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Clinton James Kimzey 4/1/12

Synthesis Towards a Constrained Paclitaxel Analog

by

Clinton James Kimzey

James P. Snyder Ph.D
Adviser

Chemistry

James P. Snyder Ph.D

Adviser

Reza Saadein Ph.D

Committee Member

Stephen Traynelis Ph.D

Committee Member

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

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Since its discovery in the 1960s, pacilitaxel (PTX) has been one of the most important discoveries in the field of cancer therapeutics, and is currently used in the treatment of metastatic breast cancer, ovarian carcinoma, and AIDS-related Kaposi-Sarcoma. PTX works by binding to the β-tubulin subunit of cellular microtubules, and this PTX-tubulin complex stabilizes the microtubule structure preventing cells from completing mitotic division. In an effort to synthesize more targeted analogs of PTX, researchers have been trying to determine the conformation PTX assumes upon binding the β-tubulin subunit. In recent years, there have been two major conformations suggested. The first is the T-Taxol conformation suggested by James P. Snyder of Emory University and the second is the REDOR-Taxol conformation suggested by Iwao Ojima of Stony Brook University. Because these two conformations contain many similarities, it is difficult to determine which is the correct conformation. It is therefore the purpose of this research to synthesize a constrained PTX analog that has the potential to shed light on this topic.

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Lastly I would like to thank my family. Mom and Dad This is all thank to you. It is because of you that I have ended up where I am today. Mom without your applesauce I probably would have ended up failing freshman year, and Father thank you for always keeping me on my toes (life has certainly been more interesting because of you.)

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List of Abbreviations

^{1}H NMR proton nuclear magnetic resonance

10-DAB 10-deacetylbaccatin III

^{13}C13 NMR carbon nuclear magnetic resonance

BzCl benzalkonium chloride

CAN ceric ammonium nitrate

$CDCl_3$ deuterated chloroform

DCM dichloromethane

DMSO dimethyl sulfoxide

FDA Food and Drug Administration

GTP guanosine 5'-triphosphate

His histidine

HPLC High Performance Liquid Chromatography

HRMS High Resolution Mass Spectrometry

KOH potassium hydroxide

NAMFIS NMR analysis of molecular flexibility in solution

NCI national cancer institute

NMR Nuclear Magnetic Resonance

PDB Protein Data Bank

PTX paclitaxel

REDOR Rotational Echo Double Resonance

THF tetrahydrofuran

Thr threonine

TLC Thin Layer Chromatography

TMS trimethylsilyl

TMSoTF TMS triflate

USDA United States Department of Agriculture

I. Introduction

Taxol: A History and Introduction

Taxol® (Paclitaxel (PTX) **Figure 1**) is an antimicrotubual drug that is currently prescribed for the treatment of breast cancer, ovarian carcinoma, AIDS-related Kaposi sarcoma, and prostate cancer[8]**.** PTX was originally extracted from the bark of the Pacific yew (*Taxus brevifolia),* a slow growing tree located primarily in coastal regions of the American west coast[20][22].

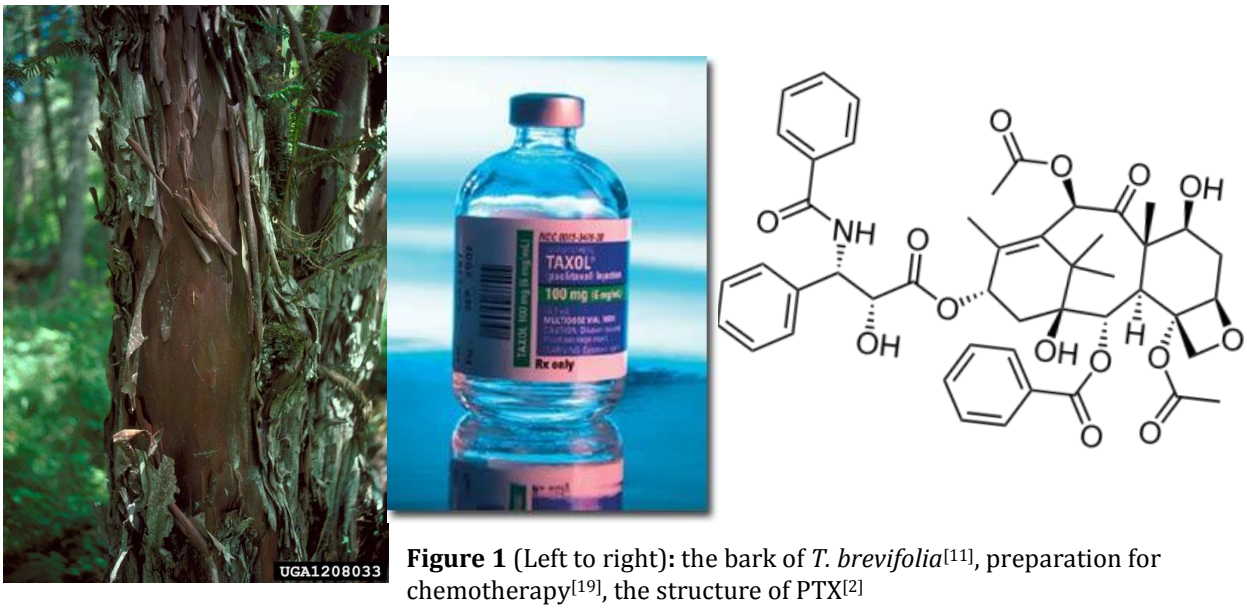


Figure 1 (Left to right)**:** the bark of *T. brevifolia*[11], preparation for chemotherapy[19], the structure of PTX[2]

Its discovery began in a 1960 collaborative effort between the USDA and the NCI Plant program, in which botanist, Arthur S. Barclay, and assistants collected 650 samples from Washington, California, and Oregon. During this collection, Barclay gathered stem samples, fruit samples, and bark samples of *T. brevifolia,* however, it was only the bark that exhibited any cytotoxic capabilities[20]. The cytotoxicity of PTX was first established in a 1964 study conducted by *Microbiological Associates,* when plant extracts were tested against KB cells[20]. Isolation of PTX proved difficult. In a 1966 experiment, *Wall et al.* were able to extract 0.5g of

PTX from a 12kg sample of air-dried stem and bark (0.004% yield)[22]. In the late 1960's, *Wall et. al.* determined through the use of mass spectrometry and elemental analysis the molecular formula of Taxol to be $C_{47}H_{51}NO_{14}$. The structure, however, proved to be more difficult to elucidate, but in 1971 *Wani et. al.* were able to determine its 2- and 3D architecture (Figure 2)[23].

