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Asymmetric Synthesis of the C29-C34 Moiety of Fragment A of the Antascomicin B & Thermal Azole Based Claisen Rearrangements

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Asymmetric Synthesis of the C29-C34 Moiety of Fragment A of the Antascomicin B & Thermal Azole Based Claisen Rearrangements

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by

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ABSTRACT

The dissertation describes asymmetric synthesis towards C29-C34 moiety of fragment A of the Antascomicin B and Thermal azole based Claisen rearrangements. In chapter 1, we describes asymmetric synthesis towards C29-C34 moiety of fragment A of the Antascomicin B. The non-immunosuppressant Rapamycin, Ascomycin, and Tacrolimus (FK506), strongly binds with FKBP12, the ligand FKBP12 complexes responsible for immunosuppressive activity. Antascomicin B structurally related to Rapamycin, Ascomycin, and Tacrolimus (FK506), binds strongly to FKBP12, yet does not shown immunosuppressive activity. The ligand FKBP12 binding complexes shown to have potent neuroprotective and neurogenerative properties in mouse models of Parkinson's disease. The linear synthesis of C29-C34 moiety of fragment A of the Antascomicin B was highlighted through chemical reactions include an Delis Alder reaction, asymmetric transfer hydrogenation (ATH), epoxide ring opening reactions. In chapter 2, we describes novel methodologies of preparing 2-butenyl benzothiazole derivatives using aza-Claisen rearrangement, through N, S-ketene acetals intermediates. The precursor N-allyl-N, S-ketene acetals were prepared in situ from the reaction of N-allyl benzothiazolium salts. N-allyl benzothiazolium salts synthesized by simply alkylated 2-methyl benzothiazole with various allyl bromide derivatives. Despite of the traditional approaches, our proposed synthetic methodology of N, S-ketene acetals that requires only weak base, possesses broad functional group compatibility, and require no cryogenic conditions.

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Finally, I am pleased for my beautiful wife Tulasi Choudary Papineni, as a supporter and believer in my career trajectory. Thank you so much for valuable decisions in the complicated situations. I believe we made an important career achievement together at University of Arkansas. Definitely, this is for you and our beloved sons Anav choudary Nannapaneni & Ayan Nannapaneni, I love you all.

Dharma Theja Nannapaneni

December 2019

DEDICATION

To my beloved parents (Vasu Chand Nannapaneni & Prameela Nannapaneni) and my wife Tulasi Choudary Papineni

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A. Introduction

Organic chemistry is a study of molecules consist of carbon, hydrogen, oxygen and nitrogen atoms, provided numerous pharmaceuticals, petrochemicals, agriculture chemicals, and various other every day necessary compounds. Synthetic chemistry is the process of building various organic molecules ranging from small to macromolecules by utilizing series of chemical organic reactions. Synthetic organic chemists have been developing new synthetic methodologies to demonstrate the efficient, economic and environmentally safe reaction conditions to build molecular complex natural products.[1, 2]

Natural products are macromolecules, which play a pivotal role in drug lead discovery. Scientists have been working to isolate biologically active natural products that generally produced by living organisms such as plants, bacteria, fungi and marine organisms. The extracted biological/chemical compounds were administered to animal models (mouse, rat and genie pigs), and identified as biologically active. The molecular structure of these compounds was determined experimentally by spectroscopic methods, thus paving the way for their synthesis on a laboratory scale.[3, 4]

The McIntosh research group involved in the asymmetric synthesis of the natural products as well as developing innovative synthetic methodologies for practical and efficient conversation. In this dissertation, we have been studied the asymmetric synthesis of the C29-C34 moiety of fragment A of the Antascomicin B (Chapter 1), and novel methodologies of preparing 2-butenyl benzothiazole derivatives using aza-Claisen rearrangement, through N, S-ketene acetals intermediates (Chapter 2).

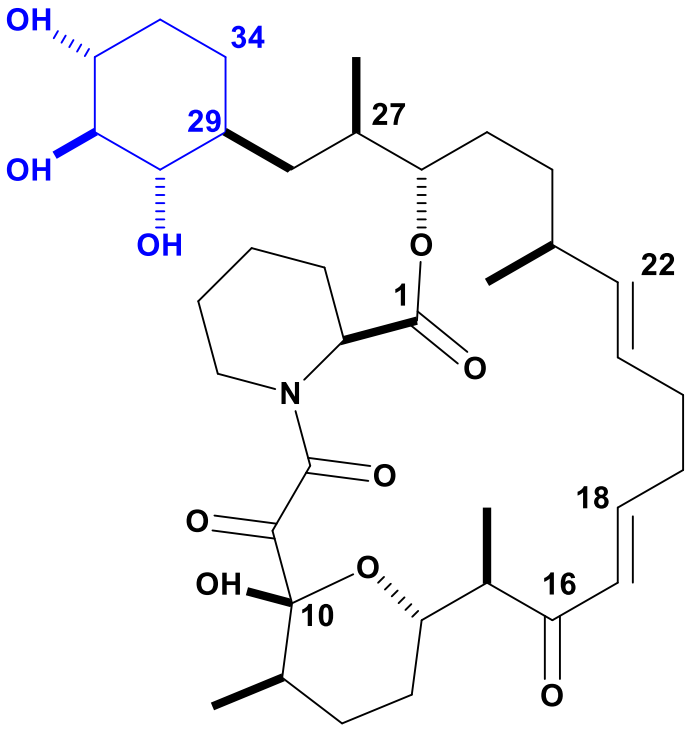
B. Chapter 1: Asymmetric synthesis towards C29-C34 moiety of fragment A of the Antascomicin

I. Introduction

Natural product synthesis is a challenging construction of a naturally occurring compound in the laboratory starting from simple, commercially available materials. There are several goals of natural products total synthesis such as provide additional quantities for biological testing, modify the natural product to improve its biological profile, e.g. improve potency, decrease side effects, increase metabolic stability, increase solubility, etc. One of the important applications of these natural products is to treat several diseases, such as Atherosclerosis (heart disease), cancer, parasitic helminthic infections, malaria and autoimmune diseases.[3, 4]

The process of synthesizing a certain molecule involves several steps. First, the structure of the desired molecule analyzed carefully in order to search for any vulnerable sites, wherein bonds could be broken. This would cause the transformation of the original molecule into smaller fragments, which can serve as precursors for the whole process. In total synthesis, desired compounds could synthesized as result of building these small fragments together in a variety of chemical reaction.[5]

Primarily, my research studies designed for the asymmetric synthesis of the C_{29}-C_{34} moiety of the Antascomicin B (Scheme 1) feasible for scale up, efficient, economic and environmentally safe reaction conditions.

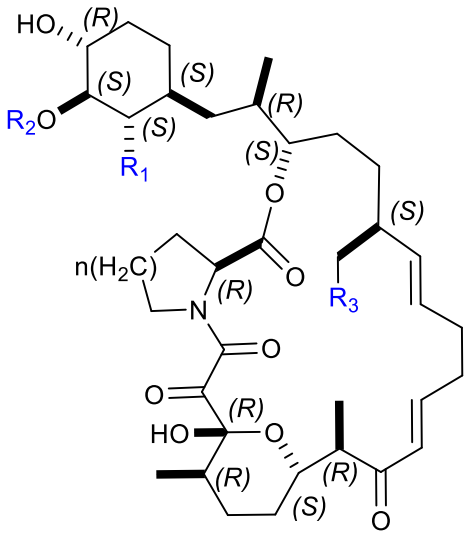


Scheme 1: Antascomicin B

II. Background: Antascomicin B

Sandoz Pharmaceuticals first isolated Antascomicin B in 1996 from Genus Micromonospora, which was collected from a soil sample in China.[6] The isolated Micromonospora bacterial strain found to contain a family of compounds known as Antascomicin A to E. Sandoz Pharmaceuticals has conducted an assay to identify active metabolites, which can bind to FKBP12. Over 12000 bacterial strains from this assay used to measure the strength of binding substrates in comparison with FK-506 and Rapamycin. According to the results, Antascomicin strain showed great binding affinity to FKBP12 compared to FK-506 and Rapamycin.[6] In the process of treating diseases, Antascomicin family (Scheme 2) binds with FKBP12, which is an immunophilin. Consequently, Antascomicin family shows a greater specificity in binding to activity domains. One characteristic of this family, which has generated considerable interest among the scientific community, is its

application in regenerating nerve tissues, namely Rapamycin and FK506. In particular, Antascomicin B can specifically bind to FKBP12 in the family.



Antascomicin Family

Antascomicin A	R_1=H	R_2=H	R_3=H	n=2
Antascomicin B	R_1=OH	R_2=H	R_3=H	n=2
Antascomicin C	R_1=OH	R_2=CH_3	R_3=H	n=2
Antascomicin D	R_1=H	R_2=H	R_3=H	n=1
Antascomicin E	R_1=H	R_2=H	R_3=OH	n=2

Scheme 2: Antascomicin family

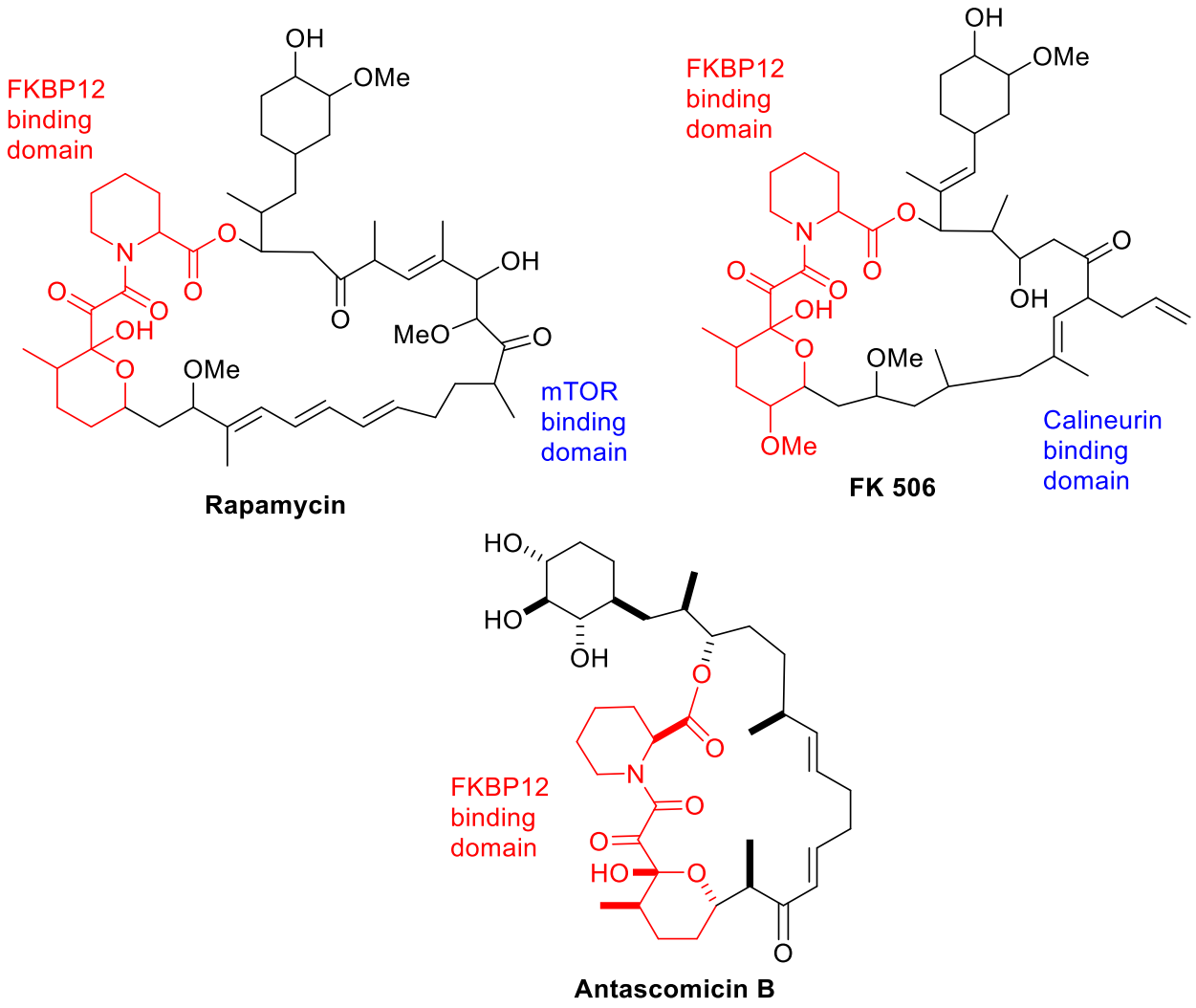
Besides the family of Antascomicin, in addition, Rapamycin, Ascomycin, and Tacrolimus (FK-506) have the potential to bind with FKBP12 (Scheme 3). As per literature, all these compounds considered as non-immunosuppressant. Upon bonding with FKBP12, all these compounds, except Antascomicin B, become immunosuppressant. They all bind to FKBP12 in the same fashion, but differ in terms of activity.

Tacrolimus (FK-506)/FKBP12 complex acts as an immunosuppression by blocking T-lymphocyte activity. As per literature, this caused due to calcineurin, which is a calcium-dependent serine phosphate. Calcineurin is responsible for dephosphorylating NF-ATP and OAP (proteins), which regulate gene transcription code for inflammatory mediators, namely IL-2 and GM-GSF. Inflammatory mediators are essential for the development of immune system.[7]

On the other hand, Rapamycin/FKBP12 complex behaves as an immunosuppression by blocking mTOR, a protein that is responsible for controlling the cell growth and proliferation by preventing the entry of lymphocytes into the cells.[8, 9]

S.H Snyder group at John Hopkins University School of Medicine discovered that FKBB12 exists at high concentration in brain than immune system.[8] This study could serve as a guiding principle to the work outlined here in order to investigate the role of immunophilins in certain regions of the neural system. The study has showed that Rapamycin/FKBP12 and FK506/FKBP12 complexes exhibit neuroprotective and neurodegenerative properties in neuronal system. In addition, these complexes have shown to possess immunosuppression, which degrades their ability to treat damaged nerves.[10, 11]

Furthermore, Antascomicin/FKBP12 used for treating damaged nerves without exhibiting immunosuppression. The hypothesis that Antascomicin and FKBP12 complexes exhibit neuroprotective and neurogenerative properties was proved to be true in animal models while treating Parkinson's disease.[13] Literature studies indicate that Antascomicin B could be a potent pharmacological agent in the treatment of Alzheimer's and Parkinson's diseases.[12, 13]

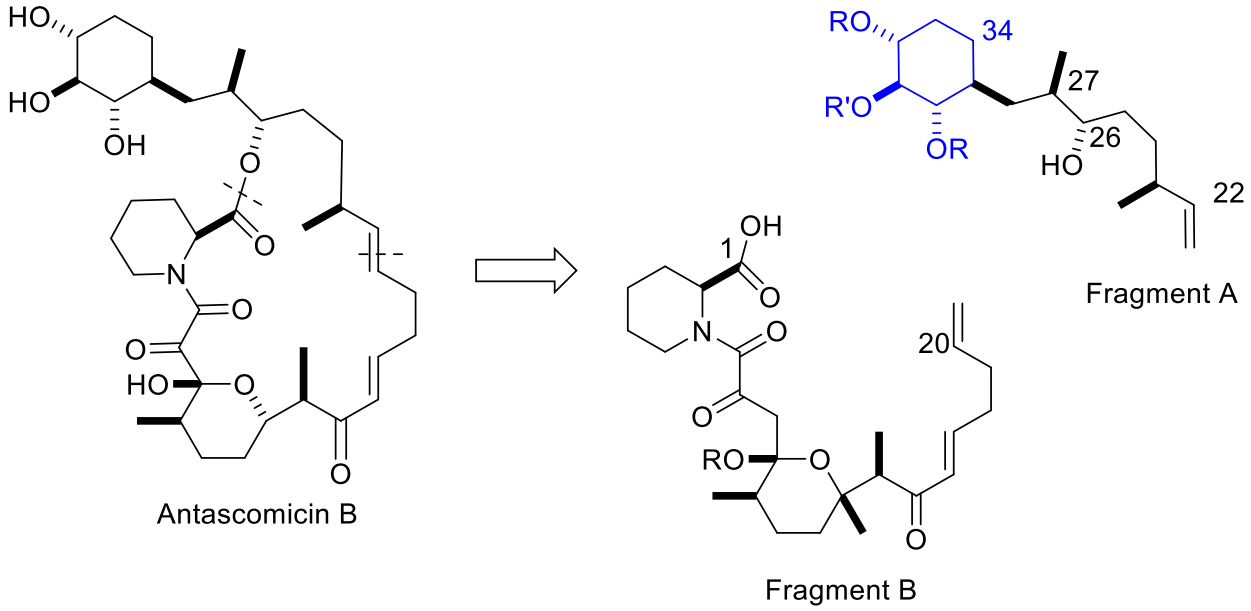


Scheme 3: FKBP12 binding domains of Rapamycin, FK506 and Antascomicin B.

III. Retrosynthesis

Retrosynthetic technique is a powerful tool for designing the synthesis of complex molecules. The proposed synthesis of Antascomicin B could be achieved by ring closing metathesis at C_{21}-C_{22} with the help of fragment A(C_{21}-C_{34}) and fragment B(C_1-C_{21}), which belong to the family of Antascomicin B (Scheme 4). In 2004, Fuwa's group has published preliminary studies on C_{18}-C_{34} fragment of Antascomicin A[14], while Chakraborty et al have published about the synthesis of fragments C_1-C_{21}[15] and C_{22}-C_{34}.[16] In addition, Stephen Leys' research group at

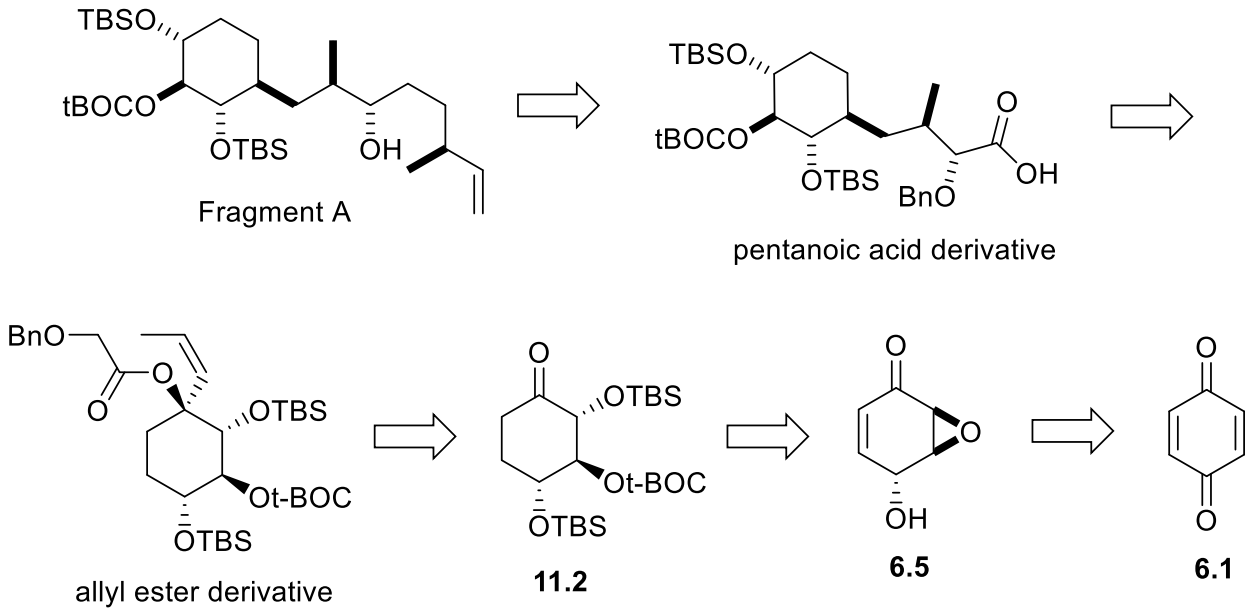
Cambridge University has published the total synthesis of Antascomicin B for the first time in 2005.[17] Their method alongside others involved high load of catalysts, and considered as a major issue hindering the scaling-up of this process.



Scheme 4: Proposed Antascomicin B retrosynthetic strategy

The retrosynthetic steps of the of the asymmetric C_{21}–C_{34} fragment of Antascomicin B was well organized by Dr. McIntosh group. The fragment A can be achieved from the pentanoic acid derivative by several reaction such as converting into corresponding Weinreb amide and hydrogenation using Crabtree catalyst to install stereocenters, allyl diazene rearrangement, catalytic hydrogenation, selective deprotection of benzyl protecting group, reduction of alkene and followed by Grieco olefination.

The pentenoic acid derivative would achieved by Ireland- Claisen rearrangement through the allylic ester derivative. The Allylic ester can be synthesized from the epoxy quinol **6.5** through the ring opening epoxide reaction, protection of the hydroxyl groups and propargylation to alkyne, BOC protection of the secondary alcohol and followed by acylation gave allylic ester. The epoxy quinol **6.5** was achieved from commercially available benzoquinone **6.1** through the 4 steps including most significant asymmetric hydrogenation.



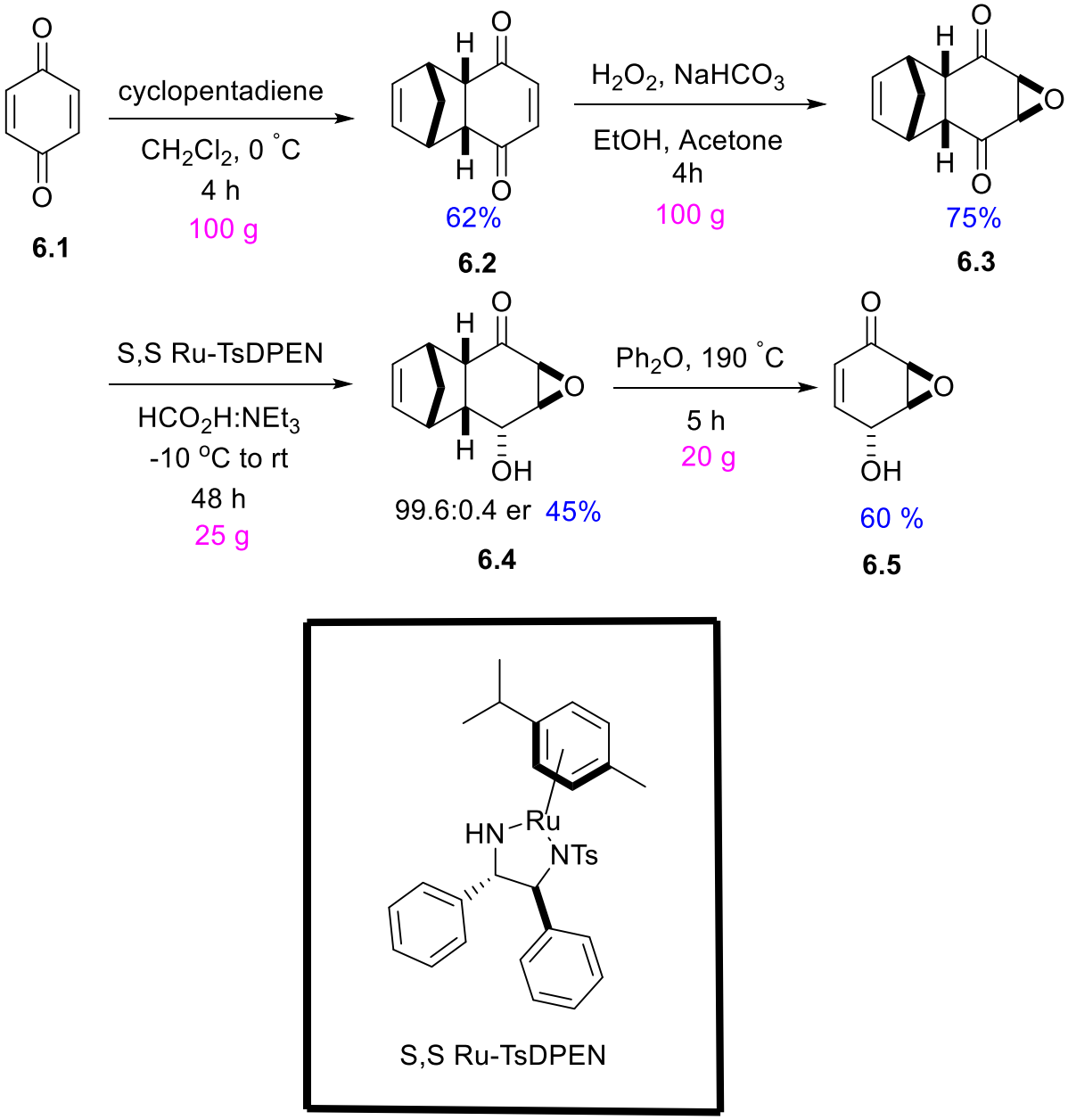
Scheme 5: Proposed Antascomicin B, fragment A retrosynthetic strategy

IV. Synthetic studies towards the C29-C34 moiety of Fragment A of the Antascomicin B

1. Preliminary studies:

The synthetic studies towards the Antascomicin B successfully reported by Dr. McIntosh group. According to our recent report about the synthesis of the C_{21}-C_{34} fragment was limited by the lack of an efficient asymmetric route due to one of the key early intermediates, trihydroxy cyclohexenone **7.1.** At the same time, the asymmetric routes available to make trihydroxy cyclohexenone **7.1** included several steps, high enzyme loading, long reaction times and limited scale.[18-20, 29-31.]

The ongoing efforts in our lab for the asymmetric synthesis of the Antascomicin B started with the commercially available benzoquinone **6.1**. The Diels-Alder reaction conditions were utilized to synthesize mesodiketone **6.2** with the benzoquinone **6.1** and freshly clacked cyclopentadiene as starting materials. The meso diketone **6.2** converted to epoxy diketone **6.3** in excellent yields with help of the epoxidation conditions. The both reactions were developed in large scale (100 g) without suffering yield of the reactions. Using Noyori's Ru (*p*-cymene) [(*S, S*)-TsDPEN] catalyst the epoxy diketone **6.3** was converted to epoxy keto alcohol **6.4** in moderate yield with the high enantiomeric ratio (>99 ee). The enantioselectivity of the reaction was 81:19 er at 5% of the starting material conversation with in 1 hour determined by chiral GC. The enantioselectivity of the reaction was achieved 93:17 in 16 hours with the 85% yield. The longer reaction times such as 48 hours leads 99.6:0.4 er with the diminishing yields of desired product (45%) due to the kinetic resolution. The epoxy keto alcohol **6.4** was converted to epoxyquinol **6.5** in good yield by the Taylor[21] variation of the Lubineau[22] procedure for the retro Diels-Alder reaction. The retro Diels-Alder reaction was successfully scale up to 20 g without diminishing the yields (Scheme 6).

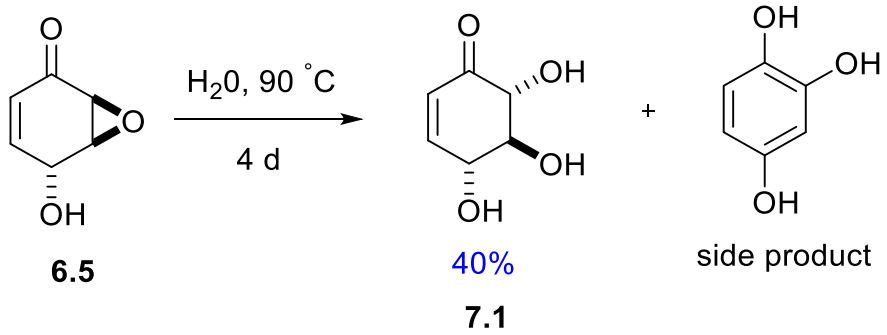


Scheme 6: Preliminary asymmetric synthesis of epoxyquinol moiety

2. Studies of ring open epoxyquinol:

Epoxides are useful building blocks in the synthesis of natural products. The epoxide ring-opening reaction occurs through S_N2 reaction under neutral or basic conditions to synthesize diols. This reaction leads to 1, 2 substituted products with a trans/anti relationship when a nucleophile attack the epoxide carbon. For these reactions, water considered a great solvent among others and it produces acceptable yields.[23, 24] Jin Qu proposed enantioselective ring opening of epoxide by hydrolysis in hot water in the absence of catalyst.[25] Also, ring-opening reaction of epoxides or aziridines with various types of nucleophiles is a well-studied field. All these studies indicate that green solvent (water) considered as the suitable solvent and nucleophile for enantioselective ring opening of epoxide. Literature studies show that the hydrolysis of epoxy cyclohexenone through reflux heating in water at 90 ^oC for four days leads to the formation of enantioselective diols.[25]

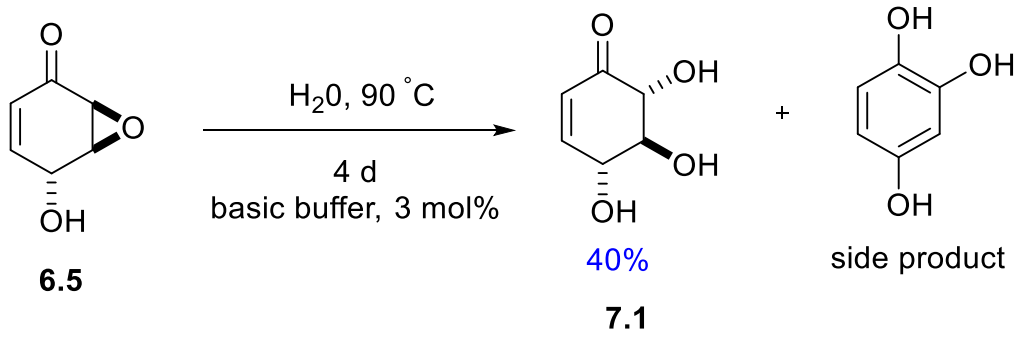
To synthesize trihydroxy cyclohexenone **7.1**, the epoxy keto alcohol **6.5** treated with water at 90 ^oC for 4 days to yield moderate yields. The aromatized byproduct (1, 2, &4-benzenetriol) formation was expected in this reaction and this was the one of the potential problems for moderate yield (Scheme 7). The desired trihydroxy cyclohexenone **7.1** converts into enol form and dehydration is followed to get by product would be the expected mechanism.



6.5 40% **7.1**

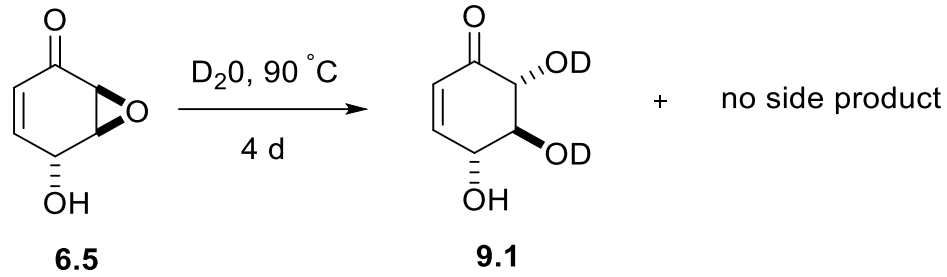
Scheme 7: Ring opening reaction of asymmetric epoxyquinol moiety

To overcome this potential problem, we were introduced useful literature techniques in the organic reaction to maximize yields. As of expected mechanism the formation of aromatized byproduct need to have slightly acidic medium and in this reaction water acts as acid catalyst, so we planned to create a slightly basic medium (used basic buffer) in the reactions conditions to mimic the side product (Scheme 8). This method was not successful to mimic the side product formation. Therefore, we planned to monitor the reaction day-to-day.



Scheme 8: Compliance of ring opening reaction of epoxyquinol

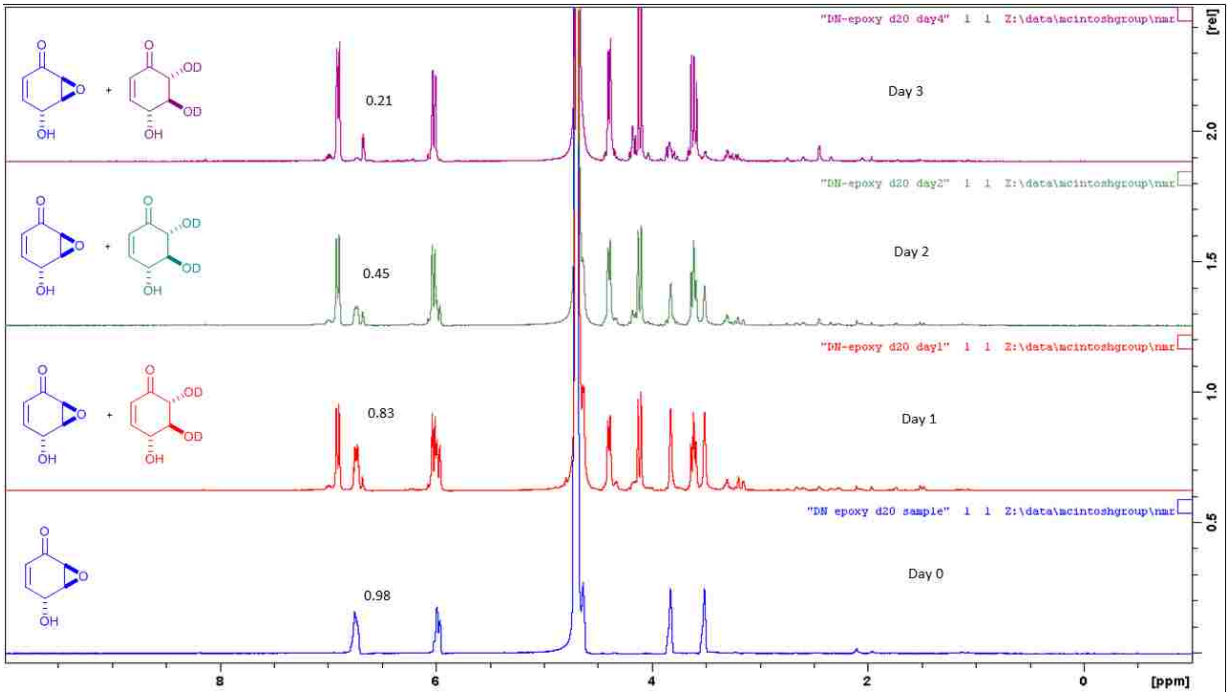
The 10 mg of epoxy keto alcohol **6.5** was taken in NMR tube with 1 mL of deuterated water and heated the closed NMR tube for 4 days at 90 ^{o}C to track the ^{1}H NMR (Scheme 9 & 10) of the crude reaction each and every day. We closely tracked the ^{1}H NMR spectra of crude reaction mixture every 24 h and we noticed no side product (1, 2, &4-benzenetriol) presence even after 4 days of heating. So finally, we came to conclude that the side product formed in process of column purification. For the column purification, we treated the silica gel with slightly basic condition (1% triethylamine) leads to decomposition of the ring open epoxide product.



