Methodology towards the Construction of Bicyclo[2.2.2]diazaoctane Cores and its Application Towards the Synthesis of Brevianamide B

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Methodology towards the Construction of Bicyclo[2.2.2]diazaoctane Cores and its Application Towards the Synthesis of Brevianamide B

A thesis submitted in partial fulfillment of the requirement for the degree of Bachelor of Science in Chemistry from The College of William and Mary

by

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Abstract Page

Outlined in this paper is a series of work done towards the construction of bicyclo[2.2.2]diazaoctane structures found in several natural products. Detailed work is shown for a general method of creating these cores by a domino sequence to rapidly generate these cores with enantio- and diastereoselectivity. A similar sequence is outlined and displayed in the formal synthesis of brevianamide B. This synthesis makes use of a similar domino sequence, but a new source of facial selectivity is used.
Acknowledgements

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Honors Thesis Chapter 1: An Introduction to the Bicyclo[2.2.2]Diazaoctane Cores

Introduction

A number of natural products belonging to a family of reverse prenylated indole alkaloids have received interest due to the presence of a bicyclo[2.2.2]diazaocatne core. There are approximately 70 molecules in the family with the most notable members being the brevianamides, stephacidins, malbrancheamides, notoamides, and paraherquamides as seen in Figure 1.¹ This structure presents a challenge for synthetic chemistry that there is no readily available solution, making it a desirable target for efforts in synthetic chemistry. These molecules are not only interesting from a chemical perspective, but from the prospective of a biologist as well due to the potent activity these molecules have demonstrated in nature. Both breviamaindes A and D have been shown to have modest insecticidal and antifeedant properties.² Additionally, the paraherquamides have been shown to display potent antihelmintic activity and are currently under study as treatments for intestinal parasites. An analog of paraherquamide A, 2-deoxyparaherquamide is currently on the market as an antihelmintic for livestock.¹ Perhaps most notably in this family, both the notoamides and stephacidins have been shown to have potent and selective antitumor activities, where the notoamides have been demonstrated to work against HeLa cancer cell lines.³
**Isolation and Biological Activity**

The first member of this family to be discovered was brevianamide A by Birch and co-workers in 1969 as a metabolite in the fungus *Penicillium brevicomactum*. Subsequently, brevianamides B-F were also isolated in the same fungus, although C and D were found to be photochemically derived products of isolation rather than synthesized naturally.\(^2\) The paraherquamides were later isolated in 1980, followed by the stephacids in 2005, and the notoamides in 2007.\(^1,2\) Most recently, the chrysogenamides have been isolated in China in 2008.\(^1\)

**Biosynthesis**

In addition to this family’s biological activities and chemical structure, these molecules are notable due to their proposed biosynthetic route. There is reasonable evidence that these molecules arise from an enzyme catalyzed Diels-Alder reaction. While this reaction is commonly employed in organic synthesis and has been known to occur in nature without enzyme activity, there are very few cases where a “Diels-Alder-ase” is used in nature. Because all members of this family of molecules have been isolated in an enantiopure form, the reaction is likely to be stereo and enantio-controlled, suggesting the possible use of an enzyme.
Shown in Scheme 1 is the original biosynthetic route proposed by the Birch first put forward shortly after its isolation. The compound brevianamide F is thought to arise from the combination of L-tryptophan and L-proline. Reverse prenylation of this intermediate would give rise to the intermediate deoxybrevianamide E. This intermediate would then be oxidized and undergo the proposed intramolecular Diels-Alder reaction (IMDA) to give a racemic mix of products. After oxidation, these intermediates would then undergo a pinacol rearrangement to give both brevianamides A and B. *In vitro* calculations of the four possible transition states of the Diels-Alder reaction showed that the energy transition states of the products which had the same stereochemistry as brevianamide A and B had the lowest energy associated with them. Additionally it showed that the product corresponding to brevianamide A had a lower energy transition state than that corresponding to brevianamide B. This data potentially shows why brevianamide A is the major metabolite in nature.
Feeding experiments with tritium labeled precursors confirmed that both brevianamide F and deoxybrevianamide E are intermediates in the synthesis of brevianamides A and B. However, these experiments also proved that Birch’s original proposed cycloadducts were not a part of the actual biosynthetic route. This does not exclude the possibility of the IMDA. A revised route by the Williams group shows very similar steps in a slightly different order (Scheme 2). While the original proposed route for brevianamides A and B was proven to be incorrect, it should be noted that when L-proline is replaced with L-isolucine, the route could potentially still hold true for paraherquamide A as the proposed cycloadduct was shown to be incorporated in feeding studies.

**Scheme 2. Williams’ Revised Biosynthesis**

Further studies have shown that both brevianamide F and deoxybreviamaide E are precursors to not just the brevianamides, but the stephacidins and notoamides as well, and are proposed to be involved in the biosynthesis of the malbrancheamides. In other studies it was seen that labeled stephacidin A was incorporated into notoamide B. It can be concluded from these results that both of these molecules likely have their diazaoctane cores constructed in a similar manner to the brevianamides. Extensive studies have been done in order to isolate the
gene cluster involved in the synthesis of the notoamides and stephacidins. Bioinformatic analysis revealed a total of 18 genes (NotA - NotR) to be involved on this pathway. Two proteins of note from this gene cluster are NotE which is responsible for the condensation reaction between tryptophan and proline to create brevianamide F, and NotF which reverse prenylates the indole of tryptophan to give deoxybrevianamide E. The presence of the bicyclo[2.2.2]diazaoctane core is almost exclusively in Aspergillus and Penicillium, two closely related fungi genuses.¹

Scheme 3. Enzymes Involved in Biosynthesis

Current Strategies to Make the Desired Core

Currently there are five strategies that have been employed to make the desired [2.2.2]-diazaoctane core. The biomimetic Diels-Alder employed by the Williams and Liebscher groups,⁹ the radical cyclization by the Myers group,¹² oxidative enolate coupling by the Baran group,¹³ the cation-olefination cyclization route used by the Simpkins group,¹⁵ and finally the S\textsubscript{N}2’ reaction also used by the Williams group.⁸,¹⁵

The first strategy discussed used a biomimetic Diels-Alder reaction, which greatly resembles the proposed biosynthesis from the Birch group. Starting from the proposed biosynthetic intermediate deoxybrevianamide, Williams forms an exocyclic diene in two steps,
which under basic conditions isomerizes to form the required endocyclic intermediate for the IMDA to take place. The resulting intermediates 19 and 20 correspond directly to the

**Scheme 4. Williams IMDA**

biosynthetic route proposed by Birch, and similarly were made to undergo an oxidation and pinacol rearrangement to form brevianamide B. While this strategy was effective at creating a reactive diene for 4+2 cycloadditions, there is no facial or diastereoselectivity, resulting in a 2:1 ratio of racemic diastereomers to be produced. Unfortunately, the minor diastereomer was required to form the desired natural product. While the cycloaddition was not selective, the synthetic route did demonstrate the viability of the Diels-Alder reaction if facial selectivity could be controlled. A very similar intermediate was produced during Williams’s synthesis of VM55599, a related structure. However, after the same IMDA, a total of 4 diastereomers were generated due to the presence of a methyl group on the proline ring.
After these initial attempts at synthesizing VM55599 by Williams and co-workers, Liebscher and co-workers used the same Diels-Alder precursor as Williams and showed that under different non-basic conditions, an IMDA reaction could be used to generate exclusively the diastereomer 26 by using acetyl chloride as a solvent and refluxing for 20 days. 10

The next synthetic strategy demonstrated was by the Myers group in their synthesis of stephacidin and its dimer avrainvillamide (Scheme 5.) 12 Starting from a known achiral cycloexanone derivative, a stereocenter was set using a Corey-Bakshi-Shibata (CBS) catalyst. That single stereoisomer was used to impart selectivity in all subsequent reactions. Since the absolute stereochemistry of stephacidin was unknown at the time, a random catalyst was picked to give the (-) enantiomer. After reaching intermediate 26, the key radical cyclization was employed. Using tert-amyl peroxybenzoate as an initiator, the aminoacyl radical shown was formed according to precedent. 11 After elimination of the 1-methyl-2,5-cyclohexadiene radical precursor as toluene, the radical then attacked the more substituted carbon of the enamide C-C double bond as Baldwin’s rules would predict, causing the expulsion of a phenylthiyl radical. While the key core-forming step had a yield of only 62%, the reaction did give an enantiopure product.
While this synthesis demonstrated a powerful technique in creating the desired bridged structure, it has a minor weakness in that it requires extra steps for the construction of the ring. The sequence required the addition of both the thiophenol group as well as the radical precursor in order to initiate the key step.\(^{12}\)

The third strategy, oxidative coupling, was employed towards these molecules by the Baran group, and was utilized in their total synthesis of the stephacidins.\(^{13}\) After failing to produce the desired core with an intramolecular Diels-Alder, the Baran group decided to turn towards chemistry the lab had previously explored. Previous work in the Baran group had demonstrated the ability to couple enolates of carbonyl compounds with indoles and pyrroles. While indole coupling would be undesirable in this case, they succeeded in demonstrating that the enolates from an ester and amide could be coupled together as well. Starting from CBz protected tryptophan 29, the intermediate 31 was produced in three steps (Scheme 6). Using
methodology from Seebach for asymmetric alkylation of amino acids, the proline derivative 32 was formed. The two fragments were then joined together using BOP-Cl as a peptide coupling agent to produce the required ester and amide for oxidative coupling to occur.

