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Synthesis of (±)-Bisavenanthramide B-6 by an Anionic Anhydride Mannich Reaction

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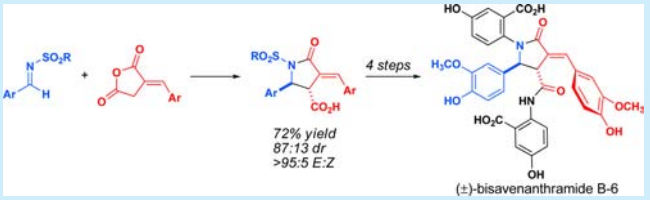
Supporting Information

ABSTRACT: Bisavenanthramide B-6 (**2**) is a highly substituted γ-lactam derived from oat leaves. Development of a new base-promoted anhydride Mannich reaction with N-sulfonylated imines that forms the core structure of **2** in a single step is presented. Further elaboration allows for a facile one-pot double Buchwald N-arylation to install the final rings onto the densely substituted γ-lactam core. This route provides the natural product in a longest linear sequence of nine steps.



Plants produce defensive molecules that accumulate rapidly at sites of stress, such as infections in leaves.[1] These compounds, known as phytoalexins, are often dimers or higher oligomers of simple secondary metabolites. One of the most studied families of phytoalexins are the phenolic compounds produced by the dimerization and oligomerization of resveratrol in the leaves of *Vitis vinifera* (grapes). Although less studied than resveratrol and its polymers, the avenanthramides, and their polymers, identified in oats (Avena sativa) are bioavailable in mammals and exhibit antioxidant, anti-inflammatory, antiatherogenic, and anticancer properties.[2] The densely substituted 2-pyrrolidinone, bisavenanthramide B-6 (**2**), can be formed by treatment of avenanthramide B (**1**) with peroxidase, supporting the hypothesis that these racemic compounds form due to oxidative stress in plant tissue (Figure 1).[3] Similar biosynthetic processes are likely responsible for the formation of heliotropamide A (**4**) from *N*-feruloyl tyramine (**3**) in *Heliotropium ovalifolium*, a flowering plant native to east Africa.[4]

Our lab specializes in the development of efficient strategies for the rapid assembly of complex 2-pyrrolidinones, also known as γ-lactams. We have developed several formal cycloadditions of imines with cyclic anhydrides[5] as variants of the Castagnoli reaction.[6] After demonstrating that thio-substituted succinic anhydrides can form γ-lactams with high diastereoselectivity, we later showed that this process could be realized in a one-pot, four-component reaction (4CR) between aldehydes, amines, thiols, and maleic anhydrides.[7] This strategy was used in an efficient synthesis of **4** shortly thereafter.[4]

At first glance, the synthesis of bisavenanthramide B-6 appears to emerge from our previous γ-lactam syntheses, but the *N*-anilide poses a significant challenge that was not amenable to our previous strategies. Although anilines are suitable substrates for both Castagnoli-type reactions and our 4CR, *ortho*-substituted or electron-deficient anilines work

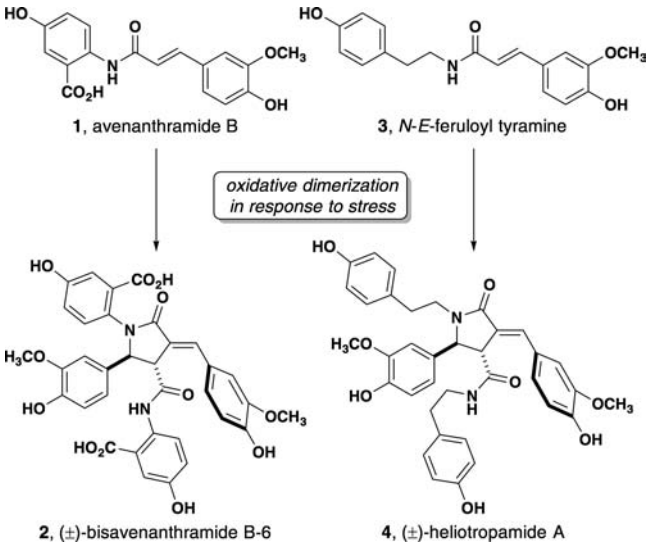


Figure 1. Oxidative dimerization of avenanthramides and *N*-feruloyl tyramine.

poorly.[7] We also documented use of an ammonia equivalent for the 4CR and found Chan–Lam arylation reactions,[8] but attempts to apply this strategy to bisavenanthramide B-6 were unsuccessful.

