Natural Product Synthesis

Total Synthesis of Cavicularin and Riccardin C: Addressing the Synthesis of an Arene That Adopts a Boat Configuration**

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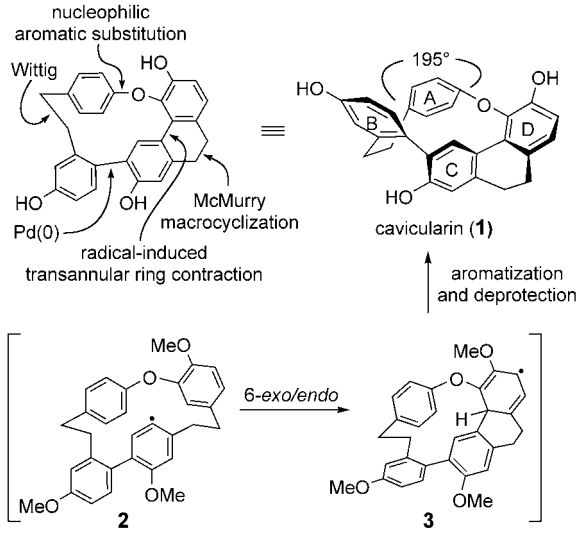
From a structural perspective cavicularin (**1**), from the liverwort *Cavicularia densa*,[1] is one of the most unusual natural products to have been isolated in the last decade. It comprises a macrocyclic core that contains dibenzyl and dihydrophenanthrene units conjoined by a biaryl bond and an ether linkage. This core imparts such strain on the system that one of the arenes, ring A, adopts a boatlike configuration and is twisted out of the plane by some 15° in the solid state. Herein, we describe the first total synthesis of cavicularin (**1**), in which a radical-induced transannular ring contraction features as a key step (Scheme 1).



Scheme 1. Synthetic strategy to cavicularin (**1**).

In planning the synthesis of cavicularin, we identified two problems that required special consideration: one was the obvious kinetic barrier to closure of the strained macrocycle;

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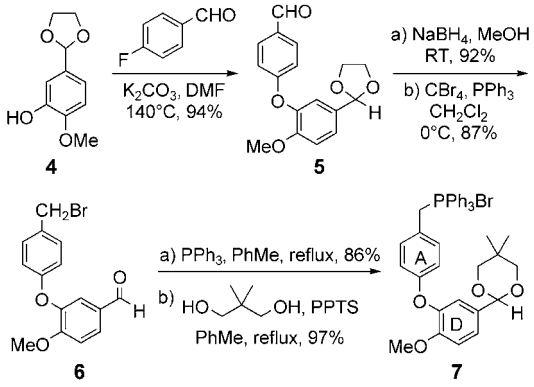
[**] Financial support from GlaxoSmithKline, Pfizer, and the EPSRC is gratefully acknowledged. Dr. Mark Bunnage (Pfizer) is thanked for helpful discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200500466

the other was a thermodynamic constraint imposed by the need to distort arene A. We felt that both of these problems could be resolved by employing a radical-induced, transannular ring-contraction strategy, such as **2**→**3** (Scheme 1).[2] In particular, by employing a larger and less-strained macrocycle as a precursor the kinetic burden would be transferred to the ring-contraction step, in which the close proximity of the aryl radical intermediate to arene D offered good prospects for a favorable outcome. It also seemed likely that cyclization could proceed without significant distortion of arene A. Indeed, that would occur in the second phase of the reaction with the collapse of **3** to cavicularin trimethyl ether, with the thermodynamic cost of bending the arene compensated by the rearomatization of arene D.[3,4]

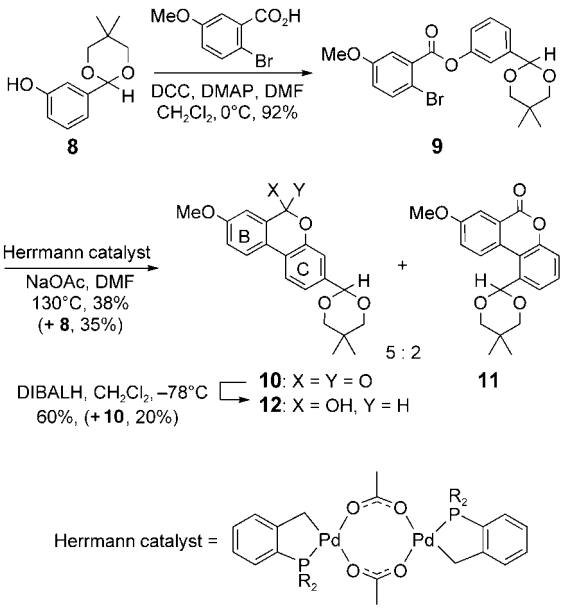
Our synthesis began with the protection of isovanillin as its dioxolane acetal **4**. Union of **4** with 4-fluorobenzaldehyde then gave diaryl ether **5**,[6] which was reduced with sodium borohydride to the corresponding alcohol. Bromination with CBr_4/PPh_3 additionally unmasked the latent aldehyde function to give **6**, which, on sequential treatment with PPh_3 and neopentyl glycol, led to the suitably functionalized AD ring system **7** (Scheme 2).



Scheme 2. Synthesis of the AD ring biaryl ether **7**. DMF = *N*,*N*-dimethylformamide, PPTS = pyridinium *p*-toluenesulfonate.

