Total Synthesis: A Crowning Achievement in Organic Chemistry

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Abstract

Discoveries in organic chemistry have had profound impacts in many disciplines of science through the past century. Within the field of organic chemistry, research in total synthesis of natural products has provided a means of developing and advancing the study of different types of chemistry. The discovery of novel chemical transformations, use of total synthesis products in biochemical assay studies and structural studies of natural products are just a few examples of how total synthesis has influenced modern day chemistry. Developments in drug discovery such as the syntheses of penicillin and Taxol have led to applicable use of the science to help the greater global community. Total synthesis provides a means for chemists to use creativity and ingenuity to further develop knowledge of bioorganic compounds and to develop novel chemical transformations useful in medicinal chemistry. Within this paper, total synthesis will be illustrated as the most crowning achievement of modern day organic chemistry based on the earliest total syntheses, modern day total syntheses, the development of novel chemical reactions and its applicability to chemical biology research.

I. Introduction and Early Total Syntheses

Albert Einstein once stated, “Any intelligent fool can make things bigger, more complex, and more violent. It takes a touch of genius - and a lot of courage - to move in the opposite direction.” The development of chemistry as a science has had an incredible impact on a multitude of different fields of study including medicinal science, physics, biology and even religion. However, this significance can be easily characterized by the vastness which the field of chemistry encompasses. Many of the modern day advances within this field have been direct products of the study of total synthesis of natural products. Total synthesis is defined as “the chemical synthesis of a molecule, usually a natural product, from relatively simple starting materials” (**1)**. The significance of this chemical synthesis derives from the fact that “every natural product type isolated from the seemingly limitless chemical diversity in nature provides a unique set of research opportunities deriving from its distinctive three-dimensional architecture and biological properties” (**2)**. It is from the study and research involved with total synthesis that natural product structure can be studied and advances using such techniques as x-ray crystallography can be accomplished. Through total synthesis, advances in medicinal chemistry and drug development are achieved as well as novel chemical reactions that allow for cleaner and more efficient reactions. The impact that total synthesis has had on society is essentially immeasurable, however it is possible to understand some of the impacts and novel chemistry that have resulted through the independent and creative study of total synthesis.

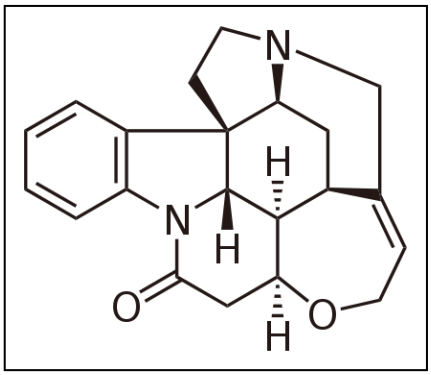
Living organisms are incredibly impressive in the way that they are able to produce novel organic compounds that can be utilized within that organism. Synthetic organic chemistry has capitalized on the biosynthetic pathways of these organisms and used natural products as the targets in total synthesis projects. The synthesis of these natural products was originally used to

aid in the determination of the molecular structure of these compounds; however its use has advanced in more recent years. Total synthesis has led to developments of new synthetic chemistry, use in biological assays and studies and the ability to mass produce a natural product when natural abundance is not useful (**2**). This progress in synthetic chemistry has advanced quite far from the Wohler synthesis in 1828, in which the first total synthesis was conducted where ammonium cyanate was converted to urea and modern day organic chemistry was begun (**3**). Now in the 21st century, important advances in methodology have resulted including the Cope rearrangement, the Shapiro asymmetric epoxidation, metathesis chemistry, the Horner-Wadsworth-Emmons reaction as well as Kharasch chemistry. Complex heterocyclic structures have been synthesized and seemingly impossible chemical transitions have been accomplished with advances in catalyst chemistry. The impact of total synthesis has advanced the field of organic chemistry and provided an avenue for scientists to develop reactions and theories that move away from traditionally accepted beliefs. The use of total synthesis in developing novel chemistry and its utilization in biological studies marks it as the most important advancement and area of study within the organic chemistry discipline, for it unifies inorganic chemistry, catalysis study, structural studies, chemical biology and a multitude of other areas of chemical research.

Total Synthesis of Strychnine

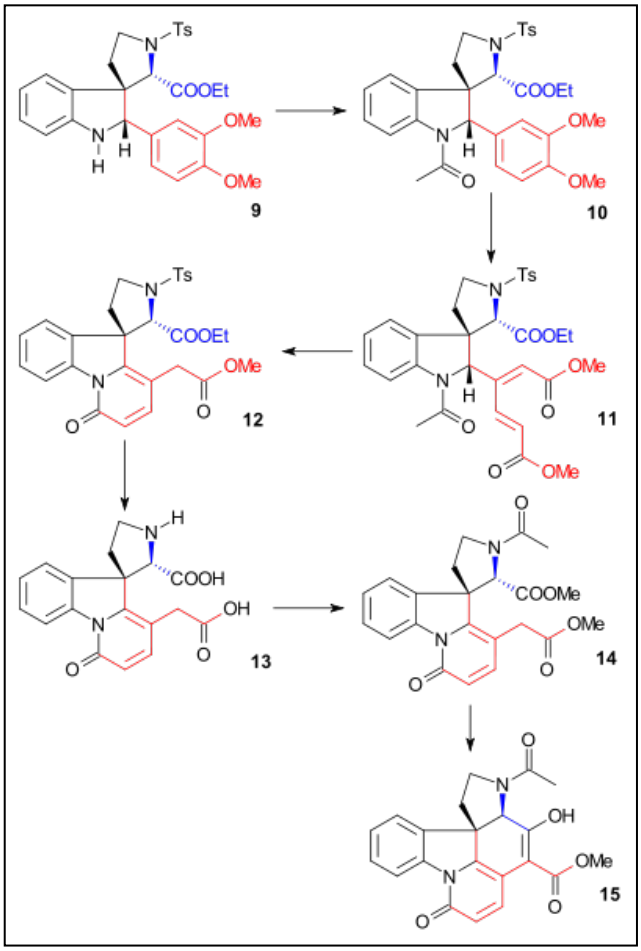
Before delving into more recent chemistry, it is essential to understand developments in total synthesis dating back over the past 60 years that have led to novel chemical transitions and reactions. The 1954 synthesis of strychnine by Woodward provided a preeminent example

Figure 1: Strychnine



of the masterful achievement that organic synthesis could accomplish. The strychnine structure is incredibly complex as a polycyclic structure although it is only composed of 24 atoms (Fig, 1). In 1952, Sir Robert Robinson remarked about strychnine that, “For its molecular size it is the most complex substance known.” (**4**). The synthesis began with the reaction of phenylhydrazine and acetoveratrone to produce 2-veratrylindole and would progress to form 22 other compounds before the final steps resulted in the synthesis of strychnine (**5**). Within the total synthesis, Woodward utilized a number of notable chemical reactions including a Dieckmann condensation, Lactam formation and imine formation that allowed for this seven ring structure to be synthesized. One of the most notable reactions within the synthesis is when compound **10** is exposed to ozone in aqueous acetic acid and an oxidative cleavage results to produce the ester (Figure 2) (**5**). Due to the free rotation of the ester, it then becomes possible for the free rotation to allow for an intramolecular attack to enable the formation of the 6-membered ring in compound **12**. Despite the complex chemical reactions, including the oxidative cleavage of an aromatic ring, displayed within this synthesis it is significant for a number of other reasons. The synthesis of this compound was completed merely eight years after the first x-ray crystallographic structures of strychnine were produced in 1948 (**6**).

Figure 2: Veratyl Ring Cleavage

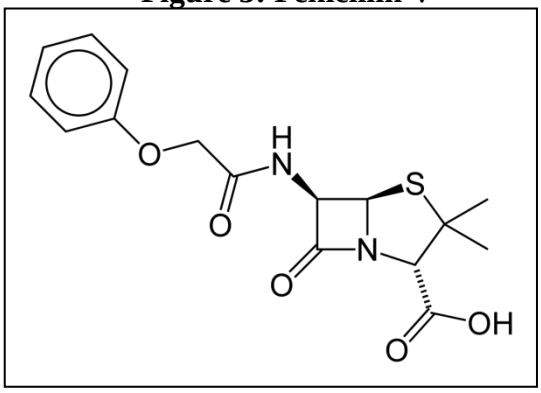


However more importantly than the relative quickness with which the synthesis was designed and completed, is the fact that such a complicated molecule had never before been synthesized in this manner. Woodward laid the groundwork for future organic chemists to realize that the complex products of living organisms could indeed be synthesized by organic chemistry techniques.

Total Synthesis of Penicillin V

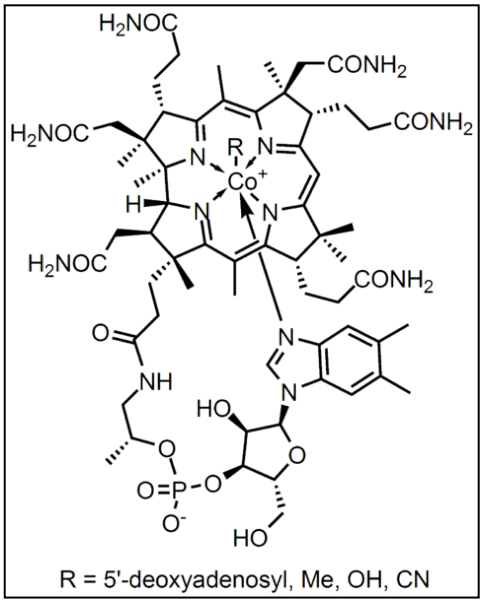
As mentioned previously, the importance of total synthesis in medicinal chemistry and the pharmaceutical industry is incredibly significant. Many natural products exhibit therapeutic qualities and therefore provide the groundwork for drug design and discovery. One such natural product is Penicillin which demonstrates impressive activity against a number of pathogens that infect and affect humans. In 1957, J.C Sheehan completed and published the synthesis of Penicillin V (Figure 3) with the use of a number of commonly utilized organic reactions (**7**). As evident within the total synthesis scheme, the accomplishment of this synthesis was conducted using relatively mild conditions with temperatures at or below room temperature. The crystalline DL-penicillin V potassium salt only demonstrated 51.4% of the activity of natural penicillin V, which was a result of the L-penicillin V exhibiting almost no antibiotic activity (**7**). However, by reacting D-penicillamine hydrochloride with *t*-butyl pthalimidomalonaldehydate, the synthesis of the natural product is able to be achieved and confirmed by microbial assay. Most notable in this synthesis was the use of previously established reactions including the use of aliphatic carbodiimides to form amide bonds in aqueous solutions. This chemistry could subsequently be used to produce racemic

Figure 3: Penicillin V



amino acids in aqueous solutions following the first few steps of Sheehan's synthesis. It is important to note that such steps seen within total synthesis frequently apply to different purposes such as the potential to develop unnatural amino acids through amide bond formation in aqueous solution. The importance of this synthesis does not merely lie in the use of chemical transformations to produce Pencillin V, but in the timing of this synthesis. Shortly after the conclusion of World War II, this total synthesis gave hope to the potential of developing a drug that could combat the infections that abounded as a product of war (**2**). The synthesis of penicillin demonstrated the ability to produce a natural product that exhibited immense bioactivity and the potential to alter the penicillin structure to deal with mutating pathogens was established. In understanding the significance of this synthesis it is important to understand that by synthesizing these natural products, biological assays can be conducted that determine the reactive pathway of these drugs in destroying harmful agents. By understanding the bioactivity of these compounds and with established syntheses it becomes much simpler to create analogues of the natural product that could also exhibit antibiotic activity. This is useful when pathogens mutate to survive the effects of drugs such as penicillin and new drugs can be created that may prove to be toxic for the pathogen.

