Chemistry of the cortistatins–a novel class of *anti*-angiogenic agents†

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Synthetic efforts culminating the construction of several highly advanced intermediates, and completed syntheses of the recently disclosed cortistatin family of *anti*-proliferative agents are described in this perspective.

Introduction

The rampant spread and prevalence of cancer in the 21st century has escalated the search for novel therapeutics in the intervention of tumour progression to an unprecedented level of urgency and intensity. Among which, angiogenesis, a physiological phenomenon responsible for the transition of tumors from a dormant to a malignant state through the generation of new blood vessels, has gained significant interest from the medical community.[1] In 2006, the Kobayashi group disclosed the cortistatin family of natural products (cortistatins A–D, **1–4**, Fig. 1) which were found to exhibit selective *anti*-angiogenic properties against human umbilical vein endothelial cells (HUVEC).[2] The most potent member of the family, cortistatin A (**1**, IC_{50} = 1.8 nM), demonstrated a remarkable selectivity index of more than 3000-fold in comparison with normal human dermal fibroblast (NHDF) and several tumor cells (KB3–1, K562 and Neuro2A). Subsequently in 2007, structurally closely related cortistatins E–H and cortistatins J–L were also reported by the same group (**5–8** and **9–11**, respectively, Fig. 1), among which cortistatin J (**9**) showed the most potent *anti*-proliferative activity (HUVEC, IC_{50} = 8 nM) with selectivity index of 300–1100 fold (against NHDF, KB3–1, K562 and Neuro2A).[3,4] The limited natural supply, impressive biological activities and their unprecedented molecular architecture presented the cortistatins as enticing targets for chemical synthesis. In this article, a comprehensive review of the synthetic studies towards cortistatin's unique abeo-9(10–19)-androstane-type steroidal skeleton are presented, together with completed (total, semi, and formal) syntheses of cortistatin A and J. Furthermore, preliminary structural-activity-studies of the cortistatin analogues and plausible biological targets of cortistatin A are path-pointing for more extensive chemical-biology investigations, and for the discovery and development

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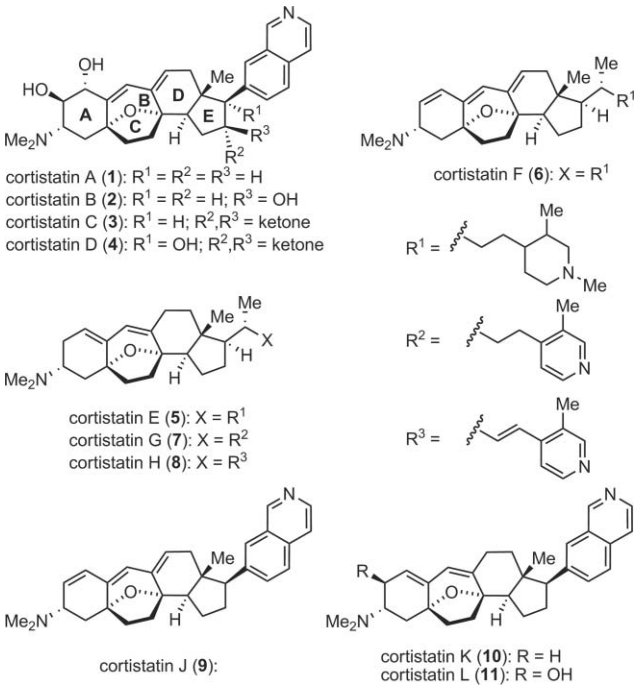


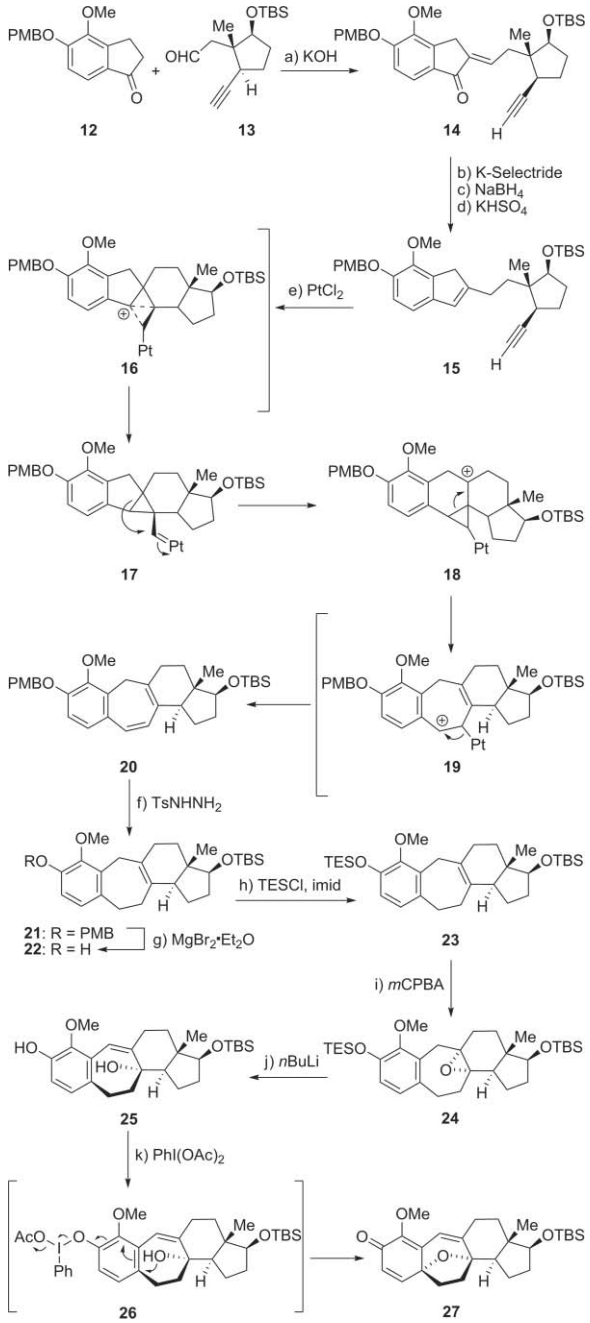
Fig. 1 Structures of the cortistatin family of *anti*-proliferative agents.

of novel *anti*-proliferative agents for the treatment of relevant diseases.

Synthetic studies towards the cortistatins

Sarpong's synthesis

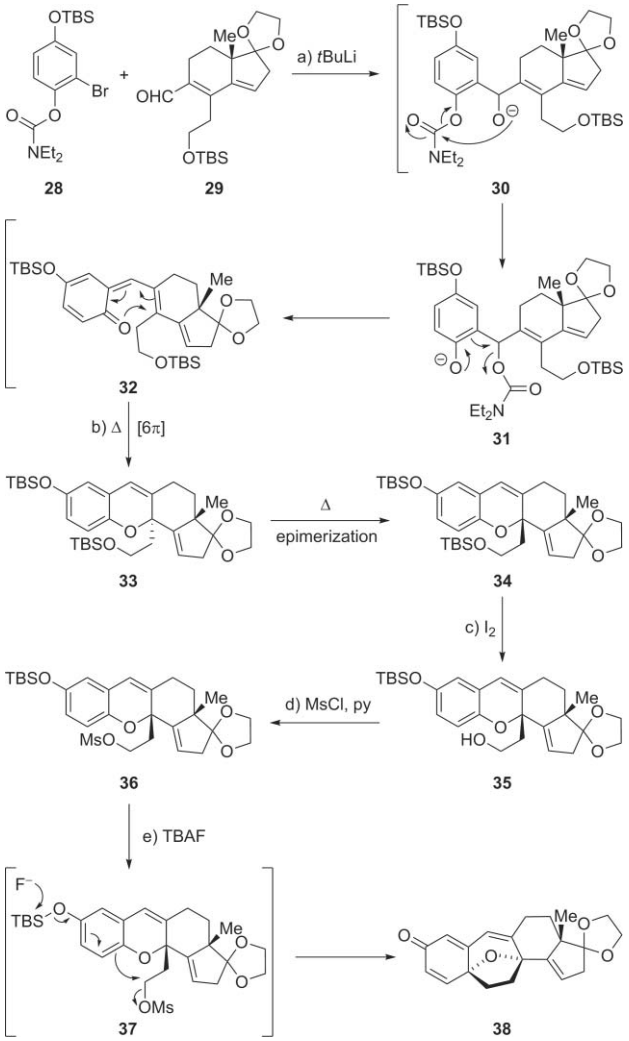
In 2006, the Sarpong laboratory reported the total synthesis of (±)-salviasperanol and demonstrated the first example of enyne cycloisomerization involving indenes to produce cycloheptadienes.[5] This technology was successfully implemented in the synthesis of the tetracyclic cycloheptadiene containing intermediate **20**, as shown in Scheme 1.[6] The synthesis commenced with an aldol condensation between indanone **12** and aldehyde **13** to give enone **14** as a single stereoisomer in 51% yield. K-selectride-mediated 1,4-reduction of enone **14**, followed by treatment of the crude mixture with $NaBH_4$ and subsequent dehydration ($KHSO_4$) of the secondary alcohol afforded alkynyl indene **15** in 65% yield over the three steps. The planned cycloisomerization of enyne **15** took place smoothly in the presence of $PtCl_2$, through the intermediacy of **16** to **19**, to furnish tetracycle **20** in 61% yield. Further elaboration of tetracycle **20** to the oxo-bridged pentacycle **27** representing the A–E ring framework of the cortistatins began with a diimide-mediated chemoselective reduction ($TsNHNH_2$, 95% yield), followed by a two-step protecting group interconversion ($MgBr_2{\cdot}OEt_2$, TESCl), to give tetracycle **23**. *m*CPBA-mediated stereoselective epoxidation of **23** (46% yield over the three steps from **21**) followed by *n*BuLi induced epoxide opening with concomitant TES ether removal delivered hydroxy phenol **25**, setting the stage for the construction of the B-ring oxo-bridge. This final transformation was smoothly accomplished upon treatment of hydroxy phenol **25** with $PhI(OAc)_2$, to give trieneone pentacycle **27** in 60% yield over the two steps from epoxide **24**.



