SYNTHETIC STUDIES TOWARDS TRICHODERMAMIDE B: EXPEDIENT SYNTHESIS ENABLED BY ARENE OXIDE EQUIVALENTS

BY

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THESIS

Submitted in partial fulfillment of the requirements
for the degree of Master of Science in Chemistry
In the Graduate College of the
University of Illinois at Urbana-Champaign, 2015

Urbana, Illinois

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ABSTRACT

Trichodermamide B, isolated from the marine fungus *Trichoderma virens* in 2003, is a potent anti-cancer agent and with complex molecular architecture. It is hypothesized herein that this molecule may be derived in nature from phenylalanine *via* a benzene oxide intermediate. Utilizing a bioinspired strategy, synthetic studies towards trichodermamide B have been conducted utilizing arene oxide equivalents as key synthetic intermediates. Notable synthetic transformations include alkylation with a novel, α–bromo oximoester electrophile and allylic bromination of an advanced, spirocyclic intermediate. This strategy has enabled access to advanced intermediates and should afford the natural product in far fewer steps than previously reported syntheses of this compound. Once complete, this concise synthetic strategy should afford enough material to conduct mechanism of action studies to uncover the origin of trichodermamide B's impressive biological activity.

ACKNOWLEDGEMENTS

I would like to thank my adviser, Professor David Sarlah, for his encouragement, advice, and support. Without his training this work would not have been possible. I would also like to thank Carrie Levinn for her significant intellectual and experimental contributions to this project. I would like to thank the members of Sarlah group for their advice and support. Finally, I would like thank the University of Illinois at Urbana-Champaign for the space and funding to make this research possible.

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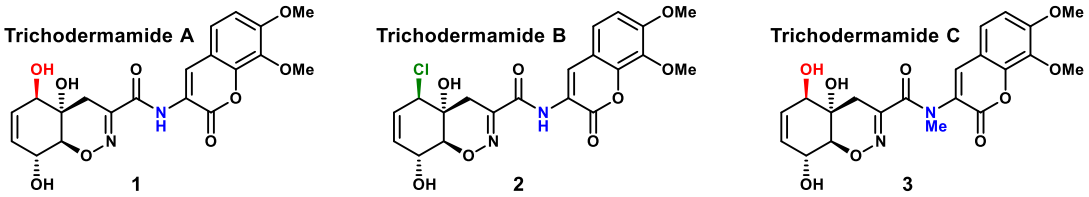
Chapter 1: Introduction

Trichodermamides

The trichodermamides constitute a small family of dipeptide, fungal-derived natural products. Trichodermamides A and B were first isolated from the marine fungus *Trichoderma virens* in 2003.[1] Five years later trichodermamide C was isolated from the terrestrial fungus *Eupenicillium* sp.[2] These compounds exhibit significant structural homology, and differ only about substitution at two positions (Figure 1).

Figure 1. *The Trichodermamide Family.*



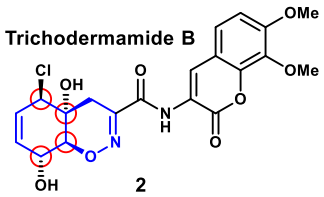
At the time of their isolation, trichodermamides A and B were tested for biological activity. Trichodermamide B exhibits significant cytotoxicity against HCT-116 human colon carcinoma, achieving an IC_{50} value of 0.32 μg/mL. Additionally, trichodermamide B displayed MIC values of ca. 15 μg/mL against amphotericin-resistant *C. albicans*, methicillin-resistant *S. aureus*, and vancomycin-resistant *E. faecium*.[1] This promising biological activity was not shared by trichodermamide A, which was completely inactive in these assays. Thus, it is clear that the chloride functional group in trichodermamide B is important for its biological activity.

Upon isolation trichodermamide C was also tested against HCT-116 human colon carcinoma cells due to its structural homology to trichodermamide B, and it displayed an IC_{50} value of 0.68 μg/mL.[2] This implies that substitution about the amide nitrogen atom may also be important for biological activity. Additionally, substitution at the amide nitrogen may enable an alternative mechanism of action than is exhibited by trichodermamide B.

Neither the mechanism of action of trichodermamide B nor trichodermamide C is known at this point. Knowledge of the mechanism of action can assist in the rational design of analogues that are more potent, more selective, or less toxic.[3,4] Alternatively, understanding of a natural product's mechanism of action can sometimes unveil unanticipated applications.[5] Accordingly, undertaking such studies of trichodermamide B, the most cytotoxic member of the trichodermamide family, could prove fruitful. Unfortunately, no reported synthesis has yet to achieve gram quantities of this natural product to enable these studies.

The key to synthesize large amounts of a particular compound is often to design a synthetic strategy which reduces the step count as much as possible. However, attempting to synthesize trichodermamide B rapidly represents a significant synthetic undertaking. The most challenging feature of this molecule is the 1,2-oxazadecaline core which is substituted with four, contiguous stereogenic centers (Figure 2).

Figure 2. *Structural features of trichodermamide B.*



In contrast the rest of the molecule can be synthesized in three steps utilizing a known procedure and can be appended to the oxazadecaline core in an amide coupling reaction.[6] Thus, if a concise strategy towards the oxazadecaline core could be developed, perhaps large amounts of this natural product could be synthesized to enable mechanism of action studies.

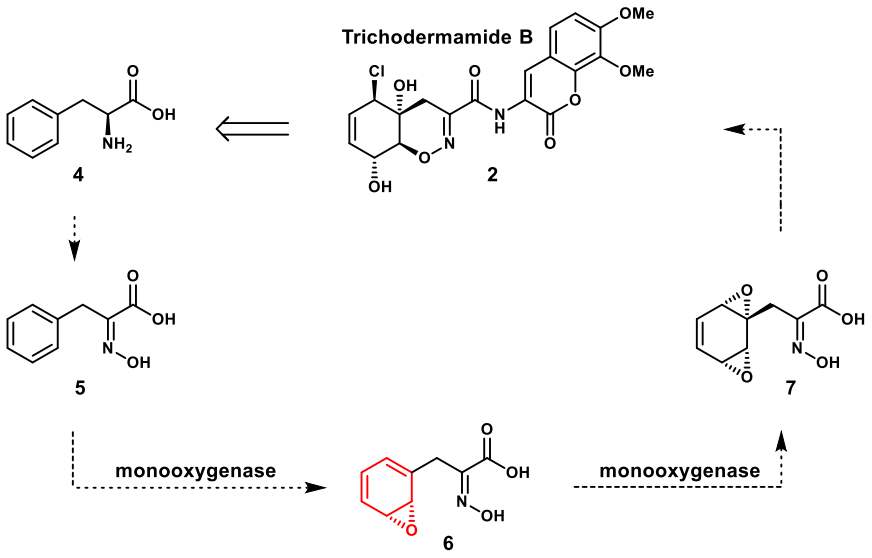
Biosynthetic Hypothesis

Before a retrosythetic strategy was developed, biosynthetic hypotheses of trichodermamide B were examined. Although the biosynthesis of trichodermamide B is unknown, an educated

biosynthetic proposal may still be valuable as it may suggest how nature is able to synthesize the fully substituted oxazadecaline core.

It is possible that trichodermamide B is derived from phenylalanine in nature. Oxidation of amine **4** would give oxime intermediate **5**. Trichodermamide B is a fungal-derived natural product. It is known that fungi possess monooxygenases capable of directly epoxidizing aromatic rings.[7] Direct epoxidation of arene **5** could afford arene oxide **6**. Subsequent epoxidation utilizing another monooxygenase could yield diepoxide **7.** Nucleophilic epoxide opening by the oxime moiety and nucleophilic epoxide opening by a chloride ion could furnish the fully substituted oxazadecaline core (Figure 3).

Figure 3. *Biosynthetic hypothesis.*



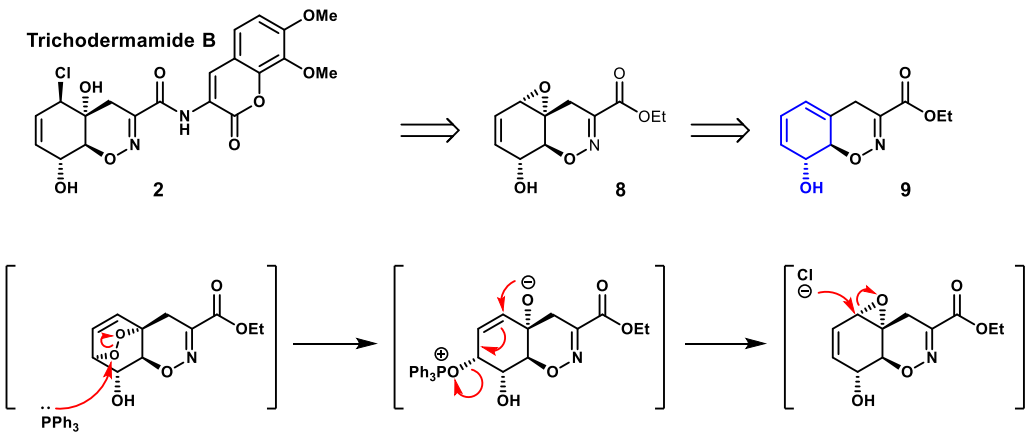
Nature may be able to synthesize trichodermamide B rapidly because direct epoxidation of an aromatic ring gives access to a versatile, arene oxide intermediate which can be converted to the fully substituted oxazadecaline core in just a few synthetic manipulations. Unfortunately, attempts to copy this exact strategy would likely not succeed. The direct epoxidation of aromatic rings remains an elusive if not impossible transformation in the flask. Additionally, attempts to

utilize traditional epoxidation conditions on arene oxide **6** would likely result in selective epoxidation of the disubstituted olefin in the presence of the trisubstituted olefin. However, utilizing similar intermediates and a similar overall strategy may enable an expedited synthesis of trichodermamide B.

Retrosynthetic Analysis

A retrosynthetic strategy which takes inspiration from the biosynthetic hypothesis is presented. The oxazadecaline core could be derived from arene oxide equivalent diene **9** (Figure 4).

Figure 4. *Retrosynthetic analysis.*

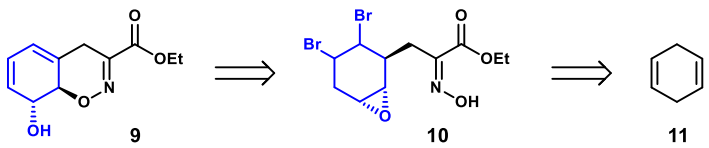


Although traditional epoxidation conditions of this compound would likely result in epoxidation of the disubstituted olefin, literature precedent suggests that the overall transformation of **9** to **8** may be possible. First a hydroxyl-directed hetero Diels–Alder reaction could give an endoperoxide with the displayed facial selectivity.[8-10] Subsequent opening of the endoperoxide moiety with triphenylphosphine would afford a Zwitter ionic intermediate. S_N2' attack by the resulting alkoxide would release triphenylphosphine oxide and afford allylic epoxide intermediate **8**.[11,12] In simple systems opening of an endoperoxide by triphenylphosphine has been shown to yield desired trisubstituted epoxide preferentially to disubstituted epoxide.[13] This may be due to

differences in steric environment on each side of the endoperoxide. Nucleophilic epoxide opening of **8** by a chloride ion would result in the formation of the fully substituted oxazadecaline core.

This strategy would result in rapid formation of the most challenging portion of the natural product. If this cascade sequence is synthetically viable, the challenge of synthesizing trichodermamide B is reduced to uncovering efficient conditions to synthesize key, arene oxide equivalent diene **9**. It is this intermediate that will enable the cascade sequence to furnish the fully substituted oxazadecaline core with correct relative stereochemistry. Diene **9** could be synthesized from **10** by elimination of dibromide and nucleophilic epoxide opening by the oxime (Figure 5).

Figure 5. *Retrosynthesis of diene* ***9****.*



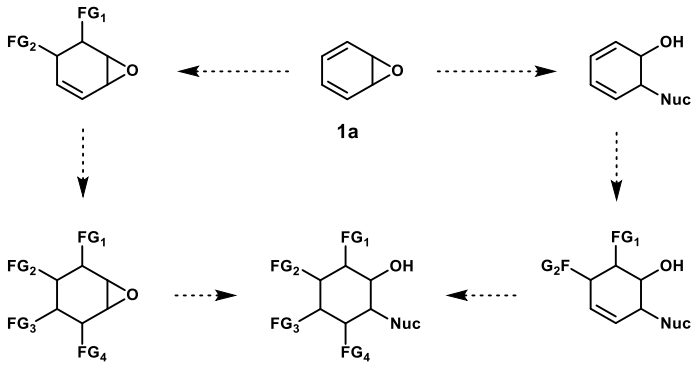
Intermediate **10** could be synthesized from 1,4-cyclohexadiene **11** *via* alkylation and subsequent olefin functionalization reactions.

In order to contextualize some of the advantages and disadvantages inherent to arene oxide chemistry, a short review on the topic is presented.

Chapter 2: Arene Oxides

Arene oxides, the formal epoxidation product of aromatic rings, are structures with great potential for simplifying synthetic endeavors. These structures contain epoxides and olefins, two of the most versatile functional groups in organic chemistry. If traditional reactivity of epoxides and olefins could be capitalized upon, these substrates could be rapidly converted into a diverse array of highly functionalized products. Therefore, the use of substrates of this type has the potential to streamline the synthesis of complex products by rapid introduction of functionality (Figure 6).

Figure 6. *Potential synthesis of highly functionalized products via arene oxides.*



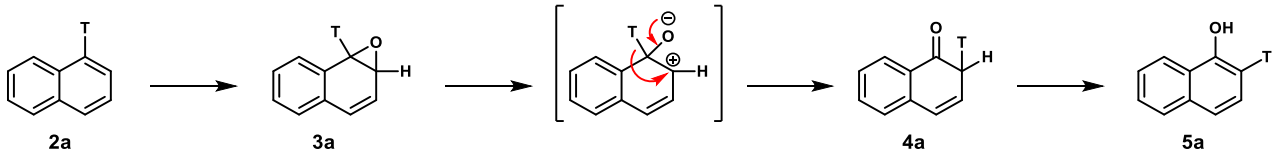
Unfortunately, much of the traditional reactivity of olefins and epoxides is inaccessible to arene oxides at this time. Many arene oxides are unstable with half-lives on the order of minutes and rapidly undergo the NIH-shift to form the corresponding phenol products.[14] In order to understand how the NIH-shift might limit applications of arene oxides in synthesis as well as to understand arene oxide behavior in biological systems, significant focus has been appropriated into understanding the mechanism of the NIH-shift.

NIH-Shift

The first clue of the NIH-shift mechanism was unveiled when tritiated naphthalene 1,2-oxide **2a** was isolated as a product of the reaction between 1-T-naphthalene **1a** and hepatic

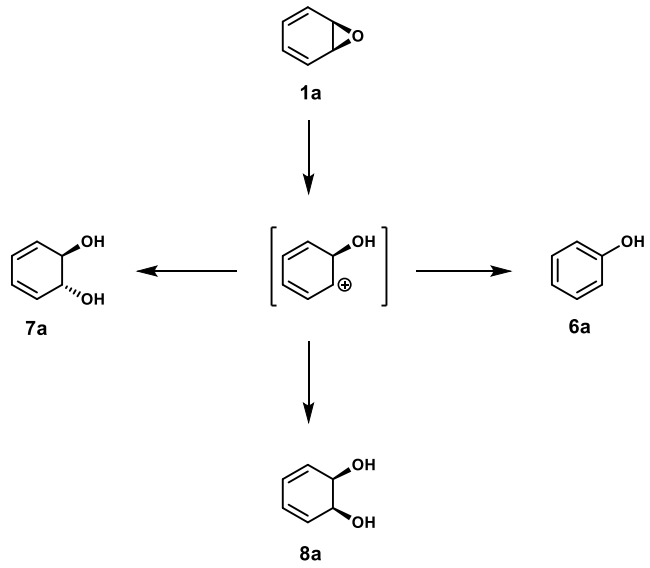
monoxygenases. Arene oxide **2a** was stable enough to be characterized. Addition of dilute acid effected its conversion to 2-T-1-naphthol **5a**. During this transformation the tritium had migrated from the 1 to the 2 position of the naphthol ring system. From this information it was postulated that conversion occurred *via* first formation of an ionic intermediate followed by collapse to form a ketone and an accompanying 1,2-shift. Tautomerization would lead to the observed phenol product (Figure 7).[14,15]

Figure 7. *Proposed mechanism of the NIH-shift.*



If the proposed mechanism of the NIH-shift is operative, a number of side products stemming from this pathway could be imagined. For example, from the carbocation intermediate derived from benzene oxide **1a**, either an NIH-shift could occur to afford phenol **6a**, or nucleophilic attack by water could occur from either face to give *trans*-diol **7a** or *cis*-diol **8a** (Figure 8).

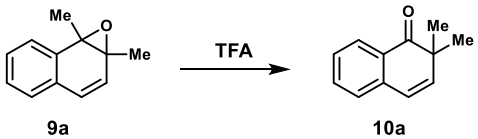
Figure 8. *Potential reaction pathways from proposed NIH-shift intermediate.*



Indeed, these three products were observed under neutral conditions from benzene oxide. The product distribution also supported this proposed mechanism. Total conversion was observed with 75% phenol product, 18% *trans*-diol product, and 7% *cis*-diol product.[16] The intramolecular NIH-shift product would be expected to dominate both thermodynamically and kinetically. This is because the product is aromatic, and the reaction leading to this product is intramolecular as opposed to competing intermolecular pathways. *Trans*-diol **7a** was formed preferentially to *cis*-diol **8a** due to steric considerations.

