Quotations

סוף דבר, אחי, כל אשר אמת, כל מה שנכבד, כל דבר ישר, טהור, מלא נעם, כל אשר שמעו טוב, כל מעשה נעלה, וכל דבר הראוי לשבח – באלה יהגה לבבכם.

מכיל אחי. אילין דשרירן ואילין דנכפן. ואילין דכאנן ואילין דדכין. ואילין דרחימן ואילין דשביחן. ואילין עבדא דשובחא ודקולסא הלין אתרעו.

Τὸ λοιπόν, ἀδελφοί, ὅσα ἐστὶν ἀληθῆ, ὅσα σεμνά, ὅσα δίκαια, ὅσα ἁγνά, ὅσα προσφιλῆ, ὅσα εὔφημα, εἴ τις ἀρετὴ καὶ εἴ τις ἔπαινος, ταῦτα λογίζεσθε·

de cetero fratres **quaecumque** sunt **vera** quaecumque pudica quaecumque iusta quaecumque sancta quaecumque amabilia quaecumque bonae famae si qua virtus si qua laus haec cogitate

X min iqqimen, a awmaten, marra min iğan d tidett, marra min iqquren, marra min iseggden, marra min izdigen, marra min iɛizzen, marra min ɣar iğa řḥess aṣebḥan, uca mařa din ca n řefḍeř niɣ ca isdaheğen ccan, xarṣem dayes.

وَخِتَاماً، أَيُّهَا الإِخْوَةُ: كُلُّ مَا كَانَ حَقّاً، وَكُلُّ مَا كَانَ شَرِيفاً، وَكُلُّ مَا كَانَ عَادلاً، وَكُلُّ مَا كَانَ طَاهِراً وَكُلُّ مَا كَانَ مُسْتَحَبّاً، وَكُلُّ مَا كَانَ حَسَنَ السُّمْعَةِ، وَكُلُّ مَا كَانَ فِيهِ فَضِيلَةٌ وَخَصْلَةٌ حَمِيدَةٌ، فَاشْغِلُوا أَفْكَارَكُمْ بِهِ.

Por último, hermanos, consideren bien todo lo verdadero, todo lo respetable, todo lo justo, todo lo puro, todo lo amable, todo lo digno de admiración, en fin, todo lo que sea excelente o merezca elogio.

To goode latst, Breeda: Wautemma woa es, wuatemma bediedensweat es, wautemma rajcht es, wautemma rein es, wautemma leeftolich es, waut goode Eajenschoffte haft, en lowensweat es, doa denkt aun!

Finally, brethren, whatsoever things are true, whatsoever things are honest, whatsoever things are just, whatsoever things are pure, whatsoever things are lovely, whatsoever things are of good report; if there be any virtue, and if there be any praise, think on these things.

(Philippians 4:8)[1]

University of Alberta

A Catalytic Asymmetric Synthesis of Palmerolide A

by

Marlin Neil Penner

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Chemistry

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Dedication

לאבא ואמא

Abstract

In the Introduction of this thesis, consideration is given to historical and ongoing value of investing research efforts in the total synthesis of natural products. Following this discussion is an explanation of the factors that guided the selection of palmerolide A as a synthetic target. The current status of palmerolide A in the academic literature is overviewed in the remainder of the introductory chapter, followed by a summary of research objectives at the conclusion.

Chapter Two begins with a consideration of overall synthetic strategy and then narrows the focus to synthetic investigations that were directed towards what is defined as the "Eastern Hemisphere" of palmerolide A. These investigations involved extension of an inverse electron demand hetero-Diels-Alder-cycloaddition/allylboration methodology catalyzed by Jacobsen's chromium(III) catalyst that was developed in the research group of Professor Dennis Hall for application to this synthesis. This highly enantioselective methodology was employed to set the desired relative and absolute stereochemistry of the entire Eastern Hemisphere through the introduction of a borono-Ireland-Claisen rearrangement; a unique variation of the Ireland-Claisen rearrangement developed during the synthesis. Also detailed are challenges and strategies employed to overcome issues in selectivity, protecting groups, and purification culminating in an optimized synthetic route to the Eastern Hemisphere.

This project was collaborative in nature and a portion of the unique contributions by collaborators Dr. Vivek Rauniyar and Dr. Ludwig Kaspar are briefly described in Chapter 3.

Chapter 4 recounts the key synthetic steps employed to join the hemispheres (Suzuki-Miyaura coupling), close the ring (Yamaguchi macrolactonization), form the dienamide side arm (Curtius rearrangement) and complete the synthesis. Of note was the challenge of overcoming a problematic late stage deprotection of a *p*-methoxybenzyl group.

Chapter 5 presents preliminary research directed towards the synthesis of palmerolide A analogues focussed on modification of the macrocyclic backbone with an aromatic ring and modifications in protecting group strategy to address the problem encountered in the total synthesis followed by a conclusion in Chapter 6.

Acknowledgements

הקדוש ברוך הוא

The Holy One blessed be He

I would be remiss in not acknowledging the Creator of all things who has made all pursuits, research or otherwise possible.

I would like to thank my supervisor Professor Dennis Hall who made a place for me in his research group and whose confidence in me enabled me to learn a great deal through the challenge of attempting a difficult and venturesome project such as a total synthesis of a complex natural product. In conjunction with the credit due my supervisor is the thanks I owe to his students, both those I have known and those who went before, who contributed intellectually and experimentally to his accomplishments and paved the way for my contribution to this body of work. In particular I would like to thank Hugo Lachance who mentored me as I joined the Hall group. I also want to make special mention of my lab mates through the years, Marie Bérubé, Ludwig Kaspar and Urmi Bhakta who each contributed in a special way to my time here. A collective thanks goes to fellow Hall group members for their useful suggestions both formal and informal through the various stages of my program from coursework to cumulative exams to research presentations and of course with respect to the research project as well. A personal thanks goes to fellow group member Raed Al Zoubi for his friendship and opening his home to me when the basement I was living in flooded. Likewise, my friend Conrad McFarlane provided me with a longer term solution to this housing shortage, which enabled me to get back on track with the research.

To the members of my supervisory and candidacy/defence examination committees: Professor Derrick Clive, Professor Frederick West, Professor Jonathan Veinot, Professor Michael Weinfeld and Professor Alan Underhill, thank you for your participation in and support through the various stages of my doctoral program.

My ability to focus on the research project was greatly enhanced by some undergraduate students who assisted me with my duty as the chemical database manager for the group: Steve Hughes and Sina Ghanbari. Their work not only benefited me, but will also be of lasting value for the whole group through the improvements they implemented.

There were some generous funding agencies that supported my research: The Natural Sciences and Engineering Research Council and Alberta Ingenuity Funds provided scholarships and the governments of Alberta, Manitoba and Canada provided more general funding support. The taxpayers who work hard and contribute through these institutions should also be recognized for their part.

I would like to thank the excellent support staff in the University of Alberta Chemistry department whose contributions to the project were invaluable from the NMR staff to the analytical staff to the mass spectrometry staff to the X-Ray crystallography staff to the stores and delivery staff to the glass shop staff to the machine shop staff to the electronics shop staff to the information technology services staff. In particular I would like to mention Mark Miskolzie, Wayne Moffat, Dr. Angie Morales-Izquierdo, Dr. Robert McDonald, Bernie Hippel, Ryan Lewis, Jason Dibbs, Paul Crothers, Allan Chilton, and John McGuigan each representing their particular division. Without the support of the people in these service divisions research in this department would grind to a halt. A special person involved in support is Diane Dowhaniuk who personally assisted in the management of a variety of administrative details that required my attention and represents the many dedicated secretaries in the department.

To the unsung cleaning, maintenance and administrative staff of the Chemistry department and university I would also like to extend my praise and thanks. Unfortunately I did not get to know you in any significant measure but your faithful and friendly service is essential and has not been unnoticed.

One person to set apart in the support staff thanks is Blake Lazurko, who purified the final product of the total synthesis by HPLC enabling a good characterization needed in order to publish the research. Another individual who

bears recognition for rendering assistance to the project is Erin Graham, who synthesized one of the catalysts used for the analogue research.

One of the excellent aspects of working in this department is the collegiality between the different research groups and its particular expression in the freedom with which chemicals are shared. I would like to express my appreciation for this spirit of generosity that was demonstrated by both students and their respective supervisors.

A salute to my collaborators in the project is definitely in order. Dr. Ludwig Kaspar and Dr. Vivek Rauniyar are talented chemists who made an invaluable contribution and I wish them great success in their future endeavours.

During the writing of this thesis Jared Jacobson read through my draft copies and made helpful suggestions that made it a better piece of writing. Kol hakavod ləkha Jared, may your altruistic spirit bring you blessing.

I would not be the research scientist I am today without the many educators (teachers, professors, lab instructors and others) who passed on their knowledge and experience to me. Thanks to you as well for helping make this project a reality.

In order not to insult anyone through omission I will make a collective mention of my appreciation for my friends who supported me emotionally, practically and spiritually.

I have benefited from the contributions of all those mentioned and more besides in the process of producing this thesis. A heartfelt acknowledgement to them and the many ways they brought it to fruition. I of course bear any responsibility for any deficiency in presentation or content.

At the end I recognize my family: Abba and Emma, Michael and Stephanie, Yadon, Asher, Mikha, Marcel and Adria, Yishayah and Yoshiah as well as all my relatives who are a part of me and whatever I do. May the Holy One blessed be He bless you and all these others for the blessing you are to me and to those He brings into your lives. Amen.

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List of Schemes

List of Symbols, Nomenclature, or Abbreviations

Symbol	Definition
9-BBN	9-borabicyclo[3.3.1]nonane
Bpin	pinacol boronate
CAN	ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata reduction
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
$(DHQD)_2PHAL$	(9*S*)-(9"*S*)-9,9"-[1,4-phthalazinediylbis(oxy)]bis[10,11-dihydro-6'-methoxy-cinchonan
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylamino pyradine
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DNA	deoxyribose nucleic acid
EDC	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDG	electron donating group
ee	enantiomeric excess

EI	electron impact ionization
ESI	electrospray ionization
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
HDA	hetero-Diels-Alder
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
IBX	2-iodoxybenzoic acid
IEDHDA	inverse electron demand hetero-Diels-Alder
*i*PrOH	isopropyl alcohol
IR	infrared
LA	Lewis acid
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
Ln	n number of ligands
LUMO	lowest unoccupied molecular orbital
MeOH	methanol
MOM	methoxymethyl
MW	molecular weight

NCI	National Cancer Institute
NMR	nuclear magnetic resonance
NRPS	nonribosomal peptide synthetase
PCR	polymerase chain reaction
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PNB	*para*-nitrobenzoyl
rac	racemic
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS/TBDMS	*tert*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
V-ATPase	vacuolar adensosine triphosphatase

Chapter One: Introduction

1.1 Total Synthesis of Natural Products and Target Selection

One of the remarkable ironies of the pharmaceutical industry is its reduction of research investment in natural products in favour of the apparently inexhaustible potential of compound libraries derived by combinatorial synthesis and high throughput screening and how little it has to show for this divergence.[2] In a 2007 David J. Newman and Gordon M. Cragg at the National Cancer Institute in Frederick, Maryland wrote a review surveying the representation of natural products as a source of drugs over a 25 year period. Their survey provided a summation of the total number of new chemical entities with pharmacological properties that had been introduced from different sources. In the review they found that even though 70% of the research time of the period was devoted to combinatorial chemical libraries only one *de novo* drug candidate (sorafenib) was discovered.[3] In contrast since the 1940's, 73% of all new drugs were derived from natural sources and 47% were actual natural products or directly derived from them. Given this scenario, investigations into biologically interesting natural products are far more than simply a worthwhile pursuit. The question however arises, what is the role of total synthesis in these investigations? In their 25 year survey Newman and Cragg noted that 4% of the drug discoveries were natural products that were accessed via total synthesis.[3] There is more than one way to interpret the modest share that total synthesis accounts for in the much larger domain of natural products in the pharmaceutical world. For instance, it might be related to the unsuitability of completely natural products as drugs. Note that 23% of the drug candidates are natural product derivatives, which is an indication of the need for some modification to make the natural products more suitable for pharmaceutical purposes. Other reasons could be discussed but from a synthetic organic chemist's point of view: probably the biggest issue is the challenge of actually making complex natural products. Syntheses of these targets often involve such a large number of steps with ever decreasing yields

such that they have no utility for producing materials that can be used to treat disease. Inherent in this challenge and limitation then is actually a motivation for overcoming it. Total syntheses of challenging natural products can only be improved when chemists are willing to devote time, energy, and intellectual creativity to making them. These efforts serve as a driving force for developing new chemistry to overcome challenges and also reveal the limitations or advantages of known chemical processes as they are applied in different contexts.

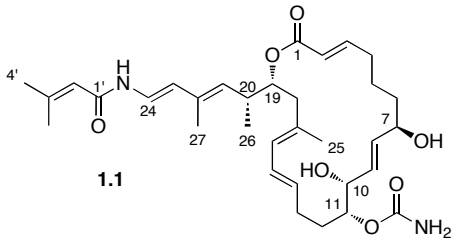
Given that natural products continue to have research importance and that total synthesis continues to have relevance as an approach to their investigation, what criteria might be used in selecting a target? As already indicated, target selection that brings greater benefit in terms of scientific advancement would be directed towards targets that are difficult to make. Another aspect already mentioned is the need for applying known chemical processes to demonstrate their generality. In the Hall laboratory there is a strong focus on the use of organo-boron chemistry to solve chemical problems. This focus has yielded a number of methodologies that have performed very well in terms of yield and selectivity on simple targets. One of our goals in selecting a target was one in which we could apply one or more of these methodologies to a larger, more challenging target. As discussed, a primary motivation for investigating natural products is their potential as a source for disease treatments. Thus, a target with interesting biological properties that might be applied to solve a pharmacological gap would also be highly desirable. To further focus the search, we wanted a target that required total synthesis in order for biological investigations to be viable. Some natural products might be very challenging, might be highly susceptible to synthesis using our methodologies and might also be extremely relevant for treatment of a particularly problematic disease. However, if these compounds could be easily and cheaply obtained by the kilogram or even on a tonne scale from the natural source they would be less satisfying as a target for total synthesis. In contrast there are natural products that can only be obtained

with utility in milligram quantities from the natural source and our ideal target would fall into this category.

In the following sections of this introductory chapter is a description of the discovery of the target we selected, palmerolide A, which indeed met all of our target criteria, followed by an overview of it in the literature. In the following chapters will be a description of the work employed in synthesizing it as well as some work directed towards analogue synthesis.

1.2 Isolation of Palmerolide A

In 2006 the research group of Professor Bill J. Baker, University of South Florida, published the structure of a bioactive compound, which they had isolated from the Antarctic tunicate *Synoicum adareanum* through their collection work based in the Palmer Research Station located on Anvers Island (64 ° 46' S, 64 ° 03') off of the Antarctic Peninsula.[4] They named the compound palmerolide A after the Palmer Station (Figure 1.1). With its five stereocentres, seven olefinic unsaturations, a carbamate unit along a 20 membered macrocyclic ring the proposed structure of palmerolide A offers a number of synthetic challenges. From a strictly stereochemical outlook, there are 2 048 possible stereoisomers and a synthesis would require very precise control in order to synthesize only one of these.



1.1

Figure 1.1 Structure of palmerolide A originally published

The exceptional property of this molecule, which is of critical interest, is its selective toxicity towards melanoma cells (LC_{50} = 18 nM for UACC-62 cell line) with three orders of magnitude greater efficacy towards melanoma than

towards other cell lines in the National Cancer Institute's (NCI) 60 cell line panel. Melanoma is a particularly lethal type of cancer for which there is a low plurality of treatment options. In the United States melanoma incidence increased rapidly during the 1970's at an approximate annual rate of 6% and continued to increase subsequently at a rate of approximately 3%.[5] It also represents a significant problem in Canada where in 2010 it represented 3% of all new cancer cases and was the 7th most common type of cancer.[6] In terms of treatment the only known effective treatment until recently has been early surgical removal. If the depth of a melanoma tumour exceeded 1.5 mm the chances of survival plummeted dramatically where late stage survival rates are measured in months.[5,7] The bleakness of the situation is exemplified when considering the efficacy of interleukin-2; previously considered one of the more promising systemic treatments for melanoma. A 2010 review of melanoma treatment options revealed that interleukin-2 treatments had response rates of ~16% and remission in only ~6% of the cases.[8] An earlier review (2008) of melanoma treatment options is illustrative in its description of the efficacy of the only FDA approved melanoma treatments of the time:

> *Even the most active cytotoxic chemotherapy agent, dacarbazine, is associated with an overall response rate (complete plus partial responses) of only approximately 20%. Dacarbazine is associated with many adverse events, including anorexia, nausea, vomiting, myelosuppression, local tissue damage caused by extravasation, and flu-like symptoms. Long-term survival without disease recurrence is attained by fewer than 10% of patients who receive dacarbazine or interleukin-2, the only other FDA-approved agent for metastatic melanoma.*[5]

More recently in March of 2011 a monoclonal antibody drug developed by Bristol-Myers Squibb, ipilimumab, was approved by the FDA for treatment of unresectable or metastatic melanoma.[9] In phase III clinical trials it was demonstrated to improve median survival rates in treated patients but albeit with low response rates and severe side effects.[10] Another recently introduced anti-

melanoma drug is the RAF (Rapidly Accelerated Fibrosarcoma) kinase inhibitor PLX4032 (vemurafinib) that was developed by Plexxikon.[11] It functions as a selective inhibitor of B-RAF mutant signalling possibly as an adenosine triphosphate-competitive inhibitor; B-RAF mutations are found in 50–60% of melanomas.[10] In a recent clinical trial this drug induced dramatic short-term tumour regression with 81% of B-RAF patients showing tumour regression. The long term effects however were less promising and on average, tumour regrowth was observed after 7 months indicating the development of drug resistance.[10] The limitations of these drugs as standalone therapies might be partially addressed via combined drug therapies[12] but this would certainly be enhanced by other options. Thus the dearth of effective chemotherapeutics for this cancer make the prospect of a highly melanoma-selective cytotoxic natural product an important possible target for total synthesis.

Palmerolide A is a challenging target with compelling biological properties, but what about its availability? Palmerolide A was isolated in milligram quantities from a marine antarctic invertebrate. Even if it were possible to obtain significant quantities of palmerolide A from this fragile ecosystem, it is prohibited by the Antarctic Treaty,[13] thus finalizing the need for accessing the natural product via total synthesis.

1.3 An Overview of Palmerolide A in the Literature

The goal of this overview is to survey the synthetic work that has been carried out on palmerolide A with a focus on the key transformations, the source of stereochemical control and the efficiency of the various approaches. Also highlighted will be any new chemistry encountered. In addition to the central concentration on synthesis an important paper on the biosynthesis of palmerolide A will be considered.

1.3.1 Total Syntheses

1.3.1.1 The De Brabander Synthesis

The first total synthesis of the structure of palmerolide A, as it was published by the Baker group, was executed by the group of Professor Jef K. De Brabander at the University of Texas.[14] Their retrosynthetic approach divides the molecule into three pieces for assembly of the core structure (Figure 1.2). Segment **1.2** was envisioned to incorporate esterification chemistry (Yamaguchi's method) to join it to segment **1.4** and a Horner-Wadsworth-Emmons (HWE) reaction to unite it with segment **1.3**. In turn, they planned to combine segment **1.3** with segment **1.4** via some type of metal catalyzed cross coupling. Ultimately they used a Suzuki-Miyaura reaction with a pinacol boronate on fragment **1.3** to join these pieces. The final elaboration of the enamide arm of the target was planned and realized through reaction of Grignard reagent **1.5** with isocyanate intermediate **1.6** originating from a Curtius rearrangement.

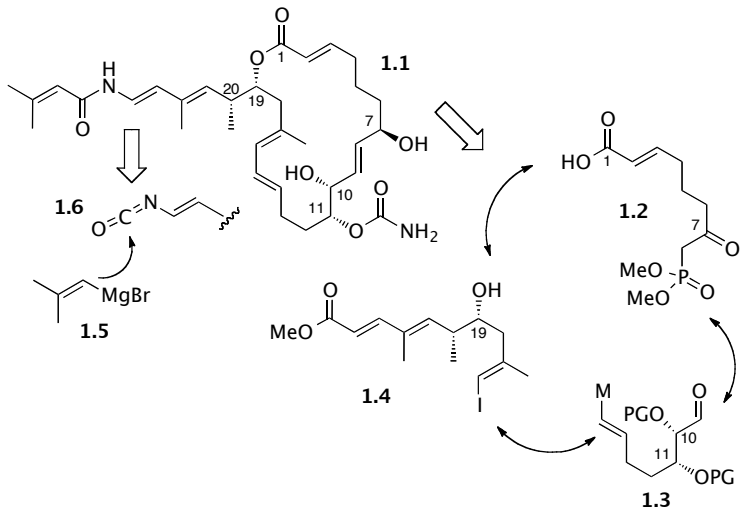


Figure 1.2 De Brabander's retrosynthetic plan

The stereocentre at C7 was attained in the synthesis through Corey-Bakshi-Shibata stereoselective reduction with a diastereoselectivity of 4:1. The origin of the asymmetry found in the C10-C11 diol of **1.3** came from the chiral

pool (derived from D-arabitol). A vinylogous Mukaiyama aldol addition was employed in constructing the C19-C20 *syn*-propionate unit with a diastereomeric ratio (dr) of 13:1. Thus the chirality attained there was by means of an Evans chiral auxiliary approach.

Assembly of the three fragments and final synthesis of the target was achieved in a longest linear sequence of 23 steps and 3% overall yield. This represents an efficiency of 86% yield per step in the longest linear sequence. Unfortunately, at this juncture De Brabander and co-workers found that the NMR data of compound **1.1** did not match the NMR data published by Baker for natural, isolated palmerolide A. The De Brabander group was quite confident that they had synthesized the originally proposed structure based on Mosher analysis of the C7 alcohol, the already established stereochemistry of D-arabitol and an X-ray structure of an intermediate containing the C19–C20 *syn*-propionate unit. Relying on the absolute stereochemical assignment of C7 and C10 by Baker but questioning the relative stereochemistry between C11 and C19 they postulated that natural palmerolide A actually comprised the structure of diastereomer **1.7** (Figure 1.3). Fortunately their synthetic route required little modification in order to obtain the new target. This could be accessed by synthesizing the enantiomer of fragment **1.4** that in turn could be accessed via their original route with the enantiomer of the chiral auxiliary that had originally employed. After carrying out a second synthesis following the same route they were gratified to find that **1.7** was indistinguishable from isolated palmerolide A in terms of its NMR spectra, TLC and analytical HPLC behavior.

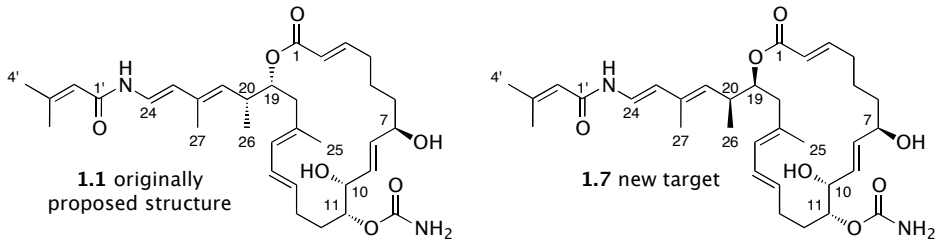


Figure 1.3 Originally proposed structure and new diastereomer proposed

However, in comparing circular dichroism spectra of their synthesized product and that of natural palmerolide A they discovered that they were mirror images of each other. This led them to conclude that the compound that they had synthesized **1.7** was actually the enantiomer of the natural product thus assigning the absolute structure of (–)-palmerolide A as **1.8** (Figure 1.4).

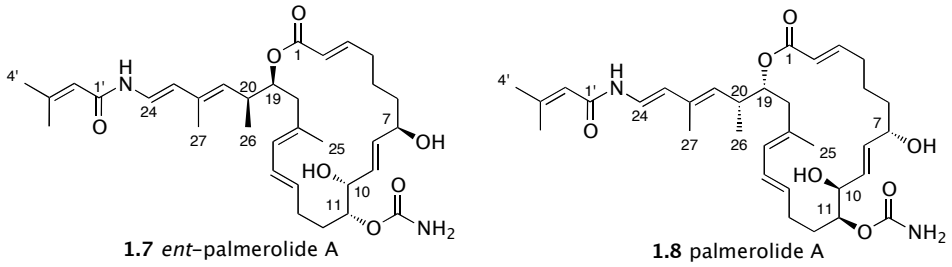


Figure 1.4 Natural palmerolide A and its enantiomer

1.3.1.2 The Chen–Nicolaou Synthesis

The second total synthesis of palmerolide A was published by the research group of Professor David Y.-K. Chen based out of the lab of Professor K. C. Nicolaou at the Institute of Chemical and Engineering Sciences in Singapore.[15]

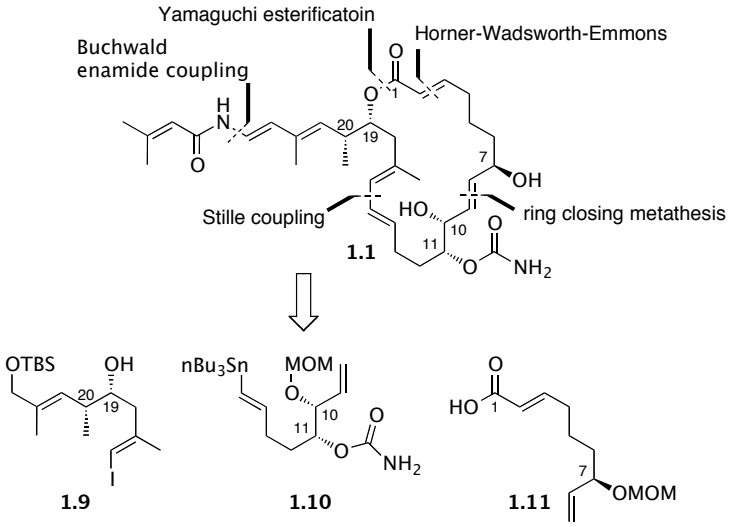


Figure 1.5 The Chen–Nicolaou retrosynthesis

As is evident in their retrosynthetic plan (Figure 1.5) Chen-Nicolaou had been targeting the originally published diastereomer **1.1** of palmerolide A. The plan is fairly convergent breaking the core ring structure into three pieces. Alkenyl iodide **1.9** was designed so that it could be joined to alkenyl tributyltin **1.10** by Stille coupling. The C19 alcohol would also serve as a handle for coupling to acid **1.11**. The terminal alkenes on **1.10** and **1.11** would also serve as functional handles for joining those fragments via cross metathesis. The final component of the plan was to complete the enamide arm via Buchwald copper catalyzed enamide coupling.[16]

Similar to the De Brabander synthesis, the chirality in the C19–C20 *syn*-propionate unit was derived stoichiometrically via Evans aldol chemistry, in this case with a diastereomeric excess (de) of >95%. Additional flexibility was demonstrated in their approach to this fragment with the optimization of two different isomers with both *syn* and *anti* stereochemistry. The stereocontrol in the synthesis of diol fragment **1.10** was the result of induction by an isopinocamphylborane auxiliary in a Brown crotylboration reaction.[17] The authors report an enantiomeric excess (ee) of 90% and a de of >95%. The asymmetric component of acid **1.11** was achieved via a Jacobsen hydrolytic kinetic resolution of an epoxide precursor and produced an ee of >99%.[18]

The total synthesis of target **1.1** was completed in a longest linear sequence of 17 steps and 9% overall yield with an efficiency of 87% per step. The efficiency in this case is very comparable to the 86% average per step obtained in De Brabander's synthesis but this route is much more convergent.

Like the De Brabander group, Chen and co-workers realized after synthesizing **1.1** that they had not synthesized the natural product through comparative analysis of the ^{1}H NMR data. Also like the De Brabander group they next targeted the diastereomer **1.7** whose synthesis they undertook and completed. Upon learning about the revision published by De Brabander and co-workers, the Chen-Nicolaou group then employed their route to synthesize structure **1.8** whose spectral data matched that published for natural palmerolide A.

A further substantiation of the absolute and relative stereochemistry of palmerolide A was published by Baker. In this publication the stereochemistry of the natural product was revised to that of **1.8** by means of a degradation study and re-evaluation of some of the originally published data.[19]

1.3.1.3 The Hall Synthesis

The third and final total synthesis (to date) of palmerolide A published was carried out in the research group of Professor Dennis Hall.[20] This synthetic work is the subject of this thesis and will be described in detail in Chapters 2–4.

1.3.2 Formal Syntheses

1.3.2.1 The Maier Formal Synthesis

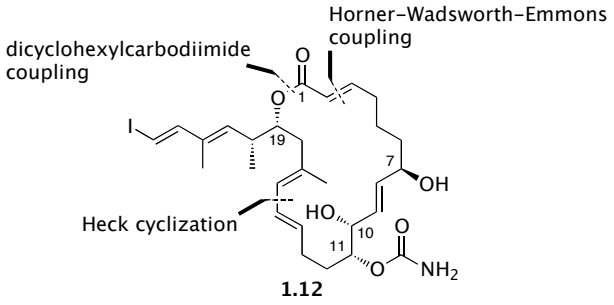


Figure 1.6 Maier's key disconnections

Julia Jägel and Professor Martin E. Maier (Institut für Organische Chemie, Universität Tübingen) published the first formal synthesis of palmerolide A.[21] Their synthetic work culminated in alkenyl iodide **1.12** (Figure 1.1), an advanced intermediate of the Chen synthesis.[15] Two key disconnections in their synthesis are a dicyclohexylcarbodiimide (DCC) promoted esterification and a Horner-Wadsworth-Emmons coupling reaction that assembled the core carbon framework of the natural product. The macrocycle was closed using Heck cyclization.

Noyori transfer hydrogenation[22] performed on an yne-one intermediate (98% ee) produced the C7 stereocentre. A Sharpless asymmetric dihydroxylation

was used to form the C10–C11 diol (no dr reported). Similar to the De Brabander and Chen-Nicolaou total syntheses, the *syn*-propionate unit was accessed via Evan's chiral enolate chemistry (no ee reported).

The synthesis of **1.12** was made in a longest linear sequence of 26 steps an overall yield of 1.9% and efficiency of 86% per step. This formal synthesis is competitive in terms of step efficiency and used a different ring closing approach but lacks the convergence of either the Chen-Nicolaou or the De Brabander total syntheses.

1.3.2.2 The Kaliappan Formal Synthesis

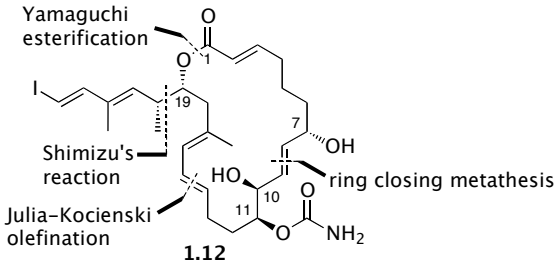


Figure 1.7 Kaliappan's key disconnections

The second of the two formal syntheses of palmerolide A published to date is that of Parthasarathy Gowrisankar, Sandip A. Pujari and Professor Krishna P. Kaliappan (Indian Institute of Technology, Bombay).[23] This formal synthesis also terminates with Chen and Nicolaou's alkenyl iodide intermediate **1.12** (Figure 1.7). Two of the key steps in this synthesis are shared with the Chen-Nicolaou synthesis. These are a Yamaguchi esterification to connect C1 to the C19 hydroxyl and a ring closing metathesis reaction between C8 and C9. One unique approach is the use of Julia-Kociensky olefination to complete the C14–C17 ring diene.

The stereochemistry at C7 was attained via a Sharpless kinetic epoxide resolution in 95% ee.[24] Like the Maier formal synthesis Sharpless asymmetric dihydroxylation provided the C10–C11 diol (88% ee). Distinct from the syntheses of De Brabander, Chen-Nicolaou and Maier, the C19–C20 syn-

propionate unit was not accessed via an Evan's chiral auxiliary aldol reaction. In this case, Shimizu's catalytic stereoselective epoxide opening chemistry was employed.[25] The asymmetric epoxide in turn was accessed through Sharpless chemistry (90% ee).[26]

Kaliappan's formal synthesis was completed in a longest linear sequence of 24 steps, an overall yield of 0.87% and an efficiency of 82% per step. One unique aspect of this synthetic work is that all stereocentres were derived catalytically (from the seminal reactions of Barry K. Sharpless) with no reliance on chiral auxiliaries or the chiral pool. The overall yield and step efficiency however, do not compare favourably.

1.3.3 Fragmentary Syntheses

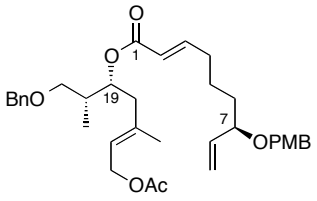
At the time of the writing of this thesis seven fragmentary syntheses of palmerolide A had been published. For the sake of brevity they will not be considered in the same detail as the total and formal syntheses. Below is a table (**Table 1.1: Sources of stereocentres and synthetic efficiency**

Synthesis	C7	C10–C11	C19–C20	Mass %	Step Eff.	Yield Eff.
	Methodology + Selectivity	Methodology + Selectivity	Methodology + Selectivity			
Kaliappan[27]	CA 95% de	NA NA	C+SC 92% de	50	2.6	78%
Maier[28]	CT 98% ee	CT NR	CA NR	67	2.7	80%
Chandrasekhar[29]	CT 97% de	CT 96%ee	NA NA	46	3.3	84%
Cossy[30]	C NA	C+CT 90% de	CA 90% de	67	2.6	82%
Baker[31]	C NA	C NA	C NA	36	2.4	66%
Dudley[32]	CT 50% de	CT >99% ee	NA NA	46	3.8	91%
Prasad[33]	K/C NA	K/C NA	NA NA	61	2.8	85%

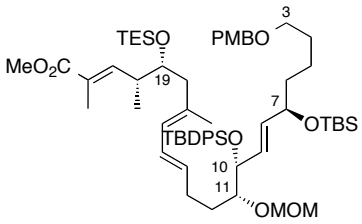
C = commercially available; CA = chiral auxiliary; CT = catalysis; K = known from the literature; NA = not applicable; NR = not reported; SC = substrate control

) summarizing the results of the fragment syntheses. The content of the table is limited to a presentation of the sources of chirality for the stereocentres as well as

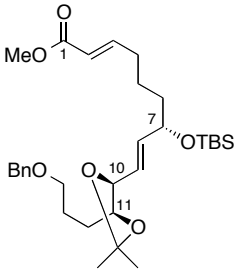
a numerical analysis of the efficiency of each synthesis. The Mass% column represents the percentage of the palmerolide A structure that was attained. For example the Kaliappan partial synthesis attained 50% of the molecular weight of the atoms found in palmerolide A. This calculation is based on the reported yields and does not account for deficiencies in the stereochemical efficiency of the transformations. The Step Efficiency column represents the number of steps needed to achieve the Mass% (Step Eff. = Mass% / Steps). Continuing with Kaliappan this signifies that 19 steps were needed to attain 50% of target. The Yield Efficiency column represents the average yield for every chemical step used in the synthesis.



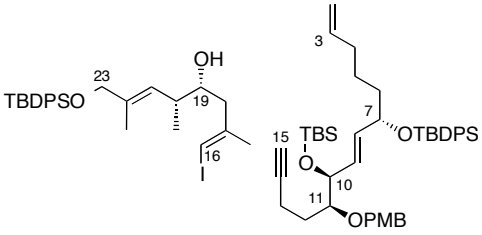
Kaliappian's fragment



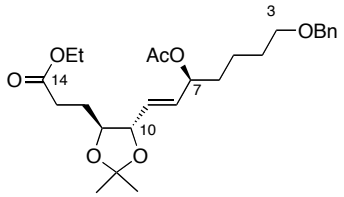
Maier's fragment



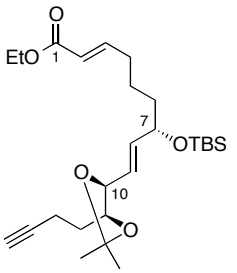
Chandrasekhar's fragment



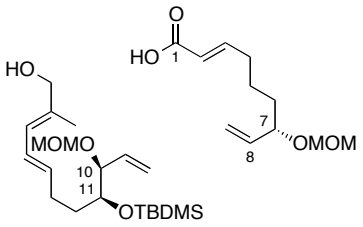
Cossy's fragments



Baker's fragment



Dudley's fragment



Prasad's fragments

Figure 1.8 Fragmentary synthesis final products

Table 1.1: Sources of stereocentres and synthetic efficiency

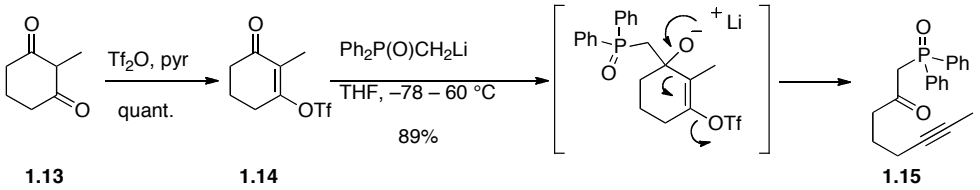
Synthesis	C7	C10–C11	C19–C20	Mass %	Step Eff.	Yield Eff.
	Methodology + Selectivity	Methodology + Selectivity	Methodology + Selectivity			
Kaliappan[27]	CA 95% de	NA NA	C+SC 92% de	50	2.6	78%
Maier[28]	CT 98% ee	CT NR	CA NR	67	2.7	80%
Chandrasekhar[29]	CT 97% de	CT 96%ee	NA NA	46	3.3	84%
Cossy[30]	C NA	C+CT 90% de	CA 90% de	67	2.6	82%
Baker[31]	C NA	C NA	C NA	36	2.4	66%
Dudley[32]	CT 50% de	CT >99% ee	NA NA	46	3.8	91%
Prasad[33]	K/C NA	K/C NA	NA NA	61	2.8	85%

C = commercially available; CA = chiral auxiliary; CT = catalysis; K = known from the literature; NA = not applicable; NR = not reported; SC = substrate control

The fragment syntheses are presented in chronological order. There is no simple organizing principle to present them either quantitatively or qualitatively. Kaliappan's synthesis uses a combination of chiral auxiliary, chiral pool and substrate control to achieve excellent stereoselection. However, this partial synthesis does not compare favourably in terms of step or yield efficiency. Maier's partial synthesis is very comparable in terms of efficiency but is more advanced in Mass% and also uses catalysis for C7. Chandrasekhar uses only catalytic methods and has the second best performance in terms of efficiency. Cossy uses a mix of commercially available chirality, chiral auxiliaries and catalysis with excellent stereoselectivity. Cossy has also attained equal Mass% to Maier with slightly better yield efficiency but marginally poorer step efficiency. Baker's partial synthesis appears to be the worst in all parameters. However, since the synthesis relies on bioavailable commercial starting materials it is possible that it could outstrip the other methods in economic terms. Prasad's partial synthesis resembles that of Baker by relying on commercially available (chiral pool) sources of chirality and is also lower on the step efficiency hierarchy.

As a general comment, choosing pre-existing chiral sources for a synthesis is probably conducive to a route that must contain extra steps to adapt the starting materials to the targets.

In author's estimation the best partial synthesis in the group is that of Dudley, who has the best step and yield efficiency and uses all catalytic methods to set stereocentres. The one sour step is the poor stereoinduction for the C7 stereocentre (50% de). The authors even note some surprise at this in the paper since the same methodology (CBS reduction) was used effectively for the same stereocentre by other groups. Dudley's partial synthesis makes a unique contribution compared to the other syntheses (total, formal and fragmentary) that the author believes is key to its superiority. Dudley makes use of a methodology developed in his group and applies it to this synthesis (Scheme 1.1).[34]



Scheme 1.1 Claisen type addition/cleavage reaction

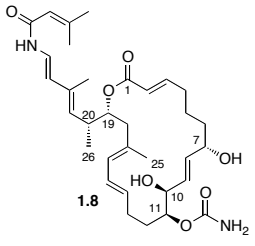
This methodology involves formation of a vinylogous acyl triflate (**1.14**) from 2-methyl-1,3-cyclohexanedione (**1.13**), whose condensation-fragmentation is triggered by a nucleophilic attack. In this particular instance a lithiated methyl phosphine oxide was employed as a nucleophile producing alkyne **1.15** in 89% yield. In one step a useful synthetic intermediate with three functional handles has been made from a commercially available starting material. This work exemplifies our goal of making a contribution testing and demonstrating the utility of reaction methodologies developed in our group.[35]

1.3.4 Analogue Syntheses and Biological Evaluation

Following the publication of their total synthesis of palmerolide A the Chen-Nicolaou group published a full paper in which they applied their synthetic strategy to the synthesis of several analogues for biological testing.[36] This was followed several months later by another paper with an even larger array of analogues and results from the biological testing of these and earlier analogues.[35] Note that tables with the full results of this study are found in Appendix A. The GI_{50} index which was used to evaluate the potency of these different compounds was a measurement of a drug concentration which causes a 50% decrease in protein production of treated cells compared to control cells (48 hour time period). Each reported value represents the mean of 2–5 experiments.

A key aspect learned from these studies was the importance of the stereochemistry of palmerolide A. In a series of analogues in which stereocentres differ from the natural product, biological activity is severely diminished or completely lost (Table 1.2). Note in particular that the originally published structure **1.1** and the subsequently targeted enantiomer **1.7** (*ent*-**1.8**) are more than a 100 fold less active than the natural product **1.8**.

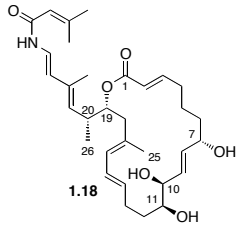
Table 1.2: GI_{50} against melanoma cell line (UACC-62) of stereoisomers

	Entry	Cmpd	Identity	GI_{50} (μM)
	1	**1.8**	Natural palmerolide A	0.057
	2	**1.8**	Synthetic palmerolide A	0.062
	3	**1.1**	7-*epi*-10-*epi*-11-*epi*-**1.8**	>10
	4	**1.7**	*ent*-**1.8**	8.077
	5	**1.16**	7-*epi*-10-*epi*-11-*epi*-19-*epi*-**1.8**	5.398
	6	**1.17**	7-*epi*-10-*epi*-11-*epi*-20-*epi*-**1.8**	8.129

During the course of their syntheses the Chen-Nicolaou group found that one of the side products was a decarbamylated analogue of palmerolide A (Entry

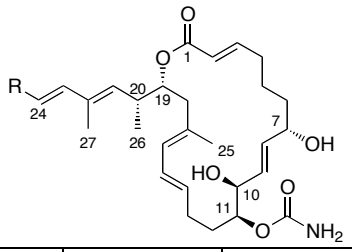
4: **1.18**, Table 1.3). By isolating **1.18** as well as decarbamylated stereoisomers **1.19–1.21** they were also able to gauge the importance of the carbamate group. The decarbamylated natural product **1.18** had a five-fold loss of activity. The decarbamylated stereoisomers showed either a 100 fold less or complete loss of activity. Thus the carbamate group was determined to be critical to the nanomolar activity of palmerolide A.

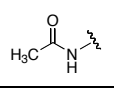
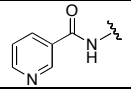
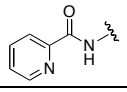
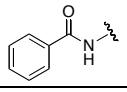
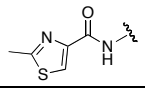
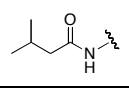
Table 1.3: GI_{50} against melanoma cell line (UACC-62) of decarbamylated analogues

	Entry	Cmpd	Identity	GI_{50} (μM)
	1	**1.8**	Natural palmerolide A	0.057
	2	**1.8**	Synthetic palmerolide A	0.062
	3	**1.18**	Decarbamylated palmerolide A	0.322
	4	**1.19**	*ent*-**1.18**	8.768
	5	**1.20**	7-*epi*-10-*epi*-11-*epi*-19-*epi*-**1.18**	>10
	6	**1.21**	7-*epi*-10-*epi*-11-*epi*-20-*epi*-**1.18**	>10

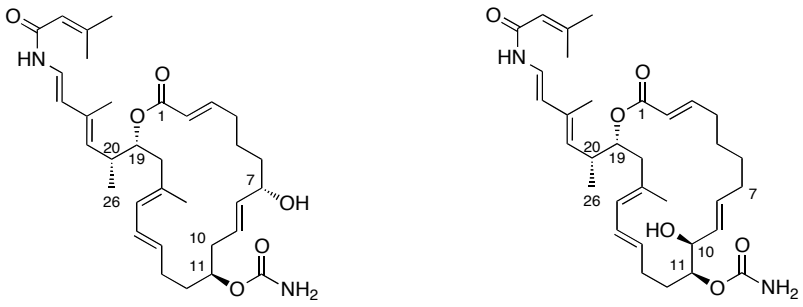
Based on earlier work that revealed a class of V-ATPase inhibitors in which an enamide moiety was important for activity[37,38] Chen and co-workers exploited the enamide coupling chemistry they had already utilised to synthesize another series of analogues (Table 1.4)[35]. Replacement of the isopropene group with a methyl resulted in a dramatic loss of activity (entry 1) but hetero-aromatic groups (entries 2,3 and 5) retained some activity. Note however that the smaller ring sized thiazole analogue (**1.26**) was an order of magnitude lower in potency relative to the six membered ring analogues. Remarkably, replacement of the isopropene group with a simple benzene ring (entry 4) actually increased the inhibitory potency relative to the natural product (9 nM compared to 62 nM). Replacement of the isopropene with its saturated counterpart (entry 6) did not result in any significant reduction of inhibition (67 nM vs. 62 nM).

Table 1.4: GI_{50} against melanoma cell line (UACC-62): enamide analogues



Entry	1	2	3	4	5	6
Compd.	**1.22**	**1.23**	**1.24**	**1.25**	**1.26**	**1.27**
R						
GI_{50} (μM)	>10	0.641	0.735	0.009	8.822	0.067

Two additional analogues that provide some important information are **1.28** and **1.29** (Figure 1.9) whose C10 and C7 hydroxyls have been deleted. Loss of the C10 hydroxyl resulted in over a 100-fold decrease in activity whereas the C7 loss had no significant impact (63 vs 62 nM).



1.28
GI_{50} = 6.979 μM

1.29
GI_{50} = 0.063 μM

Figure 1.9: Analogues with hydroxyl deletions

Thus, the testing of analogues carried out in this publication has highlighted the importance of palmerolide A's stereochemistry as well as its carbamate group and shown potential for more analogue design with respect to the also critical enamide unit and potential simplification of synthesis with respect to the C7 region.

Two years subsequent to their first analogue testing paper the Chen[1] group published a study containing the biological evaluation of a series of second-generation analogues.[39] To further evaluate the importance of the enamide moiety, aldehyde **1.30** and α,β-unsaturated methyl ester **1.31** were obtained (Figure 1.10).

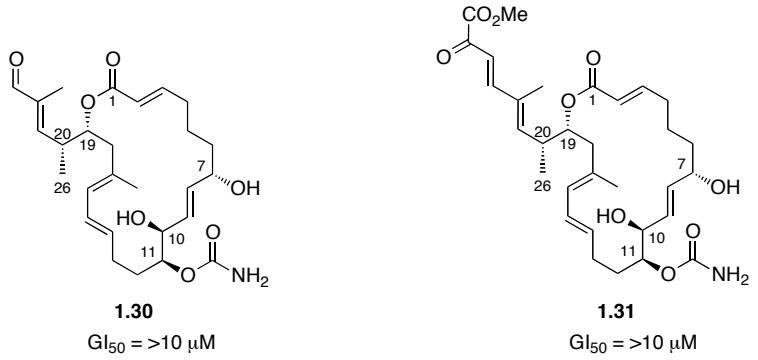


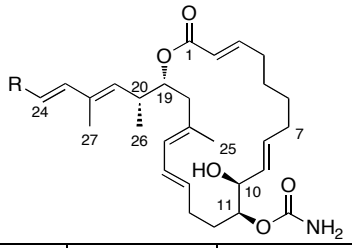
Figure 1.10: Analogues with enamide deletions

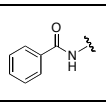
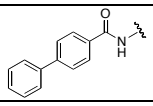
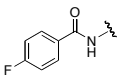
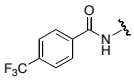
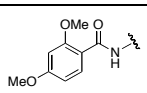
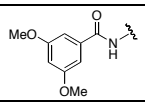
As in the previous study the analogues deprived of an enamide group lost the potent anticancer activity found in the natural product. This is consonant with a publication by De Brabander and co-workers in which they evaluate the biological activity of another V-ATPase inhibitor containing an enamide moiety.[38]

In their previous study Chen and co-workers learned that an analogue with a benzamide substitution (**1.25**) was more potent than natural palmerolide A (GI_{50} of 9 nM vs 62 nM). They also noticed that removal of the C7 hydroxyl group of analogue **1.29** did not greatly impact biological activity (GI_{50} of 63 nM vs 62 nM). Based on this information they decided to test a series of analogues with no C7 hydroxyl group and vary the benzamide moiety (**Table 1.5**).

[1] Professor K. C. Nicoloau's name did not appear on this publication.

Table 1.5: GI_{50} against melanoma cell line (UACC-62): C7 hydroxyl deletion enamide analogues



Entry	1	2	3	4	5	6
Compd.	**1.32**	**1.33**	**1.34**	**1.35**	**1.36**	**1.37**
R						
GI_{50} (μM)	0.055	5.823	0.227	0.822	9.026	0.753

The series of benzamide analogues reveals that the simple benzamide (entry 1) has the superior activity (cf. entries 2–6). Steric factors apparently outweigh any benefit that might be gained by extra lipophilicity or electron withdrawal or donation. Although the C7 hydroxyl was deemed dispensable the benzamide analogue without it is six times less potent than the one with it (0.055 μM vs 0.009 μM). A comparison of methoxy-substituted **1.36** and **1.37** does possibly indicate an electronic effect. Electron donation from the *ortho* and *para* positions on analogue **1.36** might be responsible for its greater than ten fold loss of growth inhibition. Chen refers to De Brabander's work with salicylihalimide inhibition of V-ATPase for a rationale.[38] De Brabander proposed an iminium species (Figure 1.11 A) as the active form of the enamide inhibitor facilitating attack by the substrate protein. However, if the enamide nitrogen were protonated then it would be hindered from following this pathway. Chen suggests that the *ortho*/*para* methoxy-substituted analogue would shift the equilibrium towards this protonated form by reduction in amide character of the C–N bond through donation of electron density from the aromatic ring to the carbonyl of the amide (Figure 1.10 B).

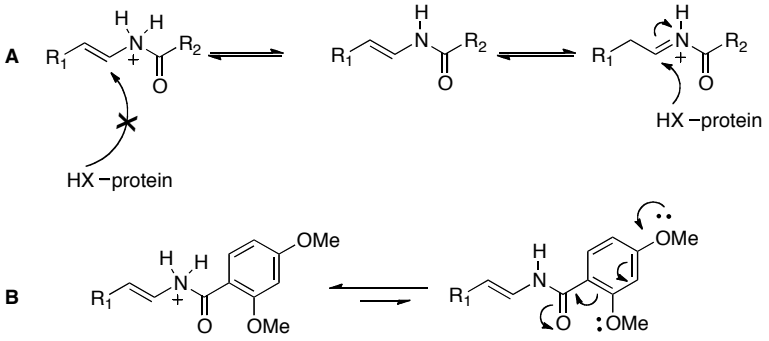
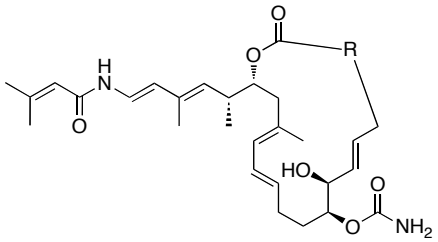


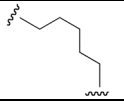
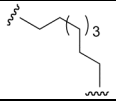
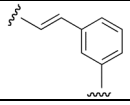
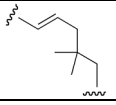
Figure 1.11 Rationale for effect of protonation on enamide inhibition

Another idea generated by the hydroxyl deletion tests was that the C7 region of the ring might be modified without loss of activity. To this end a number of analogues were synthesized in which the carbon framework in the C2–C7 region was modified (Table 1.6). The simplest analogue featured the removal the unsaturation of the C2–C3 in analogue **1.38**. There was also an analogue with an expanded ring **1.39** and ones where ring flexibility was hampered by incorporation of an aromatic ring **1.40** or addition of steric bulk **1.41**.

These modifications of the ring in the C2–C7 region indicate that this region of the molecule is very sensitive to tampering with. Thus a greater than ten fold loss of activity occurs simply by removing the unsaturation and an order of magnitude greater loss for more significant changes.

Table 1.6: GI_{50} against melanoma cell line (UACC-62): C7 hydroxyl deletion enamide analogues



Entry	1	2	3	4
Compd.	**1.38**	**1.39**	**1.40**	**1.41**
R				
GI_{50} (μM)	0.750	6.857	4.958	>10

One additional insight gained from this study should be mentioned (cf. Appendix A for full data set). Control studies measuring the GI_{50} of the analogues were also directed towards normal melanocytes and this allowed the calculation of a selectivity index. Not only do palmerolide A and its most potent analogues inhibit the growth of melanoma at nanomolar concentrations, they also do so with 25–64 times greater selectivity than Taxol and 126–321 times greater selectivity than doxorubicin. This higher selectivity is an additional reason to continue studying palmerolide A in terms of its potential as a therapeutic for melanoma.

1.3.5 Biosynthetic Investigation

In 2008 a palmerolide A paper was published that differed significantly from other papers that had been published concerning this natural product. Therein, Professor Bill Baker, Professor Alison Murray and Christian Riesenfeld undertook a preliminary study to probe the possible biosynthetic origins of palmerolide A.[40] They hypothesized based on the structure that palmerolide A might originate via a hybrid polyketide synthase (PKS)/nonribosomal peptide synthetase (NRPS) pathway in bacteria.

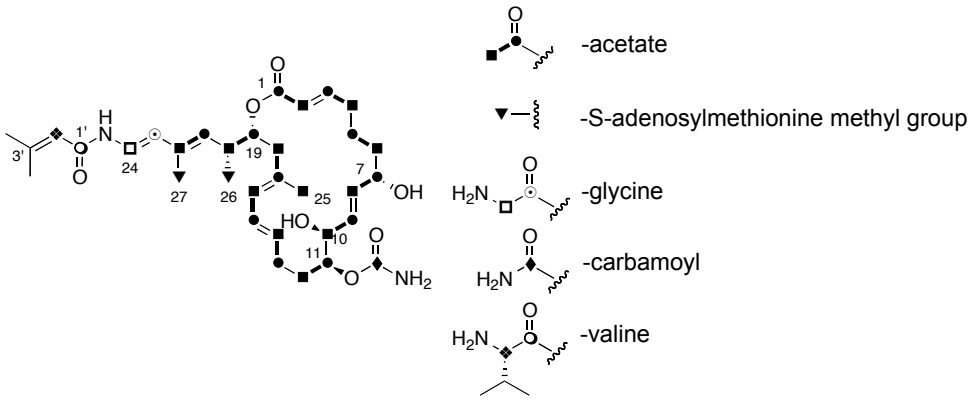


Figure 1.12 Possible biosynthetic origin of palmerolide A

They proposed that the biosynthesis would begin with NRPS-catalyzed ligation of valine and glycine units making up the first part of palmerolide A's enamide arm

(Figure 1.12). Then the carbon backbone of the macrocyclic component would be synthesized by a series of PKS catalyzed steps. They envisioned that most of the carbon would be coming from acetyl CoA units but also some methylation from *S*-adenosylmethionine. They suggested that the carbamate addition would possibly proceed via the same mechanism that has been observed for geldanamycin.[41,42]

The authors spent some time discussing the challenges involved in identifying and benefiting from marine micro-organisms that produce natural products of interest. The focus here is symbiotic bacteria that colonize marine invertebrates such as *S. adareanum*. Bacteria such as these are often difficult to isolate as pure cultures making it difficult to know precisely which strain is actually producing the natural product. In addition the inability to grow a pure culture of the natural product producing bacteria hinders the use of these bacteria for obtaining the product. To get an idea for how challenging this problem is, the following quotation is revealing:

> *Present-day biotechnology programs are based on the observation that almost 99% of the microbiota is reluctant to be cultured under laboratory conditions.*[43]

Given this challenge the authors propose an alternative metagenomic approach in which fragments of DNA are cloned and characterized in the hopes that biosynthetic genes can be identified and exploited.

Their first metagenomic approach was to make 16S rRNA libraries from *S. adareanum* extracts and upon sequencing, search for homology with known bacterial species. This informed them that the *S. adareanum* sample they used contained genetic material from known pure culture isolates such as *Pseudovibrio ascidiaceicola, Microbulbifer maritimus*, and *Polaribacter glomeratus*. In addition to these known bacterial strains there were sequences with homology to bacterial strains, which have resisted cultivation (eg. TM7) and are only known from environmentally sampled sequences. However, tentative identification of known species could facilitate isolation and culturing since known culturing

conditions could be applied. For instance the authors cite marine agar as a known medium for growing *Microbulbifer* lineages.[44,45]

A second metagenomic approach employed by the authors was an attempt to identify PKS ketosynthase genes that might be part of the biosynthetic machinery utilized to synthesize palmerolide A. In this instance they used PCR primers for conserved regions of ketosynthase domains for type I PKS to amplify DNA from their *S. adareanum* extracts. From this effort they identified an ~700 base pair fragment that was sequenced. A homology search revealed sequence similarity to bacterial type I PKS enzymes that are known to function during the synthesis of natural products. The authors suggest very tentatively that there could be correspondence between the *Microbulbifer*-like strains in *S. adareanum* and the ketosynthase used in palmerolide A but emphasize that this is far from definite. They offer that one way to gain more secure evidence would be to clone and sequence a larger DNA fragment that would include multiple domains.

This publication is unique among all concerning palmerolide A as it addresses the biosynthesis of the natural product. The microbial community of one *S. adareanum* sample has been characterized but this needs to be expanded in order to determine which microbes generally inhabit this invertebrate. The information derived regarding these communities could be helpful for finding the right conditions to culture a pure strain of the organism that produces palmerolide A. Some preliminary work has also been done on identifying a possible PKS gene used for the biosynthesis.

1.4 Conclusion

As seen in this literature review there has been a great deal of research activity devoted to palmerolide A, particularly in synthetic activity. Thus our target selection criteria appear to find resonance with the criteria of other synthetic chemists. The value of total synthesis was demonstrated early on in the process with the classical phenomenon of structural revision. De Brabander's synthetic work has enabled all who follow to know the actual structure of

palmerolide A. The synthetic work of the Chen-Nicolaou group in conjunction with their biological testing has also shown how important the correct stereochemistry is for the biological activity of this natural product. Noteworthy is the predominant use of classical stoichiometric asymmetric reaction methodologies such as Evan's aldol chemistry to set stereochemistry or the use of the chiral pool. While this approach has been used to great effect in completing total syntheses of palmerolide A, it does not address our criterion of expanding the scope of newer methodologies leaving room for other approaches to the synthesis of palmerolide A.

1.5 Research Objectives

The primary research objective guiding the work of this thesis was to apply Hall group methodologies towards the synthesis of a natural product such as palmerolide A based on it meeting the following criteria: 1) significant biological properties; 2) inaccessible in sufficient quantities from the natural source 3) challenging synthetic problems particularly stereochemical ones for which our methodologies could be useful. A corollary to the primary objective was developing a synthetic route to palmerolide A that would allow expansion and/or demonstration of the scope of the key methodologies employed. Another major research objective was designing and optimizing a synthetic route to the natural product as well as analogues that could provide materials for biological testing. Ideally the synthetic route would allow the synthesis of analogues that are less accessible via other approaches to palmerolide A.

Chapter Two: Synthesis of the Eastern Hemisphere

2.1 Synthetic Strategy

2.1.1 Retrosynthetic Approach

As previously discussed, palmerolide A met our target criteria in terms of its unique structural features, potent biological activity and limited accessibility. The retrosynthetic disconnections depicted in Figure 2.1 reveal our preliminary approach to its synthesis. It is important to note that our work began in 2006, the year the original structure (**1.1**) was published, and this is reflected in the preliminary approach.

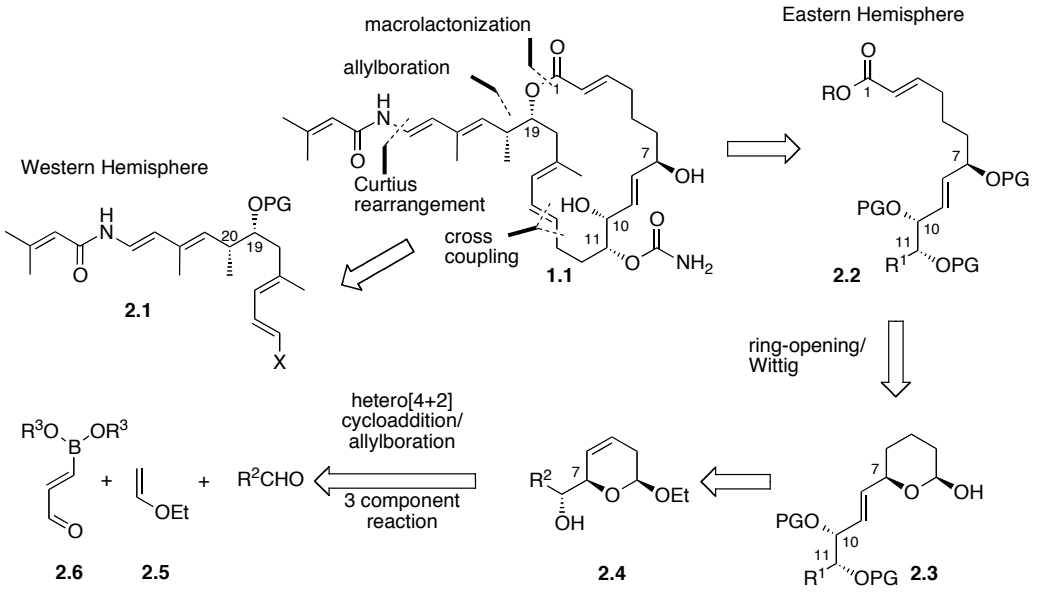
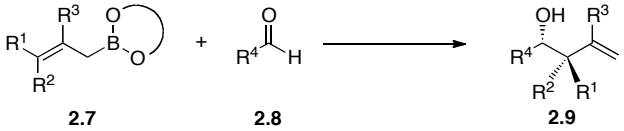


Figure 2.1 Retrosynthetic approach to palmerolide A

Similar to the De Brabander group[46] we envisioned that the amide component of the dienamide arm of palmerolide A would come from a Curtius rearrangement. One of the more obvious methods for closing the ring was some type of macrolactonization but other means were not ruled out at this stage. Another area of design flexibility was envisioned for the diene unit within the ring where some type of cross coupling might be employed (eg. olefin metathesis or Suzuki-Miyaura coupling).