6.5 **9.1**

Scheme 9: Tracking ring opening reaction of epoxyquinol through ^{1}H-NMR

NMR Study of ring opening epoxide in D_2O



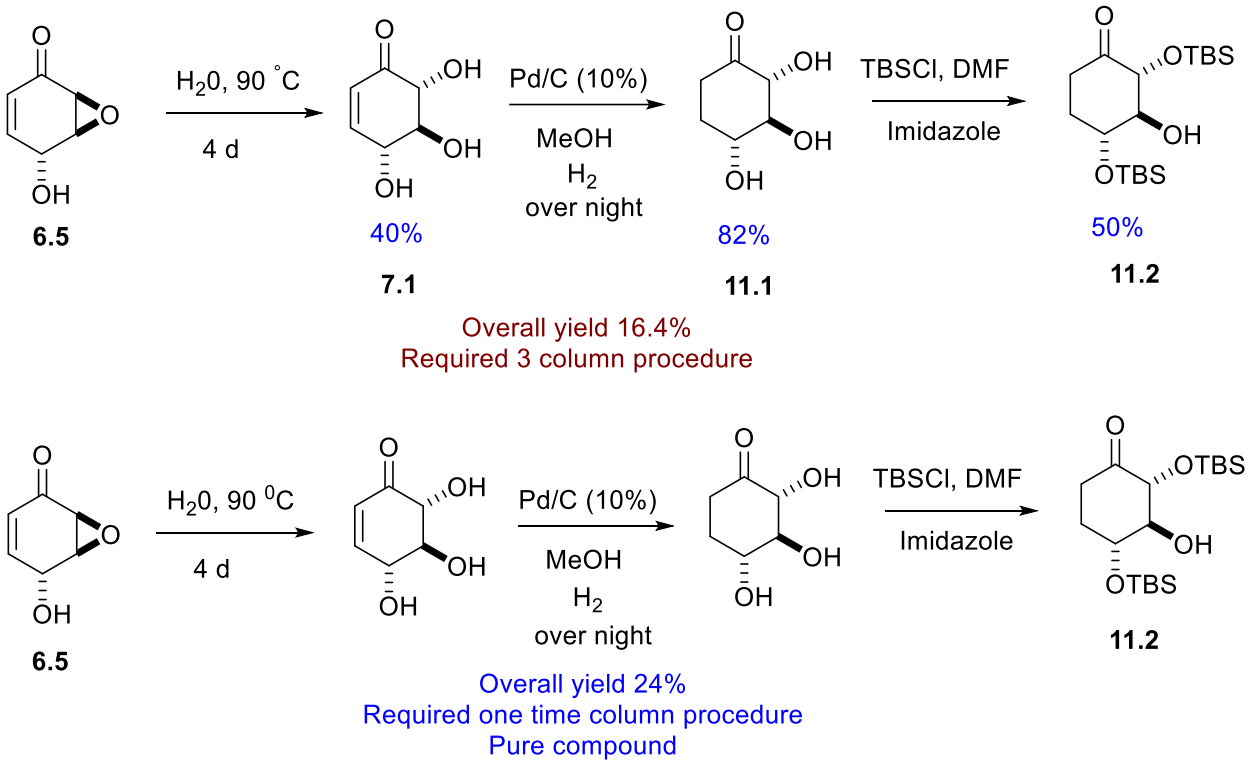
Scheme 10: Analyzing day-to-day ^{1}H-NMR spectra of the ring open reaction.

From the expected mechanism, the double bond in epoxyquinol **6.5** would help to develop a stable aromatized compound (side product) followed by dehydration of enol form of desired compound **7.1**. As of literature, the substituted epoxyquinol derivatives gave good yields of the hydrogenated products with the Pd metal on carbon.[26] The epoxyquinol **6.5** was treated with hydrogen gas with Pd metal on carbon was gave no reaction. Therefore, the proposed plan of hydrogenated product of epoxyquinol would treated with H_20 at 90 ^oC for 4 days was obstacle to generate good yield of desired trihydroxy cyclohexenone **7.1**.

3. Studies towards the asymmetric trihydroxy cyclohexanone:

The enantiopure trihydroxy cyclohexenone **7.1** served as the precursor for the synthesis of the fragment A of the Antascomicin B. The free hydroxyl groups needed to survive in order to achieve the final Antascomicin B. As of original plan, trihydroxy cyclohexenone **7.1** hydrogenated with Pd metals on carbon in methanol, leads to the formation of trihydroxy cyclohexanone **11.1** in good yields. As per literature, various protecting groups, such as Acetyl, Benzoyl, Benzyl, Silyl ether and TBSCl can used to protect the hydroxyl group in trihydroxy cyclohexanone **11.1**. Furthermore, hydroxyl cyclohexanone **11.2** was successfully prepared from trihydroxy cyclohexanone **11.1** treated with TBSCl as the protective groups, imidazole and DMF as the base and solvent, respectively. (Scheme 11). The overall yield of the 3-step reaction starting from the epoxy keto alcohol **6.5** to the hydroxyl cyclohexanone **11.2** was 16.4%. This procedure require 3-column chromatography purification each after the reaction. As of our investigation, the yield of trihydroxy cyclohexenone **7.1** from epoxy keto alcohol **6.5** diminished because of the column purification**.** Therefore, we decided to utilize the crude trihydroxy cyclohexenone **7.1** for further reactions without column purification. The crude trihydroxy cyclohexenone **7.1** treated with the hydrogenated condition to yield the trihydroxy cyclohexanone **11.1** and the crude trihydroxy

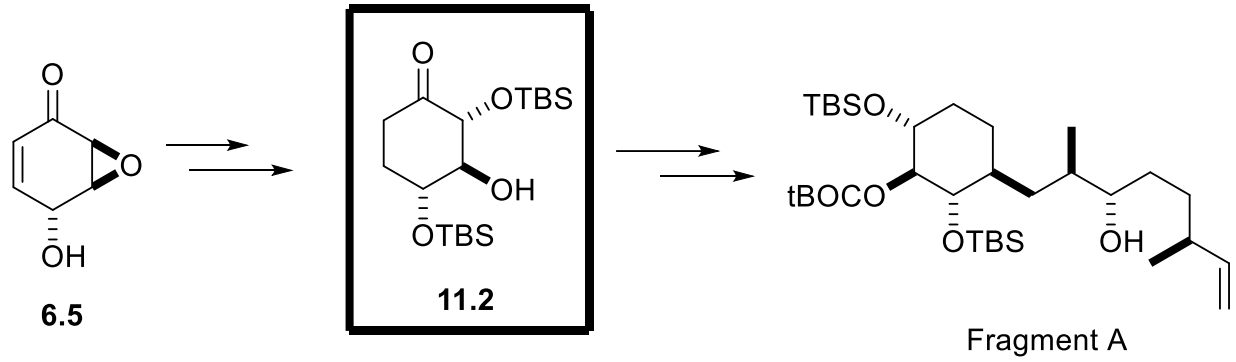
cyclohexanone **11.1** treated with the TBSCl as the protective groups gave the hydroxyl cyclohexanone **11.2** overall 24% yield. The proposed revised synthetic strategy successfully demonstrated 7.6% higher yield of hydroxyl cyclohexanone **11.2** with single column chromatography versus the traditional 3 continuous step reaction conditions. The purity of the hydroxyl cyclohexanone **11.2** compared with the standard molecule and confirmed.



Scheme 11: Revised synthetic route for asymmetric hydroxyl cyclohexanone moiety

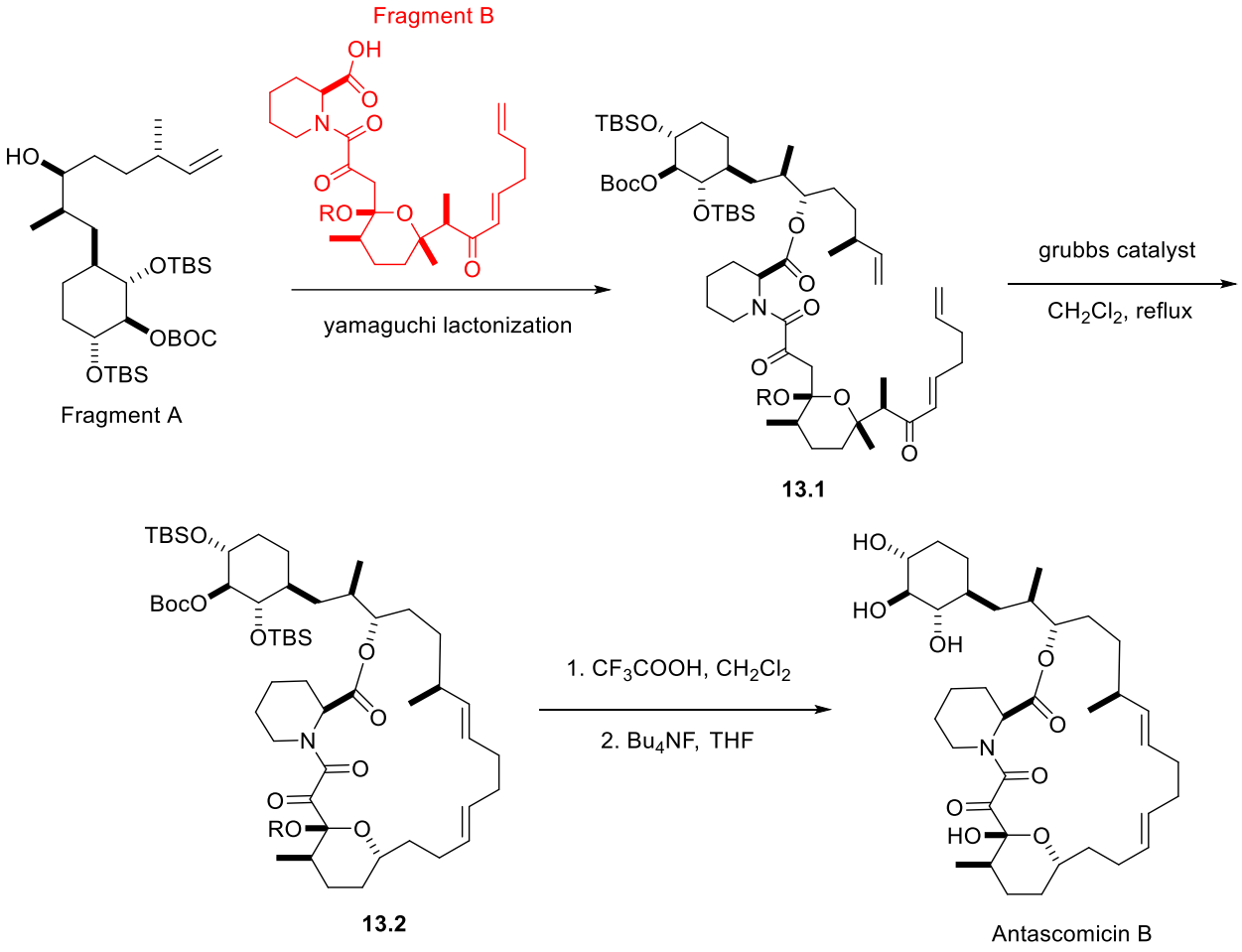
V. Future studies:

The hydroxyl cyclohexanone **11.2**, would be valuable intermediate for the asymmetric synthesis of the desired fragment A (C_{21}-C_{34}) of Antascomicin B (Figure 12). The synthetic methods developed by colleagues for the efficient construction of fragment A (C_{21}-C_{34}) from hydroxyl cyclohexanone **11.2**, through various rearrangements, namely Ireland-Claisen and allylic diazene rearrangements. The asymmetric synthesis toward the fragment B (C_1-C_{21}) was commenced with pipecolinic acid, and its synthetic route was traced by Claisen rearrangement and asymmetric Suzuki cross coupling.



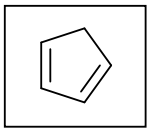
Scheme 12: Proposed synthetic steps of Antascomicin B, fragment A.

As final steps in Antascomicin B total synthesis, fragment A (C_{21}-C_{34}) should conjoin with fragment B (C_1-C_{21}) to produce compound **13.1**. As per literature, the two free hydroxyl groups on each fragment can attached by Yamaguchi Lactonization.[27] Compound **13.2** could synthesized from compound **13.1** by ring closing metathesis[28]. The final product, Antascomicin B, could be prepared from compound **13.2** by the removal of all protecting groups by universal deprotection reaction conditions. (Figure 13).

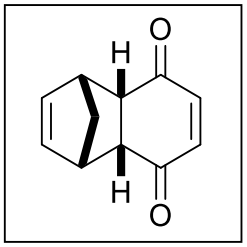


Scheme 13: Proposed final steps of Antascomicin B total synthesis

VI. Experimental section

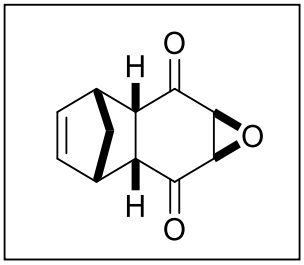


Cyclopentadiene. The dicyclopentadiene (250 mL) placed in a 1L round bottom flask equipped with a magnetic stirring bar. The round bottom flask connected with a vigreux column, which attached to a continuous circulating ice water condenser. The flask heated with oil bath at 210 ^{o}C and the condensation temperature of cyclopentadiene monitored by thermometer. The distillation of the cyclopentadiene should not occur above 40 ^{o}C on thermometer. The cracked cyclopentadiene collected at -78 ^{o}C and stored at -78 ^{o}C for maximum for 20 days.

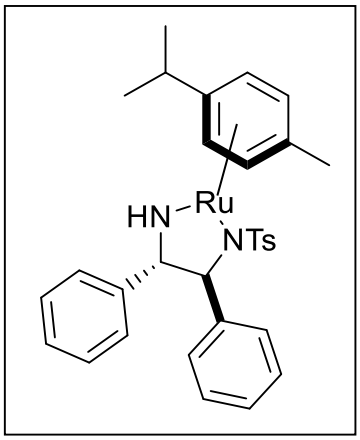


Meso diketone 6.2. The *p*-Benzoquinone (100.00 g, 0.92 mol) and dichloromethane (800 mL) was allocated in a 2 L three necked round bottom flask, equipped with a magnetic stirrer bar and thermometer. The round flask was cooled to -10 ^{o}C with methanol and ice bath. Freshly cracked cyclopentadiene (40 mL, 0.46 mol) added over a period of 30 min. A second 40 mL portion of cyclopentadiene added in a similar fashion (The cyclopentadiene added in two portions to mitigate the dimerization that occurs upon warming to room temperature). The mixture then stirred in the ice bath for 1 h and then stirred at room temperature for 1 h. The solvent removed in vacuo and the crude brick red oil material purified by recrystallization from hexanes. The light-yellow crystals were washed with hexanes, and then dried completely under high vacuum to give meso

diketone **6.2** as pale yellow crystals (117.7 g, 68%): spectral data matched those previously reported.[32, 34, 35.]

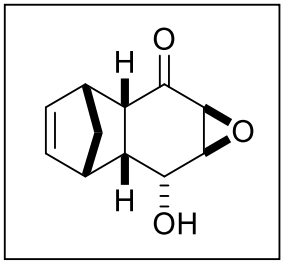


Epoxy diketone 6.3. The meso diketone **6.2** (100.00 g, 0.57 mol) and THF (1250 mL) was transferred to 2L three necked round bottom flask, equipped with a magnetic stir bar. The H_2O_2 (35%, 120 mL) was added dropwise via addition funnel approximately 1 h while the reaction mixture stirring at room temperature. To the solution, $NaHCO_3$ (sat., 133 mL) was added dropwise via addition funnel approximately 1 h. The reaction mixture stirred for another 2 h and monitored starting material consumption by TLC. The solvent was removed in vacuo and the crude material (pale white solid) was purified by recrystallization (white solid) from ethanol to give epoxide diketone (81.7 g, 75%). spectral data matched those previously reported. [20, 34, 35]

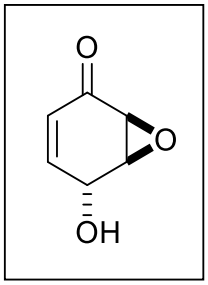


Ru (p-Cy) TsDPEN: Ru (p-Cy) TsDPEN was prepared by dissolving $[RuCl_2\ (p\text{-}Cy)]_2$ (1.00 g, 1.63 mmol) and (*S, S*) - TsDPEN (1.20 g, 3.27 mmol) in dichloromethane (25 mL) and allowing

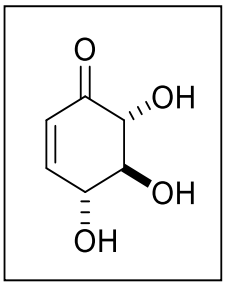
to stir for 5 minutes. KOH (1.31 g, 2.3 mmol) and water (25 mL) was then added and the mixture was allowed to stir for an additional 5 minutes. Reaction was complete when the color turned from orange to deep purple. Reaction mixture extracted in dichloromethane, dried over CaH_2, and then concentrated in vacuo to give Ru (p-Cy) TsDPEN as dark purple crystals (quantitative yield). Data matched that previously reported. [33]



Epoxy keto alcohol 6.4. Ru (p-Cy) (S,S-TsDPEN) (0.42 g, 0.68 mmol, 0.65 mol %) and epoxy diketone **6.3** (25.0 g, 0.13 mol) were added to a solution of formic acid (6.75 mL), triethylamine (25.0 mL) and acetonitrile (1000 mL) at -10 °C. The reaction mixture allowed to warm to room temperature and stirred for 48 h. The mixture was concentrated in vacuo and then stirred for 16 h in 40/60 ethyl acetate/hexanes (300 mL) with activated charcoal (1 g). The mixture was filtered through a plug of Celite with 40/60 ethyl acetate/hexanes and concentrated in vacuo. At this point, the residue could be purified by flash chromatography (20/80 ethyl acetate/hexanes) to give keto alcohol **6.4** as colorless crystals (10.12 g, 40%, 99.6:0.4 er). Spectral data matched those previously reported. [20, 34, 35]

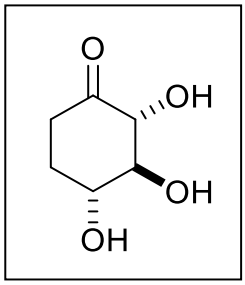


Epoxyquinol 6.5. A solution of monoreduced epoxy keto alcohol **6.4** (20 g, 104 mmol) in diphenyl ether (200 mL) was dissolved and stirred at room temperature while degassed with nitrogen for 30 minutes. The reaction mixture was then heated to 180 ^{o}C (still gently bubbling through with nitrogen) until decomposition product became a significant spot as monitored by TLC. After cooling to room temperature, the reaction mixture poured onto a column of silica gel using hexane to elute diphenyl ether solvent. After elution with hexane, the reaction mixture was eluted with 1/99-9/91 MeOH/CH_2Cl_2 1% gradient followed by recrystallization with diethyl ether to yield pure epoxyquinol **6.5** as white crystals (7.87 g, 60%). Spectral data matched those previously reported.[20, 34, 35]

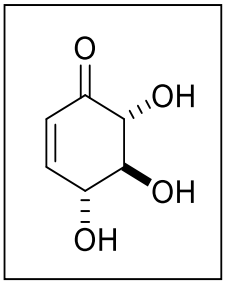


Trihydroxy cyclohexenone 7.1: Epoxyquinol **6.5** (12 g, 79.30 mmol) was distributed in 1 gram aliquots to 12 parallel synthesizer tubes and H_2O (12 mL) with stir bar. Each tube heated to 90 ^{o}C for 4 days on the heating mantle. H_2O then co-evaporated with MeCN and the brown residue adsorbed on silica gel. The silica gel/residue was added to a silica gel column using CH_2Cl_2. Mixture was eluted with 0/99-10/90 MeOH/CH_2Cl_2 at 1% gradient. The second fraction was collected and recrystallized in EtOH to give trihydroxy cyclohexanone **7.1** (6.03 g, 41.84 mmol,

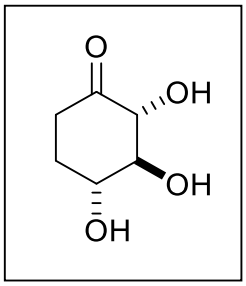
40%) as colorless crystals. M.P. 136-138 ºC; [α]23 D -0.885 (*c* 0.437 1:1MeOH:CH_2Cl_2); IR (film) 3400, 2835, 1693. ^{1}H NMR (400 MHz, CD_3OD) δ 3.58 (dd, J = 10.87 Hz, 8.28 Hz, 1H), 4.03 Hz (d, J = 10.88 Hz, 1H), 4.36 (m, 1H), 6.04 (dd, J = 10.33 Hz, 2.56 Hz, 1H), 6.92 (d, J = 10.33 Hz, 1.94 Hz, 1H); ^{13}C NMR (400 MHz, CH_3OD) δ 70.12, 75.17, 76.99, 124.57, 150.36, 197.21. Anal Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59. Found; C, 49.89; H, 5.65.65. Spectral data matched those previously reported. [34, 35.]



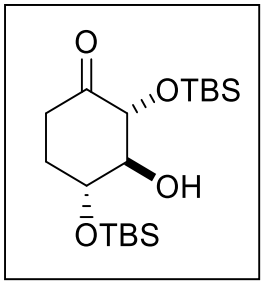
Trihydroxy cyclohexanone 11.1. A mixture of trihydroxy cyclohexenone **7.1** (5.28 g, 14.17 mmol) and 10% Pd/C (0.950 g, 0.90 mmol Pd) in dry methanol (100 ml) was stirred under an H_2 atmosphere (1 atm) for 7 h. Following completion of the reaction by TLC, the reaction mixture filtered through celite and concentrated. The crude product was purified by flash column chromatography on silica gel using 1/99-4/96 gradient of ethyl acetate/hexane, followed by recrystallization with cold hexane to give trihydroxy cyclohexanone **11.1** (4.67 g, 12.47 mmol, 80%) as white crystals. [α]23D = +4.6 (*c* 0.5 CH_2Cl_2); IR (film) 3414, 1736 cm-1; ^{1}HNMR (400 MHz, CDCl3) δ 1.60 (m, 1H), 2.04 (m, 1H), 2.37 (m, 2H), 2.53 (d, J = 2.53 Hz, 1H), 3.47 (td J = 9.96, 1.54, 1H), 3.87 (ddd, J = 11.21, 8.67, 4.69, 1H), 4.07 (d, J = 9.77 Hz, 1H); ^{13}CNMR (400 MHz, $CDCl_3$) δ - 34.67, 35.72, 72.84, 77.57, 79.71, 205.66. Spectral data matched those previously reported.[34, 35]



Trihydroxy cyclohexenone 7.1. The epoxyquinol **6.5** (1 g, 7.9 mmol) was dissolved in 12mL of H_2O in a pressure with a magnetic stir bar. The pressure tube heated to 90 ^oC for 4 days on the oil bath. H_2O then co-evaporated with MeCN and the crude brown residue used without any further purification.



Trihydroxy cyclohexanone 11.1. A mixture of crude trihydroxy cyclohexenone **7.1 (**1.14 g, 7.9 mmol, expected from previous reaction) and 10% Pd/C (0.21 g, 2 mmol Pd) in dry methanol (20 mL) was stirred under an H_2 atmosphere (1atm) overnight. Following completion of the reaction, the mixture filtered through celite and concentrated crude product used without further purification.



Hydroxy ketone 11.2. The crude trihydroxy cyclohexanone **11.1** (1.14 g, 7.9 mmol, expected from previous reaction) in 10 mL dry DMF was added to the solution of TBSCl (3.57 g, 23.7 mmol) and imidazole (2.15 g, 31.6 mmol) in dry DMF (20 mL). After stirring at room temperature for 4 h, the reaction mixture was quenched with ice-cold water, extracted with ether, dried over $MgSO_4$, and concentrated in vacuo. The crude product purified by flash column chromatography on silica gel using 3:97 ethyl acetate: hexane, followed by recrystallization with hexane to give hydroxy ketone **11.2** (0.71 g, 1.9 mmol, 24% over 3 steps).

Alternatively solution of TBSCl (5.82 g, 38.6 mmol) and imidazole (3.50 g, 51.4 mmol) in dry DMF (30 mL) was added to trihydroxy cyclohexanone **7.1** (1.88 g, 12.9 mmol) in 10 mL dry DMF. After stirring at room temperature for 4 h, the reaction mixture quenched with ice water, extracted with ether, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using 3/97 ethyl acetate/hexane, followed by recrystallization with cold hexane to give hydroxy ketone **11.2** (2.40 g, 6.42 mmol, 50% single step) as white crystals. M.P. 76-78 ^oC; $[\alpha]23$ D = +0.084 (*c* 0.26 CH_2Cl_2); IR (film) 3414, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.14 (s, 3H), 0.16 (s, 3H), 0.17 (s, 3H), 0.92 (s, 9H), 0.94 (s, 9H), 1.60 (m, 1H), 2.04 (m, 1H), 2.37 (m, 2H), 2.53 (d, J = 2.53 Hz, 1H), 3.47 (td J = 9.96, 1.54, 1H), 3.87 (ddd, J = 11.21, 8.67, 4.69, 1H), 4.07 (d, J = 9.77 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ -5.33, -4.49, -4.44, 18.10, 18.59, 25.78, 25.84, 29.65, 34.67, 35.72, 72.84, 79.71, 205.66. Spectral data matched those previously reported. [34, 35.]

VII. References:

1. Carey, F. A; Sundberg, R. J. Advanced Organic Chemistry, Part B: Reactions and Synthesis. *J. Chem. Educ* **1979**, *56*, (11), A352.

2. Corey E. J; Cheng X. M. The logic of Chemical Synthesis. *John Wiley & Sons*, New York, **1989**.

3. Koehn, F.E; Carter, G.T. The evolving role of natural products in drug discovery. *Nature Reviews Drug Discovery* **2005**, *4*, 206-220.

4. Chin, Y.W; Balunas, M.J; Chai, H. B; Kinghorn, A. D. Drug Discovery from Natural Sources. *The AAPS Journal* **2006,** *8* (2), E239-E253.

5. Hughes, J.P; Rees, S; Kalindjian, S.B; Philpott, K.L. Principles of early drug discovery. *Br J Pharmacology* **2011**, *162* (6), 1239–1249.

6. Fehr, T. S.; Sanglier, J. J; Schuler, W; Gschwind, L; Ponelle, M; Schilling, W; Wioland, C. Antascomicin A, B, C, D, and E. Novel FKBP12 Binding Compounds from a Micromonospora. *J. antibiotic* **1996**, *49* (3), 230-233.

7. Larry, M. Drug therapy in dermatology. *Taylor and Francis e-library* **2005,** 162-163.

8. Salituro, G.M; Zink, D.L; Dahl, A; Nielsen, J; Wu, E; Huang, L; Kastner, C; Dumont, F.J. Meridamycin; A Novel nonimmunosuppresive FKBP12 Ligand from Streptomyces Hygroscopicus. *Tetrahedron Lett* **1995**, *36*, 997-1000.

9. Somers, P.K; Wandless, T.J; and Schreiber, S.L. Synthesis and Analysis of 506BD, a High-Affinity Ligand for the Immunophilin FKBP. *J. Am. Chem. Soc* **1991,** *113*, 8045- 8056.

10. Liu, J; Farmer, J.D.J; Lane, W.S; Friedman, J; Schreiber, S.L. Calcineurin is a Common Target of Cyclophilin-Cyclosporin A and FKBP-FK506 Complexes, *Cell* **1991**, *66*, 807-815.

11. Steiner, J.P; Dawson, M.T; Fotuhi, M; Glatt, C.E; Snowman, A.M; Cohen, N; Snyder, S.H. High Brain Densities of the Immunophilin FKBP Colocalized with Calcernium. *Nature* **1992**, *358*, 584-587.

12. Snyder, S.H; Sabatini, D.M; Lai, M.M; Steiner, J.P; Hamilton, G.S; Suzdak, P.D. Neural actions of immunophilin ligands. *Trends in Pharm. Sci* **1998,** *19*, 21-25.

13. Hamilton, G. S; Huang, W; Connolly, M. A; Ross, D. T; Guo, H; Valentine, H. L; Suzdak, P. D; Steiner, J. P. FKBP12-binding domain analogues of FK506 are potent, non-immunosuppressive neurotrophic agents in vitro and promote recovery in a mouse model of Parkinson's disease. *Bioorg. Med. Chem. Lett* **1997**, *7*, 1785-1790.

14. Fuwa, H; Okamura, Y; Natsugari, H. Synthetic studies on Antascomicin A, construction of the C_{18}-C_{34} fragment. *Tetrahedron* ***2004,*** *60*, 5341-5452.

15. Chakraborty, T. K; Mohan, B.K. Studies Directed Towards the Synthesis of Antascomicin A: Stereoselective Synthesis of the C_1-C_{21} Fragment of the Molecule. *Tetrahedron Lett* **2006,** *47*, 4999-5002.

16. Chakraborty, T.K; Mohan, B.K; Sreekanth, M. Studies Directed Towards the Synthesis of Antascomicin A: Stereoselective Synthesis of the C_{22}-C_{34} Fragment of the Molecule, *Tetrahedron Lett* **2006**, *47*, 5003-5005.

17. Brittain, D. E. A; Griffiths Jones, C. M; Linder, M. R; Smith, M. D; McCuskey, C; Barlow, J. S; Akiyama, R; Yasuda , K; Ley, S. V. Total Synthesis of Antascomicin B. *Angew. Chem. Int. Ed* **2005,** *44*, 2732-7.

18. Qi, W; McIntosh, M. C. Towards the synthesis of Antascomicin B. Synthesis of a model of the C_{22}-C_{34} fragment via Ireland-Claisen and allylic diazene rearrangements. *Tetrahedron* **2008**, *64*, 7021-7025.

19. Hutchison, J. M; Gibson, A. S; Williams, D. T; McIntosh, M. C. Synthesis of the C_{21}-C_{34} fragment of Antascomicin B. *Tetrahedron Lett* **2011**, *52*, 6349-6351.

20. Clay, D. R; Rosenberg, A. G; McIntosh, M. C. Efficient, scalable asymmetric synthesis of an epoxy quinol via Noyori desymmetrization of a meso diketone, *Tetrahedron-Asymmetry* **2011**, *22*, 713.

21. Genski, T; Taylor, R. J. K. The synthesis of epi-epoxydon utilizing the Baylis-Hillman reaction. *Tetrahedron Letters* **2002,** *43* (19), 3573-3576.

22. Lubineau, A; Billault, I. Synthesis of polyhydroxylated cyclohexenyl sulfides and sulfoxides. Evaluation of their inhibitory activity on alpha- and beta-D-glucosidases. *Carbohydrate Research* **1999,** 320 (1-2), 49-60.

23. Simona, B; Daniela, L; Luigi, V. Ring-Opening of Epoxides in Water. *Eur. J. Org. Chem* **2011,** 2587–2598.

24. David, A; Francesco, F; Oriana, P; Simone, T; Luigi, V. Nucleophilic ring opening of 1, 2-epoxides in aqueous medium. *ARKIVOC* **2002,** *11*, 293-311.

25. Wang. Z; Cui, Y.T; Xu, Z.B; Qu, J. Hot water promoted ring opening of epoxide and Aziridines by water and other Nucleophiles. *J. Org. Chem* **2008,** *73*, 2270-2274.

26. Regina, T; Grety, R; Paul, H; Heinrich, H, P. Cladospirone bisepoxide: Definite assignment including absolute configuration and selective chemical transformations. *Tetrahedron* **1995**, *51*(3), 733-742.

27. Inanaga, J; Hirata, K; Saeki, H; Katsuki, T; Yamaguchi, M. A Rapid Esterification by Mixed Anhydride and its Application to Large Ring Lactonization. *Chem Soc Jap* **1979,** *52*, 1989-1993.

28. Gradillas, A; Perez-Castells, J. Macrocyclization by Ring-Closing Metathesis in the Total Synthesis of Natural Products: Reaction Conditions and Limitations. *Angew. Chem. Int. Ed* **2006**, *45*(37), 6086-6101.

29. Takano, S; Higashi, Y; Kamikubo, T; Moriya, M; Ogasawara, K. Enantiodivergent preparation of chiral 2, 5-cyclohexadienone synthons. *Synthesis-Stuttgart* **1993,** *10*, 948-950.

30. Konno, H; Ogasawara, K. A practical preparation of versatile cyclohexenoid chiral building blocks. *Synthesis-Stuttgart* **1999,** *7*, 1135-1140.

31. Bachu, P; Gibson, J. S; Sperry, J; Brimble, M. A. The influence of microwave irradiation on lipase-catalyzed kinetic resolution of racemic secondary alcohols. *Tetrahedron-Asymmetry* **2007,** *18* (13), 1618-1624.

32. Oda, M; Kawase, T; Okada, T; Enomoto, T. 2-cyclohexene-1, 4-Dione. *Organic Synthesis* **1996,** *73*, 253-261.

33. Haack, K. J; Hashiguchi, S; Fujii, A; Ikariya, T; Noyori, R. The catalyst precursor, catalyst, and intermediate in the Ru-II-promoted asymmetric hydrogen transfer between alcohols and ketones. *Angew. Chem. Int. Ed* **1997,** *36* (3), 285-288.

34. Clay, D. Studies toward the total synthesis of antascomicin B. Ph.D., University of Arkansas, Ann Arbor, **2012**.

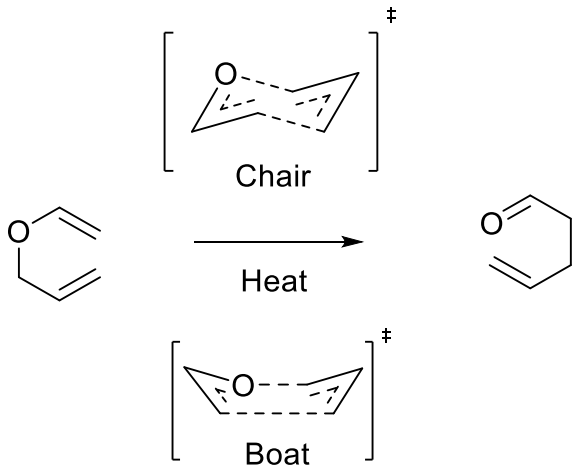
35. Walker, B. Studies in the Asymmetric Synthesis of the C_{21}-C_{34} Fragment of the Natural Product, Antascomicin B. Ph.D., University of Arkansas, Ann Arbor, **2016**.