Scheme 6. Baran Oxidative Coupling

In the key ring forming step, a multivalented iron complex Fe(AcAc)_3 was used in order to coordinate the amide and ester together. This combined with the Thorpe-Ingold effect from the quaternary proline carbon was thought to drive the reaction forward. While the exact mechanism of the coupling is unknown, the Baran group did offer several potential explanations ranging from a concerted ionic rearrangement to the formation of a diradical intermediate (Figure 3).
The Williams group executed another synthetic strategy for constructing the desired diazoctane core (Scheme 7). This strategy employs an $S_{N}2'$ ring closing step, and was used in the first total synthesis of brevianamide B. Williams starts with a chiral starting material generated according to procedures developed by Seebach and converts it in three steps to an intermediate containing a diketopiperazine (DKP) core and a p-methoxybenzyl (PMB) group on one of the nitrogens. Ten steps later, the molecule contained the proper functionality to undergo the $S_{N}2'$ ring closing step.
The desired material 46 was produced along with the undesired diastereomer 47 in a ratio of 2:1 with a yield of 62% overall. Treatment of the desired diastereomer with HCl and H₂O served to remove the N-\(t\)-BOC protecting group on the indole as well as to facilitate the cationic cyclization to form the final ring structure. The material was then oxidized using \(m\)-CPBA, and made to undergo the pinacol rearrangement as proposed by Birch in his original biosynthetic scheme, leaving only the removal of a protecting group to give brevianamide B. The synthesis was a total of 21 steps long from commercially available proline.
The $S_N2'$ cyclization demonstrated a variety of possible products based on the temperature and solvent conditions. Most notably, when the reaction took place with NaH in benzene at elevated temperatures, the undesired product was produced almost exclusively (97:3 ratio). However in the presence of 18-crown-6 ether, the selectivity was reversed, giving a ratio of 3.85:1 in favor of the desired diastereomer 46.

The authors proposed that in the absence of a cation complexing agent, the steric interactions between the allylic chloride and the $p$-methoxybenzyl group force the allylic chloride over the enolate formed during cyclization. In addition, the chloride ion and the sodium ion associated with the enolate would have stabilizing interactions, further selecting for the undesired epimer. However, in the presence of a good cation complexing agent, it was suggested that the crown ether sodium complex would generate a much larger amount of steric hindrance compared to the $p$-methoxybenzyl group, selecting for the other epimer. The employment of this cyclization demonstrated the use of crown ethers in generating facial selectivity in $S_N2'$ reactions.\(^{14}\)

The final strategy employed initially looks similar to the Williams group $S_N2'$ synthesis. However, rather than using an $S_N2'$ reaction to initiate the ring closure, the Simpkins group demonstrated a cationic cascade sequence.\(^{15}\) The route shown below was used to form two rings in the fused system after generating a single cation, which is passed through the molecule through intramolecular transfer events (Scheme 8.) Simpkins starts from diastereopure 48, which is a single step away from commercially available proline.\(^{16}\)
Despite the large amount of complexity built in a single step, the key cationic cascade produced a good yield of 82%. Additionally, it was found that facial selectivity could be imparted on the reaction based on the stereoisomer at the prenylated position, much like what was seen in the Baran strategy. This key step allowed the Simpkins group to develop the shortest currently recorded route to brevianamide B in only 9 steps. However, despite its brevity, the synthesis is not without its drawbacks. The diastereoselectivity at the C6 position seemed to depend on the steric bulk of the protecting group associated with the amide, as an erosion of selectivity was observed when moving from a PMB group, which gave a single diastereomer, to the OBn group which gave a 4:1 mixture of diastereomers.15
Conclusion

While all of the routes shown successfully afforded the desired diazaoctane core, there is still room for improvement. Each synthesis was highly specific to the construction of that molecule. None of the strategies shown could be easily generalized to address the problem of making a whole family of molecules containing the core. These routes also tended to be very linear rather than convergent in nature. It was noted that reaction schemes that employed cascadre reactions of multiband forming reactions were more efficient. Our work was motivated by a desire to design a more general route for constructing the core with diastereo- and facial selectivity.

Table 1. A Comparison of Routes

<table>
<thead>
<tr>
<th>Author</th>
<th>Technique Employed</th>
<th>Molecule</th>
<th>Longest Linear Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams</td>
<td>Intramolecular Diels-Alder</td>
<td>Brevianamide B</td>
<td>12 steps</td>
</tr>
<tr>
<td>Myers</td>
<td>Radical Cyclization</td>
<td>Stephacidin A</td>
<td>12 steps</td>
</tr>
<tr>
<td>Baran</td>
<td>Oxidative Coupling</td>
<td>Stephacidin A</td>
<td>11 steps</td>
</tr>
<tr>
<td>Williams</td>
<td>S_{N2}' Cyclization</td>
<td>Brevianamide B</td>
<td>18 steps</td>
</tr>
<tr>
<td>Simpkins</td>
<td>Cationic Cascade Sequence</td>
<td>Brevianamide B</td>
<td>9 steps</td>
</tr>
</tbody>
</table>
References

Introduction

Based on previous syntheses, it was clear that a more general strategy for preparing the key [2.2.2] diazaoctane core was required. In response to this need we began work on a novel domino reaction sequence consisting of an aldol condensation, an isomerization, and intramolecular Diels-Alder reaction (IMDA.) The potential of this sequence was first demonstrated during the work of Stephen Laws in his attempts to make malbrancheamide B (Scheme 2 vide infra). The initial hope was to use an aldol condensation reaction to create an exocyclic diene which would then isomerize to create the endocyclic intermediate under basic conditions. This intermediate would then be able to participate in an IMDA to create the desired ring.

Methods

Scheme 1. Chiral Diketopiperazine Core

Diketopiperazines (DKP) 2 and 3 were produced according to Scheme 1 from commercially available N-chloroacyl L-serine methyl ester as a pair of separable diastereomers. The absolute stereochemistry of these substrates was confirmed by x-ray crystallography. Substrate 3 was then submitted to basic conditions in the presence of aldehyde 4 in the hopes that it would undergo the reaction sequence described above. It was expected that each step of the reaction would occur in a stepwise manner.
Scheme 2. Initial Evidence for Domino Sequence

![Scheme 2](image)

To our delight the condensation intermediate underwent the subsequent isomerization and [4+2] cycloaddition in the same reaction vessel (Scheme 2). Additionally, the chiral phenyl aminal functionality provided good facial selectivity, giving product 5 as a single diastereomer (dr 95:5). The steric bulk of the phenyl group was able to direct the dienophile to approach from the opposite face, giving the major diastereomer. Since the dienophile group was tethered to the molecule, there were no issues with regioselectivity.

While a simple NaOMe/MeOH solution was effective at driving the domino sequence with aldehydes which did not contain enolizable protons, new conditions needed to be determined for enolizable substrates (Scheme 3). Certain substrates such as aldehyde 4 were compatible with a sodium methoxide solution, aldehydes which had enolizable protons would self condense under these conditions.

Scheme 3. Conditions for the Domino Sequence

![Scheme 3](image)
By controlling the order of the addition of reagents, the domino sequence could still continue.

Addition of LiHMDS to a solution of DKP at -78°C provided exclusive enolization of the desired material, rather than the aldehyde. The resulting alcohol was then acetylated with 1.3 equivalents (-78 °C → rt) of acetic anhydride. Addition of DBU, an organic base, would then drive the elimination of the acetyl group and isomerization to the endocyclic diene.

While the previous steps occurred relatively rapidly, heating overnight at 90 °C was required to drive the Diels-Alder cycloaddition reaction to completion.

Results

The two conditions were then applied towards the substrates shown in Table 1.

With these two sets of conditions, it
shown that the strategy was applicable to a variety of functionalities and gave us the ability to construct a variety of ring sizes, from five membered rings to the seven membered ring made in the initial example. Additionally, it was observed that alkynes were capable of cycloadditions as well. While good selectivity could be obtained for all substrates, there was a decline noted for the 3,3-dimethyl-hexenal substrate. It was noted that reactions performed under conditions B generally gave lower yields than those obtained under conditions A.