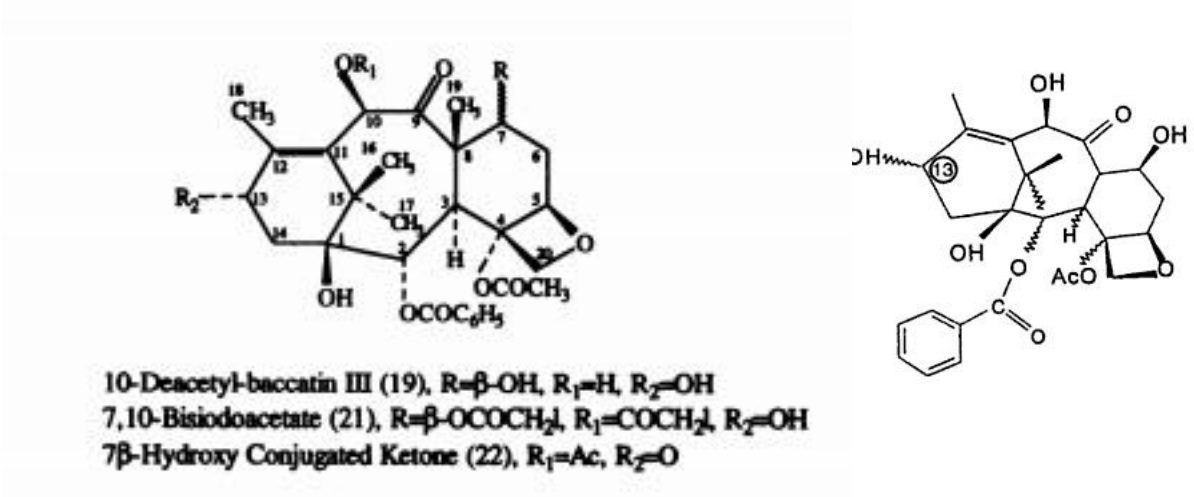


Figure 2- (right) Structure determined by *Wani et. al*[23], (left)- Structure of 10-DAB[7]

The seventies continued to be an exciting decade for PTX. In 1978, the compound proved to show activity against lung cancer, colon cancer, and breast cancer. During the same year, Deborah Fuchs and Rachel Johnson determined that PTX acted as agonist for mitotic spindle-arresting cellular mitosis[4]. The arguably most significant discovery, however, occurred in 1979 when *Horwitz et. al.* discovered that PTX served as a promoter for the assembly of microtubules. They found that in a calf brain, Taxol reduced the time required for microtubule assembly**[16]**. This was an interesting find, for this was the first known natural product to act in this way (colchicine and podophyllotoxin, two other important plant-derived drugs were known to inhibit microtubule assembly[16].)

As mentioned previously, there were two problems associated with the production of Taxol. The first was that its source *T. brevifolia* grows at a very slow rate, and the second was that isolation of PTX from the Yew tree bark resulted in a 0.004% yield (meaning in a short time there would be a eventual deficit in supply[22].) It therefore became necessary to fashion a new method for deriving the compound, and in 1981 Pierre Portier of the Institut de Chimie des Scientifique and his colleagues developed such a method. Portier hypothesized that while PTX was not present in large quantities in other *Taxus* species (as per Wall and Wani's findings), perhaps there was some precursor involved in the synthesis of PTX[7]. Following this hypothesis, Portier found and isolated such a precursor, 10-deacetylbaccatin III (10-DAB) (Figure 2), from the leaves of *Taxus baccata*[7]. 10-DAB was not only much easier to isolate, but it also granted much higher yields (0.5-1 gram per kilogram[7].) This discovery paved the way for a semi-synthetic synthesis pathway, which was published in 1988.

In 1984, Taxol's investigational new drug application was approved by the FDA, and Taxol began a phase I clinical trial the same year. In 1985 it proceeded to phase II clinical trials, but it was not until 1992 that Taxol was approved by the FDA for use in the treatment of refractory ovarian cancer[20]. Two years later, Taxol received approval for use as a treatment of metastatic breast cancer[20]. In recent years, it has been used in the treatment of various head, neck, lung and prostate cancers, as well as AIDS-related Kaposi sarcoma[3][8].

While the benefits of Taxol are tremendous, so too are its side effects, which include neutropenia, leucopenia, bleeding, nausea, myalgia, alopecia[8]. Many patients also develop resistance to PTX, reducing its treatment efficiency**[14]**. In an effort to overcome these problems, researchers have been examining resistance mechanisms as well as exploring the structure of the Taxol-tubulin complex in the effort to synthesize novel analogs.

Microtubules: Background and Interactions with Taxol

As previously mentioned, PTX interacts with microtubules in a manner drastically different from that of other plant derived compounds, that is, it promotes the assembly of stable microtubules. Microtubules serve an essential cytoskeleton role in nearly all eukaryotic cells, and are involved in cell movement, cell transport, cell shape, and more importantly cellular division[10]. They are comprised of α-tubulin and β-tubulin heterodimers that polymerize to form long hollow cylindrical structures (Figure 3).