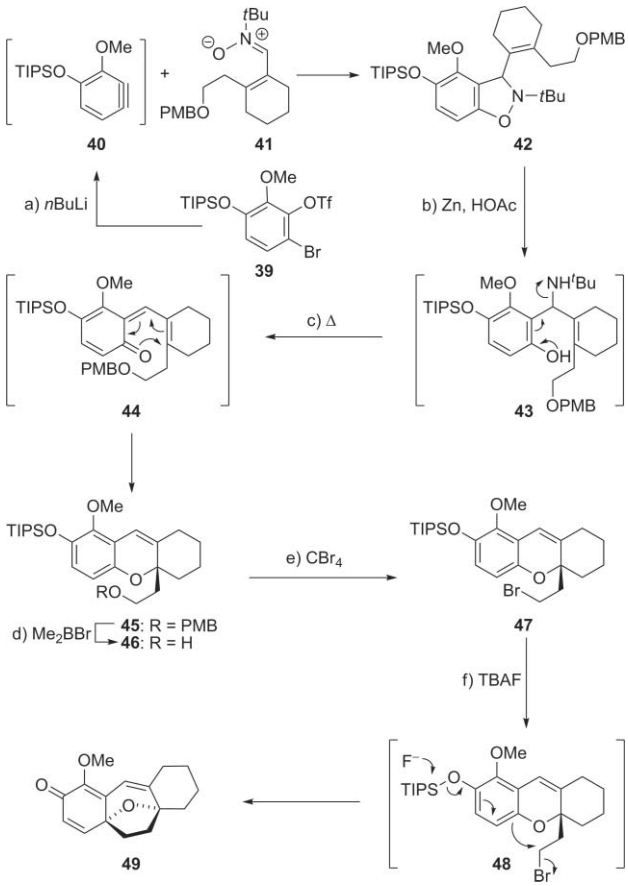
Scheme 1 Sarpong's synthesis of pentacycle **27**. Reagents and conditions: a) KOH (1.0 equiv.), EtOH–CH_2Cl_2 (3 : 1), 23 °C, 2.5 h, 51%; b) K-Selectride (3.0 equiv.), THF, −78 °C, 2 h; −78 → 23 °C, 2 h; c) $NaBH_4$ (1.0 equiv.), MeOH–CH_2Cl_2 (1 : 1), 0 °C, 1 h; d) $KHSO_4$ (1.0 equiv.), toluene, 50 °C, 18 h, 65% over the three steps; e) $PtCl_2$ (0.1 equiv.), PhH, 40 °C, 61%; f) $TsNHNH_2$ (8.0 equiv.), Et_3N (16 equiv.), 1,2-dichloroethane, 65 °C, 24 h, 95%; g) $MgBr_2{\cdot}Et_2O$ (6.0 equiv.), Me_2S (20 equiv.), CH_2Cl_2, −78 → 23 °C, 3 h; h) TESCl (1.5 equiv.), imidazole (3.0 equiv.), DMF, 23 °C, 3 h; i) *m*CPBA (1.2 equiv.), $NaHCO_3$ (2.0 equiv.), CH_2Cl_2, 0 °C, 1.5 h, 46% over the three steps; j) *n*BuLi (5.0 equiv.), THF, 0 °C, 1 h; k) $PhI(OAc)_2$ (1.5 equiv.), CH_2Cl_2/*i*PrOH/TFE (5 : 3 : 2), 0 °C, 30 min, 60% over the two steps. PMB = *para*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; K-Selectride = potassium tri-*sec*-butyl(hydrido)borate; Ts = *para*-toluenesulfonyl; TES = triethylsilyl; imid = imidazole; *m*CPBA = *meta*-chloroperoxybenzoic acid; DMF = *N*,*N*′-dimethylformamide, TFE = 2,2,2-trifluoroethanol; THF = tetrahydrofuran; Ac = acetyl.

Danishefsky's syntheses

The Danishefsky group successfully developed two elegant approaches toward the cortistatin core structure, based on a [6π]-electrocyclization and a subsequent Masamune alkylative dearomatization,[7] as shown in Scheme 2 and 3.[8,9] In their first approach (Scheme 2), the [6π]-electrocyclization precursor **32** was synthesized with an application of the Snieckus cascade[10] between aryl bromide **28** and aldehyde **29** in the presence *t*BuLi. Upon warming the reaction mixture to 80 °C and heating for 12 h, tetracycle **33** was isolated in 44% yield as a single isomer from bromide **28**. The incorrect stereochemistry in tetracycle **33** was fortuitously corrected upon further heating tetracycle **33** at 130 °C, presumably through a retro-[6π]-electrocyclization/[6π]-electrocyclization sequence, to give tetracycle **34** in quantitative yield. In preparation for the Masamune alkylative dearomatization, TBS ether **34** was converted to mesylate **36** (I_2, MsCl-py) in 78% over the two steps. Finally, treatment of the latter compound with TBAF smoothly delivered pentacycle **38** in 88% yield.



Scheme 2 Danishefsky's synthesis of pentacycle **38**. Reagents and conditions: a) **28** (1.1 equiv.), *t*BuLi (2.4 equiv.), Et_2O, −78 °C, 30 min; then **29**, −78 °C, 30 min; b) 80 °C, 12 h, 44% over the two steps; c) I_2 (0.1 equiv.), THF–MeOH (1 : 1), 23 °C, 2 h, 83%; d) MsCl (10.0 equiv.), py (19.4 equiv.), CH_2Cl_2, 0 °C, 15 h, 94%; e) TBAF (1.2 equiv.), THF, 23 °C; then 130 °C, 20 min, 88%. Ms = methanesulfonyl; py = pyridine; TBAF = tetra-n-butylammonium fluoride.

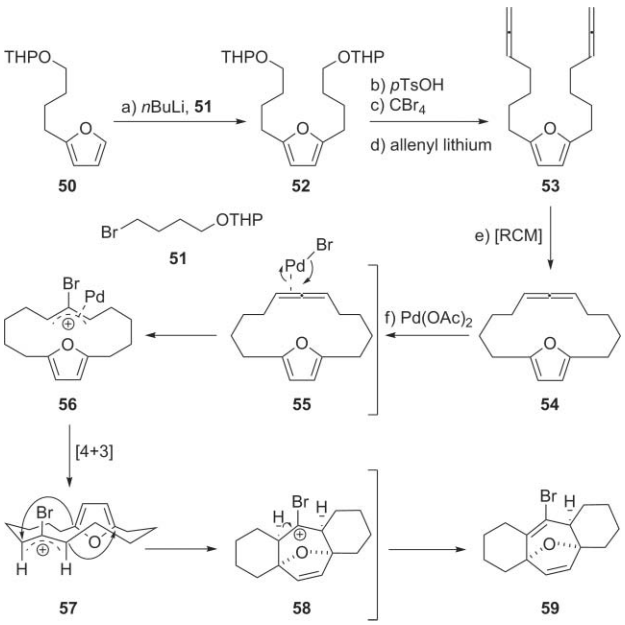


Scheme 3 Danishefsky's synthesis of tetracycle **49**. Reagents and conditions: a) **39** (2.3 equiv.), *n*BuLi (2.5 equiv.), THF, −78 °C, 20 min; b) Zn (10.0 equiv.), HOAc, 23 °C, 16 h; c) toluene, 170 °C, 12 h, 55% over the three steps; d) Me_2BBr (6.4 equiv.), *i*Pr_2NEt (5.2 equiv.), anisole (14.8 equiv.), CH_2Cl_2, −78 °C, 20 min, 84%; e) CBr_4 (3.0 equiv.), PPh_3 (3.0 equiv.), CH_2Cl_2, 23 °C, 1 h, 87%; f) TBAF (3.0 equiv.), THF, 23 °C, 5 min; then 50 °C, 20 min, 52%. TIPS = triisopropylsilyl; OTf = trifluoromethanesulfonate.

Alternatively, the construction of the [6π]-electrocyclization precursor **44** was successfully executed based on a nitrone-aryne [3+2] cycloaddition/N–O bond cleavage/1,4-elimination sequence, as shown in Scheme 3.[9] Upon treating of a solution of bromophenyl triflate **39** and nitrone **41** with *n*BuLi, the *in situ* generated aryne **40** smoothly underwent [3+2] cycloaddition to give benzoisoxazoline **42** as a single stereoisomer. Reductive cleavage of the N–O bond within **42** was accomplished with Zn/AcOH, followed by thermal induced 1,4-elimination with extrusion of *t*$BuNH_2$ and subsequent [6π]-electrocyclization, afforded tricycle **45** in 55% yield over the three steps from **41**. In an analogous sequence as in the conversion from **35** to **38** (Scheme 2), PMB ether **45** was converted to bromide **47** (Me_2BBr, CBr_4, 73% yield over the two steps), followed by treatment of the latter compound with TBAF to afford tetracycle **49** in 52% yield.

Gung's synthesis

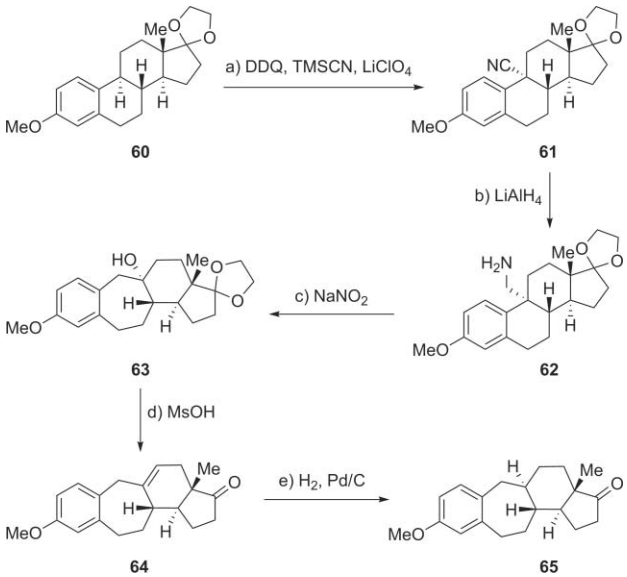
The Gung group recognized the oxabicyclo[3.2.1]-octene motif of the cortistatins as an opportunity to demonstrate the transannular [4+3] cycloaddition for its construction (Scheme 4).[11] Starting from mono-alkylated furan **50**, lithiation and alkylation with bromide **51** afforded bis-THP ether **52** in 87% yield. Simultaneous conversion of the two THP termini to the corresponding bis-allene **53** was accomplished through a bis-deprotection/bromination sequence (*p*TsOH, CBr_4, 82% yield over the two steps), followed by double displacement of the intermediate di-bromide with allenyl lithium, to afford the RCM[12] precursor **53** in 76% yield. Under the influence of Grubbs' first generation catalyst, ring-closing allene metathesis delivered macrocyclic furanyl allene **54** in 47% yield, setting the stage for the transannular [4+3] cycloaddition. After some initial explorations to identify reaction conditions to selectively activate the allene moiety of **54** in the presence of the electron-rich furan, it was found by treating of furanyl allene **54** with catalytic $Pd(OAc)_2$ in the presence of LiBr, presumably through the intermediacy of (π-allyl)palladium intermediate **56**, tetracyclic bromide **59** was obtained in 37% yield.