**Discussion**

There are several strong points to the described strategy that make it a potent response to the problem of constructing the bicyclo[2.2.2]diazaocatne core. The Diels-Alder reaction has always been desirable due to its ability for form two bonds simultaneously. The reaction is able to generate the desired core structure with good enantioselectivity as well as diastereoselectivity due to the chirality of the phenyl aminal group. Additionally, the reaction has the advantage of taking place in a single reaction vessel, which allows rapid generation of a large amount of complexity. While our synthesis does bear strong similarities to IMDAs employed the by the Williams group, there are key differences which distinguish the two. This is most apparently seen in the Williams synthesis of malbrancheamide B with our own strategy (Scheme 4). 4-5
Williams’s strategy involves constructing the molecule in a completely linear fashion, while our strategy allows for variable aldehydes to be condensed onto a DKP core which can have different functionalities installed on it, increasing the ease of generating analogs of the molecule. This more convergent synthesis has an advantage over linear ones due to its increased yield and the relative ease in constructing smaller fragments separately rather than a large molecule. By separating a molecule into smaller fragments, different functionalities can be installed without worry about more distant functionalities located on other fragments. Furthermore, it takes three separate steps with the Williams route to form the DKP core, the diene precursor, and finally undergo the Diels-Alder reaction. Our route reduces this time intensive strategy to a single one-pot reaction. Finally due to the presence of a chiral aminal auxiliary, facial selectivity allows the synthesis of enantiopure material.
However, our route is not without its flaws. While good facial and diastereoselectivity were shown during all model reactions, during our application towards the total synthesis of malbrancheamide B, there was a degradation of selectivity. It was seen that while the chiral aminal could still generate good facial selectivity, the dr: declined from 95:5 to 2:1, giving the “syn” product over the “anti.” These results are consistent with previous work done by the Williams group with the model system and the IMDA used in their synthesis of brevianamide B shown in Scheme 4. The anti and syn relationship in this case refers to the endo and exocyclic orientations of the IMDA reaction, with the endo product corresponding to the anti configuration (Scheme 5). It was seen during trial runs of the synthesis that after the addition of the indole, the anti-selectivity was unobtainable. In fact, after addition of the indole, the system was shown to give a ratio of 2:1 in favor of the syn product.

Scheme 5. Effects of an Indole Diastereoselectivity

It was theorized that the added rigidity of the indole system was responsible for this change in
selectivity. Comparison between the model shown and other models generated by the Williams group demonstrated that the gem dimethyl groups had a negligible effect on selectivity, leaving the indole responsible for the undesired syn bias. *Ab initio* calculations later showed that in the presence of the indole there was a 1.2 kcal/mol difference in energy favoring the syn relationship while in the model system, anti-stereochemistry was favored by 4-7 kcal/mol. Comparing our work with the IMDA reactions employed by Williams in his syntheses of brevianamide B shows that while our reaction imparted facial selectivity, the diastereoselectivity was comparable to achiral analogs. Another drawback of the route is one that is intimately tied to one of its successes. While the chiral phenyl aminal provides good facial selectivity of the reaction, it is not present in any of the structures containing the diazaoctane core. This means that it must be removed eventually. Although there is precedent for easy removal of the aminal chiral auxiliary by reduction, the methods proved to be harsh on other functionalities on the molecule, requiring additional steps in order to remove.

**Conclusion**

Outlined in this chapter was an efficient way to generate a large amount of complexity in the form of a bicyclic[2.2.2]diazaoctane core from a one-pot domino reaction. Good enantioselectivity could be imparted on the molecule from a chiral phenyl aminal auxiliary. The sequence showed a wide range of applications by creating three different ring sizes as well as proving accessible to alkynes. The route showed competitive results with all other strategies currently available to make the desired core due to its enantioselectivity and amount of complexity generated in a single step. This synthetic strategy should be applicable towards a wide range of biologically active molecules containing the signature bicyclo[2.2.2]diazaoctane core.
Experimental Procedures

**Diketopiperazine lactim methyl ether 2, 3.** To *N*-chloroacyl L-serine methyl ester \(^8\) (4.5 g, 22.8 mmol) in toluene (220 ml) at rt was added benzaldehyde dimethyl acetal (2.9 ml, 27.4 mmol) and *p*-toluenesulfonic acid monohydrate (108 mg, 0.57 mmol). The solution was heated at reflux for 16 h with a Dean-Stark trap. After cooling to rt, the solution was diluted with saturated aqueous NaHCO\(_3\) (2 x 50 ml). The organic layer was removed and the aqueous portion extracted with Et\(_2\)O (75 ml). The combined organic layers were washed with brine (50 ml), dried with Na\(_2\)SO\(_4\), and concentrated *in vacuo*. The viscous product was purified by flash column chromatography on silica gel (elution: 10% to 60% EtOAc in hexane) to afford a yellow oil (5.48 g, 19.23 mmol, dr ca. 2:1). This intermediate product was dissolved in butanone (110 ml), sodium azide (2.50 g, 38.5 mmol) was added, and the heterogeneous mixture was heated to 80 °C for 15 h. After cooling to rt, the mixture was concentrated to a syrup and diluted with a halvesaturated NaCl solution (100 ml) and extracted with Et\(_2\)O (3 x 50 ml). The combined organic phases were dried with Na\(_2\)SO\(_4\), and concentrated to afford a reddish-brown oil (5.34 g, 18.3 mmol). This intermediate azide product was used without purification in the subsequent Staudinger reduction. After dissolving the intermediate azide product (2.3 g, 7.9 mmol) in toluene (45 ml), resin-bound triphenylphosphine (3.3 g, ~10.0 mmol) was added at rt. The mixture was stirred for 10 min at rt until gas evolution steadied and was heated to 90 °C for 20 h. Additional resin-bound triphenylphosphine was added (0.5 g), until consumption the starting material was apparent by TLC. After cooling to rt, the phosphine resin was removed by vacuum filtration. The filtrate was concentrated and purified by flash column chromatography on silica (elution: 30% to 100% EtOAc in hexane) to afford product 2 (0.88 g, 36% yield, 3 steps) as a colorless solid and 3 (0.44 g, 19% yield, 3 steps) as a light yellow oil: 2: mp 133 °C; TLC (60% EtOAc in hexane), *R*\(_f\): 0.15 (K MnO\(_4\)); [\(\alpha\)]\(_{D25}^-\) = −63.2° (c = 2.02, CH\(_2\)Cl\(_2\)); IR (film) 3022, 2948, 2872, 1684, 1559, 1361, 1265, 1185, 1048, 934, 760 cm\(^{-1}\); 1HNMR (400MHz, CDCl\(_3\)) 7.37 (m, 3H), 7.29 (m, 2H), 6.25 (s, 1H, C\(_8\)H), 4.49 (m, 1H), 4.31 (m, 1H), 4.28 (d, \(J\) = 19.5 Hz, 1H), 4.12 (dd, \(J\) = 19.9, 3.9 Hz, 1H), 4.04 (t, \(J\) = 9.0, 1H, C\(_6\)H), 3.83 (s, 3H); 13C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.0, 161.3, 136.9, 129.6, 128.9, 126.8, 90.2, 65.7, 55.1, 54.1, 53.6; Exact mass calcd for C\(_{13}\)H\(_{14}\)N\(_2\)O\(_3\)Na [M+Na\(^+\)], 269.0897. Found 269.0892.

X-ray structure.

3: TLC (60% EtOAc in hexane), *R*\(_f\): 0.20 (K MnO\(_4\)); [\(\alpha\)]\(_{D25}^-\) = −107° (c = 2.30, CH\(_2\)Cl\(_2\)); IR (film)2993, 2950, 2892, 1704, 1438, 1338, 1315, 1224, 1113, 1011, 850, 769 cm\(^{-1}\); 1H NMR
(400MHz, CDCl3) 7.50 (m, 3H), 7.40 (m, 2H), 6.50 (s, 1H, C8H), 4.49 (dd, obs triplet, J = 6.6 Hz, 1H), 4.37 (m, 1H), 4.23 (s, 2H), 3.88 (t, J = 9.0 Hz, 1H, C6H), 3.76 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 165.4, 158.6, 138.2, 129.3, 128.8, 126.5, 88.9, 69.4, 54.3, 53.8, 52.2; Exact mass calcd for C13H14N2O3Na [M+Na]+, 269.0897. Found 269.0901.

**General conditions A** for aldol condensation / alkene isomerization / DKP Diels-Alder cycloaddition. To diketopiperazine 2 (0.2–0.3 mmol) in methanol (1.0–2.0 mL, degassed with nitrogen) at rt was added the dieneopholic aldehyde substrate (1.2–1.3 equiv) and a freshly prepared solution of sodium methoxide (3 equiv, 0.45–1.0 mL, 2.0 M). The reaction mixture was heated to 65 °C for 16–24 h. After cooling to rt, the reaction mixture was diluted with sat. aqueous NH4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na2SO4), filtered and concentrated in vacuo.

