The formal total synthesis of (-)-laulimalide supramolecular self-assembly : transition metal encapsulation
by Christopher John Markworth

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University

Abstract:
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APPROVAL

of a dissertation submitted by

Christopher John Markworth

This dissertation has been read by each member of the dissertation committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

Paul A. Grieco, Ph.D. _____ (Signature) 8-25-03 (Date)

Approved for the Department of Chemistry and Biochemistry

Paul A. Grieco, Ph.D. _____ (Signature) 8-25-03 (Date)

Approved for the College of Graduate Studies

Bruce R. McLeod, Ph.D. Bruce R. McLeod (Signature) 8-27-03 (Date)

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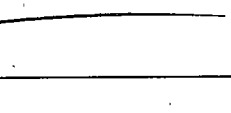
Signature 

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My father once warned me that a classmate of his traveled to Bozeman shortly after graduation. The classmate enjoyed life out west so much that he never returned. As much as I hinted at staying, the support of my parents and siblings was unwavering. Thank you. I will come home.

Finally to Kim, thank you for illuminating the end of the tunnel.

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LIST OF ABBREVIATIONS:

Ac	acetyl
Bn	benzyl
n-Bu	*normal*-butyl
i-Bu	*iso*-butyl
cat	catalytic
CSA	camphorsulfonic acid
°C	degrees Celsius
CI	chemical ionization
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
EI	electron impact
en	ethylenediamine
equiv	equivalents
Et	ethyl
g	gram
h	hour

HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant in hertz
LDA	lithium diisopropylamide
M	molarity
MALDI	matrix-assisted laser desorption ionization
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
μL	microliter
mmol	millimole
MOM	methoxymethyl
MS	mass spectrum
NMR	nuclear magnetic resonance
OAc	acetyloxy
Ph	phenyl
PivCl	pivaloyl chloride
PMB	4-methoxybenzyl
i-Pr	*iso*-propyl

ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
py	pyridine
Red-Al®	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
Tf	trifluoromethanesulfonyl
Ts	*para*-toluenesulfonyl

ABSTRACT

Laulimalide is a 20-membered ring macrolide of marine origin. It displays potent antitumor activity that is derived from its role as a microtubule stabilizer, a mode of action similar to that of Taxol. The formal total synthesis of (-)-laulimalide is described. The convergent synthesis utilizes a Myers asymmetric alkylation followed by a cuprate-mediated epoxide opening to establish the vast majority of the carbon framework.

Supramolecular self-assembly chemistry is a rapidly expanding area of research. Recent studies have utilized the cyclobutadienylcyclopentadienylcobalt metallocene as a rigid scaffold for displaying substituted pyridine ligands in specified orientations. Upon coordination to a transition metal, the pyridine ligands undergo self-assembly, giving rise to thermodynamically-derived complexes with empty interior cavities. Herein are described studies toward the synthesis of self-assembly complexes designed to encapsulate the transition metal in the interior cavity of the self-assembly molecule. The syntheses of two separate pyridine ligands and studies of their respective self-assembly complexes are discussed.

THE FORMAL TOTAL SYNTHESIS OF (–)-LAULIMALIDE

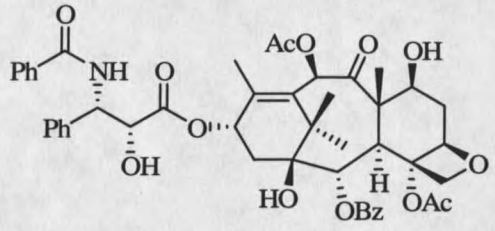
Introduction

Background

In 1962, extracts of the Pacific yew, *Taxus brevifolia*, were collected and screened against several cell lines with one extract in particular displaying cytotoxic activity.[1] The active component, taxol **1**, was isolated, and its structure was identified by 1971.[2] While taxol was interesting from a synthetic standpoint,[1] interest waned quickly as it was believed that taxol was simply another compound in a line of known microtubule-destabilizers such as colchicine or the vinca alkaloids. This, coupled with difficulties in isolating abundant quantities of the compound, quickly led to diminished interest in taxol. However, interest was rekindled after a report in 1979 by Horowitz and coworkers[3] that identified the actual mode of action as an antimitotic agent: taxol is a microtubule stabilizer that prevents microtubule depolymerization. This discovery placed taxol in an entirely new class of compounds, eventually resulting in its development as a billion-dollar drug.[1]