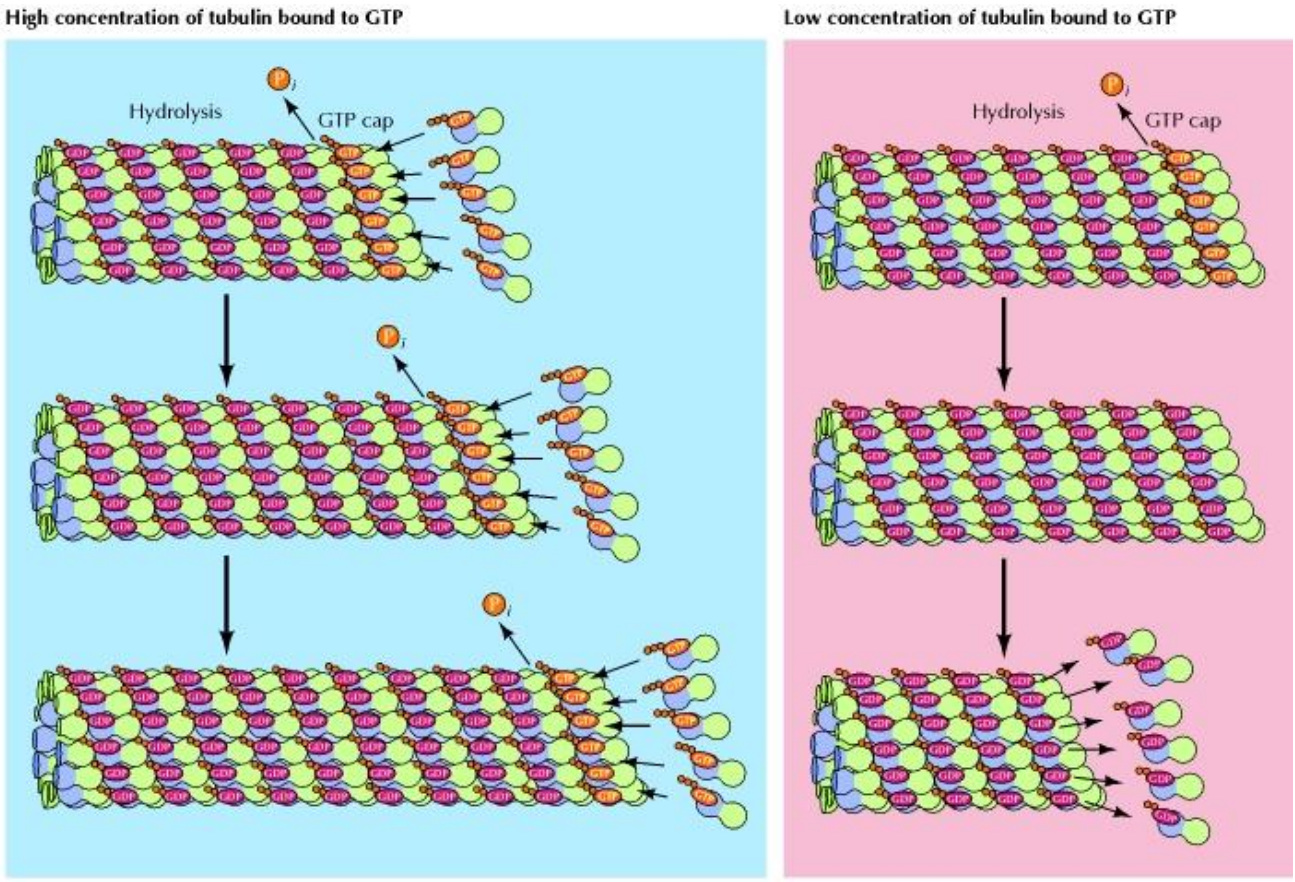


Figure 3- (left) α/β heterodimers adding to the positive end of a growing microtubule (right) heterodimers disassociating from an established microtubule[1].

The α/β heterodimers are assembled laterally in a head to tail fashion through a reversible reaction that utilizes GTP[10]. Because the polymerization is reversible, microtubules are

incredibly dynamic protein complexes capable of rapidly switching from growing (polymerizing) phases to shrinking (depolymerizing) phases, doing so in a "nonequilibrium" fashion[10][14]. The instability of these formations is essential in cellular replication. As mitosis begins, the cell signals for the disassociation of established microtubules into its free tubulin subunits. These free subunits then reassemble on one of the two centrosomes (proteins responsible for establishing the poles of the dividing cell) forming the mitotic spindle[1]. The microtubules assembled on the centrosome can be organized into one of three classes: kinectochore microtubules, astral microtubules, and polar microtubules. The first of these classes is responsible for the separation of the chromosomes while the later two are responsible for driving the two cellular poles apart[1]. Upon chromosome alignment and when cellular division becomes possible, the microtubules begin to depolymerize separating the chromosomes[1]. Taxol binds to the inner-surface of β-tubulin (Figure 4) stabilizing the protein thus making the microtubules unable to depolymerize[10]. This inability to disassemble micotubules arrests the mitotic process, and unable to proceed, the cell initiates apoptosis[4][15]. PTX therefore works well against rapidly replicating cells like cancer cells.

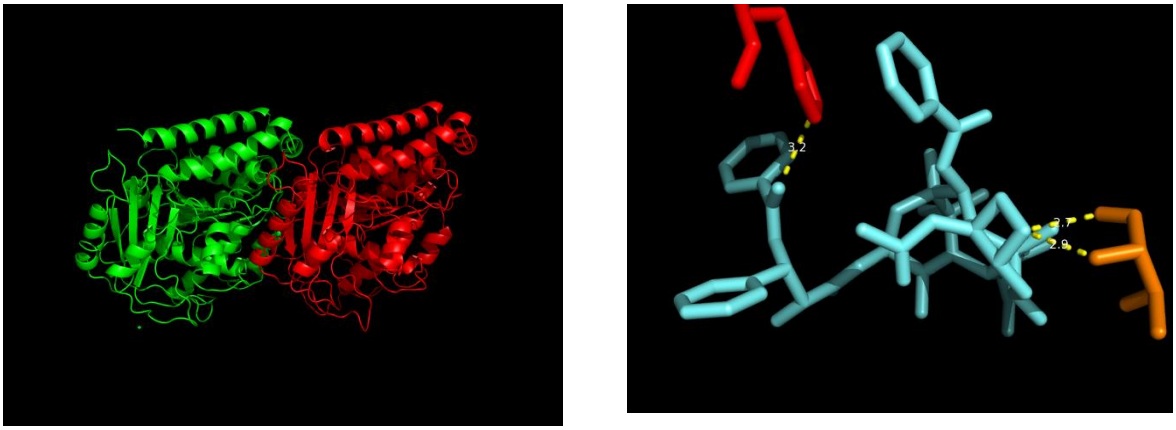


Figure 4-(right)- PTX (yellow) coordinated with tubulin hetreodimer (pdb 1JFF) (left)- TX (blue) interacting with residues His229 (red) and Thr276 (orange) (pdb 1JFF)

Conformationally Constrained Taxol

In a 2000 study, James Snyder noted an inherent flaw in the belief that Taxol assumes a dominant conformation in solution, and that is that there are at a minimum seven easily rotated single bonds[17]. In an effort to elucidate the conformation that Taxol assumes in the β-tubulin binding site, *Snyder et. al.* used NMR analysis of molecular flexibility in solution (NAMFIS) methodology, and confirmed the existence of eight previously unobserved Taxol conformations[17]. In a later study, using an electron-density map, they determined that the conformation with the Taxol side chain in a T-conformation (T-Taxol) (Figure 5) was the favored conformation[18].