**General conditions B** for aldol condensation / alkene isomerization / DKP Diels-Alder cycloaddition. To diketopiperazine 2 (0.2 mmol) in toluene (2 mL) at –78 °C was added LiHMDS (1.0M in THF, 1.1 equiv) dropwise over 5 min by syringe. After stirring for 15 min at –78 °C, the aldehyde substrate (1.1–2 equiv) was added to the solution. After stirring for an additional 15 min at –78 °C, Ac2O (1.3 equiv) was added and the cooling bath removed. The reaction mixture was stirred at room temperature for 1–2 h. DBU (2 equiv) was added and the reaction was heated to 90 °C for 16–24 h. After cooling to rt, the reaction mixture was diluted with sat. aqueous NH4Cl (20 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine (10 mL), dried (Na2SO4), filtered and concentrated in vacuo.

**Cycloadduct 5.** Prepared according to general procedure A. To a solution of compound 2 (40.4 mg, 0.25 mmol) in methanol (2.0 mL) under nitrogen was added salicaldehyde 4 (57.1 mg, 0.23 mmol) and sodium methoxide (0.37 mL, 2M, 0.75 mmol). The reaction vessel was fitted with are flux condenser and heated to 65 °C. After stirring at reflux for 21 h, the mixture was cooled to 23 °C, diluted with sat. aqueous NH4Cl and extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated in vacuo. The unpurified product was a single diastereomer as judged by 1H NMR. Purification by flash chromatography on silica gel (elution: 20% to 60% EtOAc in hexane) afforded product 5 (68.7 mg, 76% yield) as a colorless amorphous solid: TLC (40% EtOAc in hexane), Rf: 0.40 (CAM); [α]D25 = −75.3° (c = 0.77, MeOH); IR (film) 2948, 2865, 1691, 1633, 1490, 1289 cm–1; 1H NMR (400 MHz, CDCl3) 7.38–7.35 (m, 3H), 7.32–7.28 (m, 3H), 7.18 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.26 (s, 1H), 4.51 (d, J = 9.3 Hz), 4.06 (dd, J = 11.7, 3.9 Hz, 1H), 4.02 (d, J = 9.4 Hz, 1H), 3.63 (s, 3H), 3.49 (d, J = 14.9 Hz, 1H), 3.42 (d, J = 14.9 Hz, 1H), 3.28 (t, J = 11.7 Hz, 1H), 2.77 (m, 1H), 2.35 (dd, J = 12.9, 9.8 Hz, 1H), 1.00 (dd, J = 12.9, 4.7 Hz, 1H);
Salicaldehyde allyl ether 4 was prepared by alkylation of salicaldehyde.9

Cycloadduct 7. Prepared according to general procedure A. The unpurified product was a 90:10 mixture of diastereomers as judged by 1H NMR. Purification by flash chromatography on silica gel (elution: 15% to 60% EtOAc in hexanes) afforded product 7 as a white solid (76.8 mg, 68% yield): mp 165.4–168.0 °C; TLC (30% EtOAc in hexane), Rf: 0.25 (CAM); [α]D25 =+21.5° (c = 0.12, CH2Cl2); IR (film) 3359, 2946, 1684, 1632, 1495, 1453, 1409, 1582, 1337, 1253, 1212, 763, 742; 1H NMR (400 MHz, CDCl3) 7.36 (m, 3H), 7.31 (m, 3H), 7.18 (t, J = 7.0 Hz, 1H), 7.11 (t, J = 7.0 Hz, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.23 (s, 1H), 4.59 (d, J = 9.4 Hz, 1H), 4.08, (d, J = 9.4 Hz, 1H), 3.77 (s, 3H), 3.74 (d, J = 18.0 Hz, 1H), 3.33 (d, J = 18.0 Hz, 1H), 2.85 (dd, J = 16.0, 5.1 Hz, 1H), 2.55–2.45 (m, 4H), 1.45 (d, J = 10.2 Hz, 1H); 13C NMR (100 MHz, CDCl3) 170.2, 169.5, 136.5, 134.4, 134.2, 129.8, 129.2, 128.5, 128.0, 126.7, 126.3, 126.3, 125.5, 88.4, 67.4, 66.5, 64.1, 62.9, 54.8, 37.6, 36.3, 34.8, 34.2, 33.; Exact mass calcd for (C23H22N2O3Na) [M+Na]+, 397.1525. Found 397.1525. X-ray structure.

Allyl benzaldehyde 8 was prepared according to the above scheme.10
Cycloadduct 9. Prepared according to a modified general procedure A, whereby additional vinyl benzaldehyde substrate 8 (1 equiv, 2.25 equiv total) was added to the reaction mixture after 1 h and the solution was maintained at 65 °C for an additional 18 h. The reaction vessel was cooled to room temperature and worked up according to the general procedure A. The unpurified product was a single diastereomer as judged by 1H NMR. Purification by flash chromatography on silica gel (elution: 10% to 40% EtOAc in hexanes) afforded product 9 (49.2 mg, 68% yield) as a pale yellow solid: mp 208 °C; TLC (40% EtOAc in hexane) Rf: 0.30 (CAM); [α]D25 = +140° (c = 1.70, CH2Cl2); IR (film) 3064, 2950, 2894, 1698, 1639, 1457, 1399, 1369, 1241, 1199, 1072, 841, 755 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.37–7.15 (m, 8H), 7.04 (d, J = 7.0 Hz, 1H), 6.24 (s, 1H), 4.58 (d, J = 9.8 Hz, 1H), 4.11 (d, J = 9.8 Hz, 1H), 3.81 (dd, J = 10.2, 6.3 Hz, 1H), 3.68 (s, 3H), 3.62 (d, J = 15.6 Hz, 1H) 3.36 (d, J = 15.6 Hz, 1H), 2.57 (t, J = 11.7, 1H), 1.95 (dd, J = 12.5, 6.3 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 171.4, 142.9, 141.8, 136.3, 129.3, 128.5, 127.0, 126.5, 125.8, 123.0, 88.58, 88.6, 77.9, 67.1, 65.4, 49.8, 36.4, 35.5, 32.2; Exact mass calcd for C22H20N2O3Na [M+Na]+, 383.1366. Found 383.1368.

Vinyl benzaldehyde 8 was prepared from 1-bromo-2-vinylbenzene via lithium-halogen exchange (n-BuLi) and trapping the derived aryl lithium with DMF.11

Cycloadduct 11. Prepared according to general procedure A. The unpurified product was a single diastereomer as judged by 1H NMR. Purification by flash chromatography on silica gel (elution: 20% to 60% EtOAc in hexanes) afforded product 11 (34 mg, 50% yield) as a white solid: mp 121.6–123.6 °C; TLC (40% EtOAc in hexanes), Rf: 0.59 (CAM); [α]D25 = +46.3° (c =0.88, CH2Cl2); IR (film) 3852, 3748, 2948, 2893, 2863, 1682, 1635, 1558, 1456, 1398, 1353, 1312, 1216, 1197 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.35 (m, 3H), 7.26 (m, 2H), 6.18 (s, 1H), 4.49 (d, J = 9.4 Hz, 1H), 4.01 (d, J = 9.4 Hz, 1H), 3.84 (s, 3H), 2.55 (m, 1H), 2.23 (d, J = 13.7 Hz, 1H), 2.18 (dd, J = 12.1, 9.4 Hz, 1H), 2.07 (d, J = 13.7 Hz, 1H), 1.73 (dd, J = 12.1, 7.0 Hz, 1H), 1.42 (dd, J = 12.1, 4.7 Hz, 1H), 1.22 (s, 3H), 1.21 (m, 1H), 1.13 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 170.1, 169.6, 136.6, 129.8, 128.4, 126.8, 88.2, 77.7, 76.7, 67.0, 64.9, 54.5, 46.1, 44.4, 43.3, 39.3, 33.7, 31.9, 31.7; Exact mass calcd C20H24N2O3Na [M+Na]+, 363.1679. Found 363.1681.
2,2-dimethyl-4-pentenal (10) was prepared according to the above scheme.\textsuperscript{12}

\begin{center}
\includegraphics[width=0.8\textwidth]{cycloadduct_13_diagram}
\end{center}

**Cycloadduct 13.** Prepared according to general procedure B. The unpurified product was a single diastereomer as judged by \( ^1H \) NMR. Purification by flash chromatography on silica gel (elution: 10\% to 50\% EtOAc in hexanes) afforded product 13 (34.2 mg, 52\% yield) as a white solid: mp 148 °C; TLC (40\% EtOAc in hexane) \( R_f\) : 0.30 (CAM); \([\alpha]^D_{25} = +118^\circ \) (\( c = 0.77, \) MeOH); IR (film) 2923, 2856, 1693, 1637, 1558, 1495, 1456, 1404, 1361, 1208, 1049, 972, 755, 697, 623 cm\(^{-1}\); 1H NMR (400MHz, CDCl3) 7.34–7.32 (m, 3H), 7.27–7.24 (m, 2H), 6.20 (s, 1H), 4.51 (d, \( J = 9.4 \) Hz, 1H), 4.01 (d, \( J = 6.6 \) Hz, 1H), 3.86 (s, 3H), 2.32 (dd, \( J = 12.5, 9.4 \) Hz, 1H), 2.16 (m, \( J = 13.6, 1H \)), 2.04 (m, 1H), 1.90 (m, 1H), 1.83–1.63 (m, 5H), 1.24 (m, 1H), 1.19 (dd, \( J = 12.5, 4.3 \) Hz, 1H), 1.09 (\( J = 12.9, 3.1 \) Hz, 1H); 13C NMR (100 MHz, CDCl3) \( \delta \) 171.1, 169.0, 136.8, 129.0, 128.5, 126.3, 88.3, 67.3, 67.0, 62.9, 54.4, 38.6, 37.3, 30.2, 29.3, 25.4, 21.0; Exact mass calcld for C19H22N2O3Na \([M+Na]^+\), 349.1523. Found 349.1524. **X-ray structure.**