Although a semi-synthetic route to taxol has provided sufficient quantities of the drug, two major problems remain.[1] The hydrophobic nature of taxol has caused difficulties for drug formulation, requiring its administration in an intravenous fashion. Additionally, this hydrophobicity associated with taxol has led to multi-drug resistance (MDR) through the cellular expression of P-glycoprotein (P-gp), a transmembrane

transporter protein. P-gp lowers the intracellular concentration of taxol and other hydrophobic antitumor compounds, decreasing efficacy and resulting in resistance. In the anticipation of surmounting these difficulties, the search for additional members of this interesting class of compounds commenced.



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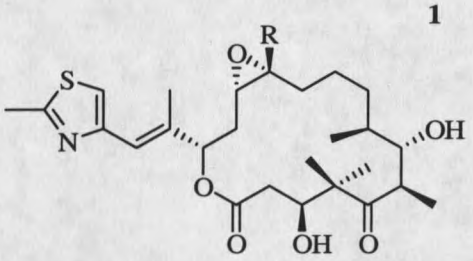
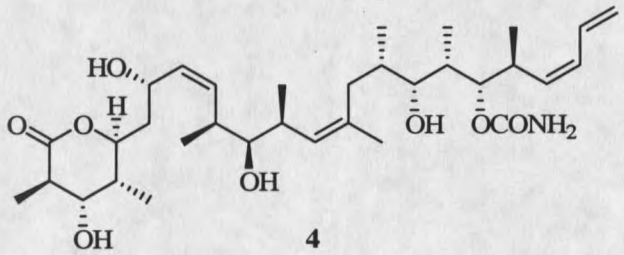


2 R = H
3 R = CH_3



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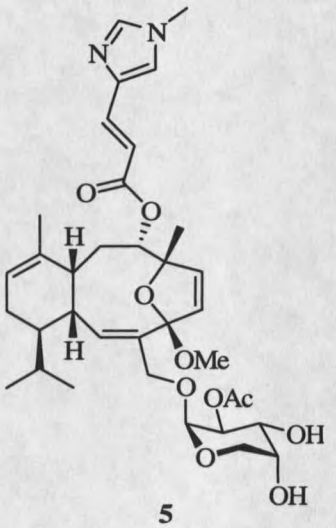

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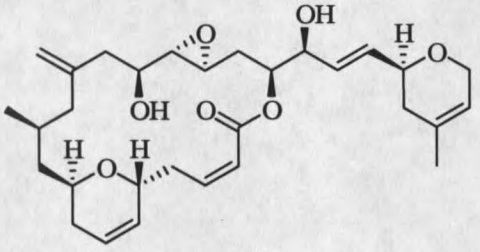
After 15 years, a number of publications appeared in the literature describing the discovery of additional microtubule stabilizing compounds. In 1995, Bollag et al.[4] disclosed that epothilones A (**2**) and B (**3**), isolated by Höfle and co-workers from the myxobacterium *Sorangium cellulosum*,[5] are microtubule stabilizers. Furthermore, the epothilones are active against taxol-resistant cell lines. Discodermolide **4**[6] and eleutherobin **5**,[7] both of marine origin, were soon reported as well. However, the

potential for isolating useful quantities of these compounds is limited as the natural abundance is decidedly low.[8] Additionally, the eleutherobins did not display sufficient activity against P-gp expressing cells. Though additional microtubule stabilizers have been discovered, alternative compounds to taxol are still being sought.

