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Total Synthesis of (±)-Cavicularin: Control of Pyrone Diels–Alder Regiochemistry Using Isomeric Vinyl Sulfones

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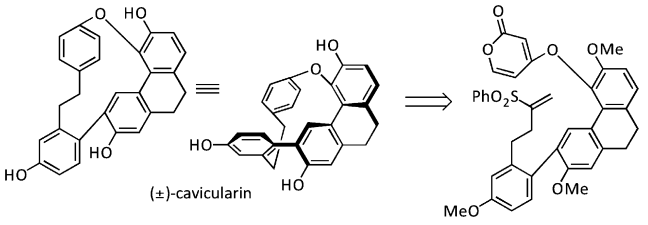
ABSTRACT



An intramolecular pyrone Diels–Alder reaction–elimination retro-Diels–Alder cascade of a vinyl sulfone was used in the synthesis of cavicularin, a molecule possessing conformational chirality. The vinyl sulfone substitution pattern allowed for regiocontrol in the Diels–Alder cascade event.

Macrocyclic bis(bibenzyls) are a class of over 70 biologically active natural products isolated from liverwort species.[1] With a few exceptions, all of these natural products fall into two structural classes: (1) C,D-ring diarylether substructure **1** (Figure 1) and (2) C,D-ring biaryl substructure **2**. Members of this family are differentiated by the oxygenation pattern of their core, and most do not possess sp^3-hybridized stereogenic carbon atoms. One C,D-biaryl member of this family, cavicularin,[2] has a fascinating (and unique) molecular architecture including a dihydrophenanthrene motif. This macrocyclic structure imparts severe strain to the molecule, and as a result, the B ring is significantly distorted (ca. 15°) from planarity. Cavicularin exists in stable chiral conformations, it is highly strained, and a member of an interesting class of biologically active molecules. For these reasons, and because of our ongoing interest in conformationally chiral molecules,[3] we decided to develop a chemical synthesis of cavicularin.

The unique molecular architecture of cavicularin also attracted attention from the synthetic community. In the inaugural synthesis, Harrowven et al. used an intramolecular radical addition to build the strained macrocyclic architecture of the natural product.[4] Baran and co-workers have also completed a synthesis of the natural product using a pyrone Diels–Alder strategy.[5]

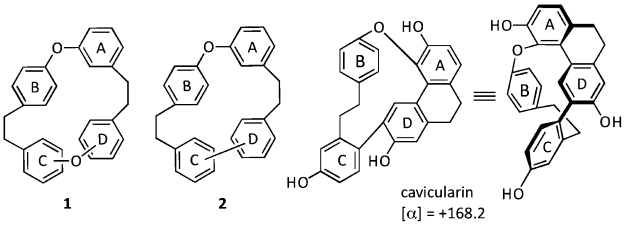


Figure 1. Macrocyclic bis(bibenzyl) natural products.

(1) (a) Keseru, G. M.; Nógrádi, M. *Nat. Prod. Rep.* **1995**, *12*, 69–75. (b) Asakawa, Y.; Toyota, M.; Hashimoto, T.; Tori, M.; Nagashima, F.; Harinantenaina, L. *Heterocycles* **2008**, *76*, 99–127.

(2) Toyota, M.; Yoshida, T.; Kan, Y.; Takaoka, S.; Asakawa, Y. *Tetrahedron Lett.* **1996**, *37*, 4745–4748.

(3) Salih, M. Q.; Beaudry, C. M. *Org. Lett.* **2012**, *14*, 4026–4029.

(4) (a) Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 3899–3901. (b) Kostiuk, S. L.; Woodcock, T.; Dudin, L. F.; Howes, P. D.; Harrowven, D. C. *Chem.—Eur. J.* **2011**, *17*, 10906–10915.