Further evidence for this mechanism has been collected in reactions where the migrating group is not hydrogen. A methyl group has also been shown to undergo a 1,2-shift in a similar manner to afford a ketone product which cannot isomerize to the corresponding phenol.[14] Generally, in these cases more forcing conditions were required to effect the transformation since the thermodynamic driving force of aromatization was not present (Figure 9).[17]

Figure 9. *Alternative migrating group in NIH shift.*

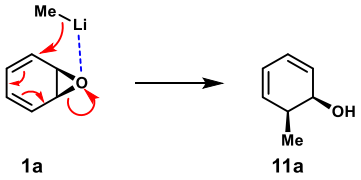


Reactivity of Arene Oxides

Arene oxides have been shown to act as competent electrophiles for several classes of nucleophiles. In general nucleophilic attack occurs most efficiently for polarizable nucleophiles; however, this is not always the case.

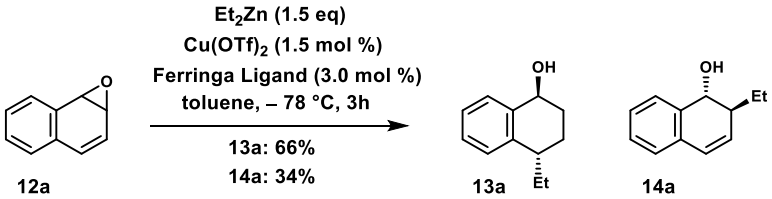
Methyl lithium reacted with benzene oxide **1a** to afford allylic alcohol **11a** in good yields. Attack in this case occurred in a 1,6 manner and give the chelation controlled *cis*-product (Figure 10).[18]

Figure 10. *1,6 – addition of methyllithium onto benzene oxide.*



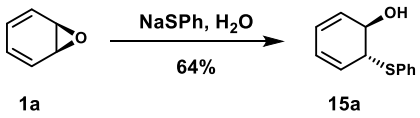
Unfortunately, the nucleophilic attack of organometallic reagents onto arene oxides has not proved to be a broadly applicable strategy. No organometallic nucleophiles other than methyllithium or dimethylmagnesium had been shown to attack benzene oxide to form alkylated products until 2001. At this time it was reported that arene oxides can be opened by use of diethyl zinc in the presence of appropriate additives. The selectivity for this reaction is orthogonal to methyllithium as the addition led to the formation of *anti*-addition products (Figure 11).[19]

Figure 11. *Reaction of diethyl zinc with naphthalene-1,2-oxide.*



Polarizable nucleophiles tend to react more efficiently with arene oxides than do non-polarizable nucleophiles. Accordingly, thiolates have been shown to attack arene oxide substrates quite smoothly. Unlike methyllithium, direct S_N2 attack at the epoxide operates in these cases (Figure 12).[20]

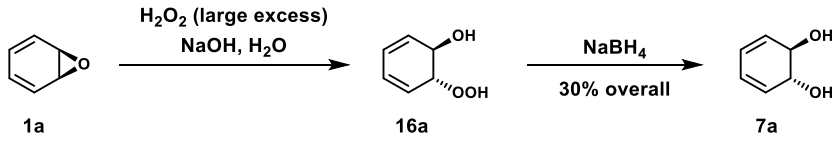
Figure 12. *S_N2 attack on benzene oxide by thiolate.*



In contrast to thiolate reactivity with arene oxides, less polarizable species such as alkoxides do not readily react with benzene oxide to form nucleophilic substitution product. In

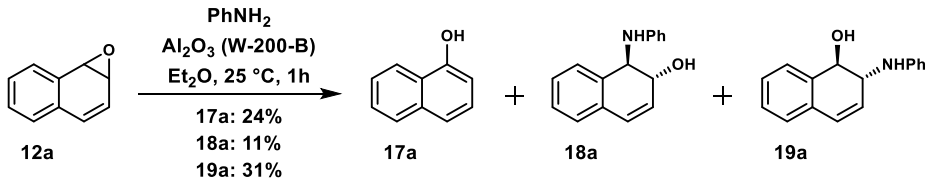
nucleophilic substitution reactions of arene oxides, a competition exists between the attack of the nucleophile and the NIH-shift pathway. Less polarizable nucleophiles are not as competent as polarizable nucleophiles to compete in this process. Thus, alkoxide nucleophiles do not react efficiently with arene oxides to form nucleophilic substitution product. However, conditions have been established to effect this transformation in low yields. Deprotonation of hydrogen peroxide led to the formation of a much more polarizable oxygen nucleophile than hydroxide. Treatment of benzene oxide **1a** with this species followed by reduction with sodium borohydride generated *trans*-diol **7a** in 30% yield (Figure 13).[21]

Figure 13. *Synthesis of diol **7a**.*



Many nitrogen nucleophiles are also unreactive towards arene oxides. For example treatment of benzene oxide with the non-polarizable sodium amide in liquid ammonia did not result in formation of an aminoalcohol product.[22] Azides, however, are very polarizable and readily react with benzene oxide to form substituted products. For example sodium azide reacted with benzene oxide to give 55% yield of the epoxide opened product.[14] In an attempt to broaden the scope of nucleophiles that can successfully attack arene oxides, Posner showed that reaction of less polarizable nucleophiles with arene oxides can be aided by addition of basic alumina. This did still result in significant aromatization however (Figure 14).[23]

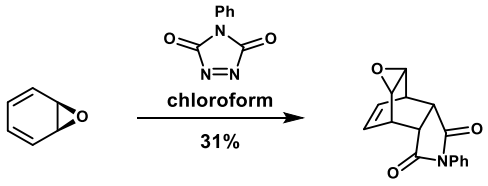
Figure 14. *Basic alumina increases nitrogen nucleophilicity towards arene oxides.*



Alternatively to NIH-shift pathway, deoxygenation pathways to form the parent aromatic species can occur from arene oxides under a variety of conditions. It is known that pyridine, thiourea, triphenylphosphine, rhodium catalysts, chromium catalysts, and others are able to successfully effect this transformation.[14] Deoxygenation in this context is of little synthetic significance, however. Destroying such a useful functional handle to afford a product which could likely be easily synthesized by other methods is likely not the most efficient synthetic strategy.

Arene oxides are known to undergo cycloaddition reactions with activated dienophiles. Benzene oxide has been shown to undergo a Diels–Alder reaction with singlet oxygen.[24] The resulting endoperoxide is crystalline and isolable. Upon dissolving in chloroform and heating to 45 ˚C, quantitative rearrangement to benzene trioxide was observed. Benzene oxide has also been shown to undergo a Diels–Alder reaction with *n*-phenyl-1,2,4-triazoline-3,5-dione (Figure 15).[25]

Figure 15. *Diels–Alder selectivity.*



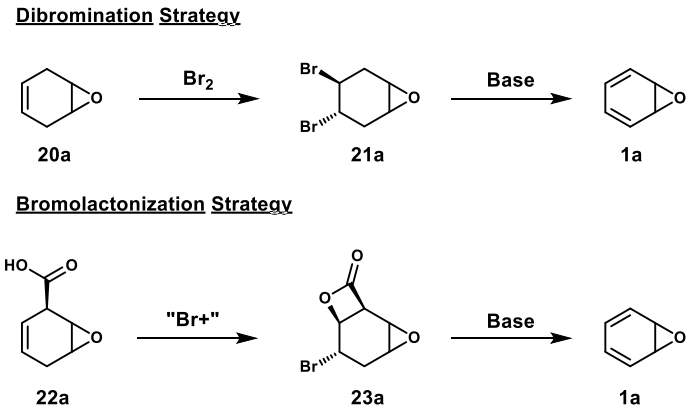
The selectivity of this reaction may be counterintuitive and is in contrast to Diels–Alder reactions of other allylic-oxygen-containing dienes. Theoretical considerations can help explain the observed selectivity. *Ab initio* calculations showed that there is no significant difference in π–density on either side of the ring. Additionally, in the four highest occupied molecular orbitals, not much electron density resided on oxygen. Thus, there was not an electronic bias to direct an incoming dienophile towards either face of the diene. In contrast, there was a steric bias stemming from interactions with the epoxide itself. Thus reaction occurred at the less sterically hindered side of the diene. Other examples of Diels–Alder reactions of arene oxides are also known.[26-28]

Synthesis of Arene Oxides

The syntheses of arene oxides which have found the most widespread application generally fall into one of two categories. Either an epoxide is synthesized followed by elimination to form a diene, or a diene is synthesized followed by S_N2 attack of an alkoxide to form the arene oxide.

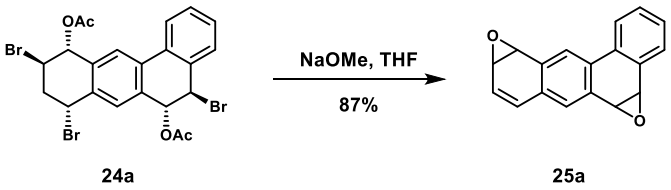
Utilizing the first strategy, elimination of dibromide species or bromolactone species have been shown to afford the corresponding arene oxides.[29, 30] Dibromide species are typically synthesized from the corresponding alkene. Subsequent treatment with base affords the arene oxide. Bromolactone species are formed from the corresponding β,γ–unsaturated acid. Bromolactonization followed by treatment with base has been shown to work in synthesizing a variety of arene oxide (Figure 16).[31]

Figure 16. *Elimination strategies towards arene oxides.*



The second type of strategy relies on formation of the epoxide in the final step. This is often achieved from the corresponding bromohydrin or bromohydrin acetate species. Formation of the alkoxide under basic conditions followed by S_N2 release of the bromide affords the epoxide. This strategy has been widely utilized in arene oxide synthesis (Figure 17).[32, 33] Alternatively, 1,2-diols can be used. Tosylation of one of the alcohols followed by S_N2 attack leads to the arene oxide product.[14]

Figure 17. *Synthesis of arene oxide through bromohydrin precursor.*

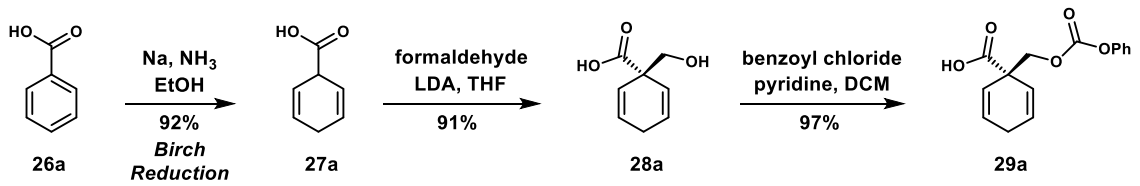


Applications of Arene Oxides in Synthesis

In 1978, Professor Bruce Ganem's group was the first to use an arene oxide intermediate in the total synthesis of a natural product, senepoxide **36a**. Highlights of this synthesis include development of new methodology towards generation of arene oxides and a hetero-Diels–Alder reaction of an arene oxide intermediate.[31] The specifics of this synthesis are detailed as follows.

A Birch reduction of benzoic acid **26a** afforded 1,4-dihydrobenzoic acid **27a**. Formation of the corresponding dianion with LDA followed by treatment with cracked formaldehyde gave access to β–hydroxylacid **28a** in good yield. Conversion of the alcohol **28a** to carbonate **29a** was accomplished with benzoyl chloride and pyridine (Figure 18).

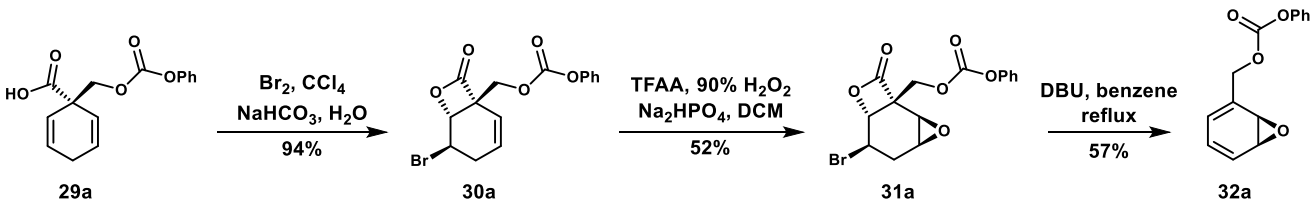
Figure 18. *Synthesis of carbonate **29a**.*



It was proposed that β,γ–unsaturated acid **29a** could function as a precursor to the corresponding arene oxide. It was envisioned that this transformation could be accomplished in a three-step procedure. Bromolactonization of acid **29a** with bromine in a biphasic mixture of aqueous sodium bicarbonate and carbon tetrachloride furnished bromolactone **30a** in high yields. Epoxidation of this substrate, however, was more challenging. Treatment with trifluoroacetic

anhydride and 90% hydrogen peroxide furnished epoxide **31a** in acceptable yields. A one-pot elimination procedure afforded desired arene oxide **32a** (Figure 19).

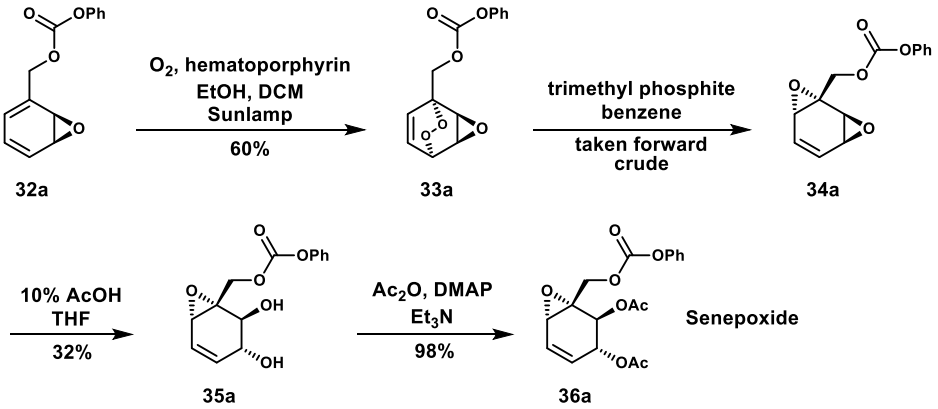
Figure 19. *Synthesis of arene oxide* ***32a.***



The transformation of β,γ–unsaturated acids to the corresponding arene oxides represented a new disconnection in organic synthesis and gave a new platform for the synthesis of alkyl-substituted arene oxides.

A Diels–Alder reaction between arene oxide **32a** and singlet oxygen generated endoperoxide **33a**. Cleavage of this endoperoxide with trimethyl phosphite afforded diepoxide **34a**. Selective hydrolysis proceeded in low yields to give diol **35a**. Finally, acetate protection furnishes Senepoxide **36a** (Figure 20).

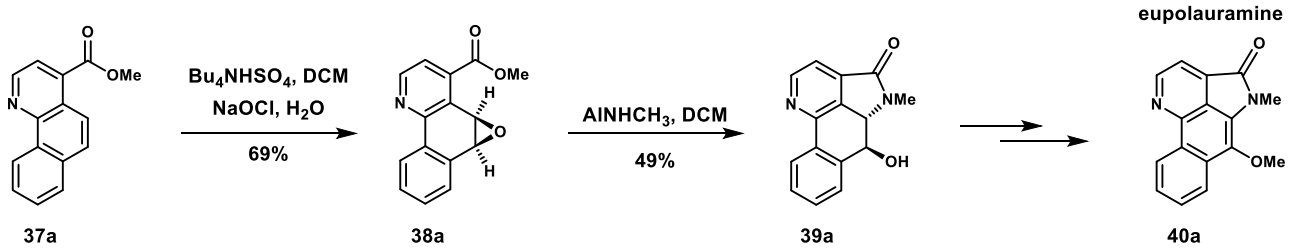
Figure 20. *Synthesis of Senepoxide* ***36a.***



In 1982, Weinreb used arene oxide formation and opening as the key steps in his synthesis of Eupolauramine.[34] Formation of the arene oxide was effected by direct epoxidation of arene **37a**. This is possible because of the reduced aromatic character of polyaromatic species. Intramolecular

epoxide opening gave access to the lactam intermediate **39a** which in just a few synthetic manipulations was converted into eurolauramine **40a** (Figure 21).

Figure 21. *Synthesis of eupolauramine* ***40a****.*



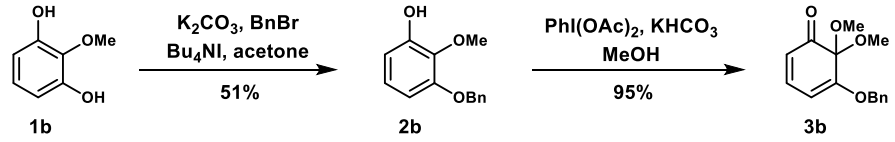
Chapter 3: Previously Reported Syntheses

It is notable that the Sarlah group is not the first to begin a synthetic program towards trichodermamide B. The synthesis of this molecule has been reported three time in the literature. The first reported synthesis was by the Zakarian group at the University of California at Santa Barbara in 2008.[35] Trichodermamide B was synthesized racemically in twenty-three longest linear steps from commercially available starting materials.

Zakarian Group

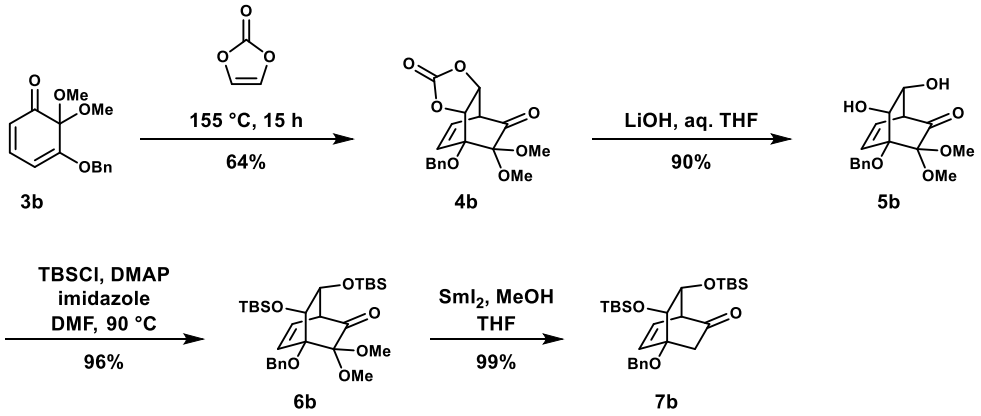
The synthesis began with the relatively expensive but commercially available 2-methoxy-1,3-benzenediol **1b**. Benzyl protection of one of the phenol groups affords **2b** in moderate yield. Dearomative functionalization of **2b** with (diacetoxyiodo)benzene in methanol generates α,β–unsaturated ketone **3b** (Figure 22).

