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# An Expeditious Asymmetric Synthesis of the Pentacyclic Core of the Cortistatins by an Intramolecular (4+3) Cycloaddition

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A concise, asymmetric synthesis of the pentacyclic framework of the cortistatins has been accomplished in 12 steps from commercially available starting materials, employing a highly diastereoselective intramolecular (4+3) cycloaddition of epoxy enol silanes as the key step.

10 The isolation and identification of cortistatin A from the marine sponge *Corticium simplex* in 2006, and subsequently its congeners have generated much interest among organic and medicinal chemists alike.[1] This family of rearranged steroidal alkaloids were discovered through a cell anti-proliferation 15 assay-guided fractionation, in which cortistatins A (**1**) and J (**2**) were identified to be the most potent, nanomolar anti-angiogenic natural products. With recent data showing that anti-angiogenics are generally well-tolerated without observable drug resistance, and when given in conjunction 20 with traditional cancer drugs could suppress cancer recurrence, the discovery and development of new anti-angiogenics hold promise for future cancer therapy.
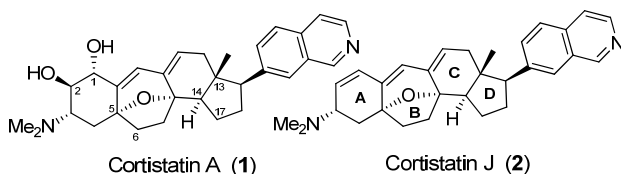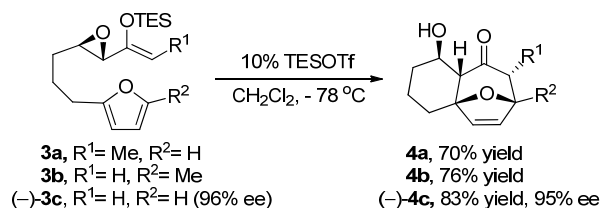


Cortistatin A (**1**)          Cortistatin J (**2**)
**Fig. 1** Cortistatins A and J

25 The bioactivity, therapeutic potential and architectural beauty of the cortistatins have inspired many efforts toward the synthesis of these molecules in the organic chemistry community.[2] The isolated quantities being too minute for further studies have motivated their semi-, total and formal 30 syntheses, as well as quite a number of synthetic studies.[4,5] Successful approaches have enabled the preparation of cortistatin derivatives and the assembly of a preliminary SAR profile of these compounds.[6]

The central bicyclic ether in the context of a seven-35 membered ring B, a feature of all of the cortistatins, has been constructed by diverse approaches, including ring expansions, cycloisomerizations, dipolar cycloadditions, RCM, cyclizations by radical, alkylation and aldol reactions.[4] In light of recent communications using cycloadditions to access 40 ring B,[5] we report herein our efforts in the application of the (4+3) cycloaddition of epoxy enol silanes that we have developed (Scheme 1),[7] to the asymmetric synthesis of these molecules. We proposed to use this reaction in the synthesis of cortistatins, not only because both rings B and C could 45 conceivably be obtained from this intramolecular (4+3) cycloaddition with furan derivatives in a concise manner, but also to put this methodology to the test for its compatibility and applicability in this context of complex synthetic targets.

Herein we outline the application of this (4+3) cycloaddition 50 to the efficient asymmetric synthesis of **5,** the pentacyclic core of cortistatins A and J.



**3a,** $R^1$= Me, $R^2$= H          **4a,** 70% yield
**3b,** $R^1$= H, $R^2$= Me          **4b,** 76% yield
(–)-**3c,** $R^1$= H, $R^2$= H (96% ee)   (–)-**4c,** 83% yield, 95% ee

**Scheme 1** Intramolecular (4+3) cycloaddition of epoxy enol silanes

In our synthetic plan, ring D derived from *meso* 55 cyclopentanedione **6** would serve as the linker to unite the diene and the dienophile for the key intramolecular (4+3) cycloaddition (Scheme 2). Desymmetrization by reduction with (*S*)-CBS-*B*-Me yielded cyclopentanol (2*R*,3*R*)-**7a** in 94% ee and its diastereomer (2*S*,3*R*)-**7b** in 78 % overall yield, 60 accompanied by 12% of over-reduced diol.[8] Using (*S*)-CBS-*B*-Bu, however, resulted in **7a** in comparable yield but with only 83% ee. Protection and addition of furanyllithium **8** to **7a** provided cyclopentanol **9**.[9] Activation and dehydration of the tertiary alcohol yielded cyclopentene **10**. A cross-65 metathesis with methyl vinyl ketone mediated by the Hoveyda-Grubbs catalyst[10] yielded the desired enone **11** without ring-opening of the cyclopentene. Chemoselective asymmetric epoxidation of the enone in the presence of the cyclopentene in **11** employing Deng's cinchona-derived 70 catalyst **12** was achieved in 96% yield to give **13** as a single diastereomer having the correct stereochemistry to direct the subsequent cycloaddition reaction.[11] Conversion to the enol silane yielded the requisite cycloaddition precursor **14**. Gratifyingly, the key (4+3) cycloaddition catalyzed by 75 TESOTf afforded the desired cycloadduct **15** having rings B, C, and D, in 87% yield as a single diastereomer.

