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Synthesis of the Cortistatin Pentacyclic Core by Alkoxide-Directed Metallacycle-Mediated Annulative Cross-Coupling

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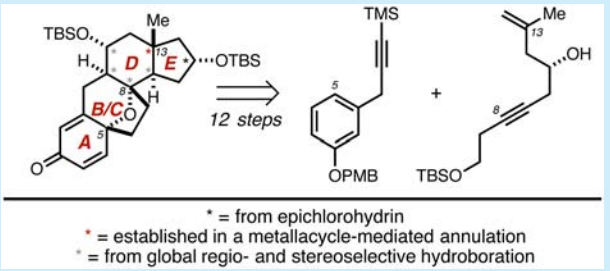
Supporting Information

ABSTRACT: The pentacyclic core skeleton of the cortistatins has been prepared in a stereoselective fashion by strategic use of an alkoxide-directed metallacycle-mediated annulative cross-coupling. This metal-centered tandem reaction delivers a polyunsaturated hydrindane and establishes the C13 stereodefined quaternary center with high levels of stereocontrol. Subsequent regio- and stereoselective global hydroboration results in the realization of the DE-*trans* ring fusion and a tertiary alcohol at C8. Establishment of the ABC-tricyclic subunit was then accomplished through phenolic oxidation/*trans*-acetalization, chemoselective reduction, regioselective cleavage, and intramolecular alkylation at C5.



In the search for agents that exhibit selective antiproliferative activity against human umbilical vein endothelial cells (HUVECs), the Kobayashi laboratory reported the discovery of a collection of steroidal alkaloids, termed cortistatins A−D (Figure 1A), from the methanol extract of the marine sponge *Corticium simplex*.[1] In the following year, seven additional members of the class were reported.[2] Cortistatins have potent and highly selective antiproliferative activity against HUVECs (low nM, with selectivity indexes up to 3000-fold in comparison to normal human dermal fibroblast and several tumor cells).[1] While the structures of the cortistatins vary, they all possess an unusual steroidal core, a unique 9(10−19)-*abeo*-androstane containing an oxabicyclo[3.2.1]octene as the B/C ring system. The initial biological observations and unique structure of these rare marine-derived agents served to stimulate great interest in the organic chemistry community, and since 2008, a number of reports have appeared that describe the syntheses of members of the natural product class, strategies toward their laboratory preparation, as well as the production of cortistatin-inspired agents that possess a variety of potentially useful properties.[3−5] Here, we report a convergent synthesis of the pentacyclic steroidal core of the cortistatins by application of an alkoxide-directed metallacycle-mediated annulative cross-coupling reaction.[6]

As illustrated in Figure 1B, our efforts began by targeting the preparation of **6**, a compound that possesses the unique cortistatin pentacyclic skeleton, while also containing functionality on the A and D rings that could be useful for generating a variety of cortistatin and cortistatin-inspired agents. While focusing on the synthesis of a pentacycle lacking C17 substitution, we speculated that our efforts could (1) solidify a means by which one could employ metallacycle-mediated annulative cross-coupling to address most of the molecular complexity of the cortistatins and (2) pave a path to future incorporation of functionality at C17 by selective functionalization of a C16-ketone.[7] Moving forward with our retrosynthesis, we anticipated that **6** could be prepared from **7** through a process that would stitch in the oxabicyclo[3.2.1] motif that defines the B/C system. The functionalized *trans*-fused hydrindane **7** was then thought to be accessible from the dihydroindane **8**, where desilylation and site- and stereoselective hydration would establish the *trans* ring fusion and the tertiary alcohol at C8. Finally, the polyunsaturated hydrindane **8** was anticipated to be the direct product of alkoxide-directed metallacycle-mediated annulative cross-coupling between enyne **9** and the simple TMS-alkyne **10**.

