Progress Towards the Synthesis of Polyalthenol

by

Erynn Wright Reichenberg

A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Approved July 2012 by the
Graduate Supervisory Committee:

David Madar, Chair
Edward Skibo
William Miller

ARIZONA STATE UNIVERSITY

August 2012

ABSTRACT

Throughout time, compounds from natural sources have provided humans with medicines, and recently become the structural inspiration for semisynthetic drugs. One arena that has benefited greatly from the use of these natural products is the discovery of novel antibacterial agents. Methicillin-resistant *Staphylcoccus aureus* (MRSA) continues to plague the United States as well as throughout the world, at least in part because of increasing antibiotic resistance. Therefore, scientists continue to scour natural products as potential leads, either directly or indirectly, for antibiotics to treat MRSA.

The structure of the indole sesquiterpene, polyalthenol, was discovered in 1976 and recent work shows a 4μg/mL minimum inhibitory concentration (MIC) against a variety of strains of MRSA. Given the unique framework of this natural product and its biological activity against MRSA, the total synthesis becomes the next logical step. Presently a racemic synthesis has successfully afforded an indole ketone with the correct relative stereochemistry of polyalthenol, however, the completion of the total synthesis of polyalthenol presents several challenges. Herein, the work towards the synthesis is described in addition to the proposed completion of the synthesis.

ACKNOWLEDGMENTS

I would like to express my deepest gratitude to my advisor, Dr. David Madar, for his excellent guidance, endless knowledge, and most of all for providing an excellent atmosphere for doing research. I would not be here if he was not willing to take a chance on me and to believe in me, even when it was difficult to believe in myself. I must thank Dr. Edward Skibo and Dr. William Miller for agreeing to take part on my defense committee and for their continued feedback. I would also like to thank Dr. Douglas Green and the Department of Applied Biological Science & Mathematics for allowing me to teach undergraduate chemistry course and for providing me with the financial means to be a successful graduate student. My experiences teaching have been invaluable and have made me a better chemist.

I would like to thank my laboratory mates, past and present, for which chemistry would be rather boring without. I must specifically acknowledge Alina Barlow, Anthony Mancuso, and Rawn Richardson for their continued encouragement during my research and for lending a helping hand whenever I asked. I would also like to thank my colleagues and other Instructional Professionals for their continued advice; these individuals truly understand the demands of being an employee first and a student second.

Finally, I must thank my husband for providing unwavering support throughout this entire process and for cheering me on during all of life's adventures. I truly would not have had enough to courage to pursue my dreams without him.

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

Chapter 1

Natural Products Chemistry

1.1 The History of Natural Products

Throughout history humans have relied on nature to meet their most basic needs, including but not limited to, the production of food, shelter and transportation. The treatment of diseases and other ailments with naturally derived medicines is no exception.[1] The use of these natural sources, most often marine organisms, plants, fungus, and recently prokaryotes, for the production of medicines represents one facet in the field natural products chemistry. Classical natural products-based drug discovery involves the extraction, isolation, purification, and characterization of compounds from their natural sources.[2] It is important to keep in mind that these natural products are just that, products of nature, and not in themselves drugs. Only through biological assays, used to determine activity against a variety of human infections, are the compounds identified as leads, which become candidates for future drug development. When compounds are deemed biologically active, organic chemists utilize synthetic methodologies to produce large quantities of the compound in a laboratory, for further research and the production of lead compounds and analogues. Throughout time, humankind has discovered and made use of an enormous range of natural compounds[3]; to date the *Dictionary of Natural Products* (DNP) has over 243,000 entries.[4]

Based solely on empirical observations and folklore, natural product extracts were the first, and for a long time, the only medicines available to

mankind.[5] The oldest medicinal texts, written on clay tablets in cuneiform, are from Mesopotamia circa 2600 BC. They describe approximately 1000 plant derived substances, such as *Cedrus* species (cedar) and *Cupressus sempevirens* (cypress), *Glycyrrhiza glabra* (licorice), *Commiphora* species (myrrh), and *Papaver somniferum* (poppy juice), all of which are still in use today for the treatment of ailments ranging from coughs to parasitic infection to inflammation. Traditional Chinese medicine is also well known for its extensive use of natural products, the first record of the Chinese *Materia Medica* dates from about 1100 BC.[1] The Indian Ayurveda (science of life), which covers disease, therapeutics, and pharmacy, has a vast literature in Sanskrit as well as other Indian languages and dates back to approximately 900 BC. The *Charaka Samhita* is the first recorded writing fully devoted to the concepts and practices of Ayurveda and lists 341 plants and plant products used for medicinal purposes.[6] In the ancient Western world, the Greeks contributed to the rational development of the use of herbal drugs. The *History of Plants* from 300 BCE dealt with the medicinal properties of herbs and around 100 CE Dioscorides, a Greek physician, recorded the collection, storage and use of medicinal herbs.[7] During the Dark and Middle Ages (401 CE – 1499 CE) the remnants of this Western knowledge were preserved in countries such as England, Ireland, France and Germany and in the early eighth century it was the Arabs that contributed much to pharmacy and medicine by publishing the *Canon Medicinae.* The *London Pharmacopoeia*, published in 1618, was the first formal compilation of these, as well as, many other ancient medicinal practices.

What followed in the early 1800's was the idea that the isolation of active components of commonly used plants and herbs such as strychnine, atropine and colchicines could be traced back to 'pure' compounds.[1] Modern chemistry provided the tools to purify a variety of compounds and to determine their structures. These advancements resulted in what became both the first pure naturally derived medicine and the first to be commercialized, morphine (Figure 1.1). Morphine, which is produced by cut seed pods of the poppy, *Papaver somniferum*, was first distributed by E. Merck in 1826.[8]

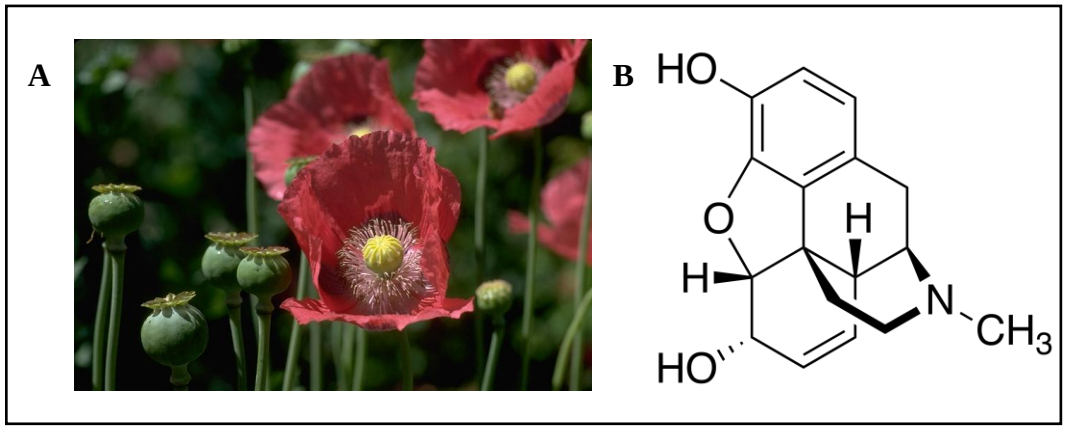


Figure 1.1. (A) *Papaver somniferum*; Opium Poppy. Jo-Ann Ordano © California Academy of Sciences; (B) Chemical structure of morphine.

The predecessor of aspirin, salicylic acid, was known at least from the fifth century BC when it was extracted by Hippocrates from the bark of the willow tree. Synthetic salicylates were produced on large scale by the Bayer Company in 1874 but it was not until twenty years later that Bayer produced aspirin, which is generally thought to be the first semi-synthetic pure drug based on a natural product.[9] These breakthroughs, as well as many others, initiated an era in which drugs from plants could be purified, studied, and administered in

precise dosages that did not depend on the original source.[10] The discovery of penicillin, derived from the mold *Penicillium notatum*, by Alexander Fleming in 1928 and its development into a medicine provided the foundation for the development of natural products as the cornerstone of new drug discovery in the 20th century and beyond.[11]

1.2 Natural Products to the Pharmacy

The examples of natural products turned successful pharmaceuticals are plentiful, and in our current view we should see natural products as both a fundamental source of new chemical diversity and an integral component of today's pharmaceutical industry.[12] We do not have to look much further than the examples of morphine from poppies, cardiotonic digitalis glycosides from foxglove, and penicillins from fungi to see the importance of natural products in the pipeline for investigational drugs. The continued influence of natural products as leads to or sources of drugs over the years 1981-2006 is evident in the work by Newman and Cragg as shown in Figures 1.2 and 1.3.[13-15]

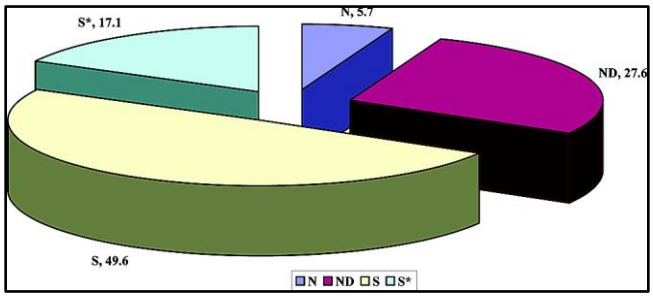


Figure 1.2. Source of small molecule drugs, 1981-2006: major categories, *N* = 983 (in percentages). Major categories are as follows: "N", natural product; "ND", derived from a natural product and usually a semi-synthetic modification; "S", totally synthetic drug often found by a random screening/modification of an existing agent; "S*", made by total synthesis, but the pharmacophore is/was from a natural product.[15]

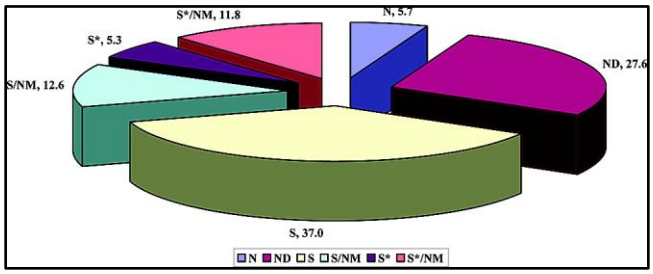


Figure 1.3. Source of small molecule drugs, 1981-2006: all categories, *N* = 983 (in percentages). Major categories are as follows: "N", natural product; "ND", derived from a natural product and usually a semi-synthetic modification; "S", totally synthetic drug often found by a random screening/modification of an existing agent; "S*", made by total synthesis, but the pharmacophore is/was from a natural product. The subcategory is as follows: "NM", natural product mimic.[15]

Although estimates vary, mostly depending on the definition of a natural product-derived drug, it is acceptable to say that somewhere between 25% and 50% of currently marketed drugs owe their origins to natural products.[16] Natural products are typically classified as such when the compound is either extracted from the source or the structure is replicated using synthetic methods. Natural product-derived drugs are derivatives of the natural product with synthetic modifications, typically to increase biological activity and/or bioavailability. Additionally, compounds may be considered a natural product despite the use of totally synthetic methods when the pharmacophore was inspired by a natural product. The amount of totally synthetic drugs, often found from random screening, is very limited. In Figure 1.3 this represents just 5.3% of small molecule drugs from 1981 to 2006.

The percentage of natural product drugs may be even higher for certain classes, specifically anticancer and anti-infective agents. It is believed that as much as two-thirds of these agents are from natural sources.[17] In the United

States it is estimated that over 50% of the most-prescribed drugs were either a natural product or a natural product was used as a template in the synthesis and design of the agent.[1] Between 1985 and 2006 almost half of new drugs introduced into the market were natural products or their derivatives and they represented over $40 billion in sales.[18]

Despite the successes in natural products chemistry, the role of natural products in drug discovery has seen many changes over the past three decades with a noticeable fall off in the early 1990's (Fig. 1.4).[10] This decline is mainly due to the launch of high-throughput screening (HTS) of combinatorial chemistry libraries followed by optimization of hits, thought to be the new frontier in drug discovery. The expected surge in productivity never materialized and the number of New Chemical Entities (NCEs) hit a 24-year low of 25 in 2004.[14] The switch

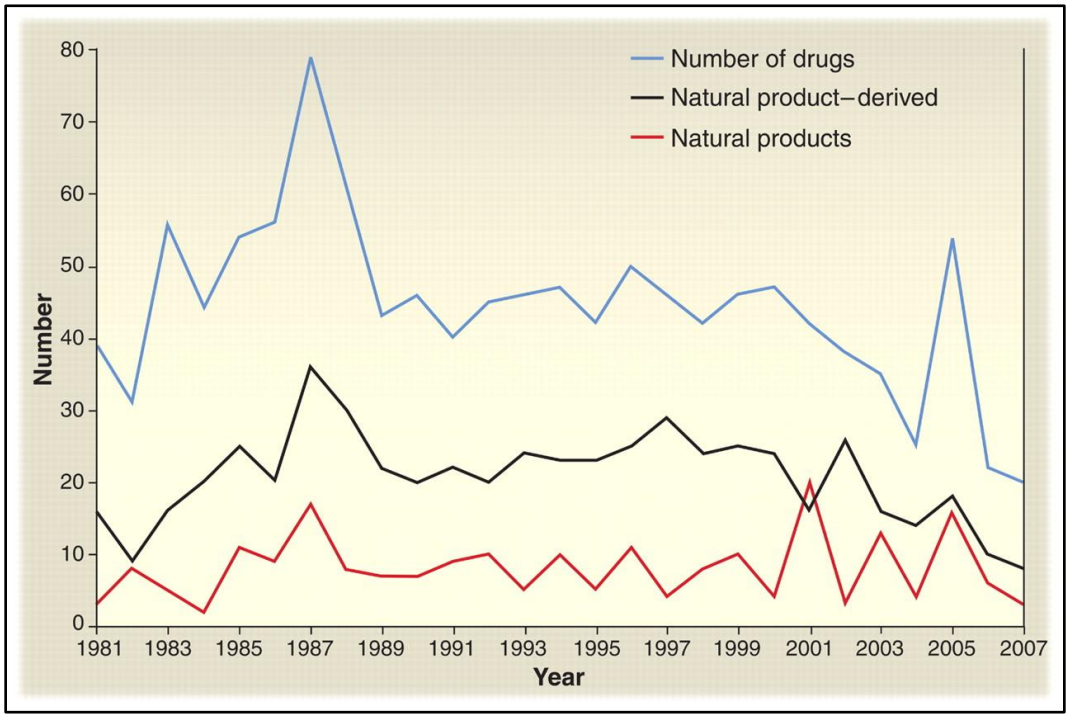


Figure 1.4. Drugs approved in the United States from 1981 – 2007.[10]

away from natural products to HTS combinatorial chemistry might have led to the current scarcity of new drug candidates in the development pipeline.[3] Over the past 20 years there has been only a handful of FDA-approved drug resulting from HTS, well-known examples include the kinase inhibitors sunitinib for renal carcinoma and sorafenib (Nexavar) both approved in 2005.[19-20] Thus natural product-based drugs (parent compounds, derivatives, analogues, and mimics) are still the major entities among the FDA-approved drugs (57.7% of all drugs).[2] The attractiveness of natural products will continue because they are ideal as sources of novel drug leads and the inspiration for the synthesis of non-natural molecules.

Thirteen natural product-derived drugs were approved in the United States between 2005 and 2007 (Table 1.1).[21] Of those, five of them represented the first members of new classes: the peptides exenatide and zironotide, and the small molecules ixabepilone, retapamulin and trabectedin.[22]

Table 1.1 NP-derived drugs launched since 2005 by year with reference to their lead compound, classification and therapeutic area.[21]

Year	Generic Name (trade name)	Lead Compound	Classification	Disease area
2005	dronabinol/ cannabidol (Sativex®)	dronabinol/	NPs	pain
2005	fumagillin (Flisint®)	fumagillin	NP	antiparasitic
2005	doripenem (Finibax®/Doribax ™)	thienamycin	NP-D	antibacterial
2005	tigecycline (Tygacil®)	tetracycline	SS* NP	antibacterial
2005	ziconotide (Prialt®)	ziconotide	NP	pain
2005	zotarolimus (Endeavor™ stent)	sirolimus	SS* NP	cardiovascular surgery
2006	anidulafungin (Eraxis™/Ecalta™)	echinocandin	SS* NP	antifungal
2006	exenatide (Byetta™)	exenatide-4	NP	diabetes
2007	lLisdexamfetamine (Vyvanse™)	amphetamine	NP-D	ADHD
2007	retapamulin (Altabax™/Altargo™)	pleuromutilin	SS* NP	antibacterial (topical)
2007	temsirolimus (Torisel™)	sirolimus	SS* NP	oncology
2007	trabectedin (Yondelis™)	trabectedin	NP	oncology
2007	ixabepilone (Ixempra™)	epothilone B	SS* NP	oncology

Classifications: “NP”, natural product; “NP-D”, Natural Product-derived; “SS* NP”, semi-synthetic Natural Product.

After more than twenty years of research and development, ziconotide, now known under the trade name Prialt, was the first marine-derived drug approved by the FDA. This peptide toxin isolated from the cone snail *Conus magus* was approved in 2004 for the treatment of chronic pain following spinal cord injuries (Figure 1.5A).[10,23] Trabectedin, with the trade name Yondelis, from *Ecteinascidia turbinata* (Figure 1.5B) has been approved in Europe since 2007 for the treatment of advanced soft-tissue carcinoma and illustrates a significant milestone in the development of marine-derived drugs. Almost four decades after its discovery and seventeen years after its structure was elucidated, Ecteinascidin-743 became the first marine-derived anticancer drug to reach the market.[23]

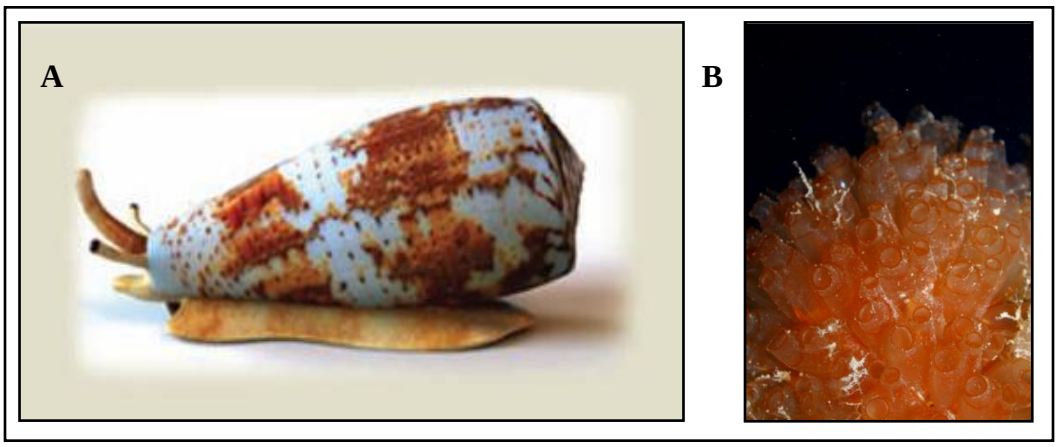


Figure 1.5. (A) Textile cone snail *Conus magus*; (B) The Caribbean sea-squirt *Ecteinascidia turbinata*. Image courtesy of Susanna Lopez-Legentil.

1.3 Antibacterials Inspired by Natural Products

The development of new anti-infective drugs is one arena in which natural products have dominated. As previously mentioned, natural products play a particularly crucial role in both anticancer and anti-infectious disease drug discovery, with approximately 60% and 75% of drug candidates respectively

coming from either natural products or natural product derivatives.[24-25] Over evolutionary time, many organisms, specifically marine eukaryotes, have developed a plethora of anti-infective molecules and strategies by which they protect themselves against attack. Given this tendency, it is understandable why efforts have been made to identify and characterize antimicrobial factors from these organisms.[26] Since their introduction, in the early part of the last century, antibiotics have been considered 'wonder drugs' but their popularity and overuse have lead to resistance as pathogens have evolved. To address the need for novel and effective antibiotics, and to fight against the continued resistance, pharmaceutical companies have recharged their efforts in the development of new antibiotics based on natural products.

The first powerful antibiotic used widely by civilians was penicillin. Following the isolation of penicillin from the fungi *Penicillium notatum* in the early 1940's, the number of penicillin-based molecules that have been produced by semi- and total synthesis to date is well over 15,000.[7] The ring-expanded version of penicillin, cephalosporin C, from the species *Cephalosporium* was reported in 1948 and its structure was determined thirteen years later.[27-28] The penicillin core served as the template for thousands of cephalosporins and in 1970 the first orally-active molecule, cephalexin, was introduced. Since that time, numerous cephalosporins including: cefalotin, cefuroxime, ceftazidime, and cefepime, have been synthesized with the aim at producing molecules that are more resistant to β-lactamases.[29] Biapenem **1** (Omegacin®) and ertapenem **2** (Invanz®) both introduced in 2002 and doripenem **3** (Finibax®) introduced in 2005

are carbapenem antibiotics (part of the β-lactam family). These three carbapenem drugs are produced synthetically but their lead structure is the natural product thienamycin.[7,14] The mechanism of action of these three drugs, like other β-lactam antibiotics, is the inhibition of bacterial cell wall synthesis.[30-31] Yet another class of natural product-inspired antibiotics is that of the tetracyclines, discovered in the 1940's. Since the discovery of chlortetracycline in 1945[32] from *Streptomyces aureofaciens*, other tetracyclines have followed, some naturally occurring, such as tetracycline from *S. aureofaciens* and others, such as doxycycline and minocycline, which are semisynthetic products.[33] The naturally occurring tetracycline pharmacophore still serves a vital role in the development of tetracycline analogues. More recently, Wyeth Pharmaceuticals received approval from the FDA to market Tygacil® (tigecycline **4**) which is the 9-*t*-butylglycylamido derivative of minocycline.[34] Tigecycline specifically inhibits protein synthesis by binding to the 30S and 70S ribosome subunits, showing 5-fold and 100-fold-greater affinity than minocycline and tetracycline, respectively.[35] Erythromycin, a product of *Saccharopolyspora erythraea*, was first reported in 1949 and represents the most classical example of a macrolide antibiotic. Telithromycin **5** (Ketek™), a semi-synthetic derivative of erythromycin A, received FDA approval in 2004 and is the first ketolide antimicrobial.[36-37] Telithromycin is a very effective inhibitor of the translational function at the level of the 50S ribosomal unit and additionally, like many other carbamate keolides, is able to inhibit the formation of the 30S ribosomal unit. This dual mechanism of action may reinforce the bactericidal nature of this compound and explains its

increased activity over other members of the macrolide class.[38] Another recently approved drug related to the macrolides is daptomycin **6** (Cubicin®), a cyclic lipopeptide derived from *Streptomyces roseosporus*, that works by disrupting multiple aspects of bacterial membrane function including the disruption of membrane potential and amino acid transport, inhibition of lipoteichoic acid synthesis and inhibition of peptidoglycan synthesis.[39] Daptomycin received US approval in 2003 for use in the treatment of complicated skin and skin structure infections.[40] Figure 1.6 shows the six new natural product-derived antibacterials launched between 2000 and 2008.

