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Synthesis of natural products containing fully functionalized cyclopentanes

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1. Introduction

The five-membered carbocycle is a familiar and widespread structural motif in natural product architectures. As a result, the collection of chemical reactions that construct cyclopentanes represents an indispensible toolbox for synthetic chemists. Moreover, methods that build cyclopentanes with control of sp^3-hybridized stereocenters are particularly valuable. The importance of creating substituted cyclopentanes with control of stereochemistry has been a driving force inspiring the creation of synthetic methods and strategies for building functionalized five-membered carbocycles. The pursuit of substituted cyclopentanes has showcased the wide scope, functional group tolerance, and elegance of many synthetic reactions. The pursuit has also exposed the limitations of various synthetic transformations, and it has inspired chemists to improve such processes. This review provides a comprehensive discussion on the methods that have been used in the synthesis of fully functionalized cyclopentanes in natural product synthesis. Previous reviews have appeared in this area; however, they are either not comprehensive for fully functionalized cyclopentanes,[1] or they are a general review of annulation.[2] We use these natural products as a lens to view the current state-of-the-art methods and strategies to form functionalized cyclopentanes.

In this review, we define fully functionalized cyclopentanes as five membered carbocycles where each of the five sp^3-hybridized carbons bears at least one non-hydrogen substituent. Such structures are exemplified by the monocyclic substituted cyclopentanoid mannostatin A and the polycyclic framework of coriolin (Fig. 1). Of course, a cyclopentane may display up to ten non-hydrogen substituents. We include the examples of such decasubstituted cyclopentanes (shinjulactone C and ryanodol), but the discussion is not limited to these cases. Not included in this review are natural products that have methylene (CH_2) groups in the five membered ring (such as neofinaconitine), nor natural products with sp^2-hybridized carbons in the five membered ring, such as antheridic acid.

Importantly, this review is organized by the reaction that assembles the 5-membered carbocycle, rather than an organizational system based on the target natural product. Particular emphasis is placed on the overall synthetic strategy used to assemble the stereochemically-rich cyclopentane. We organize this Report in 10 distinct sections based on the method by which the key five-membered carbocycle is forged. Within each main section we group mechanistically or topologically-related strategies into well-defined subsections. Within each subsection, reports are grouped according to the natural product target, and presented in chronological order of the earliest total synthesis.

Throughout the review, the carbon atoms that will constitute the cyclopentane have been color coded in red; if two fully functionalized cyclopentanes exist in the target, then the carbons are

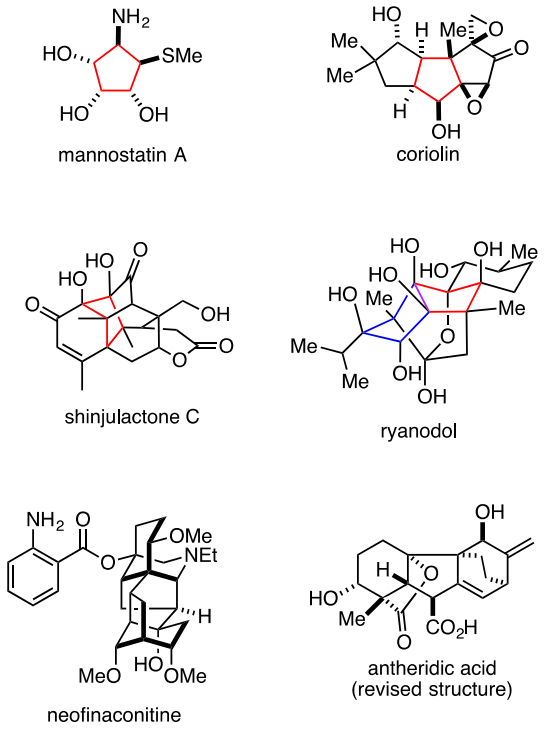


Fig. 1. Selected Natural Products Containing Functionalized Cyclopentanes.

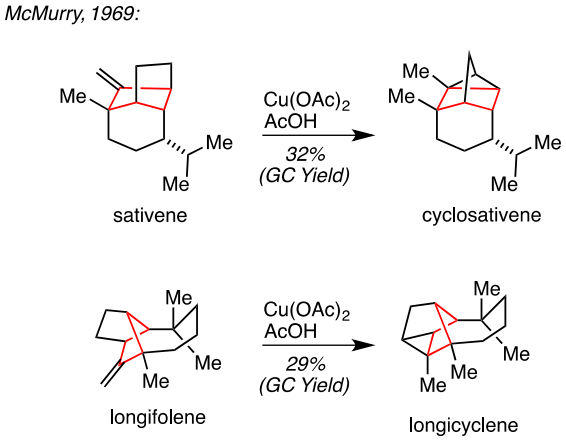
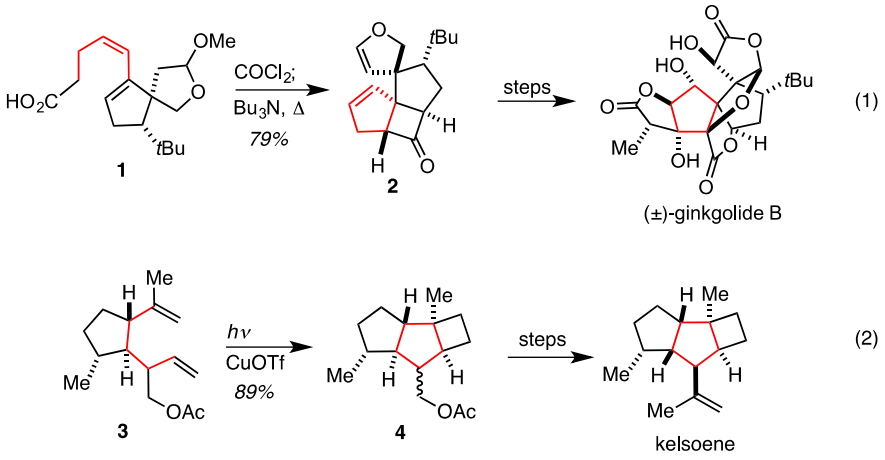
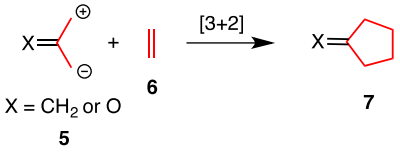


Fig. 2. Interconversion of Natural Products with Functionalized Cyclopentanes.



Scheme 1. The [2 + 2]-Cycloaddition in the Synthesis of Fully Functionalized Cyclopentanes.



Scheme 2. All-Carbon [3 + 2]-Cycloadditions in the Synthesis of Fully Functionalized Cyclopentanes.

color-coded red and blue, as appropriate. This review focuses on the key steps in constructing and functionalizing the cyclopentane, and is not an exhaustive analysis of each total synthesis. Comparative reviews of total syntheses of target natural products in this Report appear elsewhere.[3] Consequently, some of the noteworthy steps in the syntheses may be excluded from the discussion if they do not contribute to the cyclopentane construction or functionalization. We show all steps that affect substitution or stereochemical changes to carbons of the eventual fully functionalized cyclopentane, and steps that do not result in changes to the cyclopentane structure or substitution are generally not shown nor discussed in detail.

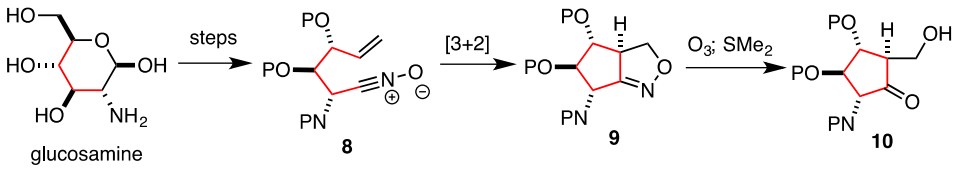
This review is limited to natural product total synthesis, and fully functionalized cyclopentanes that are not natural products have not been included. Also omitted are synthetic studies toward natural products that did not result in completion of the target. However, in the event that a partial synthesis bears close similarity to related total syntheses, we included those studies. Simple interconversions between natural products with fully functionalized five membered rings performed upon isolation are not covered. Similarly, studies of rearrangements between natural product congeners, such as those shown in Fig. 2, are not covered. Of course, we recognize that the studies above render all previous and future syntheses of sativene and longifoline *formal syntheses* of cyclosativene and longicyclene, respectively; however, the syntheses of the former molecules do not address the complexities of forming fully functionalized cyclopentanes, and are not covered here. We cover those syntheses that have appeared through the first half of 2016. In the event that an example from the literature has been missed, the authors deeply regret the omission.

2. Cycloadditions

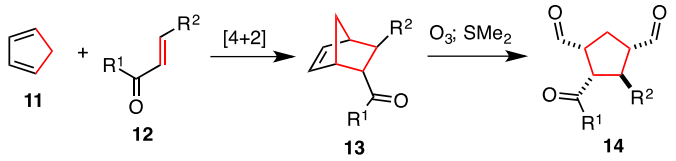
Cycloadditions represent versatile and powerful transformations for the formation of ring structures, and it is not surprising that they are employed in preparing functionalized cyclopentane architectures. There are examples of [2 + 2]-,[4] [3 + 2]-, [4 + 2]- (the Diels–Alder reaction), and [5 + 2]-cycloadditions[5] that are used in the formation of fully functionalized cyclopentane natural products.

The [2 + 2]-cycloaddition of 1,5-dienes leads to *cis*-fused bicyclo[3.2.0]heptane archtitectures, and these reactions have been used in the synthesis of targets with fully functionalized cyclopentanes (Scheme 1). The key five-membered ring is formed from the carbons in the intramolecular tether connecting the alkene functional groups. Strategically, functional groups may be installed in the tether to enable subsequent transformations that create substitution in the target cyclopentane (such as in eq. 1). Alternatively, substituents with appropriate stereochemistry may be established prior to the cycloaddition event (eq. 2). The stereochemistry at the bridgehead atoms favors the *cis*-fused diastereomer that delivers the substituents in sterically less-hindered positions. The synthesis of ginkgolide exemplifies use of the [2 + 2]-cycloaddition where the reactivity of the cylcobutane is leveraged in the formation of additional rings, and the strategic use of the [2 + 2]-cycloaddition is non-obvious. The bicyclo[3.2.0]heptane moiety in the kelsoene target is more suggestive of the use of the [2 + 2]-cycloaddition.

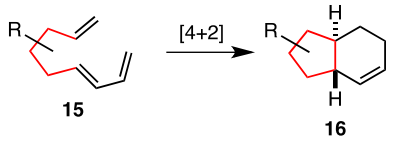
The intermolecular combination of an all-carbon 1,3-dipole (**5**) with an alkene (**6**) produces a 5-membered carbocycle (**7**) (Scheme 2).[6] These reactions often proceed with high levels of substrate-controlled diastereoselectivity. Five natural products with fully



Scheme 3. Heteroatom [3 + 2]-Cycloadditions in the Synthesis of Fully Functionalized Cyclopentanes.



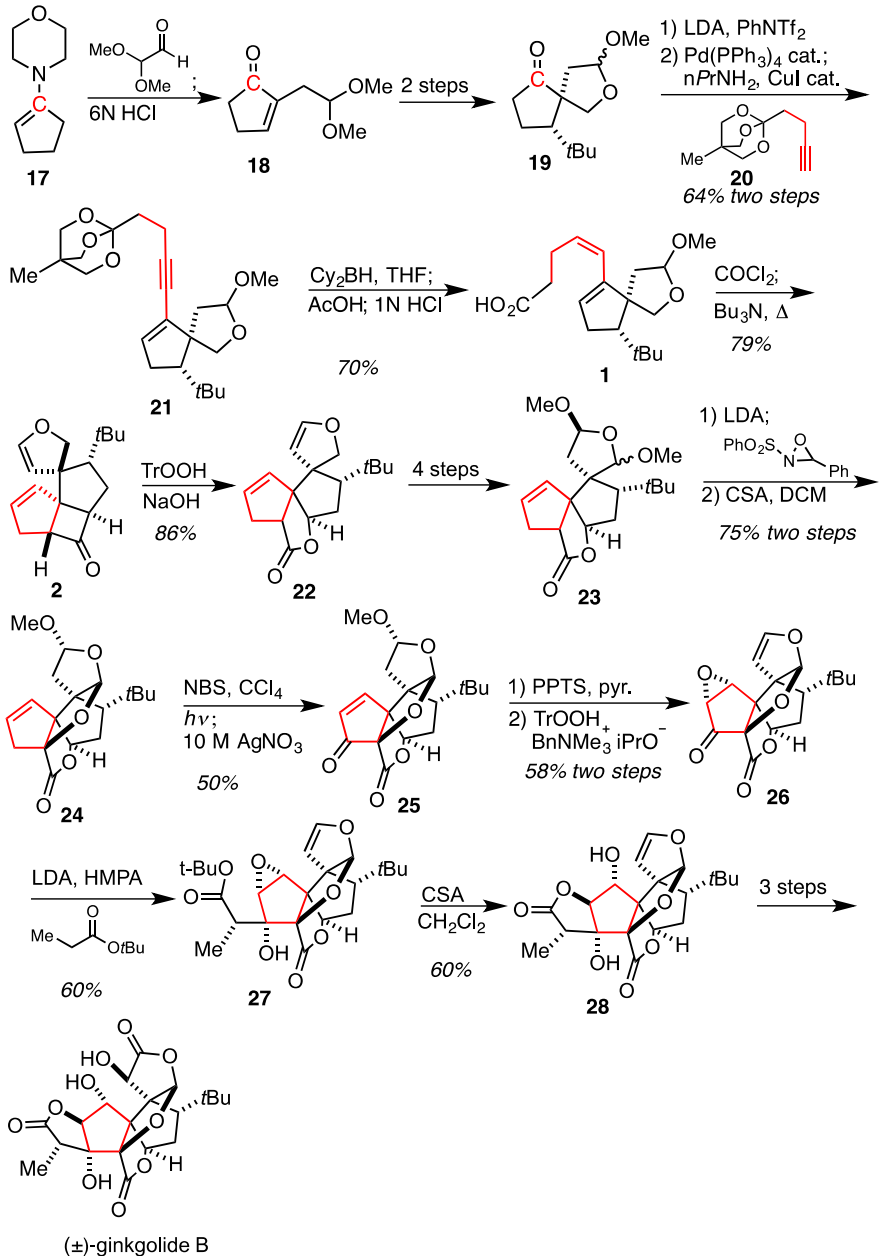
Scheme 4. Cyclopentadiene Diels–Alder Cycloadditions in the Synthesis of Fully Functionalized Cyclopentanes.



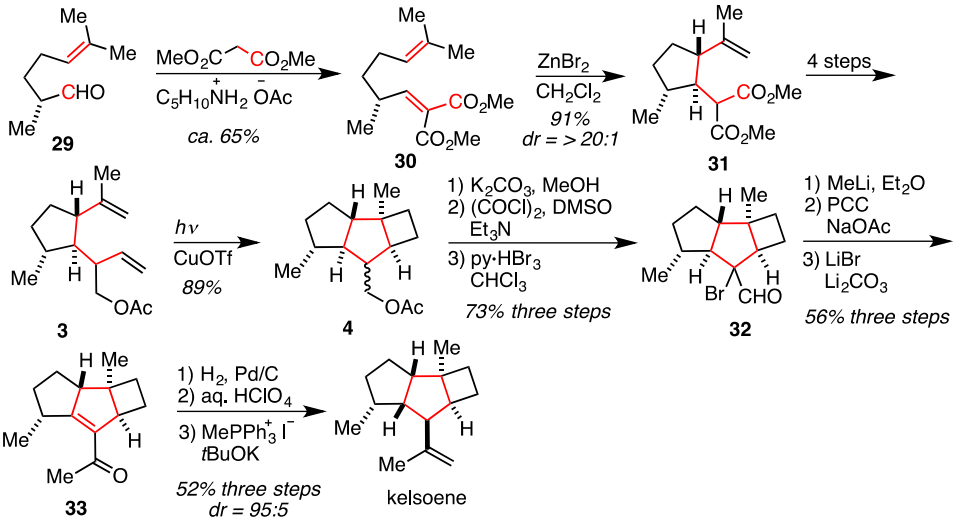
Scheme 5. Intramolecular Diels–Alder Cycloadditions in the Synthesis of Fully Functionalized Cyclopentanes.

functionalized cyclopentanes have been prepared using all-carbon [3 + 2]-cycloadditions to construct the five-membered ring. It is perhaps surprising that relatively few fully functionalized cyclopentanes are made with this reaction because it inherently constructs a five-membered carbocycle, vis-à-vis the Diels–Alder reaction, which inherently forms a six-membered ring. However, methods available for the formation of all-carbon dipoles are relatively few in number.[7]

Intramolecular [3 + 2]-cycloadditions may also deliver functionalized cyclopentanes where the tether carbons become the eventual carbocycle (Scheme 3). In the context of this review, the stereogenic carbons in the tether are derived from carbohydrate feedstock molecules. The cycloaddition involves reaction of a nitrile oxide **8** or a nitrone dipole (not shown) to give an isoxazoline (**9**) or isoxazolidine, respectively. The stereochemistry of the bridgehead carbon is controlled by the adjacent stereocenter, leading to positioning of the substituent on the less hindered face of the bicycle.



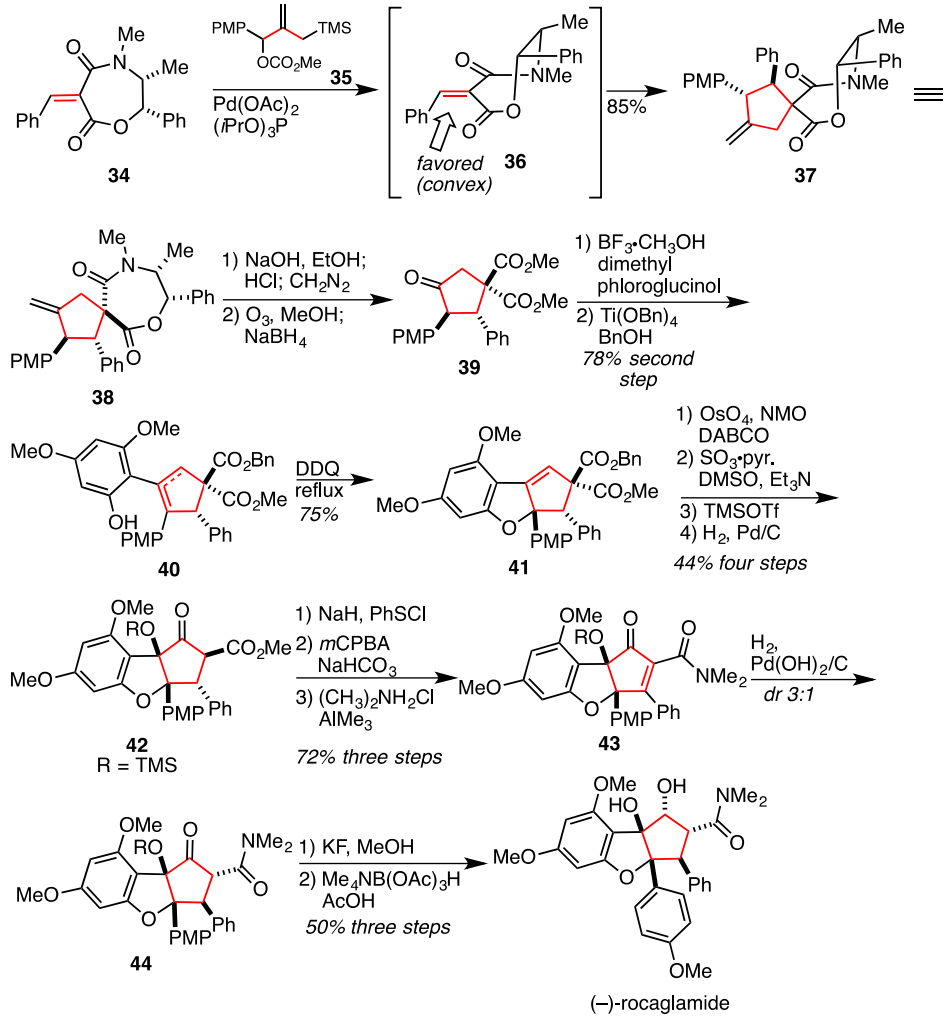
Scheme 6. Total Synthesis of (±)-Ginkgolide B (Corey, 1988).



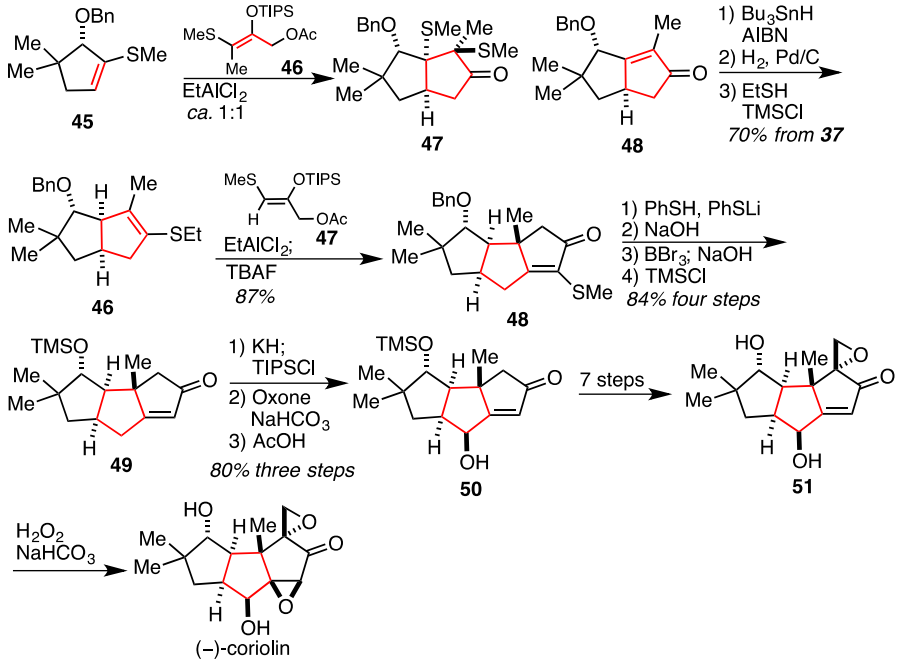
Scheme 7. Total Synthesis of (±)-Kelsoene (Bach, 2002).

The heterocyclic five-membered ring is subsequently opened using standard conditions to give **10**.

The intermolecular Diels–Alder reaction of cyclopentadienes with alkenes leads to the formation of substituted cyclopentanes that are part of bicyclo[2.2.1]heptenes (Scheme 4). Cases related to this review (with one exception: Zhai's biomimetic synthesis of absinthin) involve relatively simple and symmetrically-substituted cyclopentadienes (**11**) reacting with substituted

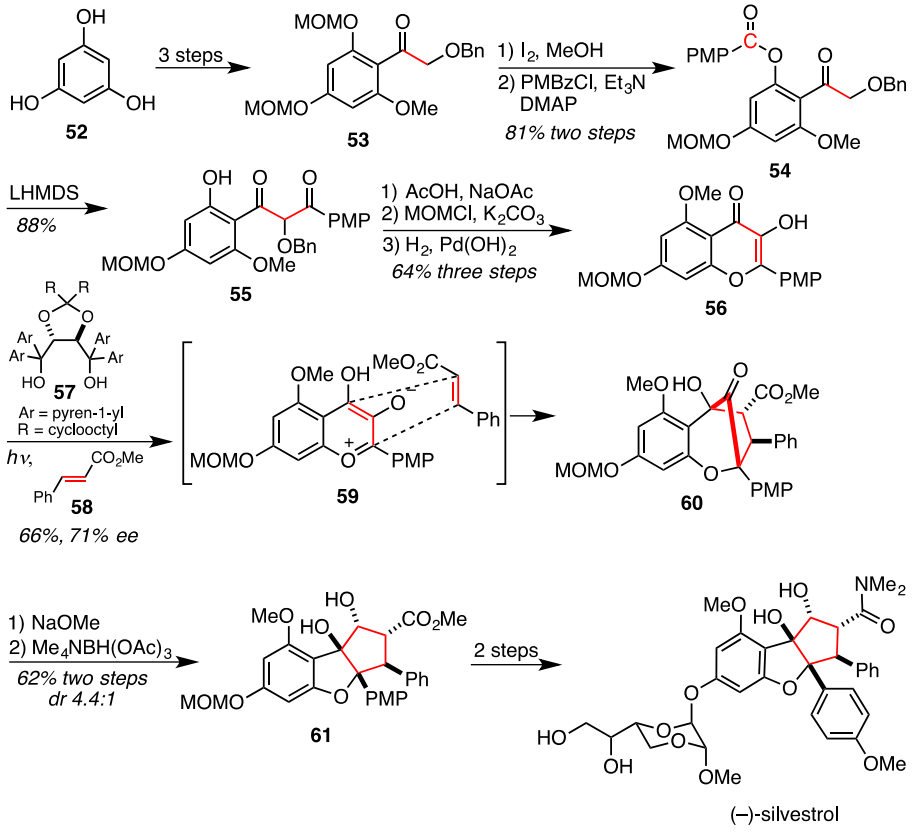


Scheme 8. Total Synthesis of (−)-Rocaglamide (Trost, 1990).

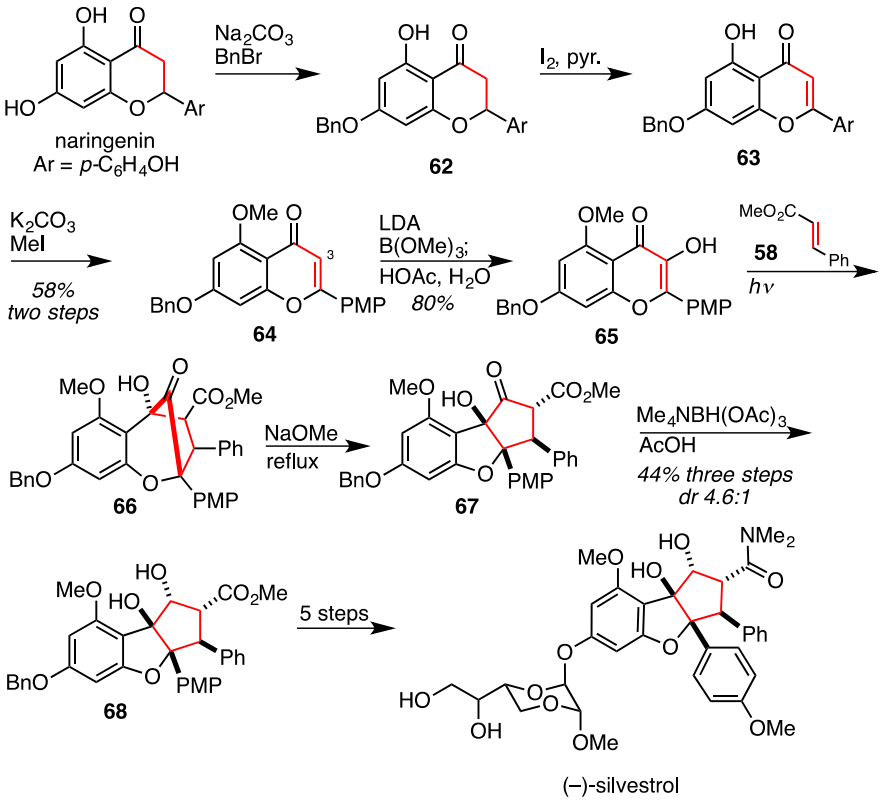


Scheme 9. Total Synthesis of (−)-Coriolin (Kuwajima, 1999).

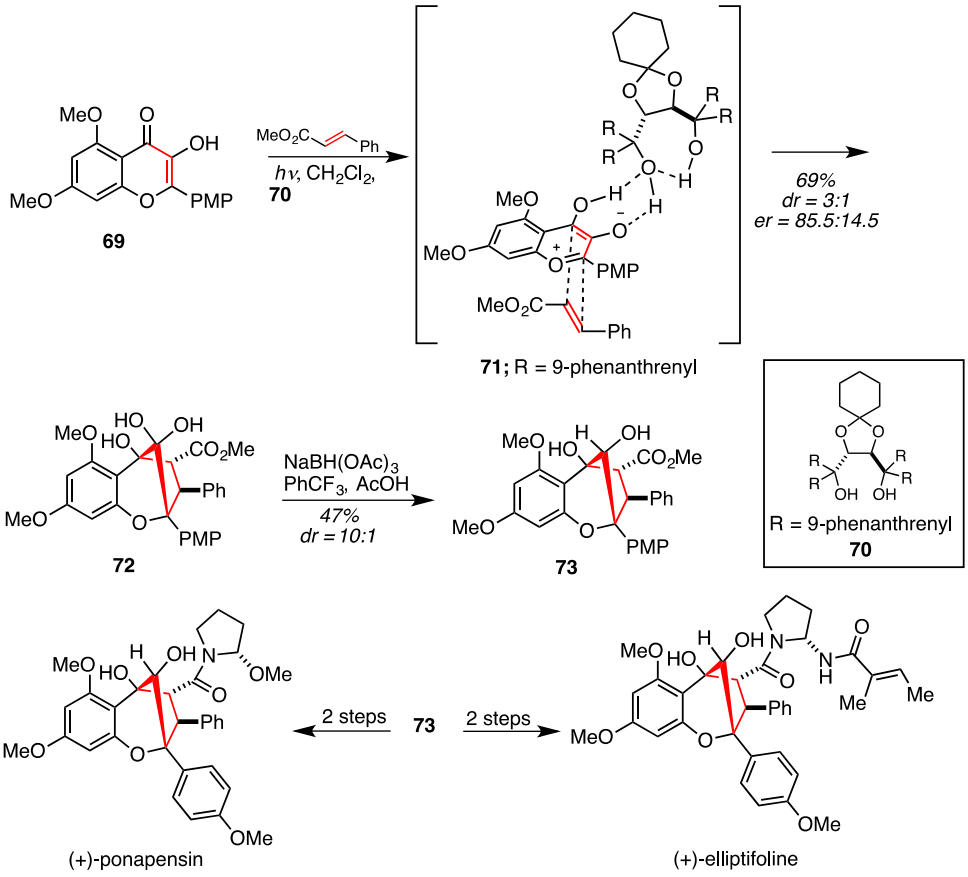
alkene dienophiles **12**. The cycloaddition proceeds with predictable *endo* diastereoselectivity, setting four carbon stereocenters in **13**. Variation in the substitution pattern of the dienophile is widely tolerated, and appropriate substitution gives functional handles for further transformations. Invariably, subsequent transformations include the oxidative cleavage of the resident alkene to reveal intermediate **14** that undergoes further processing. A possible limitation of this synthetic strategy is the



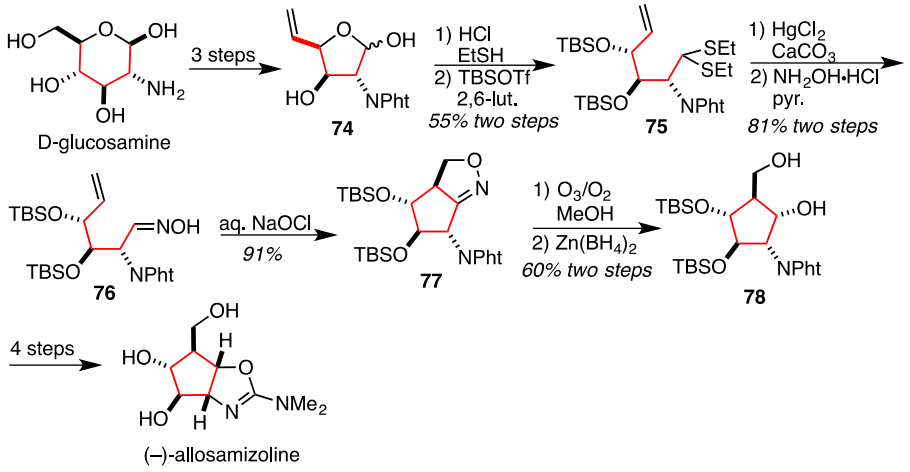
Scheme 10. Total Synthesis of (−)-Silvestrol (Porco, 2007).



Scheme 11. Total Synthesis of (−)-Silvestrol (Rizzacasa, 2007).



Scheme 12. Total Synthesis of (+)-Ponapensin and (+)-Eliptifoline (Porco, 2012).



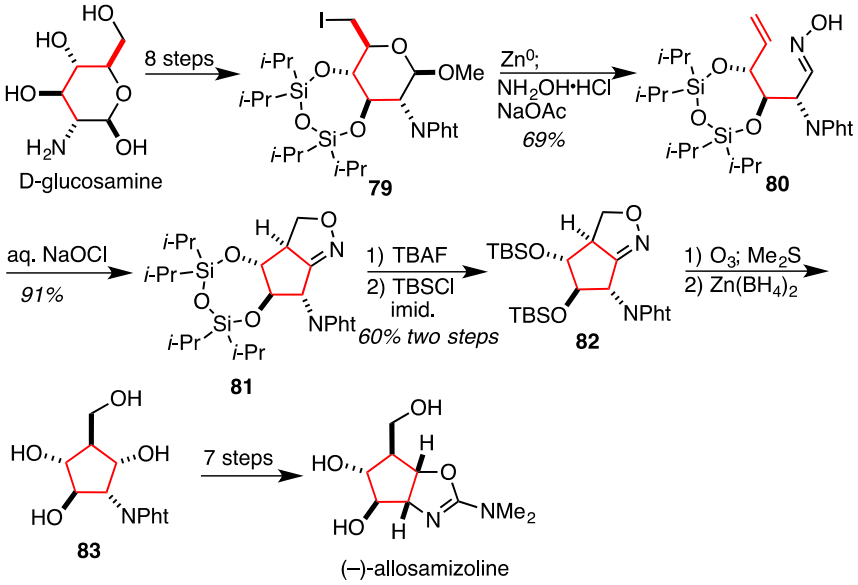
Scheme 13. Total Synthesis of (−)-Allosamizoline (Tatsuta, 1991).

relatively few methods for the preparation of functionalized non-symmetric cyclopentadienes.[8] Likely as a result of this limitation, this type of Diels–Alder reaction occurs early in the synthetic route to the natural product target.

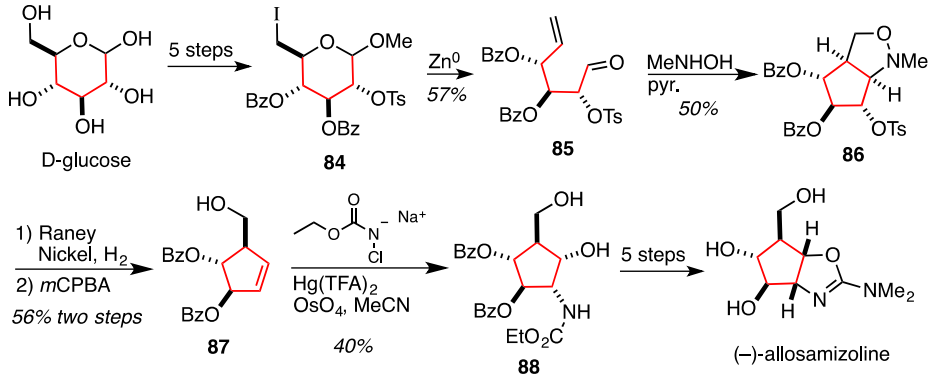
The intramolecular Diels–Alder reaction of skipped trienes **15** may also be used in the formation of substitituted cyclopentanes embedded in hydrindane architectures **16** (Scheme 5). In such cases, the functionalized cyclopentane is made from the molecular tether connecting the diene and dienophile. A key consideration of this strategy is the establishment of substitution on the tether with the desired stereochemical configuration. The intramolecuar Diels–Alder reaction is a well-studied and dependable transformation, even with quite complex substrates.[9,10] The hydrindanes formed show *trans* ring fusions that position the tether substituents in the sterically less hindered location. As a result of such dependability and predictable control elements, this type of Diels–Alder reaction has been used late in the synthetic route to complex natural product targets.

2.1. [2 + 2] cycloadditions

In the synthesis of (±)-ginkgolide B, Corey[11] uses a [2 + 2] cycloaddition to construct a polycyclic ring system containing the five-membered ring of interest (Scheme 6). The synthesis begins with 1-morpholinocyclopentene (**17**), which was converted to cyclopentanone **18** by reaction with dimethoxyacetaldehyde followed by hydrolysis with HCl. This cyclopentenone was advanced to spirocyclic intermediate **19** over two steps. Conversion to the enol triflate and coupling with alkyne **20** gave **21**. Partial reduction of the alkyne furnished the desired *Z*-alkene. Acidic hydrolysis of the ortho-ester revealed carboxylic acid **1**. Formation of the acid chloride with oxalyl chloride was followed by slow addition to tri-*n*-butylamine to give a ketene intermediate that underwent a [2 + 2] cycloaddition to give **2**. Baeyer-Villiger oxidation with *tert*-butyl hydrogen peroxide produced γ-lactone **22**. This material was advanced over four steps to **23**. Enolate formation and addition to the Davis oxaziridine gave an α-hydroxy lactone. The ether bridge in **24** could then be constructed with catalytic camphorsulfonic acid



Scheme 14. Total Synthesis of (−)-Allosamizoline (Koseki, 1993).



Scheme 15. Total Synthesis of (−)-Allosamizoline (Ferrier, 1994).

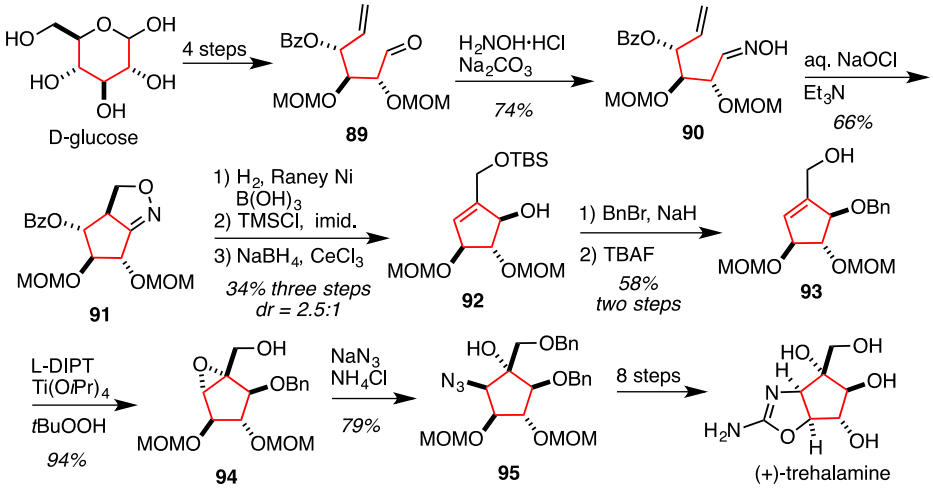
in methanol. Oxidation of the cyclopentene to cyclopentenone **25** was completed by allylic bromination and subsequent oxidation with silver nitrate. An acid-promoted elimination of methanol gave a dihydrofuran. Stereoselective nucleophilic epoxidation yielded **26**. Introduction of the final required substituent was accomplished by a diastereoselective aldol addition with *tert*-butyl propionate to give **27**. Lactonization with camphorsulfonic acid delivered bislactone **28** and a fully functionalized cyclopentane with the desired substitution in (±)-ginkgolide B.

The Bach[12] synthesis of (±)-kelsoene utilizes a [2 + 2] photocycloaddition of a 1,6-diene to construct a fully functionalized cyclopentane (Scheme 7). The route begins with a Knovenagal condensation of citronellene-dervied aldehyde **29** with dimethyl malonate to give **30**. An Alder-ene reaction using conditions developed by Tietze[13] delivered cyclopentane **31**. This material was advanced over four steps to cycloaddition precursor **3**. A [2 + 2] photocycloaddition in the presence of CuOTf delivered a fully functionalized cyclopentane (**4**) as a mixture of diastereomers. Acetate cleavage, oxidation of the resulting alcohol and α-bromination delivered **32** as a single diastereomer. Addition of methyllithium, oxidation of the resulting alcohol to the ketone, and elimination of bromide gave enone **33**. Hydrogenation occurred preferentially from the face opposite the methyl groups. An acid-catalyzed epimerization of the resulting ketone delivered a fully functionalized cyclopentane with the desired stereochemistry for the target. A Wittig olefination completed the synthesis of (+)-kelsoene.

