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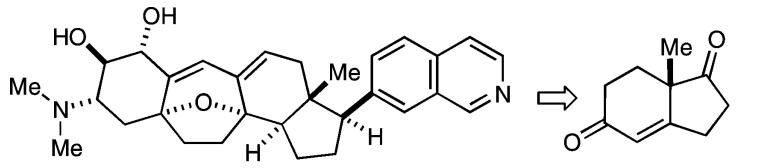

cortistatin A *Hajos-Parrish ketone*

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Enantioselective Synthesis of (+)-Cortistatin A, a Potent and Selective Inhibitor of Endothelial Cell Proliferation

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Angiogenesis, the process by which new blood vessels are formed, has become an important area of modern drug discovery with therapeutic applications in cancer, obesity, macular degeneration, and rheumatoid arthritis.[1] Accordingly, there are intensive efforts to discover and develop selective, nontoxic small molecule inhibitors of angiogenesis.[2] In 2006, Kobayashi and colleagues reported the isolation, biological evaluation, and structure determination of cortistatin A (**1**), a unique marine natural product with potent antiangiogenic activity (Figure 1).[3,4]

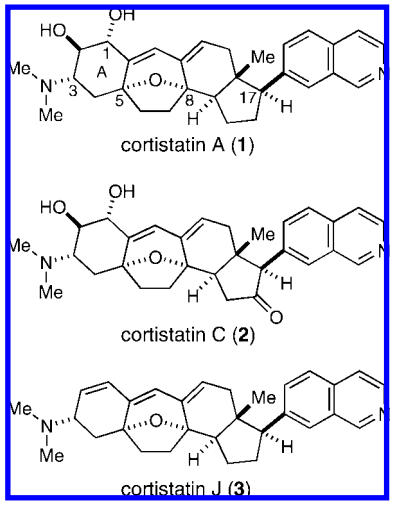


Figure 1. Structures of cortistatins A, C, and J.

One striking aspect of **1** is its selectivity inhibiting the proliferation of human umbilical vein endothelial cells (HUVECs), a cell line used to model angiogenesis. Compound **1** inhibits the proliferation of HUVECs (GI_{50} = 1.8 nM), while the GI_{50} = 6−7 μM in several human and murine cancer cell lines and one normal human dermal fibroblast cell line. The selectivity of **1** for HUVECs suggests that it might be a useful antiangiogenesis small molecule lead or drug. However, to date, in vivo studies of **1** have not been reported. In addition to the use of **1** for treatment of human diseases, elucidation of its yet undetermined cellular target may lead to new mechanisms of inhibiting angiogenesis.

Ten additional cortistatins have been isolated from the marine sponge *Corticium simplex*, the most potent angiogenesis inhibitors being **2** and **3**, along with **1**.[5] The structure of **1** is unusual among natural products, comprising a rearranged steroid in the form of a 9(10−19)-*abeo*-androstane skeleton, an ether bridge connecting C5 and C8, and a C17 isoquinoline. The structure of **1** was confirmed by X-ray crystallography, while its absolute configuration was determined using circular dichroism.

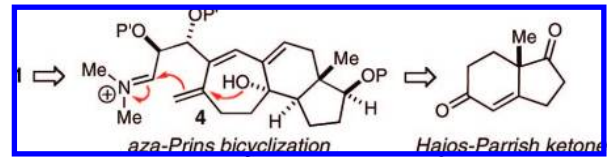
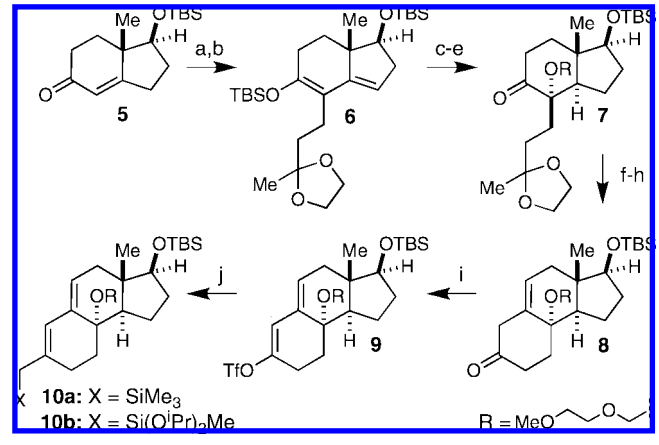


Figure 2. A key step of the cortistatin A synthesis is an aza-Prins/transannular etherification reaction. Enantiomerically enriched Hajos−Parrish ketone is the starting material.