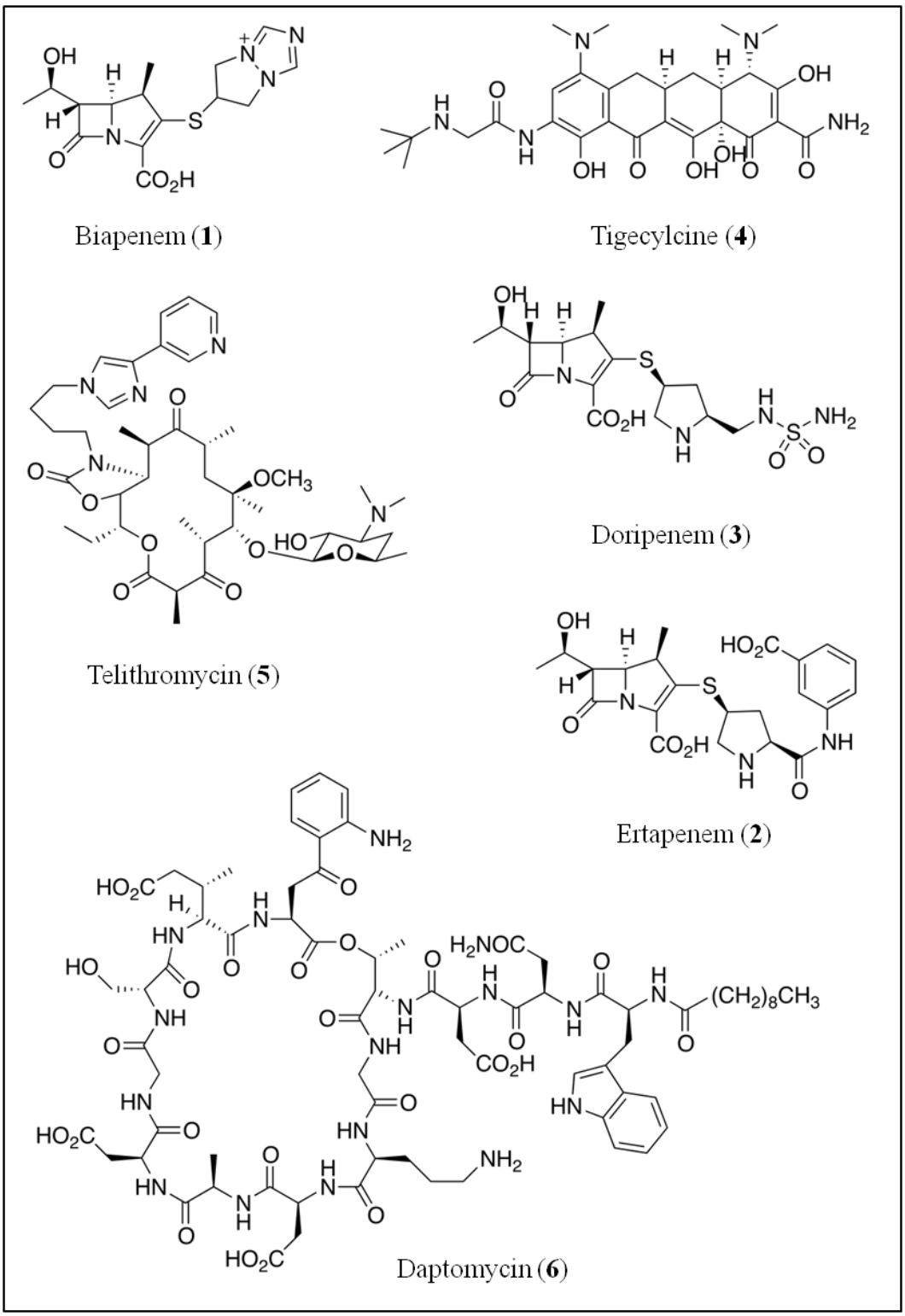


Figure 1.6. Antibacterials: Natural Product-derived drugs launched between 2000 and 2008.

Chapter 2

Understanding Methicillin-Resistant *Staphylococcus aureus*

2.1 Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus was first discovered in the late 1880's when Alexander Ogston described what he called 'staphylococcal disease' based on the organisms role in sepsis and abscess formation.[41] *S. aureus* is classified as a gram-positive cocci and is a member of the Micrococcaceae family[42] (Figure 2.1).[43] The bacteria permanently colonize the moist squamous epithelium of the nares in 20% of the population and is transiently associated with another 60%, occasionally causing infection.[44-45] Described as one of the most dangerous human bacterial pathogens, *S. aureus* causes a variety of infections and toxinoses; most commonly skin and soft tissue infections (SSTI's), bacteremia or sepsis, pneumonia, endocarditis, and osteomyelitis.

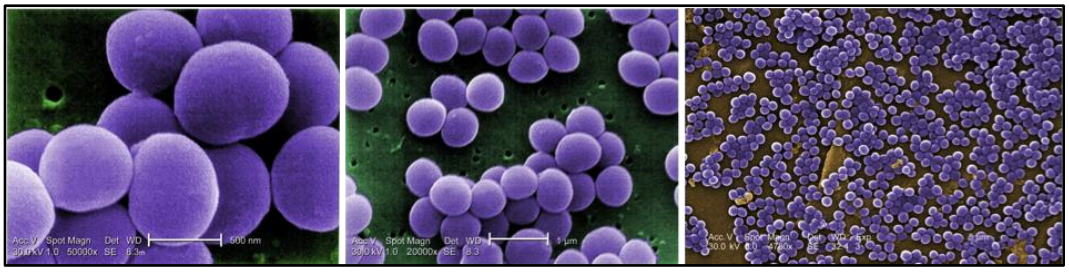


Figure 2.1. Microscopic structure of S. aureus. Courtesy of the Centers for Disease Control and Prevention (CDC). Images 11159, 11157, and 10045 respectively.

The common use of penicillin and other β-lactam antimicrobial drugs in the 1940's, although considerably improving the management of staphylococcal infections, contributed to the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA).[46] The origin of the first MRSA strain resulted from the

staphylococcal cassette chromosome *mec* (SCC*mec*), with a β-lactam resistant gene *mecA,* being integrated into the chromosome of a *S. aureus* susceptible strain.[47-48] Only a few short years after the introduction of the methicillin antibiotic, the appearance of these *S. aureus* strains, that were resistant to methicillin (Celbenin), were reported in the United Kingdom.[49] Although the United Kingdom was the first to report methicillin resistant strains in 1961, many other regions followed, including the first case of MRSA in Sydney, Australia in 1965 and the first hospital outbreak in the United States at Boston City Hospital in 1968.[50] Up until the mid-1990's our understanding of MRSA was limited mainly to information obtained from health care settings, mostly because it was rare that MRSA would infect otherwise healthy individuals. However, since then there has been an explosion in the number of infections reported in low-risk populations.

The terms healthcare associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) are typically used to describe microbiological and genetic differences as well as epidemiological, clinical, and therapeutic differences in the infections that they cause (Table 2.1).[51-52] Healthcare associated strains are generally found to be resistant to a broader spectrum of antimicrobial agents and/or classes and are often multidrug-resistant (MDR-MRSA), on the other hand CA-MRSA are resistant to a limited number of antibacterial agents, most often clindamycin and the tetracyclines.[53] Community associated strains historically have the following traits: predominantly from strain ST8:USA300 which belongs to the CC8 clonal complex of pulsed-field gel electrophoresis (PFGE) type, carry their mutant penicillin-binding protein 2a

(PBP2a) on mobile genes classified as SCC*mec* type IV, and typically possess the two genes encoding Panton-Valentine leukocidin (PVL). In comparison, HA-MRSA is typically characterized by a more heterogeneous PFGE type, carry SCC*mec* type I, II and III, and often lack PVL genes.[46,53-54] Since about 2003, the ability to differentiate between CA-MRSA and HA-MRSA strains have become increasingly more difficult. Occasionally, HA-MRSA isolates do circulate in the community and many reports have demonstrated that CA-MRSA, particularly the most dominate of strain USA300, now cause nosocomial MRSA outbreaks and infections among patients suffering from chronic illnesses.[51] In 2004-2005, CA-MRSA accounted for more than 80% of all MRSA infections; this statistic highlights the changing paradigm of MRSA as the prevalence of CA-MRSA surpasses that in the hospitals.[55]

Table 2.1. Common Characteristics of Infection Caused by MRSA[51-52]

Characteristic	HA-MRSA	CA-MRSA
Year of Discovery	1961	1980's
Population at Risk	Patients having previous hospitalizations, surgery, residence in long-term care facilities, dialysis, permanent indwelling catheters, ICU	Children, homeless, men who have sex with men, athletes, military recruits, jail inmates, native Americans, Pacific Islanders, adult emergency department patients
Main Clinical Symptoms	Bacteremia, HAP, VAP, catheter- and prosthetic-related infections	SSTI, necrotizing CAP, bacteremia, osteomyelitis
Antibiotic Resistance Profile	MDR; including β-lactams, macrolides, TMP-SMX, lincosamides, tetracyclines, rifampin, quinolones Growing resistance to glycopeptides	Resistant to β-lactams. Variable susceptibility to macrolides, TMP-SMX, tetracyclines, lincosamides
SCC*mec* type associated with strains causing infection	I, II, and III	IV and V
Expression of PVL	Rare	Common
ICU: intensive care unit; HAP: hospital-associated pneumonia; VAP: ventilator-associated pneumonia; SSTI: skin and soft tissue infection; CAP: community-associated pneumonia; MDR: multidrug resistant; TMP-SMX: trimethoprim-sulfamethoxazole; SCC*mec*: staphylococcal chromosomal cassette *mec*; PVL: Panton-Valentine leukocidin; PFGE: pulsed-field gel electrophoresis.		

2.2 Statistics on MRSA

In the United States it is estimated that each year over 1.5 million individuals acquire an infection while hospitalized, resulting in nearly 100,000 deaths. A great number of these infections are caused by antimicrobial resistant organisms, and MRSA ranks among the most prevalent pathogens in hospitals worldwide.[56] According to the CDCs Active Bacterial Core Surveillance (ABCs) Report in 2009, approximately 90,000 cases of invasive MRSA were estimated with around 14,000 mortalities reported.[57] Although the rates of infection are declining, the CDC still estimates that the number of CA-MRSA and HA-MRSA infections and mortalities in the United States in 2010 will reach 82,000 and almost 12,000 respectively, based on the most current ABCs Report (Table 2.2).[58] Although MRSA continues to be a burden both nationally and internationally, the lack of international standards makes the interpretation of data difficult and impedes on prevention efforts.[59]

Table 2.2. National Estimates and Adjusted Incidence Rates of Invasive MRSA Infections and Mortality among Cases[58]

Epidemiological Category	Estimated Cases of Infection		Estimated Rates of Mortality	
	Estimated No.	Incidence Rate (Confidence Interval)[a]	Estimated No.	Incidence Rate (Confidence Interval)[a]
CA	13,799	4.47 (4.17-4.79)	665	0.22 (0.14-0.36)
HCA	67,034	21.76 (21.08-22.46)	10,202	3.31 (3.04-3.59)
HCA-HO	15,744	5.10 (4.78-5.44)	3,507	1.14 (0.98-1.31)
HCA-HACO	51,290	16.61 (16.02-17.23)	6,695	2.17 (1.95-2.40)
Overall	82,042	26.57 (25.82-27.34)	11,478	3.737 (3.44-4.02)

[a] National estimates and Incidence (no. per 100,000 population per year) are adjusted for age, race, and gender using 2010 US Census data.
CA: community-associated; HCA: healthcare-associated; HO: hospital-onset; HACO: healthcare-associated community-onset.

2.3 Current Treatments for MRSA and Expected Need for New Antibiotics

Before the introduction of antibiotics, the mortality rate of staphylococcal bacteremia was greater than 70%, that was of course until the widespread use of penicillin decreased the rate of mortality by approximately 25%.[60] This same trend continues with the introduction of new antibiotics, initially the rate of mortality decrease, but as resistant *Staphylococcus aureus* develops the drugs become less effective and an increase in mortality is seen (Figure 2.2).[61-63] It is not surprising then that clinical isolates resistant to linezolid (ZYVOX®), one of the newest antibiotics used to treat MRSA, have already been reported.[64] This evolution shines a light on the impact of staphylococcal resistance in the past 60 years and highlights the continued need for the development of novel antibiotics.

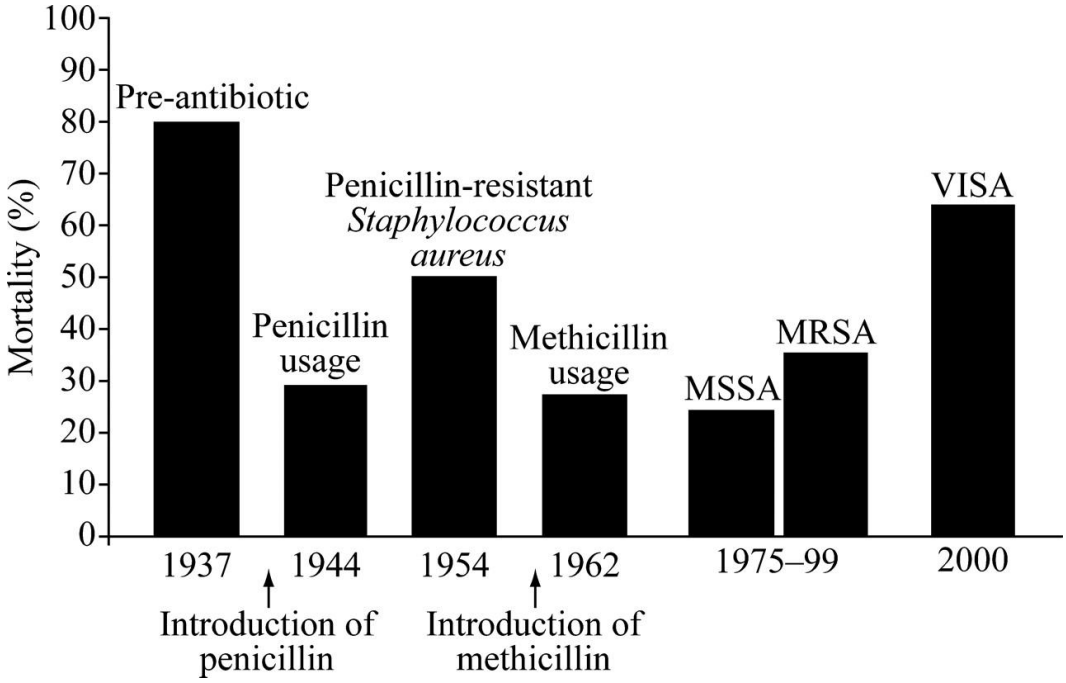


Figure 2.2. Mortality rate of staphylococcal bacteremia over time. MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*; VISA: vacomycin-intermediate *S. aureus*. Image reproduced with permission from Oxford Journals, United Kingdom.[61-63]

Vancomycin

Vancomycin is a glycopeptides antibiotic isolated in 1956 by scientists at Eli Lilly[65] from the fermentation broth of the actinomycete *Amycolatopis orientalis*, formally *Streptomyces orientalis*[66] (Figure 2.3). It is active against Gram-positive cocci, particularly streptococci, staphylococci, and pneumococci and its mode of action is inhibition of cell wall synthesis.[67] The rather large vancomycin molecule inhibits cell wall synthesis by interfering with the synthesis of the peptidoglycan of bacterial cell walls.[68] Vancomycin received FDA approval in 1958 but its clinical uses were overshadowed by the introductions of methicillin, cephalosporins, and linomycins which had wider clinical acceptance. Vancomycin was not commonly used until the 1980's after its purity was improved, which alleviated many unwanted side-effects, and drug resistance to other antibacterial agents increased.[69]

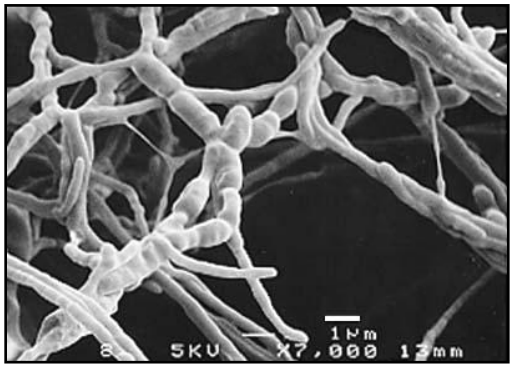


Figure 2.3. *Amycolatopsis orientalis*. Image reproduced with permission from the Digital Atlas of Actinomycetes, contributor of this image Y. Gyobu.

What is extremely unique about vancomycin is that, unlike any of the other antistaphylococcal antimicrobials, resistance to this agent among *S. aureus* strains was very slow. Although the emergence of resistance was predicted, as

high levels of resistance to vancomycin in enterococci (VRE) were seen in the late 1980's, it took almost 40 years to isolate MRSA with reduced susceptibility to vancomycin.[70] In January 1996, a clinical strain of MRSA labeled Mu3 (heterogeneously vancomycin-resistant *S. aureus*) was isolated and 6 months later another strain designated Mu50 (vancomycin-resistant *S. aureus*) was isolated from a pediatric patient in Japan.[71-72] Despite the evolution of vancomycin resistant *S. aureus*, it has been the mainstay for methicillin-resistant isolates and remains the drug of choice in severe infections that require intravenous antibiotics. Additionally, vancomycin (Figure 2.4) is typically used to treat staphylococcal infections caused by bacteremia, endocarditis, pneumonia, cellulitis, and osteomyelitis.[73-74] Patients unable to tolerate vancomycin have been treated with fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, or minocycline, as these drugs have shown efficacy in cases that require bactericidal therapy.[42]

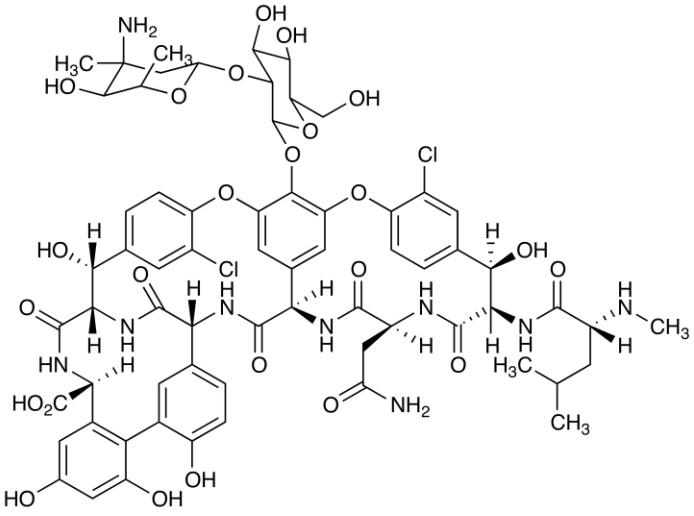


Figure 2.4. Chemical Structure of Vancomycin

Clindamycin

Clindamycin (Figure 2.5) is approved by the FDA for the treatment of serious infections caused by *S. aureus*, although not specifically for the treatment of MRSA. However, it has become widely used for the treatment of SSTI's, bone and joint infections, and has been successfully used for CA-MRSA infections in children.[75] Clindamycin, much like macrolides and other lincosamides, binds to the 50S ribosomal subunit which in turn disrupts protein synthesis by interfering with the transpeptidation reaction.[76] Its action may be bacteriostatic or bactericidal depending on various factors, including drug concentration, bacterial species, and inoculum.[77] Evidence of the efficacy of clindamycin as the sole agent against MRSA strains with macrolide resistance has been shown in the United Kingdom, however the risk of emergence of resistance is still warranted, as 80% of CA-MRSA strains are reported to be susceptible.[73,78] Just recently, high frequencies of clindamycin resistance in MRSA were reported among the predominate USA300 strain in Boston, Massachusetts.[79]

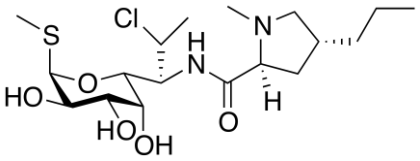


Figure 2.5. Chemical Structure of Clindamycin

Rifampicin

Rifampicin (known as rifampin in the United States) is a semisynthetic compound derived from *Amycolatopsis mediterranei*[80] and has bactericidal activity against *S. aureus*.[75] The high level of antibacterial activity of rifampicin is based on a specific and unique mechanism of action, the inhibition of DNA-dependant RNA polymerase to prevent chain elongation.[81] Rifampicin indications include bone and joint infections, SSTI's, eradication therapy, and adjunct treatment of prosthetic infections.[78,82] Rifampicin (Figure 2.7) has good activity against CA-MRSA but should not be used as a monotherapy because of the rapid development of resistance, even during single drug administration.

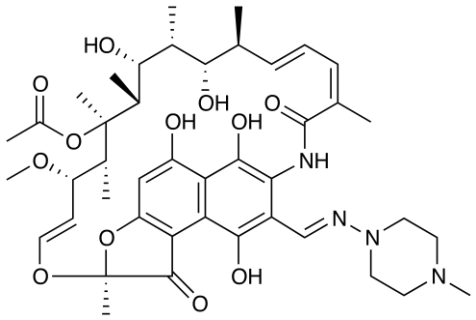


Figure 2.6. Chemical Structure of Rifampicin

Tetracyclines: Doxycycline, Minocycline, Tigecycline

The tetracycline family of antibiotics have historically maintained activity against a wide spectrum of bacteria, however, because of widespread use resistance to this class of antibiotics is now extensive.[83] The tetracyclines specifically inhibit bacterial protein synthesis by preventing the binding of aminoacyl tRNA to the ribosomal acceptor (A) site.[84] The FDA has approved the use of doxycycline (Figure 2.9) for the treatment of SSTI's caused by *S. aureus*,

although not specifically those due to MRSA infections. In cases of doxycycline resistance, minocycline (Figure 2.9) represents an alternative that is available orally. Tigecycline (Tygacil™), a glycylcycline and derivative of the tetracyclines, received FDA approval for the treatment of SSTI's and intrabdominal infection in 2004.[75] Its activity against MRSA is superior to older agents, in addition tigecycline possess a modest Gram-negative spectrum of activity. As mentioned in the previously, tigecycline inhibits protein synthesis by binding to both the 30S and 70S ribosomal subunits, showing a 5-fold-greater affinity than minocycline.[35] Tigecycline (Figure 2.9) has also shown efficacy in infections caused by glycopeptide/vancomycin-intermediate (G/VISA) *S. aureus*.[83] All the tetracycline antibiotics are contradicted in children younger than 8.[43]

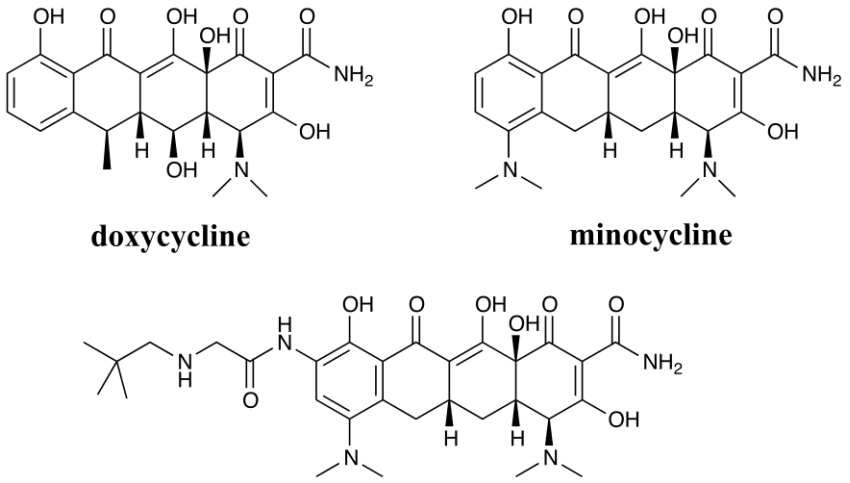


Figure 2.7. Chemical Structures of the Tetracyclines

Linezolid

The discovery of linezolid (ZYVOX®) is a unique story, mainly because it is a representative of the first new structural class of antibacterial agents in over 35 years, the oxazolidinones. Prior to the discovery of this novel class the vast majority of antibiotics were either natural products or chemically modified derivatives of known scaffolds. In 1987, information out of DuPont revealed that a number of oxazolidinone compounds showed potent inhibition of Gram-positive bacteria, including MRSA, and most importantly their activity was not affected by any known antibiotic resistance mechanism.[85] Two new agents, DuP 721 (Figure 2.10) and DuP 105, were identified by DuPont as potential leads, however, the group discontinued the oxazolidinone program, presumably because of toxicology findings. Dr. Steven Brickner at the Upjohn Company, in Kalamazoo, Michigan, recognized the potential of this class and set a goal of identifying potent, yet safer oxazolidinones. Thousands of analogs were synthesized with the aim of identifying the best compound that had both potent *in vivo* and *in vitro* antibacterial activity, high water solubility, and a good safety profile.[86] This work lead to the discovery of linezolid, which was approved by the FDA in 2000 for adults and children for the treatment of SSTI's and nosocomial pneumonia due to MRSA.[75] Oxazolidinones disrupt bacterial growth by binding to the 50S subunit of the bacterial ribosome, preventing it from complexing with the 30S subunit, mRNA, initiation factors and formylmethionyl-tRNA. The overall result is the inability of the prokaryote to assemble a functional initiation complex for protein synthesis, preventing the translation of the mRNA. This site of inhibition occurs

earlier in the initiation process than other protein synthesis inhibitors, which either block polypeptide extension or cause misreading of the mRNA.[87] Linezolid (Figure 2.10) represents the first and only pharmacologically active oxazolidinone in clinical use, is the only FDA approved oral medication for MRSA skin infections, and is considered to be one of the last lines of defense against MRSA. Linezolid has become recognized as an important alternative for infections caused by multidrug-resistant (MDR) pathogens, and its use continues to increase globally.[88] Not surprisingly though, the first reports of resistant bacterial strains to linezolid started to appear shortly after its clinical introduction.[64] Although the number of resistant strains remains low, there are nonetheless reports of linezolid resistance involving a variety of clinical settings.[89]

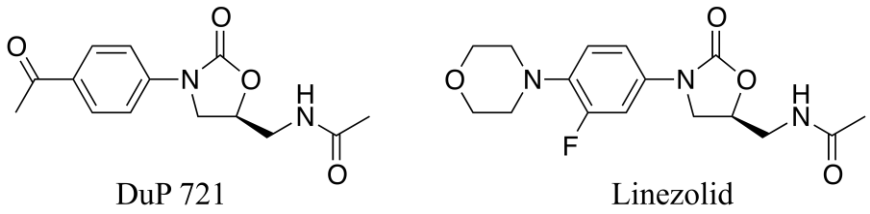


Figure 2.8. Chemical Structures of DuP 721 and Linezolid (ZYVOX®)