Figure 4: Vitamin B_{12}



Approximately 15 years after the synthesis of Penicillin V, Woodward and Eschenmoser provided the total synthesis of Vitamin B_{12}. The immense structure of the compound and the novel bond formations marked this as one of the most significant organic syntheses. The structure of vitamin B_{12} (Figure 4) exhibits complex stereochemistry where a central macrocyclic nucleus is

present in which are embedded four, five-membered heterocyclic rings with a number of side chains where the majority of them have a simple amide group at the terminus while one exhibits an isopropanolamine group (**8**). The difficulty in how to approach the synthesis of this large macrocyle was simplified slightly because in 1960, Bernhauer demonstrated that cobyric acid was a product of the degradation of vitamin B_{12} and therefore demonstrated the partial synthesis of vitamin B_{12} from the cobyric acid natural product (**9**). However this simplification was just the first step in what would be a 12 year process to synthesize the natural product. Woodward and Eschenmoser separated the compound into four main ring structures that would need to be synthesized in the retrosynthetic scheme. As illustrated in Figure 4, the four rings would be the four, five-membered outer rings of the macrocylce in each corner. They would be denoted A-D in a counter clockwise manner where rings A and D would be fused together while rings B and C were fused together and eventually these two molecules would be couples and chemical modified to produce cobyric acid (**8**. As discussed above, the final step would be the conversion of the acid to vitamin B_{12} based on Bernhauer's 1960 paper.

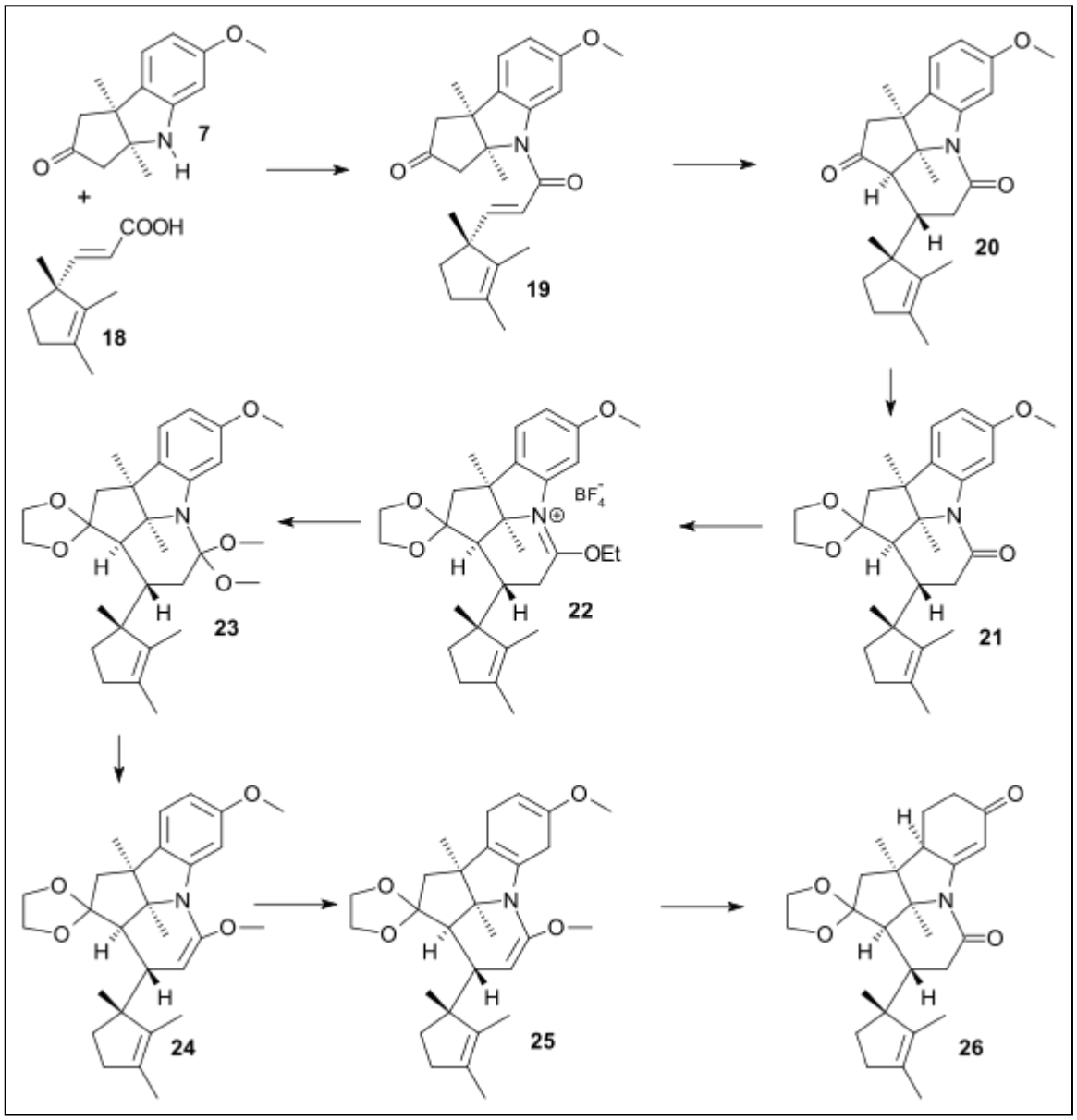
Total Synthesis of Vitamin B_{12}

Due to the significance of the vitamin B_{12} total synthesis, it is important to demonstrate the synthetic scheme that Woodward presented in 1873 that led to one of the most remarkable syntheses ever completed. The first part of the total synthesis of vitamin B_{12} involved the coupling of rings A and D to each other. As illustrated below, ring 7 is representative of ring A, which was synthesized utilizing metathesis chemistry and a final ring closure (**2**). Compound 7 in Figure 5 is the enantiometrically pure form of the diastereomer necessary to retain the correct stereochemistry in the final product. Compound 18 is representative of ring D which was synthesized from camphor as the starting material and utilizes the well-established Wittig

reaction to produce the trans C=C bond. There are nine overall steps to produce the final coupled product that will subsequently be coupled to the B-C rings including the initial conversion of compound 18 to the acid chloride.

Compounds **7** and **18** are initially coupled through a condensation reaction to form the

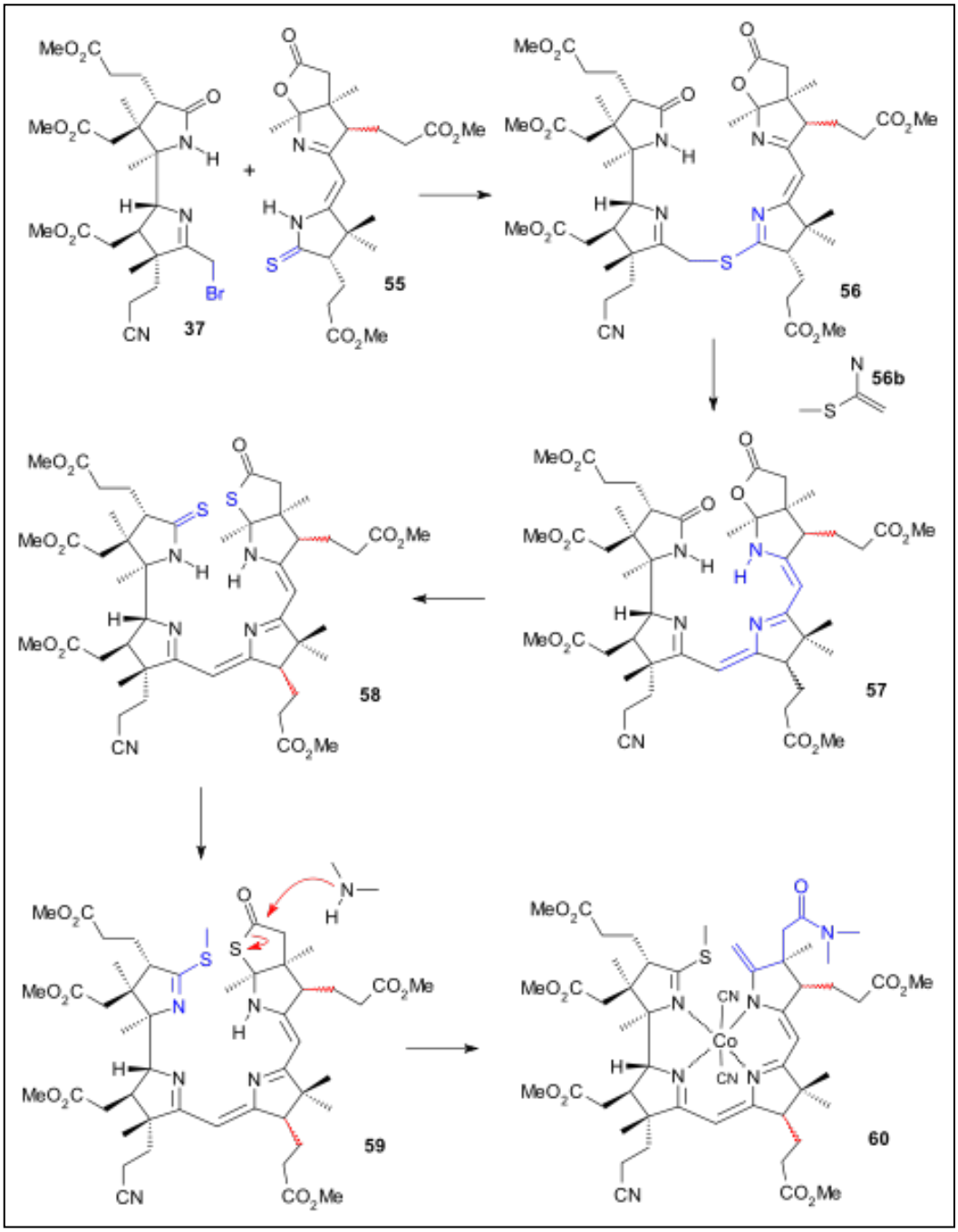
Figure 5: A-D Ring Coupling



amide that is reacted with potassium *tert*-butoxide to allow for an intramolecular Michael addition that results in compound **20**. Selective alkylation utilizing Meerwein's salt produces compound **22** which is subsequently converted to **24** with NaOMe, $PhCH_3$ and heat. Compound

24 then undergoes a Birch reduction where the aromatic ring is reduced to the dihydro level utilizing lithium metal in liquid ammonia and *tert*-butanol to produce the intermediate pentacyclenone. Although the coupling is complete, a fair amount of tailoring steps must be conducted to produce the correct ring structure which include oxime formation, oxidative cleavage, mesylation, esterification and eventually an acid-catalyzed reaction to produce corrnorsterone. A base induced conversion is utilized in order to convert all of the corrnorsterone to the beta form (**2**). The β-corrnorsterone is converted to the desired cyanobromide compound that will be coupled with the tailored product of the coupling

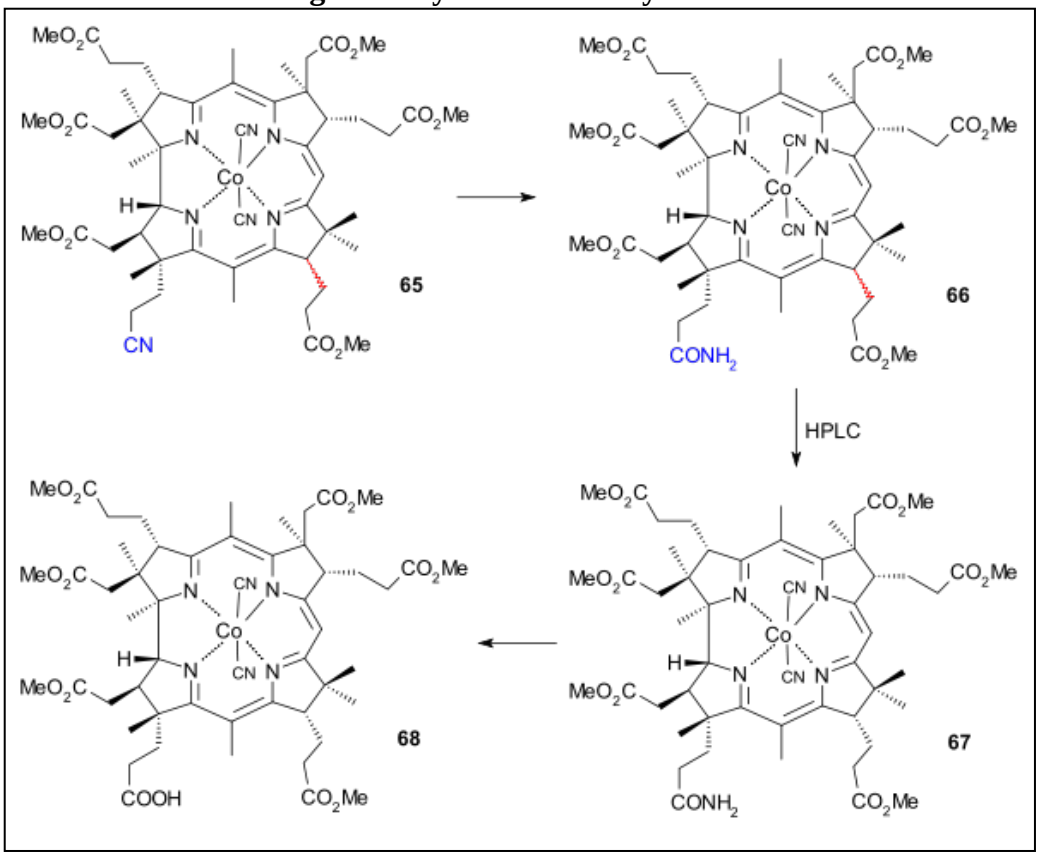
Figure 6: AD-BC Ring Coupling



of ring B and ring C to each other.