Figure 22. *Preparatioin of Diels–Alder Substrate **3b**.*



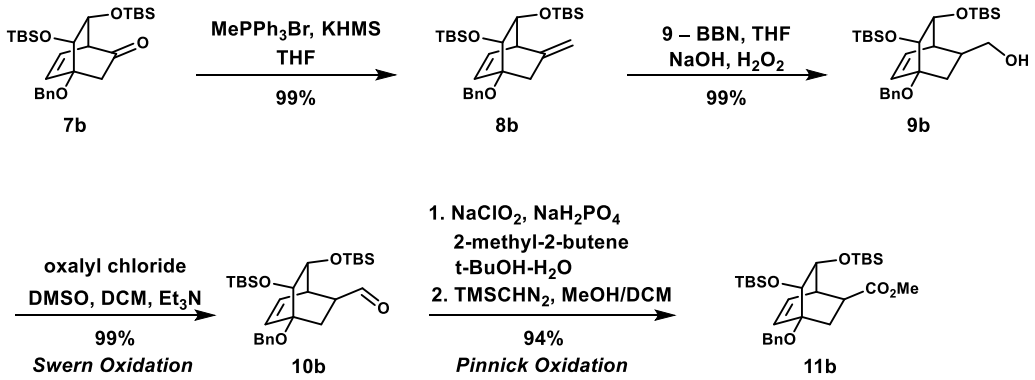
Utilizing conditions established by Liao and coworkers, a Diels–Alder reaction of **3b** with vinylene carbonate gives bicycle **4b** in 64% yield.[36, 37] Serendipitously, treatment of **4b** with LiOH results not only in hydrolysis of the carbonate moiety, but also almost complete inversion of stereochemistry at position C7. Zakarian *et. al.* reasoned that a retro-aldol pathway was operative and resulted in the more thermodynamically favorable *trans*-diol **5b**. TBS-protection of diol **5b** followed by α–deoxygenation with samarium iodide affords ketone **7b** in excellent yields (Figure 23).

Figure 23. *Synthesis of* ***7b****.*



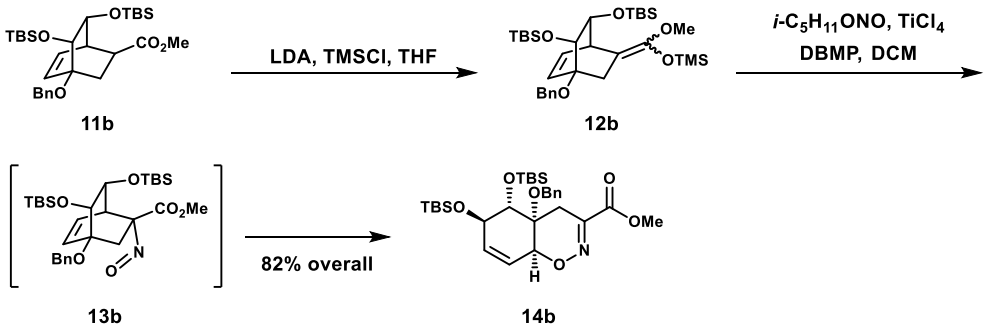
The key step of this synthesis was envisioned to be an oxaza-Cope rearrangement to furnish the oxazadecaline core of trichodermamide B. This reaction was expected to proceed from silyl ketene acetal **12b** as previous work had shown that direct treatment with the corresponding ester failed to give desired reactivity.[38] Silyl ketene acetal **12b** can be made in a single step from ester **11b**. Conversion of ketone **7b** to ester **11b** was accomplished in five steps. Wittig olefination of ketone **7b** and subsequent hydroboration in the presence of hydroxide furnished alcohol **9b**. Conversion of this alcohol to the corresponding carboxylic acid was accomplished *via* Swern and Pinnick oxidations. Trimethylsilyl-diazomethane was then used to convert this carboxylic acid to methyl ester **11b** (Figure 24).

Figure 24. *Synthesis of methyl ester* ***11b****.*



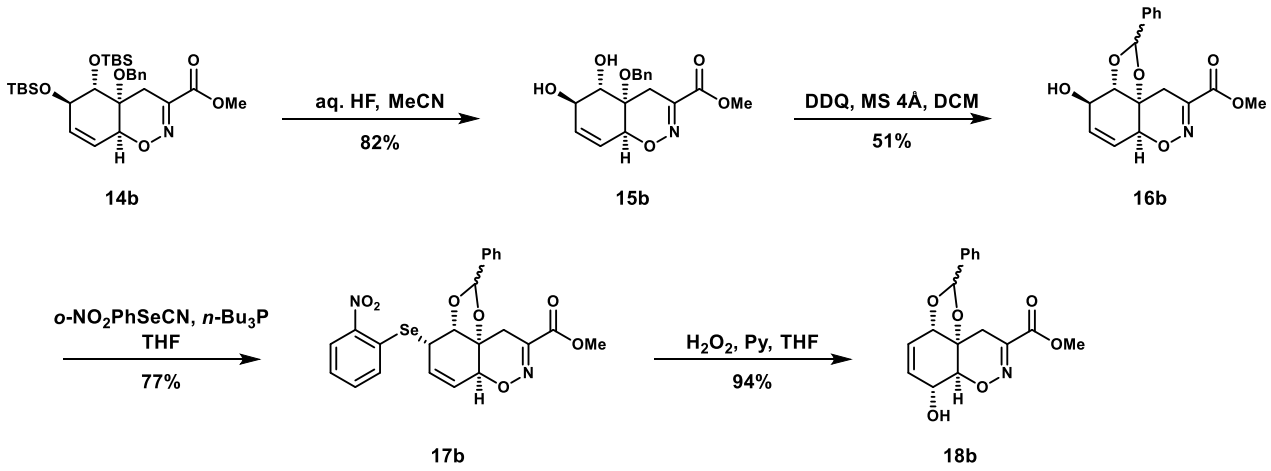
Treatment of **11b** with LDA and TMSCl affords silyl ketene acetal **12b**. This substrate was then poised to undergo the key oxaza-Cope rearrangement. Nitrosation of **12b** with isopentyl nitrate at –78 ˚C in the presence of a Lewis acid afforded intermediate **13b**, which underwent oxaza-Cope rearrangement to generate cyclized product **14b** (Figure 25). Better conversions were observed when excess Lewis acid was used for this transformation; however, under these conditions partial debenzylation was also observed.

Figure 25. *Key oxaza-Cope rearrangement.*



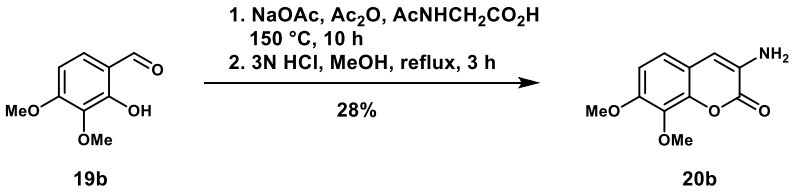
With the oxazadecaline core installed, functional group manipulations led to the fully substituted core with correct relative stereochemistry. Global TBS-deprotection with HF afforded diol **15b**. Comparing this intermediate to the natural product, the alcohol and alkene functionalities must be transposed. This net transformation is achieved in three steps. First, using DDQ, the benzyl group was converted into an acetal protecting group to prevent chemoselectivity issues in further steps. Use of Greico's conditions on allylic alcohol **16b** led to formation of transposed product **18b** (Figure 26).

Figure 26. *Synthesis of allylic alcohol* ***18b****.*



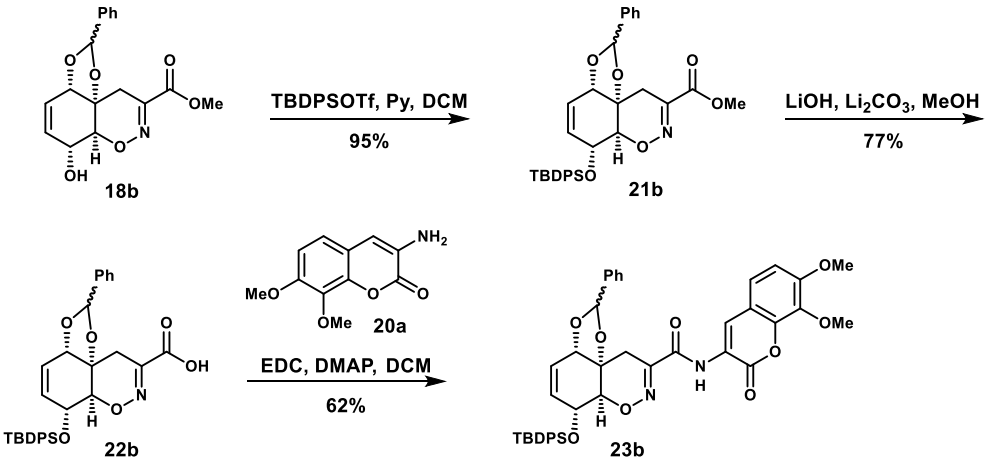
With allylic alcohol **18b** in hand, the oxazadecaline core was only a few steps away from completion. However, at this stage it was deemed advantageous to pursue amide coupling on this protected intermediate rather than to attempt amide coupling on the fully functionalized core. Amide coupling partner **20b** can be synthesized in two steps from commercially available aldehyde **19b** (Figure 27).

Figure 27. *Synthesis of amine* ***20b****.*



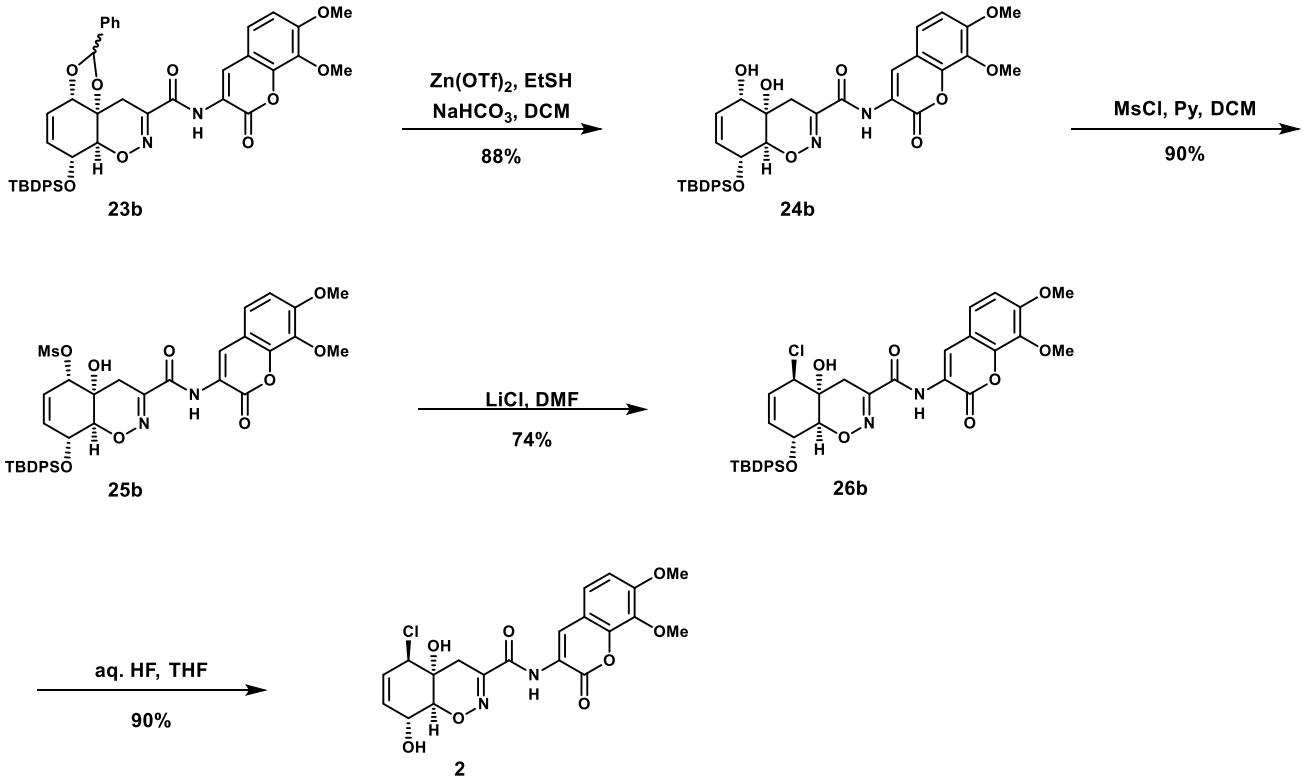
Protection of allylic alcohol **18b** with TBDPSOTf afforded **21b**. Hydrolysis of the ester with LiOH led to formation of carboxylic acid **20b** which was set to undergo the amide coupling reaction. EDC coupling conditions with acid **22b** and amine **20b** afforded amide **23b** in acceptable yields (Figure 28).

Figure 28. *Amide coupling gives advanced intermediate* ***23b****.*



The only task remaining was to deprotect the alcohols and to effect a substitution reaction to install the chloride moiety. Deprotection of acetal **23b** with $Zn(OTf)_2$ and EtSH afforded

Figure 29. *End game towards trichodermamide B.*



diol **24b**. Subsequent treatment with mesyl chloride selectively mesylates the secondary alcohol

of **24b** in the presence of the tertiary alcohol to afford **25b**. Treatment with LiCl effected an S_N2 reaction to afford **26b**. Deprotection of the TBDPS group with HF was the last step needed to achieve the synthesis of **2**, trichodermamide B (Figure 29).

This seminal synthesis of trichodermamide B impressively used an oxaza-Cope rearrangement as a key step. However, this synthesis suffered from a fairly large step count. Functional group manipulations and oxidation state changes often took several steps, and this led to a relatively low yield of the target compound. This synthesis did not successfully generate enough material for further biological study.

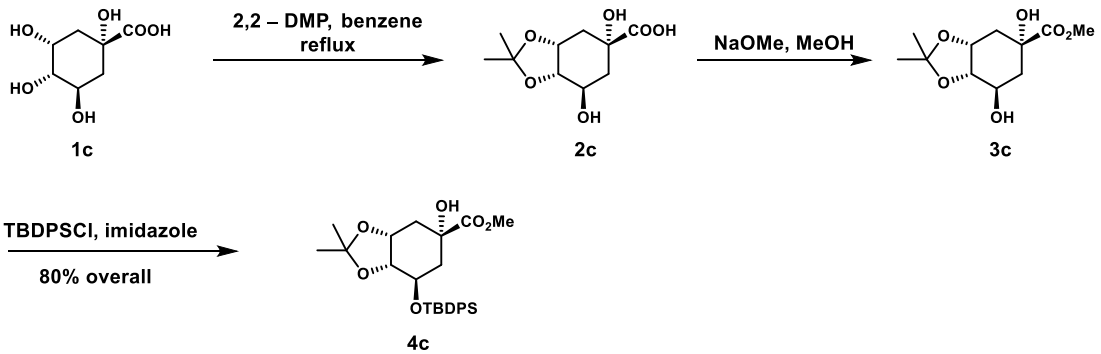
Joullié Group

Later that same year, the Joullié group at the University of Pennsylvania was able to effect the enantioselective synthesis of trichodermamide B in thirty-two longest linear steps from a chiral pool starting material.[6]

The reported synthetic strategy really began from key diol intermediate **15c** which had been previously reported by the Joullié group.[39] This intermediate was accessed in thirteen steps from (–)-quinic acid.

Protection of (–)-quinic acid **1c** with 2,2-dimethoxypropane afforded acetal **2c**.

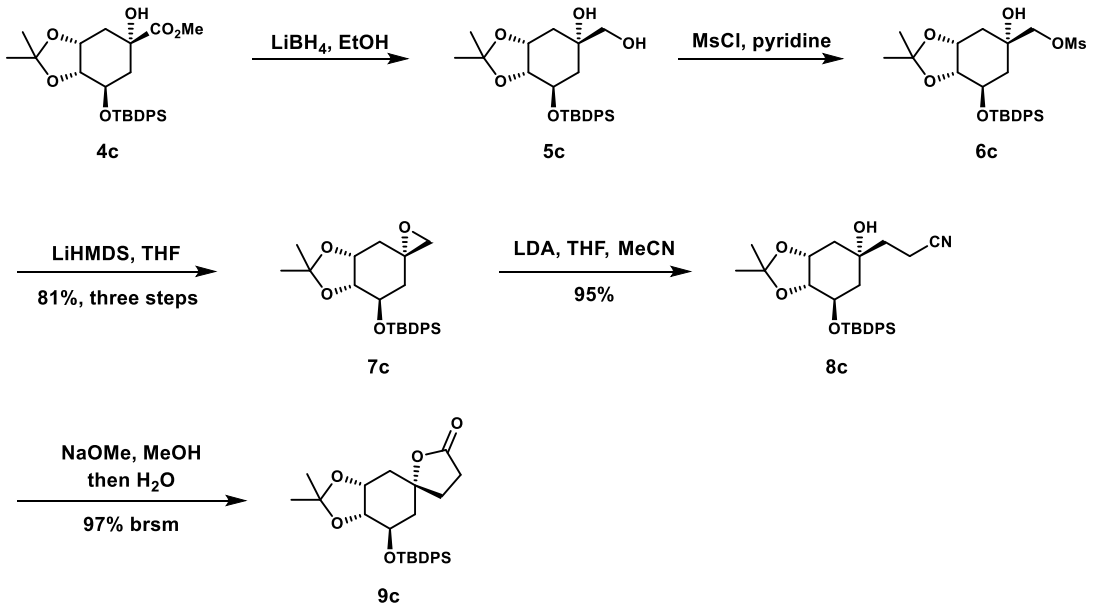
Figure 30. *Synthesis of ester **4c**.*



Esterification followed by selective TBDPS protection of the secondary alcohol furnished ester **4c** (Figure 30).