C. Chapter 2

Thermal azole based Claisen rearrangements

I. Introduction

The Claisen rearrangement, discovered in early twentieth century,[1] provided a very powerful synthetic procedure for carbon-carbon bond formation. Over the past few decades, the importance of the reaction has been well known and drawn the attention of numerous research groups, which has been reflected in the number of papers published in the literature. The [3,3] sigmatropic rearrangement of allyl vinyl ethers, which allows the preparation of γ,δ-unsaturated carbonyl compounds (Scheme 1). This reaction was first reported by Ludwig Claisen in 1912,[1] which described as the thermal isomerization of allyl vinyl ether to 4-pentenal.

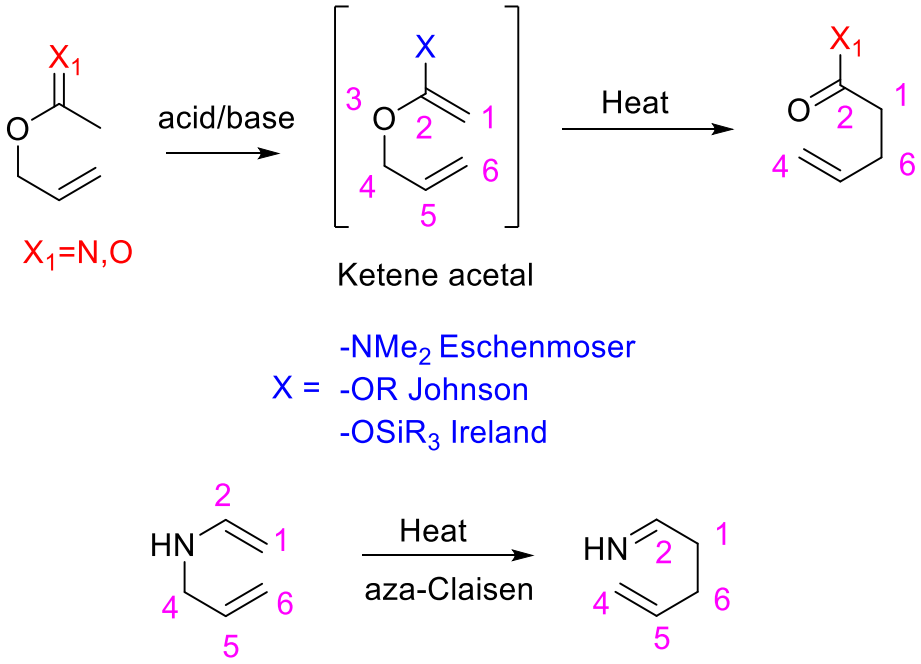


Scheme 1: Simplest aliphatic Claisen rearrangement

Eschenmoser[2], Johnson[3] and Ireland[4] extensively expanded the initial Claisen rearrangement (Scheme 2). As of their findings, the ketene acetal formation was fundamental for the [3,3] sigmatropic rearrangement and it was achieved by *in situ*.

The significant difference from the simplest allyl-vinyl ether framework with presence of the heteroatom at the C2 position, which result in formation of corresponding amides, esters and

silyl esters called Eschenmoser[2], Johnson[3] and Ireland[4] Claisen variations respectively. Another variant arises from the replacement of the oxygen atom by a nitrogen atom called the aza-Claisen rearrangement[5] (also known as 3-aza-Cope or amino-Claisen rearrangement) (Scheme 2).

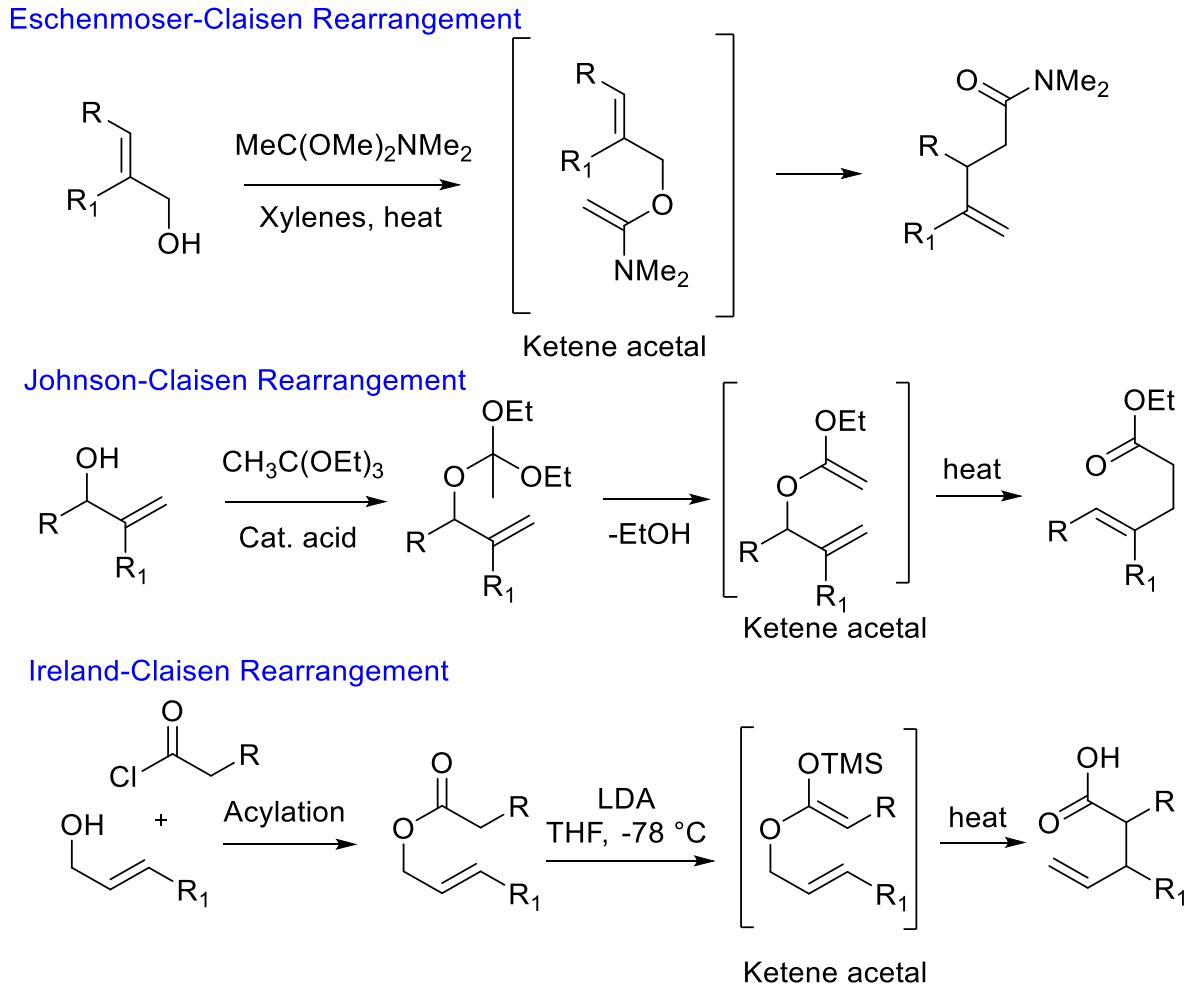


Scheme 2: Variations on Claisen rearrangement system

In 1964, Eschenmoser[2] observed the [3,3] rearrangement of N,O-ketene acetals to yield γ,δ-unsaturated amides. The N,O-ketene acetals was generated by reacting allyl alcohols with N,N-dimethylacetamide dimethyl acetal (Scheme 3).

In 1970, Johnson[3] reported the synthesis of trisubstituted alkenes. The allyl alcohol was heated with excess ethyl ortho acetate with presence of catalytic acid yields ortho ester and losses the ethanol to generate the ketene acetal, which undergoes sigmatropic rearrangement leading to γ,δ-unsaturated ester.

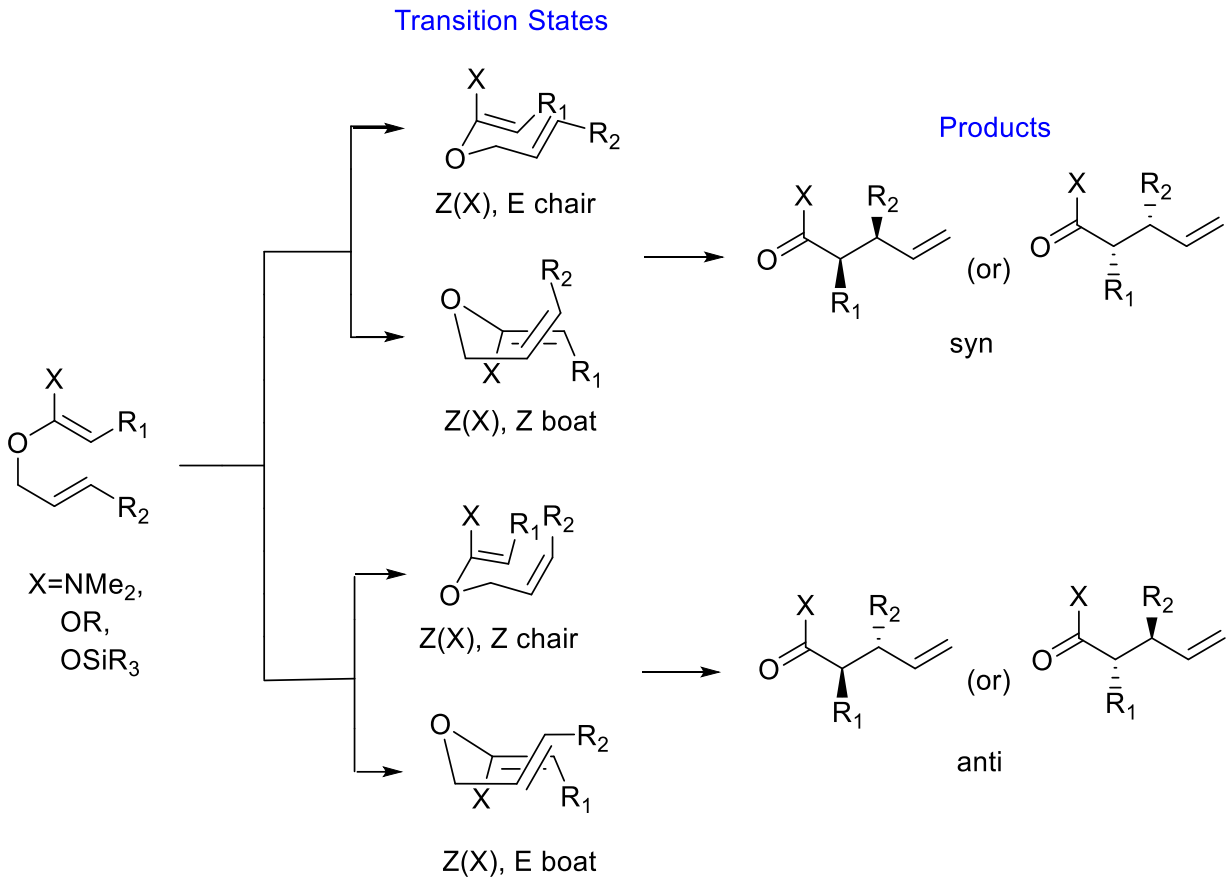
In 1972, Ireland[4] reported the rearrangement of allyl trimethylsilyl ketene acetal. The ketene acetal was generated *in situ* from allylic esters with LDA base to corresponding silyl enolate to yield γ,δ-unsaturated carboxylic acids upon heat (Scheme 3).



Scheme 3: Variations on Claisen rearrangement system

In acyclic systems, Claisen rearrangement occurs preferentially through a chair-like transition state over the boat-like transition state, however, the rearrangement happened through boat transition state in the presence of steric effects.[6] The Claisen products were formed when the steric substituents were present at C1 and C6 positions of the parent allyl vinyl ether frame through

both chair and boat like transition states (Scheme 4). The relative configuration of the newly formed stereocenters determined by configuration of the double bond, and the chair or boat confirmation of the transition states.



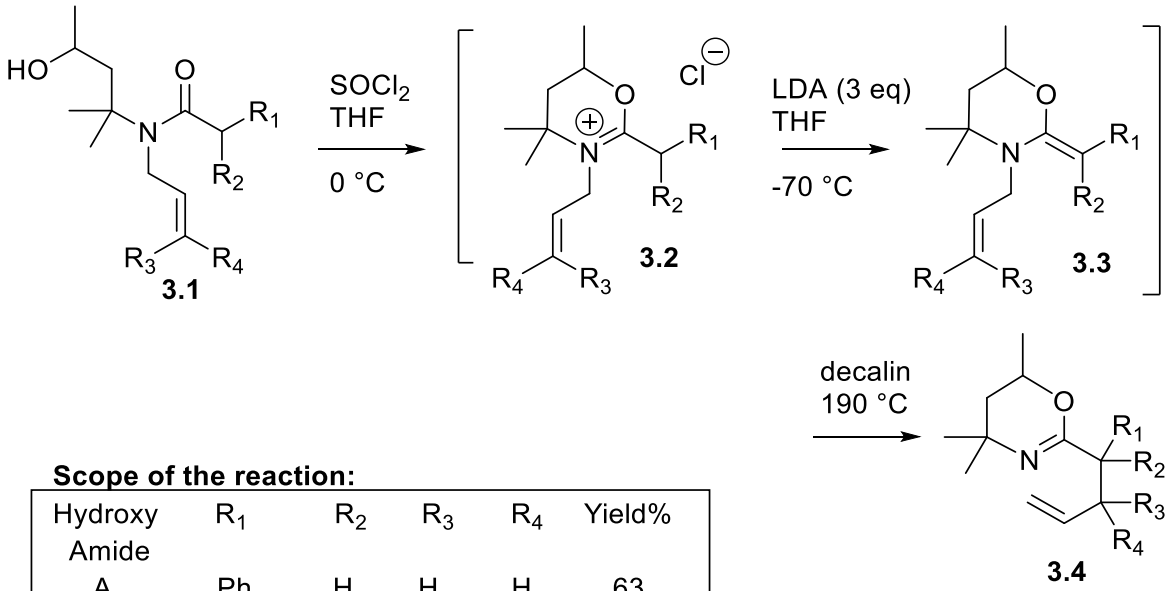
Scheme 4: Transition states and products of the Claisen rearrangement

The variation on initial Claisen rearrangements were well studied and reported in literature. Our primary moto in this project is to develop a feasible methodology of Claisen rearrangement without harsh condition to possess broad functional group compatibility. The accomplishment of this goal will provide a practical and scalable synthetic method for building biological important macromolecules.

II. Significant reports of Claisen rearrangements

1. **Robert E. Ireland: The Claisen rearrangement from N, O-ketene acetals**

Ireland *et al* adopted the concepts of the Claisen rearrangement to synthesize substituted dihydro-1,3-oxazine derivatives **3.4**.[7] Among the various Claisen rearrangement procedures, the excess utilization of precursors for the 1,5-diene system (*in-situ* formation of ketene acetals) was necessary to produce γ, δ unsaturated acid equivalents. Here in the report, the economical utilization of γ-hydroxyl amide **3.1** was used to convert dihydro-1,3-oxazine derivatives **3.4** by series of the 3-step reaction performed in one pot thus providing good yields.



Scope of the reaction:

Hydroxy Amide	R_1	R_2	R_3	R_4	Yield%
A	Ph	H	H	H	63
B	n-Bu	H	H	H	66
C	n-Bu	H	CH_3	H	60
D	n-Bu	CH_3	H	H	17
E	n-Bu	H	CH_3	CH_3	13

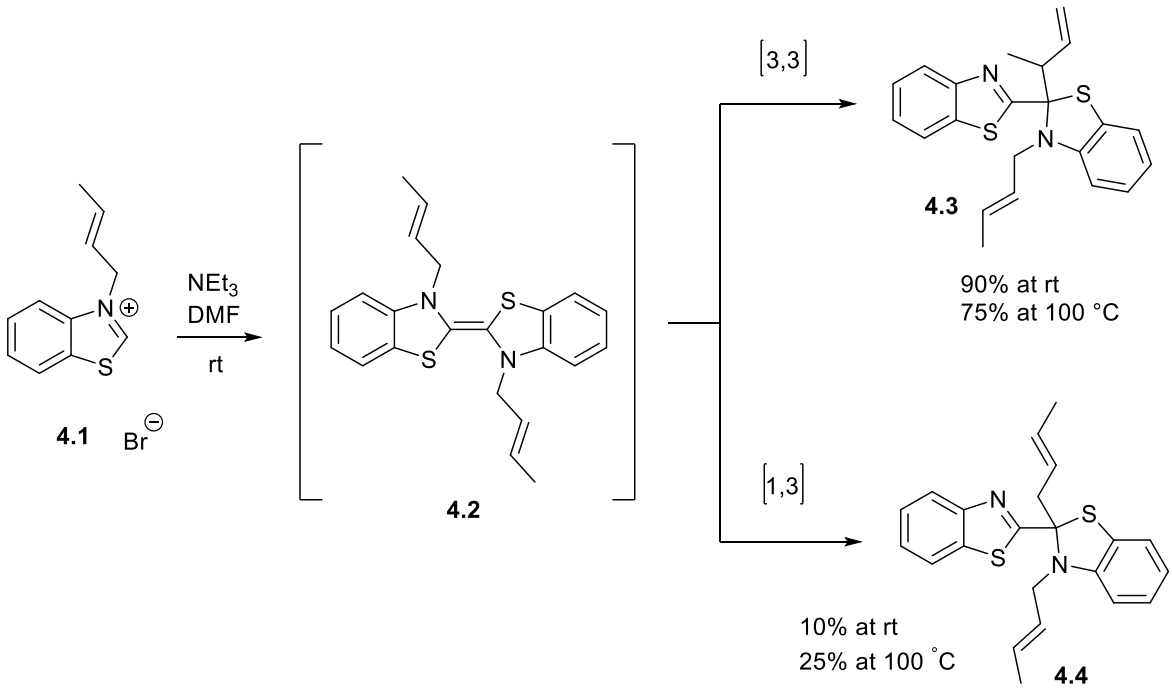
Scheme 5: The Claisen rearrangement from N, O-ketene acetals

The γ- hydroxyl amides **3.1** treated with thionyl chloride to yielded ketene acetal precursor oxazonium salt **3.2**. The oxazonium salts treated with lithium diisopropylamide (LDA) to generate the ketene acetals **3.3** *in situ*. Heating reaction at 190 ^{0}C for 1 hour gave the corresponding γ,δ-

unsaturated oxazine derivatives **3.4**. The two-alkyl groups on the either terminus of the ketene acetals might responsible for the considerable low yield of desired product (Scheme 5).

2. Jack E. Baldwin: [3,3] Sigmatropic rearrangement of electron rich olefins

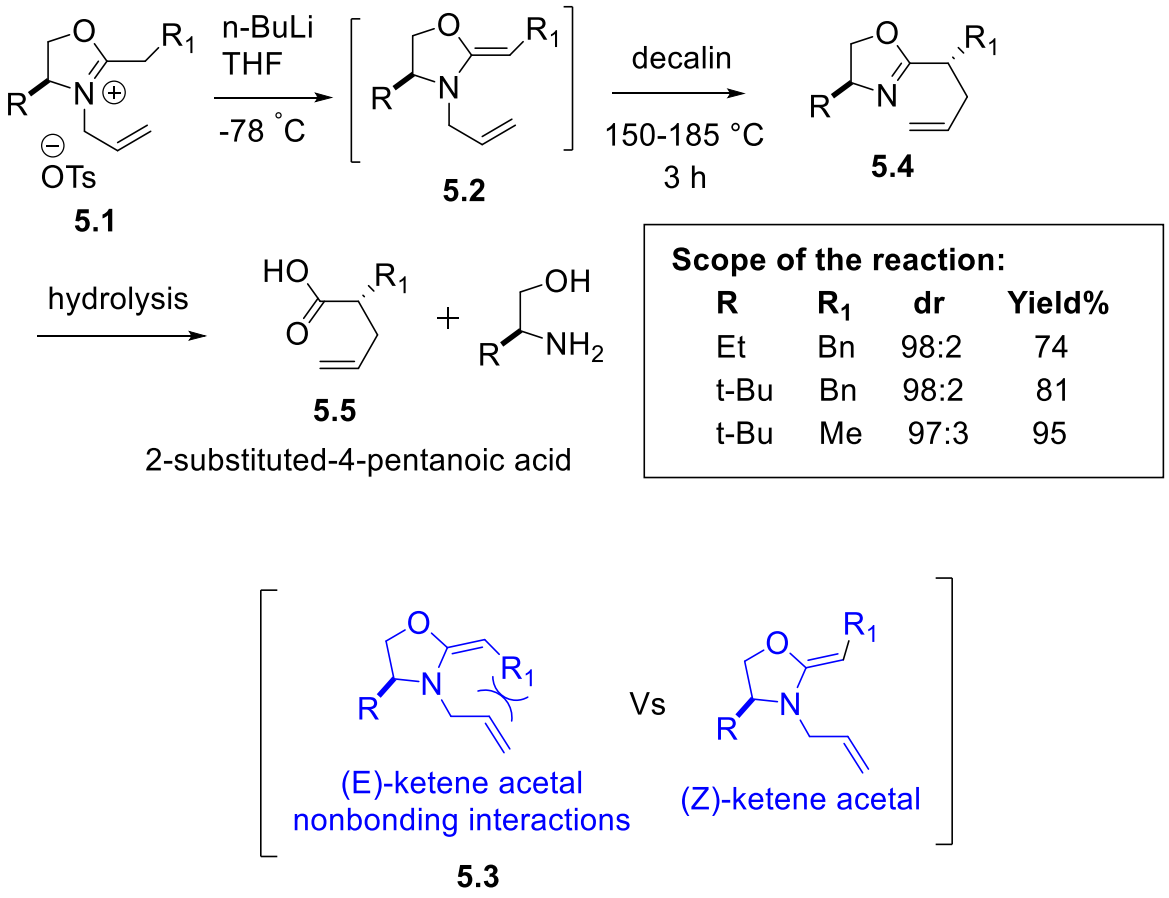
As of the Baldwin's report in 1974, N-substituted benzothiazole derivatives were studied for competing [1,3] and [3,3] sigmatropic rearrangements.[8] He discovered that the two competing reaction pathways for the rearrangement of diaminofulvalene were dependent on reaction temperature and the benzothiazolium *N*-substituents. Reactions conducted at higher temperatures with the N-allyl benzothiazolium salts **4.1** yielded predominantly [3,3]-rearrangement products **4.3,** and the reactions that were run with highly radical stabilizing N-alkyl groups predominantly yielded radical [1,3]-rearrangement products **4.4**. On the other hand, N-benzyl benzothiazolium salts were exclusively produced radical [1,3]-rearrangement products irrespective of temperature (Scheme 6).



Scheme 6: [1,3] & [3,3] Sigmatropic rearrangement of electron rich olefins

3. Mark J. Kurth: Asymmetric synthesis through aza- Claisen rearrangement

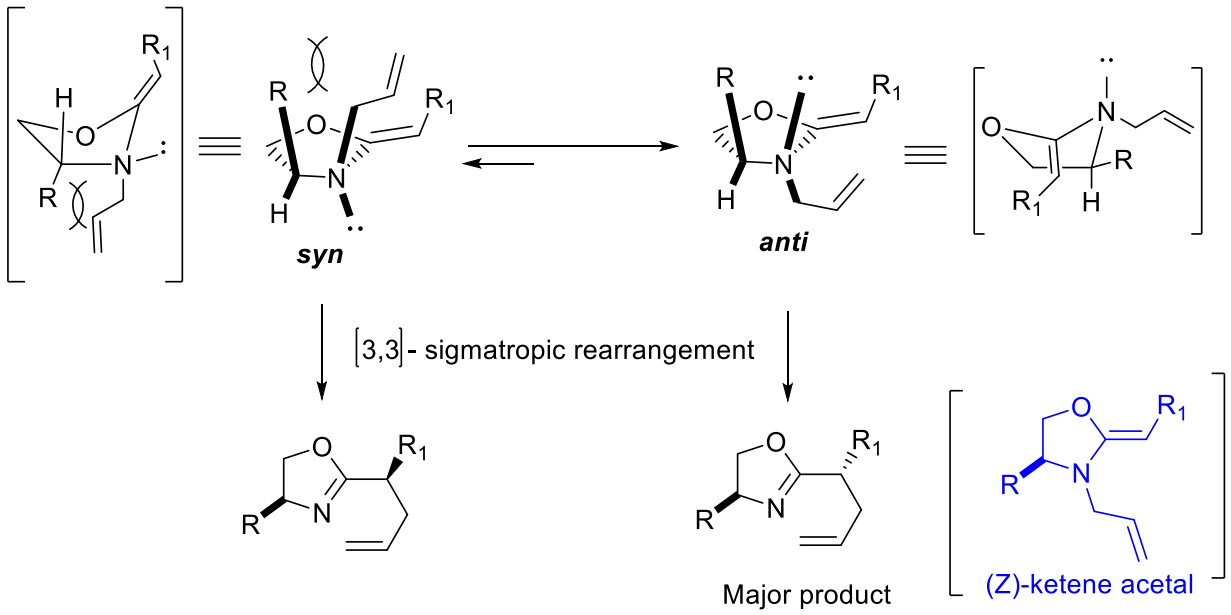
In 1985, Kurth *et al* described first asymmetric synthesis for the 2-substitued-4-pentenoic acid **5.5** by aza-Claisen rearrangement of N-allyl-N, O-ketene acetals **5.2**[9] (Scheme 7).



Scheme 7: Asymmetric synthesis through aza- Claisen rearrangement

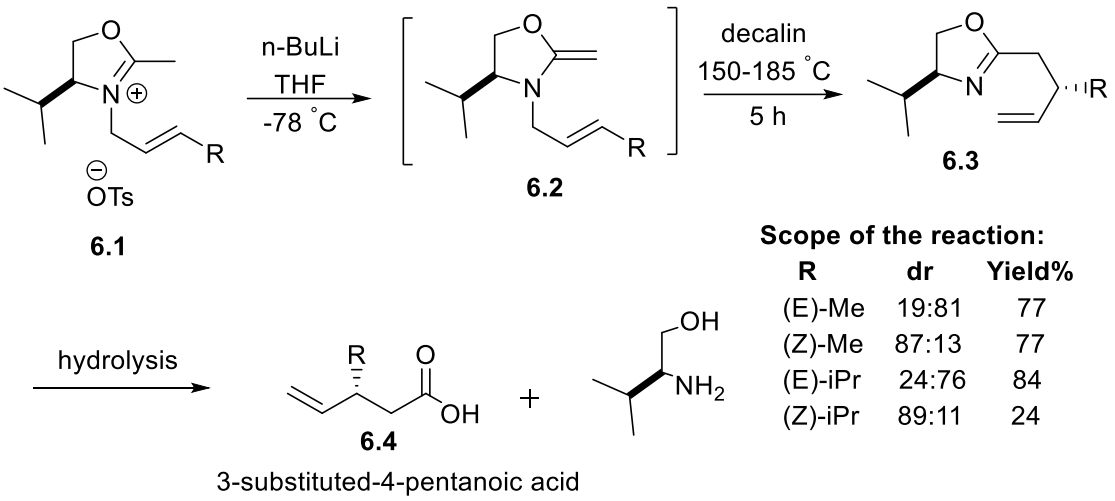
The intermediate (Z)-N, O-ketene acetal is preferred over the (E)-N, O-keteneacetal formation due to nonbonding interactions (Scheme 7). The (Z) - N, O-ketene acetal face selectivity of two transition states called as *syn* or *anti.* Then *anti* face intermediate preferable over the *syn* face intermediate occurs at sp^3-hybridized nitrogen center due to steric interactions. The facial

conversion of *anti* (Z)-N, O-ketene acetal from *syn* (Z)-N, O-ketene acetal presumably increased diastereoselective products (Scheme 8).



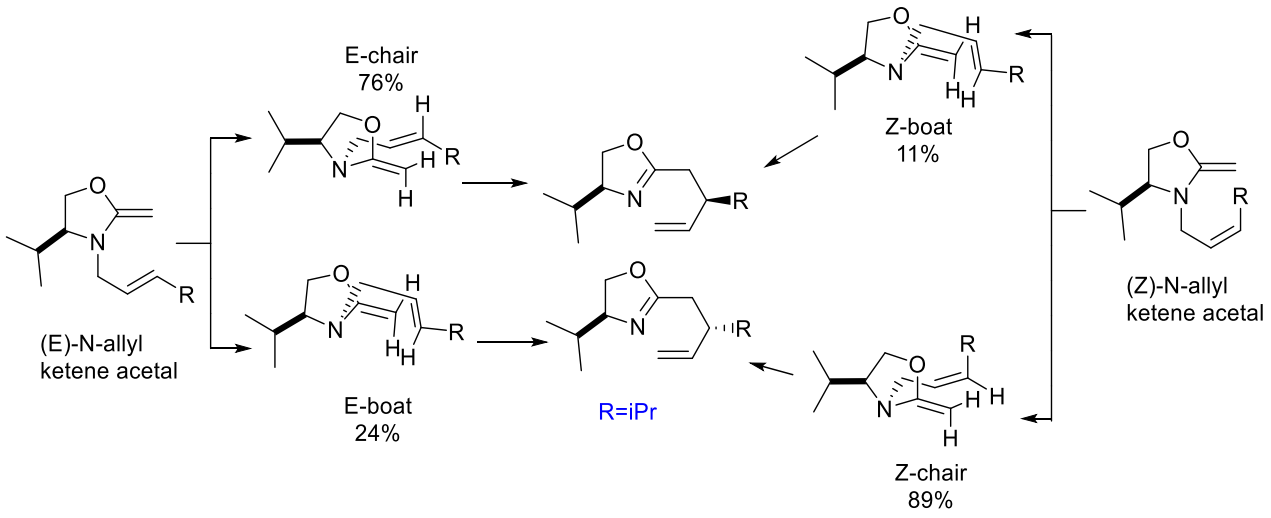
Scheme 8: *syn* vs *anti* face intermediates of aza- Claisen rearrangement

They extended the same methodology to synthesize asymmetric 3-substituted-4-pentenoic acid derivative **6.4**[10] (Scheme 9). The contention between E/Z-allyl olefin moiety, the transition state of the (Z)/ (E)-allyl olefin of N, O-ketene acetal face selectivity and the transition state of the chair/boat confirmation selectivity.



Scheme 9: Asymmetric synthesis through aza- Claisen rearrangement

As of his findings, the chair/boat transition state selectivity is a crucial factor for the asymmetric synthesis of 3-substituted-4-pentenoic acid derivative. In either alkene geometry, the chair-like transition state is more favorable than the boat-like transition state because the substituents of the nascent C-C bond in chair-like transition state are nearly staggered while in boat-like transition state are approximately eclipsed. However, the energy differences between the chair/ boat transition states on Z-alkene geometry are higher than the energy differences in E-alkene geometry. The diastereoselectivity outcomes as 76:24 for (E) N-allyl-N,O-ketene acetals and 89:11 for (Z) N-allyl-N,O-ketene acetals when R=iPr (Scheme 9). In general, the higher chair/boat selectivity contributing the diastereoselectivity outcomes and here the boat confirmation destabilized by the eclipsing interactions (Scheme 10).



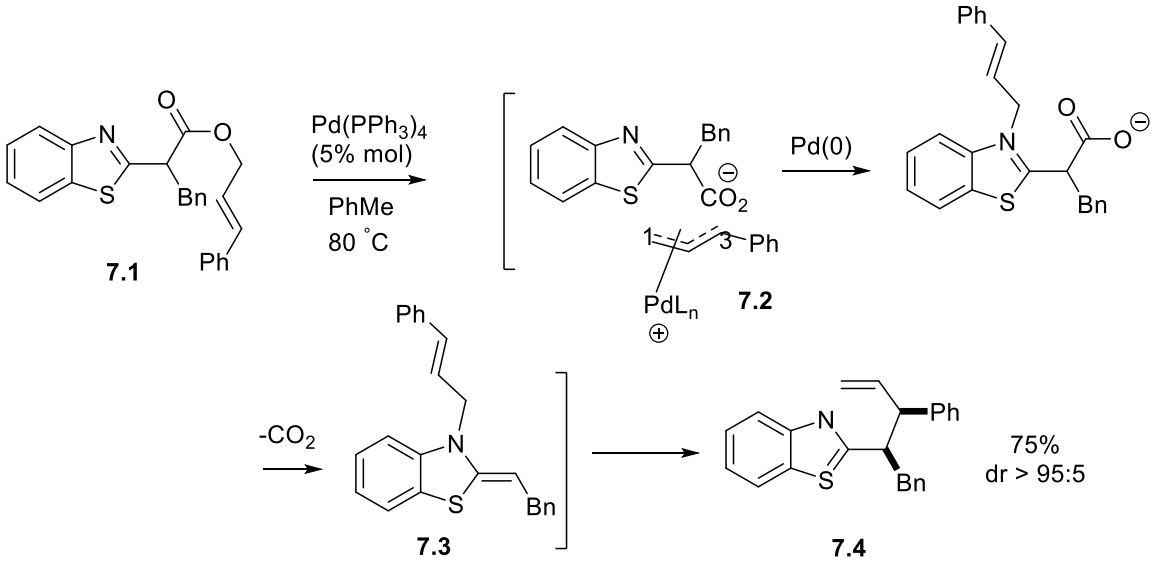
Scheme 10: Transition states of aza- Claisen rearrangement

Both cases of asymmetric synthetic studies revealed that the (Z) - N, O-ketene acetal face selectivity is a consequence of the interconversion to anti face selectivity responsible for the good diastereoselective for synthesis of the 2-substitued-4-pentenoic acid derivatives. On other hand, the asymmetric synthesis of the 3-substitued-4-pentenoic acid derivatives reflected the impact of chair/boat transition states selectivity.

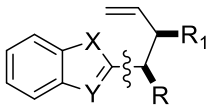
4. Jon A.Tunge: Regio-and diastereoselective decarboxylative coupling of Heteroaromatic alkanes.