By 2006 our group had published 26 research papers on the subject of allylboration, and employment of such a strategy seemed natural for constructing the *syn* propionate unit centred on C19 and C20. In particular we envisioned the application of methodologies developed for stereo-controlled addition of allyl/crotyl-boronates to aldehydes that were published by former group members Hugo Lachance[47,48] and Vivek Rauniyar (Equation 2.1).[49,50] During the synthesis this approach was directed towards synthon **2.1** that came to be referred to as the "Western Hemisphere." This work will be elaborated in Chapter 3.



2.7 **2.8** **2.9**

Equation 2.1

The project, however, was initiated with a focus on synthesizing the Eastern Hemisphere (**2.2**). The stereocentres found in the Eastern Hemisphere were to originate in a three-component one pot reaction that had been developed by my predecessor in the Hall group, Dr. Xuri Gao.[51] This three component reaction, discussed in the next section, gives access to α-hydroxyalkylated dihydropyrans such as **2.4** in an enantioselective fashion. Thus the C7 stereocentre of the natural product would be defined and the C8 hydroxyl group might be used for further stereoselective functionalization leading to an intermediate such as **2.3** containing all of the stereocentres of the Eastern Hemisphere. A tandem ring opening Wittig reaction might then be employed on the latent aldehyde contained in the ring giving access to the complete carbon skeleton of the Eastern Hemisphere **2.2**.

2.1.2 Three-Component Hetero-Diels-Alder/Allylboration Reaction

2.1.2.1 Jacobsen's Catalyst

The foundation for Gao's work was a chiral tridentate chromium (III) catalyst (**2.10**) published in 1999 by Professor Eric N. Jacobsen and co-workers (Figure 2.2).[52]

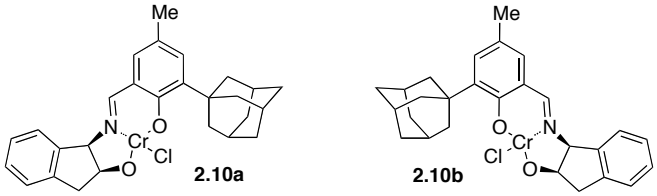
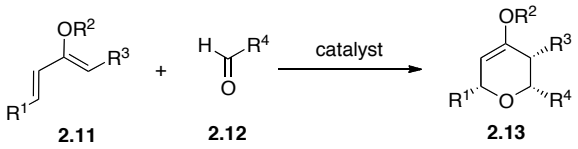


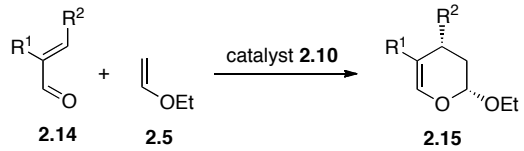
Figure 2.2 Jacobsen's tridendate Schiff base Cr (III) catalyst

The catalyst was discovered as part of a search for methods to asymmetrically catalyze hetero-Diels-Alder (HDA) reactions in systems of lower reactivity. Using catalyst **2.10** they were able to catalyze HDA reactions such as in Equation 2.2 between substituted dienes (**2.11**) and aldehydes (**2.12**) to make dihydropyrans (**2.13**) with yields in the 90's and ee's up to 99%.



Equation 2.2

Following the initial publication Jacobsen and co-workers published another paper (2002) in which the same catalyst was applied to the promotion of asymmetric inverse-electron-demand hetero-Diels-Alder (IEDHDA) reactions of the type found in Equation 2.3.[53]



Equation 2.3

In this case they reacted α/β-unsaturated aldehydes **2.14** with ethyl vinyl ether **2.5** to form dihydropyrans of type **2.15**. Once again catalyst **2.10** performed remarkably well with excellent diastereoselectivities (de >95%), enantioselectivities (89-98% ee) and yields (70-95%) for a range of substrates.

The difference between normal and inverse electron demand Diels-Alder reactions can be described using a frontier molecular orbital approach (Figure 2.3).[54,55]

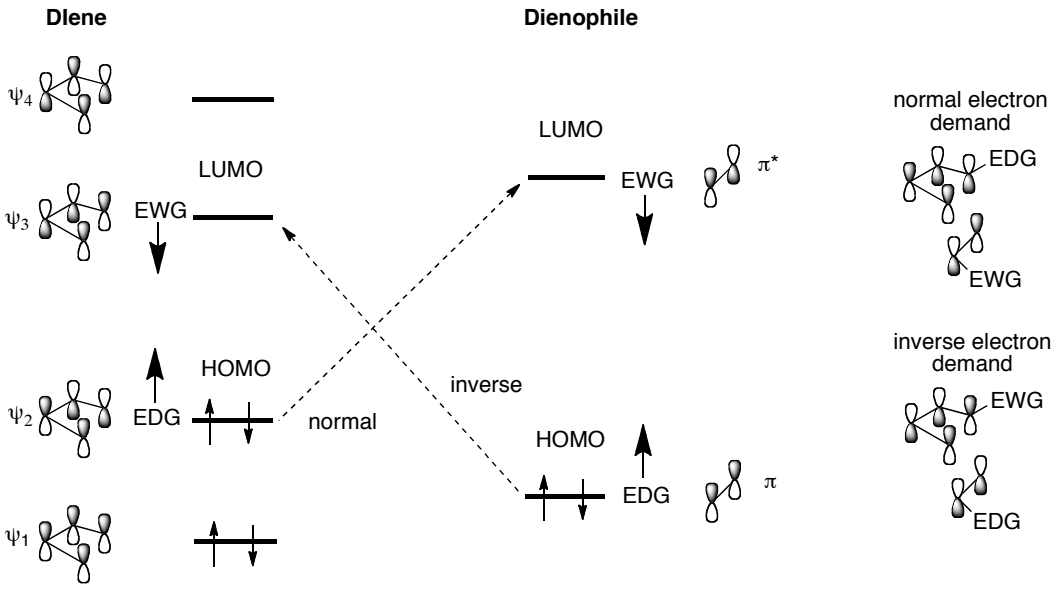


Figure 2.3 Frontier molecular orbital representation of normal and inverse electron demand Diels-Alder reactions

In normal electron demand cases the highest occupied molecular orbital (HOMO) of the diene (ψ_2) has the correct symmetry to overlap with the lowest unoccupied molecular orbital (LUMO) of the diene (π^*). This interaction is more favourable when the diene has an electron donating group (EDG) attached which raises

energy of the HOMO. Conversely when the dienophile has an electron withdrawing group (EWG) attached this lowers the energy of the LUMO favouring better orbital overlap. Inverse electron demand Diels-Alder reactions operate as the name implies in an opposite manner. In these cases the LUMO of the diene interacts with the HOMO of the dienophile and favourable overlap is enhanced by attached EWG's and EDG's respectively.

One can apply a frontier molecular orbital understanding to the work of Jacobsen and co-workers, wherein the chromium (III) catalyst acting as a Lewis acid to **2.14** lowers its LUMO energy and the ethoxy group of **2.5** acts as an EDG raising its energy (Figure 2.4). Together these features promote the reaction as an IEDHDA.

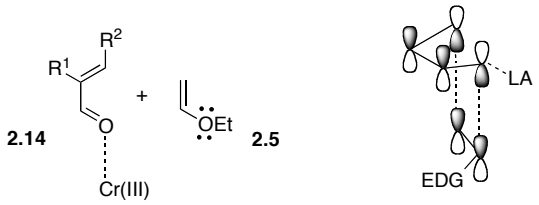
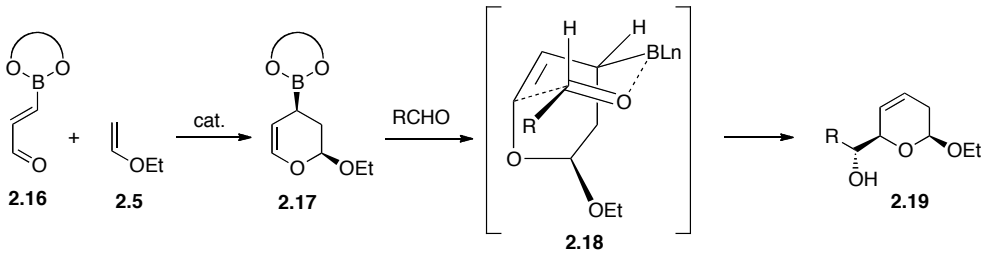


Figure 2.4 Lewis acid promotion of IEDHDA reaction

2.1.2.2 IEDHDA/Allylboration

It was in this time frame that Gao had begun investigations towards a multicomponent process in which an IEDHDA reaction between a boronoacrolein **2.16** and ethyl vinyl ether **2.5** would produce an allyl boronate such as **2.17** (Scheme 2.1). This asymmetric product would then be ideally situated to immediately undergo a stereospecific (via a six membered chairlike transition state **2.18**) allylboration with an aldehyde to form dihydropyrans of type **2.19**.



Scheme 2.1 Inverse-electron-demand hetero-Diels-Alder/allylboration

Upon encountering Jacobsen's catalyst (**2.10**) Gao recognized its potential for application to the desired chemistry and began work toward this end. The frontier molecular orbital approach can also be utilized to predict a favourable IEDHDA outcome for the reaction between boronoacroleins such as **2.16** and ethyl vinyl ether **2.5** (Figure 2.5).

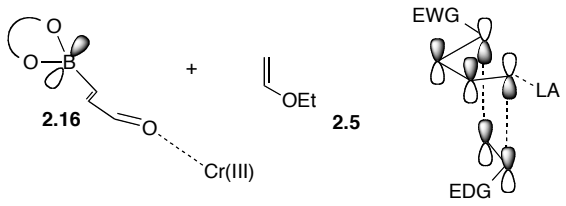
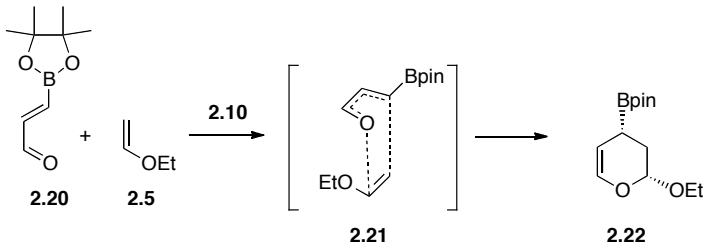


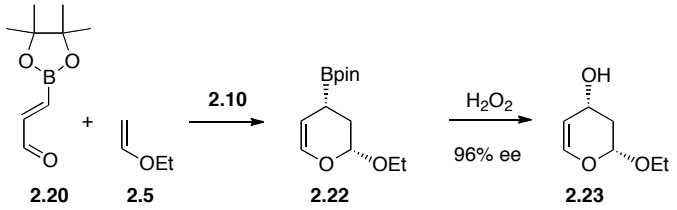
Figure 2.5 Enhanced IEDHDA selectivity

In the case of boronates such as **2.16** it is possible that there will be an even greater depression in the energy level of the diene's HOMO since it has two groups capable of receiving electron density: the Cr(III) coordinated to the aldehyde oxygen and the boron with its vacant p orbital available to receive electron density. 3-Boronoacrolein pinacolate **2.20** was selected as a reaction partner for **2.5** based on its successful employment in previous projects in the group (Scheme 2.2).[56,57] From Jacobsen's results, an endo transition state **2.21** is anticipated which would result in a *cis*-configuration for the allylboronate product **2.22** of the IEDHDA reaction.



Scheme 2.2 Use of pinacol boronate with anticipated endo selectivity

In order to optimise the reaction a method was needed for evaluating its enantioselectivity. This was performed by oxidizing the allylboronate product with hydrogen peroxide and then subjecting the resultant alcohol **2.23** to chiral HPLC analysis (Scheme 2.3).

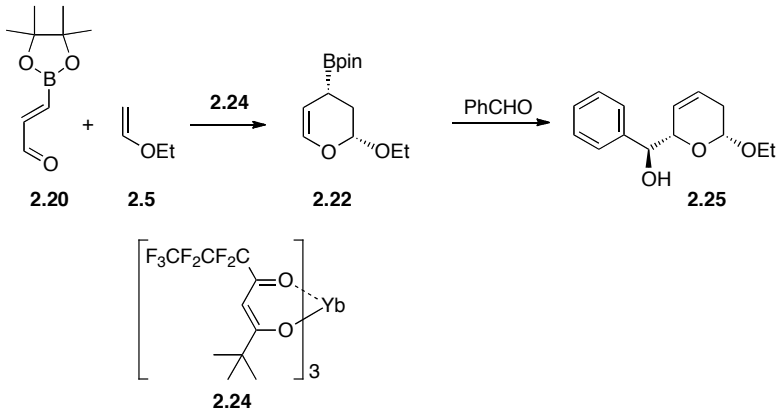


Scheme 2.3 Determination of enantiomeric excess

Using this method it was possible to find reaction conditions that achieved a maximum of 96% ee.

2.1.2.3 Determination of Relative and Absolute Stereochemistry

Chiral HPLC however, does not give information regarding the actual stereochemistry. Fortunately, concurrent with Gao's work the research group of Professor Bertrand Carboni (Institut de Chimie, CNRS-Université de Rennes, France) had been working on the same chemistry and they arrived at crystal structure data to support the stereochemical assignments of the products.[58,59] In their preliminary work they had been catalyzing the IEDHDA with a racemic catalyst known as $Yb(fod)_3$ **2.24** followed by allylboration with benzaldehyde to produce **2.25** (Scheme 2.4).[60]



Scheme 2.4 Carboni's IEDHDA/allylboration using Yb(fod)$_3$

They were able to achieve a crystal structure by further derivatizing **2.25** with osmium tetroxide placing a diol on the pyran ring of **2.26** (Figure 2.6). The crystal structure substantiated the relative stereochemistry expected in the reaction.

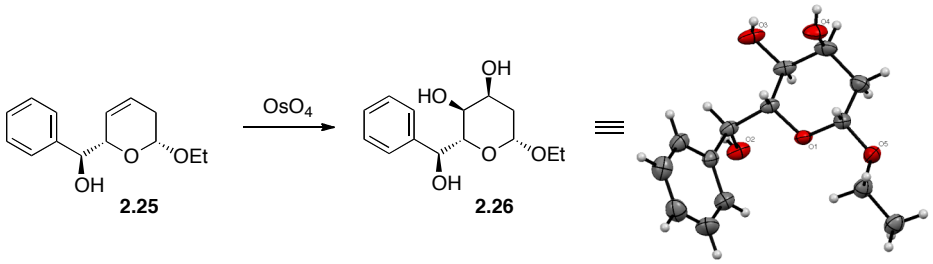


Figure 2.6 Substantiation of relative stereochemistry

Following their studies on the racemic reaction they also investigated the application of Jacobsen's catalyst **2.10** to IEDHDA/allylboration.[59] They were able to attain comparable enantioselectivity (93–96% ee) to Gao's for a range of products but did not replicate his low catalyst load one pot version. However, arguably the most important contribution of this work was the demonstration of the relative and absolute stereochemistry of one of their products (**2.27**) from a crystal structure (Figure 2.7).

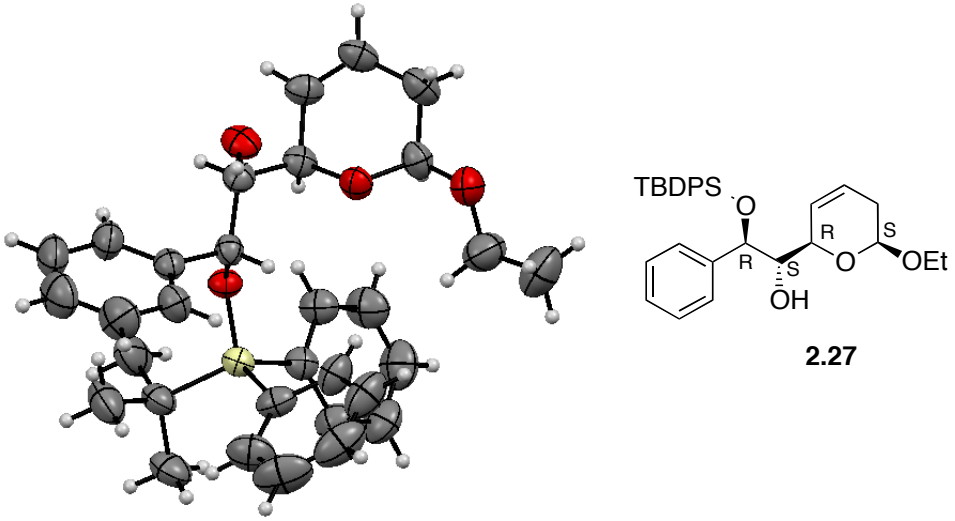


Figure 2.7 Crystal structure substantiating absolute stereochemistry

Product **2.27** was obtained by the established methodology using catalyst **2.10b** and its absolute stereochemistry was determined as *2S,6R,7S,8R*. The reliability of the absolute determination relies on the Flack parameter they report, x = 0.02 (u = 0.09). According to Flack and Bernardinelli crystal structures derived from known enantiopure material with uncertainty factors $u < 0.1$ indicate "sufficient inversion-distinguishing power"[61] to determine absolute stereochemistry. Thus Carboni and co-workers result facilitates the ability to predict which absolute stereochemistry can be derived using catalysts **2.10a** and **2.10b**.

Gao also demonstrated this predictive power in his total synthesis of a natural product **2.28** (Figure 2.8), a biologically derived analogue of thiomarinol. This natural product's spectral data were consistent with those published in the literature (eg Synthetic: $[\alpha]_D^{23}$ = –2.25 (c = 0.004, MeOH); Lit.: $[\alpha]_D^{23}$ = –1.8 (c = 0.003, MeOH)).[62,63]

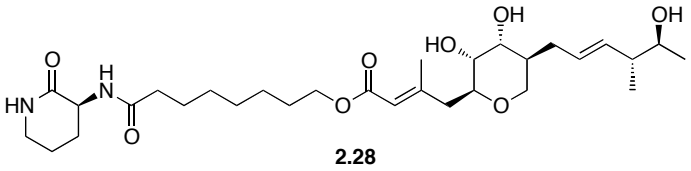
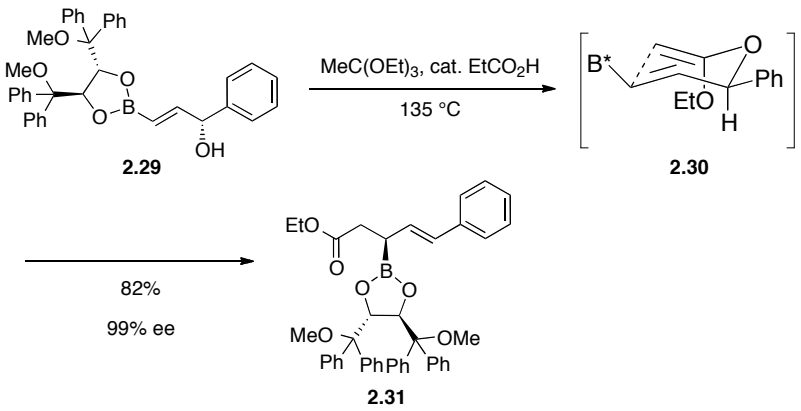


Figure 2.8 Thiomarinol derivative synthesized via IEDHDA/allylboration

2.1.3 Pietruszka's Borono-Johnson-Claisen Rearrangement

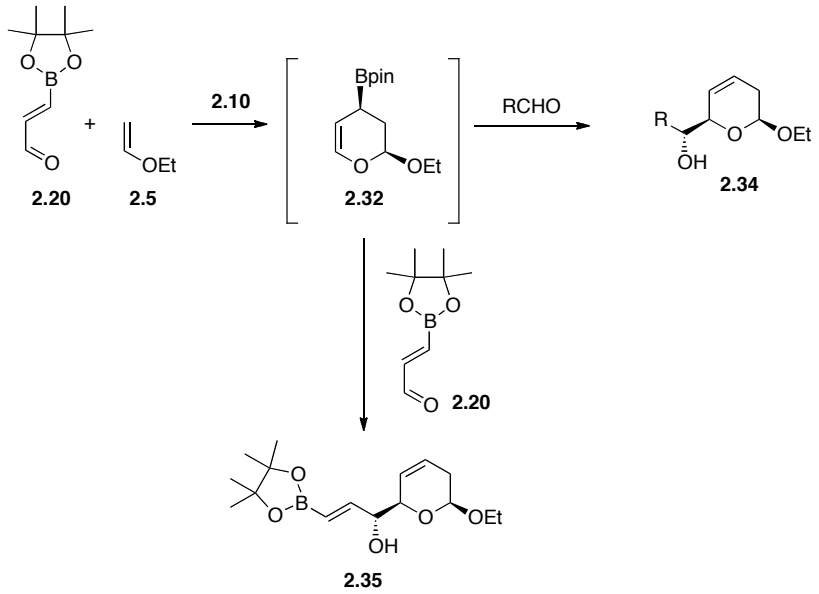
Equipped with a reliable catalytic methodology for introducing stereochemistry the subsequent goal was to find an appropriate methodology for exploiting it to generate other stereocentres. The inspiration for this was found in a borono-Johnson-Claisen rearrangement developed in the laboratories of Professor Jörg Pietruszka at the Institut für Organische Chemie der Universität Stuttgart.[64,65] Pietruszka's methodology involves performing Johnson-Claisen rearrangements on alkenyl boronate esters of chiral allylic alcohols such as **2.29** (Scheme 2.5).



Scheme 2.5 Borono-Johnson rearrangement

Chiral allylic boronates such as **2.31** produced by the rearrangement were attained with good yields and excellent diastereoselectivity. The high enantiomeric excesses attained can be attributed to a highly ordered six-membered transition state **2.30**, with phenyl group occupying a pseudoequatorial position, that ensures efficient chirality transfer.

Remarkably the application of the borono-Johnson rearrangement to the synthesis of palmerolide A was dependent on a side product that Gao had been avoiding during his development of the IEDHDA/allylboration (Scheme 2.6).[66]



Scheme 2.6 Gao's possible undesired allylboration side product

There was a concern that following the formation of the intermediate allylboronate species **2.32**, it would undergo an allylboration with a second equivalent of unreacted boronoacrolein **2.20** prior to the addition of the desired allylboration aldehyde substrate **2.34**. In the course of his work Gao found that this did not take place since the IEDHDA reaction was much faster than the self allylboration and no undesired side product **2.35** was produced.

Note however, the remarkable similarity between the undesired side product **2.35** and the starting material for Pietruszka's borono-Johnson-Claisen rearrangement (Figure 2.9).

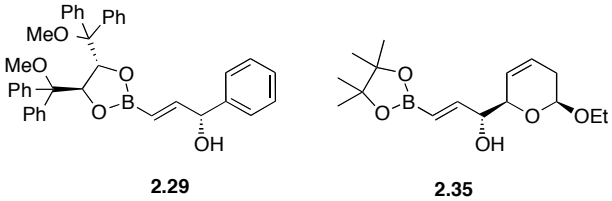
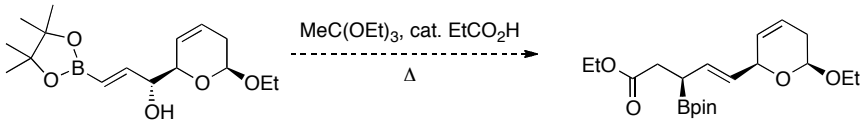


Figure 2.9 Borono-Johnson rearrangement substrates

In both cases a chiral allylic alcohol is flanked by a six membered ring and an alkenyl boronate, which in one case has been proven to undergo Johnson-Claisen

rearrangements in good yield and high diastereoselectivity. Our initial synthetic strategy relied on this similarity; anticipating that a substrate such as **2.35** would also undergo a borono-Johnson-Claisen rearrangement and afford the analogous allylboronic ester **2.36** (Equation 2.4).



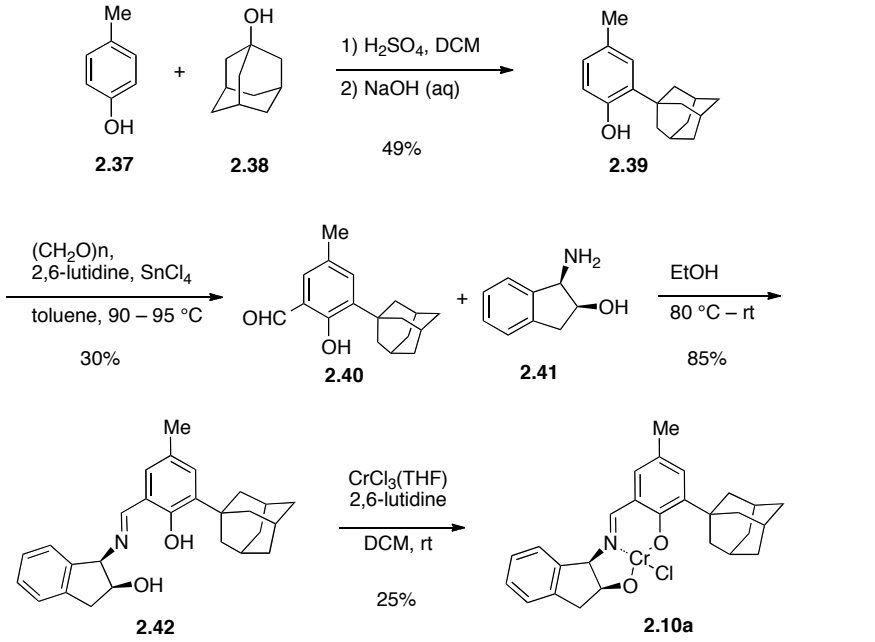
2.35 **2.36**

Equation 2.4

2.2 Preliminary Synthetic Investigations

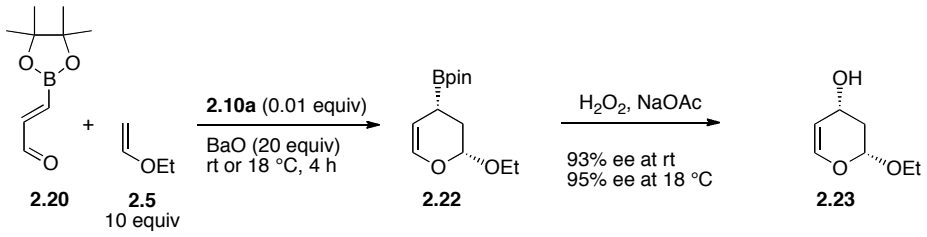
2.2.1 Reproducing the IEDHDA/Allylboration Chemistry

The first task in initiating the project was to reproduce the work of Gao that was relevant to the proposed synthetic strategy. This began with a synthesis of catalyst **2.10** (Scheme 2.7). The first step was an electrophilic aromatic substitution reaction between *p*-cresol **2.37** and 1-adamantanol **2.38** in the presence of sulphuric acid to form 2-adamanytl-*p*-cresol **2.39** in 49% yield.[53] The synthesis from **2.39** followed Jacobsen's preparative procedure found in *Organic Syntheses*.[67] Another electrophilic aromatic substitution reaction was carried out wherein formaldehyde was added at the remaining *meta* position catalyzed by tin (IV) chloride affording aldehyde **2.40** 30% yield. (1*R*, 2*S*)-1-Amino-2-indanol **2.41** condensed with **2.40** forming the Schiff base ligand **2.42** in 85% yield. The final step involved coordination of the ligand to chromium (III) affording the active catalyst **2.10a** after crystallization of the crude product from acetone and water in 25% yield. Crystallization as reported by Jacobsen and co-workers was done from pure acetone. Product **2.10**, however was determined to be highly soluble in acetone. It was found that adding water allowed more crystal formation but too much water resulted in amorphous semisolid product that was difficult to isolate. These are contributing factors to the low yield.



Scheme 2.7 Synthesis of Jacobsen's tridendate Schiff base Cr (III) catalyst

The next objective was testing the performance of the catalyst in IEDHDA reactions in terms of its enantioselectivity. To achieve this, Gao's methodology was employed (Scheme 2.8).



Scheme 2.8 Evaluation of enantioselectivity

The first test of the catalyst yielded only 93% ee when the reaction was run at room temperature. Consultation with a senior group member, Dr. Hugo Lachance, revealed that temperature control was important and that running the reaction at 18 °C would facilitate better stereocontrol. Repetition of the experiment bore this out and a reproducible 95% ee was attained comparable to the 96% ee reported by Gao.[51]

It should be noted that the aqueous workup and isolation of the catalyst are critical to its performance. Anecdotal evidence from the group relayed in this time frame indicated that incorrect isolation of the catalyst would result in low enantioselectivity and even racemic products. This is supported by a paper published by Jacobsen wherein two different complexes of the catalyst are formed, dependent on the workup procedure, with very different catalytic performance.[68] The optimal catalysts for hetero-Diels-Alder reactions exist in a dimeric form with a bridging water molecule (Figure 2.10), while the other form is monomeric.[53,68,69]

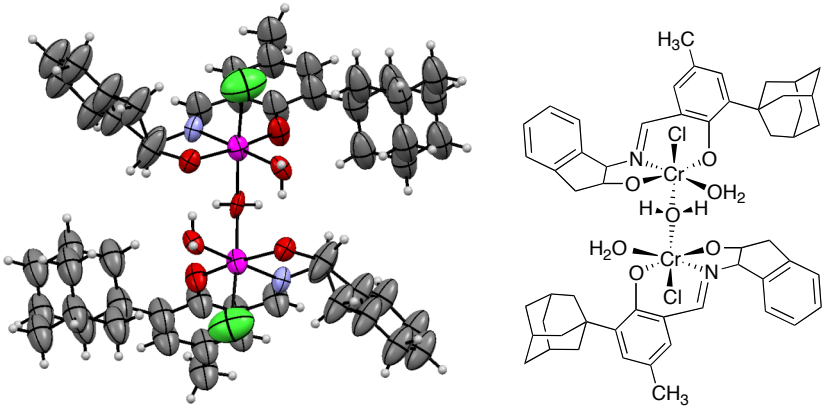


Figure 2.10 Active dimer of Jacobsen's catalyst

Note also that this dimeric structure was utilized by Jacobsen's student David E. Chavez in his thesis dissertation to propose a model to explain the relative and absolute stereochemical induction in hetero-Diels-Alder reactions (Figure 2.11).[70]

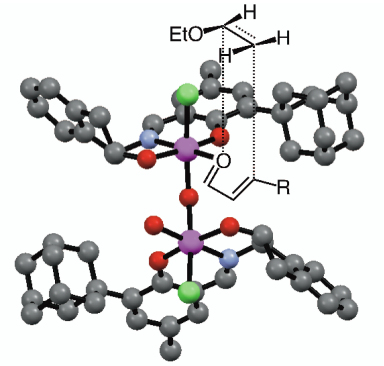


Figure 2.11 Chavez' model of HDA stereochemical induction

The model assumes displacement of one of the equatorial water ligands by the oxygen of the hetero-diene. This displacement can be rationalized by the importance of using a drying agent such as molecular sieves[53] or barium oxide[51] in the reaction to allow access to the coordination site. The binding of the hetero-diene would derive its specificity from the chiral steric environment of the catalyst. Endo approach by the electron rich dienophile on the open face of the dimer would then explain the final component of selectivity.

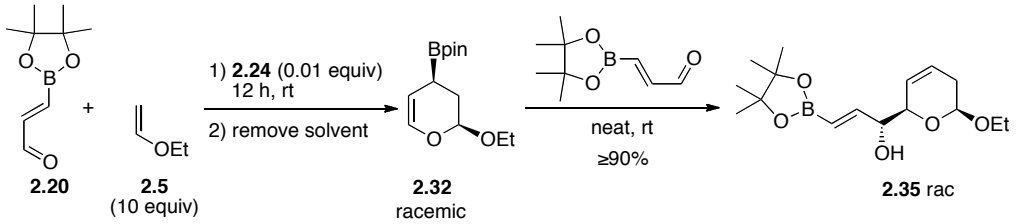
2.2.2 The Third Component of the IEDHDA/Allylboration

With the reliability of stereocontrol established, the next target became using 3-boronoacrolein pinacolate **2.20** as the third component in the three component IEDHDA/allylboration reaction.

Note that during the following optimization stages of the project, racemic $Yb(fod)_3$ **2.24** was used to catalyze the IEDHDA reactions. This was decided for reasons of economy of time and money since **2.24** is inexpensive and commercially available.

Recall that in Gao's work involvement of **2.20** as a third component did not take place due to its sluggishness as an allylboration reagent relative to the IEDHDA reaction (Scheme 2.6). In our case this became a challenge since we also wanted to avoid isolation of the cyclic allylboronate product **2.32**. The difficulty lies in the reaction conditions for the first step in which a large excess of

ethyl vinyl ether **2.5** is used. If a second equivalent of **2.20** were added it would likely undergo further IEDHDA chemistry with the remaining **2.5**. The problem was managed simply by first removing the excess ethyl vinyl ether and then reacting the two components neat (Scheme 2.9). This process might be described as an A+B+A three component sequential IEDHDA/allylboration.

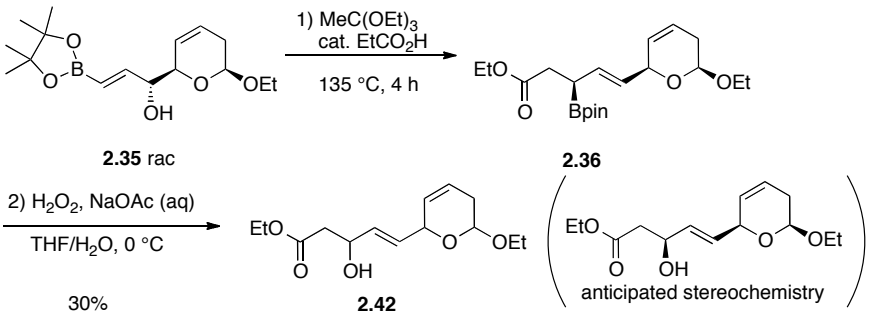


Scheme 2.9 A+B+A three component IEDHDA/allylboration

Isolation of the alkenylboronate product **2.35** in good yield required some special considerations. Chromatography with the normative acidic silica resulted in extensive decomposition. Deactivation of the silica with triethylamine and passing the crude product through a very short silica column prevented the decomposition. The product then required codistillation with a volatile solvent such as dichloromethane to remove the residual triethylamine. In spite of the precautions taken some decomposition took place and a trace of pinacol could always be found in the purified product. Dissolution in diethyl ether and washing with water facilitated its removal and pure product **2.35** (racemic) could consistently be obtained with percent yields greater than or equal to 90%.

2.2.3 Execution of the Borono-Johnson-Claisen Rearrangement

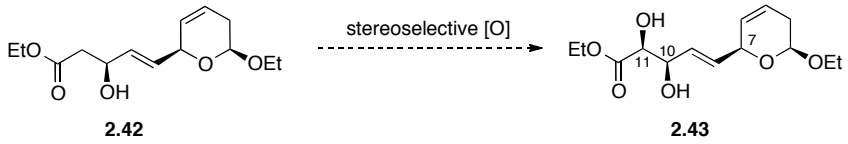
After successfully synthesizing alkenylboronate **2.35,** embedding the desired allylic alcohol unit, the moment had arrived to ascertain whether it would undergo a borono-Johnson-Claisen rearrangement similar to the Pietruszka analogue.



Scheme 2.10 Execution of the borono-Johnson-Claisen rearrangement

The reaction was carried out and a product was isolated in 30% yield with ^{1}H NMR and ^{13}C NMR as well as high resolution mass spectrometry data consistent with the expected product **2.42**. The relative stereochemistry of the product was undefined but expected to be as depicted in Scheme 2.10 based on our mechanistic understanding.

Pending optimization of the rearrangement the next envisioned step was a stereoselective oxidation of the C11 carbon adjacent to the C10 hydroxyl (Equation 2.5). If this were successful the three stereocentres of the eastern fragment would be installed.



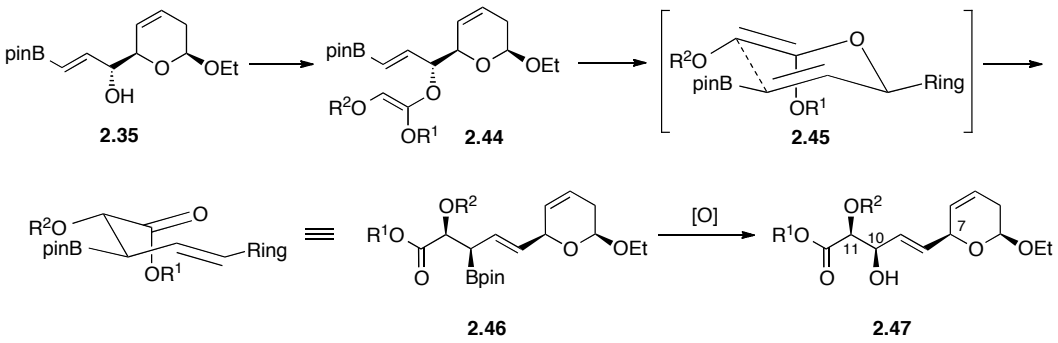
Equation 2.5

No further investigations into this particular strategic path were undertaken however, as a different, more direct strategy was employed.

2.3 Borono-Ireland-Claisen Rearrangement

2.3.1 Extending the Borono-Johnson-Claisen Rearrangement Concept

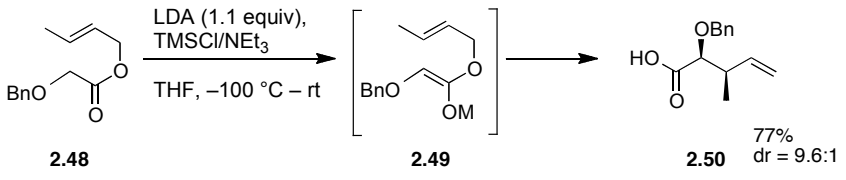
At this juncture consideration was given to the possibility of employing an Ireland-Claisen type arrangement as an alternative to the originally conceived Johnson-Claisen rearrangement (Scheme 2.11).



Scheme 2.11 Proposed borono-Ireland-Claisen reaction

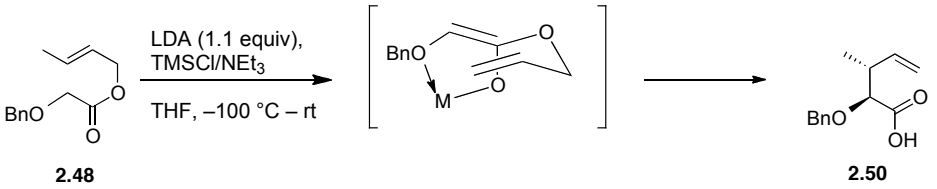
If an appropriately oxygenated olefinic appendage could be placed on the hydroxyl group of **2.35** then **2.44** would have the necessary prearrangement to pass through a six-membered chairlike transition state such as **2.45** and yield chiral allyl boronates with the configuration of **2.46**. The steric bulk of the dihydropyran ring and of the alkenyl boronate might be expected to favour equatorial and pseudo equatorial geometries respectively in transition state **2.45** facilitating diastereoselectivity of the reaction. Oxidation of the boronate with retention of stereochemistry would then furnish **2.47** containing all three Eastern Hemisphere stereocentres. An additional benefit would be the differentiation of the C10 and C11 hydroxyls, which is essential for selective placement of the carbamate of palmerolide A downstream in the synthesis.

On the basis of this synthetic proposition a literature search was conducted to determine if any precedents existed. No borono-Ireland-Claisen rearrangements were disclosed by the search but an approximately analogous boron-less reaction from the lab of Professor Steven D. Burke at the University of South Carolina was found (Scheme 2.12).[71]



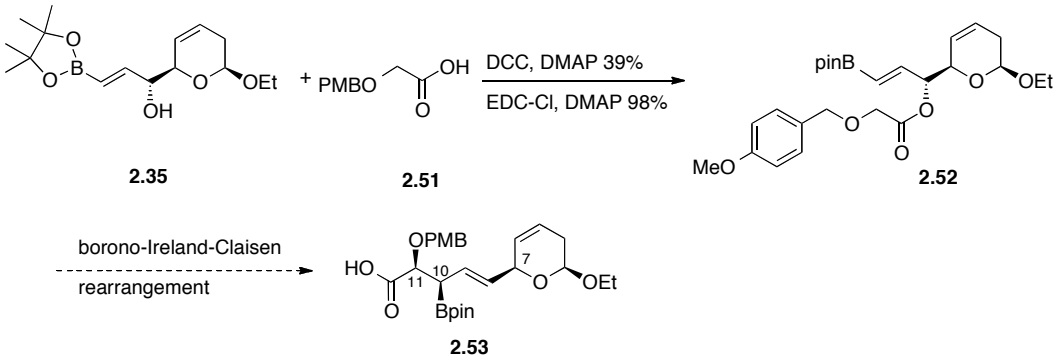
Scheme 2.12 Burke's Ireland-Claisen rearrangement analogy

In this case starting material **2.48** contained an allylic benzyloxy acetate unit that was transformed into **2.49**, analogous to **2.44**, under basic conditions and underwent an Ireland-Claisen rearrangement forming acid **2.50** in 77% yield and with a dr equal to 9.6:1. Burke proposed that diastereoselectivity in the reaction was enhanced via chelation (Scheme 2.13).



Scheme 2.13 Stereocontrol by intramolecular coordination in Ireland-Claisen rearrangement

Proceeding on the basis of this analogue a rearrangement substrate was designed that would be accessible via the chemistry that we had developed, **2.52** (Scheme 2.14). Note the use of a *para*-methoxy benzyl (PMB) group rather than simply using a benzyl group as in Burke's rearrangement substrate. The intention here was to facilitate placement of a PMB protecting group on the rearrangement product's (**2.53**) latent hydroxyl that could be selectively removed by standard oxidative procedures downstream in the synthesis. The strategic importance of this selectivity becomes apparent when considering that the C11 oxygen will require discriminatory carbamylation relative to the proximal C10 and C7 oxygen's in order to attain the natural product.

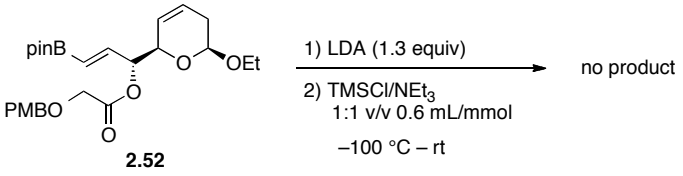


Scheme 2.14 Synthesis of borono-Ireland-Claisen substrate

Synthesis of **2.52** derived from the coupling of **2.35** and *p*-methoxybenzyloxy acetic acid **2.51**. Initial attempts at the synthesis using dicylohexylcarbodiimide (DCC) coupling were met with low and inconsistent isolated yields. Although the reaction itself proceeded smoothly to completion, purification was not trivial. Removal of the dicyclohexylurea by-product of the coupling reaction by flash chromatography required significant quantities of silica to be effective. This had a deleterious effect on the product resulting in its decomposition. Attempts to use silica deactivated with triethylamine did not enjoy the benefits associated with isolation of upstream boronate precursors. The isolation difficulty was addressed by switching to 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) as a coupling reagent. Once again the reaction proceeded smoothly to completion but purification only required an aqueous workup with no need for chromatography and allowed excellent yields of the desired carboxyester **2.52**.

2.3.2 Execution of Borono-Ireland-Claisen Rearrangement

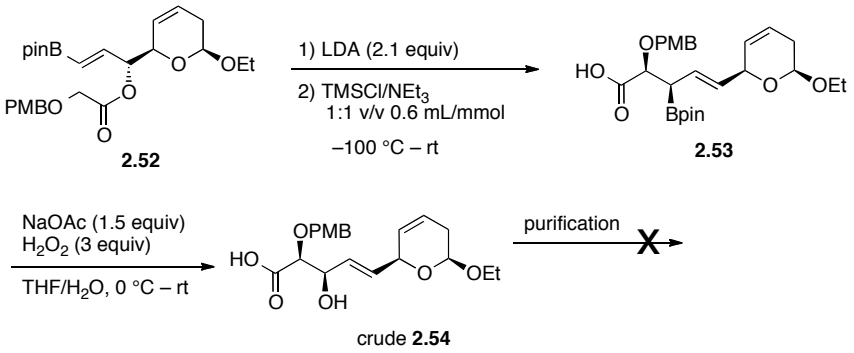
Once again the moment had arrived to determine whether or not the execution of the plan corresponded to expectation. The first attempt followed the conditions utilized by Burke and co-workers (Equation 2.6).



Equation 2.6

The reaction was monitored by ^{1}H NMR analysis of aliquots taken from the reaction mixture with no clear conversion apparent in the signals. Acidic workup following Burke's procedure and flash chromatography of the ensuing complex mixture also did not afford the desired product. The reaction conditions were repeated a number of times allowing the reaction to stir overnight and also heating

to reflux; all resulting in mixtures of starting material and decomposition products. Consideration was given to the key difference between **2.52** and Burke's substrate; this being the alkenyl boronate moiety. It is possible that the Lewis acidic boron sequesters an equivalent of the base, which hinders formation of the enolate and progress of the rearrangement. To address this possibility the reaction was repeated changing the LDA stoichiometry from 1.3 to 2.1 equivalents (Scheme 2.15).



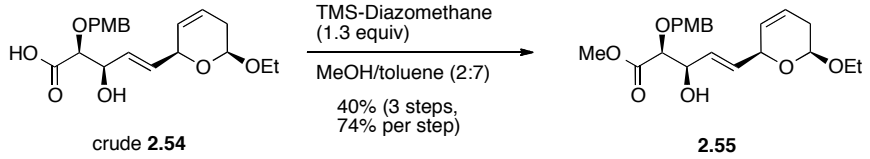
Scheme 2.15 First successful borono-Ireland-Claisen rearrangement

Once again progress was monitored by sequential ^{1}H NMR analysis of aliquots taken from the reaction mixture. During the course of the reaction clear disappearance of starting material resonances were observed in conjunction with the appearance of new resonances. Due to difficulties encountered previously in isolating precursor boronates by chromatography, oxidation was employed immediately following the rearrangement step as part of a one-pot protocol. After aqueous acidic workup, ^{1}H NMR analysis of the crude material appeared to be consistent with the anticipated acid **2.54**. High resolution mass spectrometry also demonstrated that the crude mixture contained a product with a mass identified with this product. Attempts to isolate the pure product by chromatography however resulted in complete decomposition.

2.3.3 Optimization of Product Isolation

Although it appeared that the desired product could be accessed via the borono-Ireland-Claisen rearrangement, isolation of pure product remained an obstacle. One of the main challenges was a large quantity of unknown polar side products combined with the obvious polarity of the product acid and its sensitivity to prolonged exposure to silica. Even deactivating the silica with triethylamine did not resolve the problem.

One way of addressing the difficulty would be by reducing the polarity of the product relative to the polar by-products. A sufficiently low polarity would lead to reduced contact with silica during chromatography and enable separation from the polar impurities without excessive product decomposition. To facilitate this change in polarity, trimethylsilyldiazomethane was added to the crude reaction product to effect esterification of the acid moiety (Equation 2.7).



Equation 2.7

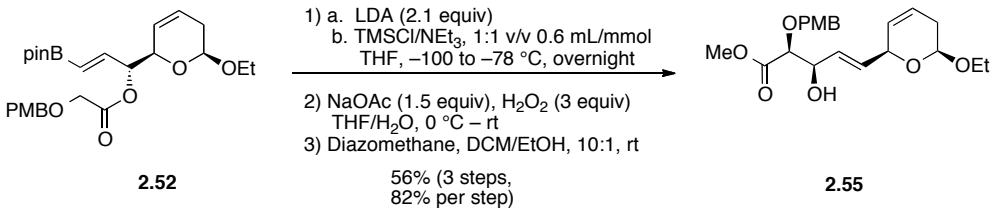
This approach was effective and the methyl ester **2.55** was isolated in 40% yield after three steps from the rearrangement substrate (74% per step). The isolated product could then be fully characterized. The approach employed here provided most of the starting material during the optimization stages of the synthesis of the Eastern Hemisphere. Later on when it was necessary to scale the reaction up towards completion of the total synthesis the yields dropped from the 40's to 30's and even 20's. For this reason further optimization efforts were undertaken.

One variable that was modified was preparation of the triethylamine/TMSCl. In Burke's paper these were mixed separately, centrifuged and then only the supernatant was added to the reaction mixture.[71] Since there were no centrifuges available in our laboratory equipment this step was

eliminated. Upon obtaining a centrifuge during subsequent optimization the centrifugation procedure was implemented. A small improvement in yield was noted (2–3%). Another variable that was modified was the method used for the methyl ester formation. During the author's candidacy exam special note was made of the excessive contaminants that obstructed the purification. It was suggested that this reaction could be improved further by using diazomethane rather than TMS-diazomethane since its side product is only nitrogen compared to the silyl by-products of TMS-diazomethane. There was initial reluctance to employ this strategy, particularly on a large scale, due to the explosive nature of diazomethane. However, eventually a safe methodology was developed that employed *in situ* generation of diazomethane (cf. Experimental section) and this too contributed to an improved yield by reducing the by products in the crude reaction mixture.

One further modification in the procedure that was employed involved temperature control. In Burke's paper, reaction mixtures were allowed to warm to room temperature.[71] When the borono-Ireland-Claisen reaction was allowed to warm to ambient temperature, a large colour change was noted wherein the reaction solution changed from a pale amber solution to a deep reddish brown mixture. When the reaction mixture was only allowed to warm to 0 °C the gradient of the colour change was reduced. Since the isolated product was pale yellow in colour the possibility was considered that the extra colour arose from decomposition products, whose formation was reduced at lower temperature. It was deemed noteworthy that the reaction components are mixed at –100 °C; presumably the rearrangement does not take place at this reduced temperature but at some temperature between –100 °C and room temperature. It seemed possible that the rearrangement might take place at a temperature substantially lower than either ambient temperature or 0 °C. If the reaction could be quenched at this lower temperature it might hinder formation of undesired side products and improve the yield. To this end, the reagents were combined at –100 °C and

subsequently only allowed to warm to –78 °C and the reaction was quenched at that temperature (Scheme 2.16).



2.52 **2.55**

Scheme 2.16 Optimized conditions for borono-Ireland-Claisen rearrangement of 2.52 and its product isolation

The combination of these three experimental modifications resulted in optimized conditions (Scheme 2.16) where grams of starting material **2.52** could be reacted to form methyl ester **2.55** in 56% yield over the three steps (average of 82% per step).

2.4 Selective Hydrogenation

It was now time to attend to a selectivity issue arising from the IEDHDA/allylboration. The product of the reaction contained a double bond between what would correspond to C5 and C6 of the targeted natural product **1.1**. Since there is no double bond located here in the natural product it would be necessary to hydrogenate at some point prior to completion of the synthesis. Noting the large number of double bonds in the natural product, selectivity for this transformation would likely be simpler earlier on in the sequence. Two early choices for when this could be undertaken are the immediate product of the IEDHDA/allylboration **2.52** or the product of borono-Ireland-Claisen rearrangement **2.55**; which upon selective hydrogenation of their respective substrates would yield saturated pyran derivatives **2.56** and **2.57**(Figure 2.12).

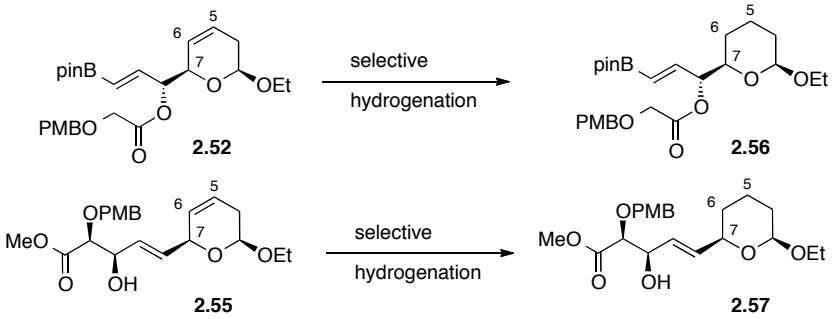


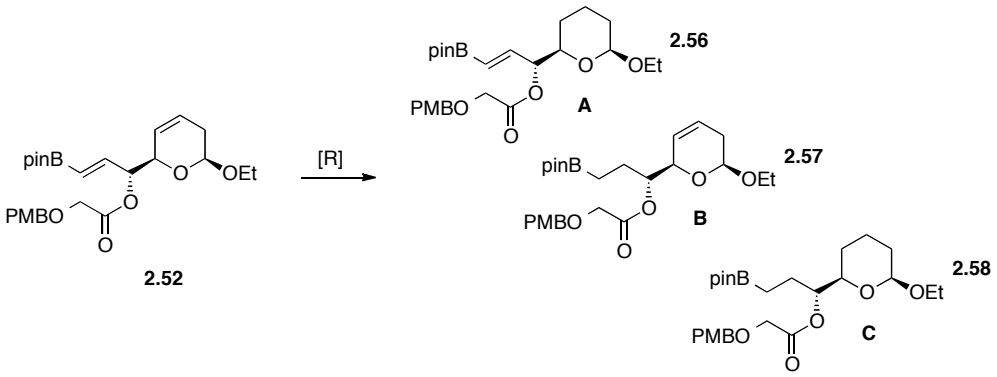
Figure 2.12 Selective hydrogenation options (pre- and post-rearrangement)

2.4.1 Selective Hydrogenation of Pre-rearrangement Substrate 2.52

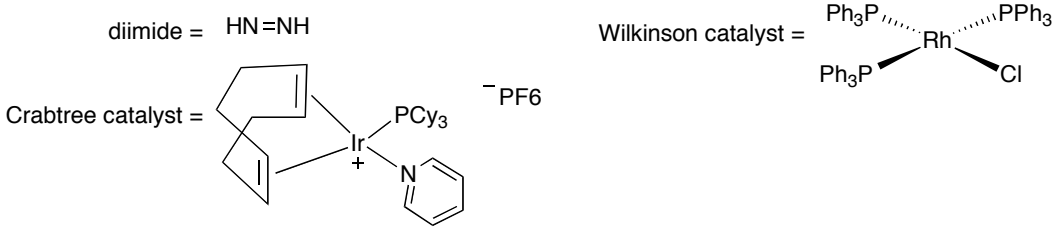
An investigation into selective hydrogenation of the pre-rearrangement substrate **2.52** was first explored based on the preference for addressing this selectivity issue as early as possible.

The initial screening revealed that although the two double bonds on **2.52** were in unique environments the selectivity was not trivial (Table 2.1). Some of the standard hydrogenation methods (entries 1–4) gave over reduction resulting in complete conversion to **2.58**. Diimide reduction and the use of Crabtree's catalyst resulted in undesired selectivity forming **2.57** by hydrogenation of the exocyclic double bond. Wilkinson's catalyst showed some promising selectivity (entries 7 and 8) and so optimization using this catalyst was pursued further.

Table 2.1 Selectivities of various hydrogenation methods on 2.52

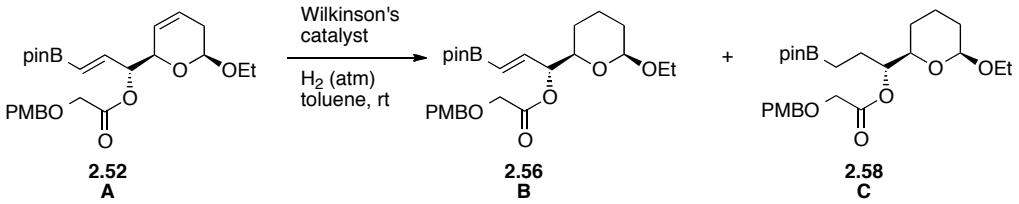


Entry	Catalyst/ Reagent	Temp	Solvent	Molar Equiv.	Time	A:B:C
1	Pd/C	rt	MeOH	0.05	1 h	0:0:100
2	$Pd(OH)_2/C$	rt	MeOH	0.05	1 h	0:0:100
3	Rh/Al_2O_3	rt	EtOAc	0.05	3 h	0:0:100
4	Raney Nickel	rt	MeOH	0.05	3 h	0:1:99
5	diimide	rt	DCM	4	Overnight	1:94:5
6	Crabtree	0 °C	DCM	0.05	3.3 h	0:57:43
7	Wilkinson	rt	Toluene	0.25	Overnight	80:20:0
8	Wilkinson	rt	Toluene	0.4	3 h	74:0:25



Investigation of catalyst loading (Table 2.2) revealed that a high catalyst loading (~0.4 equiv) was needed for complete conversion of the starting material.

Table 2.2 Optimization of catalyst loading for hydrogenation of 2.52



2.52 A **2.56 B** **2.58 C**

Entry	Catalyst load	Time	Product Ratio A:B:C
1	0.25	Overnight	20:60:20
2	0.3	4 h	20:60:20
3	0.35	3 h	0:63:37
4	0.4	3 h	0:57:43

Next an investigation into the optimal solvent was undertaken (Table 2.3). Of the solvents investigated dichloromethane (entry 6) gave the most promising product ratio.

Table 2.3: Optimization of solvent for selective hydrogenation of 2.52

Entry	Solvent	Catalyst load	Time	Product Ratio A:B:C
1	Toluene	0.4	3 h	0:58:42
2	THF	0.4	4 h	100:0:0
3	iPrOH	0.4	4 h	2:16:82
4	1,2-dichlorobenzene	0.4	Overnight	100:0:0
5	o-xylene	0.4	Overnight	82:12:6
7	EtOAc	0.4	2 h	10:57:33
6	**DCM**	**0.4**	**2 h**	**6:65:29**

This solvent optimization study was followed by a reinvestigation of catalyst load with the optimal solvent (Table 2.4). Low catalyst loading was detrimental to the reaction resulting in low to no conversion both at 10% and 20% catalyst loading. However, at 40% catalyst loading the reaction proceeded quickly to completion within 1.5 hours providing the best attained product to over-reduced product ratio of 75:25 (entry 3).

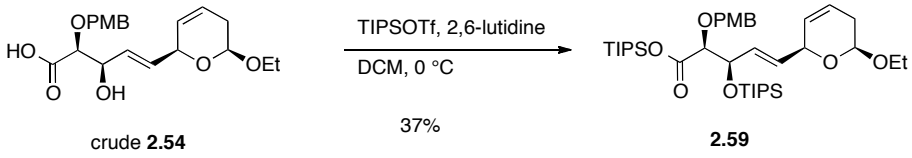
Table 2.4: Reinvestigation of catalyst loading using dichloromethane.

Entry	Solvent	Catalyst load	Time	Product Ratio A:B:C
1	DCM	0.1	Overnight	Virtually no conversion
2	DCM	0.2	Overnight	Virtually no conversion
3	**DCM**	**0.4**	**1.5 h**	**0:75:25**

Unfortunately attempts at separating the resulting mixtures by chromatography were unsuccessful due to the similar retention factors (rf) of the products and proclivity of the substrate to decompose on silica. The idea was proposed that the borono-Ireland-Claisen rearrangement might be employed on the crude mixture followed by separation of the more stable product but this only yielded complex mixtures. Thus, attention was turned to selective hydrogenation of the post-rearrangement product.

2.4.2 Selective Hydrogenation of the Post-Rearrangement Product

In order to enhance hydrogenation selectivity in the rearrangement substrate the post rearrangement product was protected with a triisopropylsilyl group (Equation 2.8).

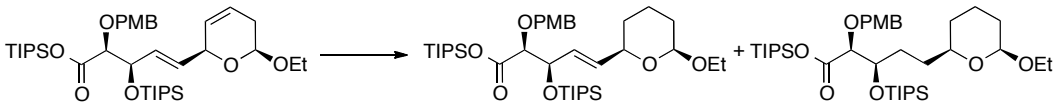


crude **2.54** **2.59**

Equation 2.8

The protection was carried out on crude acid **2.54** from the rearrangement employing triisopropylsilyl trifluoromethanesulfonate (TIPSOTf).[72] The presumption was that the steric bulk of the protected allylic alcohol would favour hydrogenation at the endocyclic olefin. Since the pre-rearrangement substrate had had demonstrable selectivity using Wilkinson's catalyst this was the starting point for the latest investigation (Table 2.5).