Scheme 4 Gung's synthesis of tetracycle **59**. Reagents and conditions: a) *n*BuLi (1.3 equiv.), **51** (1.3 equiv.), THF, −78 → 23 °C, 1 h, 87%; b) *p*TsOH·H_2O (0.2 equiv.), MeOH, 23 °C, 6 h, 91%; c) CBr_4 (3.0 equiv.), PPh_3 (3.4 equiv.), CH_2Cl_2, 0 → 23 °C, 14 h, 90%; d) allene (3.1 equiv.), *n*BuLi (3.1 equiv.), HMPA (0.5 equiv.), THF, −78 °C, 2 h, 76%; e) Grubbs' first generation catalyst (0.2 equiv.), CH_2Cl_2, 45 °C, 31 h, 47%; f) $Pd(OAc)_2$ (0.1 equiv.), LiBr (5.0 equiv.), $Cu(OAc)_2·H_2O$ (2.3 equiv.), K_2CO_3 (1.3 equiv.), O_2 (1 atm), MeCN, 23 °C, 10 h, 37%. THP = tetrahydropyran; *p*TsOH = *para*-toluenesulfonic acid; HMPA = hexamethylphosphoramide.

Corey's synthesis

The Corey group developed a rapid and scalable synthesis of tetracycle **65** based on the expansion of the estrone B-ring, utilizing a benzylic cyanation and a Demjanov rearrangement,[13] as shown in Scheme 5.[14] After extensive experimentation, regio- and stereoselective benzylic cyanation of dioxolane protected

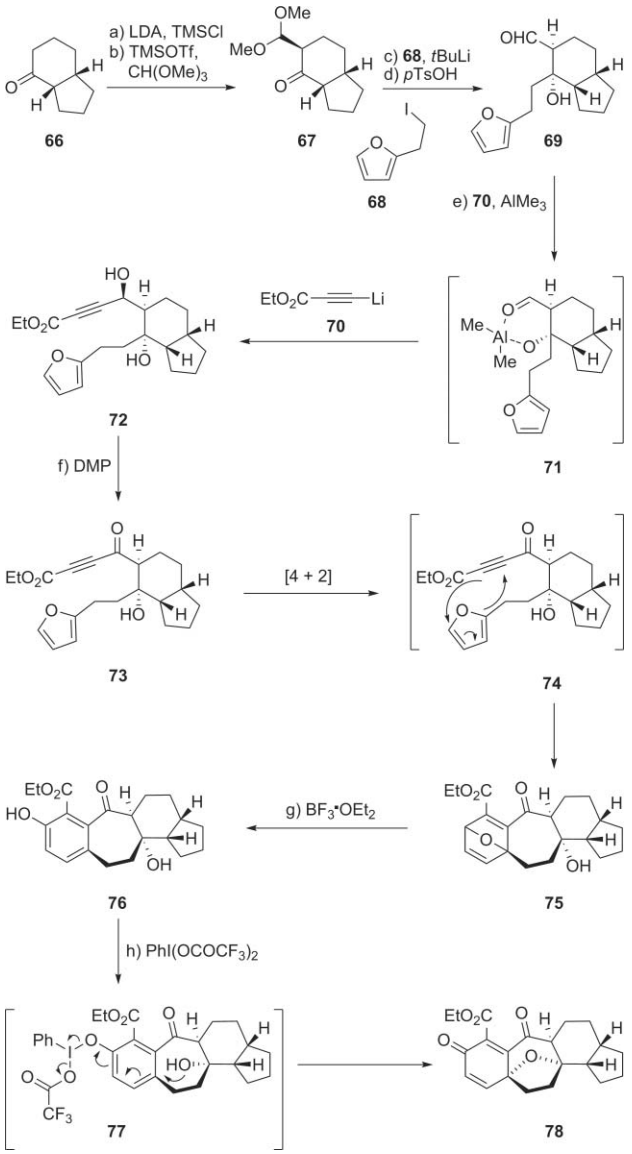


Scheme 5 Corey's synthesis of tetracycle **65**. Reagents and conditions: a) TMSCN (5.0 equiv.), DDQ (1.08 equiv.), $LiClO_4$ (1.0 equiv.), CH_2Cl_2, −10 °C, 30 min, 95%; b) $LiAlH_4$ (3.5 equiv.), THF, 0 → 23 °C; then reflux, 2 h, 98%; c) $NaNO_2$ (5.0 equiv.), H_2O–HOAc–THF (1 : 1 : 2), 0 °C, 2 h, 61%; d) MsOH (2.0 equiv.), CH_2Cl_2, reflux, 2 h, 74%; e) Pd/C (20% wt/wt), H_2 (250 psi), EtOAc, 23 °C, 12 h, 95%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TMS = trimethylsilyl; MsOH = methanesulfonic acid.

estrone **60** was accomplished in the presence of DDQ, TMSCN and $LiClO_4$, furnishing cyanide **61** in a nearly quantitative yield. Reduction of cyanide **61** ($LiAlH_4$, 98% yield), followed by treatment of the resulting amine **62** with $NaNO_2$, led to a smooth and efficient aryl Demjanov rearrangement to provide the carbocyclic core of the cortistatins in 61% yield. Further transformation of tertiary alcohol **63** (MsOH, H_2–Pd/C, 70% yield over the two steps) delivered B-ring expanded estrone **65**, which may possess interesting biological properties based on clinical indications of related estrone derivatives.[15]

Yang's synthesis

An intramolecular Diels–Alder[16] entry to the carbocyclic core of the cortistatins was first demonstrated by Yang and co-workers in the preparation pentacycle **78**.[17] As shown in Scheme 6, preparation of the intramolecular Diels–Alder precursor **73** commenced with the alkylation of ketone **66** with $CH(OMe)_3$, followed by addition of the lithiated species derived from furanyl alkyl iodide **68** and removal of the dimethyl acetal (*p*TsOH), to give furanyl aldehyde **69** in 45% yield over the four steps. Introduction of the dienophile component of the intramolecular Diels–Alder reaction onto aldehyde **69** was carried out with alkynyl lithium **70** in the presence of $AlMe_3$, presumably through the chelated transition state **71**, to give propargyl alcohol **72** in 71% yield as a single stereoisomer. While compound **72** failed to participate in an intramolecular Diels–Alder reaction, upon its oxidation under the DMP conditions, the corresponding ynone **73** underwent spontaneous [4+2] cycloaddition to afford pentacycle **75** in an impressive 91% overall yield as a *ca.* 3 : 1 mixture of diastereoisomers. Rupture of the oxo-bicyclic motif within compound **75** in the presence of $BF_3·Et_2O$ yielded phenolic carbinol **76**, which was subjected to an

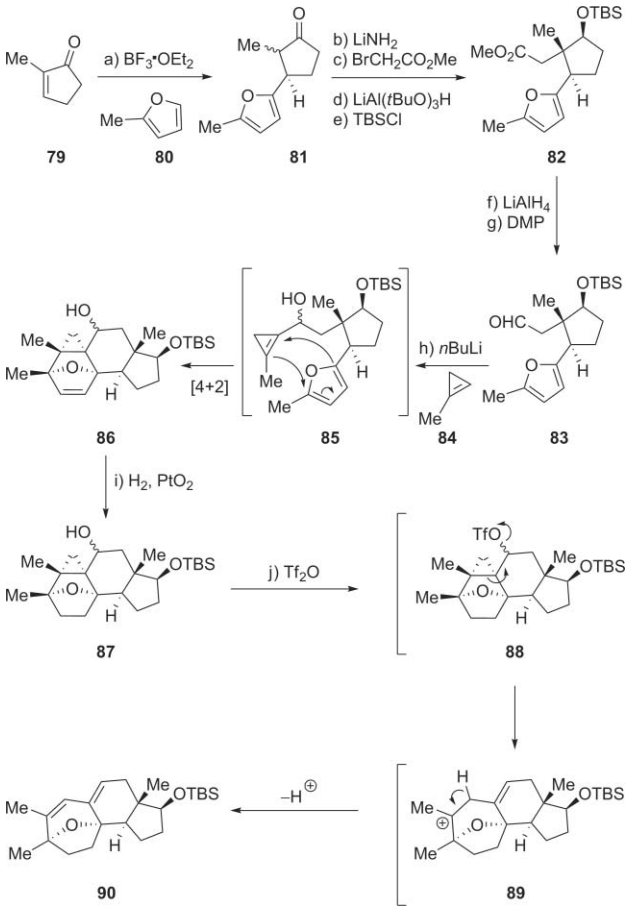


Scheme 6 Yang's synthesis of pentacycle **78**. Reagents and conditions: a) LDA (0.11 equiv.), TMSCl (1.5 equiv.), THF, −78 °C, 2 h; b) TMSOTf (0.05 equiv.), $CH(OMe)_3$ (1.2 equiv.), CH_2Cl_2, −78 °C, 12 h, 89%; c) **68** (1.3 equiv.), *t*BuLi (2.6 equiv.), Et_2O, −78 °C, 3 h, 58%; d) *p*TsOH·H_2O (0.1 equiv.), acetone, 0 °C, 3 h, 87%; e) **70** (3.0 equiv.), $AlMe_3$ (1.0 equiv.), THF, −78 °C, 1 h, 71%; f) DMP (1.5 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, 23 °C, 1 h, 91%; g) BF_3·Et_2O (3.0 equiv.), CH_2Cl_2, −20 °C, 63%; h) $PhI(OCOCF_3)_2$ (1.2 equiv.), 4 Å MS, $MeNO_2$, 23 °C, 30 min, 60%. LDA = lithium diisopropylamide; DMP = Dess–Martin periodinane.

analogous oxidative dearomatization conditions [$PhI(OCOCF_3)_2$, 60% yield] reported by Sarpong and co-workers[6] to complete the oxo-bridged pentacyclic core structure **78**.

