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Concise Synthesis of Riccardin C, Macrocyclic Bisbibenzyl Natural Product

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Riccardin C (**1**) has been synthesized by exploiting an intramolecular S_NAr reaction of α-sulfinylfluorobenzene by an internal phenolate, providing the key 18-membered ring closure in excellent yield.

Riccardin C (**1**) represents a class of macrocyclic bisbibenzyl natural products, which are phenolic metabolites characteristic to liverworts.[1] The intriguing structure of **1** featuring an 18-membered macrocycle as well as the interesting biological activities[2] stimulated considerable synthetic interests toward this and related compounds.[3]

The major synthetic challenge is the construction of the strained macrocyclic ring including *ortho*-, *meta*-, and two *para*-substituted benzenes. Upon comparison of five previous syntheses of **1** by how the 18-membered ring was constructed (Figure 1), four syntheses employed intramolecular C–C bond formation at the benzylic positions (bond a or b),[3a–3d] whereas one relied on biaryl bond formation (bond c).[3e] The critical issue, however, is that these macrocyclizations generally suffer from poor yields, due mostly to the *molecular strain* within the macrocycle.

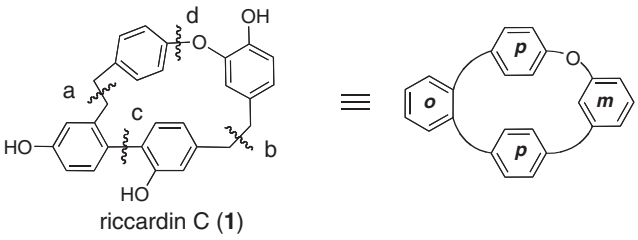


Figure 1. Riccardin C (**1**) and the disconnectivity.

In our recent interest in cyclophanes,[4] we became interested in the synthesis of **1** by exploiting the biaryl ether formation (bond d in Figure 1) through an intramolecular S_NAr reaction, converting the acyclic starting material **I** to the strained cyclized product **II** (Figure 2). *Our hope* was that the Meisenheimer intermediate **A** would be less strained by the nonplanar structure around the ether linkage. The conversion of **A** to **II** would increase the strain, which would, however, be compensated by the aromatization energy.

Herein, we describe a positive answer to this assumption, achieving the concise synthesis of **1** via the high-yield S_NAr reaction for the key macrocyclization.[5]

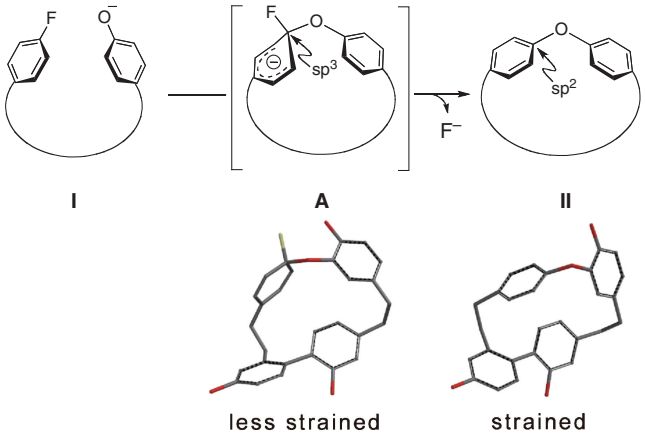
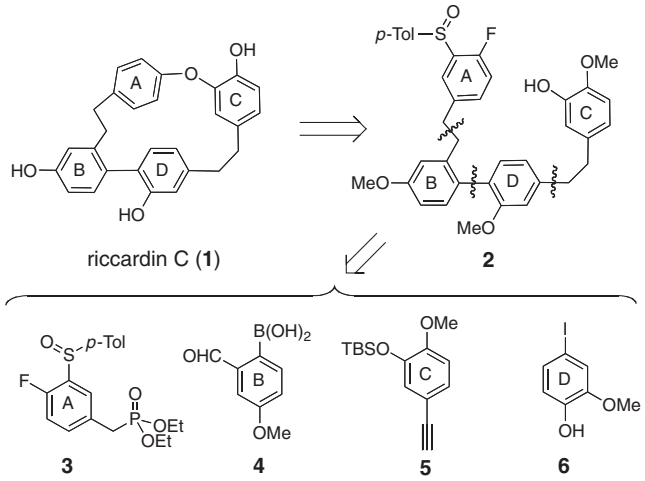


