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Scalable Synthesis of Cortistatin A and Related Structures

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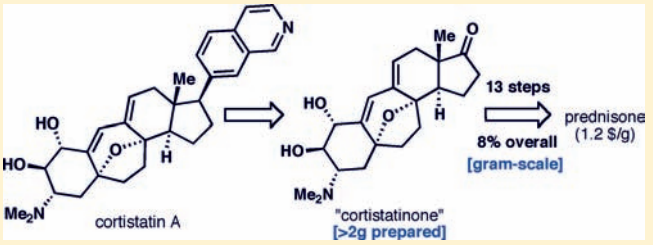
Supporting Information

ABSTRACT: Full details are provided for an improved synthesis of cortistatin A and related structures as well as the underlying logic and evolution of strategy. The highly functionalized cortistatin A-ring embedded with a key heteroadamantane was synthesized by a simple and scalable five-step sequence. A chemoselective, tandem geminal dihalogenation of an unactivated methyl group, a reductive fragmentation/trapping/elimination of a bromocyclopropane, and a facile chemoselective etherification reaction afforded the cortistatin A core, dubbed "cortistatinone". A selective Δ^{16}-alkene reduction with Raney Ni provided cortistatin A. With this scalable and practical route, copious quantities of cortistatinone, Δ^{16}-cortistatin A (the equipotent direct precursor to cortistatin A), and its related analogues were prepared for further biological studies.



INTRODUCTION

Steroids are beyond "privileged" structures, playing a vital role not only in biology, medicine, and society but also in the origins and development of organic synthesis.[1] In 1815, the first steroid, cholesterol (**1**, Figure 1), was isolated from gallstones by Chevreul.[2] But the correct chemical structure of cholesterol was not elucidated until 1932. Subsequently, during the 1930s to the 1950s, the discovery of steroids' useful biological activities coupled with the need for cortisone (**2**) specifically in World War II immensely stimulated the development of chemical syntheses of steroids in both academic and industrial settings. In 1939, the first total synthesis of a steroid, equilene, was accomplished by Bachmann.[3] Meanwhile, the Robinson,[4] Fieser,[5] Woodward,[6] Barton,[7] and Jones[8] groups investigated numerous synthetic methods aimed at the synthesis of steroids, and a number of total syntheses of cortisone (**2**) were reported. The mechanistic, stereochemical model for steroid biosynthesis proposed by Stork and Eschenmoser,[9] and related studies on polyene cyclization, ultimately led to Johnson's biomimetic steroid syntheses, including his landmark total synthesis of progesterone (**3**) in 1971.[10] Academic inquiry into the synthesis of steroids has thus resulted in an immense body of knowledge in the realms of both fundamental organic chemistry and medicine.

In parallel to academic endeavors on the synthesis of steroids, the need for commercialization of certain steroid targets steered the pharmaceutical industry toward more efficient and practical approaches to semisynthesis. Starting from diosgenin, an abundant ingredient in wild Mexican yams, Marker achieved the commercialization of progesterone at Syntex by a six-step sequence (known as "Marker's degradation") in 1940.[11] In 1946, Sarett at Merck accomplished the first semisynthesis of cortisone (**2**) from bile acid in 36 steps.[12] In 1951, a group of chemists at Syntex, led by Carl Djerassi, achieved the semisynthesis of cortisone (**2**) from diosgenin in a 14-step sequence.[13] In the same year, a highly innovative microbiological fermentation approach was disclosed by Upjohn to functionalize the C11 position of progesterone (**3**), which led to the successful commercialization of cortisone (**2**).[14] Currently, most steroid-based medicines (Figure 2) are prepared by semisynthesis, including Deltasone (**5**, anti-inflammatory agent), Flovent (**6**, antiasthmatic and antiallergic agent), Lanoxin (**7**, cardiovascular agent), Mifepristone (**8**, pregnancy termination agent), Testosterone (**9**, treatment of male hypogonadism), and Mestranol (**10**, oral contraceptive).

In 2006 and 2007, the Kobayashi group elucidated structures of novel steroidal alkaloids, cortistatins A−J (**11**−**21**, Figure 3), and disclosed their highly selective antiangiogenic activity.[15] Angiogenesis, a process that involves the formation of new capillary blood vessels from pre-existing ones, is fundamental and vital to growth, development, and wound healing but also to cancer metastasis.[16] Currently, Avastin, Erbitux, Vectibix, and Herceptin are the major monoclonal antibody drugs for cancer treatment based on the inhibition of this mechanism.[17] Therefore, the isolation and study of new small-molecule natural products with highly selective antiangiogenic activity is of great interest and significance. Interestingly, cortistatin A (**11**) showed antiproliferative activity against human umbilical vein endothelial cells (HUVECs) at a low concentration with an IC_{50} = 1.8 nM, while it demonstrated a selectivity index of more than 3000-fold against HUVECs in comparison with NHDF (normal human dermal fibroblast), KB3-1 (KB epidermoid carcinoma cells),

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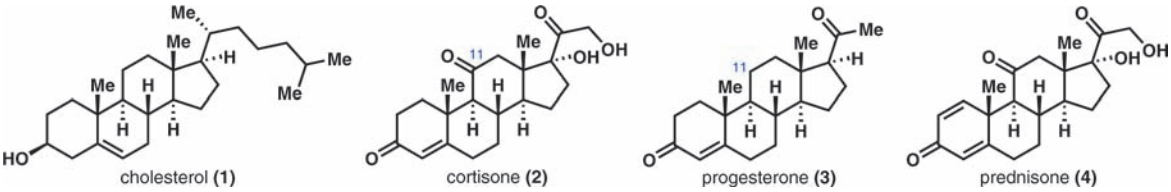

Figure 1. Representative steroids.

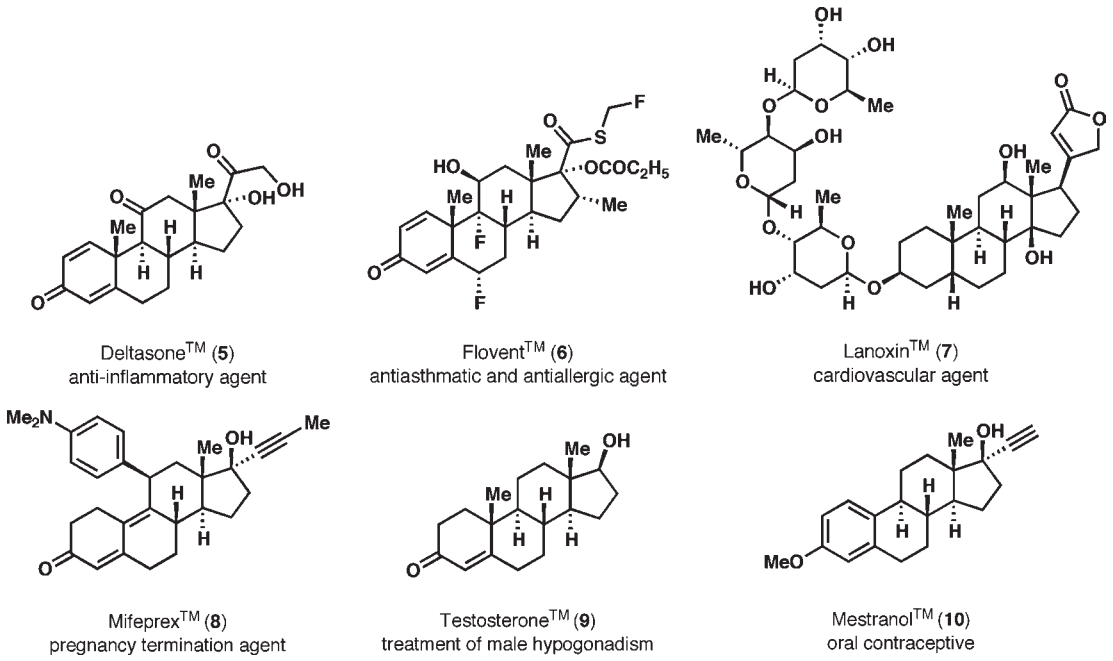

Figure 2. Commercial steroid-based medicines prepared by semisynthesis.

K562 (human chronic myelogenous leukemia cells), and Neuro2A (murine neuroblastoma cells), indicating that cortistatin A selectively inhibits angiogenesis but has no apparent cytotoxicity toward cancer cells. As such, cortistatin A could be a promising agent not only in cancer biology but also in other angiogenesis-dependent ailments such as macular degeneration, rheumatoid arthritis, etc. However, to date, *in vivo* studies of cortistatin A have not been published due to its low availability. The significant potential of its antiangiogenic activity and high selectivity suggested that it would involve a unique mechanism of action.[18]

Structurally, all of the cortistatins possess an unusual 9(10,19)-*abeo*-androstane skeleton with an oxabicyclo[3.2.1]octene core. The combination of their exciting bioactivity and scarce availability from Nature makes the cortistatins worthy candidates for synthesis. Indeed, these marine sponge (*Corticium simplex*)-derived molecules are so rare and valuable that the isolation chemists have reported efforts toward their total synthesis.[19] Not surprisingly, the past 3 years have witnessed dozens of publications on the chemistry of the cortistatins.[19−24] Four elegant total syntheses of cortistatin A have emerged from the Nicolaou−Chen,[20] Shair,[21] Myers,[22] and Hirama[23P] laboratories, and many approaches have been reported.[23] Our own efforts were inspired by the rich history of steroid semisynthesis and a desire to procure gram quantities of the cortistatins for biological evaluations.[24] Thus, a route was devised beginning from the abundant terrestrially derived steroid prednisone (**4**, available for $1.2/gram). This full account describes our studies toward an improved synthesis of cortistatin A and related structures as well as the underlying logic and evolution of strategy.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. Given the tremendous success of steroid semisyntheses to prepare large quantities of biologically valuable compounds, we decided to explore this higher-level substructure search strategy to identify candidate steroid starting materials. In concert with this global search, an initial retrosynthetic excision of the isoquinoline allowed a bidirectional search for methods of heterocycle installation to the D-ring, and for steroid scaffolds that lacked the C17 side chain. Further considerations for the starting material derived from "ideality" criteria,[25] particularly for an overall isohypsic (redox-neutral) conversion from commercial steroid to target.[26] Since there are few affordable steroids that bear the appropriate methine oxidation state at C19, a strategic sacrifice was made to introduce this oxidized carbon from the very common C19 methyl. A look-ahead search for appropriate A-ring precursors proved more straightforward, since the cortistatin A-ring is in the same oxidation state as a cyclohexadienone, which is a common motif in commercial steroids. Similarly, the C-ring allylic ether motif corresponded in oxidation state to a C-ring cyclohexanone, a substructure that has been made available in commercial steroids