Magnus's synthesis

In contrast to the intramolecular Diels–Alder reaction employed by the Yang group in the construction of the A-ring of cortistatin, the Magnus group demonstrated, as shown in Scheme 7, an intramolecular cyclopropene-furan [4+2] cycloaddition followed by a cyclopropylcarbinyl rearrangement to furnish the oxo-bicyclic B-ring of cortistatin.[18] Commenced from a Friedel–Crafts reaction

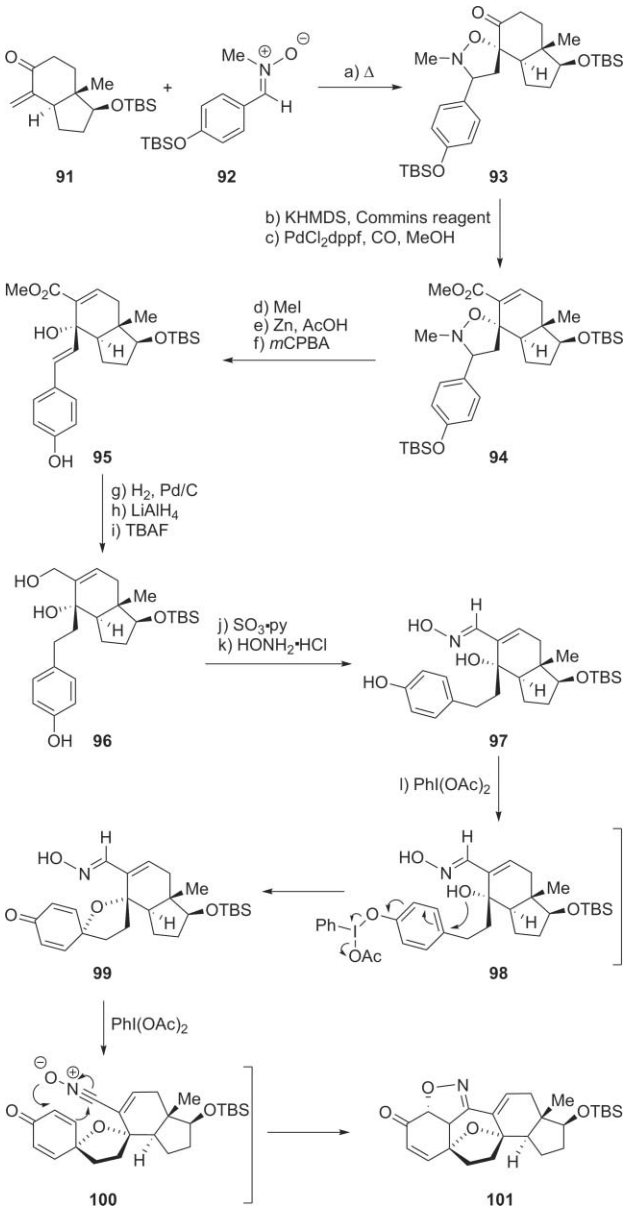


Scheme 7 Magnus's synthesis of tetracycle **90**. Reagents and conditions: a) **80** (1.5 equiv.), BF_3·Et_2O (0.1 equiv.), EtOH (1.0 equiv.), $MeNO_2$, 23 °C, 3 h, 82%; b) $LiNH_2$ (2.0 equiv.), THF, reflux, 4 h; c) $BrCH_2CO_2Me$ (3.0 equiv.), THF, −78 °C, 4 h, 75%; d) $LiAl(tBuO)_3H$ (1.1 equiv.), THF, 0 °C, 2 h; 95%; e) TBSCl (3.0 equiv.), imidazole (1.5 equiv.), DMF, 23 °C, 18 h, 97%; f) $LiAlH_4$ (2.1 equiv.), THF, 0 °C, 30 min, 92%; g) DMP (1.1 equiv.), CH_2Cl_2, 23 °C, 4 h, 98%; h) **84** (3.9 equiv.), *n*BuLi (7.8 equiv.), THF, −50 → 23 °C, 4 h, 85%; i) PtO_2·H_2O (0.25 equiv.), H_2 (1 atm), EtOH, 23 °C, 3 h, 98%; j) 2,6-*tert*-butyl-4-methylpyridine (3.0 equiv.), Tf_2O (2.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 70%. Tf_2O = trifluoromethanesulfonic anhydride.

between enone **79** and furan **80** under the influence of BF_3·Et_2O, the resulting cyclopentanone derivative **81** was alkylated with $BrCH_2CO_2Me$ followed by a ketone reduction [$LiAl(tBuO)_3H$] and silyl protection (TBSCl), to give furanyl methyl ester **82** in 57% yield over the five steps as a single stereoisomer. Further oxidation state adjustments ($LiAlH_4$, DMP, 90% yield over the two steps) of the ester terminus within **82** led to aldehyde **83**, followed by treatment of the latter compound with lithiated cyclopropene **84** and gently warming the reaction mixture to room temperature, smoothly delivered the [4+2] cycloaddition adduct **86** in 85% yield as a separable mixture of two secondary hydroxyl stereoisomers. Hydrogenation of **86** (H_2, PtO_2, 98% yield) yielded cyclopropane **87**, in readiness for the ring expansion into the 7-membered B-ring of cortistatins. Indeed, after careful experimentation, it was found the treatment of cyclopropyl alcohol **87** with Tf_2O led to the ionization of the secondary hydroxyl, followed by a cyclopropylcarbinyl rearrangement to give compound **90** in 70% yield resembling the BCDE framework of the cortistatins.

Sorensen's synthesis

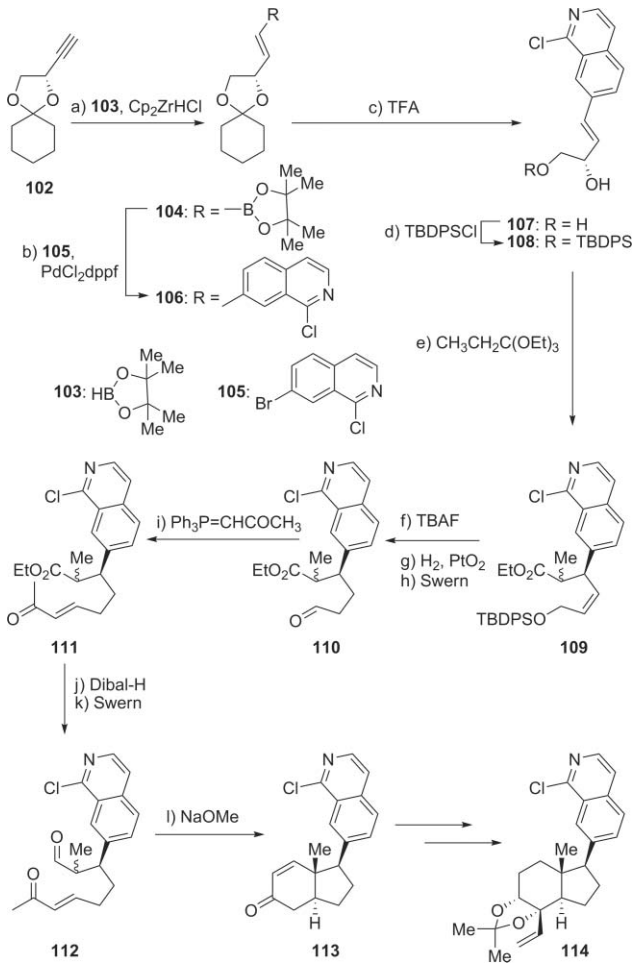
With a cascade process[19] in mind, the Sorensen group developed a tandem oxidative dearomatization/nitrile oxide [3+2] cycloaddition strategy to install the oxo-bicyclic B-ring of the cortistatins, as shown in Scheme 8.[20] Starting from bicyclic enone **91**, a synthetic intermediate readily available from Hajos-Parrish ketone according to procedures developed by Danishefsky,[21] [3+2] cycloaddition engaging nitrone **92** proceeded with complete regio- and stereoselectivity to give isoxazoline **93** in 54% yield. Homologation of ketone **93** to enoate **94** involved enol triflate formation (KHMDS, Commins reagent) and subsequent carboxymethylation ($PdCl_2$dppf, CO, MeOH), in an overall yield of 73% yield for the two steps. Cleavage of N–O bond and removal of the superfluous nitrogen atom in **94** was executed by first *N*-methylation (MeI, 100% yield), followed by reductive rupture of the N–O bond (Zn, AcOH, 97% yield) and Cope elimination[22] through the intermediate *N*-oxide (*m*CPBA, 73% yield) to give olefin **95**. In preparation for the key oxidative dearomatization/[3+2] nitrile oxide cycloaddition cascade, a five-step functional group transformation sequence was carried out, involving, (i) hydrogenation of the styryl double bond (H_2, Pd/C, 100% yield); (ii) reduction of the methyl ester ($LiAlH_4$, 68% yield); (iii) selective desilylation of the phenolic TBS ether (TBAF, 99% yield); (iv) oxidation of allylic alcohol **96** to the corresponding enal (SO_3·py, 57% yield); and (v) oxime formation ($HONH_2$·HCl, 100% yield). Gratifyingly, treatment of oxime **97** with $PhI(OAc)_2$ led to concomitant formation of the oxo-bridge through oxidative dearomatization and oxidation of the oxime moiety to the nitrile oxide, leading to transient species **100** which underwent spontaneous intramolecular [3+2] cycloaddition to give hexacyclic compound **101** in an impressive 73% yield over these series of transformations.



