Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2020, **18**, 3965

Synthetic approaches towards cortistatins: evolution and progress through its ages

Satrajit Indu and Krishna P. Kaliappan *

Received 14th April 2020,
Accepted 11th May 2020

DOI: 10.1039/d0ob00770f

rsc.li/obc

Cortistatins are a family of steroidal alkaloids with a unique pentacyclic skeleton, having immensely potent anti-angiogenetic activities. Given the scarcity in the natural availability of these compounds, their syntheses became major attractions in organic chemistry. Along with total synthesis of the most potent congeners in the family: cortistatins A and J, the synthesis of two other members have been successfully completed, while various other analogues have also been designed with variable degrees of biological activities. This review is an exhaustive coverage of the significant attempts towards constructing this highly challenging molecule and also aims to highlight the deep understanding of the structure–activity relationships of these compounds, which have been garnered over time.

1. Introduction

Steroidal alkaloids are the most prominent alkaloids derived from a triterpenoid nucleus and form a class of secondary metabolites isolated from plants, amphibians and marine organisms.[1] A lot of studies over the last three decades have demonstrated that steroidal alkaloids and their semisynthetic products possess a range of anti-cancer, anti-microbial and anti-inflammatory activities, which renders them as promising prospects in discovering new drug candidates.[2] Their anti-cancer activities have been most widely explored with respect to various types of cancers: osteosarcoma, glioblastoma, breast, gastric, colon, liver and lungs. Though they are most

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India. E-mail: kpk@chem.iitb.ac.in

Satrajit Indu

Satrajit Indu received his BSc degree from the erstwhile Presidency College in Kolkata in 2010 and then pursued his MSc in Chemistry at the Indian Institute of Technology Kanpur, from where he graduated in 2012. He then joined the Indian Institute of Technology Bombay for his PhD under the supervision of Prof. Krishna P. Kaliappan where worked on the total synthesis of biologically active natural products and development of transition metal catalyzed new synthetic methods. He graduated from IIT Bombay in August, 2019 and is currently working as a Research Associate in Prof. Kaliappan's group.

Krishna P. Kaliappan

Krishna P. Kaliappan, after his Ph.D from Indian Institute of Science, Bangalore, spent two years each at University of Geneva (97–98) and at Duke University (99–00) for his post-doctoral studies before joining IIT Bombay as an Assistant Professor in 2001. He became full Professor in 2009 and Institute Chair Professor in 2014. He served as Associate Dean (R & D) at IIT Bombay (2012–2015), Head of Chemistry Department (2016–2018) and currently serving as Dean (Faculty Affairs). He is currently on the Editorial Advisory Boards of Organic & Biomolecular Chemistry and Chemistry An Asian Journal. He is a Fellow of the Royal Society of Chemistry (FRSC) since 2008 and Fellow of Indian Academy of Sciences, Bangalore (FASc) since 2016. His current research interests include total synthesis of natural products, domino strategy to synthesis of complex natural products and natural product like molecules.

commonly isolated from terrestrial life forms, there are some steroidal alkaloids isolated from marine sources (Fig. 1).[3] Plakinamines A (**1**) and B (**2**), the first marine steroidal alkaloids to be isolated showed significant antimicrobial and antifungal activities against *Staphylococcus aureus* and *Candida albicans* respectively. Soon after, Rao *et al.* isolated the first member of a new class of alkaloids called zoanthamines (**3**).[4] They were extracted from colonial zoanthid of the genus *Zoanthus* originating in the Bay of Bengal and the Karachi coast of the Arabian Sea. This was followed by the isolation of zoanthenamine (**4**),[5] zoanthaminone (**5**)[6] and other members of the family.[7] Later in 1994, two other natural products lokysterolamines A (**6**) and B (**7**) were isolated from the Indonesian species *Corticium* and were shown to possess antimicrobial activities against *Bacillus subtilis* and *C. albicans*.[8] They also showed cytotoxicity against several cancer cell lines such as P-388, A-549, HT-29, and MEL-28 (IC_{50} values 0.5 to >2 μg ml^{-1}), as well as immunomodulatory activity (LcV/MLR > 187).[9]

After the turn of the century, during the course of their studies on marine bioactive substances, Kobayashi and coworkers in 2006, isolated a family of *abeo*-9(10-19)-androstane-type steroidal alkaloids called cortistatins, from the Indonesian marine sponge *Corticium simplex*.[10–12] These compounds showed highly selective anti-proliferative activity against human umbilical vein endothelial cells (HUVECs), which could inhibit the formation of new capillary blood vessels from pre-existing ones-a process called angiogenesis. While angiogenesis is an extremely important process for embryogenesis, on the flip side, undesired neovascularization also brings about tumour growth and metastasis; potentially leading to diseases like obesity,[13] atherosclerotic plaques,[14] endometriosis[15] and rheumatoid arthritis.[16]

Owing to this obvious threat of cancer, anti-angiogenesis has also become a major avenue towards cancer related drug discovery and therapeutic applications.[17] Of this new family of steroidal alkaloids, cortistatin A (**8**) showed anti-proliferative activity against HUVECs in the range 100 pM to 1 μM, which was 3000 times more selective than normal human dermal fibroblast (NHDF) and several tumor cells (KB epidermoid carcinoma cells (KB3-1), human chronic myelogenous leukemia cells (K562), and murine neuroblastoma cells (Neuro2A)). Cortistatin A also inhibited the migration and tubular formation of HUVECs induced by Vascular Endothelial Growth Factor (VEGF) of Fibroblast Growth Factor-basic (bFGF) at 2 nM concentrations.[10] Cortistatin J showed cytostatic anti-proliferative activity against HUVECs (IC_{50} = 8 nM), with a selectivity of 300–1100 times compared to NHDF and several other tumor cell lines. Cortistatins K and L showed less selective anti-proliferative activity against HUVECs (IC_{50} = 40 and 23 nM, respectively) with a selectivity index of 60–610.[11] However, cortistatins E, F, G and H showed very low anti-proliferative activity (IC_{50} = 0.35–1.9 μM) against HUVECs and no selectivity between HUVECs and other cell lines.[12]

An exhaustive study of the marine sponge extracts using extensive 2D NMR along with all other spectroscopic techniques and X-ray crystallographic studies helped to confirm the relative stereochemistry of the cortistatin stereocenters. Circular dichroism exciton chirality method has been used to determine the absolute stereochemistry of cortistatins A and J.[11,12] The absolute stereochemistries of cortistatins E–H and K–L were assumed to be the same as that of cortistatin A, because of the similarity in their steroidal skeletons.[11,12] Structurally all of the congeners have an unusual *abeo*-9(10,19)-androstane type skeleton, with a pentacyclic core structure, with the B and C rings connected through an interesting and characteristic oxo-bridge. A unique isoquinoline moiety decorates the 5-membered E-ring for cortistatins A–D and J–L, while a dimethylamine group is present on the A-ring for every congener (Fig. 2). Structure activity relationships (SAR), including the fact that cortistatins E–H do not show any selective anti-proliferative activity towards HUVECs, indicate that the isoquinoline functionality along with the 9(11), 10(19) diene units are essential for the anti-angiogenic activities of cortistatins A and J. In more recent times, cortistatin A has been reported as one of the notable small molecule inhibitors of CDK8, which is a cyclin-dependent kinase, forming a part of a multiprotein assembly for regulation of gene transcription.[18] Structural and mechanical studies have revealed that cortistatin A utilizes the isoquinoline moiety to attach to the kinase hinge segment and the steroidal core is used to attach itself to the ATP binding cavity.[19]

The fascinating structural intricacies of these biologically important steroidal alkaloids have naturally stimulated the imaginations of synthetic chemists worldwide, resulting in a

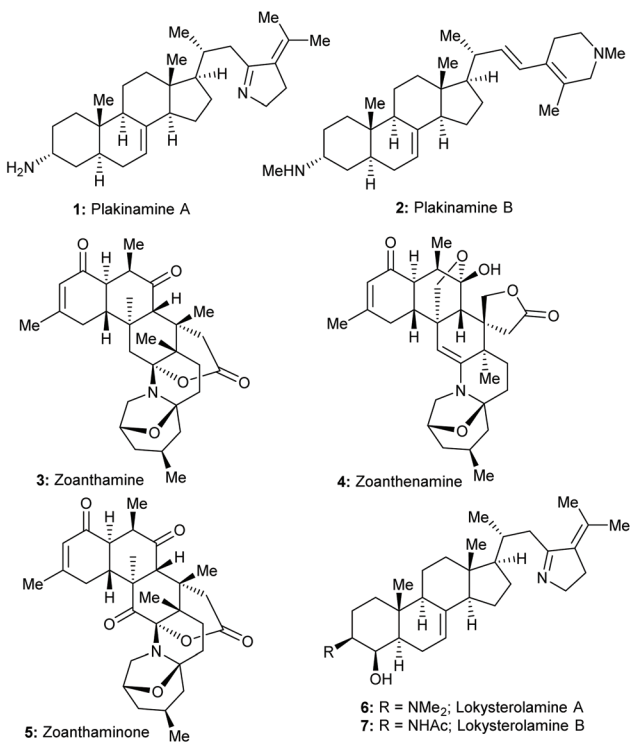


Fig. 1 Steroidal alkaloids of marine origin.

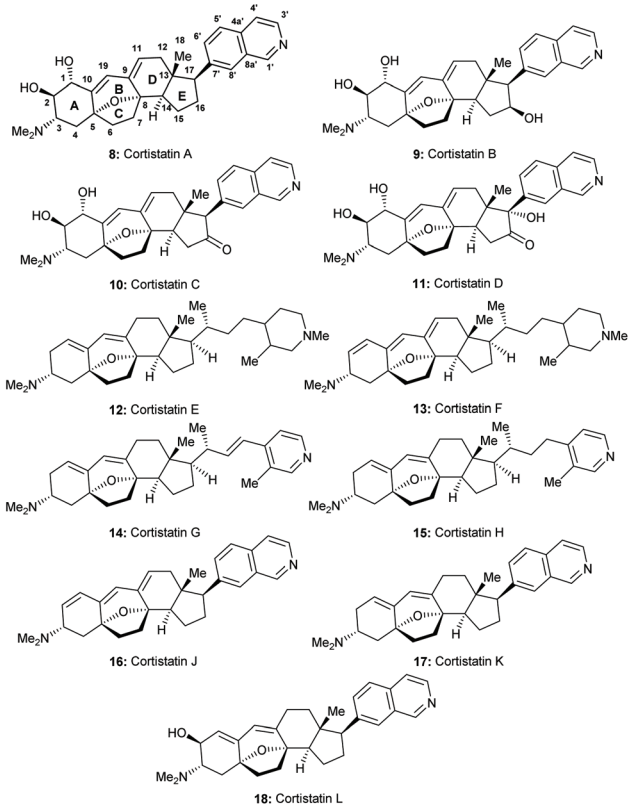


Fig. 2 Members of the cortistatin family.

handful of total syntheses, along with quite a few formal syntheses. Numerous other approaches towards different fragments of the core structure also have been reported. Given the scarcity of reviews on cortistatins,[20] this work would showcase an exhaustive coverage of the various strategies employed to construct the fundamental building blocks and gradually build towards the echelons of the complex architecture of this family of steroidal alkaloids.

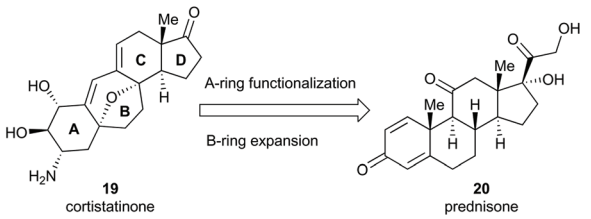
2. Total syntheses

2.1. Baran's total synthesis of cortistatin A[21]

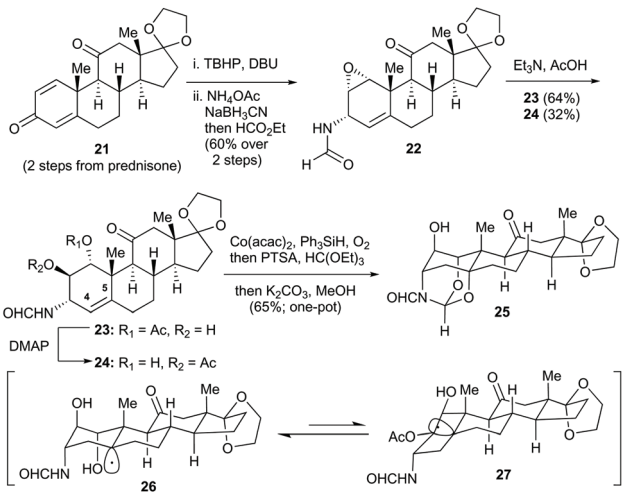
Inspired by the rich history of steroid semisynthesis,[22] generally leading to large quantities of the target molecules, Baran's group selected the terrestrially derived prednisone (**20**) as a cheap and abundantly available starting material. Despite looking for a redox-neutral strategy (following the "ideality" criteria), the lack of financially affordable steroids with the desired C19-methine oxidation state led to a minor sacrifice in terms of redox economy. As a consequence, the C19 angular methyl had to be oxidised to the aldehyde. It was also identified that the pentacyclic core structure of cortistatin could be framed in the key ketonic intermediate **19**, which was termed as (+)-cortistatinone. A preliminary retrosynthetic analysis from **19** could be traced to prednisone, *via* a ring expansion of the B-ring, followed by the required functionalizations on the A-ring (Scheme 1).

The known steroid core **21** was obtained in 2 steps from prednisone through a side-chain cleavage and selective ketalization. Nucleophilic epoxidation on **21** using DBU/*t*-BuOOH was followed by conversion of the C3 ketone into the formamide **22** using a modified reductive amination strategy.

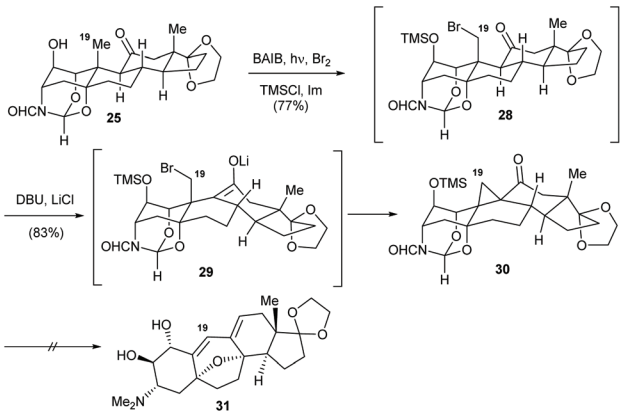
The C1–C2 epoxide opening was carried out with modest regioselectivity using *n*-Bu_4OAc assisted by a catalytic amount of $Co(acac)_2$ as a Lewis acid additive. However, the moderate yield of this transformation was later improved by the use of Et_3N/AcOH for epoxide opening and the undesired regioisomeric C1 acetate was converted to the desired C2 acetate (**24**) by treatment with DMAP. The next requirement was introduction of the C5 tertiary alcohol with α-orientation, in order to form the C-ring. After screening of various conditions, Co-catalyzed Mukaiyama hydration of the C4–C5 double bond in **24** was employed to achieve the C5 hydroxylation with the desired α-stereochemistry. This stereoselectivity may be attributed to the greater stability of the radical configuration **27**, as compared to **26**. The key "heteroadamantane" intermediate **25** paved the way for the B-ring expansion and led to the automatic protection of the three heteroatoms on the A-ring (Scheme 2).



Scheme 1 Cortistatin core structure from prednisone.



Scheme 2 Baran's design of the A-ring stereocenters.



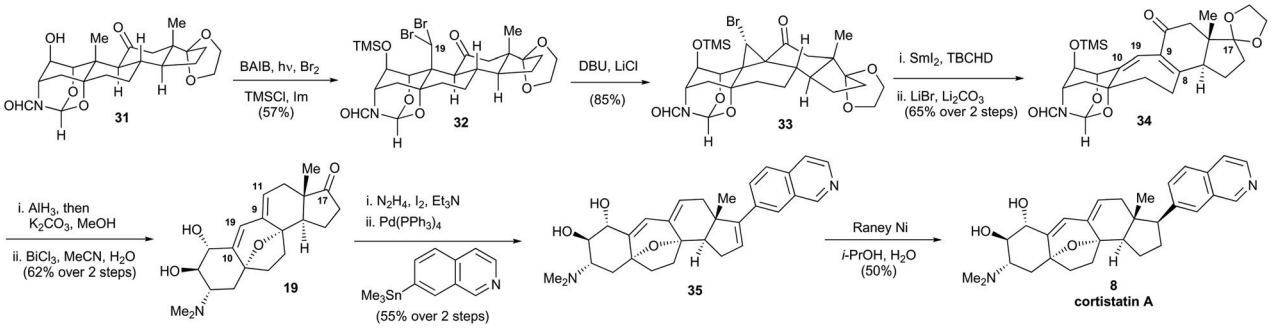
Scheme 3 Attempted cyclopropane expansion towards B-ring.

After obtaining the A-ring with all the required stereocenters intact, the next task was to achieve the B-ring expansion. To this end, the hypothetical biosynthesis of the cortistatins proposed by Kobayashi and co-workers starting from 3,29-diaminosterol proved to be a major bearing for designing the ring expansion step. Starting with this precursor, C19 methyl activation followed by cyclopropane formation and subsequent ring expansion would produce the *abeo*-9(10,19)-diene system (**31**). It was observed that a modified version of Suarez's protocol[23] for remote activation of angular methyl group using $PhI(OAc)_2$ and Br_2 resulted in monobromination at C19. The oxygen radical generated on the C2 hydroxyl group, displaced the C19 bromine and resulted in a competitive O–C bond formation in substantial proportions. To prevent this problem, the oxygen radical was trapped *in situ* as the corresponding TMS ether, but their subsequent efforts to expand the cyclopropane into the seven membered ring were met with failure (Scheme 3).

At this stage, it occurred to them that a potential dibromination on the C-19 carbon through double C–H activation would generate the required oxidation state on the C19 centre and with this idea in mind, the dibromination was optimized and carried out with 57% yield. Treatment with DBU immediately generated the bromocyclopropane **33**. Treatment with SmI_2 generated the C10–C19 double bond through a radical induced ring expansion leading to extrusion of the bromine radical. The resulting dienolate was quenched with 2,4,4,6-tetrabromo-2,5-dienone (TBCHD) to obtain the C9-brominated intermediate with the correct orientation, in order to be eliminated in the presence of LiBr, Li_2CO_3, thereby producing the C10–C19, C8–C9 diene unit (**34**).

At this stage, all that remained was formation of the THF C-ring and chemoselective cleavage of the heteroadamantane ring to complete the core structure. Treatment with AlH_3 not only reduced the heteroadamantane fragment with concomitant formation of the dimethylamino-diol triad on the A-ring, but also reduced the C11 ketone. The reaction was quenched with methanol to remove the excess hydride and treatment with K_2CO_3 hydrolyzed the C2 TMS ether. After screening various Lewis and Brønsted acids, $BiCl_3$ proved to be most efficient in effecting the S'_N cyclisation of the C5-hydroxyl onto the C8 centre, thereby forming the C-ring, along with the desired C10–C19, C9–C11 diene unit. The C17 ketal was also hydrolyzed in the same pot, to afford the pentacyclic core structure cortistatinone (**19**).

The final steps required the installation of the isoquinoline moiety in the presence of all the other functional groups. This was achieved through preparation of the C17 vinyl iodide using Barton's protocol,[24] which was subsequently coupled with 7-(trimethylstannyl)isoquinoline through a Stille coupling (Scheme 4). Selective reduction of the double bond in the 5-membered ring using RANEY® Ni completed the first total synthesis of cortistatin A over 15 steps with an overall yield of 1.7%. The key steps involved: (a) construction of the "heteroadamantane" skeleton, holding the C1, C3 and C5 stereocenters in place until a late stage; (b) C2-hydroxyl directed geminal dihalogenation on an unactivated methyl group; (c) reductive fragmentation/trapping/elimination of the bromocyclopropane **33** to establish the 7-membered B-ring; (d) chemoselective etherification to construct the C-ring *via* the oxo-bridge; and (e) the highly selective C16–C17 olefin reduction using RANEY® Ni. This short and efficient synthesis leading to gram-scale production of cortistatin A is ideal for analogue preparation and has also led the way towards industrial applications of the same.[21]



Scheme 4 Baran's total synthesis of cortistatin A.

2.2. Nicolaou's total synthesis of cortistatin A[25]

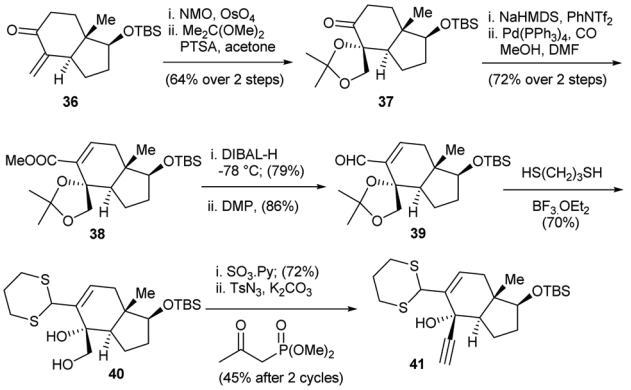
Shortly afterwards, Nicolaou's group reported the second total synthesis of cortistatin A starting from the known enantioenriched enone **36**. A stereoselective dihydroxylation followed by protection of the diol produced the acetonide **37** in good yield. A 5-step protocol was then employed to convert the ketone to the corresponding 1,3-dithiane **40**. Use of $BF_3{\cdot}OEt_2$ during the dithiane formation generated back the diol where the primary alcohol was selectively oxidised using Parikh–Doering oxidation, followed by subsequent homologation into the alkyne **41** *via* Bestmann Ohira method (Scheme 5).

The terminal alkyne was then subjected to a Sonogashira coupling with the freshly prepared enol triflate **42** to obtain the enynone **43** in 85% yield. Hydrolysis of dithiane and selective reduction of the triple bond over the conjugated double bonds afforded the precursor **44** for the key tandem reaction. Treatment with K_2CO_3 in dioxane at 125 °C triggered off the cascade transformation, starting with the intramolecular oxa-Michael addition of the tertiary alcohol on the enone, followed by an intramolecular aldol condensation to complete the B and C-rings in a single remarkable step (Scheme 6).