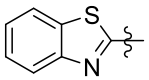
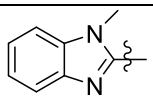
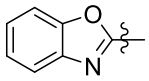
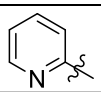
In 2007 Tunge and Waetzig has demonstrated the high regio- and diastereoselectivity synthesis of 2-butenyl azole derivatives (aza-Claisen products) **7.4** using a Pd catalyst through the intermediate N-allyl-N, O-ketene acetals **7.3**[11]. In this method, the aromatic ester **7.1** utilized as a starting material, and the Pd (0) catalyst used to form the Pd (II)-allyl complex, which fragmented to aryl carboxylate and Pd (II) allyl complex **7.2**. The fragmented aryl carboxylate and Pd (II) allyl complex recombined through the electron rich nitrogen with organometallic complex and

proceeded the decarboxylative dearomatization, which leads to the necessary ketene acetal **7.3**. The ketene acetal **7.3** was rearranged to compound **7.4** by restoring the lost aromaticity via [3,3]-sigmatropic rearrangement. Tunge proposed that the rearomatization was the reason for modest reaction temperature at 80 ^{0}C needed for rearrangement products compared to traditional Claisen rearrangement temperatures at 200 ^{0}C. The relative configuration of the newly formed stereocenters was revealed to be anti, consistent with a boat-like transition state coupled with a Z-configuration for the keteneacetal in aza Claisen precursor **7.3** [11] (Scheme 11).



Scope

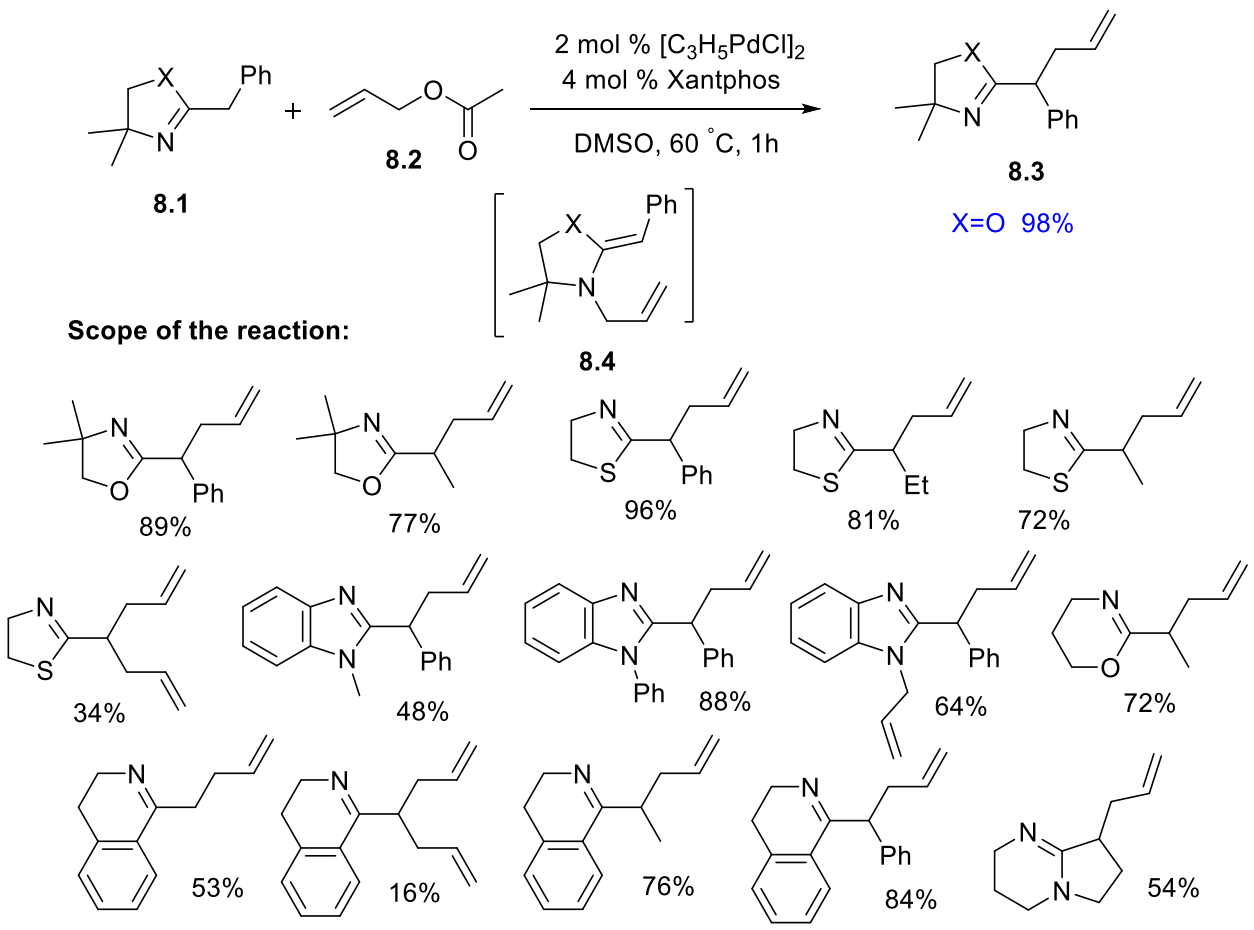


Entry	Substrate	R	R_1	time(h)	yield(%) (dr)
1		Bn	Ph	4	75 (95:5)
2		Bn Me	Ph Ph	16 4	52 (74:26) 43 (69:31)
3		Bn Me Me	Ph Ph Me	4 4 2	66 (95:5) 71 (93:7) 61 (73:28)
4		Bn	Ph	20	53 (95:5)

Scheme 11: Regio-and diastereoselective coupling of Claisen type rearrangement

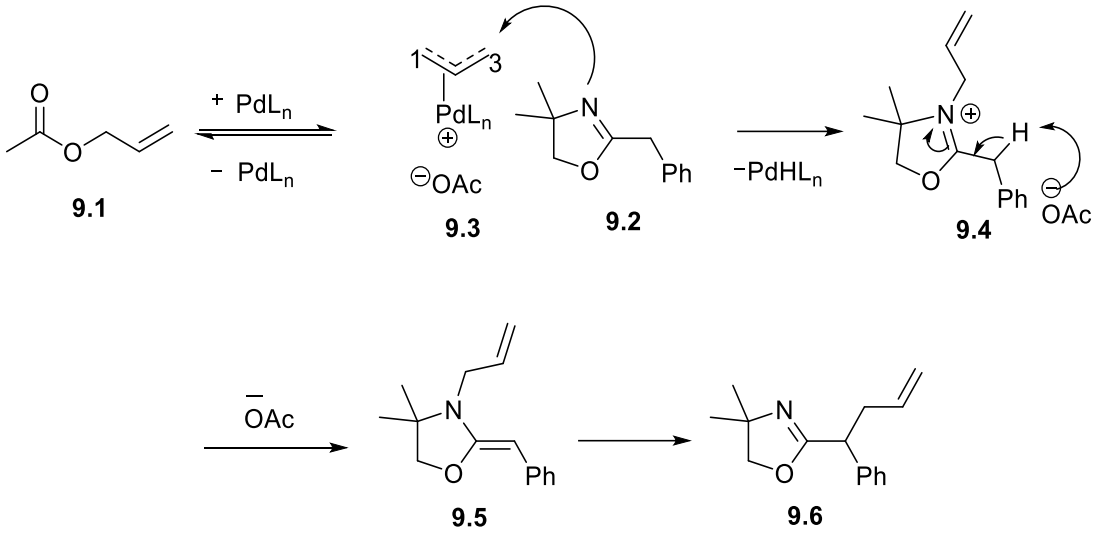
5. Rolf Breinbauer: Pd catalyzed allylation of imine heterocycles through aza-Claisen rearrangement.

Breinbauer utilized the aza-Claisen rearrangement of N-allyl, N, X-ketene acetal (X= N, S, O, C) in the allylation of the nitrogen containing heterocycles.[12] The oxazoline derivative **8.1** was utilized as a test substrate of imine moiety to study the leaving group, solvent, temperate and influence of ligand for the parent allylation reaction. Initials studies revealed that the combination of allyl acetate, 4 mol% Xantphos ligand and 2 mol% palladium catalyst for excellent yield of the allylation of imine heterocycles through aza-Claisen rearrangement. These optimized conditions used to test various imine heterocycles with scope and limitation of the reactions (Scheme 12).



Scheme 12: Pd catalyzed allylation of imine heterocycles through aza-Claisen rearrangement.

As per Breinbauer's proposed mechanism, the η^3-Pd (II)-allyl complex **9.3** forms from allyl acetate **9.1** with the Pd (0) catalyst, due to the displacement of the acetate anion. The intermediate iminium ion **9.4** formed from the alkylation of the η^3-Pd (II)-allyl complex **9.3** with the electron rich imine **9.2**. The deprotonation of the acidic CH bond with the acetate anion leads to the formation N-vinyl allyl amine (ketene acetal) **(9.5)**, which undergoes through [3,3]-sigmatropic rearrangement catalyzed by Palladium[12] (Scheme 13).



Scheme 13: Proposed mechanism of aza-Claisen rearrangement

Unfortunately, all the aforementioned literature of the Claisen rearrangement variations were suffering from at least one or more limitations. The Claisen rearrangement methods involved with the oxazine derivatives (Ireland and Kurth) employed stoichiometric amounts of strong base. Strong base requires cryogenic conditions and possess functional group limitations in the presence of alcohols, primary and secondary amines, and various acidic functionalities. In Baldwin's report, the Claisen product diaminofulvalene had a limited functionality because of the homodimer starting material. The palladium catalyzed (Tunge and Breinbauer) Claisen variations suffers from several important limitations. The use of Pd (0) catalyst, for instance, raises functional group compatibility issues, as substrates containing terminal alkynes or other moieties that can engage in oxidative addition like vinyl or aryl halides, which would presumably not tolerated. As per Breinbauer's report, the alkylation with several heterocycle derivatives such as benzothiazole and benzoxazole were not successful with the applied reaction condition to furnish the Claisen type rearrangement.

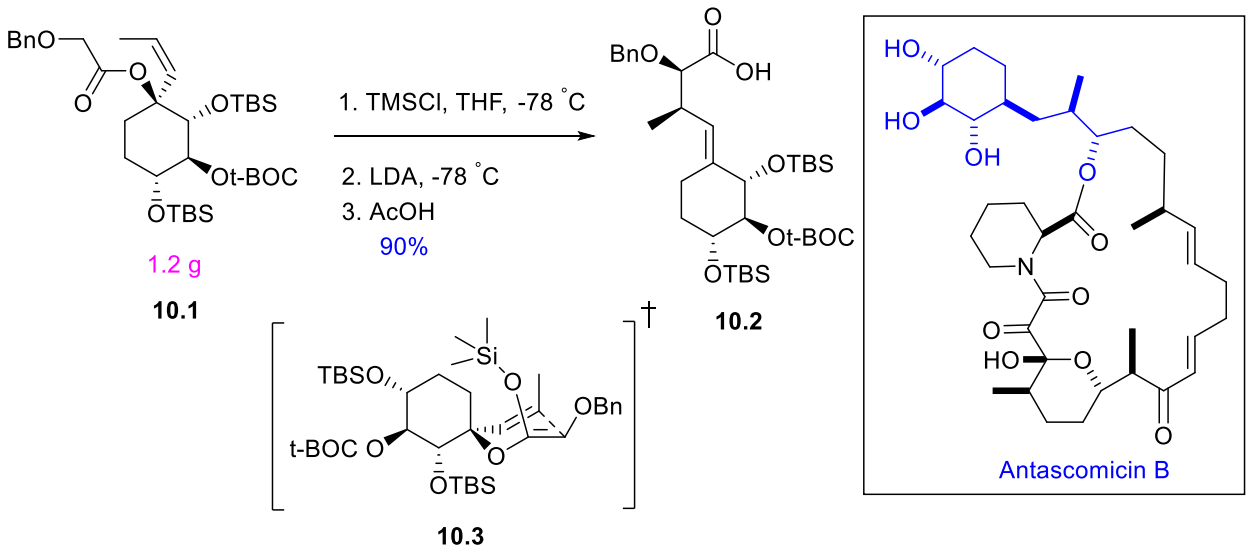
With compilation of aforementioned literature precedence, we have couple of concern such as

1. Why only the strong bases (LDA and n-BuLi) employed for the ketene acetals generation (Ireland and Kurth)? What happen if we use weak base for the ketene acetals formation?
2. Why Tunge's palladium catalyzed Claisen variations did not success with parent rearrangement?

All these questions complemented us to testify the benzothiazole based Claisen rearrangements (alternative approach to the Ireland-Claisen rearrangement) to find the experimental evidence.

I. Alternative approach to the Ireland-Claisen rearrangement

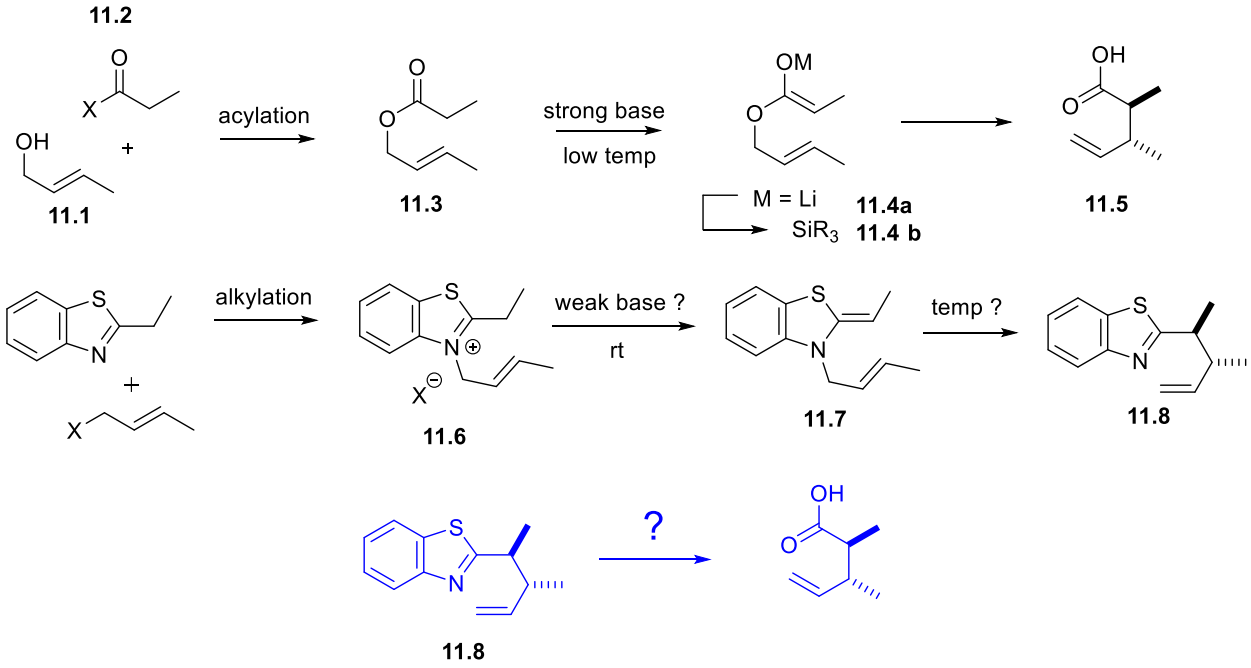
Our interest in Claisen rearrangement started with Ireland-Claisen rearrangement reaction. In Antascomicin B synthesis, the Ireland-Claisen rearrangement reaction employed in synthesis of γ,δ-unsaturated acid **10.2** from corresponding allylic ester **10.1**. In this synthesis, the allylic ester derivatives **10.1** employed with strong base, as only deprotonation that occurred has led to the desired ketene acetal **10.3** to make the Claisen rearrangement product **10.2**. In general, the acidic functionalities with greater pK_a values such as alcohols, terminal alkynes and other enolizable carbonyl-containing groups would need to protect or would otherwise suffer deprotonation in Ireland-Claisen rearrangement (Scheme 14).



Scheme 14: Ireland-Claisen rearrangement in Antascomicin B synthesis

This limitation prompted us to consider alternative ways of accessing γ,δ-unsaturated acids using milder conditions that would allow for a broader functional group tolerance. We began by considering the preparation of the simplest possible γ,δ-unsaturated acid with two adjacent

stereocenters **11.5.** Traditionally, the acid derivative can accessed through the Ireland-Claisen rearrangement of ketene acetal **11.4**. The ketene acetal **11.4** formed from the allyl acetate **11.3** in the presence of the strong base. Allyl acetates **11.3** generally synthesized by acylation of allyl alcohols **11.1** with acyl halides **11.2**. We reasoned that acid derivative **11.5** could also be deliver by hydrolysis of 2-butenyl benzothiazole **11.8,** which is the rearrangement product of ketene acetal **11.7**. This option could be useful if ketene acetal **11.7** could formed under milder conditions than its analog **11.4b**. The benzothiazolium salt **11.6** simply prepared by alkylation of benzothiazole with allyl halide derivatives. In order to test our hypothesis, we turned our attention to the preparation of quaternary salts derived from 2-methylbenzothiazole (Scheme 15).

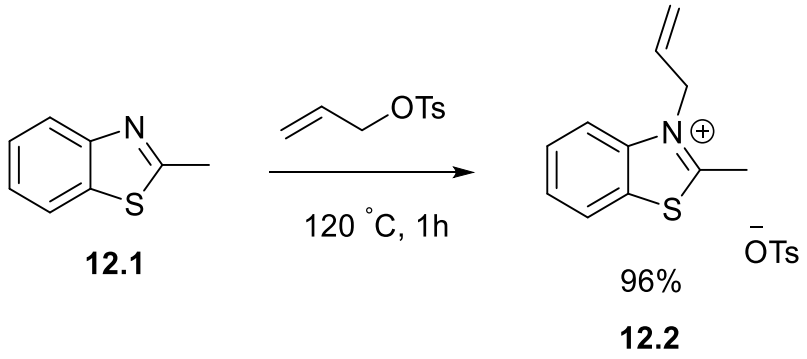


Scheme 15: Alternative to the Ireland-Claisen rearrangement

II. Results and discussion:

1. Reaction conditions and optimization.

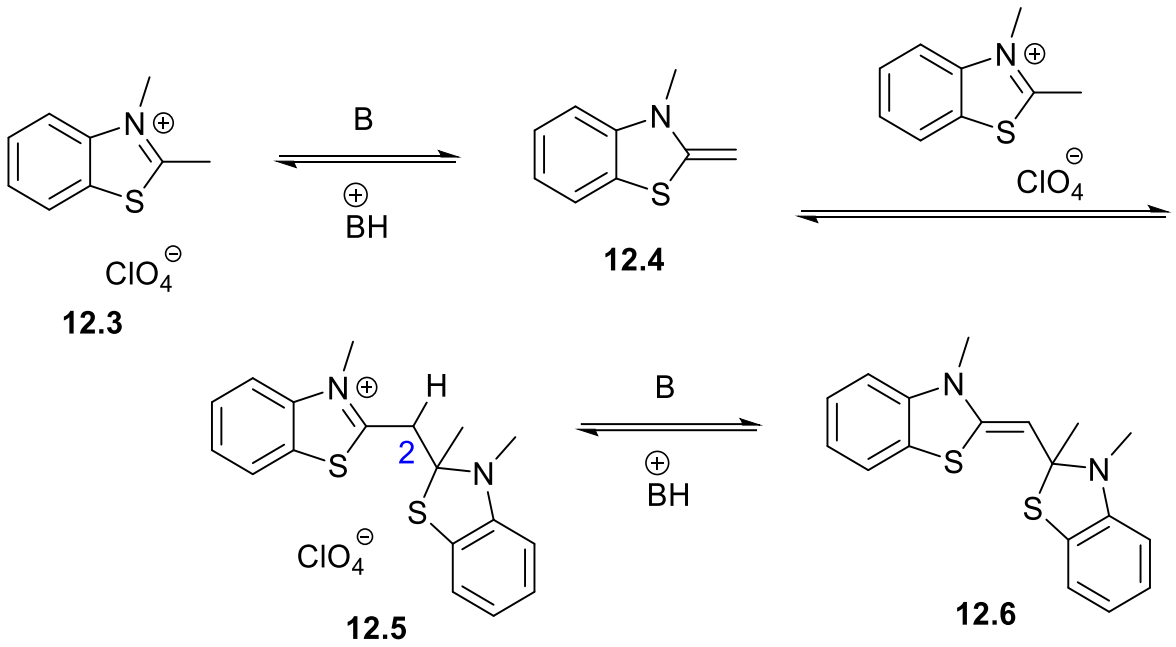
Our interest apropos Claisen rearrangement started with the N-allyl benzothiazole salts derived from 2-methyl benzothiazole **12.1**. The preparation of N-allyl benzothiazolium salt **12.2** well studied by Dr. McIntosh group's former member Silvana S. Dormi.[13] In her study; the N-allyl 2-methyl benzothiazolium tosylate **12.2** achieved in quantitative yields by treating 2-methyl benzothiazole with allyl tosylate at 120 ^{0}C for 1 hour. In contrast to traditional column purification, the benzothiazolium salt purified by simple trituration of the crude reaction material with the diethyl ether to remove excess starting materials (Scheme 16).



Scheme 16: Alkylation of benzothiazole

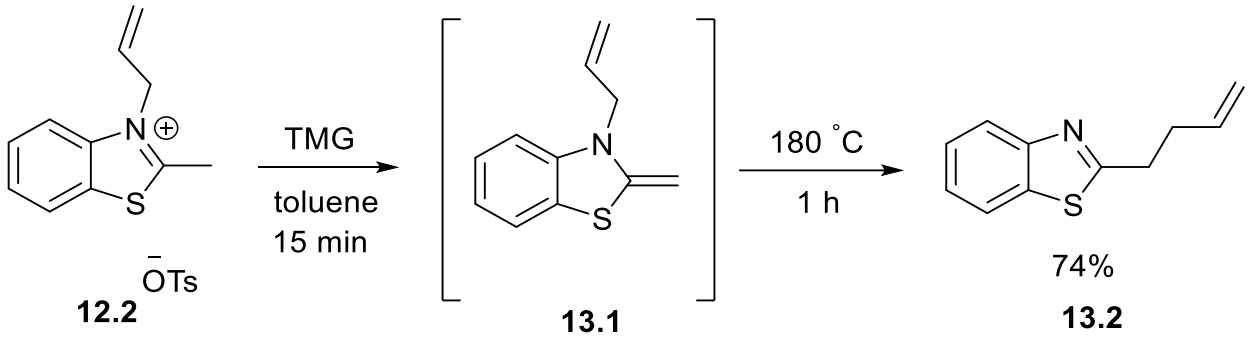
The studies towards the ketene acetal formation was uncertain and literature revealed that 2, 3-dimethylbenzothiazolium perchlorate **12.3** was treated with aqueous base yields dimer **12.6**.[14] As per the proposed mechanism, the dimerization **12.6** was the result of desired ketene acetal **12.4** addition its precursor **12.3**. The quaternary salt **12.5** was deprotonated at C2 resulted the dimer **12.6**. Owen[15] developed condition to minimize the side reaction of dimer formation with employing a large excess (8.0 eq) of the base, tetramethylguanidine (TMG). As of Owens report the addition of sodium hydride (1.5 eq) with using a non-polar solvent (*e.g.* benzene) and slow addition of the salt **12.3** to ice-cold TMG-NaH-solvent mixture to lower the concentration of the

salt in solution, which led to minimizing dimer formation **12.6**. The reaction was continued to stir at 0 ^{o}C for 1 hour and warmed to room temperature over 20 hours. Filtration followed by solvent removal gave the corresponding ketene acetal **12.4** (Scheme 17).



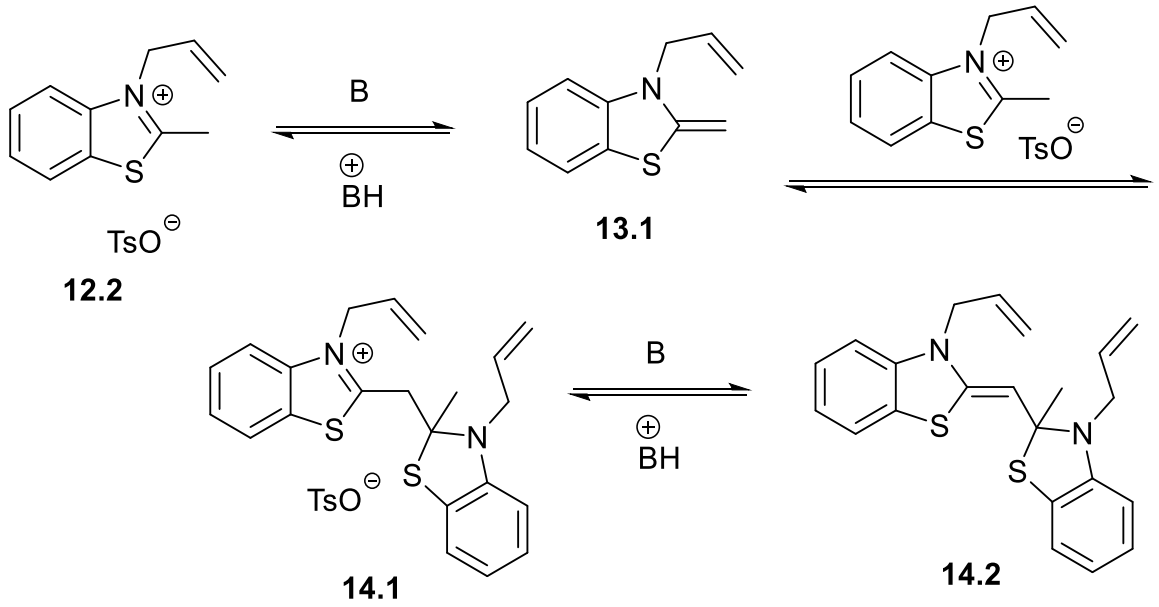
Scheme 17: Dimer formation as side product

The ketene acetal **13.1** formation from the N-allyl benzothiazolium salt **12.2** was extensively studied by Dormi stared with the Owen's conditions. The investigation revealed that the 1 equivalent of tetramethylguanidine (TMG) was enough to deliver the corresponding ketene acetal **13.1** from the N-allyl 2-methylbenzothaizolium salt **12.2**. The ketene acetal heated at 180 ^{0}C for 1 hour, which leads to the final product in good yield[13]. By using tetramethylguanidine (TMG) as base for ketene acetal formation, the Claisen rearrangement compound synthesis depends on heating method and temperature, which influenced the outcome of the reaction after removal of the $TMGH^{+}$ salt through Celite® filter (Scheme 18).



Scheme 18: Demonstrated Claisen rearrangement sequence

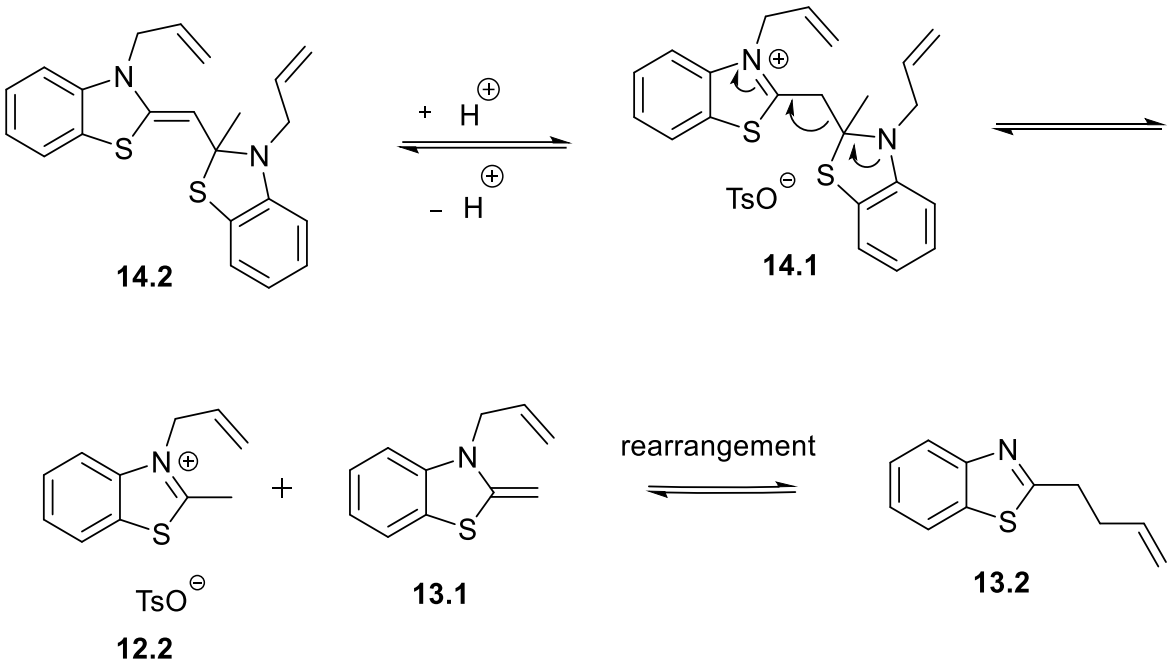
As per Dormi's Claisen rearrangement, dimer **14.2** formation from the benzothiazolium salt (**12.2**) was the main side product that was observed at heating temperatures lower than 160 ^{0}C. In presence of the tetramethylguanidine (TMG), the benzothiazolium salt **12.2** was in equilibrium with its ketene acetals **13.1**, which in turn was in equilibrium with the dimer benzothiazolium salt **14.1** through unreacted benzothiazolium salt. The dimer benzothiazolium salt **14.1** was in equilibrium with the stable dimer of the benzothiazole **14.2** in presence of the base (Scheme 19).[13]



Scheme 19: Dimer formation as side product in Claisen rearrangement

The fact that the dimer product slowly converted into Claisen rearrangement product at greater than 180 ^{0}C can explained through an acid catalyzed mechanism (Scheme 20).[13]

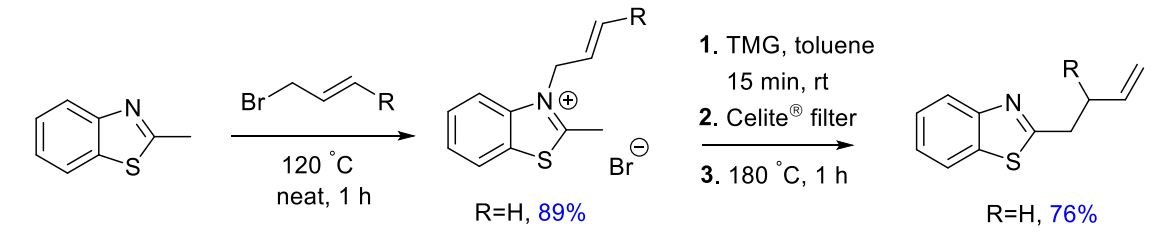
In presence of an acid, dimer **14.2** was in equilibrium with its conjugate acid **14.1**, which in turn was in equilibrium with ketene acetal **12.2** and its corresponding conjugate acid **13.1**. Eventually, ketene acetal **12.2** irreversibly rearranged with the consequent Claisen product **13.2**. We believe that the surface of the glass vessel could have been the source of catalytic H^{+}.



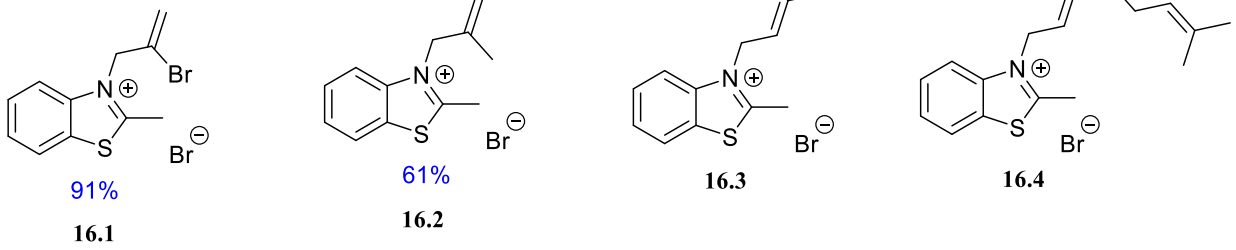
Scheme 20: Claisen rearrangement formation through dimer

2. Study of the reaction scope.

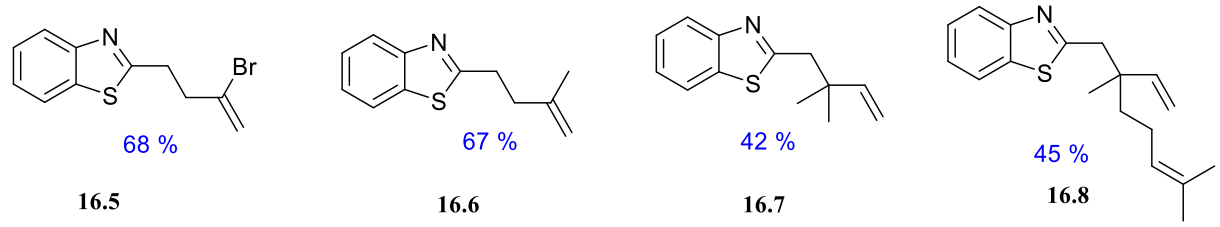
The optimized conditions for the Claisen rearrangement were successfully developed, and we began studying the scope of the reaction. The studies started with the alkylation of 2-methyl benzothiazole with commercially available allyl bromide derivatives at 120 ^{0}C for 1hour without solvent to yield the benzothiazolium salts. The allyl bromide derivatives included 2,3-dibromopropene, 2-methyl-3-bromopropene, 1,1-dimethyl-3-bromopropene and geranyl bromide which provided benzothiazolium salts **16.1, 16.2, 16.3** and **16.4** with moderate to excellent yields. The benzothiazolium salts treated with tetramethylguanidine (TMG) in toluene for 15 min and the TMGHBr salt removed by Celite® filter. The crude filtrate transferred to sealed tube and heated at 180 ^{0}C for 1 hour to yield corresponding Claisen rearrangement products. Column chromatography was required to purify the products **16.5, 16.6, 16.7** and **16.8** in moderate to good yields (Scheme 21).