Many research groups have targeted **1** for synthesis as a consequence of its unusual structure, its promising antiangiogenic activity, and its scarcity from natural sources.[6] Recently, Baran[7] and Nicolaou[8] reported syntheses of **1**. Our synthesis plan was guided by a desire to produce **1**−**3** for biological and medicinal studies and to generate diverse analogues to systematically determine the structural elements required for antiangiogenic activity. Eventually, this may enable us to discover molecules less complex than **1** but that maintain its biological activity and that have improved drug properties. The key step of our synthesis plan (Figure 2) is an aza-Prins cyclization via iminium ion **4** with transannular cyclization by a C8 tertiary carbinol.[9] This reaction would simultaneously form the A ring and the oxabicyclo[3.2.1]octene as well as control the C3 *N*,*N*-dimethyl-

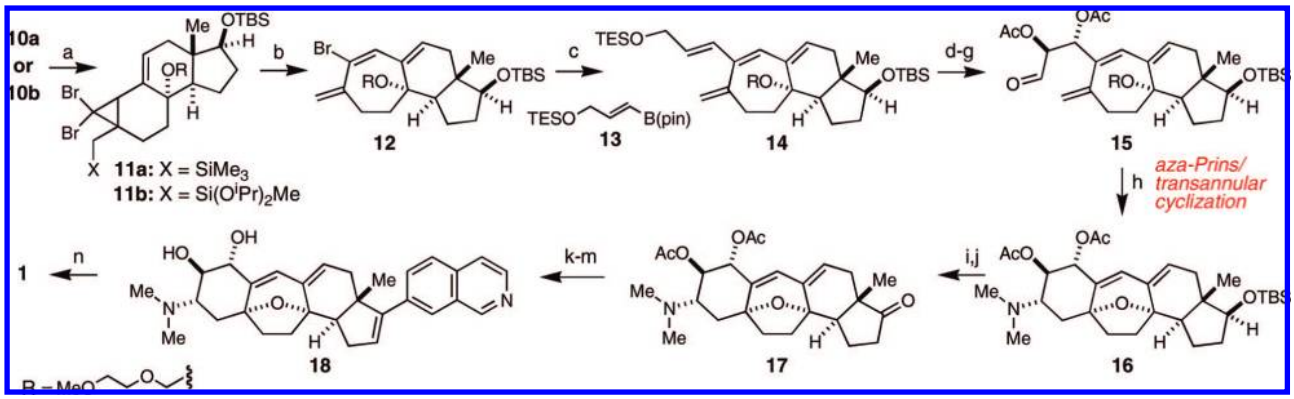
Scheme 1. Synthesis of Dienes **11a** and **11b**[a]



[a] Conditions: (a) NaH (1.05 equiv), DMSO, rt, 3 h, 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (1.1 equiv), rt, 12 h (63%); (b) TBSOTf (1.2 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, 0 °C, 2 h; (c) H_2 (1 atm), Pd/C (0.08 equiv), EtOAc, rt, 12 h; (d) *m*CPBA (1.1 equiv), $NaHCO_3$ (10 equiv), toluene, −10 °C, 30 min, HF (10 equiv), THF/toluene, 0 °C, 30 min (66% over four steps); (e) MEMCl (2 equiv), *i*PrNEt$_2$ (4 equiv), 1,2-dichloroethane, 80 °C, 18 h (88%); (f) PPTS (0.1 equiv), acetone/water (4:1), 60 °C, 4 h; (g) NaOMe (5 equiv), MeOH, 70 °C, 1 h (49% over two steps); (h) $SOCl_2$ (1.5 equiv), pyridine (3 equiv), CH_2Cl_2, −10 °C, 30 min; (i) NaHMDS (1.1 equiv), THF, −78 °C, 1 h, $PhNTf_2$ (1.05 equiv), 0 °C, 2 h; (j) Me_3SiCH_2MgBr (3 equiv) for **10a** or $Me(OiPr)_2SiCH_2MgCl$ (3 equiv) for **10b**, $Pd(PPh_3)_4$ (0.05 equiv), THF, rt, 30 min (62% over three steps).