These limitations drove us to develop a more robust version of the anhydride Mannich reaction (AMR). Given the pseudosymmetry within the target molecule, we envisioned forming the two *N*-aryl bonds in **5** by a double Buchwald N-arylation with aryl iodide **6** in the late stages of the synthesis (Scheme 1). Required diamide **7** could be synthesized in

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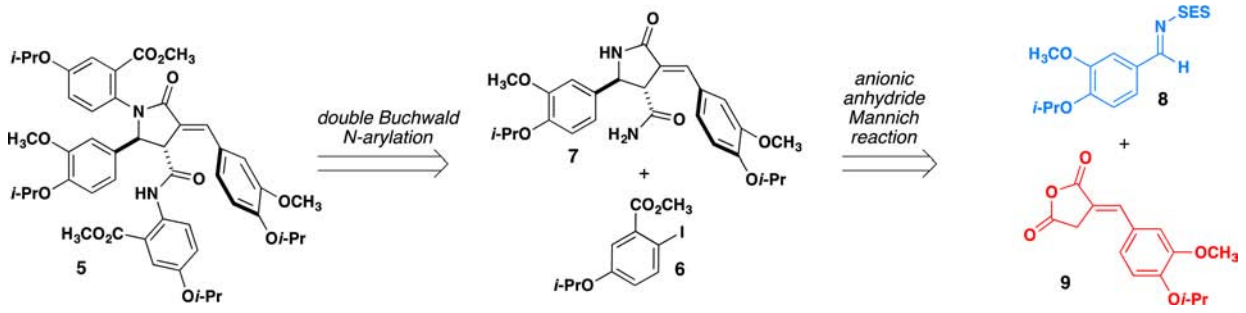
Scheme 1. Retrosynthetic Analysis of Bisavenanthramide B-6



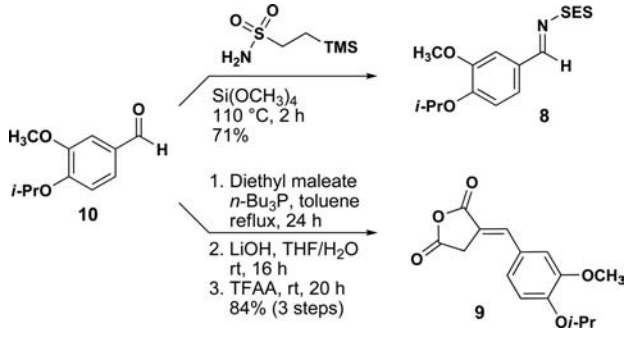
short sequence and high diastereoselectivity from the anionic AMR of imine **8** and anhydride **9**.

We speculated that anhydride **9** would be capable of forming an enolate, similar to one derived from deprotonation of homophthalic anhydride. Although anhydride enolates are rare, recent advances from the Connon group demonstrate the synthetic utility of anhydride enolates that can be accessed reversibly by treatment with tertiary amines.[9] The reaction of anhydrides with imines has, until recently, been believed to proceed via an *N*-acyl iminium ion intermediate, similar to the Staudinger synthesis with ketenes, instead of the anhydride enolate. However, our work has shown that the *N*-acyl iminium intermediates are kinetically inaccessible under the reaction conditions with activated anhydrides, and the reaction of succinic or glutaric anhydrides with imines proceeds by a Mannich-like mechanism involving either H-bonding or proton transfer to the basic imine nitrogen.[10] Previous work demonstrated a limited scope for cleavable groups that could reveal the NH lactam core required for the proposed Buchwald N-arylation.[8]