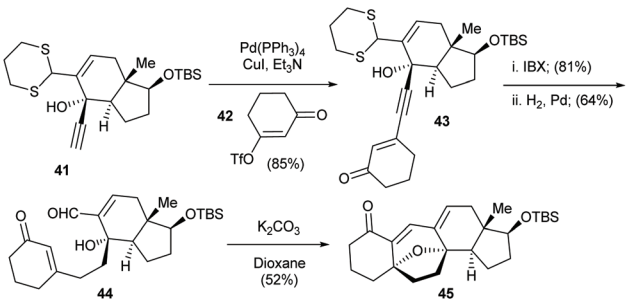
All that remained at this stage was to functionalize the A-ring and forge the biologically relevant isoquinoline moiety to the E-ring. The C1 ketone was protected as a cyclic ketal and the C17 TBS ether was cleaved and the resulting hydroxyl group was oxidised to compound **46**. Introduction of the isoquinoline fragment was achieved through a Suzuki–Miyaura coupling of the pinacol boronate **47** and the enol triflate generated from **46**. Hydrolysis of the cyclic ketal at C1 followed by chemo- and stereoselective reduction of the C16–C17 double bond using H_2/Pd–C afforded **49** in moderate yield. The final introduction of the A-ring substituents was planned through the manipulation of the C2–C3 epoxide. To this end, the dienone **49** was converted to its corresponding TMS-enol ether, which was subsequently reacted with IBX and 4-methoxypyridine-*N*-oxide (MPO) to furnish the trienone **50**. Treatment of **50** with *t*-BuOOH and DBU yielded the epoxide, which was reduced with $NaBH_4$, $CeCl_3$ to generate the hydroxy epoxide **51**, along with its C1 epimer. The C1 epimer (**52**) could be chromatographically separated and was recycled through an oxidation–reduction sequence to improve the overall conversion. Finally, the epoxide was opened with dimethylamine, in the presence of $Ti(O^iPr)_4$ to obtain cortistatin A in 45% yield (Scheme 7). This completed Nicolaou's total synthesis of cortistatin A over a sequence of 25 steps with an overall yield of 0.02%, starting from the known enantioenriched enone **36**.

The key steps of Nicolaou's synthetic route could be summarized as: (a) early generation of the C8 stereocenter through a dihydroxylation; (b) Sonogashira coupling to introduce the A-ring; (c) intramolecular cascade oxa-Michael addition followed by aldol condensation to construct the B- and C-rings in one-pot; (d) epoxide mediated late-stage incorporation of the A-ring functionalities.

Having completed the total synthesis of cortistatin A, the previously undesired C1-epimer among the diastereomeric hydroxy epoxides (**52**) was utilized by treatment with $Ti(O^iPr)_4$ and Me_2NH to obtain the dimethylamino diol **53**. The diol was subjected to thiocarbonate formation and the same was cleaved in $P(OEt)_3$ to obtain cortistatin J with 40% yield (Scheme 8). The total synthesis of cortistatin J was completed with an overall yield of 0.004% over a linear sequence of 27 steps from the known enone **36**.[25b]



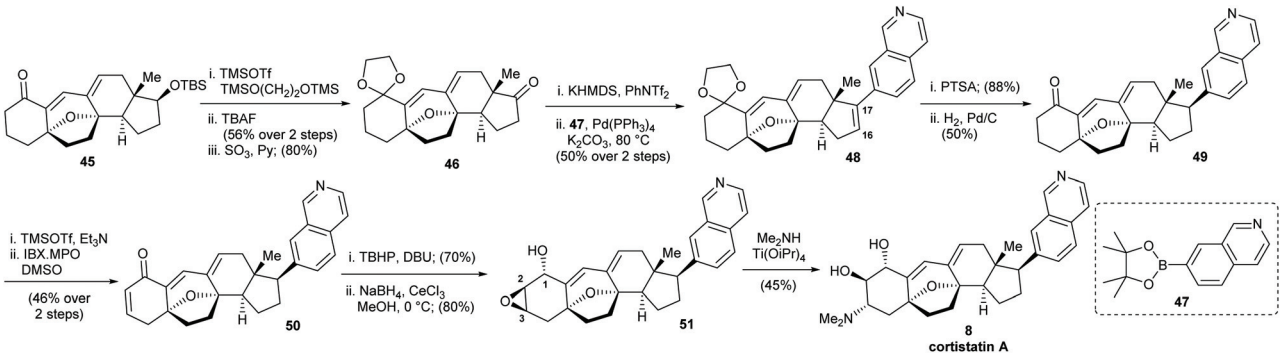
Scheme 5 Nicolaou's synthesis of alkyne **41**.



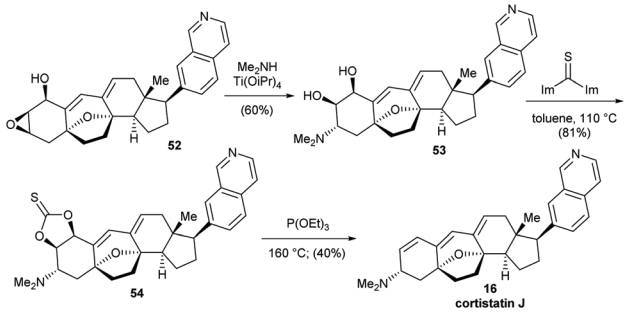
Scheme 6 Cascade transformation to construct the pentacyclic core.

2.3. Shair's total synthesis of cortistatin A[26]

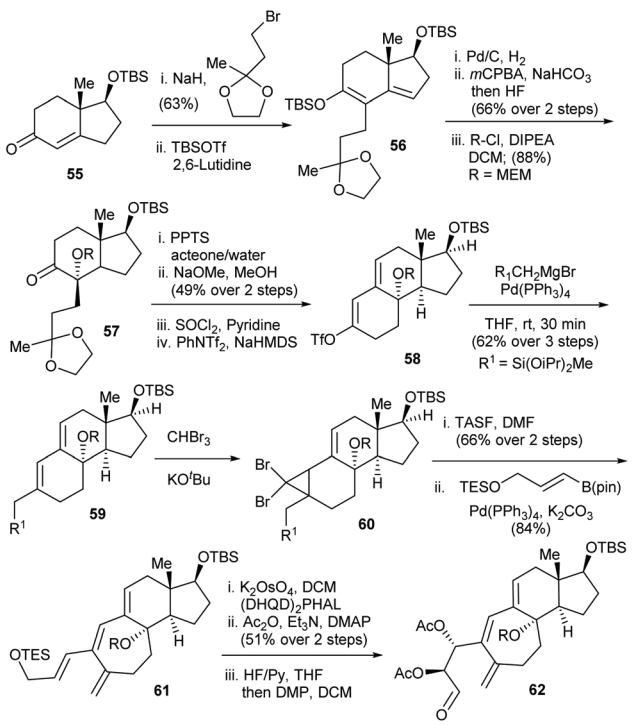
The final report on cortistatins in the year 2008 appeared in the form of a total synthesis of cortistatin A, from Shair and co-workers. The key step in this strategy is the formation of A and C-rings *via* an iminium ion triggered aza-Prins cyclisation followed by a transannular cyclisation. The known enone **55**, derived from Hajos–Parrish ketone, was converted in to its thermodynamic dienolate, alkylated with the dioxolane of 4-bromo-2-butanone, and TBSOTf and 2,6-lutidine to afford the silyloxydiene **56**. A highly chemo and diastereoselective hydrogenation followed by Rubottom oxidation and subsequent protection of C8 tertiary hydroxyl group as a MEM ether led to the formation of **57**. Hydrolysis of the ketal, followed by an intramolecular aldol reaction and subsequent treatment with phenyl triflimide generated the enol triflate **58**. The enol triflate was subjected to Pd(0)-catalyzed coupling to generate the allylsilane **59**. In order to pursue a ring expansion, the allylsilane was regio- and diastereoselectively converted to the corresponding dibromocyclopropane **60** (Scheme 9).



Scheme 7 Nicolaou's total synthesis of cortistatin A.



Scheme 8 Nicolaou's total synthesis of cortistatin J.

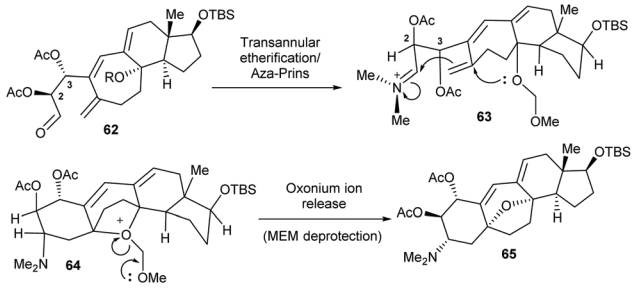


Scheme 9 Shair's synthesis of aza-Prins cyclisation precursor.

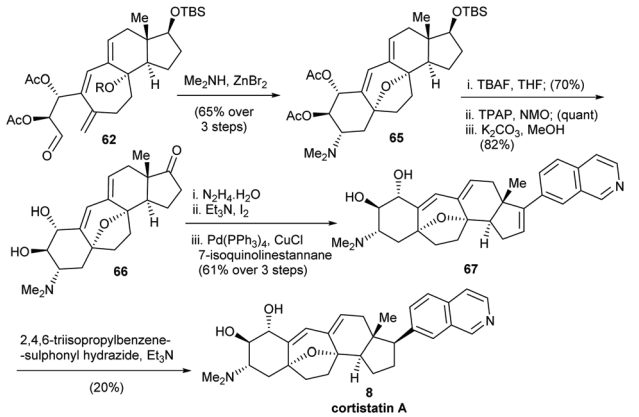
Treatment of the dibromocyclopropane with TASF yielded the brominated cycloheptadiene intermediate, which underwent a Suzuki coupling to form the tetraene **61**. The use of the disiloxane group in **60** was essential to promote the fluoride mediated silicate elimination to obtain the bromo cycloheptadiene intermediate. Previous reports on catalytic enantioselective dihydroxylation indicated that the 1,2-disbustituted olefin would get dihydroxylated first.[27] As predicted, this particular double bond was dihydroxylated with 10 : 1 diastereoselectivity, installing the C1–C2 diol system. The diol was acylated and subsequent cleavage of the primary TES ether and oxidation of the resulting allylic alcohol furnished the precursor aldehyde **62** (Scheme 9), required for the key aza-Prins cyclisation as planned earlier.

The all important key step was performed by treating the above mentioned aldehyde **62** with $ZnBr_2$ (1.5 eq.) and Me_2NH (3 eq.) in MeCN, to obtain the desired product with 65% yield over the last 3 steps. Mechanistically the reaction proceeded *via* iminium ion formation, followed by transannular etherification and cascade aza-Prinz cyclisation, ultimately ending with concomitant MEM deprotection to release the incumbent oxonium ion. This highly challenging and novel transformation to assemble the ABC-ring framework of cortistatin A has indeed been a landmark in the history of cortistatin synthesis. The excellent diastereoselectivity of the aza-Prins cyclisation has been explained through calculations, which suggested that the cyclisation would occur through a 6-membered boat-like transition state, where the C2–OAc hinders attack on the iminium ion from the *Re*-face (β-face). So the relay nucleophilic attack takes place from the less hindered *Si*-face (α-face), which dictates the high degree of selectivity (Scheme 10).

With the key reaction successfully achieved, all that remained now was to attach the isoquinoline moiety on the E-ring. With this in mind, the TBS ether in **65** was cleaved and the resulting alcohol was oxidised to the ketone and the C2, C3 acetates were hydrolyzed to obtain compound **66**. After this, Baran's route was followed, by hydrazone formation, conversion to the corresponding vinyl iodide and Stille coupling with 7-trimethylstannyl isoquinoline to obtain the compound **67**. After testing a large number of reducing agents for the final olefin reduction, it was observed that hydrazine, derived



Scheme 10 Cascade Prins-cyclisation/etherification reaction.



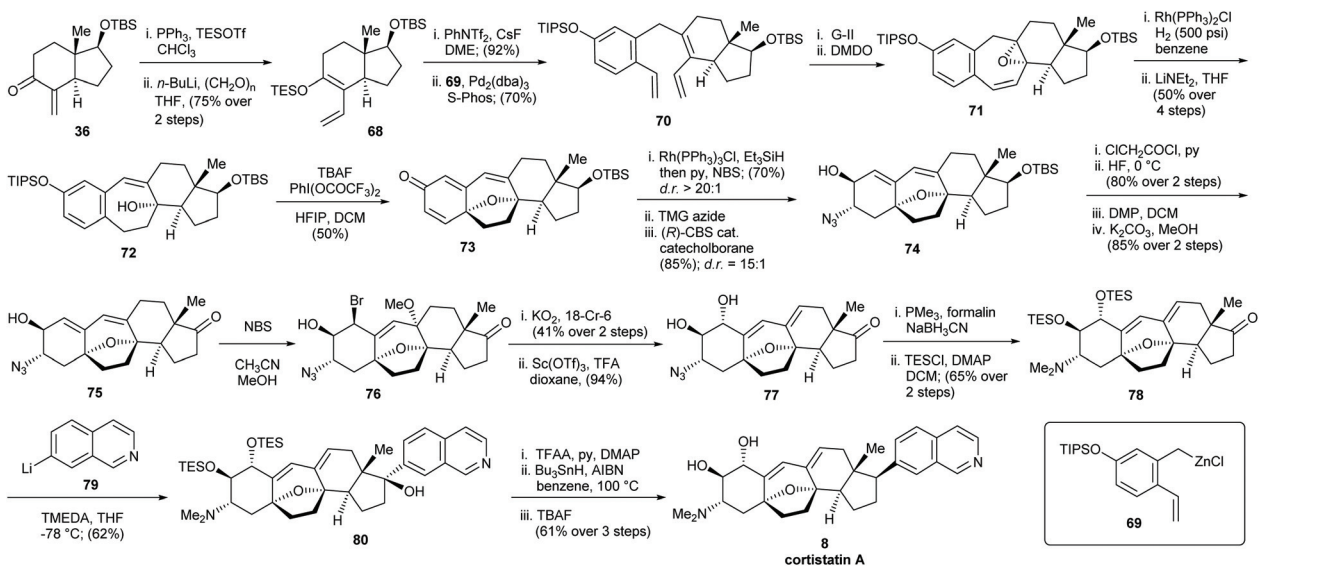
Scheme 11 Shair's total synthesis of cortistatin A.

in situ from 2,4,6-triisopropylsulfonyl hydrazide, could generate the natural product in 20% yield (Scheme 11). This concluded Shair's synthesis of cortistatin A with an overall yield of 0.14% over 25 steps, starting from the chiral enone **55**.[26]

2.4. Myers' unified approach towards cortistatins A, J, K and L[28]

In 2010, Myers and co-workers very elegantly designed a divergent synthetic strategy of four different members of the cortistatin family from a common intermediate **74**. The synthetic journey started with the known chiral α-methylene ketone **36**,[29] which could be obtained from Hajos–Parrish ketone. This was converted into the dienol TES ether **68** in 2 steps through a phosphoniosilylation process, which was then converted to the enol triflate by treatment with $PhNTf_2$. Negishi coupling of this enol triflate with the organozinc reagent **69** was successfully carried out to furnish **70** in 70% yield. Ring closing metathesis of **70** with G-II catalyst followed by a regio- and stereoselective epoxidation of the tetrasubstituted olefin gave the epoxide **71** much alike Sarpong's synthesis of a similar intermediate (discussed in section 3.1).[30] Reduction of the double bond with Wilkinson's catalyst and opening of the epoxide with lithium diethyl amide generated the allylic tertiary alcohol **72** in 50% yield over the previous 4 steps. The key oxidative dearomatization of the A-ring with concomitant cyclisation formed the tetrahydrofuran C-ring in moderate yield. The dienone **73** was regioselectively reduced with Wilkinson's catalyst and triethylsilane and the resulting enolate was subsequently quenched with NBS to obtain the α-brominated ketone. The bromide was displaced with TMG azide followed by CBS reduction of the ketone to obtain the key azido alcohol **74** (Scheme 12).

The azido alcohol **74** was subjected to a 4-step reaction sequence to obtain the ketone **75**, which upon treatment with NBS in methanol and acetonitrile afforded the bromide **76**. Substitution of the bromide was achieved with potassium superoxide followed by elimination of the angular methoxy group to obtain the conjugated diene system **77** across the B and D-rings. Reductive dimethylation of the azide in the pres-

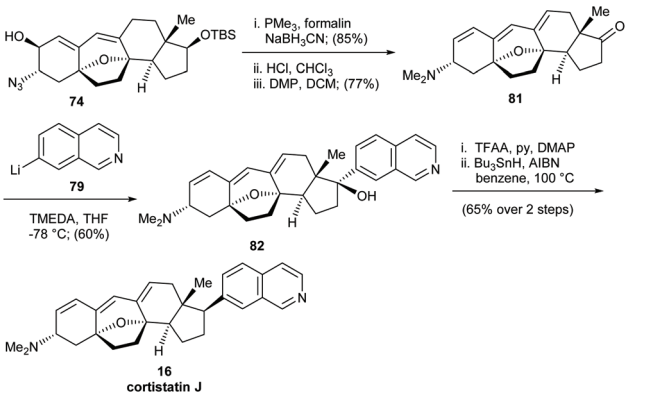


Scheme 12 Myers' total synthesis of cortistatin A.

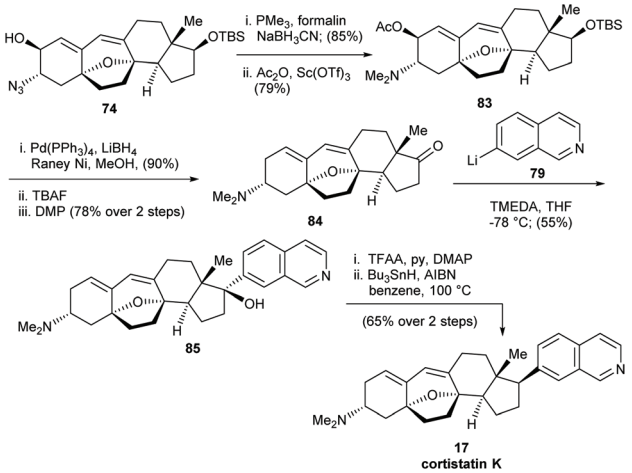
ence of PMe_3, formalin and $NaBH_3CN$ generated the desired dimethylamino group on the A-ring and the two alcohols were later protected as TES ethers to generate the intermediate **78**. Addition of 7-lithioisoquinoline **79** to the E-ring ketone generated the tertiary alcohol **80** in 62% yield. The tertiary alcohol was eliminated and then the resulting olefin was reduced in the presence of Bu_3SnH and AIBN to obtain the required β-isoquinoline group. Finally the TES ethers were cleaved to furnish the natural product in 61% yield over the final 3 steps (Scheme 12). This completed one of the most strategically elegant total syntheses of cortistatin A with an overall yield of ~0.36% across a longest linear sequence of 25 steps starting from the chiral enone **36**.

As part of this unified approach towards the total synthesis of a variety of cortistatin family congeners, Myers and co-workers then elaborated the common azido alcohol intermediate **74** to accomplish the total synthesis of cortistatin J, K and L. Reductive amination of the azide **74** followed by dehydration with concomitant cleavage of TBS ether and oxidation of the resultant alcohol gave the desired triene **81** across the A, B and D-rings. Addition of 7-lithio isoquinoline (**79**) to **81** provided the tertiary alcohol **82** in 60% yield. Finally the tertiary alcohol was removed by converting it to a trifluoroacetyl ester and treatment with AIBN, Bu_3SnH to obtain cortistatin J with 65% yield over the 2 steps. The total synthesis of cortistatin J was thus accomplished with an overall yield of ~1.8% over a longest linear sequence of 18 steps starting from the known α-methylene ketone **36** (Scheme 13).

In order to functionalize the A-ring for cortistatin K, the azide **74** was reductively aminated and the secondary alcohol was acetylated to afford the intermediate **83**. Reductive removal of the acetate was carried out by employing $LiBH_4$, RANEY® Ni and $Pd(PPh_3)_4$ to obtain 90% of the intermediate diene. Removal of the TBS group followed by oxidation of the secondary alcohol led to the corresponding ketone **84**. The isoquinoline was then introduced following the same protocol as earlier and finally the resulting secondary alcohol was removed to obtain cortistatin K with an overall yield of ~1.2% over 20 steps starting from the known exocyclic enone **36** (Scheme 14).



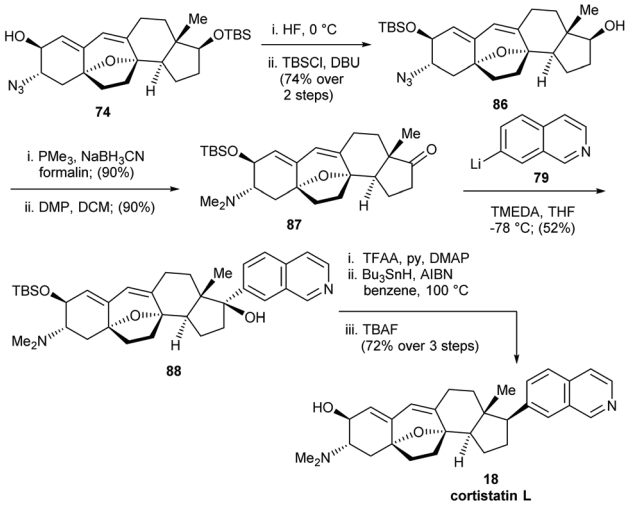
Scheme 13 Myers' total synthesis of cortistatin J.



Scheme 14 Myers' total synthesis of cortistatin K.

Cortistatin L was also successfully synthesized through a similar sequence of reactions, starting with the controlled removal of the C17–TBS ether, followed by selective protection of the C1–hydroxyl group. Then the azide was reductively aminated and converted to the $-NMe_2$ group and the E-ring alcohol was oxidised to the ketone **87**. Finally, like in the other congeners, the isoquinoline moiety was introduced and the resulting tertiary alcohol **88** was reductively eliminated to obtain cortistatin L with an overall yield of ~1.6% over a sequence of 20 steps starting from the same α-methylene ketone **36** (Scheme 15).