Scheme 8 Sorensen's synthesis of hexacycle **101**. Reagents and conditions: a) toluene, 110 °C, 15 h, 54%; b) KHMDS (1.4 equiv.), THF, −78 °C; then Commins' reagent (1.1 equiv.), −78 °C, 1 h, 96%; c) $PdCl_2$dppf (0.1 equiv.), Et_3N (3.0 equiv.), CO (1 atm), DMF–MeOH (1 : 1), 60 °C, 15 h, 76%; d) MeI (65 equiv.), THF, 23 °C, 48 h, 100%; e) Zn (5.5 equiv.), THF–H_2O–HOAc (1 : 1 : 2), 23 °C, 2 h, 97%; f) *m*CPBA (2.2 equiv.), 0 °C, 30 min; then 65 °C, 2 h, 73%; g) Pd/C (10% wt), H_2 (1 atm), CH_2Cl_2, 3 h, 23 °C, 100%; h) $LiAlH_4$ (1.5 equiv.), THF, −40 → 23 °C, 1 h, 68%; i) TBAF (1.0 equiv.), THF, 0 °C, 30 min, 99%; j) SO_3·py (3.0 equiv.), Et_3N (3.0 equiv.), DMSO/CH_2Cl_2 (1 : 1), 0 → 23 °C, 1 h, 57%; k) $HONH_2$·HCl (2.0 equiv.), NaOAc (2.0 equiv.), EtOH, 60 °C, 30 min, 100%; l) $PhI(OAc)_2$ (2.2 equiv.), TFE, 23 → 50 °C, 75 min, 73%. KHMDS = potassium hexamethyldisilazide; Commins' reagent = *N*,*N*′-bis-(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine; dppf = 1,1′-bis(diphenylphosphino)ferrocene; DMSO = dimethylsulfoxide.

Kobayashi's synthesis

While the synthetic strategies described thus far have primarily focused on the preparation of the oxo-bridged carbocyclic domain of the cortistatins, Kobayashi and co-workers reported an approach towards the isoquinoline appended CD-ring system of the cortistatins, as shown in Scheme 9.[23] Starting from D-mannitol derived alkyne **102**, zirconium-catalyzed hydroboration[24] followed by palladium-mediated coupling of the resulting boronic ester **104** with 7-bromo-1-chloroisoquinoline (**105**) under the Suzuki-Miyaura conditions,[25] afforded alkenyl isoquinoline **106** in 75% yield over the two steps. Protecting group manipulation of cyclohexylidene **106** to mono-TBDPS ether **108** (TFA, TBDPSCl, 57% yield over the two steps), followed by a Johnson-Claisen rearrangement[26] of the latter compound in the presence of triethyl orthopropionate and a catalytic amount of propionic acid, led to ethyl ester **109** as a *ca.* 1 : 1 mixture at the tertiary carbon center bearing the methyl group and a single isomer at the isoquinoline bearing center. Three-carbon homologation of TBDPS ether **109** to methyl enone **111** was carried out in a four-step sequence, involving, desilylation (TBAF, 96% yield), chemoselective hydrogenation (H_2, PtO_2, 93% yield), oxidation (**110**, Swern, 79% yield) and Wittig olefination (**111**, 97% yield). In preparation for the CD-ring annulation, ethyl ester **111** was converted to aldehyde **112** *via* a reduction-oxidation sequence (Dibal-H, Swern, 72% yield over the two steps), setting the stage for the proposed Michael-aldol double cyclization cascade. Gratifyingly, upon treatment of enone aldehyde **112** with NaOMe at elevated temperature, bicyclic enone **113** was isolated in 69%



Scheme 9 Kobayashi's synthesis of tetracycle **114**. Reagents and conditions: a) **103**, Cp_2ZrHCl, Et_3N, 92%; b) **105**, $Pd(dppf)Cl_2$, K_2CO_3, 1,4-dioxane, 82%; c) TFA; d) TBDPSCl, imid, DMF, 57% over the two steps; e) $CH_3CH_2C(OEt)_3$, propionic acid, toluene, reflux, 99%; f) TBAF, THF, 96%; g) H_2 (1 atm), PtO_2, EtOAc, 93%; h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 79%; i) $Ph_3P{=}CHCOCH_3$, THF, 60 °C, 97%; j) Dibal-H, THF, 87%; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 83%; l) NaOMe, THF, 23 → 70 °C, 69%. Cp = cyclopentadienyl; TFA = trifluoroacetic acid; TBDPS = *tert*-butyldiphenylsilyl; Dibal-H = diisobutylaluminium hydride.

yield as a *ca.* 5 : 1 mixture of stereoisomers in favour of the desired stereotriad as depicted in Scheme 9. Bicyclic enone **113** has been further elaborated to alkenyl dioxolane **114**, a potential building block for the synthesis of the cortistatins.

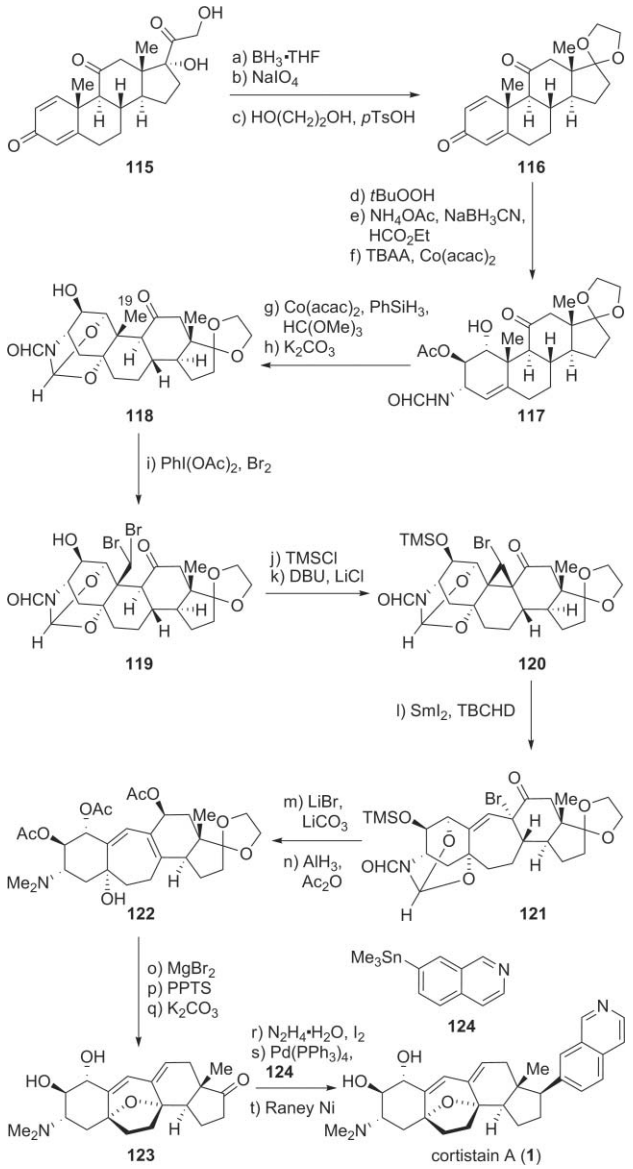
Completed syntheses of cortistatins A (1) and J (9)

Baran's semi-synthesis of cortistatin A (1)

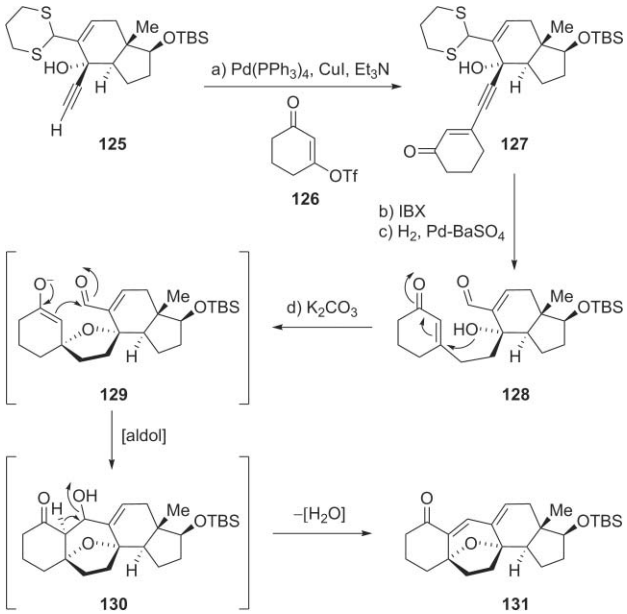
The first completed synthesis of a member of the cortistatin family was accomplished by Baran and co-workers of The Scripps Research Institute.[27] As shown in Scheme 10, a highly innovative and ingenious approach utilizing prednisone as an economical and readily available starting material was envisaged and successfully executed. Starting from prednisone (**115**), a three-step sequence involving a chemoselective ketone reduction (BH_3·THF), oxidative cleavage ($NaIO_4$) and selective ketalization [$HO(CH_2)_2OH$, *p*TsOH] provided dioxolane dienone **116** in 92% yield over the three steps. Installation of the dihydroxy amino functionalities on the A-ring of cortistatin A was addressed next. In this instance, a chemo- and stereoselective epoxidation of dienone **116** (*t*BuOOH, DBU), followed by a reductive amination (NH_4OAc, $NaBH_3CN$) with subsequent protection of the resulting primary amine as its formamide derivative (HCO_2Et) and regioselective epoxide opening (TBAA), furnished acetoxy formamide **117** in 29% overall yield as a single stereoisomer. Orthoamide **118** was thought to be the next key intermediate, where the orthoamide functionality serves the dual purpose as a protecting group guarding the amine and hydroxyl groups, and as a precursor to the dimethylamine moiety in cortistatin A. After extensive experimentation, it was found that the orthoamide functionality could be formed by treating hydroxy formamide **117** under the Mukaiyama hydration[28] conditions [$Co(acac)_2$, $PhSiH_3$] followed by reaction of the intermediate amidodiol with $HC(OMe)_3$, where upon further deacetylation (K_2CO_3) gave hydroxy orthoamide **118** in 63% yield over the three steps. In preparation for the construction of the seven-membered B-ring of cortistatin, a hydroxyl-directed, selective dibromination of the C19 methyl group was achieved with *in situ* generated AcOBr [$PhI(OAc)_2$, Br_2], followed by protection of the sensitive dibromo alcohol **119** as its TMS ether (TMSCl) in 57% yield over the two steps. Intramolecular cyclopropanation in the presence of DBU provided bromo cyclopropane **120** (85% yield), which was subjected to a SmI_2-mediated[29] carbon-carbon bond cleavage to unveil the seven-membered cortistatin B-ring, and the intermediate samarium enolate was trapped with TBCHD to give cycloheptenyl α-bromo ketone **121**. With the [6.7.6.5] ring framework in place, installation of the oxo-bridge in the B-ring of cortistatin became the next objective. In this instance, extrusion of HBr from α-bromo ketone **121** ($LiCO_3$), followed by reductive removal of the orthoamide moiety (with concomitant stereoselective reduction of the C-ring ketone) in the presence of AlH_3 and tris-acetoxylation (Ac_2O) afforded dimethylamino triacetate **122** in 56% yield over the three steps from bromocyclopropane **120**. The closure of the B-ring oxo-bridge was achieved by subjecting hydroxy diene **122** under the influence of $MgBr_2$, followed further deketalization (PPTS) and deacetylation (K_2CO_3) to give dihydroxy ketone **123** in 82% yield over the three steps. The final stereoselective attachment of the isoquinoline was accomplished through a palladium-mediated cross coupling with isoquinoline stannane **124**, *via* the intermediate vinyl iodide derived from ketone **123** ($N_2H_4{\cdot}H_2O$, I_2), followed by chemo- and stereoselective hydrogenation (RANEY® Ni) of the intermediate cyclopentenyl isoquinoline to complete the synthesis of cortistatin A in 27% yield over the three steps from ketone **123**.