Conversion of α–hydroxyester **4c** to the corresponding epoxide was accomplished in a three step procedure. First, reduction of **4c** with $LiBH_4$ gave the corresponding alcohol **5c**. Next, selective mesylation of the newly generated primary alcohol was accomplished by treatment with mesyl chloride to afford **6c**. Intramolecular S_N2 displacement of the mesylate by the adjacent alcohol was effected upon deprotonation with LHMDS to afford epoxide **7c**. From this epoxide, a formal, carbonylative ring expansion was accomplished in two steps. First nuclephilic epoxide opening by deprotonated acetonitrile afforded **8c**. Next, treatment with sodium methoxide in anhydrous methanol followed by addition of water effected cyclization and hydrolysis to afford lactone **9c** (Figure 31).

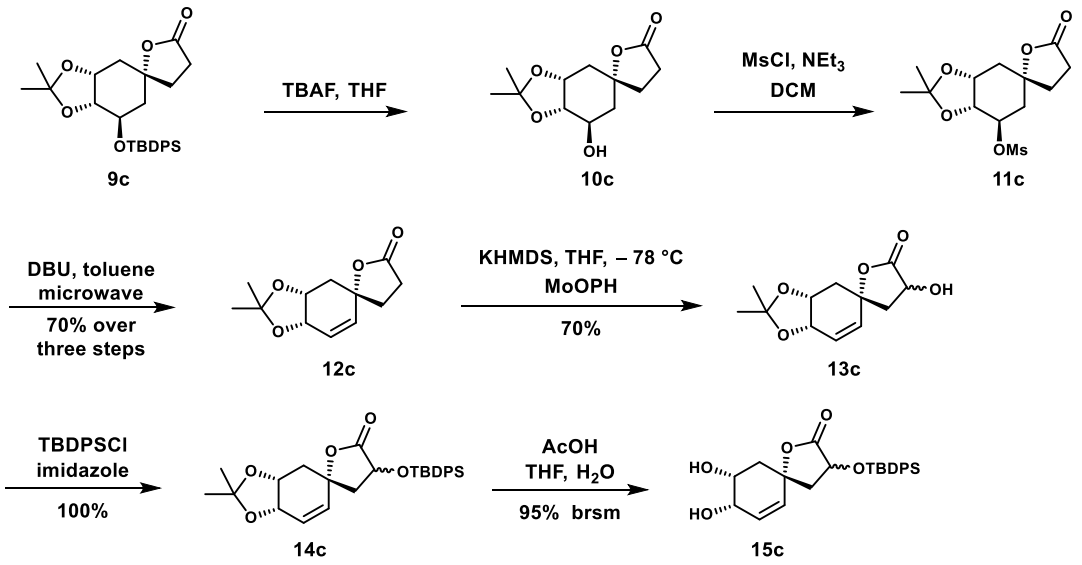
Figure 31. *Synthesis of lactone 9**c**.*



Elimination of the protected alcohol of **9c** was accomplished in a three step procedure. Deprotection with TBAF, mesylation, and elimination with DBU afforded olefin **12c**. α–oxygenation of the lactone was accomplished by formation of the corresponding enolate and

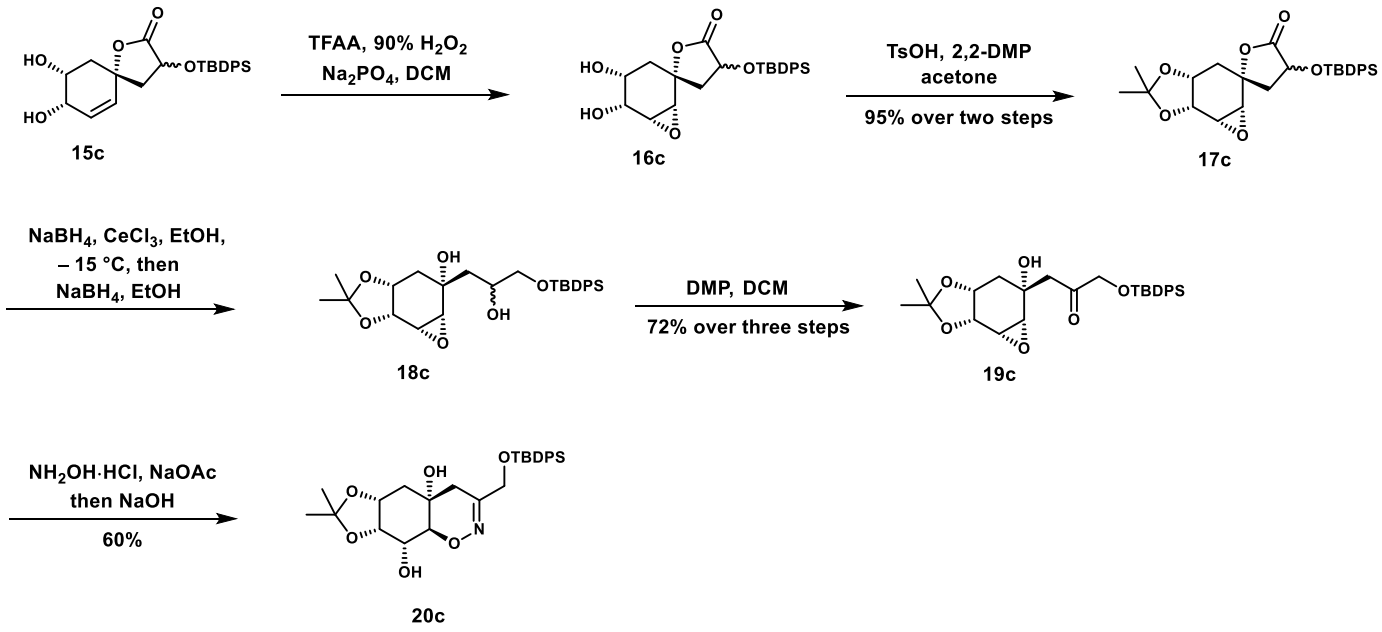
treatment with MoOPH. Protection of alcohol **13c** with TBDPSCl followed by ketal deprotection with acetic acid generated intermediate **15c**. It is from this intermediate that the Joullié group began reporting new steps for their 2008 synthesis (Figure 32).

Figure 32. *Synthesis of diol* ***15c***.



Continuing from intermediate **15c**, directed epoxidation using trifluoroacetic anhydride and 90% H_2O_2 gave epoxide **16c**. Protection of the diol using 2,2-dimethoxypropane afforded acetal **17c**. From this intermediate, synthesis of the oxazadecaline core could be accomplished *via* cleavage of the lactone, formation of an oxime, and nucleophilic epoxide opening with the oxime. In this manner three of the four contiguous stereocenters of the core can be installed with the correct absolute stereochemistry. Conditions were discovered to effect these transformations over four synthetic steps. A two-step reduction procedure based upon previous work by Wipf *et. al.* effected lactone opening and silyl migration to give intermediate **18c**.[40] Oxidation of the secondary alcohol with Dess–Martin periodinane afforded ketone **19c**. Condensation of hydroxylamine and nucleophilic epoxide opening furnished the oxazadecaline core (Figure 33).

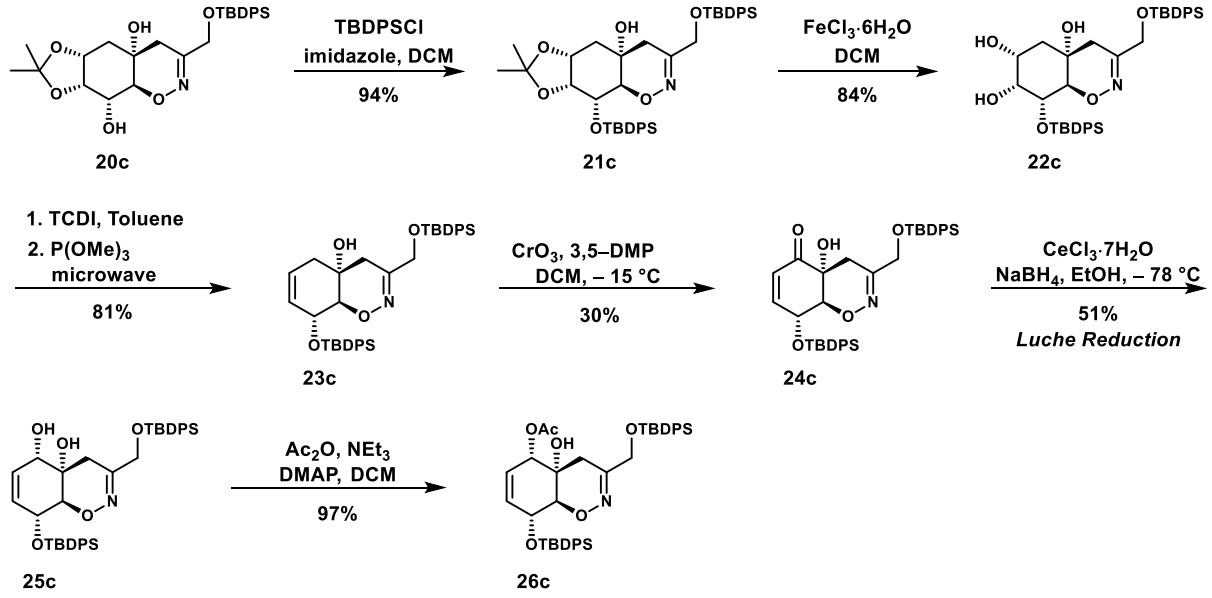
Figure 33. *Synthesis of the oxazadecaline core.*



Although the oxazadecaline core had been synthesized, several important challenges still remained. Most notably, to synthesize trichodermamide B a chlorine must be installed in a position which in **20c** appears to have no functional handle. This issue was tackled by a formal elimination of the ketal followed by allylic oxidation.

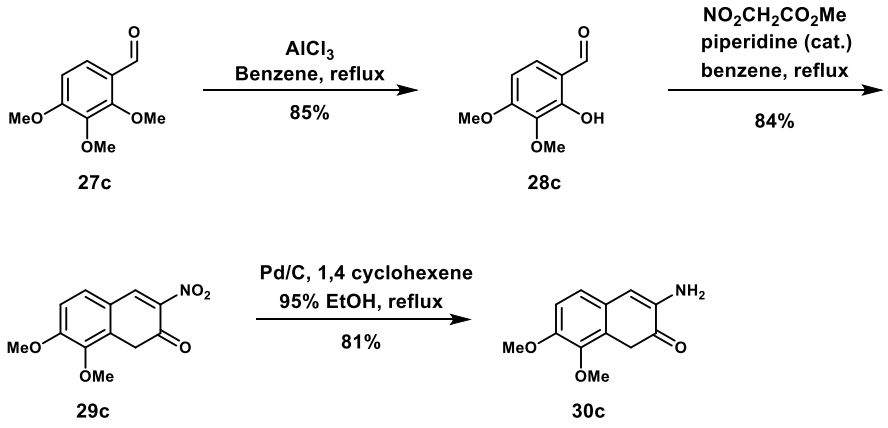
Protection of the free, secondary alcohol of **20c** proceeded with TBDPSCl and imidazole in excellent yields. Deprotection of ketal **21c** with $FeCl_3$• 6 H_2O afforded diol **22c**. Barton–McCombie deoxygenation of diol **22c** afforded intermediate **23c** in 81% yield over two steps. Allylic oxidation with chromium trioxide furnished α,β–unsaturated ketone **24c** in poor yields. Luche reduction generated allylic alcohol **25c** which was subsequently acetylated to **26c** (Figure 34). Thus, using this elimination / allylic oxidation strategy, the Joullié group was able to synthesize intermediate **26c** which was, following oxidation state manipulations, an amide coupling and a substitution reaction away from the natural product.

Figure 34. *Synthesis of* ***26c****.*



The amide coupling partner was prepared in three steps from commercially available starting materials. Lewis acid deprotection of 2,3,4-trimethoxybenzaldehyde **27c** afforded phenol **28c**. An aldol condensation of aldehyde **28c** with methyl-2-nitroacetate gave α–nitro ketone **29c**. Reduction to the corresponding amine was accomplished with palladium on carbon in the presence of a dihydrogen source to complete coupling partner **30c** (Figure 35).

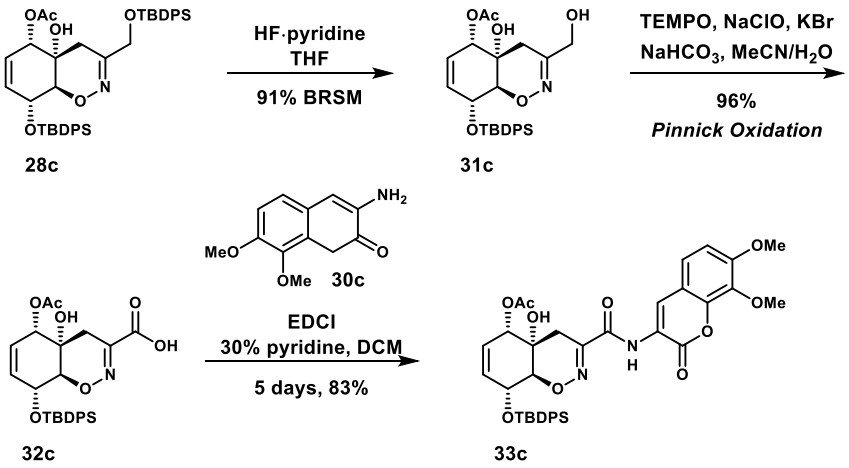
Figure 35. *Synthesis of amide coupling partner* ***30c****.*



Intermediate **28c** was only a couple functional group manipulations away from being able to participate in the coupling reaction. Selective deprotection of the primary alcohol with

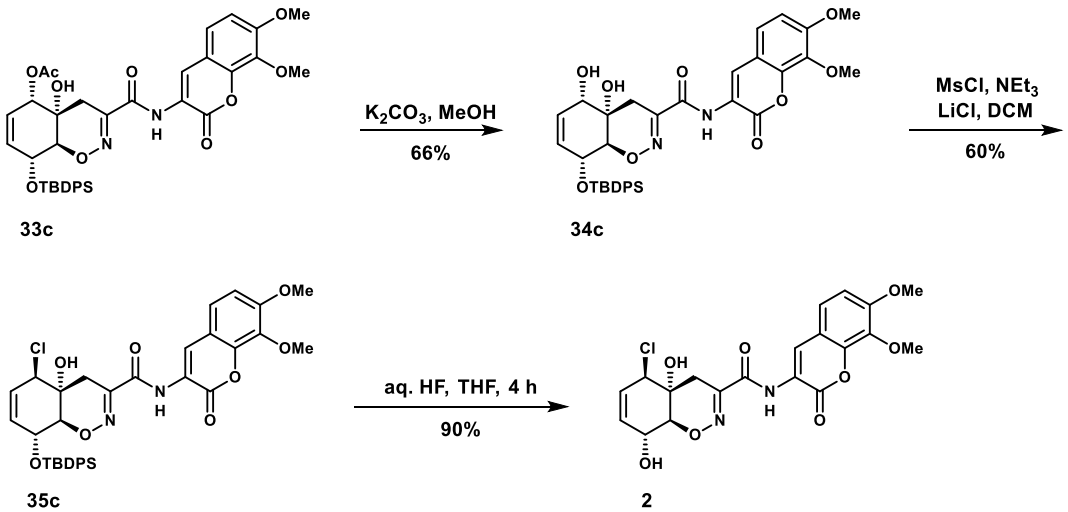
HF•pyridine followed by oxidation with TEMPO and *in situ* Pinnick oxidation afforded carboxylic acid **32c**. EDCI coupling of this acid with amine **30c** furnished the amide coupled product **33c** (Figure 36).

Figure 36. *Amide coupling.*



At this stage deprotection and substitution would afford the natural product. Deacetylation with base, mesylation of the resulting alcohol, S_N2 attack by chloride, and deprotection with HF furnished the natural product, trichodermamide B (Figure 37).

Figure 37. *Completion of enantioselective synthesis.*



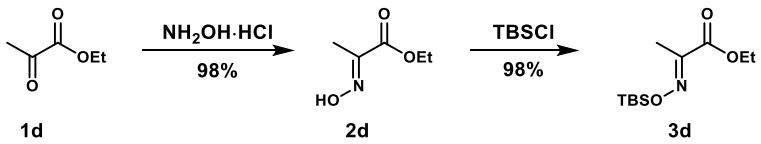
This impressive synthesis was able to give access to enantiomerically pure trichodermamide B. However, much like the synthesis by the Zakarian group, many steps were required to reach this target, and this highlights an important fact. It took established, respected synthesis groups well over twenty steps to complete the synthesis of this molecule. Obviously, trichodermamide B is a challenging target, and synthesizing this molecule efficiently requires a clever strategy. At the time that synthetic studies towards trichodermamide B were initiated in Sarlah group, these were the only two syntheses reported in the literature.

Larionov Group

However, in 2015 the Larionov group at the University of Texas at San Antonio reported the total synthesis of trichodermamide B in fourteen longest linear steps from ethyl pyruvate.[41] This expedited appoach was made possible through efficient synthesis of the oxazadecaline core.

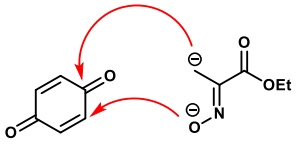
Condensation of hydroxylamine onto ethyl pyruvate afforded oxime **2d**. Protection of the oxime with TBSCl gave **3d** (Figure 38).

Figure 38. *Synthesis of* ***3d****.*



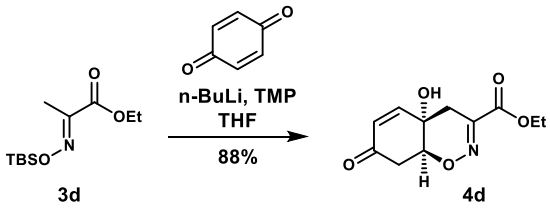
The key step of this synthesis was proposed to construct the oxazadecaline core by treatment of the corresponding dianion of α–oximoester **3d** with benzoquinone. If successful, this reaction would furnish the oxazadecline core of trichodermamide B in three steps from ethyl pyruvate (Figure 39).