10.1021/ja8071918 CCC: $40.75

Scheme 2. Completion of a Synthesis of (+)-Cortistatin A (**1**)[a]



[a] Conditions: (a) $CHBr_3$ (3 equiv), KO*t*Bu (4 equiv), hexane, 0 °C, 2 h; (b) TASF (1.2 equiv), DMF, 80 °C, 30 min (66% over two steps); (c) **13** (2 equiv), $Pd(PPh_3)_4$ (0.04 equiv), K_2CO_3 (3 equiv), THF/water (5:1), 80 °C, 4 h (84%); (d) $K_2OsO_4 \cdot 2H_2O$ (0.02 equiv), $(DHQD)_2PHAL$ (0.05 equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (1 equiv), *t*BuOH/water (1:1), 0 °C, 2 h; (e) Ac_2O (2.5 equiv), NEt_3 (3 equiv), DMAP (0.2 equiv), CH_2Cl_2, rt, 18 h (51% over two steps); (f) HF/pyr, THF, rt, 5 min; Dess−Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 1 h; (h) Me_2NH (3 equiv), $ZnBr_2$ (1.5 equiv), CH_3CN, 50 °C, 40 min (65% over three steps); (i) TBAF (1.2 equiv), THF, 70 °C, 4 h (70%); (j) TPAP (0.05 equiv), NMO (1.3 equiv), CH_2Cl_2, rt, 2.5 h (quant.); (k) K_2CO_3 (5 equiv), MeOH, rt, 30 min (82%); (l) $N_2H_4 \cdot H_2O$ (10 equiv), NEt_3 (10 equiv), EtOH, 80 °C, 6 h; NEt_3 (3 equiv), I_2 (1 equiv), THF, rt, 5 min; (m) $Pd(PPh_3)_4$ (0.5 equiv), 7-isoquinolinestannane (3 equiv), LiCl (10 equiv), CuCl (10 equiv), DMSO, 60 °C, 1 h (61% over three steps); (n) 2,4,6-triisopropylbenzenesulfonyl hydrazide (4 equiv), NEt_3 (20 equiv), THF, 60 °C, 9 h (20%).

amine and C5 tertiary ether stereocenters. Substructure matching of **4** suggested that it could be derived from enantiomerically pure Hajos−Parrish ketone.[10] Herein we report achievement of the aforementioned aza-Prins cyclization reaction and its use in a synthesis of **1**.

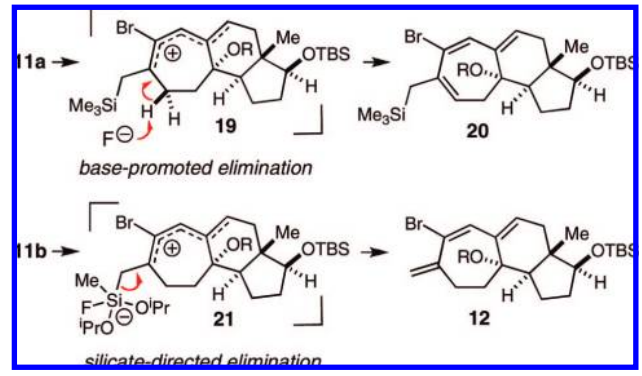
Our synthesis of **1** begins with known enone **5**, produced in two steps from enantiomerically pure Hajos−Parrish ketone (Scheme 1).[11] The thermodynamic enolate of **5** was alkylated with the dioxolane of 4-bromo-2-butanone[12] followed by generation of silyloxydiene **6**. Diastereoselective hydrogenation of the cyclopentene of **6**,[13] Rubottom oxidation of the remaining enolsilane and protection of the tertiary carbinol with MEMCl produced **7**. A three-step procedure was used to convert **7** to β,γ-unsaturated enone **8**, comprising ketal removal, hydroxide-promoted aldol addition, and $SOCl_2$-mediated elimination.

In preparation for ring expansion, vinyl triflate **9** was prepared, followed by Pd(0)-catalyzed formation of allylsilanes **10a** and **10b**. Regioselective and diastereoselective cyclopropanation of **10a** with dibromocarbene produced **11a** (Scheme 2).[14] In the key ring expansion reaction, warming of **11a** in the presence of fluoride sources (TBAF or TASF) produced an equal mixture of desired cycloheptadiene **12** and allylsilane **20** in low yields (see Scheme 3). During this reaction, ring opening of **11a** and ejection of bromide produces pentadienyl cation **19** (Scheme 3), which partitions between base-promoted elimination affording **20** and fluoride attack on the TMS group, leading to **12**. Attempts to convert **20** to **12** were unsuccessful. We reasoned that the ring opening/elimination reaction might produce more **12** if a disiloxane were used in place of the TMS group since the disiloxane would have a higher propensity for pentacoordinate (or hexacoordinate) fluorosilicate formation (see **21**), leading to **12** via silicate-directed elimination. We were pleased to find that exposure of disiloxane **11b**[15] (Scheme 2) to TASF at 80 °C in DMF produced *exclusively* **12** in 66% yield from **10b** (two steps). Pd-catalyzed cross-coupling between **12** and vinyl boronic ester **13** afforded **14** in 84% yield. Although **14** presents four double bonds, the reported rates of catalytic enantioselective dihydroxylation[16] could be used to predict that the 1,2-disubstitutued olefin would be dihydroxylated first, which occurred with 10:1 diastereoselectivity, installing the C1−C2 diol. Acetylation of the diol, removal of the TES group and oxidation of the primary alcohol with Dess−Martin periodinane delivered marginally stable aldehyde **15**.