This completed Myers' significant efforts to achieve the total synthesis of four different members of the cortistatin family involving a unified approach, from a common late stage intermediate. The scope for diversity from the common pentacyclic intermediate **74** was the hallmark of Myers' synthetic route and this strategy opened the door for a wide range of

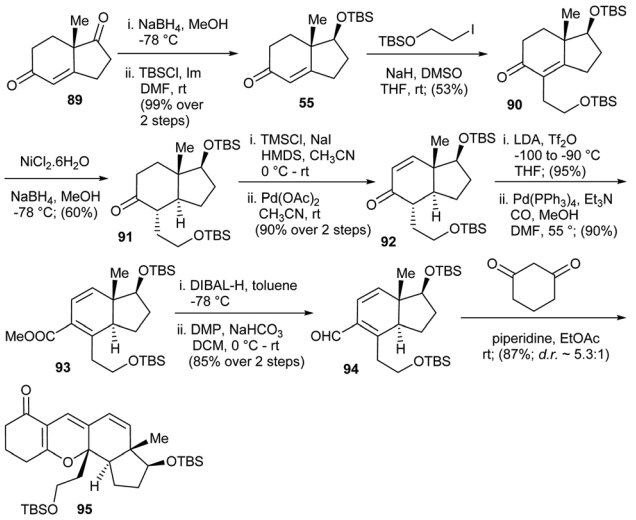


Scheme 15 Myers' total synthesis of cortistatin L.

functional as well as stereochemical diversification, which can lead to a range of structure activity relationship studies.[28]

2.5. Hirama's total synthesis of cortistatins A and J[31]

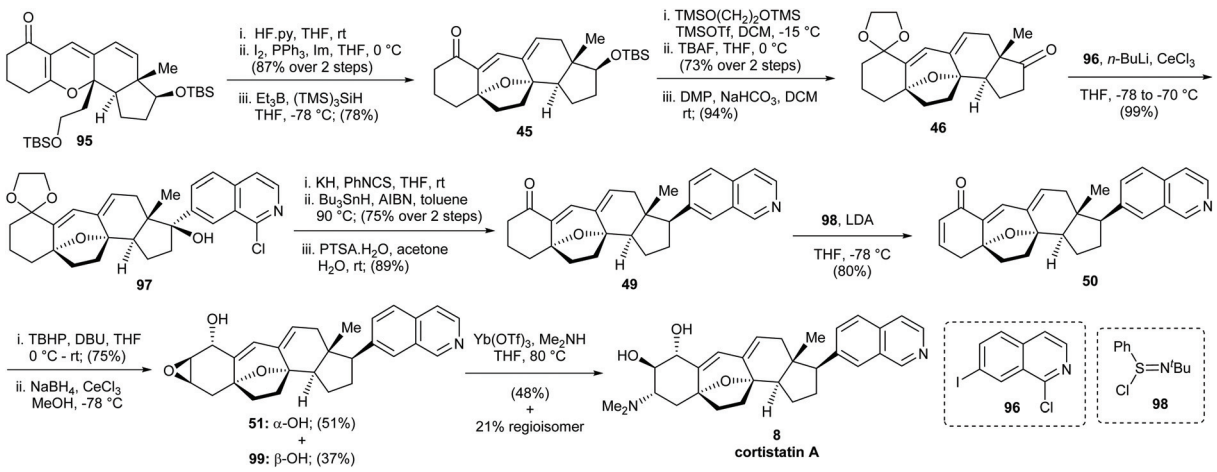
In 2011, Hirama's group extended their formal synthesis reported earlier,[32] to the total synthesis of cortistatins A and J. Hajos–Parrish ketone (**89**) was once again chosen as the starting material and the TBS ether **55** was generated in good quantities over a 2-step sequence. Then the 2-carbon unit was introduced using Molander's protocol[33] to obtain the α-substituted enone **90** in 53% yield. Stereoselective reduction of the enone was achieved through $NaBH_4$ reduction in presence of $NiCl_2{\cdot}6H_2O$ to obtain the desired *trans*-ring junction. Treatment of the ketone **91** with HMDS and TMSCl generated the TMS enol ether, which was subjected to Saegusa oxidation conditions to obtain the conjugated enone **92** in 90% over 2 steps. The ketone was then converted to the enol triflate followed by a Pd-catalyzed methoxycarbonylation to obtain the dienyl ester **93**. The newly formed ester was reduced to the aldehyde **94** and subjected to Knoevenagel condensation with cyclohexan-1,3-dione to obtain the key tetracyclic intermediate **95** with 87% yield and a diastereoselectivity of up to 5.3 : 1 with respect to the ring junction stereocenter (Scheme 16).



Scheme 16 Hirama's synthesis of the tetracyclic intermediate **95**.

The primary TBS ether was removed and the resulting alcohol was converted into the corresponding iodo-compound, which was treated with Et_3B and tris-(trimethylsilyl)silane to complete the 5-*exo-trig* radical cyclisation and isomerization to form the C-ring with 78% yield. This completed the core structure of cortistatins and these results were published by Hirama's group in 2008.[34] Protection of the ketone followed by removal of the TBS group and oxidization led to the corresponding ketone **46**. Addition of 1-chloro-7-lithioisoquinoline to ketone **46** generates the tertiary alcohol **97** in quantitative yield. The tertiary alcohol **97** was deoxygenated *via* its thiocarbamate and subsequent treatment with AIBN and Bu_3SnH. During this reaction, the chloride in the isoquinoline nucleus also was removed to obtain the E-ring isoquinoline unit with the desired configuration. The ketone **49** was oxidised into the conjugated enone **50** following Mukaiyama's protocol in 80% yield. The resulting enone **50** was stereoselectively epoxidised and the ketone was reduced under Luche conditions to obtain 51% of the desired α-alcohol (**51**) along with 37% of the β-alcohol (**99**). These two diastereomers were separated and the required α-hydroxylated epoxide (**51**) was opened with dimethylamine in the presence of $Yb(OTf)_3$ to obtain cortistatin A (**8**) in 48% yield along with 21% of the regioisomeric ring opened product (Scheme 17).

After completing the total synthesis of cortistatin A, they also extrapolated their strategy to achieve the total synthesis of cortistatin J by late stage functional group manipulations on the A-ring enone intermediate **50**. A 3-step sequence was employed starting with 1,4-addition of dimethylamine followed by reduction of the resulting ketone to generate an intermediate secondary alcohol on the A-ring.



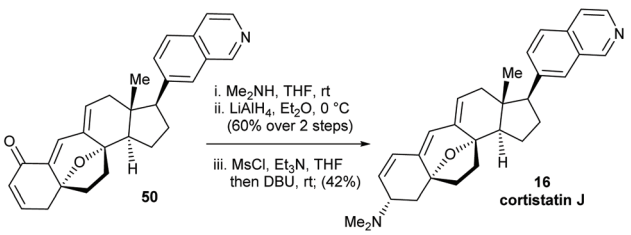
Scheme 17 Hirama's total synthesis of cortistatin A.

This was finally functionalized into a mesylate and eliminated by treatment with DBU to obtain the natural product in 42% yield (Scheme 18).[31] Hirama's total synthesis of cortistatin J was hence completed with an overall yield of ~1.1% over a linear sequence of 25 steps starting from Hajos–Parrish ketone **89**.

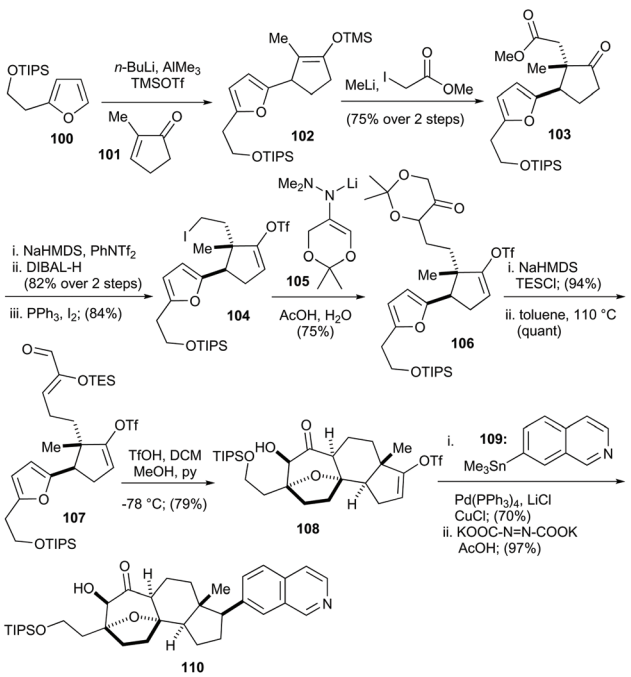
2.6. Funk's total synthesis of cortistatin J[35]

In 2011 Funk and co-workers reported the total synthesis of cortistatin J, by employing their own method of [4 + 3] cycloaddition of (*Z*)-2-(silyloxy)-2-enals as the key step in completing the [3.2.1] BC-ring system of cortistatin. The synthesis of cortistatin J was in line with the fact that after cortistatin A, it was the most biologically active congener in the family with respect to their selectivity towards the HUVECs and there had not been too many synthetic approaches towards the same.

Funk's racemic synthesis commenced with the 2-substituted furan derivative **100** which was substituted with the 5-membered cyclic enone **101** in the presence of $AlMe_3$ and TMSOTf. The resulting vinyl ether **102** was quenched with methyl iodoacetate to obtain the ester **103** in 75% yield over 2 steps. The ketone was converted to the corresponding enol triflate, while the ester was reduced and converted into the side chain iodide **104**. The freshly generated iodide was then substituted with the aza-enolate of the dimethyl hydrazone **105** to generate the alkylated hydrazone intermediate, which was hydrolyzed during the work-up to afford the ketone **106** in 75% yield. Treatment with NaHMDS and TESCl generated the kinetic TES enol ether of the dioxanone **106** which underwent a retro cycloaddition type transformation to generate the key (*Z*)-2-(triethylsilyloxy)-2-enal **107** when refluxed in toluene. After substantial optimization, treatment with triflic acid and pyridine at −78 °C generated the [4 + 3]-cycloadduct **108** in 79% yield with the *endo*-adduct as the sole diastereomer produced in the reaction. Stille coupling of the enol triflate **108** with 7-(trimethylstannyl) isoquinoline (**109**) followed by diimide reduction of the resulting double bond furnished the intermediate **110** (Scheme 19).



Scheme 18 Hirama's total synthesis of cortistatin J.



Scheme 19 Funk's synthesis of the key pentacyclic framework.

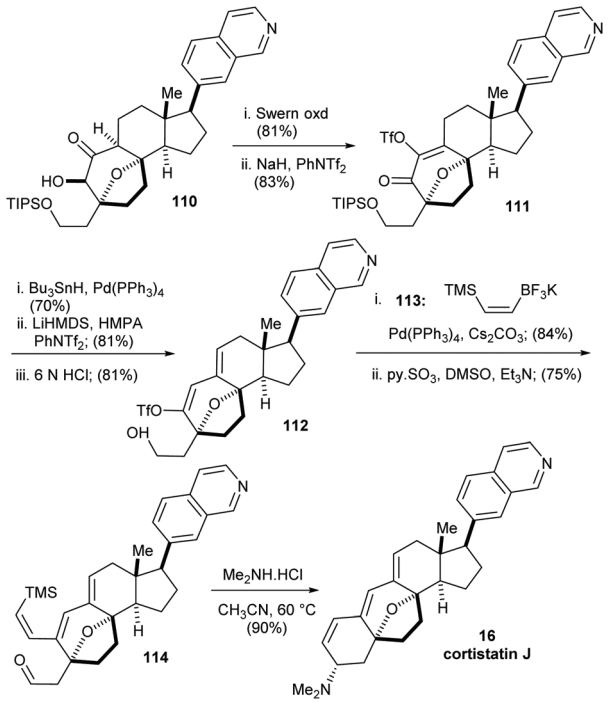
Now the stage was set for constructing the A-ring which was initiated through Swern oxidation of the secondary alcohol and conversion of the other ketone into the corresponding enol triflate **111**. The newly generated triflate was hydrogenated by Pd-catalysis and further treatment with LiHMDS and $PhNTf_2$ generated the dienol triflate **112**, which was isolated after subsequent treatment with 6 N HCl to hydrolyze the TIPS ether in the side chain. Suzuki–Miyaura coupling of the freshly generated dienol triflate **112** and the known trifluoroborate reagent **113**[36] using Molander's conditions[37] resulted in the formation of the silylated diene unit. Parikh–Doering oxidation of the side chain primary alcohol generated the aldehyde precursor **114** for the natural product in 75% yield. Treatment of this aldehyde **114** with excess of dimethylamine hydrochloride in acetonitrile at 60 °C generated the natural product as a single diastereomer in 90% yield (Scheme 20).

This completed Funk's total synthesis of racemic cortistatin J where the key steps involved the first application of their own [4 + 3] cyclisation between (*Z*)-2-(silyloxy)-2-enal and a 2,5-disubstituted furan appended in the same molecule. This was followed by a final step Overman type (*Z*)-vinylsilane/iminium ion cyclisation to construct the A-ring. The total synthesis was completed in 19 steps starting from the 2-substituted furan **100** with an overall yield of ~3.4% and remains the last completed total synthesis of any of the members from the cortistatin family.[35]

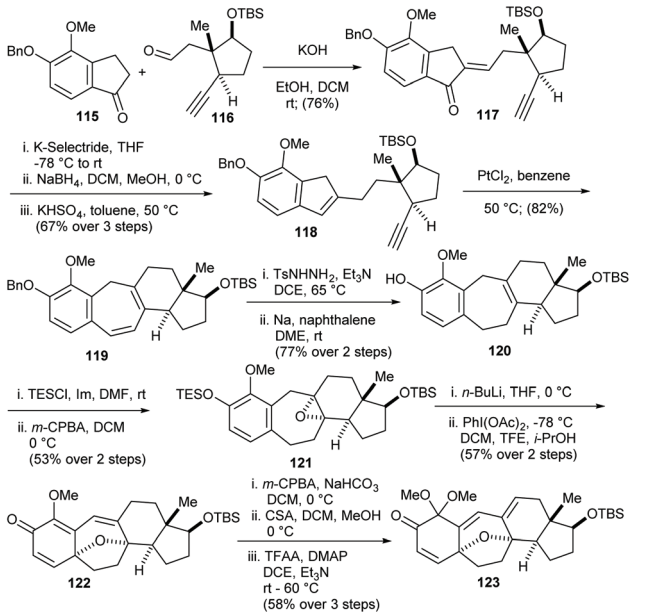
3. Formal syntheses

3.1. Sarpong's formal synthesis of cortistatin A[30]

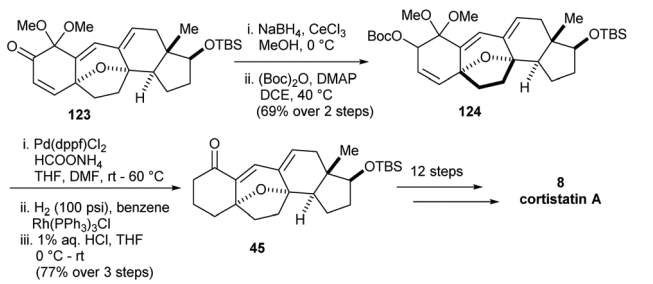
Divergent synthesis of various members of the same family of natural products from a common intermediate has always been a highly sought-after exercise because of the obvious advantages of such strategies. Indeed, it was the search for such a common and flexible intermediate, which formed the lynchpin for Sarpong's strategy towards the pentacyclic core structure of cortistatins. Their synthetic route commenced



Scheme 20 Funk's total synthesis of (±)-cortistatin J.



Scheme 21 Sarpong's synthesis of the pentacyclic intermediate.



Scheme 22 Sarpong's formal synthesis of cortistatin A.

with the racemic compound **116**, obtained from a known starting material in only 4 steps. An intermolecular aldol condensation of the same with the known indanone **115** afforded the enone **117** as a single diastereomer.

Consecutive treatments with K-Selectride and $NaBH_4$ completely reduced the enone **117** to the indanone, which was dehydrated in the presence of $KHSO_4$ in warm toluene to generate the indene **118** with 67% yield over the 3-step sequence. Treatment of **118** with a catalytic amount of $PtCl_2$ in benzene resulted in the planned cycloisomerization product **119** in 82% yield, without the formation of any other by-products. Chemoselective reduction of the less substituted double bond by *in situ* generated diimide and subsequent removal of the benzyl group afforded **120** in good yield. Reprotection of the phenol as a TES ether followed by stereoselective epoxidation with *m*-CPBA afforded the epoxide **121**. After several experimentations, regioselective opening of the epoxide was successfully achieved with *n*-BuLi, which also removed the TES group under the reaction conditions. Now the stage was set up for the formation of the oxa-bridge by the key oxidative dearomatization of the aromatic residue. Treatment of **121** with PhI$(OAc)_2$ in a non-nucleophilic protic solvent like TFE/i-PrOH provided the oxo-bridge and completed the pentacyclic core structure **122** of cortistatins (Scheme 21).[38]

In a subsequent communication in 2010, Sarpong's group elaborated the functionalities on the A-ring to match those of the natural product. The trienone **122** was epoxidised with *m*-CPBA at 0 °C followed by opening of the same using CSA/MeOH. The resulting tertiary alcohol was then dehydrated to obtain the dimethoxy diene **123** in 58% yield over the 3-step sequence (Scheme 21). Luche reduction of the A-ring enone resulted in the secondary alcohol, which was then protected as the Boc-carbonate **124**. After extensive studies, treatment of the Boc-carbonate with Pd(dppf)Cl_2 and ammonium formate produced a methoxy diene intermediate, which upon reduction using Wilkinson's catalyst and hydrolysis of enol ether furnished the ketone **45** in 77% yield over 3 steps (Scheme 22). This ketone was in fact identical to that of Nicolaou's synthesis, from which cortistatin A could be achieved in 12 steps.

This completed a formal synthesis from Sarpong's group with an overall yield of ~3.07% over a linear sequence of 19 steps, starting from the indanone **115** and aldehyde **116**. This second generation synthesis marked an improvement in the overall yield, compared to their earlier synthetic route from the same starting fragments.[38]

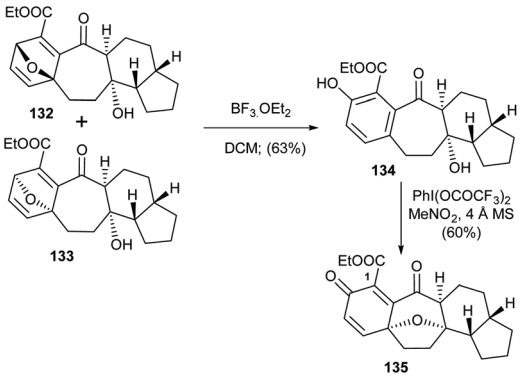
3.2. Yang's formal synthesis of cortistatins[39]

In late 2008, Yang reported a first generation approach towards the oxa-pentacyclic core structure of cortistatins, through a

furan based intramolecular Diels–Alder approach.[40] The known chiral bicyclic ketone **125**[41] was converted to its kinetic enol-TMS ether, which was quenched with trimethyl orthoformate to obtain the dimethoxy acetal **126**. Addition of lithiated furan **127** to the ketone **126** generated the required C8 tertiary alcohol **128** in 56% yield. Hydrolysis of the acetal generated the key aldehyde **129**, which was treated with Me_3Al in THF to form a chelate along with the C8 alcohol. The formation of the chelate **130** ensures addition of the lithiated alkyne from the less hindered face to provide only a single diastereomer of the propargylic alcohol **131**. However this substrate failed to deliver the IMDA adduct under any of the conditions which were attempted. But when the alcohol was oxidised with DMP, the IMDA reaction worked spontaneously to afford the products **132** and **133** in the ratio 3 : 1, with excellent overall yield of the process (Scheme 23).

Having assembled the [6.7.6.5] core structure, formation of the [3.2.1]-oxabicyclo system was attempted under the influence of a variety of Lewis acids. But probably due to the sterically hindered nature of the C8 tertiary alcohol, it failed to cyclize on to the A-ring. During one of these attempts however, it was observed that $BF_3{\cdot}OEt_2$ could easily aromatize the A-ring, which could then be treated with hypervalent iodine reagents to execute the cyclic etherification. To this end the phenol derivative **134** was treated with $PhI(OCOCF_3)_2$ to obtain the desired [3.2.1]-oxabicyclo system **135** as part of the pentacyclic framework of cortistatins. This final transformation was observed to be highly solvent specific, with the 60% yield being obtained in highly anhydrous grades of nitromethane (Scheme 24).

However, while attempting to extrapolate the core structure towards the total synthesis of cortistatin J, the C1 carboxylate group proved difficult to remove and hence this strategy had to be abandoned. So in a newly developed second generation strategy, Yang and co-workers resorted to an intramolecular

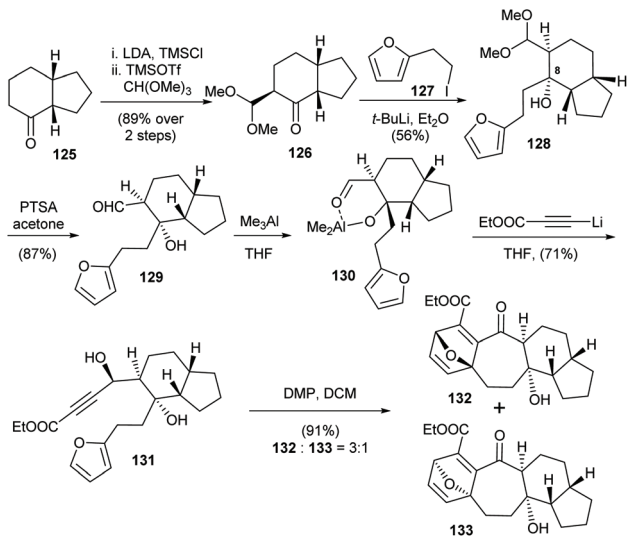


Scheme 24 Yang's first generation synthesis of core structure.

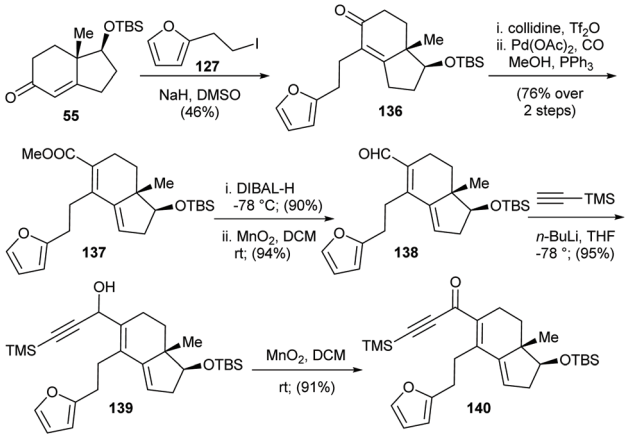
oxa-Michael addition in order to forge the pentacyclic core, which could then be elaborated towards the total synthesis. The new strategy also had to be equipped in such a way that the core structure would be incorporated with suitable functionalities to be extrapolated towards total synthesis.

To this end, Yang's second generation strategy commenced with the same chiral pool **55** as utilized by Nicolaou, Danishefsky and Shair previously. The bicyclic enone **55** and the furan based alkyl iodide were coupled using NaH in DMSO to obtain compound **136**. The corresponding dienol triflate was prepared and subsequently made to undergo Pd-catalyzed methoxycarbonylation to obtain the ester **137**. A reduction, oxidation sequence generated the aldehyde **138**, which was treated with lithiated TMS acetylene to obtain the propargylic alcohol **139**. This diastereomeric mixture of alcohols was oxidised with MnO_2 to obtain the key IMDA precursor **140** (Scheme 25).

After encountering failure to achieve the IMDA reaction in the presence of a variety of Lewis acids like $TiCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf and $Zn(OTf)_2$, it was hypothesized that Al-based Lewis acids might help in catalyzing the IMDA transformation better, because of their higher oxygenophilicity. With this idea in mind, $EtAlCl_2$ was employed for this purpose and at −78 °C,



Scheme 23 Yang's synthesis of the key intermediate.

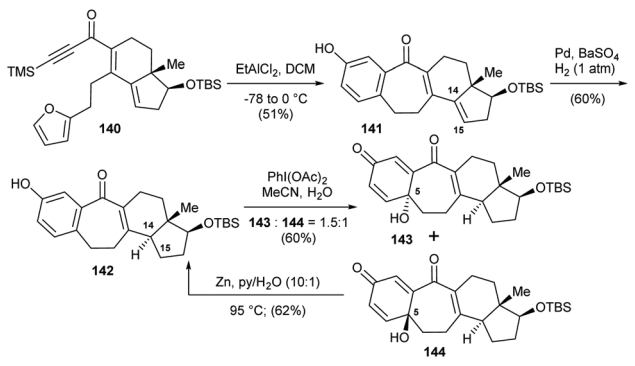


Scheme 25 Yang's synthesis of the IMDA precursor.