5-hexenal\textsuperscript{13} (18) was prepared from 5-hexen-1-ol by Parikh-Doering oxidation (SO3•pyr, DMSO, \( i\)-Pr2NEt).

\begin{center}
\includegraphics[width=0.8\textwidth]{cycloadduct_19_diagram}
\end{center}

**Cycloadduct 19.** Prepared according to general procedure B. The unpurified product was a single diastereomer as judged by \( ^1H \)NMR. Purification by flash chromatography on silica gel (elution: 30\% to 80\% EtOAc in hexanes) afforded product 19 (20.2 mg, 31.2\%) as a white solid: mp 132.6–133.8 °C; TLC (60\% EtOAc in hexanes), \( R_f\) : 0.46 (KMnO4); \([\alpha]^D_{25} = +42.7^\circ \) (\( c = 0.80, \) CH2Cl2); IR (film) 2947, 2869, 1689, 1635, 1558, 1540, 1398, 1353, 1317, 1255, 1212, 1196, 1018, 915, 759, 736, 697, 621, 551 cm\(^{-1}\); 1H NMR (400 MHz, CDCl3) 7.34 (m, 3H), 7.26 (m, 2H), 6.19 (s, 1H), 4.51 (d, \( J = 9.8 \) Hz, 1H), 4.09 (d, \( J = 9.8 \) Hz, 1H), 3.83 (s, 3H), 2.34 (m, 2H), 2.22 (dd, \( J = 12.5, 9.5 \) Hz, 1H), 2.20 (m, 1H), 2.10–1.86 (m, 3H), 1.48 (dd, \( J = 12.5, 5.1 \) Hz, 1H), 1.26 (m, 1H); 13C NMR (100 MHz, CDCl3) \( \delta \) 170.3, 170.1, 136.6, 129.1, 128.5, 126.4, 88.4, 76.7, 67.1, 65.2, 54.6, 45.6, 34.1, 30.0, 28.1, 23.6; Exact mass calculated for C18H20N2O3Na \([M+Na]^+\), 335.1366. Found 335.1364.
Cycloadduct 15. Prepared according to general procedure B. The unpurified product was a single diastereomer as judged by 1H NMR. Purification by flash chromatography on silica gel (elution: 10% to 50% EtOAc in hexanes) afforded product 15 (23.9 mg, 37% yield) as a yellow oil: TLC (40% EtOAc in hexane) Rf = 0.40 (CAM); [α]D 25 = +59° (c = 2.70, MeOH); IR (film) 3312, 3064, 2946, 2864, 2366, 1691, 1559, 1268, 1110, 1028, 735 cm⁻¹; 1H NMR (400 MHz, CDCl3) 7.33 (m, 3H), 7.26 (m, 2H), 6.26 (s, 1H), 5.86 (s, 1H), 4.73 (d, J = 9.4 Hz, 1H), 4.31 (d, J = 9.8 Hz, 1H), 3.84 (s, 3H), 2.67 (m, 1H), 2.52–2.36 (m, 2H), 2.12 (m, 1H), 1.81–1.66 (m, 3H), 1.61 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 174.1, 169.2, 155.4, 129.2, 128.4, 126.6, 126.1, 87.9, 74.6, 68.6, 66.9, 66.1, 55.7, 26.9, 25.9, 20.9, 19.3; Exact mass calcd for C19H20N2O3Na [M+Na]+, 347.1366. Found 347.1355.

5-hexynal14 (14) was prepared from 5-hexyn-1-ol by Parikh-Doering oxidation (SO₃•pyr, DMSO, i-Pr₂NEt).

Cycloadduct 17. Prepared according to general procedure B. The unpurified product was a 85:15 ratio of diastereomers as judged by 1H NMR. Purification by flash chromatography on silica gel (elution: 10–50% EtOAc in hexanes) could not separate the diastereomers; product 17 (31.5 mg, 44% yield) was afforded as a pale yellow oil (data for major isomer): TLC (40% EtOAc in hexane) Rf: 0.40 (CAM); [α]D25 = +24° (c = 2.14, CH2Cl2); IR (film) 2951, 2866,1683, 1458, 1398, 1353, 1216, 1029, 936, 738 cm−1; 1H NMR (400 MHz, CDCl3) 7.32 (m,3H), 7.25 (m, 2H), 6.17 (s, 1H), 4.51 (d, J = 9.4 Hz, 1H), 4.04 (d, J = 9.8 Hz, 1H), 3.83 (s, 3H), 2.51 (m, 1H), 2.22 (dd, J = 10.2, 6.3 Hz, 1H), 2.15 (m, 1H), 2.11 (dd, J = 20.7, 8.6 Hz, 1H), 1.90 (m, 1H), 1.80 (m, J = 5.1 Hz, 1H), 1.57 (dd, J = 12.5, 6.3 Hz, 1H), 1.04 (s, 3H), 0.87 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 170.4, 169.4, 129.0, 128.5, 128.4, 128.4, 126.4, 126.0, 88.2, 77.8, 67.1, 65.9, 55.0, 54.3, 41.7, 39.1, 30.7, 29.5, 27.3, 25.0; Exact mass calcd for C20H24N2O3Na [M+Na]+, 363.1679. Found 363.1667.
References

Honors Thesis Chapter 3: Efforts Towards the Total Synthesis of Brevianamide B

An Introduction to Brevianamide B

After demonstrating the utility of our synthetic strategy discussed in chapter 2, we sought to apply our methods towards the total synthesis of the molecule brevianamide B. As previously mentioned, brevianamide B is part of a larger family of reverse prenylated alkaloid indoles containing a unique bicyclo[2.2.2]diazaoctane core. Brevianamide A was the first member of this family of molecules to be isolated in 1969 in the fungi *Penicillium brevicomatum* by the Birch group. Later, brevianamimides B through F were isolated in the same fungus. The brevianamides are structurally unique from most other members of the bicyclo[2.2.2]diazaoctane in that the ring structure fused to the core has the opposite stereochemistry from most members of the family (Figure 1).\(^1\) This stereochemistry aligns with the “*syn*” diastereomer according to nomenclature established by Williams.\(^2\) Along with most members of this family, brevianamide B displays biological activity as an insecticide.\(^3\)

Figure 1. Stereochemical Relationships to the Diazaoctane Core

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\(^1\) Figure 1: Stereochemical Relationships to the Diazaoctane Core

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\(^2\) This stereochemistry aligns with the “*syn*” diastereomer according to nomenclature established by Williams.

\(^3\) Along with most members of this family, brevianamide B displays biological activity as an insecticide.
While we had already devised a viable strategy for creating the key diazaoctane core, we chose to use the challenges presented by brevianamide B to expand upon our earlier efforts at constructing bicyclo[2.2.2]diazaoctane cores. We desired to revise the previous strategy in order to overcome the limitations encountered in previous work. Primary, these limitations were a lack of diastereoselectivity of the “syn” and “anti” products and the removal of the chiral aminal. With this goal in mind, a new strategy was designed where facial would be generated from the dieneophile rather than the diene. Conditions for this reaction could largely be kept the same as they previously were (scheme 1).

