### Synthesis of Cortistatin Alkaloids and a Versatile Synthesis of Isoquinolines

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Synthesis of Cortistatin Alkaloids and a Versatile Synthesis of Isoquinolines

Abstract

The cortistatins are a recently identified class of marine natural products that were found to exhibit potent and selective inhibition of human umbilical vein endothelial cells (HUVECs), making them promising leads for the development of anti-angiogenic drugs. In our synthesis, we envisioned that natural cortistatins and unnatural analogs could be prepared by late-stage introduction of isoquinolines to 17-keto precursors, and that these differentially substituted precursors could all be derived from a common key intermediate 112.

We developed a robust synthetic route to prepare gram quantities of key intermediate 112 starting from readily available benzylzinc reagent 116 and enol triflate 117. Key intermediate 112 was next converted to cortistatin precursors 108, 109, 110, and 111 in three to eight steps, representing each of the four natural cortistatin ABC-ring substitution patterns. Subsequently, a generally applicable method was developed to introduce the isoquinoline moiety. After complexation to \( N,N,N',N' \)-tetramethylethylenediamine (TMEDA), 7-lithio-isoquinoline added to 17-keto precursors to provide the corresponding 1,2-addition products; the resulting tertiary alcohols underwent radical deoxygenation via their trifluoroacetates to afford the desired (17\( S \))-products. This organolithium-addition-deoxygenation sequence provided cortistatins A (1, on a 20-mg scale), J (9), K (10), and L (11) in good overall yields. We also synthesized
cortistatin primary amines (176 and 186) and used them to prepare several cortistatin based affinity reagents. By employing these reagents in pull-down experiments, we identified a 55-kD membrane kinase as a putative protein target of cortistatins.

We wanted to prepare cortistatin analogs with isoquinoline modifications due to the importance of this ring for the biological activity of cortistatins. This led us to develop a novel and versatile synthesis of substituted isoquinolines. In our method, lithiated o-tolualdehyde tert-butylimines were condensed with different nitriles to generate eneamido anion intermediates, which were trapped in situ with various electrophiles at the C4-position, affording a wide range of substituted isoquinolines. Further diversification was achieved by modification of the work-up conditions and by subsequent transformations.
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### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>Burgess reagent</td>
<td>methyl N-(triethylammoniumsulphonyl)carbamate</td>
</tr>
<tr>
<td>BzCl</td>
<td>benzoyl chloride</td>
</tr>
<tr>
<td>$c$</td>
<td>concentration (g/100 mL)</td>
</tr>
<tr>
<td>CAM</td>
<td>aqueous ceric ammonium molybdate solution</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization</td>
</tr>
<tr>
<td>cis</td>
<td>$L_-$, on the same side</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>dimethyldioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethyl sulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>$E$</td>
<td>Ger., entgegen</td>
</tr>
<tr>
<td>ED$_{50}$</td>
<td>50% effective dose</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
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</table>
**ent**  enantiomer
equiv  equivalent
ESI  electrospray ionization
Et$_3$N  triethylamine
EtOH  ethanol
FTIR  Fourier transform infrared
g  gram
GI$_{50}$  50% growth inhibition
hv  light
HFIPA  1,1,1,3,3,3-hexafluoro-2-propanol
HMBC  heteronuclear multiple bond correlation
HPLC  high-pressure liquid chromatography
HRMS  high-resolution mass spectrometry
HSQC  heteronuclear single quantum coherence
Hz  hertz
IBX  o-iodoxybenzoic acid
$J$  coupling constant
K562  human chronic myelogenous leukemia cells
KB3-1  KB epidermoid carcinoma cells
KHMDS  potassium hexamethyldisilazide
KMnO$_4$  aqueous potassium permanganate solution
K-selectride  potassium tri-sec-butylborohydride
LRMS  low-resolution mass spectrometry
M     molar

m-CPBA  meta-chloroperoxybenzoic acid

MEMCl  methoxyethoxymethyl chloride

mg     milligram

MHz    megahertz

mL     milliliter

m/z    mass to charge ratio

μL     microliter

mmol   millimole

μmol   micromole

MOM    methoxymethyl

MPO    4-methoxypyridine N-oxide

MsCl   methanesulfonyl chloride

NaHMDS sodium hexamethyldisilazide

NBS    N-bromosuccinimide

Neuro2A murine neuroblastoma cells

NHDF   normal human dermal fibroblasts

NOE    nuclear Overhauser effect

NMR    nuclear magnetic resonance

p-anisaldehyde  acidic ethanolic p-anisaldehyde solution

Pd₂(dba)₃  tris(dibenzylideneacetone)dipalladium

ppm    parts per million

PPTS   pyridinium p-toluenesulfonate
psi pounds per square inch

\( p\)-TsOH \( p\)-toluenesulfonic acid

Py pyridine

\( R \) rectus (Cahn–Ingold–Prelog system)

\( R_f \) retention factor

rt room temperature

\( S \) sinister (Cahn–Ingold–Prelog system)

S-Phos 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TASF tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAA tetra-\( n\)-butylammonium acetate

TBAF tetra-\( n\)-butylammonium fluoride

TBCHD 2,4,4,6-tetrabromo-2,5-cyclohexadienone

TBSCI \( tert\)-butyldimethylsilyl chloride

TBSOTf \( tert\)-butyldimethylsilyl trifluoromethanesulfonate

TESCl chlorotriethylsilane

TESOTf triethylsilyl trifluoromethanesulfonate

TFA trifluoroacetic acid

TFE 2,2,2-trifluoroethanol

THF tetrahydrofuran

TIPSOTf triisopropylsilyl trifluoromethanesulfonate

TLC thin-layer chromatography

TMEDA \( N,N,N',N'\)-tetramethylethlenediamine

TMSCI chlorotrimethylsilane
<table>
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<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>TMSOTf</td>
<td>trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>trans</td>
<td>$L.$, across</td>
</tr>
<tr>
<td>Z</td>
<td>$Ger.$, zusammen</td>
</tr>
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Chapter 1

Introduction to the Cortistatin Family of Natural Products
Isolation and Biological Activities of the Cortistatins

The cortistatins are a family of eleven steroidal alkaloids isolated from the marine sponge *Corticium simplex* by the Kobayashi group in 2006 and 2007 (Figure 1.1).\(^1\) Structurally, there are four types of substitution patterns in the ABC-ring part among all the cortistatins, as in cortistatin A (1), B (2), C (3), and D (4); cortistatin E (5), G (7), H (8), and K (10); cortistatin F (6), and J (9); and cortistatin L (11). They all share the same 9(10→19)-abeo-androstane core structure\(^2\) with an unusual C5,C8 oxa-bridge and a C3 dimethylamino group, but are different in the degree and position of oxygenation and unsaturation along the northern edge of ABC-ring. In the D-ring part, most cortistatins have a unique isoquinoline substituent attached at C17 position, while cortistatin E (5), F (6), G (7), and H (8) have an N,3-dimethylpiperidine or 3-methylpyridine ring in their C17 side chains.

More significantly, several of cortistatins exhibit strong inhibition against the proliferation of human umbilical vein endothelial cells (HUVECs), but are much less potent against a panel of other cancerous and normal human cell lines (Table 1.1).\(^1,3\) The HUVECs are isolated from normal human umbilical vein, and are a standard model to study angiogenesis.\(^4\) Angiogenesis is the growth of new capillary blood vessels from pre-

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2. In the 9(10→19)-abeo-androstane structure, the C19 angular methyl group of a typical steroid framework (androstane) is incorporated into the B-ring to form a seven-membered ring.


Figure 1.1 The Cortistatin Family of Natural Products.

Table 1.1 Growth Inhibitions of Cortistatins against HUVECs and other Cell Lines.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Cortistatin A (1)</th>
<th>Cortistatin J (9)</th>
<th>Cortistatin K (10)</th>
<th>Cortistatin L (11)</th>
</tr>
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<tr>
<td>HUVECs</td>
<td>0.0018</td>
<td>0.008</td>
<td>0.04</td>
<td>0.023</td>
</tr>
<tr>
<td>KB3-1</td>
<td>7.0</td>
<td>9.1</td>
<td>10.2</td>
<td>14</td>
</tr>
<tr>
<td>Neuro2A</td>
<td>6.0</td>
<td>3.3</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>K562</td>
<td>7.0</td>
<td>3.3</td>
<td>3.9</td>
<td>4.3</td>
</tr>
<tr>
<td>NHDF</td>
<td>6.0</td>
<td>2.4</td>
<td>2.5</td>
<td>2.4</td>
</tr>
</tbody>
</table>
existing ones. Physiological angiogenesis could occur during reproduction, development, or wound healing, and is strictly controlled by a host of angiogenic factors; while pathological angiogenesis can be unregulated and persistent, and is responsible for a wide range of diseases, including many types of cancers, autoimmune disease, age-related macular degeneration, and atherosclerosis.

In 1971, Judah Folkman, a young surgeon at that time, first hypothesized that angiogenesis is necessary for the growth and metathesis of tumor cells, and identified the first angiogenesis promoting factor named tumor angiogenesis factor (TAF). Nine years later, the same laboratory isolated the first angiogenesis inhibitor, interferon-α/β. Following the pioneering work of the Folkman group, more than 30 additional angiogenic factors, and over 400 endogenous and synthetic angiogenesis inhibitors have been discovered over the past three decades. Noteworthily, the Folkman group identified several steroids (e.g. medroxyprogesterone, cortisone, and dexamethasone) that inhibit angiogenesis in vivo in the presence of heparin or a heparin fragment with an unknown mechanism. In the mid-1990s, a couple of anti-angiogenic drugs started to enter clinical trials. In 2004, Bevacizumab, an antibody that neutralizes vascular endothelial growth factor (VEGF), was approved by the Food and Drug Administration (FDA) to treat colorectal cancer, which is the first drug developed solely as an

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angiogenesis inhibitor.\textsuperscript{12,13} A number of small molecule entities, including Sorafenib (Bayer and Onyx, approved in 2005),\textsuperscript{14} Sunitinib (Pfizer, approved in 2006),\textsuperscript{15} Pazopanib (GlaxoSmithKline, approved in 2009),\textsuperscript{16} and Vandetanib (AstraZeneca, approved in 2011),\textsuperscript{17} have been developed as tyrosine kinase inhibitors (TKIs) of vascular endothelial growth factor receptors (VEGFRs) and other related receptor tyrosine kinases to treat different types of cancers (Figure 1.2). Anti-angiogenic drugs have also been approved to treat diseases other than cancer: Ranibizumab, a fragment of Bevacizumab,\textsuperscript{18} and Pegaptanib, an anti-VEGF aptamer,\textsuperscript{19} were both approved for the treatment of age-related macular degeneration (AMD). In addition, several drugs that were previously approved for unrelated purposes, like Thalidomide,\textsuperscript{20} Bortezomib,\textsuperscript{21} and


\textsuperscript{13} Bevacizumab has since also been approved for the treatment of certain lung cancers, renal cancers, and glioblastoma multiforme of the brain; but its approval for the treatment of breast cancer was revoked in 2011; its major side effects include high blood pressure and bleeding.


\textsuperscript{20} Thalidomide was used to treat morning sickness in the late 1950s but was later withdrawn as it caused severe birth defects; in 2006, thalidomide was approved by the FDA to treat multiple myeloma in combination with dexamethasone: Weber, D.; Rankin, K.; Gavino, M.; Delasalle, K.; Alexanian, R. \textit{J. Clin. Oncol.} \textbf{2003}, \textit{21}, 16–19.

Celecoxib\textsuperscript{22} were found to also have potent anti-angiogenic effects. To date, no fewer than 14 anti-angiogenic-related drugs have been approved in the United States, along with more than 30 anti-angiogenic drug candidates in clinical trials.\textsuperscript{23}

**Figure 1.2** Selected FDA Approved Small Molecule Entities with Anti-angiogenic Effect.

The potent and selective inhibition of cortistatins against HUVECs made them promising lead compounds for anti-angiogenic therapeutics; yet the molecular mechanism of cortistatins of inhibiting angiogenesis remains unclear to date. Kobayashi and co-workers observed an unidentified 110 kDa protein whose phosphorylation was inhibited by the treatment of cortistatin A.\textsuperscript{3} In collaboration with Amgen, the Nicolaou–Chen group used an activity-based kinase profiling assay and screened 359

\begin{itemize}
  \item Celecoxib was developed as a cyclooxygenase-2 enzyme (COX-2) inhibitor and also identified to possess anti-angiogenic properties: Greene, A. K.; Alwayn, I. P.; Nose, V. Ann. Surg. \textbf{2005}, \textit{242}, 140–146.
  \item Li, W. W.; Li, V. W.; Hutnik, M.; Chiou, A. S. \textit{J. Oncology} \textbf{2012}, Article ID 879623, 1–23.
\end{itemize}
The top four putative targets identified in the study were ROCK I, ROCK II, CDK8, and CDK 11, with CDK8 and CDK11 having binding constants (K_d values of 10 nM and 17 nM respectively) in the same range of the IC_{50} of cortistatin A in HUVECs. They further conducted homology modeling and suggested that cortistatin A might bind to the kinase hinge region through its isoquinoline substituent, with its polar A-ring exposing to solvent.

The hypothesis that the isoquinoline ring is essential for the cortistatin activity, while the ABC-ring part could tolerate certain degrees of modifications is consistent with the preliminary structure-activity relationship (SAR) data obtained from natural cortistatins as well as several synthetic cortistatin analogs (Figure 1.3). The Kobayashi group found that with different oxidation states at C16 and C17, cortistatin B (2), C (3), and D (4) exhibited different degrees of reduced activities in comparison with cortistatin A (1); and cortistatin E (5), G (7), and H (8), which share the same ABC-ring substitution pattern as cortistatin K (10) but do not possess the C17 isoquinoline substituent, lost most of their activities; in contrast, cortistatin A (1), J (9), K (10), and L (11), which contain the same D-ring pattern but are different in the ABC ring functionality, had similar low nano-molar activities against HUVECs.\textsuperscript{1,3} The Baran group reported that Δ^{16}-cortistatin A (12) is almost as active as cortistatin A (1), while C17-\textit{epi}-cortistatin A (13), with an inverse stereochemistry at C17 isoquinoline moiety, is 500-fold less active.\textsuperscript{25} In addition, a late-stage synthetic intermediate 14 reported by the Nicolaou–Chen group, which lacks the C3 dimethylamino group and A-ring hydroxyl groups but has the C17 isoquinoline

substituent installed, retained the potency of cortistatins; 26 an estrone-derived cortistatin analog 15 synthesized by the Corey group, 27 and a simplified cortistatin analog 16 prepared in the Kobayashi group, 28 both lacking the oxabicyclo[3.2.1]octene core structure but keeping the isoquinoline appendage, also exhibited good GI50 values against HUVECs.

**Figure 1.3** GI50 Values against HUVECs of Selected Natural Cortistatins and Synthetic Cortistatin Analogs.

![Chemical Structures](image)

Synthetic Approaches towards the Cortistatins

The remarkable biological profile, the unique molecular architecture, and the scarce of cortistatins (as the isolation chemists were also pursuing a total synthesis of cortistatins, see below) have attracted enormous efforts towards the synthesis of this class of natural products during the past few years. To date, five research groups (including our own laboratory) have accomplished the synthesis of cortistatin A, and four have finished synthesizing cortistatin J. In addition, at least two formal syntheses of cortistatins have been reported, along with numerous synthetic studies towards the cortistatin pentacyclic core structure.29,30

In early 2008, the Baran group form Scripps reported the first synthesis of cortistatin A starting from prednisone (17) (Scheme 1.1).31,32 This inexpensive steroid was first converted to amide 18 in a six-step sequence. Subsequent Mukaiyama hydration was followed by a couple protection group manipulations to afford orthoamide 19. The C19 angular methyl group was then selectively bis-brominated by an in situ generated acetoxy hypobromite (AcOBr) from bromine and bisacetoxyiodobenzene, and the C2 free alcohol was protected, providing β-keto dibromide 20. Treating this bromide with 1,8-
diazabicycloundec-7-ene (DBU) gave a cyclopropane intermediate, which was opened by exposure to samarium diiodide; the resulting samarium enolate intermediate was trapped with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) to furnish bromide 21. Allylic bromide elimination followed by alane reduction and then deprotection afforded intermediate 22, setting the stage ready for the C5,C8 oxa-bridge closure. Bismuth(III) chloride was found to be an optimal Lewis acid which also effected deketalization after heating with water to afford cortistatinone 23. This ketone was converted to a vinyl iodide by Barton’s method via a hydrazone and then cross-coupled with 7-

**Scheme 1.1** Baran’s Synthesis of Cortistatin A.

**Reagents and conditions:** (a) BH₃•THF; NaIO₄, acetone–H₂O, 0 → 23 °C; (b) ethylene glycol, p-TsOH•H₂O, PhCH₃, 110 °C, 92% (2 steps); (c) t-BuO₂H, DBU, THF, 23 °C, 72 h, 82%; (d) NH₄OAc, Na(BH₃)CN, CH₃OH, THF, 23 °C; then HCO₂Et, Et₃N, 54 °C, 73%; (e) TBAA, Co(acac)₂, PhH, 90 °C, 48%; (f) Co(acac)₂, PhSiH₃, O₂, THF, HC(OCH₃)₃, 23 °C; then TsOH•H₂O, 23 °C; then K₂CO₃, CH₃OH, 65%; (g) Ph(OAc)₂, Br₂, CH₂Cl₂, −30 °C; then TMSCl, imidazole, 0 °C, 57%; (h) DBU, LiCl, THF, 23 °C, 85%; (i) SmI₂, DMPU–THF (1:9), 23 °C; then TBCHD, 23 °C; (j) LiBr, Li₂CO₃, DMF, 80 °C, 65% (2 steps); (k) AlH₃, THF, 23 °C; then K₂CO₃, CH₃OH, 23 °C, 85%; (l) BiCl₃, CH₃CN, 40°C; then water, 40°C, 73%; (m) N₂H₄, Et₃N, EtOH, 50 °C; (n) I₂, Et₃N, THF; (o) 7-(trimethylstannyl)isoquinoline, Pd(PPh₃)₄, CuCl, LiCl, DMSO, 23 °C, 53% (3 steps); (p) Raney Ni, i-PrOH, H₂O, 50 °C, 25% (50% brsm).
-(trimethylstannyl)isoquinoline. Finally, the trisubstituted olefin in Δ^{16}\text{-cortistatin A} (12) was reduced with Raney Nickel to complete the semi-synthesis of cortistatin A (1).

A couple months later, the Nicolaou–Chen group in Singapore completed the second synthesis of cortistatin A;\(^{33}\) and in 2009, the same group reported the first synthesis of cortistatin J (Scheme 1.2).\(^{26}\) Commencing from a known α-methylene ketone 24 prepared in five steps from Hajo s-Parrish ketone, dihydroxylation, diol protection, and triflation gave intermediate 25, which was elaborated to aldehyde 26 in another five steps. Subsequent acetylene formation and Sonogashira coupling provided alkyne 27, the thio-ketal in which was cleaved and the triple bond hydrogenated, affording aldehyde 28. An impressive oxa-Michael–Aldol–dehydration cascade reaction was subsequently accomplished by heating a solution of 28 with potassium carbonate in dioxane at 125°C to provide cortistatin core structure 29. The C1 ketone was then temporally ketalized and the C17 tert-butyldimethylsilyl ether group was removed and oxidized to give ketone 30. The isoquinoline substituent was incorporated at this stage by converting the C17 ketone to a vinyl triflate and Suzuki–Miyaura coupling with 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline. Selective hydrogenation of the C16,C17 tri-substituted olefin was achieved after deprotection of the C-1 ketal. The resulting ketone 14 underwent Saegusa desaturation and nucleophilic epoxidation to afford keto epoxide 31, which was reduced under Luche conditions to give a 1:1 mixture of diastereomers 32 and 33. 32 was treated with dimethylamine in the presence of titanium tetraisopropoxide to effect nucleophilic epoxide opening to afford cortistatin A (1); while 33 was converted to cortistatin J (9) in three steps: the epoxide was opened.

with dimethylamine in the presence of titanium tetraisopropoxide, the resulting cis-diol product was converted to a thiocarbonate and then eliminated with Corey–Winter’s conditions.

**Scheme 1.2** Nicolaou–Chen’s Synthesis of Cortistatin A and Cortistatin J.

Reagents and conditions: (a) OsO₄, NMO, acetone–H₂O, 73%; (b) (CH₃)₂C(OCH₃)₂, p-TsOH, acetone, 87%; (c) NaHMDS, PhNTf₂, THF, 0 °C; (d) Pd(PPh₃)₄, Et₃N, CO, DMF–CH₂OH, 70 °C, 72% (2 steps); (e) DIBAL-H, PhCH₃, −78 °C, 79%; (f) DMP, NaHCO₃, CH₂Cl₂, 23 °C, 86%; (g) HS(CH₂)₃SH, BF₃•OEt₂, CH₂Cl₂, −78°C, 70%; (h) SO₃•Py, Et₃N, CH₂Cl₂–DMSO, 72%; (i) p-TsN₃, dimethyl-2-oxopropylphosphonate, K₂CO₃, CH₃CN, CH₂OH–THF–CH₃CN, 45% (2 cycles); (j) Pd(PPh₃)₄, CuI, Et₃N, 3-oxocyclohex-1-enyl trifluoromethanesulfonate, DMF, 85%; (k) IBX, DMSO, 0 → 23 °C, 81%; (l) Pd/BaSO₄, H₂, CH₂OH–THF (1:1), 64%; (m) K₂CO₃, dioxane, 125 °C, 52%; (n) TMSO(CH₂)₂OTMS, TMSOTf, CH₂Cl₂, −60 → −10 °C; (o) TBAF, THF, 56% (2 steps); (p) p-TsOH, acetone–H₂O, 88%; (q) TMSOTf, CH₂Cl₂, 23 °C, 50%; (r) KHMDS, THF, −78 °C, then PhNTf₂; (s) 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline, Pd(PPh₃)₄, K₂CO₃, THF, 80 °C, 50% (2 steps); (t) p-TsOH, acetone–H₂O, 88%; (u) Pd/C, H₂, CH₂OH, 23 °C, 50%; (v) TMSOTf, CH₂Cl₂, THF, −78 → 0 °C; (w) IBX•MPO, DMSO, 23 °C, 6 h, 46% (2 steps); (x) t-BuO₂H, DBU, CH₂Cl₂, 0 → 23 °C, 70%; (y) NaBH₄, CeCl₃, CH₂OH, 0 °C, 80% (1:1 mixture of diastereomers 32 and 33); (z) (CH₃)₂NH, Ti(O-i-Pr)₄, THF, 80 °C, 45%; (a') (CH₃)₂NH, THF, 80 °C, 60%; (a’) thiocarbonyl diimidazole, PhCH₃, 110 °C, 81%; (b') P(OEt)₃, 160 °C, 40%.
Scheme 1.3 Shair’s Synthesis of Cortistatin A.

Reagents and conditions: (a) NaH, DMSO, 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 23 °C, 63%; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C; (c) H₂, Pd/C, EtOAc, 23 °C; (d) m-CPBA, NaHCO₃, PhCH₃, −10 °C; then HF, THF–PhCH₃, 0 °C, 66% (4 steps); (e) MEMCl, i-PrNEt₂, 1,2-dichloroethane, 80 °C, 88%; (f) PPTS, acetone–water, 60 °C; (g) NaOCH₃, CH₃OH, 70 °C, 49% (2 steps); (h) SOCl₂, pyridine, CH₂Cl₂, −10 °C; (i) NaHMDS, −78 °C, PhN petroleum, 0 °C; (j) CH₃(O-i-Pr)₂SiCH₂MgCl (37), Pd(PPh₃)₄, THF, 62% (3 steps); (k) CHBr₃, KO⁻t-Bu, hexane, 0 °C; (l) TASF, DMF, 80 °C, 66% (2 steps); (m) TESOCH₂CH=CH-B(pin), Pd(PPh₃)₄, K₂CO₃, THF–H₂O, 80 °C, 84%; (n) K₂OsO₄•2H₂O, (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, CH₃SO₂NH, t-BuOH–H₂O, 0 °C; (o) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 51% (2 steps); (p) HF·Py, THF; DMP, CH₂Cl₂; (q) (CH₃)₂NH, ZnBr₂, CH₃CN, 50 °C, 65% (3 steps); (r) TBAF, THF, 70 °C, 70%; (s) TPAP, NMO, CH₂Cl₂, 100%; (t) K₂CO₃, CH₃OH, 82%; (u) N₂H₄•H₂O, Et₃N, EtOH, 80 °C; Et₃N, I₂, THF; (v) Pd(PPh₃)₄, 7-(trimethylstannyl)isoquinoline, LiCl, CuCl, DMSO, 60 °C, 61% (3 steps); (w) 2,4,6-triisopropylbenzenesulfonylhydrazide, Et₃N, THF, 60 °C, 20%.

In the fall of 2008, the Shair group at Harvard reported the third synthesis of cortistatin A (Scheme 1.3). In the Shair synthesis, known enone 34 was alkylation with 2-(2-bromoethyl)-2-methyl-1,3-dioxolane and then converted to an extended silyl enol ether; subsequent hydrogenation and Rubottom oxidation afforded tertiary alcohol 35. This alcohol was converted to ketone 36 in four steps (including methoxyethoxymethyl ether protection, deketalization, aldol reaction and dehydration), which was further transformed to an extended enol triflate and then cross-coupled with a Grignard reagent.

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37 to give allylsilane 38. Cyclopropane formation with dibromocarbene followed by its opening trigged by tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) furnished vinyl bromide 39. Another palladium catalyzed cross-coupling, then selective Sharpless dihydroxylation and a couple functional group manipulations afforded aldehyde 40. In the subsequent key step, a remarkable tandem aza-Prins-transannular etherification cascade was realized by heating aldehyde 40 with dimethylamine in the presence of zinc bromide, to provide compound 41 with a full cortistatin A ABC-ring skeleton. The C-17 tert-butylidimethylsilyl ether group was then cleaved and the secondary alcohol was oxidized; after deacetylation, the same cortistatinone 23 reported by the Baran group was obtained. The isoquinoline appendage was then introduced by a similar Stille coupling between the 23-derived vinyl iodide and 7-(trimethylstannyl)-isoquinoline to provide Δ16-cortistatin A (12). Finally, diimide reduction of 12 afforded the natural product cortistatin A (1).

In 2011, the Hirama group from Tohoku University finished the total synthesis of cortistatin A and cortistatin J (Scheme 1.4). Starting from enone 34, alkylation, nickel boride reduction and Saegusa reaction provided intermediate 42, which was converted to aldehyde 43 in four straightforward steps. In the subsequent key step, Knoevenagel condensation of 43 with cyclo-hexane-1,3-dione was followed by a tandem 6π-electrocyclization to afford intermediate 44. C6 tert-butylidimethylsilyl ether was then selectively removed and the primary alcohol product was converted to iodide 45. A radical cyclization initiated with triethylborane and oxygen closed the C6,C7 carbon

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bridge, affording the Nicolaou–Chen intermediate 29. 29 was then transformed to ketone 30, and the isoquinoline ring was introduced to C17 ketone of 30 by the addition of an organocerium reagent derived from 1-chloro-7-iodoisoquinoline (46). The addition product 47 underwent radical deoxygenation via its 17-O-thiocarbamate to give intermediate 48 with C1'-chloride dehalogenated in the same operation. Deketalization

**Scheme 1.4** Hirama’s Synthesis of Cortistatin A and Cortistatin J.

**Reagents and conditions:** (a) NaH, TBSOCH₂CH₂I, DMSO–THF, 23 ºC, 53%; (b) NiCl₂•6H₂O, NaBH₄, CH₃OH, −70 ºC, 60%; (c) TMSCl, HN(TMS)₂, NaI, CH₃CN, 23 ºC; (d) Pd(OAc)₂, CH₃CN, 23 ºC, 90% (2 steps); (e) Tf₂O, LDA, THF, −100 → −90 ºC, 95%; (f) Pd(PPh₃)₄, CO, Et₃N, CH₃OH–DMF, 55 ºC, 90%; (g) Dibal–H, PhCH₃, −78 ºC; (h) DMP, NaHCO₃, CH₂Cl₂, 23 ºC, 85% (2 steps); (i) cyclohexene-1,3-dione, piperidine, EtOAc, 23 ºC, 87%, 5:1 dr; (j) HF•Py, THF, 23 ºC; (k) I₂, PPh₃, imidazole, THF, 23 ºC, 87% (2 steps); (l) EtB, (TMS)₂SiH, THF, −78 ºC, 78%. (m) TMSO(CH₂)₂OTMS, TMSOTf, CH₂Cl₂, −60 → −20 ºC; (n) TBAF, THF, 0 ºC; (o) DMP, NaHCO₃, CH₂Cl₂, 23 ºC, 73% (3 steps); (p) n-BuLi, CeCl₃, isoquinoline 46, THF, −78 ºC, 99%; (q) KH, PhNCS, THF, 23 ºC; (r) AIBN, Bu₃SnH, PhCH₃, 90 ºC, 74% (2 steps); (s) TsOH•H₂O, acetone–H₂O, 71%. (t) LDA, Ph(Cl)S=N-t-Bu, THF, −78 ºC, 80%; (u) t-BuO₂H, DBU, CH₂Cl₂, 0 → 23 ºC, 75%; (v) NaBH₄, CeCl₃, CH₃OH, 0 ºC, 51%; (w) (CH₃)₂NH, Yb(OTf)₃, THF, 80 ºC, 48%; (x) (CH₃)₂NH, THF, 23 ºC; (y) LiAlH₄, ether, 0 ºC, 60% (two steps); (z) MsCl, Et₃N, THF, 0 ºC; DBU, 23 ºC, 42%.
and Mukaiyama unsaturation provided enone 49, which was converted to cortistatin A (1) in three steps analog to the Nicolaou–Chen synthesis;\textsuperscript{33} and converted to cortistatin J (9) also in three steps including dimethylamine conjugate addition, LAH reduction, and finally mesylation and elimination of the resulting C1 allylic alcohol.

In the summer of 2011, the Funk group from Pennsylvania State University reported a racemic synthesis of cortistatin J starting from furan 50 (Scheme 1.5).\textsuperscript{37} This furan was first metallated and added conjugatively to enone 51; the resulting enolate intermediate was trapped with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and

\begin{center}
\textbf{Scheme 1.5 Funk’s Synthesis of (±)-Cortistatin J.}
\end{center}

\textbf{Reagents and conditions:} (a) \textit{n}-BuLi; AlMe3; TMSOTf, 51; (b) CH$_3$Li; ICH$_2$CO$_2$CH$_3$, 75% (two steps); (c) NaHMDS, PhNTf$_2$; (d) DIBAL-H, 82% (two steps); (e) PPh$_3$, I$_2$; (f) 54+55; AcOH, H$_2$O, 75%; (g) NaHMDS, TESCl, 94%; (h) PhCH$_3$, 100 °C, quant.; (i) 50 mol% TfOH, CH$_2$Cl$_2$, -78 °C; pyridine, CH$_3$OH, 79%; (j) Pd(PPh$_3$)$_4$, 7-(trimethylstannyl)isoquinoline, LiCl, CuCl, 70%; (k) KO$_2$N=NCO$_2$K, AcOH, 97%; (l) DMSO, (COCl)$_2$, Et$_3$N, 81%; (m) NaH; PhNTf$_2$, 83%; (n) Bu$_3$SnH, Pd(PPh$_3$)$_4$, 70% (o) LiHMDS, HMPA, PhNTf$_2$, 81%; (p) 6N HCl, 81%; (q) (Z)-TMS-CH=CH-BF$_3$K, Cs$_2$CO$_3$, Pd(PPh$_3$)$_4$, 84%; (r) Py:SO$_3$, DMSO, Et$_3$N, 75%; (s) (CH$_3$)$_2$NH·HCl, CH$_3$CN, 60 °C, 90%.

the silyl enol ether product was subsequently converted to primary iodide 53 in a four-step sequence (including alkylation, triflation, DIBAL-H reduction, and iodination). An azaenolate 54 was then alkylated with this iodide, and the resulting alkylation product underwent triethylsilylation formation and thermal retro-cycloaddition to afford intermediate 55. A key [4+3] cycloaddition to construct the cortistatin core oxabicyclo[3.2.1]octene structure was triggered by treating a solution of 55 in dichloromethane with triflic acid (0.5 equiv) at −78°C, affording intermediate 56 in good yield. The isoquinoline moiety was then introduced by Stille cross-coupling with 7-(trimethylstannyl)isoquinoline, and a global diimide reduction afforded tetrahydrofuran 57. Swern oxidation, triflation, and palladium catalyzed triflate reduction with ammonium formate provided enone 58. This enone underwent another triflation, then Suzuki–Miyaura coupling, and a couple functional group manipulations to provide aldehyde 59 with a (Z)-vinyl silane installed. Finally, a solution of aldehyde 59 in acetonitrile was treated with excess dimethylamine hydrochloride at 60°C to effect a stereoselective A-ring closure, affording (±)-cortistatin J (9) as a single diastereomer.

The Sarpong group at Berkeley completed a formal synthesis of racemic cortistatins in 2010 (Scheme 1.6). Starting from aldol condensation between indanone 60 and aldehyde 61, reduction and subsequent elimination afforded indene 62. This indene underwent a platinum dichloride catalyzed enyne cycloisomerization, a methodology previously developed in the Sarpong group, affording diene 63. The C6,C7 disubstituted double bond in 63 was then selectively reduced under diimide reduction conditions to give 64; the remaining tetra-substituted olefin was epoxidized with sodium

bicarbonate neutralized 3-chloroperoxybenzoic acid (mCPBA), and the epoxide product was
eliminatively opened with n-butyllithium at the benzylic position to afford allylic
alcohol 65 (obtained after a couple protection group manipulations). This phenol 65 was
subsequently oxidatively cyclized by exposure to bisacetoxyiodobenzene, a hypervalent
iodine reagent, to provide cortistatin core structure 66. Selective epoxidation of C9,C19
trisubstituted olefin was followed by acidic opening of the epoxide product and then
elimination of the resulting C9 allylic alcohol, affording diene 67. The C2 enone was then
reduced under Luche conditions and temporarily protected; a palladium catalyzed,
ammonium formate promoted reduction and rearrangement provided intermediate 68.
Finally, hydrogenation and isomerization afforded Nicolaou–Chen’s intermediate 29.33

**Scheme 1.6** Sarpong’s Formal Synthesis of (±)-Cortistatins.

**Reagents and conditions:** (a) KOH, EtOH–CH2Cl2, 76%; (b) K-Selectride, THF, −78→23 °C; (c) NaBH4,
CH2OH–CH2Cl2, 0 °C; (d) KH2SO4, PhCH3, 50 °C, 67% (3 steps); (e) PtCl2, PhH, 50 °C, 82%; (f)
TsNHNH2, Et2N, 1,2-DCE, 65 °C, (2 cycles); (g) Na/naphthalene, DME, 23 °C, 77% (2 steps); (h) TESCl,
imidazole, DMF, 23 °C; (i) m-CPBA, NaHCO3, CH2Cl2, 0 °C, 53% (2 steps); (j) n-BuLi, THF, 0 °C; (k)
Phl(OAc)2, CH2Cl2→i-PrOH–TFE, −78 °C, 57% (2 steps). (l) m-CPBA, NaHCO3, CH2Cl2, 0°C; (m) CSA,
CH2Cl2–CH2OH, 0 °C; (n) TFAA, DMAP, DCE-Et3N, 23→60°C , 58% (three steps); (o) NaBH4, CeCl3,
CH2OH, 0 °C ; (p) (Boc)2O, DMAP, DCE, 40 °C, 69% (two steps); (q) Pd(dppf)Cl2, NH4CO2H,
23→60°C; (r) H2 (100 psi), Rh(PPh3)3Cl, PhH; (s) 1% aq HCl, THF, 0→23°C, 77% (three steps).
The Yang-Li group from Peking University also reported a formal synthesis of cortistatins in early 2011 (Scheme 1.7). Enone \textbf{34} was first alkylated with iodide \textbf{69} to provide intermediate \textbf{70}, which was subsequently transformed to alkyne \textbf{71} in five steps. An intramolecular furan Diels–Alder reaction was catalyzed by ethylaluminium dichloride to forge the 7-membered B ring, providing phenol product \textbf{72}. The C14,C15 double bond was then selectively hydrogenated, and a tertiary hydroxyl group was introduced at C5 with modest diastereoselectivity by bisacetoxyiodobenzene promoted oxidative dearomatization of A-ring phenol in the presence of water, affording dienone intermediate \textbf{73}. Finally, sodium acetate triggered oxa-Michael addition, selective reduction of C19 ketone, and subsequent mesylation and elimination of the C19 allylic alcohol product furnished Myers’ intermediate \textbf{74}.

### Scheme 1.7 Yang-Li’s Formal Synthesis of Cortistatins.

![Diagram of Scheme 1.7](image)

**Reagents and conditions:** (a) NaH, \textbf{69}, DMSO, 46%; (b) collidine, Tf\textsubscript{2}O; (c) Pd(OAc)\textsubscript{2}, PPh\textsubscript{3}, CO, CH\textsubscript{3}OH, 76% (two steps); (d) DIBAL-H, –78 °C, 90%; (e) MnO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, 94%; (f) TMSC≡CH, n-BuLi, THF, –78°C, 95%; (g) MnO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, 91%; (h) EtAlCl\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, –78→0 °C, 51%; (i) Pd/BaSO\textsubscript{4}, H\textsubscript{2} (1 atm), 60%; (j) BAIB, CH\textsubscript{3}CN-H\textsubscript{2}O, 60%, \textbf{73}:\textbf{5-epi-73} = 1:1.5; (k) NaOAc·3H\textsubscript{2}O, EtOH, 50°C, 70%; (l) LiBHEt\textsubscript{3}, THF, –78 °C; (m) MsCl, Et\textsubscript{3}N, DMAP, CH\textsubscript{2}Cl\textsubscript{2}; (n) LiBr, Li\textsubscript{2}CO\textsubscript{3}, DMF, 100°C, 28% (three steps).

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Scheme 1.8 Danishefsky’s Approach to Cortistatins via a Sniekus Reaction Cascade.

Reagents and conditions: (a) t-BuLi, 76, Et₂O, −78 °C, then 130 °C, 50%, 80 : C8-epi-80 = 1 : 10; (b) 192→198 °C, 80 : C8-epi-80 = 2.3 : 1; (c) I₂, CH₃OH, 54%; (d) TsCl, Py, DMAP, CH₂Cl₂, 0→23 °C, 95%; (e) TBAF, THF, 70 °C, 94%.

The Danishefsky group developed two different strategies to construct the cortistatin core structure and the approach via a Sniekus reaction initiated cascade is presented here (Scheme 1.8). Lithiated aryl bromide 75 added to aldehyde 76 at −78 °C to form intermediate 77; the crude reaction mixture was then heated to 130 °C to trigger a Sniekus rearrangement; the C19 carbamate of the resulting intermediate 78 was believed to eliminate at this temperature and the resulting o-quinonemethide 79 underwent a tandem 6π-electrocyclization to afford 2H-pyran 80. The C8-epi isomer which dominated in the product mixture, was mostly epimerized to the desired isomer by heating at 192–198 °C. Selective desilylation and tosylation at C6 provided compound 81, which was alkylatively dearomatized by the treatment with tetra-n-butylammonium fluoride in.

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refluxing tetrahydrofuran, affording cortistatin core structure 82. This enone was then elaborated to 83 in a couple of steps, which possessed a fully functionalized cortistatin A ABC-ring system.

