectra of Novel Compounds….....182

Chapter 1 – Introduction

1.1 Overview

This work is divided into five parts. The first of these parts, Chapter 1, provides a very brief chronological introduction to the intersection of antimicrobial compounds with human health, followed by a detailed introduction to the principle subject of this work: the baulamycin natural products, their proposed and revised stereochemical assignments, and our initial retrosynthetic analysis of their proposed structure. The second part of this work, Chapter 2, describes our subsequent efforts towards the synthesis of the proposed structures of the baulamycins.

Part three of this work provides an overview of how the originally-proposed stereochemical assignment was discovered to be incorrect, how we addressed this revelation and set about attempting to deduce the correct structure of the natural products, and how the correct structures of the baulamycins ultimately came to be revealed through total synthesis. Chapter 4 details our retrosynthetic analysis of the newly-revealed revised structure, followed by our efforts toward and eventual total synthesis of the baulamycins.

The fifth and final part of this work gives detailed accounts of all experimental procedures employed in our work on the baulamycins, including analytical data for all newly-described compounds. Copies of NMR spectra for such compounds may be found in Appendix I.

1.2 A Brief History of Antimicrobial Chemotherapy

The attempted use of natural and artificial agents to eliminate disease while sparing the host dates to ancient times. While reports of purely empirical remedies for infectious disease – the use of emetine in the form of ipecac for dysentery or quinine in the form of cinchona extracts for

fever, for example – have a long and complex history, antimicrobial chemotherapy as we know it, founded on the principles of germ theory, dates only to the dawn of the 20th century[1].

Sometime between 1889 and 1901, Paul Ehrlich, building on the foundational theories of Louis Pasteur and others, and drawing on his own earlier work in immunology for which he would later win the Nobel Prize, first formulated the idea of a "magic bullet"[2]. This magic bullet was to be a substance which, taken internally, would harm only pathogenic microorganisms while leaving the patient unscathed. This dream began to come to fruition in 1909, when the antisyphilitic properties of arsphenamine, an organoarsenical, became established in Ehrlich's laboratories[2]. The subsequent marketing of arsphenamine as Salvarsan in 1910 marked the beginning of a new era in Western medicine: the era of effective antimicrobial chemotherapy.

Although widespread adoption of synthetic antimicrobials was not immediate, and was at times hampered by opposing theories concerning the most effective strategies for the treatment of infectious disease, Salvarsan opened the door to an entirely new world of treatment for human disease. This path of discovery was extended by Gerhard Domagk, whose 1935 discovery of Prontosil marked the first of many successful sulfonamide antibiotics which would go on to be therapeutically valuable[3]. However, it was Alexander Fleming's discovery of penicillin in 1928, made therapeutically practical in the 1940's by Howard Florey and others, which truly ushered in the modern era of antibiotic discovery[4-5].

The discovery of penicillin, unlike that of Salvarsan, Prontosil, or other sulfa drugs, marked a sea change in the ongoing quest to discover new and more effective agents for the treatment of infectious disease. For the first time since the general acceptance of germ theory, a natural product had been harnessed as a therapeutic weapon against infectious disease. Penicillin inaugurated the new era of *antibiotics*, or naturally-occurring antibacterial compounds. In this new paradigm,

Earth's vast diversity of natural products would be tirelessly mined for agents capable of killing pathogens, and the substances thus identified developed into the scores of marketed drugs which form the modern armamentarium of antimicrobial chemotherapy. This period extends to the present day, with the list of available antibiotics continuing to grow, albeit perhaps more slowly now than in decades past[1].

Despite the impressive advances of the past century, many have imagined a future where bacterial evolution outpaces our ability to respond with new and more effective antimicrobial agents[6-9]. The so-called "post-antibiotic era"[10-11] – a time when pandemic resistance to both first-line agents and drugs of last resort leads to skyrocketing mortality from common pathogens – has not yet arrived. Such a development has been feared and foretold since the earliest days of antibiotic use: Fleming himself, in 1945, during the very Nobel lecture given upon receipt of his shared prize for the discovery of penicillin, warned that "it is not difficult to make microbes resistant to penicillin in the laboratory… and the same thing has occasionally happened in the body."[12] He then narrated a pointed anecdote in which improper use of antibiotics by one patient leads to the death of another from a resistant infection. Clearly, the idea of antibiotic resistance as a serious threat to public health is not new; rather, this danger has been foreseen from the beginning. Yet despite these early warnings, the glut of discovery over the two decades subsequent to the discovery of penicillin quieted fears somewhat, until it seemed that there would always be an adequate supply of new antibiotics to replace the ones which had succumbed to resistance[8].

The ongoing quest for the discovery of new and more efficacious antibiotics is rooted in this century-long history of warfare against humanity's oldest scourge. Resistance – a phenomenon present since before the beginning of antimicrobial chemotherapy – drives this search, as bacteria and our weapons against them co-evolve in a never-ending arms race of natural selection. Thus, it

was with great excitement that the Williams group received Sherman and co-workers' 2014 report of novel broad-spectrum antibiotic activity in what appeared to be a new, structurally-distinct class of antibiotics: the baulamycins[13].

1.3 The Baulamycins: History, and Proposed and Revised Structures

Baulamycins A and B (**Figure 1**) were first described in 2014, when Sherman reported their isolation from cultures of *Streptomyces tempesquensis*, an actinomycete identified in soil sediment taken from Playa Grande, Costa Rica, near Las Baulas National Marine Park[13].

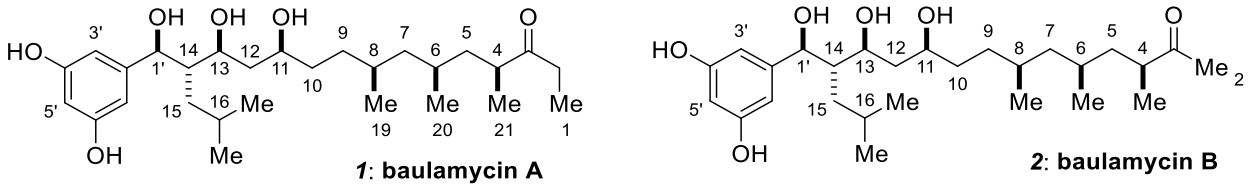


Figure 1. Baulamycins A and B.

The baulamycins were notable for their broad-spectrum antibiotic activity (i.e., activity against both Gram-positive and Gram-negative species), as well as for their unusual structure, apparently unrelated to other known classes of antibiotics. The baulamycins also appeared unusual in the nature of their suspected mechanism of action. At the time of their isolation, it was believed that the baulamycins exerted their biological effects by inhibiting the biosynthesis of siderophores. Siderophores, small-molecule chelators of iron, are produced and excreted by many bacteria, facilitating access to iron, particularly in environments where iron is scarce or tightly controlled[14]. Production of siderophores has been linked to virulence in a number of human pathogens, and siderophore production has been repeatedly validated as a promising drug target[15-18]. The baulamycins were identified as part of a high-throughput screening campaign for inhibitors of enzymes linked to siderophore biosynthesis (**Figure 2**).

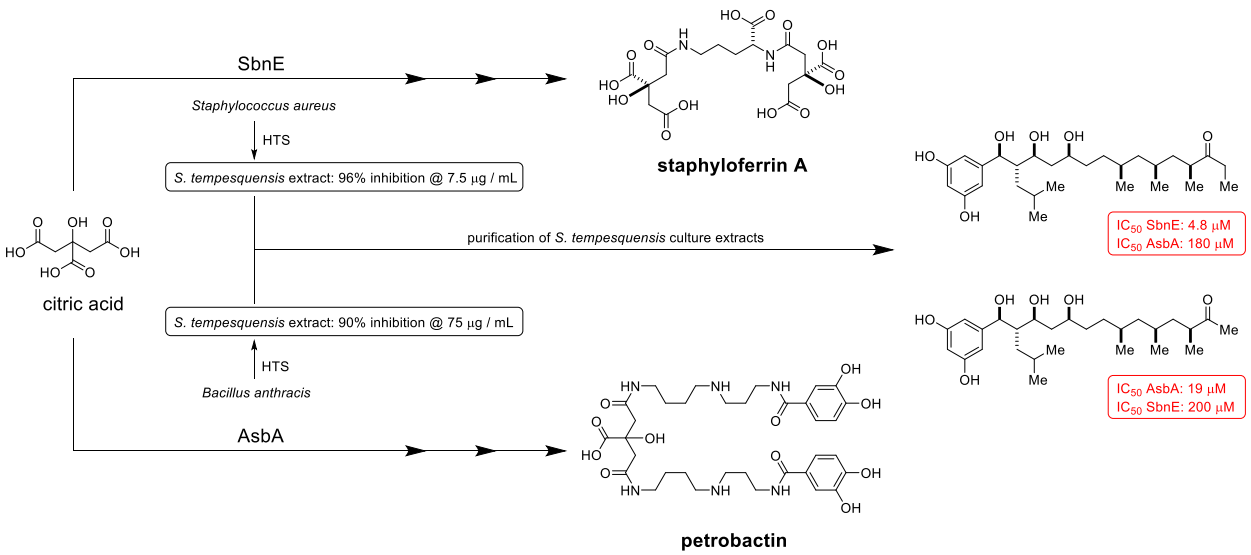


Figure 2. High-throughput screening identification of the baulamycin antibiotics.

Sherman and coworkers found that the baulamycins inhibited both SbnE and AsbA, enzymes involved in siderophore biosynthesis in *Staphylococcus aureus* and *Bacillus anthracis*, respectively. Additionally, the baulamycins were found to inhibit the growth of Gram-positive (*S. aureus*, including methicillin-resistant *S. aureus* (MRSA), and *B. anthracis*) and Gram-negative (*Shigella flexneri* and *Escherichia coli*) species in culture; however, for most species, the effect appeared independent of medium iron availability, raising the idea that the mechanism of action might not be fully dependent on inhibition of siderophore biosynthesis[13].

The biological findings detailed in Sherman's initial report were fascinating; however, further study of the baulamycins was severely hampered by the low yield of the baulamycins from their natural source: 39 L of bacterial culture were laboriously extracted and purified to obtain a mere 3.6 mg of baulamycin A, along with 2.1 mg of baulamycin B. This predicament, along with a desire to study unnatural and otherwise inaccessible derivatives of the natural products, led us to envision a total synthesis of the baulamycins.

These interests were not unique to the Williams group, and the baulamycin story became only more interesting when, in February of 2017, Guchhait *et al* published a total synthesis of the

originally proposed structure of baulamycin A, demonstrating that this structure was *not* in fact the structure of the natural product[19]. In fact, when Sherman and coworkers first assigned the stereochemical configuration of the baulamycins, their initial assignment (**Figure 3**) differed substantially from that which would later be shown to be correct (**Figure 1**).

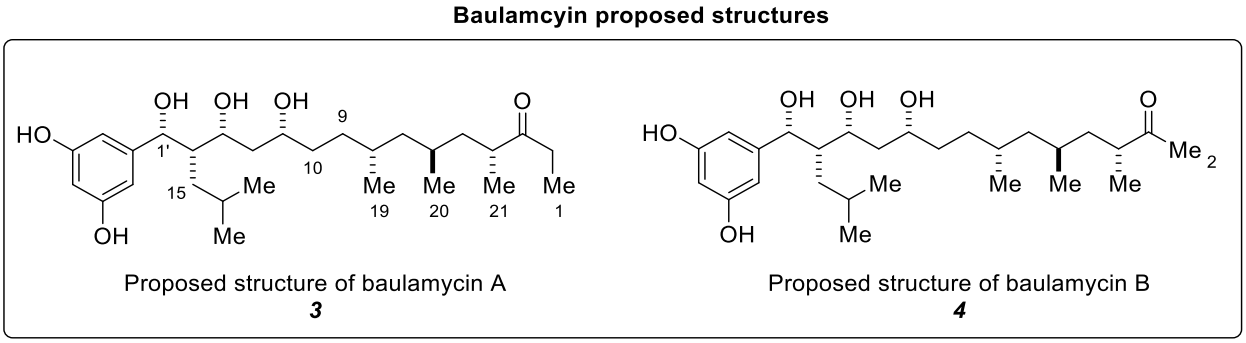


Figure 3. Proposed structures of baulamycins A and B, later invalidated by total synthesis.

Indeed, mere months after Guchhait *et al* published their work falsifying the original structural assignment, Aggarwal and coworkers published their seminal work on the baulamycins, revising the structure, identifying the absolute stereochemistry, and reporting the first total syntheses of baulamycins A and B[20], an achievement paralleled and closely followed by Sengupta *et al*'s synthesis of the antipode of baulamycin A[21]. Although we, along with these others, initially targeted the structures shown in **Figure 3** in our retrosynthetic analysis, we were fortunate in that our chosen strategy allowed us freedom with respect to alterations to the stereochemical configuration of the baulamycins. This fundamental flexibility of approach paved the way for our rapid pivot toward the revised structures of baulamycins A and B, ultimately culminating in our synthesis of the natural products.

In the course of our studies toward the revised structure of the baulamycin scaffold, we were all the more intrigued by the work at hand when a report from Wuest and co-workers suggested the possibility of an alternate or additional mechanism of action for the baulamycins in the form of possible interference with bacterial membranes[22].

1.4 Retrosynthetic Analysis of the Proposed Structures

Conceptually, the baulamycin scaffold lends itself to disconnection into left- and right-hand sides (LHS and RHS, respectively; **Figure 4**). Retrosynthetically, we imagined the baulamycin scaffold dissected between C11 and C12, giving rise to synthons **4** and **5** (**Figure 4**).

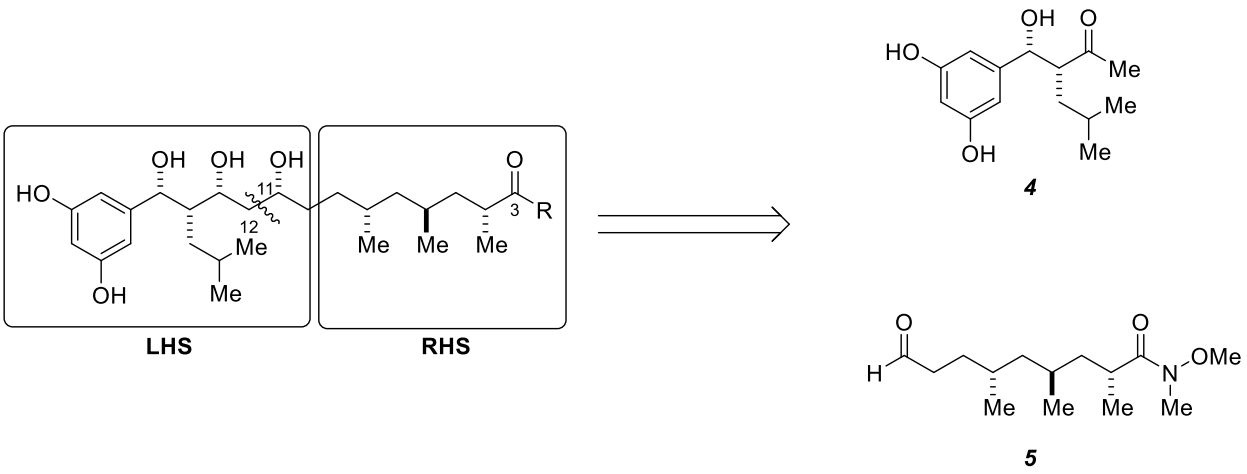


Figure 4. Key retrosynthetic disconnection of baulamycin scaffold in to LHS and RHS.

We imagined **4** arising from a stereoselective aldol reaction between synthon **6**, derived from 3,5-dihydroxybenzaledehyde, and a nucleophilic coupling partner in the form of **7** (**Figure 5**).

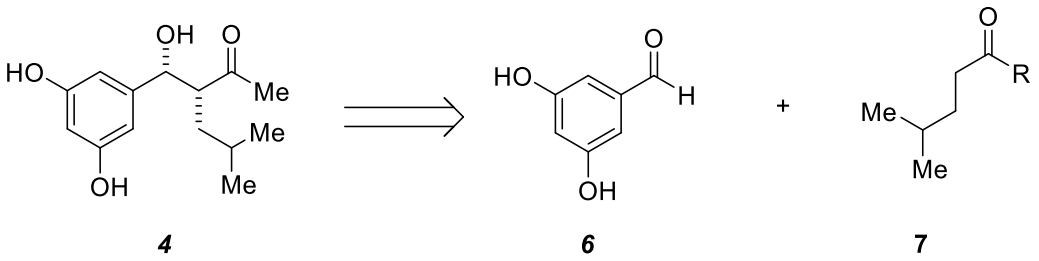


Figure 5. Retrosynthetic analysis showing **4** arising from a stereoselective aldol reaction.

While the approach to the LHS immediately suggested several well-known strategies for the stereoselective synthesis of aldol products, further analysis of tactics to synthesize **5** seemed warranted. While the LHS retains the polyketide's natural oxidation state, inspiring a (presumably) biomimetic approach involving aldol couplings, the fully-reduced RHS portion of the baulamycin

scaffold poses a more interesting synthetic challenge, with the lack of functional handles limiting options towards the C4, C6 and C8 methyl-bearing stereocenters.

The synthesis of reduced polyketides, or deoxypolypropionates, is not a new problem, and a number of synthetic approaches have been developed and reviewed[23-24]. A handful of non-iterative approaches to deoxypropionates have been reported; however, thus far these methods have remained relatively underdeveloped compared to the plethora of stepwise approaches[25-26]. Rovis' formal synthesis of ionomycin beginning with the desymmetrization of methyl-substituted anhydrides showcases the potential of these approaches in select cases, and undoubtedly these tactics will continue to be an area of active research[27].

Of the iterative approaches to the polydeoxypropionates, a handful of methods stood out as maximizing efficiency while keeping functional group manipulations to a minimum. These methods were Burgess' asymmetric hydrogenations of trisubstituted olefins[28-29], Breit's zinc-catalyzed coupling of alkylmagnesium chlorides with chiral triflates derived from D- and L-lactic acid[30-31], Feringa's copper-catalyzed asymmetric conjugate addition of Grignard reagents to unsaturated thioesters[32] and Negishi's one pot zirconium-catalyzed asymmetric carboalumination (ZACA) and palladium-catalyzed vinylation.

1.4.1 Previous Work: Burgess' Asymmetric Hydrogenations

Burgess' approach to the deoxypropionates relies on the use of chiral analogues of Crabtree's catalyst (**Figure 6**) capable of catalyzing the asymmetric hydrogenation of trisubstituted allylic alcohols or α,β-unsaturated carbonyls. The work has been applied in total synthesis by Burgess and coworkers (**Figure 7**), and appears to allow general access to all deoxypropionates stereoisomers of various chain lengths[33-34].

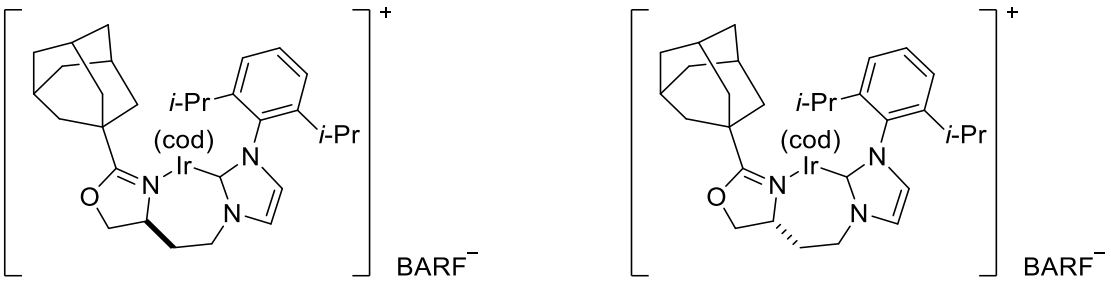


Figure 6. Chiral catalysts developed by Burgess and coworkers.

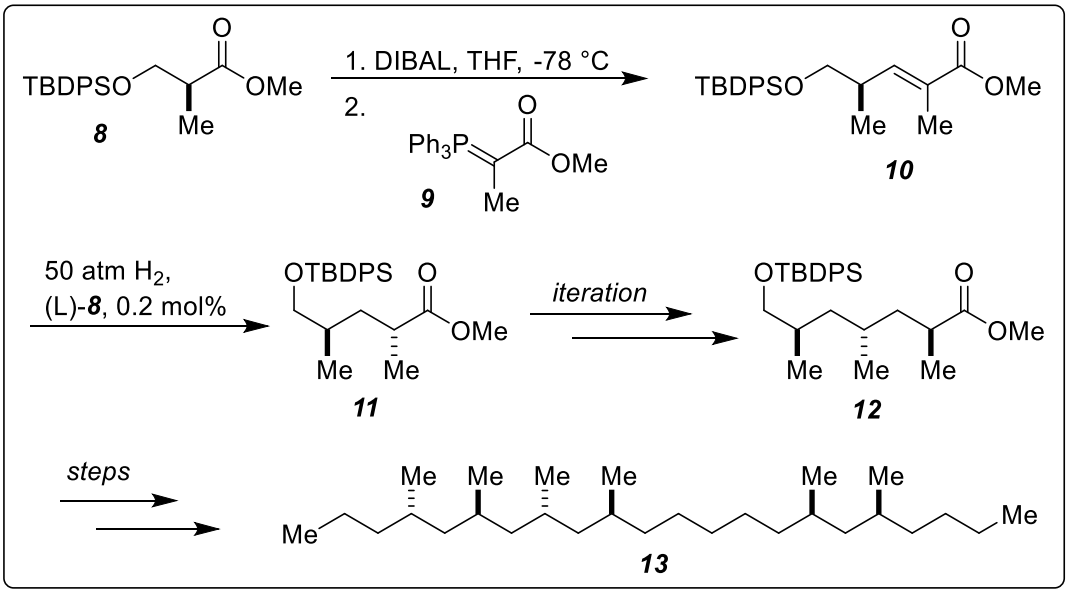


Figure 7. Application of Burgess' hydrogenation to the synthesis of (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-hexamethyldocosane[28, 33].

Initially, we noted several limitations to Burgess' approach. First, the methodology requires the synthesis of both enantiomers of the chiral iridium catalyst, each synthesis requiring seven steps from commercially available materials – a high cost of investment to test the method's suitability on our substrates[35]. Second, Burgess notes that although the reactions are nominally under catalyst control, substrate configuration does appreciably influence stereochemical outcome, sometimes requiring "optimization" of substrate to achieve acceptable levels of diastereocontrol. Finally, while not fundamentally limiting, the requirement that all hydrogenations be run at 50 atm after freeze-pump-thaw degassing of the reaction mixture was deemed inconvenient. With these

considerations in mind, Burgess' method did not seem a good initial starting point for our work on the right-hand side of the baulamycins.

1.4.2 Previous Work: Breit's Zinc-Catalyzed Cross-Coupling

A second option for the synthesis of deoxypolypropionates is found in Breit's zinc-catalyzed cross-coupling of alkylmagnesium halides and lactate-derived triflates (**Figure 8a**). In this method, methyl-bearing stereocenters are derived stoichiometrically from the chiral pool by way of **17** and *ent*-**17**. These triflates are coupled to alkylmagnesium halides, a transformation which, under Breit's conditions, proceeds with complete inversion of configuration. The resulting ester products may then be reduced, halogenated and re-subjected to the coupling conditions as Grignard reagents (**Figure 8b**).

While Breit and coworkers have applied these conditions in total synthesis, in these cases the cross-coupling strategy played an isolated role in the construction of the relevant natural products: it was not the foundation of the larger strategy, nor were multiple iterations employed[36-37]. Nonetheless, the strategy *had* been used to produce intermediates with the desired *anti*/*anti*-stereochemistry in hundred-milligram quantities. However, despite the demonstrated efficacy

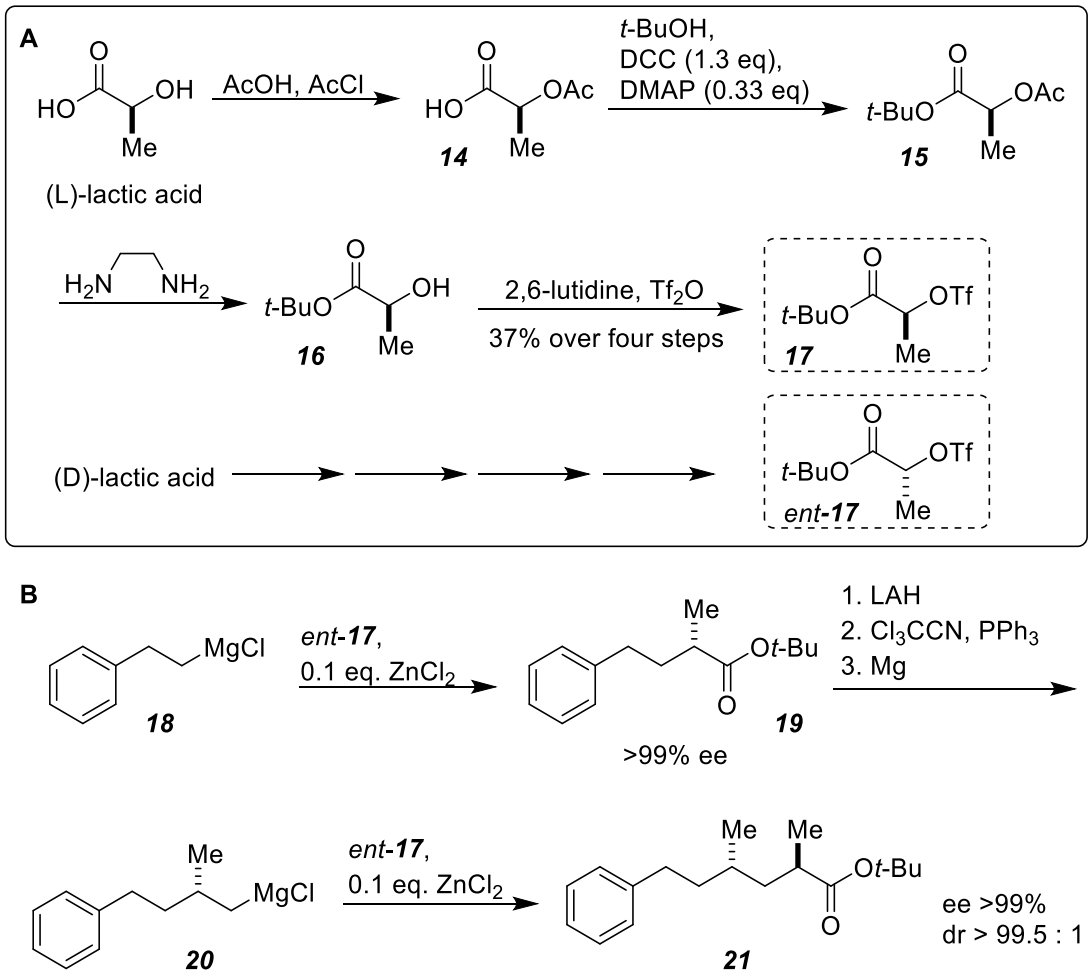


Figure 8. (A) Synthesis of (*R*)- and (*S*)-lactic acid triflate esters in four steps from lactic acid. (B) Application of **17** and *ent*-**17** in the synthesis of deoxypropionates[31].

towards structures like **5**, Breit's method suffers from the severe drawback that all stereocenters are derived from either (D)- or (L)-lactic acid in 37% yield across four steps. Considering the expense of D-lactate (>$7000/mol), and in light of the fact that the absolute configuration of the baulamycins was hitherto unknown, the possibility that two stereocenters might be derived from D-lactic acid was deemed an economically prohibitive barrier to implementing Breit's chemistry. Nonetheless, extensive work by Breit and coworkers on the synthesis and characterization of polydeoxypropionates would ultimately prove vital to the baulamycin project, as will be seen later.

1.4.3 Previous Work: Feringa's Asymmetric Conjugate Addition

Feringa and coworkers have shown that the copper-catalyzed conjugate addition of Grignard reagents to thioesters proceeds with high enantioselectivity in the presence of catalytic amounts of Josiphos ligand (**Figure 9**)[32]. The asymmetric conjugate addition of organometallic reagents to unsaturated systems is well-known, and has been reviewed[38-39]; however, the work by Feringa and coworkers is notable for overcoming several practical limitations to these methods.

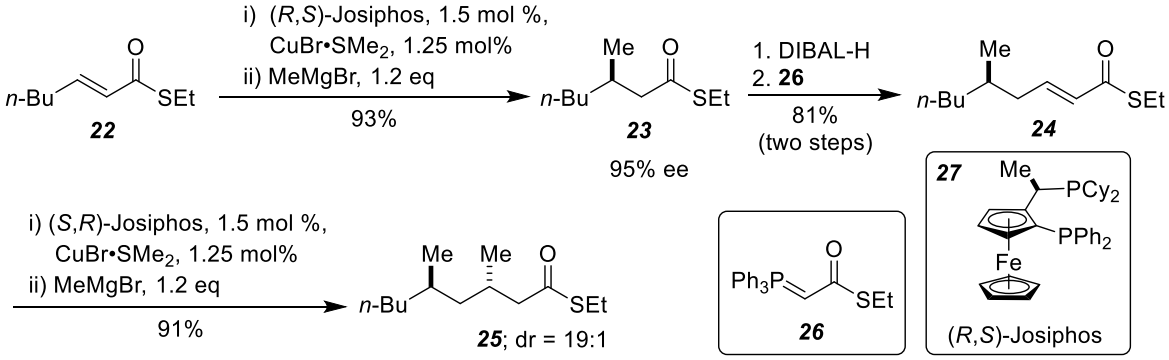


Figure 9. Asymmetric conjugate addition of Grignard reagents to unsaturated thioesters[32].

Historically the 1,4-addition of relatively unreactive methylmagnesium bromide to conjugated systems containing a carbonyl carbon in the acid oxidation state (e.g., esters, amides) has proved particularly challenging when compared to conjugate addition on more electron deficient systems such as enones[40-41]. Feringa's work solves this problem by employing thioesters, which are more susceptible to conjugate addition while still remaining capable of undergoing many of the same functional group transformations as their oxo-analogues. On these substrates, the reaction with methylmagnesium bromide proceeds to high conversion (>90%) on reasonable timescales (12 -16 hrs)[32].

Another area in which Feringa's methodology improves on previous methods is the high stereoselectivity of the transformation. The use of CuBr-DMS and Josiphos gives consistently high enantio- and diastereoselectivity with methylmagnesium bromide and other Grignard

reagents, with the reaction apparently taking place under almost complete catalyst control even at low catalyst loadings. Combined with the fact that all of the necessary reagents, catalysts, and ligands are commercially available and relatively cheap, these attributes make Feringa's strategy towards the polydeoxypropionates particularly appealing. Moreover, Feringa's method has been repeatedly applied in total synthesis[32, 42-43].

1.4.4 Previous Work: Negishi's Zirconium-Catalyzed Carboalumination

Negishi has reported that that polydeoxypropionate motifs may be rapidly constructed by a combined approach utilizing a zirconium-catalyzed asymmetric carboalumination (ZACA) reaction in sequence with a nominally-*in situ* Negishi cross-coupling (**Figure 10**)[44]. Negishi's

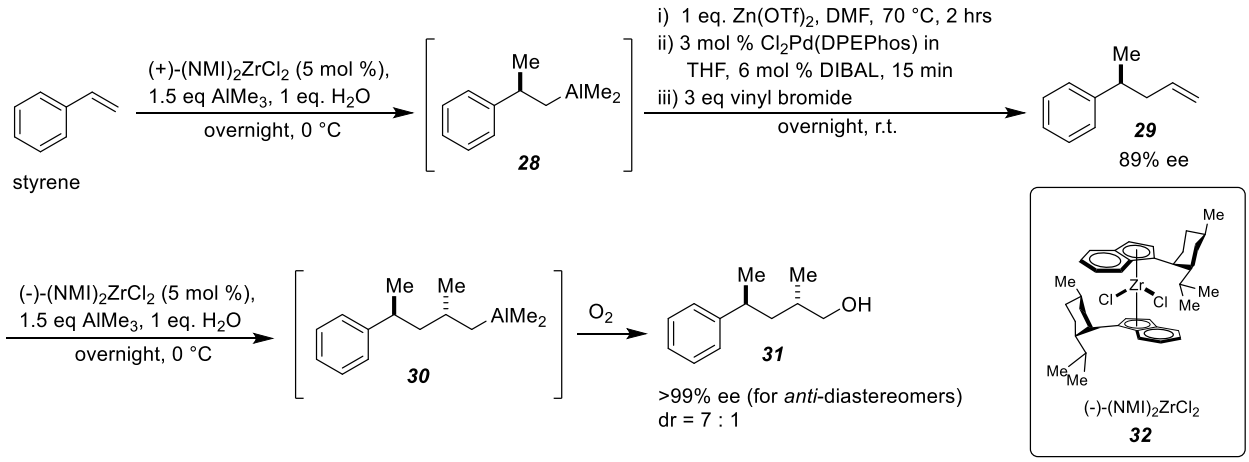


Figure 10. Zirconium-catalyzed carboalumination and homologation of alkenes to give polydeoxypropionates under Negishi's conditions.

approach achieves chiral induction through the use of Erker's catalysts[45] (-)-bis(1-neomenthylindenyl)zirconium dichloride and (+)-bis(1-neomenthylindenyl)zirconium dichloride (henceforth (-)-$(NMI)_2ZrCl_2$ and (+)-$(NMI)_2ZrCl_2$). These catalysts are available from (-)- and (+)-menthol in three steps, respectively; at the time of our retrosynthetic analysis, they were also available commercially on a very limited basis.

The promising nature of this strategy with respect to the synthesis of the baulamycin is immediately apparent, as each methyl-bearing stereocenter nominally requires only a single pot

for installation. The development of the ZACA/cross-coupling approach was reported following extensive research[46-49] by Negishi and coworkers into zirconium catalyzed carboalumination, and these protocols were thus well-represented in the literature, albeit primarily in reports by Negishi *et al*. An important insight was contributed to the field by Wipf and coworkers when they reported that addition of stoichiometric water to the ZACA reaction results in a dramatic rate acceleration without any apparent loss of enantioselectivity; this observation would later become instrumental in the practical application of the ZACA methodology[50]. The ZACA/homologation strategy toward polydeoxypropionates has been applied in total synthesis, again mostly[51-56], although not exclusively[57], by Negishi and coworkers.

1.4.5 Summary of Previous Approaches to Deoxypropionates

Of the several strategies toward the synthesis of polydeoxypropionate motifs considered, each had respective advantages and disadvantages. Burgess' method offered the advantage of operational simplicity in the form of hydrogenation as the stereodetermining step; at the same time, the appeal of such an approach was mitigated by the lengthy syntheses required to obtain the necessary catalysts. Similarly, while the operational simplicity of Breit's $ZnCl_2$-catalyzed cross-coupling, with its cheap and air stable catalyst and well-understood coupling partners (i.e., a Grignard reagent and a triflate) was appealing, the extreme expense of D-lactic acid as a stoichiometric starting material proved prohibitive to pursuing this strategy.

On the other hand, Feringa's conjugate addition had much to recommend it. All of the reagents and catalysts were commercially available, cheap, and relatively simple to manipulate; moreover, the methodology appeared to give good enantio- and diastereoselectivity on a variety of substrates and the yields were reported to be excellent. Likewise, Negishi's protocol had a number of apparent advantages, the most obvious and compelling being the enticing prospect of a

"one pot, one stereocenter" approach. In addition, the ZACA reaction had seen numerous applications in total synthesis, albeit largely by Negishi and coworkers.

In the event, the incredible step economy of Negishi's ZACA/cross-coupling approach was simply too attractive to pass up. Despite the necessity of preparing Erker's catalysts on scale if the method were to be viable, Negishi's ZACA/homologation protocol initially seemed to constitute an ideal initial starting point for our burgeoning attack on the baulamycin scaffold. Thus, without further consideration, the first salvo was launched.

Chapter 2 – Partial Synthesis of the Proposed Structures of Baulamycins A and B

2.1 Overview of Synthetic Strategy

Considering Negishi's ZACA protocol as our most promising avenue towards the deoxygenated portion of the baulamycins, we imagined a straightforward synthesis of the RHS beginning with styrene as shown below (**Figure 11**).

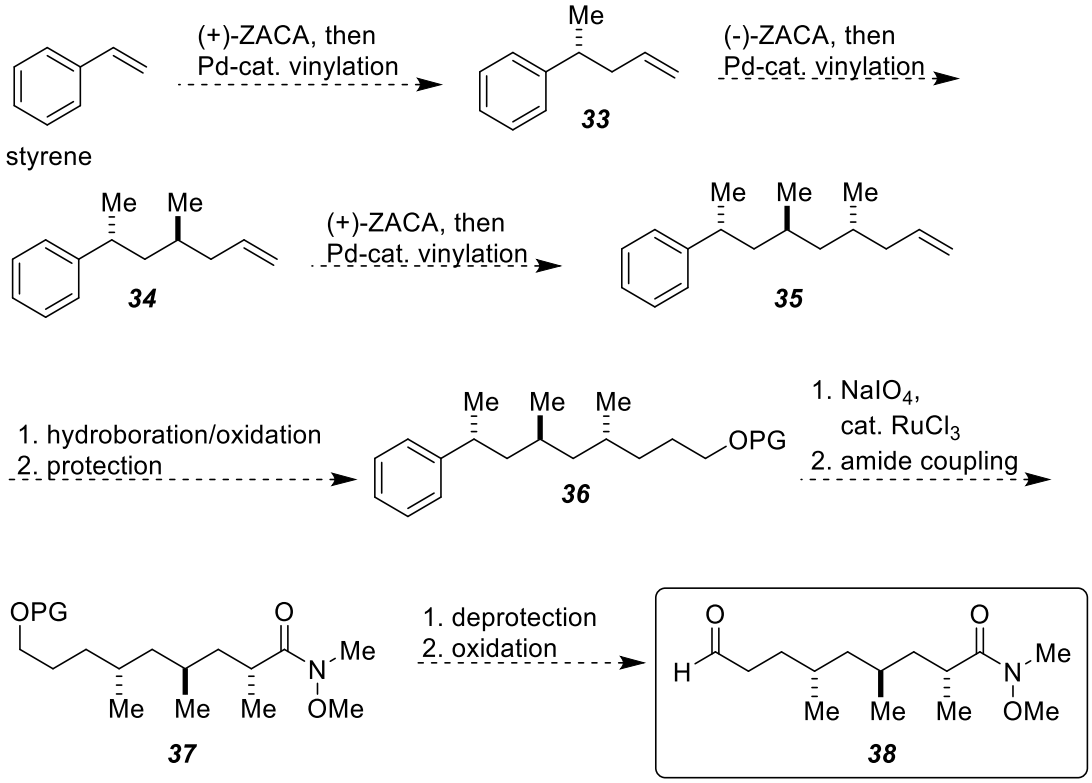


Figure 11. Proposed synthesis of RHS synthon and aldol coupling electrophile **38**.

Simultaneously, we imagined the synthesis of the LHS coupling partner by way of a diastereoselective Evans-style aldol reaction[58] (**Figure 12**). Transamidation of the chiral auxiliary to give the Weinreb ketone, followed by protection and Weinreb ketone synthesis would give LHS methyl ketone coupling partner **43**.

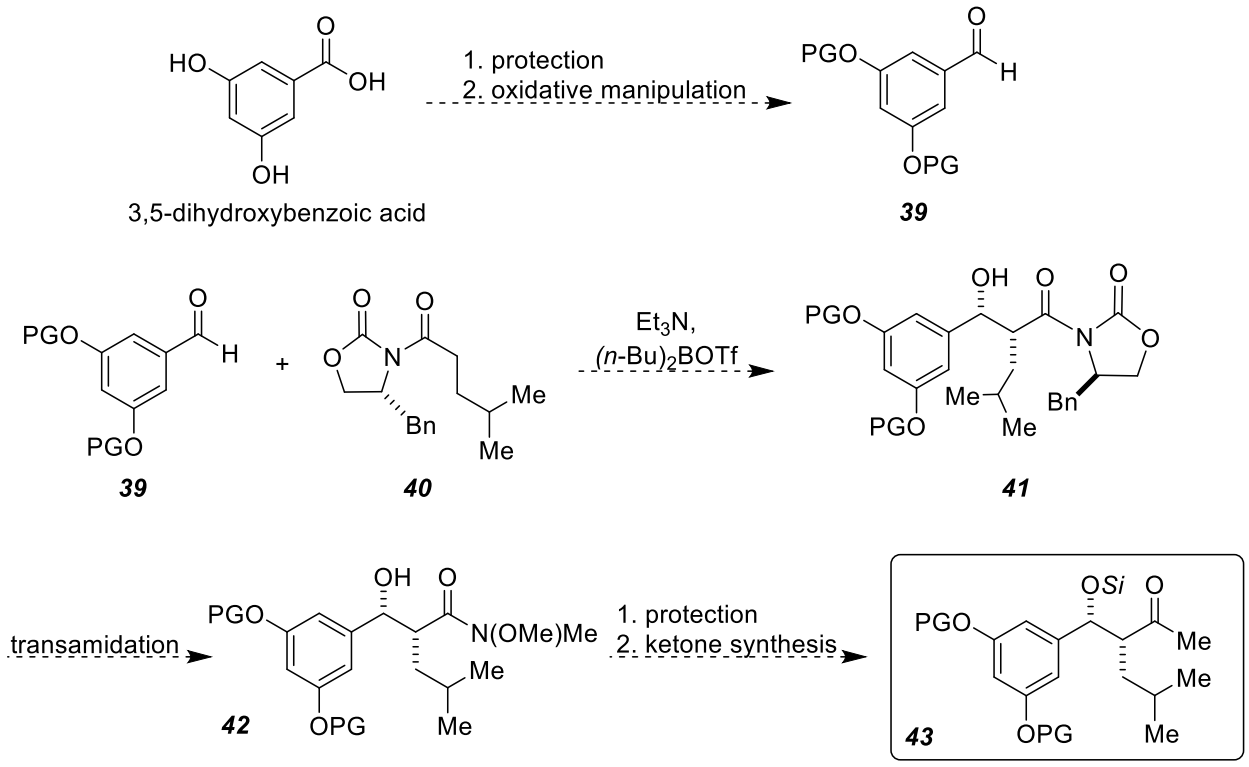


Figure 12. Proposed synthesis of LHS synthon and aldol coupling nucleophile **43**. PG = protecting group, *Si* = "super silyl", e.g., tris(triethylsilyl)silyl.

We initially hoped to couple the LHS and RHS using a 1,4-*syn* selective aldol reaction under Yamamato's conditions[59], exploiting the directing effects of an extremely bulky silyl protecting group on the C1'-hydroxyl. The resulting aldol product would then be subjected to stereoselective reduction, again directed by steric bulk pendant to C1', to give *syn*-diol **45**. Weinreb ketone synthesis followed by global deprotection would then reveal the baulamycins (**Figure 13**).

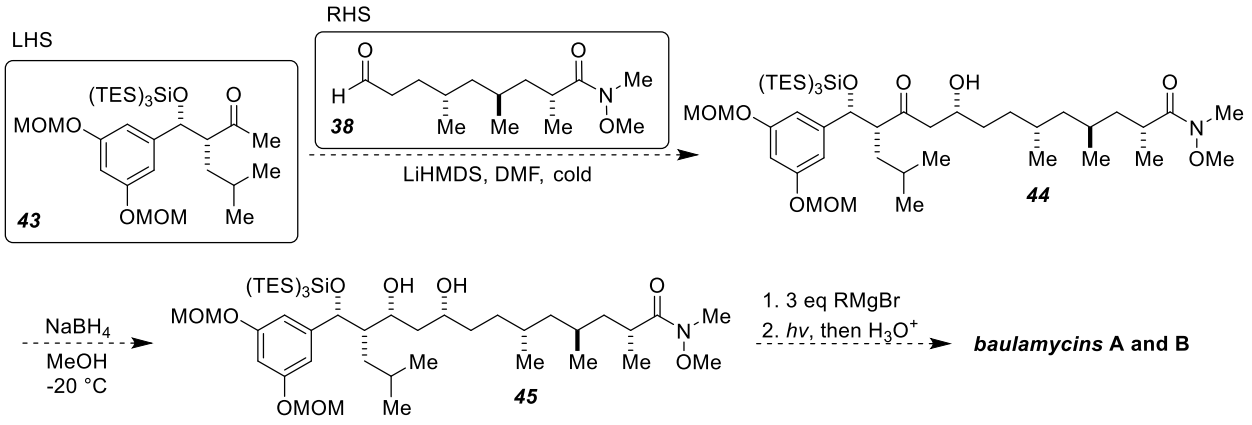


Figure 13. Proposed coupling of LHS and RHS followed by completion of the total synthesis of the baulamycins**.**

2.2 Synthesis of the Right-Hand Side

Negishi's methodology for the synthesis of polydeoxypropionates relies on the use of Erker's chiral catalysts, (-)-$(NMI)_2ZrCl_2$ and (+)-$(NMI)_2ZrCl_2$. Although both enantiomers of this catalyst were available in limited quantities from commercial suppliers at the time of our initial synthetic studies, the cost of using these sources on scale was prohibitive. In order to be assured of our supply of these materials, we elected to begin our attack on the RHS with the synthesis of (-)-$(NMI)_2ZrCl_2$ from (-)-menthol as described by Erker and coworkers[45] (**Figure 14**).

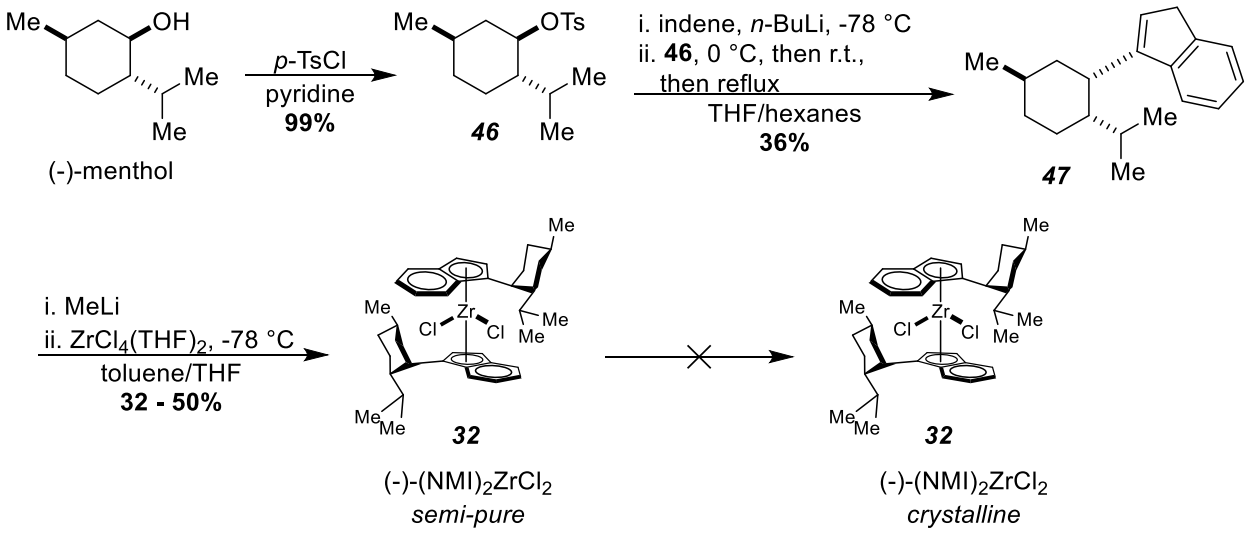


Figure 14. Preparation of (-)-$(NMI)_2ZrCl_2$ according to Erker's method.

Tosylation of (-)-menthol proceeded in high yield under standard conditions as expected, giving menthyl tosylate **46** as a white crystalline solid. Displacement of the tosylate with indenyl lithium was sluggish; however, after 3 days at reflux in THF neomenthyl indene **47** was obtained as a colorless, waxy solid in poor yield, as reported. Deprotonation of **47** with methyl lithium and addition to zirconium(IV) chloride-THF in toluene did indeed give **32** as a yellow solid contaminated with minor amounts of diastereomeric products as described by Erker and coworkers. However, further purification of this material proved challenging.

Erker reports trituration of crude **32** with pentane, followed by extraction and filtration with DCM in order to remove residual lithium chloride, yielding a DCM solution of **32** as the filtrate. This solution is then partially concentrated, and subsequent repeated recrystallizations at -28 °C give the product in an overall 61% yield. In our hands, we found that while organic impurities could indeed be removed by trituration with pentane, and while a white insoluble material indeed appearing to be lithium chloride (hygroscopic; magenta flame test) could be removed by filtration from DCM, further recovery of the dissolved product in crystalline form proved intractable. Aging of the air-sensitive yellow filtrates at -25 °C overnight did indeed induce the formation of solids; however, despite repeated attempts, these appeared to be solely precipitants of a non-crystalline nature (or at least, they were never crystalline in their entirety). A range of solution concentrations, handling methods and recrystallization temperatures were employed without success; ultimately, the product was always obtained as a free-flowing yellow powder with evidence of residual impurities by ^{1}H and ^{13}C NMR. Possibly, some failure to precisely replicate the conditions of Erker's synthesis introduced contaminants which preferentially precipitated from solution before recrystallization could take place. Alternatively, such unknown contaminants might have induced product decomposition over the relatively long timescales necessary for recrystallization. At any

rate, the isolation of air-sensitive substances from solution by recrystallization at low temperature and subsequent low-temperature filtration without exposure to oxygen is an endeavor fraught with challenge from the outset.

Whatever the reason for our failure to obtain rigorously-pure (-)-$(NMI)_2ZrCl_2$, we nonetheless remained undeterred in our resolution to implement the ZACA reaction in the pursuit of the baulamycins. Hoping to work out the purification of **32** at a later date, we decided to attempt the zirconium-catalyzed carboalumination of styrene with semi-pure catalyst, in the hopes of demonstrating the viability of the route while the latent purification issues were being resolved (**Figure 15**).

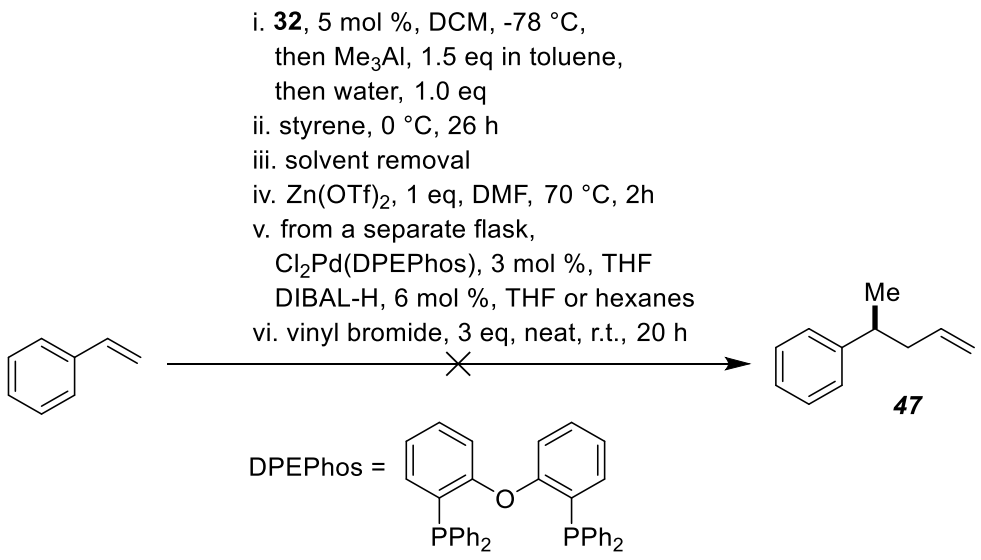


Figure 15. Attempted application of Negishi's ZACA protocol to styrene.

Our initial attempts at the carboalumination and *in situ* homologation of styrene met with failure. The mechanism of the ZACA reaction is believe to involve an initial transmetalation between Me_3Al and the zirconocene dichloride precatalyst, giving rise to a catalytically-active species containing a methyl-zirconium bond (**Figure 16**) [46]. Association of this active catalyst (perhaps in cationic form as part of a "tight ion pair" with $Cl_2AlMe_2^-$) to the alkene π-bond leads

to stereospecific migratory insertion, and subsequent transmetalation with aluminum gives the dimethylalkylaluminum product while regenerating the zirconocene dichloride precatalyst.

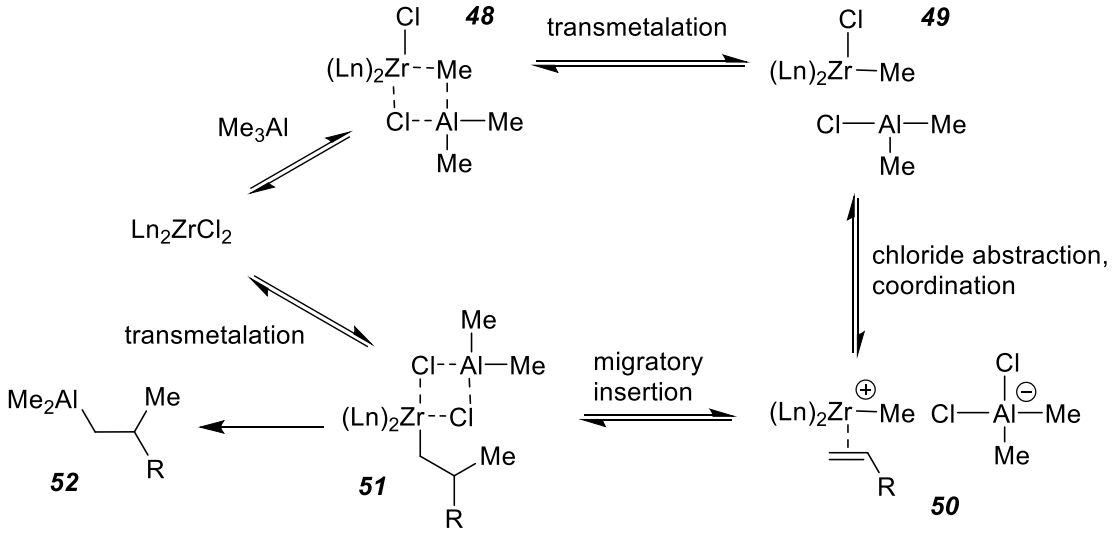


Figure 16. Proposed mechanism of zirconium-catalyzed methylalumination.

Previous work[47] has shown that the efficiency of the carbozirconation and subsequent transmetalation is heavily solvent-dependent, with polar solvents, in particular methylene chloride, proving optimal. Accordingly, in our initial studies we employed anhydrous dichloromethane as the solvent for the carboalumination; trimethylaluminum was introduced as a solution in toluene. When the combined ZACA-homologation protocol failed to give **47** as expected, we attempted to intercept the carboalumination product by oxidation (**Figure 17**). Unfortunately, none of the expected (*R*)-2-phenylpropanol (**48**) could be isolated. At this juncture, exhaustive attempts to characterize the complex product mixtures obtained were undertaken.

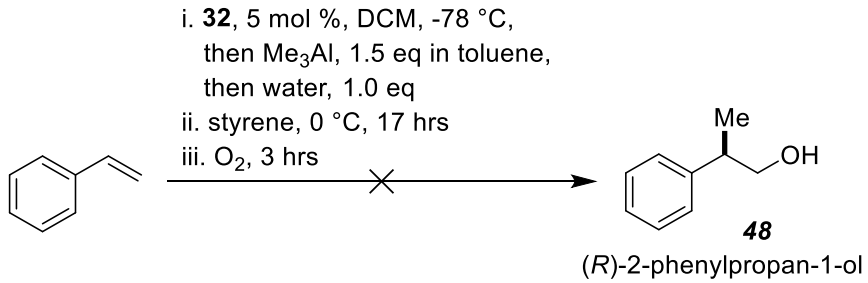


Figure 17. Attempted carboalumination-oxidation of styrene.

Ultimately, we realized that the major products of our endeavors were in fact a series of isomeric bistolylmethanes formed from the Friedel-Crafts alkylation of methylene chloride with two equivalents of toluene derived from our commercial solution of trimethylaluminum. A single account[60] of the Friedel-Crafts reaction between toluene and methylene chloride is known, and reports of Friedel-Crafts alkylations[61] and acylations[62] catalyzed by trimethylaluminum are not unheard of; however, a Friedel-Crafts alkylation of toluene with methylene chloride under trimethylaluminum catalysis has not been reported. Pleasingly, treatment of our semi-pure **32** with *neat* trimethylaluminum followed by carboalumination and oxidation gave the desired 2-phenylpropanol, albeit in low yield (**Figure 18**).

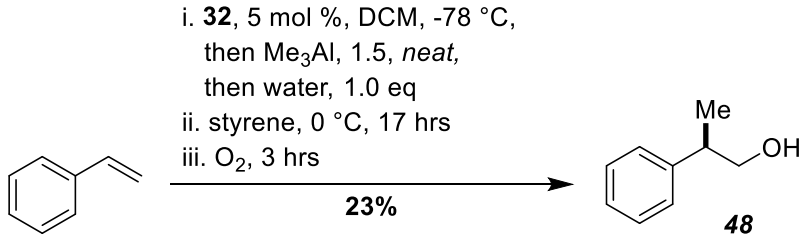


Figure 18. Successful zirconium-catalyzed carboalumination with neat trimethylaluminum.

At this stage, despite our success in converting styrene to **48** with our semi-pure catalyst, we were concerned that the as-yet-unresolvable impurities in **32** might be impacting the yield of the carboalumination step. Consequently, we obtained a small supply of commercial *ent*-**32** (TCI America, Inc.) in order to continue our studies on the ZACA-homologation sequence. In the event,

commercial *ent*-**32** gave methylated olefin **49** in 24 – 54% yield (**Figure 19**), showing little improvement over our catalyst. Preliminary investigations of enantioenrichment by polarimetry revealed the correct sign of optical rotation, but a disappointing enantiomeric excess of only 38%.

Despite the lackluster enantioselectivity, the modest yield of desired product seemed encouraging, and a number of attempts were made to install the second methyl group by way of a further round of zirconium-catalyzed carboalumination (**Figure 19**).

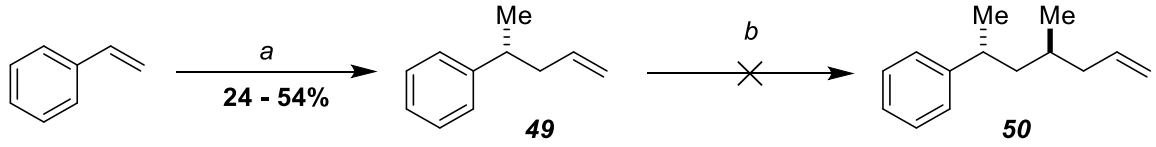


Figure 19. ZACA-homologation of styrene and attempted ZACA-homologation of **49**. (a) i. 5 mol % *ent*-**32**, DCM, -78 °C, then1.5 eq Me_3Al, then 1.0 eq water; ii. 1 eq styrene, 0 °C, 26 h; iii. solvent removal; iv. 1 eq $Zn(OTf)_2$, DMF, 70 °C, 2h; v. from a separate flask: 3 mol % Cl_2Pd(DPEPhos), 6 mol % DIBAL-H, THF or THF/hexanes; vi. 3 eq vinyl bromide, r.t., 20 h (b)) i. 5 mol % **32**, DCM, -78 °C, then1.5 eq Me_3Al, then 1.0 eq water; ii. 1 eq styrene, 0 °C, 26 h; iii. solvent removal; iv. 1 eq $Zn(OTf)_2$, DMF, 70 °C, 2h; v. from a separate flask: 3 mol % Cl_2Pd(DPEPhos), 6 mol % DIBAL-H, THF or THF/hexanes; vi. 3 eq vinyl bromide, r.t., 20 h.

Frustratingly, conditions identical to those used successfully on styrene failed unequivocally on **49**. Meanwhile, acylation of **48** obtained using the ZACA-oxidation protocol with our semi-pure **32** gave known compound **51**, which, when subjected to chiral-phase HPLC analysis was shown to be essentially racemic **(Figure 20**). Simultaneously, all our considerable efforts to obtain useful quantities of crystalline **32** continued to be met with failure.

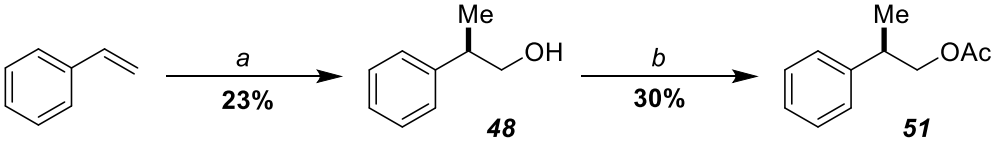


Figure 20. Synthesis of (*R*)-2-phenylpropyl acetate. (a) i. 5 mol % **32**, then 1.5 eq Me_3Al, then 1.0 eq water; ii. styrene, 17 h; iii. O_2, 3 h. (b) 5 mol % DMAP, 1.5 eq. pyridine, 1 eq. acetyl chloride.

In light of these ongoing issues, and with extensive efforts to effect the second methylation on **49** proving fruitless, we chose to abandon further development of the ZACA/homologation

route. While initially promising, the modest-to-poor yields, poor enantioselectivities, intractable catalyst purification, long reaction times, tedious manipulations of material under both air- and moisture-free conditions and the necessity of using stoichiometric quantities of highly pyrophoric neat trimethylaluminum ultimately sounded the death knell for this route.

We next considered that Feringa's asymmetric conjugate addition approach might provide a tractable alternative to the ZACA strategy (**Figure 21**). We imagined that addition of methylmagnesium bromide to unsaturated thioester **53** (derived from hydrocinnamaldehyde) would allow the installation of the first stereocenter. Reduction and Wittig-based homologation would give unsaturated thioester **56**, which would undergo a second conjugate addition to install the second methyl-bearing stereocenter. Homologation of **57** followed by oxidation to the alcohol, protection, and oxidation of the phenyl group to reveal carboxylic acid **60** would set the stage for the installation of the third stereocenter by auxiliary-directed alkylation. Methylation, auxiliary removal, deprotection and oxidation of alcohol to aldehyde would then give key intermediate **38**.

While both Wittig[43] and Horner-Wadsworth-Emmons[63] homologations of thioesters are known, we elected a Wittig-based synthesis of the requisite unsaturated starting materials for two reasons. First, phosphonium ylide **26** was reported to be an air-stable, crystalline solid available in three steps from cheap bromoacetic acid[64]. Large scale production of this reagent in line with the quantities necessary for use throughout the synthesis thus seemed feasible. Second, in contrast to the conditions required for the Horner-Wadsworth-Emmons reaction, the use of preformed ylide **26** obviates the need for an exogenous base in the olefination, leading to supreme operational simplicity in these reactions.

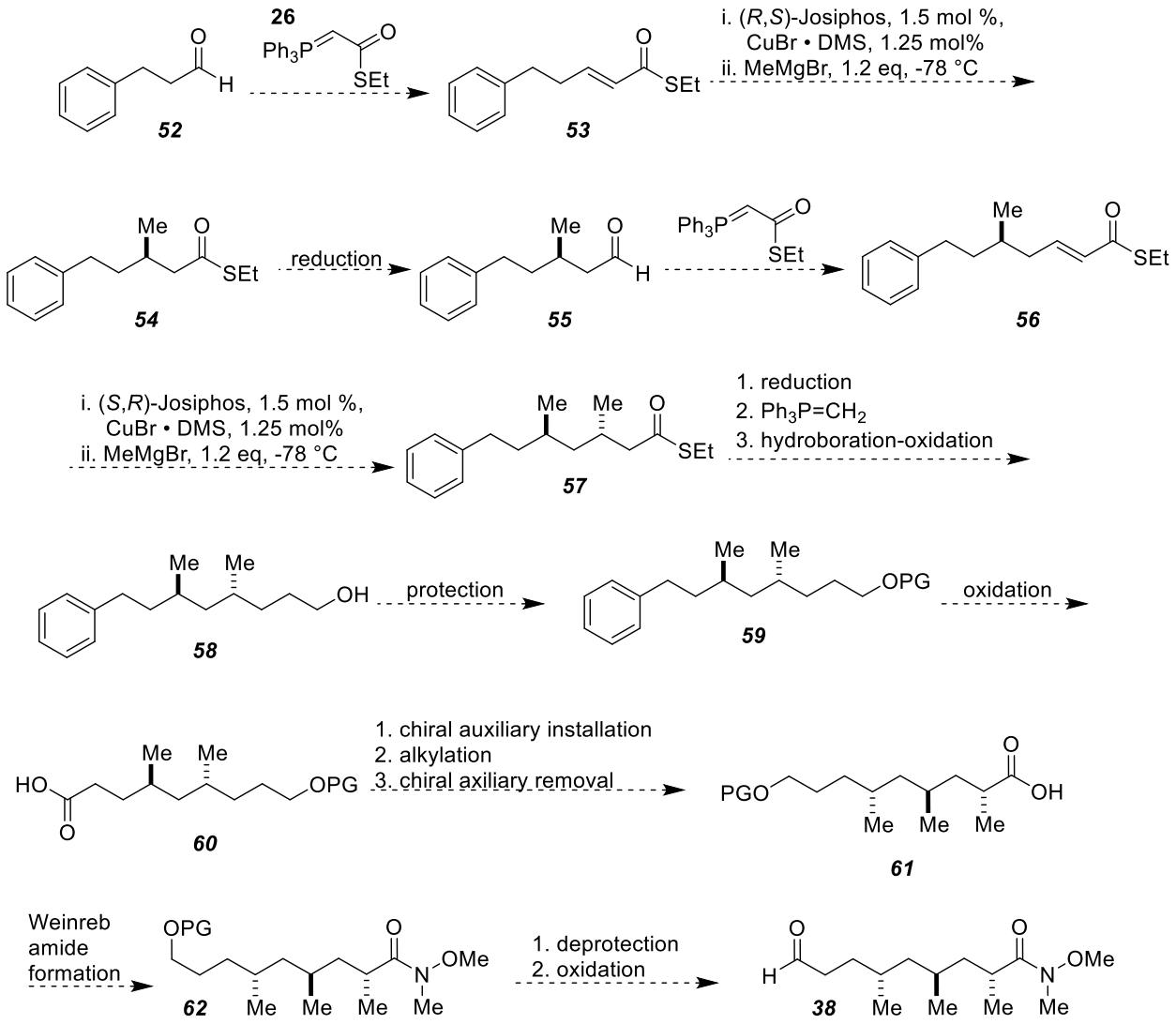


Figure 21. Proposed synthesis of RHS according by asymmetric conjugate additions.

With these considerations in mind, we began our renewed attack on the RHS with the synthesis of phosphonium ylide **26**. Steglich-type thioesterification cleanly gave **64**; excess dicyclohexylurea byproducts were readily removed by filtration through Celite. Reaction of crude **64** with triphenylphosphine gave phosphonium bromide **65** as colorless crystals; subsequent deprotonation with sodium carbonate afforded **26** as a crystalline solid in 82% yield over three steps on a hundred gram scale (**Figure 22**).

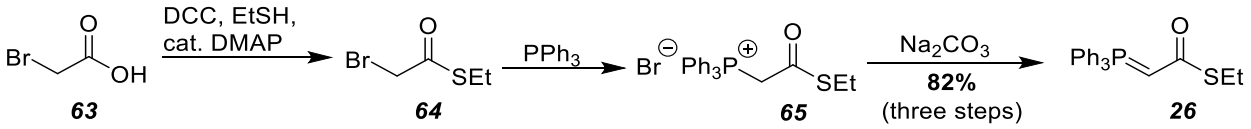


Figure 22. Synthesis of phosphonium ylide **26** from bromoacetic acid.

With access to a plentiful supply of **26** secured, we turned our attention to the synthesis of the first thioester substrate for conjugate addition. Cheap ($60/kg) and readily available hydrocinnamaldehyde provided an ideal starting material, giving **53** in 86% yield and 17:3 d.r. after Wittig olefination (**Figure 23**). *E*- and *Z*-isomers were readily separated by a single round of flash chromatography, a necessary evil since the *cis*-thioesters were known[65] to react giving the opposite sense of enantioselectivity relative to the corresponding *cis*-isomers.

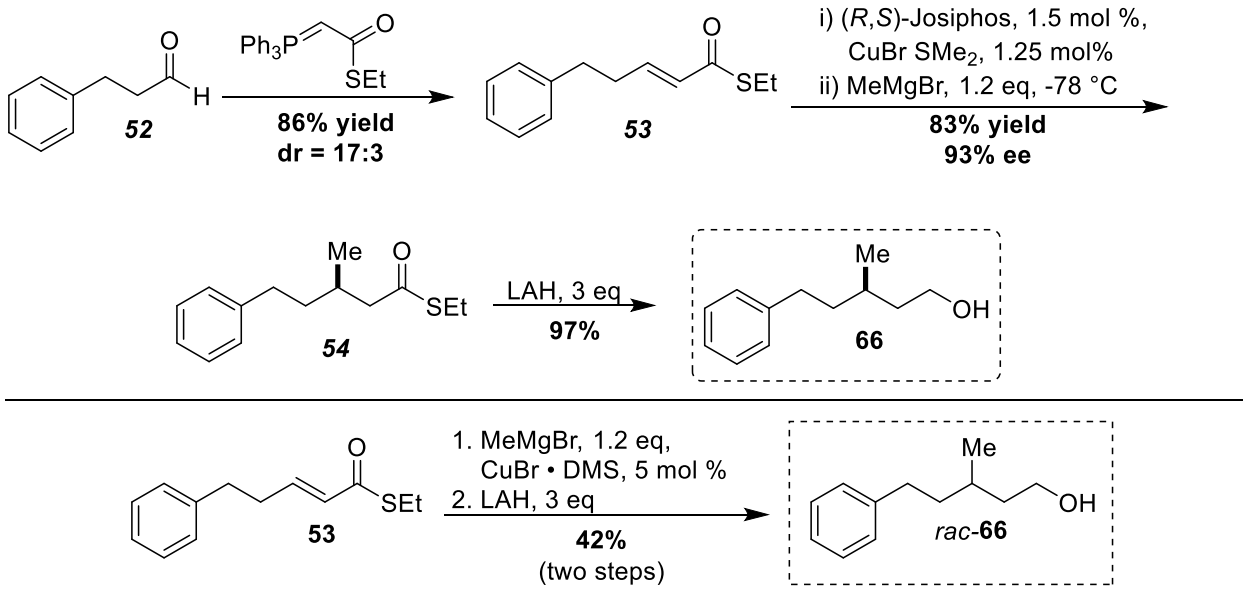


Figure 23. Synthesis of thioester and first asymmetric conjugate addition; synthesis of alcohol derivatives for HPLC analysis.

To our great delight, slow addition of **53** to 1.2 equivalents of methylmagnesium bromide, 1.5 mol % (*R*,*S*)-Josiphos and 1.25 mol % CuBr-DMS over two hours at low temperature, followed by stirring overnight gave methylated product **54** in 83% yield and 93% ee. Enantiomeric excess was determined by reduction to known (*R*)-3-methyl-5-phenylpentanol **66** with LAH; comparison

with racemic **66** generated in two steps from **53** showed an e.r. of 96.5 : 3.5 by chiral-phase HPLC analysis under known conditions[66].

With an effective approach to the first stereocenter in hand, we attempted the homologation of **54** in preparation for a second round of asymmetric conjugate addition. Reduction of **54** with DIBAL-H initially proved challenging, not due to a tendency to overreduction as might be expected by analogy to the reduction of esters, but rather due to the opposite problem: a complete lack of reactivity (**Figure 24**). When DIBAL-H in THF was employed, the reaction failed to go to completion even when excess reagent and long reaction times were employed.

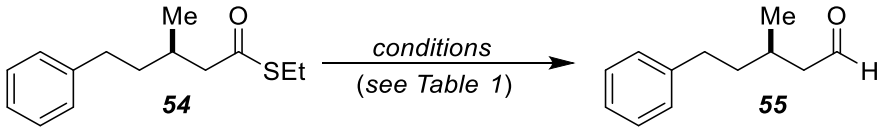


Figure 24. Attempted reduction of thioester **54**.

Table 1. Conditions attempted for the reduction of **54**; N.R. = no reaction.

Reagents	Solvent	Temperature	Time	Result
DIBAL-H, 1.05 eq	THF	-65 °C	5 h	N.R.
DIBAL-H, 1.05 eq	THF	-78 °C to -10 °C	60 h	N.R.
DIBAL-H, 3.00 eq	THF	-78 °C to r.t.	12 h	N.R.
DIBAL-H, 1.05 eq	DCM	-65 °C	40 min	>99% of **55**

Eventually, a renewed survey of the literature revealed that these reactions have only been reported in non-coordinating solvents, with DCM and toluene being predominant[67]. Gratifyingly, when the reaction was repeated with 1.05 equivalents of DIBAL-H in DCM, aldehyde **55** was obtained in near-quantitative yield in less than one hour.

With reliable access to **55** in hand, we next attempted conversion to **56** by Wittig olefination. This transformation also proved challenging, with conditions successfully employed previously on hydrocinnamaldehyde giving rise to unacceptably-long reaction times for **55** (**Figure 25**). While the reason for this behavior remains unclear, it is possible that the added steric bulk of **55**'s additional methyl group relative to **52** was enough to slow the reaction considerably.

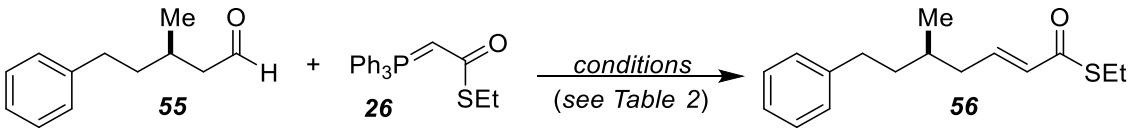


Figure 25. Attempted olefination of **55**.

Table 2. Conditions for attempted olefination of **55**.

Amount of 26	Solvent	Concentration (55)	Temperature	Time	Yield
1.3 eq	DCM	0.3 M	r.t.	36 h	66%
1.3 eq	DCM	0.3 M	reflux	108 h	79%
2.0 eq	DCM	0.1 M	reflux	26 h	67%
2.0 eq	DCM	0.4 M	reflux	26 h	87%
2.0 eq	$CHCl_3$	0.1 M	reflux	2 h	87%

In practice, while temperature, concentration, and the number of equivalents of ylide all influenced the reaction kinetics in predictable ways, it was ultimately found that conversion to **56** was best effected with two equivalents of ylide at reflux in chloroform. Under these conditions, **56** could be isolated in 87% yield after only two hours (**Table 2**). Presumably, the reaction could be further accelerated by increasing the reaction concentration; however, this line of investigation was not pursued further. The diastereoselectivity of the reaction was measured to be 17:1 by ^{1}H NMR analysis of the crude material; once again, a single iteration of flash chromatography was sufficient to readily separate E- and Z-isomers.

Second methylation and confirmation of stereochemistry

With homologated thioester **56** in hand, the stage was set for the second asymmetric conjugate addition and installation of the second methyl-bearing stereocenter. Treatment of **56** with methylmagnesium bromide, CuBr-DMS and (*S*,*R*)-Josiphos under Feringa's conditions gave dimethyl thioester **57** in excellent yield and appreciable diastereoselectivity. Subsequent reduction gave aldehyde **67** in excellent yield, and a final Wittig homologation with $Ph_3P{=}CH_2$ proceeded

accordingly to give terminal olefin **68**, thus installing the final carbon in the nine-carbon backbone of the RHS (**Figure 27**).

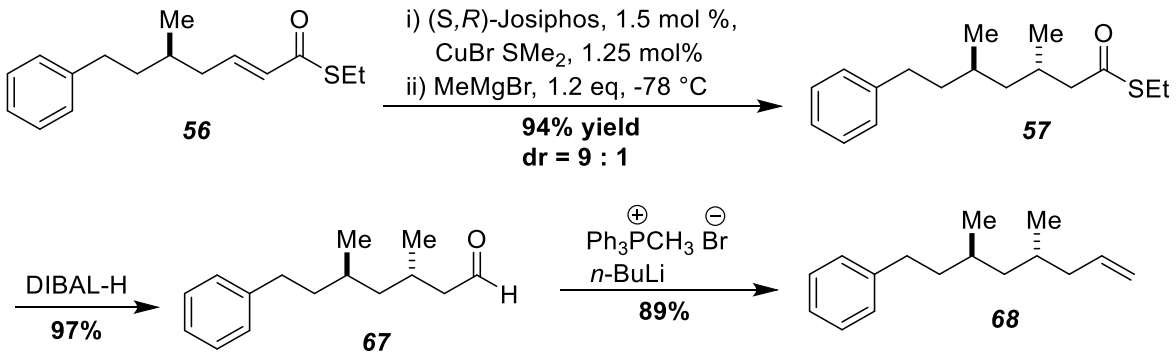
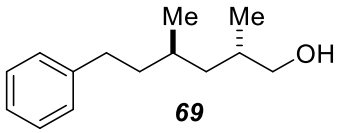


Figure 27. Second methylation and synthesis of terminal olefin **68**.

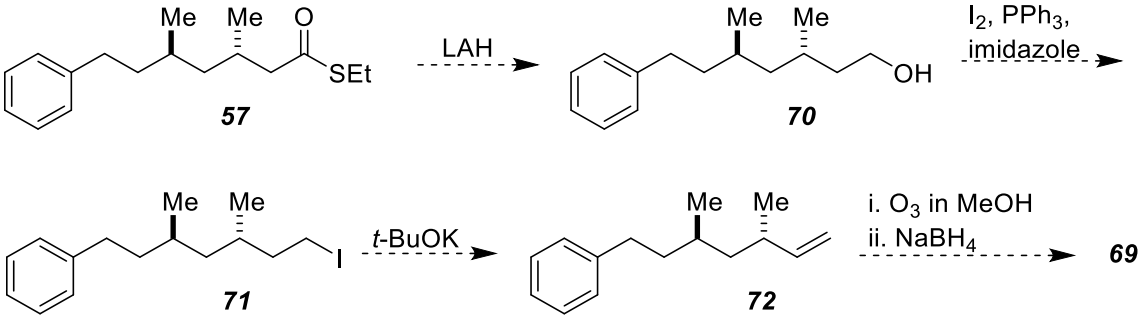
With the installation of the second methyl-bearing stereocenter, it became necessary once again to determine whether we had succeeded in accessing the correct stereoisomer of our desired intermediates. While the sense of the first asymmetric conjugate addition was efficiently confirmed by conversion to a known compound in a single step, such a strategy seemed less appealing for more advanced intermediate **57**. In fact, according to a literature search done at the time, the known structure most closely related to **57** was **69** (**Figure 28**), synthesized by Breit and coworkers in the course of their own efforts toward polydeoxypropionates[31]. While conversion of **57** to **69** was deemed possible (**Figure 28**), it would certainly have constituted an inconvenient detour, one which we were reluctant to take if it was unnecessary. Accordingly, we sought a more general means of investigating the stereochemistry of our growing polydeoxypropionate scaffold.

Breit and coworkers, in addition to their own synthetic work on such substrates, noted an interesting phenomenon in the ^{1}H NMR spectra of the polydeoxypropionates[68-69]. Breit's work exploits the fact that the magnetic environment of methylenes separating aliphatic stereocenters in



69

OL **2009**, *11*, 4668.



57 ***70*** ***71*** ***72***

Figure 28. Imagined conversion of **57** into known compound **69**.

deoxypropionates is primarily dependent on the relative configuration of those stereocenters. The result of this is a set of empirical rules that can provide strong evidence for the configuration of deoxypropionates moieties based on the difference in chemical shift between the diastereotopic protons on the intervening methylene in deoxygenated stereodiads (**Figure 29**).

If R = R'	H_a and H_b are enantiotopic and indistinguishable by NMR	H_a and H_b are diastereotopic and potentially distinguishable by NMR
If R ≠ R'	H_a and H_b are *pseudo* enantiotopic Thus, $\lvert\sigma_a - \sigma_b\rvert$ *relatively* small	H_a and H_b are diastereotopic Thus, $\lvert\sigma_a - \sigma_b\rvert$ *relatively* large.

Figure 29. Symmetry observations allowing the development of Breit's empirical rules.

Breit has shown that, for a series of over 70 compounds containing 1,3-dimethyl stereodiads, the compounds were always *syn* when the difference in chemical shift between the diastereotopic protons on the intervening methylene was greater than 0.40 ppm, and the compounds were always *anti* when the difference was less than 0.15 ppm[69]. While not providing

strict "proof" of stereochemistry without the synthesis of both the *syn* and *anti* diastereomers, in conjunction with the presumption of stereochemical outcome provided by Feringa's work, Breit's rules could give strong evidence that we had in fact obtained **57** rather than its *syn*-epimer.

In the event, assignment of the signals in the ^{1}H NMR spectrum of **57** by HSQC analysis showed that the diastereotopic protons on the methylene intervening between the methyl-bearing stereocenters differed in chemical shift by a mere 0.10 ppm (**Figure 30**), thus conclusively falling within the trends established by Breit's rule for *anti*-methyl stereodiads. With our confidence in the stereochemical assignment of **57** thus re-affirmed, we turned our attention to other synthetic problems.

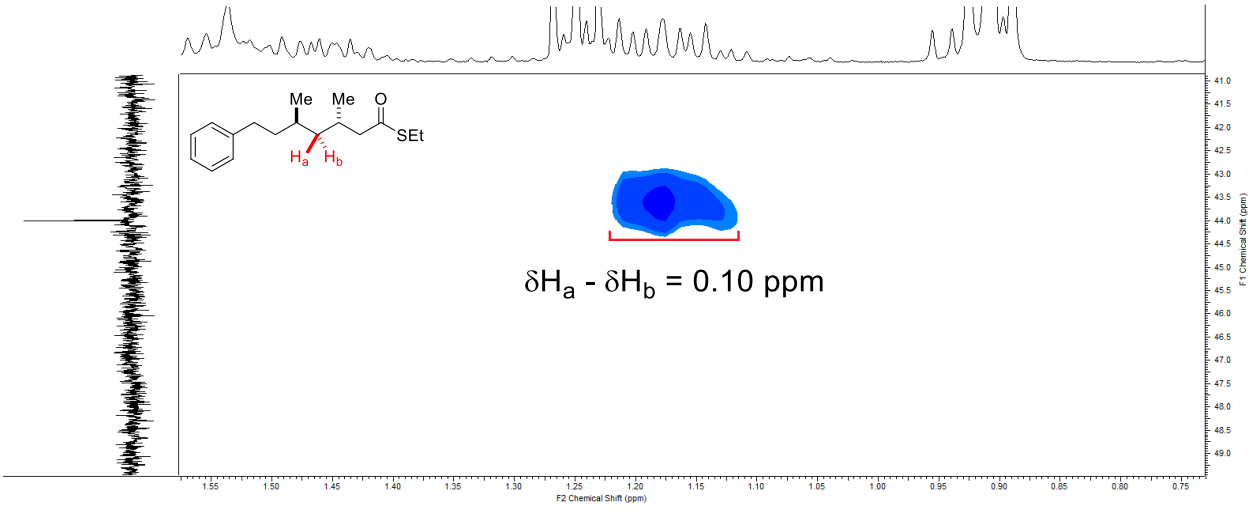


Figure 30. Application of Breit's rule to **57**, showing diastereotopic protons less than 0.10 ppm apart.

When aldehyde **67** first became available from thioester **57**, an interim of several days passed before the subsequent olefination could be effected. In this way it became apparent that **67** was rather unstable, even when rigorously pure and stored under inert atmosphere in the cold. While we at first imagined that **67** was perhaps suffering autooxidation or self-condensation, the former hypothesis did not match the chromatographic characteristics of the single impurity we observed: the contaminant eluted faster than **67** under normal-phase conditions, seemingly

inconsistent with oxygen incorporation. Moreover, the IR spectrum of the unknown material was devoid of any sign of a carbonyl resonance, and the material itself was inert to reduction with borane in THF. At the same time, the ^{1}H NMR spectrum of the isolated impurity was inconsistent with self-condensation, and was indeed strikingly similar to the spectrum of **67** itself, with the exception of the loss of the aldehyde signal and the appearance of a new signal integrating to 1H at 4.94 ppm in $CDCl_3$.

After much thought, it was considered that the NMR spectra and chromatographic behavior of this decomposed material were consistent with structure **73**, formed from the spontaneous trimerization of **67** to give a substituted 1,3,5-trioxane (**Figure 31**). The spontaneous trimerization of aldehydes is well-known[70-71] and has been identified as a mechanism of undesired spontaneous decomposition even in long-chain aldehydes[72]. Our suspicions were confirmed when refluxing the unknown contaminant in 1:1 THF / 6 N HCl overnight regenerated monomeric aldehyde **67**, albeit with concomitant partial decomposition.

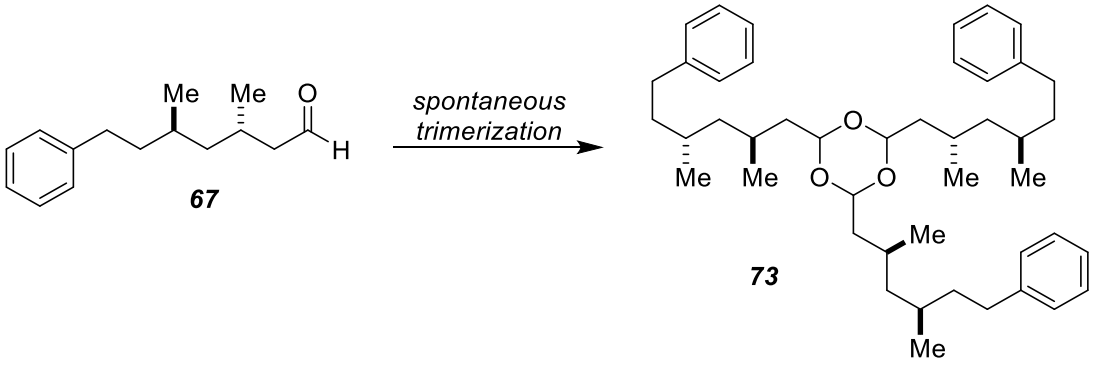


Figure 31. Spontaneous decomposition of aldehyde **67** by trimerization.

Armed with the knowledge that **67** was subject to a thermodynamically-favored decomposition on relatively short timescales, we elected to eschew storing this material, instead generally converting it to **68** in its entirety immediately after synthesis. This knowledge would

inform our ideas about the storage of other key aldehydes in the baulamycin synthesis, as will be seen later.

With an adequate supply of olefin **68**, we turned our attention to the necessary installation of the first terminal oxygen in the RHS scaffold. Hydroboration-oxidation appeared to be the obvious choice, and our efforts commenced with 9-BBN as the borylating reagent (**Figure 32**).

