Asymmetric Synthesis

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Enantioselective and Regioselective Pyrone Diels–Alder Reactions of Vinyl Sulfones: Total Synthesis of (+)-Cavicularin**

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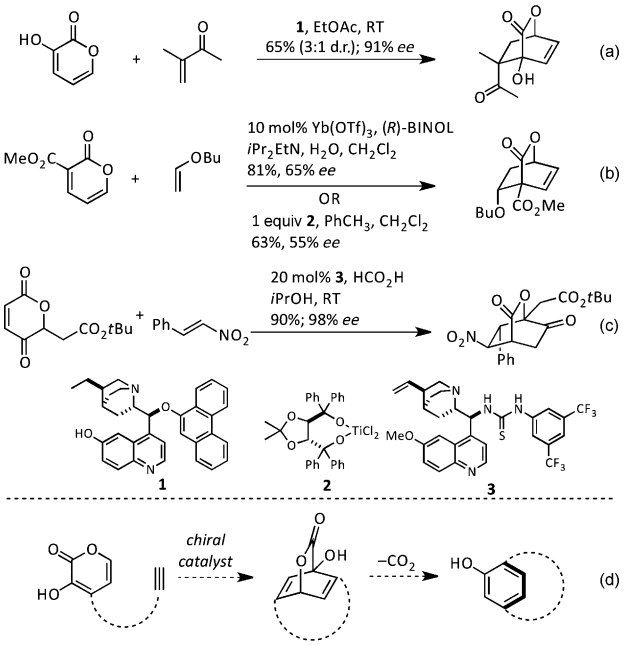
Abstract: *The total synthesis of (+)-cavicularin is described. The synthesis features an enantio- and regioselective pyrone Diels–Alder reaction of a vinyl sulfone to construct the cyclophane architecture of the natural product. The Diels–Alder substrate was prepared by a regioselective one-pot three-component Suzuki reaction of a non-symmetric dibromoarene.*

The Diels–Alder cycloaddition[1] is a protean organic reaction; the variety of dienes and dienophiles that participate is practically endless. Moreover, the enantioselective Diels–Alder reaction[2] is a well-developed process for the asymmetric construction of stereogenic carbon centers. Many complex target molecules have been made using the enantioselective Diels–Alder reaction.[3]

α-Pyrones are useful dienes for Diels–Alder reactions.[4,5] Not surprisingly, enantioselective α-pyrone Diels–Alder reactions exist. Enantioselective Diels–Alder reactions that involve α-pyrone dienes fall into three well-defined subtypes as exemplified in Scheme 1: 1) normal-electron-demand Diels–Alder reactions of 5-hydroxy-α-pyrones and electron-deficient alkenes promoted by cinchona alkaloid[6] or aminoindanol-derived[7] catalysts (Scheme 1 a), 2) inverse-electron-demand Diels–Alder reactions of 5-acyl-α-pyrones and electron-rich alkenes (Scheme 1 b),[8] and 3) normal-electron-demand Diels–Alder reactions of 2*H*-pyran-2,5-diones with electron-deficient alkenes catalyzed by a cinchona-based thiourea (Scheme 1 c).[9]

Our interest in the Diels–Alder reaction of α-pyrones arose from the observation that α-pyrone Diels–Alder reactions with alkynes (or alkyne equivalents) are followed by retro-Diels–Alder events that deliver phenyl rings.[10] The enantioselective α-pyrone Diels–Alder reaction could, in principle, be used in an intramolecular context for an enantioselective cyclophane synthesis (Scheme 1 d); however, such a strategy has not been reported. We evaluated this concept in an enantioselective synthesis of cavicularin.

Cavicularin (Scheme 2) is a cyclophane natural product that was isolated from the liverwort *Cavicularia densa*.[11] The natural product displays a strained molecular architecture; crystallographic studies of cavicularin show that the A ring is distorted in a boat-shaped configuration. As a result of the rigidified molecular architecture, cavicularin displays conformational chirality.



Scheme 1. Enantioselective Diels–Alder reactions of α-pyrones. BINOL = 1,1′-bi-2-naphthyl, Tf = trifluoromethanesulfonyl.