**Scheme 1. Creating an Achiral Azadiene**

By stopping the reaction sequence after the isomerization step, a variety of dienophiles with various auxiliaries could be tested in an attempt to generate enantio-, diastereo-, and regioselectivity (Figure 1).
Finding and Effective Diels-Alder Auxiliary

Lewis Acid Catalysis

One route which was explored for creating the desired core was the use of Lewis acid catalysis to give diastereoselectivity. Diels-Alder reactions result from interactions between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. The lower the energy difference between these two transition states is, the more favorable the interactions between the molecular orbitals are, which leads to a lowering of the activation energy. It has long been known that the addition of a Lewis acid to a dienophile containing a Lewis basic site would result in the lowering of the energy state of the LUMO, thereby allowing more favorable interactions between the HOMO and
Figure 2. Decrease in LUMO Energy Values From Lewis Acids

LUMO levels. The lowered energy levels lead to an increase in reaction rates, generating products faster, and at lower temperatures. While the increased reaction rate is certainly desirable, Lewis acid catalysis is more notable for its increase in diastereoselectivity. While the increase in diastereoselectivity has traditionally been explained by increased interactions between secondary orbitals (those not involved in bond formation) it has been called into question by work done by the Houk group.\textsuperscript{5,6} While the exact source of stereoselectivity is not known, Lewis acid catalysis is still a powerful tool for generating diastereoselective Diels-Alder reactions. The Lewis acids explored consisted of LiCl, Sc(Otf)\textsubscript{3}, and Cu(Otf)\textsubscript{2}. An alkylated oxazolidinone was used as an auxiliary for the dienophile in order to promote good coordination with a bidentate ligand. If success was seen with any of these catalysts in affecting the diastereoselectivity, then the Lewis acids associated with chiral ligands would be explored to try and enhance the enantioselectivity.\textsuperscript{7}
Despite the potential and precedent of Lewis acid catalysis, all Lewis acids explored showed no increase in diastereoselectivity by spectroscopic standards.\textsuperscript{4,5,6} This lack of selectivity is likely due to the presence of a Lewis basic site on the diene in addition to the dienophile. As shown in previous schemes, there is a nitrogen atom present in the diene system whose lone pairs could potentially act as electron donors to a Lewis acid. Despite the bidentate ligand present on the dienophile, it is likely that the Lewis acid coordinated with the diene instead, giving no enantioselectivity.

**Imminium Ion Catalysis**

In addition to trying Lewis acid catalysis, a set of organic amine catalysts pioneered by the MacMillian in the early 2000s were examined (substrates 6 and 7).\textsuperscript{8} These catalysts consisted of series of chiral, enantiopure, secondary amines, which were able to mimic properties of Lewis acid catalysis as well as use steric interactions to generate facial selectivity. In the presence of a carbonyl, secondary amines will reversibly condense to form imminium ions.
Because the positive charge is connected to the olefin through resonance, the overall electron density of the dienophile will decrease, lowering the LUMO energy level much like Lewis acids will. In addition to increasing reaction rates, these catalysts also demonstrated the ability generate enantioselectivity as well, due to a sterically bulky directing group such as a phenyl group. Geminal methyl groups were used on the catalysts in order to direct the formation of the E isomer of the imminium ion. A second set of catalysts generated by the Johannes group was shown to generate competitive enantiomeric excess despite lacking the germinal methyl groups.\textsuperscript{9} Catalysts would follow the general cycle shown in scheme 3.\textsuperscript{8}

**Scheme 2. Catalytic Cycle for Secondary Chiral Amines**
These catalysts looked especially promising due to a second paper published by the MacMillian group detailing the utility of the reaction in 1,3 dipolar cycloadditions with nitrones to form nitrogen containing rings similar to the desired diazaoctane core.\textsuperscript{10}

However, despite the promise these catalysts presented, they were unable to promote the desired Diels-Alder reaction. Despite using conditions optimized by the Macmillan and Johannes groups, reactions involving these catalysts did not generate anything which could be identified as a cycloaddition product. These reactions either did not consume starting material, or produced a series of decomposition products which made interpretation of crude NMRs and separation by chromatography impossible. Substrate 6 appeared to generate a small amount of cycloaddition product, but it was deemed to be minimal enough that a new pathway needed to be explored.

**Sultam Chiral Auxiliary**

The final auxiliary used was a camphor-derived bornane-10,2 sultam 11. While this auxiliary did not have some of the electronic advantages the two previous catalysts discussed did, it was desirable for its low cost, ease of preparation (one step from commercially available material), and its ease of removal.\textsuperscript{11,12} Much like the previously explored Diels-Alder auxiliary, this substrate was originally designed to work with Lewis acid catalysis by providing two chelating sites. However, due to the large steric bulk of the molecule, good facial selectivity could be generated regardless of presence of a Lewis acid or not.
To our delight, the sultam auxiliary was able to not only exhibit regioselectivity but diastereoselectivity as well. Only a single diastereomer could be seen in the unpurified mixture of the reaction spectroscopically. While normally more advanced methods would be required to determine the enantiomeric excess, the presence of a single diastereomer was sufficient due to the enantiopure sultam. Because the sultam was enantiopure, a change in facial selectivity would show up as two diastereomers, rather than the single observed diastereomer.

**Synthetic route**

With a proper source of selectivity, a full route was finally able to be constructed.
Starting from a DKP core similar to the phenyl aminal auxiliary variant used in previous efforts, a Diels-Alder precursor was rapidly constructed using reaction conditions previously explored (Scheme 1).
The azadiene intermediate however proved to be more difficult to work with than was initially predicted. The molecule was oxygen sensitive and would decompose if caution was not used. In addition, the molecule proved to be sensitive to the mildly acidic conditions of silica gel, making chromatography and TLC monitoring methods impossible. Fortunately the substrate proved to be crystalline and could be purified by recrystallization. While a maximum yield of 42% by recrystallization was recorded, it is suspected that this yield could increase with subsequent recrystallizations and if exposure to air could be minimized.

After generating the azadiene diene, the material was submitted to heating conditions for 24 hours in DMF with the acryloyl sultam chiral auxilarly, giving the desired cycloadduct as a single enantiomer and diastereomer. It was originally planned to perform the Diels-Alder reaction in the same “pot” that the aldol addition and isomerization took place in. However in the presence of the excess DBU needed to drive the isomerization step, the dienophile would add in a Michael addition, rather than the desired cycloaddition (Figure 6).

**Figure 5. Achiral Diketopiperazine Core**

![Figure 5](image)

1. NEt₃, CICH₂, CH₂Cl₂
2. NaN₃, Butanone, 80 °C
3. PPh₃, PhMe, 90 °C
4. 80% yield over 3 steps

**Figure 6. Michael Addition Product**

![Figure 6](image)
The Michael addition was seen to occur with as little as 1.2 equivalents of base present. Because of this undesired product, the one-pot reaction sequence from previous work was not entirely applicable in this scenario. The azadiene could also be submitted to similar conditions with achiral dienophiles. The substrate showed reactivity with both benzyl and ethyl acrylate to generate racemic cycloadducts. These products showed a 3:1:1 ratio of the potential 4 diastereomers as determined by NMR spectroscopy. While separation of these diastereomers was possible for cycloadducts derived from ethyl acrylate, the benzyl acrylate cycloadducts proved inseparable, making it impossible to get an accurate yield of a single diastereomer. Yields for the major diastereomer of the ethyl cycloadduct were seen to be lower than yields from the chiral sultam reactions (48% vs. 62%) However, the yield of all diastereomers together (64%) gave an almost equivalent amount, showing equal reactivity across substrates, but not equal selectivity.

The sultam cycloadduct was then submitted to a solution of n-BuLi and benzyl alcohol to produce either an ethyl ester or benzyl ester. Initial efforts to convert the sultam cycloadduct to the benzyl ester proved to be difficult. It was found that small amounts of ethyl acetate from purification steps would lead to a mixture of the benzyl and ethyl esters. In an attempt to avoid this issue, efforts were made to convert the sultam to the ethyl ester instead. While these efforts proved to be mildly successful, it was ultimately decided to use the benzyl ester in the final synthesis as attempts to generate the ethyl ester appeared to give a greater ratio of unwanted products. It should be noted that both products could still successfully generate 15. However the benzyl ester proved to have problems of its own. Due to the unique solubility of benzyl alcohol it is largely soluble in both organic solvents and water. This made quenching and extracting reactions difficult, as a large portion of the product would be unrecoverable from the aqueous layer. After trying a variety of solvents to extract the organic product from the aqueous layer, it
was eventually found that extracting from a brine solution directly could give a good unpurified yield from extractions. It is not understood why benzyl alcohol is significantly more soluble in the NH₄Cl solution rather than a NaCl solution. It was thought that this issue could be circumvented entirely by converting the sultam directly to substrate 15 by adding in two equivalents of a nucleophilic methyl organometalic. This would simultaneously shorten the synthetic route as well as avoid low yields from the transesterification reaction. However MeMgBr proved to be insufficient to generate the tertiary alcohol directly from the sultam cycloadduct and LiMe led to decomposition of the molecule.

The ester was then reacted with two equivalents of methyl Grignard reagent in order to create tertiary alcohol 15. Finally, exposure of 15 to HCl effectively generated a carbocation, which then underwent an electrophilic addition to the indole to form the six membered ring. This final step successfully formed the molecule “pre-brevianamide,” an intermediate used during the Williams synthesis which utilized the biomimetic Diels-Alder. Although the final two steps followed precedent set by the Williams group, we were unable to generate the final product. Williams uses m-CPBA to generate an epoxide, which can undergo a pinacole rearrangement to give the natural product. While NMR spectroscopy determined that the epoxided formed well, the pinacole rearrangement proved difficult to perform.

