Total Synthesis of (+)-Cavicularin: The Pyrone Diels–Alder Reaction in Enantioselective Cyclophane Synthesis.

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Abstract: A pyrone-Diels–Alder strategy was developed for the synthesis of the cyclophane natural product, cavicularin. The strategy uses a vinyl sulfone as an alkyne-equivalent dienophile. An enantioselective variant delivered (+)-cavicularin.

Key words: Diels–Alder, pyrone, cyclophane, chirality, total synthesis

Recently, we have been investigating natural products that display conformational chirality.[1] In particular, we became interested in families of cyclophane natural products where the presence of molecular chirality could not be deduced by inspection of the molecular structure. In the course of these studies we were attracted to the macrocyclic bis(bibenzyl) natural products.[2] These natural products have the general structure shown in Figure 1, which contains two bibenzyl moieties that are joined by either biphenyl or diphenylether linkages. The linkages of the bibenzyl units can result in *para-*, *meta*-, or *ortho*-substituted phenyl rings (cf. isoplagiochin A and marchantin A).

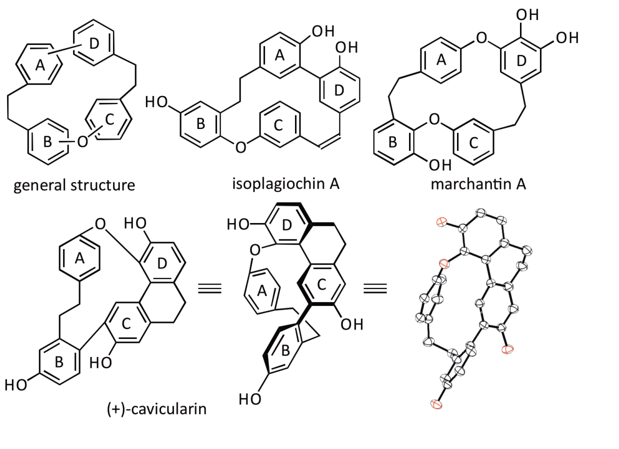
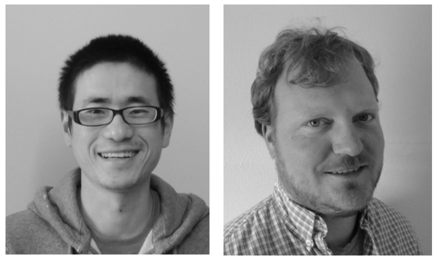


Figure 1. Selected Macrocyclic Bis(bibenzyl) Natural Products.

Cavicularin possesses a strained molecular architecture containing a dihydrophenanthrene.[3] Crystallographic studies indicated that the A-ring of cavicularin was distorted from planarity. The molecule was isolated as an optically active substance, which indicated it was a chiral non-racemic molecule in Nature. The beautiful molecular structure has attracted the attention of several groups, and other than our work[4] there have been three syntheses of racemic cavicularin[5] and one synthesis of (–)-cavicularin using a chiral auxiliary approach.[6]

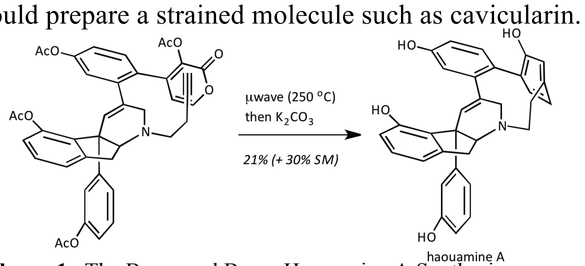


Christopher M. Beaudry joined the department of chemistry at Oregon State University in 2009 as an Assistant Professor. He received his B.S. degree from the University of Wisconsin in 2000. As an undergraduate, he conducted research with Prof. Steven D. Burke. He obtained his Ph.D. at the University of California, Berkeley under the direction of Prof. Dirk Trauner. He was an NIH postdoctoral fellow in the lab of Prof. Larry Overman at the University of California, Irvine.