Syntheses of the coupling partners required for the targeted annulation reaction are illustrated in Figure 2. Metalation of the TBS-protected homopropargylic alcohol **11** with BuLi was followed by $BF_3{\cdot}OEt_2$-promoted addition to epichlorohydrin. The resulting chlorohydrin was converted to an intermediate epoxide (KO-*t*-Bu, THF) that was subsequently treated with the organocopper reagent generated from the combination of 2-propenylmagnesium bromide and CuI. Overall, this three-step process delivered **9** in 65% yield. Through a similarly straightforward sequence, TMS-alkyne **10** was derived from the commercially available aldehyde **12** by (1) PMB protection, (2) carbonyl reduction, (3) mesylation of the resulting benzylic alcohol, and (4) acetylide addition.

With enyne **9** and TMS-alkyne **10** in hand, we moved forward to explore their potential utility in the planned annulative cross-coupling reaction. As illustrated in Figure 3, treatment of **10** with the combination of $Ti(O\text{-}i\text{-}Pr)_4$ and *n*-BuLi, followed by warming to 50 °C, then introduction of the Li-alkoxide of enyne **9**, resulted in the formation of hydrindane **8** in 64%

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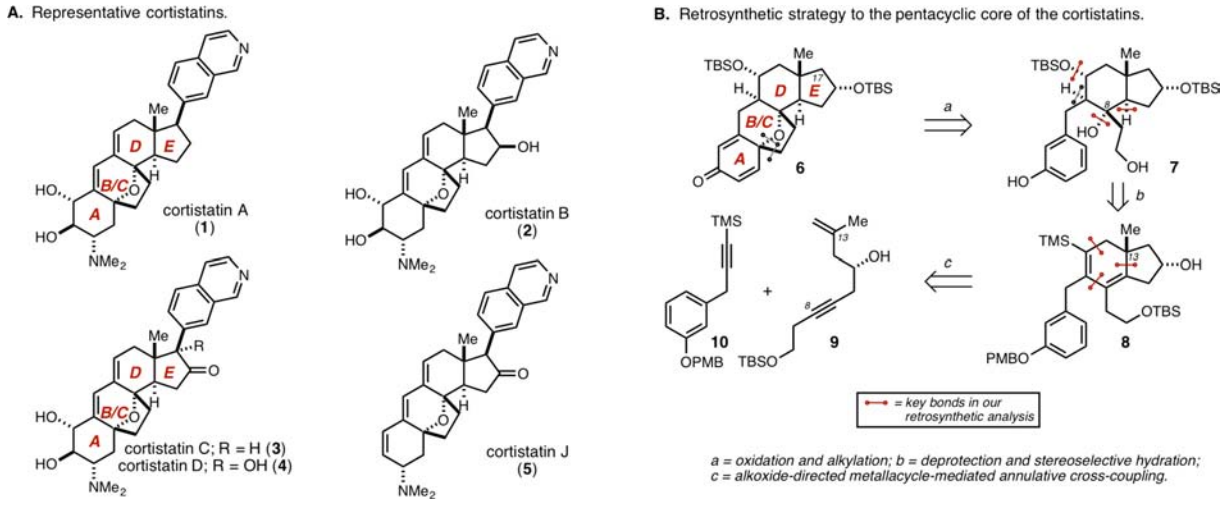

Figure 1. Introduction to the cortistatins and an approach to their pentacyclic core by metallacycle-mediated annulative cross-coupling.