Discussion

The synthetic route displayed has several key advantages which make this strategy preferable to others employed to make the diazaoctane core. While the key ring forming step does not take place in a single flask like previous work showed, the domino sequence is still able to undergo three steps of the original four in a single pot and could generate the azadiene requiried for the Diels-Alder to occur. This sequence also addresses issues encountered in our
previous work. The route showed an inherent bias towards the syn diastereomer (3:1:1), even in
the presence of an indole, while previous work done in the lab and by Williams showed
preference for the anti transition state. Not only was there an inherent biased for the desired
stereomer 6, but it was able to be exclusively produced with the sultam chiral auxiliary.
Additionally, by having facial selectivity come from the dienophile, the chiral auxiliary is easily
removed from the final product through methods such as the transesterification demonstrated in
the synthesis. The most notable advantage of this strategy is the convergent nature of the
synthesis. The key sequence brings three separate fragments together, rather than constructing an
equivalent structure in a linear sequence or two fragments as we previous used. This strategy
allows for a much wider diversity in fragment construction.

Table 1. A Comparison of Current Brevianamide B Synthetic Routes

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<th>Author</th>
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A comparison of our synthetic route to others shows that it has competitive yields and brevity,
while still producing enantiopure material. Additionally this route could be shortened by one step
to produce racemic brevianamide in 9 steps.

Conclusion

Outlined in this paper is a direct and novel strategy for the construction of enantiopure
bicyclo[2.2.2]diazaoctane cores and its applications towards brevianamide B. The current route
gives enantiopure “pre-brevianamide” in eight steps from commercially available proline with a
total yield of 7.2%. This yield is believed will be improved after refocused efforts on the processing of the azadiene 5. Good reactivity was seen with a variety of dienohpiles, although good diastereoselectivity was only seen in the presence of the chiral auxiliary. The divergent nature of the molecule allows for variability in the fragments used in its construction.
Experimental Procedures

**Diketopiperazine 1.** To a suspension of proline methyl ester • HCl (8.04 g, 42.87 mmol) in CH₂Cl₂ (86 ml) at 0 °C was added NEt₃ (11.98 ml, 85.74 mmol) followed by 1.1 equivalents of chloroacetyl chloride (1.1 equivalents, 3.72 g, 47.16 mmol) dropwise via syringe. The reaction mixture was allowed to warm to rt for 16 h. After warming to rt, the mixture was diluted with NaHCO₃ and was extracted with CH₂Cl₂ (25 ml). The combined organic layers were washed with brine (25 ml), dried with NaSO₄, filtered through celite, and concentrated in vacuo to afford a brown oil. (7.85 g, 38.17 mmol). To the brown oil (5.25 g, 25.53 mmol) dissolved in butanone (51 ml) at rt was added NaN₃ (3.67 g, 50.89 mmol). The reaction vessel was fitted with a reflux condenser and heated at 80 °C for 20 h. The resulting product was filtered and concentrated in vacuo to afford a reddish-brown oil (5.37 g, 25.31 mmol). To the oil (1.97 g, 9.28 mmol) in anhydrous toluene (38 ml) was added 1.05 equivalents of PPh₃ (2.55 g, 9.75 mmol). The reaction mixture was heated at 90 °C for 20 h. The resulting mixture was concentrated in vacuo and triturated with Et₂O and hexanes in order to remove a bulk of the PPh₃. The resulting residue was further purified by flash column chromatography on silica gel (elution: 1% MeOH to 10% MeOH in 50/50 ethyl acetate/toluene, 1% triethylamine). The resulting product was a light, yellow oil (1.43 g, 8.48 mmol, 80% yield, 3 steps). TLC (60% EtOAc in hexane), Rf: 0.2 (CAM); [α]D²⁵ = +102 °. IR (film): 2951, 2984, 2889, 2360, 2107, 1685, 1457, 1322, 1263, 1022, 751, 673, 625, 573⁻¹; ¹H NMR (400 MHz, CDCl₃) 4.21 (dd, J=9.5 Hz, 1.6Hz, 1H), 4.11 (d, J=4.9 Hz, 1H) 4.03 (m, 1H), 3.68 (s, 3H), 3.47 (m, 1H), 2.03 (m, 1H), 1.83 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 161.8, 56.5, 53.3, 52.3, 44.2, 29.3, 22.2; Exact mass calcd for C₈H₁₂N₂O₂[M+Na⁺], 191.0791. Found 191.0790.
Azadiene 5. To Diketopiperazine 1 (2.29 mmol) in THF (16.7 mL) at −78 °C was added LiHMDS (1.0M in THF, 1.1 equiv) dropwise over 5 min by syringe. After stirring for 15 min at −78 °C, the indole aldehyde (1.0 equiv) was added and the reaction was stirred for an additional 15 min at −78 °C. Ac₂O (1.3 equiv) was added and the cooling bath was removed. The reaction mixture was stirred at rt for 2 hours. DBU (1.4 equiv) was added and the reaction was stirred at rt for 18 hours. The reaction was then quenched with 0.2 M HCl and extracted with EtOAc (3 x 20mL). The combined organic layers were then washed with brine, dried with NaSO₄, and concentrated in vacuo. The resulting residue was then recrystallized (hexanes in EtOAc) to afford the product (.380 g, 42% yield) as a yellow solid; TLC (100% EtOAc in hexanes), Rf: 0.40 in CAM; IR (film) 2976.2, 2938.7, 1730.2, 1653.1, 1583.6, 1578.9, 1451.6, 1369.1, 1256.18, 1156.8, 1079.8, 1046.2, 1016.2, 855.4, 749.6; ¹H NMR (400 MHz, CDCl₃) 8.10 (s,1H), 7.75 (d, J=7.3, 1H), 7.61 (s,1H), 7.29-7.19 (m, 2H), 4.19 (s, 2H), 3.82 (s, 3H), 3.04 (t, J=7.4, 2H), 2.21 (q, J=7.4, 2H), 2.05 (s, 1H), 1.65 (s, 9H); ¹³C NMR (100 MHz, CDCl₃)δ 153.9, 149.4, 142.5, 130.7, 125.4, 124.0, 122.1, 119.9, 116.6, 115.0, 83.2, 77.2, 54.7, 49.5, 28.3, 28.1, 28.0, 21.5; Exact mass calculated for C₂₂H₂₅N₃O₄ [M+Na]⁺, 418.1845, Found 418.1743

Acylated sultam 11 was prepared by alkylation of Bornane-2,10-sultam

Sultam Cycloadduct 12. To a flame dried flask, was added acylated sultam 11 (135 mg, 0.51 mmol) and azadiene 5 (188 mg, .48 mmol). The flask was fitted with a condenser, purged with
N₂, and the reactants were dissolved in DMF (3.18 ml, 0.15 M). The reaction was heated at 60 °C for 24 h, cooled to rt, and concentrated in vacuo to afford a brown oil. Purification by flash column chromatography on silica gel (elution: 30% to 70% EtOAc in hexanes) afforded the desired product (260 mg, 0.31 mmol, 62% yield) TLC: (80% EtOAc in hexane), Rf: 0.3 (CAM); [α]D²⁵ = +59 °. IR (film): 3854, 3744, 3061, 2986, 2882, 2360, 2337, 1730, 1683, 1648, 1635, 1452, 1363, 1351, 1308, 1298, 1268, 1258, 1218, 1164, 1135, 1083, 1015, 987, 768, 735, 667, 533 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 8.1 (s, 1H), 7.77 (d, J=1.14 Hz, 1H), 7.66 (s, 1H), 7.23 (m, 4H), 3.76 (s, 3H), 3.50 (d, J=3.1 Hz, 1H), 3.46 (t, J=7 Hz, 2H), 3.37 (t, J=13.1 Hz, 2H), 3.29 (t, J=14.9 Hz, 2H), 2.09 (t, J=5.1 Hz, 2H), 2.04 (t, J=1.6 Hz, 2H), 1.99 (t, J=6.6 Hz, 2H), 1.93 (t, J=2 Hz, 2H), 1.85 (m, 2H), 1.70 (s, 3H), 1.68 (s, 3H), 1.66(s, 3H), 1.30 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 170.9, 169.5, 149.8, 135.1, 132.1, 125.5, 123.6, 121.9, 120.4, 116.5, 114.8, 83.1, 66.3, 66.2, 65.4, 54.5, 53.1, 49.0 48.2, 47.7, 44.6, 43.2, 38.5, 34.9, 32.9, 28.8, 28.2, 27.2, 26.3, 24.4, 20.9, 19.8; Exact mass calcd for C₃₅H₄₄N₄O₇[S+Na⁺], 687.2823. Found 687.2813.