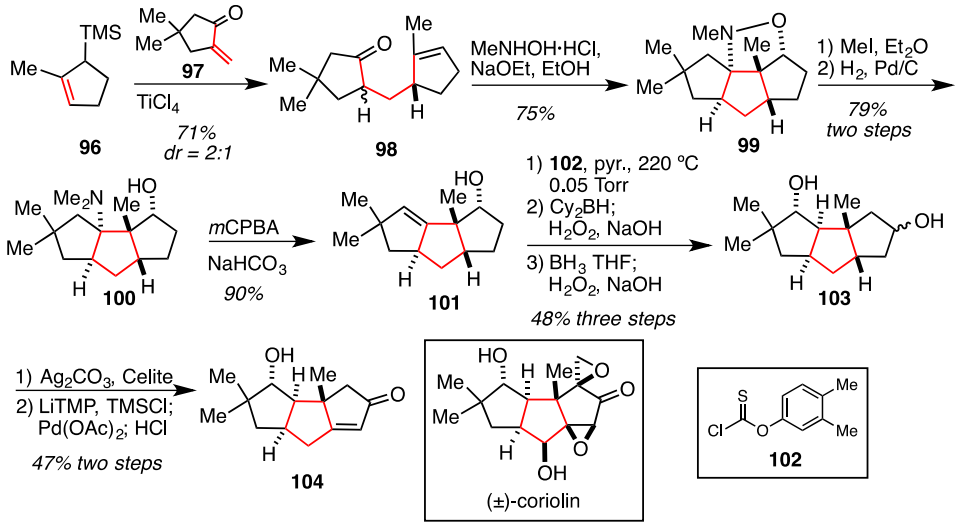
2.2. [3 + 2] cycloadditions

2.2.1. Bimolecular reactions of all-carbon dipoles

The Trost[14] synthesis of (−)-rocaglamide begins with a palladium-catalyzed cycloaddition of the trimethylenemethane (TMM)[15] precursor **35** and alkene **34** (Scheme 8). The chiral-auxiliary[16] promotes addition of the TMM from the convex face of the boat-like confomer **36** and delivers **37** as a single diastereomer. Removal of the auxiliary, and oxidative cleavage produces cyclopentanone **39**. Condensation with dimethyl phloroglucinol followed by selective transesterification gave **40** as a mixture of alkene regioisomers. Oxidative cyclization with DDQ delivers **41**. Note the oxidative cyclization gives the undesired *trans* relationship between the phenyl and PMP groups, which must be corrected. In a preliminary study, the TMM [3 + 2] cyclization of model compounds lacking the auxiliary set the tertiary stereocenter with the desired *cis* configuration, albeit as a racemate. Dihydroxylation occurs from the top face of the cyclopentene promoting a *cis* fusion of the 5-membered rings. Functional group manipulation (oxidation, silylation, and hydrogenolysis/decarboxylation) gave cyclopentanone **42**. Reaction with phenylsulfenyl chloride/*m*CPBA delivers a cyclopentenone, which installs the necessary functionality to set the desired stereochemical configuration. Amide formation under Weinreb's conditions gives **43**. Hydrogenation using Pearlman's catalyst sets the two tertiary stereocenters and delivers **44** as a 3:1 diastereomeric mixture. Presumably, the *syn* delivery of hydrogen is followed by epimerization of the methyl ester, which



Scheme 16. Total Synthesis of (+)-Trehalamine (Shiozaki, 1994).



Scheme 17. Formal Synthesis of (±)-Coriolin (Funk, 1985).

affords the *trans* relationship on the five-membered ring. Desilylation and stereoselective reduction with hydride directed by the vicinal hydroxide completes the synthesis of (−)-rocaglamide.

Kuwajima's[17] total synthesis of (−)-coriolin begins with a [3 + 2] cycloaddition to construct the cyclopentane that will eventually become fully functionalized (Scheme 9). This [3 + 2] reaction of vinyl sulfide **45** and the silyloxy allyl species **46** delivers two annulation products (**47** and **48**) in a 1:1 ratio. This mixture was subjected to an additional three steps to deliver **46**. The appropriate *cis* fusion of the cyclopentanes has been installed for coriolin. A second [3 + 2] cycloaddition with silyloxy allyl species **47** gave triquinane **48** and sets the quaternary stereocenter found in coriolin. With three stereocenters in place, functional group manipulation (β-elimination with fluoride, desulfurization with phenyl thiolate, elimination, and silylation) delivered **49** with the necessary functionality to install the final two stereocenters. Deprotonation of the enone and silylation of the extended enolate was performed with potassium hydride and TIPSCl. An epoxide was formed on the less hindered top face of the molecule. Epoxide opening under acidic conditions delivered **50** and set the secondary alcohol stereocenter of coriolin. This material was advanced over seven steps to **51**. Nucleophilic epoxidation of the enone set the final stereocenter on the fully functionalized cyclopentane and completed the synthesis of (−)-coriolin.

The total synthesis of (−)-silvestrol by Porco[18,19] features a [3 + 2] photocycloaddition between a 3-hydroxyflavone and a cinnamate dipolarophile to assemble a functionalized cyclopentane (Scheme 10). The route commences with aryl ketone **53** (synthesized from phloroglucinol **52** in three steps). Deprotection of the MOM group (cat. I_2/MeOH) was followed by acylation with 4-methoxybenzoyl chloride to give **54**. Treatment with LHMDS promoted a Baker-Venkataraman rearrangement[20] yielding diketone **55**. Sodium acetate in acetic acid promoted cyclization, dehydration and MOM deprotection. Reintroduction of the MOM group and hydrogenolysis of the benzyl ether delivers **56**. The enantioselective [3 + 2] photocycloaddition was performed with methyl cinnamate (**58**) and chiral TADDOL derivative **57**, leading to cycloadduct **60** in 71% ee. An α-ketol (acyloin) rearrangement promoted by sodium methoxide was followed by a hydroxyl-directed reduction to complete to give the molecular architecture of (−)-silvestrol.

In a synthesis of (−)-silvestrol, Rizzacasa[21] uses the photocycloaddition developed by Porco (see above) to assemble the fully functionalized cyclopentane (Scheme 11). The route to the 3-hydroxyflavone starting material began with the commercially available natural product naringenin. Selective benzylation delivered **62**. An oxidation with iodine yielded a flavone **63**, which upon methylation furnished **64**. The desired 3-hydroxyflavone **65** could be obtained by deprotonation at C3 position followed by boration and oxidative workup. The photocycloaddition with methyl cinnamate (**58**) resulted in bicyclic intermediate **66** as a racemate. Treatment with base promoted an α-ketol rearrangement to the β-ketoester **67**. Hydride reduction from the convex face of the bicycle delivers the desired hydroxyl configuration in a 4.6:1 ratio. This advanced intermediate has a fully functionalized cyclopentane, and it was advanced to the natural product. Racemic intermediate **68** was advanced and subsequently conjugated with an enantioenriched chiral sugar moiety; separation of the diastereomers allowed for a synthesis of non-racemic (−)-silvestrol.

The synthesis of (+)-ponapensin and (+)-elliptifoline by Porco[22] (Scheme 12) uses a similar [3 + 2] photocycloaddition strategy to that discussed above. The 3-hydroxyflavone **69** underwent a TADDOL (**70**) promoted [3 + 2] photocycloaddition to give cycloadduct **72** in good yield and good stereochemical control. Hydride reduction of the ketone hydrate delivered the fully functionalized cyclopentane **73** with the desired stereochemistry for (+)-ponapensin and (+)-elliptifoline, and it could be converted to either natural product in an additional two steps.

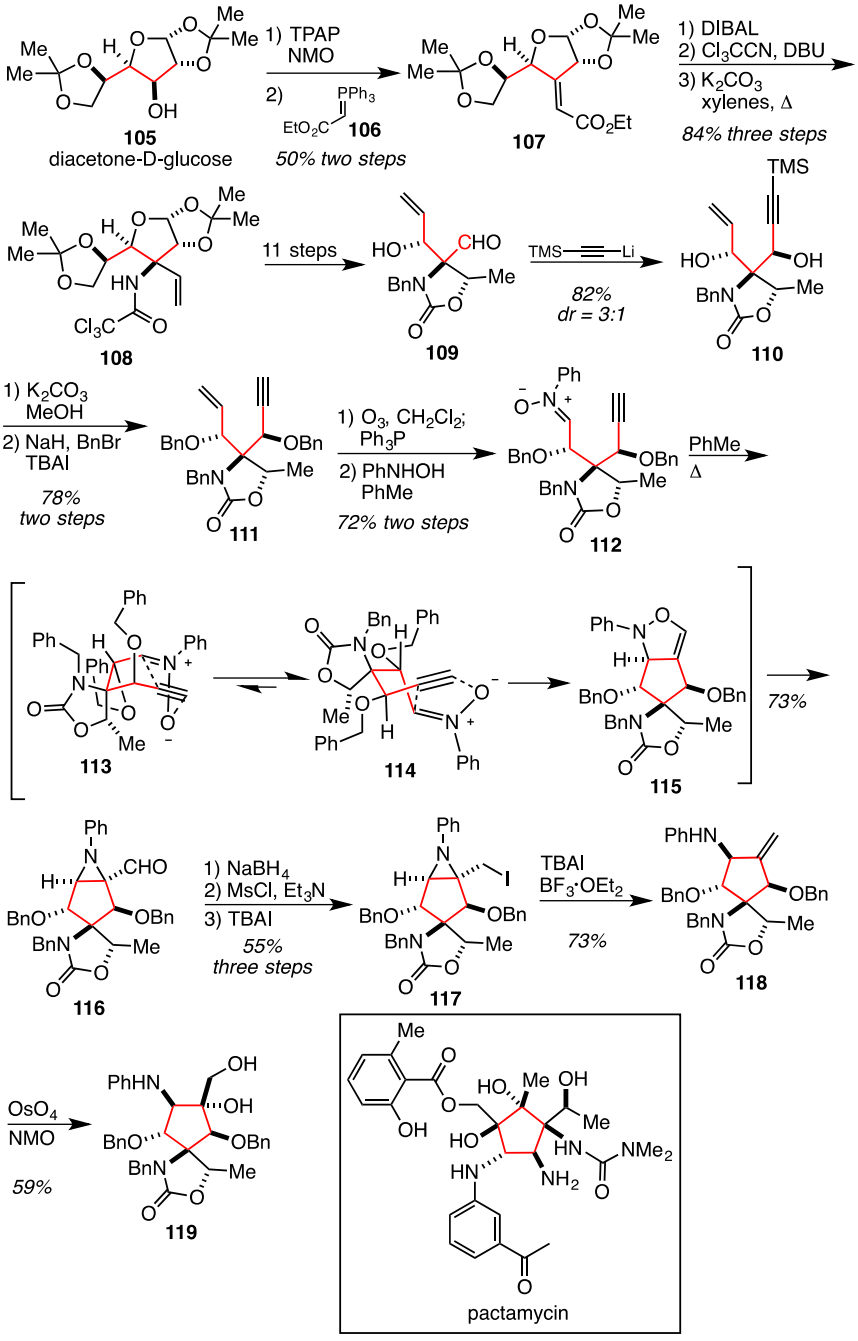
2.2.2. *Intramolecular reactions of heteroatom dipoles*

Tatsuta's[23] synthesis of (−)-allosamizoline begins with D-glucosamine, which contains the desired configuration at four of the five allosamizoline stereocenters (Scheme 13). The route begins with the conversion of D-glucosamine to furanose **74** over three steps. Treatment with ethanethiol and HCl delivered a dithioacetal, which underwent TBS protection of the secondary alcohols to give **75**. Desulfurization was performed with mercuric chloride and the resulting aldehyde was transformed into oxime **76**. Oxidation to a nitrile oxide with sodium hypochlorite promoted an intramolecular 1,3-dipolar cycloaddition to deliver isoxazoline **77**. Fragmentation of the isoxazoline with ozone yielded a β-hydroxy ketone. The final stereocenter of allosamizoline was set by hydroxyl-directed reduction of the ketone with zinc borohydride giving **78**. This advanced interemediate contains a fully functionalized

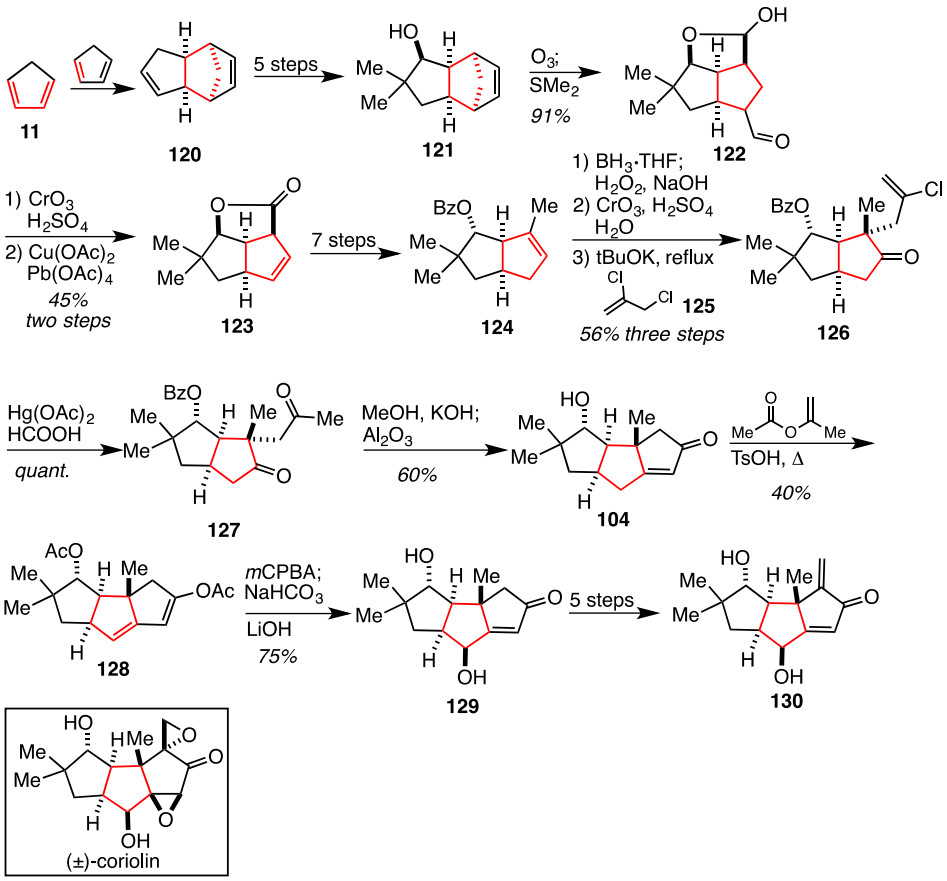
cyclopentane, and the natural product was completed in an additional four steps.

In a synthesis of (−)-allosamizoline, Koseki[24] uses a similar 1,3-dipolar cyclization of a nitrile oxide (Scheme 14). Beginning with the stereochemically rich glucosamine, intermediate **79** could be obtained over eight steps. Ring cleavage was achieved by reduction with activated zinc powder in wet THF delivering an aldehyde. The unpurified mixture was treated with hydroxylamine hydrochloride to afford oxime **80**. A 1,3-dipolar cyclization was promoted by treatment with sodium hypochlorite to deliver isoxazoline **81**. Protecting group exchange affords the TBS-protected intermediate **82**. Oxidative cleavage with ozone was followed by hydroxyl-directed reduction to give **83**, which installed the final stereocenter of the fully functionalized cyclopentane. This intermediate was converted to the natural product over an additional seven steps.

The Ferrier[25] synthesis of (−)-allosamizoline utilized a 1,3-dipolar cycloaddition to assemble a fully functionalized cyclopentane (Scheme 15). The route begins with D-glucose, which was converted to **84** over five steps. Reductive opening of the substituted pyranoside was accomplished by treatment with zinc powder to afford enal **85**. This intermediate contains three of the required stereocenters for allosamizoline. Heating enal **85** with *N*-methylhydroxylamine produced an intermediate nitrone that cyclized to form isoxazolidine **86**. The [3 + 2] cycloaddition sets the eventual hydroxymethyl stereocenter, but the adjacent amino



Scheme 18. Synthetic Studies Towards Pactamycin (Nishikawa, 2012).



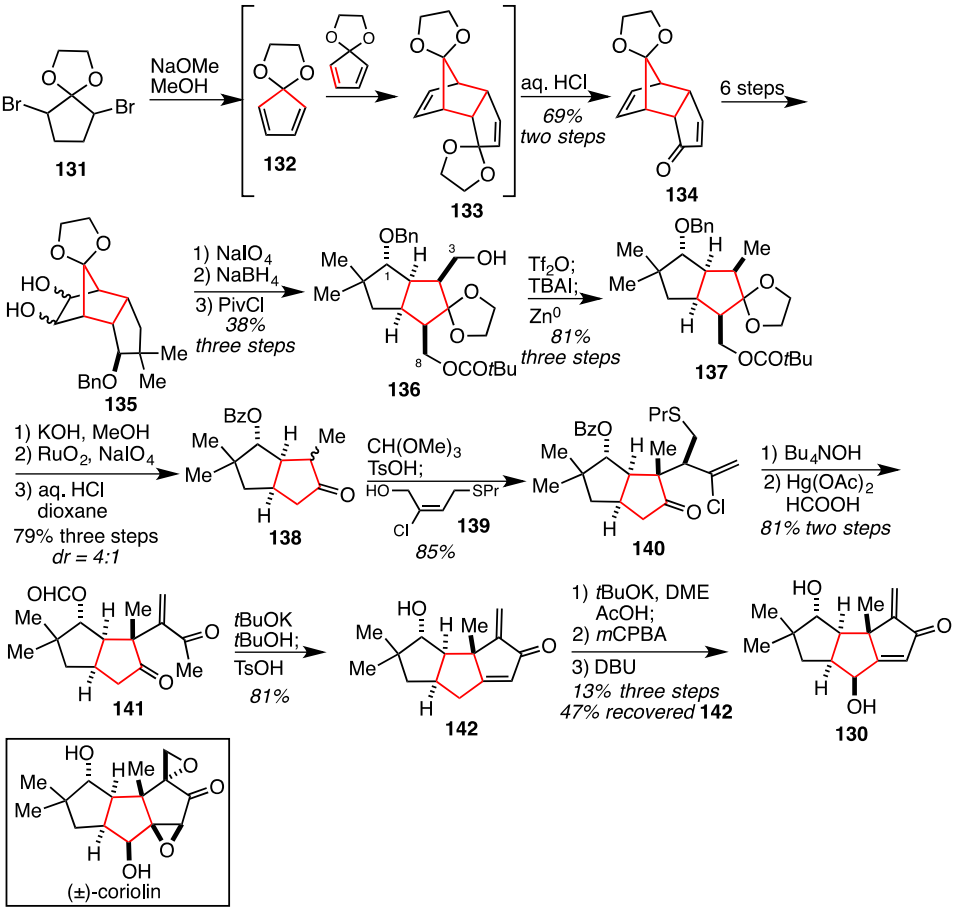
Scheme 19. Formal Synthesis of (±)-Coriolin (Matsumoto, 1982).

alcohol stereodiad requires adjustment. Reduction with hydrogen and Raney nickel delivered an aziridine. Peracid oxidation of the aziridine resulted in elimination to form cyclopentene **87**. The final two stereocenters were installed by way of a modified Sharpless aminohydroxylation[26] to give **88**. This intermediate was advanced five steps to (−)-allosamizoline.

The Shiozaki[27] synthesis of (+)-trehalamine featured a nitrile oxide [3 + 2] cycloaddition to construct the five-membered ring (Scheme 16). The synthesis begins with D-glucose, which could be advanced over standard transformations to aldehyde **89**. Oxime formation delivered cyclization precursor **90**. The [3 + 2] cycloaddition was effected by treatment with sodium hypochlorite to form a nitrile oxide which cyclized to isoxazoline **91**. Hydrogenolysis of the isoxazoline gave a hydroxymethyl ketone and led to β-elimination of the benzoyl group. Silyl protection of the primary alcohol and Luche reduction of the ketone gave desired diastereomer **92** with its hydroxyl epimer (*dr* = 2.5:1). Benzyl protection of the secondary alcohol and fluoride-mediated removal of the silyl ether gives **93**. Asymmetric epoxidation with Sharpless conditions gave **94** as a single isomer. Nucleophilic opening of the epoxide with azide delivers fully functionalized cyclopentane **95** with appropriate stereochemistry and substitution for (+)-trehalamine. This advanced intermediate underwent an additional eight steps to complete the natural product.

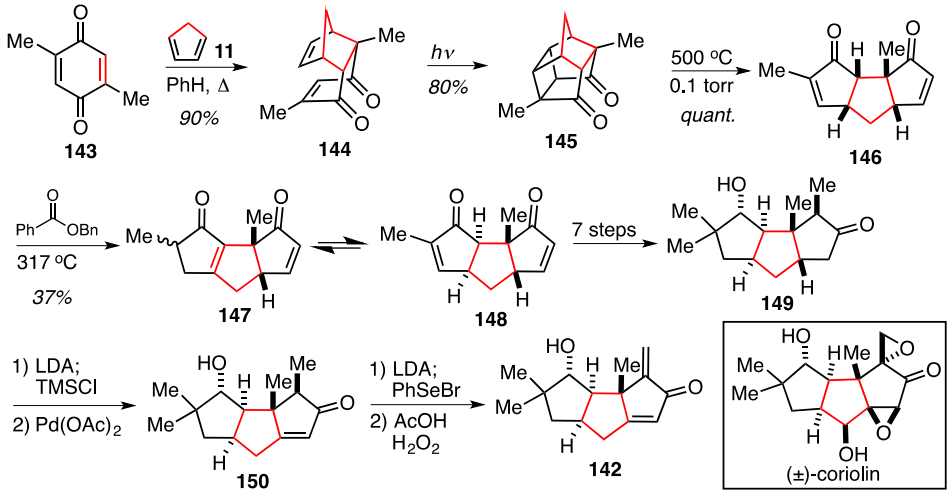
In the formal synthesis of (±)-coriolin by Funk,[28] a functionalized cyclopentane is formed in a nitrone [3 + 2] cyclization (Scheme 17). The route begins with a conjugate addition of allylsilane **96** to enone **97** delivering **98** as a mixture of diastereomers. The mixture was separated and individual diastereomers were converted to the corresponding nitrone and heated to give cyclization product **99**. Methylation of the nitrogen atom was followed by reduction of the N–O bond to give amino alcohol **100**. Treatment with peracid formed an *N*-oxide and selective Cope elimination gave olefin **101**. Hydroboration-oxidation of intermediate **101** was plagued by low regio- and stereoselectivity as a result of the resident hydroxyl group. Therefore, this functional group was removed by dehydration following the method of Gerlach[29] with chloridothioate **102** to give a diene. Hydroboration of this diene proceeded with complete control of chemo- and regioselectively to give an inconsequential mixture of diastereomers. A second hydroboration-oxidation proceeded to give alcohol **103** with control of alcohol stereochemistry. Selective oxidation with Fetizon's reagent[30] delivered a hydroxyketone, and Saegusa oxidation gave enone **104**, which is an intermediate previously taken to coriolin by Matsumoto.[32]

In the synthetic effort towards the cyclopentane core of pactamycin, Nishikawa[31] utilized a 1,3-dipolar cycloaddition of a nitrone and an alkyne (Scheme 18). The synthesis begins glucose derivative **105**. The unprotected hydroxyl undergoes an oxidation/Wittig olefination sequence with ylide **106** to obtain the desired *Z*-alkene product **107** as the major isomer in a 5:1 ratio with its geometric isomer. Reduction to the allylic alcohol and subsequent Overman rearrangement afforded **108**. This material was advanced over 11 steps to enal **109**. Acetylide addition proceeded with moderate stereocontrol to give the desired **110** in a 3:1 diastereomer ratio. Desilylation of the alkyne and protection of the hydroxyl groups as benzyl ethers delivers **111**. Chemoselective ozonolytic cleavage of the alkene was followed by condensation with *N*-hydroxyaniline to give nitrone **112**. The [3 + 2] cycloaddition was performed in refluxing toluene and a single product was isolated. The major

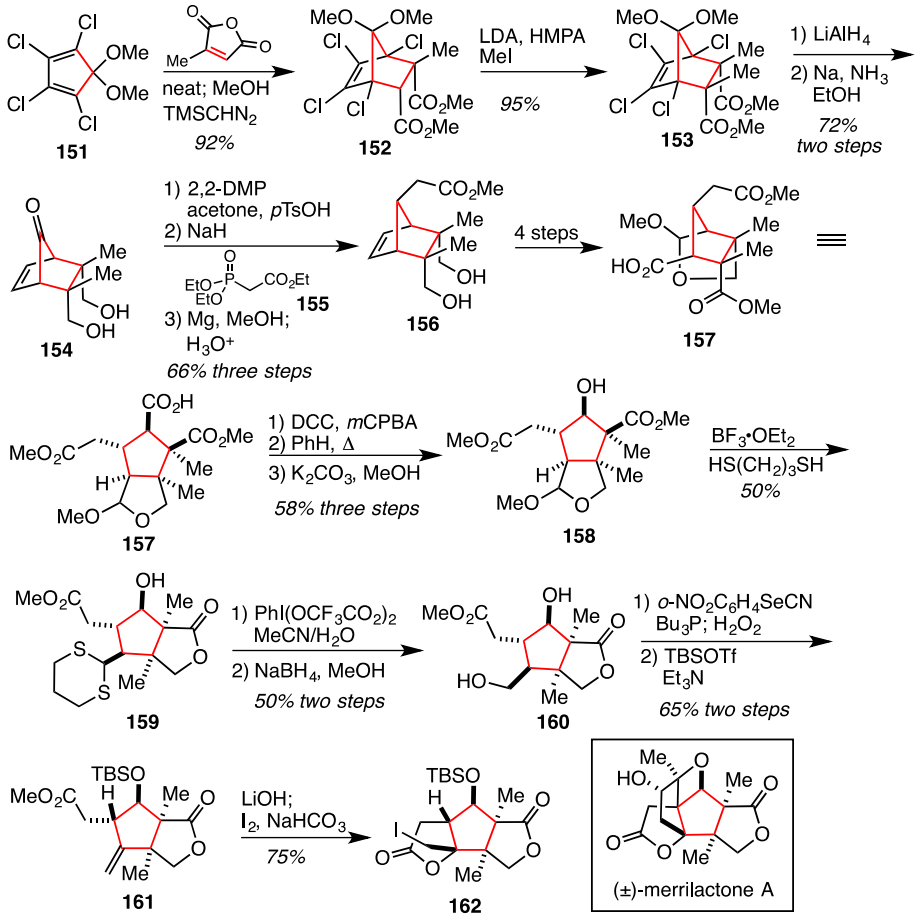


Scheme 20. Formal Synthesis of (±)-Coriolin (Schuda, 1984).

diastereomer is the result of a favored transition state that positions the benzyl ethers in the pseudo-equatorial position (**114**). The expected cycloaddition product **115** was not obtained; however aziridine **116** was isolated. Presumably, the aziridine arises from rearrangement of the isoxazoline **115**. The stereochemical assignment of the aziridine was ambiguous at this stage, but was later clarified following dihydroxylation (see below). The aldehyde was reduced, activated as the sulfonate and displaced with iodide to give **117**. Treatment with TBAI and Lewis acid opened the aziridine to give allylic amine **118**. Dihydroxylation of this intermediate delivered fully functionalized cyclopentane **119**. While the functionalization and stereochemistry do not directly correspond to pactamycin, in principle this route could be used to obtain the target.



Scheme 21. Formal Synthesis of (±)-Coriolin (Mehta, 1986).



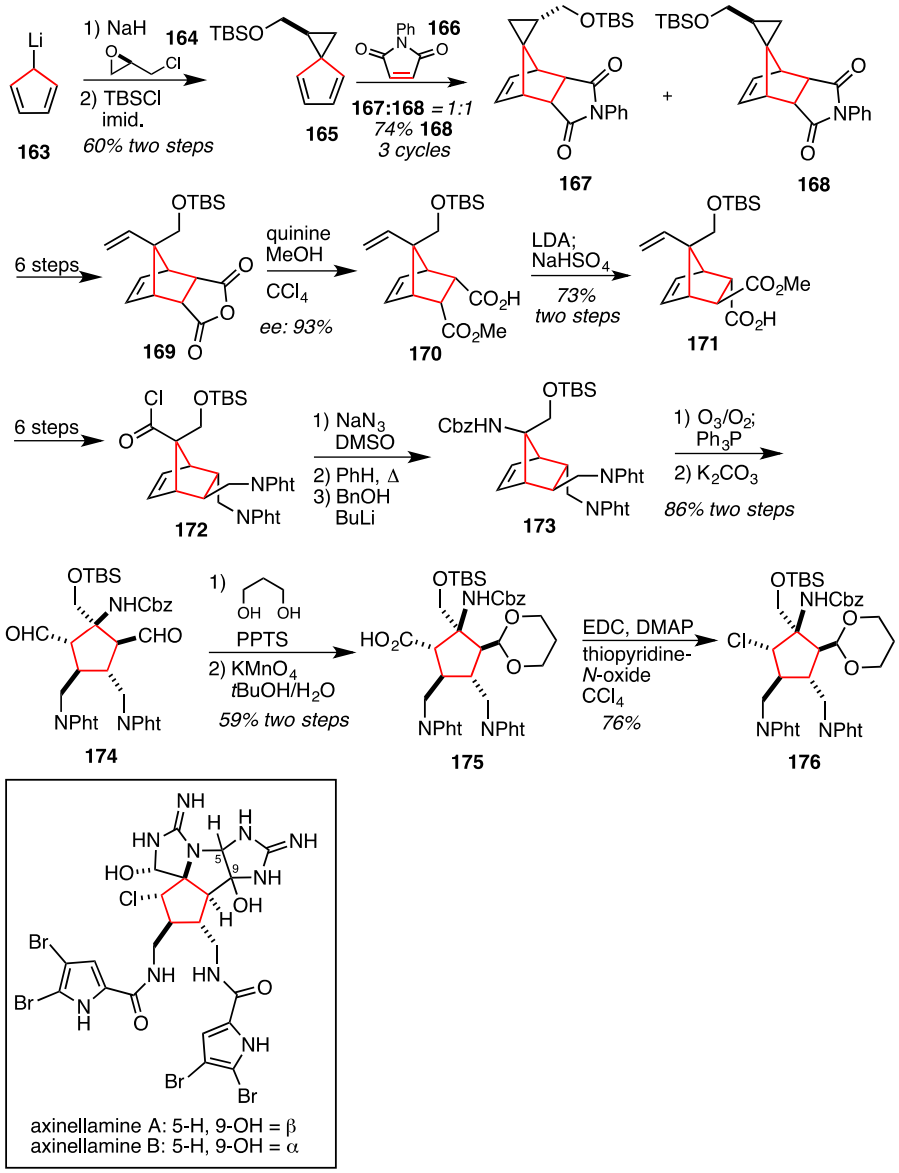
Scheme 22. Formal Synthesis of (±)-Merrilactone A (Danishefsky, 2005).

2.3. *[4 + 2] cycloadditions*

2.3.1. *Bimolecular Diels–Alder reactions of cyclopentadienes*

In the formal synthesis of (±)-coriolin by Matsumoto,[32] dimerization of cyclopentadiene (**11**) assembles two of the three five-membered rings contained in the target architecture (Scheme 19). Dicyclopentadiene (**120**) was advanced five steps to intermediate **121**. Ozonolytic cleavage of the alkene forms a dialdehyde, which exists as hemiacetal **122**. Oxidation followed by decarboxylation leads to cyclopentene **123**. Standard functional group manipulations converted this material to substituted cyclopentene **124** over seven steps. Hydroboration-oxidation followed by Jones oxidation furnishes a ketone. Formation of the thermodynamic enolate is followed by alkylation with 2,3-dichloropropene (**125**) on the convex face of the bicyclic ring system to deliver **126** with good control of stereochemistry. Oxymercuration of the vinyl chloride following Matsumoto's method[33] gave methyl ketone **127**. An aldol condensation delivered the triquinane ring system (**104**) of (±)-coriolin. Treatment with isopropenyl acetate converted cyclopentenone **104** to linear dienol acetate **128** under acidic conditions. Epoxidation was followed by an elimination to give enone **128**. In this case, epoxidation on the hindered face of the polycycle is driven by the preferential formation of a *cis*-fused diquinane substructure. This material was advanced over five steps to an intermediate published by Danishefsky and Tatsuta (**130**) in their coriolin syntheses.[34,35]

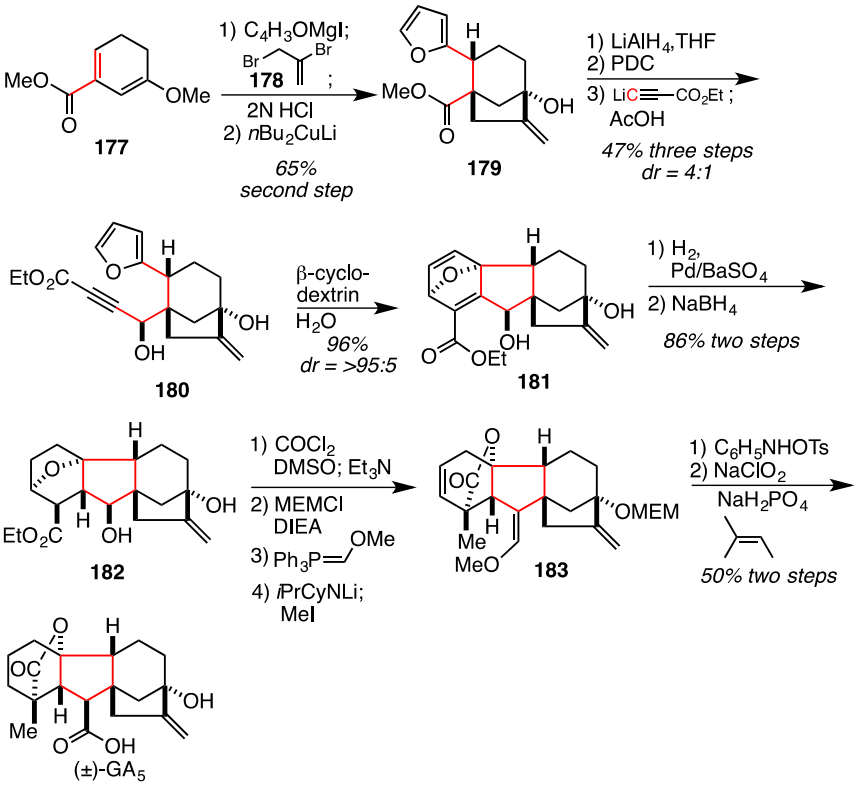
The formal synthesis of (±)-coriolin by Schuda[36] begins with dibromo ketal **131**, which could be obtained from cyclopentanone in two steps (Scheme 20). Double elimination of bromide gave a cyclopentadiene (**132**) that dimerized via the Diels–Alder reaction to give the bicyclo[2.2.1]heptane substructure in **134** after hydrolysis. This material was functionalized over six steps to give **135**. Oxidative cleavage of **135** was followed by reduction giving a diol. Selective protection of the hydroxyl at C8 delivers **136**. It is proposed that an intramolecular hydrogen bond between the C1 oxygen and the C3 carbinol renders the C3 alcohol less reactive. A one-pot three-step sequence (triflic anhydride, *tert*-butyl ammonium iodide, zinc metal) reduces the primary alcohol to a methyl group yielding **137**. This intermediate is functionalized to cyclopentanone **138** over three steps: ester hydrolysis, oxidation of the alcohol and benzyl ether, and acid-promoted decarboxylation and simultaneous ketal hydrolysis. The acidic conditions led to epimerization of the methyl group to give an inconsequential mixture of diastereomers. Treatment of ketone **138** with alcohol **139** induces enol ether formation and subsequent Claisen rearrangement on the convex face of the ring system to give **140**. Saponification of the benzoate gave an intermediate alcohol. Treatment with mercuric acetate induced hydrolysis of the vinyl chloride and elimination of the thiopropyl group to give desired enone **141**. Aldol condensation of **141** was promoted by potassium *tert*-butoxide to deliver the triquinane ring system (**142**) of coriolin. Deconjugation of enone **142** gave a β,γ-unsaturated ketone. Epoxidation with peracid occurs from the top face, forming a *cis*-fused diquinane substructure. Epoxide opening and subsequent elimination with DBU delivers **130** and intersects a published intermediate used in the Danishefsky and Tatsuta syntheses of coriolin.[34,35]



Scheme 23. Synthetic Studies Towards Axinellamines (Carreira, 2000).

In the formal synthesis of (±)-coriolin, Mehta[37] functionalizes cyclopentadiene through a Diels–Alder cycloaddition and a photo-induced rearrangement (Scheme 21). The route commences with the *endo* selective Diels–Alder of quinone **143** and cyclopentadiene (**11**) to give **144**. Upon irradiation, a [2 + 2] cycloaddition delivers pentacyclic dione **145**. A [2 + 2] cycloreversion reaction occurred under flash vacuum pyrolysis conditions to yield triquinane **146**. The desired *cis,anti,cis* diastereomer (in **148**) was obtained by establishing a thermal equilibrium of enone isomers by refluxing in benzyl benzoate. The resulting mixture contained a 1:3:3.5 ratio of starting material **146** and isomers **147** and **148**. While the isolated yield of **148** was 35–40%, starting material **146** and enone **147** could be recycled by reestablishing the thermal equilibrium. This material was advanced seven steps to intermediate **149**. A Saegusa oxidation gave enone **150**. Enolate addition to phenylselenyl bromide followed by oxidation and elimination provided advanced intermediate **142**. This material was prepared in the syntheses of (±)-coriolin by Ikegami[38] and Schuda.[36]

In Danishefsky's second generation[39] approach to (±)-merrilactone A[40] the cyclopentane is constructed in the first step using a Diels–Alder reaction to form a bicyclo[2.2.1]heptane (Scheme 22). Specifically, the cycloaddition between the chlorinated cyclopentadiene **151** and 2-methylmaleic anhydride proceeds with *endo* selectivity and sets the quaternary stereocenter. Methanolysis of the anhydride and subsequent esterification of the free acid delivered **152**. Installation of the second required methyl group for merrilactone A was accomplished by standard alkylation. This two-step sequence successfully produced **153**, where as Diels–Alder cycloaddition of **150** with dimethylmaleic anhydride was unsuccessful. Reduction of the esters and global halide reduction occurs over two steps with concomitant ketal hydrolysis to give **154**. Ketone **154** was advanced to ester **156** over three steps featuring a Horner–Wadsworth–Emmons olefination with **155** and subsequent alkene reduction. This material was advanced four steps to intermediate **157**. The carboxylic acid was converted to alcohol **158** over three steps through carboxy inversion.[41] Lewis acid opening of the acetal induced lactonization with the tethered methyl ester, and the aldehyde was concomitantly protected as the



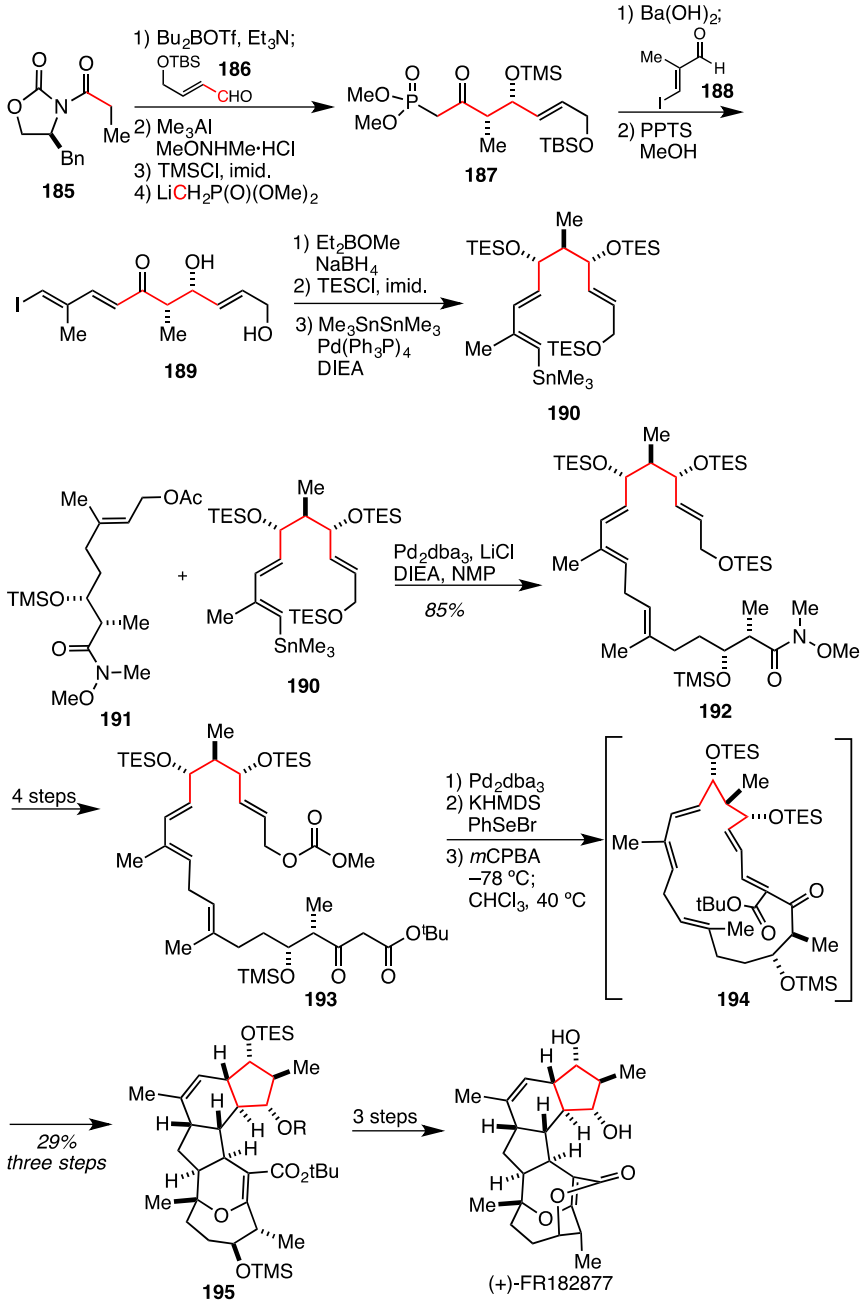
Scheme 24. Total Synthesis of (±)-GA_5 (De Clercq, 1986).

dithiane **159**. Removal of the dithiane and reduction of the corresponding aldehyde gave primary alcohol **160**. Elimination using the method developed by Grieco[42] delivered the exocyclic cyclopentene **161**. Iodolactonization furnishes tricyclic compound **162**, which is an intermediate that intersects the first route to (±)-merrilactone A published by Danishefsky.[43]

In the synthetic effort towards the axinellamines by Carreira,[44] a Diels–Alder reaction of the spiro-cyclopentadiene **165** is used to synthesize a bicyclo[2.2.1]heptane (Scheme 23). The synthesis begins with lithiocyclopentadienide (**163**), which is converted to spirocyclic intermediate **165** by addition to epichlorohydrin (**164**) and silylation. The cycloaddition of **165** with *N*-phenylmaleimide (**166**) delivers a 1:1 mixure of diastereomers. The desired stereoisomer **168** could be obtained preferentially through recrystallization from cyclohexane. Resubjection of the undesired **167** in hot chlorobenzene gave the 1:1 mixture, which could then be crystallized as before. Desired intermediate **168** is functionalized over six steps to give cyclic anhydride **169**. A desymmetrization sequence using the method developed by Bolm, produced acid-ester **170**.[45] Epimerization of the methyl ester with LDA gave the *trans* configuration of the acid-ester **171**. This material was advanced six steps to acid chloride **172**. Conversion of **172** to the corresponding Cbz carbamate **173** was accomplished using the Curtius procedure, and it elegantly establishes the α-tertiary amine with the desired stereochemistry for the axinellamines. Ozonolysis of the cyclopentane and subsequent treatment with base resulted in dialdehyde **174**. The base selectively epimerizes the aldehyde with the more accessible α-position. Note that this transformation converts the α-tertiary amine stereocenter into a non-stereogenic chirotopic center. Interestingly, a selective mono-protection of the dialdehyde was possible, which results in desymmetrization of the pseudo-C_2 symmetry in the molecule. The factors responsible for the difference in reactivity of the two aldehydes are unknown; however, it may be attributable to either the steric difference or the proximity of the Cbz-carbamate versus the silyloxymethyl group. Oxidation of the remaining aldehyde to the corresponding carboxylic acid was performed with Masamune's conditions to give **175**.[46] The hindered chloride was installed by radical decarboxylation in the presence of carbon tetrachloride. This advanced intermediate (**176**) displays a fully functionalized cyclopentane with the required substitution and stereochemistry found in the axinellamines.