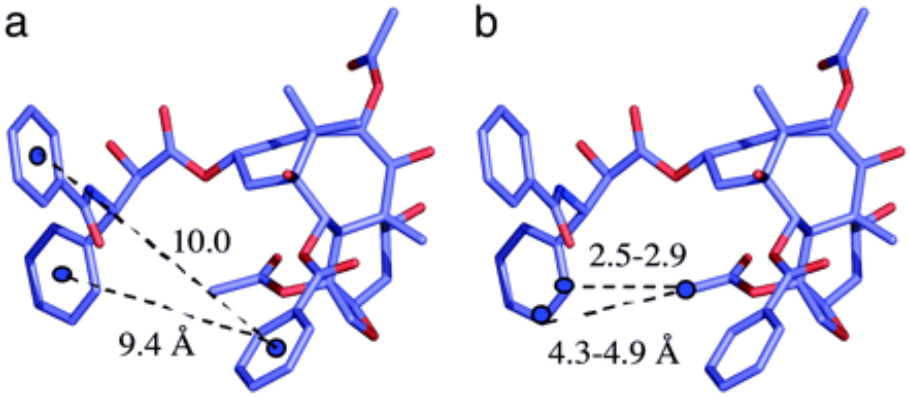


Figure 5- T-Taxol conformation (Right)- ring-to-ring distances between C-2 and C-3' phenyl centers (Left)- Hydrogen separation distances between ortho and meta positions of of C-3' phenyl ring and C-4 acetate methyl [6]

The activity of the T-taxol conformation was confirmed in 2004 when *Ganesh et. al.* showed that compounds synthesized using T-Taxol as a template showed cytotoxicity that was more potent that that of natural Taxol[6].

In 2005, Iwao Ojima published a differing opinion regarding the binding conformation. Utilizing REDOR-NMR (rotational echo double resonance), *Ojima et. al.* described the discovery of a different conformation labeled "REDOR-Taxol[12]." It was noted that REDOR-Taxol and T-Taxol shared some common features but differed in hydrogen bonding

partners within the β-Tubulin binding site. The structure of REDOR-Taxol allows for hydrogen bonding interactions between the C-2' hydroxyl group with residue His[227], while the structure of T-Taxol allows for hydrogen bonding interactions between the C-2' hydroxyl group and residue Arg[359][12]. The structural differences between the two compounds can be observed in Figure 6.

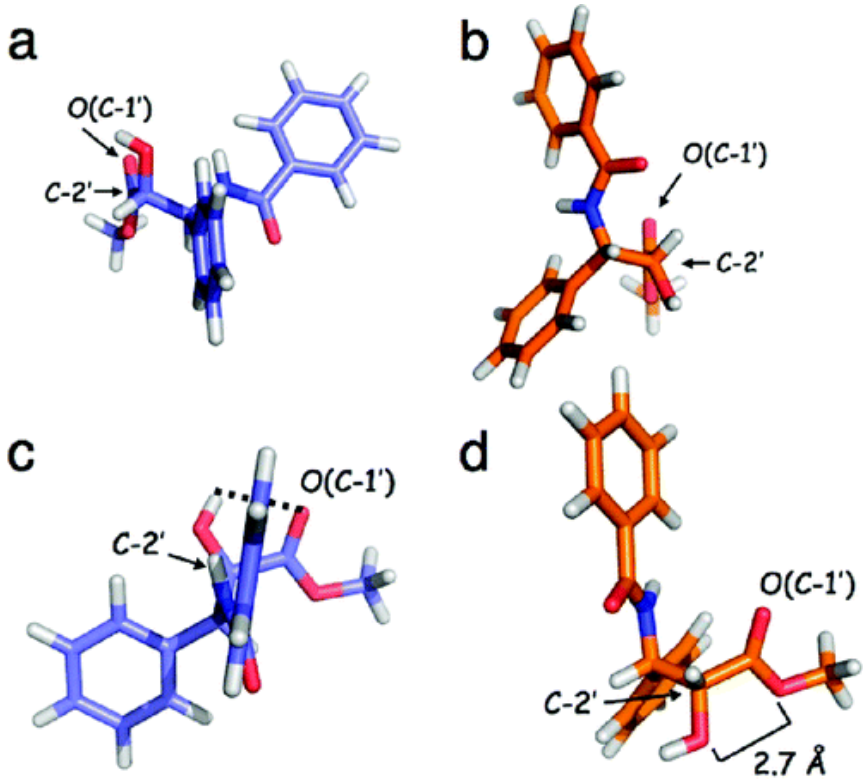


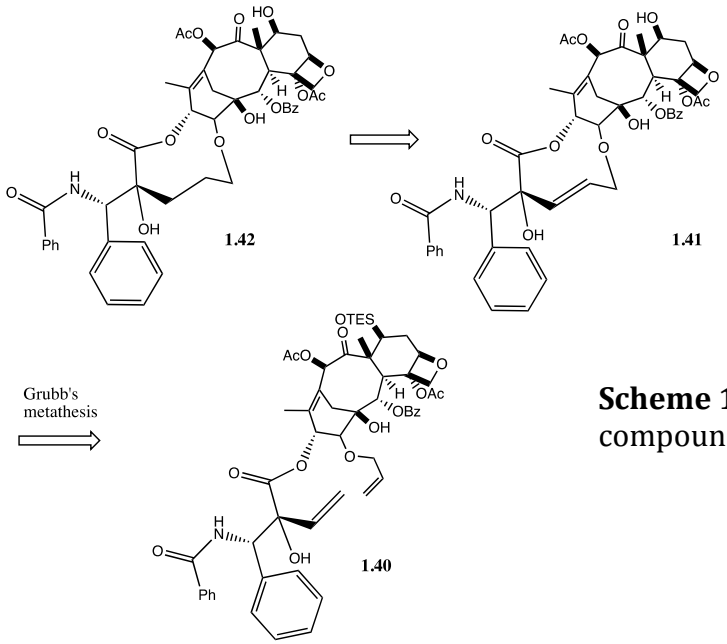
Figure 6- (upper)- a comparison of the side chain conformations of a) T-Taxol and b) REDOR- Taxol looking down the C2'-C1' bonds (lower)- side view showing the internal hydrogen bonding found in T-Taxol and the repulsive O-O interaction of REDOR-Taxol[24]

In a 2009 modeling study conducted by *Snyder et. al.*, it was observed that the REDOR-Taxol conformation and the T-taxol conformation differ by a rotation of approximately 165° around the C1'-C2' bond. This rotation causes the hydroxyl group located at C2' of REDOR-Taxol to experience repulsive interactions with the ester oxygen (Figure 6)[24]. Recently, *Snyder*

et. al. have designed a PTX analog **1.42** that features a four member carbon bridge between C2'-C14'[25]. It has been hypothesized that **1.42** will provide a method for differentiating between REDOR-Taxol and T-Taxol by comparing the bioactivity of compound **1.42** with its non-bridged counterpart[25]. Should the activity of **1.42** be similar to that of its non-bridged counterpart **1.40** then this would serve as evidence for the REDOR-Taxol Structure. However, should its bioactivity be less, this would serve as evidence in favor of the T-Taxol conformation[25]. It is the purpose of this experiment to synthesize compound **1.42** in the effort to determine which is the correct binding conformation.