Peng Zhao was born in Zhengzhou, China. After receiving his B.S. in chemistry from Xiamen University (China), he went to Zhengzhou University and obtained a M.S. in organic chemistry with Professor Junbiao Chang. Currently, he is a Ph.D. candidate in the chemistry department of Oregon State University working with Professor Beaudry on the synthesis of macrocyclic bis(bibenzyl) natural products.

We desired a strategy for preparing cavicularin that satisfied the following three criteria: 1. The strategy could assemble cyclophane architectures with considerable ring strain; 2. It could be applicable to other macrocyclic bis(bibenzyl) natural products that contained different connectivity in the A-ring (i.e. *meta-* or *para*-substitution or diphenylether- and biphenyl-linkages); 3. It would deliver (+)-cavicularin in non-racemic form.

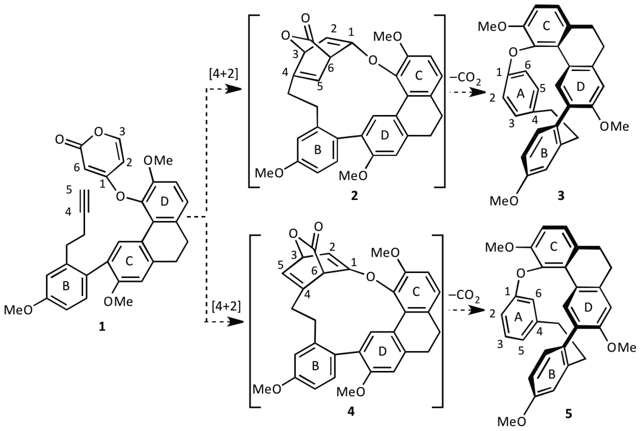
In 2006, Baran and Burns reported an elegant strategy for the formation of haouamine A, which contains a bent aromatic ring, using a pyrone-alkyne Diels–Alder reaction (Scheme 1).[7] The strategy benefits from the fact that the bent arene is prepared during the macrocyclization by way of a bicyclic intermediate that is a conformational mimic of the final strained arene. This precedent suggested that such a process could prepare a strained molecule such as cavicularin.



Scheme 1. The Baran and Burns Haouamine A Synthesis.

Consideration of the pyrone-alkyne Diels–Alder reaction in the context of (+)-cavicularin initially led to terminal alkyne **1**. In the forward sense, bond formation should occur between the nucleophilic C6 of the pyrone and the terminal C5 of the alkyne to give intermediate **2**. Retro-Diels–Alder reaction would deliver the desired connectivity in **3**.

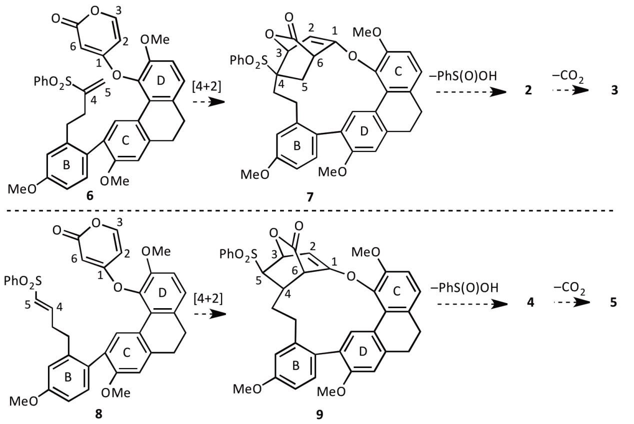
However, this synthetic strategy was not without potential pitfalls. Simple hand-held models revealed that both regiochemical outcomes of the Diels–Alder cycloaddition could be possible[8] – the constraints of the molecular tether would not guarantee bond formation between C6 and C5 in **1**, and the regiochemical alternative (Scheme 2, bottom) would deliver **4** and lead to a *meta*-substituted A-ring (**5**). Morevover, although the pyrone-alkyne Diels–Alder reaction can be well-behaved, it commonly requires high temperatures (>200 °C) and often gives modest yields, potentially making the reaction unsuitable for use as a general strategy for other macrocyclic bis(bibenzyl) family members.



Scheme 2. Pyrone-Alkyne Diels–Alder Reaction for Cavicularin.