The Magnus group developed an efficient approach to (±)-cortistatin BCD rings commencing from Lewis acid promoted addition of 2-methylfuran to enone 51 (Scheme 1.9). The addition product was then converted to aldehyde 84 in a couple of steps. Cyclopropenyllithium 85 added to this aldehyde at −50 °C; upon warming the reaction mixture to 23 °C, a cyclopropene-furan [2+4] cycloaddition proceeded to afford compound 86 as a 1:1 mixture of diastereomers at C10. Hydrogenation of C6,C7 olefin with Adam’s catalyst followed by cyclopropylcarbinyl rearrangement triggered by triflation of the C10 hydroxyl group provided compound 87 in good yield with a cortistatin BCD-ring skeleton.

**Scheme 1.9** Magnus’s Approach to (±)-Cortistatin BCD Rings via Cyclopropene-Furan [2+4] Cycloaddition followed by Cyclopropylcarbinyl Rearrangement.

Reagents and conditions: (a) 85, −50→23 °C, 85%, 1:1 dr at C-10; (b) H₂, PtO₂·H₂O, THF-EtOH, AcOH (cat.), 98%; (c) Tf₂O, DTBMP, CH₂Cl₂ 0→23 °C, 70%.

The Sorensen synthesis started from a [3+2] dipolar cycloaddition of nitrone 88 and α-methylene ketone 24, and the addition product was transformed to oxime 89 in a

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couple of steps (Scheme 1.10). Upon treatment of a solution 89 in trifluoroethanol with bisacetoxyiodobenzene at 23 °C, the phenol underwent oxidative dearomatization to form the C5,C8 oxa-bridge and the oxime was also oxidized to give nitrile oxide 90; when this crude reaction mixture was further heated to 50 °C, an intramolecular [3+2] dipolar cycloaddition proceeded, yielding compound 91 with the cortistatin pentacyclic core structure.

**Scheme 1.10** Sorensen’s Approach to Cortistatin Core Structure via Hypervalent Iodine-Induced Double Annulation.

The Stoltz group approached the pentacyclic cortistatin core structure using a cascade enyne-ene metathesis strategy (Scheme 1.11). Lithiated iodide 92 was added to ketone 93, affording a tertiary alcohol 94 after desilylation. The C5,C8 oxa-bridge was constructed by a magnesium bromide catalyzed S$_{N2}'$ reaction, providing tetrahydrofuran 95 and 96 as a 1:1 mixture of diastereomers at the C5 position. When this mixture was subjected to Grubbs second-generation catalyst, the desired diastereomer 95 underwent the expected enyne-ene metathesis to yield the 14-epi-cortistatin core structure 97, while the undesired diastereomer 96 stopped at the diene stage to afford compound 98.

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Scheme 1.11 Stoltz’s Approach to 14-epi-Cortistatin Core via Enyne-ene Metathesis.

Reagents and conditions: (a) t-BuLi, 93, Et₂O-THF, −78 °C; (b) TBAF, THF, 25 °C, 77% (two steps), 94: 8-epi-94 = 2.2 : 1; (c) DDQ, CH₂Cl₂-H₂O, 25 °C, 75%; (d) Ac₂O, pyridine, CH₂Cl₂, 25 °C, 94%; (e) MgBr₂·Et₂O, 2,6-DTBP, PhH-CH₃CN, 80°C, 79%, 95:96 = 1 : 1; (f) Grubbs-II, CH₂Cl₂, 25 °C, 37% of 97 and 44% of 98.

The Zhai group constructed a racemic cortistatin core structure also starting from furan (Scheme 1.12). The core oxabicyclo[3.2.1]octene structure was constructed by an intermolecular [4+3] cycloaddition of 2,5-disubstituted furan 99 with 1,1,3-trichloroacetone and then zinc-copper mediated dehalogenation to give ketone 100. Following bis-dihydroxylation of the two terminal olefins, hydrogenation of the remaining C6,C7 double bond, and bis-vicinal diol cleavages afforded ketodialdehyde 101. This aldehyde then underwent a double, intramolecular aldol reaction upon treating with potassium carbonate to furnish the cortistatin core structure 102.

Scheme 1.12 Zhai’s Approach to (±)-Cortistatin Core via Double Aldol Reaction.

Reagents and conditions: (a) Cl₂CHCOCH₂Cl, Et₃N, (CF₃)₂CHOH; (b) Zn-Cu, NH₄Cl, CH₃OH, 46%; (c) OsO₄, NMO, acetone, H₂O; (d) H₂, Pd/C, EtOH; (e) NaIO₄, acetone, H₂O, 68% (three steps); (f) K₂CO₃, CH₃OH, 23 °C, 82%.

The Kobayashi group (the isolation chemists) also developed several different strategies to construct the cortistatin core structure\textsuperscript{28,30b} and their intramolecular Heck approach is described here (Scheme 1.13).\textsuperscript{46} In this approach, the Hajos–Parrish ketone derived enone 103 was alkylated with primary iodide 104, and in a couple steps transformed to triflate 105. Intramolecular 7-endo Heck reaction was catalyzed by tris(dibenzylidene-acetone)dipalladium(0) and the ligand 1,3-bis(diphenylphosphino)-propane (dppp) in the presence of cesium acetate and tetra-n-butylammoniumacetate to afford intermediate 106. After C5 desilyation, C10 deacetylation and oxidation, the oxabridge was then constructed by acid catalyzed, intramolecular oxa-Michael addition of the C5 tertiary alcohol to enone at C8 position. Finally, diene 107 was obtained after sodium borohydride reduction of C10 ketone and then Burgess elimination of the resulting secondary alcohol.

**Scheme 1.13** Kobayashi’s Approach to Cortistatin Core via Intramolecular Heck Reaction.

![Chemical reaction diagram](image)

**Reagents and conditions:** (a) Pd\(_2\)(dba)\(_3\), dppp, CsOAc, \(n\)-Bu\(_4\)NOAc, DMF, 70 °C, 56%; (b) TBAF, THF, 0 °C, 88%; (c) DIBAL, CH\(_2\)Cl\(_2\), −78 °C, 94%; (c) DMP, NaHCO\(_3\), CH\(_2\)Cl\(_2\), 0 °C, 81%; (e) CSA, THF, 0 °C, 60%; (f) NaBH\(_4\), CH\(_3\)OH, 0 °C, 83%; (g) Burgess’ reagent, toluene, 85 °C, 62%.

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A Divergent Synthetic Strategy towards the Cortistatins

In our synthetic planning, we wished to develop a general approach that would allow us to access not only different members of cortistatin natural products, but also a diverse array of cortistatin analogs and biological probes. We envisioned that this goal could be achieved by efficient preparation of a suitable key intermediate which could be easily diversified to different cortistatin precursors, and then installing the isoquinoline moiety at the final stage in order to maximize the possibility of diversification on this important ring substituent (see SAR data for details).

With these principles in mind, we believed that the isoquinoline substituent could be introduced to different C17-keto cortistatin precursors under suitable conditions to afford the final products (Figure 1.4). In order to access these different cortistatin precursors, we identified azido alcohol as an appropriate candidate for the key intermediate: it possesses the pentacyclic core structure of cortistatins; the azido group at C3 provides a versatile handle for the introduction of the dimethylamino group in the natural cortistatins, as well as other nitrogen-containing functional groups in analog preparation; in addition, the C2 allylic alcohol and northern diene moiety should be readily transformed to obtain diverse cortistatin ABC-ring substitution patterns; to meet the requirements as a key intermediate, what we need would be to develop a robust and scalable route to prepare this azido alcohol.

Figure 1.4 Syntheses of Cortistatins by Late Stage Introduction of Isoquinoline Moiety to 17-Keto Cortistatin Precursors Derived from a Common Key Intermediate 112.

Retrosynthetically, this azido alcohol 112 could be derived from a cyclohexadienone 74 by selectively functionalizing the A-ring enone moiety (Figure 1.5). This cortistatin core structure 74 could be further simplified to phenol 113 by installing the C5,C8 oxa-bridge via oxidative dearomatization, a strategy independently conceived and previously demonstrated by Sarpong and coworkers, as well as others.30f,38,42 Phenol 113 could be prepared from diene 114, and the seven-membered B-ring in 114 could be constructed from triene 115 by ring-closing metathesis. Triene 115 could be in turn assembled from a benzylzinc reagent 116 and an enol triflate 117 via Negishi cross-coupling. Benzylzinc reagent 116 could be obtained from a known phenyl iodide 118,48

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while the enol triflate 117 could be synthesized from a known α-methylene ketone 24 derived from Hajos-Parrish ketone.49,50

Figure 1.5 Retrosynthetic Analysis of Key Intermediate 112.

![Figure 1.5](image)

In this thesis, Chapter 2 presents an efficient synthesis of key intermediate 112 and diversification of this azido alcohol to different cortistatin precursors 108, 109, 110, and 111, representing each of the four ABC-ring substitution patterns in natural cortistatins; Chapter 3 details the conversion of these cortistatin 17-keto precursors to different cortistatin natural products as well as unnatural cortistatin analogs using a generally applicable isoquinoline-addition-radical-deoxygenation sequence; and Chapter 4 describes a versatile methodology to synthesize a diverse array of substituted isoquinolines, allowing the preparation of cortistatin analogs with isoquinoline modifications.

50 This α-methylene ketone 24 was also used by the Nicolaou group and the Sorensen group independently in the synthesis of cortistatins: see: Ref 33 and Ref 43.
Chapter 2

Synthesis of Cortistatin Precursors from a Common Key Intermediate
Introduction

As outlined in Chapter 1, this chapter presents an efficient synthesis of the azido alcohol 112 as the key intermediate on gram quantities starting from A-ring precursor 118 and CD-ring precursor 24 (Figure 2.1). This key intermediate was subsequently converted to different cortistatin 17-keto precursors 108, 109, 110, and 111, representing all four natural cortistatin ABC-ring substitution patterns.

Figure 2.1 Converting Key Intermediate 112 to Different Cortistatin Precursors.
Synthesis of the Key Intermediate Azido Alcohol

Graduate student Dr. Alec Flyer developed an efficient synthesis of the cortistatin core structure 74 (Scheme 2.1).\(^1\) I was able to further optimize and scale up this route to produce this cyclohexadienone on gram quantities. Benzyl bromide 119 was prepared in amounts up to 47 g by a straightforward five-step sequence [including methylation, phenol protection, Negishi cross-coupling, diisobutylaluminium hydride (DIBAL-H) reduction, and bromination] from a known phenyl iodide 118,\(^2\) and then transformed to the \(\alpha\)-vinyl benzylzinc reagent 116 by magnesium insertion and transmetallation with zinc chloride. Meanwhile, a known \(\alpha\)-methylene ketone 24\(^3,4\) was subjected to a phosphoniosilylation-Wittig reaction sequence to afford the \(\alpha\)-vinyl triethylsilyl enol ether 120,\(^5\) which was then converted to enol triflate coupling partner 117 on a 15-g scale by using Corey’s triflation conditions.\(^6\)

Coupling of the enol triflate 117 with the benzylzinc reagent 116 was achieved in the presence of tris(dibenzylideneacetone)dipalladium (0.045 equiv) and the ligand 2-dicyclohexylphosphino-2',6'-dimethoxy-biphenyl (S-Phos, 0.18 equiv) in a mixture of \(N\)-methylpyrrolidone, tetrahydrofuran, and ether (the latter two from the preparation of the

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\(^2\) Iodide 118 was prepared in one step from commercial available 2-amino-5-hydroxylbenzoic acid as reported: Moss, R. A.; Alwis, K. W.; Shin, J. S. *J. Am. Chem. Soc.* 1984, 106, 2651–2655.


Scheme 2.1 Synthesis of Cortistatin Core Structure 74.

benzylzinc reagent 116) at 70 °C to afford triene 115 in 70% yield on a 16-g scale.\(^7\)

Warming the triene product with the second-generation Grubbs catalyst (0.025 equiv) in dichloromethane at 45 °C furnished the tetracyclic diene 114;\(^8\) the crude reaction mixture was diluted with dichloromethane, cooled in an ice-bath and treated with a solution of dimethylidioxirane (DMDO) in acetone,\(^9\) which led to a stereoselective epoxidation of the tetrasubstituted alkene, providing a tetracyclic diene monoepoxide 121. Without purification, this epoxide was hydrogenated in benzene under 500 psi hydrogen in the

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\(^9\) Murray, R. W.; Singh, M. *Organic Syntheses*; Wiley & Sons: New York, 1997; Vol. 74, pp 91–100. The procedure was slightly modified and scaled up to produce DMDO solution in acetone (typically 0.06 M) on liter-scale.
presence of Wilkinson’s catalyst (0.15 equiv) to afford epoxide 122. The latter product then underwent selective eliminative opening at C19 benzylic position with lithium diethylamide,10 furnishing the conjugated allylic alcohol 123 in 50% yield over three steps. Selective removal of the phenolic triisopropylsilyl protective group with tetra-n-butylammonium fluoride (TBAF) at 0 °C was followed by oxidative cyclization of the resulting phenol 113 with [bis(trifluoroacetoxy)-iodo]benzene in a mixture of dichloromethane and hexafluoroisopropanol,11 providing the cyclohexadienone core structure 74 in 50% yield on a 2-g scale.12 By applying this optimized procedure, over 10 g of the cyclohexadienone 74 have been prepared to date.

With gram-quantities of cyclohexadienone 74 in hand, the next stage was to functionalize the A ring to prepare the key intermediate 112. It was found that the disubstituted C3,C4 double bond of 74 could be selectively hydrogenated under 500 psi hydrogen in the presence of Wilkinson’s catalyst (0.1 equiv) to provide mono-enone 124 in 80% yield (Scheme 2.2). This enone was converted to an extended silyl enol ether 126 by treating with triethylsilyl trifluoromethanesulfonate (1.5 equiv) in the presence of 2,6-lutidine (2 equiv), which was brominated in the same pot with N-bromosuccinimide (NBS, 2 equiv) to afford keto-bromide 125 as a single diastereomer in 75% yield. The exclusive axial bromination selectivity was likely due to a favorable chair-like conformation rather than a twisted-boat-like conformation in the transition state.13

Scheme 2.2 Synthesis of Keto Bromide 74 by Hydrogenation and Bromination.

The knowledge learned in the two-step synthesis of keto bromide 125 informed a more efficient, one-pot hydrosilylation-bromination sequence (Scheme 2.3). After extensive experimentation, it was found that heating cyclohexadienone 74 with triethylsilane (2 equiv) in the presence of Wilkinson’s catalyst (0.05 equiv) in toluene at 50 °C provided the same extended triethylsilyl enol ether intermediate 126;\(^\text{14}\) without isolation, pyridine was added as a co-solvent (14% by volume) followed by N-bromosuccinimide (NBS, 2 equiv), affording the (3R)-keto bromide 125, again as a single diastereomer, in 70% yield. In the absence of pyridine, or with lesser quantities of pyridine,\(^\text{15}\) the bromination reaction was much less stereoselective, which suggested that Wilkinson’s catalyst might not be innocent during the bromination.

Scheme 2.3 Synthesis of Keto Bromide 125 by a One-pot Hydrosilylation-Bromination.


The keto bromide in 125 was subsequently displaced to introduce a C3 azide as a nitrogen-containing handle. However, when 125 was treated with excess sodium azide (10 equiv) in N,N-dimethylformamide at room temperature for 12 h, an unexpected keto enamine product 127 was isolated as the major product (Scheme 2.4). Mechanistically, we speculated that after the initial S_N2 substitution, the α-proton of the keto azide 128 could be deprotonated by the basic azide anion to afford intermediate 129; a molecule of nitrogen was then released and the resulting imine 130 was isomerized to afford the more stable keto enamine 127.\(^{17,18}\)

**Scheme 2.4 Unexpected Formation of Keto Enamine 127 from Keto Bromide 125.**

The problem was solved by using a milder organic azide, tetramethylguanidinium azide (TMGA, 2 equiv)\(^{19,20}\) which is soluble in a number of organic solvents, and the reaction could be conducted in a much less polar solvent system (a mixture of 2:1

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\(^{16}\)** When 1 equiv of sodium azide was used in the same reaction condition for 12 h, an approximately 1:1:1 mixture of starting keto bromide 125, keto enamine 12, and desired keto azide 125 was observed.


\(^{18}\)** In a recent report, Danishefsky and co-workers also observed a similar reaction in their cortistatin synthesis, see: Wang, Z.; Dai, M. J.; Park, P. K.; Danishefsky, S. J. *Tetrahedron* 2011, 67, 10249–10260.


\(^{20}\)** For a review article on the use of TMGA, see: Błaszczyk, R. *Synlett* 2008, 299–300.
acetonitrile and tetrahydrofuran), which we believed to help suppressing the formation of the undesired keto enamine side product. In the optimal conditions, the displacement proceeded within 5 h at room temperature with clean inversion of C3-stereochemistry, providing desired (3S)-α-azido ketone 131 as a yellow solid, with less than 5% of keto enamine 127 observed.

Scheme 2.5 Synthesis of Keto Azide 131 with Tetramethylguanidinium Azide (TMGA).

Without purification, this azido ketone 131 was directly reduced to give the key intermediate azido alcohol 112 (Scheme 2.6). In order to achieve high diastereoselectivity, a number of different conditions were screened. Metal hydride reductions gave modest selectivity in favor of the desired (2S)-alcohol (entries 1–3); (S)-Corey-Bakshi-Shibata (CBS) catalyst (0.2 equiv) provided mostly (2R)-alcohol (entry 4), while (R)-CBS with borane dimethyl sulfide complex catalyst afforded almost exclusively (2S)-alcohol (>20:1 dr, entry 5).21 This selectivity is in agreement with Corey’s model if considering the azide side as the large group and the diene side as the small group.21 Despite the great selectivity, reduction by employing borane dimethyl sulfide complex gave only modest yield, most likely due to competing hydroboration on the diene moiety during the transformation. Thus, a more hindered borane source, catecholborane (2 equiv) was used

at a lower temperature (–40 ºC) in the presence of (R)-CBS catalyst (0.2 equiv) and an additive tetramethylguanidine (1 equiv), and the yield was improved to 85% over two steps with a slightly diminished diastereoselectivity (15:1 dr, entry 7). Addition of tetramethylguanidine was found to be beneficial for the reproducibility of the reaction (entry 6); a similar phenomena was observed by Corey and coworkers by using N,N'-diethylaniline as an additive in their catecholborane mediated CBS reduction. With this optimized sequence (Scheme 2.7), the key intermediate 112 was prepared on 1.0-g batches, and over 3 g of this azido alcohol has been produced to date.

Scheme 2.7 Optimized Synthesis of Key Intermediate 112 from Cyclohexadienone 74.

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Synthesis of Cortistatin J, Cortistatin K, and Cortistatin L Precursors

With gram-quantities of the key intermediate 112 in hand, the next step was to convert it to different cortistatin 17-keto precursors 108, 109, 110 and 111 (Figure 2.1). In cortistatin J, a triene is present along the northern edge of the ABC-ring (Scheme 2.8). The azide was first reduced under Staudinger reaction conditions with excess trimethylphospine (5 equiv) in a mixture of tetrahydrofuran and 1N aqueous sodium hydroxide solution (4:1) to provide an amino alcohol 132;\(^{23}\) without isolation, this amine intermediate was reductively (di)aminated with a large excess of sodium formalin and cyanoborohydride under slightly acidic condition to afford dimethylamino alcohol 133 in 85% yield. When this amino-alcohol product was treated with concentrated hydrochloride acid in chloroform at 23 ºC, a 1,6-elimination reaction took place cleanly and the C17 tert-butyldemethylsilyl ether was also cleaved at the same time, giving triene 134 with a cortistatin J skeleton in good yield. Finally, the resulting C17 alcohol was

Scheme 2.8 Synthesis of a Cortistatin J Precursor 109.

\(^{23}\) Aqueous sodium hydroxide solution was found to be necessary for the Staudinger reduction; using water instead led to no desired product.
oxidized with Dess–Martin periodinane\textsuperscript{24} to provide a 17-keto cortistatin J precursor \textbf{109} in 90\% yield (three steps from key intermediate \textbf{112} in 65\% overall yield).

Interestingly, it was found that amino alcohol \textbf{132} also underwent a facile 1,6-elemination upon mesylation in the presence of triethylamine to give triene \textbf{135} in good yields (Scheme 2.9), which served as a good evidence for the biosynthetic origins of cortistatin J.\textsuperscript{1,25} Meanwhile, my coworker, Dr. Ge Zou found that treating the key intermediate \textbf{112} directly with hydrofluoric acid also led to a 1,6-elemination-desilylation product \textbf{136}, which was used in the synthesis of a cortistatin J-based affinity probe (see Chapter 3 for details).

\textbf{Scheme 2.9} Base and Acid Induced 1,6-Elemination to Give Cortistatin J Frameworks.

In the synthesis of a cortistatin K precursor \textbf{110}, the C2 allylic alcohol needs to be removed (Scheme 2.10). Key intermediate \textbf{112} was converted to dimethylamino alcohol \textbf{133} via the same Staudinger-reductive-(di)amination sequence as described in the cortistatin J series. Initial attempts to remove the hydroxyl group under radical

deoxygenation,\textsuperscript{26} ionic hydrogenation,\textsuperscript{27} or nickel boride reduction conditions\textsuperscript{28} were not successful, thus reduction via palladium $\pi$-allyl complex was next pursued. After acetylation of C2 alcohol with excess acetic anhydride in the presence of scandium triflate (0.003 equiv),\textsuperscript{29} regioselective reductive cleavage of the allylic C-O bond of acetate 137 was achieved by employing tetrakis(triphenylphosphine)palladium (0.2 equiv) and excess lithium borohydride (2 equiv) at 23 °C,\textsuperscript{30} producing an unexpected dimethylamino-borane complex 138 as a non-polar, chromatography-stable white solid. Decomplexation was achieved in the same pot by using a known protocol with catalytic amount of Raney nickel in methanol,\textsuperscript{31} affording the free amine 139, also as a white solid, in excellent yield. Subsequently, silyl ether cleavage with tetra-$n$-butylammonium fluoride (TBAF) and Dess–Martin periodinane oxidation completed the route to the cortistatin K precursor 110 (five steps from key intermediate 112 in 54% overall yield).

\textbf{Scheme 2.10} Synthesis of a Cortistatin K Precursor 110.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_2.10.png}
\end{figure}

\begin{itemize}
\item \textsuperscript{26} For a general review of radical deoxygenation, see: Hartwig, W. \textit{Tetrahedron} \textbf{1983}, \textit{39}, 2609–2645.
\end{itemize}
In the synthesis of a cortistatin L precursor \textbf{111} (in corporation with Dr. Alec Flyer, Scheme 2.11), hydrofluoric acid promoted C17 desilylation of \textbf{112} was followed by selective protection of its less hindered C2 hydroxyl group by using a combination of \textit{tert}-butyldimethylsilyl chloride and 1,8-diaza-bicycloundec-7-ene (DBU) in tetrahydrofuran\textsuperscript{32} to provide intermediate \textbf{140} in 78\% yield over two steps. The C3 azide group was then reduced to amine. However, standard Staudinger conditions proved to be slow and low-yielding, presumably due to the bulk of the adjacent \textit{tert}-butyldimethylsilyl ether. After much experimentation, a novel procedure was developed, in which azide \textbf{140} was first stirred with excess anhydrous trimethylphosphine (5 equiv) for 20 h to allow its complete conversion to an iminophosphorane intermediate \textbf{141}; then formalin was added to react with \textbf{141} in an \textit{aza}-Wittig manner;\textsuperscript{33} and the resulting imine \textbf{142} was reductive (di)aminated with excess sodium cyanoborohydride in the presence of formalin under acidic conditions, furnishing dimethylamine \textbf{143} in 90\% yield. Finally, the C17 hydroxyl group of \textbf{143} was oxidized with Dess–Martin periodinane to afford cortistatin L precursor \textbf{111} (four steps from key intermediate \textbf{112} in 67\% overall yield).

\textbf{Scheme 2.11} Synthesis of a Cortistatin L Precursor \textbf{112}.


\textsuperscript{33} Treatment of the iminophosphorane \textbf{141} with water led to low yield of the desired product.
A Formal Synthesis of Cortistatin A and Synthesis of a Cortistatin A Precursor

Dr. Alec Flyer observed that treating diene 144 (prepared in two steps from keto bromide 125) with dimethyldioxirane (DMDO) afforded a highly sensitive epoxide 145 as the primary product, which upon standing in benzene solution underwent spontaneous 1,4-eliminative opening to form dienyl alcohol 146 (Scheme 2.12).

Scheme 2.12 A Formal Synthesis of a Cortistatin A.

From 146, a three-step sequence was developed to synthesize Shair’s intermediate 41. The C-3 secondary bromide in 146 was displaced with a large excess sodium azide (50 equiv) in a 4:1 mixture of N,N-dimethylformamide and pH=7 aqueous potassium phosphate buffer solution at 100 ºC, in which the pH=7 buffer was found to significantly reduce the amount of the bromide elimination side product; the C-2 triethylsilyl ether was also cleaved in the same operation, affording azido trans-diol 147 in 60% yield. Subsequently, a Staudinger-reductive-(di)amination sequence similar to the one used in

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the cortistatins J and K series afforded dimethylamino trans-diol 148 in 80% yield, which was bis-acetylated with excess acetic anhydride (10 equiv) and 4-dimethylaminopyridine (DMAP, 2 equiv) in pyridine as a solvent to provide the Shair’s intermediate 41 in modest yield.

Despite the successful preparation of acetate 41, the lengthy and low-yielding sequence prevented us from large-scale production of the cortistatin A precursor. Therefore, a more efficient route was developed (Scheme 2.13). Dr. Alec Flyer was able to convert key intermediate 112 to azido trans-diol 153 in six steps. The C2 hydroxyl group of key intermediate 112 was temporarily protected as a chloroacetate, and C17 tert-butylidimethylsilyl ether was cleavage with hydrofluoric acid at 0 ºC to provide intermediate 149 in 80% yield over two steps. This C17 alcohol was oxidized with Dess-Martin periodinane, and in the same pot, the C2 chloroacetate was removed by addition of methanol and potassium carbonate, to afford ketone 150 in 85% yield. Addition of N-bromosuccinimide (1.02 equiv) to a solution of 150 in a 3:1 mixture of acetonitrile and methanol led to a stereoselective, trans-diaxial 1,4-bromoetherification of the conjugated diene to provide C1 axial, allylic bromide product 151.35 Without purification, this bromide was displaced with potassium superoxide in the presence of 18-crown-6,36 affording trans-diol methyl ether 152 in 41% yield over two steps. The C9 axial methyl ether in 152 then underwent 1,2-elimination by exposure to a mixture of scandium triflate (0.03 equiv) and excess trifluoroacetic acid (9.4 equiv) in dioxane, furnishing azido trans-diol 153.

The azido diol 153 was subsequently transformed to a cortistatin A precursor 108.

A previously described Staudinger-reductive-(di)amination sequence in which the azide 153 was first reduced by exposure to excess trimethylphospine (5 equiv) in a 2:1 mixture of tetrahydrofuran and 1N aqueous sodium hydroxide solution, then (di)aminated in the same pot with a large excess of sodium cyanoborohydride and formalin under slightly acidic environment afforded dimethylamino diol 23. The two hydroxyl groups of 23 were subsequently protected with chlorotriethylsilane (6 equiv) in the presence of triethylamine (12 equiv) and 4-dimethylaminopyridine (DMAP, 2 equiv) in N,N-dimethylformamide, providing a protected 17-keto cortistatin A precursor 108 in 60% yield over three steps on a 75-mg scale (8 steps from key intermediate 112 with 17% overall yield).
Conclusion

In summary, we have developed a robust route to produce the key intermediate azido alchol 112 on gram scale by an efficient assembly of a readily available benzyl zinc reagent 116 and an enol triflate reagent 117 in eight steps (including Negishi cross-coupling, Ring-closing-metathesis-then-epoxidation, hydrogenation, epoxide-opening, oxidative-dearomatization, hydrosilylation-bromination, nucleophilic-displacement, and CBS-reduction) (Figure 2.2). This key intermediate was subsequently transformed to cortistatin J precursor 109, cortistatin K precursor 110, cortistatin L precursor 111, and cortistatin A precursor 108 in three to eight steps. These precursors represent each of the four natural cortistatin ABC-ring substitution patterns, which were elaborated to final cortistatin natural products as described in Chapter 3.

Figure 2.2 Summary of the Syntheses of Cortistatin Precursors from Key Intermediate 112.
Experimental Section

**General Experimental Procedures.** All reactions were performed in round-bottomed flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM) or acidic ethanolic \( p \)-anisaldehyde solution (\( p \)-anisaldehyde) then briefly heated on a hot plate. Flash-column chromatography was performed as described by Still et al.,\(^37\) employing silica gel (60 Å, 32–63 μM, standard grade, Dynamic Adsorbents, Inc.).

**Materials.** Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran, dichloromethane, benzene, toluene, dioxane, and ether were purified by the method of Pangborn et al.\(^38\) \( N \)-Bromosuccinimide was recrystallized from water. The molarity of \( n \)-butyllithium solutions was determined by titration against a standard solution of diphenylacetic acid in tetrahydrofuran (average of three determinations).\(^39\)


**Instrumentation.** Proton magnetic resonance ($^1$H NMR) spectra were recorded on Varian INOVA 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent (CHCl₃, δ 7.26; C₆D₅H, δ 7.15). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, and coupling constant (J) in Hertz. Carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded on Varian INOVA 500 (126 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent (CDCl₃, δ 77.0; C₆D₆, δ 128.0). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer and were referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm⁻¹), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with 154).*
Triene 115.

Note: Magnesium turnings used in this procedure were washed sequentially with 1 N aqueous hydrochloric acid solution (2 × 10 mL), 0.1 N aqueous hydrochloric acid solution (10 mL), water (6 × 10 mL), ethanol (3 × 10 mL), then ether (3 × 10 mL). The washed turnings were dried under high vacuum for 12 h prior to use.

To a flame-dried, 250-mL flask fitted with a reflux condenser and a stirring bar were added magnesium turnings (14.3 g, 587 mmol, 15 equiv) followed by ether (50 mL). The reaction flask was placed in a water bath at 23 ºC. 1,2-dibromoethane (4.05 mL, 47.0 mmol, 1.2 equiv) was added dropwise over a period of 10 min. After 30 min, visible gas evolution had ceased, and a solution of benzyl bromide \( \text{119} \) (17.4 g, 47.0 mmol, 1.2 equiv) in ether (30 mL) was added. After 30 min, the dark green reaction mixture was transferred via cannula to a flask containing a solution of zinc chloride (6.41 g, 47.0 mmol, 1.2 equiv) in tetrahydrofuran (60 mL). The transfer was quantitated with tetrahydrofuran (2 × 10 mL). The resulting cloudy white mixture was allowed to stir at 23 ºC for 40 min. To a separate flame-dried, 1-L flask was added enol triflate \( \text{117} \) (17.3 g, 39.2 mmol, 1 equiv)\(^\text{40}\) and \( N \)-methyl-2-pyrrolidinone (160 mL). The resulting solution was degassed by sparging for 20 min with a slow stream of argon gas through a 20-gauge

\(^{40}\) Used as a 10:1 mixture of diastereomers (epimeric at C14) carried from \( \alpha \)-methylene ketone \( \text{24} \); the major diastereomer is depicted in the equation above. The minor diastereomer was separated after the Negishi coupling.
stainless steel needle. Tris(dibenzylideneacetone)dipalladium (1.62 g, 1.76 mmol, 0.045 equiv) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (2.90 g, 7.05 mmol, 0.18 equiv) were added in sequence. After 10 min, the organozinc reagent prepared in the paragraph above was transferred to the reaction flask via cannula. The resulting cloudy orange suspension was sparged for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle. The flask was capped with a glass stopper under argon and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 70 ºC. After 20 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was partitioned between aqueous hydrochloric acid solution (1.0 N, 400 mL) and ether (1.5 L). The layers were separated. The aqueous layer was extracted with ether (2 × 250 mL). The organic layers were combined. The combined solution was washed sequentially with saturated aqueous sodium bicarbonate solution (400 mL), water (400 mL), then saturated aqueous sodium chloride solution (400 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through silica (hexanes initially, grading to 10:1 hexanes–ether) and the filtrate was concentrated. The residue was purified by flash-column chromatography (hexanes initially, grading to 20:1 hexanes–ether) to furnish a single diastereomer of coupling product 115 as a pale yellow oil (16.0 g, 70%).

**1H NMR:**

(500 MHz, CDCl₃)

| 7.35 (dd, 1H, J = 8.3, 2.5 Hz), 6.89 (dd, 1H, J = 17.3, 11.0 Hz), 6.70 (dd, 1H, J = 8.5, 2.7 Hz), 6.61 (d, 1H, J = 2.4 Hz), 6.45 (dd, 1H, J = 17.6, 11.2 Hz), 5.51 (dd, 1H, |
$J = 17.6, 1.5 \text{ Hz}, 5.15 \text{ (dd, 1H, } J = 11.2, 1.5 \text{ Hz)}, 5.09–
5.01 \text{ (m, 2H), 3.66 \text{ (app t, 1H, } J = 8.1 \text{ Hz), 3.54 \text{ (d, 1H, } J
= 15.7 \text{ Hz), 3.42 \text{ (d, 1H, } J = 15.6 \text{ Hz), 2.31–2.23 \text{ (m, 1H)},
2.08–1.96 \text{ (m, 3H), 1.94–1.85 \text{ (m, 4H), 1.69 \text{ (ddd, 1H, } J = 12.5, 6.3,
1.7 \text{ Hz), 1.59–1.52 \text{ (m, 1H), 1.49 \text{ (dd, 1H, } J = 12.2, 5.4 \text{ Hz), 1.28–1.16
\text{ (m, 4H), 1.07 \text{ (d, 18H, } J = 7.3 \text{ Hz), 0.87 \text{ (s, 9H), 0.74 \text{ (s, 3H), 0.01 \text{ (s,}
3H), 0.01 \text{ (s, 3H).}}}$

$^{13}\text{C NMR :}$

(126 MHz, CDCl$_3$)

155.9, 139.2, 134.5, 134.2, 133.1, 132.9, 130.0, 126.6,
119.6, 117.9, 115.1, 113.3, 80.2, 44.8, 43.5, 35.8, 33.7,
31.5, 29.1, 25.9, 24.5, 18.1, 18.0, 12.7, 11.1, −4.5, −4.8;

FTIR (neat), cm$^{-1}$ 2945 (m), 2891 (m), 1603 (m), 1491
(m), 1258 (s).

FTIR, cm$^{-1}$:

(Thin film) 2945 (m), 2891 (m), 1603 (m), 1491 (m), 1258 (s).

HRMS: Calcd for (C$_{36}$H$_{60}$O$_2$Si$_2$+H)$^+$ 581.4205,

(ESI) Found 581.4183.

TLC R$_f$ = 0.90 (UV, p-anisaldehyde)

(10:1 hexanes–ethyl acetate)
Allylic Alcohol 123.

Note: Dichloromethane used in this procedure was degassed just prior to use by sparging for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle.

To a flame-dried, 250-mL flask fitted with a reflux condenser and a stirring bar were added sequentially coupling product 115 (11.2 g, 19.2 mmol, 1 equiv), dichloromethane (96 mL), and the 2nd generation Grubbs catalyst (407 mg, 0.480 mmol, 0.025 equiv). The reaction flask was placed in an oil bath preheated to 40 ºC. After 5 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was transferred to a 3-L flask and dichloromethane (1.2 L) was added. The reaction flask was placed in an ice bath, and a solution of dimethyldioxirane in acetone (0.060 M, 480 mL, 28.8 mmol, 1.5 equiv) was then added. After 1 h, hexanes (700 mL) were added and the diluted product solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The black oily residue (vinyl epoxide 121) was transformed in the following step directly without purification.

Benzene (5 mL) was added to the oily residue prepared above and volatiles were removed in vacuo through a 16-gauge needle in order to effect azeotropic drying. A
second portion of benzene (5 mL) was added, and the volatiles were again removed. Benzene (64 mL) was added to the concentrate. To the resulting solution was added sodium bicarbonate (2.42 g, 28.8 mmol, 1.5 equiv), followed by Wilkinson’s catalyst (2.67 g, 2.88 mmol, 0.15 equiv). The reaction flask was placed in a hydrogenation vessel and the vessel was pressurized to 500 psi with hydrogen. The reaction mixture was stirred vigorously. After 20 h, the pressure was released. Solids were removed by filtration through a pad of Celite, washing with ethyl acetate (3 × 30 mL). The filtrates were combined and the combined organic solution was concentrated. The residue was purified by flash-column chromatography on triethylamine-deactivated silica gel (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate) to furnish epoxide 122 as a yellow oil (7.67 g, >80% purity by 1H NMR analysis).

A solution of n-butyllithium in hexanes (2.50 M, 10.7 mL, 26.8 mmol, 2 equiv) was added dropwise to a solution of diethylamine (3.48 mL, 33.6 mmol, 2.5 equiv) in tetrahydrofuran (60 mL) at −78 °C. After 15 min, the cooling bath was exchanged for an ice bath and the reaction flask was allowed to warm to 0 °C. After 15 min, the ice-cold solution was transferred by cannula to a solution of epoxide 122 (7.67 g, 13.4 mmol, 1 equiv) in tetrahydrofuran (200 mL) cooled to −15 °C in an ice-salt bath. After 20 min, saturated aqueous sodium bicarbonate solution (10 mL) was added. The product solution was concentrated to remove the bulk of solvent. The concentrate was partitioned between water (100 mL) and 1:1 ether–hexanes (300 mL). The layers were separated. The aqueous layer was extracted with ether (2 × 50 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The dried
solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on triethylamine-deactivated silica gel (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate) to provide allylic alcohol 123 as a pale yellow foam (5.37 g, 50% three).

\[ \text{1H NMR:} \]

\[
(500 \text{ MHz, CDCl}_3) \quad 7.00 \text{ (d, 1H, } J = 8.0 \text{ Hz)}, 6.71 \text{ (d, 1H, } J = 2.5 \text{ Hz)}, 6.65
\]

\[
\text{(dd, 1H, } J = 8.0, 2.5 \text{ Hz)}, 6.31 \text{ (s, 1H)}, 3.66 \text{ (app t, 1H, } J = 8.6 \text{ Hz)}, 2.84–2.68 \text{ (m, 3H)}, 2.44–2.35 \text{ (m, 1H)}, 2.19–2.11
\]

\[
\text{(m, 1H), 2.07 (s, 1H), 2.04–1.96 (m, 2H), 1.96–1.89 (m, 1H), 1.70–1.59 (m, 3H), 1.58–1.50 (m, 1H), 1.48–1.38}
\]

\[
\text{(m, 1H), 1.29–1.19 (m, 3H), 1.09 (d, 18H, } J = 7.6 \text{ Hz), 0.87 (s, 9H), 0.73 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H).}
\]

\[ \text{13C NMR:} \]

\[
(126 \text{ MHz, CDCl}_3) \quad 154.4, 145.7, 137.4, 133.7, 129.8, 127.4, 121.8, 118.2,
\]

\[
82.5, 74.9, 52.8, 42.6, 39.4, 36.3, 31.2, 30.8, 29.6, 25.8,
\]

\[
19.9, 18.0, 17.9, 13.8, 12.6, -4.4, -4.8.
\]

\[ \text{FTIR, cm}^{-1}: \quad \text{(thin film)} \quad 3414 \text{ (br), 2949 (s), 2866 (m), 1462 (m), 1281 (s).}
\]

\[ \text{HRMS:} \]

\[
\text{(ESI) Calcd for (C}_{34}\text{H}_{58}\text{O}_{3}\text{Si}_{2}^{+}\text{Na}^{+} \quad 593.3817}
\]

\[
\text{Found} \quad 593.3803
\]

\[ \text{TLC} \]

\[
R_f = 0.38 \text{ (UV, } p\text{-anisaldehyde)}
\]

\[
\text{(5:1 hexanes–ethyl acetate)}
\]
Cyclohexatrienone 74.

A solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1.0 M, 10.3 mL, 10.3 mmol, 1.1 equiv) was added to an ice-cooled solution of allylic alcohol 123 (5.33 g, 9.33 mmol, 1 equiv) in dichloromethane (75 mL). After 15 min, 1,1,1,3,3,3-hexafluoro-2-propanol (50 mL) was added, followed by 2,6-lutidine (4.35 mL, 37.4 mmol, 4 equiv). A solution of [bis(trifluoroacetoxy)iodo]benzene (7.23 g, 16.8 mmol, 1.8 equiv) in dichloromethane (25 mL) was then added by cannula over 10 min, forming a bright red solution. After 30 min, the bright red reaction mixture was concentrated to remove the bulk of solvent. The residue was partitioned between aqueous hydrochloric acid solution (0.5 N, 50 mL) and ethyl acetate (300 mL). The layers were separated. The aqueous layer was extracted with ether (3 × 70 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (70 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on triethylamine-deactivated silica gel (15:1 hexanes–ethyl acetate initially, grading to 7:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate, two purifications were necessary to obtain product of >95% purity by 1H NMR analysis), affording cyclohexatrienone 74 as a pale yellow solid (1.98 g, 50%).

\[
\begin{align*}
\text{1H NMR:} & \quad 6.43 \text{ (d, 1H, } J = 9.8 \text{ Hz)}, \quad 6.20 \text{ (dd, 1H, } J = 10.0, 1.7 \text{ Hz)},
\end{align*}
\]
<table>
<thead>
<tr>
<th>(500 MHz, CDCl₃)</th>
<th>5.93 (s, 1H), 5.49 (d, 1H, $J = 2.0$ Hz), 3.37 (app t, 1H, $J = 8.1$ Hz), 2.12–2.02 (m, 1H), 1.93 (dd, 1H, $J = 17.0$, 3.4 Hz), 1.85 (dd, 1H, $J = 11.5$, 7.5 Hz), 1.80–1.72 (m, 1H), 1.71–1.60 (m, 3H), 1.57 (ddd, 1H, $J = 13.1$, 6.3, 1.6 Hz), 1.51–1.41 (m, 3H), 1.20–1.13 (m, 1H), 0.98 (s, 9H), 0.89 (app td, 1H, $J = 12.9$, 4.9 Hz), 0.70 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H).</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{13}$C NMR:</td>
<td>185.7, 157.4, 154.4, 146.6, 129.9, 119.8, 119.1, 86.2, 81.7, 75.3, 47.7, 43.9, 37.3, 36.2, 30.8, 29.1, 28.9, 26.0, 19.7, 18.3, 11.0, −4.3, −4.7.</td>
</tr>
<tr>
<td>(126 MHz, CDCl₃)</td>
<td>2955 (s), 2857 (m), 1661 (vs), 1611 (s), 1354 (m), 1257</td>
</tr>
<tr>
<td>FTIR, cm⁻¹:</td>
<td>(thin film)</td>
</tr>
<tr>
<td></td>
<td>(s).</td>
</tr>
<tr>
<td>HRMS:</td>
<td>Calcd for (C$<em>{25}$H$</em>{36}$O$_3$Si+H)$^+$ 413.2507</td>
</tr>
<tr>
<td>(ESI)</td>
<td>Found 413.2505</td>
</tr>
<tr>
<td>TLC</td>
<td>$R_f = 0.40$ (UV, $p$-anisaldehyde)</td>
</tr>
<tr>
<td>(4:1 hexanes–ethyl acetate)</td>
<td></td>
</tr>
</tbody>
</table>
Bromo Ketone 125.

Note: Toluene used in this procedure was degassed using the freeze-pump-thaw method (4 iterations). Triethylsilane was filtered through a pipette packed with neutral alumina just prior to use.

To a flame-dried flask charged with cyclohexatrienone 74 (1.96 g, 4.74 mmol, 1 equiv) was added toluene (2 mL). Volatiles were removed in vacuo through a 20-gauge needle in order to effect azeotropic drying. A second portion of toluene (2 mL) was added, and the volatiles were again removed. Triethylsilane (1.52 mL, 9.50 mmol, 2 equiv) was added to the concentrate followed by a solution of Wilkinson’s catalyst (220 mg, 0.238 mmol, 0.05 equiv) in toluene (96 mL), the latter added via cannula. The reaction flask was then placed in an oil bath preheated to 50 ºC. After 4 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. Pyridine (16 mL) was added. After 12 h, the reaction flask was cooled to −78 ºC and a solution of N-bromosuccinimide (1.69 g, 9.48 mmol, 2.0 equiv) in tetrahydrofuran (10 mL) was added by cannula. After 1 h, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 0.5 h, the reaction mixture was partitioned between saturated aqueous sodium thiosulfate solution (50 mL) and ethyl acetate (250 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (80 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified
by flash-column chromatography on silica gel (20:1 hexanes–ethyl acetate initially, grading to 8:1 hexanes–ethyl acetate) to provide diastereomerically pure bromo ketone 125 as a white solid (1.63 g, 70%).

<table>
<thead>
<tr>
<th><strong>1H NMR:</strong> (500 MHz, CDCl₃)</th>
<th>5.92 (d, 1H, ( J = 2.3 ) Hz), 5.61 (s, 1H), 4.59 (ddd, 1H, ( J = ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.6, 2.3, 1.1 Hz, 3.64 (app t, 1H, ( J = 8.2 ) Hz), 2.93 (dd, 1H, ( J = 15.0, 4.7 ) Hz), 2.59–2.36 (m, 3H), 2.31 (ddd, 1H, ( J = 13.4, 9.4, 6.0 ) Hz), 2.09 (app td, 1H, ( J = 11.4, 5.8 ) Hz), 2.04–1.94 (m, 1H), 1.90 (dd, 1H, ( J = 10.6, 8.8 ) Hz), 1.86–1.73 (m, 2H), 1.69–1.48 (m, 4H), 1.23 (ddd, 1H, ( J = 12.9, 4.5 ) Hz), 0.89 (s, 9H), 0.84 (s, 3H), 0.02 (s, 6H).</td>
</tr>
</tbody>
</table>

| **13C NMR:** (126 MHz, CDCl₃) | 191.2, 160.3, 158.9, 119.4, 116.5, 83.4, 81.4, 76.0, 47.7, 44.7, 43.9, 41.1, 37.2, 36.1, 30.6, 29.9, 29.3, 25.8, 19.4, 18.1, 10.9, −4.4, −4.9. |

| **FTIR, cm⁻¹:** (thin film) | 2953 (m), 2856 (m), 1668 (s), 1618 (s), 1250 (m). |

| **HRMS:** (ESI) | Calcd for \((C_{25}H_{37}BrO_3Si+H)^+\) 493.1768  |
|                | Found 493.1768 |

| **TLC** (5:1 hexanes–ethyl acetate) | \( R_f = 0.50 \) (UV, \( p \)-anisaldehyde) |
Keto Enamine 127.

Sodium azide (26.0 mg, 0.406 mmol, 10 equiv) was added to a solution of bromo ketone 125 (20.0 mg, 0.041 mmol, 1 equiv) in N,N-dimethylformamide (1.0 mL) at 23 °C. After 12 h, the reaction mixture was partitioned between half saturated aqueous sodium chloride solution (10 mL) and ether (15 mL). The layers were separated. The aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined. The combined solution was washed with water (10 mL) and then saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to provide keto enamine 127 as a yellow solid (14.9 mg, 85%).

$^1$H NMR:  (500 MHz, C$_6$D$_6$)  

5.94 (s, 1H), 5.51 (s, 1H), 5.36 (s, 1H), 3.48 (br. s., 2H), 3.38 (t, 1H, $J = 8.1$ Hz), 2.11 (app td, 1H, $J = 15.5, 3.0$ Hz), 1.96 (dd, 1H, $J = 16.9, 4.6$ Hz), 1.90 (dd, 1H, $J = 12.2, 7.0$ Hz), 1.84 (ddd, 1H, $J = 14.0, 10.5, 2.6$ Hz), 1.80–1.75 (m, 1H), 1.75–1.67 (m, 3H), 1.62–1.55 (m, 2H), 1.52 (dd, 1H, $J = 12.0, 4.9$ Hz), 1.48–1.42 (m, 1H), 1.17 (ddd, 1H, $J = 12.5, 9.2, 2.7$ Hz), 0.98 (s, 9H), 0.93
(app td, 1H, $J = 12.9, 4.8$ Hz), 0.74 (s, 3H), 0.01 (d, 6H, $J = 2.5$ Hz);

$^{13}$C NMR:

(126 MHz, C$_6$D$_6$)

181.5, 158.8, 154.1, 138.7, 118.6, 116.7, 111.4, 84.3, 80.8, 75.4, 46.9, 42.9, 36.5, 35.2, 29.8, 28.1, 27.0, 25.0, 18.7, 17.3, 10.1, -5.3, -5.7;

FTIR, cm$^{-1}$:

(thin film)

3468 (br), 3362 (br), 2955 (s), 2926 (s), 2857 (m), 1641 (m), 1616 (s), 1464 (m), 1250 (m).

HRMS:

(ESI)

Calcd for (C$_{25}$H$_{38}$NO$_3$Si+H)$^+$ 428.2615

Found 428.2631

TLC

$R_f = 0.47$ (UV, $p$-anisaldehyde)

(2:1 hexanes–ethyl acetate)
Azido Alcohol 112.

Tetramethylguanidinium azide (960 mg, 6.08 mmol, 2 equiv) was added to a solution of bromo ketone 125 (1.50 g, 3.04 mmol, 1 equiv) in a mixture of acetonitrile (60 mL) and tetrahydrofuran (30 mL). After 12 h, the solution was concentrated to remove the bulk of solvent. Ethyl acetate (100 mL) and ether (50 mL) were added. Solids were removed by filtration, washing with ether (3 × 50 mL). The filtrates were combined and the combined solution was concentrated.

Toluene (2 mL) was added, and volatiles were removed in vacuo through a 20-gauge needle in order to effect azeotropic drying. A second portion of toluene (2 mL) was added, and the volatiles were again removed. Toluene (60 mL) was added to the concentrate. Tetramethylguanidine (382 µl, 3.04 mmol, 1 equiv) and a solution of (R)-tetrahydro-1-methyl-3,3,-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole catalyst in toluene (1.0 M, 608 µl, 0.608 mmol, 0.2 equiv) were added in sequence. The reaction flask was then cooled to −40 ºC. A solution of catecholborane in toluene (1.0 M, 6.08 mL, 6.08 mmol, 2 equiv) was added dropwise over 5 min. After 2 h, excess catecholborane was quenched by the addition of methanol (2 mL). The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was then partitioned between aqueous sodium hydroxide solution (1.0 N, 15 mL) and ethyl acetate (120 mL). The layers were separated. The organic layer was washed with aqueous sodium hydroxide solution (1.0 N, 3 × 15 mL). The aqueous layers were combined. The
combined aqueous solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (9:1 hexanes–ether, grading to 3:1 hexanes–ether) to furnish azido alcohol \textbf{112} as a white foam (1.18 g, 85%, a 15:1 mixture of diastereomers).\textsuperscript{41}

\textbf{\textsuperscript{1}H NMR:} \\
(500 MHz, CDCl\textsubscript{3}) \hspace{1cm} 5.69 (d, 1H, \textit{J} = 2.3 Hz), 5.14 (d, 1H, \textit{J} = 2.3 Hz), 4.24 (app td, 1H, \textit{J} = 5.4, 2.5 Hz), 3.60 (app t, 1H, \textit{J} = 8.5 Hz), 3.49 (ddd, 1H, \textit{J} = 12.7, 8.6, 3.9 Hz), 2.52–2.37 (m, 1H), 2.34–2.23 (m, 1H), 2.18 (d, 1H, \textit{J} = 5.0 Hz), 2.13–2.00 (m, 4H), 2.00–1.89 (m, 2H), 1.89–1.77 (m, 2H), 1.73 (ddd, 1H, \textit{J} = 12.5, 5.6, 1.6 Hz), 1.68–1.55 (m, 2H), 1.55–1.43 (m, 1H), 1.13 (app td, 1H, \textit{J} = 13.2, 4.8 Hz), 0.87 (s, 9H), 0.79 (s, 3H), 0.01 (s, 6H).

\textbf{\textsuperscript{13}C NMR:} \\
(126 MHz, CDCl\textsubscript{3}) \hspace{1cm} 148.6, 142.0, 118.5, 118.4, 83.9, 81.6, 78.0, 72.4, 63.4, 47.8, 43.9, 38.3, 38.3, 36.3, 32.5, 30.5, 28.6, 25.8, 19.6, 18.0, 10.8, –4.5, –4.9.

\textsuperscript{41} The product obtained in this procedure is a 15:1 mixture of diastereomers (epimeric at C2); the major diastereomer is depicted in the equation above. The minor diastereomer was removed at different points in the syntheses of the cortistatins, as detailed in the procedures that follow.
**FTIR, cm⁻¹:**

(thin film)

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>3431 (br), 2953 (m), 2857 (m), 2102 (vs), 1251 (s).</td>
<td></td>
</tr>
</tbody>
</table>

**HRMS:**

(ESI)

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Calcd for (C₂₅H₃₉N₃O₃Si+Na)⁺</td>
<td>480.2653</td>
</tr>
<tr>
<td>Found</td>
<td>480.2651</td>
</tr>
</tbody>
</table>

**TLC**

(3:1 hexanes–ethyl acetate)

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>R$_f$ = 0.34 (UV, $p$-anisaldehyde)</td>
<td></td>
</tr>
</tbody>
</table>
Dimethylamino Alcohol 133 (Cortistatin J and K Series).

A solution of azido alcohol 112 (80 mg, 175 µmol, 1 equiv) in a mixture of tetrahydrofuran (5 mL) and aqueous sodium hydroxide solution (1.0 N, 1 mL) was degassed by sparging for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle. To the degassed solution was added a solution of trimethylphosphine in tetrahydrofuran (1.0 M, 525 µL, 525 µmol, 3 equiv). After 2 h, methanol (6 mL) was added, followed by aqueous hydrochloric acid solution (1.0 N, 1 mL) then acetic acid (200 µL, 3.50 mmol, 20 equiv). Formalin (37 wt %, 710 µL, 8.75 mmol, 50 equiv) and a solution of sodium cyanoborohydride (110 mg, 1.75 mmol, 10 equiv) in methanol (1 mL) were added in sequence. After 1 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish diastereomerically pure dimethylamino alcohol 133 (cortistatin J and K series) as a white solid (68 mg, 85%).
| **^1H NMR:** | 5.70 (d, 1H, *J* = 2.1 Hz), 5.29 (d, 1H, *J* = 1.5 Hz), 4.22 (d, 1H, *J* = 9.2 Hz), 3.59 (app t, 1H, *J* = 8.5 Hz), 3.48 (br s, 1H), 2.59 (ddd, 1H, *J* = 12.5, 9.4, 2.5 Hz), 2.49–2.37 (m, 1H), 2.30 (s, 6H), 2.29–2.20 (m, 1H), 2.12–1.89 (m, 3H), 1.89–1.75 (m, 5H), 1.71 (dd, 1H, *J* = 12.5, 4.0 Hz), 1.67–1.54 (m, 2H), 1.54–1.43 (m, 1H), 1.12 (app td, 1H, *J* = 13.0, 4.6 Hz), 0.87 (s, 9H), 0.79 (s, 3H), 0.01 (s, 6H). |
| **(500 MHz, CDCl₃)** | |

| **^13C NMR :** | δ147.3, 141.0, 119.9, 119.1, 83.7, 81.6, 79.5, 67.6, 66.2, 48.0, 43.9, 40.4, 38.4, 36.4, 32.5, 30.6, 30.3, 28.6, 25.8, 19.6, 18.0, 10.9, –4.5, –4.9. |
| **(126 MHz, CDCl₃)** | |

| **FTIR, cm⁻¹:** | 3431 (br), 2955 (s), 2859 (m), 1462 (m), 1250 (s), 1134 (s), 1044 (s). |
| **(thin film)** | |

| **HRMS:** | Calcd for (C₂₇H₄₅NO₃Si+H)⁺ 460.3242 |
| **(ESI)** | Found 460.3259. |

| **TLC** | R_f = 0.32 (UV, *p*-anisaldehyde) |
| **(methanol)** | |
Dimethylamino Ketone 109 (Cortistatin J Series).

Concentrated aqueous hydrochloric acid solution (37 wt %, 2.15 mL, 26.1 mmol, 300 equiv) was added to a solution of dimethylamino alcohol (cortistatin J and K series) 133 (40 mg, 87.0 µmol, 1 equiv) in chloroform (4 mL). The resulting biphasic mixture was stirred vigorously. After 20 min, the reaction flask was placed in an ice bath and saturated aqueous sodium carbonate solution (20 mL) was added dropwise over 10 min (CAUTION: gas evolution). The layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish trienyl alcohol 134 (cortistatin J series) as a white solid (25 mg, 87%) which was transformed in the following step directly.

Dess-Martin periodinane (97 mg, 229 µmol, 3 equiv) was added to an ice-cooled solution of the trienyl alcohol 134 prepared above (25 mg, 76.3 µmol, 1 equiv) in dichloromethane (3.5 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 °C. After 2 h, ethyl acetate (10 mL) was added, followed by a mixture of water (4 mL), saturated aqueous sodium thiosulfate solution (4 mL), and saturated aqueous sodium bicarbonate solution (2 mL). The resulting biphasic mixture
was stirred vigorously until both layers were clear. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish dimethylamino ketone 109 (cortistatin J series) as a white solid (22 mg, 77% over two steps).

**1H NMR:**

(500 MHz, CDCl₃)

| 6.09 (dd, 1H, J = 9.7, 2.6 Hz), 5.83 (d, 1H, J = 9.7 Hz), 5.82 (s, 1H), 5.43 (dd, 1H, J = 5.0, 3.0 Hz), 3.44 (d, 1H, J = 11.0 Hz), 2.52 (dd, 1H, J = 18.8, 8.7 Hz), 2.44 (dd, 1H, J = 12.6, 5.5 Hz), 2.31 (s, 6H), 2.29–2.26 (m, 1H), 2.26–2.19 (m, 3H), 2.19–2.14 (m, 1H), 2.08 (ddd, 1H, J = 11.0, 9.0, 2.2 Hz), 1.99 (app t, 1H, J = 12.0 Hz), 1.95–1.87 (m, 2H), 1.85–1.77 (m, 1H), 1.76–1.69 (m, 1H), 0.95 (s, 3H). |

**13C NMR :**

(126 MHz, CDCl₃)

<p>| 220.5, 141.1, 140.1, 132.5, 127.2, 121.0, 120.8, 81.9, 79.2, 60.4, 47.9, 47.3, 40.5, 38.0, 35.9, 34.2, 31.4, 31.0, 18.9, 17.1. |</p>
<table>
<thead>
<tr>
<th><strong>FTIR, cm⁻¹:</strong> (thin film)</th>
<th>2967 (s), 2864 (m), 1744 (vs), 1454 (m), 1153 (m), 1078 (m).</th>
</tr>
</thead>
</table>
| **HRMS:** (ESI) | Calcd for \((C_{21}H_{27}NO_2+H)^+\) 326.2115  
Ffound 326.2119. |
| **TLC** (methanol) | \(R_f = 0.32\) (UV, \(p\)-anisaldehyde) |
**Triene 135.**

Methanesulfonyl chloride (3.3 µL, 41.3 µmol, 2 equiv) was added to an ice-cooled solution of the dimethylamino alcohol 133 (9.5 mg, 20.7 µmol, 1 equiv) and triethylamine (9.0 µL, 62.0 µmol, 3 equiv) in dichloromethane (0.50 mL). After 40 min, saturated aqueous sodium bicarbonate solution (0.20 mL) was added. The reaction mixture was then partitioned between saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 ethyl acetate–methanol initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol) to afford triene 135 as a pale yellow solid (6.8 mg, 75%).

| **^1H NMR:** | 6.10 (d, 1H, J = 10.0 Hz), 5.83 (s, 1H), 5.78 (d, 1H, J = 9.6 Hz), 5.49–5.32 (m, 1H), 3.77 (app t, 1H, J = 8.7 Hz), 3.47 (br d, 1H, J = 10.0 Hz), 2.33 (s, 6H), 2.25 (app t, 1H, J = 12.0 Hz), 2.21–2.09 (m, 2H), 2.09–1.92 (m, 4H), 1.88 (dd, 1H, J = 11.0, 4.6 Hz), 1.83–1.60 (m, 4H), 1.60–1.47 (m, 1H), 0.89 (s, 9H), 0.77 (s, 3H), 0.03 (s, |
\[ \text{\(^{13}\text{C NMR :} \quad 141.0, 139.4, 131.3, 127.7, 122.7, 121.5, 82.4, 81.7, \)} \]
\[ \text{(126 MHz, CDCl₃)} \]
\[ \text{78.8, 60.5, 46.4, 43.5, 40.4, 39.6, 38.1, 30.9, 30.7, 30.6,} \]
\[ \text{25.8, 19.5, 18.1, 13.4, -4.4, -4.8.} \]

\[ \text{\textbf{FTIR, cm}^{-1}:} \quad 2957 \text{ (s), 2859 \text{ (m), 1620 \text{ (s), 1572 \text{ (s), 1514 \text{ (m), 1462} \text{ (m), 1248 \text{ (s).} \}} \]

\[ \text{(thin film)} \]

\[ \text{\textbf{HRMS:} \quad \text{Calcd for (C}_{27}\text{H}_{43}\text{NO}_{2}\text{Si+H})^{+} \quad 442.3136} \]
\[ \text{(ESI)} \]
\[ \text{Found} \quad 442.3139 \]

\[ \text{\textbf{TLC} \quad R_f = 0.45 \text{ (UV, p-anisaldehyde) \}} \]
\[ \text{(methanol)} \]
Acetate 137 (Cortistatin K Series).

Scandium trifluoromethanesulfonate (2.68 mg, 5.44 µmol, 0.05 equiv) was added to an ice-cooled solution of dimethylamino alcohol 133 (cortistatin J and K series) (50 mg, 109 µmol, 1 equiv) and acetic anhydride (205 µL, 2.175 µmol, 20.0 equiv) in a mixture of acetonitrile (1.0 mL) and dichloromethane (1.0 mL). After 1 h, saturated aqueous sodium bicarbonate solution (200 µL) was added and the resulting biphasic mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between ethyl acetate (30 mL) and saturated aqueous potassium carbonate solution (10 mL). The layers were separated. The organic layer was washed with saturated aqueous potassium carbonate solution (10 mL). The aqueous layers were combined. The combined aqueous solution was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide acetate 137 (cortistatin K series) as an off-white solid (51 mg, 93%).

$^1$H NMR: (500 MHz, CDCl$_3$)

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity</th>
<th>Coupling常数 (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.67</td>
<td>d, 1H, $J = 2.0$ Hz</td>
<td></td>
</tr>
<tr>
<td>5.55</td>
<td>d, 1H, $J = 8.8$ Hz</td>
<td></td>
</tr>
<tr>
<td>5.09</td>
<td>d, 1H, $J = 2.4$ Hz</td>
<td></td>
</tr>
<tr>
<td>3.60</td>
<td>app t, 1H, $J = 8.3$ Hz</td>
<td></td>
</tr>
<tr>
<td>2.89</td>
<td>ddd, 1H, $J = 12.7$, 9.3, 3.4 Hz</td>
<td>2.49–2.39 (m, 1H), 2.29 (s, 6H), 2.30 (s, 6H), 2.30–2.25 (m, 1H), 2.07 (s, 3H), 2.06–1.99 (m, 2H), 1.98–1.79 (m, 6H), 1.75–1.69</td>
</tr>
</tbody>
</table>
(m, 1H), 1.68–1.55 (m, 2H), 1.54–1.45 (m, 1H), 1.14
(app td, 1H, J = 13.2, 4.9 Hz), 0.90–0.85 (m, 9H), 0.79
(s, 3H), 0.01 (s, 6H).

$^{13}$C NMR:

(126 MHz, CDCl$_3$)

171.0, 148.4, 143.1, 118.6, 116.7, 83.5, 81.6, 78.8, 70.2,
62.4, 47.9, 43.9, 40.6, 37.6, 36.3, 32.6, 32.3, 30.5, 28.5,
25.8, 21.6, 19.6, 18.0, 10.9, −4.5, −4.9.

FTIR, cm$^{-1}$:

(Thin film)

2953 (m), 2858 (m), 1734 (m), 1369 (m), 1238 (s).

HRMS:

(ESI) Calcd for (C$_{29}$H$_{47}$NO$_4$Si+H)$^+$                       502.3347
Found                                             502.3327

TLC

(methanol) $R_f = 0.69$ (UV, $p$-anisaldehyde)
**tert-Butyldimethylsilyl Ether 139 (Cortistatin K Series).**

**Note:** Tetrahydrofuran used in this procedure was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle prior to use. Raney nickel was prepared according to the procedure of Baran and coworkers.42

A solution of lithium borohydride in tetrahydrofuran (1.0 M, 1.0 mL, 1.0 mmol, 10 equiv) was added dropwise to a solution of acetate 133 (cortistatin K series) (50 mg, 99.6 µmol, 1 equiv) and tetrakis(triphenylphosphine)palladium(0) (23 mg, 19.9 µmol, 0.2 equiv) in tetrahydrofuran (4 mL). After 1 h, methanol (10 mL) was added, followed by a slurry of Raney nickel in water (4 drops, ca. 0.2 mL). After 16 h, the reaction mixture was filtered through a pad of Celite, washing with methanol (3 × 10 mL). The filtrates were combined and the combined organic solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish *tert*-butyldimethylsilyl ether 139 (cortistatin K series) as a pale yellow solid (39 mg, 90%).

### H NMR:

| 5.69 (d, 1H, J = 2.0 Hz), 5.26–5.20 (m, 1H), 3.59 (app t, (500 MHz, CDCl₃) | 1H, J = 8.3 Hz), 2.77–2.65 (m, 1H), 2.52–2.37 (m, 1H), |
| 2.33 (s, 6H), 2.30 (s, 1H), 2.27–2.20 (m, 2H), 2.19–2.07 (m, 1H), 2.07–1.89 (m, 4H), 1.89–1.76 (m, 3H), 1.76– |

---

1.68 (m, 1H), 1.68–1.54 (m, 2H), 1.54–1.42 (m, 1H),
1.12 (app td, 1H, $J = 13.1$, 4.6 Hz), 0.88 (s, 9H), 0.79 (s, 3H), 0.01 (s, 6H).

$^{13}$C NMR:
(126 MHz, CDCl$_3$)
145.4, 140.2, 119.4, 117.4, 83.3, 81.7, 79.2, 58.8, 48.0,
43.9, 41.1, 38.8, 36.6, 36.5, 33.0, 30.6, 28.5, 28.2, 25.8,

FTIR, cm$^{-1}$:
(thin film)
2955 (s), 2657 (m), 1738 (m), 1472 (m), 1252 (s).

HRMS:
(ESI)
Calcd for (C$_{27}$H$_{45}$NO$_2$Si+H)$^+$ 444.3292
Ffound 444.3293.

TLC
(methanol)
$R_f = 0.31$ (UV, p-anisaldehyde)
Dimethylamino Alcohol 154 (Cortistatin K Series).

A solution of tetra-$n$-butylammonium fluoride in tetrahydrofuran (1.0 M, 250 µL, 250 µmol, 3 equiv) was added to a solution of tert-butyldimethylsilyl ether 139 (cortistatin K series) (37 mg, 83.4 µmol, 1 equiv) in tetrahydrofuran (2.1 mL). The reaction flask was placed in an oil bath preheated to 65 ºC. After 3 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was then concentrated to remove the bulk of solvent. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol) to furnish dimethylamino alcohol 154 (cortistatin K series) as a white solid (24 mg, 87%).

$^1$H NMR: (400 MHz, CDCl$_3$) 5.70 (d, 1H, $J$ = 1.8 Hz), 5.29–5.15 (m, 1H), 3.70 (app t, 1H, $J$ = 8.6 Hz), 2.79–2.62 (m, 1H), 2.45 (app t, 1H, $J$ = 13.5 Hz), 2.32 (s, 6H), 2.31–2.22 (m, 2H), 2.20–2.07 (m, 2H), 2.06–1.93 (m, 4H), 1.93–1.74 (m, 5H), 1.74–1.44 (m, 3H), 1.21 (ddd, 1H, $J$ = 13.0, 4.5 Hz), 0.85 (s, 3H).

$^{13}$C NMR: (126 MHz, CDCl$_3$) 145.0, 140.1, 119.6, 117.4, 83.1, 81.7, 79.2, 58.7, 48.4, 43.5, 40.8, 38.8, 36.4, 36.1, 33.1, 30.1, 28.4, 27.9, 19.6, 10.7.
<table>
<thead>
<tr>
<th><strong>FTIR, cm(^{-1}):</strong> (thin film)</th>
<th>3443 (br), 2955 (s), 2860 (m), 1738 (m), 1462 (m), 1254 (s).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRMS:</strong> (ESI)</td>
<td>Calcd for (\text{C}<em>{21}\text{H}</em>{31}\text{NO}_{2}+\text{H}^+) (330.2428)</td>
</tr>
<tr>
<td>Found</td>
<td>(330.2438)</td>
</tr>
<tr>
<td><strong>TLC</strong> (methanol)</td>
<td>(R_f = 0.30) (UV, (p)-anisaldehyde)</td>
</tr>
</tbody>
</table>
Dimethylamino Ketone 110 (Cortistatin K Series).

Dess-Martin periodinane (77 mg, 183 µmol, 3 equiv) was added to an ice-cooled solution of dimethylamino alcohol 154 (cortistatin K series) (20 mg, 61 µmol, 1 equiv) in dichloromethane (4 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 °C. After 2 h, ethyl acetate (10 mL) was added, followed by a mixture of water (4 mL), saturated aqueous sodium thiosulfate solution (4 mL), and saturated aqueous sodium bicarbonate solution (2 mL). The resulting biphasic mixture was stirred vigorously until both layers were clear and colorless. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol) to furnish dimethylamino ketone 110 (cortistatin K series) as a pale yellow solid (18 mg, 90%).

**1H NMR:**

<p>| (500 MHz, CDCl3) | 5.74 (d, 1H, J = 2.4 Hz), 5.34–5.27 (m, 1H), 2.66 (br s, 1H), 2.51 (dd, 1H, J = 19.0, 9.0 Hz), 2.53–2.43 (m, 1H), 2.41–2.35 (m, 1H), 2.32 (s, 6H), 2.31–2.23 (m, 1H), 2.23–2.07 (m, 4H), 2.07–1.95 (m, 3H), 1.95–1.78 (m, |</p>
<table>
<thead>
<tr>
<th><strong>13C NMR</strong></th>
<th>( \text{Calcd for (C}<em>{21}\text{H}</em>{29}\text{NO}_{2}+\text{H})^+ )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{(126 MHz, CDCl}_3 \text{)} )</td>
<td>(ESI)</td>
</tr>
<tr>
<td>219.8, 143.8, 139.8, 120.4, 118.3, 82.8, 79.5, 58.7, 49.5, 48.1, 41.1, 38.8, 36.6, 35.9, 34.3, 31.3, 28.1, 27.8, 18.8, 14.0.</td>
<td>Found</td>
</tr>
<tr>
<td><strong>FTIR, cm(^{-1}):</strong></td>
<td>( \text{R}_f = 0.30 ) (UV, ( p )-anisaldehyde)</td>
</tr>
<tr>
<td>( \text{(thin film)} )</td>
<td>(methanol)</td>
</tr>
<tr>
<td>2955 (s), 2857 (m), 1740 (vs), 1472 (m), 1252 (s).</td>
<td></td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td></td>
</tr>
<tr>
<td>( \text{(ESI)} )</td>
<td></td>
</tr>
<tr>
<td>( \text{Calcd for (C}<em>{21}\text{H}</em>{29}\text{NO}_{2}+\text{H})^+ )</td>
<td>328.2271</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td></td>
</tr>
<tr>
<td>( \text{(methanol)} )</td>
<td>328.2273.</td>
</tr>
</tbody>
</table>
Dienyl Diol 155 (Cortistatin L Series).

Concentrated aqueous hydrofluoric acid solution (48 wt %, 573 µL, 15.9 mmol, 152 equiv) was added dropwise to a polypropylene vessel containing an ice-cooled solution of azido alcohol 112\(41\) (48 mg, 105 µmol, 1 equiv) in a mixture of tetrahydrofuran (0.9 mL) and acetonitrile (1.8 mL). After 3 h, the product solution was poured into water (30 mL) containing dipotassium hydrogen phosphate (10 g). The reaction vessel was rinsed with ethyl acetate (40 mL) and the rinse was transferred to the product mixture. The resulting biphasic mixture was stirred vigorously, then was transferred to a separatory funnel. The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL). The organic layers were combined. The combined solution was washed sequentially with saturated aqueous sodium bicarbonate solution (30 mL) then saturated aqueous sodium chloride solution (2 × 30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (initially 20:1 benzene–acetone, grading to 10:1 benzene–acetone, then 5:1 benzene–acetone, then 3:1 benzene–acetone) to furnish diastereomerically pure dienyl diol 155 (cortistatin L series) as a white powder (29.5 mg, 82%).

\(\text{^1H NMR:} \) .71 (d, 1H, \(J = 2.3\) Hz), 5.16 (s, 1H), 4.24 (d, 1H, \(J = 7.8\) Hz), 3.71 (dd, 1H, \(J = 8.7, 8.6\) Hz), 3.50 (ddd, 1H, \(J = \)
12.6, 8.5, 3.7 Hz), 2.52–2.40 (m, 1H), 2.32 (ddd, 1H, \( J = 16.5, 4.6, 1.8 \) Hz), 2.19–2.00 (m, 5H), 2.00–1.84 (m, 3H), 1.80 (ddd, 1H, \( J = 12.4, 5.5, 1.8 \) Hz), 1.73–1.46 (m, 4H), 1.42 (br s, 1H), 1.22 (ddd, 1H, \( J = 12.8, 12.7, 4.6 \) Hz), 0.84 (s, 3H).

**\(^{13}\text{C NMR} :\)**

(126 MHz, CDCl\(_3\))

148.1, 141.8, 118.8, 118.7, 83.6, 81.6, 78.1, 72.3, 63.4, 48.3, 43.5, 38.3, 38.3, 35.9, 32.6, 30.1, 28.5, 19.5, 10.6.

**FTIR, cm\(^{-1}\):**

(Thin film)

3383 (br), 2926 (m), 2100 (vs), 1255 (m).

**HRMS:**

Calcd for (C\(_{19}\)H\(_{25}\)N\(_3\)O\(_3\)+Na\(^+\))\(^{\dagger}\) 366.1788

Found 366.1790.

**TLC**

\( R_f = 0.28 \) (UV, \( p \)-anisaldehyde)

(4:1 benzene-acetone)
Azido tert-Butyldimethylsilyl Ether 140 (Cortistatin L Series).

A freshly-prepared solution of tert-butyldimethylsilyl chloride in tetrahydrofuran (1.0 M, 134 µL, 134 µmol, 2 equiv) was added dropwise to a solution of dienyl diol 155 (cortistatin L series) (23 mg, 67.0 µmol, 1 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (100 µL, 670 µmol, 10 equiv) in tetrahydrofuran (0.5 mL). After 24 h, a second portion of tert-butyldimethylsilyl chloride solution in tetrahydrofuran (1.0 M, 67 µL, 67 µmol, 1 equiv) was added. After an additional 36 h, the reaction mixture was partitioned between aqueous hydrochloric acid solution (1.0 N, 10 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to furnish azido tert-butyldimethylsilyl ether 140 (cortistatin L series) as a colorless oil (28 mg, 90%).

$$\text{1H NMR:} \hspace{1cm} 5.70 \text{ (s, 1H)}, \ 5.05 \text{ (s, 1H)}, \ 4.20 \text{ (d, 1H, } J = 7.9 \text{ Hz)}, \ 3.71$$

$$\text{(500 MHz, CDCl}_3\text{)} \hspace{1cm} (\text{app t, 1H, } J = 8.6 \text{ Hz}), \ 3.46 \text{ (ddd, 1H, } J = 12.3, 8.1, 4.2 \text{ Hz)}, \ 2.53-2.38 \text{ (m, 1H)}, \ 2.30 \text{ (dd, 1H, } J = 16.3, 3.7 \text{ Hz)}, \ 2.20$$
2.18–2.06 (m, 2H), 2.05–1.96 (m, 2H), 1.96–1.91 (m, 1H), 1.91–1.81 (m, 2H), 1.79 (dd, 1H, $J = 12.3$, 4.4 Hz), 1.74–1.55 (m, 3H), 1.50 (app tdd, 1H, $J = 12.4$, 8.3, 3.7 Hz), 1.41–1.34 (m, 1H), 1.21 (app td, 1H, $J = 13.0$, 4.7 Hz), 0.91 (s, 9H), 0.83 (s, 3H), 0.17 (s, 3H), 0.12 (s, 3H).

$^{13}$C NMR:

(126 MHz, CDCl$_3$)

147.5, 140.7, 120.6, 118.9, 83.5, 81.6, 78.0, 73.3, 63.7, 48.3, 43.5, 38.9, 38.2, 36.0, 32.6, 30.1, 28.5, 25.8, 19.5, 18.0, 10.6, –4.5, –4.8.

FTIR, cm$^{-1}$:

(thin film)

3421 (br), 2955 (s), 2857 (m), 2101 (vs), 1464 (m), 1258 (s).

HRMS:

(ESI)

Calcd for (C$_{25}$H$_{39}$N$_3$O$_3$Si+Na)$^+$

480.2653

Found

480.2640.

TLC

$R_f = 0.39$ (UV, $p$-anisaldehyde)

(2:1 hexanes–ethyl acetate)
Dimethylamino Alcohol 143 (Cortistatin L Series).

A solution of trimethylphosphine in tetrahydrofuran (1.0 M, 306 µL, 306 µmol, 5 equiv) was added to a solution of azido tert-butyldimethylsilyl ether 140 (cortistatin L series) (28 mg, 61.2 µmol, 1 equiv) in tetrahydrofuran (3 mL). After 24 h, formalin (37 wt %, 480 µL, 6.12 mmol, 100 equiv) was added. After 20 h, methanol (3 mL) was added, then acetic acid (70 µL, 1.22 mmol, 20 equiv) and, lastly, a solution of sodium cyanoborohydride (77 mg, 1.22 mmol, 20 equiv) in methanol (1 mL). After 2 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 15 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (66:33:1 hexanes–ethyl acetate–triethylamine initially, grading to 50:49:1 hexanes–ethyl acetate–triethylamine) to provide dimethylamino alcohol 143 (cortistatin L series) as a pale yellow solid (25 mg, 90%).

$^1$H NMR: 5.70 (d, 1H, $J = 2.4$ Hz), 5.10 (d, 1H, $J = 2.0$ Hz), 4.23 (d, 1H, $J = 8.3$ Hz), 3.71 (app td, 1H, $J = 8.4$, 5.6 Hz),
2.67–2.51 (m, 1H), 2.51–2.38 (m, 1H), 2.36–2.28 (m, 1H), 2.27 (s, 6H), 2.18–1.95 (m, 3H), 1.93–1.75 (m, 3H), 1.74–1.59 (m, 2H), 1.58–1.44 (m, 2H), 1.38 (d, 1H, $J = 5.4$ Hz), 1.25–1.16 (m, 1H), 0.89 (s, 9H), 0.83 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).

$^{13}$C NMR:

(126 MHz, CDCl$_3$)

146.6, 140.2, 122.9, 119.4, 83.2, 81.7, 79.3, 69.3, 65.7, 48.4, 43.5, 41.0, 37.8, 36.1, 32.7, 32.5, 30.1, 28.4, 26.0, 19.5, 18.3, 10.7, −4.1, −4.7.