Daptomycin

Much like linezolid, daptomycin represents the first antibacterial agent in a new class of antibiotics known as lipopeptides. Initially developed by Eli Lilly in the early 1980's, but not FDA approved until 2003 after being purchased by Cubist Pharmaceuticals[90], daptomycin is a naturally occurring cyclic lipopeptide that is a fermentation byproduct of *Streptomyces roseosporus*.[74] The FDA originally approved daptomycin for the treatment of complicated skin and skin-structure infections (cSSSI's), three years later in 2006, it gained additional

approval for the treatment of blood stream infections and endocarditis caused by methicillin-sensitive *S. aureus* (MSSA) and MRSA.[91] The primary mechanism of action involves the disruption of bacterial membrane function.[92] The mechanism is distinct from previous classes of antibiotics that inhibit bacterial cell wall biosynthesis, bacterial DNA replication, and folate coenzyme biosynthesis. Daptomycin (Figure 2.11) should not be used for the treatment of respiratory infections such as Community-acquired pneumonia (CAP) because its activity is inhibited by pulmonary surfactant.[75,78, 91] Resistance in MRSA has rarely been reported, however it should be noted that many of the systems used for reporting resistance have yet to incorporate daptomycin into standard panels.[74]

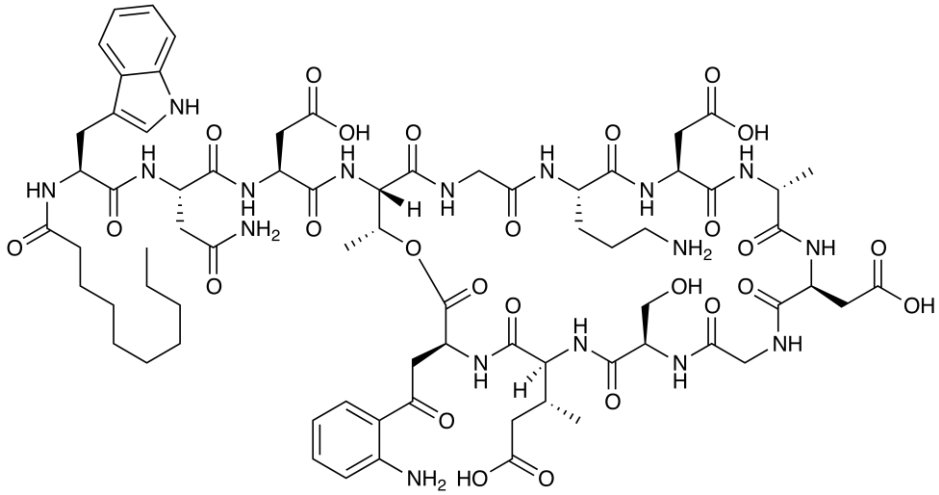


Figure 2.9. Chemical Structure of Daptomycin

Telavancin

Telavancin (Figure 2.12) is a bactericidal lipoglycopeptide and a semisynthetic derivative of vancomycin, related both structurally and mechanistically.[74] It possess a dual mechanism of action, inhibiting peptidoglycan synthesis by binding to D-Ala-D-Ala-containing residues of peptidoglycan intermediates and also causing membrane depolarization.[93] Telavancin, approved in 2009, represents the newest FDA-approved antimicrobial agent for SSTI's in adults. It exhibits superior *in vitro* activity compared to vancomycin, including rapid bactericidal activity against glycopeptide-susceptible organisms as well as glycopeptide-intermediate susceptible and vancomycin-resistant *S. aureus*.[94] Telavancin has a longer half-life than vancomycin which allows for daily infusions and simplifies the intravenous regimen for those patients who are being discharged or receive long-term outpatient therapy.[74]

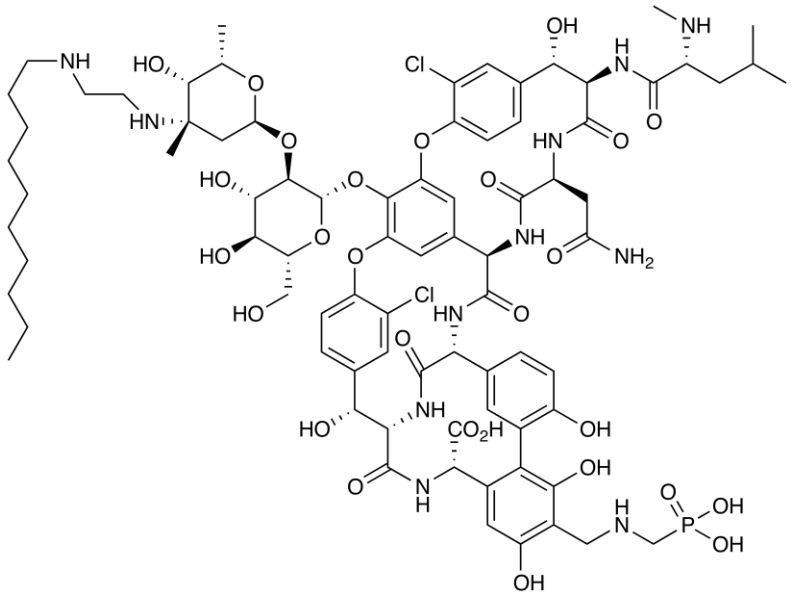


Figure 2.10. Chemical Structure of Telavancin

Despite our best efforts, and the introduction of numerous antibiotics to treat MRSA infections over the last nine decades (Figure 2.11), none of these drugs fully addresses the problem of antibiotic resistance.[82] As the inevitable development of resistant bacteria erodes the utility of today's antibiotics, scientists are left with the unending task of discovering and developing novel antibiotics, in particular those with new mechanisms of action.

Figure 2.11. The Introduction of New Antibiotic Classes and the Emergence of Resistance (1925-2010).

Chapter 3

Polyalthenol

3.1 Discovery, Structure and Biological Activity

The genus *Polyalthia* (Annonaceae) encompasses a variety of species, including *Polyalthia suaveolens* and *Polyalthia oliveri* (Figure 3.1)[95-96], which are known to contain compounds with medicinal properties. *P. suaveolens* is a small tree from the tropical forest zone of West Africa and decoctions of its bark have been used in the treatment of blackwater fever and stomach disorders.[97] Additionally, the triterpene polycarpol from *P. suaveolens* has shown inhibitory activities on the vitality of adult male worms of *Onchocerca gutturosa* and is considered a promising naturally occurring filaricide.[98] In earlier papers it was reported that both polycarpol and polyalthenol were found in *P. oliveri,*[97,99] however it is believed that polycarpol is present in both *P. suaveolens* and *P. oliveri*. Yet another species, *Polyalthia lateriflora* is used as an antibacterial in Malaysia.[100]

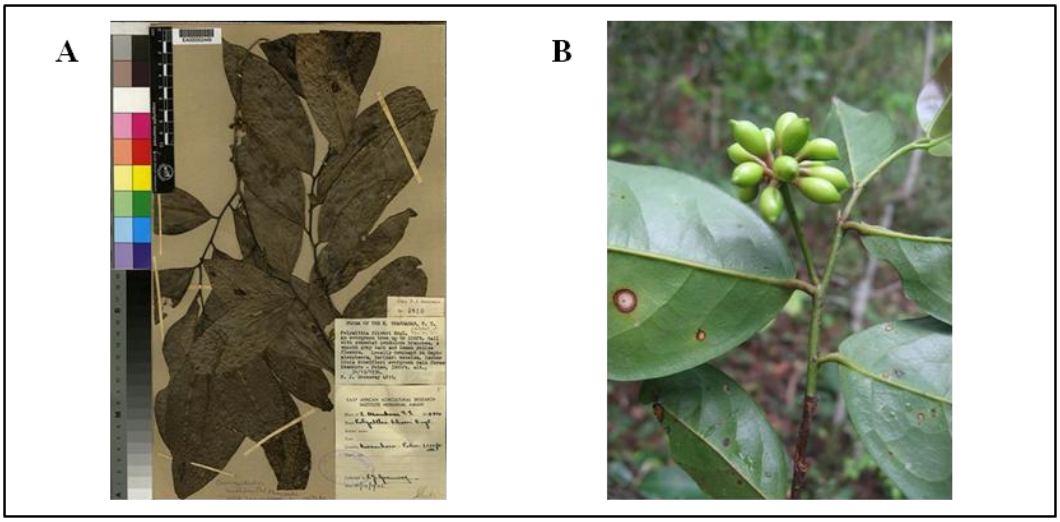


Figure 3.1. (A) Polyalthia oliveri Engl. (B) African Annonaceae Polyalthia

The genus *Greenwayodendron* has been split off from the genus *Polyalthi*a[101] and there are now two species of *Greenwayodendron* (*G. oliveri* and *G. suaveolens*), both of which are commonly found in tropical Africa.[102-103] Both *Polyalthia* and *Greenwayodendron* are known to possess indole sesquiterpenes, however in contrast to *Polyalthia*, *Greenwayodendron* has not been widely studied.[104] The indole sesquiterpene alkaloid, polyalthenol, from the roots of the West-African plant *Greenwayodendron* (*Polyalthia*) *oliveri* was first reported in 1976.[105] The majority of indole sesquiterpenes, such as polyalthenol **1**, have been reported from plants and indole diterpenes, such as paxilline, have been reported from fungi. Recently the first indole sesquiterpenes, oridamycin A and oridamycin B, have been isolated from bacteria. These novel indole sesquiterpenes are the first described from a prokaryotic source.[106]

Leboeuf et al. was able to utilize ^{1}H-NMR and ^{13}C-NMR to confirm the gross structure of polyalthenol which allowed for the determination of the relative stereochemistry.[105] However, because the structural assignment was based on biogenetic grounds, specifically by analogy to a known sesquiterpene skeleton, there remained twenty-two possible structures not excluded using the data presented by LeBoeuf et al.[107] Of these possible structures, another eleven were deemed unlikely due to bicyclic ring systems with an exocyclic double bond and bicyclic ring systems bearing a double bond at a bridgehead. The latter is energetically less favorable because it violates Bredt's Rule.[108] The relative configuration outlined in 2010 by Williams et al. shows the close relationship between the structure of polyalthenol **1** and another indole sesquiterpene

pentacyclindole **2**, the latter most likely being the result of cyclization of C-2 and C-17 of polyalthenol (Figure 3.2).[109]

Despite a known relative structure for almost four decades, the biological activity of polyalthenol **1** and a group of structurally related indole sesquiterpene alkaloids from the genus *Greenwayodendron* was not investigated until 2010, even though the total synthesis and establishment of absolute configuration of at least one of the related compounds, suaveolindole **3**, had already been reported.[110]

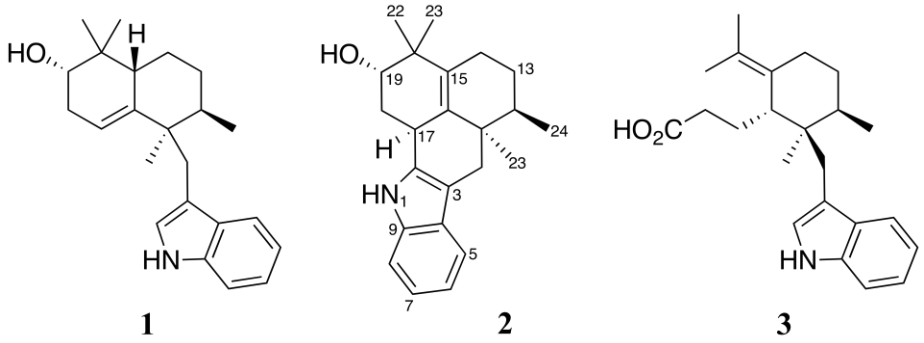


Figure 3.2. Structures of Polyalthenol, Pentacyclindole, and Suaveolindole.

The biological activity of suaveolindole was reported by Yoo et al. in 2005, and the natural product shows a minimum inhibitory concentration (MIC) of 8 µg/mL for staphylococcus aureus, stain ATTC 6538P, and MRSA strain ATTC 33591.[104] The biologically activity of pentacyclindole **2** is similar to suaveolindole, however, polyalthenol **1** shows superior antibacterial activity against a variety of MRSA stains (Table 3.1). Additionally, polyalthenol **1** and pentacyclindole **2** showed good inhibitory activity, both compounds possessing MICs of 4 µg/mL, against MSSA strain ATCC 25923.[98]

Table 3.1. MIC of Polyalthenol Determined against Clinical Isolates of *Staphylococcus aureus*[98]

	Virulence gene expression				MIC (μg/mL)	
isolate	PVL	ACME	bsa	Agr	**1**	**2**
cutaneous						
MRSA-105	+	+	B +	1	1	8
MRSA-106	+	+	B +	1	2	8
MRSA-107	+	+	B +	1	1	8
MRSA-108	+	-	A +	1	2	8
MRSA-109	+	-	B +	1	1	8
MRSA-111	+	+	B +	1	2	8
MRSA-148	+	+	B +	1	2	8
MRSA-158	+	+	B +	1	4	8
MRSA-175	+	-	B +	1	4	8
MRSA-295	-	-	B +	1	4	NT[a]
invasive						
MRSA-186	+	-	A +	1	4	8
MRSA-194	+	+	B +	1	2	NT[a]

[a] Not tested due to insufficient material.

3.2 Natural Products with Unique Frameworks

Since its inception in the early 1990's high-throughput screening (HTS) has dominated lead discovery in pharmaceutical research and chemical biology. These screens have proven beneficial with regards to traditional drug targets such as ligand-gated ion channels and kinases, however, screening libraries of synthetic molecules have been problematic for antimicrobial targets.[110] One unintended consequence of this type of screening is a growing bias towards already known scaffolds. Additionally, synthetic organic chemists continue to alter known scaffolds or natural product frameworks, trying to improve the pharmacokinetic properties of established drugs. This bias towards the use of known structures is one explanation for the lack of diversity among organic compounds. A recent quantitative examination of the CAS registry showed that only 143 frameworks accounted for 50% of the over 24 million cyclic organic compounds.[111] This lack

of structural diversity creates vast opportunities for synthetic organic chemists to expand around neglected and novel frameworks to identify lead compounds.

One of the promising aspects of polyalthenol **1**, as well as the other natural products isolated from *Greenwayodendron*, is its unique framework. Based on the ^{1}H-NMR data, polyalthenol **1** appears to be structurally related to pentacyclindole **2**. A SubScape analysis of the pentacyclindole **2** framework indicates that there are only 213 compounds with the same framework at the graph level, indicated by connectivity, but only 7 at the node level, indicated by connectivity and heteroframework (Figure 3.3).[109] Of the 213 compounds with the same graph framework, only 2 of them appear to be natural products[112] and only 12 were listed as being bioactive in SubScape. Given the close structural relationship between polylathenol **1** and pentacyclindole **2**, and the limited number of similar structures, these molecules present a potential new scaffold for diversity directed at organic synthesis. In addition to the total synthesis of polyalthenol **1**, the identification of a novel scaffold will contribute to our body of knowledge in the field of synthetic organic chemistry.

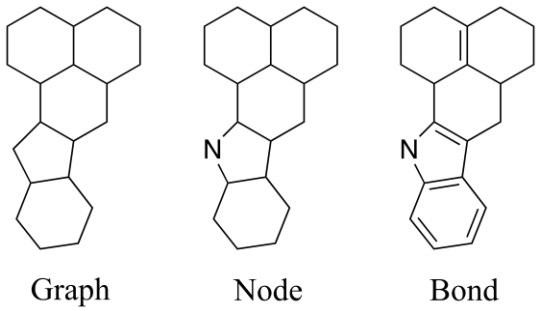


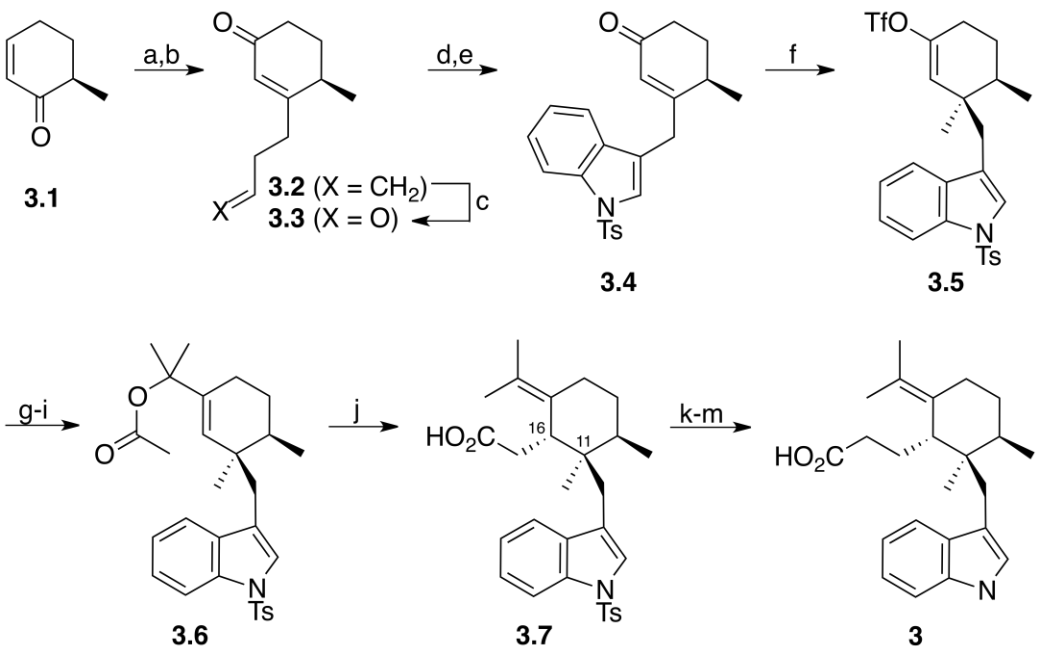
Figure 3.3. SubScape frameworks for pentacyclindole at graph, node, and bond levels.[109]

3.3 Closely Related Natural Products

Suaveolindole

The original synthetic strategy towards suaveolindole involved an intramolecular Heck reaction followed by a cross-coupling with a protected indole. This route, however, proved not to be viable partially because of difficulties introducing the isopropylidene group. The heart of the new plan centered on the stereoconnectivity of $C_{11} - C_{16}$ and acquiring the proper relative stereochemistry. Formation of the indole was accomplished by ozonolysis of the terminal olefin and subsequent annulation of the aldehyde with 2-iodoaniline. All-carbon quaternary stereocenters were efficiently installed through conjugate addition of lithium dimethyl cuprate to the enone. The carbon framework for the isopropylidene group, which had previously eluded the group, was installed through carbomethoxylation of the enol triflate species. Treatment of the allylic acetate with LiHMDS/TMSCl provided the desired rearrangement and highlights an unprecedented use of the Ireland-Claisen reaction. The resulting carboxylic acid was homologated and the protecting group removed to afford synthetic (+)-suaveolindole (Scheme 3.1).[113]

Scheme 3.1.[a] Total Synthesis of Suaveolindole



[a]Reagents and conditions: (a) 4-bromo-1-butene, Mg, THF; (b) PCC, DCM, (47% from **12**); (c) O_3, MeOH, Me_2S, (88%); (d) 2-iodoaniline, $Pd(OAc)_2$ (5 mole %), DABCO, DMF, (68%); (e) TsCl, TBAB, aq. NaOH/benzene, (91%); (f) i) CuI, MeLi; ii) $PhNTf_2$, Et_2O/THF; (g) CO, $Pd(PPh_3)_4$, *i*-Pr_2EtN, MeOH/DMF, (45% from **15**); (h) MeLi, Et_2O, (84%); (i) Ac_2O, *i*-Pr_2EtN, DMAP, DCM, (83%); (j) LiHMDS, TMSCl, THF, -78ºC, (56%); (k) i) oxalyl chloride, DMF (cat.), DCM; ii) CH_2N_2, *i*-Pr_2EtN, THF, (62%); (l) CF_3CO_2Ag, Et_3N, THF/H_2O, (74%); (m) naphthalene, Na, DMF, (94%).

Chapter 4

Towards the Synthesis of Polyalthenol

4.1 Introduction

As discussed in previous chapters natural products have in the past and continue to have an influence on the pharmaceutical industry, providing sources of new chemical diversity. Historically, plants have provided us with a variety anti-infective agents as well as a number of important antibacterial agents such as the alkaloids quinine, emetine and berberine.[114] In light of this information, along with the growing concern over MRSA infections, it is of no surprise that scientists continue to look at natural product sources as new leads for antibacterials. A number of compounds isolated from the roots of *Greenwayodendron suaveolens* demonstrate activity against clinical isolates of MRSA. One of the most promising of these compounds, polyalthenol, shows good inhibitory activity exhibiting a MIC_{90} value of 4 μg/mL.[109]

Completing a total synthesis of polyalthenol will be significant given the continual need for new antibiotics to treat MRSA and the encouraging preliminary data on the biological activity of this natural product. The retrosynthetic analysis (Figure 4.1) of polyalthenol **1** is envisioned to establish ketone **4** as the initial target structure, with the insertion of the methyl groups by first, an asymmetric conjugate addition followed by a *trans* addition, to enone **5**. Enone **5** can be prepared using known chemistry outlined by Baraldi et al.[3] and further analysis of **5** yields the commercially available starting materials cyclohexenone **6** and 1*H*-indole-3-carboxaldehyde **7**.

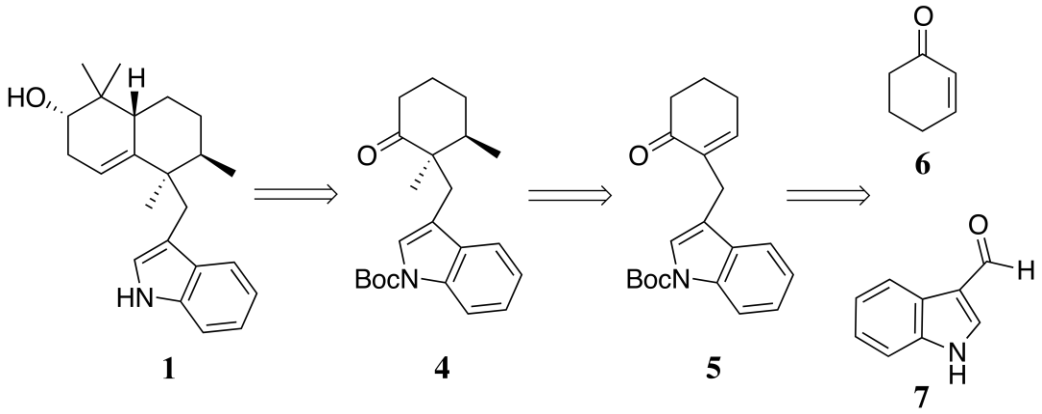


Figure 4.1. Retrosynthesis of Polyalthenol

4.2 Results and Discussion

The initials steps in the synthesis involve the formation of the two subunits, bicyclic ketone **8** and indole bromide **11**, necessary for the coupling reaction and subsequent alkylation (Figure 4.2).

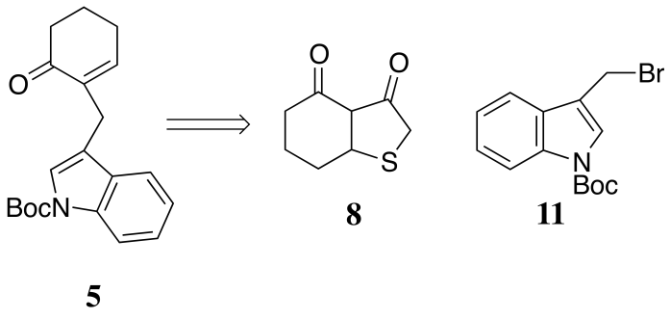
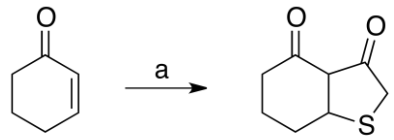


Figure 4.2. Retrosynthesis of Alkylation Reaction

The first ring of the indole sesquiterpene alkaloid, polyalthenol **1**, came from the commercially available starting material cyclohexenone **6**. Sodium methoxide was generated *in situ* and provide the base necessary for the base-catalyzed addition of methyl thioglycolate to cyclohexenone **6 (**Scheme 4.1). The initial product of the Michael addition is the enolate anion which undergoes a spontaneous cyclization with loss of methoxide to afford the bicyclic ketone **8**.

Known spectroscopic data indicates that the bicyclic ketone **8** is highly enolized in $CDCl_3$ and is best represented as the equilibrium mixture of keto-enol tautomers.[116] The present ^{1}H-NMR data indicates the presence of the enolized structures (Appendix A). The 47 % yield of the bicyclic ketone **8** was comparable to previously reported yields for this reaction.