Table 2.5: Unusual performance of "Wilkinson's catalyst"



2.59 A **2.60 B** **2.61 C**

Entry	Catalyst	Equiv	Solvent	Time	H_2 psi	A:B:C
1	**"Wilkinson's +"**	0.3	DCM	Overnight	50	15:85:0
2	Wilkinson's	0.3	DCM	1 d	50	>99:1:0
3	Wilkinson's	0.3 + 0.2	DCM	2 d	50	>99:1:0
4	Wilkinson's	0.3	DCM	Overnight	600	>99:1:0

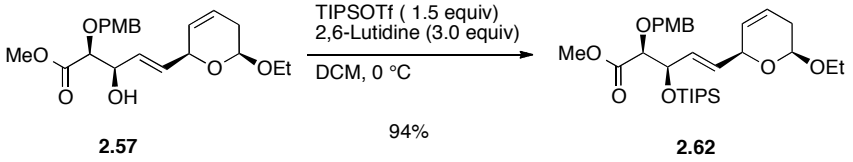
At the suggestion of a fellow group member, Dr. Vivek Rauniyar, the use of hydrogen pressure greater than atmospheric was introduced as a new variable in the screening. This employed a communal Parr Shaker® owned by the University of Alberta Chemistry Department. The first time this apparatus was used the experiment was contaminated with a black substance remaining from a previous unknown experiment. Remarkably this experiment resulted in a higher level of selectivity than any previously seen (entry 1). All attempts to repeat this result however failed even when the experiment time was lengthened and the hydrogen pressure was increased (entries 2–4). Wilkinson's catalyst at this loading appeared to be completely inert. The only reasonable conjecture was that the contaminant in the first experiment had been responsible for the selectivity. Reasoning that palladium on carbon (Pd/C) was the most common hydrogenation catalyst used with the apparatus this possibility was investigated (Table 2.6).

Table 2.6: Investigating the selectivity of Pd/C on hydrogenation of 2.59

Entry	Catalyst	Equiv	Solvent	Time	H_2 psi	A:B:C
1	Pd/C 10%	5% wt	DCM	Overnight	50	64:36:0
2	Pd/C 10%	5% wt	MeOH	Overnight	50	0:0:100
3	Pd/C 10%	5% wt	EtOAc	Overnight	50	0:0:100
4	Pd/C 10%	5% wt	DCM	44 h 45 min	50	0:79:21

The investigation was initiated by exactly repeating the original reaction conditions including the use of dichloromethane as the solvent; only the catalyst identity and loading were different. This reaction did indeed result in some selectivity (entry 1), spurring further investigation. Next other more typical solvents used with Pd/C were screened and in both cases complete reduction of both double bonds took place (entries 2 and 3). Switching back to dichloromethane and increasing reaction time allowed complete conversion of starting material with a favourable ratio of (79:21; entry 4). Attempts to separate the two reduction products were again not successful due to complete identity in terms of rf values.

Further screening however was impeded at this point in time with the discovery that all of the doubly TIPS protected starting material had decomposed in the freezer. Since by this time an effective method for isolating methyl ester **2.57** had been developed, the TIPS protection methodology was applied producing TIPS protected methyl ester **2.62** (Equation 2.9).

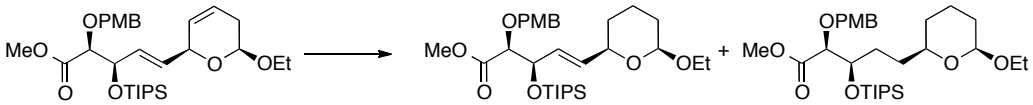


2.57 **2.62**

Equation 2.9

The first test of the new substrate **2.62** showed similar selectivity to that of the doubly TIPS protected one **2.59** (Table 2.7: entry 1). Next an investigation into catalyst loading was undertaken (entries 2–4). The result was acutely distressing; selectivity was completely lost in the newest experiments. There is a significant difference between entry 1 and 2–4; a new bottle of Pd/C was employed for the latter. The conclusion was drawn from this that the old bottle was poisoned in some way making it less active. The reduced potency of the catalyst facilitated the selectivity seen previously by diminishing its ability to catalyze hydrogenations of the more hindered exocyclic double bond.

Table 2.7 Attempt at optimizing catalyst loading for selective hydrogenation on substrate 2.62



2.62 A **2.63 B** **2.64 C**

Entry	Catalyst	Load	Time	Pressure	Product Ratio A:B:C
1	Pd/C	5 wt%	18 h	50psi	21:79:0
2	Pd/C	10 wt%	24 h	50psi	0:0:100
3	Pd/C	20 wt%	24 h	50psi	0:0:100
4	Pd/C	30 wt%	24 h	50psi	0:0:100

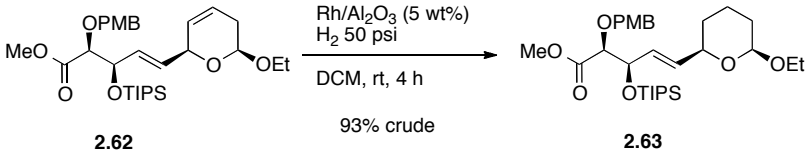
Given these results, a new round of catalyst screening in search of a more selective catalyst was initiated (Table 2.8).

Table 2.8: New round of catalyst screening for selective hydrogenation on substrate 2.62

Entry	Catalyst	Load	Time	Pressure	Product Ratio A:B:C
1	$Pd(OH)_2/C$	10wt%	17 h	Atm	0:0:100
2	PtO_2	10wt%	17 h	Atm	0:36:64
3	Rh/Alumina	10wt%	17 h	Atm	20:80:0
4	Rh/Alumina	10wt%	17 h	50psi	0:100:0
5	Rh/Alumina	5wt%	18 h	50psi	0:100:0
6	Rh/Alumina	10wt%	18 h	50psi	0:100:0
7	Rh/Alumina	20wt%	18 h	50psi	0:100:0

Pearlman's catalyst (entry 1) showed no selectivity and platinum (II) oxide showed slight selectivity (entry 2). Remarkably, rhodium on alumina showed complete selectivity under initial screening conditions (entry 3). Further testing of rhodium on alumina at different catalyst loadings and at higher hydrogen pressure revealed no variations in the selectivity (entries 4–7). Attempts to isolate the selectively reduced product **2.63** by flash chromatography significantly lowered the yield when carried out on a larger scale. However, some further experimentation resulted in optimized conditions wherein high yields on a

gram scale could be obtained of the crude material simply by filtering the product after the reaction through Celite® (Equation 2.10).



2.62 **2.63**

Equation 2.10

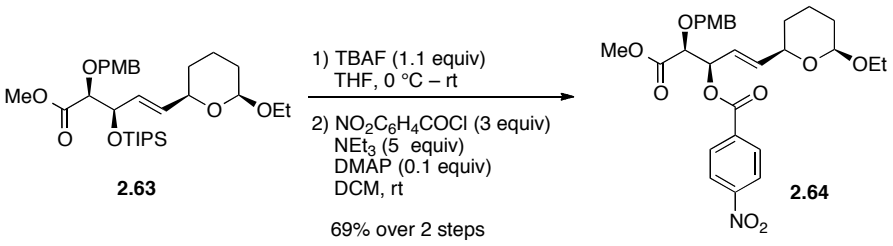
The selectivity was obtained through purely empirical developments and no investigations were carried out to explain it since the focus of the project was directed towards the synthesis of palmerolide A. A literature search revealed that the results might even be interpreted as counter intuitive. For example publications by Otto Beeck (Shell Development Company, Emeryville, California) reveal that in ethylene hydrogenations, metals were vapour deposited on glass, rhodium has a higher activity than palladium.[73,74] Given this result one might also expect rhodium to be a more active catalyst for more complex substrates such as **2.62** and suffer in terms of selectivity. It could be suggested that the different surface material, aluminium oxide, modifies the reactivity order. However, a more recent publication by Professor Marcus Bäumer and co-workers at the Fritz-Haber-Institut, Berlin, contains evidence that negates this possibility.[75] They discuss the primary role of a π bonded ethylene intermediate in hydrogenation and through IR measurements reveal that rhodium on Al_2O_3 contains a higher population of π bonded ethylene than palladium. Returning to Beeck's investigations, consideration of the basis for rhodium's higher activity might provide a clue to its better selectivity in hydrogenation of **2.62**. Notably, of the metals tested for hydrogenation by Beeck, rhodium was found to have the lowest level of adsorption towards both hydrogen and ethylene gases. Clearance of the surface due to desorption facilitates higher rates of hydrogenation. If substrates are held more tightly by palladium on the exocyclic double bond this might facilitate hydrogenation at the more hindered exocyclic double bond that is

not capable of being held as tightly to the rhodium surface due to the steric interference of the TIPS group. This however, is pure speculation.

2.5 Crystallographic Evidence for Relative Stereochemistry

Although the precedents applied towards predicting the stereoselectivity of the rearrangement chemistry were strong, it was deemed beneficial to seek crystallographic data that would support the predicted outcome. Towards this end attempts were made to crystallize the post rearrangement product. The primary target of these attempts was initially the acid **2.54** that unfortunately resisted all attempts at crystallization. There were two key known factors believed to account for this failure. Firstly the product was an oil; secondly it was never effectually purified. When acid **2.54** was isolated by chromatographic methods it always co-eluted with a significant quantity *p*-methoxybenzyloxy acetic acid that was a side product of the reaction. The oil issue was addressed by making potassium and dicyclohexylamine salts of the acid allowing formation of a solid. Nevertheless, with the purity issue unaddressed even this did not allow formation of X-ray quality crystals.

Attention was subsequently turned to a downstream intermediate in the synthesis that was effectually purified of all rearrangement contaminants, the TIPS protected reduced product **2.63**. This too was an oil but a derivatization strategy found for an analogous compound in the literature was employed.[76] In the literature example a structure with a free alcohol attached to a dihydropyran core was derivatized with a *p*-nitrobenzoyl group in order to make the compound sufficiently crystalline to successfully obtain a crystal structure, thereby providing hope that this derivatization of our compounds would also facilitate the formation of X-ray quality crystals (Scheme 2.17).



Scheme 2.17 Derivatization of 2.63 with *p*-nitrobenzoyl chloride

Placement of a *p*-nitrobenzoyl group on the allylic alcohol after removing the TIPS protecting group did indeed yield a highly crystalline yellow product **2.64**. Twenty three crystallization experiments were set up with different solvents using liquid and vapour diffusion techniques (Table 2.9).

Table 2.9: Crystallization experiments

Entry	**Liquid Diffusion**		Entry	**Vapour Diffusion**	
1	DCM/hexanes	C	13	DCM/hexanes	O
2	DCM/pentane	C	14	DCM/pentane	C
3	DCM/pet. ether	C	15	DCM/pet. ether	C
4	chloroform/hexanes	O	16	chloroform/hexanes	O
5	chloroform/pentane	C	17	chloroform/pentane	N
6	chloroform/pet. ether	C	18	chloroform/pet. ether	C
7	ethyl acetate/hexanes	N	19	ethyl acetate/hexanes	O
8	ethyl Acetate/pentane	C	20	ethyl acetate/pentane	√
9	THF/pentane	√	21	THF/pentane	C
10	**toluene/hexanes**	√	22	toluene/pentane	C
11	ether/pet. ether	C	23	methanol/pentane	C
12	THF/hexanes	O			

√ = suitable quality; C = crystals; O = oiled out; N = no change

A large number of the experiments yielded crystals after 22 days but only three of them (entries 9, 10 and 20) produced crystals that were considered of sufficient quality to attempt X-ray diffractometry crystallography. The remainder either oiled out or produced no crystals whatsoever. Of the three selected, the crystals derived by liquid diffusion from toluene and hexanes yielded an X-ray crystal structure (Figure 2.13); the THF/pentanes crystals did not and the ethyl acetate/pentane crystals were not attempted.

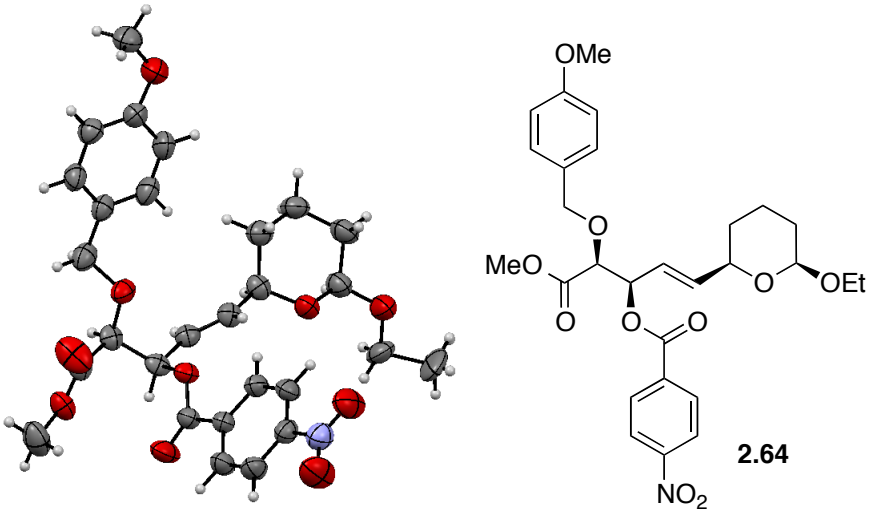


Figure 2.13 X-ray crystallographic evidence for relative stereochemistry

The crystal structure data substantiated the predicted relative stereochemistry for the product bolstering our confidence in the synthetic strategy we had employed.

2.6 Installation of Coupling-Handle

Since a route to the stereo-defined core of the Eastern Hemisphere had now been elucidated, attention shifted to completion of the complete carbon skeleton with a particular focus on the method by which it would be joined to the Western Hemisphere. With reference to the preliminary retrosynthetic plan the most accessible end for modification is that of the methyl ester containing C12 of the final product (Figure 2.14).

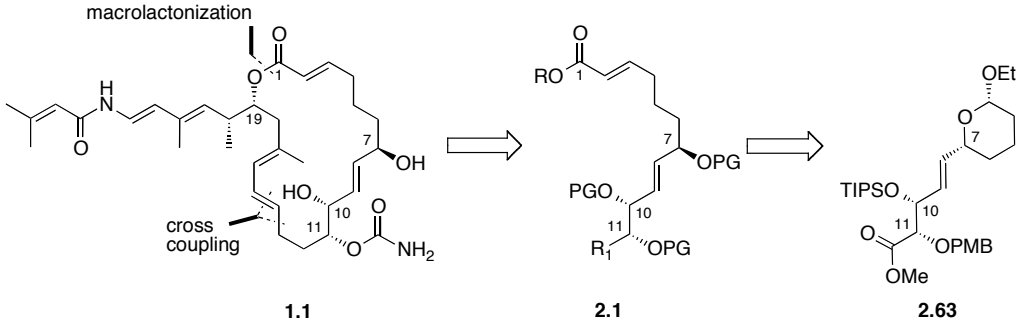


Figure 2.14 Advanced intermediate 2.63 in the context of retrosynthesis of 1.1

One possible functional group substituting for R^1 in **2.1** that could be readily utilized would be an olefin; immediately amenable to B-alkyl Suzuki cross coupling (Figure 2.15).

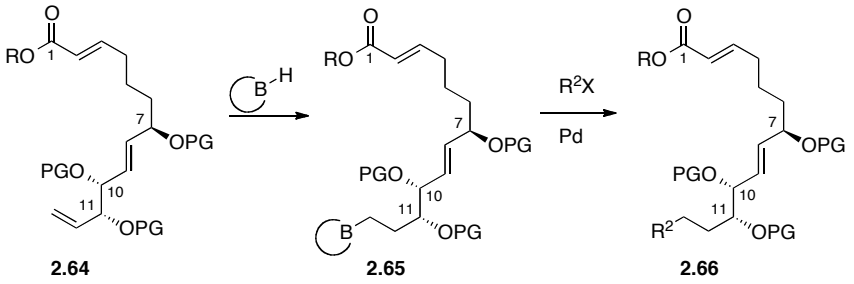
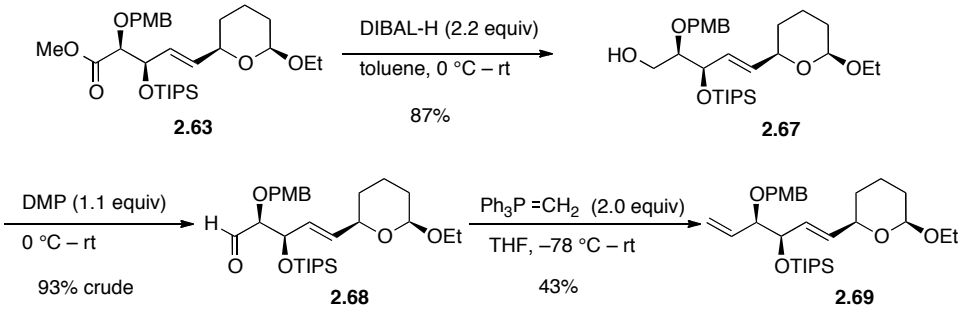


Figure 2.15 B-alkyl Suzuki coupling strategy for combining the hemispheres

A substrate such as **2.64** with a pendant olefin when subjected to hydroboration would give rise to borane intermediate **2.65** that could then be cross coupled to an appropriately activated coupling partner connecting the two hemispheres together to form intermediates of type **2.66**.

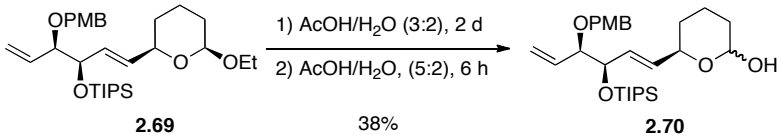
The first attempt to install the handle proceeded smoothly (Scheme 2.18). First, methyl ester **2.63** was reduced to alcohol **2.67** with diisobutylaluminum hydride (DIBAL-H) in 87% yield. Second, oxidation with Dess-Martin periodinane (DMP) afforded crude aldehyde **2.68** which was used directly with no further purification in a Wittig reaction furnishing olefin **2.69** in 43% yield. The final yield was suboptimal but not unreasonable on the milligram scale employed in the first attempt; the yield was optimized later in the synthesis.



Scheme 2.18 First installation of coupling-handle

2.7 Completion of the Eastern Hemisphere's Carbon Skeleton

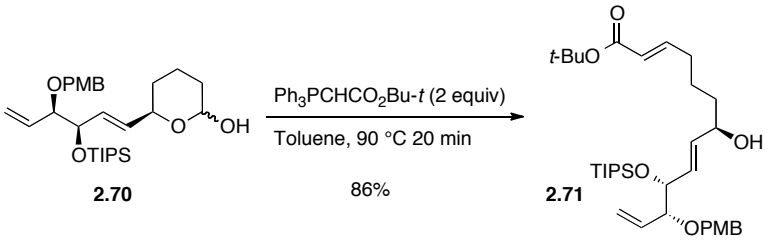
The move towards completion of the Eastern Hemisphere of palmerolide A continued with hydrolysis of the acetal unit contained in the 2-ethoxy dihydropyran ring of **2.69** (Equation 2.11).



Equation 2.11

The hydrolysis proceeded very slowly initially with less than 50% conversion after 2 days. It was noted that the "solution" was turbid, indicating poor solubility of the substrate due to high water content. Increasing the percentage of acetic acid from 60% to 71% clarified the solution and disappearance of starting material detected by thin layer chromatography (TLC) occurred within 6 hours. The yield was poor but a small quantity of substrate did not allow for optimization at this time and the product was carried forward to the next step.

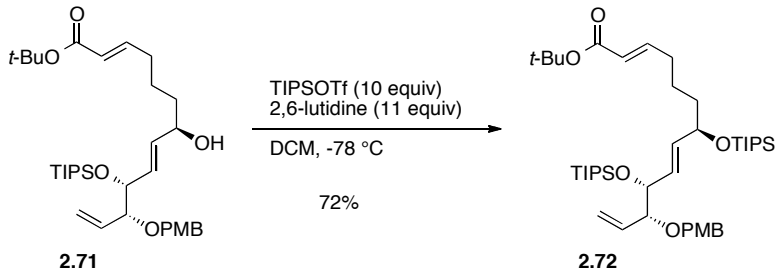
The ring opening Wittig reaction that elaborated the remainder of the carbon skeleton of the Eastern Hemisphere proceeded smoothly on first attempt with an 86% yield of **2.71** (Equation 2.12).



Equation 2.12

The remaining step was to protect the allylic alcohol on C7. The TIPS protecting group was selected as a robust protecting group expected to remain in

place until the end of the synthesis when it could be removed in a global deprotection along with the other TIPS protected alcohol at C10. Earlier in the synthesis it had been discovered that TIPSOTf would cleave *tert*-butyl esters under the standard conditions employed in protecting the C10 alcohol. A literature precedent was found for the application of a TIPS protecting group using TIPSOTf in the presence of a *tert*-butyl ester and successfully employed for the protection (Equation 2.13).[77] Following the original procedure, only two equivalents of TIPSOTf were added initially but this was increased incrementally along with the equivalents of 2,6-lutidine after the reaction proved to be sluggish.



Equation 2.13

2.8 Asymmetric Synthesis of the Eastern Hemisphere

Armed with a viable racemic route to the Eastern Hemisphere, synthetic efforts were directed towards an asymmetric synthesis wherein all stereocentres would be absolutely determined; coincident with the objective of improving suboptimal steps in the sequence. At this point in time we were aware of the revised structure of palmerolide A that had been published (Figure 2.16).[15,19,46]

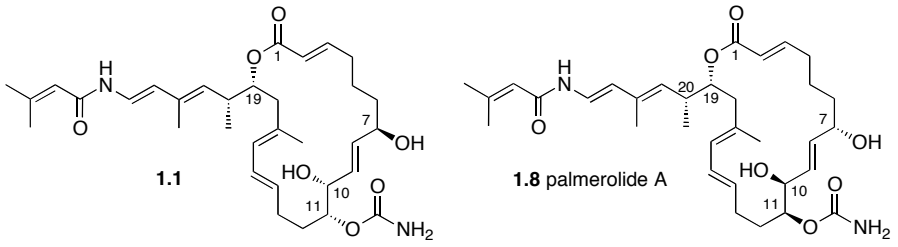
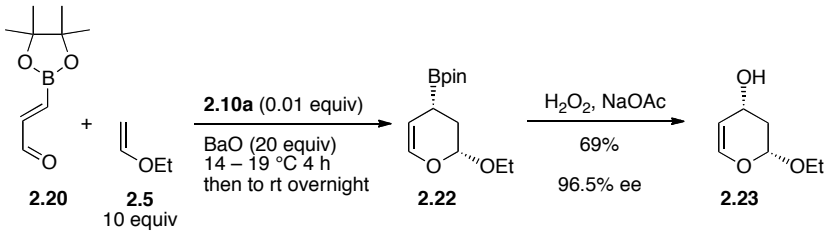


Figure 2.16 Originally published (1.1) and revised (1.8) structures of palmerolide A

The revision fortunately did not obviate the synthetic strategy that had been employed in the racemic synthesis of the Eastern Hemisphere. Both the originally published **1.1** and revised structures **1.8** have the same relative stereochemistry within the Eastern Hemisphere. Obtaining the correct isomer thus depended only on selection of the correct enantiomer of Jacobsen's catalyst; either **2.10a** or **2.10b**. Predicated upon the work of Gao and the Carboni group, catalyst **2.10a** would provide the desired absolute stereochemistry.

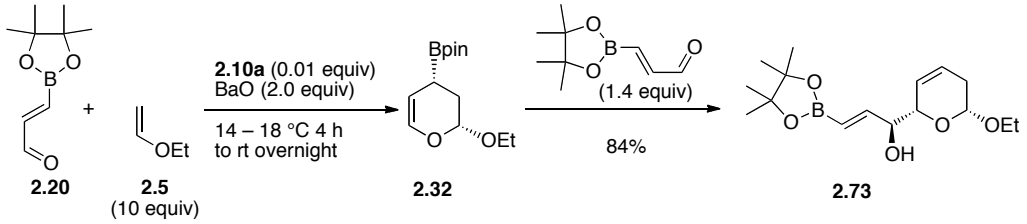
2.8.1 Asymmetric IEDHDA/Allylboration

After synthesizing a fresh supply of **2.10a** the standard test of enantioselectivity was employed (Scheme 2.19). There was a slight increase in enantiomeric excess of 96.5% compared with the 95% first attained now matching that achieved by Gao. There are four variables to which this might be attributed: 1) A different supplier of the amino-indanol **2.41** was employed; 2) An extra chromatographic step was introduced; 3) Schlenk techniques were utilized in the preparation; 4) The technical skills employed in the synthesis had improved since the first synthesis.



Scheme 2.19 Enantioselectivity of newly synthesized catalyst 2.10a

Following substantiation of the catalyst's efficacy, efforts were directed in applying it to synthetically meaningful IEDHDA/allylborations. As already noted, application of **2.10** to IEDHDA reactions requires a drying agent such as molecular sieves or barium oxide. This proved to be problematic in transferring the developed methodology from the racemic to the asymmetric reaction; $Yb(fod)_3$ **2.24** does not require any drying agent. The molecular sieves interfered with the removal of excess ethyl vinyl ether necessary for the allylboration with **2.20** to occur. For this reason the sequential A+B+A multicomponent one pot reaction required a simple additional operation that converted it into a two pot reaction. After the IEDHDA stage in the sequence it was necessary to filter the reaction product through Celite® prior to removing the excess ethyl vinyl ether (Scheme 2.20).

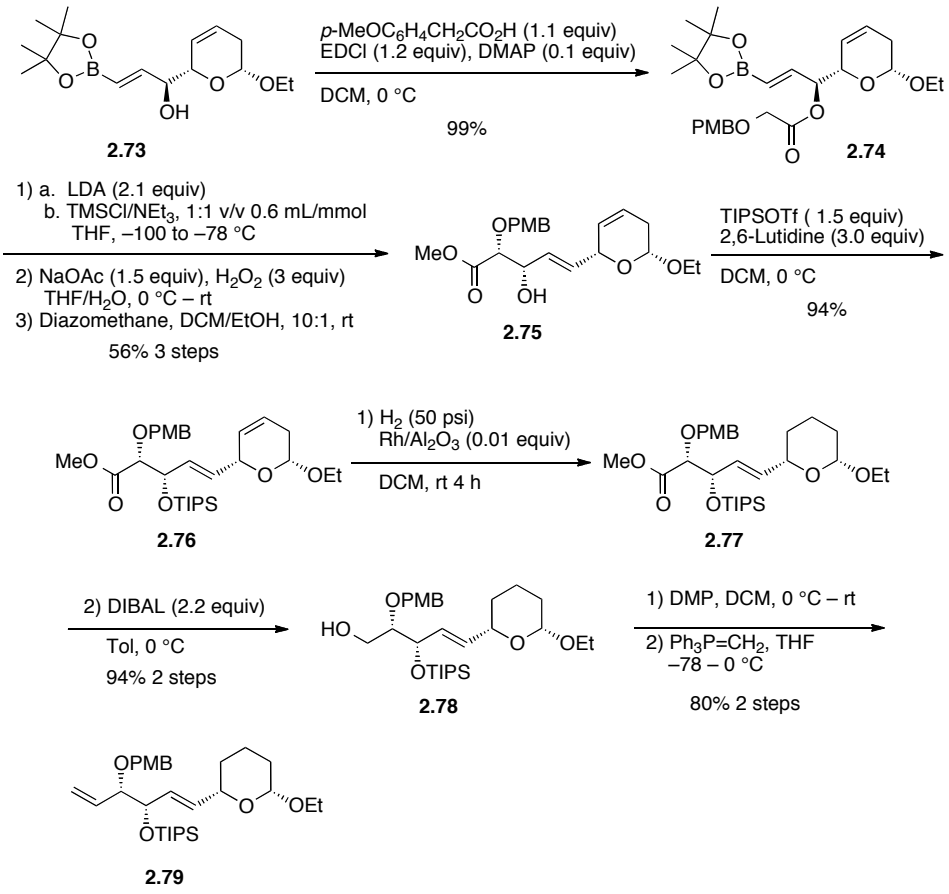


Scheme 2.20 Asymmetric IEDHDA/allylboration

The modified procedure was still high yielding (84%) for **2.73** but not as high as the racemic version (93%) and could also be carried out on a multigram scale.

2.8.2 Execution of the Asymmetric Borono-Ireland-Claisen Rearrangement and Elaboration to the Downstream Olefin

Following the optimization of the asymmetric variant of the IEDHDA/allylboration the subsequent nine steps developed for the racemic synthesis were readily transferred (Scheme 2.21). Attachment of the PMB acetate unit to **2.73** was carried out many times over the course of the synthesis in yields of **2.74** approaching quantitative. The subsequent borono-Ireland-Claisen sequence was also optimized effectively such that an average of 82% per step was attained enroute to methyl ester **2.75**. Formation of **2.76** by TIPS protection was another high yielding reaction 94%. While optimizing on the current larger scale it was noted that better yields could be obtained by reducing the number of purifications employed. For instance, alcohol **2.78** was carried through two uninterrupted steps in 94% yield rather than purifying **2.77** after the selective hydrogenation before subjecting it to DIBAL-H reduction followed by another purification. Likewise, oxidation of alcohol **2.78** immediately followed by a Wittig reaction gave access to the desired olefin **2.79** in 80% yield over the two steps.

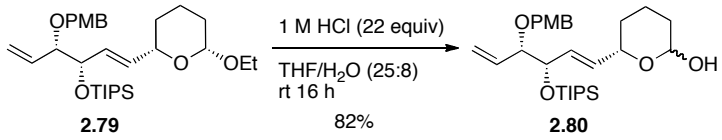


Scheme 2.21 Optimised sequence of nine steps from 2.73

2.8.3 Hydrolysis and Ring-Opening/Wittig

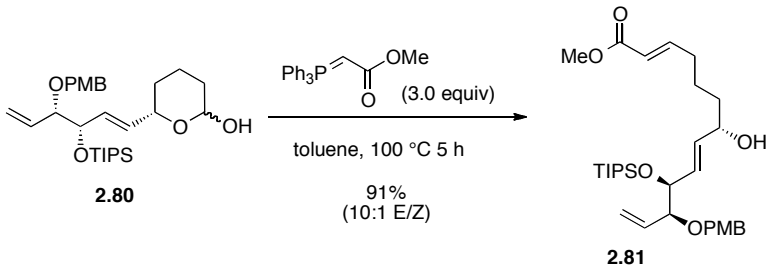
During the last stages of the racemic synthesis of the Eastern Hemisphere none of the transformations were optimized due to the limited quantity of available substrate; hence the poor yield (38%) of the acetal hydrolysis of **2.69** to **2.70** (Equation 2.11). Attempts to optimize the methodology using acetic acid and water on a large scale were frustrated by reaction times of days, incomplete conversions and substrate decomposition during those long reaction times. The use of various Lewis acids resulted in even greater decomposition. At the suggestion of a collaborator in the project, Dr. Vivek Rauniyar, hydrolysis conditions employing aqueous hydrochloric acid in THF were attempted. One of the problems associated with other hydrolysis conditions was the insolubility of

substrate **2.79** in aqueous acidic solutions. The use of THF in the correct ratio with water addressed this issue effectively. Thus an efficient hydrolysis condition was found after optimizing this ratio providing **2.80** in good yield (Equation 2.14).



Equation 2.14

The remaining critical transformation was the ring opening/Wittig reaction. During the racemic synthesis (*t*-butoxycarbonylmethylene)-triphenylphosphorane was used to form *t*-butyl ester **2.71** (Equation 2.12). Dr. Ludwig Kaspar and Dr. Vivek Rauniyar, who were occupied with the synthesis of the Western Hemisphere, suggested that it would be preferable to synthesize a methyl ester here instead of the *t*-butyl ester in order to avoid conflicting protecting group strategies between the Western Hemisphere and Eastern Hemispheres. Thus, (methoxycarbonylmethylene)triphenylphosphorane was employed as a reagent for the ring opening/Wittig reaction (Equation 2.15).

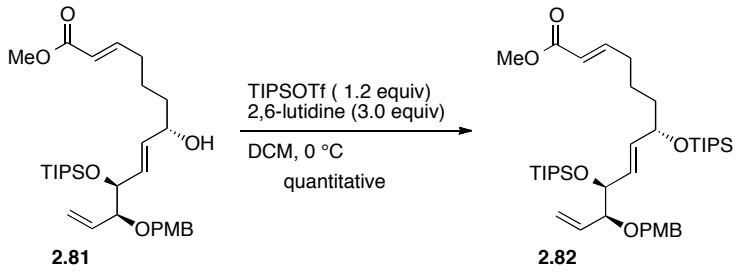


Equation 2.15

Under optimized conditions the transformation required slightly more forcing conditions (more equivalents, higher temperature & longer reaction time) than the previous ring opening/Wittig but it still proceeded in excellent yield (91%) and good diastereoselectivity (E/Z, 10:1).

2.8.4 Completion of the Eastern Hemisphere

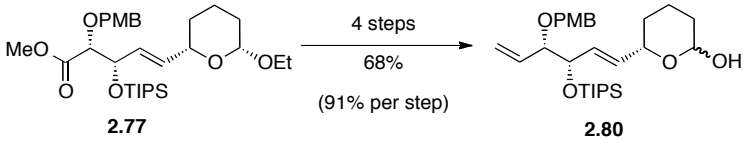
The last obstacle to completion of the Eastern Hemisphere within the scope of the synthetic plan was protection of the free alcohol on **2.81**. In the racemic synthesis this was complicated by loss of the *t*-butyl ester in the presence of TIPSOTf. With the introduction of the methyl ester this was no longer an issue and standard protection conditions were employed with no complication allowing quantitative yields of the fully TIPS protected product **2.82** (Equation 2.16).



Equation 2.16

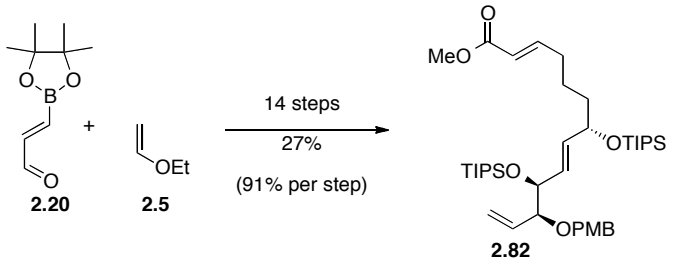
2.9 Final Optimizations

During the scale up operations towards completion of the natural product further optimizations took place by carrying crude material forward over multiple steps with only one chromatographic purification at the end. In one case the selectively hydrogenated substrate **2.77** underwent four transformations to the hemiacetal ring opening precursor **2.80** in 68% overall yield, averaging 91% per step (Scheme 2.22).



Scheme 2.22 Efficient multi-step conversions

Thus it became possible to synthesize Eastern Hemisphere coupling partner **2.82** in an overall yield of 27% over 14 steps from borono acrolein pinacolate **2.20** and ethyl vinyl ether **2.5** with an overall step efficiency of 91% per step (Scheme 2.23).



Scheme 2.23 Peak efficiency attained for the synthesis of the Eastern Hemisphere

2.10 Summary

The synthesis of the Eastern Hemisphere **2.82** was thus accomplished essentially in accordance with the retrosynthetic plan originally envisioned. A significant modification was necessitated by the modification of the originally published structure but this had no detrimental impact since it only affected the selection enantiomer selection of Jacobsen's catalyst **2.10** and the revision occurred during the racemic work. In the course of exploring the transformations necessary to synthesize the Eastern Hemisphere a unique variation of the Claisen rearrangement, the borono-Ireland-Claisen rearrangement, was developed. This enabled the generation of all the stereocentres of the Eastern Hemisphere from a single catalytic enantioselective event; within an inverse electron demand hetero Diels-Alder/allyboration sequence. The key [4+2] reaction was also demonstrated to have high enantioselectivity (96.5%). A few key selectivity difficulties arose (eg. selective hydrogenation) but were overcome and the overall route was optimized such that there was an excellent average step efficiency of 91% per step.

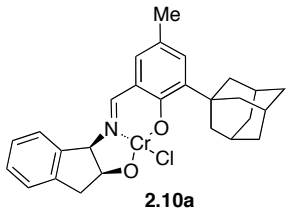
2.11 Experimental

2.11.1 General

Experiments were conducted under an argon atmosphere using oven or flame dried glassware unless otherwise noted. During the segment of the project devoted to the total synthesis, reaction solvents were prepared as follows: THF was distilled over sodium/benzophenone; toluene, methanol, acetonitrile and DCM were distilled over calcium hydride. During the portion of the project devoted to analogue synthesis, the following solvents were pre-treated with a Fisher Scientific-MBraun MB SPS* solvent system: THF, methanol and DCM. Other solvents were used directly from the manufacturer or differences are detailed in the individual experiments. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254. NMR measurements were performed with Varian INOVA-300, INOVA-400, INOVA-500, Unity 500, INOVA-700 and INOVA-800 instruments. Residual solvent protons (^{1}H) and carbons (^{13}C) were used as internal standards. Boron NMR spectra used BF_3•OEt as an external standard. ^{1}H NMR reports use the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; b, broad; m, mulitplet; and combinations thereof (e.g. dd, doublet of doublets). Coupling constants are reported with an expected error of ± 0.1. High resolution mass spectrometry measurements were made by the University of Alberta Mass Spectrometry Services Laboratory on the following instruments: Kratos Analytical MS-50 (electron impact ionization = EI), Applied Biosystems Mariner Workstation (electrospray ionization = ESI) and Agilent 6220 Accurate-Mass TOF (ESI). The University of Alberta Analytical Services performed the following measurements on their respective instruments: infrared (IR Nicolet Magna-IR Spectromer 750 with a Nic-Plan IR Microscope and a Nicolet 8700 IR with a Nicolet-Continuμm); optical rotation (Perkin Elmer 241 Polarimeter); elemental analysis (Carlo Erba Insruments CHNS-0 EA1108-Elemental Analyzer); and differential scanning calorimetry (DSC Perkin Elmer Pyrus 1 DSC). Mass measurements were generally made on a Denver Instruments M-220 balance in triplicate (minimum) taking the average. The late

stage products of the total synthesis were weighed on a Sartorius micro balance. Chiral HPLC measurements were made on a Hewlett Packard Series 1100 instrument. High vacuum used for flame drying or removing residual solvent was provided by an Edwards RV5 pump attached to a glass manifold manufactured by the University of Alberta Chemistry Department Glass Shop.

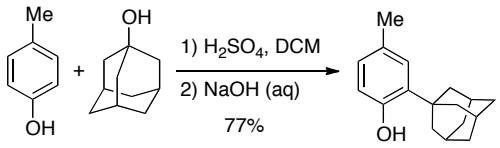
2.11.2 Chloro[(1R,2S)-2,3-dihydro-1-[[[2-(hydroxy-κO)-5-methyl-3-tricyclo[3.3.1.13,7]dec-1-ylphenyl]methylene]amino-κN]-1H-inden-2-olato(2-)-κO]-chromium (2.10a)



2.10a

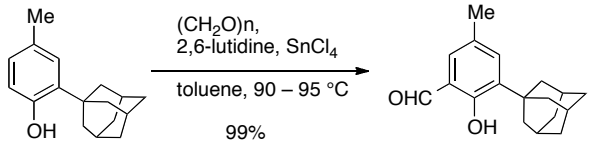
2.11.2.1 Preparation of 2.10a

The following section describes the preparation of the best performing batch of **2.10a**.



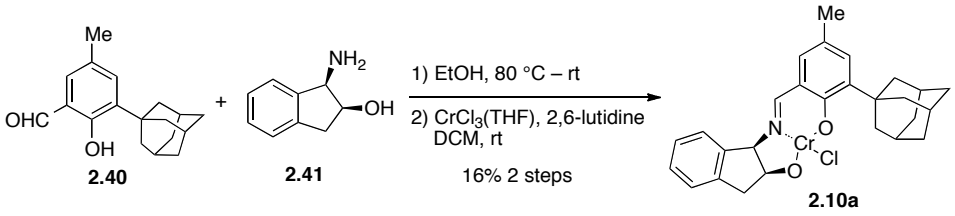
2.37 **2.38** **2.39**

Preparation of **2.39** followed that of Jacobsen's published work[53] with exception that product **2.39** was purified by flash chromatography following the synthesis rather than directly moving the crude product to the next step.



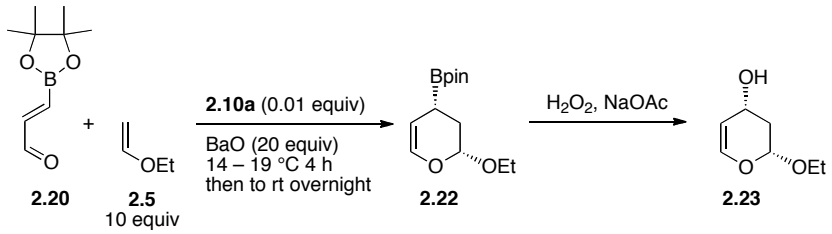
2.39 **2.40**

Preparation of **2.49** followed Jacobsen's published procedure[67] with the additional use of Schlenk apparatus to maintain inert atmosphere conditions during reagent additions.



Synthesis of **2.10a** followed Jacobsen's published procedure[67] with the exception that a 9:1 acetone/water mixture was used to isolate the product after workup. The use of water enhanced the yield by forcing more product out of solution.

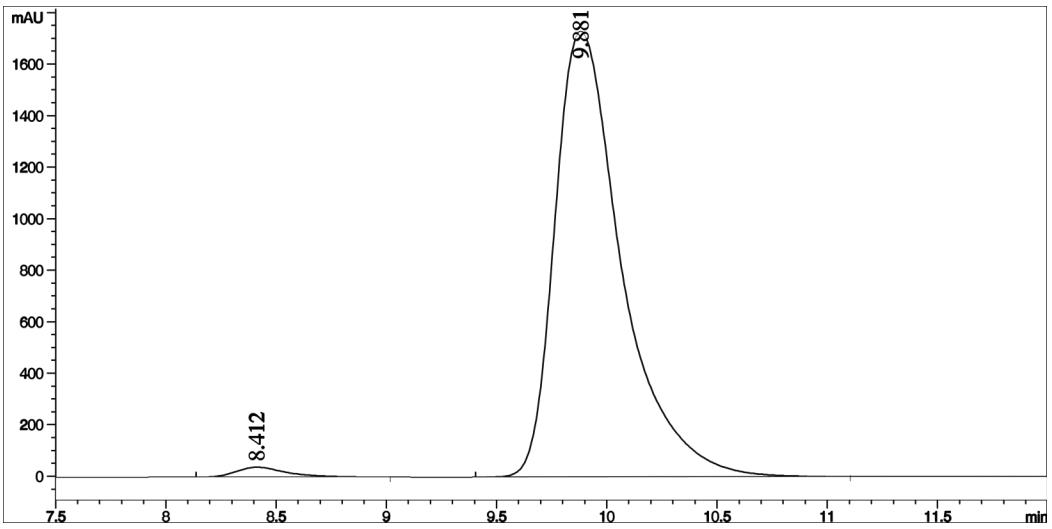
2.11.2.2 Evaluation of Catalyst Performance



Ethyl vinyl ether was freshly distilled off of potassium hydroxide after stirring over potassium hydroxide for 30 minutes and stored under argon until ready for use. E-3-boronoacrolein **2.20a** (0.500 g, 5.01 mmol, 1.1 equiv) was stirred with pinacol (0.538 g, 4.55 mmol, 1.0 equiv) in THF (5 mL) for 30 minutes. The reaction mixture was co-distilled (3 X 5 mL) with THF and purified by bulb-to-bulb distillation with a Kugelrohr apparatus (T = 100 ºC; under high vacuum; collection bulb cooled with dry ice). The purified E-3-boronoacrolein pinacolate (0.498 g, 2.74 mmol, 1.0 equiv) was combined with ethyl vinyl ether (1.97 g, 27.4 mmol, 10.0 equiv) and barium oxide (0.84 g, 5.5 mmol, 2.0 equiv) and cooled to 18 ºC. Catalyst **2.10a** (0.845 g, 0.0820 mmol, 0.03 equiv) was added and the reaction mixture was stirred for 5 hours while maintaining the temperature at 14–19 ºC and then allowed to warm to ambient temperature stirring overnight. The reaction mixture was filtered through Celite® rinsing with THF and concentrated under reduced pressure. It was then diluted with THF (10 mL) and cooled to 0 °C. A 3M solution aqueous sodium acetate (1.4 mL, 4.11 mmol, 1.5 equiv) was added dropwise followed by dropwise addition of 9.79 M aqueous hydrogen

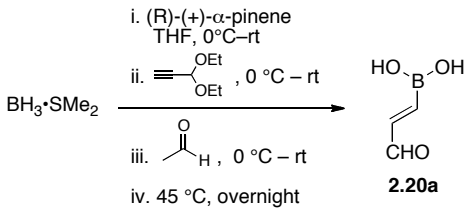
peroxide (0.92 mL, 9.01 mmol, 3.3 equiv) and stirred for 1 hour at 0 °C. The reaction mixture was diluted with water (10 mL), extracted with Et_2O (2 x 30 mL), washed once with saturated aqueous ammonium chloride, once with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane/diethyl ether, 5:1) with silica deactivated with triethylamine affording 0.274 g of **2.23** as a colourless oil. Yield: 69%. NMR spectral data matched those found in the literature[66] but traces of impurity were visible thus necessitating a second purification by flash chromatography in order to have suitable material for determination of enantiomeric excess.

A 1.4 mg/mL solution of **2.23** was prepared and the enantiomeric excess of **2.23** was assayed by chiral HPLC under the following conditions: Column: Chiralpak AD-RH; Mobile phase: 50% 2-propanol/H_2O; Injection volume: 0.5 μL; λ = 210.8 nm; t_R (minor) = 8 min; t_R (major) = 10 min; 96.5% ee.



Iteration	1		2		3	
Peak #	1	2	1	2	1	2
Retention Time (min)	8.412	9.881	8.412	9.893	8.419	9.891
Area (%)	1.7569	98.2431	1.7708	98.2292	1.7480	98.252
%ee	96.49		96.46		96.50	

2.11.3 E-3-Boronoacrolein (2.20a)



A 350 mL pressure flask was charged with borane dimethyl sulfide complex[2] (5.85 g, 77.0 mmol, 1.1 equiv) and THF (20 mL) under nitrogen. It was cooled to 0 ˚C and (R)-(+)-α-pinene (21.0 g, 154 mmol, 2.2 equiv) was added dropwise. The reaction mixture was allowed to stir for 10 minutes at 0 ˚C then for 2 hours at room temperature. The solution turned from clear to cloudy and white. The suspension was cooled to 0 ˚C and to it was added propionaldehyde diethylacetal (8.97 g, 70.0 mmol, 1.0 equiv) dropwise. The suspension clarified into a solution after the addition was complete. The reaction was stirred for 1 hour at 0 ˚C then for 1 hour at room temperature. It was then cooled to 0 ˚C and freshly distilled acetaldehyde (35.5 g, 805 mmol, 11.5 equiv) was added. The septum was replaced with a pressure cap. The reaction was stirred at room temperature for 30 minutes then moved to 45 ˚C and stirred overnight. The reaction mixture was then placed in a 0 ˚C ice bath and water (27 mL) was added. The solution turned cloudy on addition. It was stirred for 3 hours at 0 ˚C. Following the 3-hour period the aqueous layer was extracted with Et_2O (2.50 mL) and ethyl acetate (2 *x* 50 mL). The combined organic layers were concentrated under reduced pressure. The solution increased in yellow colour and a white solid precipitated out. The concentrated solution and precipitate were cooled to 0 ˚C and more product was crashed out by addition of ice-cold hexanes. The product was collected by

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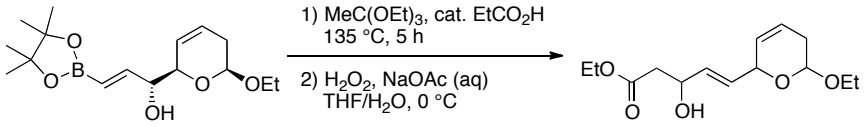
[2] Note: Quality of the borane dimethyl sulfide complex is critical to the outcome of this reaction. It was found that if it was not properly stored under inert atmosphere conditions, yield and quality of the product suffered.

vacuum filtration affording 5.2 g of **2.20a** as an off-white to pale yellow solid. Yield: 74%. **^{1}H NMR** (500 MHz; CD_3OD): δ 9.75 (d, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 18.0 Hz, 1H), 6.87 (dd, *J* = 18.0, 7.7 Hz, 1H). **^{13}C NMR** (125.692 MHz; CD_3OD): δ 197.7, 145.9

2.11.4 ethyl (4E)-5-(6-ethoxy-5,6-dihydro-2H-pyran-2-yl)-3-hydroxypent-4-enoate (2.42)

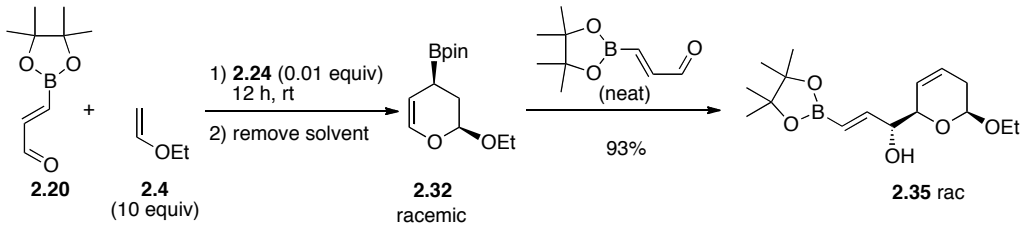


2.35 rac 30% **2.42**

Pinacol boronate **2.35** (0.102 g, 0.328 mmol, 1.0 equiv) and triethylorthoacetate (0.373 g, 2.30 mmol, 7.0 equiv) and propionic acid (1.46 mg, 0.0197 mmol, 0.06 equiv) were added sequentially to a 5 mL round bottom flask. The reaction mixture was stirred at 135 °C for 5 hours, interrupted periodically for removal of aliquots for NMR analysis. After 3 hours, additional triethylorthoacetate (0.44, 2.7 mmol, 8.2 equiv) along with a drop of propionic acid were added due to volume loss. Crude ^{1}H NMR revealed consumption of the majority of the starting material after 5 hours. The reaction mixture was cooled to 0 °C and 3 M aqueous sodium acetate (0.2 mL) was added dropwise and diluted with THF (0.5 mL). Aqueous hydrogen peroxide (0.11 mL, ~9.8 M) was added dropwise and the mixture was stirred for 1 hour at 0 °C. It was diluted with water (2 mL) and extracted with diethylether (3 *x*), washed with saturated aqueous ammonium chloride (3 *x*) and brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (Et_2O/hexanes, 1:1) affording 26.6 mg of **2.42** as an oil. Yield: 30%. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 5.83-5.79 (m, 2H), 5.77-5.71 (m, 1H), 5.59 (dq, J = 10.1, 1.9 Hz, 1H), 4.73 (t, J = 5.5 Hz, 1H), 4.70 (m, 1H), 4.55 (dt, J = 8.3, 4.1 Hz, 1H), 4.18 (d, J = 7.1 Hz, 1H), 4.16 (d, J = 7.1 Hz, 1H), 3.95 (dq, J = 9.5, 7.1 Hz, 1H), 3.52 (dq, J = 9.5, 7.1 Hz, 1H), 2.96 (bs, 1H), 2.61-2.48 (m, 2H), 2.21-2.18 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz;

$CDCl_3$): δ 172.1, 132.3, 130.6, 128.0, 123.2, 98.2, 74.4, 68.1, 63.9, 60.7, 41.2, 30.7, 15.0, 14.1; **HRMS** (EI) Calcd. $C_{14}H_{22}O_5$: 270.14673 Found: 270.14575.

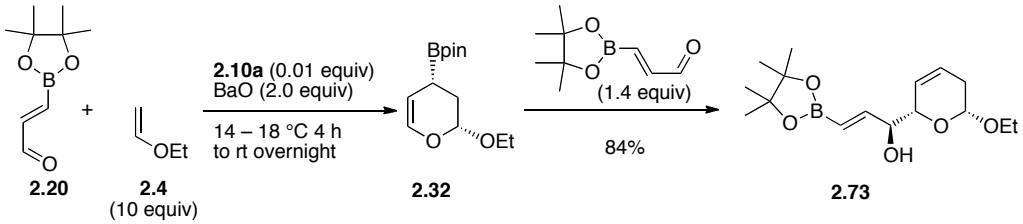
2.11.5 (2E)-1-[(2S,6R)/(2R,6S)-6-ethoxy-5,6-dihydro-2H-pyran-2-yl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (2.35)



Ethyl vinyl ether was freshly distilled off of potassium hydroxide after stirring over potassium hydroxide for 30 minutes and stored under nitrogen until ready for use. E-3-boronoacrolein **2.20a** (1.1 g, 11.2 mmol, 1.1 equiv) with pinacol (1.2 g, 10.2 mmol, 1.0 equiv) were stirred in THF (5 mL) for 30 minutes then co-distilled (5 *x* 5 mL) with THF and purified by bulb to bulb distillation with a Kugelrohr apparatus (T = 100 ˚C; under high vacuum; collection bulb cooled with dry ice). Purified E-3-boronoacrolein pinacolate (1.34 g, 7.36 mmol, 1.0 equiv) was combined with ethyl vinyl ether (5.31 g, 73.6 mL, 10 equiv) and Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium **2.24** (0.074g, 7.4 mmol, 0.01 equiv) and stirred overnight at room temperature. Excess ethyl vinyl ether was removed under reduced pressure and resulting product was combined with E-3-boronoacrolein pinacolate (1.46 g, 8.02 mmol, 1.1 equiv) and stirred overnight at room temperature. The resulting product was pale yellow in colour and too viscous to stir. It was diluted with ether (6 mL) combined with a saturated aqueous solution of sodium bicarbonate (6 mL) and stirred 1 hour. The aqueous layer was extracted with ether (4 *x*), washed with water (3 *x*) and washed with brine (1 *x*), dried with magnesium sulphate, filtered and concentrate under reduced pressure. The crude product was filtered or flashed through a short silica column deactivated with triethyl amine eluting with a pentane/ether (1:1) solution affording 2.1 g of 2.35 as a viscous yellow coloured oil. Yield: 93%. **IR** (cast film) 3470, 2978, 2931, 2874, 1644, 1357, 1323, 1146, 1062, 850 cm^{-1}; **^{1}H NMR**

(500 MHz; $CDCl_3$): δ 6.67 (dd, *J* = 18.1, 5.3 Hz, 1H), 5.87-5.80 (m, 2H), 5.69 (dq, *J* = 10.3, 1.9 Hz, 1H), 4.77 (dd, *J* = 6.6, 4.0 Hz, 1H), 4.26-4.21 (m, 1H), 4.16-4.13 (m, 1H), 3.98-3.92 (m, 1H), 3.60-3.53 (m, 1H), 3.09-2.94 (m, 1H), 2.30-2.16 (m, 2H), 1.27 (s, 12H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 150.6, 125.7, 124.7, 98.13, 150.61, 125.7, 124.7, 98.1, 83.3, 76.8, 75.7, 64.5, 30.8, 24.78, 24.71, 15.1; **^{11}B NMR** (128 MHz; $CDCl_3$): δ 29.8; **HRMS** (ESI) Calcd. $C_{16}H_{27}BO_5$+Na: 333.18438 Found: 333.18452.

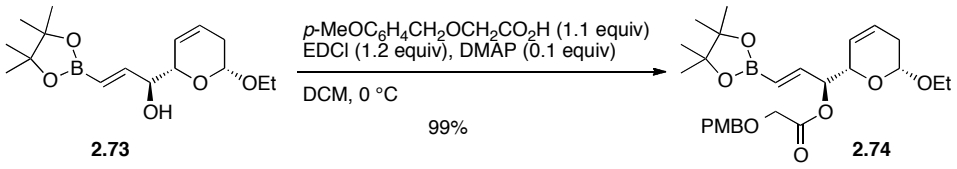
2.11.6 (2E)-1-[(2S,6R)-6-ethoxy-5,6-dihydro-2H-pyran-2-yl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (2.73/2.55)



Ethyl vinyl ether was freshly distilled off of potassium hydroxide after stirring over potassium hydroxide for 30 minutes and stored under argon until ready for use. E-3-boronoacrolein **2.20a** (2.0 g, 20.0 mmol, 1.1 equiv) was stirred with pinacol (2.1 g, 18.2 mmol, 1.0 equiv) in THF (10 mL) for 30 minutes. The reaction mixture was co-distilled (5 *x* 10 mL) with THF and purified by bulb to bulb distillation with a Kugelrohr apparatus (T = 100 ºC; under high vacuum; collection bulb cooled with dry ice). The purified E-3-boronoacrolein pinacolate (1.86 g, 10.2 mmol, 1.0 equiv) was combined with ethyl vinyl ether (7.36 g, 102 mmol, 10 equiv) and barium oxide (3.13g, 20.4 mmol, 2.0 equiv) and cooled to 18 ºC. Catalyst **2.10a** (0.105 g, 0.102 mmol, 0.01 equiv) was added and the reaction mixture was stirred for 5 h maintaining the temperature at 14–18 ºC and then allowed to warm to ambient temperature stirring overnight. Vacuum filtration through Celite® was used to remove barium oxide rinsing with dichloromethane. Solvent was removed under reduced pressure co-distilling with dichloromethane to remove traces of ethyl vinyl ether. The inverse electron demand hetero-Diels-Alder product **2.32** was dark brown in colour due to presence of Jacobsen's

catalyst. More E-3-boronoacrolein pinacolate (2.64 g, 14.5 mmol, 1.4 equiv) was prepared as above and combined with **2.32** and stirred at ambient temperature overnight. The product became too viscous to stir and was dark brown in colour. The crude product was diluted with THF (10 mL) and to it was added a saturated solution of sodium bicarbonate (10 mL). This was diluted further with water to dissolve solids that formed and stirred for 1 hour. The aqueous layer was extracted with ether (4 *x*). The combined organic layer was washed with water (4 *x*) and brine (1 *x*), dried with magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by passing it through a short column of silica gel (pentane/Et_2O, 1:1, 1% triethylamine). Solvent was removed under reduced pressure codistilling with dichloromethane to remove traces of triethylamine. Product **2.73** was redissolved in ether and washed with water (4 *x*) and brine (1 *x*), to remove pinacol contamination, dried with magnesium sulphate, filtered and concentrated under reduced pressure, affording 2.7 g of **2.73** as a rust coloured viscous oil. Yield: 84%. $[\alpha]_D^{25}$–64.0 (*c* 1.02, $CHCl_3$); **IR** (cast film) 3470, 2978, 2931, 2874, 1644, 1357, 1323, 1146, 1062, 850 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 6.64 (dd, *J* = 18.1, 5.3 Hz, 1H), 5.85-5.80 (m, 2H), 5.70-5.67 (m, 1H), 4.76 (dd, *J* = 6.6, 3.9 Hz, 1H), 4.23-4.20 (m, 1H), 4.12-4.08 (m, 1H), 3.95 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.55 (dq, *J* = 9.6, 7.1 Hz, 1H), 2.90 (d, *J* = 5.0 Hz, 1H), 2.29-2.17 (m, 2H), 1.27 (s, 12H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 150.6, 125.7, 124.7, 98.13, 150.61, 125.7, 124.7, 98.1, 83.3, 76.8, 75.7, 64.5, 30.8, 24.78, 24.71, 15.1; **^{11}B NMR** (128 MHz; $CDCl_3$): δ 29.8; **HRMS** (ESI) Calcd. $C_{16}H_{27}BO_5$+Na: 333.18438. Found: 333.18452.

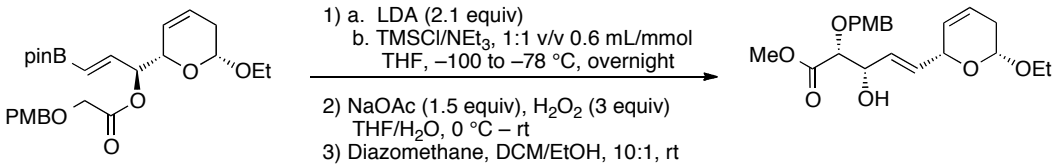
2.11.7 (2E)-1-[(2S, 6R)-6-Ethoxy-5,6-dihydro-2-pyran-2-yl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-yl[(4-methoxybenzyl)oxy]acetate (2.74/2.52)



Alcohol **2.73** (5.37 g, 17.3 mmol, 1.0 equiv), p-methoxybenzyloxy acetic acid (3.73, g, 19.0 mmol, 1.1 equiv) and dimethylamino pyridine (0.211 g, 1.73 mmol, 0.1 equiv) were combined in DCM (50 mL) and cooled to 0 ºC.

N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.99 g, 20.8 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 0 ºC and allowed to warm to ambient temperature overnight. The crude mixture was concentrated under reduced pressure then partitioned between ethyl acetate and water. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (3 *x*), water (3 *x*) and once with brine. The organic layer was dried with magnesium sulphate, filtered, and concentrated under reduced pressure, affording 7.4 g of **2.74** as a rust coloured oil. Yield: 99%. $[\alpha]_D^{25}$ –73.8 (*c* 1.00, $CHCl_3$); **IR** (cast film) 2978, 2934, 2837, 1757, 1645, 1613, 1515, 1363, 1330, 1250, 1144, 1124 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.31-7.29 (m, 2H), 6.89-6.88 (m, 2H), 6.60 (dd, *J* = 18.2, 5.1 Hz, 1H), 5.81 (ddt, *J* = 10.2, 4.8, 2.5 Hz, 1H), 5.70 (dd, *J* = 18.2, 1.6 Hz, 1H), 5.62-5.59 (m, 1H), 5.56 (dt, *J* = 5.3, 1.6 Hz, 1H), 4.67 (dd, *J* = 7.0, 4.2 Hz, 1H), 4.57 (ABq, *J* = 11.3 Hz, 2H), 4.40-4.37 (m, 1H), 4.11 (ABq, *J* = 16.6 Hz, 2H), 3.91 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.51 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.24-2.15 (m, 2H), 1.26 (s, 12H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 169.6, 159.5, 145.9, 129.8, 129.2, 125.8, 125.1, 113.9, 98.6, 83.4, 75.9, 75.1, 72.9, 66.7, 64.3, 55.3, 31.0, 24.8, 24.7, 15.2; **^{11}B NMR** (128 MHz; $CDCl_3$): δ 29.3; **HRMS** (ESI) Calcd. $C_{26}H_{37}BO_8$+Na: 511.24737. Found: 511.24777.

