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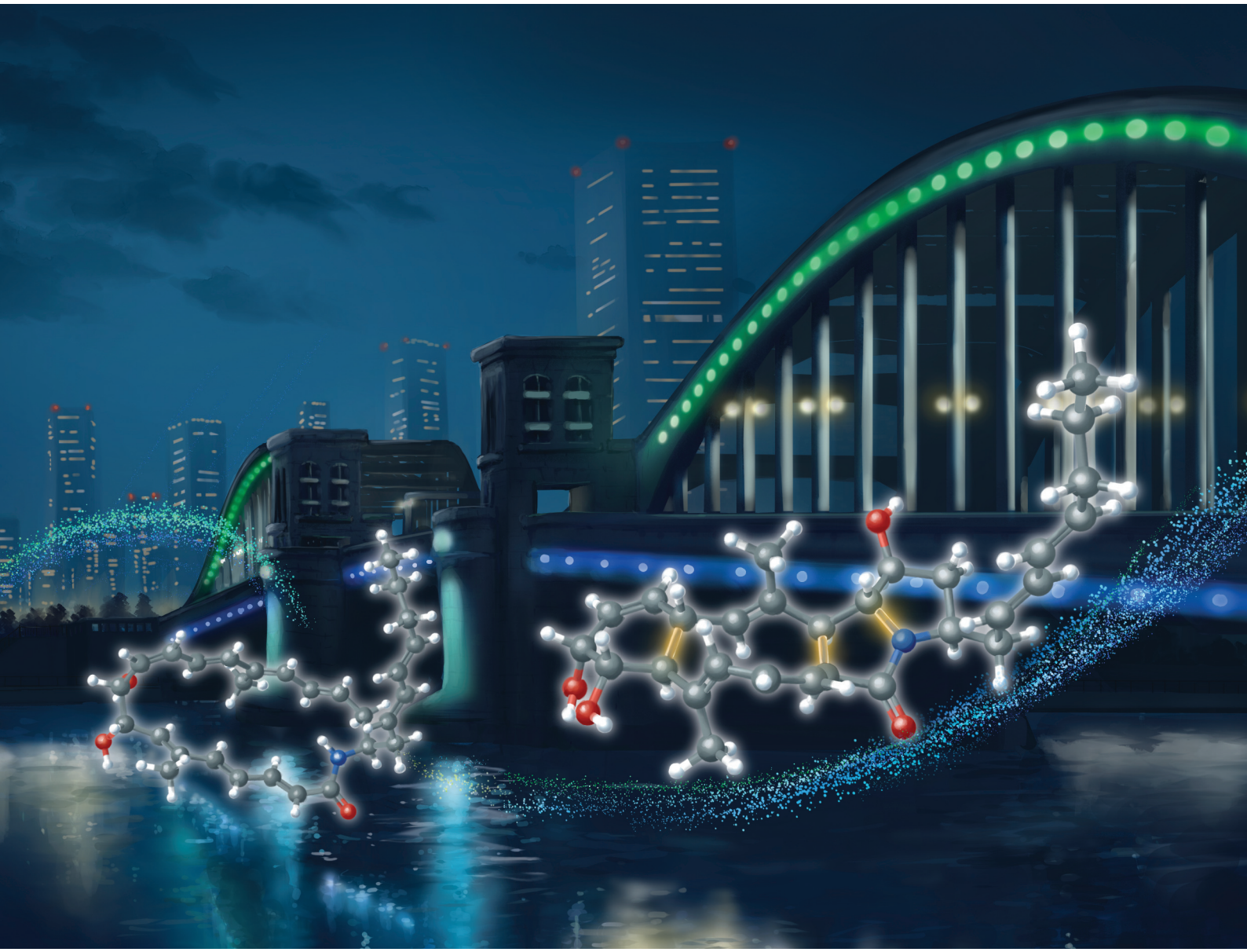

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REVIEW ARTICLE
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Late-stage chirality generation strategies for the total synthesis of macrocyclic natural products

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Macrocyclic natural products, including macrolactones, macrolactams, macrocyclic (depsi)peptides, and macrocyclic cyclophanes, occupy a chemical space that does not overlap significantly with that of traditional low molecular weight and sp^2-carbon rich pharmaceuticals. Traditionally, total synthesis toward macrocyclic natural products has been typically based on installation of backbone stereogenic centers at early- to mid-stage and closure of the macrocyclic backbone at late stage. However, these synthesis strategies suffer from multiple concession steps, making them less attractive in terms of step-economy. In this review, we provide an overview of late-stage chirality generation strategies in macrocyclic natural product synthesis, embodying stereoselective functional group and/or skeletal transformations that take advantage of macrocyclic conformational constraints. Expanding our repertoire of transformations amenable to late-stage chirality generation as well as advancing controllability over the conformational property of macrocycles will facilitate future developments in the total synthesis of macrocyclic natural products.

Introduction

Chemical space that has been less explored because of synthetic hurdles may represent a promising source of new chemotherapeutics for the treatment and cure of intractable human diseases.[1] It has been argued that the chemical space occupied by macrocyclic natural products, such as macrolactones, macrolactams, macrocyclic (depsi)peptides, and macrocyclic cyclophanes, is considerably different from that occupied by traditional low-molecular-weight, sp^2-carbon-rich pharmaceuticals.[2,3] Typical macrocyclic natural products have molecular weights of greater than 500 Dalton, large molecular surface areas, multiple functional groups on the edge of their macrocyclic skeletons, and the unique ability to bind with the shallow or flat surface of proteins. Importantly, such protein binding sites are often involved in 'undruggable' protein–protein interactions that are difficult to be accessed by traditional small molecules.

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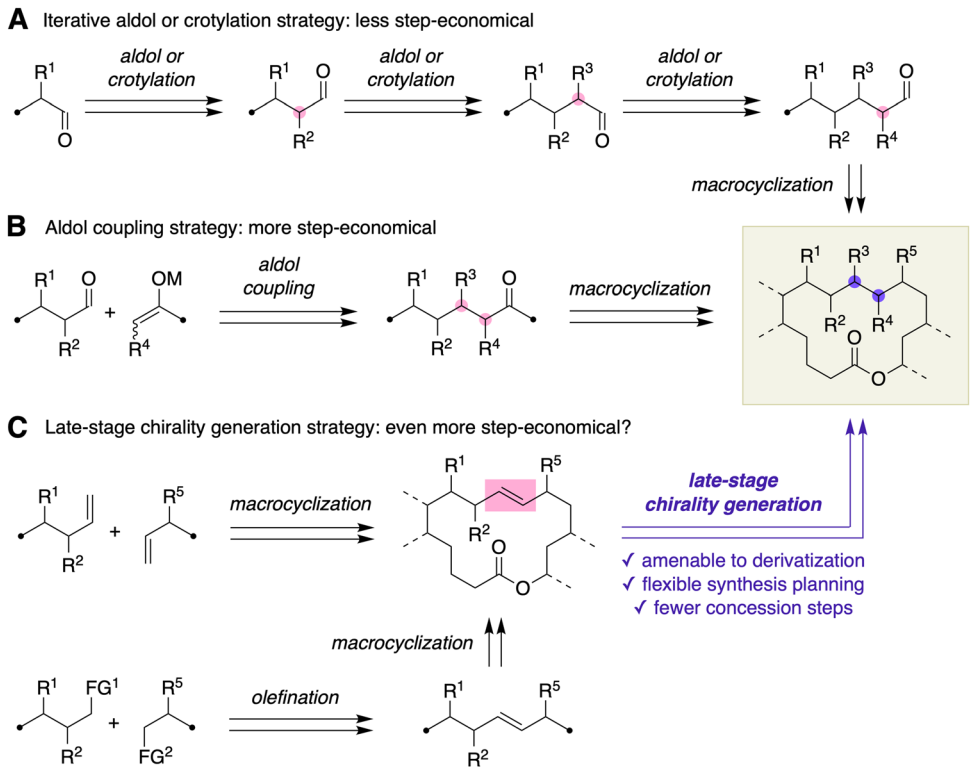
While macrocyclic (depsi)peptides are becoming accessible by *in vitro* ribosomal synthesis,[4] total synthesis is a gold standard for the practical supply of macrocyclic natural products and their analogues for detailed biological testing and applications in medicinal chemistry and chemical biology. However, at the same time, it is still a challenging task for chemists to synthesize macrocyclic natural products, especially those having a stereochemically complex backbone structure. For example, the total synthesis of macrocycles often requires more than 20 steps from commercially available inexpensive materials, though a body of reliable methods are currently available for the stereocontrolled synthesis of substructures and efficient macrocyclization. Total synthesis of macrocycles has been typically achieved in the way in which backbone stereogenic centers are installed precisely at early- to mid-stage and macrocyclic skeleton is closed at late stage.[5] It appears reasonable to circumvent late-stage chirality-generating transformations because of the ambiguity in anticipating the conformation and reactivity of macrocycles with varying degrees of conformational flexibility. At the same time, the traditional synthesis strategies toward macrocycles tend to require many concession steps such as protecting group manipulations and oxidation state adjustments due to the early to mid-stage installation of multiple functional groups. For example, in polyketide macrocycle synthesis, substructures are accessible in a solid manner through iterative asymmetric aldol or crotylation reactions.[6] However, such iterative strategies require multiple transformations for oxidation/reduction and protection/deprotection, which make them less attractive in terms of step-economy (Scheme 1A). A more step-economical approach can be envisioned by considering an aldol coupling of aldehydes and metal enolates, although it is still not free from concession steps and its stereochemical outcome is substantially affected by substrate bias (Scheme 1B). In contrast, it may be even more step-economical if we could install the requisite stereogenic center(s) at the late stage by making use of prochiral functional groups, such as olefins and ketones, under macrocyclic conformational constraints (Scheme 1C).

Late-stage functionalization of structurally intricate natural products enables the generation of an array of structural analogues that are previously difficult to access by traditional target-oriented total synthesis, thereby facilitating natural product chemical biology and drug discovery.[7] The past two decades have seen significant progress in late-stage functionalization with the advent of new synthetic methods such as C–H functionalization, photocatalysis, and biocatalysis. Nevertheless, it appears that the application of these new synthetic methods has been mostly limited to late-stage functionalization of natural products with rigid scaffolds so far.

Now that a body of efficient macrocyclization reactions are made available to the synthetic community, an emerging frontier in the total synthesis of macrocyclic natural products in the age of synthetic efficiency is late-stage chirality generation by taking advantage of macrocyclic conformational constraint.



Scheme 1 Strategies for total synthesis of macrocyclic polyketide natural products. (A) Iterative aldol or crotylation strategy. (B) Aldol coupling strategy. (C) Late-stage chirality generation strategy.

Stereoselective functional group transformations at a late stage should increase the flexibility of synthesis design and facilitate derivatization and even stereodivergent synthesis. Meanwhile, stereoselective skeletal transformations including macrocyclizations,[8] transannular reactions,[9] and skeletal reorganizations would likely help increase the molecular complexity with high step-economy[10] but are largely underexplored in macrocycle synthesis. This review provides an overview of late-stage chirality generation strategies for the total synthesis of macrocyclic natural products by highlighting selected examples.

Early development

Alkylation of carbonyls, conjugate addition to α,β-unsaturated carbonyls, oxidation of olefins, and reduction of ketones and olefins embedded within macrocycles are known to proceed diastereoselectively to create a new stereogenic center(s) when the two faces of the double bond of these functional groups are differentiable by the virtue of the intrinsic conformational constraints of macrocycles, *i.e.*, "macrocyclic stereocontrol".[11] Pioneering works on such chirality-generating functional group transformations on macrocycles were published during the late 1970s to the 1980s.

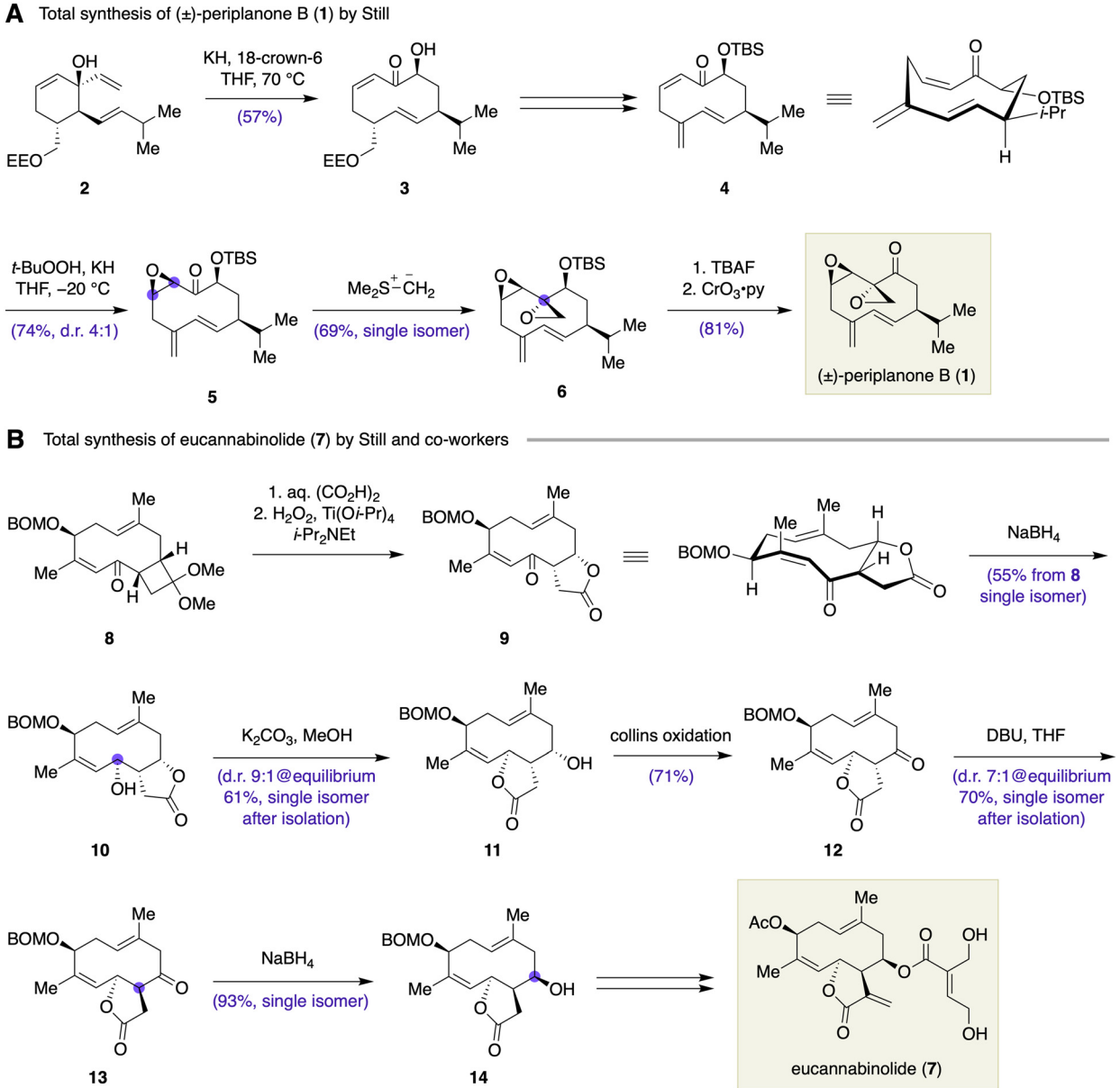
Significant contributions were made by Still and co-workers to formulating the concept "macrocyclic stereocontrol" during the late 1970s to the early 1980s. The Still group investigated chirality-generating functionalization on macrocycles of various ring sizes.[12] In 1979, Still described that chirality-generating oxidations were very effective for installing two epoxides onto the macrocyclic skeleton of (±)-periplanone B (**1**) with good to excellent diastereoselectivities at the late stage of the synthesis (Scheme 2A).[13]

Thus, macrocyclic α,β-unsaturated ketone **4**, derived from a simple cyclohexanone derivative **2** *via* an oxy–Cope rearrangement, was epoxidized chemo- and stereo-selectively with *t*-BuOOH/KH to give epoxy ketone **5** in 74% yield with 4 : 1 diastereoselectivity, which was then subjected to Corey–Chaykovsky epoxidation using dimethylsulfonium methylide to afford diepoxide **6** in 69% yield as a single isomer. The exo-methylene group was installed to the macrocycle prior to the epoxidations for controlling the conformation. Desilylation and oxidation completed the synthesis of **1**. Two additional diastereomers of periplanone B were also synthesized by modifying the peripheral substituents and reaction conditions to control the conformation of the macrocyclic backbone. In the total synthesis of eucannabinolide (**7**) by the Still group, a four-step sequence of functional group transformations, *i.e.*, ketone reduction (**9** → **10**), acyl migration (**10** → **11**), epimerization (**12** → **13**), and ketone reduction (**13** → **14**), were performed on late-stage macrocyclic intermediates to establish the three contiguous stereogenic centers of the target natural product (Scheme 2B).[14]

Takahashi and colleagues demonstrated total syntheses of sesquiterpene lactones, costunolide (**15**) and haageanolide (**16**), empowered by transannular [2,3]-Wittig rearrangement of macrocyclic diallyl ethers (Scheme 3A).[15] Thus, treatment of macrocyclic diallyl ether **17**, prepared from farnesyl acetate, with *t*-BuLi in Et_2O at −78 to 0 °C provided a 75 : 25 mixture of ring-contracted product **19** and its isomer **20**. The lithiation of **17** preferred the α position relative to the α′ position. The stereochemical course of the rearrangement, giving the desired product **19** exclusively as *trans* isomer, was reasoned by transition state **18** that was generated by MM2 transition structure models. A regioselective lithiation/oxidation of **19** followed by MnO_2 oxidation afforded costunolide (**15**). Total synthesis of haageanolide (**16**) was achieved in a similar fashion. Transannular [2,3]-Wittig rearrangement of macrocyclic diallyl ether **21** led to a mixture of ring-contracted products **22**, **23**, and **24**. In this case, lithiation of **21** occurred with no regioselectivity between the α and α′ positions. Marshall *et al.* reported the total synthesis of aristolactone (**25**), in which a transannular [2,3]-Wittig rearrangement of macrocyclic propargylic ether **26** was used for obtaining ring-contracted product **27** in 92% yield as a single *trans* isomer (Scheme 3B).[16] It appears that the lithiation of **26** with *n*-BuLi occurred exclusively at the α position to secure the desired product **27** in a high yield. These works represent an early example of late-stage skeletal reorganization in the total synthesis of macrocyclic natural products.

Because of their stereochemically rich, complex macrocyclic structures, macrolide antibiotics spurred the interest of the synthetic community during the late 20th century and stimulated investigations into macrocyclic stereocontrol. In 1978, the Corey group completed the total synthesis of erythronolide B (**28**) for the first time, in which they exploited macrocyclic stereocontrol to establish the C10 and C11 stereogenic centers at the final stage of the synthesis (Scheme 4A).[17] Thus, stereoselective epoxidation of an α,β-unsaturated ketone derived from **29** by MnO_2 oxidation, followed by the hydrogenolysis of the resultant epoxy ketone **30** gave alcohol **31**, which underwent thermodynamic epimerization at C10 upon treatment with K_2CO_3 in methanol. The removal of acetonide completed the total synthesis of **28**. A similar tactic was used in the Corey synthesis of erythronolide A.[18]

Thereafter, Still and Novack demonstrated an elegant synthesis of 3-deoxyrosaranolide (**32**) from macrolactone **33** through an extensive use of chirality-generating transformations on the macrocyclic backbone (Scheme 4B).[11] Regioselective deprotonation of **33** at C8 with KHMDS and alkylation of the derived potassium enolate with MeI provided C8 methylated product **34** in 70% yield with 20 : 1 diastereoselection. Removal of the dithioacetal (>95%), followed by regio- and stereo-selective alkylation with LHMDS/$BrCH_2CO_2t$-Bu, gave C6 alkylated product **35** in 73% yield with *ca.* 6–10 : 1 dr. After transformation of **35** into α,β-unsaturated ketone **36**, conjugate addition of PhSH and Raney Nickel desulfurization afforded C4 methylated product **37** in 44% overall yield with greater than 25 : 1 diastereomer ratio. Cleavage of the *t*-butyl ester, acylation with $ClCO_2Et$, and $NaBH_4$ reduction provided alcohol **38** with 5 : 1 diastereoselectivity at C5. After MnO_2 oxidation of the C9 hydroxy group (75%), regio- and stereo-selective epoxidation of the $\Delta^{12,13}$ olefin with *m*CPBA gave rise to the corresponding epoxide in 88% yield with greater than



Scheme 2 (A) Total synthesis of periplanone B (**1**) by Still. (B) Total synthesis of eucannabinolide (**7**) by Still and co-workers.

15 : 1 diastereoselectivity. Finally, oxidation of the 1,4-diol moiety with $(Ph_3P)_3RuCl_2$ furnished 3-deoxyrosaranolide (**32**) in 47% yield at 56% conversion. It is remarkable that all but two stereogenic centers along the macrocyclic backbone of **32** were set up at the post-macrocyclization stage.

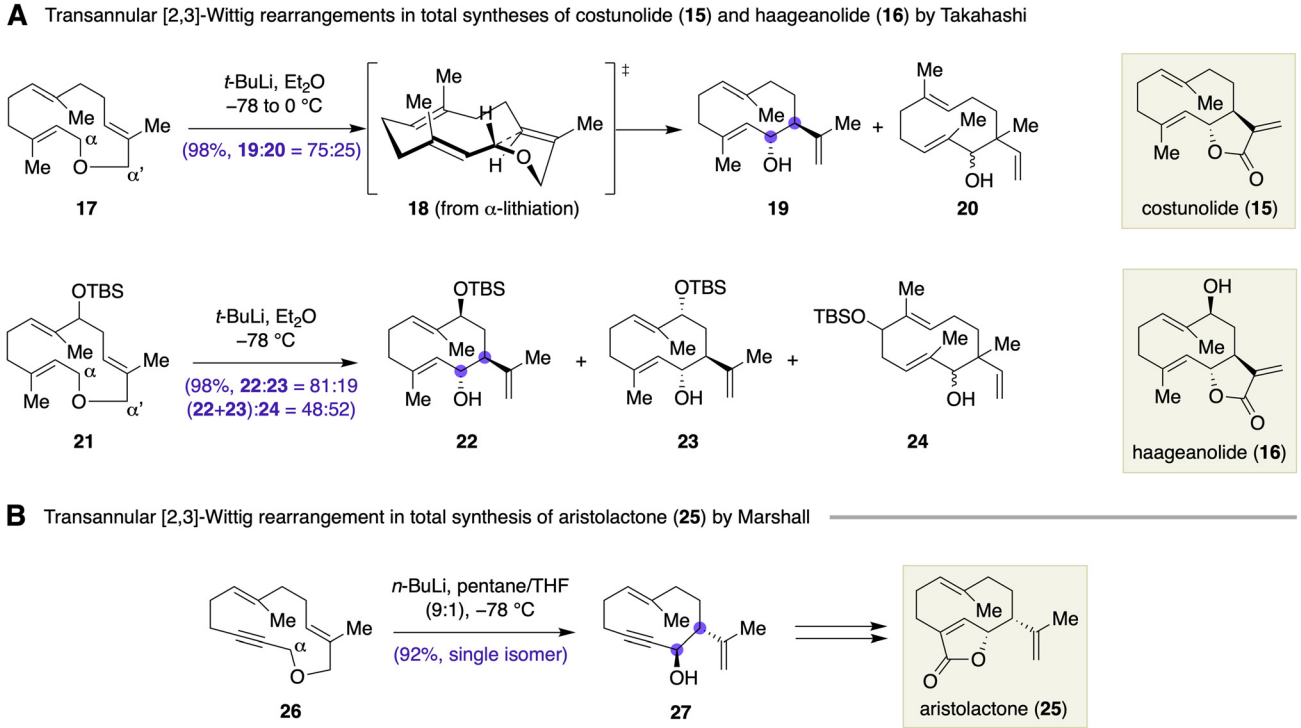
Paterson and Rawson described an elegant synthesis of (+)-(9*S*)-dihydroerythronolide A (**39**), which involved chemo- and stereo-selective dihydroxylation of macrocyclic enol silyl ether **40**, chelate-controlled zinc borohydride reduction of ketone **41**, desilylation of **42**, and stereoselective dihydroxylation of **43** (Scheme 4C).[19] Thus, four out of eleven stereogenic centers of **39** were established at the final stage of the synthesis. Empowered by a late-stage chirality generation strategy, the present synthesis was completed in 20 steps from a simple starting material, (±)-2-methyl-3-phenylthiopropanal, and is remarkably concise given the complexity of the target molecule.

Late-stage chirality-generating functional group transformations

Succeeding examples

The scope of late-stage chirality-generating functional group transformations has now been extended to various macrocyclic natural products, demonstrating the conceptual generality of macrocyclic stereocontrol.

Oxidations. Höfle and co-workers investigated derivatizations of soraphen A (**44**, Scheme 5A), a macrocyclic natural

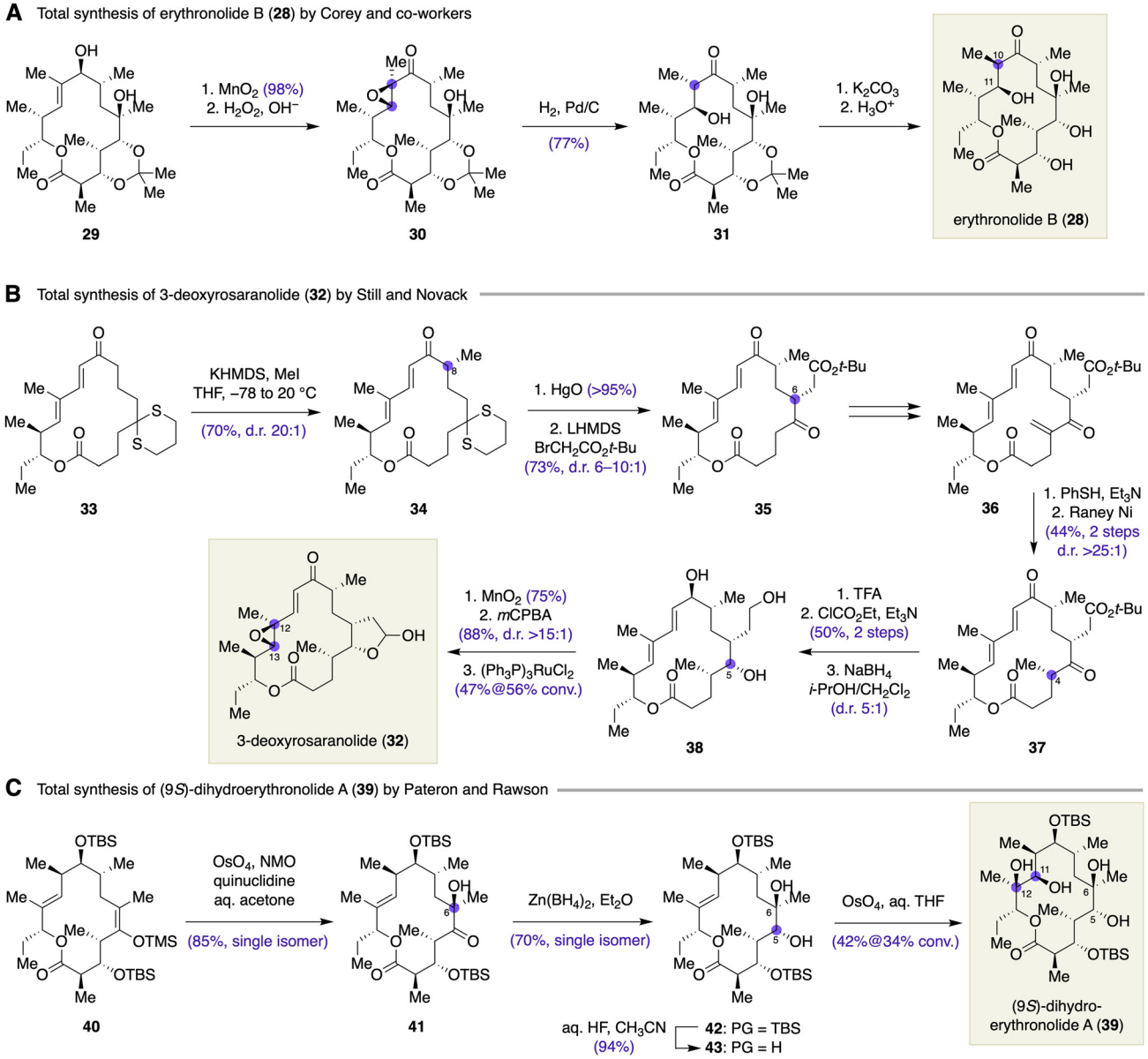


Scheme 3 (A) Transannular [2,3]-Wittig rearrangement in the total syntheses of costunolide (**15**) and haageanolide (**16**) by Takahashi. (B) Transannular [2,3]-Wittig rearrangement in the total synthesis of aristolactone (**25**) by Marshall.

product with potent fungal growth inhibitory activity, by focusing on the $\Delta^{9,10}$ olefin.[20] Because soraphen A (**44**) contains a six-membered hemiacetal, it readily tautomerizes into hydroxy ketone **45** and its enol tautomer **46**. Höfle *et al.* envisaged that different forms of soraphen A would show different reactivity and stereoselectivity in electrophilic reactions on the $\Delta^{9,10}$ olefin. In the event, dihydroxylation of **44** proceeded on the *Si* face of the $\Delta^{9,10}$ olefin to deliver diol **47** in 88% yield (Scheme 5B). Similarly, epoxidation of 5-*O*-silylated derivative **48** with *m*CPBA afforded epoxide **49** in 73% yield. The diastereoselectivities of these reactions could be reasoned by the crystal structure of **44**, wherein the *Si* face of the $\Delta^{9,10}$ olefin directed toward the outside of the macrocycle. In contrast, dihydroxylation and epoxidation of silyloxy ketone derivative **50** took place on the *Re* face of the $\Delta^{9,10}$ olefin to afford diol **51** and epoxide **52** in 63% and 32% yields, respectively (Scheme 5C). While not discussed in detail, it appears that the conformation of silyloxy ketone derivative **50** should be significantly different from that of soraphen A (**44**), and thus, the stereochemical outcome of these oxidation reactions reversed completely. Treatment of 5-*O*-silylated derivative **48** with pyridinium tribromide resulted in an intramolecular bromoetherification, which involved an intramolecular attack of the C12-OMe group to the transient bromonium cation to give 2,5-*trans*-configured tetrahydrofuran derivative **53** in 94% yield (Scheme 5D). In a similar fashion, exposure of **48** to NCS afforded the chloride counterpart **54** in 87% yield. The stereochemical course of these haloetherifications was in accordance with the *m*CPBA epoxidation described above. Meanwhile, phenylselenylation of **48** proceeded through an intramolecular trapping of the selenonium cation intermediate by the C7-OH group, leading to 2,5-*trans*-configured tetrahydrofuran derivative **56** in 53% yield. It was proposed that phenylselenyl cation generated from *N*-phenylselenyl phthalimide and CSA engaged the *Re* face of the $\Delta^{9,10}$ olefin of the hydroxy ketone form **55**. Notably, these transannular reactions were effective for skeletal diversification of soraphen A, although the products did not show significant activity in greenhouse trials.