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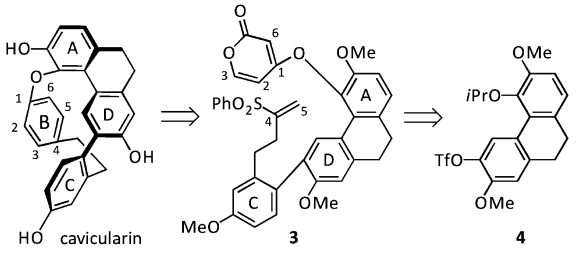
Our synthetic approach to cavicularin also focused on the use of a Diels–Alder cascade to form the nonplanar B ring (Scheme 1). Diels–Alder-retro-Diels–Alder cascades to build phenyl rings are well precedented,[6] including the elegant synthesis of the strained-ring alkaloid haouamine by Baran and Burns.[7] The regiochemistry of the Diels–Alder addition must be controlled in the cyclization event, because there are two regiochemical outcomes of the cascade. Cavicularin displays a para-substituted B-ring, which requires formation of a bond between C6 and C5 (cavicularin numbering). Diels–Alder addition with the undesired regiochemistry would give a meta-substituted B-ring (*vide infra*). Intermolecular pyrone Diels–Alder reactions often give mixtures of regioisomeric products,[8] and we suspected that the constraints of the molecular architecture would not be sufficient to guarantee formation of the desired regioisomer in the Diels–Alder event.

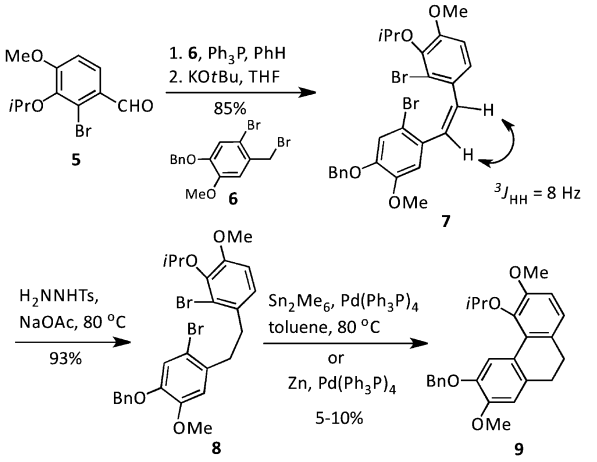
Accordingly, we planned to use an alkyne equivalent functional group with suitable electronic bias to favor formation of the desired regioisomer. Of the various alkyne-equivalent functional groups for Diels–Alder reactions,[9] a vinyl sulfone (**3**) was selected as a substrate. The electronic bias of the sulfone was anticipated to induce the desired bond formation between the electrophilic C5 atom of the vinyl sulfone and the nucleophilic C6 atom of the pyrone. Vinyl sulfones have been used as alkyne equivalents in pyrone Diels–Alder reactions.[10] Intermediate **3** was envisioned to arise from differentially functionalized dihydrophenanthrene **4**.

Scheme 1. Retrosynthetic Analysis of Cavicularin



Our initial attempt at the synthesis of **4** began with benzaldehyde **5** (Scheme 2).[11] Wittig olefination of **5** with the ylide derived from known benzyl bromide **6**[12] gave substituted stilbene **7** as a single geometrical isomer. The stereochemistry of the stilbene was assigned as *Z* based on the coupling constant ($^3J_{HH}$ = 8 Hz) of the vinylic protons. Reduction of the alkene in the presence of the aryl bromides was accomplished using *in situ* generated diimide to yield dibromide **8**.[13]

Scheme 2. First-Generation Dihydrophenanthrene Synthesis



Reductive cyclization of **8** using Stille or Ullman conditions[14] gave only trace amounts of the desired dihydrophenanthrene **9**. Attempts to improve the yield of the intramolecular coupling were not successful. Cyclization of *Z*-configured **7** using such conditions led to dehalogenation of the starting material without formation of any detectable phenanthrene product. Similarly, Wurtz-type conditions failed to advance either **7** or **8** to cyclized products.