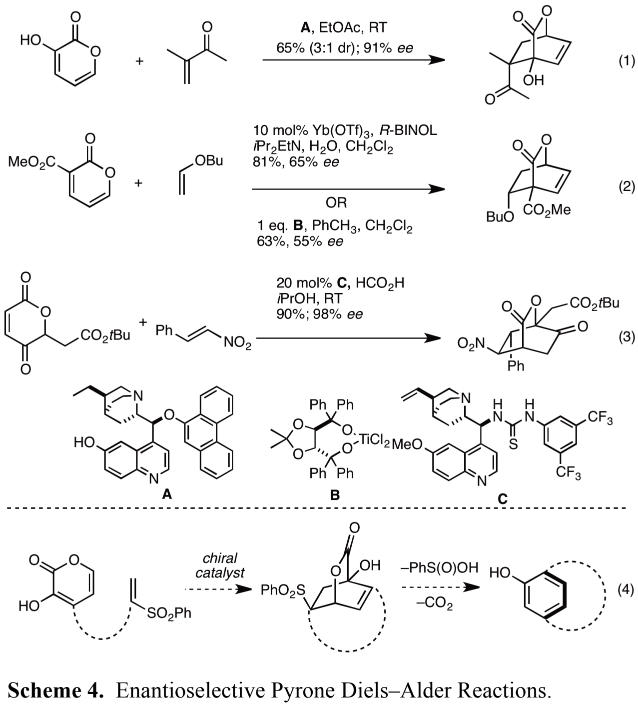
With the above concerns in mind, we considered using a vinyl sulfone (**6**) as an alkyne-equivalent dieneophile (Scheme 3).[9] The vinyl sulfone dienophile is more electronically polarized than a terminal alkyne, and would likely result in a high regiochemical preference for **7** in the Diels–Alder event. Phenylsulfinic acid could be eliminated under the conditions of the Diels–Alder reaction to give **2**, followed by loss of CO_2 to give the cavicularin architecture (**3**).

Vinyl sulfone regioisomer **8** could also be prepared, which would give the opposite regiochemical outcome in the Diels–Alder reaction (**9**) allowing for control of the connectivity in the macrocyclization. Intermediate **9** would undergo elimination to give *meta*-substituted **5**. This regiocontrolled strategy may also be applicable to other macrocyclic bis(bibenzyl) natural products with both *meta*- and *para*-substituted A-rings. Moreover, as the vinyl sulfone was more electrophilic than an alkyne, we anticipated the reaction would occur at lower temperatures (and potentially with higher yields) relative to the alkyne substrate.



Scheme 3. Vinyl Sulfones as Alkyne Equivalent Dienophiles.

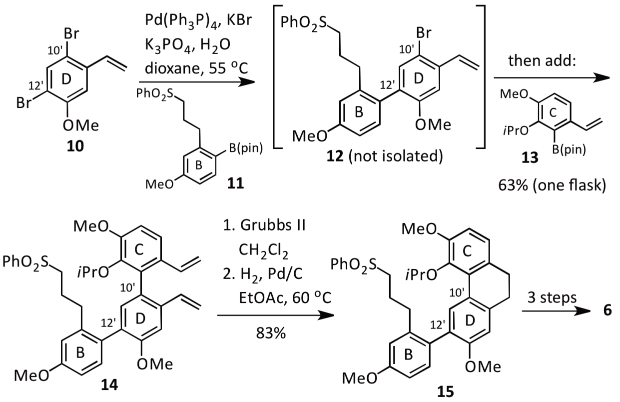
Enantioselective Diels–Alder reactions of pyrone dienes have been explored. These reactions form oxabicyclo[2.2.2]octanones with high to excellent enantioselectivities, and generally fall into three types: 1. Normal-electron-demand Diels–Alder reactions of 3-hydroxy-2-pyrones and electron deficient alkenes promoted by cinchona alkaloid or amino-indanol-derived catalysts (Scheme 4, eq. 1);[10,11] 2. Inverse-electron-demand Diels–Alder reactions of 3-acyl-2-pyrones and electron-rich alkenes (eq. 2);[12] 3. Normal electron-demand Diels–Alder reactions of 2H-pyran-2,5-diones with electron deficient alkenes catalyzed by a cinchona-based thiourea (eq. 3).[13]



Scheme 4. Enantioselective Pyrone Diels–Alder Reactions.