II. Results and Discussion

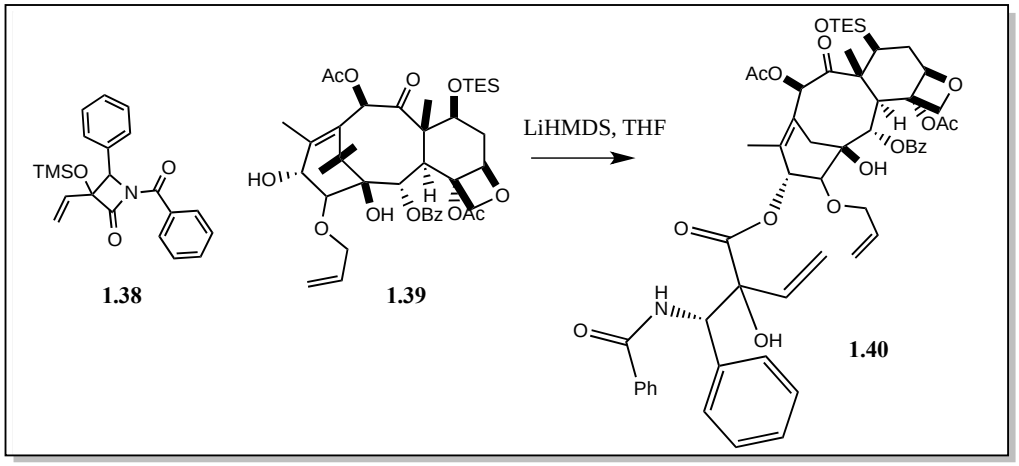
Results and Discussion



Scheme 1- Retrosynthesis of compound **1.42**[25]

The retrosynthesis of the constrained T-Taxol compound is shown in Scheme 1. The bridge between the C2' and the C14' molecules can be formed through Grubb's metathesis on compound **1.40**. It had been observed by *Grubbs et. al.* that vinyl ethers are not effective

coupling partners in ring-closing metathesis reactions; thus, we hypothesize that switching the coupling partners from vinyl ether/allyl-substituted β-lactam, as proposed by *Zhao et al.*, to an allyl ether/vinyl-substituted β-lactam could be advantageous[5]. Although the initial compound **1.41** presents the double bond in a different location, subsequent hydrogenation of the double bond would result in the formation of **1.42**. Energetically, the vinyl carbon is more favorable in the ring closing metathesis than the allyl. We believe that compound **1.40** can be synthesized in the presence of a strong base through the reaction proposed in scheme 2 using compound **1.38** (responsible for forming the side chain) and the baccatin derivative **1.39**. These conditions should allow the C13' hydroxyl group of compound **1.39** to nucleophillicly attack the carbonyl carbon located on the β-lactam ring of compound **1.38.**