Compounds **37** and **55** in Figure 6 respectively represent the coupling products of rings A and D as well as rings B and C. Illustrated above is preliminary final coupling steps to put the macrocyle together. The first step involves the formation of a carbon-sulfur bond through the use of *tert*-butoxide followed by the use of cyanoethyl phosphine, trifluoroacetic acid and sulfolane to produce compound **57** known as cyanocorrigenolide. A selective alkylation of the thiolactam sulfur atom in ring A produce **59** which then undergoes cleavage of the thiolactone and treatment with cobalt chloride produce compound **60** (**2**). The cyclic structure will be fully closed using diazabicyclononane followed by treatment of that compound with iodine and acetic acid. Phenylthiomethyl groups will eventually be incorporated and reductive removal of the phenylthio group using Raney nickel will produce the cobrynic acid structure represented by compound **65** in Figure 7. Sulfuric acid is used for the transformation from compound **65** to compound **66** which is subsequently purified via HPLC and deaminated in a solution of carbon tetrachloride and dinitrogen tetraoxide with sodium acetate. Compound **68**

Figure 7: Synthesis of Cobyric Acid



will be subjected to a solution of liquid ammonia and ethylene glycol to produce the desire cobyric acid (**2**).

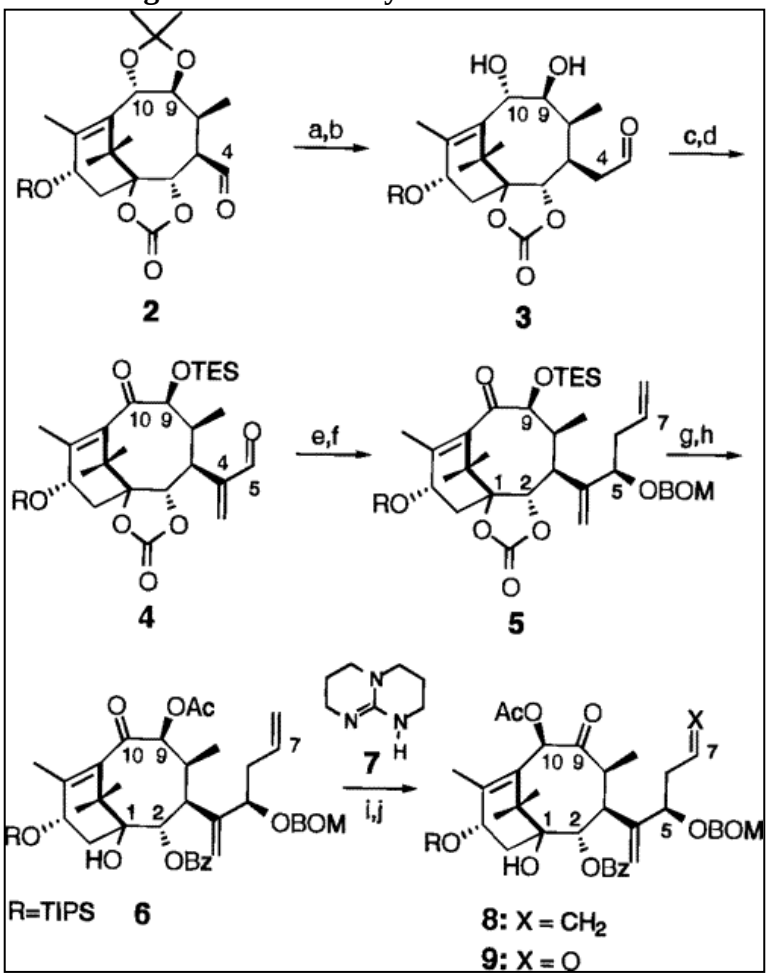
Although not all of the steps were illustrated through figures, the significance of this synthesis is evident in the numerous unique cyclization reactions to produce the desired compound. Following Bernhauer's research the cobyric acid would be transformed to (-)-vitamin B_{12}. The synthesis itself utilizes dozens of established chemical reactions to perform transformations that are difficult to align together. The use of Schiff base reactions, Grignard chemistry, aldol condensations, selective alkylations, oxidative cleavage, esterification and deamination are only a few of the many types of organic reactions that Woodward and Eschenmoser utilized. The most remarkable part of this synthesis however lies in the vision of the chemists and their ability to develop a retrosynthesis that so logically worked. Within a molecule characterized by numerous stereocenters focused around a macrocyclic ring it is nothing short of astonishing how effective the total synthesis was. This synthesis laid the groundwork for future organic chemists to utilize novel bond-forming techniques, especially with respect to cyclic structures. It was one of the first natural product total syntheses that was undertaken with the hopes of discovering new chemical techniques and transformations to create complex products. Due to its structure already being determined, the focus did not lie in simply making the molecule, but synthesizing it in an efficient and ingenious manner. It is evident that Woodward's involvement in this synthesis would begin to lay the foundation for the Woodward-Hoffman Rules where stereospecificity in pericyclic reactions would be characterized by orbital symmetry.

II. Recent Total Synthesis Projects

Synthesis of Taxol

The original synthesis of Taxol was completed in 1994 and published by Nicolaou in *Nature* after the development and total synthesis of the cancer drug had posed an incredible challenge for many years. In 1971, the structure of Taxol was published and its potential as a cancer therapy agent was analyzed (**10**). It is derived from the stem bark of the Pacific yew tree, *Taxus brevifolia*, and was the first compound with a taxane ring to demonstrate tumor inhibitory properties (**11**). Therefore, when Nicolaou completed the first synthesis of the cancer drug, its impact was significant. Nicolaou produced a convergent synthesis that involved key chemical steps including a pinacol-coupling reaction and a Shapiro reaction (**12**). This synthesis was significant because produced the natural product, but once again enabled the production of different analogues of the compound to produce a vast array of taxoids.

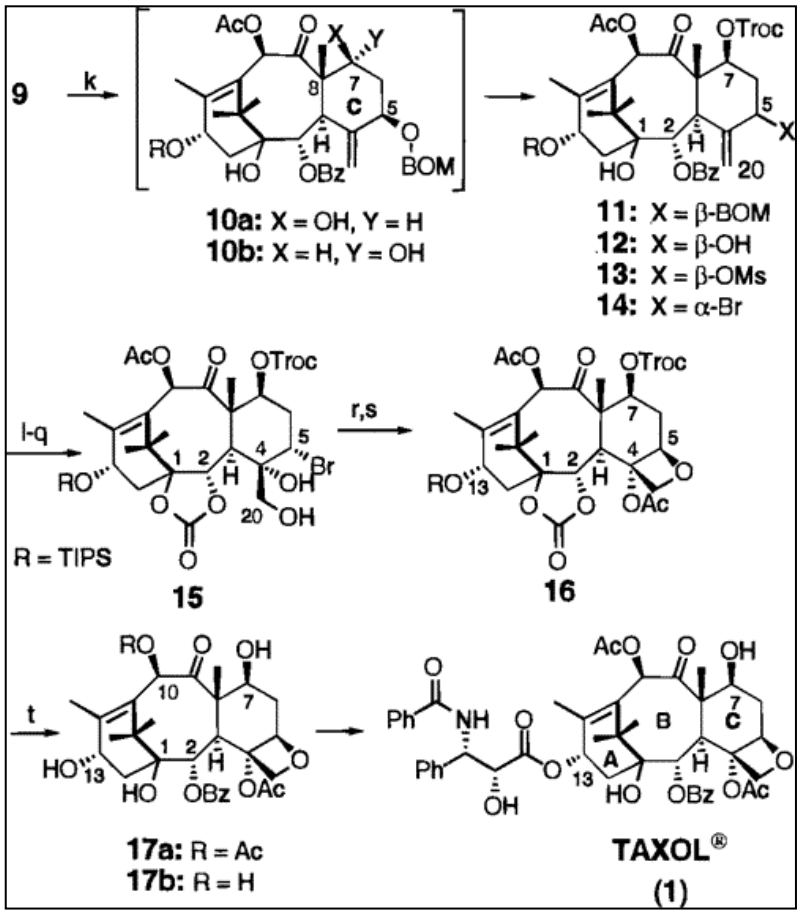
Figure 8: Wender Synthesis of Taxol



A few years later, Wender produced his own synthesis of Taxol with a different approach than that of Nicolaou since it was a linear synthesis and was the shortest synthesis of the potent natural product to that time (**13**). Wender's synthesis involved the use of pinene as the starting material which underwent

chemical transformations to produce the taxane precursor depicted in Figure 8 as compound **2**. A one-step hydrolysis produces the aldehyde of compound **3**. The hydroxide is subsequently selectively protected using TESCL and pyridine and a Dess-Martin periodinane oxidation is performed to produce the enal observed as **4** which is added to a solution of allylmagnesium bromide and $ZnCl_2$ and subsequently BOM protected. The C9 silyl group of **5** is removed using NH_4F and MeOH which reacts with PhLi to produce compound **6**, the acetate. With the use of the guanidinium base, **7**, transposition of the acetoxyketone was successful and the monosubstituted alkene was cleaved by ozonolysis to form aldehyde **9** which was then exposed to 4-pyrrolidinopyridine to produce a mixture of **10a** and **10b**. **10a** was then protected with TrocCl to produce **11** which was then converted to the alcohol **12**. The mesylate product was formed using MsCl, DMAP and pyridine which ultimately produced a labile bond that when exposed to LiBr produced compound **14**. Diol **15** was formed using osmium tetroxide to introduce oxygen which formed oxetane and caused a benzoyl migration to produce diol **15** as it was removed with KCN in ethanol. Acetylation of the C4 hydroxyl produced **16** which was exposed to TASF to remove the TIPS group and PhLi to produce