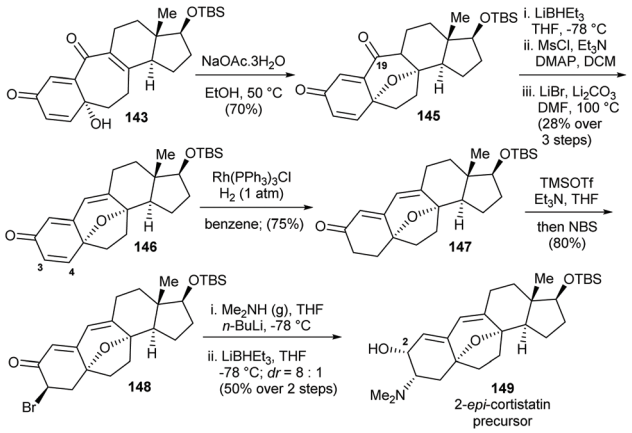
the IMDA adduct was obtained, accompanied by concomitant aromatization and removal of TMS group to furnish the desired tetracyclic product **141** in 51% yield. It was also observed that the presence of the TMS group was beneficial for carrying out the Diels–Alder reaction, as compared to starting with a free terminal alkyne. The C14–C15 olefin was hydrogenated with high facial selectivity, which could be attributed to the steric effects of the angular methyl group and the high stability of the resulting 6,5-*trans*-ring junction in **142**. With the construction of the tetracyclic framework established, the next job was to attempt the intramolecular oxa-Michael addition in order to construct the characteristic oxo-bridge.

For introduction of the key C5 tertiary alcohol, it was proposed that oxidative dearomatization of the A-ring by employing water as a nucleophile could generate the desired C5-hydroxyl group. So the phenol derivative **142** when treated with BAIB in a solvent combination of acetonitrile and water underwent oxidative dearomatization followed by nucleophilic attack with water at C5 during the course of the reaction. This furnished an epimeric mixture of C5-tertiary alcohols with a 1.5 : 1 majority of the desired α-epimer **143**. The undesired β-C5-alcohol **144** could be converted back to the aromatic compound **142** by treatment with Zn, py/H_2O and thereby be recycled (Scheme 26).

After installing the C5-alcohol with correct stereochemistry, transannular oxa-Michael addition was attempted with NaOAc in ethanol to afford the annulated product **145** with 70% yield to complete the formation of the pentacyclic skeleton. In order to incorporate the B-ring double bond, the C19 ketone was reduced with $LiBHEt_3$ and the resulting olefin was dehydrated *via* its mesylate and then treated with LiBr and Li_2CO_3 at high temperatures to obtain the required olefin **146**. Wilkinson's catalyst regioselectively reduced the C3–C4 double bond and the dienone **147** was converted to its TMS enol ether, followed by treatment with NBS to obtain Myers' key intermediate **148** in regio and stereoselective fashion. Finally the bromine was displaced in S_N2 fashion by treatment with gaseous dimethyl amine in solution and the C2 ketone was reduced stereoselectively using $LiBHEt_3$, though the configuration of the resulting C2–hydroxyl was found to be opposite to that of the natural



Scheme 26 Yang's construction of the pentacyclic intermediate.



Scheme 27 Yang's formal synthesis of cortistatin A.

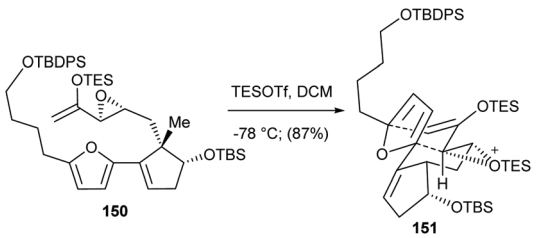
product. This may also be a pathway to synthesize the 2-*epi*-cortistatin analogues (Scheme 27).

In conclusion, Yang and co-workers introduced yet another new avenue towards the construction of the oxabicyclo-[3.2.1]-heptane core using a furan based intramolecular Diels–Alder reaction and an intramolecular oxa-Michael addition as the key steps. Myers' key intermediate **148** was synthesized, which may be extended to the total synthesis of cortistatins A, J, K and L. In addition, Yang's group also paved the way for a possible extrapolation of the compound **148** to synthesize (C2)-*epi*-cortistatins, leading to unexplored stereochemical analogues of the natural products.[39]

3.3. Chiu's formal total synthesis of cortistatins A and J[42]

In 2011, Chiu and co-workers reported an intramolecular [4 + 3]-cycloaddition strategy to access the bicyclo-[3.2.1]-octane ring system of cortistatins. A substituted furan would serve as the diene and the 5-membered E-ring tethered to the furan would serve as an intramolecular dienophile. Employing this strategy as the key step, the core structure of cortistatins was constructed.[43] Later in 2015, the first generation synthetic route was simplified and by using a similar protocol to construct the key bicyclo-BC-ring framework, Chiu and co-workers completed the formal total synthesis of cortistatins A and J.

Their synthetic journey commenced with the desymmetrization of the commercially available cyclopentanedione **152** by asymmetric transfer hydrogenation using the Ru-based (*R*,*R*)-Ts-DENEB catalyst (**153**).[44] This proved to the most robust catalyst for scale-up purposes, as compared to other methods including CBS-reduction which was employed in their first generation synthesis.[43] So the pure enantiomer of the alcohol **154** was synthesized with excellent enantioselectivity and acceptable diastereoselectivity. The newly generated alcohol was protected as a TBS ether followed by generation of the enol triflate on the remaining ketone. The enol triflate was then subjected to Pd-catalyzed Stille coupling with the furan-2-yl stannane **155** to obtain 93% of the cross-coupled product **156**. The terminal olefin was made to undergo cross meta-



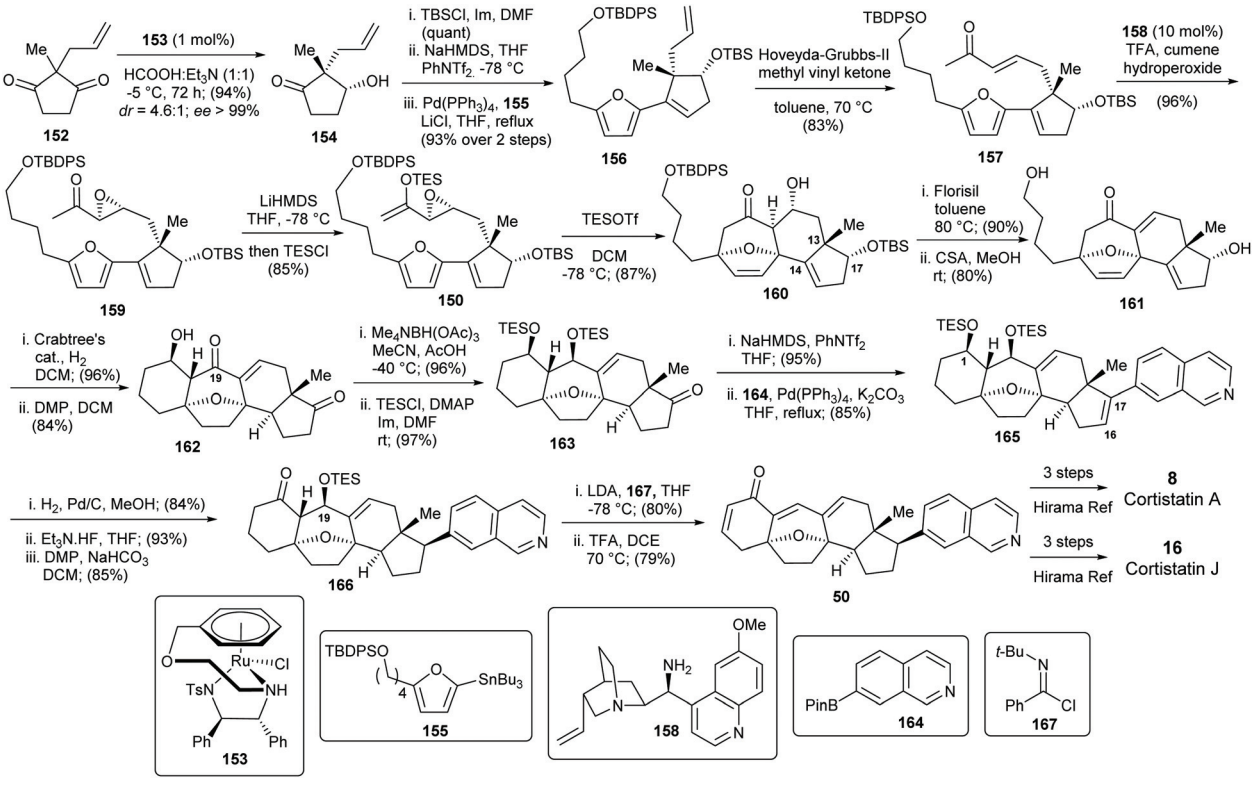
Scheme 28 Mode of chirality transfer in [4 + 3]-cycloaddition.

thesis with methyl vinyl ketone in the presence of Grubbs–Hoveyda 2nd generation catalyst. The newly generated enone **157** was epoxidised using Deng's cinchona derived catalyst **158** and the epoxy ketone **159** was obtained as a single diastereomer in 96% yield. The methyl ketone was converted to the corresponding TES ether **150** and now the stage was set for exploring the key [4 + 3]-cycloaddition to construct the BC-ring framework of cortistatins (Scheme 29).

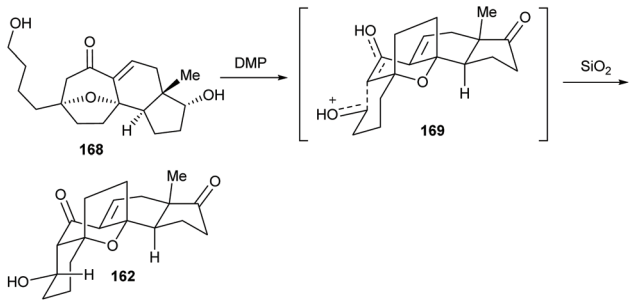
It was ascertained through computational studies that the [4 + 3]-cycloaddition does not take place *via* the putative oxyallyl carbocation, but it was the activated form of the epoxide itself, which was acting as a masked "dienophile". This fact made the stereochemistry of the epoxide crucial for achieving the correct diastereoselectivity during the key cycloaddition process, as the "backside attack" on the epoxide by the diene would be directly translated to the chirality obtained in the cycloaddition product (Scheme 28).

Among other reagents screened for this purpose, TESOTf proved to be the most versatile and tolerant towards all the functional groups present in the molecule, as the [4 + 3]-cycloadduct was obtained with 87% yield as a single diastereomer (Scheme 28). With the tetracyclic framework **160** in hand, the next task was to construct the A-ring and organize the other required functional groups in the natural product. Hydrogenation of the D-ring double bond afforded the undesired *cis* ring junction at the C13–C14 fusion. In order to ensure *trans* ring junction at the C13–C14 positions, the C17-TBS ether had to be removed. With this in mind, the compound **160** was dehydrated by Florisil and the C17–TBS ether was removed in the presence of CSA to obtain the intermediate **161**. Hydrogenation in the presence of Crabtree's catalyst yielded the reduced product with excellent yield and chemoselectivity. Bis-oxidation using DMP afforded the intermediate keto aldehyde, which concomitantly cyclised during silica gel column chromatography *via* an intramolecular aldol condensation to afford the intermediate **162**, having the complete pentacyclic framework of cortistatins. The stereochemistry of the intramolecular aldol reaction could be explained *via* the formation of a six-membered transition state **169** (Scheme 30).

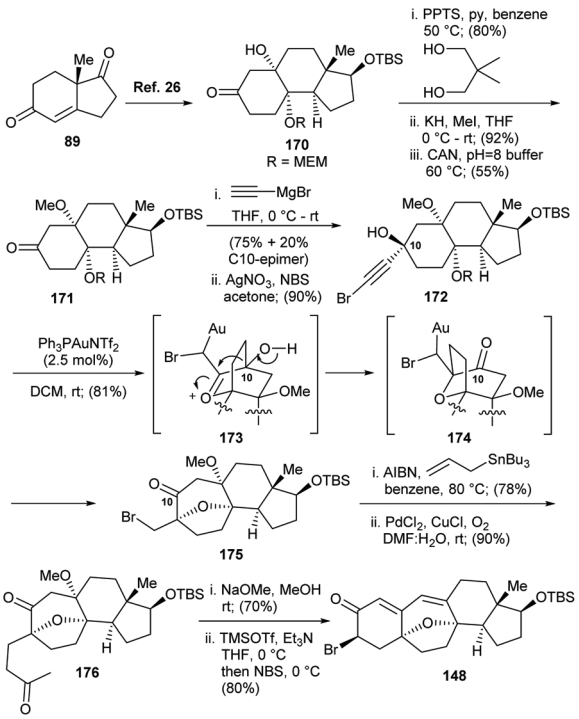
The C19 ketone in **162** was reduced by employing tetramethylammonium triacetoxyborohydride in a hydroxy-directed chemo-as well as stereoselective fashion over the C17 ketone. Di-TES protection was achieved using TESCl to obtain the key intermediate **163** with 97% yield. The C17 ketone was then enolized and the resulting enol triflate was then coupled with



Scheme 29 Chiu's formal total syntheses of cortistatins A and J.



Scheme 30 Stereodynamics of the intramolecular aldol reaction.



Scheme 31 Yang's 2nd generation formal synthesis of cortistatins.

isoqinolinyl pinacol boronate **164** to obtain the compound **165** with 85% yield. Chemo- and stereoselective hydrogenation of the C16–C17 double bond was followed by chemoselective deprotection of the less hindered C1–TES ether and subsequent oxidation of the resulting secondary alcohol to obtain the C1 ketone **166**. Finally Mukaiyama oxidation protocol was followed according to the Hirama synthesis,[31] to generate the A-ring enone. Subsequent treatment with TFA in refluxing dichloroethane resulted in the TES removal and subsequent dehydration of the resulting C19–hydroxyl to obtain the trienone **50** with 79% yield (Scheme 29).

The trienone **50** has been converted independently to cortistatin A and J by Hirama and co-workers over 3 additional steps each.[31] Thus the Chiu group established a formal total synthesis of cortistatins A and J, by constructing Hirama's intermediate **50** over 21 linear steps and an overall yield of 7.7% from the commercially available 1,3-cyclopentanedione **152**. The salient features of the Chiu route involved: (a) implementation of asymmetric transfer hydrogenation to obtain the chiral D-ring skeleton on a multigram scale and (b) execution of the substrate controlled diastereoselective intramolecular [4 + 3]-cycloaddition on the optically pure epoxy enolsilane **150** with a tethered furan moiety to construct the B and C-ring system of cortistatins in a single step. Indeed such an ingenious [4 + 3]-cycloaddition transformation laid the foundation to explore the construction of a variety of other chiral polycyclic scaffolds.

3.4. Yang's 2nd generation formal synthesis[45]

In 2015, Yang's group reported an alternative route to Myer's common intermediate **148** *via* a novel Au-catalyzed annulation as the key step. Hajos–Parrish ketone was converted to the tricyclic intermediate **170** following a modified version of Shair's protocol as mentioned earlier (Scheme 9). Then the angular hydroxyl group was functionalized as the methyl ether following a ketalization, methylation, deketalization sequence to obtain **171**.

Addition of ethynyl magnesium bromide to the C10 ketone resulted in 75% formation of the desired propargyl alcohol, along with 20% formation of its undesired C10-epimer. This was followed by bromination of the terminal alkyne using $AgNO_3$ and NBS to obtain the brominated alkyne **172**. Now the stage was set for attempting the Au-catalyzed cascade cyclisation method developed by the same group, which was achieved by treatment with $Ph_3PAuNTf_2$ in DCM to obtain the desired tetracyclic framework **175** with 81% yield. The alkyl bromide was then displaced by treatment with allyltributyltin in the presence of AIBN, followed by Wacker oxidation of the resulting terminal alkene to obtain the methyl ketone **176**. Reaction with NaOMe in MeOH resulted in an intramolecular aldol condensation to obtain the 6-membered A-ring, which was subsequently brominated at the α-position to obtain Myer's intermediate **148**, which could be extrapolated towards the total synthesis of cortistatins A, J, K and L to complete the formal synthesis of these four congeners of the cortistatin family (Scheme 31).[45]

4. Synthetic approaches

4.1. Gung's approach towards the ABCD core structure of cortistatins[46]

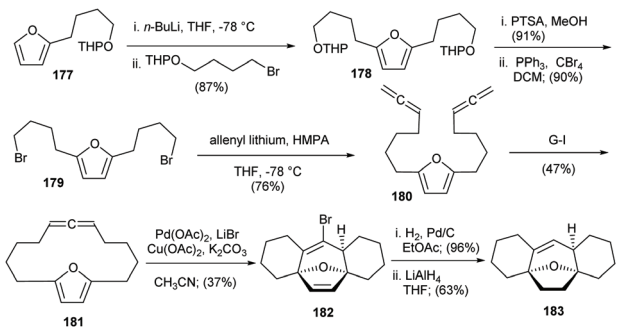
Shortly after Baran's total synthesis was published, Gung and co-workers reported their efforts towards construction of the ABCD core structure of cortistatin A. The central 7-membered ring of the cortistatin family was constructed *via* a highly innovative transannular [4 + 3]-cycloaddition. A suitably placed furan and an allenyl carbocation were conceived to be the appropriate partners for the transannular [4 + 3]-cycloaddition. In this regard, the macrocyclic allene **181** in the presence of a transition metal was identified as an allenyl carbocation equivalent.

With this in mind, a rapid entry to the allenyl furan **181** was developed. The known monoalkylated furan (**177**)[47] was

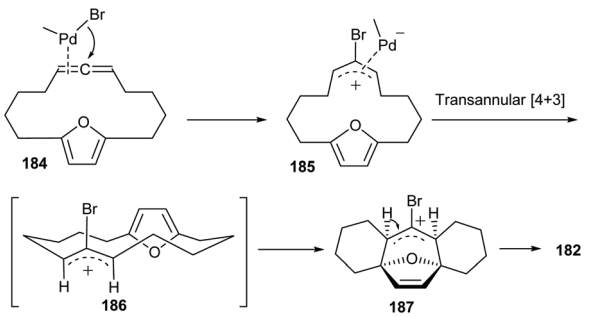
lithiated and alkylated to obtain the di-THP ether **178**, which upon removal of THP groups followed by treatment with Ph_3P and CBr_4 furnished the dibromide **179**. Upon further treatment with allenyl lithium, the bromides were displaced to generate the diallene **180**. Inspired by Janssen and Krause's work on allene RCM reactions,[48] the diallene **180** was then treated with G–I catalyst to construct the 14-membered macrocycle **181** (Scheme 32).

Treatment of the macrocycle with DMDO or $PtCl_2$ failed to generate the required [4 + 3]-adduct. Finally according to a report by Backvall and co-workers,[49] treatment with $Pd(OAc)_2$ generated the allene–Pd complex, which equilibrated to the π–allyl complex **185**. The π–allyl complex acts as an allenyl carbocation equivalent, which is encapsulated in the form of a compact *endo*-tethered transition state **186**, to generate the cationic intermediate **187**. Elimination of a proton furnished the key tetracyclic [4 + 3]-adduct **182** with 37% yield (Scheme 33). The stereochemistry of the oxo-bridge was driven by the compact π-transition state with *endo* tether and it was unequivocally confirmed through an X-ray crystal structure. Finally, the tetracyclic compound **182** was treated with H_2, Pd/C to selectively reduce the dihydrofuran double bond, while treatment with $LiAlH_4$ displaced the bromine to generate the ABCD-ring core structure of cortistatins (Scheme 32).

This report from Gung's group illuminated the power of a unique transannular [4 + 3] cycloaddition, utilized towards the construction of a natural product skeleton. This ingenious transformation showcased that a Pd–π–allyl complex could act as a three carbon component for a [4 + 3]-cycloaddition, *en route* to the formation of as many as four rings from one single macrocycle in one operation. The remarkable stereoselectivity of this transformation paved the way for a novel entry to the ABCD core of the cortistatin family, albeit compromising on the scope for further diversification.



Scheme 32 Gung's synthesis of the ABCD core of cortistatins.

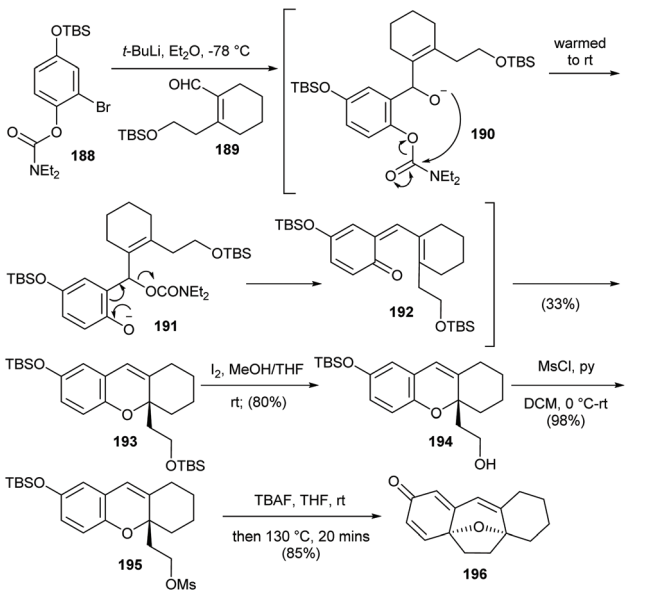


Scheme 33 Mechanism of transnnular [4 + 3] cycloaddition.

4.2. Danishefsky's approaches towards the cortistatin core[50]

In accordance with most other synthetic strategies, Danishefsky and co-workers also designed a route towards the pentacyclic core structure of cortistatins with an idea to extrapolate the same to various other members of the family and towards other analogues. A few months after Baran's first total synthesis of cortistatin A, Danishefsky's group devised an elegant approach towards the construction of the pentacyclic core structure of cortistatins.[50a] They envisioned the construction of the complex tetracyclic architecture by employing the Snieckus cascade protocol,[51] followed by a Masamune type alkylative dearomatization.[52]

Their synthetic journey commenced with a model study in order to ascertain the feasibility of the cascade transformation. The aromatic bromide **188** was lithiated with *t*-BuLi and added to the α,β-unsaturated aldehyde **189** to generate the alkoxide intermediate **190**. Intramolecular carbamate transfer followed by elimination afforded the quinomethide **192**. Upon warming to room temperature, the quinomethide underwent 6π-electrocyclisation to complete the tricyclic intermediate **193**, with a very moderate yield of 33%. The primary TBS-ether was selectively cleaved and the resulting hydroxyl group was converted to the mesylate **195**. TBAF removed the remaining TBS group and the resulting phenoxide upon heating to 130 °C afforded the desired tetracyclic product **196** (Scheme 34).



