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Total Synthesis of (±)-Cortistatin J from Furan

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Abstract

A concise, diastereoselective total synthesis of (±)-cortistatin J has been completed in 20 steps from furan. Key steps include an intramolecular [4 + 3] cyclization of a disubstituted furan with a (Z)-2-(trialkylsilyloxy)-2-enal to construct the tetracyclic core and a (Z)-vinylsilane/iminium ion cyclization to form the A ring.

The cortistatins are a family of novel steroidal alkaloids recently isolated by Kobayashi and co-workers from the marine sponge *Corticium simplex* collected off Flores Island, Indonesia.¹ The unprecedented reorganization of the steroidal framework in addition to the unusual amino and isoquinoline substituents contribute to the appeal of these natural products as targets for total synthesis. However, their biological properties are even more significant. Cortistatins A-D^{1a} and J-L^{1c} inhibited the proliferation of human umbilical vein endothelial cells (HUVECs) with high selectivity. Cortistatins J (**1**) and A (**2**) (Figure 1) are the most active and selective of the natural products, having shown cytostatic and anti-proliferative activity (IC₅₀ = 8 and 1.8 nM for **1** and **2** respectively) against HUVECs with a selective index of 300–1100 for **1** and greater than 3000 for **2** in comparison with that of normal human dermal fibroblast or several tumor cell lines. The anti-angiogenic properties of **2** were also evaluated and it was found that the migration and tubular formation of HUVECs induced by VEGF or bFGF could be inhibited at 2 nM concentration. Thus, the cortistatins represent exciting new leads for anticancer drug discovery efforts based upon the inhibition of angiogenesis.² Accordingly, these natural products have attracted significant attention from the synthetic community, resulting in numerous approaches³ and several total⁴ and formal⁵ syntheses.

We recognized that the cortistatins represented the ideal targets to apply our methodology for the [4 + 3] cyclization of (Z)-2-(trialkylsilyloxy)-2-enals,⁶ which are readily prepared via retrocycloaddition of 5-(trialkylsilyloxy)-1,3-dioxins.⁷ Two representative and relevant examples are shown in Scheme 1. Thus, thermally promoted retrocycloaddition of dioxins **3** provided (Z)-enals **4**, which underwent Lewis acid catalyzed [4 + 3] cyclizations⁸ with a variety of dienes, in this case furan to yield cycloadducts **5**.⁹ During the course of this study we made several key findings: (1) *endo* adducts are uniformly preferred over *exo* adducts, (2) the stereoselectivity is better with smaller silyl substituents (e.g. TES vs. TBS) and (3) the *endo/exo* ratio can be significantly improved by the choice of Lewis acid. These results encouraged us to advance a retro-synthetic analysis of cortistatin J, outlined in Scheme 2. Thus, the dimethylaminocyclohexene A ring could be stereoselectively constructed by intramolecular addition of (Z)-vinylsilane **6** onto the equatorially oriented *exo*-iminium ion following the Overman protocol.¹⁰ The (Z)-vinylsilane moiety of **6** could be installed by a

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ASSOCIATED CONTENT

Supporting Information. Spectroscopic data and experimental details for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Sonagashira coupling of triflate **7** with (trimethylsilyl)acetylene followed by semi-reduction with DIBAL-H. Oxidation of the alcohol functionality would provide the aldehyde precursor to the iminium ion. Dienol triflate **7** could be obtained via triflation of the dienolate derived from enone **8**. In turn, enone **8** would be provided by oxidation of α -hydroxy ketone **9** to an α -hydroxy enone and reductive removal of the superfluous hydroxyl functionality. Stille coupling with of the enol triflate moiety of **9** with 7-(trimethylstannyl)isoquinoline would install the isoquinoline functionality. In the key step, it was hoped the tetracyclic core **9** could be constructed by a diastereoselective, *endo* [4 + 3] cyclization between the disubstituted furan and (Z)-2-(triethylsilyloxy)-2-enal moiety in **10**, which could be obtained by stereoselective retrocycloaddition of 5-(triethylsilyloxy)-1,3-dioxin **11**.