Figure 9: Wender Synthesis of Taxol



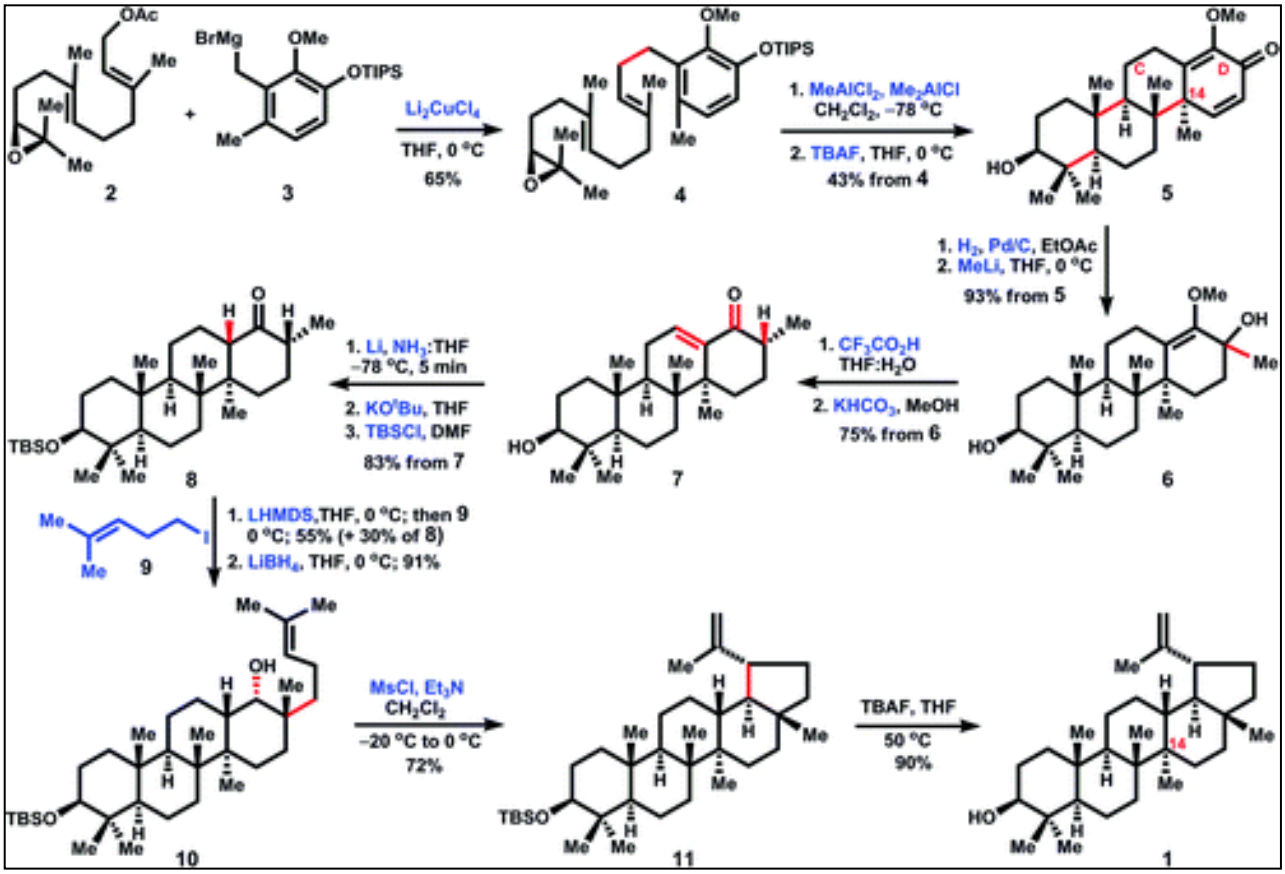
compounds **17a** and **17b**. The conversion from this compound to Taxol is done using an established procedure in which NaH is added to produce the sodium salt followed by l-benzoyl-(3R,4S)-3-(l-ethoxyethoxy)-4-phenyl-2-azetidinone and a final deprotection step using 0.5% HCl (**14**).

The final product of Wender's synthesis is the desired product Taxol, which is currently being developed by Bristol-Meyers Squibb. The drug has produced great success within breast, lung and ovarian cancer. The significance of such total syntheses as the initial success of Nicolaou and the simplified synthesis of Wender lie in the ability to mass produce these drugs at reasonable cost. Cancer therapy is incredibly expensive which stems largely from the cost of production of the drug cocktails to aid in the destruction of tumors. By advancing and shortening the total synthesis, as well as improving the yield, a greater percentage of drugs can be developed and used. This therefore allows for the impact of the total synthesis to be felt by society as a whole where advances in total synthesis can lead to more cost efficient processes and novel reactions that allow for complex syntheses to become more reasonable.

Synthesis of (+)-Lupeol

Lupeol is a pentacyclic triterpene that is found in a number of compounds including mangos. It has been shown to decrease the swelling of paws in mice by as much as 39% but does not exhibit the same mechanism as non-steroidal anti-inflammatory drugs do (**15**). In addition, it has been shown to inhibit skin cancer in mouse models where it is believed to affect the promotion stage of tumorigenisis at several different pathways(**16**). The first enantioselective total synthesis of lupeol was completed just a year and a half ago by Corey where two cation-π cyclization leads to the formation of the pentacyclic triterpene (**17**).

Figure 10: Synthesis of Lupeol



The first step of the synthesis as illustrated in Figure 10 is the copper catalyzed coupling utilizing the Grignard reagent **3**. Compound **4** was then activated using a Lewis acid to allow for the first cyclization reaction to occur and form compound **5**. The tertiary alcohol, **6**, was then synthesized though a selective Pd catalyzed hydrogenation and methylation. Compound **7** was synthesized using acid and base to produce the enone and subsequent reduction of the α,β-double bond produced the ketone, **8**. Compound **10** was formed by an alkylation and reduction of the ketone **8** and **10** was then exposed to mesylation conditions which allowed for the spontaneous second cyclization and subsequent TBAF deprotection to produce the desired compound, (+)-Lupeol, **1**.

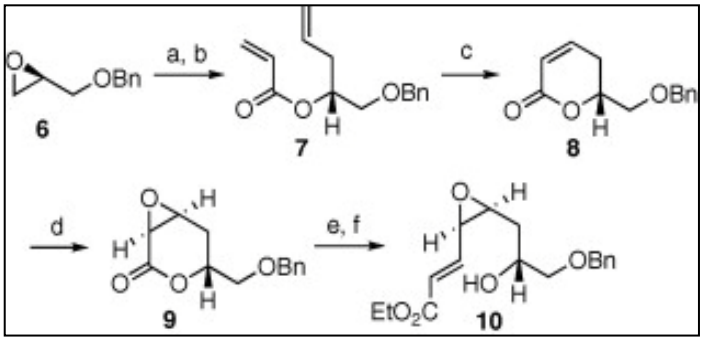
The significance of this synthesis is characterized by its brevity as well as the unique chemical transformations it employs. There is a distinct choice in ring structures used to allow for the Lewis Acid activated cyclization which is sterically hindering (**17**). In addition, the

cyclization from **10** to **11** is unique in that it does not require very acidic conditions to allow for the ring closure. The importance of a short enantioselective synthesis such as this one is reminiscent of the synthesis associated with Taxol. By minimizing the number of steps involved and capitalizing on strategic choice of substrates, the synthesis is brief and introduces new chemical transformations that allow for seemingly difficult transitions, such as sterically hindered cyclizations, to occur.

Total Synthesis of (+)-aspergillide C

The aspergillides A-C are a group of compounds that are characterized by a 14-membered macrolide where a 2,6-*anti*-dihydropyran moiety is incorporated (**18**). Although all three compounds have shown bioactivity, aspergillide-C demonstrated the most potent activity against mouse lymphatic leukemia cells. Based on this potent activity, there is potential within this group of novel compounds to develop new cancer therapy drugs. The most recent synthesis of aspergillide-C was completed and published in early 2011 where the key step involves an "intramolecular oxy-Michael reaction of the substrate with a *cis*-epoxide" that is extremely diasterioselective (**18**).

Figure 11: Synthesis of aspergillide C



The synthesis begins with the conversion of *R*-(-)-benzyl glycidyl ether to compound **7** via a reaction with vinylmagensium chloride and CuI in THF followed by acryloyl chloride and EtMgBr in THF as depicted in Figure 11. Compound **7** then undergoes a metathesis reaction utilizing Grubbs 2nd generation catalyst in dichloromethane to produce the lactone **8** which is treated with peroxide to produce the diasterioselective epoxide, **9**. This is followed by a DIBAL-H reduction and a Horner-Wadsworth-Emmons reaction, which is just a

modified Wittig reaction, in which the six-membered ring structure is opened. Compound **10** was then studied as it would undergo the key intramolecular oxy-Michael, IMOM, reaction. When it was exposed to a solution of KH in THF at -78°C for 3 hours, a mixture of 1.3:1 of **12**:**13** was purified at 74% yield. The carboxylic acid, **11**, was prepared from **10**, and used to try and produce the desired product of **14**. The best yield for this anti-pyran carboxylic acid, **14**, however resulted from the reaction with LiOH*H_2O in THF/ H_2O (3:1) for 12 hours where 94% conversion was measured.

Figure 11: IMOM of aspegillide C

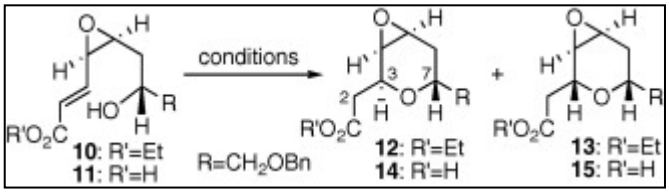
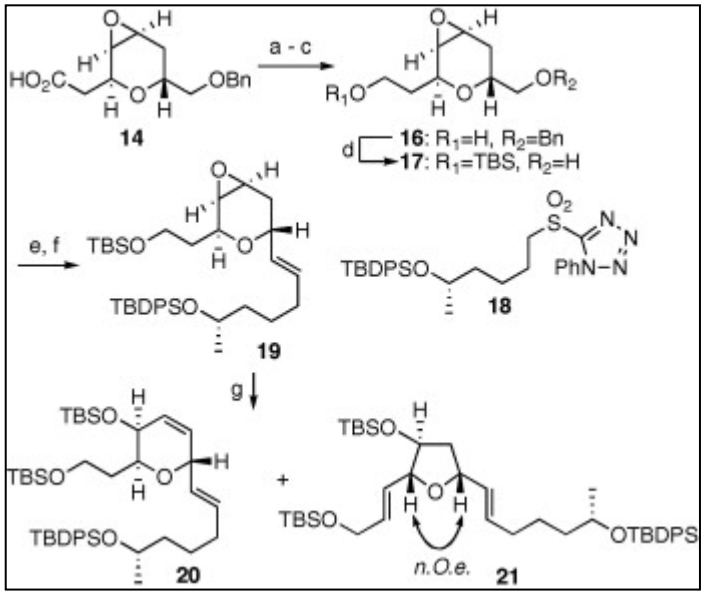


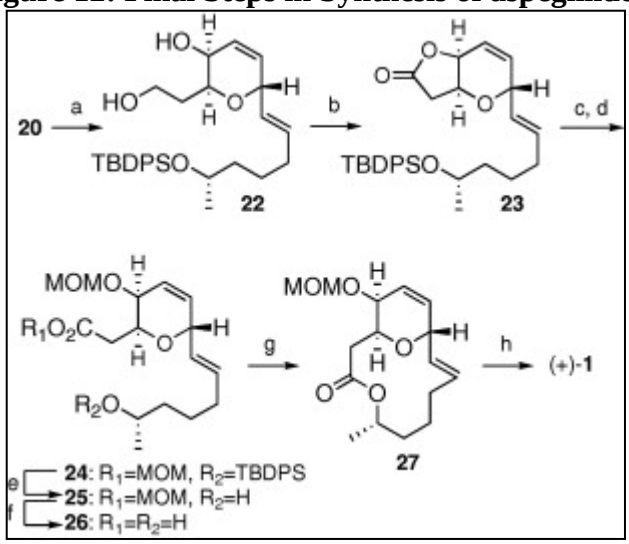
Figure 12: Synthesis of aspegillide C



The anti-pyran was then reduced to the primary alcohol and debenzylation followed producing compound **17**. An IBX-oxidation produced an aldehyde which underwent Kocienski-Julia olefination which is simply a modified Julia olefination where the reaction is completed in one pot and produces the *E*-olefin in the presence of LiHMDS and compound **18**. **19** is then converted to the allylic alcohol using TBSOTf, Hunig's base, and DBU to produce the desired compound **20** in a 51% yield. The rearranged product of **21** is able to be separated by chromatographic means and accounted for 20% yield from the reaction of **19**. The synthesis is completed by a selective deprotection of the TBS ethers and subsequent TEMPO oxidation that produces compound **23**, a lactone. A sequence of four reactions involving MOM protection and deprotection produces

compound **26** which reacts with 2,4,6-trichlorobenzoyl chloride, triethyl ether and THF to allow for the Yamaguchi macrolactonization to produce compound **27**. Finally, 6M HCL is used to finish the reaction with acid hydrolysis and (+)-aspergillide C is produced.

Figure 12: Final Steps in Synthesis of aspegillide C



A number of important factors contribute to the significance of this most recent total synthesis. The ability to capitalize on advanced chemistry such as in the modified Julia-olefination allows for the practicality of this synthesis to be used in medicinal chemistry. By eliminating some steps, the potential for the overall yield to increase is improved. With respect to the key IMOM reaction, an impressive 94% yield is afforded within an incredibly diastereoselective reaction. The natural potency of the compound is favorable for further testing on its potential potency, and as already noted, its cytotoxicity in a model mouse lymphocytic leukemia cell is promising (**18**). Most interestingly however, is the uniqueness of these compounds. They are the only known natural products with three stereogenic centers incorporated in a 2,6-*anti*-dihydropyran moiety of a macrolide. The ability to now synthesize these novel compounds is intriguing, yet most importantly informative.