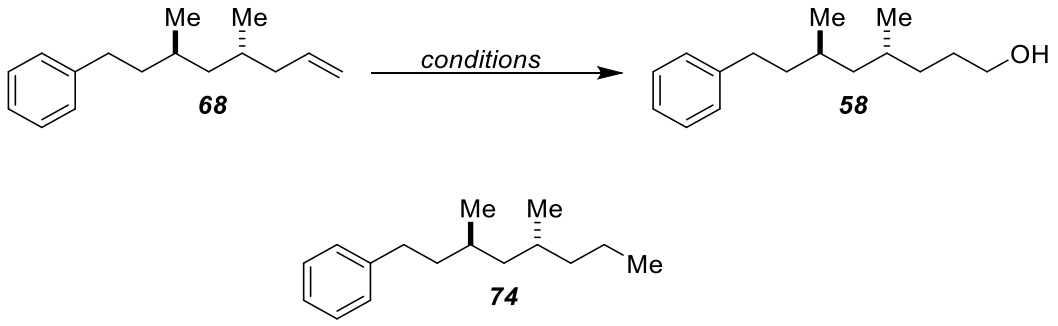


Figure 32. Attempted hydroboration-oxidation of olefin **68**.

Table 3. Conditions surveyed in attempted hydroboration-oxidation of **68**.

Conditions	Result (% yield)
9-BBN, THF, r.t., then NaOH	inconclusive: product not fully separated from 1,5-octanediol after chromatography
BH_3-THF, THF, r.t., then NaOH	**58** (56%), **74** (32%)
disiamyl borane,	**58** (83%)

Hydroboration with 9-BBN appeared to give **58** with good regioselectivity by ^{1}H NMR analysis of the crude product; however, chromatographic purification gave material still contaminated with what appeared to be residual 1,5-cyclooctandiol (this diol has been reported to be soluble in water[73], but see[74]). Rather than optimize purification conditions, we chose to test other borylating agents in the hopes of avoiding the issue entirely. Borane in THF, despite exhibiting a surprising degree of regioselectivity (only a single regioisomer could be isolated), proved unsuitable due to the formation of substantial amounts of alkane **74**, an outcome we could only assume to be the result of competing protodeboronation during the oxidation step. Finally, it

was determined that disiamylborane, generated *in situ* from BH_3-THF and 2-methyl-2-butene, provided optimal results, giving **58** in 83% yield as a single regioisomer.

With **58** in hand, we turned our attention to the next synthetic hurdle: the unmasking of the latent carboxylic acid represented by the phenyl moiety of **58**. Our plan had been to avail ourselves of Sharpless' well-known conditions[75] for the RuO_4-catalyzed oxidation of arenes; however, before we could attempt this transformation, we needed to find a suitable protecting group for the primary alcohol of **58**.

Secondary TBS ethers are well known[76-79] to survive the RuO_4-catalyzed oxidation of unactivated phenyl moieties to carboxylic acids, and Schreiber notes good stability of a primary TBS ether during the RuO_4 oxidation of an alcohol[80]. Thus, considering the many advantages of silyl protecting groups in general, we first attempted protection of **58** as the TBS ether (**Figure 33**). Silylation proceeded as expected, giving TBS-ether **75** in 75% unoptimized yield; however, ruthenium(VIII) oxide oxidation under Sharpless' conditions failed to give any of protected acid **76**.

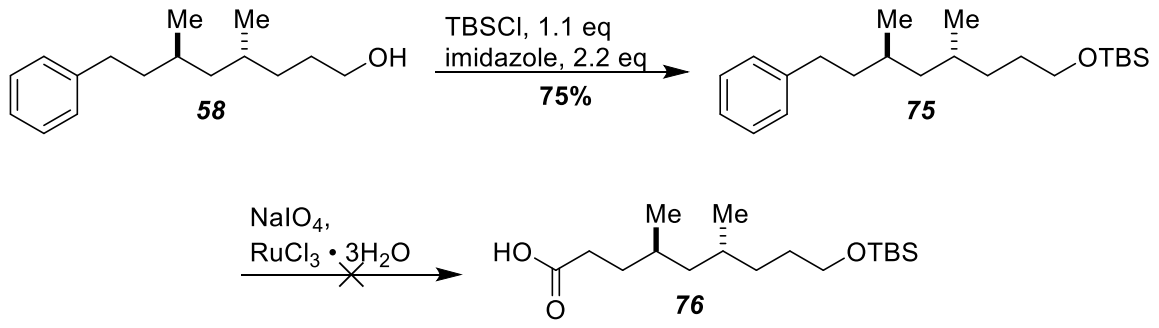


Figure 33. Attempted protection of alcohol **58** as *tert*-butyldimethylsilyl ether **75**.

Since ruthenium tetroxide oxidations have been reported to be relatively sensitive to steric factors, we next toyed with the idea of employing a more sterically demanding silyl protecting group[76]. With this in mind, we considered the use of a *tert*-butyldiphenylsilyl ether. Although the TBDPS group itself contains unsaturated moieties, it has been known[81-82] to survive the ruthenium

tetroxide oxidation of other arenes (albeit only that of electron-rich arenes), and it was hoped that its extensive bulk would provide additional protection for the masked alcohol. In retrospect, it seems clear that this line of thinking probably ascribes too great a significance to the role that sterics play in determining the outcome of complex ruthenium tetroxide oxidations. In any event, silylation with TBDPSCl proceeded uneventfully, but subjection of the resulting silyl ether to oxidation gave none of the desired acid (**Figure 34**).

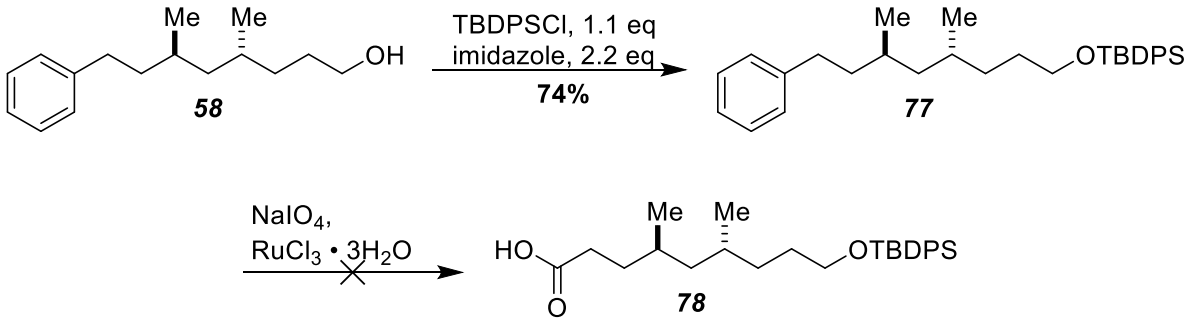


Figure 34. Attempted oxidation of TBDPS-protected **58**.

With several attempts at oxidation of our advanced substrate having met with failure, the decision was made to continue our studies on more readily-accessible model systems rather than continue to deplete our stock of **58**. Accordingly, several test substrates were prepared in order to investigate different aspects of the problem at hand.

TBS-protected 4-phenylbutanol **80** was prepared under standard conditions and subjected to ruthenium tetroxide oxidation (**Figure 35**). It was hoped that careful analysis of the products obtained might shed light on the mechanism of failure in our previous silyl-protected oxidations. In particular, we speculated that failure to this point might have been caused by overoxidation, specifically oxidation of the "protected" alcohol moiety. Indeed, when **80** was subjected to ruthenium-tetroxide catalyzed oxidation, we obtained glutaric acid (**82)** as the sole product, isolated from the aqueous phase in 80% yield.

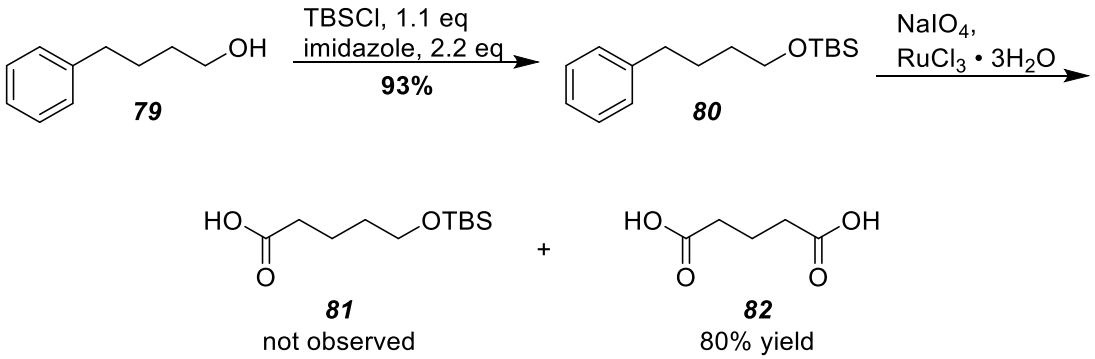


Figure 35. Attempted oxidation of *tert*-butyldimethyl(4-phenylbutoxy)silane.

With strong evidence that our difficulties did indeed stem from adventitious oxidation of the silyl ether (rather than, say, incomplete oxidation of the phenyl moiety or oxidation at a methine position – another known[76] reaction of ruthenium tetroxide systems), a possible mechanism for this process suggested itself.

The RuO_4-catalyzed oxidation of ethers to esters is well-known[83], and proceeds preferentially to the oxidation of unactivated aromatics[75, 84]. In light of the neutral conditions of our oxidation, it seems plausible that, rather than undergoing solvolysis, primary silyl ethers instead suffer oxidation to the corresponding silyl esters in the presence of ruthenium tetroxide (**Figure 36**). These presumably-unstable[85-86] silyl esters might then suffer spontaneous hydrolysis[87] under the conditions of the reaction, giving the corresponding diacid.

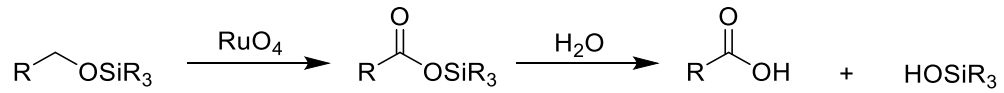


Figure 36. Proposed mechanism for the oxidative decomposition of primary silyl ethers by RuO_4.

Conversely – and oddly – it has been reported that simple sodium periodate alone, in THF/water[88] or heterogeneously in THF[89-90], is capable of rapidly deprotecting a variety of silyl ethers (including secondary TBS ethers) in excellent yields at room temperature. How this observation can co-exist with the well-established stability of secondary TBS ethers to Sharpless' conditions remains a mystery. The idea that perhaps sodium periodate, soluble in water, remains

largely sequestered from the organic substrate in Sharpless' biphasic CCl_4/ACN/H_2O solvent system comes to mind as one of few possible explanations. Given that Sharpless notes Oxone as a viable, although less active, alternative to $NaIO_4$ in catalytic RuO_4 oxidations, one cannot help but wonder whether such a system might give better results for silylated substrates.

Regardless of the mechanism of overoxidation, it seemed clear that further optimization of a silyl-protection strategy was unlikely to see success. Several alternate avenues presented themselves. One the one hand, we considered pursuing an early oxidation of the alcohol followed by protection as the acetal (**Figure 37**).

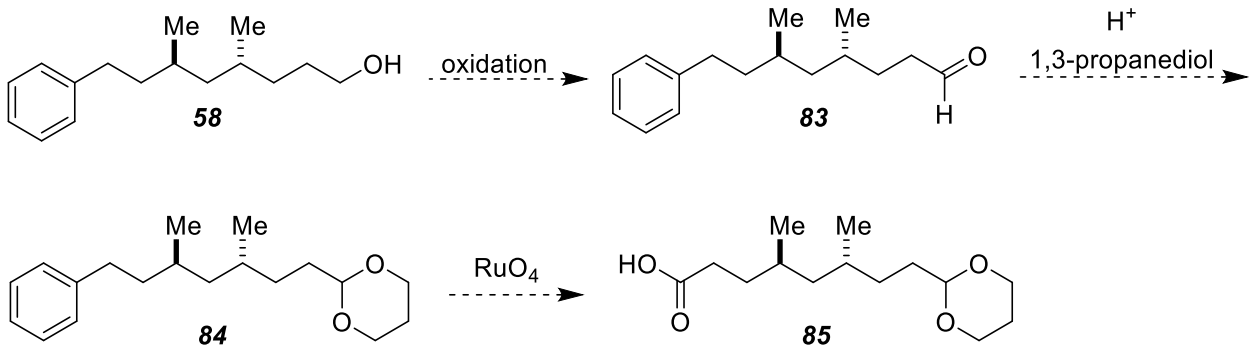


Figure 37. Imagined oxidation and protection of **58** as the cyclic acetal **84**.

Accordingly, acetal-protected hydrocinnamaldehyde was subjected to ruthenium tetroxide oxidation conditions (**Figure 38**). Desired acid **87** could not be isolated; however, overoxidation product succinic acid (**88**) was obtained in 48% yield.

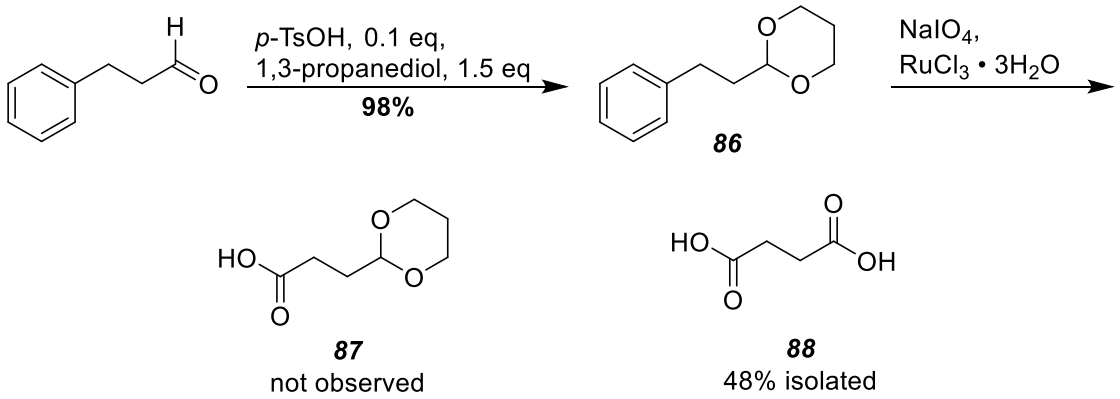


Figure 38. Attempted oxidation of acetal **86** with ruthenium tetroxide.

Previous work[44, 75] has shown that esters fare well as protecting groups for primary alcohols during the oxidation of phenyl moieties. Initially, we had been reluctant to employ an ester as protection for **58** since we believed that most esters would be incompatible with the strongly-basic conditions proposed for the installation of the third methyl stereocenter (**Figure 21**). On the other hand, we reasoned that a carbonate ester, without acidic protons, would be well-suited to survive both ruthenium tetroxide as well as strong, but non-nucleophilic, base.

Methyl carbonates, a relatively underutilized protecting group, are nonetheless well-documented in the literature[85]. With typical removal effected by catalytic base in protic solvent, we were concerned that removal of such a protecting group might prove intractable without concomitant epimerization of the third stereocenter, adjacent to what we hoped would be the Weinreb amide of **37**. Nonetheless, with few other obvious options for protection of **58** remaining, we attempted an ester-based protection strategy.

Preparation of 4-phenylbutyl acetate **89** proceeded as expected under standard conditions (**Figure 39**). Pleasingly, when **89** was subjected to ruthenium tetroxide oxidation, the desired protected acid **81** was isolated as the sole product. Emboldened by the success of the acetate, we turned our attention to modeling our proposed methyl carbonate protection strategy.

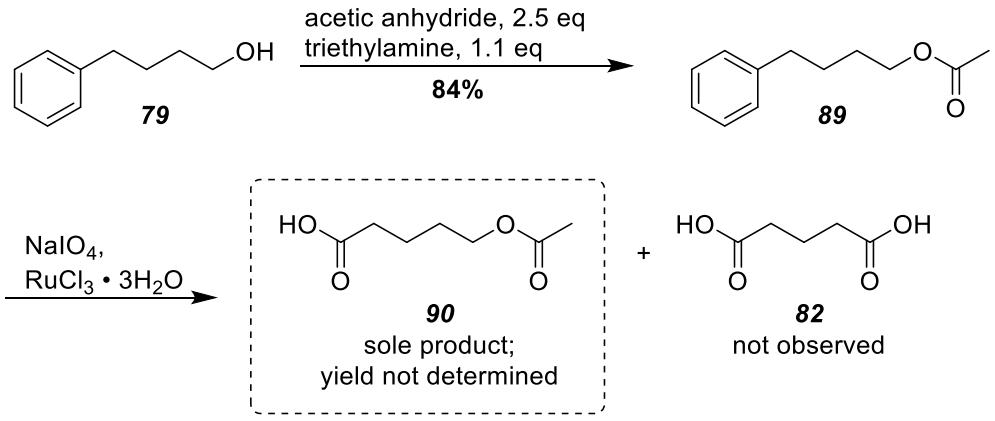


Figure 39. Synthesis and controlled oxidation of 4-phenylbutyl acetate with RuO_4.

Installation of the carbonate proceeded uneventfully (**Figure 40**) in good yield. To our delight, upon subjection of **79** to Sharpless' conditions, we obtained protected carboxylic acid **92** as the sole product of the reaction.

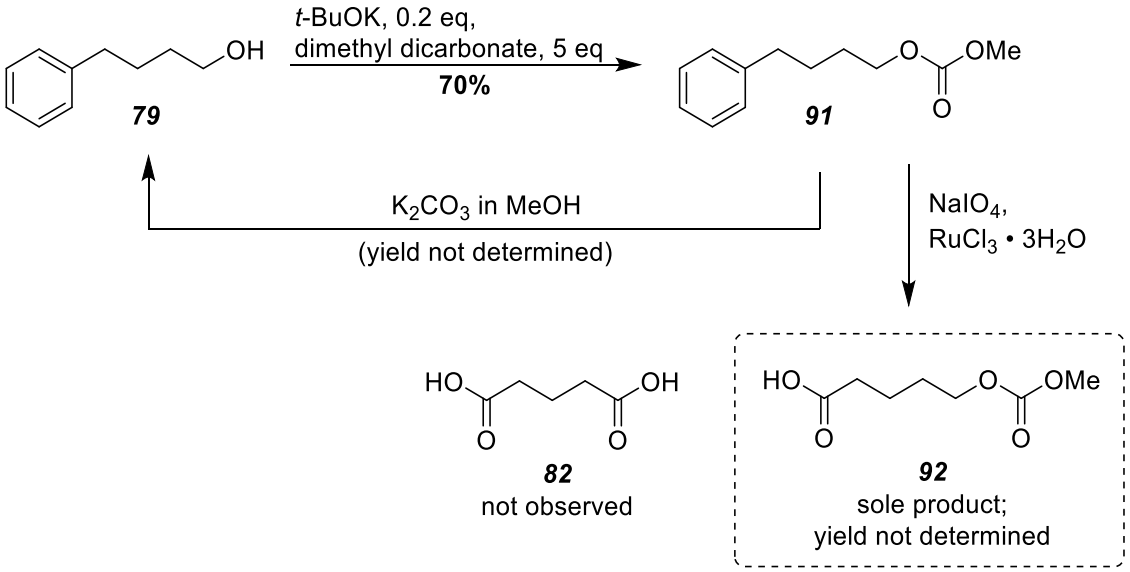


Figure 40. Synthesis and controlled oxidation of methyl (4-phenylbutyl)carbonate **91**.

Trial deprotection with potassium carbonate in methanol also proceeded efficiently as previously reported[91], thus cementing methyl carbonate as the promising option for protection of **58**.

Setting about to implement our previous findings, we commenced with the carbonate protection of **58**. In the event, conditions which had been successful on **79** proved sluggish when applied to **58**; however, a brief screen for suitable conditions soon yielded success and the carbonate was successfully installed in good yield (**Figure 41**).

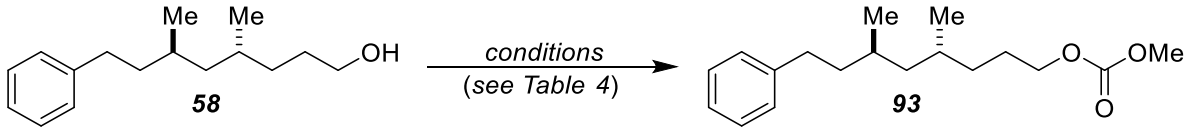


Figure 41. Attempted methyl carbonate protection of alcohol **58**.

Table 4. Conditions attempted for protection of **58**. N.R.= no reaction; temp. = temperature.

Reagents	**Solvent**	**Temp.**	**Time**	**Result** (% yield)
t-BuOK, 0.20 eq; dimethyl dicarbonate, 5.0 eq	THF	r.t.	24 h	N.R.
t-BuOK, 0.20 eq; dimethyl dicarbonate, 5.0 eq	THF	reflux	12 h	N.R.
methyl chloroformate, 2.95 eq	DCM	r.t.	10 h	N.R.
pyridine, 43 eq; methyl chloroformate, 45 eq	DCM	r.t.	12 h	**93** (71%)
methyl chloroformate, 1.3 eq; DMAP, 2 mol %; pyridine, 1.3 eq	DCM	r.t.	4 h	**93** (87%)

Gratifyingly, when methyl carbonate **93** was subjected to ruthenium tetroxide oxidation under Sharpless' conditions, desired acid product **94** was obtained in acceptable 52% yield, or 61% based on recovered starting material (**Figure 42**). Benzyl ketone **95** was also isolated in 9.2% yield as a minor byproduct from benzylic oxidation.

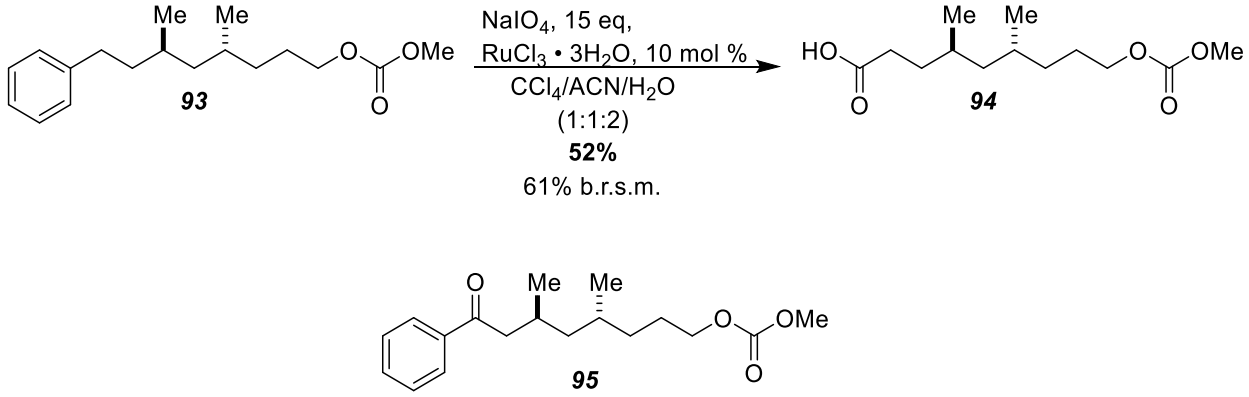


Figure 42. Oxidation of methyl carbonate **93** with ruthenium tetroxide.

With a suitable strategy for the oxidation of **58** finally in place, we turned our attention to the installation of an appropriate chiral auxiliary to direct the installation of the final methyl-bearing stereocenter. While several[92-94] strategies for auxiliary-controlled alkylations are known, we settled on an Evans-style oxazolidinone primarily for its supreme ease of installation and removal, coupled with its satisfactory diastereoselectivity. Pleasingly, amide coupling of **94** with commercially-available (*R*)-4-phenyloxazolidinone oxazolidinone under standard conditions[95] gave *N*-acyl oxazolidinone **97** in good yield (**Figure 43**). Alkylation of the sodium enolate of **97**

at low temperature with methyl iodide gave **98** as a single detectable diastereomer, and removal of the chiral auxiliary was effected under Evans' conditions[96].

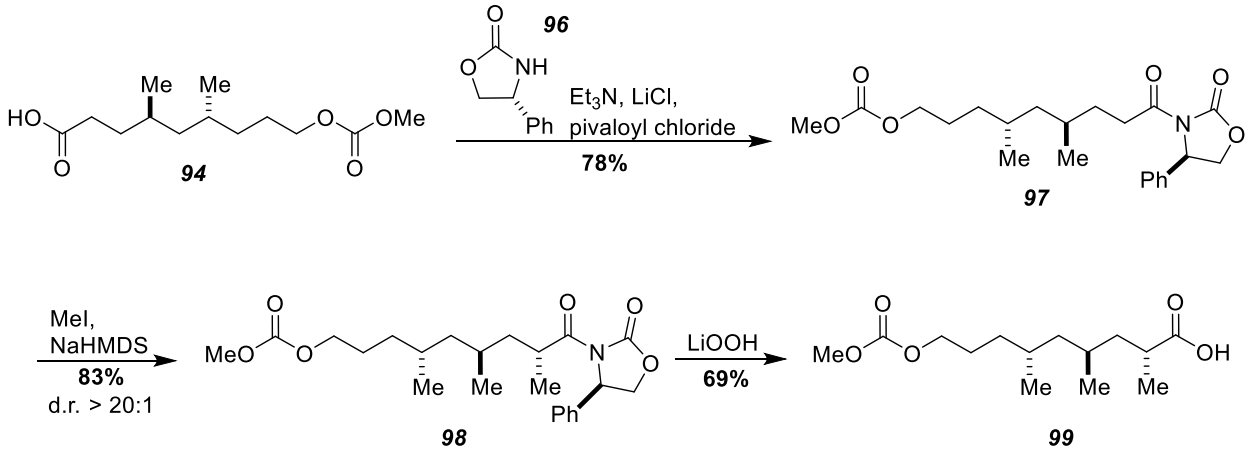


Figure 43. Installation of the chiral auxiliary, methylation and auxiliary removal.

Assignment of the signals in the ^{1}H NMR spectrum of **98** by HSQC showed that the diastereotopic protons on the methylene β to the exocyclic carbonyl exhibit a chemical shift difference of 0.29 ppm (**Figure 44**). This value is inconclusive for the general formulation of Breit's rule in the sense that, according to Breit's most general formulation, a *syn*-configuration could not be ruled out. However, Breit has also identified a rule specific to stereodiads in which one methyl is adjacent to carbonyl functionality[69].

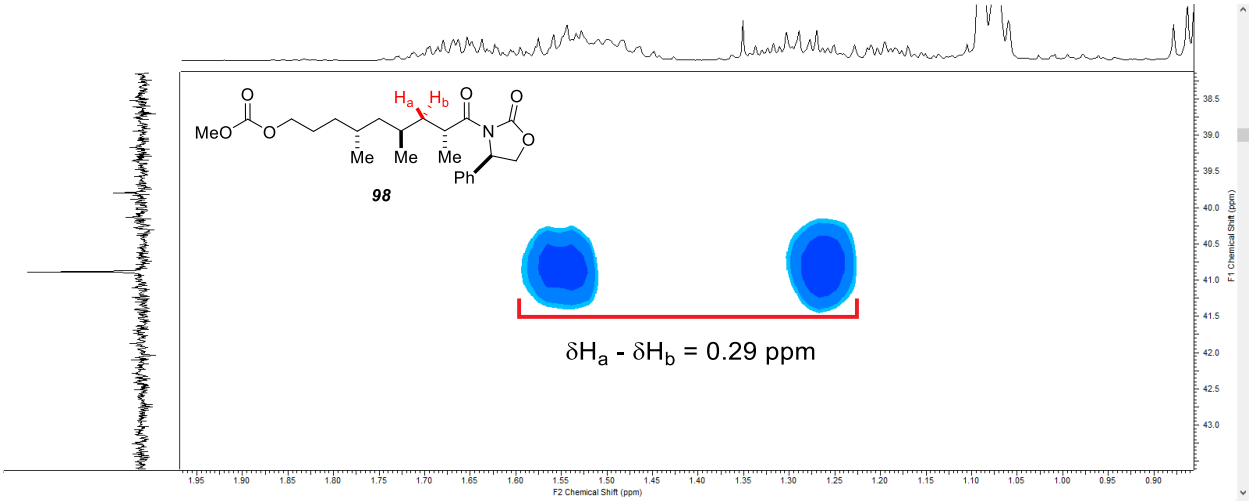


Figure 44. Chemical shifts for diastereotopic protons at the β-position of *N*-acyloxazolidinone **98**.

Using this more restricted subset of the large database from which the general rule is drawn, we see that such compounds are always *syn* when the chemical shift difference for the diastereotopic protons on the intervening methylene is larger than 0.5 ppm, and always *anti*-when the chemical shift difference is less than 0.45 ppm. While again not providing absolute proof of stereochemistry, this variant of Breit's rule, combined with the known, highly reliable stereochemical outcome of the Evans alkylation, provided strong evidence that the methylation had proceeded with the desired sense of stereoinduction to give **98** rather than its *anti*/*syn*-epimer.

With the third methyl-bearing stereocenter in place, and an effective strategy for the removal of the Evans-type chiral auxiliary in play, completion of the remainder of the RHS synthesis proceeded smoothly. PyBOP-mediated coupling of **99** with *N*,*O*-dimethylhydroxylamine hydrochloride provided Weinreb amide **100**, and removal of the methyl carbonate proceeded uneventfully under basic conditions in methanol to give **101** (**Figure 45**). Finally, oxidation under Swern's conditions gave ultimate RHS intermediate **38** in 60% unoptimized yield on a small scale.

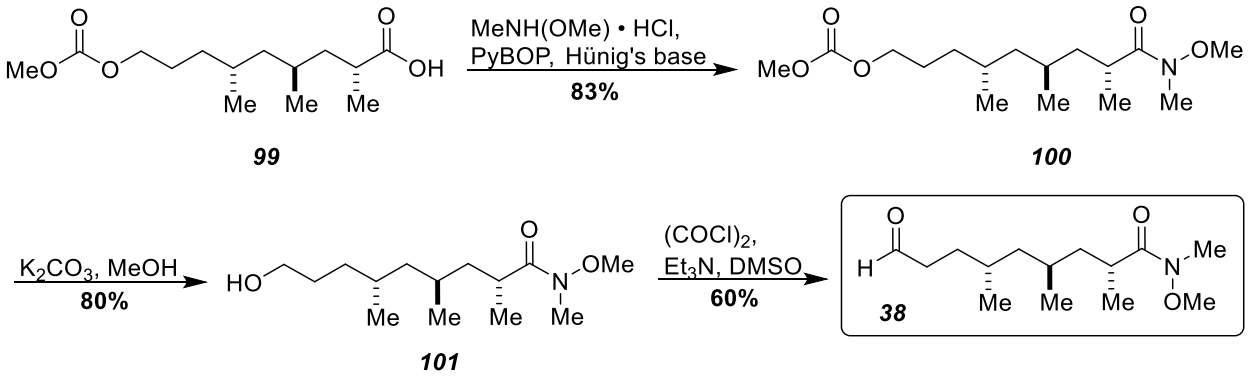


Figure 45. Completion of the synthesis of RHS aldehyde **38**.

While **38** was isolable and appropriate analytical data for it could indeed be obtained, **38**, like aldehyde **67** before it, proved generally unstable. Unlike **67**, **38** did not (at least in our observation) seem particularly susceptible to trimerization. Instead, **38** appeared to exhibit an exquisite sensitivity to oxidation, giving polar decomposition products even on short timescales.

This decomposition pathway appeared particularly rapid in solution, necessitating short reaction times and expeditious workups to obtain good yields. However, **38** was also resistant to storage, and appeared to suffer oxidation even when stored cold in seemingly oxygen-free environments. Thus, while the small-scale (~10 mg) oxidation of **101** provided an important benchmark, demonstrating that **38** was indeed accessible by our newly-developed route, we elected to store the remainder of our material as **101** rather than attempt to identify conditions for the storage of **38**. The successful oxidation of **101** thus marked the conclusion of our synthesis of the RHS of the proposed structure, with **38** obtained in 3% overall yield from hydrocinnamaldehyde. While prepared to pursue further optimization of this route should the need arise, at this point we turned our attentions to the completion of the LHS.

2.3 Synthesis of the Left-Hand Side

While development on the right-hand side progressed, work on the left-hand side of the baulamycin scaffold was in full swing as well. With our aldol-based proposed strategy (**Figure 12**) in mind, the first task in hand was to decide on a protecting group strategy for the LHS phenols. Judicious choice of these protecting groups was particularly important, given that they would be required to survive from the first step of the synthesis to the final global deprotection giving rise to the natural products. Accordingly, we hoped for protecting groups that would be (1) stable to a wide variety of conditions, while also (2) being relatively easy to remove. Finally, we hoped to maintain orthogonality to the silyl ethers, as it was imagined that at least one of the alcohols on the LHS might be protected by silylation and that differential deprotection might be required. Methyl ethers, although consummately stable, were ruled unsuitable according to criterion 2, as conditions for the cleavage of phenoxymethyl ethers remain relatively harsh. Similarly, silyl ethers were viewed as a suboptimal solution, since stability during the removal of other silyl protecting

groups later in the synthesis might have required extensive optimization. Benzylation, while otherwise attractive, appeared a risky choice in light of the native benzylic alcohol at C-1'; we feared that debenzylation might proceed with concomitant reduction at C-1'. Protecting groups susceptible to hydride reduction or nucleophilic attack were unsuitable due to the proposed late stage reduction of a carbonyl at C-13 as well as the late-stage installation of the C-3 ketone by Weinreb ketone synthesis, ruling out carbonates, esters, and similar moieties. Allyl ethers were considered; however, our desire to effect a global deprotection in the final step of the synthesis using uniform, simple conditions led us to look elsewhere, as we believed that removal of allyl ethers would probably require a catalytic isomerization best effected as a separate step.

Ultimately, given our desire to reserve silyl ethers for elsewhere on the baulamycin scaffold, a mixed acetal such as a methoxymethyl ether seemed like the most attractive candidate for protection of the LHS phenols. Methoxymethyl ethers, stable to base, nucleophilic attack, hydrogenation and many sources of fluoride ion, are ideal in that they nonetheless succumb to protic acids under mild conditions. They thus appeared to perfectly suit our goal of a simple, global deprotection, while hopefully maintaining adequate stability through the rest of the route.

Accordingly, we begin our synthesis of the left-hand side of the baulamycins with a screen of routes towards MOM-protected 3,5-dihydroxybenzaldehyde **104** (**Figure 46**).

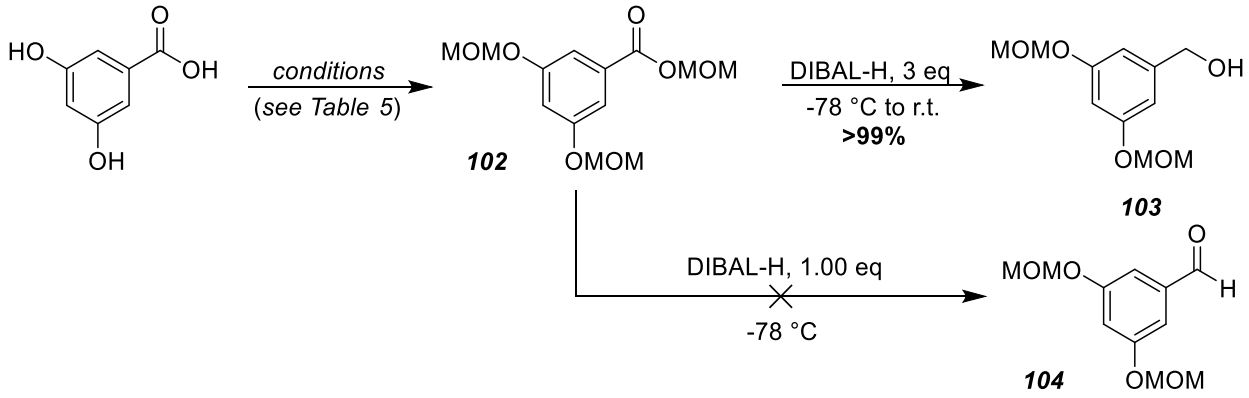


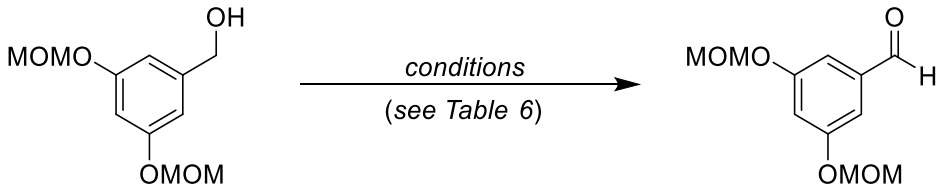
Figure 46. MOM-protection of 3,5-dihydroxybenzoic acid and subsequent reduction with DIBAL.

Table 5. Conditions employed for the MOM-protection of 3,5-dihydroxybenzoic acid.

Electrophile	Base	Solvent	Time	Result
MOMCl, 3.00 eq	DIPEA, 3.0 eq	DCM	16 h	23%
MOMCl, 3.00 eq	NaH, 3.0 eq	THF	1 h	30%
MOMCl, 3.00 eq	DIPEA, 6.0 eq	DCM	1 h	46%
MOMCl, 3.05 eq	NaH, 3.65 eq	THF/Et_2O	5 h	74%
MOMCl, 4.00 eq	DIPEA, 6.00 eq	DCM	12 h	80%
MOMCl, 4.50 eq	DIPEA, 6.00 eq	DCM	24 h	90%

An extensive screen of conditions for the MOM-protection of 3,4-dihydroxybenzoic acid with methoxymethyl halides revealed that alkylation with 4.5 eq methoxymethyl chloride in the presence of 6.00 eq Hünig's base gave the exhaustively protected ester **102** in >90% yield. A simple base wash effectively removed all partially-protected contaminants, allowing isolation of pure **102** without chromatographic purification. All attempts to effect the direct reduction of **102** to aldehyde **104** with DIBAL-H were unsuccessful, giving exclusively alcohol **103** in quantitative yields in as little as 5 minutes at -78 °C. Lower temperature reductions were not pursued.

With **103** in hand, a simple screen of oxidation conditions revealed the optimal route to **104** (**Figure 47**). Despite the marginally-higher yield of the Parikh-Doering oxidation, oxidation with activated manganese dioxide became the obvious choice for its supreme operational simplicity: the reaction is run at room temperature, is insensitive to oxygen, and the product can be isolated in relatively pure form by simple filtration through Celite followed by solvent removal.



103 ***104***

Figure 47. Oxidation of benzylic alcohol **103** to aldehyde **104.**

Table 6. Conditions for the oxidation of benzylic alcohol **103** to aldehyde **104**.

Conditions	Yield of 104
SO_3•pyridine, 2.00 eq; DIPEA, 3.50 eq; DCM/DMSO (10:1)	83%
MnO_2, 20 eq; DCM	81%

Despite our development of this efficient route to aldehyde **104**, we nevertheless hoped that we might identify a strategy that would avoid the use of nearly five equivalents of expensive and highly carcinogenic methoxymethyl chloride. We first considered conditions reported[97] to give the methoxymethyl ethers of phenols from 2,2-dimethoxymethane (**Figure 48**); unfortunately, these conditions, which relied on the use of a Soxhlet extractor and molecular sieves to remove methanol from the reaction, did not go to completion on 3,5-dihydroxybenzoic acid. Believing that the low solubility of the bisphenol acid in DCM might be a contributing factor, we prepared methyl 3,5-dihydroxybenzoate (**105**) and subjected it to similar conditions, with the addition of acetonitrile as an additional solubilizing factor; however, these conditions also failed to afford appreciable yields of the protected product.

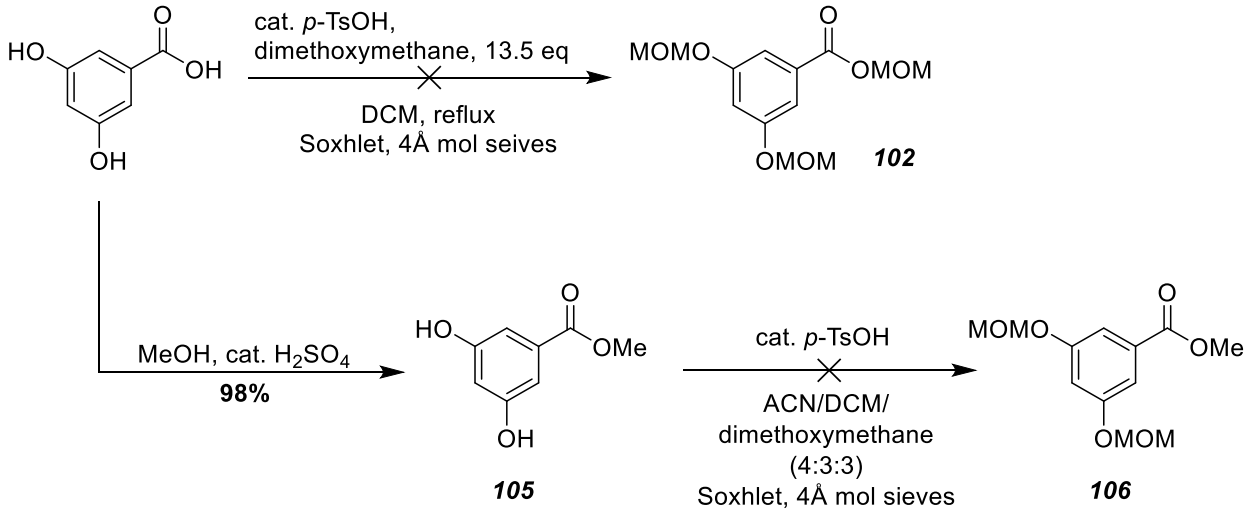


Figure 48. Attempted protection of 3,5-dihydroxybenzoic acid with 2,2-dimethoxymethane.

Undeterred, we considered the possibility that perhaps an alternate order of operations might allow us to access more soluble material, or at least forgo one or more equivalents of methoxymethyl halide. Thus, we envisioned that borane reduction of 3,5-dihydroxybenzoic acid would give **107**, which would then undergo oxidation to 3,5-dihydroxybenzaldehyde **108** (**Figure 49**).

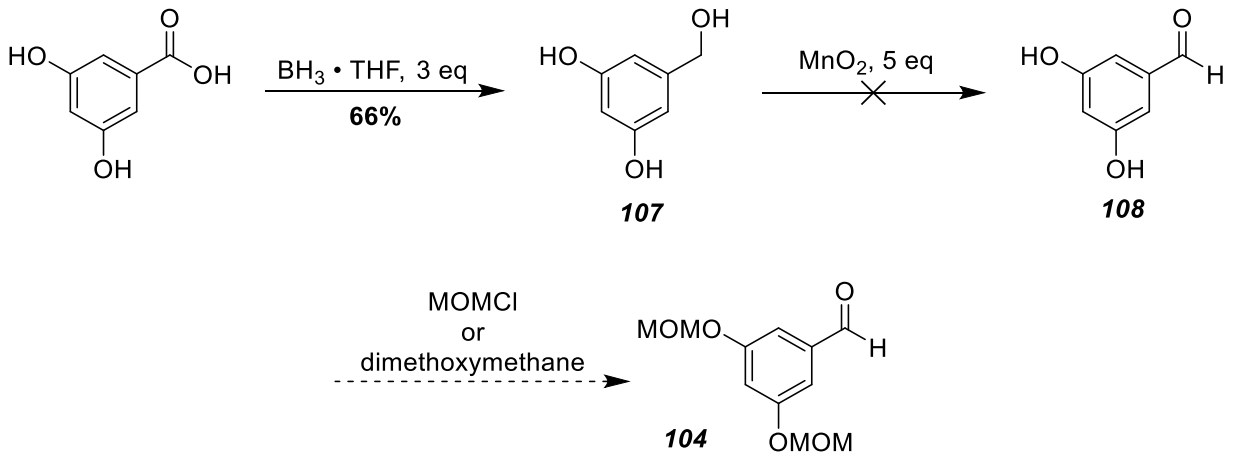


Figure 49. Attempted construction of aldehyde **104** via triol **107**.

The bisphenol could then be protected either (1) with fewer equivalents of methoxymethyl halide, or, ideally, (2) with 2,2-dimethoxymethane under acid-catalyzed conditions. While reduction of 3,5-dihydroxybenoic acid proceeded smoothly, giving triol **107** as a colorless crystalline solid, attempted oxidation of **107** to **108** with MnO_2 gave only extensive decomposition. We later learned that activated manganese dioxide is known to promote the oxidative polymerization of unprotected phenols, most likely via a radical mechanism, suggesting a possible reason for the failure of these conditions[98]. In light of the success of the extant route to **104**, other oxidative conditions were not investigated, and further attempts to optimize the synthesis of **104** were abandoned.

With access to a steady supply of benzaldehyde **104**, we turned our attention to accomplishing the diastereoselective aldol reaction of **104** with some analogue of 4-methylvaleric acid. While a vast number of approaches to the *syn*-aldol reaction have been reported, and have been extensively reviewed[99], Evan's *N*-acyl oxazolidinone-based strategy seemed most appealing, not only for the exquisitely high levels of diastereocontrol afforded (for so-called "Evans *syn*" aldol reactions of boron enolates, often as high as 200:1 d.r.), but also for the remarkably-well documented, mild and varied known methods for auxiliary removal[58].

Pleasingly, enolization of known[100] oxazolidinone **109** – prepared in good yield from commercial material in one step – with dibutylboron triflate in the presence of triethylamine followed by reaction with aldehyde **104** gave *syn*-aldol **110** in excellent yield as a single detectable diastereomer (**Figure 50**). Crucial to the success of this reaction was the use of freshly-prepared (n-Bu)$_2$BOTf, which was prepared according to Evans' modification[101] of Mukaiyama's procedure[102] in good yield from tributylborane and triflic acid. Dibutylboron triflate obtained in this way could be carefully stored in a Schlenk tube for future use; however, no rigorous studies correlating the age of the reagent with its activity were undertaken, and the material was generally used shortly after preparation.

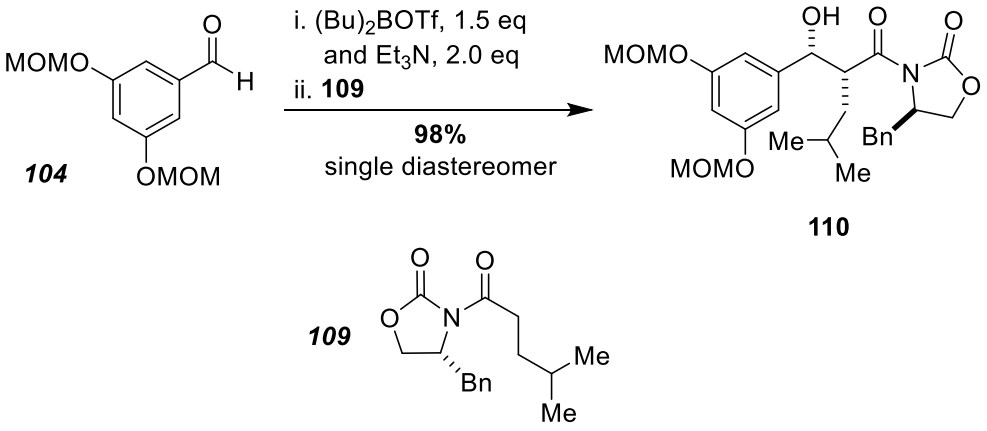


Figure 50. Boron-mediated *syn*-selective aldol reaction between aldehyde **104** and *N*-acyl oxazolidinone **109**.

We next undertook to verify the relative stereochemistry of **110**. Hydrolysis of the aldol with lithium hydroperoxide under Evans' conditions[96] gave hydroxy acid **111** in excellent yield (**Figure 51**). Reduction with borane in THF gave diol **112**, which provided acetonide **113** as the sole product when treated with pyridinium *p*-toluenesulfonate and 2,2-dimethoxymethane.

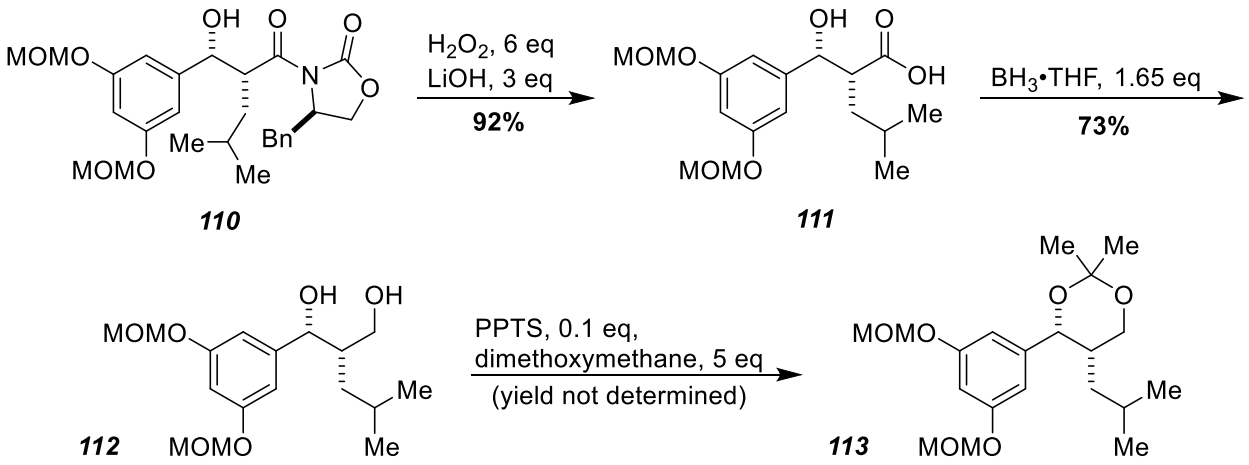


Figure 51. Removal of chiral auxiliary, reduction, and acetalization of **110** for determination of stereochemistry.

Careful examination of the ^{1}H NMR spectrum of acetonide **113** reveals strong evidence that the stereochemistry of aldol **110** is in fact *syn* as expected. The coupling constant for the benzylic methine proton reveals a *gauche* relationship between that proton and the neighboring proton on C-14 (**Figure 52**). Ignoring the presumably-negligible conformer in which both the aromatic ring *and* the isobutyl group are in the axial position, the *anti*-product should demonstrate an antiperiplanar relationship between the protons on C-1' and C-14, giving rise to a coupling constant greater than 10 Hz[103]. Conversely, both populated conformers of the *syn*-product should exhibit coupling constants less than 5.5 Hz, corresponding to the *gauche* relationship between the neighboring protons. In fact, the coupling constant for the methine proton at C-1' was measured at 2 Hz. Thus, we conclude that the stereochemistry of **110** is indeed *syn*, as expected.

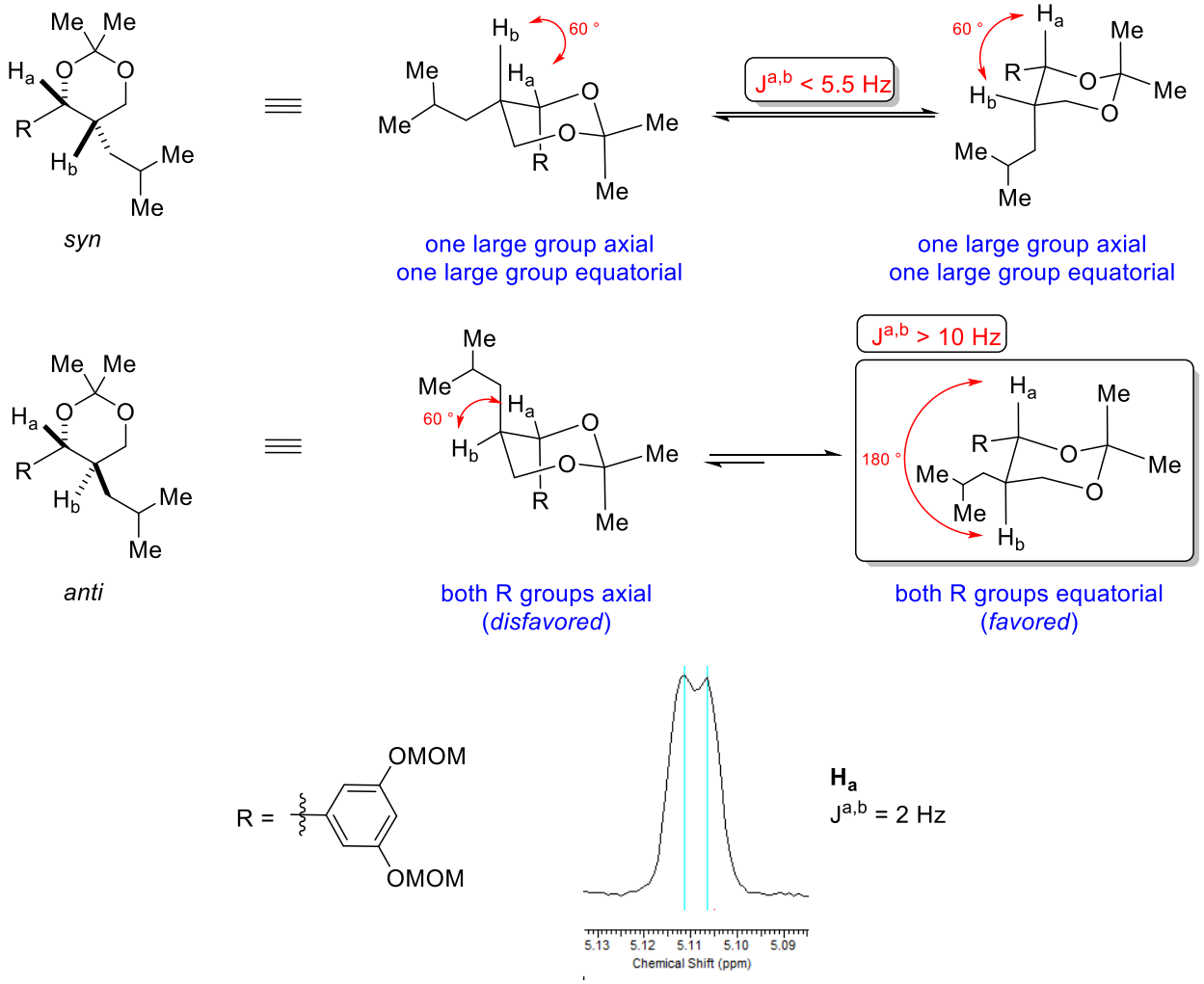
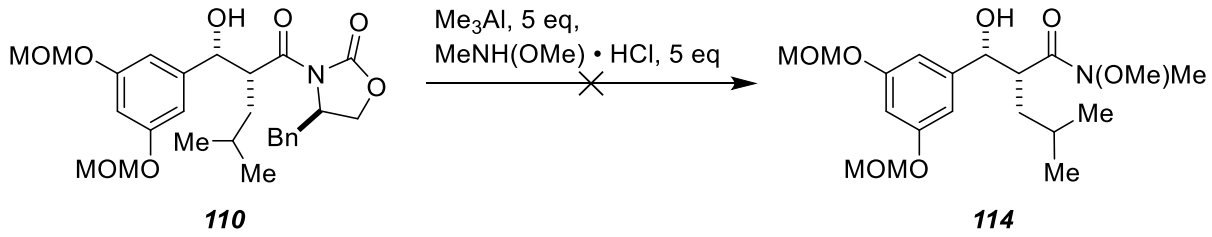


Figure 52. Confirmation of stereochemistry in LHS acetonide **113**.

With the relative stereochemistry of **110** assured, we set about attempting to effect the installation of the Weinreb amide. It was Weinreb himself who first noted that esters could be efficiently converted to the corresponding amides by the action of aluminum amides generated from the reaction of trimethylaluminum with primary or secondary amines[104] or (as Weinreb later demonstrated) their hydrochloride salts[105]. Evans subsequently noted the applicability of these conditions to the direct conversion of *N*-acyl oxazolidinones to amides in the course of his work on the polyether antibiotic X-206 [106]. Significantly, as Evans pointed out later, an unprotected alcohol at the β-position of such *N*-acyl oxazolidinones (such as that present in the products of

oxazolidinone-directed aldol reactions, for example) plays a crucial role in directing the attack of the aluminum amide to the exocyclic carbonyl[107].

With this precedent in mind, we first attempted chiral auxiliary removal by trimethylaluminum-mediated transamidation of **110** (**Figure 53**). Unfortunately, despite a number of attempts, Weinreb's conditions led only led to decomposition. In some cases, retro-aldol products were significant components of the crude. Evans has noted poor results for the direct transamidation of *N*-acyloxazolidinones with substantial steric hindrance[96], and later work on our part demonstrated that **110** and related compounds are prone to decomposition by way of base-catalyzed retro-aldol reactions.



110 ***114***

Figure 53. Attempted direct transamidation of **110** to Weinreb amide **114**.

Despite the failure of the direct route to **114**, we were nonetheless keen to remove the oxazolidinone moiety without first protecting the C-14 hydroxyl. Our motivation lay in our firm intent to implement Yamamoto's "supersilyl"-directed 1,4-*syn* selective aldol reaction in the coupling of the right- and left-hand sides. Given the extreme steric hindrance engendered by Yamamoto's tris(trialkylsilyl)silyl ethers, we desired to avoid installing these massive protecting groups until as late as possible in the synthesis of the LHS. We reasoned that such large moieties might well interfere with other synthetic transformations, including the synthesis of the requisite methyl ketone or even the removal of the chiral auxiliary itself. With Weinreb's direct transamidation approach effectively dead in the water, our next move was to attempt a standard hydrolysis of **110**, with the hope that traditional amide coupling conditions would be effective for

the installation of the Weinreb amide even without prior protection of the C-14 hydroxyl. A "protecting group swap" strategy was considered, but was deemed unpalatable on principle.

Accordingly, we subjected **110** to lithium hydroperoxide-mediated hydrolysis as previously described, obtaining **111** in excellent yield on scale (**Figure 54**).

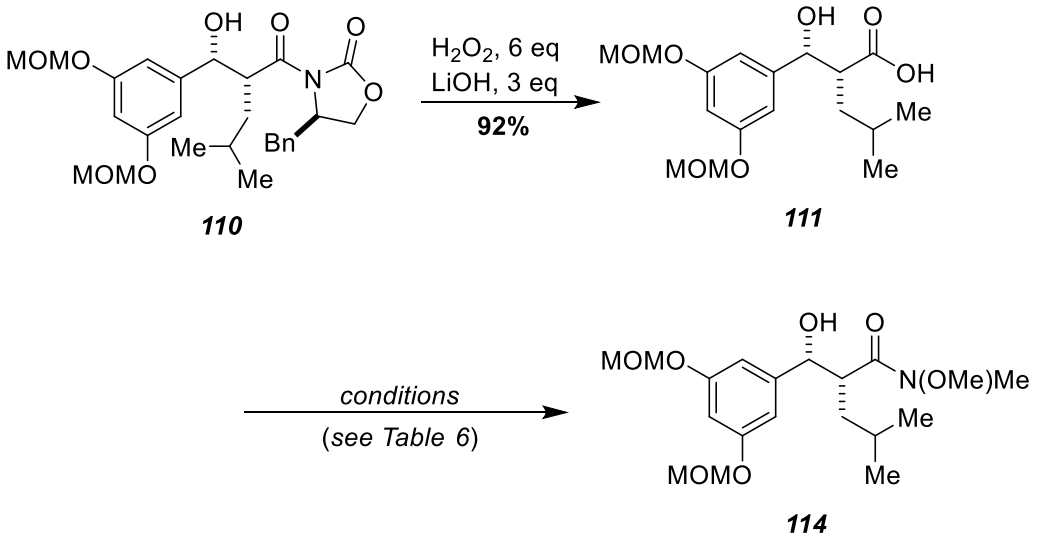


Figure 54. Hydrolysis and attempted amidation of aldol **110**.

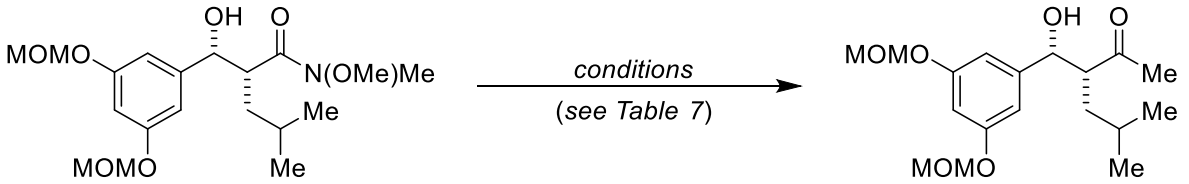
Table 6. Conditions for amide formation with hydroxy acid **111**.

Conditions	Yield
EDCI, 1 eq *N*-methylmorpholine, 3.5 eq *N*,*O*-dimethylhydroxylamine HCl, 1.5 eq	31%
EDCI, 3 eq *N*-methylmorpholine, 15 eq *N*,*O*-dimethylhydroxylamine HCl, 10 eq	82%
N-methylmorpholine, 4.10 eq *N*,*O*-dimethylhydroxylamine HCl, 3.00 eq 2-chloro-4,6-dimethoxy-1,3,5-triazine, 1.10 eq	58%
N-methylmorpholine, 5.10 eq 4-(dimethylamino)pyridine, 0.20 eq *N*,*O*-dimethylhydroxylamine HCl, 2.00 eq 2-chloro-4,6-dimethoxy-1,3,5-triazine, 1.10 eq	95%

Our attempts at the amidation of **111** began with the use of EDCI; however, despite initial optimization attempts, results with this reagent were inconsistent, with some reactions failing to go to completion after up to one week, and others giving good yields after approximately 36 hours.

Consequently, we sought more reliable conditions. 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) seemed like an attractive choice, as it has been known to allow the formation of amides from β-hydroxy acids without prior protection of the alcohol[108]. After some optimization, 1.10 eq of CDMT with catalytic DMAP and excess *N*-methylmorpholine were found to give ideal results, affording 95% of relatively pure **114** after 12 hours.

With access to Weinreb amide **114** thus secured, we next chose to investigate whether the methyl ketone could be installed without prior protection of the C-1' hydroxyl (**Figure 55**).



114 ***115***

Figure 55. Attempted installation of methyl ketone without C-1' hydroxy protection.

Table 7. Conditions attempted for the conversion of **114** to **115**. N.R. = no significant reaction, decomp. = unidentified decomposition products, retro-aldol = retro-aldol reaction products.

Reagents	**Temp.**	**Time**	**Result** (% yield)
MeMgBr, 4.50 eq	0 °C to r.t.	36 h	**115** (23%)
MeLi, 3.00 eq	0 °C to r.t.	2 h	retro-aldol
MeLi, 5.00 eq	-78 °C	1 h	N.R.
MeLi, 1.2 eq; TMSCl, 1.1 eq; then MeMgBr, 3 eq	-78 °C	6 h	N.R.
MeMgBr, 4.10 eq	-65 to -25 °C	60 h	N.R.
$CeCl_3$, 3.00 eq; MeMgBr, 3.00 eq; then **114**	0 °C to r.t.	55 h	N.R.
$CeCl_3$, 1 eq; MeMgBr, 3.00 eq	0 °C to r.t.	12 h	retro-aldol
$Ph_3P{=}CH_2$, 2.1 eq	-78 °C	28 h	decomp.

Our first attempt at the formation of **115** met with limited success – 4.5 equivalents of methylmagnesium bromide gave **115** in low but appreciable yield over 36 hours. Heartened, we set about trying variations of these conditions, with the hope of improving the yield of the reaction. Methyllithium between 0 °C and room temperature gave only the products of the corresponding retro-aldol reaction, readily identifiable by the presence of aldehyde **104** as a major product. Even larger quantities of methyllithium at cryogenic temperatures gave primarily starting material.

Attempts at transient protection as the TMS ether were likewise unsuccessful. Organocerium reagents – which may be generated by the action of organolithium or Grignard reagents on anhydrous ceriu(III) chloride, among other methods – have proved superior as carbon nucleophiles in cases where addition into carbonyl compounds otherwise unstable to basic conditions is desired[109-110]. Among other advantageous qualities, organocerium species are known to avoid adventitious retro-aldol-type reactivity during addition to sensitive unprotected β-hydroxy ketones[111]. Disappointingly, the use of a pre-formed organocerium reagent gave no reaction at room temperature, even after prolonged reaction times. The use of a 1:3 ratio of $CeCl_3$ to methylmagnesium bromide gave retro-aldol products, suggesting that the organocerium species was indeed formed but was simply not reactive enough to alkylate **114**. Reaction with phosphonium ylide $Ph_3P{=}CH_2$, reported to react with Weinreb amides to give methyl ketones, gave only unidentified decomposition products[112].

With development of the Weinreb ketone synthesis on **114** thus stalled at an unacceptably low yield of 23%, we turned our attention to other approaches. Isolated attempts (**Figure 56**) to directly convert **110** to the methyl ketone were unsuccessful. Treatment of **110** with MeLi gave endocyclic cleavage product **117** as the sole product in 61% yield, without any evidence of the formation of **116**. Likewise, treatment of **110** with 5 equivalents of $Ph_3P{=}CH_2$ gave only aldehyde **104** and *N*-acyloxazolidinone **109** as the sole products, presumably as the result of a retro-aldol-type reaction.

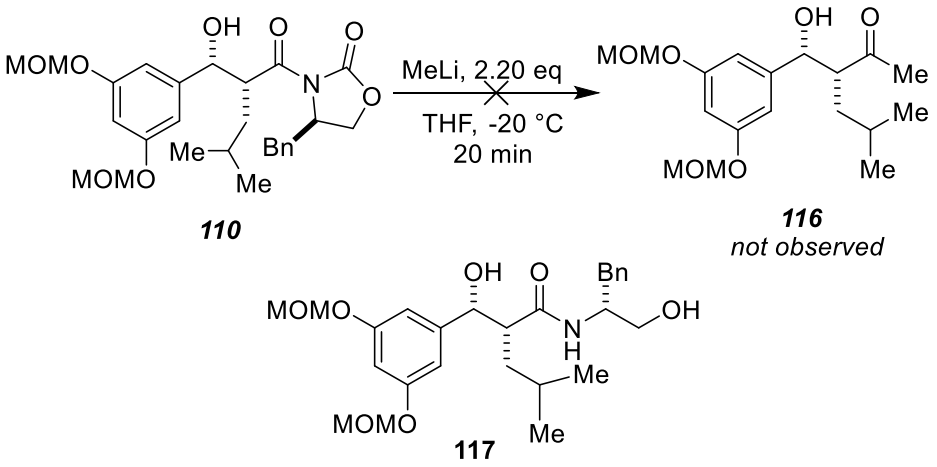


Figure 56. Failed attempt at methyl ketone formation from **110** using methyllithium.

We next considered the possibility of eliminating the Weinreb amide from the synthesis altogether, forming **116** directly from unprotected hydroxy acid **111**. A number[113-117] of methods for the direct conversion of acids to ketones are known, and the topic has been briefly reviewed[118]. We elected to start with the reaction of organic acids with organocuprates[116]. Despite the successful and quantitative conversion of hydrocinnamic acid to methyl ketone **119** in a test reaction, subjection of **111** to identical and similar conditions gave only starting material (**Figure 57**).

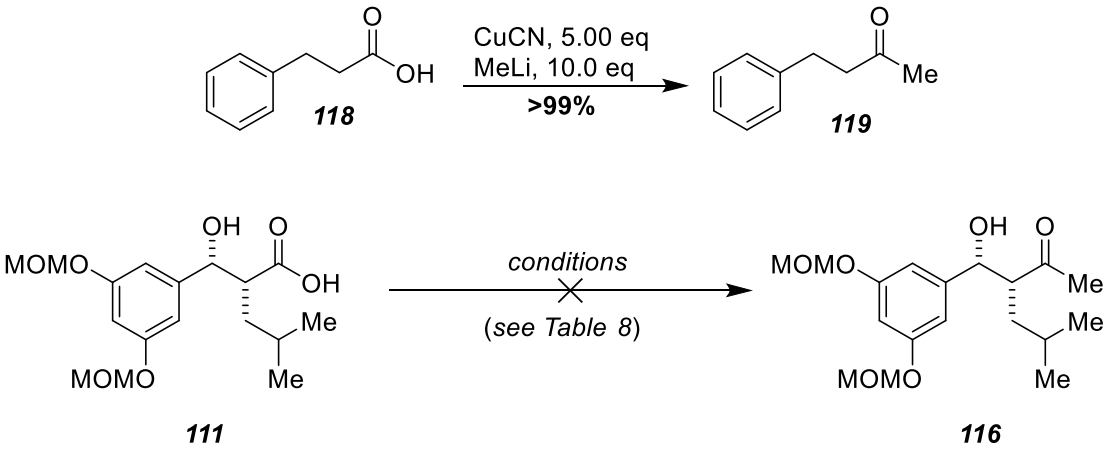


Figure 57. Attempted conversion of hydroxy acid **111** directly to methyl ketone **116**.

Table 8. Conditions attempted for the conversion of **111** to **116**. N.R. = no reaction.

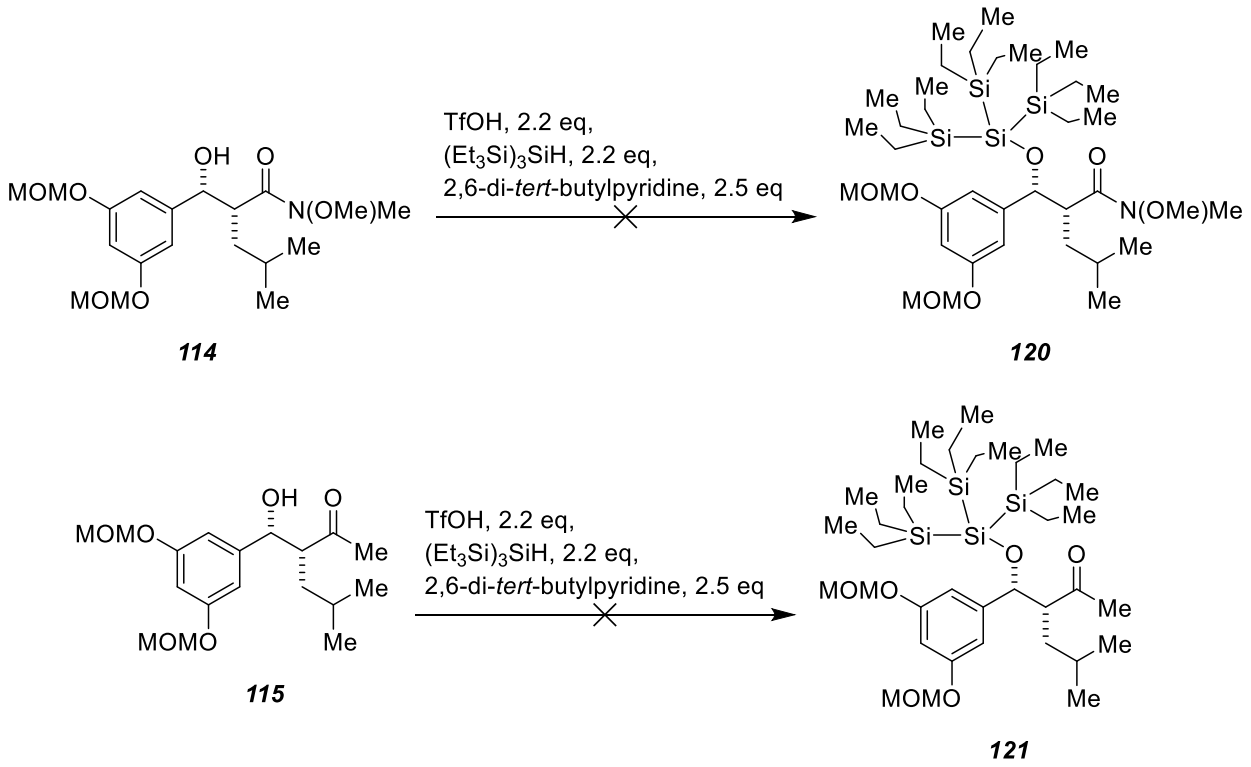
Conditions	Result
MeLi, 4.00 eq; then TMSCl, 10.0 eq	decomposition
MeLi, 5.00 eq; CuCN, 5.00 eq	N.R.
MeLi, 10.0 eq; CuCN, 5.00 eq	N.R.

Likewise, treatment of **111** with methyllithium followed by quenching with excess TMSCl[119] led only to extensive decomposition, presumably mediated by the basicity of methyllithium under the reaction conditions.

In light of this slew of failures to access **116** by any method, we abandoned the idea of proceeding with the C-1' hydroxyl unprotected. At this point, we elected to proceed with the installation of the desired "supersilyl" protecting group. Thus, we first attempted the reaction of tris(triethylsilyl)silyl triflate (generated *in situ* from tris(triethylsilyl)silane and triflic acid) with β-hydroxy amide **114**; however, neither the use of 2.2 equivalents $(TES)_3SiOTf$ (Yamamoto reports[120] the use of 1.05 eq of the analogous tris(trimethylsilyl)silyl triflate in a similar reaction) nor the use of very large excesses of this reagent (up to 24 equivalents) ever produced isolable product (**Figure 58**). A similar attempt on **115** gave only starting material, even after one week at room temperature. Hoping that the marginally less hindered tris(trimethylsilyl)silyl protecting group might prove more amenable to installation on our scaffold, we attempted the analogous reaction using **114** as our test substrate (**Figure 59**). Disappointingly, these attempts met the same fate as their earlier analogues with $(TES)_3SiOTf$, giving either decomposition or no reaction.

With all attempts to access "supersilyl"-protected structures thus stymied, we were forced to reconsider our approach to the stereoselective aldol reaction we proposed would couple the left- and right-hand sides. With no proof that the "supersilyl" strategy would prove fruitful, and with our long efforts in pursuit of any protected LHS methyl ketone thus far unproductive, it was

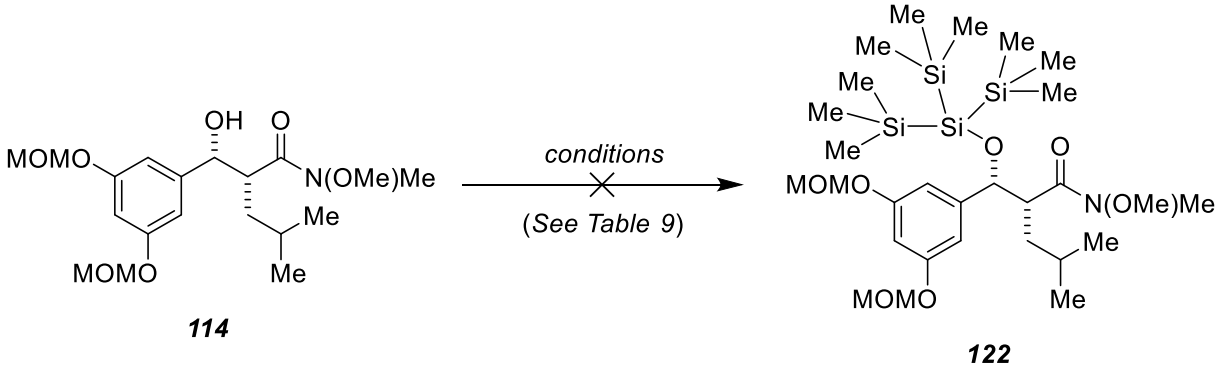
decided that a simple TBS ether would serve the purpose of protecting the alcohol at C-1', at least until experimental evidence from attempted aldol reactions could inform us otherwise.



114 **120**

115 **121**

Figure 58. Attempted installation of tris(triethylsilyl)silyl protecting group on **114** and **115**.



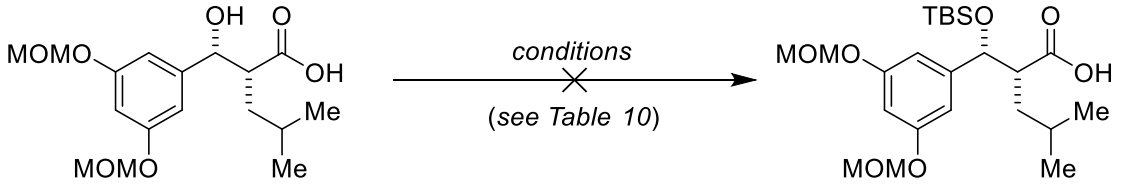
114 **122**

Figure 59. Attempted installation of the tris(trimethylsilyl)silyl protecting group on **114**.

Table 9. Conditions attempted for tris(trimethylsilyl)silylation of **114**. N.R. = no reaction

Conditions	Result
$(Me_3Si)_3SiCl$, 25 eq; imidazole, 50 eq	decomposition
TfOH, 2.20 eq; $(Me_3Si)_3SiH$, 2.21 eq; triethylamine, 2.50 eq	N.R.

With a large amount of hydroxy acid **111** on hand at the time, we first attempted TBS-protection of the acid, reasoning that upon treatment of **111** with silylating reagents, bis-silylation would ensue; the silyl ester moiety could then be removed by basic hydrolysis. In the event, however, despite apparent transient protection of **111** under a variety of conditions, basic hydrolysis always gave starting material back as the major product (**Figure 60**).



111 ***123***

Figure 60. Attempted TBS-protection of hydroxy acid **111**.

Table 10. Conditions attempted for the TBS-protection of **111**. SM = starting material.

Silylation Reagents	Solvent	Hydrolysis Conditions	Result
TBSCl, 2.10 eq imidazole, 3.50 eq	DCM	10% aq. K_2CO_3 (w/w)	SM recovered
DMAP, 0.40 eq TBSCl, 2.10 eq imidazole, 3.50 eq	DMF	sat. sol'n of K_2CO_3 in H_2O/MeOH	SM recovered
DMAP, 0.40 eq TBSCl, 2.44 eq imidazole, 5.90 eq	$CDCl_3$	1% aq. K_2CO_3 (w/w)	SM recovered

Based on TLC analysis of the reaction of **111** and TBSCl in DCM, as well as real-time ^{1}H NMR analysis of the reaction conducted in $CDCl_3$, it appears that silylation was indeed happening (as evidence by disappearance of starting material by both TLC and ^{1}H NMR); however, basic hydrolysis invariably regenerated **111**. Considering the available evidence, it seems most likely that silylation was happening preferentially at the less-sterically-encumbered acid moiety (**Figure 61**), giving rise to silyl ester **124**. The added bulk of the *tert*-butyldimethylsilyl moiety adjacent to the C-13 carbonyl might then have proved sufficient to prevent a second silylation reaction, preventing formation of **125** altogether. Under these circumstances, despite the initial consumption of starting material, basic hydrolysis would of course regenerate **111**.

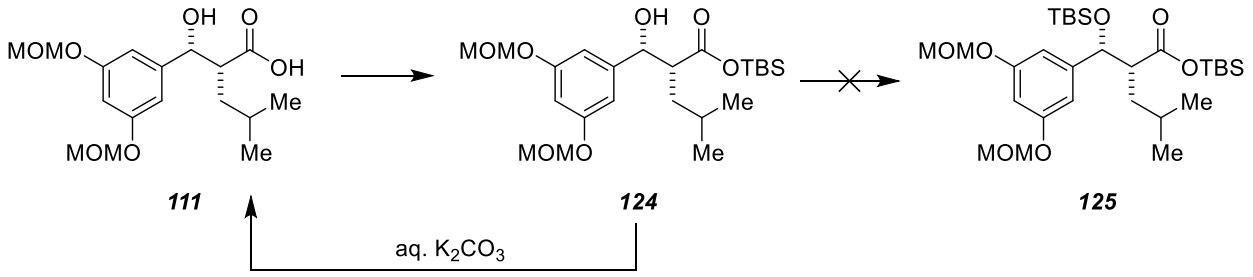


Figure 61. Possible explanation for silylation reaction outcomes.

In light of our inability to successfully silylated hydroxy acid **111**, we finally chose to employ the straightforward strategy of TBS-protecting Weinreb amide **114**. While reaction between **114** and TBSCl in the presence of imidazole alone or imidazole and 0.20 or 0.40 eq DMAP proved sluggish (data not shown); we were gratified to find that treatment of **114** with TBSOTf and 2,6-lutidine gave TBS-ether **126** in good yield (**Figure 62**). Likewise, treatment of **126** with methyllithium successfully gave protected LHS methyl ketone **127** in good yield, thus completing our first attempt at the synthesis of the left-hand side of the baulamycin scaffold, albeit with alternate protection for the C-1' hydroxyl.

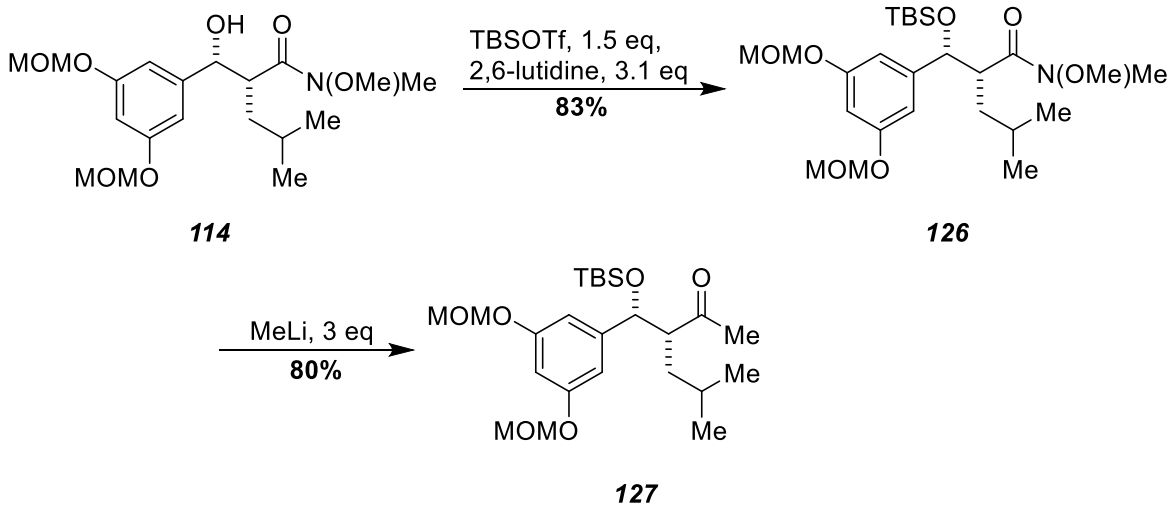


Figure 62. Completion of the synthesis of LHS methyl ketone **127**.

2.4 Attempted Aldol Coupling of Left- and Right-Hand Sides

With the synthesis of both RHS aldehyde **38** and LHS ketone **127** in place, our next task was to develop conditions leading to the diastereoselective aldol coupling of **38** with **127**. While aldehyde **38** was available, it remained precious to us in light of the sixteen steps required to prepare it from hydrocinnamaldehyde. Thus, we elected to begin our studies by investigating the couplings of methyl ketone **127** with commercially-available aliphatic aldehydes.

Our initial investigations were conducted with heptanal (**Figure 63**); however, several attempts at deprotonation of **127** with lithium hexamethyldisilazide followed by treatment with a slight excess of heptanal gave only recovered ketone, despite a separate experiment showing incorporation of one deuteron at C-12 after quenching of the (presumed) lithium enolate of **127** with deuterium oxide (data not shown).

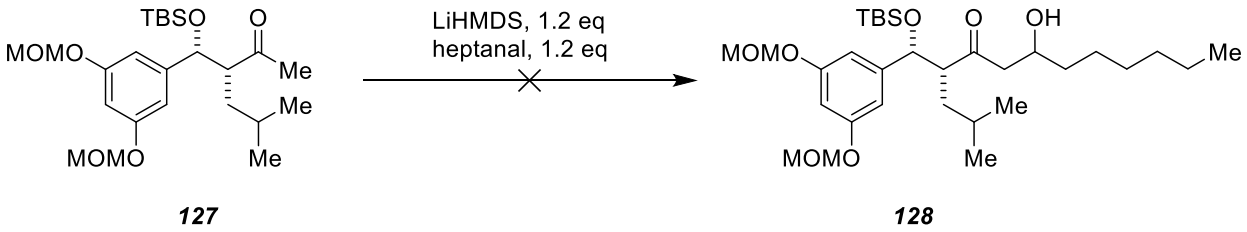


Figure 63. Attempted aldol reaction between **127** and heptanal.

With evidence of enolization in hand, we turned our attention to heptanal as a potential source of our reactivity issues. Examination of our material immediately prior to use revealed the unfortunate explanation: even *freshly distilled* heptanal is highly unstable and prone to rapid trimerization. In the event, we observed up to 35% trimerization to 2,4,6-trihexyl-1,3,5-trioxane over a period of just 3 hrs at room temperature. Examination of an old bottle of heptanal by ^{1}H NMR showed an approximately 8:1 ratio of trimer to monomer, suggesting that the monomer and trimer may be in a relatively fast equilibrium; however, with no desire to add this unexpected set

of variables to our already complex reaction manifold, we chose to investigate other aldehydes as models for the RHS.

A single experiment in which **127** was deprotonated with lithium diisopropylamide and subsequently treated with freshly purified butanal gave recovered **127** as the only product after workup; butanal was not recovered (**Figure 64**). Meanwhile, we were pleased to discover that pentanal, after purification by distillation, remains stable at room temperature under argon for timescales approaching weeks rather than hours. Armed with the increased certainty afforded by this discovery, we undertook a screen of aldol conditions between freshly purified pentanal and ketone **127**.

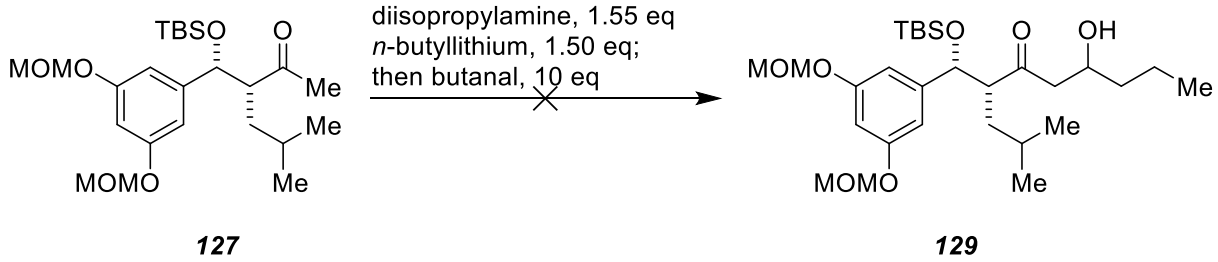


Figure 64. Attempted reaction between the lithium enolate of **127** and butanal.

A number of conditions were attempted (**Figure 65**); however, despite the use of fresh and purified reagents and starting materials, as well as favorable results from control reactions showing enolization under a variety of conditions, results were generally poor (**Table 11**).