Benzothiazolium salts

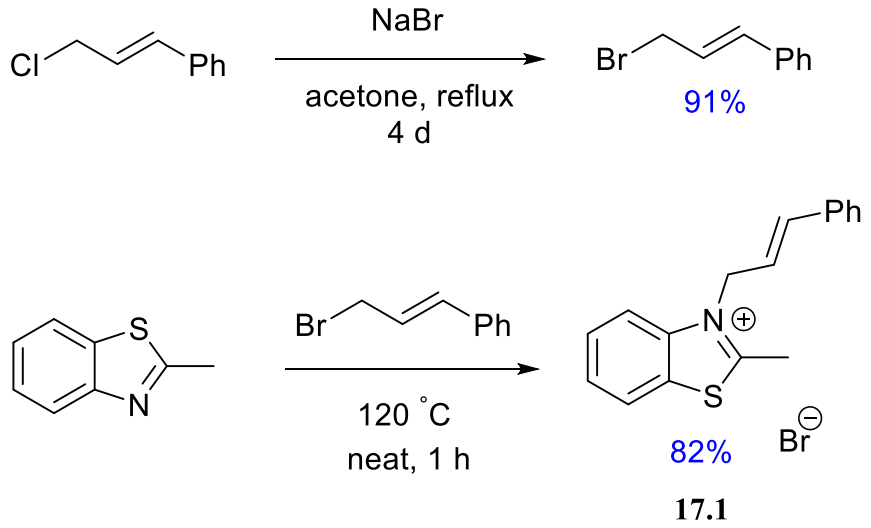


Claisen products



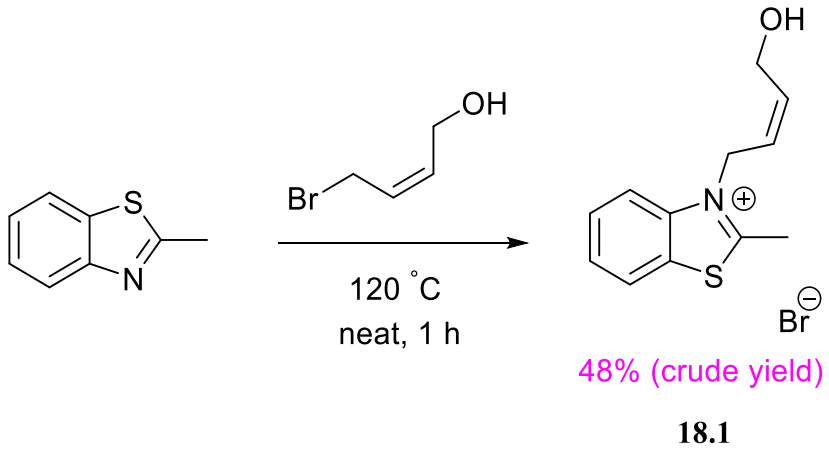
Scheme 21: Scope of proposed Claisen rearrangement

The commercially available cinnamyl chloride was unreactive in the alkylation but was treated with sodium bromide in acetone to yield cinnamyl bromide (Finkelstein variation on Wagner reaction).[17] Alkylation of 2-methyl benzothiazole with the cinnamyl bromide successfully produced the N-cinnamyl benzothiazolium bromide **17.1** salt in 82% yield (Scheme 22).



Scheme 22: Synthesis of N-cinnamyl benzothiazolium bromide salt

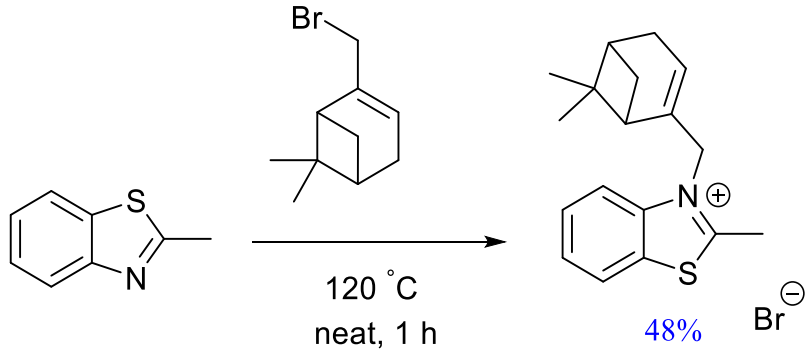
The compound cis-4-chloro-2-butene-1-ol also converted to cis-4-bromo-2-butene-1-ol by the Finkelstein variation on Wagner reaction[17] methodology yielded 78%. The alkylation of the 2-methyl benzothiazole with the cis-4-bromo-2-butene-1-ol gave the corresponding benzothiazolium salt **18.1** in 48% with 20% recovery of the starting materials (Scheme 23).



18.1

Scheme 23: Synthesis of (N)-cis-2-butenol benzothiazolium salt

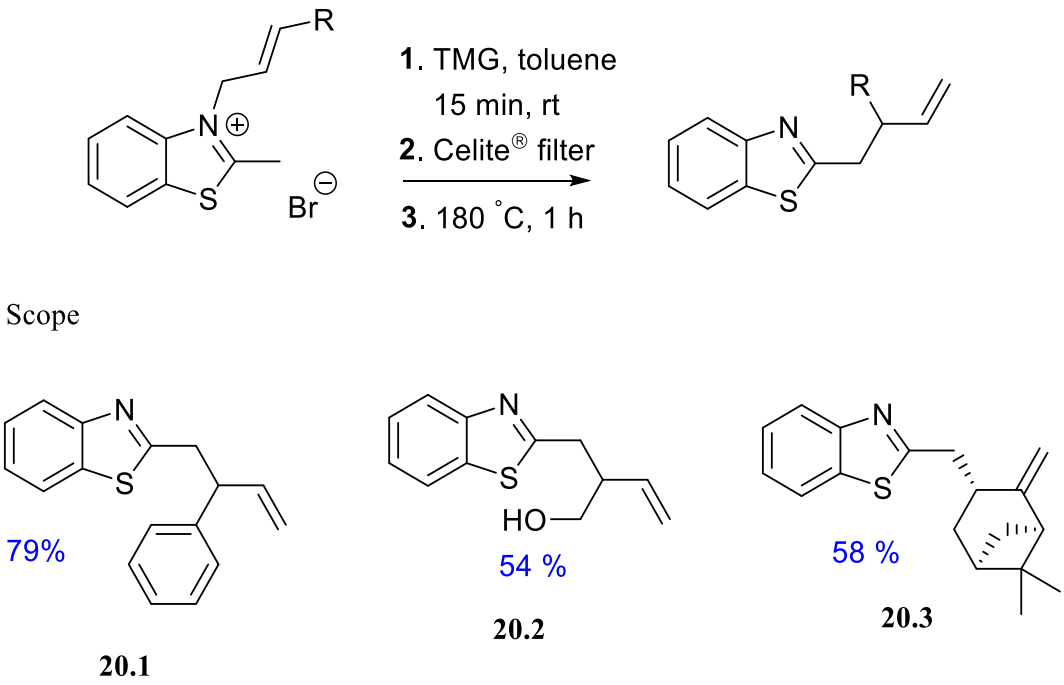
Myrtenol is a commercially available allyl alcohol, which easily converted to the allyl bromide derivative in 90% yield through the reaction conditions with PBr_3.[19] The Myrtenol bromide alkylated with 2-methyl benzothiazole at 120 ^{0}C to produce N-myrtenyl benzothiazolium bromide salt **(19.1)** in 48% yield (Scheme 24).



19.1

Scheme 24: Synthesis of N-myrtenyl benzothiazolium salt

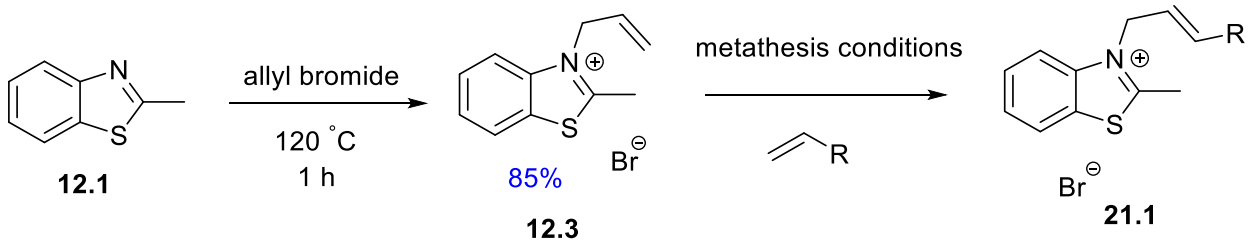
After obtaining N-cinnamyl benzothiazolium bromide salt **17.1**, (N)-cis-2-butenol benzothiazolium bromide salt **18.1** and N-myrtenyl benzothiazolium bromide salt **19.1** in good yields, we treated with the optimized conditions for the Claisen rearrangement and produced the corresponding products **20.1, 20.2** and **20.3** with moderate to good yields, following column purification (Scheme 25).



Scheme 25: Expanded scope of Claisen rearrangement

So far, the proposed Claisen rearrangement methodology explored with unprotected alcohol, aliphatic, and aromatic groups. This methodology further need to be modify for the exploration of acidic functional groups such as aldehydes, amides, alkynes and many more.

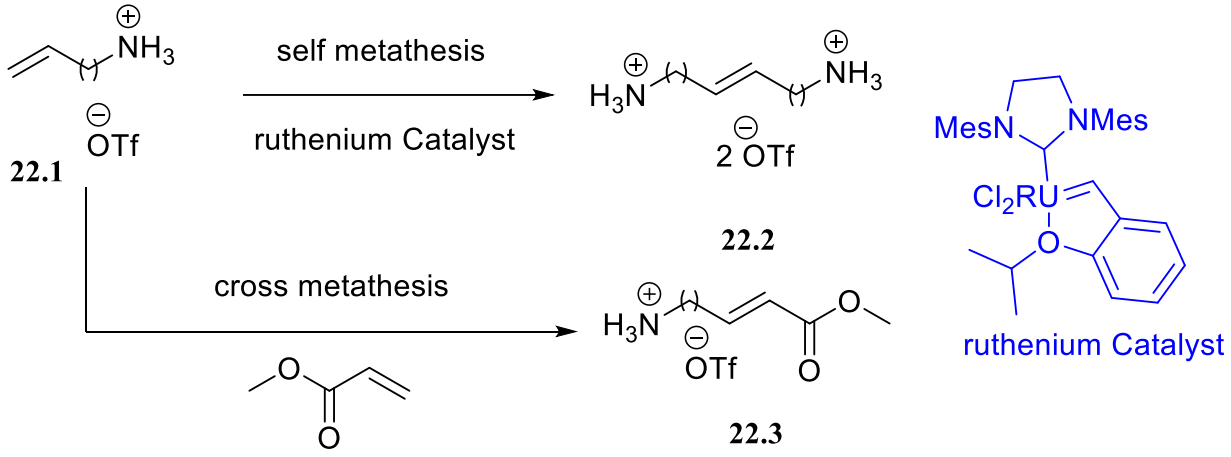
Due to the limited supply of commercially available allyl halide derivatives, we decided to synthesize the allyl halide derivatives with having the board functional groups for their feasibility in the Claisen rearrangement. The conventional synthesis of various complex allyl bromide were unsuccessful and we were in need to derivatization of N-allyl benzothiazolium salts for the Claisen rearrangement. As we mentioned previously, the N-allyl benzothiazolium salts triturated with ether has led to the pure salts from the unreacted starting materials. The advantage of purifying salts without performing a column chromatography prompted us to produce the N-allyl benzothiazolium bromide **21.1** derivatives by utilizing the N-allyl benzothiazolium bromide **12.3** with cross metathesis conditions (Scheme 26). The metathesis attempts with N-allyl benzothiazolium bromide slats and different olefin derivatives might have advantage of demonstrating broad functional group compatibility, and simple purification method.



Scheme 26: Proposed synthesis of N-allyl benzothiazolium derivatives

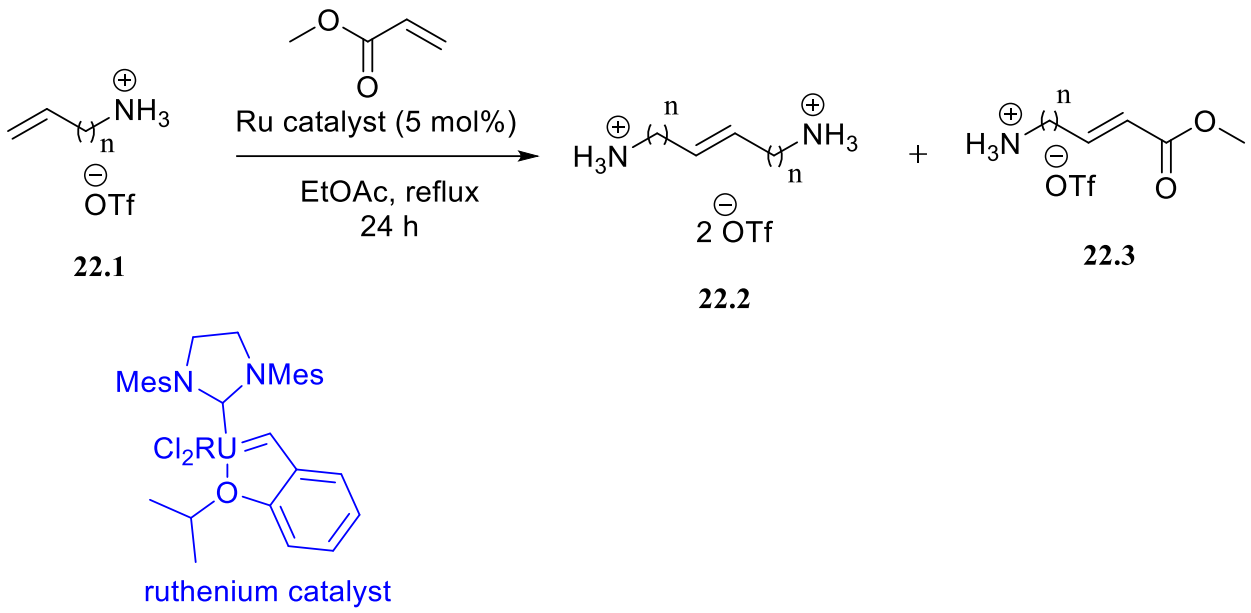
At this point, we need to ascertain the conditions for the metathesis reaction of olefin derivatives with benzothiazolium salts. A literature studies revealed first ever self-metathesis of N-alkenyl amine salts and cross metathesis of N-alkenyl amine salts with the acrylate derivative.[20] The optimized reaction conditions for tandem self-metathesis with 5 mol% Ru catalyst, ethyl acetate, excess acrylate, triflate as counter ion and reflux reaction for 24 hours gave the good yield. The choice of the solvent and counter ion were the most important controlling factors due to

solubility[20] (Scheme 27). The optimized reaction conditions were utilized to study the cross metathesis of the N-allyl amine triflate salts with the acrylate derivatives. This investigation revealed that the large excess (20 eq) of the acrylate derivative leads to the formation of cross metathesis products.



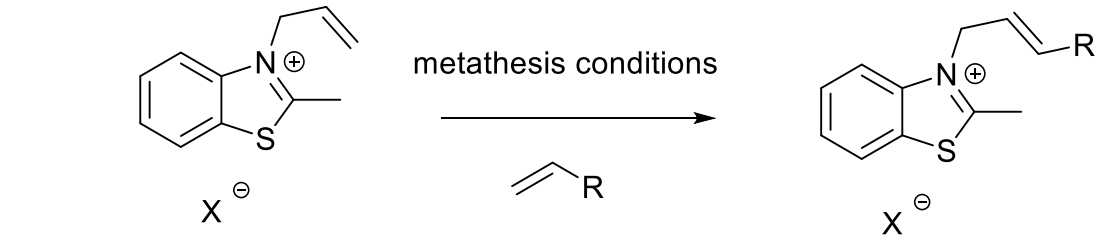
Scheme 27: Self-metathesis Vs cross metathesis of alkenyl amine with acrylate

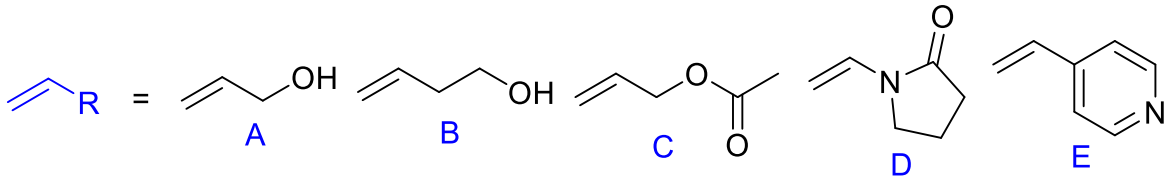
According to Robinson's report, the self-metathesis product of the unsaturated ammonium salts **22.2** competes with the cross-metathesis product unsaturated ester ammonium salts **22.3**. The molar ratios of the N-alkenyl ammonium salts **22.1** with acrylate derivatives less than the 1:10 responsible for the major self-metathesis product **22.2**. On the other hand, the molar ratios of ammonium salts with the acrylate derivative more than 1:10, yields major cross metathesis product **22.3**. The large excess (20 eq) of the acrylate derivative with the N-alkenyl ammonium triflate salt **22.1** yielded 95% of the cross metathesis **22.3** with only 2% of the self-metathesis **22.2** product (Scheme 28).



Scheme 28: Cross metathesis of alkenyl amine with acrylate

Based on closest preceding literature[20], we started metathesis reaction of N-allyl benzothiazole bromide salt with the allyl alcohol in excess gave unidentified products. We explored the reaction with different olefin moieties such as 3-butenol, allyl acetate, 2-vinylpyridine and 1-vinyl pyrrolidinone which gave unidentified products. The metathesis reaction conditions modified with the catalysts Grubbs -II and Hoveyda Grubbs -II, at reaction temperature of 40 ^{0}C and 65 ^{0}C, and solvents such as methanol and dichloromethane. However, these attempts were unsuccessful for the metathesis reaction (Scheme 29). The unsuccessful attempts of metathesis of benzothiazolium slats with olefin derivatives guided us to synthesize the various allyl bromide derivatives through metathesis conditions. The following alkylation of allyl bromides with 2-methyl benzothiazole for benzothiazolium slats preparation, which might provide an advantage for the functional group compatibility in the proposed Claisen rearrangement.



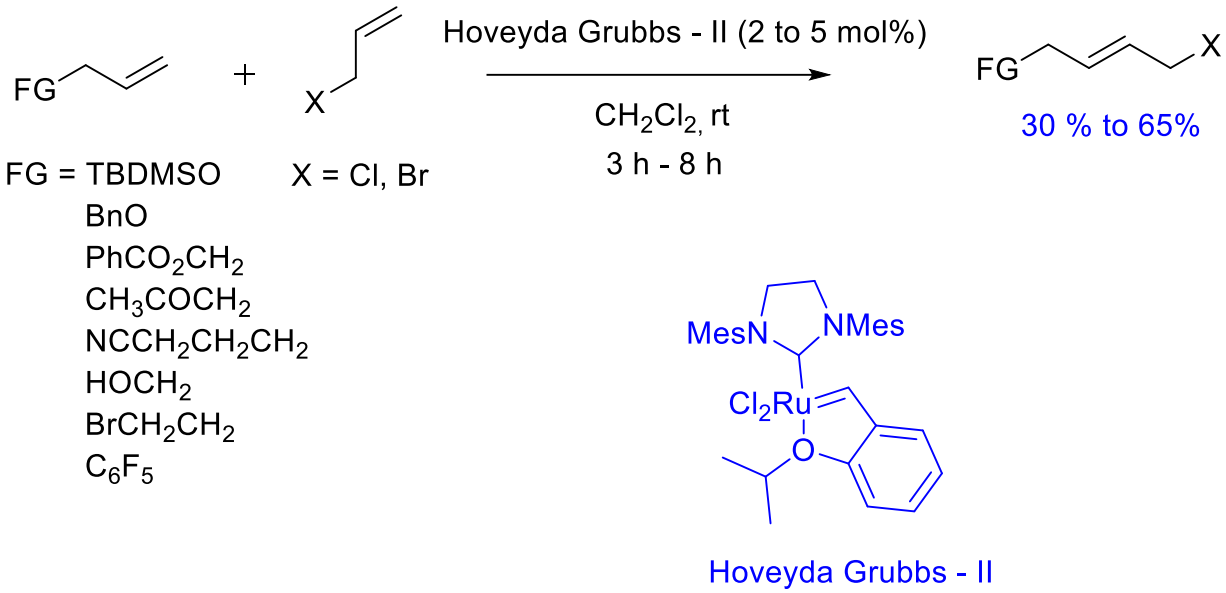


Scope of the reaction:

X	Olefin	metathesis conditions	Product
Br	A	G-II, 40 °C,16 h-48 h, CH_2Cl_2	No reaction (salt recovered)
		H.G-II, 40 °C,16 h-48 h, CH_2Cl_2	No reaction (salt recovered)
		H.G-II, 65 °C,16 h-48 h, CH_3OH	No reaction (salt recovered)
OTs	A	G-II, 65 °C,16 h-48 h, CH_3OH	No reaction (salt recovered)
		H.G-II, 65 °C,16 h-48 h, CH_3OH	No reaction (salt recovered)
OTs	B	G-II, 65 °C,16 h-48 h, CH_3OH	No reaction (salt recovered)
		H.G-II, 65 °C,16 h-48 h, CH_3OH	No reaction (salt recovered)
OTs	C	G-II, 65 °C,16 h-48 h, CH_3OH	No reaction (salt recovered)
		H.G-II, 65 °C,16 h-48 h, CH_3OH	No reaction (salt recovered)
OTs	D	G-II, 65 °C,16 h-48 h, CH_3OH	Unidentified product
		H.G-II, 65 °C,16 h-48 h, CH_3OH	Unidentified product
OTs	E	G-II, 65 °C,16 h-48 h, CH_3OH	Unidentified product
		H.G-II, 65 °C,16 h-48 h, CH_3OH	Unidentified product

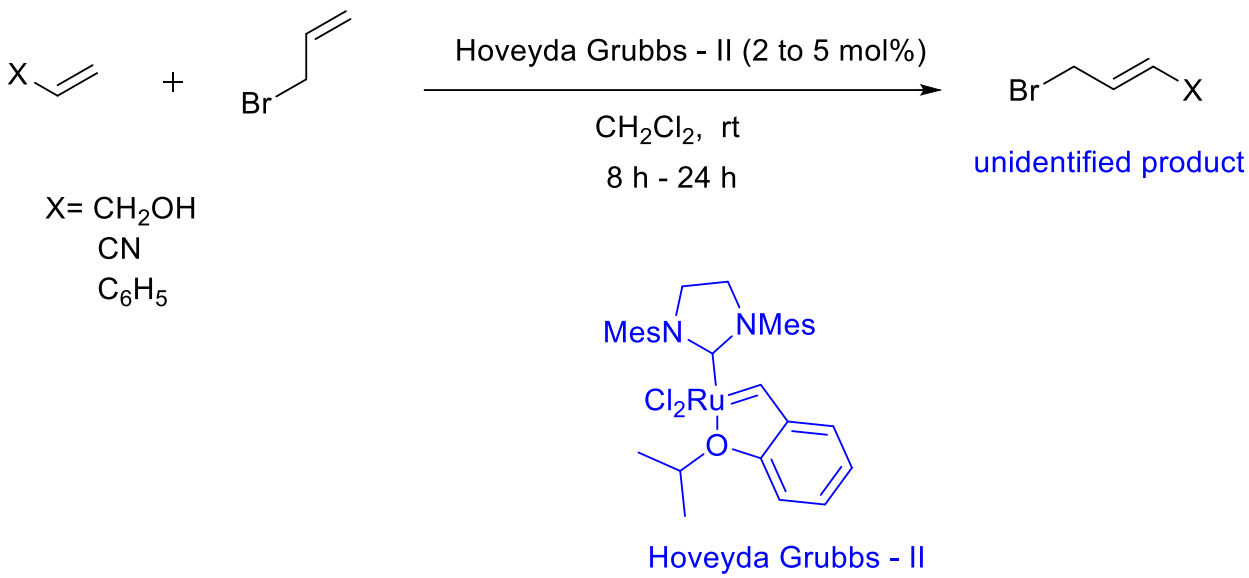
Scheme 29: Metathesis attempts with N-allyl benzothiazolium and olefin derivatives

The allyl bromide and allyl chloride with the different olefin derivatives utilized metathesis conditions for the synthesis of allyl halide derivatives successfully synthesized in moderate to good yields. The metathesis reaction with allyl bromide derivatives was little more complicated when compared to allyl chloride derivatives[21] (Scheme 30).



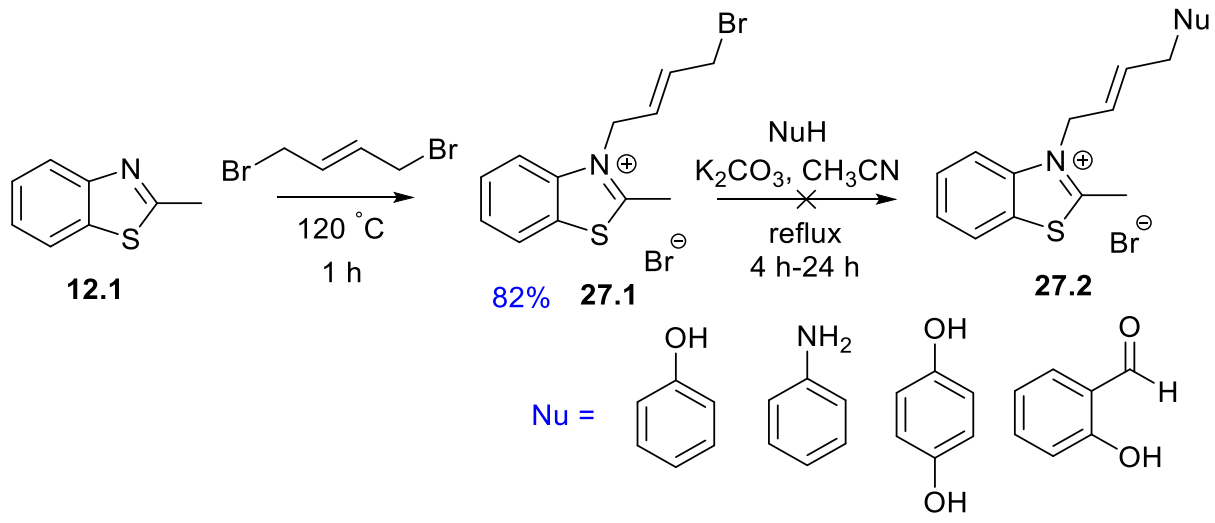
Scheme 30: Synthesis of allyl halides using alkene metathesis.

According to the literature, [21] the allyl bromide was reacted with different olefin derivatives such as allyl alcohol, acrylonitrile and styrene in presence of the Hoveyda Grubbs-II catalyst to yield the unidentified product (Scheme 31). At this point, the metathesis reaction involved with the allyl bromide yielded unidentified products and we decided to explore optimized reaction conditions for the synthesis of allyl bromide derivatives.



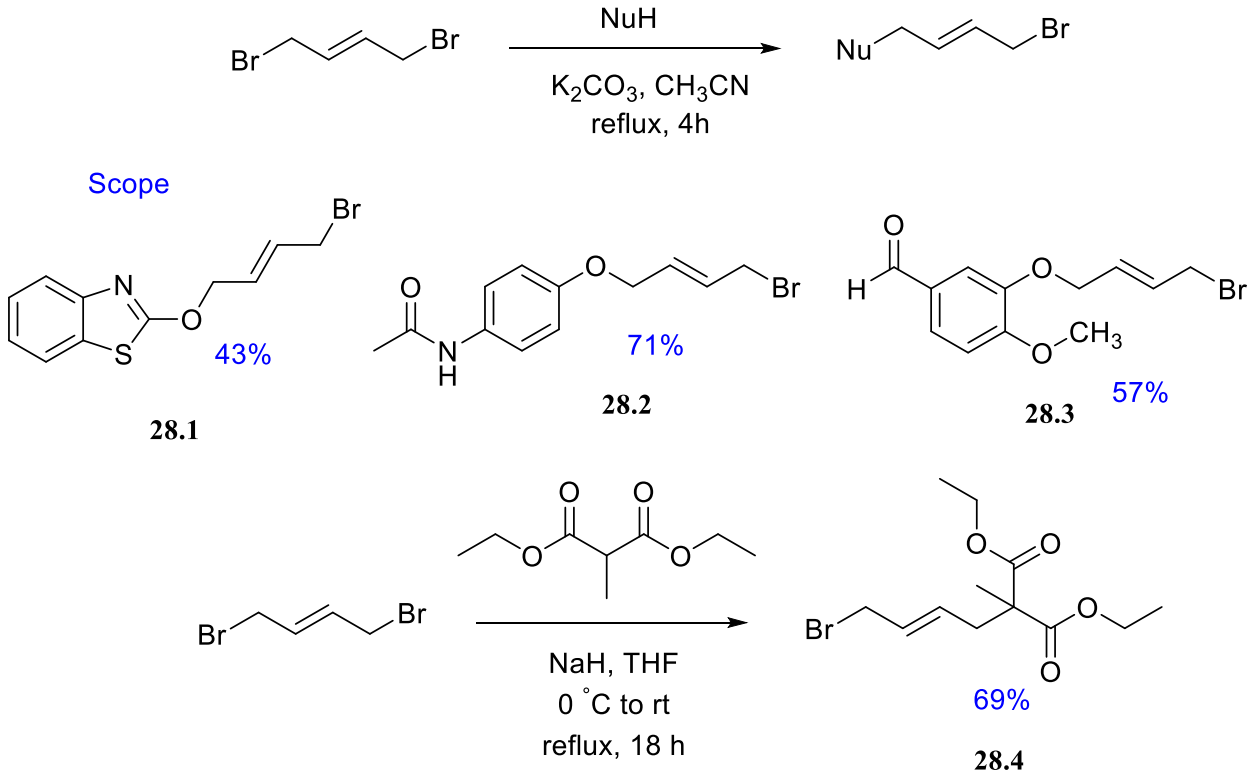
Scheme 31: Synthetic attempts for allyl halide derivatives

The commercially available 1,4-dibromo-2-butuene was testified for the alkylation with 2-methyl benzothiazole, successfully yielding the mono alkylated benzothiazolium salt **27.1** in 82%. The benzothiazolium salt **27.1** was treated with the various nucleophiles utilizing under nucleophilic substitution conditions for the derivatization of benzothiazolium salts **27.2** gave unsuccessful result **27.2** (Scheme 32).



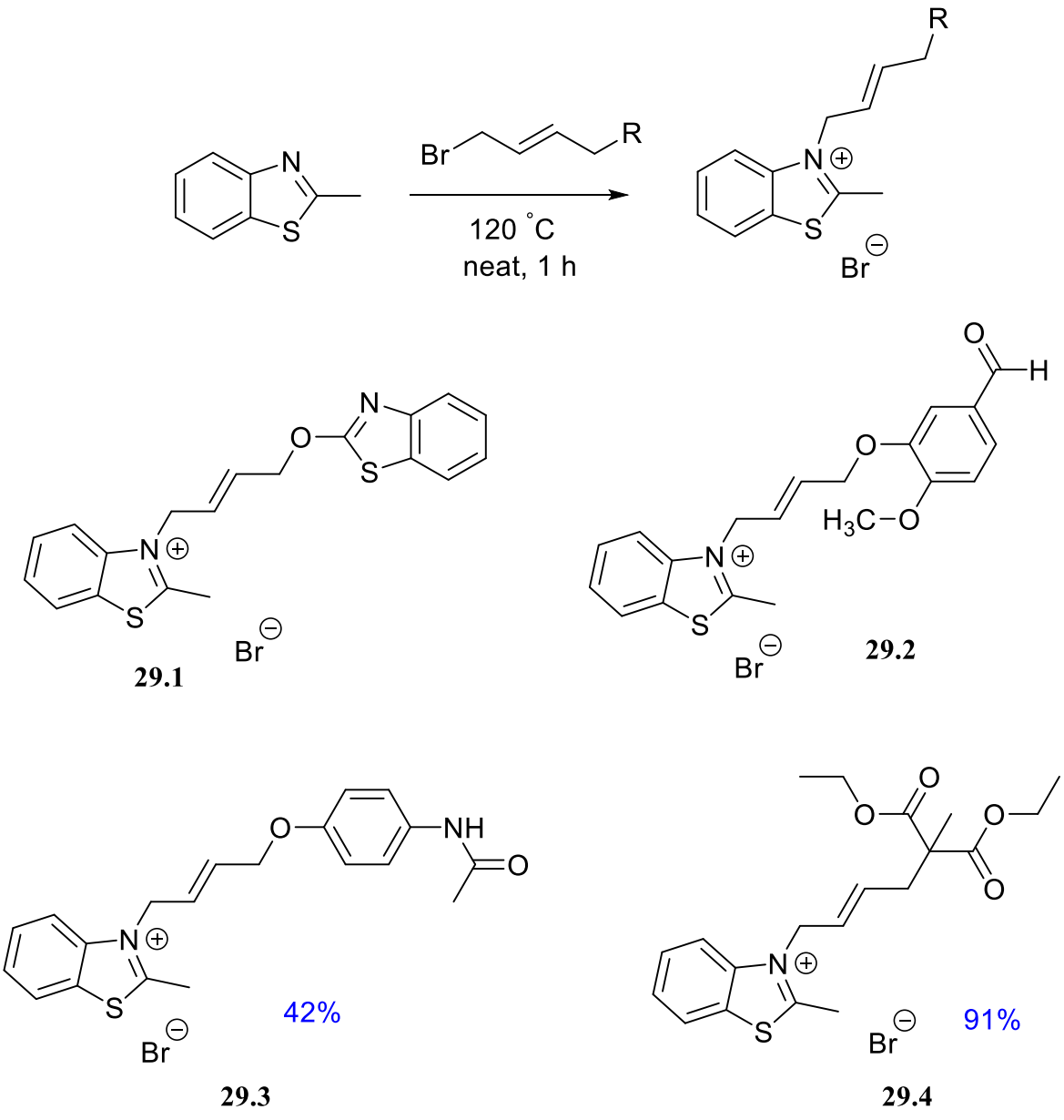
Scheme 32: Alkylation of benzothiazole with 1,4-dibromo-2-butene

The mono alkylation of the 1,4-dibromo-2-butene with the 2-methylbenzothiazole prompted us to synthesize various allyl bromide derivatives through nucleophilic substitution reaction with 1,4-dibromo-2-butene. We adopted the reaction conditions from the nucleophilic substitution with allyl bromide[23] to synthesize complex allyl bromide derivatives from 1,4-dibromo-2-butene. The 2-hydroxybenzothiazole, 4-acetamidophenol, vanillin and diethyl methyl malonate were treated with 1,4-dibromo-2-butene for the nucleophilic substitution in the specified conditions to produce the corresponding complex allyl bromide derivatives with moderate to good in yields (Scheme 33).