The preparation of the key dioxin **11** began with utilization of Kim's protocol for the conjugate addition of organoaluminates to α,β unsaturated ketones.¹¹ Thus, TIPS-protected 2-furylethanol¹² **12** was metalated with *n*-butyllithium and then converted to the lithium trimethylaluminate, which underwent trimethylsilyl triflate-promoted conjugate addition to 2-methylcyclopenten-1-one to afford the TMS enol ether **13** (Scheme 3). The enolate derivative of **13**, generated upon treatment of with methyllithium, was diastereoselectively alkylated with methyl iodoacetate to provide ketone **14**. A simple three step sequence (preparation of the enol triflate **15**, ester reduction and iodination) yielded iodide **16**, which was used to alkylate the azaenolate of the dimethyl hydrazone¹³ of 2,2-dimethyl-1,3-dioxan-5-one. The alkylated hydrazone was hydrolyzed during workup to yield dioxanone **17**. Silylation of the kinetic enolate of dioxanone **16** followed by thermally-promoted retrocycloaddition of the resultant silyloxydioxin gave the requisite (Z)-2-(triethylsilyloxy)-2-enal **10**. After much experimentation,¹⁴ it was found that subsection of silyloxyenal **10** to catalytic triflic acid in dichloromethane at $-78\text{ }^{\circ}\text{C}$ for 1 hour effected the desired [4 + 3] cyclization with TES cleavage in the same pot to provide the tetracyclic core **9** as a single diastereomer, whose structural assignment was based on extensive nOe experiments.

With gram quantities of the tetracyclic core **9** in hand, we turned our attention to installation of the isoquinoline functionality at this point in the synthesis since its presence was not expected to complicate subsequent steps. (Scheme 4). Thus, Stille coupling of the enol triflate moiety of **9** with 7-trimethylstannylisoquinoline **18**¹⁵ proceeded uneventfully to give isoquinoline **19**. Stereoselective and global alkene reduction was achieved with diimide¹⁶ and provided tetrahydrofuran **20** in excellent yield. A three step oxidation/deoxygenation sequence (Swern oxidation of α hydroxy ketone **20**, α -hydroxy enone triflation and Pd-catalyzed reduction of triflate **21**) gave enone **8**. The 9(11),10(19)-diene unit was introduced as a dienol triflate via generation of the dienolate of enone **8** with LiHMDS and sulfonylation with PhNTf₂. Removal of the TIPS protecting group with aqueous HCl yielded alcohol **7**. The (Z)-vinylsilane was incorporated in one step¹⁷ utilizing the known potassium trifluoroborate reagent **22**¹⁸ and Molander's conditions for Suzuki-Miyaura coupling.¹⁹ Parikh-Doering oxidation of the alcohol smoothly provided key aldehyde **23**. To our delight, we found that heating aldehyde **23** in the presence of excess dimethylamine hydrochloride in aceto-nitrile at $60\text{ }^{\circ}\text{C}$ overnight provided cortistatin J as a single diastereomer in excellent yield. The cyclization presumably proceeds through iminium ion conformer **6** (Scheme 2), with the dimethyliminium ion adopting a pseudo-equatorial position to avoid an incipient 1,3-diaxial interaction with the ethylene bridge of the tetrahydrofuran.

In summary, we have completed a concise total synthesis of ($\pm$)-cortistatin J in 20 steps from furan. The tetracyclic core was assembled by an intramolecular, diastereoselective [4 + 3] cyclization of a disubstituted furan and a (Z)-2-(triethylsilyloxy)-2-enal, obtained by retrocycloaddition of a 5-(triethylsilyloxy)-1,3-dioxin, and represents the first application of

our methodology. The total synthesis was completed with the Overman-type (Z)-vinylsilane/iminium ion cyclization to construct the A ring. The preparation of other cortistatin congeners, in particular, cortistatins A and K via the pivotal enone **8** are now under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Prepared via alkylation of 2-lithiofuran with (2-iodoethoxy)triisopropylsilane, see Supporting Information.
13. Prepared via condensation of 2,2-dimethyl-1,3-dioxan-5-one with dimethylhydrazine, see Supporting Information.
14. Lewis acids such as Sc(OTf)₃, TESOTf, and BF₃·OEt₂ effected the desired [4 + 3] cyclization, but cleaved the TIPS group. Interestingly, cyclizations with a derivative of enal **10** with the isoquinoline in place of the triflate substituent provided a mixture of *endo/exo* products.
15. Prepared on a 20 gram scale in three steps from 3-benzyloxybenzaldehyde.

16. Conventional heterogeneous and homogeneous hydrogenations resulted in reduction of the isoquinoline and/or decomposition.
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Figure 1.
Structures of cortistatin J (**1**) and A (**2**).

Scheme 1.
[4 + 3] Cyclizations of (Z)-2-(Silyloxy)-2-enals

Scheme 2.
Retrosynthetic Analysis of Cortistatin J (1)

Scheme 3.
Tetracyclic Core Synthesis by [4 + 3] Cyclization

Scheme 4.
Completion of the Total Synthesis of Cortistatin J