Cavicularin has captured the attention of synthetic chemists, and the groups of Harrowven,[12] Baran,[13] Fukuyama,[14] Suzuki,[15] and our own[16] have reported syntheses of cavicularin. The synthesis by Suzuki and coworkers featured an elegant use of a chiral sulfoxide auxiliary for the synthesis of (−)-cavicularin. Herein, we report the first synthesis of (+)-cavicularin using enantioselective catalysis.

Consideration of the enantioselective α-pyrone Diels–Alder reactions depicted in Scheme 1 suggested that an asymmetric Diels–Alder reaction of a hydroxy-α-pyrone would serve in an enantioselective cavicularin synthesis. Specifically, phenol **4** may be the product of an enantioselective Diels–Alder cycloaddition of **5** (Scheme 2). It was presumed that **5** may undergo enantioselective cycloaddition in the presence of cinchona-based catalysts to give enantioenriched **6**. We anticipated that the regiochemical outcome would be the result of interactions between the electrophilic C5 position of the vinyl sulfone moiety and the presumed nucleophilic C6 position of the α-pyrone motif.[16] Bicyclic compound **6** may undergo elimination of phenylsulfinic acid to produce **7**. Unsaturated bicycles such as **7** undergo rapid retro-Diels–Alder reactions to produce arenes such as **8**.[10] Key intermediate **5** could then be prepared from terphenyl **8**.

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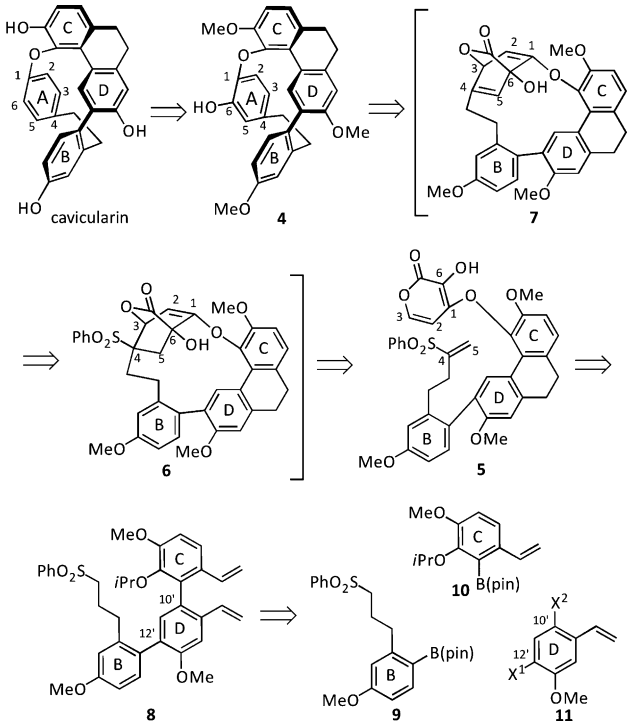
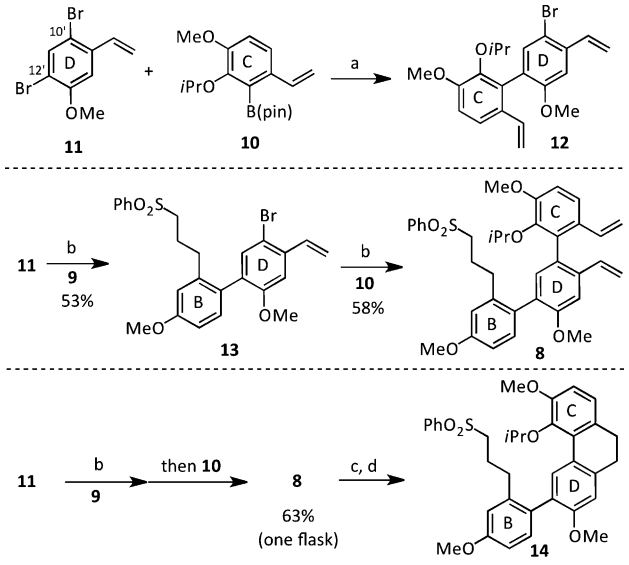


Scheme 2. Retrosynthetic analysis of (+)-cavicularin.