Figure 39. *Proposed synthesis of oxazadecaline core.*



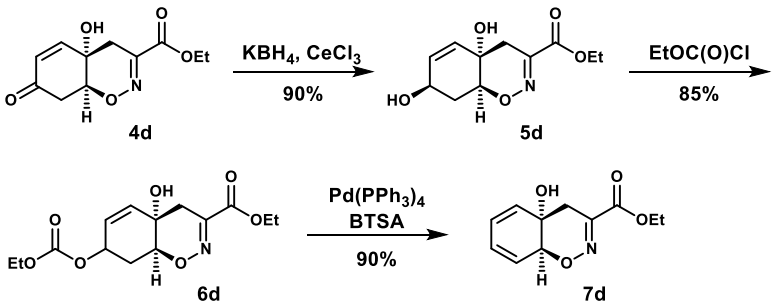
Indeed, conditions were identified to successfully effect this transformation (Figure 40). Screening bases revealed that LiTMP was necessary as other bases such as LDA, KHMDS, and LHMDS were unsuccessful.

Figure 40. *Conditions for key dianion attack.*



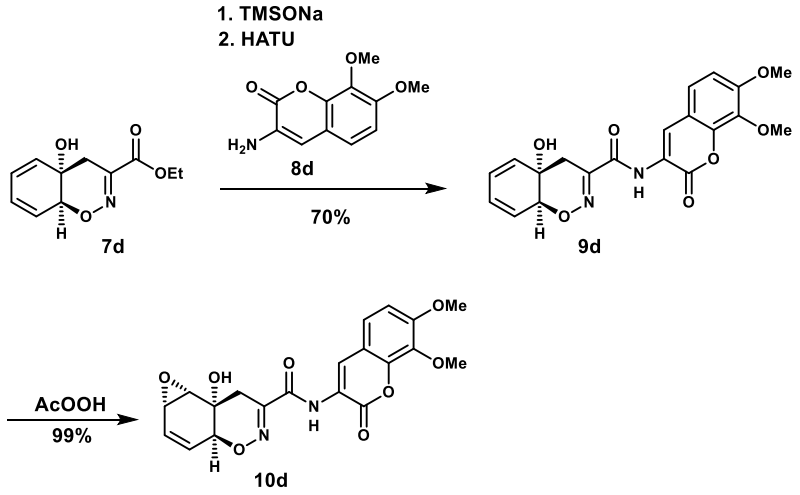
Now with easy access to advanced intermediate **4d**, the challenge of synthesizing trichodermamide B was reduced to effecting functional group manipulations of the completed oxazadecaline core. Luche reduction of α,β–unsaturated ketone **4d** using potassium borohydride and cerium trichloride afforded allylic alcohol **5d** in good yield. Subsequent carbonate protection of the secondary allylic alcohol with ethyl chloroformate afforded carbonate **6d**. Elimination of the carbonate was accomplished by treatment with a Pd(0) species in the presence of N,O-bis-(trimethylsilyl)acetamide. Under these conditions formation of a π–allyl complex followed by β–hydride elimination furnished diene **7d** (Figure 41).

Figure 41. *Synthesis of diene* ***7d****.*



The Larionov group next completed the amide coupling reaction to install the other half of the molecule. Amine **8d** was synthesized under conditions that had been previously reported by the Zakarian group. Following hydrolysis of ester **7d**, the coupling between the resulting carboxylic acid and amine **8d** proceeded smoothly to generate amide **9d**. Selective epoxidation of the allylic alcohol in presence of the homoallylic alcohol was achieved in excellent yields by treatment with peracetic acid to afford epoxide **10d** (Figure 42).

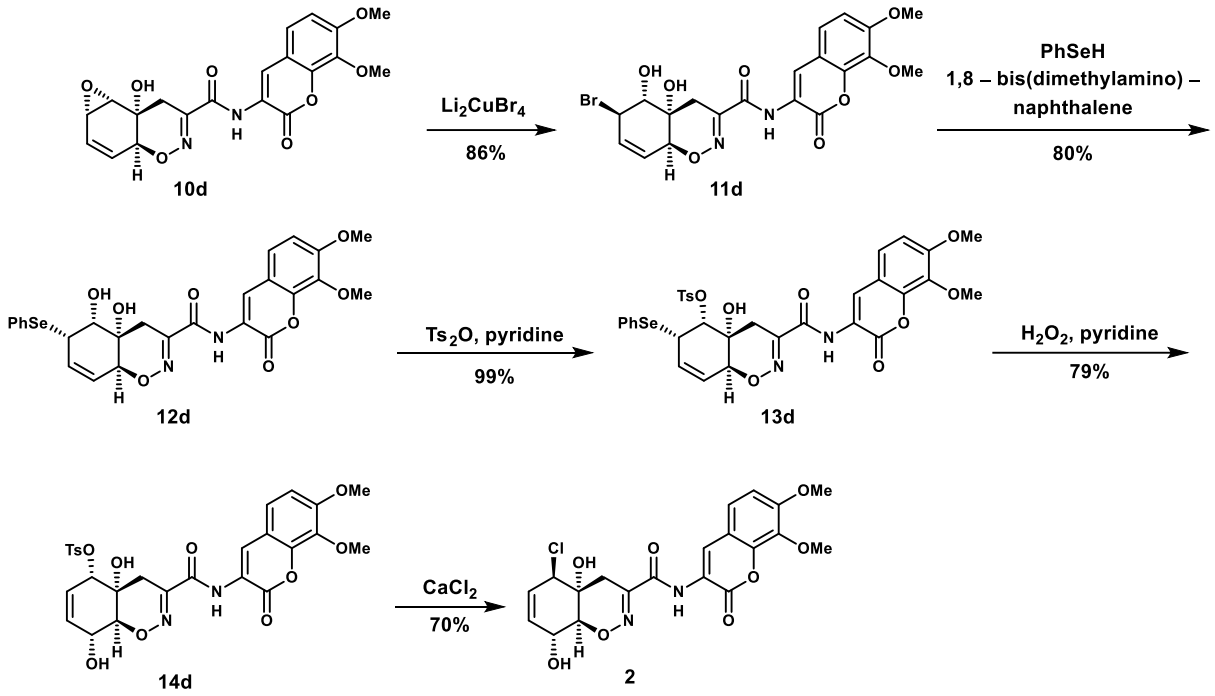
Figure 42. *Synthesis of epoxide* ***10d****.*



From this point the synthesis of trichodermamide B could be completed with only a few functional group manipulation reactions. Li_2CuBr_4 served as a nucleophilic bromide source which could open epoxide **10d** to form bromohydrin **11d**. S_N2 attack by phenyl selenium ion afforded intermediate **12d**. Tosyl protection of the alcohol gave **13d**. Treatment with hydrogen peroxide

afforded a selenoxide intermediate which underwent a sigmatropic rearrangement to afford allylic alcohol **14d**. S_N2 attack by a chloride ion afforded trichodermamide B (Figure 43).

Figure 43. *Synthesis of trichodermamide B.*

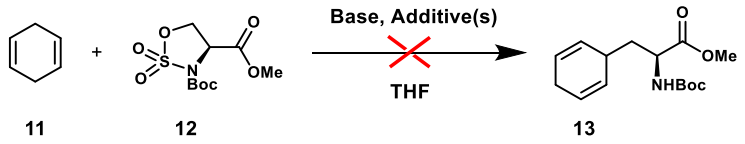


This sequence completed the most efficient synthesis of trichodermamide B to date. However, utilizing a biomimetic strategy, it was envisioned that trichodermamide B could be synthesized in eight or nine steps and that this short synthesis could enable the first gram-scale access of this natural product. This material could then be used to conduct mechanism of action studies to help design analogues to capture the biological potential of this chemical scaffold.

Chapter 4: Cyclohexadiene Alkylation Strategy

The first challenge towards the synthesis of trichodermamide B was to find efficient alkylation conditions for cyclohexadiene **11** as discussed previously (Figure 5). It is known that organolithium nucleophiles derived from cyclohexadiene can perform S_N2 attack on simple alkyl halides at –78 ˚C without olefin isomerization.[42] Unfortunately, attempts to effect this transformation in our system were unsuccessful (Figure 44).

Figure 44. *Attempted alkylation of 1,4-cyclohexadiene.*

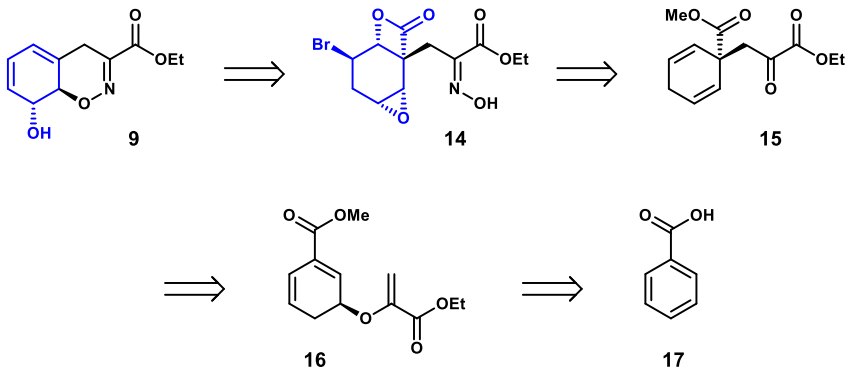


The cyclic sulfamidate electrophile used had been precedented to undergo S_N2 attack at the carbon β to the carbonyl.[43] It was envisioned that the resulting sulfamidate could be cleaved to the corresponding amine upon acidic workup.[44] However, utilization of these conditions did not result in formation of the desired product. Attempts to screen lithium bases *n*-BuLi, *sec*-BuLi, and *t*-BuLi were unsuccessful. Attempts to break up lithium aggregates with addition of tetramethylethylenediamine did not improve results. Transmetallation to copper to avoid chemoselectivity issues with the ester and carbamate moieties of the electrophile did not allow for successful alkylation. Alternatively, aziridine electrophiles have been precedented to undergo S_N2 attack at the terminal position.[45 – 47] Unfortunately, this electrophile also did not enable alkylation under the reaction conditions. At this point it seemed that an alternative route would be necessary to provide access to advanced intermediates.

Chapter 5: Claisen Rearrangement Strategy

Although the alkylation strategy had run into road blocks, the goal for any strategy devised would still be the same. Each route would need to give access to the key, arene oxide equivalent diene **9** because this is the intermediate that would enable the cascade sequence to furnish the fully substituted oxazadecaline core. An alternative scheme towards this key intermediate is shown below (Figure 45).

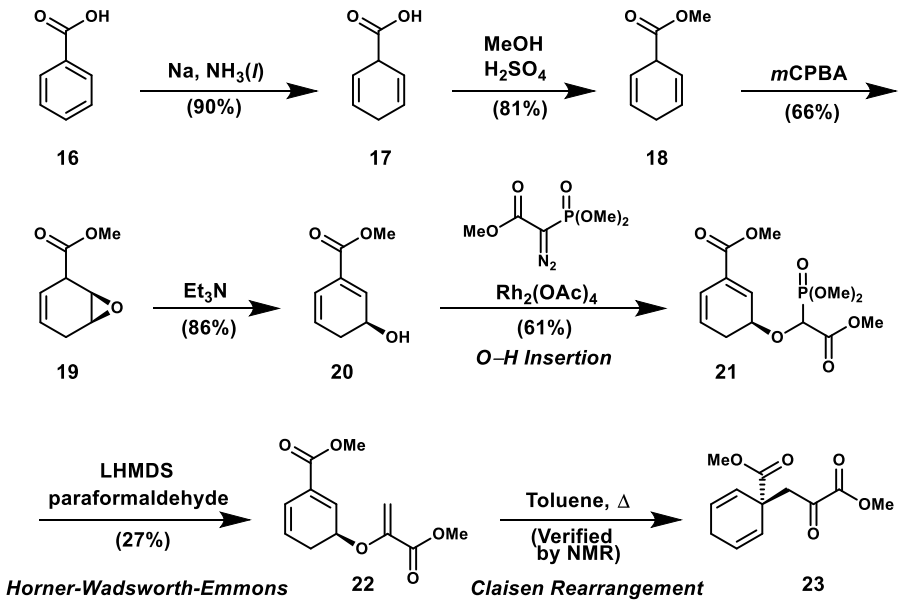
Figure 45. *Claisen rearrangement strategy.*



Key diene **9** could be synthesized from bromolactone **14** *via* first nucleophilic epoxide opening by the oxime and second elimination of the bromolactone utilizing Ganem's conditions.[31] Bromolactone **14** could be synthesized from α–ketoester **15** *via* condensation of hydroxylamine, epoxidation, ester deprotection, and bromolactonization. α–ketoester **15** could be synthesized *via* Claisen rearrangement of α,β–unsaturated ester **16**. This intermediate was deemed to be convenient because, although unknown in the literature, the corresponding alcohol is known.[48] Additionally, the corresponding aromatic variant of α,β–unsaturated ester **16** is also known.[49] The aromatic variant is synthesized from the corresponding phenol. Thus, using a literature precedented strategy, intermediate **16** should be easily accessible and should enable access to more advanced intermediates along this route. α, β–unsaturated ester **16** was envisioned to be accessible in a few steps from benzoic acid.

Utilizing this strategy, many steps experienced immediate success. The steps are shown below (Figure 46).

Figure 46. *Synthesis of α–ketoester* ***23****.*



Birch reduction of cheap, commercially available benzoic acid **16** yielded 1,4-dihydrobenzoic acid **17** in 90% yield.[50] This reaction has been performed on up to fifteen gram scale without reduction in yield. Utilizing Fischer's esterification conditions afforded methyl ester **18** in good yields. Epoxidation using meta-chloroperbenzoic acid (*m*CPBA) followed by elimination with triethyl amine afforded known allylic alcohol **20**.[48]

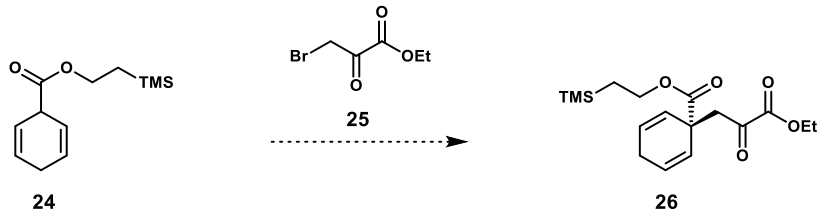
An O-H insertion reaction of a rhodium carbene into allylic alcohol **20** afforded phosphonate **21** in acceptable yields. A Horner–Wadsworth–Emmons reaction of **21** with cracked paraformaldehyde gave α, β–unsaturated ester **22** in poor yields.[49] However, at this stage optimization was not a priority. The goal was to show the viability of the proposed strategy. Heating α,β–unsaturated ester **22** in toluene to 120 ˚C overnight resulted in the formation of α–ketoester **23**.

The ability of this route to afford advanced intermediate had been demonstrated. However, in order to push forward with this strategy, an alternative ester protecting group would be needed to enable orthogonal deprotection. The ethyltrimethylsilyl protecting group was chosen for its facile deprotection conditions. The previously employed, synthetic sequence was scaled up using the new, ester protecting group. Using this new protecting group, the O-H insertion reaction proceeded at 27% yield. The subsequent Horner–Wadsworth–Emmons reaction no longer gave any product. Attempts to optimize the conditions for this transformation were unfruitful.

Chapter 6: Enolate Alkylation Strategy

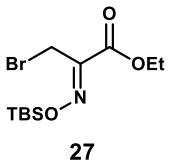
At the same time that the Claisen rearrangement route was stalling, other strategies towards the ketoester were being pursued. One option that had not previously been considered was the direct alkylation of ester **24** with an α–bromo ketoester such as **25** to give desired α–ketoester **26** (Figure 47). If successful, this would provide the first example of this type of selective S_N2 reaction with an α–bromo ketoester.

Figure 47. *Proposed alkylation of ester **24**.*



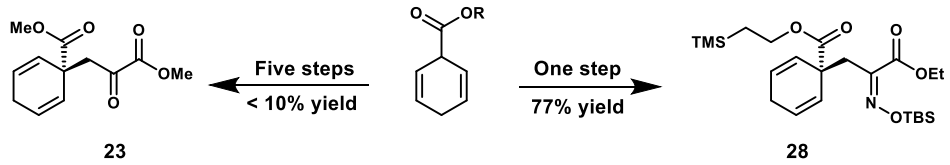
Unfortunately, the desired alkylated product **26** was not formed under the reaction conditions. It was reasoned that the electrophile was too activated to undergo a selective S_N2 reaction. This gave some hope, however, that if the electrophile could be sufficiently deactivated, selective S_N2 attack could occur. One way to deactivate this electrophile could be to first condense TBS-protected hydroxylamine onto the ketone (Figure 48).

Figure 48. *Novel α–bromo oximoester electrophile.*



In the event, formation of the lithium enolate of **24** by LHMDS followed by treatment with α–bromo oximoester **27** afforded alkylated product **28** in 77% yield (Figure 49).