2.3.2. *Intramolecular Diels–Alder reactions of skipped trienes*

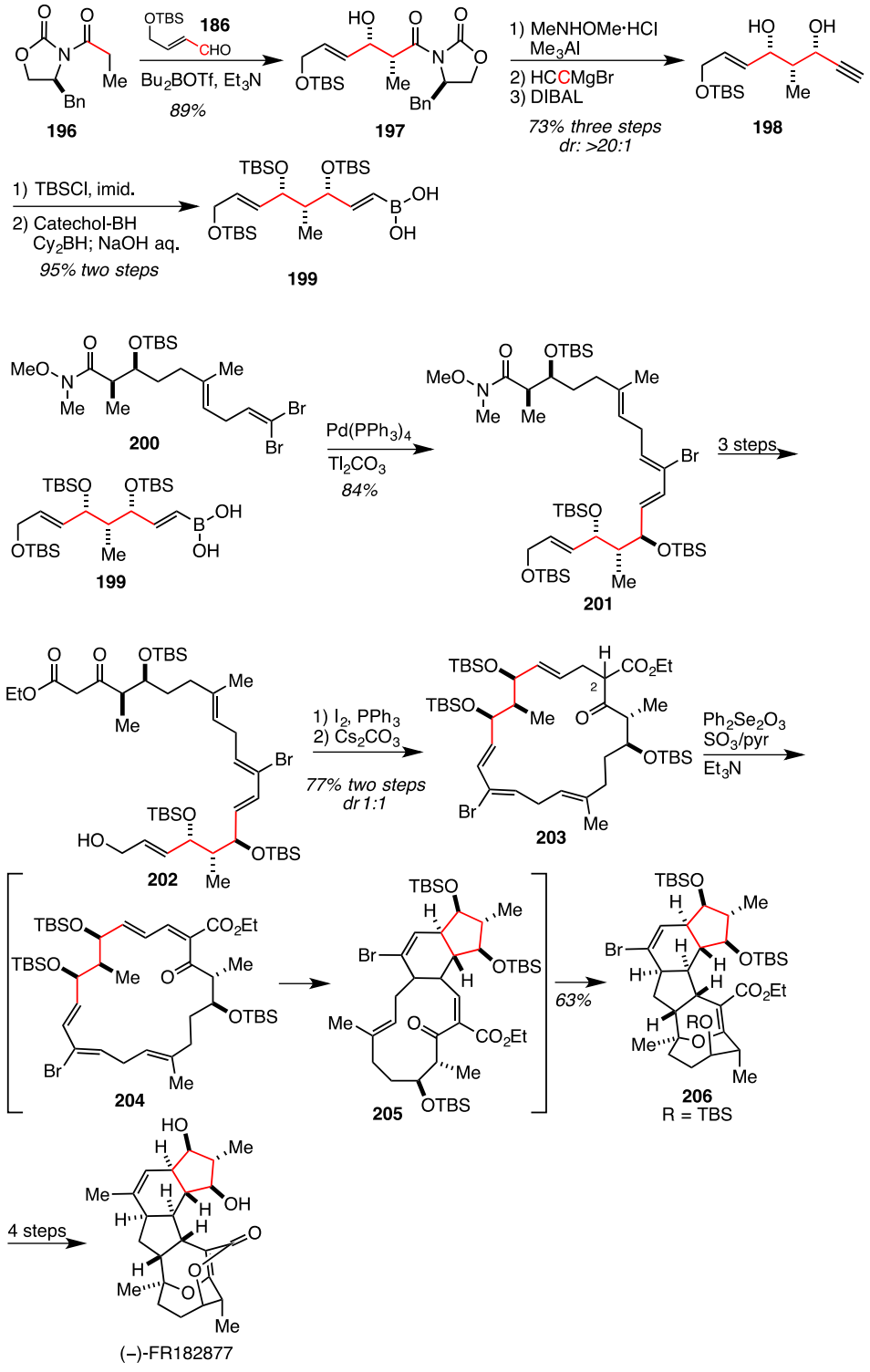
The De Clerq[47] synthesis of the gibberellin natural product (±)-GA_5 uses an intramolecular Diels–Alder reaction, where the molecular tether connecting the diene and dienophile forms the five-membered ring (Scheme 24). The route begins with conjugate addition of a furan-derived Grignard reagent to **177**, followed by intermolecular enolate trapping with 2,3-dibromopropene (**178**). The alkylation occurs on the face opposite the furan substituent setting the first two stereocenters of the eventual fully functionalized cyclopentane. Enol ether hydrolysis gives a ketone. Lithium-halogen exchange of the vinyl bromide induces ring closure to give **179**. Reduction of the ester and oxidation of the resulting alcohol gives an aldehyde. Addition of the lithiated propiolate gave **180** as the major product in 4:1 diastereomeric ratio, presumably as a result of Felkin–Anh selectivity. Intramolecular Diels–Alder reaction of **180** in the presence of β-cyclodextrin gave cycloadduct **181** in high yield and high dr; however, there was no explanation given for the diastereoselectivity. Selective hydrogenation of the strained disubstituted alkene with $Pd/BaSO_4$ was followed by hydride reduction of the unsaturated ester to give the thermodynamically favored *trans*-ring fusion in **182**. At this stage, the cyclopentane is fully functionalized with five stereocenters; however, in order to complete the synthesis of GA_5, the secondary alcohol must be converted to a carboxy substituent. Oxidation of the secondary



Scheme 25. Total Synthesis of (+)-FR182877 (Sorensen, 2002).

alcohol, protection of the tertiary alcohol and olefination gave a methyl vinyl ether. An ester methylation and transesterification sequence delivers **183**. Hydrolysis of the vinyl ether proceeded with protonation on the less hindered face to set the final stereocenter on the fully functionalized cyclopentane. Pinnick[48] oxidation completed the synthesis of (±)-GA_5.

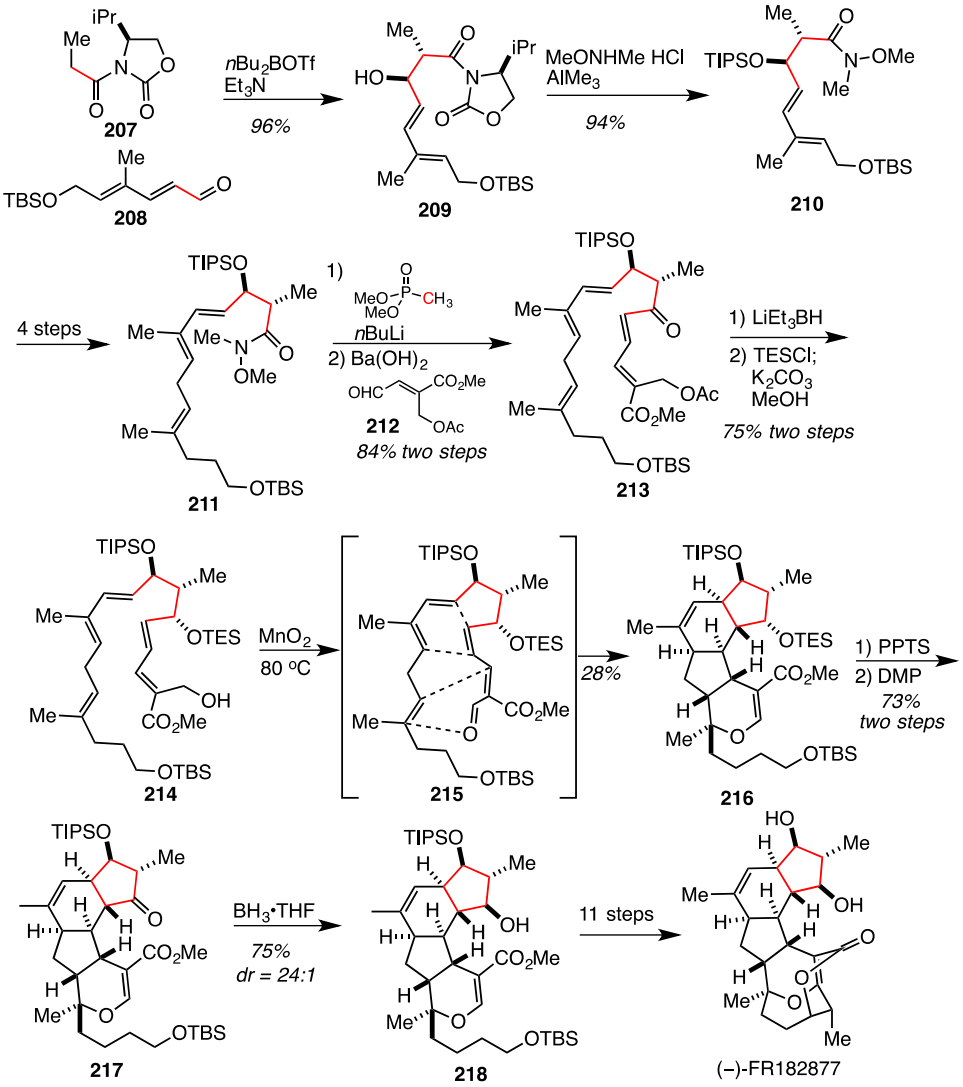
Sorensen's[49] biogenetic synthesis of (+)-FR182877 employs a double transannular Diels–Alder reaction to construct five rings, including a fully functionalized cyclopentane (Scheme 25). This remarkable transformation forms seven stereocenters with complete stereocontrol. The route commences with the assembly of coupling fragment **190**. An Evans syn-aldol reaction between **185** and aldehyde **186** sets two stereocenters for the eventual fully functionalized cyclopentane. The chiral auxiliary was then cleaved with conditions delivering a Weinreb amide. Silylation of the secondary alcohol and addition of dimethyl lithiomethylphosphonate gives ketophosphonate **187**. Olefination with (*E*)-3-iodo-2-methacrolein (**188**) and subsequent cleavage of the silyl ethers delivers diol **189**. A chelation-controlled reduction of the ketone gave a *syn*-1,3-diol. Silylation and stannylation delivers coupling fragment **190**. Cross-coupling of the dienylstannane and allyl acetate **191** delivered **192**. This intermediate was functionalized over four steps to give **193**. Exposure to Pd_2dba_3 promoted macrocyclic ring closure. To install the necessary unsaturation for the Diels–Alder reaction, the stabilized enolate was formed and reacted with phenylselenyl bromide to afford an inseparable mixture of organoselenide diastereomers (*dr* = 3:1). When this mixture was treated with *m*CPBA and warmed to 40 °C in chloroform,



Scheme 26. Total Synthesis of (−)-FR182877 (Evans, 2003).

Diels–Alder substrate **194** was formed and the cyclization cascade occurred spontaneously to furnish **195**. The cycloaddition leads to the establishment of seven stereogenic centers including the final two stereocenters for the fully functionalized cyclopentane. After this spectacular transformation, an additional three steps were required to complete the synthesis of the natural product.

In the Evans synthesis of (−)-FR182877,[50] a similar cascade of transannular [4 + 2] cycloadditions construct much of the molecular architecture of the natural product, including the fully functionalized cyclopentane (Scheme 26). The route begins with the assembly of coupling fragment **199**. An Evans syn-aldol reaction between **196** and aldehyde **186** sets two stereocenters for the eventual fully functionalized cyclopentane. Cleavage of the auxiliary and formation of a Weinreb amide was followed by addition of magnesium acetylide. A stereoselective DIBAL reduction delivered *syn*-1,3-diol **198**.[51] Silylation and hydroboration-oxidation of the

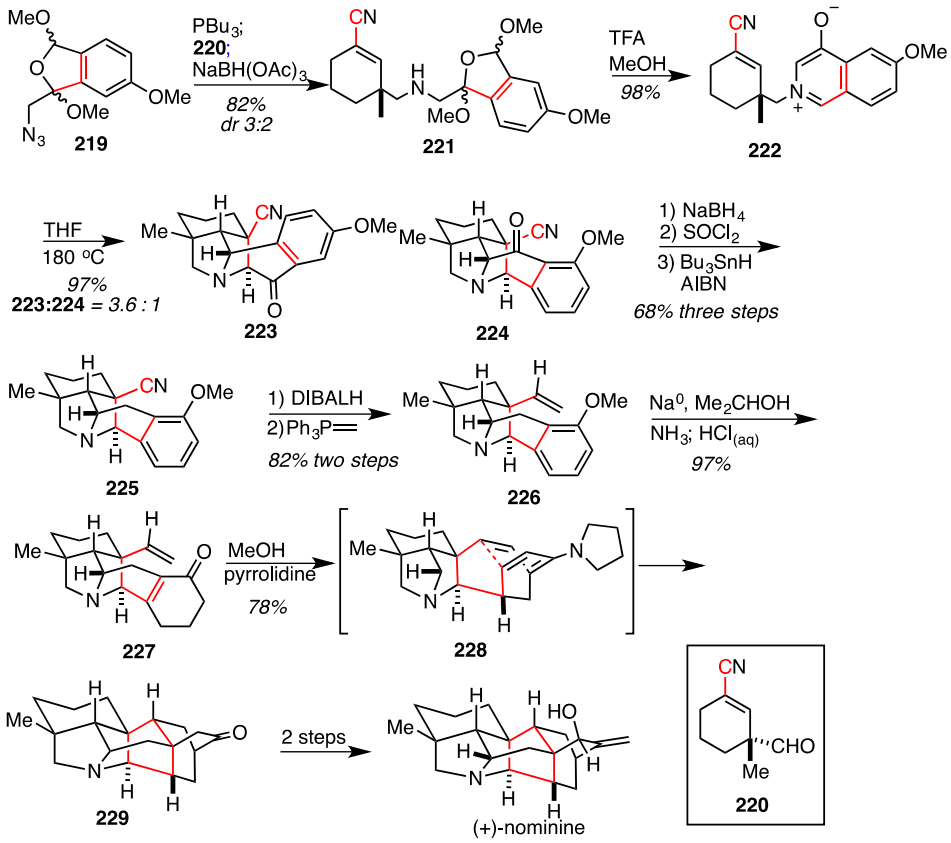


Scheme 27. Total Synthesis of (−)-FR182877 (Nakada, 2009).

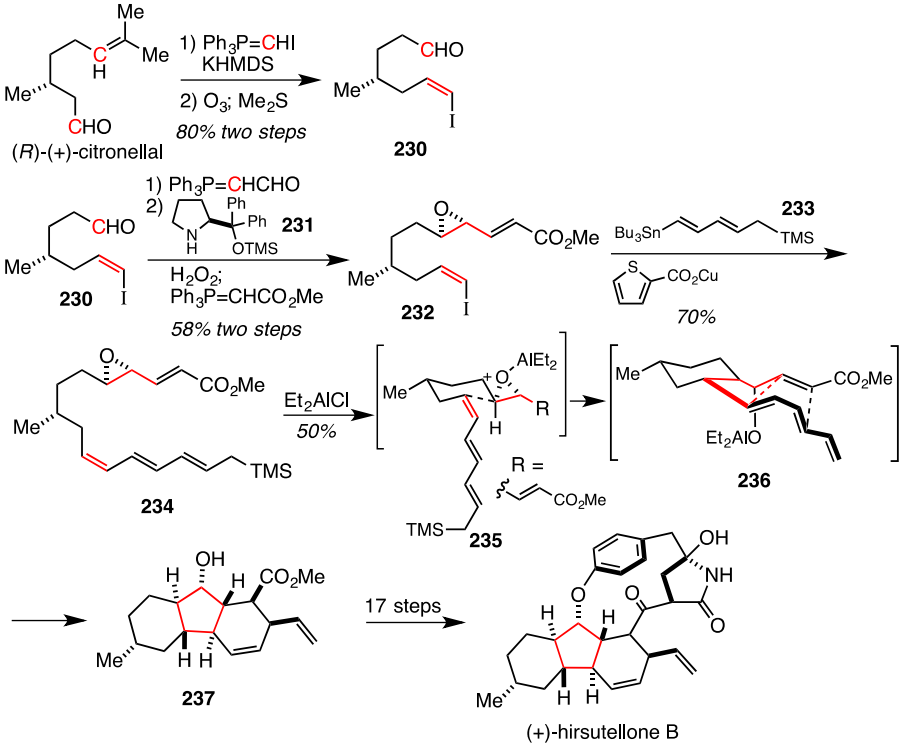
alkyne delivered boronic acid coupling partner **199**. The Suzuki coupling of fragments **199** and **200** gave bromodiene **201** as the desired geometrical diene isomer. Three additional steps including installation of the β-keto ester gave **202**. Iodination delivered an allyl iodide that cyclized upon exposure to cesium carbonate furnishing macrocycle **203** as an inconsequential 1:1 mixture of diastereomers (epimeric at C2). Oxidation produced a diene (**204**) and initiated the first transannular Diels–Alder reaction. The initial cycloadduct **205** proceeded through the cyclization cascade resulting in **206** as the only isolable product. The result of the cascade is a fully functionalized cyclopentane bearing all the required stereochemistry for (−)-FR182877. The target was completed in four additional steps.

In the synthesis of (−)-FR182877 by Nakada[52] an intramolecular Diels–Alder reaction cascade constructs the polycyclic ring system (Scheme 27). The route begins with an Evans aldol between **207** and aldehyde **208**. The chiral auxiliary was cleaved to give a Weinreb amide, which was advanced to intermediate **211** over four steps. Addition of dimethyl lithiomethylphosphonate installs the final carbon atom of the eventual cyclopentane to give a keto-phosphonate. Olefination with aldehyde **212** gives intermediate **213**. Reduction of the ketone gave the undesired *anti*-1,3-diol as the major product and subsequent TES protection delivered **214**. The allylic alcohol was oxidized to give **215**, which spontaneously underwent the intramolecular Diels–Alder (IMDA) reaction cascade to give **216**. While a fully functionalized cyclopentane has been assembled, the stereochemistry of the TES-protected hydroxyl required stereochemical inversion. Desilylation with PPTS and oxidation with DMP gave cyclopentanone **217**. A stereoselective reduction from the less hindered face gave alcohol **218** bearing the desired stereochemistry for the natural product. The completion of (−)-FR182877 was completed after an additional 11 steps.

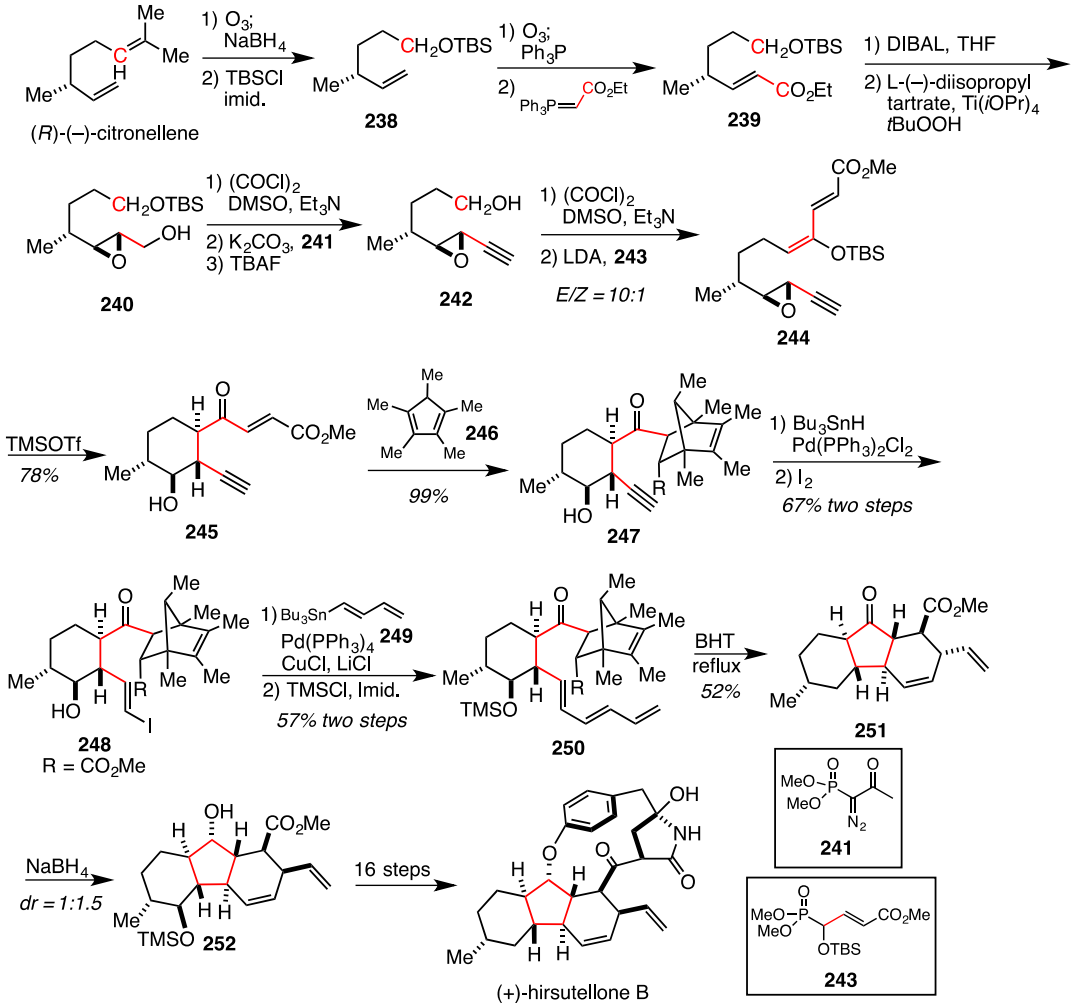
In the synthesis of the C20-diterpenoid alkaloid (+)-nominine, Gin[53] uses a pyrrolidine-induced dienamine isomerization/Diels–Alder cascade to construct the fully functionalized cyclopentane (Scheme 28). Synthetic fragments **219** and **220** were condensed via a Staudinger-aza-Wittig reaction, and a subsequent hydride reduction of the resultant imine gave amine **221**. This mixture of four diastereomers converged through a TFA-catalyzed MeOH extrusion and isomerization to provide the aza-1,3-dipole **222**. The 1,3-dipolar cycloaddition between the betaine and unsaturated nitrile groups yields desired isomer **224** as a minor product with its constitutional isomer **223**. The mixture is a result of thermodynamic selection, and resubjection of pure **223** to the reaction



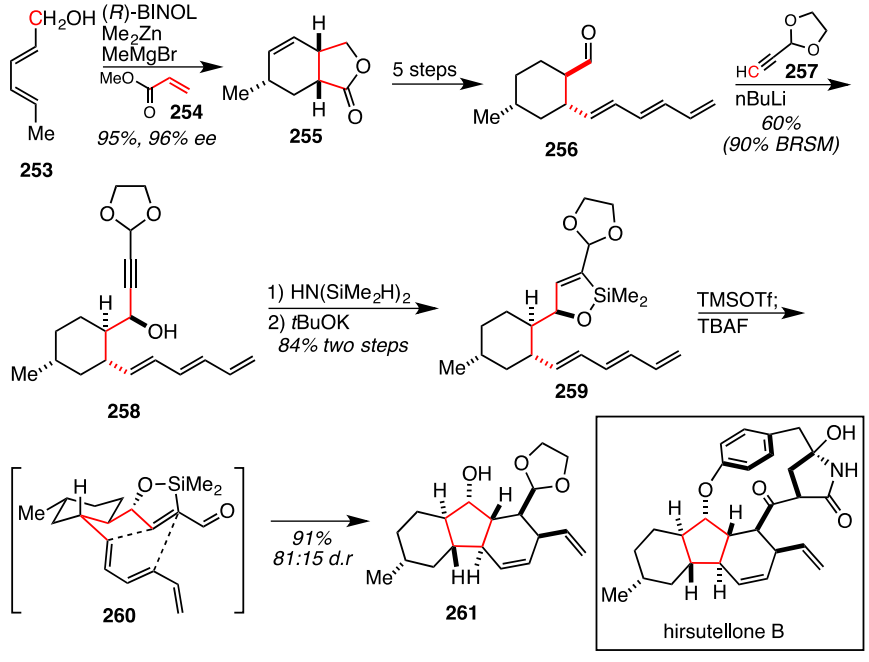
Scheme 28. Total Synthesis of (+)-Nominine (Gin, 2008).



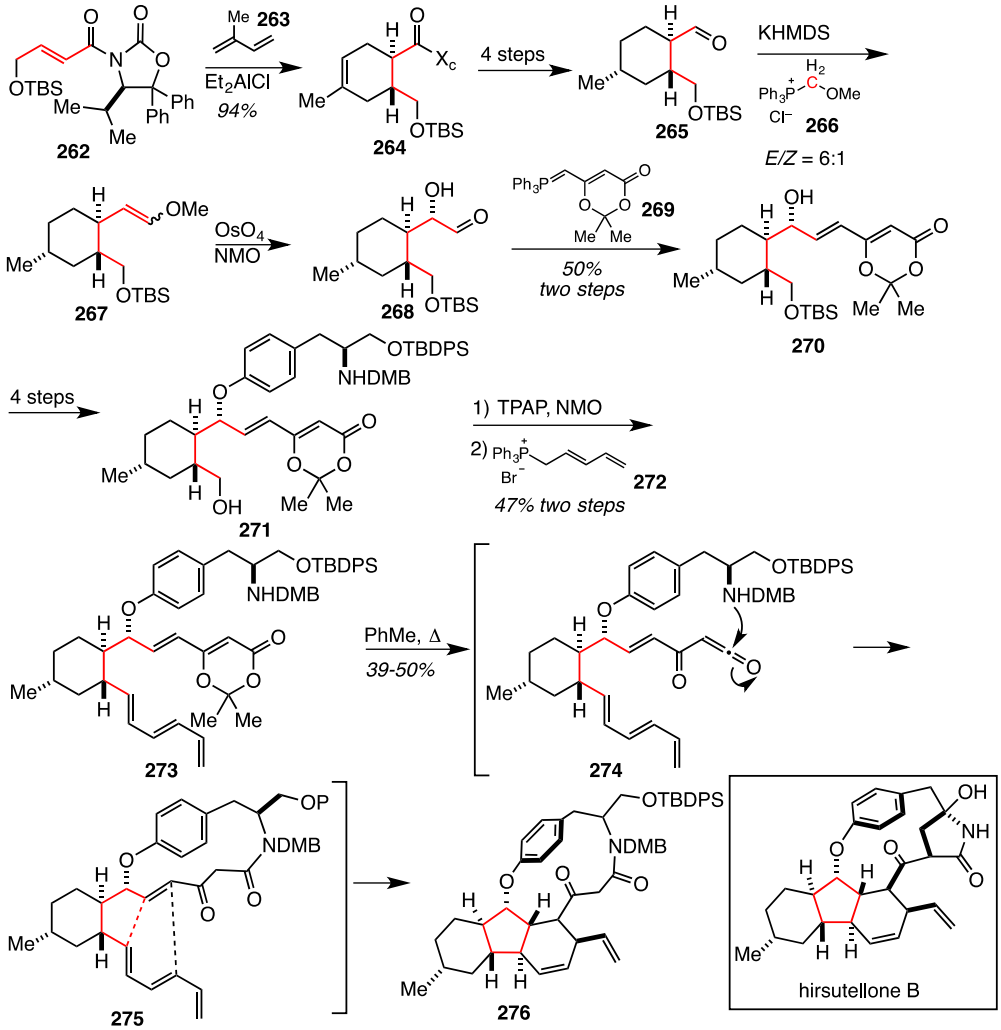
Scheme 29. Total Synthesis of (+)-Hirsutellone B (Nicolaou, 2009).



Scheme 30. Total Synthesis of (+)-Hirsutellone B (Uchiro, 2011).

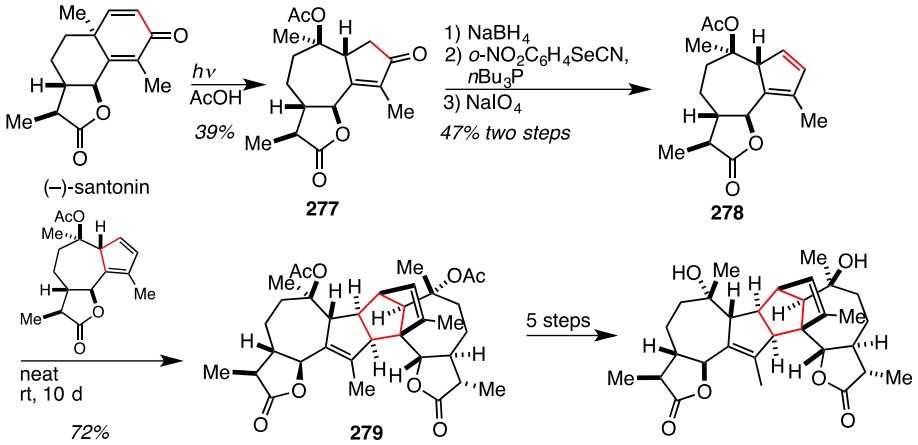


Scheme 31. Synthetic Studies Towards Hirsutellone B (Roush, 2011).

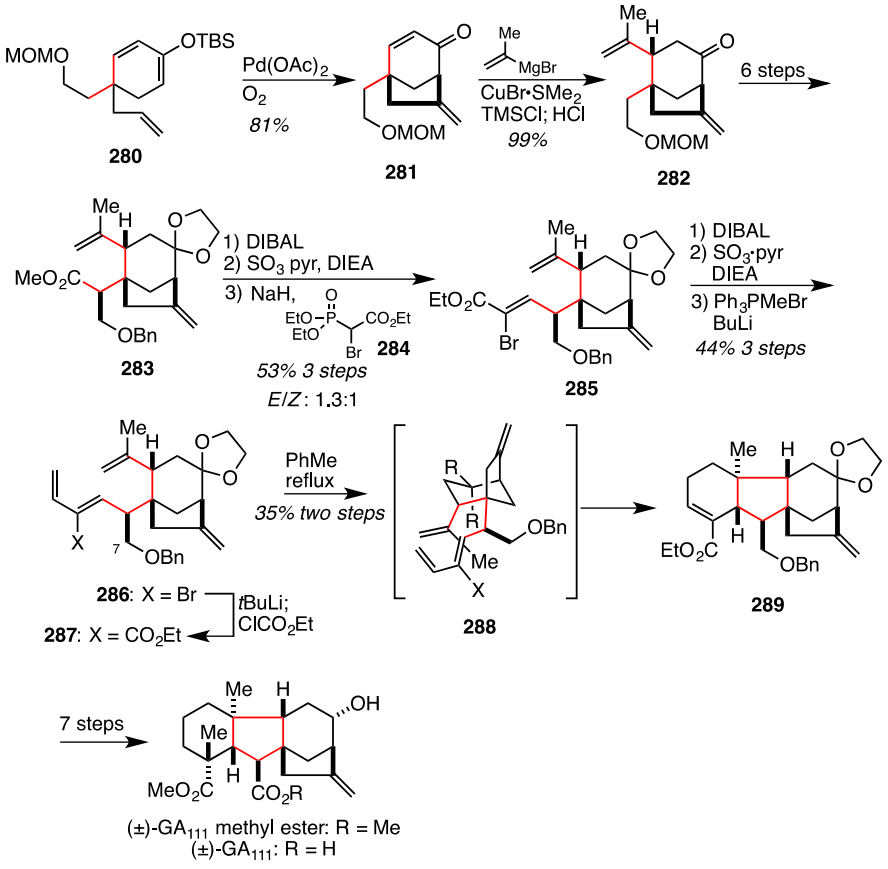


Scheme 32. Synthetic Studies Towards the Hirsutellones (Sorensen, 2013).

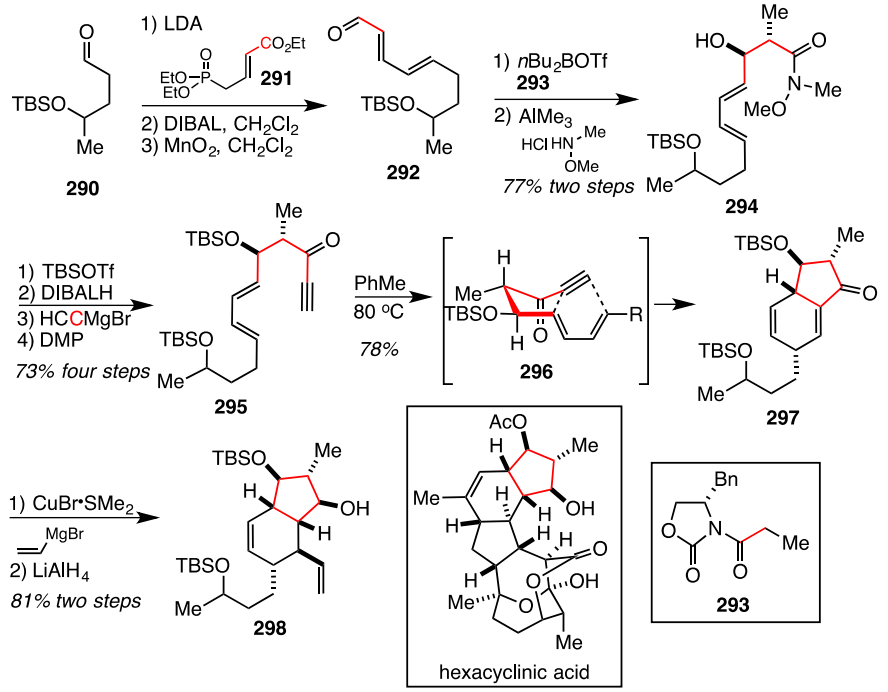
conditions allowed for the undesired material to be recycled. This transformation builds a substantial portion of the natural product architecture including two stereocenters of the fully functionalized cyclopentane. Exhaustive reduction of the ketone carbon to a methylene delivers **225**. Conversion of the nitrile to alkene **226** was completed through DIBAL reduction followed by a Wittig olefination that unveiled the dienophile functionality. A Birch reduction of the aromatic ring furnished the β,γ-unsaturated cyclohexanone



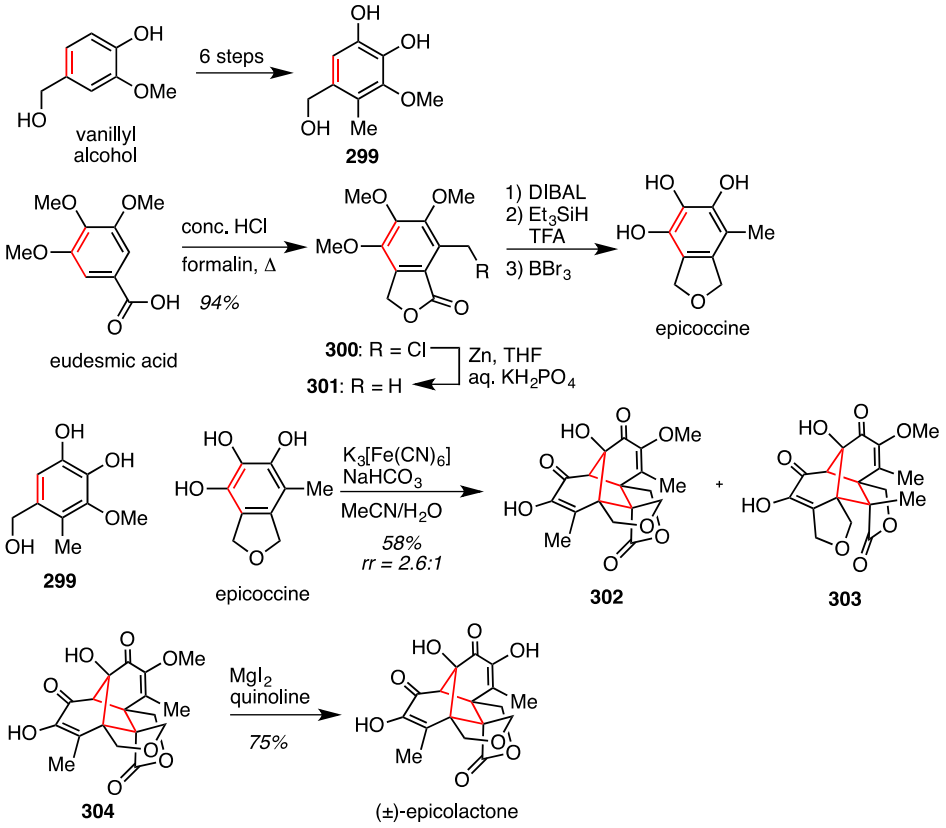
Scheme 33. Total Synthesis of (+)-Absinthin (Zhai, 2005).



Scheme 34. Total Synthesis of (±)-GA_{111} Methyl Ester (Ihara, 2000).