Nicolaou-Chen's total syntheses of cortistatin A (1) and J (9)

The Nicolaou-Chen group reported the first total synthesis of cortistatin A and J, which featured a hetero-Michael/aldol/dehydration cascade sequence to construct the pentacyclic core structure of the cortistatins as illustrated in Scheme 11.[30,31] Enantiomerically pure alkyne **125** was readily synthesized from commercially available Hajos-Parrish ketone, which served as the key building block for the synthesis. Sonogashira[32] coupling between alkyne **125** and enol triflate **126** gave alkynyl enone **127** in 85% yield, followed by removal of the dithiane moiety and a chemoselective hydrogenation engaging the alkynyl domain



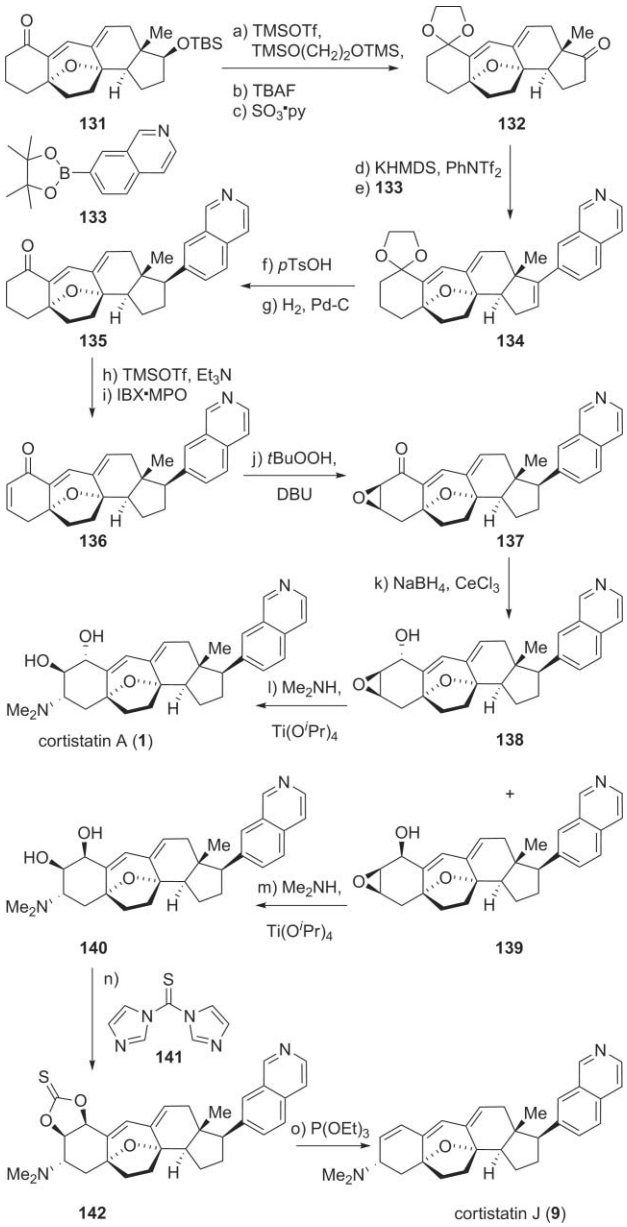
Scheme 10 Baran's semi-synthesis of cortistatin A (**1**). Reagents and conditions: a) BH_3·THF (1.0 equiv.), THF, 0 → 23 °C, 1.2 h; b) $NaIO_4$ (5.0 equiv.), acetone/H_2O (1 : 1), 0 → 23 °C, 3 h; c) $HO(CH_2)_2OH$ (25.0 equiv.), *p*TsOH·H_2O (0.07 equiv.), toluene, reflux, 1 h, 92% over the three steps; d) *t*BuOOH (2.0 equiv.), DBU (2.0 equiv.), THF, 23 °C, 72 h, 82%; e) NH_4OAc (10.0 equiv.), $NaBH_3CN$ (1.5 equiv.), THF–MeOH (1 : 2.4), 23 °C, 24 h; then HCO_2Et (74 equiv.), Et_3N (11 equiv.), 54 °C, 24 h, 73%; f) TBAA (5.0 equiv.), $Co(acac)_2$ (0.2 equiv.), PhH, 90 °C, 24 h, 48%; g) $Co(acac)_2$ (0.2 equiv.), $PhSiH_3$ (2.2 equiv.), O_2 (1 atm), $HC(OMe)_3$/THF (1 : 3), 23 °C, 12 h; then *p*TsOH·H_2O (3.0 equiv.), 23 °C, 1 h; h) K_2CO_3 (5.0 equiv.), MeOH, 23 °C, 1 h, 63% over the three steps; i) $PhI(OAc)_2$ (5.0 equiv.), Br_2 (8.0 equiv.), CH_2Cl_2, 75 W sunlamp, 50 °C, 10 h; j) TMSCl (5.0 equiv.), imidazole (5.0 equiv.), CH_2Cl_2, 0 °C, 15 min, 57% over the two steps; k) DBU (2.0 equiv.), LiCl (5.0 equiv.), THF, 23 °C, 24 h, 85%; l) SmI_2 (2.2 equiv.), DMPU/THF (1 : 9), 23 °C, 5 min; then TBCHD (2.0 equiv.), 23 °C, 30 min; m) Li_2CO_3 (20.0 equiv.), LiBr (20.0 equiv.), DMF, 60 °C, 1 h, 63% over the two steps; n) AlH_3 (5.0 equiv.), THF, 1 h, 23 °C; K_2CO_3 (2.0 equiv.), MeOH, 23 °C, 12 h; Ac_2O (20.0 equiv.), Et_3N (40.0 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 23 °C, 5 h, 89%; o) $MgBr_2$·Et_2O (1.1 equiv.), 2,6-(*t*Bu)$_2$Py (2.1 equiv.), PhH, 78 °C, 1.5 h; p) PPTS (5.0 equiv.), butanone/H_2O (1 : 1), 90 °C, 2 h; q) K_2CO_3 (10.0 equiv.), 23 °C, 5 h, 82% over the two steps; r) N_2H_4·H_2O (10.0 equiv.), Et_3N (10.0 equiv.), EtOH, 50 °C, 6 h; I_2 (2.0 equiv.), Et_3N (3.0 equiv.), THF, 23 °C, 5 min; s) **124** (4.0 equiv.), $Pd(PPh_3)_4$ (0.5 equiv.), CuCl (10.0 equiv.), LiCl (10.0 equiv.), DMSO, 23 °C, 10 min, 53% over the two steps; t) RANEY® Ni (88 wt. equiv.), *i*PrOH/H_2O (1 : 1), 50 °C, 1 h, *ca.* 50%. TBAA = tetra-n-butylammonium acetate; acac = acetylacetone; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBCHD = 2,4,4,6-tetrabromo-2,5-cyclohexadienone; PPTS = pyridinium *p*-toluenesulfonate; DMPU = 1,3-dimethyltetrahydropyrimidin-2(*1H*)-one; DMAP = *N*,*N*′-dimethylamino pyridine.



Scheme 11 Nicolaou-Chen's synthesis of pentacycle **131**. Reagents and conditions: a) $Pd(PPh_3)_4$ (0.1 equiv.), CuI (0.1 equiv.), Et_3N (3.0 equiv.), **126** (1.4 equiv., freshly prepared from 1,3-cyclohexadione, Tf_2O and Et_3N), DMF, 23 °C, 1 h, 85%; b) IBX (4.0 equiv.), DMSO, 0 → 23 °C, 4 h, 81%; c) Pd/$BaSO_4$ (5% wt/wt, 0.24 equiv.), H_2, MeOH–THF (1 : 1), 23 °C, 30 min, 64%; d) K_2CO_3 (1.2 equiv.), dioxane, 125 °C, 12 h, 52%. IBX = *o*-iodoxybenzoic acid.

to furnish the cascade cyclization precursor **128** in 52% yield over the two steps. Gratifyingly, upon heating a dioxane solution of hydroxy enone enal **128** in the presence of K_2CO_3, the proposed cascade sequence took place smoothly, presumably through the intermediacy of **129** and **130**, to afford pentacyclic dienone **131** in 52% yield.

