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Highly Efficient Method for Coriolin Synthesis

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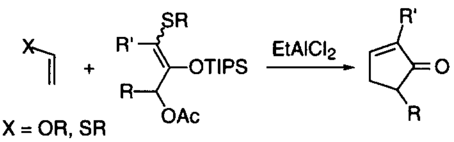
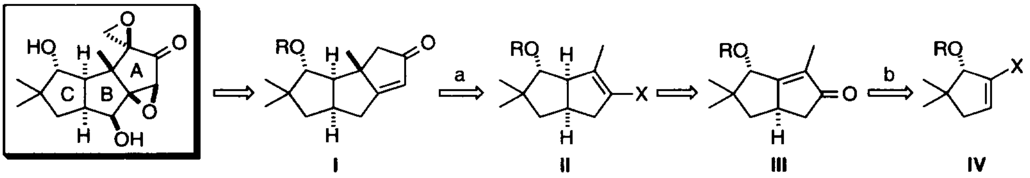
Abstract: Formal total synthesis of coriolin has been accomplished on the basis of a [3+2] cycloaddition reaction of a vinylsulfide with 3-(methylthio)-2-siloxyallyl cation. A five-membered vinylsulfide as a C ring unit was prepared in five steps from commercially available compounds. The first [3+2] cycloaddition reaction gave the BC ring intermediate, which was then converted into a bicyclic vinylsulfide in three steps. The construction of the A ring by the second [3+2] cycloaddition reaction followed by two-step-conversion afforded the tricyclic enone (30% overall yield from isobutyronitrile) which has previously been synthesized and converted into coriolin.

We recently reported the synthetic utility of 3-(alkylthio)-2-siloxyallyl acetate as a three-carbon unit for cyclopentanone annulation.[1] The features of this transformation seem to be quite useful for the successive construction of cyclopentenone generally found in triquinane-type natural products. Among these natural products, coriolin[2] has attracted much attention from the synthetic viewpoint due to its highly functionalized unique carbon framework as well as important biological activity. This paper describes a synthetic application of the annulation to coriolin synthesis.[3] In our synthetic approach (Scheme 1), stereocontrol of ring fusion may be crucial, but by using the starting materials containing a sterically demanding RO group as the C ring component, the B ring may be constructed from the opposite side of the alkoxy group to form III (step b). After appropriate conversion of III to II, the A ring may be formed from the opposite face of the C ring (step a) to produce the desired intermediate I having the correct stereochemistry.

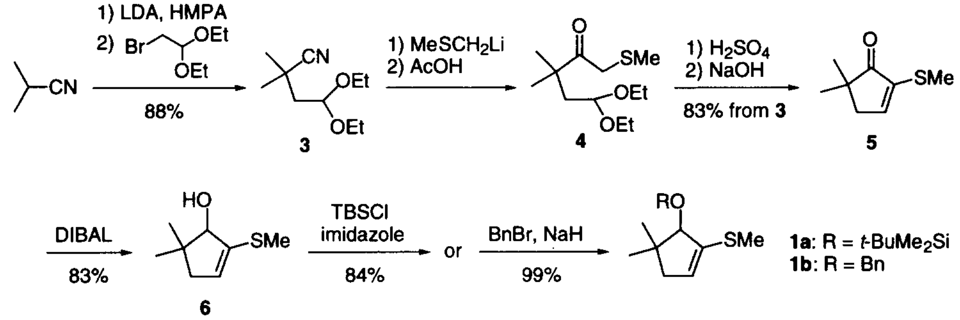


(Eq 1)