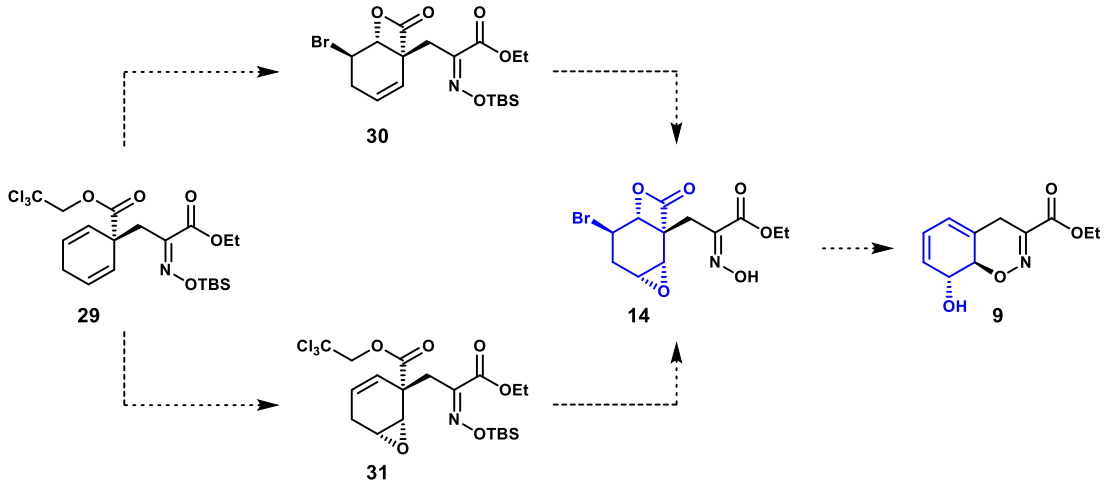
Figure 49. *Expedited synthesis through alkylation*



This alkylation afforded an intermediate in one step and high yield that is more advanced than the intermediate formed in five steps and very low yields using the Claisen rearrangement strategy. At this stage gram quantities of alkylated product **28** were easily accessible, and this facilitated advancement of the front line of the synthesis.

At this stage it was envisioned that either of two routes could lead to the desired product. Either first deprotection and bromolactonization or epoxidation, followed by the other, could lead to the desired arene oxide equivalent diene **9** (Figure 50). It was imagined that one of these routes would work more effectively than the other and that it would be advantageous to test both. Again,

Figure 50. *Revised strategy towards key intermediate **9**.*

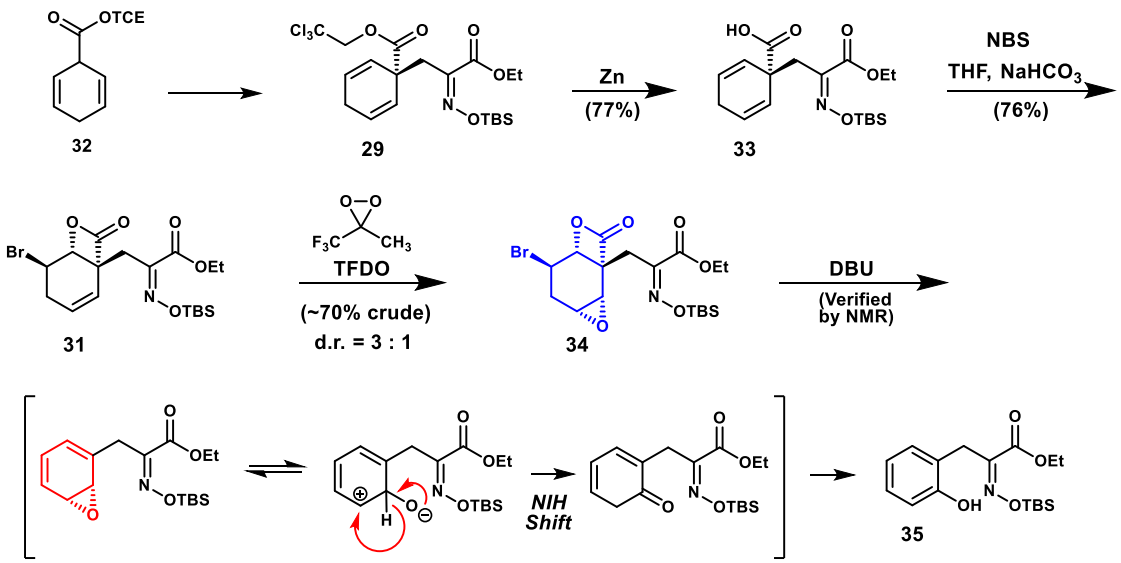


the ester protecting group had to be switched to enable orthogonal deprotection with other functional groups. The trichloroethyl protecting group was chosen for its facile deprotection conditions with zinc.

Moving forward with the bromolactonization strategy, deprotection of **29** with zinc afforded carboxylic acid **33** in good yields.[51] Bromolactonization on substrates of this type are typically performed utilizing bromine in a 1:1 mixture of aqueous sodium bicarbonate and dichloromethane.[31] Attempts to use these conditions on carboxylic acid **33** resulted in 37% yield of desired bromolactone **30** along with a mixture of bromohydrin side products. Attempts to optimize these conditions by lowering the temperature or slowing the addition of bromine were unsuccessful.

Alternatively, it is known that asymmetric bromolactonization can be conducted with *N*-bromosuccinimide at –40 ˚C with $(DHQD)_2PHAL$ in a ligand accelerated manner.[52] Utilizing these conditions on acid intermediate **33** resulted in 40% yield of desired product with no side

Figure 51. *Synthesis of bromolactone **34** en route to undesired aromatization.*



products. This was a clear improvement over the previous set of conditions. However, the reaction still suffered from relatively low yields. It was reasoned that perhaps if this reaction worked at cold temperatures in a ligand accelerated manner, it would be possible to take out the expensive, chiral

ligand and run the reaction at room temperature. Gratifyingly, this was successful, and good yields were obtained using this procedure (Figure 51).

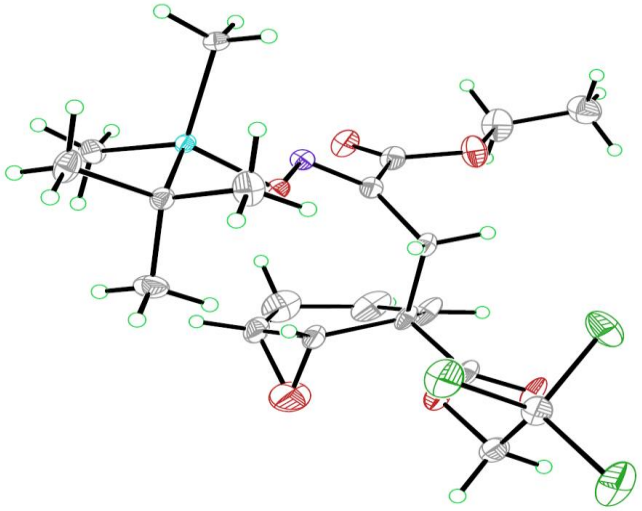
Epoxidation of the resulting bromolactone proved challenging. Treating **31** with five equivalents of *m*CPBA and stirring at room temperature overnight resulted in recovered starting material. More activated peroxyacids such as trifluoroperoxyacetic acid also did not successfully effect this transformation. Use of dimethyldioxirane also did not work. However, the more activated methyl(trifluoromethyl)dioxirane afforded the arene oxide equivalent **34** in approximately 70% yield in a 3:1 mixture of diastereomers.

It had been observed by Carrie Levinn in Sarlah Group that deprotection of bromolactone **34** with TBAF did not afford the desired product. Instead, the deprotected oxime opened the strained, four-member lactone to give a bromohydrin product. Since this strategy did not work, an alternative strategy was pursued. Perhaps arene oxide equivalent **9** could be synthesized from the corresponding arene oxide. Deprotection with TBAF should afford an oxime nucleophile without another intramolecular electrophile to compete with the epoxide, so selective attack at the epoxide should occur. It had been reported that substituted arene oxides can be much more stable than benzene oxide, which has a half-life on the order of minutes at room temperature.[14] Certain substituted arene oxides were even stable to flash chromatography.[31] Unfortunately, treatment of bromolactone **34** with DBU formed the corresponding phenol **35**, likely through NIH shift of the arene oxide.[53] Thus, neither proposed strategy from bromolactone **34** successfully afforded the key diene **9**.

Alternatively, deprotection of epoxide **31** could possibly afford the 1,2-oxazadecaline core. There would not be a strained lactone to act as a competing electrophile in this case. Using conditions that had been previously optimized by Carrie Levinn, epoxidation of **29** with *m*CPBA

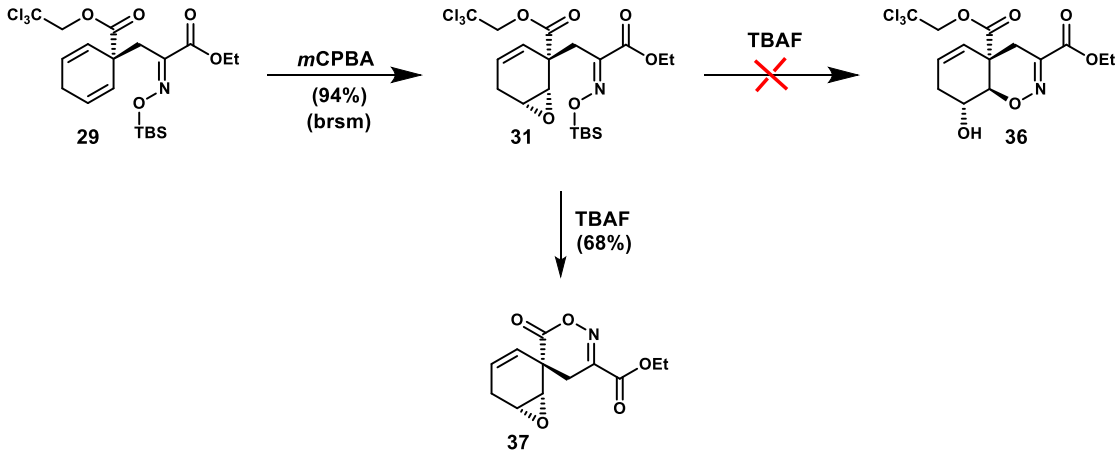
gave a single diastereomer in 94% yield by recovered starting material. A crystal structure of this epoxide was obtained and revealed the oxime stereochemistry (Figure 52).

Figure 52. *Crystal structure of epoxide* ***30****.*



Treatment of epoxide **31** with TBAF was expected to afford ring closed product **36**.

Figure 53. *Synthesis of spirocycle* ***37****.*

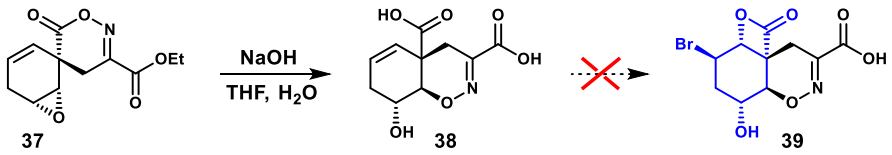


However, this was not the observed product. Instead, the oxime attacked the ester to afford spirocycle **37** (Figure 53).

This was discouraging until it was noted that if treated with sodium hydroxide, a carboxylate species would be form, releasing a deprotected oxime. This oxime would certainly

have no competing electrophile to the epoxide for nucleophilic attack. Utilizing these conditions on spirocycle **37** afforded a product whose proton NMR is consistent with diacid **38** (Figure 54). Attempts to isolate this compound and to perform a bromolactonization reaction were unsuccessful.

Figure 54. *Synthesis of diacid **38**.*

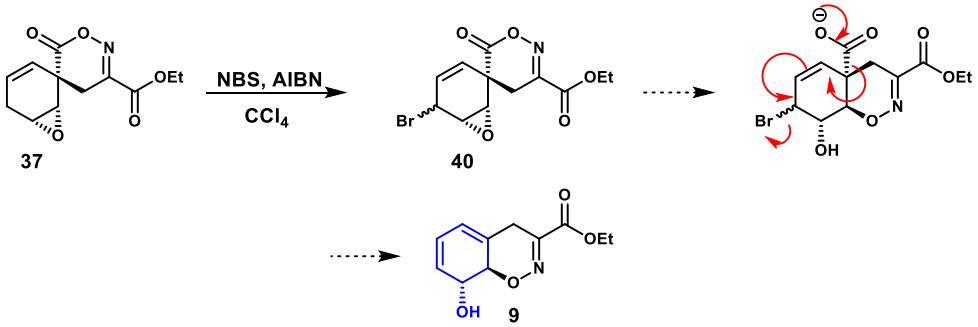


Distinguishing between ring closed **38** and a ring opened product containing an epoxide and an oxime proved to be a challenging task by NMR. Current efforts are attempting to unveil efficient crystallization conditions of this compound.

Diacid **38** would be difficult to use as a synthetic intermediate. It contains two carboxylic acids and an alcohol, and extraction of **38** from the aqueous layer was unlikely. In order to avoid synthesizing an intermediate so polar, a one-pot procedure was attempted. The goal was to form diacid **38** using sodium hydroxide, to quench basicity with sodium bicarbonate, and to add NBS to effect bromolactonization and afford bromolactone **39**. If successful, the product of this sequence would likely be much less polar than diacid **38** and could potentially be extracted from the aqueous later. Unfortunately, this procedure did not afford the desired product.

An alternative strategy to avoid the formation of water soluble intermediate was devised. First allylic bromination of spirocycle **37** could afford allylic bromide **40**.[54, 55] Treatment of this compound with sodium hydroxide could effect a decarboxylative debromination reaction to directly afford key diene **9** (Figure 55).[56]

Figure 55. *Decarboxylative debromination strategy towards* ***9****.*

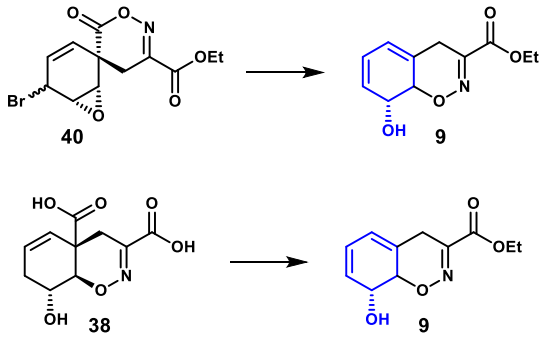


Allylic bromination of spirocycle **37** using NBS and AIBN afforded allylic bromide **40**. The conditions for this reaction are at present unoptimized. Current efforts are focusing on synthesizing large quantities of **40** in order to optimize conditions for the decarboxylative debromination step.

Chapter 7: Future Directions

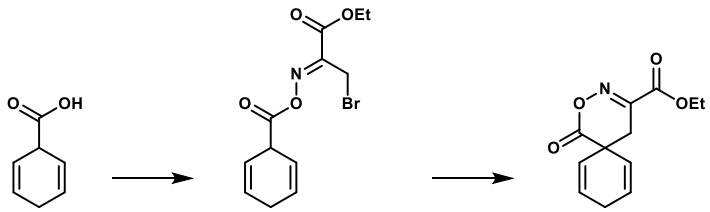
Future work will focus on identifying conditions to synthesize key diene intermediate **9** and to effect the cascade sequence to furnish the fully substituted oxazadecaline core. This could be done from either of the two advanced intermediates previously synthesized (Figure 56).

Figure 56. *Strategies towards diene* ***9****.*



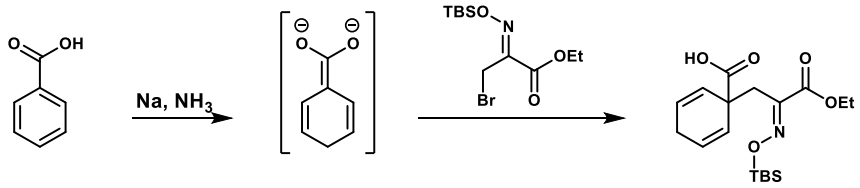
Additionally, a goal will be to cut out unnecessary steps wherever possible. One way to do this may be to use a novel oxime protecting group on the carboxylic acid followed by intramolecular alkylation (Figure 57). Epoxidation of this intermediate would yield epoxide **31**.

Figure 57. *Intramolecular alkylation strategy.*



Another strategy to reduce the step count could be to quench the Birch reduction with an electrophile instead of a proton source (Figure 58).

Figure 58. *Alternative Birch reduction procedure*



Chapter 8: Conclusion

A concise strategy affording advanced intermediates *en route* to the total synthesis of trichodermamide B has been presented. This strategy was enabled by the discovery of a novel α–bromo oximoester electrophile for alkylation. The goal moving forward will be to synthesize the key arene oxide equivalent diene **9** which could be accomplished in a single step from allylic bromide **40**. Once diene **9** is synthesized, a cascade sequence featuring a hetero-Diels–Alder reaction with singlet oxygen should furnish the fully substituted oxazadecaline core. Subsequently, an amide coupling reaction should furnish the natural product. This strategy will enable access to trichodermamide B in far fewer steps than any previously reported synthesis and should afford enough material to conduct mechanism of action studies.

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Appendix

General Procedures

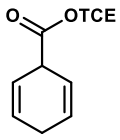
All reactions were performed without rigorous drying of solvents or glassware unless otherwise noted. Dry tetrahydrofuran (THF) was obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields reported are of chromatographically and spectroscopically (^{1}H NMR) homogenous materials. Reagents were purchased and used without further purification unless otherwise noted.

^{1}H NMR and ^{13}C NMR were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for 13C) or a VXR-500 MHz spectrometer. Spectra were referenced using $CDCl_3$ as solvents with the residual solvent peak as the reference (^{1}H NMR: δ 7.26 ppm, ^{13}C NMR: δ 77.00 ppm for $CDCl_3$). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in Hertz and integration is provided.

High-resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof Ultima spectrometer using ESI (electrospray ionization). Infrared (IR) spectra were recorded on an ATR FT-IR spectrometer.

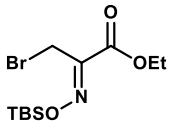
Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and a solution of $KMnO_4$, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

Experimental Procedures and Characterization



32

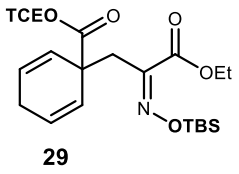
Ester 32: To a 50 mL round – bottom flask was added a stir bar, 1,4 – dihydrobenzoic acid **17** (2.00 g), trichloroethanol (20 mL), and H_2SO_4 (1.0 mL). The round – bottom flask was covered with a yellow cap and was sealed with parafilm. This solution was stirred at room temperature for 48 hours. The solution was cooled to 0 ˚C and was quenched with aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried over $MgSO_4$ and filtered. Flash chromatography (13:1 Hex/EtOAc) gave the title compound (3.05 g, 74% yield). R_f = 0.4 in 10:1 Hex/EtOAc. FT-IR (neat) ν_{max} = 1750, 1268, 1143, 1084, 1032, 893, 777, 714, 666, 569. HRMS (ESI-TOF) calcd for $C_9H_9O_2Cl_3$ $[M + Na]^+$ = 253.9669, found 253.9659. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 5.95 (m, 2 H), 5.87 (m, 2 H), 4.77 (s, 1 H), 3.89 (m, 2 H), 2.72 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 171.0, 127.3, 121.3, 74.3, 41.6, 26.0.