Li, Yue, and co-workers described the total synthesis of (−)-ivorenolide A (**57**, Scheme 6), the unnatural enantiomer of an immunosuppressive 18-membered macrolide.[21] This natural product is structurally unusual in that it contains a conjugated diyne in the macrocyclic skeleton. The Li/Yue synthesis of **57** involved stereoselective epoxidation of macrocyclic olefin **58**, prepared *via* a Yamaguchi macrolactonization. Specifically, treatment of **58** with *m*CPBA in CH_2Cl_2 at room temperature furnished ivorenolide A (**57**) in 84% yield as the sole product. The stereochemical consequence may be counterintuitive but can be reasoned by the conformation of the precursor **58**; it was assumed that *m*CPBA approached from the less hindered face of **58**.[22]

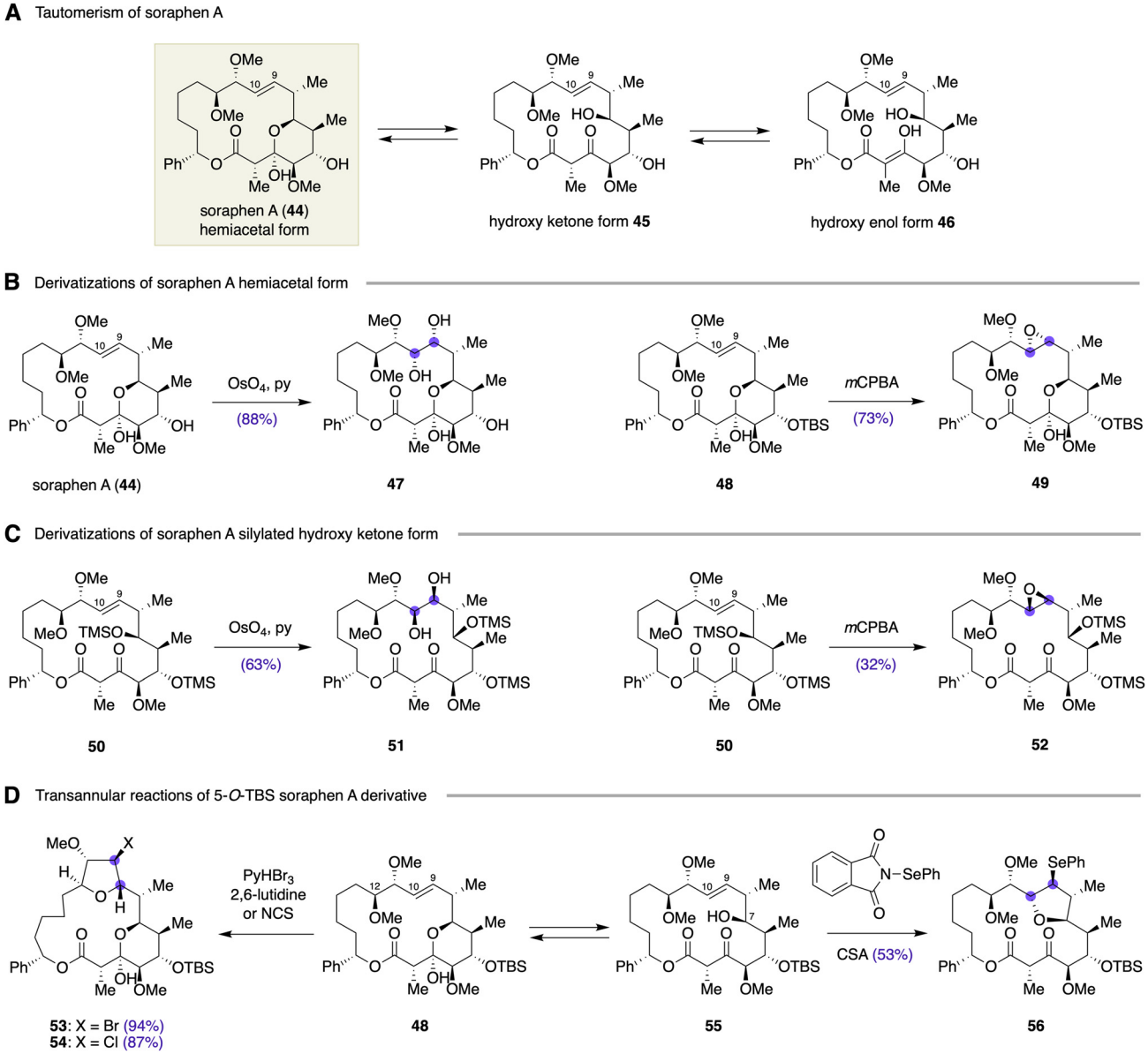
Clark and Romiti reported the total synthesis of amphidinolide T1, T3, and T4 (**59**, **60**, and **61**, respectively, Scheme 7) from a common advanced intermediate by late-stage chirality-generating functional group transformations.[23] Macrocyclic alkyne **62** was synthesized *via* a Yamaguchi macrolactoniza-



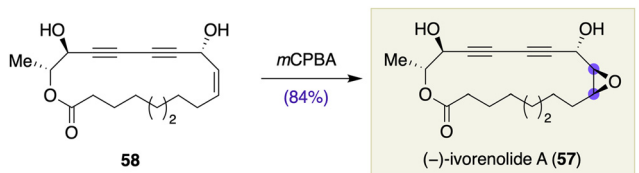
Scheme 4 (A) Total synthesis of erythronolide B (**28**) by Corey and co-workers. (B) Total synthesis of 3-deoxyrosaranolide (**32**) by Still and Novack. (C) Total synthesis of (9*S*)-dihydroerythronolide A (**39**).

tion. Ruthenium-catalyzed hydrosilylation of **62** under the catalysis of $[Cp^*Ru(MeCN)_3]PF_6$ in the presence of $(EtO)_2MeSiH$[24] provided an approximately 1 : 1 separable mixture of vinylsilane **63** (44%) and **64** (45%). *m*CPBA epoxidation of **63** proceeded in a regio- and stereo-selective manner, and subsequent Tamao–Fleming oxidation of the derived silyl epoxide furnished amphidinolide T1 (**59**) and its 13-epimer 13-*epi*-**59** in 73% and 7% yields, respectively. When the regioisomeric vinylsilane **64** was subjected to the same reaction sequence, however, amphidinolide T3 (**60**) and T4 (**61**) were afforded in 30% and 49% yields, respectively. This result indicated that only a moderate level of conformational bias was operating in the epoxidation of **64**. In contrast, Shi asymmetric epoxidation[25] of **64** with D-fructose-derived ketone **65** and Oxone, followed by Tamao–Fleming oxidation, gave rise to amphidinolide T3 (**60**) in 61% yield as a single diastereomer. Using L-fructose-derived ketone, *ent*-**65**, the same reaction sequence afforded amphidinolide T4 (**61**) in 57% yield as a single stereoisomer. This is a nice piece of work that illustrates substrate- and reagent-controlled epoxidations of macrocyclic olefins, which resulted in a collective synthesis of amphidinolides T1, T3, and T4.

An expedient synthesis of sarcodictyin B (**66**) and eleutherobin (**67**) has been recently disclosed by Britton and colleagues, wherein late-stage oxidations on the carbon skeleton of eunicellin diterpenoid **68** was exploited for installing stereogenic centers at the C4, C7, and C8 positions (Scheme 8).[26] Based on the X-ray structure and solution conformation of **68**, Britton

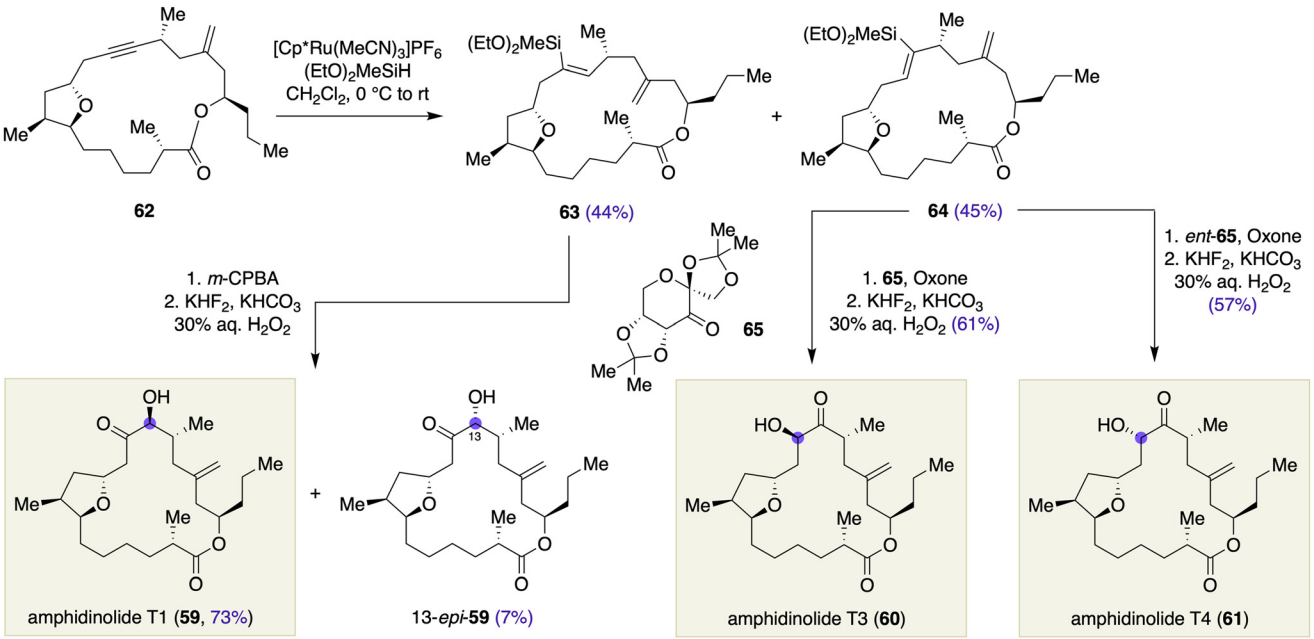


Scheme 5 (A) Tautomerism of soraphen A (**44**). (B) Derivatizations of soraphen A hemiacetal from **44** and its 5-*O*-TBS derivative **48**. (C) Derivatization of soraphen A-silylated hydroxy ketone from **50**. (D) Transannular reactions of 5-*O*-TBS soraphen A derivative **48**.

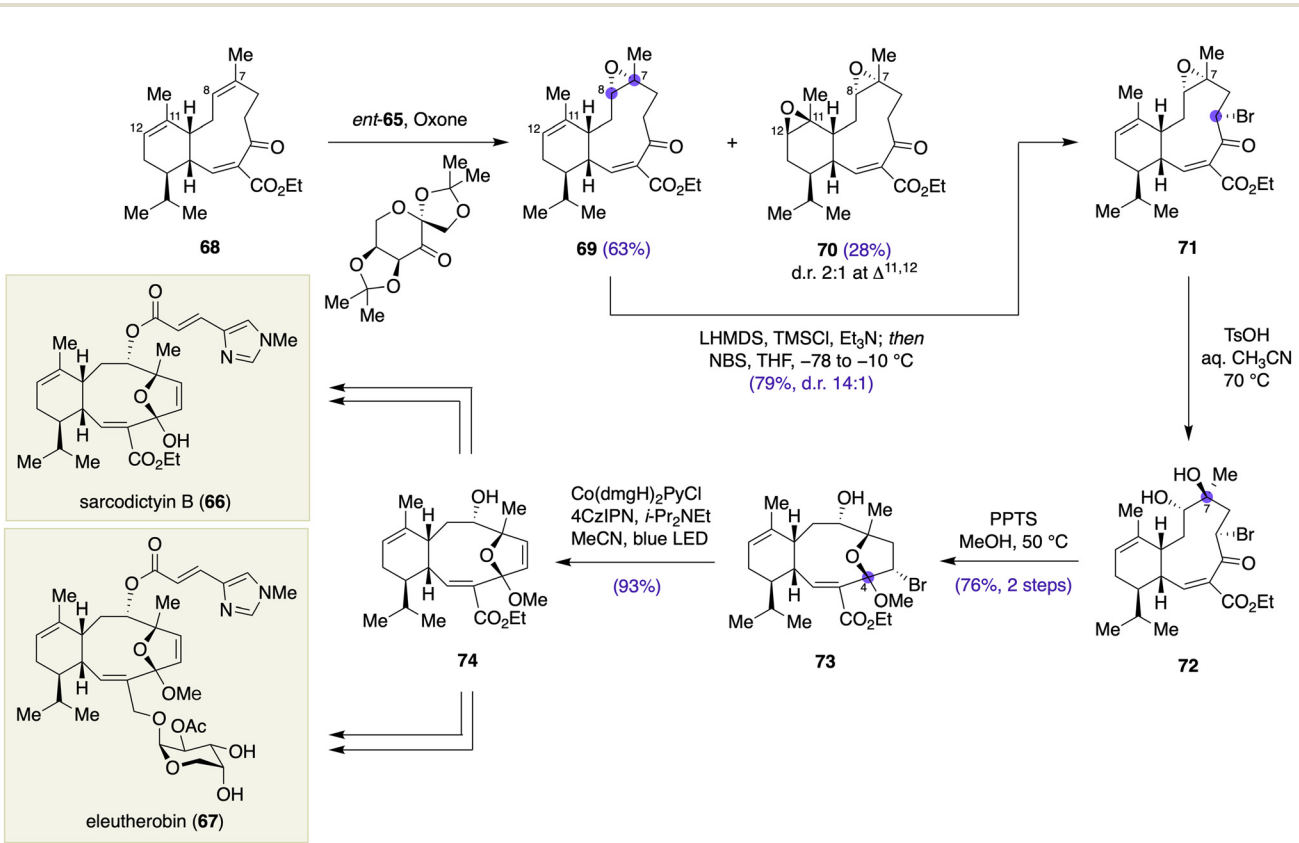


Scheme 6 Stereoselective epoxidation in the total synthesis of (–)-ivorenolide A (**57**) by Li, Yue, and co-workers.

et al. envisioned that epoxidation of the $\Delta^{7,8}$ olefin would proceed on the *Si* face to give the corresponding epoxide with the correct configuration at C8. However, standard epoxidation conditions were problematic due to a competing side reaction at the $\Delta^{11,12}$ olefin. After screening a variety of reaction conditions, Shi asymmetric epoxidation of **68** using L-fructose-derived ketone *ent*-**65** was found to provide the desired $\Delta^{7,8}$ epoxide **69** in 63% yield, along with diepoxide **70** in 28% yield (dr 2 : 1 at $\Delta^{11,12}$ epoxide). Treatment of **69** with LHMDS in the presence of TMSCl/Et_3N, followed by NBS, gave bromide **71** in 79% yield with 14 : 1 diastereoselection. Acidic hydrolysis of the epoxide moiety of **71** occurred with an inversion of the configuration at C7 to deliver diol **72**, which was then transformed to methyl ketal **73** upon exposure to PPTS in MeOH (76%, two steps), thereby establishing the stereogenic center at the C4 position. The subsequent photocatalytic halogen-atom transfer reaction under Leonori conditions[27] cleanly eliminated the superflu-



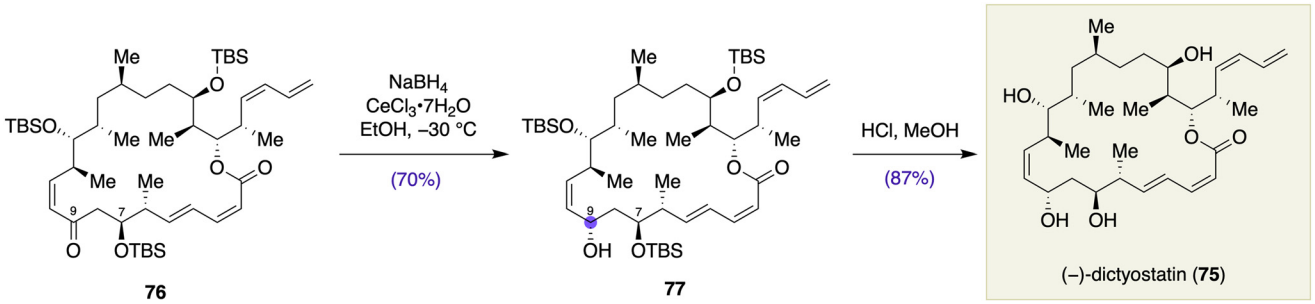
Scheme 7 Substrate- and reagent-controlled epoxidations in the collective total synthesis of amphidinolides T1, T3, and T4 (**59**, **60**, and **61**) by Clark and Romiti.



Scheme 8 Stereoselective oxidations in the total synthesis of sarcodictyin B (**66**) and eleutherobin (**67**) by Britton and co-workers.

ous bromide to furnish dihydrofuran **74** (93%). Additional two- to five-step sequences of transformations completed the synthesis of sarcodictyin B (**66**) and eleutherobin (**67**).

Reductions. A highly stereoselective ketone reduction under macrocyclic stereocontrol was demonstrated at the final stage of the total synthesis of (–)-dictyostatin (**75**) by Paterson *et al.*

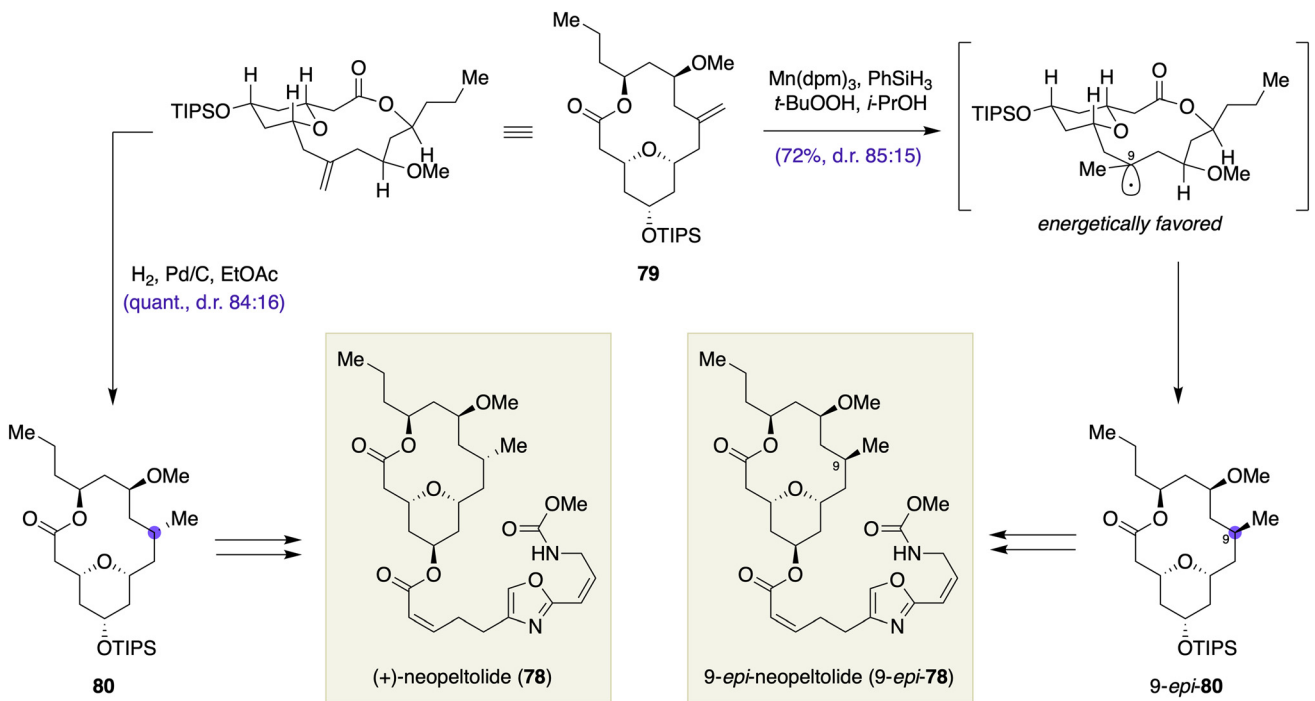


Scheme 9 Stereoselective ketone reduction in the total synthesis of (–)-dictyostatin (**75**) by Paterson and co-workers.

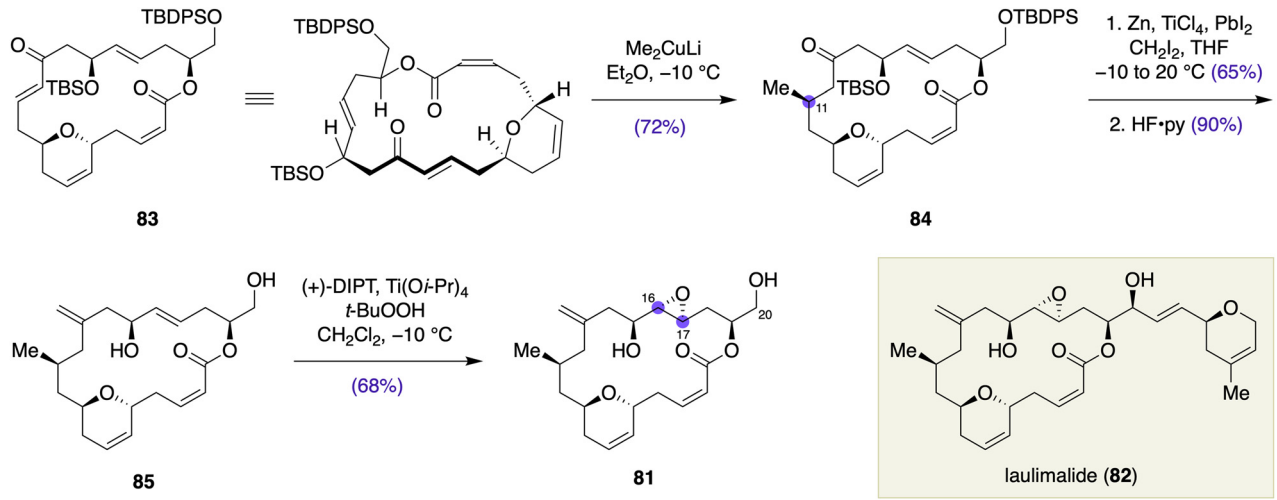
(Scheme 9).[28] Based on molecular mechanics calculation, it was anticipated that the *Si* face of the carbonyl group of **76** would be blocked by the β-silyloxy group, so that reduction of **76** takes place on the *Re* face to avoid the unfavorable steric repulsion. In the event, treatment of **76**, obtained through a Yamaguchi macrolactonization, with $NaBH_4/CeCl_3{\cdot}7H_2O$ in EtOH at −30 °C furnished alcohol **77** in 70% yield with the desired configuration at the C9 position. Deprotection of the silyl groups completed the total synthesis of (–)-dictyostatin (**75**).

Our group has recently reported the total synthesis of (+)-neopeltolide (**78**) and its C9-epimer, 9-*epi*-**78** (Scheme 10).[29] Earlier studies by Kozmin,[30] Floreancig,[31] and us[32] suggested that catalytic hydrogenation of *exo*-olefin **79** would proceed favorably on the sterically less encumbered β-face to deliver **80**. *Exo*-olefin **79** could be synthesized by our tandem macrocyclization/pyran cyclization strategy (*vide infra*). As anticipated, hydrogenation of **79** provided **80** quantitatively with 84 : 16 diastereoselection. Meanwhile, Mn-catalyzed hydrogen-atom transfer conditions ($Mn(dpm)_3$, $PhSiH_3$, *t*-BuOOH, i-PrOH)[33] led to 9-*epi*-**80** in 72% yield with 85 : 15 diastereoselection. The stereochemical consequence could be reasoned by a late transition state model involving a tertiary alkyl radical intermediate with the C9 methyl group equatorially disposed to favor the 'thermodynamic' product 9-*epi*-**80**. Thus, late-stage stereodivergent reduction of **79**, making use of its conformational bias, allowed an expedient access to (+)-neopeltolide (**78**) and 9-*epi*-neopeltolide (9-*epi*-**78**), both of which were potent antiproliferative agents against various human cancer cell lines.

Conjugate additions. The Paterson group developed a concise synthesis of the macrolactone core structure **81** of laulimalide (**82**) (Scheme 11).[34] Macrocyclic α,β-unsaturated ketone **83** was synthesized *via* a chiral boron enolate-mediated aldol coupling and a Mitsunobu macrolactonization. Stereoselective conjugate addition to **83** using Me_2CuLi in Et_2O at −10 °C delivered methylated product **84** in 72% yield



Scheme 10 Stereodivergent synthesis of (+)-neopeltolide (**78**) and its 9-epimer (9-*epi*-**78**) by late-stage chirality generation.

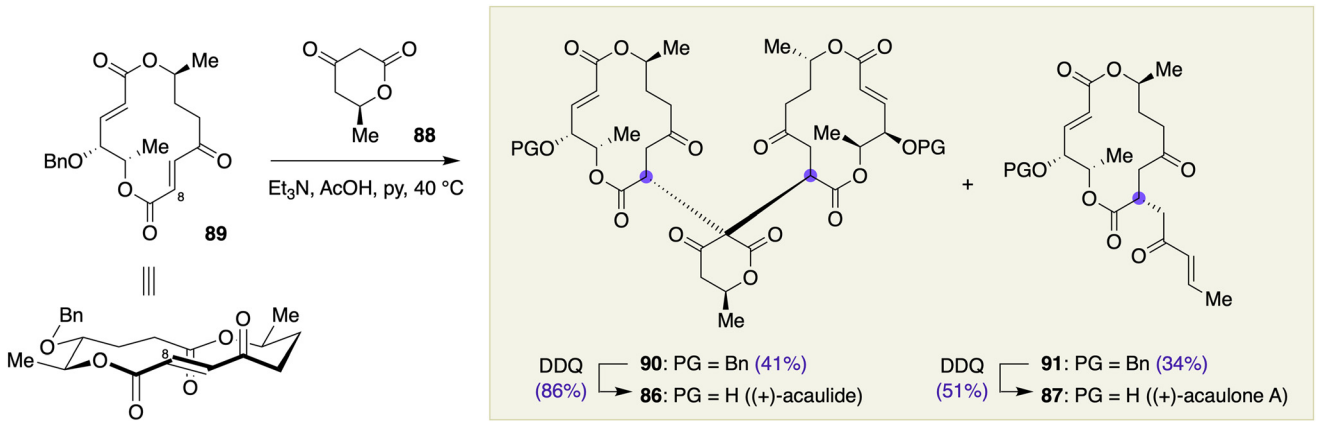


Scheme 11 Stereoselective conjugate addition and Sharpless asymmetric epoxidation in the synthesis of the macrocyclic core **81** of laulimalide (**82**) by Paterson and co-workers.

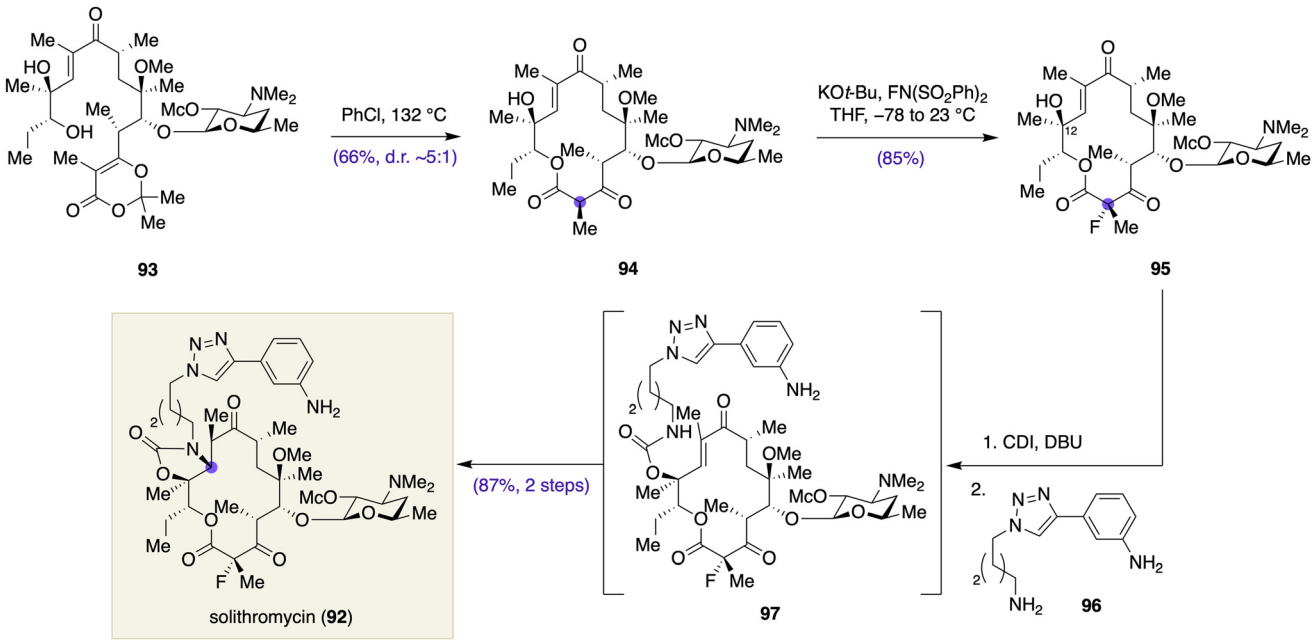
as a single stereoisomer. The stereochemical consequence of the present conjugate addition was predicted based on molecular mechanics calculation, which suggested that the α-face of the α,β-unsaturated ketone moiety of **83** oriented toward the inner cavity of the macrocycle. Accordingly, the β-face would react preferentially with an organocuprate under macrocyclic stereocontrol. After Takai methylenation (Zn, $TiCl_4$, PbI_2, CH_2I_2, 65%) and desilylation (HF·py, 90%), Sharpless asymmetric epoxidation of the derived allylic alcohol **85** ((+)-DIPT, Ti(Oi-Pr)$_4$, *t*-BuOOH) afforded **81** in 68% yield without intervention of the C20–OH group. Thus, three stereogenic centers were installed with full stereocontrol after the closure of the macrocyclic skeleton.