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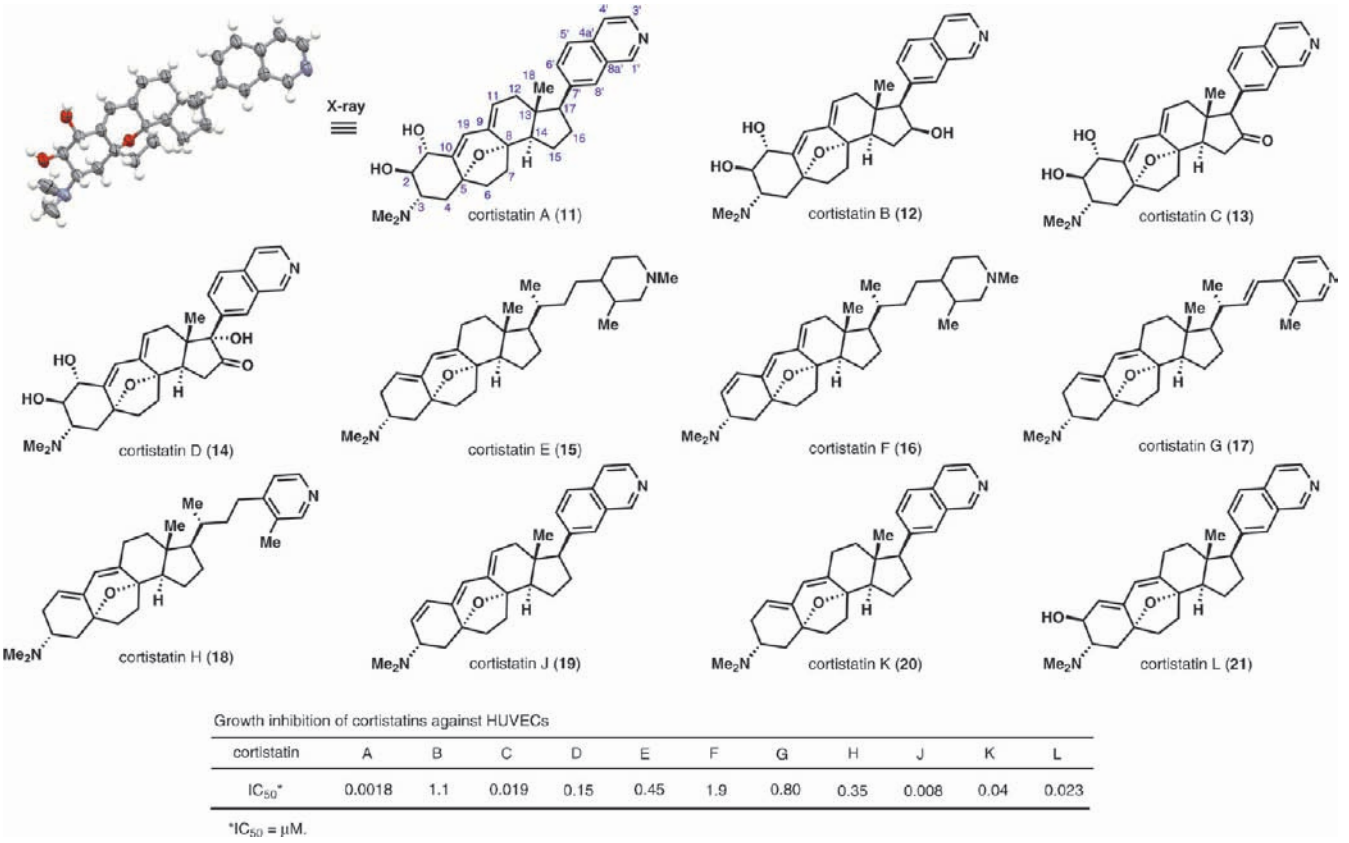


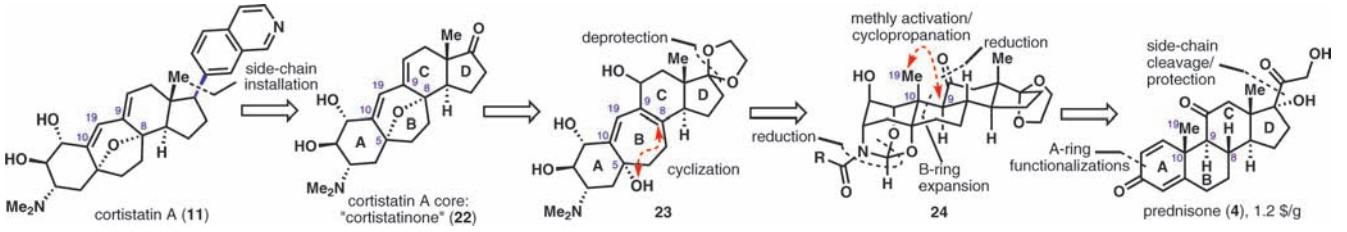
Growth inhibition of cortistatins against HUVECs

cortistatin	A	B	C	D	E	F	G	H	J	K	L
IC_{50}*	0.0018	1.1	0.019	0.15	0.45	1.9	0.80	0.35	0.008	0.04	0.023

*IC_{50} = μM.

Figure 3. Cortistatin family members and their biological activities.

Scheme 1. A General Retrosynthetic Strategy To Target the Cortistatin A (11) Core: Cortistatinone (22)



by microbial oxidation. When these structures are amalgamated into an imaginary steroid, the result bears striking resemblance to predisone, with the exception of the pregnane side chain. Fortunately, there are several methods for oxidative cleavage of this side chain to the corresponding cyclopentanone, which serves as a useful handle for appending the isoquinoline.

Further considerations that bolstered the proposal to begin from an abundant terrestrial steroid include (1) the unique strategic opportunities that could arise from rendering a semisynthesis amenable to the construction of analogues with deep-seated modification; (2) the occasion to develop new chemical methods and tactics to achieve such ends; and (3) the economies of using prednisone, which possesses ca. 70% of the carbon atoms and the corresponding enantiopure chirality of the cortistatins. As discussed above, a crucial target structure became the cortistatin A ketonic core that we termed (+)-cortistatinone (**22**, Scheme 1). This key structure was anticipated to allow for straightforward elaboration to the natural product, as well as divergence to other family members and unnatural analogues. As part of this plan, numerous exciting challenges had to be addressed, including control of all four A-ring stereocenters, oxidation of the unfunctionalized C19 and C8 centers, expansion of the B-ring, and chemo-/stereoselective installation of the isoquinoline side chain.

A-Ring Functionalization. Our initial efforts for A-ring functionalization are depicted in Scheme 2. Starting from prednisone (**4**), side-chain cleavage and subsequent ketalization led to the known steroid core **25** in 92% overall yield after recrystallization.[27] Nucleophilic epoxidation of enone **25** generated epoxide **26** in 82% yield (>30 g) under the mediation of *t*-BuOOH, a protocol that is operationally superior on a large scale to a reported dimethyldioxirane procedure.[28] For our first forays, a straightforward hydride reduction/activation/displacement sequence was pursued to install the C3 amino group. In the event, ketone reduction provided α-hydroxyl derivative **27** as a major diastereomer, which upon activation with *p*-TsCl led to allylic chloride **29** in 75% yield over two steps. Treatment of **29** with NaN_3 delivered the corresponding allylic azide **30**, which

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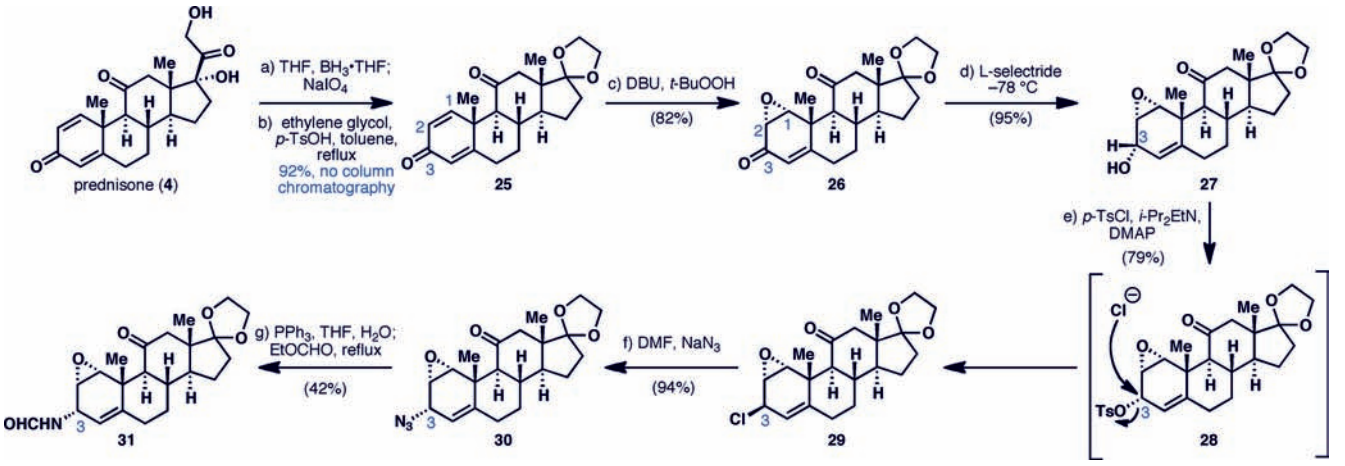
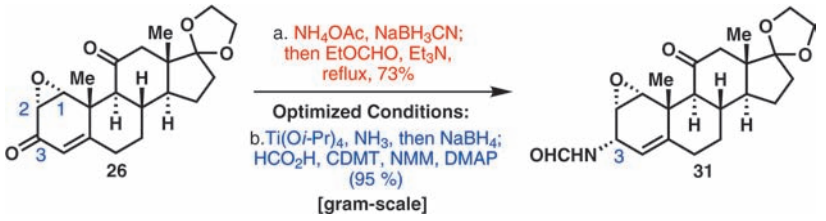
Scheme 2. Initial Efforts To Install the C3 Amino Group on the A-Ring[a]