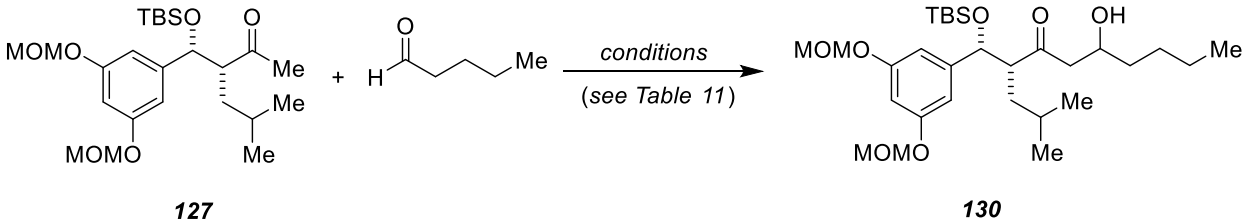
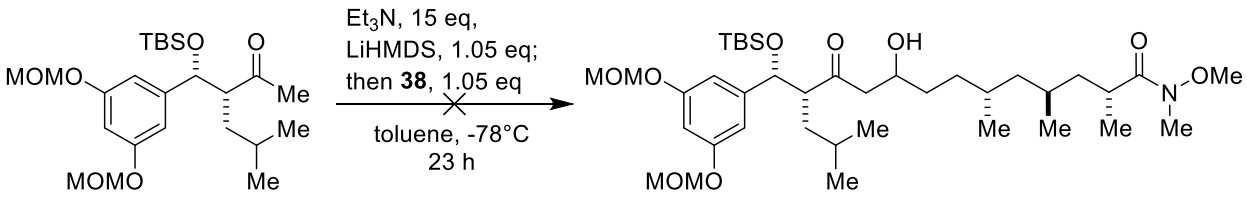


Figure 65. Conversion of **127** to model aldol **130** by aldol reaction with pentanal.

Table 11. Conditions employed in the conversion of **127** to **130**.

Entry	Conditions	Result
1	Et_3N, 1.10 eq; $(Cy)_2BCl$, 1.05 eq	no reaction
2	Et_3N, 2.00 eq; $(Cy)_2BCl$, 2.00 eq; then D_2O, excess	deuteration at C-12
3	Et_3N, 5.00 eq; TMSOTf, 1.50 eq; then BF_3•Et_2O, 1.05 eq, r.t.	decomposition
4	(*n*-Bu)$_2$BOTf, 1.10 eq, Et_3N, 1.50 eq; DCM, 0 °C, 3 hr	no reaction
5	(*n*-Bu)$_2$BOTf, 1.10 eq, Et_3N, 1.50 eq; DCM, 0 °C, 60 hr	decomposition
7	(+)-DIP-Cl, 2.70 eq, Et_3N, 3.0 eq; DCM, -78 °C	no reaction
8	L-proline, 0.50 eq; $CHCl_3$	no reaction
9	L-proline, 0.50 eq; THF/H_2O (1:1)	no reaction
10	LiHMDS, 3.00 eq; Et_3N, 15.0 eq; toluene, -60 °C	decomposition
11	LiHMDS, 3.00 eq; Et_3N, 15.0 eq; DMF, -78 °C	decomposition
12	LiHMDS, 3.00 eq; Et_3N, 15.0 eq; toluene, -78 °C	64%, dr = 1 : 1

The one exception to the generally poor results of various hard and soft enolization, as well as direct, approaches to the aldol reaction was the reaction of the lithium enolate of **127** generated by LiHMDS in the presence of a large excess of triethylamine in toluene at -78 °C, which gave a 64% yield of **130**, but no diastereoselectivity. Increasing the temperature led to decomposition products. With reasonable yields in hand, we decided that it was worth trying these conditions on actual RHS aldehyde **38**; however, when the reaction was carried out, regenerated **127** was the sole product, and precious aldehyde **38** could not be recovered (**Figure 66**).



127 ***131***

Figure 66. Attempted aldol reaction between **127** and RHS aldehyde **38.**

Recognizing that continued optimization of these conditions was required, but loathe to sacrifice more of **38**, we resolved to develop a more pertinent model of **38**. Accordingly, we proposed to synthesize the tris-*des*-methyl analogue of **38**, *N*-methoxy-*N*-methyl-9-oxononanamide **137**, as a model for **38** to be used in future aldol reactions (**Figure 67**).

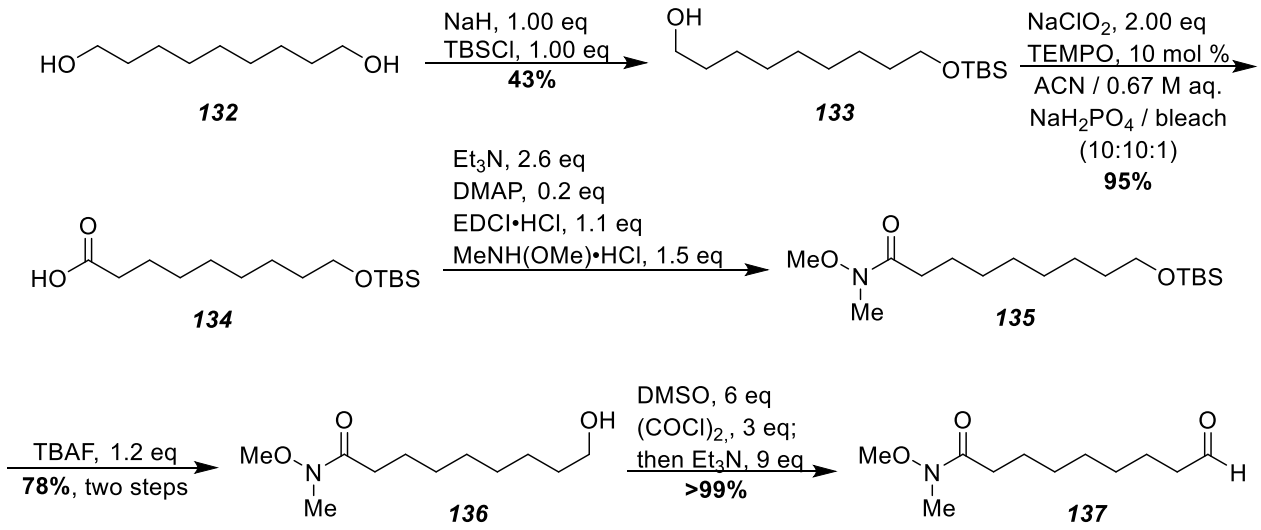


Figure 67. Synthesis of model RHS aldehyde **137** from 1,9-nonanediol.

Synthesis began with the monoprotection of 1,9-nonanediol as its TBS-ether **133**. Under conditions[121] which have been employed on other α,ω-diols, we received no better than a statistical yield of the diol; however, the ease of separating the various products and the extreme cheapness of the starting materials mitigated the issue, allowing us to proceed with little difficulty. Oxidation with TEMPO, bleach and sodium chlorite[122] afforded acid **134** in excellent yield in a single operation. Subsequent Weinreb amide installation and deprotection with TBAF gave amide alcohol **136** in good yield over two steps; oxidation under Swern's conditions then gave aldehyde **137** quantitatively. We were thus able to rapidly access **137** in 32% overall yield from commercial material, providing a straightforward source of model aldehyde for future investigations of our key aldol reaction.

It should be noted that, like a number of other aldehydes previously employed, **137** proved to be relatively unstable to prolonged storage. Storage in an apparently air-free environment at room temperature led to ~35% decomposition (byproducts unknown) after 20 days; storage in the cold profoundly worsened the issue, giving *complete* decomposition in mere days. Like so many

other aldehydes employed thus far, we elected not to prepare large quantities of **137**, but rather to prepare it from **136** immediately prior to use.

With model aldehyde **137**, we immediately set about testing conditions for its coupling with LHS ketone **127**. Subjection of **127** to soft enolization conditions followed by exposure to **137** gave no product (**Figure 68**), a result consistent with that observed when pentanal was used as the electrophile. Conversely, hard enolization conditions similar to those which had been successful on pentanal (**Figure 69**) were successful, giving aldol product **138** in 27% yield as a 1:1 mixture of diastereomers.

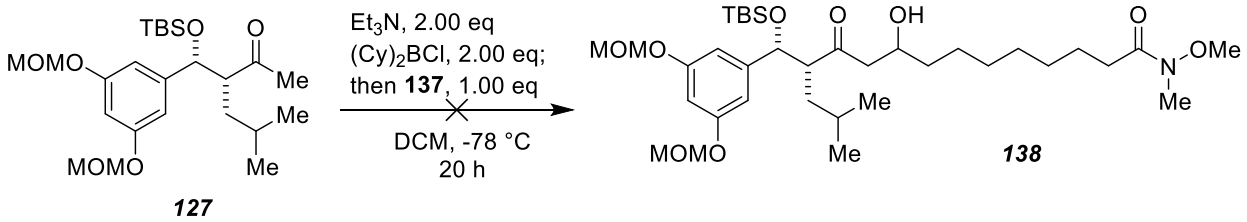


Figure 68. Attempted soft-enolization aldol reaction of **127** with model RHS aldehyde **137**.

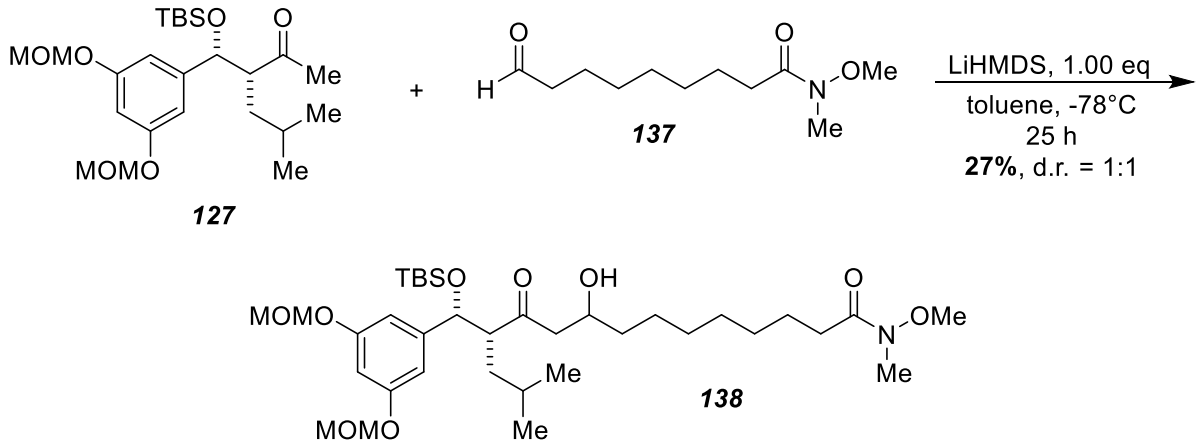


Figure 69. Aldol reaction between the lithium enolate of **127** and model RHS aldehyde **137**.

At this point, with unequivocally poor yields and non-existent diastereoselectivity, we considered the idea of employing a chiral directing group in order to influence the outcome of aldol reaction. Ellman has shown that sulfinimines derived from the condensation of (*R*)- or (*S*)-2-

methylpropane-2-sulfinamide with ketones can be deprotonated to give nucleophiles that perform stereoselective additions to aldehydes[123]. The resulting β-hydroxy sulfinimines can then be converted under mild conditions to β-hydroxy ketones. Thus, we envisioned a route to aldol **138** in which **127** would undergo condensation with (*R*)-2-methylpropane-2-sulfinamide to give sulfinimine **139** (**Figure 70**). This latent nucleophile would then suffer deprotonation, reacting with **137** to give β-hydroxy sulfinimine **140**, which, following acidic hydrolysis was imagined to give aldol **138** with good specificity for the desired C-11 stereochemistry.

We began our attack with the synthesis of **139**; reflux of **127** in THF with 4 equivalents of titanium(IV) ethoxide did indeed give **139**, albeit in mediocre yield (**Figure 71**). However, all attempts to promote the reaction of **139** with **137** failed, giving only recovered **139** upon workup.

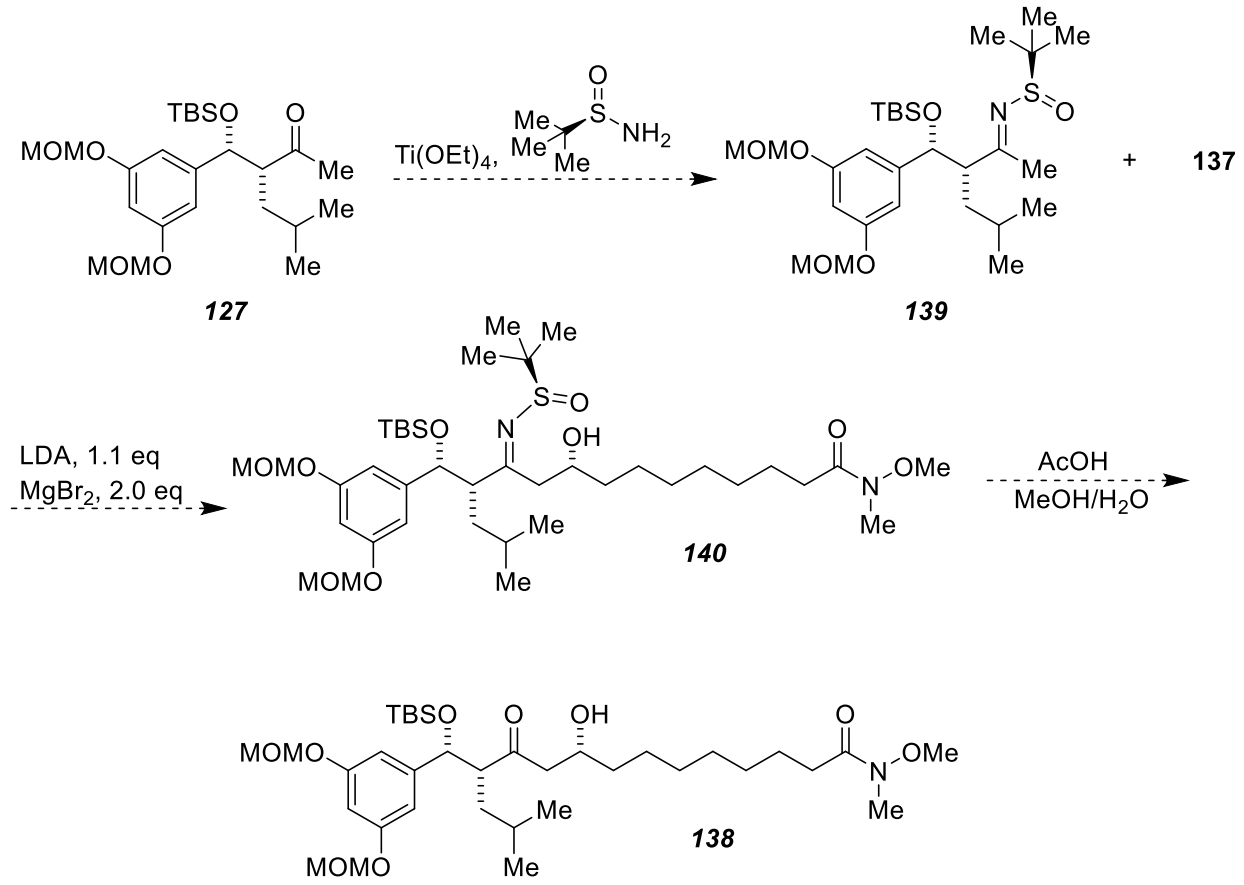


Figure 70. Proposed approach to **138** based on Ellman's chiral sulfinamide auxiliaries.

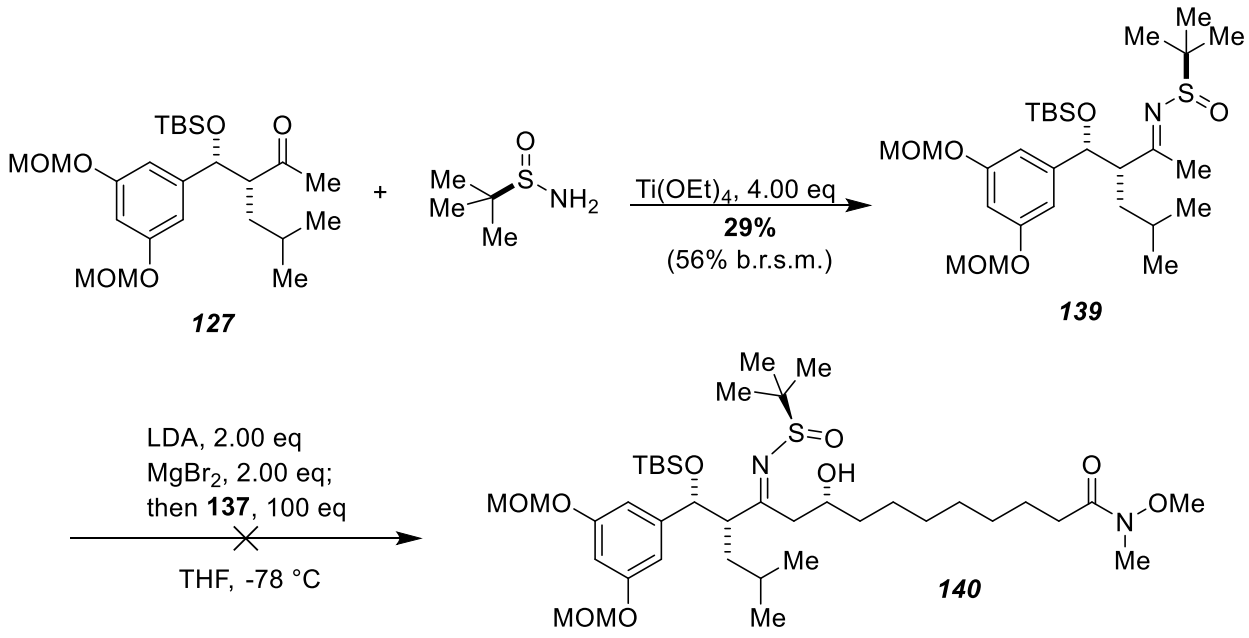


Figure 71. Attempted aldol-type coupling of the lithium enolate of **139** with **137**.

With Ellman's chemistry out of the question, we considered other, less-straightforward approaches. β-Hydroxy diketoesters are known to be reduced stereoselectively to the *syn* triols by sodium borohydride in the presence of titanium(IV) isopropoxide[124]; we hoped that a similar pattern of reactivity might be operative on β-hydroxy diketones. Accordingly, we oxidized a 1:1 mixture of **138** stereoisomers to diketone **141** in good yield under Parikh-Doering conditions (**Figure 72**); however, a several attempts to effect the deprotection of diketone **141** were unsuccessful.

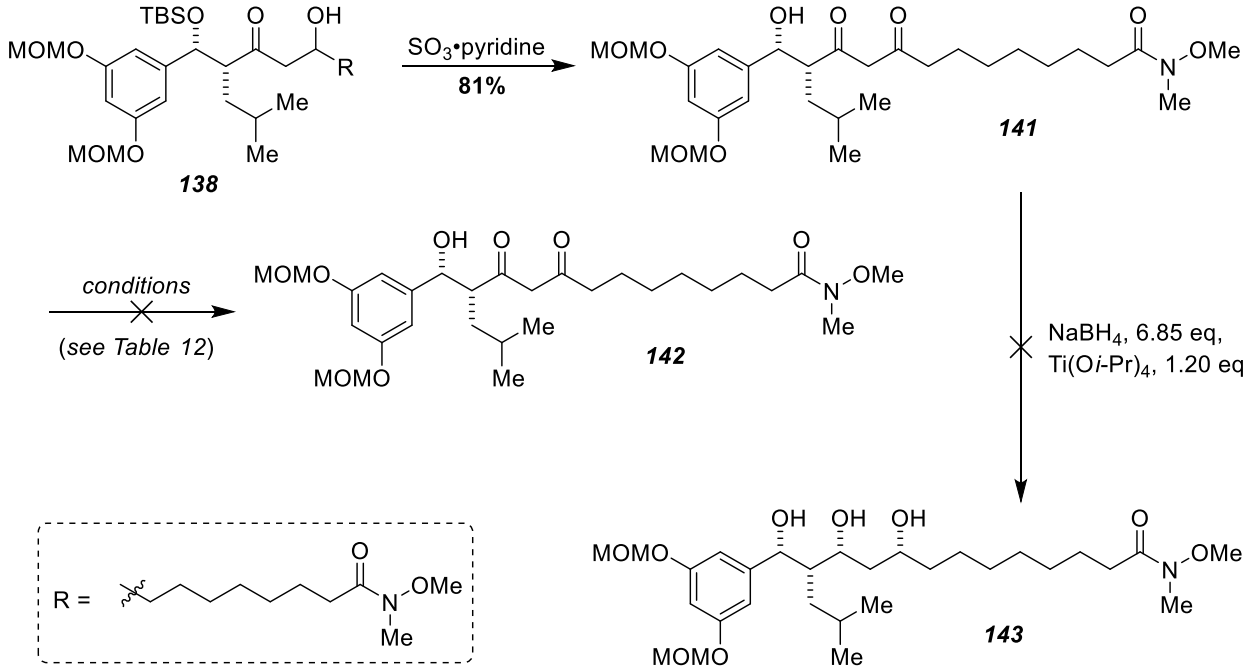


Figure 72. Oxidation of aldol **138** to diketone **141**; attempted deprotection and reduction of **141**.

Table 12. Conditions attempted for deprotection of **141**.

Conditions	Result
TBAF, 1.20 eq; THF	decomposition
TBAF, 1.00 eq; NH_4F, 1.00 eq; THF	decomposition

In retrospect, it seems likely that the basic nature of the fluoride sources employed proved a poor match to the relatively acidic diketone. When deprotection failed, reduction was attempted

on TBS-ether **141** directly; however, this reaction gave an intractable mixture of unknown products.

2.5 Revised Retrosynthetic Analysis

With all attempts to effect an aldol-type coupling of the LHS and RHS having been thus far unsuccessful at producing any reasonable amount of diastereoselectivity, we considered that it was time to re-tool our core retrosynthetic strategy towards the baulamycins. Taking our cues from the structures of the advanced intermediates accessible from our previous synthetic work, we imagined that a Horner-Wadsworth-Emmons or Wittig-type reaction between a left-hand side nucleophile and a right-hand side electrophile would give rise to an enone containing the complete carbon skeleton of the baulamycins (**Figure 73**). This enone might then undergo a formal diastereoselective hydration by any number of methods in order to give rise to aldol **131**. *Syn*-selective diastereoselective reduction, Weinreb ketone synthesis and global deprotection would then give the baulamycins as formerly planned.

Our inintial inclination was the incorporation of a stabilized phosphonium ylide into the left-hand side synthon; we reasoned that since the high *E*-selectivity of resonance-stabilized Wittig reagents is well-known, we would stand a good chance of accessing a single diastereomer of the desired product. Moreover, we knew that the required phosphorane could be generated under mild conditions, avoiding the liabilities associated with the use of strong base.

With the above Wittig-based strategy in mind, we set about the synthesis of the α-bromoketone from **127** (**Figure 74**). Deprotonation of **127** with lithium diisopropylamide followed by treatment with stoichiometric bromine at -78 °C gave a mixture of starting material and an unknown product, which we hoped was α-bromoketone **148**. Unfortunately, treatment with a single equivalent of triphenylphosphine did not produce identifiable phosphonium bromide **147**,

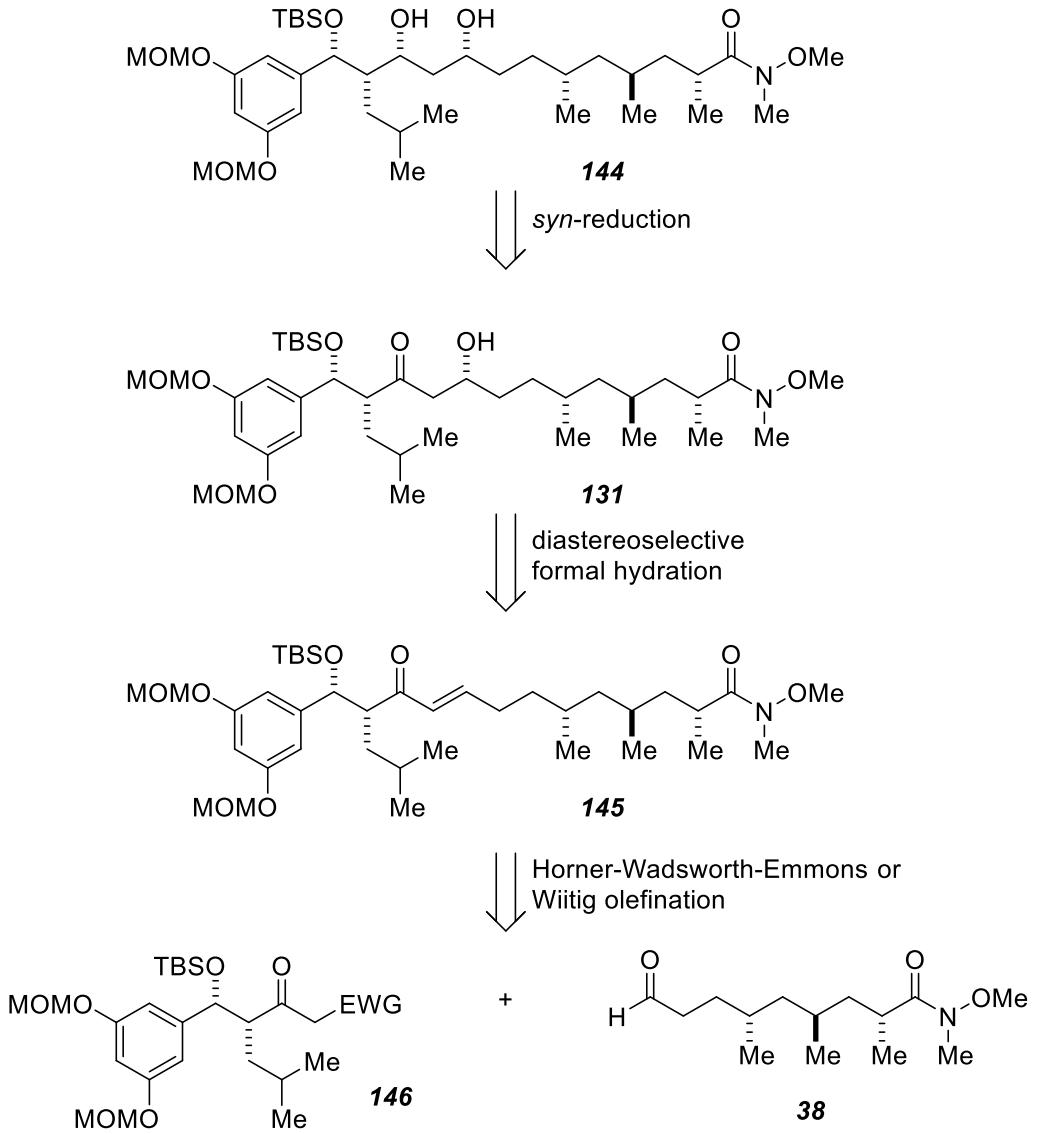


Figure 73. Revised retrosynthetic analysis of the baulamycins using Horner-Wittig reactivity.

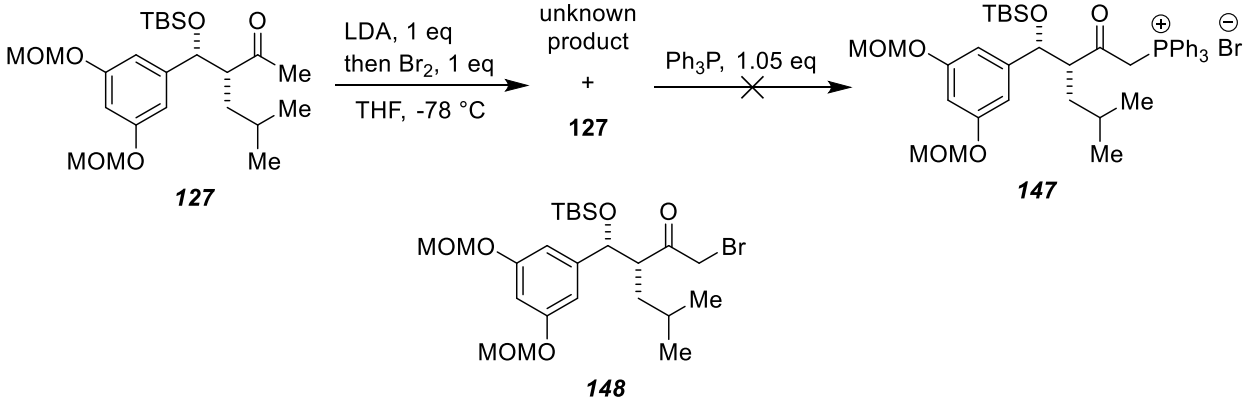


Figure 74. Attempted formation of phosphonium bromide salt **148** from LHS ketone **127**.

but instead yielded an unidentified, phosphorous-containing (^{31}P NMR) white solid which was unstable to oxygen, decomposing to give a greenish-black substance. Deprotonation of **127** with LiHMDS under the same conditions yielded identical results. All attempts to identify either the product of bromination or the subsequently-formed adduct with triphenylphosphine were unsuccessful. We considered the possibility that bromination was taking place at the aromatic ring rather than at the carbonyl α-position; however, no convincing evidence for this was ever obtained, and the route was eventually abandoned.

Unsuccessful in our attempts to prepare a Wittig-style nucleophile from **127**, we turned our attention to the construction of the analogous Horner-Wadsworth-Emmons reagent, β-ketophosphonate **149** (**Figure 75**).

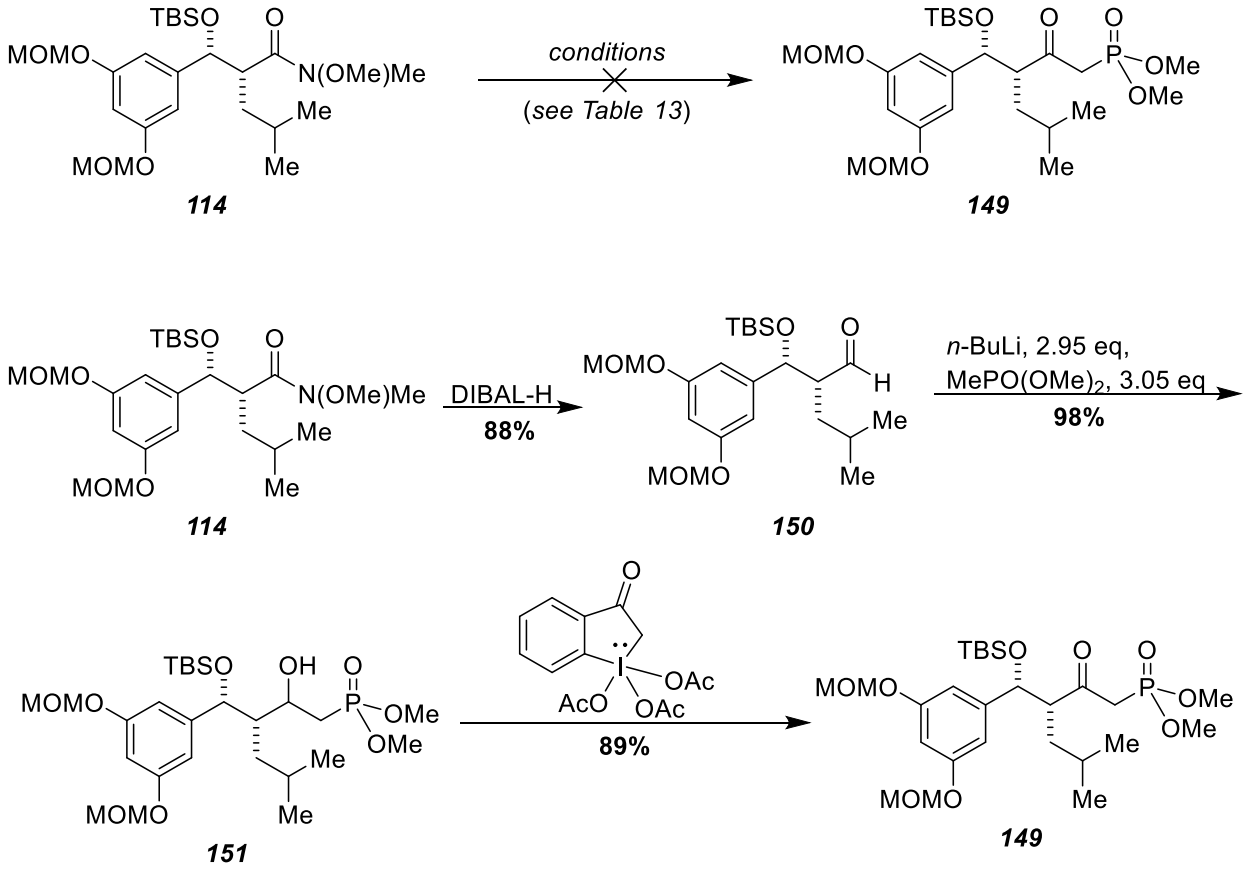


Figure 75. Synthesis of β-ketophosphonate **149** from Weinreb amide **114**.

Table 13. Conditions employed for the conversion **114** directly to **149**. N.R. = no reaction.

Reagents	Temperature and Time	Results
$MeP{=}O(OMe)_2$, 3.05 eq; *n*-BuLi, 3.00 eq, THF	-78 °C, 0.5 h; then -20 °C, 12 h	N.R.
$MeP{=}O(OMe)_2$, 3.05 eq; *n*-BuLi, 3.00 eq, THF	-78 °C, 2 h; then r.t., 12 h	N.R.
$MeP{=}O(OMe)_2$, 3.05 eq; KHMDS, 3.00 eq, THF	-78 °C, 2 h; then r.t.,12 h	N.R.

We first attempted the conversion of Weinreb amide **114** directly to desired β-ketophosphonate; however, **114** proved remarkably inert to attack with a variety of anions of methyl dimethylphosphonate, perhaps due to the severe steric constraints imposed by the isobutyl substitution at the α-position. With this in mind, we hypothesized that perhaps a less-bulky carbonyl might be more susceptible to nucleophilic attack by lithiated methyl dimethylphosphonate. Accordingly, we prepared aldehyde **150**, which was available in good yield by reduction of **114** with two equivalents of DIBAL-H. Pleasingly, when **150** was subjected to the same conditions which had proved ineffective Weinreb amide **114**, β-hydroxy phosphonate **151** was obtained smoothly in excellent yield. Oxidation with Dess-Martin periodinane rapidly gave desired β-ketophosponate **149** in good yield. Efforts to effect the same transformation with cheaper activated-DMSO-type conditions were unsuccessful; no reaction was observed even after 29 hours under Parikh-Doering conditions.

With an effective route to β-ketophosphonate **149** thus securely in hand, we moved to effect the coupling of **149** with model RHS aldehyde **137** as a surrogate for our proposed coupling of **149** with **38**. In the event, Paterson's mild olefination conditions[125], catalyzed by a suspension of activated barium hydroxide in THF/water (40:1), provided enone **152** with perfect *E*-selectivity in 69% (unoptimized) yield from β-ketophosphonate **149** and aldehyde **137** (**Figure 76**). At this point, having successfully coupled a key analogue of the baulamycin RHS to our LHS synthon, we turned our attentions to the problem of effecting a diastereoselective formation hydration of **152**.

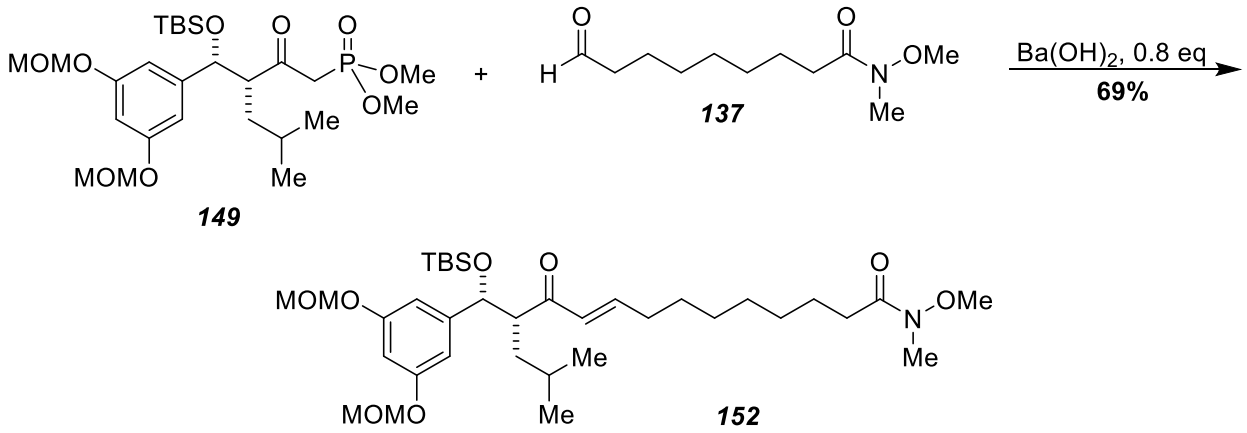


Figure 76. Successful Horner-Wadsworth-Emmons olefination of **137** with **149** under Paterson's conditions.

The enantio- and diastereoselective formal hydration of various Michael acceptors is a topic of general interest and has been reviewed[126]. One well-known strategy for the enantioselective formal addition of water to enones is the cinchona-alkaloid-catalyzed addition of peroxides followed by facile reduction of the resulting β-peroxyketones to aldols. Variations on this protocol have been independently described by List and coworkers[127] as well as Deng *et al*[128]; a similar addition of oximes to enones has also been independently described[129]. Although only moderate yields were reported for substrates other than methyl ketones, the relatively-mild conditions and the fact that List's protocol reportedly facilitates the preparation of the aldol products from their enone precursors in one pot made these approaches attractive first strategies. Accordingly, catalyst 9-amino-9-deoxy-*epi*-quinine was synthesized from quinine in one step as reported[130], and enone **152** was subjected to List's conditions (**Figure 77**).

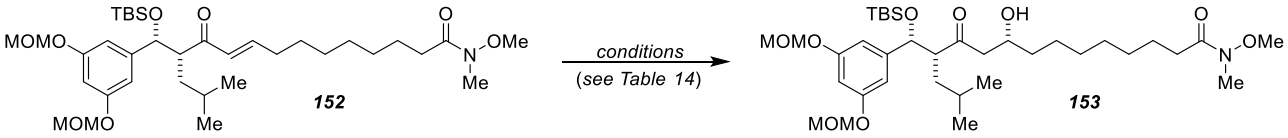


Figure 77. Conditions attempted for the diastereoselective formal hydration of enone **152**.

Table 14. Conditions attempted for the diastereoselective formal hydration of enone **152**. N.R. = no reaction. Decomp. = decomposition.

Conditions	Result
9-amino-9-deoxy-*epi*-quinine, 0.1 eq; Cl_3COOH, 0.2 eq; H_2O_2, 3 eq; 50 h	N.R.
9-amino-9-deoxy-*epi*-quinine, 1 eq; Cl_3COOH, 2 eq; H_2O_2, 30 eq; 7 days	N.R.
NaOH, 0.375 M in THF/H_2O (1:1), 36 h	N.R.
(*S*,*S*)-5-isopropyl-2-methylcyclohex-2-enol, 1.5 eq; *n*-BuLi, 1.45 eq; THF, 12 h	N.R.
D-phenylalanine, 1.60 eq; allyl alcohol; 6 days	N.R.
p-TsOH, 2.5 eq; allyl alcohol; 24 h	decomp.

Disappointingly, even after prolonged reaction times in the presence of either catalytic or stoichiometric amounts of cinchona-alkaloid catalyst, no reaction was observed under List's conditions and **152** was recovered unchanged.

In light of this failure, and hypothesizing that perhaps the steric bulk of the catalytic species might have played a role, we considered that perhaps the direct addition of various oxygen nucleophiles to unactivated **152** should be investigated before proceeding with more complex routes. Accordingly, **152** was treated with a variety of oxygen-centered nucleophiles, beginning with hydroxide itself; however, all of these conditions led simply to the recovery of unchanged starting material, with the exception of 2.5 equivalents *para*-toluenesulfonic acid in allyl alcohol, which led to the loss of both MOM groups as well as the silyl ether with no evidence of Michael addition.

At this point, although many other strategies for effecting the formal hydration on enone **152** could have been investigated, other developments concerning the revision of the proposed stereochemistry of the baulamycins had become too pressing to ignore. Specifically, it was around this time in our efforts that Guchhait *et al* published their independent synthesis of the proposed structure of baulamycin A and several diastereomers, conclusively demonstrating that structure **3** was in fact wrong and was *not* the structure of the natural product[19].

Chapter 3 – Structural Revision of the Baulamycins

In their foundational synthesis of the proposed structure of the baulamycins, Guchhait *et al* synthesized not only **3**, the proposed structure of baulamycin A, but also several additional diastereomers of **3** (**Figure 78**). However, despite their best efforts, Guchhait *et al* were unable to identify the correct structures of the baulamycins.

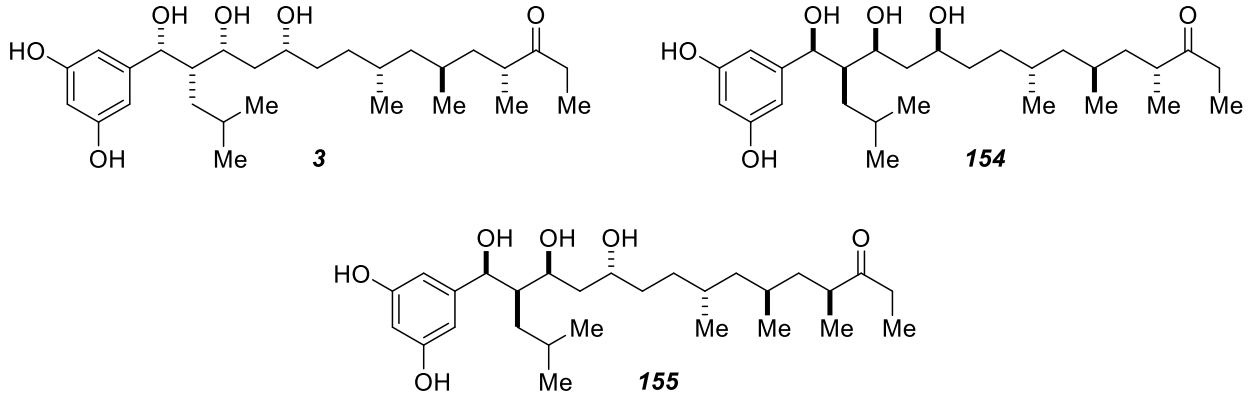


Figure 78. Compounds prepared by Guchhait *et al*.

Guchhait *et al* reported the synthesis of the proposed structure in February of 2017; in July of the same year, Aggarwal and coworkers unveiled their seminal work encompassing the total synthesis of the proposed structures of the baulamycins, as well as the synthesis of a number of diastereomers, and culminating in the identification and total synthesis of the structures of natural baulamycins A and B. Direct comparison of the spectral data for synthetic baulamycins A and B with that reported by Sherman and coworkers convincingly confirmed their revised structures for the natural products, and good agreement with the optical rotation of isolated baulamycin A allowed the assignment of the absolute stereochemistry of the natural products as well.

Between February and July of 2017, little additional information prevailed concerning possibilities for the true structure of the baulamycin scaffold. Paladugu *et al* reported[131] their

synthesis of the complete carbon framework of proposed structure **3**, in which the most advanced intermediate differed from **3** only by the presence of various protecting groups and an olefin between C-9 and C-10; however, apart from this isolated report, which did little to add to that of Guchhait *et al*, we had scant data to inform our understanding of the structures of the natural products we were ostensibly preparing.

Clearly, in light of these developments, serious reconsideration our strategy was required. Rather than continue in the Sisyphean endeavor of performing the total synthesis of an invalidated structure, we resolved to deduce the correct structure of the baulamycins based on all data available at the time, if at all possible. In this endeavor we were encouraged and inspired by R. B. Woodward's elegant and landmark work elucidating the structure of oxytetracycline, a highlight of inspiration for any natural product chemist[132-133]. Meanwhile, we continued in our attempts to identify tractable conditions for diastereoselective formal hydration on **152**, a system we now considered a "model of a model".

One aspect of the baulamycins' structural assignment which had proved puzzling from the outset was the apparent violation of Breit's rule (see Chapter 2) by the right-hand side polydeoxypropionate motif. Sherman reports that the diastereotopic methylene protons at C-5 and C-7 exhibit chemical shift differences of 0.75 ppm and 0.27 ppm, respectively (**Figure 79**). While the chemical shift difference observed for C-7 would not violate (in the sense of "provide the only known exception to") Breit's most general formulation of his empirical rule (which observes that the relative stereochemistry of 1,3-dimethyl stereodiads exhibiting chemical shift differences over 0.40 ppm for the protons on the intervening methylene have been *syn* in all known examples[68]),

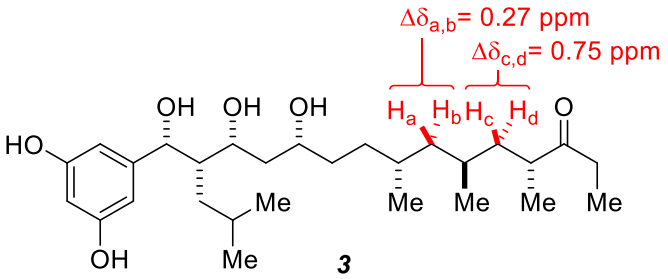


Figure 79. Chemical shift differences for diastereotopic methylene protons reported by Sherman in baulamycin A.

the 0.27 ppm chemical shift difference at C-7 *would* violate Breit's narrower observation that, for all known cases, when the moieties adjacent to such a stereodiad are entirely aliphatic and the stereodiad is *anti*, the chemical shift differences observed for the intervening methylene protons are always less than 0.10 ppm.

The chemical shift difference observed for the diastereotopic protons at C-5 is another matter entirely. Besides being fundamentally intriguing in its own right, the fact that one of these protons is reported to appear at 0.98 ppm while the other is found at 1.73 ppm in the ^{1}H NMR spectrum of baulamycin A renders this segment of the baulamycin scaffold in *flagrant* violation of Breit's rule. Specifically, Breit records no cases of an *anti*-configuration in which a chemical shift difference greater than 0.40 ppm has been observed. While it is clear that exceptions to empirical guidelines such as Breit's rule can indeed be found, the demonstration of a 0.75 ppm chemical shift difference at C-5 of structure **3** would provide such a remarkable deviation from Breit's rule as to render the rule as a whole useless, since there would be essentially *no* known threshold above which a chemical shift difference could empirically be taken to imply an *anti*-configuration (the highest chemical shift difference Breit has noted for *any* case is in fact 0.76 ppm, roughly equivalent to that observed at C-5 of the baulamycins). Thus, it seemed clear that either, on the one hand, Breit's rule was completely without basis, or, alternatively, the C-4 and C-6

stereocenters should be assigned a relative configuration of *syn* (**Figure 80**). In a word, either Breit was wrong, or Sherman.

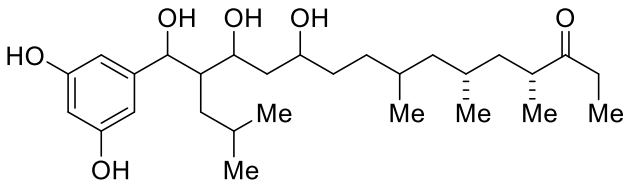


Figure 80. Revised proposal for RHS stereochemistry based on Breit's rule.

In addition to the relative stereochemistry of the C-4 and C-6 stereocenters, Breit's rule provided a strong argument for the relative configuration of the C-6 and C-8 stereocenters as well. As noted above, at least according to the more narrow formulation of Breit's rule specific to alkane motifs, one should be able to conclude that the relative configuration of C-6 and C-8 is also *syn*. While less data supports this particular set of empirical guidelines, other observations give us aid in making the necessary assignment.

Hanessian[23] and others[134] have noted that Nature rarely deviates from an all-*syn* configuration in preparing polydeoxypropionate natural products. In fact, so axiomatic is this preference that only three exceptions to the general rule are known: ionomycin[135], and two closely-related cuticular hydrocarbons from the cane beetle, 4,6,8,10,16-pentamethyldocosane and 4,6,8,10,16,18-hexamethyldocosane[136]. This well-documented natural bias, combined with the evidence provided by Breit's rule, left us confident that the relative stereochemistry of the baulamycins' right-hand side was indeed all-*syn* (**Figure 81**).

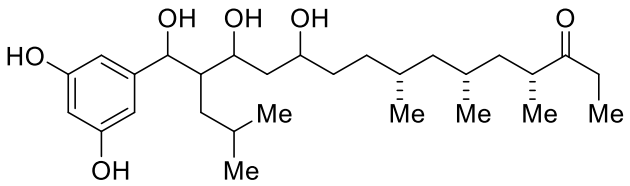
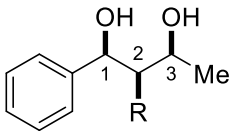


Figure 81. Revised proposal for RHS stereochemistry showing an all-*syn* polydeoxypropionate motif.

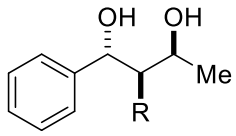
On the other side of the baulamycin scaffold, we were particularly intrigued by the large discrepancy between the coupling constant reported by Guchhait *et al* for the C-1' methine of **3** (J = 3.7 Hz) and that reported by Sherman and coworkers for isolated baulamycin A (J = 7.0 Hz). On the surface, the significance of such a coupling constant in an acyclic system such as **3** might have seemed insignificant; however, we noted that for at least one pair of homologous series resembling the baulamycin LHS, a strong pattern was discernible in which the analogous methine showed the largest coupling to its neighbor when the configuration of the system was *anti*/*anti* (**Figure 82**)[137].

syn / *syn*



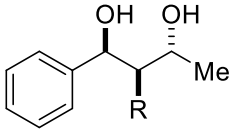
156: R = Me, $J_{H1,H2}$ = 3.3 Hz
157: R = *n*-hexyl, $J_{H1,H2}$ = 3.2 Hz

anti / *syn*



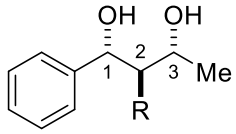
158: R = Me, $J_{H1,H2}$ = 3.0 Hz
159: R = Me, $J_{H1,H2}$ = 1.1 Hz

syn / *anti*



159: R = Me, $J_{H1,H2}$ = 7.2 Hz
160: R = Me, $J_{H1,H2}$ = 1.8 Hz

anti / *anti*



161: R = Me, $J_{H1,H2}$ = 9.1 Hz
162: R = Me, $J_{H1,H2}$ = 8.9 Hz

Moreover, the coupling constants observed in these cases, and particularly in the *anti*/*anti* cases, resembled that reported by Sherman and coworkers for the C-1' methine (J = 7.0 Hz). We rationalized these observations using a mnemonic that envisioned a pseudo-chair-like conformation containing an intramolecular hydrogen bond between the C-1' hydroxyl and its neighbor at C-13 (**Figure 83**). According to this mnemonic, the *anti*/*anti*-configuration of the baulamycin LHS should experience the strongest bias towards the (imaginary) conformation in which the C-1' methine and the C-14 methine are in an antiperiplanar relationship, at least for

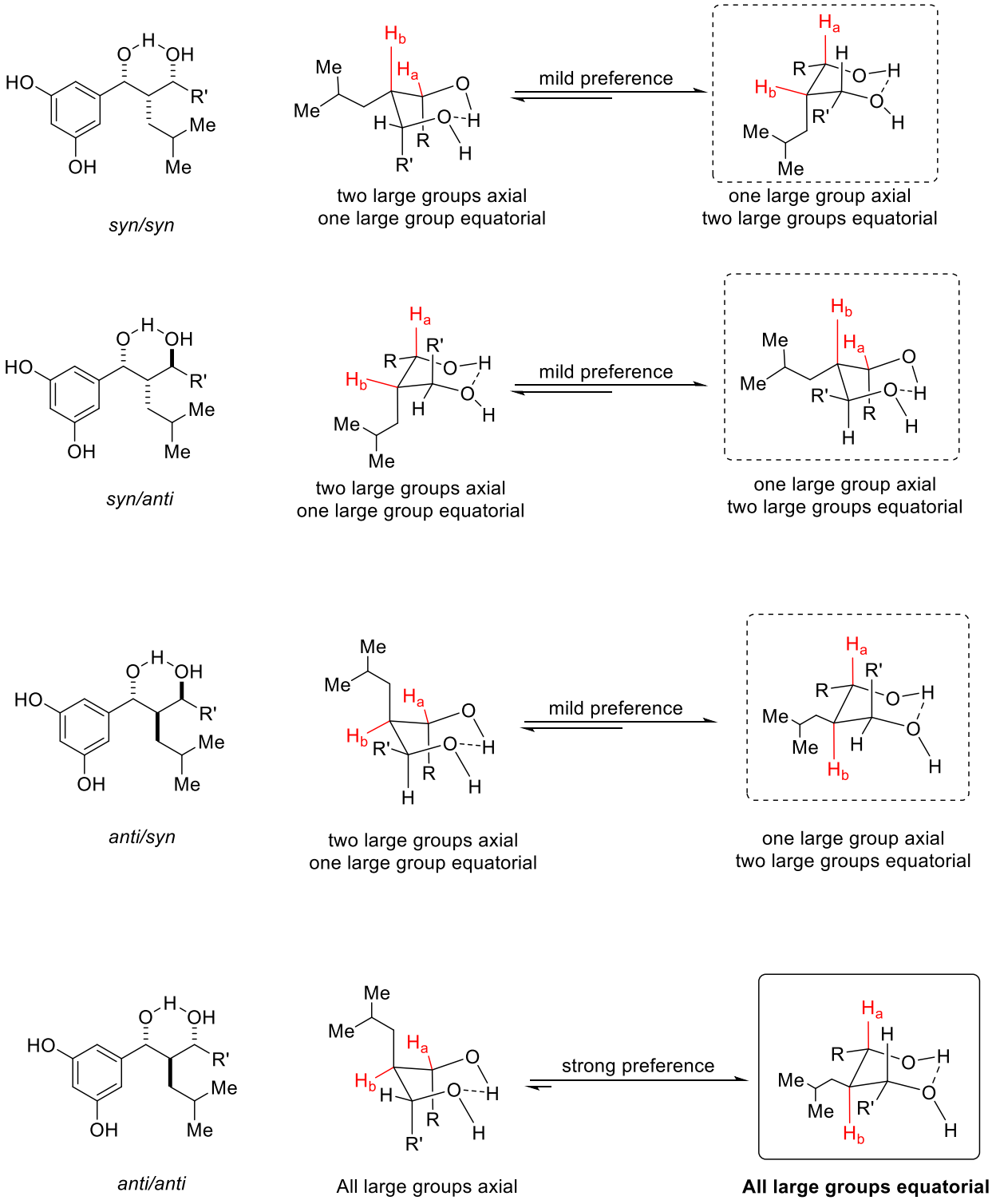


Figure 83. Mnemonic for one contribution to the baulamycin C-1'-C-14 ^{1}H-^{1}H coupling constant influenced by a theoretical intramolecular hydrogen bond between the C-1' and C-13 hydroxyls.

conformations in which intramolecular hydrogen bonding is present. While the above description is clearly an oversimplification of the baulamycins in some ways (for example, by leaving out the possible effects of the C-11 hydroxyl), we noted that further perturbation of the proposed structure reported by Guchhait *et al* in which other stereocenters were inverted (including a stereocenter on the LHS in **155**) without disturbing the *syn*-relationship between the C-1' and C-13 stereocenters always led to small (< 4Hz) coupling constants. Based on the above observations, we thus tentatively assigned the relative configuration of the baulamycin C-1', C-14, and C-13 stereocenters as *anti*/*anti* (**Figure 84**) by analogy to structures like **161** and **162**.

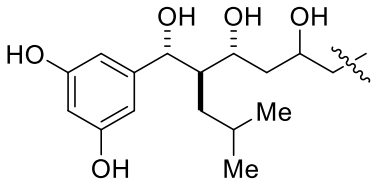


Figure 84. Proposed relative configuration of the LHS stereocenters with the exception of C-11.

The next logical part of the puzzle appeared to be the relative relationship of the C-13 and C-11 stereocenters. In tackling this problem, we imagined that some insights might be gained by examining the NMR spectra of compounds **154** and **155**, reported by Guchhait *et al*. These compounds, diastereomers of **3**, differ from each other in the relative configurations of only two pairs of stereocenters: C-13 and C-11 on the LHS, and C-4 and C-6 on the RHS. Significantly, **154** exhibits a *syn*-relationship between C-13 and C-11, while **155** exhibits an *anti*-relationship between the two stereocenters.

Before we could begin to tease out the apparent effects of inverting the relative relationship between the C-13 and C-11 stereocenters, it was necessary to convince ourselves that the inversion of the stereocenter at C-4 would have little to no effect on the relevant portions of the ^{1}H and ^{13}C NMR spectra for **154** and **155** (i.e., the portions of those spectra which corresponded to the LHS stereocenters). Fortunately, the problem of deciphering the relationship between the proton and

carbon NMR spectra of polyketide natural products and their respective stereochemical configurations has been approached many times, and significant developments have been made. In particular, Kishi and coworkers have attempted to exhaustively characterize these relationships for a number of common polyketide motifs[138-139]. While perhaps Kishi's best known work correlating structure to spectrum has been his work on contiguous polyols[140], Kishi has also made a number of other, more general observations about such relationships. In particular, in one such guideline (which we will henceforth refer to as Kishi's postulate), Kishi argues that:

> "…the spectroscopic profiles of the stereoclusters present in [certain] natural products are inherent to the specific stereochemical arrangement of the small substituents on the carbon backbone... and *interactions between stereoclusters connected with a two- or more-methylene bridge are negligible*" (italics added)[140].

This observation, borne out by Kishi's extensive work on a variety of polypropionate-containing natural products, suggests that the portion of the proton and carbon spectra for **154** and **155** corresponding to the stereocenters on the LHS should be relatively insensitive to any variation in the stereochemistry on the RHS, by virtue of the fact that the two stereoclusters are separated by two contiguous methylene units as illustrated in **Figure 85**.

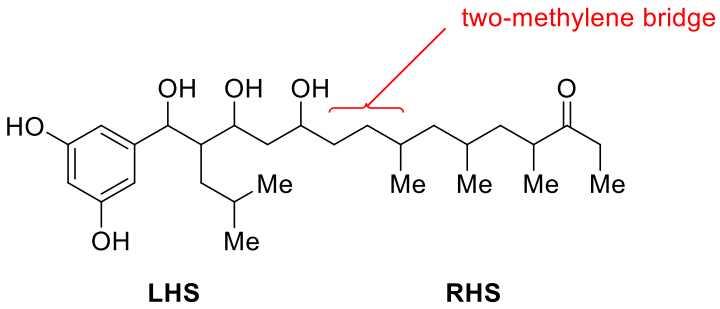


Figure 85. Structure of baulamycin A showing two contiguous methylenes separating LHS and RHS.

Thus, if Kishi's postulate holds true for the baulamycin scaffold, we would expect that the inversion of the C-4 stereocenter in **155** relative to **154** should have little to no impact on the portion of the proton and carbon NMR spectra that are derived from the LHS stereocluster. In fact,

excellent evidence that Kishi's postulate does indeed hold true for the baulamycins was provided, ironically, by no other than Guchhait *et al* themselves. After analysis of **3** showed that it was clearly distinct from isolated baulamycin A, their next move was to synthesize diastereomer **154**, which differs from **3** *only* in the relative configuration of the left- and right-hand sides; all other stereochemical relationships are identical. In fact, the proton and carbon spectra of these two compounds precisely follow Kishi's predictions: they are indeed *nearly indistinguishable*, with the ^{13}C NMR spectra in particular showing exquisite similarity (**Table 15**).

Table 15. Chemical shifts of ^{1}H and ^{13}C NMR signals for compounds **3** and **154** in ppm.

	^{1}H NMR		**^{13}C NMR**	
Atom Number	**3**	**154**	**3**	**154**
1	2.52	2.52	8.1	8.1
2	1.00	1.04	35.1	35.1
3	-	-	218.4	218.4
4	2.70	2.69	45.0	44.8
5	1.20, 1.46	1.20, 1.46	42.4	42.4
6	1.50	1.49	29.2	29.3
7	1.09	1.09	46.2	45.8
8	1.48	1.48	31.4	31.4
9	1.28	1.40, 1.16	34.4	34.5
10	1.44	1.49, 1.40	35.9	36.0
11	3.69	3.69	72.3	72.4
12	1.63, 1.67	1.65	42.4	42.3
13	3.96	3.98	75.1	75.1
14	1.67	1.68	49.3	49.3
15	1.38, 1.23	1.39, 1.23	33.4	33.4
16	1.23	1.23	28.3	28.3
17	0.78	0.77	23.4	23.4
18	0.64	0.63	22.9	23.0
19	1.03	1.03	17.0	17.0
20	0.83	0.83	19.8	19.8
21	0.84	0.84	19.8	20.0
1'	4.82	4.83	76.8	76.8
2'	-	-	148.6	148.6
3'	6.32	6.33	105.7	105.7
4'	-	-	159.3	159.3
5'	6.12	6.12	102.0	102.0

Based on the above data, we were confident that the inversion of the C-4 stereocenter in **155** relative to **154** would have essentially no effect on our comparison of the LHS components of both ^{1}H and ^{13}C NMR spectra of these compounds. Accordingly, we performed a systematic comparison of the ^{1}H NMR signals for the relevant portions of **154** and **155** with the corresponding signals in the ^{1}H NMR spectrum of isolated baulamycin A (**Chart 1**). We then performed the same comparison for the ^{13}C NMR spectra of these compounds (**Chart 2**). As can be seen, there is little-to-no difference in the degree of deviation from isolated baulamycin A for the non-backbone signals (i.e., C-15, C-16, C-17 and C-18) in the LHS of either **154** or **155**. On the other hand, clear differences between **154** and **155** can be seen in the agreement of each compound's spectra with natural baulamycin A for signals produced by C-1', C-14, C-13, C-12 and C-11, corresponding to the LHS backbone.

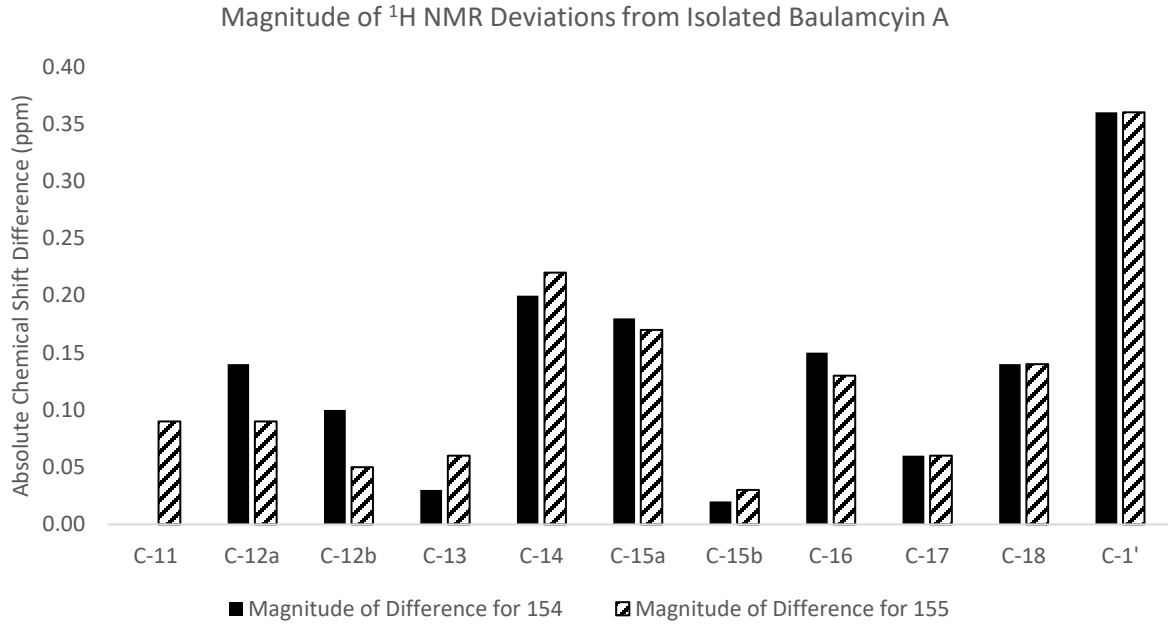


Chart 1. Magnitude of deviation in chemical shift from isolated baulamycin A for key ^{1}H NMR signals in **154** and **155**.

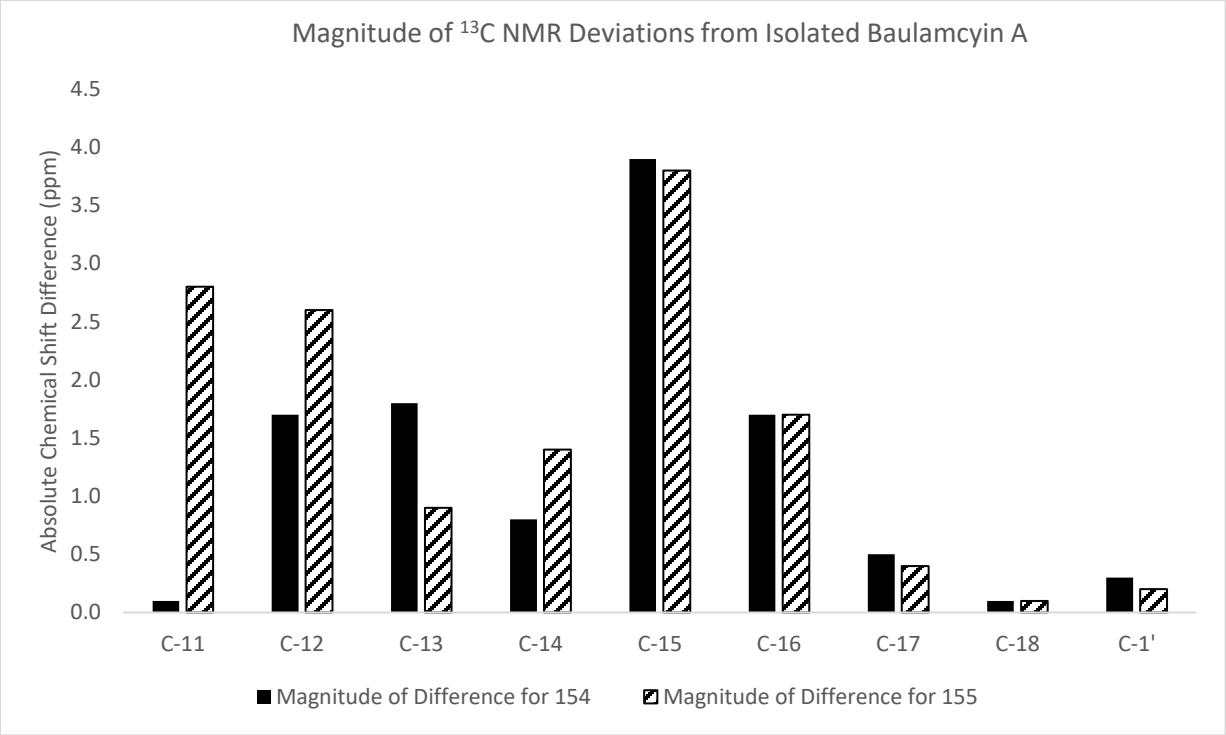


Chart 2. Magnitude of deviation in chemical shift from isolated baulamycin A for key ^{13}C NMR signals in **154** and **155**.

These differences can be summed up in two key observations based on the above data. First, agreement of the spectra collected with that of natural baulamycin differ sharply when it comes to C-11. In both the proton and carbon spectra of **154**, the signals produced by C-11 and its corresponding methine proton are in nearly exact agreement with the spectrum of natural baulamycin. Conversely, there is a relatively sharp disagreement between the natural signals and the signals for C-11 in the ^{1}H and ^{13}C spectra of **155**, with the ^{13}C signal deviating by almost 3 ppm and the proton signal deviating by nearly 0.10 ppm. Thus, at least when it comes to C-11, it is clear that **154**, with a *syn*-relationship between the C-13 and C-11 stereocenters is in closest agreement with the natural product itself. Second, by aggregating the data above, we can come up with values for the "total discrepancy" in both ^{1}H and ^{13}C spectra for compounds **154** and **155**. These values are shown below in **Table 16**.

Table 16. Total deviation from natural baulamycin A for **154** and **155** in both ^{1}H and ^{13}C spectra.

Compound	^{1}H NMR	^{13}C NMR
154	1.38 ppm	10.9 ppm
155	1.40 ppm	13.9 ppm

Clearly, both **154** and **155** are in relatively close agreement with the spectra of natural baulamycin A. However, between the two and overall, it is again compound **154** which finds itself in closest agreement with the spectra of natural baulamycin A. In particular, we note that there is almost an additional 3 ppm of discrepancy in the agreement of the ^{13}C NMR spectrum of **155** with that of natural baulamycin as compared to that of compound **154**. Ultimately, considering the overall superior agreement of **154** with the spectra of natural baulamycin, and taking into particular consideration the better agreement of the signals for C-11, the stereocenter in question, we felt confident in concluding that there must exist a *syn*-relationship between the C-13 and C-11 stereocenters in natural baulamycin A, mirroring that observed in compound **154** (**Figure 86**).

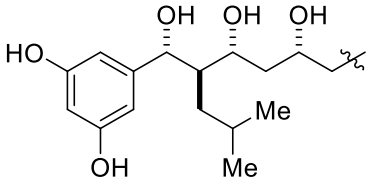


Figure 86. Proposed relative stereochemistry of the LHS.

The last task in the establishment of the relative stereochemistry of the baulamycin scaffold was to assign the relative stereochemical relationship between the LHS as a whole and the RHS as a whole (i.e., between the stereocenter at C-11 and the stereocenter at C-8). In other words, we still needed a means to discriminate between structure **163** and structure **164** (**Figure 87**).

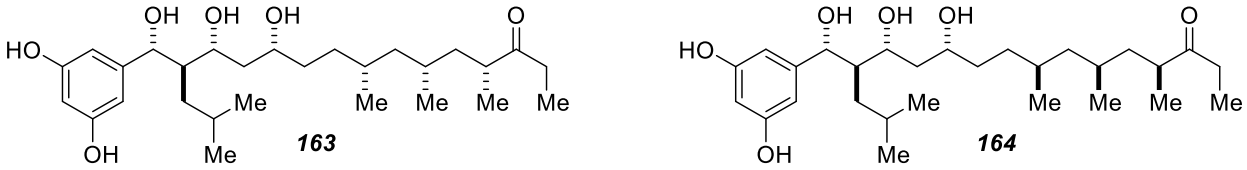


Figure 87. Two possible configurations of the baulamycin scaffold, based on the available evidence to this point.

Of all the stereochemical relationships in the baulamycin scaffold, the relative relationship between C-11 and C-8, separated as they were by two contiguous methylene units, seemed to us to be by far the most obscure. We expected that the ^{1}H and ^{13}C NMR spectra of **163** and **164** should be near-identical in accordance with Kishi's postulate, as had been so aptly demonstrated by Guchhait *et al* in the case of **154** and **155**. Thus, the problem appeared at first glance intractable.

Nonetheless, wanting to stake our claim one way or another, we considered that perhaps a clue might be found in the original work performed by Sherman and coworkers in their initial assignment of the relative stereochemistry of the baulamycins. Specifically, Sherman's group had employed what has become known as *J*-Based Configuration Analysis (JBCA), a method of assigning relative stereochemistry in acyclic systems based on the use of both $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ coupling constants to establish the relative relationships of sequential non-quaternary stereocenters[141]. JBCA, as used by Sherman and coworkers, relies on the assumption that the most-populated conformations in acyclic systems like the baulamycins are all staggered, with little (i.e., < 10°) deviation from ideality. While this assumption appears to generally hold true for acyclic systems in which branching is confined to relatively small substituents, larger substituents may render this supposition invalid. Significantly, in their seminal paper establishing the principles of JBCA, Matsumori *et al* note that substituents bulkier than methyl and hydroxyl may perturb the conformation distribution of polyketide-like scaffolds such that the application of JBCA becomes impossible[141].

Among other possible issues, it appears likely that one of the pitfalls in Sherman's application of JBCA to the baulamycin scaffold was interference from the isobutyl/phenyl substitutions on the LHS, and conformational perturbation engendered by the carbonyl adjacent to the methyl-bearing stereocenter at C-4. On the other hand, the core of the baulamycin scaffold, consisting of the

methyl-bearing stereocenter at C-11, the methyl-bearing stereocenter at C-8, and the two methylene units between them, provides a perfect example of the type of system JBCA is apparently well-suited to analyze. Barring errors in the data which form the basis of the analysis, there appeared to be absolutely no reason why the particular analysis employed by Sherman and coworkers should have failed for this particular portion of the baulamycin scaffold. Thus, it seemed reasonable to us to assume that, if any of the relative stereochemical relationships assigned by Sherman and coworkers were in fact correct, it might well be the relationship between C-11 and C-8. Thus, in the absence of data to the contrary, we tentatively proposed that the correct structure of baulamycin A was in fact **163**, exhibiting a *syn*-relationship between the "innermost" stereocenters on the left- and right-hand sides.

Before we were able to find further ways to investigate our proposed stereochemical assignment for the baulamycin scaffold, we were gratified to learn of its validation by Aggarwal's seminal report of the total synthesis of baulamycin A, in which the natural product was shown to exhibit the structure shown in **1**, the optical antipode of structure **163**. Thus, our tentative hypothesis concerning the *syn*-relationship between the stereocenters at C-11 and C-8 was in fact borne out, and the necessity for further investigations into the stereochemical configuration of the baulamycins was simultaneously eliminated. Accordingly, we turned our attention to the completion of a redesigned synthesis toward revised structures **1** and **2**.

Chapter 4 – Total syntheses of baulamycins A and B

4.1 Overview of Synthetic Strategy

With the stereochemical configuration of the baulamycin scaffold confirmed and the absolute stereochemistry assigned by Aggarwal's total synthesis, our next task was to revise our plan of attack in order to target the corrected structures. The intentional flexibility of our initial approach now paid rich dividends, and we rapidly devised a new approach based on our previous work toward the both sides of the proposed structure (**Figure 88** and **Figure 89**).

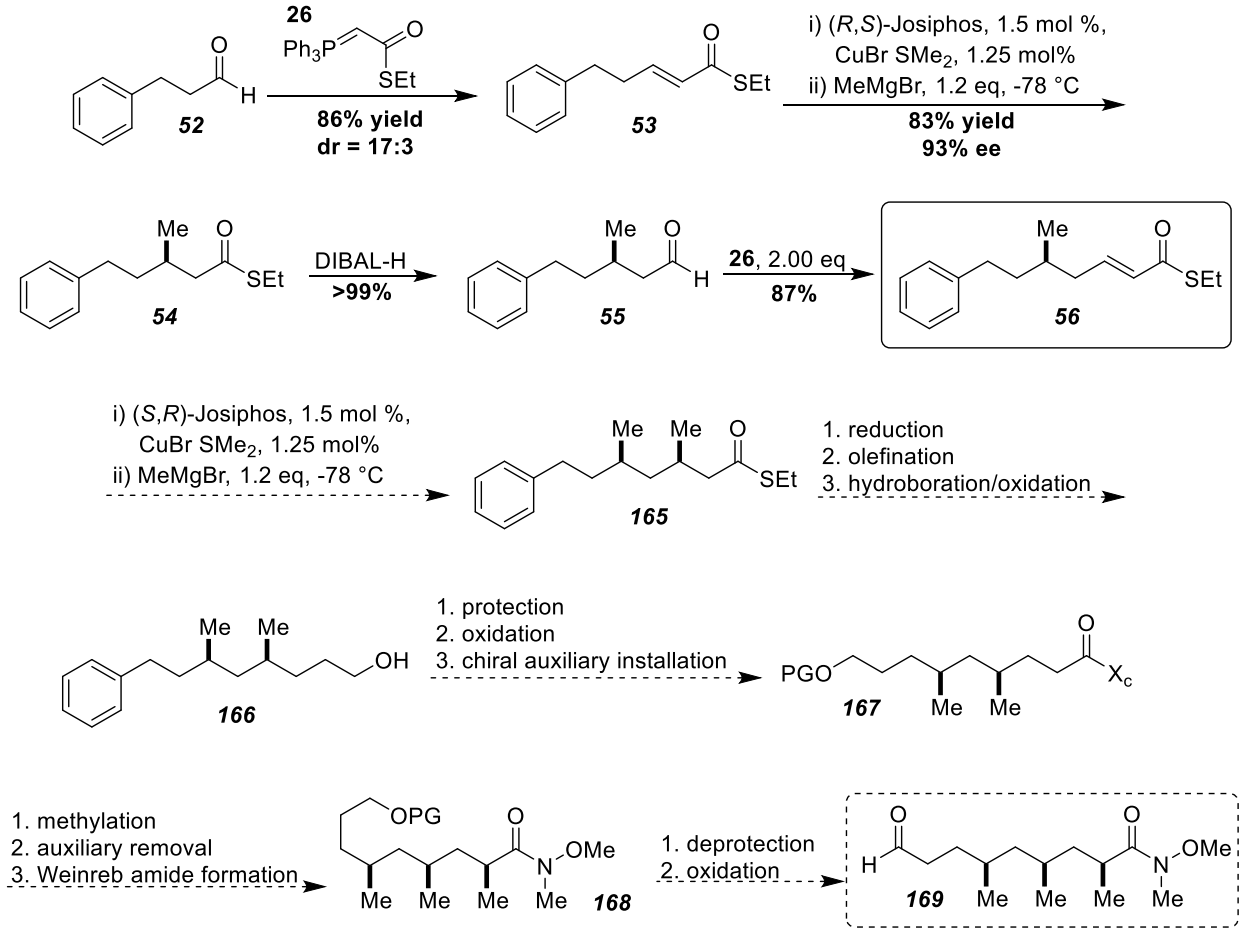


Figure 88. Proposed approach to the revised RHS starting with known compound **56**. PG = protecting group; X_c = chiral auxiliary.

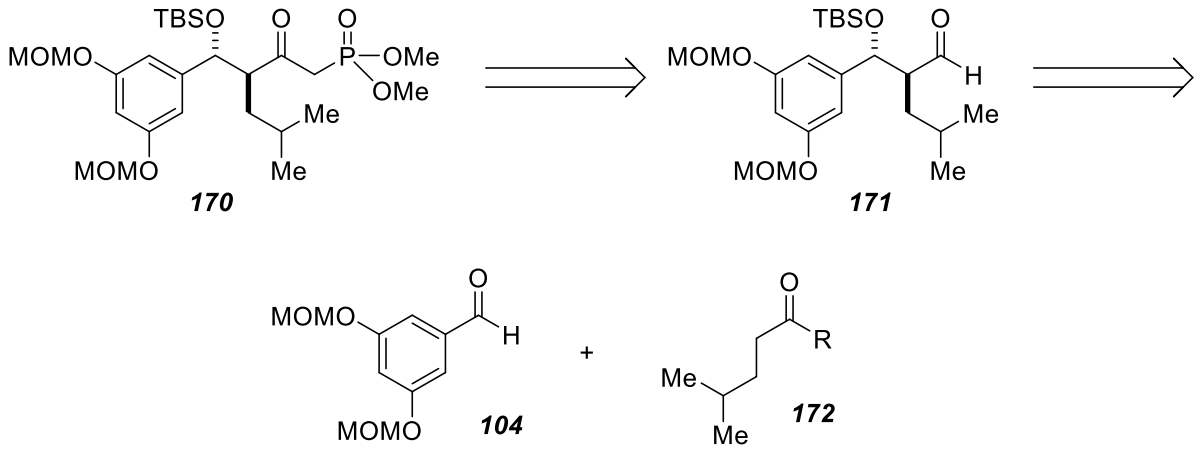


Figure 89. Retrosynthetic analysis of the revised LHS.

4.2 Synthesis of the Right-Hand Side

Since the absolute configuration of the first stereocenter in our synthesis of the proposed RHS matched that of the corresponding stereocenter in the newly-revised structure, we were able to begin our synthesis of the revised RHS with known α,β-unsaturated-γ-methyl thioester **56** (**Figure 90**).

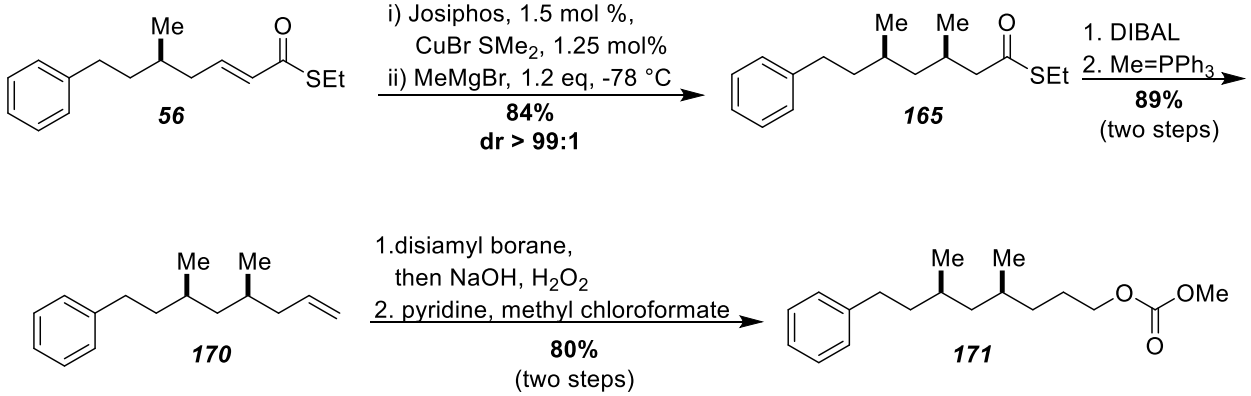


Figure 90. Installation of second stereocenter in the revised RHS synthesis and subsequent steps.

Pleasingly, installation of the critical second methyl-bearing stereocenter by asymmetric conjugate addition proceeded in good yield and excellent diastereoselectivity to afford β,γ-dimethyl thioesters **165**. Indeed, we found that the diastereoselectivity of this conjugate addition was actually improved relative to the analogous construction of *anti*-dimethylthioester **57** in the synthesis of the proposed RHS, perhaps indicating a slight substrate bias towards the *syn*-

configuration. Feringa has reported slightly higher diastereoselectivity for *syn*-products; however, the effect was very slight, with a 24:1 d.r. for *syn*-addition and a 19:1 d.r. for *anti*-addition in the example given[32]. Since we had previously synthesized the corresponding *anti*-diastereomer (**57**), the relative stereochemistry of **165** could be unequivocally confirmed by the application of Breit's rule (**Figure 91**), establishing conclusively that **165** did indeed exhibit a *syn*-configuration.

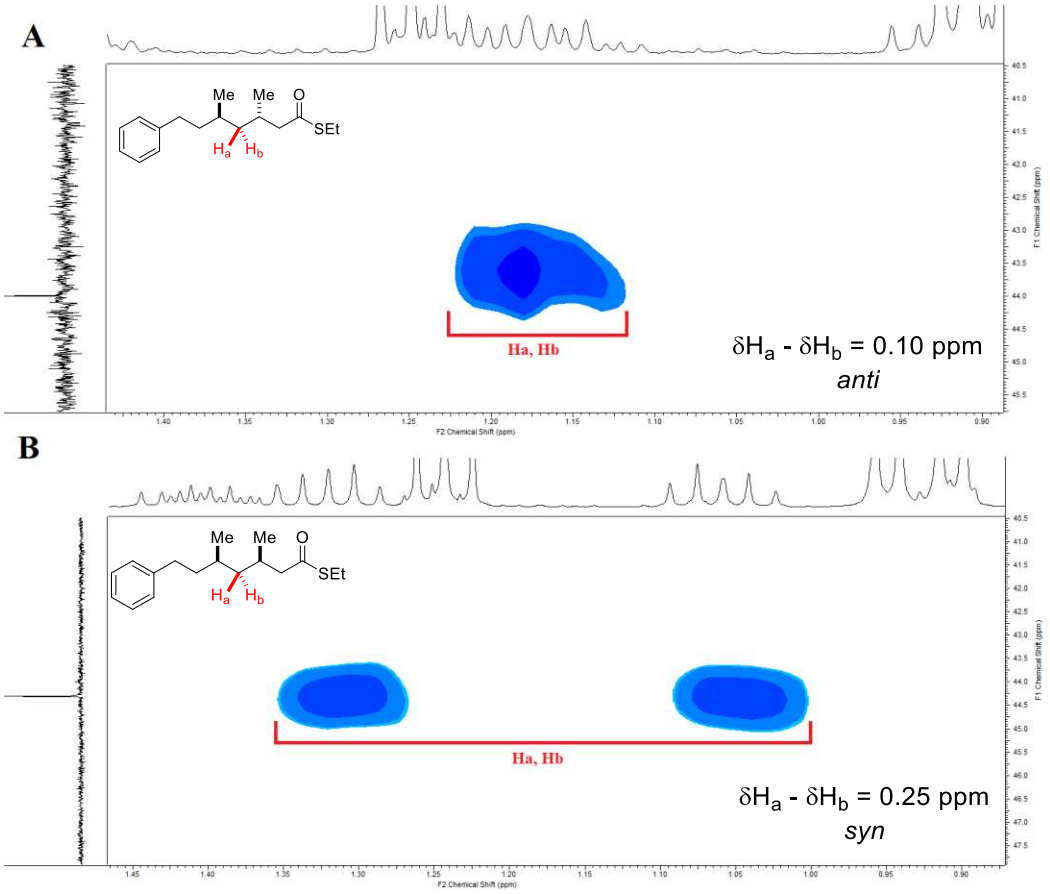


Figure 91. Proof of stereochemistry for **165** showing (A) the chemical shift difference for the diastereotopic protons on the corresponding *anti*-diastereomer, which is smaller (B) the chemical shift difference for the analogous protons on **165**, demonstrating a *syn*-configuration for **165**.

Reduction of **165** with DIBAL-H afforded the corresponding aldehyde in near-quantitative yields, and subsequent Wittig olefination also proceeded in good yield to give terminal olefin **170** in 89% yield over two steps. Hydroboration-oxidation using our optimized condition with our

optimized conditions using disiamylborane was quantitative, and subsequent protection proceeded as expected to afford carbonate **171** in 80% yield.