27

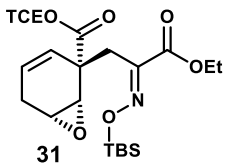
Bromide 27: To a 1L round – bottom flask was added a stir bar, ethyl bromopyruvate (8.43 mL, 67.0 mmol), DCM (300 mL), and TBS – hydroxylamine (9.87 g, 67.0 mmol), pyridinium *p* – toluenesulfonate (100 mg, 0.40 mmol), and 4 Å mol sieves (100 mg). The round – bottom flask was covered with a yellow cap, sealed with parafilm, and wrapped in aluminum foil. This mixture was allowed to stir for 48 hours. The solution was diluted with DCM (200 mL) and filtered over a frit covered with celite and sea sand layers. The filtrate was washed with saturated aqueous $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organics were washed with brine then dried over $MgSO_4$ and filtered. Flash chromatography (20:1 Hex/EtOAc → 10:1 Hex/EtOAc → 5:1 Hex/EtOAc, ensuring to wet load the compound onto a layer of sand and not directly onto the silica gel) gave the title compound (18.24 g, 84%). R_f = 0.7 in 5:1 Hex/EtOAc. FT-IR (neat) ν_{max}

= 1722, 1332, 1253, 1224, 1181, 1013, 987, 833, 785, 686. HRMS (ESI-TOF) calcd for $C_{11}H_{23}NO_3BrSi$ $[M + Na]^+$ = 324.0631, found 324.0631. ^1H NMR ($CDCl_3$, 500 MHz) δ = 4.33 (q, J = 7.0 Hz, 2 H), 4.23 (s, 2 H), 1.35 (t, J = 7.0 Hz, 3 H), 0.97 (s, 9 H), 0.25 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 162.5, 152.5, 62.1, 25.9, 18.2, 16.2, 14.2, – 5.2.



29

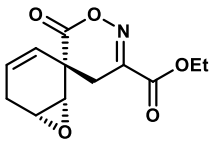
Alkylated Product 29: To a flame-dried, 200 mL round-bottom flask under a nitrogen atmosphere was added THF (50 mL) and HMDS (1.65 mL, 7.86 mmol). This solution was cooled to -78˚C. n-BuLi (4.53 mL, 7.86 mmol) was added dropwise. This was allowed to stir for fifteen minutes. 26 (1.54 g in 2 mL THF, 6.04 mmol) was added dropwise, and the resulting solution was allowed to stir for thirty minutes. 23 (1.96 g in 2 mL THF, 6.04 mmol) was added dropwise. This solution was allowed to stir for one hour before quenching with NH_4Cl (sat. aq., 15 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The combined organics were dried over $MgSO_4$ and filtered. Flash chromatography (25:1 Hex/EtOAc) gave the title compound (1.58 g, 52% yield). R_f = 0.6 in 5:1 Hex/EtOAc. FT-IR (neat) ν_{max} = 1747, 1721, 1185, 1138, 992, 967, 837, 781, 715, 686. HRMS (ESI-TOF) calcd for $C_{20}H_{30}NO_5NaSiCl_3$ $[M + Na]^+$ = 520.0843, found 520.0857. ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.83 (m, 4 H), 4.75 (s, 2 H), 4.23 (q, J = 7.1 Hz, 2 H) 3.24 (s, 2 H), 2.59 (m, 2 H), 1.30 (t, J = 7.1 Hz, 3 H), 0.95 (s, 9 H), 0.19 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 172.1, 164.8, 153.8, 126.9, 125.6, 95.1, 74.5, 61.6, 47.9, 33.6, 26.2, 26.0, 18.2, 14.3, – 5.0.



31

Epoxide 31: To a 50 mL round – bottom flask was added a stir bar, alkylated product **29** (768 mg, 1.40 mmol), and DCM (16 mL). The flask was cooled to 0 ˚C. $NaHCO_3$ (647 mg, 7.00 mmol) was added followed by mCPBA (414 mg, 70% pure, 1.68 mmol). The round – bottom flask was allowed to warm to room temperature, and the mixture was stirred for 48 hours. The reaction was quenched with saturated aqueous $Na_2S_2O_3$

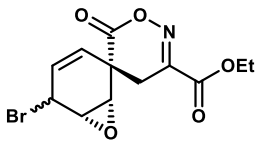
(8 mL). Water (15 mL) was added to dissolve the white solid. The layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried over $MgSO_4$ and filtered. Flash chromatography (20:1 Hex/EtOAc → 8:1 Hex EtOAc) gave the title compound (299 mg, 43% yield) and recovered starting material (391 mg, 51%). R_f = 0.5 in 5:1 Hex/EtOAc. FT-IR (neat) ν_{max} = 1753, 1720, 1253, 1197, 978, 910, 837, 785, 730, 687. HRMS (ESI-TOF) calcd for $C_{20}H_{31}NO_6SiCl_3$ $[M + Na]^+$ = 514.0986, found 514.0993. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 5.71 (m, 1 H), 5.48 (m, 1 H), 4.83 (d, J = 2.2 Hz, 2 H), 4.24 (m, 2 H), 3.67 (m, 1 H), 3.40 (d, J = 12.5 Hz, 1 H), 3.23 (m, 1 H), 3.16 (d, J = 12.5 Hz, 1 H), 2.51 (m, 1 H), 2.34 (dq, J = 19.5, 2.4 Hz, 1 H), 1.31 (t, J = 12.5, 3 H), 0.95 (s, 9 H), 0.20 (d, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 171.0, 164.3, 152.8, 123.6, 123.3, 94.8, 74.5, 61.7, 55.6, 51.4, 48.3, 30.3, 26.0, 24.7, 18.2, 14.2, -5.0, -5.1.



37

Spirocycle 37: To a 4 mL vial was added a stir bar, epoxide **31** (30 mg, 0.058 mmol), and DCM (580 μL). To this vial was added TBAF (15 mg, 0.057 mmol) in a single portion. This solution was allowed to stir at room temperature for thirty minutes. The reaction was quenched by addition of aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with DCM (3 x 500 μL). The combined organics were dried over $MgSO_4$ and filtered. Flash chromatography (2:1 Hex/EtOAc) gave the title compound (9.6 mg, 68%). R_f = 0.6 in 1:1 Hex/EtOAc. FT-IR (neat) ν_{max} = 1774, 1714, 1281, 1142, 993, 935, 916, 859, 815, 692. HRMS (ESI-TOF) calcd for $C_{12}H_{14}NO_5$ $[M + Na]^+$ = 252.0872, found 252.0861. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 5.97 (d, J = 9.4 Hz, 1 H), 5.30 (d, J = 9.4 Hz, 1 H), 4.99 (s, 1 H), 4.36 (q, J = 7.2 Hz, 2 H), 4.00 (d, J = 5.6, 1 H), 2.97 (d, J = 18.6 Hz, 1 H), 2.77 (d, J = 18.6 Hz, 1 H), 2.65 (d, J = 20.1 Hz, 1 H), 2.55 (d, J = 20.1, 1 H), 1.38 (t, J = 7.2 Hz, 3 H).

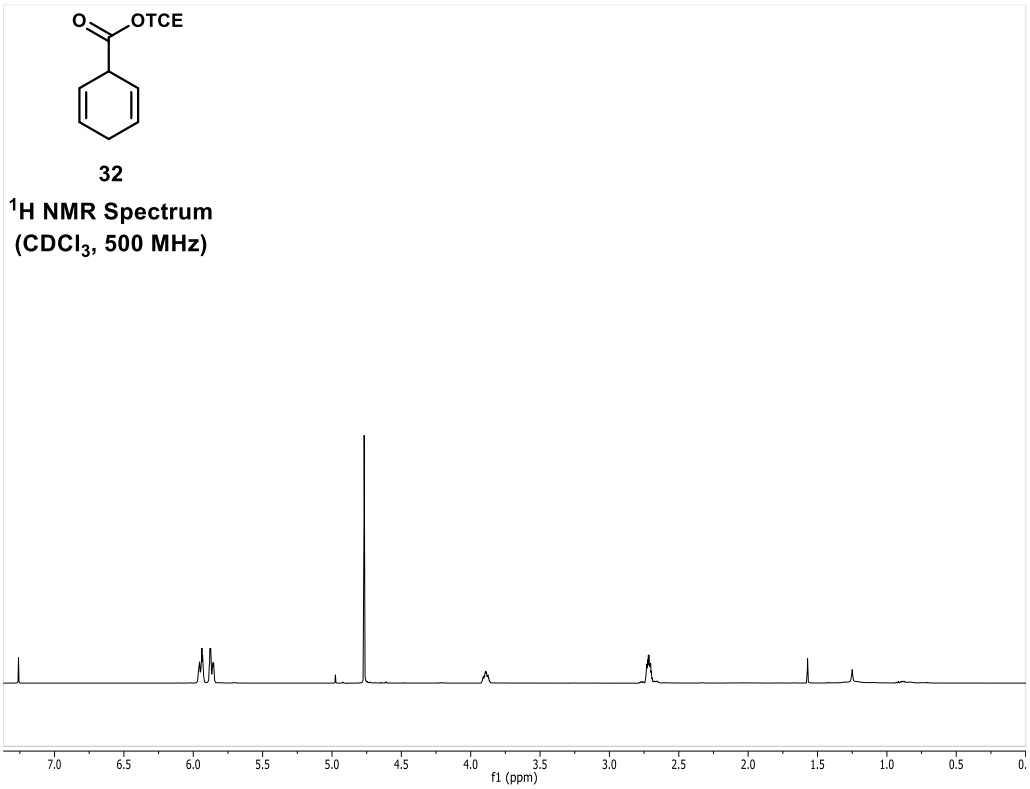
^{13}C NMR ($CDCl_3$, 125 MHz) δ = 172.3, 162.7, 148.4, 130.8, 123.8, 75.2, 72.0, 62.8, 38.7, 29.7, 27.0, 14.4.



40

Allylic bromide 40: To a 4 mL vial was added spirocycle **37** (45 mg, 0.18 mmol), dichlorobenzene (1.8 mL), NBS (35 mg, 0.20 mmol), and AIBN (6 mg, 0.036 mmol). The vial was sealed with a screw cap. This solution was heated to 90 ˚C for four hours. The solution was allowed to cool to room temperature. The reaction mixture was filtered over a celite covered frit. Flash chromatography (4:1 Hex/EtOAc) gave the title compound (6.1 mg, 10% yield). R_f = 0.4 in 3:2 Hex/EtOAc. FT-IR (neat) ν_{max} = 1794, 1717, 1280, 1258, 1137, 1004, 979, 940, 794, 738. HRMS (ESI-TOF) calcd for $C_{12}H_{13}NO_5Br$ $[M + Na]^+$ = 329.9977, found 329.9969. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.07 (dt, J = 9.5, 2.3 Hz, 1 H), 5.40 (dt, J = 9.5, 2.3 Hz, 1 H), 5.11 (dt, J = 5.8, 2.2 Hz, 1 H), 4.96 (q, J = 2.5 Hz, 1 H), 4.36 (q, J = 7.2 Hz, 2 H), 4.11 (dt, J = 5.8, 1.2 Hz, 1 H), 3.03 (d, J = 18.8 Hz, 1 H), 2.77 (d, J = 18.8 Hz, 1 H), 1.37 (t, J = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 171.0, 162.4, 148.7, 132.7, 125.4, 77.9, 74.7, 63.1, 41.6, 38.4, 29.2, 14.3.

Figure 59. *NMR Spectra of* ***32****.*



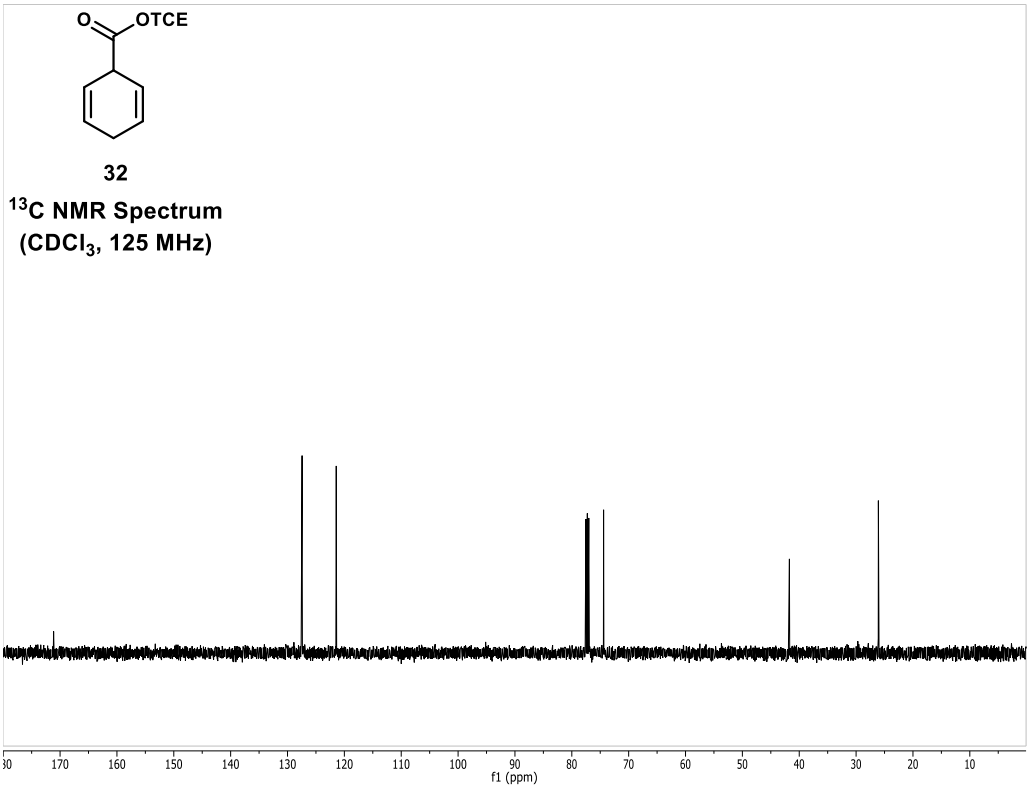
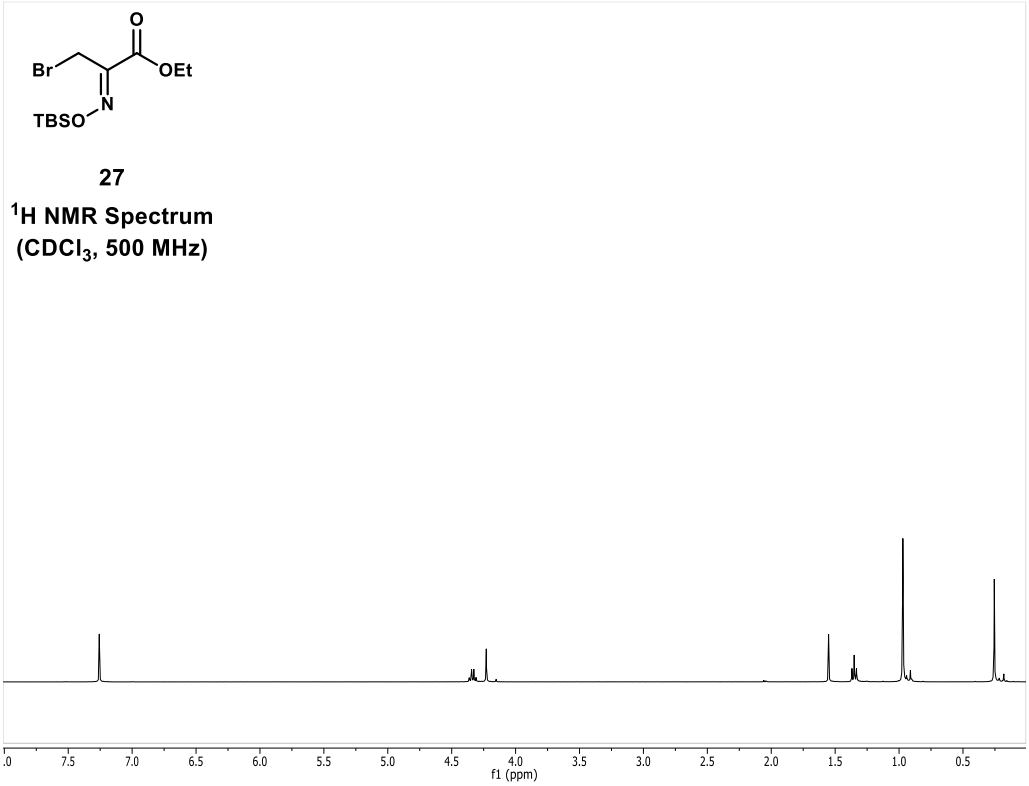