The isolation of laulimalide **6** (fijianolide B) and its isomer isolaulimalide **7** was reported in two back-to-back papers in 1988.[9] The structure of laulimalide was definitively determined by X-ray crystallographic analysis.[10] In 1999, it was reported that, like taxol, laulimalide acts as a microtubule stabilizer.[11] More notably, however, laulimalide displays activity against cell lines which have shown P-glycoprotein-mediated multi-drug resistance. While laulimalide and taxol both act as microtubule stabilizers, Hamel and co-workers reported in 2002[12] that, unlike other taxol-like compounds, laulimalide does not inhibit the binding of taxol to microtubules. This finding suggests that laulimalide is the first compound in this class to bind to an alternative site on microtubules.



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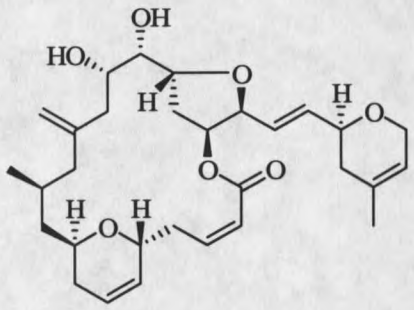

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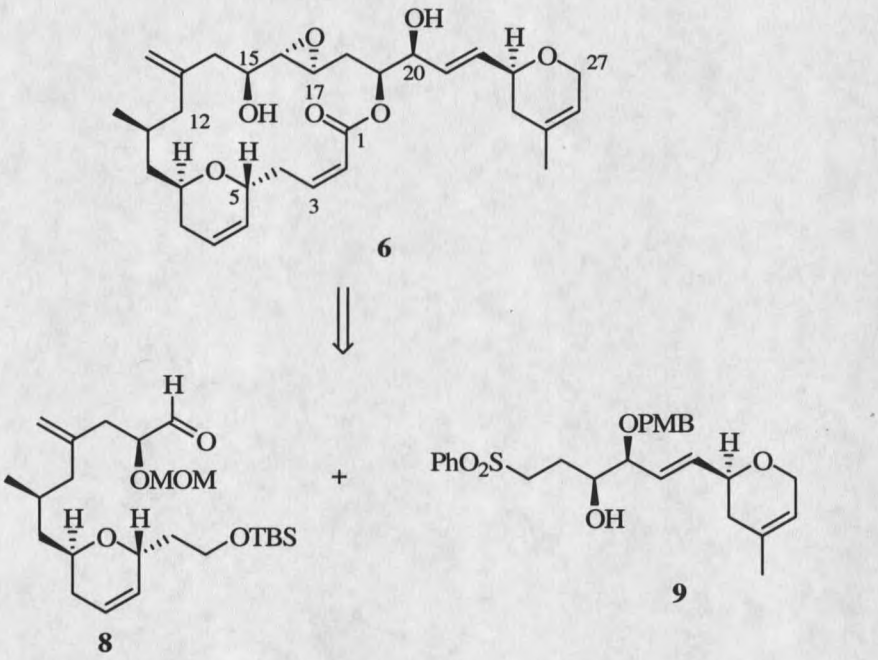
Laulimalide is isolated from marine sponges found in a variety of locations in the Pacific Ocean. Unfortunately, this particular source provides the compound in limited supply. Therefore, the goal of total synthesis should have one or two objectives: an

efficient total synthesis to provide additional material for biological studies, and a flexible synthesis to allow for modifications to the compound for further evaluation of analogues as potential antitumor agents. To date, several approaches to laulimalide have been reported[13] as have numerous total syntheses.[14]

Scheme 1.1



The first total synthesis of laulimalide was reported by Ghosh and Wang at the University of Illinois at Chicago (Scheme 1.1).[14a] In this approach the two main fragments, aldehyde **8** and sulfone **9**, were joined by a Julia olefination reaction to establish the *trans* C(16)-C(17) olefin. Macrocyclic ring closure by a Still modification of the Horner–Wadsworth–Emmons reaction followed by a Sharpless asymmetric epoxidation provided (-)-laulimalide.