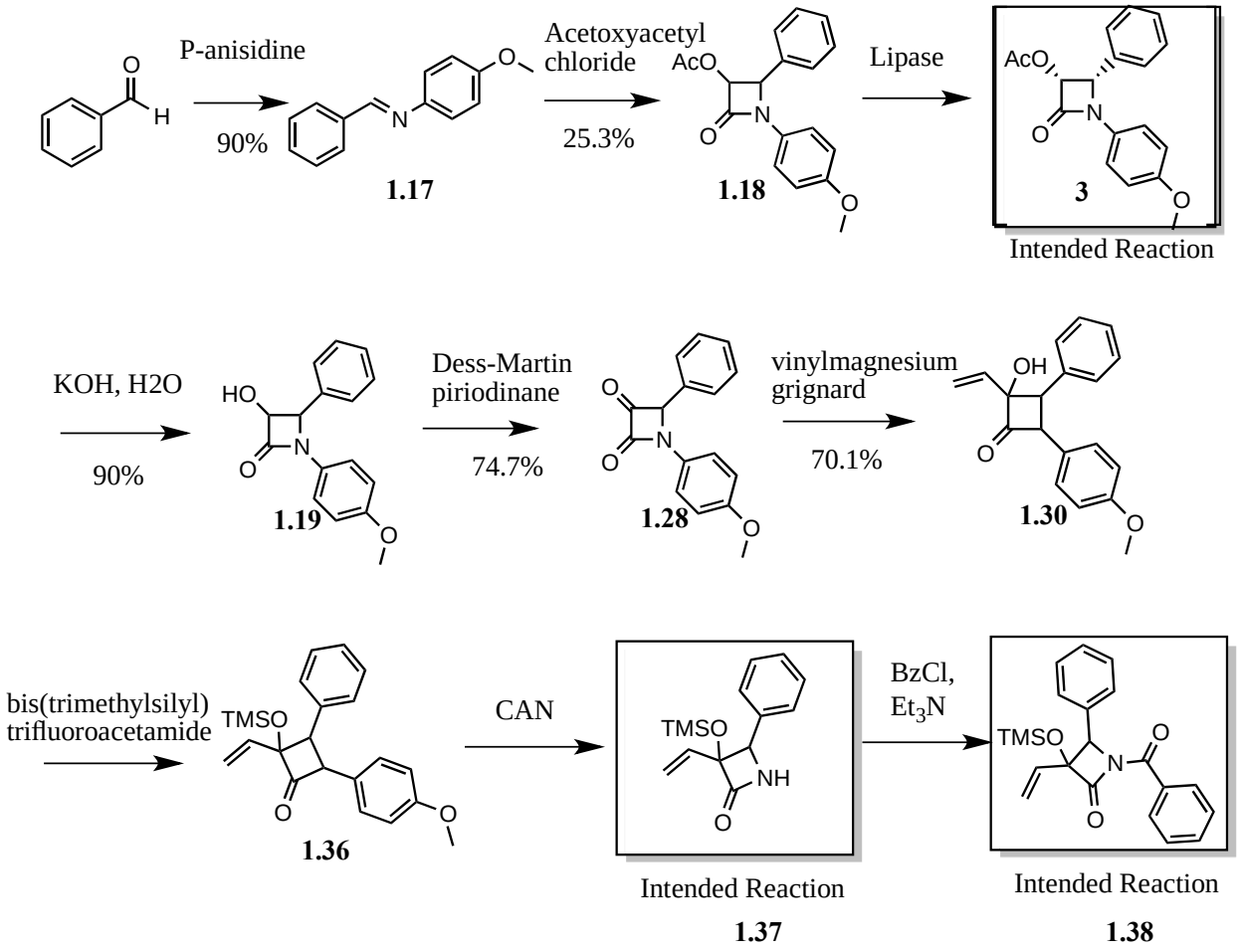


Scheme 2- Proposed synthesis for the formation of **1.40**

Intended Reaction

Compound **1.38** can be synthesized in 10 steps (Scheme 3). Benzyldahyde imine **1.17** was obtained in 90% yield from the condensation of P-anisidine with benzyldahyde in cold DCM[21]. The resulting imine was combined with acetoxyacetyl chloride and triethylamine in cooled DCM to form compound **1.18** with an overall yield of 25.3%[13]. Removal of the acetate group from the β-lactam was carried out by treating compound **1.18** with KOH in cold THF for

one hour producing **1.19** in 90% yield[9]. Originally, we attempted the oxidation of the β-lactam using Swern oxidation, however after analysis by NMR and HPLC we noticed that the desired **1.28** had failed to form. We decided to instead use Dess-Martin periodinane in cold DCM resulting in the formation of compound **1.28** in 74.7% yield. Following the aforementioned hypothesis, we chose to react the oxidized β-lactam with vinyl grignard instead of allyl grignard. By reacting compound **1.28** with vinyl magnesium grignard in cold dry THF, we were able to produce compound **1.30** in 70.1% yield. During the course of our experiments, we never observed the total conversion of alcohol **1.30** to TMS ether **1.36**. In fact, by means of NMR and HPLC we discovered that additional equivalents of TMSOTf resulted in a decrease in conversion. We hypothesized that this problem was caused by the trifoliate anion deprotecting the already formed TMS ether complex. To avoid this problem, we chose instead to use bis(trimethylsilyl) trifluoroacetamide as our silylating agent, and this change has resulted in higher crude yields than were observed when using TMSOTf, but the purification methods are still being developed.



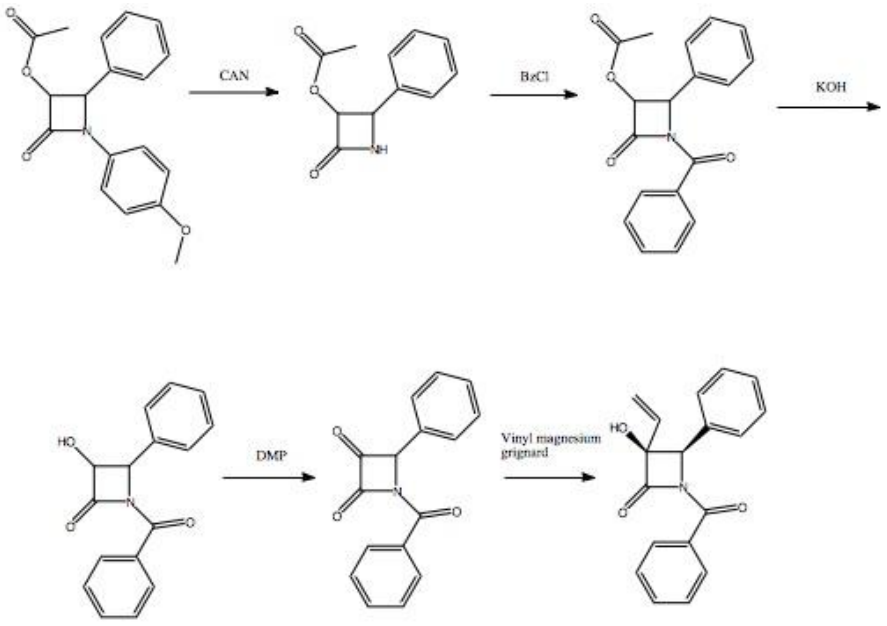
Scheme 3: Synthesis of compound **1.38**

Conclusion

In an effort to synthesize the conformationally constrained PTX compound presented by *Snyder et al.,* a series of reactions were run to optimize the route to important intermediates originally explored by *Zhao and Kingston* (2006) [25]. However due to time constraints, the necessary products for installation on the baccatin derivative have not yet been synthesized. Nonetheless, this project has paved the way by developing a clear path of action for future individuals to follow.

Future Plans

In the effort to synthesize the important precursor **1.38**, three steps must still be completed; the protection of the hydroxyl group on compound **1.30**, the reaction of compound **1.36** with CAN, and the subsequent reaction of **1.37** with BzCl[25]. Due to difficulties in purifying the desired compound **1.36**, we have proposed two new plans of action. The first is to react compound **1.30** with a larger protecting group (i.e. TBDPS.) The second is to synthesize compound **1.38** following the reaction scheme pictured in Scheme 4.



Scheme 4- Newly proposed reaction order

In previous attempts conducted by *Zhao et. al.*, they were unable to couple compounds **1.38** and **1.39** citing the potential steric hindrance between the baccatin core and the side chain precursor as well as the small scale under which coupling was attempted[25]. We wish to first reattempt the reactions he proposed on a larger scale. Should the reactions fail to go to completion, we would try swapping the base or raising the temperature. Upon coupling and

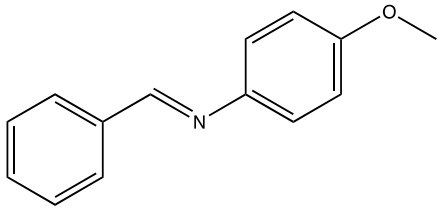
subsequent metathesis with the baccatin derivative, we will be able to use X-Ray crystallography to determine if the molecule is in fact constrained as modeled by *Snyder and Kriel* as well as being able to compare the conformation with that of the taxol conformation in PDB file 1JFF.

III. Experimental

Experimental Methods

Chemicals were obtained from Sigma-Aldrich, and compounds were used as received. All experiments were run under argon using dry solvents. When needed, glassware was flame dried under vacuum, and allowed to cool to room temperature before reactions were started. Reaction progress was monitored using EMD Chemicals glass silica plates (60 F_{254})**.** When workups were necessary, organic solvents were washed with brine (unless otherwise stated), and dried over $MgSO_4$, before being filtered and concentrated at room temperature under reduced pressure using a Buchi Rotovapor R200. Column Chromatography was conducted on a Teledyne Isco Combiflash Companion using pre-fabricated columns from Teledyne Isco RediSep®RF Flash Column. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 on a Varian INOVA 400 spectrophotometer (^{1}H: 400MHz and ^{13}C: 400 MHz). Coupling constants are reported in Hertz, and chemical shifts were referenced relative to a baseline $CDCl_3$. High resolution mass spectra (HRMS) were obtained from the Emory University Mass Spectrometry Center. The 14-Hydroxy-10-deacetylbaccatin was supplied by Dr. David Kingston, Virginia Tech.