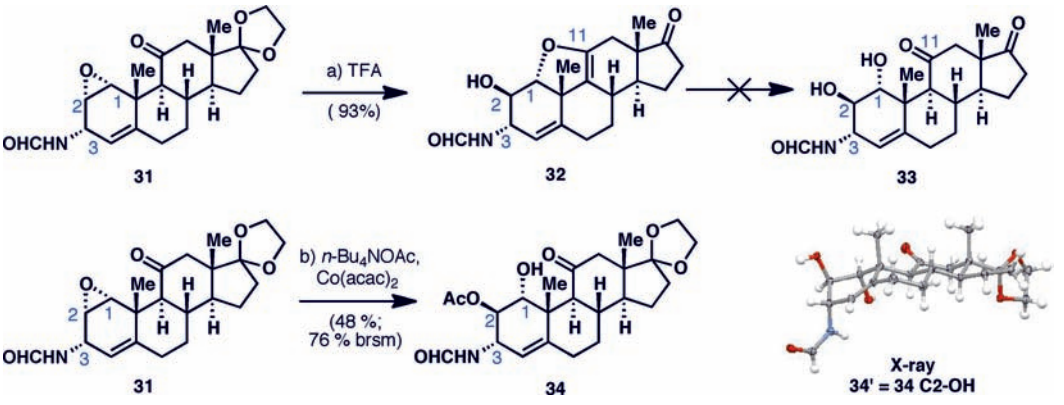
[a] Reagents and conditions: (a) $BH_3 \cdot THF$ (1.05 equiv), THF, 0 °C, 1.2 h; $NaIO_4$ (5.0 equiv), H_2O, acetone, 0 °C → 23 °C, 3 h; (b) *p*-TsOH (0.07 equiv), ethylene glycol (25 equiv), toluene, reflux, 1 h, 92% over two steps; (c) *t*-BuOOH (2 equiv), DBU (1.8 equiv), THF, 23 °C, 72 h, 82%; (d) L-selectride (1.5 equiv), THF, −78 °C, 30 min, 95%; (e) *p*-TsCl (3.0 equiv), *i*-Pr_2EtN (5.0 equiv), DMAP (1.0 equiv), 23 °C, CH_2Cl_2, 16 h, 79%; (f) NaN_3 (5.0 equiv), DMF, 23 °C, 14 h, 94%; (g) PPh_3 (10 equiv), THF, H_2O, 23 °C, 5 h; EtOCHO, reflux, 2 h, 42%. THF = tetrahydrofuran, *p*-TsOH = *p*-toluenesulfonic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, L-selectride = lithium tri(*s*-butyl)borohydride, *p*-TsCl = *p*-toluenesulfonyl chloride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*′-dimethylaminoformamide.

Scheme 3. Simplified Route to Epoxy Alkenyl Formamide 31[a]



[a] Reagents and conditions: (a) NH_4OAc (15 equiv), $NaBH_3CN$ (1.2 equiv), MeOH, THF, 23 °C, 18 h; then HCO_2Et (74 equiv), Et_3N (11 equiv), reflux, 12 h, 73%; (b) $Ti(Oi\text{-}Pr)_4$ (2.0 equiv), NH_3 (4.0 equiv), CH_2Cl_2, 6 h, 23 °C; $NaBH_4$ (1.0 equiv), 1 h, 23 °C; HCO_2H (1.1 equiv), CDMT (1.2 equiv), DMAP (0.3 equiv), NMM (1.1 equiv), CH_2Cl_2, 0 °C → 23 °C, 6 h, 95%. CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine, NMM = *N*-methylmorpholine.

Scheme 4. First Approach To Open Epoxide 31[a]



[a] Reagents and conditions: (a) TFA, 60 °C, 14 h, 93%; (b) *n*-Bu_4NOAc (5 equiv), $Co(acac)_2$ (0.2 equiv), PhH, 90 °C, 24 h, 48%, 76% brsm. TFA = trifluoroacetic acid, acac = acetylacetonate.

was subjected to a Staudinger reduction with PPh_3, followed by formylation of the resulting amine, to afford epoxy alkenyl formamide **31** in 39% overall yield.

Capitalizing on the observation that hydride attacks the β-face of ketone **26**, a more concise route to epoxy alkenyl formamide **31** was formulated (Scheme 3). Thus, reductive amination of the

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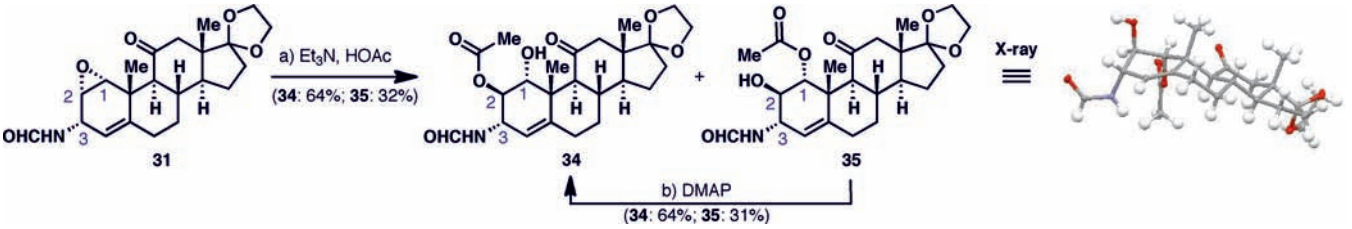
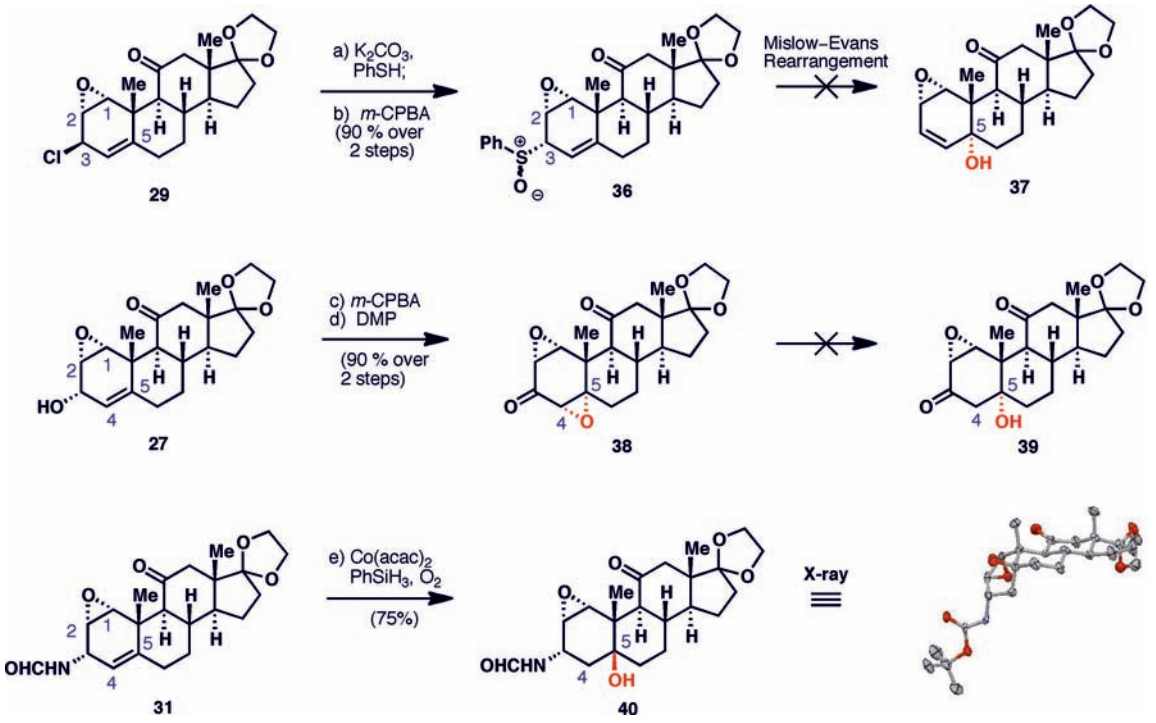
Scheme 5. Second Approach To Open Epoxide 31[a]



[a] Reagents and conditions: (a) Et_3N (10 equiv), HOAc (10 equiv), 130 °C, 16 h; **34**, 64%; **35**, 32%; (b) DMAP (0.1 equiv), toluene, reflux, 24 h; **34**, 64%; **35**, 31%.

Scheme 6. Attempts at Installing the Requisite α-Disposed C5-Tertiary Alcohol[a]



[a] Reagents and conditions: (a) PhSH (1.5 equiv), K_2CO_3 (2 equiv), acetone, 65 °C, 15 h, 96%; (b) *m*-CPBA (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 94%; (c) *m*-CPBA (1.4 equiv), CH_2Cl_2, 0 °C, 1 h; (d) DMP (1.1 equiv), CH_2Cl_2, 23 °C, 2 h, 90% over two steps; (e) $Co(acac)_2$ (0.2 equiv), $PhSiH_3$ (4 equiv), THF, O_2 (1 atm), 12 h, 23 °C, 75%. *m*-CPBA = *m*-chloroperoxybenzoic acid, DMP = Dess–Martin periodinane.

C3 ketone moiety of **26** with NH_4OAc and $NaBH_3CN$ furnished the corresponding allylic amine, which was directly formylated, to give formamide **31** in 73% overall yield. After extensive optimization, formamide **31** was obtained in 95% overall yield by using $Ti(Oi\text{-}Pr)_4$, NH_3, and $NaBH_4$ for reductive amination followed by formylation.

With a scalable (>25 g) route to the epoxy alkenyl formamide **31** secured, attention was turned to the C1,C2 *trans*-vicinal diol formation via epoxide opening. Acid (TFA)-mediated opening of the 1,2-epoxide was initially attempted, resulting in cyclization to the proximal C11 ketone and then dehydration to form dihydrofuran **32** in 93% yield (Scheme 4). Solvolysis of **32** to the desired *trans*-diol **33** met with failure. Ultimately, it was found that the epoxide opening could be accomplished with complete positional selectivity using *n*-Bu_4NOAc as a soluble and highly nucleophilic source of acetate anion in the presence of catalytic $Co(acac)_2$ as a Lewis acid additive.

While the above-mentioned epoxide-opening reaction provided a decent quantity (hundreds of milligrams) of material for our early-stage studies, the moderate yield for this transformation deterred us from the preparation of alcohol **34** on a gram scale. A number of conditions were subsequently investigated, and alternative epoxide-opening conditions were established (Scheme 5). By treatment of epoxide **31** with triethylamine and acetic acid, both C2 acetate **34** and C1 acetate **35** were obtained in a 2:1 ratio (**34**, 64%; **35**, 32%). The undesired C1 regioisomer **35** can be recycled using DMAP in refluxing toluene to deliver the same equilibrium mixture (**34**, 64%; **35**, 31%; **34**:**35** = 2:1).