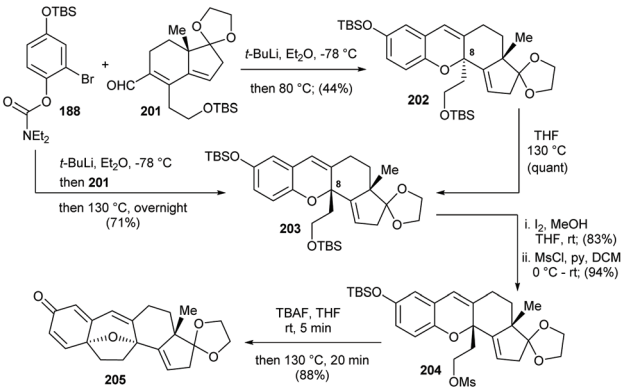
Scheme 34 Model study towards the tetracyclic framework.

Buoyed by the success of the above model study, the actual synthesis was carried forward, starting with the synthesis of the chiral aldehyde **201**. The ketal **197** derived from Hajos–Parrish ketone was alkylated to obtain compound **198**, which was converted to the thermodynamic dienol triflate, by treatment with 2,6-di-*tert*-butyl-4-methylpyridine (**199**) and Tf_2O. Pd-Catalyzed methoxycarbonylation of the crude triflate yielded the corresponding methyl ester, which was later reduced to the primary alcohol **200**. Oxidation of **200** with IBX furnished the required aldehyde **201** in 90% yield (Scheme 35).

Having established the feasibility of the Snieckus' cascade protocol for the formation of the core structure, the same aromatic bromide **188** was lithiated with *t*-BuLi and added to the freshly generated aldehyde **201**. The intermediate 1,2-adduct was heated at 80 °C overnight to trigger the intramolecular carbamate transfer and subsequent 6π-electrocyclic ring closure. Though the reaction proceeded smoothly, undesired configuration at the C8 stereocenter (as confirmed by single crystal XRD analysis) coupled with poor yield (44%) forced them to heat the C8-α-isomer in THF at 130 °C to epimerize the center through a (i) retro-6π-electrocyclisation and (ii) 6π-electrocyclisation sequence to obtain the desired isomer **203**. Selective removal of the primary TBS-ether followed by mesylation of the resulting hydroxyl group afforded compound **204**. Finally, TBAF mediated removal of the phenolic-TBS-group followed by heating to 130 °C provided the pentacyclic core structure **205** of the cortistatin family (Scheme 36).[50a]

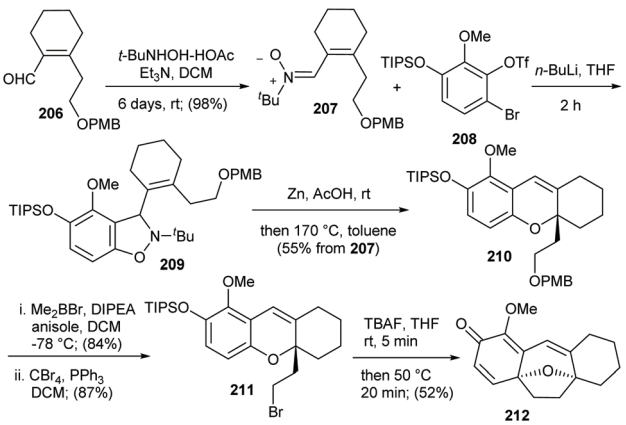
This short and novel route to the cortistatin core structure was established over 9 steps starting from the bromide **188** and demonstrated the power of the Snieckus' cascade protocol in assembling a complex structure from simple starting materials. The alkylative dearomatization provided a definitive route to similar analogues for carrying out SAR studies.

In a subsequent publication, Danishefsky and co-workers published an alternative nitrone–aryne [3 + 2]-cycloaddition strategy towards the formation of compound **212**. This route was in tune with the previously illustrated 6π-electrocyclisation to complete the tricyclic framework and also employed a similar alkylative dearomatization as the key final step (Scheme 37).

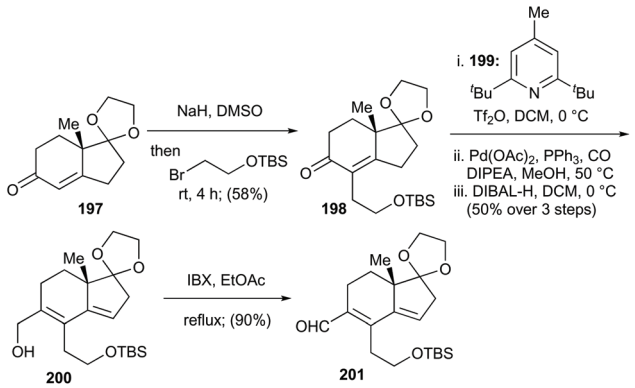


Scheme 36 Danishefsky's synthesis of the pentacyclic core.

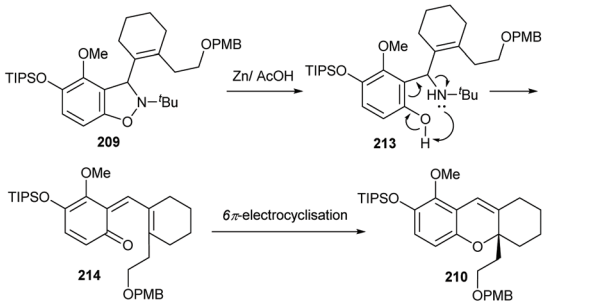
The aldehyde **206** was converted to the corresponding nitrone **207**, and subsequently treated with the *in situ* generated benzyne from *o*-bromophenyl triflate **208** to afford the [3 + 2]-adduct in good yield after extensive optimization. Reductive N–O cleavage was pursued with Zn/AcOH and further heating to 170 °C in toluene resulted in elimination of t-$BuNH_2$ and subsequent 6π-electrocyclisation to obtain the tricyclic intermediate **210** (Scheme 38). Removal of the PMB-ether followed by bromination yielded the precursor for the



Scheme 37 Nitrone–aryne [3 + 2]-cycloaddition strategy.



Scheme 35 Synthesis of aldehyde **201**.



Scheme 38 Mechanistic route to cortistatin core structure.

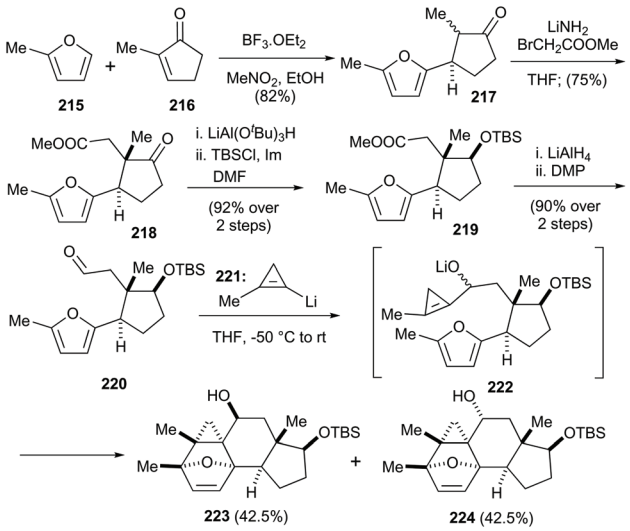
final alkylative dearomatization. Treatment with TBAF followed by warming to 50 °C formed the tetracyclic intermediate **212** with 52% yield (Scheme 37).[50b]

The design of these two very short routes to the core structure of the cortistatin family was an effort to focus on the approach, rather than completion of the total synthesis of any of the family members. With two such robust strategies, Danishefsky and his group sought to open the avenues for a generalized synthetic approach towards these steroidal alkaloids and their analogues.

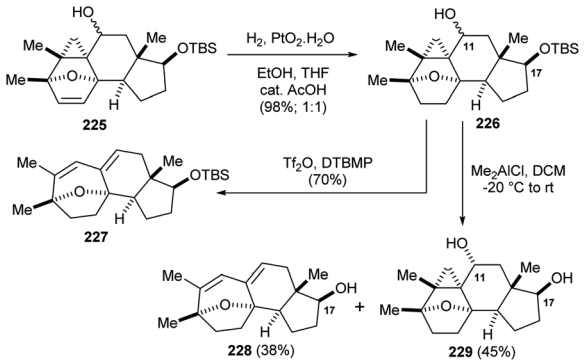
4.3. Magnus' approach[53]

In 2009, Magnus and co-workers explored an innovative cyclopropene-furan [4 + 2]-cycloaddition route to the BCDE-ring core structure of cortistatins. Literature precedence of similar transformations indicated that out of 4 possible diastereomers, only the *exo*-products were formed during such cycloaddition reactions.[54] 2-Methylfuran (**215**) upon treatment with 2-methylcyclopentenone in the presence of $BF_3{\cdot}OEt_2$ afforded **217** as a mixture of diastereomers. Alkylation with methyl bromoacetate obtained 75% of the ketoester **218** as a single diastereomer. Diastereoselective reduction of the ketone, followed by TBS protection of the resulting secondary alcohol yielded the TBS ether **219**. The ester was then converted to the aldehyde **220** followed by addition of cyclopropenyl lithium reagent (**221**) at −50 °C and warming to room temperature furnished the two separable diastereomeric [4 + 2]-adducts **223** and **224** in equal proportions (Scheme 39).

The final part of the strategy involved a cyclopropylcarbinol rearrangement, which may reasonably be considered to be a key part of the biosynthesis of the BC ring fragment of cortistatins. To this end, the mixture of the two diastereomeric alcohols **225** was hydrogenated over Adam's catalyst to obtain an inseparable mixture of cyclopropyl alcohols (**226**). In an attempt to achieve the cyclopropylcarbinol rearrangement, the



Scheme 39 Magnus' cyclopropene-furan [2 + 4]-cycloaddition.



Scheme 40 Cyclopropylcarbinyl rearrangement.

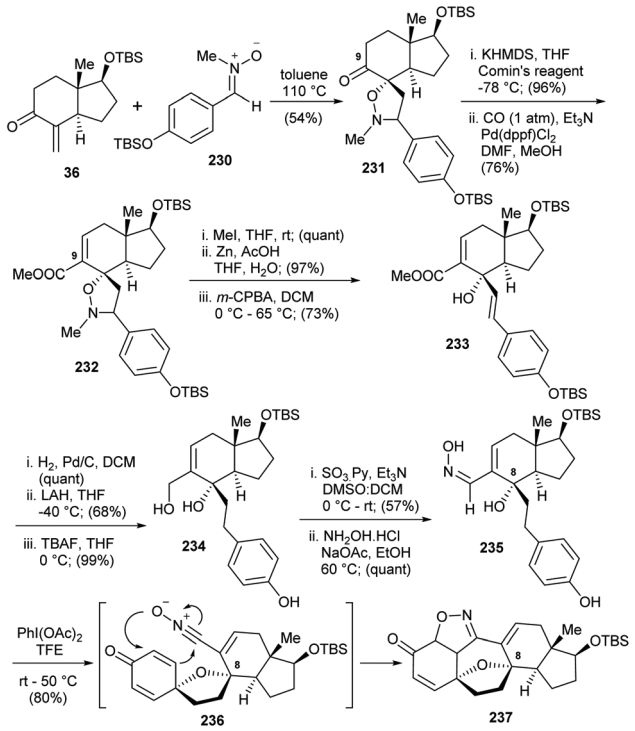
mixture **226** was treated with Me_2AlCl at −20 °C and slowly brought to room temperature. It was observed that the C11-β-epimer, where the hydroxyl group was in the axial position, underwent the rearrangement to the BC-ring diene **228** accompanied by C17 desilylation. On the other hand, the C11-α-epimer with equatorially oriented hydroxyl group did not undergo the rearrangement and produced only desilylated carbinol **229**. In order to circumvent this problem, the mixture **226** was treated with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) which provided a better yield of the product **227** with the TBS ether intact. Obviously both the isomers of the cyclopropyl carbinol participated in the reaction, which led to a much improved yield of 70% (Scheme 40).

Magnus' effort towards construction of the BCDE-ring system of cortistatins was accomplished over 9 steps, starting from two commercially available starting materials with a good overall yield of 30%.[53]

4.4. Sorensen's approach[55]

In 2009, Sorensen and co-workers added a new dimension towards approaching the construction of the pentacyclic core structure of cortistatins, by utilizing two [3 + 2]-dipolar cycloadditions. Their synthetic route began with Hajos–Parrish ketone, which was converted to the bicyclic enone **36**. The exocyclic double bond would act as the dipolarophile for the first [3 + 2]-cycloaddition with the nitrone **230**. Combination of the two species in toluene at 110 °C obtained the cycloaddition product with complete regio- and diastereoselectivity to furnish the isoxazolidine **231** in 54% yield. The diastereoselectivity could be attributed to the disposition of the angular methyl group and the orientation of the *trans*-ring junction. With the C8 tertiary oxygen installed with the required stereochemistry, the next task at hand was to elaborate towards the B and C-rings. The C9 ketone was enolized with KHMDS and Comins reagent, followed by Pd-catalyzed carbonylative ester formation to obtain the methyl ester **232**. The isoxazolidine nitrogen was quantitatively methylated followed by cleavage of the N–O bond to obtain an intermediate dimethylamine.

This was oxidised using *m*-CPBA, which upon heating to 65 °C underwent Cope elimination to furnish the styrene derivative **233**. The newly generated double bond was hydro-



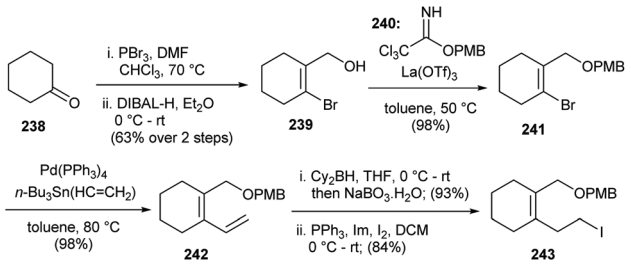
Scheme 41 Sorensen's approach to the pentacyclic core.

genated, the methyl ester was reduced and the phenolic TBS ether was selectively cleaved to obtain the triol **234**. Parikh–Doering oxidation of the allylic primary alcohol generated the aldehyde which was quantitatively converted into the corresponding oxime **235**. Inspired by a report from Ciufolini's group which demonstrated that aldoximes could be oxidised to nitrile oxides in tandem with oxidative dearomatization in the presence of bis(acetoxy)-iodobenzene in trifluoroethanol,[56] the oxime was treated with BAIB. The multiple processes were achieved with great success, as the product **237** was isolated as a single diastereomer with 80% yield (Scheme 41).

This interesting transformation comprised of the following steps: (a) cyclic ether formation with the C8 tertiary alcohol; (b) oxidation of the aldoxime to an intermediate nitrile oxide (**236**); (c) [3 + 2]-diploar cycloaddition to form the hexacyclic product **237**. The construction of such a complicated structure in one pot, involving the formation of 3 rings at such a late stage was the first approach of its kind to synthesize the core structure of cortistatins.[55]

4.5. Stoltz's approach[57]

In 2010, Stoltz and co-workers reported their approach towards the cortistatins core structure and their emphasis, much like Danishefsky earlier,[50a] lay on devising a general route for a rapid entry to the pentacyclic core structure of cortistatins. In this regard, the cornerstone of their strategy was laid through an intramolecular domino enyne-ene metathesis to frame the [6,7,6,5]-tetracyclic backbone.



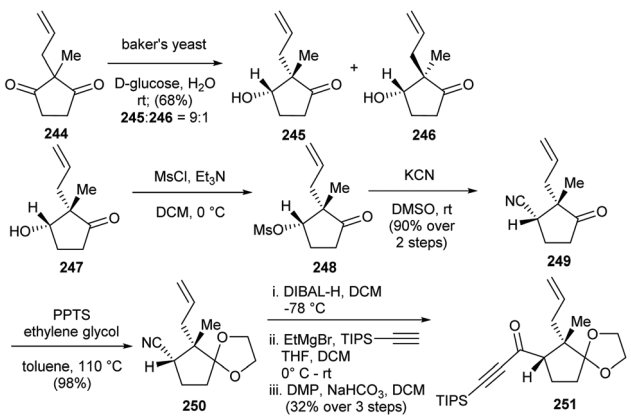
Scheme 42 Stoltz's synthesis of the A-ring fragment.

The A-ring fragment was synthesized starting from cyclohexanone, which was treated with PBr_3 and DMF, followed by reduction of the resulting aldehyde to provide the allylic alcohol **239**. PMB protection of the same followed by Stille coupling with vinyl stannane furnished the diene **242**. Finally the terminal alkene was hydrated *via* hydroboration–oxidation and the resulting primary alcohol was converted into the iodide **243** under Appel conditions (Scheme 42).

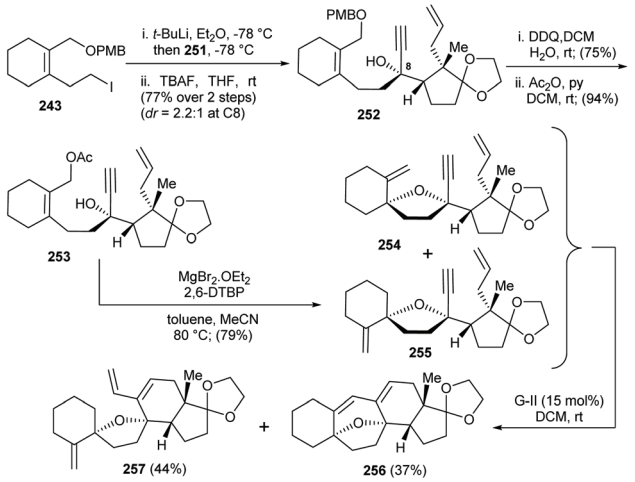
The synthesis of the D-ring was started with an enzymatic reduction of dione **244** to **245** as the major diastereomer. The mesylate **248** of the major isomer on treatment with KCN in DMSO gave the nitrile **249** with the retention of configuration. Protection of the ketone followed by conversion of the nitrile **250** to **251** was done in 3 steps as shown in Scheme 43.

Now with the A-ring fragment and the *epi*-D-ring fragment in hand, the stage was set for coupling the two fragments together. To this end, the iodide **243** was lithiated using *t*-BuLi and the resulting species was added to the ketone **251**. The addition occurred with a diastereomeric selectivity of 2.2 : 1 at the C8 center, in favour of the desired Felkin–Anh adduct. Treatment with TBAF generated a mixture of tertiary propargylic alcohols **252**, retaining the same diastereomeric ratio as earlier. The desired isomer was separated through column chromatography and the PMB ether was cleaved and the resulting hydroxyl group was acylated in 94% yield.

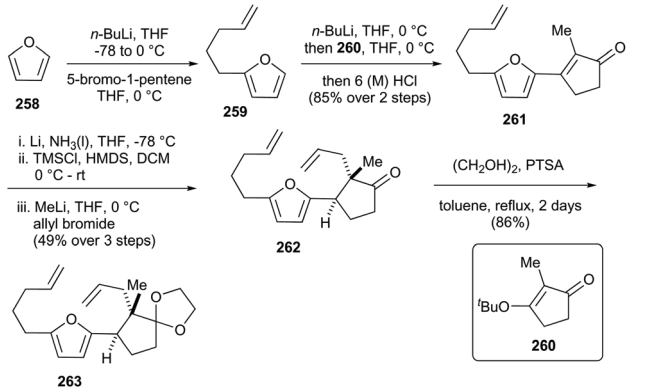
Treatment of the acetate **253** with $MgBr_2{\cdot}OEt_2$ and 2,6-di-*tert*-butylphenol in a mixture of toluene and acetonitrile at



Scheme 43 Stoltz's synthesis of enyne **251**.



Scheme 44 Stoltz's construction of the core structure.



Scheme 45 Zhai's synthesis of intermediate **263**.

80 °C produced an inseparable mixture of the tetrahydrofuran compounds **254** and **255**. Finally this mixture was subjected to treatment with Grubbs' 2nd generation catalyst in DCM to obtain the desired enyne–ene metathesis product (**256**) and the enyne metathesis product (**257**) (Scheme 44).

In order to confirm the absolute stereochemistry of the pentacyclic [6,7,6,5] structure, all attempts towards crystallising the compound **256** or **257** were unsuccessful. So instead, the undesired diastereomer of the propargylic alcohol **252**, which was earlier separated out, was converted to its corresponding pentacyclic framework using an identical reaction sequence as before. This new pentacyclic compound was further derivatised and studied through X-ray crystallography to confirm the absolute stereochemistry of the [6,7,6,5] structure. Stoltz's strategy towards the core structure of cortistatin was the first one to explore the formation of the pentacyclic skeleton by employing domino metathesis as the key step. A novel enyne–ene metathesis led to the swift formation of a highly complex pentacyclic framework from a relatively simpler structure **254** in a single step.[57]

4.6. Zhai's approach[58]

Zhai and co-workers reported the second route to the pentacyclic core structure of cortistatins using a [4 + 3]-cycloaddition approach following Gung's earlier work. This route also commenced with furan as the starting material, but in contrast to Gung's strategy, Zhai's group employed an intermolecular cycloaddition to construct the [3.2.1]-bicyclo skeleton.

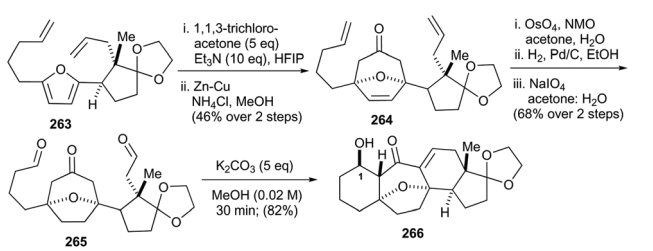
Furan was lithiated with *n*-BuLi and the resulting species was added to 5-bromo-1-pentene to obtain the known intermediate **259**.[59] Now, the C5-proton of the furan ring was lithiated and the resulting anion was quenched with the enone **260** followed by acidic hydrolysis to obtain compound **261** in 85% yield over 2 steps. The enone **261** was first reduced under Birch conditions followed by generation of the thermodynamic enolate and stereoselective allylation gave the ketone **262** with the desired quarternary center. Protection of the ketone was done with ethylene glycol in 86% yield (Scheme 45).

With the key intermediate **263** in hand, the key intermolecular [4 + 3]-cycloaddition was pursued and after detailed optimization, the best possible results were observed when 1,1,3-trichloroacetone (5 eq.) and triethylamine (10 eq.) in HFIP were used followed by reductive dihalogenation using Zn–Cu couple. Although accompanied by an almost equal proportion of the undesired diastereomer (β-oxo bridge), the required isomer was obtained in 46% yield over 2 steps. The terminal olefins were dihydroxylated, the internal olefin was hydrogenated and finally the 1,2-diol systems were cleaved under oxidative conditions to obtain the keto-dialdehyde **265**.