Figure 60. *NMR Spectra of* ***27****.*



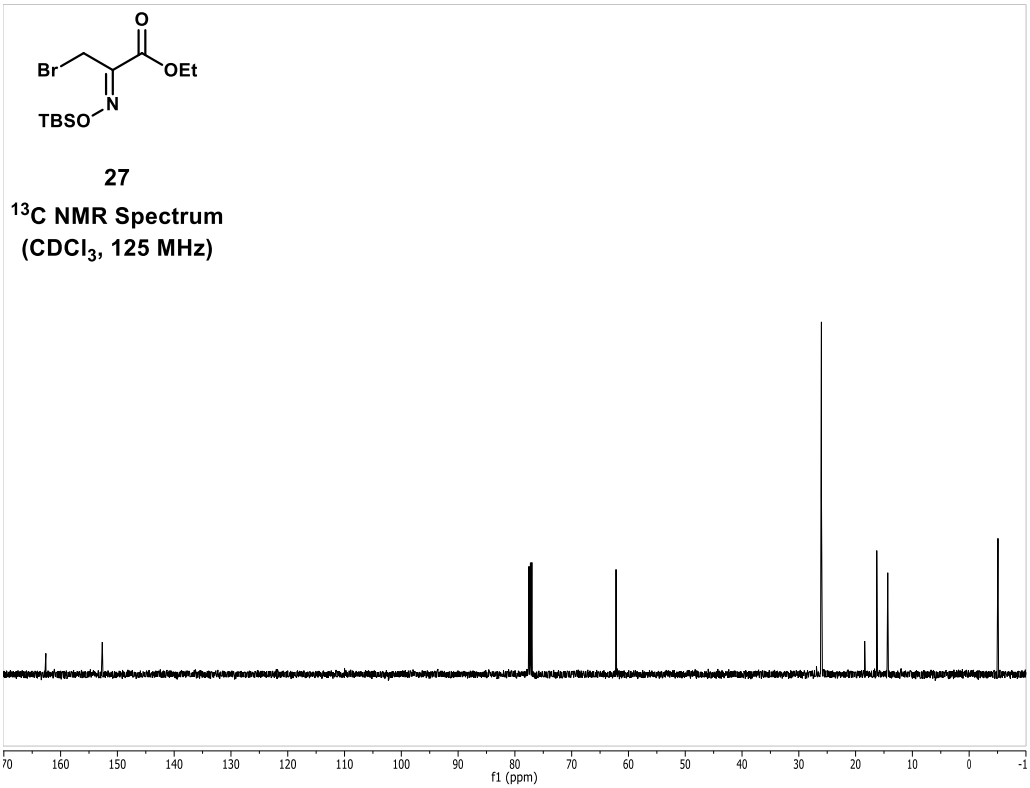
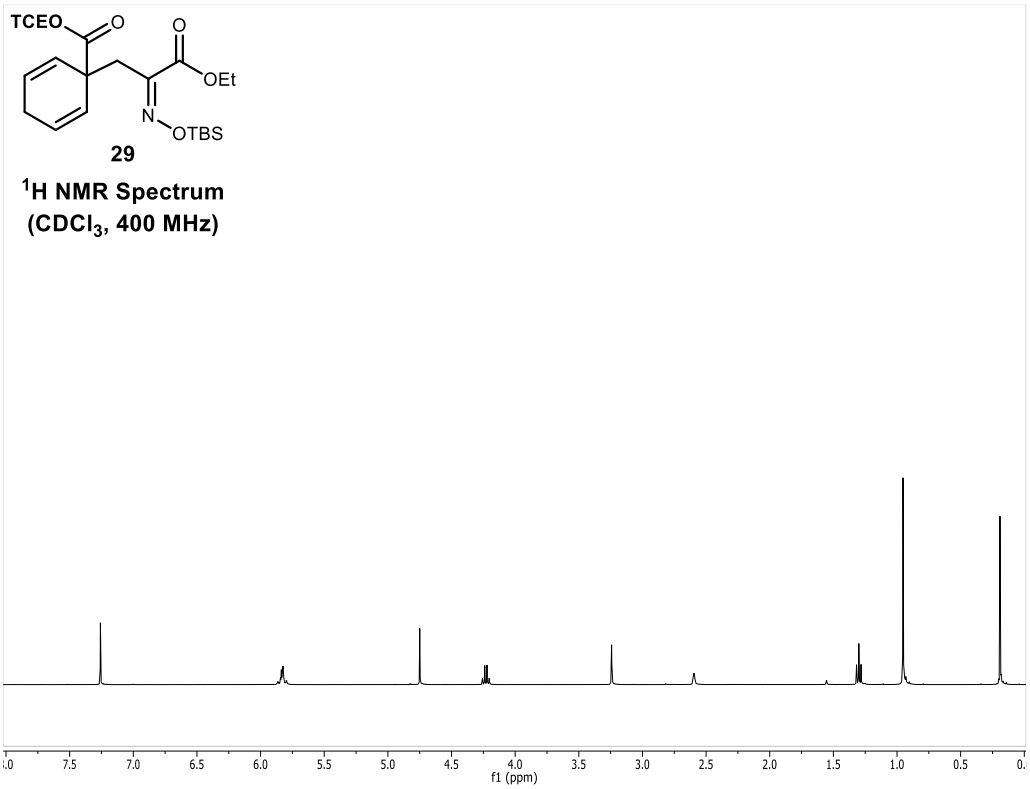


Figure 61. *NMR Spectra of* ***29****.*



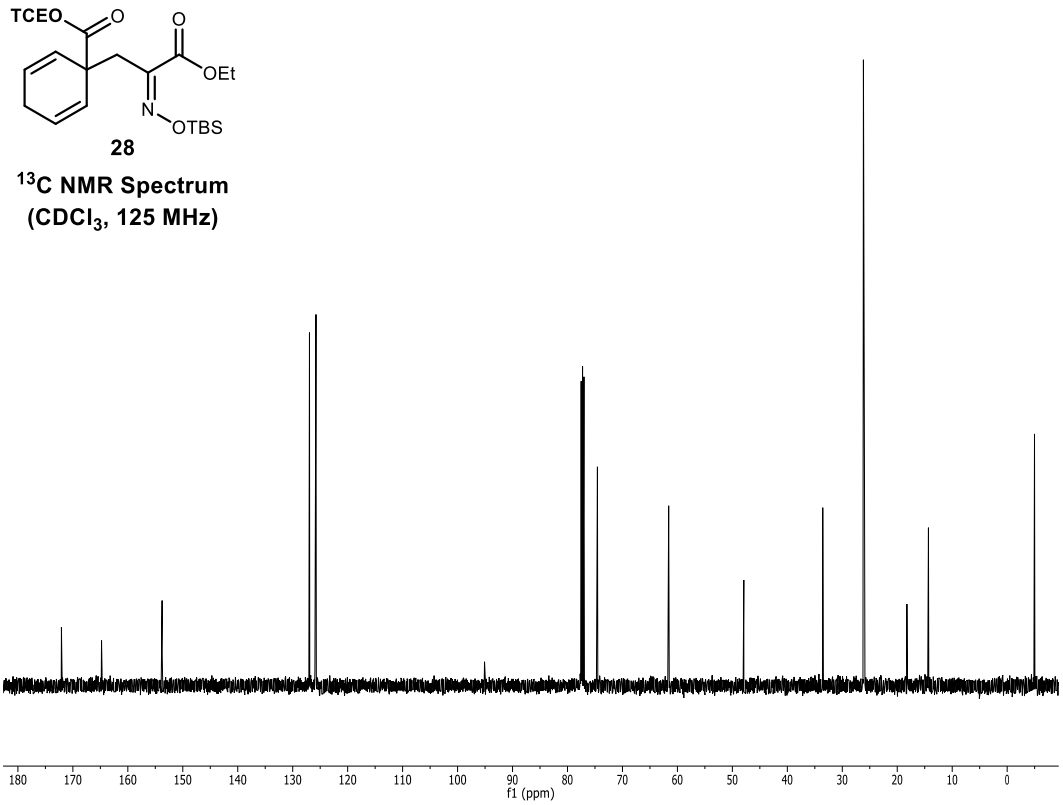
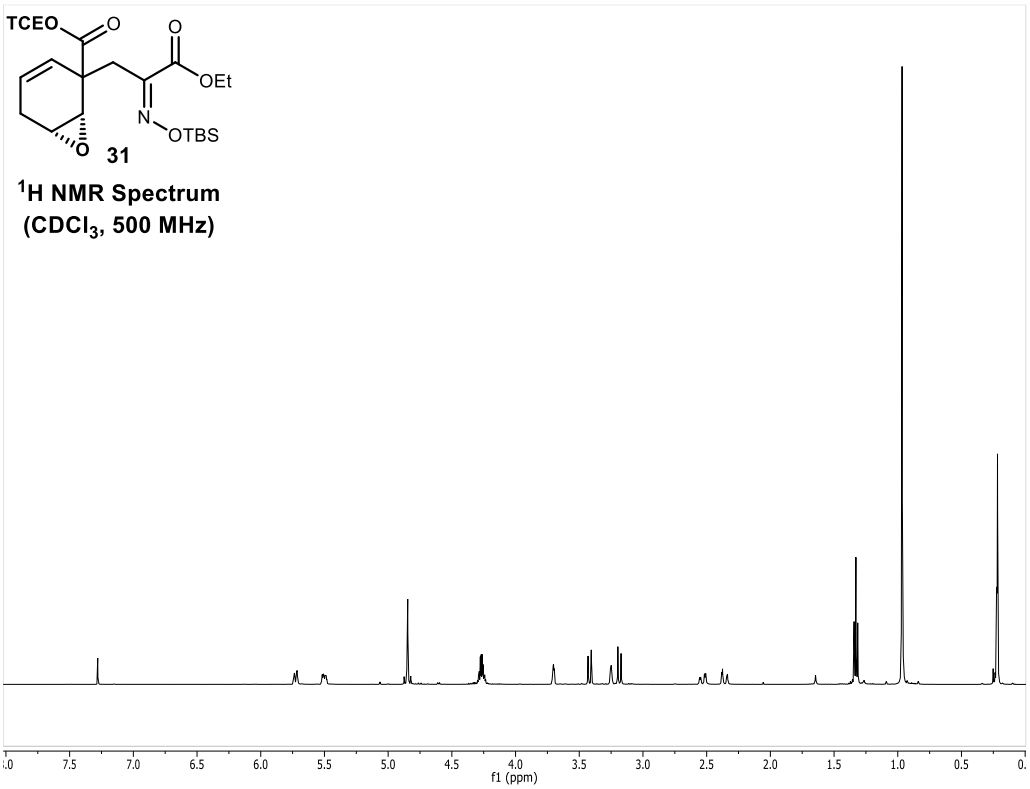


Figure 62. *NMR Spectra of* ***31****.*



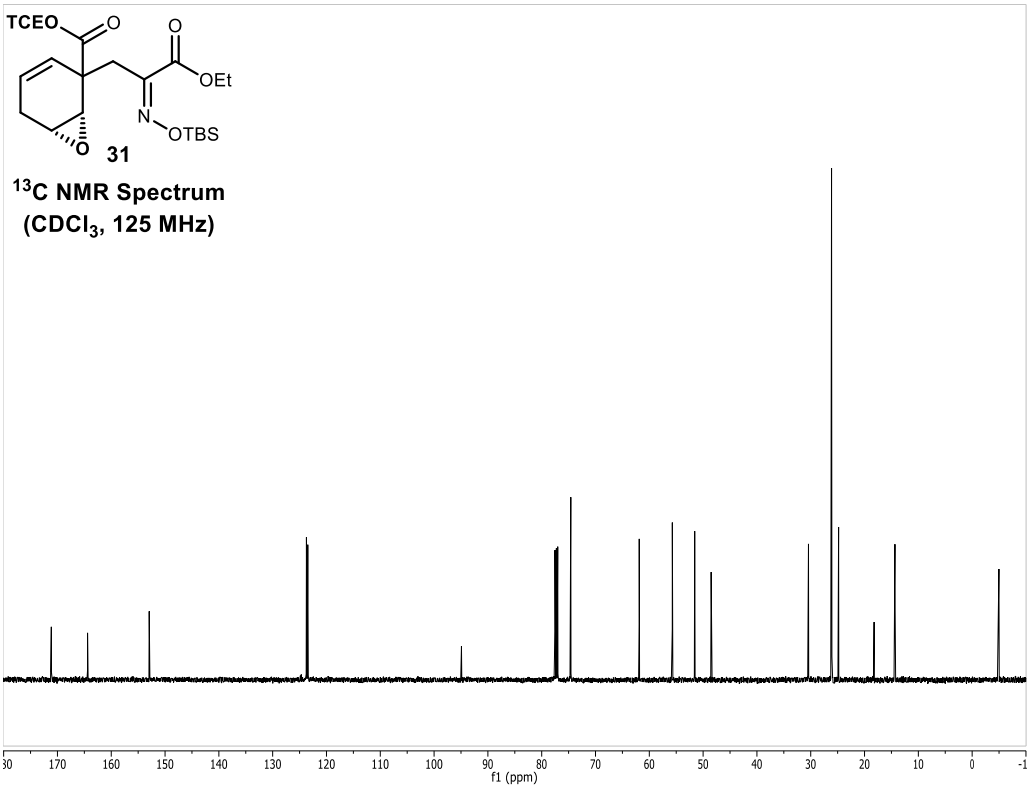
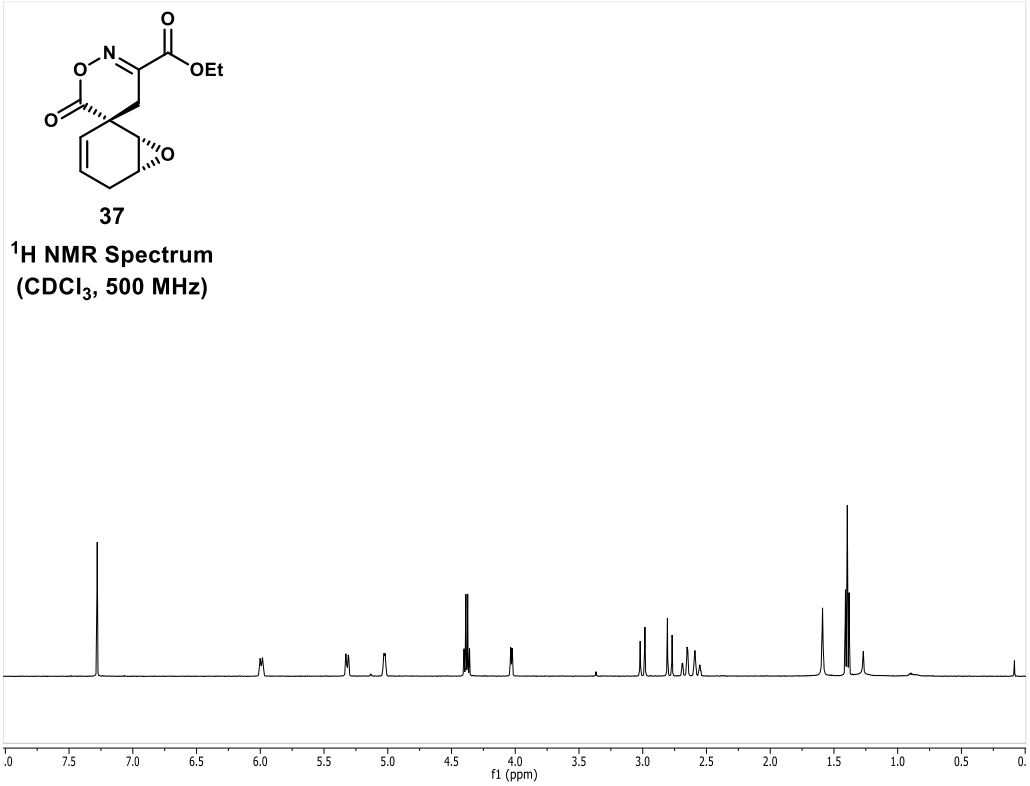


Figure 63. *NMR Spectra of* ***37****.*



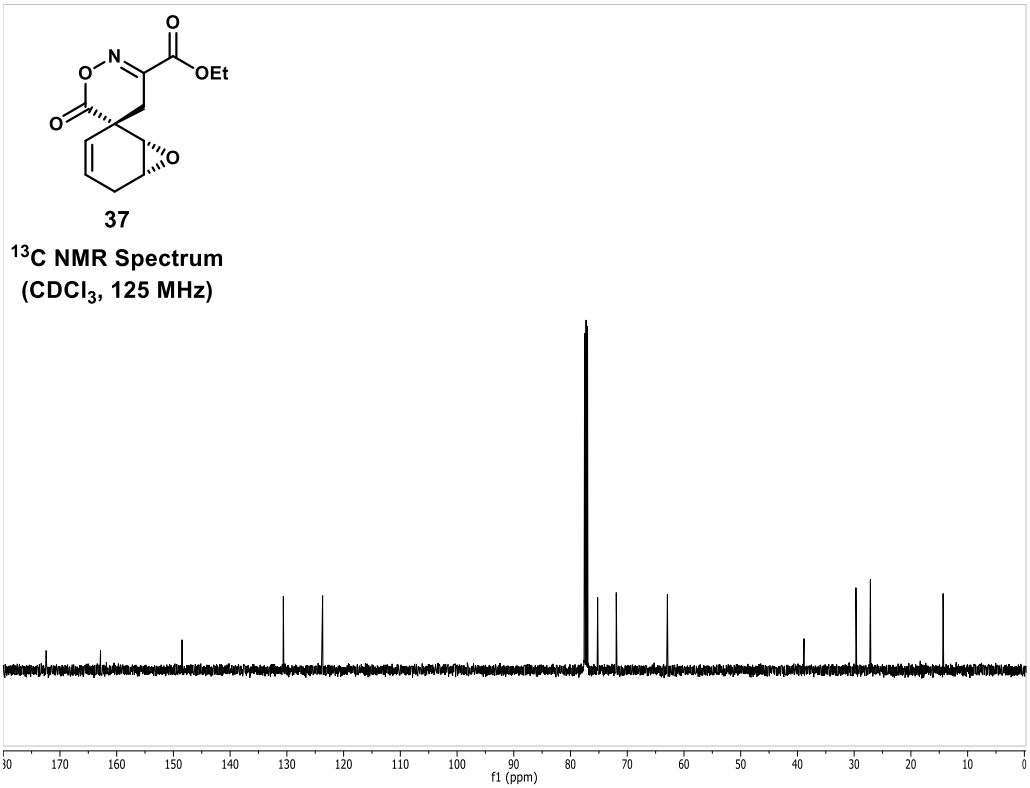


Figure 64. *NMR Spectra of* ***40****.*