2.11.8 Methyl (3S,4S,5E)-6-[(2S,6R)-6-ethoxy-5,6-dihydro-2H-pyran-2-yl]-4-hydroxy-3-[(4-methoxybenzyl)oxy]hex-5-enoate (2.75/2.55)

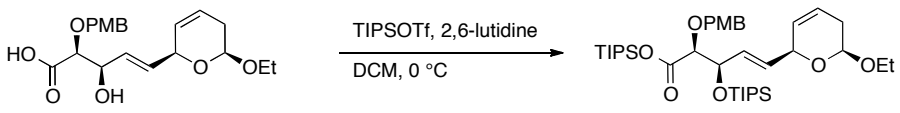


2.52 56% (3 steps, 82% per step) **2.55**

A long necked 500 mL round bottom flask was charged with THF (85 mL) and diisopropylamine (1.9 mL, 13 mmol, 2.2 equiv) freshly distilled from calcium hydride and cooled to –78 °C. To this was added *n*-butyllithium (1.5 M in hexanes, 8.4 mL, 13 mmol, 2.2 equiv) dropwise. The reaction was allowed to stir for 15 minutes at –78 ºC, 15 minutes at 0 ºC and then returned to –78 ºC. Chlorotrimethylsilane (6 mL) was freshly distilled from calcium hydride and placed under argon. To this was added triethylamine (6 mL) also freshly distilled from calcium hydride. On addition of the triethylamine the solution turned cloudy and a gas evolved. The one to one mixture was centrifuged for 15 minutes on the maximum setting and supernatant (10.8 mL) was transferred via syringe to the flask containing the LDA. Boronate **2.52** (2.99 g, 6.12 mmol, 1.0 equiv) was dissolved in THF (85 mL) and both it and the LDA mixture were cooled to –100 ºC (50% Et_2O/2-propanol/N_2(*l*) slurry). The boronate was transferred via cannula into the LDA reaction mixture rinsing with THF (2 *x* 30 mL). The reaction pot was allowed to stir for 1 hour at –100 °C and then moved to –78 °C and allowed to stir overnight. The reaction was quenched with a 3 M aqueous solution of sodium acetate (3.1 mL, 9.2 mmol, 1.5 equiv). To the reaction pot was added aqueous hydrogen peroxide (1.9 mL, 18 mmol, 3 equiv) which was then moved to 0 ºC and allowed to stir for 2 hours. The resulting suspension was diluted with water (200 mL) and acidified to pH ~5 with 1 N HCl and extracted with dichloromethane (3 *x*). The combined organic layers were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude acid (brown oil) was dissolved in a 10:1 mixture of DCM/ethanol (33 mL). A 250 mL round bottom flask was charged with Diazald (3.28 g, 15.3

mmol, 2.5 equiv), which was dissolved in ethanol (40 mL). It gave a pale yellow solution. Argon was bubbled through the Diazald solution and via cannula from there through the solution of acid and finally allowed to escape from the reaction flask via a fine venting needle. To the Diazald reaction pot a 5 M aqueous solution of sodium hydroxide (100 mL, 50 mmol, 82 equiv) was added dropwise over an hour. On addition of the base the yellow colour deepened to a bright yellow, which over the remainder of the addition faded until the solution was colourless. Once the addition was complete the argon sweep was allowed to continue overnight to remove any remaining traces of diazomethane. The crude methyl ester was concentrated under reduced pressure and purified by flash chromatography (pentane/ethyl acetate, 7:3; ~1% triethylamine). Some pinacol contamination was removed by dissolving the product in ether and washing with water (3 *x*). The solution was then washed with brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure affording 1.36 g of **2.55** as a yellow oil. Yield: 56%. $[\alpha]_D^{25}$–52.5 (*c* 1.00, $CHCl_3$); **IR** (cast film) 3475, 2976, 2953, 2934, 2907, 2838, 1748, 1613, 1514, 1250, 1110, 1054, 1026 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): 7.30-7.25 (m, 2H), 6.90-6.87 (m, 2H), 5.85-5.72 (m, 3H), 5.58 (dq, *J* = 10.1, 2.0 Hz, 1H), 4.75-4.69 (m, 3H), 4.45-4.38 (m, 2H), 3.99-3.91 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.53 (dq, *J* = 9.5, 7.1 Hz, 1H), 2.52 (d, *J* = 6.7 Hz, 1H), 2.23-2.20 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 170.9, 159.6, 132.4, 130.0, 129.4, 128.8, 128.1, 123.2, 113.8, 98.2, 80.5, 74.4, 72.77, 72.59, 64.0, 55.3, 52.0, 30.8, 15.2; **HRMS** (ESI) Calcd. $C_{21}H_{28}O_7$+Na: 415.17273. Found: 415.17158.

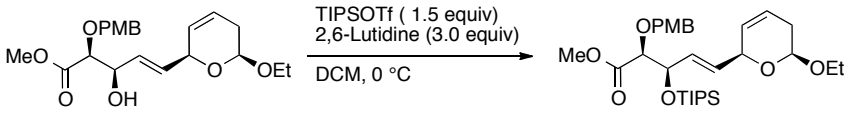
2.11.9 Tri(propan-2-yl)silyl (4E)-4,5-dideoxy-5-[(2S,6R)-6-ethoxy-5,6-dihydro-2H-pyran-2-yl]-2-O-(4-methoxybenzyl)-3-O-[tri(propan-2-yl)silyl]-L-threo-pent-4-enonate (2.59)



2.54 **2.59**

In a reaction carried out similarly to the above (omitting step 3), crude acid **2.54** (theoretically 0.264 mmol, 1.0 equiv) was dissolved in DCM (4 mL) and cooled to 0 °C. 2,6-Lutidine (0.178 g, 0.581 mmol, 6.0 equiv) was added followed by dropwise addition of TIPSOTf (0.178 g, 0.581 mmol, 2.2 equiv) and then stirred for 3 hours at 0 °C. The reaction mixture was diluted with Et_2O and washed with a saturated aqueous solution of sodium bicarbonate (3 *x*), brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude mixture (brown oil) was purified by silica gel chromatography (hexanes/ethyl acetate, 9:1, ~1% triethylamine). Solvent was removed under reduced pressure to afford 57 mg of **2.59** as a yellow oil. Yield: 37%. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.32-7.25 (m, 2H), 6.90-6.84 (m, 2H), 5.93-5.85 (m, 1H), 5.76-5.67 (m, 2H), 5.57-5.53 (m, 1H), 4.72-4.65 (m, 2H), 4.53-4.45 (m, 1H), 4.39 (dd, J = 11.5, 1.9 Hz, 1H), 3.98-3.94 (m, 2H), 3.80 (s, 3H), 3.54-3.46 (m, 1H), 2.19-2.17 (m, 2H), 1.43-0.88 (m, 45H).[3]

2.11.10 Methyl (3S,4S,5E)-6-[(2S,6R)-6-ethoxy-5,6-dihydro-2H-pyran-2-yl]-3-[(4-methoxybenzyl)oxy]-4-[(tripropan-2-ylsilyl)oxy]hex-5-enoate (2.76/2.62)



2.75 **2.76**

Alcohol **2.75** (2.90 g, 7.39 mmol, 1.0 equiv) was dissolved in DCM (40 mL) and cooled to 0 ºC. To this was added 2,6-lutidine (2.6 mL, 2.2 mmol, 3.0 equiv) followed by a dropwise addition of triisopropylsilyltrifluoromethanesulfonate (2.4 mL, 8.87 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ºC for 2 hours. The reaction mixture was diluted with Et_2O and washed with a saturated aqueous solution of sodium bicarbonate (3 *x*), brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product (brown oil)

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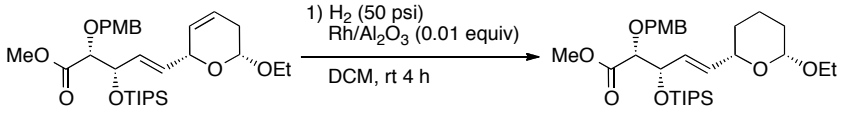
[3] Product was unstable and decomposed in subzero storage conditions. Since this turned out to be an unproductive intermediate it was never resynthesized and fully characterized.

was purified by flash chromatography on silica gel (pentane/ethyl acetate, 9:1, ~1% triethylamine) affording 3.81 g of **2.76** as a yellow oil. Yield: 94%. $[\alpha]_D^{25}$ – 36.1 (*c* 1.24, $CHCl_3$); **IR** (cast film) 2944, 2893, 2867, 1748, 1613, 1514, 1250, 1113 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.28-7.25 (m, 2H), 6.87-6.84 (m, 2H), 5.83 (ddd, *J* = 15.6, 7.6, 1.1 Hz, 1H), 5.72 (dtd, *J* = 10.1, 3.9, 2.4 Hz, 1H), 5.64 (ddd, *J* = 15.6, 7.0, 0.8 Hz, 1H), 5.53 (dq, *J* = 10.1, 2.0 Hz, 1H), 4.71 (dd, *J* = 5.9, 5.1 Hz, 1H), 4.69-4.66 (m, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.50 (ddd, *J* = 7.5, 5.5, 0.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 3.95-3.89 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.52 (dq, *J* = 9.6, 7.1 Hz, 1H), 2.23-2.15 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.06-1.02 (m, 21H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 170.9, 131.8, 130.8, 129.7, 129.4, 128.3, 123.1, 113.6, 98.1, 82.5, 74.8, 74.5, 72.3, 63.9, 55.2, 51.5, 30.8, 17.98, 17.96, 15.2, 12.4; **HRMS** (ESI) Calcd. $C_{30}H_{48}O_7Si$+Na: 571.30615. Found: 571.30684.

2.11.11 Methyl (3S,4S,5E)-6-[(2S,6R)-6-ethoxytetrahydro-2H-pyran-2-yl]-3-[(4-methoxybenzyl)oxy]-4-[(tripropan-2-ylsilyl)oxy]hex-5-enoate (2.77/2.63)



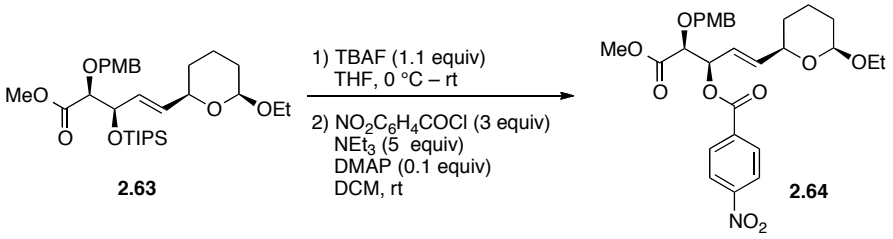
2.76 **2.77**

Alkene **2.76** (2.59 g, 4.72 mmol, 1.0 equiv) was added to a 500 mL Parr reaction bottle in DCM (35 mL) along with 5% rhodium on alumina (0.130 g, 0.0632 mmol, 0.01 equiv). The suspension was shaken under 50 psi hydrogen for 4 hours. The reaction mixture was filtered through Celite® and concentrated under reduced pressure affording >2.6 g of **2.77** as a yellow oil. Yield (crude): >99%. The crude reaction mixture was moved on to the next step without further purification. A small analytical sample of the product was obtained by flash chromatography (Et_2O/hexanes, 0–5%). $[\alpha]_D^{25}$ –9.98 (*c* 1.00, $CHCl_3$); **IR** (cast film) 2944, 2894, 2866, 1748, 1613, 1587, 1514, 1250, 1117, 1037 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.28-7.25 (m, 2H), 6.87-6.84 (m, 2H), 5.79-5.66 (m, 2H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.49 (dd, *J* = 6.4, 5.9 Hz, 1H), 4.44-4.41 (m, 2H),

3.98-3.87 (m, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 3.52 (dq, *J* = 9.6, 7.1 Hz, 1H), 1.89-1.83 (m, 1H), 1.78-1.74 (m, 1H), 1.60-1.50 (m, 3H), 1.44-1.35 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.09-0.97 (m, 21H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 171.0, 159.4, 133.1, 129.8, 129.6, 129.1, 113.7, 101.8, 82.8, 75.8, 74.6, 72.4, 64.0, 55.3, 51.5, 31.0, 22.2, 18.04, 18.03, 15.3, 12.4;

HRMS (ESI) Calcd. $C_{30}H_{50}O_7Si$+Na: 573.32180. Found: 573.32162.

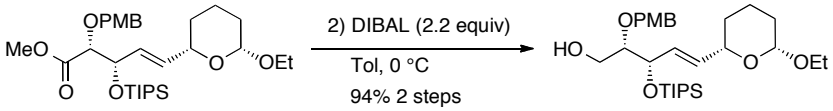
*2.11.12 Methyl (4E)-4,5-dideoxy-5-[(2S,6R)-6-ethoxytetrahydro-2H-pyran-2-yl]-2-O-(4-methoxybenzyl)-3-O-[(4-nitrophenyl)carbonyl]-L-*threo*-pent-4-enonate (2.64-racemic)*



A round bottom flask was charged with racemic **2.63** (0.287 g, 0.728 mmol, 1.00 equiv) p-nitrobenzoylchloride (0.405 g, 2.18 mmol, 3.0 equiv), triethylamine (0.50 mL, 3.6 mmol, 5.0 equiv) and 4-dimethylaminopyridine (0.0089 g, 2.2 mmol, 0.1 equiv). The contents were dissolved in DCM (10 mL) and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (ethyl acetate/hexanes, 2:3; ~1% triethylamine) affording 0.390 g of **2.64** as a yellow solid. Yield: 98%. This product was then further purified by recrystallization (Et_2O/petroleum ether) to afford 0.327 g of **2.64** as a pale yellow crystalline solid. Yield: 83%. A sample of this material was recrystallized to obtain a suitable single crystal for X-ray analysis. **mp** 84 – 92 ºC; **IR** (cast film) 2948, 2877, 2857, 1734, 1721, 1616, 1531, 1515, 1270, 1247, 1009 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 8.28-8.26 (m, 2H), 8.18-8.15 (m, 2H), 7.26-7.24 (m, 2H), 6.86-6.83 (m, 2H), 5.97-5.92 (m, 1H), 5.87-5.83 (m, 2H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.45-4.42 (m, 2H), 4.17 (d, *J* = 4.6 Hz, 1H), 3.97-3.90 (m, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.51 (dq, *J* = 9.6, 7.1 Hz, 1H), 1.90-1.84 (m, 1H), 1.79-1.75 (m, 1H), 1.59-1.36 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125

MHz; $CDCl_3$): δ 169.8, 163.5, 159.6, 150.6, 136.5, 135.3, 130.9, 129.9, 128.8, 123.5, 123.1, 113.8, 101.9, 78.8, 75.13, 74.98, 72.6, 64.0, 55.3, 52.2, 30.98, 30.80, 22.1, 15.3; **HRMS** (ESI) Calcd. $C_{28}H_{33}NO_{10}$+Na: 566.19967. Found: 566.19933; **Anal.** Calcd. $C_{28}H_{33}NO_{10}$: C, 61.87; H, 6.12; N, 2.58. Found: C, 61.89; H, 6.10; N, 2.70.

2.11.13 (3S,4S,5E)-6-[(2S,6R)-6-Ethoxytetrahydro-2H-pyran-2-yl]-3-[(4-methoxybenzyl)oxy]-4-[(tripropan-2-ylsilyl)oxy]hex-5-en-1-ol (2.78/2.67)

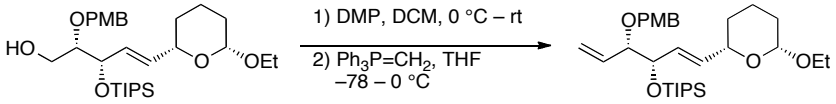


2.77 **2.78**

Methyl ester **2.77** (2.6 g, 4.7 mmol, 1.0 equiv) was dissolved in toluene (30 mL) and cooled to 0 ºC. A solution of diisobutylaluminum hydride (1 M in toluene, 10.4 mL, 10.4 mmol, 2.2 equiv) was added dropwise and the solution was stirred for 1 hour at 0 ºC. The reaction was quenched with methanol (1 mL) and treated with a saturated aqueous solution of sodium potassium tartrate (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 *x*). The combined organic layers were washed with brine, dried with magnesium sulphate, filtered and concentrated under reduced pressure to give a yellow oil. The crude material was then purified by flash chromatography on silica gel (pentane/ethyl acetate, 4:1; ~1% triethylamine) affording 2.47 g **2.78** as a near colourless oil. Yield: 94% (carried from **2.76** over two steps). $[\alpha]_D^{25}$ –61.3 (*c* 1.00, $CHCl_3$); **IR** (cast film) 3487, 2943, 2891, 2866, 1613, 1586, 1514, 1464, 1249, 1142, 1100, 1079, 1067, 1038 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.29-7.26 (m, 2H), 6.90-6.86 (m, 2H), 5.80 (t, *J* = 3.2 Hz, 2H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.50-4.47 (m, 1H), 4.45 (dd, *J* = 9.4, 2.1 Hz, 1H), 4.00-3.92 (m, 2H), 3.81 (s, 3H), 3.76-3.71 (m, 1H), 3.62-3.49 (m, 3H), 1.91-1.84 (m, 1H), 1.81-1.75 (m, 1H), 1.62-1.27 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.09-0.99 (m, 21H); **^{13}C NMR-APT** (100 MHz; $CDCl_3$): δ 159.3, 132.3, 130.4, 129.5, 128.7, 113.8, 101.8, 81.2, 75.8, 73.0, 72.3, 64.0, 61.7, 55.3, 31.10, 31.02, 22.2,

18.05, 18.02, 17.7, 15.3, 12.3; **HRMS** (ESI) Calcd. $C_{29}H_{50}O_6Si+Na$: 545.32689. Found: 545.32681.

2.11.14 ({(1E,3S,4S)-1-[(2S,6R)-6-Ethoxytetrahydro-2H-pyran-2-yl]-4-[(4-methoxybenzyl)oxy]hexa-1,5-dien-3-yl}oxy)(tripropan-2-yl)silane (2.79/2.69)

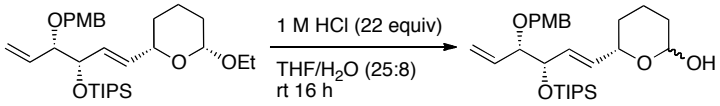


2.78 80% **2.79**

Alcohol **2.78** (2.32 g, 4.44 mmol, 1.0 equiv) was dissolved in DCM (20 mL) and cooled to 0 ºC. Dess-Martin periodinane (2.07 g, 4.88 mmol, 1.1 equiv) was dissolved in DCM (10 mL) and added to the reaction pot dropwise followed by a rinse with DCM (5 mL). The reaction mixture was stirred for 2 hours and allowed to warm to ambient temperature over that time period. During this time period an additional amount of DMP (94 mg, 0.05 equiv) was added. The reaction mixture turned cloudy over time. The reaction was quenched by pouring into a 1:1 mixture of saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$ (60 mL). This biphasic mixture was then stirred for 30 minutes until the dichloromethane layer became clear. The aqueous layer was cloudy and off-white in colour. It was then extracted with Et_2O (3 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. This crude residue was moved to the next step with no further purification. Methyl triphenyl phosphine bromide (3.17 g, 3.88 mmol, 2.0 equiv) was dissolved in THF (100 mL) and cooled to –78 ºC. To this was added a solution of *n*-butyllithium (1.6 M in hexanes, 5.6 mL, 8.9 mmol, 2.0 equiv), dropwise. The reaction mixture turned bright yellow on addition and was cloudy. It was then warmed to 0 ºC for 20 minutes and then returned to –78 ºC. On warming reaction mixture the solution turned homogeneous and the colour deepened. The crude aldehyde was dissolved in THF (20 mL) and added to the reaction pot dropwise along with a rinse of THF (2 *x* 5 mL). The colour deepened to a rust and turned cloudy on addition of the aldehyde. The reaction mixture was allowed to warm to 0 ºC and stirred for 1

hour. It was then quenched with a saturated aqueous solution of ammonium chloride (50 mL) and poured into an additional 50 mL of this solution. It was then extracted (3 *x*) with Et_2O, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes, 1:25, ~1% triethylamine) affording 1.8 g of **2.79** as a colourless oil. Yield: 80%. $[\alpha]_D^{25}$ –36.5 (*c* 1.00, $CHCl_3$); **IR** (cast film) 2943, 2892, 2866, 1613, 1587, 1514, 1248, 1068, 1039 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.27-7.24 (m, 2H), 6.87-6.84 (m, 2H), 5.80-5.73 (m, 3H), 5.27-5.21 (m, 2H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.44 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.38-4.34 (m, 2H), 3.99-3.91 (m, 2H), 3.83-3.80 (m, 4H), 3.53 (dq, *J* = 9.6, 7.1 Hz, 1H), 1.89-1.83 (m, 1H), 1.78-1.74 (m, 1H), 1.59-1.50 (m, 2H), 1.44-1.27 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.06-0.98 (m, 21H); **^{13}C NMR-APT** (100 MHz; $CDCl_3$): δ 159.0, 135.1, 132.1, 130.9, 129.6, 129.1, 118.1, 113.6, 101.8, 83.0, 76.0, 74.3, 70.1, 63.9, 55.2, 31.16, 31.05, 30.3, 22.2, 18.1, 15.3, 12.4; **HRMS** (ESI) Calcd. $C_{30}H_{50}O_5Si$+Na: 541.33198. Found: 541.33191.

2.11.15 (6S)-6-{(1E,3S,4S)-4-[(4-Methoxybenzyl)oxy]-3-[(tripropan-2-ylsilyl)oxy]hexa-1,5-dien-1-yl}tetrahydro-2H-pyran-2-ol (2.80/2.70).

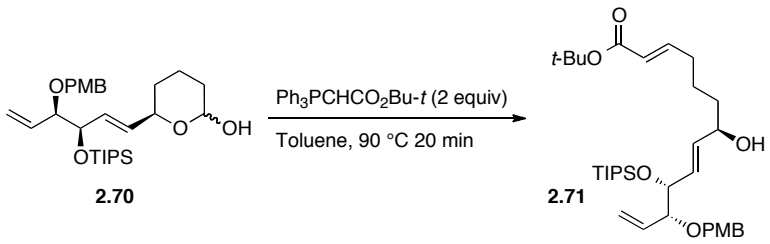


2.79 **2.80**

Acetal **2.79** (0.115 g, 0.222 mmol, 1.0 equiv) was dissolved in THF (15 mL). To this was added 1 M hydrochloric acid (4.8 mL, 4.8 mmol, 22 equiv) and the solution was stirred for 16 hours. The reaction mixture was extracted with Et_2O (3 *x*). The combined ether layers were washed with a saturated aqueous solution of sodium bicarbonate (3 *x*) and with brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (pentane/ethyl acetate, 4:1) affording 90 mg of **2.80** as a colourless oil (mixture of anomers). Yield: 82%. **IR** (cast film) 3404, 2892, 2866, 1613, 1587, 1514, 1464, 1249, 1067 cm^{-1}; **^{1}H NMR** (400 MHz;

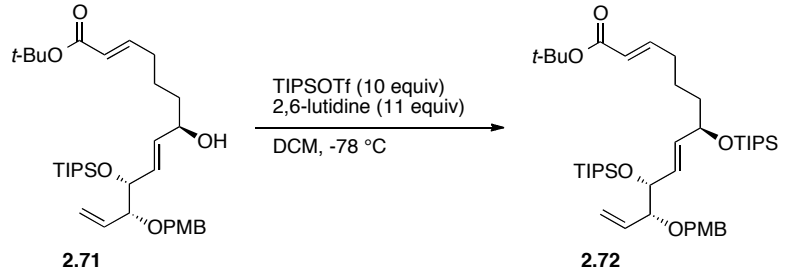
$CDCl_3$): δ 7.26-7.24 (m, 2H), 6.88-6.84 (m, 2H), 5.81-5.66 (m, 3H), 5.32 (s, 0.6H), 5.27 (s, 1H), 5.24-5.22 (m, 1H), 4.75 (d, *J* = 9.0 Hz, 0.6H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.51-4.46 (m, 0.6 H), 4.40-4.26 (m, 1.8H), 4.00-3.96 (m, 0.6H), 3.82-3.79 (m, 3.8 H), 3.10 (s, 0.6H), 2.61 (s, 0.4H), 1.94-1.25 (m, 6H), 1.09-0.84 (m, 21H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 170.99, 170.94, 159.24, 159.22, 133.4, 132.4, 129.87, 129.73, 129.61, 129.50, 129.47, 129.39, 113.69, 113.66, 96.2, 91.8, 82.25, 82.13, 77.2, 76.1, 74.43, 74.23, 72.31, 72.27, 68.8, 55.31, 55.28, 51.54, 51.53, 32.2, 31.2, 30.5, 29.5, 21.9, 18.0, 17.2, 12.34, 12.33; **HRMS** (ESI) Calcd. $C_{28}H_{46}O_5Si$+Na: 513.30067. Found: 513.30148.

2.11.16 t-Butyl (2E,7S,8E,10S,11S)-7-hydroxy-11-[(4-methoxybenzyl)oxy]-10-[(tripropan-2-ylsilyl)oxy]trideca-2,8,12-trienoate (2.71)



Hemiacetal **2.70** **(**24 mg, 0.049 mmol, 1.0 equiv) and (*t*-butoxycarbonylmethylene)triphenylphosphorane (37 mg, 0.0998 mmol, 2.0 equiv) were combined in toluene (1 mL) and heated at 90 °C for 30 minutes. The reaction mixture was cooled to room temperature and was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane/ethyl acetate, 4:1) affording 25 mg of **2.71** as colourless oil. Yield: 86%. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.26-7.23 (m, 2H), 6.89-6.81 (m, 3H), 5.79-5.67 (m, 4H), 5.31-5.22 (m, 2H), 4.59 (d, J = 11.7 Hz, 1H), 4.40-4.33 (m, 2H), 4.13 (q, J = 5.6 Hz, 1H), 3.84 (dd, J = 6.5, 5.3 Hz, 1H), 3.83 (s, 3H), 2.21-2.17 (m, 2H), 1.61-1.43 (m, 13H), 1.49 (s, 9H), 1.05-1.02 (m, 21H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 166.0, 159.1, 147.5, 134.8, 134.1, 130.68, 130.64, 129.3, 123.2, 118.2, 113.7, 82.6, 80.0, 73.8, 72.3, 70.2, 55.3, 36.4, 31.9, 28.2, 23.8, 18.10, 18.06, 18.05, 12.3.

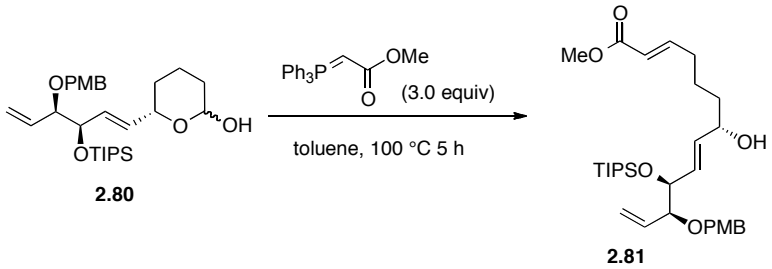
2.11.17 t-Butyl (2E,7S,8E,10S,11S)-11-[(4-methoxybenzyl)oxy]-7,10-bis[(tripropan-2-ylsilyl)oxy]trideca-2,8,12-trienoate (2.72)



2.71 **2.72**

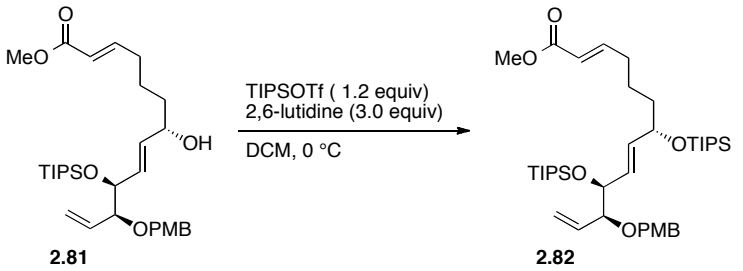
Alcohol **2.71** (25 mg, 0.042 mmol, 1.0 equiv) was dissolved in DCM (4 mL) along with 2,6-lutidine (54 μL, 0.47 mmol, 11 equiv) and cooled to –78 °C. TIPSOTf (23 μL, 0.085 mmol, 2.0 equiv) was added dropwise and the reaction was stirred at –78 °C 1 hour. Another 2 equivalents of TIPSOTf were added and reaction was stirred overnight warming to room temperature. Reaction was cooled to –78 °C and another two equivalents of TIPSOTf were added and reaction was stirred for 4 hours. Another 4 equivalents of TIPSOTf plus 10 equivalents of 2.6-lutidine were added and reaction was stirred an additional 1.5 hours. It was quenched with water, diluted with ether, washed three times with saturated aqueous sodium bicarbonate, dried over magnesium sulphate, filtered and concentrated under reduced pressure. It was purified by flash chromatography (pentane/ethyl acetate, 9:1) affording 23 mg of product **2.72** as a colourless oil. Yield: 72%. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.26-7.24 (m, 2H), 6.88-6.80 (m, 3H), 5.79-5.59 (m, 4H), 5.28-5.23 (m, 2H), 4.56 (dd, J = 11.7, 2.6 Hz, 1H), 4.38-4.21 (m, 3H), 3.83 (t, J = 5.0 Hz, 1H), 3.81 (s, 3H), 2.16-2.12 (m, 2H), 1.61-1.35 (m, 13H), 1.08-0.93 (m, 41H), 0.65-0.61 (m, 1H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 166.07, 166.06, 159.0, 147.8, 134.96, 134.93, 134.5, 130.9, 129.19, 129.00, 128.96, 123.06, 123.06, 118.00, 117.96, 113.6, 82.9, 79.9, 74.23, 74.21, 72.85, 72.77, 70.15, 70.14, 55.3, 38.14, 38.03, 32.16, 32.13, 28.24, 28.16, 23.1, 22.9, 18.9, 18.16, 18.14, 18.09, 17.8, 17.1, 14.1, 12.87, 12.85, 12.44, 12.43, 12.42.

2.11.18 Methyl (2E,7S,8E,10S,11S)-7-hydroxy-11-[(4-methoxybenzyl)oxy]-10-[(tripropan-2-ylsilyl)oxy]trideca-2,8,12-trienoate (2.81).



Hemiacetal **2.80** (1.08 g, 2.20 mmol, 1.0 equiv) and methoxycarbonylmethylene)triphenylphosphorane (2.21, 6.60 mmol, 3.0 equiv) were dissolved in toluene (100 mL) and heated at 100 ºC for 5 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (pentane/ethyl acetate, 3:1) affording 1.09 g of **2.81** as a colourless oil. Yield: 91%. $[\alpha]_D^{25}$ –9.87 (*c* 1.07, $CHCl_3$); **IR** (cast film) 3446, 2944, 2891, 2866, 1726, 1657, 1613, 1587, 1514, 1249, 1065 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.27-7.24 (m, 2H), 6.96 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.88-6.86 (m, 2H), 5.83 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.79-5.67 (m, 3H), 5.28-5.23 (m, 2H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.38-4.34 (m, 2H), 4.15-4.12 (m, 1H), 3.85-3.83 (m, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.24-2.20 (m, 2H), 1.62-1.46 (m, 5H), 1.08-0.99 (m, 21H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 167.1, 159.1, 149.2, 134.8, 134.1, 130.71, 130.63, 129.3, 121.1, 118.2, 113.7, 82.6, 73.8, 72.2, 70.2, 55.3, 51.4, 36.4, 32.0, 23.8, 18.053, 18.047, 12.3; **HRMS** (ESI) Calcd. $C_{31}H_{50}O_6Si$+Na: 569.32689. Found: 569.32769.

2.11.19 Methyl (2E,7S,8E,10S,11S)-11-[(4-methoxybenzyl)oxy]-7,10-bis[(tripropan-2-ylsilyl)oxy]trideca-2,8,12-trienoate (2.82)



2.81 **2.82**

Alcohol **2.81** (0.495 g, 0.905 mmol, 1.0 equiv) was dissolved in DCM (15 mL) and cooled to 0 ºC. 2,6-Lutidine (0.32 mL, 2.7 mmol, 3.0 equiv) was added followed by a dropwise addition of triisopropylsilyltrifluoromethanesulfonate (0.29 mL, 1.1 mmol, 1.2 equiv) and the reaction mixture was stirred at 0 ºC for 2 hours. The reaction mixture was diluted with Et_2O and washed with a saturated aqueous solution of sodium bicarbonate (3 *x*), with brine (1 *x*) then dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was then purified by flash chromatography on silica gel (pentane/ethyl acetate, 15:1) affording 0.657 g of **2.82** as a clear and colourless oil. Yield: quantitative. $[\alpha]_D^{25}$ –8.57 (*c* 1.00, $CHCl_3$); **IR** (cast film) 2944, 2892, 2866, 1728, 1659, 1613, 1587, 1514, 1249, 1120, 1086, 1066, 1014 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.25-7.22 (m, 2H), 6.94 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.87-6.83 (m, 2H), 5.88-5.70 (m, 2H), 5.67-5.56 (m, 2H), 5.30-5.15 (m, 2H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.36 (t, *J* = 4.8 Hz, 1H), 4.32 (d, *J* = 11.7 Hz, 1H), 4.29 (q, *J* = 5.0 Hz, 1H), 3.83-3.80 (m, 4H), 3.72 (s, 3H), 2.18-2.14 (m, 2H), 1.57-1.43 (m, 4H), 1.08-0.99 (m, 42H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 167.1, 159.1, 149.6, 135.0, 134.6, 130.9, 129.24, 129.07, 120.9, 118.0, 113.6, 83.0, 74.2, 72.8, 70.2, 55.3, 51.4, 38.2, 32.4, 22.9, 18.20, 18.19, 18.13, 12.48, 12.47; **HRMS** (ESI) Calcd. $C_{40}H_{70}O_6Si_2$+Na: 725.46031. Found: 725.45925.

Chapter Three: Synthesis of the Western Hemisphere and Completion of the Total Synthesis

3.1 Introduction to the Western Hemisphere Synthesis

While the author was engaged in synthesis of the Eastern Hemisphere of palmerolide A, two colleagues, Dr. Ludwig Kaspar and Dr. Vivek Rauniyar, developed a route to the Western Hemisphere. The culmination of this development will be succinctly presented as it pertains to the total synthesis of palmerolide A[20] but will not be elaborated since it is not the work of the author. For further details the thesis of Dr. Rauniyar and relevant papers cited therein should be consulted.[78]

3.2 Retrosynthetic Approach

As discussed in Chapter 2, the synthetic plan for the Western Hemisphere was directed towards a lactonization disconnection between C1 and the C19 oxygen and a cross coupling disconnection between C13 and C14 (Figure 3.1). The trajectory was towards a late stage installation of the amide component via Curtius rearrangement chemistry. These features anticipated construction of a Western Hemisphere fragment of type **3.1**.

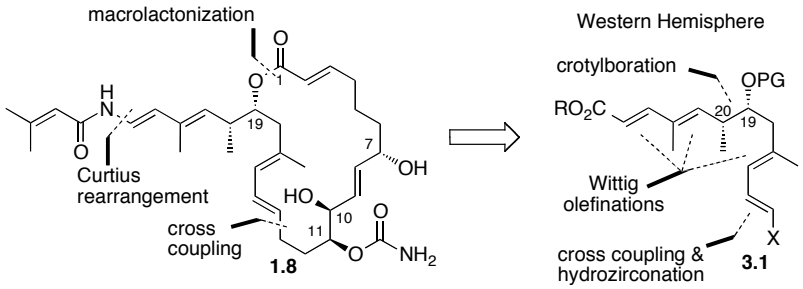


Figure 3.1 Retrosynthetic approach to the Western Hemisphere

To facilitate the Curtius rearrangement, a masked acid was targeted for C25; a hydrolysable ester being a good protecting group. At the other end of fragment **3.1,** a pendant dialkenyl halide would be ideal for carrying out a cross-coupling to join it to the Eastern Hemisphere. The completion of this moiety was to be

achieved via cross-coupling to an alkyne followed by hydrozirconation. Following cross-coupling to the Eastern Hemisphere, the C19 oxygen would then need to be available for macrolactonization. Orthogonal placement of a protecting group on this hydroxy group would ensure flexibility in case the order was reversed and lactonization was used to join the hemispheres followed by cross-coupling to close the ring. The majority of the double bonds would come from Wittig olefination chemistry carried out in sequence. The key feature of the synthesis of the Western Hemisphere was the use of one of the Hall group's methodologies for catalytic enantio- and diastereo-selective crotylboration giving access to the *syn*-propionate unit centred on C19 and C20.

3.3 Construction of the *Syn*-Propionate Unit

3.3.1 Catalytic Crotylboration

The anchor point in the design of the Western Hemisphere was the application of a crotylboration methodology that was the fruition of Rauniyar's Ph.D. research.[78] Rauniyar had devoted efforts towards developing an allylboration system in which a chiral Brønsted acid (BA) assisted by a Lewis acid (LA) would facilitate enantiocontrol as part of a Zimmerman-Traxler[79] transition state (**3.4** and **3.7**) during the reaction (Figure 3.2). This is defined as Lewis acid assisted Brønsted acid (LBA) catalysis.

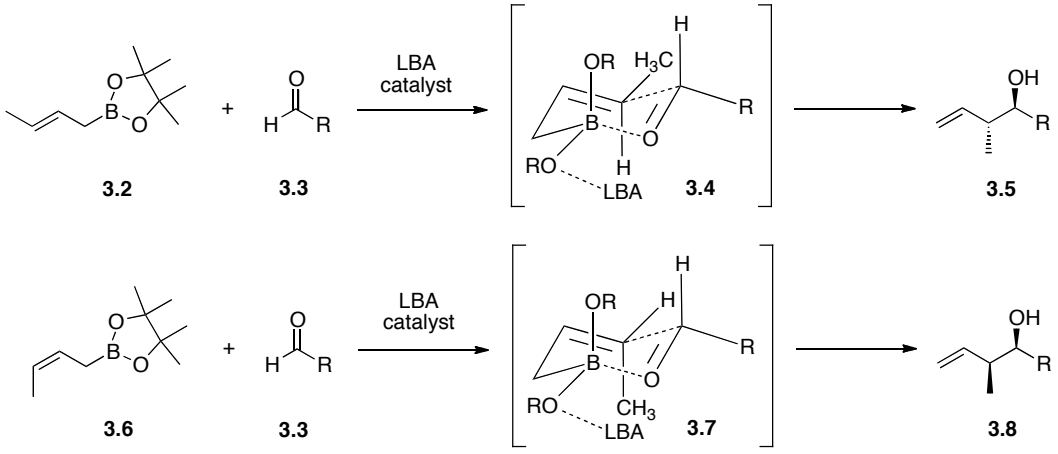


Figure 3.2 Stereocontrol in LBA assisted crotylboration

Crotylboronates with a defined geometry (**3.2** and **3.6**) when reacted with aldehydes **3.3** through six membered cyclic transition states provide predictable *anti* **3.5** and *syn* **3.8** products.[80] This diastereocontrol was further enhanced by Rauniyar's discovery of an asymmetric diol **3.9**, Vivol (Figure 3.3), that proved to be an excellent catalytic inducer of enantioselectivity when combined with catalytic amounts of tin (IV) chloride in crotylboration reactions.[80]

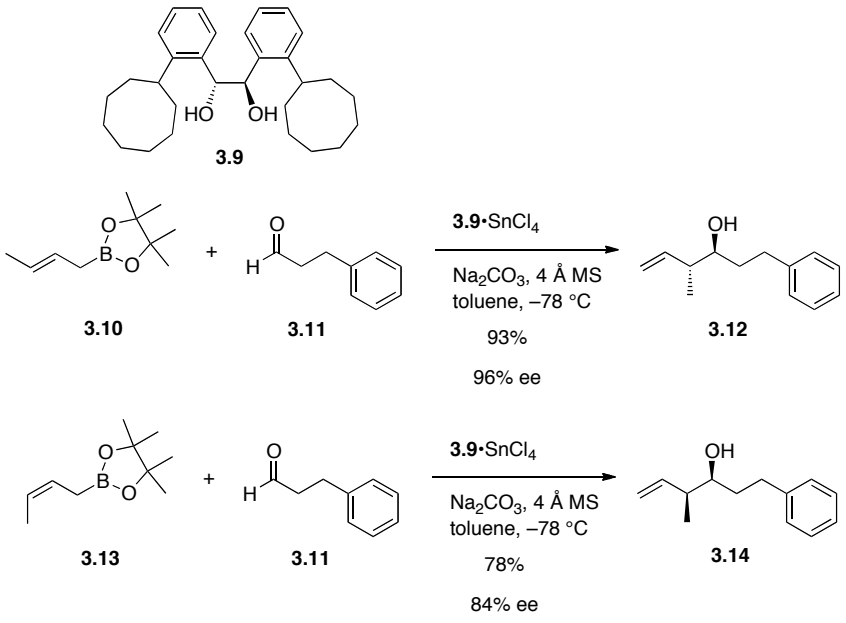
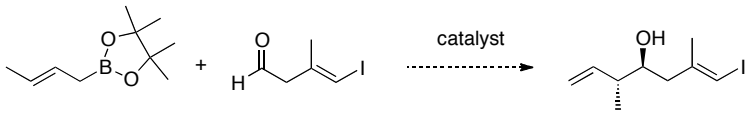


Figure 3.3 Catalytic enantioselective allylboration with Vivol•$SnCl_4$

Notably, *E*-crotylboronate **3.10** reacted with hydrocinnamaldehyde **3.11** (the standard test reaction employed) to produce superior yields and enantioselectivities in forming the *anti* product **3.12** compared to *Z*-crotylboronate **3.13** in forming the *syn* product **3.14**. Consequently, we chose to target an *anti* product whose alcohol stereocentre would subsequently be inverted with concomitant protection in order to obtain a product with higher enantiopurity.

3.3.2 Synthesis of the Aldehyde Substrate

Prior to applying the crotylboration chemistry, a suitable aldehyde **3.15** was needed that upon transformation to the *anti* product **3.16** would contain functional groups pertinent for elaboration towards the Western Hemisphere (Equation 3.1).

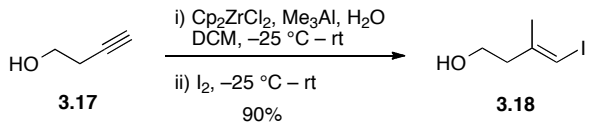


3.10 **3.15** **3.16**

Equation 3.1

The terminal monosubstituted of **3.16** would function as a masked aldehyde and the alkenyl iodo-group would facilitate a downstream coupling reaction.

The approach selected employed but-3-ynol **3.17** as a starting material that when subjected to Negishi carboalumination conditions[81] with Wipf's modification[82] produced the targeted alkenyl iodide alcohol **3.18** in excellent yield (Equation 3.2).

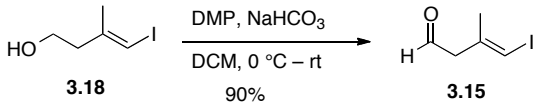


3.17 **3.18**

Equation 3.2

Synthesis of aldehyde **3.15** from alcohol **3.18** was not a trivial exercise; the aldehyde manifested extreme sensitivity and was subject to rapid

decomposition, even when stored at subzero temperatures. Dess-Martin periodinane proved to be an effective and mild oxidant when the reaction was buffered with $NaHCO_3$ (Equation 3.3). However, the only effective method for making use of the aldehyde upon oxidation was to isolate via vacuum distillation (0.13 *torr*; 80 °C) and to use immediately in the crotylboration reaction. The glassware used to distil the aldehyde was also pre-washed with a basic solution prior to flame drying. If insufficient vacuum was available (>0.13 *torr*) necessitating the use of a higher temperature than 80 °C, the aldehyde would also decompose.

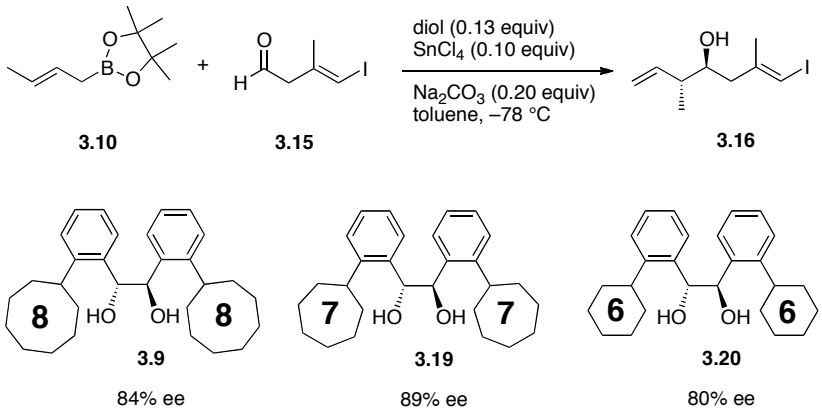


3.18 **3.15**

Equation 3.3

3.3.3 Catalyst Optimization

Application of Rauniyar's chemistry to crotylboration of aldehyde **3.15** revealed a 6% loss in enantiomeric excess with respect to the model substrates (cf. Figure 3.3 and Figure 3.4).



3.10 **3.15** **3.16**

3.9 **3.19** **3.20**

84% ee 89% ee 80% ee

Figure 3.4 Enantioselectivities of Vivols with differential ring sizes

Considering that the model substrate **3.11** contains an extra methylene between the aldehyde and its R group compared to **3.15**, consideration was given to the

possibility that steric conflict between the large cyclooctyl ring of Vivol (**3.9**) hindered its catalytic efficiency. Subsequently chiral diols were synthesized substituting cycloheptyl (**3.19**) and cyclohexyl (**3.20**) rings and applied to the reaction. A rising and falling trend of enantiomeric excess was observed wherein **3.19** provided the highest level of ee in producing **3.16**.

Rauniyar's contribution in this regard benefited from the introduction of a second generation of catalysts that came to be known as the F-Vivol series. The member of the series named F-Vivol[7] **3.21** was utilized for the crotylboration reaction resulting in a slight increase in enantiomeric excess and excellent yield with a lower catalyst loading than previously employed (Figure 3.5).

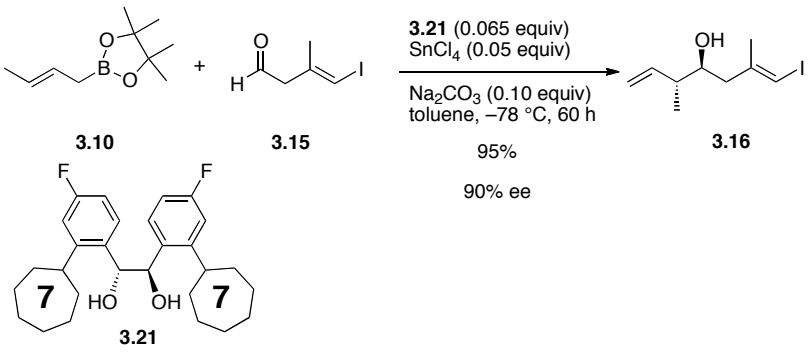
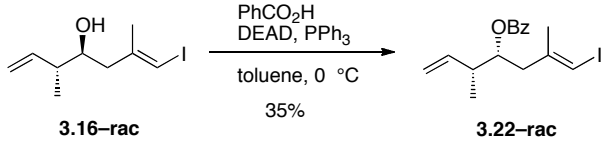


Figure 3.5 Enhanced crotylboration performance with F-Vivol-[7]

3.3.4 Inversion to Complete the Syn-Propionate Unit

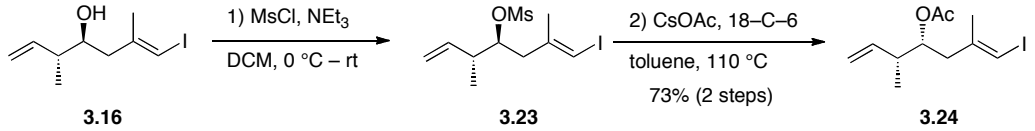
Equipped with a method for accessing **3.16** in high yield and good enantiomeric excess it was now necessary to invert the alcohol stereocentre to form the *syn* stereochemistry found in the natural product. During earlier work with racemic substrates Kaspar had found that a Mitsunobu inversion was very poor, producing product **3.22** in only 35% yield (Equation 3.4).



3.16–rac **3.22–rac**

Equation 3.4

Fortunately Kaspar found an alternative inversion method in the literature[83] that was far more effective (Scheme 3.1).



3.16 **3.23** **3.24**

Scheme 3.1 Effective method of inversion

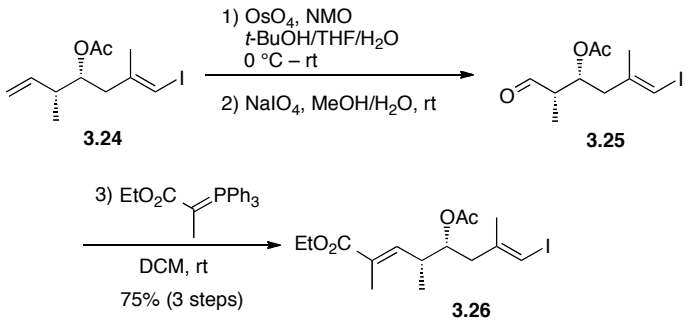
This approach involved mesylating the alcohol, producing intermediate **3.23**, followed by S_N2 displacement through attack of acetate. The use of 18-crown-6 ether was found to be essential for the reaction with losses in yield up to 33% when not present. Rauniyar later applied this methodology to the enantiopure case with similar results that could also be scaled to multigram quantities with no loss in yield.

3.4 Completion of the Western Hemisphere

Once the method for obtaining the *syn* propionate core of the Western Hemisphere in high yield and enantioselectivity was actualized, synthesis of the remainder of the hemisphere was carried forward to its conclusion. This portion of the synthesis was characterized by high yielding transformation sequences wherein some intermediates were carried forward with no intervening purifications.

3.4.1 Diene Construction

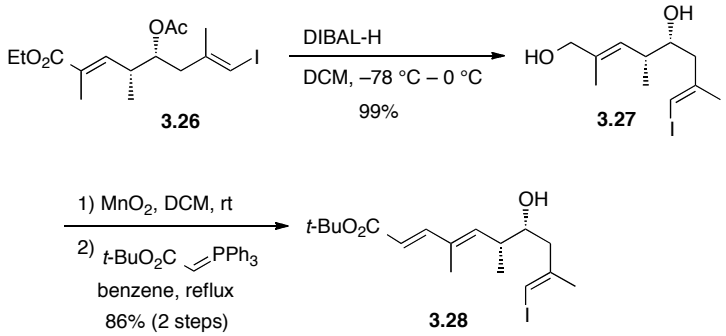
Synthesis of the diene component of the enamide arm of palmerolide A began with osmium tetroxide dihydroxylation of the pendant alkene (Scheme 3.2).



Scheme 3.2 Installation of the first alkene

This transformation was followed by a sodium periodate cleavage affording aldehyde **3.25**. Next a Wittig reaction was performed delivering the desired methylated alkene **3.26** with a pendant ethyl ester as a handle for installation of the next olefin. The three transformations produced the desired product in excellent yield.

Installation of the second alkene commenced with DIBAL-H reduction of the ethyl ester to alcohol **3.27** in near quantitative yield (Scheme 3.3).



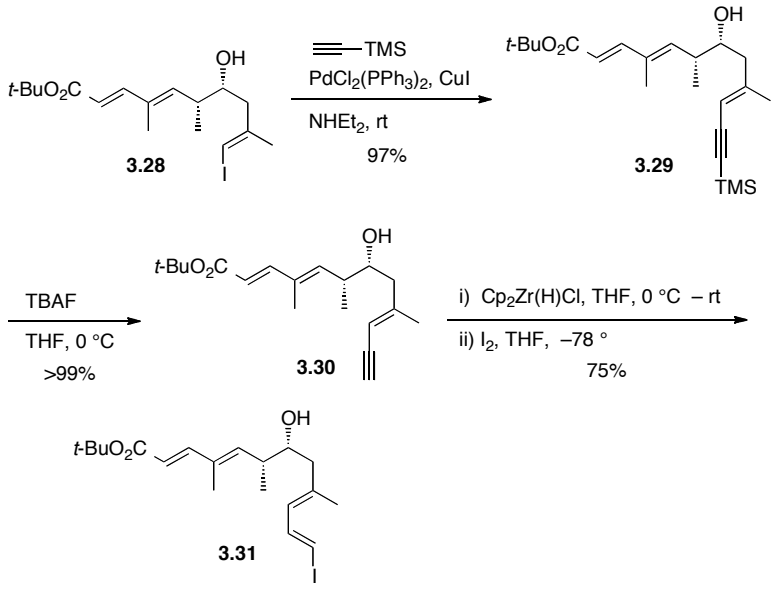
Scheme 3.3 Installation of the second alkene to complete the diene

Allylic oxidation with manganese oxide was a convenient and mild method for transforming the alcohol to an aldehyde. Simple filtration and solvent replacement was all that was needed before proceeding to the Wittig reaction that supplied α,γ-dienyl-*tert*-butyl ester **3.28** in 86% over the two steps. Recall from Section 2.8.3 that a methyl ester was installed on the Eastern Hemisphere

intermediate **2.81** in place of the original plan for a *t*-butyl ester. That modification was in coordination with the placement of a *t*-butyl ester here on **3.28** in order to maintain protecting group orthogonality when the two hemispheres would be combined.

3.4.2 Installation of the 1-Iodobutadiene

The alkenyl iodide terminus of **3.28** was now addressed by means of a Sonogashira coupling, transforming it into TMS protected ene-yne **3.29** in excellent yield (Scheme 3.4). TMS deprotection was accomplished employing *tert*-butylammonium fluoride (TBAF), providing ene-yne **3.30** in near quantitative yield. To convert the alkyne into an iodoalkene, hydrozirconation was performed with Schwartz's reagent accompanied with iodine treatment, which furnished 1-iodobutadiene **3.31** in 75% yield.



Scheme 3.4 Installation of the 1-iodobutadiene

3.5 Summary of the Western Hemisphere Synthesis

Thus, the Western Hemisphere was completed in a linear sequence of 14 steps in an overall yield of 26% with an average yield of 91% per step. The key reaction in the sequence set the stereochemistry of the C19–C20 *syn* propionate

unit in 90% ee using the catalytic crotylboration developed by Dr. Rauniyar. The crotylboration was accomplished with excellent yield using the latest developments in the Vivol catalyst series and demonstrated the potential of fine tuning the catalyst by adjustment of ring size and substituents on the aromatic ring. All steps in the sequence were executed in good to excellent yield facilitating the high overall and average yield. The next stage in the project was combining the two hemispheres, closing the macrocycle and performing the necessary transformations to complete the total synthesis of palmerolide A. Experimental details for this section are located in Appendix D.

3.6 Introduction to the Completion of the Total Synthesis

The final stages of the total synthesis of palmerolide A were a collaborative effort including synthetic transformations by both Rauniyar and the author. With the exception of the Yamaguchi macrolactonization, performed by Rauniyar, both Rauniyar and the author carried out all reactions independently. Rauniyar brought the first batch through to the final product and the author later brought more material to the final product in order to characterize it. The earlier steps in the sequence were optimized by Rauniyar, while the latter ones were optimized by the author. Appendix D contains experimental details of reactions in the project that were performed exclusively by the author's collaborators Rauniyar and Kaspar.

3.7 Retrosynthetic Approach

The retrosynthetic approach to the completion of palmerolide A in the latter stages remained largely unchanged from that originally envisioned at the project's inception (Figure 3.6). Some type of cross coupling would be employed to join the two completed hemispheres followed by macrolactonization to ligate the ends of the natural product macrocycle. The remainder of the synthesis would then be directed towards completion of the dienamide arm employing Curtius rearrangement chemistry and manipulations of the protected hydroxyl groups for

regioselective placement of a carbamate group followed by deprotection affording the completed natural product.

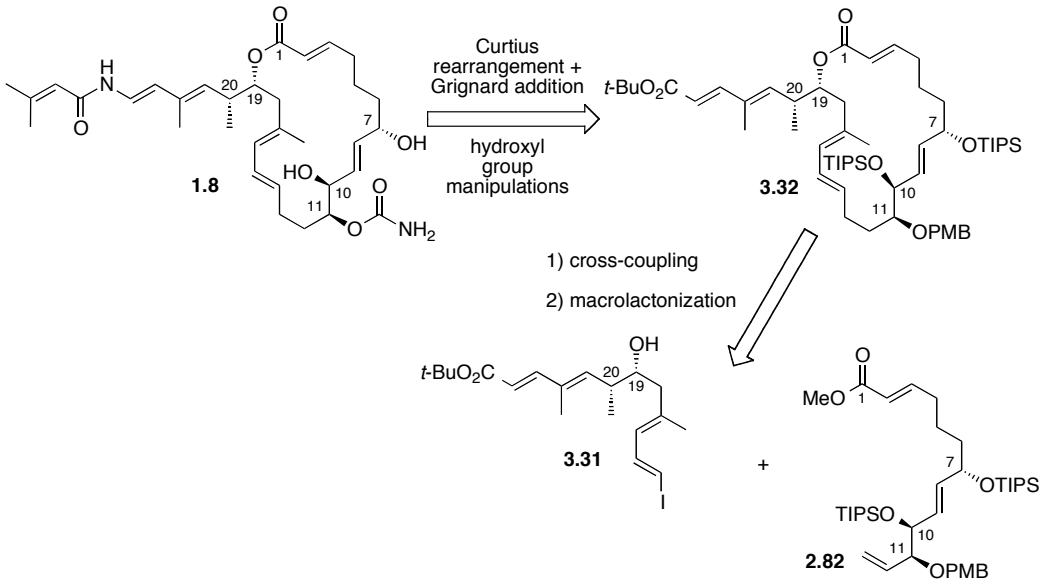


Figure 3.6 Retrosynthesis for completion of palmerolide A

3.8 Boron-Alkyl Suzuki-Miyaura Coupling

The method of combining the two hemispheres selected was B-alkyl Suzuki-Miyaura cross coupling. The first instance of this type of coupling was reported by Professor Akira Suzuki, Norio Miyaura and co-workers in 1986 at Hokkaido University in Sapporo, Japan.[84] The particularly attractive aspect of this variation of the Suzuki-Miyaura coupling reaction is that it facilitates coupling between sp^3 and sp^2 carbon centres which directly applies to the requisite C13–C14 bond of palmerolide A. In their paper Suzuki and co-workers address one of the challenges associated with forming bonds to alkyl groups using palladium (or other transition metal) mediated cross coupling: β-hydride elimination. They found that changing from the typical triphenylphosphine ligand to bis(diphenylphosphino)ferrocene (dppf) was key to making B-alkyl coupling successful. Their inspiration derived from a paper by Professor Tamio Hayashi and co-workers at Kyoto University, Japan, in which they also addressed the

problem of β-hydride elimination but in their case applied to palladium catalyzed coupling between alkyl Grignard reagents or alkyl zincs and organic halides.[85] In the coupling reactions which they investigated they found that the performance of the catalytic system was greatly enhanced by use of the dppf ligand. Efforts towards synthesizing and isolating palladium (II) chloride species provided Hayashi and co-workers with crystal structure data (Figure 3.7).[69,85,86]

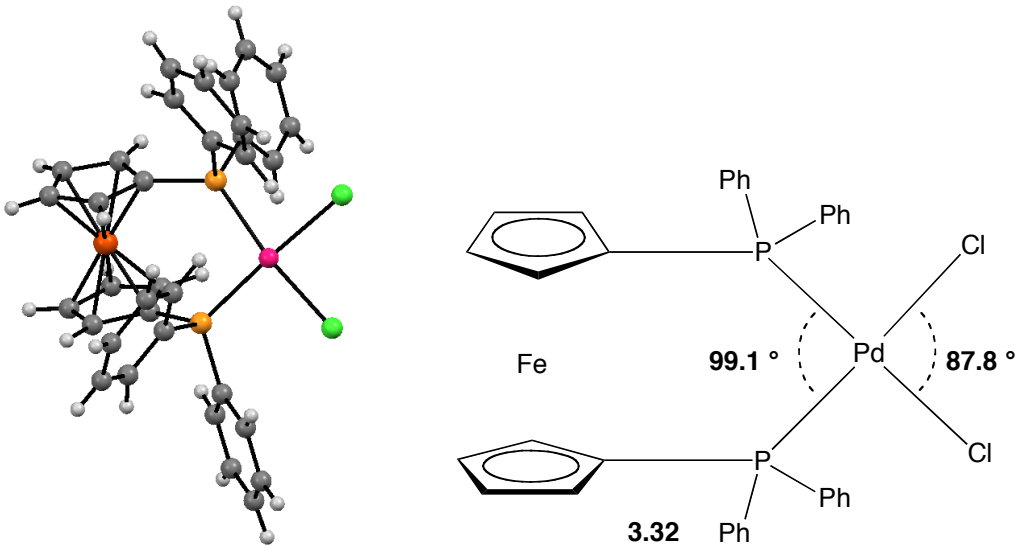
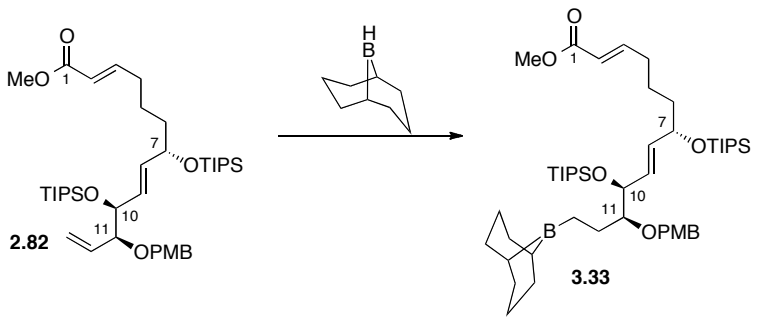


Figure 3.7 Ligand angles around palladium

Particularly revealing was the differential bite angle of the dppf ligand on the palladium *versus* the Cl–Pd–Cl angle (99.1 *vs* 87.8). They proposed that during the catalytic cycle the large ligand angle would force proximity for the species to be reductively eliminated, facilitating that step in the reaction. This would compete favourably with the undesired β-hydride elimination.