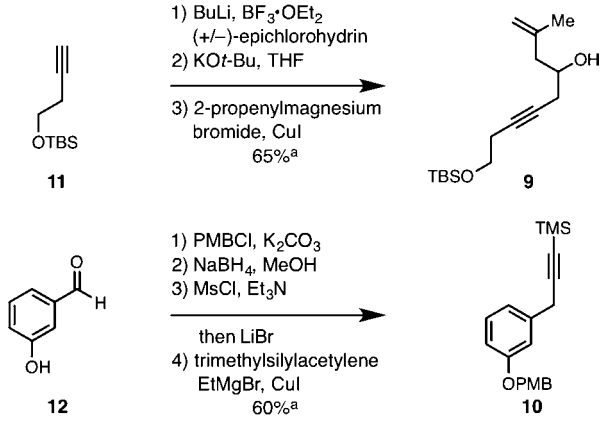

Figure 2. Synthesis of the coupling partners. (a) Yield reported is for the three-step sequence.

yield. This process is anticipated to proceed through initial alkoxide-directed alkyne–alkyne coupling (to generate a metallacyclopentadiene),[8] followed by stereoselective intramolecular [4 + 2] cycloaddition, and cheletropic extrusion of Ti (**A** → **B** → **8**). Overall, this annulation proceeded with exquisite levels of regio- and stereoselection, establishing the C13 quaternary center *anti*- to the E-ring alcohol and positioning the benzyl substituent at C9 of the developing steroidal system. While these studies were conducted with (±)-**9**, enantiospecific access to hydrindane **8** would be easily accomplished if **9** was generated from optically pure epichlorohydrin.[6a]

Global desilylation of **8** was then accomplished by treatment with HCl to deliver diene **13** in 59% yield. To our great delight, hydroboration of **13** proceeded with regio- and stereoselection to deliver, after silylation (TBSCl, imid, DMF), the desired hydrindane **14** in 61% yield (ds = 4:1). Notably, selective hydroboration of the tetrasubstituted alkene of **13** established both the *trans*-fusion of the product as well as the desired stereochemistry of the C8 tertiary alcohol. We believe that selectivity in hydroboration of the tetrasubstituted alkene is based on initial reaction of borane with the primary alcohol and subsequent intramolecular hydroboration of the tetrasubstituted alkene to generate an oxaboracyclopentane, while stereoselectivity of this process is likely influenced by the C9 stereochemistry (formed upon initial steoselective hydroboration of the C9–C11 trisubstituted olefin). Moving forward, hydrogenolysis of the PMB ether of **14** was accompanied by loss of the primary TBS group, delivering triol **7** in 84% yield. Selective oxidation of the phenol with (diacetoxyiodo)benzene (PIDA) in MeOH[9] delivered an intermediated dimethyl acetal that was readily converted to the bicyclic acetal **15** by treatment with PPTS in benzene.