Our retrosynthetic strategy uses a vinyl sulfone, which precluded the inverse-electron-demand Diels–Alder reaction. The substitution pattern of cavicularin more closely matched the substitution present in the Diels–Alder reactions exemplified by eq. 1, and our overall plan was to pursue the enantioselective (+)-cavicularin synthesis using an application of this reaction where the initial cycloaddition would give a non-racemic oxabicyclo[2.2.2]octanone, which would undergo sequential eliminations of phenylsulfinic acid and CO_2 to deliver the chiral cyclophane structure in non-racemic form (eq. 4).

The first objective was to create an efficient synthesis of the achiral Diels–Alder substrate. The synthesis began with dibromostyrene **10**.[14] It was envisioned that **10** could serve directly in regioselective Suzuki reactions without the need for protecting groups to differentiate the bromine atoms.



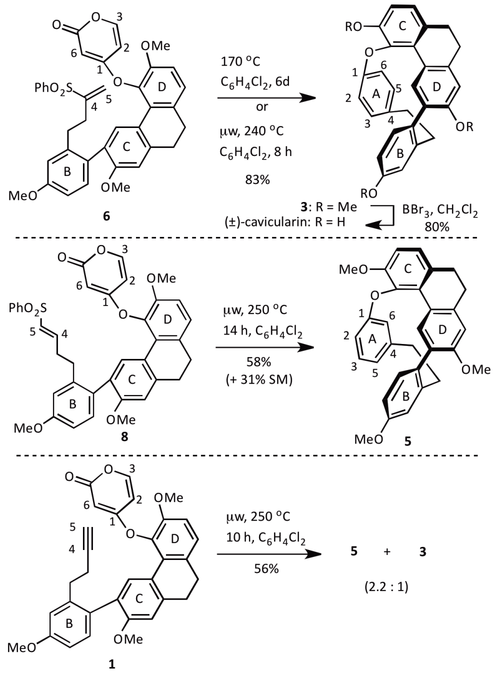
Scheme 5. Suzuki Reactions for Cavicularin.

In the event, we were delighted to observe complete regioselectivity in the Suzuki reaction of dibromide **10** with **11**. We believe the regioselectivity can be attributed to the alkene: bromides with proximal vinyl groups undergo oxidative addition at a reduced rate.[15] Related reactions of dibrominated heteroaromatic systems have been reported in the literature.[16] However, such Suzuki reactions of dibromobenzenes are quite rare,[17] and we believe this is the first example of using an alkene to control the site-selectivity in a dibromobenzene Suzuki.[18]

Although Suzuki product **12** could be isolated, it was more convenient to perform the subsequent Suzuki reaction with **13** *in situ*. When TLC indicated consumption of **10**, boronic ester **13** was added and the reaction proceeded to completion. A single regioisomer of terphenyl **14** was isolated. Two additional transformations gave **15** and three transformations produced **6**. Using a related synthetic strategy the other vinyl sulfone isomer **8** and alkyne **1** were prepared.

We began our Diels–Alder reaction investigations using pyrone substrate **6**. We found that the cycloaddition of **6** occurred with complete regiochemistry and in good chemical yield to give **3**. This reaction could be performed using microwave irradiation (240 °C, 8 h) or using a standard heating mantle at 170 °C for 6 d. Presumably, the cycloaddition delivers bicyclic intermediate **7** which undergoes sequential elimination of phenylsulfinic acid and CO_2 as outlined in Scheme 3. The order of the elimination is inconsequential, and no intermediates were observed or isolated from the reaction. Deprotection of **3** gave cavicularin.