Scheme 3. Reagents and Conditions: a) $[Pd(PPh_3)_4]$, K_3PO_4, DMSO, 70 °C, 52 %; b) $[Pd(PPh_3)_4]$, K_3PO_4, KBr, dioxane, H_2O, 55 °C; c) Grubbs II catalyst, CH_2Cl_2, 50 °C, 95 %; d) H_2 (600 psi), Pd/C, EtOAc, 60 °C, 87 %. pin = pinacolato.

Our first objective was to develop an efficient synthesis of **8**. The terphenyl architecture of **8** suggested that Suzuki reactions[17] would be well suited for its construction from starting materials **9**–**11**. One option for the assembly of intermediate **8** would be to use distinct halogen atoms that undergo chemoselective cross-couplings (e.g., **11**, where X^1 = I and X^2 = Br).[18]

A conceptually different strategy developed for heteroaromatic systems makes use of the different reactivity of non-symmetry-related bromides (e.g., **11**, where $X^1 = X^2$ = Br).[18a,19] Handy and co-workers found that in polybrominated heteroarenes, the more reactive bromide can be predicted by the ^{1}H NMR chemical shifts of the non-halogenated congener.[20] However, there are no examples of non-symmetric dibromoarenes participating in this type of reaction. The predicted chemical shifts[21] for 3-vinylanisole suggested that the bromide substituent at the C10′ position of **11** would be more reactive.

Gratifyingly, subjecting dibromide **11**[22] to boronic ester **10**[23] under Suzuki reaction conditions induced a regioselective cross-coupling forming **12** as a single regioisomer (Scheme 3). A combination of 2D NMR techniques revealed that although dibromide **11** reacted regioselectively, biphenyl **12** possessed the undesired connectivity.[24] Fortunately, when boronic ester **11** was first coupled with **9**, the reaction was again completely selective and produced **13** in good yield. Subjecting **13** to boronic ester **10** under the same Suzuki reaction conditions gave the desired terphenyl **8** with the correct regiochemistry.

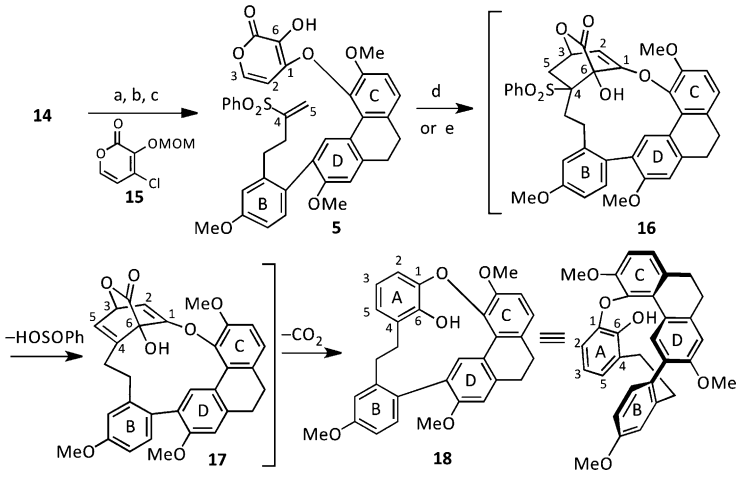
The successful sequential Suzuki couplings suggested that a one-pot Suzuki reaction[25] would be possible to construct **8** in one step. In the event, **11** was coupled with **9** using standard Suzuki conditions. When dibromide **11** was consumed (as observed by thin-layer chromatography (TLC)), boronic ester **10** was added, and the reaction proceeded to completion. This three-component coupling gave terphenyl **8** in good yields, and no regioisomers were isolated. To the best of our knowledge, this is the first regioselective one-pot three-component Suzuki reaction of a dibromoarene.

Terphenyl **8** underwent ring-closing metathesis and subsequent phenanthrene hydrogenation to give **14**.[26] The synthetic route to **14** consisted of three steps and proceeded in 52 % overall yield from known building blocks.

With convenient access to **14**, the material was advanced to the Diels–Alder substrate (Scheme 4). A one-pot phosphorylation/Horner–Wadsworth–Emmons reaction was followed by a deprotection, pyrone conjugate addition,[27] elimination sequence delivering Diels–Alder substrate **5**.