Having now arrived at the crucial task of oxidizing **171** to the acid, we considered ways in which we could optimize the as-yet moderate yields of this important oxidation. One transformation which had come to our attention since we had last required the conversion of R-Ph to R-COOH was a procedure which has been referred to as "dry ozonolysis".

Dry ozonolysis, or the co-adsorption of a substrate and O_3 to silica gel at cryogenic temperatures followed by warming, has been known for at least forty years; the propensity of ozone to adsorb to silica at low temperatures has been known for at least forty years before that[142]. Dry ozonolysis exhibits considerably enhanced oxidative power relative to "traditional" ozonolysis procedures, and has been shown to induce the oxidation of a wide variety of recalcitrant and non-traditional substrates, including unactivated tertiary hydrocarbons and aromatics. The transformation has been the subject of at least one *Org. Syn.* preparation[143], has been partially reviewed[144], and contains an entry in the *Encyclopedia of Reagents for Organic Synthesis* as the reagent "Ozone-Silica Gel" [145]. Despite this extensive documentation, little recent application of dry ozonolysis has been noted, with essentially no reports of preparative use during the last twenty years[142].

Far from being deterred by this neglect of an apparently-useful transformation, we viewed this as an opportunity to bring a safe, convenient, and highly economic transformation into the twenty-first century. We were of the opinion that O_3-SiO_2 had the potential to be uniquely suited to the task of oxidizing **171** to acid **172**, as the use of dry ozonolysis to transform arenes to acids was already well-known[146]. In the event, we were delighted to find that this was indeed the case, with oxidation under dry ozonolysis conditions proceeding in near-quantitative yields on scales up

to 7 grams (**Figure 92**). Moreover, the simplicity of the procedure was itself a valuable asset, as workup consisted of simply eluting the product from silica with ethyl acetate.

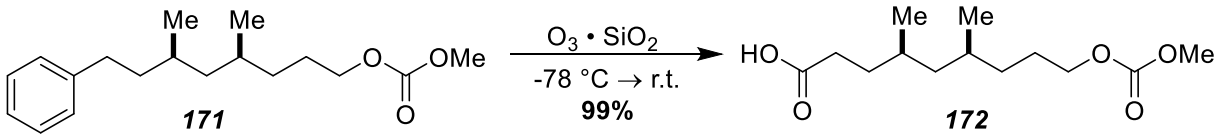


Figure 92. Successful application of dry ozonolysis in the oxidation of **171**.

Having thus handily solved what we viewed as the major supply problem in our proposed route to RHS aldehyde **169**, we turned our attention to the coupling of **172** with commercially-available (*S*)-4-benzyloxazolidinone **173** (**Figure 93**). Lithiation of **173** under mild conditions followed by treatment with the mixed anhydride of **172** and pivalate smoothly gave *N*-acyloxazolidinone **174** as expected, and diastereoselective methylation of the sodium enolate of **174** gave alkylated *N*-acyloxazolidinone **175** in good yield as a single detectable diastereomer.

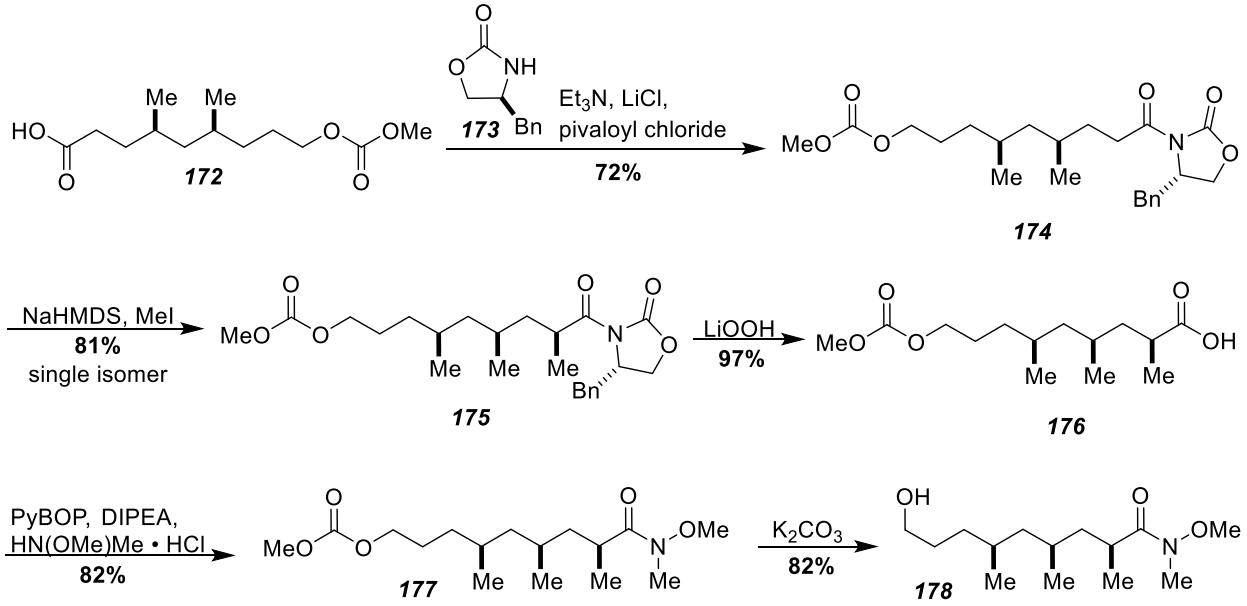


Figure 93. Synthesis of revised RHS alcohol **178** from protected acid **172**.

Once again, Breit's rule allowed confirmation of the stereochemistry of the newly-formed stereogenic center at C-4: we observed a remarkable 0.84 ppm difference in chemical shift between the two diastereotopic protons at C-5, thus confirming that the C-4 methyl group had indeed been installed in a *syn*-relationship with C-6 (**Figure 94**).

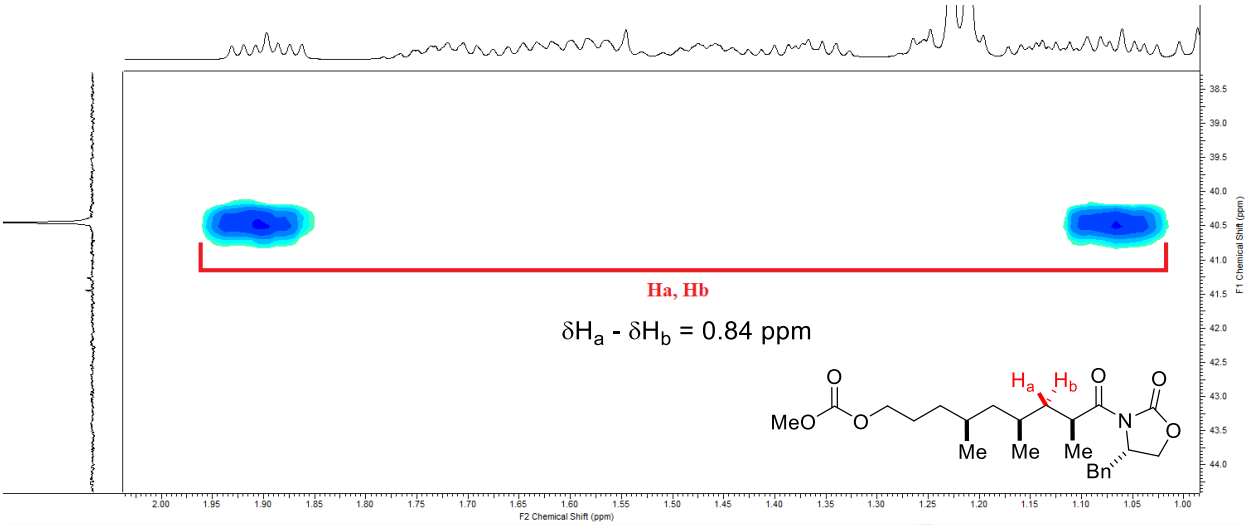


Figure 94. HSQC spectrum of **175** showing a 0.85 ppm difference in chemical shift between the protons on the C-5 methylene, confirming the *syn*-relationship of the C-4 and C-6 stereocenters.

Removal of the oxazolidinone auxiliary with lithium hydroperoxide gave acid **176** in near-quantitative yield, and subsequent treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) smoothly gave Weinreb amide **177**. Finally, deprotection was achieved by hydrolysis of the methyl carbonate ester under basic conditions in good yield. It is interesting to note that the methyl carbonate could also be removed by treatment with resin-bound lipase from *Candida antarctica* (sold as "Novozyme 435" by Sigma-Aldrich) and five equivalents of water in *tert*-butyl methyl ether at 35 °C. Subjection of **177** to the latter conditions for eleven hours followed by evaporation of volatiles revealed 66% conversion to **178**; however, the reaction was not further developed.

4.3 Synthesis of the Left-Hand Side

While work on the right-hand side was underway, progress on the left-hand side of the revised structure was proceeding apace. In our retrosynthetic analysis, we envisioned that MOM-protected 3,5-dihydroxybenzaldehyde **102** would undergo an enantio- and diastereoselective aldol reaction with some analogue of 4-methylvaleric acid to give the key *anti*-aldol motif of the revised RHS. One possibility that seemed particularly appealing was MacMillan's report of a direct, enantioselective aldol reaction between non-equivalent (i.e., non-identical) aldehydes[147], which, in addition to being fundamentally appealing for its simplicity and step- and atom-economy, has seen use in total synthesis[148]. The fact that one of our aldehydes (**102**) would be non-enolizable also seemed promising. Accordingly, volatile 4-methylpentanal was prepared in one step and modest (unoptimized) yield from 4-methylpentanol (**Figure 95**), and subjected to MacMillan's conditions with **102**. Unfortunately, despite prolonged reaction times and increases in temperature, starting material was the major component of this reaction even after one week. Given our uncertainty about the level of *anti*-selectivity in this reaction (MacMillan reports excellent enantioselectivity but a 3:1 d.r. for similar substrates), minor constituents were not separated and development of this reaction was abandoned.

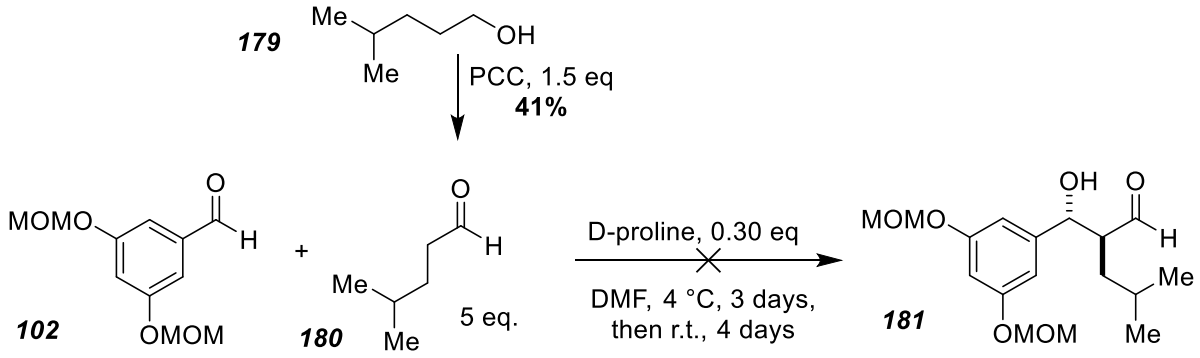


Figure 95. Attempted MacMillan-style aldol reaction between 4-methylpentanal and **102**.

With MacMillan's chemistry out of the question, we next turned ourselves to more traditional approaches to the LHS aldol motif. Evans' magnesium-halide catalyzed *anti*-selective aldol reactions of *N*-acylthiazolidinethiones with aryl aldehydes[149] were an attractive choice for several reasons: the diastereoselectivities were reportedly >19:1 for similar substrates, and the thiazolidinethione auxiliaries could be easily removed to yield the aldehyde in a single step under known conditions[150].

Accordingly, known[149] *N*-acylthiazolidinethione **182** was synthesized as described[151] from 4-methylvaleric acid and (*R*)-4-benzylthiazolidine-2-thione (in turn prepared by reduction of D-phenylalanine[152] followed by condensation with carbon disulfide[153]). Reaction of **182** with **102** under Evans' conditions (**Figure 96**) proceeded smoothly, giving the TMS-aldol in excellent yield as a single diastereomer.

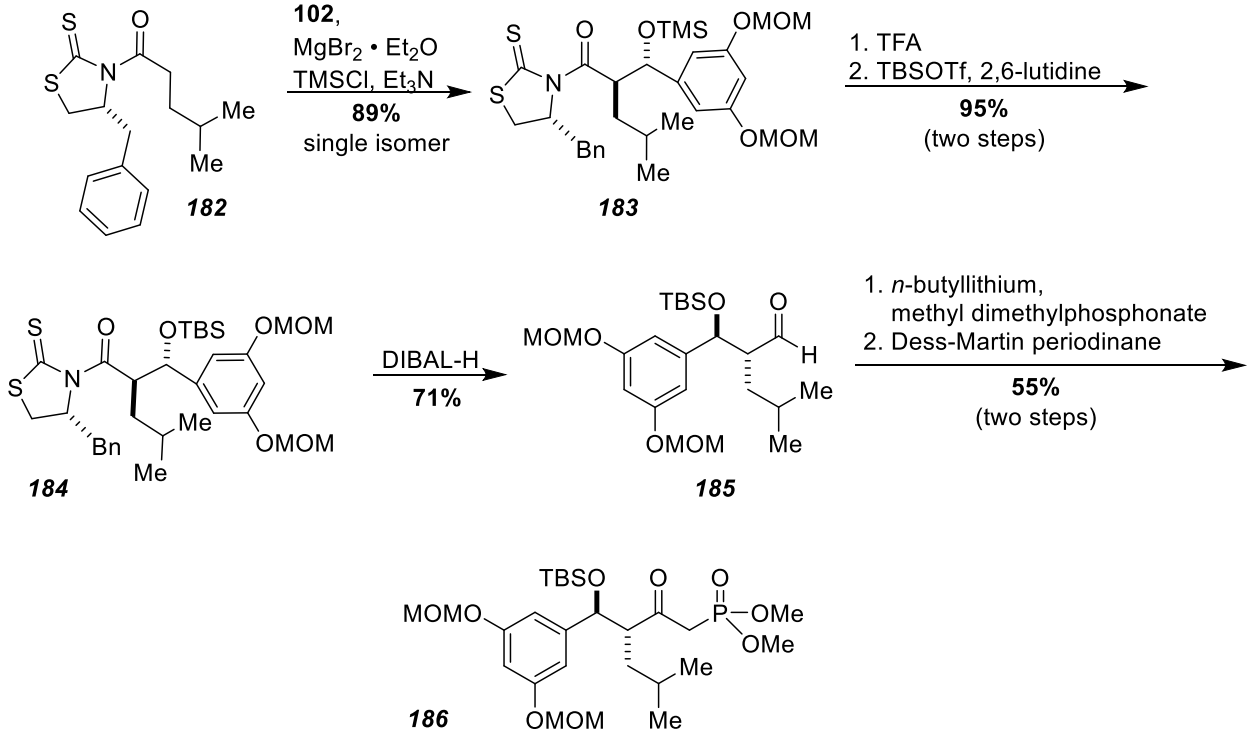
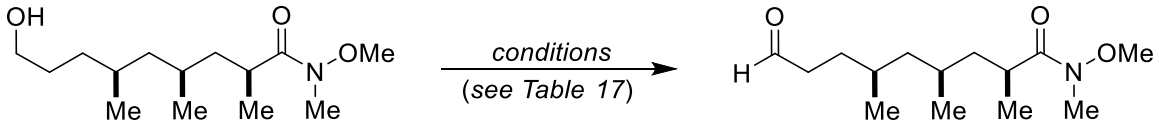


Figure 96. Synthesis of LHS aldehyde **186** using Evans' *anti*-selective aldol.

Desilylation with TFA in DCM spared the methoxymethyl ethers; subsequent re-protection as the TBS-ether gave **184** in near-quantitative yield over two steps. Half-reduction of **184** with two equivalents of DIBAL-H smoothly gave known[21] aldehyde **185**, thus confirming the *anti*-relationship between C-1' and C-14. Finally, treatment of **185** with the lithium anion of methyl dimethylphosphonate followed by oxidation of the resulting inconsequential mixture of β-hydroxyphosphonate diastereomers easily gave β-ketophosphonate **186** in respectable yield over two steps.

4.4 Coupling and Formal Hydration of Coupled Scaffold

Having established a path to important RHS precursor **178** and an efficient route to LHS β-ketophosphonate **186**, we now turned our attention to the oxidation of **178** to aldehyde **169**. Unsurprisingly, identifying appropriate conditions for the isolation of pure **169** proved challenging. Like model RHS aldehyde **137** before it, **169** proved highly susceptible to autooxidation in solution and upon storage, and a number of conditions were screened (**Figure 97**). Eventually, it was found that oxidation by the Dess-Martin periodinane, which was rapid, followed by filtration through a plug of silica eluting with 1:1 hexanes ethyl acetate provided **169** in good yield and in sufficient purity for immediate use in the next step (immediate use was crucial to achieving good yields in the subsequent step).



177 ***169***

Figure 97. Conditions attempted for the oxidation of **177** to **169**.

Table 17. Conditions for the oxidation and purification of **177**. N.D. = not determined.

Oxidation Conditions	Purification	Yield of 169
$(COCl)_2$, 3 eq; DMSO, 6 eq; Et_3N, 9 eq	(none)	9%*
Dess-Martin periodinane, 1.5 eq	partitioning btw. ether and water	N.D. (impure)
Dess-Martin periodinane, 1.5 eq	column chromatography and isolation	N.D. (oxidized on storage)
Dess-Martin periodinane, 1.5 eq	silica plug; immediate use	83 - 90%

* yield of enone after subsequent coupling with **186** under Paterson's conditions.

Horner-Wadsworth-Emmons olefination of freshly-prepared **169** with β-ketophosphonate **186** proceeded in good yield and excellent *E*-selectivity to give fully-elaborated enone **187** (**Figure 98**). The *cis*-isomer was never detected, even upon close examination of the crude ^{1}H NMR spectrum. Crucially, the reaction proceeded to completion even with equimolar amounts of **169** and **186**, ensuring maximally-efficient use of these advanced and precious intermediates. Masamune's conditions[154] were also explored; however, in our hands the corresponding reaction was extremely sluggish, resulting in the consumption of **169** through autooxidation before the reaction could reach completion.

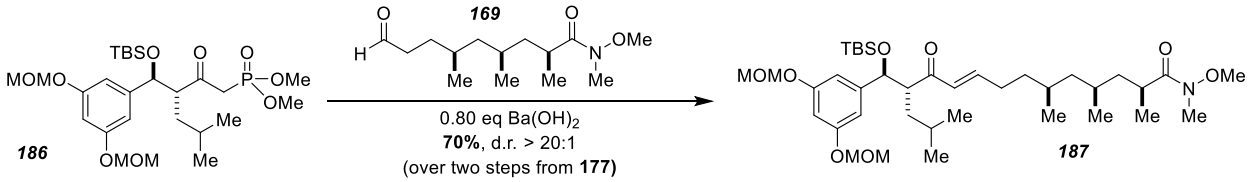


Figure 98. Successful Horner-Wadsworth-Emmons olefination of **169** with **186** under Paterson's conditions.

Pleasingly, Paterson's conditions performed well even on a gram scale, and we were thus able to isolate over 1 gram of **187** in pure form. With ample quantities of **187** in hand, we turned our attention to the critical task of developing condition for the diastereoselective formal hydration of **187** (**Figure 99**).

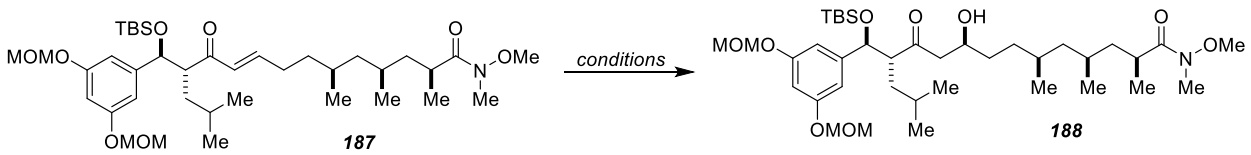


Figure 99. Proposed diastereoselective formal hydration of **187** to give **188**.

Having experienced little success with the direct addition of oxygen nucleophiles to unsaturated model systems (see Chapter 2), we considered the use of a two-step approach, in which conjugate addition of a nucleophile to the enone would give an intermediate which could then be oxidized to provide the desired β-hydroxyketone (**Figure 100**). Historically, this strategy has been generally accomplished by the use of boron and silicon nucleophiles, both of which give rise to products susceptible to oxidation; however, in light of our choice of a silicon-based protecting group for the C-1' hydroxyl, we chose to eschew silicon nucleophiles for fear of an inability to selectively oxidize a β-silyl ketone to a β-hydroxyketone in the presence of a silyl ether. Thus, the addition of boron nucleophiles to enones appeared to be the best alternative to direct addition of oxygen-centered nucleophiles, and we began to investigate various conditions for β-borylation on model systems. While we primarily employed enone **152** in this capacity, we also investigated certain transformations on cheap, commercially-available *trans*-chalcone, which figured centrally in a variety of methodology reports concerning the formal addition of water to α,β-unsaturated systems.

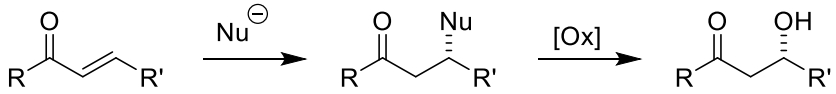


Figure 100. Employing a water surrogate in the form of an oxidizable nucleophile.

Beginning with our studies on chalcone, we first investigated conditions developed by Santos and coworkers (**Figure 101**)[155]. These conditions, run "on water", appeared to effect β-borylation with bis(pinacolato)diboron by copper(II) catalysis. The presence of an amine base was required, with 4-picoline having been shown to be optimal in Santos' work. By employing THF as a cosolvent and slightly increasing the amounts of 4-picoline employed relative to those reported, we were able to achieve good yields of β-borylated product; however, we still needed to solve the problem of stereoselectivity.

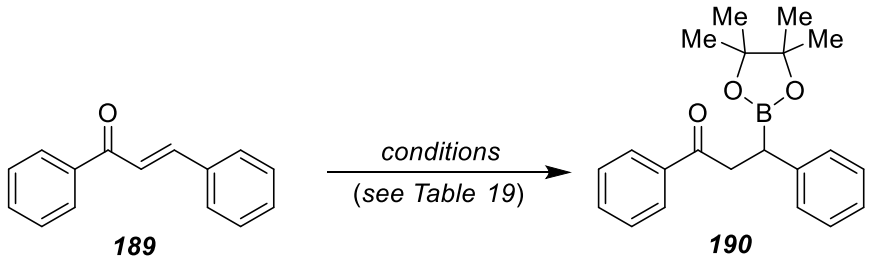


Figure 101. Attempted β-borylation of chalcone.

Table 19a. Conditions attempted for the β-borylation of chalcone.

Conditions	Yield of 190
$CuCl_2$, 1 mol %; 4-picoline, 2 mol %; $B_2(pin)_2$, 1.1 eq, THF/H_2O, 22 h	40%
$CuSO_4$, 1 mol %; 4-picoline, 5 mol %; $B_2(pin)_2$, 1.1 eq, THF/H_2O, 1 h	62%
$CuSO_4$, 1 mol %; 4-picoline, 5 mol %; $B_2(pin)_2$, 1.1 eq, THF/H_2O, 3.5 h	79%

Since Santos and coworkers had not reported any attempts to exploit chiral ligands of any kind in their reaction, we hoped that the simple addition of a chiral base to the reaction might lead to at least some level of stereoinduction. Accordingly, we attempted the use of several chiral additives (**Table 19b**); however, these conditions, perhaps predictably, gave only racemic **190**.

Table 19a. Conditions attempted for the β-borylation of chalcone. ee = enantiomeric excess.

Conditions	Yield	ee
$CuCl_2$, 1 mol %; strychnine, 2 mol %; $B_2(pin)_2$, 1.1 eq, THF/H_2O, 22 h	31%	0%
$CuSO_4$, 1 mol %; strychnine, 5 mol %; $B_2(pin)_2$, 1.1 eq, THF/H_2O, 22 h	38%	0%
$CuSO_4$, 1 mol %; 9-deoxy-9-amino-epiquinine, 5 mol %; $B_2(pin)_2$, 1.1 eq, 17 h	38%	0%
$CuSO_4$, 10 mol %; 9-deoxy-9-amino-epiquinine, 12 mol %; $B_2(pin)_2$, 1.2 eq, 12 h	67%	0%
$CuSO_4$, 1 mol %; L-proline, 5 mol %; $B_2(pin)_2$, 1.1 eq, 12 h	0%	-

Turning our attention to previously-reported strategies for chiral induction, we attempted Kobayashi's $Cu(OH)_2$-catalyzed borylation conditions[156] employing chiral bipyridyl diol **191**, reported to give good yields and excellent enantioselectivities on chalcone and other acyclic enones (**Figure 102**). Unfortunately, in our hands, these conditions failed to produce product with meaningful enantioenrichment (**Table 20**).

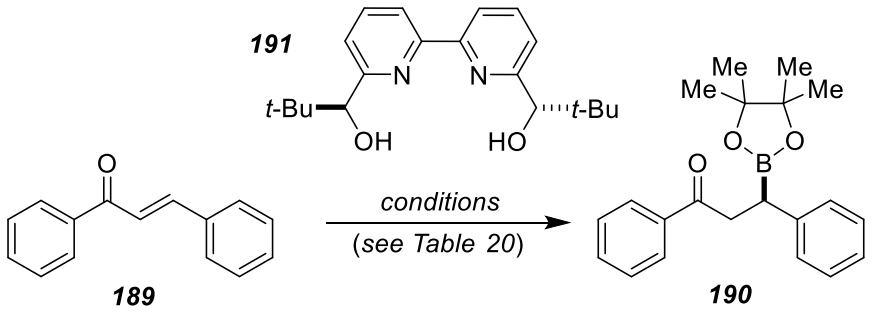


Figure 101. Attempted application of Kobayashi's enantioselective β-borylation of enones.

Table 20. Attempted borylation of chalcone using Kobayashi's catalyst. N.R. = no reaction.

Conditions	Yield	ee
$Cu(OH)_2$, 5 mol %, AcOH, 6 mol %, **191**, 6 mol %, $B_2(pin)_2$, 1.2 eq	66%	0%
$Cu(OAc)_2$, 5 mol %, **191**, 6 mol %, $B_2(pin)_2$, 1.2 eq	50%	0%
$Cu(OH)_2$, 25 mol %, AcOH, 30 mol %, **191**, 30 mol %, $B_2(pin)_2$, 1.2 eq	N.R.	-

Without having had success in the enantioselective borylation of chalcone, we considered that perhaps we would have more success achieving stereoselectivity via substrate control. Not yet having access to revised enone **187**, we began our studies with model enone **152** (**Figure 102**).

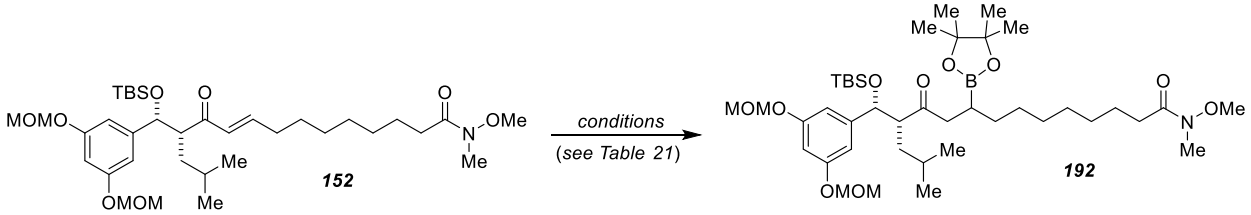


Figure 102. Attempted diastereoselective β-borylation of model enone **152**.

Table 21. Conditions employed for the diastereoselective β-borylation of **152**. N.R. = no reaction.

Conditions	Yield	dr
$CuSO_4$, 1 mol %, 4-picoline, 5 mol %, $B_2(pin)_2$, 1.2 eq, THF/H_2O	N.R.	-
$CuSO_4$, 10 mol %, 4-picoline, 50 mol %, $B_2(pin)_2$, 2.4 eq, THF/H_2O	82%	1.85 : 1
CuCl, 10 mol %, KOAc, 10 mol %, $B_2(pin)_2$, 1.1 eq, DMF	84%	2.45 : 1
$Cu(OAc)_2$, 5 mol %, **191**, 6 mol %, $B_2(pin)_2$, 1.2 eq, THF/H2O	87%	2.50 : 1

We first investigated Santos' conditions, which had afforded good yields on chalcone; however, exposure of **152** to 1 mol % copper(II) sulfate, 5 mol % 4-picoline and 1.2 eq bis(pinacolato)diboron gave only starting material after 27 hours at room temperature. Undeterred, we increased the concentrations of both copper(II) and base; this gave good yields and a d.r. of

approximately 2:1. A movement in the correct direction, this level of diastereoselectivity was nonetheless too low for preparative use on the baulamycin scaffold. Accordingly, we continued our search for conditions which might provide additional selectivity. In their seminal report describing the first example of copper-catalyzed beta borylation of enones, Miyaura and coworkers accomplish the reaction with a system containing Cu^{I} and inorganic base[157]. When applied to **152**, these conditions gave β-borylketone **192** in 84% yield with a diastereoselectivity of 2.45 to 1. Hoping to improve the diastereoselectivity still further, we applied Kobayashi's conditions to **152**; however, despite the use of chiral ligand **191**, they offered little advantage over Miyaura's protocol, giving **192** in 87% yield with a diastereoselectivity of 2.5 to 1. Meanwhile, we had perfected the oxidation of our β-borylated substrates, allowing easy access to the β-hydroxy ketones (**Figure 103**).

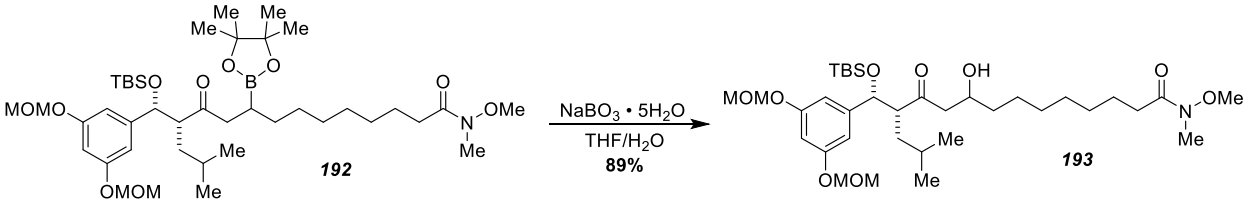


Figure 103. Simple oxidation of β-borylketone **192** to aldol **193** with sodium perborate.

Around this time we completed our synthesis of revised-structure enone **187**. With several sets of conditions providing appreciable, albeit low, diastereoselectivity on model substrate **152**, we now turned our attention to the diastereoselective borylation of our true target (**Figure 104**).

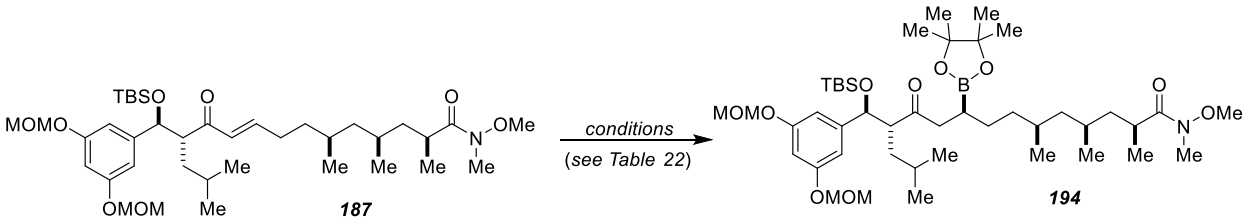


Figure 104. β-Borylation of enone **187**.

Table 22a. Conditions attempted for the β-borylation of **187**. N.R. = no reaction.

Conditions	Yield	dr
CuCl, 0.55 eq, 1.12 eq AcOK, 1.1 eq $B_2(pin)_2$, DMF	N.R.	-
$CuSO_4$, 10 mol %, 4-picoline, 1.0 eq, $B_2(pin)_2$, 1.2 eq, THF/H_2O	84%	1 : 1
$CuSO_4$, 10 mol %, NaOAc, 15 eq, $B_2(pin)_2$, 1.2 eq, THF/H_2O	47%	2 : 1
$CuSO_4$, 10 mol %, NaOAc,15 eq, $B_2(pin)_2$, 1.2 eq, L-proline, 10 eq, THF/H_2O	N.R.	-
$CuSO_4$, 10 mol %, L-proline, 10 mol %, $B_2(pin)_2$, 1.2 eq, THF/H_2O	N.R.	-

In our first attempt at the borylation of **187** we chose to investigate Miyaura's conditions, since they had provided an equivalently-high d.r. to the more-complex Kobayashi conditions with less expensive reagents. Unfortunately, subjection of **187** to Miyaura's conditions gave only starting material, even with high catalyst loadings. Undeterred, we next investigated Santos' conditions. While an optimized version of the conditions employing stoichiometric 4-picoline as the base did indeed provide a good yield of **194**, the reaction proceeded without any diastereoselectivity. Conversely, use of superstoichiometric sodium acetate gave a 2:1 diastereomeric ratio, but the reaction failed to go to completion, giving **194** in a mere 47% yield. Attempts to introduce chiral bases once again met with failure, as addition of L-proline completely abolished reactivity in this system, presumably by trapping the available copper in an inactive form.

With Santos' conditions out of the question, we attempted Kobayashi's conditions (**Table 22b**); however, no reaction was observed under these conditions except when stoichiometric cupric acetate and ligand were employed. In this case, the starting material was indeed consumed, but the unidentified product of the reaction was not **194**.

Table 22b. Attempted use of Kobayashi's conditions for β-borylation of **187**. N.R. = no reaction.

Conditions	Yield	dr
$CuSO_4$, 10 mol %; **191**, 12 mol %; $B_2(pin)_2$, 1.2 eq; THF/H_2O	N.R.	-
$CuSO_4$, 9.0 mol %; **191**, 35 mol %; $B_2(pin)_2$, 2.4 eq; THF/H_2O	N.R.	-
$Cu(OAc)_2$, 1 eq; **191**, 1 eq; MeOH, 1 eq; $B_2(pin)_2$, 2.0 eq; THF/H_2O	0%	-

We next attempted a set of conditions first reported by Yun and coworkers (**Table 22c**)[158]. We elected to carry out our initial test reactions under stoichiometric conditions; gratifyingly, when **187** was treated with bis(pinacolato)diboron in the presence of stoichiometric CuCl, (*R*,*S*)-Josiphos and NaO*t*-Bu, 11-*epi*-**194** was obtained in 90% yield and > 15:1 d.r. Unfortunately, the analogous application of (*S*,*R*)-Josiphos under identical conditions failed to replicate this excellent diastereoselectivity, giving desired β-borylated ketone **194** with a diastereomeric ratio of only 3:1. Reductions in catalyst, ligand and base loadings were successfully implemented, ultimately giving **194** in good yield under catalytic conditions, but the diastereomeric ratio remained low despite repeated attempts. Apparently, **187** exhibits an inherent bias towards conjugate addition with the undesired facial selectivity; comparisons of the results of β-borylation under Yun's conditions with those performed earlier using achiral catalysts and reagents revealed that the major diastereomer produced under those non-asymmetric conditions was also 11-*epi*-**194**, rather than desired isomer **194**. Oxidation of both **194** and 11-*epi*-**194** with sodium perborate proceeded as expected to give **188** and 11-*epi*-**188**, respectively, in good yield.

Table 22c. Yun's conditions for β-borylation of **187**. N.D. = not determined.

Conditions	Yield	dr
CuCl, 1 eq; (*R*,*S*)-Josiphos, 1 eq; NaO*t*-Bu, 1 eq; $B_2(pin)_2$, 1.1 eq, THF	90% *	15 : 1
CuCl, 1 eq; (*S*,*R*)-Josiphos, 1 eq; NaO*t*-Bu, 1 eq; $B_2(pin)_2$, 1.1 eq, THF	36%	3 : 1
CuCl, 10 mol %; (*S*,*R*)-Josiphos, 30 mol %; NaO*t*-Bu, 15 mol %; $B_2(pin)_2$, 1.1 eq, THF	78%	3 : 1

* yield of 11-*epi*-**194**.

With consistently poor diastereoselectivity in the formation of **194**, but consistently excellent diastereoselectivity under Yun's conditions for the formation of the C-11 epimer of **194**, we imagined that it might be possible to produce 11-*epi*-**188** in good yield via 11-*epi*-**194**, then invert the C-11 stereocenter under Mitsunobu-type conditions with a suitable oxygen nucleophile. Hydrolysis at the C-11 oxygen would then afford β-hydroxyketone **188**. Accordingly, 11-*epi*-**194**

was prepared from **187** using Yun's conditions and oxidized to provide 11-*epi*-**188** (**Figure 105**). We then screened a series of Mitsunobu reaction conditions to attempt to identify conditions that could provide inversion of the C-11 stereocenter.

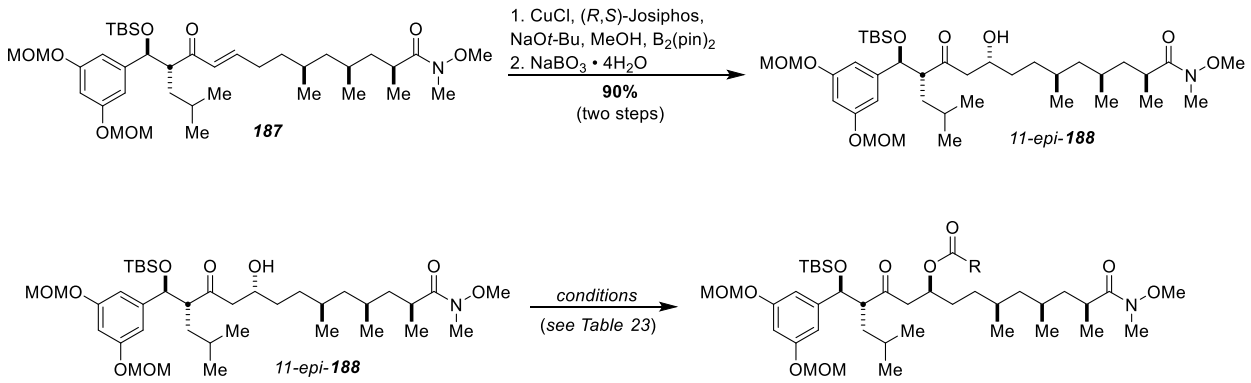


Figure 105. Preparation of 11-*epi*-**194** from **187** and subsequent screen of Mitsunobu inversions.

Table 23. Attempted Mitsunobu-type inversion of 11-*epi*-**194**. Decomp. = decomposition.

Reagents	R	Solvent	Results
2-picolinic acid, 4 eq; Ph_3P, 4 eq; DIAD, 4 eq	2-pyr	THF	decomp.
2-picolinic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	2-pyr	THF	decomp.
2-picolinic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	2-pyr	$CHCl_3$	no reaction
2-picolinic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	2-pyr	Et_2O	no reaction
2-picolinic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	2-pyr	DCM	no reaction
2-picolinic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	2-pyr	benzene	no reaction
2-picolinic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	2-pyr	toluene	no reaction
acetic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	Me	benzene	no reaction
acetic acid, 8 eq; Ph_3P, 4 eq; DIAD, 4 eq	Me	THF	no reaction
acetic acid, 8 eq; Ph_3P, 8 eq; DIAD, 8 eq	Me	THF	no reaction
acetic acid, 8 eq; Me_3P, 4 eq; TMAD, 4 eq	Me	THF	no reaction
chloroacetic acid, 3 eq; Ph_3P, 3 eq; DIAD, 3 eq	$-CH_2Cl$	THF	no reaction

Our initial endeavors were performed with 2-picolinic acid as the nucleophile. It was believed that many esters would prove challenging to remove by basic hydrolysis due to competing elimination. Conveniently, 2-picolinate esters are known to be cleaved under exceptionally mild conditions by treatment with 1 – 5 equivalents of cupric acetate in methanol, a fact which has been exploited in the context of Mitsunobu inversion of base-sensitive alcohols[159]. Unfortunately, in our system, 2-picolinate proved to be an inadequate nucleophile, showing no conversion to the ester under a variety of conditions. We next explored the use of acetic acid as the Mitsunobu

nucleophile, hoping to perhaps remove the acetate ester by enzymatic hydrolysis under neutral conditions; however, again, we observed a complete lack of conversion under a number of conditions. Puzzlingly, chloroacetic acid also failed in our hands, leading us to abandon our attempts at the Mitsunobu reaction on this substrate.

Undeterred, we considered that perhaps strategies other than conjugate addition might be exploited to eventually provide desired aldol **188**. We believed that a diastereoselective epoxidation of **187** could provide an intermediate amenable to conversion into **188** by reduction with samarium diiodide (**Figure 106**)[160].

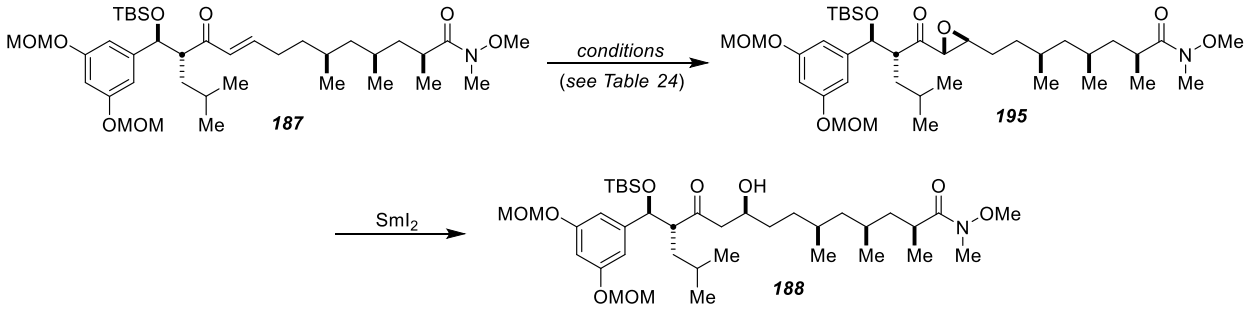


Figure 106. Proposed epoxidation of **187**.

Table 24. Conditions attempted for the epoxidation of **187**. N.R. = no reaction. N.D. = not determined.

Conditions	Yield	d.r.
(*R*,*R*)-*N*-methylpseudoephedrine, 2.4 eq; diethyl zinc, 1.1 eq; O_2, 85 h	N.R.	-
(*S*)-BINOL, 0.25 eq; Ph_3AsO, 0.25 eq; $La(iOPr)_3$, 0.25 eq; TBHP, 1.2 eq, 4 Å MS	N.R.	-
tert-butyl hydroperoxide, 20 eq; *n*-butyllithium, 15 eq, THF	N.D.	1 : 1

We began our investigations with Enders' conditions, in which asymmetric epoxidation is effected by an alkyl zinc peroxide generated *in situ* from diethyl zinc and molecular oxygen in close association with chiral amino alcohol *N*-methylpseudoephedrine[161-162]. Disappointingly, when applied to **187**, these conditions gave only recovered starting material, even after prolonged reaction times. Undeterred, we next considered Shibasaki's asymmetric epoxidation conditions employing a chiral lanthanum-BINOL-triphenylarsine oxide complex which, in the presence of

tert-butyl hydroperoxide, yields an active oxidant capable of the asymmetric epoxidation of enones[163-164]. Unfortunately, when these conditions were applied to **187**, no reaction took place. Fearing that our implementation of Shibasaki's conditions was somehow flawed, we subjected chalcone to the same conditions, which smoothly gave the desired α,β-epoxyketone. We thus concluded that, for whatever reason, **187** appeared inert to these conditions despite their demonstrated activity on other substrates. Finally, having had no luck with the asymmetric methods described above, we reasoned that perhaps the sluggish reactivity of **187** under these epoxidation conditions might translate to some substrate-controlled diastereoselectivity under more aggressive oxidation conditions. Accordingly, we treated **187** with a large excess of lithium *tert*-butyl peroxide. To our delight, we did indeed observe formation of α,β-epoxyketone under these conditions; however, subsequent successful reduction of the epoxyketone to the aldol revealed that **188** had been formed as a 1:1 mixture of diastereomers. We thus chose to abandon the idea of pursuing an asymmetric epoxidation of **187** as a route to diastereomerically-pure **188**.

At the same time, we were encouraged by the apparent susceptibility of **187** to oxidation under select conditions. Re-tooling our approach, we noted that acetonides of α,β-dihydroxyketones have been reported to be reduced efficiently to the corresponding β-hydroketones with samarium diiodide[165]. Additionally, we observed that the Sharpless asymmetric dihydroxylation[166] has been employed successfully on enones, including in the context of total synthesis[167]. Thus, we envisioned an asymmetric dihydroxylation of **187** leading to α,β-dihydroxyketone **196**, which, after protection in the form of the acetonide, could be reduced with samarium diiodide to give β-hydroxyketone **188** (**Figure 107**).

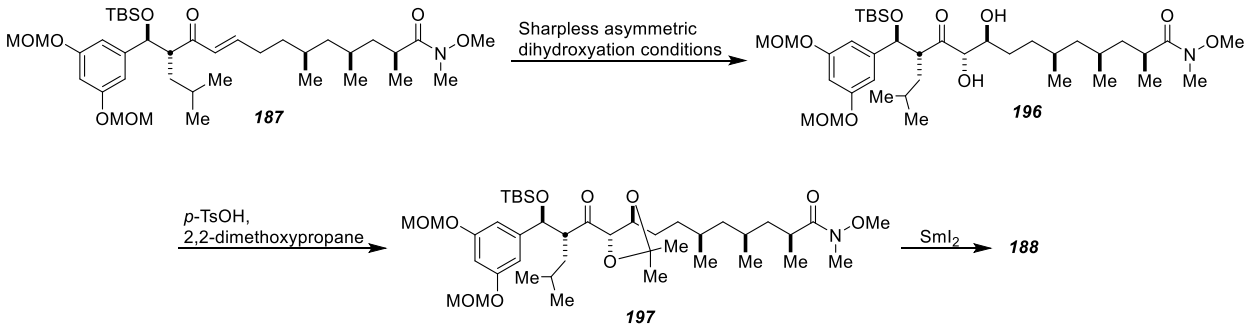


Figure 107. Proposed conversion of **187** to **188** by asymmetric dihydroxylation, protection and reduction.

Accordingly, we attempted the Sharpless asymmetric hydroxylation protocol on **187**, with the modification that 1 mol % potassium osmate and 5 mol % $(DHQ)_2PHAL$ ligand were employed rather than the traditional 0.2 mol % osmate and 1 mol % ligand as a means of compensating for the rather electron-poor nature of the enone substrate. Three equivalents each of potassium ferricyanide and potassium carbonate were employed as usual, along with one equivalent of methanesulfonamide as described by Sharpless[166]. As expected, the reaction was in fact sluggish, failing to reach completion even after 60 hours; however, we were pleased to see that, despite the low conversion, dihydroxylation was in fact observed. Integration of the C-1' protons in the crude ^1H NMR spectrum appeared to show a d.r. of 1.8:1. Unfortunately, when an aliquot of purified α,β-hydroxyketone was quantitatively protected as its acetonide and reduced with SmI_2, an unknown product, not **188**, was obtained, which appeared to be a corresponding mixture of diastereomers. Further increases in catalyst loading up to stoichiometric quantities failed to rectify the low yield and diastereoselectivity, and the unknown product of SmI_2 reduction was never conclusively identified, leading us to abandon further development of the reaction.

Finally, without many plausible alternatives, and considering that *tert*-butyl peroxide had proven an effective oxidant of **187** under select conditions, we considered an adaption of List's asymmetric hydroperoxidation conditions which had earlier proven unsuccessful in standard form

against model substrate **152**. Accordingly, we treated **187** with 20 mol % of 9-deoxy-9-amino-*epi*-quinine and 1.5 eq *tert*-butyl hydroperoxide in the presence of 60 mol % trifluoroacetic acid; however, after 3 days, **187** was uncovered unchanged with no evidence of epoxidation or hydroperoxidation at C-11.

Ultimately, despite our extensive efforts to identify alternative strategies for the introduction of the C-11 hydroxyl in a stereoselective fashion, and notwithstanding our considerable efforts to identify ways of converting 11-*epi*-**188** to **188**, it now appeared that the Cu^{I}-catalyzed β-borylation of **187** in the presence of (*S*,*R*)-Josiphos was the most effective route to diastereomerically-pure **188** available to us, despite its modest-at-best 3:1 diastereoselectivity. Fortunately, the C-11 epimers of **188** are separable by flash chromatography, although the procedure itself is tedious, as multiple iterations of chromatography are required.

Determined to proceed at all costs, we scaled up the β-borylation of **187**, achieving a 23% yield of **188** over two steps after chromatographic purification, which nonetheless provided us with sufficient material to proceed. With pure **188** in hand, we turned our attention to what appeared to be the final synthetic challenge in the synthesis of the baulamycins, the diastereoselective *syn*-reduction of the C-13 ketone (**Figure 108**).

4.5 Synthesis of Baulamycin A

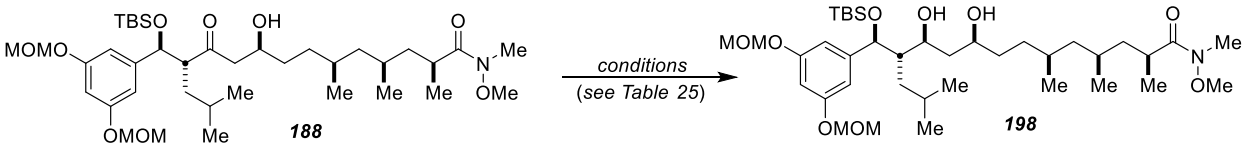


Figure 108. Diastereoselective *syn*-reduction of β-hydroxyketone **188**.

Table 25 Conditions for the *syn*-selective reduction of β-hydroxyketone **188**. N.R. = no reaction. N.D. = not determined.

Conditions	Yield	d.r.
Et_2BOMe, 1.1 eq; $NaBH_4$, 1.1 eq; THF/MeOH, -78 °C, 4 h	N.R.	-
Et_2BOMe, 1.1 eq; $LiBH_4$, 1.1 eq; THF/MeOH, -78 °C, 2 h	decomp.	-
$NaBH_4$, 2.5 eq; MeOH, 4 h, 0 °C	70%	2:1
$Zn(BH_4)_2$, 3.0 eq; toluene, -25 °C to 4 °C, 21 h	N.D.	1:1
BH_3•DMS, 2.2 eq; THF, r.t. 16 h	32%	3:1
BH_3•DMS, 4.0 eq; $TiCl_4$, 1.20 eq; DCM, -78 °C, 20 h	decomp.	-
BH_3•DMS, 2.2 eq; THF, -20 °C, 14 h	96%	4:1
BH_3•DMS, 2.2 eq; THF, -78 °C, 20 h	N.R.	-

We began our investigations with the well-known Narasaka-Prasad reduction[168-169], which frequently proceeds with exceptional *syn*-selectivity and was viewed as all-the-more attractive for its not-inconsiderable use in total synthesis[170-171]. Unfortunately, when applied to **188**, standard Prasad conditions with sodium borohydride as the reductant gave only recovered starting material. Conversely, modified conditions employing lithium borohydride reported[172] to be more active gave complex mixtures of products involving partial or complete deprotection of the methoxymethyl ethers with or without concomitant reduction.

It is interesting to note that, in their synthesis of the proposed structure of baulamycin A, Guchhait *et al* also attempted a Narasaka-Prasad-type reduction of a β-hydroxyketone at C-13, and under standard conditions they too saw no reactivity. With this in mind, we considered the possibility that the generally-congested steric environment around C-13 might be hindering reactivity under mild conditions. If so, we reasoned that diastereoselective reduction under substrate-controlled conditions might thus be possible. Accordingly, we attempted the reduction

of **188** with sodium borohydride alone at 0 °C. Pleasingly, this did indeed lead to excellent yields of the 1,3-*syn*-diol; however, the diastereoselectivity was undesirably low (d.r. = 2:1).

We next investigated the use of zinc borohydride, which has been reported[173] to give excellent selectivity for *syn*-reduction under certain conditions, not the least of which being those employed for analogous reduction by Wuest and coworkers of none other than the baulamycin scaffold itself[22]. However, as has been noted[174], achievement of excellent diastereoselectivity appears to be dependent on the presence of γ,δ-conjugation, and in our hands, freshly-prepared[175] zinc borohydride proved nonselective.

Finally, it came to our attention that a highly-selective-selective *syn*-reduction of aldols with BH_3-pyridine or BH_3-DMS in the presence of $TiCl_4$ has been reported[176]. While the use of these precise conditions led to decomposition of our substrate, we were gratified to find that reduction with BH_3-DMS alone in THF at room temperature afforded **198** with 3:1 diastereoselectivity. Further optimization of these conditions eventually led to the discovery that the use of BH_3-DMS at -20 °C in THF gave *syn*-diol **198** in near-quantitative yields and 4:1 d.r. Further reduction in temperature abolished reactivity. While these results were promising, their effectiveness was enhanced tremendously by the recognition that **198** could be rendered diastereomerically pure by protection as the acetonide followed by treatment with *p*-TsOH in DCM at 0 °C. These conditions selectively deprotected the *anti*-epimer while leaving the *syn*-acetonide intact, allowing a rapid chromatographic purification to provide pure *syn*-acetonide in 67% yield over two steps (**Figure 109**)[177-178]. The initial acetonide protection required optimization, and initial attempts using 2,2-dimethoxypropane without a dehydrating agent did not proceed to completion even over long reaction times.

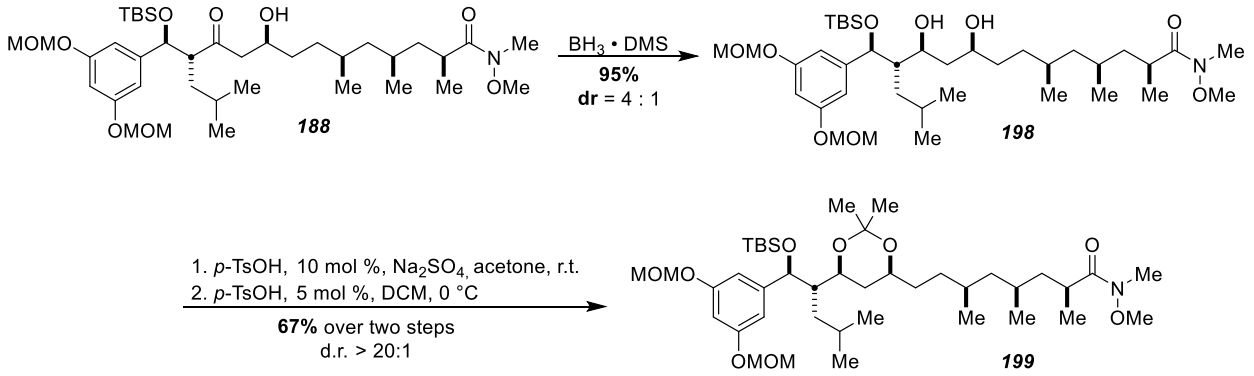


Figure 109. Protection of *syn*-diol **198** as the acetonide and subsequent purification by selective hydrolysis of its C-11 epimer.

With pure **199** in hand, we first confirmed that the sense of reduction with BH_3-DMS was indeed *syn*; Rychnovsky's method[179-180] rapidly assured us that this was indeed the case. With this last hurdle thus surpassed, we subjected acetonide **199** to Weinreb's conditions using ethylmagnesium bromide, which smoothly gave ethyl ketone **200**. Finally, treatment of **200** with 2 N hydrochloric acid in THF/methanol conveniently effected the global deprotection of the baulamycin scaffold, providing **1** in good yield over two steps (**Figure 110**).

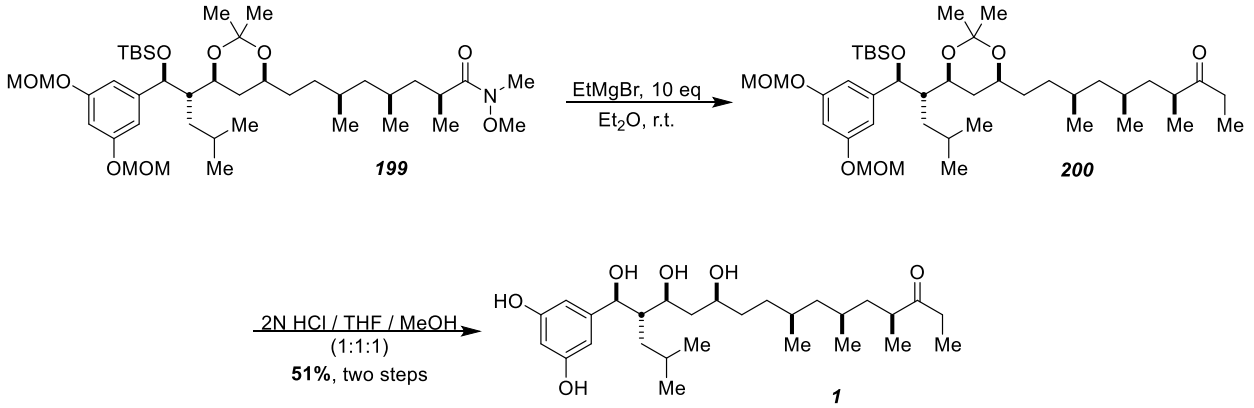


Figure 110. Weinreb ketone synthesis and final deprotection to provide baulamycin A (**1**).

Gratifyingly, comparison of the ^{1}H and ^{13}C NMR spectra and optical rotation of synthetic **1** showed it to be identical to natural baulamycin A in every way, marking a satisfying conclusion to our efforts to synthesize the natural product (**Figure 111**).

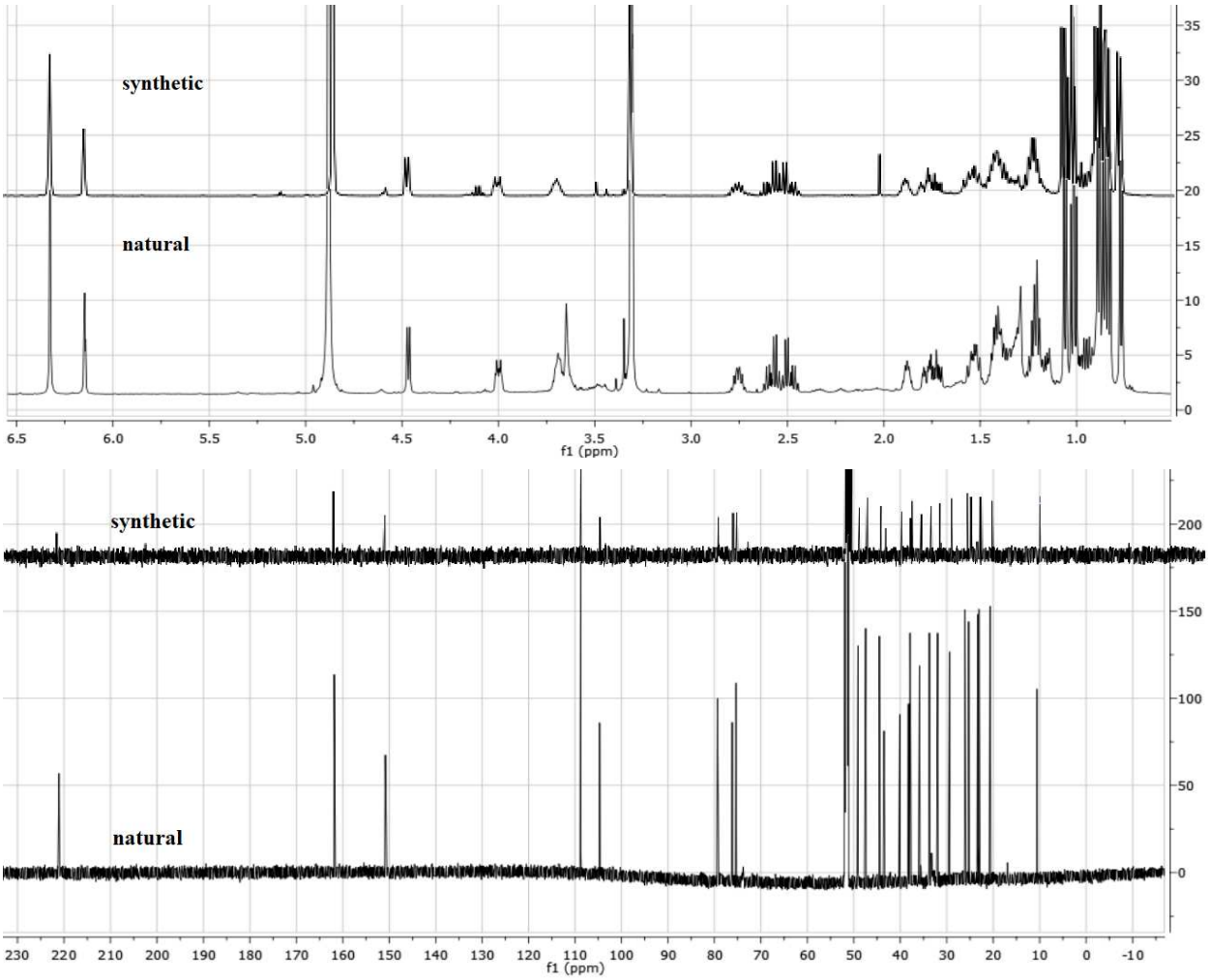


Figure 111. Overlay of 1H and 13C NMR spectra for synthetic and natural baulamycin A.

4.6 Synthesis of Baulamycin B

Having established an effective route to baulamycin A, with the opportunity to divert the synthesis toward baulamycin B in the penultimate step, we of course set our sights on an attempt at baulamycin B, the less-potent, chain-shortened analogue of baulamycin A. Accordingly, we treated Weinreb amide **199** with methyllithium at -78 °C, giving methyl ketone **201** as a single diastereomer (i.e., without epimerization, based on a lack of split signals in the crude ^{1}H NMR) in quantitative yield (**Figure 112**).

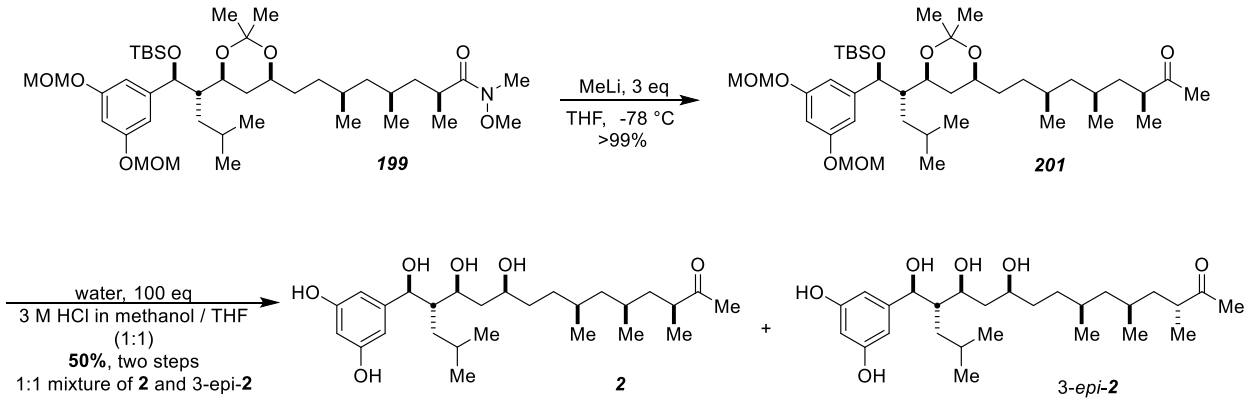


Figure 112. Synthesis of baulamycin B (**2**) as an inseparable mixture with its C-3 epimer.

Deprotection under conditions analogous to those employed on baulamycin A did indeed afford **2** in 50% yield as confirmed by ^{1}H and ^{13}C NMR (**Figure 113**); however, to our chagrin, 3-*epi*-**2** was also present in equal amounts!

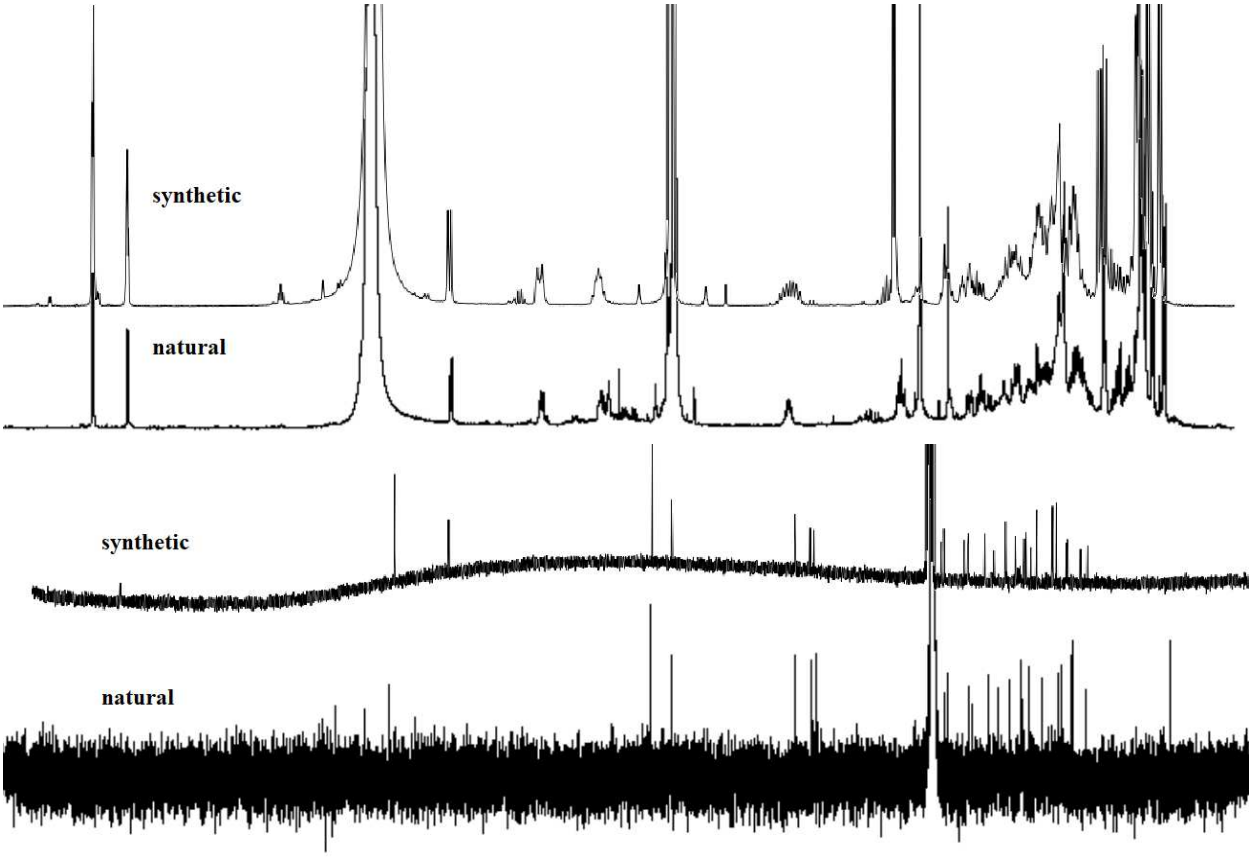


Figure 113. Overlay of 1H and 13C NMR spectra for synthetic and natural baulamycin B.

Apparently, acid-catalyzed deprotection had also catalyzed the epimerization of the C-3 stereocenter, presumably through keto-enol tautomerization, despite the complete lack of evidence for any such degradation pathway in the deprotection of baulamycin A. Unfortunately, despite extensive efforts, 3-*epi*-**2** could not be separated from **2**, and, with our supplies of readily-available **199** exhausted, we abandoned further efforts to isolate baulamycin B in pure form. Ultimately, we viewed this as a minor blemish on our overall efforts towards the baulamycins in light of the superior biological activity of baulamycin A with respect to baulamycin B and their extreme structural similarity. Undoubtedly, should it become desirable in the future to obtain further access to baulamycin B in pure form, the problem of deprotecting **201** without epimerization at C-3 will be readily solved. For our part, with both baulamycin A and baulamycin B in hand (albeit in impure form in the case of baulamycin B), we viewed these experiments as the natural conclusion to our rewarding and challenging efforts in the total synthesis of these natural products.

Chapter 5 – Detailed Descriptions of Experimental Work

4.1 General Considerations

The use of flame- or oven-dried glassware, inert atmosphere and specific elements of air-free technique are explicitly noted and described in detail for each experimental procedure in which they were used. The use of dried glassware or inert atmosphere should not be assumed for reactions which do not explicitly describe their use.

Where used below, the term *high vacuum* refers to the vacuum generated by a Welch 1399 DuoSeal pump producing a vacuum typically measuring 0.10 – 0.05 mm Hg. The term *purge* is used to refer to the evacuation of an experimental apparatus by high vacuum and subsequent back-filling with a specified inert gas at least three times. The term *sparge* indicates that a gas was vigorously bubbled through a solvent, typically from a stainless steel needle positioned with its tip at the lowest point of the vessel. The term *oven-dried* refers to an apparatus which has been kept at a temperature of 120 °C overnight; the term *flame-dried* refers to glassware placed under high vacuum and heated with a propane torch until frosting of glass components was no longer observed, then cooled under positive pressure of a dry inert gas. *Freeze-pump-thaw degassed* denotes that the material thus described has been placed in a Schlenk flask sealed with a fresh rubber septum, connected to high vacuum by a sidearm equipped with a closed stopcock, magnetically stirred at -196 °C until frozen, exposed to high vacuum by opening of the stopcock for at least 3 minutes, resealed by closing of the stopcock, thawed, and thus treated a total of three times.

Reactions conducted in flame- or oven-dried glassware were conducted with anhydrous solvents and reagents. In these cases, toluene, THF, DMF, diethyl ether, dichloromethane,

acetonitrile, DMSO, pyridine, benzene, methanol, triethylamine and diisopropylamine were sparged with argon then dried by passage through a Glass Contour solvent purification system. Anhydrous *n*-pentane, hexanes and *tert*-butyl methyl ether were obtained by drying over 4 Å molecular sieves (20% w/w) for at least 12 hours prior to use. Acetone was dried over 3 Å molecular sieves (20 % w/w) overnight immediately prior to use (when drying acetone with molecular sieves, immediate use of the dried solvent is essential to prevent re-equilibration to a higher water content through self-condensation; even then, acetone dried in this manner should not be assumed to contain less than ~320 ppm water)[181]. Concentrations of acids, bases, and hydrogen peroxide refer to aqueous solutions except where otherwise noted. Unless otherwise noted, reactants and reagents were obtained commercially and used without further purification. The terms *freshly distilled* and *freshly purified*, when used without citing an alternative reference, refer to purification according to the procedures described in *Purification of Laboratory Chemicals*[182], the *Encyclopedia of Reagents for Organic Synthesis*[183], or references contained therein.

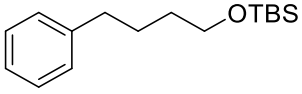
Flash chromatography was performed on "Standard Grade" 60 Å porosity, 230-400 mesh silica gel from Sorbent Technologies. Analytical and preparative TLC were conducted on glass-backed plates precoated (0.21 – 0.27 mm) with Merck Silica Gel 60 F254. Preparative TLC was conducted by loading 10 mgs or less of sample onto 20 cm x 20 cm plates. In the case of analytical TLC, unless otherwise noted, compounds were visualized by 254 nm UV light or by immersion in Seebach's stain[184] followed by heating in a stream of hot air until the plate evolved a uniform blue color.

^{1}H and ^{13}C NMR spectra were acquired at various field strengths as indicated using Varian and Bruker spectrometers. ^{1}H NMR spectra were referenced internally to residual undeuterated

solvents ($CHCl_3$ σ = 7.26 ppm, CH_3OH σ = 3.31 ppm, DMSO, σ = 2.50 ppm, CH_3CN σ = 1.94 ppm, H_2O σ = 4.79 ppm, C_6H_6 σ = 2.50 ppm, acetone σ = 2.05 ppm). ^{13}C NMR spectra were referenced internally to the solvent ($CHCl_3$ σ = 77.0 ppm, CH_3OH σ = 49.0 ppm). Splitting patterns are described using the following abbreviations: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet. More than one abbreviation may be used to describe more complex splitting patterns, with the form "*ab*" denoting that splitting pattern *a* modifies pattern *b*. Thus, for example, the compound abbreviation "*dt*" denotes a "doublet of triplets". Melting points were taken on a Mel-Temp capillary melting point apparatus equipped with a partially-immersed partial immersion thermometer and thus did not require correction[185]. Infrared spectra were recorded on a Nicolet iS5 or Nicolet iS50 FT-IR spectrometer. Mass spectra were obtained by the Colorado State University Central Instrument Facility on various TOF or QTOF spectrometers. Optical rotations were obtained on Rudolf Research Autopol III polarimeter operating at 589 nm at room temperature (typically 25 °C).

4.2 Experimental Procedures

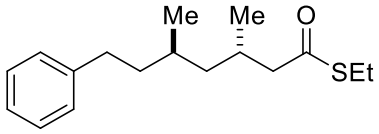
tert-butyldimethyl(4-phenylbutoxy)silane (**80**)



To a 35-mL round bottom flask equipped with a magnetic stir bar and containing 4-phenylbutanol (0.200 g, 1.30 mmol, 1.00 eq), imidazole (0.199 g, 2.9 mmol, 2.2 eq) and *tert*-butyldimethylsilyl chloride (0.221 g, 1.5 mmol, 1.1 eq) was added anhydrous DCM (10 mL) to give a colorless mixture which was stirred 44 hrs, at which time TLC indicated complete consumption of starting material. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting biphasic mixture stirred until two clear phases were obtained. The layers were separated and the aqueous phase extracted with DCM (3 x 10 mL); the organics were then

combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure onto silica. CC on silica gel (15 g) eluting with 9:1 pentane / ethyl acetate gave **80** (0.320 g, 93%) as a colorless oil. Analytical data were in complete agreement with those previously reported[186]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H), 7.22 – 7.15 (m, 3H), 3.63 (t, J = 6.2 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.73 – 1.51 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H).

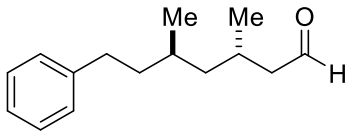
S-ethyl (3*S*,5*R*)-3,5-dimethyl-7-phenylheptanethioate (**57**)



A flame-dried 1-L round bottom flask equipped with a magnetic stir bar was charged with (S,R_P)-Josiphos ethanol adduct (12 mgs, 0.019 mmol, 1.7 mol %) and copper(I) bromide-dimethyl sulfide complex (3.2 mgs, 0.016 mmol, 1.4 mol %), sealed with a rubber septum and purged with argon. *tert*-Butyl methyl ether (7.5 mL) was added and the resulting solution stirred 30 min at room temperature. The reaction solution was then cooled to -78 °C and methyl magnesium bromide (0.5 mL of a 3.0 M solution in Et_2O, 1.5 mmol, 1.3 eq) was added. **56** (0.300 g, 1.14 mmol, 1.00 eq) was then added as a solution in *tert*-butyl methyl ether (2 mL) via syringe pump over 1.5 hrs, and the resulting solution stirred 13 hrs, at which time TLC showed complete consumption of starting material. MeOH was added at -78 °C and the resulting solution allowed to warm slowly to r.t. Saturated aqueous NH_4Cl was then added and the resulting biphasic mixture stirred an additional 30 min. The resulting layers were separated and the aqueous phase extracted three times with diethyl ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to reveal 0.280 g of yellow oil. Flash chromatography on silica gel (15 g) gave **57** (0.300 g, 94%) as an inseparable mixture with trace amounts of *syn*-isomer **165** as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H),

2.88 (q, *J* = 7.4 Hz, 2H), 2.70 – 2.54 (m, 2H), 2.52 – 2.29 (m, 2H), 2.21 – 2.05 (m, 1H), 1.67 – 1.39 (m, 4H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.21 – 1.13 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.2, 142.9, 128.3, 128.3, 52.1, 44.0, 39.5, 33.4, 29.7, 28.6, 23.3, 19.3, 19.2, 14.8. ^{13}C NMR signals from minor *syn*-isomer **165**: 51.3, 44.3, 38.4, 33.2, 20.1, 20.0. **$[\alpha]^{25}_D$** = -17.4° (*c* 0.43, $CHCl_3$). **IR** (neat): 2927, 1689, 1455, 1001, 699 cm^{-1}. **HRMS** (ESI): calc'd for $C_{17}H_{27}OS$ $[M + H]^+$ 279.1777, found 279.1780.

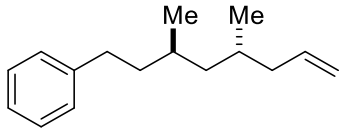
(3*S*,5*R*)-3,5-dimethyl-7-phenylheptanal (**67**)



A flame-dried 500-mL round bottom flask equipped with a magnetic stir bar and charged with **57** (4.57 g, 16 mmol, 1.00 eq) was sealed with a rubber septum and purged with argon. DCM (160 mL) was added and the resulting solution was cooled to -65 °C; DIBAL-H (17.2 mL of a 1.0 M solution in hexanes, 17 mmol, 1.05 eq) was then added slowly against the wall of the reaction flask. After addition of DIBAL-H was complete, the reaction solution was stirred 15 min, at which time TLC showed complete consumption of starting material. MeOH (9 mL) was added and the resulting mixture was stirred an additional 5 min, then warmed to 0 °C. Saturated aqueous Rochelle's salt was added; the biphasic mixture was then allowed to warm to r.t. and stirred overnight (note: workup after 3 hrs gave similar yields). The resulting layers were separated and the aqueous phase extracted twice with DCM. The combined organics were dried over Na_2SO_4, decanted, and concentrated under reduced pressure to reveal **67** (3.49 g, 97%) as a colorless oil which was used immediately in the next step without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.2 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.21 – 7.13 (m, 3H), 2.74 – 2.50 (m, 2H), 2.41 – 2.10 (m, 3H), 1.67 – 1.41 (m, 3H), 1.33 – 1.20 (m, 1H), 1.20 – 1.07 (m, 1H), 0.98 – 0.87

(m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.9, 142.8, 128.3, 128.3, 125.6, 51.7, 44.4, 39.4, 33.3, 29.7, 25.5, 19.6, 19.3. ^{13}C NMR signals from minor *syn*-isomer: 203.0, 50.9, 44.6, 38.5, 33.2, 25.6, 20.5, 19.9. **$[\alpha]^{25}_D$** = -8.2° (*c* 0.18, $CHCl_3$). **IR** (neat): 2955, 1726, 1455, 1704, 746, 699 cm^{-1}. **HRMS** (ESI): calc'd for $C_{15}H_{26}NO$ $[M + NH_4]^+$ 236.2009, found 236.2006.

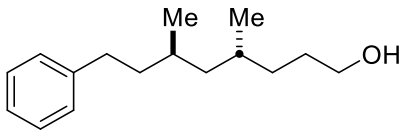
((3*R*,5*R*)-3,5-dimethyloct-7-en-1-yl)benzene (**68**)



A flame-dried 500 mL round bottom flask was charged with methyltriphenyl-phosphonium bromide (6.45 g, 18.1 mmol, 1.13 eq), sealed with a rubber septum and purged with argon. THF (130 mL) was added, giving a colorless suspension, which was cooled to 0 °C. *n*-Butyl lithium (11.3 mL of a 1.6 M solution in hexanes, 18.1 mmol, 1.13 eq) was added slowly and an orange color evolved, lightening to yellow over 1 hr. **67** (3.49 g, 16.0 mmol, 1.00 eq) was then added portionwise as a solution in THF (50 mL over an additional 1 hr. The cooling bath was then removed and the orange reaction mixture stirred 12 hrs at room temperature, at which time TLC showed complete consumption of starting material. Saturated aqueous ammonium chloride and Et_2O were added and the resulting biphasic mixture stirred until colorless; the layers were then separated and the aqueous phase extracted with diethyl ether. The organics were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure onto silica. Flash chromatography on silica gel eluting with pentane gave **68** (3.10 g, 89%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 5.89 – 5.64 (m, 1H), 5.03 – 4.98 (m, 1H), 4.98 – 4.95 (m 1H), 2.62 (m, 2H), 2.02 (m, 1H), 1.95 – 1.79 (m, 1H), 1.70 – 1.51 (m, 3H), 1.50 – 1.37 (m, 1H), 1.15 (dd, J = 6.9 Hz, 2H), 0.90 (d, J = 6.4 Hz, 3H), 0.84 (dd, J = 6.6, 3.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.1, 137.7, 128.3, 128.2, 125.5, 115.5, 44.1, 42.2, 39.7, 33.5, 30.1,

29.9, 19.43, 19.24. ^{13}C NMR signals from minor *syn*-isomer **170**: 137.5, 115.6, 44.3, 41.2, 38.7, 33.3, 30.0, 29.8, 20.2, 20.0. $[\alpha]^{25}_{D}$ = -10.3° (*c* 1.03, $CHCl_3$). **IR** (neat): 2910 (C-H stretch), 1640 (C=C), 1454, 910 (vinyl C-H) cm^{-1}.

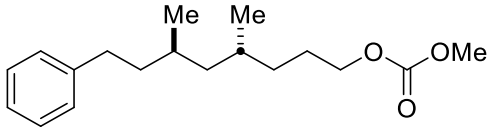
(*4R*,*6R*)-4,6-dimethyl-8-phenyloctan-1-ol (**58**)



An oven-dried 50-mL round bottom flask containing a magnetic stir bar was capped with a rubber septum, purged with argon and charged with BH_3 • THF (18.3 mL of a 1.0 M solution in THF, 18.3 mmol, 1.10 eq). The reaction vessel was cooled to -40 °C and 2-methyl-2-butene (4.26 mL, 40.3 mmol, 2.42 eq) was added rapidly with stirring. The colorless solution was brought to 0 °C and stirred for 2.75 hrs, at which time the entire solution was transferred via cannula to a 25-mL pressure-equalized dropping funnel attached to a 2-neck, 100-mL round bottom flask. The flask was equipped with a magnetic stir bar and sealed at the other neck with a rubber septum. The reaction vessel was then purged with argon and charged with a solution of **68** (3.60 g, 16.6 mmol, 1.00 eq) in THF (7 mL), then cooled to 0 °C. The freshly-prepared solution of disiamylborane was added dropwise over 30 min via dropping funnel; the resulting colorless solution was then stirred an additional 30 min at 0 °C before being allowed to come to r.t. and stirring for a further 18 hrs. The reaction solution was then cooled to -10 °C and quenched with ethanol (0.3 mL); sodium hydroxide (6.3 mL of a 3 M aqueous solution, 18.9 mmol, 1.14 eq) was then added, followed by a slow addition of 30% (w/w) aqueous hydrogen peroxide (6.3 mL) with concomitant exotherm and evolution of gas. Once the exotherm had ceased, the cloudy mixture was brought to r.t. and stirred 3 hrs, at which time a heavy white precipitant had formed. Liquids were decanted and the layers separated. The precipitant was washed with ether (2 x 50 mL) and the washings used to extract the

aqueous layer (2 x 50 mL). After a third ether extraction of the aqueous layer (1 x 50 mL), the organics were combined, rinsed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal a colorless oil. Flash chromatography on silica gel (200 g) eluting w/ pentane followed by 2:1 pentane/ether gave **58** (3.24 g, 83%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.29 – 7.19 (m, 3H), 3.68 (t, J = 6.7 Hz, 2H), 2.80 – 2.55 (m, 2H), 1.82 – 1.12 (m, 10H), 0.99 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 128.3, 128.2, 125.5, 63.4, 44.6, 39.7, 33.7, 33.4, 30.3, 29.9, 29.8, 19.5. ^{13}C NMR signals from minor *syn*-isomer: 44.8, 38.7, 33.3, 32.7, 30.1, 29.9, 20.2, 20.1. **$[\alpha]^{25}_D$** = +8.0° (*c* 0.20, CH_2Cl_2). **IR** (neat): 3319 (br, O-H), 2912 (C-H), 1453, 1055 (C-O) cm^{-1}. **HRMS** (ESI): calc'd for $C_{16}H_{26}NaO$ $[M + Na]^+$ 257.1876, found 257.1876.

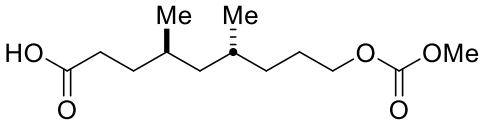
(*4R*,*6R*)-4,6-dimethyl-8-phenyloctyl methyl carbonate (**93**)



To a flame-dried, argon-purged 500-mL round bottom flask containing **58** (3.26 g, 13.9 mmol, 1.00 eq) and equipped with a magnetic stir bar was added DCM (28 mL) to give a colorless solution. Pyridine (1.46 mL, 18.1 mmol, 1.30 eq) and 4-(dimethylamino)pyridine (0.034 g, 0.278 mmol, 2 mol %) were then added, and the resulting clear solution cooled to 0 °C. Methyl chloroformate (1.40 mL, 18.1 mmol, 1.30 eq) was added slowly, and the reaction mixture stirred 4 hrs as the ice bath expired naturally, at which time TLC showed complete consumption of starting material. Saturated aqueous NH_4Cl was added and the resulting biphasic mixture stirred; layers were then separated and the aqueous phase extracted with diethyl ether (3 x 75 mL). The organics were combined, rinsed with brine and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal a colorless oil. Purification by flash

chromatography on silica gel (200 g) eluting with 95:5 hexanes / ethyl acetate followed by 9:1 hexanes / ethyl acetate gave **93** (3.76 g, 93%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 2H), 7.21 – 7.14 (m, 3H), 4.12 (t, *J* = 6.8 Hz, 2H), 3.78 (s, 3H), 2.73 – 2.46 (m, 2H), 1.78 – 1.07 (m, 10H), 0.89 (d, *J* = 6.3 3H), 0.84 (d, *J* = 6.5, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 143.0, 128.3, 128.2, 125.5, 68.5, 54.6, 44.4, 39.7, 33.6, 33.4, 29.8, 29.8, 26.2, 19.4, 19.3. ^{13}C NMR signals from minor *syn*-isomer **171**: 44.8, 38.6, 33.3, 32.6, 29.7, 26.1, 20.2, 20.0. **$[\alpha]^{25}_D$** = -5.7° (*c* 0.82, $CHCl_3$). **IR** (neat): 2957 (C-H stretch), 1752 (carbonate C=O stretch), 1443, 1277 (carbonate asymmetric stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{18}H_{29}O_3$ $[M + H]^+$ 293.2111, found 293.2112.