FTIR, cm$^{-1}$:

(thin film)

3431 (br), 2930 (s), 2857 (m), 1715 (m), 1472 (m), 1250 (s).

HRMS:

(ESI) Calcd for (C$_{27}$H$_{45}$NO$_3$Si+H)$^+$ 460.3242 Found 460.3250

TLC

Rx = 0.19 (UV, $p$-anisaldehyde)

(50:49:1 hexanes–ethyl acetate–triethylamine)
Dimethylamino Ketone 111 (Cortistatin L Series).

Dess-Martin periodinane (69 mg, 163 µmol, 3 equiv) was added to an ice-cooled solution of dimethylamino alcohol 143 (cortistatin L series) (25 mg, 54.4 µmol, 1 equiv) in dichloromethane (2.7 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 2 h, ethyl acetate (10 mL) was added, followed by a mixture of water (4 mL), saturated aqueous sodium thiosulfate solution (4 mL), and saturated aqueous sodium bicarbonate solution (2 mL). The resulting biphasic mixture was stirred vigorously until both layers were clear. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (66:33:1 hexanes–ethyl acetate–triethylamine initially, grading to 50:49:1 hexanes–ethyl acetate–triethylamine) to furnish dimethylamino ketone 111 (cortistatin L series) as a pale yellow oil (23 mg, 90%).

\[ \text{\textit{1H NMR:}} \]

| (500 MHz, CDCl₃) | 5.73 (d, 1H, \( J = 2.3 \text{ Hz} \)), 5.14 (d, 1H, \( J = 2.5 \text{ Hz} \)), 4.25 (d, 1H, \( J = 8.2 \text{ Hz} \)), 2.66–2.55 (m, 1H), 2.55–2.43 (m, 2H), 2.42–2.33 (m, 1H), 2.28 (s, 6H), 2.24–2.06 (m, 5H), 2.02 (dd, 1H, \( J = 12.0, 6.5 \text{ Hz} \)), 1.96–1.78 (m, 5H), 1.39 (app td, 1H, \( J = 13.2, 5.2 \text{ Hz} \)), 0.97 (s, 3H), 0.89 (s, |
| **13C NMR:** (126 MHz, CDCl$_3$) | 219.7, 145.5, 139.9, 123.6, 120.1, 82.9, 79.6, 69.3, 65.7, 49.4, 48.1, 41.0, 37.8, 35.8, 33.9, 32.4, 31.2, 27.8, 26.0, 18.8, 18.3, 14.0, –4.1, –4.7. |
| **FTIR, cm$^{-1}$:** (thin film) | 2934 (s), 2863 (m), 1740 (vs), 1460 (m), 1248 (s). |
| **HRMS:** (ESI) | Calcd for (C$_{27}$H$_{43}$NO$_3$Si+H)$^+$ 458.3085 Found 458.3088. |
| **TLC** (50:49:1 hexanes–ethyl acetate–triethylamine) | $R_f = 0.24$ (UV, $p$-anisaldehyde) |
Azido Dienyl Diol 147.

A solution of bromo dienyl bromide 146 (10 mg, 16.0 µmol, 1 equiv) and sodium azide (52 mg, 800 µmol, 50 equiv) in a mixture of N,N-dimethylformamide (0.8 mL) and aqueous potassium phosphate buffer solution (pH 7.0, 0.5 M, 0.20 mL) was degassed by sparging for 10 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The reaction flask was capped with a glass stopper and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 100 ºC. After 12 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium chloride solution (10 mL) and 1:1 hexanes–ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with 1:1 hexanes–ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed sequentially with water (10 mL) then saturated aqueous sodium chloride solution (2 × 10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to furnish azido dienyl diol 147 as a white solid (4.5 mg, 60%).
**$^1$H NMR:**

(500 MHz, CDCl₃)

6.18 (d, 1H, J = 2.3 Hz), 5.46 (dd, 1H, J = 5.0, 2.3 Hz),

4.07 (d, 1H, J = 8.2 Hz), 3.76 (app t, 1H, J = 8.7 Hz),

3.48–3.26 (m, 2H), 2.25 (app t, 1H, J = 11.0 Hz), 2.19–

2.06 (m, 3H), 2.06–1.92 (m, 3H), 1.82–1.61 (m, 4H),

1.61–1.44 (m, 2H), 0.88 (s, 9H), 0.74 (s, 3H), 0.03 (s, 3H),

0.02 (s, 3H).

**$^{13}$C NMR:**

(126 MHz, CDCl₃)

139.0, 138.6, 123.0, 119.9, 82.1, 81.6, 78.4, 78.2, 72.3,

60.3, 46.2, 43.4, 39.8, 39.3, 37.5, 30.7, 25.8, 19.4, 18.0,

13.3, −4.4, −4.8.

**FTIR, cm$^{-1}$:**

(Thin film) 3466 (br), 2955 (s), 2857 (m), 2099 (vs), 1472 (m),

1362 (m), 1250 (s).

**HRMS:**

Calcd for (C$_{25}$H$_{39}$N$_3$O$_4$Si+Na)$^+$: 496.2602

(ESI)

Found: 496.2619

**TLC**

$R_f$ = 0.55 (UV, p-anisaldehyde)

(1:1 hexanes–ethyl acetate)
Dimethylamino Diol 148.

A solution of azido dienyl diol 147 (4.0 mg, 8.44 µmol, 1 equiv) in a mixture of tetrahydrofuran (1.0 mL) and aqueous sodium hydroxide solution (1.0 N, 0.50 mL) was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. To the degassed solution was added a solution of trimethylphosphine in tetrahydrofuran (1.0 M, 43 µL, 43 µmol, 5 equiv). After 2 h, methanol (2 mL) was added, followed by aqueous hydrochloric acid solution (2.0 N, 0.25 mL) then acetic acid (10 µL, 169 µmol, 20 equiv). To the resulting solution were added sequentially formalin (37 wt %, 70 µL, 844 µmol, 100 equiv) and a solution of sodium cyanoborohydride (11 mg, 169 µmol, 20 equiv) in methanol (0.5 mL). After 1 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 10 mL) and dichloromethane (15 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 ethyl acetate–methanol initially, grading to 1:1 ethyl acetate–methanol) to furnish dimethylamino diol 148 as a white solid (3.2 mg, 80%).
$^1$H NMR: 
(500 MHz, CDCl$_3$) 
6.23 (s, 1H), 5.44 (br s, 1H), 4.09 (d, 1H, $J$ = 9.3 Hz), 3.76 (app t, 1H, $J$ = 8.5 Hz), 3.33 (app t, 1H, $J$ = 9.8 Hz), 2.49 (app t, 1H, $J$ = 10.0 Hz), 2.33 (s, 6H), 2.23 (app t, 1H, $J$ = 11.5 Hz), 2.20–2.07 (m, 2H), 2.04–1.92 (m, 2H), 1.92–1.82 (m, 2H), 1.81–1.64 (m, 3H), 1.64–1.47 (m, 3H), 0.88 (s, 9H), 0.74 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

$^{13}$C NMR: 
(126 MHz, CDCl$_3$) 
139.4, 139.3, 122.2, 119.6, 82.1, 81.7, 79.3, 74.1, 73.7, 62.3, 46.3, 43.4, 40.0, 39.8, 39.3, 30.7, 30.6, 29.2, 25.8, 19.4, 18.1, 13.2, −4.4, −4.8.

FTIR, cm$^{-1}$: 
(thin film) 
3399 (br), 2955 (s), 2858 (m), 1472 (m), 1387 (m), 1250 (s).

HRMS: 
(ESI) 
Calcd for ($\text{C}_{27}\text{H}_{45}\text{NO}_{4}\text{Si}+\text{H}$)$^+$: 476.3191
Found: 476.3199

TLC 
(methanol) 
$R_f$ = 0.24 (UV, p-anisaldehyde)
Dimethylamino Diacetate 41 (Shair’s Intermediate).

Acetic anhydride (16 µL, 168 µmol, 40 equiv) was added to a solution of dimethylamino diol 148 (2.0 mg, 4.20 µmol, 1 equiv) and 4-dimethylaminopyridine (2.0 mg, 16.4 µmol, 4 equiv) in pyridine (0.21 mL). After 24 h, the reaction mixture was partitioned between ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (5:1 hexanes–ethyl acetate initially, grading to 2:1 hexanes–ethyl acetate, then 1:1 hexanes–ethyl acetate) to furnish dimethylamino diacetate 41 as a pale yellow foam (1.2 mg, 50%). The $^1$H NMR data for 41 was identical to that reported by Shair and coworkers for this compound.$^{34}$
Dimethylamino Ketone 108 (Cortistatin A Series).

A solution of dienyl azido diol (cortistatin A series) 153 (70 mg, 0.196 mmol, 1 equiv) in a mixture of tetrahydrofuran (6 mL) and aqueous sodium hydroxide solution (1.0 N, 3 mL) was degassed by sparging for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle. To the degassed solution was added a solution of trimethylphosphine in tetrahydrofuran (1.0 M, 588 µL, 0.588 mmol, 3 equiv). After 2 h, methanol (9 mL) was added, followed by aqueous hydrochloric acid solution (3.0 N, 1 mL) then acetic acid (224 µL, 3.92 mmol, 20 equiv). To the resulting solution were added sequentially formalin (37 wt. %, 795 µL, 9.80 mmol, 50 equiv) and a solution of sodium cyanoborohydride (123 mg, 1.96 mmol, 10 equiv) in methanol (1 mL). After 1 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 20 mL) and dichloromethane (40 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (4:1 ethyl acetate-methanol initially, grading to 2:1 ethyl acetate-methanol) to afford dimethylamino keto diol 23 (cortistatin A series) as a white solid (59
mg, 84%). The characteristic data for 23 was identical to that reported by the Baran group and by the Shair group.\textsuperscript{34,43}

Chlorotriethylsilane (166 µL, 0.985 mmol, 6 equiv) was added dropwise to an ice-cooled solution of the residue prepared above (59 mg, 0.164 mmol, 1 equiv), triethylamine (275 µL, 1.97 mmol, 12 equiv), and 4-dimethylaminopyridine (40.0 mg, 0.328 mmol, 2 equiv) in \(N,N\)-dimethylformamide (2.0 mL). After 30 min, the ice bath was removed and the reaction flask was allowed to warm to 23 °C. After 3 h, the reaction mixture was partitioned between ethyl acetate (30 mL) and a 1:1:1 mixture of water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (2 × 20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to afford dimethylamino ketone 108 (cortistatin A series) as a colorless oil (75 mg, 77%).

\[\text{\textsuperscript{1}H NMR:} \quad \begin{array}{l}
(500 \text{ MHz, CDCl}_3) \\
6.02 (d, 1H, \(J = 2.0\) Hz), 5.38 (dd, 1H, \(J = 4.9, 2.9\) Hz),
3.99 (d, 1H, \(J = 7.8\) Hz), 3.50 (app t, 1H, \(J = 7.6\) Hz),
2.57–2.44 (m, 2H), 2.39 (dd, 1H, \(J = 12.7, 5.4\) Hz), 2.22
\end{array}\]

(s, 6H), 2.30–2.17 (m, 5H), 2.16–2.10 (m, 1H), 1.95 (app t, 1H, $J = 12.7$ Hz), 1.91–1.79 (m, 2H), 1.79–1.60 (m, 2H), 0.98 (s, 3H), 0.97–0.92 (m, 18H), 0.69–0.58 (m, 12H).

**$^{13}$C NMR :**

(126 MHz, CDCl$_3$)

220.6, 143.1, 140.5, 120.4, 119.6, 81.2, 79.5, 75.9, 75.3, 64.8, 47.9, 47.2, 41.3, 38.9, 35.9, 33.9, 31.6, 28.9, 18.9, 17.0, 7.1, 7.0, 5.3, 5.1.

**FTIR, cm$^{-1}$:**

(Thin film)

2955 (s), 2876 (s), 1742 (s), 1622 (s), 1456 (m), 1238 (m).

**HRMS:**

(ESI) Calcd for (C$_{33}$H$_{57}$NO$_4$Si$_2$+H)$^+$ 588.3899 Found 588.3889.

**TLC**

(1:1 hexanes–ethyl acetate)

$R_f$ = 0.66 (UV, $p$-anisaldehyde)
Chapter 3

Synthesis of Cortistatins A, J, K, and L, and Cortistatin Based Affinity Reagents
Introduction

The previous chapter described an efficient synthesis of the key intermediate 112 on gram scale and the conversion of this azido alcohol into cortistatin A, J, K, and L precursors, representing each of the four natural cortistatin ABC-ring substitution patterns. With these 17-keto precursors in hand, the next stage was to find a generally applicable way to introduce the C17 isoquinoline substituent, which is detailed in this chapter (Figure 3.1).

Figure 3.1 Introduction of the 17-Isoquinolinyl Appendage.

In the published syntheses of cortistatins, different strategies were employed to introduce the isoquinoline moiety (Figure 3.2). The Baran group\(^1\) and the Shair group\(^2\)

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used similar strategies starting from cortistatinone 23. This ketone was first converted to a vinyl iodide via hydrazone iodination, and the vinyl iodide product was cross-coupled with 7-(trimethylstannyl)-isoquinoline to afford Δ16-cortistatin A (12). However, the final selective hydrogenation of the tri-substituted benzylic olefin in the presence of the diene moiety proved to be challenging. Baran and co-workers used Raney nickel reduction in heated methanol to provide cortistatin A in 25% yield with 50% conversion on a 2.3-mg scale,\(^1\) while Shair and co-workers used diimide reduction and obtained cortistatin A with 20% yield on a 1.0-mg scale.\(^2\) Meanwhile, the Nicolaou–Chen group,\(^3\) the Hirama group,\(^4\) and the Funk group\(^5\) introduced the isoquinoline ring early in their syntheses before functionalizing/forming the A-ring (see Chapter 1 for details).

**Figure 3.2** Literature Approaches to Introduce the 17-Isoquinolinyl Appendage.

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In our synthetic plan, we wished to introduce the 17-isoquinolinyl appendage at the final stage of our synthesis in order to achieve maximum diversification of this important ring appendage with respect to analog preparation. Therefore, we imagined a different strategy by applying an organometallic isoquinoline addition to 17-keto cortistatin precursors (in which the organometallic reagent would presumably attack from the less hindered bottom face), followed by deoxygenation of the newly formed tertiary C17 alcohol to produce the final products (Figure 3.3). We speculate that in the deoxygenation process, e.g. a radical deoxygenation reaction, the hydrogen radical (or an equivalent) would also come from the less-hindered bottom face to provide the desired stereochemistry at C17. This approach proved to be quite general and was successfully employed in the synthesis of natural cortistatins A, J, K, and L, as well as unnatural cortistatin analogs and affinity probes as detailed in this chapter.

Figure 3.3 Our Approach to Introduce the 17-Isoquinolinyl Appendage.

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6 During our work, the Hirama group also used an organometallic isoquinoline addition-deoxygenation sequence to introduce the isoquinoline appendage, although at an earlier stage with an unfunctionalized A-ring (ketone 30), see: Yamashita, S.; Kitajima, K.; Iso, K.; Hirama, M. *Tetrahedron Lett.* **2009**, *50*, 3277–3279; see also ref 4.
A General Applicable Isoquinoline-Addition-Deoxygenation Sequence to Synthesize Cortistatins A, L, J and K

The readily available 3-\textit{O}-methyl estrone 156 was selected as a model system to study the organometallic isoquinoline addition (Scheme 3.1). 7-Iodoisoquinoline (157) was prepared by iodination of 7-trimethylstannylisoquinoline as detailed in the experimental section. It was found that when a solution of 7-iodoisoquinoline (157) in tetrahydrofuran at −78 °C was treated with 1 equiv of \textit{n}-butyllithium, it underwent lithium-halogen exchange to generate a dark red solution within 30 min; without any additives, this 7-lithioisoquinoline reagent did not add to the C17 ketone of 156, presumably because of the more rapid, competing enolization process. A number of additives were thus screened (entries 2−8). While additives like triethylamine (entries 2) or hexamethylphosphoramide (HMPA, entries 3) did not benefit the reaction, \textit{N,N,N′,N″}-

\begin{scheme}
\textbf{Scheme 3.1} Isoquinoline Additions to an Estrone Model System.
\end{scheme}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>only 156, −78 → 23 °C</td>
<td>&lt;10% (80% SM)</td>
</tr>
<tr>
<td>2</td>
<td>NEt₃ then 156, −78 → 23 °C</td>
<td>&lt;10% (80% SM)</td>
</tr>
<tr>
<td>3</td>
<td>HMPA then 156, −78 → 23 °C</td>
<td>&lt;10% (80% SM)</td>
</tr>
<tr>
<td>4</td>
<td>TMEDA then 156, −78 °C</td>
<td>60% (35% SM)</td>
</tr>
<tr>
<td>5</td>
<td>a mixture of BF₃Et₂O and 156, −78 °C</td>
<td>40% (30% SM)</td>
</tr>
<tr>
<td>6</td>
<td>a mixture of La(OTf)₃ and 156, −78 °C</td>
<td>35% (25% SM)</td>
</tr>
<tr>
<td>7</td>
<td>a mixture of CeCl₃-2LiCl and 156, −78 °C</td>
<td>35% (40% SM)</td>
</tr>
<tr>
<td>8</td>
<td>CeCl₃ (slurry) then 156, −78 °C</td>
<td>&lt;10% (80% SM)</td>
</tr>
</tbody>
</table>

* yield was determined by NMR using an internal standard.
tetramethylethlenediamine (TMEDA), a reagent used by Jaouen and co-workers to complex with differently substituted phenyllithium reagents to improve their addition to a similar 17-keto steroid system,\(^7,8\) was found to effectively promote the nucleophilic addition, in which 60% of the addition product \(158\) was obtained (as a single diastereomer) along with 35% of the starting ketone recovered (entry 4).

This isoquinoline addition protocol was successfully applied to the natural cortistatin system (Scheme 3.2). After complexation to TMEDA (15 equiv), 7-lithio-isoquinoline (5 equiv) added to 17-keto cortistatin precursors to provide the corresponding addition products \(159, 160, 161,\) and \(162\) in 52–62% yield, along with 35–

\[\text{Scheme 3.2. Isoquinoline Additions to Cortistatin A, L, J, and K Precursors.}\]

\[\text{[Diagram with structures and reagents]}\]


\(^8\) During our work, the Baran group also reported a similar reaction condition by lithiation of 7-bromoisoquinoline and then complexation to TMEDA to enable its addition to 17-ketone in a cortistatin system, see: Shi, J.; Shigehisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C. C.; Baran, P. S. *Angew. Chem., Int. Ed.* 2009, 48, 4328–4331.
45% of the starting ketone recovered. The recovered ketones could be re-subjected to the isoquinoline addition condition, and after a typical 3-cycle procedure, >80% overall yield of the addition products could be obtained for the addition.

Now that the isoquinoline addition was working, the next step would be removing the C17 hydroxyl group. Barton deoxygenation conditions were first tried (Scheme 3.3a). In the model system, xanthate 163 was formed with excess potassium hydride and 1-(methyl)dithiocarbonyl)imidazole in a modest yield (about 20% of elimination product was also obtained), and subsequent radical deoxygenation went on smoothly, affording the desired deoxygenated 17-(S) product 164 as a single diastereomer, in which the hydrogen radical presumably came from the less hindered bottom face as expected (the stereochemistry was proved by NOE studies). However, in every attempt to apply this and a number of other conditions to make the xanthate or other thiocarbonyl derivatives of the real cortistatin J system, no desired product could be formed. This was thought to be due to the more sensitive starting material as well as a more hindered C17 tertiary alcohol (likely because of the push from the C6,C7 carbon bridge to the C18 angular methyl group and then to the C17 alcohol, Scheme 3.3b). Many other conditions were screened (Scheme 3.3c). Several ionic hydrogenation and metal boride reduction conditions resulted in the reduction of the isoquinoline ring first. A reported general zinc iodide-sodium cyanoborohydride mediated reduction of benzylic alcohols afforded

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only returning starting material.\textsuperscript{12} Raney Nickel\textsuperscript{13,14} and photochemistry via acetates\textsuperscript{15} were also unsuccessful in our hands.

\textbf{Scheme 3.3} Attempts to Remove C17 Hydroxyl Group with Barton Radical Deoxygenation and Other Conditions.

\begin{center}
\includegraphics[width=\textwidth]{Scheme3.3.png}
\end{center}

Given the initial modest success in the model system, we decided to turn our attention back to the radical deoxygenation process, which is ideal with its mild reaction condition, orthogonality to all the functional groups, and a presumably stable radical.

\textsuperscript{14} During our work, the Baran group reported a Raney Nickel mediated deoxygenation of the benzylic, tertiary alcohol, but giving the wrong stereochemistry at C17 position, see Ref 8.
intermediate at the tertiary, benzylic C17 position. What we needed was to find an easily obtained activating group to activate the hindered C17 tertiary alcohol. Initial attempts with C17 alcohol derived oxalate\textsuperscript{16} or phosphate\textsuperscript{17} led to complex decomposition (Scheme 3.3c). After extensive literature search, we found that Jiang and co-workers reported a radical deoxygenation condition with readily available trifluoroacetates (Scheme 3.4).\textsuperscript{18} For instance, when trifluoroacetate 165 was heated with di-\textit{tert}-butyl peroxide (1 equiv, as the radical initiator) in diphenylsilane as a solvent (as the hydrogen donor) at 130 °C, a smooth radical deoxygenation occurred within 12 h to provide cumene (166) in excellent yield.

**Scheme 3.4** Jiang’s Radical Deoxygenation with Trifluoroacetates.

![Scheme 3.4](image)

This promising protocol was first applied to the estrone model system (Scheme 3.5). The trifluoroacetate 167 was readily prepared by stirring tertiary alcohol 158 with trifluoroacetic anhydride (5 equiv) in the presence of pyridine (10 equiv) and 4-dimethylaminopyridine (DMAP, 0.5 equiv) in dichloromethane at 0 °C for 0.5 h in almost quantitative yield. However, when this trifluoroacetate 167 was subjected to the Jiang’s condition with di-\textit{tert}-butyl peroxide (1–3 equiv) in diphenylsilane as a solvent at 130 °C,

only the elimination product 168 was obtained. It was speculated that the high temperature employed in this reaction might caused the exclusive elimination in our system. Therefore, azobisisobutyronitrile (AIBN, 1.5 equiv), a radical initiator that could be triggered at much lower temperature, \(^{19}\) was employed with a commonly used hydrogen donor, tributyltin hydride (5 equiv) in heated benzene at 100 °C in a sealed tube. To our delight, a clean radical deoxygenation proceeded and the starting trifluoroacetate was consumed within 1 h, affording the desired product 164 with 17-(S) configuration as a single diastereomer in 80% yield, along with less than 10% elimination product 168. It was found that the use of excess radical initiator and hydrogen donor was necessary for the reaction, otherwise leading to much more elimination product. The reaction temperature was also critical, as reaction at 120 °C (1 h) resulted in more elimination

**Scheme 3.5** Deoxygenation with Trifluoroacetate 167 in an Estrone Model System.

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\(^{19}\) The half-life \(t_{1/2}\) of di-tert-butyl peroxide at 130 °C is 6.4 h, at 100 °C is 219 h; while the \(t_{1/2}\) of AIBN is 0.13 h at 100 °C, 1.0 h at 80 °C; for a complete chart, see: Polymer Handbook, Eds. Brandrup, J; Immergut, E.H.; Grulke, E.A., 4th Edition, John Wiley, New York, 1999, II/2-69 or the Sigma-Aldrich online chart: “Applications: Free Radical Initiators”.

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product (>40%) while reaction at 80 ºC (12 h) led to mostly the recovered starting trifluoroacetate.

The optimized reaction condition was successfully translated to the real cortistatin system (Scheme 3.6). The C17 tertiary alcohol of addition products 159, 160, 161, and 162 were readily transformed to the corresponding trifluoroacetates using the previous condition with excess trifluoroacetic anhydride (5 equiv) in the presence of pyridine (10 equiv) and 4-dimethylaminopyridine (DMAP, 0.5 equiv) in dichloromethane at 0 ºC; following radical deoxygenation with azobisisobutyronitrile (AIBN, 1.5 equiv) and excess tributyltin hydride (5–10 equiv) in benzene at 100 ºC for 1–2 h led to the desired deoxygenated products with the correct 17-((S) configuration in 60–70% yield over two steps (about 10% of the corresponding elimination products were also observed). In the cortistatin J and K series, deoxygenation led to these substances directly; while in the

**Scheme 3.6 Syntheses of Cortistatin A, L, J, and K.**
cortistatin A and cortistatin L series, a final cleavage of the silyl ether protective group(s) with tetra-n-butylammonium fluoride (TBAF) at 23 °C afforded the desired natural products in good yields. In all cases, spectroscopic data for the synthetic materials matched values reported for the natural products; and by employing this sequence, we were able to prepare 20 mg of cortistatin A in a single batch.

In addition to spectroscopic characterization, synthetic cortistatins A, J, K, and L were evaluated for their ability to inhibit the growth of HUVECs in culture (Figure 3.4). My co-worker, Dr. Ge Zou measured the GI\textsubscript{50} values after a 96-h incubation. It was found that for synthetic cortistatin A, we observed growth inhibition of HUVECs consistent with reported values,\textsuperscript{20} while measurements for synthetic cortistatin J more closely matched reports from the Nicolaou–Chen group\textsuperscript{3b} than initial reports,\textsuperscript{21} and GI\textsubscript{50} values for synthetic cortistatins K and L fell within the range of those originally reported to slightly higher.\textsuperscript{21}

**Figure 3.4 GI\textsubscript{50} Values of Natural and Synthetic Cortistans against HUVECs.**


An Improved Synthesis of Cortistatin A

During our work, the Hirama group reported an efficient cerium (III) chloride promoted isoquinoline addition to C17 ketone in a cortistatin system (Scheme 3.7).¹ ¹-Chloro-7-iodo isoquinoline (47) and n-butyllithium was added sequentially to a slurry of anhydrous cerium (III) chloride in tetrahydrofuran at –78 °C to afford an isoquinoline derived organocerium reagent,²² which add to ketone 30 in almost quantitative yield. The authors found that incorporation of 1'-chloride in the isoquinoline was important to prevent the C1' addition in the reaction conditions; when 7-iodo-isoquinoline (157) was subjected to the same reaction condition, no addition product could be observed, which was in consistent with our own observations (Scheme 3.1, entry 8).

Scheme 3.7 Hirama’s Isoquinoline Addition Condition with Cerium (III) Chloride.

We thought applying Hirama’s condition in our fully functionalized cortistatin system would effect a more efficient isoquinoline addition; we also envisioned that we should be able to remove the C1' chloride in our radical deoxygenation step (Scheme 3.8). To our delight, Hirama’s organocerium reagent derived from 1-chloro-7-iodo isoquinoline (46) also effectively added to the C17 ketone in the cortistatin A precursor.

to afford the addition product 169 in 85% yield. After trifluoroacetate formation, the subsequent radical deoxygenation with azobisisobutyronitrile (AIBN, 3 equiv) and excess tributyltin hydride (15 equiv) in benzene at 100 °C also cleaved the C1' chloride as expected, providing protected cortistatin A 170 in 70% yield over two steps. The final deprotection with triethylamine trihydrofluoride23 furnished cortistatin A (1) in 95% yield on a 10.8-mg batch.

**Scheme 3.8 An Improved Synthesis of Cortistatin A.**

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**Synthesis of Cortistatin Probes and Their Use in Target Identification**

To date, the mechanism of action of the cortistatins on inhibition of HEVECs remained unclear. An objective of our research was the synthesis of cortistatin-based biological probes and their use to identify the biological target(s) of this class of natural

23 In the previous tetra-n-butylammonium fluoride (TBAF)-mediated deprotection procedure, TBAF was found to co-spot with the final natural product, which makes the purification step difficult.
products. After study the preliminary SAR data of cortistatins (see Chapter 1 for details), we identified C3 amino group as a suitable place to install an affinity isolation tag which is likely to be far away from the binding site as suggested by Nicolaou-Chen’s homology model.\textsuperscript{24} Therefore, synthesis of a cortistatin A based C3-primary amine 176 was carried out (Scheme 3.9).

Our synthesis commenced from the azido transdiol 153 (prepared in 6 steps from key intermediate 112 as described in Chapter 2). The diol was bis-protected with chlorotriethylsilane to provide intermediate 171; TMEDA-mediated 7-lithioisoquinoline addition to the C17 ketone of 171 proceeded smoothly, affording tertiary alcohol 172 in 50\% yield, along with 30\% of ketone 171 recovered. The subsequent reduction of the hindered C3 azide was not straightforward. After much experimentation, an optimized

\textbf{Scheme 3.9 Synthesis of a Cortistatin A Primary Amine 176.}

procedure was developed, in which azide 172 was first heated with excess anhydrous trimethylphosphine (5 equiv) in benzene at 55 °C for 2 h to effect its complete conversion to an iminophosphine intermediate 173; without isolation, the reaction mixture was cooled in an ice-bath and sequentially treated with pyridine (20 equiv), DMAP (1 equiv), followed by trifluoroacetic anhydride (TFAA, 10 equiv), to furnish a trifluoroacetamide 174 with the C17 alcohol also trifluoroacetylated in the same operation. Subsequent radical deoxygenation with azobisisobutyronitrile (AIBN, 1.5 equiv) and excess tributyltin hydride (8 equiv) in benzene at 100 °C cleaved the C17 trifluoroacetate as expected, providing intermediate 175 in 60% yield over two steps. Finally, a global deprotection by stirring 175 in a 4:1 mixture of methanol and 1N aqueous sodium hydroxide afforded a cortistatin A C3 primary amine 176 in 80% yield.

The isoquinoline addition to ketone 171 could be further improved by employing Hirama’s organocerium reagent (Scheme 3.10). Despite a potentially reactive azide group at C3, the organocerium reagent derived from 1-chloro-7-iodo isoquinoline (47) added to

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**Scheme 3.10 Synthesis of Intermediate 175 Using Hirama’s Organocerium Reagent.**

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25 Addition of water with trimethylphosphine led to complex decomposition of the starting material.
the C17 ketone exclusively at $-78^\circ$C to give tertiary alcohol product 177 in 80% yield. The same Staudinger-trifluoroacetylation sequence afforded 178, and subsequent radical deoxygenation-dehalogenation with azobisisobutyronitrile (AIBN, 3 equiv) and excess tributyltin hydride (20 equiv) at 100 $^\circ$C proceeded uneventfully, providing the same intermediate 175 in 60% yield over two steps.

**Scheme 3.11** Preparation of Cortistatin A Based Affinity Reagents.

The cortistatin A amine 176 was subsequently linked to sepharose beads with an activated N-hydroxysuccinimide (NHS) ester to provide an immobilized affinity isolation reagent 179; this amine was also converted to amide 180 containing a diazirine as a photo-cross-linker$^{26}$ and a terminal alkyne as a cycloaddition partner,$^{27}$ which could potentially be used for target identification studies in live cells (by Dr. Ge Zou, Scheme 3.11).$^{28}$ In addition, a cortistatin J derived C3 primary amine 186 (prepared using the

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same isoquinoline-addition-radical-deoxygenation sequence by Dr. Ge Zou) was also transformed to an immobilized affinity isolation reagent 181, and amides 182 and 183; an Δ^{16}, naphthalene-containing inactive competitor 184 was also synthesized (Figure 3.5).

Interestingly, amides 180, 182 and 183 were all about 5–20 fold less active than the parent natural products even with a large substitution group at C3, indicating that the immobilized reagents 179 and 181 were also likely to be active; while naphthalene-containing amide 184 was another 18 fold less active than the isoquinoline-containing amide 182.29

**Figure 3.5** Cortistatin J Based Affinity Isolation Reagents and Related Amides.

The immobile affinity reagents 179 and 181 were subsequently used by Dr. Ge Zou in pull-down experiments in HUVEC and HEK293T cell lysates to identify the molecular target(s) of cortistatins as depicted in Figure 3.6. In theory, the cortistatin target protein(s) should be pulled down by an affinity reagent alone, or by the affinity

29 The C16,C17 double bond were not likely to be responsible for loss of much activity, as suggested by the good GI_{50} of Δ^{16}-cortistatin A (12) identified by Baran and co-workers: Shi, J.; Shigehisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4328–4331.
reagent in the presence of the negative competitor 184; but should not be pulled down when the active competitor cortistatin A (1) was added. By applying these principles, a 55-kD, membrane kinase was identified as a putative cortistatin target after initial validation studies. Further validations of this protein target and in vivo pull-down experiments using affinity reagent 180 are currently underway.

Figure 3.6 Pull-down Experiments with Cortistatin Based Affinity Isolation Reagents.

<table>
<thead>
<tr>
<th>Description</th>
<th>Peptide Counts from HEK293T Pull Down</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>only probe (179 or 181) probe + cortistatin A (1) probe + inactive competitor (184)</td>
</tr>
<tr>
<td>55-kD protein</td>
<td>12 0 11</td>
</tr>
</tbody>
</table>

Conclusion

Our synthesis of cortistatin alkaloids are summarized in Figure 3.7. We developed a robust synthetic route to prepare gram quantities of key intermediate 112 starting from readily available benzylzinc reagent 116 and enol triflate 117. This key intermediate 112 was then successfully diversified to different cortistatin 17-keto precursors 108, 109, 110, and 111, representing each of the four natural occurring cortistatin ABC-ring substitution
patterns; 112 was also converted to ketones 171 and 185, which retained the C3 azido group as a handle for further functionalization. Subsequently, a general applicable, isoquinoline-addition-radical-deoxygenation sequence was developed to introduce the C17 isoquinoline substituent at the final stage of our synthesis. By applying this strategy, natural products cortistatin A (1), J (9), K (10), and L (11) were prepared, as well as a number of unnatural cortistatin analogs and cortistatin primary amines 176 and 186. These primary amines were used to prepare several biological probes. By employing these probes in pull-down experiments, we identified a 55-kD membrane kinase as a putative protein target of cortistatins.

**Figure 3.7 Summary of the Syntheses of Cortistatin Alkaloids.**
Experimental Section

General Experimental Procedures. All reactions were performed in round-bottomed flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM) or acidic ethanolic $p$-anisaldehyde solution ($p$-anisaldehyde) then briefly heated on a hot plate. Flash-column chromatography was performed as described by Still et al.,\textsuperscript{30} employing silica gel (60 Å, 32–63 μM, standard grade, Dynamic Adsorbents, Inc.).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetramethylethylenediamine (TMEDA) was distilled from calcium hydride under an atmosphere of argon. Tetrahydrofuran, dichloromethane, benzene, toluene, dioxane, and ether were purified by the method of Pangborn et al.\textsuperscript{31} $N$-Bromosuccinimide was recrystallized from water. The molarity of $n$-butyllithium solutions was determined by titration against a standard solution of diphenylacetic acid in tetrahydrofuran (average of three determinations).\textsuperscript{32}

**Instrumentation.** Proton magnetic resonance (\(^1\)H NMR) spectra were recorded on Varian INOVA 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent (CHCl\(_3\), δ 7.26; C\(_6\)D\(_5\)H, δ 7.15). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, and coupling constant (\(J\)) in Hertz. Carbon nuclear magnetic resonance spectra (\(^1\)C NMR) were recorded on Varian INOVA 500 (126 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent (CDCl\(_3\), δ 77.0; C\(_6\)D\(_6\), δ 128.0). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer and were referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm\(^{-1}\)), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility. High performance liquid chromatography purifications were performed using an Agilent Technologies 1200 Series preparative HPLC system. Optical rotations were measured using a 2-mL cell with a 10-cm path length on a Jasco DIP 370 digital polarimeter.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with 187).*
7-Trimethylstannylisoquinoline (188).

Hexamethylditin (1.20 mL, 5.73 mmol, 1.1 equiv) was added to a solution of 7-isoquinolyl trifluoromethylsulfonate (187) \(^{33}\) (1.44 g, 5.21 mmol, 1 equiv), lithium chloride (1.33 g, 31.3 mmol, 6 equiv), and tetrakis(triphenylphosphine)palladium(0) (600 mg, 0.521 mmol, 0.1 equiv) in dioxane (10.4 mL). The reaction mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel. The flask was capped with a glass stopper under argon and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 100 ºC. After 5 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. Solids were removed by filtration through a pad of Celite, washing with ethyl acetate (3 × 30 mL). The filtrates were combined and the combined organic solution was concentrated. The residue was purified by flash-column chromatography (7:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 3:1 hexanes–ethyl acetate) to furnish 7-trimethylstannylisoquinoline (188) as a pale yellow solid (1.14 g, 75%).

\(^{1}\text{H NMR:}\) 

\[
\begin{align*}
\text{9.23 (s, 1H), 8.50 (dd, 1H, } J = 6.0, 0.9 \text{ Hz), 8.09 (m, 1H, CDCl}_3) \\
\text{7.81–7.74 (m, 2H), 7.60 (d, 1H, } J = 6.0 \text{ Hz, 0.38 (m, CDCl}_3)}
\end{align*}
\]

| **13C NMR**: (126 MHz, CDCl₃) | 152.3, 142.9, 142.2, 136.8, 135.5, 128.3, 125.4, 120.3, –9.5. |
|**FTIR, cm⁻¹**: (thin film) | 3047 (m), 2982 (s), 2913 (m), 1618 (s), 1402 (m), 1337 (m). |
|**HRMS**: (ESI) | Calcd for (C₁₂H₁₅NSn+H)⁺ 294.0299  
Found 294.0313. |
|**TLC**: (1:1 hexanes–ethyl acetate) | R_f = 0.57 (UV) |
7-Iodoisoquinoline (157).

Iodine (525 mg, 2.07 mmol, 1.1 equiv) was added to a solution of 7-trimethylstannylisoquinoline (188) (550 mg, 1.88 mmol, 1 equiv) in chloroform (19 mL). After 1 h, a second portion of iodine (52.5 mg, 0.207 mmol, 0.11 equiv) was added. After 1 h, the reaction mixture was partitioned between saturated aqueous sodium thiosulfate solution (20 mL) and ethyl acetate (60 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5:1 hexanes–ethyl acetate initially, grading to 3:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford 7-iodoisoquinoline (157) as a white solid (475 mg, 90%).

$^1$H NMR: (500 MHz, CDCl$_3$) 9.14 (s, 1H), 8.54 (d, 1H, $J = 6.0$ Hz), 8.33 (d, 1H, $J =$ 0.9 Hz), 7.90 (dd, 1H, $J = 8.7, 1.8$ Hz), 7.58 (d, 1H, $J = 6.0$ Hz), 7.53 (d, 1H, $J = 8.7$ Hz).

$^{13}$C NMR: (126 MHz, CDCl$_3$) 151.2, 143.5, 138.8, 136.4, 134.3, 129.8, 128.0, 120.1, 92.3.
**FTIR, cm⁻¹:**

(thin film)  
3057 (m), 2916 (m), 2849 (m), 1562 (s), 1489 (s), 1204 (s).

**HRMS:**

(ESI)  
Calcd for (C₉H₆IN+H)⁺  
255.9618  
Found  
255.9620

**TLC**

(1:1 hexanes–ethyl acetate)  
R_f = 0.42 (UV)
Isoquinolyl Estrone (164).