The regiochemical preference of 3,4-dioxygenated α-pyrones in Diels–Alder reactions was previously unknown; however, we anticipated that bond formation would occur between the C5 and C6 carbon atoms of **5**. Heating of **5** induced the Diels–Alder cycloaddition. Presumably, the initial cycloaddition gave **16**. Elimination of phenylsulfinic acid led to **17**, and retro-Diels–Alder reaction to liberate CO_2 gave **18**. No intermediates were observed in the reaction, and the order of elimination events is inconsequential. Evidently, the resonance contribution from the additional hydroxy group of the pyrone in **5** resulted in the undesired regiochemical preference in the initial cycloaddition, and the undesired *meta*-substituted aryl ring was observed as the only product (**18**).[28]

Cinchona-based catalysts did not reverse the regiochemical outcome, and **18** was still formed (conditions e). However, in the presence of quinidine, the reaction occurred at lower temperature (100 °C) than the background reaction

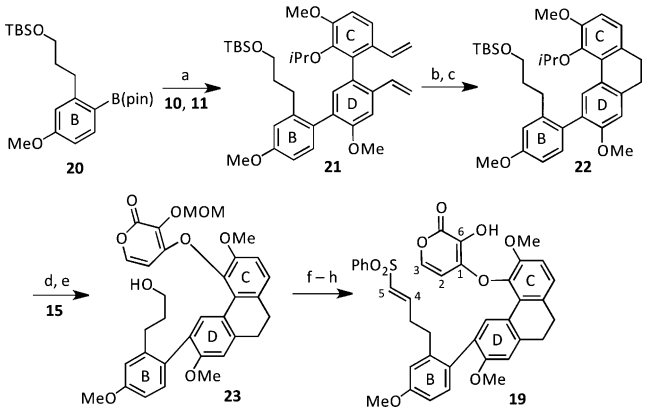


Scheme 4. Reagents and Conditions: a) $(EtO)_2P(O)Cl$, LDA, THF, −78 °C, then $(CH_2O)_n$, THF, 0 °C, 68%; b) BCl_3, $C_6(Me)_5H$, CH_2Cl_2, −40 °C, 90%; c) **15**, Cs_2CO_3, MeCN, 65 °C, then TFA, CH_2Cl_2, 0 °C, 56%; d) BHT, *o*-DCB, 240 °C, 29%; e) quinidine, EtOAc, 100 °C, 46%. BHT = *tert*-butylhydroxytoluene, LDA = lithium diisopropylamide, MOM = methoxymethyl, *o*-DCB = *ortho*-dichlorobenzene, TFA = trifluoroacetic acid.

(240 °C). Furthermore, a modest level of enantioselectivity (e.r. = 58:42) was observed. Although this was not the desired regioisomer, the ability of the cinchona alkaloid amine to increase the rate of the reaction and deliver modest enantioselectivity suggested that an enantioselective Diels–Alder cascade of an α-pyrone to form a cyclophane was possible.

The regiochemical outcome of the reaction of **5** revealed that the C3 position was the nucleophilic position of the pyrone. A convenient approach to recover the desired connectivity was to change the substitution pattern of the vinyl sulfone.

Isomeric Diels–Alder substrate **19** was therefore prepared (Scheme 5). Three-component Suzuki coupling of **20**, **11**, and **10** gave terphenyl **21** in good yield as a single regioisomer. Ring-closing metathesis and reduction gave dihydrophenanthrene **22**. Deprotection and addition to pyrone **15** led to the formation of **23**. Oxidation, olefination, and removal of the MOM ether[29] gave Diels–Alder substrate **19**.