In parallel to the epoxide-opening studies, installation of the requisite C5 hydroxyl was investigated on several different intermediates (Scheme 6). For instance, displacement of allylic chloride **29** with PhSH under basic media followed by *m*-CPBA oxidation delivered sulfoxide **36** in 90% overall yield. It was expected that sulfoxide **36** would undergo a Mislow–Evans

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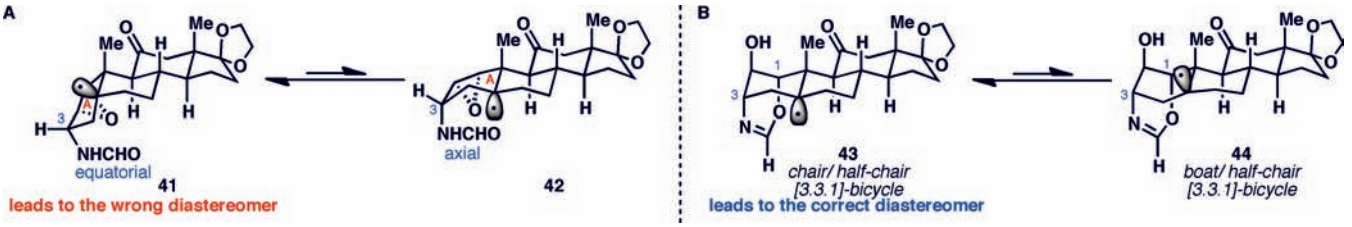
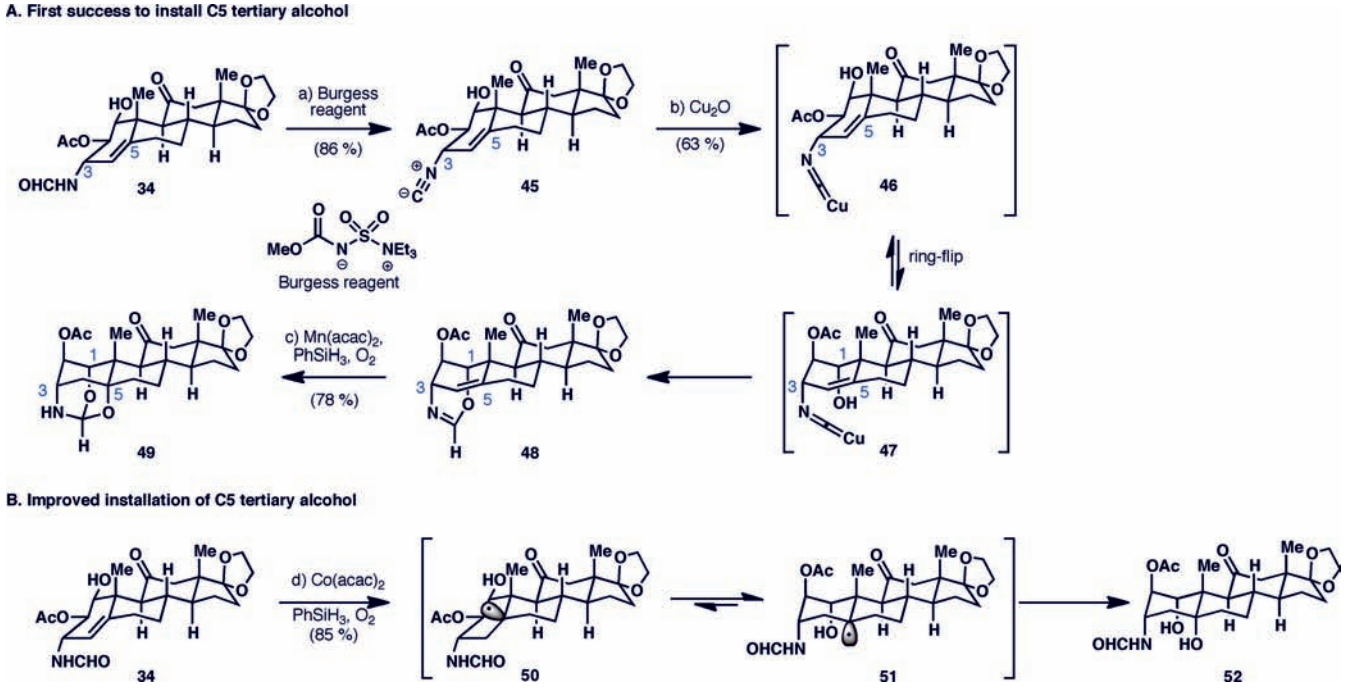


Figure 4. Rationale for the stereoselectivity of the C5 hydration.

Scheme 7. Successful Installation of the Requisite α-Disposed C5-Tertiary Alcohol[a]



[a] Reagents and conditions: (a) Burgess reagent (1.1 equiv), benzene, 20 °C, 30 min, 86%; (b) Cu_2O (1.0 equiv), benzene, 80 °C, 1 h, 63%; (c) $Mn(acac)_2$ (0.2 equiv), $PhSiH_3$ (4 equiv), O_2 (1 atm), THF, 50 °C, 6 h, 78%; (d) $Co(acac)_2$ (0.2 equiv), $PhSiH_3$ (4 equiv), O_2 (1 atm), THF, 23 °C, 12 h, 85%.

rearrangement[29] to furnish allylic alcohol **37**. However, **37** was not observed under a variety of conditions, presumably due to the pseudoequatorial orientation of the sulfoxide group which lacks the necessary proximity to C5 for the rearrangement to occur. An alternative approach for the installation of the C5 hydroxyl group was carried out by treating allylic alcohol **27** with *m*-CPBA followed by Dess−Martin periodinane oxidation to generate bisepoxy ketone **38** (90% yield over two steps). However, the C4−C5 epoxide could not be opened to the desired C5 alcohol **39** under a variety of reductive conditions. Finally, Co-catalyzed Mukaiyama hydration[30] of the C4−C5 olefin in **31** delivered the undesired *β*-oriented tertiary alcohol **40** in 75% yield. An X-ray crystallographic analysis of **40** confirmed its stereochemical assignment.

The origin of this selectivity likely arises from the preference of the A-ring to adopt a half-chair conformation (**41**) with the C3 formamide group in an equatorial rather than an axial position (**42**, Figure 4A).[31] It was reasoned that a complete reversal of selectivity would arise if a tether was present between the C1 and C3 atoms as shown in Figure 4B. To test this hypothesis, the requisite substrate **48** was synthesized in 54% overall yield by the following sequence (Scheme 7A): (1) dehydration of formamide **34** to isonitrile **45** by using the Burgess reagent and (2) Cu-catalyzed cyclization of the C1 hydroxyl onto the isonitrile.[32] When imidate **48** was subjected to $Mn(acac)_2$, $PhSiH_3$, and O_2,[33] the desired C5-oxgenated α-isomer **49** was produced in 78% yield. Subsequently, it was found that simply reacting **34** with $Co(acac)_2$, $PhSiH_3$, and O_2 produced the desired C5-OH α-isomer **52**, which can be rationalized as arising from the greater stability of the desired radical configuration **51** over **50** (Scheme 7B).

After extensive experimentation, C5-oxygenated orthoamide **24** was synthesized in one pot from intermediate **34** in 65% yield via (1) Mukaiyama hydration of the trisubstituted C4−C5 olefin, (2) condensation of the formamido-diol with trimethyl orthoformate, and (3) solvolysis of the C2 acetate (Scheme 8). Thus, the final optimized route to the fully functionalized cortistatin A-ring is described in Scheme 8. This simple five-step sequence provides scalable entry to the highly functionalized A-ring steroid

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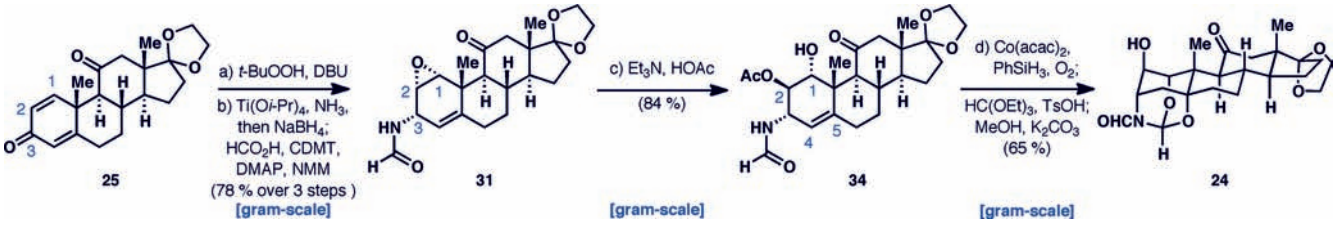
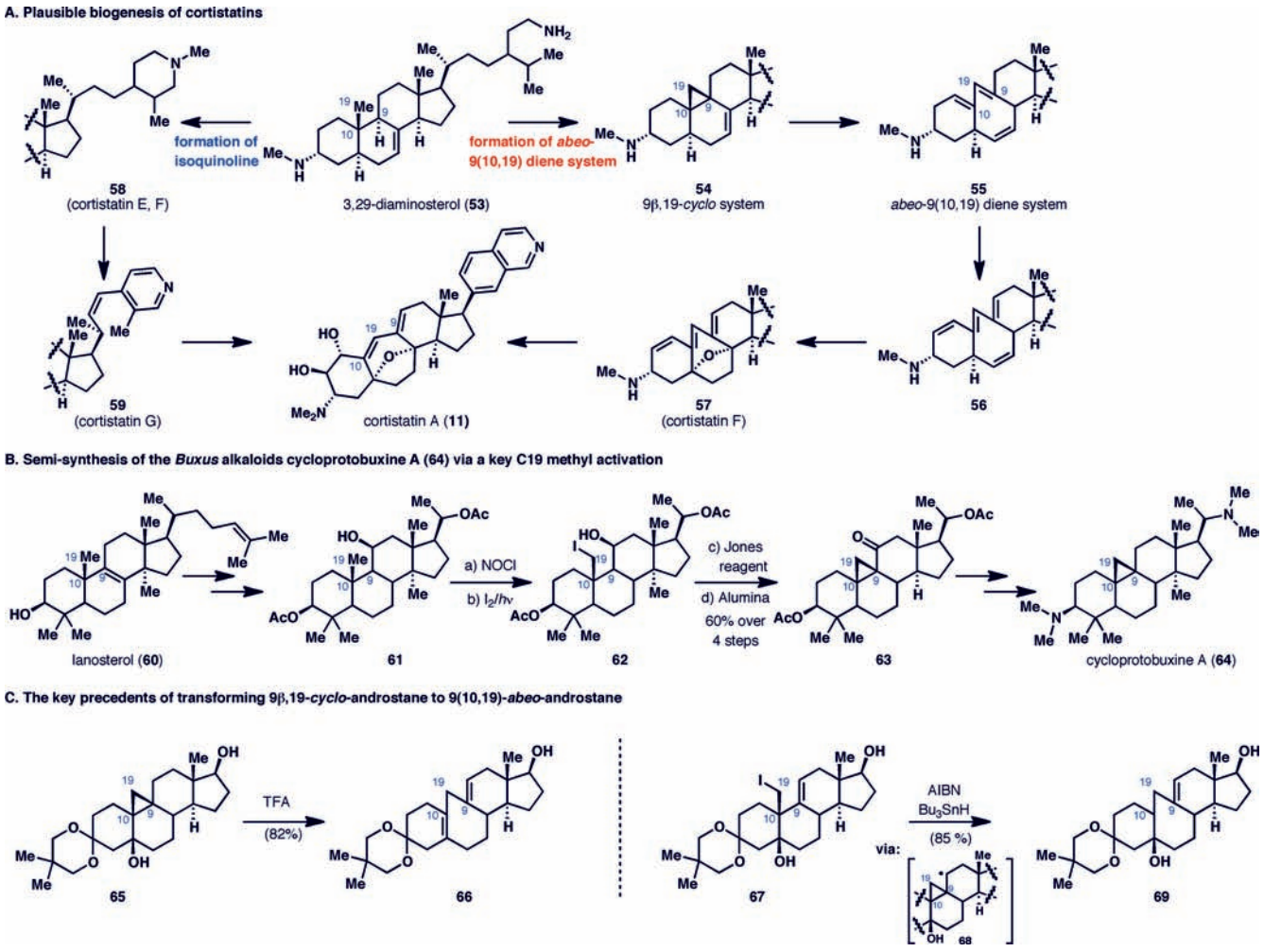
Scheme 8. A Simple Five-Step Stereoselective Process for Converting the Known Steroid Core 25 into the Fully A-Ring-Functionalized Intermediate 24[a]