We turned to *N*-sulfonyl protected imines as reactive imines that also offer opportunities for subsequent N-functionalization. While this class of imines has never been utilized in an anhydride Mannich reaction, we saw two distinct advantages to their use. First, the sulfonyl group would act as a cleavable protecting group. Second, the electron-withdrawing capability of the sulfonyl group would diminish the basicity of the nitrogen lone pair of the imine while maintaining electrophilic character similar to that of an iminium ion.[11] This loss of basicity would allow us to access the anhydride enolate with a variety of exogenous bases, thus developing a new variant of the Castagnoli reaction. Early attempts with 4-toluenesulfonyl (Ts) and 4-nitrobenzenesulfonyl (Ns) protected imines proved difficult to deprotect under a number of conditions; therefore, we turned our attention to the 2-trimethylsilyl sulfonyl (SES) group developed by Weinreb.[12] This group maintains the desired properties of a sulfonyl imine and can be cleaved under mild fluoride conditions.

To begin our synthetic efforts, we took advantage of the symmetry of bisavenanthramide B-6 and synthesized imine **8** and anhydride **9** in short sequences from 4-isopropyl vanillin (**10**, Scheme 2). Aldehyde **10** was condensed with 2-trimethylsilylethyl sulfonamide[13] using conditions developed by Love.[14] Next, we employed a modified one-pot condensation in which tributylphosphine mediates a Wittig-like reaction with **10** to form the intermediate benzylidene diethyl succinate as one detectable alkene isomer (*E*).[15] Saponification of the diester provided the diacid, which could be easily purified by recrystallization on a multigram scale.

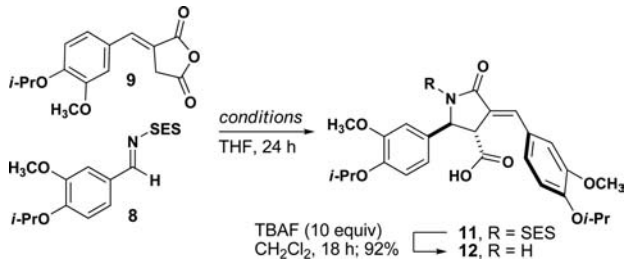
Scheme 2. Synthesis of Imine and Anhydride Precursors



Dehydration of this diacid provided anhydride **9** in 84% yield over three steps.

With gram quantities of both intermediates in hand, we investigated the anionic anhydride Mannich reaction, starting with a series of reactions with anhydride **11**. Our initial attempts to induce the anhydride to react with alkyl imines proceeded with moderate success. We discovered the reactivity of **9** is comparable to that of phenylsuccinic anhydride, requiring mild heating to achieve low conversion and diastereoselectivity. Initial attempts at enolization with diisopropylethylamine provided no product (Table 1). We posited that LDA would completely deprotonate the

Table 1. Optimization of the Anionic Anhydride Mannich Reaction



entry	conditions	temp (°C)	dr	yield (%)
1	*i*-Pr$_2$NEt	rt		trace
2	LDA	−78	87:13	72[a]
3	LiTMP·LiBr	−78	80:20	80[b]
4	KHMDS	−78	80:20	81[b]
5	LiHMDS	−78	79:21	60[b]
6[c]	NaH	−78	82:18	75[a]
7[d]	NaH	−78	82:18	71[a]

[a]Isolated yield. [b]Yield determined by ^{1}H NMR. [c]Gram scale. [d]5.6 gram scale.