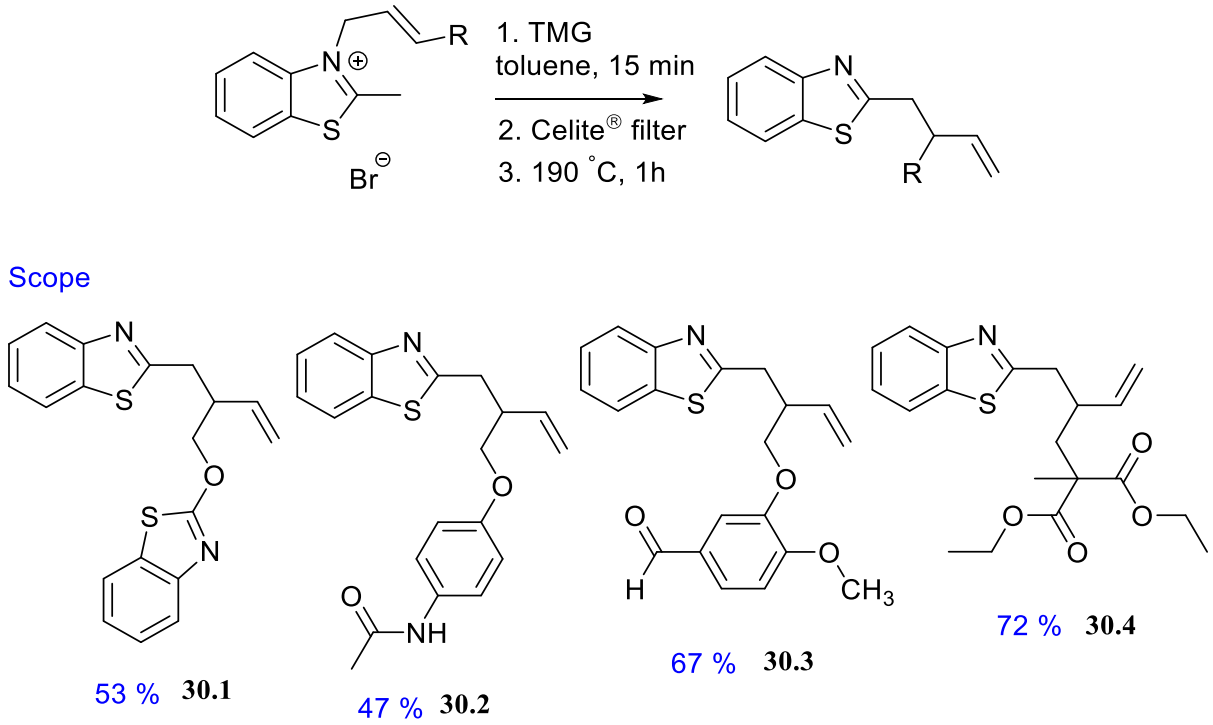
Scheme 33: Synthesis of complex allyl bromide derivatives

By having complex allyl bromide derivatives in hand, we demonstrated the alkylation reaction under optimized conditions with 2-methyl benzothiazole and allyl bromide derivatives **28.1**, **28.2**, **28.3** and **28.4** that gave successful benzothiazolium salts **29.1**, **29.2**, **29.3** and **29.4** with moderate to good yields (Scheme 34).



Scheme 34: Synthesis of complex benzothiazolium salts

The complex benzothiazolium salts **29.1**, **29.2**, **29.3** and **29.4** tested with the optimized conditions for the Claisen rearrangement and successfully gave the corresponding products **30.1**, **30.2**, **30.3** and **30.4** moderate to good yields. The results, suggest that the various functional groups such as aldehyde, amide and alcohols tolerated with optimized conditions. As of now, we clearly demonstrated that the functional groups such as unprotected aldehydes, unprotected alcohols, unprotected amides, esters, ethers, and unsaturated aliphatic were tolerated in the proposed Claisen rearrangement (Scheme 35).



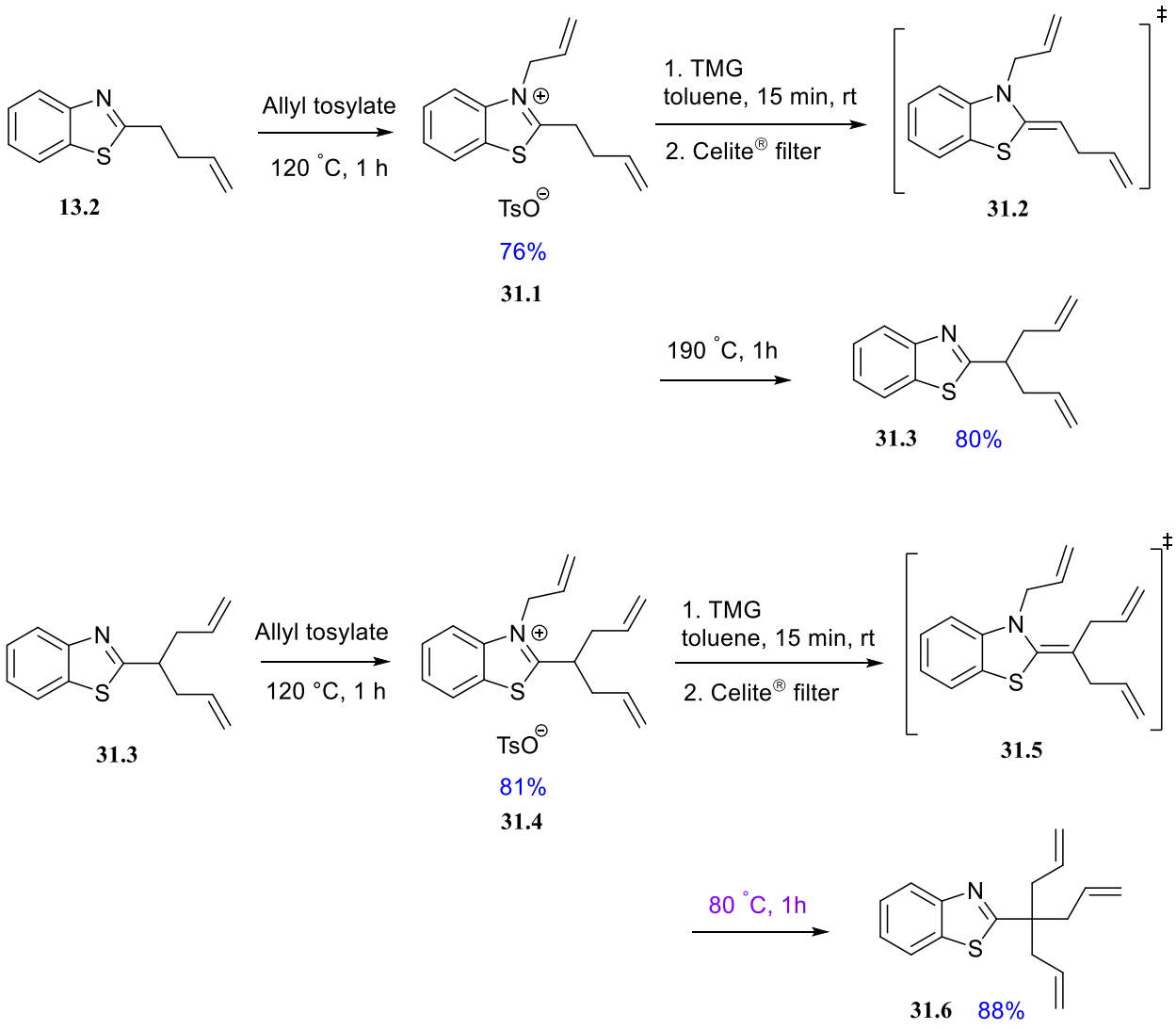
Scheme 35: Complex Claisen rearrangement products

3. Iterative Claisen rearrangement:

Iterative synthesis is a useful technique in the organic synthesis, to allow the similar reaction sequences for the stepwise synthesis of repeated building blocks. In the process of iterative Ireland-Claisen rearrangement, the Claisen product γ,δ-unsaturated acid need to activated for the successive alkylation/acylation. The alkylation product could converted to ketene acetal in presence of base and followed by the rearrangement to complete the iterative process. In proposed iterative Claisen rearrangement, the Claisen product benzothiazole derivative readily available for the successive alkylation, which will converted to ketene acetal and followed by the rearrangement to complete the process. This ideology prompted us to testify the advantage of the benzothiazole based iterative Claisen rearrangement.

The successive alkylation of the Claisen rearrangement products not listed in the literature and the reasons for those alkylation attempts were unclear. In this proposed Claisen rearrangement, the ketene acetal formation from benzothiazolium salt with basic condition was necessary. The parent benzothiazole Claisen rearrangement product **13.2** has two α- hydrogens (to benzothiazole moiety), which might lead to successive ketene acetal formation for the iterative synthesis. To explore the available options, we started the alkylation of Claisen product **13.2** with allyl tosylate, which gave the benzothiazolium salt **31.1** in 76% yield. The benzothiazolium salt was treated with the previous developed conditions successfully resulted in iterative Claisen product **31.3** with 80% yield. The intermediate ketene acetal formation **31.2** tracked through the NMR spectroscopy. The iterative Claisen product **31.3** still had the α-hydrogen to allow a similar reaction. The iterative benzothiazole Claisen product **31.3** alkylated with allyl tosylate, which successfully gave the benzothiazolium salts **31.4** in 81% yield. The steric hindered benzothiazolium salt **31.4** treated with TMG base for the ketene acetal formation **31.5** and confirmed through the NMR

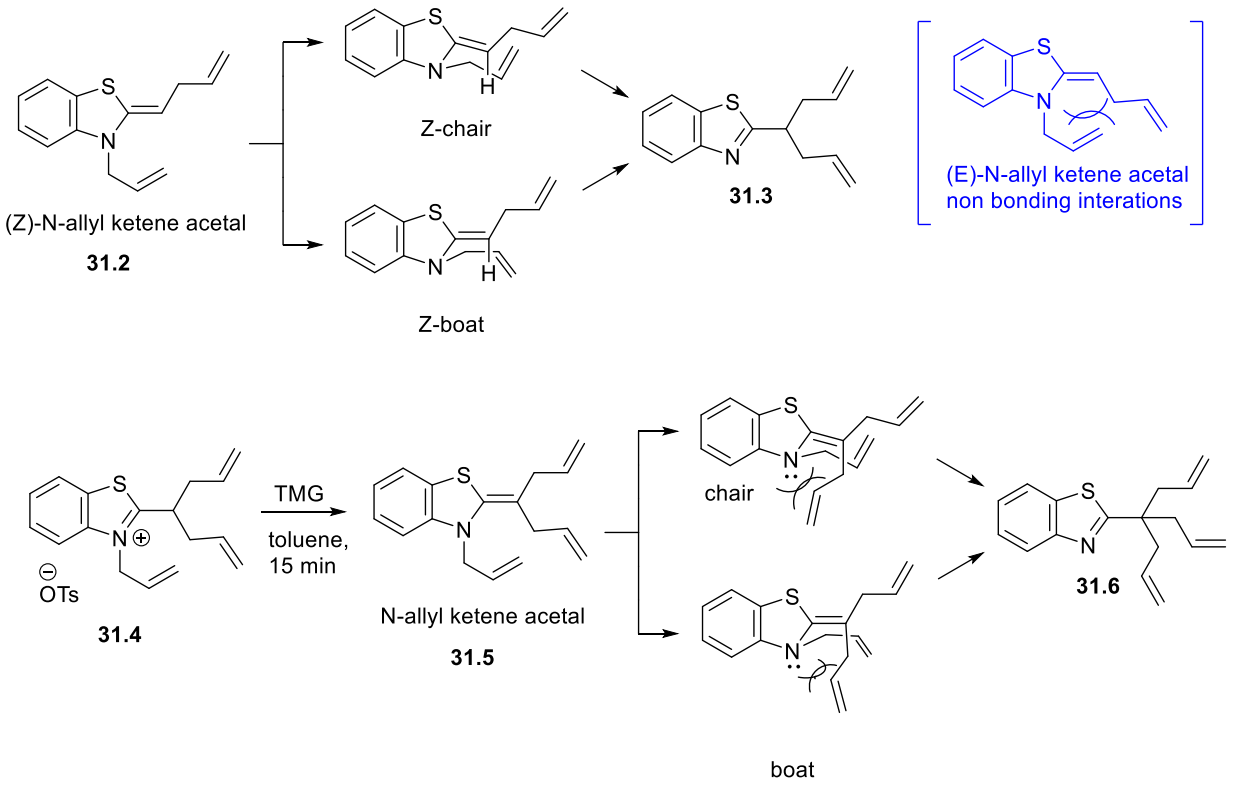
spectroscopy. As per computational studies, the Claisen rearrangement should happen at the lower temperature than the reported reaction temperature of 180 ^{0}C. The crude ketene acetal **31.5** heated at 80 ^{0}C, which successfully produced the iterative Claisen product **31.6** in 88% yield (Scheme 36). At explored reaction heating conditions starting from the room temperature to 60 ^{0}C, the Claisen product did not formed.



Scheme 36: Iterative Claisen rearrangement

According to the transition states, (Z)-N-allyl ketene acetal **31.2** was favorable than the (E)-N-allyl ketene acetal due the nonbonding interactions. The iterative Claisen product **31.3** was formed through both chair and boat confirmation of the (Z)-N-allyl ketene acetal **31.2.** The non-bonding interaction due to steric C-2 substitution in N-allyl ketene acetal **31.5** clearly disfavored the both chair and boat transition states for the corresponding iterative Claisen product **31.6** (Scheme 37). Despite of these unfavorable conditions the iterative Claisen product **31.6** reported at much lower temperature than the traditional high heating temperatures.

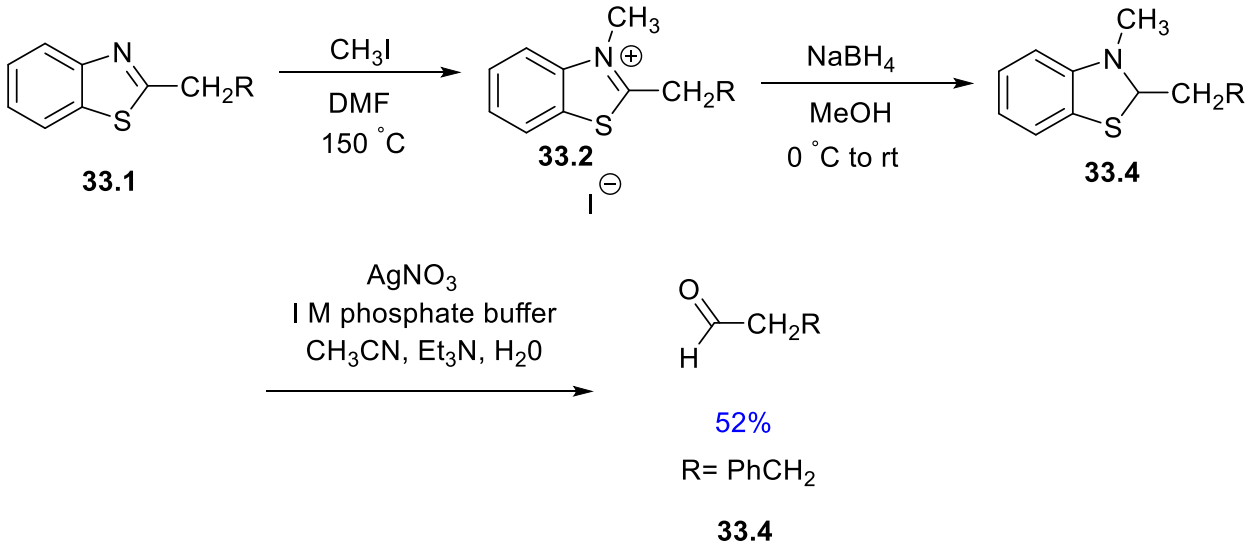
As per computational studies, we believe that the N-C bond in the N-allyl ketene acetal **31.5** bent due to the steric C-2 substitution on the N-allyl ketene acetal, which resembles the transition state of the conceding Claisen rearrangement.



Scheme 37: Transition states of iterative Claisen rearrangement

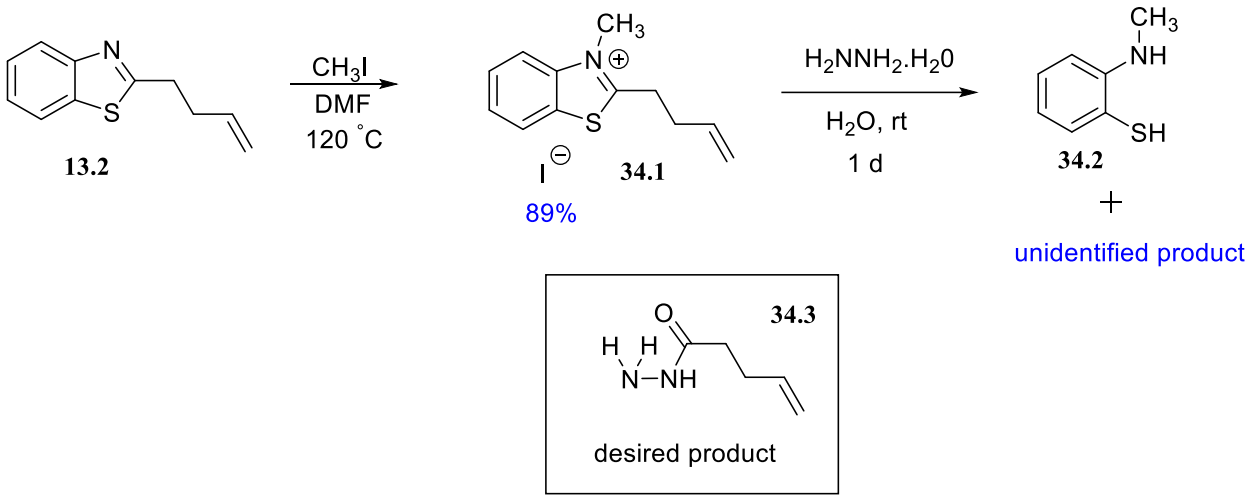
4. Preparation of pentenoic acid derivatives through benzothiazole cleavage

Benzothiazole derivatives can serve as carboxylic acid surrogates and many methods were available for their successful transformation. To demonstrate the alternative approach for the Ireland-Claisen rearrangement as our proposed benzothiazole based Claisen rearrangement, we need to achieve acid derivatives through cleavage of the benzothiazole derivatives, which were readily available from Claisen rearrangement. As per literature Dondoni *et al*, have reported few methods for the synthesis of acids and/or aldehyde derivatives by hydrolysis of benzothiazole moiety[24]. The benzothiazole hydrolysis typically begins with the alkylation of the benzothiazole **33.1** with strong alkylating agents such as methyl triflate or a large excess of methyl iodide to afford the activated benzothiazolium salt **33.2**. The benzothiazolium salt is reduced with sodium borohydride and this was followed by hydrolysis methodology with mercury, silver and copper to provide the acid and/or aldehyde derivatives **33.4**[25, 26] (Scheme 38).



Scheme 38: Scheme of benzothiazole cleavage

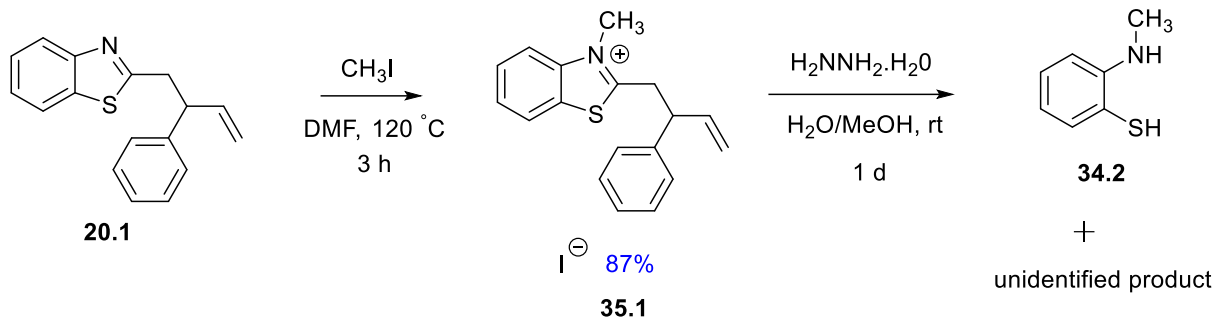
Our studies commenced with alkylation of benzothiazole derivative **13.2** with excess methyl iodide, which resulted the activated N-methyl benzothiazolium salt **34.1** in good yields. In literature, the hydrazine's react with the carbonyl compounds and its equivalents to synthesize various organic compounds[27, 28 and 29]. The N-methyl benzothiazolium salt treated with hydrazine to synthesize corresponding acid derivative but gave unsuccessful results. The reaction conditions were encouraging with the cleavage of the benzothiazole ring that formed the 2-thiomethylaniline **34.2** with unidentified product. At this stage, we believed that the desired acid derivative **34.3** was not identified and isolated might account of low molecular weight and/or high volatility of the compound (Scheme 39).



Scheme 39: Proposed benzothiazole hydrogenolysis reaction

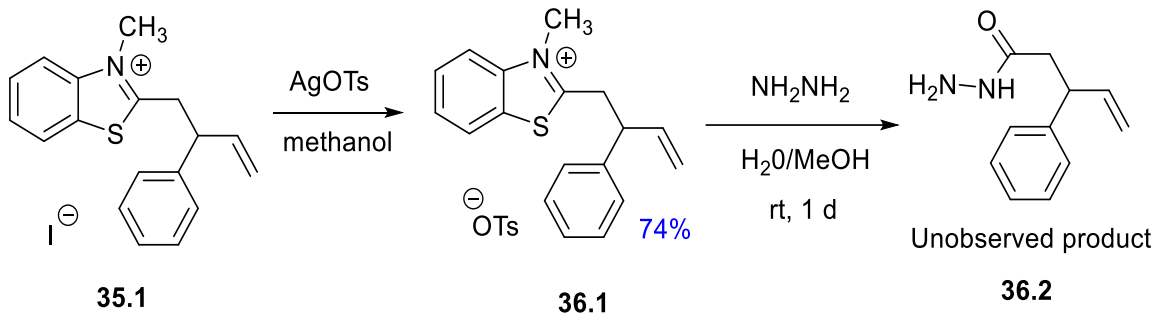
We further employed the higher molecular weight 2-(2-phenylbut-3-enyl) benzothiazole compound **20.1**. The benzothiazole derivative methylated with excess methyl iodide and delivered the N-methyl benzothiazolium salt **35.1** in excellent yield. The N-methyl benzothiazolium salt treated with hydrazine to produce acid derivative. Clearly, the hydrogenolysis of the N-methyl

benzothiazolium salt with the hydrazine derivative yielded the undesired 2-thiomethylaniline **34.2** with no sign of the desired product (acid derivative) (Scheme 40). With compilation of spectroscopic methods, we assumed that the unsaturation (double bond) of the substituted part of benzothiazole or the iodine counter ion somehow resulted in the reaction to produce the unidentified product.



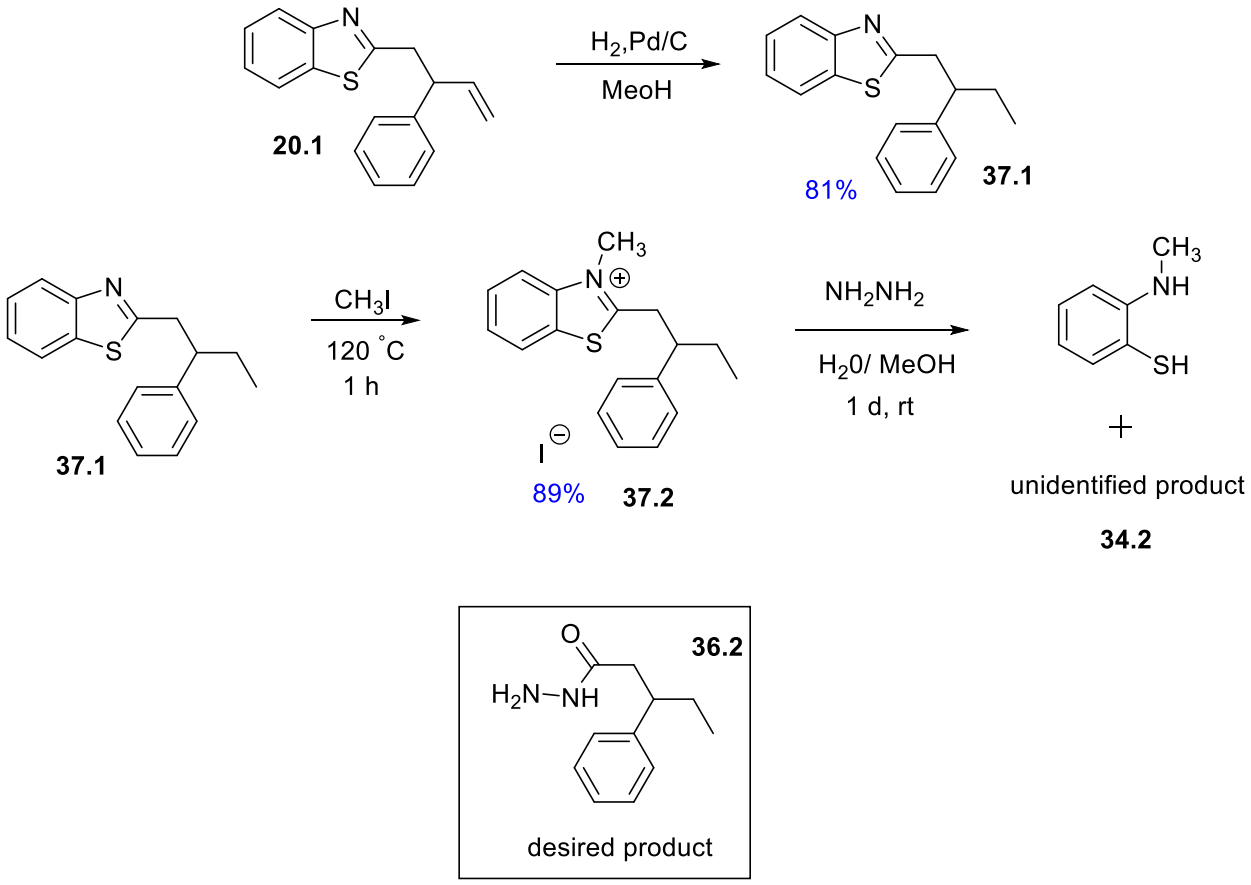
Scheme 40: Hydrogenolysis attempt with benzothiazolium salts.

The investigation started with switching the counter ion in the N-methyl benzothiazolium iodide salt **35.1**. The ion exchange of the iodine counter ion with the tosylate counter ion by simply triturating the benzothiazolium iodide salt **35.1** with the silver tosylate in presence of methanol yielded the insoluble silver iodide and benzothiazolium tosylate salt **36.1**. The benzothiazolium salt with the tosylate counter ion was proceeded with the hydrogenolysis conditions to cleave the benzothiazolium salt resulted in formation of 2-thiomethylaniline with unidentified product. This result clearly intrigued the counter ion did not have any impact on the hydrogenolysis reaction (Scheme 41).



Scheme 41: Ion exchange reaction of benzothiazolium salts

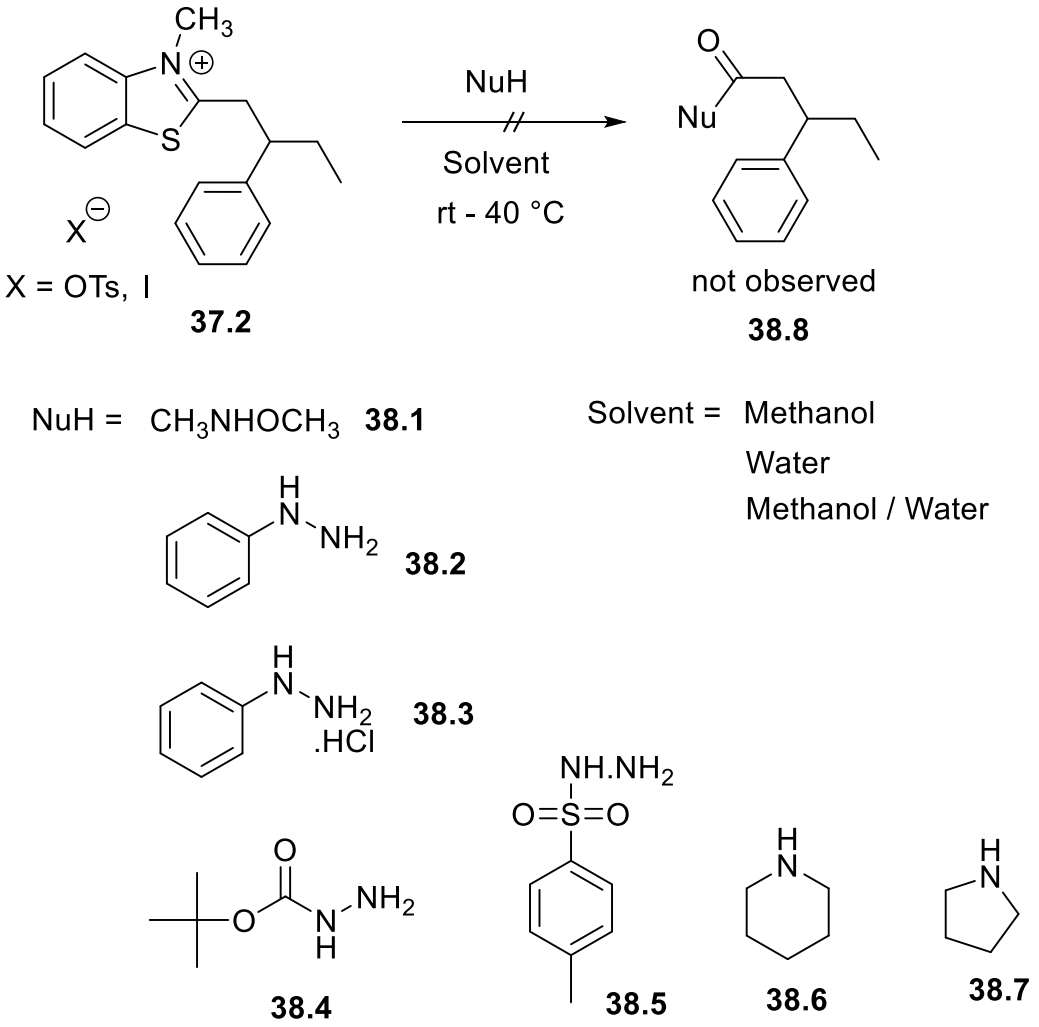
The investigation continued with the saturation of terminal alkene in benzothiazole derivative. The benzothiazole derivative **20.1** successfully saturated by hydrogen gas and Pd/C metal to provide the desired product **37.1**. The saturated benzothiazole derivative **37.1** alkylated with methyl iodide producing N-methyl benzothiazolium salt **37.2** in good yield. The N-methyl benzothiazolium salt **37.2** was treated with hydrazine to cleave the benzothiazolium salt resulted in formation of 2-thiomethylaniline with unidentified product. The results of exploring saturated benzothiazole derivative for the hydrogenolysis did not have any impact on the outcome of the reaction. All of our hydrogenolysis experimental studies gave successful results of hydrolysis of the benzothiazole ring, but we ended up with separating the aromatic part of 2-thiomethylaniline **34.2** product rather than the intended acid derivative (Scheme 42).



Scheme 42: Hydrogenolysis attempts of benzothiazolium salts with hydrazine

At this stage, we used hydrazine and hydrazine monohydrate as nucleophile to cleave the benzothiazolium salts for the synthesis of corresponding acid derivative. We decided to explore the possible amine derivatives as a reagent for the benzothiazole hydrogenolysis. The commercially available amine derivatives such as N, O-dimethyl hydroxylamine **38.1**, phenyl hydrazine **38.2**, phenyl hydrazine hydrochloride **38.3**, tert-butyl carbazide **38.4**, tosyl hydrazine **38.5**, piperidine **38.6** and pyrrolidine **38.7** tested with hydrogenolysis conditions. All of these reaction attempts with the amine derivatives and the N-methyl benzothiazolium salts resulted in the starting material recovery. The solvent combination of water and methanol with temperature adjustments did not make any impact on the product formation. Finally, hydrazine and hydrazine

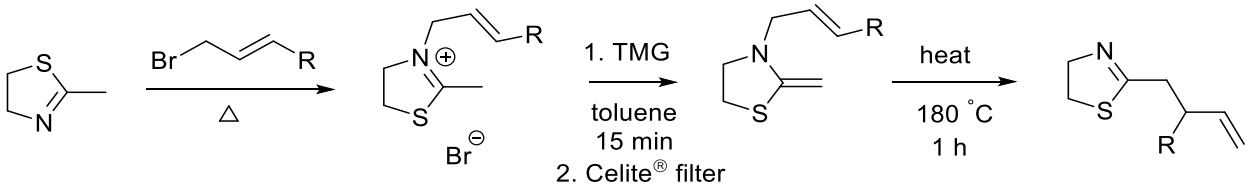
monohydrate successfully cleaved the benzothiazole ring producing only the aromatized product 2-thiomethylaniline **34.2** with unidentified products. At same time, not all other amine derivatives have made any impact to cleave the benzothiazole ring (Scheme 43).



Scheme 43: Hydrogenolysis attempts of benzothiazolium salts with various nucleophiles

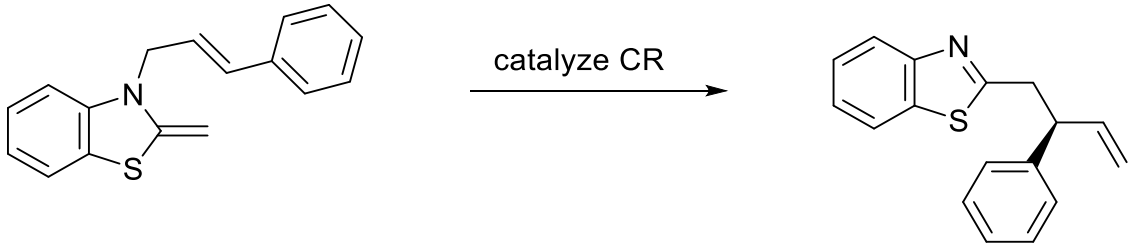
III. Future studies:

The Claisen rearrangement under milder conditions were successfully developed and demonstrated the functional group (unprotected alcohols, aldehydes, amides, ester and ethers) compatibility. This methodology of Claisen rearrangement was established and studied with heterocycle benzothiazole and various allyl bromide derivatives. We want to expand our methodology for other feasible heterocycle compounds such as thiazoline and many more. The proposed methodology for the future work shown below in Scheme 44.



Scheme 44: Proposed Claisen rearrangement with 2-methyl thiazoline

The demonstrated Claisen rearrangement methodology was limited to racemic synthesis and we are planning to demonstrate the asymmetric synthesis of the Claisen rearrangement by gaining the advantage of catalyzing reaction conditions (Scheme 45).