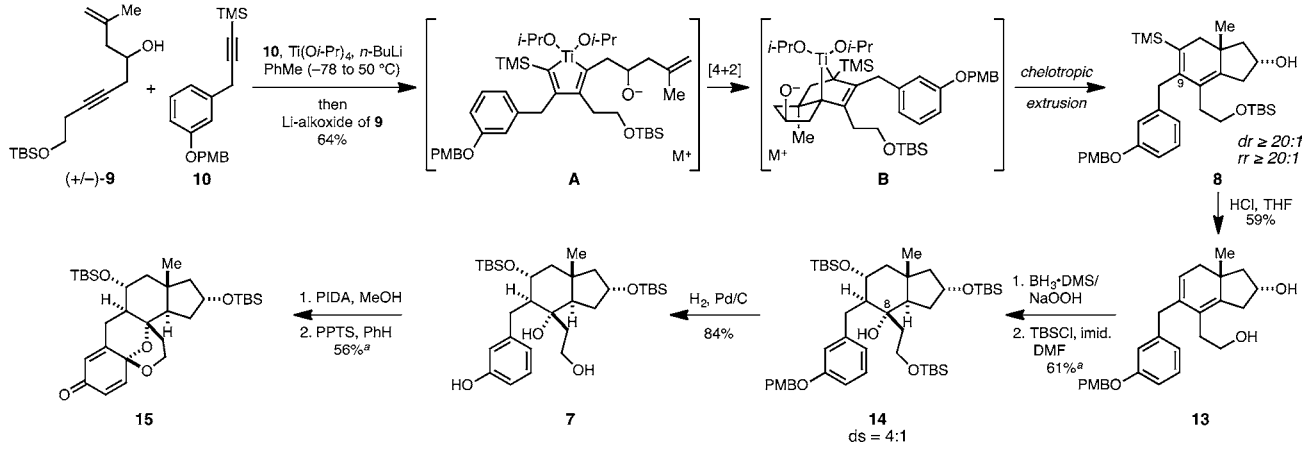

Figure 3. Alkoxide-directed metallacycle-mediated annulative cross-coupling, regio- and steresoselctive hydration, and oxidation/acetalization delivers a densely functinalized pentacyclic acetal in a concise fashion. (a) Yield reported is for the two-step sequence.

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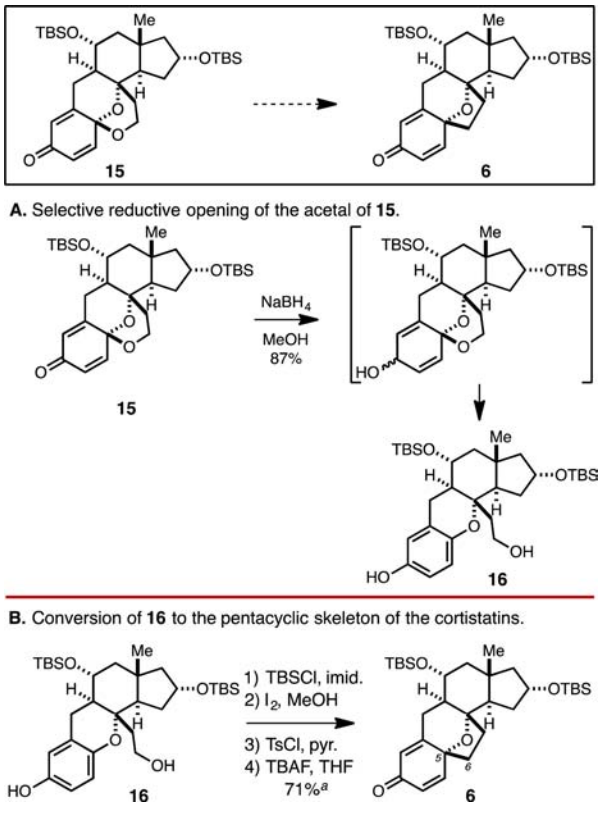

Figure 4. Conversion of the polycyclic acetal to the pentacyclic core of the cortistatins. (a) Yield reported is for the four-step sequence.

With **15** in hand, we focused our attention on developing a straightforward sequence for its conversion to the desired cortistatin system **6**. As illustrated in Figure 4A, treatment with $NaBH_4$ resulted in reduction of the ketone to deliver a crude diastereomeric mixture of allylic alcohols that, during purification, were selectively converted to the desired phenolic ether in 87% yield; no evidence was found for formation of the regioisomer having an 8-membered oxacyclic B-ring.[10]

As depicted in Figure 4B, the tetracyclic phenol **16** was advanced to **6** by a simple four-step sequence. Bis-silylation (TBSCl, imid, DMF) was followed by selective desilylation[3c] to unveil a primary alcohol. Then, tosylation (TsCl, pyr) was followed by selective deprotection of the phenol and intramolecular alkylation to establish the C5−C6 bond.[3c]

Overall, we have established a concise synthesis of a highly functionalized pentacyclic steroidal system of potential value in efforts directed toward the synthesis of cortistatins and analogues thereof. The route is characterized by strategic application of a recently discovered Ti-mediated annulative cross-coupling between simple enynes and TMS-alkynes, use of regio- and stereoselective hydroboration to establish the *trans*-fused hydrindane system, and establishment of the B/C oxabicyclic system through initial formation of a bridged bicyclic acetal and late-stage formation of the C5−C6 bond.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01048.

Procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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