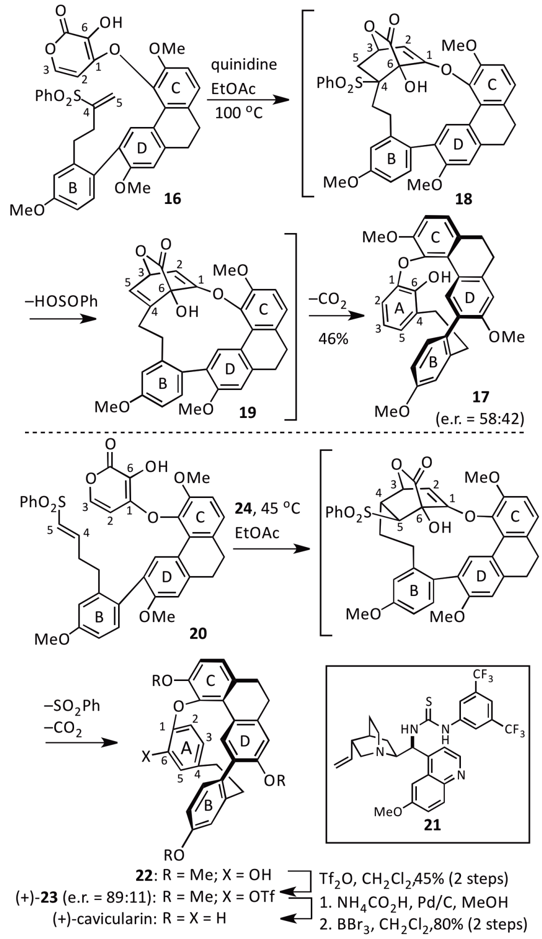
When isomeric vinyl sulfone **8** was subjected to microwave irradiation, Diels–Alder cascade product **5** was isolated in good yield. Again, the regioselectivity was high and only a single isomer of **5** was obtained. This indicates that the regiochemistry of the Diels–Alder cycloaddition can be controlled by the electronics of the substrate, and it is not strictly a result of constraints of the intramolecular tether.



Scheme 6. Synthesis of (±)-Cavicularin.

Alkyne **1** underwent the Diels–Alder cascade as well. The reaction occured at 250 °C under microwave irradiation (no reaction occurred at temperatures of 200 °C using a heating mantle); the reaction requires more forcing conditions because the alkyne is less activated than vinyl sulfone **6**. The reaction was unselective, leading to a mixture of both regioisomeric Diels–Alder products **5** and **3**.

With access to synthetic samples of cavicularin, attention was turned to performing an enantioselective synthesis. The enantiomers of cavicularin cleanly separated on chiral HPLC (Diacel OD-H) and we resolved approximately 5 mg of each enantiomer. Preliminary experiments indicated that cavicularin is stable as a single enantiomer up to 150 °C, where it begins to undergo slow racemization ($t_{1/2}$ approximately 4 h).[19] Thus, any enantioselective reaction to produce (+)-cavicularin should occur at temperatures below 150 °C.



Scheme 7. Synthesis of (+)-Cavicularin.

Hydroxypyrone substrate **16**[14] was then subjected to the cinchona-based alkaloid quinidine in EtOAc following the report of Deng. We were delighted to observe reaction at the more mild temperature of 100 °C. However, the reaction produced the undesired regioisomer **17**. The addition of the hydroxy group renders the C3 position of the pyrone nucleophilic, and bond formation occurs at C5 of the vinyl sulfone to give **18**. Elimination of phenylsulfinic acid and CO_2 gave **17**. As above, no intermediates were observed in this reaction. Interestingly, the reaction was modestly enantioselective, but no effort was made to improve the enantioselectivity of this reaction.

Isomeric vinyl sulfone **20** was prepared.[14] Mild heating of **20** in the presence of cinchona-based thiourea **21** gave **22** with good enantioselectivity (e.r. = 89:11). The resulting phenol was a delicate intermediate that was prone to decomposition, so this intermediate was immediately converted to the corresponding triflate **23**. The yield of the overall process was good (45% from **20**). Removal of the triflate and methyl groups gave (+)-cavicularin.

In conclusion, a vinyl sulfone-pyrone Diels–Alder strategy was developed for the synthesis of cavicularin. The substitution of the vinyl sulfone allows for control of the regiochemistry in the reaction. A hydroxypyrone substrate also participated in an enantioselective Diels–Alder reaction using a chiral cinchona-based thiourea. The regiochemistry of the reaction could again be controlled by choice of the vinyl sulfone substitution pattern.

Acknowledgment

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