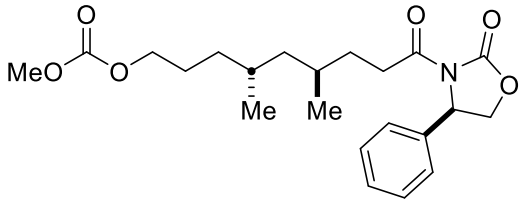
(*4R*,*6R*)-9-((methoxycarbonyl)oxy)-4,6-dimethylnonanoic acid (**94**)



To a 3000-mL three-neck round bottom flask equipped with an enlarged (7.5 cm x 3 cm) ellipsoid magnetic stir bar was charged with sodium periodate (43.21 g, 202 mmol, 15.0 eq), ruthenium(III) chloride trihydrate (0.352 g, 1.35 mmol, 10 mol %) and water (270 mL) to give an amber solution. **93** (3.94 g, 13.5 mmol, 1.00 eq) was added as a solution in CCl_4 (135 mL) and the walls of the reaction flask rinsed with acetonitrile (135 mL). One of the outer necks of the reaction flask was sealed with a glass stopper; the other neck was equipped with a thermometer adapter and thermometer placed below the surface of the reaction mixture. The center neck of the flask was fitted with an efficient condenser and the reaction mixture brought to reflux with a heating mantle while maintaining an internal temperature of 60 – 65 °C. The reaction was refluxed with vigorous stirring for 2.5 hrs, at which time an off-white or tan color had evolved. The reaction mixture was then filtered through Celite twice; layers were separated and the aqueous phase extracted several

times with DCM. The organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal 3.3 g black residue. Flash chromatography on silica gel (175 g) eluting with 9:1 pentane/ether, followed by 4:1 pentane ether, followed by 3:2 pentane/ether + 0.76 % (v/v) acetic acid gave 0.550 g recovered starting material and product (1.84 g, 52%, 61% b.r.s.m.) as colorless oils. Residual acetic acid from chromatography was azeotropically removed from the final product with toluene (1x) and heptane (2x). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.12 (t, J = 6.7 Hz, 2H), 3.78 (s, 3H), 2.44 – 2.28 (m, 2H), 1.76 – 1.07 (m, 10H), 0.91 – 0.81 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.7, 155.9, 128.5, 128.0, 68.5, 54.6, 44.1, 33.5, 32.3, 31.7, 29.7, 29.6, 26.2, 19.2, 19.0. ^{13}C NMR signals from minor *syn*-isomer **176**: 44.5, 32.6, 31.5, 31.2, 29.5, 26.04, 19.9, 19.8. **$[\alpha]^{25}_D$** = -8.9° (*c* 0.99, $CHCl_3$). **IR** (neat): 2957 (C-H stretch), 1747 (carbonate C=O stretch), 1706 (acid C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{13}H_{23}O_5$ $[M - H]^-$ 259.1551, found 259.1574.

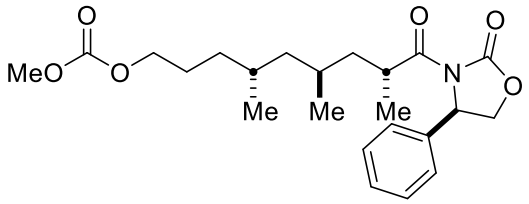
(*4R*,*6R*)-4,6-dimethyl-9-oxo-9-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)nonyl methyl carbonate (**97**)



To a 100-mL round bottom flask containing a magnetically-stirred solution of **94** (1.79 g, 6.88 mmol, 1.00 eq) in THF (10 mL) was added triethylamine (2.40 mL, 17.2 mmol, 2.5 eq) followed by pivaloyl chloride (0.85 mL, 6.88 mmol, 1.00 eq) at 0 °C. The resulting white slurry was stirred 1.5 hrs, at which point (*R*)-(-)-4-phenyl-2-oxazolidinone (1.12 g, 6.88 mmol, 1.00 eq) and lithium chloride (0.437 g, 10.3 mmol, 1.5 eq) were added and the reaction allowed to come to room temperature. After stirring 18 hrs, TLC showed complete consumption of starting material. The reaction mixture was diluted with Et_2O and saturated aqueous NH_4Cl, stirred, then further

diluted with water to give to clear phases. Layers were separated and the aqueous phase extracted with Et_2O (3 x 50 mL); organics were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal a yellow oil. Purification by flash chromatography eluting with 3:2 pentane / ethyl acetate gave **97** (2.50 g, 90%) as a colorless oil.

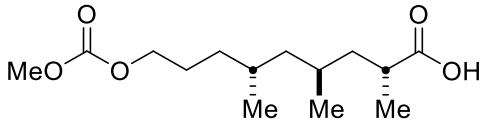
methyl ((*4R*,*6S*,*8R*)-4,6,8-trimethyl-9-oxo-9-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)nonyl) carbonate (**98**)



A flamed-dried 250 mL round bottom flask equipped with a magnetic stir bar was charged with **97** (2.47 g, 6.09 mmol, 1.00 eq), purged with argon, sealed with a rubber septum and charged with THF (30 mL) to give a stirred solution which was cooled to -78 °C. Sodium hexamethyldisilazide (1.34 g, 7.31 mmol, 1.20 eq) was added slowly as a solution in THF (20 mL, followed by 2 x 5 mL rinses). The resulting pale yellow solution was stirred 1 hr at -78 °C, at which time methyl iodide (0.95 mL, 15.2 mmol, 2.50 eq) was added slowly. The reaction solution was allowed to stir 1 hr, at which time TLC indicated complete consumption of starting material. The reaction solution was quickly warmed to near room temperature, then diluted with saturated aqueous NH_4Cl and diethyl ether and stirred. Addition of a generous spatula-tip of $Na_2S_2O_3$ followed by vigorous shaking gave two colorless and distinct layers which were then separated. The aqueous phase was extracted with Et_2O (2 x 125 mL) followed by DCM (1 x 125 mL); the organics were then combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (125 g) eluting with 3:1 pentane / ethyl acetate gave **98** (1.59 g, 62%) as a white crystalline solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 –

7.25 (m, 5H), 5.43 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.67 (t, *J* = 8.8 Hz, 1H), 4.25 (dd, *J* = 8.9, 3.7 Hz, 1H), 4.11 (t, *J* = 6.7 Hz, 2H), 3.94 – 3.81 (m, 1H), 3.77 (s, 3H), 1.75 – 1.41 (m, 5H), 1.39 – 1.12 (m, 3H), 1.12 – 1.03 (m, 5H), 0.87 – 0.79 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.9, 155.9, 153.3, 139.3, 129.2, 128.6, 125.7, 69.7, 68.5, 57.8, 54.6, 44.7, 40.9, 35.4, 33.5, 29.8, 27.9, 26.2, 19.2, 19.2, 17.2. **$[\alpha]^{25}_D$** = -73.1° (*c* 1.49, $CHCl_3$). **IR** (neat): 2965 (C-H stretch), 1783 (C=O), 1745 (C=O), 1700 (C=O) cm^{-1}. **HRMS** (ESI): calc'd for $C_{23}H_{34}NO_6$ $[M + H]^+$ 420.2386, found 420.2374.

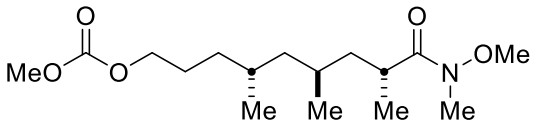
(*2R,4S,6R*)-9-((methoxycarbonyl)oxy)-2,4,6-trimethylnonanoic acid (**99**)



To a 250-mL round bottom flask containing a magnetically-stirred solution of **98** (0.580 g, 1.38 mmol, 1.00 eq) in THF (12 mL) was added a pre-mixed, clear solution of lithium hydroxide (1.73 mL of a 2 N aqueous solution, 3.46 mmol, 2.50 eq) and 30% (w/w) hydrogen peroxide (0.84 mL, 8.28 mmol, 6.00 eq) at 0 °C. The reaction mixture was stirred 5.5 hrs, at which time TLC showed complete consumption of starting material. The reaction mixture was quenched with the addition of 0.1 M aqueous $Na_2S_2O_3$ (3 mL), followed by Et_2O and water. Addition of additional $Na_2S_2O_3$ gave a clear biphasic mixture. The layers were separated and the aqueous phase acidified to pH 2.5 with 2 N HCl, then extracted with Et_2O (3 x 50 mL). The organics were combined, washed with bring, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal a colorless solid. Flash chromatography on silica gel eluting with 4:1 hexanes / ethyl acetate gave **98** (0.260 g, 69%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.12 (t, *J* = 6.7 Hz, 2H), 3.78 (s, 3H), 2.63 – 2.46 (m, 1H), 1.78 – 1.43 (m, 5H), 1.41 – 1.20 (m, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.13 – 1.03 (m, 2H), 0.89 – 0.79 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.8, 155.9, 68.5, 54.6, 44.4,

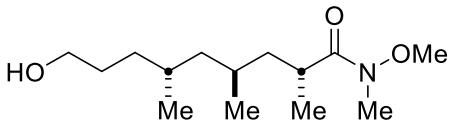
41.6, 29.7, 27.8, 26.2, 19.2, 16.9. **[α]^{25}D** = -1.85° ($CHCl_3$). **IR** (neat): 2958 (alkane C-H stretch), 1749 (carbonate C=O stretch), 1705 (acid C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{14}H_{27}O_5$ $[M + H]^+$ 275.1853, found 275.1857.

(*4R*,*6S*,*8R*)-9-(methoxy(methyl)amino)-4,6,8-trimethyl-9-oxononyl methyl carbonate (**100**)



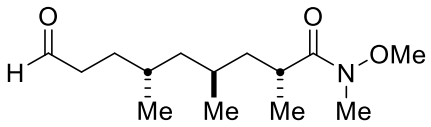
To a 20-mL glass scintillation vial containing a magnetically-stirred solution of **99** (0.260 g, 0.948 mmol, 1.00 eq) in DCM (3.5 mL) was added PyBOP (0.518 g, 0.995 mmol, 1.05 eq) and diisopropylethylamine (0.40 mL, 2.32 mmol, 2.45 eq). The resulting pale yellow reaction solution was allowed to stir 5 min, then *N*,*O*-dimethylhydroxylamine hydrochloride (0.125 g, 1.28 mmol, 1.35 eq). The reaction solution was allowed to stir 6 hrs, at which time TLC showed complete consumption of starting material. The reaction was diluted with DCM, washed with 1 N HCl (1 x 10 mL), water (1 x 10 mL) and saturated aqueous $NaHCO_3$ (1 x 10 mL). The basic wash was then back-extracted with DCM (3 x 10 mL) and the organics combined, dried over Na_2SO_4 and concentrated under reduced pressure to reveal a viscous, translucent, amorphous solid. Flash chromatography on silica gel eluting with 3:1 hexanes / ethyl acetate gave pure **100** (0.240 g, 80%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.12 (t, J = 6.7 Hz, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 3.18 (s, 3H), 3.06 – 2.90 (m, 1H), 1.77 – 1.57 (m, 2H), 1.57 – 1.43 (m, 3H), 1.41 – 1.13 (m, 3H), 1.13 – 1.02 (m, 4H), 0.91 – 0.78 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.4 (weak), 155.8, 68.5, 61.4, 54.6, 44.6, 41.8, 33.7, 32.6, 29.7, 27.9, 26.2, 19.3, 19.1, 17.4. **[α]^{25}D = XX°** (*c* 0.X, $CHCl_3$). **IR** (neat): 2958 (alkane C-H stretch), 1747 (carbonate C=O stretch), 1633 (amide C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{16}H_{32}NO_5$ $[M + H]^+$ 318.2275, found 318.2266.

(*2R*,*4S*,*6R*)-9-hydroxy-*N*-methoxy-*N*,2,4,6-tetramethylnonanamide (**101**)



A 25-mL round bottom flask equipped with a magnetic stir bar was charged with **100** (0.095 g, 0.299 mmol, 1.00 eq) followed by MeOH (5 mL) to give a stirred solution. Potassium carbonate (5 mL of a 1% (w/v) solution in MeOH) was then added and the resulting mixture stirred 19 hrs, at which time TLC indicated complete consumption of starting material. Solvent was evaporated to give a pale yellow residue, which was then partitioned between water and Et_2O. The aqueous phased was extracted with Et_2O (2 x 10 mL); the organics were then combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal **101** (0.062 g, 79%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.61 (t, J = 6.7 Hz, 2H), 3.16 (s, 3H), 3.06 – 2.89 (m, 1H), 1.64 – 1.43 (m, 5H), 1.35 – 1.22 (m, 2H), 1.21 – 1.12 (m, 1H), 1.12 – 1.03 (m, 5H), 0.90 – 0.76 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 63.3, 61.4, 44.8, 41.7, 33.8, 32.6, 30.2, 29.8, 27.9, 19.3, 17.3 (C=O not observed). **$[\alpha]^{25}_D$** = -12.7° (*c* 0.33, $CHCl_3$). **IR** (neat): 3430 (O-H stretch), 2927 (alkane C-H stretch), 1642 (C=O) cm^{-1}. **HRMS** (ESI): calc'd for $C_{14}H_{30}NO_3$ $[M + H]^+$ 260.2220, found 260.2180.

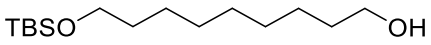
(*2R*,*4S*,*6R*)-*N*-methoxy-*N*,2,4,6-tetramethyl-9-oxononanamide (**38**)



To a 10-mL round bottom flask containing **101** (0.031 g, 0.120 mmol, 1.00 eq), equipped with a magnetic stir bar and purged with argon was added DCM (2 mL). To the resulting magnetically-stirred solution was added Dess-Martin periodinane (0.152 g, 0.36 mmol, 3.00 eq) and the reaction mixture stirred 4 hrs, at which time TLC appeared to indicate complete

consumption of starting material. Saturated aqueous $NaHCO_3$ was added, followed by 0.1 M aqueous $Na_2S_2O_3$ until the biphasic mixture clarified. Layers were separated and the aqueous phase extracted with DCM (3 x 10 mL). Organics were combined, dried over Na_2SO_4 and concentrated under reduced pressure to reveal **38** (0.014 g, 50%) as a colorless unstable oil. **^{1}H NMR** (300 MHz,$CDCl_3$) δ 9.77 (t, J = 2.0 Hz, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 2.98 (s, 2H), 2.44 (m, 2H), 1.70 – 1.15 (m, 7H), 1.10 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.0 Hz, 6H).

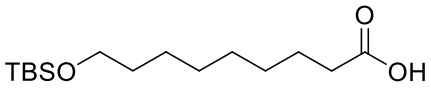
9-((*tert*-butyldimethylsilyl)oxy)nonan-1-ol (**133**)



To a flame-dried 3-neck 500-mL round bottom flask equipped with a reflux condenser and magnetic stir bar was added sodium hydride (2.50 g, 60% dispersion in mineral oil, 62.4 mmol, 1.00 eq). The system was sealed with rubber septa and purged with argon; the sodium hydride dispersion was then rinsed (2x) with hexanes and suspended in THF (125 mL). 1,9-nonanediol (10.00 g, 62.4 mmol, 1.00 eq) was then added against a stream of argon through the right neck; the system was re-sealed with septa and the thick white suspension brought to 55 °C and stirred 18 hrs. Evolution of gas was initially observed, and the mixture thickened over the first hour of stirring. At 18 hrs, the slurry had thinned considerably – the mixture was allowed to cool to r.t. and *tert*-butyldimethylsilyl chloride (9.40 g, 62.4 mmol, 1.00 eq) was added. The resulting mixture was stirred 24 hrs, then poured into an equal volume Et_2O and rinsed with 10% (w/w) aqueous K_2CO_3 followed by brine. The organics were then dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a pale yellow oil which solidified into a white amorphous mass on exposure to high vacuum. Flash chromatography on silica gel eluting with 9:1 pentane/ethyl acetate followed by 3:1 pentane/ethyl acetate gave **133** (7.45 g, 43%) as a colorless oil. Analytical data were in accordance with those previously reported[187]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.71 –

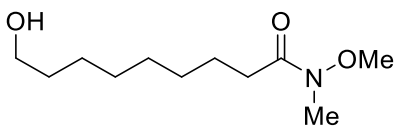
3.49 (m, 4H), 1.63 – 1.42 (m, 4H), 1.30 (s, 10H), 0.89 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 63.3, 63.1, 32.9, 32.8, 29.6, 29.4, 26.0, 25.8, 25.7, 18.4, -5.3.

9-((*tert*-butyldimethylsilyl)oxy)nonanoic acid (**134**)



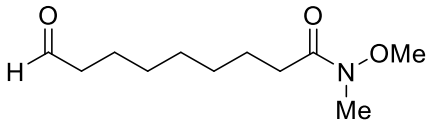
To a 1000-ml round bottom flask containing a magnetically-stirred solution of alcohol **133** (7.43 g, 27.1 mmol, 1.00 eq) in ACN / 0.67 M aqueous monobasic sodium phosphate (1:1, 275 mL) was added TEMPO (0.423 g, 2.71 mmol, 10 mol %), giving a mild orange solution. Bleach (13.5 mL, 6% (w/w) aqueous sodium hypochlorite) was added, at which time a pale yellow color evolved. Addition of sodium chlorite (4.90 g, 54.1 mmol, 2.00 eq) was followed by the evolution of a dark brown color which eventually lightened to a dark yellow. Evolution of a green-yellow gas was observed and a mild exotherm was noted. The reaction mixture was stirred 16 hrs, at which time TLC indicated the absence of starting material. Saturated aqueous $Na_2S_2O_3$ (100 mL) was added, instantly decolorizing the reaction solution. The mixture was allowed to stir briefly, then extracted with diethyl ether (3x). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal **134** (7.45 g, 95%) as a colorless oil. Analytical data were in accordance with those previously reported[188]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.59 (t, J = 6.6 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.69 – 1.58 (m, 2H), 1.53 – 1.44 (m, 2H), 1.31 (m, 9H), 0.89 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.8, 63.3, 34.0, 32.8, 29.2, 29.0, 26.0, 25.7, 24.7, 18.4, -5.3. **IR** (neat) 3250-3050 (very broad, acid O-H stretch), 2929 (C-H stretch), 1709 (C=O stretch) cm^{-1}.

9-hydroxy-*N*-methoxy-*N*-methylnonanamide (**136**)



To a 1000-mL round bottom flask containing a magnetically-stirred solution of **134** (7.43 g, 25.8 mmol, 1.00 eq) in DCM (240 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (3.76 g, 38.6 mmol, 1.50 eq) and triethylamine (9.3 mL, 67.0 mmol, 2.60 eq). After 15 minutes, EDCI•HCl (5.43 g, 28.3 mmol, 1.10 eq) and 4-(dimethylamino)pyridine (0.629 g, 5.15 mmol, 20 mol %) were added and the colorless reaction solution stirred 4 hrs, at which time TLC indicated complete consumption of starting material. The reaction solution was rinsed three times with water, three times with 1 N HCl, twice with brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure into a 1000-mL round bottom flask to reveal 8.75 g of yellow oil. A magnetic stir bar, THF (30 mL) and tetrabutlylammonium fluoride (31.0 mL of a 1.0 M solution in THF, 31.0 mmol, 1.20 eq) were added to the flask to give a yellow solution which was allowed to stir 14 hrs, then evaporated to reveal a yellow oil. Purification by flash chromatography on silica gel (500 g) eluting with 1:1 hexanes / ethyl acetate followed by neat ethyl acetate gave **136** (4.38 g, 78%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.62 (t, J = 6.6 Hz, 2H), 3.16 (s, 3H), 2.39 (t, J = 7.6 Hz, 2H), 1.67 – 1.49 (m, 5H), 1.40 – 1.26 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 62.9, 61.2, 32.7, 32.1, 31.8, 29.3, 29.3, 29.2, 25.6, 24.5 (C=O not observed[189]). **IR** (neat): 3049 (O-H stretch), 2928 (alkane C-H stretch), 1642 (amide C=O) cm^{-1}. **HRMS** (ESI): calc'd for $C_{11}H_{24}NO_3$ $[M + H]^+$ 218.1751, found 218.1748.

<u>*N*-methoxy-*N*-methyl-9-oxononanamide</u> (**137**)



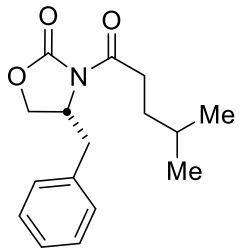
A flame-dried, argon-purged 1000-mL round bottom flask containing a magnetically stirred solution of oxalyl chloride (5.09 mL, 60.2 mmol, 3.00 eq) in DCM (100 mL) was cooled to -78 °C. DMSO (8.52 mL, 120 mmol, 6.00 eq) was added dropwise over 1 hr as a solution in DCM

(10 mL). To the resulting clear solution was added alcohol **136** (4.36 g, 20.1 mmol, 1.00 eq) via cannula as a solution in DCM (30 mL + 50 mL washings). A white suspension formed and was stirred 30 min, at which time triethylamine (25.2 mL, 181 mmol, 9.00 eq) was added quickly, giving first a colorless solution, then a thick white suspension. This suspension was stirred 15 minutes, then was allowed to come to r.t. overnight, during which time a dark yellow color evolved. Water was added; the organics were separated, washed with water (3 x 200 mL) and 1 N HCl (1 x 300 mL), followed by water and brine. The organics were then concentrated, re-diluted with ether, washed with water followed by brine, dried over $MgSO_4$, filtered and concentrated to give a brown oil which was then passed through a plug of silica eluting with ethyl acetate to give **137** (3.16 g, 73%) as a yellow oil.

Note: aldehyde **137** is unstable and should be used soon after purification. At room temperature, **137** is observed to have a half-life of approximately 1 month under inert gas. Cooling dramatically accelerates the rate of decomposition, with complete degradation ensuing on a timescale of days at -30 °C. The identity of the degradation product (a white solid) remains unknown; however, the absence of acetal protons in the ^{1}H NMR spectrum suggests that it is not simply a trimer or other oligomer of **137**. Although cyclizations and polymerizations of aliphatic aldehydes are well-known, and although the apparent increase in reaction rate at low temperature suggests an entropically-disfavored process such as trimerization, other mechanisms cannot be ruled out. In particular, the IR and ^{1}H NMR spectra of the degradation product are not inconsistent with oxidation of the aldehyde to the acid, with a broad increase in absorbance from 3600 - 3000 cm^{-1} in the IR and a faint hint of signal around 10.5 ppm in the ^{1}H NMR. As autooxidation of aldehydes proceeds stoichiometrically in oxygen, it is certainly possible than trace oxygen dissolved in **137** could be sufficient to give rise to the observed decomposition over time, even

when the product has been stored under an inert atmosphere. Regardless of the exact nature of its decomposition, **137** remains resistant to long-term storage; thus, in our own work, we have chosen to prepare it (and some other aliphatic aldehydes) only immediately prior to use. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (t, J = 1.9 Hz, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.45 – 2.35 (m, 4H), 1.67 – 1.54 (m, 4H), 1.39 – 1.26 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.8, 61.2, 43.8, 32.1, 31.8, 29.1, 29.1, 28.9, 24.5, 22.0. **IR** (neat): 2931 (C-H stretch), 2721 (aldehyde C-H stretch), 1722 (aldehyde C=O stretch), 1660 (amide C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{11}H_{21}NO_3$ $[M + H]^+$ 216.1594, found 216.1595.

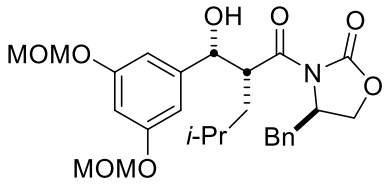
(*R*)-4-benzyl-3-(4-methylpentanoyl)oxazolidin-2-one (**109**)



Compound **109** was prepared using a modification of one of many literature procedures[100]. Thus, a flamed-dried, argon-purged, 500-mL round bottom flask equipped with a magnetic stir bar and sealed with a rubber septum was charged with 4-methylvaleric acid (11.5 mL, 90.8 mmol, 1.00 eq) and THF (50 mL) to give a colorless stirred solution. Triethylamine (31.6 mL, 227 mmol, 2.5 eq) was added and the resulting clear solution was cooled to 0 °C. Pivaloyl chloride (11.17 mL, 90.8 mmol, 1.00 eq) was added, with the concomitant evolution of a thick white slurry. After 50 min, (*R*)-4-benzyl-2-oxazolidinone (16.09 g, 90.8 mmol, 1.00 eq) and lithium chloride (5.77 g, 136 mmol, 1.50 eq) were added and the reaction mixture allowed to come to r.t. After stirring for 20 hrs, the reaction mixture was quenched with saturated aqueous NH_4Cl, then diluted with H_2O and stirred to give two clear phases. Layers were separated and the aqueous phase extracted twice with diethyl ether. The organics were combined, dried over Na_2SO_4, decanted, and evaporated

onto Celite. The Celite-adsorbed crude material was then added to a silica plug and eluted with 1:1 hexanes / ethyl acetate to give **109** (22.33 g, 89 %) as a colorless oil that solidified on standing. Characterization was in agreement with that previously reported in the literature[100]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 5H), 4.72 – 4.62 (m, 1H), 4.24 – 4.11 (m, 2H), 3.30 (dd, J = 13.4, 3.4 Hz, 1H), 3.06 – 2.84 (m, 2H), 2.76 (dd, J = 13.3, 9.6 Hz, 1H), 1.72 – 1.51 (m, 3H), 0.95 (d, J = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6, 153.4, 135.3, 129.4, 128.9, 127.3, 66.1, 55.1, 37.9, 33.6, 33.1, 27.6, 22.3.

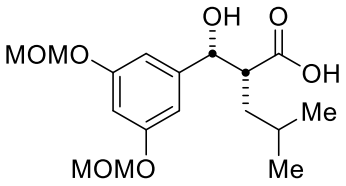
(*R*)-4-benzyl-3-((*R*)-2-((*R*)-(3,5-bis(methoxymethoxy)phenyl)(hydroxy)methyl)-4-methylpentanoyl)oxazolidin-2-one (**110**)



A flamed-dried 1000-mL round bottom flask equipped with a magnetic stir bar was charged with *N*-acyl oxazolidinone **109** (21.45 g, 77.9 mmol, 1.50 eq), capped with a rubber septum and purged with argon. DCM (200 mL) was added to give a colorless stirred solution which was cooled to 0 °C. Freshly-prepared[101] dibutylboron triflate (19.70 mL, 77.9 mmol, 1.50 eq) was then added via syringe, followed by triethylamine (14.47 mL, 104 mmol, 2.00 eq). The resulting pale yellow solution was stirred 3.5 hrs at 0 °C, then cooled to -78 °, at which time **104** (11.74 g, 51.9 mmol, 1.00 eq) was added via cannula as a solution in DCM (150 mL). The flask previously containing **104** was rinsed with DCM (2 x 75 mL), the rinsings added to the reaction flask and the reaction solution allowed to come to room temperature. The reaction solution was then stirred 25 hrs, at which time TLC indicated consumption of **104**. pH 7 buffer and 20 mL of 30% (w/w) H_2O_2 were added and the mixture stirred overnight, at which time the layers were separated, the aqueous layer

extracted with DCM, the organics combined, dried over Na_2SO_4 and concentrated onto silica. The silica-adsorbed crude material was then purified by flash chromatography on silica gel (2 kg) in a 6000-mL separatory funnel eluting with 3:1 hexanes / ethyl acetate followed by 3:2 hexanes / ethyl acetate to give pure **110** (25.63 g, 98%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 3H), 7.21 – 7.16 (m, 2H), 6.73 (d, J = 2.2 Hz, 2H), 6.62 (t, J = 2.3 Hz, 1H), 5.19 – 5.10 (m, 4H), 4.75 (d, J = 6.1 Hz, 1H), 4.49 – 4.35 (m, 2H), 4.01 (dd, J = 8.9, 2.2 Hz, 1H), 3.77 (t, J = 8.8, 1H), 3.42 (s, 6H), 3.27 – 3.18 (m, 1H), 2.67 (dd, J = 13.3, 9.9 Hz, 1H), 2.36 (br. s, 1H), 2.02 – 1.91 (m, 1H), 1.63 – 1.47 (m, 2H), 0.91 (d, J = 6.5 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8, 158.0, 153.0, 144.1, 135.3, 129.4, 128.9, 127.3, 107.6, 104.4, 94.4, 75.8, 65.9, 56.0, 55.7, 37.9, 36.8, 26.6, 23.6, 21.9. **$[\alpha]^{25}_D$** = -79.1° (*c* 2.13, $CHCl_3$). **IR** (neat): 3478 (O-H stretch), 2955 (alkane C-H stretch), 1777 (C=O stretch), 1691 (C=O stretch), 1597 cm^{-1}. **HRMS** (ESI): calc'd for $C_{27}H_{35}NNaO_8$ $[M + Na]^+$ 524.2255, found 524.2268.

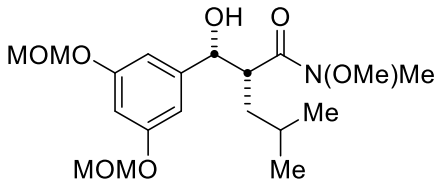
(*R*)-2-((*R*)-(3,5-bis(methoxymethoxy)phenyl)(hydroxy)methyl)-4-methylpentanoic acid (**111**)



To a 1000-mL round bottom flask containing a magnetically-stirred solution of **110** (25.90 g, 51.8 mmol, 1.00 eq) at 0 °C was added 30% (w/w) hydrogen peroxide (31.4 mL, 311 mmol, 6.00 eq). Lithium hydroxide (64.8 mL of a 2 N aqueous solution, 130 mmol, 2.50 eq) was then added over 10 minutes via dropping funnel. The reaction mixture was allowed to come to r.t. and stir 5.5 hrs, at which time TLC showed no starting material remaining. The mixture was then cooled to 0 °C and Na_2SO_3 (45 mL of a 1.3 M aqueous solution) was added; the mixture was then stirred a further 30 minutes. THF was evaporated under reduced pressure and the remaining

aqueous phase extracted with DCM (3x) and Et_2O (2x). The aqueous phase was then acidified to pH 4 and extracted with DCM (1x) and Et_2O (4x). The latter (2nd) set of organic extracts were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **111** (16.38 g, 92%) as an extremely viscous, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.71 (d, J = 2.2 Hz, 2H), 6.65 (t, J = 2.3 Hz, 1H), 5.15 (s, 4H), 4.98 (d, J = 4.6 Hz, 1H), 3.47 (s, 6H), 1.71 (m, 1H), 1.59 – 1.47 (m, 1H), 1.34 (m, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.1, 158.2, 143.8, 107.5, 104.2, 94.4, 73.7, 56.0, 50.3, 35.0, 26.1, 23.4, 21.3. **$[\alpha]^{25}_D$** = +27.4° (*c* 1.0, $CHCl_3$). **IR** (neat): 3428 (O-H stretch), 2956 (alkane C-H stretch), 1706 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{17}H_{25}O_7$ $[M - H]^-$ 341.1606, found 341.1615.

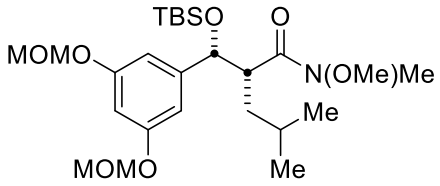
(*R*)-2-((*R*)-(3,5-bis(methoxymethoxy)phenyl)(hydroxy)methyl)-*N*-methoxy-*N*,4-dimethylpentanamide (**114**)



To a 250-mL, argon-purged round bottom flask containing a magnetically-stirred solution of **111** (5.82 g, 17.0 mmol, 1.00 eq) in THF (35 mL) were added 2-chloro-4,6-dimethoxy-1,3,5-triazine (3.28 g, 18.7 mmol, 1.10 eq) and *N*-methylmorpholine (2.05 mL, 18.7 mmol, 1.10 eq) at 0 °C; the walls of the reaction vessel were then rinsed with THF (10 mL). After ~2 min, the stirred solution became opaque; stirring then continued for 1 hr, at which time *N*,*O*-dimethylhydroxylamine hydrochloride (4.97 g, 51.0 mmol, 3.00 eq) and additional *N*-methylmorpholine (5.60 mL, 51.0 mmol, 3.00 eq) were added. After 15 min, the reaction was brought to r.t. and allowed to stir 20 hrs, then filtered through a Büchner funnel equipped with a

medium-porosity glass frit. The filter cake was washed with Et_2O (3x) and the combined filtrate washed with water (1x), 1 N HCl (2 x 65 mL), water (2 x 100 mL) and saturated aqueous $NaHCO_3$ (2 x 55 mL). The organics were then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to reveal a pale brown oil. Flash chromatography on silica gel (220 g) eluting with 3:2 hexanes/ethyl acetate gave the product as a colorless oil (3.82 g, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.73 (dd, J = 2.3, 0.7 Hz, 2H), 6.62 (t, J = 2.3 Hz, 1H), 5.15 (s, 4H), 4.89 (d, J = 3.5 Hz, 1H), 3.66 (s, 3H), 3.46 (s, 6H), 3.31 – 3.22 (m, 1H), 3.19 (s, 3H), 1.82 – 1.69 (m, 1H), 1.39 – 1.23 (m, 2H), 0.80 (d, J = 6.2 Hz, 3H), 0.74 (d, J = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.0, 158.1, 144.6, 107.5, 103.6, 94.5, 73.8, 56.0, 45.0, 34.8, 32.0, 26.1, 23.4, 21.8. **IR** (neat): 3419 (O-H stretch), 2955 (alkane C-H stretch), 1594 cm^{-1}. **HRMS** (ESI): calc'd for $C_{19}H_{30}NO_7$ $[M - H]^-$ 384.2028, found 284.2022.

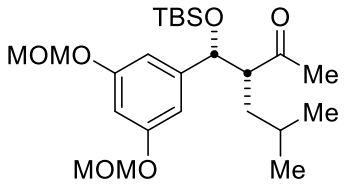
(*R*)-2-((*R*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-methoxy-*N*,4-dimethylpentanamide (**126**)



To an argon-purged 250-mL round bottom flask containing a magnetically stirred colorless solution of **114** (3.80 g, 9.86 mmol, 1.00 eq) in DCM (90 mL) were added 2,6-lutidine (3.56 mL, 30.6 mmol, 3.10 eq) and *tert*-butyldimethylsilyl triflate (3.40 mL, 14.8 mmol, 1.50 eq) at 0 °C. The reaction was then allowed to stir 18 hrs, at which time TLC indicated complete consumption of starting material. Saturated aqueous NH_4Cl and H_2O were added and the biphasic mixture stirred; layers were then separated and the aqueous layer extracted with DCM (2 x 75 mL). The combined organics were washed with water, dried over Na_2SO_4, decanted and concentrated under

reduced pressure. ^{1}H NMR indicated residual 2,6-lutidine – the crude material was thus taken up in Et_2O (150 mL), washed with 1 N HCl (1 x 100 mL), water (1 x 100 mL), and saturated aqueous $NaHCO_3$ (1 x 100 mL). The organics were then dried over $MgSO_4$, filtered and re-concentrated under reduced pressure to reveal the product (4.10 g, 83%) as a pale yellow viscous oil. Colorless but spectroscopically identical material could be obtained by flash chromatography on silica gel eluting with 4:1 hexanes / ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 (d, J = 2.3 Hz, 2H), 6.54 (t, J = 2.4 Hz, 1H), 5.11 (s, 4H), 4.69 (d, J = 8.4 Hz, 1H), 3.43 (s, 6H), 3.16 (s, 3H), 3.16 – 3.08 (m, 1H), 2.97 (s, 3H), 1.81 – 1.58 (m, 3H), 1.50 – 1.35 (s, 1H), 0.89 (s, 9H), 0.88 – 0.83 (m, 6H), 0.04 (s, 3H), -0.18 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0, 157.7, 146.8, 108.3, 104.0, 94.4, 76.1, 60.7, 55.8, 49.2, 39.0, 31.7, 26.2, 25.8, 23.9, 22.0, 18.2, -4.6, -5.1. **IR** (neat): 2954 (alkane C-H stretch), 1652 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{25}H_{46}NO_7Si$ $[M + H]^+$ 500.3038, found 500.3083.

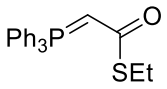
(R)-3-((R)-(3,5-bis(methoxymethoxy)phenyl)((tert-butyldimethylsilyl)oxy)methyl)-5-methylhexan-2-one (**127**)



To a flamed-dried, argon-purged 250-mL round bottom flask containing a magnetically-stirred solution of **126** (4.10 g, 8.20 mmol, 1.00 eq) in THF (125 mL) was added methyllithium (15.4 mL of a 1.6 M sol'n in Et_2O, 24.6 mmol, 3.00 eq) portionwise at -78 °C. The resulting solution was then stirred 3.5 hours, at which time TLC indicated complete consumption of starting material. The reaction solution was quenched at -78 °C by the addition of saturated aqueous NH_4Cl; the resulting mixture was allowed to come to r.t. with stirring. Et_2O was then added, the

resulting layers separated and the aqueous phase extracted with Et_2O (3 x 150 mL). Organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal 3.84 g amber oil. CC on silica gel eluting with 4:1 hexanes / ethyl acetate gave **127** (2.99 g, 80%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.60 (s, 3H), 5.13 (s, 2H), 4.52 (d, J = 7.7 Hz, 1H), 3.46 (s, 4H), 2.89 (t, J = 9.1 Hz, 1H), 1.81 (s, 3H), 1.76 – 1.62 (m, 1H), 1.52 – 1.33 (m, 2H), 0.87 (s, 15H), 0.02 (s, 3H), -0.20 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0, 157.7, 146.8, 108.3, 104.0, 94.4, 76.1, 60.7, 55.8, 49.2, 39.0, 31.7, 26.2, 25.8, 23.9, 22.0, 18.2, -4.6, -5.1. **HRMS** (DART): calc'd for $C_{24}H_{43}O_6Si$ $[M + H]^+$ 455.2823, found 455.2851.

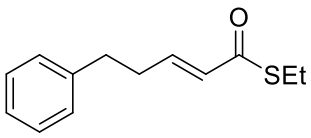
S-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate (**26**)



Following the previously described procedure[64], a 2-L round-bottom flask containing a magnetically-stirred solution of bromoacetic acid (50.0 g, 360 mmol, 1.00 eq) in DCM (700 mL) was charged with ethanethiol (34.6 mL, 468 mmol, 1.3 eq) and 4-dimethylaminopyridine (4.40 g, 36.0 mmol, 0.10 eq) at 0 °C. *N*,*N*-dicyclohexylcarbodiimide (77.94 g, 378 mmol, 1.05 eq) was then added portionwise, and the addition funnel rinsed with DCM (50 mL). The resulting thick white slurry was stirred 20 hrs, at which point the reaction mixture was filtered through Celite® and the filter cake washed with DCM (4 x 200 mL). The filtrate was concentrated under reduced pressure to give the crude thioester as a tan oil with particulate inclusions. This material was taken up in benzene (500 mL) and charged to a 1-L Erlenmeyer flask, to which triphenylphosphine (99.15 g, 378 mmol, 1.05 eq) was added. The reaction mixture was allowed to sit for four days with periodic agitation, at which point the mixture was filtered to reveal a white solid which was washed with toluene (2 x 100 mL) to give the triphenylphosphonium bromide salt as free-flowing crystalline powder. This solid was taken up in DCM (500 mL) and charged to a 3-L round-bottom

flask containing a 10% w/w solution of Na_2CO_3 (500 mL). The reaction vessel was then equipped with a mechanical stirring apparatus and the biphasic mixture stirred for 6 hrs, evolving a yellow color. The layers were separated and the aqueous phase extracted with DCM (3 x 500 mL); the combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to give a light yellow solid. Precipitation from DCM with pentane (2:1 pentane / DCM) and filtration, followed by repeated concentration and precipitation of the mother liquor as above, afforded **26** (108 g, 82% over three steps) as a free-flowing, white crystalline powder. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 – 7.51 (m, 9H), 7.51 – 7.41 (m, 6H), 3.66 (d, J = 22.5 Hz, 1H), 2.84 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.5, 133.0 (d, J = 10.3 Hz), 132.2 (d, J = 2.9 Hz), 128.9 (d, J = 12.5 Hz), 126.8 (d, J = 90.9 Hz), 46.9 (d, J = 109.7 Hz), 23.1 (d, J = 2.4 Hz), 16.3. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.5. **IR** (neat) 1578, 1336, 1085, 871, 691, 501 cm^{-1}. **HRMS** (ESI): calc'd for $C_{22}H_{21}OPS$ $[M + H]^+$ 365.1124, found 365.1122. Characterization was in accordance with that previously reported[190].

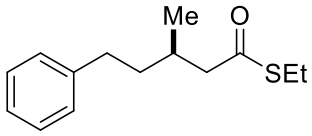
S-ethyl (*E*)-5-phenylpent-2-enethioate (**53**)



The procedure described in the literature[191] was adapted as follows: to a 1-L round-bottom flask containing a magnetically-stirred solution of hydrocinnamaldehyde (5.56 mL, 42 mmol, 1.0 eq) in DCM (200 mL) was added **26** (20.00 g, 55 mmol, 1.3 eq). The resulting solution was stirred 22 hrs at room temperature, at which time TLC showed complete consumption of starting material. The reaction mixture was concentrated under reduced pressure and the residue repeatedly extracted under sonication with pentane (4 x 100 mL). The combined washings were then purified by flash chromatography on silica gel (300 g) eluting with 49:1 pentane / Et_2O to give **53** (7.93 g, 86%) as

a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (apparent t, J = 7.4 Hz, 2H), 7.24 – 7.15 (m, 3H), 6.92 (dt, J = 15.5, 6.8 Hz, 1H), 6.12 (dt, J = 15.5, 1.5 Hz, 1H), 2.94 (q, J = 7.4 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.56 – 2.47 (m, 2H), 1.28 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.0, 143.9 140.6, 129.1, 128.5, 128.3, 126.2, 34.3, 33.9, 23.1, 14.8. Characterization agreed with that previously reported in the literature[191].

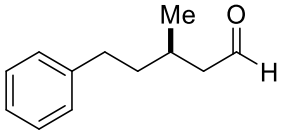
S-ethyl (*R*)-3-methyl-5-phenylpentanethioate (**54**)



An argon-purged, 250-mL round-bottom flask equipped with a magnetic stir bar as charged with $CuBr{\cdot}Me_2S$ (0.065 g, 0.32 mmol, 0.014 eq) and (R,S_P)-Josiphos ethanol adduct (0.247 g, 0.390 mmol, 0.017 eq), followed by *tert*-butyl methyl ether (125 mL). The resulting orange solution was stirred at r.t. for 30 min, then cooled to -78 °C. To this solution was added methylmagnesium bromide (9.1 mL of a 3.0 M solution in Et_2O, 27.0 mmol, 1.2 eq); **53** (5.00 g, 23 mmol, 1.00 eq) was then added as a solution in *tert*-butyl methyl ether (33 mL) over 1.5 hrs via syringe pump. The reaction mixture was allowed to stir for 14 hrs at -78 °C, at which time TLC showed complete consumption of starting material. MeOH (8 mL) was added at -78 °C and the mixture allowed to warm to room temperature; saturated aqueous NH_4Cl was then added and the biphasic mixture stirred 30 min. The layers were separated and the aqueous layer extracted with a 1:1 mixture of DCM / Et_2O (3 x 100 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography on silica gel (250 g) eluting with 49:1 pentane / Et_2O gave **54** (4.49 g, 83%, 93% e.e.) as a colorless oil. Enantiomeric excess was determined by reduction to the alcohol followed by HPLC analysis on a chiral column using the following conditions: column = Chiralpak® IB, eluent = 97:3

hexanes/*iso*-propanol, flow = 1.0 mL/min; t_R = 12.55 min (*R*), 13.51 min (*S*). Absolute configuration was established by conversion to the known[192] aldehyde **55** in the next step. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 – 7.25 (m, 3H), 7.21 – 7.15 (m, 3H), 2.88 (q, *J* = 7.4 Hz, 2H), 2.72 – 2.54 (m, 3H), 2.41 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.16 – 2.02 (m, 1H), 1.74 – 1.62 (m, 1H), 1.57 – 1.46 (m, 1H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.0, 142.3, 128.3, 128.3, 125.7, 51.2, 38.4, 33.2, 30.8, 23.3, 19.5, 14.8. **IR** (neat): 3026, 2930, 1685, 1454, 1003, 754, 698 cm^{-1}. **$[\alpha]^{25}_D$** = +6.5° (*c* 0.83, CH_2Cl_2). **HRMS** (ESI): calc'd for $C_{14}H_{21}OS$ $[M + H]^+$ 237.1308, found 237.1310.

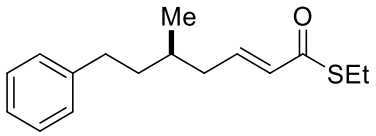
(*R*)-3-methyl-5-phenylpentanal (**55**)



A 1-L flame-dried round bottom containing **54** (8.05 g, 34.1 mmol, 1.00 eq) and equipped with a magnetic stir bar was capped with a rubber septum, purged with argon and charged with DCM (340 mL) to give a colorless, magnetically-stirred solution which was then cooled to -65 °C. DIBAL-H (35.8 mL of a 1.0 M solution in hexanes) was added slowly, and the resulting colorless solution stirred 50 minutes, at which time TLC showed complete consumption of starting material. MeOH (3 mL) was added at -65 °C and the solution stirred 10 min; the solution was then allowed to warm to rt. Saturated aqueous Rochelle's salt was added and the resulting biphasic mixture stirred until two clear phases were obtained; layers were then separated and the aqueous phase extracted with DCM. The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal **55** (6.01 g, 100%) as a colorless oil. Characterization agreed with that previously reported[192]: $[\alpha]^{25}_D$ = +22.8° (*c* 1.0, CH_2Cl_2); lit. $[\alpha]^{25}_D$ = +22.9°(*c* 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.4 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.21 - 7.15 (m, 3H), 2.73

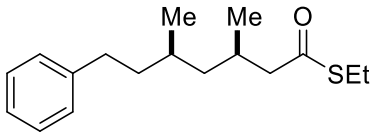
– 2.55 (m, 2H), 2.45 (ddd, *J* = 16.1, 5.7, 2.0 Hz, 1H), 2.28 (ddd, *J* = 16.1, 7.9, 2.6 Hz, 1H), 2.18 – 2.04 (m, 1H), 1.74 – 1.62 (m, 1H), 1.62 – 1.50 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 142.1, 128.4, 128.3, 125.8, 51.0, 38.6, 33.3, 27.8, 19.8.

S-ethyl (*R*,*E*)-5-methyl-7-phenylhept-2-enethioate (**56**)



To a 1-L round bottom flask containing a colorless, magnetically-stirred solution of **55** (6.01 g, 34.1 mmol, 1.00 eq) in $CHCl_3$ (340 mL) was added **7** (24.84 g, 68.2 mmol, 2.00 eq), giving a pale gold solution which was brought to reflux and stirred 12 hrs, at which time ^{1}H NMR of a reaction aliquot showed no aldehyde signal. The reaction solution was allowed to cool to r.t., then concentrated onto silica (50 g) and purified by flash chromatography on silica gel (400 g) eluting with 98:2 pentane / ether to give **56** (6.41 g, 72%) as a colorless oil. The *Z*-isomer of **56** was also isolated as a colorless oil; integration of the corresponding signals in the ^{1}H NMR spectrum of the crude reaction mixture indicate a d.r. > 20:1. Other instances of this reaction were observed to reach completion in 2 – 5 hrs, with yields averaging 87% after chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 6.86 (dt, *J* = 15.2, 7.5 Hz, 1H), 6.10 (apparent d, *J* = 15.4 Hz, 1H), 2.94 (q, *J* = 7.4 Hz, 2H), 2.72 – 2.53 (m, 2H), 2.31 – 2.19 (m, 1H), 2.13 – 2.01 (m, 1H), 1.76 – 1.60 (m, 2H), 1.57 – 1.41 (m, 1H), 1.28 (d, *J* = 7.5 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.0, 143.8, 142.3, 129.9, 128.34, 128.30, 125.7, 39.5, 38.4, 33.4, 32.2, 23.0, 19.5, 14.8. **IR** (neat): 3026, 2927, 1668, 1631, 1453 cm^{-1}. **$[\alpha]^{25}_D$** = +6.6° (*c* 0.37, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{16}H_{23}OS$ $[M + H]^+$ 263.1464, found 263.1470.

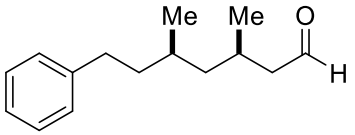
S-ethyl (*3R*,*5R*)-3,5-dimethyl-7-phenylheptanethioate (**165**)



To a flame-dried, argon-purged 500-mL round bottom flask were added CuBr•DMS (0.070 g, 0.341 mmol, 1.4 mol %) and (R,S_P)-Josiphos (0.266 g, 0.415 mmol, 1.7 mol %); the flask sealed with a rubber septum and *tert*-butyl methyl ether (100 mL) was added to give an orange solution. This solution was stirred 10 min, then cooled to -78 °C and stirred a further 15 min. Methylmagnesium bromide (9.8 mL of a 3.0 M solution in Et_2O, 29.3 mmol, 1.20 eq) was then added dropwise, giving a yellow solution. **56** (6.39 g, 24.4 mmol, 1.00 eq) was then added dropwise via syringe pump as a solution in *tert*-butyl methyl ether (25 mL) over 2 hrs. The resulting solution was stirred 16 hrs, at which time TLC showed complete consumption of starting material. The reaction was quenched with methanol (~3 mL) at -78 °C to give an opaque yellow-white suspension which was stirred 5 min, then allowed to come to r.t. Et_2O and saturated aqueous NH_4Cl were added, the mixture stirred, water added and the layers separated. The aqueous phase was then extracted with Et_2O (2 x 200 mL), the organics combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal an orange oil (6.80 g). This crude material was adsorbed onto silica, loaded onto a column containing silica gel (170 g), and purified by flash chromatography eluting with 98:2 pentane/ether to reveal the product as a colorless oil (5.73 g, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 2.87 (q, J = 7.4 Hz, 2H), 2.73 – 2.61 (m, 1H), 2.61 – 2.46 (m, 2H), 2.29 (dd, J = 14.4, 8.3 Hz, 1H), 2.21 – 2.06 (m, 1H), 1.74 – 1.59 (m, 1H), 1.59 – 1.48 (m, 1H), 1.45 – 1.36 (m, 1H), 1.36 – 1.28 (m, 1H), 1.24 (t, J = 7.4 Hz, 3H), 1.06 (dt, J = 13.6, 7.3 Hz, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.3, 142.9, 128.3, 128.3, 125.6, 51.3, 44.3, 38.4, 33.2, 29.7,

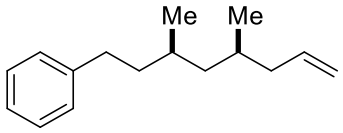
28.6, 23.3, 20.1, 20.0, 14.8. **[α]$^{25}_{D}$** = +4.56° (*c* 1.54, $CHCl_3$). **IR** (neat): 2928 (alkane C-H stretch), 1686 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{17}H_{27}OS$ $[M + H]^+$ 279.1777, found 279.1777.

(*3R*,*5R*)-3,5-dimethyl-7-phenylheptanal (**S1**)



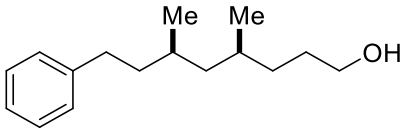
To a 2000-mL, flame-dried, argon-purged round bottom flask containing a magnetically stirred, colorless solution of **165** (6.21 g, 22.3 mmol, 1.00 eq) was added DIBAL-H (33.4 mL of a 1.0 M solution in toluene, 33.4 mmol, 1.50 eq) dropwise over 15 min at -65 °C. The resulting colorless solution was stirred an additional 10 min, after which time TLC showed no starting material remaining. Methanol (4 mL) was added at -65 °C and the solution stirred until gas evolution ceased. The reaction solution was then allowed to warm to r.t. and saturated aqueous Rochelle's salt was added; the resulting mixture was then stirred until two clear phases were obtained. Layers were separated and the aqueous phase extracted with DCM (2 x 150 mL). The organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the pure product (4.68 g, 96%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.31 – 7.25 (m, 2H), 7.21 – 7.14 (m, 3H), 2.68 (ddd, *J* = 13.6, 10.3, 5.5 Hz, 1H), 2.55 (ddd, *J* = 13.7, 10.1, 6.1 Hz, 1H), 2.44 – 2.31 (m, 1H), 2.23 – 2.09 (m, 2H), 1.73 – 1.61 (m, 1H), 1.60 – 1.48 (m, 1H), 1.47 – 1.37 (m, 1H), 1.37 – 1.23 (m, 1H), 1.11 (dt, *J* = 13.7, 7.0 Hz, 1H), 1.00 – 0.89 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.9, 142.8, 128.3, 125.6, 50.9, 44.6, 38.5, 33.2, 29.7, 25.6, 20.5, 19.9. **[α]$^{25}_{D}$** = +15.3° (*c* 1.17, $CHCl_3$). **IR** (neat): 2914 (alkane C-H stretch), 1722 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{15}H_{22}NaO$ $[M + Na]^+$ 241.1563, found 241.1552.

((*3R*,*5S*)-3,5-dimethyloct-7-en-1-yl)benzene (**170**)



To a 500-mL, flame-dried, argon-purged round bottom flask containing a magnetically stirred suspension of freshly-dried methyltriphenylphosphonium bromide (9.17 g, 25.7 mmol, 1.20 eq, dried by heating at 100 °C under high vacuum for 2 hrs) in THF (105 mL) was added *n*-butyllithium (9.4 mL of a 2.5 M solution in hexanes, 23.5 mmol, 1.10 eq) at 0 °C; an orange color evolved and most of the solid dissolved. The reaction mixture was brought to r.t. and stirred for 1 hr, at which time **S1** (4.68 g, 21.4 mmol, 1.00 eq) was added as a solution in THF (40 mL + 3 x 10 mL washes). The resulting cloudy orange reaction suspension was stirred 40 min, at which time TLC showed complete consumption of starting material. Saturated aqueous NH_4Cl, Et_2O and water were added and stirred to give a colorless, biphasic mixture. The aqueous phase was separated, extracted with Et_2O (2 x 200 mL); the organics were then combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a colorless oil. Passage of this crude material through a plug of SiO_2 eluting with pentane gave pure **170** (4.30 g, 93%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.12 (m, 3H), 5.85 – 5.68 (m, 1H), 5.05 – 4.91 (m, 2H), 2.66 (ddd, J = 13.6, 10.4, 5.4 Hz, 1H), 2.54 (ddd, J = 13.6, 10.4, 5.8 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.88 – 1.78 (m, 1H), 1.70 – 1.49 (m, 3H), 1.45 – 1.21 (m, 3H), 1.00 (dd, J = 13.8, 6.9 Hz, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 137.5, 128.3, 128.3, 125.5, 115.6, 44.3, 41.2, 38.7, 33.3, 30.1, 29.8, 20.2, 20.0. **$[\alpha]^{25}_D$** = +9.86° (*c* 0.77, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{16}H_{25}$ $[M + H]^+$ 217.1951, found 217.1964.

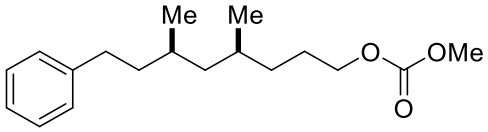
(*4S*,*6R*)-4,6-dimethyl-8-phenyloctan-1-ol (**S2**)



A 2-necked, 250-mL round bottom flask was outfitted with a pressure-equalized dropping funnel and magnetic stir bar, then sealed with rubber septa. The entire apparatus was then flame dried under high vacuum and purged with argon. The round bottom flask was charged with BH_3•THF (40.4 mL of a 1.0 M solution in THF, 40.4 mmol, 1.10 eq), and 2-methyl-2-butene (9.40 mL, 88.8 mmol, 2.42 eq) was added via the dropping funnel as a solution in THF (20 mL) over 30 min at 0 °C. The colorless reaction solution was then stirred 2.5 hrs, at which time **170** (7.94 g, 36.7 mmol, 1.00 eq) was added as a solution in THF (20 mL + 2 x 5 mL washes). The resulting solution was allowed to gradually come to r.t. over 1 hr, then stirred an additional 1 hr. TLC indicated complete consumption of starting material. The reaction vessel was cooled to 0 °C and aqueous sodium hydroxide (13.93 mL of a 3 M solution, 41.8 mmol, 1.14 eq) was added portionwise, with an initial evolution of gas. The reaction mixture evolved a cloudy, opaque appearance. The reaction vessel was then equipped with an internal thermometer and 30% aqueous hydrogen peroxide (w/w) (13.93 mL) was then added very slowly, keeping the reaction temperature below 20 °C. The resulting cloudy mixture was stirred 2 hrs, then water and Et_2O were added and the resulting layers separated. The pH of the aqueous phase was adjusted to 7.5 with saturated aqueous NH_4Cl, then the aqueous phase was extracted with Et_2O (3 x 120 mL) and the organics combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal **S2** (8.63 g, 100%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 3.69 – 3.56 (m, 2H), 2.67 (ddd, J = 13.6, 10.5, 5.4 Hz, 1H), 2.54 (ddd, J = 13.6, 10.4, 5.9 Hz, 1H), 1.72 – 1.45 (m, 4H), 1.45 – 1.23 (m, 3H), 1.23 – 1.04 (m, 2H), 1.00 (dt, J

= 13.9, 7.2 Hz, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 128.3, 128.3, 125.5, 63.4, 44.8, 38.7, 33.3, 32.7, 30.2, 29.9, 29.8, 20.2, 20.1. **$[\alpha]^{25}_D$** = +10.6° (*c* 1.45, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{16}H_{30}NO$ $[M + NH_4]^+$ 252.2322, found 252.2317.

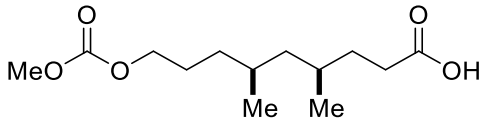
(*4S,6R*)-4,6-dimethyl-8-phenyloctyl methyl carbonate (**171**)



To a 500-mL round bottom flask purged with argon, sealed with a rubber septum, and containing a magnetically stirred, colorless solution of **Y** (8.60 g, 36.7 mmol, 1.00 eq), pyridine (3.84 mL, 47.7 mmol, 1.30 eq) and 4-dimethylaminopyridine (0.090 g, 0.734 mmol, 2 mol %) in DCM (75 mL) was added methyl chloroformate (3.69 mL, 47.7 mmol, 1.30 eq) dropwise over 5 min. A pale pink color evolved, and the reaction solution was stirred 3 hrs, at which time ^{1}H NMR of a reaction aliquot confirms the absence of starting material. Saturated aqueous NH_4Cl and water were added and the biphasic mixture stirred until two clear, distinct phases were obtained. The layers were separated and the aqueous phase extracted with DCM (2 x 120 mL); the organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal 9.85 g colorless oil. This crude material was adsorbed onto SiO_2 and loaded onto a column of silica gel (300 g). Flash chromatography eluting with 95:5 hexanes / ethyl acetate gave **171** (8.60 g, 80%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 7.18 (m, 3H), 4.11 (t, *J* = 6.8, 2H), 3.78 (s, 3H), 2.66 (ddd, *J* = 13.6, 10.5, 5.4 Hz, 1H), 2.54 (ddd, *J* = 13.6, 10.4, 5.9 Hz, 1H), 1.77 – 1.46 (m, 5H), 1.44 – 1.22 (m, 3H), 1.12 (m, 1H), 1.00 (dt, *J* = 13.9, 7.2 Hz, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 143.1, 128.3, 128.2, 125.5, 68.6, 54.6, 44.8, 38.6, 33.3, 32.6, 29.8, 29.8, 26.1, 20.2, 20.0. **$[\alpha]^{25}_D$** = +5.6° (*c* 0.34,

$CHCl_3$). **IR** (neat): 2955 (alkane C-H stretch), 1747 (carbonate C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{18}H_{32}NO_3$ $[M + NH_4]^+$ 310.2377, found 310.2383.

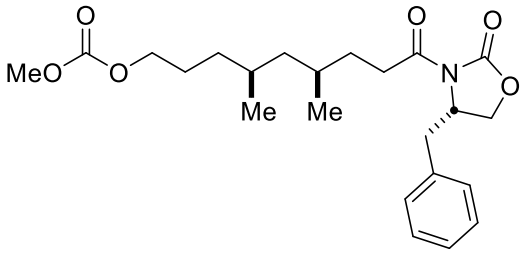
(*4R,6S*)-9-((methoxycarbonyl)oxy)-4,6-dimethylnonanoic acid (**172**)



171 (7.00 g, 23.9 mmol) was dissolved in DCM; silica (175 g, 7.3 g/mmol **171**) was then added and the DCM removed under reduced pressure to give a free-flowing white powder. This powder was charged to a 1000-mL round bottom flask equipped with a magnetic stir bar. The flask was sealed with a plastic cap and a stainless steel needle was introduced through the cap in such a way that the tip of the needle rested at the bottom of the flask below the surface of the silica. A second needle of slightly-narrower gauge was introduced through the cap such that its tip was positioned in the headspace of the flask; this needle would serve as a point of efflux. A stream of ozone in oxygen (OREC ozone generator, high-purity oxygen as input) was introduced into the flask through the longer needle and the flask cooled to -78 °C with magnetic stirring. After approximately 2 hrs, the silica obtained a pale blue coloration; the flask was uncapped and allowed to warm to r.t. The reaction was monitored by TLC on aliquots of the silica extracted with ethyl acetate; after three cycles of ozone saturation at -78 °C followed by warming to r.t., TLC indicated the complete consumption of starting material. The room-temperature silica was loaded into a glass column and eluted with two column volumes of ethyl acetate; the combined ethyl acetate washings were then concentrated under reduced pressure to give pure **172** (6.22 g, 100%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.38 (br. s, 1H), 4.12 (t, J = 6.7, 2H), 3.78 (s, 3H), 2.45 – 2.25 (m, 2H), 1.79 – 1.46 (m, 5H), 1.45 – 1.30 (m, 2H), 1.29 – 1.18 (m, 1H), 1.18 – 1.05 (m, 1H), 1.05 – 0.93 (m, 1H), 0.92 – 0.80 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.8, 155.9, 68.5, 54.6, 44.5,

32.6, 31.5, 31.2, 29.7, 29.5, 26.1, 19.9, 19.8. **[α]$^{25}_{D}$** = +1.6° (*c* 4.2, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{13}H_{24}NaO_5^+$ $[M + Na]^+$ 283.1516, found 283.1523.

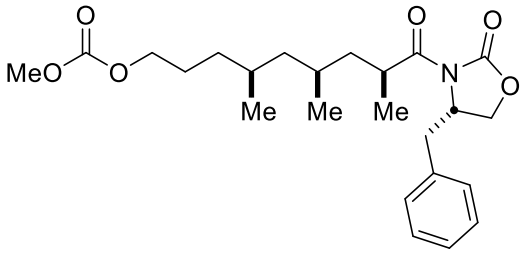
(*4S*,*6R*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4,6-dimethyl-9-oxononyl methyl carbonate (**174**)



To a 50-mL flame-dried, argon-purged round bottom flask equipped with a magnetic stir bar and capped with a rubber septum was added **172** (0.250 g, 0.96 mmol, 1.00 eq) as a solution in THF (1.5 mL, including washes) followed by triethylamine (0.33 mL, 2.40 mmol, 2.50 eq) and pivaloyl chloride (0.12 mL, 0.960 mmol, 1.00 eq) at 0 °C. A white precipitant formed and the resulting suspension was stirred 1 hr, then (*S*)-4-benzyl-2-oxazolidinone (0.170 g, 0.96 mmol, 1.00 eq) and lithium chloride (0.061 g, 1.44 mmol, 1.50 eq). The resulting mixture was stirred 24 hrs, then saturated aqueous ammonium chloride was added, the resulting mixture stirred, layers separated and the aqueous layer extracted with Et_2O. The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a brown oil. This crude material was purified by flash chromatography on silica gel (25 g) eluting first with 9:1 hexanes/ethyl acetate followed by 3:2 hexanes/ethyl acetate gave **174** (0.30 g, 72%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 3H), 7.23 – 7.17 (m, 2H), 4.66 (ddt, *J* = 10.3, 6.8, 3.2 Hz, 1H), 4.23 – 4.14 (m, 2H), 4.11 (t, *J* = 6.8 Hz, 2H), 3.76 (s, 3H), 3.29 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.98 (ddd, *J* = 15.8, 9.9, 5.5 Hz, 1H), 2.87 (ddd, *J* = 16.4, 9.8, 5.9 Hz, 1H), 2.74 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.78 – 1.49 (m, 5H), 1.48 – 1.32 (m, 2H), 1.26 (dt, *J* = 13.6, 6.9 Hz, 1H), 1.18 – 1.07 (m, 1H), 1.01 (dt, *J* = 14.0, 7.2 Hz, 1H), 0.94 – 0.83 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$)

δ 173.6, 155.9, 153.4, 135.3, 129.4, 128.9, 127.3, 68.5, 66.1, 55.2, 54.6, 44.7, 37.9, 33.2, 32.6, 30.9, 29.7, 29.6, 26.1, 19.9. $\mathbf{[\alpha]^{25}_D}$ = +39.5° (*c* 0.24, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1779 (C=O stretch), 1745 (C=O stretch), 1698 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{23}H_{34}NO_6$ $[M + H]^+$ 420.2381, found 420.2383.

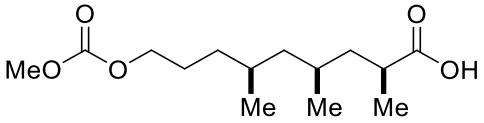
(*4S*,*6S*,*8S*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4,6,8-trimethyl-9-oxononyl methyl carbonate (**175**)



To a 500-mL argon-purged round bottom flask capped with a rubber septum and containing a magnetically-stirred colorless solution of **174** (5.00 g, 11.9 mmol, 1.00 eq) in THF (90 mL) was added sodium hexamethyldisilazide (14.3 mL of a 1.0 M solution in THF, 14.3 mmol, 1.20 eq) dropwise at -78°C. The resulting pale brown solution was stirred 1 hr, at which time methyl iodide (1.85 mL, 29.8 mmol, 2.50 eq) was added dropwise. The resulting solution was then stirred 4.5 hrs, at which time TLC indicated complete consumption of starting material. Saturated aqueous NH_4Cl, water, Et_2O and saturated aqueous $Na_2S_2O_3$ were added and the mixture allowed to warm to r.t. with stirring overnight. The layers were separated and the aqueous phase extracted with Et_2O (2 x 100 mL); the organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a dark yellow oil. Flash chromatography on silica gel (250 g) eluting first with 9:1 hexanes / ethyl acetate followed by 3:1 hexanes / ethyl acetate gave **175** (4.66 g, 81%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 3H), 7.22 (d, *J* = 6.7, 2H), 4.69 (ddt, *J* = 10.3, 7.4, 3.1 Hz, 1H), 4.25 – 4.15 (m, 2H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.94 – 3.83

(m, 1H), 3.77 (s, 3H), 3.25 (dd, J = 13.4, 3.3 Hz, 1H), 2.77 (dd, J = 13.4, 9.6 Hz, 1H), 1.90 (ddd, J = 13.7, 9.3, 4.7 Hz, 1H), 1.80 – 1.67 (m, 1H), 1.67 – 1.52 (m, 2H), 1.52 – 1.41 (m, 1H), 1.41 – 1.31 (m, 1H), 1.30 – 1.18 (m, 4H), 1.18 – 1.01 (m, 2H), 1.01 – 0.92 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2, 155.8, 152.9, 68.5, 65.9, 55.1, 54.5, 45.0, 40.5, 37.7, 35.2, 32.5, 29.6, 28.0, 26.0, 20.4, 19.9, 18.6. **$[\alpha]^{25}_D$** = +46.1° (c 0.20, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1778 (C=O stretch), 1746 (C=O stretch), 1695 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{24}H_{36}NO_6$ $[M + H]^+$ 434.2537, found 434.2532.

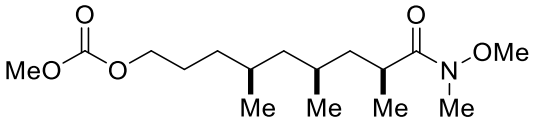
(2S,4S,6S)-9-((methoxycarbonyl)oxy)-2,4,6-trimethylnonanoic acid (**176**)



To a 500-mL round bottom flask containing a magnetically stirred colorless solution of **175** (4.19 g, 9.67 mmol, 1.00 eq) in THF (100 mL) was added a solution of lithium hydroxide monohydrate (0.811 g, 19.3 mmol, 2.00 eq) and 30% (w/w) hydrogen peroxide (7.83 mL, 77.3 mmol, 8.00 eq) in water (25 mL + 25 mL of washings) at 0 °C. Gas evolution was noted; the walls of the flask were then rinsed with an additional 50 mL THF and the resulting cloudy, colorless mixture was stirred 45 min, at which time TLC indicated the complete consumption of starting material. $Na_2S_2O_3$ (8.00 eq) dissolved in water was added, followed by saturated aqueous NH_4Cl as well as solid NH_4Cl to give a biphasic mixture of approximately neutral pH. Et_2O was added, layers were separated and the aqueous phase extracted with ethyl acetate (3 x 300 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil. Flash chromatography on silica gel (250 g) eluting with 13:5 hexanes / ethyl acetate + 1% (v/v) AcOH gave **176** (2.58 g, 97%) colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 4.12 (t, J = 6.8 Hz, 2H), 3.78 (s, 3H), 2.67 – 2.49 (m, 1H), 1.79 – 1.46 (m, 5H),

1.41 – 1.29 (m, 1H), 1.24 – 1.02 (m, 6H), 0.97 (dt, J = 14.0, 7.2 Hz, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.8, 155.9, 68.5, 54.6, 45.0, 40.9, 37.2, 32.7, 29.6, 28.1, 26.1, 20.3, 19.7, 18.1. **$[\alpha]^{25}_D$** = +12.9° (*c* 0.57, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1747 (C=O stretch), 1704 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{14}H_{27}NO_5$ $[M + H]^+$ 275.1853, found 275.1858.

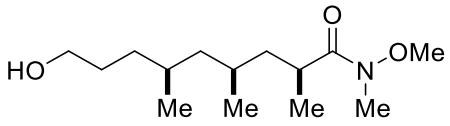
(*4S*,*6S*,*8S*)-9-(methoxy(methyl)amino)-4,6,8-trimethyl-9-oxononyl methyl carbonate (**177**)



To an argon-flushed, 500-mL round bottom flask containing a magnetically stirred colorless solution of **176** (2.48 g, 9.04 mmol, 1.00 eq) in DCM (20 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (4.94 g, 9.49 mmol, 1.05 eq) and diisopropylethylamine (3.85 mL, 22.1 mmol, 2.45 eq). The resulting near-colorless solution was stirred 10 min, at which time *N*,*O*-dimethylhydroxylamine hydrochloride (1.19 g, 12.2 mmol, 1.35 eq) was added and the reaction solution stirred an additional 1.5 hrs. At this time, TLC indicated complete consumption of starting material. The reaction solution was charged to a separatory funnel and rinsed with 1N HCl (1 x 30 mL), water (1 x 30 mL), saturated aqueous $NaHCO_3$ (1 x 30 mL), dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a glassy solid. This crude material was dissolved in DCM, adsorbed onto SiO_2 (35 g); subsequent purification by flash chromatography on silica gel (250 g) eluting with 3:1 hexanes / ethyl acetate gave **177** (2.24 g, 82%) as a colorless, low-viscosity oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (t, J = 6.8 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 3.18 (s, 3H), 3.01 (s, 1H), 1.79 (ddd, J = 13.9, 9.6, 4.7 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.66 – 1.50 (m, 2H), 1.50 – 1.40 (m, 1H), 1.40 – 1.29 (m, 1H), 1.24 – 1.15 (m, 1H), 1.15 – 1.06 (m, 4H), 1.04 – 0.89 (m, 2H), 0.87 (d, J = 4.2 Hz, 3H), 0.85 (d, J = 4.2

Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 68.6, 61.4, 54.6, 45.2, 41.1, 32.7, 32.6, 29.6, 28.1, 26.2, 20.6, 19.9, 18.5. **$[\alpha]^{25}_D$** = +16.1° (*c* 0.27, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1747 (C=O stretch), 1662 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{16}H_{32}NO_5$ $[M + H]^+$ 318.2275, found 318.2272.

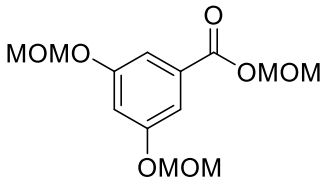
(*2S*,*4S*,*6S*)-9-hydroxy-*N*-methoxy-*N*,2,4,6-tetramethylnonanamide (**178**)



To an argon-purged 500-mL round bottom flask equipped with a magnetic stir bar, sealed with a rubber septum and containing **177** (2.17 g, 6.84 mmol, 1.00 eq) was added 1% (w/w) K_2CO_3 in methanol (60 mL). The resulting colorless solution was stirred 1 hr, at which time ^{1}H NMR of a reaction aliquot appeared to indicate the complete consumption of starting material. The reaction solution was diluted with Et_2O and washed with water. These washings were then back-extracted twice with Et_2O and the combined organics dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil with included water. This material was dissolved in DCM, re-dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a colorless oil. Despite the apparent lack of starting material in the reaction mixture, flash chromatography on silica gel (150 g) gave both starting material (0.52 g) and product (1.22 g, 69%) as colorless oils. The recovered starting material was re-subjected to the conditions described above (13 mL 1% (w/w) K_2CO_3 in methanol for 2 hrs); workup without chromatography gave additional pure product (0.22 g) which was combined with the previously-obtained material to give **178** (1.46 g, 82%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.68 – 3.56 (m, 2H), 3.18 (s, 3H), 3.02 (s, 1H), 1.80 (ddd, *J* = 13.8, 9.6, 4.4 Hz, 1H), 1.67 – 1.40 (m, 4H), 1.40 – 1.29 (m, 2H), 1.26 – 1.16 (m, 1H), 1.16 – 1.06 (m, 4H), 1.06 – 0.90 (m, 2H), 0.87 (d, *J* = 4.1 Hz, 3H), 0.86 (d, *J* = 4.1 Hz,

3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 63.4, 61.5, 45.3, 41.3, 32.7, 32.5, 32.4, 30.0, 29.8, 28.3, 20.5, 20.1, 18.5. **$[\alpha]^{25}_D$** = +28.5° (*c* 0.22, $CHCl_3$). **IR** (neat): 2931 (alkane C-H stretch), 1643 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{14}H_{30}NO_3$ $[M + H]^+$ 260.2220, found 260.2193.

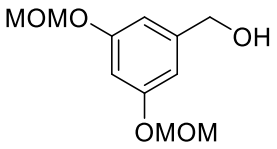
methoxymethyl 3,5-bis(methoxymethoxy)benzoate (**102**)



To a 500-mL, flame-dried three neck round bottom flask equipped with a magnetic stir bar and pressure-equalized dropping funnel was added 3,5-dihydroxybenzoic acid (10.63 g, 69.0 mmol, 1.00 eq); the flask was then sealed with rubber septa and purged with argon. DCM (80 mL) was added, followed by Hünig's base (72.11 mL, 414 mmol, 6.00 eq). The resulting off-white suspension was then cooled to 0 °C with stirring and methoxymethyl chloride (25.00 g, 311 mmol, 4.5 eq) was added dropwise (dropping funnel) over 1.5 hrs with some evolution of white gas. The resulting opaque, dark brown solution was allowed to come to r.t. and stirred 23 hrs, at which time TLC appeared to show complete consumption of starting material. Saturated aqueous $NaHCO_3$ was added and the biphasic mixture stirred until color had lightened considerably. Layers were then separated and the aqueous phase extracted with DCM (2 x 150 mL). Organics were combined and back-extracted with aqueous KOH (1 N, 2 x 250 mL), washed with brine, and dried over Na_2SO_4, then decanted and concentrated under reduced pressure to reveal the product as a brown oil (17.84 g) which was used directly in the next step without further purification. Pure **102** could be obtained as a colorless oil by purification by flash chromatography on silica gel eluting with 3:1 hexanes / ethyl acetate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.3 Hz, 2H), 6.95 (t, *J* = 2.3 Hz, 1H), 5.47 (s, 2H), 5.20 (s, 4H), 3.54 (s, 2H), 3.49 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ

165.5, 158.1, 131.9, 110.9, 109.9, 94.5, 91.1, 57.8, 56.1. **IR** (neat): 2956 (C-H stretch), 1723 (C=O stretch), 1595 (C=C stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{13}H_{19}O_7$ $[M+H]^+$ 287.1125, found 287.1116.

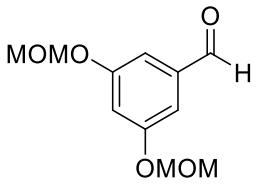
(3,5-bis(methoxymethoxy)phenyl)methanol (**103**)



A flame-dried 1000-mL round bottom flask equipped with a magnetic stir bar, purged with argon and containing crude **102** (14.53 g, 50.8 mmol, 1.00 eq) was sealed with a rubber septum and charged with DCM (100 mL) to give a pale yellow stirred solution. The reaction vessel was cooled to -78 °C and DIBAL-H (100 mL of a 1.0 M solution in hexanes, 100 mmol, 1.97 eq) was added over 15 minutes via cannula. The yellow reaction solution was stirred an additional 5 minutes, at which time TLC showed complete consumption of starting material. Excess MeOH was added at -78 °C; once gas evolution had ceased, the reaction mixture was allowed to warm somewhat and saturated aqueous Rochelle's salt was added. The biphasic mixture was allowed to warm to r.t. and stirred overnight, at which time layers were separated. The aqueous phase was extracted with diethyl ether (3 x 150 mL); organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the crude product (12.04 g) as a viscous, yellow oil which was used directly in the next step without further purification. Pure **103** could be obtained as a colorless oil after purification by flash chromatography on silica gel eluting with 98:2 DCM/MeOH. Of note, when a 1.0 M solution of DIBAL-H in THF was used in place of DIBAL-H in hexanes in this reaction, the reaction failed to progress even after warming to r.t., and the starting material was recovered unchanged. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.72 (d, J = 2.3 Hz, 2H), 6.66 (t, J = 2.3 Hz, 1H), 5.16 (s, 4H), 4.64 (s, 2H), 3.48 (s, 6H), 1.68 (s, 1H). **^{13}C NMR** (101

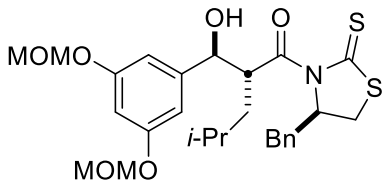
MHz, $CDCl_3$) δ 158.4, 143.5, 107.9, 104.0, 94.4, 65.1, 56.0. **IR** (neat): 3401 (br, O-H stretch), 2902 (C-H stretch), 1596 cm^{-1}. **HRMS** (ESI): calc'd for $C_{13}H_{19}O_7$ $[M+H]^+$ 287.1125, found 287.1116.

3,5-bis(methoxymethoxy)benzaldehyde (**104**)



To a 1000-mL round bottom flask containing a magnetically-stirred solution of crude **103** (12.04 g) in DCM (200 mL) was added activated manganese dioxide (88.33 g, 1.02 mol). The walls of the flask were rinsed with DCM (2 x 25 mL) and the black suspension cooled with an ice bath until the reaction was no longer exothermic. The reaction was then brought to r.t. and stirred 21 hrs, at which time TLC showed complete consumption of starting material. The reaction mixture was filtered through Celite and the filter cake thoroughly washed with DCM and the combined filtrates concentrated under reduced pressure to reveal 9.40 g yellow oil. Flash chromatography on silica gel (330 g) eluting with 85:15 hexanes/ethyl acetate gave **104** (9.16 g, 59% over three steps) as a colorless oil that solidified on standing at -30 °C over a period of months. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.21 (d, J = 2.3 Hz, 2H), 6.98 (t, J = 2.3 Hz, 1H), 5.21 (s, 4H), 3.49 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.6, 158.7, 138.5, 111.1, 110.4, 94.5, 56.2. **IR** (neat): 2904 (C-H stretch), 2827 (aldehyde C-H stretch), 1700 (C=O stretch), 1593 cm^{-1}. **HRMS** (ESI): calc'd for $C_{11}H_{14}O$ $[M+H]^+$ 227.0910, found 227.0912.

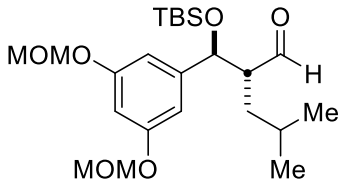
(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-2-((*S*)-(3,5-bis(methoxymethoxy)phenyl)(hydroxy)methyl)-4-methylpentan-1-one (**S3**)



To a 500-mL round bottom flask containing freshly-prepared[149] (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)-4-methylpentan-1-one (3.43 g, 11.2 mmol, 1.00 eq) was added $MgBr_2 \bullet Et_2O$ (0.434 g, 1.68 mmol, 15 mol %). The flask was equipped with a magnetic stir bar, sealed with a rubber septum and purged with argon. Ethyl acetate (10 mL) was then added, followed by **104** (2.53 g, 11.2 mmol, 1.00 eq) as a solution in ethyl acetate (5 mL + 3 mL washings). Triethylamine (3.12 mL, 22.4 mmol, 2.00 eq) and trimethylsilyl chloride (2.13 mL, 16.8 mmol, 1.50 eq) were then added to give a pale yellow opaque suspension. The reaction mixture was stirred 43 hrs, at which time TLC indicated complete consumption of starting material. The reaction mixture was filtered through a plug of silica gel, eluting with Et_2O. The filtrate was then concentrated under reduced pressure into a 500-mL round bottom flask to give the crude trimethylsilyl ether as a viscous, yellow oil. This material was dried under high vacuum overnight; the flask was then charged with a magnetic stir bar, sealed with a rubber septum and purged with argon. DCM (100 mL) was added to give a yellow solution, then trifluoroacetic acid (1.72 mL, 22.4 mmol, 2.00 eq) was added dropwise over 5 min. The resulting solution was stirred 1.5 hrs; saturated aqueous $NaHCO_3$ was then added and the resulting biphasic mixture stirred until gas evolution had ceased. The layers were separated and the aqueous phase extracted with DCM (2 x 100 mL); the organics were then combined, dried over Na_2SO_4, decanted, and concentrated under reduced pressure onto SiO_2 (25 g). This silica-adsorbed material was then loaded onto a

silica gel (250 g) column and purified by flash chromatography eluting with 9:1 hexanes / ethyl acetate followed by 7:3 hexanes / ethyl acetate to give **S3** (5.31 g, 89%) as a light yellow amorphous solid after azeotropic drying with heptane and drying on high vacuum. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.18 (m, 3H), 6.65 (d, J = 2.2 Hz, 2H), 6.56 (t, J = 2.3 Hz, 1H), 5.22 – 5.14 (m, 3H), 5.06 (d, J = 6.8 Hz, 2H), 4.86 (dt, J = 8.3, 4.1 Hz, 1H), 4.80 (td, J = 6.7, 3.3 Hz, 1H), 3.34 (s, 6H), 3.27 (d, J = 9.1 Hz, 1H), 3.10 (dd, J = 13.2, 3.8 Hz, 1H), 2.89 (dd, J = 13.2, 10.7 Hz, 1H), 2.70 (dd, J = 11.3, 6.8 Hz, 1H), 2.61 (d, J = 11.3 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.79 (t, J = 7.1 Hz, 2H), 1.00 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.0, 177.1, 158.3, 145.5, 136.4, 129.4, 128.8, 127.2, 106.0, 103.9, 94.3, 74.2, 68.8, 56.0, 48.1, 37.8, 36.5, 31.9, 25.7, 23.7, 22.2. **$[\alpha]^{25}_D$** = -200° (c 0.24, $CHCl_3$). **IR** (neat): 3491 (O-H stretch), 2952 (alkane C-H stretch), 1667 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{27}H_{35}NNaO_6S_2$ $[M + Na]^+$ 556.1798, found 556.1821.

(*R*)-2-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylpentanal (**185**)

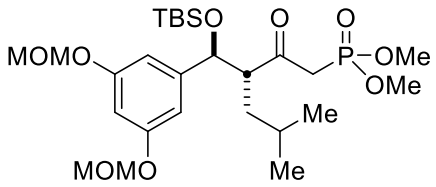


A 500-mL flame-dried round bottom flask charged with **X** (5.31 g, 9.95 mmol, 1.00 eq) was equipped with a magnetic stir bar, sealed with a rubber septum and purged with argon. DCM (80 mL) was added to give a yellow solution, then 2,6-lutidine (2.32 mL, 19.9 mmol, 2.00 eq) was added at 0 °C, followed by *tert*-butyldimethylsilyl triflate (3.43 mL, 14.9 mmol, 1.50 eq) dropwise. The cooling bath was then removed and the yellow reaction solution allowed to warm towards ambient temperature over 20 min, at which time TLC indicated the complete consumption of

starting material. Saturated aqueous $NaHCO_3$ and water were added and the biphasic mixture stirred; the layers were then separated and the aqueous phase extracted with Et_2O (2 x 100 mL). The combined organics were then rinsed with 1 N HCl (1 x 200 mL), water (1 x 200 mL), saturated aqueous $NaHCO_3$ (1 x 200 mL) and dried over Na_2SO_4. The organics were then decanted and concentrated under reduced pressure to reveal a viscous yellow oil that contained residual 2,6-lutidine. This crude material was then redissolved in Et_2O (200 mL), re-washed with 1 N HCl (2 x 100 mL), rinsed with water (1 x 150 mL) and saturated aqueous $NaHCO_3$ (1 x 150 mL), then dried over $MgSO_4$. Filtration and concentration under reduced pressure followed by stirring under high vacuum overnight gave the crude TBS ether as a viscous yellow oil. This material was then charged to a flame-dried 500-mL round bottom flask equipped with a magnetic stir bar; the flask was sealed with a rubber septum and purged with argon. DCM (100 mL) was added to give a stirred rich yellow solution. DIBAL-H (19.5 mL of a 1.0 M solution in hexanes, 19.5 mmol, 2.00 eq) was then added dropwise at -78 °C over 30 min to give a near-colorless solution. This solution was then immediately quenched with saturated aqueous Rochelle's salt at -78 °C; the resulting heterogeneous mixture was then allowed to warm to r.t. with stirring and stirred an additional 2 hrs to give two clear phases. The layers were separated and the aqueous phase extracted with DCM (2 x 100 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a yellow oil. Flash chromatography on silica gel (250 g) eluting with 9:1 hexanes / ethyl acetate gave **185** (3.18 g, 73%) as a colorless oil. Characterization agreed with that previously reported[21]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (d, J = 3.8 Hz, 1H), 6.65 (d, J = 2.3 Hz, 2H), 6.63 (d, J = 2.2 Hz, 1H), 5.14 (s, 4H), 4.73 (d, J = 6.7 Hz, 1H), 3.46 (s, 6H), 2.69 – 2.58 (m, 1H), 1.62 – 1.51 (m, 1H), 1.46 (dt, J = 13.5, 6.5 Hz, 1H), 1.04 (ddd, J = 13.6, 8.7, 4.7 Hz, 1H), 0.85 (s, 9H), 0.83 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.5 Hz, 3H), 0.01 (s, 3H), -0.20 (s, 3H). **^{13}C**

NMR (101 MHz, $CDCl_3$) δ 204.3, 158.1, 145.0, 108.1, 104.1, 94.5, 75.8, 58.1, 55.9, 35.1, 25.7, 25.6, 23.1, 21.8, 18.0, -4.6, -5.2.