Scheme 4.1.[a] Synthesis of Bicyclic Ketone



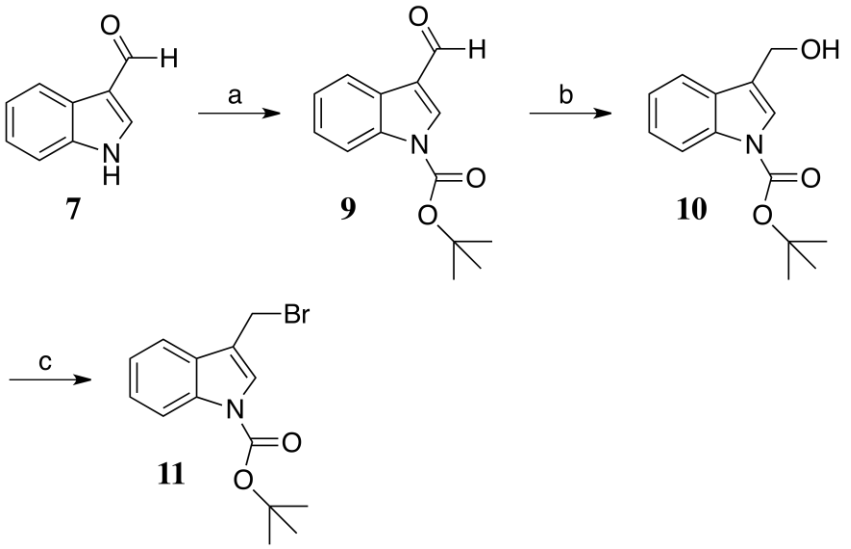
6 **8**

[a]Reagents and conditions: (a) $HSCH_2CO_2CH_3$, $NaOCH_3$, MeOH, reflux, 47%

The synthesis proceeded in order to obtain the second subunit, indole bromide **11**, necessary for the coupling alkylation reaction (Scheme 4.2). The nitrogen of commercially available starting material 1*H*-indole-3-carboxaldehyde **7** was Boc protected using Boc anyhydride in benzene-water and tetrabutylammonium iodide as a phase transfer catalyst. The 90 % yield of the crude Boc protected indole aldehyde **9** was higher than previously reported yields for this reaction[117] because of the omission of purification prior to moving forward with the synthesis. Tetrabutylammonium iodide was used in place of the prescribed tetrabutylammonium bromide because it was on hand. The crude Boc protected indole aldehyde **9** was reduced using sodium borohydride in ethanol to afford Boc protected indole alcohol **10**. This reaction proceeds rather quickly and was monitored by Thin Layer Chromatography (TLC). At the completion of the reaction, determined by TLC, hydrogen gas was still being liberated and therefore

it was necessary to quench any unreacted sodium borohydride with 1.0*M* NaOH. The final reaction to complete the alkylation coupling partner is the conversion of the hydroxyl group to a bromide. This reaction was initially attempted using N-bromosuccinimide (NBS) as the source of bromide; however, the literature procedure[118] required stirring at -40 ºC for 12 h and satisfactory yields were not accomplished even after the addition of higher equivalences of both NBS and triphenyl phosphine (PPh_3). Using carbon tetrabromide (CBr_4) as the bromide source allowed the reaction to proceed much faster with higher yields and at room temperature (RT). The Appel reaction proceeds by activation of PPh_3 with CBr_4 to form the phosphonium salt, followed by attack of the alcohol oxygen at phosphorus which displaces the bromide ion.[119] Additionally, deprotonation of the alcohol can occur, forming bromoform, and this may facilitate the attack at the phosphorus. The oxygen is transformed into a good leaving group and an S_N2 displacement by the bromide takes place. The resulting indole bromide **11** was rapidly filtered through silica powder to minimize decomposition on silica gel and to remove any triphenylphosphine oxide from the reaction. The overall yield for the three steps was 65%.

Scheme 4.2.[a] Synthesis of Boc Protected Indole Bromide



[a]Reagents and conditions: (a) NaOH, Boc_2O, NBu_4^+ Γ, benzene, H_2O, 90%; (b) $NaBH_4$, EtOH, 99%; (c) CBr_4, PPh_3, CH_2Cl_2, 73%

The enone **5** that is required for the alkylation reaction is prepared by treating the bicyclic ketone **8** with potassium carbonate (K_2CO_3), followed by addition of the indole bromide **11** (Scheme 4.3). The alkylation reaction with the reactive indole bromide **11** proceeded smoothly in the presence of the anhydrous K_2CO_3 in refluxing acetone to afford the alkylated intermediate **12** with a crude yield of 89%. The conditions for the retro-Dieckmann (Figure 4.3) reaction proved to be more difficult.

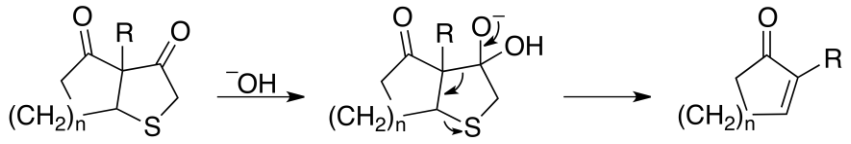
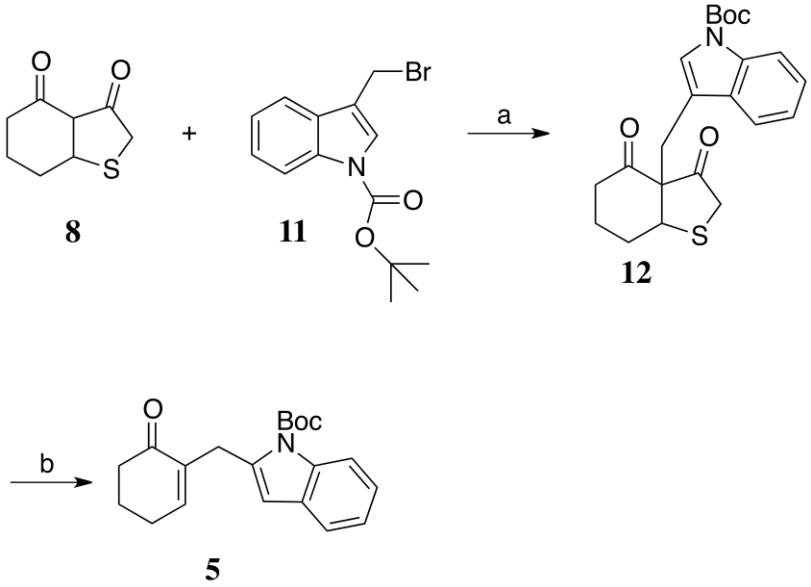


Figure 4.3. Retro-Dieckmann Reaction

Originally the reaction was carried out using 5% aqueous sodium hydroxide in a two phase, water/diethyl ether, as outlined by Baraldi et al.[115] However, the reaction did not proceed to completion and provided very little yield, therefore a variety of conditions were evaluated to determine the highest yield procedure. Initially lithium chloride was added to the reaction mixture in order to generate lithium hydroxide *in situ*, which was not immediately available. It was determined that the reaction proceeds faster, and with higher yield when lithium hydroxide is substituted for sodium hydroxide. This can be explained by the enhanced solvation of the lithium ions in a protic solvent, which is most likely due to the ease of hydrogen bonding with the smaller lithium atoms.[120] After determining the increased rate with lithium hydroxide it was necessary to run the reaction in a more polar protic solvent system such as methanol:water. The alkylated intermediate **12** is only partially soluble in the methanol:water solution, so in order to completely solublize the intermediate, ethyl acetate was added to the reaction mixture. The retro-Dieckmann reaction in the presence of lithium hydroxide in MeOH:H_2O yielded the enone **5** with 34% overall yield.

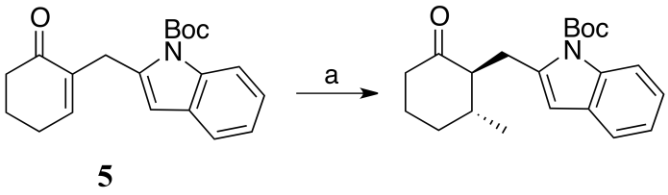
Scheme 4.3.[a] Synthesis of Enone



[a]Reagents and conditions: (a) K_2CO_3, acetone, reflux; (b) LiOH, MeOH, EtOAc, 34%

The asymmetric conjugate addition (A.C.A.) was initially attempted using a chiral ferrocenyl diphosphine catalyst (CFDC) as outlined by Feringa et al.[121] in the presence of copper chloride and the Grignard reagent methyl magnesium bromide (Scheme 4.4). However the results yielded only starting material. After the initial attempts at the enantioselective synthesis were unsuccessful the decision was made to proceed through with the racemic synthesis.

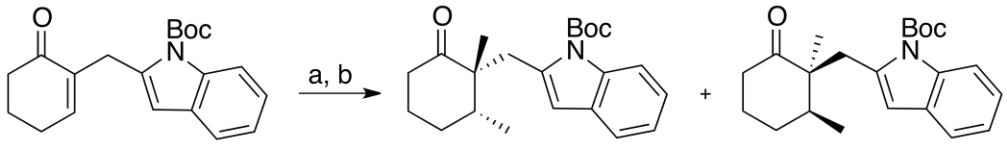
Scheme 4.4.[a] Attempted Asymmetric Conjugate Addition



[a]Reagents and conditions: (a) CuCl, CFDC, Et_2O, 0.5h, 0ºC

The racemic synthesis of ketone **4a** and **4b** are generated by addition of lithium dimethylcuprate prepared from copper iodide and methyl lithium *in situ* (Scheme 4.5). This procedure circumvents the known problems associated with polyalkylation when using Grignard reagents. Additionally, this reaction takes advantage of the higher stereoselectivity and higher yields of 1,4-addition products versus addition to the carbonyl (1,2-addition) formed with organocopper reagents.[122] The second methyl group was installed under normal alkylating conditions; methyl iodide, diethyl ether, 25ºC, in the presence of lithium chloride. Lithium chloride was initially used as a substitute for hexamethylphosphoric triamide (HMPA), which is a well-known solvent additive used to coordinate the lithium and accelerate the alkylation reaction.[123] The presence of lithium chloride has been shown to accelerate the rate of enolate alkylation reactions in a highly diastereoselective manner.[124-125] Eventually 1-methyl-2-pyrrolidone (NMP) was substituted due to the known toxicity of HMPA. The reaction was very low yielding, 20% over two steps, and further work is required to improve on this.

Scheme 4.5.[a] Synthesis of Ketone

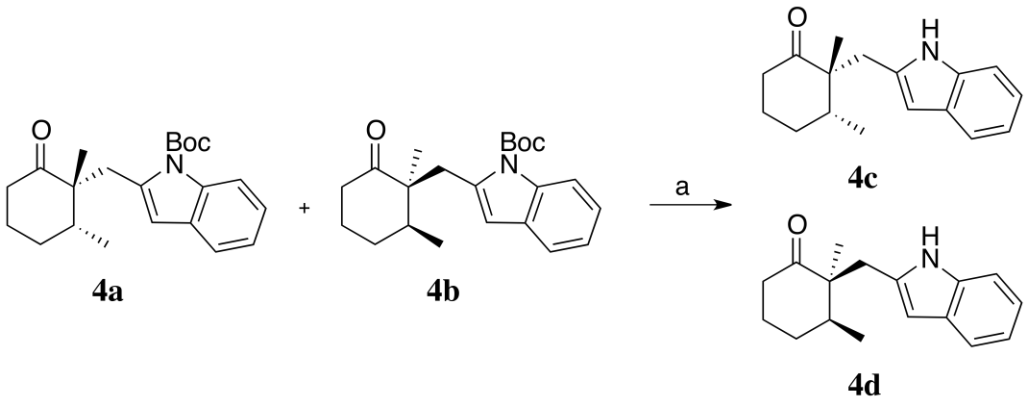


5 **4a** **4b**

[a]Reagents and conditions: (a) CuI, MeLi, Et_2O, 0ºC, 1h; (b) NMP, MeI, RT, 3h, 20%

The Boc protecting group was removed from the mixture of diastereomers **4a-4b** to afford compounds **4c-4d** (Scheme 4.6), which were subsequently sent to Arizona State University's Biodesign Institute, Tempe, AZ, for biological testing under the direction of Dr. Shelley Haydel. Unfortunately the compounds were not active, leading to the conclusion that the fourth ring of polyalthenol **1** is required for biological activity.

Scheme 4.6.[a] Boc Deprotection

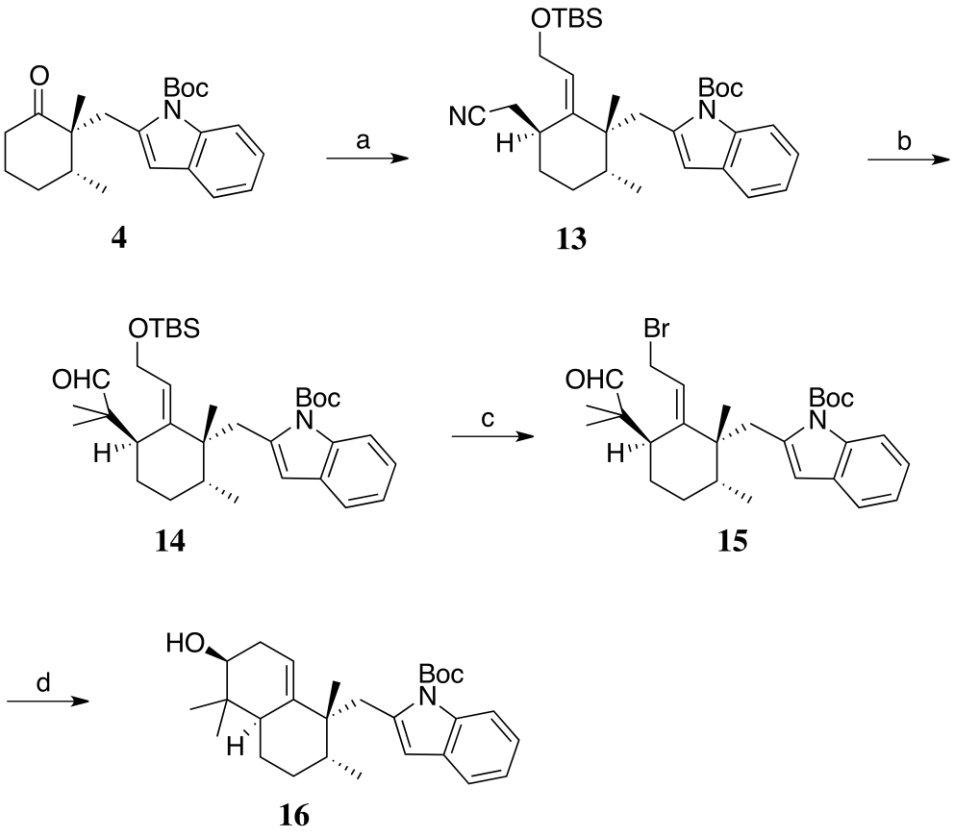


[a]Reagents and conditions: (a) TFA, CH_2Cl_2

Initially it was proposed to complete the synthesis of polyalthenol **1** as outlined in Scheme 4.7. The introduction of the carbon chain required for the subsequent cyclization would be accomplished by treating ketone **4** with bromoacetonitrile. The resulting ketone will then be treated with the stabilized ylide to afford the α,β-unsaturated ester which can be selectively reduced in the presence of nitrile with lithium N,N-dimethylaminoborohydride. The protection of the allylic alcohol can be accomplished with a *tert*-butyl dimethyl silyl group (TBS) to give the nitrile **13**. The geminal dimethyl group can then be installed by treatment of the nitrile **13** with sodium hydride or lithium diisopropylamine

(LDA) and excess methyl iodide. The conversion of the nitrile to aldehyde **14** can then be accomplished using diisobutyl aluminum hydride (DIBAL). In order to complete the intramolecular cyclization the silyl ether protecting group can be converted to the allyl bromide **15** by action of fluoride ion then triphenylphosphine and carbon tetrabromide. The initial proposal planned to use indium in order to catalyze the cyclization and afford the Boc protected polyalthenol **16**, which can be deprotected with trifluoroacetic acid to complete the synthesis of the natural product.

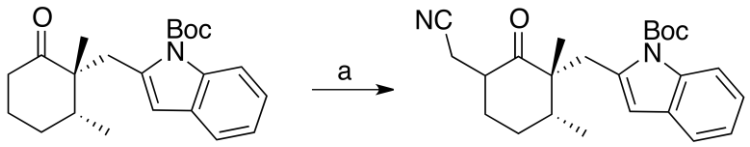
Scheme 4.7.[a] Initial Proposed Completion of the Synthesis of Polyalthenol



[a]Reagents and conditions: (a) i) LDA trap with $BrCH_2CN$, ii) $Ph_3PCHCO_2CH_3$, iii) $LiMe_2NBH_3$, iv) TBS-Cl; (b) i) NaH, MeI, ii) DIBAL; (c) i) F^-, ii) PPh_3, CBr_4; (d) metal catalyst

As outlined in scheme 4.7, the carbon chain required for the subsequent cyclization can be accomplished by treating ketone **4** with bromoacetonitrile. This reaction was attempted substituting chloroacetonitrile (Scheme 4.8), however the reaction proceeded very slowly. In order to make the chloroacetonitrile more reactive, potassium iodide was added, yet there was no change in the reaction. Upon obtaining ^{1}H-NMR it was determined that the reaction was unsuccessful, and resulted in starting material.

Scheme 4.8.[a] Introduction of Carbon Chain

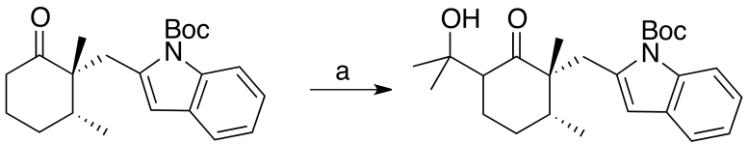


4 **17**

[a]Reagents and conditions: (a) i) DIA, DME, BuLi, 0ºC, ii) ketone **4** in DME, -70ºC, iii) $ClCH_2CN$

Another attempt was made to introduce the carbon chain, this time by means of an aldol reaction with acetone. This step theoretically would also insert the geminal dimethyl group present in polyalthenol **1** (Scheme 4.9) in a one pot step. The reaction was monitored by TLC and left overnight. There appeared to be new compounds present before the workup, however after washing with brine and extracting with ethyl acetate, the TLC showed only starting material was present.

Scheme 4.9.[a] Introduction of Carbon Chain and Geminal Dimethyl Group

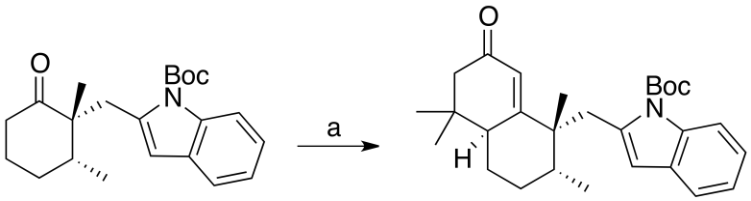


4 **18**

[a]Reagents and conditions: (a) i) LDA, -78ºC, ii) ketone **4** in THF, iii) dry acetone, RT, 1.5 h

After futile attempts at the installation of the carbon chain, it was hypothesized that the final ring of polyalthenol **1** could be accomplished using a Robinson annulation with mesityl oxide. This would allow for an overall shorter synthesis, as compared to the proposed synthesis in Scheme 4.7, and the installation of the geminal dimethyl group in one step. Previously, Jahnke et al. and Dauben et al. have reported successful Robinson annulations using mesityl oxide, albeit using harsh conditions.[126-127] Given the results of their work on the Robinson Annulation with hindered enones, it is believed that under high pressure the annulation product **19** of ketone **4a** and mesityl oxide is possible. Initial attempts at this reaction (Scheme 4.10) in THF:H_2O at atmospheric pressure have been unsuccessful and further work is required.

Scheme 4.10.[a] Synthesis of Ring Core by Robinson Annulation



14a **19**

[a]Reagents and conditions: (a) mesityl oxide, THF:H_2O, 1.0*M* KOH

4.3 Experimental

General Methods. DCM refers to dichloromethane, THF to tetrahydrofuran, and NMP to N-methylpyrrolidone. All reagents and solvents were purchased from Acros Organics (Fisher Scientific, Pittsburg, PA), Sigma-Aldrich Chemical Company (Milwaukee, WI), TCI America (Portland, OR), or Alfa Aesar (Ward Hill, WI) and used as received. All ^{1}H-NMR and ^{13}C-NMR spectra were obtained using Varian Unity 400 MHz with $CDCl_3$ (tetramethylsilane internal reference) as solvent unless otherwise noted. IR spectra were obtained using a Jasco FT/IR-4100.

All reactions were monitored by thin-layer chromatography using Analtech silica gel Uniplates and visualized under long-wave and short-wave UV radiation. Vanillin stain (6.0 g vanillin, 1.5 mL conc. H_2SO_4, 95 mL EtOH) was used when compounds were not UV active. Solvent extracts were dried over anhydrous sodium sulfate unless otherwise noted. When appropriate, crude reaction products were separated using column chromatography, AnaLogics IntelliFlash 280, and silica columns provided by Varian.

Tetrahydrobenzo[*b*]thiophene-3,4(2*H*,3*aH*)-dione(8). To 100 mL methanol was slowly added sodium solid (2.34 g, 101.8mmol) in pieces at 23.0 ºC over 25 minutes. The methanolate solution was then cooled to 0 ºC and treated dropwise with a solution of methyl thiolglycolate (10.8 g, 101.8 mmol) dissolved in 20 mL methanol. Next, a solution of cyclohexenone (9.78 g, 101.8 mmol) in 20 mL methanol was added dropwise to the reaction at 0 ºC. The reaction mixture was allowed to warm up to 23.0 ºC and refluxed overnight at 80.0 ºC. The solvent

was removed *in vacuo* to afford a brown residue. The brown residue was dissolved in 150 mL ethyl acetate and extracted with 2*N* sodium hydroxide. The alkaline extracts were acidified with concentrated hydrochloric acid, extracted with ethyl acetate, and removal of the solvent *in vacuo* to yield 8.15 g of a brown oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.20 (br s, 1, 3-OH), 4.07 (br s, 1H, CH), 3.64 and 3.28 (AB q, 2H, 2-CH_2); IR 1654 cm^{-1} (HCO), 1591 cm^{-1} (C=C).

***tert*-butyl 3-formyl-1-*H*-indole-1-carboxylate(9).** Commercially available 1*H*-indole-3-carboxaldehyde (10.63 g, 72.23 mmol) was suspended in 200 mL benzene at 23.0 ºC. To the aldehyde suspension was added aqueous 30% sodium hydroxide (200 mL), Boc anhydride (17.58 g, 80.55 mmol), and tetrabutylammonium iodide (2.70 g, 7.32 mmol). Reaction was stirred vigorously for 30 minutes. At the completion of reaction, the solution was placed in a separatory funnel and the organic layer was dried over sodium sulfate. The solvent was removed *in vacuo* to afford a white solid.

***tert*-butyl 3-(hydroxymethyl)-1*H*-indole-1-carboxylate(10).** To *tert*-butyl 3-formyl-1-*H*-indole-1-carboxylate (17.48 g, 67.5 mmol) in 75.0 mL ethanol was added sodium borohydride (2.96 g, 78.4 mmol) slowly at 23.0 ºC. After completion of reaction (monitored by TLC) the solvent was removed *in vacuo*. The solid was extracted with ethyl acetate (3 × 50.0mL) and brine (3 × 50.0mL), the organic extracts were dried over sodium sulfate, and the solvent was removed *in vacuo* to yield a light yellow solid (16.54 g, 99%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, Ar), *J* = 8.1 Hz; 7.64 (d, 1H, Ar), *J* = 8.0 Hz; 7.57 (s, 1H); 7.34 (t, 1H), *J* = 7.1 Hz; 7.26 (t, 1H), *J* = 7.1 Hz; 4.83 (s, 2H, CH_2OH); 1.66 (s, 9H, Boc).

***tert*-butyl 3-(bromomethyl)-1*H*-indole-1-carboxylate(11).**

To *tert*-butyl 3-(hydroxymethyl)-1*H*-indole-1-carboxylate (1.89 g. 7.64 mmol) under an argon atmosphere was added 25 mL DCM using a syringe at room temperature. Then a solution of PPh_3 (2.20 g, 8.41 mmol) in 20 mL DCM was added. The carbon tetrabromide (2.79 g, 8.41 mmol) was added slowly and the reaction stirred at 23.0 ºC for 0.5 h. A deep orange-brown solution was obtained. The reaction was rapidly filtered through silica powder and concentrated *in vacuo* to yield a light orange solid (1.73 g,73%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 (d, CH), 7.3-7.7 (m, Ar), 4.67(s, $3CH_2$), 1.65 (s, *t*-Bu); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 24.4, 28.1, 84.1, 115.4, 117.1, 119.3, 122.8, 124.9, 128.7, 149.3.