III Novel Reactions in Total Synthesis

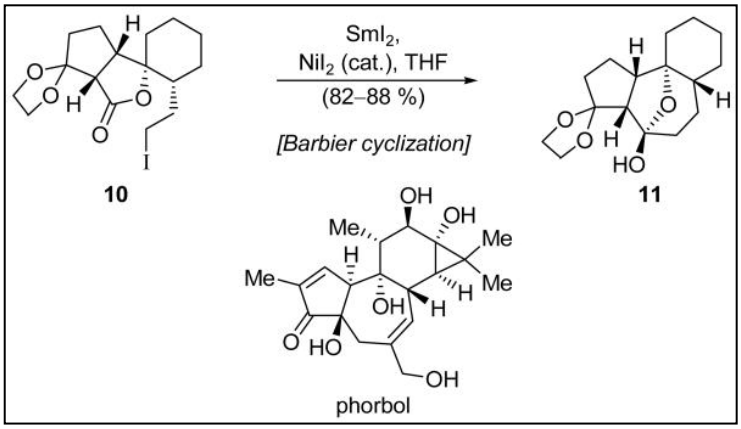
The previous six total syntheses described above were significant for their novel chemistry and in some cases ground-breaking discoveries. They utilized a multitude of different chemical reactions and procedures in order to produce on a nature's products. One of the most important contributions that total synthesis can make to the scientific community is the incorporation of novel reactions and transformations. It is creative and ingenious chemistry that advances the field and allows for progress to be made within the organic chemistry discipline. As Albert Einstein stated, moving in the opposite direction requires genius and it is only by challenging older chemistry and developing new chemistry that this genius will produce incredible advance in science. In a review by Nicolaou in 2009 he wrote, "Complex target total synthesis provides a compelling proving ground for promising new reagents and novel applications of existing reagents, some of which eventually become recognized as invaluable tools in the synthetic chemist's arsenal." (**19).**

Samarium Diiodide Mediated Reactions

Samarium diiodide has demonstrated many capabilities within organic reactions including but not limited to reduction of an alkyl halide, mediated radical-alkene/alkyne reactions and the fragmentation of cyclopropane and cyclobutane systems (**19**). SmI_2 is highly reactive, however what makes it so useful is the ability to optimize reaction conditions in order to enable the exact reaction one wants accomplished. The compounds usefulness is growing and it is one of the best single-electron reducing agents available for purchase.

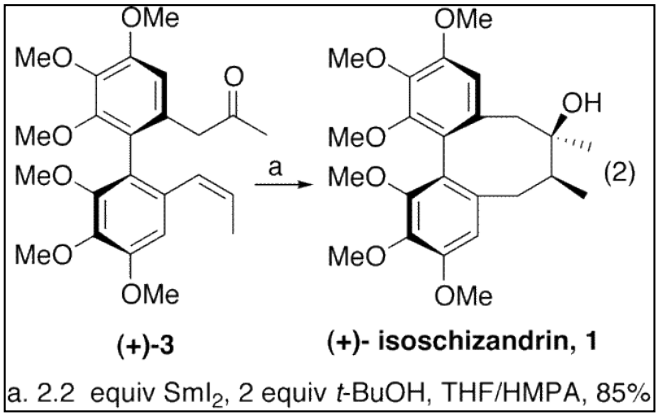
Samarium diiodide was first used in a SmI_2 – mediated Barbier reaction in 1977 by Kagan (**19**). The Barbier reaction is similar to a Grignard reaction, however it utilizes the reactive halide and the carbonyl within the same reaction mixture. The reaction produces the addition of an alkyl halide to a carbonyl group and is believed to have an organosamarium intermediate product formed when SmI_2 is used. The synthesis has been used in the synthesis of natural product vinigrol as well as in the synthesis of the phorbol system. In Figure 13, the reaction used in the phorbol system is depicted where a hemiketal is produced by the SmI_2-promoted Barbier reaction (**20**). It is important to note that by use of nickel instead of samarium, the reaction rate was improved, however the reason for this improvement is not fully understood. The impressiveness of this reaction is characterized by the fact that it only took 1 hour, was very clean and produced up to an 88% yield of only one isomer (**20**). This is incredibly important in the scheme of total synthesis as the relatively good yield and quick reaction allows for continued progress to be made in subsequent steps in the total synthesis.

Figure 13: SmI_2 in Phorbol Synthesis



Samarium diiodide is also useful in ring closing reactions in which the compound is used in a carbonyl-alkene/alkyne reaction. In this reaction, a ketyl radical forms and couples to an olefin which can be activated or unactivated. In Figure 14, the final step in the synthesis of isoschizandrin is

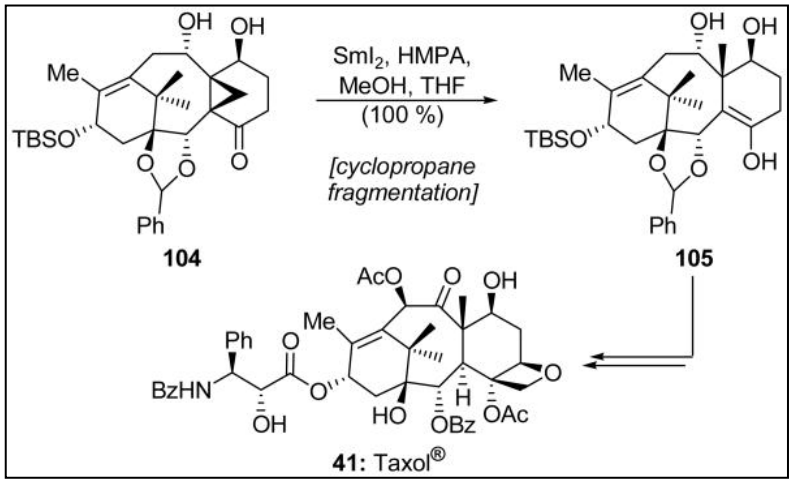
Figure 14: SmI_2 Cyclization Reaction



illustrated where samarium diiodide is used to enable a carbonyl-alkene cyclization reaction. There is great importance to the presence of the HMPA as it serves as a bound ligand to the samarium metal which is forced into a pseudo--equatorial position therefore enabling the correct stereochemistry to form during the cyclization and the absolute configuration of isoschizandrin is produced (**21**).

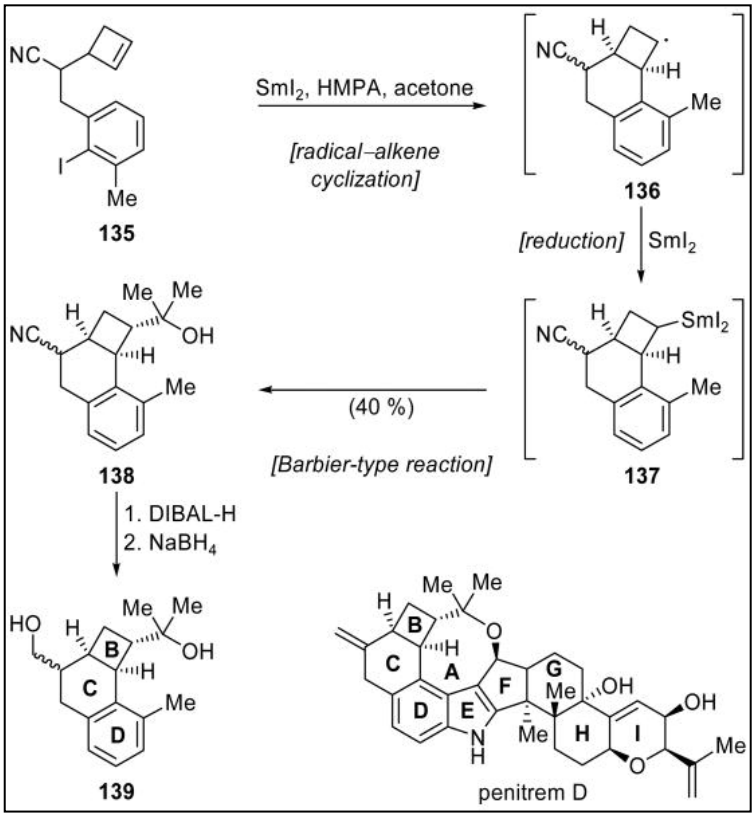
Within many total syntheses it is common to see various ring formations and fragmentations. Although unnecessary steps with simply functional group changes want to be minimized, the formation or breaking of rings can often times be key steps in a synthesis. Samarium diiodide has proved incredibly useful in the fragmentation of cyclopropane and cyclobutane ring systems. It serves as a manner of adding hindered constituents by opening rings and crowding the complex ring structures even more (**19**). A notable use of SmI_2 in a total synthesis is the 1998, Kuwajima synthesis of Taxol as illustrated in Figure 15 where the sterically hindered cyclopropane ring is fragmented to produce the enol, compound **105** (**22**). In this case, there is no new, more complex ring system formed, but instead the crowded cyclopropane is fragmented opening the structure up slightly.

Figure 15: SmI_2 in Taxol Synthesis



The final example that will be provided of a SmI_2 – promoted reaction is the impressive cascade reaction in which a series of reaction result from the use of one set of reagents. Within cascade reactions it is possible to produce a number of different reaction, cyclizations and even

Figure 15: Cascade SmI_2 Reaction in Penitrem D



numerous stereogenic centers (**19**). One prime example of this is the use of SmI_2 – promoted cyclization in the synthesis of penitrem D by Curran in 2004. Within this cascade reaction depicted in Figure 16, the samarium diiodide forms a cyclobutyl radical that is then reduced to form the organosamarium complex. The following step is the "tandem radical/polar crossover reaction" with acetone that produces the desire cascade product, **138** (**23**). The reaction with the acetone is similar to a Barbier-type reaction that will produce a tertiary alcohol. A number of different substrates were tested with respect to the cascade reaction depicted in Figure 15 where different groups from cyanide were placed alpha to the four-membered ring. In the synthesis above with respect to the procedure followed for penitrem D the overall yield of the cascade reaction was 40%, however different substrates had as high of a yield as 60%, mainly with various oxygen complexes in place of the cyano group.

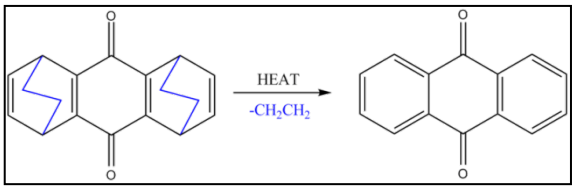
It appears that many of the earliest syntheses that utilized the samarium diiodide complex stemmed directly from Henri Kagan. His first use of the reagent in the Barbier reaction laid the groundwork for new chemistry to be accomplished with the use of SmI_2. It has proven to be incredibly helpful in synthesizing C-C bonds and sometimes breaking those bonds in a fragmentation process. The use of SmI_2 in cascade chemistry is incredibly promising as the use

of tandem reactions minimizes cost, use or reagents and waste products while often times accelerating the reaction. There are hundreds more reactions that utilize this SmI_2 – mediated chemistry and its widespread use and ability to serve as a strong reducer are what make it such a promising reactant in many types of reactions.

Birch Reduction and Total Synthesis

The Birch reduction is an incredibly useful tool in organic chemistry whereas aromatic compounds are reduced using sodium in liquid ammonia to produce some analogue of a 1,4- or 1,3 -cyclohexadiene (**24**). Interestingly, it the use of the Birch reduction as a precursor to other organic chemistry reactions that makes it so useful in total synthesis projects. The accessibility of numerous enol ethers as defined above as the product of the Birch reduction, allow for the use of a multitude of synthetic reactions and novel transformations (**25**). One example of a potential reaction utilizing two 1,4-cyclohexadienes is the Alder-Rickert reaction illustrated in Figure 16. The lack of aromaticity in the molecule on the left can be a direct result of eliminating that aromaticity through a Birch reduction. It is clear that the Birch reduction will produce different substituted cyclohexadienes and in this case the 1,4-cyclohexadienes will undergo pyrolysis to produce the aromatic rings on the right side of Figure 16. (**24**). In addition to the example above, there are a vast number of natural product syntheses that have utilized the 1,4- and 1,3-cyclohexadiene structure produced by the Birch reaction including the fungal metabolite, altenusin; the isocoumarin natural product, mullein; the macrolide, curvularin and the metabolite, stemphol (**24**).