The key step of our synthesis, a tandem aza-Prins cyclization and transannular etherification, was performed by exposing aldehyde **15** to Me_2NH (3.0 equiv) and $ZnBr_2$ (1.5 equiv) in MeCN at 50 °C for 40 min. The aza-Prins cyclization occurred with in situ removal of the MEM protecting group producing *directly* **16** in 65% yield over three steps (TES deprotection, oxidation, aza-Prins cyclization), averaging 87% yield per step. In light of the potential for aldehyde **15** to undergo facile β-elimination, the success of the aza-Prins cyclization reaction is striking.

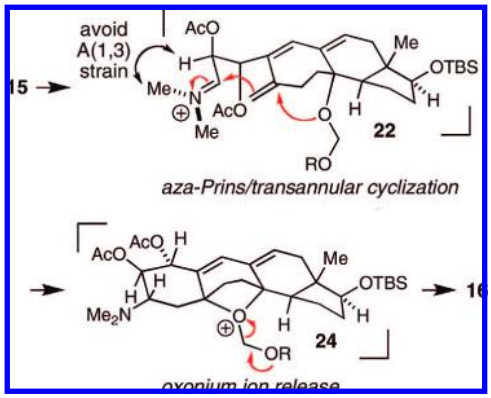
In the aza-Prins cyclization, the C3-amine stereocenter was formed with >95% diastereoselectivity. The high diastereoselectivity in this reaction can be rationalized by examining iminium ion intermediate **22** (Scheme 4). According to calculations of **22**, the forming A ring exists in a boat conformation. The internal methyl group of the iminium ion and C2−H are coplanar to avoid A(1,3) strain, while the C2−OAc blocks addition from the *Re* face, guiding addition to the *Si* face of the iminium ion. Intermediate **24** is generated by transannular cyclization of the C8 ether oxygen. Oxonum ion release from **24** affords **16**. In support of this sequence of events, rather than MEM deprotection preceding aza-Prins cyclization, is our

Scheme 3. Mechanistic Rationale for Generation of **12** and **20**



observation that exposure of the TES ether precursor of **15** to the aza-Prins reaction conditions *does not* lead to MEM deprotection.

Scheme 4. Mechanistic Rationale for the Highly Diastereoselective aza-Prins Cyclization



Removal of the silyl protecting group from **16**, followed by oxidation of the resulting secondary carbinol with TPAP/NMO delivered ketone **17** in 70% yield over two steps. To install the C17 isoquinoline, we followed the precedent of Baran by deacetylation of **17** followed by hydrazone formation, conversion to the vinyl iodide and Stille cross-coupling with 7-trimethylstannyl isoquinoline to deliver 16,17-didehydrocortistatin A (**18**).[7] The hydrogenation of **18** to produce **1** proved very challenging. Many hydrogenation catalysts and conditions were screened, but these all afforded little, if any **1**. However, it was discovered that diimide, generated from 2,4,6-triisopropylsulfonyl hydrazide affords **1** in 20% yield. The spectroscopic properties of synthetic **1** were identical to those reported in the literature for natural **1**.

An enantioselective synthesis of cortistatin A has been achieved using a highly diastereoselective aza-Prins cyclization coupled with transannular etherification. Another key reaction is a silicate-directed elimination, using a disiloxane to favor fluorosilicate formation and regioselective elimination. This synthesis was designed so that each ring can be evaluated for its contribution to the antiangiogenic activity of **1**. This synthesis may be useful in evaluating the therapeutic potential of **1** and analogues, and elucidation of their cellular target.

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Supporting Information Available: Complete ref 2b; detailed experimental procedures, copies of spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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