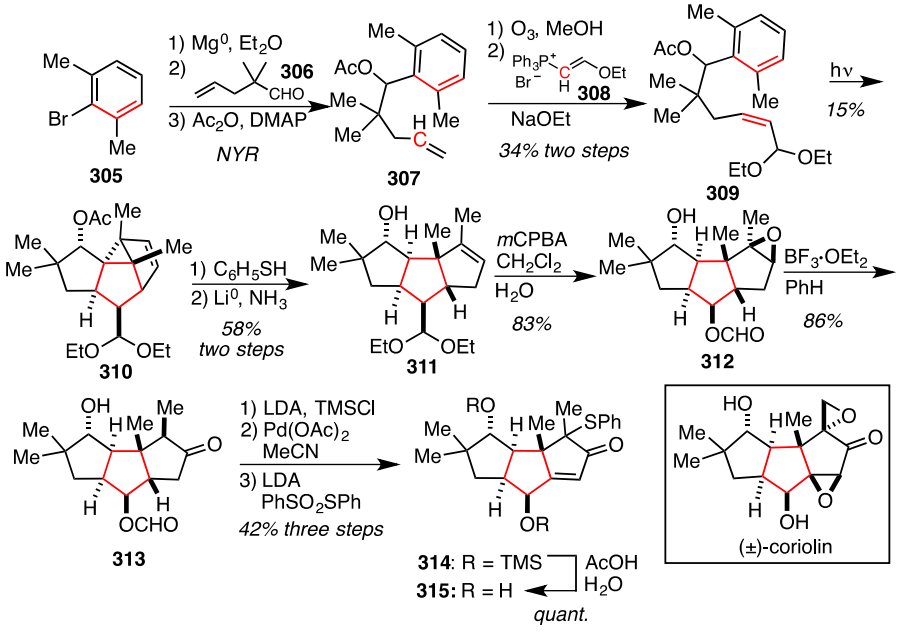
Scheme 35. Synthetic Studies Towards Hexacyclinic Acid (Kalesse, 2004).



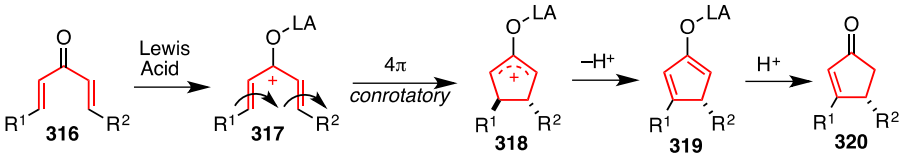
Scheme 36. Total Synthesis of (±)-Epicolactone (Trauner, 2015).

227. Treatment with MeOH and pyrrolidine promoted the formation of a dienamine (**228**) that participated in the IMDA to deliver fully functionalized cyclopentane **229**. The synthesis of (+)-nominine was completed in two additional steps.

The Nicolau[54] synthesis of (+)-hirsutellone B employs an epoxide opening/Diels–Alder reaction sequence to construct a fully functionalized cyclopentane (Scheme 29). The route begins with a Stork–Zhao olefination of (*R*)-(+)-citronellal followed by oxidative cleavage to give iodo aldehyde **230**. An olefination reaction of aldehyde **230** gives an α,β-unsaturated aldehyde. A Jørgensen asymmetric epoxidation[55] with proline-derived catalyst **231** yielded an epoxyaldehyde. This was immediately exposed to



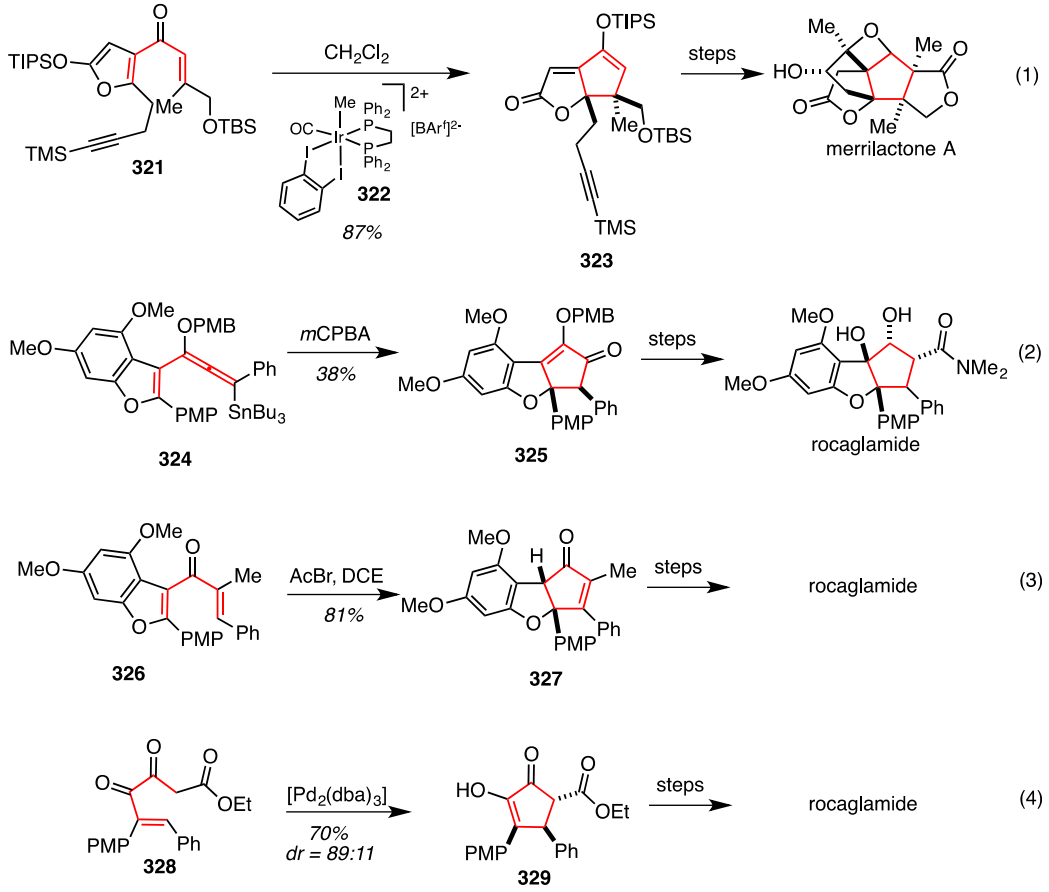
Scheme 37. Formal Synthesis of (±)-Coriolin (Wender, 1983).



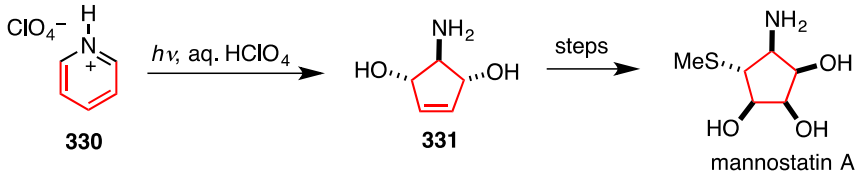
Scheme 38. The Nazarov Reaction Mechanism.

Ph_3PCHCO_2Me to furnish intermediate **232** with the expected *E*-geometry. A coupling reaction with stannane **233** yielded annulation precursor **234**. The epoxide opening/Diels–Alder cascade was promoted with Et_2AlCl to give the tricyclic core of hirsutellone B. The stereochemical outcome of the epoxide opening was postulated to result from the preferred conformation **235**, and the subsequent Diels–Alder reaction delivered a single diastereomer (**237**) that resulted from *endo*-transition state **236**. The resulting fully functionalized cyclopentane contains the desired stereochemistry for (+)-hirsutellone B. The natural product was completed in 17 additional steps.

The Uchiro[56] synthesis of (+)-hirsutellone B features a cascade Diels–Alder reaction sequence to form a functionalized cyclopentanone (Scheme 30). The route begins with an oxidative cleavage of the tertiary alkene in (*R*)-(−)-citronellene. Reductive workup and silylation gives TBS ether **238**. Ozonolysis of the remaining alkene and Wittig homologation delivers **239**. Ester reduction delivered an allylic alcohol, which underwent reagent-controlled epoxidation using the Sharpless[57] method to furnish **240**. A Swern oxidation of the primary alcohol gave an aldehyde that was homologated using the Ohira–Bestmann reagent (**241**).[58] Fluoride-mediated removal of the silyl ether delivers alcohol **242**. A Swern oxidation gave the corresponding aldehyde, which was olefinated with **243** to give diene **244** as the desired geometrical isomer (*E*/*Z* = 10:1). Treatment with TMSOTf promoted an intramolecular cyclization, presumably through a chair-like intermediate, yielding **245** as a single diastereomer. A Diels–Alder reaction of the alkene and 1,2,3,4,5-pentamethylcyclopentadiene (**246**) served to protect the eventual alkene dienophile in **247**. Conversion of the alkyne group to the olefinic iodide was achieved via hydrostannylation followed by iodination to deliver **248**. A Stille cross-coupling reaction with **249** gave trienyl stannane, which was followed by silylation of the secondary alcohol yielding **250**. Warming to reflux in the presence of BHT promoted a retro-DA-IMDA reaction sequence and the cycloadduct **251** was obtained. In this particular IMDA no hypothesis was given for the diastereoselectivity; however, a rationale similar to that discussed above (**234** → **237**) could be used to explain the selectivity. Reduction with $NaBH_4$ installs the final stereocenter of the fully functionalized cyclopentane. The reduction gave the desired product **252** in a 1:1.5



Scheme 39. Nazarov Reactions in the Synthesis of Fully Functionalized Cyclopentanes.



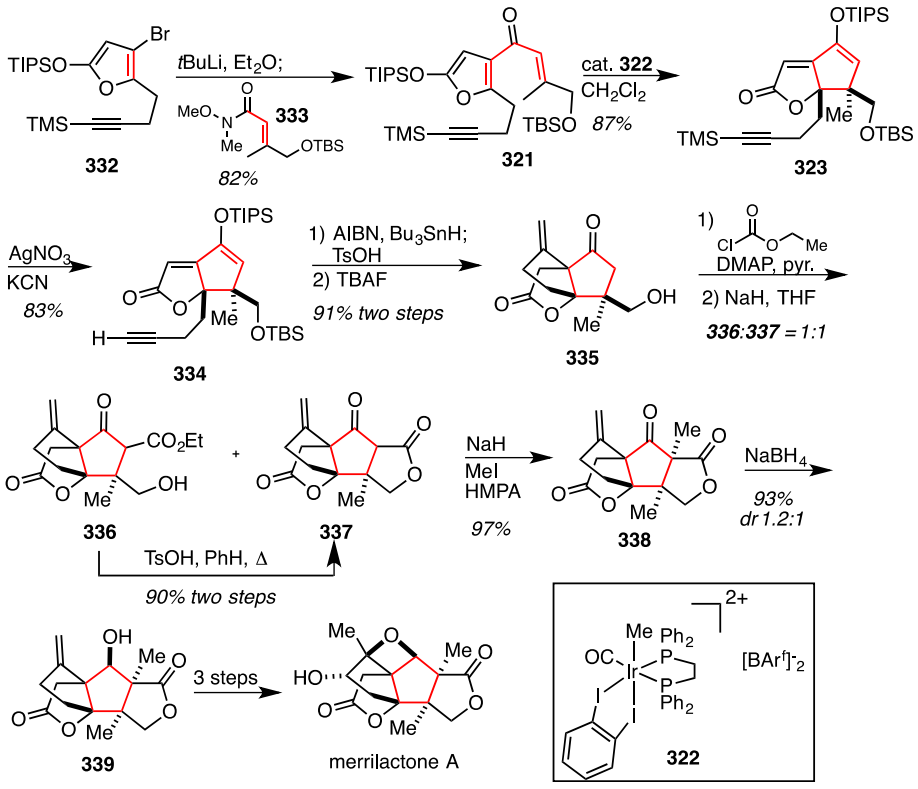
Scheme 40. Pyridine Electrocyclization in the Synthesis of a Fully Functionalized Cyclopentane.

ratio with the undesired alcohol epimer. The undesired diastereomer could be converted to **252** using standard transformations. The completion of (+)-hirsutellone B was completed with an additional 16 steps (longest linear sequence).

Roush[59] reported synthetic studies toward hirsutellone B where the cyclopentane core was constructed with an IMDA reaction of a siloxacyclopentene (Scheme 31). The route begins with an enantioselective Diels–Alder reaction of the dienol **253** with methyl acrylate (**254**) in the presence of the reagent derived from (*R*)-BINOL, Me_2Zn, and MeMgBr.[60] Cycloadduct **255** was converted to the trienyl aldehyde **256** over five steps. Exposure to the lithium acetylide derived from **257** afforded alcohol **258** with Felkin-Anh selectivity (*dr* > 95:5). This propargyl alcohol was hydrosilylated with tetramethyldisilizane. Addition of *t*BuOK gave siloxacyclopentene **259**. Treatment with TMSOTf promoted the Diels–Alder cycloaddition and a subsequent protodesilylation of the crude cycloadduct delivered decahydrofluorene **261**. The Diels–Alder proceeds through the *endo* conformation **260** and delivers the product with good diastereoselectivity. Advanced intermediate **261** possesses the required substitution and stereochemical configuration present in hirsutellone B.

In the synthesis of the decahydrofluorene core of the hirsutellones, Sorensen[61] employs a tandem ketene-trapping/Diels–Alder cyclization sequence (Scheme 32). The synthesis commences with a diastereoselective Diels–Alder reaction of olefin **262** and diene **263** to form cyclohexene **264** as a single diastereomer. This intermediate was carried forward to the aldehyde **265** over four steps. Homologation with phosphonium **266** following Kluge's method[62] gave enol ether **267** as an inconsequential mixture of alkene isomers (*E*/*Z* = 6:1). This mixture of alkenes was subjected to dihydroxylation conditions giving α-hydroxylated aldehyde **268**. Direct treatment with ylide **269** gave alkene **270** with complete control of alkene stereochemistry. This material was converted to the primary alcohol **271** over four steps. Oxidation and Wittig olefination with **272** gave cyclization substrate **273**. Upon heating in toluene, elimination of acetone reveals both an electron withdrawing goup conjugated to the dienophile and an electrophilic ketene (**274**). Trapping of the ketene with the tethered amine forms the macrocyclic substructure of hirsutellone B (**275**). The Diels–Alder reaction then spontaneously occurs to complete the molecular architecture of the natural product in **276**. This advanced intermediate contains a fully functionalized cyclopentane with the desired substitution and stereochemistry for hirsutellone B.

In the synthesis of the dimeric guaianolide (+)-absinthin by Zhai,[63] the construction of the five-membered carbocycle arises from a dimerization reation of **278** via a Diels–Alder cycloaddition (Scheme 33). The route commences with natural product (−)-santonin, which was photolyzed to give cyclopentenone **277**. A



Scheme 41. Total Synthesis of (±)-Merrilactone A (Frontier, 2007).

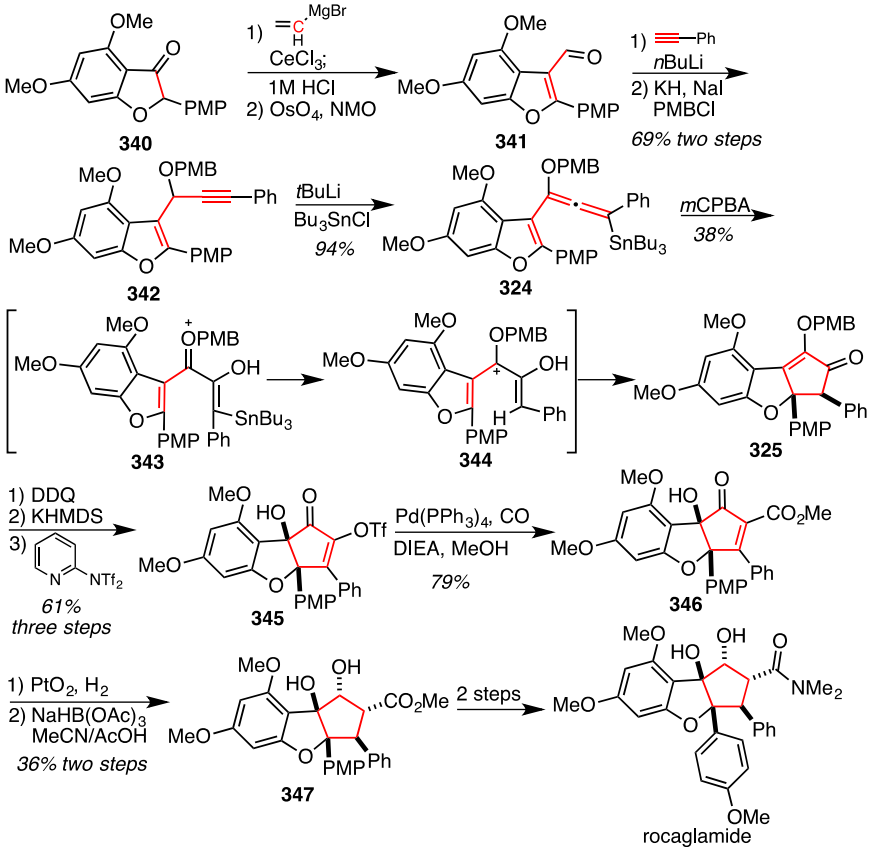
three-step sequence (hydride reduction, selenylation, and oxidation/elimination) leads to cyclopentadiene **278**. When stored neat under an inert atmosphere, the slow dimerization of **278** via a Diels–Alder reaction proceeded to deliver fully functionalized cyclopentane **279**. This intermediate was advanced to the natural product over an additional five steps.

In the total synthesis of (±)-GA_{111} methyl ester, Ihara[64] employs a Diels–Alder reaction of a skipped triene to construct the hydrindane substructure of the target (Scheme 34). The synthesis begins with a palladium-catalyzed cycloalkenylation of **280** to form cyclohexenone **281**. Conjugate addition of the vinyl cuprate occurred from the less hindered face to give **282**. This material was advanced to intermediate **283** over six steps. Ester reduction and alcohol oxidation gave an aldehyde. Olefination with **284** delivered the desired *E*-alkene **285** in a 1.3:1 ratio. A similar sequence was repeated (reduction, oxidation, olefination) furnishing the skipped triene **286**. Lithium-halogen exchange of the vinyl bromide and addition to ethyl chloroformate gave **287**. An inverse electron demand Diels–Alder reaction formed the hydrindane core of the gibberellins (**289**) and delivered the product as a single diastereomer. The authors hypothesize that the high facial selectivity may be attributed to the avoidance of steric interactions between the carboethoxy group and the C7 methylene protons in the transition state **288**. This reaction delivers a fully functionalized cyclopentane intermediate that was converted to the (±)-GA_{111} methyl ester over seven steps.

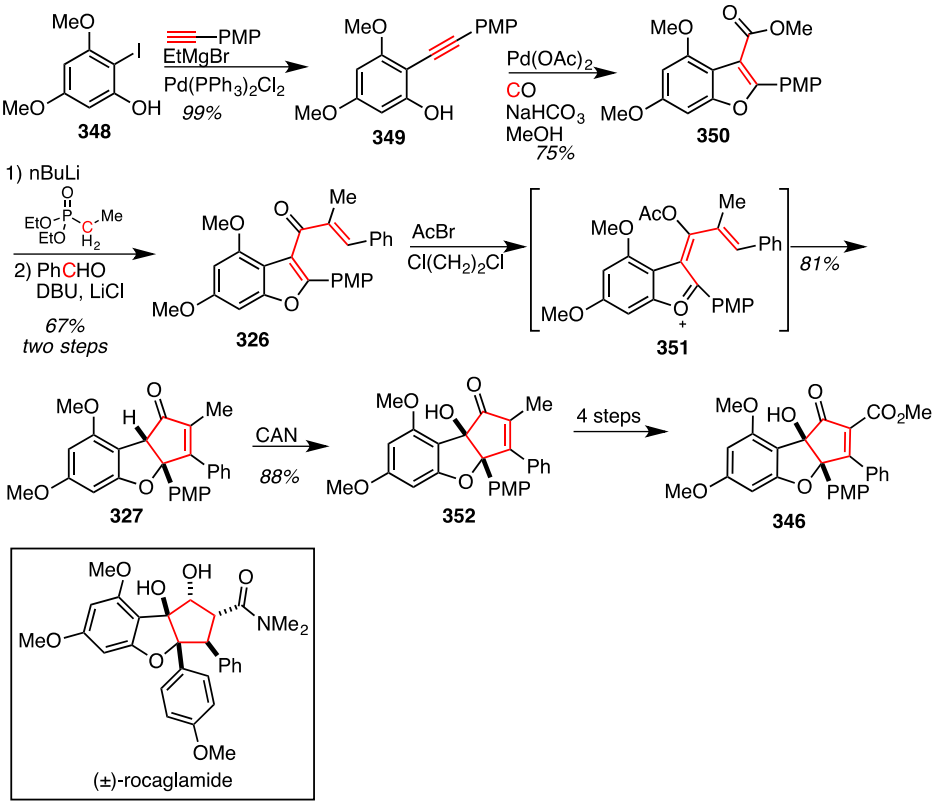
In the synthetic effort towards hexacyclinic acid, Kalesse[65] constructs a fully functionalized cyclopentane with an intramolecular Diels–Alder reaction (Scheme 35). The route begins with the olefination of aldehyde **290**, followed by a two-step oxidation state adjustment to give unsaturated aldehyde **292**. An Evans aldol reaction of the aldehyde with **293** and subsequent conversion to the Weinreb amide provided **294**. The aldol reaction appropriately sets two of the stereocenters for the fully functionalized cyclopentane. Following silylation of the secondary alcohol, the Weinreb amide was reduced to the aldehyde. Acetylide addition and oxidation of the resulting alcohol provided ynone **295**. The IMDA reaction proceeded to furnish the hydrindane core in **297** with complete diastereocontrol. The selectivity can be attributed to the pseudo-equatorial positioning of the silyl ether in the boat-like transition state **296**. Addition of vinyl cuprate occurs *trans* to the adjacent substitutent, and the resulting enolate protonates to give the *cis*-fused hydrindane structure. Hydride reduction occurs on the concave face presumably to avoid interactions with the TBS ether delivering **298**. This advanced intermediate contains appropriate substitution and stereochemical configuration for hexacyclinic acid.

2.4. [5 + 2] cycloadditions

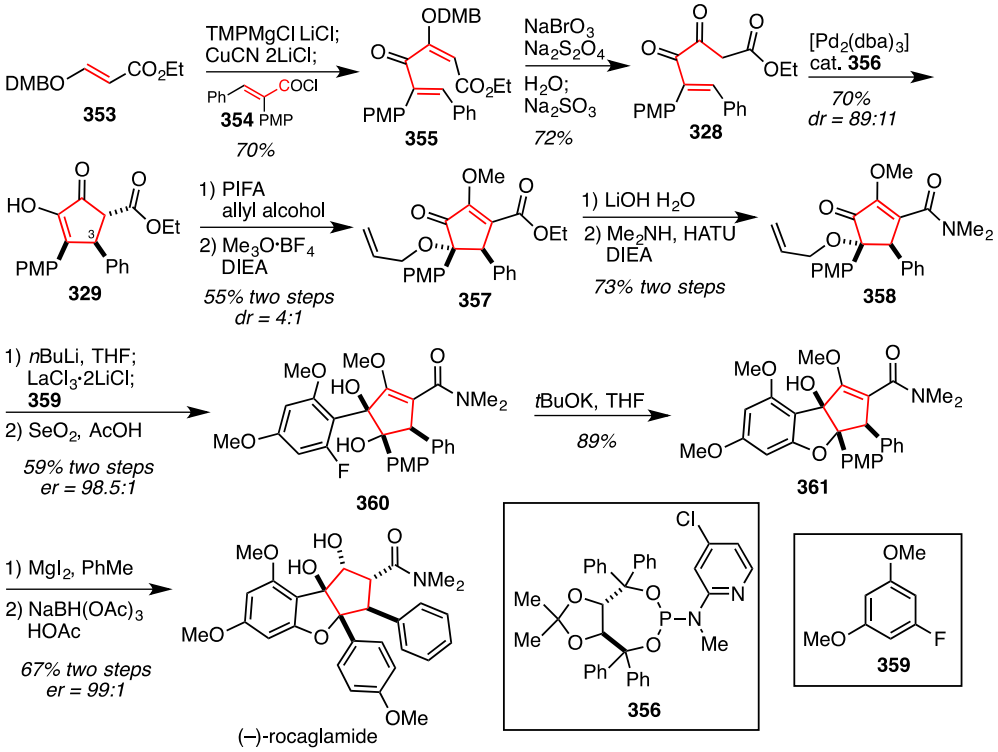
The synthesis of (±)-epicolactone by Trauner used a biomimetic cycloaddition of two oxygenated arenes to construct a fully functionalized cyclopentane (Scheme 36). The route commences with vanillyl alcohol, which could be converted to cycloaddition partner **299** over six steps. The known metabolite epicoccine was synthesized in five steps from eudesmic acid. Addition of two equivalents of formalin to eudesemic acid in the presence of HCl resulted in chlorinated isobenzofuranone **300**. Dechlorination with zinc delivered **301**. The lactone was reduced in two steps with DIBAL followed by TFA and triethylsilane. Demethylation with boron tribromide furnished epicoccine. The key cycloaddition takes place in the presence of oxidant potassium ferricyanide to give epicolactone



Scheme 42. Total Synthesis of (±)-Rocaglamide (Frontier, 2009).



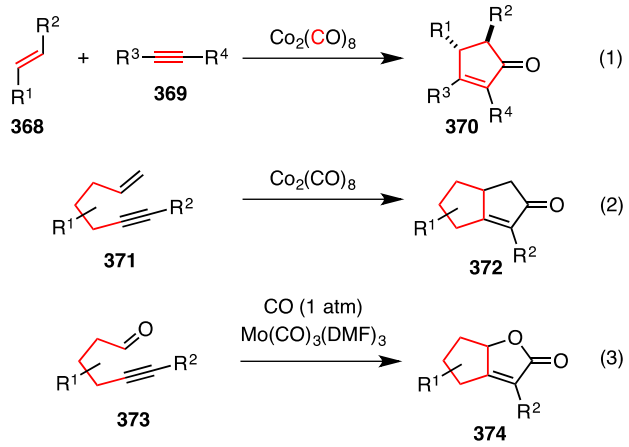
Scheme 43. Formal Synthesis of (±)-Rocaglamide (Magnus, 2012).



Scheme 44. Total Synthesis of (−)-Rocaglamide (Tius, 2015).

methyl ether **302** and the regioisomeric heterodimer **303**. The cycloaddition sequence results in a pentacyclic cage-like structure with three contiguous quaternary stereocenters. Demethylation yields (±)-epicolactone.

The formal synthesis of (±)-coriolin was completed by Wender[66] and employs an arene-olefin photocyclization to construct a highly congested ring system containing a fully functionalized cyclopentane (Scheme 37). The synthesis begins with an addition of the Grignard derived from bromide **305** to aldehyde **306**. An in situ acetylation of the alkoxide delivers **307**. Oxidative cleavage and Wittig olefination gave acetal **309**. This material underwent photocyclization to give adduct **310** as the major product. Upon cleavage of the cyclopropane ring and reductive desulfuration, the triquinane structure is revealed in **311**. Oxidation with peracid in the presence of water stereoselectively epoxidizes the cyclopentene and performs a Baeyer–Villiger oxidation of a transient aldehyde to give a formate (**312**). Semi-pinacol rearrangement of the epoxide gave cyclopentanone **313**. Oxidation to the cyclopentenone proceeded with concomitant transformation of the formate to the corresponding silyl ether. The α-sulfenyl group was installed providing compound **314**. Acidic removal of the TMS group delivers intermediate **315**, which was previously taken forward to (±)-coriolin by Danishefsky.[34]



Scheme 46. Pauson–Khand Reactions in the Synthesis of Fully Functionalized Cyclopentanes.

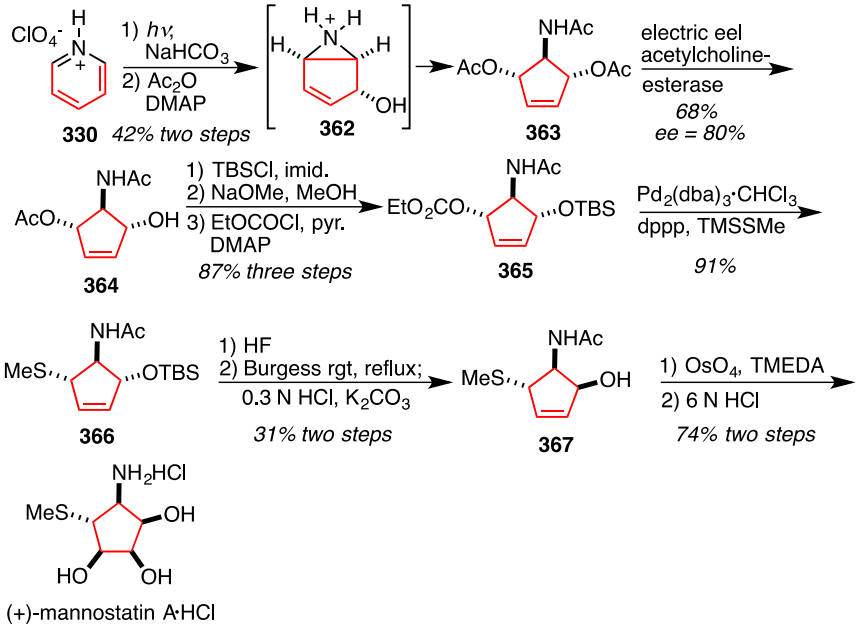
3. Electrocyclizations

Electrocyclizations[67] are powerful ring-closing reactions that predictably follow the Woodward–Hoffman rules[68] for conservation of orbital symmetry. As reactions that tolerate diverse substrates and predictably deliver cyclic products as single diasteromers, it is not surprising that they have been used to create fully functionalized cyclopentanes.

The Nazarov[69] mechanism (Scheme 38) involves a pentadienyl cation (**317**) derived from Lewis (or Brønsted) acid complexation of a divinyl ketone (**316**), which undergoes a thermally promoted conrotatory 4π-electrocyclization to give an oxyallyl cation (**318**). Loss of a proton gives dienolate **319**, which may be protonated to give the final cyclopentenone product **320**. A main concern with the Nazarov cyclization of substituted non-symmetric substrates is the deprotonation of the locally symmetric oxyallyl cation **318**. There are two regioisomeric possibilities for the deprotonation, and regioisomeric mixtures of products can be observed.

Modern advances in controlling the Nazarov reaction rely on substrates with coordinating groups, electronic polarization, or cation-stabilizing atoms to control the fate of the oxyallyl cation.[70] The Nazarov reactions in this review all utilize electronically polarized divinyl ketones that contain a furan (Scheme 39, eq. 1), benzofuran (eq. 2–3), or tricarbonyl (eq. 4) motif to give a single regioisomeric product. The reaction shown in eq. 1 is a particularly elegant example where silyl transfer arrests the Nazarov reaction at the dienolsilane **323**, preserving both fully-substituted stereocenters created in the conrotatory electrocyclization. Two distinct Nazarov reactions of benzofuran-containing substrates have been used in the stereoselective synthesis of functionalized cyclopentenones related to rocaglamide (eq. 2–3).

There has been one electrocyclization of a pyridine used in the synthesis of mannostatin A (Scheme 40). Photochemical cyclization of pyridinium chlorate (**328**) in the presence of water gave



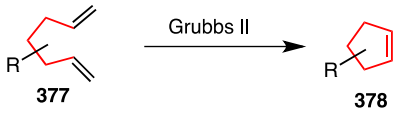
Scheme 45. Total Synthesis of (+)-Mannostatin A (Mariano, 1998).

symmetric cyclopentene **329**, which contained an amino-diol stereotriad. Subsequent steps, including an enzymatic desymmetrization, were used to prepare the natural product.

3.1. Nazarov reactions

In the synthesis of (±)-merrilactone A, Frontier[71] employs a Nazarov cyclization with a siloxyfuran to construct a functionally rich five-membered carbocycle (Scheme 41). Beginning with furan **332**, lithiation and addition to Weinreb amide **333** furnishes divinyl ketone **321**. Treatment with the dicationic iridium catalyst **322** promotes the 4π-electrocyclic ring closure to deliver **323** as a single diastereomer. As anticipated, the stereospecific nature of the conrotatory electrocyclization ensures that the alkene stereochemistry is translated to the desired diastereomeric product. This is an elegant application of the Nazarov reaction that leads to vicinal fully substituted carbons, and the use of the siloxyfuran functional group allows for regioselective trapping of the oxy-allyl cationic intermediate to form the dienoate. Chemoselective removal of the trimethyl silyl group was accomplished to give 1,6-enyne **334**. Radical cyclization of the enyne gave a vinyl stannane intermediate, which upon protonolysis delivered an exocyclic alkene. Desilylation with fluoride provides the functionalized cyclopentanone **335**. Conversion of the primary alcohol to the ethyl carbonate was followed by treatment with sodium hydride leading to a Diekmann cyclization yielding **337**. This product was obtained in a 1:1 ratio with the uncyclized β-ketoester **336**, which could be converted to the desired lactone by treatment with TsOH. Stereoselective methylation occurs to give the more stable *cis*-fused ring system in **338**. Hydride reduction gave fully functionalized cyclopentane **339** as a 1.2:1 mixture with the undesired alcohol epimer. The undesired material could, however, be recycled by near quantitative oxidation with DMP and resubjection to the reduction conditions. An additional three steps were required to convert advanced intermediate **339** to the natural product.

The synthesis of (±)-rocaglamide by Frontier[72] utilizes a Nazarov cyclization of a benzofuran and a stannyl alkoxyallene to form a cyclopentenone (Scheme 42). The synthesis begins with addition of vinylmagnesium bromide to the known benzofuranone **340**, dehydration and subsequent oxidative cleavage gave aldehyde **341**. Addition of phenyl acetylide and subsequent protection of the resulting alcohol as the PMB ether delivered **342**. Deprotonation of the propargylic position with *tert*-butylithium and trapping gave stannyl alkoxyallene **324**. Reaction with excess *m*CPBA promoted the oxidation/Nazarov cyclization cascade to give cyclopentenone **325** as a single diastereomer. The reaction is thought to proceed by oxidation of the central allene carbon to give pentadienyl cation **343**. Protodestannylation and conrotatory electrocyclization delivers cyclopentenone **325**. Treatment with DDQ resulted in both removal of the PMB-ether and oxygenation of the bridgehead carbon. Triflation of the enolizable ketone delivers **345**. A palladium-mediated carbonylation installs the final carbon substituent on the five-membered ring to give ester **346**. Hydrogenation over platinum oxide delivers hydrogen from the concave face, and

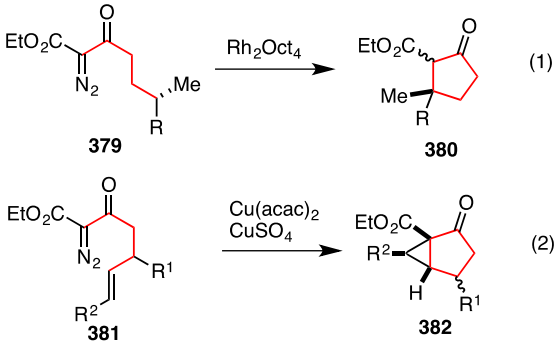


Scheme 48. Ring-Closing Metathesis.

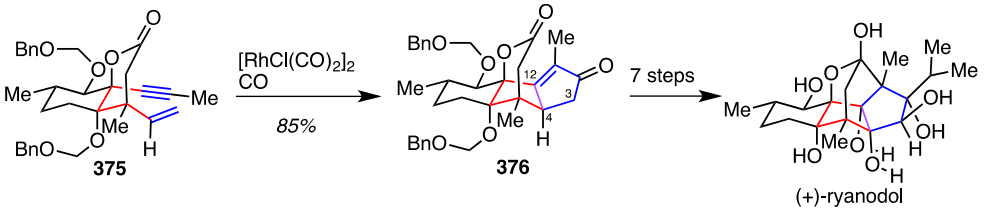
epimerization of the ester yields a single diastereomer. Finally, ketone reduction of the cyclopentenone proceeds with substrate-directed delivery of hydride to afford a fully functionalized cyclopentane **347**. The synthesis of (±)-rocaglamide was completed in two additional steps.

In the formal synthesis of (±)-rocaglamide by Magnus,[73] the five-membered ring of interest is formed through a Nazarov cyclization reaction (Scheme 43). The synthesis begins with an alkynylation of iodophenol **348** under Kumada conditions to give **349**. Palladium-catalyzed carbonylative cyclization delivered benzofuran **350**. Addition of diethyl ethylphosphonate gave a ketophosphonate. Olefination with benzaldehyde was performed under Masamune–Roush[74] conditions to deliver (*E*)-configured **326**. After experimentation with several Lewis acids, it was discovered that acetyl bromide gave the desired Nazarov cyclization product **327**. It is postulated that acetylation of **326** gives an oxonium ion (**351**) which proceeds through the Nazarov cyclization to give **327** after aqueous workup. Oxidation with ceric ammonium nitrate installed the tertiary alcohol in **352**. Four additional steps advanced intermediate **352** to functionalized cyclopentenone **346**, which has been taken to (±)-rocaglamide by Frontier.[72]

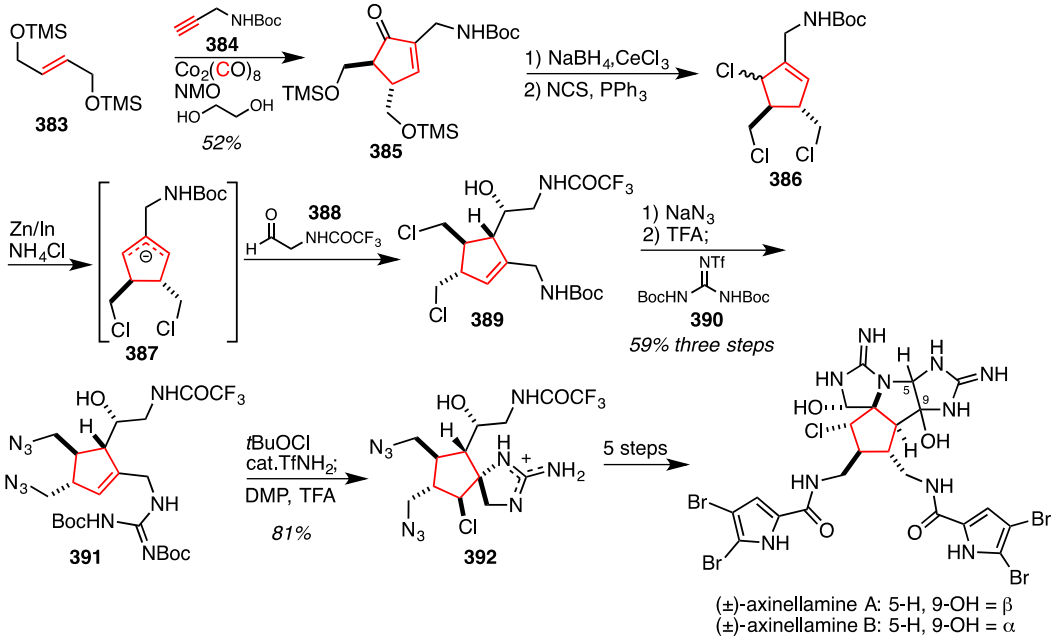
The total synthesis of (−)-rocaglamide by Tius[75] used an enantioselective Nazarov-type cyclization to construct a functionalized cyclopentenone (Scheme 44). The route begins with reaction of vinyl carbonate **353** with cinnamate derivative **354** to deliver dienone **355**.[76] Oxidative cleavage of the DMB protecting group gave tricarbonyl **328**. Palladium-catalyzed Nazarov electrocyclization proceeded in the presence of ligand **356** derived from D-(−)-tartrate, and gave desired product **329** with the appropriate (*S*)-C3 stereochemistry. Oxidative etherification and enol ether



Scheme 49. Cyclization Reactions of α-Diazocarbonyls in the Synthesis of Fully Functionalized Cyclopentanes.



Scheme 47. Application of the Pauson–Khand Reaction in the Synthesis of (+)-Ryanodol.