A solution of \( n \)-butyllithium in hexanes (2.50 M, 81 \( \mu \)L, 0.202 mmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (157) (51.6 mg, 0.202 mmol, 5 equiv) in tetrahydrofuran (1.0 mL) at \(-78^\circ \)C, producing a dark red solution. After 30 min, \( N,N,N',N' \)-tetramethylethylenediamine (92 \( \mu \)L, 0.607 mmol, 15 equiv) was added. After 10 min, a solution of ketone 156 (11.5 mg, 0.0404 mmol, 1 equiv) in tetrahydrofuran (0.20 mL) was added via cannula. After 30 min, saturated aqueous sodium bicarbonate solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \(^\circ \)C. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (30 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (\( 4 \times 15 \) mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (4:1 hexanes–ethyl acetate initially, grading to 2:1 hexanes–ethyl acetate, then 1:1 hexanes–ethyl acetate) to afford isoquinolyl alcohol 158 (estrone series) as a white solid (10.0 mg, 60%), and, separately, recovered ketone 156 (4.0 mg, 35%).
Trifluoroacetic anhydride (17.0 µL, 121 µmol, 5 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol 158 (10.0 mg, 24.2 µmol, 1 equiv), pyridine (19.0 µL, 242 µmol, 10 equiv) and 4-dimethylaminopyridine (1.5 mg, 12.1 µmol, 0.5 equiv) in dichloromethane (1.5 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5:1 hexanes–ethyl acetate initially, grading to 3:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (ca. 1.0 mL) was added, and the resulting solution was transferred by cannula to a capped 10-mL microwave vessel (CEM Corporation, cat. #908035, cap affixed by crimping). The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.40 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2′-azobisisobutyronitrile (6.0 mg, 36 µmol, 1.5 equiv) in benzene (80 µL). The reaction mixture was degassed by sparging for 10 min with a slow stream of argon gas through a 22-gauge stainless steel needle. Tributyltin hydride (33.0 µL, 121 µmol, 5.0 equiv) was added. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 1 h, the oil
bath was removed and the reaction flask was allowed to cool to 23 °C. The reaction mixture was directly purified by flash-column chromatography on silica gel (8:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to furnish isoquinolyl estrone (164) as a white solid (7.7 mg, 80% over two steps).

**1H NMR:**

(500 MHz, CDCl₃)

<p>| | |</p>
<table>
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</tr>
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<td>9.23 (s, 1H), 8.48 (d, 1H, J = 5.9 Hz), 7.81 (s, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.63 (d, 1H, J = 1.5 Hz), 7.62 (dd, 1H, J = 10.6, 1.0 Hz), 7.20 (d, 1H, J = 8.8 Hz), 6.70 (dd, 1H, J = 8.8, 2.4 Hz), 6.65 (s, 1H), 3.78 (s, 3H), 2.99 (app t, 1H, J = 9.8 Hz), 2.94–2.85 (m, 2H), 2.36–2.26 (m, 2H), 2.17–2.06 (m, 1H), 2.04–1.92 (m, 2H), 1.74 (d, 1H, J = 12.2 Hz), 1.70–1.61 (m, 1H), 1.61–1.51 (m, 2H), 1.50–1.40 (m, 2H), 1.36 (dd, 1H, J = 15.1, 7.3 Hz), 1.32–1.28 (m, 1H), 0.92 (app t, 1H, J = 7.3 Hz), 0.54 (s, 3H);</td>
<td></td>
</tr>
</tbody>
</table>

**13C NMR:**

(126 MHz, CDCl₃)

<p>| | |</p>
<table>
<thead>
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<tbody>
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<td>157.4, 152.3, 142.3, 140.7, 138.0, 134.6, 132.7, 132.4, 128.6, 126.3, 126.1, 125.5, 120.1, 113.8, 111.4, 57.2, 55.3, 55.2, 45.1, 44.0, 39.3, 37.8, 29.9, 27.8, 26.4, 26.2, 24.3, 12.9;</td>
<td></td>
</tr>
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</table>

**FTIR, cm⁻¹:**

2957 (s), 2926 (s), 2872 (m), 1454 (m), 1387 (m), 1370
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<th>Method</th>
<th>Details</th>
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<tr>
<td>HRMS:</td>
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</tr>
<tr>
<td>(ESI)</td>
<td>Found 398.2468</td>
</tr>
<tr>
<td>TLC</td>
<td>(R_f=0.15) (UV, (p)-anisaldehyde)</td>
</tr>
</tbody>
</table>

(hr film) (m).
Isoquinolyl Alcohol 159 (Cortistatin A Series).

A solution of \( n \)-butyllithium in hexanes (2.50 M, 232 \( \mu \)L, 0.578 mmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (157) (148 mg, 0.578 mmol, 5 equiv) in tetrahydrofuran (4.5 mL) at \(-78^\circ\text{C}\), producing a dark red solution. After 30 min, \( N,N,N',N' \)-tetramethylethylenediamine (261 \( \mu \)L, 1.74 mmol, 15 equiv) was added. After 10 min, a solution of bistriethylsilyl ether ketone 108 (68 mg, 0.116 mmol, 1 equiv) in tetrahydrofuran (0.7 mL) was added via cannula. The flask containing dimethylamino ketone 108 (cortistatin A series) was rinsed with tetrahydrofuran (2 \( \times \) 0.3 mL), and the rinses were added to the reaction mixture. After 30 min, saturated aqueous sodium bicarbonate solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \(^\circ\text{C}\). The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (30 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 \( \times \) 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil\textsuperscript{®} silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 then 1:2 hexanes–ethyl acetate) to afford isoquinolyl alcohol 159 (cortistatin A series) as a pale yellow oil (52 mg, 62%), and, separately, recovered dimethylamino ketone 108 (cortistatin A series) (23 mg, 34%).
**$^1$H NMR:** (500 MHz, CDCl$_3$)  
9.21 (s, 1H), 8.48 (d, 1H, $J = 6.0$ Hz), 7.93 (br s, 1H), 7.86 (d, 1H, $J = 5.5$ Hz), 5.90 (d, 1H, $J = 1.8$ Hz), 5.15 (dd, 1H, $J = 5.0$, 2.3 Hz), 3.94 (d, 1H, $J = 7.8$ Hz), 3.41 (app t, 1H, $J = 7.8$ Hz), 2.62 (ddd, 1H, $J = 14.2$, 9.6, 4.6 Hz), 2.50–2.39 (m, 2H), 2.39–2.26 (m, 2H), 2.20 (s, 6H), 2.19–2.02 (m, 3H), 1.95–1.72 (m, 4H), 1.67–1.57 (m, 2H), 1.17 (s, 3H), 0.95–0.89 (m, 18H), 0.66–0.55 (m, 12H).

**$^{13}$C NMR:** (126 MHz, CDCl$_3$)  
153.1, 145.7, 143.2, 142.6, 139.4, 135.0, 130.6, 128.3, 125.8, 125.4, 121.1, 120.5, 120.2, 85.8, 82.1, 79.6, 76.3, 75.5, 64.9, 47.9, 46.2, 41.5, 39.3, 38.9, 35.7, 31.6, 29.4, 20.9, 17.6, 7.3, 7.2, 5.6, 5.3.

**FTIR, cm$^{-1}$:** (thin film)  
3391 (br), 2924 (s), 2878 (m), 1782 (s), 1624 (s), 1458 (s), 1244 (m).

**HRMS:** (ESI)  
Calcd for (C$_{42}$H$_{64}$N$_2$O$_4$Si$_2$+H)$^+$ 717.4477  
Found 717.4480

**TLC**  
$R_f = 0.13$ (UV, $p$-anisaldehyde) (1:2 hexanes–ethyl acetate)
Cortistatin A Bis(triethylsilyl) Ether (170).

Trifluoroacetic anhydride (48 µL, 348 µmol, 5 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol (cortistatin A series) 159 (50 mg, 69.6 µmol, 1 equiv), pyridine (55 µL, 696 µmol, 10 equiv) and 4-dimethylaminopyridine (4.3 mg, 34.8 µmol, 0.5 equiv) in dichloromethane (7 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 °C. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 20 mL) and ethyl acetate (30 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (2:1 hexanes–ethyl acetate initially, grading to 1:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (1 mL) was added to the oily residue and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. A second portion of benzene (1 mL) was added, and the volatiles were again removed. Benzene (1.2 mL) was added to the concentrate. To the resulting solution was added a solution of 2,2′-azobisisobutyronitrile (34 mg, 209 µmol, 3 equiv) in benzene (0.5 mL) followed by
tributyltin hydride (150 µL, 557 µmol, 8 equiv). The reaction mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The flask was capped with a glass stopper under argon and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 100 ºC. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford cortistatin A bis(triethylsilyl) ether (170) as a pale yellow oil (34 mg, 70% over two steps).

**1H NMR**:  
(500 MHz, CDCl₃)  
9.23 (s, 1H), 8.49 (d, 1H, J = 5.4 Hz), 7.79 (s, 1H), 7.76 (d, 1H, J = 8.3 Hz), 7.63 (d, 1H, J = 5.4 Hz), 7.61–7.56 (dd, 1H, J = 8.5, 1.5 Hz, 1H), 6.03 (d, 1H, J = 1.5 Hz), 5.35 (dd, 1H, J = 4.9, 2.4 Hz), 3.99 (d, 1H, J = 7.8 Hz), 3.50 (app t, 1H, J = 7.8 Hz), 3.14 (app t, 1H, J = 9.8 Hz), 2.56–2.41 (m, 2H), 2.41–2.28 (m, 2H), 2.23 (s, 6H), 2.28–2.21 (m, 1H), 2.21–2.14 (m, 2H), 2.12–1.99 (m, 1H), 1.99–1.89 (m, 2H), 1.89–1.80 (m, 1H), 1.75–1.68 (m, 1H), 1.68–1.59 (m, 2H), 1.01–0.87 (m, 18H), 0.71–0.57 (m, 12H), 0.55 (s, 3H).

**13C NMR**:  
152.4, 142.7, 142.5, 140.6, 140.1, 134.7, 132.0, 128.6,
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<tr>
<td>(1:1 hexanes–ethyl acetate)</td>
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</table>
Cortistatin A (1).

A solution of tetra-\(n\)-butylammonium fluoride in tetrahydrofuran (1.0 M, 291 \(\mu\)L, 291 \(\mu\)mol, 6 equiv) was added to a solution of cortistatin A bis(triethylsilyl) ether (170) (34 mg, 48.5 \(\mu\)mol, 1 equiv) in tetrahydrofuran (2.4 mL) at 23 °C. After 20 min, the reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was further extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (5:1 ethyl acetate–methanol initially, grading to 2:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol). Fractions containing cortistatin A (1) were collected and the pooled fractions were concentrated. The residue was further purified by flash-column chromatography on Sephadex® LH-20 resin (methanol) to afford cortistatin A (1) as a white solid (20 mg, 87%, >85% purity by \(^1\)H NMR analysis).

Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 60 min, flow rate: 3 mL/min). Fractions eluting at 28–31 min were collected and concentrated. To the residue was added saturated aqueous sodium
bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was then purified by flash column chromatography on Sephadex® LH-20 resin (methanol) to afford cortistatin A (1) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.3 mg of cortistatin A (1) of >95% purity.

**1H NMR:**

(500 MHz, CDCl₃)  
9.22 (br s, 1H), 8.49 (d, 1H, \( J = 5.4 \) Hz), 7.79 (s, 1H), 7.76 (d, 1H, \( J = 8.8 \) Hz), 7.63 (d, 1H, \( J = 5.4 \) Hz), 7.59 (dd, 1H, \( J = 8.5, 1.6 \) Hz), 6.25 (d, 1H, \( J = 2.4 \) Hz), 5.44 (dd, 1H, \( J = 5.2, 2.2 \) Hz), 4.09 (d, 1H, \( J = 9.3 \) Hz), 3.33 (app t, 1H, \( J = 9.8 \) Hz), 3.15 (app t, 1H, \( J = 9.9 \) Hz), 2.51 (dd, 1H, \( J = 11.5, 8.5 \) Hz), 2.42 (ddd, 1H, \( J = 12.7, 9.6, 3.1 \) Hz), 2.41–2.32 (m, 2H), 2.30 (s, 6H), 2.29–2.23 (m, 1H), 2.22–2.14 (m, 2H), 2.10–2.01 (m, 1H), 1.96 (dd, 1H, \( J = 17.6, 5.4 \) Hz), 1.95–1.89 (m, 1H), 1.89–1.84 (m, 2H), 1.83–1.75 (m, 1H), 1.66 (app td, 1H, \( J = 10.5, 8.5 \) Hz), 0.54 (s, 3H).

**13C NMR:**

(126 MHz, CDCl₃)  
152.3, 142.6, 140.0, 139.9, 139.6, 134.7, 132.0, 128.6, 126.3, 125.8, 121.4, 120.1, 119.4, 81.9, 79.5, 74.1, 73.7, 62.2, 56.9, 51.7, 44.8, 40.1, 40.0, 39.7, 30.6, 29.0, 26.4,
20.5, 15.2.

**FTIR, cm**⁻¹:

(s, 1263 (s).

**HRMS:**

Calcd for (C₃₀H₃₆N₂O₃+H)⁺ 473.2799
found 473.2796

**TLC**

Rᵥ = 0.20 (UV, p-anisaldehyde)

**Optical Rotation**

[α]D²⁵ = +31.1° (c = 0.090 in methanol);

lit.²⁰: [α]D²⁰ = +30.1° (c = 0.56 in methanol)
Isoquinolyl Alcohol 160 (Cortistatin L Series).

A solution of \( n \)-butyllithium in hexanes (2.50 M, 62 µL, 153 µmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (157) (39 mg, 153 µmol, 5 equiv) in tetrahydrofuran (1.5 mL) at \(-78 \, ^\circ\text{C}\), producing a dark red solution. After 30 min, \( N,N,N',N' \)-tetramethylethylenediamine (69 µL, 459 µmol, 15 equiv) was added. After 10 min, a solution of dimethylamino ketone 111 (cortistatin L series) (14 mg, 30.6 µmol, 1 equiv) in tetrahydrofuran (0.3 mL) was added via cannula. The flask containing dimethylamino ketone 111 (cortistatin L series) was rinsed with tetrahydrofuran (2 × 0.1 mL), and the rinses were added to the reaction mixture. After 30 min, saturated aqueous sodium bicarbonate solution (0.5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \(^\circ\text{C}\). The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (90:9:1 hexanes–acetone–triethylamine initially, grading to 80:19:1 then 66:33:1 hexanes–acetone–triethylamine) to afford isoquinolyl alcohol 160 (cortistatin L
series) as a pale yellow solid (9.3 mg, 52%) and, separately, recovered dimethylamino ketone 111 (cortistatin L series) (5.6 mg, 40%).

$^1$H NMR:  
(500 MHz, CDCl$_3$) 9.22 (s, 1H), 8.50 (d, 1H, $J = 5.9$ Hz), 7.88 (br s, 1H), 7.83 (d, 1H, $J = 8.3$ Hz), 7.61 (d, 1H, $J = 5.9$ Hz), 7.51 (d, 1H, $J = 2.0$ Hz), 5.02 (d, 1H, $J = 2.4$ Hz), 4.19 (d, 1H, $J = 8.3$ Hz), 2.68–2.53 (m, 2H), 2.42–2.33 (m, 1H), 2.32–2.24 (m, 2H), 2.27 (s, 6H), 1.96–1.76 (m, 4H), 1.55–1.49 (m, 1H), 1.21 (s, 3H), 0.86 (s, 9H), 0.54 (app td, 1H, $J = 13.2$, 4.9 Hz), 0.05 (s, 3H), 0.03 (s, 3H).

$^{13}$C NMR:  
(126 MHz, CDCl$_3$) 153.0, 146.0, 144.7, 143.1, 139.8, 134.8, 130.5, 127.9, 125.4, 125.3, 123.3, 119.9, 119.3, 85.7, 83.7, 79.3, 69.2, 65.6, 47.7, 47.2, 41.0, 38.5, 37.8, 33.2, 32.6, 28.4, 25.9, 25.9, 20.5, 18.3, 14.6, −4.2, −4.7.

FTIR, cm$^{-1}$:  
(thin film) 3264 (br), 2930 (s), 2857 (m), 1455 (m), 1250 (s).

HRMS:  
(ESI) Calcd for ($C_{36}H_{50}N_2O_3Si+H)^+$ 587.3664  
Found 587.3652

TLC  
$R_f = 0.35$ (UV, $p$-anisaldehyde)  
(66:33:1 hexane–acetone–triethylamine)
Cortistatin L tert-Butyldimethylsilyl Ether (189).

Trifluoroacetic anhydride (6.1 µL, 44 µmol, 5.0 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol (cortistatin L series) 160 (5.2 mg, 8.8 µmol, 1 equiv), triethylamine (12 µL, 88 µmol, 10 equiv) and 4-dimethylaminopyridine (0.54 mg, 4.4 µmol, 0.50 equiv) in dichloromethane (1.7 mL). After 5 min, the ice bath was removed and the reaction flask was allowed to warm to 23 °C. After 10 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (88:11:1 hexanes–acetone–triethylamine) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (ca. 1.5 mL) was added, and the resulting solution was transferred by cannula to a a capped10-mL microwave vessel (CEM Corporation, cat. #908035, cap affixed by crimping). The vessel was placed in a water bath at 23 °C and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.80 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (4.4 mg, 26 µmol, 3.0 equiv) in benzene (80 µL) followed by tributyltin hydride (14 µL, 52 µmol, 6.0 equiv). The reaction mixture was
degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 °C. After 1 h, the oil bath was removed and the reaction flask was allowed to cool to 23 °C. The reaction mixture was transferred by pipette to a round-bottom flask and the product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (90:9:1 hexanes–acetone–triethylamine initially, grading to 80:19:1 hexanes–acetone–triethylamine) to furnish cortistatin L tert-butyldimethylsilyl ether (189) as a pale yellow oil (4.0 mg, 80% over two steps).

**1H NMR:**

(500 MHz, CDCl₃)

<table>
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<th>Chemical Shift</th>
<th>Description</th>
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<tr>
<td>9.22 (s, 1H)</td>
<td>8.48 (d, 1H, J = 5.9 Hz)</td>
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<td>7.62 (d, 1H, J = 5.9 Hz)</td>
<td>7.57 (dd, 1H, J = 8.8, 1.5 Hz)</td>
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<td>4.26 (d, 1H, J = 7.8 Hz)</td>
<td>3.00 (app t, 1H, J = 10.0 Hz)</td>
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<td>2.20–2.03 (m, 3H)</td>
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<td>1.67–1.56 (m, 2H)</td>
<td>1.52 (app td, 1H, J = 12.7, 5.9 Hz)</td>
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<td>0.09 (s, 3H)</td>
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**13C NMR:**

(126 MHz, CDCl₃)

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<th>Description</th>
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<td>152.4, 146.6, 142.5, 140.2, 139.9, 134.7, 132.3, 128.6, 126.4, 125.7, 123.0, 120.1, 119.4, 83.4, 79.3, 69.4, 65.8,</td>
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### FTIR, cm⁻¹:

(Thin film) 3393 (br), 2936 (m), 2857 (m), 1792 (m), 1724 (s), 1464 (m), 1256 (m).

### HRMS:

(ESI) Calcd for (C₃₆H₅₀N₂O₂Si+H)+ 571.3714

Found 571.3713

### TLC

Rᵣ = 0.55 (UV, p-anisaldehyde)

(66:33:1 hexanes–acetone–triethylamine)
Cortistatin L (11).

A solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1.0 M, 62 µL, 62 µmol, 10 equiv) was added to a solution of cortistatin L tert-butyldimethylsilyl ether 189 (3.5 mg, 6.1 µmol, 1 equiv) in tetrahydrofuran (0.30 mL) at 23 ºC. After 5 h, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (5 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 2:1 methanol–ethyl acetate) to furnish cortistatin L (11) as a white solid (2.5 mg, 90%, >90% purity as judged by 1H NMR analysis).

Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 60 min, flow rate: 3 mL/min). Fractions eluting at 27–30 min were collected and concentrated. To the residue was added saturated aqueous sodium bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium...
chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (1:1 methanol–ethyl acetate) to afford cortistatin L (11) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.0 mg of cortistatin L (11) of >95% purity.

| **1H NMR:** (600 MHz, CDCl₃)          | 9.22 (s, 1H), 8.48 (d, 1H, J = 5.6 Hz), 7.78 (s, 1H), 7.75 (d, 1H, J = 8.5 Hz), 7.62 (d, 1H, J = 5.6 Hz), 7.50 (dd, 1H, J = 8.5, 1.5 Hz), 5.75 (d, 1H, J = 1.8 Hz), 5.35 (d, 1H, J = 2.1 Hz), 4.23 (d, 1H, J = 9.1 Hz), 3.13 (br s, 1H), 3.00 (app t, 1H, J = 9.8 Hz), 2.59 (dd, 1H, J = 11.8, 8.8 Hz), 2.31 (s, 6H), 2.41–2.28 (m, 3H), 2.28–2.22 (m, 1H), 2.20–2.13 (m, 1H), 2.12–2.04 (m, 2H), 2.02–1.94 (m, 1H), 1.94–1.89 (m, 1H), 1.89–1.76 (m, 4H), 1.62 (dd, 1H, J = 12.5, 5.0 Hz), 1.51 (app td, 1H, J = 12.5, 5.0 Hz), 0.60 (s, 3H). |
| **13C NMR:** (126 MHz, CDCl₃)         | 152.4, 146.8, 142.6, 140.9, 139.8, 134.7, 132.2, 128.6, 126.4, 125.7, 120.2, 120.1, 119.4, 83.7, 79.7, 67.8, 66.1, 57.5, 53.5, 45.2, 40.5, 38.5, 37.2, 32.5, 30.2, 28.5, 25.9, 20.7, 12.8. |
| **FTIR, cm⁻¹:**                       | 3404 (br), 2932 (s), 2857 (m), 1792 (m), 1624 (s), 1456 |
(thin film) \( (s), 1254 \text{ (m).} \)

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| **TLC (methanol)** | \( R_f = 0.29 \text{ (UV, } p\text{-anisaldehyde)} \) |

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Isoquinolyl Alcohol 161 (Cortistatin J Series).

A solution of \( n \)-butyllithium in hexanes (2.50 M, 117 \( \mu \)L, 292 \( \mu \)mol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (157) (75 mg, 292 \( \mu \)mol, 5 equiv) in tetrahydrofuran (2.4 mL) at \(-78 \, ^\circ\text{C}\), producing a dark red solution. After 30 min, \( N,N,N',N' \)-tetramethylethylenediamine (132 \( \mu \)L, 876 \( \mu \)mol, 15 equiv) was added. After 10 min, a solution of dimethylamino ketone 109 (cortistatin J series) (19 mg, 58.4 \( \mu \)mol, 1 equiv) in tetrahydrofuran (0.3 mL) was added via cannula. The flask containing dimethylamino ketone 109 (cortistatin J series) was rinsed with tetrahydrofuran (2 \( \times \) 0.1 mL), and the rinses were added to the reaction mixture. After 1 h, saturated aqueous sodium bicarbonate solution (0.5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \( ^\circ\text{C} \). The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 \( \times \) 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol, then 1:2 ethyl acetate–methanol) to
afford isoquinolyl alcohol 161 (cortistatin J series) as a pale yellow solid (16 mg, 60%) and, separately, recovered dimethylamino ketone 109 (cortistatin J series) (6.7 mg, 35%).

**1H NMR:**

(500 MHz, CDCl₃)

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**13C NMR:**

(126 MHz, CDCl₃)

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**FTIR, cm⁻¹:**

(thin film)

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**HRMS:**

(ESI)

Calcd for (C₃₀H₃₄N₂O₂+H)⁺ 455.2692

Found 455.2707

**TLC**

(methanol)

Rₓ = 0.22 (UV, p-anisaldehyde)
Cortistatin J (9).

Trifluoroacetic anhydride (6.1 µL, 44 µmol, 5.0 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol 161 (cortistatin J series) (4.0 mg, 8.8 µmol, 1 equiv), pyridine (7.2 µL, 88 µmol, 10 equiv) and 4-dimethylaminopyridine (0.54 mg, 4.4 µmol, 0.50 equiv) in dichloromethane (1.7 mL) at 0 ºC. After 5 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 2:1 methanol–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (ca. 1.5 mL) was added, and the resulting solution was transferred by cannula to a capped 10-mL microwave vessel (CEM Corporation, cat. #908035, cap affixed by crimping). The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.80 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (4.4 mg, 26 µmol, 3.0 equiv) in benzene (80 µL) followed by tributyltin hydride (14 µL, 52 µmol, 6.0 equiv). The reaction mixture was
degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 °C. After 1 h, the oil bath was removed and the reaction flask was allowed to cool to 23 °C. The reaction mixture was transferred by pipette to a round-bottom flask and the product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 2:1 methanol–ethyl acetate) to furnish cortistatin J (9) as a white solid (2.5 mg, 65% over two steps, >90% purity as judged by 1H NMR analysis).

Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 45 min, flow rate: 3 mL/min). Fractions eluting at 22–26 min were collected and concentrated. To the residue was added saturated aqueous sodium bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was then purified by flash column chromatography on Davisil® silica gel (1:1 methanol–ethyl acetate) to afford cortistatin J (9) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.0 mg of cortistatin J (9) of >95% purity.
$^1$H NMR: (500 MHz, CDCl$_3$)
9.23 (s, 1H), 8.49 (d, 1H, $J=5.9$ Hz), 7.80 (s, 1H), 7.76 (d, 1H, $J=8.3$, 1.5 Hz), 6.09 (dd, 1H, $J=10.0$, 2.7 Hz), 5.84 (s, 1H), 5.81 (d, 1H, $J=9.8$ Hz), 5.42 (dd, 1H, $J=5.1$, 2.7 Hz), 3.45 (d, 1H, $J=10.7$ Hz), 3.17 (app t, 1H, $J=10.0$ Hz), 2.56 (dd, 1H, $J=11.5$, 8.5 Hz), 2.41 (d, 1H, $J=19.0$ Hz), 2.32 (s, 6H), 2.36–2.26 (m, 2H), 2.25–2.14 (m, 1H), 2.12–1.96 (m, 4H), 1.95–1.84 (m, 2H), 1.81–1.65 (m, 2H), 0.58 (s, 3H).

$^{13}$C NMR: (126 MHz, CDCl$_3$)
152.4, 142.6, 141.2, 140.0, 139.8, 134.7, 132.2, 132.0, 128.6, 127.4, 126.3, 125.8, 121.8, 121.1, 120.1, 82.3, 79.0, 60.5, 57.0, 51.7, 44.9, 40.6, 40.3, 38.0, 31.1, 30.5, 26.5, 20.6, 15.4.

FTIR, cm$^{-1}$: (thin film)
2933 (s), 1716 (s), 1647 (s), 1450 (m), 1366 (s).

HRMS: (ESI)
Calcd for (C$_{30}$H$_{34}$N$_2$O+H)$^+$ 439.2744
Found 439.2743

TLC (methanol) $R_f = 0.32$ (UV, $p$-anisaldehyde)

Optical Rotation
$[\alpha]_D^{23} = -51.7^\circ$ (c = 0.041 in chloroform)

lit. $^{21}$: $[\alpha]_D^{20} = -54.0^\circ$ (c = 0.26 in chloroform)
Isoquinolyl Alcohol 162 (Cortistatin K Series).

A solution of \( n \)-butyllithium in hexanes (2.50 M, 92 \( \mu \)l, 229 \( \mu \)mol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (157) (59 mg, 229 \( \mu \)mol, 5 equiv) in tetrahydrofuran (1.8 mL) at \(-78^\circ\)C, producing a dark red solution. After 30 min, \( N,N,N',N' \)-tetramethylethylenediamine (103 \( \mu \)L, 687 \( \mu \)mol, 15 equiv) was added. After 10 min, a solution of dimethylamino ketone 110 (cortistatin K series) (15 mg, 45.8 \( \mu \)mol, 1 equiv) in tetrahydrofuran (0.3 mL) was added via cannula. The flask containing dimethylamino ketone 110 (cortistatin K series) was rinsed with tetrahydrofuran (2 \( \times \) 0.1 mL), and the rinses were added to the reaction mixture. After 1 h, saturated aqueous sodium bicarbonate solution (0.5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \(^\circ\)C. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 \( \times \) 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 then 1:1 ethyl acetate–methanol) to afford isoquinolyl alcohol 162 (cortistatin K series) as a pale
yellow solid (11.5 mg, 55%), and separately, recovered dimethylamino ketone 110 (cortistatin K series) (6.0 mg, 40%).

| **1H NMR:**  | 9.23 (s, 1H), 8.50 (d, 1H, $J = 5.9$ Hz), 7.89 (br s, 1H), 7.83 (d, 1H, $J = 5.6$ Hz), 5.53 (d, 1H, $J = 2.1$ Hz), 5.17 (dd, 1H, $J = 4.7$, 2.6 Hz), 2.70–2.57 (m, 2H), 2.47–2.34 (m, 1H), 2.30 (s, 6H), 2.32–2.27 (m, 1H), 2.27–2.13 (m, 4H), 2.13–2.00 (m, 4H), 2.00–1.82 (m, 4H), 1.55–1.50 (m, 1H), 1.21 (s, 3H), 0.54 (app td, 1H, $J = 13.2$, 5.0 Hz). |
| **(500 MHz, CDCl$_3$)** | |

| **13C NMR:** | 153.0, 144.8, 144.4, 143.0, 139.7, 134.8, 130.5, 127.9, 125.4, 119.9, 119.5, 118.0, 85.7, 83.6, 79.2, 58.7, 47.8, 47.2, 41.0, 38.8, 38.5, 36.5, 33.6, 33.2, 28.3, 27.9, 20.6, 14.6. |
| **(126 MHz, CDCl$_3$)** | |

| **FTIR, cm$^{-1}$:** | 3234 (br), 2930 (s), 2859 (m), 1454 (m), 1279 (m). |
| **(thin film)** | |

| **HRMS:** | Calcd for $(C_{30}H_{36}N_2O_2+H)^+$ 457.2850 |
| **(ESI)** | Found 457.2856 |

| **TLC** | $R_f = 0.23$ (UV, $p$-anisaldehyde) |
| **(methanol)** | |
Cortistatin K (10).

Trifluoroacetic anhydride (6.1 µL, 44 µmol, 5 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol (cortistatin K series) 162 (4.0 mg, 8.8 µmol, 1 equiv), pyridine (7.2 µL, 88 µmol, 10 equiv) and 4-dimethylaminopyridine (0.54 mg, 4.4 µmol, 0.50 equiv) in dichloromethane (1.7 mL). After 5 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 1:1 methanol–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (ca. 1.0 mL) was added, and the resulting solution was transferred by cannula to a 10-mL microwave vessel (CEM Corporation, cat. #908035), to which a cap had been affixed by crimping. The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.20 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2’-azobisisobutyronitrile (4.4 mg, 26 µmol, 3.0 equiv) in benzene (80 µL) followed by tributyltin hydride (19 µL, 70.1 µmol, 8.0 equiv). The reaction
mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was transferred by pipette to a round-bottom flask and the product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish cortistatin K (10) as a white solid (2.5 mg, 65% over two steps, >90% purity as judged by ¹H NMR analysis).

Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 45 min, flow rate: 3 mL/min). Fractions eluting at 20–25 min were collected and concentrated. To the residue was added saturated aqueous sodium bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was then purified by flash column chromatography on Sephadex® LH-20 resin (methanol) to afford cortistatin K (10) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.2 mg of cortistatin K (10) of >95% purity.

¹H NMR: 9.22 (s, 1H), 8.48 (d, 1H, J = 5.9 Hz), 7.79 (s, 1H), 7.75
(500 MHz, CDCl₃) (d, 1H, J = 8.8 Hz), 7.62 (d, 1H, J = 5.9 Hz), 7.58 (d, 1H, J = 8.3 Hz), 5.74 (s, 1H), 5.27 (br s, 1H), 3.00 (app t, 1H, J = 9.8 Hz), 2.67 (app br s, 1H), 2.33 (s, 6H), 2.45–2.23 (m, 5H), 2.22–2.06 (m, 3H), 2.05–1.97 (m, 3H), 1.95–1.78 (m, 4H), 1.65–1.58 (m, 1H), 1.51 (app td, 1H, J = 12.9, 4.9 Hz), 0.60 (s, 3H).

¹³C NMR :

(100 MHz, CDCl₃) δ 152.4, 144.9, 142.5, 140.2, 140.0, 134.7, 132.3, 128.7, 126.4, 125.7, 120.1, 119.7, 117.7, 83.3, 79.3, 58.9, 57.5, 53.5, 45.3, 41.1, 38.9, 37.2, 36.6, 33.1, 28.4, 28.3, 26.0, 20.7, 12.8.

FTIR, cm⁻¹:

(thin film) 2955 (s), 2930 (s), 2857 (m), 1599 (m), 1472 (m), 1371 (s), 1254 (s).

HRMS:

(ESI) Calcd for (C₃₀H₃₆N₂O+H)+ 441.2900 Found 441.2892

TLC

(methanol) Rₛ = 0.30 (UV, p-anisaldehyde)

Optical Rotation

[α]₀° = –50.1º (c = 0.077 in chloroform);

lit. ²¹: [α]₀° = –47.1º (c = 0.32 in chloroform)
1'-Chloro-Isoquinolyl Alcohol 169 (Cortistatin A Series).

To a flame-dried, 10-mL Schlenk flask fitted with a stirring bar was added anhydrous cerium(III) chloride powder (101 mg, 408 µmol, 10 equiv) in glovebox. The reaction flask was placed under high vacuum (0.5 mmHg) and heated in an oil bath at 90 ºC with vigorous stirring. After 2 h, the oil bath was removed. The reaction flask was back filled with Ar and cooled in an ice bath. Tetrahydrofuran (1.0 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The white suspension was stirred vigorously. After 16 h, a solution of 1-chloro-7-iodoisoquinoline (47) (65 mg, 224 µmol, 5.5 equiv) in tetrahydrofuran (0.25 mL) was added. The reaction flask was cooled to −78 ºC in a dry ice-acetone bath. A solution of n-butyllithium in hexanes (2.50 M, 82 µl, 204 µmol, 5 equiv) was added, producing a chartreuse suspension. After 30 min, a solution of dimethylamino ketone 108 (cortistatin A series) (24.0 mg, 40.8 µmol, 1 equiv) in tetrahydrofuran (0.25 mL) was added. After 30 min, saturated aqueous ammonium chloride solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered.
and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate, finally 1:1 hexanes–ethyl acetate) to afford 1'-chloro-isoquinolyl alcohol 169 (cortistatin A series) as a pale yellow foam (26.0 mg, 85%).

\[ ^{1}H \text{ NMR:} \]
(500 MHz, CDCl\textsubscript{3})

\begin{align*}
8.37 & \text{ (br s, 1H)}, \ 8.26 \ (d, \ 1H, \ J = 6.0 \ Hz), \ 7.86 \ (br \ d, \ 1H, \ J = 10.1 \ Hz), \\
7.77 & \ (d, \ 1H, \ J = 9.2 \ Hz), \ 7.57 \ (d, \ 1H, \ J = 5.5 \ Hz), \\
5.91 & \ (s, \ 1H), \ 5.16 \ (dd, \ 1H, \ J = 4.8, \ 2.5 \ Hz), \ 3.93 \ (d, \ 1H, \ J = 7.8 \ Hz), \\
3.40 & \ (app t, \ 1H, \ J = 8.0 \ Hz), \ 2.63 \ (app td, \ 1H, \ J = 9.5, \ 4.8 \ Hz), \\
2.48–2.40 & \ (m, \ 1H), \ 2.39–2.27 \ (m, \ 2H), \ 2.20 \ (s, \ 6H), \\
2.17–2.07 & \ (m, \ 4H), \ 1.91 \ (dd, \ 1H, \ J = 17.9, \ 5.0 \ Hz), \ 1.87–1.74 \ (m, \ 2H), \\
1.67–1.58 & \ (m, \ 1H), \ 1.51 \ (d, \ 1H, \ J = 17.9 \ Hz), \ 1.29–1.23 \ (m, \ 1H), \\
1.17 & \ (s, \ 3H), \ 0.98–0.89 \ (m, \ 18H), \ 0.67–0.56 \ (m, \ 12H);
\end{align*}

\[ ^{13}C \text{ NMR:} \]
(126 MHz, CDCl\textsubscript{3})

\begin{align*}
151.8, & \ 146.8, \ 142.5, \ 141.5, \ 139.1, \ 136.7, \ 131.0, \ 126.3, \ 126.2, \\
124.0, & \ 120.8, \ 120.2, \ 120.0, \ 85.7, \ 81.7, \ 79.3, \ 76.1, \ 75.3, \ 64.5, \\
47.6, & \ 46.0, \ 41.2, \ 39.1, \ 38.6, \ 35.5, \ 31.3, \ 29.1, \ 20.7, \ 17.3, \ 7.1, \\
7.0, & \ 5.3, \ 5.0;
\end{align*}

\[ \text{FTIR, cm}^{-1}: \]
(thin film)

\begin{align*}
3327 & \text{ (br), } 2953 \ (s), \ 2876 \ (m), \ 1701 \ (s), \ 1456 \ (s), \ 1146 \ (s).
\end{align*}
HRMS:  Calcd for (C_{42}H_{63}ClN_{2}O_{4}Si_{2}+H)^{+}  750.4015
(ESI)  Found  750.4088

TLC  \text{R}_f = 0.21 \ (\text{UV, } p\text{-anisaldehyde})
(2:1 \text{ hexane–ethyl acetate})
Cortistatin A Bis(triethylsilyl) Ether (170).

Trifluoroacetic anhydride (24.1 µL, 173 µmol, 5 equiv) was added dropwise to an ice-cooled solution of 1'-chloro-isoquinolyl alcohol 169 (26.0 mg, 35 µmol, 1 equiv), pyridine (28 µL, 346 µmol, 10 equiv) and 4-dimethylaminopyridine (2.1 mg, 17 µmol, 0.5 equiv) in dichloromethane (3.5 mL). After 30 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (4:1 hexanes–ethyl acetate initially, grading to 2:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow foam.

Benzene (0.6 mL + 2 × 0.2 mL wash) was added, and the resulting solution was transferred by cannula to a flame-dried, 10-mL Schlenk flask fitted with a stirring bar. The reaction flask was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. The flask was back filled with Ar and added a solution of 2,2'-azobisobutyronitrile (17.2 mg, 105 µmol, 3.0 equiv) in benzene (0.7 mL). The reaction mixture was degassed by freeze-pump-thaw for four cycles. To the resulting solution was added tributyltin hydride (139 µL, 525 µmol,
15 equiv). The stopcock was closed and the reaction flask was placed in an oil bath preheated to 100 °C. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 °C. The product solution was directly purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford cortistatin A bis(triethylsilyl) ether (170) as a pale yellow oil (17.1 mg, 70% over two steps). The spectral properties were identical to those previously reported.
Cortistatin A (1).

Triethylamine trihydrofluoride (39.5 µL, 242 µmol, 10 equiv) was added to a solution of cortistatin A bis(triethylsilyl) ether (170) (17.0 mg, 24.2 µmol, 1 equiv) in tetrahydrofuran (1.0 mL) at 23 ºC. After 30 min, the reaction mixture was partitioned between dichloromethane (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated. The aqueous layer was further extracted with dichloromethane (5 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (50:1 ethyl acetate–methanol initially, grading to 2:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to afford cortistatin A (1) as a white solid (10.8 mg, 95%, >90% purity by 1H NMR analysis). The spectral properties were identical to those previously reported.
Azido Ketone 171 (Cortistatin A Primary Amine Series).

Chlorotriethylsilane (37 µL, 0.218 mmol, 6 equiv) was added dropwise to an ice-cooled solution of azido diol (153) (13.0 mg, 0.036 mmol, 1 equiv), triethylamine (51 µL, 0.364 mmol, 10 equiv), and 4-dimethylaminopyridine (8.9 mg, 0.073 mmol, 2 equiv) in N,N-dimethylformamide (1.0 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 3 h, the reaction mixture was partitioned between ether (15 mL) and a 1:1:1 mixture of water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution (12 mL). The layers were separated. The aqueous layer was extracted with ether (4 × 10 mL). The organic layers were combined. The combined solution was washed with water (15 mL) and saturated aqueous sodium chloride solution (2 × 15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate) to afford azido ketone 171 (cortistatin A primary amine series) as a pale yellow oil (20 mg, 94%).