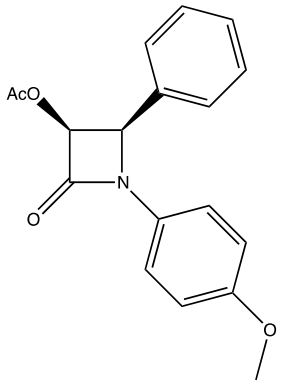
(E)-N-benzylidene-4-methoxyaniline[20]



1.17

A 100 mL 3-necked, round bottomed flask was charged with 45mL of dichloromethane and benzaldehyde (9.42 ml, 28.3 mmol). The solution was cooled in ice water bath while a solution of 4-methoxyaniline (3.5g, 28.4 mmol) in 5 mL of dichloromethane was added drop-wise via syringe for 15 min. After 30 minutes, 7.5 g of magnesium sulfate was added in one portion. The ice-water bath was removed, and the reaction was stirred at room temperature for 2 hours. The resulting compound was filtered through a sintered glass funnel with the aid of two portions of 5 mL of dichloromethane, and the filtrate was concentrated at reduced pressure through rotary evaporation at room temperature yielding (E)-N-benzylidene-4-methoxyaniline (5.37 g, 25.4 mmol, 90 % yield). 1H NMR (400 MHz, CHLOROFORM-d, d ppm 3.82 (s, 3 H) 6.93 (AA'XX', Jlarge=8.8 Hz, 2 H) 7.24 (AA'XX', Jlarge=9.2 Hz, 2 H) 7.43 - 7.48 (m, 3 H) 7.86 - 7.91 (m, 2 H) 8.47 (s, 1 H) 13C NMR (100 MHz, CHLOROFORM-d) d ppm 77.0, 77.3, 77.6, 110.5, 114.8, 128.7, 128.8, 136.6, 145.1, 158.5, 163.8 (ppm), HRMS (ESI) calcd for $C_{14}H_{13}NO$ *m/z* 212.1069 ($[M+H]^+$), found *m/z* 212.1070

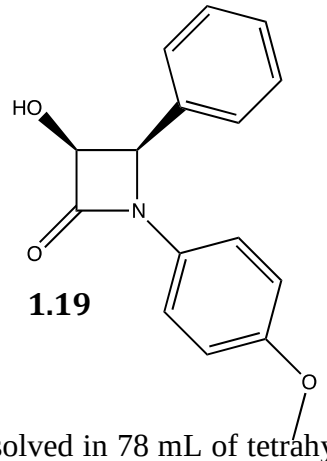
(3R,4S)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl acetate[11]



1.18

1.17 (3.75 g, 17.75 mmol) was dissolved in 200 mL of dry dichloromethane. The solution was cooled to 0°C. Triethylamine (5.39 g, 53.3 mmol) was added, followed by 2-chloro-2-oxoethyl acetate (2.91 g, 21.30 mmol) which was dissolved in 20 mL of dichloromethane. The reaction mixture was allowed to stir overnight. The solvent was concentrated at reduced pressure and room temperature through rotary evaporation. The crude product was the dissolved in 15 mL of dichloromethane, and adsorbed onto silica gel. The silica gel was run through HPLC in a solvent system of up to 75% ethyl acetate: hexane. Fractions were concentrated under reduced pressure at room temperature using rotary evaporation yielding (3R,4S)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl acetate (1.40 g, 4.50 mmol, 25.3 % yield. 1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.65 (s, 3 H) 3.70 - 3.74 (m, 3 H) 5.32 (d, J=4.9 Hz, 1 H) 5.91 (d, J=4.9 Hz, 1 H) 6.78 (AA'XX', Jlarge=8.8 Hz, 2 H) 7.23 - 7.35 (m, 7 H)(ppm) 13C NMR (100 MHz, CHLOROFORM-d d ppm 20.0, 55.6, 61.7, 76.6, 100.8, 114.6, 119.0, 128.1, 128.7, 129.0, 130.5, 132.5, 156.8, 161.5, 169.4 ppm/ref, HRMS (ESI) calcd for $C_{18}H_{17}NO_4$ *m/z* 312.1230 ($[M+H]^+$), found *m/z* 312.1232

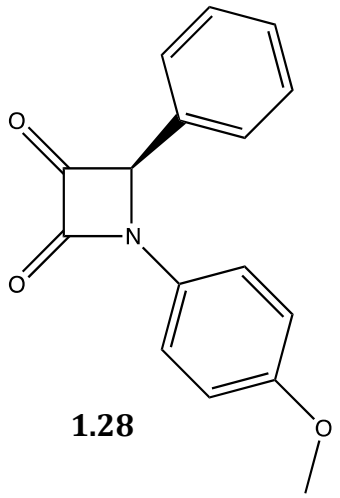
3-hydroxy-1-(4-methoxyphenyl)-4-phenylazetidin-2-one[8]



1.19

1.18 (1.3 g, 4.18 mmol) was dissolved in 78 mL of tetrahydrofuran, and was added to a solution containing 78 mL of 1M potassium hydroxide and 52 mL of tetrahydrofuran which was stirred at 0°C for 1 hour. Upon completion, the solution was diluted with 65 mL of tetrahydrofuran. Saturated sodium bicarbonate was added until the organic layer had a pH of approximately 11. Solution was extracted with ethyl acetate (3X20mL), and was concentrated under reduced pressure at room temperature to yield 3-hydroxy-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (1.01 g, 3.74 mmol, 90 % yield). 1H NMR (400 MHz, CHLOROFORM-d) d ppm 5.32 (d, J=4.9 Hz, 4 H) 5.92 (d, J=4.9 Hz, 4 H) 6.79 (AA'XX', Jlarge=9.2 Hz, 6 H) 7.24 (s, 2 H) 7.25 - 7.30 (m, 17 H) 7.30 - 7.34 (m, 13 H)13C NMR (100 MHz, CHLOROFORM-d) d ppm20.0, 20.0, 55.6, 61.7, 76.6, 76.6, 114.6, 119.0, 128.1, 128.7, 129.0, 130.5, 132.5, 156.8. 161.5, 169.4 ppm/ref, HRMS (ESI) calcd for $C_{16}H_{16}NO_3$ *m/z* 270.1124 ($[M+H]^+$), found *m/z* 270.1126