[a] Reagents and conditions: (a) *t*-BuOOH (2 equiv), DBU (1.8 equiv), THF, 23 °C, 72 h, 82%; (b) $Ti(Oi\text{-}Pr)_4$ (2.0 equiv), NH_3 (4.0 equiv), CH_2Cl_2, 6 h, 23 °C; $NaBH_4$ (1.0 equiv), 1 h, 23 °C; HCO_2H (1.1 equiv), CDMT (1.2 equiv), DMAP (0.3 equiv), NMM (1.1 equiv), CH_2Cl_2, 0 °C → 23 °C, 6 h, 95%; (c) Et_3N (10 equiv), HOAc (10 equiv), 130 °C, 16 h, 64%; (d) $Co(acac)_2$ (0.2 equiv), $PhSiH_3$ (4 equiv), O_2 (1 atm), THF, 23 °C, 20 h; $HC(OMe)_3$ (30 equiv), *p*-TsOH (0.5 equiv), 23 °C, 10 h; then K_2CO_3 (8 equiv), MeOH, 12 h, 65%.

Scheme 9. Key Considerations and Historical Context for the B-Ring Expansion



intermediate **24**. The salient strategic aspect of this work involves the construction of the key "heteroadamantane" system expressed in ring A which served three pivotal roles: (1) it preorganized the system for the ensuing B-ring expansion (*vide infra*); (2) it protected three of the four A-ring heteroatoms; and (3) its subsequent removal would, in principle, not necessitate additional concession steps[25] since the orthoester and formamide carbons are oxidized forms of the C3 dimethylamino group found in the cortistatins.

B-Ring Expansion. The hallmark seven-membered B-ring of the cortistatins (9(10,19)-*abeo*-androstane, which contains the 6-7-6-5 ring system) presented the exciting challenge of developing a practical and scalable method for B-ring expansion of a "normal" steroid (containing the 6-6-6-5 ring system). The presumed biosynthesis of the cortistatins, initially proposed by the Kobayashi group,[15c] was particularly path-pointing to us (Scheme 9A). Inspired by the known biosynthesis of the *Buxus* alkaloids where both the 9β,19-*cyclo* system (**54**) and the

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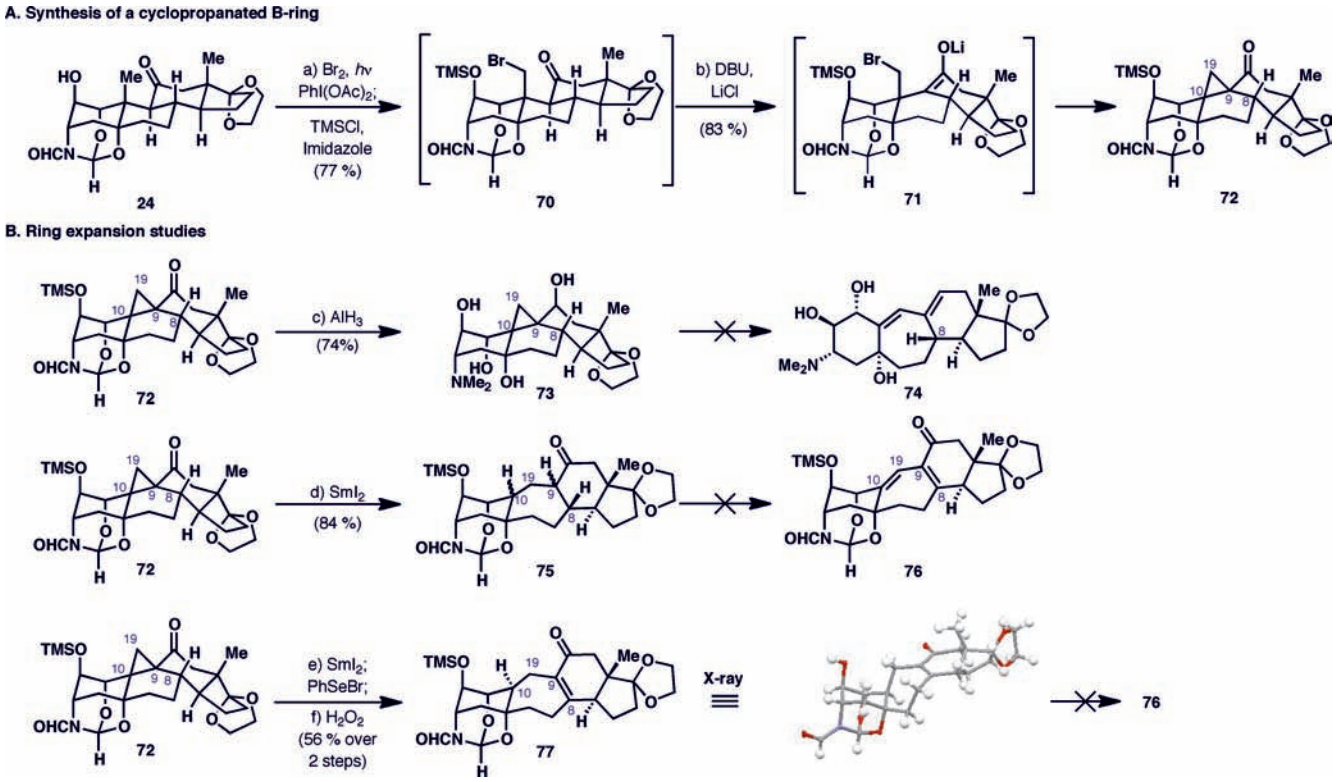
Scheme 10. Synthesis of Cyclopropane 72 and Its B-Ring Expansion[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$ (2 equiv), Br_2 (3 equiv), CH_2Cl_2, light, −10 °C, 5 min; then TMSCl (5 equiv), imidazole (5 equiv), CH_2Cl_2, 0 °C, 15 min, 77%; (b) DBU (2 equiv), LiCl (10 equiv), THF, 23 °C, 24 h, 83%; (c) AlH_3 (0.5 M in THF, 5 equiv), THF, 23 °C, 1 h; then K_2CO_3 (4 equiv), MeOH, 23 °C, 12 h, 74%; (d) SmI_2 (3.0 equiv), 1:9 DMPU:MeCN, 23 °C, 10 min, 84%; (e) SmI_2 (3.0 equiv), 1:9 DMPU:MeCN, 23 °C, 10 min; then PhSeBr (4 equiv), 0 °C, 30 min, 23 °C, 1 h; (f) H_2O_2 (30% aqueous solution, 135 equiv), NH_4Cl (sat. aqueous solution), $CHCl_3$, 23 °C, 30 min, 56% over two steps. DMPU = *N*,*N*′-dimethylpropyleneurea, TMSCl = trimethylsilyl chloride.

abeo-9(10,19)-diene (**55**) are naturally occurring, **54** was proposed to be the biogenetic precursor of **55**. Based on this information, the Kobayashi group proposed that the cortistatin family might be generated from 3,29-diaminosterol (**53**), a hypothetical metabolite that bears resemblance to related natural products (Scheme 9A).[34] Starting with this key precursor, cyclopropane formation via C19-methyl activation followed by subsequent ring expansion should produce **55**. Dehydrogenation to triene **56** and oxidation would afford the unique THF (5,8-oxide) ring system in **57** and in all other members of the cortistatin family. This biosynthetic pathway has parallels in a number of early synthetic studies. For instance, in Martín and co-workers' semisynthesis of the *Buxus* alkaloid cyclovirobuxine A (**64**) from lanosterol (**60**, Scheme 9B),[35] the C19 methyl group in **61** was transformed into the alkyl iodide **62** via Barton nitrite photolysis and trapping with I_2. Subsequent ketone formation and cyclopropanation delivered cyclopropane **63** in 60% yield over four steps. In other reports, B-ring expansions of steroids have also been documented (Scheme 9C),[36] such as in the case of **65** which was smoothly transformed to *abeo*-9(10,19)-diene **66** in 82% yield under TFA mediation.[36a] Radical conditions (AIBN, Bu_3SnH) have also been used in these types of fragmentations, as illustrated with the conversion of **67** to **69** via the cyclopropyl radical **68**.[36b] It was within this context that a synthetic plan for cortistatin B-ring formation was devised, involving a remote C19 methyl group functionalization/cyclopropanation/ring expansion sequence.