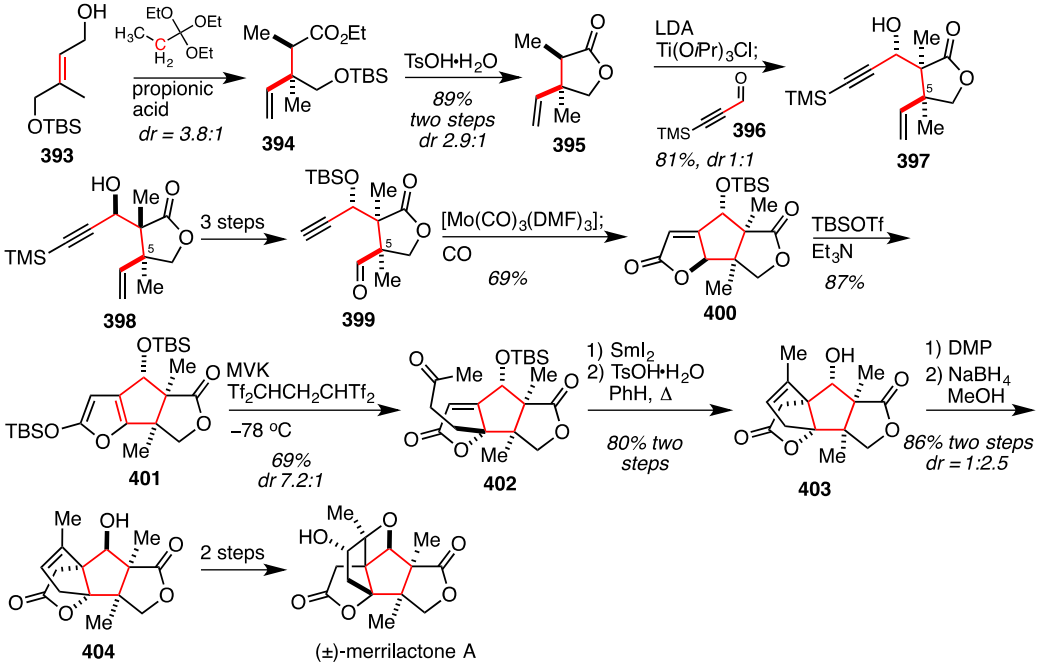


Scheme 50. Total Synthesis of (±)-Axinellamines A and B (Baran, 2011).

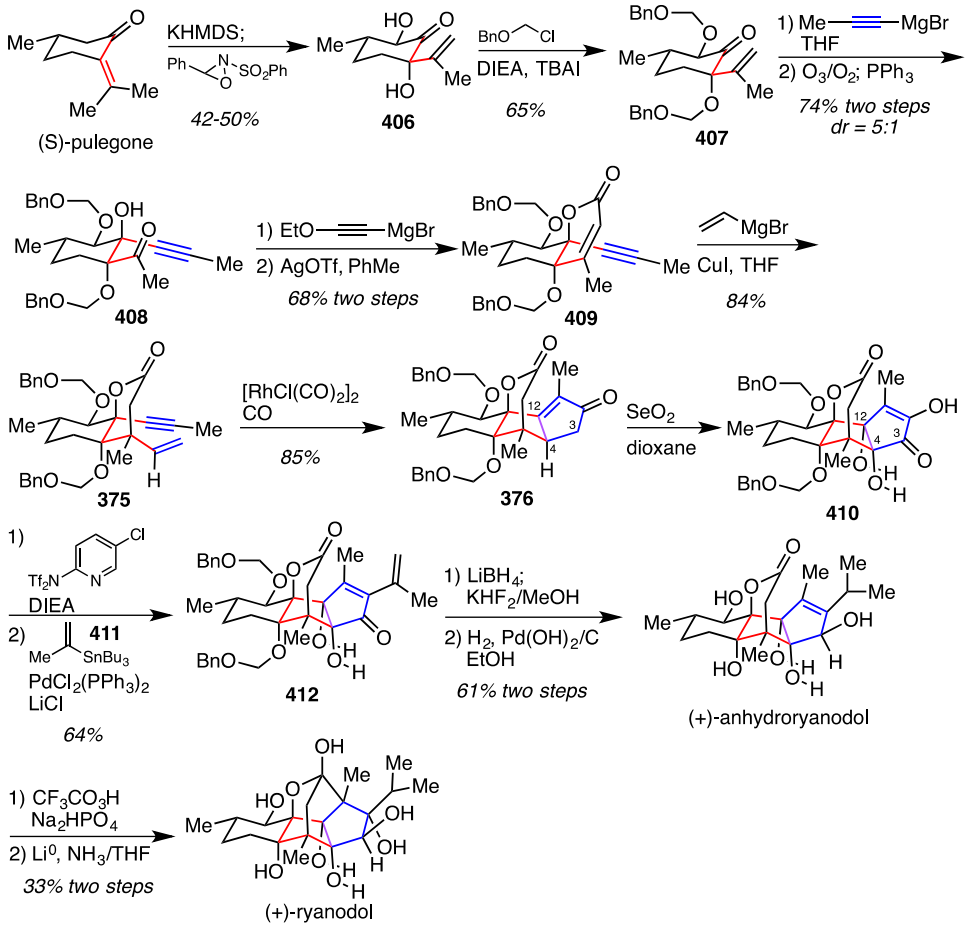
formation gave **357**. Hydrolysis of the ethyl ester and conversion of the resulting carboxylate to the dimethyl amide delivered **358**. The aryl lithium derived from 1-fluoro-3,5-dimethoxybenzene (**359**) was transmetallated with $LaCl_3$ and added to ketone **360**. Oxidative cleavage of the allyl protecting group furnished diol **361**. Treatment with base led to formation of the core dihydroxybenzofuran substructure of rocaglamide via a nucleophilic aromatic substitution. Cleavage of the enol ether delivered a cyclopentanone, which was stereoselectively reduced following the method of Qin[77] completing the synthesis of (−)-rocaglamide.

3.2. Pyridinium ring contraction

In the synthetic approach to members of the aminocyclopentitol family, Mariano[78] developed a ring contraction of a pyridine to give a symmetric cyclopentene (Scheme 45). Specifically, photolysis of pyridinium perchlorate (**330**) induces a disrotatory 4π electrocyclization to give cation **362**, which is intercepted by water. Treatment with acetic anhydride and DMAP leads to the isolated product **363**. Enzymatic desymmetrization delivers chiral cyclopentene **364**. Protecting group manipulation over three steps provides orthogonally protected diol **365**. A Pd-catalyzed addition of



Scheme 51. Total Synthesis of (±)-Merrilactone A (Zhai, 2012).



Scheme 52. Total Synthesis of (+)-Ryanodol (Reisman, 2016).

methylthiol delivers **366** with retention of stereochemistry.[79] Removal of the silyl protecting group was performed with hydrofluoric acid. Inversion of the secondary alcohol following the conditions developed by Wipf[80] delivers *cis*-amido alcohol **367**. Directed dihydroxylation delivers a triol and completes the fully functionalized cyclopentane. Amide hydrolysis yields (+)-mannostatin A as its hydrochloride salt.

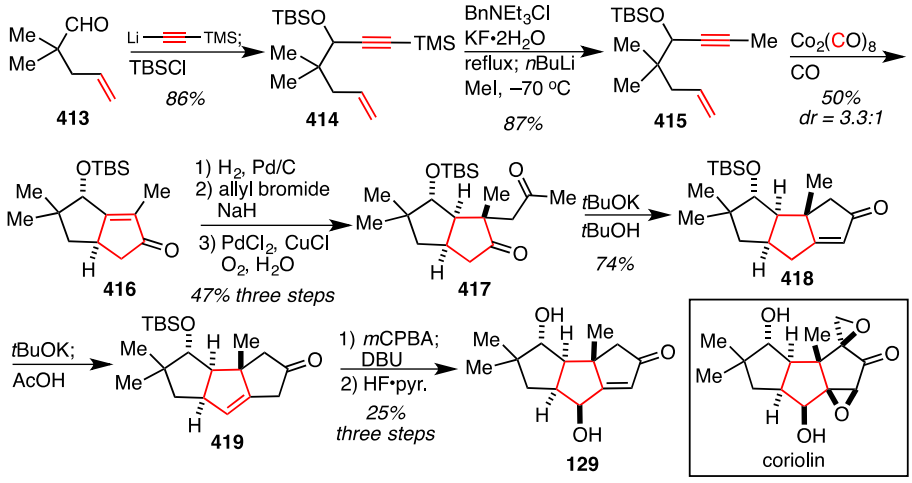
4. Transition-metal mediated cyclizations

Transition metal complexes mediate a diverse variety of ring-forming reactions.[81] Control of regio- and stereoselectivity can be quite high in these transformations, and as a result, it is not surprising that transition metal-mediated reactions have been used in the assembly of fully functionalized cyclopentane natural products.

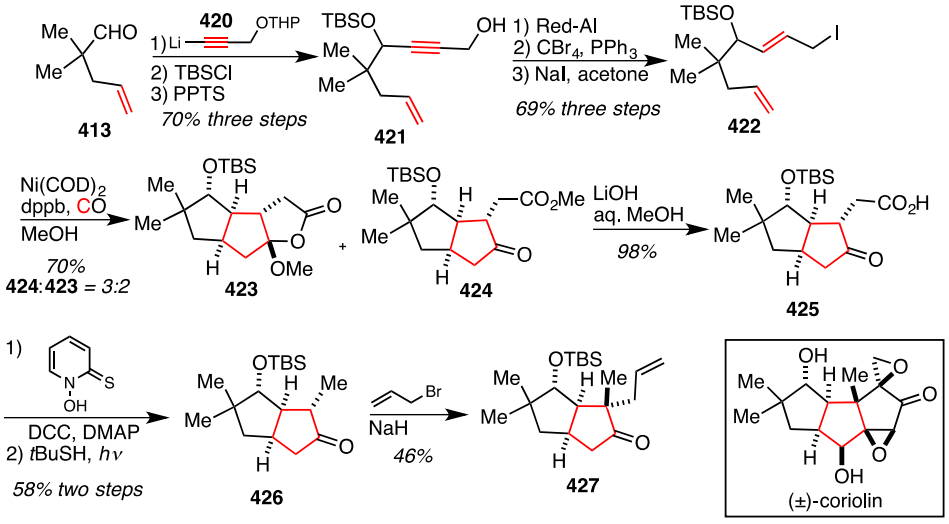
The Pauson–Khand[82,83] reaction is a well-established method for the construction of five-membered rings. In principle, up to four substituents and two stereocenters can be installed on a five-membered carbocycle in a single transformation (Scheme 46, eq. 1). The regiochemistry and stereochemistry are key concerns in the strategic use of this reaction, and tethering the reactive components is a common strategy that limits the regiochemical possibilities. The Pauson-Khand has been used in three distinct strategies directed toward the synthesis of natural products with fully functionalized cyclopentanes. The intermolecular Pauson–Khand has been used to combine an alkene (e.g. **368**), an alkyne (e.g. **369**), and a molecule of CO to construct a 5-membered carbocycle (**370**, eq. 1). The intramolecular Pauson–Khand of a skipped enyne (**371**) has been used, which converts the molecular tether into the functionalized carbocycle (**372**) as part of a fused bicycle (eq. 2). Finally, there is an example of a Mo-promoted intramolecular Pauson–Khand reaction where an aldehyde (**373**) serves as a reactive component in the cyclization to form furanone **374**. In this case, the five-membered carbocycle is also formed from the atoms in the intramoleclar tether (eq. 3). The latter two strategies are particularly well-suited for the synthesis of polyquinanes and related structure types with fused five-membered rings.

An attractive strategic advantage of the Pauson–Khand reaction is the production of an enone product, which can be subsequently manipulated with countless alkene or carbonyl transformations. In the context of the synthesis of cyclopentane targets, this advantage is accompanied by the requirement that the sp^2-hybridized carbons must be processed into substituted sp^3-hybridized carbons. Perhaps for this reason, many examples of the Pauson–Khand in this review occur early in the synthetic route. However, judicious use of reactions that simultaneously leverage the reactivity of the enone and build complexity can be quite powerful. For a particularly elegant example, the Pauson–Khand reaction to form **376** establishes two fused five-membered carbocycles, and just seven subsequent transformations established the required susbstitution and stereochemistry on the adjacent fully functionalized cyclopentanes of ryanodol (Scheme 47).

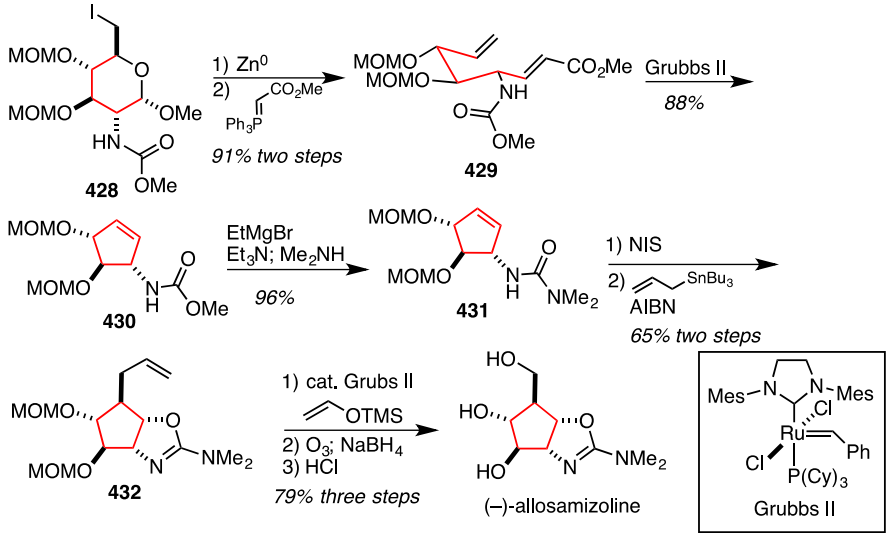
Ring-closing metathesis[84] is another venerable reaction that performs reliably to construct five-membered rings from 1,6-diene starting materials (Scheme 48). An auspicious feature of alkene metathesis using Grubbs' catalyst is the high functional-group



Scheme 53. Formal Synthesis of (±)-Coriolin (Magnus, 1983).



Scheme 54. Formal Synthesis of (±)-Coriolin (Oppolzer, 1992).



Scheme 55. Total Synthesis of (−)-Allosamizoline (Donohoe, 2007).

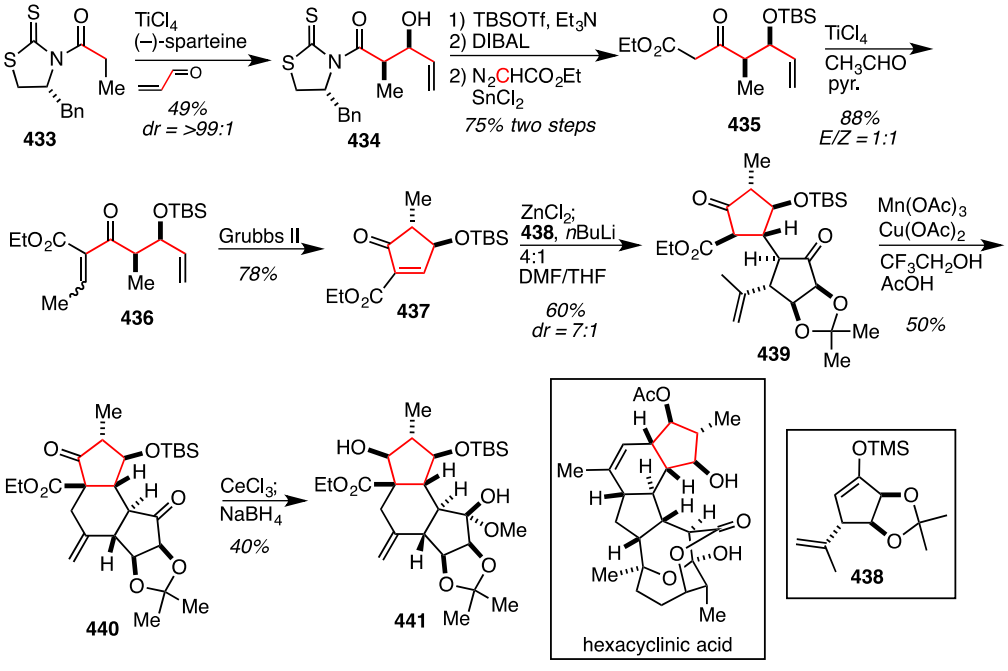
tolerance of the reaction, and this aspect of the reaction allows cyclization of **377** to cyclopentene **378** to take place in the presence of many resident functional groups. In order to form a fully functionalized cyclopentane, the alkene product must undergo further transformations. As with other cyclization strategies where the tether becomes the eventual cyclopentane, establishing the stereocenters on the tether is a key strategic consideration.

α-Diazocarbonyls (e.g. **379**, **381**) react with metals to form metal carbenoid intermediates that may undergo cyclization reactions to form cyclopentanones (e.g. **380**, **382**) (Scheme 49). In the context of fully functionalized cyclopentane synthesis, a C–H insertion reaction and a cyclopropanation and have been performed. Notably, both reactions form all-carbon quaternary stereocenters on the functionalized cyclopentane.

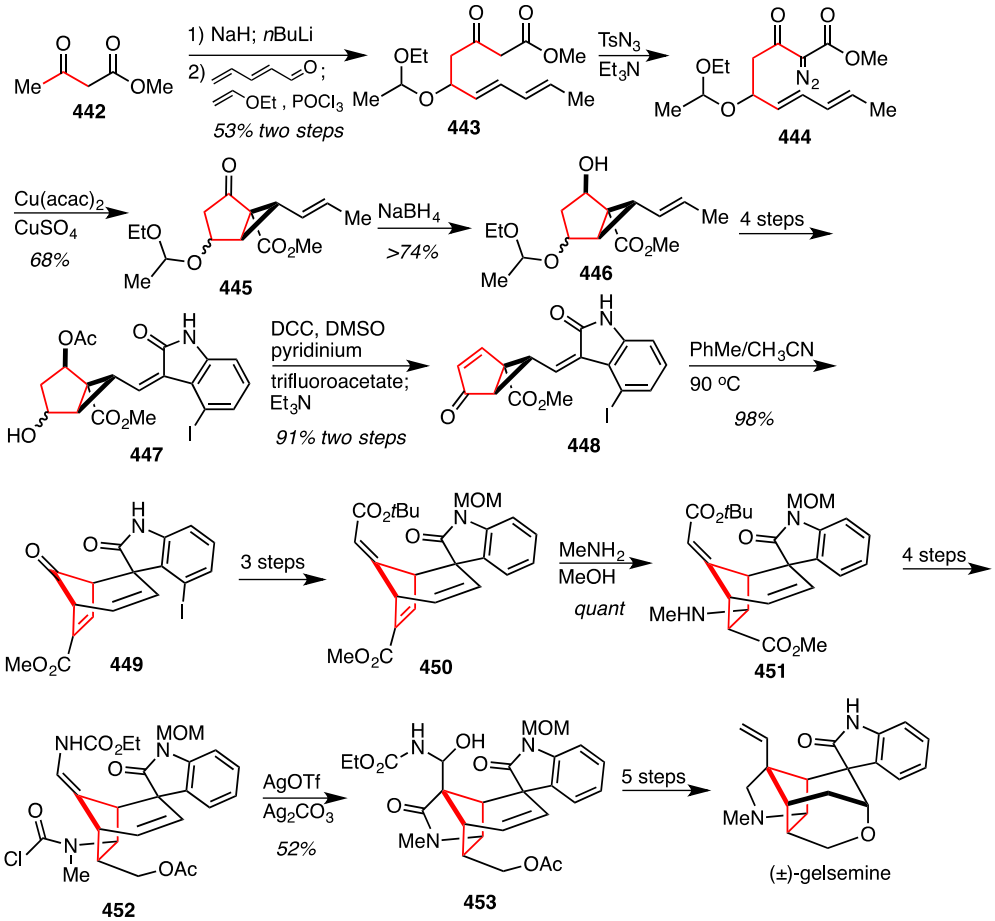
4.1. Pauson–Khand reactions

In the synthesis of (±)-axinellamines A and B, Baran[85] utilizes a Pauson-Khand reaction of a symmetric unactivated alkene to construct a functionalized cyclopentenone (Scheme 50). Initial efforts towards cyclization of alkene **383** and propargyl amine **384** led to a decomposition of the alkyne cobalt complex. Conditions were developed using NMO and ethylene glycol as an additive to dramatically improve the yield of the desired cyclopentenone **385**. Luche reduction of the ketone proceeded with concomitant desilylation. The resulting crude mixture was chlorinated to give trichloride **386** as an inconsequential mixture of epimers. A desymmetrizing Barbier reaction was performed with zinc and indium metals to give addition product **389**. In the addition step, the aldehyde **388** approaches opposite the chloromethyl group of **387** to set the sterocenter on the cyclopentene. Displacement with azide, Boc-deprotection and installation of the guanidine (with **390**) yielded **391**. A chlorination-induced cyclization was achieved with *t*-butyl hypochlorite with $TfNH_2$ as an essential required additive delivering **392** as a single diastereomer. Presumably, stereoselective formation of a bridged-chloronium species forms opposite the adjacent alkyl substituents. Opening of the chloronium ion with the tethered guanidine furnishes the spirocycle with complete stereocontrol. This transformation completes the fully functionalized cyclopentane in (±)-axinellamines A and B, and the natural product was completed in an additional five steps.

The pentacyclic sesquiterpene (±)-merrilactone A was synthesized by Zhai,[86] and utilizes a hetero-Pauson-Khand reaction to construct a γ-lactone fused to a functionalized cyclopentane (Scheme 51). The route begins with a Johnson–Claisen rearrangement of alcohol **393**. The rearrangement occurs through the anticipated chair-like transition state and proceeds with a *dr* of 3.8:1 favoring the desired product **394**. Simultaneous desilylation and lactonization yields substituted γ-lactone **395** as an inconsequential mixture of racemic diastereomers. Deprotonation of lactone **395** gave a single racemic (*E*)-enolate that added to 3-trimethylsilylpropynal (**396**) to deliver **397** and **398** as a 1:1 mixture of racemic distereomers. The aldol reaction proceeds with near complete Zimmerman–Traxler control but with no facial selectivity with respect to the chiral racemic enolate. This mixture of distereomers was advanced 3 steps to give aldehyde **399**, which was purified from the undesired diastereomer. Note that the undesired diastereomer could be recycled to **397** over three steps. The key hetero-PKR was accomplished by stirring aldehyde **399** with $[Mo(CO)_3(DMF)_3]$ first in an atmosphere of argon and then under 1 atm of carbon monoxide to give tricycle intermediate **400**. The unsaturated lactone was converted to siloxyfuran **401** by treatment with TBSOTf. Conjugate addition to methyl vinyl ketone (MVK) delivers adduct **402**. The good facial selectivity ($dr = 7.2{:}1$) is presumably because of the addition of MVK on the face opposite the large TBS-ether. A radical cyclization gives a tetracyclic product in good (albeit inconsequential) selectivity yielding a tertiary alcohol. Simulateneous desilylation and dehydration occurred with acid in refluxing benzene to yield alkene **403**. The alcohol stereocenter could be inverted by oxidation to a ketone and hydride reduction, which gave a mixture of the desired alcohol **404** with its alcohol epimer, which could be recycled. This intermediate was advanced two steps to the natural product.

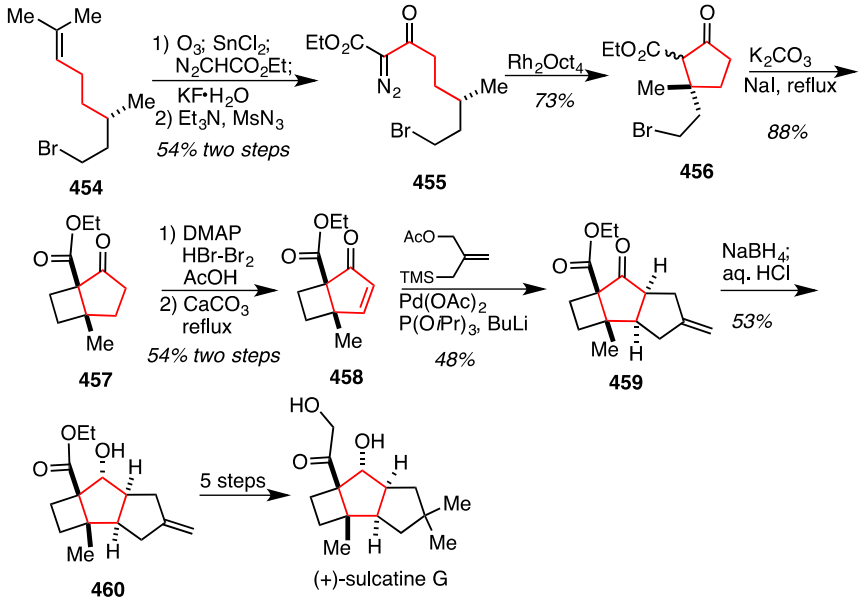


Scheme 56. Synthetic Studies Towards Hexacyclinic Acid (Prunet, 2008).



Scheme 57. Total Synthesis of (±)-Gelsemine (Fukuyama, 1996).

In the Reisman[87] synthesis of (+)-ryanodol, a Pauson-Khand reaction constructs two five-membered rings that eventually become fully functionalized (Scheme 52). The route begins with a stereoselective oxidation of (*S*)-pulegone to give diol **406**. The hydroxyl groups were protected as benzyloxymethyl ethers to give **407**. Addition of the magnesium acetylide occurred

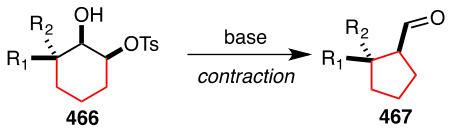


Scheme 58. Total Synthesis of Sulcatine G (Taber, 2005).

preferentially with equatorial approach (*dr* = 5:1). Chemoselective ozonolysis of the alkene gave methyl ketone **408**. The unsaturated lactone of **409** was installed by a 1,2-addition of ethoxyethynylmagnesium bromide followed by a silver-catalyzed cyclization and elimination. Conjugate addition of divinyl cuprate occurred stereoselectively to construct the all quaternary stereocenter and deliver enyne **375**. The Pauson–Khand cyclization occurred with high yield and good *dr* when using $[RhCl(CO)_2]_2$ to furnish **376**. This spectacular transformation creates two fused five-membered rings with substitution and stereochemistry appropriate for the congested *cis*-diquinane embedded in the ryanodol architecture. Heating of the enone with selenium dioxide and molecular sieves enabled the stereoselective installation of the C4, C12 *syn*-vicinal diol and oxidation of C3 in a single step producing the first fully functionlized cyclopentane in **410**. Enol triflate formation was followed by a Pd-catalyzed cross-coupling with stannane **411** to install the final carbons of the target in **412**. Hydride reduction occurred from the less hindered face of the ring system, and hydrogenation of the disubstituted alkene with simultaneous hydroxyl deprotection delivered (+)-anhydroryanodol. Epoxidation with trifluoroperacetic acid and reductive cyclization onto the lactone delivered (+)-ryanodol.

In the formal synthesis of (±)-coriolin, Magnus[88] employs a Pauson-Khand reaction to construct a functionalized cyclopentanone (Scheme 53). The synthesis begins with addition of lithium-TMS acetylide to aldehyde **413**, and TBS protection of the resulting alcohol delivers **414**. Removal of the TMS ether and methylation gave cyclization precursor **415**. Heating enyne **415** with $Co_2(CO)_8$ in a solution saturated with carbon monoxide yielded cyclopentenone **416** as the major diastereomer. The origin of the diastereoselectivity is not known; however, the silyl acetylene analog gave a much higher diastereomer ratio (*dr* = 26:1). Hydrogenation of the enone gave a *cis*-bicyclo[3.3.0]octane which could be allylated on the convex face. A Wacker oxidation delivers diketone **417**. Treatment with *t*BuOK induced an aldol condensation yielding tricyclic enone **418**. Deprotonation with *t*BuOK followed by acidic workup gave deconjugated β,γ-enone **419**. Epoxidation with *m*CPBA proceeds to give the *cis*-fused dihydroquinane substructure. Basic workup induces elimination to form the enone. Deprotection of the silyl group delivers **129** which is an intermediate in a synthesis of coriolin by Matsumoto.[32]

In the formal synthesis of (±)-coriolin, Oppolzer[89] employs a nickel-catalyzed metallo-ene-type cyclization to construct a cyclopentanone (Scheme 54). Beginning with aldehyde **413**, addition of a lithium acetylide **420** delivers a 1,5-enyne. The resulting alcohol was silylated and the THP group was removed to give **421**. *Trans*-selective reduction of the alkyne was followed by two-step iodination of the alcohol to give allylic iodide **402**. The key



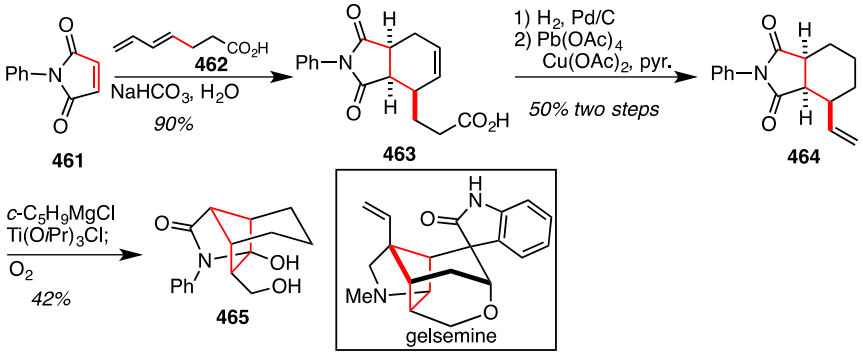
Scheme 60. Semipinacol Rearrangements in the Synthesis of Fully Functionalized Cyclopentanes.

cyclization reaction was performed by stirring diene **422** with $Ni(COD)_2$ under an atmosphere of carbon monoxide to deliver two isolable products. The desired ketoester **424** was obtained as a 3:2 ratio with the isomeric lactone **423**. The authors did not comment on the origin of diastereoselectivity; however, it is plausible the favored diastereomer positions the ether and alkyl groups on the less hindered convex face of the *cis*-fused bicycle. Saponification of this mixture with lithium hydroxide in aqueous methanol provided ketoacid **425**. The unpurified material was taken forward to a Barton-type decarboxylation[90] yielding methylcyclopentanone **426**. Stereoselective allylation occurs from the convex face of the ring system to furnish **427**, which is an intermediate synthesized by Magnus[88] in a synthesis of coriolin.

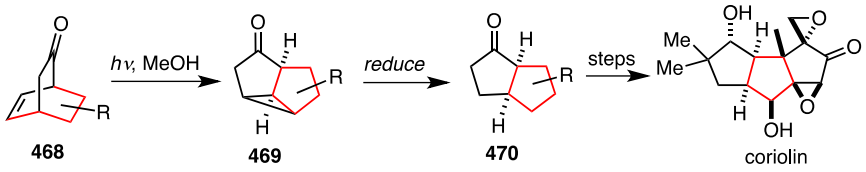
4.2. Ring-closing metathesis

In the synthesis of (−)-allosamizoline, Donohoe[91] employs a ring-closing metathesis to construct a functionalized cyclopentene (Scheme 55). The synthesis begins with methyl pyranoside **428,** which was synthesized from D-glucosamine over four steps. Reductive cleavage of the ring gives an aldehyde that was directly subjected to Wittig olefination delivering diene **429**. Ring closing metathesis with Grubbs 2nd generation catalyst furnishes substituted cyclopentene **430**. Conversion of the methyl carbamate to the urea **431** was accomplished using the procedure developed by Basha.[92] Iodocyclization of **431** gave an oxazoline. Reaction of the intermediate iodide using conditions developed by Keck[93] led to carbon-carbon bond formation on the less hindered face of the cyclopentane affording **432** as a single diastereomer. Isomerization of the terminal alkene with Grubbs II catalyst gave an inconsequential mixture of alkene isomers. Ozonolysis with reductive workup and a global MOM deprotection yields (−)-allosamizoline.

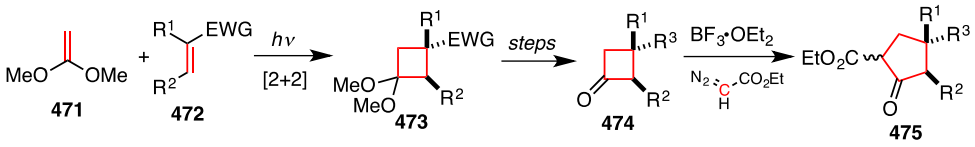
In the synthetic effort towards hexacyclinic acid, Prunet[94] uses ring-closing metathesis to construct a functionalized cyclopentenone (Scheme 56). The route commences with the asymmetric *syn*-aldol of **433** with acrolein to give **434**. Cleavage of the chiral auxiliary delivered an aldehyde, and a subsequent tin-mediated addition of ethyl diazoacetate gave β-ketoester **435**. A Lewis acid promoted condensation with acetaldehyde gives enone **436** as a 1:1 mixture of inconsequential alkene isomers. Ring-



Scheme 59. Synthetic Studies Towards Gelsemine (Cha, 1999).



Scheme 61. Oxa-di-π-methane Rearrangements in the Synthesis of Coriolin.

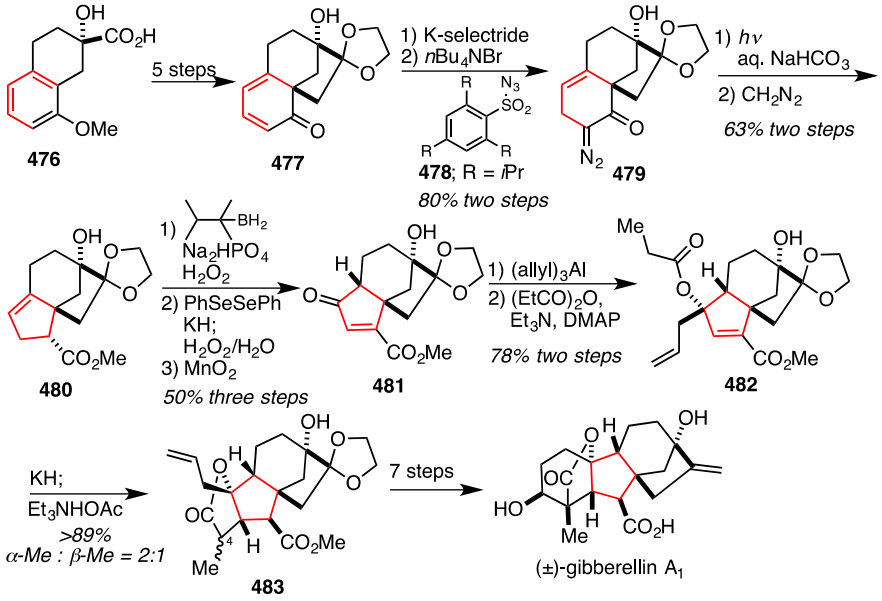


Scheme 62. Cyclobutane Expansion Reactions in the Synthesis of Fully Functionalized Cyclopentanes.

closing metathesis proceeded smoothly to deliver functionalized cyclopentenone **437**. Mukaiyama Michael addition of enol silane **438** to **437** led to the formation of three stereocenters and highly functionalized cyclopentanone **439**. In this key Michael reaction the forming stereocenters are the result of the stereochemical preference of each of the reactive coupling partners. It was hypothesized that conducting the reaction in a polar solvent reduces complexation of the reactants and allows addition of each reactive component on their respective least hindered diastereoface.[95] A radical cyclization of β-ketoester **439** furnishes the fused carbocyclic ring system **440**. Finally, Luche reduction proceeds with hydride delivery from the convex face of the ring system to deliver fully functionalized cyclopentane **441**. This advanced intermediate contains much of the hexacyclinic acid structure including the fully functionalized cyclopentane.[96]

4.3. Carbenoid cyclizations

In Fukuyama's[97] first total synthesis of (±)-gelsemine, a copper-mediated cyclopropanation results in the formation of a functionalized cyclopentanone (Scheme 57).[98] Beginning with a protocol first published by Kondo,[99] addition of the dianion derived from methyl acetoacetate (**442**) to sorbic aldehyde was followed by protection with ethyl vinyl ether to deliver intermediate **443**. Treatment with tosyl azide and triethylamine results in diazo transfer to give the β-ketoester **444**. The copper-mediated cyclopropanation was successful in constructing cyclopentanone **445** as an inconsequential mixture of diastereomers. Hyride reduction of the ketone occurs from the convex face of the bicycle to deliver **446**, although the diastereoselectivity is inconsequential. This intermediate was advanced over four standard transformations to give **447**. A Pfitzner–Moffatt[100] oxidation followed by elimination of acetic acid produced enone **448**. Refluxing intermediate **448** in a toluene/acetonitrile mixture promotes a divinylcyclopropane Cope rearrangement to furnish the bicyclo[3.2.1]octadienone system **449**. This material was converted to unsaturated ester **450** by radical deiodination, a Horner-Wadsworth-Emmons reaction of the cyclopentenone, and protection of the indole nitrogen as an *N,O*-acetal. Conjugate addition of dimethylamine occurred exclusively from the less hindered *exo*-face yielding *trans*-amino ester **451**. This material was advanced four steps through functional group manipulations to deliver intermediate **452**. Upon exposure to silver triflate and silver carbonate an unusual lactam formation occurred to provide fully functionalized cyclopentane **453**. This advanced



Scheme 63. Total Synthesis of (±)-Gibberellin A_1 (Mander, 1980).

intermediate contains the fully functionalized cyclopentane core of (±)-gelsemine, and it was advanced to the natural product over an additional five steps.

The synthesis of (+)-sulcatine G by Taber[101] employs a rhodium catalyzed intramolecular C–H insertion for the construction of the cyclopentane ring (Scheme 58). The route begins with commercial (*S*)-(+)-citronellyl bromide **454**. This was subjected to an ozonolysis/diazocoupling sequence[102] to deliver a β-ketoester. Diazotransfer using methanesulfonyl azide furnished cyclization substrate **455**. Rhodium catalyzed intramolecular C–H insertion gave cyclopentane **456** without erosion of enantiomeric excess, although the product was isolated as an inconsequential mixture of ethyl ester epimers. Treatment of **456** with base under Finkelstein conditions induced intramolecular alkylation to give the *cis*-bicyclo[3.2.0]heptane (**457**). Oxidation of the cyclopentenone was accomplished by monobromination of the ketone followed by dehydrobromination with calcium carbonate yielding **458**. A Trost annulation[103] occurs from the convex face of the bicyclic ring system and formed the tricyclic intermediate **459** with good diastereocontrol. Hydride reduction occurs to give the desired diastereomer of the secondary alcohol (**460**) in good yield, which represents delivery of hydride on the diastereoface of the cyclopentanone with no less than four substituents. No explanation was given for the origin of this diastereoselectivity.[104] This advanced intermediate contains a fully functionalized cyclopentane, and (+)-sulcatine G was completed in an additional five steps.

4.4. Intramolecular Kulinkovich reaction

In the efforts towards the gelsemine skeleton, Cha[105] utilizes a titanium-mediated cyclization of an ω-vinylamide to construct the tricyclic core the natural product (Scheme 59). A Diels–Alder reaction between *N*-phenylmaleimide (**461**) and (*E*)-4,6-heptadienoic acid (**462**) provided cycloadduct **463** with good *endo* selectivity. Hydrogenation of the cyclohexene was followed by oxidative decarboxylation to yield **464**. Treatment of **464** with modified Kulinkovic conditions led to intramolecular addition of an organotitanium intermediate to the imide carbonyl. Oxidative workup with oxygen gave the primary alcohol **465**. This intermediate contains a fully functionalized cyclopentane with substitution and stereochemistry that matches many of the structural features found in gelsemine.

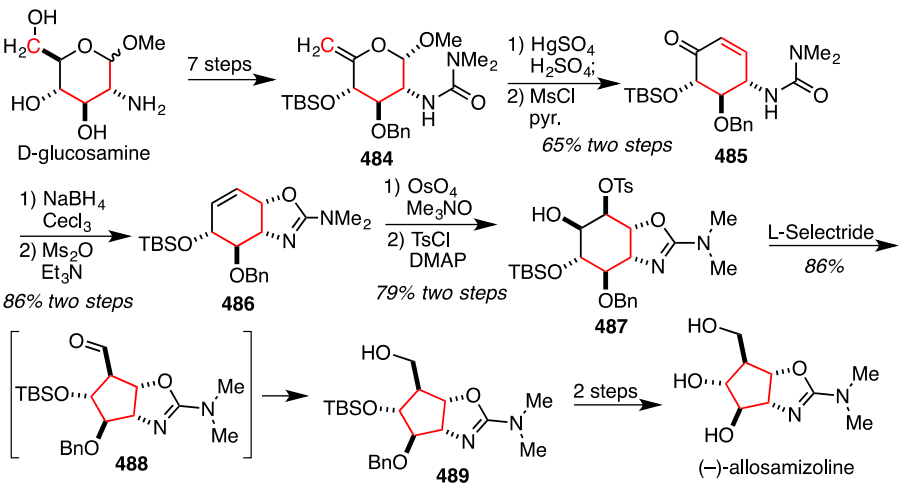
5. Rearrangements

Several natural products contianing fully functionalized cyclopentanes have been prepared using a skeletal rearrangement to build the five-membered ring. In such cases, stereogenic carbon atoms are installed on a larger or smaller ring; a subsequent transformation either contracts or expands, respectively, the carbocyle size to arrive at the cyclopentane. All examples of rearrangements in the context of this review fall into four well-defined categories: ring contraction of six-membered rings, oxa-di-π-methane rearrangements, ring expansion of cyclobutanes, and a Cope rearrangement.