An additional favourable feature in the B-alkyl Suzuki-Miyaura approach is its use of 9-borabicyclo[3.3.1]nonane (9-BBN) as the borane of hydroboration.[84] The large steric bulk of 9-BBN and resistance to migration by the bridgehead carbons of the borane would impart selectivity such that only the C13 terminus of the eastern hemisphere would be a viable coupling partner after hydroboration (Equation 3.5).



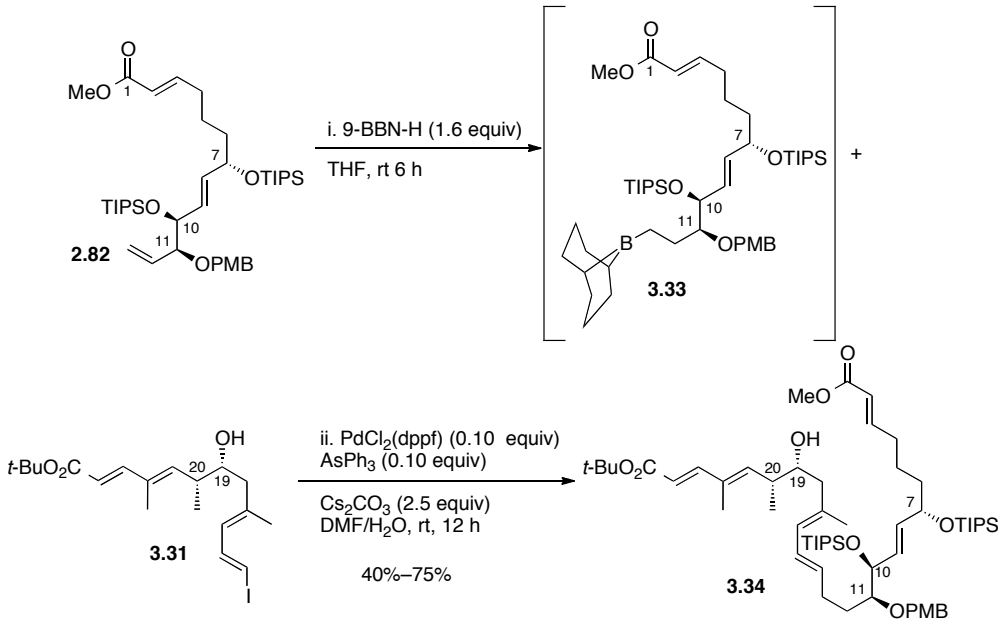
Equation 3.5

One further aspect that made this coupling reaction attractive was the use of basic conditions, which were more compatible with the protecting groups employed.

Due to the highly functionalized and sensitive nature of the coupling hemispheres (**2.82** and **3.31**) it was deemed strategic to find a literature precedent that would minimize the possibility of undesired side reactions. This was found in the work of Matthew Braun and Professor Carl Johnson at Wayne State University, Detroit, who carried out an extensive survey of reaction conditions for palladium catalyzed B-alkyl couplings that would tolerate a variety of functional groups.[87] Some of the unique features of the conditions they arrived at are the use of cesium carbonate as a base in a DMF/THF/water system along with triphenylarsine as an additive. They cite no rationale for the advantage gained by their choice of base and solvent system, having arrived at them empirically. Regarding the triphenylarsine additive they cite a paper by Farina in which Stille couplings were found to undergo rate accelerations when triphenylarsine was used as an additive.[88] Farina explains the role of the additive as facilitating transmetallation through labile exchange with the alkenic substrate.

Application of the Farina conditions to the coupling of the Eastern and Western hemispheres produced a favourable result yielding coupling product **3.34** (Scheme 3.5). On a smaller scale (~100 mg) the product was obtained in a good yield of 75%. Later iterations on a larger scale (100's of milligrams) were

significantly lower (as low as 40%). One possible source of the diminished yield on the larger scale was differential reaction concentration relative to the smaller scale reactions. Another possibility was the use of different catalyst batches in the different cases. Nevertheless these valuable intermediates were not devoted to further optimization studies and **3.34** was carried forward to the next step.



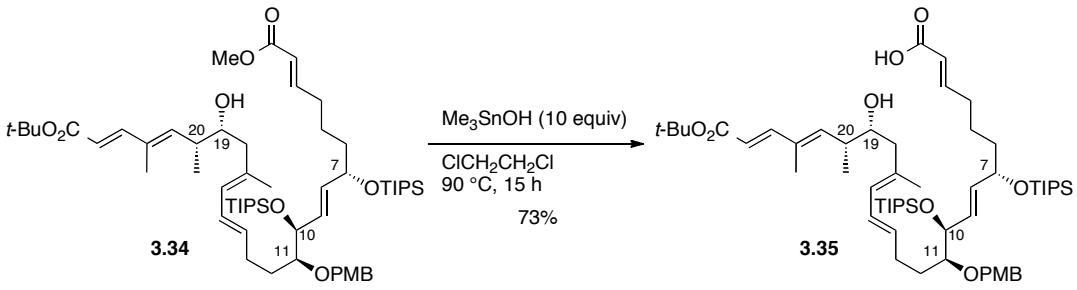
Scheme 3.5 B-alkyl Suzuki-Miyaura coupling of the hemispheres

3.9 Formation of the Macrocycle

3.9.1 Selective Methyl Ester Hydrolysis

At this juncture the selectivity strategy in employing methyl and *t*-butyl esters came to its culmination. The strategy was based on a publication by Nicolaou and co-workers in which they demonstrated that trimethyltin hydroxide could selectively and mildly hydrolyze methyl esters in the presence of other esters as well as a variety of other sensitive functional groups in good to quantitative yield.[89] For our purposes this was necessary in order to attain the correct acid for the next step, macrolactonization.

Upon subjection of methyl ester **3.34** to the reaction conditions seco-acid **3.35** was obtained in 73% yield confirming the anticipated selectivity (Equation 3.6).

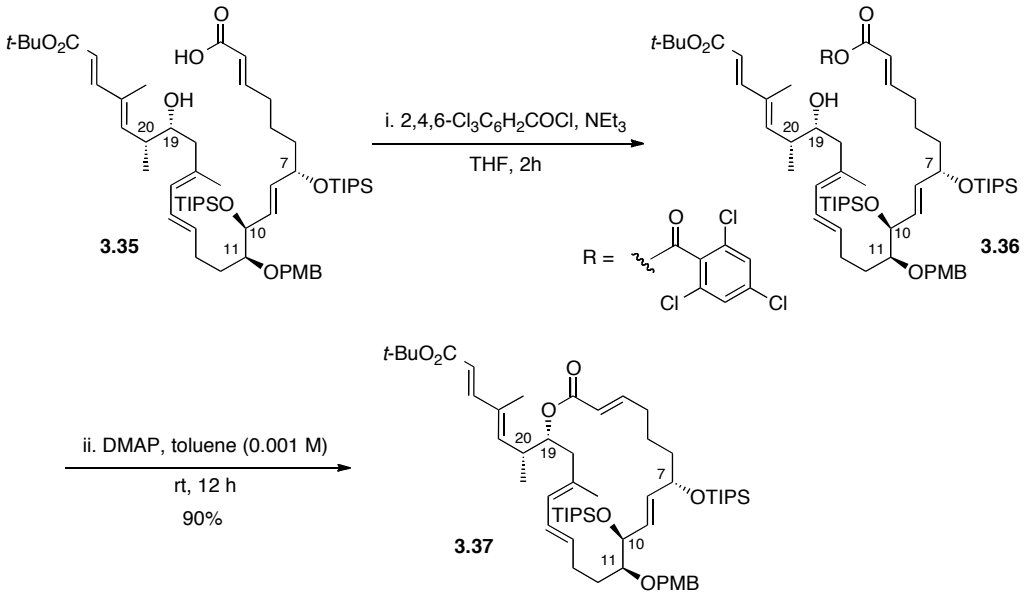


Equation 3.6

3.9.2 Yamaguchi Macrolactonization

Yamaguchi macrolactonization[90] was selected as the method for closing the ring. In a 2006 review of macrolactonization strategies in natural product synthesis, Parenty, Moreau and Campagne describe Yamaguchi macrolactonization as the leading methodology for macrolactonization with more than 200 papers employing it.[91]

Our implementation followed the classical Yamaguchi method (Scheme 3.6). First, a mixed anhydride **3.36** was formed by treatment of seco-acid **3.35** with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine. Upon formation, **3.36** was filtered, concentrated under reduced pressure and redissolved in toluene. It was then added over 4 hours to a dilute (0.001 M) solution of DMAP in toluene by means of a syringe pump and allowed to stir overnight. Following workup, macrocycle **3.37** was isolated in excellent yield (90%) demonstrating once again how powerful the Yamaguchi macrolactonization methodology is for the synthesis of natural products. It is perhaps noteworthy to point out that both of the other total syntheses[15,46] of palmerolide A used Yamaguchi esterification to make this connection although different ring closing strategies were employed.

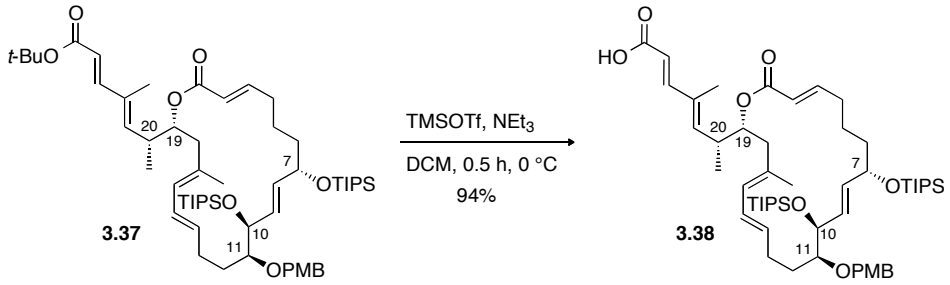


Scheme 3.6 Yamaguchi macrolactonization on 3.35

3.10 Completion of the Dienamide Arm

3.10.1 Selective Hydrolysis of t-Butyl Ester

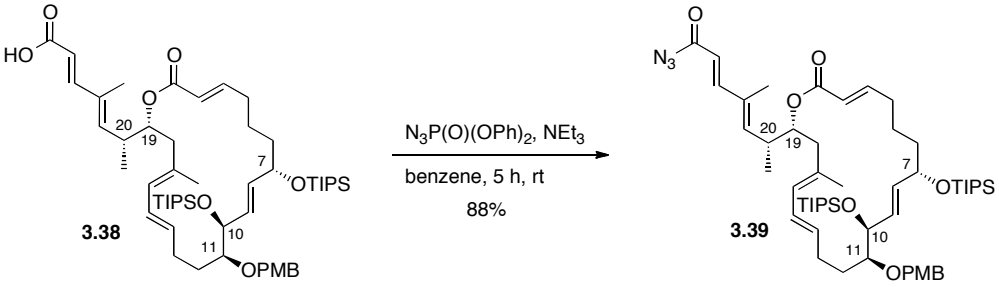
Towards the completion of the dienamide arm of palmerolide A it was now necessary to selectively hydrolyze the *t*-butyl ester of macrolactone **3.37**. Earlier in the synthesis when C1 of the eastern hemisphere was functionalized as a *t*-butyl ester it was found that TIPSOTf was effective at removing the *t*-butyl group. Consultation with Greene's protecting group book[92] revealed that trialkylsilyl triflates could be used for deprotection of *t*-butyl esters. Specifically, reference was made to a paper by Bannwarth and Trecziak[93] in which they treated *t*-butyl esters with trimethylsilyl triflate in the presence of triethylamine, forming TMS esters that upon aqueous workup underwent hydrolysis to acids. This methodology was successfully applied to the *t*-butyl moiety of **4.7** transforming it into acid **3.38** in excellent yield (Equation 3.7).



Equation 3.7

3.10.2 Formation of Acyl Azide Followed by Curtius Rearrangement and Isocyanate Trapping

With the acid in hand it was now necessary to transform it into an acyl azide as a precursor to the desired Curtius rearrangement. This was accomplished by treatment of acid **3.38** with diphenylphosphoryl azide in the presence of triethylamine (Equation 3.8). The reaction was smoothly performed with a high yield of 88%.



Equation 3.8

At this stage in the synthesis we benefited from information derived from the total synthesis that had been carried out by De Brabander and co-workers.[46] They too had targeted a late stage completion of the dienamide arm of palmerolide A accessed via Curtius rearrangement chemistry. Note the similarity between their late stage acid **3.40** and **3.38** (Figure 3.8). Other than the fact that they are enantiomeric with respect to the core framework their disparity lies in the protecting group strategy. The only significant difference from a physical chemical perspective is the use of a TMS protecting group on the C11 hydroxyl of

3.40 compared to the PMB group on **3.38**. Thus our acyl azide installation, Curtius rearrangement and isocyanate trapping operations were all highly informed by their preceding work.

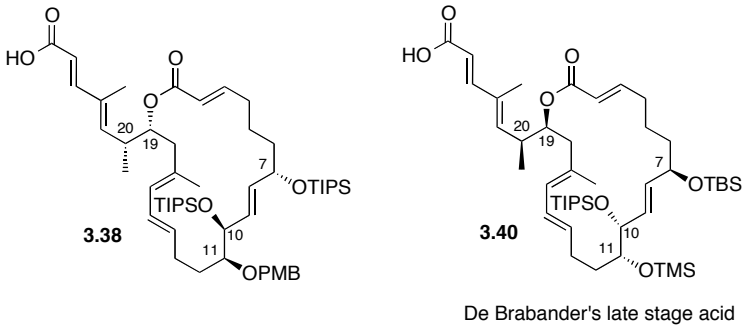
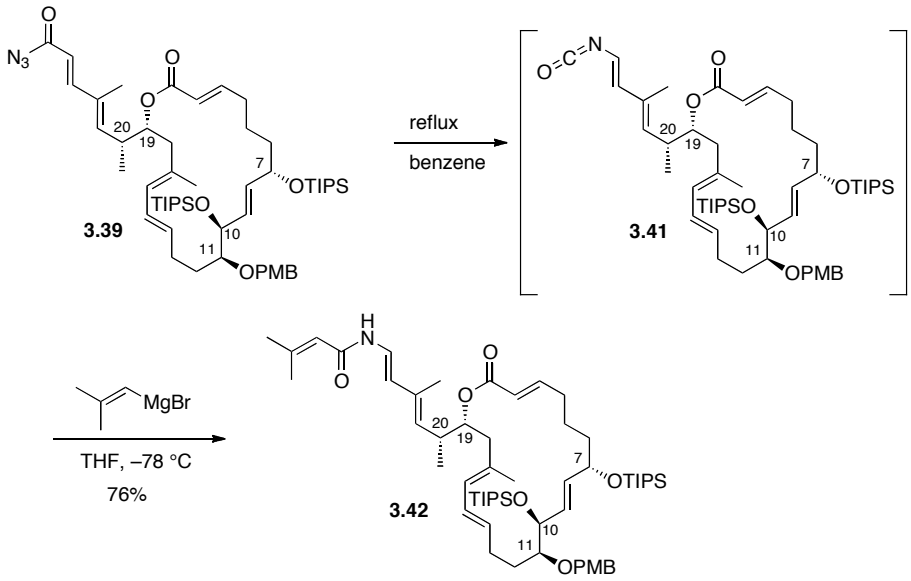


Figure 3.8 De Brabander's late stage acid 3.40 compared to 3.38

A Curtius rearrangement was now executed on azide **3.39** by refluxing it in benzene to form isocyanate intermediate **3.41** (Scheme 3.7). Isocyanate **3.41** was not isolated but was directly moved to the next step where it was trapped with (2-methylpropenyl)magnesium bromide completing the dienamide arm of palmerolide A, affording intermediate **3.42** in 76% yield.



Scheme 3.7 Curtius rearrangement and isocyanate trapping on 3.39

3.11 *p*-Methoxybenzyl Protecting Group Removal

With the completion of palmerolide A's core and dienamide arm only three steps remained: 1) selective deprotection of the C11 hydroxyl; 2) installation of the carbamate; 3) global deprotection. To our surprise, step one was not trivial. The first attempts at PMB deprotection using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) resulted in immediate decomposition of substrate **3.42** (Figure 3.9). Buffering the system and slow addition made no difference.

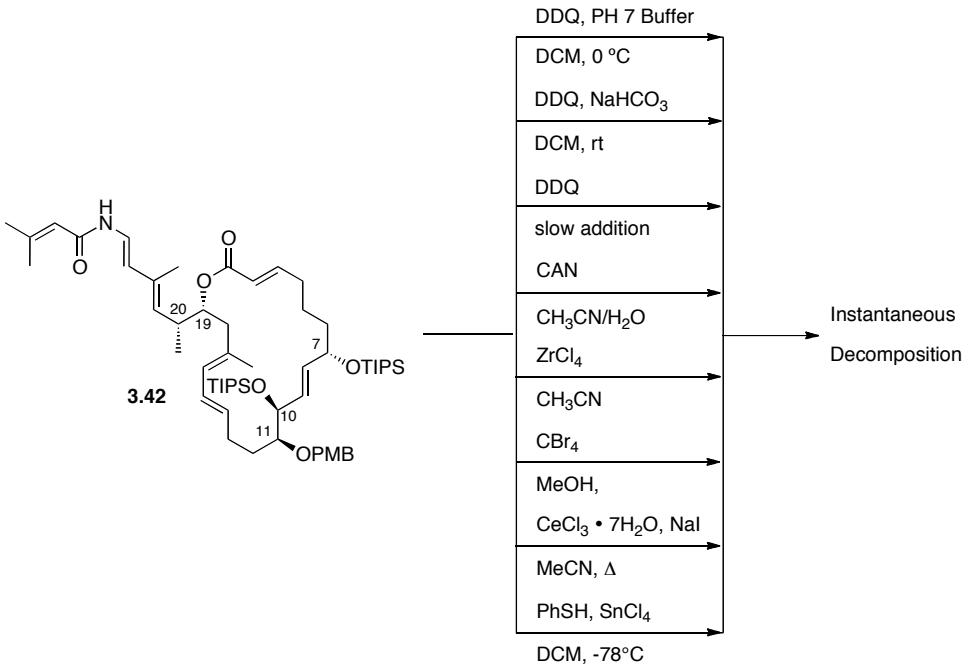


Figure 3.9 Failed attempts at PMB deprotection on 3.42

Upon consulting Greene's protecting group book[92] a number of different deprotection methodologies were screened, all resulting in decomposition of the substrate (Figure 3.9). At this stage in the synthesis there were only milligram quantities of substrate to work with and each deprotection methodology attempted did not allow for starting material recovery. Fortuitously, a PMB deprotection methodology was encountered that appeared to address our problem quite specifically. Professor Shigeo Iwasaki and co-workers (University of Tokyo) had encountered a PMB deprotection problem that was quite analogous to ours in their

synthesis of a long chain bioactive marine natural product.[94] This challenge involved terminal PMB cleavage from diene **3.43** (Figure 3.10). They found that the use of DDQ and other typical cleavage conditions resulted in complex mixtures from which they were unable to isolate their desired deprotected alcohol. In their search for conditions that worked, even a simplified diene analogue **3.44** decomposed when treated with DDQ.

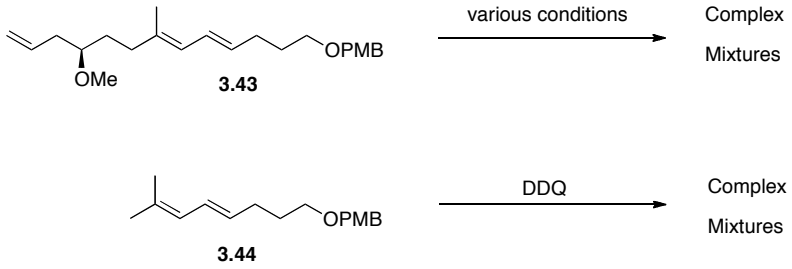


Figure 3.10 Problematic cleavage of PMB substituted dienes

Presumably, the diene reacts quickly in an unfavourable manner in the presence of single electron oxidants that are typically used to cleave PMB ethers. This would correlate to an even higher degree in our substrate that contains two diene units and a multiplicity of double bonds. Given the large number of alkenic electrons available in our substrate the possibility of rapid decomposition through undesired single electron reactivity is enhanced. The Iwasaki group addressed this problem by seeking a different reactive model to accomplish the deprotection (Figure 3.11).

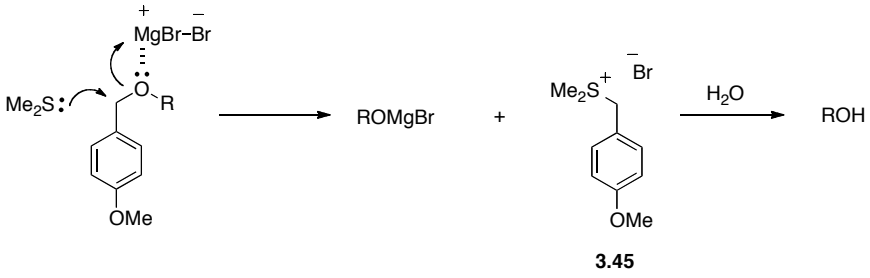
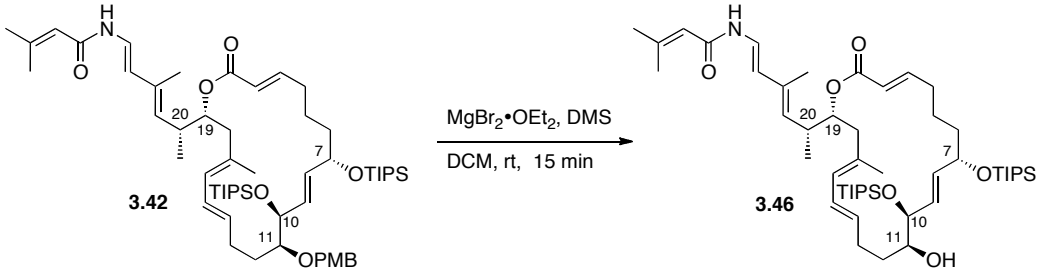


Figure 3.11 Presumed PMB cleavage mechanism by Iwasaki

Following the principle published by Fuji and Manabu,[95] that a hard Lewis acid with a strong affinity for oxygen might facilitate cleavage of a C–O ether bond through an S_N2 attack by a soft nucleophile, they employed magnesium dibromide etherate ($MgBr_2 \bullet OEt_2$) as the Lewis acid and dimethyl sulfide as the nucleophile. Treating their diene substrates with these reagents did indeed facilitate the deprotection affording the desired product in moderate yields after optimization of the reaction conditions. Evidence for their proposed S_N2 mechanism was found in identification of byproduct **3.45** by mass spectral analysis of the reaction mixture.

This protocol was applied to substrate **3.42** yielding the desired deprotected alcohol **3.46**. To avoid long reaction times the quantities from the original protocol ($MgBr_2 \bullet OEt_2$/DMS, 3:10 equivalents) were increased as part of an optimization effort that was extremely limited due to miniscule quantities of available substrate (Table 3.1).

Table 3.1 Limited optimization of PMB deprotection



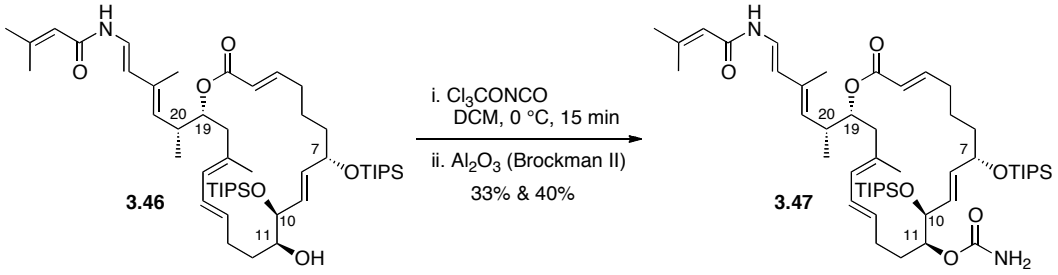
Entry	Equivalents $MgBr_2 \bullet OEt_2$	Equivalents DMS	%Yield
1	6	20	46
2	6	439	60
3	24	48	50
4	12	24	29

The early tests were closely monitored by TLC, revealing 15 minutes of reaction time to be optimal, less time resulting in low conversion but longer reaction times leading to significant decomposition. Entries 1 and 2 indicate that

an increase in reagents had the potential to improve the yield. Excess reagent, however was undesirable from a purification standpoint, thus entry three was an attempt to reduce reagent quantities, which however led to a lower isolated yield. Nevertheless, entry 3 was slightly better than entry 1 and a further reduction in reagents was sought in the experiment represented by entry 4. Disappointingly, this case demonstrated a reduced yield. However, this might not be entirely representative since the substrate used was **3.42** recovered from the preceding experiments and was not completely pure and no definitive conclusions could be drawn.

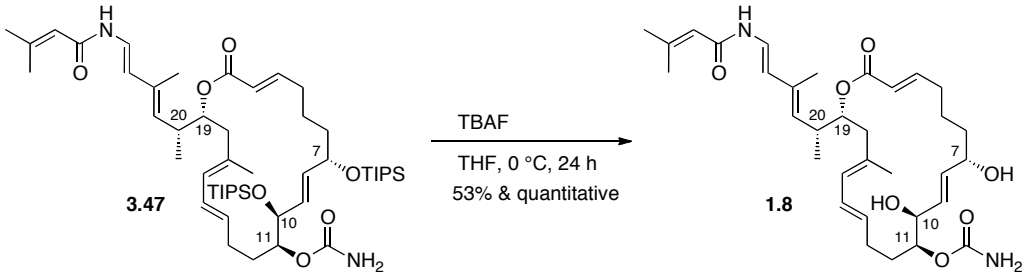
3.12 Carbamate Placement and Global Deprotection

The quantities of product **3.46** in hand were pooled into two different batches that were independently functionalized with a carbamate group following De Brabander's protocol, affording carbamate **3.47** in low yield (Equation 3.9).[46]



Equation 3.9

The two carbamate batches were subsequently subjected to tetrabutylammonium fluoride in order to remove the TIPS protecting groups (Equation 3.10).



Equation 3.10

The first batch was isolated in ~53% yield (<1 mg) and the second batch appeared to be quantitative (Theoretical: 1.4 mg, Obtained: 1.5 mg). The small quantities of these yields naturally reduce their reliability.

3.13 Substantiating the Identity of the Natural Product

Mass spectral analysis and ^{1}H NMR indicated that the product was a match with natural product palmerolide A **1.8**. The ^{1}H NMR spectrum however, contained some impurity in the 1.5–0.5 ppm range that obscured definitive identification of the resonances in that region. For this reason the larger sample was subjected to HPLC purification. The yield after HPLC purification was 43%. The HPLC purified product contained all of the expected ^{1}H NMR resonances matching both the natural product and those of the two other total syntheses (cf. Appendix B). The optical rotation ($[\alpha]_D^{25}$ –37.9 (*c* 0.048, Methanol)) matched the rotation reported by Baker[4] ($[\alpha]_D^{24}$ –1.6 (*c* 0.5, Methanol)) in sign but was much greater in magnitude. Nicolaou–Chen however, had obtained a sample of authentic palmerolide A from Baker and in their publication, report a rotation of even greater magnitude than ours ($[\alpha]_D^{25}$ –99.0 (*c* 0.24, Methanol)).[36] De Brabander made no report of an optical rotation.[46]

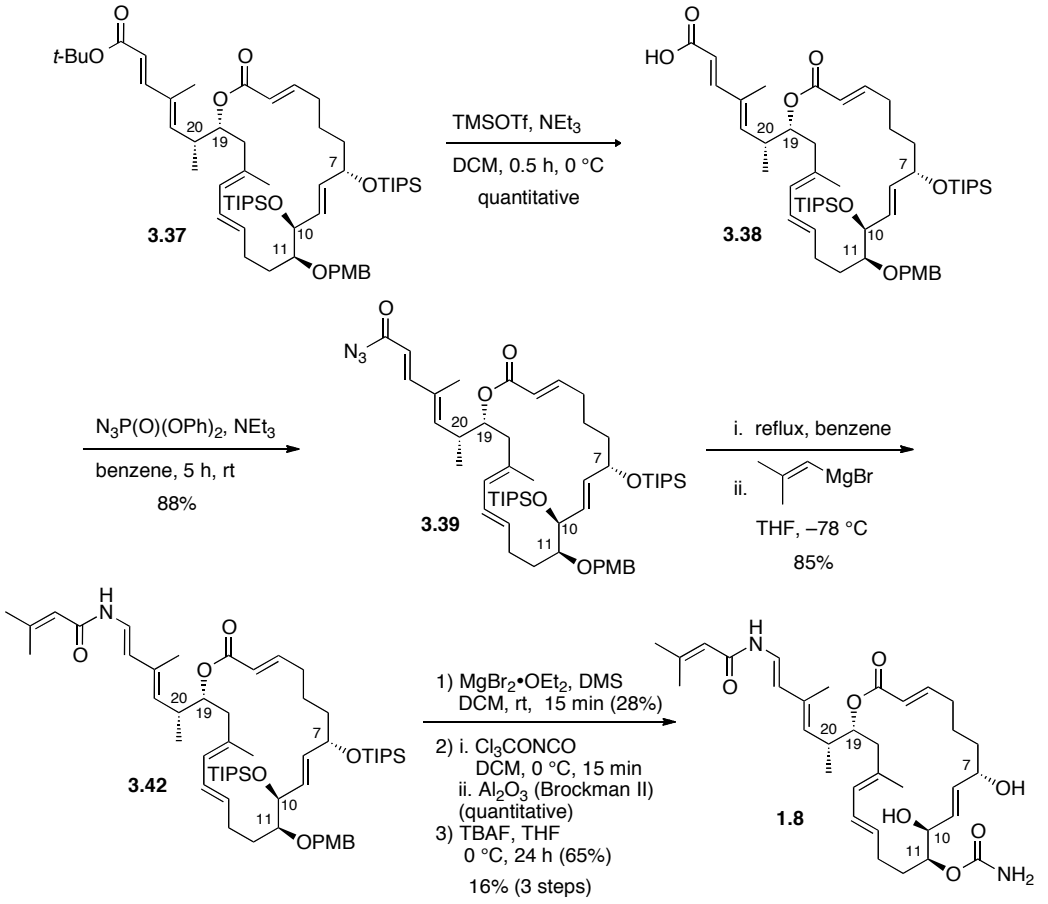
Subsequent to HPLC purification a number of low magnitude resonances appeared in the spectrum that mirrored some of the larger palmerolide A resonances in terms of their splitting pattern. Consultation with De Brabander revealed that they too had encountered this isomeric byproduct, which they believed was the result of migration of the carbamate group from the C10 to the

C11 hydroxyl. The presence of this isomer might account for the lower optical rotation in comparison to that reported by Nicolaou–Chen. Another possible source of error is the much lower concentration of our sample used in obtaining the optical rotation that was unavoidable due to limited product quantity.

Confident regarding the identity of the natural product we had synthesized, we submitted the work for publication in the *Journal of the American Chemical Society*. The paper was conditionally accepted subject to minor revisions and with the suggestion that a comparison table of proton and carbon resonances be included in the Supporting Information. Unfortunately, the synthetic work towards palmerolide A had not yielded sufficient quantities of product to obtain a good ^{13}C NMR spectrum.

3.14 An Additional Synthesis

In order to obtain a ^{13}C NMR spectrum it became necessary to complete another synthesis of palmerolide A. Fortunately, there was an advanced intermediate available and it was not necessary to start the synthesis from the beginning. Starting from macrocycle **3.37** additional palmerolide A **1.8** was synthesized (Scheme 3.8) in sufficient quantity to obtain the necessary ^{13}C NMR data allowing definitive identification of the synthetic material with natural palmerolide A (cf. Appendix B).



Scheme 3.8 Additional synthesis of palmerolide A from advanced intermediate 3.37

In this latter synthesis some of the steps performed in the earlier synthetic work were improved upon (eg. **3.37** to **3.38**, quantitative vs 94%; **3.39** to **3.42**, 85% vs 76%), but the PMB deprotection was once again problematic leading to significant decomposition losses. Nevertheless, the data obtained allowed for the necessary revisions and publication of the synthesis.[20]

3.15 Summary

The final steps to completion of the synthesis of palmerolide A **1.8** was initiated by joining the Eastern and Western Hemispheres (i.e. **2.82** and **3.31**, respectively) via B-alkyl Suzuki-Miyaura cross-coupling. This critical key

reaction attained moderate yields on a small scale but these were diminished on a larger scale. Nevertheless, the majority of the remaining chemical transformations enroute to the final product were achieved in isolated cases in moderate to excellent yield. The strategy in selecting Yamaguchi macrolactonization for closing the ring was particularly pleasing given the efficiency in which it was carried out. The weakest step in the synthesis was the selective deprotection of the PMB group that resulted in significant product decomposition. This was especially notable in the synthesis of palmerolide A that was carried out on a larger scale from intermediate **3.37**. Taking the lower range of yields executed in the synthesis the final sequence was attained in 9 steps with an overall yield of 0.84% and an average yield of 59% per step (Figure 3.12).

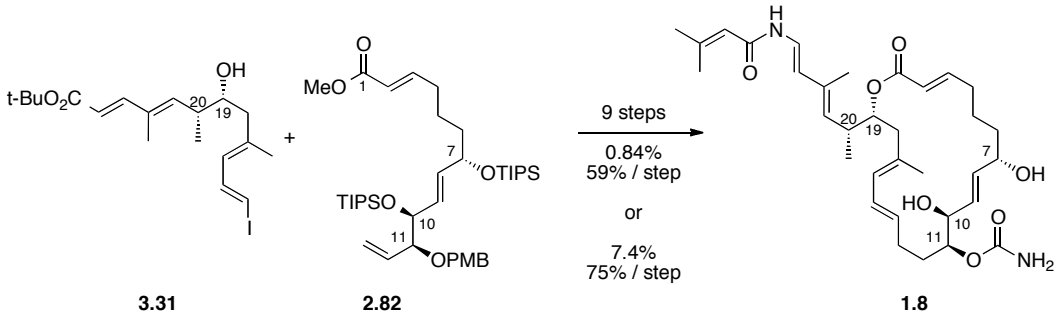


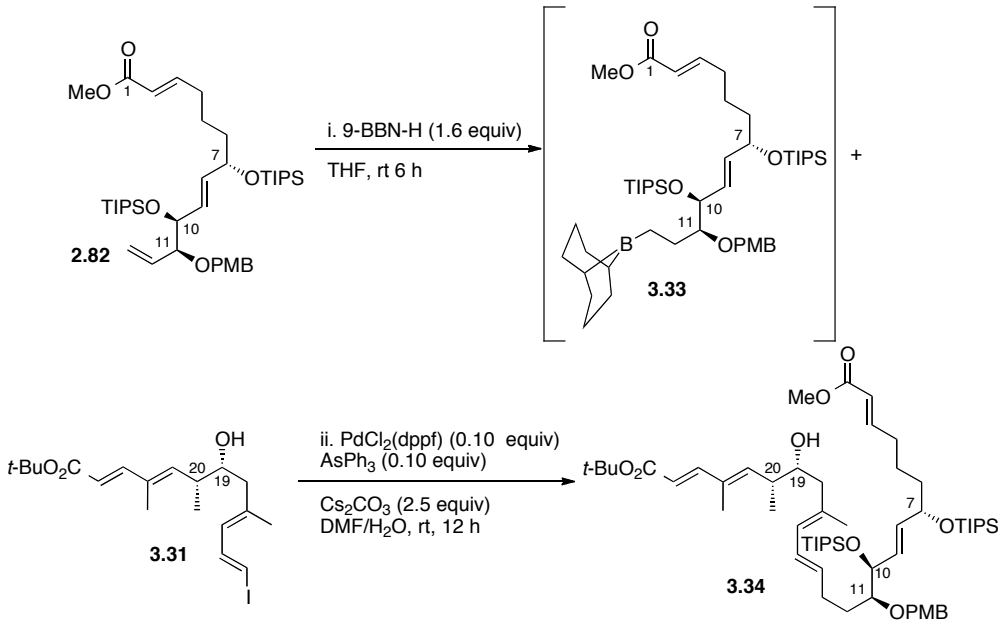
Figure 3.12 Summary of the final steps to completion of palmerolide A 1.8

Taking the upper range of yields, the final sequence was attained with an overall yield of 7.4% and an average of 75% per step.

3.16 Experimental

Note: The author carried out all the following reactions. Rauniyar however, characterized compounds **3.34** through **3.39**.

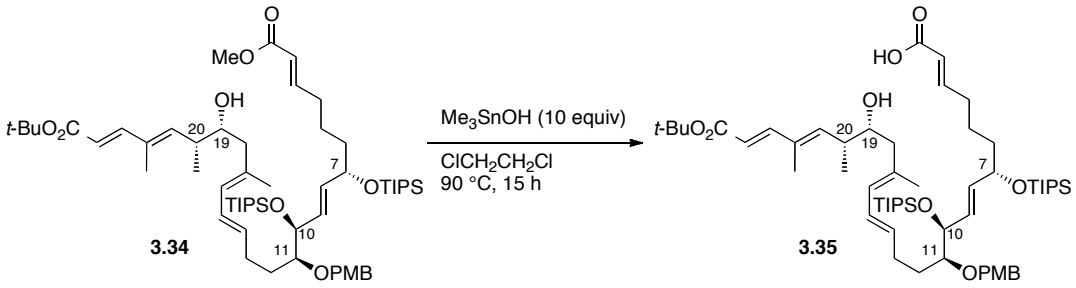
*3.16.1 1-*tert*-butyl 25-methyl (2E,4E,6R,7R,9E,11E,15S,16S,17E,19S,23E)-7-hydroxy-15-[(4-methoxybenzyl)oxy]-4,6,9-trimethyl-16,19-bis[(tripropan-2-ylsilyl)oxy]pentacosa-2,4,9,11,17,23-hexaenedioate (3.34)*



Alkene **2.82** (266 mg, 0.379 mmol, 1.30 equiv) was dissolved in anhydrous THF (1.5 mL). This was followed by the addition of 9BBN-H (0.5 M in THF, 0.930 mL, 0.466 mmol, 1.60 equiv) and the reaction mixture was stirred at room temperature for 6 hours. The solvent volume was reduced *in vacuo* to approximately half of the original volume. Degassed water (165 µL, 9.18 mmol, 31.5 equiv) was added and the obtained mixture was cannulated into a round bottom flask containing vinyl iodide **3.31** (126 mg, 0.291 mmol, 1.00 equiv), $PdCl_2$dppf (10.7 mg, 0.0146 mmol, 0.050 equiv), triphenylarsine (8.9 mg, 0.029 mmol, 0.10 equiv), caesium carbonate (237 mg, 0.730 mmol, 2.50 equiv) and DMF (1.0 mL). The reaction mixture was degassed and allowed to stir for 16 h at room temperature. Brine was added, and the mixture was diluted with Et_2O. The

biphasic mixture was separated and the aqueous layer was extracted with Et_2O (1 *x*). The combined organic layers were dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 1:5, 1% triethylamine) affording 129 mg of **3.34** as a colourless oil. Yield: 44%. $[\alpha]_D^{25}$ +12 (*c* 0.060, $CHCl_3$); **IR** (cast film) 3504, 2943, 2866, 1726, 1711, 1619, 1514, 1464, 1385, 1316, 1248, 1152, 1090, 883, 681 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 15.0 Hz, 1H), 7.02 (dt, *J* = 7.0, 15.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.17 (dd, *J* = 11.0, 15.0 Hz, 1H), 5.83 (d, *J* = 11.0 Hz, 1H), 5.79 (d, *J* = 17.5 Hz, 1H), 5.77 (d, *J* = 16.0 Hz, 1H), 5.72 (d, *J* = 10 Hz, 1H), 5.68-5.67 (m, 2H), 5.54 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.46-4.45 (m, 1H), 4.34-4.29 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.54 (ddd, *J* = 2.5, 7.5, 9.5 Hz, 1H), 3.39 (ddd, *J* = 2.5, 4.5, 9.5 Hz, 1H), 2.63-2.56 (m, 1H), 2.25 (d, *J* = 12.0 Hz, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 2.07 (dddd, *J* = 7.5, 9.4, 9.4, 11.3 Hz, 1H), 1.98 (dd, *J* = 10.0, 13.5 Hz, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.76 (d, *J* = 1.0 Hz, 1H), 1.72 (s, 3H), 1.58-1.56 (m, 5H), 1.50 (s, 9H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.07-1.00 (m, 42H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 167.1, 166.8, 159.1, 149.5, 148.4, 143.1, 134.1, 134.0, 132.7, 132.1, 131.1, 129.2, 128.8, 128.4, 126.3, 120.9, 118.2, 113.7, 81.5, 80.1, 77.2, 72.8, 72.4, 72.2, 71.9, 55.2, 51.3, 45.8, 39.4, 38.1, 32.3, 29.5, 29.1, 28.2, 24.7, 22.9, 18.1, 16.5, 16.2, 12.6, 12.4; **HRMS** (ESI) Calcd. $C_{59}H_{100}O_9Si_2$+Na: 1031.67981. Found: 1031.67996.

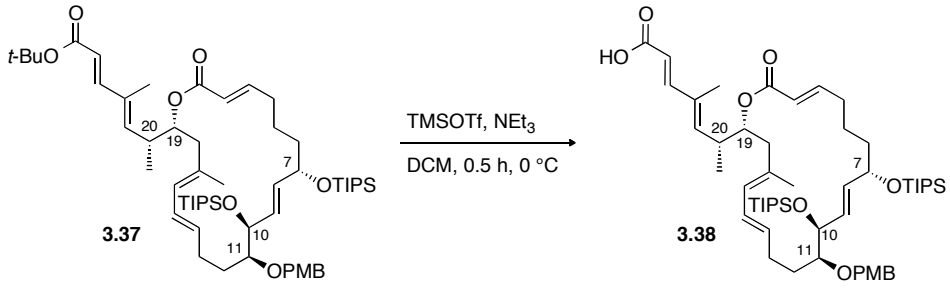
*3.16.2 (2E,7S,8E,10S,11S,14E,16E,19R,20R,21E,23E)-25-*tert*-butoxy-19-hydroxy-11-[(4-methoxybenzyl)oxy]-17,20,22-trimethyl-25-oxo-7,10-bis[(tripropan-2-ylsilyl)oxy]pentacosa-2,8,14,16,21,23-hexaenoic acid (3.35)*



Charge pressure flask with Trimethyltinhydroxide (14.7 mg, 0.815 mmol, 10.0 equiv) then add methylester **3.34** (82.8 mg, 0.0815 mmol, 1.00 equiv) dissolved in dichloroethane (2 mL) and cap flask under argon. The reaction vessel was heated to 90 °C overnight. The reaction vessel was opened and another 10 equivalents of trimethyltinhydroxide was added. The vessel was sealed and heated to 90 °C for another 24 hours. The process was repeated with an additional 5 equivalents of trimethyltinhydroxide heating for an additional 4 hours. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes, 3:10) affording 65 mg of **3.35** as a white solid. Yield: 80%. $[\alpha]_D^{25}$ +4.9 (*c* 0.32, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5, 2H), 7.23 (dd, *J* = 1.0, 15.5 Hz, 1H), 6.93 (dt, *J* = 7.0, 15.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.17 (dd, *J* = 10.5, 15 Hz, 1H), 5.83 (d, *J* = 11.0 Hz, 1H), 5.79 (dt, *J* = 1.5, 15.5 Hz, 1H), 5.75 (d, *J* = 15.5 Hz, 1H), 5.73 (d, *J* = 11 Hz, 1H), 5.68-5.66 (m, 2H), 5.56 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.46-4.45 (m, 1H), 4.33-4.30 (m, 1H), 3.80 (s, 3H), 3.56 (app t, *J* = 7.5 Hz, 1H), 3.39 (ddd, *J* = 2.0, 4.0, 9.5 Hz, 1H), 2.63-2.56 (m, 1H), 2.32-2.23 (m, 1H), 2.24 (d, *J* = 13.0 Hz, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 2.07 (dddd, *J* = 9.7, 7.6, 7.5, 7.5 Hz, 1H), 1.97 (dd, *J* = 10.0, 13.5 Hz, 1H), 1.79 (s, 3H), 1.72 (s, 3H), 1.69-1.66 (m, 1H), 1.60-1.50 (m, 4H), 1.50 (s, 9H), 1.40-1.32 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.06-1.00 (m, 42H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 171.0, 166.8, 159.1, 151.7, 148.4, 143.0, 134.0, 133.9,

132.8, 131.9, 131.0, 129.2, 129.0, 128.5, 126.3, 120.8, 118.2, 113.7, 81.7, 80.1, 72.9, 72.6, 72.0, 71.9, 55.2, 45.7, 39.5, 38.1, 32.4, 29.7, 29.2, 28.2, 21.9, 18.1, 16.4, 16.2, 12.6, 12.4; **HRMS** (ESI) Calcd $C_{58}H_{98}O_9Si_2$+Na: 1017.66416. Found: 1017.66471.

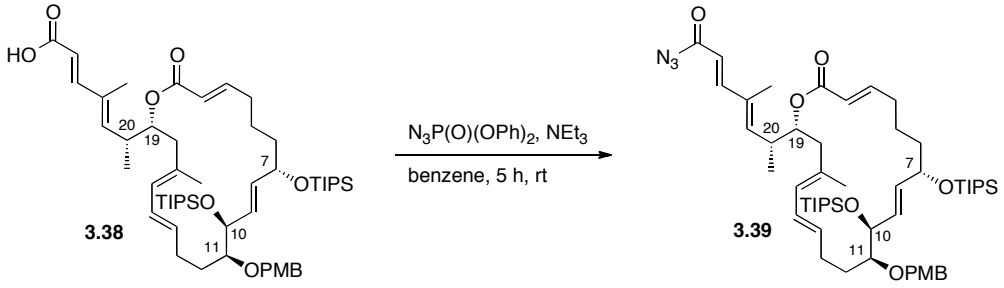
3.16.3 (2E,4E,6R)-6-{(2R,4E,6E,10S,11S,12E,14S,18E)-10-[(4-methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-4-methylhepta-2,4-dienoic acid (3.38)



t-Butylester **3.37** (37 mg, 0.038 mmol, 1.0 equiv) was dissolved in DCM (2 mL) and cooled to 0 ºC. Triethylamine (32 µL, 0.23 mmol, 6.0 equiv) was added TMSOTf (21 µL, 0.11 mmol, 3.0 equiv). The reaction mixture was stirred for 30 minutes. The reaction mixture was moved to room temperature and stirred 1.5 hours. The reaction mixture was cooled to 0 °C and an additional 3 equivalents of triethylamine and an additional 1.5 equivalents of TMSOTf were added. The reaction mixture was moved to room temperature and stirred for an additional hour. The reaction was then quenched with a saturated aqueous solution of sodium bicarbonate. The biphasic mixture was extracted with Et_2O (3 *x*), washed with an aqueous saturated solution of sodium bicarbonate (1 *x*) and water (1 *x*) and the combined organic layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by passing it through a pad of silica gel (eluent: hexanes/ethyl acetate, 1:1), affording 36 mg of **3.38** as a white solid. Yield: quantitative. $[\alpha]_D^{25}$ –58 (*c* 0.045, $CHCl_3$); **IR** (cast film) 2942, 2866, 1720, 1688, 1618, 1513, 1463, 1250, 1124, 1088, 981, 883, 682 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 16.0 Hz, 1H), 7.27 (d,

J = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.80 (ddd, *J* = 6.0, 9.0, 15.5 Hz, 1H), 6.11 (dd, *J* = 11.0, 14 Hz, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 5.77 (d, *J* = 10.0 Hz, 1H), 5.72 (d, *J* = 15.5 Hz, 1H), 5.68-5.62 (m, 3H), 5.43 (ddd, *J* = 4.5, 10.5, 15.0 Hz, 1H), 4.99 (app t, *J* = 9.5 Hz, 1H), 4.58 -4.51 (m, 2H), 4.13-4.10 (m, 1H), 3.81 (s, 3H), 3.36 (m, 1H), 2.80-2.76 (m, 1H), 2.28-2.05 (m, 6H), 1.83 (s, 3H), 1.68 (s, 3H), 1.70-1.16 (m, 6H), 1.06-1.00 (m, 45H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 172.4, 166.1, 159.3, 151.5, 149.4, 143.7, 133.3, 133.0, 132.8, 131.2, 130.8, 129.5, 128.5, 125.5, 126.6, 120.6, 115.8, 113.8, 82.5, 74.8, 73.5, 72.5, 70.5, 55.3, 43.9, 39.4, 37.8, 33.5, 30.9, 30.8, 30.3, 25.0, 18.2, 18.1, 16.6, 16.5, 12.6, 12.5, 12.4; **HRMS** (ESI) Calcd. $[C_{54}H_{87}O_8Si_2–H]^-$: 919.5945. Found: 919.59445.

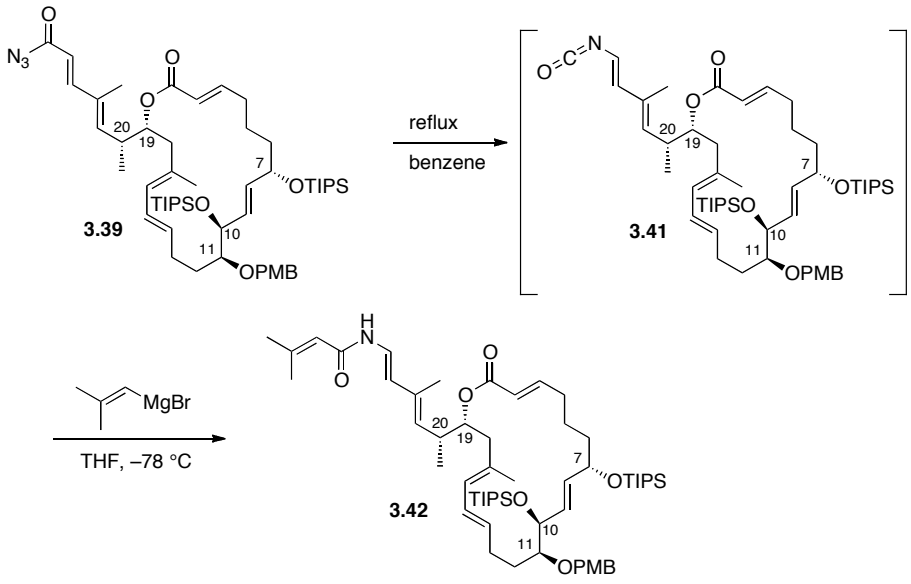
3.16.4 (2E,4E,6R)-6-{(2R,4E,6E,10S,11S,12E,14S,18E)-10-[(4-methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-4-methylhepta-2,4-dienoyl azide (3.39)



Acid **3.38** (35.7 mg, 0.0387 mmol, 1.00 equiv) was dissolved in benzene (4 mL). Triethylamine (100 μL, 0.76 mmol, 20 equiv) and diphenylphosphoryl azide (35 μL, 0.16 mmol, 4.2 equiv) were added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was then concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 1:5, 1% triethylamine) affording 32.4 mg of **3.39** as a white solid. Yield: 88%. $[\alpha]_D^{25}$ –49 (*c* 0.050, $CHCl_3$); **IR** (cast film) 2943, 2866, 2169, 2139, 1720, 1687, 1612, 1513, 1464, 1250, 1209, 1181, 1090, 977, 883, 684 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 15.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.80 (ddd, *J* = 6.0, 8.8, 14.8 Hz, 1H), 6.10 (dd,

J = 10.8, 14.8 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 5.81 (d, *J* = 10.0 Hz, 1H), 5.72 (d, *J* = 15.6 Hz, 1H), 5.64-5.61 (m, 3H), 5.43 (ddd, *J* = 4.0, 10.4, 14.8 Hz, 1H), 4.99 (ddd, *J* = 2.4, 7.6, 10.8 Hz, 1H), 4.55 (d, *J* = 3.2, 2H), 4.15 (d, *J* = 0.4 Hz, 1H), 3.81 (s, 3H), 3.34 (ddd, *J* = 1.2, 4.4, 5.6 Hz, 1H), 2.83-2.73 (m, 1H), 2.28-2.01 (m, 5H), 1.93-1.80 (m, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.69 (s, 3H), 1.65-1.15 (m, 6H), 1.06-1.00 (m, 45H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 172.3, 166.0, 159.3, 151.3, 149.5, 145.2, 133.4, 133.0, 132.9, 131.1, 130.8, 130.0, 129.5, 128.6, 126.5, 126.1, 120.5, 113.8; 82.5, 74.8, 73.3, 72.5, 70.5, 50.3, 43.9, 39.4, 38.1, 33.5, 30.9, 30.8, 25.0, 18.2, 18.1, 16.5, 16.4, 12.6, 12.5, 12.4; **HRMS** (ESI) Calcd. $C_{54}H_{87}N_3O_7Si_2$+Na: 968.59748. Found: 968.59646.

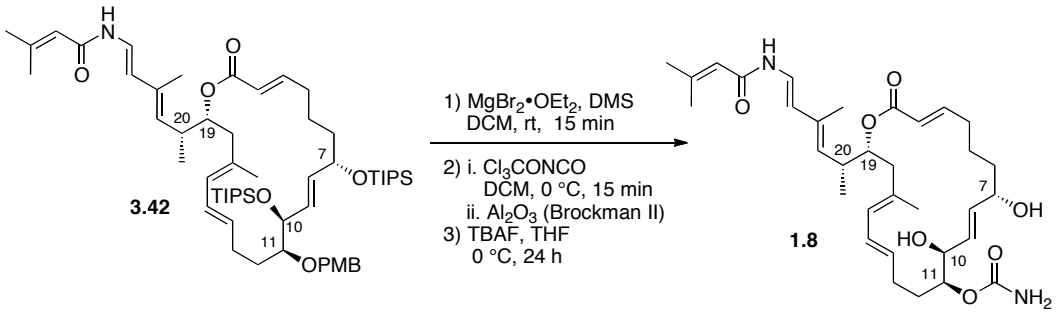
3.16.5 N-*[(1E,3E,5R)-5-{(2R,4E,6E,10S,11S,12E,14S,18E)-10-[(4-methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-3-methylhexa-1,3-dien-1-yl]-3-methylbut-2-enamide (3.42)*



Azide **3.39** (32.4 mg, 0.0342 mmol, 1.00 equiv) was dissolved in benzene (4 mL) and the mixture was heated to reflux at 100 ºC for 5 hours to form isocyante **3.41**. The reaction mixture was cooled and the solvent was then evaporated under a stream of argon and the crude isocyanate was dissolved in THF (3 mL). The solution of isocyanate was added slowly over 13 minutes to a solution of 2-

methyl-1-propenylmagnesium bromide (0.5 M in THF, 0.62 mL, 0.311 mmol, 9.1 equiv) in THF (2 mL) stirring at –78 °C and then stirred for 30 minutes at that temperature. The reaction mixture was then diluted with Et_2O (20 mL) that had been cooled to –78 ºC (added in one portion). A saturated aqueous solution of ammonium chloride (1.6 mL) was added and the reaction mixture was immediately poured into a separatory funnel, some water was added and the biphasic mixture was separated. The aqueous layer was extracted with Et_2O (1 *x*) and the combined organic layers were dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash passing it through a pad of silica gel (eluent: ethyl acetate/hexanes, 1:4, 1% triethylamine) affording 28.4 mg of **3.42** as an off white solid. Yield: 85%. $[\alpha]_D^{25}$ –21 (*c* 0.080, $CHCl_3$); **IR** (cast film) 3280, 2943, 2893, 2866, 1718, 1674, 1641, 1514, 1463, 1248 cm^{-1}; **^{1}H NMR** (500 MHz; C_6D_6): δ 7.40 (dd, *J* = 14.4, 10.9 Hz, 1H), 7.30-7.25 (m, 2H), 6.99 (dt, *J* = 15.3, 7.6 Hz, 1H), 6.83-6.78 (m, 2H), 6.64 (d, *J* = 10.9 Hz, 1H), 6.39 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.02-5.75 (m, 4H), 5.82 (d, *J* = 15.6 Hz, 1H), 5.68-5.62 (m, 1H), 5.61 (d, *J* = 14.5 Hz, 1H), 5.28 (ddd, *J* = 11.2, 8.1, 2.1 Hz, 1H), 5.20 (d, *J* = 9.9 Hz, 1H), 5.17-5.11 (m, 1H), 4.77 (d, *J* = 4.4 Hz, 1H), 4.57 (s, 1H), 4.16-4.11 (m, 1H), 3.57-3.55 (m, 1H), 3.30 (s, 3H), 2.72-2.58 (m, 2H), 2.3-1.4 (m, 11H) 2.23 (s, 3H), 1.78 (s, 3H), 1.60 (d, *J* = 1.0 Hz, 3H), 1.51 (s, 3H), 1.22-1.10 (m, 42H), 1.08 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz; C_6D_6): δ 166.3, 163.1, 160.0, 153.2, 149.3, 133.64, 133.59, 132.9, 132.3, 131.3, 130.7, 130.3, 129.88, 129.79, 129.1, 128.6, 128.34, 128.15, 127.95, 127.4, 122.5, 121.5, 118.3, 117.1, 114.2, 83.0, 75.4, 74.5, 73.0, 71.4, 54.8, 53.3, 44.9, 40.1, 37.9, 33.6, 31.70, 31.61, 27.1, 25.4, 18.53, 18.50, 18.49, 18.46, 18.43, 17.6, 13.03, 12.94, 12.83, 12.80; **HRMS** (ESI) Calcd. $C_{58}H_{95}NO_7Si_2$+Na: 996.65478 Found: 996.65393.

3.16.6 (2R,4E,6E,10S,11S,12E,14S,18E)-11,14-Dihydroxy-4-methyl-2-{(2R,3E,5E)-4-methyl-6-[(3-methylbut-2-enoyl)amino]hexa-3,5-dien-2-yl}-20-oxooxacycloicosa-4,6,12,18-tetraen-10-yl carbamate (palmerolide A) (1.8)



PMB-ether **3.42** (6.9 mg, 7.1 μmol, 1.0 equiv) was combined with magnesium bromide diethyl etherate (44 mg, 170 μmol, 24 equiv) in a vial and dissolved in DCM (0.3 mL). To this mixture was added dimethyl sulfide (19 μL, 340 μmol, 48 equiv). The reaction mixture was stirred for 15 minutes at room temperature and quenched by addition of an aqueous saturated solution of sodium bicarbonate (0.5 mL). The biphasic solution was diluted with Et_2O (10 mL) and the organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The organic residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 10–30%; ~1% triethylamine) affording 3.0 mg of white solid. Yield: 50%. The deprotected alcohol (5.0 mg, 5.9 μmol, 1.0 equiv) [4] was dissolved in DCM (1.0 mL) and cooled to 0 ºC. Trichloroacetyl isocyanate (3.0 μL, 25 μmol, 4.3 equiv) was added and the reaction mixture was stirred for 30 minutes at 0 °C. The reaction mixture was applied to a one-inch pad of Brockmann II basic alumina and allowed to stand for 2 hours at room temperature under argon. The pad was then rinsed with ethyl acetate (40 mL) and the crude reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 80–60%; 1% triethylamine) affording 2.1 mg of white

solid. Yield: 40%. The carbamate (2.1 mg, 2.3 μmol, 1.0 equiv) was dissolved in THF (1.0 mL) and cooled to 0 °C. To this was added 1.0 M tetrabutylammonium fluoride (70 μL, 70 μmol, 30 equiv) and the reaction mixture was stirred for 24 hours at 0 °C. After the elapsed time, the mixture was diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel. The silica gel was pre-treated by washing with DCM (0.5% triethylamine). The sample was loaded with DCM and eluted with a gradient of MeOH/DCM (1% to 10%). To remove co-eluted silica, the sample was dissolved in DCM and centrifuged. Evaporation of the supernatant yielded 1.5 mg of palmerolide A as an off-white solid. Yield: quantitative, 20% over the 3 steps. $[\alpha]_D^{25}$ –38 (*c* 0.048 , Methanol); **^{1}H NMR** (800 MHz; DMSO-d_6): δ 9.89 (d, *J* = 10.3 Hz, 1H), 6.85 (dd, *J* = 14.6, 10.3 Hz, 1H), 6.71 (ddd, *J* = 15.3, 10.1, 5.0 Hz, 1H), 6.60-6.38 (bd, 2H), 6.04 (dd, *J* = 14.3 Hz, 10.9, 1H), 5.85 (d, *J* = 14.4 Hz, 1H), 5.77 (d, *J* = 15.5 Hz, 1H), 5.70 (s, 1H), 5.60 (d, *J* = 11.0 Hz, 1H), 5.55 (ddd, *J* = 15.4, 8.3, 1.8 Hz, 1H), 5.48 (dd, *J* = 15.5, 3.0 Hz, 1H), 5.41 (ddd, *J* = 14.7, 10.2, 4.5 Hz, 1H), 5.17 (d, *J* = 4.9 Hz, 1H), 5.13 (d, *J* = 9.8 Hz, 1H), 4.84 (ddd, *J* = 11.3, 7.9, 2.0 Hz, 1H), 4.68 (d, *J* = 4.2 Hz, 1H), 4.48 (ddd, *J* = 10.9, 5.1, 1.7 Hz, 1H), 4.14-4.13 (m, 1H), 3.83-3.80 (m, 1H), 2.70-2.67 (m, 1H), 2.19-2.15 (m, 1H), 2.12 (s, 3H), 2.02-1.90 (m, 5H), 1.83 (s, 3H), 1.71 (s, 3H), 1.61 (s, 3H), 1.60-1.58 (m, 1H), 1.50-1.46 (m, 1H), 1.32-1.29 (m, 2H), 1.07-1.03 (m, 1H), 1.00-0.96 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz; DMSO-d_6): δ 166.0, 163.8, 157.3, 152.5, 150.0, 134.3, 133.3, 132.6, 132.3, 130.5, 129.6, 128.4, 127.1, 122.9, 121.3, 118.8, 117.1, 75.8, 74.5, 73.2, 69.9, 63.2, 43.9, 38.5, 37.3, 33.1, 30.1, 27.7, 25.7, 20.3, 18.6, 17.8, 16.9, 13.4; **HRMS** (ESI) Calcd. $C_{33}H_{48}N_2O_7$+Na: 607.3354, Found: 607.3349.