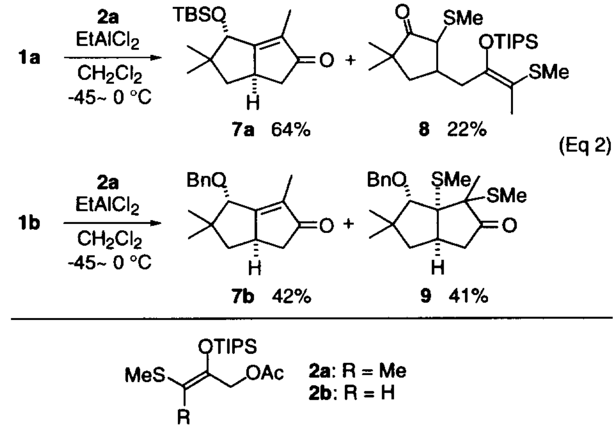
Scheme 1 Retrosynthetic Analysis of Coriolin

Anticipating the directing effect of the RO group of IV, we chose vinylsulfides **1a** and **1b** as the C ring unit, which were easily prepared as shown in Scheme 2.



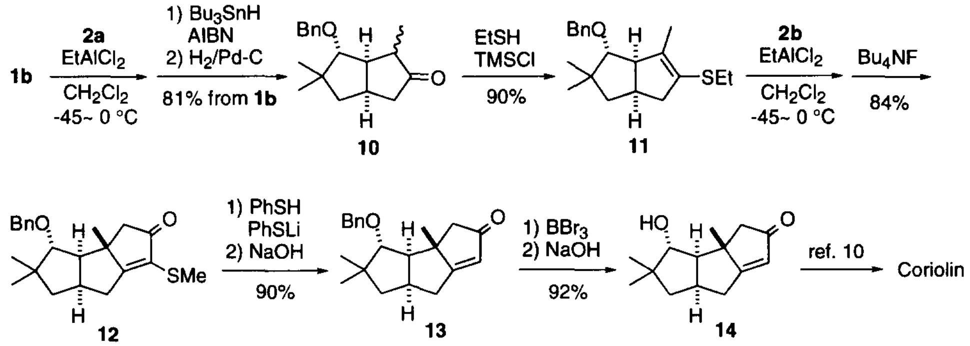
Scheme 2 Preparation of the C ring Precursors

Under the influence of $EtAlCl_2$, the reaction of **1a** with **2a** took place to give the desired bicyclic product **7a**[4] in 64% yield, but a substantial amount of a side product arising from hydride shift **8** was also formed in 22% yield. On using the benzyl ether **1b**, however, cyclopentanone anunulation took place selectively to produce two bicyclic compounds **7b** and **9** in 83% combined yield.



(Eq 2)

Selective formation of **7b** and **9** has clearly shown the benzyloxy group plays the expected role in determining the stereochemical outcome of cyclopentanone annulation. Since several attempts to convert **9** to **7b** were not so successful, the mixture was exposed to tributyltin hydride[5] and then hydrogenation catalyzed by Pd-C to lead to the formation of **10** (81% from **1b**). Further, by treating with a mixture of EtSH and TMSCl in CH_2Cl_2 at room temperature,[6] **10** was selectively converted to **11** in 90% yield, which set the stage for the next annulation. The second annulation was cleanly accomplished on the C-C double bond of **11** with **2b** to form the tricarbocycle **12** as the single product (84% yield). Removal of the sulfur moiety was readily performed by treating with a mixture of PhSH/PhSLi,[7] and after removal of the benzyl group with BBr_3,[8] the alcohol **14**[9] was obtained in 92% (30% overall yield from isobutyronitrile). Since the conversion of **14** to coriolin has already been accomplished by Matsumoto and co-workers,[10] the total synthesis has been thus formally completed.



Scheme 3 Formal Total Synthesis of Coriolin

The present cyclopentanone annulation methodology has proven to be of promising use for the synthesis of molecules containing various cyclopentanone moieties. We are currently studying the total syntheses of other natural triquinanes.

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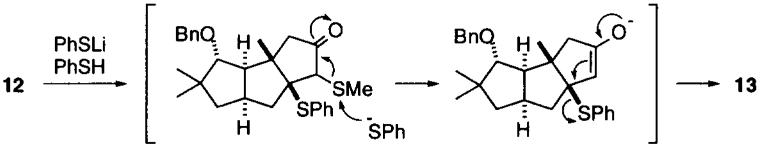

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