For the first stage of the planned B-ring expansion, a mild method was needed for C19 methyl functionalization. Conveniently, the rigidity imparted by the "heteroadamantane" A-ring forced the C2 hydroxyl and the C19 methyl groups into a pseudo-1,3-diaxial conformation and thus in very close proximity to one another (distance between C2-oxygen and C19 is 2.894 Å based on the X-ray crystal structure of **24**). Several potential methods were therefore at our disposal for an alcohol-directed C−H functionalization. The Barton nitrite ester reaction was attempted first, but unfortunately, this chemistry failed to produce the desired result from **24**. Subsequently, conditions for the controlled halogenation of C19 were explored. It was found that modification of Suárez's conditions[37] for remote methyl oxidation using $PhI(OAc)_2$ and Br_2 effected monobromination of C19 (Scheme 10A). The reaction proceeds by *in situ* formation of AcOBr that most likely leads to formation of an O−Br bond at the C2 hydroxyl, subsequent O−Br bond homolysis, hydrogen atom abstraction, and recombination with bromine radical or Br_2 at C19. The intermediate hydroxy bromide was not isolated due to its rapid closure to a tetrahydrofuran; instead, immediate protection of the C2 alcohol as a trimethylsilyl ether and base-induced cylcopropanation afforded cyclopropane **72** in 64% yield over two steps. It should be noted that the use of the well-precedented $PhI(OAc)_2/I_2$ conditions for monoiodination resulted in competitive THF formation, likely due to a much larger coefficient of the σ^*_{C-I} orbital.[38] For the

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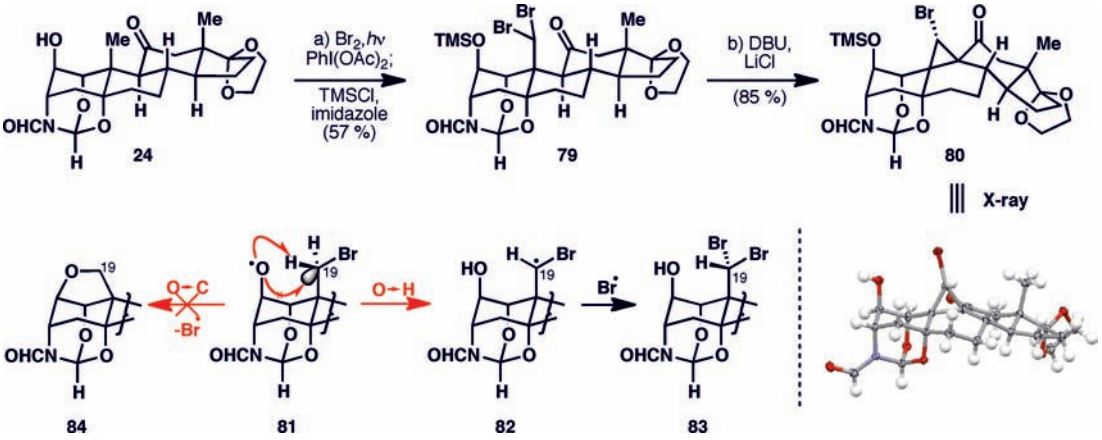
Scheme 11. Synthesis of Bromocyclopropane 80[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$ (5 equiv), Br_2 (8 equiv), CH_2Cl_2, light, −30 °C, 10 h; then TMSCl (5 equiv), imidazole (5 equiv), CH_2Cl_2, 0 °C, 15 min, 57%; (b) DBU (2 equiv), LiCl (5 equiv), THF, 23 °C, 24 h, 85%.

subsequent B-ring expansion, selected attempts to open cyclopropane **72** are shown in Scheme 10B. AlH_3-mediated reduction of the orthoamide moiety provided **73** in 74% yield. Unfortunately, acid-catalyzed fragmentation of cyclopropyl alcohol **73** to diene **74** was unsuccessful. After extensive experimentation, cyclopropyl ketone **72** could be efficiently fragmented to give cycloheptyl ketone **75** upon exposure to SmI_2 followed by acidic workup in 84% yield. Alternatively, quenching the reaction with PhSeBr and subsequent oxidative elimination furnished conjugated enone **77** in 56% yield over two steps. Clearly, the obtention of cycloheptyl ketones **75** and **77** marked a milestone in our studies since they were the first intermediates to bear a seven-membered B-ring. Cycloheptyl ketones **75** and **77** merely required a loss of four or two hydrogens, respectively, in order to arrive at the desired cycloheptyl dienone **76**. The realization of this crucial dehydrogenation, however, proved challenging: no reaction conditions were identified to perform this transformation chemoselectively on these ketones.

Since dehydrogenation at C10 and C19 following the B-ring expansion proved difficult, establishing the desired oxidation state on C19 prior to B-ring expansion was evaluated. Fortuitously, during our studies on the Suárez-type monobromination[37] (Scheme 10A), small quantities of bis-brominated material were always isolated. It was reasoned that this geminal dibromide (see **79**, Scheme 11) possessed the exact oxidation state required of the C19 carbon atom for its eventual expression in **76**. After substantial optimization, **79** was obtained in 53% yield via an iterative, double C−H activation process, while suppressing S_N2 attack of the alcohol on the σ^*_{C-Br} orbital of monobromide **81**. To the best of our knowledge, this is a rare example of an alcohol-directed, geminal dihalogenation of an unactivated hydrocarbon.[39] The unstable dibromo alcohol **83** was capped with a trimethylsilyl group to prevent an unwanted intramolecular cyclization. α-Alkylation of the C11 ketone with the proximal dibromomethyl group proceeded with DBU and LiCl to generate the exotic bromocyclopropane **80** as a single diastereomer in 48% yield over two steps, whose configuration was confirmed by X-ray crystallographic analysis.

Now that the desired oxidation state at C19 was obtained, bromocyclopropane **80** was subjected to the SmI_2 reductive fragmentation conditions. Pleasingly, **80** underwent B-ring expansion as anticipated and unconjugated enone **88** was obtained, bearing no bromine atom but rather a C10−C19 alkene (Scheme 12A). This product is presumably formed via radical-induced ring expansion from **85** to **86**, extrusion of bromine radical, and quenching of dienolate **87** with H_2O.[40] Reduction of the C11 ketone in **88**, elimination of resulting hydroxyl group, and heteroadamantane reduction with AlH_3 afforded diene **89** in 23% yield over three steps. Thus, the oxidation state deliberately embedded into C19-methyl dibromide **79** was translated smoothly into the olefinic C19-methine of the cortistatin core. In addition, **89** possessed all of the correct A-ring functionalities with their correct stereochemistry and the hallmark C10−C19/C9−C11 diene expressed in the natural product. However, thereafter, all attempts to oxidize the C8 position in order to form the THF ring unfortunately met with failure. In essence, what we hoped to achieve was an isohypsic reaction[26] (in this case an isomerization) to convert bromocyclopropane **80** into the redox-isomeric dienone **76** in a single operation. Thus, a set of trapping experiments on the reactive samarium dienolate **87** was investigated as shown (Scheme 12B). Trapping dienolate **87** with O_2 afforded γ-hydroxy enone **91** in 72% yield, whose structure was identified by X-ray crystallographic analysis. Dehydration of **91** turned out to be difficult, and the desired product was not observed. Eventually, it was found that trapping dienolate **87** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCHD) delivered the α-disposed allylic C9-bromide **92** with high diastereoselectivity, which could be converted to the cross-conjugated dienone **76** on a gram scale under mildly basic conditions (LiBr, Li_2CO_3). This two-step process took place in 65% overall yield, and the structure of the coveted dienone **76** was verified by X-ray crystallographic analysis.

THF Ring Closure. Dienone **76** represented a "point of no return" in our path to the cortistatins with carbons 8, 9, 10, and 19 having the correct oxidation state. All that remained in order to complete the core synthesis was a THF ring formation and a chemoselective dismantling of the heteroadamantane-cloaked A-ring. It was reasoned that the THF ring could be constructed by attack of the C5 tertiary alcohol onto the C8 position by an S_N1' or S_N2' mechanism. Treatment of dienone **76** with AlH_3 led to a notably clean and precise delivery of five hydrides to give an intermediate dimethylamino triol. Addition of MeOH to the

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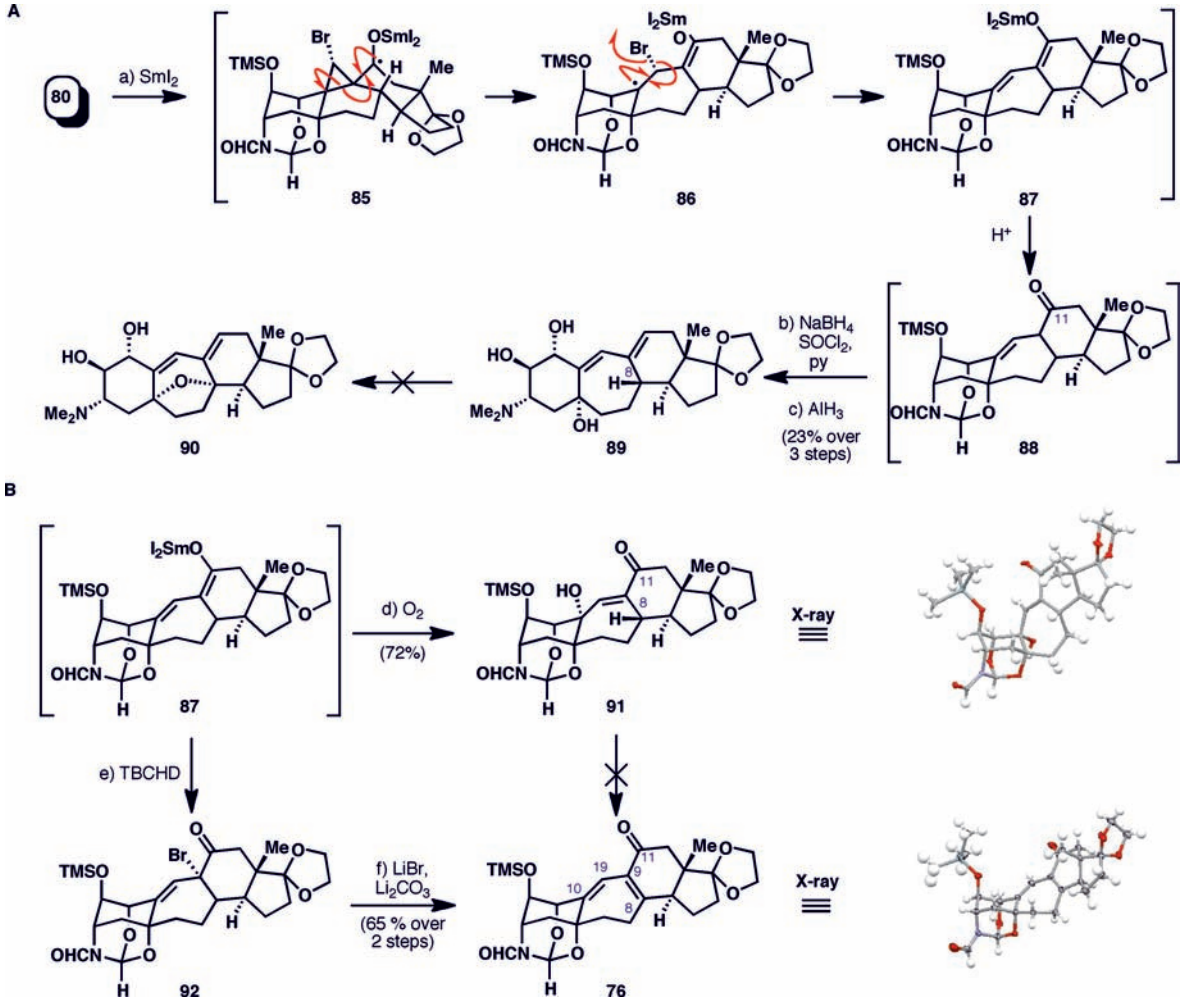
Scheme 12. Ring-Opening of the Bromocyclopropane[a]