**Ethyl Ester 14.** To a flame dried flask, was added ethyl acrylate (114 mg, 1.14 mmol) and azadiene 5 (227 mg, .575 mmol). The flask was fitted with a condenser, purged with N₂, and the reactants were dissolved in DMF (3.18 ml, 0.15 M). The reaction was heated at 60 °C for 24 h, cooled to rt, and concentrated in vacuo to afford a brown oil. Purification by flash column chromatography on silica gel (elution: 30% to 90% EtOAc in hexanes) afforded the desired product 1₄a (183 mg, 0.109 mmol, 48% yield) and a minor diastereomer 1₄b (46 mg, 0.092 mmol, 16% yield) 1₄a. TLC: (60% EtOAc in hexane), Rf: 0.3 (CAM); IR (film): 2985, 2945, 2876, 1736, 1683, 1642, 1456, 1456, 1416, 1308, 1260, 1156, 1085, 1016, 852, 768, 745 cm⁻¹; ¹H NMR (400 MHz, CDCl₃); 8.10 (s, 1H), 7.78 (d, J=7.5, 1H), 7.78 (s, 1H), 7.24 (m, 2H), 4.07 (m, 2H), 3.74 (s, 3H), 3.40 (m, 4H), 2.78 (q, J=5.1, 1H), 2.61 (m, 1H), 2.00 (m, 4H), 1.80 (q, J=3.9, 1H), 1.56 (s, 9H), 1.18 (t, J= 7.2, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 170.9, 169.5, 149.8, 135.1, 132.1, 125.5, 123.6, 121.9, 120.4, 116.5, 114.8, 83.1, 66.3, 66.2, 65.4, 54.5, 53.1, 49.0 48.2, 47.7, 44.6, 43.2, 38.5, 34.9, 32.9, 28.8, 28.2, 27.2, 26.3, 24.4, 20.9, 19.8; Exact mass calcd for C₂₇H₃₃N₃O₆[M+Na⁺], 518.2261. Found 518.2259.
14b: TLC: (60% EtOAc in hexane), Rf: 0.20 (CAM); IR (film): 2361, 1736, 1686, 1651, 1576, 1456, 1370, 1254, 1148, 1083, 849, 751, 764, 705, 14 cm; 1H NMR (400 MHz, CDCl3): 8.11 (s, 1H), 7.81 (d, J=7.5, 1H), 7.68 (s, 1H), 7.26 (t, 1H, J=1.5), 7.19 (t, J= 6.8, 1H), 4.18 (m, 2H), 3.65 (s, 3H), 3.54 (t, J=7.2, 3H), 2.75 (q, J=4.8, 1H), 2.57 (s, J=6.2, 1H), 1.95 (m, 5H), 1.65 (s, 9H), 1.26 (t, J= 7.2, 3H)

13C NMR (100 MHz, CDCl3) δ 172.7, 172.6, 170.1, 125.4, 124.6, 123.7, 122.9, 121.7, 121.2, 116.5, 115.1, 114.7, 77.3, 68.9, 63.3, 61.2, 60.4, 57.2, 54.1, 44.6, 43.4, 36.2, 28.6, 28.2, 27.1, 24.6, 14.2, 14.1

Exact mass calcd for C_{27}H_{33}N_3O_6[M+Na^+], 518.2261. Found 518.2259.

Benzyl Ester 13. To a flame dried flask, benzyl alcohol (13 µl, 0.12 mmol) in THF (0.6 ml) was added 3 M n-butyllithium (33 µl, 0.1 mmol) at -78 °C. To this solution was added a 0.5 M solution of the sultam cycloadduct (20 mg, 0.03 mmol) in THF was added to the solution and allowed to warm to 0 °C for 8 h. The reaction was quenched with ammonium chloride and concentrated. It was then partitioned with EtOAc and washed with sodium bicarbonate and brine. The solution was purified using flash column chromatography on silica gel (elution: 30% EtOAc to 70% EtOAc in hexanes) to afford a yellow oil (13 mg, 75% yield). TLC (60% EtOAc in hexane), Rf: 0.6 (CAM); [α]_D^{25} = +25 °, IR (film): 2985, 2942, 2882, 2358, 2330, 1730, 1686, 1639, 1452, 1370, 1308, 1257, 1160, 1085, 1015, 912, 857, 746, 668, 664 cm; 1H NMR (400 MHz, CDCl3) 8.11 (s, 1H), 7.77 (d, J=8 Hz, 1H), 7.65 (s, 1H), 7.43-7.33 (m, 5H), 5.05 (d, J=12.1 Hz, 1H), 4.99 (d, J=12.1 Hz, 1H), 3.77 (d, J=6.7 Hz, 1H), 3.65 (s, 3H), 3.49 (m, 3H), 3.46 (d, J=4.7 Hz, 1H), 3.35 (m, 2H), 2.85 (d, J=5.5 Hz, 1H), 2.82 (d, J=5.5 Hz, 1H) 2.58 (m, 2H), 2.05 (s, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 1.28 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 172.4, 171.4, 169.6, 135.3, 132.3, 128.8, 125.8, 124.1, 122.3, 120.7, 116.7, 115.1, 83.4, 67.2, 66.6, 65.9, 54.6, 49.3, 43.6, 34.2, 30.6, 29.1, 28.5, 28.4, 24.9, 13.8

Exact mass calcd for C_{32}H_{35}N_3O_6[M+Na^+], 580.2418. Found 580.2405.
Tertiary Alcohol 15. Benzyl ester 13 (0.90g, 0.162 mmol) was dissolved in toluene (7.0 mL) and cooled to 0 °C. A 1.4 M solution of methyl magnesium bromide (3.5 equiv) was then added dropwise, and the reaction was left to react over 30 minutes. The reaction was then quenched with de-ionized water, diluted with NH₄Cl and extracted with ethyl acetate (3x 10 ml). The combined organic layers were then washed with brine, dried with Na₂SO₄, and concentrated in vacuo. Purification of the resulting residue by flash chromatography on silica gel (elution: 60% to 100% EtOAc in hexanes) afforded the desired product (0.055 g, 0.114 mmol, 71% yield) as a clear oil: TLC (100% EtOAc in hexanes) Rf: 0.50 in CAM; [α]D²⁵ = +9.84°; IR (film) 3854.5, 3744.9, 1844.3, 1752.9, 1730.1, 1695.9, 1576.3, 1542.2, 1368.8, 1308.3, 1257.2, 1084.7, 768.2; ¹H NMR (400 MHz, CDCl₃) δ 8.11 (s, 1H), 7.79 (d, J= 7.4, 1H), 7.68 (s, 1H), 7.33-7.19 (m, 2H), 3.72 (s, 3H), 3.59 (t, J=8.2, 1H), 3.42 (d, J=4.9, 1H), 3.30 (t, J=7.7, 2H), 3.21 (m, 3H), 2.61 (m, 1H), 2.30 (m, 1H), 2.06 (m, 5H), 1.64 (s, 9H), 1.04 (s, 3H), 2.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 128.9, 128.1, 125.2, 125.1, 123.7, 122.0, 116.9, 120.2, 116.9, 114.8, 72.7, 66.9, 65.7, 54.6, 54.1, 43.0, 33.6, 30.0, 29.7, 29.7, 29.1, 28.2, 28.1, 25.5, 24.9; Exact mass calculated for C₂₇H₃₅N₅O₅ [M+Na⁺] 482.2577, Found 488.214

Prebrevianamide 16. A solution of the tertiary alcohol (0.100g, 0.208 mmol) in 1:1 dioxane/concentrated HCl was stirred under N₂ at 0 °C for 8 hours and then room temperature for 16 hours. The reaction mixture was diluted with de-ionized water, made basic with 1M NaOH, and extracted with chloroform (5 x 10 ml). The combined organic layers were then washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. Purification by flash chromatography (elution 3-5% MeOH in CHCl₃) afforded the desired product as a white solid (0.049g, 0.135 mmol, 64.9% Rf: 0.40; [α]D²⁵ = -25.83 °. IR (film) 3854.5, 3801.8, 3744.9, 3382.5, 2975.4, 2358.9, 1844.3, 1751.5, 1684.7, 1616.8, 1576.3, 1456.9, 1436.8, 1010.5, 744.0,
667.6; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) 8.59 (s, 1H), 7.61 (d, J=7.82, 1H), 7.28 (d, J= 7.82, 1H), 7.23-7.10 (m, 3H), 6.15 (s, 1H), 3.64 (t, J=9.34, 1H), 3.56 (d, J=15.24, 1H), 3.23-3.17 (m, 1H), 3.16 (s, 1H), 2.83-2.75 (m, 1H), 2.21-2.05 (m, 4H), 2.00-1.90 ( m, 1H), 1.74 (s, 2H), 1.22 (s, 3H), 1.11 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CdCl\textsubscript{3}) \delta 172.7, 170.3, 136.1, 128.1, 124.7, 122.2, 120.0, 118.2, 111.5, 108.4, 7.205, 72.3, 69.3, 60.8, 53.9, 43.5, 36.5, 30.6, 29.8, 27.4, 26.3, 25.5; Exact mass calculated for C\textsubscript{22}H\textsubscript{25}N\textsubscript{3}O\textsubscript{2} [M+H]\textsuperscript{+}, 350.1790, Found 351.1859
References