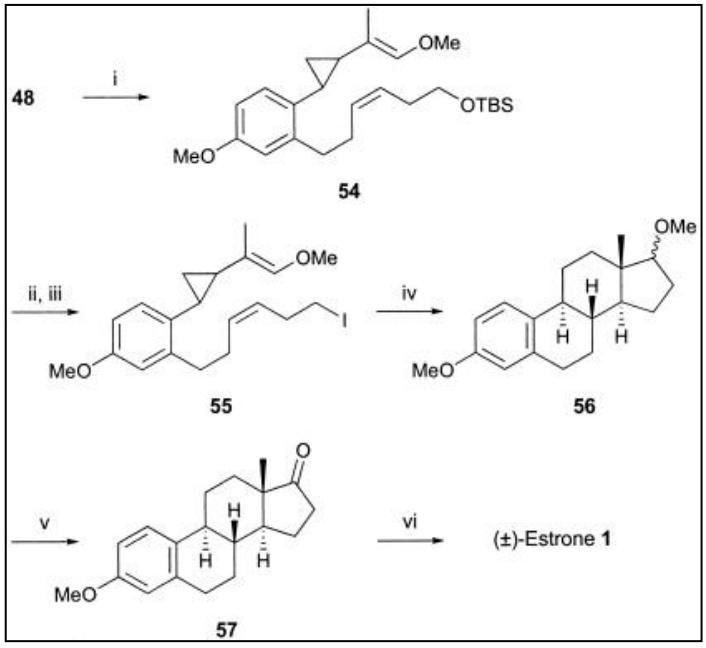
Figure 16: Alder-Rickert Reaction



Cascade of Radical Cyclizations in Estrone Synthesis

Steroids are organic compounds that are composed of four fused ring structures that can have a number of different functionalizations attached to the fused core. One specific steroid that has been synthesized numerous times is estrone based on its importance in female biology as an estrogenic hormone that is secreted by the ovaries and the fact that its structure is not incredibly complex (**26**). With respect to many syntheses of estrogens, the importance of the Diels-Alder reaction is immeasurable as it enables the formation of the fused ring structures to produce the steroid backbone. However, there have been advances in utilizing different means to create the steroid such as a cascade radical-mediated process (**27**). The Woodhead group in England demonstrated the use of radical chemistry to enable the cascade reactions. The first step in the synthesis, as depicted in Figure 17 involved synthesis of two different iodotrienones that would undergo subsequent chemical transformations to eventually lead to the formation of a vinyl methyl ketone that would be subjected to methoxymethyldiphenylphosphine oxide in the presence of lithium diisopropylamide to enable a Horner-Wittig reaction and the production of compound **54** (**27**.) TBAF would then be used to deprotect the TBS group before iodine, triphenyl phosphine and

Figure 17: Estrone Radical Cascade Synthesis



imidazole would be used to produce the iodated intermediate, **55**. This intermediate would then be exposed to Bu_3SnH/AIBN which would enable the metal catalyzed radical cyclization that would construct the steroid backbone of compound **56**. The overall yield for the radical reaction is approximately 15% which equates to about 65% for each step. The synthesis is then completed with a Jones' oxidation to produce estrone methyl ether which is demethylated with boron tribromide leading to the synthesis of estrone.

The radical cascade that produced estrone is interesting in that it utilizes radical chemistry to allow for a number of different transformations. The closing of three ring structures in a one pot reaction is important in total synthesis as it complete numerous transformations in one step which in turn save chemicals, time and money. Although the overall yield of the reaction is not fantastic at only 15%, it is necessary to take into account that all of the reactions could be individual steps in the synthesis that would be more time consuming and perhaps not improve the yield all that much as more steps essentially always decreases the reaction's overall yield. The use of these cascade reactions as well as tandem synthesis is truly important. It is allowing for more complex reactions to be completed as novel organic chemistry reactions simplify syntheses time and time again by utilizing reagents to their fullest capacity.

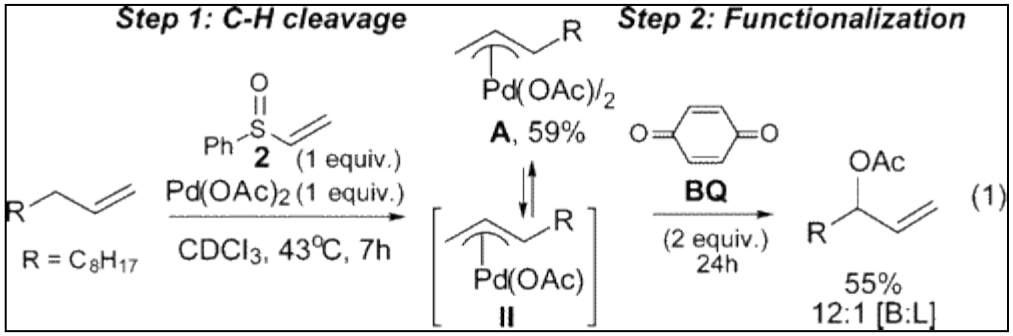
Metal-Catalyzed C-H Bond Functionalization

One of the greatest challenges in total synthesis is the inert character of the C-H bond that can prevent organic chemists from completing the synthesis of natural products. The reason for this inert character lies in the fact that the C-H bond is extremely strong and has a low polarity (**28**). However, despite the inevitable difficulties, recent developments in chemistry using metals as catalysts have allowed for a number of new transformations to be accomplished. These developments are incredibly significant because essentially all organic natural products are

composed of a framework of C-H bonds and the ability to selectively activate them to allow for chemical tranformations will enable the completion of more total syntheses. In addition, previously uncompleted total syntheses of complex natural products, may be able to be accomplished with novel chemical reactions.

In 2005, the White group from Harvard published a JACS paper in which a novel catalysis mechanism was used where two different ligands enabled the reaction to be completed. They illustrated a "mild, chemo-, and highly regioselective Pd(II)-catalyzed allylic oxidation of α-olefins" to produce allylic esters (**29**). As illustrated in Figure 18, compound **2** and **BQ** are used to enable the formation the product from the α-olefin. The use of **2**, enables to allylic C-H cleavage that forms the Pd−π-allyl intermediate **II**. Following this step, **BQ**, which serves as a functionalization-promoting ligand, is added to enable the formation of the allylic ester (**29**).The significance of such a reaction sequence lies in the fact that the conditions are incredibly mild as compared to previous reactions that utilized metal ligands. In addition, the use of two different ligands in sequence allow this challenging transformation as each ligand reacts in a different manner to form two distinct steps within the synthesis and catalytic cycle. This reaction lays the groundwork for further serial ligand catalysis reactions where difficult transformations may be accomplished using multiple ligands that can react in sequence to each other. The ability to functionalize a C-H bond is important for the advancement of organic chemistry and this reaction

Figure 18: Pd(II)-Catalyzed Allylic Oxidation



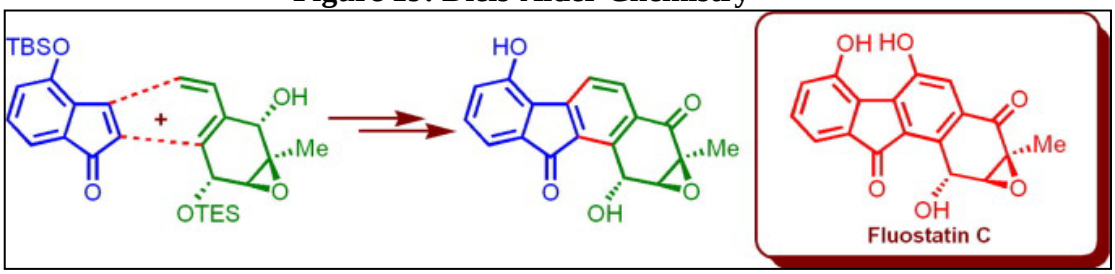
sequence can be added to the toolbox of organic reactions for further total synthesis and organic chemistry research.

In addition to the above example, many other advances in C-H activation have been demonstrated to be useful in total synthesis chemistry. Pd(II)-catalyzed allylic C–H oxidation, palladium-catalyzed C–H oxidation/macrocyclisation reactions, C–H oxidation using metalloporphyrin systems and Pd(0)-catalyzed C–H activation of sp^3 C–H bonds are just some examples of the types of activation that can be accomplished to produce cyclic structures, esters and a number of other chemical functionalities (**28**). The use of these reactions in the total synthesis itself is evidence of the significance of total synthesis chemistry. Many of the above examples of C-H activation have been utilized and essentially discovered within the total synthesis of a natural product. Therefore, the desire to synthesize natural products has led to a number of novel chemical transformations that can be useful within total synthesis and within organic chemistry in general.

Novel Diels-Alder Reaction

The Diels-Alder reaction has been used effectively and frequently over the past 80 years as it allows for the formation of substituted cyclohexene systems through a reaction of a diene and a dienophile. In 2011, the Das group in Bangalore, India illustrated that the reaction of the epoxyquinone which served as the diene and the 4-hydroxy-indenone which served as the dienophile was a key step in a total synthesis of Fluostatin C as illustrated in Figure 19. The importance of the synthesis of

Figure 19: Diels-Alder Chemistry



Fluostatin C is based on its biological activity as it has demonstrated some inhibitory effects against HMO2, HepG2 and MCF7 cell lines (**30**). Although Danishefky, reported the synthesis in 2008, the synthesis by the Das group was shorter, largely due to the recognition of the epoxyquinone's characteristic as a good diene to be used in a Diels-Alder reaction. Danishefky also used a Diels-Alder cyclization, however between as vinyl-indene and quinoneketal which formed a tetracylce that required many tailoring steps to complete the synthesis (**30**). In the synthesis by Das, the pentacycle is synthesized during the Diels-Alder reactions and much fewer steps are needed to complete the synthesis of Fluostatin C. Danishefky was able to use Diels-Alder chemistry for this synthesis, however Das demonstrated a different reaction that allowed for a more efficient synthesis. Considering that many natural products contain ring structures, the novel key step in Das' synthesis provides an example of how new transformations and different reactions can be used for the same synthesis. In this case, a different fragmentation of the final product allowed for the use of a different Diels-Alder reaction.

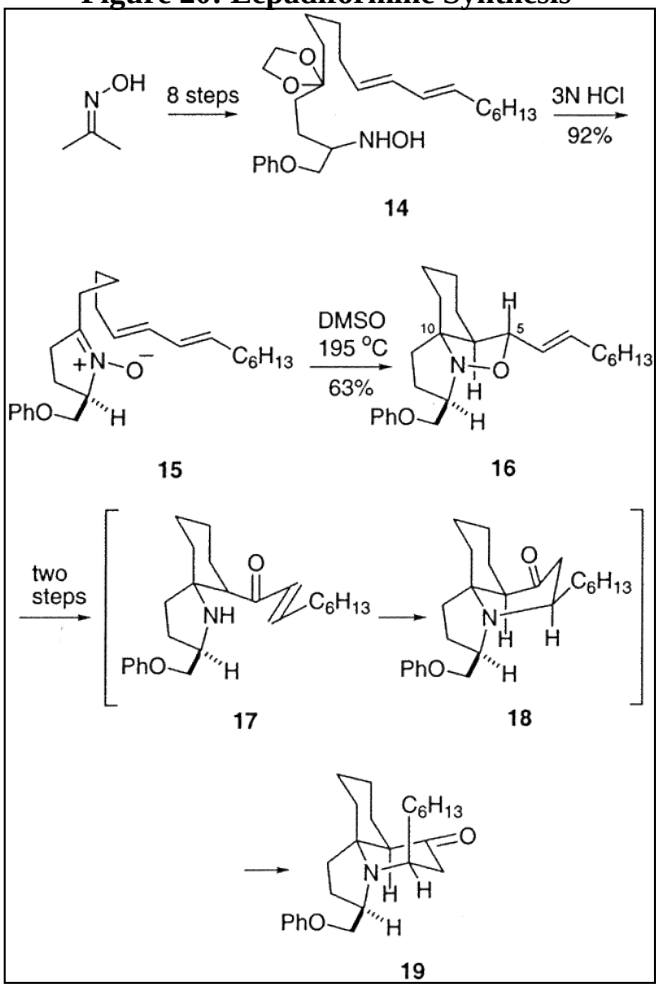
IV Total Synthesis and Chemical Biology

Chemical research in total synthesis has proven to be essential in the development of novel organic transformations; however the scope of total synthesis is not exclusively limited to organic applications. Advances in other fields, such as chemical biology, have been largely influenced by advances in total synthesis. Total synthesis provides an additional tool for developing novel chemical transformations that can be used to synthesize products for biochemical assays as well as has provided an additional way to confirm the structures of bioorganic compounds. The use of such techniques as X-ray crystallography in conjunction with total synthesis can provide a lot of information about the structure and function of various compounds found in biological systems. Total synthesis of alkaloids, protein ligands and peptide building blocks are just a few examples of how organic chemistry and total synthesis can impact studies in biology.