***tert*-butyl 2-((2-oxocyclohexyl)methyl)-1*H*-indole-1-carboxylate(5).**

Tetrahydrobenzo[*b*]thiophene-3,4(2*H*,3*aH*)-dione (2.03 g, 11.87 mmol) and potassium carbonate (1.64 g, 11.87 mmol) was added to refluxing acetone (25 mL). To the reaction was added *tert*-butyl 3-(bromomethyl)-1*H*-indole-1-carboxylate (3.68 g, 11.87 mmol) in 10 mL of acetone. The reaction remained under reflux for 2 h and was monitored by TLC. The alkylated product was isolated by simple filtration and concentrated *in vacuo*. The crude alkylation product was added to methanol:water (20 mL). Ethyl acetate (5 mL) was added to the reaction while stirring until complete salvation, followed by addition of lithium hydroxide (0.65g, 15.6 mmol). The solvent was removed *in vacuo* and extracted with ethyl acetate (3 × 50.0mL) and brine (3 × 50.0mL), the organic extracts were dried over sodium sulfate, and the solvent was removed *in vacuo* to yield a brown oil (4.04 g, 34%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 1H, Ar), *J*

= 8.1 Hz; 7.37 (d, 1H, Ar), *J* = 7.9 Hz; 7.3 (t, 1H); 7.26 (s, 1H); 7.18 (t, 1H); 6.603 (s, 1H); 3.588 (s, 2H); 2.4 (t, 2H); 1.95 (m, 4H); 1.646 (s, 9H, Boc).

***tert*-butyl 2-(((1*R*,2*R*)-1,2-dimethyl-6-oxocyclohexyl)methyl)-1*H*-indole-1-carboxylate(4a).** Under an argon atmosphere a solution of lithium dimethylcuprate in anhydrous diethyl ether (20 mL) was prepared from purified copper iodide (2.21 g, 11.62 mmol) in 10 mL diethyl ether and 1.6*M* methyl lithium (14.5 mL, 23.23 mmol) at 0 ºC. After 15 minutes at 0 ºC**,** the enone (**13** 1.26 g, 3.87 mmol) was added. The reaction mixture was maintained at 0 ºC for 1h. To the reaction mixture was added NMP (7.5 mL) followed by rapid addition of methyl iodide (2.4 mL, 38.6 mmol). The reaction was allowed to warm up to 23.0 ºC and stirred for 3 h. The reaction mixture was poured onto 1.48*M* ammonium hydroxide and the organic layer was extracted with ethyl acetate (3 × 50 mL) and washed with brine (3 × 50 mL), the organic extracts were dried over magnesium sulfate, and the solvent was removed *in vacuo* to yield a dark brown oil (1.38 g, 70%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 1H, Ar), *J* = 8.1 Hz; 7.55 (d, 1H, Ar), *J* = 7.9 Hz; 7.26 (s, 1H); 7.20 (t, 1H); 7.18 (t, 1H); 3.144,3.179, 2.792, 2.830 (AB q, 2H); 2.407 (t, 2H); 1.95 (m, 4H); 1.645 (s, 9H, Boc); 1.8 (m, 2H); 1.68 (m, 1H); 1.44 (m, 1H); 1.069 (s, 3H); 0.965, 0.982 (dd, 3H).

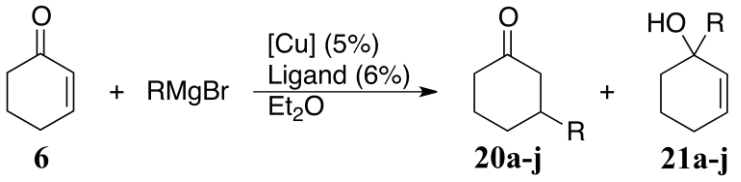
Chapter 5

Proposed Completion of Synthesis

5.1 Future Work

The Asymmetric Conjugate Addition (A.C.A.) proved more difficult than initially anticipated and therefore progress on the racemic synthesis moved forward. There are a variety of reasons that make copper-catalyzed conjugate addition with Grignard reagents problematic; including the presence of competing chiral and achiral copper complexes in solution, the sensitivity of reaction parameters, and the known deleterious effects of halides on enantioselectivity.[128-129] Furthermore, the 1,4-addition with Grignard reagents remains challenging because of the possibility of the competing 1,2-addition to the carbonyl group. The copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclic enones with enantioselectivities up to 96% was reported in 2004. The use of CuCl over either CuBr or CuBr•SMe_2 as the metal source increased the regioselectivity (95:5). The use of simple alkylmagnesium bromides as nucleophiles and commercially available ferrocenyl diphosphines as chiral ligands afforded the best results (Table 5.1).[130] This work provides the foundation for the A.C.A. on the 2-substituted enone **5.** The crucial aspect will be determination of the correct ferrocenyl diphosphine ligand .

Scheme 5.1. Enantioselective Copper-Catalyzed Conjugate Addition of Grignard Reagents to Cyclohexenone[130]



6 **20a-j** **21a-j**

Table 5.1. Enantioselective Copper-Catalyzed Conjugate Addition of Grignard Reagents to Cyclohexenone[130]

Entry*	RMgBr	Ligand	Regio, %[a]	ee **20**, %	**20**	Conf, *R*/*S* [b]
1[c]	EtMgBr	**1**	95 [69]	96	**20a**	(+)-*R*
2	EtMgBr	**2**	80	10	**20a**	(+)-*R*
3	EtMgBr	**3**	96	94	**20a**	(+)-*R*
4	EtMgBr	**4**	92	93	**20a**	(+)-*R*
5	EtMgBr	**5**	69	45	**20a**	(+)-*R*
6[d]	EtMgBr	**5**	89	40	**20a**	(+)-*R*
7[e]	EtMgBr	**6**	99	56	**20a**	(-)-*S*
8*	EtMgBr	**6**	93	30	**20a**	(-)-*S*
9	MeMgBr	**1**	83	90	**20b**	n.d.
10	PrMgBr	**1**	81	94	**20c**	n.d.
11	BuMgBr	**1**	88	96	**20d**	n.d.
12[c]	*i*-PrMgBr	**1**	78 [72]	1	**20e**	n.d.
13[c]	*i*-BuMgBr	**1**	62 [70]	33	**20f**	(+)
14[c]	*i*-Bu$(CH_2)_2$MgBr	**1**	76 [75]	95	**20g**	(+)
15	Ph$(CH_2)_2$MgBr	**1**	80	77	**20h**	(+)-*S*
16	4-Cl-BuMgBr	**1**	79	85	**20i**	n.d.
17[e]	*i*-PrMgBr	**6**	99	54	**20e**	n.d.
18[e]	*i*-BuMgBr	**6**	99	92	**20f**	(-)
19[e]	PhMgBr	**6**	50	40	**20j**	n.d.

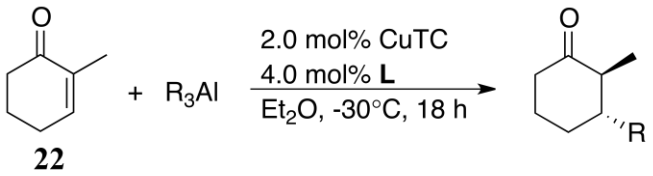
Conf, absolute configuration; n.d.; not determined.
*More than 98% conversion after 15 min at 0ºC using CuCl.
[a] Regioselectivity [9/(9+10)] × 100.
[b] Absolute configuration and/or sign of optical rotation.
[c] Isolated yields are given in brackets.
[d] More than 98% conversion after 2 h at -60ºC using CuCl.
[e] More than 98% conversion after 2 h at -60ºC using CuBr•SMe_2.

More recently the Feringa group has expanded on the knowledge base of catalytic A.C.A. with Grignard reagents and enantioselective copper-catalyzed 1,4-addition.[121,131] With increasing interest in the enantioselective 1,4-addition of carbon nucleophiles to α,β-unsaturated compounds in which a carbon – carbon bond and a new stereogenic center are formed, the ability to use this chemistry on the 2-substituted enone **5** will show great progress in this arena.

There has been at least one example on the copper-catalyzed A.C.A. of 2-trisubstituted α,β-unsaturated ketones, however, it involves the use of a triorganoaluminum species (R_3Al). Alexakis et al. was able to show *trans* 1,4-addition (*trans*/*cis* ratio around 80:20) to 2-methylcyclohex-2-en-1-one using

catalytic amounts of copper thiophene carboxylate (CuTC) and binaphthol ligands as outlined in table 5.2.[132] The best results using Me_3Al produced enantiomeric excess of 90%. In the present work it will be necessary to determine the appropriate ligand necessary for the desired stereochemistry, however, this work further supports the ability to use A.C.A. in order to install the enantioselective methyl group in the natural product polyalthenol **1**.

Table 5.2. Copper-Catalyzed Asymmetric Conjugate Addition of R_3Al to 2-Methyl-2-Cyclohexenone[132]



22

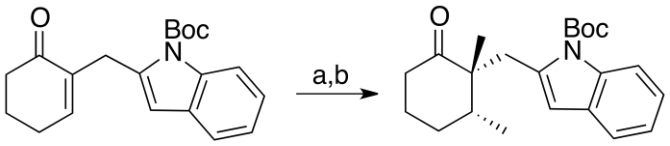
23a: R = Me
23b: R= Et

Entry	Ligand	R_3Al (eq.)	Adduct	Conv. %[a]	*ee* %[b]	Abs. Conf.
1	**L1**	Me_3Al (2.0)	**23a**	> 95	88	(2*S*,3*R*)
2	**L3**	Me_3Al (2.0)	**23a**	> 95	86	(2*R*,3*S*)
3	**L4**	Me_3Al (2.0)	**23a**	> 95	80	(2*S*,3*R*)
4	**L6**	Me_3Al (2.0)	**23a**	> 95	87	(2*R*,3*S*)
5	**L7**	Me_3Al (2.0)	**23a**	> 95	76	(2*S*,3*R*)
6	**L8**	Me_3Al (2.0)	**23a**	> 95	90	(2*S*,3*R*)
7	**L1**	Et_3Al (1.4)	**23b**	> 95	84	(2*S*,3*R*)
8	**L4**	Et_3Al (1.4)	**23b**	86	63	(2*S*,3*R*)
9	**L8**	Et_3Al (1.4)	**23b**	> 95 (50)[c]	93	(2*S*,3*R*)

[*a*] Conversion determined by GC-MS.
[*b*] *ee* determined by chiral GC.
[*c*] Isolated yield.

Theoretically the second methyl group can be installed using normal alkylating conditions with methyl iodide. Previous work by Boeckman[122] supports this addition from the opposite face, which should establish the proper relative stereochemistry of the natural product (Scheme 5.2).

Scheme 5.2.[a] Enantioselective Methylation



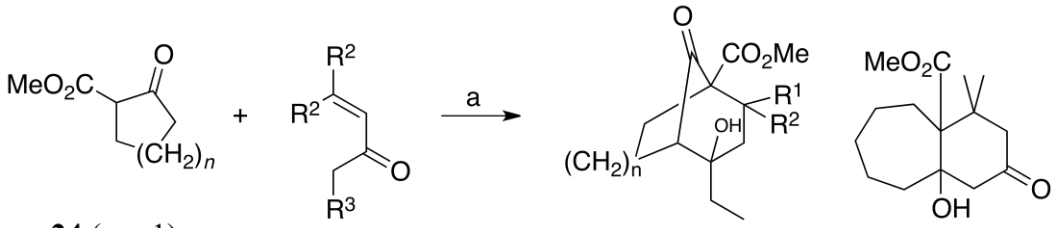
5 **4a**

[a]Reagents and conditions: (a) MeMgBr, CuCl (5%), CFDC (6%) or Me_3Al, CuTC (2%), binaphthol L (4%), Et_2O, -30ºC, 18 h; (b) CuI, MeLi, Et_2O, 0ºC, 1h

The installation of the final ring of polyalthenol **1** proved more difficult than initially anticipated. The attempts previously made to insert the carbon chain necessary for cyclization were unsuccessful and the aldol reaction with acetone, upon workup, only showed the presence of starting material. It was hypothesized that the introduction of the final ring could be accomplished using a Robinson annulation with mesityl oxide. This alternative pathway will also insert the required geminal dimethyl group.

A review of literature found at least two instances in which the Robinson annulation was performed on hindered ketones. Jahnke et al. reported the successful annulation product of 2-oxocyclohexanecarbonitrile with mesityl oxide, albeit with a rather disappointing yield of 16%, accounted for by the steric demand of the Michael acceptor.[126] Dauben initially reported the addition products of a variety of cyclic β-keto esters and enone Michael acceptors at high pressures (Scheme 5.3).[127] In the case of five and six member the major products (**28**-**30**) are bicyclic ketols whereas the product of 2-carbomethoxycycloheptanone with mesityl oxide affords the fused ketol (**31**) as the major product.

Scheme 5.3.[a] Michael Addition Products[127]



24 (n = 1)
25 (n = 2)
26 (n = 3)

27a, $R^1 = R^2 = R^3 = H$
27b, $R^1 = R^2 = H$; $R^3 = Me$
27c, $R^1 = Me$; $R^2 = R^3 = H$
27d, $R^1 = R^2 = Me$; $R^3 = H$

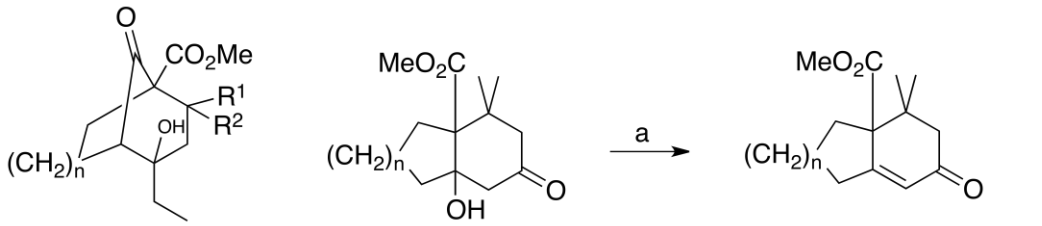
28a-d (n = 1)
29a-d (n = 2)
30a-d (n = 3)

31

[a]Reagents and conditions: (a) 15 kbar, 3:1 CH_3CN/base, 20-40ºC

With the bicyclic ketols (**28d-29d**) now available and procedures already outlined[133-134] for their conversion to unrearranged bicyclic ketones, it was possible to get the desired fused Robinson products (Scheme 5.4) Rearrangement catalyzed by hydroxide or alkoxide base proceeds poorly, causing the retro-Michael reaction, however, it was discovered that treatment of catalytic amounts of *p*-toluenesulfonic acid in benzene with removal of water yields the Robinson annulations products (**33d-35d**).

Scheme 5.4.[a] Robinson Annulation Products[127]



28a-d (n = 1)
29a-d (n = 2)

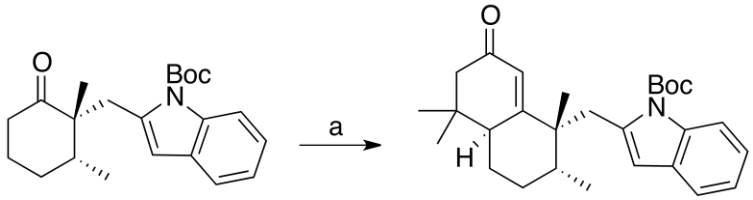
32 (n = 3)

33d (n = 1, 86%)
34d (n = 2, 89%)
35d (n = 3, 92%)

[a]Reagents and conditions: (a) cat. TsOH, C_6H_6, 80ºC, $-H_2O$

Based on the previous works outlined, Robinson annulations on hindered ketones with mesityl oxide are possible, and hindered ketone **14a** should be no exception. Under the proper conditions, increased pressure and/or heat, the Robinson annulation of ketone **14a** with mesityl oxide should establish the proper ring core of the natural product to afford the annulation product **19** (Scheme 5.5).

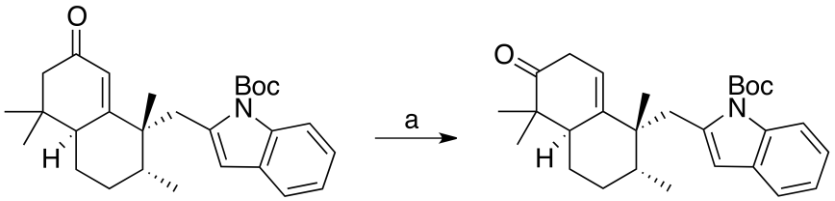
Scheme 5.5.[a] Synthesis of Ring Core by Robinson Annulation



14a **19**

With the Robinson annulation product **19** on hand, the next critical step will be a carbonyl transposition out of conjugation in order to set up for the subsequent selective reduction and the proper placement of the hydroxyl group present in the natural product. A review of literature identifies vinyl thioethers as key intermediates for the 1,2-transposition of ketone groups.[135] Using this approach annulation product **19** can be converted into a sulphonylhydrazone derivative using dimethyl disulfide and tosylhydrazone. This initial derivative can be broken down to the key vinylthioether intermediate in the presence of excess MeLi. Hydrolysis in the conventional manner with mercuric chloride should afford the transposed ketone **36** (Scheme 5.6).[136]

Scheme 5.6.[a] Carbonyl Transposition

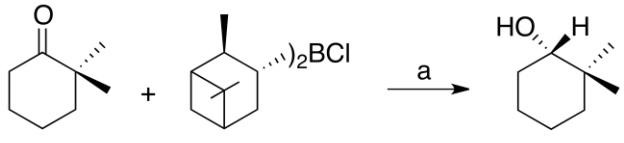


19 **36**

[a]Reagents and conditions: (a) i) MeSSMe; ii) $TsNHNH_2$; iii) MeLi (excess); iv) $HgCl_2$

After the completion of the carbonyl transposition, an enantioselective reduction of the ketone using a chloroborane reagent is proposed. The Brown reagents di-(isopinocampheyl)chloroborane, $(Ipc)_2BCl$, and di-(iso-2-ethylapopinocampheyl)chloroborane, $(Eap)_2BCl$, have previously achieved high enantioselectivity for aryl and branched dialkyl ketones.[137-138] Brown et al. showed that the reduction of hindered cyclic derivatives is considerably fast, yet optical yields are excellent. For example the reduction of 2,2-dimethylcyclohexanone **37** with Ipc_2BCl **38** yields the corresponding alcohol **39** in 91% *ee* (Scheme 5.7).

Scheme 5.7.[a] Reduction of Prochiral Ketones with Ipc_2BCl[14]

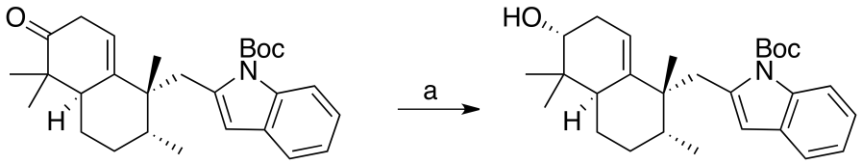


37 **38** **39 (*S*)**

[a]Reagents and conditions: (a) 25° C, neat, 12 h

The use of a Brown's reagent with ketone **36** should provide the enantioselective alcohol **40** that is required by the natural product, with a high degree of selectivity (Scheme 5.8).

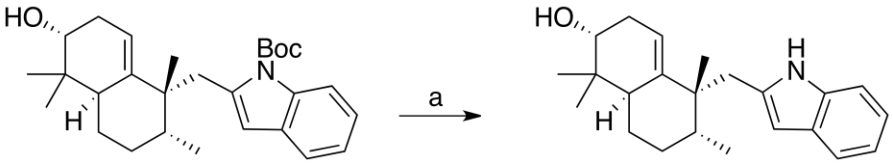
Scheme 5.8.[a] Enantioselective Reduction to Alcohol



36 **40**

The final step in completion of the total synthesis of polyalthenol **1** is the removal of the Boc protecting group. *N*-Boc deprotection has been successful using mild acidic conditions such as trifluoracetic acid (TFA) in dichloromethane.[139]

Scheme 5.9.[a] Boc Deprotection



40 **1**

[a]Reagents and conditions: (a) TFA, CH_2Cl_2

REFERENCES

1. Newman, D.J.; Cragg, G.M.; Snader, K.M. *Nat. Prod. Rep.* **2000**, *17*, 215-234.

2. Ojima, I. *J. Med. Chem.* **2008**, *51*, 2587-2588.

3. Ji, H.F.; Li, X.J.; Zhang, H.Y. *EBMO Rep.* **2009**, *10*, 194-200.

4. Dictionary of Natural Products; Buckingham, J., Ed.; Chapman and Hall, 1993, Vol. 1-7.

5. Ganesan, A. *Curr. Opin. Chem. Biol.* **2008**, *12*, 306-317.

6. Dev, S. *Environ. Health Persp.* **1999**, *107*, 783-789.

7. Butler, M.S.; Newman, D.J. *Prog. Drug Res.* **2008**, *65*, 3-44.

8. Hamilton, G.R.; Baskett, T.F. *Can. J. Anaesth.* **2000**, *47*, 367-374.

9. Grabley, S.; Thiericke, R. *Adv. Biochem. Eng. Biot.* **1999**, *64*, 104-154.

10. Li, J.W.H.; Vederas, J.C. *Science.* **2009**, *325*, 161-165.

11. Challis, G.L. *Microbiology.* **2008**, *154*, 1555-1569.

12. Saleem, M.; Nazir, M.; Ali, M.S.; Hussain, H.; Lee, Y.S.; Riaz, N.; Jabbar, A. *Nat. Prod. Rep.* **2010**, *27*, 238-254.

13. Cragg, G.M.; Newman, D.J. Natural Product Sources of Drugs: Plants, Microbes, Marine Organisms, and Animals. In Comprehensive Medicinal Chemistry II; Kennewell, P.; Ed.; Elsevier Science, 2006; Vol. 1, pp. 355-403.

14. Newman, D.J.; Cragg, G.M. *J. Nat. Prod.* **2007**, *70*, 461-477.

15. Newman, D.J. *J. Med. Chem.* **2008**, *51*, 2589-2599.

16. Kingston, D.G.I. *J. Nat. Prod.* **2011**, *74*, 496-511.

17. McChesney, J.D.; Venkataraman, S.K.; Henri, J.T. *Phytochemistry.* **2007**, *68*, 2015-2022.

18. Demain, A.L. *Med. Res. Rev.* **2009**, *29*, 821-842.

19. Motzer, R.J.; Rini, B.I.; Bukowski, R.M.; Curti, B.D.; George, D.J.; Hudes, G.R.; Redman, B.G.; Margolin, K.A.; Merchan, J.R.; Wilding, G.; Ginsberg, M.S.; Bacik, J.; Kim, S.T.; Baum, C.M.; Michaelson, M.D. *J. Am. Med. Assoc.* **2006**, *295*, 2516-2524.

20. Wilhelm, S.; Carter, C.; Lynch, M.; Lowinger, T.; Dumas, J.; Smith, R.A.; Schwartz, B.; Simantov, R.; Kelley, S. *Nat. Rev. Drug Discovery.* **2006**, *5*, 835-844.

21. Butler, M.S. *Nat. Prod. Rep.* **2008**, *25*, 475-516.

22. Harvey, A.L. *Drug Discov. Today*. **2008**, *13*, 894-901.

23. Molinski, T.F.; Dalisay, D.S.; Lievens, S.L.; Saludes, J.P. *Nat. Rev. Drug Discov.* **2009**, *8*, 69-85.

24. Cragg, G.M.; Kingston, D.G.I.; Newman, D.J. Anticancer Agents from Natural Products. CRC Press, Taylor & Francis Group, Boca Raton, FL., 2005.

25. Newman, D.J.; Cragg, G.M.; Snader, K.M. *J. Nat. Prod.* **2003**, *66*, 1022-1037.

26. Smith, V.J.; Desbois, A.P.; Dyrynda, E.A. *Mar. Drugs.* **2010**, *8*, 1213-1262.

27. Newton, G.G.F.; Abraham, E.P. *Biochem. J.* **1956**, *62*, 651-658.

28. Abraham, E.P.; Newton, G.G.F. *Biochem. J.* **1961**, *79*, 377-393.

29. Fischbach, M.A.; Walsh, C.T. *Science*. **2009**, *325*, 1089-1093.

30. Boyer-Joubert, C.; Lorthiois, E.; Moreau, F. In *Annual Reports in Medicinal Chemistry*; Doherty, A.M., Ed.; Academic Press: Amsterdam, 2003; Vol. 38, pp 347-374.

31. Paterson, D.L.; DePestel, D.D. *Clin. Infect. Dis.* **2009**, *49*, 291-298.

32. Sum, P.E.; Lee, V.J.; Testa, R.T.; Hlavka, J.J.; Ellestad, G.A.; Bloom, J.D.; Gluzman, Y.; Tally, F.P. *J. Med. Chem.* **1994**, *37*, 184-188.