Construction of the BC ring system began with the protection of 3-hydroxybenzaldehyde as its neopentyl glycol acetal **8**. Coupling of **8** and 2-bromo-5-methoxybenzoic acid in the presence of DCC then gave ester **9**, which, on heating in the presence of the Herrmann catalyst, underwent cyclization to benzo[*c*]chromen-6-ones **10** and **11** (Scheme 3).[6] Though low-yielding, the rapidity with which this sequence led to the BC ring system of cavicularin (**1**) offered practical advantages over the alternative routes investigated. Most notably, reduction of **10** with DIBALH provided lactol **12**, which was appropriately functionalized for union with **7** and primed to facilitate regioselective iodination of arene C at a later stage.

The coupling of phosphonium salt **7** and lactol **12** by using standard Wittig protocols proved troublesome at first. However, through the simple expedient of adding 18-crown-6 to the reaction mixture, stilbene **13** was formed in 66% yield as a mixture of *E* and *Z* isomers in 2:1 ratio.[7] Next, reduction of the alkene gave phenol **14**, which was selectively iodinated under basic conditions to give tetraarene **15**.[8] Protection of



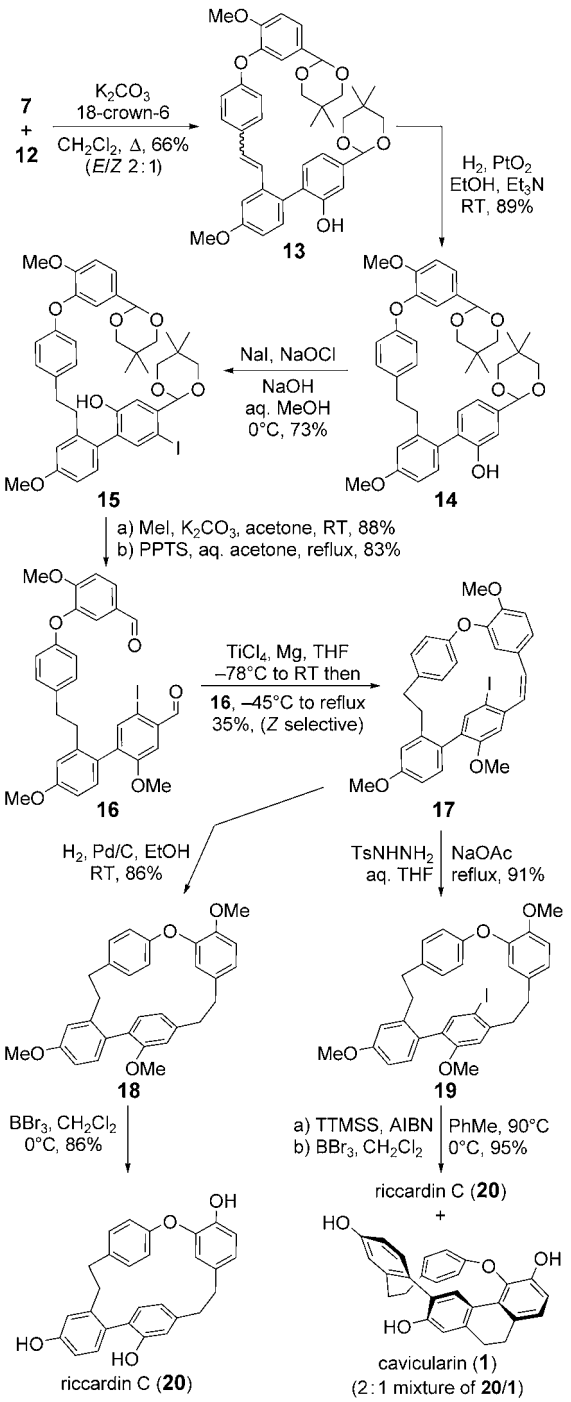
Scheme 3. Synthesis of the BC ring system. DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DIBALH = diisobutylaluminum hydride, R = *o*-tolyl.

the phenol group as its methyl ether and removal of the acetal functions then provided dialdehyde **16**, which underwent macrocyclization on treatment with low-valent titanium to yield (*Z*)-**17** (Scheme 4).[9]

We were now in a position to address the synthesis of riccardin C (**20**) and cavicularin (**1**). Catalytic hydrogenation of **17** using palladium on carbon simultaneously effected hydrogenolysis of the aryl iodide to give riccardin C trimethyl ether (**18**). Deprotection of the phenolic groups with boron tribromide then gave riccardin C (**20**) in 86% yield.[10,11] Reduction of the alkene in **17** also proceeded smoothly to give **19** without concomitant reduction of the aryl iodide.[12] A solution of macrocycle **19** in toluene was then heated at 90 °C with TTMSS and AIBN to induce homolysis of the carbon–iodine bond.[13] This procedure gave an inseparable mixture of riccardin C trimethyl ether (**18**) and cavicularin trimethyl ether in 2:1 ratio. Exposure of the mixture to boron tribromide provided riccardin C (**20**) and cavicularin (**1**), which were readily separated by column chromatography. Pleasingly, data recorded on our synthetic samples matched those reported for the natural products.[1,10,11]

In summary, we have completed the first total synthesis of cavicularin (**1**), a cyclic dibenzyldihydrophenanthrene ether from *Cavicularia densa*, in which one of the arenes is under such strain that it is forced to adopt a boat configuration. The key step involved the addition of an aryl radical intermediate to a proximal arene to facilitate a transannular ring contraction with concomitant bending of aromatic ring A (Scheme 1). The macrocyclic precursor **19** was also transformed into riccardin C (**20**) to complete the shortest synthesis of this natural product described to date.[11]

Received: February 7, 2005
Published online: May 18, 2005



Scheme 4. Total synthesis of cavicularin (**1**) and riccardin C (**20**). Ts = *p*-toluenesulfonyl, TTMSS = tris(trimethylsilyl)silane, AIBN = azobis(isobutyronitrile).

Keywords: arenes · macrocycles · radical reactions · ring contraction · total synthesis

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