Attachment of the isoquinoline moiety onto growing pentacycle **131** was carried out next (Scheme 12), where upon protecting group manipulations and oxidation state adjustments, the resulting ketone **132** was converted to its corresponding enol triflate (KHMDS, $PhNTf_2$) and subsequently engaged in a Suzuki-Miyaura[25] coupling reaction with isoquinoline boronic ester **133**, to give cyclopentenyl isoquinoline **134** in 30% yield over the five steps. Removal of the dioxolane protecting group in **134** (*p*TsOH), followed by chemo- and stereoselective hydrogenation of the cyclopentene olefin afforded dienone **135** in 44% yield, ready for the final installation of A-ring functionalities required in cortistatin A and J. Thus, application of the IBX chemistry[33] smoothly converted dienone **135** to trienone **136** (TMSOTf-Et_3N, IBX·MPO), and a chemo- and stereoselective epoxidation



Scheme 12 Nicolaou-Chen's total syntheses of cortistatin A (**1**) and J (**9**). Reagents and conditions: a) $TMSO(CH_2)_2OTMS$ (5.0 equiv.), TMSOTf (1.5 equiv.), CH_2Cl_2, −50 → −10 °C, 4 h; b) TBAF (3.5 equiv.), THF, 23 °C, 2 h, 63% over the two steps; c) SO_3·py (6.0 equiv.), Et_3N (10.0 equiv.), CH_2Cl_2/DMSO (3 : 1), 23 °C, 3 h, 80%; d) KHMDS (2.0 equiv.), Commins reagent (2.0 equiv.), THF, −78 °C, 1 h; e) **133** (3.0 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), K_2CO_3 (3.0 equiv.), THF, 80 °C, 3 h, 60% over the two steps; f) *p*TsOH·H_2O (1.5 equiv.), acetone/H_2O (10 : 1), 23 °C, 1 h, 88%; g) Pd/C (10% wt/wt, 0.3 equiv.), H_2, MeOH, 23 °C, 1 h, 50% (30% recovered starting material); h) TMSOTf (14 equiv.), Et_3N (30 equiv.), THF, −78 → 0 °C, 1.5 h; i) IBX·MPO (6.0 equiv.), DMSO, 23 °C, 6 h, 46% for two steps; j) *t*BuOOH (6.0 equiv.), DBU (3.0 equiv.), CH_2Cl_2, 0 → 23 °C, 5 h, 70%; k) $NaBH_4$ (1.0 equiv.), $CeCl_3$ (4.0 equiv.), MeOH, 0 °C, 10 min, 80% (*ca.* 1 : 1 mixture of diastereoisomers); l) Me_2NH, $Ti(OiPr)_4$ (5.0 equiv.), 80 °C, 5 h, 45% m) $Ti(Oi\text{-}Pr)_4$ (5.0 equiv.), Me_2NH (2.0 M solution in THF, as solvent), 80 °C, 1 h, 70%; n) thiocarbonyl diimidazole (**141**) (1.5 equiv.), toluene, 110 °C, 12 h, 81%; o) $P(OEt)_3$ (as solvent), 160 °C, 24 h, 42%. Tf = trifluoromethanesulfonyl; MPO = 4-methoxypyridine *N*-oxide.

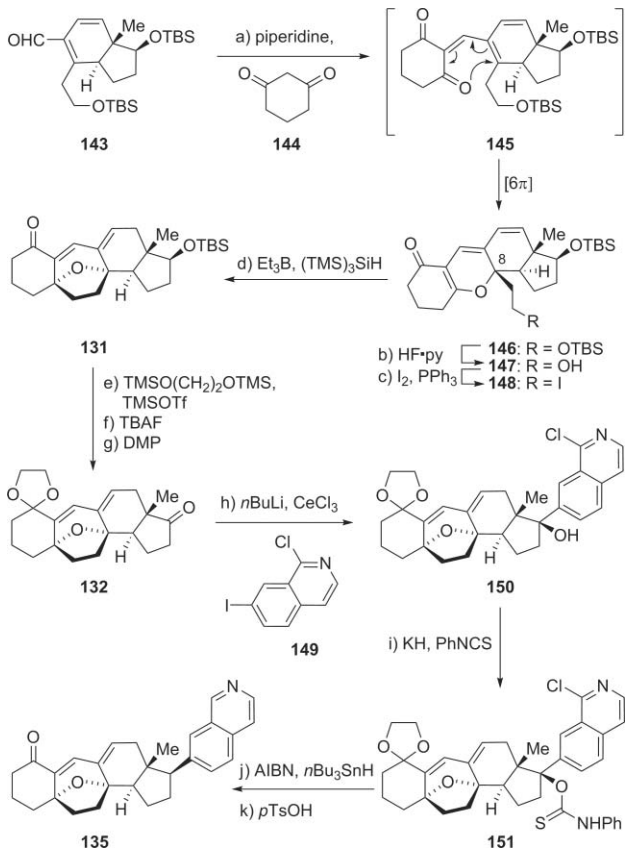
(*t*BuOOH, DBU) gave epoxy ketone **137** in 32% yield over the three steps. Reduction of epoxy ketone **137** under the Luche conditions[34] ($NaBH_4$-$CeCl_3$) afforded a *ca.* 1 : 1 mixture of diastereoisomeric hydroxy epoxides **138** and **139** in 80% yield, where the former (**138**) was converted to cortistatin A (**1**) *via* epoxide opening under the Sharpless conditions[35] [Me_2NH–$Ti(OiPr)_4$, 45% yield], and the latter (**139**) was converted to cortistatin J (**9**) *via* a similar epoxide opening [Me_2NH–$Ti(OiPr)_4$, 60% yield] followed by Corey-Winter[36] elimination of the intermediate dimethylamino *syn* diol in 32% overall yield.

Hirama's formal syntheses of cortistatin A (1) and J (9)

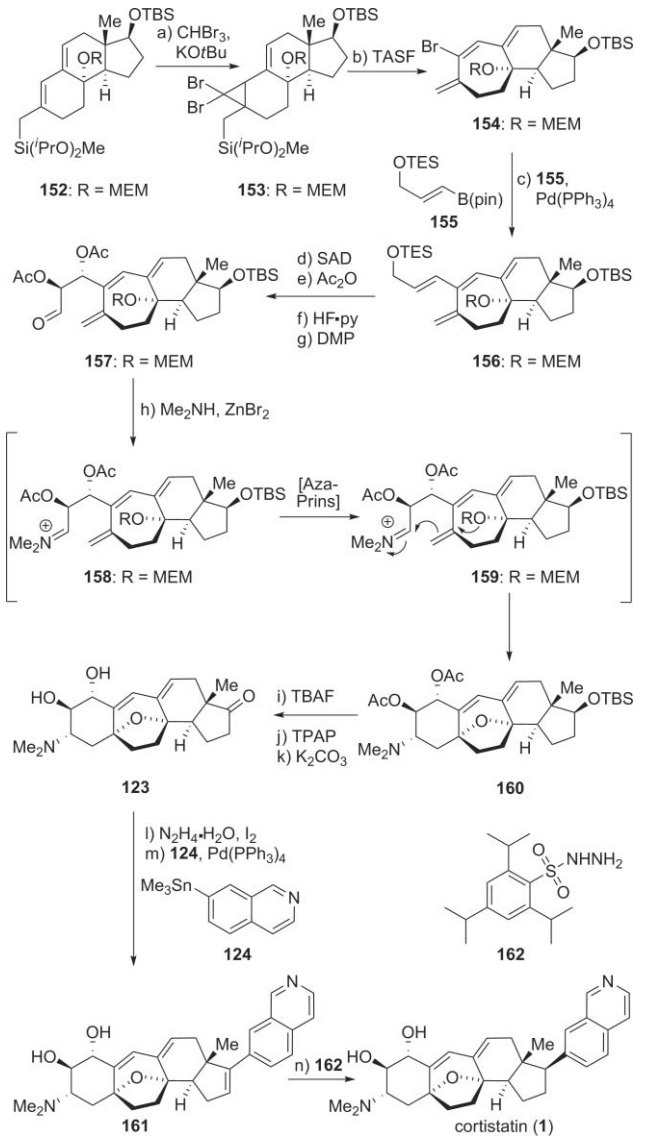
As shown in Scheme 13, the Hirama group reported a formal synthesis of cortistatin A (and J)[37,38] by intercepting two late stage intermediates (**131** and **135**) reported in the Nicolaou-Chen synthesis. Starting from diene aldehyde **143**, a synthetic intermediate readily derived from Hajos-Parrish ketone, a Knoevenagel condensation[39]/[6π] electrocyclization cascade smoothly delivered tetracycle **146**, *via* the intermediacy of **145**, in 87% yield as a *ca.* 5 : 1 mixture in favour of the desired C8 diastereoisomer. The conversion of TBS ether **146** to iodide **148** was carried out in a two-step sequence (HF·py, I_2-PPh_3, 87% yield for the two steps). The diastereoisomeric purity of iodide **148** at the C8 center was enhanced to 10 : 1, and can be further enriched to 20 : 1 upon recrystallization at low temperature. Interestingly, this ratio changed to 7 : 1 on standing in $CDCl_3$ at room temperature for 1 h, and to 5 : 1 after 7 h, suggesting an equilibrating process through a retro-[6π]-electrocyclization/[6π]-electrocyclization mechanism. Completion of the pentacyclic core structure **131**, therefore a formal synthesis of cortistatin A and J, was achieved *via* an intramolecular radical cyclization of iodide **148** in the presence of Et_3B and $(TMS)_3SiH$ in 78% yield. In contrast to the palladium-mediated cross couplings reported by Baran[27] and Nicolaou-Chen[30,31] (and Shair,[40] see Scheme 14) in the installation of the isoquinoline moiety of the cortistatins, the Hirama group carried out an nucleophilic addition of lithiated 7-iodo-1-chloroisoquinoline (**149**) to ketone **132** (derived from dienone **131** *via* an analogous sequence as reported by Nicolaou-Chen,[30,31] 78% yield over the three steps) to give tertiary alcohol **150** in nearly quantitative yield as a single isomer. Deoxygenation of the tertiary hydroxyl in **150** was accomplished *via* its thiocarbamate derivative **151** (KH, PhNCS), in the presence of AIBN and nBu_3SnH, which concomitantly removed the chlorine substituent on the isoquinonline to afford a single stereoisomer in 74% yield over the two steps. Finally, removal of the dioxolane protecting group under mild acidic conditions (*p*TsOH) provided dienone **135**, a second common intermediate reported in the Nicolaou-Chen total synthesis of cortistatin A and J.[30,31]