33. Zhanel, G.G.; Homenuik, K.; Nichol, K.; Noreddin, A.; Vercaigne, L.; Embil, J.; Gin, A.; Karlowsky, J.A.; Hoban, D.J. *Drugs*. **2004**, *64*, 63-88.

34. Stein, G.E.; Craig, W.A. *Clin. Infect. Dis.* **2006**, *43*, 518-524.

35. Olsen, M.W.; Ruzin, A.; Feyfant, E.; Rush, T.S.; O'Connell, J.; Bradford, P.A. *Antimicrob. Agents Chemother.* **2006**, *50*, 2156-2166.

36. Chin, Y.W.; Balunas, M.J.; Chai, H.B.; Kinghorn, A.D. *AAPS J.* **2006**, *8*, E239-E253.

37. Nguyen, M.; Chung, E.P. *Clin. Ther.* **2005**, *27*, 1144-1163.

38. Bryskier, A. *Clin. Microbiol. Infect.* **2000**, *6*, 661-669.

39. Hedge, S.; Carter, J. In *Annual Reports in Medicinal Chemistry*; Doherty, A.M., Ed.; Academic Press: Amsterdam, 2004; Vol. 39, pp 337-368.

40. Fenton, C.; Keating, G.M.; Curran, M.P. *Drugs*. **2004**, *64*, 445-455.

41. Ogston, A. *J. Anat.* **1882**, *16*, 526-567.

42. Lowy, F.D. *N. Engl. J. Med.* **1998**, *339*, 520-532.

43. Centers for Disease Control and Prevention. Public Heath Image Library.

44. Peacock, S.J.; de Silvia, I.; Lowy, F.D. *Trends Microbiol.* **2001**, *9*, 605-610.

45. Foster, T.J. *Nat. Rev. Microbiol.* **2005**, *3*, 948-958.

46. Diep, B.A.; Carleton, H.A.; Chang, R.F.; Sensabaugh, G.F.; Perdreau-Remington, F. *J. Infect. Dis.* **2006**, *193*, 1495-1503.

47. Ito, T.; Katayama, Y.; Asada, K.; Mori, N.; Tsutsumimoto, K.; Tiensasitorn, C.; Hiramatsu, K. *Antimicrob. Agents Chemother.* **2001,** *45*, 1323-1336.

48. Berglund, C.; Söderquist, B. *Clin. Microbiol. Infect.* **2008**, *14*, 1048-1056.

49. Jevons, M.P. *Brit. Med. J.* **1961**, *1*, 124.

50. Barrett, F.F.; McGehee, R.F.; Finland, M. *N. Engl. J. Med.* **1968**, *279*, 441-448.

51. David, M.Z.; Daum, R.S. *Clin. Microbiol. Rev.* **2010**, *23*, 616-687.

52. Rodríguez-Noriega, E.; Seas, C. *Braz. J. Infect. Dis.* **2010**, *14*, S87-S96.

53. Flynn, N.; Cohen, S.H. *J. Infect. Dis.* **2008**, *197*, 1217-1219.

54. David, M.Z.; Glikman, D.; Crawford, S.E.; Peng, J.; King, K.J.; Hostetler, M.A.; Boyle-Vavra, S.; Daum, R.S. *J. Infect. Dis.* **2008**, *197*, 1235-1243.

55. Liu, C.; Graber, C.J.; Karr, M.; Diep, B.A.; Basuino, L.; Schwartz, B.S.; Enright, M.C.; O'Hanlon, S.J.; Thomas, J.C.; Perdreau-Remington, F.; Gordon, S.; Gunthorpe, H.; Jacobs, R.; Jensen, P.; Leoung, G.; Rumack, J.S.; Chambers, H.F. *Clin. Infect. Dis.* **2008**, *46*, 1637-1646.

56. Diekema, D.J.; Climo, M.C. *J. Am. Med. Assoc.* **2008**, *299*, 1190-1192.

57. Centers for Disease Control and Prevention. ABCs Report: Methicillin-Resistant *Staphylococcus aureus*, 2009.

58. Centers for Disease Control and Prevention. ABCs Report: Methicillin-Resistant *Staphylococcus aureus*, 2010.

59. Lessa, F.C.; Mu, Y.; Davies, J.; Murray, M.; Lillie, M.; Pearson, A.; Fridkin, S.K. *Clin. Infect. Dis.* **2010**, *51*, 925-928.

60. Dancer, S.J. *J. Antimicrob. Chemother.* **2008**, *61*, 246-253.

61. Rubin, R.J.; Harrington, C.A.; Poon, A.; Dietrich, K.; Greene, J.A.; Moiduddin, A. *Emerging Infect. Dis.* **1999**, *5*, 9-17.

62. Cosgrove, S.E.; Sakoulas, G.; Perencevich, E.N.; Schwaber, M.J.; Karchmer, A.W.; Carmeli, Y. *Clin. Infect. Dis.* **2003**, *36*, 53-59.

63. Fridkin, S.K.; Hageman, J.; McDougal, L.K.; Mohammed, J.; Jarvis, W.R.; Perl, T.M.; Tenover, F.C. *Clin. Infect. Dis.* **2003**, *36*, 429-439.

64. Tsiodras, S.; Gold, H.S.; Sakoulas, G.; Eliopoulos, G.M.; Wennersten, C.; Venkataraman, L.; Moellering, R.C.; Ferraro, M.J. *Lancet.* **2001**, *358*, 207-208.

65. McCormick, M.H.; Stark, W.M.; Pittenger, G.E.; Pittenger, R.C.; McGuire, J.M. *Antibiot. Annu.* **1955**, *3*, 606-611.

66. Lechevalier, M.P.; Prauser, H.; Labeda, D.P.; Ruan, J.S. *Int. J. Syst. Bacteriol.* **1986**, *36*, 29-37.

67. Watanakunakorn, C. *Rev. Infect. Dis.* **1981**, *3*, S210-S215.

68. Perkins, H.R.; Nieto, M. *Ann. N.Y. Acad. Sci.* **1974**, *235*, 348-363.

69. Nicolaou, K.C.; Boddy, C.N.C.; Bräse, S.; Winssinger, N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2096-2152.

70. Sakoulas, G.; Moellering, R.C. *Clin. Infect. Dis.* **2008**, *46*, S360-S367.

71. Hiramatsu, K. *Drug Resist. Updates.* **1998**, *1*, 135-150.

72. Hiramatsu, K.; Hanaki, H.; Ino, T.; Yabuta, K.; Oguri, T.; Tenover, F.C. *J. Antimicrob. Chemother.* **1997**, *40*, 135-136.

73. Cataldo, M.A.; Taglietti, F.; Petrosillo, N. *Postgrad. Med.* **2010**, *122*, 16-23.

74. Nailor, M.D.; Sobel, J.D. *Infect. Dis. Clin. N. Am.* **2009**, *23*, 965-982.

75. Liu, C.; Bayer, A.; Cosgrove, S.E.; Daum, R.S.; Fridkin, S.K.; Gorwitz, R.J.; Kaplan, S.L.; Karchmer, A.W.; Levine, D.P.; Murray, B.E.; Rybak, M.J.; Talan, D.A.; Chambers, H.F. *Clin. Infect. Dis.* **2011**, *52*, e18-e55.

76. Tenson, T.; Lovmar, M.; Ehrenberg, M. *J. Mol. Biol.* **2003**, *330*, 1005-1014.

77. Beale, J.M. Antibacterial Antibiotics. In Organic Medicinal and Pharmaceutical Chemistry, 12th Edition; Beale, J.M., Block, J.H., Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, 2011, pp 258-329.

78. Gould, F.K.; Brindle, R.; Chadwick, P.R.; Fraise, A.P.; Hill, S.; Nathwani, D.; Ridgway, G.L.; Spry, M.J.; Warren, R.E. *J. Antimicrob. Chemother.* **2009**, *63*, 849-861.

79. Han, L.L.; McDougal, L.K.; Gorwitz, R.J.; Mayer, K.H.; Patel, J.B.; Sennott, J.M.; Fontana, J.L. *J. Clin. Microbiol.* **2007**, *45*, 1350-1352.

80. D'Costa, V.M.; McGrann, K.M.; Hughes, D.W.; Wright, G.D. *Science*. **2006**, *311*, 374-377.

81. Wehrli, W. *Rev. Infect. Dis.* **1983**, *5*, S407-S411.

82. Aboltins, C.A.; Page, M.A.; Buising, K.L.; Jenney, A.W.J.; Daffy, J.R.; Choong, P.F.M.; Stanley, P.A. *Clin. Microbiol. Infect.* **2007**, *13*, 586-591.

83. Alekshun, M.N. *Expert Opin. Invest. Drugs.* **2005**, *14*, 117-134.

84. Chopra, I.; Roberts, M. *Microbiol. Mol. Biol. Rev.* **2001**, *65*, 232-260.

85. Slee, A.M.; Wuonola, M.A.; McRipley, R.J.; Zajac, I.; Zawada, M.J.; Bartholomew, P.T.; Gregory, W.A.; Forbes, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1791-1797.

86. Leach, K.L.; Brickner, S.J.; Noe, M.C.; Miller, P.F. *Ann. N.Y. Acad. Sci.* **2011**, *1222*, 49-54.

87. Livermore, D.M. *J. Antimicrob. Chemother.* **2003**, *51*, S2, ii9-ii16.

88. Biedenbach, D.J.; Farrell, D.J.; Mendes, R.E.; Ross, J.E.; Jones, R.N. *Diagn. Microbiol. Infect. Dis.* **2010**, *68*, 459-467.

89. Skripkin, E.; McConnell, T.S.; DeVito, J.; Lawrence, L.; Ippolito, J.A.; Duffy, E.M.; Sutcliffe, J.; Franceschi, F. *Antimicrob. Agents Chemother.* **2008**, *52*, 3550-3557.

90. Lee, S.Y.; Fan, H.W.; Kuti, J.L.; Nicolau, D.P. *Expert Opin. Pharmacother.* **2006**, *7*, 1381-1397.

91. Beiras-Fernandez, A.; Vogt, F.; Sodian, R.; Weis, F. *Infect. Drug Resist*. **2010**, *3*, 95-101.

92. Baltz, R.H. *Curr. Opin. Chem. Biol.* **2009**, *13*, 144-151.

93. Saravolatz, L.D.; Stein, G.E.; Johnson, L.B. *Clin. Infect. Dis.* **2009**, *49*, 1908-1914.

94. Higgins, D.L.; Chang, R.; Debabov, D.V.; Leung, J.; Wu, T.; Krause, K.M.; Sandvik, E.; Hubbard, J.M.; Kaniga, K.; Schmidt, D.E.; Gao, Q.; Cass, R.T.; Karr, D.E.; Benton, B.M.; Humphrey, P.P. *Antimicrob. Agents Chemother.* **2005**, *49*, 1127-1134.

95. JSTOR Plant Science. http://plants.jstor.org/specimen/ea000002450 (accessed July 3, 2012).

96. The Annonaceae of Africa. http://afroannons.myspecies.info/category/african-annonaceae/annonaceae/polyalthia (accessed July 3, 2012).

97. Okorie, D.A. *Tetrahedron*. **1980**, *36*, 2005-2008.

98. Nyasse, B.; Ngantchou, J.J.; Schneider, B. *Nat. Prod. Res.* **2006**, *20*, 391-397.

99. Hamonnière, M.; Leboeuf, M.; Cavè, A. *Phytochemistry*. **1977**, *16*, 1029-1034.

100. Wiart, C.; Mogana, S.; Khalifah, S.; Mahan, M.; Ismail, S.; Buckle, M.; Narayana, A.K.; Sulaiman, M. *Fitoterapia*. **2004**, *75*, 68-73.

101. Achenbach, H.; Lowel, M. *Planta Med.* **1993**, *59*, 388-388.

102. Mabberley, D.J.; *The Plant-Book, a Portable Dictionary of the Vascular Plants, 2nd ed.;* Cambridge, U.K., 1997; p 315.

103. Viisteensaari, J.; Johansson, S.; Kaarakka, V.; Luukkanen, O. *Environ. Conserv.* **2000**, *27*, 76-81.

104. Yoo, H.D.; Cremin, P.A.; Zeng, L.; Garo, E.; Williams, C.T.; Lee, C.M.; Goering, M.G.; O'Neil-Johnson, M.; Eldridge, G.R.; Hu, J.F. *J. Nat. Prod.* **2005**, *68*, 122-124.

105. Leboeuf, M.; Hamonnière, M.; Cavé, A. *Tetrahedron Lett.* **1976**, *39*, 3559-3562.

106. Takada, K.; Kajiwara, H.; Imamura, N. *J. Nat. Prod.* **2010**, *73*, 698-701.

107. Djerassi, C.; Smith, D.H.; Varkony, T.H. *Naturwissenschaften*. **1979**, *66*, 9-21.

108. Lederberg, J. (1977). *Medical Experimental Computer Resource* [Grant RR – 00785 proposal to the National Institutes of Health, Agency for Biotechnology Resources Program].

109. Williams, R.B.; Hu, J.F.; Olson, K.M.; Norman, V.L.; Goering, M.G.; O'Neil-Johnson, M.; Eldridge, G.R.; Starks, C.M. *J. Nat. Prod.* **2010**, *73*, 1008-1011.

110. Hert, J.; Irwin, J.J.; Laggner, C.; Keiser, M.J.; Shoichet, B.K. *Nat. Chem. Biol.* **2009**, *5*, 479-483.

111. Lipkus, A.H.; Yuan, Q.; Lucas, K.A.; Funk, S.A.; Bartelt, W.F.; Schenck, R.J.; Trippe, A.J. *J. Org. Chem.* **2008**, *73*, 4443-4451.

112. Marcos, I.S.; Moro, R.F.; Costales, I.; Escola, M.A.; Basabe, P.; Díez, D.; Urones, J.G. *Tetrahedron.* **2009**, *65*, 10235-10242.

113. Velthuisen, E.J.; Danishefsky, S.J. *J. Am. Chem. Soc.* **2007**, *129*, 10640-10641.

114. Shahid, M.; Shahzad, A.; Sobia, F.; Sahai, A.; Tripathi, T.; Singh, A.; Khan, H.M.; Umesh. *Anti-Infect. Agents Med. Chem.* **2009**, *8*, 211-225.

115. Baraldi, P.G.; Barco, A.; Benetti, S.; Pollini, G.P.; Zanirato, V. *Tetrahedron Lett.* **1984**, *25*, 4291-4294.

116. Confalone, P.N.; Baggiolini, E.; Hennessy, B.; Pizzolato, G.; Uskoković, M.R. *J. Org. Chem.* **1981**, *46*, 4923-4927.

117. Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E.M. *J. Am. Chem. Soc.* **2006**, *128*, 11693-11712.

118. Venkatachalam, T.K.; Mzengeza, S.; Diksic, M. *Org. Prep. Proced. Int.* **1993**, *25*, 249-251.

119. Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801-811

120. Khim, S.K.; Dia, M.; Zhang, X.; Chen, L.; Pettus, L.; Thakkar, K.; Schultz, A.G. *J. Org. Chem.* **2004**, *69*, 7728-7733.

121. Harutyunyan, S.R.; den Hartog, T.; Geurts, K.; Minnaard, A.J.; Feringa, B.L. *Chem. Rev.* **2008**, *108*, 2824-2852.

122. Boeckman, R.K. *J. Org. Chem.* **1973**, *38*, 4450-4452.

123. Sikorski, W.H.; Reich, H.J. *J. Am. Chem. Soc.* **2001**, *123*, 6527-6535.

124. Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D.J.; Gleason, J.L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

125. Seebach, D.; Bossler, H.; Grundler, H.; Shoda, S.I. *Helv. Chim. Acta.* **1991**, *74*, 197-124.

126. Jahnke, A.; Burschka, C.; Tacke, R.; Kraft, P. *Synthesis*. **2009**, *1*, 62-68.

127. Dauben, W.G.; Bunce, R.A. *J. Org. Chem.* **1983**, *48*, 4642-4648.

128. Feringa, B.L.; de Vries, H.M. In *Advances in Catalytic Processes: Asymmetric Chemical Transformation*. Doyle, M.P. JAI: Greenwich, CT, 1995; 1, 151-192.

129. Jansen, J.F.G.A.; Feringa, B.L. *J. Org. Chem.* **1990,** *55*, 4168-4175.

130. Feringa, B.L.; Badorrey, R.; Peña, D.; Harutyunyan, S.R.; Minnaard, A.J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834-5838.

131. Jerphagnon, T.J.; Pizzuti, M.G.; Minnaard, A.J.; Feringa, B.L. *Chem. Soc. Rev.* **2009,** *38*, 1039-1075.

132. Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007***, 13*, 9647-9662.

133. Dauben, W.G.; McFarland, J.W.; Rogan, J.B. *J. Org. Chem.* **1961**, *26*, 297-300.

134. Liu, H.J.; Ho, L.K.; Lai, H.K. *Can. J. Chem.* **1981,** *59,* 1685-1688.

135. Kano, S.; Tokomatsu, T.; Ono, T.; Hibino, S.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1978**, *9*, 414-415.

136. Morris, D.G. *Chem. Soc. Rev.* **1982**, *11*, 397-434.

137. Brown, H.C.; Chandrasekharan, J.; Ramachandran, P.V. *J. Am. Chem. Soc.* **1988**, *110*, 1539-1546.

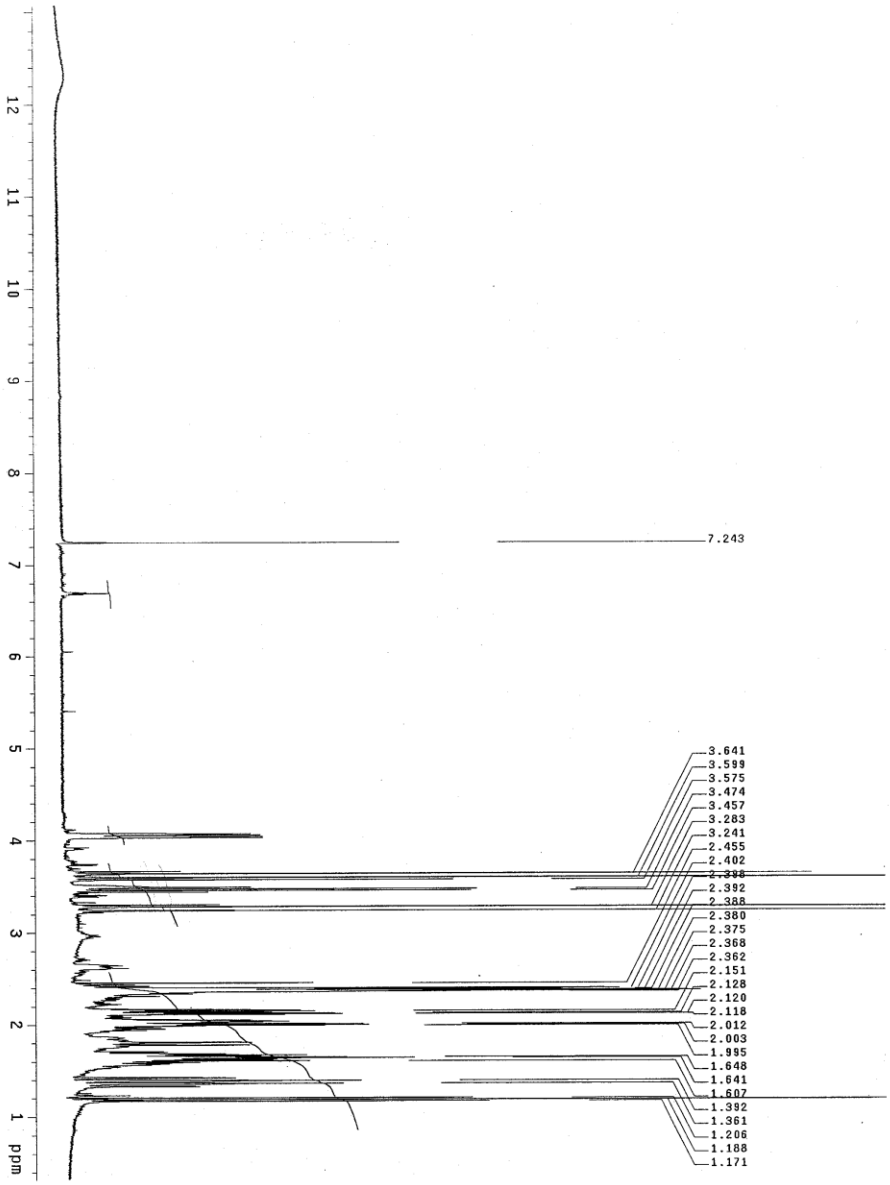
138. Brown, H.C.; Ramachandran, P.V.; Teodorovic, A.V.; Swaminathan, S. *Tetrahedron Lett.* **1991,** *32*, 6691-6694.

139. Wuts, P. G. M.; Greene, T. W. *Greene's protective group in organic synthesis*, 4th Ed.; John Wily & Sons: New York, 2007.