The second-generation synthesis of dihydrophenanthrene **4** builds on a related strategy reported by Castle (Scheme 3).[15] Isovanillin derivative **5** was olefinated to produce bromostyrene **10**. Intermediate **10** was transformed into coupling partner **12** using standard conditions. Suzuki coupling of boronic ester **12** and bromide **13** (prepared from the corresponding benzaldehyde[16]) led to biphenyl **14**. Ring-closing metathesis gave a phenanthrene, which underwent partial reduction of the phenanthrene and hydrogenolysis of the benzyl ether to produce the corresponding phenol. Activation of the phenol as the

(5) (a) Dam, J. H., Ph.D. Thesis, Technical University of Denmark, 2009. (b) Gulder, T.; Dam, J. H.; Baran, P. S. Abstracts of Papers, Western Regional Meeting of the American Chemical Society, Las Vegas, NV, Sept 23–27, 2008.

(6) Gulder, T.; Baran, P. S. *Nat. Prod. Rep.* **2012**, *29*, 899–934.

(7) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908–3909.

(8) Woodard, B. T.; Posner, G. H. *Adv. Cycloaddition* **1999**, *5*, 47–83.

(9) For example: (a) Ono, N.; Kamimura, A.; Kaji, A. *Tetrahedron Lett.* **1986**, *27*, 1595–1598. (b) Anderson, W. K.; Dewey, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 7161–7162. (c) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc.* **1978**, *100*, 2918–2920.

(10) (a) Pindur, U.; Erfanian–Abdoust, H. *Liebigs Ann. Chem.* **1989**, *12*, 1275–1276. (b) Pratt, A. J.; Rendle, P. M.; Steel, P. J. *Aust. J. Chem.* **2011**, *64*, 945–950.

(11) Prepared from 2-bromo-3-hydroxy-4-methoxybenzaldehyde: (a) Hamann, P. R.; Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1984**, *49*, 3865–3867. (b) Natarajan, S.; Rajeswari, S.; Chandrasekaran, S.; Pai, B. R.; Shanmuganathan, S.; Rao, K. U. *Ind. J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **1982**, *21*, 95–97.

(12) (a) Berger, D. M.; Birnberg, G.; DeMorin, F.; Dutia, M.; Powell, D.; Wang, Y. D. *Synthesis* **2003**, *11*, 1712–1716. (b) Fukuyama, Y.; Yaso, H.; Mori, T.; Takahashi, H.; Minami, H.; Kodama, M. *Heterocycles* **2001**, *54*, 259–274.

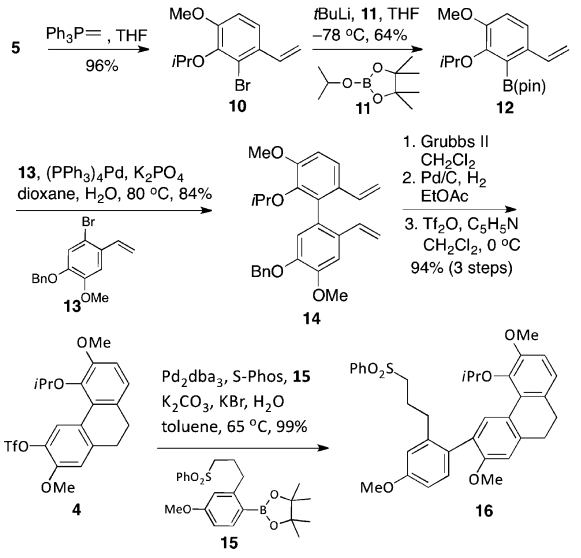
(13) (a) Marshall, J. A.; Gung, W. Y. *Tetrahedron* **1989**, *45*, 1043–1052. (b) Dewey, R. S.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1961**, *83*, 3729.

(14) For reviews, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652. (b) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265–555.

(15) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757–3760.