[a] Reagents and conditions: (a) SmI_2 (2.5 equiv), LiCl (0.4 M in THF), THF, 23 °C, 5 min; (b) $NaBH_4$ (1.05 equiv), MeOH, 23 °C, 5 min; then $SOCl_2$ (1.5 equiv), pyridine (3 equiv), CH_2Cl_2, 0 °C → 23 °C, 30 min; (c) AlH_3 (0.5 M in THF, 5 equiv), THF, 23 °C, 30 min, 23% over three steps; (d) SmI_2 (2.5 equiv), 1:9 DMPU:THF, 23 °C, 5 min; then O_2 (1 atm), 23 °C, 5 min, 72%; (e) SmI_2 (2.5 equiv), 1:9 DMPU:THF, 23 °C, 10 min; then TBCHD (2 equiv), −78 °C, 1 h; (f) LiBr (20 equiv), Li_2CO_3 (20 equiv), DMF, 60 °C, 1 h, 65% over two steps. TBCHD = 2,4,4,6-tetrabromocyclohexa-2,5-dienone.

reaction mixture served to quench any remaining hydride, and the addition of K_2CO_3 removed the TMS group on the C2 alcohol to afford tetraol **23** in 85% yield. Acetylation of tetraol **23** furnished triacetate **93** in 93% yield, which allowed us to test the hypothesis that the bicyclic ether in cortistatin A might be formed through selective ionization. After screening a number of conditions, it was found that $MgBr_2 \cdot Et_2O$ and 2,6-di-*tert*-butylpyridine was an effective combination of reagents to perform the desired cyclization. Subsequent deketalization and saponification delivered cortistatinone (**22**) in 82% overall yield. Comparison of the ^1H NMR data with those of cortistatin A (**11**) was encouraging, as all of the non-aliphatic carbons bore strong resemblance to the natural product spectra.

The three-step sequence from tetraol **23** to cortistatinone (**22**), while easy to perform, was not efficient in terms of step count and reaction time. Therefore, a direct route from tetraol **23** to cortistatinone (**22**) was investigated. A variety of acids were screened to effect this transformation (Scheme 13B), upon which it was found that both Lewis and Brønsted acids (for example, HCl, entry 5) were able to produce the desired compound — cortistatinone (**22**). $BiCl_3$ was identified as the superior reagent to perform the cyclization and deketalization simultaneously in 73% yield. This improvement reduced the operations of the original route by three and enabled the preparation of multigram quantities of cortistatinone (**22**).

The final optimized route from orthoamide **24** to cortistatinone (**22**) is shown in Scheme 14. It features a number of gram-scale transformations: (1) a newly invented alcohol-directed dibromination; (2) an isohypsic cascade to access the 9(10,19)-*abeo*-androstane skeleton; (3) an olefin-sparing, heteroadamantane fragmentation to differentiate the tethered aminodiol; and (4) a mild S_N' cyclization to close the THF ring. With this robust pathway developed, over 2 g of cortistatinone (**22**) has been prepared to date.

Isoquinoline Installation. In parallel to our efforts to synthesize cortistatinone (**22**), methods were evaluated for the introduction of the C17 isoquinoline moiety at earlier stages in our

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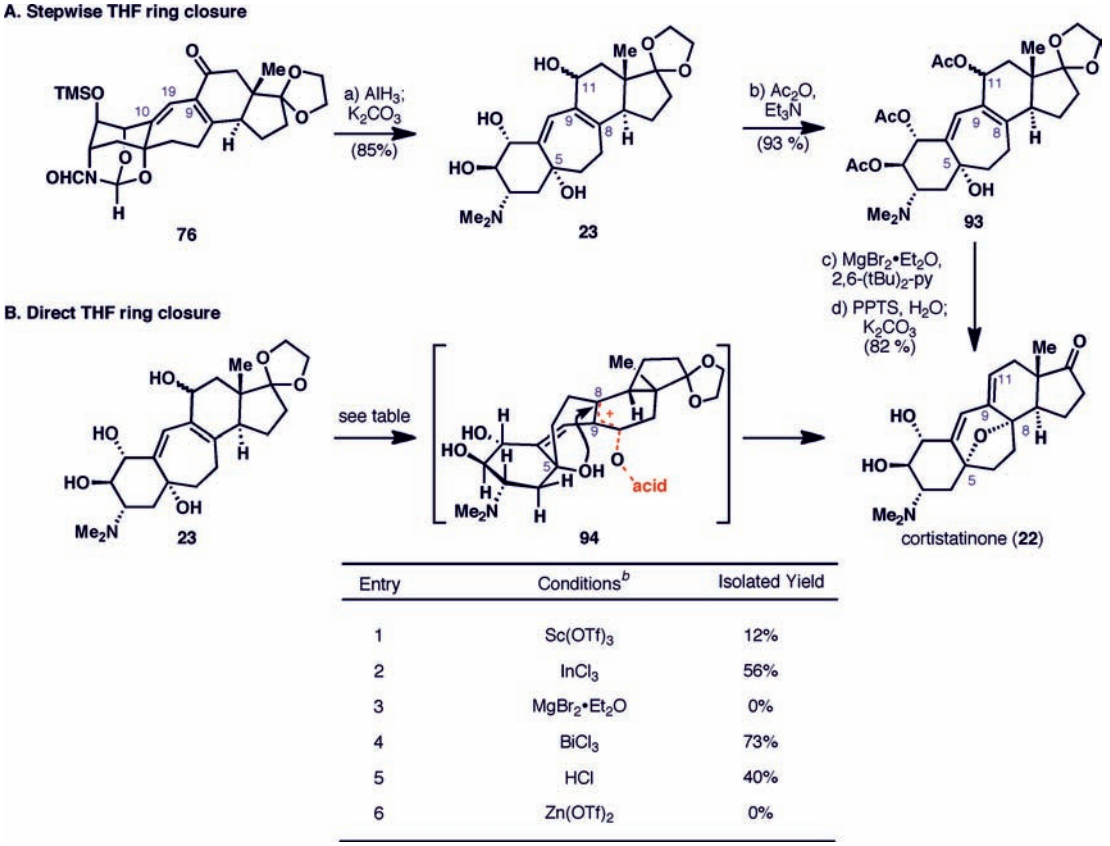
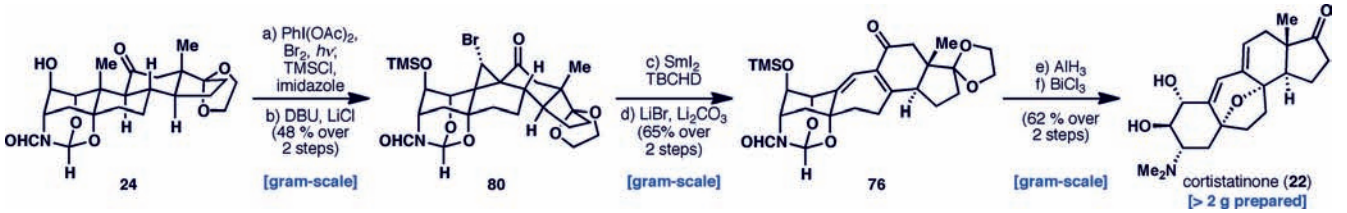
Scheme 13. THF Ring Closure[a]



Entry	Conditions[b]	Isolated Yield
1	$Sc(OTf)_3$	12%
2	$InCl_3$	56%
3	$MgBr_2 \cdot Et_2O$	0%
4	$BiCl_3$	73%
5	HCl	40%
6	$Zn(OTf)_2$	0%

[a] Reagents and conditions: (a) AlH_3 (0.5 M in THF, 6 equiv), THF, 23 °C, 1 h; then K_2CO_3 (5 equiv), MeOH, 23 °C, 12 h, 85%; (b) Ac_2O (20 equiv), Et_3N (40 equiv), DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 3 h, 93%; (c) $MgBr_2 \cdot Et_2O$ (1.1 equiv), 2,6-(*t*-Bu)$_2$-pyridine (2.1 equiv), PhH, 80 °C, 1 h; (d) PPTS (5 equiv), butanone:H_2O (1:1), 90 °C, 2 h; then K_2CO_3 (10 equiv), 23 °C, 5 h, 82% over two steps. PPTS = pyridinium *p*-toluenesulfonate. [b] Reagents and conditions: acid (4 equiv), MeCN, 40 °C, 2 h; H_2O, 40 °C, 4 h.

Scheme 14. Final Optimized Route to Cortistatinone (22)[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$ (5 equiv), Br_2 (8 equiv), CH_2Cl_2, light, −30 °C, 10 h; then TMSCl (5 equiv), imidazole (5 equiv), CH_2Cl_2, 0 °C, 15 min, 57%; (b) DBU (2 equiv), LiCl (5 equiv), THF, 23 °C, 24 h, 85%; (c) SmI_2 (2.5 equiv), 1:9 DMPU:THF, 23 °C, 5 min; then TBCHD (2 equiv), −78 °C, 1 h; (d) LiBr (20 equiv), Li_2CO_3 (20 equiv), DMF, 80 °C, 1 h, 65% over two steps; (e) AlH_3 (0.5 M in THF, 6 equiv), THF, 23 °C, 1 h; then K_2CO_3 (5 equiv), MeOH, 23 °C, 12 h, 85%; (f) $BiCl_3$ (5 equiv), MeCN, 40 °C, 2.5 h; H_2O, 40 °C, 5 h, 73%.

synthesis (Scheme 15). The fundamental strategic problem with such an approach is that it prevents the desired late-stage diversification, and the isoquinoline moiety itself poses incompatibilities with key reactions. For example, intermediate **24** could be transformed to isoquinoline-containing steroid **96** in 10% overall yield by a sequence employing ketal cleavage, Barton vinyl iodide formation (leading to **95**),[41] Stille coupling[42] with stannane **105**, and stereoselective hydrogenation with Pd/C. Unfortunately, the isoquinoline moiety was incompatible with halogenation conditions.[37] In a similar vein, bromocyclopropane–isoquinoline conjugate **99** could be prepared in 16% overall yield, but bromocyclopropane was not compatible with hydrogenation conditions. Therefore, the original plan for late-stage isoquinoline installation remained the most logical, and indeed the only viable option.