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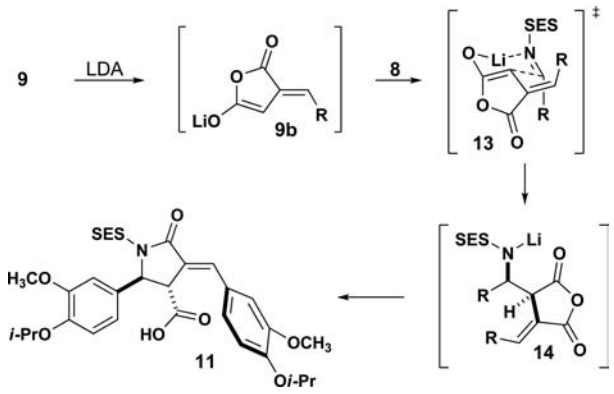
anhydride and allow the reaction to proceed. This change in base provided the product with complete conversion, in good diastereomeric ratio, and with no erosion in the alkene geometry. A screen of other strong amide bases provided the product with only mild erosion of diastereoselectivity. The product was determined to be the *trans*-isomer (vide infra). For multigram reactions, we found that sodium hydride worked as well as LDA and avoided the use of pyrophoric reagents.

Our current mechanistic hypothesis draws from our previous work with *N*-alkyl and *N*-aryl imines (Scheme 3).[10]

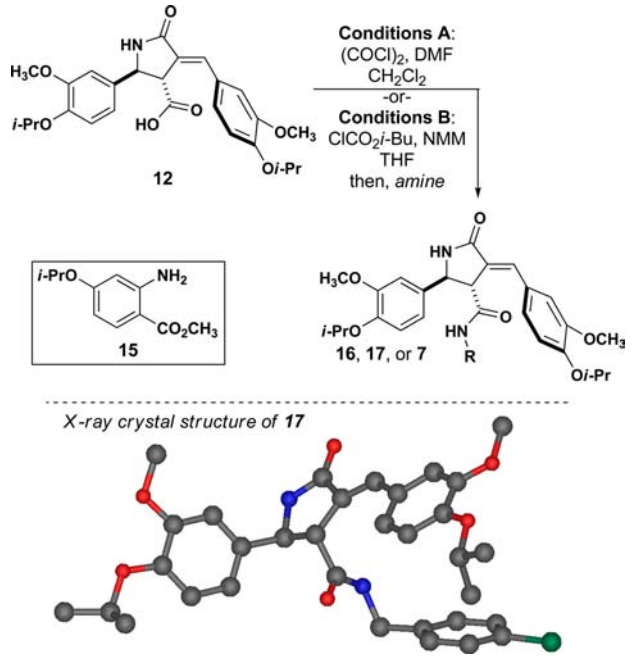
Scheme 3. Proposed Model for the Observed Diastereoselectivity of the Anionic AMR



Deprotonation of the anhydride provides enolate **9b**. We envision the Mannich reaction occurring through a Zimmerman−Traxler-like transition state **13**, similar to other Mannich reactions with various electrophilic imines.[16] The cyclic anhydride is locked in the (*E*)-enolate geometry. The *syn*-product **14** is observed as the imine lone pair must be correctly aligned to bind with the metal. Similar reversals in expected diastereoselectivity have also been observed in enamine-catalyzed Mannich reactions using proline.[17] Further studies to understand and expand upon this new anionic anhydride Mannich are currently underway in our laboratory. The SES group was easily cleaved to provide **12** with the contiguous carbon framework of bisavenanthramide B-6 with the required functionality to complete our synthesis.

The challenge of forming the aniline amide required the development of a new strategy to install this group (Table 2). We believe the large steric demand of both reacting partners (an α-tertiary, densely substituted carboxylic acid and an *ortho*-substituted, electron-deficient aniline) prevents the desired bond formation. In our attempts to prove the stereochemistry of the molecule (Table 2, entry 2), we discovered that even routine couplings with benzyl amines were low yielding, thus supporting our hypothesis. The *para*-chlorobenzyl amide **17** provided single crystals not only to prove the *trans*-substitution on our lactam core but also to provide the first concrete evidence to support the *E* geometry of the alkene.[18] Conversion of the carboxylic acid **12** to the desired primary amide proceeded smoothly via the mixed anhydride derived from ethyl chloroformate on a gram scale and with no purification. This alternate construction provided access to the essential amide by an arylation reaction, which we reasoned might be possible given that bond formation would be one atom further removed from the congested carbonyl.