Careful optimization of the reaction time, solvent, substrate concentration and the base led to the formation of the pentacyclic product **266** in 82% yield by treatment with K_2CO_3 in MeOH while maintaining a substrate concentration of 0.02 M to prevent *in situ* elimination of the C1 hydroxyl group. The structure of **266** was unambiguously proved through X-ray studies later (Scheme 46). This completed a well-directed synthesis of the core structure of the cortistatin family in 11 steps from furan and had every scope of being extrapolated to a total synthesis in future.[58]

4.7. Kobayashi's approach towards the core structure[60]

After isolation of all the congeners of the cortistatin family, Kobayashi's group reported an approach towards the construction of the CD-ring system of cortistatins, by employing a 1,3-chirality transfer and a late stage Michael addition/double



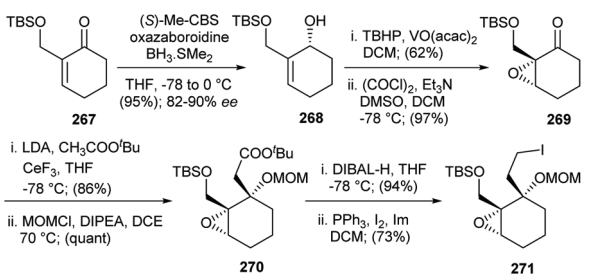
Scheme 46 Zhai's [4 + 3]-cycloaddition.

cyclisation as the key steps.[61] Later, they also reported a stereoselective synthesis of the core structure of cortistatin A with an intramolecular Heck reaction as the key step.[60]

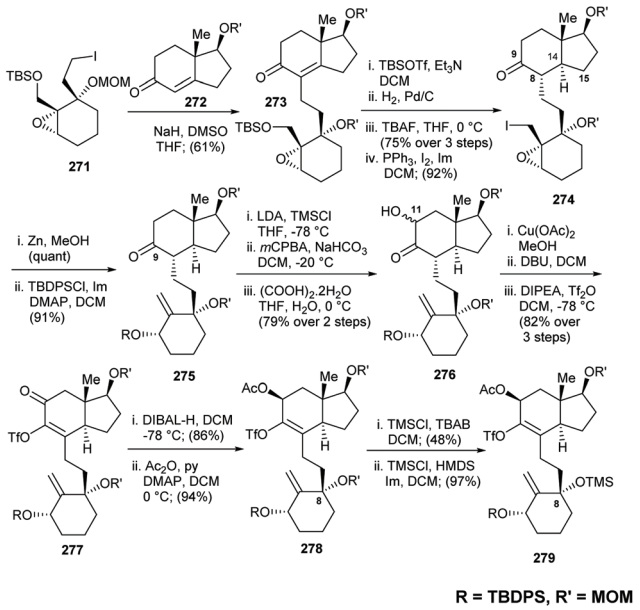
The A-ring fragment was synthesized from the known enone **267**, derived from 2-cyclohexenone. CBS reduction of the ketone afforded the allylic alcohol **268** with up to 90% *ee* (as confirmed from the corresponding (+) and (−)-MTPA esters). Subsequent Vanadium mediated epoxidation followed by Swern oxidation produced the chiral epoxy ketone **269**. *t*-BuOAc was lithiated with LDA and the resulting enolate was added on to the epoxy ketone **269** in the presence of CeF_3. The resulting tertiary alcohol was protected as a MOM ether **270**. Reduction of the ester **270** and the resultant alcohol was converted into the corresponding iodo-compound **271** with 73% yield (Scheme 47).

The DE-ring fragment **272**, derived from Hajos–Parrish ketone, was treated with NaH, followed by addition to the iodo compound **271** furnished the adduct **273** in 61% yield. Generation of the thermodynamic dienol–TBS ether was followed by diastereoselective reduction of the C14–C15 olefin. The TBS enol ether along with the primary TBS ether were removed with TBAF and the resulting primary alcohol was converted to the iodide **274** in 92% yield. Treatment with Zn dust in MeOH resulted in the reductive opening of the epoxide to generate the exocyclic olefin, while the resulting secondary alcohol was protected as a TBDPS ether. The C9–ketone was hydroxylated at its α-position using Rubottom oxidation to obtain the mixture of C11-epimers **276**. Formation of 1,2-diketone using $Cu(OAc)_2$, followed by enol triflate generation produced the compound **277**. The C11–ketone was diastereoselectively reduced and acylated to obtain the precursor for Heck coupling **278**. Finally to investigate the steric effects of substituents on the tertiary alcohol, the C8–TMS ether **279** was also synthesized through a 2-step protocol (Scheme 48).

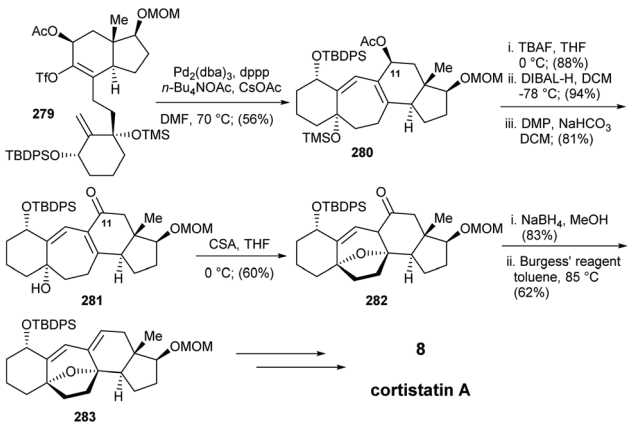
With the two coupling precursors **278** and **279** in hand, the key Heck coupling reaction was attempted. After thorough screening of several reaction conditions, it was observed that the addition of tetra-*n*-butylammonium acetate resulted in the formation of the desired 7-*endo*-cyclisation product exclusively **280** in 56% yield. With the tetracyclic framework in hand, the next objective was to accomplish the cyclic etherification to complete the C-ring formation. Selective removal of TMS followed by reduction of the C11–acetate and subsequent oxidation furnished the C11–ketone **281**, The key oxa-Michael addition of **281** was not successful with bases like K_2CO_3 and Et_3N and finally, CSA in THF provided the pentacyclic intermediate **282** in 60% yield. Reduction of the C11–ketone followed by dehydration using Burgess' reagent produced the pentacyclic core structure of cortistatin A (Scheme 49).[60]



Scheme 47 Kobayashi's synthesis of the A-ring fragment.



Scheme 48 Synthesis of the Heck coupling precursor.



Scheme 49 Kobayashi's synthesis of the pentacyclic skeleton.

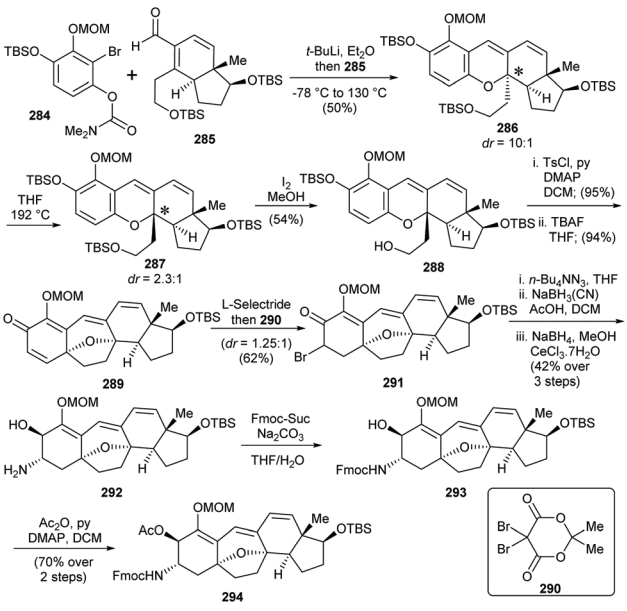
4.8. Danishefsky's 2nd generation approach towards cortistatin A[62]

In continuation of their earlier strategy based on a Snieckus type cascade cyclisation to achieve the pentacyclic core structure (as described in Scheme 36), Danishefsky and co-workers forged the two required fragments **284** and **285** in the presence of *t*-BuLi. Lithium halogen exchange of **284** followed by addition of the lithiated species on to the aldehyde **285** was followed by the cascade cyclisation at elevated temperatures to obtain the complex tetracyclic framework of cortistatins in

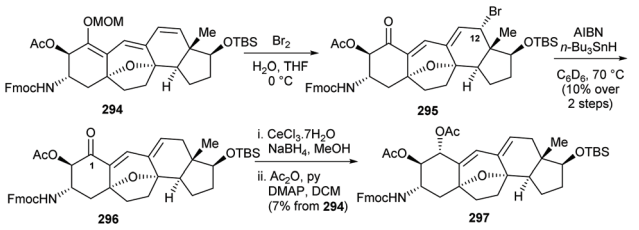
50% yield. The C8 center formed a 10 : 1 (α-side chain major) diastereomeric mixture **286** under the cascade reaction conditions, which could be inverted *via* reversible electrocyclisation to a 2.3 : 1 ratio (β-side chain major) of the thermodynamically stable product **287** by heating at above 190 °C. These inseparable diastereomers were subjected to iodine mediated selective desilylation of the primary TBS ether to obtain the respective primary alcohols, which could be separate at this stage. The desired alcohol was then tosylated and subsequent treatment with TBAF accomplished the desired alkylative dearomatization with 94% yield.

With the pentacyclic core structure in hand, the stage was set for incorporating the A-ring functionalities. Among these, the C1, C2 and C3 functionalities (OH, OH and NMe_2 respectively) all occupied equatorial position on the 6-membered ring. So it was postulated that each of these could be obtained from reduction of ketones or imines. To this end, the enone **289** was treated with L-Selectride followed by addition of the electrophilic brominating agent **290**. This afforded the C3–bromo intermediate, which was displaced with tetra-*n*-butylammonium azide and the resulting enamine was then stereoselectively reduced with $Na(CN)BH_3$ to obtain the free amine. The air sensitive α-aminoketone was immediately reduced under Luche conditions to obtain the C2–alcohol **292**, also in diastereoselective manner. The amine was then protected in the form of an Fmoc–carbamate **293** while the C2–alcohol was functionalized as the corresponding acetate **294** (Scheme 50).

Removal of MOM under standard conditions was not successful due to the labile trienone system. In this regard, it was envisaged that if a suitable electrophile could attack the C12-terminus of the trienone unit, then the MOM deprotection could be facilitated. With this idea in mind, the compound **294** was treated with Br_2 and the resulting C12–Br species was



Scheme 50 Danishefsky's functionalization of the A-ring.



Scheme 51 Danishefsky's attempted formal synthesis.

debrominated using AIBN and *n*-Bu_3SnH to obtain the required dienone **296**, but with a very low yield of only 10% over the last 2 steps. The C1–ketone was reduced under Luche conditions and the resulting alcohol was converted to the corresponding acetate **297** (Scheme 51). Subsequent Fmoc removal followed by reductive methylation would have generated Shair's intermediate **65**, which could have completed the formal total synthesis of cortistatin A. But unfortunately at this stage, very scarce quantities of material were left over and the synthesis had to be abandoned.[62]

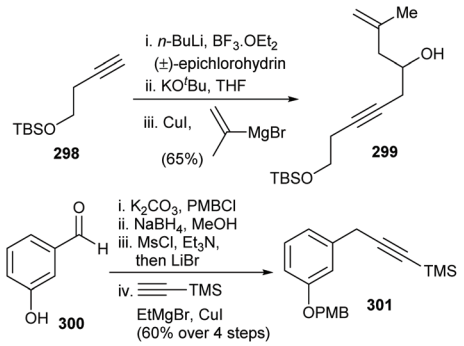
While the Snieckus-type cascade protocol worked quite well to kick-start the synthetic strategy and the A-ring functionalizations were achieved successfully, Danishefsky's attempt towards the formal total synthesis of cortistatin A ended a few steps short due to the low yields obtained in few of the late stage reactions.

4.9. Micalizio's approach[63]

In 2016, Micalizio's group reported their efforts towards the construction of the pentacyclic framework of cortistatins. Their synthetic route was based on the central idea of a metallacycle-based annulative cross coupling to generate most of the molecular complexity in a single step.

To this end, the coupling partners for this key step were sought to be the hydroxy enyne **299** and the alkyne **301**. To this end, the TBS protected homopropargylic alcohol **298** was lithiated and treated with racemic epichlorohydrin in the presence of $BF_3{\cdot}OEt_2$ to obtain the corresponding chlorohydrins. This was then treated with KO^tBu to form an intermediate epoxide, which was finally opened with isopropenyl magnesium bromide to obtain the enyne **299** with 65% yield over the 3 steps. For the alkyne partner, commercially available 3-hydroxybenzaldehyde was subjected to PMB protection, followed by reduction of the aldehyde, conversion of the resulting benzylic alcohol to the corresponding mesylate and finally substitution with TMS–acetylide. This 4-step sequence was carried out with an overall yield of 60% (Scheme 52).

With both the desired coupling partners ready, the key annulative cyclisation was attempted. The alkyne **301** was treated with $Ti(O^iPr)_4$ and *n*-BuLi, warmed to 50 °C and this was followed by the addition of the Li–alkoxide of enyne **299** to trigger the hydroxy-directed alkyne–alkyne coupling to form the metalla-cyclopentadiene intermediate **302**.[64] This was followed by stereoselective intramolecular [4 + 2]-cycloaddition followed by chelotropic extrusion of Ti to obtain the hydrin-



Scheme 52 Synthesis of coupling partners.

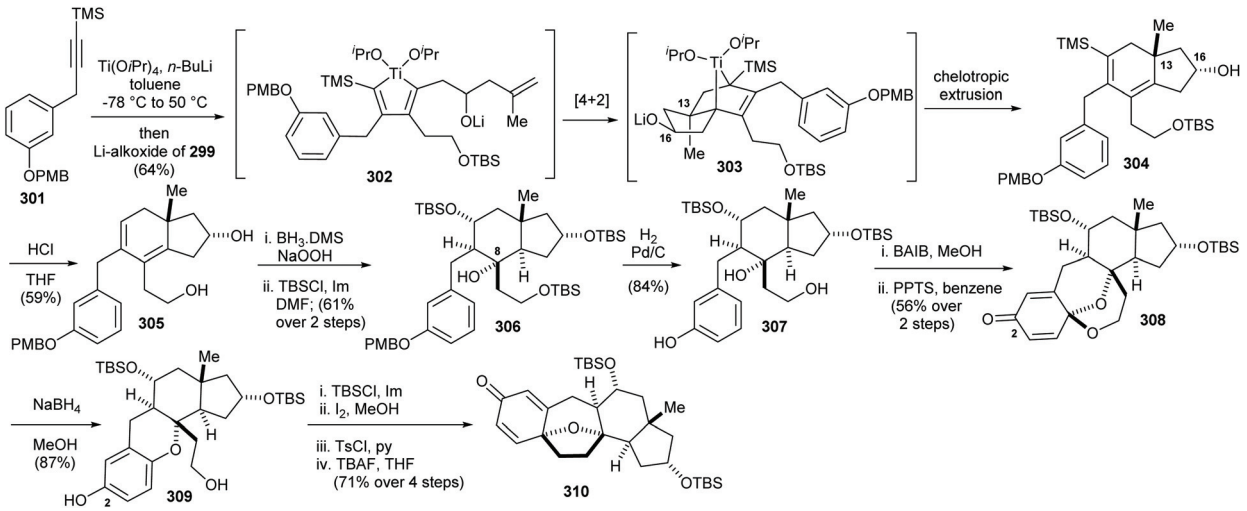
dane **304** with 64% yield. This key annulation was achieved with excellent regio- and stereoselectivity to establish the C13 quarternary centre *anti* to the C16 alcohol. It is striking that this racemic synthesis could easily be extrapolated to an enantiospecific version, by starting with optically pure epichlorohydrin in the synthesis of the enyne **299**.

Global desilylation was achieved by treatment with HCl in THF to obtain the diene **305**. Hydroboration of the diene system proceeded with excellent regio- and stereoselectivity to afford the dihydroxylated intermediate, which was converted to the tri-TBS ether **306** with 61% yield over the 2-step sequence. This hydroboration sequence helped to incorporate the desired *trans*-ring junction at the DE-ring fusion and also established the correct stereochemistry of the C8-tertiary alcohol. The PMB group was cleaved *via* hydrogenolysis, which also resulted in cleavage of the primary TBS ether to provide 84% of the trihyrdoxy compound **307**. Phenolic oxidation using BAIB, followed by treatment with PPTS in refluxing benzene furnished the bicyclic acetal with an overall yield of 56%.

In order to convert this bicyclic acetal to the desired pentacyclic cortistatin scaffold, the C2–ketone was reduced with $NaBH_4$, which gave a pair of intermediate diastereomeric allylic alcohols. This mixture was transformed into the desired phenolic ether **309** during purification with 87% yield. Finally the compound **309** was advanced to the cortistatin skeleton using a simple 4-step sequence. Both free hydroxyl groups were protected as TBS ethers followed by selective removal of the primary TBS ether. The free primary alcohol was then tosylated followed by selective removal of the phenolic TBS ether over the secondary TBS ether to achieve the alkylative cyclisation and complete the formation of the C-ring, in a way similar to Danishefsky's route (Scheme 53).[50a] The synthetic efforts of Micalizio's group focused on the assembly of a highly functionalized *trans*-fused hyrdindane nucleus in a regio- and stereoselective manner. The use of a Ti-mediated annulative alkyne–alkyne cross coupling strategy was showcased with remarkable regio- and stereocontrol and this may create yet another new entry towards such polycyclic scaffolds with high degree of selectivity. Additionally, the robust nature of the starting materials used leaves a viable scope for extrapolation towards an enantiospecific synthesis of the same.

4.10. Kaliappan's approaches[65]

Despite the numerous synthetic routes described so far, the scope for developing a robust, divergent synthetic strategy towards the cortistatin family and indeed towards its analogues was still worth pursuing. Inspired by the increasing diversity of the above-mentioned approaches and driven on by the long-standing interest of our group in the synthesis of natural products and natural product like molecules,[66] our group also designed a possible route for construction of this unique class of steroidal alkaloids. Like most other groups earlier, it was realized that construction of the pentacyclic core structure would provide an entry towards multiple members of the family and indeed provide a pathway towards other analogues. Incorporation of the key isoquinoline moiety on the

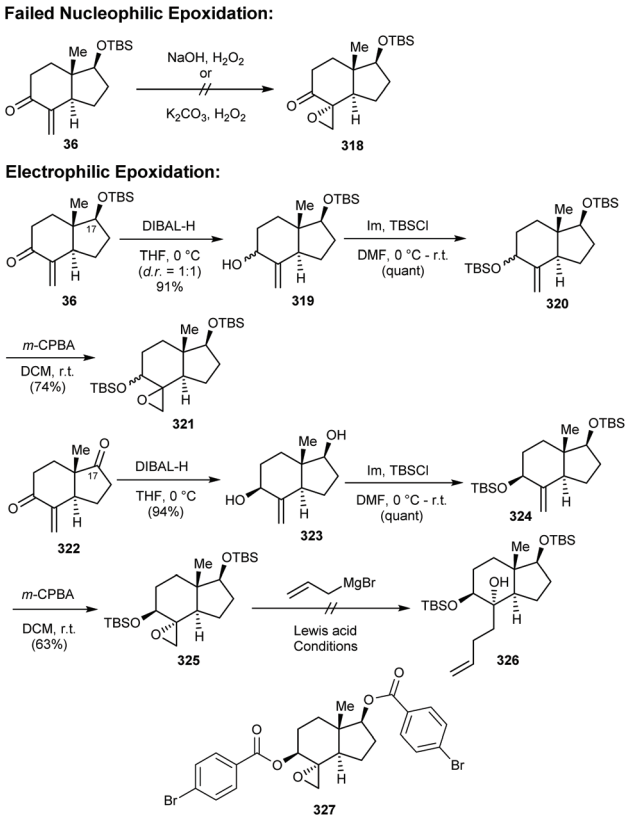


Scheme 53 Micalizio's synthesis of the pentacyclic core structure of cortistatins.

E-ring was planned through a late stage coupling with 7-bromoisoquinoline.

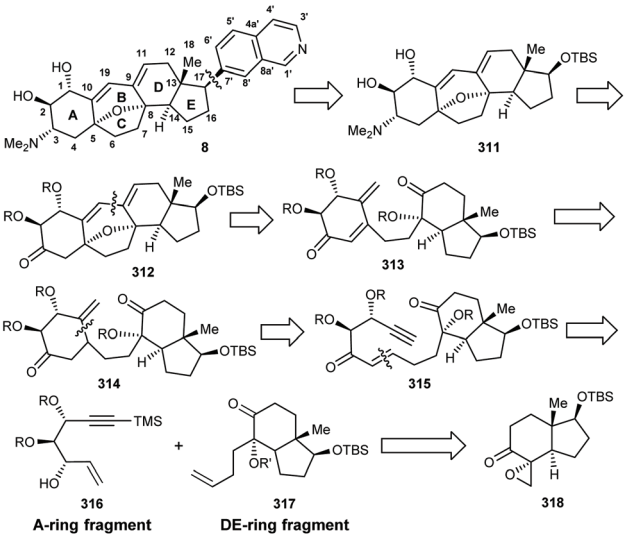
Contrary to any of the earlier methods, the B-ring could be forged through an intramolecular Heck coupling between the exocyclic double bond in **313** and the corresponding enol triflate, derived from the ketone present on the D-ring. The C8 tertiary alcohol could be utilized for an oxa-Michael addition on to the enone in the A-ring to construct the tetrahydrofuran C-ring. The key step of the route was fashioned to be an intramolecular radical cyclisation of the terminal alkyne **315** in conjugate fashion with the enone, followed by oxidation to generate back the C4–C5 double bond in compound **313**. The alkyne **315** could be generated from a cross metathesis of the olefin fragments **316** and **317**, derived from D-glucose and Hajos–Parrish ketone respectively. The bulky TMS protection on the terminal alkyne was designed to prevent any interference from its part during the key cross metathesis. Finally, the epoxide **318** could be allylated to generate the alkene **317** (Scheme 54).

To this end, the exocyclic enone **36** was prepared starting from Hajos–Parrish ketone, which would serve as the DE-ring fragment for our synthesis. But to our disappointment, nucleophilic epoxidation conditions remained unsuccessful and we had to switch to electrophilic epoxidation on the allylic TBS ether **320**, which was obtained upon reduction of the enone with DIBAL-H followed by TBS protection of the resulting secondary alcohol. This di-TBS ether was epoxidised using *m*-CPBA to obtain the diastereomeric mixture of epoxides **321** (Scheme 55). In order to overcome the lack of diastereoselectivity during epoxide formation, the known diketone **322** was also prepared[67] and to our pleasant surprise, global reduction of the diketone **322** with DIBAL-H yielded a single diastereomer of the diol **323** in good yield. After conversion to the corresponding di-TBS ether, the double bond was epoxidised to obtain a single diastereomer of the epoxide **325** in 63% yield (Scheme 55). To confirm the epoxide stereochemistry, global TBS deprotection was carried out and the bis (4-bromobenzoyl) ester **327** of the resulting diol was crystallized and studied by single crystal XRD. Pleasingly, the epoxide stereochemistry was observed to be the desired one, which paves a new way for future access towards the CDE ring system of cortistatins with the correct stereochemistry. However, to our disappointment, all efforts aimed towards opening of the epoxide were met with failed results as the epoxide proved to be surprisingly reluctant towards opening. A closer look at the crystal structure of the diester **327** suggested that the angular methyl group clearly hinders any nucleophilic attack on the "backside" of the target C–O bond of the epoxide and this was a major contributing factor for this observation (Scheme 55).