$^1$H NMR: (500 MHz, CDCl$_3$) 6.08 (d, 1H, $J = 1.8$ Hz), 5.43 (dd, 1H, $J = 4.5$, 2.9 Hz), 3.97 (d, 1H, $J = 8.7$ Hz), 3.41 (t, 1H, $J = 8.5$ Hz), 3.33 (ddd, 1H, $J = 12.1$, 8.0, 4.3 Hz), 2.52 (dd, 1H, $J = 19.2$, 8.7 Hz), 2.38 (dd, 1H, $J = 12.7$, 5.8 Hz), 2.28–2.18 (m, 4H),
2.18–2.09 (m, 3H), 1.97 (t, 1H, $J = 12.6$ Hz), 1.92–1.82 (m, 1H), 1.78–1.69 (m, 2H), 1.03–0.95 (m, 18H), 0.93 (s, 3H), 0.76–0.63 (m, 12H);

$^{13}$C NMR:

(126 MHz, CDCl$_3$)

220.4, 141.8, 139.7, 120.5, 119.7, 81.3, 78.8, 78.5, 73.9, 62.6, 47.7, 47.2, 39.3, 37.4, 35.9, 33.9, 31.6, 18.9, 16.9, 7.0, 5.2, 5.0;

FTIR, cm$^{-1}$:

(Thin film)

2957 (s), 2878 (m), 2106 (vs), 1741 (vs), 1641 (m), 1460 (m), 1150 (s).

HRMS:

Calcd for (C$_{31}$H$_{51}$N$_3$O$_4$Si$_2$+Na)$^+$ 608.3310

Found 608.3306

TLC

$R_f = 0.50$ (UV, $p$-anisaldehyde)

(4:1 hexane–ethyl acetate)
Isoquinolyl Alcohol 172 (Cortistatin A Primary Amine Series).

A solution of \( n \)-butyllithium in hexanes (2.50 M, 68 µL, 0.171 mmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (157) (43.5 mg, 0.171 mmol, 5 equiv) in tetrahydrofuran (2 mL) at −78 °C, producing a dark red solution. After 30 min, \( N,N,N',N' \)-tetramethylethylenediamine (79 µL, 0.512 mmol, 15 equiv) was added. After 10 min, a solution of bistriethylsilyl ether ketone 171 (20 mg, 0.034 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added via cannula. The flask containing 171 was rinsed with tetrahydrofuran (2 × 0.2 mL), and the rinses were added to the reaction mixture. After 30 min, saturated aqueous sodium bicarbonate solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 °C. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 1:1 hexanes–ethyl acetate) to afford isoquinolyl alcohol 172 (cortistatin A primary amine series) as a pale yellow oil (12.2 mg, 50%), and,
separately, recovered azido ketone 171 (cortistatin A primary amine series) (6.0 mg, 30%).

**1H NMR:**
(500 MHz, CDCl₃)

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**FTIR, cm⁻¹:**
(thin film)

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| **TLC**         | R\textsubscript{f} = 0.18  (UV, \textit{p}-anisaldehyde) (2:1 hexane–ethyl acetate) |
Trifluoroacetamide 175 (Cortistatin A Primary Amine Series).

A solution of trimethylphosphine in toluene (1.0 M, 35 µL, 35 µmol, 5 equiv) was added to a solution of azido isoquinolyl alcohol 172 (cortistatin A primary amine series) (5.0 mg, 7.0 µmol, 1 equiv) in benzene (1.5 mL). The reaction flask was placed in an oil bath pre-heated to 55ºC. After 1.5 h, the reaction flask was cooled in an ice bath. Pyridine (11 µL, 140 µmol, 20 equiv) and 4-dimethylaminopyridine (0.85 mg, 7.0 µmol, 1 equiv) were added followed by trifluoroacetic anhydride (9.7 µL, 70 µmol, 10 equiv). After 30 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a colorless oil.

Benzene (0.6 mL + 2 × 0.2 mL wash) was added, and the resulting solution was transferred by cannula to a 10-mL microwave vessel (CEM Corporation, cat. #908035), to which a cap had been affixed by crimping. The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect
azeotropic drying. Benzene (0.65 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2’-azobisisobutyronitrile (3.4 mg, 21 µmol, 3.0 equiv) in benzene (50 µL). The reaction mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. Tributyltin hydride (15 µL, 56 µmol, 8.0 equiv) was then added. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 1 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was directly purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to furnish trifluoroacetamide 175 (cortistatin A primary amine series) as a pale yellow oil (3.2 mg, 60% over two steps).

$^{1}$H NMR: 

$\text{(500 MHz, CDCl}_3\text{)}$

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161
\( ^{13}C \text{ NMR} \) :

156.2 \((q, J = 35.7 \text{ Hz})\), 152.3, 142.5, 141.5, 140.0, 139.7, 134.7, 132.0, 128.1, 126.3, 125.9, 121.5, 120.2, 120.0, 84.3, 80.7, 79.9, 75.3, 56.8, 53.3, 51.9, 44.5, 40.0, 38.1, 30.6, 29.7, 29.3, 26.4, 20.6, 15.3, 7.0, 6.9, 4.8;

\( ^{19}F \text{ NMR} \) :

\(-76.7 \text{ (s)}\);

\( \text{FTIR, cm}^{-1} \) :

3315 (br), 2955 (s), 2928 (vs), 1724 (vs), 1458 (m), 1379 (m);

\( \text{HRMS} \) :

Calcd for \((\text{C}_{42}\text{H}_{59}\text{F}_{3}\text{N}_{2}\text{O}_{4}\text{Si}_{2}+\text{H})^+\) 769.4038

Found 769.4054

\( \text{TLC} \) :

\( R_f = 0.14 \) (UV, \( p \)-anisaldehyde)

(4:1 hexane–ethyl acetate)
1'-Chloro-Isoquinolyl Alcohol 177 (Cortistatin A Primary Amine Series).

To a flame-dried, 10-mL Schlenk flask fitted with a stirring bar was added anhydrous cerium(III) chloride powder (56.8 mg, 230 µmol, 10 equiv) in glovebox. The reaction flask was placed under high vacuum (0.5 mmHg) and heated in an oil bath at 90 ºC with vigorous stirring. After 2 h, the oil bath was removed. The reaction flask was back filled with Ar and cooled in an ice bath. Tetrahydrofuran (1.0 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The white suspension was stirred vigorously. After 16 h, a solution of 1-chloro-7-iodoisoquinoline (47) (36.7 mg, 127 µmol, 5.5 equiv) in tetrahydrofuran (0.2 mL) was added. The reaction flask was cooled to −78 ºC in a dry ice-acetone bath. A solution of n-butyllithium in hexanes (1.60 M, 72 µl, 115 µmol, 5 equiv) was added, producing a chartreuse suspension. After 30 min, a solution of dimethylamino ketone 171 (cortistatin A primary amine series) (13.5 mg, 23 µmol, 1 equiv) in tetrahydrofuran (0.2 mL) was added. After 30 min, saturated aqueous ammonium chloride solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was
filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford 1'-chloro-isoquinolyl alcohol 177 (cortistatin A primary amine series) as a pale yellow oil (13.8 mg, 80%).

<p>| 1H NMR:                        | 8.35 (br s, 1H), 8.26 (d, 1H, (J = 6.0) Hz), 7.86 (d, 1H, (J = 9.2) Hz), 7.78 (d, 1H, (J = 8.7) Hz), 7.57 (d, 1H, (J = 5.5) Hz), 5.96 (s, 1H), 5.20 (dd, 1H, (J = 5.0, 2.7) Hz), 3.92 (d, 1H, (J = 7.8) Hz), 3.33–3.27 (m, 2H), 2.64 (ddd, 1H, (J = 14.1, 9.5, 4.3) Hz), 2.46–2.35 (m, 2H), 2.32 (td, 1H, (J = 13.4, 6.8) Hz), 2.20–2.09 (m, 3H), 1.96–1.88 (m, 2H), 1.81–1.74 (m, 1H), 1.69 (dd, 1H, (J = 18.8, 10.1) Hz), 1.51 (d, 1H, (J = 17.4) Hz), 1.28–1.23 (m, 1H), 1.17 (s, 3H), 1.00–0.91 (m, 18H), 0.72–0.58 (m, 12H); |
| 13C NMR:                       | 151.9, 146.7, 141.6, 141.3, 138.3, 136.7, 130.9, 126.3, 126.2, 124.0, 121.8, 120.2, 119.6, 85.6, 81.8, 78.7, 78.3, 73.8, 62.6, 47.5, 45.9, 39.2, 39.0, 37.8, 35.4, 31.3, 20.7, 17.3, 7.0, 7.0, 5.1, 5.0; |
| FTIR, cm(^{-1}):             | 3343 (br), 2955 (m), 2934 (m), 2104 (s), 1604 (s), 1454 (s). |</p>
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Trifluoroacetamide 175 (Cortistatin A Primary Amine Series).

A solution of trimethylphosphine in toluene (1.0 M, 77 µL, 77 µmol, 5 equiv) was added to a solution of 1'-chloro-isoquinolyl alcohol 177 (cortistatin A primary amine series) (11.5 mg, 15 µmol, 1 equiv) in benzene (3.0 mL). The reaction flask was placed in an oil bath pre-heated to 55 ºC. After 1.5 h, the reaction flask was cooled in an ice bath. Pyridine (25 µL, 307 µmol, 20 equiv) and 4-dimethylaminopyridine (1.9 mg, 15 µmol, 1 equiv) were added followed by trifluoroacetic anhydride (21 µL, 153 µmol, 10 equiv). After 30 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 15 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow solid.

Benzene (0.6 mL + 2 × 0.2 mL wash) was added, and the resulting solution was transferred by cannula to a 10-mL microwave vessel (CEM Corporation, cat. #908035), to which a cap had been affixed by crimping. The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect
azeotropic drying. Benzene (0.70 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (7.4 mg, 45 µmol, 3.0 equiv) in benzene (50 µL). The reaction mixture was degassed by sparging for 10 min with a slow stream of argon gas through a 22-gauge stainless steel needle. Tributyltin hydride (81 µL, 300 µmol, 20 equiv) was then added. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 °C. After 1.5 h, the oil bath was removed and the reaction flask was allowed to cool to 23 °C. The reaction mixture was directly purified by flash-column chromatography on Davisil® silica gel (40:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 4:1 hexanes–ethyl acetate) to furnish trifluoroacetamide 175 (cortistatin A primary amine series) as a pale yellow oil (7.0 mg, 61% over two steps). The spectral properties were identical to those previously reported.
Cortistatin A Primary Amine (176).

Aqueous sodium hydroxide solution (1.0 N, 0.20 mL) was added to a solution of trifluoroacetamide 175 (cortistatin A primary amine series) (2.1 mg, 2.7 µmol, 1 equiv) in methanol (0.80 mL) at 23 °C. After 12 h, the reaction mixture was partitioned between a mixture of saturated aqueous sodium chloride solution (10 mL) and dichloromethane (10 mL). The layers were separated. The aqueous layer was further extracted with dichloromethane (5 × 10 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was directly used in subsequent steps without further purification (a pale yellow solid, 1.1 mg, 90%, >90% purity by \(^1\)H NMR analysis).

\(^1\)H NMR: \((500 \text{ MHz, CDCl}_3)\)

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Chapter 4

A Versatile Synthesis of Substituted Isoquinolines
Introduction

The previous two chapters detailed an efficient and general approach towards the cortistatin family of natural products. In addition to natural cortistatins, our synthetic strategy should allow us to prepare a diverse array of cortistatin analogs. As described in Chapter 1, the isoquinoline substituent is known to be essential to the biological activity of the cortistatins. Therefore, we are particularly interested in preparing cortistatin analogs with differentially substituted isoquinolines, requiring a versatile methodology to synthesize differently substituted isoquinolines (Figure 4.1).

Figure 4.1 Diverse Cortistatin Derivatives by Isoquinoline Modification.

Isoquinoline was first isolated by Hoogewerf and van Dorp from coal tar in 1885 and its structure was elucidated in the subsequent year.\(^1\) Since then, isoquinolines have been recognized as one of the most important class of heterocycles: medicinally important isoquinolines include papaverine (used for multiple indications to improve blood flow),\(^2\) fasudil (approved for the treatment of cerebral vasospasm in Japan),\(^3\)

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BMS-6500324 and MK-12205 (candidates for the treatment of hepatitis C), and numerous dihydro-, tetrahydro-, as well as decahydro isoquinoline derivatives.6

Figure 4.2 Synthetic Approaches to Isoquinolines.

The literature approaches to construct this important class of heterocyclic rings are briefly summarized in Figure 4.2. Traditional methods to the synthesis of isoquinolines include the Pomeranz-Fitsch,7 the Bischler-Napieralski,8 and the Pictet-Spengler reactions;9 however, their substrate scope is often limited due to the use of strong acids and elevated temperatures in the reaction condition. In recent years, Larock and co-workers have pioneered transition-metal-catalyzed annulation reactions to

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6 For a general review, see Bentley, K. W. In The Isoquinoline Alkaloids, CRC Press, 1998.


construct isoquinoline rings from \( o \)-iodoaldimines and alkynes.\(^\text{10,11}\) People have also used electrophilic cyclization reactions,\(^\text{12}\) aryne annulation,\(^\text{13}\) ring expansion,\(^\text{14}\) and numerous other methods\(^\text{15}\) to synthesize isoquinoline rings.

Despite the large number of known methods, however, literature routes to many of the isoquinoline structures we envisioned were either lengthy or impractical. Thus we decided to develop a new, versatile synthesis of substituted isoquinolines. Two important precedents informed our present work. The first was the Poindexter synthesis of 3-substituted isoquinoline (191) by deprotonation of \( N,2 \)-dimethylbenzamide (190) and subsequent addition of the resulting \( o \)-tolylbenzamide dianions to nitriles followed by aqueous ammonium chloride workup (Scheme 4.1).\(^\text{16}\) The second was the Forth method to prepare \( o \)-substituted benzaldehyde derivative (193) by metalation and subsequent alkylation of \( o \)-tolualdehyde tert-butylimines (192).\(^\text{17,18}\) We imagined that trapping the

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metalated o-tolualdehyde tert-butylimine anions with nitriles might provide a direct route to 3-substituted isoquinolines. As detailed in this chapter, the chemistry proved to be much more versatile than we initially imagined, by virtue of transformations that ensue subsequent to addition of the nitrile.¹⁹

Scheme 4.1 Literature Precedents and Our Approach to Construct Isoquinoline Rings.

A Versatile Synthesis of Substituted Isoquinolines

Initial experiments were conducted in a simple system with the readily available o-tolualdehyde tert-butylimine (192, Scheme 4.2). The Forth’s condition¹⁷ was applied, in which n-butyllithium (1.05 equiv) was added slowly to an ice-cooled solution of o-

tolualdehyde *tert*-butylimine (192, 1 equiv) in the presence of a catalytic amount of tetramethylpiperidine (TMP, 0.10 equiv) in tetrahydrofuran (0.5 M) over 40 min, generating the *o*-tolyl anion as a deep purple solution. This deep purple solution was then cannulated to benzonitrile (1.5 equiv) at −78 ºC, forming a dark red solution within 3 min. Upon warming to 23 ºC, the reaction mixture became dark brown. Aqueous work-up with ammonium chloride followed by chromatography purification provided 3-phenylisoquinoline (194) in 42% yield and, separately, 3,3'-diphenyl-1,1'-biisoquinoline (195), in 35% yield. This by-product probably arose by base-induced dimerization of 3-phenylisoquinoline followed by oxidation, suggesting that formation of the isoquinoline ring had occurred prior to quenching with ammonium chloride. By adopting a different quenching protocol, addition of excess trifluoroacetic acid at −78 ºC then warming to 23 ºC, formation of 195 was avoided and 3-phenylisoquinoline (194) could be isolated in 80% yield.

Scheme 4.2 Initial Studies to Synthesize 3-Substituted Isoquinoline.

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Mechanistically, we considered that after the initial metalation, the deep purple anion 196 would add to benzonitrile, affording an imido anion 197, which subsequently cyclized to give a tert-butylamido anion 198. However, neither 197 nor 198 seemed likely to account for the dark red color that we observed upon addition of anion 196 to benzonitrile. We speculated that the tert-butylamido anion 198 might react further by intra- or intermolecular proton transfer to form an extended eneamido anion 199, and this did appear to be a reasonable candidate to account for the red color we observed.21 To test this hypothesis, methyl iodide (2 equiv) was added to the deep red solution shortly after its formation at –78 °C, producing an orange solution within minutes. Addition of trifluoroacetic acid (excess) after 30 min, also at –78 °C, followed by warming, aqueous workup, and chromatography purification provided 4-methyl-3-phenyl-isoquinoline (200) in 80% yield.22,23

Scheme 4.3 Synthesis of 4-Methyl-3-phenylisoquinoline (200) and a Plausible Mechanism.

21 An alternative sequencing of steps is feasible; e.g., tautomerization of intermediate 197 may occur prior to ring closure to form 199.
23 3,4-dihydro-1(2H)-isoquinolones have been synthesized by the condensation of N,N-diethyl-o-toluamide anions with aldimes. Lithiation (and subsequent trapping) of the benzylic position was reported in this study: Clark, R. D.; Jahangir J. Org. Chem. 1987, 52, 5378–5382.
As illustrated in Table 4.1, a wide range of substituted isoquinolines could be synthesized by the direct condensation of o-tolualdehyde tert-butylimine anions with different nitriles followed by electrophilic trapping at C4. The Forth protocol\textsuperscript{17} was found to be quite general for the metalation of different o-tolualdehyde tert-butylimines, except for the halogenated ones, in which lithium diisopropylamide (LDA, 1.05 equiv) was found to be superior and led to higher yields (entries 2, 6 and 8). Entries 1–4 demonstrated the use of aliphatic nitriles as substrates and showed that a variety of alkyl halides were suitable for C4 alkylation, including ethyl iodide (entry 1), n-butyl iodide (entry 2), allyl bromide (entry 3), and benzyl bromide (entry 4). Although a number of potentially enolizable aliphatic nitriles were successfully employed, thus far, acetonitrile has not proven to be a viable coupling partner, likely because enolization was more rapid than addition to the nitrile.\textsuperscript{24} Entries 5–9 illustrated that N,N-dialklycyanamides were also effective substrates for the condensation, and the subsequent C4 trapping could be successfully achieved not only with alkylation reagents like para-bromobenzyl bromide (entry 5) and methyl iodide (to afford a hindered 4,5-dimethylisoquinoline structure, entry 7), but also with Mander’s reagent to introduce a C4 carbomethoxy group (entry 6),\textsuperscript{25} and with N-fluorobenzenesulfonylimide to produce isoquinolines with C4 fluorine (entries 8 and 9). Entries 10–13 exemplified couplings with arylnitriles and trapping reactions for the introduction of C4 heteroatoms other than fluorine, including chlorine (using hexachloroethane, entry 10), oxygen [using oxodiperoxymolybdenum (pyridine)(hexamethylphosphoric triamide), MoOPH, entry 11],\textsuperscript{26} sulfur (using methyl

\textsuperscript{24} Poindexter had also noted that acetonitrile was not a suitable substrate in his method for isoquinolone formation, see: Ref 16.
\textsuperscript{25} S. R. Crabtree, W. L. Alex Chu, L. N. Mander, Synlett 1990, 169–170.
Table 4.1 Synthesis of a Wide Range of Substituted Isoquinolines by Condensation of Lithiated o-Tolualdehyde tert-Butylimines with Nitriles Followed by Trapping at C4 with Various Electrophiles.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Nitrile</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Imine 1" /></td>
<td>NC-CH₃</td>
<td>EtI</td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>52</td>
</tr>
<tr>
<td>2[c]</td>
<td><img src="image3.png" alt="Imine 2" /></td>
<td>NC-OC₃H₅</td>
<td>n-BuI</td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>50</td>
</tr>
<tr>
<td>3[d]</td>
<td><img src="image5.png" alt="Imine 3" /></td>
<td>NC-NEt₂</td>
<td>1-Br</td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Imine 4" /></td>
<td>NC-OEt</td>
<td>BnBr</td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>50</td>
</tr>
<tr>
<td>5[d]</td>
<td><img src="image9.png" alt="Imine 5" /></td>
<td>NC-N-OH</td>
<td>Br-CH₂OBr</td>
<td><img src="image10.png" alt="Product 5" /></td>
<td>52</td>
</tr>
<tr>
<td>6[c]</td>
<td><img src="image11.png" alt="Imine 6" /></td>
<td>NC-N-O</td>
<td>CO-OC₃H₅</td>
<td><img src="image12.png" alt="Product 6" /></td>
<td>66</td>
</tr>
<tr>
<td>7[d]</td>
<td><img src="image13.png" alt="Imine 7" /></td>
<td>NC-N-CH₃</td>
<td>CH₃I</td>
<td><img src="image14.png" alt="Product 7" /></td>
<td>54</td>
</tr>
<tr>
<td>8[c]</td>
<td><img src="image15.png" alt="Imine 8" /></td>
<td>NC-N-Bn</td>
<td>NFSI</td>
<td><img src="image16.png" alt="Product 8" /></td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17.png" alt="Imine 9" /></td>
<td>NC-N-PMB</td>
<td>NFSI</td>
<td><img src="image18.png" alt="Product 9" /></td>
<td>60</td>
</tr>
</tbody>
</table>
Table 4.1 (Continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>Condition</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>10[c]</td>
<td><img src="image1" alt="Structure 10" /></td>
<td>C₂Cl₆</td>
<td>54</td>
</tr>
<tr>
<td>11[f]</td>
<td><img src="image2" alt="Structure 11" /></td>
<td>MoOPH</td>
<td>40</td>
</tr>
<tr>
<td>12[d]</td>
<td><img src="image3" alt="Structure 12" /></td>
<td>CH₃SSCH₃</td>
<td>68</td>
</tr>
<tr>
<td>13[d]</td>
<td><img src="image4" alt="Structure 13" /></td>
<td></td>
<td>55</td>
</tr>
</tbody>
</table>

[a] For transformations with enolizable nitriles as substrates (entries 1–4) the nitriles were used as the limiting reagent (1 equiv) and the tert-butilaldimines were used in excess (1.25 equiv); in most other cases the tert-butilaldimine was used as the limiting reagent (1 equiv) and the nitrile was used in excess (1.25–1.5 equiv). Metalation of the tert-butilaldimine was achieved by the method of Forth et al.\(^\text{17}\) [b] Isolated yields based on the limiting reagent. In the fluorinations of entries 8 and 9 the fluorinating agent N-fluorobenzene-sulfonimide (NFSI) was used as the limiting reagent (the tert-butilaldimine was used in excess, 1.25 equiv). [c] With the halogenated tert-butilaldimine substrates of entries 2, 6, and 8, lithium diisopropylamide (LDA, 1.05 equiv) was used for metalation in lieu of TMP-n-BuLi. [d] Hexamethylphosphoramide (HMPA, 2 equiv) was added prior to the addition of the electrophile. [e] Electrophilic trapping with hexachloroethane was conducted by addition of the reaction mixture by cannula to a large excess of the electrophile (4 equiv) at –78 °C. [f] Potassium hexamethyldisilazide (KHMDs, 1 equiv) was added just prior to addition of MoOPH (1.5 equiv).
disulfide, entry 12), and nitrogen (using diethylazodicarboxylate, entry 13). In the latter two instances we found that the efficiencies of C4 trapping were enhanced in the presence of the additive hexamethylphosphoramide (HMPA, 2 equiv). This additive also proved to enhance the yield of C4-alkylation products in the cases of entries 3, 5, and 7, which we believe was due to acceleration of an otherwise slow proton-transfer reaction that formed the eneamido anion intermediate.27

4-Chloroisooquinolines, 1-tert-butylamino isoquinolines, or 4,4'-biisoquinolines were obtained selectively by modification of the protocol after trapping with hexachloroethane (Scheme 4.4). After metalation and condensation with benzonitrile, the putative eneamido anion 199 was quenched by addition to an excess of hexachloroethane (4 equiv) at –78 °C. Work-up under standard acidic conditions, with excess

Scheme 4.4 Selective Preparation of Isoquinolines by Variation of Reaction Conditions.

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27 In the absence of HMPA C4-unsubstituted isoquinolines were formed as major by-products in each of these cases; In the cases of entries 3, 5, and 7, where proton transfer to form the eneamide intermediate is believed to be slow, addition of HMPA caused a noticeable darkening of the red or orange solutions.
trifluoroacetic acid, led to the expected 4-chloroisouquinoline product 202 (also see Table 4.1, entry 10). Interestingly, using an alternative basic work-up procedure with excess diethylamine, elimination of hydrogen chloride in intermediate 201 occurred, providing 1-tert-butylamino isoquinoline derivative 203, which proved valuable for subsequent diversification of C1. Also, upon addition of substoichiometric amount of the electrophile (0.4 equiv, added slowly) to the eneamido anion 199, a 4,4′-biisoquinoline derivative 205 was formed as the primary product, which likely arose from the dimerization product 204 formed between the remaining 4-lithiated isoquinolinyl intermediate 199 and the newly formed 4-chloro isoquinolinyl intermediate 201.

With tert-butylaldimine substrates containing a second ortho directing group, such as a 3-fluoro substituent, it was possible to assemble substituted isoquinolines from as many as four components in sequence in a single operation (Scheme 4.5). For example, metatlation of 3-fluoro-5-(trimethylsilyl)benzaldehyde tert-butylimine (206) with lithium

**Scheme 4.5** One-pot Synthesis of Isoquinolines from Aldimines with a Second o-Directing Group.

28 For an example where an isoquinolinyl dimer was formed by a similar mechanism, see: Ref 22b.
2,2,6,6-tetramethylpiperidide (LTMP, 1.05 equiv) initially formed an o-lithio intermediate that was trapped with methyl iodide (0.90 equiv); subsequent deprotonation of the methylated product in the same pot with lithium diisopropylamide (LDA, 1.05 equiv) at −40 ºC formed a dark red solution of the presumed o-toly1 anion; addition of benzonitrile, followed by C4-trapping with a second equivalent of methyl iodide afforded 5-fluoro-4-methyl-3-phenyl-7-(trimethylsilyl)isoquinoline (207) in 45% yield. A second example featured a simpler, three-component assembly by condensation of the presumed o-toly1 anion with N,N-bis(p-methoxybenzyl)cyanoamide to provide isoquinoline 208 in 55% yield, which proved to be a highly versatile intermediate for further elaboration (see below).

Some of the isoquinolines prepared above could be further derivatized to highly halogenated structures (Scheme 4.6). For example, treatment isoquinoline 209 (prepared in Table 4.1, entry 9) with iodine monochloride in dichloromethane at 0 ºC afforded product of 7-iododesilylation; subsequent addition of trifluoroacetic acid (neat) led to cleavage of the p-methoxybenzyl groups, providing 3-amino-4-fluoro-7-iodoisoquinoline (210) in 75% yield. Diazotization of the latter product 210 in the presence of fluoride and chloride sources gave rise to the corresponding 3-fluoroisoquinoline 211 and 3-chloroisoquinoline 212 in good yields. Application of the same sequence to isoquinoline 208 (prepared in Scheme 4.5) proceeded with chlorination at C4 followed by a slower 7-iododesilylation reaction during initial treatment with iodine monochloride; subsequent deprotection provided a 3-aminooisoquinoline 213, which was further transformed to polyhalogenated isoquinolines 214 and 215. Lastly, 1-tert-butylaminoisoquinoline

derivatives 217, prepared by a modified basic work-up (see Scheme 4.4), was transformed directly into 1-fluoroisoquinoline 218 by dealkylative diazotization in the presence of fluoride ions,\(^{31}\) which we anticipate should allow for further diversification of position C1 by standard nucleophilic aromatic substitution reactions. These isoquinolines with a halogen-handle at C7 should find applications in the synthesis of cortistatin analogs, which is the currently ongoing in our laboratory.

**Scheme 4.6 Preparation of Poly-halogenated Isoquinolines.**

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Conclusion

In summary, we have developed a versatile synthesis of substituted isoquinolines, in which lithiated o-tolualdehyde tert-butylimines were condensed with a wide range of nitriles to form eneamido anion intermediates that were trapped in situ with various electrophiles, affording a diverse array of highly substituted isoquinolines, many of which were difficult to access by known methods (Figure 4.4). Further substitutational diversification can be achieved by modification of the work-up conditions and by subsequent transformations. This method should be useful for the preparation of many biological active isoquinolines, especially for the synthesis of cortistatin analogs with isoquinoline modifications.

Figure 4.4 Summary of Our Synthetic Approach to Substituted Isoquinolines.
Experimental Section

**General Experimental Procedures.** All reactions were performed in round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM) or acidic ethanolic \( p \)-anisaldehyde solution (\( p \)-anisaldehyde) followed by brief heating on a hot plate. Flash-column chromatography was performed as described by Still *et al.*,\(^{32}\) employing silica gel (60 Å, 32–63 μM, standard grade, Dynamic Adsorbents, Inc.).

**Materials.** Commercial solvents and reagents were used as received with the following exceptions. 2,2,6,6-Tetramethylpiperidine, diisopropylamine, benzonitrile, isobutyronitrile, diethylamine, trimethylsilyl chloride, and hexamethylphosphoramide were distilled from calcium hydride under an atmosphere of argon or dinitrogen. Tetrahydrofuran was purified by the method of Pangborn *et al.*\(^{33}\) \( N \)-fluorobenzenesulfonylimide was recrystallized from ether. Iodomethane, iodoethane, 1-iodobutane, allyl bromide, benzyl bromide, and dimethyl disulfide were passed through

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basic alumina immediately prior to use. 2-Methoxyl-6-methylbenzaldehyde\textsuperscript{34} and oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH)\textsuperscript{35} were prepared according to literature procedures. The molarity of n-butyllithium solutions was determined by titration against a standard solution of diphenylacetic acid in tetrahydrofuran (average of three determinations).\textsuperscript{36}

**Instrumentation.** Proton magnetic resonance (\(_1^H\) NMR) spectra were recorded on Varian INOVA 400 (400 MHz), 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, \(\delta\) scale) and are referenced to residual protium in the NMR solvent (CHCl\(_3\), \(\delta\) 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, and coupling constant (\(J\)) in Hertz. Carbon nuclear magnetic resonance spectra (\(^{13}\)C NMR) were recorded on Varian INOVA 500 (126 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, \(\delta\) scale) and are referenced to the carbon resonances of the NMR solvent (CDCl\(_3\), \(\delta\) 77.0; C\(_6\)D\(_6\), \(\delta\) 128.0). Fluorine nuclear magnetic resonance spectra (\(^{19}\)F NMR) were recorded on Varian INOVA 500 (470 MHz) NMR spectrometers at 23 °C. Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer and were referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm\(^{-1}\)), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry

Facility. Melting points were measured using a Thomas Hoover uni-melt apparatus (6427F10) and were uncorrected.

(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the Supporting Information beginning with 219.)
2-Methyl-5-(trimethylsilyl)benzaldehyde (222)

A solution of borane-tetrahydrofuran in tetrahydrofuran (1.0 M, 123 mL, 123 mmol, 1.2 equiv) was added dropwise to a solution of 5-bromo-2-methylbenzoic acid (219, 22.0 g, 102 mmol, 1 equiv) in ether (120 mL) (CAUTION: gas evolution). After 1 h, the reaction flask was placed in an oil bath preheated to 50 ºC. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. Methanol (20 mL) was added dropwise (gas evolution) and the product solution was concentrated to remove the bulk of solvent. The residue was purified by flash-column chromatography (10:1 initially, grading to 5:1 hexanes–ethyl acetate) to provide 220 as a white solid (19.5 g, 95%).

A solution of n-butyllithium in hexanes (2.50 M, 77.6 mL, 194 mmol, 2.0 equiv) was added dropwise to a cooled solution of 220, (19.5 g, 97 mmol, 1 equiv) in tetrahydrofuran (200 mL) at –78 ºC. After 40 min, chlorotrimethylsilane (25.8 mL, 204 mmol, 2.1 equiv) was added. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, aqueous hydrochloric acid solution (4.0 N, 50 mL) was added. The product solution was concentrated to remove the bulk of solvent. The concentrate was partitioned between water (100 mL) and 2:1 hexanes–ethyl acetate (300 mL). The layers were separated. The aqueous layer was extracted with 2:1 hexanes–ethyl acetate (2 × 100 mL). The organic layers were combined. The combined solution was washed sequentially with water (100 mL), saturated aqueous sodium bicarbonate solution (100 mL), and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The
dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 initially, grading to 20:1 then 10:1 hexanes–ethyl acetate), furnishing 221 as a colorless oil (13.2 g, 70%).

Pyridinium chlorochromate (22.0 g, 102 mmol, 1.5 equiv) was added to an ice-cooled solution of 221, (13.2 g, 67.9 mmol, 1 equiv) in dichloromethane (120 mL). After 30 min, the cooling bath was removed. After 1 h, the reaction mixture was filtered through silica, washing with dichloromethane (3 × 100 mL). The filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate) to furnish 2-methyl-5-(trimethylsilyl)benzaldehyde (222) as a colorless oil (12.1 g, 93%).

\[^{1}H\text{ NMR}:\] (400 MHz, CDCl\(_3\))
10.30 (s, 1H), 7.93 (d, 1H, \(J = 1.5\) Hz), 7.62 (dd, 1H, \(J = 7.3, 1.5\) Hz), 7.25 (d, 1H, \(J = 7.3\) Hz), 2.67 (s, 3H), 0.30 (s, 9H).

\[^{13}C\text{ NMR:}\] (100 MHz, CDCl\(_3\))
193.3, 141.1, 138.5, 138.4, 137.2, 133.4, 131.2, 19.6, –1.2.

**FTIR**, cm\(^{-1}\): (thin film) 2957 (m), 1697 (vs), 1595 (m), 1265 (m), 1250 (s).

**HRMS**: Calcd for (C\(_{11}\)H\(_{16}\)OSi+H\(^+\))
(ESI) Found 193.1043 193.1051

**TLC**
\(R_f = 0.49\) (UV)
(9:1 hexanes–ethyl acetate)
3-Fluoro-5-(trimethylsilyl)benzaldehyde (224)\textsuperscript{37}

1,3-Dibromo-5-fluorobenzene (223, 2.52 mL, 20 mmol, 1 equiv) was added dropwise to a cooled solution of \textit{n}-butyllithium (2.50 M in hexanes, 8.0 mL, 20 mmol, 1 equiv) in ether (40 mL) at \(-78 \, ^\circ\text{C}\). After 40 min, chlorotrimethylsilane (2.54 mL, 20 mmol, 1 equiv) was added, followed by the addition of tetrahydrofuran (40 mL). After 40 min, a second portion of \textit{n}-butyllithium (2.50 M in hexanes, 8.8 mL, 22 mmol, 1.1 equiv) was added. After 30 min, \textit{N,N}-dimethylformamide (4.65 mL, 60 mmol, 3 equiv) was added. After 40 min, the cooling bath was removed and the reaction flask was allowed to warm to \(23 \, ^\circ\text{C}\). After 1 h, the product solution was concentrated to remove the bulk of solvent. The concentrate was partitioned between 2:1 hexanes–ethyl acetate (150 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (100:1 hexanes–ethyl acetate initially, grading to 40:1 hexanes–ethyl acetate, then 20:1 hexanes–ethyl acetate), furnishing 3-fluoro-5-(trimethylsilyl)benzaldehyde (224) as a yellow oil (3.14 g, 80%).

\(\text{\textsuperscript{1}H NMR:}\) 10.02 (dd, 1H, \(J = 1.8, 0.9 \text{ Hz}\)), 7.78 (s, 1H), 7.51 (ddd,

<table>
<thead>
<tr>
<th>Technique</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$^1$H NMR</strong></td>
<td>(500 MHz, CDCl$_3$) 1H, $J$ = 8.6, 2.6, 1.6 Hz), 7.45 (ddd, 1H, $J$ = 8.2, 2.3, 1.4 Hz), 0.32 (d, 10H, $J$ = 0.9 Hz).</td>
</tr>
<tr>
<td><strong>$^{19}$F NMR</strong></td>
<td>(470 MHz, CDCl$_3$) –113.1 (ddd, $J$ = 8.2, 8.0, 2.3 Hz).</td>
</tr>
<tr>
<td><strong>$^{13}$C NMR</strong></td>
<td>(126 MHz, CDCl$_3$) 191.4 (d, $J$ = 1.8 Hz), 162.9 (d, $J$ = 251.7 Hz), 145.4 (d, $J$ = 3.7 Hz), 137.8 (d, $J$ = 5.5 Hz), 130.7 (d, $J$ = 2.7 Hz), 125.9 (d, $J$ = 19.2 Hz), 115.5 (d, $J$ = 21.1 Hz), –1.4.</td>
</tr>
<tr>
<td><strong>FTIR, cm$^{-1}$</strong></td>
<td>(thin film) 2957 (m), 1703 (vs), 1582 (m), 1375 (s), 1254 (vs).</td>
</tr>
<tr>
<td><strong>HRMS</strong></td>
<td>(ESI) Calcd for (C$<em>{10}$H$</em>{13}$FOSi+H)$^+$ 197.0798 Found 197.0790</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>(9:1 hexanes–ethyl acetate) $R_f$ = 0.49 (UV)</td>
</tr>
</tbody>
</table>
\(N,N\)-bis(4-methoxybenzyl)cyanamide (225)\(^{38}\)

Cyanamide (2.10 g, 50 mmol, 1 equiv) was added portionwise over 10 min to a suspension of sodium methylsulfinylmethide prepared in situ from a 60% dispersion of sodium hydride in mineral oil (5.00 g, 125 mmol, 2.5 equiv) and dimethyl sulfoxide (50 mL).\(^{39}\) After 40 min, 4-methoxybenzyl chloride (17.0 mL, 125 mmol, 2.5 equiv) was added slowly. After 16 h, the reaction mixture was poured into ice-water (100 g). The resulting mixture was partitioned between ether (200 mL) and saturated aqueous sodium chloride solution (100 mL). The layers were separated. The aqueous layer was extracted with ether (3 \(\times\) 150 mL). The organic layers were combined. The combined organic layers were washed sequentially with water (200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was recrystallized from ether, affording \(N,N\)-bis(4-methoxybenzyl)cyanamide (225) as a white solid (10.5 g, 74%).

**Melting Point**

78–79 \(^\circ\)C

**\(^1\)H NMR:**

7.22 (d, 4H, \(J = 8.8\) Hz), 6.90 (d, 4H, \(J = 8.8\) Hz), 4.03

---


(400 MHz, CDCl₃) (s, 4H), 3.81 (s, 6H).

**¹³C NMR**: 159.7, 130.0, 126.3, 118.4, 114.2, 55.2, 53.5.

(100 MHz, CDCl₃)

**FTIR, cm⁻¹**: 2959 (m), 2936 (m), 2837 (m), 2207 (s), 1611 (s), 1512 (vs), 1472 (m), 1246 (s), 1175 (s).

**HRMS**: Calcd for (C₁₇H₁₈N₂O₂+H)⁺ 305.1261
(ESI) Found 305.1254

**TLC** R<sub>f</sub> = 0.38 (UV)
(2:1 hexanes–ethyl acetate)
General Procedure to Prepare tert-Butyl Aldimines (20–40 mmol scale). tert-Butylamine (3 equiv) was added to a solution of the corresponding aldehyde (1 equiv) in benzene (1.0 M). The reaction flask was placed in an oil bath preheated to 80 °C. After 16 h, the oil bath was removed and the reaction flask was allowed to cool to 23 °C. Hexanes (30 equiv) were added and the resulting solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The aldimines were isolated by distillation at reduced pressure or by recrystallization from hexanes, or in some cases (so noted) were used directly without further purification. In all cases yields were 70–100%.