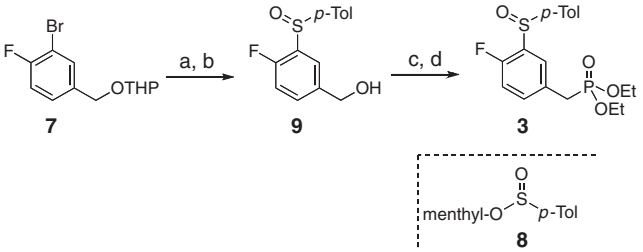
Figure 2. S_NAr cyclization to strained macrocycle.

Scheme 1 shows the retrosynthesis, assuming the cyclization of *seco*-precursor **2**. The cyclization would hopefully be achieved by an S_NAr reaction of α-sulfinylfluorobenzene[6] (A-ring) by the internal phenolate (C-ring). The acyclic precursor **2** would be assembled from four fragments, **3**–**6**.[7–9]



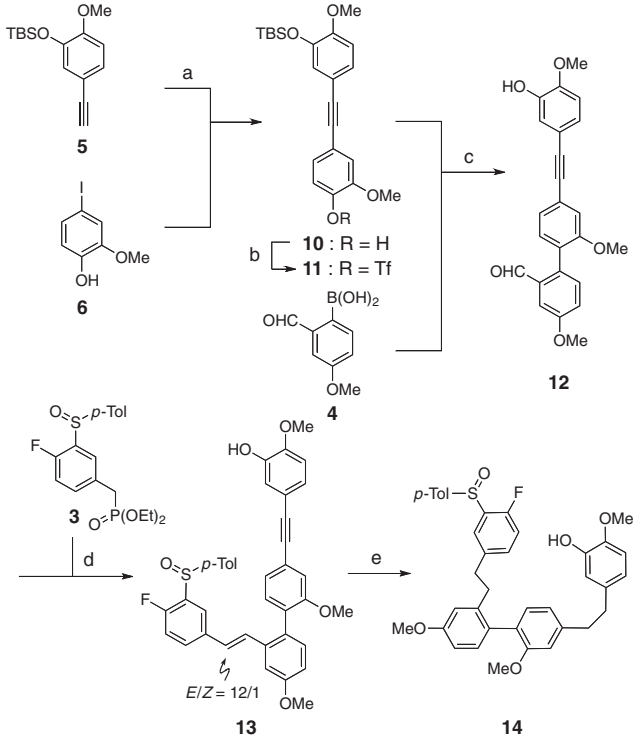
Scheme 1. Retrosynthesis.

Scheme 2 illustrates preparation of phosphonate **3**.[18] The aryllithium species, generated from bromide **7**,[10] (*n*-BuLi, THF, −78 °C, 1 h) was combined with sulfinate **8**,[11,12] and removal of the THP protection afforded alcohol **9** in 87% yield (2 steps). Mesylation of alcohol **9** followed by the reaction with NaH and diethyl phosphite gave the desired phosphonate **3** in 78% yield (2 steps).