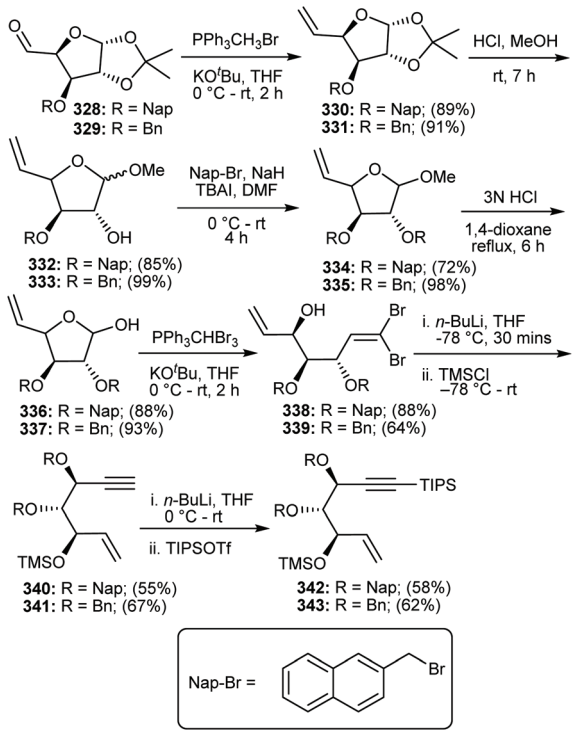


Scheme 55 Diastereoselective epoxidation of enone.

For the synthesis of the enyne fragment, we started with the D-glucose derived aldehyde **328**, which was generated from D-glucose diacetonide over a 3-step sequence. Wittig homologation of the aldehyde was followed by acidic hydrolysis of the secondary acetonide to afford the anomeric mixture of methylated lactols **332** in good yield. The newly generated free secondary alcohol was subsequently protected as the (2-naphthyl) methyl ether in compound **334**. The methylated lactol in **334** was hydrolyzed using HCl in dioxane and the free lactol **336** was then homologated using Ramirez's salt[68] to obtain the dibromoalkene **338** with 63% yield. Treatment with *n*-BuLi and subsequent quenching of the reaction with excess TMSCl pro-



Scheme 54 Radical cyclisation strategy towards cortistatin A.

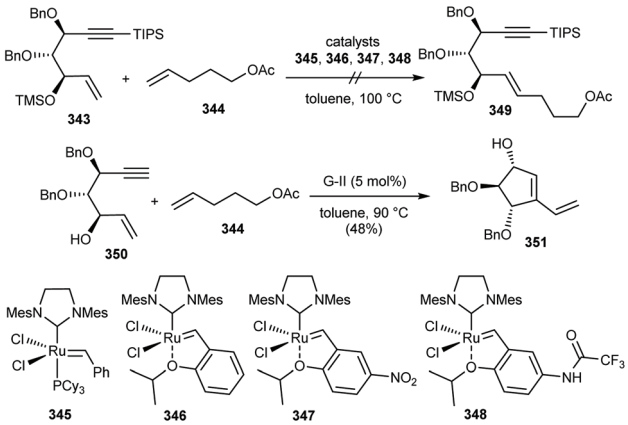


Scheme 56 Synthesis of D-glucose derived A-ring fragment.

vided the TMS ether **340**, with the free terminal alkyne. Deprotonation of the terminal alkyne was carried out with *n*-BuLi and the resulting acetylide was quenched with TIPSOTf to obtain the enyne **342** in 58% yield (Scheme 56).

The free alcohols in the sugar moiety were protected as (2-naphthyl)methyl ethers (or benzyl ethers for practicability of scale-up purposes), because they could be removed as a late stage in the presence of other functional groups present in the molecule. It is important to note that the enyne fragments **342** and **343** are actually enantiomeric to the enyne **316** and would end up affording a diastereomer of the natural product, with respect to the stereocenters on the A-ring. However, this would provide a valuable opportunity to study the feasibility of our synthetic plan, with a gateway to novel analogues of cortistatins, which is always a welcome prospect.

Having the enyne fragments (**342** and **343**) in hand, our attention shifted to a model study of the key cross metathesis step. To this end, 4-pentenyl acetate (**344**) and the enyne **343** were exposed to a number of Ru-based metathesis catalysts, but to our disappointment, even at high temperatures and prolonged reaction times afforded only the self metathesis product of 4-pentenyl acetate was obtained, with no trace of our desired compound **349**. This model substrate **349**, if formed, could be used for the radical cyclization as planned, followed by the intramolecular oxa-Michael addition in order to synthesize the A–C spiro ring junction. It was postulated that the allylic TMS ether might have been hindering the coordination of the Ru-catalysts on to the double bond and to address this issue, selective TMS removal was attempted. But

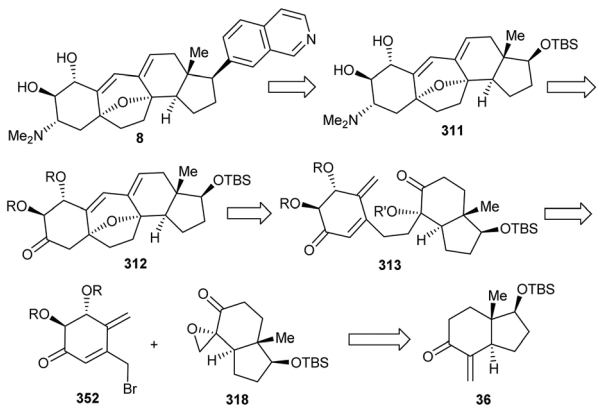


Scheme 57 Attempted cross metathesis model study.

unfortunately the alkyne–TIPS linkage proved to be too labile, and selective TMS removal has remained unsuccessful. Predictably when **350** was treated with 4-pentenyl acetate, any chance of a cross metathesis was overruled by a highly facile intramolecular enyne metathesis to generate the diene **351** (Scheme 57).[69]

In an independent and alternative cross enyne metathesis strategy towards the assembly of the same core structure **311**, the key intermediate would once again be the ketone **313**, which is in perfect orientation for intramolecular Heck coupling with a suitable derivative of the exocyclic double bond on the A-ring. The C-ring formation was once again planned through a conjugate oxa-Michael addition with the C8 tertiary alcohol. The key step of this route would be opening of the epoxide **318** (derived from the earlier strategy) with a suitable organometallic reagent of the allylic bromide **352**, which could be made from D-glucose (Scheme 58).

Our synthetic journey towards this alternate scheme began with the D-glucose derived aldehyde **353**, which was treated with Ohira–Bestmann reagent (**354**) to obtain the terminal alkyne **355**. Following this route, the C1*, C2* and C3* stereocenters of the glucose moiety would appear as the C1, C2 and

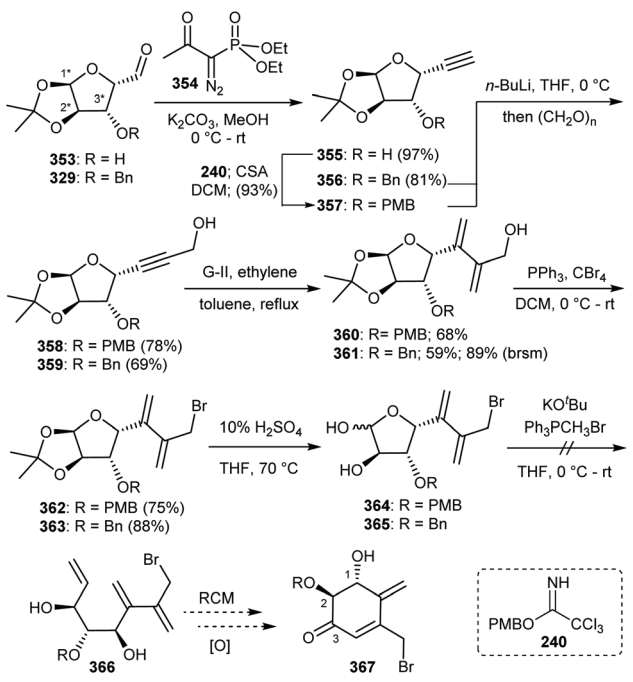


Scheme 58 Our cross enyne metathesis based approach.

C3 centers of the A-ring of cortistatin A (**8**) respectively. Treatment of the alcohol **355** with PMB-trichloroacetimidate (**240**) under mild acidic conditions afforded very good conversion to the corresponding PMB ether **357**. The terminal alkyne was lithiated and quenched with paraformaldehyde to obtain the propargylic alcohol **358**. Cross enyne metathesis with ethylene afforded the diene **360** following which the allylic alcohol was substituted with the bromide **362** in good yield. Acidic hydrolysis of the secondary acetonide **362** led to very poor conversion, or in some cases, deprotection of the PMB ether. Unavoidable deprotection of the PMB group led to the belief that PMB was probably not the right choice for protecting these two alcohols and a similar route using benzyl protection was carried out later. Subjecting the crude mixture of lactols **364** for Wittig reaction was unsuccessful and led to complete decomposition of the starting material. Further work is underway in order to convert this bromo intermediate into the A-ring derivative (Scheme 59).

Unable to hydrolyze the secondary acetonide, the feasibility of epoxide opening with allylic bromide **362** was also investigated. The allylic bromide **362** could serve as an appropriate model for the bromide **367**, which would have the A-ring appropriately designed. But even after employing a range of organometallic reagents derived from the allyl bromide **362**, the epoxide **318** proved to be extremely inert.

Finally, as per our retrosynthetic analysis, the isoquinoline moiety which is a unique functionality on the E-ring of many congeners of the cortistatin family, was sought to be introduced through a coupling reaction. To this end, 7-bromoisoquinoline was prepared by following Baran's 5-step protocol starting from tetrahydroisoquinoline.[21b]



Scheme 59 Attempted synthesis of the alternative A-ring precursor.

With the three major fragments in hand, efforts are underway in our laboratory to forge the three fragments together and build towards the pentacyclic core structure of cortistatins and extrapolate the same to newer and simpler steroidal analogues, which have formed the crux of recent biological studies dealing with inhibition of HUVECs and CDK8.[19b]

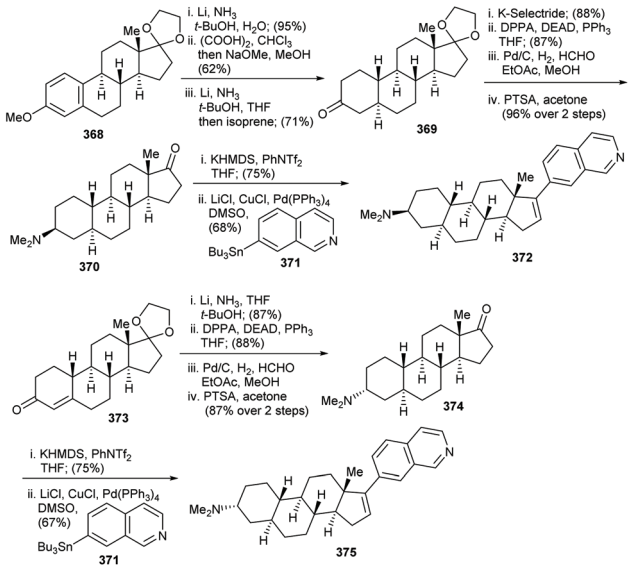
5. Syntheses of cortistatin analogues

5.1. Corey's approach towards cortistatin analogues and related biological studies[70]

Following the series of innovative efforts towards the total synthesis of cortistatin family members and related SAR studies, it was soon evident that the biological activities of cortistatins could be attributed to certain structural features of these steroidal alkaloids. In 2008 Kiyota had reported that the estrone–isoquinoline hybrid (EI-Hybrid A) was a promising candidate for anti-angiogenesis, due to its inhibitory activities against proliferation and migration of endothelial HUVEC cells.[71]

In 2009, Corey's group laid down the following conclusions based on the earlier reported biological assays of all cortistatin family members: (a) the C3–dimethylamino group and the C17–isoquinoline moiety play vital roles, as they are present in the more active family members (cortistatins A and J); (b) despite the absence of the C1 and C2 hydroxyl groups, cortistatin J showed strong activity, thereby indicating that this diol unit was perhaps not essential; (c) the significant reduction in activity shown by cortistatins B and D proved that substitutions at the C16 and C17 centres were not tolerated; (d) replacement of the isoquinoline fragment with other heterocycles reduces the activities significantly. The need for diversity based analogue synthesis on the above mentioned fundamental observations led Corey and his group to design some pertinent analogues of similar structures and study the relevant properties of the same.[70b] They focused on maintaining a similar distance between the all-important dimethylamino group and the isoquinoline moiety, which made steroidal structures the easiest to explore. Steroidal backbones are highly practical for therapeutic purposes, because of the ease of their availability and synthesis.

In this regard, Corey's group started from the C17 ketal of 3-*O*-methyl estrone (**368**) and subjected it to Birch reduction, followed by acidic hydrolysis of the resulting enol ether and base mediated isomerization of the final double bond. The intermediate enone was finally reduced with Li/NH_3 once again to obtain the ketone **369** in 71% yield. Reductive amination of the C3–ketone yielded a diastereomeric mixture of the dimethylamine **370** with poor selectivity, so a 4-step sequence had to be pursued for the introduction of the 3-NMe_2 group. The ketone was diastereoselectively reduced with K-Selectride followed by inversion to the corresponding azide. The azide was reduced and methylated to obtain the desired dimethylamino group and finally the C17 ketal was hydrolyzed with PTSA to obtain the compound **370** with 96% yield over the final 2 steps. The newly obtained C17 ketone was converted to



Scheme 60 Corey's synthesis of steroidal analogues **372** and **375**.

the enol triflate, which was coupled with 7-tributylstannyl isoquinoline to obtain the analogue **372** (Scheme 60).

The other diastereomer with the opposite configuration of the dimethylamino group was also sought for studies and for this purpose, the enone **373** was reduced with Li/NH_3 to obtain the thermodynamically favoured C3-β-alcohol, which was inverted to the corresponding azide. The azide was reduced, methylated and finally the C17–ketal was hydrolyzed to obtain the compound **374**. The newly obtained C17–ketone was converted to the corresponding enol triflate, which was then coupled with 7-tributylstannyl isoquinoline to obtain the analogue **375** (Scheme 60).

Detailed biological evaluation showed that compound **372** was more active than **375** and hence all further analogues were synthesized with the 3-β-series of dimethylamino derivatives. Intermediate **370** allowed the introduction of various groups at the C17 position, which resulted in the synthesis of compounds **376–379**. The 19-norsteroid derivatives were also made in the form of compounds **380**, while the 3-β-dimethylamino group was replaced with 3-β-pyrolidino (**381**) or 3-β-morpholino (**382**) groups for further diversity (Fig. 3).

These compounds were found to inhibit angiogenic effects of VEFG and some members also inhibited cell sensitivity to multiple angiogenic factors. Comparative studies of the synthetic compounds **379A**, **379C** and **379D** with the published data for cortistatin A proved that these 3 compounds inhibited the VEFG-induced cell migration of HUVECs more strongly than cortistatin A. **379A** proved to be the most active analogue, with very efficient anti-angiogenic activity at very low nanomolar concentrations in *in vitro* assays. Apart from this, locally administered picomolar quantities of compound **379A** inhibited retinal vessel formation in P6 mice, a recognized animal model for ocular wet macular degeneration. This indicated that such compounds could be utilized at very low concentrations, in the treatment of ocular wet macular degeneration, which is a major cause for blindness. These results were quite significant, as these analogues were much easier to obtain than the natural product itself and a few of them proved to be more potent in their biological activities.

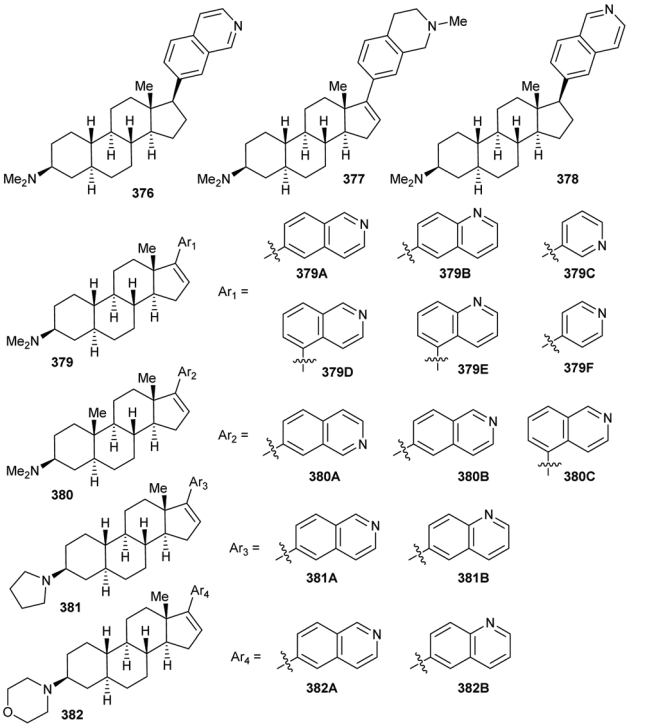


Fig. 3 Analogues made by Corey for SAR studies.

5.2. Kobayashi's synthesis of cortistatin analogues[72–74]

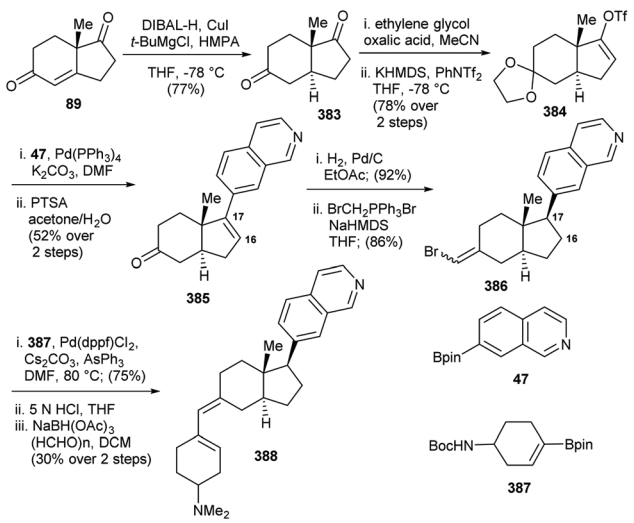
After reporting their own their Heck coupling based strategy towards designing the core structure of cortistatins, Kobayashi and co-workers set about synthesizing other simplified analogues of this class of steroidal alkaloids. The architectural designs of these analogues were based on the conclusions drawn from structure–activity relationship studies carried out earlier on the full family of cortistatins. Based on the structures elucidated by X-ray studies, two analogues were designed, having an anthracene-like planar ABC-ring system. The CD-ring system would possess the all-important isoquinoline moiety, while the A-ring having a dimethylamino group was connected through a single sp^2-carbon linker. This was done to keep the relative positions of the isoquinoline fragment and the NMe_2 group in correct order.

The synthesis of the analogue **388** commenced with the diastereoselective conjugate addition of Hajos–Parrish ketone using *t*-BuMgCl, DIBAL-H and CuI to generate the *trans*-hydrindanedione **383** according to literature protocols. This was followed by protection of the less hindered ketone as a cyclic ketal, followed by conversion of the other ketone into the corresponding enol triflate **384**. Suzuki–Miyaura coupling

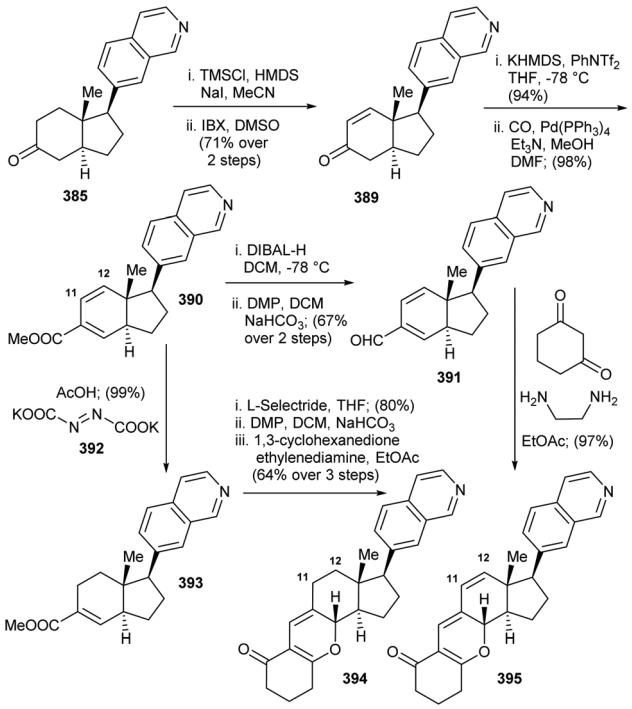
was employed by using the isoqinolinyl pinacol boronate **47** to functionalize the enol triflate. Then the 6-membered ketal was hydrolyzed and the C16–C17 double bond was hydrogenated stereoselectively with 92% yield. This was followed by Wittig olefination using (bromomethyl)triphenylphosphonium bromide to obtain the vinyl bromide **386** as a 1 : 1 mixture of *E* : *Z* isomers. Finally the A-ring fragment was forged through a Suzuki–Miyaura coupling with the boronic acid **387** to obtain a 1 : 1 mixture of the two isomeric target analogues, which were separated through reverse-phase HPLC (Scheme 61).

The intermediate **385** was further treated with HMDS, NaI and TMSCl to generate the kinetic enolate, which was oxidised using IBX to obtain the enone **389** with 71% yield over 2 steps. Generation of the dienolate was followed by Pd-catalyzed carboxymethylation to obtain the methyl ester **390**. The ester was converted to the aldehyde **391**, followed by treatment with 1,3-cyclohexanedione in the presence of ethylene diamine to undergo Knoevenagel condensation followed by concomitant electrocyclisation to obtain the desired tetracyclic analogue **395** (Scheme 62). The intermediate ester **390** was also made to undergo selective diimide reduction of the disubstituted C11–C12 olefin to obtain the conjugated ester **393**. A further 3-step protocol, ending with a similar type of Knovenagel condensation as above provided the 11,12-dihydro analogue **394** (Scheme 62).