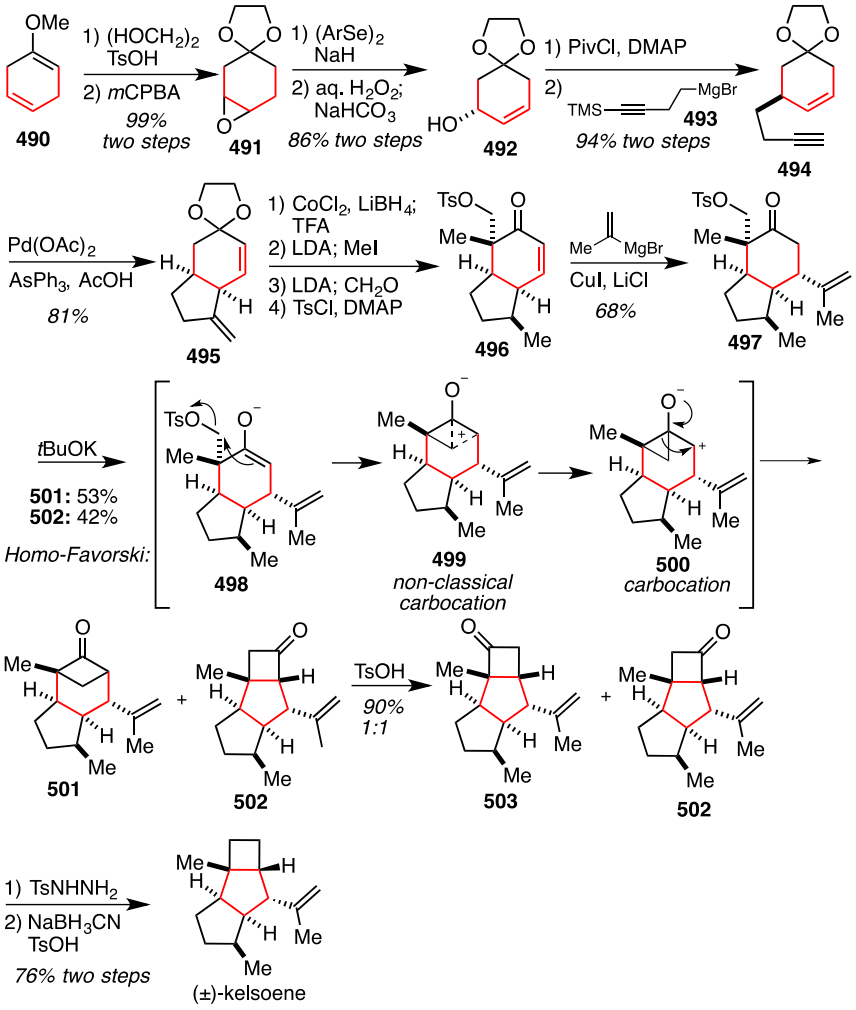
Ring contraction of six-membered rings represents a common strategy for the formation of cyclopentane architectures. The value of this strategy stems from the myriad of sources of six-membered rings; suitably substituted benzenes, cyclohexenes prepared in Diels–Alder reactions, δ-valerolactone derivatives, or other cyclohexane derivatives could all conceivably undergo contraction to a substituted cyclopentane. A common strategy for ring-contraction features a 1,2-disubstituted cyclohexane starting material (**466**) that undergoes the semipinacol[106] (Scheme 60), Wolff,[107] or acyloin-type rearrangements (less common regarrangements have also been used) to give cyclopentanes (e.g. **467**). A useful feature of these reactions is that migrating carbon retains its stereochemical configuration during the rearrangement.

The oxa-di-π-methane rearrangement[108] is a process by which six-membered rings can be contracted into suitably functionalized cyclopentanes with predictable control of resident stereochemical configuration (Scheme 61). The bicyclic starting materials (**468**) are produced using standard Diels–Alder cycloaddition reactions. Exposure to UV light induces the rearrangement to give the products **469**. A subsequent cleavage of the embedded cyclopropane gives a *cis*-fused bicyclo[3.3.0]heptanone (**470**). In the context of this review, this strategy has been used in three separate examples, all in the context of a coriolin synthesis. Depending on the substitution pattern of the rearrangement substrate **468**, the reaction can deliver a fused-diquinane or fused-triquinane molecular architecture.

Substituted cyclobutanes may undergo ring expansion to give cyclopentanes (Scheme 62). In the context of this review, all such cyclobutanes are prepared using photochemical [2 + 2]-cycloadditions between alkenes (**471**) and substituted unsaturated carbonyls (**472**). The stereospecificity of the cycloaddition allows for the controlled production of several stereogenic carbons. The ring



Scheme 64. Total Synthesis of (−)-Allosamizoline (Kuzuhara, 1991).



Scheme 65. Total Synthesis of (±)-Kelsoene (Koreeda, 2002).

strain in the cyclobutane provides a potent driving force for the subsequent cyclopentane formation. A potential limitation of this strategy is that regioselectivity in the photochemical event requires careful selection of alkene substitution; as a result, several steps are required to transform the cycloaddition product (**473**) to the substrate for ring enlargement (**474**). The reaction used to expand the four-membered ring to the cyclopentane varies widely. A Tiffeneau–Demjanov-type rearrangement has been used (e.g. **474** → **475**), but more unusual rearrangements also appear in this review.

5.1. Ring contractions of cyclohexane derivatives

In the synthesis of (±)-gibberellin A_1 and gibberellic acid, Mander[109] employs a photochemical ring contraction of an α-diazo cyclohexenone to produce a cyclopentene (Scheme 63). Cyclohexadienone **477** was obtained after a five step conversion from starting material **476**. Conjugate reduction of the enone was accomplished using standard conditions, and the unpurified material was transformed into diazoketone **479** using sulfonyl azide **478**. Irradiation of the diazo species initiated a Wolff rearrangement to furnish **480** as a mixture of carboxylic acids ($dr = 3.6{:}1$) that were methylated with diazomethane. A three-step oxidation sequence furnished cyclopentenone **481**. Organometallic addition followed by esterification gave intermediate **482**. Finally, conjugate addition of the propionate ester to the enone delivered fully functionalized cyclopentane **483** as a mixture of C4 epimers. This advanced intermediate contains the substituents and stereochemistry suitable for the synthesis of the target gibberellins, and completion of (±)-gibberellin A_1 required an additional seven steps.

In the synthesis of (−)-allosamizoline, Kuzuhara[110] performs a ring contraction of a six-membered sugar derivative to a fully functionalized cyclopentane (Scheme 64). The synthetic intermediate **484** was obtained from D-glucosamine over seven steps. A modified Ferrier reaction was performed using mercuric sulfate to give a β-hydroxy ketone, which underwent dehydration to give enone **485**. A Luche reduction was followed by activation of the resulting allylic alcohol as the mesylate. Displacement with the pendant urea delivered the dimethylamino oxazoline ring **487**. Dihydroxylation of the cyclohexene with OsO_4 proceeded from the less hindered convex face giving a *syn*-diol. Monosulfonylation of the hydroxyl group was accomplished using tosyl chloride in pyridine. Treatment with L-Selectride initiated semi-pinacol rearrangement to give transient intermediate aldehyde **488,** which was reduced under the conditions to give fully functionalized cyclopentane **489**. This advanced intermediate was advanced to (−)-allosamizoline over two additional transformations.

In the synthesis of (±)-kelsoene by Koreeda,[111] the key step is a homo-Favorskii rearrangement which effects a ring contraction from a six-membered carbocycle to a bicyclo[3.2.2]heptane and

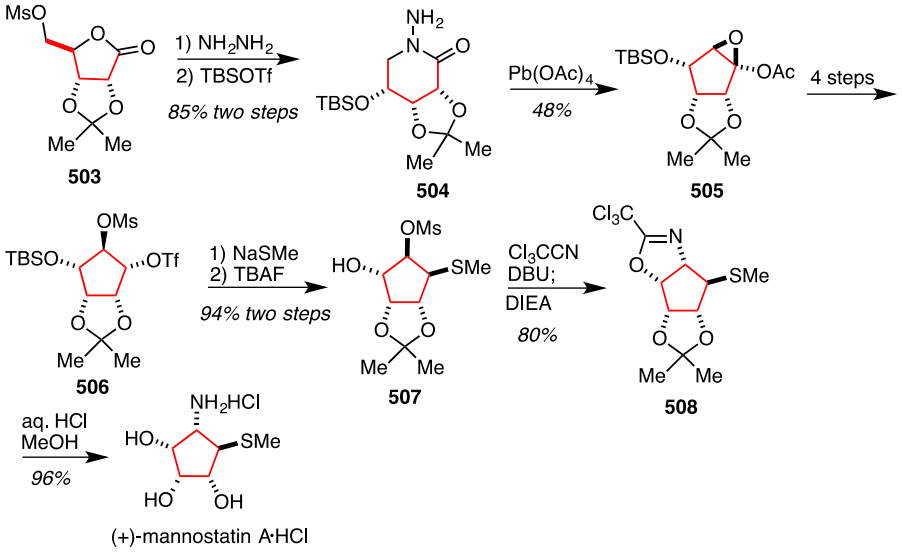
delivers a fully functionalized cyclopentane (Scheme 65). The synthesis begins with methoxycyclohexa-1,4-diene (**490**) which is hydrolyzed, protected as the ketal and epoxidized to give **491**. Regioselective epoxide opening with selenium occurred away from the ketal and upon elimination gave allylic alcohol **492**. Chlorination and addition of Grignard **493** gave enyne **494**. A Pd-catalyzed cyclization of enyne **494** delivers annulation product **495**. This material was carried forward over four steps to cyclohexenone **496**. Conjugate addition occurs under conditions developed by Kharasch[112] on the less hindered face of the enone to give intermediate **497**. Exposure of the β-keto tosylate **497** to base resulted in a mixture of two cyclobutanones. Minor product **502** results from the desired homo-Favorskii rearrangement producing a fully functionalized cyclopentane (*mechanism shown*), and **501** is the product of intramolecular enolate alkylation with the tethered tosylate. The crude ketone mixture was treated with acid, which induced the isomerization of the undesired **501** to an inconsequential mixture of cyclobutanones containing the desired **502**. The isomerization of **501** to **502**/**503** may proceed via intermediates **498**–**500** The separable cyclobutanones were converted to their respective tosylhydrazone derivatives, and they were subsequently reduced to (±)-kelsoene.

In the synthesis of the α-mannosidase inhibitor, (+)-mannostatin A, Vasella[113] employs a ring contraction from an *N*-aminolactam (**504**) to form a fully functionalized cyclopentane (Scheme 66). Mesylate **503** (derived from D-ribonolactone) was converted to *N*-aminolactam **504** over two steps. Oxidation with lead (IV) acetate provided fully functionalized cyclopentane **505**. This oxidative ring contraction was developed by Vasella and has multiple proposed mechanistic pathways.[114] This material was converted over four steps to the orthogonally protected triol **506**. Substitution with methanethiolate installed the thioether. Fluoride-mediated removal of the silyl protecting group furnished **507**. The final stereocenter of the cyclopentane was installed by imidate formation with spontaneous displacement of the mesylate to give fully functionalized cyclopentane **508**. Hydrolysis of the oxazoline delivers (+)-mannostain A as the hydrochloride salt.

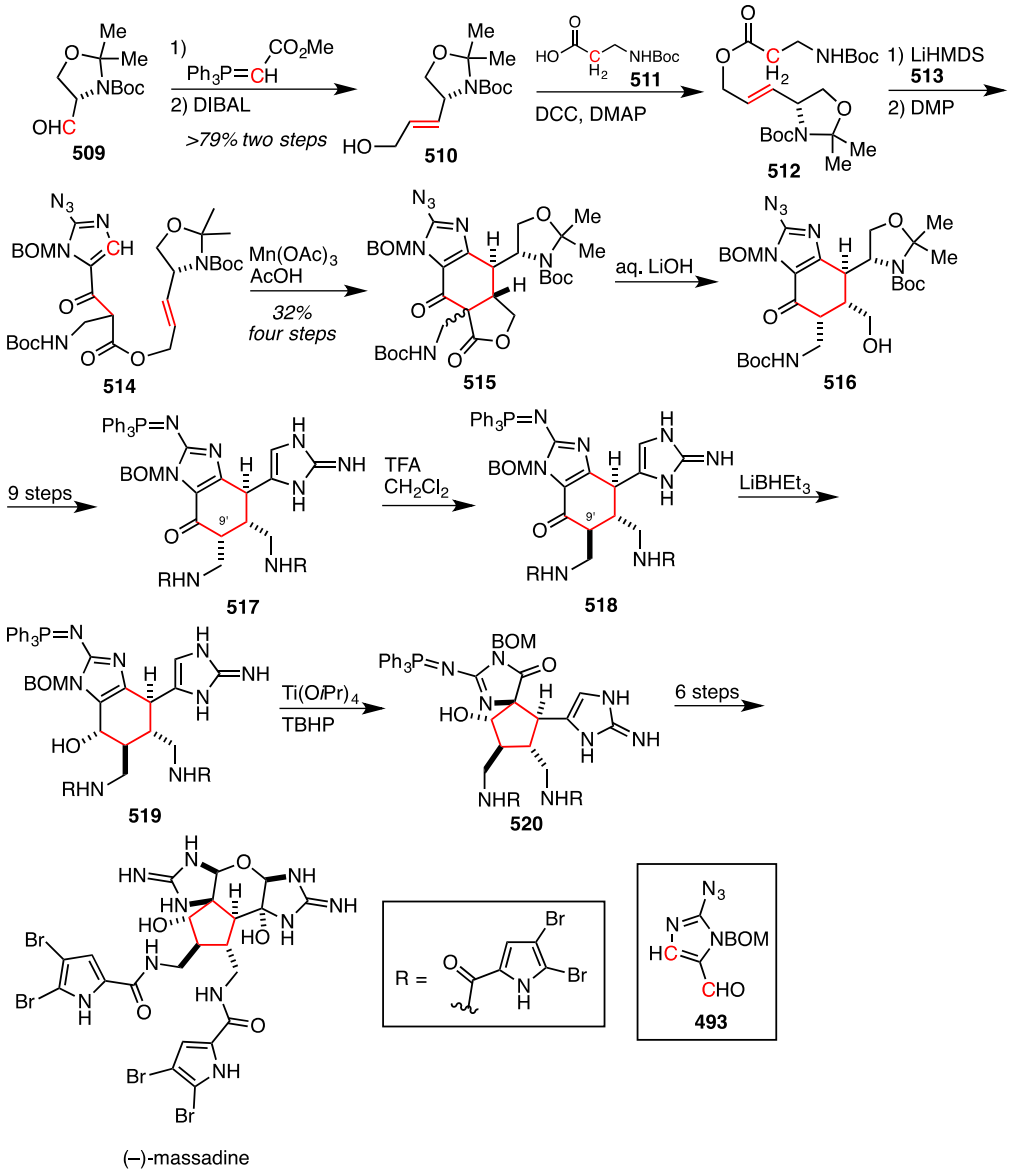
The total synthesis of (−)-massadine was completed by Baran and Chen utilizing a ring contraction (Scheurer rearrangement) to give a fully functionalized cyclopentane (Scheme 67).[115] The route begins with (*S*)-Garner's aldehyde (**509**), which was olefinated and reduced to give allylic alcohol **510**.[116] Carbodiimide coupling with carboxylic acid **511** delivers ester **512**. Enolate formation and addition to aldehyde **513** was followed by oxidation of the resulting alcohol giving cyclization precursor **514**. Treatment with $Mn(OAc)_3$ induced a radical cyclization resulting in the formation of three stereocenters in **515**. Hydrolysis of the lactone delivered **516**, which was advanced nine steps to intermediate **517**. Epimerization of the C9' (massadine numbering) stereocenter was performed under acidic conditions to deliver **518**. Reduction of the ketone proceeded with axial attack by the hydride reagent to deliver alcohol **519**. Treatment of **519** with titanium isopropoxide and TBHP induced the bioinspired skeletal rearrangement proposed by Scheuer[117,118] to give fully functionalized cyclopentane **520**. An additional six steps were required to complete the synthesis of (−)-massadine.

The Chen[119] synthesis of (−)-axinellamines A and B takes advantage of a similar ring-contraction (Scheuer rearrangement) to give the fully functionalized cyclopentane core (Scheme 68). The route begins with **516**, which was prepared as shown above. This intermediate was advanced six steps to **521**. Basic epimerization of the C12 (axinellamine numbering) stereocenter delivered **522**. Ketone reduction proceeded with axial attack of hydride to give **523**. The oxidative cyclization delivered **524** and the spiro-cyclic core of the axinellamines. Installation of the chlorine atom with retention of configuration was accomplished by activation of the alcohol as the sulfonate and treatment with nucleophilic chloride to give **525**. Mechanistically, the reaction proceeds through intermediate aziridine **525**. Advanced intermediate **526** has the appropriate substitution and stereochemistry for the axinellamines, and the synthesis was completed in an additional 13 steps.

The formal synthesis of (±)-gymnomitrol by Itô[120] employs a skeletal rearrangement of a bicyclo[2.2.2]octane derivative (Scheme 69). The synthesis commences with an alkene isomerization/Diels–Alder cycloaddition between diene **527** and cyclopentene-1,2-dicarboxylic anhydride (**528**). Refluxing in toluene with TsOH delivered *endo*-adduct **529** as the only product. Four functional group manipulations were used to convert cycloaddition product **509** to intermediate **530**. Desulfurization gave intermediate **531**. Epoxidation with *m*CPBA gave epoxy alcohol **532**. Upon alumina chromatography a skeletal rearrangement took place to deliver keto-alcohol **533**. Finally, Jones oxidation yielded diketone **534,** which intersected a synthetic intermediate previously taken to



Scheme 66. Total Synthesis of (+)-Mannostatin A (Vasella, 2003).



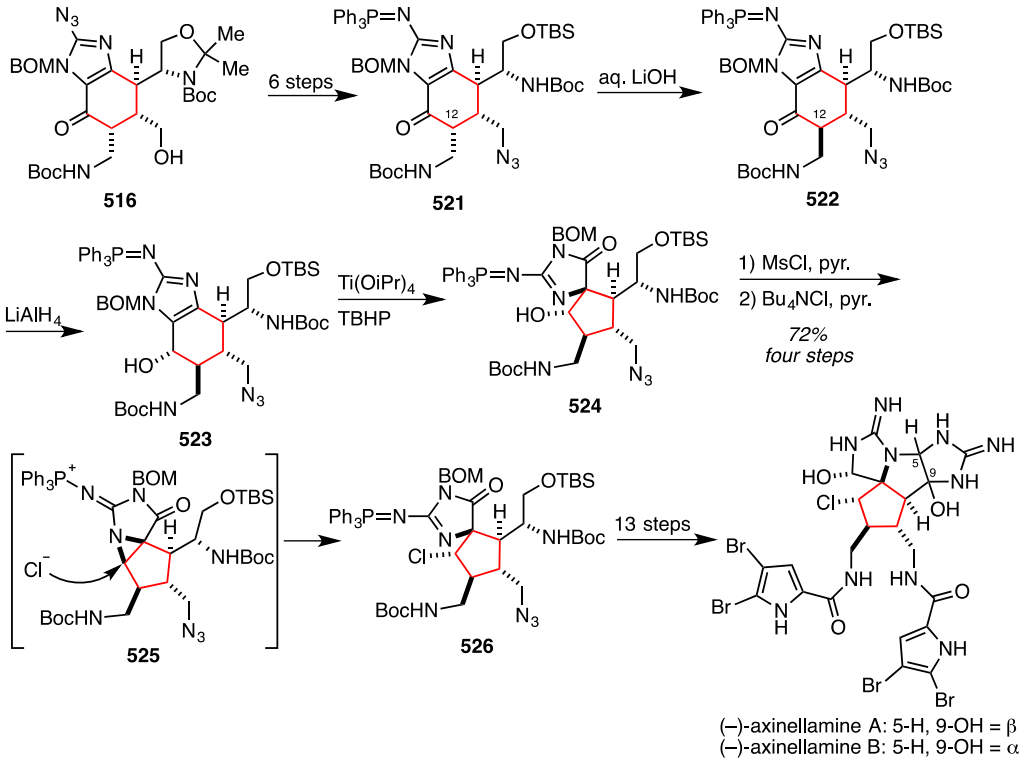
Scheme 67. Total Synthesis of Massadine (Chen, 2014).

(±)-gymnomitrol by Coates.[121]

In an approach toward gelsemine, Fleming[122] assembles a fully functionalized cyclopentane using a rearrangement from a bicyclo [2.2.2]octane into a bicyclo[3.2.1]octane (Scheme 70). The route commences with a Diels–Alder reaction of diene **535** and β-nitroacrylate to give desired bicycle **536** in a 1:1 diastereomer ratio. Functional group manipulation was performed over five steps to deliver **537**. Epoxidation with perbenzoic acid **538** occurred unexpectedly on the more hindered face to give **539**. Opening of the epoxide with magnesium bromide gave a bromohydrin (**540**), which underwent a skeletal rearrangement to give **541**. This material was advanced to tricyclic intermediate **542** over four steps. While a fully functionalized cyclopentane was formed in **543**, the substitution pattern needed to be adjusted for gelsemine. Oxidation of the secondary alcohol and addition of vinylmagnesium bromide gave allylic alcohol **543**. Chloride **544** was obtained by reaction with thionyl chloride. Presumably, chloride substitution of the alcohol was followed by an S_N2' process resulting in the trisubstituted alkene. Substitution of the allylic chloride gave an allyl silane, and treatment with trioxane in formic acid induced an allyl silane addition to an acyl iminium ion. This reaction gives advanced intermediate **545**, which contains a fully functionalized cyclopentane and the core molecular architecture of gelsemine.

Romo[123,124] developed an enantioselective strategy to the spirocyclic core of palau'amine in which a chlorination/ring contraction sequence delivers a fully functionalized cyclopentane (Scheme 71). A Diels–Alder reaction of vinyl imidazolone **546** with the chiral lactam **547** provides the tricyclic product with good control of regioselectivity. Under the conditions of the cycloaddition the double bond migrates regenerating the imidazolone ring. Silyl protection of the primary alcohol delivers **548**. An oxidation/elimination sequence performed with dimethyldioxirane provides carbinolurea **549**. Ring contraction with *N*-chlorosuccinimide furnished the chlorinated spirocyclic hydantoin and fully functionalized cyclopentane **550**.

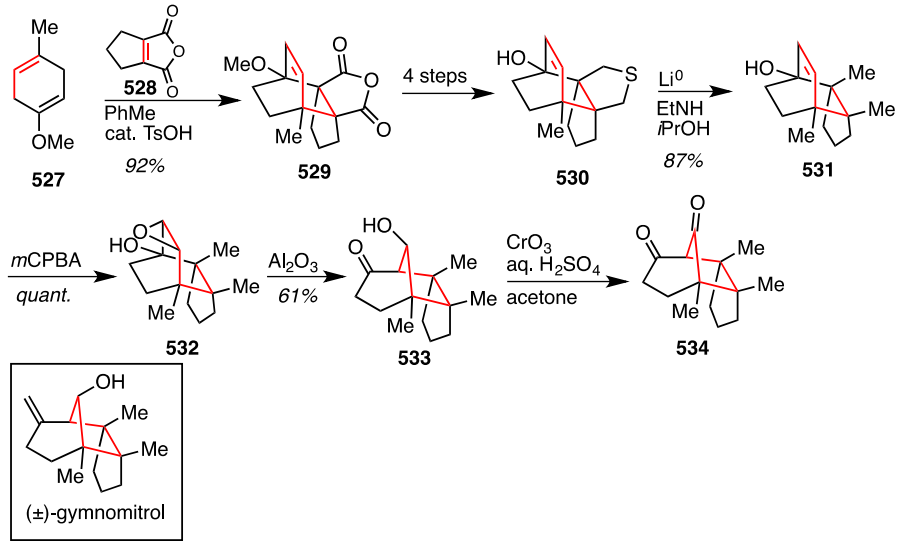
In the synthetic effort towards massadine, Carreira[125] reports a silver-promoted norbornyl skeletal rearrangement to form the cyclopentane of massadine (Scheme 72). The route begins with a



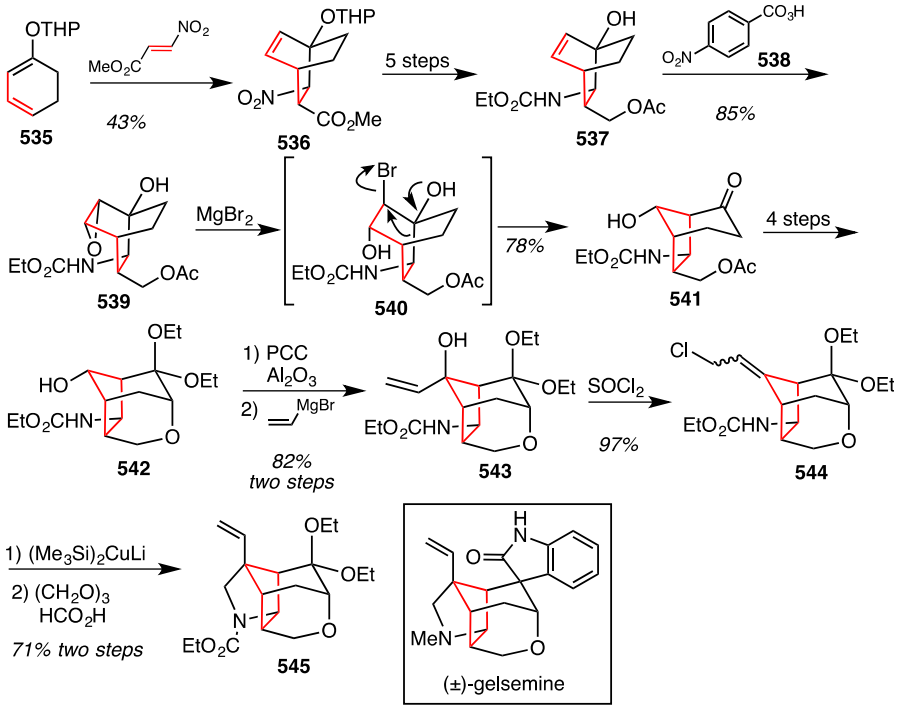
Scheme 68. Total Synthesis of Axinellamines A and B (Chen, 2016).

cycloaddition of cyclopentadiene **551** with dimethyl fumarate delivering norbornylsilane **552**. Bromolactonziation provided tricyclic intermediate **553**. The skeletal rearrangement occurs upon treatment with silver nitrate wherein desilylation and bond migration occurs with elimination of bromide giving intermediate lactone **555**. Cleavage with methanol furnishes alcohol **556**. A Swern oxidation gave ketone **557**, which was advanced to **558** over four steps. Imine formation with 2,4-dimethoxybenzylamine was followed by addition of cyanide in the presence of zinc chloride to deliver iminonitrile **559** with good diastereoselectivity (>95:5). The selectivity can be attributed to addition of TMS-cyanide to the ketone face opposite the benzyloxymethylene groups. This material was advanced over six steps to intermediate **560**. Ozonolysis fragmented the norbornene skeleton. Workup with acetic anhydride and triethylamine resulted in regioselective ester formation,[126] which successfully differentiated the carbonyls to give **561** and completed the core of massadine.

In an alternative route towards, Carreira[127] uses the same skeletal rearrangement to construct the cyclopentane but functionalizes the core using a 4-component-Ugi-reaction (Scheme 73). Ketone **557** underwent an Ugi-reaction with 2,2-dimethoxybenzylamine and 2-nitrophenylisonitrile (**563**) to give



Scheme 69. Formal Synthesis of (±)-Gymnomitrol (Itô, 1979).

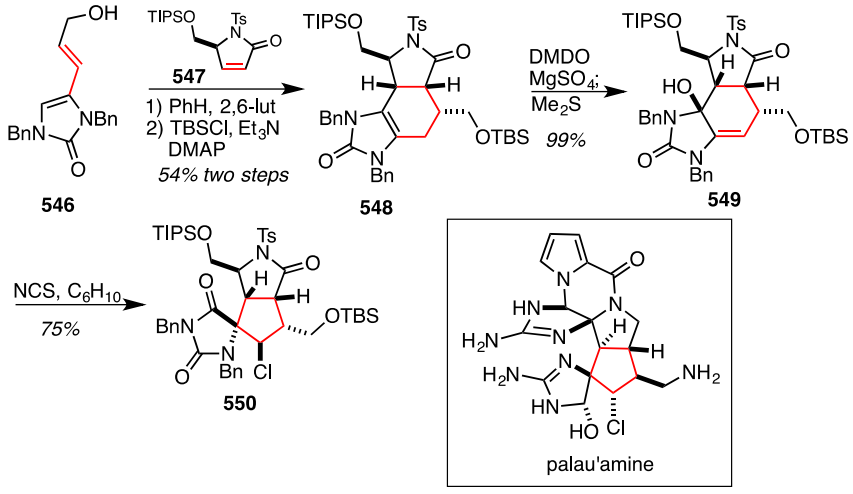


Scheme 70. Synthetic Studies Towards Gelsemine (Fleming, 1988).

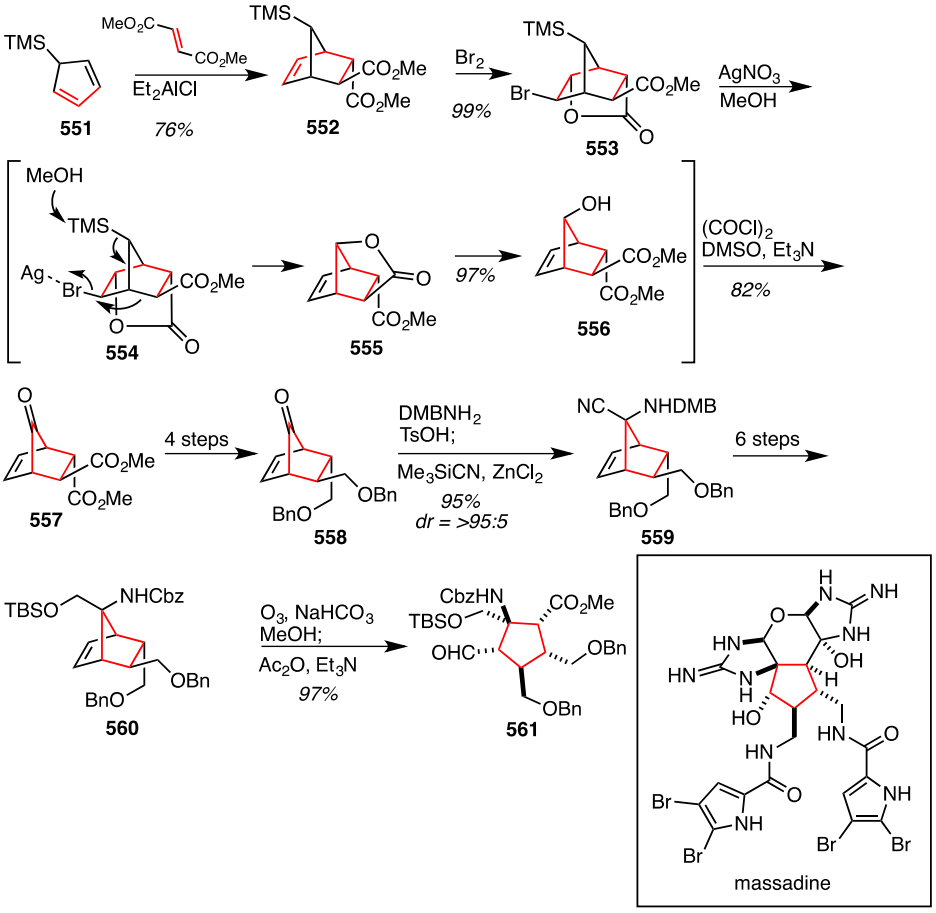
amide **564**. As above, the major diastereomer results from nucleophilic attack on the less hindered imine face. Over the next seven steps this material was advanced to intermediate **565**. Ozonolytic cleavage and workup according to Schreiber's method differentiates the resulting carbonyl groups and gives **566**.[126] A Barton decarboxylation/oxygenation[90] was used to convert the aldehyde to secondary alcohol of **567,** which proceeded with retention of configuration. To complete the core of massadine, the alcohol was silylated and the ester stereocenter was epimerized yielding **568**. This advanced intermediate contains a fully functionalized cyclopentane with appropriate substitution for a massadine synthesis.

5.2. Oxa-di-π-methane rearrangements

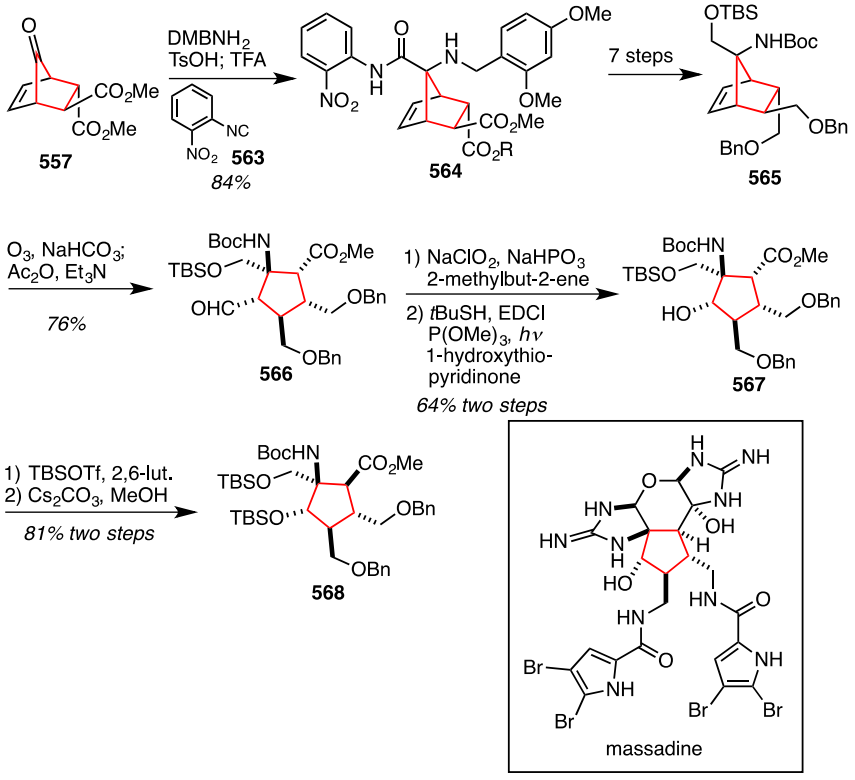
In the first enantioselective synthesis of (−)-coriolin, Demuth[128] utilizes an oxa-di-π-methane rearrangement to assemble the cyclopentane (Scheme 74). The synthesis begins with chiral resolution of racemic diketone (±)-**569** to deliver (−)-**569** over three steps. Methylation of enantiopure **569** was carried out with two equivalents of sodium hydride and methyl iodide; subsequently, an additional equivalent of sodium hydride and 18-crown-6 with excess methyl iodide gave tri-methyl diketone **570**. When this mixture was irradiated in acetone, the oxa-di-π-methane rearrangement occurred to give cyclopentanone **571** with it's α-methyl diastereomer. The unpurified product mixture was alkylated with chloride **572** under standard conditions. Dissolving metal conditions resulted in cyclopropane fragmentation and selective ketone reduction. Finally, oxidative cleavage of the alkene furnished **573**. A base-catalyzed aldol condensation formed the triquinane core. Direct reaction with isopropenyl acetate formed the dienol acetate,



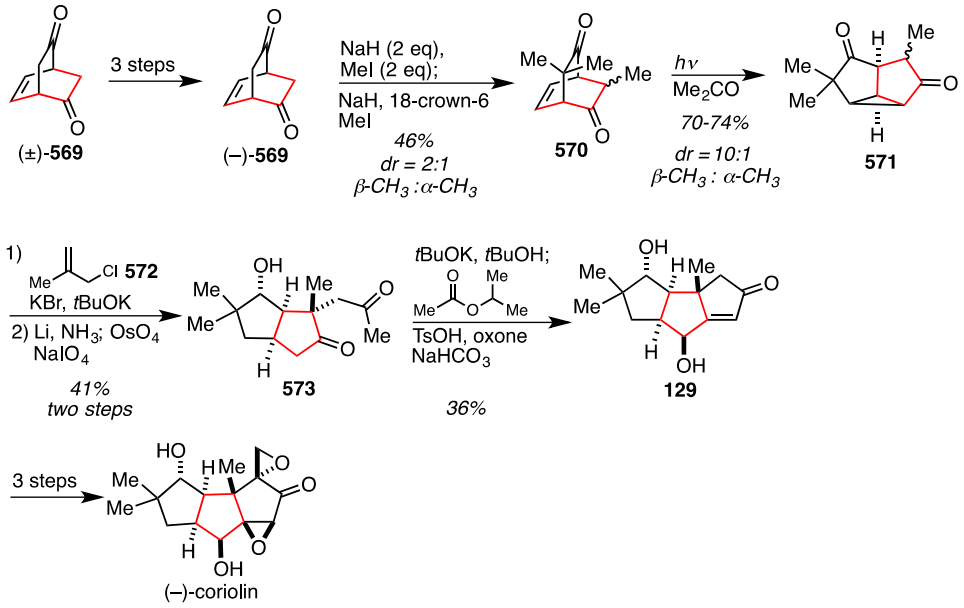
Scheme 71. Synthetic Studies Towards Palau'amine (Romo, 2001).



Scheme 72. Synthetic Studies Towards Massadine (Carreira, 2008).



Scheme 73. Synthetic Studies Towards Massadine (Carreira, 2011).



Scheme 74. Total Synthesis of (−)-Coriolin (Demuth, 1986).