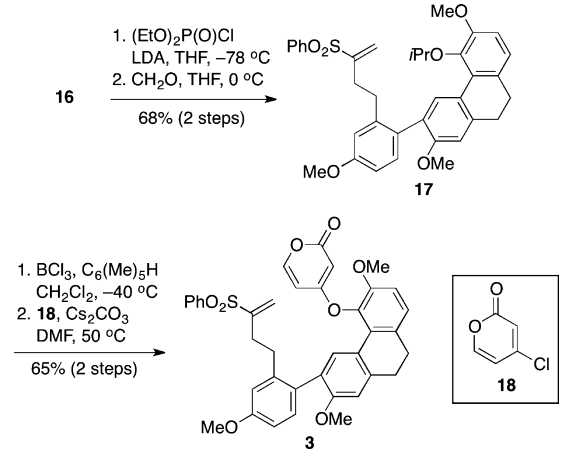
(16) Kobayashi, S.; Okimoto, K.; Imakura, Y. *Chem. Pharm. Bull.* **1982**, *30*, 1567–1573.

Scheme 3. Second-Generation Dihydrophenanthrene Synthesis



triflate (**4**) was uneventful. Coupling of **4** with boronic ester **15** (prepared in 5 steps from *m*-anisaldehyde)[17] proceeded in high chemical yield to give tetracycle **16**.

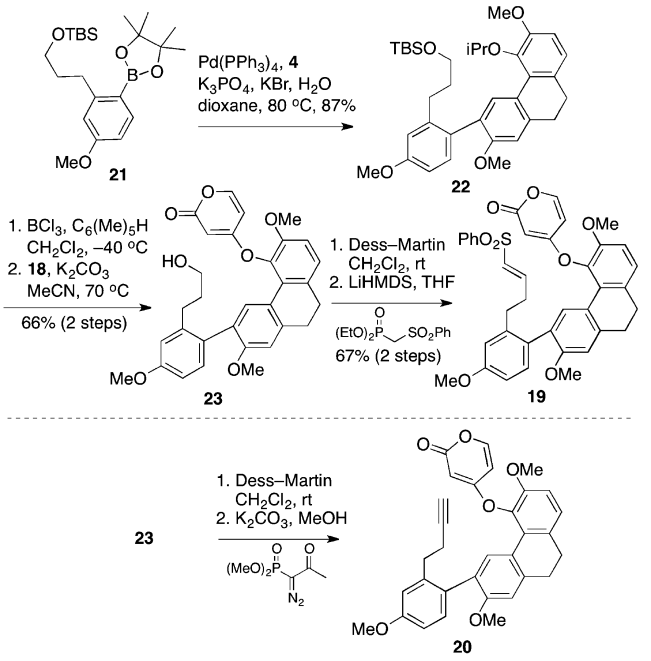
Scheme 4. Synthesis of Key Diels–Alder Substrate **3**



Functional group manipulation gave the key Diels–Alder substrate (Scheme 4). Claisen-like condensation of **16** gave a phosphonate, which underwent Horner–Wadsworth–Emmons reaction with formaldehyde to give vinyl sulfone **17**.[18] A one-pot procedure involving generation of the phosphonate and *in situ* treatment with paraformaldehyde gave superior yields of the vinyl sulfone compared to the two-step procedure. Removal of the isopropyl ether[19] and addition to chloropyrone **18** gave the desired cycloaddition cascade substrate **3**.

In order to test our hypothesis that the substitution of the vinyl sulfone would control the regiochemistry of the Diels–Alder cascade, we constructed alternative substrates **19** and **20** (Scheme 5). These substrates were conveniently prepared from related boronic ester **21**[20] and dihydrophenanthrene **4**, using a similar synthetic strategy. Coupling of **4** and **21** gave tetracycle **22**. Subjection of **22** to BCl_3 induced removal of both the TBS and *i*Pr groups. Addition of the phenol to **18** gave **23**. Alcohol **23** was oxidized to the corresponding aldehyde and olefinated to prepare vinyl sulfone **19**. Alkyne **20** was prepared from **23** by oxidation and subsequent homologation using the Ohira-Bestmann reagent.[21] These alternative Diels–Alder cascade substrates would be used to test our hypothesis that the substitution of the vinyl sulfone would control the regiochemistry of the Diels–Alder cascade.