When studied for their anti-proliferative activities against HUVEC, the 11,12-dehydro analogue **394** proved to be comparable in activity as compared to cortistatin A with IC_{50} value of 0.035 μM and a very high selectivity (>100-fold) over KB3-1 cells (IC_{50} = 10.5 μM each). This proved the hypothesis that the tetracyclic core of these steroidal alkaloids was essential for their potent biological activities. Evaluation of *in vivo* activity of analogue **394** on the formation of new blood vessels by matrigel plug assay,[75] indicated that analogue **394** also inhibited *in vivo* angiogenesis. In addition to these properties, this simplified analogue also exhibited anti-tumor activities resulting in a weight reduction of ~90% of tumors.[72]

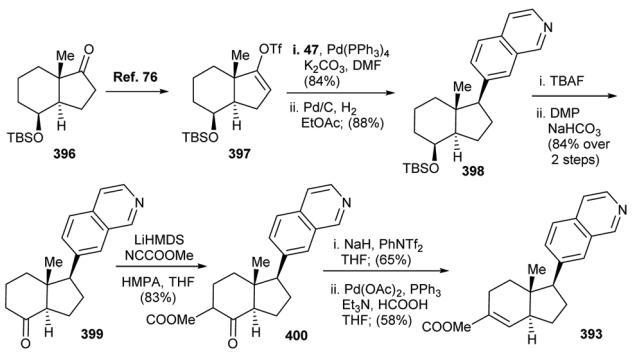


Scheme 61 Kobayashi's synthesis of cortistatin analogue **388**.



Scheme 62 Kobayashi's synthesis of analogues **394** and **395**.

In a subsequent report in 2013, Kobayashi's group reported a synthesis of the same analogue **393** starting from a vitamin-D_2 degradation product (**396**). The C17 ketone was converted to the corresponding enol triflate,[76] followed by coupling of the same with isoqinolinyl pinacol boronate (**47**) and subsequent hydrogenation of the C16–C17 olefin to obtain the intermediate **398**. The TBS ether was cleaved and the resulting secondary alcohol was oxidised to obtain the ketone **399**. Generation of the enolate using LiHMDS was followed by quenching of the same using Mander's reagent to obtain the β-ketoester **400**. Finally the ketone was converted to its enol triflate and made to undergo Pd-catalyzed reduction to obtain the ester **393** with an overall yield of 19% from the known enol triflate **397** over 7 steps (Scheme 63). This ester could be con-



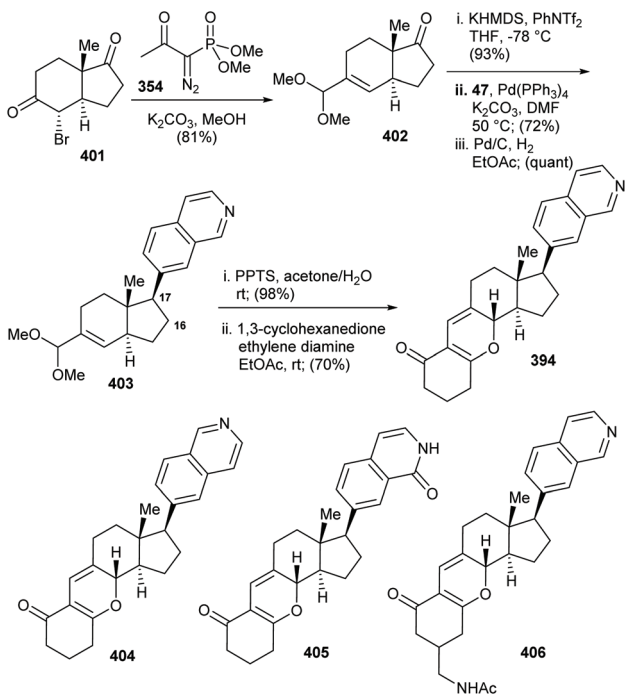
Scheme 63 Kobayashi's synthesis of precursor of analogue **393** from vitamin D_2 degradation product **396**.

verted to the desired cortistatin analogue **394** by employing the same 3-step protocol as mentioned in the previous report.[72] No isomerization to the thermodynamically stable *cis*-fused hydrindane was observed over the course of this route and this was an obvious advantage of this second generation strategy over the earlier one.[73]

In order to further stem down the number of steps by reducing the iterative oxidation–reduction sequences, Kobayashi's group developed yet another route to the potent cortistatin analogue **394**. To this end, the bromo compound **401**, which could be prepared from Hajos–Parrish ketone in bulk scales, was treated with Ohira–Bestmann reagent (**354**) in the presence of K_2CO_3 and methanol to provide the dimethyl acetal **402** in 81% yield.

This was a serendipitous result, which afforded the desired transformation around the ketone in a single step. The five-membered ring ketone was then converted to the corresponding enol triflate, coupled using isoqinolinyl pinacol boronate (**47**) and finally the C16–C17 double bond was hydrogenated as before to obtain the intermediate **403**. The dimethyl acetal was hydrolyzed and the resulting aldehyde was condensed with 1,3-cyclohexanedione to obtain the tetracyclic scaffold **394** (Scheme 64).

Contrary to the earlier routes, this strategy introduces the isoquinoline fragment at a late stage, which helps in diversification. This was used to synthesize three other analogues (**404**, **405** and **406**) of the same tetracyclic framework, by coupling other heterocyclic fragments (Scheme 64). The novel compound **406** with an acetamide side chain on the A-ring showed very promising anti-angiogenesis activity.[74] Since their isolation of this group of highly complex steroidal alkaloids, Kobayashi's research group have thoroughly studied the intricacies of this unique steroidal alkaloid backbone and paved the way for the synthesis of a large variety of biologically potent analogues of this family.[77]



Scheme 64 Kobayashi's third generation synthesis of analogues **394** and **404–406**.

6. Conclusions

In summary, the cortistatins form a unique class of steroidal alkaloids having immense potential as anti-angiogenic agents. Ever since their isolation in 2006, a multitude of synthetic efforts have been devoted towards the construction of various members of this family of natural products. Not only have the molecules been synthesized to various degrees of complexity by different groups, but there has also been a thorough screening of their biological activities. Novel analogues based on previously established structure–activity relationships have been designed and synthesized, often showcasing remarkable potency comparable even to the most illustrious member of the family: cortistatin A. Given that the cortistatins are a very young family of natural products in terms of their isolation dates, it is really amazing to note the deep level of understanding that has already been mustered about even the smallest structural fragments of the molecule and how each of them contributes toward their significant properties.

This review was an attempt to put together as much of an exhaustive compilation as possible of the various synthetic approaches designed and developed since the isolation of the cortistatin family. Focus has been laid to illuminate each and every synthetic strategy employed to construct this unique pentacyclic framework, either in an attempt towards total synthesis, or towards the construction of structurally viable analogues. Given the enormous potential of structural diversity in cortistatins, we hope this review provides a base for future attempts from the scientific community to explore newer strategies to construct analogous compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

K. P. K. thanks SERB (EMR/2017/000578), New Delhi, for the financial support. S. I. thanks CSIR, New Delhi and IIT Bombay for research fellowships.

Notes and references

1 A.-U. Rahman and M. I. Choudhary, *The Alkaloids: Chemistry and Biology*, Elsevier Ltd., 1999, vol. 52, pp. 233–260.

2 (*a*) Q.-W. Jiang, M.-W. Chen, K.-J. Cheng, P.-Z. Yu, X. Wei and Z. Shi, *Med. Res. Rev.*, 2016, **36**, 119–143; (*b*) N. U. Jan, B. Ahmad, S. Ali, A. Adhikari, A. Ali, A. Jahan, A. Ali and H. Ali, *Front. Pharmacol.*, 2017, **8**, 1–13.
3 Y. Nakao and N. Fusetani, *Marine Invertebrates: Sponges*, Elsevier Ltd., 2010, vol. 2, pp. 327–362.
4 C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkateswarlu, R. M. Rosser, D. J. Faulkner, M. H. M. Chen and J. Clardy, *J. Am. Chem. Soc.*, 1984, **106**, 7983–7984.
5 C. B. Rao, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkateswarlu, R. M. Rosser and D. J. Faulkner, *J. Org. Chem.*, 1985, **50**, 3757–3760.
6 A.-U. Rahman, K. A. Alvi, S. A. Abbas, M. I. Choudhary and J. Clardy, *Tetrahedron Lett.*, 1989, **30**, 6825–6828.
7 C. B. Rao, D. V. Rao, V. S. N. Raju, B. W. Sullivan and D. J. Faulkner, *Heterocycles*, 1989, **28**, 103–106.
8 R. M. Rosser and D. J. Faulkner, *J. Org. Chem.*, 1984, **49**, 5157–5160.
9 J. Jurek, P. J. Scheuer and M. Kelly-Borges, *J. Nat. Prod.*, 1985, **50**, 1004–1007.
10 S. Aoki, Y. Watanabe, M. Sanagawa, A. Setiawan, N. Kotoku and M. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 3148–3149.
11 S. Aoki, Y. Watanabe, D. Tanabe, A. Setiawan, M. Arai and M. Kobayashi, *Tetrahedron Lett.*, 2007, **48**, 4485–4488.
12 Y. Watanabe, S. Aoki, D. Tanabe, A. Setiawan and M. Kobayashi, *Tetrahedron*, 2007, **63**, 4074–4079.
13 M. G. Kolonin, P. K. Saha, L. Chan, R. Pasqualini and W. Arap, *Nat. Med.*, 2004, **10**, 625–632.
14 K. S. Moulton, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 4736–4741.
15 (*a*) J. Folkman, *J. Invest. Dermatol.*, 1972, **59**, 40–43; (*b*) X. Zeng, J. Chen, Y. I. Miller, K. Javeherian and K. S. Moulton, *J. Lipid Res.*, 2005, **46**, 1849–1859.
16 J. Folkman, *Harrison's Textbook of Internal Medicine*, McGraw-Hill, New York, 2001.
17 (*a*) J. Folkman, *N. Engl. J. Med.*, 1971, **285**, 1182–1186; (*b*) P. Carmeliet and R. K. Jain, *Nature*, 2000, **407**, 249–257; (*c*) J. Folkman, *Nat. Rev. Drug Discovery*, 2007, **6**, 273–286.
18 (*a*) T. Rzymski, M. Mikula, K. Wiklik and K. Brzozka, *Biochim. Biophys. Acta*, 2015, **1854**, 1617–1629; (*b*) H. E. Pelish, B. B. Liau, I. I. Nitulescu, A. Tangpeerachaikul, Z. C. Poss, D. H. Da Silva, B. T. Caruso, A. Arefolov, O. Fadeyi, A. L. Christie, K. Du, D. Banka, E. V. Schneider, A. Jestel, G. Zou, C. Si, C. C. Ebmeier, R. T. Bronson, A. V. Krivtsov, A. G. Myers, N. E. Kohl, A. L. Kung, S. A. Armstrong, M. E. Lemieux, D. J. Taatjes and M. D. Shair, *Nature*, 2015, **526**, 273–276.
19 (*a*) D. J. Cee, D. Y.-K. Chen, M. R. Lee and K. C. Nicolaou, *Angew. Chem., Int. Ed.*, 2009, **48**, 8952–8957; (*b*) J. M. Hatcher, E. S. Wang, L. Johannessen, N. Kwiatkowski, T. Sim and N. S. Gray, *ACS Med. Chem. Lett.*, 2018, **9**, 540–545.
20 (*a*) C. F. Nising and S. Brase, *Angew. Chem., Int. Ed.*, 2008, **47**, 9389–9391; (*b*) M. Shoji, *J. Synth. Org. Chem., Jpn.*, 2009, **67**, 949–950; (*c*) D. Y. K. Chen and C. C. Tseng, *Org. Biomol. Chem.*, 2010, **8**, 2900–2911; (*d*) A. R. Hardin-Narayan, E. M. Simmons and R. Sarpong, *Eur. J. Org. Chem.*, 2010, 3553–3567.
21 (*a*) R. A. Shenvi, C. A. Guerrero, J. Shi, C.-C. Li and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7241–7243; (*b*) J. Shi, G. Manolikakes, C.-H. Yeh, C. A. Guerrero, R. A. Shenvi, H. Shigehisa and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 8014–8027.
22 J. R. Hanson, *Nat. Prod. Rep.*, 2007, **24**, 1342–1349.
23 C. C. Gonzalez, E. I. Leon, C. Riesco-Fagundo and E. Suarez, *Tetrahedron Lett.*, 2003, **44**, 6347–6350.
24 D. H. R. Barton, R. E. O'Brian and S. J. Sternhell, *J. Chem. Soc.*, 1962, 470–478.
25 (*a*) K. C. Nicolaou, Y.-P. Sun, X.-S. Peng, D. Polet and D. Y.-K. Chen, *Angew. Chem., Int. Ed.*, 2008, **47**, 7310–7313; (*b*) K. C. Nicolaou, X.-S. Peng, Y.-P. Sun, D. Polet, B. Zou, C. S. Lim and D. Y.-K. Chen, *J. Am. Chem. Soc.*, 2009, **131**, 10587–10597.
26 H. M. Lee, C. Nieto-Oberhuber and M. D. Shair, *J. Am. Chem. Soc.*, 2008, **130**, 16864–16866.
27 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.
28 A. N. Flyer, C. Si and A. G. Myers, *Nat. Chem.*, 2010, **2**, 886–892.
29 R. C. A. Isaacs, M. J. Digrandi and S. J. Danishefsky, *J. Org. Chem.*, 1993, **58**, 3938–3941.
30 E. M. Simmons, A. R. Hardin-Narayan, X. Guo and R. Sarpong, *Tetrahedron*, 2010, **66**, 4696–4700.
31 (*a*) S. Yamashita, K. Iso, K. Kitajima, M. Himuro and M. Hirama, *J. Org. Chem.*, 2011, **76**, 2408–2425; (*b*) S. Yamashita and M. Hirama, *J. Synth. Org. Chem., Jpn.*, 2013, **71**, 768–778.
32 S. Yamashita, K. Kitajima, K. Iso and M. Hirama, *Tetrahedron Lett.*, 2009, **50**, 3277–3279.
33 G. A. Molander, M. S. Quirmbach, L. F. Silva Jr., K. C. Spencer and J. Balsells, *Org. Lett.*, 2001, **3**, 2257–2260.
34 S. Yamashita, K. Iso and M. Hirama, *Org. Lett.*, 2008, **10**, 3413–3415.
35 M. G. Nilson and R. L. Funk, *J. Am. Chem. Soc.*, 2011, **133**, 12451–12453.
36 G. A. Molander and N. M. Ellis, *J. Org. Chem.*, 2008, **73**, 6841–6844.
37 G. A. Molander and L. A. Felix, *J. Org. Chem.*, 2005, **70**, 3950–3956.
38 E. M. Simmons, A. R. Hardin, X. Guo and R. Sarpong, *Angew. Chem., Int. Ed.*, 2008, **47**, 6650–6653.
39 L. Fang, Y. Chen, J. Huang, L. Liu, J. Quan, C.-C. Li and Z. Yang, *J. Org. Chem.*, 2011, **76**, 2479–2487.
40 L. Liu, Y. Gao, C. Che, N. Wu, D. Z. Wang, C.-C. Li and Z. Yang, *Chem. Commun.*, 2009, 662–664.
41 S. Boßhammer and H.-J. Gais, *Synthesis*, 1998, 919–927.
42 L. Kuang, L. L. Liu and P. Chiu, *Chem. – Eur. J.*, 2015, **21**, 14287–14291.
43 L. L. Liu and P. Chiu, *Chem. Commun.*, 2011, **47**, 3416–3417.

44 (*a*) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 2521–2522; (*b*) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki and T. Ikariya, *J. Am. Chem. Soc.*, 2011, **133**, 14960–14963.

45 (*a*) J. Fu, Y. Gu, H. Yuan, T. Luo, S. Liu, Y. Lan, J. Gong and Z. Yang, *Nat. Commun.*, 2015, **6**, 8617–8625; (*b*) Y. Gu, H. Yuan, J. Fu, J. Gong and Z. Yang, *Acta Chim. Sin.*, 2017, **75**, 798–807.

46 D. T. Craft and B. W. Gung, *Tetrahedron Lett.*, 2008, **49**, 5931–5934.

47 C.-C. Lin, L.-H. Chen and H.-J. Wu, *J. Chin. Chem. Soc.*, 1991, **38**, 613–617.

48 C. E. Janssen and N. Krause, *Eur. J. Org. Chem.*, 2005, 2322–2329.

49 (*a*) C. Jonasson, A. Horvath and J. E. Backvall, *J. Am. Chem. Soc.*, 2000, **122**, 9600–9609; (*b*) I. Dorange, J. Lofstedt, K. Narhi, J. Franzen and J. E. Backvall, *Chem. – Eur. J.*, 2003, **9**, 3445–3449.

50 (*a*) M. Dai and S. J. Danishefsky, *Tetrahedron Lett.*, 2008, **49**, 6610–6612; (*b*) M. Dai, Z. Wang and S. J. Danishefsky, *Tetrahedron Lett.*, 2008, **49**, 6613–6616.

51 (*a*) B. A. Chauder, A. V. Kalinin, N. J. Taylor and V. Snieckus, *Angew. Chem., Int. Ed.*, 1999, **38**, 1435–1438; (*b*) B. A. Chauder, A. V. Kalinin and V. Snieckus, *Synthesis*, 2001, 140–144.

52 S. Masamune, *J. Am. Chem. Soc.*, 1961, **83**, 1009–1010.

53 P. Magnus and R. Littich, *Org. Lett.*, 2009, **11**, 3938–3941.

54 (*a*) L. A. Van Royen, R. Mijngheer and P. J. De Clercq, *Bull. Soc. Chim. Belg.*, 1984, **93**, 1019–1036; (*b*) L. A. Van Royen, R. Mijngheer and P. J. De Clercq, *Tetrahedron Lett.*, 1982, **23**, 3283–3286; (*c*) L. A. Van Royen, R. Mijngheer and P. J. De Clercq, *Tetrahedron*, 1985, **41**, 4667–4680.

55 J. L. Frie, C. S. Jeffrey and E. J. Sorensen, *Org. Lett.*, 2009, **11**, 5394–5397.

56 B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh and M. A. Ciufolini, *Org. Lett.*, 2009, **11**, 1539–1542.

57 C. Baumgartner, S. Ma, Q. Liu and B. M. Stoltz, *Org. Biomol. Chem.*, 2010, **8**, 2915–2917.

58 F. Yu, G. Li, P. Gao, H. Gong, Y. Liu, Y. Wu, B. Cheng and H. Zhai, *Org. Lett.*, 2010, **12**, 5135–5137.

59 W. K. Chung, S. K. Lam, B. Lo, L. L. Liu, W. T. Wong and P. Chiu, *J. Am. Chem. Soc.*, 2009, **131**, 4556–4557.

60 N. Kotoku, Y. Sumii and M. Kobayashi, *Org. Lett.*, 2011, **13**, 3514–3517.

61 N. Kotoku, Y. Sumii, T. Hayashi and M. Kobayashi, *Tetrahedron Lett.*, 2008, **49**, 7078–7081.

62 Z. Wang, M. Dai, P. K. Park and S. J. Danishefsky, *Tetrahedron*, 2011, **67**, 10249–10260.

63 C. Aquino, S. N. Greszler and G. C. Micalizio, *Org. Lett.*, 2016, **18**, 2624–2627.

64 J. Ryan and G. C. Micalizio, *J. Am. Chem. Soc.*, 2006, **128**, 2764–2765.

65 S. Indu, R. D. Telore and K. P. Kaliappan, *Org. Biomol. Chem.*, 2020, **18**, 2432–2446.

66 (*a*) K. P. Kaliappan and N. Kumar, *Tetrahedron Lett.*, 2003, **44**, 379–381; (*b*) K. P. Kaliappan and P. Gowrisankar, *Tetrahedron Lett.*, 2004, **45**, 8207–8209; (*c*) K. P. Kaliappan and N. Kumar, *Tetrahedron*, 2005, **61**, 7461–7469; (*d*) K. P. Kaliappan and R. S. Nandurdikar, *Org. Biomol. Chem.*, 2005, **3**, 3613–3614; (*e*) K. P. Kaliappan and P. Gowrisankar, *Synlett*, 2007, 1537–1540; (*f*) K. P. Kaliappan and V. Ravikumar, *Org. Lett.*, 2007, **9**, 2417–2419; (*g*) K. P. Kaliappan and V. Ravikumar, *J. Org. Chem.*, 2007, **72**, 6116–6126; (*h*) K. P. Kaliappan and D. Si, *Synlett*, 2009, 2441–2444; (*i*) P. Gowrisankar, S. A. Pujari and K. P. Kaliappan, *Chem. – Eur. J.*, 2010, **16**, 5858–5862; (*j*) D. Si, N. M. Sekar and K. P. Kaliappan, *Org. Biomol. Chem.*, 2011, **9**, 6988–6997; (*k*) S. A. Pujari, P. Gowrisankar and K. P. Kaliappan, *Chem. – Asian J.*, 2011, **6**, 3137–3151; (*l*) K. Palanichamy, A. V. Subrahmanyam and K. P. Kaliappan, *Org. Biomol. Chem.*, 2011, **9**, 7877–7886; (*m*) V. V. Betkekar, A. A. Sayyad and K. P. Kaliappan, *Org. Lett.*, 2014, **16**, 5540–5543; (*n*) K. Ramakrishna and K. P. Kaliappan, *Org. Biomol. Chem.*, 2015, **13**, 234–240.

67 H. Nemoto, H. Kurobe, K. Fukumoto and T. Kametani, *J. Org. Chem.*, 1986, **51**, 5311–5320.

68 N. V. Desai, N. McKelvie and F. Ramirez, *J. Am. Chem. Soc.*, 1962, **84**, 1745–1747.

69 (*a*) T. Imahori, H. Ojima, Y. Yoshimura and H. Takahata, *Chem. – Eur. J.*, 2008, **14**, 10762–10771; (*b*) A. Furstner, *Chem. Commun.*, 2011, **47**, 6505–6511; (*c*) J. Ramharter and J. Mulzer, *Eur. J. Org. Chem.*, 2012, 2041–2453; (*d*) C. Lentsch, R. Furst and U. Rinner, *Synlett*, 2013, 2665–2670.

70 (*a*) L. Kurti, B. Czako and E. J. Corey, *Org. Lett.*, 2008, **10**, 5247–5250; (*b*) B. Czako, L. Kurti, A. Mammoto, D. E. Ingber and E. J. Corey, *J. Am. Chem. Soc.*, 2009, **131**, 9014–9019.

71 Y. Sato, H. Kamiyama, T. Usui, T. Saito, H. Osada, S. Kuwahara and H. Kiyota, *Biosci., Biotechnol., Biochem.*, 2008, **72**, 2992–2997.

72 N. Kotoku, Y. Sumii, T. Hayashi, N. Tamura, T. Kawachi, S. Shiomura, M. Arai and M. Kobayashi, *ACS Med. Chem. Lett.*, 2012, **3**, 673–677.

73 N. Kotoku, K. Mizushima, S. Tamura and M. Kobayashi, *Chem. Pharm. Bull.*, 2013, **61**, 1024–1029.

74 N. Kotoku, A. Ito, S. Shibuya, K. Mizuno, A. Takeshima, M. Nogata and M. Kobayashi, *Tetrahedron*, 2017, **73**, 1342–1349.

75 M. Arai, A. Hayashi, M. Sobou, S. Ishida, T. Kawachi, N. Kotoku and M. Kobayashi, *J. Nat. Med.*, 2011, **65**, 149–156.

76 E. Moman, D. Nicoletti and A. Mourino, *J. Org. Chem.*, 2004, **69**, 4615–4625.

77 N. Kotoku, *Yakugaku Zasshi*, 2013, **133**, 867–872.