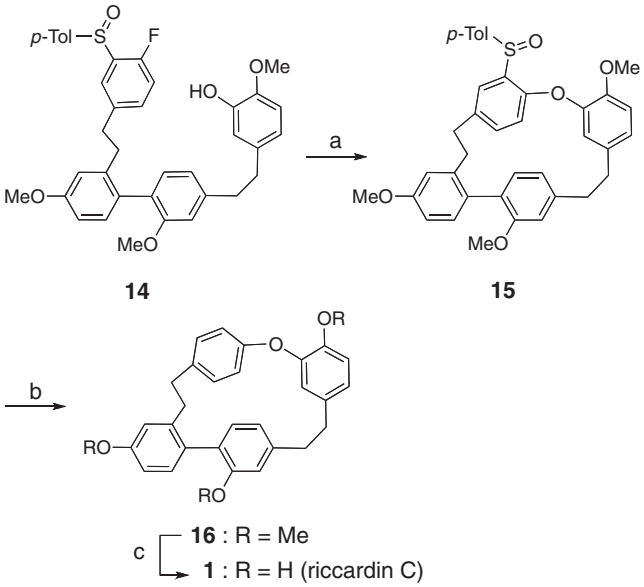
Scheme 2. (a) *n*-BuLi, THF, −78 °C, 1 h; **8**, THF, −78 °C, 10 min; (b) PPTS, EtOH, 65 °C, 3 h, 87% (2 steps); (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 5 min; (d) NaH, $HP(=O)(OEt)_2$, THF, room temp., 2 h, 78% (2 steps); THP: tetrahydropyranyl, PPTS: pyridinium *p*-toluenesulfonate.

Scheme 3 shows the assembly of four fragments.[18] Coupling of alkyne **5**[7] and iodobenzene **6**[8] proceeded smoothly in the presence of $[Pd(PPh_3)_4]$ and CuI, and triflation of the resulting phenol **10** gave triflate **11** in 83% yield. Biarylcarbaldehyde **12**, obtained by the coupling of triflate **11** and boronic acid **4**,[9] was subjected to the Horner–Wadsworth–Emmons reaction with phosphonate **3** to give stilbene **13** in 70% yield in two steps. Having enyne **13** with the full carbon skeleton of **1**, the next stage needed saturation of the double and triple bonds in **13** *while keeping the sulfinyl group intact*. After several unsuccessful trials by catalytic hydrogenations,[13] the projected conversion was achieved in excellent yield by diimide reduction.[14]



Scheme 3. (a) $[Pd(PPh_3)_4]$, CuI, THF, NEt_3, room temp., 10 min; (b) $PhNTf_2$, K_2CO_3, acetone, room temp., 1 h, 83% (2 steps); (c) $[Pd(PPh_3)_4]$, K_3PO_4, $(n\text{-}Bu)_4N^+Br^-$, DME, H_2O, 70 °C, 3 h; (d) NaH, DMF, 0 °C → room temp, 3 h, 70% (2 steps), $E/Z = 12/1$; (e) $TsNHNH_2$, $NaHCO_3$, $EtOCH_2CH_2OH$, reflux, 1 h, 92%.

Scheme 4 illustrates the end game.[18] Pleasingly, the crucial macrocyclization of **14** was achieved via an intramolecular S_NAr reaction under high-dilution conditions [CsF, $CaCO_3$, MS3A, DMF (1.0 mM), 140 °C, 4 h],[15] giving the cyclized product **15** in 92% yield.[16] Upon sulfoxide–lithium exchange[17] of **15** followed by quenching with MeOH, macrocyclic ether **16** was obtained in 95% yield. Finally, removal of three methyl groups by using BBr_3 afforded riccardin C (**1**), whose physical data (^1H and ^{13}C NMR, IR, and combustion analysis) were fully consistent with those reported in the literature.[1]



Scheme 4. (a) CsF, $CaCO_3$, MS3A, DMF, 140 °C, 4 h, 92%; (b) *t*-BuLi, THF, −78 °C, 10 min; MeOH, −78 °C, 10 min, 95%; (c) BBr_3, CH_2Cl_2, 0 °C → room temp., 2 h, 93%.

In summary, a concise synthesis of riccardin C (**1**) was achieved by an intramolecular S_NAr reaction to form the key 18-membered ring. This strategy would be effective for the synthesis of other more complex bisbibenzyl natural products.

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16 The ^{1}H NMR of the product **15** showed two sets of broad peaks, reflecting the restricted rotation of the biaryl ether bond or the biaryl bond relative to the chiral center at the sulfur atom.

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18 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