Scheme 5. Synthesis of Alternate Diels–Alder Substrates



In the event, we were pleased to find that the key cascade reaction generated the cavicularin skeleton (Scheme 6). Diels–Alder substrate **3** was heated to 240 °C using microwave irradiation. The isolated product was methyl cavicularin (**24**), produced in high yields as a single regioisomer. Presumably, Diels–Alder cycloaddition occurs first giving **25**. Elimination of phenylsufinic acid gives intermediate **26**. Intermediate **26** undergoes a retro Diels–Alder with loss of CO_2 to give **24**. The precise order of the elimination events is inconsequential, and no intermediates or byproducts were isolated or observed in this

(17) See Supporting Information.

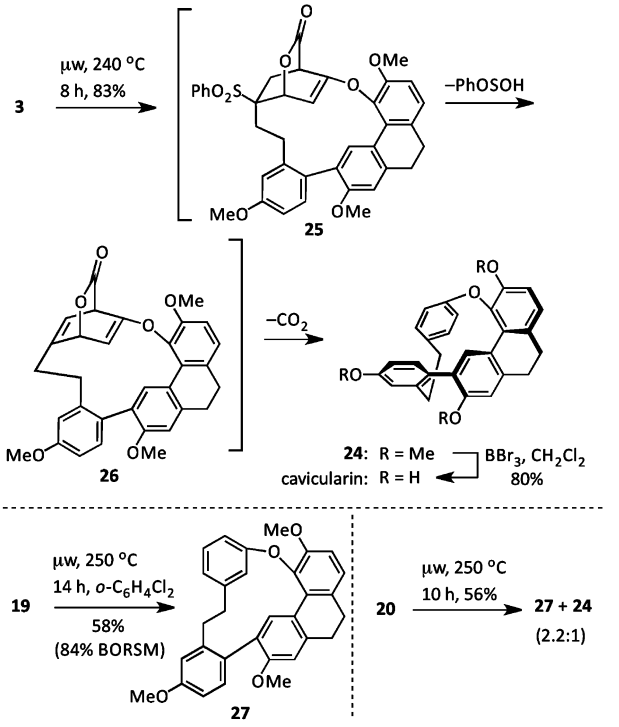
(18) Clasby, M. C.; Craig, D.; Slawin, A. M. C.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 1509–1532.

(19) Okano, K.; Okuyama, K.–i.; Fukuyama, T.; Tokuyama, H. *Synlett* **2008**, *13*, 1977–1980.

(20) Prepared in 5 steps from *m*-iodoanisole. See Supporting Information.

(21) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Roth, G. J.; Liepold, B.; Mueller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59–62.

Scheme 6. Synthesis of Cavicularin and its Regioisomer



reaction. The desired regioisomer **24** was produced as the sole isolable product. Demethylation using standard conditions completed the synthesis of cavicularin. The spectral data (e.g., ^{1}H, ^{13}C NMR) of synthetic cavicularin was identical to that reported for the natural substance.

Interestingly, when isomeric vinyl sulfone **19** was heated, the key cascade reaction occurred, but only the undesired regioisomer **27** was produced. This result indicated that the regiochemistry of the Diels–Alder addition reaction was influenced by the electronics of the substrate and was not solely dependent on the constraints of the intramolecular tether. When the less electronically biased alkyne substrate **20** was heated, a mixture of regioisomers **27** and **24** was produced. Furthermore, longer reaction times were required for full consumption of the starting material, which is consistent with an electronically less-activated substrate.

In summary, we have synthesized the conformationally chiral macrocyclic bis(bibenzyl) natural product cavicularin. Our synthetic strategy features a pyrone Diels–Alder reaction to construct the strained B-ring of the natural product. A vinyl sulfone served as an alkyne equivalent dienophile that controlled the regiochemical outcome of the Diels–Alder reaction. To the best of our knowledge, this is the first example of complete regiocontrol in the Diels–Alder reaction of a pyrone using a vinyl sulfone. Efforts to apply our synthetic strategy to other macrocyclic bis(bibenzyl) natural products and to develop an enantioselective synthesis of cavicularin are underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds including depiction of their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.