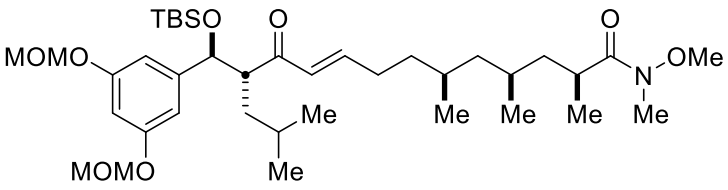
dimethyl ((*R*)-3-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-2-oxohexyl)phosphonate (**186**)



To a 500-mL flame-dried, argon-purged round bottom flask containing a colorless, magnetically stirred solution of dimethyl methylphosphonate (2.39 mL, 22.0 mmol, 3.05 eq) in THF (35 mL) was added *n*-BuLi (8.64 mL of a 2.5 M solution in hexanes, 21.6 mmol, 3.00 eq) dropwise over 8 min at -78 °C; approximately halfway through this addition the reaction solution became opaque as a fine white suspension appeared to form. This suspension was stirred 1.5 hrs, at which time **185** (3.18 g, 7.22 mmol, 1.00 eq) was added dropwise over 25 min as a solution in THF (20 mL + 25 mL washings). The reaction mixture was then stirred an additional 10 min, at which time TLC showed complete consumption of **25**. The reaction was quenched via the addition of saturated aqueous NH_4Cl and Et_2O at -78 °C; the biphasic mixture was stirred as it was allowed to come to r.t. gradually. Water and additional Et_2O were added to obtain two clear phases; the layers were then separated and the aqueous phase extracted with Et_2O (2 x 150 mL). The organics were then combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to reveal the crude β-hydroxyphosphonate as a yellow oil. ^1H NMR indicated an inconsequential 1:1 mixture of diastereomers at C13. This crude material was then charged to a 2000-mL round bottom flask equipped with a magnetic stir bar; the flask was charged with DCM (65 mL) to give a pale yellow solution. Dess-Martin periodinane (4.60 g, 10.8 mmol, 1.50 eq) was then added to the

reaction flask against a stream of argon; the reaction vessel was capped with a rubber septum and the opaque white reaction suspension stirred 30 min, at which time TLC indicated complete consumption of starting material. The reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ and the resulting the biphasic mixture stirred. Water and solid $Na_2S_2O_3$ were then added portionwise with shaking until two clear phases were obtained. Layers were then separated and the aqueous phase extracted twice with Et_2O. The organics were combined, rinsed with water (1x) and brine (1x), then dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a milky, off-white oil. This crude material was then purified by flash chromatography on silica gel (250 g) eluting with ethyl acetate to give **186** (3.65 g, 90%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.65 (d, J = 2.2 Hz, 2H), 6.62 (t, J = 2.2 Hz, 1H), 5.15 (s, 4H), 4.50 (d, J = 8.5 Hz, 1H), 3.79 (dd, J = 11.2, 9.4 Hz, 6H), 3.46 (s, 6H), 3.35 (dd, J = 20.9, 15.1 Hz, 1H), 3.21 – 3.05 (m, 2H), 1.65 – 1.54 (m, 1H), 1.34 – 1.21 (m, 1H), 0.81 (s, 9H), 0.77 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.5 Hz, 3H), -0.05 (s, 3H), -0.25 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.1, 158.0, 145.1, 108.5, 104.3, 94.4, 78.5, 58.7, 55.9, 52.8 (d, J = 6.4 Hz), 52.7 (d, J = 6.3 Hz), 43.6 (d, J = 133 Hz), 37.7, 25.7, 25.4, 23.5, 21.6, 18.0, -4.8, -5.3. **$[\alpha]^{25}_D$** = -79.5° (*c* 0.38, $CDCl_3$). **IR** (neat): 2954 (alkane C-H stretch), 1712 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{26}H_{47}NaO_9PSi$ $[M + Na]^+$ 585.2619, found 585.2601.

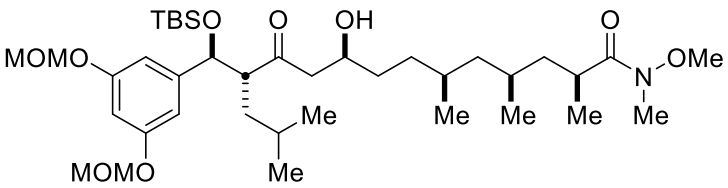
(*2S*,*4S*,*6S*,*12R*,*E*)-12-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-methoxy-*N*,2,4,6,14-pentamethyl-11-oxopentadec-9-enamide (**187**)



To a 500-mL flame-dried, argon-purged round bottom flask containing a magnetically stirred colorless solution of **177** (0.620 g, 2.39 mmol, 1.00 eq) in DCM (24 mL) was added Dess-Martin periodinane (1.52 g, 3.59 mmol, 1.50 eq). The flask was sealed with a rubber septum and the reaction mixture stirred; most of the solid dissolved to give a slightly cloudy, colorless mixture which was stirred 18 min, at which time TLC showed no starting material. Ethanol (0.07 mL, 1.20 mmol, 0.50 eq) was added to quench any excess periodinane, and the resulting mixture was stirred an additional 30 min. All volatiles were then evaporated under reduced pressure to leave a white residue which was sonicated with 1:1 hexanes / ethyl acetate. The resulting suspension was then passed through a plug of silica gel, eluting with 1:1 hexanes / ethyl acetate. The combined eluent was concentrated under reduced pressure into a 100-mL round bottom flask to reveal the crude aldehyde as a colorless oil. This flask was then charged with a magnetic stir bar and THF (12 mL) to give a colorless stirred solution. Barium hydroxide octahydrate (0.603 g, 1.91 mmol, 0.80 eq) which had been pre-treated at 120 °C for 2 hrs was added at room temperature. The reaction flask was sealed with a rubber septum and a wide-bore stainless steel needle inserted through the septum such that the needle reached the bottom of the flask. A vigorous stream of argon was bubbled through the white reaction suspension, vented by way of a second needle piercing the rubber septum which in turn was exhausted through a mineral oil bubbler. The reaction was thus stirred 25 min, at which time **186** (1.34 g, 2.39 mmol, 1.00 eq) was added as a solution in THF (12 mL), followed by water (0.3 mL). The opaque white reaction mixture was stirred 1.5 hrs, during which time the reaction mixture obtained a gel-like consistency and TLC indicated complete consumption of the aldehyde starting material. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and Et_2O; the aqueous phase was then diluted with water, the layers separated, and the aqueous phase extracted with additional Et_2O (3 x 25 mL). The organics were

then combined, rinsed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal 1.51 g pale yellow oil. Flash chromatography on silica gel eluting with 1:1 hexanes/ethyl acetate gave a viscous, colorless oil. Azeotropic drying with DCM followed by heptane gave **187** (1.17 g, 70% over two steps) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89 (dt, J = 15.6, 6.9 Hz, 1H), 6.67 (d, J = 2.3 Hz, 2H), 6.62 (t, J = 2.2 Hz, 1H), 6.28 (d, J = 15.6 Hz, 1H), 5.15 (s, 4H), 4.58 (d, J = 9.2 Hz, 1H), 3.71 (s, 3H), 3.47 (s, 6H), 3.19 (s, 3H), 3.18 – 3.10 (m, 1H), 3.02 (s, 1H), 2.35 – 2.11 (m, 2H), 1.80 (ddd, J = 13.8, 9.4, 4.7 Hz, 1H), 1.66 – 1.41 (m, 4H), 1.35 – 1.17 (m, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.07 – 0.93 (m, 2H), 0.90 (d, J = 3.0 Hz, 3H), 0.88 (d, J = 2.9 Hz, 3H), 0.75 (s, 9H), 0.72 (app. d, J = 6.6 Hz, 4H), 0.69 (d, J = 6.6 Hz, 3H), -0.11 (s, 3H), -0.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.7, 157.9, 147.5, 145.8, 131.9, 108.7, 104.0, 94.5, 78.4 61.4, 55.9, 55.6, 45.1, 41.1, 38.4, 35.3, 32.6, 30.1, 29.7, 28.1, 25.7, 25.6, 23.7, 21.5, 20.5, 19.9, 18.5, 18.0, -4.8, -5.5. **$[\alpha]^{25}_D$** = -40.2° (*c* 0.84, $CHCl_3$). **IR** (neat): 2926 (alkane C-H stretch), 1665 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{38}H_{68}NO_8Si$ $[M + H]^+$ 694.4709, found 694.4701.

(*2S*,*4S*,*6S*,*9S*,*12R*)-12-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-9-hydroxy-*N*-methoxy-*N*,2,4,6,14-pentamethyl-11-oxopentadecanamide (**188**)



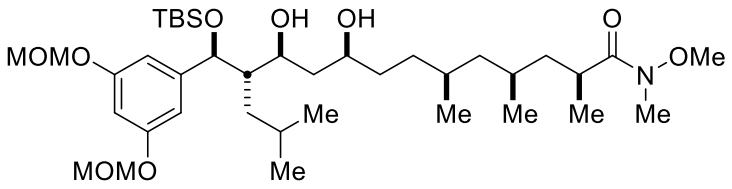
A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with copper(I) chloride (6.8 mgs, 0.0687 mmol, 12 mol %) and (S,R_P)-Josiphos ethanol adduct (0.132 g, 0.173 mmol, 36 mol %), sealed with a rubber septum, and purged with argon. To this vial was then added

dry, degassed toluene (1 mL) to give a dark orange, homogenous solution (henceforth "Solution A"). Solution A was stirred 30 min, then sodium *tert*-butoxide (0.05 mL of a 2.0 M solution in degassed THF, 0.0864 mmol, 18 mol %) was added. Meanwhile, a flame-dried 25-mL round bottom flask was charged with **187** (0.400 g, 0.576 mmol, 1.00 eq), bis(pinacolato)diboron (0.249 g, 0.979 mmol, 1.70 eq) and a magnetic stir bar, then sealed with a rubber septum and purged with argon. Dry, degassed toluene (3 mL) was then added to this flask, yielding a colorless, homogenous solution. To this solution was then added 0.83 mL of Solution A (a volume such that the reaction vessel contained 10 mol % CuCl and 30 mol % (*S*,*R*)-Josiphos), yielding a bright orange homogenous reaction solution which was stirred 19 hrs, at which time ^{1}H NMR of an aliquot indicated complete consumption of starting material. The reaction was quenched by the addition of saturated aqueous NH_4Cl and water. The layers were then separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a viscous orange oil. This crude material was then purified by flash chromatography on silica gel (50 g) eluting with 4:1 hexanes/ethyl acetate to give the boronate ester as a pale yellow oil; ^{1}H NMR analysis showed a 3:1 mixture of C-11 epimers which were carried on to the next step without further purification.

The mixed boronate ester isomers were charged to a 20-mL glass vial equipped with a magnetic stir bar, and THF (3 mL) was added to give a colorless solution. Sodium perborate tetrahydrate (0.412 g, 2.68 mmol, 5.00 eq) was added, followed by water (3 mL). The resulting brown mixture was stirred 13 hrs, at which time the reaction mixture was partitioned between water and EtOAc to obtain two phases. The layers were separated and the aqueous phase extracted with Et_2O (3 x 7 mL). The organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a yellow oil. This crude material was then purified

by flash chromatography on silica (50 g) gel eluting with 4:1 hexanes / ethyl acetate to give recovered starting material (0.113 g) and pure **188** (0.077 g) as colorless oils; additional product contaminated with 11-*epi*-**188** was also isolated as a colorless oil. The recovered starting material was then oxidized as follows: to a colorless, magnetically stirred solution of recovered starting material in THF (5 mL) was added a freshly-prepared homogenous solution of sodium perborate tetrahydrate (0.105 g, 0.687 mmol, 5.00 eq) in water (5 mL). The resulting opaque colorless mixture was then stirred 15 hrs, at which time TLC indicated complete consumption of starting material. The reaction was then worked up in a manner directly analogous to that described above, giving a colorless oil which was then combined with the impure product obtained above to give a colorless oil (0.250 g). A second round of flash chromatography on silica (25 g) gel again eluting with 4:1 hexanes / ethyl acetate yielded further pure product (0.027 g), which was combined with that obtained above, giving pure **188** (0.094 g, 23% over two steps) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 – 6.62 (m, 3H), 5.18 (s, 4H), 4.61 (d, J = 9.0 Hz, 1H), 4.09 – 3.98 (m, 1H), 3.73 (s, 3H), 3.49 (s, 6H), 3.40 (s, 1H), 3.21 (s, 3H), 3.04 (s, 1H), 2.96 (ddd, J = 10.5, 8.9, 3.7 Hz, 1H), 2.75 – 2.68 (m, 2H), 1.82 (ddd, J = 13.7, 9.1, 4.9 Hz, 1H), 1.65 – 1.44 (m, 5H), 1.44 – 1.32 (m, 2H), 1.32 – 1.19 (m, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.09 – 0.94 (m, 2H), 0.91 (d, J = 7.4 Hz, 3H), 0.89 (d, J = 7.4 Hz, 3H), 0.83 (s, 9H), 0.78 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H), -0.02 (s, 3H), -0.24 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 216.2, 158.0, 145.1, 108.6, 104.2, 94.4, 78.1, 67.7, 61.4, 58.8, 55.9, 51.9, 45.3, 41.1, 38.2, 33.8, 32.6, 32.4, 29.8, 28.1, 25.8, 25.8, 23.7, 21.5, 20.7, 20.0, 18.4, 18.0, -4.8, -5.2. **$[\alpha]^{25}_D$** = -13.2 ° (c 1.1, $CHCl_3$). **IR** (neat): 3447 (alcohol O-H stretch), 1701 (ketone C=O stretch), 1663 (amide C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{38}H_{69}ClNO_8Si$ $[M + Cl]^-$ 746.4436, found 746.4421.

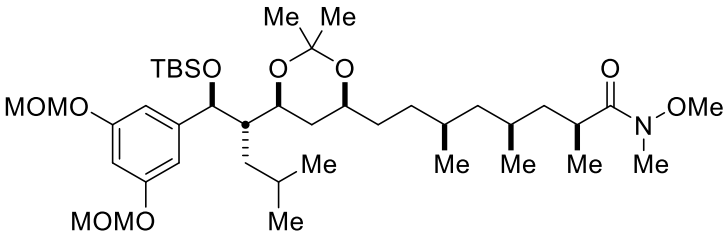
(*2S*,*4S*,*6S*,*9S*,*11S*,*12S*)-12-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-9,11-dihydroxy-*N*-methoxy-*N*,2,4,6,14-pentamethylpentadecanamide (**198**)



To a 20-mL glass scintillation vial containing **188** (0.093 g, 0.131 mol, 1.00 eq) and equipped with a magnetic stir bar was added anhydrous THF (1.5 mL) to give a colorless solution. The vial was blown out with argon, capped with a rubber septum and cooled to -30 °C. BH_3•DMS (27 μL, 0.287 mmol, 2.20 eq) was then added via syringe through the rubber septum and the resulting solution stirred 14 hrs, at which time TLC indicated complete consumption of starting material. Saturated aqueous $NaHCO_3$ (0.75 mL) and 30% (w/w) H_2O_2 (0.70 mL) were added sequentially, with gas evolution observed upon the initial addition of base. The resulting mixture was stirred 15 min, then Et_2O and water were added and the biphasic mixture sonicated to give two clear phases. The layers were separated and the aqueous phase extracted with Et_2O (2 x 10 mL); the organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the product (0.090 g, 96%) as a colorless oil was used in the subsequent step without further purification. ^{1}H NMR showed a 3:1 mixture of **198** and 13-*epi*-**198**; epimers were separated in the subsequent step. **^{1}H NMR** (400 MHz, $CDCl_3$) Major (*syn*) isomer: δ 6.66 (d, J = 2.3 Hz, 2H), 6.61 – 6.57 (m, 1H), 5.14 (s, 4H), 4.63 (d, J = 5.6 Hz, 1H), 3.97 (dd, J = 9.5, 5.1 Hz, 1H), 3.75 (br s, 1H), 3.70 (s, 3H), 3.46 (s, 6H), 3.18 (s, 3H), 3.01 (br s, 1H), 1.83 – 1.71 (m, 4H), 1.59 – 1.14 (m, 12H), 1.10 (d, J = 6.7 Hz, 3H), 1.07 – 0.95 (m, 1H), 0.90 (s, 9H), 0.89 – 0.82 (m, 9H), 0.75 (d, J = 6.5 Hz, 3H), 0.04 (s, 3H), -0.20 (s, 3H). Minor (*anti*) isomer: δ 6.74 – 6.52

(m, 3H), 5.14 (s, 4H), 4.82 (d, *J* = 3.5 Hz, 1H), 4.24 (d, *J* = 10.3 Hz, 1H), 3.76 (br s, 1H), 3.69 (s, 3H), 3.47 (s, 6H), 3.17 (s, 3H), 3.00 (br s, 1H), 1.85 – 1.10 (m, 16H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.00 (m, 2H), 0.92 (s, 9H), 0.91 – 0.82 (m, 9H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.08 (s, 3H), -0.17 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) Major (*syn*) isomer: δ 157.9, 146.5, 108.3, 103.6, 94.4, 74.6, 73.6, 61.4, 55.9, 49.5, 45.2, 41.2, 39.7, 36.1, 35.3, 32.7, 32.2, 29.9, 28.2, 25.8, 23.0, 22.3, 20.7, 20.0, 18.4, 18.1, -4.5, -5.2. Minor (*anti*) isomer: δ 158.0, 145.9, 107.9, 103.7, 94.5, 78.0, 69.3, 67.3, 61.4, 56.0, 55.9, 47.7, 45.1, 41.2, 40.4, 34.5, 34.3, 32.7, 29.8, 28.2, 25.9, 25.7, 23.4, 22.0, 20.6, 20.0, 18.4, 18.0, -4.5, -5.3. **HRMS** (ESI): calc'd for $C_{38}H_{71}NNaO_9Si$ $[M + Na]^+$ 736.4790, found 736.4848.

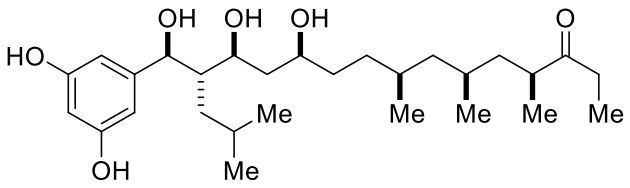
(*2S*,*4S*,*6S*)-8-((*4S*,*6S*)-6-((*1S*,*2S*)-1-(3,5-bis(methoxymethoxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-*N*-methoxy-*N*,2,4,6-tetramethyloctanamide (**200**)



To a 20-mL glass scintillation vial equipped with a magnetic stir bar and containing **198** and 13-*epi*-**198** (0.051 g, 0.0714 mmol, 1.00 eq, 3:1 ratio of epimers) was added dry acetone (2 mL) to give a colorless solution. Sodium sulfate (0.101 g, 0.714 mmol, 10.0 eq) was added, followed by *p*-TsOH (1.2 mgs, delivered as 0.1 mL of a freshly-prepared solution of 12 mgs *p*-TsOH in 1 mL dry acetone, 0.00714 mmol, 10 mol %) to give a colorless suspension. This reaction mixture was then stirred 1 hr, at which time TLC indicated complete consumption of starting material. The reaction was quenched with saturated aqueous $NaHCO_3$ (12 drops) to obtain a near-neutral mixture which was then partitioned between EtOAc (7 mL) and water (5 mL). The resulting

layers were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil (0.051 g, 94%). This crude residue was then dissolved in anhydrous DCM (3.5 mL) and transferred to a 20-mL glass scintillation vial containing a magnetic stir bar. The vial was blown out with argon, capped with a rubber septum and cooled to 0 °C, at which time *p*-TsOH (0.6 mgs, delivered as 0.1 mL of a freshly-prepared solution of 5.8 mgs *p*-TsOH in 1 mL dry DCM, 0.00338 mmol, 5 mol %) was added. This colorless solution was then stirred 4 hr 15 min, at which time the solution was quenched with Et_3N (5 drops) and concentrated under reduced pressure to give **200** together with 13-*epi*-**198** as a pale yellow oil. This crude material was then dissolved in DCM and loaded directly onto a silica gel (2.5 g) plug, which was eluted with several plug volumes of 7:3 hexanes / ethyl acetate, giving pure **200** (0.036 g, 67%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.3 Hz, 2H), 6.58 (t, J = 2.2 Hz, 1H), 5.18 – 5.09 (m, 4H), 4.73 (d, J = 5.5 Hz, 1H), 3.96 – 3.83 (m, 1H), 3.70 (apparent s, 4H), 3.46 (s, 6H), 3.18 (s, 3H), 3.01 (s, 1H), 1.89 – 1.82 (m, 1H), 1.78 (ddd, J = 13.7, 9.0, 4.9 Hz, 1H), 1.59 – 1.42 (m, 5H), 1.38 (s, 3H), 1.34 (s, 3H), 1.34 – 1.15 (m, 5H), 1.10 (apparent d, J = 6.8 Hz, 5H), 1.01 (ddd, J = 13.6, 8.4, 5.2 Hz, 1H), 0.98 – 0.89 (m, 1H), 0.88 (s, 9H), 0.87 – 0.82 (m, 6H), 0.81 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H), 0.01 (s, 3H), -0.21 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 146.3, 108.7, 103.3, 98.1, 94.5, 74.7, 69.2, 69.0, 61.4, 55.9, 48.4, 45.1, 41.1, 34.9, 34.0, 33.6, 32.6, 32.5, 31.9, 30.2, 28.1, 26.1, 25.8, 23.2, 22.5, 20.7, 20.0, 19.8, 18.4, 18.1, -4.7, -5.1. **$[\alpha]^{25}_D$** = -12.8° (*c* 0.95, $CHCl_3$). **IR** (neat): 2952 (alkane C-H stretch), 1669 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{41}H_{79}N_2O_9Si$ $[M + NH_4]^+$ 771.5549, found 771.5594.

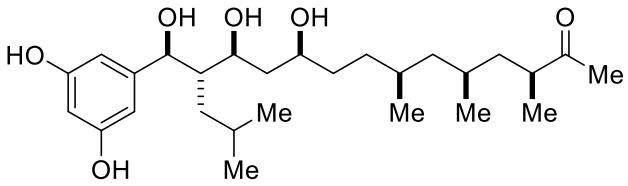
Baulamycin A (**1**)



A 2-dram vial equipped with a magnetic stir bar and containing **200** (29.9 mgs, 0.0396 mmol, 1.00 eq) was sealed with a rubber septum, purged with argon and charged with Et_2O (2 mL) to give a colorless solution. Ethyl magnesium bromide (0.13 mL of a 3.0 M solution in diethyl ether, 0.396 mmol, 10.0 eq) was added dropwise at room temperature, and the resulting solution was stirred 19 hrs, at which time the reaction mixture was cooled to 0 °C and saturated aqueous NH_4Cl was added dropwise until gas evolution ceased. Water and additional diethyl ether were added and the resulting biphasic mixture stirred until two clear phases were obtained. The layers were then separated and the aqueous phase extracted with diethyl ether (3 x 10 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the ethyl ketone (23.1 mg) as a colorless oil. A portion of this material was then deprotected as follows: a 20-mL glass vial equipped with a magnetic stir bar crude was charged with crude ethyl ketone (20.4 mg, 0.0282 mmol, 1.00 eq) followed by THF (1 mL) and methanol (1 mL) to give a colorless solution. 2 N HCl (1 mL) was then added dropwise to give an opaque white mixture which clarified upon stirring. The reaction solution was stirred 36 hrs, then quenched by the slow, portionwise addition of solid $NaHCO_3$ until gas evolution ceased and the pH of the reaction approached neutrality. EtOAc and water were added to give two clear phases, which were then separated. The aqueous phase was then extracted with EtOAc (4 x 10 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil. This crude residue was dissolved in EtOAc and purified by PTLC eluting with 1:1

heptane / ethyl acetate to reveal baulamycin A (8.9 mgs, 51% over two steps) as a colorless oil. Characterization matched that previously reported in the literature in all respects. **^{1}H NMR** (400 MHz, MeOD) δ 6.33 (d, J = 2.2 Hz, 2H), 6.15 (t, J = 2.2 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.00 (dt, J = 10.0, 3.4 Hz, 1H), 3.74 – 3.64 (m, 1H), 2.75 (dqd, J = 9.1, 6.9, 5.0 Hz, 1H), 2.64 – 2.242 (m, 2H), 1.88 (m, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.61 – 1.46 (m, 2H), 1.46 – 1.27 (m, 5H), 1.27 – 1.13 (m, 4H), 1.06 (d, J = 6.9 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H), 0.99 – 0.90 (m, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD) δ 218.6, 159.3, 148.3, 106.3, 102.2, 76.9, 73.7, 72.9, 48.8, 46.6, 45.0, 42.0, 41.0, 37.6, 35.7, 35.4, 33.4, 31.2, 29.5, 26.9, 23.6, 22.8, 20.9, 20.6, 18.2, 8.1. **$[\alpha]^{25}_D$** = -15.3° (c 0.65, CH_3OH). **HRMS** (ESI): calc'd for $C_{28}H_{49}O_6$ $[M + H]^+$ 481.3524, found 481.3529.

Baulamycin B (**2**)



To a 2-dram vial containing a colorless solution of **200** (4 mgs, 0.0053 mmol, 1.00 eq) in anhydrous THF (0.35 mL) was added methyllithium (0.01 mL of a 1.6 M solution in Et_2O, 0.0159 mmol, 3.00 eq) at -78 °C. The resulting solution was then stirred 2.75 h, at which time TLC showed complete consumption of starting material. The reaction solution was quenched by the addition of saturated aqueous NH_4Cl and water at -78 °C; the resulting mixture was then extracted with Et_2O (4 x 4 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless residue. This crude material was then charged to a 2-dram vial equipped with a magnetic stir bar, and THF (0.5 mL) was added to give a colorless solution. Water (10 µL, 0.564 mmol, 100 eq) was then added, followed by 3 M HCl in methanol (0.5 mL).

The vial was then sealed and the reaction solution stirred 14 hours, at which time TLC showed complete consumption of starting material. Solid $NaHCO_3$ (0.126 g) was added portionwise slowly to quench the reaction, giving an opaque colloidal suspension. This suspension was sparged with argon for 15 minutes, then evaporated under reduced pressure at 32 °C to give a solid white residue. This crude material, which was assumed to be primarily NaCl, was dissolved in water (1.5 mL); this aqueous solution was then extracted with ethyl acetate (3 x 1.5 mL). The combined organics were then dried over Na_2SO_4, decanted and concentrated once again under reduced pressure to reveal a colorless resuide (2.8 mg). This crude material was purified by PTLC eluting with 13:7 ethyl acetate / hexanes, providing a 1:1 mixture of baulamycin B and 3-*epi*-baulamycin B as a colorless oil (1.3 mg, 50% combined yield of diastereomers). **^{1}H NMR** (400 MHz, MeOD) Baulamycin B: δ 6.32 (d, J = 2.2 Hz, 2H), 6.14 (t, J = 2.2 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.00 (d, J = 10.0 Hz, 1H), 3.74 – 3.64 (m, 1H), 2.76 – 2.62 (m, 1H), 2.15 (s, 3H), 1.92 – 1.85 (m, 1H), 1.82 – 1.68 (m, 2H), 1.65 – 1.14 (m, 11H), 1.08 (d, J = 7.0 Hz, 3H), 0.91 – 0.85 (m, 6H), 0.83 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H). 3-*epi*-Baulamycin B: δ 6.32 (d, J = 2.2 Hz, 2H), 6.14 (t, J = 2.2 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.00 (d, J = 10.0 Hz, 1H), 3.74 – 3.64 (m, 1H), 2.76 – 2.62 (m, 1H), 2.16 (s, 3H), 1.92 – 1.85 (m, 1H), 1.82 – 1.68 (m, 2H), 1.65 – 1.14 (m, 11H), 1.06 (d, J = 6.9 Hz, 3H), 0.91 – 0.85 (m, 6H), 0.83 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD) Baulamycin B: δ 216.1, 159.4, 148.3, 106.3, 102.3, 76.9, 73.7, 72.9, 46.6, 46.0, 41.8, 41.0, 37.6, 35.7, 33.3, 31.2, 29.4, 28.2, 26.9, 23.6, 22.8, 20.8, 20.6, 20.4, 17.8. 3-*epi*-Baulamycin B: δ 216.0, 159.4, 148.3, 106.3, 102.3, 76.9, 73.7, 72.9, 46.7, 46.0, 41.2, 41.0, 37.6, 35.7, 33.3, 31.3, 29.1, 28.1, 26.9, 23.6, 22.8, 20.8, 20.5, 20.4, 16.4.

References

1. Finch, R. G.; Greenwood, D.; Norrby, S. R., *Antibiotic and Chemotherapy: Anti-infective Agents and Their Use in Therapy*. Churchill Livingstone: 2003.
2. Winau, F.; Westphal, O.; Winau, R., Paul Ehrlich — in search of the magic bullet. *Microbes and Infection* **2004,** *6* (8), 786-789.
3. Aminov, R. I., A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol* **2010,** *1*, 134-134.
4. Chain, E.; Florey, H. W.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J.; Sanders, A. G., PENICILLIN AS A CHEMOTHERAPEUTIC AGENT. *The Lancet* **1940,** *236* (6104), 226-228.
5. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Florey, H. W., FURTHER OBSERVATIONS ON PENICILLIN. *The Lancet* **1941,** *238* (6155), 177-189.
6. *Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2016-2017*; World Health Organization: Geneva, 2017.
7. *Antibiotic Resistance Threats in the United States*; Centers for Disease Control and Prevention: 2013.
8. Nathan, C.; Cars, O., Antibiotic Resistance — Problems, Progress, and Prospects. *New England Journal of Medicine* **2014,** *371* (19), 1761-1763.
9. Ventola, C. L., The antibiotic resistance crisis: part 1: causes and threats. *P & T : a peer-reviewed journal for formulary management* **2015,** *40* (4), 277-283.
10. Kåhrström, C. T., Entering a post-antibiotic era? *Nature Reviews Microbiology* **2013,** *11*, 146.
11. Reardon, S., WHO Warns against "Post-Antibiotic" Era. . *Nature* 2014.
12. *Nobel Lectures, Physiology or Medicine 1942–1962*. Elsevier Publishing Company: New York, 1964.
13. Tripathi, A.; Schofield, M. M.; Chlipala, G. E.; Schultz, P. J.; Yim, I.; Newmister, S. A.; Nusca, T. D.; Scaglione, J. B.; Hanna, P. C.; Tamayo-Castillo, G.; Sherman, D. H., Baulamycins A and B, Broad-Spectrum Antibiotics Identified as Inhibitors of Siderophore Biosynthesis in Staphylococcus aureus and Bacillus anthracis. *J. Am. Chem. Soc.* **2014,** *136* (4), 1579-1586.
14. Saha, R.; Saha, N.; Donofrio, R. S.; Bestervelt, L. L., Microbial siderophores: a mini review. *Journal of Basic Microbiology* **2013,** *53* (4), 303-317.
15. Miethke, M.; Marahiel, M. A., Siderophore-Based Iron Acquisition and Pathogen Control. *Microbiology and Molecular Biology Reviews* **2007,** *71* (3), 413-451.
16. Dale, S. E.; Doherty-Kirby, A.; Lajoie, G.; Heinrichs, D. E., Role of Siderophore Biosynthesis in Virulence of Staphylococcus aureus: Identification and Characterization of Genes Involved in Production of a Siderophore. *Infection and Immunity* **2004,** *72* (1), 29-37.
17. Ferreras, J. A.; Ryu, J.-S.; Di Lello, F.; Tan, D. S.; Quadri, L. E. N., Small-molecule inhibition of siderophore biosynthesis in Mycobacterium tuberculosis and Yersinia pestis. *Nat Chem Biol* **2005,** *1* (1), 29-32.
18. Neres, J.; Labello, N. P.; Somu, R. V.; Boshoff, H. I.; Wilson, D. J.; Vannada, J.; Chen, L.; Barry, C. E.; Bennett, E. M.; Aldrich, C. C., Inhibition of Siderophore Biosynthesis in Mycobacterium tuberculosis with Nucleoside Bisubstrate Analogues: Structure−Activity Relationships of the Nucleobase Domain of 5′-O-[N-(Salicyl)sulfamoyl]adenosine. *Journal of Medicinal Chemistry* **2008,** *51* (17), 5349-5370.
19. Guchhait, S.; Chatterjee, S.; Ampapathi, R. S.; Goswami, R. K., Total Synthesis of Reported Structure of Baulamycin A and Its Congeners. *The Journal of Organic Chemistry* **2017,** *82* (5), 2414-2435.
20. Wu, J.; Lorenzo, P.; Zhong, S.; Ali, M.; Butts, C. P.; Myers, E. L.; Aggarwal, V. K., Synergy of synthesis, computation and NMR reveals correct baulamycin structures. *Nature* **2017,** *547*, 436.

21. Sengupta, S.; Bae, M.; Oh, D.-C.; Dash, U.; Kim, H. J.; Song, W. Y.; Shin, I.; Sim, T., Structural Revision of Baulamycin A and Structure–Activity Relationships of Baulamycin A Derivatives. *The Journal of Organic Chemistry* **2017,** *82* (24), 12947-12966.
22. Steele, A. D.; Ernouf, G.; Lee, Y. E.; Wuest, W. M., Diverted Total Synthesis of the Baulamycins and Analogues Reveals an Alternate Mechanism of Action. *Org. Lett.* **2018,** *20* (4), 1126-1129.
23. Hanessian, S.; Giroux, S.; Mascitti, V., The Iterative Synthesis of Acyclic Deoxypropionate Units and Their Implication in Polyketide-Derived Natural Products. *Synthesis* **2006,** *2006* (07), 1057-1076.
24. ter Horst, B.; Feringa, B. L.; Minnaard, A. J., Iterative strategies for the synthesis of deoxypropionates. *Chem. Commun.* **2010,** *46* (15), 2535-2547.
25. Cook, M. J.; Rovis, T., Rhodium-Catalyzed Enantioselective Desymmetrization of meso-3,5-Dimethyl Glutaric Anhydride: A General Strategy to syn-Deoxypolypropionate Synthons. *J. Am. Chem. Soc.* **2007,** *129* (30), 9302-9303.
26. Ota, Y.; Murayama, T.; Nozaki, K., One-step catalytic asymmetric synthesis of all-syn deoxypropionate motif from propylene: Total synthesis of (2R,4R,6R,8R)-2,4,6,8-tetramethyldecanoic acid. *Proceedings of the National Academy of Sciences* **2016,** *113* (11), 2857.
27. Oberg, K. M.; Cochran, B. M.; Cook, M. J.; Rovis, T., The Catalytic Alkylative Desymmetrization of Anhydrides in a Formal Synthesis of Ionomycin. *Synthesis* **2018,** *50* (22), 4343-4350.
28. Zhou, J.; Burgess, K., α,ω-Functionalized 2,4-Dimethylpentane Dyads and 2,4,6-Trimethylheptane Triads through Asymmetric Hydrogenation. *Angew. Chem.* **2007,** *119* (7), 1147-1149.
29. Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K., Asymmetric Hydrogenation Routes to Deoxypolyketide Chirons. *Chemistry – A European Journal* **2007,** *13* (25), 7162-7170.
30. Studte, C.; Breit, B., Zinc-Catalyzed Enantiospecific sp3–sp3 Cross-Coupling of α-Hydroxy Ester Triflates with Grignard Reagents. *Angew. Chem. Int. Ed.* **2008,** *47* (29), 5451-5455.
31. Brand, G. J.; Studte, C.; Breit, B., Iterative Synthesis of (Oligo)deoxypropionates via Zinc-Catalyzed Enantiospecific sp3−sp3 Cross-Coupling. *Org. Lett.* **2009,** *11* (20), 4668-4670.
32. Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L., An Iterative Catalytic Route to Enantiopure Deoxypropionate Subunits: Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Thioesters. *J. Am. Chem. Soc.* **2005,** *127* (28), 9966-9967.
33. Zhou, J.; Zhu, Y.; Burgess, K., Synthesis of (S,R,R,S,R,S)-4,6,8,10,16,18- Hexamethyldocosane from Antitrogus parvulus via Diastereoselective Hydrogenations. *Org. Lett.* **2007,** *9* (7), 1391-1393.
34. Zhu, Y.; Loudet, A.; Burgess, K., An Asymmetric Hydrogenation Route To (−)-Spongidepsin. *Org. Lett.* **2010,** *12* (19), 4392-4395.
35. Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K., Optically Active Iridium Imidazol-2-ylidene-oxazoline Complexes: Preparation and Use in Asymmetric Hydrogenation of Arylalkenes. *J. Am. Chem. Soc.* **2003,** *125* (1), 113-123.
36. Schmidt, Y.; Lehr, K.; Breuninger, U.; Brand, G.; Reiss, T.; Breit, B., Enantioselective Total Synthesis of the Unnatural and the Natural Stereoisomers of Vittatalactone. *The Journal of Organic Chemistry* **2010,** *75* (13), 4424-4433.
37. Haydl, A. M.; Breit, B., The Total Synthesis of Epothilone D as a Yardstick for Probing New Methodologies. *Chemistry – A European Journal* **2017,** *23* (3), 541-545.
38. Rossiter, B. E.; Swingle, N. M., Asymmetric conjugate addition. *Chem. Rev.* **1992,** *92* (5), 771-806.
39. Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L., Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents. *Chem. Rev.* **2008,** *108* (8), 2824-2852.
40. López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L., Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to α,β-Unsaturated Esters. *Angew. Chem. Int. Ed.* **2005,** *44* (18), 2752-2756.
41. Wang, S.-Y.; Ji, S.-J.; Loh, T.-P., Cu(I) Tol-BINAP-Catalyzed Enantioselective Michael Reactions of Grignard Reagents and Unsaturated Esters. *J. Am. Chem. Soc.* **2007,** *129* (2), 276-277.

42. ter Horst, B.; Feringa, B. L.; Minnaard, A. J., Catalytic asymmetric synthesis of mycocerosic acid. *Chem. Commun.* **2007,** (5), 489-491.
43. ter Horst, B.; Feringa, B. L.; Minnaard, A. J., Catalytic Asymmetric Synthesis of Phthioceranic Acid, a Heptamethyl-Branched Acid from Mycobacterium tuberculosis. *Org. Lett.* **2007,** *9* (16), 3013-3015.
44. Novak, T.; Tan, Z.; Liang, B.; Negishi, E.-i., All-Catalytic, Efficient, and Asymmetric Synthesis of α,ω-Diheterofunctional Reduced Polypropionates via "One-Pot" Zr-Catalyzed Asymmetric Carboalumination−Pd-Catalyzed Cross-Coupling Tandem Process. *J. Am. Chem. Soc.* **2005,** *127* (9), 2838-2839.
45. Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermuehle, D.; Krueger, C.; Nolte, M.; Werner, S., The role of torsional isomers of planarly chiral nonbridged bis(indenyl)metal type complexes in stereoselective propene polymerization. *J. Am. Chem. Soc.* **1993,** *115* (11), 4590-4601.
46. Kondakov, D. Y.; Negishi, E.-i., Zirconium-catalyzed enantioselective methylalumination of monosubstituted alkenes. *J. Am. Chem. Soc.* **1995,** *117* (43), 10771-10772.
47. Kondakov, D. Y.; Negishi, E.-i., Zirconium-Catalyzed Enantioselective Alkylalumination of Monosubstituted Alkenes Proceeding via Noncyclic Mechanism. *J. Am. Chem. Soc.* **1996,** *118* (6), 1577-1578.
48. Huo, S.; Negishi, E.-i., A Convenient and Asymmetric Protocol for the Synthesis of Natural Products Containing Chiral Alkyl Chains via Zr-Catalyzed Asymmetric Carboalumination of Alkenes. Synthesis of Phytol and Vitamins E and K. *Org. Lett.* **2001,** *3* (21), 3253-3256.
49. Huo, S.; Shi, J.-c.; Negishi, E.-i., A New Protocol for the Enantioselective Synthesis of Methyl-Substituted Alkanols and Their Derivatives through a Hydroalumination/Zirconium-Catalyzed Alkylalumination Tandem Process. *Angew. Chem.* **2002,** *114* (12), 2245-2247.
50. Wipf, P.; Ribe, S., Water/MAO Acceleration of the Zirconocene-Catalyzed Asymmetric Methylalumination of α-Olefins. *Org. Lett.* **2000,** *2* (12), 1713-1716.
51. Zhu, G.; Negishi, E.-i., Fully Reagent-Controlled Asymmetric Synthesis of (−)-Spongidepsin via the Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction). *Org. Lett.* **2007,** *9* (15), 2771-2774.
52. Magnin-Lachaux, M.; Tan, Z.; Liang, B.; Negishi, E.-i., Efficient and Selective Synthesis of Siphonarienolone and Related Reduced Polypropionates via Zr-Catalyzed Asymmetric Carboalumination. *Org. Lett.* **2004,** *6* (9), 1425-1427.
53. Xu, Z.; Negishi, E.-i., Efficient and Stereoselective Synthesis of Yellow Scale Pheromone via Alkyne Haloboration, Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction), and Pd-Catalyzed Tandem Negishi Coupling. *Org. Lett.* **2008,** *10* (19), 4311-4314.
54. Pitsinos, E.; Athinaios, N.; Xu, Z.; Wang, G.; Negishi, E.-i., Total synthesis of (+)-scyphostatin featuring an enantioselective and highly efficient route to the side-chain via Zr-catalyzed asymmetric carboalumination of alkenes (ZACA). *Chem. Commun.* **2010,** *46* (13), 2200-2202.
55. Liang, B.; Negishi, E.-i., Highly Efficient Asymmetric Synthesis of Fluvirucinine A1 via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA)−Lipase-Catalyzed Acetylation Tandem Process. *Org. Lett.* **2008,** *10* (2), 193-195.
56. Zhu, G.; Liang, B.; Negishi, E.-i., Efficient and Selective Synthesis of (S,R,R,S,R,S)-4,6,8,10,16,18-Hexamethyl- docosane via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction). *Org. Lett.* **2008,** *10* (6), 1099-1101.
57. Cooksey, J. P.; Kocienski, P. J.; Li, Y.-f.; Schunk, S.; Snaddon, T. N., Synthesis of the C1–C16 fragment of ionomycin using a neutral (η3-allyl)iron complex. *Organic & Biomolecular Chemistry* **2006,** *4* (17), 3325-3336.
58. Evans, D. A.; Bartroli, J.; Shih, T. L., Enantioselective aldol condensations. 2. Erythro-selective chiral aldol condensations via boron enolates. *J. Am. Chem. Soc.* **1981,** *103* (8), 2127-2129.

59. Yamaoka, Y.; Yamamoto, H., Super Silyl Stereo-Directing Groups for Complete 1,5-Syn and -Anti Stereoselectivities in the Aldol Reactions of β-Siloxy Methyl Ketones with Aldehydes. *J. Am. Chem. Soc.* **2010,** *132* (15), 5354-5356.
60. Yu, Z.; Korolev, A. V.; Heeg, M. J.; Winter, C. H., Synthesis and structural characterization of complexes derived from treatment of gallium trichloride with 3,5-diphenylpyrazole. *Polyhedron* **2002,** *21* (11), 1117-1123.
61. Maddess, M. L.; Scott, J. P.; Alorati, A.; Baxter, C.; Bremeyer, N.; Brewer, S.; Campos, K.; Cleator, E.; Dieguez-Vazquez, A.; Gibb, A.; Gibson, A.; Howard, M.; Keen, S.; Klapars, A.; Lee, J.; Li, J.; Lynch, J.; Mullens, P.; Wallace, D.; Wilson, R., Enantioselective Synthesis of a Highly Substituted Tetrahydrofluorene Derivative as a Potent and Selective Estrogen Receptor Beta Agonist. *Organic Process Research & Development* **2014,** *18* (4), 528-538.
62. Petit, S.; Duroc, Y.; Larue, V.; Giglione, C.; Léon, C.; Soulama, C.; Denis, A.; Dardel, F.; Meinnel, T.; Artaud, I., Structure–Activity Relationship Analysis of the Peptide Deformylase Inhibitor 5-Bromo-1H-indole-3-acetohydroxamic Acid. *ChemMedChem* **2009,** *4* (2), 261-275.
63. ter Horst, B.; van Wermeskerken, J.; Feringa, B. L.; Minnaard, A. J., Catalytic Asymmetric Synthesis of Mycolipenic and Mycolipanolic Acid. *Eur. J. Org. Chem.* **2010,** *2010* (1), 38-41.
64. Keck, G. E.; Boden, E. P.; Mabury, S. A., A useful Wittig reagent for the stereoselective synthesis of trans-.alpha.,.beta.-unsaturated thiol esters. *The Journal of Organic Chemistry* **1985,** *50* (5), 709-710.
65. Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L., On the Mechanism of the Copper-Catalyzed Enantioselective 1,4-Addition of Grignard Reagents to α,β-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **2006,** *128* (28), 9103-9118.
66. Akagawa, K.; Sen, J.; Kudo, K., Peptide-Catalyzed Regio- and Enantioselective Reduction of α,β,γ,δ-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.* **2013,** *52* (44), 11585-11588.
67. SciFinder Search.
68. Schmidt, Y.; Breit, B., Direct Assignment of the Relative Configuration in 1,3,n-Methyl-Branched Carbon Chains by 1H NMR Spectroscopy. *Org. Lett.* **2010,** *12* (10), 2218-2221.
69. Schmidt, Y.; Lehr, K.; Colas, L.; Breit, B., Assignment of Relative Configuration of Desoxypropionates by 1H NMR Spectroscopy: Method Development, Proof of Principle by Asymmetric Total Synthesis of Xylarinic Acid A and Applications. *Chemistry – A European Journal* **2012,** *18* (23), 7071-7081.
70. Grammer, G. N. The Trimerization of Aldehydes. Louisiana State University and Agricultural & Mechanical College, 1958.
71. Starr, J.; Vogl, O., Higher Aliphatic Aldehyde Polymers. V. Cyclic Trimers of C9 to C12, Normal Aliphatic Aldehydes. *Journal of Macromolecular Science: Part A - Chemistry* **1978,** *12* (7), 1017-1039.
72. Dunkelblum, E.; Kehat, M.; Klug, J. T.; Shani, A., Trimerization of Earias insulana sex pheromone, (E,E)-10,12-Hexadecadienal, A phenomenon affecting trapping efficiency. *J. Chem. Ecol.* **1984,** *10* (3), 421-428.
73. 9-Borabicyclo[3.3.1]nonane Dimer. In *Encyclopedia of Reagents for Organic Synthesis*.
74. Loiseleur, O.; Koch, G.; Wagner, T., A Practical Building Block for the Synthesis of Discodermolide. *Organic Process Research & Development* **2004,** *8* (4), 597-602.
75. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B., A greatly improved procedure for ruthenium tetroxide catalyzed oxidations of organic compounds. *The Journal of Organic Chemistry* **1981,** *46* (19), 3936-3938.
76. Ruthenium(VIII) Oxide. In *Encyclopedia of Reagents for Organic Synthesis*.
77. Solladié-Cavallo, A.; Quazzotti, S., 1,1-Dichloro-2,2,2-trifluoroethyllithium in Asymmetric Synthesis, II. A Route to Optically Pure 4,4,4-Trifluoro-2-hydroxybutanoic Acid. *Synthesis* **1991,** *1991* (02), 177-180.

78. Jones, D. M.; Nilsson, B.; Szelke, M., A short stereocontrolled synthesis of hydroxyethylene dipeptide isosteres. *The Journal of Organic Chemistry* **1993,** *58* (8), 2286-2290.
79. Yadav, J. S.; Rajendar, G.; Rao, R. S.; Pabbaraja, S., Total Synthesis of Nhatrangin A. *The Journal of Organic Chemistry* **2013,** *78* (17), 8524-8530.
80. Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L., Two-directional chain synthesis: an application to the synthesis of (+)-mycoticin A. *J. Am. Chem. Soc.* **1993,** *115* (8), 3360-3361.
81. Qu, J.-P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang, Y., Highly Diastereoselective Construction of Fused Carbocycles from Cyclopropane-1,1-dicarboxylates and Cyclic Enol Silyl Ethers: Scope, Mechanism, and Origin of Diastereoselectivity. *Chemistry – A European Journal* **2012,** *18* (8), 2196-2201.
82. Xu, H.; Qu, J.-P.; Liao, S.; Xiong, H.; Tang, Y., Highly Enantioselective [3+2] Annulation of Cyclic Enol Silyl Ethers with Donor–Acceptor Cyclopropanes: Accessing 3a-Hydroxy [n.3.0]Carbobicycles. *Angew. Chem. Int. Ed.* **2013,** *52* (14), 4004-4007.
83. Smith, A. B.; Scarborough, R. M., Ruthenium Tetroxide Oxidation of Simple Ethers: A Systematic Study. *Synth. Commun.* **1980,** *10* (3), 205-211.
84. Ilsley, W. H.; Zingaro, R. A.; Zoeller, J. H., The reactivity of ruthenium textroxide towards aromatic and etheric functionalities in simple organic compounds. *Fuel* **1986,** *65* (9), 1216-1220.
85. Wuts, P. G. M.; Greene, T. W., *Greene's Protective Groups in Organic Synthesis*. Wiley: 2012.
86. Soto-Cairoli, B.; Justo de Pomar, J.; Soderquist, J. A., Enantiomerically Pure α-Amino Aldehydes from Silylated α-Amino Acids. *Org. Lett.* **2008,** *10* (2), 333-336.
87. Chen, B.; Sun, H.-X.; Qin, J.-F.; Wang, B., DMF-mediated deprotection of bulky silyl esters under neutral and fluoride-free conditions. *Tetrahedron Lett.* **2016,** *57* (3), 253-255.
88. Smith, A. B.; Richmond, R. E., Total synthesis of the paniculides. *J. Am. Chem. Soc.* **1983,** *105* (3), 575-585.
89. Wang, M.; Li, C.; Yin, D.; Liang, X.-T., A mild and efficient approach for the deprotection of silyl ethers by sodium periodate. *Tetrahedron Lett.* **2002,** *43* (48), 8727-8729.
90. Wu, Y.; Yang, Y.-Q., An Expeditious Enantioselective Synthesis of Antimycin A3b. *The Journal of Organic Chemistry* **2006,** *71* (11), 4296-4301.
91. Meyers, A. I.; Tomioka, K.; Roland, D. M.; Comins, D., Progress toward the total synthesis of maytansinoids. An efficient route to two major precursors (western-southern zone). *Tetrahedron Lett.* **1978,** *19* (16), 1375-1378.
92. Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D., The SAMP-/RAMP-hydrazone methodology in asymmetric synthesis. *Tetrahedron* **2002,** *58* (12), 2253-2329.
93. Evans, D. A.; Ennis, M. D.; Mathre, D. J., Asymmetric alkylation reactions of chiral imide enolates. A practical approach to the enantioselective synthesis of .alpha.-substituted carboxylic acid derivatives. *J. Am. Chem. Soc.* **1982,** *104* (6), 1737-1739.
94. Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L., Use of Pseudoephedrine as a Practical Chiral Auxiliary for Asymmetric Synthesis. *J. Am. Chem. Soc.* **1994,** *116* (20), 9361-9362.
95. Sabitha, G.; Shankaraiah, K.; Prasad, M. N.; S. Yadav, J., Studies toward the Total Synthesis of Carolacton. *Synthesis* **2013,** *45* (02), 251-259.
96. Evans, D. A.; Britton, T. C.; Ellman, J. A., Contrasteric carboximide hydrolysis with lithium hydroperoxide. *Tetrahedron Lett.* **1987,** *28* (49), 6141-6144.
97. Yardley, J. P.; Fletcher, H., Introduction of the Methoxymethyl Ether Protecting Group. *Synthesis* **1976,** *1976* (04), 244-244.
98. Fatiadi, A. J., Active Manganese Dioxide Oxidation in Organic Chemistry - Part I. *Synthesis* **1976,** *1976* (02), 65-104.
99. Mahrwald, R., *Modern Methods in Stereoselective Aldol Reactions*. Wiley: 2013.
100. Siva Senkar Reddy, N.; Srinivas Reddy, A.; Yadav, J. S.; Subba Reddy, B. V., The stereoselective total synthesis of (−)-dihydrotetrabenazine. *Tetrahedron Lett.* **2012,** *53* (51), 6916-6918.

101. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R., Stereoselective aldol condensations via boron enolates. *J. Am. Chem. Soc.* **1981,** *103* (11), 3099-3111.
102. Inoue, T.; Mukaiyama, T., Regio- and Stereoselective Cross-aldol Reactions via Dialkylboryl Triflates. *Bull. Chem. Soc. Jpn.* **1980,** *53* (1), 174-178.
103. Friebolin, H., *Basic One- and Two-Dimensional NMR Spectroscopy*. Wiley: 2005.
104. Basha, A.; Lipton, M.; Weinreb, S. M., A mild, general method for conversion of esters to amides. *Tetrahedron Lett.* **1977,** *18* (48), 4171-4172.
105. Levin, J. I.; Turos, E.; Weinreb, S. M., An Alternative Procedure for the Aluminum-Mediated Conversion of Esters to Amides. *Synth. Commun.* **1982,** *12* (13), 989-993.
106. Evans, D. A.; Bender, S. L.; Morris, J., The total synthesis of the polyether antibiotic X-206. *J. Am. Chem. Soc.* **1988,** *110* (8), 2506-2526.
107. Evans, D. A.; Gage, J. R.; Leighton, J. L., Total synthesis of (+)-calyculin A. *J. Am. Chem. Soc.* **1992,** *114* (24), 9434-9453.
108. Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Daeffler, R.; Osmani, A.; Schreiner, K.; Seeger-Weibel, M.; Bérod, B.; Schaer, K.; Gamboni, R.; Chen, S.; Chen, W.; Jagoe, C. T.; Kinder, F. R.; Loo, M.; Prasad, K.; Repič, O.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xu, D. D.; Xue, S., Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 1: Synthetic Strategy and Preparation of a Common Precursor. *Organic Process Research & Development* **2004,** *8* (1), 92-100.
109. Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y., Organocerium compounds in synthesis. *Tetrahedron* **1999,** *55* (13), 3803-3830.
110. Imamoto, T.; Sugiura, Y.; Takiyama, N., Organocerium reagents. Nucleophilic addition to easily enolizable ketones. *Tetrahedron Lett.* **1984,** *25* (38), 4233-4236.
111. Bartoli, G.; Bosco, M.; Van Beek, J.; Sambri, L.; Marcantoni, E., Organo cerium reagents in organic chemistry: General method of synthesis of alkyl substituted 1,3-diols by RLi-CeCl3 addition to β-hydroxyketones. *Tetrahedron Lett.* **1996,** *37* (13), 2293-2296.
112. Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R., Direct Conversion of N-Methoxy-N-methylamides (Weinreb Amides) to Ketones via a Nonclassical Wittig Reaction. *Org. Lett.* **2005,** *7* (7), 1427-1429.
113. Hamilakis, S.; Tsolomitis, A., ONE-POT CONVERSION OF A REPRESENTATIVE SERIES OF CARBOXYLIC ACIDS TO THE CORRESPONDING METHYL KETONES. In *Heterocycl. Commun.*, 2005; Vol. 11, p 149.
114. Norikazu, M.; Tsuyoshi, M.; Masashi, A.; Aki, M.; Makoto, W., A New Synthetic Method for Methyl Ketones from Carboxylic Acids Using Metallic Strontium and Methyl Iodide. *Chem. Lett.* **2007,** *36* (1), 28-29.
115. Maria, O.; Morio, A., Synthesis of Ketones from Carboxylic Acids with R(PrNH)Mg. *Chem. Lett.* **2009,** *38* (8), 856-857.
116. Genna, D. T.; Posner, G. H., Cyanocuprates Convert Carboxylic Acids Directly into Ketones. *Org. Lett.* **2011,** *13* (19), 5358-5361.
117. Murata, R.; Hirano, K.; Uchiyama, M., Highly Chemoselective and Versatile Method for Direct Conversion of Carboxylic Acids to Ketones Utilizing Zinc Ate Complexes. *Chemistry – An Asian Journal* **2015,** *10* (6), 1286-1290.
118. Nicholson, J. W.; Wilson, A. D., The Conversion of Carboxylic Acids to Ketones: A Repeated Discovery. *J. Chem. Educ.* **2004,** *81* (9), 1362.
119. Rubottom, G. M.; Kim, C., Preparation of methyl ketones by the sequential treatment of carboxylic acids with methyllithium and chlorotrimethylsilane. *The Journal of Organic Chemistry* **1983,** *48* (9), 1550-1552.

120. Brady, P. B.; Albert, B. J.; Akakura, M.; Yamamoto, H., Controlling stereochemistry in polyketide synthesis: 1,3- vs. 1,2-asymmetric induction in methyl ketone aldol additions to β-super siloxy aldehydes. *Chemical Science* **2013,** *4* (8), 3223-3231.
121. McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D., A convenient procedure for the monosilylation of symmetric 1,n-diols. *The Journal of Organic Chemistry* **1986,** *51* (17), 3388-3390.
122. Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J., Oxidation of Primary Alcohols to Carboxylic Acids with Sodium Chlorite Catalyzed by TEMPO and Bleach. *The Journal of Organic Chemistry* **1999,** *64* (7), 2564-2566.
123. Kochi, T.; Tang, T. P.; Ellman, J. A., Asymmetric Synthesis of syn- and anti-1,3-Amino Alcohols. *J. Am. Chem. Soc.* **2002,** *124* (23), 6518-6519.
124. Bonini, C.; Righi, G.; Rossi, L., Iterative diastereoselective reduction of hydroxy diketoesters to all 1,3,5 syn triols: synthesis of C1-C10 fragment of Nystatin A1. *Tetrahedron* **1992,** *48* (44), 9801-9808.
125. Paterson, I.; Yeung, K.-S.; Smaill, J. B., The Horner-Wadsworth-Emmons Reaction in Natural Products Synthesis: Expedient Construction of Complex (E)-Enones Using Barium Hydroxide. *Synlett* **1993,** *1993* (10), 774-776.
126. Hartmann, E.; Vyas, D. J.; Oestreich, M., Enantioselective formal hydration of α,β-unsaturated acceptors: asymmetric conjugate addition of silicon and boron nucleophiles. *Chem. Commun.* **2011,** *47* (28), 7917-7932.
127. Reisinger, C. M.; Wang, X.; List, B., Catalytic Asymmetric Hydroperoxidation of α,β-Unsaturated Ketones: An Approach to Enantiopure Peroxyhemiketals, Epoxides, and Aldols. *Angew. Chem. Int. Ed.* **2008,** *47* (42), 8112-8115.
128. Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L., Catalytic Enantioselective Peroxidation of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **2008,** *130* (26), 8134-8135.
129. Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P., Organocatalytic Asymmetric β-Hydroxylation of α,β-Unsaturated Ketones. *Eur. J. Org. Chem.* **2007,** *2007* (33), 5492-5495.
130. Medina, S.; Harper, M. J.; Balmond, E. I.; Miranda, S.; Crisenza, G. E. M.; Coe, D. M.; McGarrigle, E. M.; Galan, M. C., Stereoselective Glycosylation of 2-Nitrogalactals Catalyzed by a Bifunctional Organocatalyst. *Org. Lett.* **2016,** *18* (17), 4222-4225.
131. Paladugu, S.; Mainkar, P. S.; Chandrasekhar, S., Synthesis of complete carbon framework of baulamycin A. *Tetrahedron Lett.* **2017,** *58* (28), 2784-2787.
132. Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Brunings, K. J.; Woodward, R. B., TERRAMYCIN. VII. THE STRUCTURE OF TERRAMYCIN. *J. Am. Chem. Soc.* **1952,** *74* (14), 3708-3709.
133. Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Gordon, P. N.; Pilgrim, F. J.; Brunings, K. J.; Woodward, R. B., The Structure of Terramycin1,2. *J. Am. Chem. Soc.* **1953,** *75* (22), 5455-5475.
134. Pischl, M. C.; Weise, C. F.; Haseloff, S.; Müller, M.-A.; Pfaltz, A.; Schneider, C., A Highly Stereoselective and Flexible Strategy for the Convergent Synthesis of Long-Chain Polydeoxypropionates: Application towards the Synthesis of the Glycolipid Membrane Components Hydroxyphthioceranic and Phthioceranic Acid. *Chemistry – A European Journal* **2014,** *20* (52), 17360-17374.
135. Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Parker, W. L.; Gougoutas, J. Z., Structure of ionomycin - a novel diacidic polyether antibiotic having high affinity for calcium ions. *J. Am. Chem. Soc.* **1979,** *101* (12), 3344-3353.
136. Chow, S.; Fletcher, M. T.; Lambert, L. K.; Gallagher, O. P.; Moore, C. J.; Cribb, B. W.; Allsopp, P. G.; Kitching, W., Novel Cuticular Hydrocarbons from the Cane Beetle Antitrogus parvulus4,6,8,10,16-Penta- and 4,6,8,10,16,18-HexamethyldocosanesUnprecedented anti-anti-anti-Stereochemistry in the 4,6,8,10-Methyltetrad. *The Journal of Organic Chemistry* **2005,** *70* (5), 1808-1827.

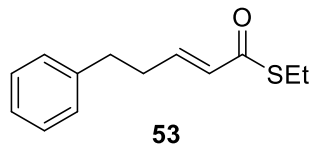
137. Morihata, K.; Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K., Stereoselective synthesis of 1,3-diol from β-hydroxyacylsilane via rearrangement of phenyl group from silicon to carbon. *Tetrahedron Lett.* **1995,** *36* (31), 5555-5558.
138. Lee, J.; Kobayashi, Y.; Tezuka, K.; Kishi, Y., Toward Creation of a Universal NMR Database for the Stereochemical Assignment of Acyclic Compounds: Proof of Concept. *Org. Lett.* **1999,** *1* (13), 2181-2184.
139. Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y., Toward Creation of a Universal NMR Database for the Stereochemical Assignment of Acyclic Compounds: The Case of Two Contiguous Propionate Units. *Org. Lett.* **1999,** *1* (13), 2177-2180.
140. Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y., Universal NMR Databases for Contiguous Polyols. *J. Am. Chem. Soc.* **2003,** *125* (47), 14379-14393.
141. Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K., Stereochemical Determination of Acyclic Structures Based on Carbon−Proton Spin-Coupling Constants. A Method of Configuration Analysis for Natural Products. *The Journal of Organic Chemistry* **1999,** *64* (3), 866-876.
142. Rubin, M. B., THE HISTORY OF OZONE. VI. OZONE ON SILICA GEL ("DRY OZONE"). *Bull. Hist. Chem.* **2008,** *33* (2), 68-75.
143. Cohen, Z. V., Haim; Keinan, Ehud; Mazu, Yehuda, Tertiary Alcohols from Hydrocarbons by Ozonation on Silica Gel: 1-Adamantanol. *Organic Syntheses* **1979,** *59*, 176.
144. Keinan, E. V., H.T., Ozonation of single bonds. In *The Chemistry of Functional Groups: Peroxides*, Patai, S., Ed. Wiley: London, 1983; pp 649-683.
145. Ozone–Silica Gel. In *Encyclopedia of Reagents for Organic Synthesis*.
146. Klein, H.; Steinmetz, A., Umsetzung adsorbierter aromaten mit ozon. *Tetrahedron Lett.* **1975,** *16* (48), 4249-4250.
147. Northrup, A. B.; MacMillan, D. W. C., The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes. *J. Am. Chem. Soc.* **2002,** *124* (24), 6798-6799.
148. Leung, G. Y. C.; Li, H.; Toh, Q.-Y.; Ng, A. M.-Y.; Sum, R. J.; Bandow, J. E.; Chen, D. Y.-K., Total Synthesis and Biological Evaluation of the Fab-Inhibitory Antibiotic Platencin and Analogues Thereof. *Eur. J. Org. Chem.* **2011,** *2011* (1), 183-196.
149. Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S., Magnesium Halide-Catalyzed Anti-Aldol Reactions of Chiral N-Acylthiazolidinethiones. *Org. Lett.* **2002,** *4* (7), 1127-1130.
150. Toshio, I.; Teruaki, M., The Partial Reduction of Carboxylic Acids to Aldehydes via 3-Acylthiazolidine-2-thiones with Diisobutylaluminum Hydride and with Lithium Tri-t-butoxyaluminum Hydride. *Bull. Chem. Soc. Jpn.* **1979,** *52* (2), 555-558.
151. Huang, D. S.; Wong, H. L.; Georg, G. I., Synthesis and Cytotoxicity Evaluation of C4- and C5-Modified Analogues of the α,β-Unsaturated Lactone of Pironetin. *ChemMedChem* **2017,** *12* (7), 520-528.
152. Granander, J.; Sott, R.; Hilmersson, G., Asymmetric addition of n-butyllithium to aldehydes: new insights into the reactivity and enantioselectivity of the chiral amino ether accelerated reaction. *Tetrahedron* **2002,** *58* (23), 4717-4725.
153. Delaunay, D.; Toupet, L.; Corre, M. L., Reactivity of .beta.-Amino Alcohols with Carbon Disulfide Study on the Synthesis of 2-Oxazolidinethiones and 2-Thiazolidinethiones. *The Journal of Organic Chemistry* **1995,** *60* (20), 6604-6607.
154. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T., Horner-wadsworth-emmons reaction: Use of lithium chloride and an amine for base-sensitive compounds. *Tetrahedron Lett.* **1984,** *25* (21), 2183-2186.
155. Thorpe, S. B.; Calderone, J. A.; Santos, W. L., Unexpected Copper(II) Catalysis: Catalytic Amine Base Promoted β-Borylation of α,β-Unsaturated Carbonyl Compounds in Water. *Org. Lett.* **2012,** *14* (7), 1918-1921.

156. Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T., Chiral Copper(II)-Catalyzed Enantioselective Boron Conjugate Additions to α,β-Unsaturated Carbonyl Compounds in Water. *Angew. Chem. Int. Ed.* **2012,** *51* (51), 12763-12766.
157. Takahashi, K.; Ishiyama, T.; Miyaura, N., A borylcopper species generated from bis(pinacolato)diboron and its additions to α,β-unsaturated carbonyl compounds and terminal alkynes. *J. Organomet. Chem.* **2001,** *625* (1), 47-53.
158. Sim, H.-S.; Feng, X.; Yun, J., Copper-Catalyzed Enantioselective β-Boration of Acyclic Enones. *Chemistry – A European Journal* **2009,** *15* (8), 1939-1943.
159. Sammakia, T.; Jacobs, J. S., Picolinic acid as a partner in the Mitsunobu reaction: Subsequent hydrolysis of picolinate esters under essentially neutral conditions with copper acetate in methanol. *Tetrahedron Lett.* **1999,** *40* (14), 2685-2688.
160. Molander, G. A.; Hahn, G., Lanthanides in organic synthesis. 4. Reduction of .alpha.,.beta.-epoxy ketones with samarium diiodide. A route to chiral, nonracemic aldols. *The Journal of Organic Chemistry* **1986,** *51* (13), 2596-2599.
161. Enders, D.; Zhu, J.; Raabe, G., Asymmetric Epoxidation of Enones With Oxygen in the Presence of Diethylzinc and (R,R)-N-Methylpseudoephedrine. *Angewandte Chemie International Edition in English* **1996,** *35* (15), 1725-1728.
162. Enders, D.; Zhu, J.; Kramps, L., Zinc-Mediated Asymmetric Epoxidation of α-Enones. *Liebigs Annalen* **1997,** *1997* (6), 1101-1113.
163. Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M., Catalytic Asymmetric Epoxidation of α,β-Unsaturated Ketones Promoted by Lanthanoid Complexes. *J. Am. Chem. Soc.* **1997,** *119* (9), 2329-2330.
164. Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M., Catalytic Asymmetric Epoxidation of Enones Using La−BINOL−Triphenylarsine Oxide Complex: Structural Determination of the Asymmetric Catalyst. *J. Am. Chem. Soc.* **2001,** *123* (12), 2725-2732.
165. Körber, K.; Risch, P.; Brückner, R., A Novel Strategy for the Convergent Synthesis of 1,3,5,…-Polyols: Enone Formation, Asymmetric Dihydroxylation, Reductive Cleavage, Hydride Addition. *Synlett* **2005,** *2005* (19), 2905-2910.
166. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M., The osmium-catalyzed asymmetric dihydroxylation: a new ligand class and a process improvement. *The Journal of Organic Chemistry* **1992,** *57* (10), 2768-2771.
167. Paterson, I.; Housden, M. P.; Cordier, C. J.; Burton, P. M.; Mühlthau, F. A.; Loiseleur, O., Synthetic studies toward the brasilinolides: controlled assembly of a protected C1–C38 polyol based on fragment union by complex aldol reactions. *Organic & Biomolecular Chemistry* **2015,** *13* (20), 5716-5733.
168. Narasaka, K.; Pai, F.-C., Stereoselective reduction of β hydroxyketones to 1,3-diols highly selective 1,3-asymmetric induction via boron chelates. *Tetrahedron* **1984,** *40* (12), 2233-2238.
169. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J., 1,3-Syn diastereoselective reduction of β-hydroxyketones utilizing alkoxydialkylboranes. *Tetrahedron Lett.* **1987,** *28* (2), 155-158.
170. Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repič, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I., Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 5: Linkage of Fragments C1-6 and C7-24 and Finale. *Organic Process Research & Development* **2004,** *8* (1), 122-130.
171. Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T., The Total Synthesis of the Oxopolyene Macrolide RK-397. *Angew. Chem. Int. Ed.* **2007,** *46* (7), 1066-1070.
172. Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A., Studies in Macrolide Synthesis: A Stereocontrolled Synthesis of Oleandolide Employing Reagent- and Substrate-Controlled Aldol Reactions of (S)-1-(Benzyloxy)-2-methylpentan-3-one. *J. Am. Chem. Soc.* **1994,** *116* (25), 11287-11314.

173. Nakata, T.; Oishi, T., Stereoselective reduction of β-keto esters with zinc borohydride. stereoselective synthesis of erythro-3-hydroxy-2-alkylpropionates. *Tetrahedron Lett.* **1980,** *21* (17), 1641-1644.
174. Zinc Borohydride. In *Encyclopedia of Reagents for Organic Synthesis*.
175. Narasimhan, S.; Madhavan, S.; Prasad, K. G., Facile reduction of carboxylic acids to alcohols by zinc borohydride. *The Journal of Organic Chemistry* **1995,** *60* (16), 5314-5315.
176. Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L., A Highly Diastereoselective TiCl4-Mediated Reduction of β-Hydroxy Ketones with BH3·py — A Very Efficient and General Synthesis of syn-1,3-Diols. *Eur. J. Org. Chem.* **2001,** *2001* (24), 4679-4684.
177. Bode, S. E.; Müller, M.; Wolberg, M., Diastereomer-Differentiating Hydrolysis of 1,3-Diol-Acetonides: A Simplified Procedure for the Separation of syn- and anti-1,3-Diols. *Org. Lett.* **2002,** *4* (4), 619-621.
178. Coste, G.; Gerber-Lemaire, S., Selective hydrolysis of anti-1,3-diol-acetonides for the differentiation of 1,3-anti and 1,3-syn diols. *Tetrahedron Lett.* **2006,** *47* (5), 671-674.
179. Rychnovsky, S. D.; Skalitzky, D. J., Stereochemistry of alternating polyol chains: 13C NMR analysis of 1,3-diol acetonides. *Tetrahedron Lett.* **1990,** *31* (7), 945-948.
180. Evans, D. A.; Rieger, D. L.; Gage, J. R., 13C NMR chemical shift correlations in 1,3-diol acetonides. Implications for the stereochemical assignment of propionate-derived polyols. *Tetrahedron Lett.* **1990,** *31* (49), 7099-7100.
181. Burfield, D. R.; Smithers, R. H., Desiccant efficiency in solvent drying. 3. Dipolar aprotic solvents. *The Journal of Organic Chemistry* **1978,** *43* (20), 3966-3968.
182. Armarego, W. L. F., *Purification of Laboratory Chemicals*. Sixth Edition ed.; Elsevier Science: 2009.
183. *Encyclopedia of Reagents for Organic Synthesis*. Wiley: 1995.
184. Seebach, D.; Imwinkelried, R.; Stucky, G., Optisch aktive Alkohole aus 1,3-Dioxan-4-onen: eine praktikable Variante der enantioselektiven Synthese unter nucleophiler Substitution an Acetal-Zentren. *Helv. Chim. Acta* **1987,** *70* (2), 448-464.
185. Tiers, G. V. D., "Melting points are uncorrected": True or false? *J. Chem. Educ.* **1990,** *67* (3), 258.
186. O'Brien, M.; Konings, L.; Martin, M.; Heap, J., Harnessing open-source technology for low-cost automation in synthesis: Flow chemical deprotection of silyl ethers using a homemade autosampling system. *Tetrahedron Lett.* **2017,** *58* (25), 2409-2413.
187. Weber, F.; Schmidt, A.; Röse, P.; Fischer, M.; Burghaus, O.; Hilt, G., Double-Bond Isomerization: Highly Reactive Nickel Catalyst Applied in the Synthesis of the Pheromone (9Z,12Z)-Tetradeca-9,12-dienyl Acetate. *Org. Lett.* **2015,** *17* (12), 2952-2955.
188. Hiroyuki, I.; Hiroki, S.; Hideo, K.; Kiyoyuki, Y., Enantioselective total synthesis of doliculide, a potent cytotoxic cyclodepsipeptide of marine origin and structure-cytotoxicity relationships of synthetic doliculide congeners. *Tetrahedron* **1994,** *50* (45), 12853-12882.
189. Block, M. H.; Cane, D. E., Synthesis of proposed chain-elongation intermediates of the monensin biosynthetic pathway. *The Journal of Organic Chemistry* **1988,** *53* (21), 4923-4928.
190. Aksakal, S.; Remzi Becer, C., Poly(thioacrylate)s: expanding the monomer toolbox of functional polymers. *Polymer Chemistry* **2016,** *7* (45), 7011-7018.
191. Li, N.; Ou, J.; Miesch, M.; Chiu, P., Conjugate reduction and reductive aldol cyclization of α,β-unsaturated thioesters catalyzed by (BDP)CuH. *Organic & Biomolecular Chemistry* **2011,** *9* (17), 6143-6147.
192. Matteoli, U.; Ciappa, A.; Bovo, S.; Bertoldini, M.; Scrivanti, A., Asymmetric catalysis in fragrance chemistry: a new synthetic approach to enantiopure Phenoxanol®, Citralis® and Citralis Nitrile®. *Tetrahedron: Asymmetry* **2007,** *18* (6), 797-802.