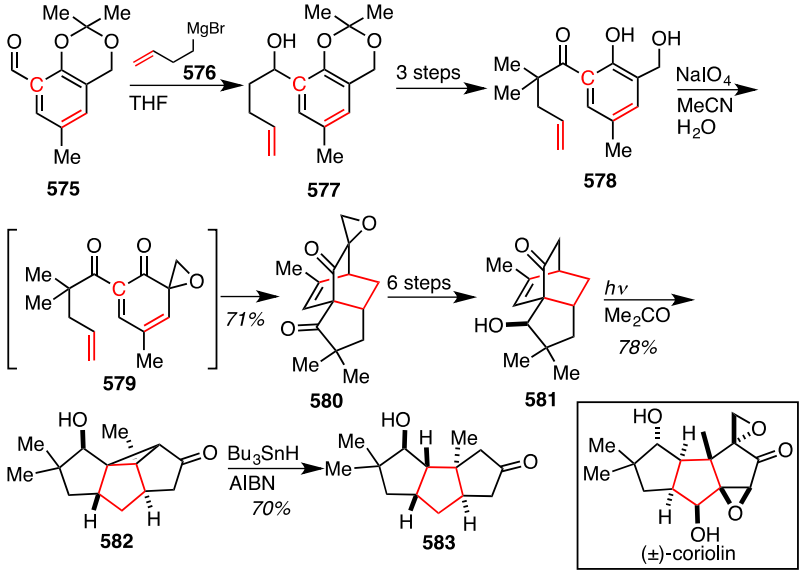
which upon epoxidation and elimination delivered alcohol **129**. The synthesis was completed in an additional three steps following the protocol of Trost.[129]

A photo-induced skeletal rearrangement was employed by Singh[130] to assemble the triquinane core of (±)-coriolin (Scheme 75). The synthesis begins with aryl aldehyde **575**, which underwent organometallic addition of **576** to give intermediate **577**. This material was advanced to β,γ-enone **578** over three steps. Aryl oxidation, under conditons developed by Adler,[131] results in an oxaspirodienone (**579**), which undergoes an IMDA reaction to give the functionalized bicyclo[2.2.2]octenone **580**. This material was advanced to intermediate **561** over six steps. Photochemical rearrangement of **581** in acetone delivered triquinane **582**. Radical cleavage of the cyclopropane delivered **583**, which is an intermediate in coriolin syntheses by both Little[132] and Funk.[28]

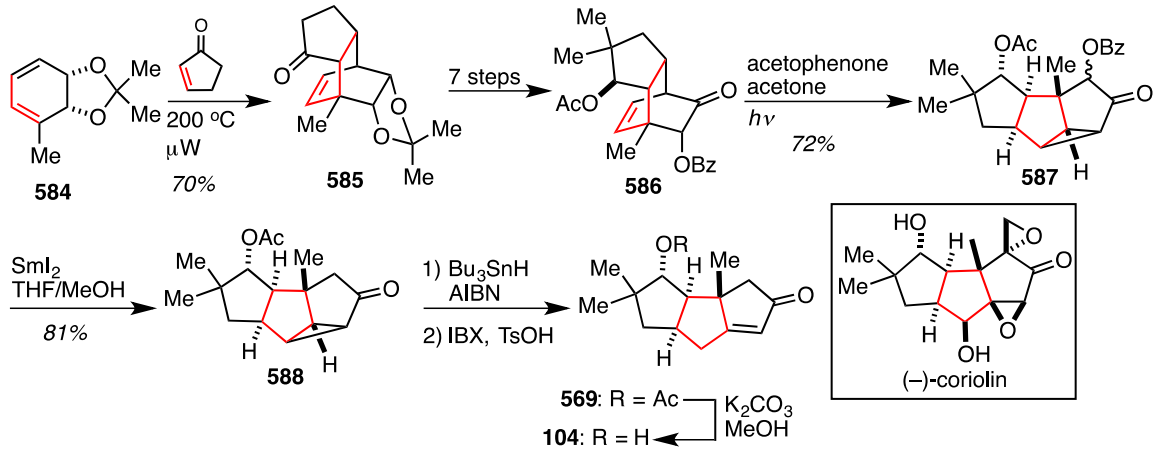
In the formal synthesis of (−)-coriolin by Banwell,[133] a key oxa-di-π-methane rearrangement was used to construct the triquinane scaffold (Scheme 76). The route commences with a Diels–Alder cycloaddition between diene **584** and cyclopentenone to deliver **585**. This cycloadduct was functionalized over seven steps to give photo-rearrangement precursor **586**. Irradiation promoted the oxa-di-π-methane rearrangement to give an inconsequential epimeric mixture of benzoyl esters (**587**). Reductive cleavage of the benzoyloxy group with samarium iodide delivered **588**. Radical cleavage of the cyclopropane ring gave a cyclopentanone that was oxidized with IBX to the corresponding cyclopentenone **589**. Acetate cleavage delivers **104**, which is an intermediate prepared by Trost in a synthesis of coriolin.[129]

5.3. Ring expansions of cyclobutane derivatives

In the total synthesis of (±)-α-caryophyllene alcohol, Corey[134]



Scheme 75. Formal Synthesis of (±)-Coriolin (Singh, 1999).

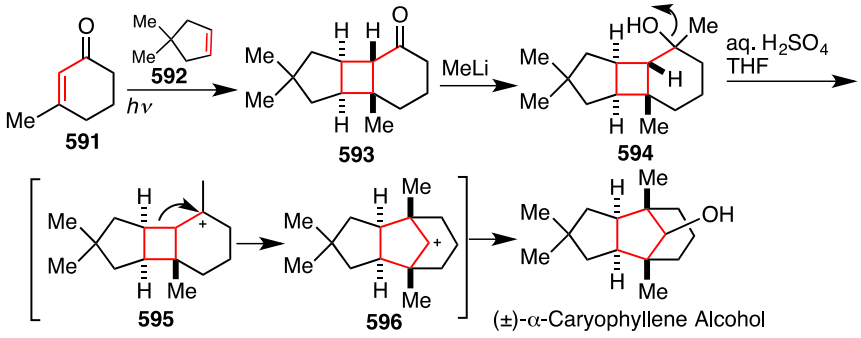


Scheme 76. Formal Synthesis of (−)-Coriolin (Banwell, 2013).

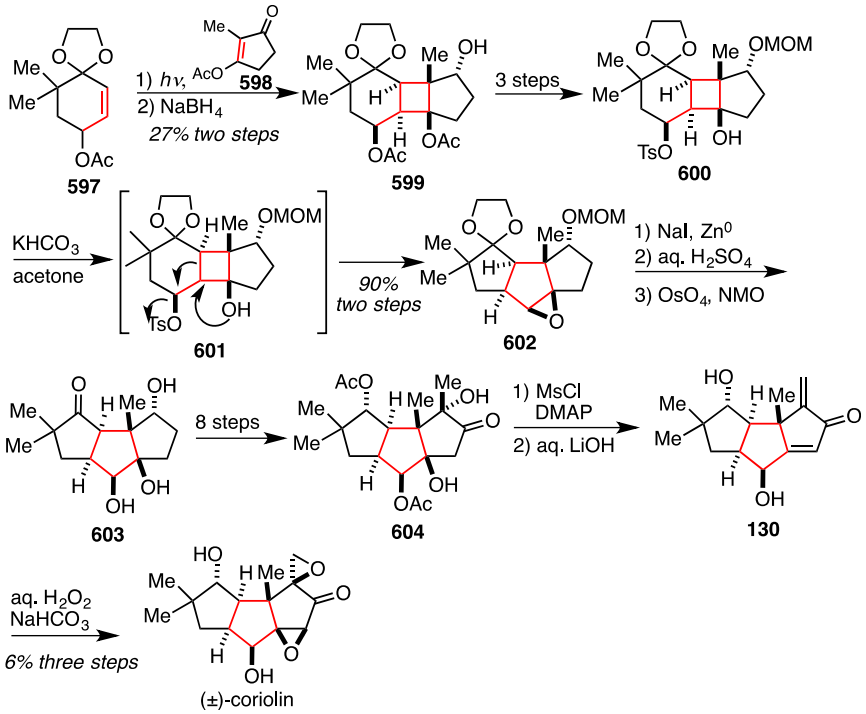
uses a skeletal rearrangement to construct a cyclopentane (Scheme 77). The route begins with a [2 + 2] photocycloaddition of cyclohexenone **591** with 4,4-dimethylcyclopentene (**592**) to give fully functionalized cyclobutane **593** as the major stereoisomer. Addition of methyllithium gave the tertiary alcohol **594**. Treatment of **594** with aqueous sulfuric acid induced fragmentation of the cyclobutane ring and skeletal rearrangement to give the natural product. The mechanism is hypothesized to proceed through intermediate carbocation **595**, which results from loss of water. Fragmentation of the cyclobutane gives a carbocation (**596**) that can be intercepted by water to give α-caryophyllene alcohol.

In the synthesis of (±)-coriolin, Tatsuta[35] constructs the triquinane ring system using a ring expansion (Scheme 78). A stereocontrolled [2 + 2] photocycloaddition of cyclohexene **597** with 3-acetoxy-2-methyl-cyclopent-2-enone (**598**) gives a fully functionalized cyclobutane. This first step sets four of the required five stereocenters for the fully functionalized cyclopentane. Ketone reduction furnishes **599**. Protecting group manipulations and activation of the secondary hydroxyl as a tosylate gave **600**. Treatment of intermediate **600** with base induced a unique skeletal rearrangement to give fully functionalized cyclopentane **602**. Reductive deoxygenation gave a cyclopentene, and the MOM ether and acetonide were hydrolyzed under acidic conditions. Dihydroxylation occurred stereoselectively from the concave face of the bicycle to form the energetically favored *cis*-fused diquinane substructure in **603**. This material was carried forward eight steps to intermediate **604**. Elimination of the two tertiary alcohols gave a cross-conjugated dienone and subsequent removal of the acetates gave intermediate **130**. A non-stereoselective epoxidation gave, among other diastereomers, (±)-coriolin.

The Greaney[135] synthesis of (±)-merrilactone A and (±)-anislactone A employs a Tiffeneau–Demjanov-type ring expansion to construct a cyclopentanone (Scheme 79). The synthesis begins with a [2 + 2] photocycloaddition of 4,5-dimethylmaleic anhydride **605** and dimethylketene acetal to deliver cyclobutane **606**. Reductive opening of the anhydride gives a diol, which is benzyl protected. Treatment with sulfuric acid delivers cyclobutanone **607**. Reaction with ethyl diazoacetate (**608**) in the presence of a Lewis acid effected a Tiffeneau–Demjanov-type reaction yielding cyclopentanone **609**. Transesterification with allyl alcohol was followed by *C*-alkylation of the β-keto ester with allyl bromide. Upon reaction with $Pd(OAc)_2$, a Tsuji-Trost decarboxylation-dehydrogenation sequence proceeded to deliver cyclopentenone **610**. A three-step functional group manipulation sequence gave alcohol **611**. Nucleophilic epoxidation gave a diastereomeric mixture favoring the undesired β-epoxide diastereomer (**612**) with the desired α-epoxide **613**. The β-diastereomer could, however, be recycled through reductive deoxygenation to regenerate enone **611**. Silyl protection of **613** was followed by a stereoselective addition of acetylide **614** on the convex face of the 6-oxabicyclo[3.1.0]hexane to deliver **615** as a single stereoisomer. Basic methanolysis of the silyl group afforded **616**. Cleavage of the epoxide with titanium was followed by a 5-*exo*-dig cyclization onto the alkyne affording a single stereoisomer **617**.[136] A fully functionalized cyclopentane has been synthesized and was elaborated to (±)-anislactone A in six steps. Additionally, advanced intermediate **617** could be advanced over eight steps to complete a synthesis of (±)-merrilactone A.



Scheme 77. Total Synthesis of (±)-α-Caryophyllene Alcohol (Corey, 1965).



Scheme 78. Total Synthesis (±)-Coriolin (Tatsuta, 1980).

5.4. Cope rearrangement

In the synthetic effort toward palau'amine, Gin[137] constructs a fully functionalized cyclopentane through a [3,3]-sigmatropic rearrangement of a bridged tricyclodecadiene (Scheme 80). The synthesis begins with the Diels–Alder reaction of 1,4-benzoquinone and cyclopentadiene (**11**) to give dihydroquinone **618**. Epoxidation of the enone was followed by a Favorskii-like rearrangement of the keto-epoxide to deliver keto-ester **619**. This intermediate underwent enolate alkylation to give **620**, which has a 1,5-diene substructure. This intermediate underwent spontaneous [3,3]-sigmatropic rearrangement to give a dynamic mixture of enone **620** and cyclopentanone **621**. This dynamic mixture was subjected to Meerwein–Pondorf–Verley reduction conditions which selectively consume the more reactive cyclopentanone and converts all the reactive mixture to secondary alcohol **622**. Chloride displacement proceeded with retention of configuration to deliver **623**.[138] This material was advanced three steps to bridged ketone **624**. Oxime formation followed by treatment with thionyl chloride induced a regioselective Beckmann rearrangement to form the lactam, which was subsequently protected as the Boc-carbamate (**625**). Oxidative cleavage of the alkene and reductive workup gave a diol that spontaneously cyclized to a lactone upon treatment with TsOH. Silylation of the primary alcohol delivered **626**. The benzyl ether was removed, and cyclization of the free alcohol with the carbamate and dimethoxymethyl benzene delivered **627**. Hydrolysis of the lactone was followed by methylation of the resulting carboxylic acid. Oxidation of the primary alcohol gave an aldehyde that was epimerized to the more stable *trans* configuration in **628**. The fully functionalized cyclopentane contains the appropriate functionalization and stereochemistry for palau'amine.

6. Aldol and related reactions

The aldol reaction and related reactions of enolate-type nucleophiles with carbonyl electrophiles are versatile processes that have been used in many syntheses of natural products with fully functionalized cyclopentanes. Such reactions have performed well in complex substrates decorated with many functional groups. The diversity in target molecules made with these reactions attests to their value as bond-forming processes.

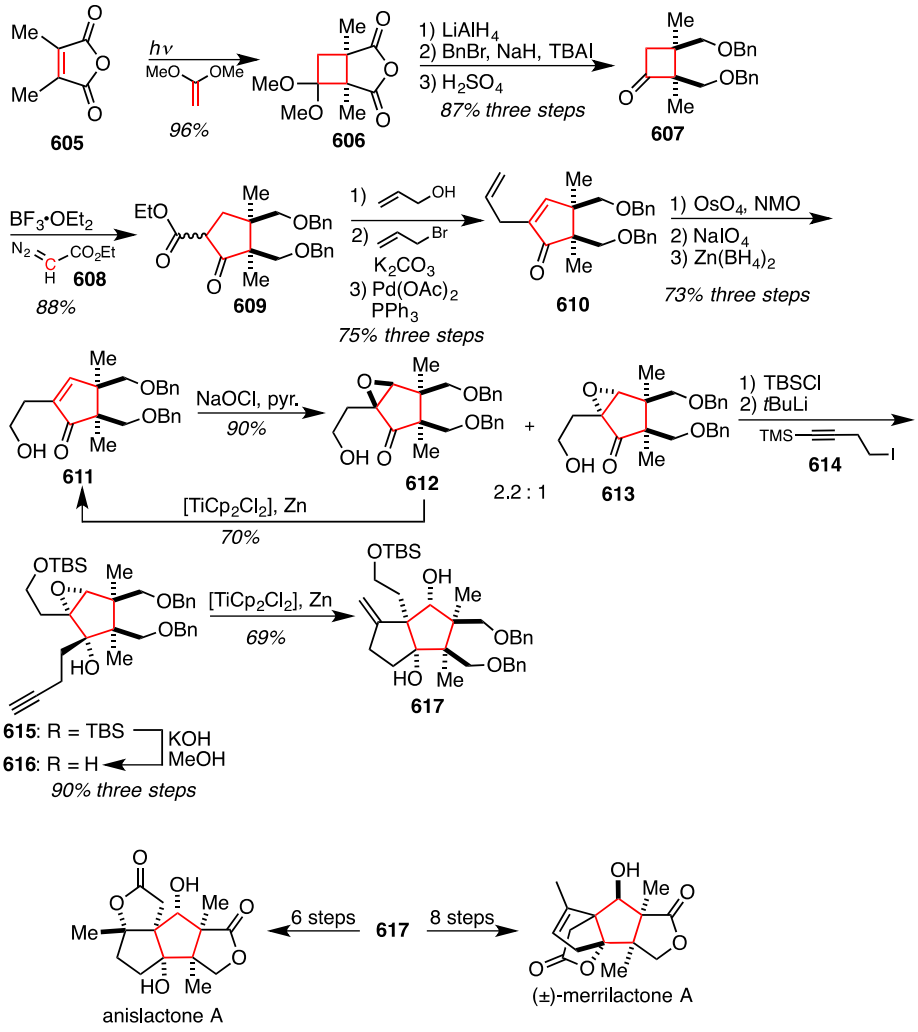
The intramolecular aldol reaction forms a five membered carbocycle when the substrate is either a 1,4- or 1,6-dicarbonyl (Scheme 81). The former synthetic strategy begins with a ketone starting material **629** (eq. 1), which undergoes functionalization (e.g. alkylation) at the α-position to reveal a 1,4-dicarbonyl (**630**). Cyclization gives the five-membered carbocycle (**631**).

The latter strategy (1,6-dicarbonyl aldol) commonly begins with cyclohexenes of the type **632** (eq. 2). Such molecules are often prepared with good control of diastereoselectivity using the Diels–Alder reaction. A subsequent oxidative cleavage reveals the 1,6-dicarbonyl adorned with stereocenters at the intervening carbons (**633**). Aldol condensation with mild buffered-acid conditions gives the five-membered ring architecture (**634**). Typically, the more hindered carbonyl acts as the electrophile.

A particularly striking strategic use of aldol reactions appears in a ryanodol synthesis where no less than three intramolecular aldol reactions are used to prepare two fused fully functionalized cyclopentanes (Scheme 82). The substrate for the final intramolecular aldol is a 1,6-dicarbonyl that is revealed from oxidative cleavage of a cyclohexene prepared by a Diels–Alder reaction.

6.1. 1,4-Dicarbonyl cyclizations

In the total synthesis of (+)-cyclosativene by Piers[139] performs an aldol reaction of a 1,4-ketoester to construct a five-membered ring (Scheme 83). The route begins with known enone **640**, which oxidation to furnish **641**. Conjugate addition of methyl cuprate and acylation of the resulting enolate delivers enol acetate **642**. Ozonolysis, oxidative workup, and methylation of the resulting carboxylic acid gave aldol cyclization precursor **643**. Enolate formation and Diekmann-type condensation delivered a

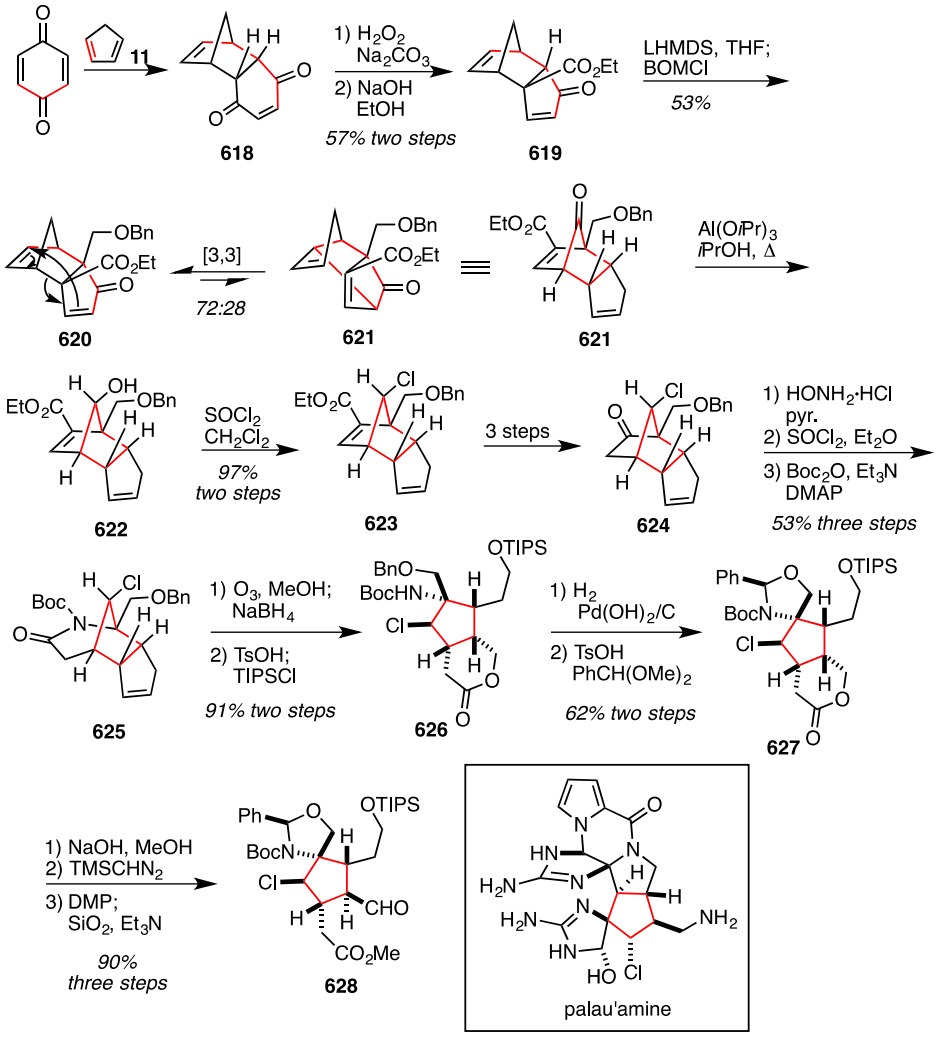


Scheme 79. Total Synthesis of (±)-Merrilactone A and (±)-Anislactone A (Greaney, 2010).

functionalized five-membered ring (**644**). The ketone bearing an acidic α-hydrogen was deprotonated and protected as the isopropyl enol ether. A Wittig olefination was performed on the remaining ketone and hydrolysis of the two enol ethers delivered keto-aldehyde **645**. Wittig olefination of the aldehyde gave alkene **646**. Ketone reduction and dehydration gave a functionalized cyclopentene. Hydroboration-oxidation of the less hindered alkene delivered **647**. Oxidation and hydrazone formation furnished **648**. Treatment with butyllithium formed the lithium salt, which upon heating induced a 1,3-dipolar cycloaddition to deliver pyrazoline **649**. Photolysis of this compound gave (+)-cycosativene displaying a fully functionalized cyclopentane.

In the formal synthesis of (+)-cyclosativene by Yoshikoshi,[140] an intramolecular aldol of a 1,4-dicarbonyl constructs the cyclopentane (Scheme 84). The synthesis begins with intermediate **650** available from (−)-carvone. Consecutive enolate additions to dimethyl carbonate and allyl bromide deliver **651**. Demethoxycarbonylation was performed by heating in DMSO with sodium cyanide. An oxidative cleavage of the allyl group gives keto-aldehyde **652**. Treatment with base induces an aldol reaction of the 1,4-dicarbonyl to form cyclopentane **653** as a mixture of alcohol epimers. Oxidation state adjustment required six steps and gave cyclopentanone **655**. Methylation of the ketone and subsequent alcohol oxidation gave a cyclopentenone, which was dehydrated to a mixture of *exo*- and *endo*-cyclic alkenes. This mixture could be resolved to give the desired *endo*-cyclic alkene by heating in the presence of iodine delivering **656** as the sole product. A Wittig reaction/hydrolysis sequence provided a mixture of aldehydes, which was epimerized with base to the more stable **657**. A second homologation sequence was performed, and the resulting aldehyde was reduced to give primary alcohol **627**. This highly functionalized cyclopentene is an intermediate taken to (+)-cyclosativene by Piers.[139]

In the synthesis of sesquiterpene natural products (±)-longicyclene and (±)-longiborneol, Welch[141] constructs the cyclopentane through a reductive aldol cyclization (Schemes 85 and 86). The synthesis begins with (−)-carvone, which can be transformed into tetrahydroeucarvone **659** over three steps. Enolate formation under thermodynamic conditions and alkylation with chloride **660** delivers keto-olefin **661** as an inconsequential mixture of diastereomers. Oxidative cleavage of the alkene produced keto-acid **662**. Acid-catalyzed lactonization delivered enol lactone **663**. Reductive cleavage of the lactone and aldol cyclization gave cyclopentanone **664**. This compound was discovered to be prone to fragmentation, so the material was immediately subjected to mesylation/elimination to give β,γ-unsaturated ketone **665**. A Wittig reaction installed the methyl enol ether **666**, and hydrolysis gave a mixture of aldehydes that underwent epimerization to the

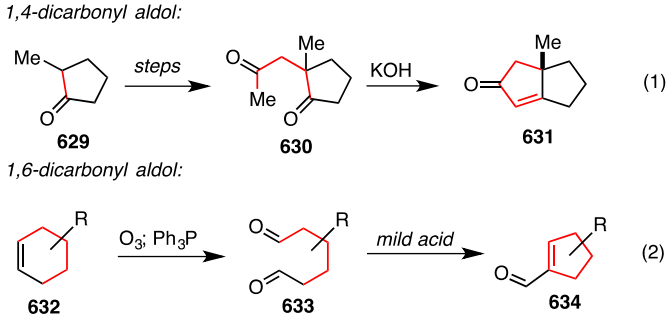


Scheme 80. Synthetic Studies Towards Palau'amine (Gin, 2008).

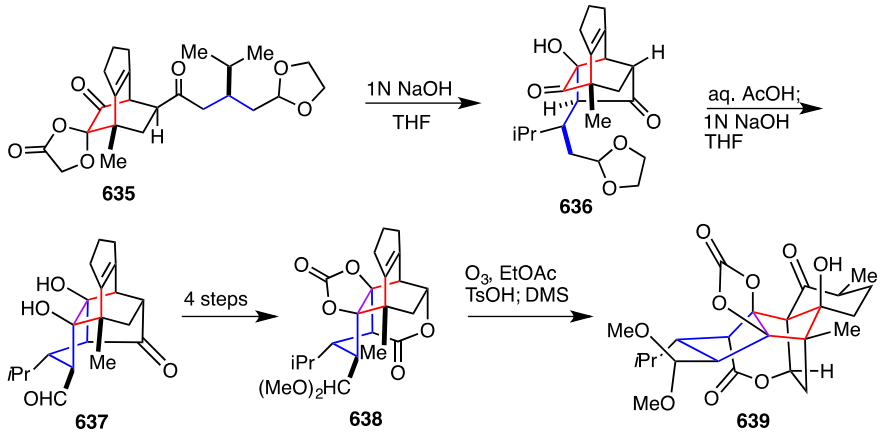
more stable configuration in **667**. This aldehyde served as a key intermediate in the synthesis of both longicyclene and longiborneol. Towards the synthesis of longicyclene, Jones oxidation provided carboxylic acid **668**. Conversion to the acid chloride and addition of diazomethane delivered a diazoketone that underwent copper-mediated cyclization yielding cyclopropyl ketone **669**. This advanced intermediate contains a fully functionalized cyclopentane with the appropriate substitution and stereochemistry for (±)-longicyclene, and an additional three steps completed the natural product.

The synthesis of (±)-longiborneol from intermediate aldehyde **667** continued with a Wittig reaction to give diene **670** (Scheme 86). Hydroboration-oxidation of the diene produced diol **671**. Sulfonylation of the primary alcohol and oxidation of the secondary alcohol delivered ketone **672**. An intramolecular enolate alkylation delivered a tetracyclic intermediate, which is the natural product longicamphor. Finally, a dissolving metal reduction with calcium delivered the fully functionalized cyclopentane of longiborneol.

In the synthesis of tricyclic sesquiterpenoid (±)-gymnomitrol, Welch[142] utilizes an aldol condensation to construct a cyclopentenone (Scheme 87). Cyclopentanone **629** was converted to 1,4-diketone **630** by alkylation with dibromide **673** and oxidation. A base-catalyzed aldol condensation furnished bicyclic cyclopentenone **631**. Conjugate addition of methyl cuprate gives the *cis*-fused diquinane, and trapping of the enolate with allyl chloride gives **674** as an inconsequential mixture of diastereomers. Formation of the thermodynamic enolate was followed by alkylation on the convex face of the bicycle to yield **675** as a single diastereomer. Hydroboration-oxidation of the alkene occurs with concomitant ketone reduction to deliver diol **676**. Jones oxidation gave a carboxylic acid, which was methylated to yield ester **677**. A Dieckmann-type condensation occurs with strong base, and silyl trapping of the enolate provides tricyclic ketone **678**.



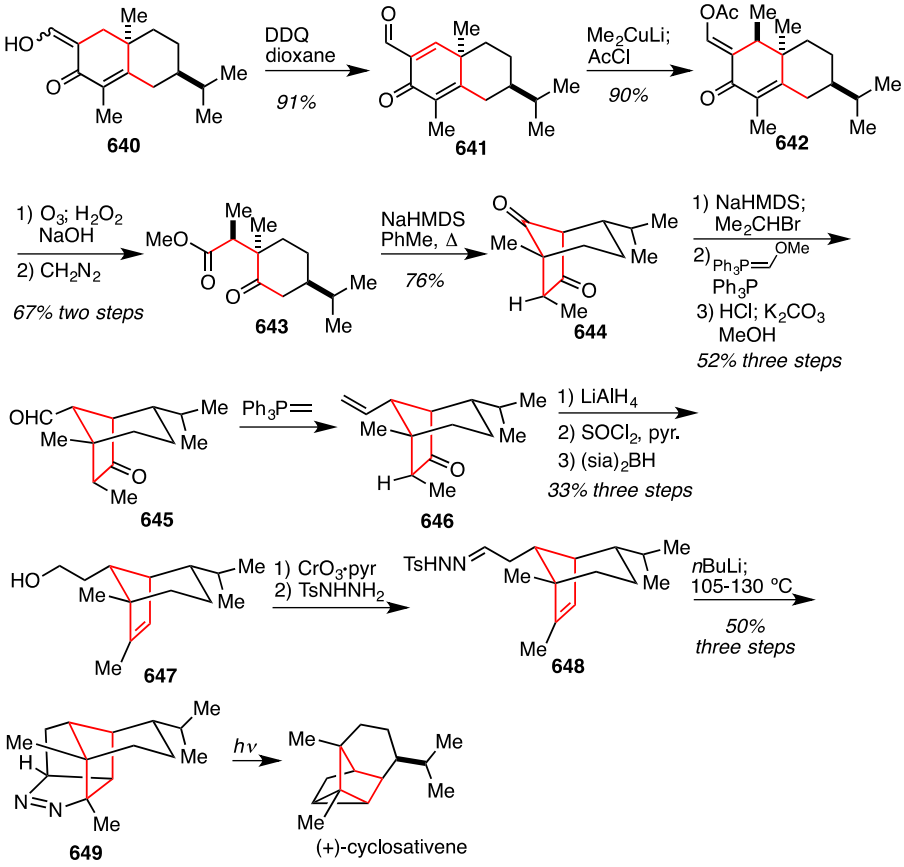
Scheme 81. Aldol Reactions in the Synthesis of Fully Functionalized Cyclopentanes.



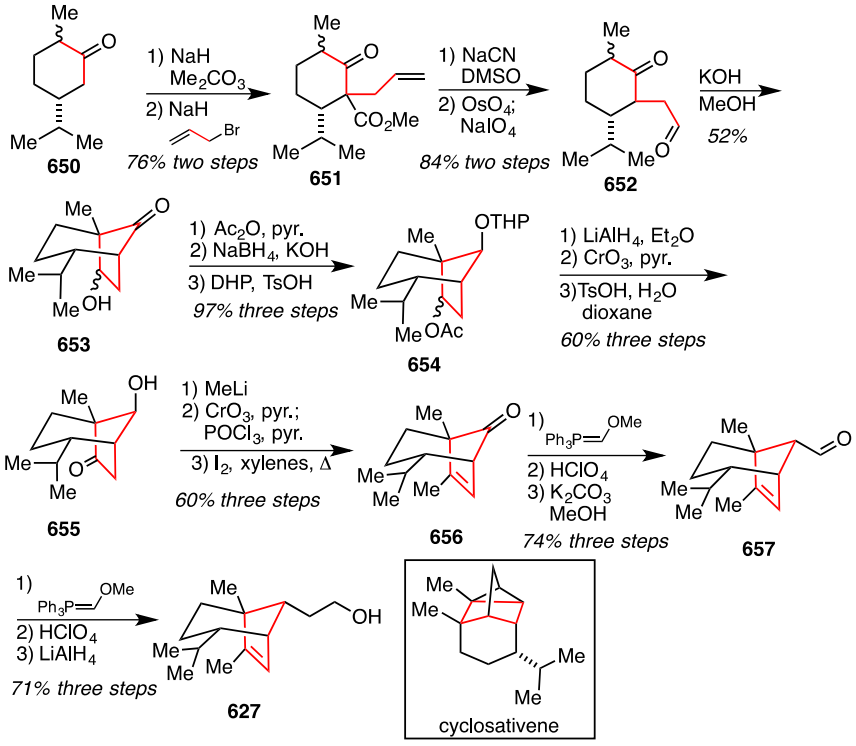
Scheme 82. Aldol Reactions in the Synthesis of Ryanodol.

Stereoselective reduction of the ketone from the less hindered face furnishes a fully functionalized cyclopentane (**679**) bearing the necessary stereochemistry for gymnomitrol. Completion of the synthesis required an additional five steps.

In the synthesis of the tricothecene mycotoxin T-2 tetraol tetraacetate, Colvin[143] builds the cyclopentane ring using an aldol addition of a 1,4-ketoaldehyde (Scheme 88). The synthetic route begins with lactone **680**, which can be advanced to bicyclic intermediate **681** over two steps. Conjugate addition of methyl cuprate occurs from the convex face of the ring system. Epoxidation and a semi-pinacol rearrangement in the presence of ethylene glycol gives **682**. Two successive oxidations gave the keto lactone **683** which existed exclusively in the enolized form. Allylation delivered enol ether **684**. Reduction of the lactone with DIBAL produced an unstable lactol, which could be further reduced with triethylsilane to give deoxygenated **685**. Hydride reduction of the ester was followed by heating in toluene to promote a Claisen rearrangement to give a ketone. Silylation of the primary alcohol gave **686**. Dihydroxylation and oxidative cleavage delivered keto aldehyde **687**. The aldol addition took place with sodium methoxide to give a 4:1 mixture of diastereomers favoring the desired **688** (the configuration of the secondary alcohol is inconsequential). The alcohol was



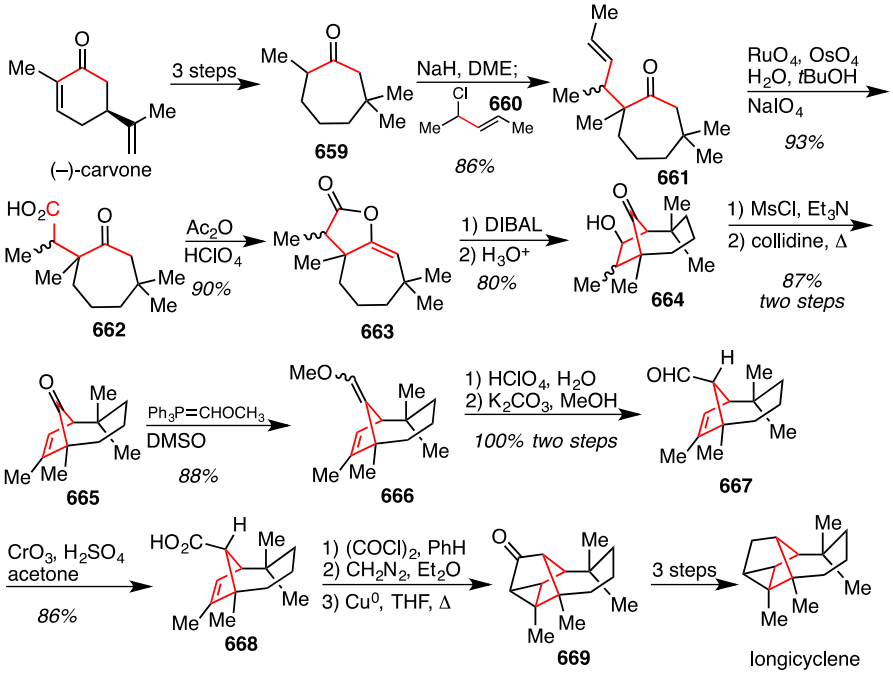
Scheme 83. Total Synthesis of (+)-Cyclosativene (Piers, 1973).



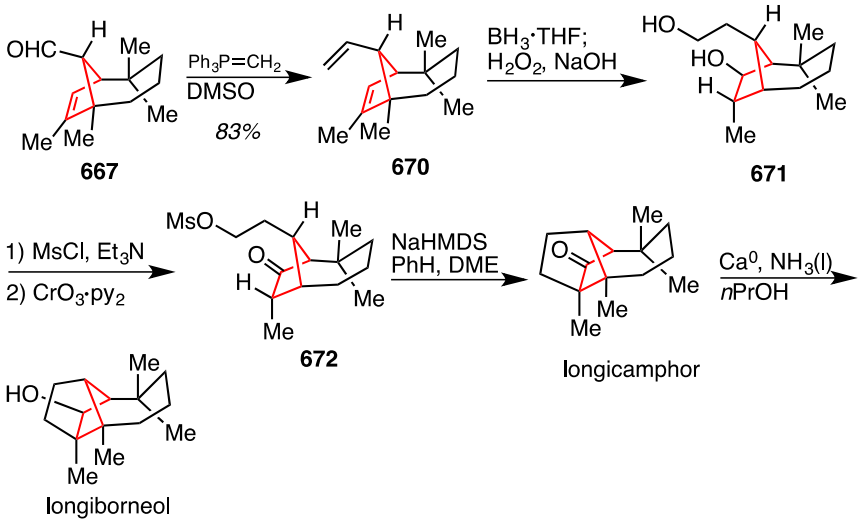
Scheme 84. Formal Synthesis of (±)-Cyclosativene (Yoshikoshi, 1975).

subsequently protected as the pyranyl ether, and olefination of the ketone gave **689**. The pyranyl ether was cleaved and the resulting alcohol oxidized to ketone **690**. The ketone was α-hydroxylated with oxaziridine **691** and then reduced with hydride to give the *trans*-1,2-diol **692**; both additions having occurred from the less substituted *exo* face of the bicycle. Treatment with PPTS selectively deprotected the ketal, and epoxidation with peracid gave fully functionalized cyclopentane **693**. This advanced intermediate was taken to **694**, a relay intermediate in the synthesis of T-2 tetraol, which was completed in an additional four steps.

The sesquiterpenoid (−)-merrilactone A was synthesized by Inoue[144] and utilized a transannular aldol reaction of a cyclooctenedione (Scheme 89). Beginning with the unsaturated γ-lactone **695**, a [2 + 2]-photocycloaddition with *trans*-1,2-



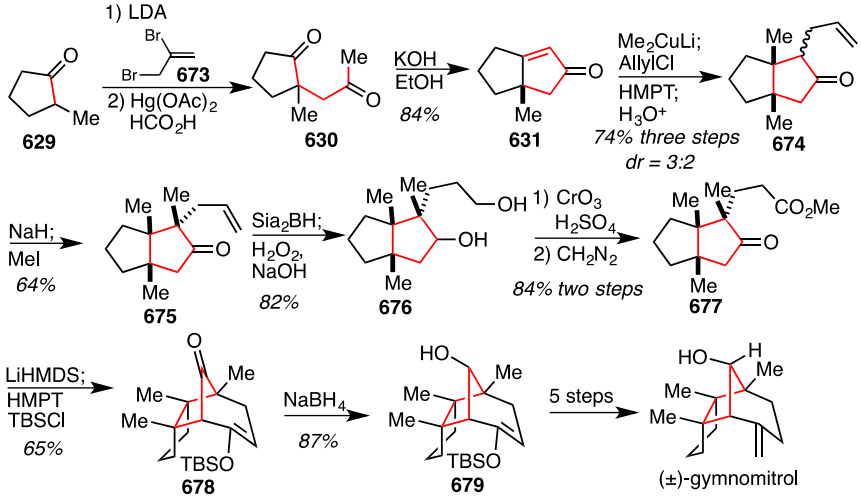
Scheme 85. Total Synthesis of (±)-Longicyclene (Welch, 1974).