Lepadiformine Synthesis

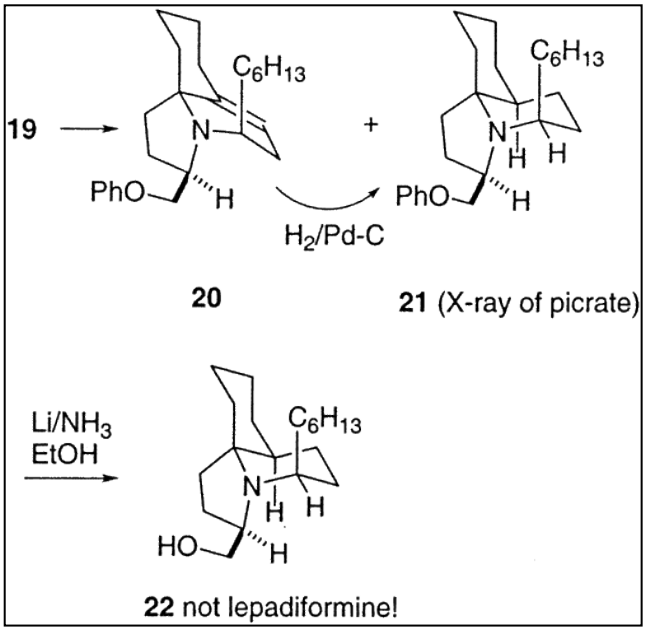
Lepadiformine is a natural product that was found in marine tunicate *Clavelina lepadiformis* and exhibited cytotoxic effects against a number of cancer cell lines according to the Biard group in 1994 (**31**). Within their publication in *Tetrahedron Letters*, they also published a structure of what they believed lepadiromine to resemble. This structure classified the natural product as a cylindricine which remained in a *cis*-1-azadecalin

Figure 20: Lepadiformine Synthesis



conformation similar to other natural products in this class of compounds (**31**). Due to the interesting structure and the exhibited biological activity of lepadiformine, the stereoselective total synthesis of the compound was undertaken. Based on the structure published by Biard, the total synthesis began as illustrated in Figure 20. Compound **14** underwent acid-promoted cyclization to produce compound **15** which was then heated in DMSO to produce the [3+2]-cycloadduct. N-O cleavage on compound **16** was completed with Zn/HOAc and the Dess-Martin reagent was then used to oxidize the intermediate that resulted in the formation of compound **19**. As illustrated in Figure 21, A Clemmensen reduction in which the ketone was reduced was then performed which produced **20** as the major product in addition to **21**. Compound **20** then underwent a Birch reduction to remove the phenyl group and produce compound **22**. Interestingly, the NMR spectra of this molecule did not match the spectra that Biard provided in determining the structure of lepadiformine, meaning that this was not actually the structure of the natural product being studied. In addition, Biard had suggested that the tricycle existed in a zwitterionic form where there is a positive charge and a negative charge at different places within the molecule, however there was no indication that the molecule synthesized by Weinreb had this character (**31**).

Figure 21: Lepadiformine Synthesis Cont.



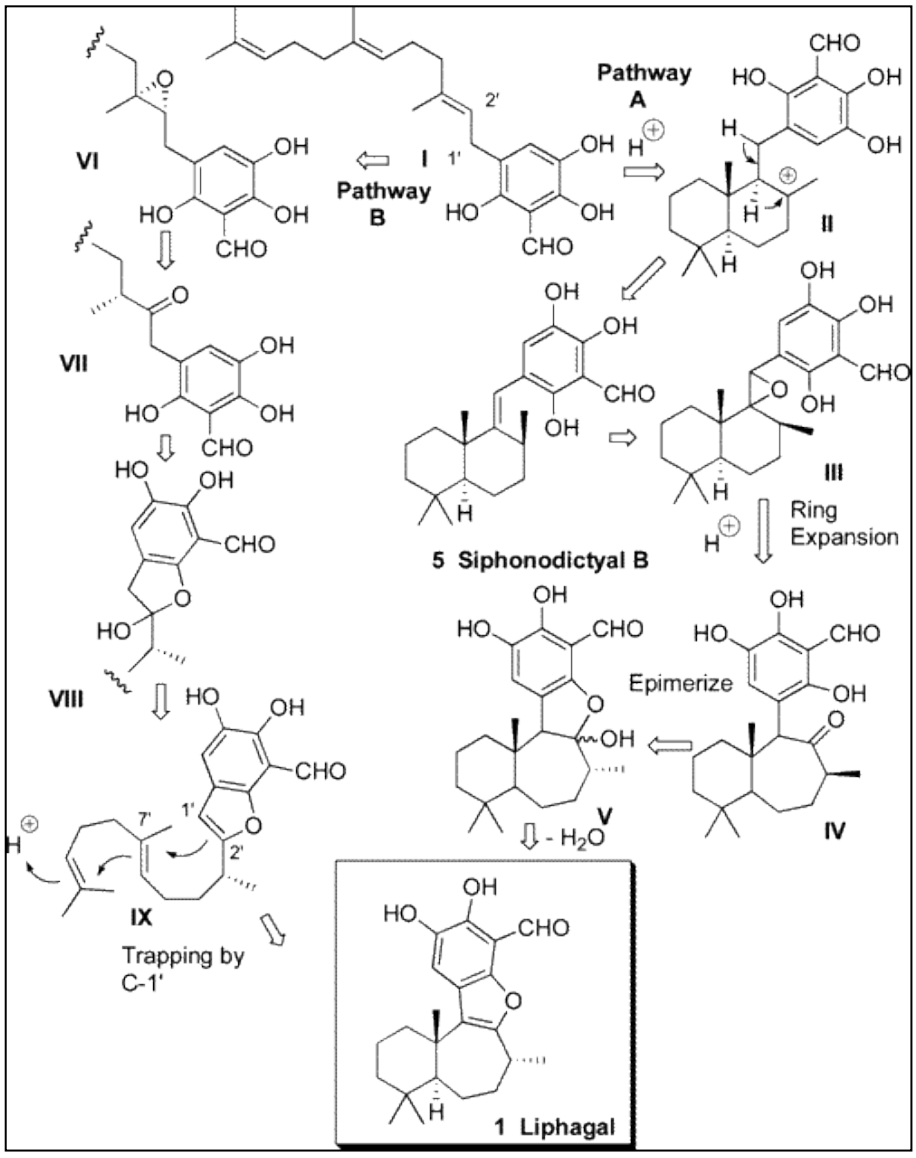
The importance of this synthesis by Weinreb, lies in the fact that it disproved a previously published and accepted structure of the natural product, lepadiformine. The actual structure was

determined by Kibayashi who demonstrated that natural lepadiformine was a hydrochloric salt of Figure 22, not a zwitterion and that it existed in a twist-boat conformation (**31**). Six years separated the publication of Biard's structure from the correct structure determine by Kibayashi in 2000 which is not insignificant. The use of synthetic chemistry in this case, was first able to disprove a previously accepted structure and subsequently determine the correct structure. Total synthesis is incredibly important in confirming natural product structure and providing an additional means of studying biological products. Although someone else may have eventually determined that the original lepadiformine structure was incorrect, the time that the structure remained published and accepted could have affected subsequent chemical studies of this compound. Total synthesis provides an avenue for confirming structure determined by other means such as x-ray crystallography and NMR studies. Therefore, the use of total synthesis is not exclusively limited, as exhibited here, to synthesis of products simply for the sake of synthesizing them, but instead can be utilized in biological studies of structure and function.

Total synthesis of (+)-Liphagal

It was previously demonstrated that synthetic chemistry can be useful for the field of chemical biology in which natural product structure can be determined and confirmed, however, biochemistry can also prove to be incredibly useful for synthetic chemistry. One example of a total synthesis that was heavily influenced by the proposed biosynthetic route of formation of the natural product is the synthesis by the Adlington group in Oxford of (+)-Liphagal. Liphagal was isolated by the marine sponge *Aka Coralliphaga*, through a study that aimed to find new inhibitors of the phosphoinositide-3-kinase signaling pathway which is responsible for proliferation and cell differentiation necessary in cancer cell lines (**32**). This natural product was interesting because it was characterized by a 6-7 ring system fused to a benzofuran (**32**). The

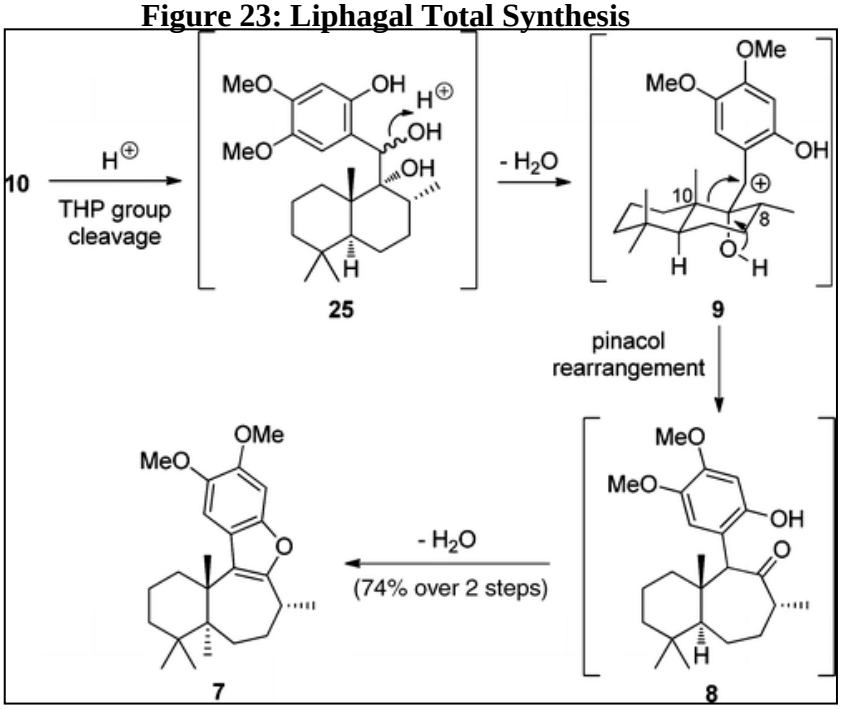
Figure 22: Liphagal Biosynthesis



preliminary studies and discovery of liphagal was determined by the Andersen group who proposed two biosynthetic pathways for the production of this natural product depicted in Figure 22 (**33**). Pathway A, would serve as the influence for Adlington in his total synthesis of this compound. Within the biosynthesis, Andersen believed a polyene cyclization would be followed by a 1,2-hydride shift. Subsequently, epoxidation would occur and then open to allow of the ring expansion of *ortho*-quinone methide (**33**). The stereochemistry at C8 would then be inverted and the final product would be formed with the removal of water. Within this biosynthesis, it is essential to remember that this was just a proposed mechanism of formation within the marine system and that a number of enzymes would likely be involved with the transformations to enable the formation of the final product. Within Adlington's synthesis, it is incredibly clear that Pathway A, depicted

above, was the major influence as the ring expansion of a benzylic carbocation to a 7-membered ring and the benzofuran is the key step in the synthesis (**32**). Displayed in Figure 23, is this major rearrangement that allows for the ring expansion and formation of the benzofuran. Compound 10 was stirred with TFA in dichloromethane at -78°C and then allowed to warm gradually. Based on these conditions, compound **25** will undergo a dehydrogenation to form **9** which will then undergo a Pinacol-type rearrangement to form the 7-membered ring of compound **8**. Compound **7** would then be formed from a dehydration reaction of **8**. These steps in Adlington's total synthesis very closely resemble the conversion of compound **III** to compound **V** in Andersen's proposed biosynthetic pathway A aside from the fact that the stereocenter at carbon 8 has already been correctly established.