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[4] Another 2.0 mg similarly deprotected in a different deprotection experiment was combined with the 3.0 mg for the carbamate formation.

Chapter Four: Synthetic Approach to Analogues of Palmerolide A

4.1 Preliminary Considerations for the Synthesis of Palmerolide A Analogues

In Chapter 1 reference was made to the serious nature of melanoma and the extreme inadequacy present in current approaches to its treatment. One of the highly attractive features of palmerolide A as a synthetic target was its demonstrated highly selective cytotoxicity for melanoma cells.[4] Since significant quantities of palmerolide A could and can currently only be obtained through synthesis, it was and is an important synthetic target in the pursuit of developing a chemotherapeutic approach towards melanoma. In addition to the importance of the synthesis of palmerolide A itself is the synthesis of analogues with improved properties. By varying different components of the natural product and subjecting the consequent analogues to biological testing one can access information regarding which elements or combination of elements in palmerolide A's structure are essential for its activity. This information in turn could be used for the design of simpler analogues that might serve as a template for research towards compounds that are sufficiently accessible to actually be used in a melanoma treatment. Another possible benefit from such structure/activity investigations would be gaining insight into the mechanism of action for palmerolide A's selective toxicity towards melanoma and thus open up other avenues of therapeutic research.

The value of analogue synthesis for medicinal chemistry research has already been demonstrated in the publications by Chen-Nicolaou as well as by Chen as an independent researcher.[35,39] Their investigations revealed an unnatural analogue **1.25** with a phenyl substituent terminating the dienamide that is actually more potent an inhibitor of melanoma growth than the natural product (Figure 4.1).

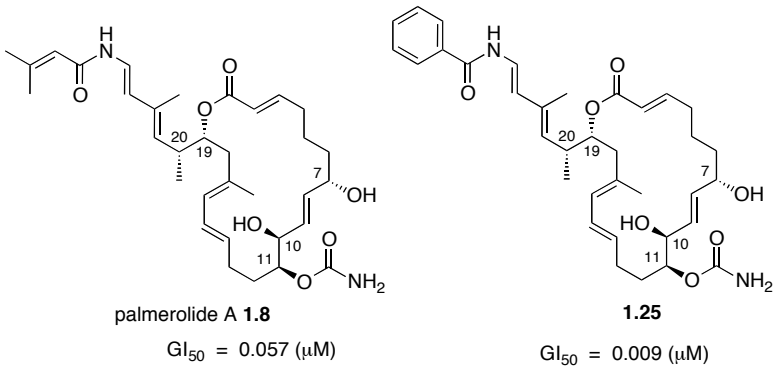


Figure 4.1 Melanoma cell-growth inhibition of Chen-Nicolaou analogue 1.25 exceeds that of natural palmerolide A

Other valuable insights gained from their medicinal chemistry research include: the critical importance of the relative and absolute stereochemistry of the stereogenic centres; the indispensable nature of the carbamate group; relatively little activity loss when deleting the C7 hydroxyl; and intolerance for modifications in the carbon chain of the C1–C7 region of palmerolide A.

During our synthesis of the natural product there were a few problematic steps that highlighted target areas for future synthetic work. If these could be improved they would make the synthesis more amenable to scale up. At the same time we wanted to make a unique contribution in terms of analogue synthesis. Combining these two principles was the guiding feature of our analogue target of type **4.1** (Figure 4.2).

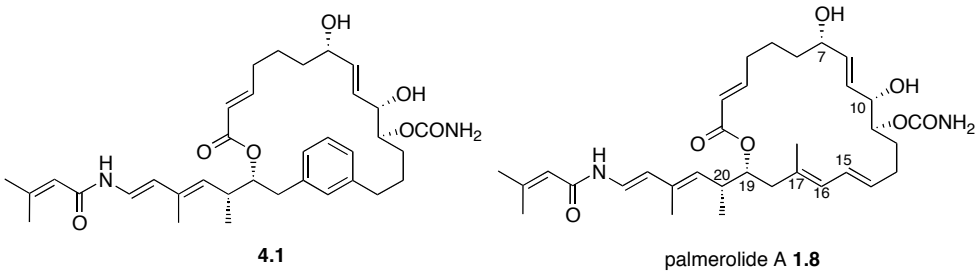


Figure 4.2 Analogue target 4.1 incorporating an aromatic ring

Note the different perspective with which palmerolide A **1.8** and the analogue are drawn. A brief conformational energy minimization with Spartan® revealed that palmerolide A is more likely to adopt an open conformation as depicted rather than the tighter one in which it was drawn in the original

publication. Incorporation of an aromatic ring into the C15–C17 region of palmerolide A to form analogue **4.1** is an attractive modification from two perspectives. It has the potential to stabilize the compound to undesired reactivity. Recall the extremely sensitive nature of the late stage intermediate of palmerolide A that resisted efforts to clean deprotection of the PMB protecting group. The high lability of this intermediate was attributed at least in part to the C14–C17 diene contained in the macrolactone. An aromatic ring taking its place would be unlikely to evince this level of reactivity. Additionally, one of the weaker steps in the synthesis was the B-alkyl Suzuki-Miyaura coupling that saw a significant decrease in yield upon scale up. It is anticipated that coupling to an aromatic ring rather than a terminally substituted iodo-alkene might also be expected to evince improved performance. In addition to these synthetic considerations, placement of an aromatic ring in the C15–C17 region of palmerolide A would have a rigidifying effect in a region that is already rigidified by the diene possibly leading to enhanced activity or at least hopefully not resulting in significant decrease. Furthermore, a semi-empirical calculation (AM1) using Spartan® was carried out on the structures of **1.8** and **4.1** to obtain optimized conformations and the two structures were superimposed (Figure 4.3).

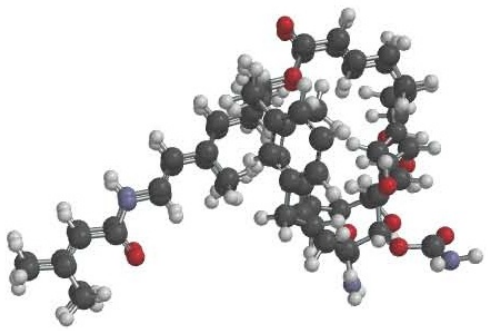


Figure 4.3 Superimposition of AM1 optimized conformations of 1.8 & 4.1

The majority of the structures appear to have favourable overlap. Finally, no analogues had (nor have) been synthesized with modifications in this region of

palmerolide A; making this a truly unique contribution, which as will be seen we believed was particularly accessible via the route we had employed in synthesizing the natural product.

4.2 Retrosynthetic Approach

The retrosynthetic approach utilized in designing the analogue synthesis was patterned on the route we had employed in synthesizing the natural product (Figure 4.4). The key disconnections for the superstructure employed Curtius rearrangement chemistry for completing the dienamide side arm, Yamaguchi macrolactonization for closing the ring and B-alkyl Suzuki-Miyaura cross coupling of a Western Hemisphere **4.2** and an Eastern Hemisphere **4.4**. The Western Hemisphere would trace back to aromatic aldehyde **4.3** by means of Vivol•$SnCl_4$ catalyzed crotylboration. The Eastern Hemisphere would once again be accessed through the IEDHDA/allylboration and borono-Ireland-Claisen methodologies starting from boronoacrolein pinacolate **2.20** and ethyl vinyl ether **2.5**.

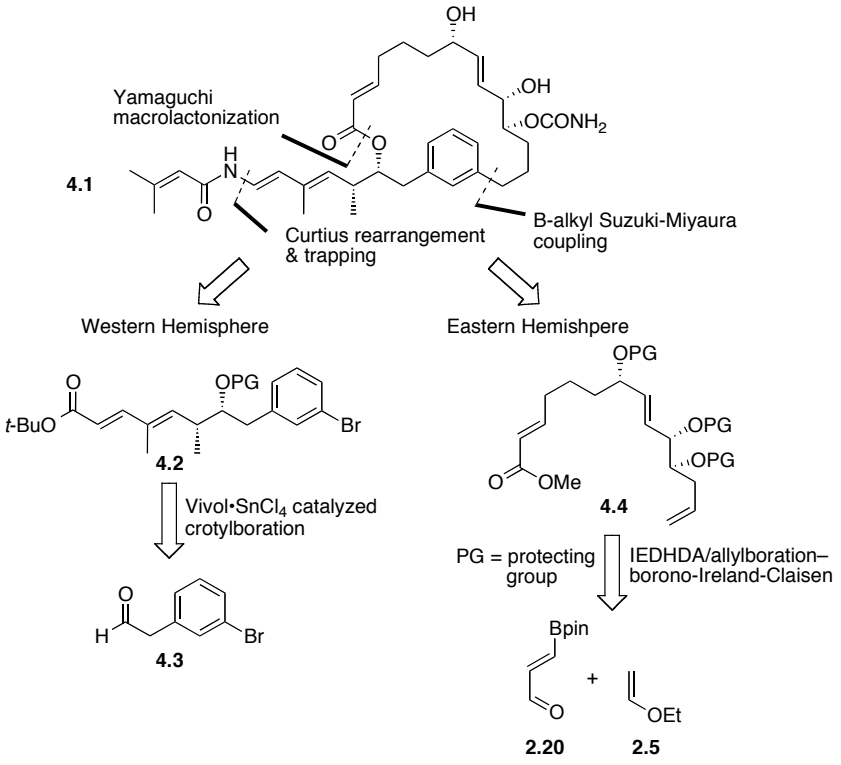


Figure 4.4 Retrosynthetic approach to analogue 4.1

4.3 Synthesis of the Eastern Hemisphere

4.3.1 One Carbon Extension of Original Synthetic Route

A comparative examination of the proposed generic Eastern Hemisphere **4.4** targeted in the analogue and the most comparable intermediate **2.82** from the synthesis of palmerolide A reveals one major difference (Figure 4.5). The analogous **4.4** contains an extra carbon terminating with a C14 olefinic carbon.

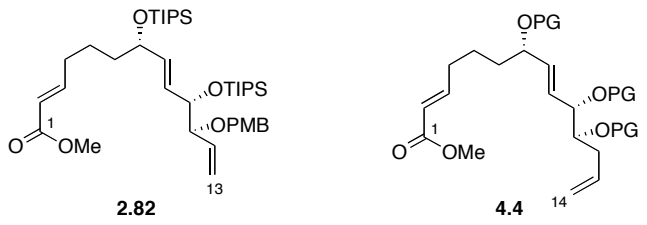


Figure 4.5 Eastern Hemisphere 2.82 compared to homologous 4.4

It was thus necessary to modify the route to the Eastern Hemisphere to incorporate this carbon chain extension. The point of divergence selected was alcohol **2.78**, which, as had been demonstrated in the natural product synthesis, could be synthesized in nine steps from starting materials **2.20** and **2.5** in an overall yield of 41% averaging 91% per step (Figure 4.6).

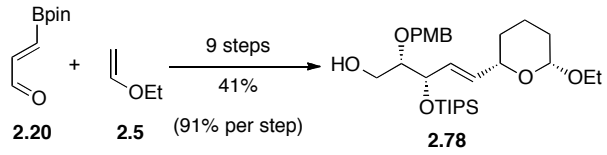


Figure 4.6 Demonstrated access to alcohol 2.78

The requisite transformation sought, was the conversion of the partially masked diol in **2.78** into a homoallyl-moiety (Figure 4.7).

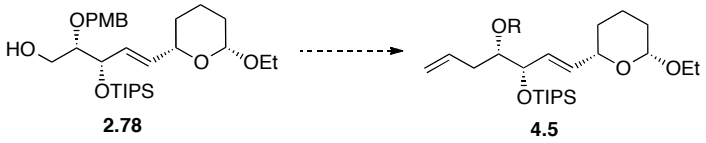
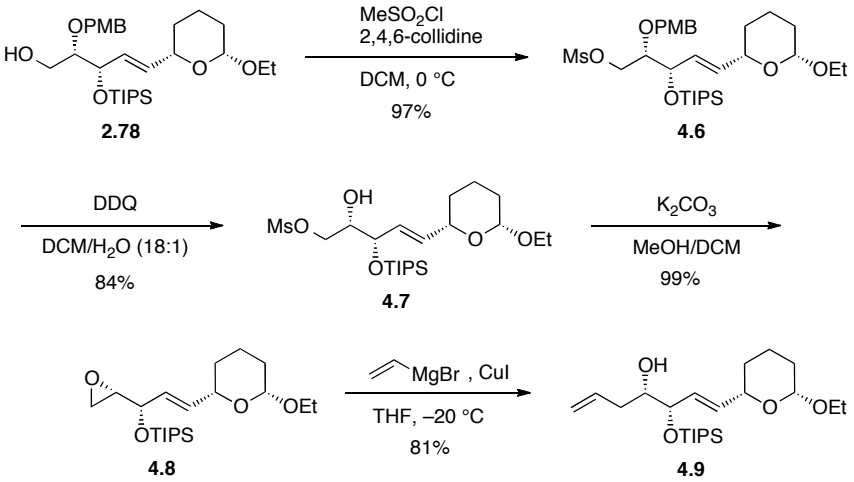


Figure 4.7 Conversion of masked diol to homoallyl-moiety

Consultation with the literature revealed a strategy by Rychnovsky and co-workers wherein a terminal diol was converted into a homoallylic alcohol during their synthesis of a fragment of amphidinol 3.[96] This strategy was adapted to the synthesis of homoallylic alcohol **4.9** (Scheme 4.1).

The first step was mesyl protection of the terminal hydroxyl group facilitating formation of mesylate **4.6** in near quantitative yield. The next step presents one of the key features in redesigning the synthesis for the analogue. Recall, the difficulties posed by removal of the PMB protecting group on the third last step of our synthesis of the natural product. Here, the PMB group was easily removed from **4.6** using standard DDQ oxidative conditions,[97,98] affording alcohol **4.7** in good yield. Early removal of the PMB group is expected to counteract any

potential problems that might arise by removing it later in the synthesis. Treatment with base then produced epoxide **4.8** in 99% yield. The last step in the sequence was a copper (I) iodide mediated addition of vinyl magnesium bromide, opening the epoxide to afford homoallylic alcohol **4.9** also in good yield. Compared to the natural product synthesis this modification adds two steps to the Eastern Hemisphere synthesis but potentially leads to the removal of a deprotection step later on.



Scheme 4.1 Synthesis of homoallylic alcohol 4.9

4.3.2 Early Installation of the Carbamate

One of the insights gained from the Chen-Nicolaou synthesis was the relatively robust nature of the carbamate moiety.[15] In their synthesis the carbamate was installed on one of the three relatively early intermediates (**1.10**) that were later assembled enroute to the final product. After placement of the unprotected carbamate group it was carried through 10 steps including both acidic and basic conditions averaging 66% per step (Figure 4.8). This was in contrast to our decision to push the carbamate placement as late as possible with the consequently problematic PMB deprotection.

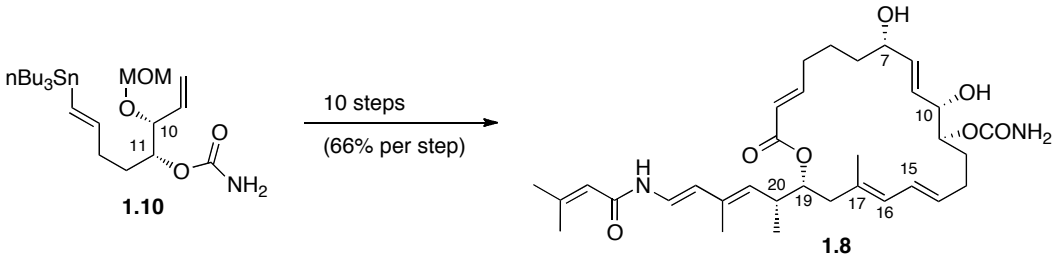
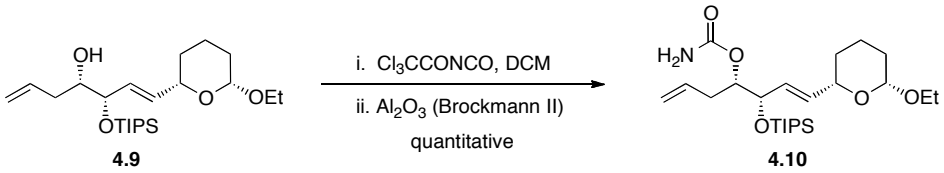


Figure 4.8 Early placement of the carbamate in the Chen-Nicolaou synthesis

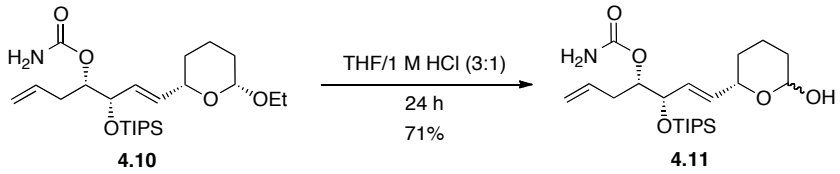
The decision was thus taken to place the carbamate early in the analogue synthesis. Providing that no undesirable chemoselectivity ensued, this would reduce extraneous protecting group manipulations and facilitate a more efficient synthesis. The free alcohol on **4.9** was carbamylated using the same procedure employed in the natural product synthesis affording carbamate **4.10** in excellent yield (Equation 4.1).



Equation 4.1

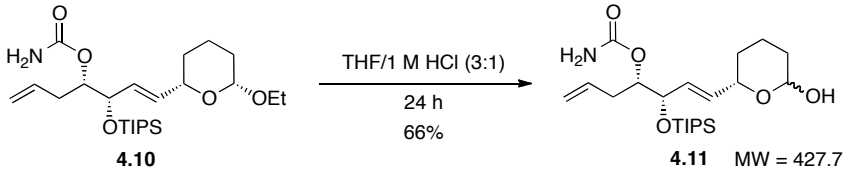
4.3.3 Hydrolysis of Acetal 4.10

The acetal hydrolysis conditions utilized in the total synthesis were initially applied to substrate **4.10** on a small scale with favourable results affording hemiacetal **4.11** in 71% yield (Equation 4.2).

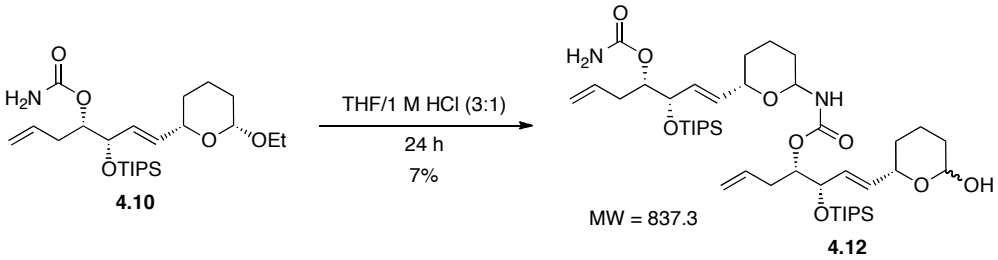


Equation 4.2

When this reaction was scaled up however, there was a small reduction in yield (Equation 4.3). A significant quantity of by product (7% of the theoretical yield) that eluted in the earlier chromatographic fractions was isolated that contained ^{1}H NMR resonances that were consistent with the desired product **4.11** but more complex in splitting and overlap patterns. Mass spectrometric analysis revealed a molecular weight that was double that of the desired product minus one water molecule (MW = 837.3). Dimerization involving an amide condensation forming **4.12** seemed to be a plausible rationale for the result (Equation 4.4).



Equation 4.3



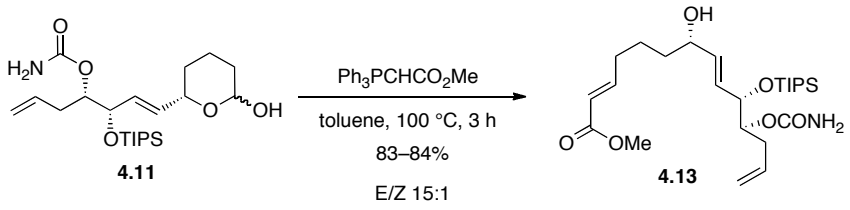
Equation 4.4

A re-examination of the reaction conditions also points to a tenable solution for improving the result. The reaction conditions employed a solvent ratio of three parts THF to one part 1 M hydrochloric acid that is consistent with previous conditions used in this hydrolysis. However, since the reaction was run on a much larger scale than previously (14 *x*) it was run more concentrated for convenience. The more concentrated conditions are more favourable to dimerization, therefore, higher dilution should address this issue. Also, of note is the longer reaction time compared to the first example. This too can possibly be linked to the concentration issue. When the hydrolysis conditions were first optimized in the natural product synthesis there was a notable increase in reaction

time when the water content in the reaction was too high which was attributed to poor substrate solvation. In addition to the isolation of dimer **4.12**, approximately 10% of the starting material was also recovered; testimony to the low efficiency of this reaction. Here in the analogue synthesis there is likely a need to find a new optimum concentration, which will also facilitate efficient acetal hydrolysis.

4.3.4 Ring Opening/Wittig and TIPS Protection

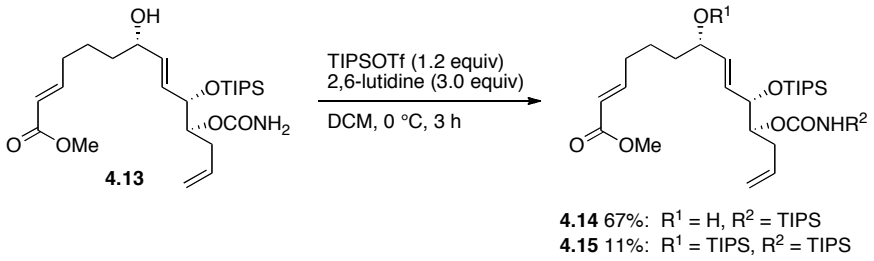
Following the acetal hydrolysis the previously employed conditions for the ring opening/Wittig were applied to hemiacetal **4.11** on scales ranging from 20 mg to 600 mg with a yield range of 83–84% for product **4.13** and an E/Z ratio of 15:1 (Equation 4.5).



Equation 4.5

At this stage no major difficulties with the unprotected carbamate had presented themselves.

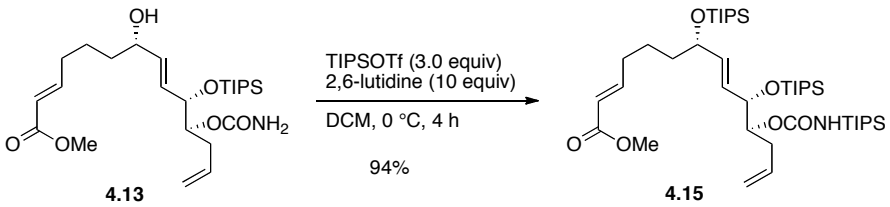
Consistent with the established synthesis a TIPS protecting group was selected for completion of the Eastern Hemisphere of the analogue. The first attempt at placing the protecting group followed previously employed conditions (Equation 4.6).



Equation 4.6

The result however was not a clean reaction, producing a mixture of singly (**4.14**) and doubly (**4.15**) protected products. Three pieces of evidence pointed to selective placement of the TIPS on the nitrogen of the carbamate rather than the free oxygen in singly protected **4.14**: 1) In the ^{1}H NMR spectrum the NH signal was reduced from 2H to 1H in the product; 2) In MS analysis **4.14** loses a water molecule as a minor fragment whereas in **4.15** the minor fragment is the result of a TIPSOH loss. This in an indication of a free alcohol in **4.14;** 3) IR analysis of **4.14** reveals an alcohol absorption. The evinced selectivity might be attributed to steric congestion where the primary carbamate nitrogen is more available than the secondary alcohol.

The reaction conditions were modified with the intent of complete protection of both alcohol and carbamate nitrogen. This simply involved increasing the number of equivalents of base and TIPSOTf. The first attempt resulted in undesired decomposition. To counteract the possibility of acidic side reactions the ratio of base to TIPSOTf was increased affording the desired **4.15** in excellent yield (Equation 4.7). The equivalents depicted in Equation 4.7 were actually delivered in two aliquots.

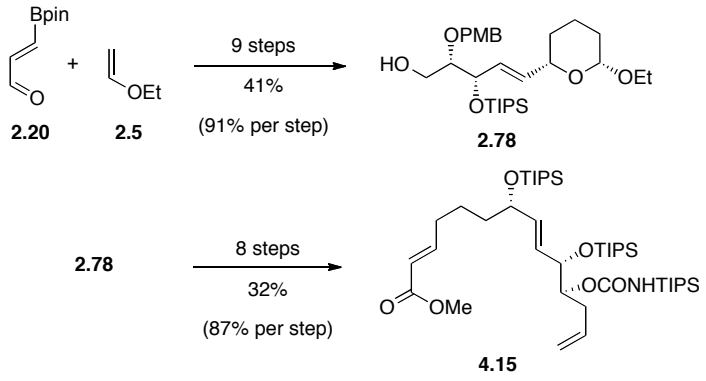


Equation 4.7

When the reaction was carried out on a larger scale it was a bit sluggish requiring extra base (5 equiv) and TIPSOTf (1 equiv) additions before it went to completion but a good yield was also obtained in this case (83%).

4.3.5 Summary of Pathway for Eastern Hemisphere 4.15

A viable pathway to the Eastern Hemisphere **4.15** was now complete. The route employed identical chemistry from the natural product synthesis until alcohol **2.78** (Scheme 4.2). From there it diverged incorporating extra steps to accomplish a necessary methylene insertion between the terminal olefin and the remainder of the molecule. Another key difference is the modification of the protecting group strategy including early carbamate incorporation and concomitant TIPS protection. From the divergence point, the synthesis is competitive with an average of 87% per step with a few transformations that can be optimized further.



Scheme 4.2 Overview of the synthesis of Eastern Hemisphere homologue 4.15

4.4 Preliminary Investigations into a Synthesis of the Western Hemisphere

4.4.1 Synthesis of Aldehyde 4.3

The first priority in beginning work on the Western Hemisphere was accessing the starting material, aldehyde **4.3** (Figure 4.9), in significant quantities.

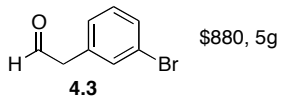


Figure 4.9 (3-Bromophenyl)acetaldehyde

A Scifinder® search reveals a number of commercial sources that do not list a catalogue price. Upon writing to several of them, one responded with a price that approached $1000 for a quantity (5 g) that would unlikely be sufficient for carrying out a total synthesis. It did not appear to be a very challenging target, and the acid analogue **4.16** (Figure 4.10) was found to be readily available from commercial sources. Therefore, a synthetic methodology to access this aldehyde from the acid was explored.

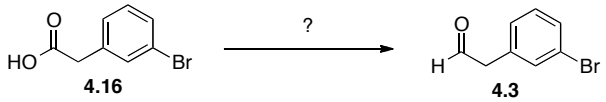
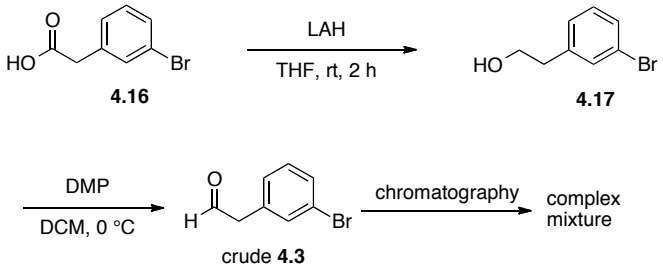


Figure 4.10 Synthesis of 4.3 from readily available acid 4.16

Based on past experience the favoured methodology would be to oxidize the analogous alcohol **4.17** to the aldehyde using Dess-Martin periodinane (Scheme 4.3). Therefore, the acid was first reduced to the alcohol with lithium aluminium hydride and filtered with no further purification. This crude mixture was then treated with Dess-Martin periodinane and oxidized to the aldehyde. By TLC, the crude reaction mixture appeared to be easily resolvable and the crude was subjected to flash chromatography using silica deactivated with triethylamine. This approach to purification resulted in product decomposition and only a small amount of aldehyde was isolated and this too was mixed with an impurity.



Scheme 4.3 First attempt at synthesizing aldehyde 4.3

An attempt was made to purify the aldehyde containing fraction from the chromatography by distillation, but it was met with mixed results. The aldehyde was only successfully distilled at over 200 °C and approximately 1 torr accompanied by significant decomposition and impure distillate. A second distillation was met with similar results. Consideration of the structure indicates the potential for undesired reactivity due to the likelihood of enolization and subsequent uncontrolled aldol chemistry (Figure 4.1).

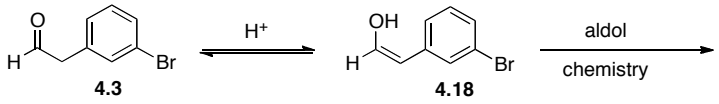
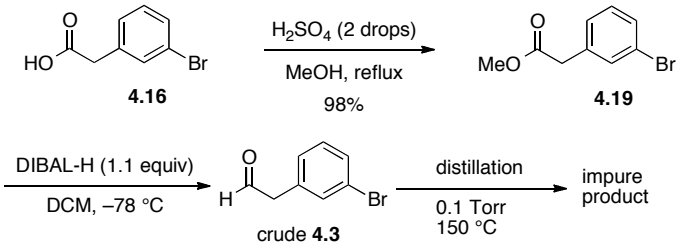


Figure 4.11 Highly enolyzable aldehyde subject to undesired reactivity

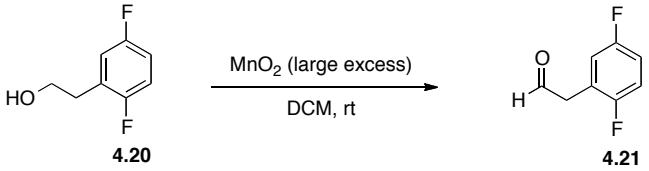
The undesired reactivity might be acid catalyzed and since the Dess-Martin reagent is acidic by virtue of persistent traces of acetic acid, a different method to access the aldehyde was conceived. This alternate approach involved conversion of the acid to a methyl ester **4.19** and then DIBAL-H reduction to the aldehyde (Scheme 4.4).



Scheme 4.4 Methyl ester approach to synthesis of aldehyde 4.3

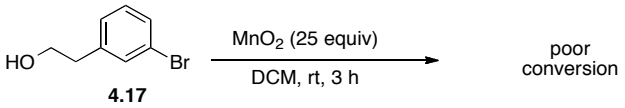
The methyl ester was easily made by refluxing the acid in methanol with catalytic sulphuric acid; affording **4.19** in 98% yield. The DIBAL-H reduction also produced the crude product in a straightforward manner. Since chromatography had previously resulted in such extensive decomposition, distillation was chosen as the preferred method of isolation. Manipulations on the vacuum apparatus facilitated a lower temperature distillation (0.1 torr and 150 °C *vs* 1 torr and 250 °C). Nevertheless the distilled aldehyde contained impurities, possibly attributed to aldehyde/enol side reactions.

Returning to the first strategy an oxidation method was pursued. Ideally an oxidation method would be employed in which it would produce aldehyde **4.3** with no need for purification due to its sensitive nature. A literature precedent by Rémy Angelaud and co-workers (Merck Process Research, Rahway, New Jersey) on an analogous alcohol **4.20** was found wherein manganese (IV) oxide was employed as an oxidant that could simply be filtered off to isolate aldehyde **4.21** (Equation 4.8).[99]



Equation 4.8

On attempting to apply their methodology to alcohol **4.17** The oxidation proved to be very sluggish (Equation 4.9), which was unacceptable since remaining starting material, would require purification.

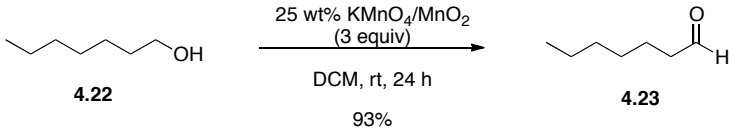


Equation 4.9

Angelaud and co-workers had not included any experimental data or description

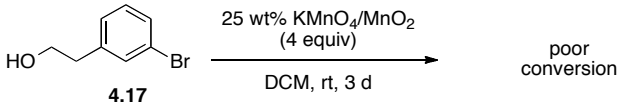
of their synthesis of **4.21** but did note a pertinent observation that provides insight into the analogous conversion of **4.17** into aldehyde **4.3**. The authors did not isolate aldehyde **4.21**; because it was, "very unstable and could not be purified . . . it was used directly in the subsequent Wittig-Horner reaction."[99] Unfortunately, this approach was not acceptable with respect to the synthesis of aldehyde **4.3** because Rauniyar had established that high purity in aldehyde was necessary for good enantioselectivity in his catalytic crotylboration system. Angelaud and co-workers had also attempted a Swern oxidation, which resulted in decomposition. Likewise Swern conditions applied to **4.17** also resulted in product decomposition.

Another precedent wherein manganese (IV) oxide served as a support for potassium permanganate was also pursued (Equation 4.10).[100] In the precedent, high conversion of aliphatic alcohol **4.22** to aldehyde **4.23** took place within 24 hours, but when the conditions were applied to alcohol **4.17** even after 3 days a significant quantity of the starting material remained (Equation 4.11).



4.22 **4.23**

Equation 4.10



4.17

Equation 4.11

Another oxidation was attempted with 2-iodoxybenzoic acid (IBX) (Figure 4.12).

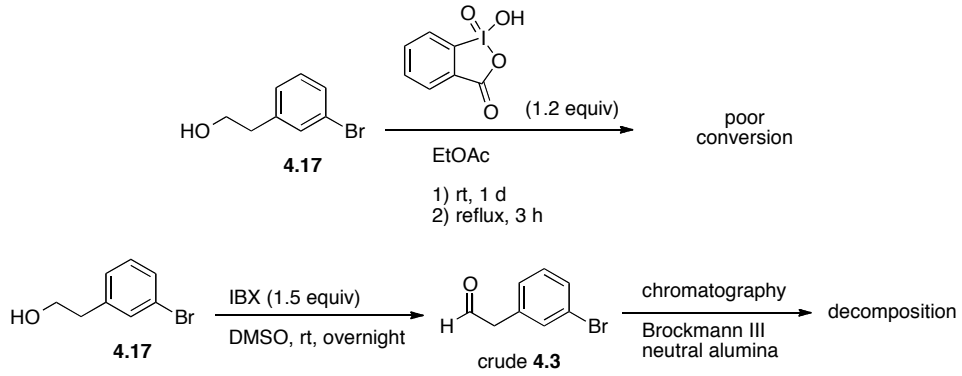


Figure 4.12 Attempts to oxidize 4.17 with IBX

The first attempt proved to be unsuccessful, likely due to solubility issues. Ethyl acetate was selected as a solvent due to the relative ease with which it might be removed once the reaction was complete. The reaction would not proceed at room temperature and even under refluxing conditions proceeded slowly along with accompanying decomposition products. At no point did the reaction mixture clarify into a solution. Dimethylsulfoxide (DMSO) was then used as a solvent and the reaction proceeded to completion at room temperature within 24 hours. Chromatography was then attempted with Brockmann III neutral alumina as an alternative purification method. This resulted in extensive decomposition and no pure aldehyde **4.3** was isolated.

A literature search revealed a patent containing a procedure for the synthesis of aldehyde **4.3**.[101] Experimental details for substrate **4.17** are not provided in the patent description but two key features in the general procedure were buffering the reaction with solid sodium bicarbonate and filtration as a workup procedure rather than the typical aqueous workup. Using these features as a basis, a synthetic procedure was devised that allowed access to aldehyde **4.3** in excellent yield and decent purity (Figure 4.13).

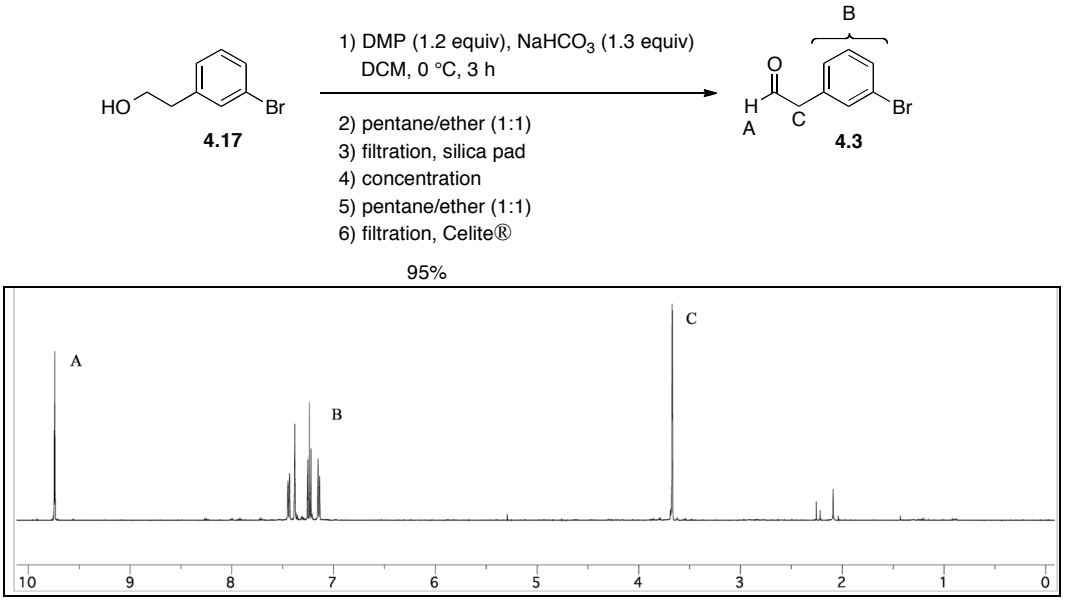
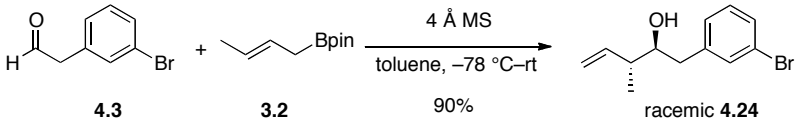


Figure 4.13 Synthesis of 4.3 and ^{1}H NMR spectrum indicating product purity

Figure 5.14 includes an NMR spectrum indicating the purity of the product. There is a small quantity of unidentified material in the vicinity of 2.1 ppm but the purity was deemed sufficient for proceeding to the next step.

4.4.2 Catalytic Crotylboration of Aldehyde 4.3

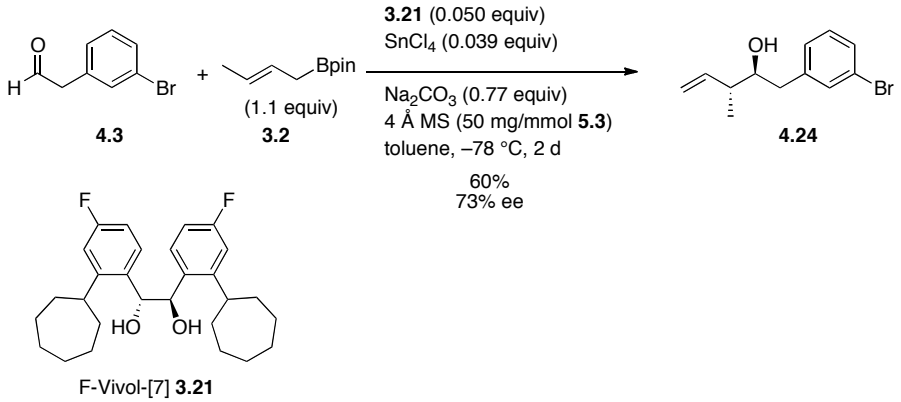
The first step in evaluating the enantiomeric purity of the product was developing an HPLC methodology to measure it. This required a racemic product **4.24** that was synthesized by a non-catalyzed crotylboration (Equation 4.12).



Equation 4.12

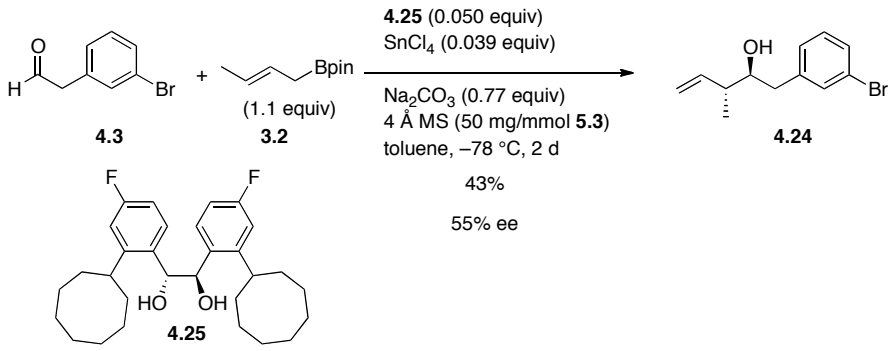
Using the same chiral column that had been used in previous HPLC enantiomeric excess measurements (Chiralpak AD RH) a method was found for resolving the two peaks of the racemate with retention times of 12 and 15 min (c.f. Experimental for further detail).

Since the F-Vivol[7]•$SnCl_4$ complex had been the catalyst that was most successfully applied in the synthesis of palmerolide A, it was used as the starting point in the analogue synthesis. Following Rauniyar's conditions a crotylboration between aldehyde **4.3** and boronate **3.2** was carried out producing *anti*-propionate **4.24** with and enantiomeric excess of 73% (Equation 4.13).



Equation 4.13

Although 73% ee is significant it was deemed worthwhile to attempt an improvement. As noted in the natural product synthesis, one observation Rauniyar had made while developing his enantioselective catalytic allyl/crotylboration methodology was that optimal performance in enantioselectivity was substrate dependent and could be tuned by using different ring sizes for the Vivol component. Since the most generally enantioselective Vivol was F-Vivol-[8] **4.25**[78], this was chosen as the next one to test (Equation 4.14).



Equation 4.14

This attempt resulted in a reduction in enantiomeric excess; 55% ee compared to the 73% ee obtained with F-Vivol-[7]. There was also a reduction in yield (43%), possibly indicating a reduction in catalyst efficiency. A control reaction using F-Vivol-[7] was run in parallel that resulted in an enantiomeric excess of 72% . An important procedural aspect should be noted. Aldehyde **4.3** as was discovered during the development of its synthesis is highly sensitive and prone to decomposition. In one instance, use of **4.3** in the crotylboration reaction catalyzed by F-Vivol-[7] **3.21** resulted in a racemate. The **4.3** used in the reaction had been synthesized the previous week and stored in a freezer. This result instigated an NMR analysis of the reagent, which revealed significant decomposition in the stored **4.3**. This once again confirmed Rauniyar's observation regarding the critical nature of aldehyde purity for enantioselectivity in the system. For this reason, subsequent test reactions involved synthesis of fresh aldehyde immediately preceding the crotylboration.

Since there appeared to be a trend of reduced catalytic activity and enantioselectivity with increasing ring size, synthetic efforts were directed towards synthesizing F-Vivol's with smaller ring sizes. In parallel to the author's work a fellow group member, Erin Graham, was also investigating the performance of different Vivols on other aldehyde substrates by modulating ring size. We collaborated by independently synthesizing Vivols of interest to each other and then sharing them. Graham synthesized F-Vivol-[5] **4.26** while the author synthesized F-Vivol-[6] **4.27** (Figure 4.14).

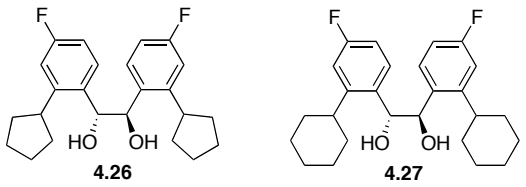


Figure 4.14 F-Vivol-[5] 4.26 and F-Vivol-[6] 4.27

Enroute to synthesizing these diols some modifications were made on Rauniyar's original procedures. These are detailed in Appendix C.

Once the syntheses of **4.26** and **4.27** were completed they were applied to the crotylboration of aldehyde **4.3** (Figure 4.15).

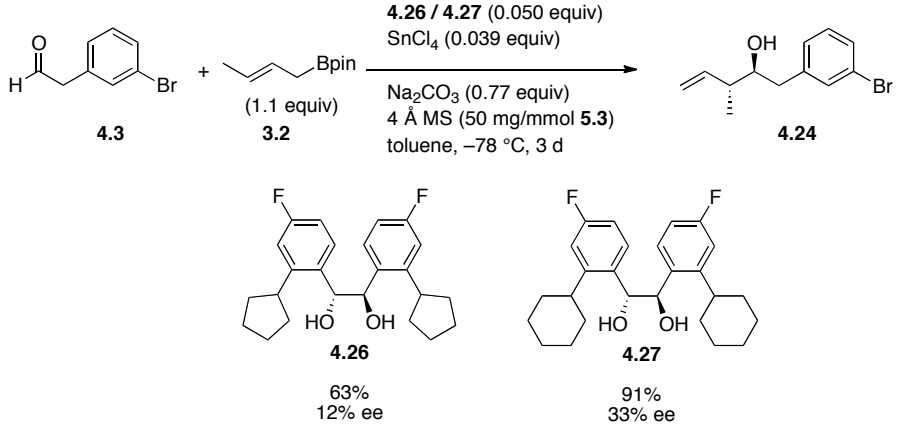


Figure 4.15 Performance of 4.26 and 4.27 in catalyzing the formation of 4.24

The smaller ring sizes unfortunately did not enhance the enantioselectivity and *anti*-propionate **4.24** was produced with a lower %ee than in the preceding cases (12%: **4.26** and 33%: **4.27**). A graphical representation of the trend (Figure 4.16) clearly shows an enantiomeric excess increase correlated with larger ring size to a maximum with F-Vivol-[7] **3.21** and dropping off at 8 membered rings. There does not appear to be any remaining benefit to be derived by making more catalysts of different ring sizes. The result is not surprising given its parallel to Rauniyar's optimization efforts towards the total synthesis of palmerolide A (cf. Chapter 3, Figure 3.4).

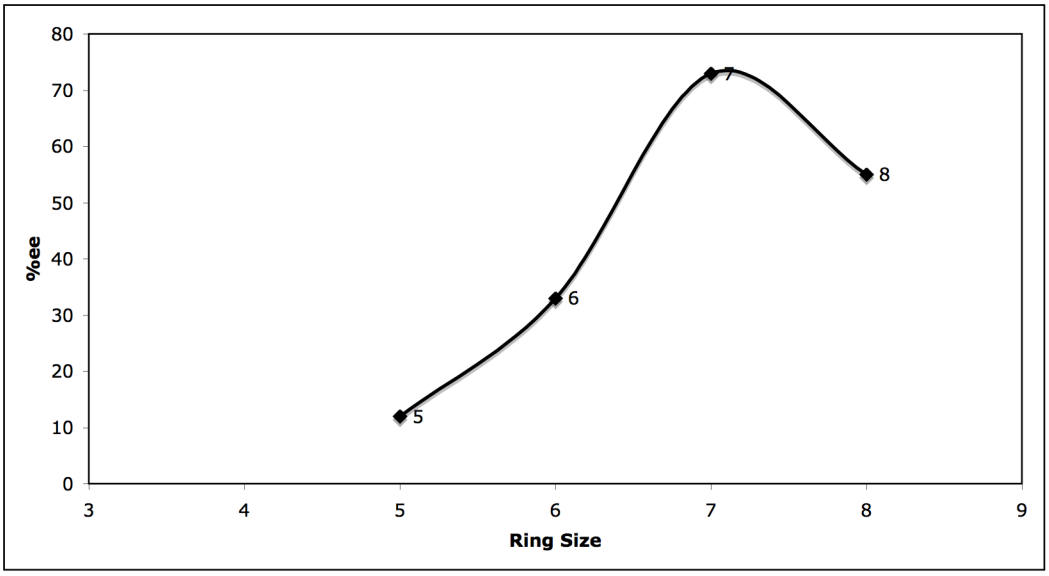


Figure 4.16 Trend in F-Vivol enantioselectivity with respect to ring size

The decision was taken at this stage to continue the synthesis using F-Vivol-[7] **3.21**. However, by this time there was insufficient quantity of the diol remaining to pursue this endeavour. Therefore, steps were taken to synthesize significant quantities of it. A description of this work in terms of divergence from Rauniyar's original synthesis is found in Appendix C. Appendix C also describes an alternative method for the synthesis of crotylboronate **3.2** also distinct from the method by which it was synthesized by Rauniyar. Ultimately, gram quantities of F-Vivol-[7] were synthesized which will now be available for the next graduate student who undertakes this project. The progress towards completion of the analogue study was terminated at this juncture due to a physical injury sustained by the author that precluded lab work.

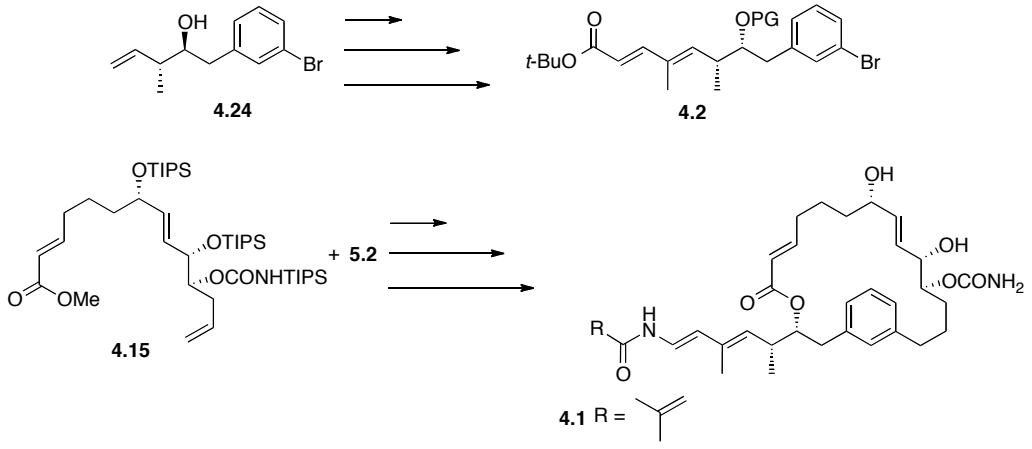
4.4.3 Summary of Western Hemisphere Synthetic Investigations

A method for obtaining significant quantities of relatively pure starting material aldehyde **4.3** was developed. This aldehyde however, is very sensitive and should be used immediately upon isolation to ensure high enantioselectivity

in the desired crotylboration. After a study of ring size effects it was concluded that the best diol for catalyzing the crotylboration of aldehyde **4.3** and crotylboronate **3.2** is F-Vivol-[7] **3.21** affording *anti*-propionate **4.24** in 73% ee. Experimental observations and modifications made during further syntheses of different Vivols now offer improved access to these diols.

4.5 Conclusion and Future Work

The preliminary investigations into the synthesis of palmerolide A analogues have provided a viable route to the Eastern Hemisphere homologue **4.15**. The Western Hemisphere component of the analogue design requires further development. This will involve transformations necessary to synthesize an ester of type **4.2** (Scheme 4.5). Based on the precedent of the palmerolide A synthesis, it should be possible to accomplish the necessary transformations in excellent yield. Next the hemispheres will need to be joined and brought forward to analogue **4.1**. Critical to this uncharted sequence will be the behaviour of the carbamate group through key steps such as the coupling, ring closing, dienamide installation and final deprotection.

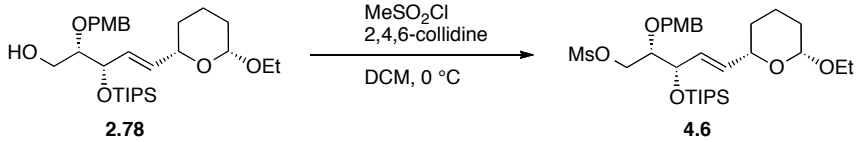


Scheme 4.5 Future steps towards analogue completion

If these steps can be successfully executed hopefully valuable medicinal chemistry studies will result from biological testing of **4.1** and variations in the dienamide terminal group.

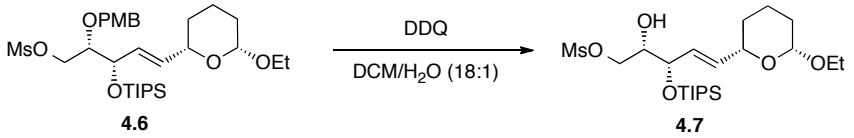
4.6 Experimental

*4.6.1 (1E)-1,2-dideoxy-1-[(2S,6R)-6-ethoxytetrahydro-2*H*-pyran-2-yl]-4-O-(4-methoxybenzyl)-5-O-(methylsulfonyl)-3-O-[tri(propan-2-yl)silyl]-L-*threo*-pent-1-enitol (4.6)*



Alcohol **2.78** (34.3 mg, 65.6 μmol, 1.00 equiv) was dissolved in DCM (5 mL) and to this was added 2,4,6-collidine (79.5 mg, 65.6 μmol, 1.00 equiv). The solution was cooled to 0 °C and methane sulfonyl chloride (10 μL, 15 mg, 2.0 equiv) was added dropwise. The reaction mixture was stirred 22 hours at 0 °C. The reaction was quenched with water, extracted with DCM, diluted with ethyl acetate, washed with water, dried with magnesium sulphate, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/ethyl acetate, 7:3; 1% triethylamine) to afford 39.4 mg of **4.6** as a colourless oil. Yield: 97%. $[\alpha]_D^{25}$ –36.1 (*c* 1.24, $CHCl_3$); **IR** (cast film) 2942, 2866, 1613, 1514, 1360, 1250, 1177, 1026, 823 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.29-7.25 (m, 2H), 6.89-6.85 (m, 2H), 5.83-5.71 (m, 2H), 4.65-4.58 (m, 2H), 4.47-4.42 (m, 3H), 4.16 (dd, *J* = 11.0, 7.7 Hz, 1H), 3.99-3.91 (m, 2H), 3.80 (s, 3H), 3.75-3.74 (m, 1H), 3.58-3.50 (m, 1H), 2.94 (s, 3H), 1.90-1.83 (m, 1H), 1.79-1.76 (m, 1H), 1.64-1.51 (m, 2H), 1.44-1.34 (m, 1H), 1.28-1.21 (m, 4H), 1.08-1.04 (m, 21H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 159.4, 132.6, 130.0, 129.6, 127.5, 113.8, 101.9, 79.8, 75.4, 72.6, 71.4, 70.6, 64.0, 55.3, 37.3, 31.08, 31.04, 22.2, 18.00, 17.9, 15.3, 12.2; **HRMS** (ESI) Calcd. $C_{30}H_{52}O_8SiS$+Na: 623.3044. Found: 623.3039.

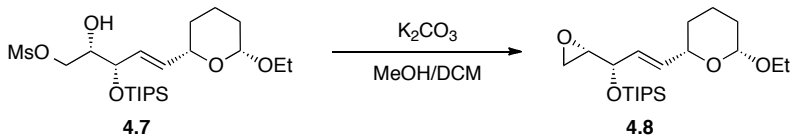
*4.6.2 (1E)-1,2-dideoxy-1-[(2S,6R)-6-ethoxytetrahydro-2*H*-pyran-2-yl]-5-O-(methylsulfonyl)-3-O-[tri(propan-2-yl)silyl]-L-*threo*-pent-1-enitol (4.7)*



4.6 **4.7**

Mesylate **4.6** (1.14 g, 1.90 mmol, 1.00 equiv) was dissolved in DCM (36 mL) and then water (2 mL) was added). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.647 g, 2.85 mmol, 1.50 equiv) was added to the reaction pot and the reaction mixture was stirred 4 hours at room temperature. The reaction mixture was diluted with ether and water followed by separation of the biphasic mixture. The organic layer was washed with a saturated solution of sodium bicarbonate (3 *x*), brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (Et_2O/hexanes, 3:2, 0.5% triethylamine) affording 0.770 g of **4.7**. Yield: 84%. $[\alpha]_D^{25}$ –31.2 (*c* 0.960, $CHCl_3$); **IR** (cast film) 3523, 2943, 2894, 2867, 1672, 1463, 1358, 1176, 970, 683 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 5.82-5.72 (m, 2H), 4.45 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.35 (dd, *J* = 11.0, 3.3 Hz, 1H), 4.28 (dd, *J* = 7.1, 6.6 Hz, 1H), 4.23-4.20 (m, 1H), 3.98-3.90 (m, 2H), 3.79-3.75 (m, 1H), 3.53 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.07 (s, 3H), 2.76 (d, *J* = 4.4 Hz, 1H), 1.91-1.85 (m, 1H), 1.80-1.77 (m, 1H), 1.61-1.51 (m, 2H), 1.43-1.35 (m, 1H), 1.29-1.20 (m, 4H), 1.13-1.01 (m, 21H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 134.8, 128.1, 101.9, 75.0, 73.9, 73.1, 70.1, 64.1, 37.7, 31.00, 30.87, 22.2, 18.06, 17.98, 15.3, 12.4; **HRMS** (ESI) Calcd. $C_{22}H_{44}O_7SiS$+Na: 503.2469. Found: 503.2464.

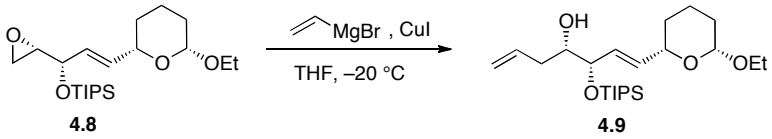
*4.6.3 (1E)-4,5-anhydro-1,2-dideoxy-1-[(2S,6R)-6-ethoxytetrahydro-2H-pyran-2-yl]-3-O-[tri(propan-2-yl)silyl]-L-*threo*-pent-1-enitol (4.8)*



4.7 **4.8**

Alcohol **4.7** (0.770 g, 1.60 mmol, 1.00 equiv) was dissolved in methanol (30 mL) and DCM (10 mL) then potassium carbonate (0.443 g, 3.20 mmol, 2.00 equiv) was added and the reaction mixture was stirred vigorously for one hour. The reaction was quenched with a saturated solution of ammonium chloride (20 mL) and diluted with Et_2O. The biphasic mixture was separated and the organic layer was washed with water (3 *x*) and brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (hexanes/ethyl acetate, 6:1, 0.5% triethylamine) affording 0.611 g of **4.8**. Yield: 99%. $[\alpha]_D^{25}$ –53.0 (*c* 1.21, $CHCl_3$); **IR** (cast film) 3046, 2943, 2893, 2866, 2726, 1463, 1378, 1071, 1024, 883, 683 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 5.81 (ddd, *J* = 15.6, 4.9, 1.1 Hz, 1H), 5.73 (ddd, *J* = 15.6, 5.7, 1.3 Hz, 1H), 4.46 (dd, *J* = 9.5, 2.2 Hz, 1H), 4.00-3.92 (m, 3H), 3.54 (dq, *J* = 9.6, 7.1 Hz, 1H), 2.99 (ddd, *J* = 6.0, 4.1, 2.7 Hz, 1H), 2.76 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.60 (dd, *J* = 4.9, 2.7 Hz, 1H), 1.90-1.85 (m, 1H), 1.81-1.76 (m, 1H), 1.61-1.52 (m, 2H), 1.44-1.36 (m, 1H), 1.32-1.23 (m, 4H), 1.15-0.93 (m, 21H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 132.2, 128.6, 101.9, 75.5, 74.9, 64.0, 55.9, 44.4, 31.07, 31.04, 22.1, 18.01, 17.96, 15.3, 12.3; **HRMS** (ESI) Calcd. $C_{21}H_{40}O_4Si$+Na: 407.2588. Found: 407.2587.

4.6.4 (1E,3S,4S)-1-[(2S,6R)-6-ethoxytetrahydro-2H-pyran-2-yl]-3-{[tri(propan-2-yl)silyl]oxy}hepta-1,6-dien-4-ol (4.9)

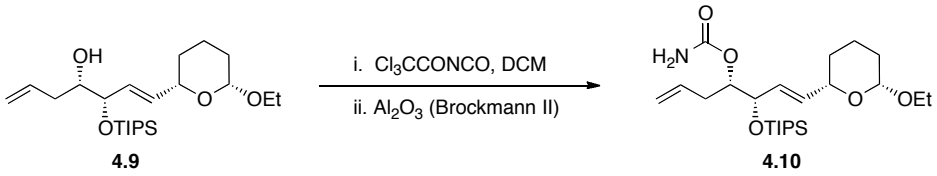


4.8 **4.9**

Copper (I) iodide (0.302 g, 1.58 mmol, 1.00 equiv) was heated under vacuum and cooled under argon. It was then suspended in THF (30 mL) and cooled to a temperature of –20 °C. A solution of 1 M vinyl magnesium bromide in THF (6.3 mL, 6.3 mmol, 4.0 equiv) was added (solution darkened on addition). Epoxide **4.8** (0.609 g, 1.58 mmol, 1.00 equiv) was dissolved in THF (10 mL) and added slowly to the reaction mixture along with a rinse of THF (1 mL). The reaction

mixture was stirred for 1 hour and 40 minutes at 20 °C and then quenched with a saturated solution of ammonium chloride (10 mL). The biphasic mixture was diluted with Et_2O, washed with water (1 *x*) and brine (2 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (hexanes/ethyl acetate, 6:1, 0.5% triethylamine) affording 0.531 g of **4.9**. Yield: 81%. $[\alpha]_D^{25}$ – 26.7 (*c* 1.35, $CHCl_3$); **IR** (cast film) 3468, 3076, 2943, 2893, 2866, 1641, 1463, 1379, 1071, 1024, 882, 681 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 5.93-5.84 (m, 1H), 5.74-5.68 (m, 2H), 5.11-5.06 (m, 2H), 4.45 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.08-4.05 (m, 1H), 3.98-3.90 (m, 2H), 3.56-3.50 (m, 2H), 2.61 (d, *J* = 3.8 Hz, 1H), 2.39-2.33 (m, 1H), 2.14-2.07 (m, 1H), 1.91-1.85 (m, 1H), 1.80-1.76 (m, 1H), 1.61-1.52 (m, 2H), 1.44-1.36 (m, 1H), 1.31-1.22 (m, 4H), 1.12-1.02 (m, 21H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 135.2, 133.8, 129.7, 116.9, 101.9, 77.2, 75.5, 74.4, 64.0, 36.9, 31.01, 30.90, 22.2, 18.12, 18.05, 12.4; **HRMS** (ESI) Calcd. $C_{23}H_{44}O_4Si$+Na: 435.2901. Found: 435.2901.