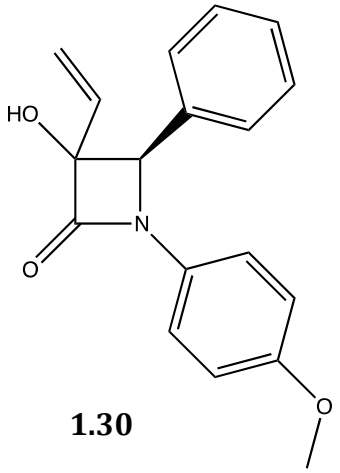
1-(4-methoxyphenyl)-4-phenylazetidine-2,3-dione



1.28

To a 2500 mL round bottomed **1.19** (4.21 g, 15.63 mmol) was added to 400 mL dichloromethane. To the solution, a few drops of pyridine was added, the solution was cooled to 0°C, and was charged with Dess-Martin piriodinane (33.20 g, 78 mmol). The reaction was allowed to stir at room temperature overnight. A solution of saturated sodium bicarbonate was added, and the reaction was extracted with ethyl acetate (3x20mL). Organic layer was concentrated under reduced pressure at room temperature yielding 1-(4-methoxyphenyl)-4-phenylazetidine-2,3-dione (3.12 g, 11.68 mmol, 74.7 % yield) 1H NMR (400 MHz, CHLOROFORM-d) d ppm 5.54 (s, 2 H) 6.86 (AA'XX', Jlarge=9.2 Hz, 3 H) 7.24 (s, 1 H) 7.28 - 7.31 (m, 4 H) 7.35 - 7.39 (m, 6 H) 7.41 - 7.46 (m, 4 H) 13C NMR (100 MHz, CHLOROFORM-d) d ppm 49.3, 49.5, 55.6, 55.6, 55.7,69.8, 69.8, 70.9, 114.5, 114.5, 114.9, 119.4, 119.5, 120.0, 126.5, 127.9, 128.1, 128.8, 128.8, 128.9, 129.6, 130.3, 130.4, 133.4, 156.6, 165.0 ppm/ref, HRMS (ESI) calcd for $C_{16}H_{16}NO_3$ *m/z* 268.0968 ($[M+H]^+$), found *m/z* 268.0966

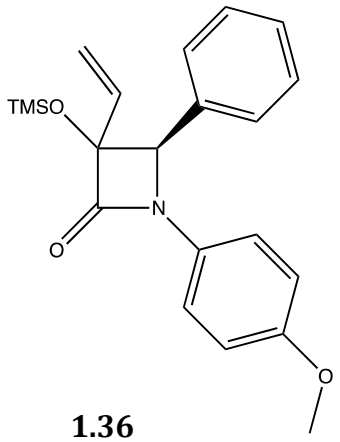
(3S,4R)-3-hydroxy-1-(4-methoxyphenyl)-4-phenyl-3-vinylazetidin-2-one



1.30

A 50mL round-bottom flask was dried, and under argon charged with **1.28** (.4 g, 1.497 mmol) and 6 mL of dry THF. The reaction mixture was cooled to -40°C. Vinylmagnesium bromide (0.393 g 2.99 mmol) was added slowly, and the reaction mixture was allowed to stir at room temperature overnight. The organic layer was removed at room temperature under reduced pressure, and the resulting solid was dissolved in 20mL of ethyl acetate. The organic layer was washed with saturated ammonium chloride (3x20mL) and was concentrated under reduced pressure at room temperature yielding (3S,4R)-3-hydroxy-1-(4-methoxyphenyl)-4-phenyl-3-vinylazetidin-2-one (.31 g, 1.05 mmol, 70.1 % yield) 1H NMR (400 MHz, CHLOROFORM-d) d ppm 5.01 (s, 3 H) 5.36 (dd, J=10.8, 0.8 Hz, 3 H) 5.59 (dd, J=17.1, 0.9 Hz, 3 H) 6.12 (dd, J=17.2, 10.8 Hz, 3 H) 6.76 (AA'XX', JLarge=9.2 Hz, 3 H) 6.88 - 6.91 (m, 1 H) 7.22 - 7.27 (m, 14 H) 7.29 - 7.37 (m, 12 H) 7.40 - 7.44 (m, 2 H) 13C NMR (100 MHz, CHLOROFORM-d) d ppm 49.4, 49.6, 55.6, 68.8, 114.3, 114.6, 114.6, 117.5, 119.2, 122.4, 127.7, 128.6, 128.9, 129.0, 130.6, 133.5, 135.1, 156.6 HRMS (ESI) calcd for $C_{18}H_{17}NO_3$ *m/z* 296.12812 ($[M+H]^+$), found *m/z* 296.12813

(3S,4R)-1-(4-methoxyphenyl)-4-phenyl-3-((trimethylsilyl)oxy)-3-vinylazetidin-2-one



1.36

A flame-dried 25mL round- bottom flask was charged under argon with **1.30** (.35 g, 1.185 mmol) and 5mL of dry DCM. To this stirring mixture, (E)-trimethylsilyl N-(trimethylsilyl) acetimidate (5.80 ml, 23.70 mmol) was added, and the reaction was allowed to stir at room temperature for 2 hours as progress was checked by TLC. The reaction was concentrated at room temperature under vacuum, and the resulting solid was dissolved in ethyl acetate and washed three times with water (3x20mL). This resulted in a crude yield of (3S,4R)-1-(4-methoxyphenyl)-4-phenyl-3-((trimethylsilyl)oxy)-3-vinylazetidin-2-one (.32 g, 0.871 mmol, 73.5 % yield). The crude product was purified using column chromatography of up to 50% ethyl acetate in hexane. 1H NMR (400 MHz, CHLOROFORM-d) d ppm -0.02 (s, 28 H) 3.74 (s, 3 H) 4.95 (s, 4 H) 5.35 (dd, J=10.5, 1.1 Hz, 4 H) 5.55 (dd, J=17.2, 1.1 Hz, 4 H) 6.15 (dd, J=17.1, 10.7 Hz, 4 H) 6.80 (d, J=9.2 Hz, 5 H) 7.22 (dd, J=7.8, 1.7 Hz, 7 H) 13C NMR (100 MHz, CHLOROFORM-d) d ppm 1.4, 76.9, 77.3, 77.6, 88.4, 128.3, 131.1, 134.4, 156.5, 165.7

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