Ichikawa and co-workers described the total synthesis of (+)-acaulide (**86**) and (+)-acaulone A (**87**), which was highlighted by a late-stage double Michael addition inspired by a plausible biosynthetic mechanism (Scheme 12).[35] Specifically, Michael addition of 6-methyldihydropyran-2,4-dione (**88**) to macrodiolide **89** under the influence of Et_3N and AcOH in pyridine at 40 °C provided double adduct **90** in 41% yield, along with single adduct **91** in 34% yield. Presumably, **91** was produced *via* a hydrolysis of the dihydropyran-2,4-dione moiety and a subsequent decarboxylation. The stereoselectivity of the Michael addition was accounted for by conformational analysis based on the X-ray structure and NOE correlations of **89**. Finally, the total synthesis of (+)-acaulide (**86**) and (+)-acaulone A (**87**) was completed by the deprotection of the benzyl groups.

Myers and co-workers reported the synthesis of a >300-membered library of macrolide antibiotic candidates, including solithromycin (**92**),[36] based on a convergent synthetic approach (Scheme 13). In the synthesis of solithromycin (**92**), Myers *et al.* forged the 14-membered macrolactone skeleton through acylketene macrocyclization of dioxinone **93**. Thus, heating a solution of **93** in chlorobenzene at 132 °C resulted in macrolactone **94** in 66% yield as an approximately 5 : 1 mixture of diastereomers at the C2 position. Stereoselective fluorination of **94** at C2 was brought about using KO*t*-Bu/FN(SO$_2$Ph)$_2$ to give fluoride **95** (85%). Treatment of **95** with carbonyldiimi-



Scheme 12 Stereoselective Michael addition in the total synthesis of (+)-acaulide (**86**) and (+)-acaulone A (**87**) by Ichikawa and co-workers.



Scheme 13 Stereoselective fluorination and intramolecular aza-Michael addition in the total synthesis of solithromycin (**92**) by Myers and co-workers.

dazole (CDI)/DBU provided the corresponding acyl imidazole at the C12 position. Finally, amide condensation with amine **96** and concomitant stereoselective intramolecular aza-Michael addition of transient intermediate **97** gave rise to solithromycin (**92**, 87% for two steps).

Late-stage chirality-generating skeletal transformations: macrocyclizations

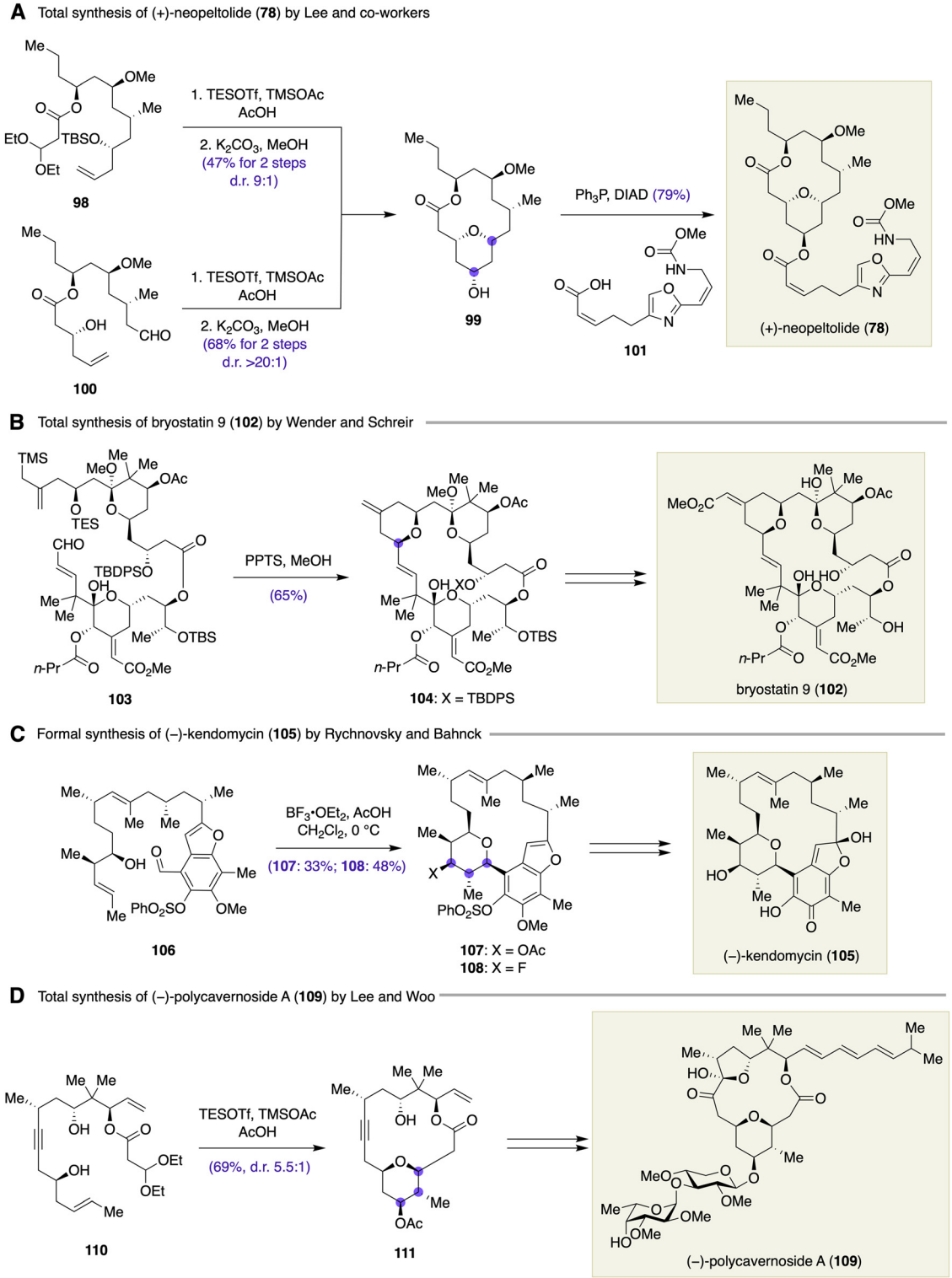
Late-stage skeletal transformations in the total synthesis of macrocyclic natural products may involve: (1) macrocyclizations for closing the macrocyclic skeleton; (2) transannular reactions for constructing embedded ring system(s) within the macrocyclic skeleton; and (3) transannular reactions for skeletal reorganizations. Concurrent generation of a stereogenic center(s) in these late-stage skeletal transformations should bring about step-economical synthesis of stereochemically rich macrocyclic natural products. In this section, selected examples of chirality-generating macrocyclizations will be discussed.

Chirality-generating macrocyclizations

Macrocyclizations with concomitant generation of a stereogenic center(s) should expedite the synthesis of naturally occurring macrocycles having multiple stereogenic centers along the macrocyclic backbone. This section will only show selected examples of chirality-generating macrocyclizations. Additional examples may be found in recent reviews on this specific topic by Zheng and Hong.[37]

Prins-type macrocyclizations. Perhaps the most widely recognized chirality-generating macrocyclization is Prins-type macrocyclization[38] (Scheme 14). The Prins reaction of aldehydes and homoallylic alcohols is known to provide 2,6-*cis*-configured tetrahydropyrans *via* oxocarbenium ions. The high stereochemical fidelity of the Prins reaction comes from the fact that the stereochemical outcome is governed by a chair-like transition state. An elegant demonstration of Prins-type macrocyclization was described by Lee and co-workers in their total synthesis of (+)-neopeltolide (**78**).[39] Thus, the treatment of olefinic diethyl acetal **98** with TESOTf/TMSOAc in AcOH provided, after methanolysis of the resultant acetate, alcohol **99** in 47% yield with 9 : 1 diastereoselectivity. In this reaction, the diethyl acetal functional group served as an equivalent to an aldehyde. Complementarily, olefinic aldehyde **100** also underwent Prins-type macrocyclization under the same reaction conditions to afford alcohol **99** in 68% yield with >20 : 1 diastereoselectivity, after methanolysis. Thus, **100** served as a better precursor than **98** in terms of product yield and diastereoselectivity. The Mitsunobu reaction of **99** with α,β-unsaturated carboxylic acid **101** furnished (+)-neopeltolide (**78**). In these examples, the 14-membered macrolactone skeleton and its engrafted tetrahydropyran ring of (+)-neopeltolide were forged with spontaneous generation of two stereogenic centers in a single transformation.

Due to the high stereochemical fidelity and mild reaction conditions, Prins-type macrocyclizations have been extensively applied to the synthesis of macrolide natural products embedded with tetrahydropyran ring(s), such as bryostatins,[40] kendomycin,[41] and polycavernoside A.[42] In these remarkable applications, allylsilanes,[40b–d] allylbis(silane)s,[40a] and dioxinones[43] were used as nucleophilic functional groups, thereby expanding the scope of Prins-type macrocyclizations.



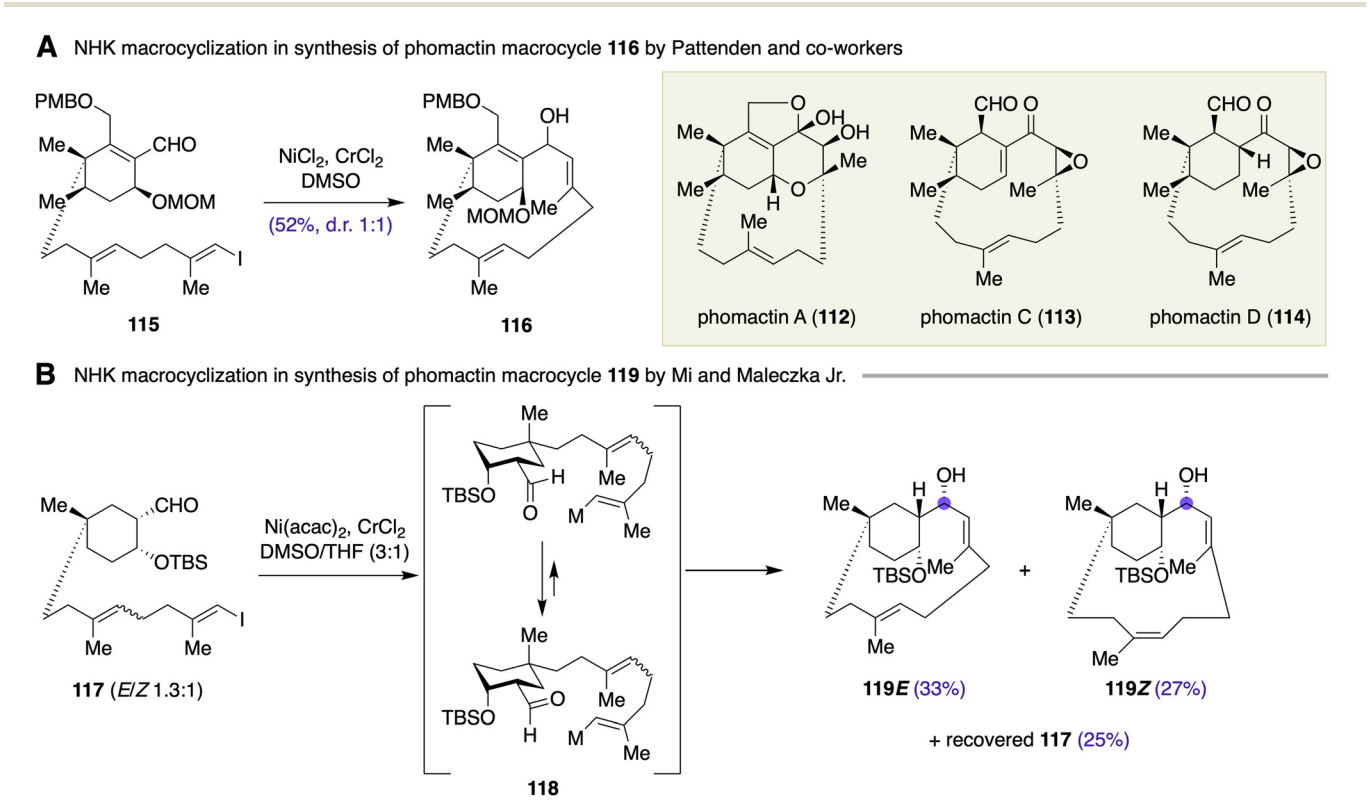
Scheme 14 (A) Prins-type macrocyclization in the total synthesis of (+)-neopeltolide (**78**) by Lee and co-workers. (B) Prins-type macrocyclization in the total synthesis of bryostatin 9 (**102**) by Wender and Schreir. (C) Prins-type macrocyclization in the formal synthesis of (–)-kendomycin (**105**) by Rychnovsky and Bahnck. (D) Prins-type macrocyclization in the total synthesis of (–)-polycavernoside A (**109**) by Lee and Woo.

Chromium-mediated macrocyclizations. Owing to the exceptional functional group tolerance and mild reaction conditions, chromium-mediated reactions, including the Ni(II)/Cr(II)-mediated Nozaki–Hiyama–Kishi (NHK) reaction,[44,45] are another powerful means to achieve chirality-generating macrocyclizations.

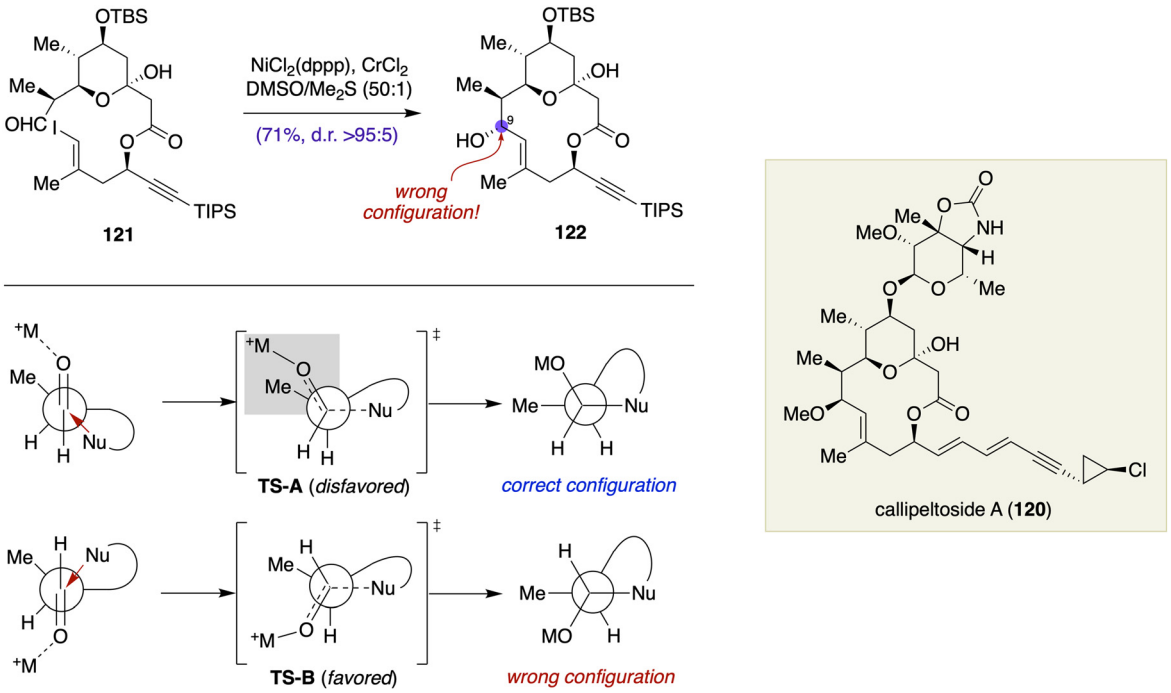
Pattenden and Maleczka independently reported NHK macrocyclization strategies for the construction of the phomactin macrocyclic backbone (Scheme 15). The Pattenden group subjected iodoolefin-tethered aldehyde **115** to NHK macrocyclization (25 mol% $NiCl_2$, 6 equiv. of $CrCl_2$, DMSO) to obtain macrocyclic alcohol **116**, representing the carbon skeleton of phomactins C and D, in 52% yield albeit as a 1 : 1 mixture of diastereomers.[46] Meanwhile, the Maleczka group found that the treatment of iodoolefin-tethered aldehyde **117** (*E*/*Z* 1.3 : 1) with 2 mol% $Ni(acac)_2$ and 10 equiv. of $CrCl_2$ in 1 : 3 THF/DMSO (9 mM) at room temperature delivered macrocyclic alcohols **119*E*** and **119*Z*** in 33 and 27% yields, respectively, along with unreacted **117** in 25% yield.[47] Importantly, the NHK macrocyclization was highly stereoselective and gave **119*E*** and **119*Z*** as single stereoisomers with respect to the newly generated stereogenic center. Maleczka *et al.* ascribed this stereochemical consequence to the steric and/or dipole interaction(s) between the formyl group and the silyloxy group in **118**. Thus, the local structure around the cyclohexane ring was crucial to the success of the chirality generation.

Marshall and Eidam disclosed the formal synthesis of callipeltoside A aglycone, in which they attempted to construct the 14-membered macrolactone skeleton with the concomitant generation of the C9 stereogenic center (Scheme 16).[48] The exposure of aldehyde iodoolefin **121** to 6 mol% $NiCl_2$(dppp) and 7 equiv. of $CrCl_2$ in DMSO/Me_2S (50 : 1, v/v) at room temperature delivered macrocyclic alcohol **122** in 71% yield as a single stereoisomer, although the configuration at the C9 position was opposite to the desired one. The stereochemical course of the NHK macrocyclization was reasoned by a torsional interaction model. Because **TS-A** suffers from the torsional strain between the existing C8 methyl group and the generating C9 alkoxy group, the reaction proceeds *via* **TS-B** to avoid such an unfavorable interaction and gives the undesired diastereomer **122**. While this example was not entirely successful, it illustrates the difficulties in predicting the stereochemistry of chirality-generating macrocyclizations.

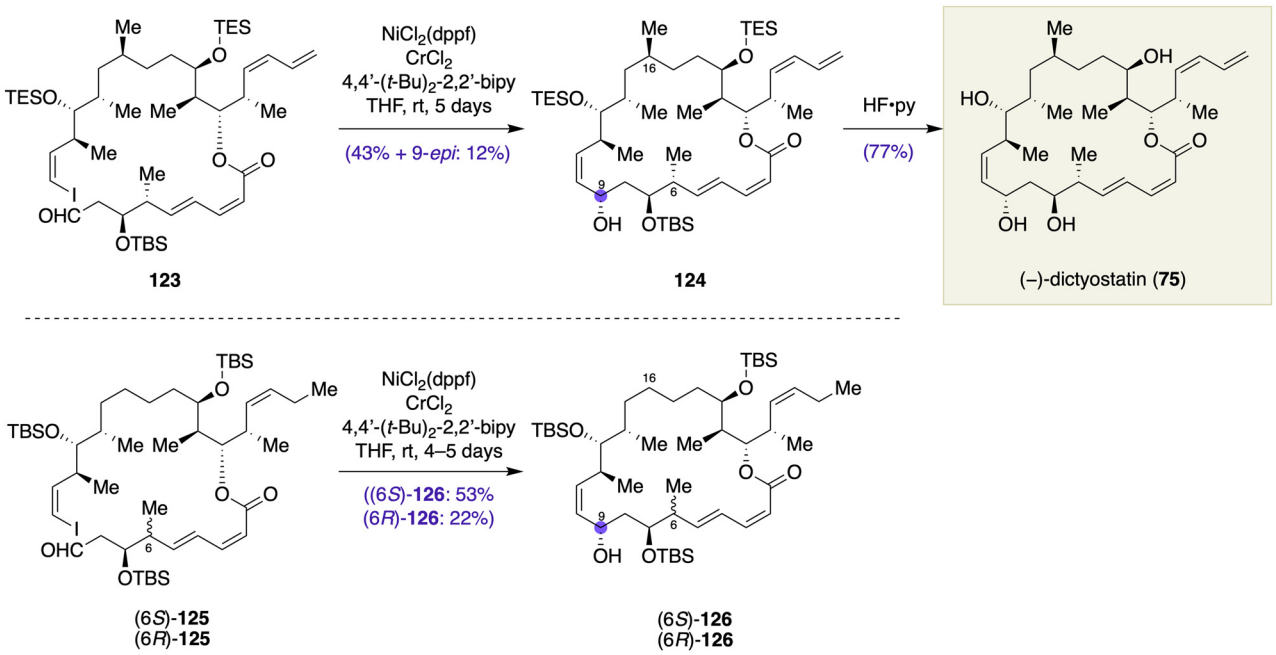
Curran and co-workers described in their total synthesis of (−)-dictyostatin (**75**) and its stereoisomers the NHK macrocyclization of aldehyde iodoolefin **123** to close the 22-membered macrocyclic skeleton with concomitant formation of the stereogenic center at the C9 position, giving macrocyclic alcohol **124** in 43% yield along with its C9 epimer in 12% yield (Scheme 17).[49] The macrocyclization was executed at the final stage of the synthesis. Importantly, Curran *et al.* observed in their preliminary optimization studies that subtle structural changes in the macrocyclization precursor had significant influence on the stereochemical consequence of the macrocyclization. Thus, NHK macrocyclization of aldehyde iodoolefin 6*S*-**125** provided macrocyclic alcohol **126** with desired C9 configuration in 53% yield as a single stereoisomer, whereas that of 6*R*-**125** resulted in a 75 : 25 mixture of diastereomers at C9 (22% isolated yield). It appears that the remote stereogenic centers at C6 and even at C16 would have an impact on the transition state of the macrocyclization.



Scheme 15 (A) NHK macrocyclization toward the total synthesis of phomactins A, C, and D (**112**–**114**) by Pattenden and co-workers. (B) NHK macrocyclization in the synthesis of phomactin macrocycle **119** by Mi and Maleczka Jr.



Scheme 16 NHK macrocyclization in the total synthesis of callipeltoside A (**120**) by Eidam and Marshall.

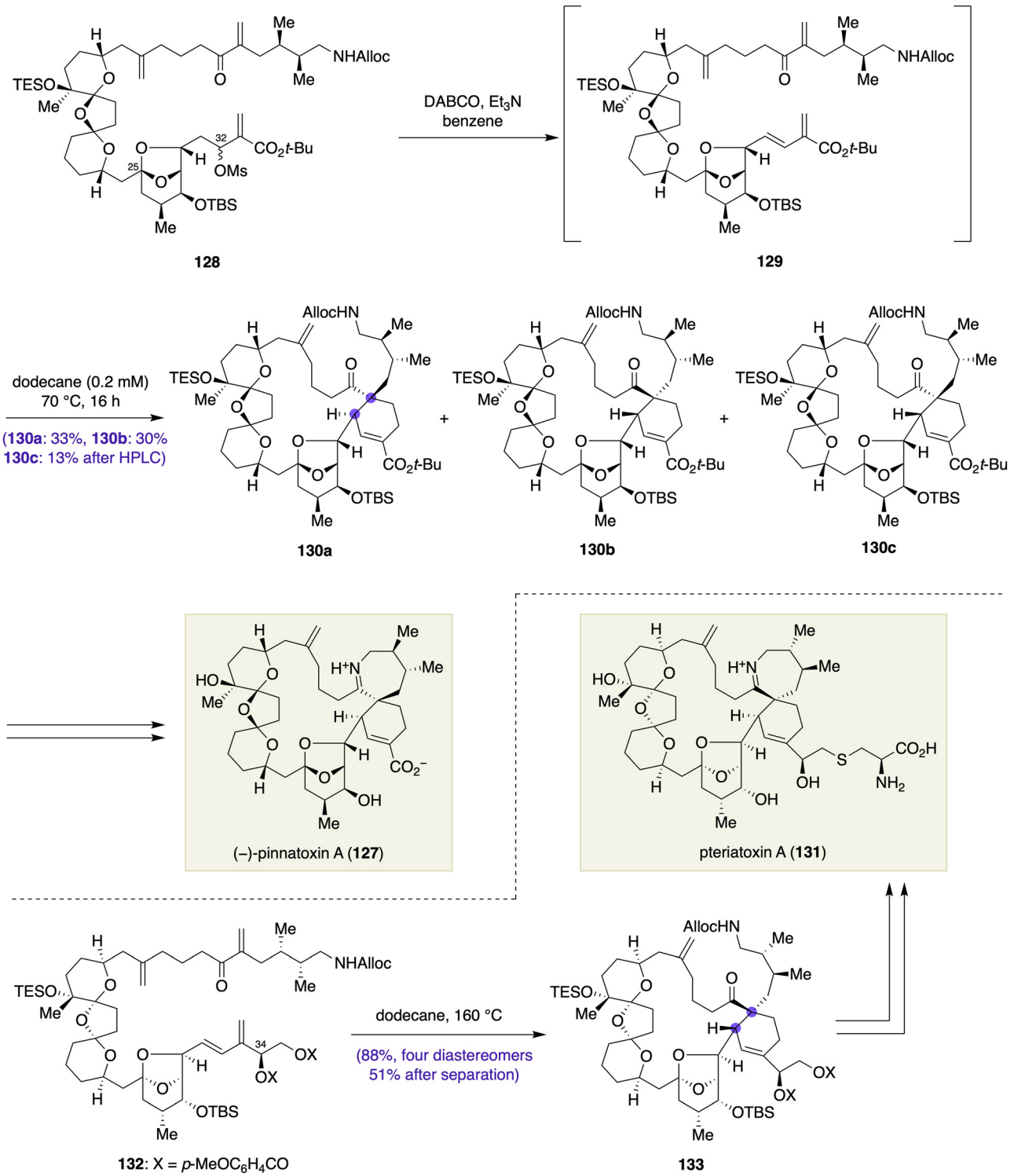


Scheme 17 NHK macrocyclization in the total synthesis of (–)-dictyostatin (**75**) by Curran and co-workers.

Diels–Alder macrocyclizations. The renowned Diels–Alder reaction is a pericyclic reaction of conjugated dienes and dienophiles, and up to four contiguous stereogenic centers are generated in the product cyclohexene derivatives.[50] Using suitably designed precursors, transannular Diels–Alder reaction occurs under relatively mild and essentially neutral conditions, making the reaction an attractive means to rapidly build up stereochemically complex polycyclic skeletons.[50d] Moreover, there are a plethora of natural products whose biosynthesis is thought to involve Diels–Alder reaction. Accordingly, a transannular Diels–Alder reaction has been implemented in the synthesis of various natural products, including alkaloids, polyke-

tides, terpenoids, and steroids. However, Diels–Alder macrocyclizations have less precedents than the typical transannular Diels–Alder reaction, although the initial concept was disclosed by Corey in 1975[51] and the earliest example in total synthesis was described by Stork and Nakamura in 1983.[52]

Total syntheses of structurally complex cyclic imine neurotoxins by Kishi and co-workers were based on a late-stage Diels–Alder macrocyclization strategy (Scheme 18).[53] In the first total synthesis of (−)-pinnatoxin A (**127**), the unnatural enantiomer, S_N2' displacement of mesylate **128** with DABCO,



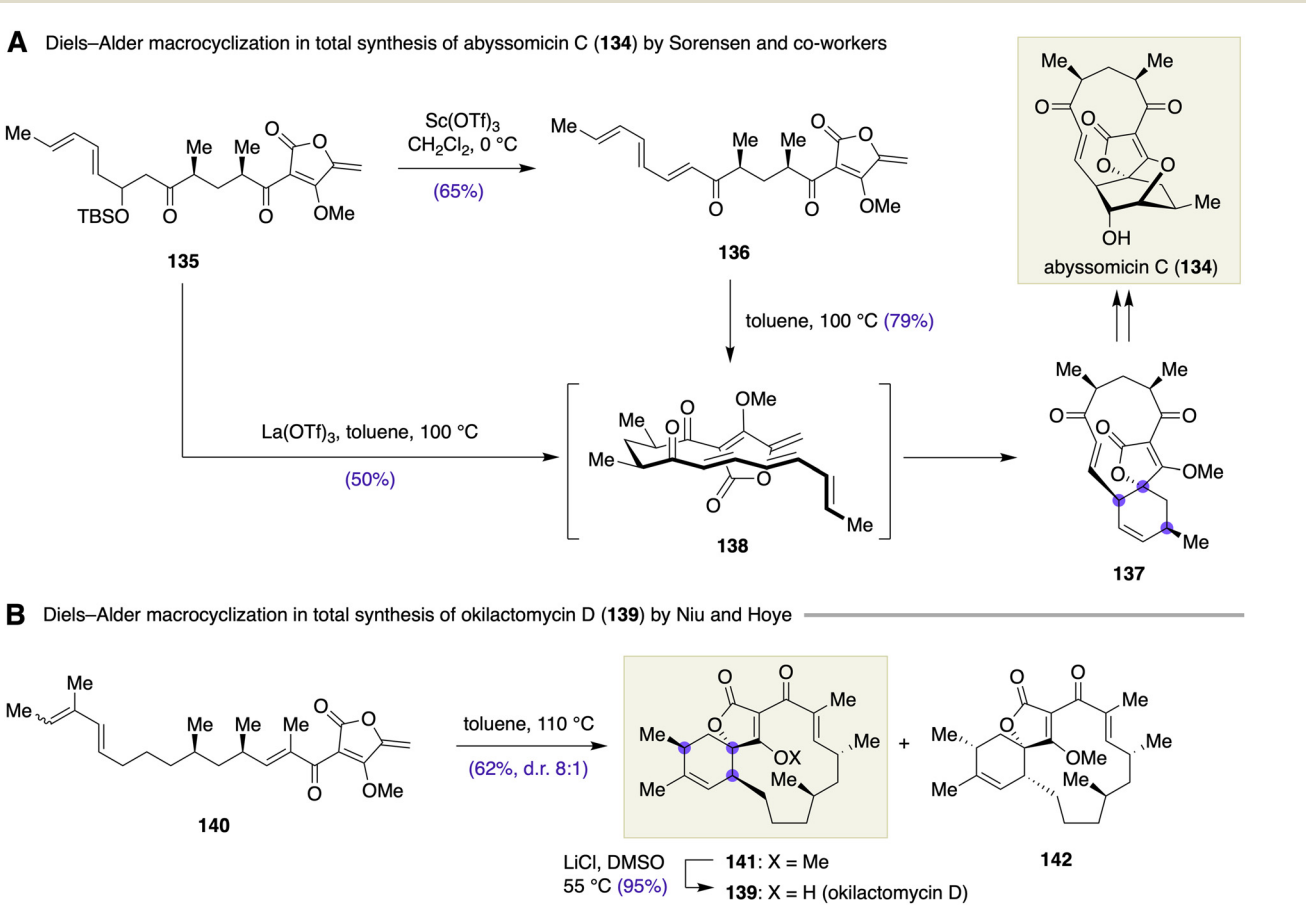
Scheme 18 Diels–Alder macrocyclizations in the total syntheses of (−)-pinnatoxin A (**127**) and pteriatoxin A (**131**) by Kishi and co-workers.

followed by elimination of the derived adduct with Et_3N, resulted in the generation of the transient diene **129**, which underwent Diels–Alder macrocyclization in dodecane (0.2 mM) at 70 °C to give the desired *exo*-product **130a**, along with the undesired *exo*-product **130b** and *endo*-product **130c** in 78% combined yield with 1.0 : 0.9 : 0.4 selectivity. Kishi *et al.* noted that the *exo*-selectivity of the Diels–Alder macrocyclization was dependent on the local structure of the C25–C32 moiety. Subsequently, in their total synthesis of pteriatoxins, the Kishi group investigated in detail into the stereochemistry of Diels–Alder macrocyclization using a series of substrates.[54] Kishi *et al.* found that the reactivity and *exo*/*endo*-selectivity of Diels–Alder macrocyclization of dienes **132** depended on the configuration at the C34 position and the protecting group 'X' of the C34 and C35 hydroxy groups. Diels–Alder macrocyclization of bis(*p*-methoxybenzoate) **132** gave the best result and provided the desired product **133** in 51% isolated yield.