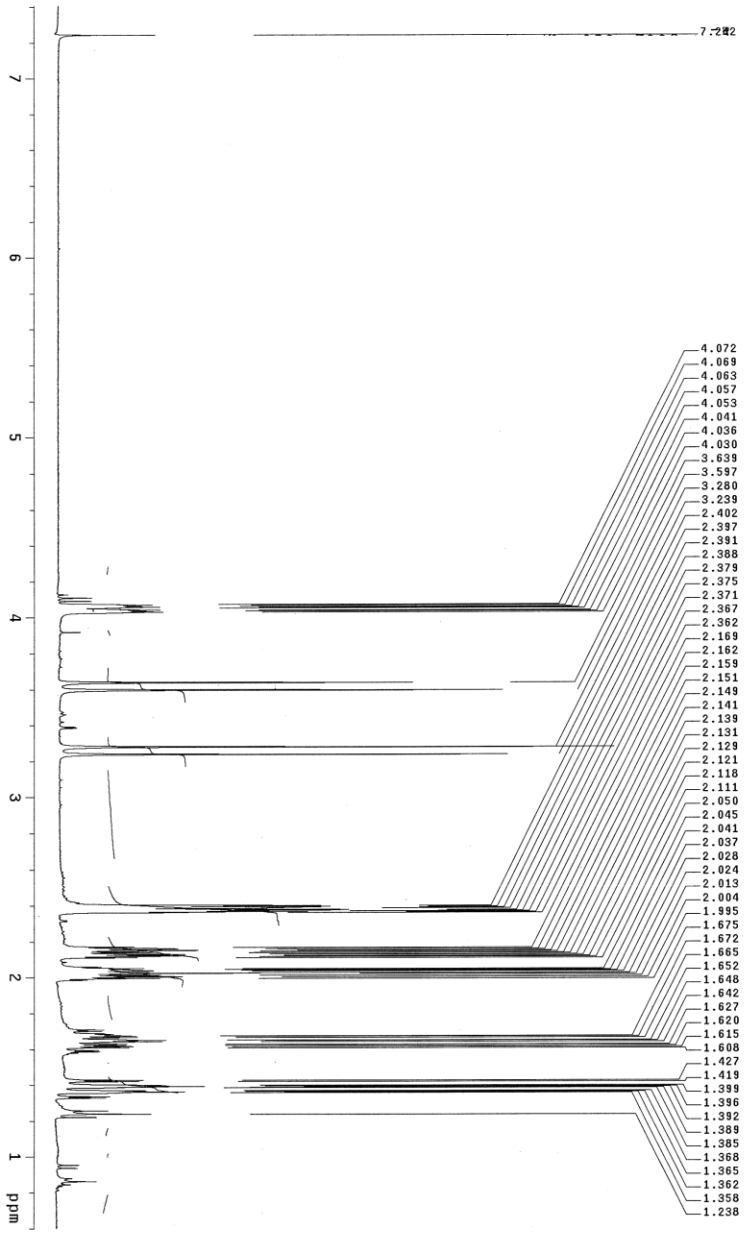
APPENDIX A

^{1}H-NMR SPECTROSCOPY

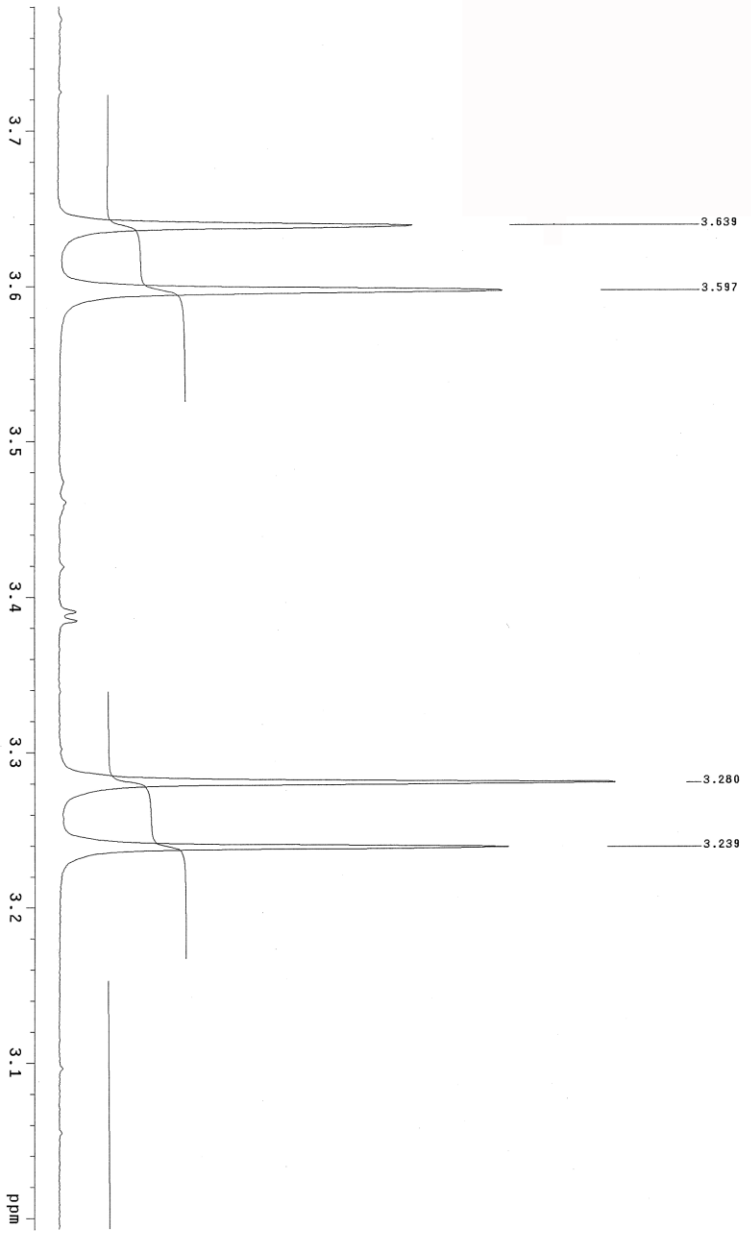
^{1}H-NMR for Bicyclic Ketone **8**



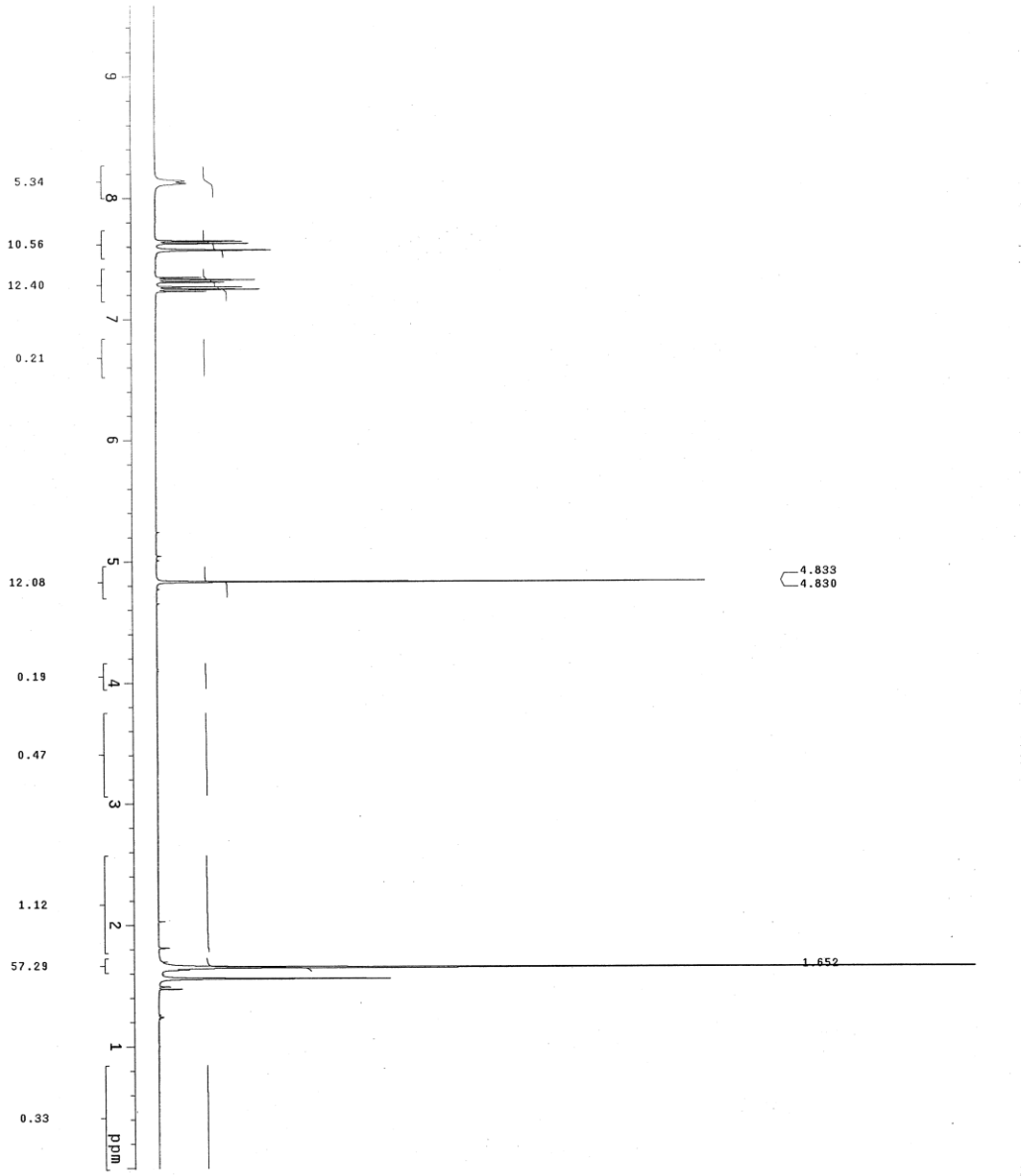
^{1}H-NMR for Bicyclic Ketone **8**



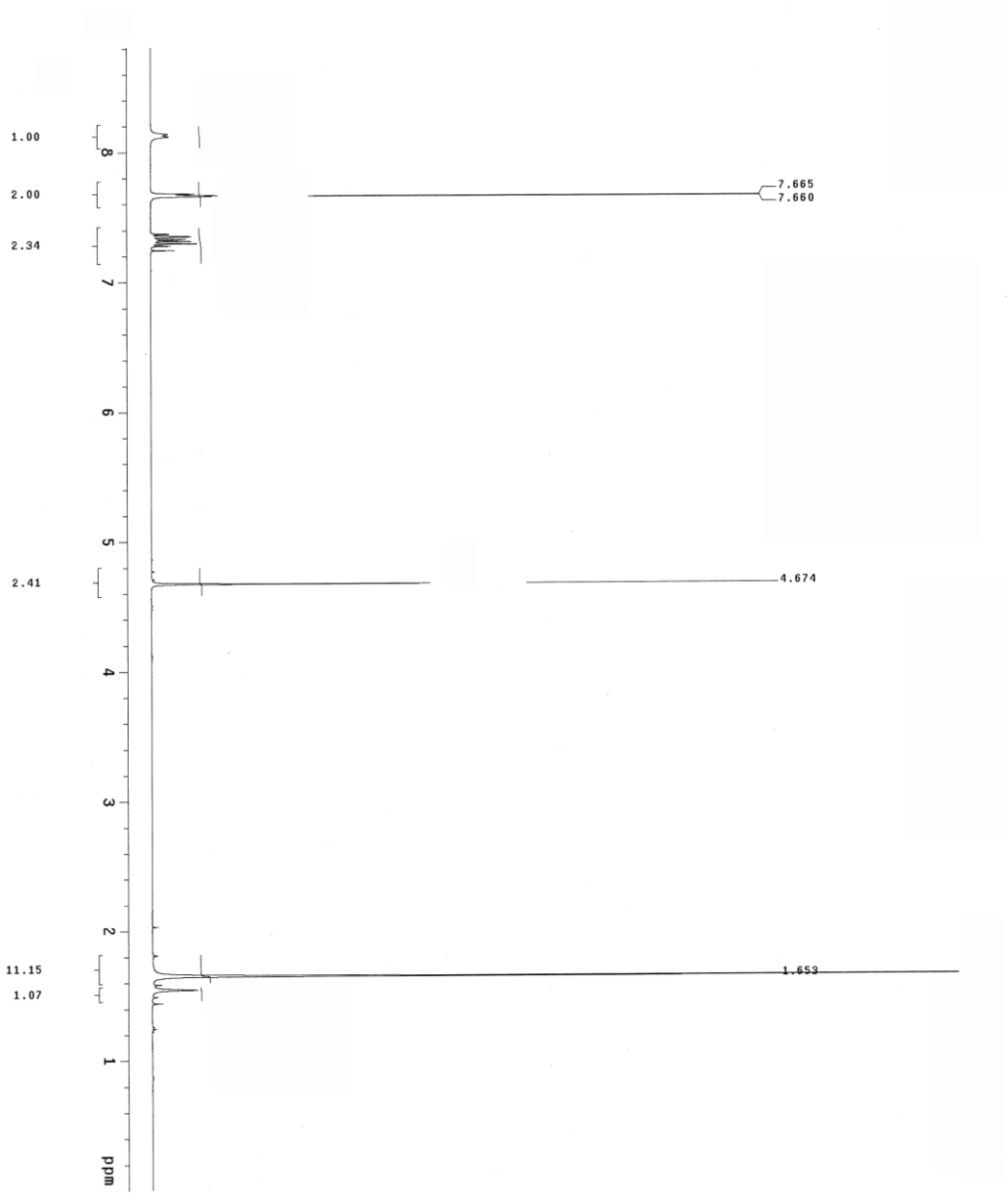
^{1}H-NMR for Bicyclic Ketone **8**



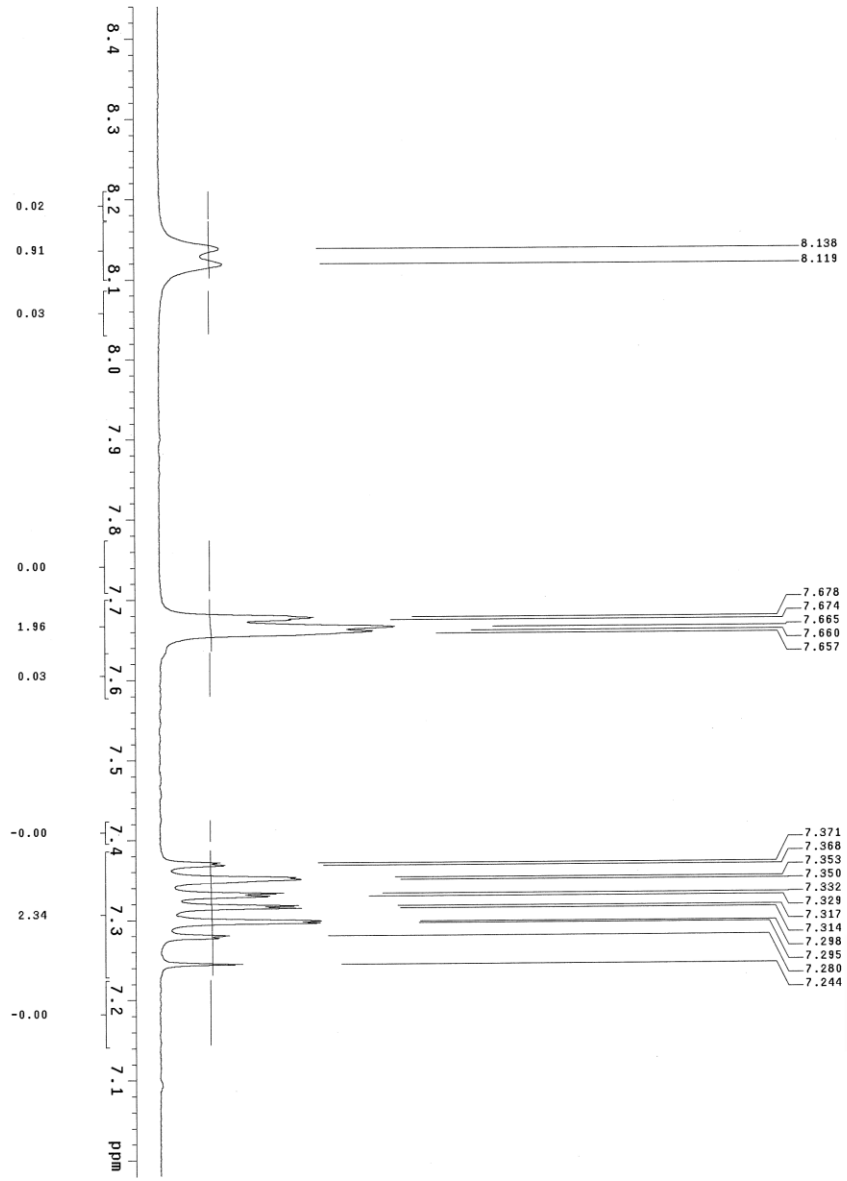
^{1}H-NMR for Boc Indole Alcohol **10**



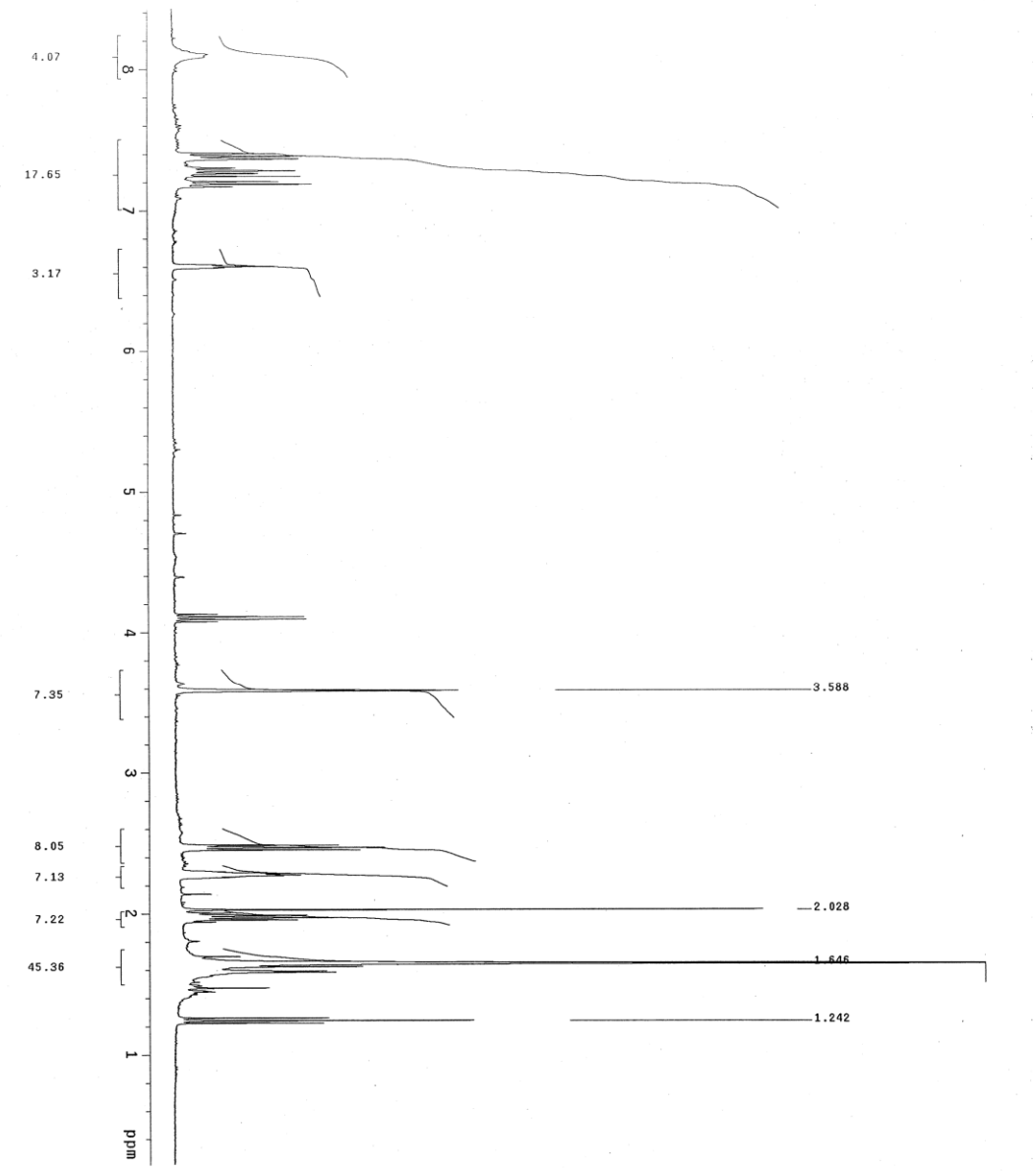
^{1}H-NMR for Boc Indole Bromide **11**



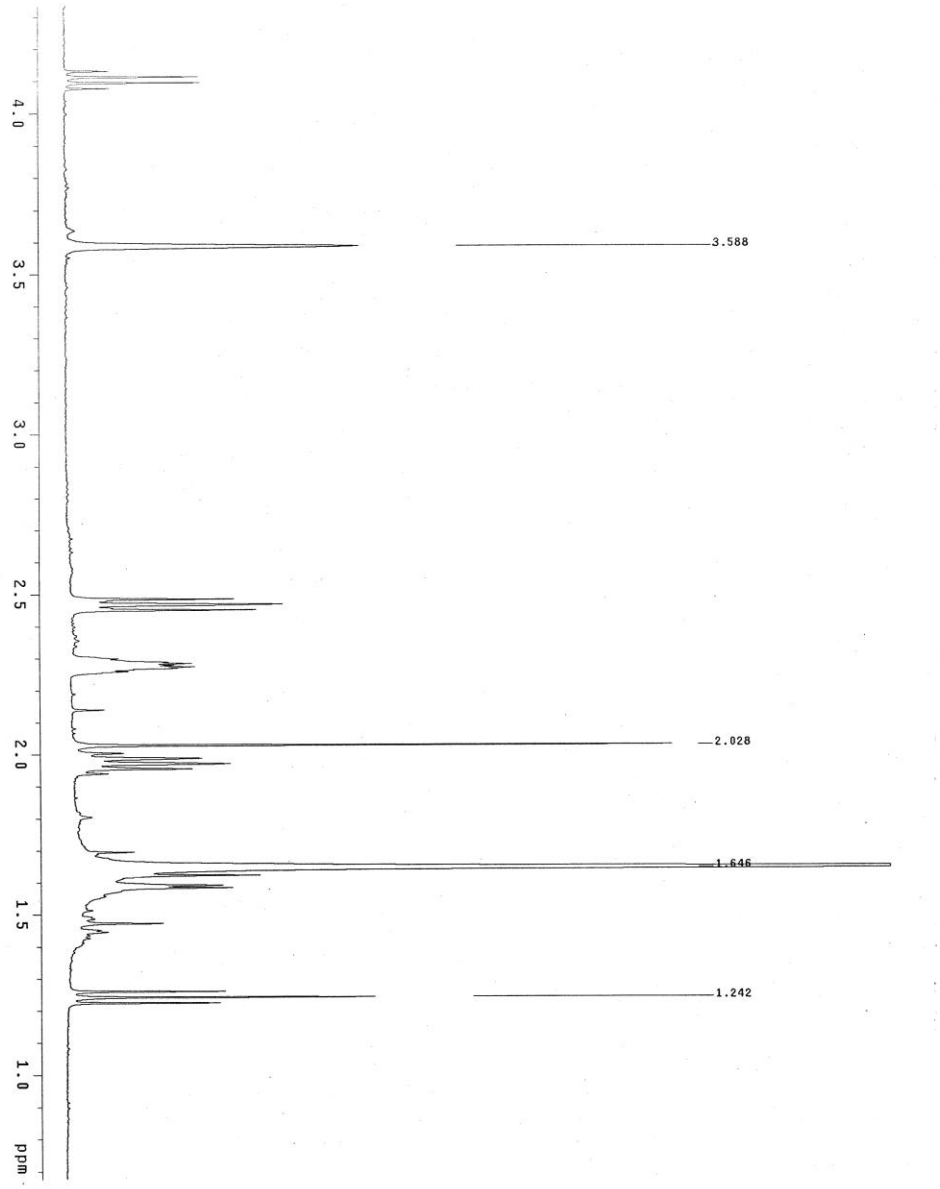
^{1}H-NMR for Boc Indole Bromide **11**



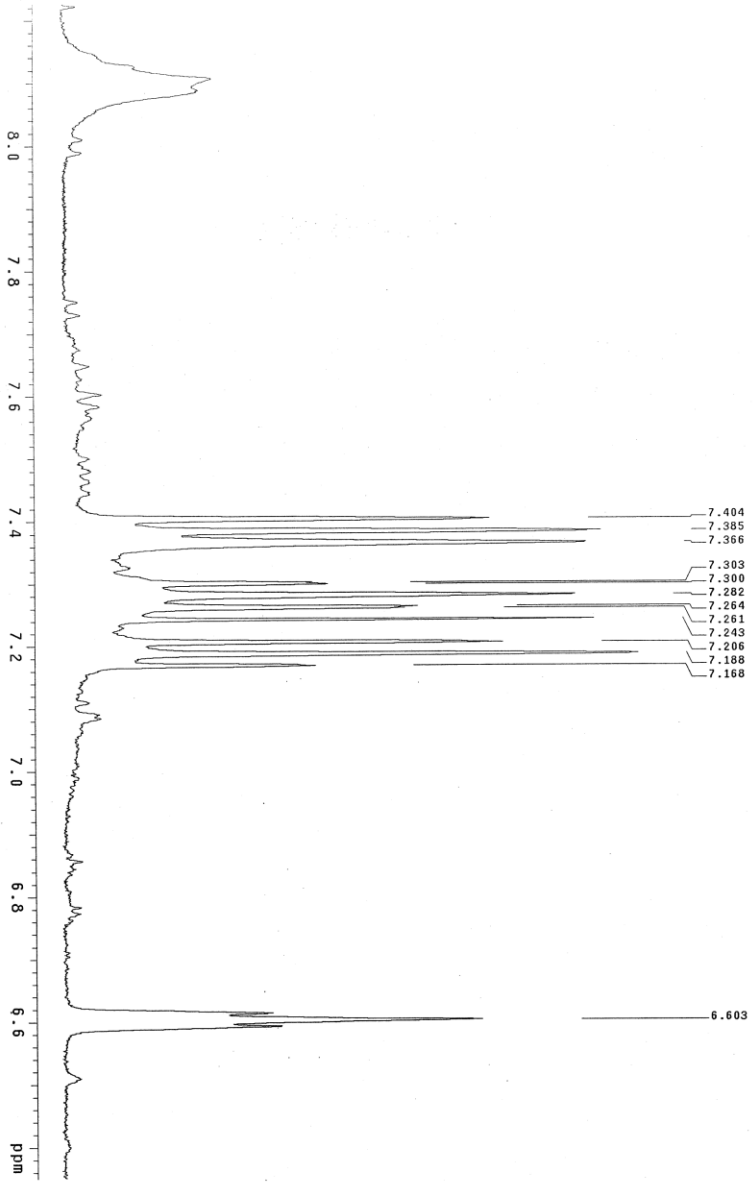
^{1}H-NMR for Boc Protected Enone **5**



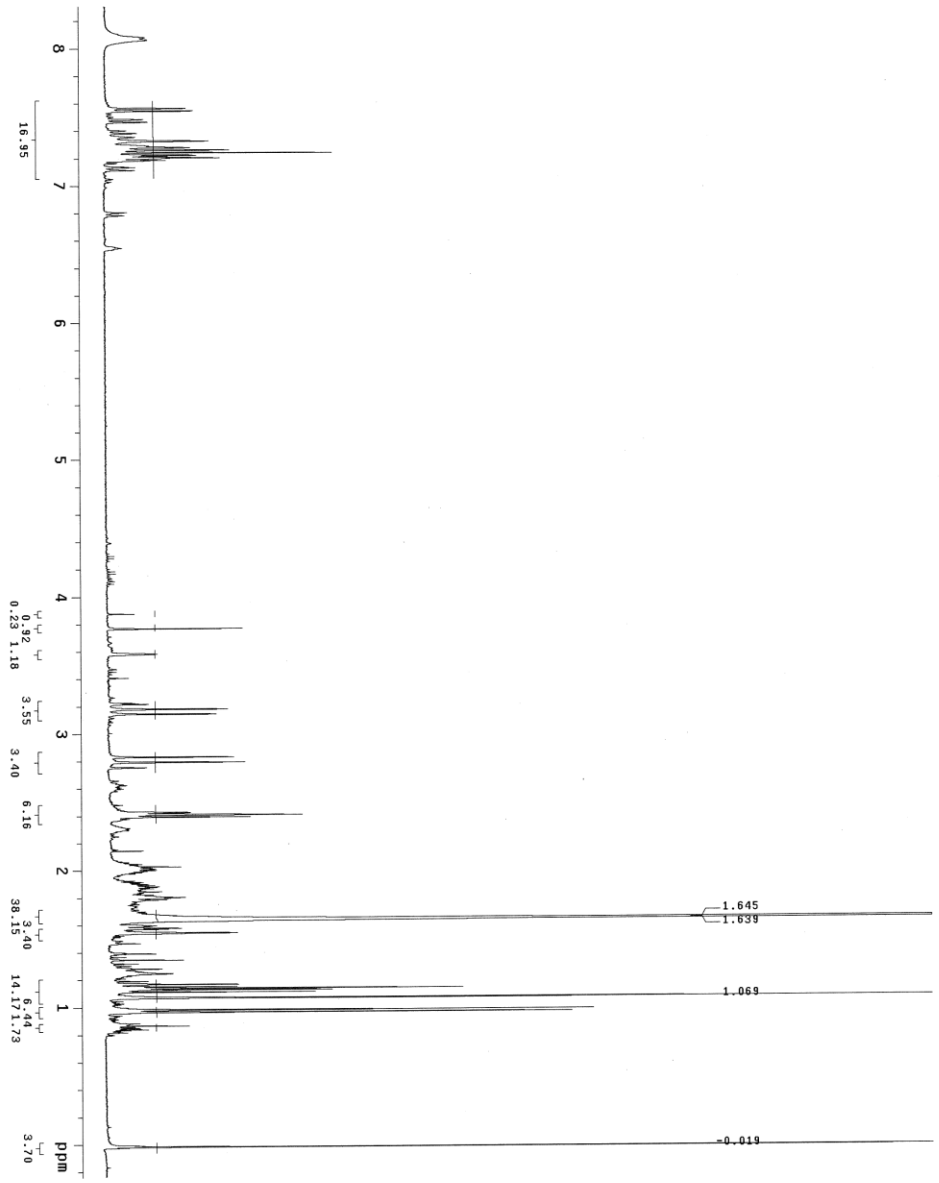
^{1}H-NMR for Boc Protected Enone **5**



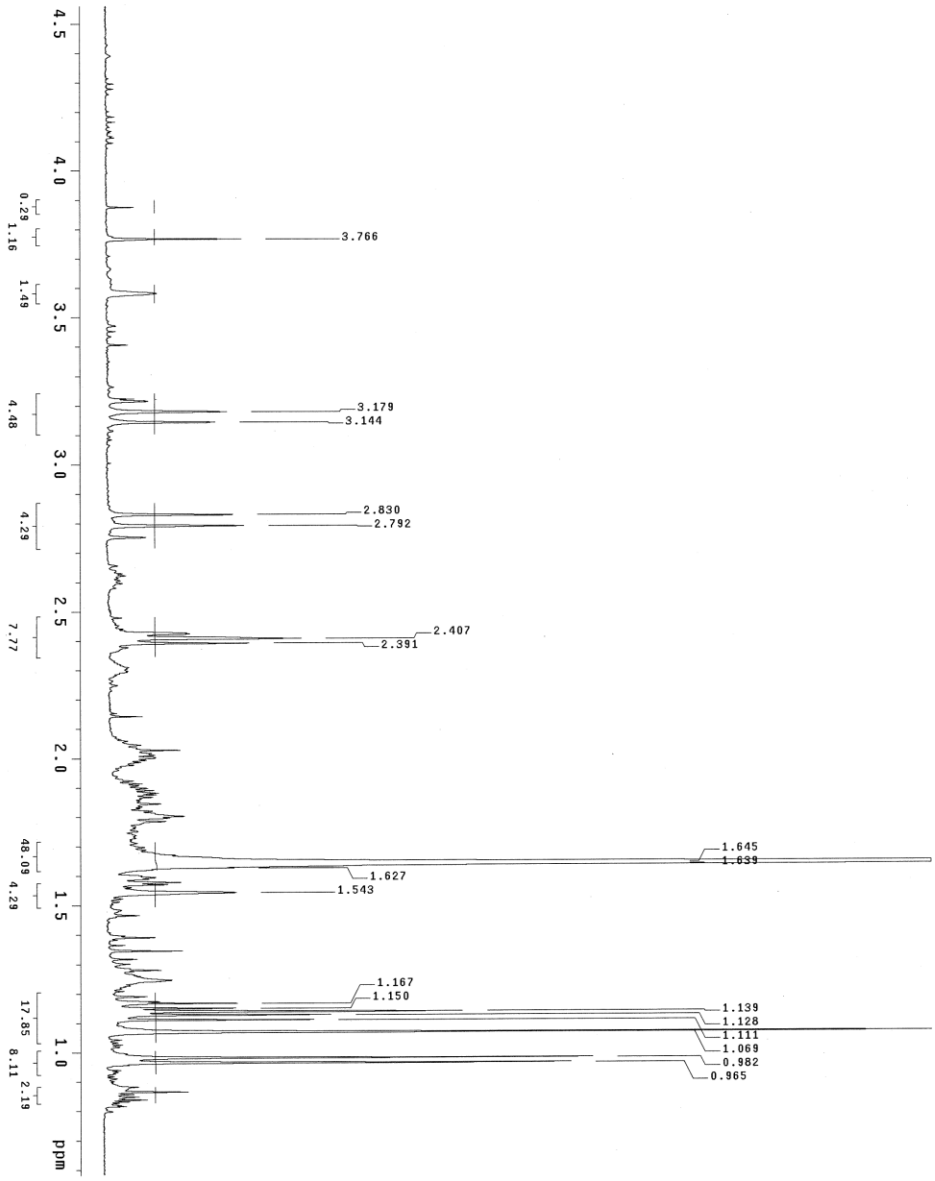
^{1}H-NMR for Boc Protected Enone **5**



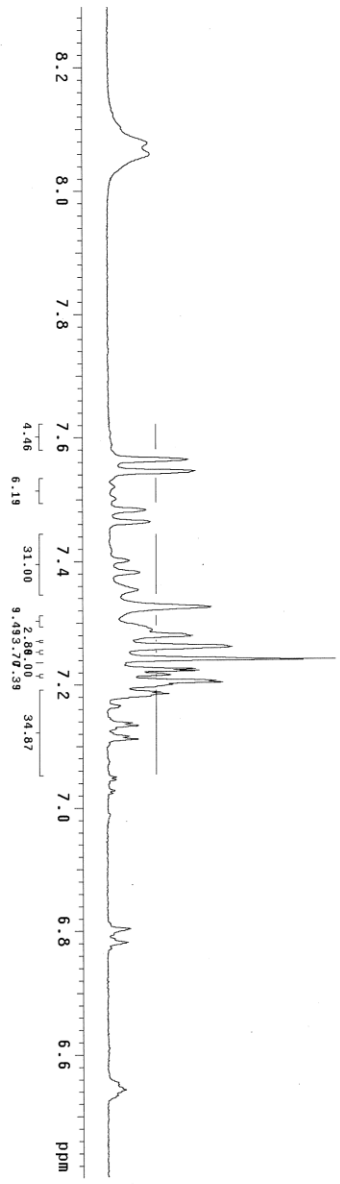
^{1}H-NMR for Boc Protected Ketone **4**



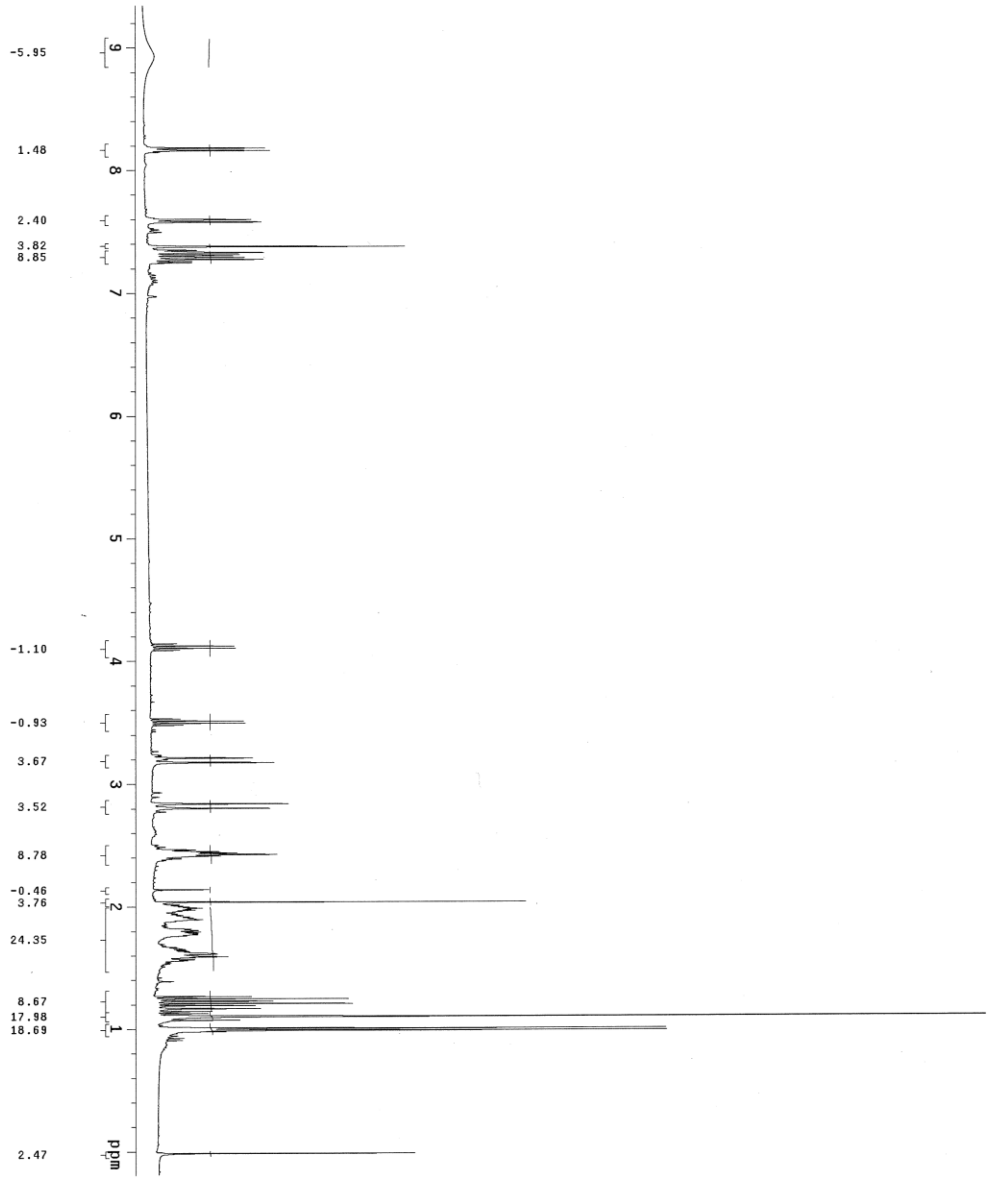
^{1}H-NMR for Boc Protected Ketone **4**



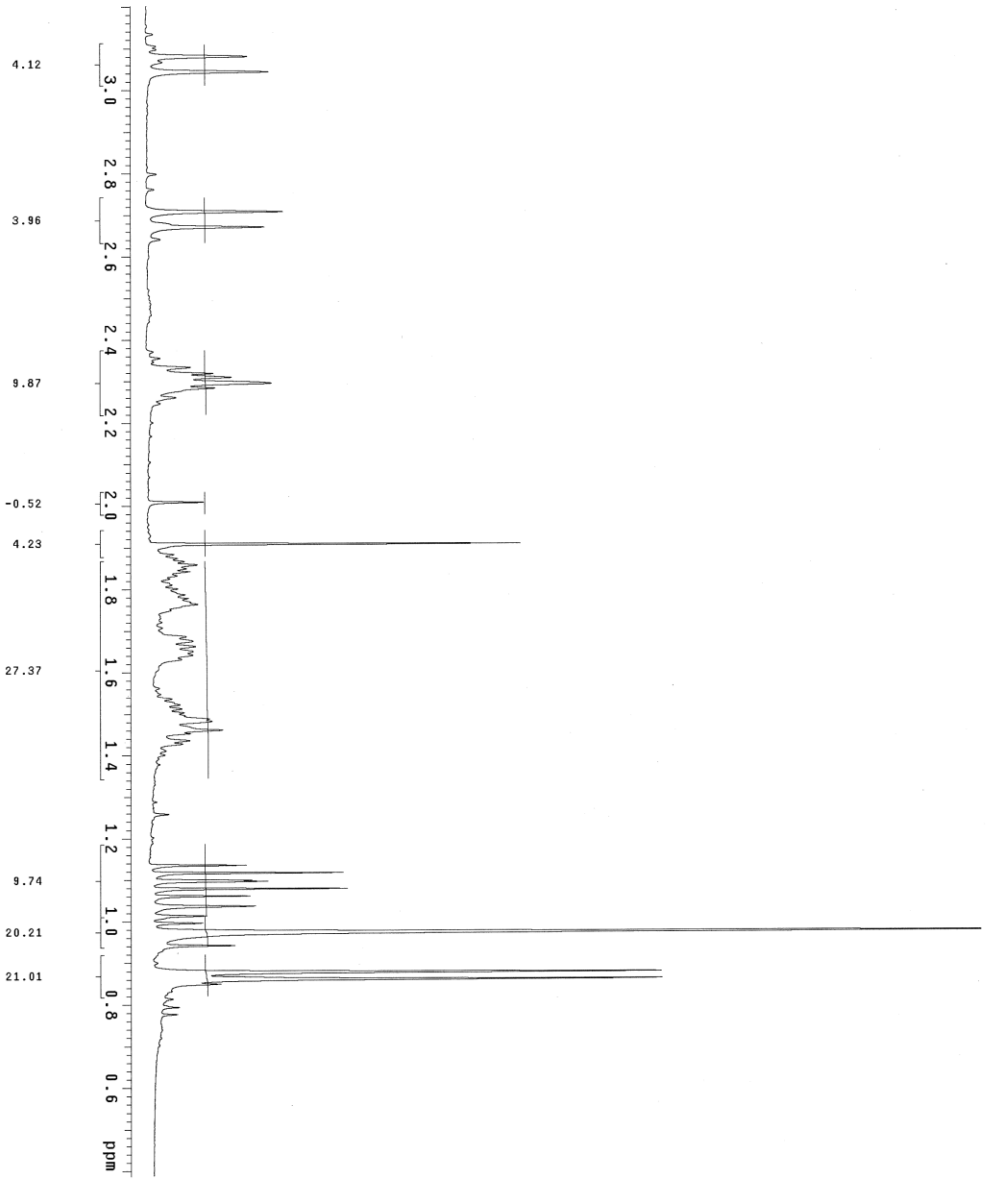
^{1}H-NMR for Boc Protected Ketone **4**