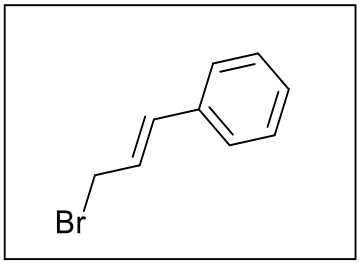


Scheme 45: Proposed asymmetric Claisen rearrangement

VI. Experimental section and spectral data:

General Information

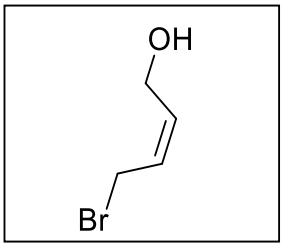
All reactions conducted under an inert atmosphere using standard conditions. Apart from this, no other precise attempt made to exclude air or moisture. The commercially available reagents used without additional purification unless otherwise indicated. Compound purification effected by flash chromatography using 230x400 mesh, 60 Å porosity obtained from Sorbent Technologies, Yamazen smart flash automatic chromatography and by recrystallization from indicated solvents. Melting points taken using a Stuart SMP 10 and a Fisher-Johns melting point apparatuses. Proton and Carbon NMR spectra obtained on availability of 300, 400 and 700 MHz Bruker Avance spectrometer. Structural assignments based on ^{1}H, ^{13}C, and IR spectroscopies. Elemental analyses performed by Atlantic Micro lab, Inc.



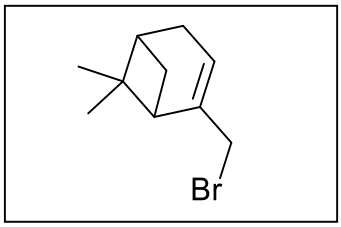
Cinnamyl bromide. This compound is commercially available; however, it is very expensive. In the literature, there is only one procedure proposed by Zhang et al to prepare such compound starting from cinnamyl chloride and using Rhodium as a catalyst.[16] It was prepared here in a new and convenient way (Finkelstein variation on Wagner reaction).[17]

A mixture of cinnamyl chloride (3 mL, 21.5 mmol) and sodium bromide (6.65 g, 6.46 mmol) in acetone (15 mL) heated under reflux for 4 days. The reaction then filtered to remove solids and

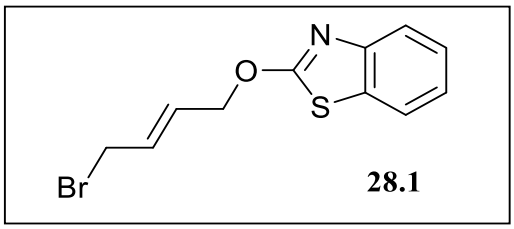
the filtrate was concentrated in vacuo to produce cinnamyl bromide (3.87 g, 91%) as a light brown oil. Analytical data matched a commercial sample.[16]



A mixture of (Z) 4-chloro-2-butenol (3 mL, 21.5 mmol) and sodium bromide (6.65 g, 6.46 mmol) in acetone (15 mL) was heated under reflux for 4 days. The reaction then was filtered to remove solids and the filtrate was concentrated in vacuo to produce (Z)-4-Bromobut-2-en-1-ol (3.87 g, 91%) as a light brown oil. Analytical data matched a reported sample.[18]

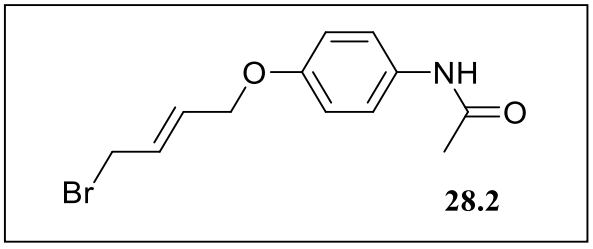


Myrtenyl bromide made from a reported procedure. Phosphorus tribromide (0.32 ml, 3.4 mmol) was added to a cooled solution of Myrtenol (0.8 ml, 5 mmol) in diethyl ether (7 ml) and was stirred at 0 ^{o}C for 1.5 hours. Reaction was quenched with saturated $NaHCO_3$ and organic product extracted into ether. Organic layer was dried with $MgSO_4$, filtered and solvent evaporated in-vacuo to obtain bromide in (0.388 g, 90%) yield. Data matched those reported by Araki *et al.*[19]



28.1

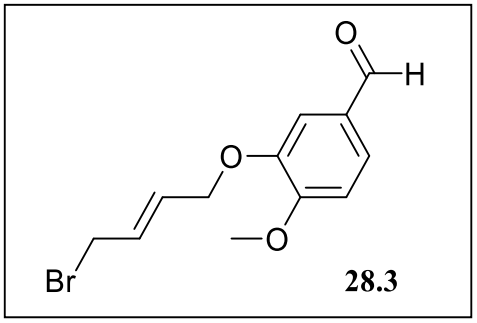
To a stirred solution of 2-hydroxy benzothiazole (500 mg, 33 mmol) and K_2CO_3 (502 mg, 36 mmol) in dry acetonitrile was added to (E)-1,4- dibromo-2-butene (778 mg, 36 mmol) in single portion. The reaction mixture heated to reflux for 4 hours and monitor the reaction through the TLC for completion of reaction. Then the reaction mixture was cooled to room temperature (rt) and filtered to remove the insoluble residues. The solvent was removed under reduced pressure to collect the crude reaction mixture and column purification (eluent: 98:02 to 95:05 Hexanes/EtOAc) was performed to yield the (404 mg, 43%) pure product as white powder. M.P 87- 88 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) 3.91 (d, *J*= 6.7 Hz, 2H), 4.59 (d, *J*=6.9 Hz, 2H), 5.82 - 5.98 (m, *J*=7.7 Hz, 2H), 7.01 (t, *J*=7.4 Hz, 1H), 7.12 (t, *J*=7.5 Hz, 1H), 7.35 (d, *J*=7.9 Hz, 1H), 7.48 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 29.72, 31.05, 43.41, 110.95, 122.71, 123.36, 126.44, 127.68, 129.96, 136.70, 169. IR (thin film) ν_{max}: 2924, 2850, 1658, 1589, 1469, 1315, 1303, 1188, 774, 621 cm $^{-1}$. Elemental Analysis: calcd for $C_{11}H_{10}NOSBr$: C 46.64 H, 3.53 N 4.94 S 11.30 Br 28.23, found C 47.23 H, 3.68 N 4.83 S 11.32 Br 28.94.



28.2

To a stirred solution of 4-acetamidophenol (1.00 g, 66 mmol) and K_2CO_3 (1.00 g, 72 mmol) in dry acetonitrile was added to (E)-1,4- dibromo-2-butene (1.56 g, 72 mmol) in single portion. The

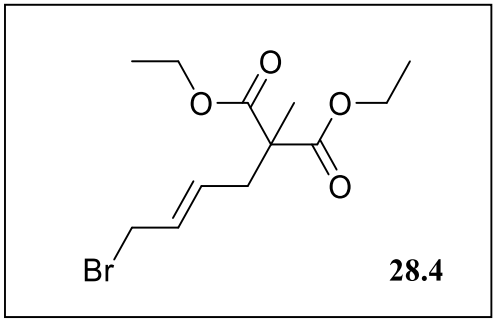
reaction mixture heated to reflux for 4 hours and monitor the reaction through the TLC for the completion of reaction. Then the reaction mixture was cooled to room temperature (rt) and filtered to remove the insoluble residues. The solvent was removed under reduced pressure to collect the crude reaction mixture and column purification (eluent: 98:02 to 90:10 Hexanes/EtOAc) was performed to yield the (0.99 g, 71%) pure product as white solid. M.P 126- 129 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.15 (s, *CH3*, 3H), 3.99 (d, *J*= 7.1 Hz, 2H), 4.53 (d, *J*=5.6 Hz, 2H), 5.85 - 5.98 (m, *J*=7.6 Hz, 2H), 6.06 (td, *J*= 7.4 Hz, 7.1 Hz 2H), 6.85 (td, *J*= 7.7 Hz, 5.1Hz 2H), 6.85 (d, *J*=8.9 Hz, 2H), 7.12 (bs, NH, 1H), 7.39 (d, *J*=8.9 Hz, 2H),); ^{13}C NMR (400 MHz, $CDCl_3$) 24.39, 31.60, 67.53, 115.05, 121.84, 129.26, 130.04, 131.30, 155.21, 168.14. IR (thin film) ν_{max}: 3317, 2924, 1654, 1616, 1521, 1462, 1408, 1373, 1315, 1300, 1246, 1215, 1010, 968, 825, 717, 601 cm $^{-1}$. Elemental Analysis: calcd for $C_{12}H_{13}NO_2Br$: C 50.87 H, 4.59 N 4.69 Br 23.23, found C 52.83 H, 5.30 N 5.03 Br 23.31.



28.3

To a stirred solution of vanillin (1.00 g, 65 mmol) and K_2CO_3 (1.02 g, 72 mmol) in dry acetonitrile was added to (E)-1,4- dibromo-2-butene (1.54 g, 72 mmol) in single portion. The reaction mixture heated to reflux for 4 hours and monitor the reaction through the TLC for completion of the reaction. Then the reaction mixture was cooled to room temperature (rt) and filtered to remove the insoluble residues. The solvent was removed under reduced pressure to collect the crude reaction mixture and column purification (eluent: 98:02 to 90:10 Hexanes/EtOAc) was performed to yield

the (0.82 g, 57%) pure product as white solid. M.P 66 - 68 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) 3.97 (s, *CH3*, 3H), 3.99 (d, *J*=7.2 Hz, 2H), 4.69 (d, *J*=4.9 Hz, 2H), 6.06 (ddd, *J*=13.3, 7.1, 4.9 Hz, 1H), 6.08 (ddd, *J*=13.3, 7.1, 6.9 Hz, 1H), 7.01 (d, *J*=8.2 Hz, 1H), 7.45 (d, *J*=1.6 Hz, 1H), 7.49 (dd, *J*=8.1, 1.7 Hz, 1H), 9.86 (s, *CHO*, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 31.37, 56.21, 68.24, 110.78, 127.05, 129.22, 130.16, 148.35, 154.85, 190.77. IR (thin film) ν_{max}: 2846, 1676, 1666, 1597, 1508, 1431, 1388, 1261, 1246, 1230, 1211, 1192, 1161, 1134, 1018, 972, 825, 810, 640 cm $^{-1}$. Elemental Analysis: calcd for $C_{12}H_{13}O_3Br$: C 50.70 H, 4.57 Br 28.13, found C 50.31 H, 4.73 Br 28.18.

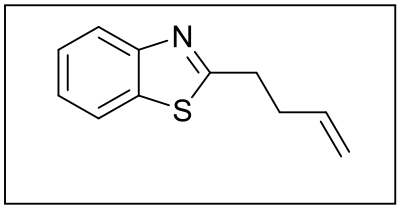


28.4

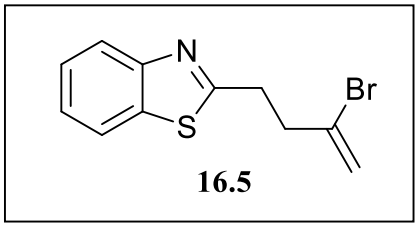
To a mixture of NaH (60% oil in suspension) (0.151 g, 63 mmol) in dry THF, the diethyl methyl malonate (1.00 g, 57 mmol) was added at 0 ^{0}C and the reaction mixture was stirred at room temperature for 1 hour. (E)-1,4- dibromo-2-butene (1.35 g, 63 mmol) was added to reaction mixture and the mixture was heated to reflux overnight. After completion of the reaction, the reaction mixture quenched with 1 M HCl, the crude product was extracted with ether, and the organic layer was separated. The organic layer washed with water and dried on Na_2SO_4. The solvent was removed under reduced pressure to collect the crude reaction mixture and column purification (eluent: 98:02 to 95:05 Hexanes/EtOAc) was performed to yield the (1.21 g, 69%) pure product as color less oil. ^{1}H NMR (400 MHz, $CDCl_3$) 1.21 (t, *J*= 7.2 Hz, 6H), 1.39 (s, *CH_3*, 3H), 2.61 (d, *J*=6.2 Hz, 2H), 3.89 (d, *J*=6.6 Hz, 2H), 4.35 (q, *J*=7.2 Hz, 4H), 5.77 - 5.82 (m, *J*=7.6 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) 14.06, 19.88, 32.34, 38.31, 53.51, 61.36, 130.00, 130.64,

171.65. IR (thin film) ν_{max}: 2924, 2850, 1658, 1589, 1469, 1435, 1369, 1357, 1141, 1095, 1080, 1060, 975, 952, 933, 744, 621 cm^{-1}. Elemental Analysis: calcd for $C_{12}H_{19}O_4Br$: C 47.05 H, 6.20 Br 26.10, found C 47.11 H, 6.26 Br 26.27.

General produced for the Claisen rearrangement products. TMG (1.1 eq) was added to a suspension of *N*-allyl-2-methylbenzothiazolium tosylate (1 eq) in toluene (20 mL for 1 mmol) at room temperature. After stirring at that temperature for 15 min, the reaction mixture filtered through a Celite® filter fritted funnel and rinsed with toluene (5-10 mL). The filtrate transferred to a pressure vessel, immersed in a pre-heated oil bath at 180 ºC and stirred at 170-175 ºC for 1 hour. Concentration in vacuo gave the title crude compound and purified by column chromatography as hexanes and ethyl acetate as solvent system.

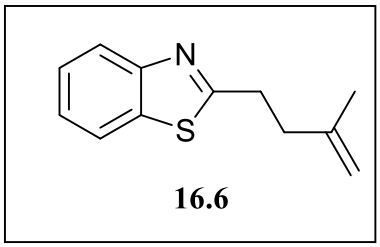


Obtained as a light brown oil with 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 2.64 (app quartet, *J*=7.4 Hz, 2H), 3.22 (t, *J*=7.8 Hz, 2H), 5.06 (d, *J*=10.2 Hz, 1H), 5.14 (d, *J*=17.1 Hz, 1H), 5.9 (ddt, *J*=16.9, 10.3, 6.5 Hz, 1H), 7.35 (t, *J*=7.5 Hz, 1H), 7.44 (t, *J*=7.5 Hz, 1H), 7.84 (d, *J*=7.8 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 33.38, 33.73, 116.21, 121.50, 122.59, 124.71, 125.91, 135.17, 136.39, 153.24, 171.19. Data matched with previous reports. [30, 31 & 32]



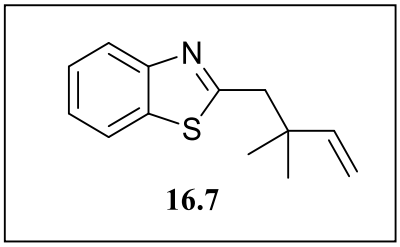
16.5

Eluent: 97:03 to 90:10 Hexanes/EtOAc; Obtained as a dark brown oil with 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 3.03 (t, *J*=7.5 Hz, 2H), 3.39 (t, *J*=7.5 Hz, 2H), 5.48 (S, 1H), 5.67 (S, 1H), 7.37 (t, *J*=7.5 Hz, 1H), 7.47 (t, *J*=7.6 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 1H); $^{`13}$C NMR (400 MHz, $CDCl_3$) 32.89, 40.80, 118.36, 121.54, 122.66, 124.90, 126.02, 131.83, 135.14, 153.21, 169.37. IR (thin film) ν_{max}: 2962, 2924, 2870, 1643, 1589, 1558, 1512, 1458, 1365, 1311, 1242, 1180, 1157, 1095, 1064, 1002, 910, 859, 810, 756, 725 cm $^{-1}$. Elemental Analysis: calcd for $C_{11}H_{10}NSBr$: C 49.44 H, 3.74 N 5.24 S 11.98 Br 29.92, found C 49.89 H, 3.83 N 5.24 S 12.32 Br 28.99.



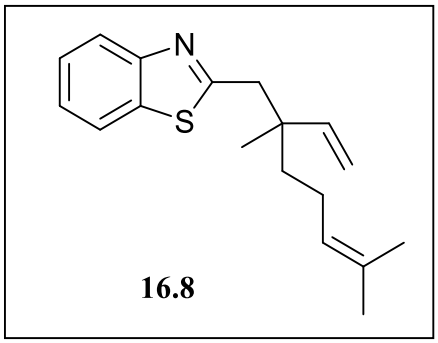
16.6

Eluent: 97:03 to 90:10 Hexanes/EtOAc; Obtained as a brown oil with 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 1.82 (S, CH_3, 3H), 2.60 (t, *J*=7.9 Hz, 2H), 3.28 (t, *J*=7.8 Hz, 2H), 4.80 (s, 2H), 7.35 (t, *J*=7.1 Hz, 1H), 7.44 (t, *J*=7.1 Hz, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 7.97 (d, *J*=8.0 Hz, 1H); $^{`13}$C NMR (400 MHz, $CDCl_3$) 22.51, 32.71, 37.24, 111.26, 121.50, 122.55, 124.69, 125.90, 135.15, 143.76, 153.22, 171.53. IR (thin film) ν_{max}: 3070, 2962, 2924, 2846, 1782, 1651, 1558, 1519, 1435, 1311, 1280, 1111, 1064, 887, 779, 725 cm $^{-1}$. Elemental Analysis: calcd for $C_{12}H_{13}NS$: C 70.90 H, 6.4 N 6.89 S 15.75, found C 71.04 H, 6.63 N 6.91 S 15.77.



16.7

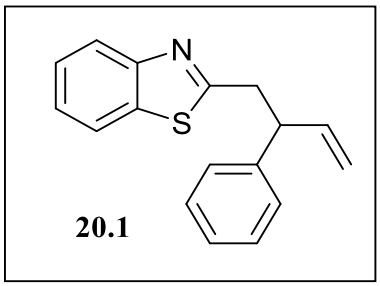
Eluent: 97:03 to 90:10 Hexanes/EtOAc; Obtained as a color less oil with 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 1.18 (S, CH_3, 6H), 3.13 (S, 2H), 5.01 (d, *J*=10.3 Hz, 1H), 5.04 (d, *J*=17.1 Hz, 1H), 5.98 (dd, *J*=17.1, 10.7 Hz, 1H), 7.36 (t, *J*=7.1 Hz, 1H), 7.45 (t, *J*=7.2 Hz, 1H), 7.83 (d, *J*=7.8 Hz, 1H), 8.00 (d, *J*=8.0 Hz, 1H); $^{`13}$C NMR (400 MHz, $CDCl_3$) 26.88, 37.66, 47.02, 112.12, 121.29, 122.66, 124.69, 125.76, 135.59, 146.670, 146.677, 152.98, 168.43. IR (thin film) ν_{max}: 3078, 2958, 2912, 1512, 1458, 1414, 1383, 1315, 1276, 1242, 1172, 1153, 1091, 1060, 1010, 999, 914, 887, 856, 833, 756, 709 cm $^{-1}$. Elemental Analysis: calcd for $C_{13}H_{15}NS$: C 71.85 H, 6.90 N 6.44 S 14.74, found C 72.06 H, 7.06 N 6.27 S 14.47.



16.8

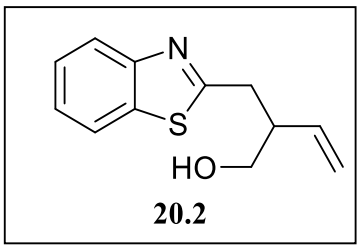
Eluent: 97:03 to 90:10 Hexanes/EtOAc; Obtained as a brown oil with 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 1.77 (S, CH_3, 3H), 1.48 (dd, *J*= 8.5, 4.8Hz, 2H), 1.62 (s, CH_3, 3H), 1.69 (s, CH_3, 3H), 2.05 (dt, *J*=16.4, 7.3 Hz 2H), 3.20 (t, *J*=7.7 Hz, 2H), 5.04 (d, *J*=10.3 Hz, 1H), 5.09 (d, *J*=17.1 Hz, 1H), 5.93 (dd, *J*= 10.3, 8.7 Hz, 1H), 7.36 (d, *J*=7.5 Hz, 2H), 7.46 (t, *J*=7.1 Hz, 1H), 7.84 (d, *J*=7.9 Hz, 1H), 8.01 (d, *J*=8.2 Hz, 1H); $^{`13}$C NMR (400 MHz, $CDCl_3$) 17.66, 22.66, 22.97, 25.70, 40.83, 45.69, 109.98, 113.58, 121.26, 122.65, 124.66, 125.72, 131.50, 135.63, 154.29, 152.93,

168.27. IR (thin film) ν_{max}: 3068, 2962, 2912, 1508, 1454, 1411, 1373, 1311, 1276, 1242, 1153, 1091, 1060, 999, 914, 887, 833, 756, 729 cm^{-1}. Elemental Analysis: calcd for $C_{18}H_{23}NS$: C 75.74 H, 8.06 N 4.90 S 11.22, found C 75.99 H, 8.11 N 4.88 S 10.96.



20.1

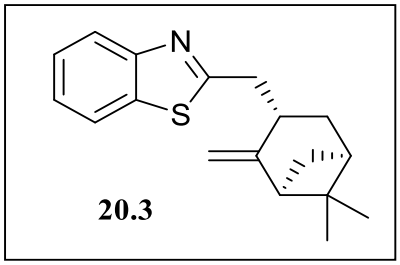
Eluent: 98:02 to 90:10 Hexanes/EtOAc; Obtained as a light brown oil with 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 3.5 (m, *J*=7.5 Hz, 1H), 3.55 (m, *J*=7.5 Hz, 1H), 4.0 (app quartet, *J*=7.4 Hz, 1H), 5.09 (d, *J*=11.4 Hz, 1H), 5.1 (d, *J*=16.1 Hz, 1H), 6.1 (ddd, *J*=17.3, 10.1, 7.2 Hz, 1H), 7.22 (t, *J*=6.9 Hz, 1H), 7.30 (m, *J*=6.7 Hz, 5H), 7.44 (t, *J*=8.0 Hz, 1H), 7.79 (d, *J*=7.9 Hz, 1H), 7.98 (d, *J*=8.1 Hz, 1H); $^{`13}C$ NMR (400 MHz, $CDCl_3$) 40.17, 49.70, 115.68, 121.477, 122.62, 124.72, 125.86, 126.85, 127.75, 128.70, 135.27, 140.112, 142.27, 153.07, 169.69. IR (thin film) ν_{max}: 3061, 3025, 2981, 1712, 1516, 1435, 1126, 917, 728, 669 cm^{-1}. Elemental Analysis: calcd for $C_{17}H_{15}NS$: C 76.95 H, 5.65 N 5.28 S 12.07, found C 76.88 H, 5.54 N 5.28 S 12.15.



20.2

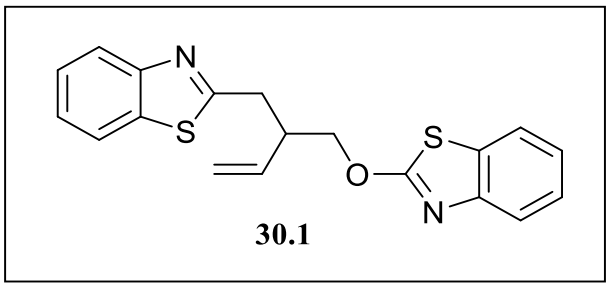
Eluent: 90:10 to 75:25 Hexanes/EtOAc; Obtained as a light brown oil with 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 2.49 (s, OH, 1H), 2.89 (m, *J*=6.7 Hz, 1H), 3.27 (dd, *J*=7.8 Hz, 2H), 3.68 (s,

2H), 5.14 (d, *J*=10.1 Hz, 1H), 5.19 (d, *J*=17.1 Hz, 1H), 5.81 (ddd, *J*=17.1, 10.3, 8.4 Hz, 1H), 7.37 (t, *J*=7.4 Hz, 1H), 7.44 (t, *J*=8.0 Hz, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 7.99 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 35.76, 46.02, 64.91, 117.65, 121.50, 122.60, 124.90, 126.03, 137.73, 153.06, 169.66. IR (thin film) ν_{max}: 3336 (bs), 3070, 2920, 2866, 1639, 1512, 1454, 1419, 1369, 1334, 1311, 1280, 1246, 1153, 1103, 1053, 1014, 991, 918, 729, 705 cm $^{-1}$. Elemental Analysis: calcd for $C_{12}H_{13}NOS$: C 75.73 H, 5.93 N 6.29 S 14.60, found C 64.62 H, 6.38 N 6.11 S 13.74.



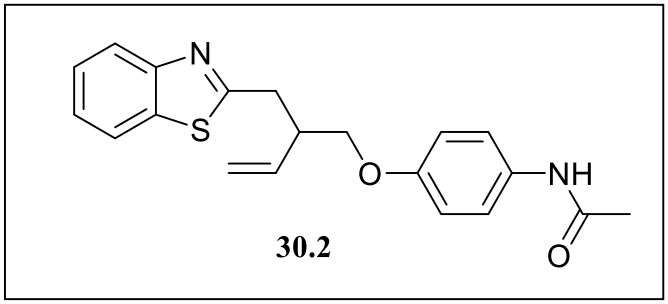
20.3

Eluent: 97:03 to 90:10 Hexanes/EtOAc; M.P 58 - 59 ^{0}C Obtained as a light green solid with 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 0.78(S, CH_3, 3H), 1.27 (S,CH_3, 3H), 1.29 (d, *J*= 10 Hz, 1H), 1.78 (dt, J=13.9 Hz, 2.8 - 3.2 Hz, 1H), 2.02 (dd, *J*=8.7, 5.5 Hz, 1H), 2.10 (dt, *J*=11.9, 1.6 Hz, 1H), 2.42 (app quartet, *J*=8.1, 5.5 Hz, 1H), 2.55 (t, *J*=7.5 Hz, 1H), 3.22 (dt, *J*=9.3, 8.7 Hz, 1H), 3.28 (dd, *J*= 14.49, 11 Hz, 1H), 3.49(dd, , *J*=14.5, 5.6 Hz, 1H), 4.83 (d, *J*=24.15 Hz, 2H), 7.39 (t, *J*=7.5 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.87 (d, *J*=7.9 Hz, 1H), 8.02 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 21.76, 25.80, 28.60, 30.21, 35.05, 40.21, 40.89, 46.70, 52.24, 109.02, 121.55, 122.61, 124.81, 125.97, 135.16, 153.09, 154.61, 171.20. IR (thin film) ν_{max}: 3042, 2962, 2908, 2866, 1635, 1516, 1454, 1435, 1257, 1246, 1114, 1095, 1064, 1041, 1014, 887, 798, 759 cm $^{-1}$. Elemental Analysis: calcd for $C_{18}H_{21}NS$: C 76.28 H, 7.41 N 4.94 S 11.30, found C 76.02 H, 7.55 N 4.83 S 11.15.



30.1

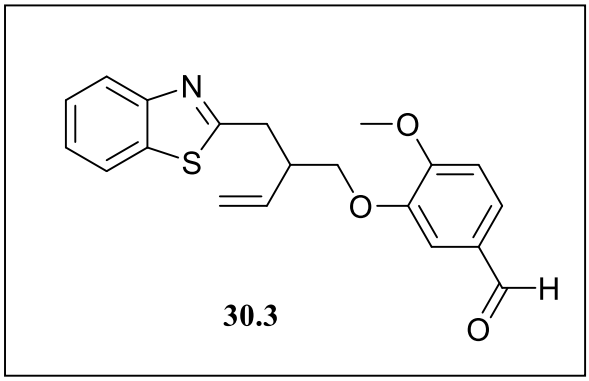
Eluent: 97:03 to 90:10 Hexanes/EtOAc; M.P 90 - 91 ^{0}C. Obtained as a pale yellow solid with 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 3.31 (dd, , *J*=7.4 Hz, 2H), 3.43 (m, *J*=7.2 Hz, 1H), 4.13 (ddd, *J*=11.6, 8.7 Hz, 2H), 5.01 (d, *J*=10.6 Hz, 1H), 5.07 (d, *J*=17.2 Hz, 1H), 5.84 (ddd, *J*=17.2, 9.9, 7.2 Hz, 1H), 7.19 (t, *J*=7.6 Hz, 1H), 7.23 (t, *J*=7.9 Hz, 1H), 7.35 (t, *J*=6.1 Hz, 1H), 7.40 (d, *J*=7.8 Hz, 1H), 7.41 (d, *J*=7.7 Hz, 1H), 7.50 (t, *J*=8.1 Hz, 1H), 7.87 (d, *J*=7.9 Hz, 1H), 7.99 (d, *J*=7.9 Hz, 1H); $^{`13}$C NMR (400 MHz, $CDCl_3$) 37.09, 42.43, 46.21, 111.12, 118.56, 121.55, 122.57, 122.64, 123.11, 124.98, 126.04, 126.33, 136.96, 153.17, 155.57, 168.13. IR (thin film) ν_{max}: 3070, 2938, 2866, 1678, 1651, 1585, 1473, 1435, 1330, 1149, 914, 748, 729, 709, 671 cm $^{-1}$. Elemental Analysis: calcd for $C_{19}H_{16}N_2OS_2$: C 64.75 H, 4.54 N 7.95 S 18.17, found C 62.84 H, 4.88 N 7.36 S 17.04.



30.2

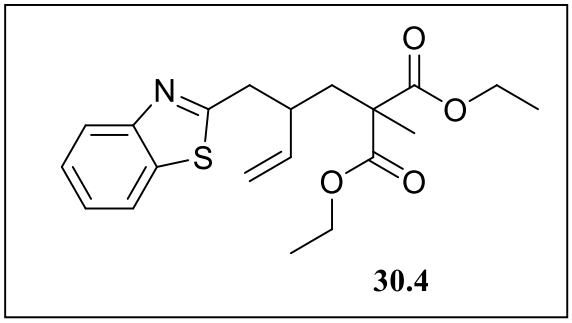
Eluent: 80:10 to 65:35 Hexanes/EtOAc; Obtained as a thick yellow oil with 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 2.15 (s, CH_3, 3H), 3.28 (dd, *J*=14.1, 6.3 Hz, 2H), 3.48 (dd, *J*=8.4, 5.7 Hz, 1H), 4.01 (t, *J*=11.3 Hz 2H), 5.16 (d, *J*=10.4 Hz, 1H), 5.21 (d, *J*=17.5 Hz, 1H), 5.93 (ddd, *J*=16.5, 9.7, 7.7 Hz, 1H), 6.86 (d, *J*=8.5 Hz, 1H), 7.31 (t, *J*=7.3 Hz, 1H), 7.39 (t, *J*=7.7 Hz, 1H), 7.46 (t, *J*=7.7

Hz, 1H), 7.85 (d, *J*=7.8 Hz, 1H), 7.99 (d, *J*=8.0 Hz, 1H); $^{`13}$C NMR (400 MHz, $CDCl_3$) 24.32, 35.98, 43.66, 70.27, 114.93, 117.59, 121.51, 121.85, 122.60, 124.81, 125.94, 131.28, 137.12, 153.17, 155.57, 168.13, 169.53. IR (thin film) ν_{max}: 3278, 3251, 3190, 3132, 3066, 2920, 1654, 1600, 1543, 1504, 1465, 1435, 1411, 1311, 1269, 1172, 1114, 1037, 1014, 968, 3070, 2938, 2866, 1678, 1651, 1585, 1473, 1435, 1330, 1234, 1149, 914, 729, 709, 671 cm $^{-1}$. Elemental Analysis: calcd for $C_{20}H_{20}N_2O_2S$: C 68.15 H, 5.67 N 7.95 S 9.08, found C 66.50 H, 6.31 N 7.39 S 6.47.



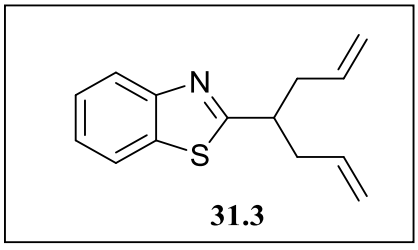
30.3

Eluent: 80:10 to 65:35 Hexanes/EtOAc; Obtained as a light brown viscous oil with 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 3.34 (app quartet, *J*=8.1 Hz, 2H), 3.54 (t, *J*=8.9 Hz, 2H), 4.15 (m, J= 8.9 Hz, 2H), 5.20 (d, *J*=14.6 Hz, 1H), 5.24 (d, *J*=21.6 Hz, 1H), 5.96 (ddd, *J*=17.1, 10.3, 9.6 Hz, 1H), 6.97(d, J=8.3 Hz, 2H), 7.37 (t, *J*=7.5 Hz, 2H), 7.44 (d, *J*=9.5 Hz, 2H), 7.46 (d, *J*=9.5 Hz, 1H), 7.85 (d, *J*=8.1 Hz, 1H), 8.01 (d, *J*=8.3 Hz, 1H), 9.83 (s, 1H); $^{`13}$C NMR (400 MHz, $CDCl_3$) 36.19, 43.39, 56.04, 71.28, 110.80, 111.25, 117.84, 121.46, 122.68, 124.76, 125.91, 126.90, 135.32, 136.82, 148.82, 153.24, 155.11, 169.40, 190.84. IR (thin film) ν_{max}: 3084, 2973, 2846, 1666, 1639, 1567, 1508, 1431, 1388, 1261, 1230, 1211, 1192, 1161, 1134, 1018, 972, 825, 756 cm $^{-1}$. Elemental Analysis: calcd for $C_{20}H_{19}NO_3S$: C 67.97 H, 5.38 N 3.96 S 9.06, found C 60.52 H, 5.99 N 3.25 S 5.11.



30.4

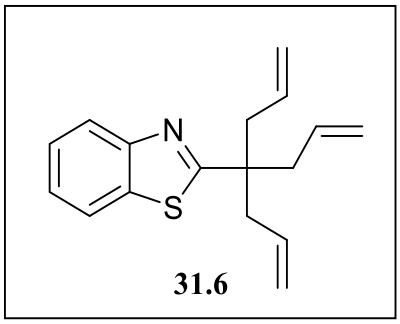
Eluent: 97:03 to 90:10 Hexanes/EtOAc; Obtained as a white semi solid with 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 1.18 (t, J=6.1Hz, 3H), 1.23 (t, J=4.8Hz, 3H), 1.45 (s, CH_3, 3H), 2.16 (ddd, J=12.0 Hz, 9.9 Hz, 6.0 Hz 2H), 2.84 (m, *J*=11.1 Hz, 1H), 3.13 (ddd, *J*=18.0 Hz, 9.0 Hz, 6.5 Hz 2H), 4.17 (q, J=10.7 Hz, 4H), 4.94 (d, J=9.9 Hz, 1H), 4.96 (d, J=17.1 Hz, 1H), 5.58 (ddd, *J*=17.1 Hz, 9.6 Hz, 7.6 Hz, 1H), 7.34 (t, *J*=7.5 Hz, 1H), 7.44 (t, *J*=7.7 Hz, 1H), 7.82 (d, *J*=7.9 Hz, 1H), 7.96 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 13.90, 13.95, 20.01, 39.33, 41.06, 41.27, 53.03, 61.05, 61.35, 116.74, 121.46, 122.68, 124.76, 125.87, 135.28, 139.88, 153.14, 169.39, 171.73, 172.35. IR (thin film) ν_{max}: 3074, 2978, 2920, 1639, 1512, 1454, 1435, 1365, 1311, 1276, 1246, 1168, 1095, 1060, 991, 914, 756, 729 cm $^{-1}$. Elemental Analysis: calcd for $C_{20}H_{25}NO_4S$: C 63.97 H, 6.66 N 3.73 S 8.52, found C 62.86 H, 6.82 N 3.58 S 8.15.