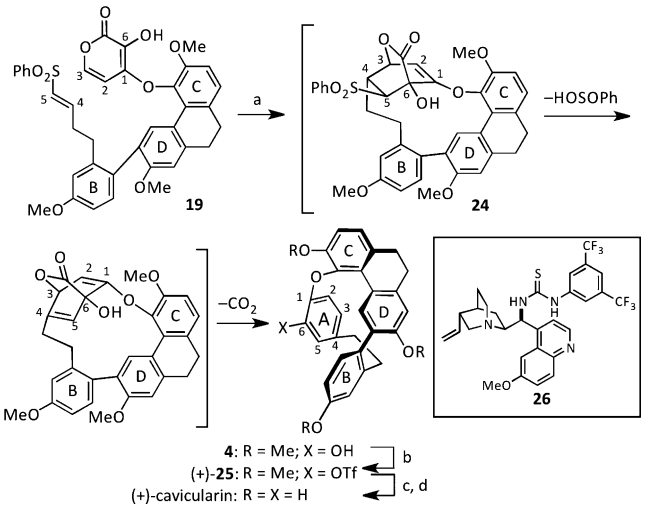


Scheme 5. Reagents and Conditions: a) $[Pd(PPh_3)_4]$, K_3PO_4, KBr, dioxane, H_2O, 55 °C; b) Grubbs II catalyst, CH_2Cl_2, 50 °C, 44% (2 steps); c) H_2 (600 psi), Pd/C, EtOAc, 84%; d) BCl_3, $C_6(Me)_5H$, CH_2Cl_2, −40 °C, 89%; e) **15**, Cs_2CO_3, MeCN, 65 °C, 72%; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 87%; g) $PhSO_2CH_2P(O)(OEt)_2$, LiHMDS, THF, −78 °C, 99%; h) TFA, CH_2Cl_2, 0 °C, 100%. LiHMDS = lithium hexamethyldisilazide, TBS = *tert*-butyldimethylsilyl.

Gratifyingly, heating of **19** in the presence of cinchona-based catalysts resulted in the desired cycloaddition, producing **4** as a single regioisomer (Scheme 6). Presumably, the initial cycloaddition gives intermediate **24**, which undergoes elimination of phenylsulfinic acid followed by elimination of CO_2 in a retro-Diels–Alder process. The order of the elimination events is inconsequential, and no intermediates were observed.[28]

The phenolic functional group in **4** was sensitive to chromatography, so the crude material from the Diels–Alder reaction was directly treated with Tf_2O to give the corresponding triflate **25**, which was reduced and dealkylated to give cavicularin.

We surveyed cinchona-based catalysts that promote enantioselective reactions. In the presence of cinchona alkaloid derivative **26**, the reaction to give **25** was enantioselective (e.r. = 89:11). To the best of our knowledge, this is the first example of an asymmetric intramolecular Diels–Alder reaction with an α-pyrone. Reduction and dealkylation of triflate (+)-**25** gave (+)-cavicularin without erosion of enantiopurity.



Scheme 6. Reagents and Conditions: a) **26**, EtOAc, 3 Å molecular sieves, 45 °C; b) Tf_2O, CH_2Cl_2, 0 °C, 45% (2 steps); c) NH_4CO_2H, Pd/C, MeOH, 70 °C, quant.; d) BBr_3, CH_2Cl_2, 80%.

In conclusion, the enantioselective synthesis of (+)-cavicularin has been reported. The synthesis features two novel reactions: a regioselective one-pot three-component Suzuki reaction of a dibromoarene to form a highly substituted terphenyl, and the first intramolecular enantioselective Diels–Alder reaction of an α-pyrone to construct the cyclophane architecture of (+)-cavicularin. The twelve-step synthesis proceeded in 7.3% overall yield from the known building blocks **10**, **11**, and **20**.

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[22] Prepared from the corresponding known aldehyde (see the Supporting Information).
[23] Boronic esters **9**, **10**, and **20** were known from our racemic cavicularin synthesis; see Ref. [16].
[24] The reason for the observed selectivity is unclear; however, it appears that the bromide substituent at the C10′ position is deactivated by the presence of the vinyl group. Control experiments indicated that the saturated congener of **11** does not react with regioselectivity in Suzuki couplings.
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[28] Diels–Alder products **18** and **25** were isolated as single species. To the best of our knowledge, there is no restricted rotation of the A ring, which would lead to atrop-diastereomers. Therefore, issues of *endo* versus *exo* diastereoselectivity do not apply to this Diels–Alder reaction.
[29] TFA deprotection of the MOM ether proceeded with quantitative conversion, but **19** was a delicate intermediate prone to decomposition and was thus advanced to **25** without purification, as indicated in Scheme 6. The overall yield for the three steps is 45%. See the Supporting Information for details.