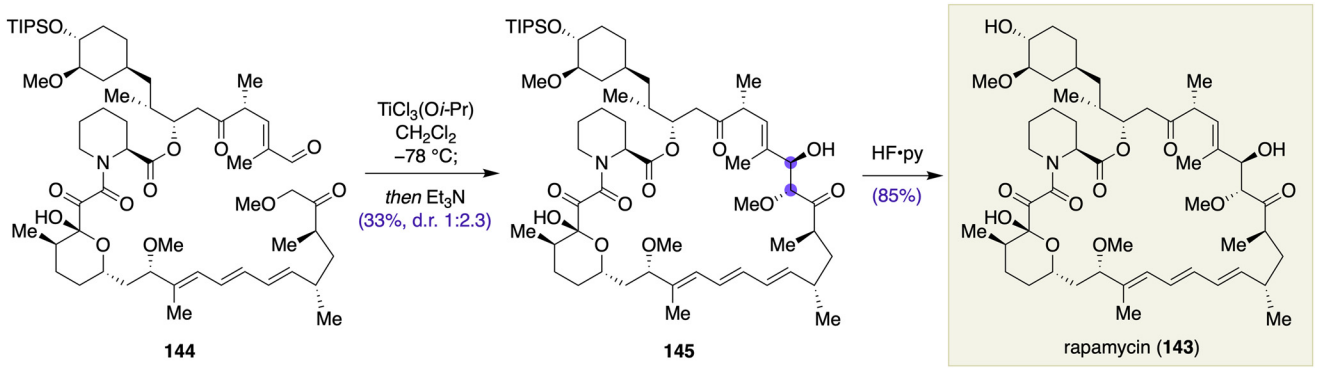
Sorensen and co-workers demonstrated that a Diels–Alder macrocyclization was remarkably effective for constructing the carbon skeleton of abyssomicin C (**134**) (Scheme 19A).[55] The elimination of the β-silyloxy group from ketone **135** led to sensitive trienone **136** (65%), which underwent Diels–Alder macrocyclization to deliver macrocycle **137** upon heating in toluene at 100 °C (79%). The reaction was supposed to proceed *via* transition state **138**, which accounted for the observed stereochemical consequence. Tandem elimination/Diels–Alder macrocyclization from **135** was also possible by treatment with $La(OTf)_3$ in toluene at 100 °C, providing **137** in 50% yield. A similar Diels–Alder macrocyclization strategy was successfully implemented in the total synthesis of okilactomycin D (**139**) by Niu and Hoye (Scheme 19B).[56]

Aldol-type macrocyclizations. Intramolecular aldol reactions represent a potentially useful yet comparatively underutilized class of transformations for macrocycle construction. In contrast to macrolactonization or ring-closing metathesis, the commonly used methods for aldol-based macrocyclizations enable the formation of a macrocycle with simultaneous installation of a stereogenic center, thereby offering opportunities for realizing step-economy and late-stage stereochemical control.

The Danishefsky group employed an intramolecular aldol reaction for the total synthesis of an immunosuppressive macrocyclic natural product, rapamycin (**143**) (Scheme 20).[57] The macrocyclization of **144** was achieved through an intramolecular aldol reaction *via* a titanium enolate generated by treatment with $TiCl_3(Oi\text{-}Pr)$, furnishing macrocycle **145** in 33% yield as a 1 : 2.3 diastereomeric mixture. Subsequent desilylation of **145** provided rapamycin (**143**) in 85% yield.



Scheme 19 (A) Diels–Alder macrocyclization in the total synthesis of abyssomicin C (**134**) by Sorensen and co-workers. (B) Diels–Alder macrocyclization in the total synthesis of okilactomycin D (**139**) by Niu and Hoye.

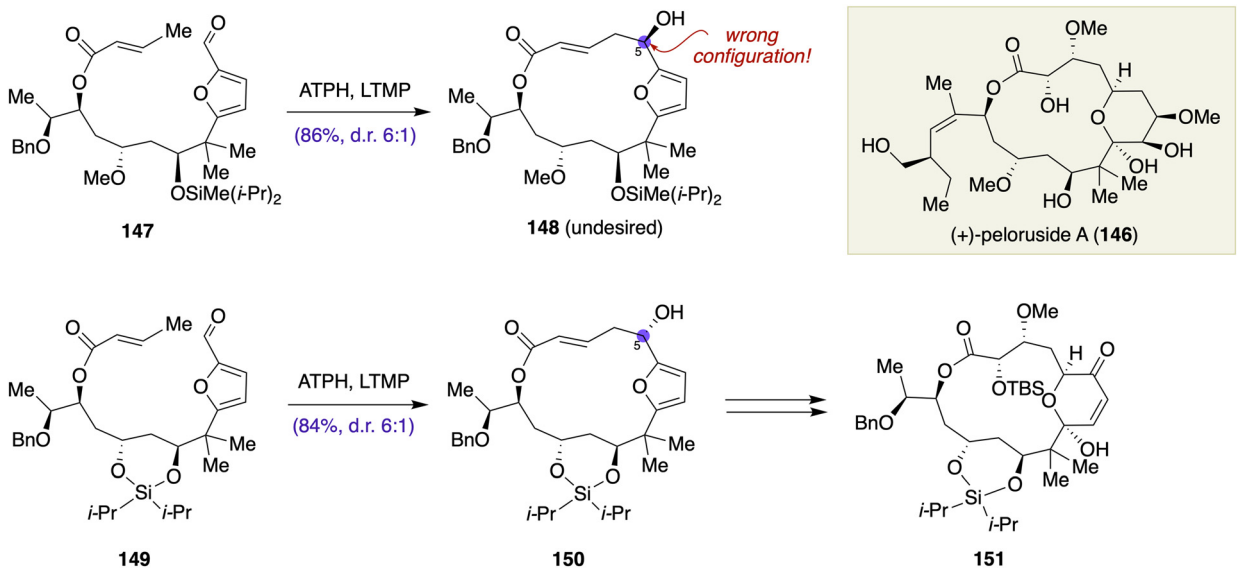


Scheme 20 Aldol macrocyclization in the total synthesis of rapamycin (**143**) by Danishefsky and co-workers.

Importantly, this titanium enolate-mediated aldol macrocyclization enabled the simultaneous construction of the 31-membered ring and installation of the two stereogenic centers, although the product yield and the diastereoselectivity were moderate. By merging macrocycle formation and chirality generation into a single transformation, this strategy provided an efficient solution to the total synthesis of a large and architecturally complex macrolide natural product, rapamycin.

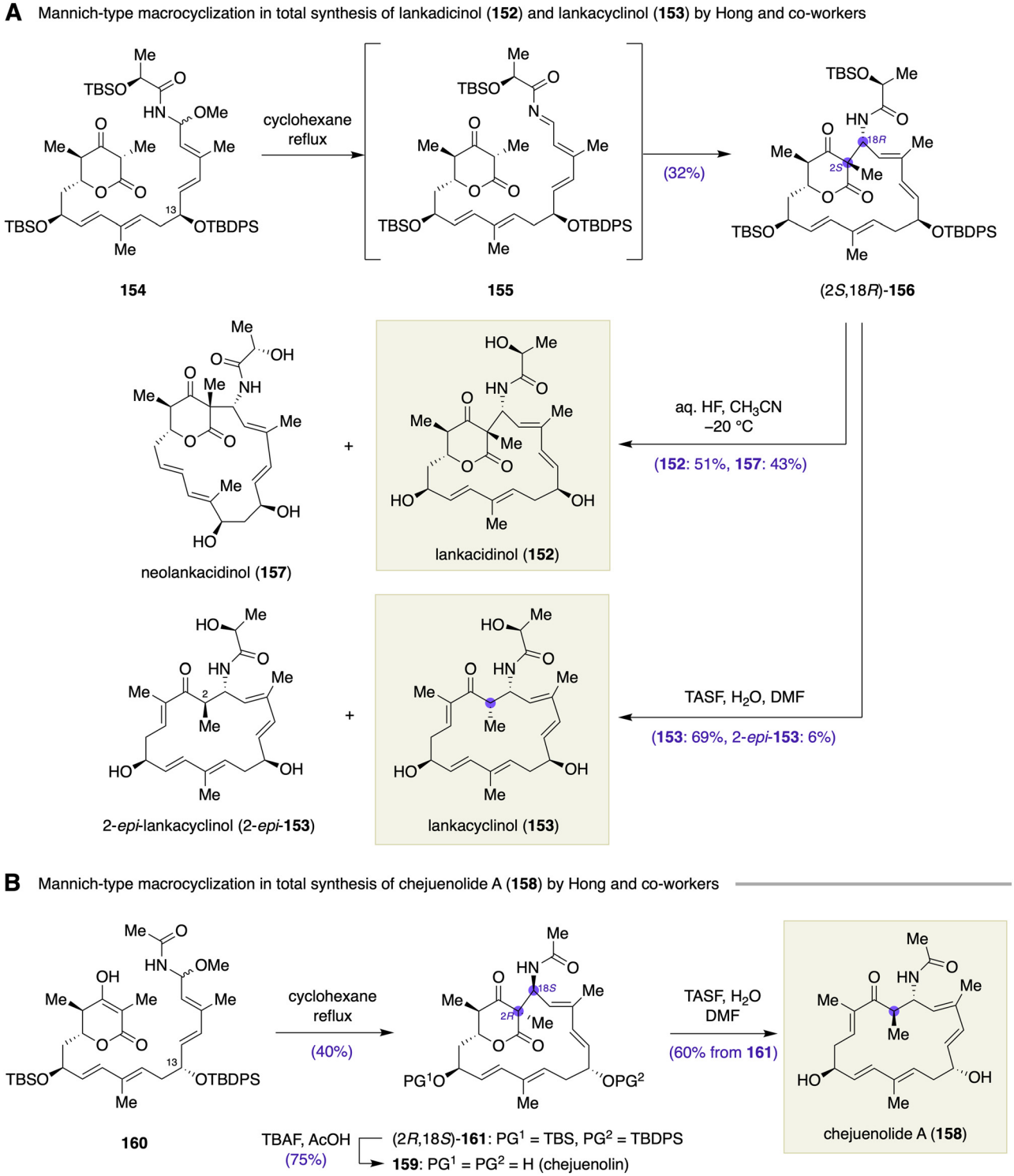
The Sammakia group assembled the macrocyclic skeleton of (+)-peloruside A (**146**) through an intramolecular vinylogous aldol reaction[58,59] (Scheme 21). The exposure of **147** to 2.0 equiv. of lithium 2,2,6,6-tetramethylpiperidine (LTMP) and 2.2 equiv. of aluminum tris(2,6-diphenylphenoxide) (ATPH)[60] in toluene/THF at −48 °C delivered macrocyclic alcohol **148** in 86% yield as a 6 : 1 diastereomeric mixture; however, the configuration at the C5 position of the major diastereomer was opposite to the desired configuration. Sammakia *et al.* noted that the stereochemistry of the cyclization could be dictated by the conformation of the forming macrocycle and that a different conformation could provide the desired stereochemical outcome. Therefore, the vinylogous aldol macrocyclization of silylene **149** was investigated. Subjection of **149** to the intramolecular vinylogous aldol reaction conditions using LTMP/ATPH provided macrocyclic alcohol **150** in 84% yield as a 6 : 1 diastereomeric mixture, where the major diastereomer had the desired absolute configuration at C5. Subsequent transformations of **150**, including an Achmatowicz reaction, afforded peloruside A macrolactone core **151**. Thus, the silylene group within **149** served successfully as a ring constraint for directing the vinylogous aldol macrocyclization to give macrocyclic alcohol **150** with correct configuration, although it is still difficult to rationalize the stereochemical consequence of this specific case.

Mannich-type macrocyclizations. The lankacidin family of macrocyclic antibiotics show potent antimicrobial activity against Gram-positive bacteria and antitumor activity in



Scheme 21 Vinylogous aldol macrocyclization in the synthesis of the macrolactone core **151** of (+)-peloruside A (**146**) by Sammakia and coworkers.

certain cancer cell lines. The Hong group described a concise synthesis of lankacidinol (**152**) and lankacyclinol (**153**), in which a biomimetic Mannich-type macrocyclization was successfully implemented as the key transformation (Scheme 22A).[61] Specifically, *N*,*O*-acetal **154** underwent elimination of methanol in refluxing cyclohexane to give transient imine **155**, which then participated in an intramolecular Mannich-type reaction with the dihydropyran-2,4-dione moiety to furnish the macrocyclization product (2*S*,18*R*)-**156** in 32% yield with simultaneous installation of the C2 and C18 stereo-



Scheme 22 (A) Mannich-type macrocyclization in the total synthesis of lankacidinol (**152**) and lankacyclinol (**153**) by Hong and co-workers. (B) Mannich-type macrocyclization in the total synthesis of chejuenolide A (**158**) by Hong and co-workers.

genic centers. Two additional diastereomers at C2 and C18, *i.e.*, (2*R*,18*R*)-**156** and (2*R*,18*S*)-**156** (structures not shown), were also isolated in 14% combined yield. Removal of the silyl groups from **156** with aq. HF in CH_3CN at −20 °C provided lankacidinol (**152**) in 51% yield, along with its unnatural isomer 'neolankacidinol' (**157**) in 43% yield. The latter was assumed to arise from a dehydration/hydration sequence on a carbocationic intermediate, as resubmission of **157** to the desilylation conditions gave a 1.5 : 1 mixture of **152** and **157** (38%, 88% based on recovered starting material). Meanwhile, treatment of (2*S*,18*R*)-**156** with TASF and H_2O in DMF resulted in a decarboxylative collapse of the δ-lactone with concomitant desilylation to deliver lankacyclinol (**153**) in 69% yield and its 2-epimer, 2-*epi*-**153**, in 6% yield. Hong *et al.* further demonstrated that (2*S*,18*R*)-**156** was a versatile intermediate for the total synthesis of other members of the lankacidin antibiotics including lankacidin A and C, lankacidinol A, and lankacyclinol A.

Hong and co-workers applied their biomimetic Mannich-type macrocyclization to the total synthesis of chejuenolide A (**158**) by assuming a hypothetical biosynthetic precursor, chejuenolin (**159**) (Scheme 22B).[62] A solution of *N*,*O*-acetal **160** in cyclohexane was refluxed to give (2*R*,18*S*)-**161** in 40% yield as the major diastereomer, along with (2*S*,18*S*)-**161** and (2*S*,18*R*)-**161** (structures not shown) in 7 and 13% yields, respectively. The major diastereomer (2*R*,18*S*)-**161** represents a protected form of chejuenolin (**159**). In comparison with the lankacidinol case, the stereochemical outcome of the Mannich-type macrocyclization of **160** was likely dependent on the configuration at the C13 position. Thus, it seems that the C13 stereogenic center has a significant impact on the conformation of *N*,*O*-acetal **160**, the macrocyclization precursor, and consequently, it affects the transition state of the Mannich-type macrocyclization. Deprotection of the silyl groups from (2*R*,18*S*)-**161** with TBAF buffered with AcOH afforded chejuenolin (**159**). Meanwhile, the desilylation of (2*R*,18*S*)-**161** with TASF and H_2O in DMF triggered concomitant decarboxylation to afford chejuenolide A (**158**) in 60% yield.

Heck macrocyclizations. Macrocyclic cyclophanes with axial- or planar-chirality including macrocyclic oligopeptide antibiotics pose a unique challenge to the synthetic community.[63] Axially/planarly chiral cyclophanes are strained and conformationally restricted compounds such that macrocyclizations to forge their backbone structure need to override the energetic barrier that the strained macrocycle poses with the concurrent generation of the axial/planar chirality.

Speicher and co-workers reported an atropselective Heck macrocyclization[64] for enantioselective total synthesis of (*M*)-isoplagiochin D (**162**), a bis(bibenzyl) natural product (Scheme 23A).[65] Heck macrocyclization of olefinic triflate **163** was examined under various conditions. When the reaction was performed in the presence of the preformed Pd((*R*)-BINAP)$_2$ complex as the catalyst and PMP as the base in DMF at 70 °C, (*M*)-**164** could be obtained in 22% yield with 37% ee. Although the product yield and optical purity were moderate, atropselective Heck macrocyclization was certainly a viable approach for the construction of the strained macrocyclic skeleton of **162**.

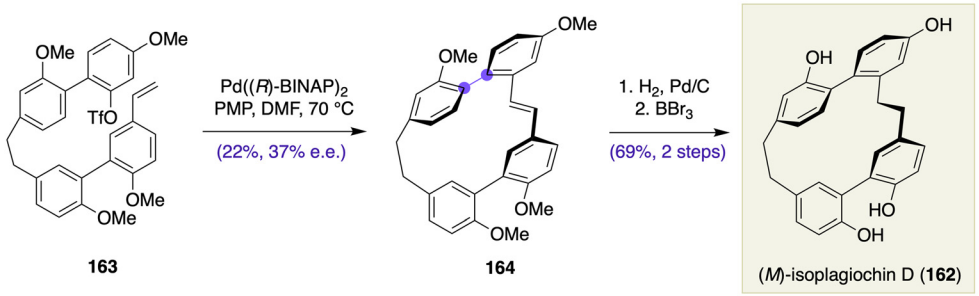
Subsequently, Speicher *et al.* described atropselective Heck macrocyclization of iodide **165** as an improved approach toward isoplagiochin D (Scheme 23B).[66] The macrocyclization precursor **165** was substituted with a chiral sulfinyl group, which served as an atropselectivity inducer. Interestingly, the atropselectivity of the macrocyclization of **165** was found to be dependent on the reaction conditions. Treatment of **165** with $Pd_2(dba)_3$/S-Phos and PMP in DMF at 110 °C provided (*P*)-**166** in 57% yield with 4 : 1 atropselectivity. Interestingly, the atropselectivity reversed upon lowering the reaction temperature to 70 °C and gave (*M*)-**166** in 60% yield with 3 : 1 atropselectivity. The reaction of **165** under the catalysis of $Pd_2(dba)_3$ resulted in further enhancement of the atropselectivity toward (*M*)-**166**, which was isolated in 80% yield with 99 : 1 selectivity. The observed atropselectivity switching between (*P*)-**166** and (*M*)-**166** could be reasoned by the following scenario. Under kinetic control ($Pd_2(dba)_3$, 1,2,2,6,6-pentamethylpiperidine (PMP), DMF, 70 °C), oxidative addition of **165** to the 'ligandless' palladium complex results in the formation of an equilibrating mixture of palladacycles (*P*)-**167** and (*M*)-**167**. Through energetically more favored (*M*)-**167**, insertion into the proximal olefin occurs to afford (*M*)-**166**. Meanwhile, oxidative addition of **165** to Pd(S-Phos) complex under thermodynamic conditions ($Pd_2(dba)_3$/S-Phos, PMP, DMF, 110 °C) gives organopalladium intermediate (*P*)-**168**, which undergoes insertion into the olefin to provide (*P*)-**166** as the major isomer. As a relevant example, Speicher *et al.* achieved an enantioselective total synthesis of (*P*)-isoriccardin C (**169**) through a chiral sulfinyl group-directed atropselective macrocyclic C–H activation (Scheme 23C).[67]

C–H oxidative macrocyclizations. C–H functionalization reactions have been extensively investigated in recent years as an enabling means to achieve the late-stage functionalization of complex molecules.[7] However, their application to chirality-generating macrocyclization has still been underdeveloped.

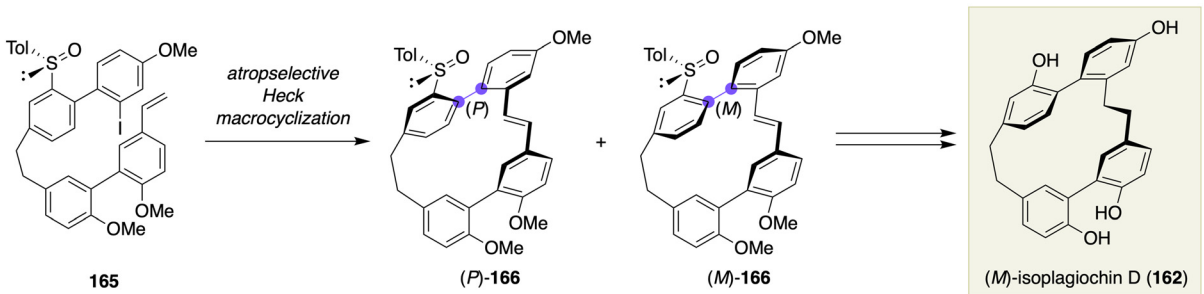
A pioneering example was described by Stang and White in their total synthesis of 6-deoxyerythronolide B (**172**) *via* a late-stage palladium-catalyzed allylic C–H oxidation in a macrocyclization format (Scheme 24A).[68] Thus, olefin-tethered carboxylic acid **173**, synthesized through standard aldol chemistry, underwent allylic C–H oxidative macrocyclization under the catalysis of $Pd(OAc)_2{\cdot}(PhS(O)CH_2)_2$ in the presence of benzoquinone to afford macrolactone **175** with the correct configuration at C13 (56% yield plus 8% r.s.m. after two recycles). The reaction was thought to involve a π-allyl–Pd–carboxylate intermediate **174** and proceed through a product-like transition state. The actual product **175** was calculated to be 3 kcal mol^{-1} more stable than 13-*epi*-**175** (structure not shown).

Haydl and Breit demonstrated in their total synthesis of epothilone D (**176**), a rhodium-catalyzed macrocyclization of an advanced alkyne carboxylic acid (Scheme 24B).[69] Specifically, the reaction of **177** in the presence of [Rh(cod)Cl]$_2$/DPEPhos and benzoic acid in DCE at 70 °C afforded macrolactone **178** in 43% yield with dr 4 : 1.

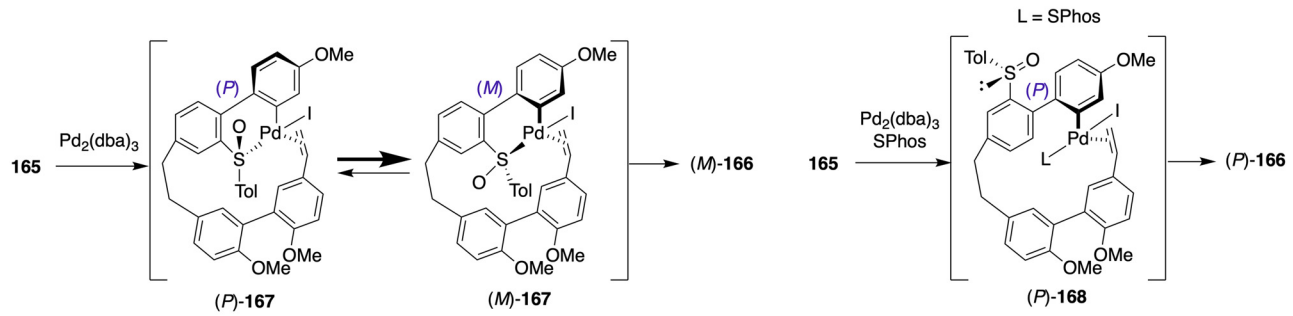
A Total synthesis of (*M*)-isoplagiochin D (**162**) by Speicher and co-workers (2012)



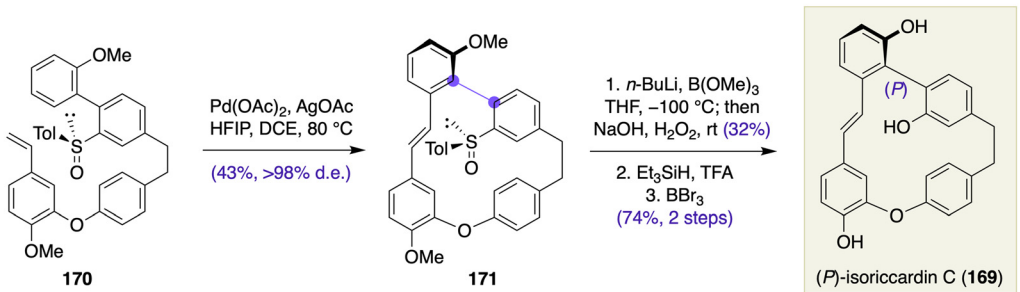
B Total synthesis of (*M*)-isoplagiochin D (**162**) by Speicher and co-workers (2018)



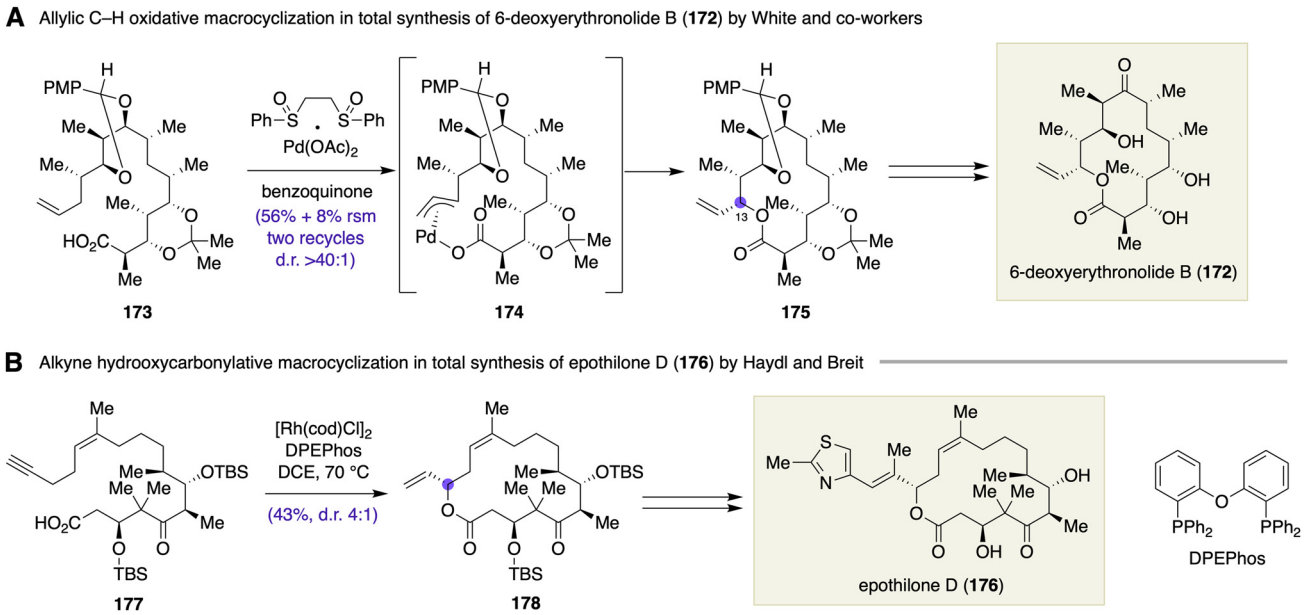
Entry	Reagents and Conditions	Yield ((*P*)-**166**/(*M*)-**166**)
1	$Pd_2(dba)_3$, S-Phos, PMP, DMF, 110 °C, 18 h	57% (4:1)
2	$Pd_2(dba)_3$, S-Phos, PMP, DMF, 70 °C, 48 h	60% (1:3)
3	$Pd_2(dba)_3$, PMP, DMF, 70 °C, 72 h	80% (1:99)



C Total synthesis of (*P*)-isoriccardin C (**169**) by Speicher and co-workers



Scheme 23 (A) Atropselective Heck macrocyclization in the total synthesis of (*M*)-isoplagiochin D (**162**) by Speicher and co-workers (2012). (B) Atropselective Heck macrocyclization in the total synthesis of (*M*)-isoplagiochin D (**162**) by Speicher and co-workers (2018). (C) Atropselective macrocyclic C–H oxidation in the total synthesis of (*P*)-isoriccardin C (**169**) by Speicher and co-workers.



Scheme 24 (A) Allylic C–H oxidative macrocyclization in the total synthesis of 6-deoxyerythronolide B (**172**) by White and co-workers. (B) Alkyne hydrooxycarbonylative macrocyclization in the total synthesis of epothilone D (**176**) by Haydl and Breit.