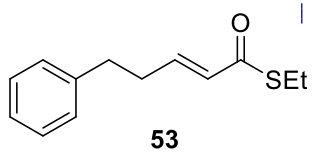
Appendix I – Spectra of Novel Compounds

^{1}H (400 MHz, $CDCl_3$)

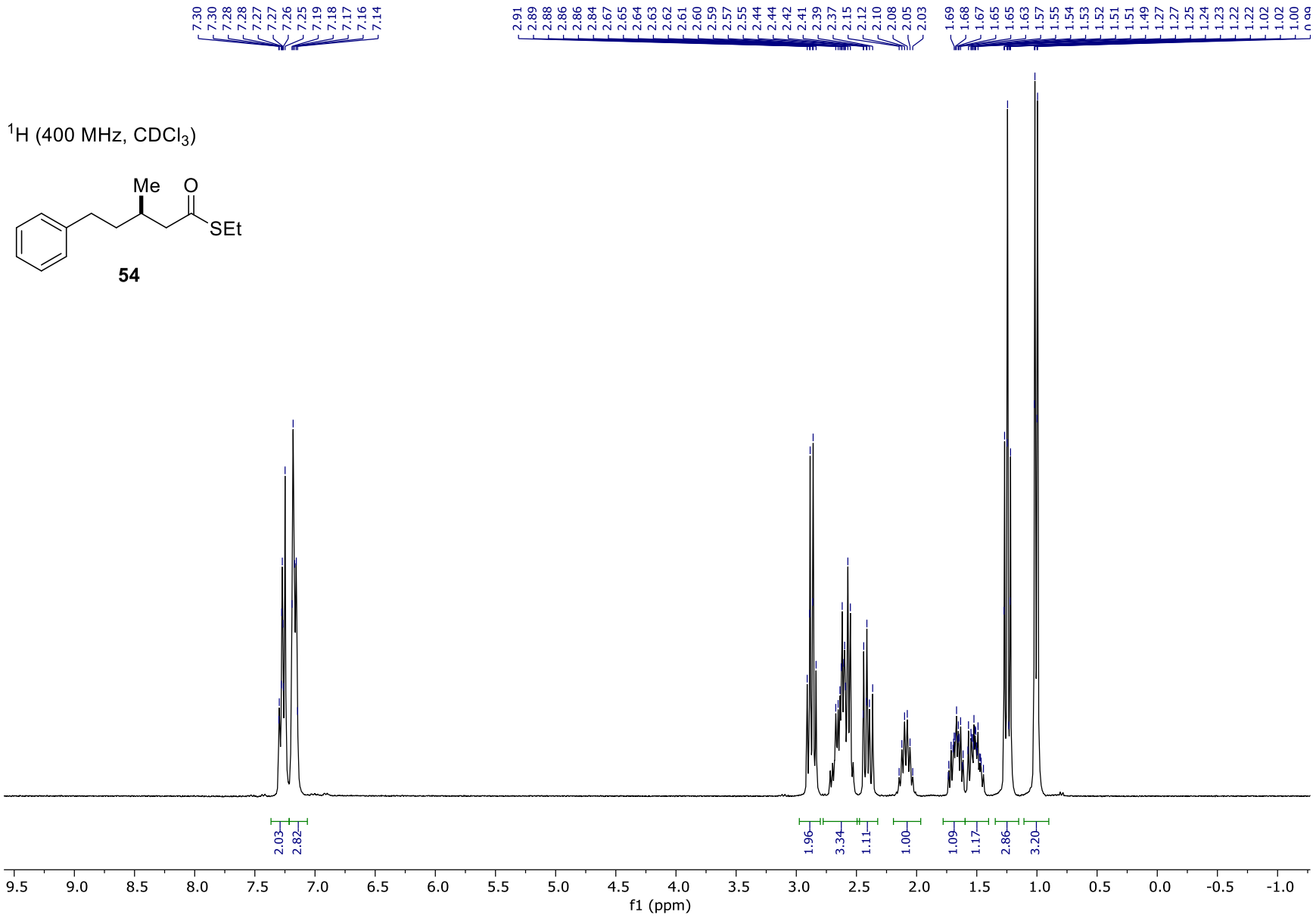


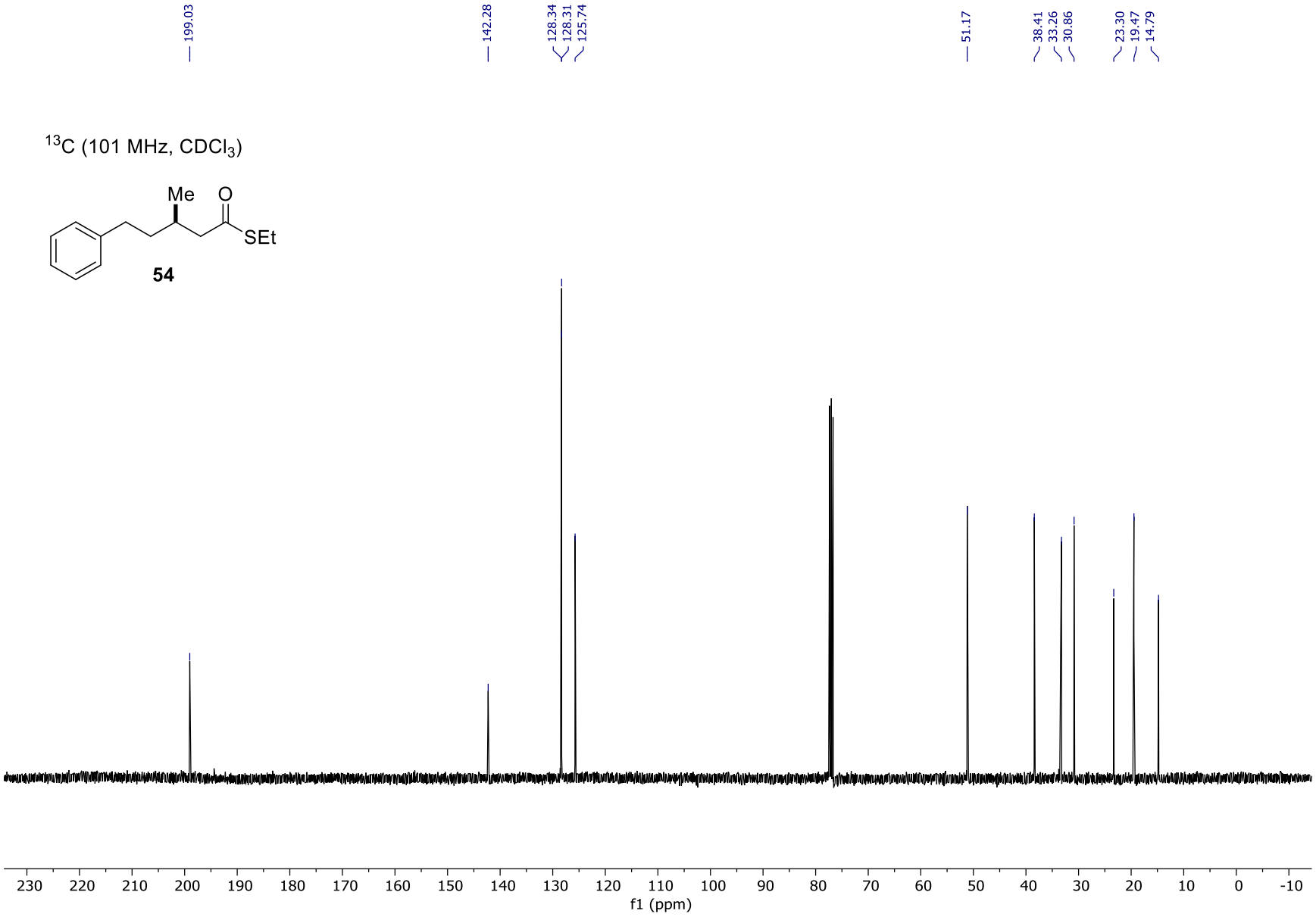
53

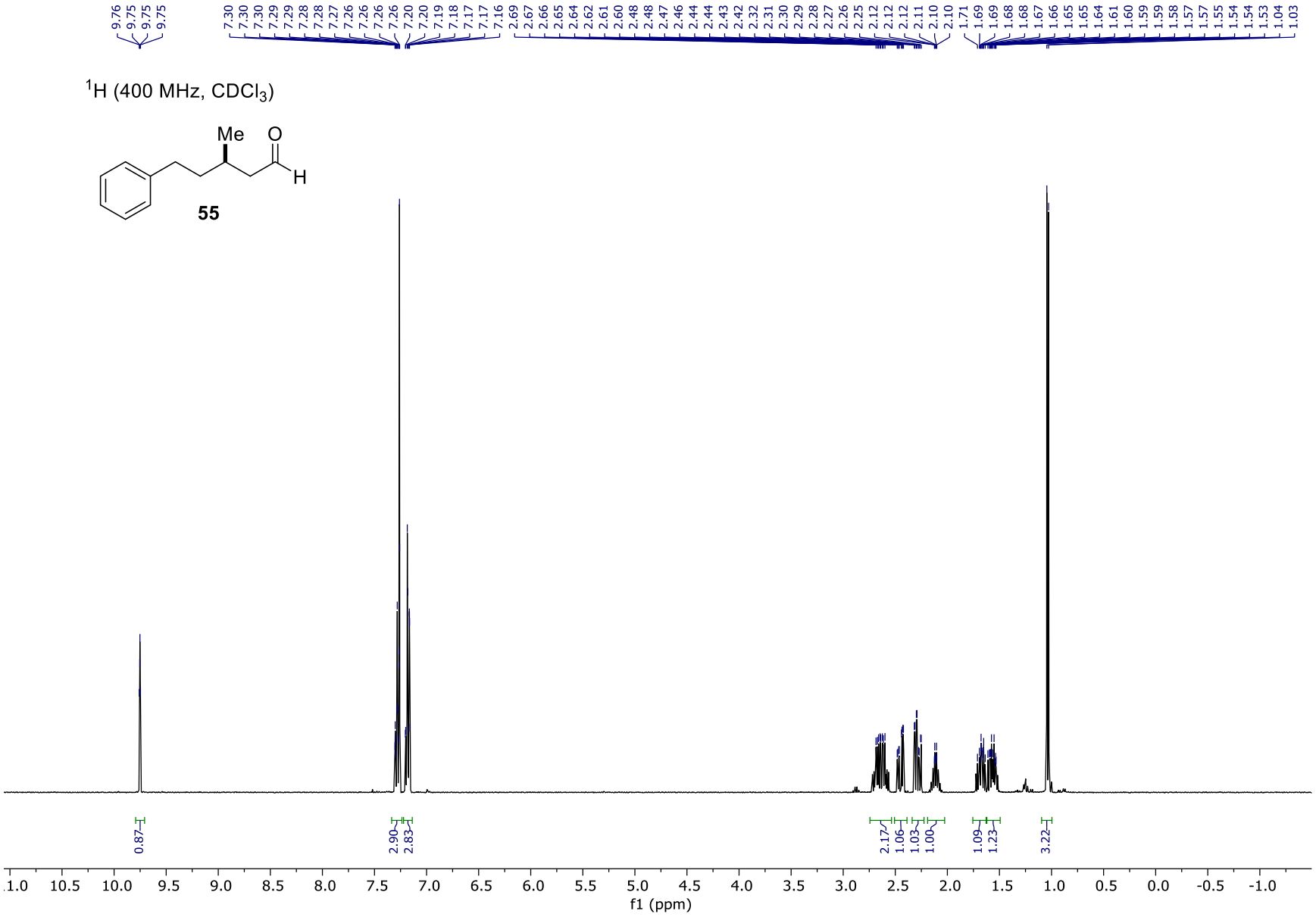
^{13}C (101 MHz, $CDCl_3$)

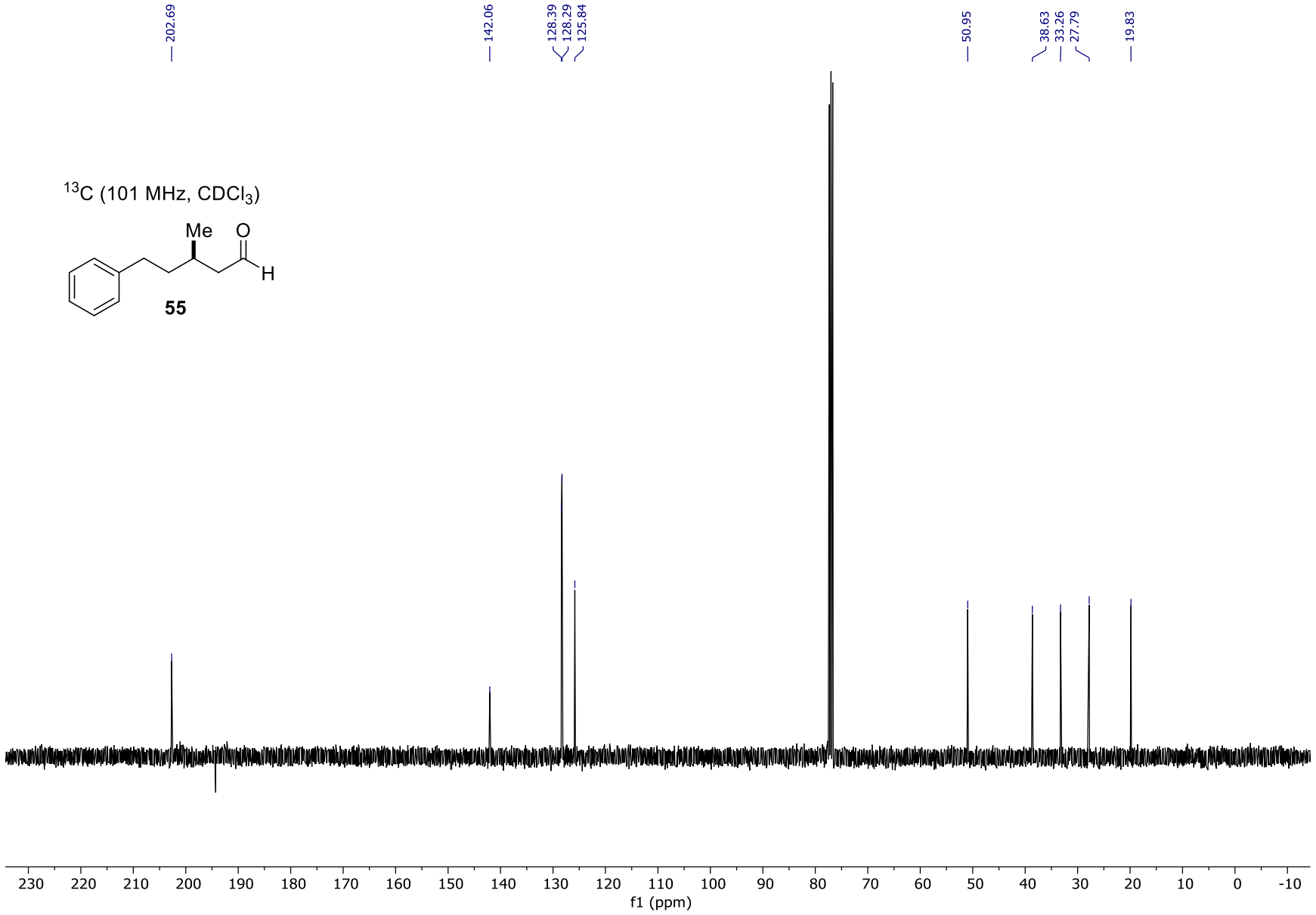


53

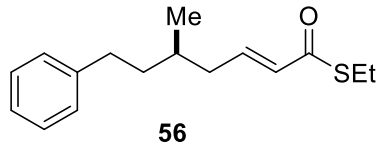

7.30 7.30 7.28 7.28 7.27 7.27 7.26 7.25 7.19 7.18 7.17 7.16 7.14
2.91 2.89 2.88 2.86 2.86 2.84 2.67 2.65 2.64 2.63 2.62 2.61 2.60 2.59 2.57 2.55 2.44 2.44 2.42 2.41 2.39 2.37 2.15 2.12 2.10 2.08 2.05 2.03
1.69 1.68 1.67 1.65 1.65 1.63 1.57 1.55 1.54 1.53 1.52 1.51 1.51 1.49 1.27 1.27 1.25 1.24 1.23 1.22 1.22 1.02 1.02 1.00
^{1}H (400 MHz, $CDCl_3$)
Me
O
SEt
54
2.03
2.82
1.96
3.34
1.11
1.00
1.09
1.17
2.86
3.20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


199.03
142.28
128.34
128.31
125.74
51.17
38.41
33.26
30.86
23.30
19.47
14.79
^{13}C (101 MHz, $CDCl_3$)
Me
O
SEt
54
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


9.76 9.75 9.75 9.75
7.30 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.26 7.26 7.26 7.26 7.20 7.20 7.19 7.18 7.17 7.17 7.16
2.69 2.67 2.66 2.65 2.64 2.62 2.61 2.60 2.48 2.48 2.47 2.46 2.44 2.44 2.43 2.42 2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.25 2.12 2.12 2.12 2.11 2.10 2.10
1.71 1.69 1.69 1.68 1.68 1.67 1.66 1.65 1.65 1.64 1.61 1.60 1.59 1.59 1.58 1.57 1.57 1.55 1.54 1.54 1.53 1.04 1.03
^{1}H (400 MHz, $CDCl_3$)
Me
O
H
55
0.87
2.90
2.83
2.17
1.06
1.03
1.00
1.09
1.23
3.22
f1 (ppm)


202.69
142.06
128.39
128.29
125.84
50.95
38.63
33.26
27.79
19.83
^{13}C (101 MHz, CDCl$_3$)
Me
O
H
55
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

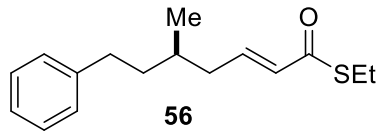
^{1}H (400 MHz, $CDCl_3$)



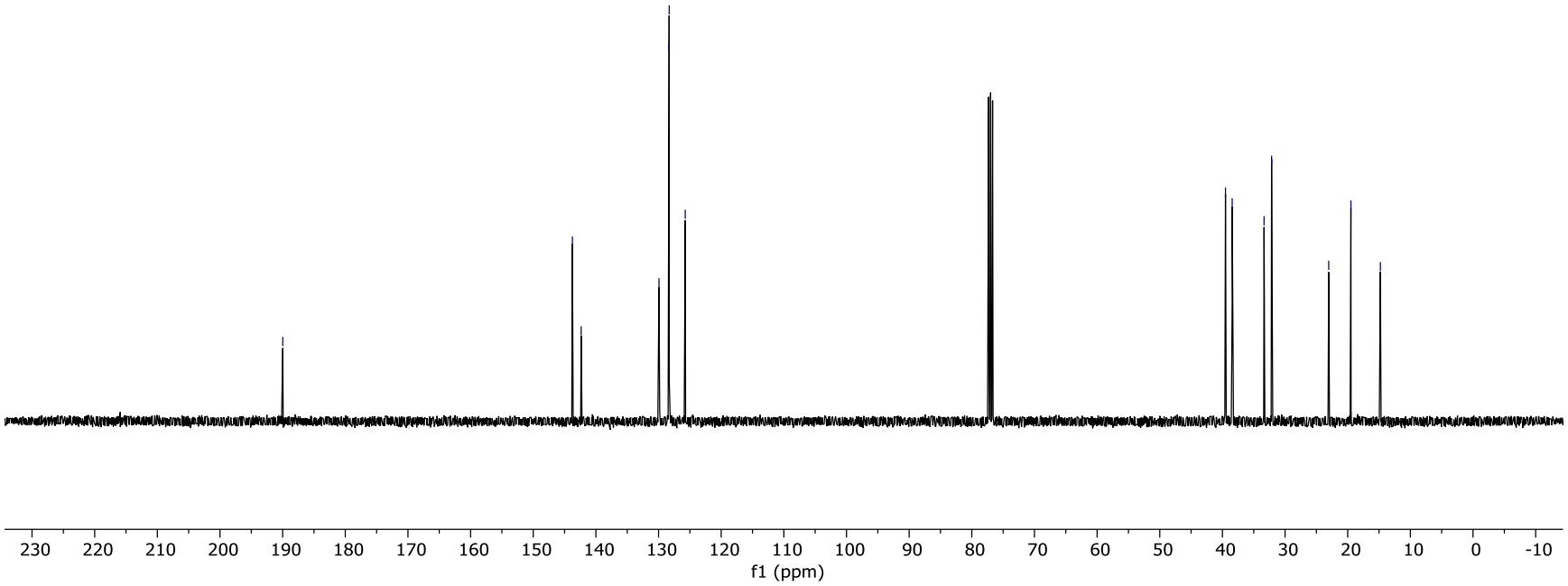
56

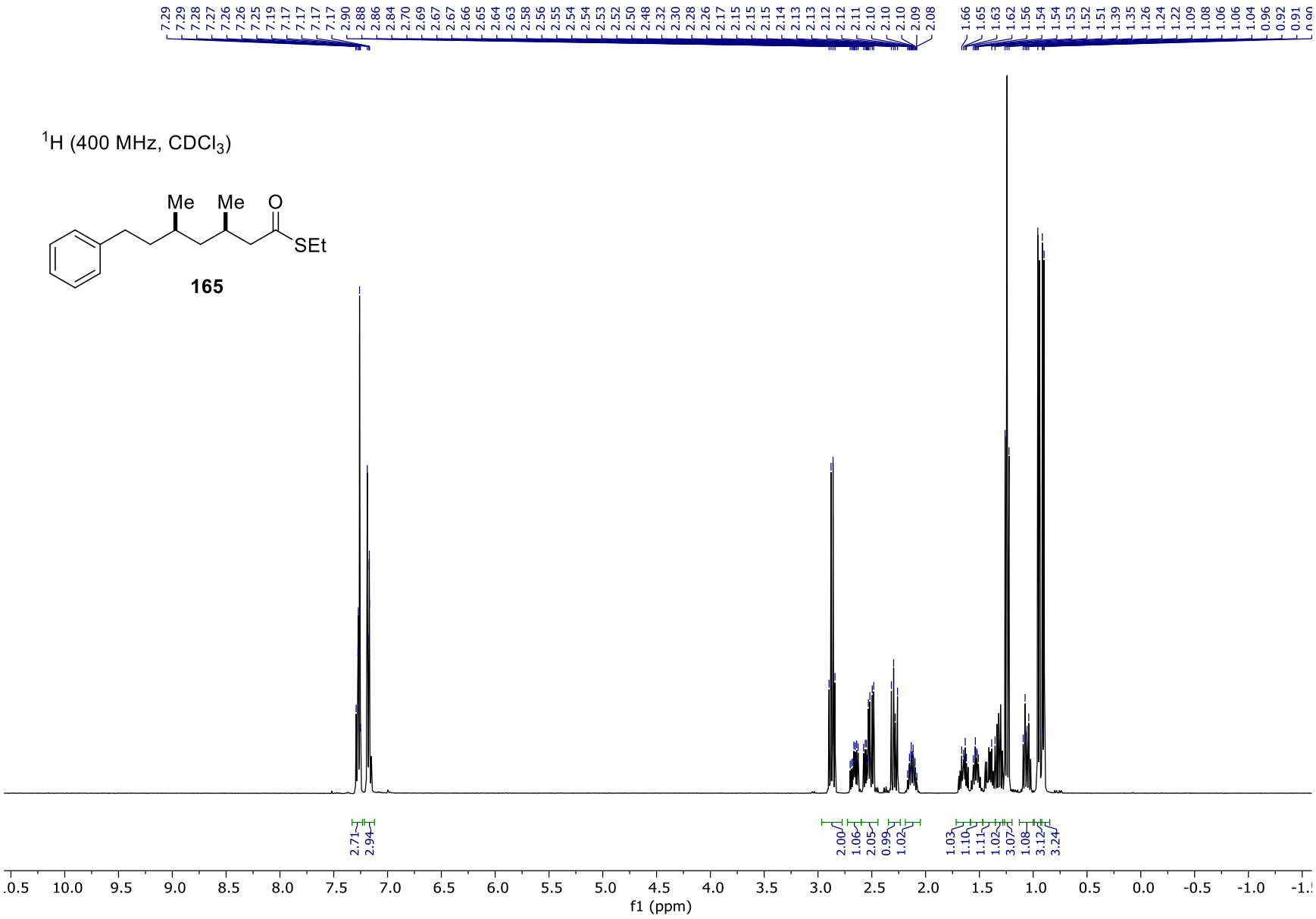
189.98
143.75
142.35
129.93
128.34
128.30
125.74
39.51
38.44
33.35
32.15
23.03
19.49
14.79

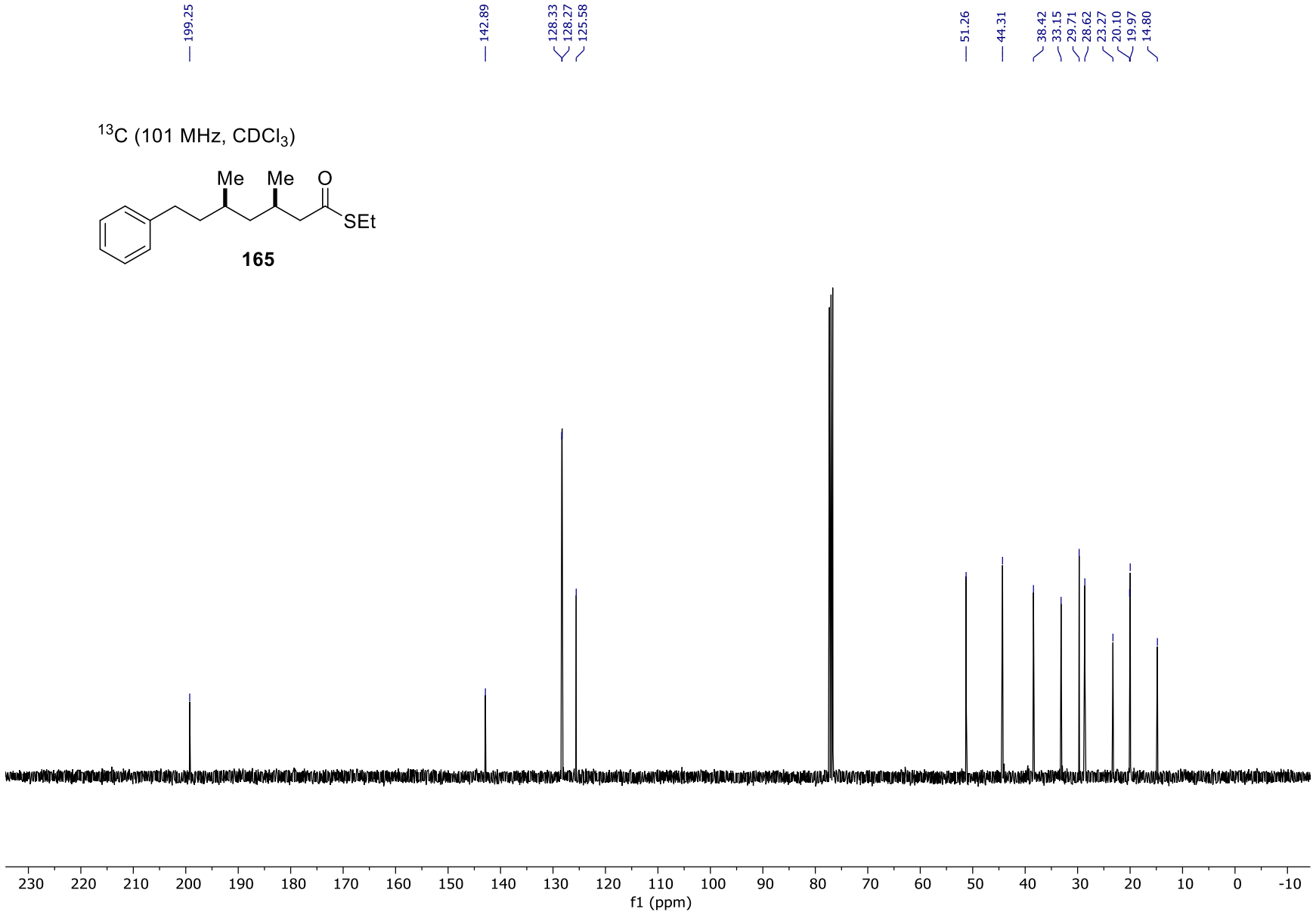
^{13}C (101 MHz, $CDCl_3$)

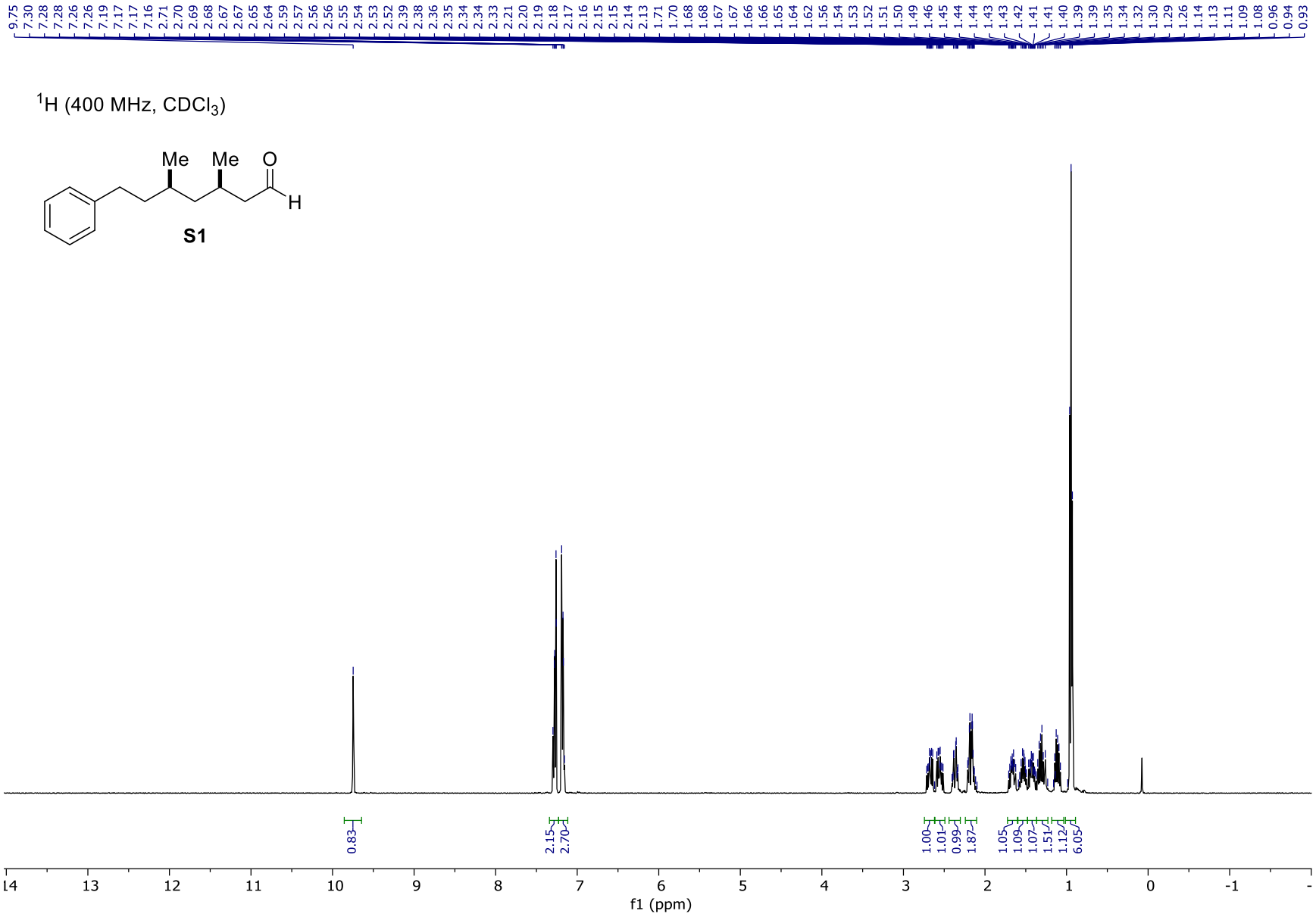


56



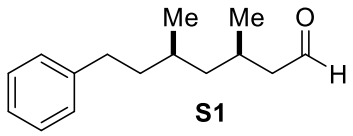

^{1}H (400 MHz, $CDCl_3$)
Me
Me
O
SEt
165
f1 (ppm)


199.25
142.89
128.33
128.27
125.58
51.26
44.31
38.42
33.15
29.71
28.62
23.27
20.10
19.97
14.80
13C (101 MHz, CDCl3)
Me
Me
O
SEt
165
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

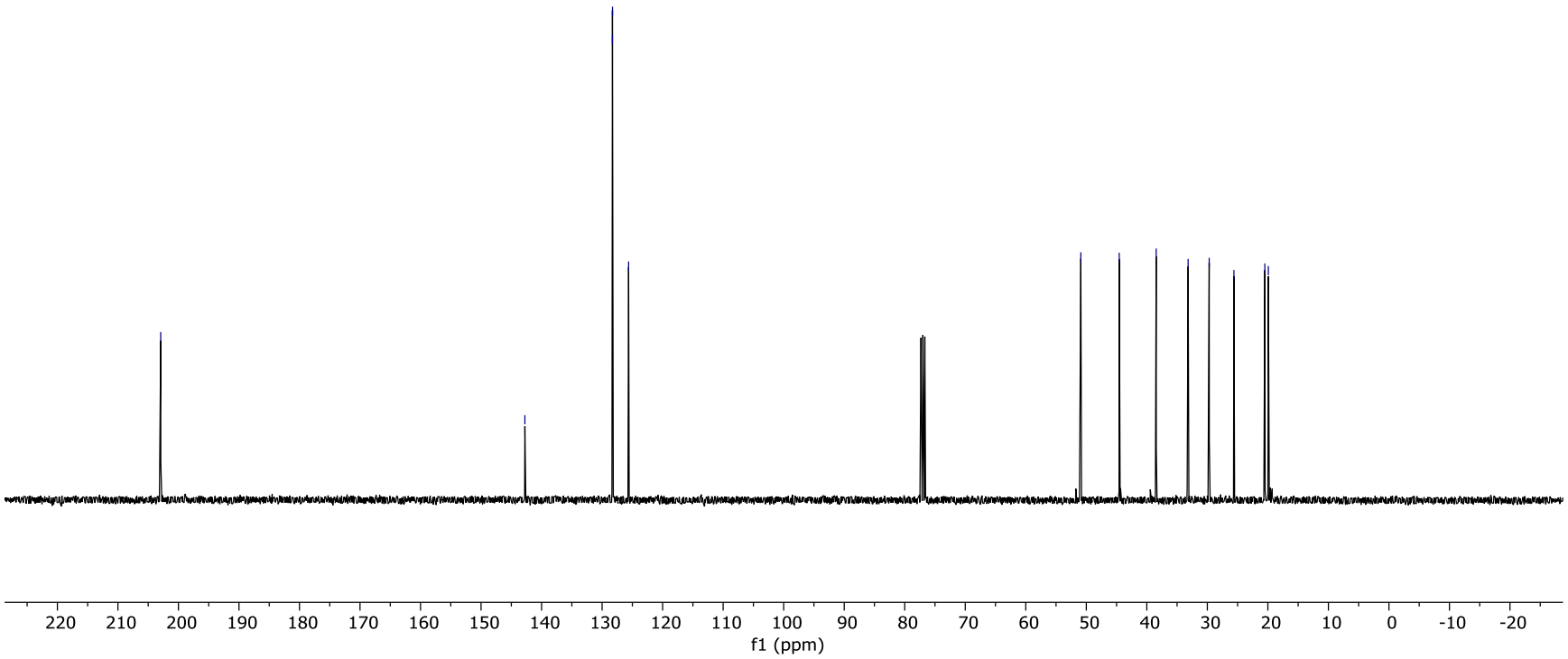

9.75 7.30 7.28 7.28 7.26 7.26 7.19 7.17 7.17 7.16 2.71 2.70 2.69 2.68 2.67 2.67 2.65 2.64 2.59 2.57 2.56 2.56 2.55 2.54 2.53 2.52 2.39 2.38 2.36 2.35 2.34 2.34 2.33 2.21 2.20 2.19 2.18 2.17 2.16 2.15 2.15 2.14 2.13 1.71 1.70 1.68 1.68 1.67 1.67 1.66 1.66 1.65 1.64 1.62 1.56 1.54 1.53 1.52 1.51 1.50 1.49 1.46 1.45 1.44 1.44 1.43 1.42 1.41 1.41 1.40 1.39 1.39 1.35 1.34 1.32 1.30 1.29 1.26 1.14 1.13 1.11 1.09 1.08 0.96 0.94 0.93
^{1}H (400 MHz, $CDCl_3$)
Me
Me
O
H
S1
0.83
2.15
2.70
1.00
1.01
0.99
1.87
1.05
1.09
1.07
1.51
1.12
6.05
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

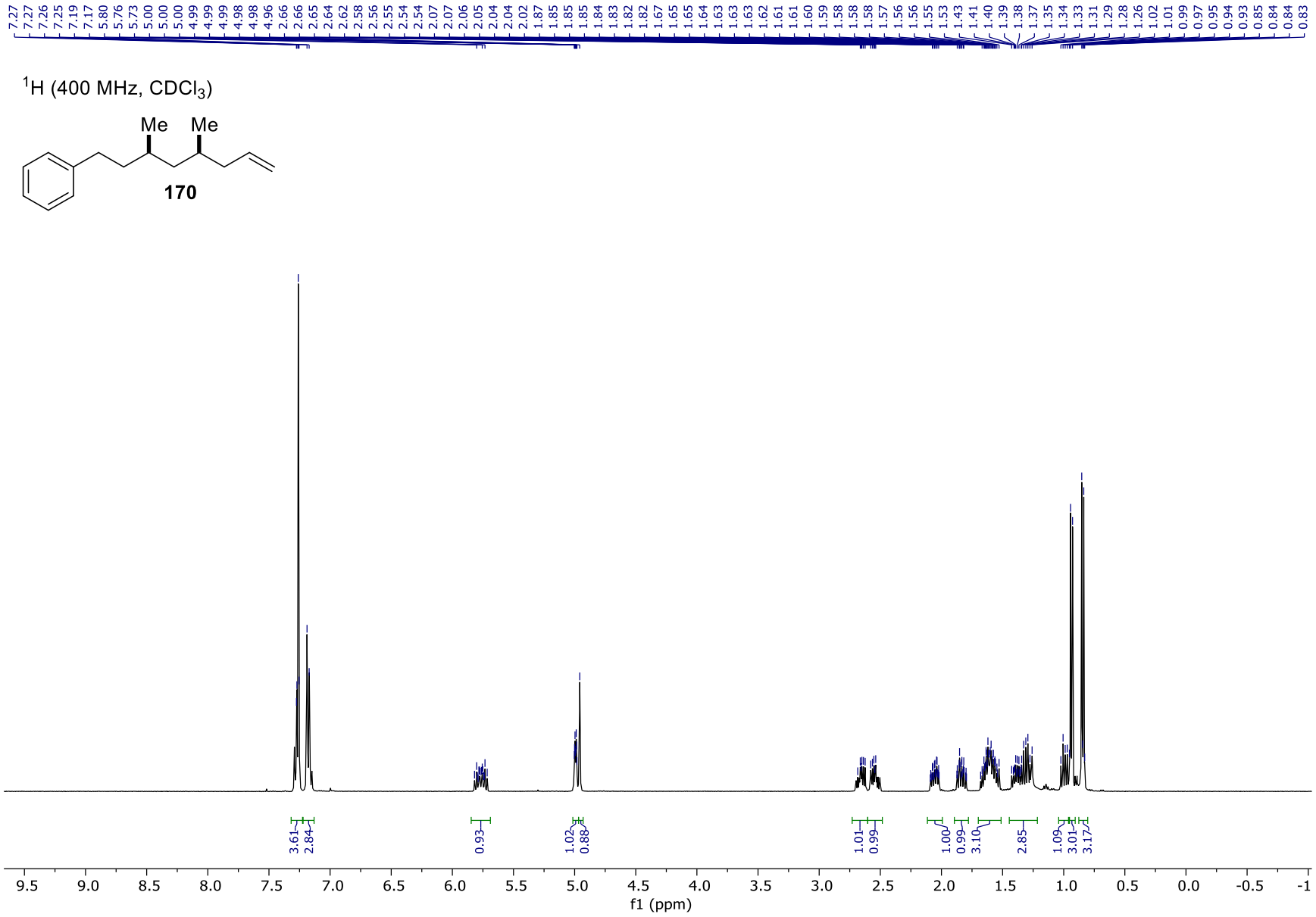
202.93
142.76
128.29
128.28
125.62
50.90
44.56
38.45
33.18
29.69
25.61
20.50
19.92

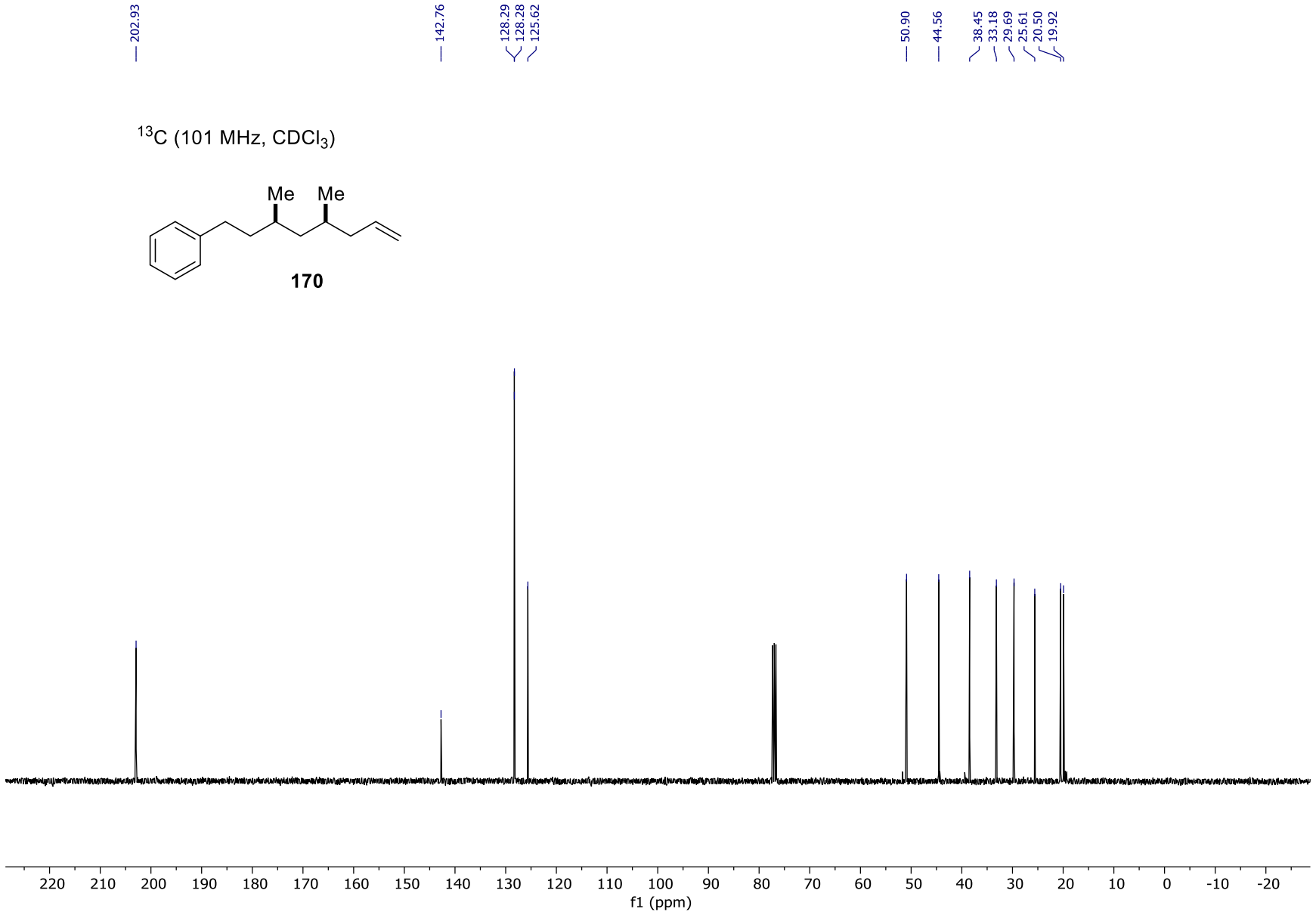
^{13}C (101 MHz, $CDCl_3$)

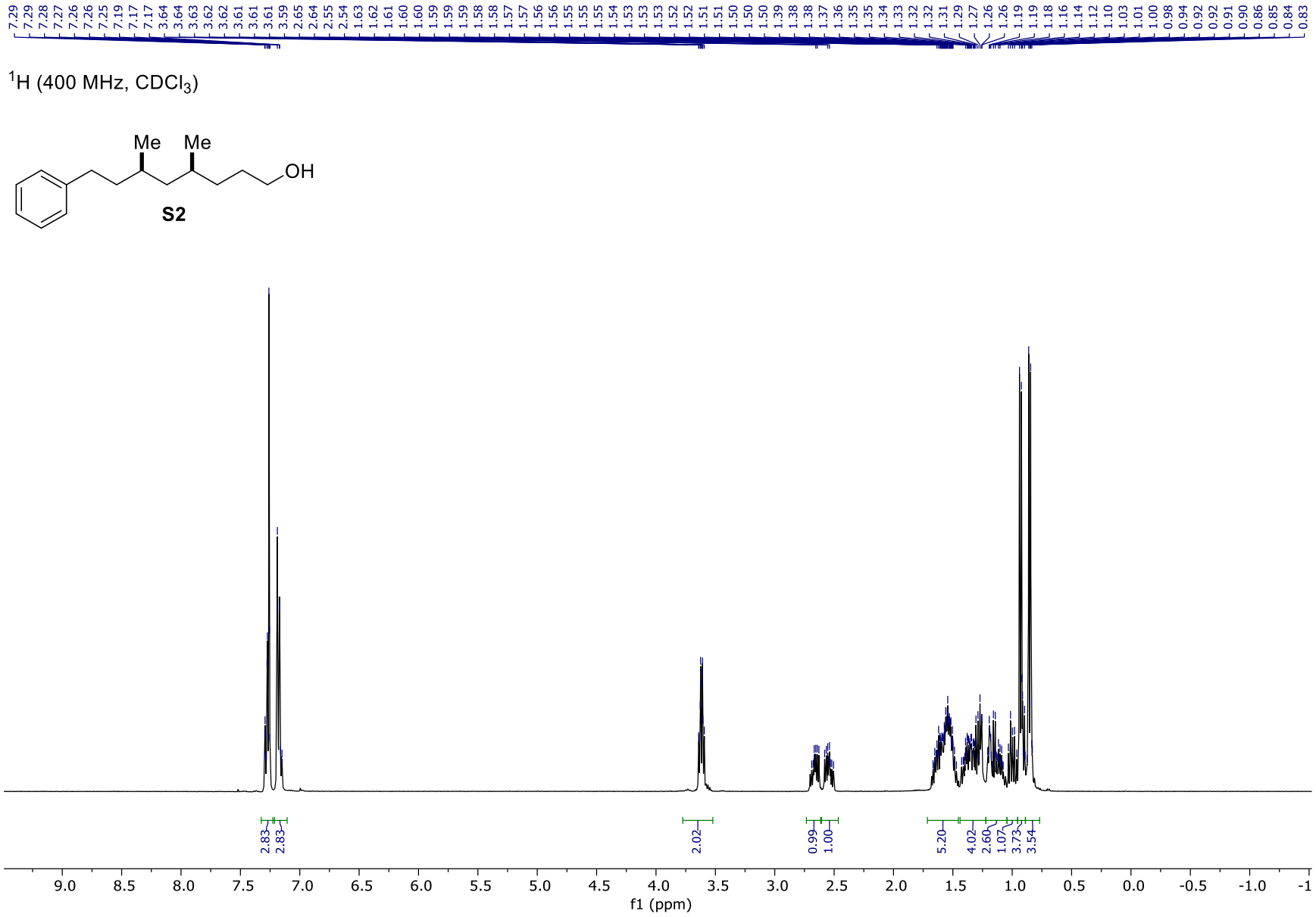


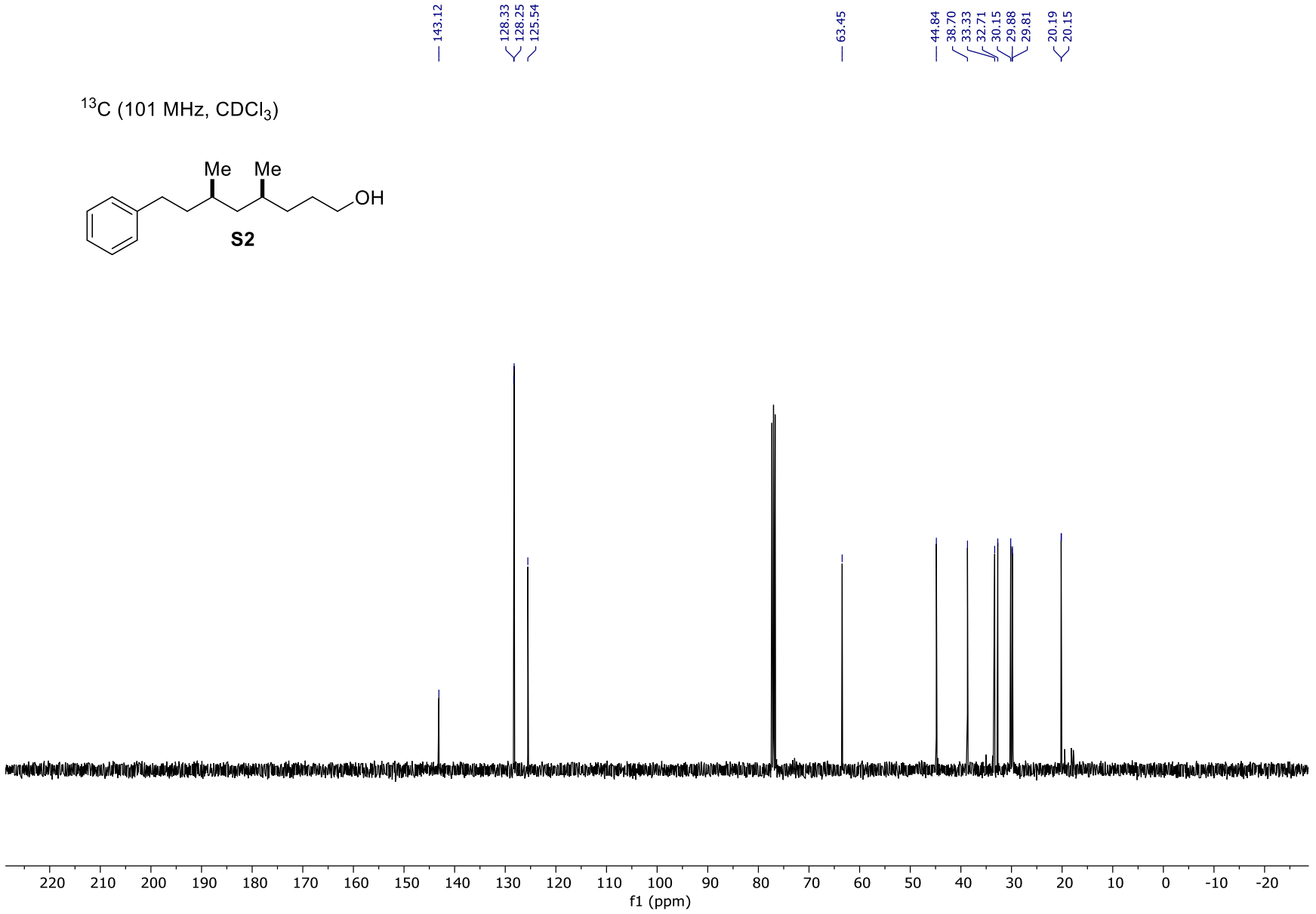
S1

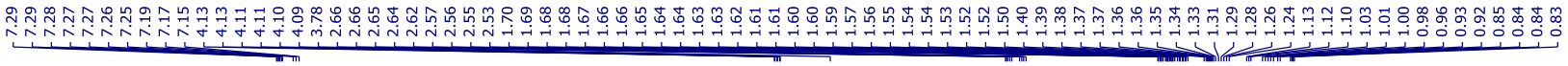



7.27 7.27 7.26 7.25 7.19 7.17 5.80 5.76 5.73 5.00 5.00 5.00 4.99 4.99 4.98 4.98 4.96 2.66 2.66 2.65 2.64 2.62 2.58 2.56 2.55 2.54 2.54 2.07 2.07 2.06 2.05 2.04 2.04 2.02 1.87 1.85 1.85 1.85 1.84 1.83 1.82 1.82 1.67 1.65 1.65 1.64 1.63 1.63 1.63 1.62 1.61 1.61 1.60 1.59 1.58 1.58 1.58 1.57 1.56 1.56 1.55 1.53 1.43 1.41 1.40 1.39 1.38 1.37 1.35 1.34 1.33 1.31 1.29 1.28 1.26 1.02 1.01 0.99 0.97 0.95 0.94 0.93 0.85 0.84 0.84 0.83
^{1}H (400 MHz, $CDCl_3$)
Me
Me
170
3.61
2.84
0.93
1.02
0.88
1.01
0.99
1.00
0.99
3.10
2.85
1.09
3.01
3.17
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

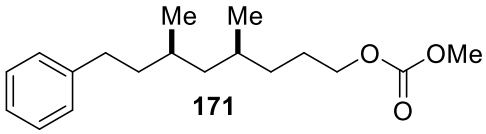

202.93
142.76
128.29
128.28
125.62
50.90
44.56
38.45
33.18
29.69
25.61
20.50
19.92
^{13}C (101 MHz, $CDCl_3$)
Me
Me
170
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


7.29 7.29 7.28 7.27 7.26 7.26 7.25 7.19 7.17 7.17 3.64 3.64 3.63 3.62 3.62 3.61 3.61 3.61 3.59 2.65 2.64 2.55 2.54 1.63 1.62 1.61 1.60 1.60 1.59 1.59 1.59 1.58 1.58 1.57 1.57 1.56 1.56 1.55 1.55 1.55 1.54 1.53 1.53 1.53 1.52 1.52 1.51 1.51 1.50 1.50 1.50 1.39 1.38 1.38 1.37 1.36 1.35 1.35 1.34 1.33 1.32 1.32 1.31 1.29 1.27 1.26 1.26 1.19 1.19 1.18 1.16 1.14 1.12 1.10 1.03 1.01 1.00 0.98 0.94 0.92 0.92 0.91 0.90 0.86 0.85 0.84 0.83
^{1}H (400 MHz, $CDCl_3$)
Me
Me
OH
S2
2.83
2.83
2.02
0.99
1.00
5.20
4.02
2.60
1.07
3.73
3.54
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

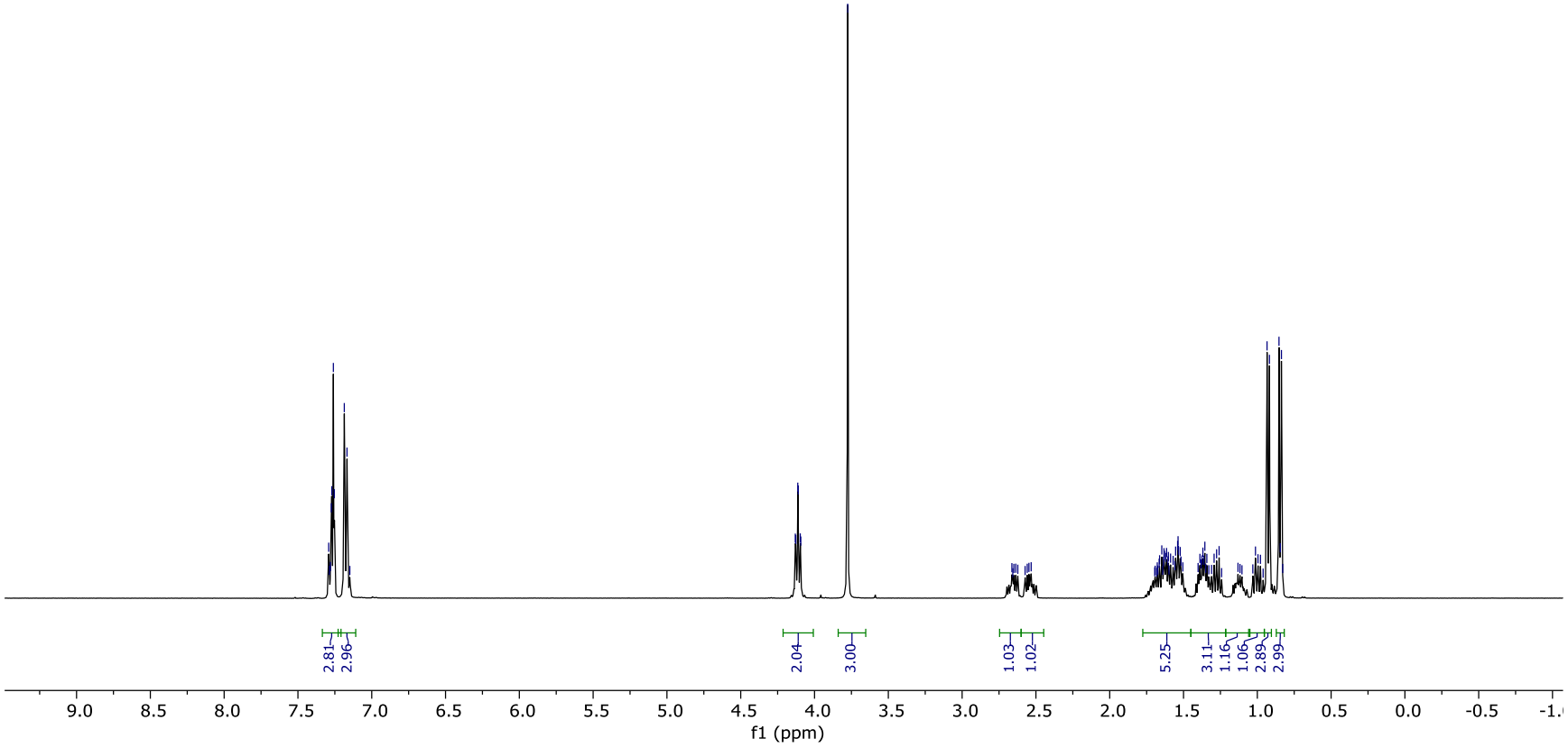

143.12
128.33
128.25
125.54
63.45
44.84
38.70
33.33
32.71
30.15
29.88
29.81
20.19
20.15
^{13}C (101 MHz, $CDCl_3$)
Me
Me
OH
S2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)



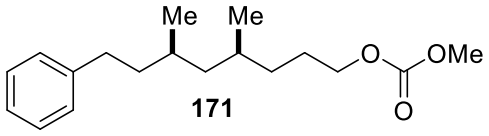
^{1}H (400 MHz, $CDCl_3$)



171

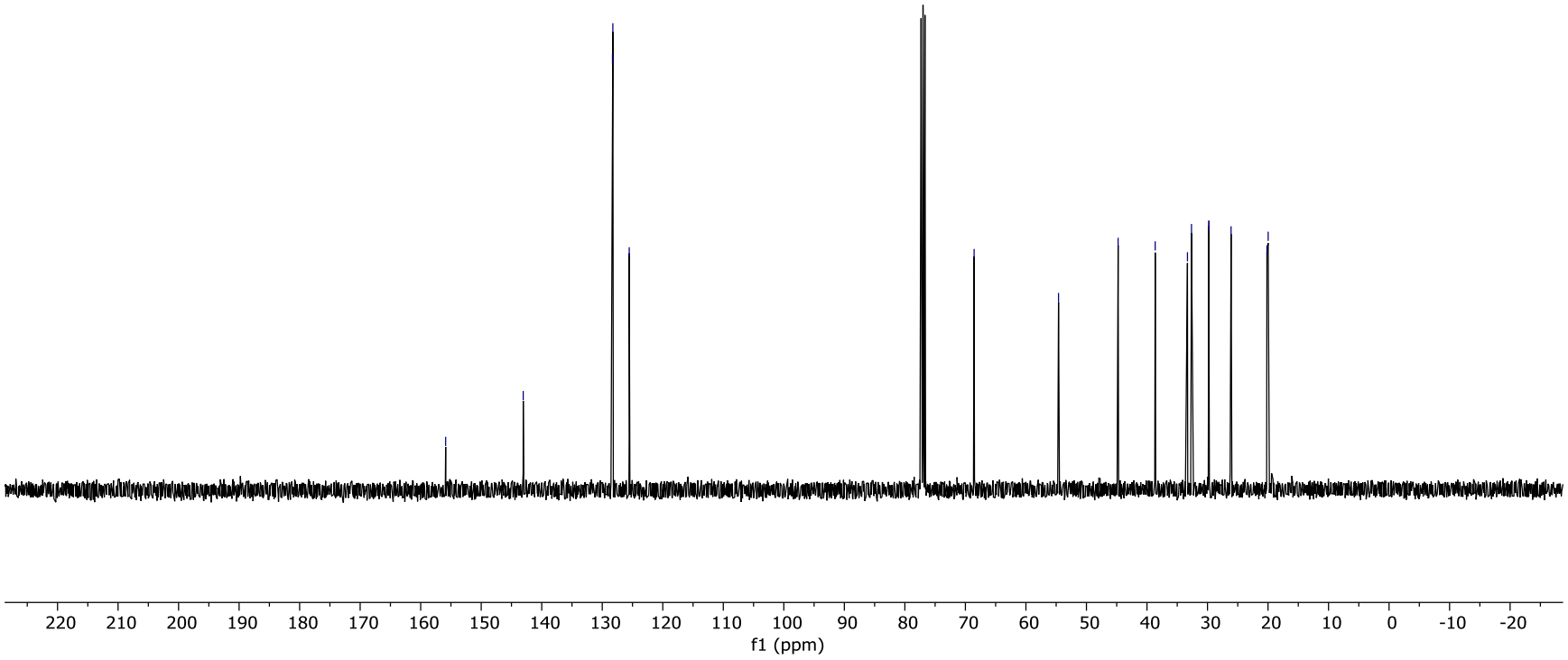


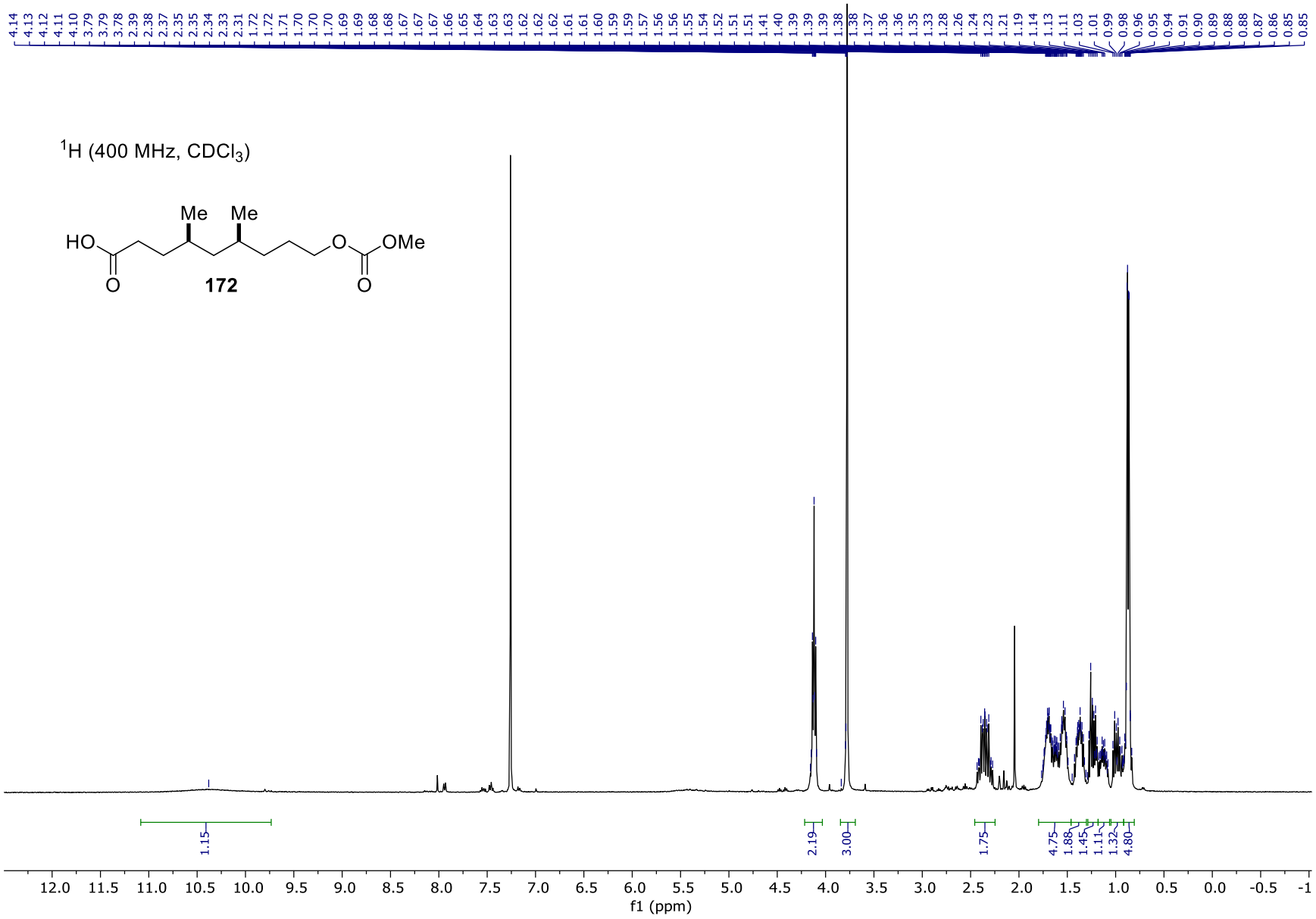
^{13}C (101 MHz, $CDCl_3$)

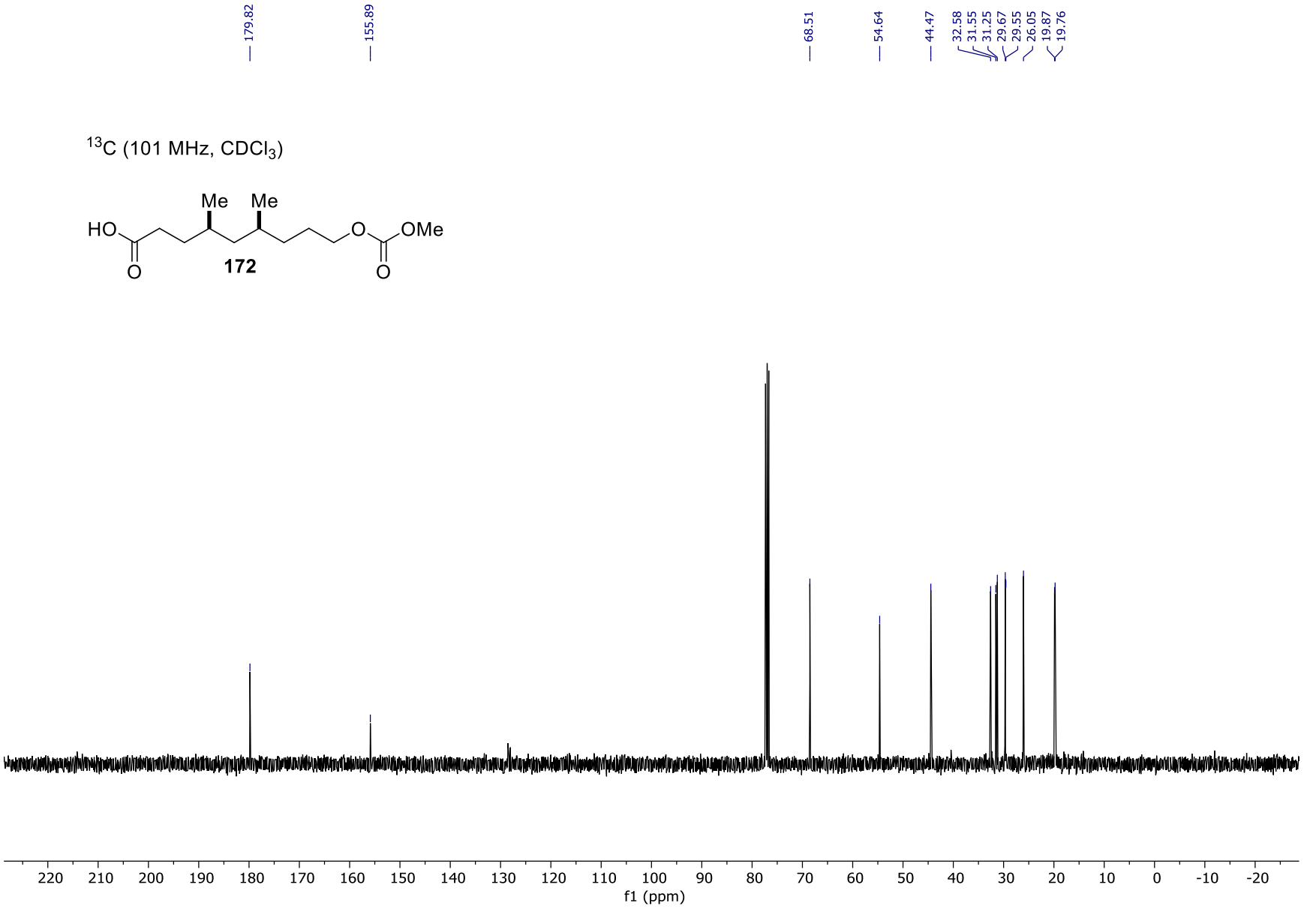


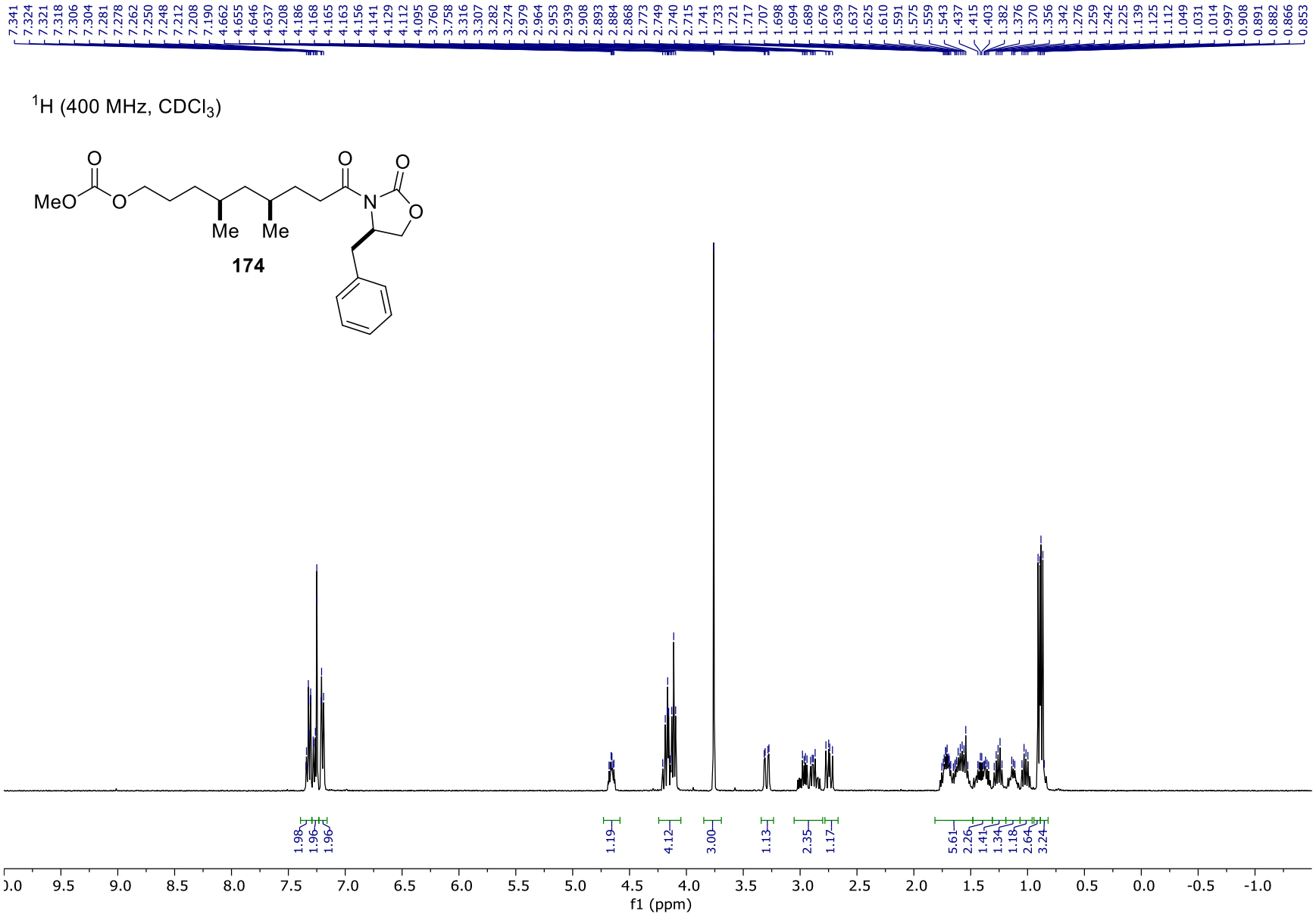
171

155.87
143.06
128.31
128.25
125.54
68.56
54.61
44.77
38.64
33.31
32.65
29.79
29.75
26.10
20.18
19.97

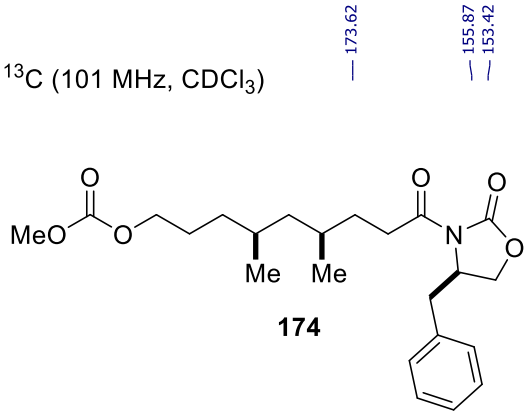



^{1}H (400 MHz, $CDCl_3$)
Me
Me
HO
O
O
OMe
O
172
f1 (ppm)

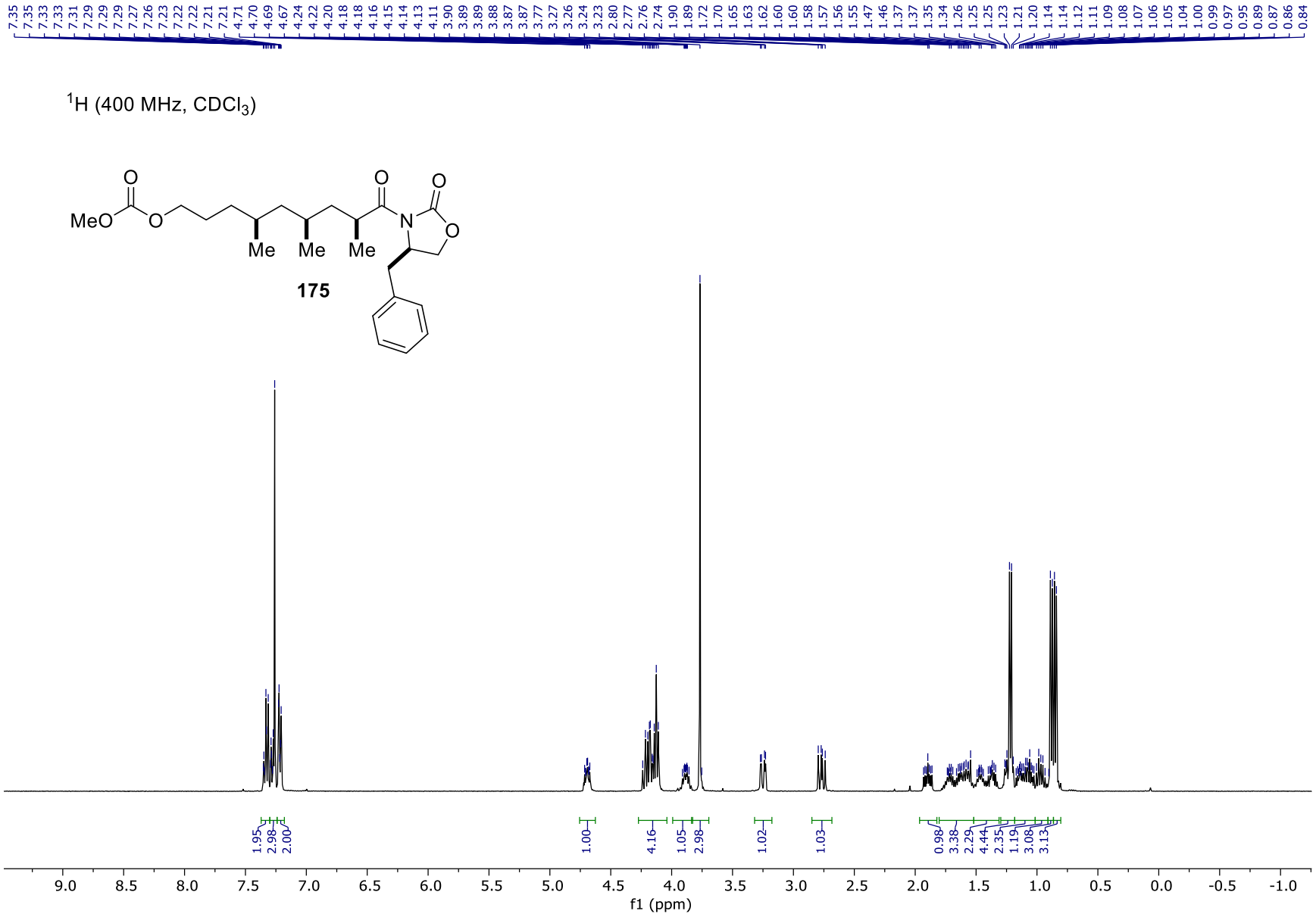

179.82
155.89
68.51
54.64
44.47
32.58
31.55
31.25
29.67
29.55
26.05
19.87
19.76
^{13}C (101 MHz, $CDCl_3$)
Me
Me
HO
O
O
OMe
O
172
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

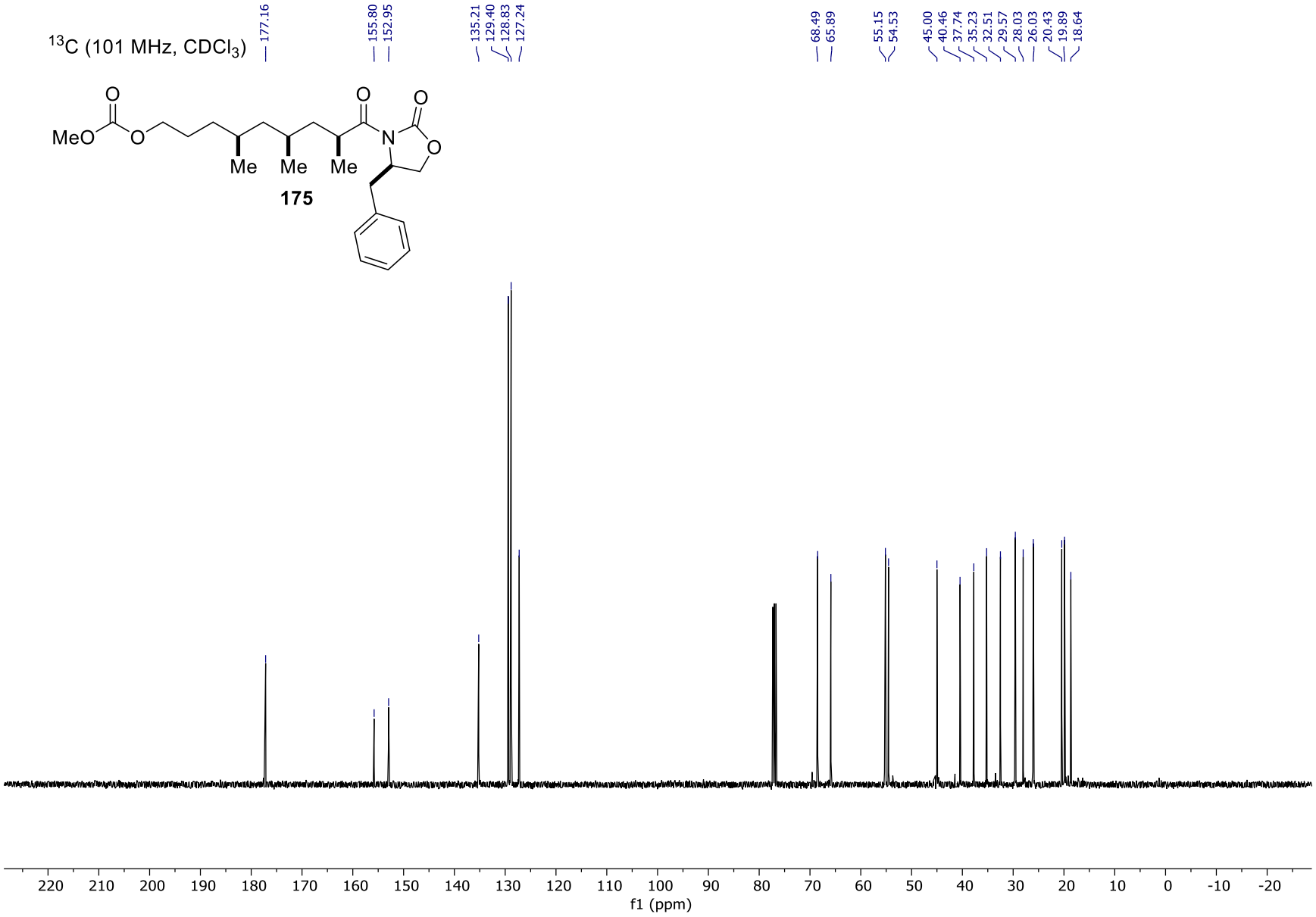

7.341 7.324 7.321 7.318 7.306 7.304 7.281 7.278 7.262 7.250 7.248 7.212 7.208 7.190 4.662 4.655 4.646 4.637 4.208 4.186 4.168 4.165 4.163 4.156 4.141 4.129 4.112 4.095 3.760 3.758 3.316 3.307 3.282 3.274 2.979 2.964 2.953 2.939 2.908 2.893 2.884 2.868 2.773 2.749 2.740 2.715 1.741 1.733 1.721 1.717 1.707 1.698 1.694 1.689 1.676 1.639 1.637 1.625 1.610 1.591 1.575 1.559 1.543 1.437 1.415 1.403 1.382 1.376 1.370 1.356 1.342 1.276 1.259 1.242 1.225 1.139 1.125 1.112 1.049 1.031 1.014 0.997 0.908 0.891 0.882 0.866 0.853
1H (400 MHz, CDCl3)
MeO
O
O
Me
Me
O
N
O
O
174
1.98
1.96
1.96
1.19
4.12
3.00
1.13
2.35
1.17
5.61
2.26
1.41
1.34
1.18
2.64
3.24
f1 (ppm)

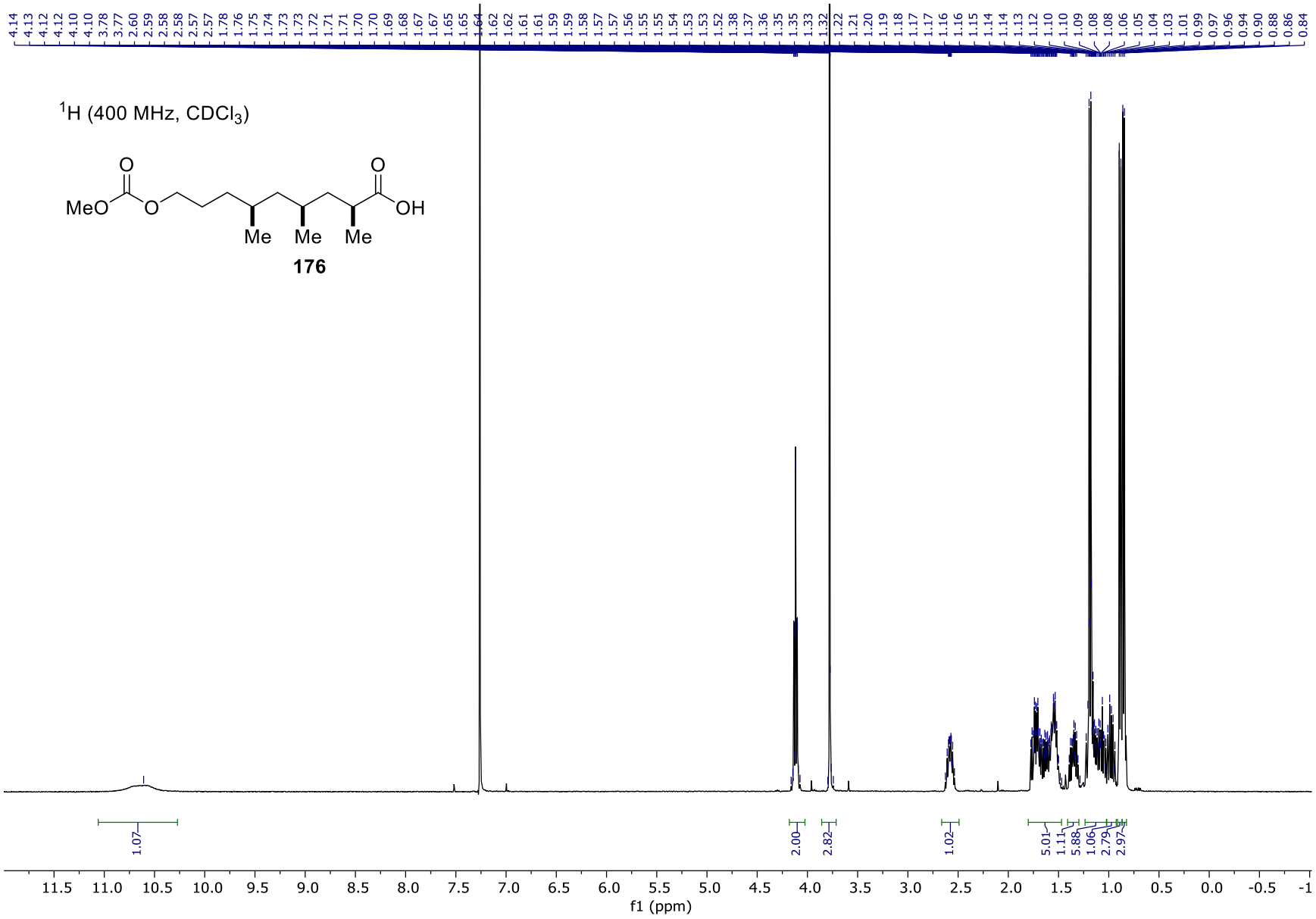
^{13}C (101 MHz, $CDCl_3$)

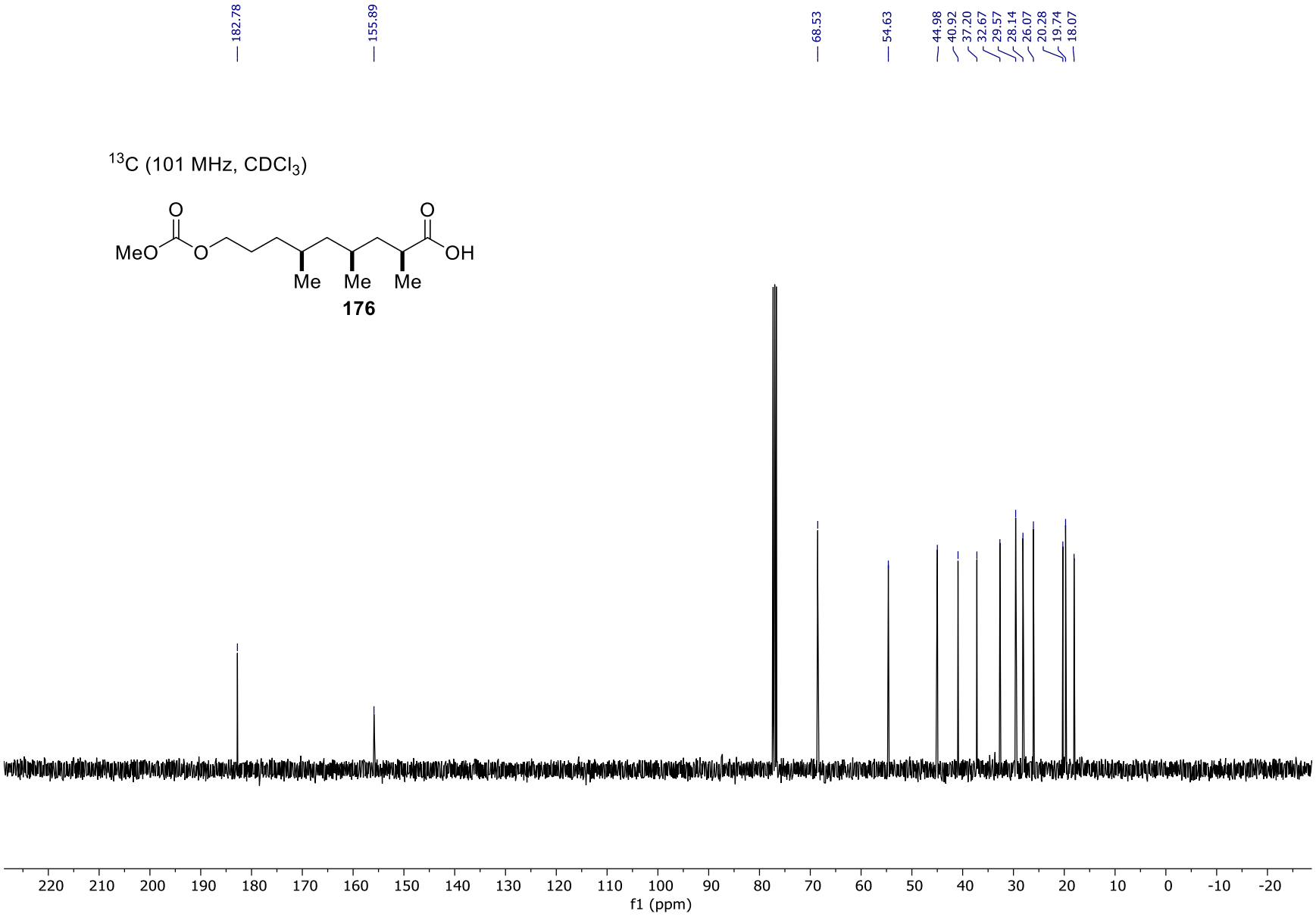


174

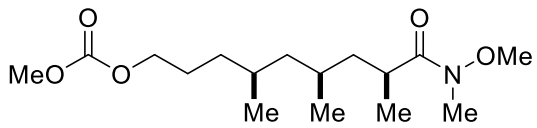

7.35 7.35 7.33 7.33 7.31 7.29 7.29 7.29 7.27 7.26 7.23 7.22 7.22 7.21 7.21 4.71 4.70 4.69 4.67 4.24 4.22 4.20 4.18 4.18 4.16 4.15 4.14 4.13 4.11 3.90 3.89 3.89 3.88 3.87 3.87 3.77 3.27 3.26 3.24 3.23 2.80 2.77 2.76 2.74 1.90 1.89 1.72 1.70 1.65 1.63 1.62 1.60 1.60 1.58 1.57 1.56 1.55 1.47 1.46 1.37 1.37 1.35 1.34 1.26 1.25 1.25 1.23 1.21 1.20 1.14 1.14 1.12 1.11 1.09 1.08 1.07 1.06 1.05 1.04 1.00 0.99 0.97 0.95 0.89 0.87 0.86 0.84
^{1}H (400 MHz, $CDCl_3$)
MeO
O
O
Me
Me
Me
O
N
O
O
175
1.95
2.98
2.00
1.00
4.16
1.05
2.98
1.02
1.03
0.98
3.38
2.29
4.44
2.35
1.19
3.08
3.13
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


13C (101 MHz, CDCl3)
177.16
155.80
152.95
135.21
129.40
128.83
127.24
68.49
65.89
55.15
54.53
45.00
40.46
37.74
35.23
32.51
29.57
28.03
26.03
20.43
19.89
18.64
MeO
O
O
O
N
O
O
Me
Me
Me
175
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

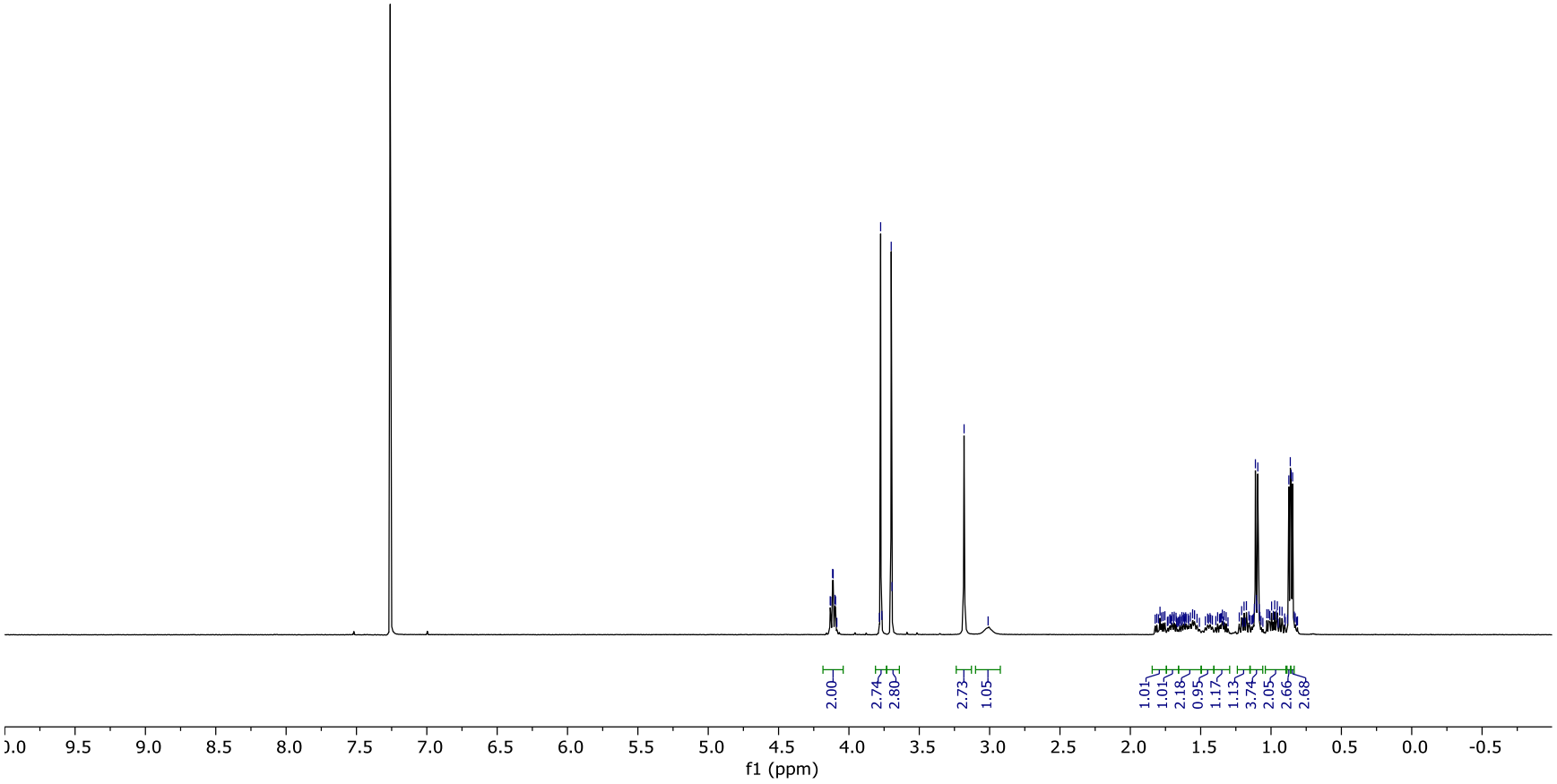

^{1}H (400 MHz, $CDCl_3$)
MeO
O
O
OH
Me
Me
Me
176
f1 (ppm)