2-Methylbenzaldehyde tert-Butylimine (192)
A colorless oil, purified by distillation at reduced pressure, bp: 70–72 °C, 0.5 mm Hg, 85%. Spectral data were identical to those previously reported.40

---

4-Fluoro-2-methylbenzaldehyde *tert*-Butylimine (226)

A colorless oil, purified by distillation at reduced pressure, 75% yield.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boiling Point</strong></td>
<td>79–81 °C, 0.5 mm Hg</td>
</tr>
<tr>
<td>(^1\text{H NMR:})</td>
<td>8.51 (s, 1H), 7.87 (dd, 1H, (J = 8.7, 6.4) Hz), 6.91 (app td, 1H, (J = 8.5, 2.7) Hz), 6.84 (dd, 1H, (J = 9.6, 2.3) Hz), 2.47 (s, 3H), 1.31 (s, 9H).</td>
</tr>
<tr>
<td>(^1\text{H NMR:})</td>
<td>(-112.4) (ddd, (J = 14.9, 6.9, 3.4) Hz).</td>
</tr>
<tr>
<td>(^1\text{F NMR:})</td>
<td></td>
</tr>
<tr>
<td>(^{13}\text{C NMR :})</td>
<td>163.4 (d, (J = 250.8) Hz), 152.3, 139.6 (d, (J = 8.2) Hz), 131.3 (d, (J = 2.7) Hz), 129.2 (d, (J = 8.2) Hz), 116.9 (d, (J = 21.1) Hz), 113.0 (d, (J = 22.0) Hz), 57.4, 29.6, 19.0.</td>
</tr>
<tr>
<td>(^{13}\text{C NMR :})</td>
<td></td>
</tr>
<tr>
<td><strong>FTIR, cm(^{-1}:)</strong></td>
<td>2971 (m), 1602 (m), 1495 (s), 1472 (m), 1265 (vs).</td>
</tr>
<tr>
<td><strong>FTIR, cm(^{-1}:)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for ((C_{12}H_{16}FN+H)^+) 194.1340</td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Found 194.1338</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>(R_f = 0.38) (UV)</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(9:1 hexanes–ethyl acetate)</td>
</tr>
</tbody>
</table>
2,4,6-Trimethylbenzaldehyde tert-Butylimine (227)

A colorless oil, purified by distillation at reduced pressure, 72% yield.

<table>
<thead>
<tr>
<th><strong>Boiling Point</strong></th>
<th>102–104 °C, 0.5 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>¹H NMR:</strong></td>
<td>8.54 (s, 1H), 6.87 (s, 2H), 2.36 (d, 6H, $J = 1.4$ Hz), 2.30 (s, 3H), 1.36 (d, 9H, $J = 1.8$ Hz).</td>
</tr>
<tr>
<td>(500 MHz, CDCl₃)</td>
<td></td>
</tr>
<tr>
<td><strong>¹³C NMR:</strong></td>
<td>155.6, 137.7, 136.3, 132.5, 128.9, 57.8, 29.6, 20.9, 19.9.</td>
</tr>
<tr>
<td>(126 MHz, CDCl₃)</td>
<td></td>
</tr>
<tr>
<td><strong>FTIR, cm⁻¹:</strong></td>
<td>2967 (s), 1638 (m), 1613 (s), 1456 (m), 1222 (s), 1204 (s).</td>
</tr>
<tr>
<td>(thin film)</td>
<td></td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C₁₄H₂₁N+H)⁺ 204.1747</td>
</tr>
<tr>
<td>(ESI)</td>
<td>Found 204.1745</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>$R_f = 0.46$ (UV)</td>
</tr>
<tr>
<td>(9:1 hexanes–ethyl acetate)</td>
<td></td>
</tr>
</tbody>
</table>
4-Methoxy-2,5-dimethylbenzaldehyde *tert*-Butylimine (228)

A white solid, purified by recrystallization from hexanes.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melting Point</strong></td>
<td>67–68 °C</td>
</tr>
<tr>
<td><strong>&lt;sup&gt;1&lt;/sup&gt;H NMR:</strong></td>
<td></td>
</tr>
<tr>
<td>(500 MHz, CDCl₃)</td>
<td>8.54 (s, 1 H), 7.71 (s, 1 H), 6.59 (s, 1 H), 3.84 (s, 3 H), 2.48 (s, 3 H), 2.22 (s, 3 H), 1.32 ppm (s, 9 H).</td>
</tr>
<tr>
<td><strong>&lt;sup&gt;13&lt;/sup&gt;C NMR:</strong></td>
<td></td>
</tr>
<tr>
<td>(126 MHz, CDCl₃)</td>
<td>158.9, 153.1, 136.2, 128.9, 127.2, 124.3, 111.6, 57.0, 55.1, 29.8, 18.9, 15.5.</td>
</tr>
<tr>
<td><strong>FTIR, cm⁻¹:</strong></td>
<td></td>
</tr>
<tr>
<td>(thin film)</td>
<td>2967 (s), 1638 (m), 1609 (s), 1505 (s), 1260 (s), 1217 (s).</td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td></td>
</tr>
<tr>
<td>(ESI)</td>
<td>Calcd for (C₁₄H₂₁NO+H)⁺ 220.1696 Found 220.1701</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td></td>
</tr>
<tr>
<td>(9:1 hexanes–ethyl acetate)</td>
<td>R&lt;sub&gt;f&lt;/sub&gt; = 0.30 (UV)</td>
</tr>
</tbody>
</table>
2-Methoxy-6-methylbenzaldehyde tert-Butylimine (229)

A pale yellow oil, purified by distillation at reduced pressure, 70% yield.

<table>
<thead>
<tr>
<th><strong>Boiling Point</strong></th>
<th>138–140 °C, 0.5 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(^1)H NMR:</strong></td>
<td>8.66 (s, 1H), 7.20 (app t, 1H, (J = 8.0) Hz), 6.85 (d, 1H, (J = 7.8) Hz), 6.75 (d, 1H, (J = 8.2) Hz), 3.82 (s, 3H), 2.53 (s, 3H), 1.37 (s, 9H).</td>
</tr>
<tr>
<td><strong>(^13)C NMR :</strong></td>
<td>158.8, 153.4, 138.5, 129.1, 125.1, 123.6, 108.0, 57.8, 55.4, 29.6, 20.7.</td>
</tr>
<tr>
<td><strong>FTIR, cm(^{-1}):</strong></td>
<td>2970 (m), 1640 (m), 1580 (m), 1470 (m), 1263 (vs).</td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C(<em>{13})H(</em>{19})NO+H(^+))(^+) 206.1539</td>
</tr>
<tr>
<td><strong>(ESI)</strong></td>
<td>found 206.1535</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>(R_f = 0.35) (UV)</td>
</tr>
<tr>
<td><strong>(9:1 hexanes–ethyl acetate)</strong></td>
<td></td>
</tr>
</tbody>
</table>

198
5-Chloro-2-methylbenzaldehyde *tert*-Butylimine (216)

A white solid, purified by recrystallization from hexanes, 80%.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melting Point</strong></td>
<td>39–40 °C</td>
</tr>
<tr>
<td><strong>^1H NMR:</strong></td>
<td>8.50 (s, 1H), 7.81 (d, 1H, ( J = 8.2 ) Hz), 7.19 (dd, 1H, ( J = 8.2, 1.8 ) Hz), 7.14 (d, 1H, ( J = 1.8 ) Hz), 2.46 (s, 3H), 1.31 (s, 9H).</td>
</tr>
<tr>
<td><strong>(500 MHz, CDCl₃)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>^13C NMR:</strong></td>
<td>152.5, 138.8, 135.3, 133.6, 130.3, 128.5, 126.3, 57.6, 29.7, 18.9.</td>
</tr>
<tr>
<td><strong>(126 MHz, CDCl₃)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FTIR, cm⁻¹:</strong></td>
<td>2969 (s), 1636 (m), 1593 (s), 1479 (m), 1371 (m), 1206 (s).</td>
</tr>
<tr>
<td><strong>(thin film)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C₁₂H₁₆ClN+H)^+ 210.1044</td>
</tr>
<tr>
<td><strong>(ESI)</strong></td>
<td>Found 210.1053</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>( R_f = 0.41 ) (UV).</td>
</tr>
<tr>
<td><strong>(9:1 hexanes–ethyl acetate)</strong></td>
<td></td>
</tr>
</tbody>
</table>
2,3-Dimethylbenzaldehyde \textit{tert}-Butylimine (230)

A light yellow oil, used directly without further purification, 100%.

<table>
<thead>
<tr>
<th><strong>¹H NMR:</strong></th>
<th>(8.71 \text{ (d, 1H, } J = 1.8 \text{ Hz)}), (7.75 \text{ (d, 1H, } J = 7.8 \text{ Hz)}), (7.24–7.10 \text{ (m, 2H)}), (7.10 \text{ (m, 2H)}), (2.42 \text{ (s, 3H)}), (2.35 \text{ (s, 3H)}), (1.39 \text{ (s, 9H)}).</th>
</tr>
</thead>
<tbody>
<tr>
<td>(500 MHz, CDCl₃)</td>
<td>(126 MHz, CDCl₃)</td>
</tr>
<tr>
<td><strong>¹³C NMR:</strong></td>
<td>(154.4, 136.7, 135.4, 135.3, 131.0, 125.5, 125.0, 57.3, 29.6, 20.1, 14.4).</td>
</tr>
<tr>
<td>(126 MHz, CDCl₃)</td>
<td>(thin film)</td>
</tr>
<tr>
<td><strong>FTIR, cm⁻¹:</strong></td>
<td>(2971 \text{ (m)}, 1638 \text{ (m)}, 1460 \text{ (m)}, 1371 \text{ (m)}, 1265 \text{ (vs)}).</td>
</tr>
<tr>
<td>(thin film)</td>
<td></td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for ((\text{C}<em>{13}\text{H}</em>{19}\text{N})^+) (190.1590)</td>
</tr>
<tr>
<td>(ESI)</td>
<td>Found (190.1591)</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>(R_f = 0.43 \text{ (UV)})</td>
</tr>
<tr>
<td>(9:1 hexanes–ethyl acetate)</td>
<td></td>
</tr>
</tbody>
</table>
3-Fluoro-2-methylbenzaldehyde *tert*-Butylimine (231)

A light orange oil, used directly without further purification, 100%.

**\(^1\)H NMR:**

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity</th>
<th>Magnetic Field Strength (MHz)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.55</td>
<td>s</td>
<td>500 MHz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>7.64</td>
<td>d</td>
<td>7.4 Hz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>7.18</td>
<td>app td</td>
<td>1H, J = 7.9, 5.7 Hz</td>
<td></td>
</tr>
<tr>
<td>7.04</td>
<td>app td</td>
<td>1H, J = 8.7, 1.4 Hz</td>
<td></td>
</tr>
<tr>
<td>2.41</td>
<td>d</td>
<td>3H, J = 1.8 Hz</td>
<td></td>
</tr>
<tr>
<td>1.33</td>
<td>d</td>
<td>9H, J = 0.9 Hz</td>
<td></td>
</tr>
</tbody>
</table>

**\(^1\)F NMR:**

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity</th>
<th>Magnetic Field Strength (MHz)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>–118.1</td>
<td>app dt</td>
<td>470 MHz</td>
<td>CDCl₃</td>
</tr>
</tbody>
</table>

**\(^{13}\)C NMR:**

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity</th>
<th>Magnetic Field Strength (MHz)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>161.2</td>
<td>d</td>
<td>126 MHz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>152.8</td>
<td>d</td>
<td>4.6 Hz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>137.3</td>
<td>d</td>
<td>16.5 Hz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>126.6</td>
<td>d</td>
<td>9.2 Hz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>124.2</td>
<td>d</td>
<td>16.5 Hz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>122.8</td>
<td>d</td>
<td>2.7 Hz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>116.0</td>
<td>d</td>
<td>22.0 Hz</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>57.7</td>
<td></td>
<td>29.6 Hz</td>
<td></td>
</tr>
<tr>
<td>29.6</td>
<td></td>
<td>9.9 Hz</td>
<td></td>
</tr>
<tr>
<td>9.9</td>
<td></td>
<td>6.4 Hz</td>
<td></td>
</tr>
</tbody>
</table>

**FTIR, cm⁻¹:**

<table>
<thead>
<tr>
<th>Frequency (cm⁻¹)</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2970</td>
<td>s</td>
</tr>
<tr>
<td>1643</td>
<td>m</td>
</tr>
<tr>
<td>1578</td>
<td>m</td>
</tr>
<tr>
<td>1462</td>
<td>s</td>
</tr>
<tr>
<td>1270</td>
<td>s</td>
</tr>
<tr>
<td>1242</td>
<td>s</td>
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</tbody>
</table>

**HRMS:**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>194.1340</td>
<td></td>
<td>(C₁₂H₁₆FN+H)⁺</td>
<td>194.1347</td>
</tr>
</tbody>
</table>

**TLC:**

<table>
<thead>
<tr>
<th>Rf</th>
<th>Solvent</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.43</td>
<td>9:1 hexanes–ethyl acetate</td>
<td>UV</td>
</tr>
</tbody>
</table>
2-Methyl-5-(trimethylsilyl)benzaldehyde tert-Butylimine (232)

A pale yellow oil, purified by distillation at reduced pressure, 75% yield.

**Boiling Point**

118–120 °C, 0.5 mm Hg.

**¹H NMR:**

(500 MHz, CDCl₃)

8.58 (s, 1H), 7.91 (s, 1H), 7.42 (d, 1H, \( J = 7.3 \) Hz), 7.16 (d, 1H, \( J = 7.8 \) Hz), 2.49 (s, 3H), 1.31 (s, 9H), 0.27 (s, 9H).

**¹³C NMR:**

(126 MHz, CDCl₃)

154.5, 137.8, 137.7, 134.6, 134.4, 132.3, 130.1, 57.6, 29.8, 19.4, –1.1.

**FTIR, cm⁻¹:**

(tin film)

2967 (s), 1641 (m), 1578 (m), 1472 (m), 1368 (s), 1252 (s).

**HRMS:**

(ESI)

Calcd for \((C_{15}H_{25}NSi+H)^+\) 248.1829

Found 248.1835

**TLC**

\( R_f = 0.51 \) (UV)

(9:1 hexanes–ethyl acetate)
**3-Fluoro-5-(trimethylsilyl)benzaldehyde tert-Butylimine (206)**

A light orange oil, used directly without further purification, 100%.

<table>
<thead>
<tr>
<th>1H NMR: (600 MHz, CDCl3)</th>
<th>8.26 (d, 1H, $J = 1.5$ Hz), 7.53 (ddd, 1H, $J = 10.0, 2.9, 1.8$ Hz), 1.29 (s, 9H), 0.29 (s, 9H).</th>
</tr>
</thead>
<tbody>
<tr>
<td>19F NMR: (376 MHz, CDCl3)</td>
<td>–114.8 (dd, $J = 10.0, 8.5$ Hz).</td>
</tr>
<tr>
<td>13C NMR: (126 MHz, CDCl3)</td>
<td>162.9 (d, $J = 240.8$ Hz), 154.2 (d, $J = 2.9$ Hz), 143.8 (d, $J = 3.7$ Hz), 139.0 (d, $J = 6.6$ Hz), 129.3 (d, $J = 2.2$ Hz), 121.5 (d, $J = 19.0$ Hz), 113.7 (d, $J = 22.0$ Hz), 57.4, 29.7, –1.2.</td>
</tr>
<tr>
<td>FTIR, cm$^{-1}$: (thin film)</td>
<td>2965 (s), 1638 (m), 1360 (m), 1248 (vs), 1090 (s).</td>
</tr>
<tr>
<td>HRMS: (ESI)</td>
<td>Calcd for (C$<em>{14}$H$</em>{22}$FNSi+H)$^+$ 252.1578, Found 252.1586</td>
</tr>
<tr>
<td>TLC</td>
<td>$R_f = 0.49$ (UV)</td>
</tr>
</tbody>
</table>
3-Phenylisoquinoline (194)

A solution of \( n \)-butyllithium in hexanes (2.40 M, 438 \( \mu \)L, 1.05 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 192 (175 mg, 1.00 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 \( \mu \)L, 0.10 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of benzonitrile (155 \( \mu \)L, 1.5 mmol, 1.5 equiv) in tetrahydrofuran (0.4 mL) at \(-78^\circ\text{C}\), forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 3 min, iodomethane (125 \( \mu \)L, 2 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \( ^\circ\text{C}\). The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \( \times \) 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 15:1 hexanes–ethyl acetate), furnishing 3-phenylisoquinoline (194) as a pale yellow solid (164 mg, 80%), mp: 96–97 \( ^\circ\text{C}\). The spectral properties were identical to those previously reported.\textsuperscript{41}

4-Methyl-3-phenylisoquinoline (200)

A solution of \( n \)-butyllithium in hexanes (2.40 M, 424 \( \mu \)L, 1.02 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 192 (170 mg, 0.970 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 \( \mu \)L, 0.097 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of benzonitrile (150 \( \mu \)L, 1.46 mmol, 1.5 equiv) in tetrahydrofuran (0.4 mL) at \(-78 \, ^\circ\text{C}\), forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 3 min, iodomethane (121 \( \mu \)L, 1.94 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \( ^\circ\text{C} \). The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \( \times \) 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 7:1 hexanes–ethyl acetate), furnishing 4-methyl-3-phenylisoquinoline (200) as a white solid (170 mg, 80%), mp: 101–102 \( ^\circ\text{C} \). The spectral properties were identical to those previously reported.\(^\text{42}\)

4-Ethyl-3-isopropylisoquinoline (233)

A solution of n-butyllithium in hexanes (2.52 M, 616 μL, 1.55 mmol, 1.31 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 192 (259 mg, 1.48 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (25 μL, 0.148 mmol, 0.125 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of isobutyronitrile (106 μL, 1.18 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) at –78 ºC, forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 5 min, iodoethane (239 μL, 2.96 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 15:1 hexanes–ethyl acetate), furnishing 4-ethyl-3-isopropylisoquinoline (233) as a pale yellow oil (122 mg, 52%).
$^1$H NMR: 9.14 (s, 1H), 7.98 (d, 1H, $J = 8.8$ Hz), 7.89 (d, 1H, $J =$ 8.3 Hz), 7.65 (ddd, 1H, $J = 8.4$, 7.0, 1.2 Hz), 7.48 (ddd, 1H, $J = 8.8$, 7.0, 1.2 Hz), 3.51 (spt, 1H, $J = 6.7$ Hz), 3.09 (q, 2H, $J = 7.3$ Hz), 1.38 (d, 6H, $J = 6.3$ Hz), 1.29 (t, 3H, $J = 7.8$ Hz).

$^{13}$C NMR: 157.0, 150.3, 134.9, 129.8, 128.1, 127.9, 127.1, 125.5, 122.9, 30.6, 22.7, 20.4, 15.2.

FTIR, cm$^{-1}$: 2965 (s), 1620 (m), 1578 (m), 1472 (m), 1377 (m), 1246 (m).

HRMS: Calcd for (C$_{14}$H$_{17}$N+H)$^+$ 200.1434 Found 200.1441

TLC: $R_f = 0.37$ (UV) (9:1 hexanes–ethyl acetate)
4-\(n\)-Butyl-6-fluoro-3-(methoxymethyl)isoquinoline (234)

A solution of \(n\)-butyllithium in hexanes (2.50 M, 435 \(\mu\)L, 1.09 mmol, 1.31 equiv) was added dropwise to an ice-cooled solution of diisopropylamine (161 \(\mu\)L, 1.14 mmol, 1.38 equiv) in tetrahydrofuran (1.5 mL). After 15 min, a solution of imine 226 (200 mg, 1.04 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the deep purple solution was transferred by cannula to a solution of methoxyacetonitrile (62 \(\mu\)L, 0.83 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) at \(-78 \, ^\circ\text{C}\), forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 60 min, 1-iodobutane (237 \(\mu\)L, 2.07 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 \(^\circ\text{C}\). After 30 min, saturated aqueous ammonium chloride (1 mL) was added. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \(\times\) 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate, and finally 1:1 hexanes–ethyl acetate), affording 4-butyl-6-fluoro-3-(methoxymethyl)isoquinoline (234) as a pale yellow oil (102 mg, 50%).
$^1$H NMR:  
(500 MHz, CDCl$_3$)  
9.08 (s, 1H), 7.97 (dd, 1H, $J = 9.0$, 5.6 Hz), 7.61 (dd, 1H, $J = 10.7$, 2.0 Hz), 7.35 (app td, 1H, $J = 8.7$, 2.2 Hz), 4.77 (s, 2H), 3.49 (s, 3H), 3.05 (t, 2H, $J = 7.5$ Hz), 1.70–1.59 (m, 2H), 1.58–1.48 (m, 2H), 1.01 (t, 3H, $J = 7.3$ Hz).

$^{19}$F NMR:  
(470 MHz, CDCl$_3$)  
$-107.0$ (ddd, $J = 11.43$, 8.00, 5.71 Hz).

$^{13}$C NMR:  
(126 MHz, CDCl$_3$)  
163.4 (d, $J = 250$ Hz), 149.7, 148.6, 137.0 (d, $J = 10.1$ Hz), 131.1 (d, $J = 10.1$ Hz), 130.9 (d, $J = 5.5$ Hz), 125.4, 117.2 (d, $J = 26.3$ Hz), 107.2 (d, $J = 21.0$ Hz), 74.3, 58.6, 32.9, 27.5, 23.2, 13.9.

FTIR, cm$^{-1}$:  
(thin film)  
2957 (m), 2928 (m), 2872 (m), 1628 (s), 1501 (s), 1435 (m), 1196 (s).

HRMS:  
(ESI)  
Calcd for (C$_{15}$H$_{18}$FNO +H)$^+$ 248.1445  
Found 248.1449

TLC  
(2:1 hexanes–ethyl acetate)  
$R_f = 0.21$ (UV)
4- Allyl-6,8-dimethyl-3-(diethylaminomethyl)isoquinoline (235)

A solution of n-butyllithium in hexanes (2.50 M, 490 μL, 1.22 mmol, 1.31 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 227 (237 mg, 1.17 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (20 μL, 0.117 mmol, 0.125 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of 2-(diethylamino)acetonitrile (121 μL, 0.866 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) at –78 °C, forming an orange solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 5 min, hexamethylphosphoramide (406 μL, 2.33 mmol, 2.5 equiv) was added. After 10 min, allyl bromide (197 μL, 2.33 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (2:1 hexanes–ethyl acetate initially, grading to 1:1 hexanes–ethyl acetate, then 1:1:0.01
hexanes–ethyl acetate–triethylamine), furnishing 4-allyl-6,8-dimethyl-3-(diethylaminomethyl)isoquinoline (235) as a pale yellow oil (158 mg, 60%).

<table>
<thead>
<tr>
<th><strong>1H NMR:</strong></th>
<th>9.26 (s, 1H), 7.61 (s, 1H), 7.17 (s, 1H), 6.11–5.99 (m, 1H), 5.07–4.98 (m, 1H), 4.95–4.86 (m, 1H), 4.02 (app dt, 2H, $J = 5.5$, 1.8 Hz), 3.86 (s, 2H), 2.73 (s, 3H), 2.58 (q, 4H, $J = 7.0$ Hz), 2.50 (s, 3H), 1.05 (t, 6H, $J = 7.1$ Hz).</th>
</tr>
</thead>
<tbody>
<tr>
<td>(500 MHz, CDCl$_3$)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>13C NMR:</strong></th>
<th>150.7, 146.5, 139.8, 136.6, 136.4, 135.4, 129.4, 127.5, 125.2, 120.5, 115.4, 58.4, 47.0, 31.1, 22.4, 18.6, 11.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>(126 MHz, CDCl$_3$)</td>
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<table>
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<tr>
<th><strong>FTIR, cm$^{-1}$:</strong></th>
<th>3389 (br), 2969 (s), 1622 (s), 1595 (m), 1452 (s), 1368 (s), 1200 (m).</th>
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</thead>
<tbody>
<tr>
<td>(thin film)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>HRMS:</strong></th>
<th>Calcd for (C$<em>{19}$H$</em>{26}$N$_2$+H)$^+$ 283.2169</th>
<th>Found 283.2170</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ESI)</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TLC</strong></th>
<th>$R_f = 0.23$ (UV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(90:9:1 dichloromethane–methanol–triethyl amine)</td>
<td></td>
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</tbody>
</table>
4-Benzyl-3-(diethoxymethyl)-6-methoxy-7-methylisoquinoline (236)

A solution of n-butyllithium in hexanes (2.52 M, 521 μL, 1.31 mmol, 1.31 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 228 (274 mg, 1.25 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (21 μL, 0.125 mmol, 0.125 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of 2,2-diethoxyacetonitrile (139 μL, 1.00 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) at –78 ºC, forming a dark orange solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 5 min, benzyl bromide (371 μL, 3.13 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate), furnishing 4-benzyl-3-(diethoxymethyl)-6-methoxy-7-methylisoquinoline (236) as a pale yellow oil (184 mg, 50%).
<table>
<thead>
<tr>
<th>Analysis</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$^1$H NMR:</strong></td>
<td>8.99 (s, 1H), 7.65 (s, 1H), 7.22–7.17 (m, 2H), 7.17–7.08 (m, 3H), 7.01 (s, 1H), 5.79 (s, 1H), 4.68 (s, 2H), 3.76 (dq, 2H, $J = 9.4$, 7.1 Hz), 3.70 (s, 3H), 3.58 (dq, 2H, $J = 9.4$, 7.1 Hz), 2.32 (s, 3H), 1.15 (t, 6H, $J = 6.9$ Hz).</td>
</tr>
<tr>
<td></td>
<td>(500 MHz, CDCl$_3$)</td>
</tr>
<tr>
<td><strong>$^{13}$C NMR:</strong></td>
<td>160.0, 149.1, 148.8, 140.9, 137.1, 129.9, 128.6, 128.3, 128.2, 126.6, 125.6, 124.2, 105.0, 101.1, 63.0, 55.2, 32.9, 16.7, 15.1.</td>
</tr>
<tr>
<td></td>
<td>(126 MHz, CDCl$_3$)</td>
</tr>
<tr>
<td><strong>FTIR, cm$^{-1}$:</strong></td>
<td>2974 (m), 1630 (s), 1495 (s), 1418 (m), 1234 (s), 1111 (s).</td>
</tr>
<tr>
<td></td>
<td>(thin film)</td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C$<em>{23}$H$</em>{27}$NO$_3$+H)$^+$ 366.2064  Found 366.2076.</td>
</tr>
<tr>
<td></td>
<td>(ESI)</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>$R_f = 0.41$ (UV)</td>
</tr>
<tr>
<td></td>
<td>(2:1 hexanes–ethyl acetate)</td>
</tr>
</tbody>
</table>
4-(4-Bromobenzyl)-8-methoxy-3-(piperidin-1-yl)isoquinoline (237)

A solution of \textit{n}-butyllithium in hexanes (2.52 M, 436 \textmu L, 1.10 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 229 (215 mg, 1.05 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (18 \textmu L, 0.105 mmol, 0.1 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to \(-78^\circ C\), and 1-piperidinecarbonitrile (182 \textmu L, 1.57 mmol, 1.5 equiv) was added. After 10 min, hexamethylphosphoramide (300 \textmu L, 1.72 mmol, 2 equiv) was added. After 10 min, a solution of 4-bromobenzyl bromide (523 mg, 2.10 mmol, 2 equiv) in tetrahydrofuran (0.5 mL) was added. After 20 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 \degree C. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \times 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 10:1 hexanes–ethyl acetate, and finally 7:1 hexanes–ethyl acetate), affording 4-(4-bromobenzyl)-8-methoxy-3-(piperidin-1-yl)isoquinoline (237) as a white solid (224 mg, 52%);
<table>
<thead>
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<th>Property</th>
<th>Details</th>
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<tr>
<td><strong>Melting Point</strong></td>
<td>152–153 °C</td>
</tr>
<tr>
<td><strong>1H NMR:</strong></td>
<td>9.43 (s, 1H), 7.40 (dd, 1H, J = 8.5, 7.6 Hz), 7.32 (d, 2H, J = 8.3 Hz), 7.19 (d, 1H, J = 8.8 Hz), 6.98 (d, 2H, J = 8.3 Hz), 6.70 (d, 1H, J = 7.3 Hz), 4.42 (s, 2H), 4.00 (s, 3H), 3.10–2.97 (m, 4H), 1.74–1.62 (m, 4H), 1.62–1.54 (m, 2H).</td>
</tr>
<tr>
<td><strong>13C NMR:</strong></td>
<td>159.6, 157.1, 145.5, 140.1, 138.7, 131.3, 130.6, 129.9, 119.4, 118.5, 118.4, 115.8, 102.8, 55.6, 52.7, 32.5, 26.5, 24.4.</td>
</tr>
<tr>
<td><strong>FTIR, cm⁻¹:</strong></td>
<td>2934 (m), 1622 (m), 1570 (s), 1487 (m), 1391 (m), 1265 (s), 1221 (s).</td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C₂₂H₂₃BrN₂O+H)⁺ 411.1067 Found 411.1063</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>R_f = 0.26 (UV)</td>
</tr>
</tbody>
</table>
Methyl 7-Chloro-3-morpholinoisoquinoline-4-carboxylate (238)

A solution of \( n \)-butyllithium in hexanes (2.50 M, 420 \( \mu \)L, 1.05 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of diisopropylamine (155 \( \mu \)L, 1.10 mmol, 1.1 equiv) in tetrahydrofuran (1.5 mL). After 15 min, a solution of imine 216 (210 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the reaction flask was cooled to \(-78^\circ\text{C}\), and 4-morpholinecarbonitrile (152 \( \mu \)L, 1.50 mmol, 1.5 equiv) was added. After 60 min, methyl cyanoformate (150 \( \mu \)L, 2.00 mmol, 2 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 \( ^\circ\text{C}\). After 30 min, saturated aqueous ammonium chloride (1 mL) was added. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \( \times \) 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate), furnishing methyl 7-chloro-3-morpholinoisoquinoline-4-carboxylate (238) as a yellow oil (208 mg, 66%).
| **1H NMR:** | \( \delta 8.89 \) (s, 1H), 8.00 (d, 1H, \( J = 1.8 \) Hz), 7.75 (d, 1H, \( J = 8.4 \) Hz), 7.28 (dd, 1H, \( J = 8.8, 1.8 \) Hz), 3.99 (s, 3H), 3.82–3.75 (m, 4H), 3.59–3.52 (m, 4H). |
| **(400 MHz, CDCl₃)** | |

| **13C NMR:** | 168.7, 156.0, 152.7, 138.4, 137.0, 129.6, 125.0, 121.6, 104.5, 67.1, 52.2, 49.1. |
| **(100 MHz, CDCl₃)** |

| **FTIR, cm⁻¹:** | 2963 (m), 2857 (m), 1707 (vs), 1611 (s), 1487 (s), 1435 (s), 1215 (s), 1115 (s). |
| **(thin film)** |

| **HRMS:** | Calcd for \((C_{15}H_{15}ClN_2O_3+H)^+\) 307.0844 |
| **(ESI)** | Found 307.0852 |

| **TLC** | \( R_f = 0.41 \) (UV) |
| **(2:1 hexanes–ethyl acetate)** |
**N,N,4,5-Tetramethylisoquinolin-3-amine (239)**

A solution of \( n \)-butyllithium in hexanes (2.50 M, 422 \( \mu \)L, 1.05 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 230 (190 mg, 1.00 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 \( \mu \)L, 0.10 mmol, 0.1 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to \(-78 \, ^\circ C\), and \( N,N \)-dimethylcyanamid 122 \( \mu \)L, 1.50 mmol, 1.5 equiv) was added, forming a dark red solution. After 15 min, hexamethylphosphoramide (349 \( \mu \)L, 2.00 mmol, 2 equiv) was added. After 15 min, iodomethane (125 \( \mu \)L, 2.00 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \( ^\circ C\). The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \( \times \) 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 15:1 hexanes–ethyl acetate), affording \( N,N,4,5 \)-tetramethylisoquinolin-3-amine (239) as a pale yellow oil (108 mg, 54%).

\[ ^1H \text{NMR:} \quad 8.82 (s, 1H), 7.67 (d, 1H, } J = 8.2 \text{ Hz), 7.35 (d, 1H, } J = \]
(500 MHz, CDCl₃)  6.9 Hz), 7.23 (dd, 1H, \( J = 8.0, 7.1 \) Hz), 2.91 (s, 6H), 2.88 (s, 3H), 2.76 (s, 3H).

\(^{13}\text{C NMR :}\) 159.7, 149.1, 138.6, 133.9, 132.9, 126.9, 126.7, 123.8, 115.6, 42.9, 25.2, 19.0.

\(\text{FTIR, cm}^{-1}:\) 2938 (m), 2861 (m), 1611 (m), 1576 (s), 1482 (s), 1400 (s), 1332 (m), 1144 (m).

\(\text{HRMS:}\) Calcd for (C_{13}H_{16}N_{2}+H)^+ 201.1386

\(\text{(ESI)}\) Found 201.1390

\(\text{TLC}\)  \(R_f = 0.35\) (UV)

\(\text{(9:1 hexanes–ethyl acetate)}\)
A solution of \( n \)-butyllithium in hexanes (2.50 M, 443 \( \mu \)L, 1.11 mmol, 1.32 equiv) was added dropwise to a cooled solution of diisopropylamine (164 \( \mu \)L, 1.16 mmol, 1.37 equiv) in tetrahydrofuran (1.5 mL) at –20 ºC. After 15 min, a solution of imine 231 (204 mg, 1.06 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the reaction flask was cooled to –78 ºC, and a solution of \( N,N \)-dibenzylcyanamide (293 mg, 1.32 mmol, 1.56 equiv) in tetrahydrofuran (1 mL) was added. After 60 min, a solution of \( N \)-fluorobenzenesulfonimide (266 mg, 0.844 mmol, 1 equiv) in tetrahydrofuran (1 mL) was added. After 10 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. Saturated aqueous sodium carbonate solution (5 mL) was added slowly. The reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between dichloromethane (60 mL) and saturated aqueous sodium carbonate solution (10 mL). The layers were separated. The organic solution was washed with water (10 mL) then saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 10:1 hexanes–ethyl acetate), furnishing \( N,N \)-dibenzyl-4,5-difluoroisoquinolin-3-amine (240) as a yellow oil (226 mg, 74%).
\textbf{{\textsuperscript{1}H NMR}}: \(\delta\) 8.78 (d, 1H, \(J = 2.3\) Hz), 7.61 (ddd, 1H, \(J = 5.3\), 3.9, 2.3 Hz), 7.41–7.32 (m, 8H), 7.31–7.26 (m, 2H), 7.25–7.21 (m, 2H), 4.85 (s, 4H).

\textbf{{\textsuperscript{19}F NMR}}: –118.8–118.4 (m), –143.5 (d, \(J = 52.0\) Hz).

\textbf{{\textsuperscript{13}C NMR}}: 155.6 (d, \(J = 255.0\) Hz), 144.9 (dd, \(J = 7.3\), 1.8 Hz), 144.5 (d, \(J = 8.2\) Hz), 138.9, 139.7 (dd, \(J = 259.0\), 2.2 Hz), 128.4, 127.7, 127.0, 126.9, 123.5 (d, \(J = 8.2\) Hz), 122.9 (d, \(J = 3.7\) Hz), 119.3 (dd, \(J = 12.6\), 12.0 Hz), 114.6 (dd, \(J = 20.2\), 1.9 Hz), 52.7 (d, \(J = 5.5\) Hz).

\textbf{FTIR, cm\(^{-1}\)}: 3028 (m), 2912 (m), 1595 (s), 1364 (s), 1244 (s), 1049 (s).

\textbf{HRMS:} Calcd for (C\textsubscript{23}H\textsubscript{18}F\textsubscript{2}N\textsubscript{2} +H\textsuperscript{+})\(^+\) 361.1511 Found 365.1510

\textbf{TLC} \(R_f = 0.38\) (UV)

(9:1 hexanes–ethyl acetate)
4-Fluoro-\(N,N\)-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (209)

A solution of \(n\)-butyllithium in hexanes (2.50 M, 1.60 mL, 4.00 mmol, 1.31 equiv) was added dropwise to an ice-cooled solution of imine 232 (943 mg, 3.81 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (65 \(\mu\)L, 0.38 mmol, 0.125 equiv) in tetrahydrofuran (5 mL) over 60 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to \(-78 \, ^\circ\text{C}\), and a solution of \(N,N\)-bis(4-methoxybenzyl)cyanamide (225) (1.35 g, 4.76 mmol, 1.56 equiv) in tetrahydrofuran (2.5 mL) was added. After 15 min, a solution of \(N\)-fluorobenzenesulfonimide (961 mg, 3.05 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added. After 10 min, trifluoroacetic acid (3 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \(^\circ\text{C}\). Saturated aqueous sodium carbonate solution (15 mL) was added slowly. The reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between dichloromethane (120 mL) and saturated aqueous sodium carbonate solution (30 mL). The layers were separated. The organic solution was washed with water (30 mL) then saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 15:1 hexanes–ethyl acetate), affording 4-fluoro-\(N,N\)-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (209) as a yellow oil (863 mg, 60%).
$^1$H NMR: 
(500 MHz, CDCl$_3$) 
8.77 (s, 1H), 7.96 (s, 1H), 7.84 (d, 1H, $J = 8.7$ Hz), 7.68 (dd, 1H, $J = 8.7$, 0.9 Hz), 7.23 (d, 4H, $J = 8.7$ Hz), 6.84 (d, 4H, $J = 8.7$ Hz), 4.70 (s, 4H), 3.79 (s, 6H), 0.34 (s, 9H).

$^{19}$F NMR: 
(470 MHz, CDCl$_3$) 
$-148.5$ (s).

$^{13}$C NMR: 
(126 MHz, CDCl$_3$) 
145.5 (d, $J = 5.5$ Hz), 143.4 (d, $J = 6.4$ Hz), 141.5 (d, $J = 252.7$ Hz), 135.7, 134.0, 132.7, 131.1, 129.0, 128.5 (d, $J = 15.6$ Hz), 124.5, 117.1 (d, $J = 5.5$ Hz), 113.7, 55.2, 51.7 (d, $J = 4.6$ Hz), $-1.2$.

FTIR, cm$^{-1}$: 
(thin film) 
2953 (m), 1732 (s), 1622 (s), 1510 (s), 1499 (s), 1246 (s).

HRMS: 
(ESI) 
Calcd for (C$_{28}$H$_{31}$FN$_2$O$_2$Si+H)$^+$ 475.2212
Found 475.2191.