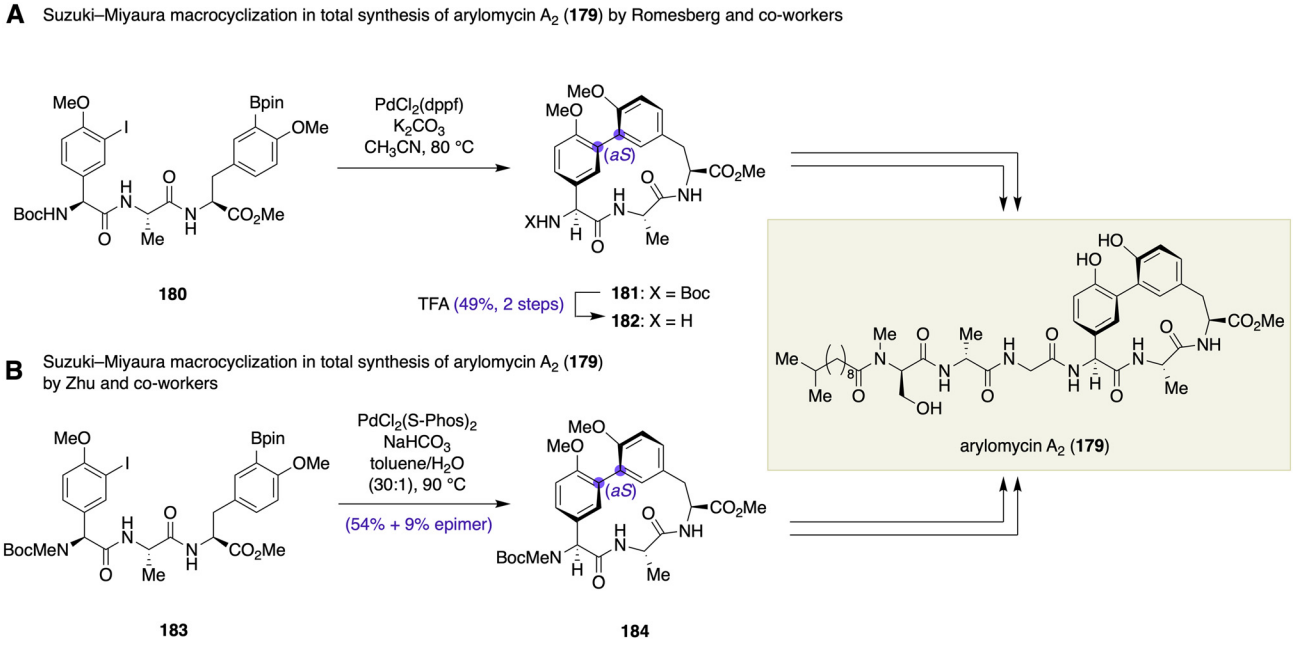
Suzuki–Miyaura macrocyclizations. Macrocyclic glycopeptide antibiotics, as exemplified by vancomycin, have spurred the interest of the synthetic chemistry community because of their characteristic and highly complex structures and medicinally important biological activities.[70] This class of macrocyclic natural products have served as an impetus to advance many synthetic methods for constructing strained macrocycles with axial or planar chirality. Total synthesis of vancomycin and related glycopeptide antibiotics has been reviewed by Boger *et al.*[71]

Because of the unique ability to inhibit bacterial type 1 signal peptidase, arylomycins have caught significant attention from the synthetic community as a promising lead for the development of new therapeutics against drug-resistant bacterial infections. Arylomycins constitute a family of lipopeptide antibiotics having a characteristic biaryl-containing 14-membered macrocycle and exist as a mixture of two atropisomers at room temperature, as indicated by NMR spectroscopy. The first total synthesis of arylomycin A_2 (**179**) was achieved by the group of Romesberg, who demonstrated a Suzuki–Miyaura macrocyclization for atropselective closure of the macrocycle of **179** (Scheme 25A).[72] After detailed optimization experiments, they found that Suzuki–Miyaura macrocyclization[73] of **180** in the presence of $PdCl_2$(dppf) as the catalyst and K_2CO_3 as the base in CH_3CN at 80 °C, followed by deprotection of the Boc group of **181**, afforded macrocycle **182** in 49% yield for the two steps. NMR studies on model macrocycles indicated that the axial chirality depends on the presence or absence of the *N*-methyl group of the phenylglycine residue; the *aS* configuration was favored in the presence of the *N*-methyl group. X-ray crystallographic analysis of an arylomycin A_2-signal peptidase complex showed that only *aS* configured arylomycin A_2 was bound to signal peptidase.[74]

Shortly after the first total synthesis of arylomycin A_2 (**179**) by the Romesberg group, Zhu and co-workers disclosed the second total synthesis of **179**, which involved an atropselective Suzuki–Miyaura macrocyclization of **183**, which corresponded to the *N*-methylated counterpart of **180** (Scheme 25B).[75] Extensive optimization experiments showed that the reaction proceeded most efficiently under the catalysis of $PdCl_2$(S-Phos)$_2$ in the presence of $NaHCO_3$ as the base in toluene/H_2O (30 : 1) at 90 °C, giving macrocycle **184** in 54% yield along with its epimer at the 4-hydroxyphenylglycine residue in 9% yield. Zhu *et al.* also completed the total synthesis of arylomycin B_2 based on the Suzuki–Miyaura macrocyclization strategy.

Even more complex macrocyclic peptides with axial chirality are chloropeptin I (**185**) and complestatin (**186**, chloropeptin II) (Scheme 26). Both natural products have an *aR* configuration at the biaryl axis, and complestatin (**186**) isomerizes to chloropeptin I (**185**) under acidic conditions with the retention of the axial configuration. These non-ribosomal peptides have a couple of strained macrocycles, one of which is responsible for their atropisomeric chirality. Because of their highly complex structures and potential as an HIV therapeutic, these macrocyclic peptides have garnered significant interest from the synthetic community.

The first total synthesis of chloropeptin I (**185**) was accomplished by Hoveyda, Snapper, and co-workers, who made use of a Stille macrocyclization[76] of aryl stannane **187** (Pd(P*t*-Bu$_3$)$_2$, collidine, CsF, dioxane, 50 °C) to forge the 'right-hand' biaryl macrocycle with the desired *aR* configuration atropselectively (Scheme 26A).[77] Hoveyda *et al.* later disclosed the total synthesis of isocomplestatin (**189**), an unnatural atropisomer of complestatin (**186**), through a Suzuki–Miyaura macrocyclization (Scheme 26B).[78] Thus, the reaction of aryl boronate **190**

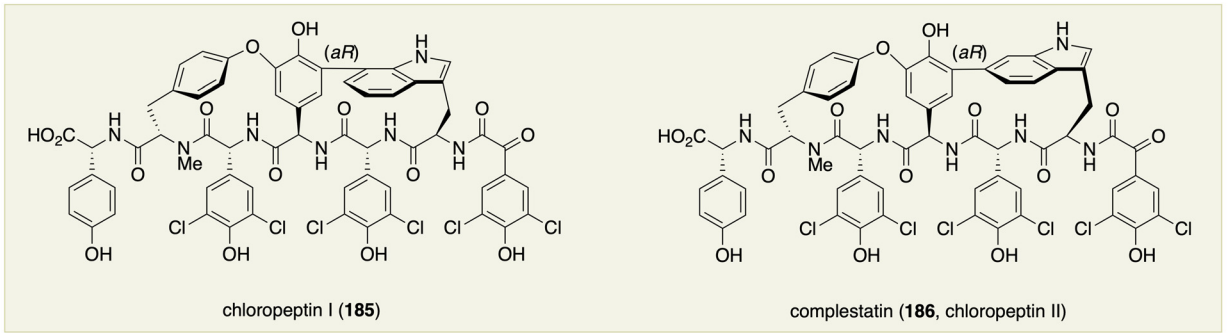


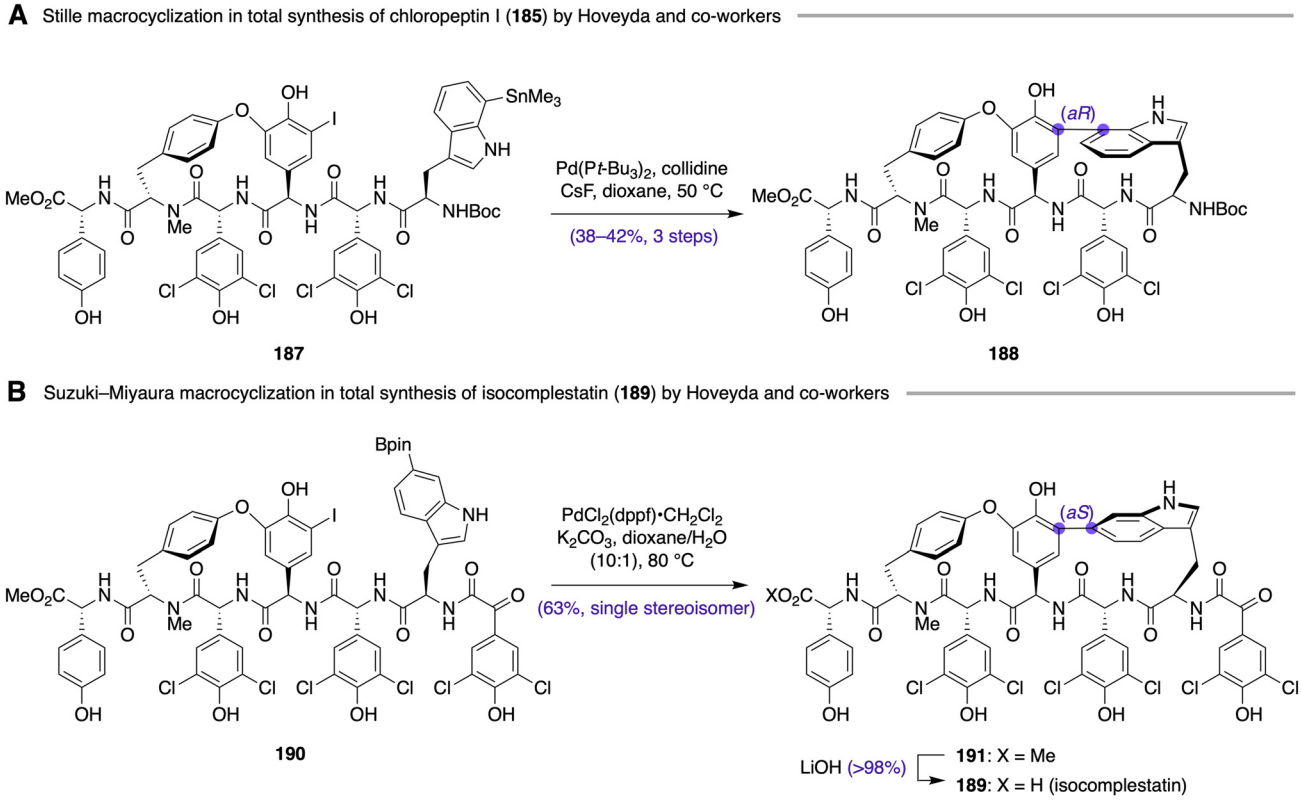
Scheme 25 (A) Atropselective intramolecular Suzuki–Miyaura macrocyclization in the total synthesis of arylomycin A_2 (**179**) by Romesberg and co-workers. (B) Atropselective intramolecular Suzuki–Miyaura macrocyclization in the total synthesis of arylomycin A_2 (**179**) by Zhu and co-workers.

under the influence of $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst and K_2CO_3 as the base in dioxane/H_2O (10 : 1) at 80 °C provided macrocycle **191**, *i.e.*, isocomplestatin methyl ester, in 63% yield as a single stereoisomer, which had an *aS* configuration at the biaryl axis. Hydrolysis of the methyl ester completed the total synthesis of isocomplestatin (**189**). Quite interesting was the observation that the Stille macrocyclization of arylstannane **187** provided chloropeptin-type bis-macrocycle **188** with the natural *aR* configuration, whereas the Suzuki–Miyaura macrocyclization of aryl boronate **190** delivered complestatin-type bis-macrocycle **191** with the unnatural *aS* configuration. Moreover, a model compound lacking the 'left-hand' biaryl ether macrocycle also underwent Suzuki–Miyaura macrocyclization but delivered the corresponding macrocyclic product without atropselectivity. These results suggested the possibility that the stereochemical consequence of macrocyclizations may be highly substrate structure dependent.

Zhu *et al.* carried out more detailed investigations into the atropselectivity of Suzuki–Miyaura macrocyclizations toward the total synthesis of complestatin (**186**) (Scheme 27).[79] Specifically, Zhu and co-workers found that Suzuki–Miyaura reaction of linear tripeptide **192** under the catalysis of $PdCl_2(dppf)\cdot CH_2Cl_2$ in the presence of K_2CO_3 in dioxane/H_2O (15 : 1) at 80 °C afforded macrocycle **193** in 66% yield with an *aR* configuration. The macrocycle **193** represents the DEFG-ring macrocycle of complestatin (**186**). In contrast, intramolecular Suzuki–Miyaura reaction of hexapeptide **194** with the biaryl ether macrocycle under essentially the same reaction conditions delivered macrocycle **195** in 52% yield with an *aS* configuration, which could be converted to isocomplestatin methyl ester (**191**) by desilylation.[80] Similarly, intramolecular Suzuki–Miyaura reaction of hexapeptide **190**, in which the D-ring phenol was unprotected, provided macrocycle **191** in 66% yield with an *aS* configuration. These results strongly indicated that the atropselectivity of Suzuki–Miyaura macrocyclization in the complestatin case was highly substrate dependent. This was further underscored by Suzuki–Miyaura macrocyclizations of **196** and **197**, both of which are epimers at the aryl glycine residue C. These isomers showed a significant change in the peptide backbone conformation, and upon exposure to the optimized conditions, it led to macrocyclization products **198** and **199** with an *aS* configuration.

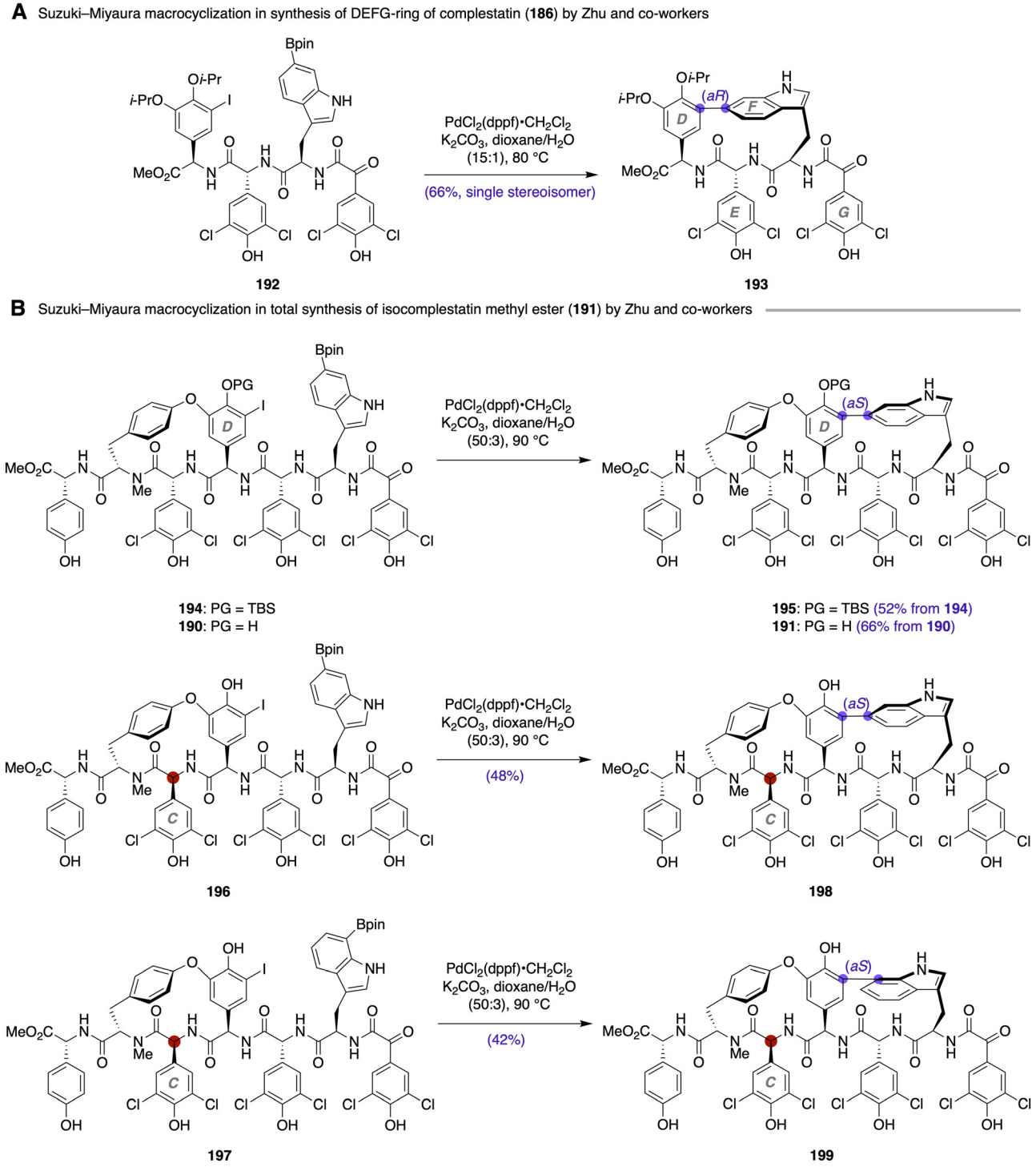
Accordingly, the Zhu group accomplished the total synthesis of complestatin (**186**) by initially forging the phenyl–indole linkage from a linear tripeptide precursor by a Suzuki–Miyaura macrocyclization to establish the desired *aR* configuration, followed by building the biaryl ether macrocycle *via* an intramolecular S_NAr cyclization (Scheme 28).[81] Thus, Suzuki–Miyaura macrocyclization of linear tripeptide **200** was achieved under the previously optimized conditions to give macrocycle **201** in 66% yield with the desired *aR* configuration. After coupling with a tripeptide fragment, the macrocyclization of the resultant hexapeptide **203** by the action of K_2CO_3 and 4 Å MS in DMSO afforded bis-macrocycle **204** in 62% yield from **202** with excellent regio- and atrop-selectivities. Although it was of no consequence, the atropselectivity of this base-mediated macrocyclization was also substrate dependent. The advanced intermediate **204** was finally transformed into complestatin (**186**) in four steps, including the removal of the superfluous nitro group and protecting groups. The Zhu synthesis of complestatin (**186**) clearly underscores the importance of substrate design in directing the stereochemical outcome of the Suzuki–Miyaura macrocyclization, although it was carried out at an early stage.





Scheme 26 (A) Stille macrocyclization in the total synthesis of chloropeptin I (**185**) by Hoveyda and co-workers. (B) Suzuki–Miyaura macrocyclization in the total synthesis of isocomplestatin (**189**) by Hoveyda and co-workers.

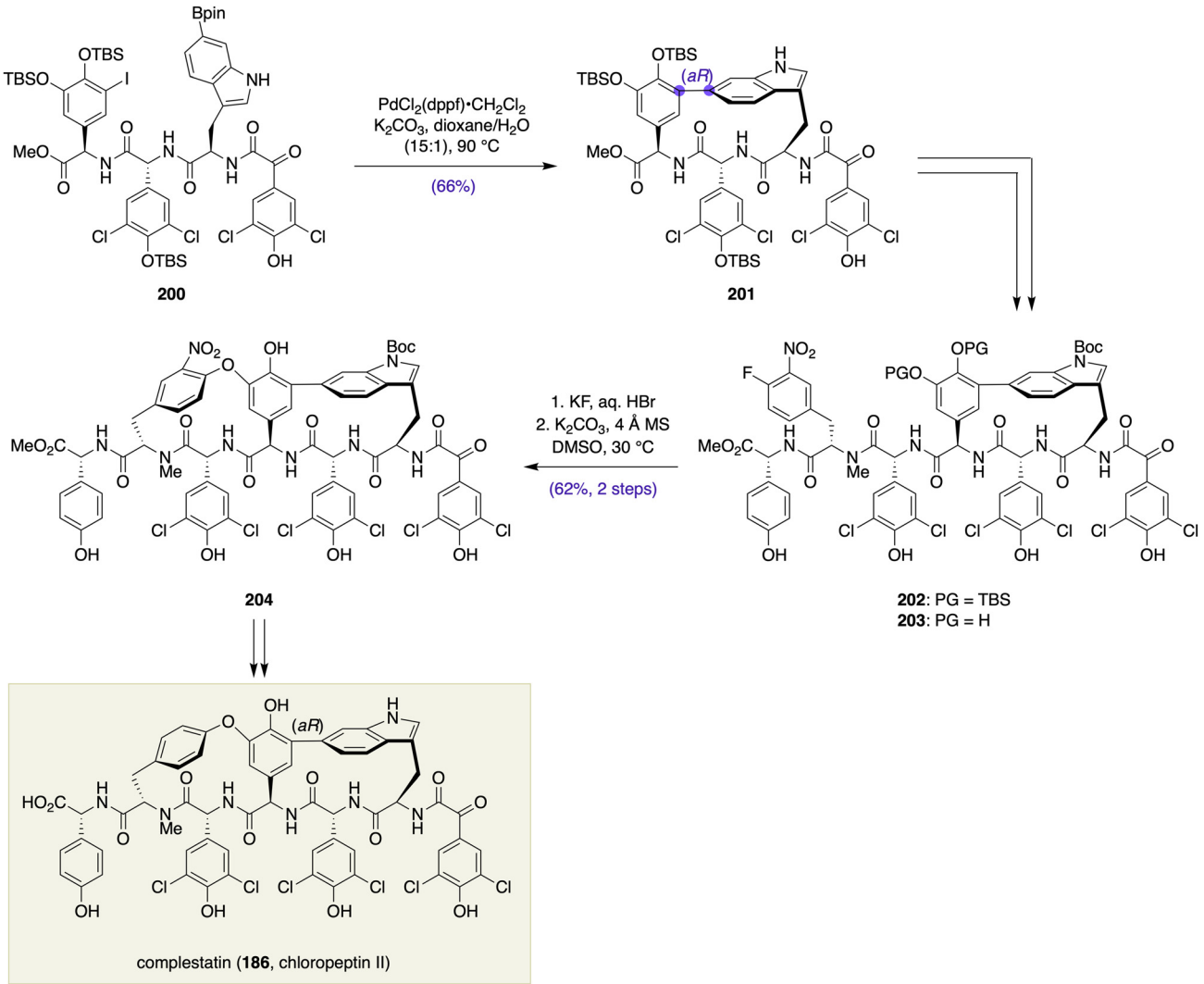
Larock macrocyclizations. Larock indole synthesis is a versatile method for the synthesis of 2,3-disubstituted indole derivatives *via* a palladium-catalyzed annulation of 2-alkynyl anilines.[82] The Boger group reported a Larock macrocyclization in the first total synthesis of complestatin (**186**) (Scheme 29). In the first-generation synthesis, Boger *et al.* envisioned the construction of the 'right-hand' biaryl macrocycle of **205** through an intramolecular Larock annulation of 2′-bromoacetanilide **206**.[83] The incorporation of a triethylsilyl group as an alkyne substituent was intended to direct the regioselectivity of the annulation. In the event, treatment of **206** with $Pd(OAc)_2$/D*t*BPF and Et_3N in toluene/CH_3CN (1 : 1) at 110 °C provided Larock macrocyclization product **205** in 89% yield with 4 : 1 atropselectivity, favoring the desired *aR* isomer. The 'left-hand' biaryl ether macrocycle was subsequently closed *via* an S_NAr macrocyclization to complete the first total synthesis of complestatin (**186**). In the second-generation synthesis, Boger *et al.* demonstrated a late-stage Larock macrocyclization on advanced intermediate **207** in which the 'left-hand' biaryl ether macrocycle was already in place.[84] Thus, exposure of **207** to the optimized reaction conditions (Pd $(OAc)_2$, D*t*BPF, Et_3N, toluene/CH_3CN (10 : 1), 110 °C) furnished bis-macrocycle **208** in 56% yield with >20 : 1 atropselectivity. The stereochemical outcome of this Larock macrocyclization was in sharp contrast to those of relevant Suzuki–Miyaura macrocyclizations previously reported by the Hoveyda/Snapper group and the Zhu group. Boger *et al.* speculated that the atropselectivity of Larock macrocyclizations in the complestatin case appeared to be governed by a steric contact between the aniline protecting group and the peptide backbone. The



Scheme 27 (A) Suzuki–Miyaura macrocyclization in the synthesis of 'right-hand' biaryl macrocycle of complestatin (**186**) by Zhu and co-workers. (B) Suzuki–Miyaura macrocyclization in the total synthesis of isocomplestatin methyl ester (**191**) by Zhu and co-workers.

Boger group also completed the total synthesis of complestatin A and B (neuroprotectin A and B), oxidized derivatives of complestatin, through a Larock macrocyclization.[85]

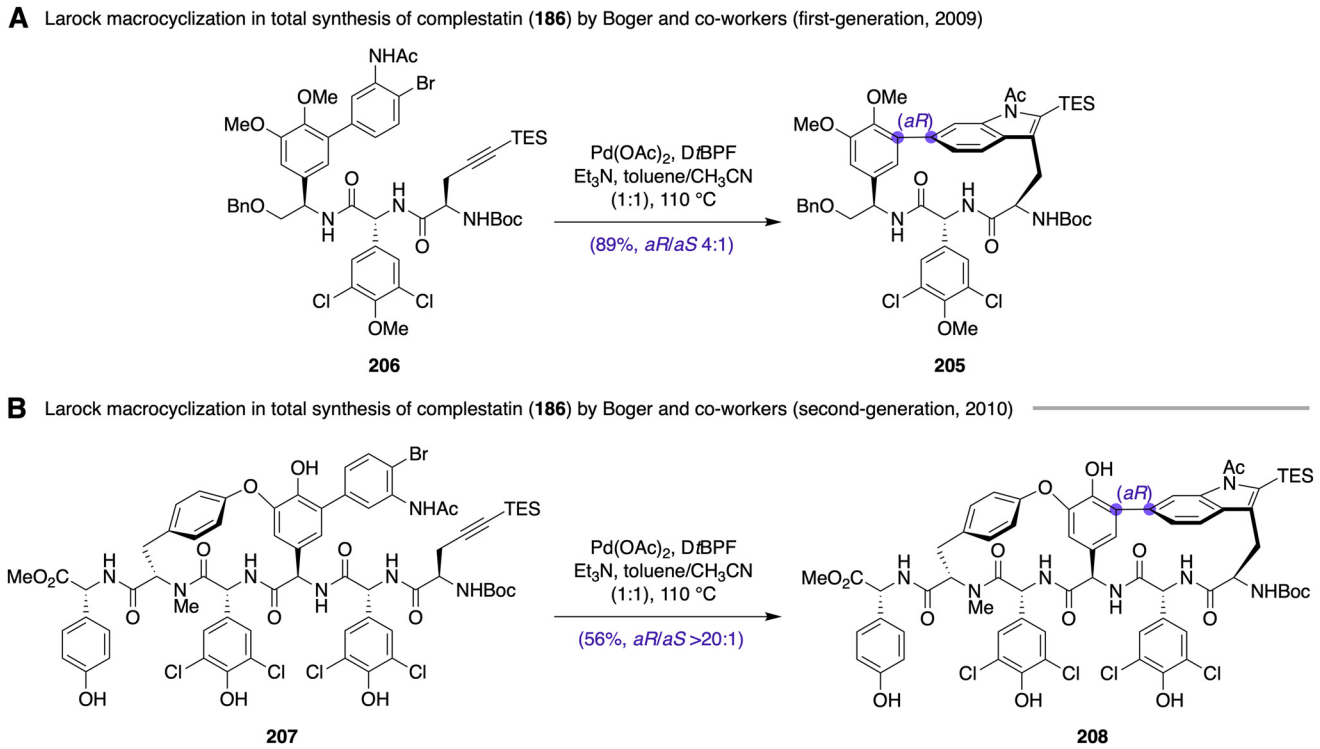
More recently, the Patel/Petrone/Sarlah group and the Baran group independently disclosed total synthesis of darobactin A (**209**) (Scheme 30). This natural product is a structurally exotic bis-macrocyclic heptapeptide that exhibits planar chirality and shows selective antibiotic activity against Gram-negative pathogens. Shared between the Patel/Petrone/Sarlah and Baran syntheses was a similar synthetic strategy that exploited two-fold Larock macrocyclization for the atropselective construction of the two tryptophan-containing strained macrocycles.



Scheme 28 Suzuki–Miyaura macrocyclization in the total synthesis of complestatin (**186**) by Zhu and co-workers.

In the Patel/Petrone/Sarlah synthesis of darobactin A (**209**),[86] exquisitely designed tripeptide **210**, harboring a silyl-substituted alkyne, an *ortho*-bromo acetanilide, and an *ortho*-iodo acetanilide, was used as a substrate for the first Larock macrocyclization (Scheme 30A). Upon exposure of **210** to Pd(*t*-$Bu_3P)_2$ and Cy_2NMe in CH_3CN/toluene (2 : 1) at 40 °C, chemoselective Larock macrocyclization occurred between the alkyne and the *ortho*-iodo acetanilide moieties, giving rise to macrocycle **211** in 52% yield with 3 : 1 atropselectivity without compromising the aryl bromide functionality. After completing the peptide backbone structure, heptapeptide **212** was subjected to the second Larock macrocyclization under the catalysis of Pd(*t*-$Bu_3P)_2$ (Cy_2NMe, CH_3CN, 80 °C) to furnish bis-macrocycle **213** in 51% yield. Finally, sequential removal of the protecting groups from **213** yielded darobactin A (**209**). The Patel/Petrone/Sarlah group described that the order of two Larock macrocyclizations was crucial for achieving the desired atropselectivity at the two indole rings and that an attempted double Larock macrocyclization resulted in a low product yield with undesired atropselectivity at the left-hand indole ring.

