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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.

The central bicyclic ether in the context of a seven-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. In light of recent communications using cycloadditions to access ring B, we report herein our efforts in the application of the (4+3) cycloaddition of epoxy enol silanes that we have developed (Scheme 1), 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 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 to the efficient asymmetric synthesis of 5, the pentacyclic core of cortistatins A and J.

In our synthetic plan, ring D derived from meso cyclopentanediene 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 (2R,3R)-7a in 94% ee and its diastereomer (2S,3S)-7b in 78% overall yield, accompanied by 12% of over-reduced diol. Using (S)-CBS-B-Bu, however, resulted in 7a in comparable yield but with only 83% ee. Protection and addition of furanylithium 8 to 7a provided cyclopentanol 9. Activation and dehydration of the tertiary alcohol yielded cyclopentene 10. A cross-metathesis with methyl vinyl ketone mediated by the Hoveyda-Grubbs catalyst10 yielded the desired enone 11 without ring-opening of the cyclopentene. Chemo- and diastereoselective epoxidation of the enone in the presence of the cyclopentene in 11 employing Deng’s cinchona-derived 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 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 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 concommitant reduction of the dihydrofuran. The bis-oxidation of diol 18 with Dess-Martin periodinane afforded the expected ketoaldehyde, which spontaneously underwent intramolecular
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.

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Notes and references

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9 The low conversion in this step remains to be optimized, but the unreacted starting material can be largely recovered.