With two free alcohols, one tertiary amine, and a sensitive diene adjacent to a THF ring, cortistatinone (**22**) requires "gentle" chemistry for derivatization. Barton's vinyl iodide preparation (*vide supra*) fulfills this requirement, as does the Stille coupling.[43] In the event, this reaction sequence works well to

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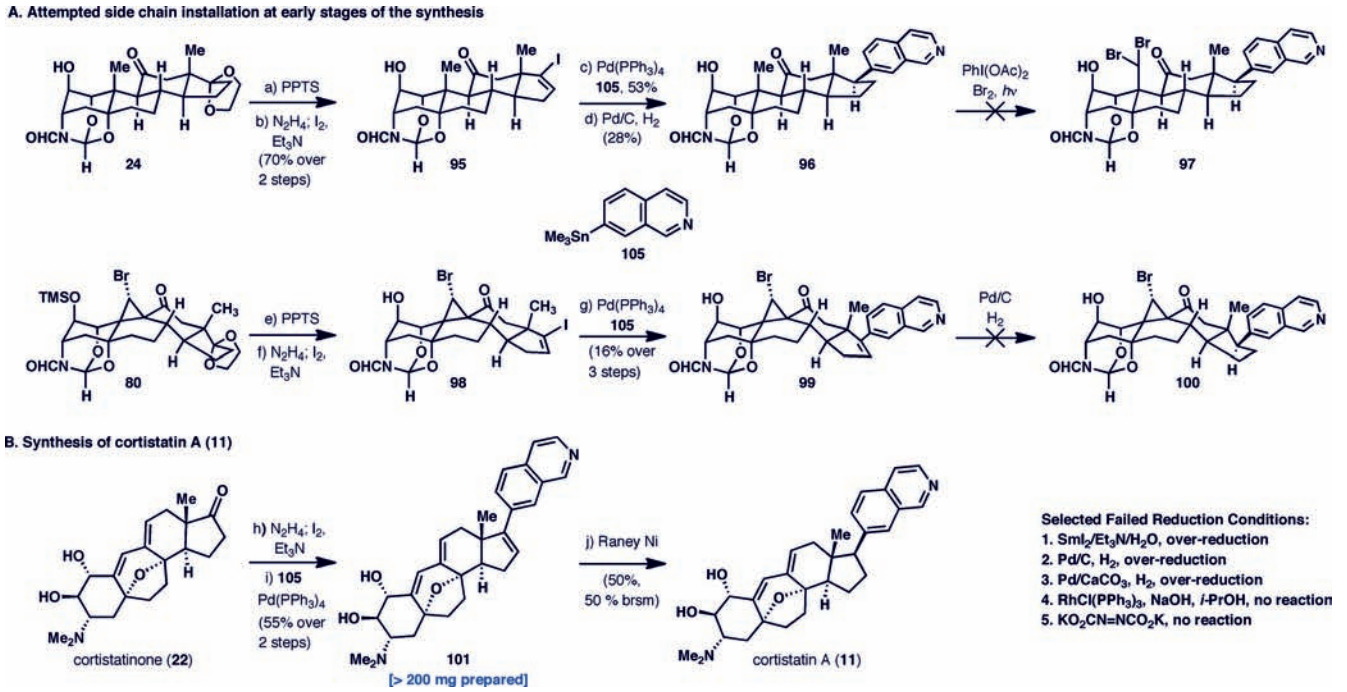
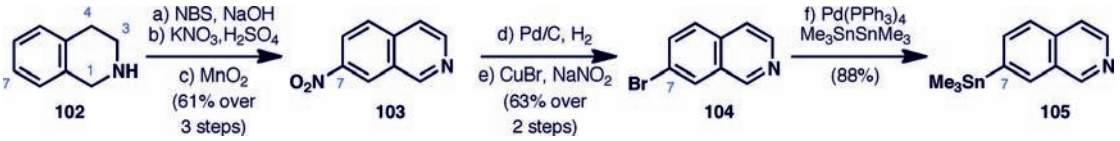
Scheme 15. Studies on Isoquinoline Installation[a]



[a] Reagents and conditions: (a) PPTS (1 equiv), 1:4 H_2O:acetone, 80 °C, 30 min; (b) NH_2NH_2 (20 equiv), Et_3N (40 equiv), EtOH, 50 °C, 2 h; I_2 (2 equiv), Et_3N (3 equiv), THF, 23 °C, 10 min, 70% over two steps; (c) **105** (1 equiv), $Pd(PPh_3)_4$ (0.5 equiv), CuCl (10 equiv), LiCl (10 equiv), DMF, 60 °C, 1 h, 53%; (d) 10% Pd/C (1.5 equiv), H_2 (1 atm), 1:1 EtOAc:MeOH, 2 h, 28%; (e) PPTS (1 equiv), 1:4 H_2O:acetone, 80 °C, 30 min; (f) NH_2NH_2 (20 equiv), Et_3N (40 equiv), EtOH, 50 °C, 2 h; I_2 (2 equiv), Et_3N (3 equiv), THF, 23 °C, 10 min; (g) **105** (1 equiv), $Pd(PPh_3)_4$ (0.5 equiv), CuCl (10 equiv), LiCl (10 equiv), DMF, 60 °C, 1 h, 16% over three steps; (h) NH_2NH_2 (10 equiv), Et_3N (10 equiv), EtOH, 50 °C, 6 h; I_2 (2 equiv), Et_3N (3 equiv), THF, 23 °C, 5 min; (i) **105** (1 equiv), $Pd(PPh_3)_4$ (0.5 equiv), CuCl (10 equiv), LiCl (10 equiv), DMSO, 60 °C, 1 h, 55% over two steps; (j) Raney Ni (10 wt equiv), *i*-PrOH, H_2O, 50 °C, 1 h, (50%, 50% brsm). DMSO = dimethyl sulfoxide.

Scheme 16. Scalable Synthesis of 7-Substituted Isoquinoline[a]



[a] Reagents and conditions: (a) NBS (1.1 equiv), NaOH (30%, 5 equiv), CH_2Cl_2, 1.5 h, 92%; (b) KNO_3 (1.5 equiv), H_2SO_4, 0 °C → 23 °C, 2 h; 60 °C, 4 h, 72%; (c) MnO_2 (7 equiv), toluene, reflux, 2 h, 91%; (d) Pd/C (10%), H_2 (1 atm), 3 h; (e) CuBr (1.2 equiv), $NaNO_2$ (1.1 equiv), H_2O, HBr, 0 °C → 75 °C, 30 min; 23 °C, 12 h, 63% over two steps; (f) $Pd(PPh_3)_4$ (0.1 equiv), hexamethylditin (1.05 equiv), LiCl (6 equiv), toluene, 105 °C, 1 h, 88%. NBS = *N*-bromosuccinimide.

deliver Δ^{16}-cortistatin A (**101**) in 53% isolated yield (on scales ranging from 1 to 300 mg). The final conversion of **101** to cortistatin A (**11**) required numerous screens in order to identify a suitably chemoselective reducing agent that could differentiate a styrene-like olefin from an isoquinoline and a diene and do so in the presence of numerous unprotected functionalities. Whereas Sm- and Pd-based agents led to over-reduction (observed by LC-MS, uncharacterized), and Rh-mediated transfer hydrogenation or diimide methods did not work in our hands, Raney Ni led to an excellent conversion to **11**, thus completing the synthesis. This reaction was never run beyond a 10 mg scale since it was soon found that **101** is nearly equipotent to **11** in all biological assays tested. In a separate report, we have demonstrated the generality of this reaction and explored its mechanism.[18d]

In passing, we note that although isoquinoline **104** is commercially available, it is prohibitively expensive (ca. $80/10 mg in 2007 when we started our studies). Furthermore, the existing method to synthesize 7-bromoisoquinoline by the Pomeranz–Fritsch reaction[44] gives 5-bromoisoquinoine as a byproduct that is difficult to separate. Therefore, a scalable and practical synthesis of 7-bromoisoquinoline was developed, as shown in Scheme 16. Starting from tetrahydroisoquinoline (**102**), imine formation with NBS/NaOH,[45] nitration at the C7 position,[46] and dehydrogenation with MnO_2 furnished 7-nitroisoquinoline (**103**) in 61% yield over three steps. Subsequent reduction of the nitro group and Sandmeyer reaction afforded the desired 7-bromoisoquinoline (**104**) in 63% yield over two steps. Lastly, stannylation of 7-bromoisoquinoline (**104**) delivered 7-trimethylstannylisoquinoline (**105**) in 88% yield.

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CONCLUSION

This full account describing a scalable synthesis of cortistatin A and related structures stands as an example of how the judicious choice of strategy can yield new insights into chemical reactivity, even in a field as exhaustively studied as steroid synthesis. Several transformations were developed that were either not feasible or not possible prior to this work: the easily scalable side-chain cleavage protocol; the chemoselective, tandem geminal dihalogenation of an unactivated methyl group; the reductive fragmentation/trapping/elimination of a bromocyclopropane to simultaneously establish both the $\Delta^{10(19)}$- and $\Delta^{8(9)}$-olefins and the 7-membered B-ring; the facile chemoselective etherification reaction for installation of the oxido bridge; and the remarkably selective Δ^{16}-alkene reduction with Raney Ni. Although our primary motive for pursuing a synthesis of the cortistatins was to uncover new reactivity, develop new strategies, and educate students, we were keenly aware of the societal need for a scalable route due to their extraordinary biological activity. With these factors in mind, a semisynthetic approach was chosen — one that successfully converted one of the most abundant terrestrial-based steroids into one of the ocean's scarcest steroidal alkaloids ever isolated. The synthesis outlined in this work is amenable, in an academic setting, to the gram-scale production of the cortistatins and has also been successfully outsourced to an industrial setting.[47] It is sufficiently short and flexible for analogue studies, especially those which vary the aromatic heterocycle at the late stage of the synthesis. Finally, the copious quantities prepared thus far, particularly of cortistatin A's equipotent analogue **101**, have been widely distributed to numerous academic laboratories and pharmaceutical companies. Indeed, extremely promising biological findings enabled by this synthesis have already been made and will be described in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental details, spectra, and X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

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