In the Baran synthesis of darobactin A (**209**),[87] tripeptide **214** decorated with a terminal alkyne and an *ortho*-bromo acetanilide underwent the first Larock macrocyclization under the influence of Pd(*t*-$Bu_3P)_2$ and *i*-Pr_2NEt in dioxane at 85 °C to deliver macrocycle **215** in 61% yield as a single atropisomer on a gram scale (Scheme 30B). In this case, the regioselectivity was substrate-directed and did not require a terminal alkyne substituent; rather, the substitution of the terminal alkyne with a triethylsilyl group made this reaction unproductive. Notably, other methods including Suzuki–Miyaura and Heck macrocyclizations and various macrolactamizations were all unsuccessful. After extending the peptide backbone and installing an *ortho*-bromo acetanilide, the second Larock macrocyclization was executed on pentapeptide **216** (Fe, NH_4Cl, AcOH, 50 °C; *then* Pd(*t*-$Bu_3P)_2$, *i*-Pr_2NEt, dioxane, 85 °C) to afford bis-macrocycle **217** in 67% yield from **216** as a single atropisomer. The Baran synthesis of darobactin A (**209**) was highlighted by



Scheme 29 (A) Larock macrocyclization in the total synthesis of complestatin (**186**) by Boger and co-workers (first-generation, 2009). (B) Lacrock macrocyclization in the total synthesis of complestatin (**186**) by Boger and co-workers (second-generation, 2010).

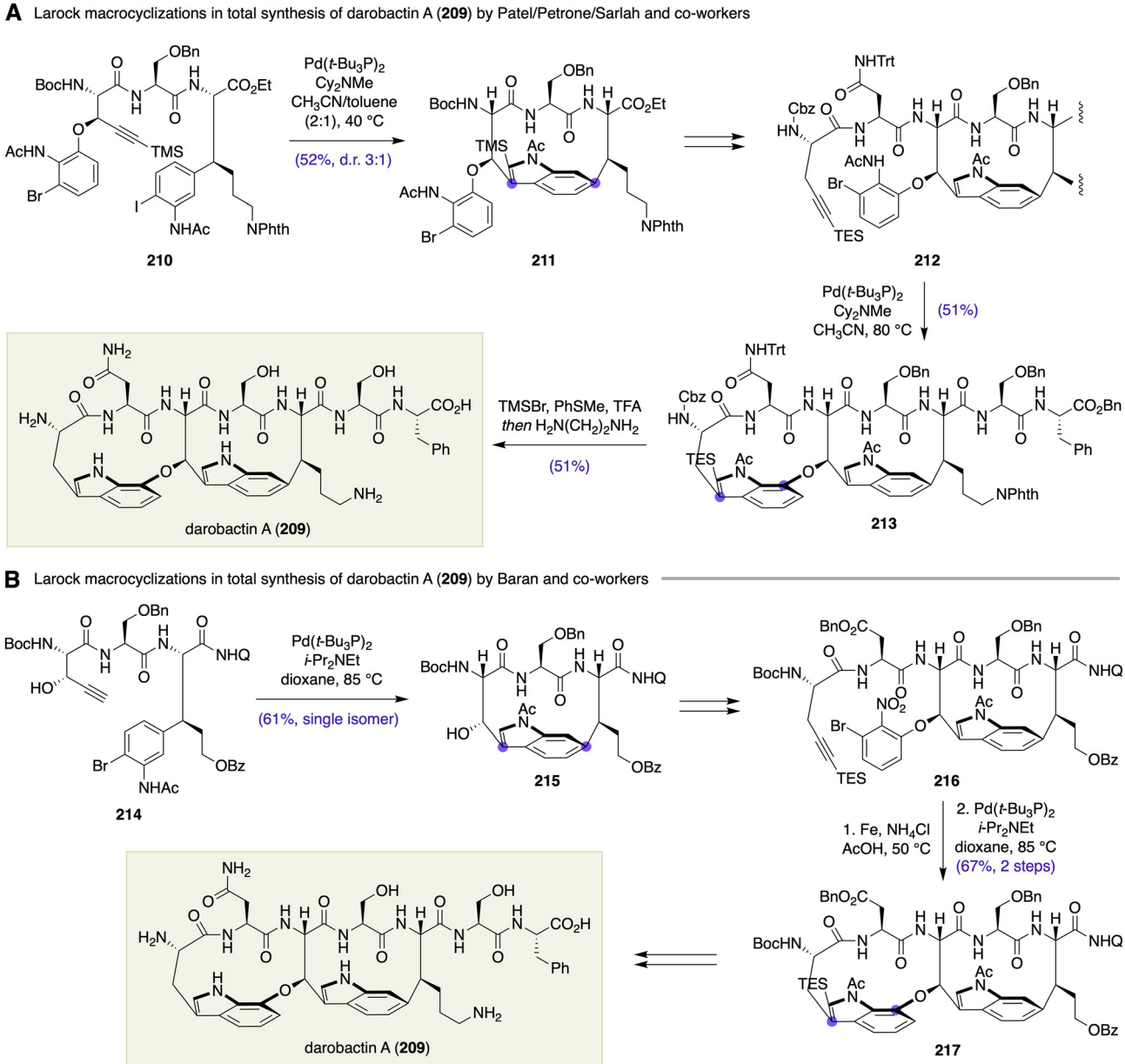
Larock macrocyclizations at the mid-stage of the synthesis. Aiming at medicinal chemistry applications, the end game involved a late-stage coupling of the C-terminus dipeptide and completion of the lysine side chain.

Nakamura and co-workers have recently disclosed their works on the total syntheses of cihunamide B and strecintide 839 based on Larock macrocyclizations.[88,89]

Chirality-generating tandem macrocyclization/transannular cyclization

Tandem (or domino, cascade) reactions are those that involve multiple transformations consecutively by taking advantage of the functional groups generated in the prior transformation.[90] Because tandem reactions obviate the need for isolating intermediates, the implementation of tandem reactions in the total synthesis helps improving the synthetic efficiency. Complementary to chirality-generating macrocyclizations, tandem reactions that involve a macrocyclization and a chirality-generating transannular cyclization(s) are a promising means to synthesize complex natural macrocycles expediently.

Tandem macrocyclization/transannular Diels–Alder cycloaddition. Roush and co-workers published a detailed paper on the stereochemistry of transannular Diels–Alder cycloaddition *en route* to (−)-spinosyn A pseudoaglycone (**218**) using four precursors with different substitution patterns (Scheme 31).[91] The Roush group exploited the steric directing group strategy[92,93] for controlling the transition state of the transannular Diels–Alder reaction toward **218**. Thus, a bromine atom and a β-alkoxy group was introduced to the C6 and C8 positions, respectively, of macrocyclization precursor **219** as temporary substituents. Upon treatment of **219** with *i*-Pr_2NEt/LiCl in CH_3CN (1 mM) at 23 °C, intramolecular Horner–Wadsworth–Emmons olefination and concomitant transannular Diels–Alder reaction of the transient macrocycle **220** occurred to afford cycloadduct **221** with the desired configuration in 78% yield as a single stereoisomer (dr > 95 : 5). The cycloadduct **221** was then transformed into the tetracyclic skeleton **222** of the spinosyn A pseudoaglycone *via* transannular vinylogous Morita–Baylis–Hillman reaction in a stereoselective manner. In contrast, Horner–Wadsworth–Emmons macrocyclization of precursor **223** lacking the C8 substituent under the same reaction conditions used for **219** provided transannular Diels–Alder cycloadduct **225** in 75% yield as a 73 : 12 : 9 : 6 mixture of four diastereomers. Thus, it was clear that the C8 silyloxy group played a significant role in destabilizing competing transition states of the transannular Diels–Alder reaction of **220**. The omission of the C6 steric directing group, *i.e.* **226**, resulted in a similar diastereoselectivity (dr 70 : 18 : 12), indicating that the C6 bromine did not have a significant impact on the stereochemical course of the transannular Diels–Alder reaction of **219** and **223**. As shown by the reaction of **229**, further deletion of the C21 ethyl group did not significantly alter the stereochemical outcome, giving cycloadduct **231** as a mixture of four diastereomers in a ratio of 71 : 18 : 6 : 5. Nonetheless, transannular Diels–Alder reaction of **223**, **226**, and **229** was clearly better than the intramolecular Diels–Alder reaction of

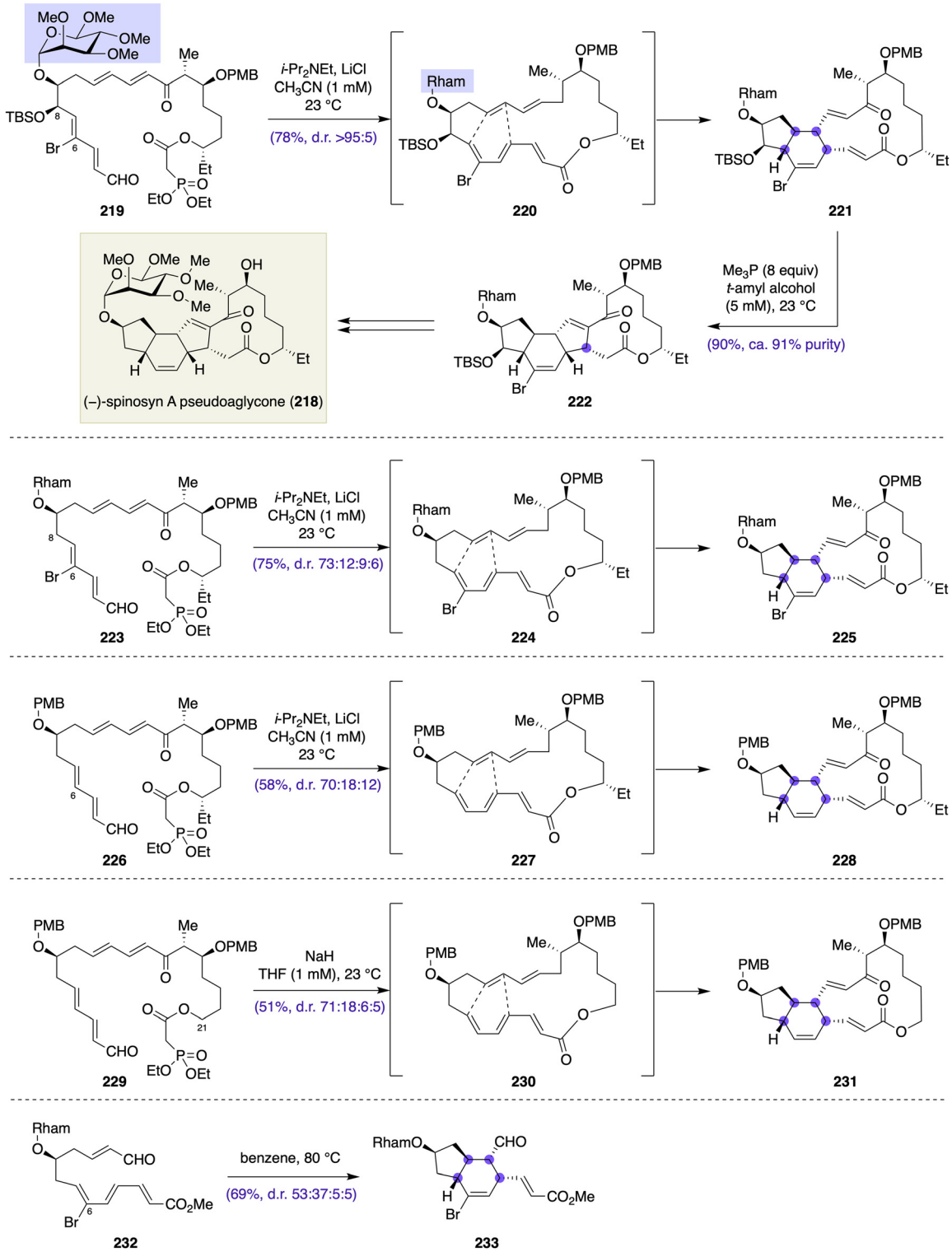


Scheme 30 (A) Larock macrocyclizations in the total synthesis of darobactin A (**209**) by Patel/Petrone/Sarlah group. (B) Larock macrocyclizations in the total synthesis of darobactin A (**209**) by Baran and co-workers.

232 (dr 53 : 37 : 5 : 5) with respect to the diastereoselectivity. Thus, the macrocyclic skeleton of **224**, **227**, and **230** must play a beneficial role in directing the stereochemical course of the transannular Diels–Alder reaction in a desired sense.

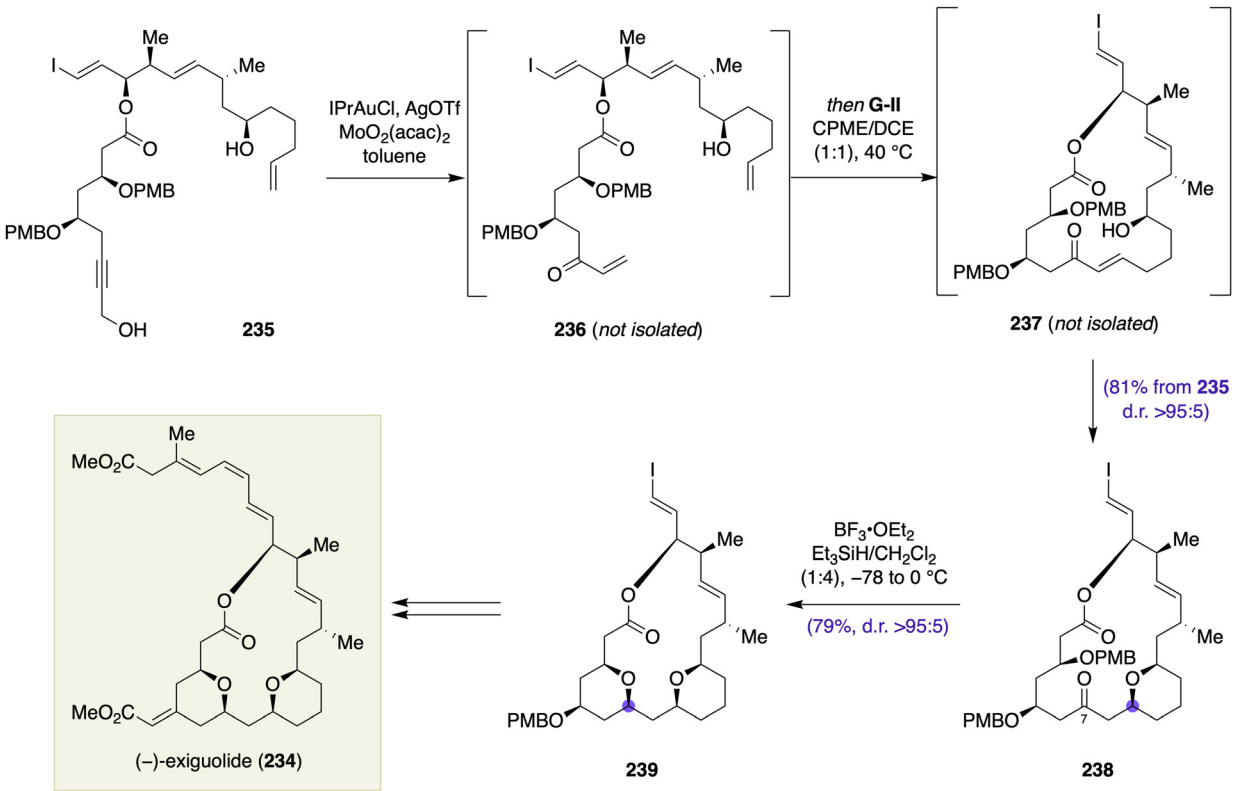
The examples shown above clearly indicate that the stereocontrol of transition states by designing appropriate precursors is vital for the successful stereochemical control of transannular Diels–Alder cycloadditions.

Tandem macrocyclization/transannular conjugate addition. Many macrocyclic natural products are embedded with a five- or six-membered ring(s). We envisioned a catalytic tandem reaction that involves a ring-closing metathesis of vinyl ketones and a subsequent transannular Michael addition of the resultant macrocyclic α,β-unsaturated ketones would realize an expedient access to tetrahydropyran-containing macrocyclic natural products.[94,95] This idea was inspired by our previous work on a tandem olefin cross-metathesis/intramolecular oxa-Michael addition[96] for stereoselective synthesis of 2,6-*cis*-configured tetrahydropyran derivatives, wherein the diastereoselectivity appears to be under kinetic control.[97] Our macrocyclization/transannular pyran cyclization strategy was successfully implemented in a concise total synthesis of (−)-exiguolide (**234**) (Scheme 32).[94] The exposure of propargylic alcohol **235** to IPrAuCl/AgOTf/$MoO_2(acac)_2$ in toluene at room temperature resulted in Meyer–Schuster rearrangement[98,99] to give vinyl ketone **236**. Without isolation, **236** was subjected to



Scheme 31 Tandem macrocyclization/transannular Diels–Alder cycloadditions in the total synthesis of (–)-spinosyn A pseudoaglycone (**218**) by Roush and co-workers.

tandem ring-closing metathesis/transannular oxa-Michael addition. Thus, treatment of a reaction mixture containing **236** with **G-II** complex in cyclopentyl methyl ether (CPME)/DCE (1 : 1) at 40 °C gave rise to 2,6-*cis*-configured tetrahydropyran **238** in 81% yield from **235** with >95 : 5 diastereoselection. The stereochemical outcome of the transannular oxa-Michael addition (**237** → **238**) was reasoned by a chair-like transition-state model, which was in accordance with the previous work



Scheme 32 Tandem macrocyclization/transannular conjugate addition in the total synthesis of (–)-exiguolide (**234**) by Fuwa and co-workers.

by Bates.[100] The C7 ketone of **238** could be directly used in the subsequent transannular Kishi reduction to afford bis-tetrahydropyran **239** in 79% yield with >95 : 5 diastereoselection. The Kishi reduction in a transannular format (**238** → **239**) proceeded under stereoelectronic control, wherein an axial hydride delivery to the intermediate macrocyclic oxocarbenium ion occurred to deliver the desired 2,6-*cis*-configured tetrahydropyran. Noteworthy is that the 20-membered macrocyclic backbone and two embedded tetrahydropyran rings were constructed in only two steps from the macrocyclization precursor **235** with perfect stereocontrol. Thus, the total synthesis of (–)-exiguolide (**234**) was completed in only 13 steps from a commercially available material, representing the shortest synthesis of this complex macrolide natural product.[101] Empowered by our tandem macrocyclization/transannular oxa-Michael addition strategy, we could make deep-seated stereochemical modifications on the macrocyclic core of (–)-exiguolide (**234**) for structure–activity relationship investigations.[95d]

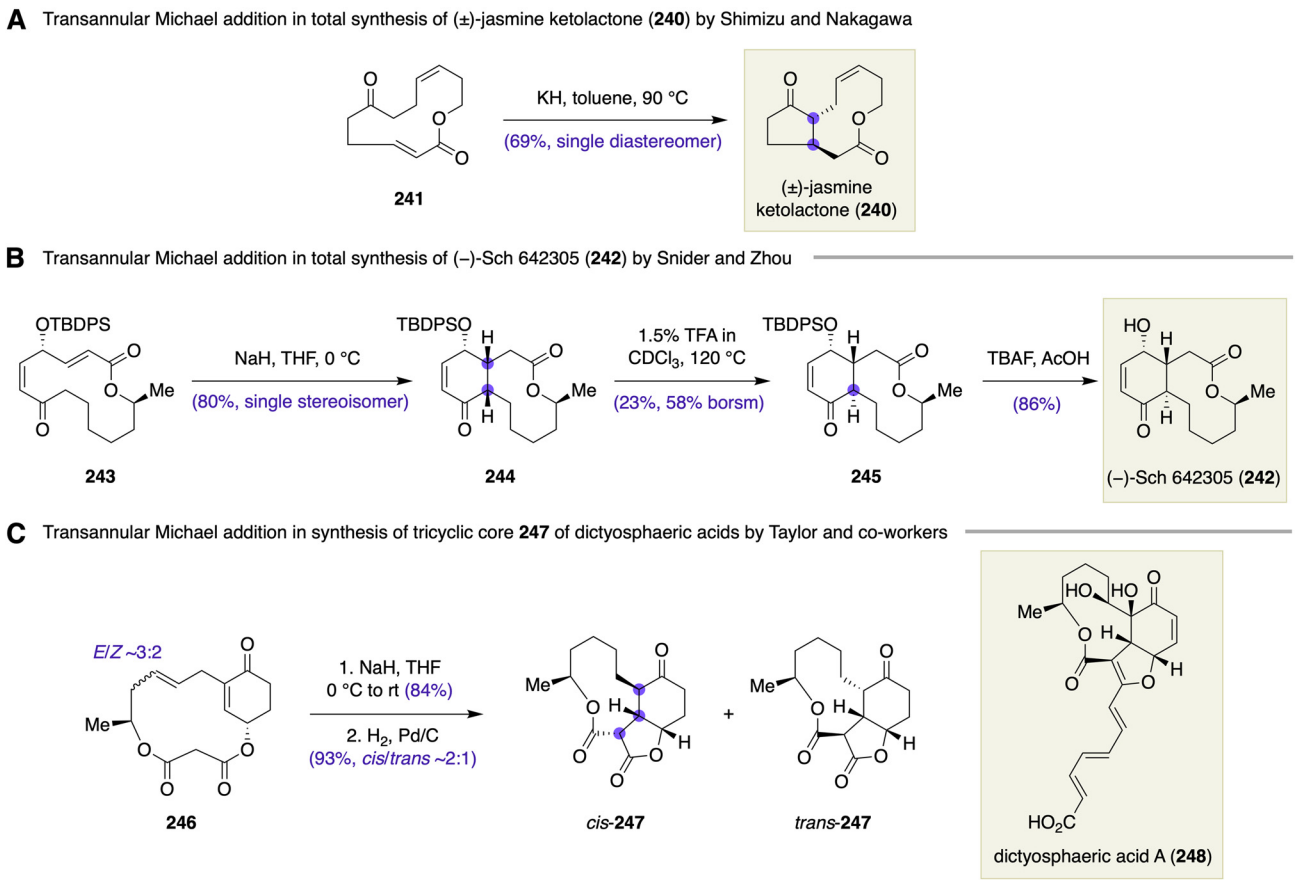
Late-stage chirality-generating skeletal transformations: transannular reactions

Transannular reactions offer late-stage opportunities for creating a new bond(s) across macrocycles with concurrent introduction of a stereogenic center(s).[9] In general, the consequence of transannular reactions largely depends on the conformational constraints of the macrocycle of interest. Thus, it is important to design macrocyclic precursors with an appropriate substitution/unsaturation pattern for achieving the desired transition state in an energetically favored way.

Transannular conjugate additions

While 10-membered rings are classified as medium-sized rings in a strict sense, there are several examples that exploit transannular Michael additions for the closure of 10-membered rings found in natural products. Shimizu and Nakagawa described the synthesis of jasmine ketolactone (**240**) in a racemic form through a transannular Michael addition (Scheme 33A).[102] The precursor macrolactone **241** was synthesized *via* a macrolactonization of the corresponding seco-ester under Otera conditions. Upon exposure of **241** to KH (2 equiv.) in toluene at 90 °C, transannular Michael addition occurred to give *trans*-fused jasmine ketolactone (**240**) in 69% yield as a single diastereomer. Interestingly, an intramolecular Michael addition using a non-tethered counterpart was not successful, indicating the importance of the macrocyclic constraint in the present case.

Snider and Zhou showed in their total synthesis of (–)-Sch 642305 (**242**) that transannular Michael addition of macrolactone **243**, accessed through a Yamaguchi macrolactonization, proceeded by the action of NaH (THF, 0 °C) to deliver *cis*-fused transannular product **244** in 80% yield as a single stereoisomer (Scheme 33B).[103] Thermodynamic epimerization under acidic



Scheme 33 (A) Transannular Michael addition in the total synthesis of (±)-jasmine ketolactone (**240**) by Shimizu and Nakagawa. (B) Transannular Michael addition in the total synthesis of (–)-Sch 642305 (**242**). (C) Transannular Michael addition in the synthesis of tricyclic core **247** of dictyosphaeric acid A (**248**) by Taylor and co-workers.

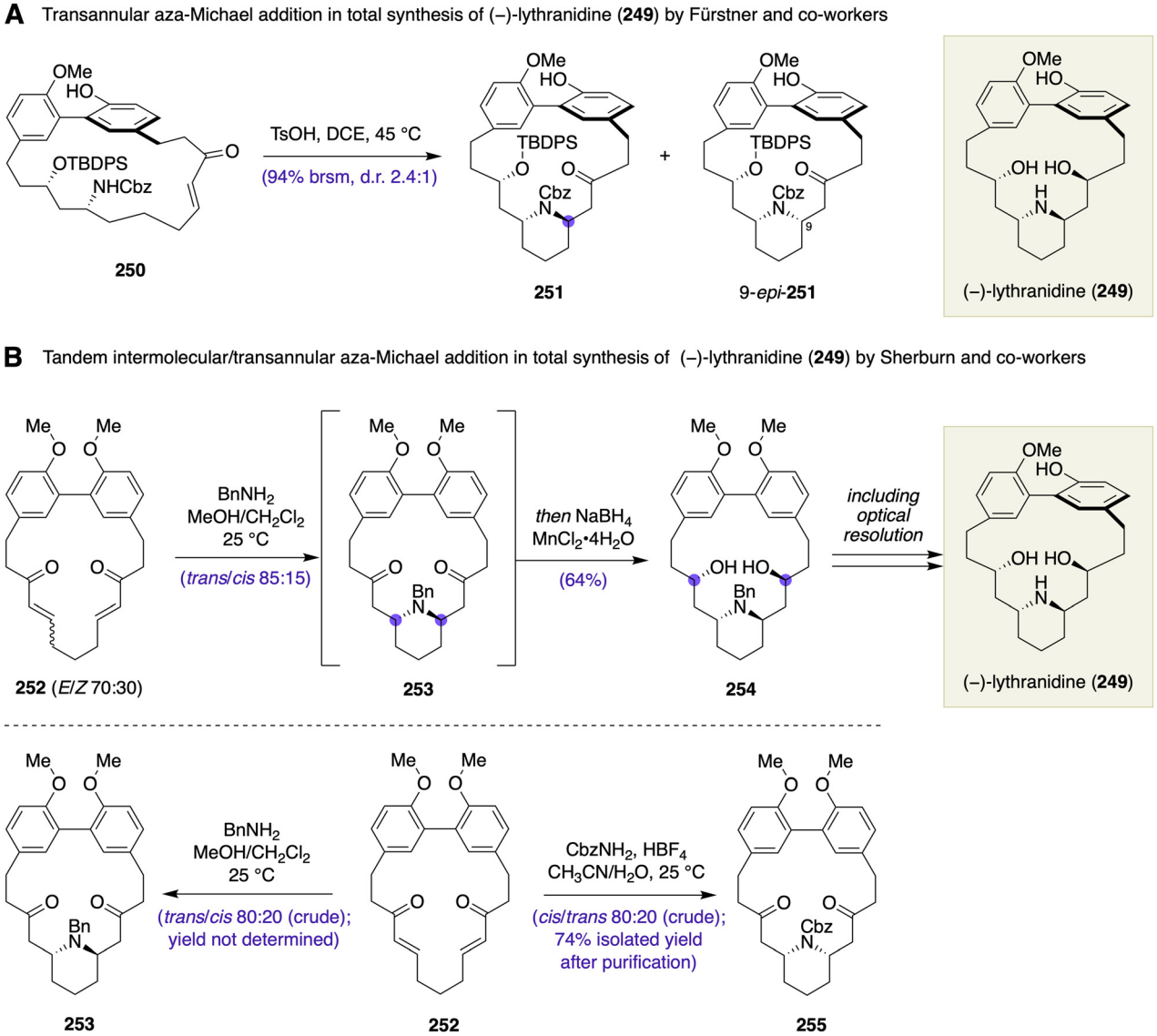
conditions gave *trans*-fused isomer **245** in 23% yield (58% based on recovered starting material), which was desilylated with TBAF/AcOH to furnish (–)-Sch 642305 (**242**). The late-stage transannular Michael reaction enabled a quick access to the bicyclic skeleton of (–)-Sch 642305, although the configuration of the transannular Michael product **244** did not correspond to that of the natural product.

In their synthetic studies on dictyosphaeric acids, Taylor *et al.* examined transannular Michael addition of macrocycle **246** to construct the tricyclic core structure **247** (Scheme 33C).[104] The precursor **246** was synthesized by means of a macrocyclic ring-closing metathesis. Treatment of **246** with NaH (1.2 equiv., THF, 0 °C to rt) resulted in a transannular Michael addition as anticipated. After hydrogenation of the double bond, an approximately 2 : 1 mixture of *cis*-**247** and *trans*-**247** was obtained in 78% yield for the two steps.

Transannular Michael additions have also found their use in the total synthesis of stereochemically complex polycyclic norcembranoids from macrocyclic precursors, which will be discussed later.

Transannular hetero-Michael additions are a powerful means to construct heterocyclic rings embedded within macrocyclic natural products. Fürstner and co-workers have been actively investigating various transannular skeletal transformations on macrocyclic alkynes in the context of total synthesis of macrocyclic natural products, by taking advantage of their ring-closing alkyne metathesis chemistry.[105] A transannular aza-Michael addition[106] was successfully implemented in the total synthesis of (–)-lythranidine (**249**), a macrocyclic piperidine alkaloid (Scheme 34A).[107] Upon exposure of α,β-unsaturated ketone **250** to TsOH in DCE at 45 °C, transannular aza-Michael addition occurred to deliver 2,6-*trans*-configured piperidine **251** in 94% yield based on the recovered starting material with approximately 2.4 : 1 diastereoselectivity. Attempts at improving the diastereomer ratio using chiral Brønsted acids were unsuccessful, suggesting that the stereochemical course of the transannular aza-Michael addition was strongly dependent on the macrocyclic conformation. The transannular product **251** was elaborated into (–)-lythranidine (**249**) through a stereoselective carbonyl reduction.