4.6.5 (1E,3S,4S)-1-[(2S,6R)-6-ethoxytetrahydro-2H-pyran-2-yl]-3-{[tri(propan-2-yl)silyl]oxy}hepta-1,6-dien-4-yl carbamate (4.10)

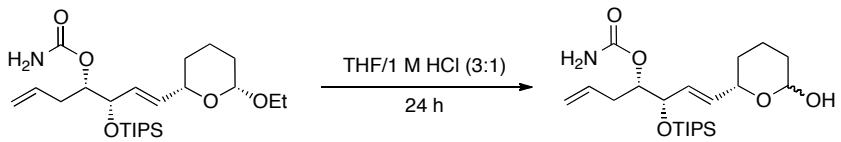


4.9 **4.10**

Homoallylic alcohol **4.9** (0.442 g, 1.07 mmol, 1.00 equiv) was dissolved in DCM (15 mL), then trichloroacetylisocyanate (0.222 g, 1.18 mmol, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was added to a pad of Brockmann II basic alumina and allowed to remain in contact with it for 3 hours. The alumina was then washed with ethyl acetate and the eluent was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 7:3, 0.5% triethylamine) affording 0.457 g of **4.10**. Yield:

quantitative. $[\alpha]_D^{25}$ –46.3 (*c* 1.08, $CHCl_3$); **IR** (cast film) 3363, 3279, 3203, 3078, 2944, 2893, 2867, 2725, 1732, 1600, 1381, 1069, 883, 683 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 6.58 (bd, *J* = 75.7 Hz, 2H), 5.83-5.65 (m, 3H), 5.10-5.00 (m, 2H), 4.80-4.72 (m, 3H), 4.45 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.38 (t, *J* = 6.0 Hz, 1H), 3.98-3.89 (m, 2H), 3.57-3.50 (m, 1H), 2.50-2.45 (m, 1H), 2.22-2.11 (m, 1H), 1.91-1.83 (m, 1H), 1.79-1.74 (m, 1H), 1.61-1.51 (m, 2H), 1.44-1.36 (m, 1H), 1.32-1.21 (m, 4H), 1.11-0.88 (m, 19H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 163.7, 156.6, 134.4, 133.1, 128.7, 117.1, 101.9, 76.6, 75.8, 73.2, 64.0, 33.5, 31.06, 31.01, 22.2, 18.0, 15.3, 12.3; **HRMS** (ESI) Calcd, $C_{24}H_{45}NO_5Si$+Na: 478.2959. Found: 478.2961.

4.6.6 (1E,3S,4S)-1-[(2S)-6-hydroxytetrahydro-2H-pyran-2-yl]-3-{[tri(propan-2-yl)silyl]oxy}hepta-1,6-dien-4-yl carbamate (4.11)

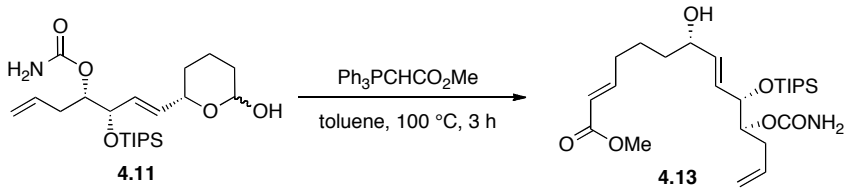


4.10 **4.11**

Carbamate **4.10** (0.477 g, 1.05 mmol, 1.00 equiv) was dissolved in THF (15 mL). A solution of 1 M hydrochloric acid in water (5 mL) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was then diluted with Et_2O, washed with a saturated solution of sodium bicarbonate (3 *x*) and brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (hexanes/ethyl acetate, 1:1, 0.5% triethylamine) affording 0.297 g of **4.11** as a mixture of epimers. Yield: 66%. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 5.84-5.63 (m, 3H), 5.35-5.35 (m, 1H), 5.11-5.02 (m, 2H), 4.83-4.73 (m, 4H), 4.54-4.50 (m, 1H), 4.44-4.38 (m, 1H), 4.03-3.98 (m, 1H), 3.73-3.71 (m, ~0.6H), 2.96-2.95 (m, ~0.4H), 2.56-2.49 (m, 1H), 2.19-2.11 (m, 1H), 1.99-1.85 (m, 1H), 1.73-1.53 (m, 3H), 1.44-1.25 (m, 2H), 1.12-0.96 (m, 19H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 156.58, 156.54, 134.66, 134.60, 133.7, 132.7, 129.9, 129.4, 117.03, 117.03, 96.5, 91.9, 76.11, 75.96, 72.82, 72.69, 69.3, 32.91, 32.78, 31.9, 31.5, 30.8,

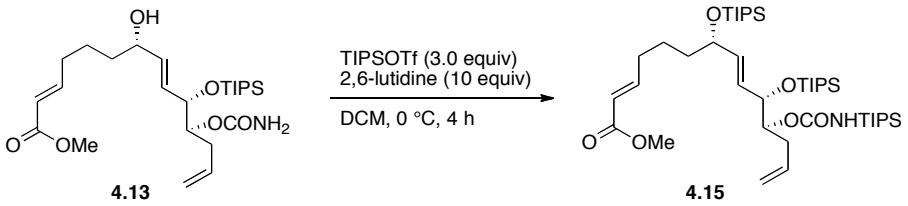
29.4, 21.9, 18.05, 18.01, 18.00, 17.98, 17.2, 12.27, 12.23; **HRMS** (ESI) Calcd. $C_{22}H_{41}NO_5Si$+Na: 450.2646. Found: 450.2643.

4.6.7 methyl (2E,7S,8E,10S,11S)-11-(carbamoyloxy)-7-hydroxy-10-{[tri(propan-2-yl)silyl]oxy}tetradeca-2,8,13-trienoate (4.13)



Hemiacetal **4.11** (0.300 g, 0.693 mmol, 1.00 equiv) and methoxycarbonylmethylene)triphenylphosphorane (0.695 g, 2.08 mmol, 3.00 equiv) were dissolved in toluene (18 mL). The reaction mixture was heated at 100 °C for 3 hours and afterwards concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 1:1, 0.5% triethylamine) affording 0.282 g of **4.13**. Yield: 84%. $[\alpha]_D^{25}$ – 14.9 (*c* 1.00, $CHCl_3$); **IR** (cast film) 3364, 3201, 3078, 2945, 2893, 2867, 1726, 1656, 1603, 1314, 1093, 883, 662 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 6.96 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.85-5.67 (m, 4H), 5.09-5.03 (m, 2H), 4.80 (ddd, *J* = 9.7, 5.1, 3.2 Hz, 1H), 4.64-4.63 (m, 2H), 4.47-4.44 (m, 1H), 4.19-4.15 (m, 1H), 3.73 (s, 3H), 2.49 (dddt, *J* = 14.9, 6.3, 3.1, 1.6 Hz, 1H), 2.26-2.22 (m, 2H), 2.20-2.11 (m, 1H), 1.65-1.49 (m, 5H), 1.13-1.03 (m, 21H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 165.6, 154.8, 147.5, 133.4, 132.9, 128.3, 119.7, 115.7, 75.0, 71.1, 70.5, 49.9, 34.9, 31.7, 30.5, 22.2, 16.54, 16.51, 10.9; **HRMS** (ESI) Calcd. $C_{25}H_{45}NO_6Si$+Na: 506.2908. Found: 506.2912.

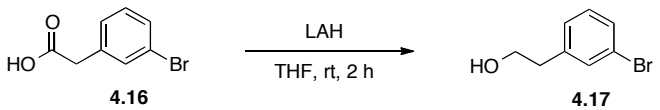
4.6.8 methyl (2E,7S,8E,10S,11S)-11-({[tri(propan-2-yl)silyl]carbamoyl}oxy)-7,10-bis{[tri(propan-2-yl)silyl]oxy}tetradeca-2,8,13-trienoate (4.15)



4.13 **4.15**

Alcohol **4.13** (0.26 g, 0.54 mmol, 1.0 equiv) was dissolved in DCM (20 mL) and cooled to 0 °C followed by addition of 2,6-lutidine (0.58 g, 5.4 mmol, 10 equiv) was added. TIPSOTf (0.49 g, 1.6 mmol, 3.0 equiv) was added dropwise and the reaction mixture was stirred approximately 2 hours at 0 °C. Another aliquot of 2,6-lutidine (5 equiv) and TIPSOTf (1 equiv) were added and the reaction was stirred for another hour at 0 °C. The reaction mixture was then diluted with Et_2O, washed with a saturated aqueous solution of sodium bicarbonate (3 *x*) and brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (hexanes/ethyl acetate, 23:2 [2 *x*] and 19:1 [1 *x*]) affording 0.356 g of **4.15**. Yield: 83%. $[\alpha]_D^{25}$ –13.2 (*c* 1.06, $CHCl_3$); **IR** (cast film) 3420, 3341, 3234, 3078, 2945, 2892, 2867, 1726, 1659, 1464, 1427, 1197, 1092, 883, 680 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 6.95 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.83-5.61 (m, 4H), 5.06-4.97 (m, 2H), 4.82-4.72 (m, 1H), 4.44-4.37 (m, 1H), 4.37-4.30 (m, 1H), 3.99 (s, 1H), 3.72 (s, 3H), 2.51-2.46 (m, 1H), 2.23-2.15 (m, 2H), 2.15-2.05 (m, 1H), 1.63-1.42 (m, 4H), 1.34-1.23 (m, 3H), 1.22-0.92 (m, 60H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 167.0, 149.3, 134.8, 128.5, 121.0, 116.8, 72.7, 51.3, 38.0, 33.5, 32.3, 22.8, 18.16, 18.13, 18.09, 18.06, 12.5, 11.4; **HRMS** (ESI) Calcd. $C_{43}H_{85}NO_6Si$+Na: 818.5577. Found: 818.5575.

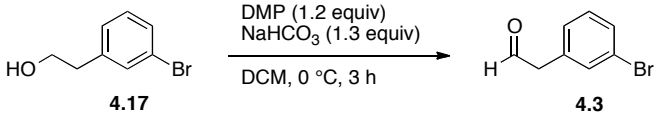
4.6.9 2-(3-bromophenyl)ethanol (4.17)



4.16 **4.17**

Lithium aluminium hydride (0.459 g, 12.1 mmol, 1.30 equiv) was suspended in THF (20 mL) and cooled to 0 °C. Acid **4.16** (2.00 g, 9.30 mmol, 1.00 equiv) was dissolved in THF (5 mL) and added to the suspension of Lithium aluminium hydride. The flask that contained the acid solution was rinsed with THF (3 *x* 5 mL) adding the washes to the reaction flask and the reaction pot was allowed to stir for 1 hour at 0 °C. The reaction was then quenched with a saturated aqueous solution of sodium potassium tartrate (20 mL) and allowed to stir for 2 hours. The biphasic mixture was then extracted with Et_2O. The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (1 *x*) and brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude liquid was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 3:2) affording 1.62 g of **4.17** as a colourless liquid. Yield: 86%. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.39-7.35 (m, 2H), 7.19-7.14 (m, 2H), 3.83 (q, *J* = 5.2 Hz, 2H), 2.82 (t, *J* = 6.5 Hz, 2H), 1.69 (s, 1H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 141.0, 132.0, 130.1, 129.6, 127.7, 122.6, 63.3, 38.8. Alcohol **5.17** has been reported.[102]

4.6.10 (3-bromophenyl)acetaldehyde (4.3)

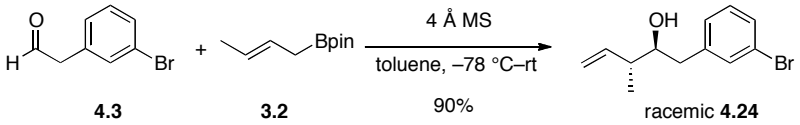


4.17 **4.3**

Alcohol **4.17** (1.00 g, 4.97 mmol, 1.00 equiv) was dissolved in DCM (50 mL). Sodium bicarbonate (0.544 g, 6.47 mmol, 1.3 equiv) was added and the suspension was cooled to 0 °C. Dess-Martin periodinane (2.53 g, 5.97 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was diluted with a mixture of pentane/Et_2O (1:1) causing precipitation of a white solid. The suspension was then passed through a pad of silica rinsing several times with the pentane/Et_2O solvent mixture. The eluent was concentrated under reduced pressure and diluted with more of the pentane/Et_2O mixture resulting in further precipitation of a small amount of solid.

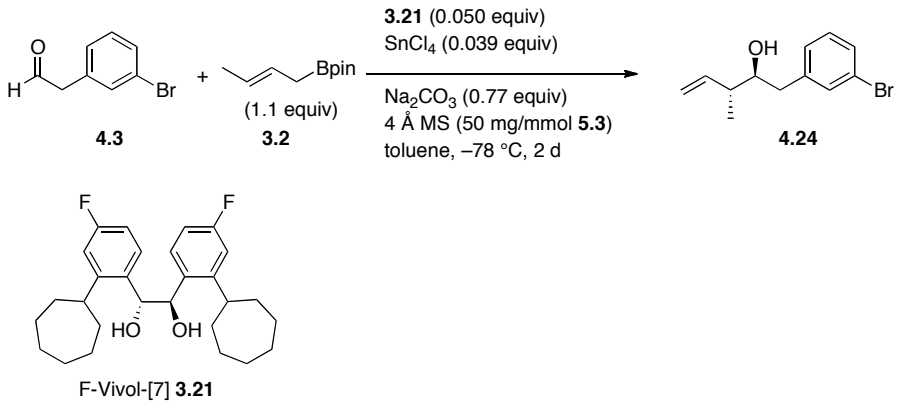
This suspension was then filtered through a pad of Celite® using the same solvent system. The liquid was then concentrated under reduced pressure affording 0.938 g of **4.3** as a colourless oil. Yield: 95%. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 9.74 (t, *J* = 2.2 Hz, 1H), 7.45-7.13 (m, 4H), 3.67 (d, *J* = 2.1 Hz, 2H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ13-C NMR (125 MHz; $CDCl_3$): δ 233.1, 168.8, 167.4, 165.37, 165.23, 163.0, 157.7, 84.7.

4.6.11 (2S,3R)-1-(3-bromophenyl)-3-methylpent-4-en-2-ol (4.24-racemic)



A flask was charged flask with 4 Å molecular sieves (50 mg), crotylboronate **3.2** (0.100 g, 0.550 mmol, 1.05 equiv), and toluene (1 mL) and contents were cooled to –78 °C. A solution of aldehyde **4.3** (1.45 M in toluene, 68 μL, 0.52 mmol, 1.0 equiv) was added to the reaction mixture and stirred at –78 °C allowing to warm to room temperature overnight and then stirred for an additional two days. The crude product was concentrated under reduced pressure and then purified by flash chromatography on silica gel (hexanes/ethyl acetate, 9:1) affording 0.133 g of **4.24** as a colourless oil (turns to a white solid at sub-zero temperatures). Yield: 90%. **IR** (cast film) 3569, 3427, 3073, 2966, 2928, 2872, 1639, 1595, 1568, 1475, 998, 775, 669 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.42-7.17 (m, 4H), 5.83 (ddd, *J* = 17.1, 10.4, 8.1 Hz, 1H), 5.19-5.12 (m, 2H), 3.66 (ddt, *J* = 9.1, 5.4, 3.7 Hz, 1H), 2.83 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.61 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.32-2.27 (m, 1H), 1.64 (d, *J* = 3.8 Hz, 1H), 1.12 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 141.5, 139.6, 132.4, 129.9, 129.4, 128.1, 122.5, 116.6, 75.5, 43.6, 40.4, 16.4; **HRMS** (EI) Calcd, $C_{12}H_{15}O^{81}Br$: 256.02859. Found: 256.02829.

4.6.12 (2S,3R)-1-(3-bromophenyl)-3-methylpent-4-en-2-ol (4.24)



A round bottom flask was charged with powdered 4 Å molecular sieves and a magnetic stir bar and heated at 100 °C while stirring under vacuum overnight. The activated molecular sieves were transferred to a laboratory oven heated to approximately 150 °C in the interim. A long necked round bottom flask was charged with diol **3.21** (22.1 mg, 50.0 μmol, 0.0500 equiv), sodium carbonate (8.2 mg, 77 μmol, 0.77 equiv), activated 4 Å molecular sieves (50 mg/mmol of aldehyde) and toluene (1 mL). While stirring 1 M in DCM tin (IV) chloride (38.5 μL, 38.5 μmol, 0.0385 equiv) was added and the reaction mixture was stirred for 5 minutes. The reaction mixture was then cooled to –78 °C and stirred for 15 minutes. Crotylboronate **3.2** (0.200 g, 1.10 mmol, 1.10 equiv) was added and the reaction mixture was stirred for 30 minutes. Then, aldehyde **4.3** (0.199 g, 1.0 mmol, 1 equiv) was added dropwise in toluene (1 mL + 2 *x* 0.5 mL rinse) and the reaction mixture was allowed to stir for 2 days at –78 °C. The reaction was quenched by dropwise addition of a 1 M in toluene solution of DIBAL-H (2.0 mL, 2.0 mmol, 2.0 equiv) and allowed to stir at –78 °C for 2 hours. A 1 M hydrochloric acid solution was added and the reaction mixture was allowed to stir open to the air and allowed to warm to room temperature over 3 hours. The reaction mixture was extracted with Et_2O (2 *x*), washed with brine (2 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexanes/ethyl acetate, 19:1) affording 0.153 g of **4.24** as a colourless oil (turns to a white solid at subzero

temperatures). Yield: 60%. $[\alpha]_D^{25}$ –26.8 (*c* 1.01, $CHCl_3$); **IR** (cast film) 3569, 3427, 3073, 2966, 2928, 2872, 1639, 1595, 1568, 1475, 998, 775, 669 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.42-7.17 (m, 4H), 5.83 (ddd, *J* = 17.1, 10.4, 8.1 Hz, 1H), 5.19-5.12 (m, 2H), 3.66 (ddt, *J* = 9.1, 5.4, 3.7 Hz, 1H), 2.83 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.61 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.32-2.27 (m, 1H), 1.64 (d, *J* = 3.8 Hz, 1H), 1.12 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 141.5, 139.6, 132.4, 129.9, 129.4, 128.1, 122.5, 116.6, 75.5, 43.6, 40.4, 16.4; **HRMS** (EI) Calcd, $C_{12}H_{15}O^{81}Br$: 256.02859. Found: 256.02829; **HPLC** (Chiralcel OD), 5:95 hexanes/2-propanol, 0.5 mL/min, Injection volume: 1.5 μL; λ = 260.1 nm, t_R (minor) = 13 min, t_R (major) = 15 min, 73% ee.

Note: this example serves as general procedure for all tests performed to determine enantioselectivity in the crotylboration.

Chapter Five: Thesis Conclusion

In concluding this thesis it is necessary to evaluate its contents with respect to the research objectives outlined in the introductory chapter (Chapter 1). The natural product palmerolide A does indeed possess the desired criterion of a biological property whose importance is compelling in light of the deadly nature of melanoma and its persistent and tenacious resistance to chemotherapy. At this point in time the only viable access to this important compound in any significant quantity is through total synthesis. Testimony to the importance of this target can be seen in the many research groups that have directed research efforts towards its synthesis. However, the criterion of synthetic challenge is also evident in these efforts since only three total syntheses have actually been completed, standing out among the more numerous assembly of fragmentary and formal syntheses. Additional testimony to the importance of this target are the efforts being directed towards the discovery of its biosynthetic origins that could potentially be applied in the future to its access via protein engineering.

The application of methodologies developed in the Hall Group to this challenging target facilitated the first total synthesis of palmerolide A in which all the stereocentres were derived by catalytic enantioselective reaction processes. This particular application of these methodologies demonstrated their utility towards the synthesis of compounds that go beyond those usually found in substrate scope investigations. In the process of applying the inverse-electron-demand-hetero-Diels-Alder-cycloaddition/allylboration methodology, a unique variation of the Ireland-Claisen rearrangement was developed (the borono-Ireland-Claisen rearrangement). These methodologies in combination facilitated the creation of three stereocentres of the natural product all derived catalytically from one stereoselective reaction. By exploiting the allylboration product of 3-boronoacrolein this sequence was also a demonstration of the value in carefully considering the utility of what might otherwise be considered an undesirable side product. The development of F-Vivol-[7] **3.21** specifically for the crotylboration

in this synthesis enhanced the understanding of how this methodology can be fine tuned.

The application of the methodologies unique to our group was also developed in the context of the broader synthesis and the other objective of formulating an optimum route to significant quantities of the natural product. This goal was effectually attained in the syntheses of the Eastern and Western Hemispheres with high yielding step efficiency from small scale to large scale. The majority of the transformations in the last sequence of the synthesis could also be carried out in good yield but a critical problem with late stage selective protecting group manipulations renders the original synthetic strategy inoperative for effective delivery of significant quantities of palmerolide A.

The final undertaking of the project, investigations into the synthesis of analogues, yielded a potential solution to the chief weakness of the original plan. By early placement of the carbamate group the difficulties encountered might be avoided completely. Following this principle an analogue of the Eastern Hemisphere was synthesized with good step efficiency and no critical problems with the carbamate group were encountered. It remains to be seen how this will impact later stages of the synthesis.

A number of other benefits were derived during the analogue investigations. The analogue development on the Western Hemisphere further enhanced the understanding of how the different ring sizes on various Vivols impact their application to enantioselective crotylborations. The best F-Vivol for the synthesis of the targeted analogue **4.1** is F-Vivol-[7]. Further benefits from this portion of the project were improvements in synthesizing starting materials and reagents.

The final research objective targeted for the analogues was a unique contribution to the field of palmerolide A through access to analogues that would be less accessible via other routes. At this point in time no analogues have been synthesized with modifications to the C14–C17 diene portion of the macrocycle. Our analogue synthesis is uniquely suited for incorporating an aromatic ring in

this portion of the structure. Information gained by other researchers from the biological testing of palmerolide A analogues makes it apparent that variations in the terminal end of the enamide moiety have enormous affects on biological activity. Our strategy is also well placed to carry out late stage alterations to this terminal moiety by trapping the Curtius derived isocyanate with different Grignard reagents.

Looking to the future of the project, after further optimization of the crotylboration reaction the resulting propionate product needs to be elaborated to complete the Western Hemisphere. Then the two hemispheres can be coupled and carried forward to a completed analogue. The completed analogue can then be tested for biological activity as compared to the natural product. If this is favourable the route employed is readily amenable to varying the terminus of the dienamide side arm by late stage Grignard addition to the isocyanate product of the Curtius rearrangement giving access to a series of possible analogues for further biological testing. Additionally, knowledge derived from the early carbamate placement in the synthetic sequence, with respect to its toleration of various downstream reaction conditions, will contribute to the design of a second generation synthesis of the natural product enabling more extensive biological testing of palmerolide A itself.

In summary, a unique catalytic enantioselective route to synthesizing the biologically important and synthetically challenging natural product palmerolide A was planned and executed. This achievement was facilitated by advances in Hall Group methodologies as well as their application to the challenge of total synthesis. The preliminary synthetic studies undertaken towards analogues of palmerolide A founded on the synthesis of the natural product show potential for further contributions to the field of palmerolide A research. It is the hope of the author that in the future these investigations along with those of other research groups will contribute to effective therapy for melanoma.

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APPENDIX A: BIOLOGICAL TESTING DATA

A.1. Chen-Nicolaou's First Panel of Biological Testing[35]

Table A.1 GI_{50} against melanoma cell line (UACC-62) of stereoisomers

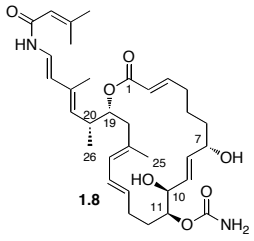
	Entry	Cmpd	Identity	GI_{50} (μM)
	1	**1.8**	Natural palmerolide A	0.057
	2	**1.8**	Synthetic palmerolide A	0.062
	3	**1.1**	7-*epi*-10-*epi*-11-*epi*-**1.8**	>10
	4	**1.7**	*ent*-**1.8**	8.077
	5	**1.16**	7-*epi*-10-*epi*-11-*epi*-19-*epi*-**1.8**	5.398
	6	**1.17**	7-*epi*-10-*epi*-11-*epi*-20-*epi*-**1.8**	8.129

Table A.2 GI_{50} against melanoma cell line (UACC-62) of decarbamylated analogues

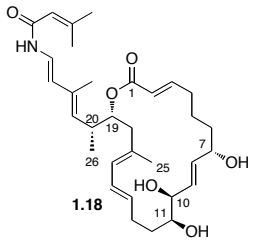
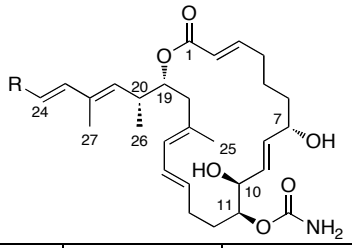
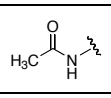
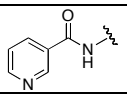
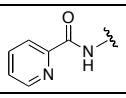
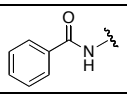
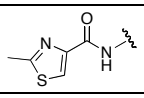
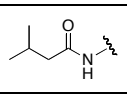
	Entry	Cmpd	Identity	GI_{50} (μM)
	1	**1.8**	Natural palmerolide A	0.057
	2	**1.8**	Synthetic palmerolide A	0.062
	3	**1.18**	Decarbamylated palmerolide A	0.322
	4	**1.19**	*ent*-**1.18**	8.768
	5	**1.20**	7-*epi*-10-*epi*-11-*epi*-19-*epi*-**1.18**	>10
	6	**1.21**	7-*epi*-10-*epi*-11-*epi*-20-*epi*-**1.18**	>10

Table A.3 GI_{50} against melanoma cell line (UACC-62): enamide analogues



Entry	1	2	3	4	5	6
Compd.	**1.22**	**1.23**	**1.24**	**1.25**	**1.26**	**1.27**
R						
GI_{50}	>10	0.641	0.735	8.822	0.009	0.067

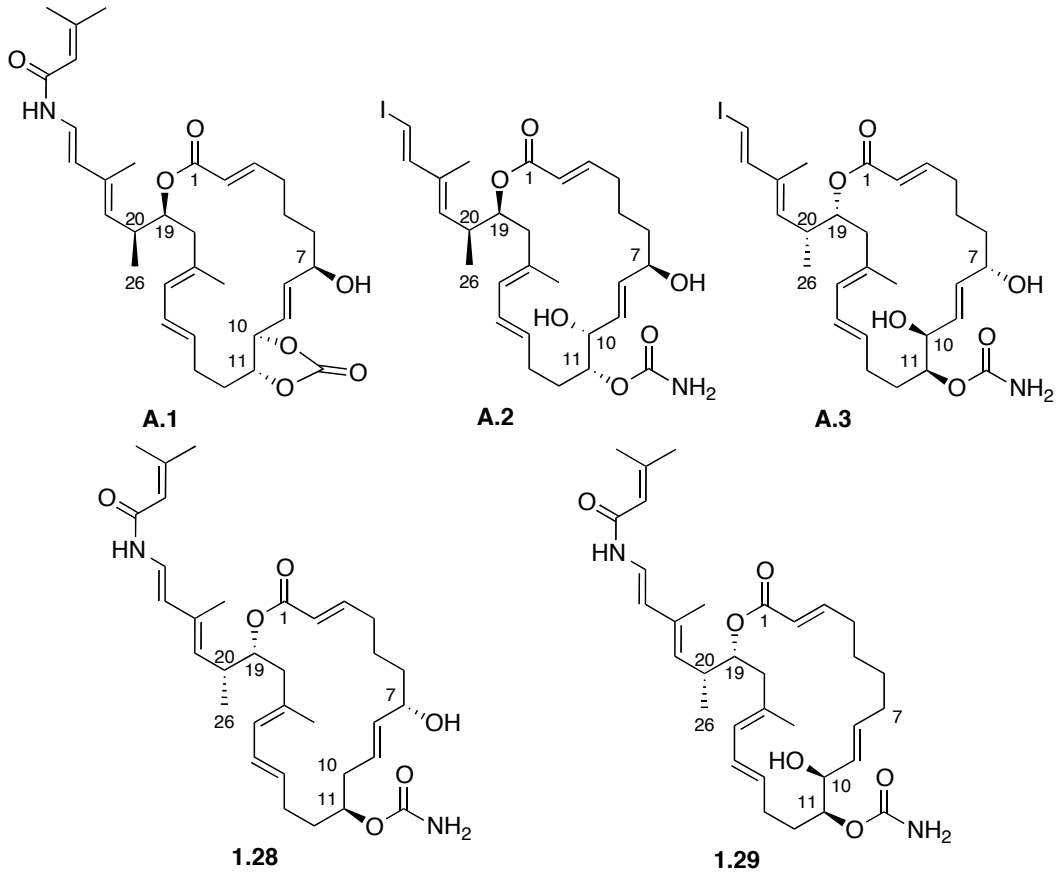
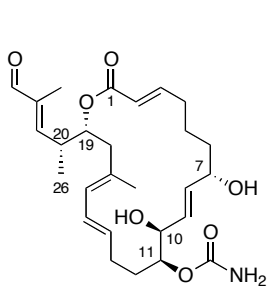


Figure A.1. Miscellaneous analogues of palmerolide A

Table A.4 Growth inhibition (GI_{50}) of cancer cell lines by palmerolide A and synthesized analogues (μM)

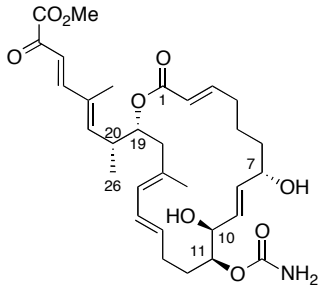
Entry	Compound	UACC-62	MCF-7	SF268	NCI-H460	IA9	PTX22	A8
1	doxorubicin	0.294	0.056	0.129	0.008	0.033	0.201	0.051
2	taxol	0.022	0.006	0.026	0.007	0.006	0.079	0.021
3	natural **1.8**	0.057	0.040	0.030	0.010	0.038	0.066	0.018
4	synthetic **1.8**	0.062	0.065	0.048	0.017	0.059	0.073	0.049
5	**1.7**	8.077	6.260	9.475	6.589	>10	>10	8.844
6	**1.1**	>10	>10	>10	>10	>10	>10	>10
7	**1.16**	5.398	5.415	6.830	6.108	>10	7.052	8.634
8	**1.17**	8.129	5.567	7.961	7.028	7.131	5.865	6.145
9	**1.18**	0.322	0.200	0.281	0.075	0.288	0.627	0.083
10	**1.19**	8.768	7.299	9.638	8.664	>10	>10	8.477
11	**1.20**	>10	>10	>10	>10	>10	>10	>10
12	**1.21**	>10	8.257	>10	>10	>10	>10	>10
13	**1.22**	>10	>10	>10	7.291	7.774	>10	6.700
14	**1.23**	0.641	0.755	0.592	0.430	0.618	0.741	0.460
15	**1.24**	0.735	0.796	0.491	0.078	0.378	0.889	0.072
16	**1.25**	8.822	7.397	>10	3.796	7.944	>10	3.514
17	**1.26**	0.009	0.007	0.007	0.007	0.009	0.039	0.006
18	**1.27**	0.067	0.071	0.054	0.061	0.067	0.081	0.057
19	**A.1**	>10	>10	>10	>10	>10	>10	>10
20	**A.2**	>10	8.786	>10	>10	>10	>10	>10
21	**A.3**	>10	7.025	>10	6.837	>10	>10	8.851
22	**1.28**	6.979	7.585	8.764	6.396	7.135	8.062	6.691
23	**1.29**	0.063	0.074	0.060	0.055	0.072	0.076	0.061

A.2. Chen's Second Panel of Biological Testing[39]



1.30

GI_{50} = >10 μM

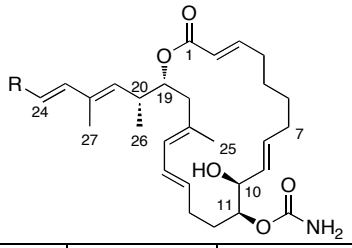


1.31

GI_{50} = >10 μM

Figure A.2. Analogues without enamide moiety

Table A.5 GI_{50} against melanoma cell line (UACC-62): C7 hydroxyl deletion enamide analogues



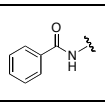
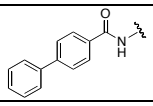
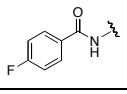
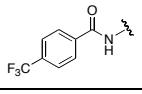
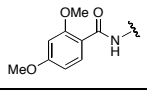
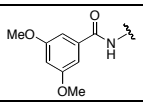
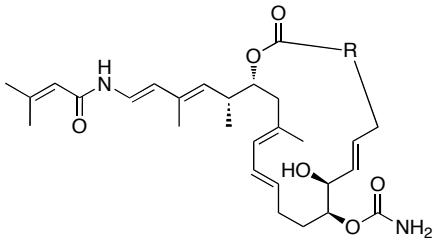
Entry	1	2	3	4	5	6
Compd.	**1.32**	**1.33**	**1.34**	**1.35**	**1.36**	**1.37**
R						
GI_{50}	0.055	5.823	0.227	0.822	9.026	0.753

Table A.6 GI_{50} against melanoma cell line (UACC-62): C7 hydroxyl deletion enamide analogues



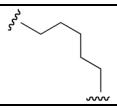
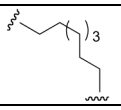
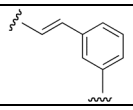
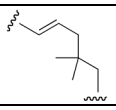
Entry	1	2	3	4
Compd.	**1.38**	**1.39**	**1.40**	**1.41**
R				
GI_{50} (μM)	0.750	6.857	4.958	>10

Table A.7 GI_{50} of palmerolide A and second-generation analogues

Entry	Cmpd	UACC-62	MCF-7	SF268	NCI-H460	IA9	PTX22	A8	HM-2	SI
1	**1.8**	0.061	0.068	0.040	0.014	0.070	0.067	0.059	6.177	101.3
2	**1.26**	0.009	0.008	0.007	0.007	0.008	0.029	0.007	2.309	256.6
3	**1.29**	0.076	0.153	0.069	0.069	0.087	0.194	0.091	14.006	184.3
4	**1.30**	>10	>10	>10	>10	>10	>10	>10	>10	—
5	**1.31**	>10	9.061	>10	>10	>10	>10	>10	>10	—
6	**1.32**	0.055	0.061	0.045	0.027	0.072	0.075	0.065	8.256	150.1
7	**1.33**	5.823	6.320	8.181	0.701	7.309	7.035	6.217	56.641	9.7
8	**1.34**	0.227	0.339	0.282	0.069	0.646	0.631	0.486	27.186	119.8
9	**1.35**	0.822	0.864	0.936	0.582	3.004	2.232	0.785	23.701	26.9
10	**1.36**	9.026	5.452	>10	5.093	>10	9.206	8.317	42.201	4.7
11	**1.37**	0.753	0.855	0.789	0.517	0.869	0.863	0.710	>100	>132.8
12	**1.38**	0.750	0.849	0.687	0.465	0.820	0.723	0.807	8.020	10.7
13	**1.39**	6.857	5.708	6.793	5.41	8.102	6.66	5.626	8.619	1.2
14	**1.40**	4.958	2.357	2.686	0.845	7.084	5.489	4.269	7.787	3.8
15	**1.41**	>10	>10	>10	>10	—	—	—	>10	—
16	taxol	0.015	0.006	0.024	0.006	0.006	0.083	0.035	0.061	4.1
17	dox.	0.207	0.057	0.160	0.008	0.035	0.159	0.063	0.172	0.8

APPENDIX B: IDENTIFICATION DATA OF PALMEROLIDE A

^{1}H NMR Comparison of Total Syntheses and Natural Product

Hall[20]	De Brabander[46]	Chen-Nicolaou[15]	Baker (Natural)[4]
^{1}H NMR (800 MHz, DMSO-d_6)	^{1}H NMR (400 MHz, DMSO-d_6)	^{1}H NMR (600 MHz, DMSO-d_6)	^{1}H NMR (500 MHz, DMSO-d_6)
9.89 (d, J = 10.3, 1H)	9.87 (d, J = 10.4, 1H)	9.85 (d, J = 10.4, 1H)	9.84 (d, J = 10.1, 1H)
6.85 (dd, J = 14.6, 10.3, 1H)	6.85 (dd, J = 14.4, 10.4 1H)	6.85 (dd, J = 14.5, 10.4, 1H)	6.86 (dd, J = 14.2, 10.1, 1H)
6.71 (ddd, J = 15.3, 10.1, 5.0, 1H)	6.71 (ddd, J = 15.2, 9.6, 5.2, 1H)	6.71 (ddd, J = 15.2, 10.1, 5.0, 1H)	6.72 (ddd, J = 15.2, 9.9, 5.0, 1H)
6.60-6.38 (bd, 2H)	6.52 (b, 2H)	6.50 (bd, 2H)	6.49 (br, 2H)
6.04 (dd, J = 14.3, 10.9, 1H),	6.05 (dd, J = 14.4, 11.2, 1H)	6.05 (dd, J = 15.1, 10.8, 1H)	6.05 (dd, J = 14.6, 11.1, 1H)
5.85 (d, J = 14.4, 1H)	5.84 (d, J = 14.4, 1H)	5.84 (d, J = 14.5, 1H)	5.85 (d, J = 14.2, 1H)
5.77 (d, J = 15.5, 1H)	5.77 (d, J = 15.6, 1H)	5.77 (d, J = 15.7, 1H)	5.78 (d, J = 15.2, 1H)
5.70 (bs, 1H)	5.69 (bs, 1H)	5.69 (brs, 1H)	5.70 (br s, 1H)
5.60 (d, J = 11.0, 1H)	5.60 (d, J = 10.4, 1H)	5.60 (d, J = 10.3, 1H)	5.60 (d, J = 11.4, 1H)
5.55 (ddd, J = 15.4, 8.3, 1.8, 1H)	5.55 (dd, J = 15.6, 7.6, 1H)	5.55 (dd, J = 15.5, 8.2, 1H)	5.55 (dd, J = 15.5, 7.7, 1H)
5.48 (dd, J = 15.5, 3.0, 1H)	5.47 (dd, J =15.6, 2.8, 1H)	5.47 (dd, J = 15.5, 2.8, 1H)	5.50 (dd, J = 15.5, 2.9, 1H)
5.41 (ddd, J = 14.7, 10.2, 4.5, 1H)	5.41 (ddd, J = 14.8, 9.6, 4.8, 1H)	5.41 (ddd, J = 14.8, 9.6, 4.8, 1H)	5.42 (ddd, J = 14.6, 10.1, 4.7, 1H)
5.17 (d, J = 4.9, 1H)	5.19 (d, J = 3.6, 1H)	5.18 (d, J = 4.9, 1H)	5.18 (d, J = 4.9, 1H)
5.13 (d, J = 9.8, 1H)	5.14 (d, J = 9.6, 1H)	5.13 (d, J = 9.6, 1H)	5.14 (d, J = 9.6, 1H)
4.84 (ddd, J = 11.2, 7.9, 1.9, 1H)	4.84 (ddd, J = 10.0, 8.0, 1.6, 1H)	4.84 (ddd, J = 10.0, 8.0, 1.6, 1H)	4.85 (ddd, J = 11.2, 7.4, 1.3, 1H)
4.68 (d, J = 4.2, 1H)	4.69 (d, J = 2.8, 1H)	4.69 (d, J = 2.8, 1H)	4.69 (d, J = 3.9, 1H)
4.48 (ddd, J = 10.9, 5.1, 1.7, 1H)	4.49 (ddd, J = 10.8, 4.8, 1.6, 1H)	4.49 (ddd, J = 10.8, 4.8, 1.6, 1H)	4.49 (ddd, J = 10.5, 5.0, 2.2, 1H)
4.14-4.13 (m, 1H)	4.14 (bs, 1H)	4.14 (brs, 1H)	4.15 (br s, 1H)
3.83-3.80 (m, 1H)	3.82 (m, 1H)	3.82 (m, 1H)	3.83 (1H, ddd, J = 7.6, 7.4, 4.4, 1H)
2.70-2.67 (m, 1H)	2.69 (m, 1H)	2.69 (m, 1H)	2.69 (1H, qdd, J = 9.6, 7.4, 6.5, 1H)
2.19-2.15 (m, 1H)		2.16 (m, 1H)	2.17 (dd, J = 13.2, 1.3, 1H)
2.12 (s, 3H)	2.12 (s, 3H)	2.12 (s, 3H)	2.13 (s, 3H)
2.02-1.90 (m, 5H)	2.18 – 1.89 (m, 6H)	2.10 (m, 2H)	2.11 (m, 2H)
		1.95 (m, 2H)	2.00 (dd, J = 13.2, 11.2, 1H)
		1.99 (m, 1H)	1.96 (m, 2H)
1.83 (s, 3H)	1.83 (s, 3H)	1.83 (s, 3H)	1.83 (s, 3H)
1.71 (s, 3H)	1.71 (s, 3H)	1.71 (s, 3H)	1.71 (s, 3H)
1.61 (s, 3H)	1.61 (s, 3H)	1.61 (s, 3H)	1.60 (s, 3H)
1.60-1.58 (m, 1H)	1.59 (m, 1H)	1.59 (m, 1H)	1.59 (m, 1H)
1.50-1.46 (m, 1H)	1.47 (m, 1H)	1.47 (m, 1H)	1.50 (ddd, J = 11.2, 8.2, 4.5, 1H)
1.32-1.29 (m, 2H)	1.30 (m, 2H)	1.30 (m, 2H)	1.30 (m, 2H)
1.07-1.03 (m, 1H)	1.04 (m, 1H)	1.04 (m, 1H)	1.05 (m, 1H)
1.00-0.96 (m, 1H)	0.97 (m, 1H)	0.97 (m, 1H)	0.98 (m, 1H)
0.90 (d, J = 6.6, 3H)	0.89 (d, J = 6.8, 3H)	0.89 ppm (d, J = 6.8, 3 H)	0.90 (d, J = 6.5, 3H)

^{13}C NMR Comparison of Total Syntheses and Natural Product

Hall[20] ^{13}C NMR (125 MHz, DMSO-d_6)	De Brabander[46] ^{13}C NMR (75 MHz, DMSO-d_6)	Nicolaou[15] ^{13}C NMR (150 MHz, DMSO-d_6)	Baker (Natural)[4] ^{13}C NMR (125 MHz, DMSO-d_6)
166.0	165.9	165.8	166.1
163.8	163.6	163.6	163.9
157.3	157.2	157.1	157.3
152.5	152.4	152.3	152.5
150.0	149.9	149.7	150.0
134.3	134.1	134.1	134.3
133.3	133.1	133.1	133.3
132.6	132.5	132.4	132.7
132.3	132.2	132.1	132.3
130.5	130.4	130.3	130.5
129.6	129.4	129.4	129.6
128.4	128.3	128.2	128.4
127.1	126.9	126.9	127.1
122.9	122.7	122.6	122.9
121.3	121.1	121.0	121.3
118.8	118.6	118.6	118.8
117.1	116.9	116.9	117.2
75.8	75.6	75.6	75.8
74.4	74.3	74.3	74.5
73.2	73.1	73.0	73.2
69.9	69.6	69.7	69.9
43.9	43.8	43.7	43.9
38.4	38.3	38.2	38.5
37.3	37.1	37.1	37.3
33.0	32.9	32.8	32.6
30.1	29.9	29.9	30.1
		29.8	
27.7	27.5	27.5	27.7
25.6	25.5	25.4	25.7
20.3	20.1	20.1	20.4
17.8	17.6	17.6	17.7
16.9	16.7	16.6	16.9
13.4	13.2	13.1	13.3

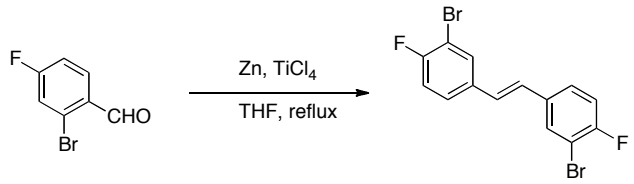
APPENDIX C: PROGRESS IN SYNTHETIC ACCESS TO PROJECT REAGENTS

C.1. Synthesis of the Vivols and Notable Observations

While carrying out synthetic work on producing F-Vivol-[6] and F-Vivol-[7] a number of observations were made that could be of utility in synthesizing these types of diols. It was requested that this information be recorded in my thesis for the benefit of future group members who might retrace these steps.

C.1.1. The Synthesis of F-Vivol-[6]

1,1'-(*E*)-ethene-1,2-diylbis(3-bromo-4-fluorobenzene) (**C.2**)

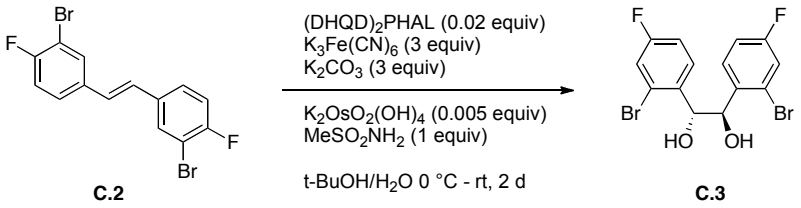


C.1 **C.2**

Powdered zinc (15.9 g, 243 mmol, 4.0 equiv) was suspended in THF (0.5 L) in a three necked flask equipped with a condenser. Titanium (IV) chloride (17.3 g, 91.2 mmol, 1.50 equiv) was slowly added dropwise. (**Note: Caution! Highly exothermic reaction with rapid evolution of yellow gas**) The suspension changes in colour from grey to green. The reaction mixture was refluxed at 80 °C for 1 hour and then cooled to room temperature. Aldehyde **C.1** (12.3 g, 50.8 mmol, 1.00 equiv) was added and then the reaction mixture was heated to reflux at 80 °C overnight. The reaction mixture was cooled to room temperature and poured over a solution of 1 N hydrochloric acid (200 mL) forming a purple coloured biphasic mixture. The biphasic mixture was filtered through Celite® rinsing with DCM. (Note: this filtration is very challenging due to the water. An extra large coarse fritted funnel is recommended) The biphasic mixture was then extracted with DCM (3 *x*) and the combine organic extracts were washed with brine (2 *x*), dried over magnesium sulphate, filtered and concentrated under

reduced pressure affording a white solid. The solid was purified by recrystallization from DCM/MeOH affording 8.75 g of **C.2** as a crystalline white solid. Yield: 77%. Characterized by Rauniyar.[78]

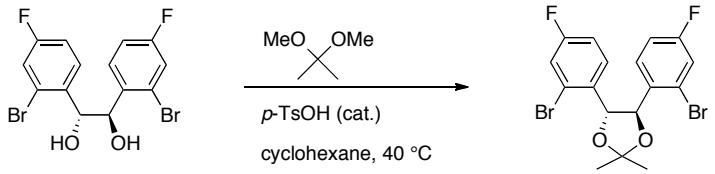
(1*R*,2*R*)-1,2-bis(2-bromo-4-fluorophenyl)ethane-1,2-diol (**C.3**)



A flask was charged with potassium carbonate (8.79 g, 63.6 mmol, 3.00 equiv), potassium ferricyanide (20.9 g, 63.6 mmol, 3.00 equiv), $(DHQD)_2PHAL$ (0.330 g, 0.424 mmol, 0.0200 equiv) and a 1:1 solvent mixture of *t*-$BuOH/H_2O$ (106 mL). The reaction mixture was cooled to 0 °C and turned into a viscous orange slurry that required vigorous stirring. After cooling the reaction mixture to 0 °C, potassium osmate (VI) dihydrate (0.0391 g, 0.0600 mmol, 0.00500 equiv), stillbene **C.2** (7.87 g, 21.2 mmol, 1.00 equiv) and methanesulfonamide (2.02 g, 21.2 mmol, 1.00 equiv) were added and the reaction mixture was allowed to warm to room temperature and stirred for 2 days. The reaction was quenched by adding sodium sulfite (3 g/mmol of stillbene) and stirred for 2 hours. The reaction mixture was diluted with ethyl acetate and water and the biphasic mixture was separated. The organic layer was washed with 1 M sodium hydroxide and the aqueous layer was extracted with ethyl acetate (4 *x*). The combine organic layers were washed with brine (2 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude solid was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 95–60%) affording 7.54 g of **C.3** as a white solid. Yield 87%. The solid was then further purified by recrystallization from DCM and hexanes. Characterized by Rauniyar.[78] Note: The optical rotation was found to be opposite in sign from that published by Rauniyar. Consultation with the analytical divisions records revealed that the

characterized result was opposite in sign from the one published. $[\alpha]_D^{25}$ +2.26 (*c* 1.00, $CHCl_3$).

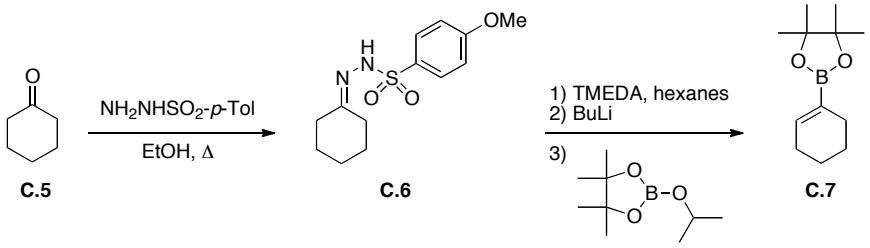
(4*R*,5*R*)-4,5-bis(2-bromo-4-fluorophenyl)-2,2-dimethyl-1,3-dioxolane (**C.4**)



C.3 **C.4**

Diol **C.3** (3.24 g, 7.94 mmol, 1.00 equiv) was suspended in cyclohexane (50 mL) followed by an addition of 2,2'-dimethoxypropane (3.47 g, 33.3 mmol, 4.2 equiv) and *p*-toluenesulfonic acid (0.0676 g, 0.397 mmol, 0.0500 equiv). The reaction mixture was heated to 50 °C for 15 minutes and then heated at 40 °C for 1 hour. The reaction was quenched by the addition of 1 N sodium hydroxide (32 mL) and stirred overnight. The biphasic mixture was separated and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure affording 3.29 g of **C.4** as a white solid. Yield: 99%. Characterized by Rauniyar.[78]

2-(cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**C.7**)

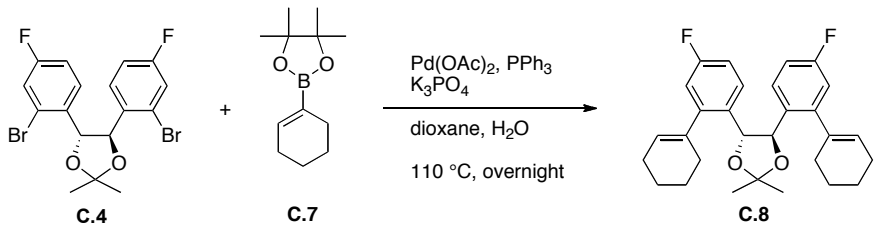


C.5 **C.6** **C.7**

Cyclohexanone **C.5** (30.0 g, 161 mmol, 1.00 equiv) was suspended in absolute ethanol (20 mL) and *p*-toluenesulfonyl hydrazide (15.8 g, 161 mmol, 1.00 equiv) was added. The reaction mixture was heated at 100 °C and a white solid immediately precipitates forming a solid mass. The white solid was cooled to 0 °C and scraped into a fritted funnel. The white solid was then washed with ice cold ethanol and dried first by passing air through and then under vacuum

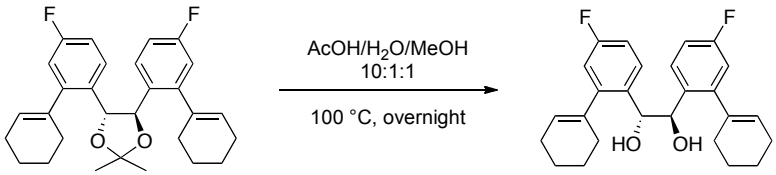
affording 40.17 g of **C.6**. Yield: 94%. Hydrazone **C.6** (7.00 g, 26.3 mmol, 1.00 equiv) was suspended in hexanes (80 mL) and cooled to –78 °C. (Note: the cooling is a departure from Rauniyar's method) Tetramethylethylenediamine (61.1 g, 526 mmol, 20 equiv) was added and the reaction mixture was stirred for 15 minutes. Butyllithium (2.5 M in hexanes, 42.0 mL, 105 mmol, 4.00 equiv) was added and the colour changed to a deep rust colour. The reaction mixture was stirred at –78 °C for 1 hour and then at room temperature for 1 hour with gas evolving and the mixture clarifying to a clear red solution. The solution was cooled to –78 °C, stirred for 15 minutes and then pinacol isopropyl borate (19.5 g, 105 mmol, 4.00 equiv) was added. A small amount of gas was observed to evolve on addition of the borate. The reaction mixture was stirred for 1 hour at –78 °C and then move to room temperature and stirred for another 3 hours. On warming to room temperature the reaction mixture became turbid and orange in colour. The reaction was quenched with an aqueous saturated solution of ammonium chloride (100 mL). The colour became white and the reaction mixture turned into a massive emulsion. The emulsion was laboriously extracted with Et_2O multiple times. An attempt to filter the emulsion was met with no success due to immediate blockage of the pores of the fritted funnel. (Note: The difficulties encountered in the workup were addressed when making F-Vivol-[[7]) The ether extracts were collected and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 95:5) affording 4.90 g of **C.7**. Yield 90%. Characterized in the literature.[103]

(4*R*,5*R*)-4,5-bis[2-(cyclohex-1-en-1-yl)-4-fluorophenyl]-2,2-dimethyl-1,3-dioxolane (**C.8**)



A reaction flask was charged with acetonide **C.4** (2.21 g, 4.93 mmol, 1.00 equiv), boronate **C.7** (4.90 g, 23.5 mmol, 4.8 mmol), palladium (II) acetate (0.332 g, 0.493 mmol, 0.100 equiv), triphenylphosphine (0.621 g, 2.37 mmol, 0.480 equiv) and dioxane (60 mL) plus water (6 mL). The reaction mixture was degassed (8 x) flushing with argon and then heated to 110 °C and refluxed for 20 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Et_2O/hexanes, 2–5%) affording 2.22 g of **C.8** as a white solid. Yield: quantitative. The product however was not pure and was repurified by chromatography and then recrystallization from MeOH affording 1.55 g of **C.8**. Yield: 70%. $[\alpha]_D^{25}$ 104 (*c* 1.08, $CHCl_3$); **IR** (cast film) 3030, 2987, 2937, 2919, 2879, 2855, 2835, 1611, 1586, 1499, 1233, 1171, 1052, 818 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.53 (dd, *J* = 8.7, 5.9 Hz, 2H), 6.99 (td, *J* = 8.5, 2.8 Hz, 2H), 6.64 (dd, *J* = 9.6, 2.7 Hz, 2H), 4.94 (s, 2H), 4.68 (s, 2H), 1.92-1.85 (m, 4H), 1.78-1.73 (m, 2H), 1.64 (s, 6H), 1.56-1.44 (m, 10H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 162.0, 147.1, 135.8, 129.09, 128.92, 127.1, 114.9, 114.0, 108.6, 81.6, 30.6, 27.4, 25.2, 22.9, 21.7; **HRMS** (EI) Calcd, $C_{29}H_{32}F_2O_2$: 450.23703. Found: 450.23698.

(1*R*,2*R*)-1,2-bis[2-(cyclohex-1-en-1-yl)-4-fluorophenyl]ethane-1,2-diol (**C.9**)

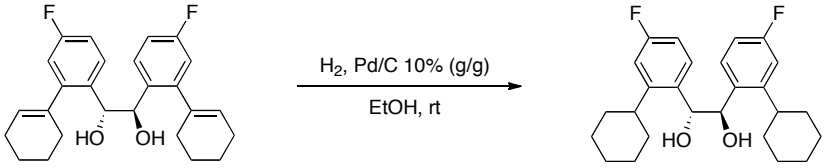


C.8 **C.9**

Acetonide **C.8** (1.48 g, 3.28 mmol, 1.00 equiv) was dissolved in a 10:1:1 mixture of acetic acid/H_2O/MeOH (60 mL) and heated at 100 °C overnight. The reaction mixture was cooled to room temperature and diluted with Et_2O. The Organic layer was then washed repeatedly with an aqueous saturated solution of sodium bicarbonate until gas no longer evolved. The solution was then basified with potassium hydroxide (and some sodium hydroxide due to insufficient potassium hydroxide) until neutral. The aqueous layer was extracted with Et_2O and the

collected organic layers were washed with an aqueous solution of potassium hydroxide. The organic extract was washed with brine (1 *x*), dried on magnesium sulphate, filtered and concentrated under reduced pressure to form a yellow solid. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 100–70%) followed by a purification by recrystallization with DCM/hexanes affording 0.903 g of **C.9**. Yield: 67%. $[\alpha]_D^{25}$ 160 (*c* 1.03, $CHCl_3$); **IR** (cast film) 3466, 3319, 3035, 2931, 2857, 2836, 1609, 1583, 1497, 1168, 1044, 822, 759 cm^{-1}; **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.44 (dd, *J* = 8.7, 5.9 Hz, 2H), 6.90 (td, *J* = 8.4, 2.8 Hz, 2H), 6.58 (dd, *J* = 9.7, 2.8 Hz, 2H), 4.96 (s, 2H), 4.91 (s, 2H), 2.85 (t, *J* = 1.1 Hz, 2H), 2.05-1.95 (m, 6H), 1.66-1.56 (m, 8H), 1.51-1.46 (m, 2H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 161.8, 146.7, 136.3, 132.6, 129.5, 127.2, 114.8, 113.6, 74.2, 30.4, 25.2, 22.9, 21.8; **HRMS** (ESI) Calcd. $C_{26}H_{28}F_2O_2$+Na: 433.1950. Found: 433.1945.

(1*R*,2*R*)-1,2-bis(2-cyclohexyl-4-fluorophenyl)ethane-1,2-diol (**4.27**)



C.9 **4.27** (F-Vivol-[6])

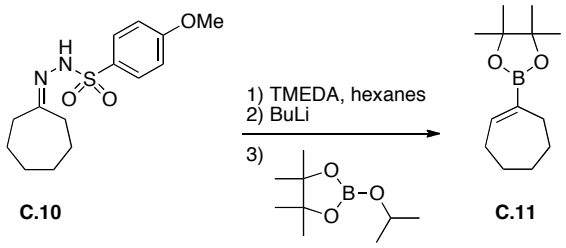
Diol **C.9** (0.679 g, 1.65 mmol, 1.0 equiv) was dissolved in ethanol (35 mL) in a Schlenk flask and the solution was degassed (3 *x*) repressurizing with argon. A 10% palladium on carbon amalgum (0.679 g, 0.638 mmol, 0.390 equiv) was added against a backflow of argon. (**Note: Caution must be exercised as palladium can ignite as it is dispersed**) The side of the flask were rinsed down with ethanol (2 mL) and the vessel was degassed and purged with hydrogen gas (3 *x*) contained in a balloon. The reaction mixture was allowed to stir under hydrogen overnight. The reaction mixture was degassed with argon and filtered through Celite® washing with DCM. The eluent was then concentrated under reduced pressure forming a white solid. The crude product was then purified by flash chromatography on silica gel (hexanes/ethyl acetate) affording 0.645 g of

4.27 as a white solid. Yield: 94%. The solid was then recrystallized from DCM/hexanes affording 0.569 g of fluffy white crystals. Yield: 83%. $[\alpha]_D^{25}$ 8.37 (*c* 1.03, $CHCl_3$); **IR** (cast film); 3528, 3499, 3322, 3024, 2921, 2854, 1612, 1589, 1497, 1265, 1038, 873, 823 cm^{-1}; **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.66 (dd, *J* = 8.7, 6.1 Hz, 2H), 6.94 (td, *J* = 8.3, 2.7 Hz, 2H), 6.71 (dd, *J* = 10.9, 2.7 Hz, 2H), 5.03 (s, 2H), 2.98 (s, 2H), 2.10-2.03 (m, 2H), 1.74-1.55 (m, 8H), 1.28-0.84 (m, 10H), 0.32-0.28 (m, 2H); **^{13}C NMR** (125 MHz; $CDCl_3$): δ 162.7, 148.4, 132.3, 129.1, 113.0, 112.5, 74.0, 39.0, 35.4, 32.4, 27.0, 26.6, 26.0; **HRMS** (ESI) Calcd. $C_{26}H_{32}F_2O_2$+Na: 437.2263. Found: 437.2263.

C.1.2. The Synthesis of F-Vivol-[7]

The same procedures used in the synthesis of F-Vivol-[6] **4.27** were used in the synthesis of F-Vivol-[7] **3.21** with primary exception being the synthesis of boronate **C.11**.