Table 2. Amide Coupling Reactions and X-ray Crystal Structure of 17



entry	conditions	amine	product	yield (%)
1	A	**15**	**16**	–
2	B	4-Cl-BnNH$_2$	**17**	57
3	B	NH$_4$OH	**7**	73

Taking advantage of the inherent symmetry of our target, we undertook the optimization of the bisarylation of **7** using Buchwald's copper-catalyzed process.[19] While γ-lactams and primary amides are exemplar reactants in these couplings, there are few examples of such sterically demanding substrates (i.e., γ-substitution of the γ-lactam nucleophiles or densely substituted primary amide nucleophiles). Additionally, *ortho*-ester substituents typically impede the reactivity of aryl iodides in these reactions; however, the early work of Ullman showed *ortho*-carboxylic acids react readily. Unfortunately, attempts with the *ortho*-acid provided no product. We thus returned to aryl iodide **6**, synthesized in one step from a known compound.[20] After optimization, the desired bisarylation product could be isolated in 72% yield.[21,22]

Final removal of the isopropyl ethers and methyl esters provided bisavenanthramide B-6 in good yield over two steps (Scheme 4). The synthetic sample of the natural product exhibited identical ^{1}H and ^{13}C NMR spectra and was found to have identical retention time by HPLC when compared directly to an authentic sample of the natural product.

In summary, we have described the first anionic anhydride Mannich reaction and its application to the densely substituted core of the complex natural product, bisavenanthramide B-6. Furthermore, this marks the first use of *N*-sulfonyl imines in an anhydride Mannich reaction and yields NH γ-lactams in high yield in a two-step process. This synthesis was also enabled by the application of Buchwald's arylation to two extremely hindered nucleophiles. Further studies into the scope, mechanism, and application of the anionic anhydride Mannich reaction are underway in our laboratory.

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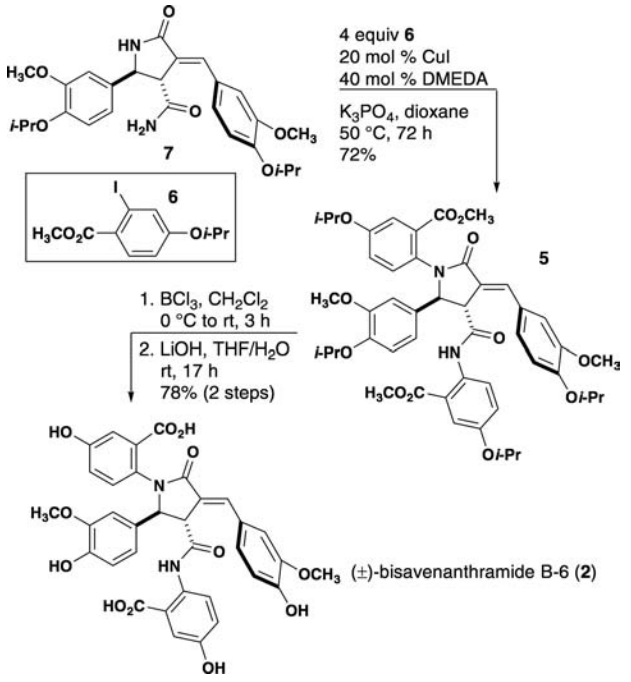
Scheme 4. Completion of Bisavenanthramide B-6



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00413.

X-ray data for **17** (CIF)

Experimental procedures, ^{1}H and ^{13}C NMR, crystallographic information, and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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(21) An optimization table is available in the Supporting Information.

(22) The related Chan−Lam couplings and Pd-catalyzed processes were not attemped due to our success with the copper catalyzed conditions.

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