Figure 23: Liphagal Total Synthesis



This synthesis by Adlington illustrates the role that biochemistry can have on total synthesis. The interesting ring opening chemistry Adlington used in order to synthesize the natural product is also of note. By utilizing the expected pathway that the natural organism follows, the total synthesis was able to be completed by using a stabilized secondary carbocation intermediate. The synthesis is only 13 steps, making it quite concise and utilizes cascade reactions as depicted above to allow for more efficient chemistry where less reactants and time

can be spent enabling various transitions. Due to the potency of liphagal as an inhibitor of the phosphoinositide-3-kinase, PI3K, signaling pathway, this synthesis provides a short and effective manner of developing the natural product. In addition, due to the fact that the aryl group is introduced late in the synthesis, novel analogues of this compound could also be synthesized that would allow for more PI3K inhibitors. Therefore, the use of the biosynthetic pathway influenced the practical total synthesis of liphagal which in turn could be used in medicinal chemistry to develop new drugs that target necessary pathways in cancer cells.

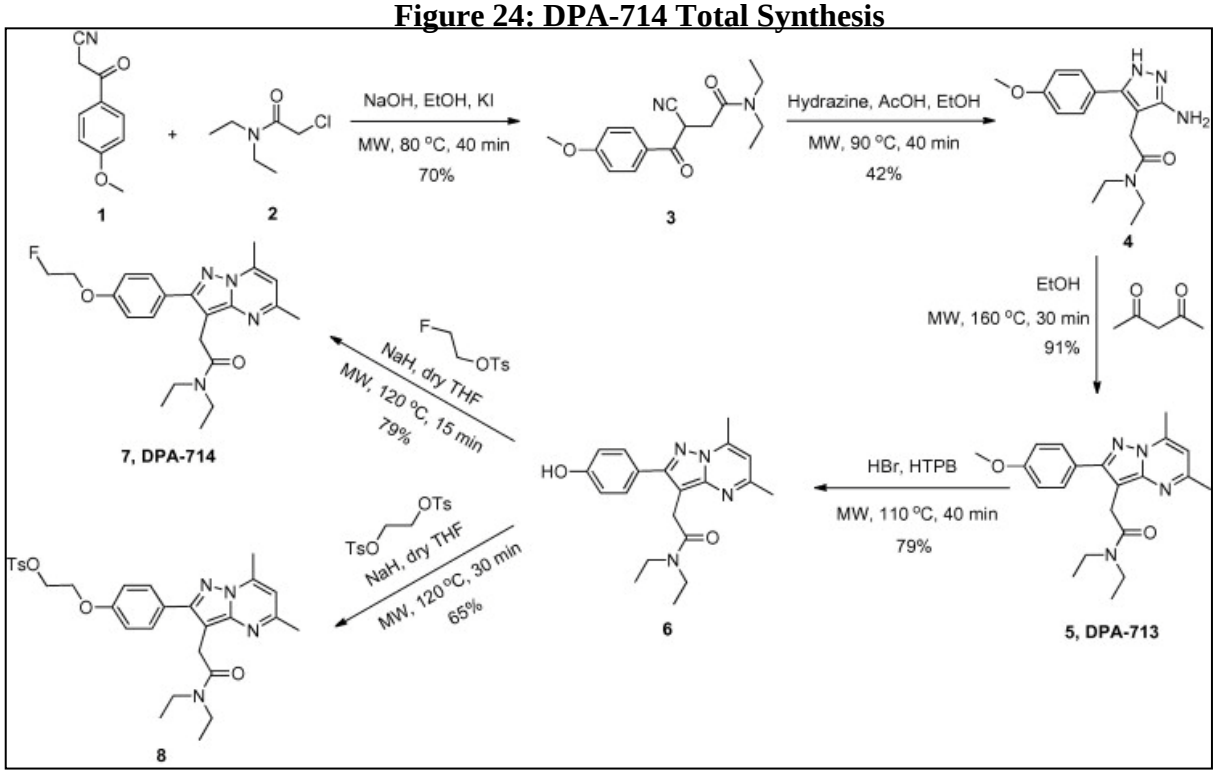
Microwave Assisted Organic Synthesis

The use of microwave assisted organic synthesis, (MAOS), has developed into a novel way to enable previously difficult transformations to occur in total synthesis chemistry. MAOS is used in order to reduce reaction time tremendously while many times maintain just as good yields as room temperature and conventional thermal heating could achieve. One such example of the use of MAOS was in the synthesis of a high-affinity pyrazolo-pyrimidinyl TSPO ligand. TSPO, translocator protein, is important due to its regulation of such processes as cholesterol metabolism, proliferation and apoptosis (**34**). The production of the protein is increased in diseased cells such as cancer cells which makes it an important target for study. By being able to locate the translocator protein, drugs could potentially be targeted to the cells that overproduce this protein and therefore cause apoptosis in a more targeted manner of cancer treatment. In order to develop such treatments however, a ligand must be designed that will be recognized by the protein and it is at this necessity that MAOS was utilized to complete a total synthesis of such a ligand.

In addition to use as a drug delivering agent, TSPO, has also shown promise in use as an imaging agent in order to locate rapidly reproducing cancer cells. The Manning group at

Vanderbilt illustrated that use of microwave chemistry could accelerate the synthesis of a number of TSPO imaging ligands such as DPA-714 while also almost always maintaining comparable overall yield and occasionally maintain superior yields (**34**). As illustrated in Figure 24, the synthesis of DPA-714 was accomplished in 5 in the same manner as its previous synthesis using conventional thermal heating; however in this case, the overall synthesis was 50 hours shorter using microwave-assisted organic synthesis in each step.

Figure 24: DPA-714 Total Synthesis



The first step involves the reaction of compounds **1** and **2** in which chloride serves as a good leaving group under the conditions of 80% ethanol, NaI/KI and NaOH. With the use of microwave chemistry, the reaction reached a temperature of 80°C for 40 minutes in order to obtain a 70% yield. This proved to be the best yield of the reaction as it only yielded 64% of product when done at room temperature. Compound **3** was the subjected to hydrazine in ethanol and acetic acid in order to allow for pyrazolo ring formation seen in compound **4**. In this case, the yield did suffer a decent amount as it dropped from 72% over 6 hours at room temperature to

42% over 40 minutes due to greater by-product formation under the MAOS conditions (**34**). Compounds **4** was then reacted with 2,4-pentanedione in ethanol to form the new 6-membered ring seen in DPA-713. This use of microwave chemistry in this transformation showed incredible benefits with reaction time as it took 12 hours under reflux conditions to attain a 93% yield, however with MAOS and a temperature of 160°C, a 91% yield was obtained in 30 minutes. The fourth reaction involved the use of HTBP, HBr and water in order to deprotect compound **5**. This reaction proceeded with 79% yield over 40 min while the best yield obtained with MAOS was a 55% yield over 2 hours with BBr_3 and dichloromethane at -60°C. The final step once again showed incredible promise for MAOS as 1-fluoroethane was attached to the hydroxy oxygen atom of compound **6** in a 79% over 15 minutes to produce the final product of DPA-714. At room temperature, the best reported yield was 80% over 16 hours while another group reported only a 56% under the same conditions.

The use of microwave-assisted organic synthesis with previously established total syntheses could truly enhance the reaction rate as well as the overall yield of many natural product synthetic schemes. By producing the product much faster, it becomes more feasible for use in applications such as imaging and drug targeting. In addition, only one of the five reactions showed a truly decreased yield from the room temperature or conventional heating method reactions. This research lays the groundwork for other TSPO ligands to be synthesized more efficiently using MAOS and therefore the ability to create a vast library of different ligands for potential applications in medicinal chemistry.

Through these few examples, the use of total synthesis is clearly connected to other fields of research, most notably that of biochemistry. Whether the use of total synthesis allows for determination of the structure of a natural product, synthesis of a natural product based on the

proposed biosynthetic scheme or the use of novel chemical techniques in order to better synthesize biologically useful compounds, it remains an integral part of different areas of study. Total synthesis has evolved greatly from its use as a means of merely synthesizing natural products, to a way to develop chemical technique, discover novel transformations and apply to structural studies of natural products.

V Total Synthesis: Organic Chemistry's Crowning Accomplishment

Throughout the past century, tremendous advances have been made in organic chemistry that have enabled the synthesis and production of a number of important compounds used worldwide. The drive to complete the total synthesis of structurally intriguing and biologically active compounds has led to developments in novel chemical transformations and further advancements in chemical biology studies. The total synthesis presents an opportunity to discover how different reagents can result in tandem reactions for more efficient syntheses. All of the many implications of total synthesis research have led to a "toolbox" of organic reactions that can be used in the design of antibiotics, solar cells and targeting ligands. As Albert Einstein reminded us, it is by taking risks and moving away from accepted actions that true genius is displayed. The ingenuity to utilize microwaves, multiple metal ligands for C-H activation, tandem or cascade reactions, and novel reagents such as samarium diiodide have led to some of the most useful and efficient reactions available. In a 2001 perspective in *Science*, István E. Markó stated, "The total synthesis of complex natural products remains the most difficult, daunting, and challenging endeavor in organic chemistry. It is also the most humbling, exhilarating, and formative enterprise in our science." (**35**).

The synthesis of drugs such as penicillin and Taxol have allowed previously viewed illnesses, whether they be the simple bacterial infection or a life threatening illness such as cancer, seem surmountable. New mechanisms in cancer therapy have been discovered as a product of the synthesis and use of Taxol which works by stabilizing the microtubules in a cell and preventing their dissociation. When the cell is subsequently unable to enter metaphase where the chromosomes line up along the middle of the cell, that cell will then be triggered to destroy itself in a process known as apoptosis (**36**). In understanding new mechanisms of

potential destruction of cancer cells, more therapies can be designed that target the microtubule assembly and thus minimize the chance of metastasis or growth of the tumor.

In addition, as discussed before, the development of novel chemical transformations is one of the greatest products of natural product total synthesis. Chemists are able to construct natural products in shorter and more efficient manners with compounds that exhibit immense complexity. The synthesis of vitamin B_{12} marked the advent of complex natural product synthesis where the field of study would be used for structural studies in addition to determining novel organic reactions. It is likely that there are numerous ways to synthesize most natural products and additional syntheses are constantly being pursued, however there is not a loss in the redundancy of the synthesis. In the example of using MAOS in order to enhance a reaction or subsequent syntheses of Taxol advances are being made that are useful in developing and enhancing chemical reactions.

The implications of total synthesis can also be extended even further to the study of protein structure and the use of organic chemistry in protein crystallography research. In 1992, an efficient synthesis of the naphthoate moiety of neocarzinostatin was published (**37**) that would be used in the eventual total synthesis of the natural product, neocarzinostatin. The simple 6 step process would also provide a means of creating various naphthoic acid analogues that could be used in biological studies of the biosynthesis of the neocarzinostatin. In a 2009 *Biochemistry* paper, a naphthoic acid analogue was used to aid in the crystallization of NcsB1, a SAM-dependent O-methyltransferase involved in the biosynthetic pathway of neocarzinostatin, and the subsequent structural determination of the enzyme was accomplished (**38**).

The implications of the study of natural products and their total synthesis have proven to be immeasurable in the sense that this field of study has progressed scientific research

drastically. It is noted that, “Contributions in organic chemistry have led to more Nobel Prizes for Chemistry than work in any other of the traditional branches of chemistry” and that “most of them have, however, been awarded for advances in the chemistry of natural products.” (**39**). This statement alone classifies the study of organic chemistry and natural products, frequently through total synthesis research, as one of the leading advances in the entire field of chemistry.

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