Shair's total synthesis of cortistatin A (1)

A second total synthesis of cortistatin A was reported by the Shair group, as shown in Scheme 14.[40] Their approach featured an aza-Prins/transannular etherification cascade reaction to simultaneously assemble the cortistatin oxo-bicyclic B-ring, and forged the A-ring with stereoselective introduction of the dimethylamine functionality. Allyl silane **152** (prepared in enantiomerically pure form from Hajos-Parrish ketone) was subjected



Scheme 13 Hirama's formal synthesis of cortistatin A (**1**) and J (**9**). Reagents and conditions: a) piperidine (1.1 equiv.), EtOAc, 23 °C, 6 h, 87%; b) HF·py, THF, 23 °C; c) I_2 (2.5 equiv.), PPh_3 (5.0 equiv.), imidazole (10.0 equiv.), THF, 23 °C, 87% over the two steps; d) Et_3B (0.2 equiv.), $(TMS)_3SiH$ (5.0 equiv.), THF, −78 °C, 78%; e) $TMSO(CH_2)_2OTMS$ (10.0 equiv.), TMSOTf (2.0 equiv.), CH_2Cl_2, −60 → −20 °C; f) TBAF (5.0 equiv.), THF, 0 °C; g) DMP (1.2 equiv.), $NaHCO_3$ (5.0 equiv.), CH_2Cl_2, 23 °C, 78% over the three steps; h) **149** (5.0 equiv.), *n*BuLi (5.0 equiv.), $CeCl_3$ (10.0 equiv.), THF, −78 °C, 99%; i) KH (10.0 equiv.), PhNCS (15.0 equiv.), THF, 23 °C; j) AIBN (0.37 equiv.), nBu_3SnH (20.0 equiv.), toluene, 90 °C, 74% over the two steps; k) *p*TsOH·H_2O (1.5 equiv.), acetone/H_2O (8 : 1), 23 °C, 71%. AIBN = azo-*bis*-isobutyronitrile.



Scheme 14 Shair's total synthesis of cortistatin A (**1**). Reagents and conditions: a) $CHBr_3$ (3.0 equiv.), KO*t*Bu (4.0 equiv.), hexane, 0 °C, 2 h; b) TASF (1.2 equiv.), DMF, 80 °C, 30 min, 66% for two steps; c) **155** (2.0 equiv.), $Pd(PPh_3)_4$ (0.04 equiv.), K_2CO_3 (3.0 equiv.), THF–H_2O (5 : 1), 80 °C, 4 h, 84%; d) $K_2OsO_4·H_2O$ (0.02 equiv.), $(DHQD)_2PHAL$ (0.05 equiv.), $K_3Fe(CN)_6$ (3.0 equiv.), $MeSO_2NH_2$ (1.0 equiv.), *t*BuOH : H_2O (1 : 1), 0 °C, 2 h; e) Ac_2O (2.5 equiv.), Et_3N (3.0 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 23 °C, 18 h, 51% over the two steps; f) HF·py, THF, 23 °C, 5 min; g) DMP (1.2 equiv.), CH_2Cl_2, 23 °C, 1 h; h) Me_2NH (3.0 equiv.), $ZnBr_2$ (1.5 equiv.), CH_3CN, 50 °C, 40 min, 65% over the three steps; i) TBAF (1.2 equiv.), THF, 70 °C, 4 h, 70%; j) TPAP (0.05 equiv.), NMO (1.3 equiv.), CH_2Cl_2, 23 °C, 2.5 h, quant.; k) K_2CO_3 (5.0 equiv.), MeOH, 23 °C, 30 min, 82%; l) $N_2H_4·H_2O$ (10.0 equiv.), Et_3N (10.0 equiv.), EtOH, 80 °C, 6 h; I_2 (1.0 equiv.), Et_3N (3.0 equiv.), THF, 23 °C, 5 min; m) **124** (3.0 equiv.), $Pd(PPh_3)_4$ (0.5 equiv.), LiCl (10.0 equiv.), CuCl (10.0 equiv.), DMSO, 60 °C, 1 h, 61% over the two steps; n) **162** (4.0 equiv.), Et_3N (20.0 equiv.), THF, 60 °C, 9 h, 20%. MEM = 2-methoxyethoxymethyl; TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate; pin = pinacol; TPAP = tetrapropylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide.

to chemo- and diastereoselective cyclopropanation with dibromocarbene ($CHBr_3$, KO*t*Bu), followed by fluoride ion induced ring expansion of dibromocyclopropane **153** with TASF, to afford trienyl vinyl bromide **154** in 66% yield over the two steps. Suzuki-Miyaura[25] cross coupling between vinyl bromide **154** with boronic ester **155** (84% yield), followed by chemo- and stereoselective dihydroxylation of tetraene **156** under the Sharpless conditions,[41] afforded the desired diol with a *ca.* 10 : 1 diastereoselectivity. Bis-acetylation (Ac_2O, 51% yield over the two steps from **156**), followed by removal of the TES ether and oxidation of the resulting alcohol gave aldehyde **157**, setting the stage for the proposed cascade ring closures. Pleasingly, upon exposure of aldehyde **157** to Me_2NH and $ZnBr_2$, the aza-Prins/transannular etherification took place smoothly with *in situ* removal of the MEM ether, to furnish dimethylamino pentacycle **160** as a single diastereoisomer in 65% overall yield for the three steps. In preparation for the installation of the isoquinoline moiety, bis-acetoxy TBS ether **160** was converted to dihydroxy ketone **123**, a previously reported intermediate in Baran's synthesis,[27] in a three steps sequence involving desilylation (TBAF, 70% yield), oxidation (TPAP, 100% yield) and saponification (K_2CO_3, 82% yield). Finally, in an

analogous sequence as reported in Baran's synthesis,[27] ketone **123** was converted to isoquinoline **161** with the application of Stille[42] cross coupling [$Pd(PPh_3)_4$, **124**], and subsequent diimide reduction (**162**, 20% yield) of cyclopentenyl isoquinoline **161** completed the total synthesis of cortistatin A (**1**).

Chemical-biology of the cortistatins

With its fascinating biological profile and potential in *anti*-angiogenic therapy in mind, several research groups have carried out the structural-activity-relationship (SAR) studies of the cortistatins.[43] While the estrone derived analogue **163** reported by the Kiyota group showed significant loss of *anti*-proliferative property (Fig. 2),[44] Corey and co-workers prepared the most potent cortistatin analogue to date by further incorporating the dimethylamino functionality and suitably positioning the isoquinoline nitrogen, as illustrated in compounds **164** and **165**.[45] The Baran group also showed that while compound **161** with sp^2 hybridized C17 center appending the isoquinoline moiety only led to a two-fold loss of activity, inversion of the C17 center completely abolished the *anti*-proliferative activity of cortistatin A.[46] Equally noteworthy, work by Nicolaou and Chen demonstrated the considerably simplified A-ring analogue **135** with only three-fold loss in potency.[31]

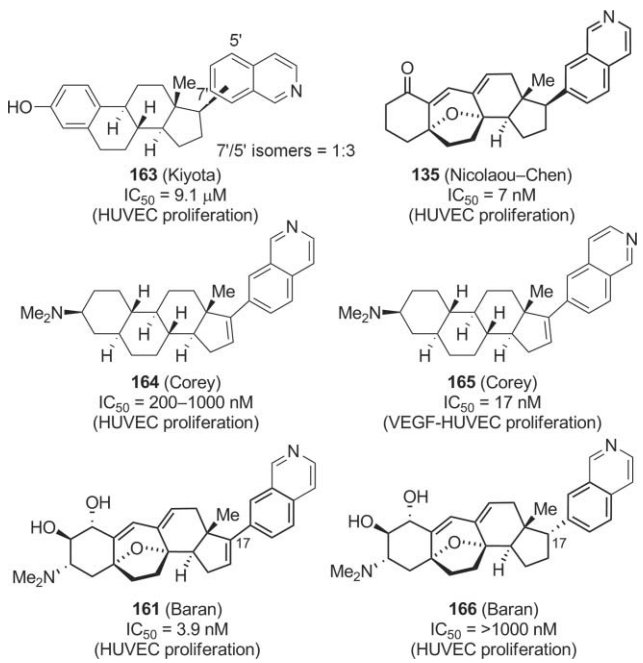


Fig. 2 Selected cortistatin analogues and their *anti*-proliferative activities.

Most recently, Cee, Chen and Nicolaou have demonstrated that cortistatin A is a ligand of a small group of kinases, with high affinity binding to CDK8 (cyclin dependent kinase 8), CDK11, ROCK (Rho associated kinase) I and ROCK II.[47] Protein crystal structure revealed CDK8, CDK11, ROCK I and ROCK II all contain an extended C-terminus, which may attribute to the high selectivity towards these kinases relative to the rest of the kinome. Furthermore, the cortistatin/kinase models put forward are supportive of the observed SAR, in particular, the significance of the isoquinoline moiety has been accounted for with several crucial hydrogen bonding and van der Waal's interactions at the ATP binding cleft.

Conclusions

The novel structure of the cortistatins served as a fertile ground for the discovery and development of novel synthetic technology and strategies.[48] In conjunction with the biological activities exhibited by these potent and selective *anti*-proliferative agents, and preliminary chemical-biology insights, research activities in the cortistatin arena is anticipated to intensify and pave a solid foundation for the discovery of novel chemotherapeutic agents in the treatment of angiogenesis-dependent diseases.

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