31.3

Eluent: 97:03 to 90:10 Hexanes/EtOAc; Obtained as a dark brown oil with 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 2.61 (dd, *J*=7.52 Hz, 4H), 3.51 (t, *J*=6.7 Hz, 1H), 5.02 (d, *J*=10.0 Hz, 2H), 5.08 (d, *J*=17.0 Hz, 2H), 5.81 (ddt, *J*=17.9, 10.0, 7.2 Hz, 2H), 7.36 (t, *J*=6.7 Hz, 1H), 7.45 (t, *J*=7.0 Hz, 1H), 7.85 (d, *J*=7.4 Hz, 1H), 7.99 (d, *J*=7.7 Hz, 1H); `^{13}C NMR (400 MHz, $CDCl_3$) 39.37,

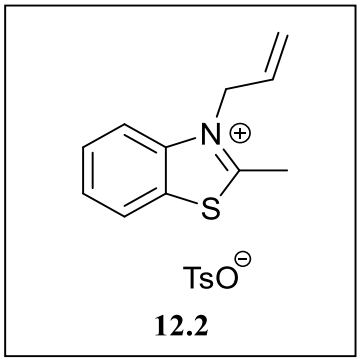
44.66, 117.44, 121.55, 122.75, 124.68, 125.82, 135.15, 153.04, 175.08. IR (thin film) ν_{max}: 3074, 2978, 2920, 1639, 1504, 1435, 1415, 1330, 1311, 1280, 1242, 1176, 1153, 1126, 1087, 1056, 995, 968, 858, 756, 729 cm^{-1}. Elemental Analysis: calcd for $C_{14}H_{15}NS$: C 73.33 H, 6.54 N 6.11 S 13.96, found C 72.57 H, 6.52 N 5.96 S 13.72.



31.6

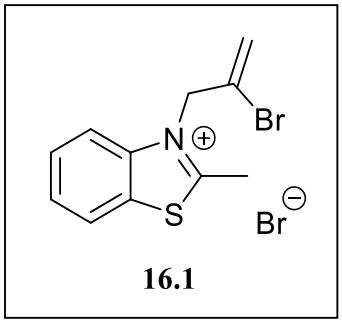
Eluent: 98:02 to 90:10 Hexanes/EtOAc; Obtained as a dark brown oil with 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 2.66 (d, *J*=7.1 Hz, 6H), 5.09 (t, *J*=10.3 Hz, 6H), 5.71 (ddt, *J*=16.3, 9.2, 7.5 Hz, 3H), 7.36 (t, *J*=7.4 Hz, 1H), 7.46 (t, *J*=7.5 Hz, 1H), 7.87 (d, *J*=7.8 Hz, 1H), 8.02 (d, *J*=8.0 Hz, 1H); $^{`13}C$ NMR (400 MHz, $CDCl_3$) 42.28, 47.61, 118.69, 121.44, 122.93, 124.66, 125.72, 133.20, 134.89, 152.91, 178.07. IR (thin film) ν_{max}: 3061, 2981, 1735, 1712, 1516, 1473, 1458, 1430, 1373, 1365, 1265, 1222, 1165, 1107, 1087, 1018, 921, 864, 771, 655 cm^{-1}. Elemental Analysis: calcd for $C_{17}H_{19}NS$: C 75.80 H, 7.06 N 5.20 S 11.89, found C 76.05 H, 7.11 N 5.16 S 11.65.

General produced for the benzothiazolium salts: 2-Methylbenzothiazole (1 eq) and allyl bromide derivatives (1.1 - 1.2 eq) were placed in a pressure vessel at room temperature. The mixture stirred and heated to 120 ºC for a total of 1 hour. The resulting oil allowed cooling down to room temperature. Diethyl ether (10 mL) added and vigorously stirred at room temperature until a solid precipitate formed. Subsequent filtration yielded salt and salt washed with excess diethyl ether.



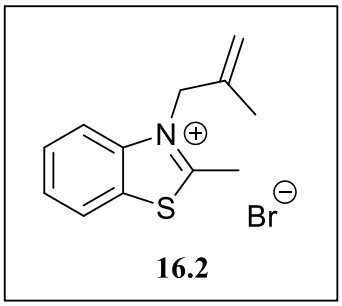
12.2

^{1}H NMR (400 MHz, $CDCl_3$) 2.27 (s, 3H), 3.29 (s, 3H), 5.02 (d, *J*=17.2 Hz, 1H), 5.32 (d, *J*=10.5 Hz, 1H), 5.53 (d, *J*=5.1 Hz, 2H), 5.98 (ddt, *J*=17.2, 10.5, 5.1 Hz, 1H), 7.01 (d, *J*=8.2 Hz, 2H), 7.60 (d, *J*=8.2 Hz, 2H), 7.64 (t, *J*=7.8 Hz, 1H), 7.72 (t, *J*=7.8 Hz, 1H), 7.90 (d, *J*=8.4 Hz, 1H), 8.15 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 17.45, 21.20, 51.92, 116.65, 119.88, 124.32, 125.75, 128.32, 128.40, 129.00, 129.70, 138.89, 140.86, 143.95, 176.78; Data matched with Silvana's thesis [13].



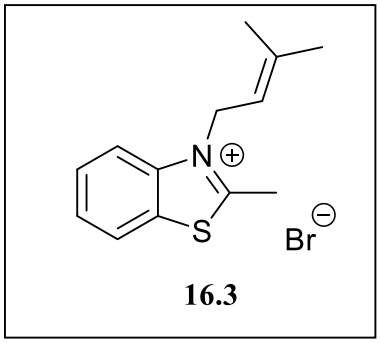
16.1

M.P 172- 174 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) 3.56 (s, 3H), 5.94 (d, *J*=2.5 Hz, 1H), 6.11 (s, 2H), 6.63 (s, 1H), 7.70 (t, *J*=7.7 Hz, 1H), 7.81 (t, *J*=7.9 Hz, 1H), 8.21 (d, *J*=8.5 Hz, 1H), 8.31 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 20.55, 55.70, 113.40, 116.78, 124.49, 128.68, 129.99, 138.41, 142.40, 177.37. IR (thin film) ν_{max}: 3410, 3375, 3363, 2924, 2360, 2337, 1465, 1450, 1419, 1338, 1249, 887, 790 cm $^{-1}$. Elemental Analysis: calcd for $C_{11}H_{11}NSBr_2$: C 38.05 H, 3.17 N 4.03 S 9.22 Br 46.06, found C 38.42 H, 3.24 N 4.20 S 9.60 Br 45.19.



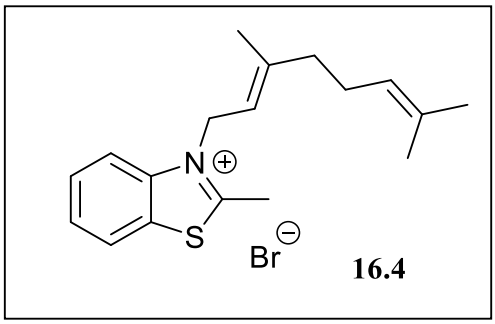
16.2

M.P 163- 164 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.94 (s, 3H), 3.47 (s, 3H), 4.36 (s, 1H), 5.03 (s, 1H), 5.58 (s, 2H), 7.70 (t, *J*=7.6 Hz, 1H), 7.79 (t, *J*=7.9 Hz, 1H), 7.95 (d, *J*=8.5 Hz, 1H), 8.32 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 19.10, 20.55, 55.70, 113.40, 116.78, 124.49, 128.68, 129.99, 138.41, 142.40, 177.37. IR (thin film) ν_{max}: 3410, 3375, 3363, 2924, 2360, 2337, 1465, 1450, 1419, 1338, 1249, 887, 790 cm $^{-1}$. Elemental Analysis: calcd for $C_{12}H_{14}NSBr$: C 50.88 H, 4.96 N 4.96 S 11.30 Br 28.23, found C 49.83 H, 5.24 N 4.80 S 11.14 Br 27.36.



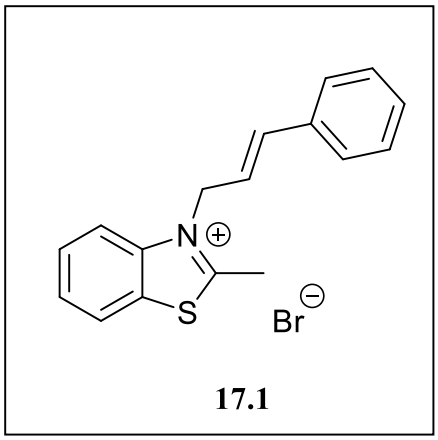
16.3

The crude solid used for Claisen rearrangement without any further purification.



16.4

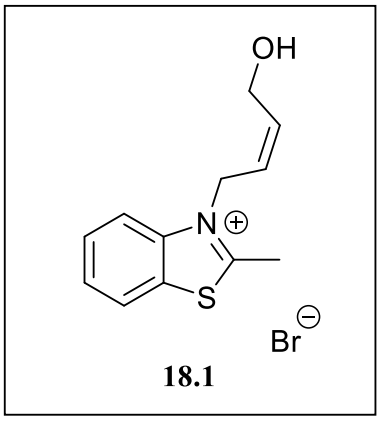
The crude solid used for Claisen rearrangement without any further purification.



17.1

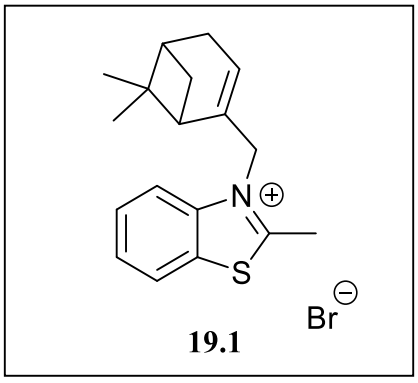
M.P 238 - 240 ^{0}C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) 3.41 (s, 3H), 3.59 (d, *J*=6.6 Hz, 2H), 5.87 (d, *J*=5.9 Hz, 2H), 6.33 (m, *J*=7.8 Hz, 1H), 6.77 (d, *J*=17.2, 15.8 Hz, 1H), 7.31 (m, *J*=7.0 Hz, 5H), 7.74 (t, *J*=7.6 Hz, 1H), 7.84 (t, *J*=7.8 Hz, 1H), 8.12 (d, *J*=8.4 Hz, 1H),8.24 (d, *J*=8.0 Hz,

1H); ^{13}C NMR (400 MHz, $CDCl_3$) 19.81, 50.67, 53.10, 116.78, 117.67, 124.49, 126.88, 128.85, 128.86, 130.99, 134.41, 136.40, 141.67, 176.98. IR (thin film) ν_{max}: 3375, 3294, 3263, 2924, 1672, 1430, 987, 952, 771, 744, 690, 675, 617 cm $^{-1}$. Elemental Analysis: calcd for $C_{17}H_{16}NSBr$: C 59.12 H, 4.63 N 4.05 S 9.27 Br 23.15, found C 58.77 H, 4.63 N 4.03 S 9.52 Br 23.01.



18.1

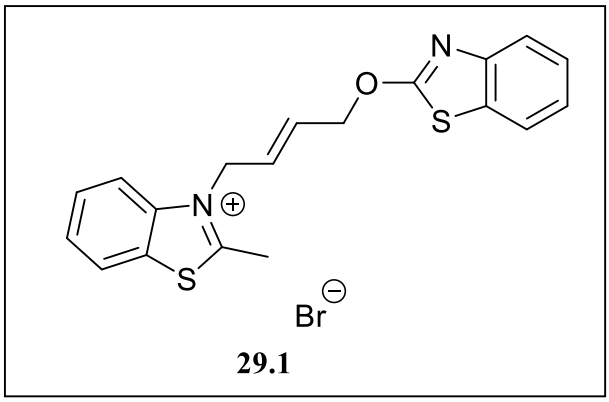
The crude solid used for Claisen rearrangement without any further purification.



19.1

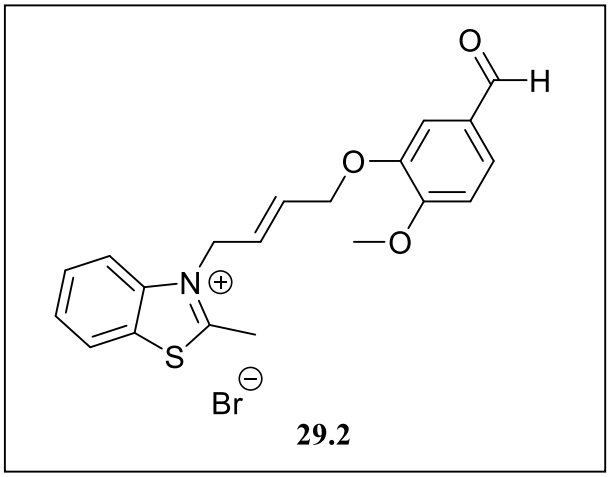
M.P 122 - 124 ^{0}C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) 0.83 (s, CH_3, 3H), 1.17 (d, J=8.9Hz, 2H), 1.29 (d, J=16.6 Hz, 1H), 1.31 (s, CH_3, 3H), 2.23 (q, J=17.9 Hz, 4H), 2.47 (m, J=4.4 Hz, 1H), 3.45 (s, CH_3, 3H), 3.47 (d, J=17.3 Hz, 1H), 5.04 (d, *J*=24.1 Hz, 1H), 5.47 (d, *J*=18.1 Hz, 2H), 7.70 (t, *J*=7.6 Hz, 1H), 7.79 (t, *J*=7.8 Hz, 1H), 7.86 (d, *J*=8.4 Hz, 1H), 8.33 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 1.01, 18.94, 21.02, 25.87, 31.11, 31.50, 38.32, 40.42, 43.69, 53.42, 54.46,

116.58, 120.63, 124.51, 128.61, 129.85, 139.41, 141.34, 178.61. IR (thin film) ν_{max}: 3228, 3178, 3055, 1678, 1600, 1543, 1505, 1465, 1438, 1411, 1375, 1315, 1211, 999, 833, 759 cm^{-1}. Elemental Analysis: calcd for $C_{18}H_{22}NSBr$: C 53.49 H, 6.05 N 3.85 S 8.81 Br 22.0, found C 53.73 H, 5.78 N 3.99 S 8.85 Br 22.19.



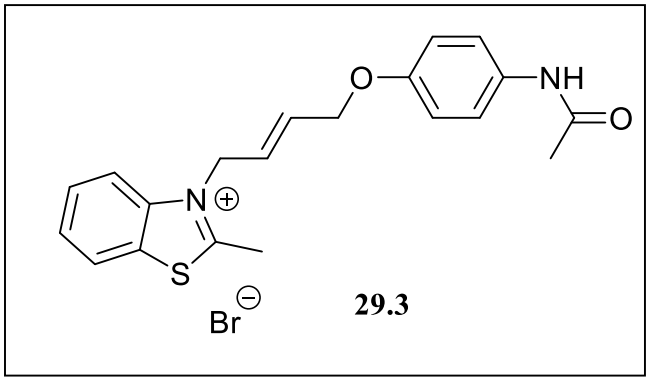
29.1

The crude solid used for Claisen rearrangement without any further purification



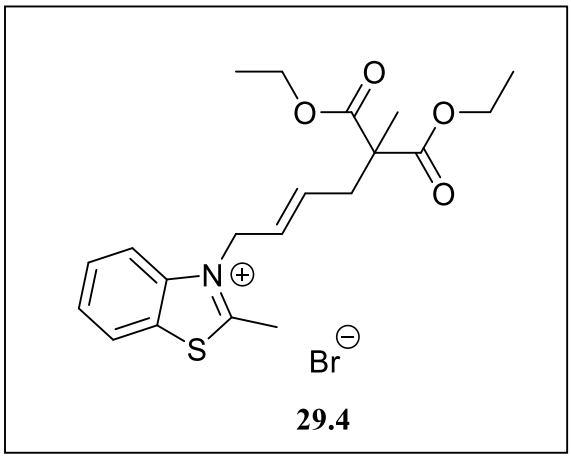
29.2

The crude semi solid used for Claisen rearrangement without any further purification.



29.3

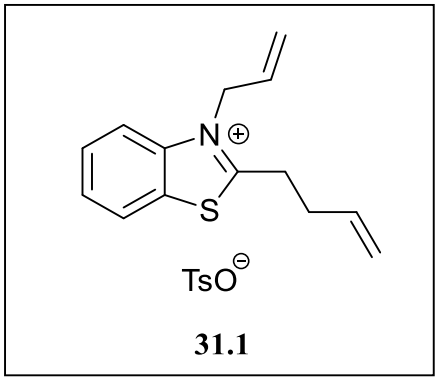
M.P 183 - 185 ^{0}C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) 1.11 (s, *3*H), 2.33 (s, 3H), 3.63 (d, *J*=4.1 Hz, 2H), 4.95 (d, *J*=5.1 Hz, 2H), 5.21 (qt, *J*=17.8, 5.5 Hz, 2H), 5.95 (d, *J*=9.0 Hz, 2H), 6.55 (d, *J*=9.2 Hz, 2H), 6.92 (t, *J*=7.4 Hz, 1H), 6.99 (t, *J*=7.3 Hz, 1H), 7.41 (d, *J*=8.4 Hz, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 8.92 (s, NH, *1*H); ^{13}C NMR (400 MHz, $CDCl_3$) 17.4, 24.0, 54.9, 69.7, 114.5, 119.3, 122.6, 124.5, 125.4, 129.7, 130.6, 130.8, 131.7, 132.4, 140.9, 153.7, 168.9, 174.2; IR (thin film) ν_{max}: 3411, 3375, 3228, 3178, 2068, 1705, 1658, 1543, 1505, 1465, 1438, 1411, 12555, 1015, 980, 751 cm $^{-1}$. Elemental Analysis: calcd for $C_{20}H_{21}N_2O_2SBr$: C 55.54 H, 4.86 N 6.84 S 7.40 Br 18.49, found C 53.35 H, 4.86 N 6.23 S 7.73 Br 18.31.



29.4

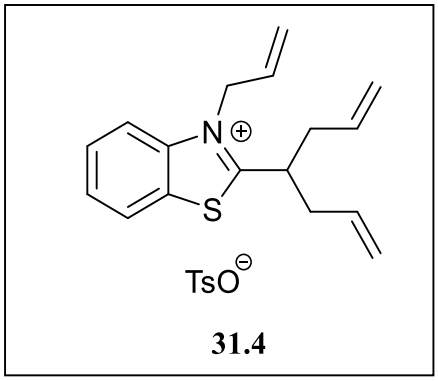
M.P 159 - 161 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.20 (t, *J*=7.2 Hz, 6H), 1.33 (s, 3H), 2.60 (d, *J*=4.6 Hz, 2H), 3.51 (s, 3H), 4.13 (q, *J*=6.8 Hz, 4H), 5.62 (t, *J*=4.2 Hz, 2H), 5.73 (t, *J*=4.2 Hz, 2H), 7.75

(t, *J*=7.7 Hz, 1H), 7.84 (t, *J*=7.7 Hz, 1H), 7.97 (d, *J*=8.5 Hz, 1H), 8.23 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 14.1, 17.4, 20.7, 42.9, 54.9, 55.6, 61.6, 119.3, 123.9, 125.4, 129.5, 129.7, 131.7, 132.4, 140.9, 175.4, 176.7; IR (thin film) ν_{max}: 3651, 3228, 3178, 2068, 1705, 1658, 1543, 1505, 1465, 1438, 1411, 1375, 1315 cm $^{-1}$. Elemental Analysis: calcd for $C_{20}H_{26}NO_4SBr$: C 52.73 H, 5.71 N 3.07 S 7.03 Br 17.55, found C 50.64 H, 5.48 N 3.03 S 7.21 Br 16.76.



31.1

Brown colored semi solid; ^{1}H NMR (400 MHz, $CDCl_3$) 2.30 (s, 3H), 2.64 (app quartet, *J*=7.4 Hz, 2H), 3.22 (t, *J*=7.8 Hz, 2H), 5.06 (d, *J*=10.2 Hz, 1H), 5.14 (d, *J*=17.1 Hz, 1H), 5.34 (d, *J*=10.6 Hz, 2H), 5.76 (m, *J*=10.3 Hz, 2H), 5.9 (ddt, *J*=16.9, 10.3, 6.5 Hz, 1H), 6.13 (ddt, *J*=17.1, 10.3, 6.5 Hz, 1H), 7.01 (d, *J*=8.2 Hz, 2H), 7.60 (d, *J*=8.2 Hz, 2H), 7.64 (t, *J*=7.8 Hz, 1H), 7.72 (t, *J*=7.8 Hz, 1H), 7.90 (d, *J*=8.4 Hz, 1H), 8.15 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 17.45, 21.20, 29.70, 39.08, 41.07, 51.92, 116.65, 119.88, 124.32, 125.75, 128.32, 128.40, 128.85, 129.00, 129.70, 132.52, 138.89, 140.86, 143.95, 176.78. Elemental Analysis: calcd for $C_{21}H_{23}NO_3S_2$: C 62.82 H, 5.73 N 3.49 S 15.95, found C 60.24 H, 6.79 N 2.98 S 10.20.



31.4

Dark brown semi solid; ^{1}H NMR (400 MHz, $CDCl_3$) 2.31 (s, 3H), 2.69 (app quartet, *J*=6.7 Hz, 4H), 4.25 (t, *J*=6.5 Hz, 1H), 5.01 (d, *J*=17.2 Hz, 1H), 5.09 (t, *J*=10.5 Hz, 2H), 5.31 (d, *J*=12.9 Hz, 1H), 5.34 (d, *J*=10.6 Hz, 2H), 5.76 (m, *J*=10.3 Hz, 4H), 6.13 (ddt, *J*=17.2, 10.5, 5.1 Hz, 1H), 7.05 (d, *J*=7.7 Hz, 2H), 7.69 (d, *J*=7.7 Hz, 2H), 7.64 (t, *J*=7.8 Hz, 3H), 7.726 (t, *J*=7.7 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 1H), 8.20 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 21.26, 29.70, 39.08, 41.07, 52.93, 117.87, 119.75, 120.29, 124.00, 126.01, 128.41, 128.68, 128.85, 129.56, 130.11, 132.52, 138.82, 141.03, 144.05, 184.25. Elemental Analysis: calcd for $C_{24}H_{27}NO_3S_2$: C 65.28 H, 6.12 N 3.17 S 14.51, found C 65.82 H, 6.58 N 2.90 S 13.69.

VII. References:

1. Claisen, L. Rearrangement of Phenyl Allyl Ethers in C-allylphenols. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157-3166.

2. (a) Martin-Castro, AM.; Tortosa, M. Claisen Rearrangements 2nd Ed. Paul, K and Gary, A. M, Eds.; Elsevier Ltd; Spain. **2014**, vol 5, pp *827-873*. (b) Gradl, N. S.; Trauner, D. The Claisen Rearrangement: Methods and Applications, M. Hiersemann and U. Nubbemeyer, Eds.; Wiley-VCH; Weinheim. **2007**, pp *367-398.* (c) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. Claisen Rearrangement of Allyl and Benzyl Alcohols by N,N-Dimethylacetamide Acetals. *Helv. Chim. Acta.* **1964**, *47*, 2425-2429; (d) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. Claisen Rearrangement of Allyl and Benzyl Alcohols with 1-Dimethylamino-1-Methoxyethene *Helv. Chim. Acta.* **1969**, *52*, 1030-1042.

3. (a) Fernandes, A. R.; Chowdhury, K. A.; Kattanguru, P. The Orthoester Johnson-Claisen Rearrangement in the Synthesis of Bioactive Molecules, Natural Products, and Synthetic Intermediates-Recent Advances. *Eur. J. Org. Chem.* **2014**, 2833-2871. (b) Langlois, Y. The Claisen Rearrangement: Methods and Applications, M. Hiersemann and U. Nubbemeyer, Eds.; Wiley-VCH; Weinheim. **2007**, pp *301-366.* (c) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. Simple Stereo Selective Version of the Claisen Rearrangement Leading to Trans Trisubstituted Olefinic Bonds. Synthesis of Squalene. *J. Am. Chem. Soc*. **1970**, *92*, 741-743.

4. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. The Ester Enolate Claisen Rearrangement. Stereochemical Control through Stereoselective Enolate Formation. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877; (b) Ireland, R. E.; Mueller, R. H. Claisen Rearrangement of Allyl Esters. *J. Am. Chem. Soc.* **1972**, *94*, 5897-5898.

5. (a) Hill, R. K.; Gilman, N. W. A Nitrogen Analog of the Claisen Rearrangement. *Tetrahedron Lett*. **1967**, *8*, 1421-1423. (b) McFarland, C.; McIntosh, M. C. The Claisen Rearrangement: Methods and Applications, M. Hiersemann and U. Nubbemeyer, Eds.; Wiley-VCH; Weinheim. **2007**, pp *117-210.* (c) Chai, Y.; Hong, S-P.; Lindsay, A.H.; McFarland, C.; McIntosh, M. C. New aspects of the Ireland and related Claisen Rearrangements. *Tetrahedron.* **2002**, 58, 2905-2928.

6. (a) Ireland, R. E.; Wipf, P.; Xiang, J. N. Stereochemical Control in the Ester Enolate Claisen Rearrangement. Chair like Vs Boat like Transition-State Selection. *J. Org. Chem.* **1991**, *56*, 3572-3582; (b) Shea, K. J.; Stoddard, G. J.; England, W. P.; Haffner, C. D. Origin of the Preference for the Chair Conformation in the Cope Rearrangement. Effect of Phenyl Substituents on the Chair and Boat Transition States. *J. Am. Chem. Soc*. **1992**, *114*, 2635-2643; (c) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. Origins of Boat or Chair Preferences in the Ireland−Claisen Rearrangements of Cyclohexenyl Esters: A Theoretical Study. *J. Org. Chem.* **2003**, *68*, 572-577.

7. Ireland, R. E.; Willard, A. K. Claisen Rearrangement of N-Allylketene O, N-Acetals. *J. Org. Chem.* **1974**, *39*, 421–424.

8. Baldwin, J. E.; Walker, J. A. Competing [1, 3] and [3, 3]-Sigmatropic Rearrangements of Electron-Rich Olefins. *J. Am. Chem. Soc.* **1974**, *96*, 596–597.

9. Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. Asymmetric Induction in the Claisen Rearrangement of N-Allylketene N,O-Acetals. *J. Am. Chem. Soc*. **1985**, *107*, 443-448.

10. Kurth, M. J.; Decker, O. H. W. Enantioselective Preparation of 3-Substituted 4-Pentenoic Acids via the Claisen Rearrangement. *J. Org. Chem.* **1985**, *50*, 5769-5775.

11. Waetzig, S. R.; Tunge, J. Regio- and Diastereoselective Decarboxylative Coupling of Heteroaromatic Alkanes. *J. Am. Chem. Soc*. **2007**, *129*, 4138-4139.

12. Kljajic, M.; Puschnig, G. J.; Weber, H.; Breinbauer, R. Additive free Pd-catalyzed α-allylation of Imine containing heterocycles. *Org. Lett*. **2017**, *19*, 126-129.

13. Silvana S. Dormi (**2011**) Studies directed toward the synthesis of sclerophytin A & novel N-based rearrangements (Doctoral Dissertation).

14. Mumm, O.; Hinz, H.; Diederichsen, J. N-Methyl-2-Benzothiazolone Methide and the N-3,3-Trimethyl-2-Indolinone Methide Ordinarily Designated as the "Fischer Base. *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 2107-2120.

15. Owen, J. R. Isolation of Monomeric Methylene Bases Derived from Benzothiazolium Quaternary Salts. *Tetrahedron Lett.* **1969**, 10, 2709-2712.

16. Wang, J.; Tong, X.; Xie, X.; Zhang, Z. Rhodium-Catalyzed Activation of C (sp^3)-X (X = Cl, Br) Bond: An Intermolecular Halogen Exchange Case. *Org. Lett*. **2010**, *12*, 5370-5373.

17. Baughman, W. T.; Sworen, C. J.; Wagener, K. B. The facile preparation of alkenyl metathesis synthons. *Tetrahedron.* **2004,** *60*, 10943–10948.

18. Li, X-W.; Ear, A.; Roger, L.; Riache, N.; Deville, A.; Nay, B. Bio-Inspired Formal Synthesis of Hirsutellones A-C Featuring an Electrophilic Cyclization Triggered by Remote Lewis Acid-Activation. *Chem. Eur. J*. **2013**, *19*, 16389-16393.

19. Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S. J.; Butsugan, Y. Preparation and Some Reactions of Allylic Indium Reagents. *J. Org. Chem.* **1991**, *56*, 2538–2542.

20. Spiccia, D. N.; Solyom, S.; Woodward, P. C.; Jackson, W.; Robinson, J. A. Cross-Metathesis of Bronsted Acid Masked Alkenylamines with Acrylates for the Synthesis of Polyamide Monomers. *J. Org. Chem*. **2016**, *81*, 1798−1805.

21. Bandini, M.; Cozzi, G. P.; Licciulli, S.; Umani-Ronchi, A. A Cross Metathesis Based Protocol for the Effective Synthesis of Functionalized Allyl Bromides and Chlorides. *Synthesis***,** **2004**, 3, 0409–0414.

22. (a) Lafaye, K.; Bosset, C.; Nicolas, L.; Guerinot, A.; Cossy, J. Beyond catalyst deactivation: cross-metathesis involving olefins containing N-heteroaromatic. *Beilstein J. Org.*

Chem. **2015**, *11*, 2223-2241. (b) Santos, G. A.; Bailey, A.G.; Santos, N-D. E.; Fogg, D. E. Overcoming Catalyst Decomposition in Acrylate Metathesis: Polyphenol Resins as Enabling Agents for PCy3-Stabilized Metathesis Catalysts. *ACS Catal*. **2017,** *7*, 3181−3189.

23. (a) Vekariya, H. R.; Liu, R.; Aube, J. A Concomitant Allylic Azide Rearrangement/ Intramolecular Azide-Alkyne Cycloaddition Sequence. *Org. Lett*. **2014**, *16*, 1844−1847. (b) Zhao, M.; Yang, H.; Li, M-M.; Chen, J.; Zhou, L. N-Heterocyclic Carbene Catalyzed Intramolecular Acylation of Allylic Electrophiles. *Org. Lett*. **2014**, *16*, 2904−2907.

24. Dondoni, A.; Marra, A. Thiazole-Mediated Synthetic Methodology. A. *Chem. Rev*. **2004**, *104*, 2557-2600.

25. Chikashita, H.; Ishibaba, M.; Ori, K.; Itoh, K. General Reactivity of 2-Lithiobenzothiazole to Various Electrophiles and the Use as a Formyl Anion Equivalent in the Synthesis of α-Hydroxy Carbonyl Compounds. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 3637-3648.

26. Corey, E. J.; Boger, D. L. Benzothiazoles as Carbonyl Equivalents. *Tetrahedron Lett*. **1978**, *19*, 5-8.

28. Legrel, P.; Baudy-Floch, M.; Robert, A. A one-pot synthesis of 3alpha-halohydrazides from alpha, alpha-dicyano epoxies. *Synthesis.* **1986,** 306-308.

29. Barre, C.; Le Grel, P.; Robert, A.; Baudy-Floch, M. Design and Synthesis of a New Series of Peptide Analogues: the Hydrazinopeptides. *J. Chem. Soc., Chem. Commun*. **1994**, 607.

30. Shvaika, N. Recyclization reactions of heterocycles. XVIII. Synthesis and recyclizations of thiazolium and benzothiazolium salts. *Himia geterocikliceskih soedinenij*. **1976**, *5*, 635-640.

31. Bastug, G.; Eviolitte, C.; Marko, I. E. Functionalized Orthoesters as Powerful Building Blocks for the Efficient Preparation of Heteroaromatic Bicycles. *Org. Lett*. **2012**, *14*, 3502-3505.

32. Babu, K. R.; Zhu, N.; Bao, H. Iron-Catalyzed C-H Alkylation of Heterocyclic C-H Bonds. *Org. Lett*. **2017**, *19*, 46-49.

33. Patel, U. N.; Jain, S.; Pandey, D. K.; Gonnade, R. G.; Vanka, K.; Punji, B. Mechanistic Aspects of Pincer Nickel (II)-Catalyzed C–H Bond Alkylation of Azoles with Alkyl Halides. *Organometallics*. **2018,** *37*, 1017−1025.

D. Conclusion

Natural product is a macromolecule produced by living organisms, and can be prepared from chemical synthesis. Natural product often possess a biological benefit to treat unmet medical condition. Natural product is a challenging synthetic target involving numerous complex organic transformations. In this work, the linear synthesis of C29-C34 moiety of fragment A of the Antascomicin B was highlighted through chemical reactions include an Delis Alder reaction, asymmetric transfer hydrogenation (ATH), epoxide ring opening reactions. Our asymmetric synthetic strategy designed and established for scale up from commercially available starting material. The synthetic route was established to achieve asymmetric compound in gram scale by more efficient and atom economic with compare to the previously developed method.

Carbon-carbon bond formation is the important transformation in organic synthesis. Since the Claisen rearrangement, discovered various research groups drawn attention to make various medication for carbon-carbon bond formation. In this work, we describes novel methodologies of preparing 2-butenyl benzothiazole derivatives using aza-Claisen rearrangement, through N, S-ketene acetals intermediates. The precursor N-allyl-N, S-ketene acetals were prepared in situ from the reaction of N-allyl benzothiazolium salts. N-allyl benzothiazolium salts synthesized by simply alkylated 2-methyl benzothiazole with various allyl bromide derivatives. Despite of the traditional approaches, our proposed synthetic methodology of N, S-ketene acetals that requires only weak base, possesses broad functional group compatibility, and require no cryogenic conditions.