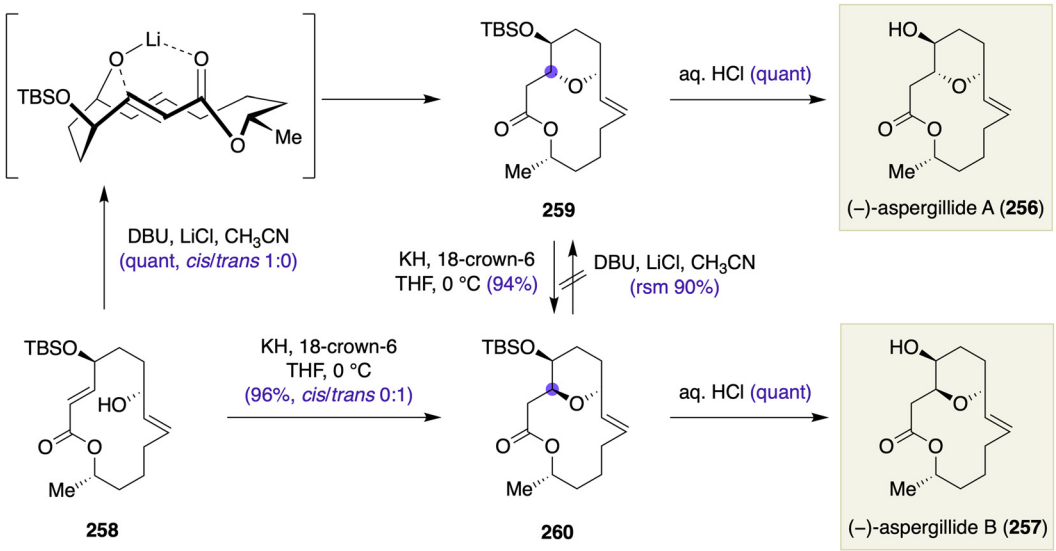
More recently, an expedient synthesis of (–)-lythranidine (**249**) was disclosed by Sherburn and co-workers (Scheme 34B).[108] Treatment of bis-α,β-unsaturated ketone **252** with benzylamine in $MeOH/CH_2Cl_2$ at ambient temperature triggered intermolecular/transannular aza-Michael additions to give piperidine **253** with *trans*/*cis* 85 : 15 selectivity. *In situ*



Scheme 34 (A) Transannular aza-Michael addition in total synthesis of (–)-lythranidine (**249**) by Fürstner and co-workers. (B) Tandem intermolecular/transannular aza-Michael additions in the total synthesis of (–)-lythranidine (**249**) by Sherburn and co-workers.

chelate controlled reduction with $NaBH_4$ in the presence of $MnCl_2{\cdot}4H_2O$ provided diol **254** in 64% yield. The stereochemical course of the transannular cyclization was under thermodynamic control, as was evidenced by a thermodynamic equilibration experiment using a separately synthesized 2,6-*cis*-configured isomer. Importantly, the stereochemical outcome of the transannular aza-Michael addition could be reversed. Upon treatment of bis-α,β-unsaturated ketone **252** with $CbzNH_2$ and HBF_4 in CH_3CN/H_2O at ambient temperature, tandem intermolecular/transannular aza-Michael additions proceeded under Brønsted acid catalysis to give 2,6-*cis*-configured piperidine **255** with approximately 80 : 20 diastereoselectivity, and **255** was isolated in a diastereomerically pure form in 74% yield after flash column chromatography using silica gel. The diastereoselectivity of the transannular aza-Michael addition was thermodynamically controlled. This was confirmed by re-subjection of the minor *trans*-configured isomer to the reaction conditions.

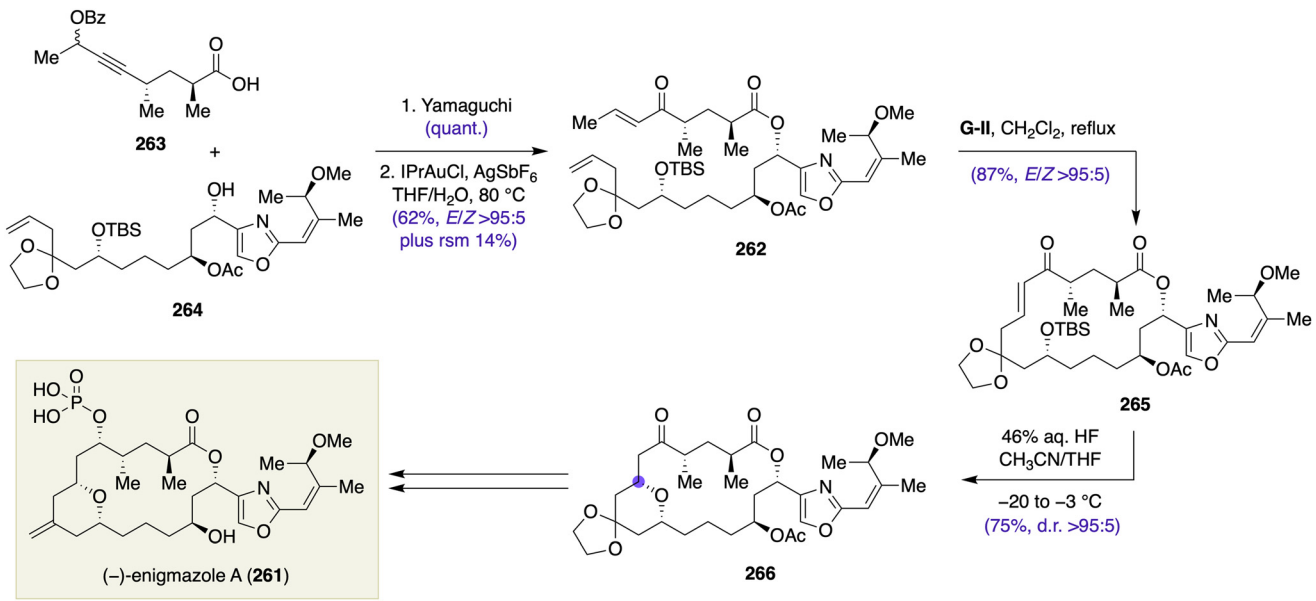
A stereodivergent transannular oxa-Michael addition was demonstrated by Shishido and co-workers in their total synthesis of aspergillides A and B (**256** and **257**, respectively) (Scheme 35).[109] Transannular oxa-Michael addition of α,β-unsaturated ester **258** using DBU/LiCl in CH_3CN at room temperature provided 2,6-*cis*-configured tetrahydropyran **259** in quantitative yield with complete diastereoselection. This stereochemical consequence could be reasoned by a transition state in which a lithium cation is coordinated to the ester carbonyl oxygen. In contrast, the reaction of **258** with KH in the presence of 18-crown-6 in THF at 0 °C afforded 2,6-*trans*-configured tetrahydropyran **260** in 96% yield as a single diastereo-



Scheme 35 Transannular oxa-Michael additions in the stereodivergent total synthesis of (–)-aspergillide A (**256**) and (–)-aspergillide B (**257**) by Shishido and co-workers.

mer. Control experiments demonstrated that 2,6-*cis*-configured tetrahydropyran **259** could be converted into 2,6-*trans*-configured tetrahydropyran **260** by treatment with KH/18-crown-6 (94%), whereas 2,6-*trans*-configured tetrahydropyran **260** remained unreactive upon treatment with DBU/LiCl in refluxing CH_3CN (90% recovery).

Recently, our group has achieved a concise total synthesis of (–)-enigmazole A (**261**) based on our macrocyclization/transannular pyran cyclization strategy (Scheme 36).[110] Macrocyclization precursor **262** was prepared through Yamaguchi esterification of carboxylic acid **263** and alcohol **264** followed by Nolan's α,β-unsaturated ketone synthesis[111] of the derived ester. The 18-membered macrocyclic backbone of **261** was closed by ring-closing metathesis of **262** under the catalysis of **G-II** complex. Treatment of the resultant macrocyclic α,β-unsaturated ketone **265** with aq. HF in CH_3CN/THF (2 : 1, v/v) at −20 to −3 °C triggered desilylative transannular oxa-Michael addition to afford 2,6-*cis*-configured tetrahydropyran **266** in 75% yield with >95 : 5 diastereoselection, in accordance with the Bates late-transition-state model. The stereochemical outcome of the transannular oxa-Michael addition could be reversed by using TBAF as a desilylation reagent.



Scheme 36 Desilylative transannular oxa-Michael addition in the total synthesis of (–)-enigmazole A (**261**) by Fuwa and co-workers.

Transannular cycloetherifications

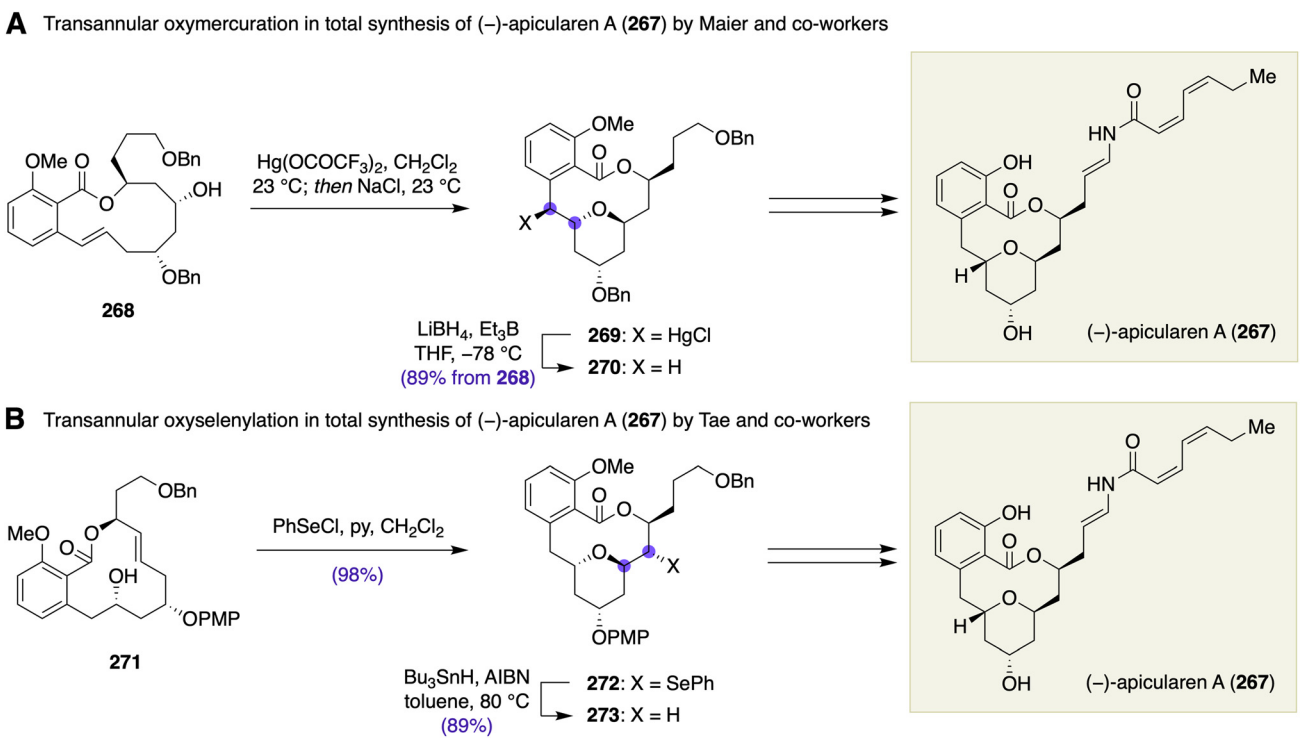
In contrast to transannular conjugate additions involving macrocyclic α,β-unsaturated carbonyls, transannular cycloetherification proceeds *via* an electrophilic activation of non-activated macrocyclic olefins.

The Maier synthesis of (–)-apicularen A (**267**) exploited a transannular oxymercuration of macrocyclic olefin **268** under the influence of $Hg(OCOCF_3)_2$ in CH_2Cl_2 at room temperature, giving 2,6-*trans*-configured tetrahydropyran **270** in 89% yield (from **268**) after reduction with $LiBH_4/Et_3B$ (Scheme 37A).[112] Interestingly, treatment of **268** with *N*-(phenylseleno)phthalimide resulted in no reaction. Turning to more electrophilic PhSeOTf, transannular oxyselenylation of **268** did proceed but was accompanied by side reactions, giving the corresponding transannular product in only 34% yield (structure not shown). Meanwhile, the Tae synthesis of (–)-apicularen A (**267**) was based on a transannular oxyselenylation using PhSeCl as an electrophile (Scheme 37B).[113] Thus, treatment of macrocyclic olefin **271** with PhSeCl, after radical reduction using Bu_3SnH/AIBN, provided 2,6-*trans*-configured tetrahydropyran **273** in 87% overall yield from **271**. Importantly, the C–O bond formed by the transannular cycloetherification in the Tae synthesis is different from that in the Maier synthesis. Tae *et al.* noted that they failed to promote transannular oxymercuration of macrocyclic olefin **271** using $Hg(OAc)_2$ or $Hg(OCOCF_3)_2$.

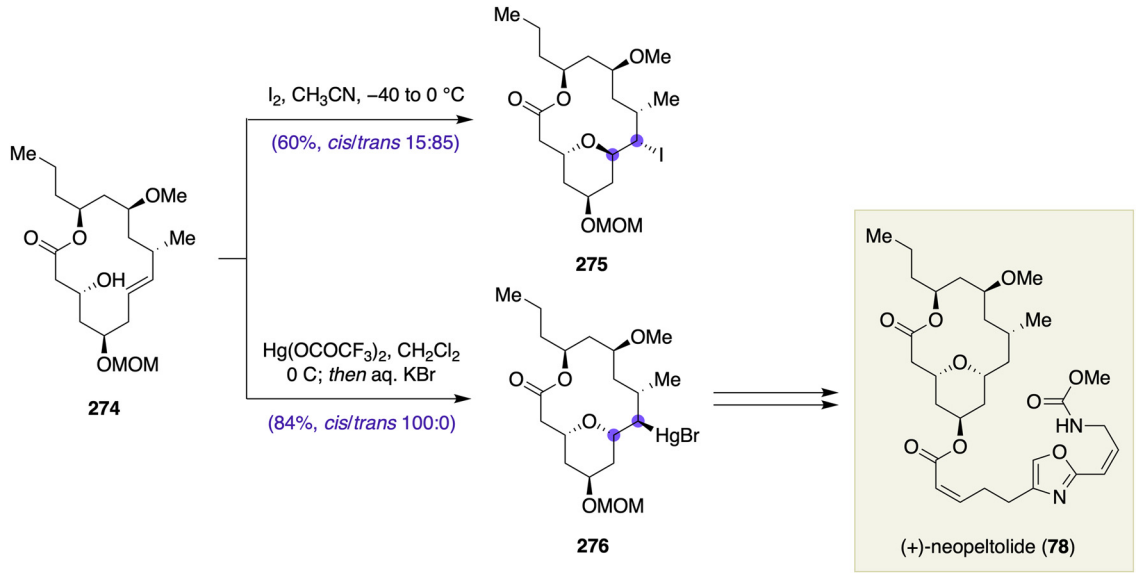
Sharma and co-workers showed in their formal synthesis of (+)-neopeltolide (**78**), transannular cycloetherifications for the stereoselective closure of the embedded tetrahydropyran ring (Scheme 38).[114] When macrocyclic olefin **274** was exposed to I_2 in CH_3CN at −40 to 0 °C, transannular iodoetherification occurred to give 2,6-*trans*-configured tetrahydropyran **275** in 60% yield as an 85 : 15 mixture of diastereomers. In contrast, treatment of **274** with $Hg(OCOCF_3)_2$ in CH_2Cl_2 at 0 °C and then with aq. KBr at room temperature brought about transannular oxymercuration to deliver 2,6-*cis*-configured tetrahydropyran **276** in 84% yield as a single diastereomer. However, the exact reason for the observed stereodivergency in transannular cycloetherifications of **274** remains elusive.

Transannular cycloadditions

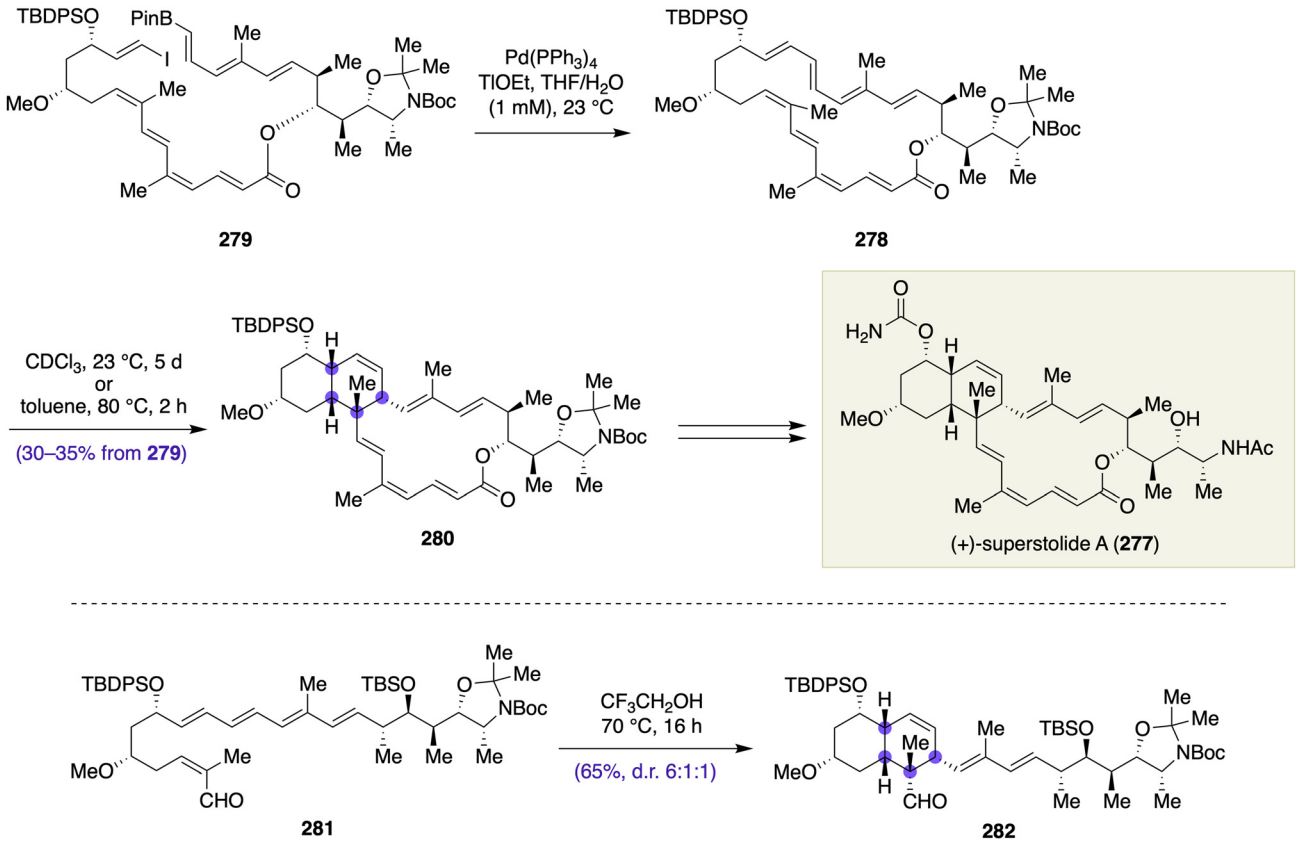
In their total synthesis of (+)-superstolide A (**277**), the Roush group envisioned that the *cis*-fused octahydronaphthalene moiety embedded within **277** could be constructed through a late-stage, bioinspired transannular Diels–Alder cycloaddition (Scheme 39).[115] The precursor octaene **278** was synthesized through Suzuki–Miyaura macrocyclization of ester **279**. The crucial transannular Diels–Alder cycloaddition of **278** proceeded in $CDCl_3$ at 23 °C for 5 days or in toluene at 80 °C for 2 h to afford cycloadduct **280** with the correct configuration in 30–35% yield over the two steps from **279** as the only isolable product. Notably, initial efforts that involved construction of the *cis*-fused octahydronaphthalene moiety at an early stage of the synthesis by means of an intramolecular Diels–Alder cycloaddition of **281** resulted in octahydronaphthalene **282** with only moderate diastereoselectivity (dr 6 : 1 : 1). Furthermore, it eventually turned out that it was difficult to close the macrocycle at a later stage of the synthesis. Thus, the order of frag-



Scheme 37 (A) Transannular oxymercuration in the total synthesis of (–)-apicularen A (**267**) by Maier and co-workers. (B) Transannular oxyselenylation in the total synthesis of (–)-apicularen A (**267**) by Tae and co-workers.



Scheme 38 Transannular iodoetherification and oxymercuration in the formal synthesis of (+)-neopeltolide (**78**) by Sharma and co-workers.

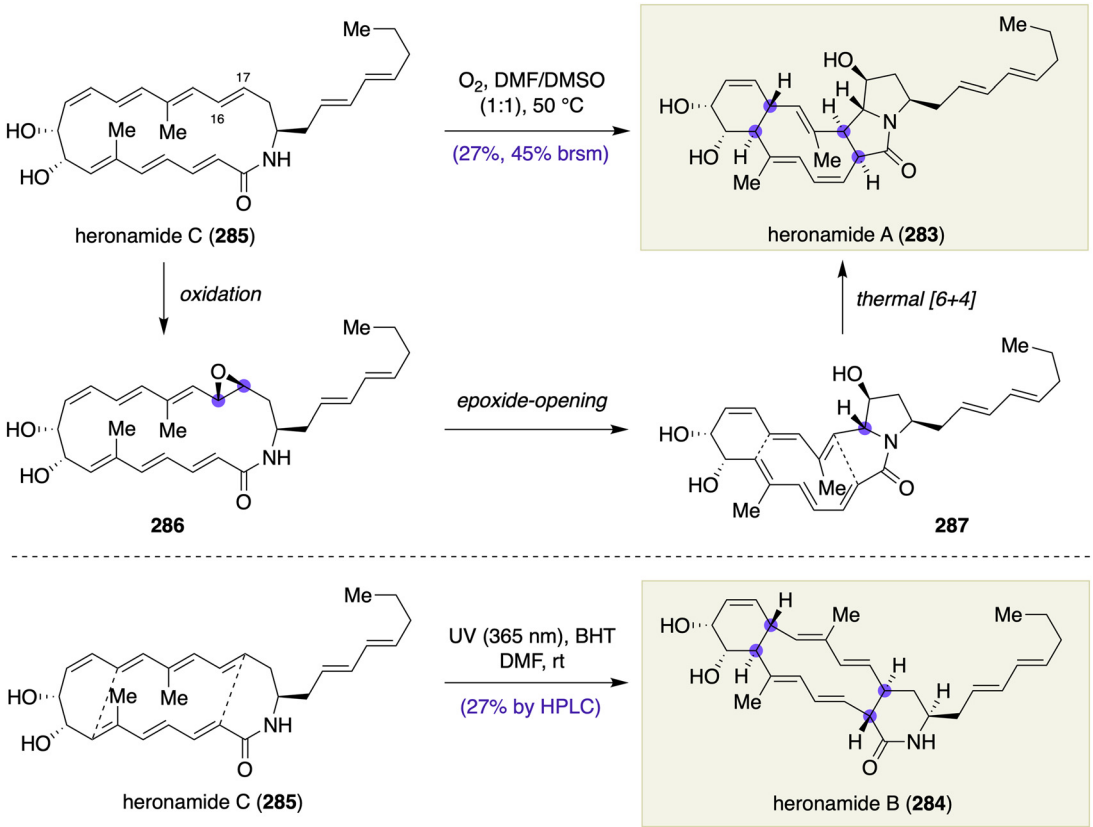


Scheme 39 Transannular Diels–Alder cycloaddition in the total synthesis of (+)-superstolide A (**277**) by Roush and co-workers.

ment assembly → macrocyclization → transannular cycloaddition was crucial for the success of the total synthesis of (+)-superstolide A (**277**).

Transannular Diels–Alder cycloaddition has also been exploited in tandem with macrocyclizations, as discussed above.

Kanoh, Kakeya, and co-workers described the total synthesis of heronamides A–C (**283**–**285**), in which they transformed heronamide C (**285**) into heronamides A and B (**283** and **284**, respectively) through a transannular thermal [6 + 4] cycloaddition and a transannular photochemical [6 + 6] cycloaddition at the final

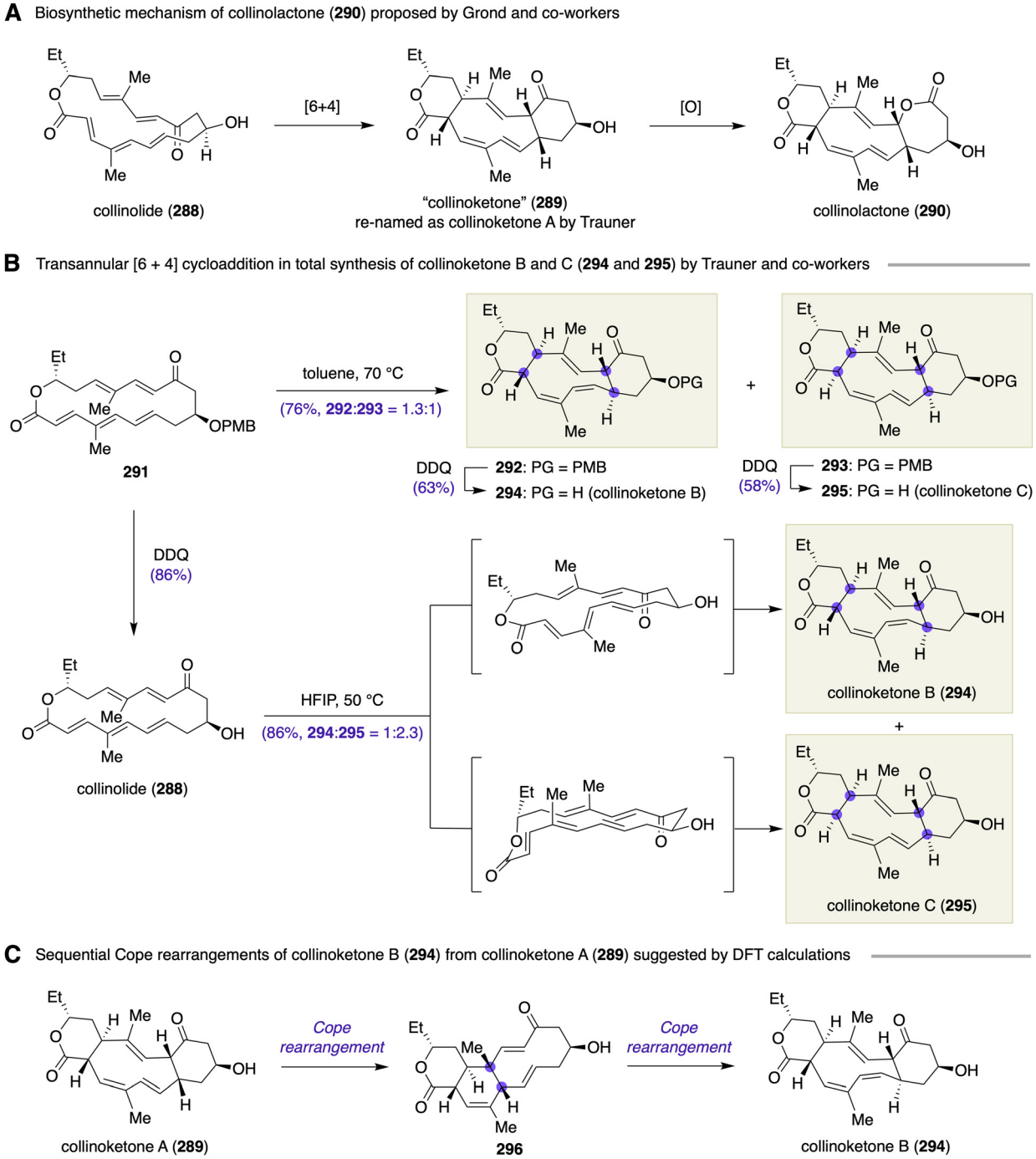


Scheme 40 Transannular cycloadditions in the total syntheses of heronamides A and B (**283** and **284**) by Kanoh, Kakeya, and co-workers.

stage of the synthesis (Scheme 40).[116] These transannular transformations were inspired by a postulated biosynthesis mechanism. Placing **285** under an atmosphere of O_2 in DMF/DMSO (1 : 1, v/v) at 50 °C for seven days provided heronamide A (**283**) in 27% yield (45% yield BORSM). Based on the proposed biosynthetic pathway, it was assumed that oxidation of the $\Delta^{16,17}$ double bond of **285** would trigger the transannular epoxide-opening reaction of **286** with the amide nitrogen to deliver pyrrolidine **287**, which would then undergo transannular [6 + 4] cycloaddition to give heronamide A (**283**). Meanwhile, UV irradiation (365 nm) of heronamide C (**285**) in the presence of BHT in DMF at room temperature caused transannular [6 + 6] cycloaddition to afford heronamide B (**284**) in 27% yield.

Trauner, Houk, and co-workers reported the synthesis of a highly unsaturated macrolactone, collinolide (**288**), and its transannular [6 + 4] cycloaddition.[117] Collinolide (**288**) has been proposed as a hypothetical biosynthetic precursor of the tricyclic cyclodecatriene "collinoketone" (re-named as collinoketone A by Trauner *et al.*, **289**) and a neuroprotective natural product, collinolactone (**290**) (Scheme 41A). According to the proposal by Grond *et al.*,[118] a transannular [6 + 4] cycloaddition of collinolide (**288**) furnishes "collinoketone" (**289**), which would then be processed to collinolactone (**290**) through an enzymatic Baeyer–Villiger oxidation. The Trauner group synthesized the precursor macrolactone **291** through a Horner–Wadsworth–Emmons macrocyclization (Scheme 41B).