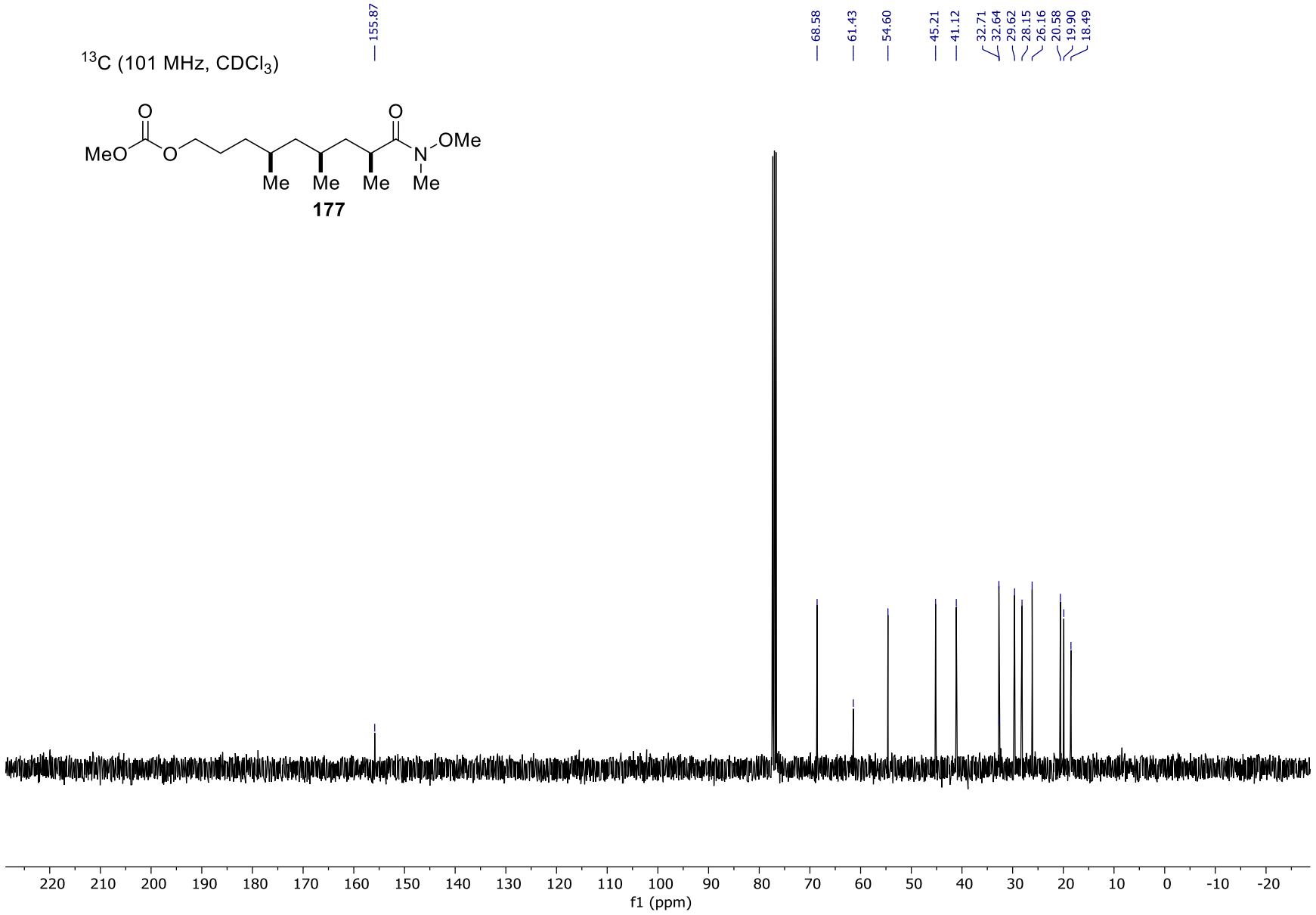

182.78
155.89
68.53
54.63
44.98
40.92
37.20
32.67
29.57
28.14
26.07
20.28
19.74
18.07
13C (101 MHz, CDCl3)
MeO
O
O
O
OH
Me
Me
Me
176
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

^{1}H (400 MHz, $CDCl_3$)

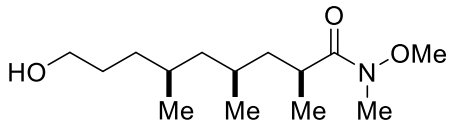


177



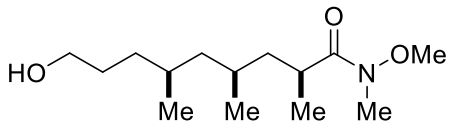

^{13}C (101 MHz, $CDCl_3$)
155.87
68.58
61.43
54.60
45.21
41.12
32.71
32.64
29.62
28.15
26.16
20.58
19.90
18.49
MeO
O
O
O
N
OMe
Me
Me
Me
Me
177
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

^{1}H (400 MHz, $CDCl_3$)



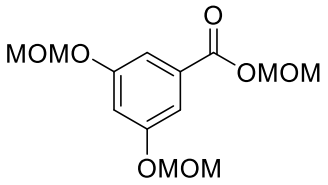
178

^{13}C (101 MHz, $CDCl_3$)

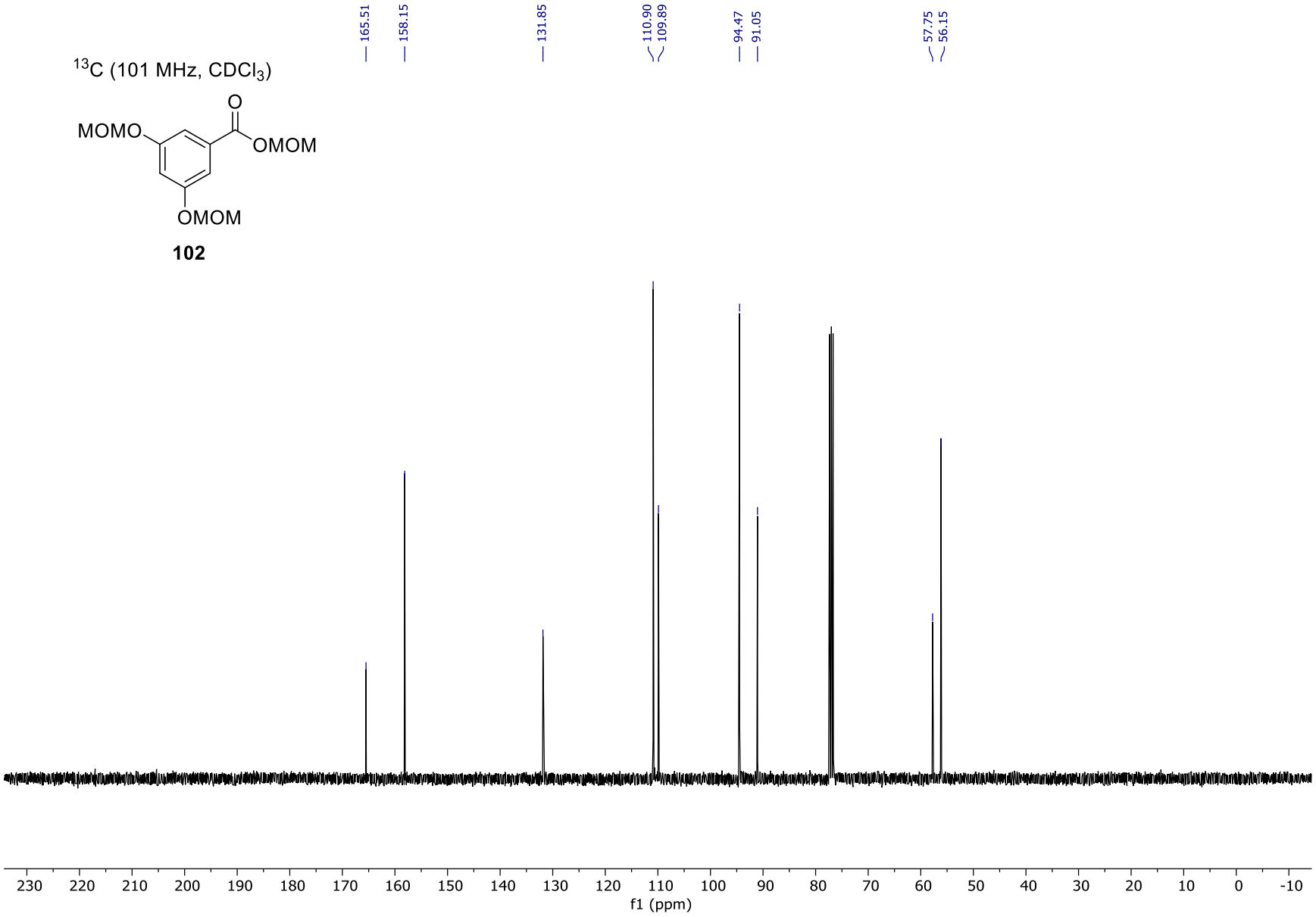


178

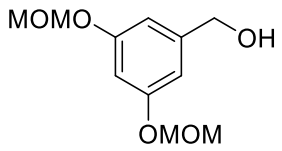
^{1}H (400 MHz, $CDCl_3$)



102


165.51
158.15
131.85
110.90
109.89
94.47
91.05
57.75
56.15
13C (101 MHz, CDCl3)
MOMO
OMOM
OMOM
O
102
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

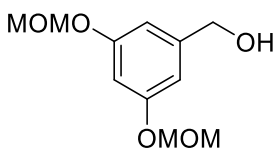
^{1}H (400 MHz, $CDCl_3$)



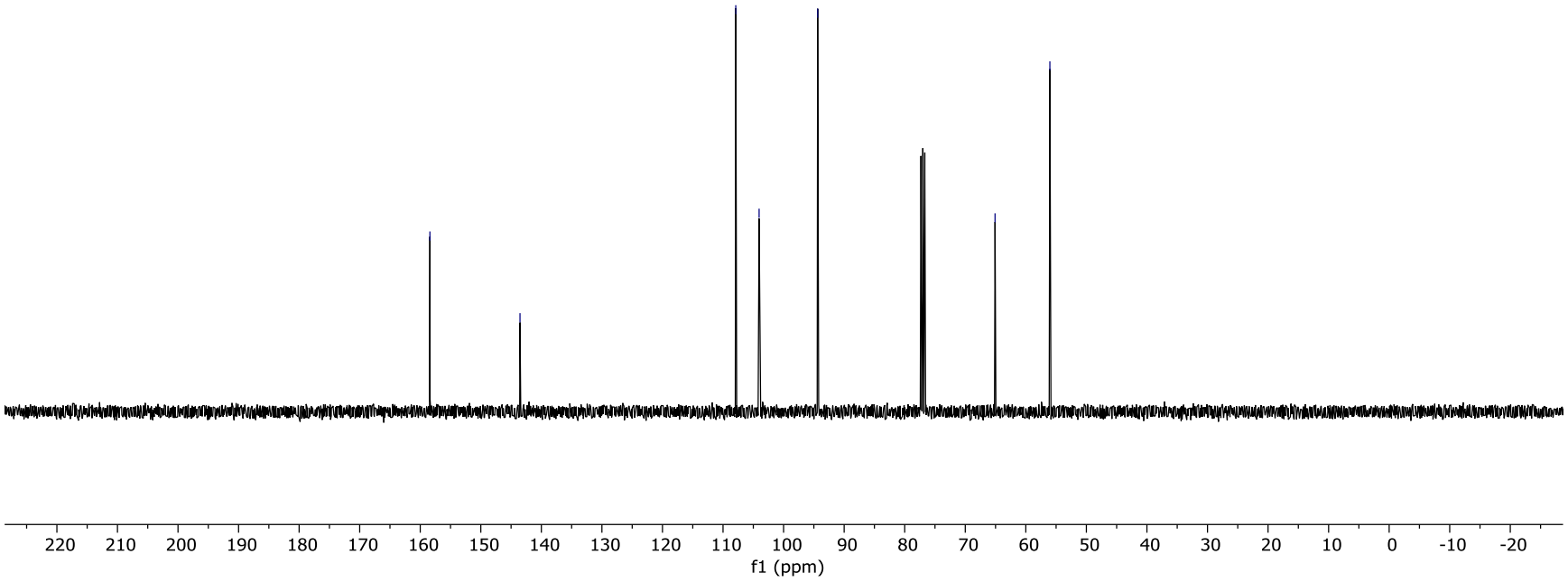
103

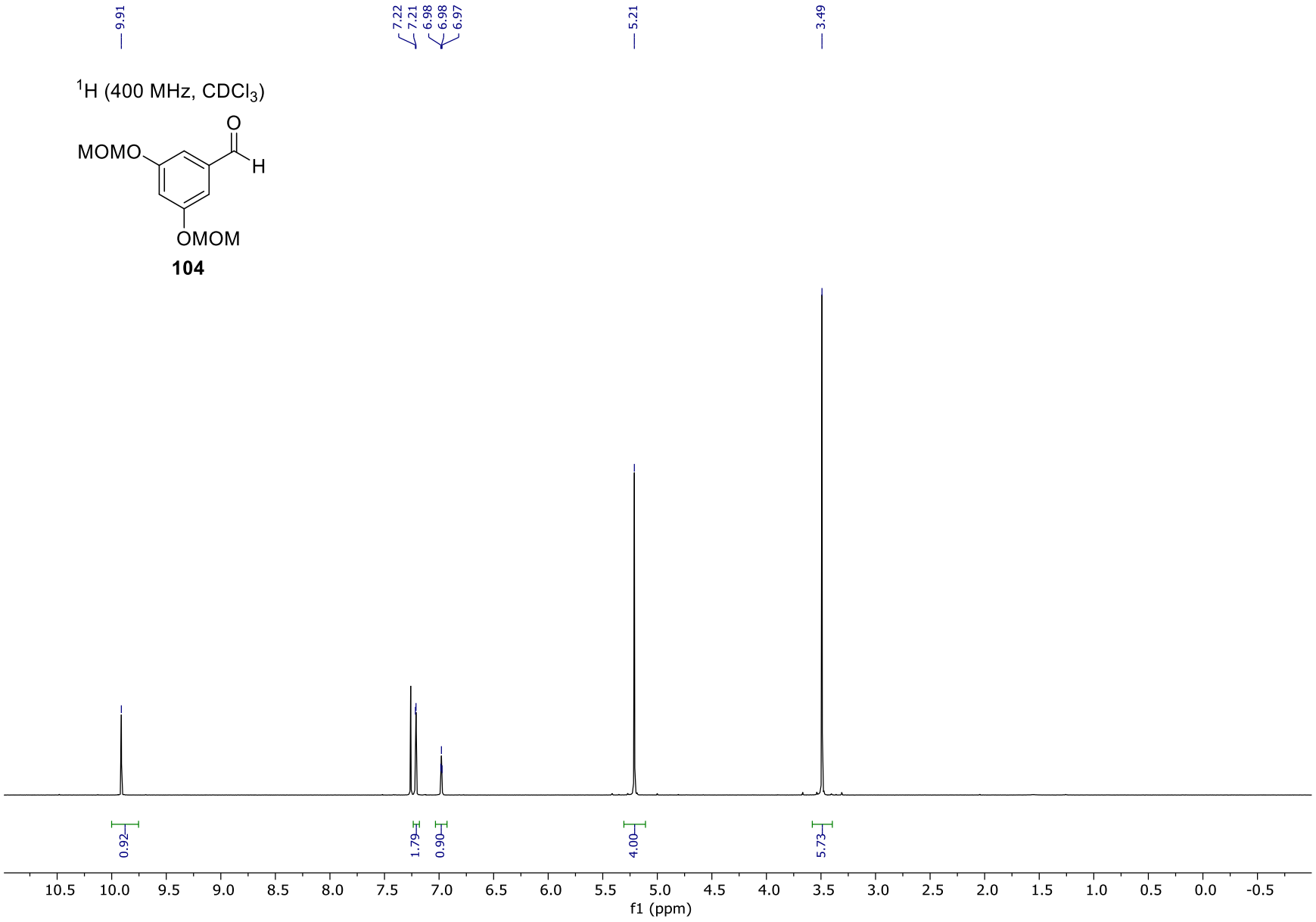
158.40
143.53
107.90
104.04
94.38
65.08
56.03

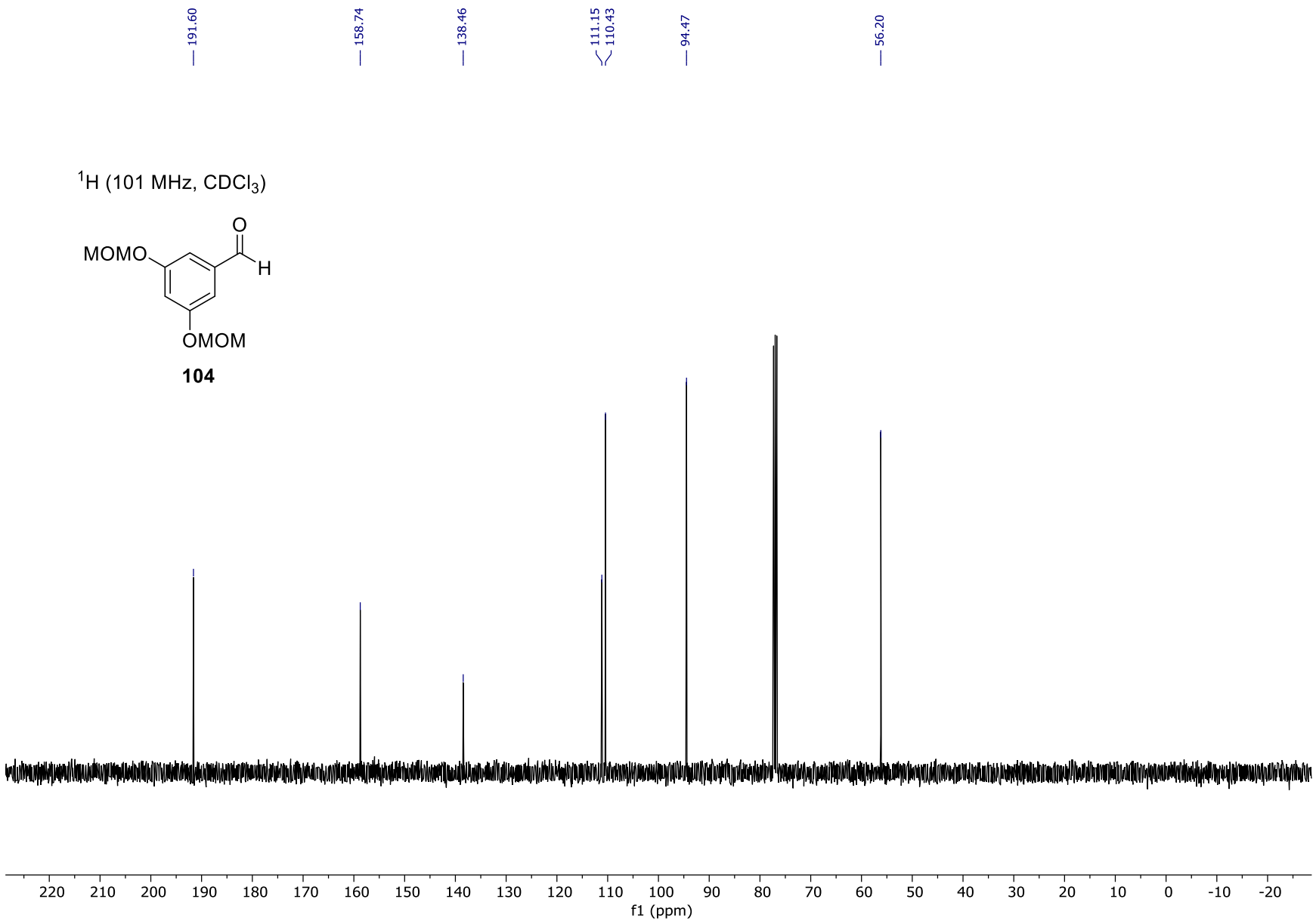
^{13}C (101 MHz, $CDCl_3$)



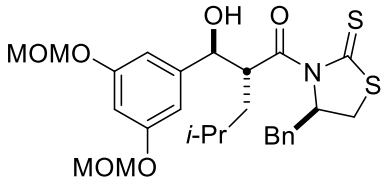
103



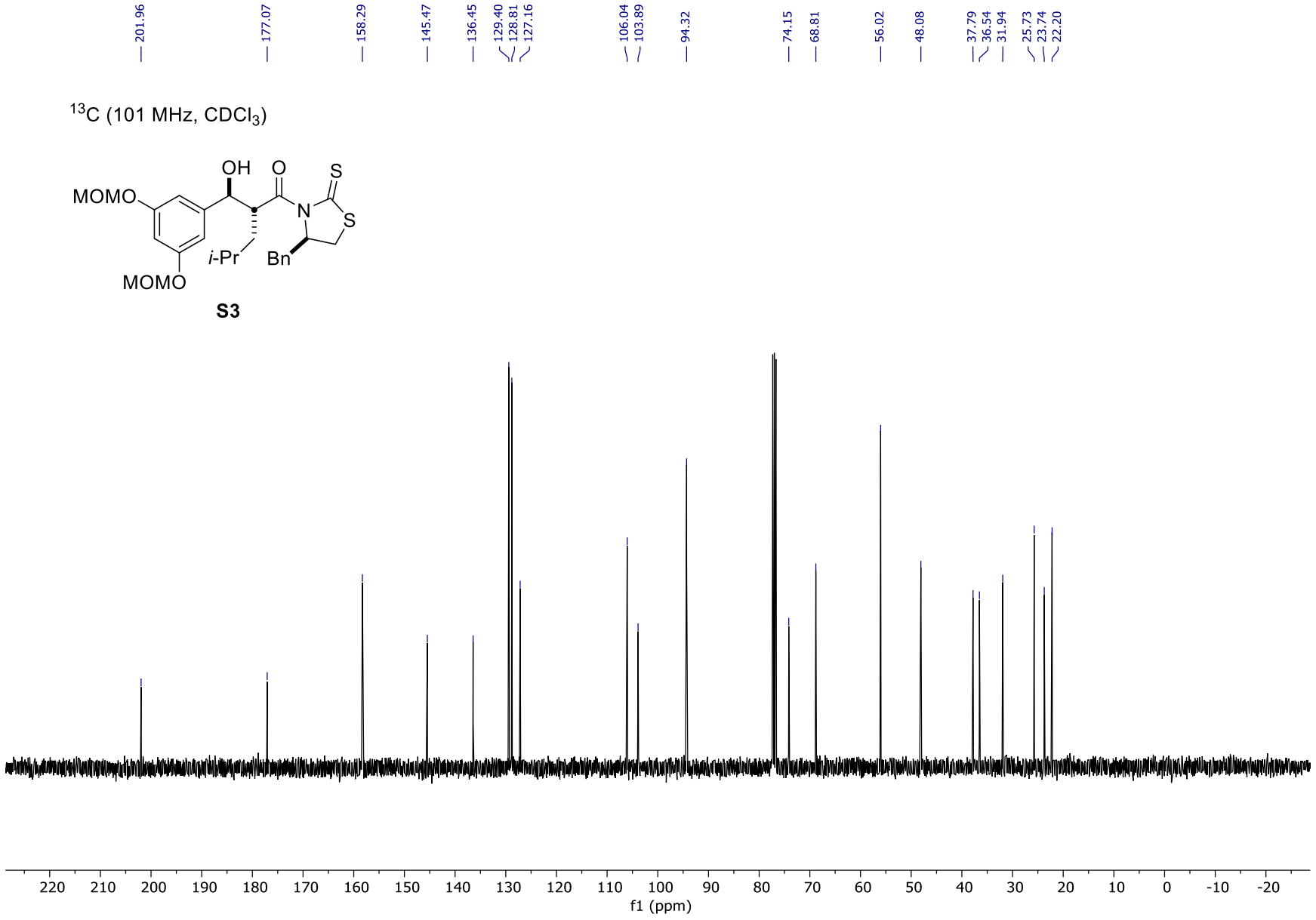

9.91
7.22
7.21
6.98
6.98
6.97
5.21
3.49
^{1}H (400 MHz, $CDCl_3$)
MOMO
O
H
OMOM
104
0.92
1.79
0.90
4.00
5.73
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


191.60
158.74
138.46
111.15
110.43
94.47
56.20
^{1}H (101 MHz, $CDCl_3$)
MOMO
O
H
OMOM
104
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

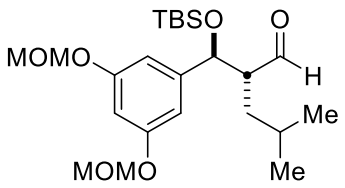
^{1}H (400 MHz, $CDCl_3$)



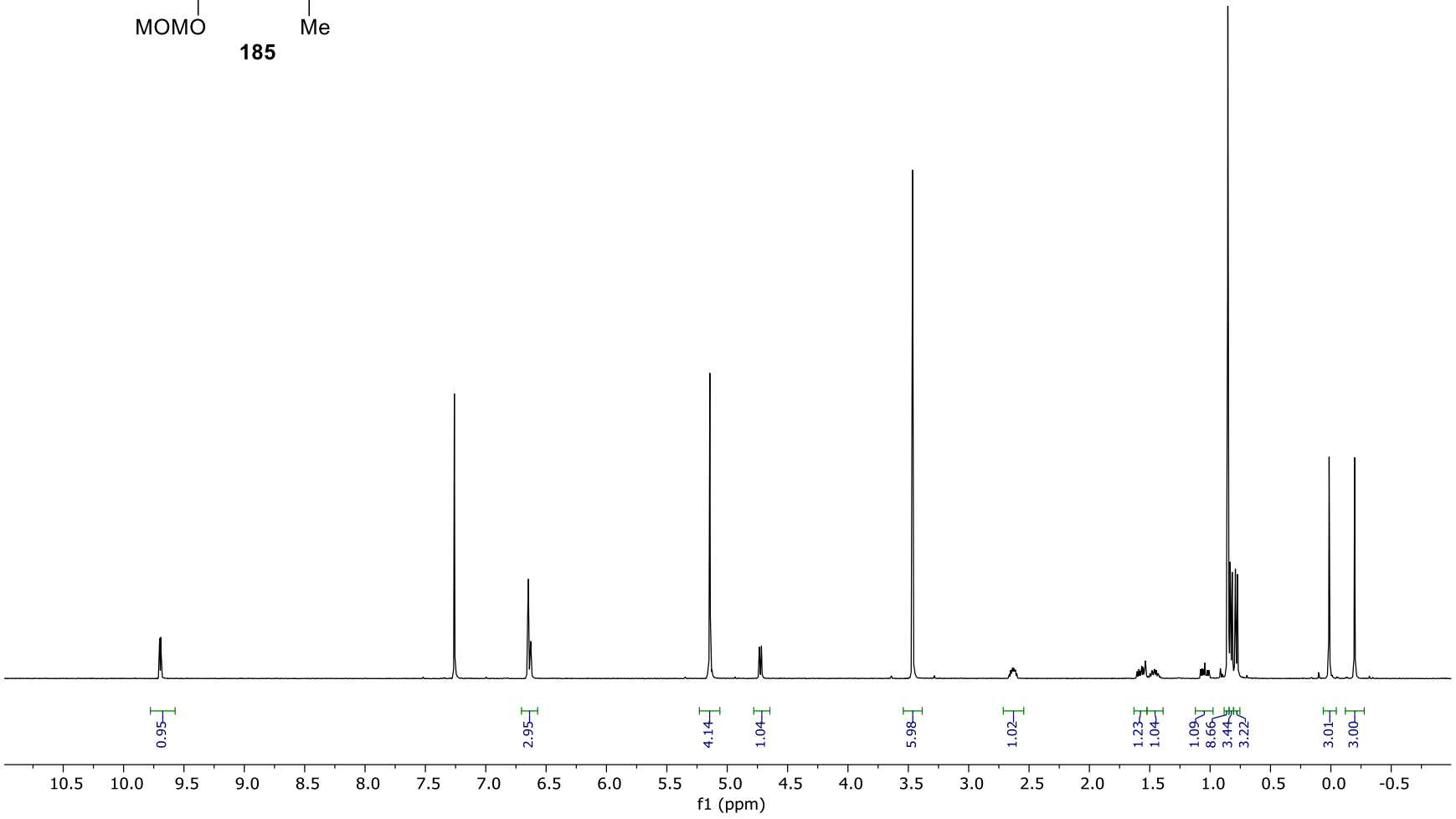
S3

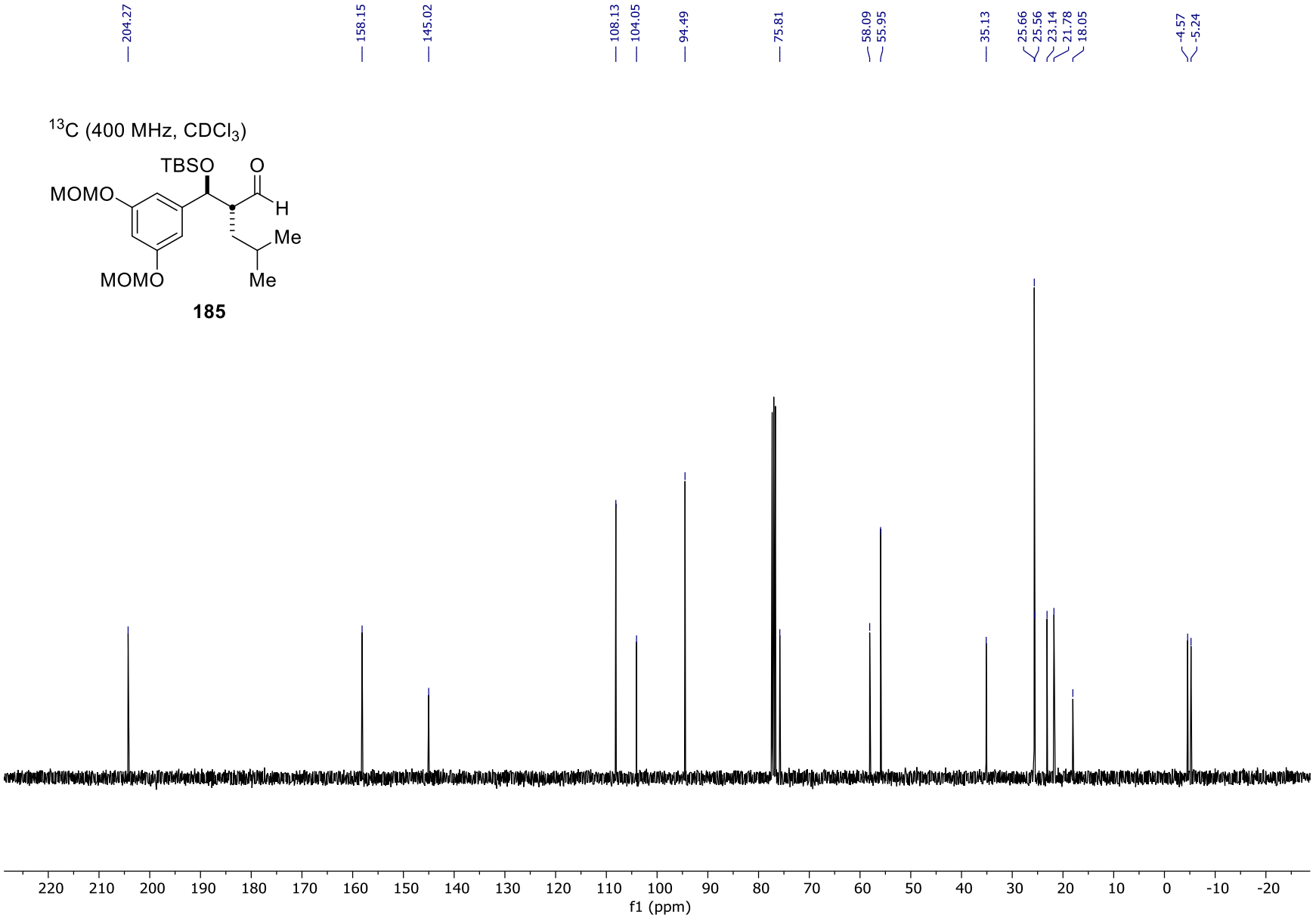

201.96
177.07
158.29
145.47
136.45
129.40
128.81
127.16
106.04
103.89
94.32
74.15
68.81
56.02
48.08
37.79
36.54
31.94
25.73
23.74
22.20
13C (101 MHz, CDCl3)
OH
O
S
MOMO
N
S
i-Pr
Bn
MOMO
S3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

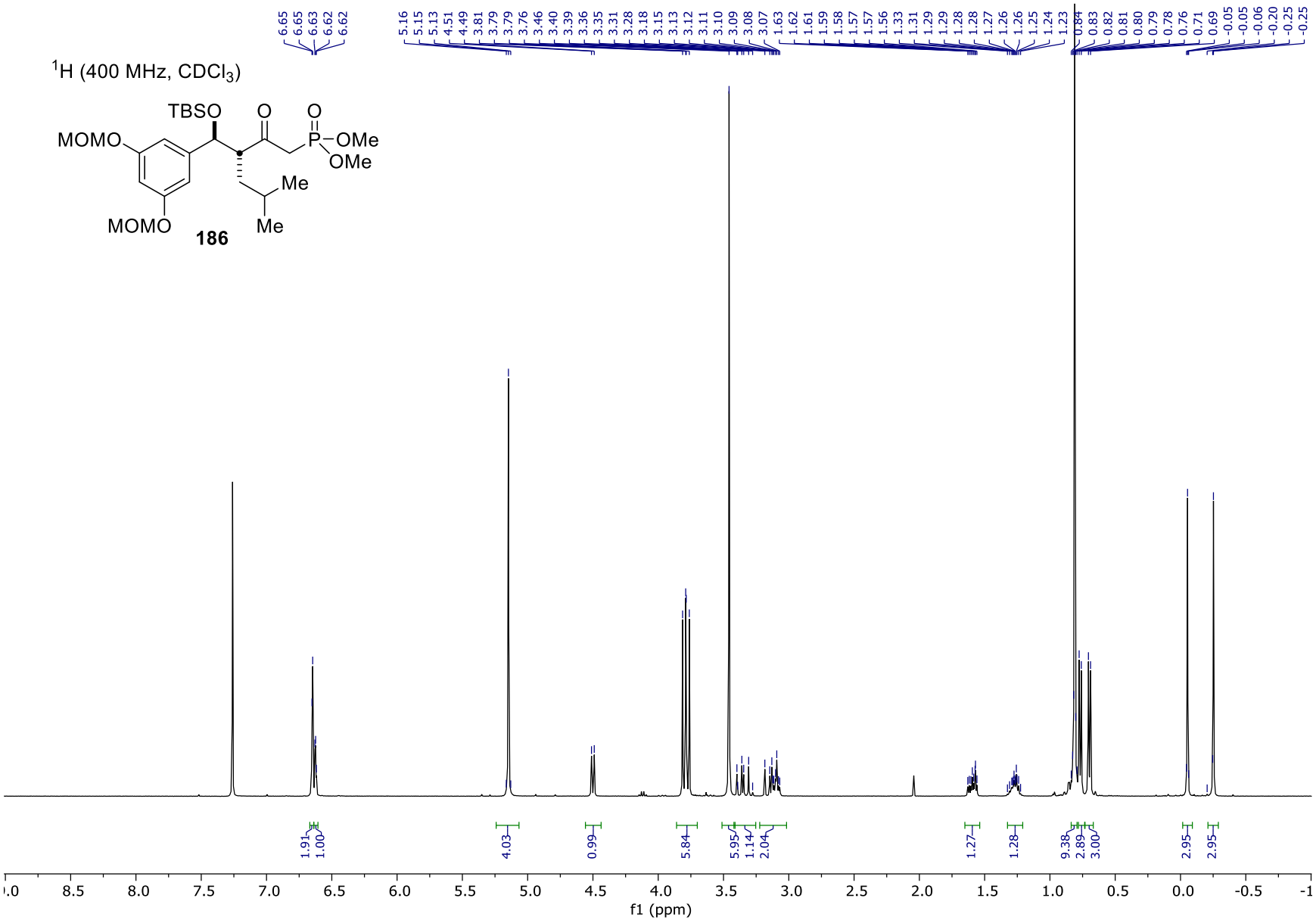
^{1}H (400 MHz, $CDCl_3$)

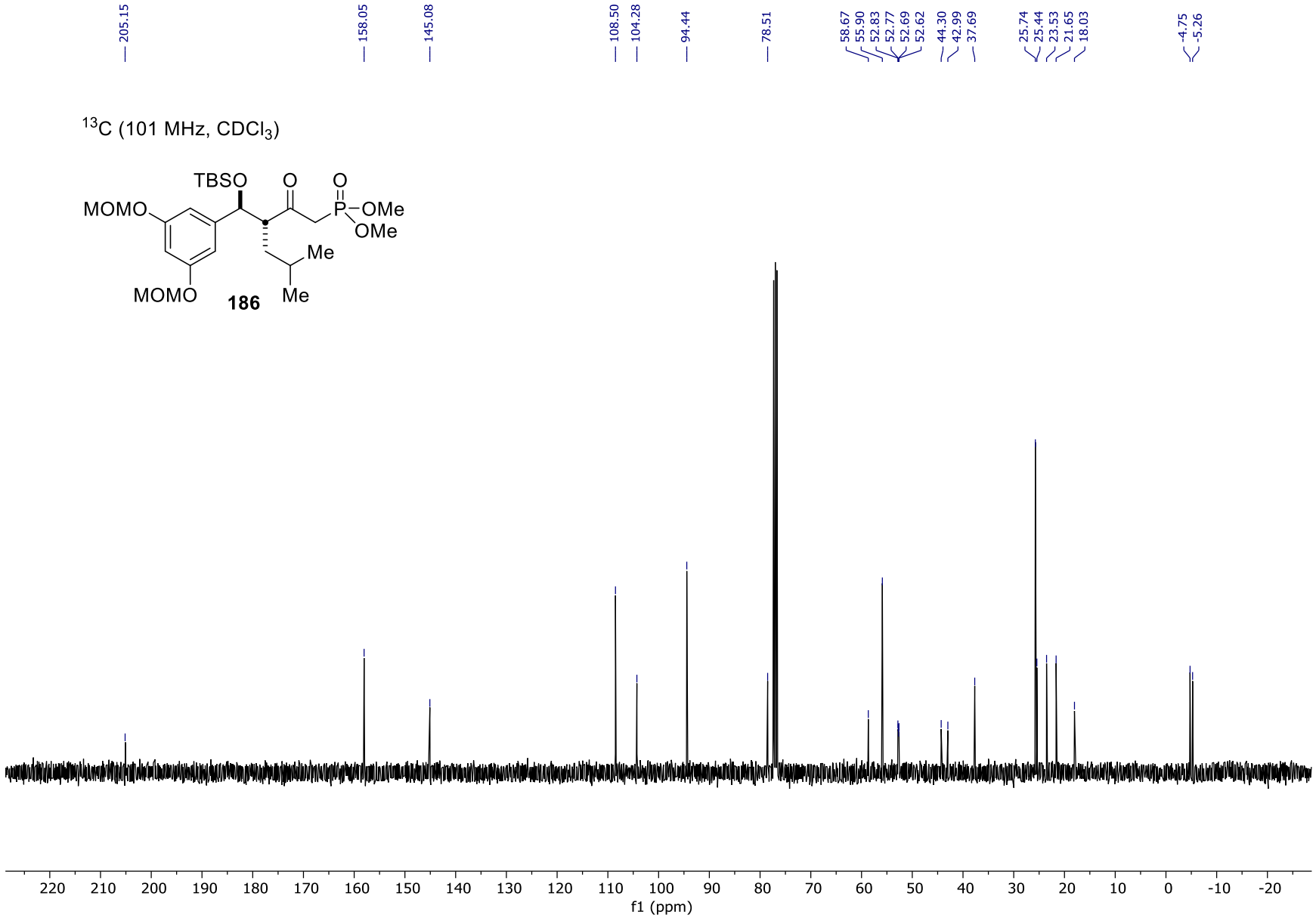


185

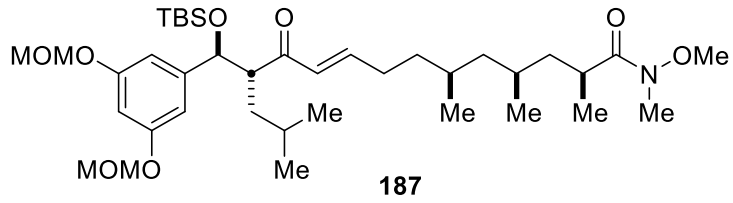



204.27
158.15
145.02
108.13
104.05
94.49
75.81
58.09
55.95
35.13
25.66
25.56
23.14
21.78
18.05
-4.57
-5.24
13C (400 MHz, CDCl3)
TBSO
O
MOMO
H
Me
MOMO
Me
185
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

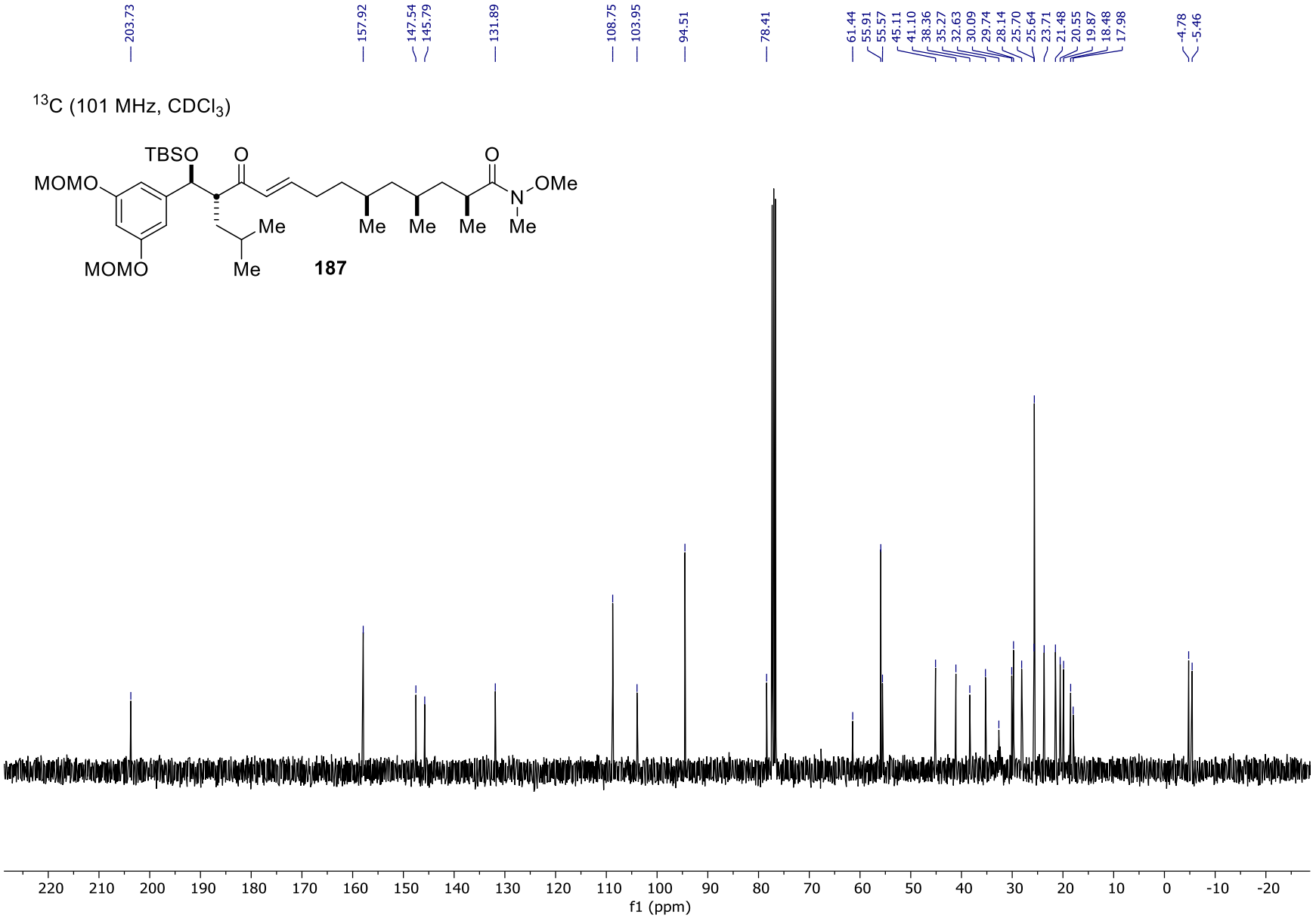

^{1}H (400 MHz, $CDCl_3$)
TBSO
O
O
MOMO
P
OMe
OMe
Me
MOMO
Me
186
f1 (ppm)

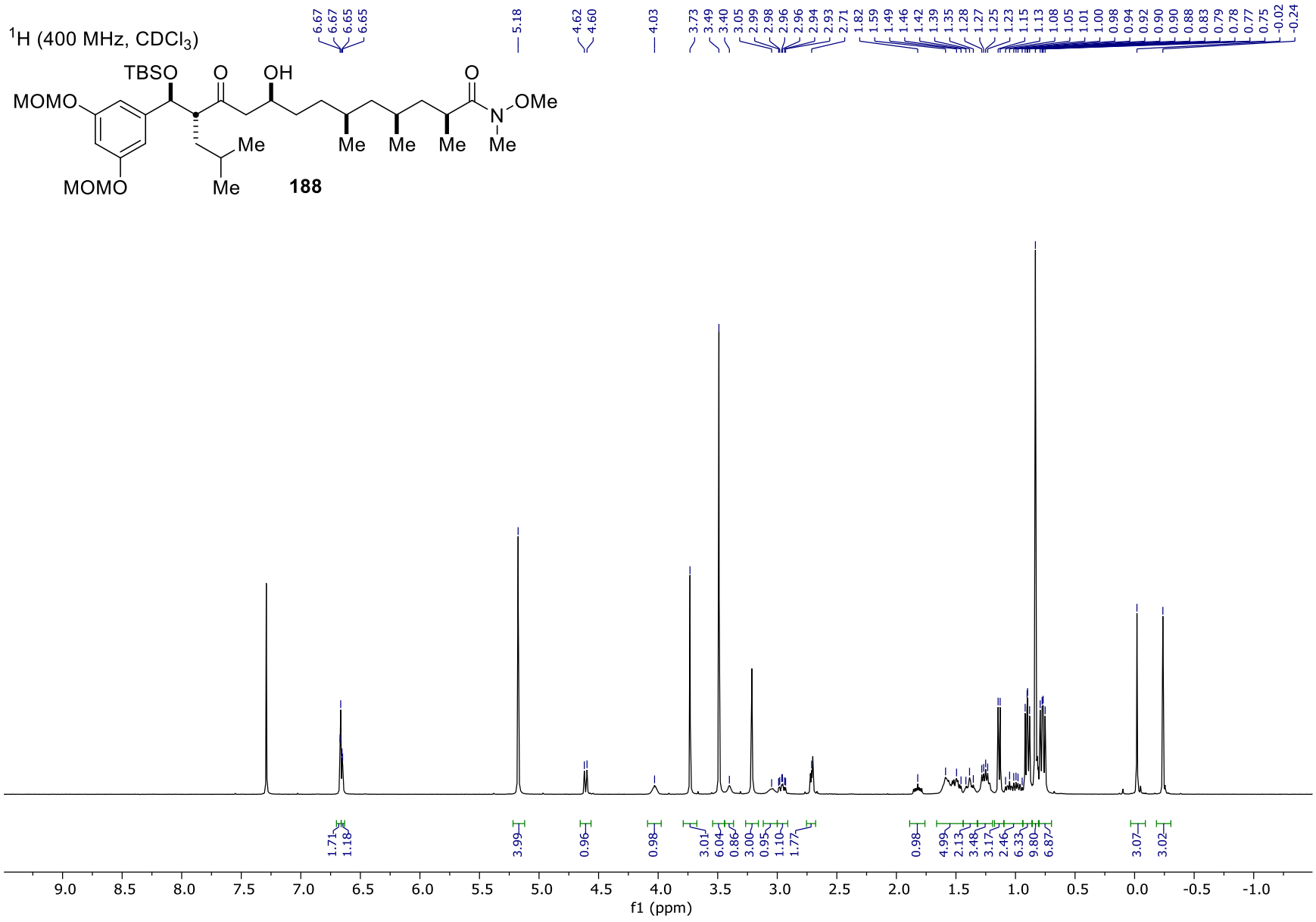

205.15
158.05
145.08
108.50
104.28
94.44
78.51
58.67
55.90
52.83
52.77
52.69
52.62
44.30
42.99
37.69
25.74
25.44
23.53
21.65
18.03
-4.75
-5.26
^{13}C (101 MHz, $CDCl_3$)
TBSO
O
O
MOMO
P
OMe
OMe
Me
MOMO
Me
186
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

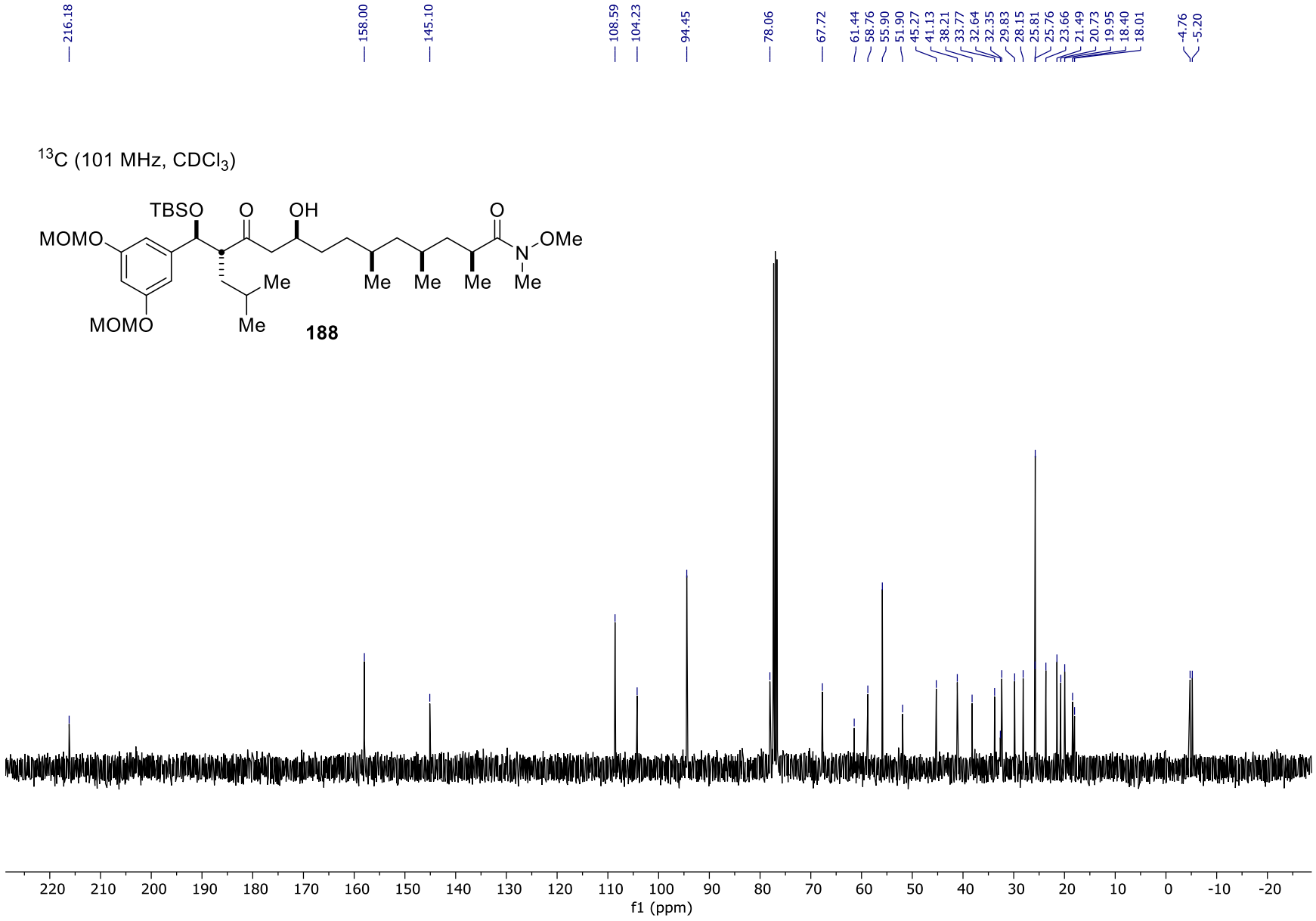
^{1}H (400 MHz, $CDCl_3$)

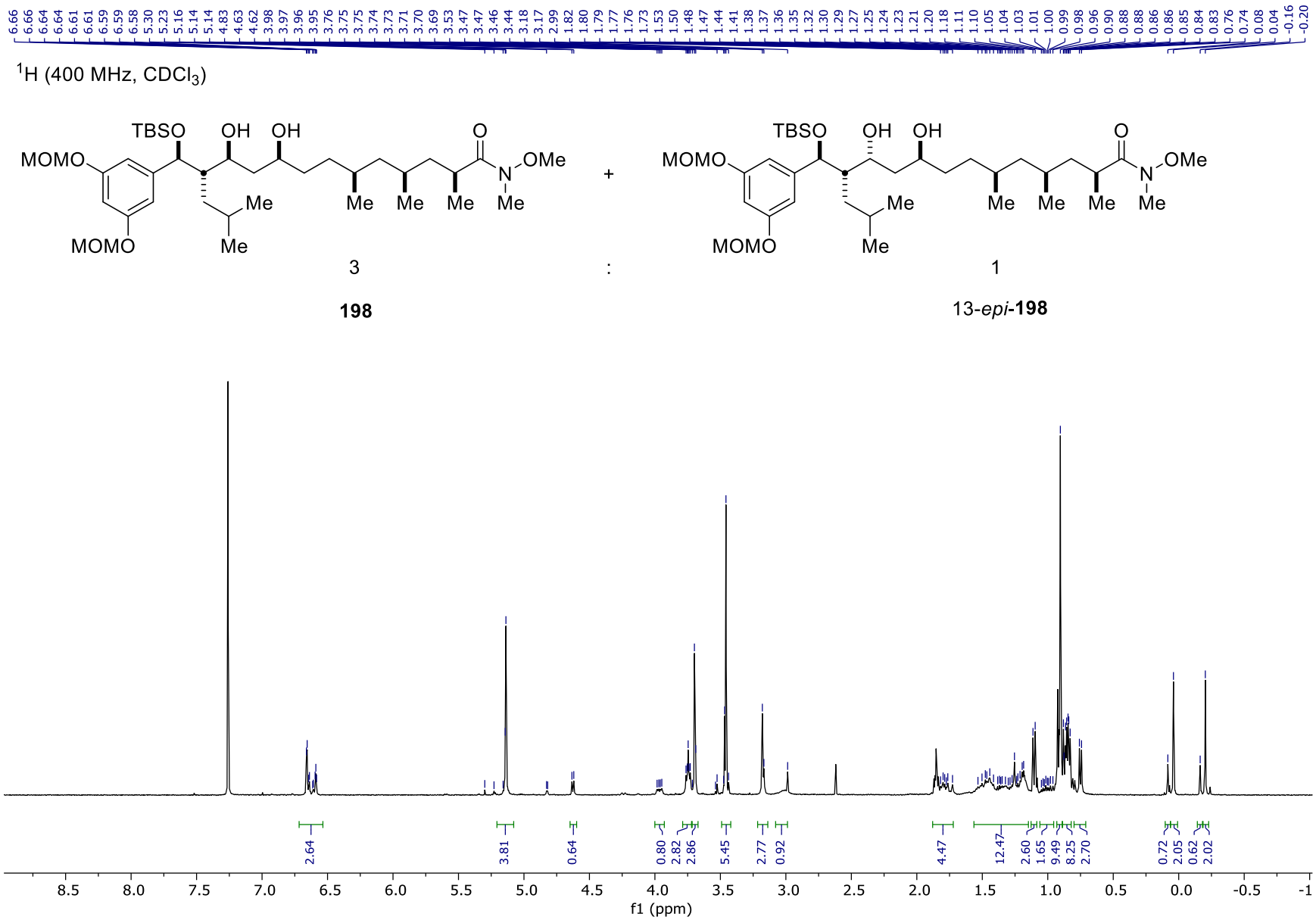


187


203.73
157.92
147.54
145.79
131.89
108.75
103.95
94.51
78.41
61.44
55.91
55.57
45.11
41.10
38.36
35.27
32.63
30.09
29.74
28.14
25.70
25.64
23.71
21.48
20.55
19.87
18.48
17.98
-4.78
-5.46
13C (101 MHz, CDCl3)
TBSO
O
O
MOMO
OMe
N
Me
Me
Me
Me
Me
MOMO
Me
187
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

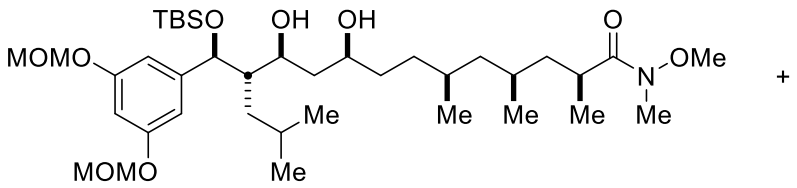

^{1}H (400 MHz, $CDCl_3$)
TBSO
O
OH
O
MOMO
N
OMe
Me
Me
Me
Me
Me
MOMO
Me
188
6.67
6.67
6.65
6.65
5.18
4.62
4.60
4.03
3.73
3.49
3.40
3.05
2.99
2.98
2.96
2.96
2.94
2.93
2.71
1.82
1.59
1.49
1.46
1.42
1.39
1.35
1.28
1.27
1.25
1.23
1.15
1.13
1.08
1.05
1.01
1.00
0.98
0.94
0.92
0.90
0.90
0.88
0.83
0.79
0.78
0.77
0.75
-0.02
-0.24
1.71
1.18
3.99
0.96
0.98
3.01
6.04
0.86
3.00
0.95
1.10
1.77
0.98
4.99
2.13
3.48
3.17
2.46
6.33
9.80
6.87
3.07
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


216.18
158.00
145.10
108.59
104.23
94.45
78.06
67.72
61.44
58.76
55.90
51.90
45.27
41.13
38.21
33.77
32.64
32.35
29.83
28.15
25.81
25.76
23.66
21.49
20.73
19.95
18.40
18.01
-4.76
-5.20
13C (101 MHz, CDCl3)
TBSO
O
OH
O
MOMO
N
OMe
Me
Me
Me
Me
Me
MOMO
Me
188
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

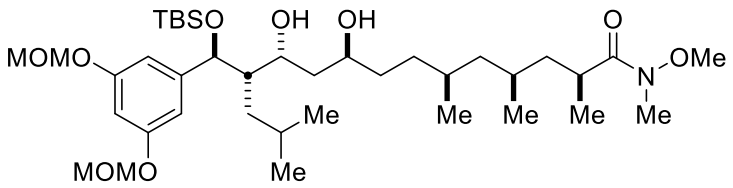

6.66 6.66 6.64 6.64 6.61 6.61 6.59 6.59 6.58 5.30 5.23 5.16 5.14 5.14 4.83 4.63 4.62 3.98 3.97 3.96 3.95 3.76 3.75 3.75 3.74 3.73 3.71 3.70 3.69 3.53 3.47 3.47 3.46 3.44 3.18 3.17 2.99 1.82 1.80 1.79 1.77 1.76 1.73 1.53 1.50 1.48 1.47 1.44 1.41 1.38 1.37 1.36 1.35 1.32 1.30 1.29 1.27 1.25 1.24 1.23 1.21 1.20 1.18 1.11 1.10 1.05 1.04 1.03 1.01 1.00 0.99 0.98 0.96 0.90 0.88 0.88 0.86 0.86 0.85 0.84 0.83 0.76 0.74 0.08 0.04 -0.16 -0.20
^{1}H (400 MHz, $CDCl_3$)
TBSO OH OH O MOMO N OMe Me Me Me Me Me MOMO Me
3
198
+
:
TBSO OH OH O MOMO N OMe Me Me Me Me Me MOMO Me
1
13-*epi*-198
2.64 3.81 0.64 0.80 2.82 2.86 5.45 2.77 0.92 4.47 12.47 2.60 1.65 9.49 8.25 2.70 0.72 2.05 0.62 2.02
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

^{13}C (101 MHz, $CDCl_3$)

158.02
157.86
146.51
145.92
108.31
107.92
103.57
94.46
94.41
77.95
74.62
73.63
69.27
61.42
55.94
55.85
49.47
45.16
45.08
41.20
39.70
36.09
35.28
34.44
34.32
32.66
32.21
29.94
29.77
29.66
28.25
28.13
25.88
25.84
25.69
23.38
22.95
22.26
21.94
20.67
20.56
20.02
18.44
18.06
17.95
-4.52
-4.56
-5.17

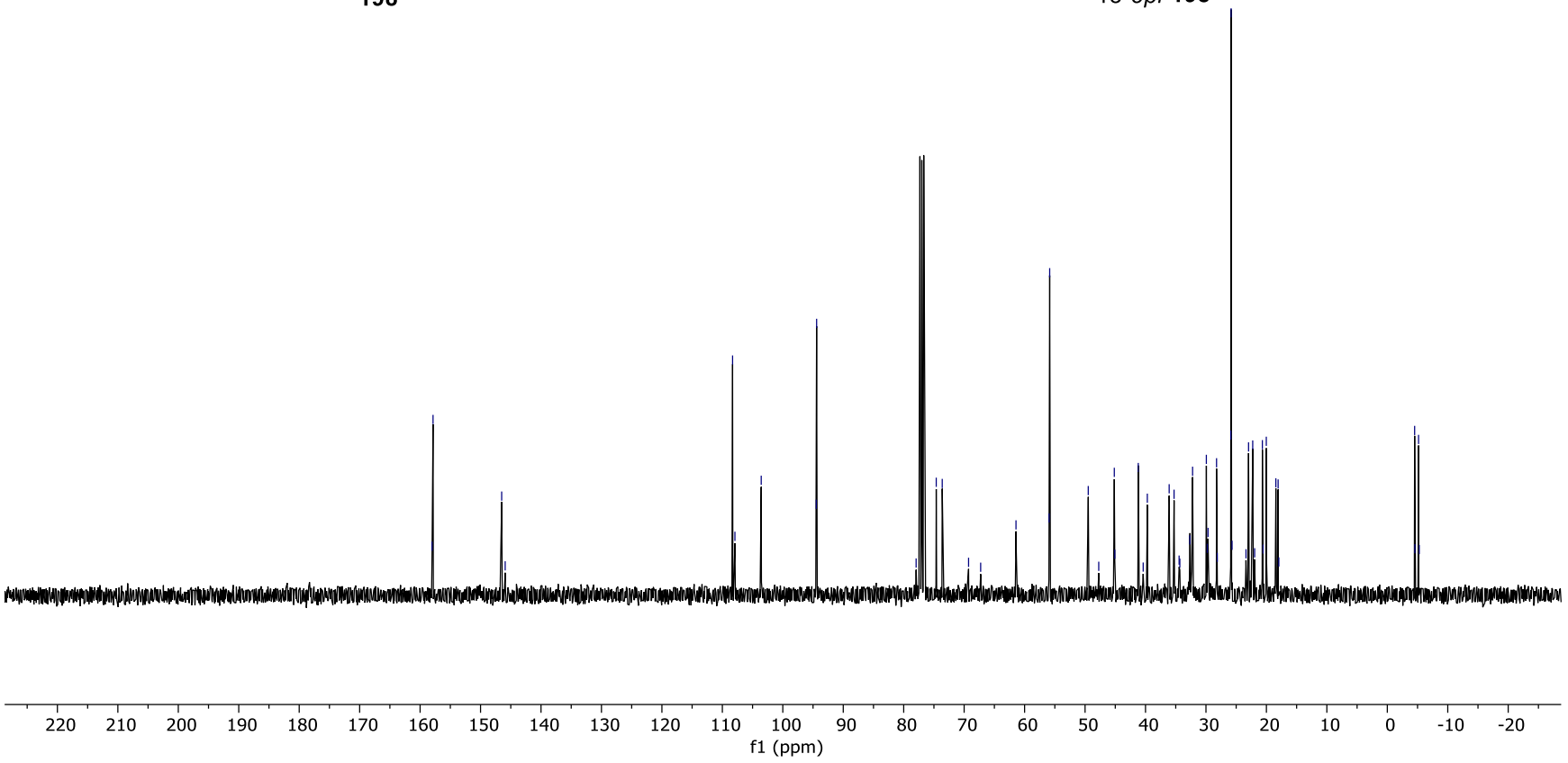


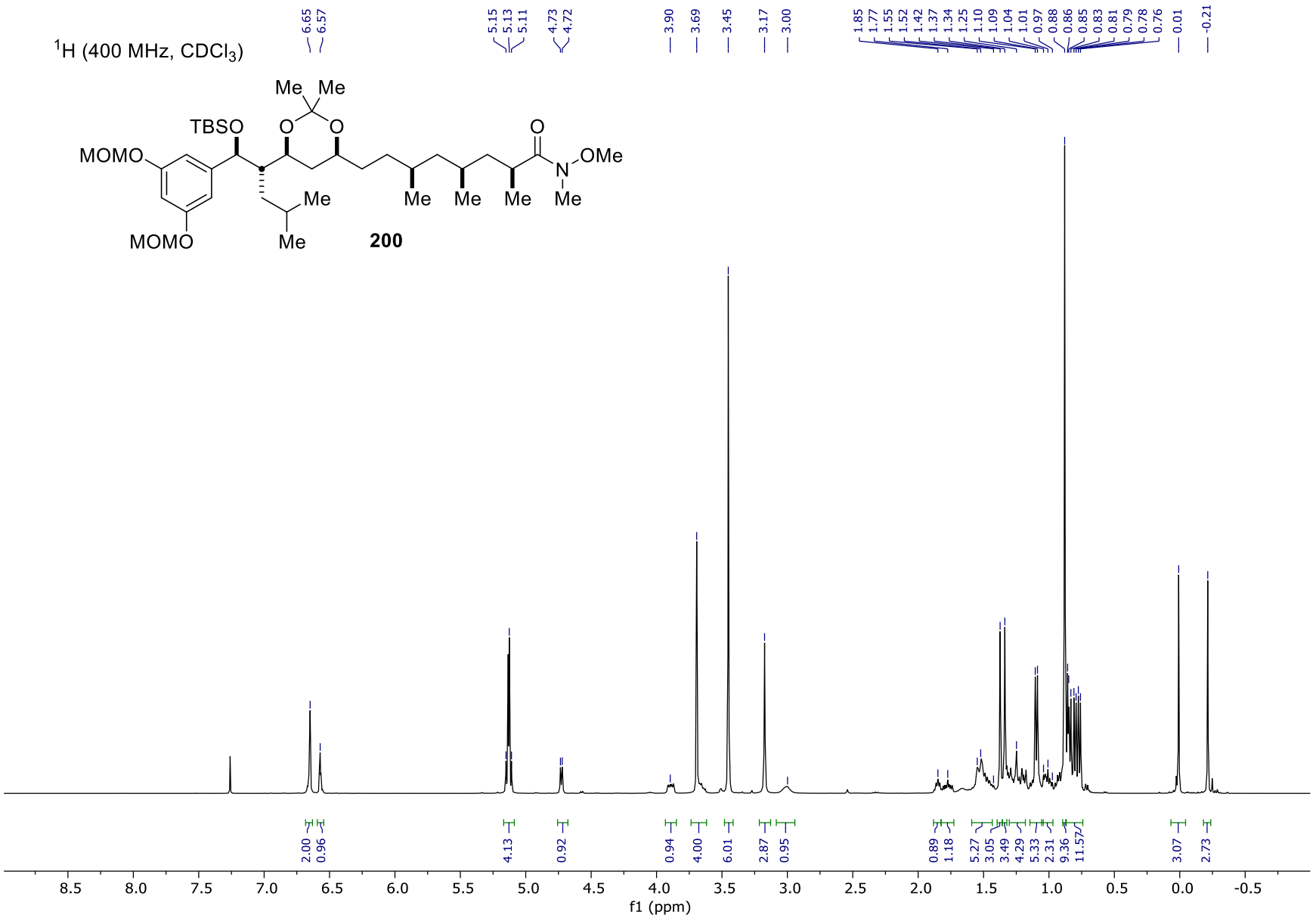
3 : 1



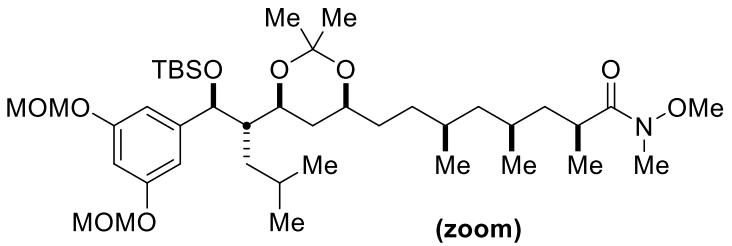
198

13-*epi*-**198**




^{1}H (400 MHz, CDCl$_3$)
6.65
6.57
5.15
5.13
5.11
4.73
4.72
3.90
3.69
3.45
3.17
3.00
1.85
1.77
1.55
1.52
1.42
1.37
1.34
1.25
1.10
1.09
1.04
1.01
0.97
0.88
0.86
0.85
0.83
0.81
0.79
0.78
0.76
0.01
-0.21
Me Me
TBSO
O
O
O
MOMO
N
OMe
Me
Me
Me
Me
Me
MOMO
Me
200
2.00
0.96
4.13
0.92
0.94
4.00
6.01
2.87
0.95
0.89
1.18
5.27
3.05
3.49
4.29
5.33
2.31
9.36
11.57
3.07
2.73
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

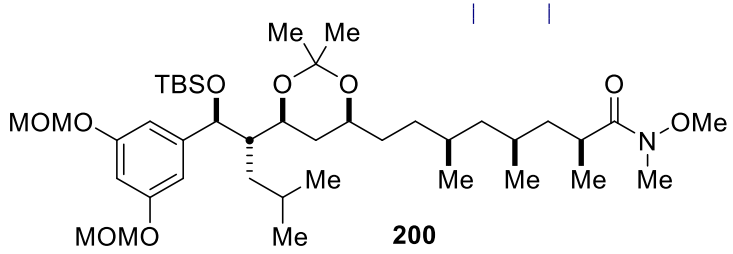
^{1}H (400 MHz, $CDCl_3$)



(zoom)

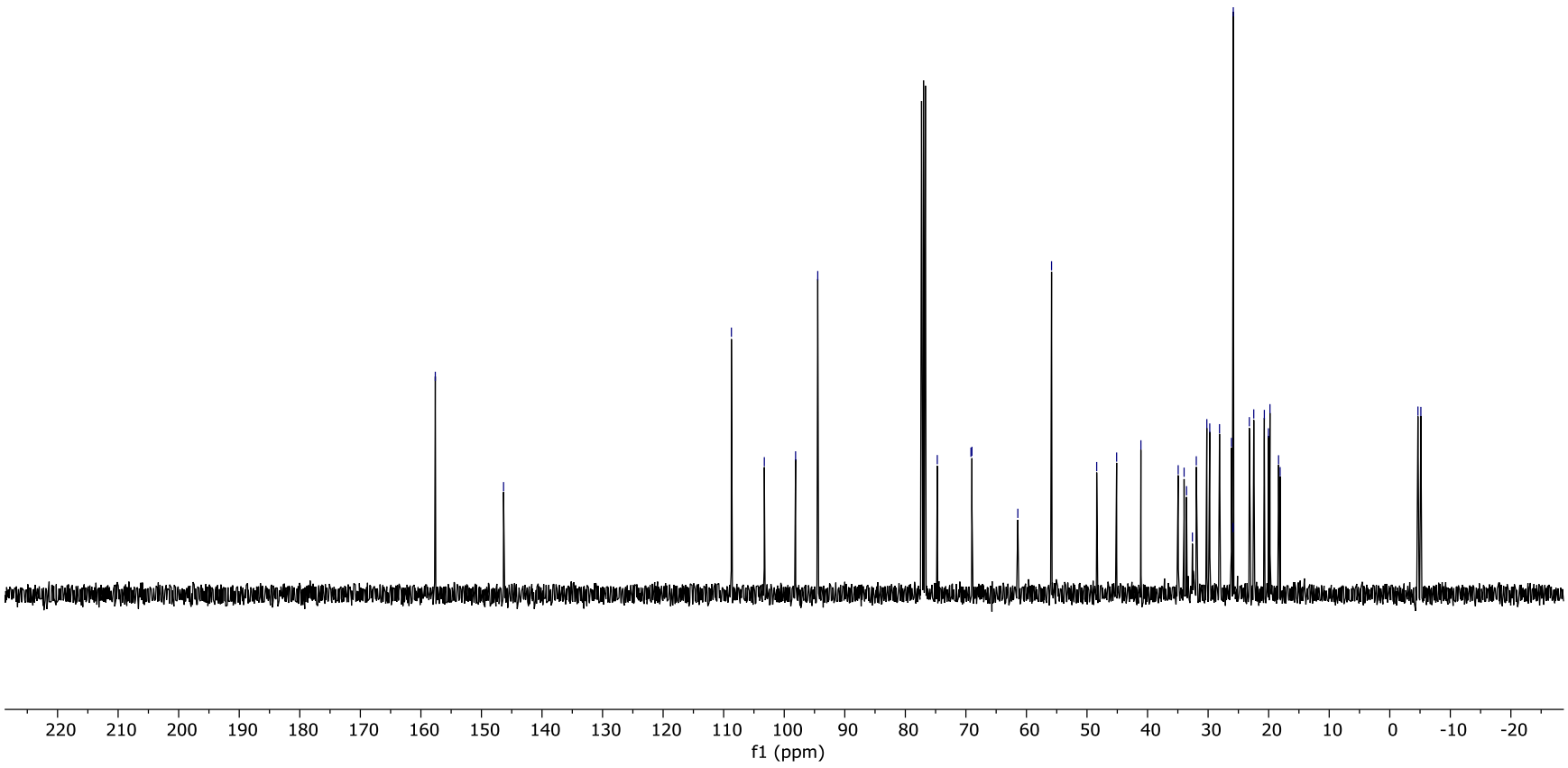
200

^{13}C (101 MHz, $CDCl_3$)

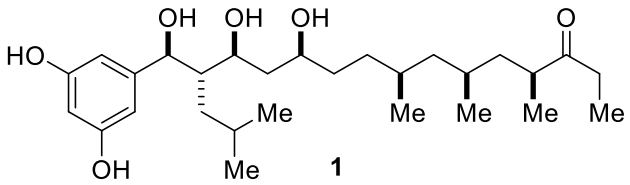


200

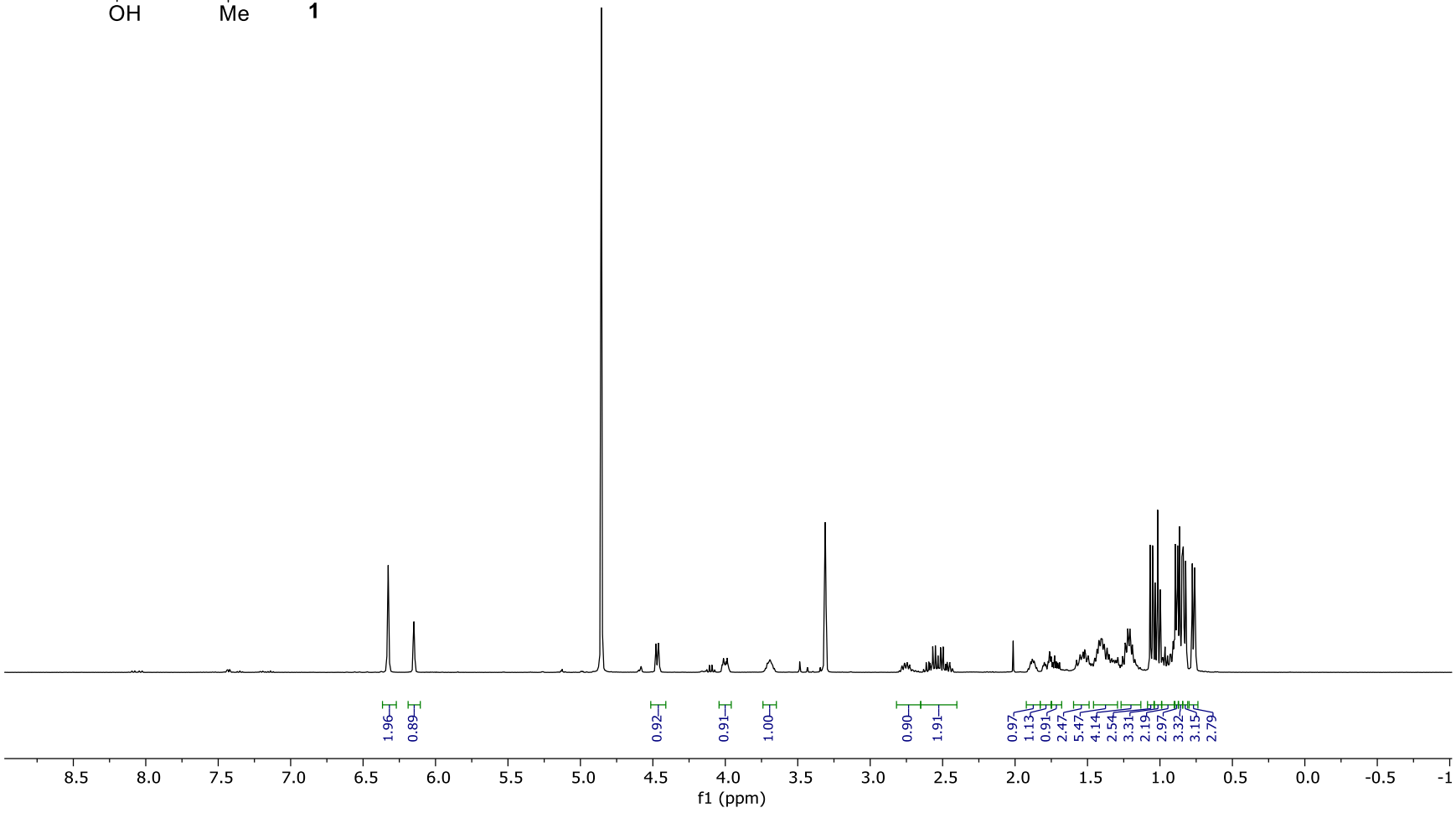
157.62
146.35
108.72
103.29
98.12
94.46
74.72
69.17
69.00
61.42
55.85
48.40
45.11
41.10
34.94
33.96
33.56
32.60
31.95
30.21
29.73
28.12
26.14
25.88
25.84
23.19
22.46
20.71
20.04
19.78
18.36
18.11
-4.65
-5.14

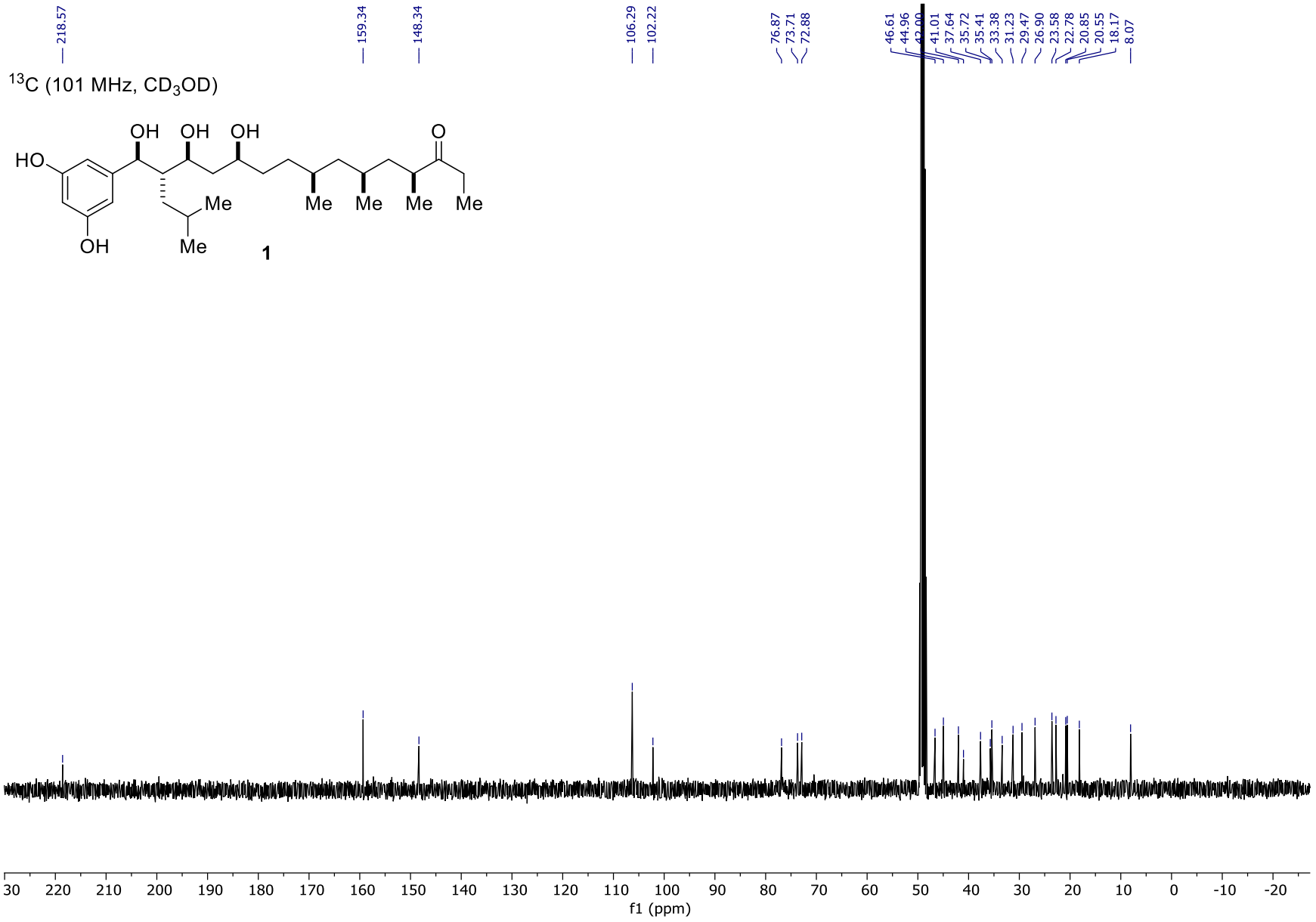


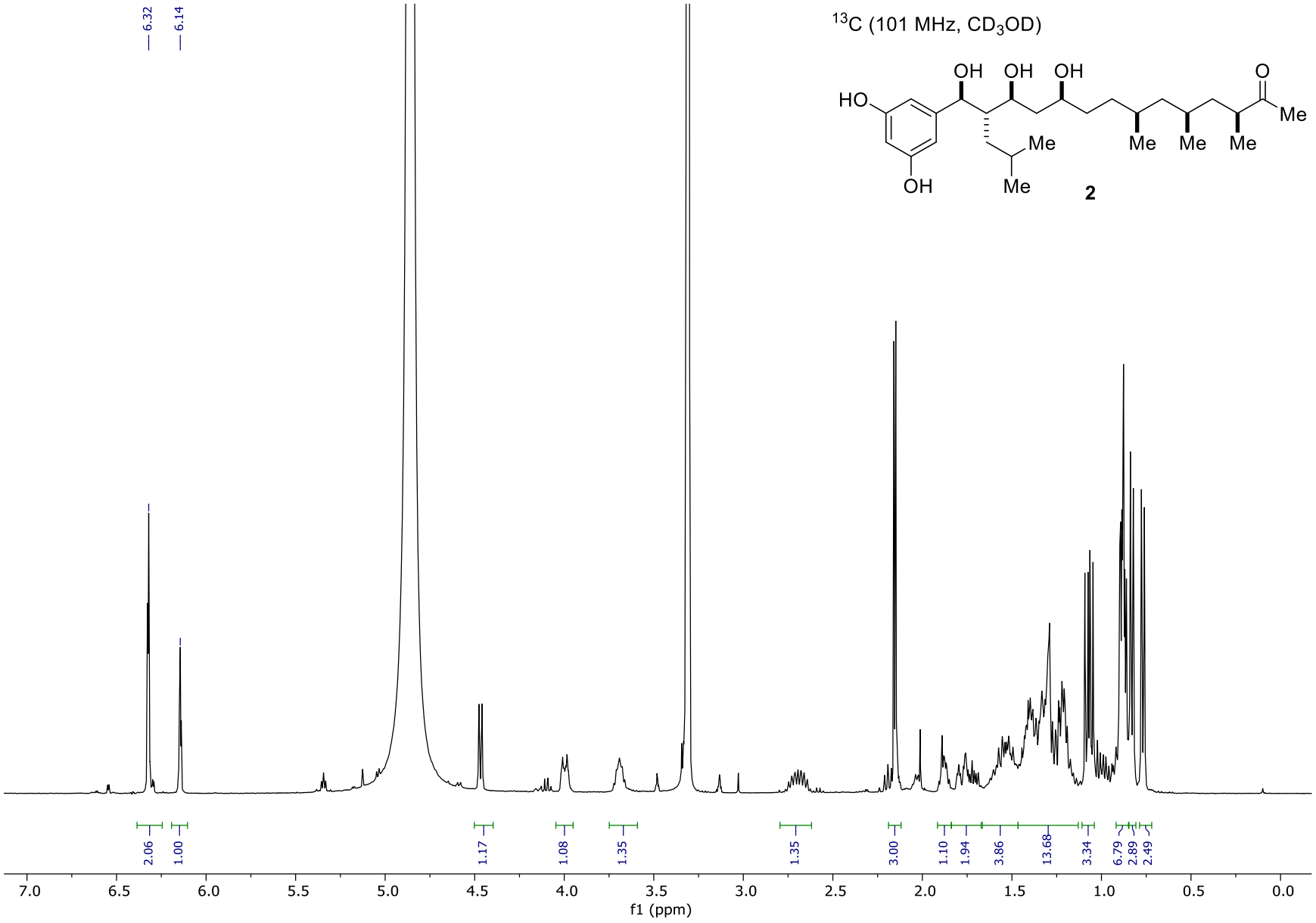
^{1}H (400 MHz, CD_3OD)



1

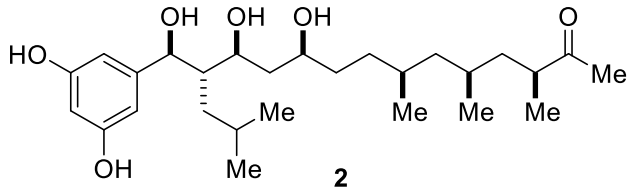



218.57
159.34
148.34
106.29
102.22
76.87
73.71
72.88
46.61
44.96
42.00
41.01
37.64
35.72
35.41
33.38
31.23
29.47
26.90
23.58
22.78
20.85
20.55
18.17
8.07
13C (101 MHz, CD3OD)
HO
OH
OH
OH
O
Me
Me
Me
Me
Me
OH
Me
1
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


^{13}C (101 MHz, CD_3OD)
6.32
6.14
OH
OH
OH
O
HO
Me
Me
Me
Me
OH
Me
2
2.06
1.00
1.17
1.08
1.35
1.35
3.00
1.10
1.94
3.86
13.68
3.34
6.79
2.89
2.49
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

JRT-2-304-PTLC_hiscan.13.fid

^{13}C (101 MHz, CD_3OD)



2