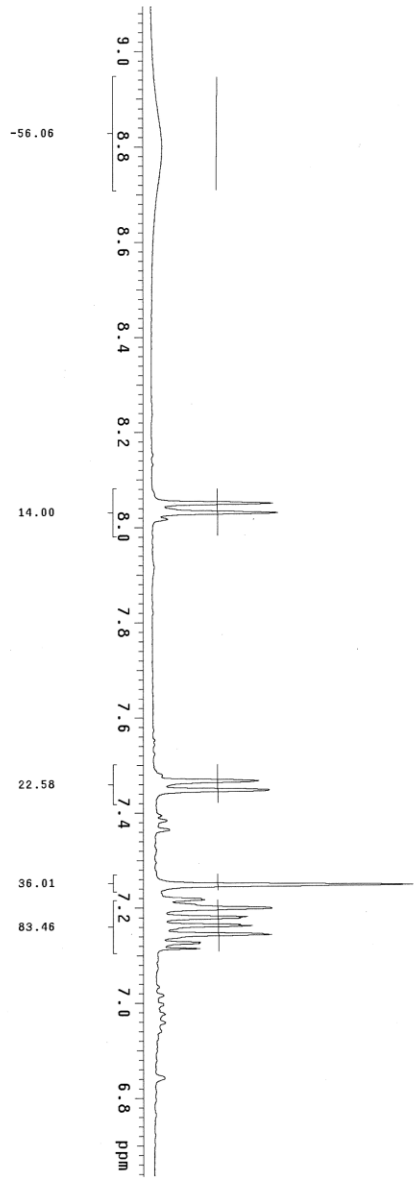
^{1}H-NMR for Boc Deprotected Ketone **4**



^{1}H-NMR for Boc Deprotected Ketone **4**



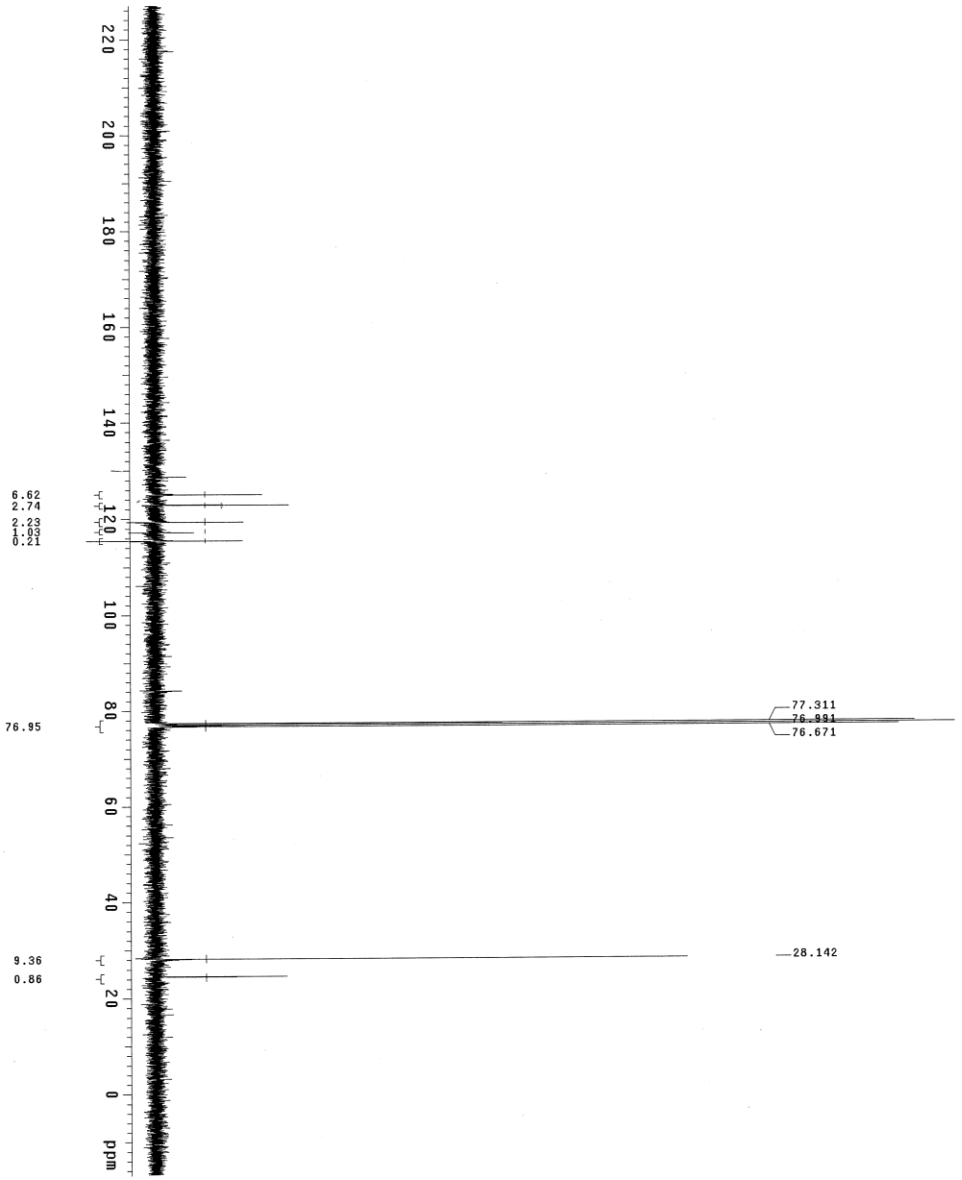
^{1}H-NMR for Boc Deprotected Ketone **4**



APPENDIX B

^{13}C-NMR SPECTROSCOPY

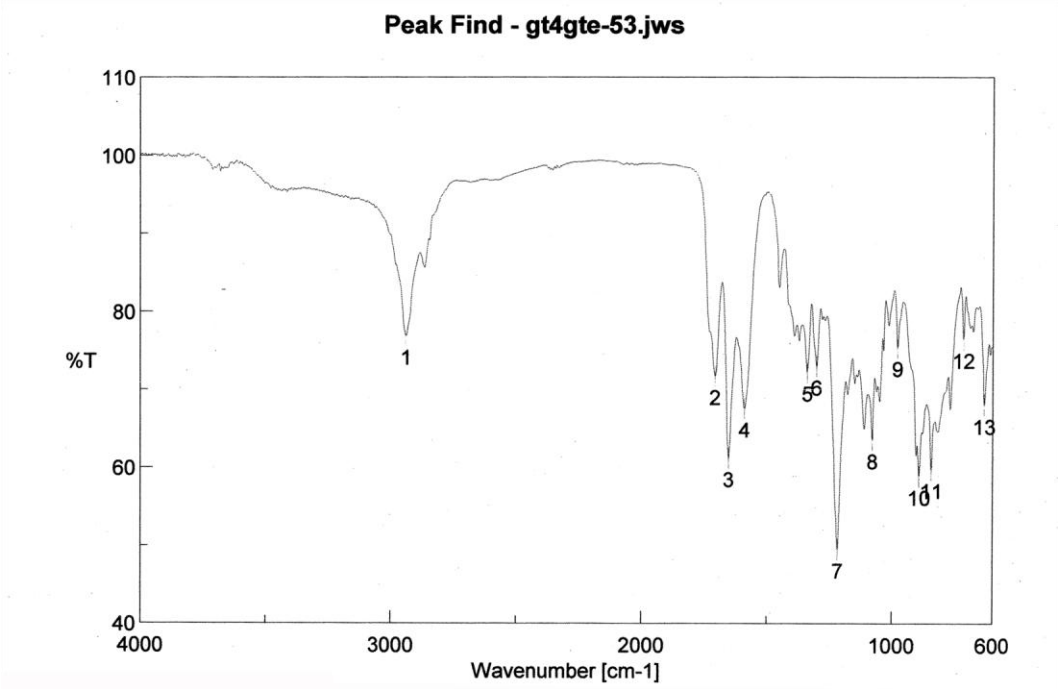
^{13}C-NMR for Boc Indole Bromide **11**



APPENDIX C

INFRARED SPECTROSCOPY

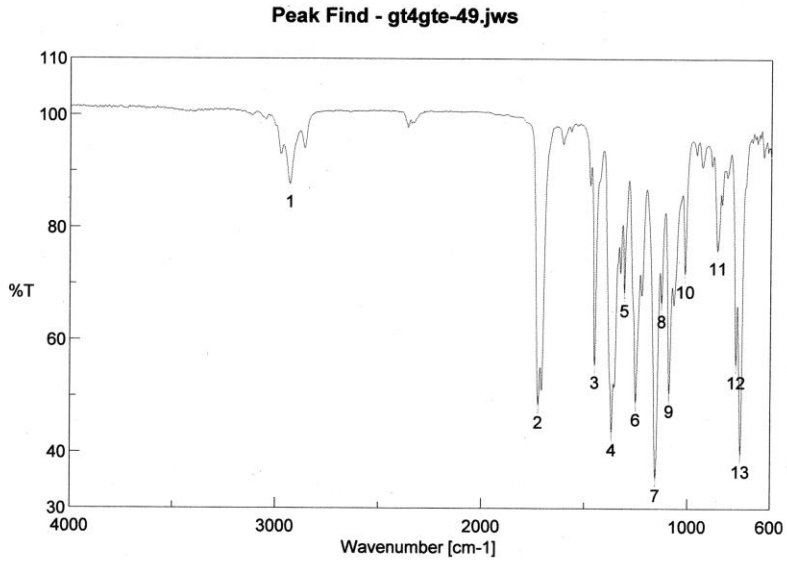
IR for Bicyclic Ketone **8**



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	2938.02	76.8368	2	1707.66	71.7394
3	1654.62	61.2162	4	1590.99	67.6046
5	1339.32	72.2145	6	1301.72	72.9824
7	1216.86	49.5147	8	1078.01	63.5553
9	977.733	75.3828	10	891.916	58.8904
11	843.704	59.769	12	715.461	76.4415
13	633.501	68.0202			

IR for Boc Protected Ketone **4**



[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	2932.23	87.7162	2	1726.94	48.5507
3	1451.17	55.6859	4	1367.28	43.7045
5	1308.46	68.4467	6	1253.5	49.0572
7	1155.15	35.5549	8	1127.19	66.57
9	1089.58	50.5609	10	1014.37	71.8412
11	856.239	75.981	12	766.566	55.7231
13	744.388	39.8141			