Upon heating in toluene at 70 °C, macrolactone **291** cleanly underwent a transannular [6 + 4] cycloaddition to afford a diastereomeric mixture of cyclodecatrienes **292** and **293** in a ratio of 1.3 : 1. The removal of the PMB group from these transannular cycloaddition products **292** and **293** afforded the final products, named collinoketone B (**294**) and collinoketone C (**295**), respectively. Notably, the ^{1}H and ^{13}C NMR spectroscopic data of collinoketone B (**294**) fully matched those reported for natural "collinoketone". Thus, the structure of "collinoketone" isolated from natural sources was revised to be that represented by the stereoisomer, collinoketone B (**294**). In contrast, the ratio was reversed to 1 : 2.3 when the transannular cycloaddition reaction was run using collinolide (**288**) in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) at 50 °C. This suggested that the (*Z*,*Z*,*E*) isomers are thermodynamic products whereas (*Z*,*E*,*E*) isomers are kinetically favored. Furthermore, DFT calculations suggested that the transannular cycloaddition proceeds through an ambimodal transition state, from which both [6 + 4] and [4 + 2] cycloadducts can arise. Finally, DFT calculations showed that collinoketone A (**289**) should readily undergo sequential Cope rearrangements to give energetically more stable collinoketone B (**294**) (Scheme 41C). Thus, it was proposed that the biosynthetic intermediate collinoketone A (**289**) would still be the most plausible precursor of collinolactone (**290**) and that an enzyme would be responsible for the preferential formation of collino-



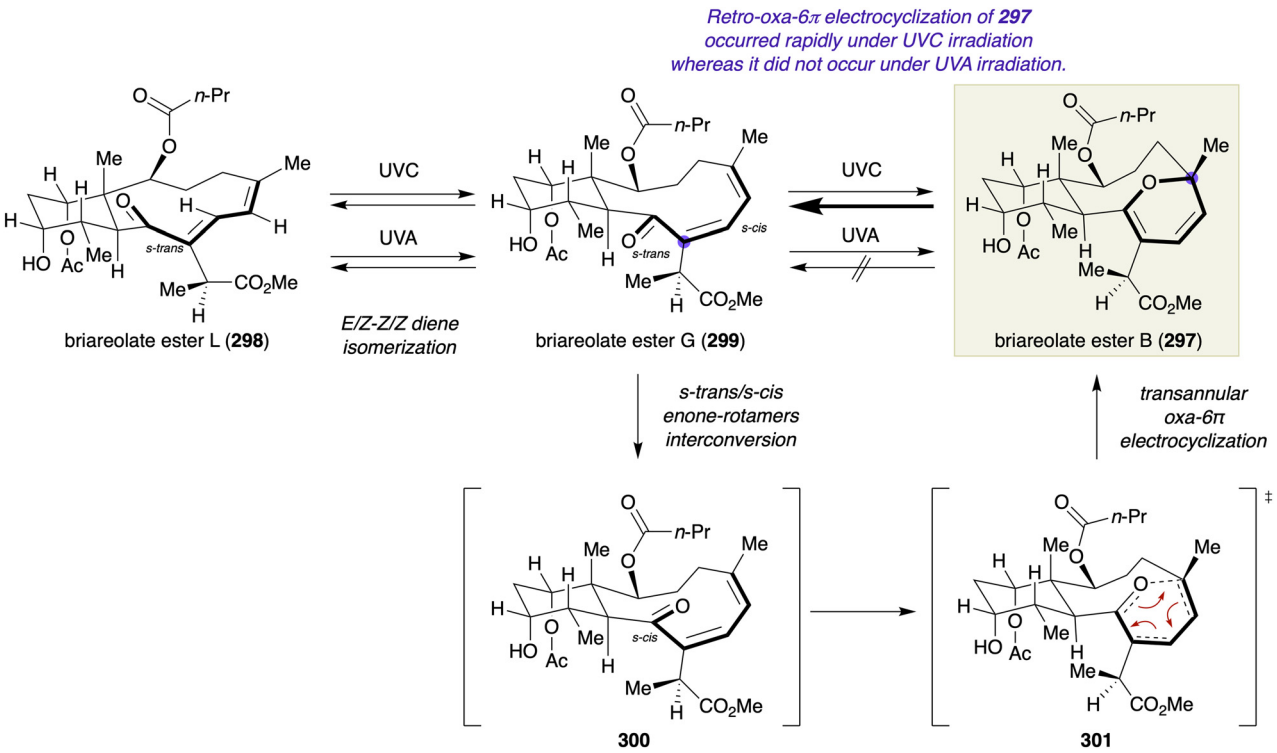
Scheme 41 (A) Biosynthetic mechanism of collinolactone (**290**) proposed by Grond and co-workers. (B) Transannular [6 + 4] cycloaddition in the total synthesis of collinoketone B and C (**294** and **295**) by Trauner and co-workers. (C) Sequential Cope rearrangements of collinoketone A (**289**) to collinoketone B (**294**) suggested by DFT calculations.

ketone A (**289**) in the transannular [6 + 4] cycloaddition of collinolide (**288**).

Transannular electrocyclizations

Pericyclic reactions play a central role in skeletal rearrangements and ring formation and have been extensively utilized in biomimetic synthesis. As shown above, transannular cycloadditions offer an exceptionally efficient approach to the assembly of complex polycyclic molecules. In contrast, successful examples of transannular electrocyclizations are extremely rare due to their innate reversibility.[119]

West *et al.* reported a bioinspired synthesis of briareolate ester B (**297**), featuring a transannular oxa-6π electrocyclization that was inspired by a biosynthetic hypothesis for briareolate



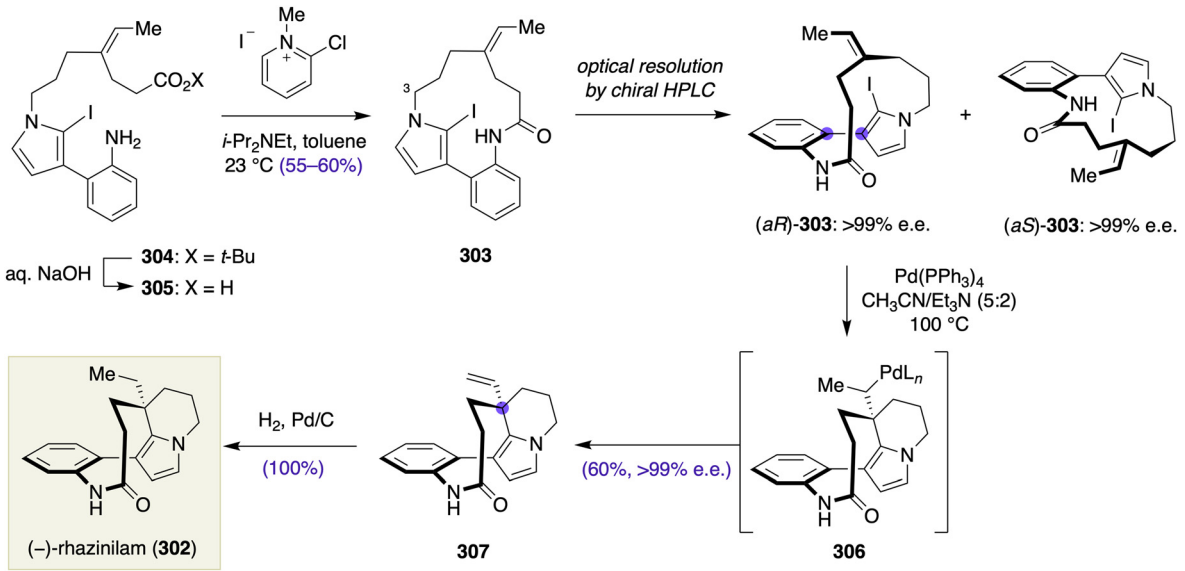
Scheme 42 Transannular oxa-6π electrocyclization in the total synthesis of briareolate ester B (**297**) by West and co-workers.

esters (Scheme 42).[120] The irradiation of a methanolic solution of briareolate ester L (**298**) with UVC light (λ < 260 nm) afforded only a mixture of **298** and **299** with no formation of **297** (**298**: **299**: **297** = 37 : 63 : 0). The formation of **297** was not observed under these conditions due to a rapid retro-oxa-6π electrocyclization from **297** to **299**. In contrast, the irradiation of a methanolic solution of **298** with low-energy UVA light (λ > 350 nm) for 3 h afforded briareolate ester B (**297**) as the major product (**298**: **299**: **2997** = 23 : 12 : 65). To follow up on these results, the irradiation of briareolate ester B (**297**) using UVA light resulted in no reaction over several hours. In contrast, the irradiation of briareolate ester B (**297**) using UVC light triggered a rapid and complete retro-6π electrocyclization to give a mixture of **298** and **299** (**298**: **299**: **297** = 37 : 63 : 0). Thus, the retro-6π electrocyclization was rapidly induced under UVC irradiation but not under UVA irradiation. These results established a unique photochemical switch in which selective irradiation with UVA or UVC light enables controlled interconversion between distinct skeletal frameworks. This study provides an insight into the transannular oxa-6π-electrocyclic reactions of macrocyclic conjugated dienone systems *via* a two-photon process and likely finds numerous applications in the synthesis of medium-sized macrocycles.

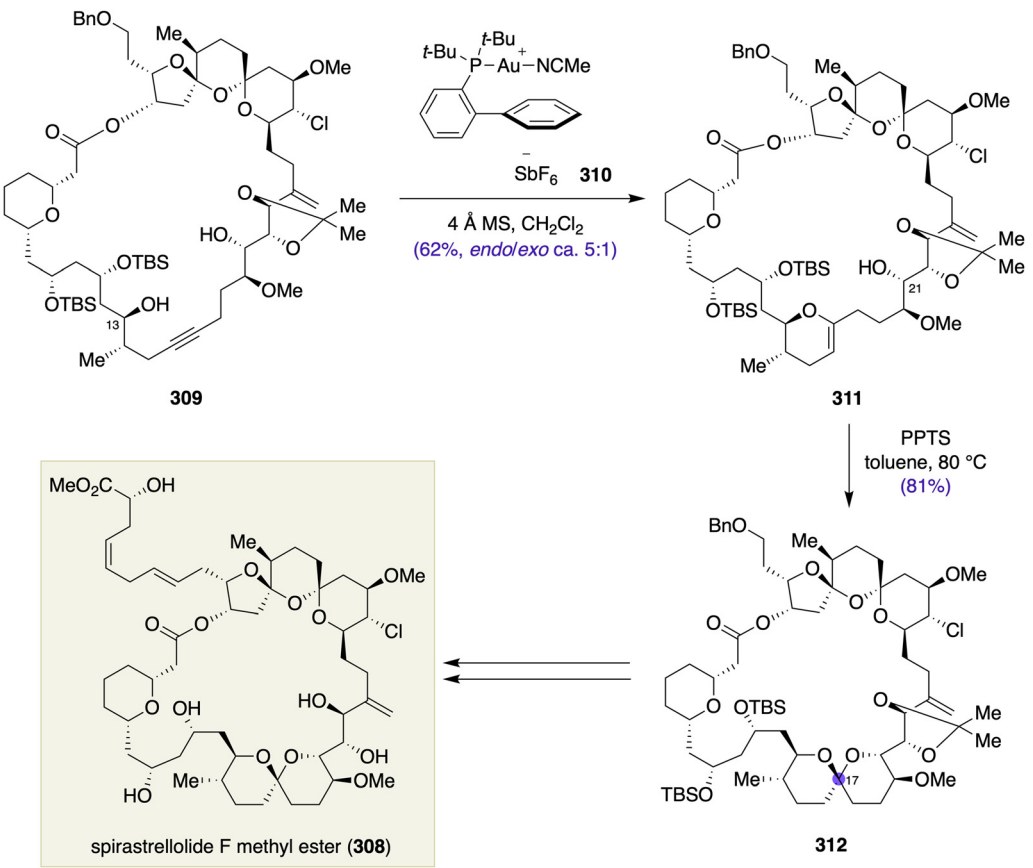
Transition metal-catalyzed transannular reactions

Despite their widespread general use in natural product synthesis, palladium-catalyzed cross-coupling reactions have been underexploited in a transannular format. A rare example of chirality-generating transannular Heck reaction was reported by Gu and Zakarian in their total synthesis of (−)-rhazinilam (**302**) (Scheme 43).[121] Lactam **303** was synthesized through a macrolactamization of acyclic amino acid **305** using 2-chloro-1-methylpyridinium iodide. The sign of axial chirality in **303** came from its ^{1}H NMR spectrum, wherein non-equivalent signals were observed for the methylene protons at the C3 position. Although enantioselective macrolactamization of amino acid **305** using several chiral reagents was unsuccessful, chiral HPLC resolution of **303** provided (*aR*)-**303** and (*aS*)-**303** with greater than 99% ee each. Transannular Heck reaction of (*aR*)-**303** under the catalysis of Pd$(PPh_3)_4$ (CH_3CN/Et_3N, 100 °C) afforded rhazinilam skeleton **307** through alkylpalladium species **306** in 60% yield with >99% ee, representing a highly efficient axial-to-point chirality transfer.[122]

Complementary to traditional intramolecular keto-diol cyclization, intramolecular alkyne hydroalkoxylation catalyzed by transition metal complexes is an efficient means to access various spiroketal derivatives, although the regioselectivity issue may be problematic in cases where *endo*/*exo* cyclization modes are both plausible.[123] In their total synthesis of spirastrellolide F methyl ester (**308**), Fürstner *et al.* closed the macrocyclic skeleton of the target by means of ring-closing alkyne metathesis (Scheme 44).[124] Upon exposure of macrocyclic alkyne **309** to cationic Au complex **310** (4 Å MS, CH_2Cl_2),[125] nucleophilic attack of the sterically less encumbered C13 hydroxy group onto the alkyne group occurred regioselectively, giving endocyclic enol ether **311** in 62% yield with 5 : 1 *endo*/*exo*. In contrast, AuCl or AuCl·SMe_2 catalyzed the alkyne hydroalkoxylation of **309** in a highly *exo* selective fashion. Treatment of **311** with PPTS in toluene at 80 °C resulted in



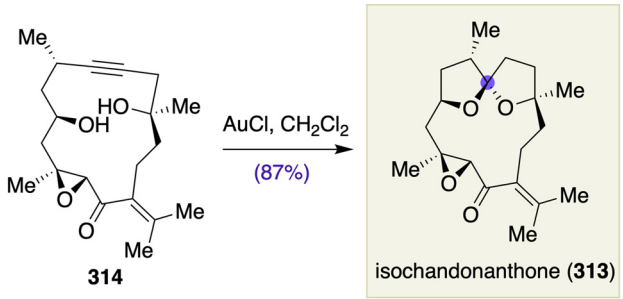
Scheme 43 Transannular Heck reaction in the total synthesis of (–)-rhazinilam (**302**) by Gu and Zakarian.



Scheme 44 Au-catalyzed transannular alkyne hydroalkoxylation and Brønsted acid-catalyzed transannular spiroketalization in the total synthesis of spirastrellolide F methyl ester (**308**) by Fürstner and co-workers.

spiroketalization with a sterically more hindered C21 hydroxy group, affording 6,6-spiroketal **312** in 81% yield with the correct configuration at the C17 position.

Hermann and Fürstner have recently disclosed a collective synthesis of cembrane diterpenoids, in which a transition metal-catalyzed transannular alkyne hydroalkoxylation was

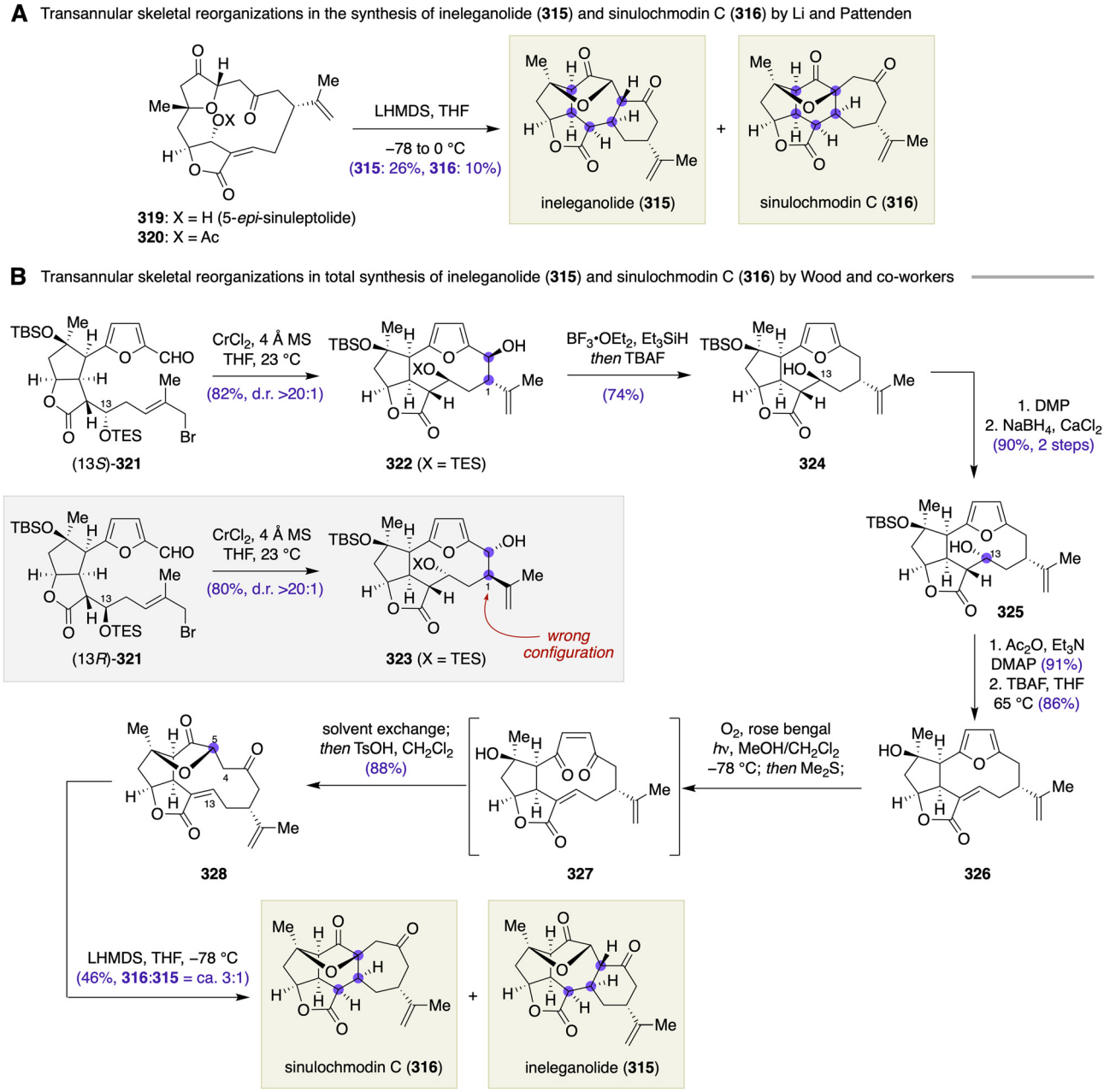


Scheme 45 Au-catalyzed transannular alkyne hydroalkoxylation in the total synthesis of isochandonanthone (**313**) by Hermann and Fürstner.

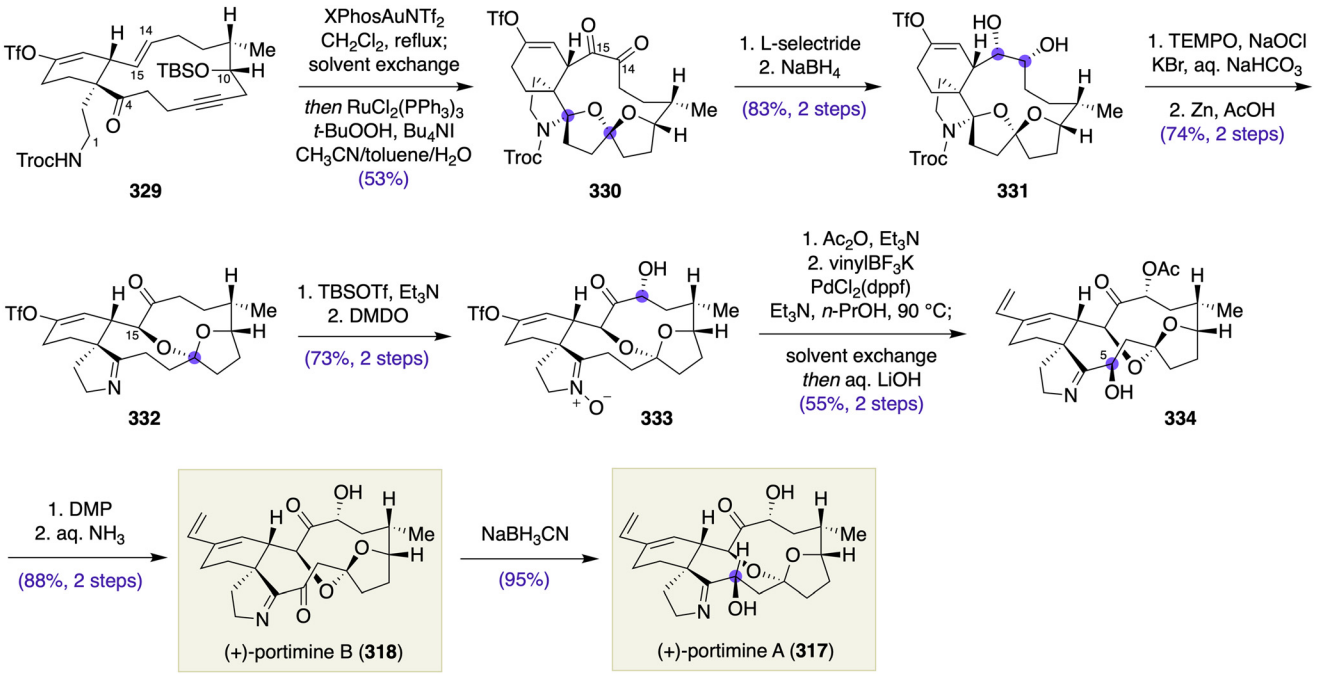
used for the stereoselective construction of the 5,5-spiroketal moiety of isochandonanthone, *i.e.*, **314** → **313** (Scheme 45).[126]

Transannular skeletal reorganizations

The power of late-stage chirality-generating transformations including transannular skeletal reorganizations was amply demonstrated in the total synthesis of polycyclic norfurano-cembranoids, (+)-ineleganolide (**315**) and (−)-sinulochmodin C (**316**), by Wood and co-workers (Scheme 46)[127] and in the total synthesis of cyclic imine toxins, (+)-portimine A (**317**) and (+)-portimine B (**318**), by Baran and co-workers (Scheme 47).[128]



Scheme 46 (A) Transannular skeletal reorganizations in the synthesis of ineleganolide (**315**) and sinulochmodin C (**316**) by Li and Pattenden. (B) Transannular skeletal reorganizations in the total synthesis of (+)-ineleganolide (**315**) and (−)-sinulochmodin C (**316**) by Wood and co-workers.



Scheme 47 Transannular skeletal reorganizations in the total synthesis of (+)-portimine A (**317**) and (+)-portimine B (**318**) by Baran and co-workers.

Although these natural products do not have a macrocycle (a 12-membered or larger ring) in a strict sense, these outstanding synthetic works involve multiple chirality-generating transformations on complex macrocyclic intermediates, which are worth mentioning in this article.

The polycyclic furanocembranoid family of natural products have attracted significant attention from the chemical community because of their densely functionalized, complicated structures and potentially useful anticancer activities. An earlier study by Li and Pattenden demonstrated a biomimetic transformation of the acetate derivative **320** of naturally occurring 5-*epi*-sinuleptolide into ineleganolide (**315**) and sinulochmodin C (**316**) through a transannular Michael addition (Scheme 46A).[129] A relevant transannular Michael addition was implemented in the total synthesis of a norcembranoid, (−)-sinulariadiolide A, by Meng and Fürstner.[130]

Building on the Pattenden's contribution, Wood and coworkers envisioned a chirality-generating NHK macrocyclization for constructing a macrocycle intermediate at the mid-stage and transannular oxa-Michael and Michael additions for completing the polycyclic skeleton at the final stage (Scheme 46B). Thus, treatment of allylic bromide (13*S*)-**321** with $CrCl_2$ in the presence of 4 Å MS in THF at 23 °C resulted in macrocyclic homoallylic alcohol **322** in 82% yield as a single diastereomer (dr > 20 : 1). In contrast, allylic bromide (13*R*)-**321** underwent the same reaction to give macrocyclic homoallylic alcohol **323** with wrong configuration at the C1 position in 80% yield as a single diastereomer (dr > 20 : 1). Accordingly, NHK macrocyclization was carried out on (13*S*)-**321** to generate the stereogenic center at C1 with the correct configuration. The configuration at C13 was subsequently reversed to achieve stereoselective elimination of the C13 hydroxy group at the late stage. The removal of the superfluous hydroxy group of the NHK macrocyclization product **322** with $BF_3{\cdot}OEt_2/Et_3SiH$, followed by *in situ* desilylation, gave alcohol **324**. Dess–Martin oxidation of **324** and stereoselective reduction of the derived ketone with $NaBH_4/CaCl_2$ provided alcohol **325** with the correct configuration at C13. After acetylation of **325**, the resultant acetate was treated with TBAF to bring about desilylation and concomitant E1cB elimination of the C13 acetate, giving rise to (*Z*)-α,β-unsaturated lactone **326**. Chemoselective oxidation of the furan ring with $^1O_2$ in the presence of Rose Bengal as the photosensitizer, followed by reductive work-up with Me_2S, delivered conjugated ene dione **327**, which without isolation was treated with TsOH to catalyze transannular oxa-Michael addition, affording tetrahydrofuran **328** in 88% yield from **326**. Finally, exposure of **328** to excess LHMDS brought about deprotonation at C4 or C5 and transannular Michael addition of the derived lithium enolates, resulting in a *ca.* 3 : 1 mixture of (−)-sinulochmodin C (**316**) and (+)-ineleganolide (**315**) in 46% yield. Notably, the final steps of the present synthesis (**328** → **316** + **315**) enabled late-stage skeletal reorganizations with the concomitant generation of three stereogenic centers, thereby completing the complex polycyclic architectures of (+)-ineleganolide (**315**) and (−)-sinulochmodin C (**316**) in a concise manner.

The Baran group assembled the carbon macrocycle of portimines at the mid-stage of the synthesis through a ring-closing alkyne metathesis (Scheme 47). Prior to the oxidation of the $\Delta^{14,15}$ double bond of **329**, the sensitive functional groups were temporarily masked as a unique tricyclic system by means of a transannular skeletal transformation. Thus, the

treatment of **329** with a catalytic amount of $XPhosAuNTf_2$ in refluxing CH_2Cl_2 enabled double spirocyclization by engaging the alkyne, C1 carbamate, C4 carbonyl, and C10 silyloxy groups. Subsequent oxidation of the double bond with $RuCl_2(PPh_3)_3$ and *t*-BuOOH in the presence of Bu_4NI afforded 1,2-diketone **330** in 53% overall yield. Next, the oxidation state at the C15 position was adjusted through a three-step sequence. Initially, the C14 carbonyl of **330** was reduced with L-selectride in a site- and stereo-selective fashion. The C15 carbonyl was then reduced with $NaBH_4$ in a stereoselective manner. The diastereoselectivities of these peripheral ketone reductions would be ascribed to the steric congestion of the α-face of **330**. The C14 hydroxy group of the derived diol **331** was oxidized selectively with TEMPO/NaOCl to give a ketone, from which the Troc group was removed with Zn/aq. AcOH at 40–75 °C. Under these conditions, the tricyclic system collapsed and transannular transketalization occurred with the C15 hydroxy group to deliver ketal **332** in 61% yield for the four steps (from **330**). After the transformation of **332** into the corresponding enol silyl ether, oxidation with dimethyldioxirane (DMDO) from the sterically less encumbered α-face gave alcohol **333** with concomitant oxidation of the imine nitrogen (73%, two steps). Upon treatment of **333** with Ac_2O/Et_3N in CH_2Cl_2 at 35 °C, the rearrangement of the nitrone occurred to provide the corresponding diacetate. Suzuki–Miyaura cross-coupling with vinylBF_3K, followed by the selective liberation of the C5 hydroxy group, furnished alcohol **334** in 55% yield in the two steps. The oxidation of **334** and acetate removal furnished (+)-portimine B (**318**) in 88% yield for the two steps, which was reduced with $NaBH_3CN$ to afford (+)-portimine A (**317**) in 95% yield. Note that the structure of (+)-portimine B (**318**) was revised through the present total synthesis. The Baran synthesis of portimines A and B is remarkable in that it followed the "two-phase strategy" originally developed for terpene synthesis and extensively exploited chirality-generating functional group transformations and transannular skeletal reorganizations in the oxidation phase.

Conclusions and prospects

Late-stage chirality generation strategies can be beneficial not only for realizing step-economy in target-oriented synthesis but also for structure diversification aiming at structure–activity relationship investigations. Nonetheless, it is still not easy to implement late-stage chirality-generating transformations in the total synthesis of macrocyclic natural products because of the difficulties in gaining an insight into the conformational landscape of complex macrocycles with moderate conformational flexibility.[131] In fact, the key to success in many of the above-described examples was conformational design.[132]

Local substituents often have a profound influence on the overall conformation of macrocycles. Steric interactions such as allylic strain and *syn*-pentane interaction, dipole interactions, and intramolecular hydrogen bonding are potentially useful structural elements for conformational design. The installation of substituents responsible for these interactions at the pre-macrocyclization stage likely result in confining the conformational flexibility of downstream intermediates at the post-macrocyclization stage, thereby making the stereochemical outcome of late-stage chirality-generating transformations easier to anticipate.

Biosynthetic mechanisms as well as their proposals[133] have served as a potential source of inspirations for late-stage transannular reactions, regardless of whether they seem to be catalyzed by an enzyme. However, it is still important to design macrocyclic substrates with an appropriate substitution pattern and stereochemistry for the success of transannular reactions, as can be seen in the synthetic studies on spinosyn A by Roush and co-workers.

The stereoselectivity observed in some examples covered in this review was reasoned by their X-ray structures and/or NMR spectroscopic data. In addition to these analytical techniques, theoretical calculation is a promising approach for visualizing the conformational landscape of complex macrocycles.[134] Recent advances in conformational search algorithms and machine learning technologies enable conformational sampling of moderately flexible macrocycles with greater accuracy than ever before.[135] Coupled with appropriate statistical analysis, theoretical calculation has been shown to be useful for configurational assignment and conformational analysis of macrocyclic natural products.[136–138] If available, NMR spectroscopic data such as *J* values or NOE correlations may be helpful for making constraints in calculation to reduce the computation costs.

Currently, late-stage chirality-generating transformations in macrocyclic natural product synthesis depend mainly on classical textbook reactions. Radical-mediated transformations, especially stereoinversions at specific tertiary chiral centers,[139] are rapidly developing in recent years and should be a potentially useful strategy for the late-stage diversification of macrocyclic natural product structures. Enzymatic late-stage transformations represent a growing area of importance in organic synthesis but their application to the synthesis of macrocyclic natural products is still limited.[140,141] Expanding our repertoire of transformations amenable to late-stage chirality generation as well as advancing our controllability and predictability of the conformational property of macrocycles will facilitate future developments in the total synthesis of macrocyclic natural products.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results have been included, and no new data were generated or analyzed as part of this review.

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