TLC 
(9:1 hexanes–ethyl acetate) 
$R_f = 0.32$ (UV)
4-Chloro-7-(trimethylsilyl)-3-(4-((trimethylsilyl)ethynyl)phenyl)isoquinoline (241)

A solution of \( n \)-butyllithium in hexanes (2.52 M, 362 \( \mu \)L, 0.912 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of imine 232 (215 mg, 0.869 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (15 \( \mu \)L, 0.087 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL) over 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to \(-78^\circ C\), and a solution of 4-[(trimethylsilyl)ethynyl]benzonitrile (216 mg, 1.09 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added, forming a dark red solution. After 5 min, the bright red solution was transferred by cannula to a suspension of hexachloroethane (823 mg, 3.48 mmol, 4 equiv) in tetrahydrofuran (1 mL) at \(-78^\circ C\). After 15 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 \(^\circ C\). The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \( \times \) 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (80:1 hexanes–ethyl acetate initially, grading to 60:1 hexanes–ethyl acetate, then 40:1 hexanes–ethyl acetate), furnishing 4-chloro-7-(trimethylsilyl)-3-(4-((trimethylsilyl)ethynyl)phenyl)isoquinoline (241) as a white solid (191 mg, 54%).
<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melting Point</strong></td>
<td>118–120 ºC</td>
</tr>
<tr>
<td><strong>$^1$H NMR:</strong></td>
<td>9.23 (s, 1H), 8.28 (d, 1H, $J = 8.7$ Hz), 8.16 (s, 1H), 7.95 (d, 1H, $J = 8.2$ Hz), 7.79 (d, 2H, $J = 8.2$ Hz), 7.61 (d, 2H, $J = 8.2$ Hz), 0.40 (s, 9H), 0.30 (s, 9H).</td>
</tr>
<tr>
<td><strong>$^{13}$C NMR:</strong></td>
<td>150.6, 149.1, 141.3, 139.0, 135.7, 134.6, 133.3, 131.5, 129.8, 127.9, 125.8, 123.1, 122.8, 105.0, 95.1, 0.0, –1.3.</td>
</tr>
<tr>
<td><strong>FTIR, cm$^{-1}$:</strong></td>
<td>2957 (m), 2158 (m), 1697 (m), 1612 (m), 1568 (m), 1427 (m), 1250 (s).</td>
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<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C$<em>{23}$H$</em>{26}$ClNSi$_2$+H)$^+$, Found 408.1365, 408.1359</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>$R_f$ = 0.45 (UV)</td>
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<tr>
<td>(9:1 hexanes–ethyl acetate)</td>
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</tbody>
</table>
3-(3-Bromophenyl)-7-(trimethylsilyl)isoquinolin-4-ol (242)

A 25-mL three-neck flask was equipped with a magnetic stirrer, two rubber septa, one affixed with an argon balloon, and an L-shaped glass tube with male joints at each ends, one inserted into a side neck of the three neck reaction flask and the other wired to a 5-mL round-bottom flask containing solid oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) (568 mg, 1.27 mmol, 1.5 equiv). The L-tube was angled such that its rotation would allow controlled addition of MoOPH to the reaction mixture. The three-neck flask was charged with imine 232 (210 mg, 0.849 mmol, 1 equiv), 2,2,6,6-tetramethylpiperidine (14 μL, 0.085 mmol, 0.1 equiv), and tetrahydrofuran (1.5 mL) and the resulting solution was cooled in an ice bath. A solution of n-butyllithium in hexanes (2.52 M, 354 μL, 0.891 mmol, 1.05 equiv) was added dropwise over a period of 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and a solution of 3-bromobenzonitrile (193 mg, 1.06 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added, forming a bright red solution. After 3 min, a solution of potassium bis(trimethylsilyl)amide (169 mg, 0.849 mmol, 1 equiv) in tetrahydrofuran (0.85 mL) was added. After another 3 min, MoOPH was added by rotating the L-tube and gently tapping the 5-mL side flask to dislodge the solids. After 60 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between dichloromethane (30 mL) and a 1:1 mixture of saturated aqueous sodium sulfite
solution and saturated aqueous sodium carbonate solution (30 mL). The layers were
separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The
organic layers were combined. The combined solution was dried over sodium sulfate.
The dried solution was filtered and the filtrate was concentrated. The residue was purified
by flash-column chromatography (20:1 to 15:1 then 10:1 hexanes–acetone), furnishing 3-
(3-bromophenyl)-7-(trimethylsilyl)isoquinolin-4-ol (241) as a white solid (126 mg, 40%).

<table>
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<th><strong>Melting Point</strong></th>
<th>215–217 ºC</th>
</tr>
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<tr>
<td><strong>¹H NMR:</strong></td>
<td>8.91 (s, 1H), 8.18 (d, 1H, J = 8.4 Hz), 8.11 (s, 1H), 7.96 (app t, 1H, J = 1.6 Hz), 7.85 (dd, 1H, J = 8.2, 0.9 Hz), 7.72 (ddd, 1H, J = 7.7, 1.2, 1.0 Hz), 7.53 (app dt, 1H, J = 8.1, 1.3 Hz), 7.37 (app t, 1H, J = 7.9 Hz), 6.10 (br s, 1H), 0.38 (s, 9H).</td>
</tr>
<tr>
<td><strong>¹³C NMR:</strong></td>
<td>145.0, 144.1, 141.0, 139.2, 134.7, 134.0, 132.8, 132.1, 131.5, 130.7, 128.7, 127.8, 127.3, 123.6, 120.2, −1.2.</td>
</tr>
<tr>
<td><strong>FTIR, cm⁻¹:</strong></td>
<td>2951 (m), 1728 (m), 1576 (m), 1557 (s), 1346 (s), 1327 (s), 1250 (s).</td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C₁₈H₁₈BrNOSi+H)⁺ 372.0414</td>
</tr>
<tr>
<td>(ESI)</td>
<td>Found 372.0427</td>
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<tr>
<td><strong>TLC</strong></td>
<td>Rᵣ = 0.19 (UV)</td>
</tr>
<tr>
<td>(10:1 hexanes–acetone)</td>
<td></td>
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</tbody>
</table>
3-(4-Methoxyphenyl)-4-(methylthio)-7-(trimethylsilyl)isoquinoline (243)

A solution of \( n \)-butyllithium in hexanes (2.52 M, 330 \( \mu \)L, 0.832 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 232 (196 mg, 0.792 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (14 \( \mu \)L, 0.079 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and a solution of 4-methoxybenzonitrile (158 mg, 1.19 mmol, 1.5 equiv) in tetrahydrofuran (0.5 mL) was added, forming a dark red solution. After 10 min, hexamethylphosphoramide (276 \( \mu \)L, 1.58 mmol, 2 equiv) was added. After 5 min, dimethyl disulfide (140 \( \mu \)L, 1.58 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \( \times \) 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 7:1 hexanes–ethyl acetate), affording 3-(4-methoxyphenyl)-4-(methylthio)-7-(trimethylsilyl)isoquinoline (243) as a white solid (190 mg, 68%).

Melting Point

122–124 ºC
**H NMR:**

(500 MHz, CDCl₃)

9.25 (s, 1H), 8.58 (d, 1H, \( J = 7.8 \) Hz), 8.15 (s, 1H), 7.94 (dd, 1H, \( J = 8.2, 1.4 \) Hz), 7.74 (d, 2H, \( J = 8.7 \) Hz), 7.02 (d, 2H, \( J = 8.7 \) Hz), 3.88 (s, 3H), 2.16 (s, 3H), 0.39 (s, 9H).

**13C NMR:**

(126 MHz, CDCl₃)

159.5, 156.3, 152.0, 139.9, 138.2, 135.2, 133.9, 133.6, 131.3, 127.2, 125.8, 124.6, 113.2, 55.3, 19.4, –1.2.

**FTIR, cm⁻¹:**

(tin film)

2953 (m), 1605 (s), 1512 (s), 1418 (s), 1246 (s), 1175 (s), 1096 (m), 1034 (m).

**HRMS:**

Calcd for \((C_{20}H_{22}NOSSi+H)^+\) 354.1342

(ESI) Found 354.1339

**TLC**

\( R_f = 0.38 \) (UV)

(4:1 hexanes–acetone)
Diethyl 1-(3-o-Tolyl-7-(trimethylsilyl)isoquinolin-4-yl)hydrazine-1,2-dicarboxylate (244)

A solution of n-butyllithium in hexanes (2.52 M, 269 μL, 0.679 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine 232 (160 mg, 0.647 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (11 μL, 0.065 mmol, 0.1 equiv) in tetrahydrofuran (1.4 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and o-tolunitrile (115 μL, 0.97 mmol, 1.5 equiv) was added, forming a dark red solution. After 15 min, hexamethylphosphoramide (203 μL, 1.29 mmol, 2 equiv) was added. After 15 min, diethyl azodicarboxylate (203 μL, 1.29 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate, and finally 3:1 hexanes–ethyl acetate), affording diethyl 1-(3-o-tolyl-7-(trimethylsilyl)isoquinolin-4-yl)hydrazine-1,2-dicarboxylate (244) as a yellow oil (165 mg, 55%).


**$^1$H NMR:**

(500 MHz, CDCl$_3$) (observed as two rotamers in the ratio of 2:1, asterisk denotes minor rotamer peaks) 9.30 (s, 1H), 8.53 (br s, 1H), 8.19 (s, 1H), 7.96 (br s, 1H), 7.44–7.12 (br m, 5H), 6.08 (br s, 1H), 4.41–3.94 (br m, 4H), 2.18* (br s, 3H), 2.15 (br s, 3H), 1.35–1.01 (br m, 6H), 0.39 (s, 9H), 0.36* (s, 9H).

**$^{13}$C NMR:**

(126 MHz, CDCl$_3$) (observed as two rotamers in the ratio of 2:1, asterisk denotes minor rotamer peaks) 156.1, 155.5, 152.5, 140.7, 138.0, 136.8, 135.3, 135.1, 134.2, 133.0, 131.4, 131.1, 131.0, 128.9, 128.0, 126.1, 122.8, 122.7*, 63.2, 63.0*, 62.2, 62.0*, 19.5, 14.6*, 14.5*, 14.4, 14.3, –1.2, –1.3*.

**FTIR, cm$^{-1}$:**

(3391 (br), 2957 (m), 1728 (vs), 1479 (m), 1373 (m), 1248 (s), 1223 (vs), 1096 (s), 1057 (s)).

**HRMS:**

Calcd for (C$_{25}$H$_{31}$N$_3$O$_4$Si+H)$^+$ 466.2157

(ESI) Found 466.2168

**TLC**

$R_f = 0.20$ (UV)
4-Chloro-3-phenylisoquinoline (202)

A solution of n-butyllithium in hexanes (2.40 M, 438 μL, 1.05 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of imine 192 (175 mg, 1.00 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 μL, 0.10 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL) over 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and benzonitrile (129 μL, 1.25 mmol, 1.25 equiv) was added, forming a dark red solution. After 5 min, the bright red solution was transferred by cannula to a suspension of hexachloroethane (710 mg, 3.00 mmol, 3 equiv) in tetrahydrofuran (1 mL) at –78 ºC. After 10 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 10:1 hexanes–ethyl acetate), furnishing 4-chloro-3-phenylisoquinoline (202) as a yellow oil (143 mg, 60%) with spectral properties identical to those previously reported.43

**N-tert-Butyl-3-phenylisoquinolin-1-amine (203)**

A solution of *n*-butyllithium in hexanes (2.40 M, 225 µL, 0.539 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of imine 192 (90 mg, 0.513 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (9 µL, 0.051 mmol, 0.1 equiv) in tetrahydrofuran (1 mL) over 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to −78 ºC, and benzonitrile (66 µL, 0.642 mmol, 1.25 equiv) was added, forming a dark red solution. After 5 min, the bright red solution was transferred by cannula to a suspension of hexachloroethane (487 mg, 2.05 mmol, 4 equiv) and diethylamine (212 µL, 2.05 mmol, 4 equiv) in tetrahydrofuran (0.5 mL) at −78 ºC. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (50:1 hexanes–ethyl acetate). The product fractions were collected and concentrated. The residue (a yellow solid) was further purified by recrystallization from hexanes, furnishing *N-tert*-butyl-3-phenylisoquinolin-1-amine (203) as a white solid (85 mg, 60%).
Melting Point  96–97 °C

\(^1\text{H NMR:}\)  
(500 MHz, CDCl\(_3\))  
8.22 (d, 2H, \(J = 8.7\) Hz), 7.78–7.69 (m, 2H), 7.57 (app t, 1H), 7.51 (app t, 2H, \(J = 7.8\) Hz), 7.45 (s, 1H), 7.45–7.38 (m, 2H), 5.22 (br s, 1H), 1.71 (s, 9H).

\(^1\text{C NMR:}\)  
(126 MHz, CDCl\(_3\))  
154.0, 148.7, 140.4, 138.0, 129.3, 128.4, 127.9, 127.8, 126.6, 125.4, 121.3, 117.8, 106.0, 51.8, 29.2.

\(\text{FTIR, cm}^{-1}:\)  
(thin film)  
3457 (m), 3059 (m), 2961 (m), 1568 (s), 1518 (vs), 1425 (s), 1323 (s), 1213 (s).

\(\text{HRMS:}\)  
(ESI)  
Calcd for \((\text{C}_{19}\text{H}_{20}\text{N}_2+\text{H})^+\)  
277.1699  
Found  
277.1700

\(\text{TLC}\)  
(9:1 hexanes–ethyl acetate)  
\(R_f = 0.46\) (UV)
A solution of \textit{n}-butyllithium in hexanes (2.40 M, 438 \(uL, 1.05 \text{ mmol}, 1.05 \text{ equiv}) was added dropwise to an ice-cooled solution of imine 192 (175 mg, 1.00 \text{ mmol}, 1 \text{ equiv}) and 2,2,6,6-tetramethylpiperidine (17 \uL, 0.10 \text{ mmol}, 0.1 \text{ equiv}) in tetrahydrofuran (1.5 mL) over 40 min, forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of benzonitrile (129 \uL, 1.25 \text{ mmol}, 1.25 \text{ equiv}) in tetrahydrofuran (0.4 mL) at –78 °C, forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 3 min, a solution of hexachloroethane (95 mg, 0.40 \text{ mmol}, 0.4 \text{ equiv}) in tetrahydrofuran (1 mL) was added dropwise over 5 min. After 60 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 °C. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate, and finally 3:1 hexanes–ethyl acetate), furnishing 3,3’-diphenyl-4,4’-bisisoquinoline 205 as a yellow solid (74 mg, 36%).
Melting Point

228–230 ºC

\(^1\text{H NMR:}\)

\((500 \text{ MHz, CDCl}_3)\)

9.40 (s, 1H), 8.12 (d, 1H, \(J = 8.3\) Hz), 7.65 (app td, 1H, \(J = 8.0, 1.2\) Hz), 7.59 (app td, 1H, \(J = 7.8, 1.2\) Hz), 7.41 (d, 1H, \(J = 8.3\) Hz), 7.07 (t, 1H, \(J = 8.9\) Hz), 6.93 (app t, 2H, \(J = 8.0, 1.5\) Hz).

\(^{13}\text{C NMR :}\)

\((126 \text{ MHz, CDCl}_3)\)

152.5, 152.2, 139.9, 137.2, 131.1, 128.9, 128.1, 127.3, 127.2, 127.1, 126.8, 125.7, 125.6.

\(\text{FTIR, cm}^{-1}:\)

\((\text{thin film})\)

3059 (m), 3026 (m), 1618 (s), 1576 (m), 1559 (s), 1497 (s), 1449 (s), 1250 (s).

\(\text{HRMS:}\)

\((\text{ESI})\)

Calcd for \((C_{30}H_{20}N_2+H)^+\)

409.1699

Found

409.1706

\(\text{TLC}\)

\(R_f = 0.17\) (UV)

(4:1 hexanes–ethyl acetate)
5-Fluoro-4-methyl-3-phenyl-7-(trimethylsilyl)isoquinoline (207)

A solution of $n$-butyllithium in hexanes (2.32 M, 436 μL, 1.01 mmol, 1.17 equiv) was added to a cooled solution of 2,2,6,6-tetramethylpiperidine (181 μL, 1.06 mmol, 1.23 equiv) in tetrahydrofuran (1 mL) at −15 ºC. After 20 min, a solution of imine 206 (242 mg, 0.963 mmol, 1.11 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a dark green mixture. The reaction mixture was allowed to warm to 0 ºC over 90 min. The reaction flask was then cooled to −78 ºC, and iodomethane (54 μL, 0.866 mmol, 1 equiv) was added. After 15 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 1 h, the reaction flask was cooled to −40 ºC, and a freshly prepared solution of lithium diisopropylamide (1.01 mmol, 1.17 equiv) in tetrahydrofuran (1.0 mL) was added by cannula, forming a dark red solution. After 60 min, the reaction flask was cooled to −78 ºC, and benzonitrile (124 μL, 1.20 mmol, 1.39 equiv) was added. After 30 min, iodomethane (120 μL, 1.93 mmol, 2.23 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 to
20:1 finally 10:1 hexanes–ethyl acetate), furnishing 5-fluoro-4-methyl-3-phenyl-7-
(trimethylsilyl)isoquinoline (207) as a light yellow solid (120 mg, 45%).

**Melting Point**

95–96 °C

**1H NMR:**

9.15 (d, 1H, $J = 2.3$ Hz), 7.90 (s, 1H), 7.56 (app dt, 2H, $J = 6.9$, 1.8 Hz),
6.9, 1.8 Hz), 7.51–7.46 (m, 2H), 7.46 (dd, 1H, $J = 13.3$, 1.0 Hz), 7.41 (app tt, 1H, $J = 7.8$, 1.4 Hz), 2.77 (d, 3H, $J = 6.4$
Hz), 0.38 (s, 9H).

**19F NMR:**

−113.6–−113.5 (m).

(470 MHz, CDCl3)

**13C NMR:**

159.1 (d, $J = 258.2$ Hz), 153.4, 149.6 (d, $J = 1.8$ Hz), 141.0,
140.9 (d, $J = 4.6$ Hz), 129.8, 129.7 (d, $J = 4.6$ Hz), 129.4 (d,
$J = 3.7$ Hz), 128.1, 127.7, 126.9 (d, $J = 12.8$ Hz), 122.6 (d, $J$
= 4.6 Hz), 119.1 (d, $J = 21.1$ Hz), 18.7 (d, $J = 11.0$ Hz), −1.3.

**FTIR, cm$^{-1}$:** (thin film) 2955 (m), 1568 (m), 1343 (m), 1248 (s).

**HRMS:**

Calcd for (C19H20FNSi+H)$^+$ 310.1422

(ESI) Found 310.1420

**TLC**

$R_f = 0.29$ (UV)

(9:1 hexanes–ethyl acetate)
5-Fluoro-\(N,N\)-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (208)

A solution of \(n\)-butyllithium in hexanes (2.50 M, 910 \(\mu\)L, 2.28 mmol, 1.17 equiv) was added to a cooled solution of 2,2,6,6-tetramethylpiperidine (407 \(\mu\)L, 2.39 mmol, 1.23 equiv) in tetrahydrofuran (3 mL) at \(-15\) \(^\circ\)C. After 20 min, a solution of imine 206 (545 mg, 2.17 mmol, 1.11 equiv) in tetrahydrofuran (1 mL) was added by cannula, forming a dark green mixture. The reaction mixture was allowed to warm to 0 °C over 90 min. The reaction flask was then cooled to \(-78\) °C, and iodomethane (122 \(\mu\)L, 1.95 mmol, 1 equiv) was added. After 15 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 1 h, the reaction flask was cooled to \(-40\) °C, and a freshly prepared solution of lithium diisopropylamide (2.28 mmol, 1.17 equiv) in tetrahydrofuran (2.0 mL) was added by cannula, forming a dark red solution. After 60 min, a solution of \(N,N\)-bis(4-methoxybenzyl)cyanamide (225) (826 mg, 2.93 mmol, 1.5 equiv) in tetrahydrofuran (2 mL) was added. After 40 min, trifluoroacetic acid (2 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 °C. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (30 mL) and dichloromethane (50 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 \(\times\) 40 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl
acetate, then 15:1 hexanes–ethyl acetate), furnishing 5-fluoro-N,N-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (208) as a yellow oil (506 mg, 55%).

| **1H NMR:** (500 MHz, CDCl₃) | 8.98 (s, 1H), 7.70 (s, 1H), 7.21 (d, 1H, J = 12.7 Hz), 7.20 (d, 4H, J = 8.7 Hz), 6.85 (d, 4H, J = 8.7 Hz), 6.77 (s, 1H), 4.83 (s, 4H), 3.80 (s, 6H), 0.33 (s, 9H). |
| **19F NMR:** (470 MHz, CDCl₃) | –128.2 (d, J = 12.7 Hz). |
| **13C NMR:** (126 MHz, CDCl₃) | 158.7, 155.9, 156.5 (d, J = 253.0 Hz), 151.2 (d, J = 2.7 Hz), 133.5 (d, J = 2.7 Hz), 130.2, 130.0 (d, J = 17.4 Hz), 129.0 (d, J = 3.7 Hz), 128.4, 124.0 (d, J = 5.5 Hz), 116.2 (d, J = 16.5 Hz), 114.0, 89.3 (d, J = 4.6 Hz), 55.2, 50.5, –1.2. |
| **FTIR, cm⁻¹:** (thin film) | 2953 (m), 2835 (m), 1626 (m), 1589 (s), 1510 (s), 1246 (s). |
| **HRMS:** (ESI) | Calcd for (C₂₈H₃₁FN₂O₂Si+H)⁺ 475.2212 |
| Found | 475.2206 |
| **TLC** | R_f = 0.30 (UV) |
| (9:1 hexanes–ethyl acetate) |
4-Fluoro-7-iodoisouquinolin-3-amine (210)

A solution of iodine monochloride in dichloromethane (1.0 M, 1.81 mL, 1.81 mmol, 2 equiv) was added slowly over 5 min to an ice-cooled solution of 4-fluoro-\(N,N\)-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (208) (430 mg, 0.906 mmol, 1 equiv) in dichloromethane (5 mL). After 60 min, saturated aqueous sodium thiosulfate solution (5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through silica gel (eluting with 7:1 hexanes–ethyl acetate) and the filtrate was concentrated. The solid residue was transformed directly in the following step.

Trifluoroacetic acid (5 mL) was added to the solid residue prepared above, forming a bright red solution. After 60 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (40 mL) and dichloromethane (40 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading
to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate), furnishing 4-fluoro-7-iodoisoquinolin-3-amine (210) as a yellow solid (196 mg, 75%).

**1H NMR:**

(500 MHz, CDCl₃) 8.58 (s, 1H), 8.19 (app t, 1H, \( J = 1.6 \) Hz), 7.78 (dd, 1H, \( J = 8.9, 1.6 \) Hz), 7.58 (d, 1H, \( J = 9.2 \) Hz), 4.58 (br s, 2H).

**19F NMR:**

(470 MHz, CDCl₃) –156.8 (d, \( J = 2.4 \) Hz).

**13C NMR:**

(126 MHz, CDCl₃) 144.8 (d, \( J = 7.3 \) Hz), 142.4 (d, \( J = 12.8 \) Hz), 138.8, 139.2 (d, \( J = 250.0 \) Hz), 135.9 (d, \( J = 1.8 \) Hz), 126.1, 125.8 (d, \( J = 12.8 \) Hz), 119.4 (d, \( J = 3.7 \) Hz), 87.5.

**FTIR, cm⁻¹:**

(thin film) 3383 (m), 3263 (m), 3160 (s), 2940 (m), 1732 (s), 1645 (s), 1584 (s), 1466 (s), 1261 (s).

**HRMS:**

(ESI) Calcd for (C₉H₆F.IN₂+H)⁺ 288.9633

Found 288.9642

**TLC**

(4:1 hexanes–ethyl acetate) \( R_f = 0.16 \) (UV)
3,4-Difluoro-7-iodoisouquinoline (211)

A solution of sodium nitrite (25 mg, 0.365 mmol, 5 equiv) in water (0.5 mL) was added dropwise to an ice-cooled suspension of 4-fluoro-7-iodoisouquinolin-3-amine (210) (21 mg, 0.073 mmol, 1 equiv) in hydrogen fluoride pyridine (70% HF, 1 mL) in a Teflon reaction vessel over 5 min. After 30 min, the cooling bath was removed and the reaction vessel was allowed to warm to 23 ºC. After 60 min, saturated aqueous sodium carbonate solution (15 mL) was added slowly (CAUTION: gas evolution). The reaction mixture was then partitioned between saturated aqueous sodium chloride (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate), affording 3,4-difluoro-7-iodoisouquinoline (211) as a white solid (18 mg, 85%).

**Melting Point**

135–136 ºC

**^1H NMR:**

8.63 (s, 1H), 8.40 (s, 1H), 7.99 (d, 1H, \( J = 8.8 \) Hz), 7.84 (d, 1H, \( J = 8.8 \) Hz).
$^{19}$F NMR: $-97.3$ (d, $J = 20.7$ Hz), $-154.6$ (d, $J = 20.7$ Hz).

(470 MHz, CDCl$_3$)

$^{13}$C NMR:

147.8 (dd, $J = 235.0$, 13.7 Hz), 143.2 (dd, $J = 13.7$, 7.7 Hz), 139.7, 139.2 (dd, $J = 262.0$, 26.4 Hz), 135.9, 130.0 (d, $J = 2.6$ Hz), 128.1 (dd, $J = 12.8$, 2.6 Hz), 121.0 (dd, $J = 7.3$, 3.0 Hz), 92.4 (d, $J = 2.6$ Hz).

(126 MHz, CDCl$_3$)

FTIR, cm$^{-1}$: 3055 (m), 2930 (m), 1732 (s), 1626 (s), 1591 (s), 1442 (s), 1263 (s).

(thin film)

HRMS: Calcd for (C$_9$H$_4$F$_2$IN+H)$^+$ 291.9429

(ESI) Found 291.9429

TLC: $R_f = 0.48$ (UV)

(9:1 hexanes–ethyl acetate)
3-Chloro-4-fluoro-7-iodoisoquinoline (212)

A solution of sodium nitrite (53 mg, 0.764 mmol, 5 equiv) in water (0.5 mL) was added dropwise to an ice-cooled suspension of 4-fluoro-7-iodoisoquinolin-3-amine (210) (44 mg, 0.153 mmol, 1 equiv) in concentrated aqueous hydrochloric acid solution (37 wt %, 1.5 mL) over 5 min. After 15 min, a solution of copper(I) chloride (76 mg, 0.764 mmol, 5 equiv) in concentrated aqueous hydrochloric acid solution (37 wt %, 0.5 mL) was added dropwise over 5 min. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 60 min, the reaction mixture was partitioned between aqueous ammonium hydroxide solution (30 wt%, 10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes(ethyl acetate), affording 3-chloro-4-fluoro-7-iodoisoquinoline (212) as a white solid (35 mg, 75%).

**Melting Point**  
145–147 °C

**$^1$H NMR:**  
8.81 (s, 1H), 8.41 (s, 1H), 8.04 (dd, 1H, $J = 8.8$, 1.0 Hz),  
[(500 MHz, CDCl$_3$) 7.81 (d, 1H, $J = 8.8$ Hz).]
$^1$H NMR: $-131.2$ (s).

($470$ MHz, CDCl$_3$)

$^13$C NMR:

$150.2$ (d, $J = 264.0$ Hz), $145.8$ (d, $J = 7.3$ Hz), $140.1$, $135.9$ (d, $J = 1.8$ Hz), $131.3$ (d, $J = 18.3$ Hz), $130.5$, $126.3$ (d, $J = 15.6$ Hz), $121.0$ (d, $J = 2.7$ Hz), $93.8$.

($126$ MHz, CDCl$_3$)

FTIR, cm$^{-1}$ :

$2930$ (m), $1734$ (s), $1578$ (m), $1406$ (s), $1217$ (m), $1153$ (m).

(thin film)

HRMS:

Calcd for ($C_9H_4ClFIN$+$H)^+$ $307.9134$

(ESI)  Found $307.9125$

TLC

$R_f = 0.43$ (UV)

(9:1 hexanes–ethyl acetate)
4-Chloro-5-fluoro-7-iodoisooquinolin-3-amine (213)

A solution of iodine monochloride in dichloromethane (1.0 M, 1.66 mL, 1.66 mmol, 2 equiv) was added slowly over 5 min to an ice-cooled suspension of 5-fluoro-\(N,N\)-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (208) (395 mg, 0.832 mmol, 1 equiv) and sodium bicarbonate (210 mg, 2.50 mmol, 3 equiv) in dichloromethane (5 mL). After 2 h, a second portion of iodine monochloride solution (1.0 M in dichloromethane, 0.42 mL, 0.416 mmol, 0.5 equiv) was added. After 60 min, saturated aqueous sodium thiosulfate solution (5 mL) was added. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (\(3 \times 30\) mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through silica gel (eluting with 7:1 hexanes–ethyl acetate) and the filtrate was concentrated. The solid residue was transformed directly in the following step.

Trifluoroacetic acid (5 mL) was added to the solid residue prepared above, forming a bright red solution. After 60 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (40 mL) and dichloromethane (40 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (\(3 \times 30\) mL). The organic layers were combined. The combined solution was dried over sodium
sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate), furnishing 4-chloro-5-fluoro-7-iodoisoquinolin-3-amine (213) as a yellow solid (174 mg, 65%).

\[ \text{\textsuperscript{1}H NMR:} \quad 8.64 \text{ (d, 1H, } J = 2.3 \text{ Hz)}, 7.95 \text{ (s, 1H), 7.50 \text{ (dd, 1H, } J = \)} \]
\[ \quad (500 \text{ MHz, CDCl}_3) \quad 11.7, 1.6 \text{ Hz)}, 5.11 \text{ (br s, 2H).} \]

\[ \text{\textsuperscript{19}F NMR:} \quad -115.5 \text{ (d, } J = 12.7 \text{ Hz).} \]
\[ (470 \text{ MHz, CDCl}_3) \]

\[ \text{\textsuperscript{13}C NMR:} \quad 155.5 \text{ (d, } J = 262.9 \text{ Hz)}, 152.4, 148.5 \text{ (d, } J = 1.8 \text{ Hz), 133.0} \]
\[ \quad (126 \text{ MHz, CDCl}_3) \quad (d, J = 5.0 \text{ Hz), 127.7 \text{ (d, } J = 3.7 \text{ Hz), 125.3 \text{ (d, } J = 10.0} \]
\[ \quad \text{Hz), 124.8 \text{ (d, } J = 23.9 \text{ Hz), 101.6, 84.0 \text{ (d, } J = 7.3 \text{ Hz).} \]

\[ \text{\textsuperscript{FTIR, cm}^{-1}:} \quad 3412 \text{ (m), 3291 \text{ (s), 3175 \text{ (s), 2934 \text{ (m), 1734 \text{ (s), 1634 \text{ (s),}} \}
\[ \quad (\text{thin film}) \quad 1582 \text{ (s), 1460 \text{ (s), 1319 \text{ (s), 1234 \text{ (s).}} \]

\[ \text{HRMS:} \quad \text{Calcd for (C}_9\text{H}_5\text{ClFIN}_2\text{H}^+} \quad 322.9243 \]
\[ \text{(ESI)} \quad \text{Found} \quad 322.9255 \]

\[ \text{TLC} \quad R_f = 0.24 \text{ (UV)} \]
\[ (4:1 \text{ hexanes–ethyl acetate)} \]
4-Chloro-3,5-difluoro-7-iodoisoquinoline (214)

A solution of sodium nitrite (21 mg, 0.310 mmol, 5 equiv) in water (0.5 mL) was added dropwise to an ice-cooled suspension of 4-chloro-5-fluoro-7-iodoisoquinolin-3-amine (213) (20 mg, 0.062 mmol, 1 equiv) in hydrogen fluoride pyridine (70% HF, 1 mL) in a Teflon reaction vessel over 5 min. After 30 min, the cooling bath was removed and the reaction vessel was allowed to warm to 23 ºC. After 60 min, saturated aqueous sodium carbonate solution (15 mL) was added slowly (CAUTION: gas evolution). The reaction mixture was then partitioned between saturated aqueous sodium chloride (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate), affording 4-chloro-3,5-difluoro-7-iodo isoquinoline (214) as a white solid (16 mg, 79%).

<table>
<thead>
<tr>
<th>Melting Point</th>
<th>151–153 ºC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR:</td>
<td>δ 8.75 (d, 1H, $J = 1.4$ Hz), 8.20 (s, 1H), 7.71 (dd, 1H, $J = 11.4, 0.9$ Hz).</td>
</tr>
<tr>
<td><strong>19F NMR:</strong></td>
<td>$-76.5 \text{ (d, } J = 5.7 \text{ Hz)}, -112.9 \text{ (dd, } J = 11.4, 6.9 \text{ Hz}).$</td>
</tr>
<tr>
<td>(470 MHz, CDCl$_3$)</td>
<td></td>
</tr>
<tr>
<td><strong>13C NMR:</strong></td>
<td>$157.4 \text{ (d, } J = 234.4 \text{ Hz)}, 156.7 \text{ (dd, } J = 267.3, 11.0 \text{ Hz)},$</td>
</tr>
<tr>
<td>(126 MHz, CDCl$_3$)</td>
<td>$147.2 \text{ (dd, } J = 14.6, 3.7 \text{ Hz)}, 133.0 \text{ (d, } J = 3.7 \text{ Hz)}, 131.0$</td>
</tr>
<tr>
<td></td>
<td>$(d, J = 2.7 \text{ Hz}), 126.6 \text{ (dd, } J = 10.5, 2.3 \text{ Hz}), 125.8 \text{ (d, } J$</td>
</tr>
<tr>
<td></td>
<td>$= 23.8 \text{ Hz)}, 108.2 \text{ (dd, } J = 34.8, 2.7 \text{ Hz)}, 89.7 \text{ (dd, } J =$</td>
</tr>
<tr>
<td></td>
<td>$7.8, 3.2 \text{ Hz}).$</td>
</tr>
<tr>
<td><strong>FTIR, cm$^{-1}$:</strong></td>
<td>$2930 \text{ (m), 1584 (s), 1429 (s), 1325 (s).}$</td>
</tr>
<tr>
<td>(thin film)</td>
<td></td>
</tr>
<tr>
<td><strong>HRMS:</strong></td>
<td>Calcd for (C$_9$H$_3$ClF$_2$IN+H)$^+$ $325.9040$</td>
</tr>
<tr>
<td>(ESI)</td>
<td>Found $325.9036$</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>$R_f = 0.39 \text{ (UV)}$</td>
</tr>
<tr>
<td>(9:1 hexanes–ethyl acetate)</td>
<td></td>
</tr>
</tbody>
</table>
Bromine (19 μL, 0.372 mmol, 6 equiv) was added to an ice-cooled suspension of 4-chloro-5-fluoro-7-iodoisoquinolin-3-amine (213) (20 mg, 0.062 mmol, 1 equiv) in concentrated aqueous hydrobromic acid solution (48 wt %, 1 mL). After 10 min, a solution of sodium nitrite (21 mg, 0.310 mmol, 5 equiv) in water (0.5 mL) was added dropwise over 5 min. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 60 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined and then dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate), affording 3-bromo-4-chloro-5-fluoro-7-iodoisoquinoline (215) as a white solid (19.5 mg, 81%).

**Melting Point**

165–167 °C

**1H NMR:**

(500 MHz, CDCl₃) 8.82 (d, 1H, $J = 2.3$ Hz), 8.18 (s, 1H), 7.74 (dd, 1H, $J =$ 11.2, 1.6 Hz).

**19F NMR:**

(470 MHz, CDCl₃) $\text{Br}$

$–109.8$ (d, $J =$ 11.8 Hz).
$^{13}$C NMR: (126 MHz, CDCl$_3$)
155.7 (d, $J = 268.2$ Hz), 148.3 (d, $J = 1.8$ Hz), 139.1, 133.0 (d, $J = 5.5$ Hz), 131.0, 126.20 (d, $J = 25.63$ Hz), 125.3 (d, $J = 3.7$ Hz), 124.9 (d, $J = 9.2$ Hz), 91.5 (d, $J = 7.3$ Hz).

FTIR, cm$^{-1}$: (thin film)
2926 (m), 1553 (s), 1460 (s), 1397 (s), 1298 (s).

HRMS: (ESI)
Calcd for (C$_9$H$_3$BrClFIN+H)$^+$ 385.8239
Found 385.8230

TLC
(9:1 hexanes–ethyl acetate)
$R_f = 0.33$ (UV)
7-Chloro-1-fluoro-3-(3-fluorophenyl)isoquinoline (218)

A solution of \(n\)-butyllithium in hexanes (2.32 M, 226 μL, 0.525 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of diisopropylamine (78 μL, 0.550 mmol, 1.1 equiv) in tetrahydrofuran (1.0 mL). After 15 min, a solution of imine 216 (105 mg, 0.500 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the reaction flask was cooled to \(-78^\circ C\), and 3-fluorobenzonitrile (67 μL, 0.625 mmol, 1.25 equiv) was added, forming a dark brown solution. After 5 min, the dark brown solution was transferred by cannula to a suspension of hexachloroethane (473 mg, 2.00 mmol, 4 equiv) and diethylamine (207 μL, 2.00 mmol, 4 equiv) in tetrahydrofuran (0.5 mL) at \(-78^\circ C\). After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 30 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (50:1 hexanes–ethyl acetate), affording \(N\)-tert-butyl-7-chloro-3-(3-fluorophenyl)isoquinolin-1-amine (217) as a pale yellow oil (75 mg, 45%).

A solution of sodium nitrite (79 mg, 1.14 mmol, 5 equiv) in water (1 mL) was added dropwise to an ice-cooled suspension of \(N\)-tert-butyl-7-chloro-3-(3-fluorophenyl)isoquinolin-1-amine (217) (75 mg, 0.228 mmol, 1 equiv) in hydrogen fluoride pyridine.
(70% HF, 2 mL) in a Teflon reaction vessel over 5 min. After 30 min, the cooling bath was removed and the reaction vessel was allowed to warm to 23 °C. After 60 min, saturated aqueous sodium carbonate solution (20 mL) was added slowly (CAUTION: gas evolution). The reaction mixture was then partitioned between saturated aqueous sodium chloride (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by recrystallization from hexanes, furnishing 7-chloro-1-fluoro-3-(3-fluorophenyl) isoquinoline (218) as a pale yellow solid (44 mg, 70%).

<table>
<thead>
<tr>
<th>Melting Point</th>
<th>118–119 °C</th>
</tr>
</thead>
</table>

**¹H NMR:**

(500 MHz, CDCl₃)

| 8.10 (d, 1H, J = 8.7 Hz), 7.89 (s, 1H), 7.85 (d, 1H, J = 8.2 Hz), 7.84 (s, 1H), 7.80 (app dt, 1H, J = 10.5, 2.1 Hz), 7.58 (dd, 1H, J = 8.7, 1.8 Hz), 7.45 (app td, 1H, J = 8.0, 6.0 Hz), 7.12 (app td, 1H, J = 8.2, 2.7 Hz). |

**¹⁹F NMR:**

(470 MHz, CDCl₃)

| –69.7 (s), –113.0 (ddd, J = 10.3, 8.0, 5.7 Hz). |

**¹³C NMR:**

| 163.3 (d, J = 246.3 Hz), 159.5 (d, J = 243.5 Hz), 148.3 |
(126 MHz, CDCl₃) (d, $J = 17.4$ Hz), 141.2 (d, $J = 5.5$ Hz), 139.8 (d, $J = 7.3$ Hz), 138.4, 130.3 (d, $J = 8.2$ Hz), 129.0, 125.8 (d, $J = 3.7$ Hz), 125.0, 122.3 (d, $J = 2.7$ Hz), 116.2 (d, $J = 22.0$ Hz), 115.1 (d, $J = 33.9$ Hz), 114.0 (d, $J = 5.5$ Hz), 113.9 (d, $J = 22.9$ Hz).

**FTIR, cm⁻¹:**
\(2980\) (m), \(2970\) (m), \(1738\) (s), \(1379\) (vs), \(1314\) (m).

**FTIR, cm⁻¹:**
(Thin film)

**HRMS:**
Calcd for \((C_{15}H_8ClF_2N+H)^+\) 276.0386
(ESI) Found 276.0378

**TLC**
\(R_f = 0.32\) (UV)
(20:1 hexanes–ethyl acetate)
Appendix A

Catalog of Spectra
Purification of Cortistatin A (1).

a) After Davisil® column

b) After LH-20 column (tetra-n-butylammonium salts)

c) After HPLC (eliminated product removed)
Purification of Cortistatin L (11).

a) After Davisil® column

elimination product as a trace impurity

b) After HPLC (eliminated product removed)
Purification of Cortistatin J (9).

a) After Davisil® column

 elimination product as a trace impurity

b) After HPLC (eliminated product removed)
Purification of Cortistatin K (10).

a) After Davisil® column

b) After HPLC (eliminated product removed)