Dehydration of **15** generated enone **16**, which was subjected to treatment with acid to give diol **17**. The C17 hydroxyl group was deprotected at this point so that it could 80 direct the subsequent reduction to set the stereochemistry of ring D. Using Crabtree's catalyst, reduction occurred on the α-face as desired to afford diol **18** in good yield, along with concomitant reduction of the dihydrofuran. The bis-oxidation of diol **18** with Dess-Martin periodinane afforded the expected 85 ketoaldehyde, whch spontaneously underwent intramolecular
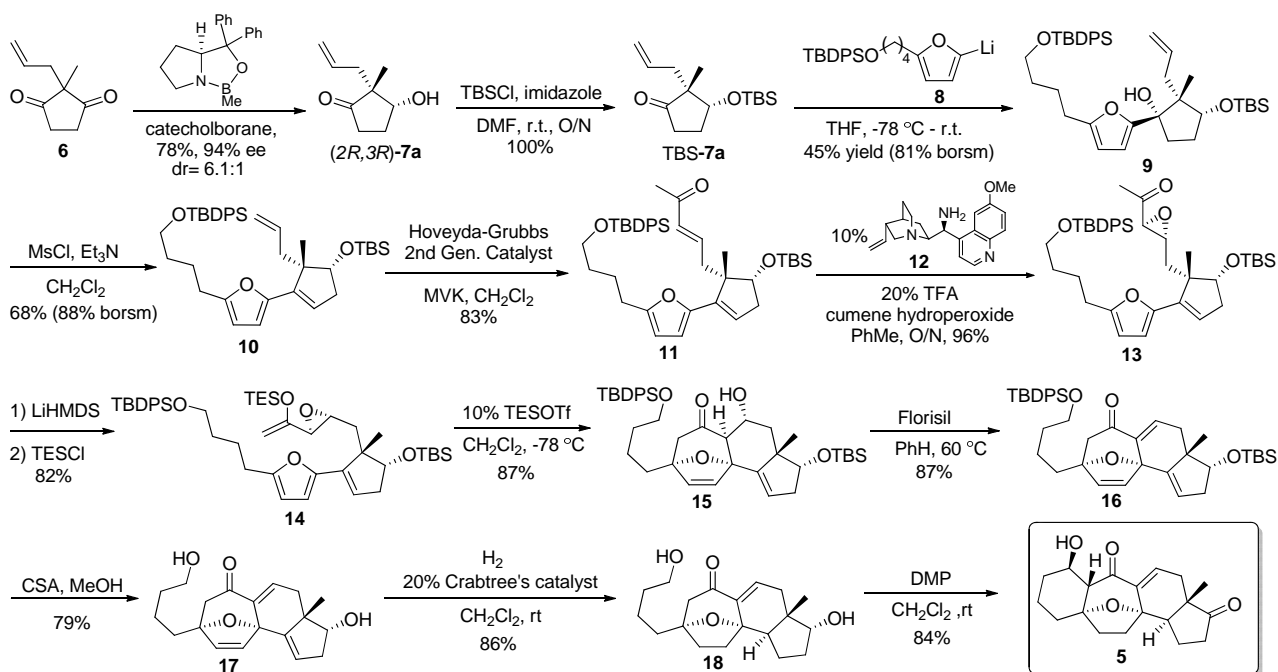
**Scheme 2** Asymmetric synthesis of pentacyclic **5**

aldol cyclization upon silica gel chromatography, to afford **5** in 84% overall yield.

In this communication, we report a succinct synthesis of the pentacyclic core of **1** and **2** in optically enriched form, in 12 steps from commercially available substrates, using the intramolecular (4+3) cycloaddition of epoxy enol silanes as the key step. The successful application of this reaction to synthesize **5** demonstrates the power of this cycloaddition and its compatibility with various functional groups for use in complex natural product synthesis. The synthetic strategy enabled by this reaction gives us access to differently functionalized cortistatin analogues complementary to those obtained using previous approaches. We are currently examining the use of an amine-substituted derivative of furanyllithium **8** for a more convergent synthesis. Our continuing studies on the total synthesis of the cortistatins and their analogues will be reported in due course.

## Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, copies of spectra and full characterization of all new compounds. See DOI: 10.1039/b000000x/

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