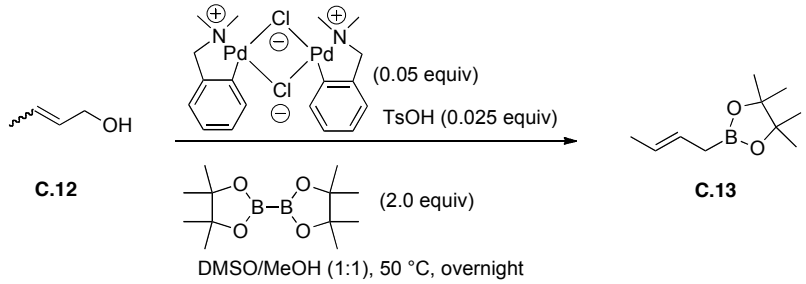
2-(cyclohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**C.11**)



Hydrazone **C.10** (10.0 g, 35.7 mmol, 1.00 equiv) was suspended in hexanes (90 mL) and cooled to –78 °C. Tetramethylethylenediamine (82.9 g, 713 mmol, 20 equiv) was added and the reaction mixture was stirred 15 minutes at –78 °C. Butyllithium (2.5 M in hexanes, 57 mL, 143 mmol, 4.00 equiv) was added dropwise and the reaction mixture was stirred for 1 hour at –78 °C (the colour turning to a deep red and turbid). The reaction mixture was moved to room temperature and stirred for 1.5 hours (clarifies to a deep red solution). The solution was cooled to –78 °C, stirred for 15 minutes and then pinacol isopropyl borate (26.6 g, 143 mmol, 4.00 equiv) was added dropwise and the reaction

mixture was stirred for 1 hour at –78 °C. The reaction mixture was subsequently stirred at room temperature for an additional 2 hours (changes from clear orange to turbid orange). The reaction mixture was cooled to 0 °C and poured over an ice cold 6 N hydrochloric acid solution (260 mL) and the biphasic mixture was separated (Note: no emulsion forms under these conditions). The aqueous layer was extracted with Et_2O (2 *x*), and the collected organic extracts were washed with water (1 *x*) and brine (1 *x*), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 100–98%) and again (hexanes/toluene/Et_2O, 96:2:2) affording 6.40 g of **C.11** as an oil. Yield: 81% Characterized by Rauniyar.[78] (Note: Impurities were the cause of the extra purifications but these do not appear to affect the following coupling step, which gave consistently high yields)

C.2. The Synthesis of 2-(2*E*)-2-buten-1-yl-4,4,5,5-tetramethyl-1,3,2-Dioxaborolane (3.2)



2-Buten-1-ol **C.12** (0.85 g, 11.8 mmol, 1.00 equiv) was dissolved in a 1:1 mixture of anhydrous dimethylsulfoxide and methanol (46 mL). *p*-Toluenesulfonic acid monohydrate (0.112 g, 0.589 mmol, 0.0500 equiv), di-μ-chlorobis[2-[(dimethylamino-κN)methyl]phenyl-κC]di-palladium (0.163 g, 0.295 mmol, 0.0250 equiv) and bis(pinacolato)diboron (5.99 g, 23.6 mmol, 2.00 equiv) were added and the reaction mixture was heated to 50 °C stirring overnight. The reaction mixture was cooled to room temperature and poured into a separatory funnel containing water and agitated with venting. The diluted mixture was then

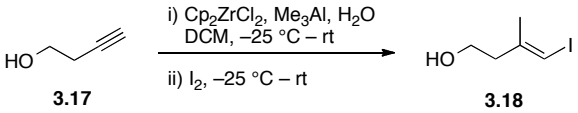
extracted with Et_2O (3 *x*) and the organic extracts were collected, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 24:1) affording 1.98 g of **C.13** as a colourless liquid. Yield: 92%. E/Z ratio: 20:1. Characterized in the literature.[104] (Note: This procedure was derived from the work of Professor Kálmán J. Szabó and coworkers.[105])

APPENDIX D: COLLABORATORS CONTRIBUTION

D.1. Synthetic transformations executed by Rauniyar and Kaspar

The following chemical transformations employed in the total synthesis of palmerolide A were carried out exclusively by Rauniyar and Kaspar. They are included for the sake of completeness.

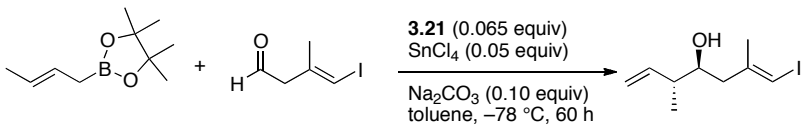
D.1.1. (E)-4-Iodo-3-methylbut-3-en-1-ol (3.18)



3.17 **3.18**

Zirconocene dichloride (3.86 g, 13.2 mmol, 0.22 equiv) was dissolved in DCM (260 mL) and cooled to −23 °C. Trimethylaluminum (2.39 M in hexanes, 78.0 mL, 186 mmol, 3.10 equiv) was added dropwise. The resulting yellow mixture was stirred 10 min at −25 °C. Water (1.68 mL, 93.0 mmol, 1.55 equiv) was added dropwise (**Note: exothermic reaction**). The reaction was then stirred 10 minutes and a mixture of 3-butyn-1-ol **3.17** (4.21 g, 60.0 mmol, 1.0 equiv) trimethylaluminum (2.39 M in hexanes, 7.80 mL, 18.6 mmol, 0.310 equiv) in anhydrous DCM (50 mL) at 0 °C, was added drop-wise *via* cannula. The reaction mixture was allowed to warm to room temperature forming a viscous yellow slurry that was stirred overnight. The reaction mixture was then cooled to −25 °C and a solution of I_2 (22.8 g, 90.0 mmol, 1.50 equiv) in anhydrous Et_2O (100 mL) was cannulated dropwise into the reaction pot. The mixture was subsequently allowed to warm to room temperature and was stirred 2 hours. The reaction was quenched by slow addition of a saturated aqueous solution of potassium tartrate (50 mL). The aqueous phase was extracted with Et_2O (3 *x* 200 mL) and washed with an aqueous solution of $Na_2S_2O_3$ and then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (pentane/Et_2O, 1:1) affording 11.5 g of **3.18** as a yellow oil. Yield: 90%. Physical and spectral data were consistent with those published in the literature.[106] Yield: 90%.

D.1.2. (1E,4S,5R)-1-Iodo-2,5-dimethylhepta-1,6-dien-4-ol (3.16)

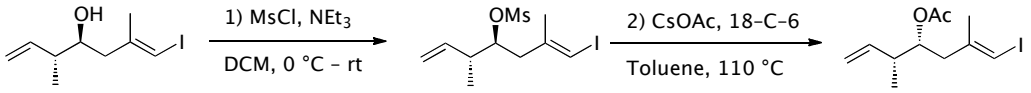


3.10 **3.15** **3.16**

Alcohol **3.18** (4.94 g, 23.3 mmol, 1.00 equiv) was dissolved in DCM (55 mL) and cooled to 0 °C. Sodium bicarbonate (9.78 g, 117 mmol, 5.00 equiv) was added followed by Dess-Martin periodinane (11.9 g, 28.0 mmol, 1.20 equiv). The solution was allowed to warm to room temperature and stirred for 1.5 hours. Saturated aqeous $Na_2S_2O_3$ (100 mL) was added and the mixture was diluted with Et_2O (200 mL). The aqueous phase was extracted with Et_2O (2 *x* 100 mL). The organic extracts were washed with water (3 *x* 100 mL), $NaHCO_3$(aq) (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The glassware used in the next step was prepared by base wash and flame drying. The crude product was transferred into a 50 mL round bottom flask and purified by bulb-to-bulb distillation in a Kugelrohr apparatus (0.13 *torr*, 80 ºC) furnishing aldehyde **3.15** as a light yellow oil. The aldehyde was directly used in the next step. (**Note: distillation temperatures >80ºC result in decomposition; vacuum strength is critical for success**). A flame dried round bottom flask was charged with catalyst **3.21** (550 mg, 1.24 mmol, 0.0650 equiv), anhydrous sodium carbonate (207 mg, 1.95 mmol, 0.100 equiv) and 4Å molecular sieves (500 mg; activated by heating at 100 °C under vacuum). The flask was further charged with toluene (12.5 mL) and stirred 2 minutes. Tin (IV) chloride (1.0 M solution in DCM, 0.956 mL, 0.956 mmol, 0.0500 equiv) was added and the mixture was stirred at room temperature for 5 minutes then cooled to –78 °C and stirred for 30 minutes. Boronoacrolein pinacolate **3.10** (4.71 g, 25.9 mmol, 1.18 equiv) was added and the reaction mixture was stirred for 30 minutes. Aldehyde **3.15** (4.20 g, 21.0 mmol, 1.00 equiv) was added dropwise and the reaction was stirred for 60 hours maintaining a temperature of –78 °C. The reaction was quenched with DIBAL-H (1.50 M in toluene, 13.3 mL, 20.0 mmol,

1.00 equiv) and stirred for 30 minutes at –78 °C. The reaction mixture was then poured over ice-cold 1N HCl (50 mL). It was then allowed to warm to room temperature and stirred for 30 minutes. The reaction mixture was extracted with Et_2O (3 *x* 200 mL), the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane/Et_2O, 20:1), affording 5.10 g of **3.16** as a colourless oil. Yield: 95%. $[\alpha]_D^{25}$ –19 (*c* 0.79, $CHCl_3$); **IR** (cast film) 3441, 3073, 2965, 2928, 1377, 1273, 1144, 1000, 917, 764 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.02 (m, 1H), 5.77 (ddd, *J* = 17.2, 10.6, 8.1 Hz, 1H), 5.15-5.09 (m, 2H) 3.62-3.57 (m, 1H), 2.39 (dd, *J* = 14.3, 3.7 Hz, 1H), 2.30 (dd, *J* = 14.3, 9.9 Hz, 1H), 2.27-2.21 (m, 1H), 1.89-1.88 (m, 3H), 1.59 (d, *J* = 3.7 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.2, 139.5, 116.5, 77.0, 72.0, 44.5, 43.6, 24.1, 16.2; **HRMS** (ESI) Calcd. $C_9H_{15}OINa$: 289.0060. Found: 289.0061; **HPLC** (chiralcel OD), 10:90 *i*-PrOH/hexane, 0.5 mL/min, λ = 254 nm, T_{major} = 12.5 min, T_{minor} = 18.0 min, 90% *ee*.

D.1.3. (E)-(1R, 1'R)-Acetic acid-4-iodo-3-methyl-1-(1-methylallyl)-but-3-enyl ester (3.24)

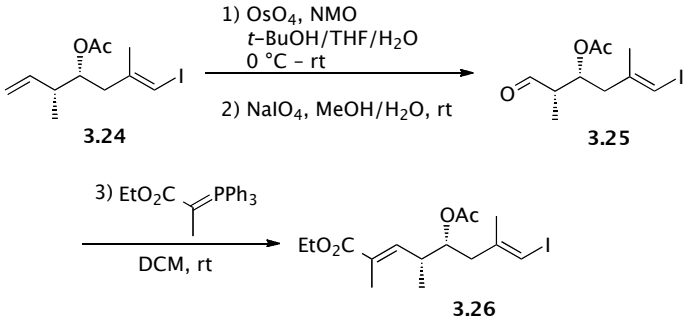


3.16 **3.23** **3.24**

Alcohol **3.16** (4.80 g, 18.27 mmol, 1.00 equiv) was dissolved in DCM (36 mL) and cooled to 0 °C. Triethylamine (3.82 mL, 27.4 mmol, 1.50 equiv) and mesylchloride (1.56 mL, 20.1 mmol, 1.10 equiv) were added dropwise. The solution was allowed to warm to room temperature and stirred for 1 hour. The reaction was diluted with Et_2O (100 mL) followed by addition of a saturated solution of ammonium chloride (50 mL). The reaction was extracted with Et_2O (2 *x* 60 mL), then the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording **3.23** as a yellow oil

that was moved to the next step with no further purification. Crude mesylate **3.23** was dissolved toluene (35 mL) and combined with cesium acetate (14.0 g, 73.1 mmol, 3.00 equiv) and 18-crown-6 ether (4.83 g, 18.3 mmol, 1.00 equiv). The reaction mixture was stirred at 110 °C for 16 hours. It was then cooled to room temperature and diluted with Et_2O (100 mL). Water was added and the biphasic mixture was extracted with Et_2O (2 *x* 60 mL). The organic extract was washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (pentane/Et_2O, 50:1) affording 4.11 g of **3.24** as a colourless liquid. Yield 73%. $[\alpha]_D^{25}$ +24 (*c* 0.37, $CHCl_3$); **IR** (cast film) 3078, 2975, 2926, 1742, 1375, 1277, 1237, 1025, 919 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.95-5.94 (m, 1H), 5.73 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H), 5.09-5.04 (m, 2H), 4.96 (ddd, *J* = 10.5, 6.5, 4.0 Hz, 1H), 2.45-2.34 (m, 3H), 2.02 (s, 3H), 1.84 (d, *J* = 0.8 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 144.3, 139.4, 115.8, 77.1, 73.7, 41.8, 41.5, 23.9, 21.0, 15.4; **HRMS** (ESI) Calcd. $C_{15}H_{23}O_2INa$: 331.0166. Found: 331.0166.

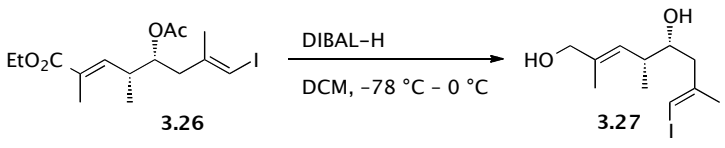
D.1.4. Ethyl (2E,4R,5R,7E)-5-(acetyloxy)-8-iodo-2,4,7-trimethylocta-2,7-dienoate (3.26)



Alkene **3.24** (4.13 g, 13.4 mmol, 1.00 equiv) was dissolved in *t*-BuOH/THF/H_2O (66 mL, 5:5:1) and cooled to 0 °C. A 4 wt% aqueous solution of osmium tetroxide (850 µL, 0.134 mmol, 0.0100 equiv) was added along with N-methylmorpholine-N-oxide (4.40 mL, 18.8 mmol, 1.40 equiv). The solution was

allowed to warm to room temperature and stirred 48 hours. The reaction mixture was diluted with ethyl acetate (100 mL) along with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and extracted with ethyl acetate (2 *x* 50 mL). The organic extract was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was redissolved in Et_2O and filtered through a 5 inch plug of silica eluting with Et_2O and concentrated under reduced pressure before moving to the next step. It was then dissolved in a mixture of MeOH/H_2O (90 mL, 2:1). Sodium periodate (17.2 g, 80.4 mmol, 6.00 equiv) was added and the reaction mixture was stirred 30 minutes at room temperature. The reaction mixture was diluted with water (100 mL) extracted with DCM (3 *x* 250 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure affording crude **3.25** that was moved to the next step with no further purification. Crude aldehyde **3.25** was dissolved in DCM (50 mL). 2-(Triphenylphosphoranylidene)-propanoic acid ethyl ester (5.82 g, 16.1 mmol, 1.20 equiv) was added and the reaction mixture was stirred 16 hours at room temperature. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 0–20%) affording 3.96 g of **3.26** as a light yellow oil. Yield 75%. $[\alpha]_D^{25}$ –33 (*c* 0.30, $CHCl_3$); **IR** (cast film) 2977, 2931, 1741, 1712, 1369, 1233, 1038 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 1.5, 10.5 Hz, 1H), 5.94-5.93 (m, 1H), 4.95 (q, *J* = 6.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.76-2.68 (m, 1H), 2.37 (d, *J* = 6.5 Hz, 2H), 2.03 (s, 3H), 1.84 (m, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 167.8, 143.8, 141.5, 128.9, 77.6, 60.7, 42.1, 37.1, 24.0, 20.98, 15.9, 14.3, 12.8; **HRMS** (ESI) Calcd. $C_{15}H_{23}O_4INa$: 417.0533. Found: 417.0536.

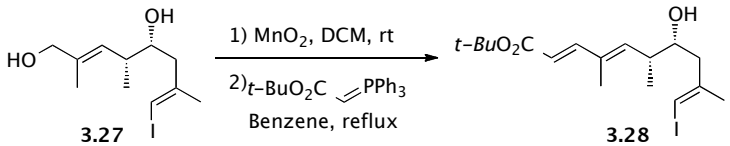
D.1.5. (2E,4R,5R,7E)-8-Iodo-2,4,7-trimethylocta-2,7-diene-1,5-diol (3.27)



3.26 3.27

Ester **3.26** (3.23 g, 8.19 mmol, 1.00 equiv) was dissolved in DCM (60 mL) and cooled to –78 °C. 1.5 M DIBAL-H in toluene (27.3 mL, 40.9 mmol, 5.00 equiv) was added and the solution was stirred 5 hours at –78 °C. The reaction was quenched by slow addition of methanol (2.6 mL) and the reaction mixture was allowed to warm to 0°C, then an aqueous saturated solution of potassium tartrate (50 mL) was added and the biphasic mixture was stirred 2 hours at 0 °C. The layers were separated and the reaction flask, which contained a white solid, was washed with DCM (100 mL). The combined organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes, 10–50%) affording 2.52 g of **32.7** as an oil. Yield: 99%. $[\alpha]_D^{25}$ –12 (*c* 0.39, $CHCl_3$); **IR** (cast film) 3334, 2960, 2914, 2870, 1616, 1449, 1377, 1273, 1047, 1008, 762 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 5.27 (dq, *J* = 1.2, 9.6 Hz, 1H), 3.99 (s, 2H), 3.55 (ddd, *J* = 3.2, 6.4, 9.6 Hz, 1H), 2.53-2.43 (m, 1H), 2.40 (dd, *J* = 2.4, 13.6 Hz, 1H), 2.24 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.96 (br s, 1H), 1.85 (s, 3H), 1.67 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.3, 135.6, 127.6, 77.0, 72.9, 68.5, 44.7, 38.0, 24.1, 16.2, 14.1; **HRMS** (ESI) Calcd. $C_{11}H_{19}IO_4Na$: 333.03219. Found: 333.03222.

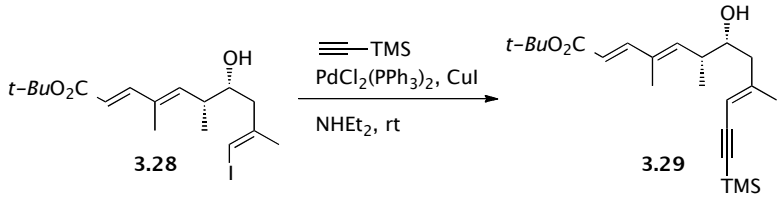
D.1.6. tert-*Butyl (2E,4E,6R,7R,9E)-7-hydroxy-10-iodo-4,6,9-trimethyldeca-2,4,9-trienoate (3.28)*



Allylic alcohol **3.27** (2.52 g, 8.14 mmol, 1.00 equiv) was dissolved in DCM (40 mL) and manganese (IV) oxide (12.2 g, 141, mmol, 17.4 equiv) was added. The suspension was stirred 30 minutes at room temperature. The solid was filtered out by passing the suspension through Celite® and the filtrate was concentrated under reduced pressure affording a crude residue that was moved directly to the next

step with no further purification. The residue was dissolved in benzene (50 mL) and 2-(triphenylphosphoranylidene)-acetic acid-1,1-dimethylethyl ester (6.12 g, 16.3 mmol, 2.00 equiv) was added and the reaction mixture was refluxed for 3 hours. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 5–10%) affording 2.90 g of **3.28** as a light yellow oil. Yield: 86%. $[\alpha]_D^{25}$ +43 (*c* 0.32, $CHCl_3$); **IR** (cast film) 3448, 2977, 2930, 1705, 1685, 1622, 1317, 1152, 981 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* =15.5 Hz, 1H), 6.00 (s, 1H), 5.75 (d, *J* = 16.0 Hz, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 3.56 (dddd, *J* = 2.5, 4.0, 7.0, 7.0 Hz), 2.62-2.55 (m, 1H), 2.38 (dd, *J* = 1.0, 13.5 Hz, 1H), 2.23 (dd, *J* = 10.0, 14.0 Hz), 1.85 (d, *J* = 0.5 Hz, 3H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.77 (d, *J* = 4.0 Hz, 1H), 1.49 (s, 9H), 1.07 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 148.1, 145.0, 133.1, 118.6, 80.2, 77.3, 76.8, 72.6, 45.3, 39.3, 28.2, 24.0, 16.2, 12.7; **HRMS** (ESI) Calcd. $C_{17}H_{27}IO_3Na$: 429.08971. Found: 429.08948.

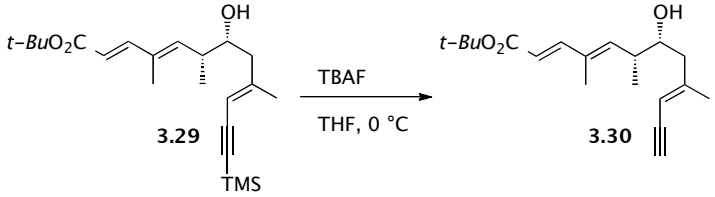
D.1.7. tert-*Butyl (2E,4E,6R,7R,9E)-7-hydroxy-4,6,9-trimethyl-12-(trimethylsilyl)dodeca-2,4,9-trien-11-ynoate (3.29)*



A round bottom flask was charged with alkenyl iodide **3.28** (2.90 g, 7.15 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (0.502 g, 0.715 mmol, 0.100 equiv), copper (I) iodide (136 mg, 0.715 mmol, 0.100 equiv) and degassed diethylamine (50 mL). Trimethylsilyl acetylene (2.02 mL, 14.3 mmol, 2.00 equiv) was added and the reaction mixture was stirred 2 hours at room temperature. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 0–20%) affording 2.61 g of **3.29** as a dark brown oil. Yield: 97%. $[\alpha]_D^{25}$ +41 (*c* 0.19, $CHCl_3$); **IR** (cast film) 3438, 2962, 2932, 2215, 2134, 1752, 1707, 1684, 1629, 1249, 1152, 844 cm^{-1}; **^{1}H NMR**

(500 MHz, $CDCl_3$) δ 7.20 (d, *J* =16.0 Hz, 1H), 5.75 (d, *J* = 16.0 Hz, 1H), 5.68 (d, *J* = 10.5 Hz, 1H), 5.37 (s, 1H), 3.56 (m, 1H), 2.62-2.54 (m, 1H), 2.05 (d, *J* = 10.0 Hz, 1H), 2.03 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.92 (s, 3H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.70 (d, *J* = 4.0 Hz, 1H), 1.48 (s, 9H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.18 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 150.2, 148.2, 142.5, 133.1, 118.5, 108.2, 102.7, 97.5, 80.1, 72.8, 44.6, 39.5, 28.2, 19.5, 16.1, 12.7, 0.0; **HRMS** (ESI) Calcd. $C_{22}H_{36}NaO_3Si$: 399.23259. Found: 399.23292.

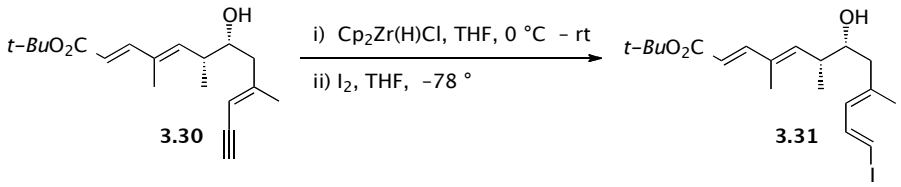
D.1.8. tert-*Butyl (2E,4E,6R,7R,9E)-7-hydroxy-4,6,9-trimethyldodeca-2,4,9-trien-11-ynoate (3.30)*



Trimethylsilylacetylene **3.29** (2.20 g, 5,86 mmol, 1.00 equiv) was dissolved in THF (30 mL) and cooled to 0 °C. A solution of 1.0 M *tert*-butylammonium fluoride in THF (8.80 mL, 8.80 mmol, 1.50 equiv) was added and the reaction mixture was stirred 15 minutes at 0 °C. The reaction mixture was diluted with water (20 mL), and then extracted with diethyl ether (3 *x* 50 mL). The organic extract was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 1:10) affording 1.78 g of **3.30** as a dark brown oil. Yield: >99%. $[\alpha]_D^{25}$ +33 (*c* 0.19, $CHCl_3$); **IR** (cast film) 3443, 3308, 2978, 2931, 2097, 1705, 1623, 1456, 1392, 1317, 1153, 982, 850 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* =16.0 Hz, 1H), 5.75 (d, *J* = 16.0 Hz, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 5.33 (s, 1H), 3.56-3.59 (m, 1H), 3.04 (d, *J* = 2.0 Hz, 1H), 2.61-2.57 (m, 1H), 2.29 (d, *J* = 13.5 Hz, 1H), 2.07 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.93 (s, 3H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.72 (br s, 1H), 1.49 (s, 9H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.18 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 150.7, 148.2,

142.4, 133.1, 118.5, 107.0, 81.1, 80.3, 80.1, 72.8, 44.5, 39.5, 28.2, 19.4, 16.1, 12.7; **HRMS** (ESI) Calcd. $C_{19}H_{28}NaO_3$: 327.19307. Found: 327.19294.

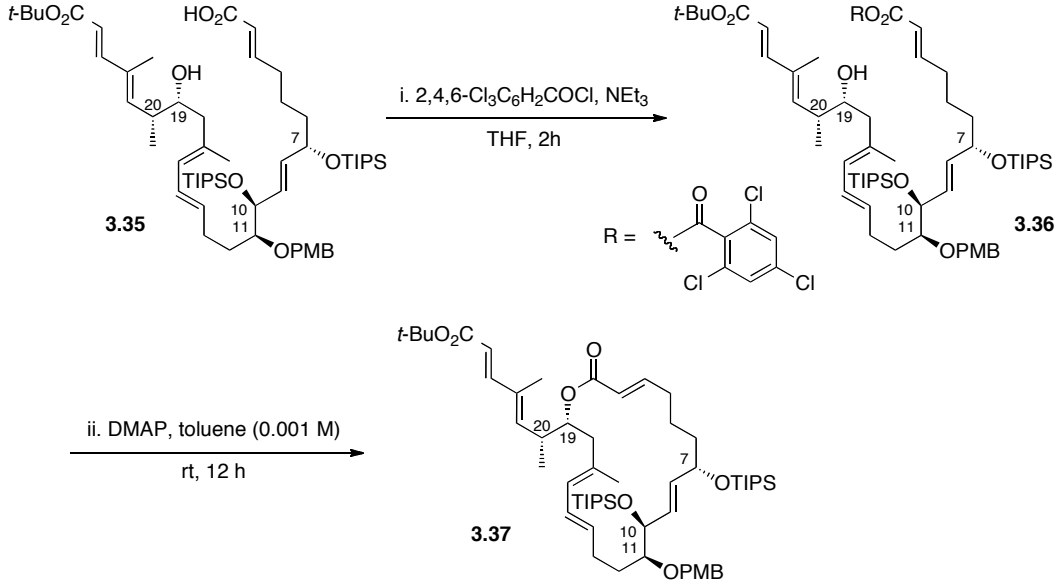
D.1.9. tert-*Butyl (2E,4E,6R,7R,9E,11E)-7-hydroxy-12-iodo-4,6,9-trimethyldodeca-2,4,9,11-tetraenoate (3.31)*



Chlorobis(η5-2,4-cyclopentadien-1-yl)hydro-zirconium (1.49 g, 5.80 mmol, 2.05) was suspended in THF (15 mL) and cooled to 0 °C. Alkyne **3.30** (859 mg, 2.82 mmol, 1.00 equiv) was dissolved in THF (10 mL) and added to the suspension. The reaction mixture was allowed to warm to room temperature and stirred for 45 minutes. The reaction mixture was then cooled to –78 °C and iodine (1.47 g, 5.80 mmol, 2.05 equiv) dissolved in THF (6 mL) was added; the mixture was dark brown in colour. The reaction mixture was stirred for 10 minutes at –78 °C. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL) and diluted with 50 mL of Et_2O (50 mL) and the biphasic mixture was separated. The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes, 1:9, 1% triethylamine) affording 961 mg of **3.31** as a faint yellow viscous oil. Yield: 75%. $[\alpha]_D^{25}$ +68 (*c* 0.32, $CHCl_3$); **IR** (cast film) 3443, 2976, 2929, 2871, 1705, 1622, 1367, 1316, 1152, 981, 849 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* =11.5, 14.5 Hz, 1H), 7.19 (dd, *J* = 0.5, 15.5 Hz, 1H), 6.21 (d, *J* = 14.5 Hz, 1H), 5.83 (d, *J* = 11.5 Hz, 1H) 5.74 (dd, *J* = 0.5, 15.5 Hz, 1H), 5.68 (dd, *J* = 0.5, 10.0 Hz, 1H), 3.57-3.54 (m, 1H), 2.63-2.54 (m, 1H), 2.21 (dd, *J* = 1.5, 13.5 Hz, 1H), 1.97 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.77 (d, *J* = 1.5 Hz, 1H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.48 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.8, 148.2, 142.7, 141.4, 136.7, 133.0, 127.9, 118.4,

80.1, 78.2, 72.6, 45.6, 39.5, 28.2, 17.1, 16.2, 12.7; **HRMS** (ESI) Calcd. $C_{19}H_{29}NaIO_3$: 455.10537. Found: 455.10539.

D.1.10. tert-*butyl (2E,4E,6R)-6-{(2R,4E,6E,10S,11S,12E,14S,18E)-10-[(4-methoxybenzyl)oxy]-4-methyl-20-oxo-11,14-bis[(tripropan-2-ylsilyl)oxy]oxacycloicosa-4,6,12,18-tetraen-2-yl}-4-methylhepta-2,4-dienoate (3.37)*



Secoacid **3.35** (127 mg, 0.124 mmol, 1.00 equiv) was dissolved in THF (10 mL). Triethylamine (347 µL, 2.48 mmol, 20.0 equiv) and 2,4,6-trichlorobenzoyl-chloride (289 µL, 1.86 mmol, 15.0 equiv) were added and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The crude mixed anhydride **3.36** was dissolved in toluene (12 mL) and added over 4 hours to a solution of 4-dimethylaminopyradine (556 mg, 4.96 mmol, 40.0 equiv) in toluene (104 mL) and the reaction mixture was stirred overnight. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate (50 mL). The biphasic mixture was separated and the aqueous layer was extracted with Et_2O (2 *x* 50 mL). The combined organic layers were dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Et_2O/hexanes, 0-20%, 1% triethylamine)

affording 109 mg of **3.37** as a white solid. Yield: 90%. $[\alpha]_D^{25}$ –92 (*c* 0.05, $CHCl_3$); **IR** (cast film) 3175, 2943, 2866, 1717, 1654, 1577, 1540, 1464, 1255, 1152, 1090, 1049, 979, 883, 682 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0, 2H), 7.21 (dd, *J* = 1.0, 15.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.79 (ddd, *J* = 5.5, 9.0, 15.0 Hz, 1H), 6.10 (dd, *J* = 11.5, 15 Hz, 1H), 5.76 (d, *J* = 16.0 Hz, 1H), 5.72 (dt, *J* = 1.5, 16.0 Hz, 1H), 5.66 (dd, *J* = 1.0, 14.0 Hz, 1H), 5.63-5.61 (m, 3H), 5.40 (ddd, *J* = 4.0, 10.5, 14.5 Hz, 1H), 4.96 (ddd, *J* = 2.0, 8.0, 11.5 Hz, 1H), 4.55 (d, *J* = 3.0 Hz, 1H), 4.52-4.49 (m, 2H), 4.14-4.10 (m, 1H), 3.81 (s, 3H), 3.34 (ddd, *J* = 1.5, 4.5, 6.0 Hz, 1H), 2.78-2.73 (m, 1H), 2.25-2.07 (m, 5H), 2.02 (dd, *J* = 11.5, 13.5 Hz, 1H), 1.90-1.86 (m, 1H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.68 (s, 3H), 1.70-1.50 (m, 3H), 1.50 (s, 9H), 1.07-1.03 (m, 42H), 1.01 (d, 6.5 Hz, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 166.7, 166.1, 159.3, 149.3, 148.1, 141.7, 133.3, 133.0, 132.7, 131.4, 130.8, 129.5, 129.4, 128.5, 126.6, 120.6, 118.6, 113.8, 82.5, 80.1, 74.8, 73.7, 72.4, 70.5, 55.3, 43.9, 39.4, 37.9, 33.4, 30.9, 30.8, 30.3, 28.2, 25.0, 18.1, 16.8, 16.5, 12.7, 12.5, 12.3; **HRMS** (ESI) Calcd. $C_{58}H_{96}O_8Si_2$+Na: 999.65360. Found: 999.65314.

APPENDIX E: CRYSTAL STRUCTURE REPORT

CCDC#: 742294

XCL Code: DGH0805 **Date:** 16 January 2008

Compound: Methyl (4*E*)-4,5-dideoxy-5-[(2*S*,6*R*)-6-ethoxytetrahydro-2*H*-pyran-2-yl]-2-*O*-(4-methoxybenzyl)-3-*O*-[(4-nitrophenyl)carbonyl]-L-*threo*-pent-4-enonate (*relative stereochemistry*)

Formula: $C_{28}H_{33}NO_{10}$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald

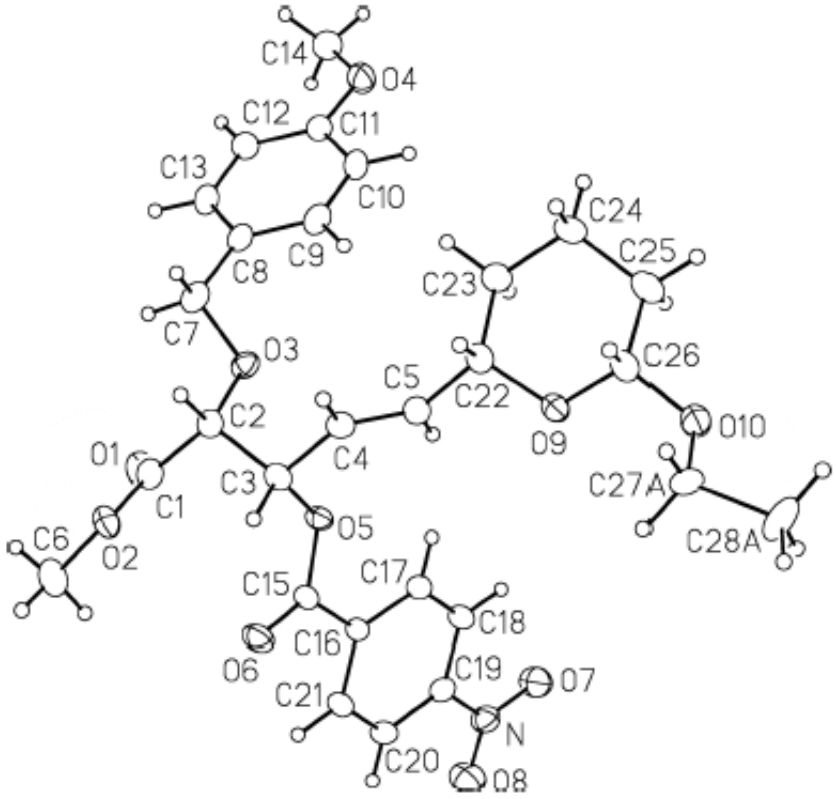
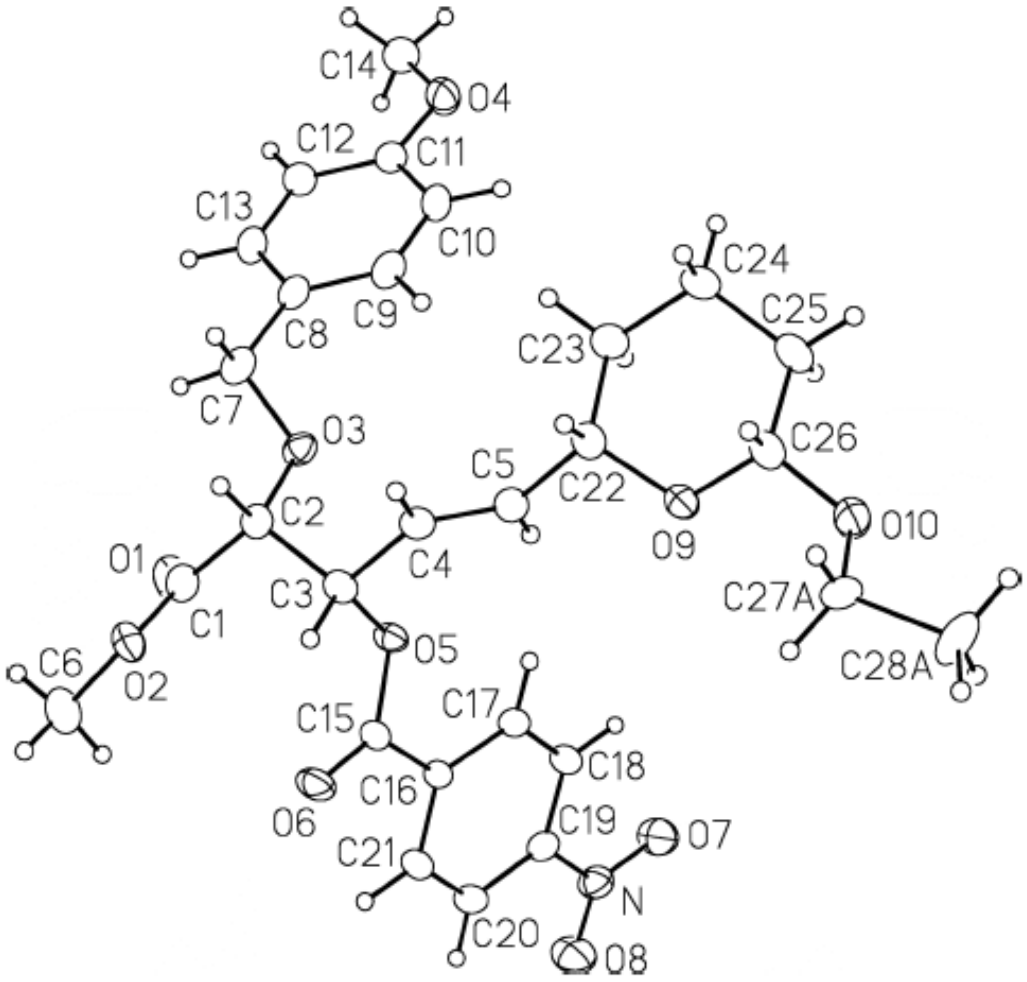
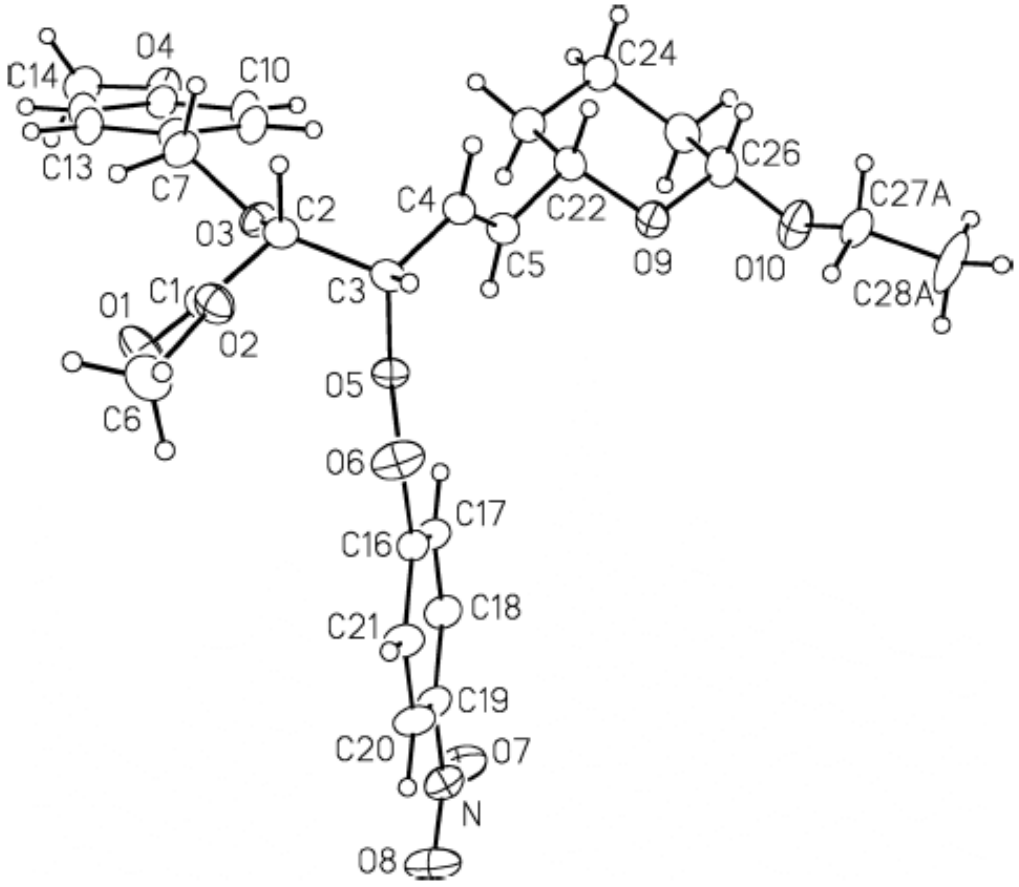


Figure Legends

Figure 1. Perspective view of the methyl (4*E*)-4,5-dideoxy-5-[(2*S*,6*R*)-6-ethoxytetrahydro-2*H*-pyran-2-yl]-2-*O*-(4-methoxybenzyl)-3-*O*-[(4-nitrophenyl)carbonyl]-L-*threo*-pent-4-enonate molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Figure 2. Alternate view of the molecule.


C14
O4
C12
C11
C13
C10
C24
C9
C25
C8
C23
C7
O3
C26
C5
C22
C2
O10
O1
C4
O9
C3
C27A
C1
O5
C6
O2
C28A
C15
C17
C18
C16
O6
C19
O7
C21
N
C20
O8


O4
C14
C10
C13
C7
O3
C2
C4
C24
C22
C26
C27A
C5
O9
O10
C28A
C1
O1
O2
C3
C6
O5
O6
C17
C16
C18
C21
C19
C20
O7
N
O8

List of Tables

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{28}H_{33}NO_{10}$
formula weight	543.55
crystal dimensions (mm)	0.84 × 0.11 × 0.06
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	5.0947 (9)
b (Å)	22.762 (4)
c (Å)	24.163 (4)
V (Å^3)	2802.1 (8)
Z	4
ρ_{calcd} (g cm^{-3})	1.288
μ (mm^{-1})	0.098
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (30 s exposures)
data collection 2θ limit (deg)	50.92
total data collected	19013 ($-6 \le h \le 6$, $-27 \le k \le 27$, $-29 \le l \le 29$)
independent reflections	5158 (R_{int} = 0.0990)
number of observed reflections (*NO*)	2966 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[c])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9941–0.9221
data/restraints/parameters	5158 [$F_o^2 \ge -3\sigma(F_o^2)$] / 3[d] / 373
Flack absolute structure parameter[e]	-0.7 (14)
goodness-of-fit (*S*)[f]	1.030 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0591
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1124
largest difference peak and hole	0.180 and –0.179 e Å^{-3}

[a]Obtained from least-squares refinement of 2851 reflections with $4.92° < 2\theta < 45.54°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[d]Distances involving the disordered ethoxy group were constrained to be equal (within 0.01 Å) during refinement: d(O10–C27A) = d(O10–C27B); d(C27A–C28A) = d(C27B–C28B); d(O10···C28A) = d(O10···C28B).

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. The low anomalous scattering power of the atoms in this structure (none heavier than oxygen) implies that the data cannot be used for absolute structure assignment, thus the Flack parameter is provided for informational purposes only. These structural data can be used to determine the relative stereochemical configurations of the stereogenic centers in the molecule.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0393P)^2]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.6641(6)	-0.10120(12)	0.32999(13)	0.0887(9)*
O2	0.2820(5)	-0.14895(10)	0.32507(10)	0.0597(7)*
O3	0.4117(5)	0.00164(9)	0.35607(9)	0.0521(6)*
O4	0.9001(6)	0.25345(11)	0.32809(10)	0.0748(8)*
O5	0.3642(4)	-0.07169(8)	0.45188(9)	0.0454(6)*
O6	0.2937(6)	-0.16931(10)	0.45365(10)	0.0709(8)*
O7	1.2544(6)	-0.09076(12)	0.66316(12)	0.0890(10)*
O8	1.2793(7)	-0.18448(13)	0.65228(13)	0.0986(11)*
O9	-0.1516(5)	0.06927(8)	0.54957(10)	0.0567(7)*
O10	-0.3369(6)	0.10245(11)	0.62906(11)	0.0833(9)*
N	1.1857(7)	-0.13659(16)	0.64073(13)	0.0660(9)*
C1	0.4310(8)	-0.10220(17)	0.33464(14)	0.0532(9)*
C2	0.2644(7)	-0.05083(13)	0.35488(14)	0.0447(9)*
C3	0.1494(7)	-0.06252(13)	0.41243(14)	0.0440(9)*
C4	-0.0108(7)	-0.01147(13)	0.43162(14)	0.0452(9)*
C5	0.0466(7)	0.02519(13)	0.47231(14)	0.0473(9)*
C6	0.4145(9)	-0.20263(16)	0.31085(17)	0.0842(14)*
C7	0.4427(8)	0.02831(15)	0.30260(14)	0.0605(11)*
C8	0.5722(7)	0.08716(15)	0.30921(14)	0.0498(9)*
C9	0.4967(8)	0.12537(17)	0.35087(15)	0.0632(10)*
C10	0.6097(8)	0.18017(16)	0.35610(14)	0.0627(10)*
C11	0.7999(8)	0.19859(15)	0.31927(15)	0.0541(10)*
C12	0.8801(7)	0.16115(15)	0.27759(15)	0.0573(10)*
C13	0.7623(7)	0.10592(16)	0.27311(14)	0.0569(10)*
C14	1.1075(8)	0.27287(16)	0.29270(16)	0.0728(12)*
C15	0.4053(7)	-0.12652(14)	0.47092(13)	0.0454(9)*
C16	0.6085(7)	-0.12789(13)	0.51559(13)	0.0419(8)*
C17	0.6939(7)	-0.07699(14)	0.54161(13)	0.0485(9)*
C18	0.8832(8)	-0.07945(14)	0.58245(14)	0.0540(10)*
C19	0.9817(7)	-0.13351(16)	0.59705(14)	0.0512(9)*
C20	0.9004(8)	-0.18480(14)	0.57213(14)	0.0592(11)*
C21	0.7115(8)	-0.18181(14)	0.53132(14)	0.0566(10)*
C22	-0.1217(7)	0.07498(13)	0.49048(14)	0.0512(9)*
C23	-0.0072(7)	0.13484(13)	0.47633(15)	0.0583(10)*
C24	-0.1688(8)	0.18416(14)	0.50226(15)	0.0608(11)*
C25	-0.2004(8)	0.17352(14)	0.56402(16)	0.0651(11)*
C26	-0.3151(8)	0.11341(14)	0.57327(16)	0.0617(11)*
C27A[a]	-0.537(2)	0.0568(5)	0.6363(5)	0.068(4)*

Table 2. Atomic Coordinates and Displacement Parameters (continued)

Atom	*x*	*y*	*z*	U_{eq}, Å^2
C28A[a]	-0.618(3)	0.0633(10)	0.6971(5)	0.117(7)*
C27B[b]	-0.446(4)	0.0500(7)	0.6557(10)	0.092(8)*
C28B[b]	-0.715(4)	0.0708(16)	0.6765(9)	0.126(10)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$. [a]Refined with an occupancy factor of 0.6. [b]Refined with an occupancy factor of 0.4.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.193(4)	C5	C22	1.487(4)
O2	C1	1.327(4)	C7	C8	1.502(4)
O2	C6	1.437(4)	C8	C9	1.385(4)
O3	C2	1.411(3)	C8	C13	1.372(5)
O3	C7	1.436(4)	C9	C10	1.380(4)
O4	C11	1.366(4)	C10	C11	1.381(5)
O4	C14	1.429(4)	C11	C12	1.381(5)
O5	C3	1.466(4)	C12	C13	1.397(5)
O5	C15	1.347(3)	C15	C16	1.496(4)
O6	C15	1.203(3)	C16	C17	1.388(4)
O7	N	1.227(3)	C16	C21	1.388(4)
O8	N	1.222(3)	C17	C18	1.381(4)
O9	C22	1.442(4)	C18	C19	1.375(4)
O9	C26	1.425(4)	C19	C20	1.378(4)
O10	C26	1.376(4)	C20	C21	1.379(5)
O10	C27A	1.468(6)[a]	C22	C23	1.521(4)
O10	C27B	1.467(7)[a]	C23	C24	1.527(4)
N	C19	1.483(4)	C24	C25	1.520(5)
C1	C2	1.525(5)	C25	C26	1.505(5)
C2	C3	1.532(4)	C27A	C28A	1.532(10)[a]
C3	C4	1.494(4)	C27B	C28B	1.533(11)[a]
C4	C5	1.322(4)			

[a]Distances constrained to be equal (within 0.01 Å) during refinement: d(O10–C27A) = d(O10–C27B); d(C27A–C28A) = d(C27B–C28B).

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O2	C6	117.1(3)	O4	C11	C12	124.6(3)
C2	O3	C7	113.4(2)	C10	C11	C12	119.4(3)
C11	O4	C14	117.8(3)	C11	C12	C13	119.0(3)
C3	O5	C15	118.0(2)	C8	C13	C12	122.3(3)
C22	O9	C26	113.3(3)	O5	C15	O6	124.0(3)
C26	O10	C27A	107.6(5)	O5	C15	C16	111.9(3)
C26	O10	C27B	127.5(10)	O6	C15	C16	124.1(3)
O7	N	O8	123.1(3)	C15	C16	C17	121.7(3)
O7	N	C19	118.3(3)	C15	C16	C21	118.5(3)
O8	N	C19	118.6(3)	C17	C16	C21	119.7(3)
O1	C1	O2	124.6(4)	C16	C17	C18	120.6(3)
O1	C1	C2	124.7(4)	C17	C18	C19	118.3(3)
O2	C1	C2	110.6(3)	N	C19	C18	118.7(3)
O3	C2	C1	111.1(3)	N	C19	C20	118.8(3)
O3	C2	C3	109.4(2)	C18	C19	C20	122.4(3)
C1	C2	C3	111.7(3)	C19	C20	C21	118.7(3)
O5	C3	C2	109.2(3)	C16	C21	C20	120.2(3)
O5	C3	C4	108.5(3)	O9	C22	C5	106.5(3)
C2	C3	C4	110.8(2)	O9	C22	C23	110.1(3)
C3	C4	C5	126.9(3)	C5	C22	C23	113.3(3)
C4	C5	C22	124.9(3)	C22	C23	C24	111.1(3)
O3	C7	C8	109.2(3)	C23	C24	C25	110.0(3)
C7	C8	C9	121.0(3)	C24	C25	C26	109.4(3)
C7	C8	C13	121.4(3)	O9	C26	O10	108.2(3)
C9	C8	C13	117.6(3)	O9	C26	C25	110.8(3)
C8	C9	C10	121.2(4)	O10	C26	C25	110.0(3)
C9	C10	C11	120.5(3)	O10	C27A	C28A	103.3(6)[a]
O4	C11	C10	116.1(3)	O10	C27B	C28B	103.4(6)[a]

[a]Angle includes distances constrained to be equal (within 0.01 Å) during refinement: d(O10–C27A) = d(O10–C27B); d(C27A–C28A) = d(C27B–C28B); d(O10···C28A) = d(O10···C28B).

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle
C6	O2	C1	O1	3.3(6)
C6	O2	C1	C2	-174.2(3)
C7	O3	C2	C1	78.6(3)
C7	O3	C2	C3	-157.6(3)
C2	O3	C7	C8	173.1(3)
C14	O4	C11	C10	176.7(3)
C14	O4	C11	C12	-1.8(5)
C15	O5	C3	C2	-107.9(3)
C15	O5	C3	C4	131.2(3)
C3	O5	C15	O6	7.4(5)
C3	O5	C15	C16	-173.2(3)
C26	O9	C22	C5	-178.5(3)
C26	O9	C22	C23	58.3(4)
C22	O9	C26	O10	177.9(3)
C22	O9	C26	C25	-61.4(4)
C27A	O10	C26	O9	-81.1(7)
C27A	O10	C26	C25	157.7(7)
C27B	O10	C26	O9	-61.0(12)
C27B	O10	C26	C25	177.9(11)
C26	O10	C27A	C28A	-160.4(9)
C26	O10	C27B	C28B	-104.7(15)
O7	N	C19	C18	1.7(5)
O7	N	C19	C20	-179.1(4)
O8	N	C19	C18	-177.5(4)
O8	N	C19	C20	1.6(5)
O1	C1	C2	O3	12.7(5)
O1	C1	C2	C3	-109.8(4)
O2	C1	C2	O3	-169.9(3)
O2	C1	C2	C3	67.7(4)
O3	C2	C3	O5	-63.4(3)
O3	C2	C3	C4	56.1(3)
C1	C2	C3	O5	60.0(3)
C1	C2	C3	C4	179.5(3)
O5	C3	C4	C5	9.0(4)
C2	C3	C4	C5	-110.9(4)
C3	C4	C5	C22	-179.0(3)
C4	C5	C22	O9	128.9(3)
C4	C5	C22	C23	-109.9(4)
O3	C7	C8	C9	-43.3(5)
O3	C7	C8	C13	139.2(3)
C7	C8	C9	C10	-178.0(3)
C13	C8	C9	C10	-0.4(5)
C7	C8	C13	C12	178.2(3)
C9	C8	C13	C12	0.6(5)
C8	C9	C10	C11	0.8(6)
C9	C10	C11	O4	-179.8(3)
C9	C10	C11	C12	-1.2(6)
O4	C11	C12	C13	179.8(3)
C10	C11	C12	C13	1.3(5)
C11	C12	C13	C8	-1.0(6)
O5	C15	C16	C17	13.6(4)
O5	C15	C16	C21	-166.9(3)
O6	C15	C16	C17	-167.1(3)
O6	C15	C16	C21	12.5(5)
C15	C16	C17	C18	-179.5(3)
C21	C16	C17	C18	1.0(5)
C15	C16	C21	C20	179.6(3)
C17	C16	C21	C20	-0.9(5)
C16	C17	C18	C19	-0.9(5)
C17	C18	C19	N	179.8(3)
C17	C18	C19	C20	0.7(5)
N	C19	C20	C21	-179.7(3)
C18	C19	C20	C21	-0.5(6)
C19	C20	C21	C16	0.6(5)
O9	C22	C23	C24	-53.5(4)
C5	C22	C23	C24	-172.7(3)
C22	C23	C24	C25	53.0(4)
C23	C24	C25	C26	-54.7(4)
C24	C25	C26	O9	58.5(4)
C24	C25	C26	O10	178.1(3)

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0416(18)	0.093(2)	0.132(3)	-0.0275(19)	0.0031(18)	0.0039(16)
O2	0.0622(18)	0.0526(15)	0.0644(17)	-0.0155(12)	-0.0015(14)	0.0067(14)
O3	0.0531(17)	0.0575(14)	0.0456(14)	0.0061(12)	-0.0055(13)	-0.0118(13)
O4	0.098(2)	0.0593(16)	0.0669(18)	-0.0056(14)	0.0119(18)	-0.0135(17)
O5	0.0473(14)	0.0350(12)	0.0540(14)	0.0025(11)	-0.0098(13)	-0.0035(11)
O6	0.100(2)	0.0394(13)	0.0728(18)	0.0017(13)	-0.0308(16)	-0.0145(15)
O7	0.112(3)	0.0733(19)	0.081(2)	0.0018(16)	-0.0426(19)	-0.0151(18)
O8	0.123(3)	0.0745(19)	0.098(2)	0.0102(17)	-0.052(2)	0.0147(19)
O9	0.0708(18)	0.0426(13)	0.0569(16)	-0.0031(12)	0.0095(14)	0.0017(13)
O10	0.127(3)	0.0547(15)	0.068(2)	-0.0051(14)	0.0342(19)	-0.0121(19)
N	0.075(3)	0.065(2)	0.058(2)	0.0068(19)	-0.011(2)	-0.006(2)
C1	0.045(3)	0.064(2)	0.051(2)	-0.0057(19)	-0.0058(19)	0.002(2)
C2	0.036(2)	0.052(2)	0.046(2)	-0.0034(17)	-0.0100(18)	-0.0038(18)
C3	0.035(2)	0.0407(19)	0.056(2)	-0.0023(17)	-0.0066(19)	-0.0041(17)
C4	0.040(2)	0.046(2)	0.050(2)	0.0038(17)	0.0004(18)	-0.0013(18)
C5	0.042(2)	0.049(2)	0.050(2)	-0.0002(18)	-0.0031(19)	-0.0015(18)
C6	0.099(4)	0.075(3)	0.079(3)	-0.025(2)	-0.007(3)	0.026(3)
C7	0.060(3)	0.075(3)	0.047(2)	0.0037(19)	-0.004(2)	-0.009(2)
C8	0.049(2)	0.062(2)	0.039(2)	0.0019(18)	-0.0037(19)	-0.002(2)
C9	0.069(3)	0.075(3)	0.045(2)	0.004(2)	0.013(2)	-0.002(2)
C10	0.079(3)	0.064(2)	0.046(2)	-0.007(2)	0.014(2)	0.004(2)
C11	0.064(3)	0.050(2)	0.048(2)	0.0031(18)	0.004(2)	-0.001(2)
C12	0.059(3)	0.057(2)	0.056(2)	0.0030(19)	0.014(2)	-0.001(2)
C13	0.060(3)	0.067(2)	0.043(2)	-0.0051(18)	0.010(2)	-0.004(2)
C14	0.084(3)	0.061(2)	0.073(3)	0.002(2)	-0.004(3)	-0.015(2)
C15	0.054(2)	0.0342(19)	0.048(2)	-0.0014(17)	0.005(2)	-0.0009(19)
C16	0.050(2)	0.0353(18)	0.0405(19)	-0.0003(16)	0.0000(18)	-0.0020(18)
C17	0.058(3)	0.0407(19)	0.047(2)	0.0034(17)	-0.005(2)	-0.0023(18)
C18	0.069(3)	0.0387(19)	0.054(2)	-0.0010(18)	-0.009(2)	-0.008(2)
C19	0.058(2)	0.053(2)	0.043(2)	0.0064(18)	-0.0060(19)	-0.005(2)
C20	0.081(3)	0.043(2)	0.054(2)	0.0072(18)	-0.015(2)	0.004(2)
C21	0.077(3)	0.038(2)	0.054(2)	-0.0019(17)	-0.011(2)	0.002(2)
C22	0.049(2)	0.051(2)	0.054(2)	-0.0057(18)	0.000(2)	0.002(2)
C23	0.061(2)	0.052(2)	0.062(2)	0.0027(19)	0.003(2)	-0.002(2)
C24	0.069(3)	0.0408(19)	0.073(3)	0.0063(18)	0.011(2)	-0.001(2)
C25	0.074(3)	0.043(2)	0.078(3)	-0.0097(19)	0.010(2)	0.000(2)
C26	0.072(3)	0.047(2)	0.065(3)	-0.0076(19)	0.018(2)	-0.002(2)
C27A	0.089(8)	0.054(5)	0.060(8)	0.020(5)	0.024(7)	0.001(6)

Table 6. Anisotropic Displacement Parameters (continued)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C28A	0.175(15)	0.122(9)	0.054(8)	0.008(8)	0.049(11)	-0.052(13)
C27B	0.135(18)	0.067(10)	0.073(16)	0.007(8)	0.001(13)	0.004(11)
C28B	0.135(16)	0.143(18)	0.10(2)	0.002(16)	-0.008(16)	-0.040(15)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2	0.1155	-0.0454	0.3284	0.054
H3	0.0368	-0.0985	0.4111	0.053
H4	-0.1710	-0.0046	0.4126	0.054
H5	0.2076	0.0193	0.4914	0.057
H6A	0.2845	-0.2335	0.3039	0.101
H6B	0.5288	-0.2145	0.3415	0.101
H6C	0.5204	-0.1965	0.2775	0.101
H7A	0.2690	0.0332	0.2848	0.073
H7B	0.5516	0.0028	0.2787	0.073
H9	0.3647	0.1136	0.3763	0.076
H10	0.5562	0.2054	0.3853	0.075
H12	1.0134	0.1728	0.2524	0.069
H13	0.8157	0.0805	0.2440	0.068
H14A	1.1661	0.3119	0.3044	0.087
H14B	1.0439	0.2748	0.2545	0.087
H14C	1.2546	0.2452	0.2950	0.087
H17	0.6214	-0.0401	0.5312	0.058
H18	0.9439	-0.0447	0.6000	0.065
H20	0.9730	-0.2215	0.5828	0.071
H21	0.6517	-0.2168	0.5139	0.068
H22	-0.2979	0.0712	0.4726	0.061
H23A	-0.0038	0.1398	0.4356	0.070
H23B	0.1757	0.1371	0.4900	0.070
H24A	-0.0800	0.2223	0.4961	0.073
H24B	-0.3437	0.1859	0.4845	0.073
H25A	-0.0275	0.1764	0.5825	0.078
H25B	-0.3176	0.2037	0.5801	0.078
H26	-0.4931	0.1115	0.5559	0.074
H27A[a]	-0.4639	0.0172	0.6290	0.081
H27B[a]	-0.6886	0.0635	0.6114	0.081
H28A[a]	-0.7581	0.0354	0.7056	0.140
H28B[a]	-0.6800	0.1034	0.7037	0.140
H28C[a]	-0.4658	0.0554	0.7209	0.140
H27C[b]	-0.3343	0.0368	0.6868	0.110
H27D[b]	-0.4653	0.0174	0.6288	0.110
H28D[b]	-0.8088	0.0377	0.6932	0.151
H28E[b]	-0.8171	0.0862	0.6453	0.151
H28F[b]	-0.6906	0.1018	0.7041	0.151

[a]Included with an occupancy factor of 0.6. [b]Included with an occupancy factor of 0.4.