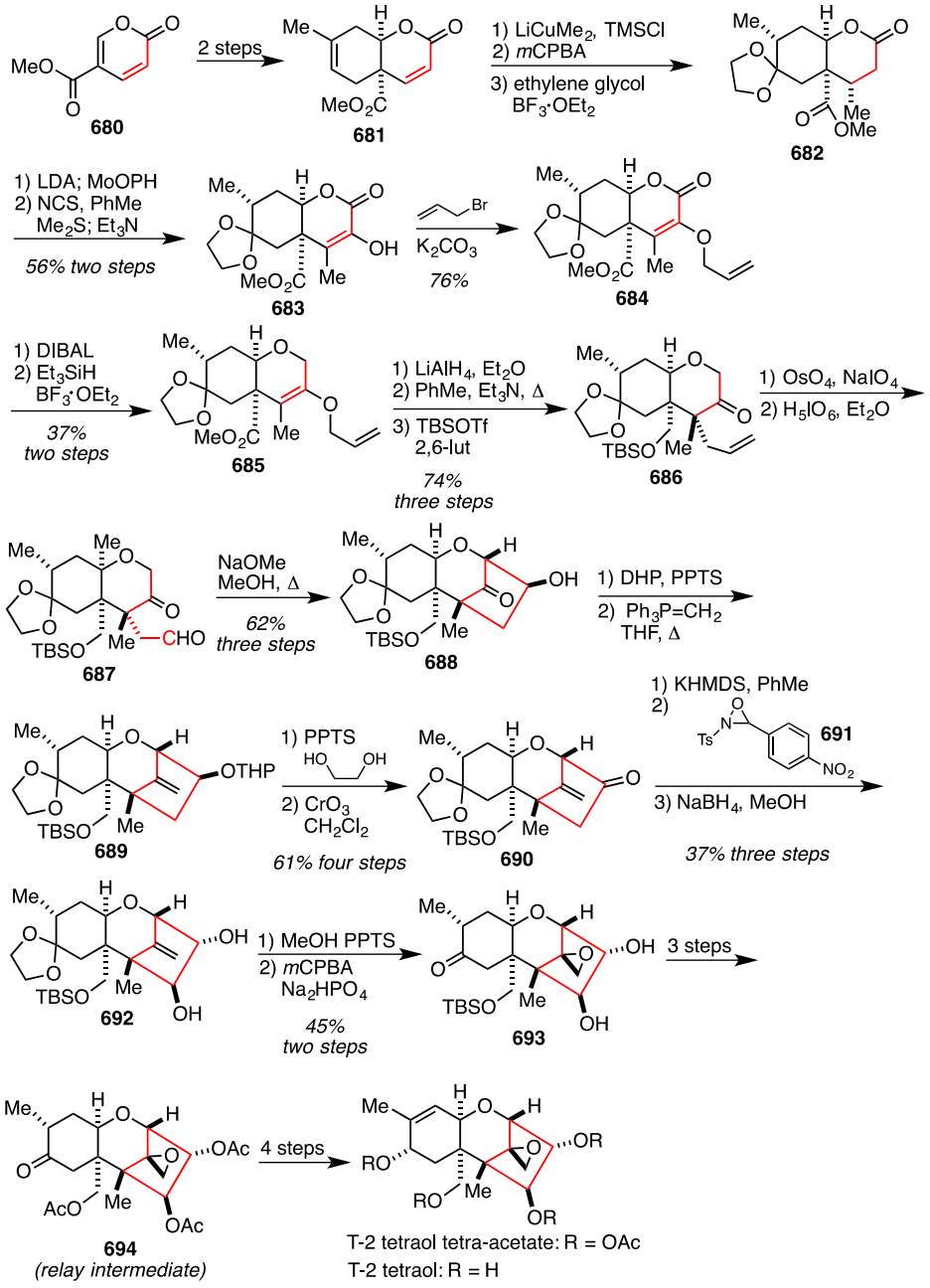
Scheme 86. Total Synthesis of (±)-Longiborneol (Welch, 1974).

dichloroethylene (**696**) successfully establishes the two methyl stereocenters with the desired *syn*-relationship. Dechlorination with zinc delivers bicyclic intermediate **697**. This material was advanced to cyclobutene **698** over six steps. Dihydroxylation, alcohol oxidation, and Grignard addition gives fully functionalized cyclobutane **699**. Ring closing metathesis was followed by oxidative cleavage of the diol yielding a cyclooctenedione (**701**). With carefully optimized conditions, the transannular aldol reaction gave diastereoselective carbon-carbon bond formation to yield the *cis*-fused diquinane **704**. Deprotonation occurs at the most sterically accessible position (distal from the BTB group) to give a favored (*E*)-configured enolate, which exists in conformation **703** that minimizes diaxial interactions of the substituents. Transannular cyclization of **703** leads to the observed product **704** with excellent stereoselectivity. This material was advanced over three steps to α-bromoacetal **705**. Treatment of **705** with radical conditions led to 5-*exo*-trig cyclization in good yield producing a mixture of diastereomers. The mixture could be simplified to isomer **707** by treatment of **706** with $EtOSiMe_3$ and Lewis acid. This material was advanced over six steps to trisubstituted alkene **708**. Reduction of the ketone with sodium in ammonia resulted in a stereoselective reduction to the desired β-hydroxy compound. This sets the final stereocenter in the fully functionalized cyclopentane, giving **710**. This advanced intermediate has appropriate substitution and stereochemistry for (−)-merrilactone A, and the synthesis was completed in an additional two steps.

The first synthesis of (+)-pactamycin was accomplished by Hannesian (Scheme 90).[145] Pactamycin has a densely functionalized cyclopentane core with three contiguous fully substituted stereocenters. The cyclopentane was constructed using an aldol condensation. Commercially available L-threonine was used to synthesize intermediate **711** over three steps. Condensation with unsaturated aldehyde **712** and silylation of the resulting secondary alcohol delivers **714**. The stereochemical outcome can be rationalized by the favored Zimmerman–Traxler transition state model **713**. Intermediate **714** was advanced three steps to ketone **715**. Ozonolysis of the alkene provides the desired 1,4-dicarbonyl relationship. A Mukaiyama-type aldol condensation proceeded in the presence of $TiCl_4$ to yield cyclopentanone **696**. Alcohol elimination yields cyclopentenone **717**. Unexpectedly, nucleophilic epoxidation occurred from the undesired bottom face of the carbocycle. Luche reduction delivered epoxy alcohol **718**. At this



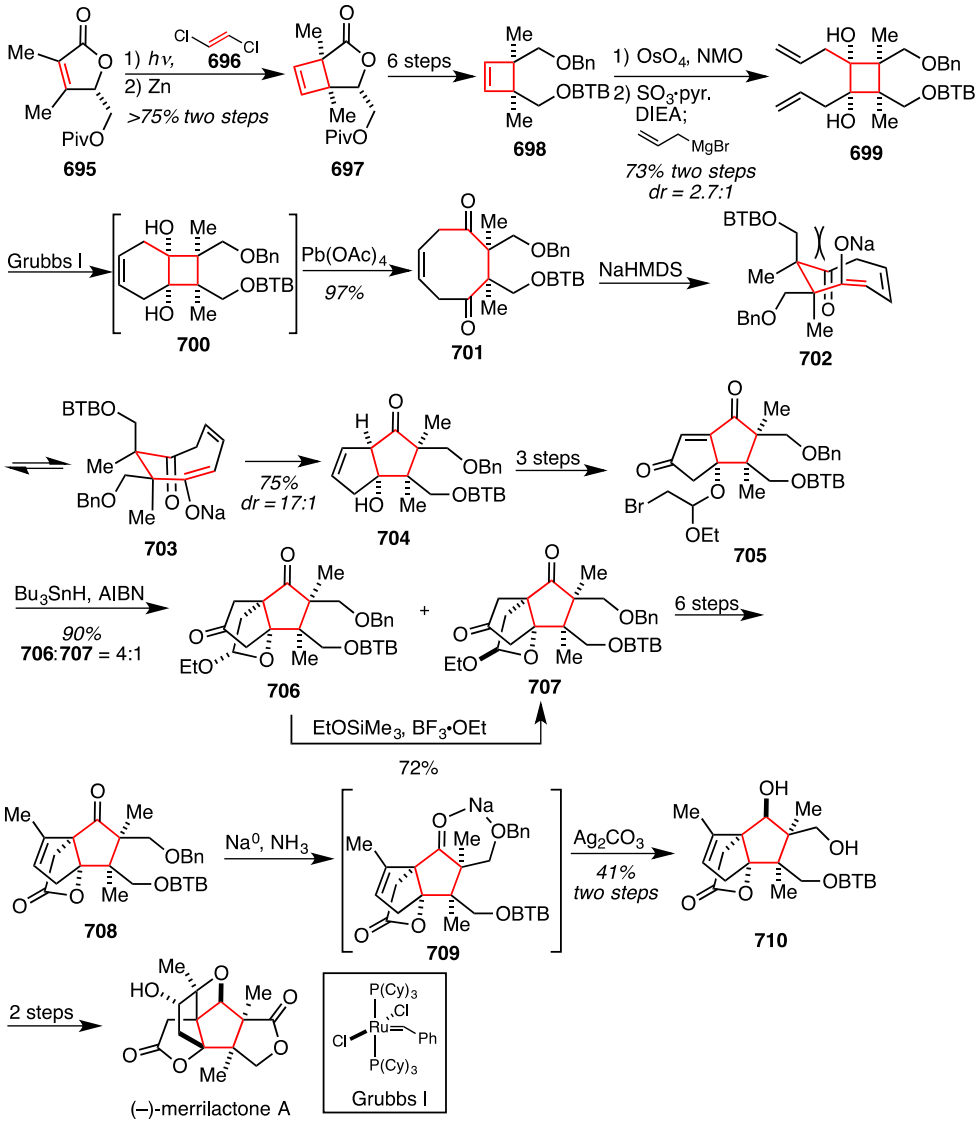
Scheme 87. Total Synthesis of (±)-Gymnomitrol (Welch, 1979).



Scheme 88. Total Synthesis of T-2 Tetraol Tetraacetate (Colvin, 1990).

stage, it was known that an inversion of the epoxide would be necessary to complete the synthesis of pactamycin. An invertive displacement of the secondary alcohol generated azide **719** with the required nitrogen stereochemistry. A three-step sequence (TES removal, oxidation, Grignard addition) delivered tertiary alcohol **720** as a single diastereomer. The epoxide inversion began with liberation of the primary alcohol with fluoride. Treatment of the epoxy alcohol with zinc triflate induces a Payne rearrangement to give an intermediate spiro-oxirane, which is subsequently opened by acetic acid giving **721**. The acetate-protected alcohol was converted to the corresponding TBDPS ether. Treatment of the diol with triflic anhydride led to Williamson-type epoxide formation yielding **722**. Finally, opening of the epoxide with aniline **723** gave advanced intermediate **724**, which has the desired substitution and stereochemistry on the five-membered ring of pactamycin. Completion of the synthesis required an additional ten steps.

In the total synthesis of pactamycin, Johnson[146] used an aldol condensation to form a highly functionalized cyclopentenone (Scheme 91). The synthesis begins with a cinchonidine catalyzed Mannich reaction of diketone **725** and imine **726**. When catalyst **727** was employed, product **728** could be obtained with good enantioselectivity. Desymmetrization of the Mannich product was accomplished using a hydride reduction where addition of hydride to a lithium chelate of **728** occurs away from the sterically large urea group. TBS protection gives **729**. An intermolecular aldol reaction with formaldehyde homologated the ketone. Oxidative cleavage of the alkene delivers the 1,4 dicarbonyl relationship in **730** necessary to deliver a cyclopentenone. Reaction with sodium methoxide promotes an aldol condensation delivering **731**.

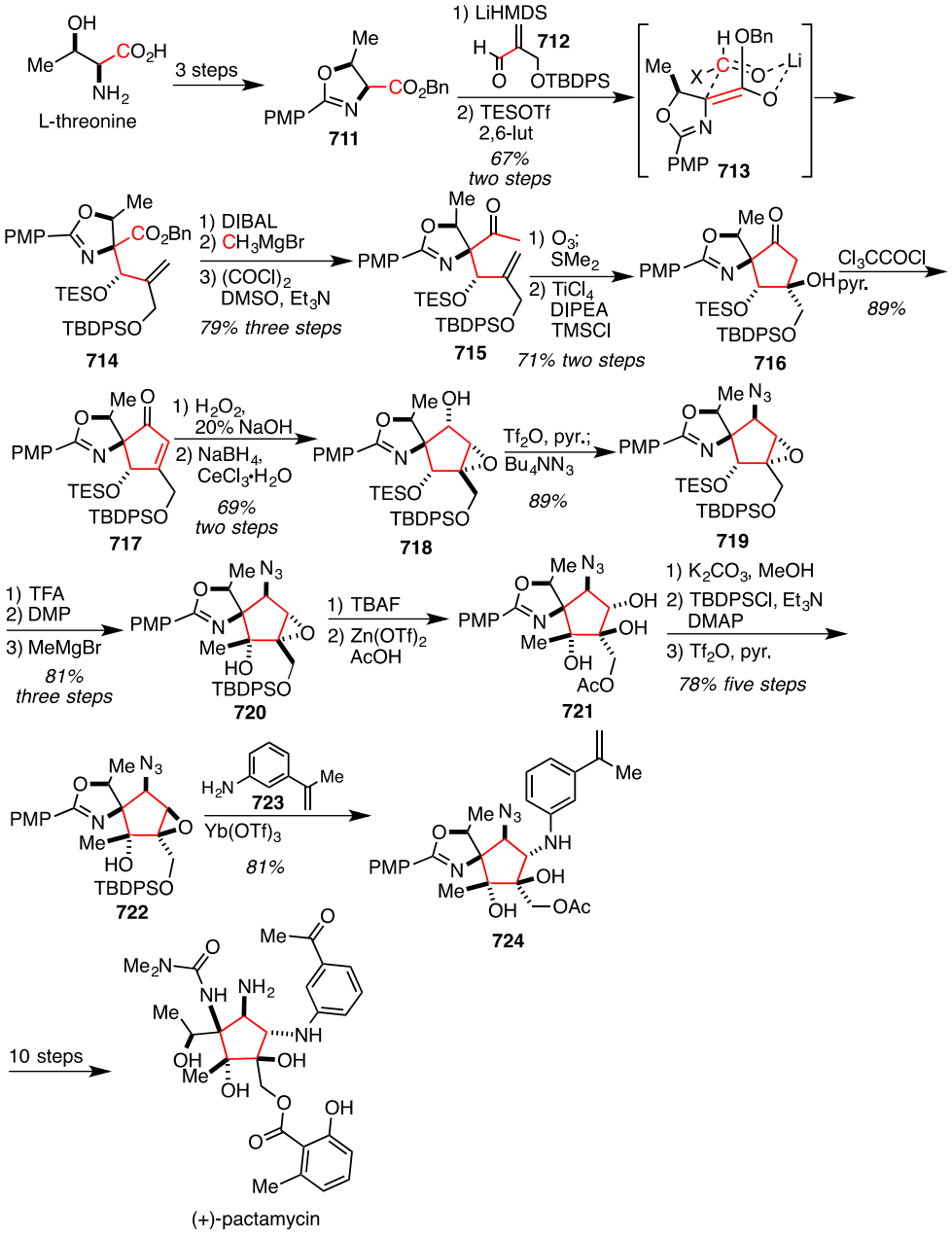


Scheme 89. Total Synthesis of (−)-Merrilactone A (Inoue, 2006).

Nucleophilic epoxidation on the same face as the nitrogen groups yields **732** in high diastereoselectivity. Silylation of the primary alcohol with the sterically demanding TBDPS group shielded one reactive diastereoface of the ketone, and addition of methyl Grignard led to the desired tertiary alcohol stereocenter on **733**. Finally, nucleophilic opening of the epoxide with 3-acetylaniline (**734**) yielded the fully functionalized cyclopentane **735**, which contains the desired molecular architecture of pactamycin. An additional three steps was required to complete the natural product.

Corey[147] reported an approach to gibberellic acid using an aldol of a 1,4-ketoaldehyde that was an improvement over their previously published route,[151] which used the aldol of a 1,6-dicarbonyl (Scheme 92). As such, this effort represents a formal (or second generation) synthesis of gibberellic acid. This route begins with the Horner–Wadsworth–Emmons olefination of ketone **736** with ylide **737**. Vinyl cuprate conjugate addition occurs to give an inconsequential mixture of diastereomers, and the product mixture undergoes oxidative cleavage to give 1,4-ketoaldehyde **738**. An aldol condensation in ethanolic sodium hydroxide furnishes spiro enone **739**. This material was advanced to the ketal **740** over six steps. Treatment with potassium *tert*-butoxide induced intramolecular alkylation to give **741**. Intermediate **741** was converted to ketone **742** over 10 steps. Selective formylation at the least hindered α-position provided **743**. Methylation of the enol tautomer **743** gave (*E*)-enol ether **744** in a 6:1 ratio with its geometrical isomer. This mixture was formylated and the aldehyde was reduced to give **745**. Subsequent ketone reduction delivered diol **746** as a mixture of alcohol epimers. Treatment with oxalic acid promoted formation of enal **747**. Finally, standard Wittig olefination completed the second generation synthesis of **748**.

In the synthetic effort towards delphinine, Wiesner[148] used an intramolecular aldol addition to create the central five-membered carbocycle of the target (Scheme 93).[149] The methoxy tetralone starting material (**749**) underwent consecutive with allyl bromide and BOMCl to give **750**. Subsequent oxidative cleavage gave aldol substrate **751**. A base-catalyzed aldol reaction constructed the five membered carbocycle (**752**). This tricyclic intermediate was functionalized over 12 steps to **753**. Amination with Raney nickel in methanolic ammonia proceeded to deliver the desired amine **754** with *dr* = 10:1. The unpurified amine was acetylated, the benzyl groups were removed by hydrogenolysis, and the diol was oxidized

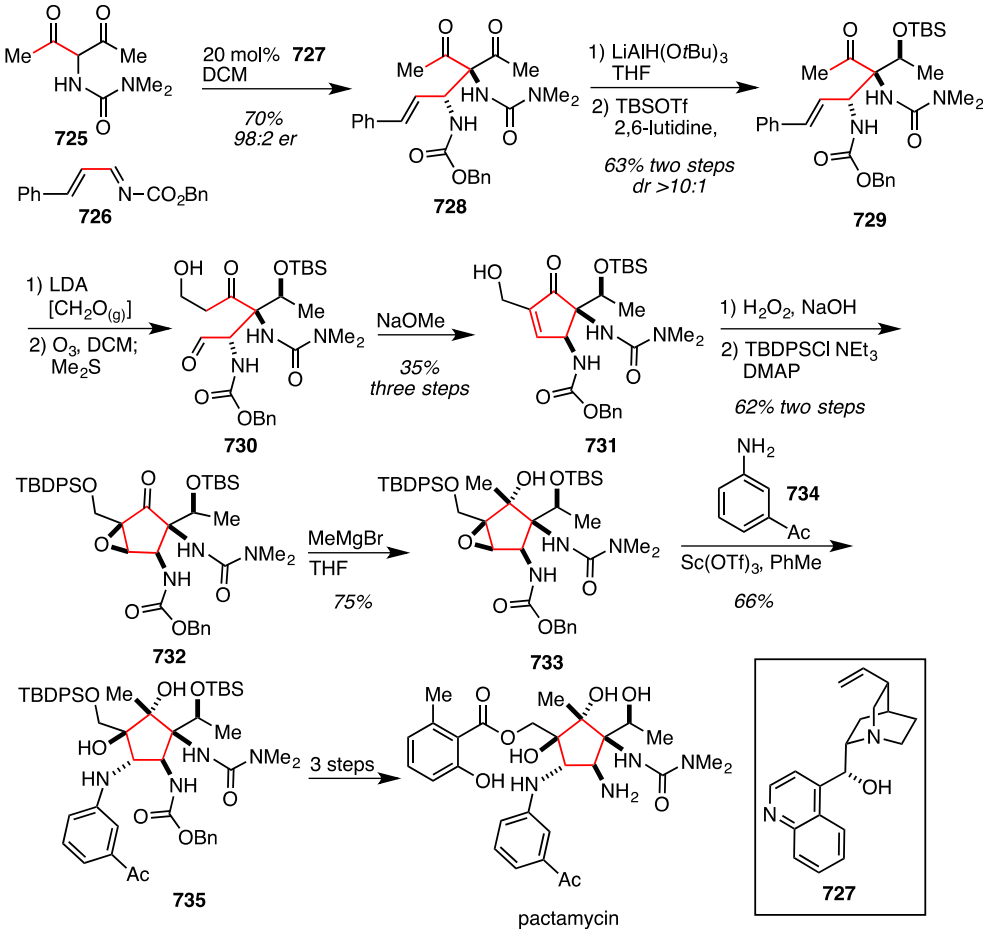


Scheme 90. Total Synthesis of (+)-Pactamycin (Hanessian, 2012).

to the diketone **755**. Heating the diketone with potassium cyanide promoted a sequence of reactions that resulted in the fully functionalized cyclopentane **759**. First, aldol condensation delivered an α,β-unsaturated ketone, which was followed by a stereoselective conjugate addition of cyanide. Subsequent hydrolysis of the nitrile provided an amide, which cyclized to the lactamol **759**. Treatment of this intermediate with acidic methanol opened the lactamol to give ketone **760**. Hydride reduction gave a separable mixture of diastereomers containing **761**. This advanced intermediate contains the central five-membered ring of the delphinine-type alkaloids with appropriate substitution and stereochemistry for delphinine.

6.2. 1,6-Dicarbonyl cyclizations

The synthesis of (±)-gibberellin A_{15} was completed by Nagata[150] and built a fully functionalized cyclopentane using an aldol cyclization of a 1,6-ketoaldehyde (Scheme 94). The synthesis begins with tricyclic ketone **762** which underwent hydrocyanation to give a mixture of *cis*- and *trans*-cyano ketones. Recrystallization of the mixture in the presence of acid caused epimerization to the more stable *trans* isomer, which was isolated as a single product (**763**). This product was advanced to amine **764** over four steps. Birch reduction gave a dienol ether, and the amine was activated as the sulfonamide. Upon acidic workup, the dienol ether isomerized to cyclcohexenone **765**. To prepare the ketoaldehyde for the aldol cyclization, the cyclohexenone was converted to the dienol and reduced to give a mixture of hydroxyl-olefin isomers. Oxidative cleavage of the alkene gave the 1,6-ketoaldehyde (**766**) that cyclized to cyclopentane **767** upon contact with neutral alumina. This material was advanced four steps to intermediate **768**. The final substituent on the fully functionalized cyclopentane was installed by elimination of the tertiary alcohol to give enone **769**

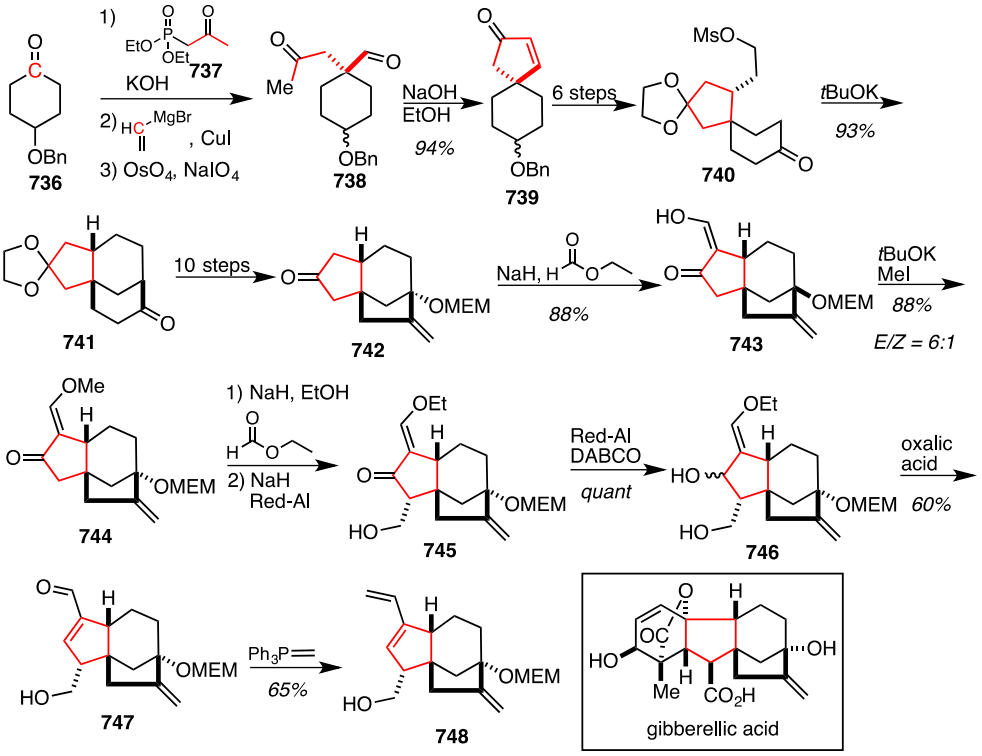


Scheme 91. Total Synthesis of (+)-Pactamycin (Johnson, 2013).

followed by hydrocyanation to give the *cis*-cyano ketone **770**. This advanced intermediate contains the appropriate functionality and stereochemistry for gibberellin A_{15} and the synthesis was completed in an additional 20 steps.

The Corey[151] synthesis of (+)-gibberellic acid commences with a Diels–Alder reaction between quinone **751** and *trans*-2,4-pentadiene-1-ol to give **772** (Scheme 95). This material was carried forward to tricyclic intermediate **773** over 10 steps. Dihydroxylation followed by oxidative cleavage furnishes 1,6-dialdehyde **774**. When treated with dibenzylammonium trifluoroacetate an aldol condensation gave the desired α,β-unsaturated aldehyde **775** and constructed the five-membered carbocycle. Olefination with methylenetriphenylphosphorane provided a diene, and acidic removal of the THP ether furnished **748**. The alcohol functional group was deprotonated and acylated with *trans*-2-chloroacrylyl chloride (**776**) to give an unsaturated ester **777**. When heated to 160 °C, an *endo*-selective Diels–Alder cycloaddition proceeded to give lactone **778** as the sole stereoisomer. Treatment of **778** with base and methyl iodide led to chloride elimination and enolate alkylation. Removal of the MEM protecting group with anhydrous zinc bromide yields (±)-**779**. This racemic intermediate was resolved by formation of two diastereomeric carbamates with (−)-α-phenethylamine, separation by chromatography, and hydrolysis to give (+)-**779**. Hydrolysis of the lactone was followed by oxidation to the diacid with sodium ruthenate in sodium hydroxide. During the oxidation the intermediate acid aldehyde undergoes base-catalyzed epimerization to the more stable β-formyl derivative before being oxidized to the diacid. Chemoselective esterification gave **780**. Hydroxylactonization was achieved by treatment with *m*CPBA. Saponification of the intermediate lactone, performed under basic conditions, was followed by iodolactonization to give **781**. This synthetic intermediate contains a fully functionalized cyclopentane with all the required stereochemistry for (+)-gibberellic acid. The synthesis was completed in an additional three steps.

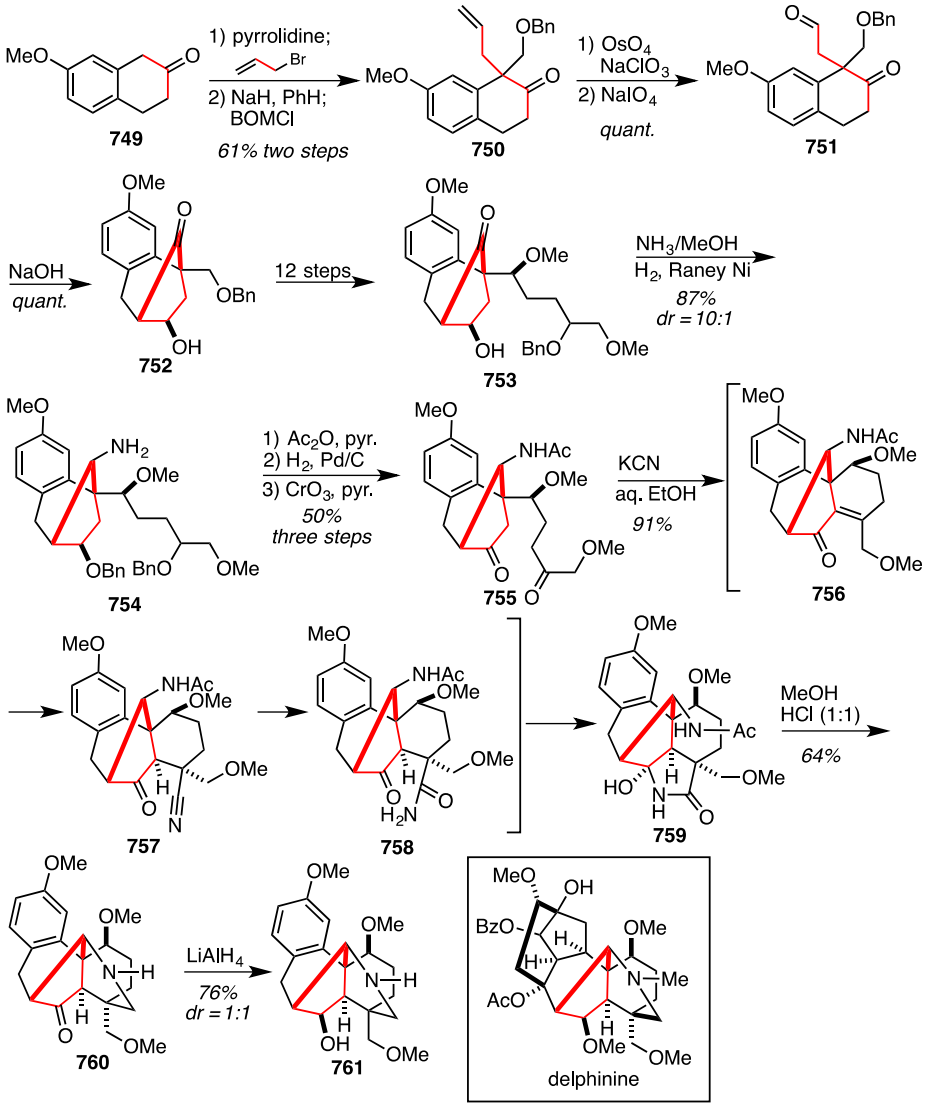
The first total synthesis of (+)-ryanodol was completed by Deslongchamps[152] in 1979 (Scheme 96). The construction of the two fully functionalized cyclopentanes was performed in separate steps each using an aldol reaction. The synthetic route commences with 5,6-dimethoxyindane (**782**). Formylation of the indane with dichloromethoxy methane (**783**) gave **784**, which was then advanced five steps to give aromatic lactone **785**. Oxidative dearomatization/rearrangement of **785** gave racemic dienone **786**. A Diels–Alder reaction occurred between racemic dienone **786** and enantiopure dienophile **787** (prepared in five steps from (+)-carvone) proceeded to give equimolar amounts of **788**, **789** and **790**, **791**. Intermediates **788** and **789** arise from Diels–Alder cycloaddition from the desired diastereoface of the diene, and they are inconsequential acetal epimers. Diels–Alder products **790** and **791** represent cycloadducts arising from addition to the undesired diene diastereoface. Nevertheless, the entire mixture was subjected to aqueous base, which induced acetal hydrolysis, ketone epimerization, enolization, and intramolecular aldol addition to give **792** and **793** as an *exo*/*endo* pair and **794** and **795** as an *exo*/*endo* pair. In this mixture, the *endo* diastereomers were favored (~3:1) over the *exo* diastereomers. Treatment of this unpurified material with



Scheme 92. Formal Syntheis of Gibberellic Acid (Corey, 1979).

aqueous acetic acid followed by 1 *N* NaOH induced an aldol reaction and delivered the first fully functionalized cyclopentane (**796**).[153] The diol was advanced four steps to intermediate **797**. Oxidative cleavage of the olefin in the presence of acid revealed a 1,6-diketone, which underwent transannular aldol addition to give **798**. This material was advanced six steps to mesylate **799**. Treatment with base induced a Grob fragmentation to give an alkene. Hydrolysis of the orthocarbonate gave **800**. Epoxidation of the alkene was performed with trifluoroperacetic acid to give β-epoxide **801**.[154] Basic hydrolysis of the lactone occurred with concomitant nucleophilic opening of the epoxide yielding lactone triol **802**. This material was advanced four steps to intermediate **803**. Treatment of **803** with acid led to enol ether **804** as a mixture of stereoisomers. Ozonolysis delivered a ketone, which was transformed to the enol acetate **805**. This material was converted to the corresponding enone **806** by an elimination reaction with DBN. Hydride reduction of the ketone gave the *endo* allylic alcohol. Hydrolysis of the acetonide with aqueous sodium hydroxide delivered anhydroryanodol (**807**) in a 3:1 ratio with the isomerized lactone epianhydroryanodol (**808**). This mixture could be separated and each alkene was epoxidized to give **809**; note that **807** undergoes oxidation with concomitant transesterification to give **809**. Finally, a reductive cyclization under dissolving metal conditions furnished (+)-ryanodol.

The complex natural product (±)-ryanodol bears two fully functionalized cyclopentanes (Scheme 97). In the Inoue[155] total synthesis both functionalized cyclopentanes are formed in a transannular aldol reaction of an eight-membered ring. The synthesis begins with a Diels–Alder reaction between 2,5-dimethylbenzene-1,4-diol (**810**) and maleic anhydride (**811**) to give **812** which creates two quaternary stereocenters. The anhydride could be hydrolyzed to the dicarboxylic acid, which underwent electrolysis with a platinum electrode to give the C_2-symmetric intermediate **813**. To obtain the fused functionalized five membered rings a two-directional functionalization with an intramolecular aldol cyclization was performed.[156] A stereoselective Corey-Chaykovsky epoxidation was followed by regioselective ring-opening with ammonia to produce **814**. Treatment with sodium nitrite in acetic acid results in two regioselective ring-expansions to give the 1,5-cyclooctanedione eight-membered ring of **815**. Formation of the silyl enol ethers was followed by double epoxidation with DMDO from the bottom face to give **816**. Desilylation with triflic acid resulted in diketone **817**. The transannular aldol was found to proceed in the presence of Brønsted acid, and the optimized conditions of 3 mol% triflic acid in methylene chloride delivered the fused five-membered ring system of **819**. This transformation is thought to proceed through intermediate **818**, which minimizes ring strain and transannular interactions and leads to the observed aldol diastereomer. The resulting *syn*-diol was protected as the acetonide, and the remaining hydroxyl group was oxidized to give ketone **820**. Ketone **820** is a C_2-symmetric molecule, and it enabled resumption of the two-directional synthetic strategy toward ryanodol. Two-fold oxidation of the diketone **820** gave **821**. The resulting hydroxyl groups were protected as the methoxymethyl ethers. Oxidation of the alkene using catalytic cobalt and molecular oxygen gave an inconsequential mixture of stereoisomers **822**.[157] Silyl protected peroxide **822** was transformed to the corresponding C_2-symmetric ketone, which underwent hydration upon chromatography to give **823**. Differential protection of the two hydroxyl groups was required at this stage. To this end, benzyl ether formation at the less hindered C15 position was followed by conversion of the remaining hydroxyl to the corresponding thiocarbonate (**825**). The C_2-symmetry of previous intermediates has now been broken and the five-membered carbocycles are further functionalized independently. Homolytic cleavage of the C–O bond of the thiocarbonate gave a bridgehead radical which successfully formed **826** upon reaction with allyltributyltin. This material was advanced over four steps to

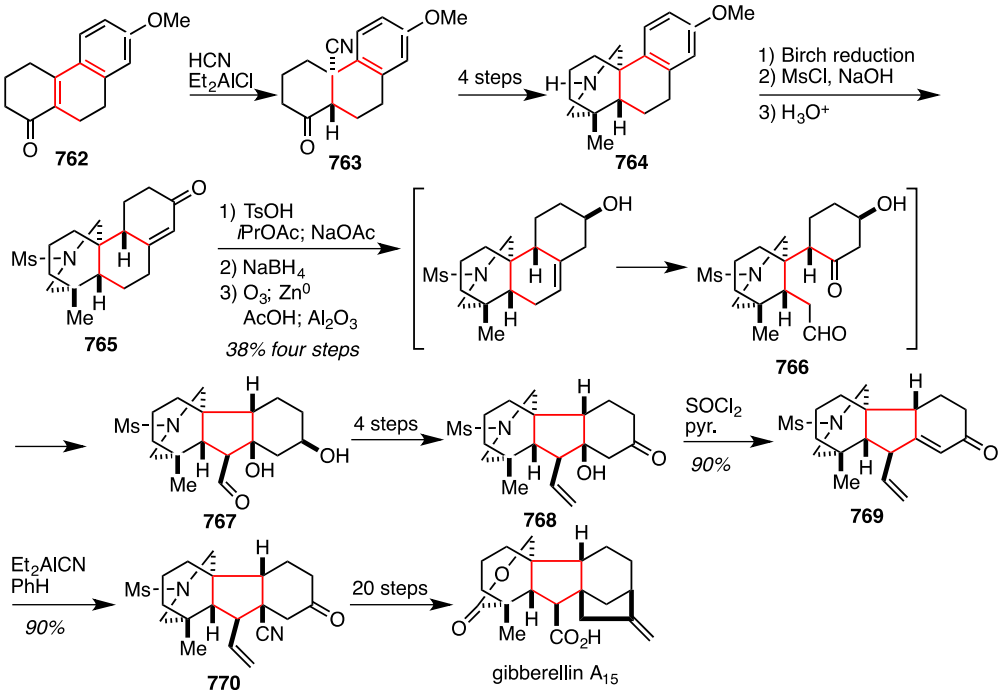


Scheme 93. Synthetic Studies Towards Delphinine (Wiesner, 1972).

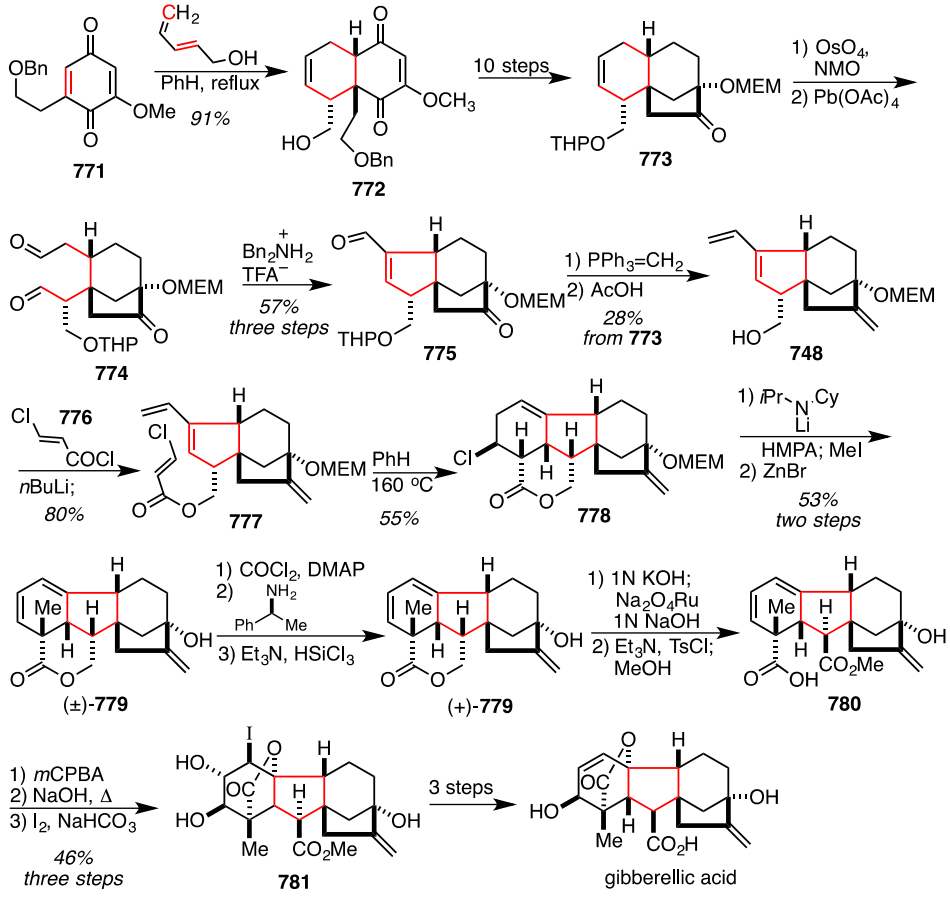
intermediate **827**. Organolithium addition to the more reactive ketone gave intermediate **829**, which has the first fully functionalized cyclopentane installed. The equatorial approach of the organolithium was attributed to sterically less hindered approach of the nucleophile. This material was advanced five steps to intermediate **830**. Oxidation of the secondary alcohol was followed by addition of isopropenyl lithium, which occurred away from the acetonide to give **831**. In the final stages of the synthesis, the silyl ethers and acetonide were cleaved. The ketone was then reduced by hydride, which is thought to be directed by the revealed tetraol to give the second fully functionalized cyclopentane. Hydrogenolysis of the benzyl ether delivered (±)-ryanodol.

The first stereoselective synthesis of (±)-orostanal, completed by Zhou,[158] begins with commercially available hyodeoxycholic acid, which could be advanced to intermediate **832** following the two-step method of Ziegler (Scheme 98).[159] Ozonolysis of the cyclohexene followed by reductive workup afforded keto-aldehyde **833**. The aldol reaction was promoted with exposure to neutral alumina and resulted in a fully functionalized cyclopentane. Axial attack on the ketone leads to the *cis*-fused hydrindane substructure with the aldehyde positioned on the convex face of the polycyclic molecular architecture in **834**. This intermediate contains a fully functionalized cyclopentane and was converted to the natural product over an additional ten steps.

Baran's[160] synthesized the fully functionalized cyclopentane **852**, which served as a common intermediate for the synthesis of the (−)-axinellamines, (−)-palau'amine, and (−)-massadine (Scheme 99). The route commences with an enantioselective Diels–Alder reaction of a 1-siloxydiene **841** and **842** to give cyclohexene **844**. This material was carried forward to the diazide **845** over six steps. Ozonolytic cleavage of the alkene gave a 1,6-diketone (**846**). Dibromination followed by exposure to dry silica promoted an intramolecular aldol reaction to form a fully functionalized cyclopentane (**847**).[161] Chlorination of the more reactive bromide and cleavage of the PMB-ether furnished diol **848**. Although a fully functionalized cyclopentane has been synthesized at this stage, it contains neither the correct substitution or desired stereochemistry for the natural targets. Tandem invertive chlorination and elimination were promoted with sulfuryl chloride to give enone **849**. A Luche reduction of the chloroketone and displacement of the bromide with *N,N'*-bis(Boc) guanidine provided **850**. Re-oxidation of the allylic alcohol with IBX induced spirocyclization to give **851** as a mixture of diastereomers favoring the desired stereoisomer. Treatment with sodium diformylamide



Scheme 94. Total Synthesis of (±)-Gibberellin A_{15} (Nagata, 1971).

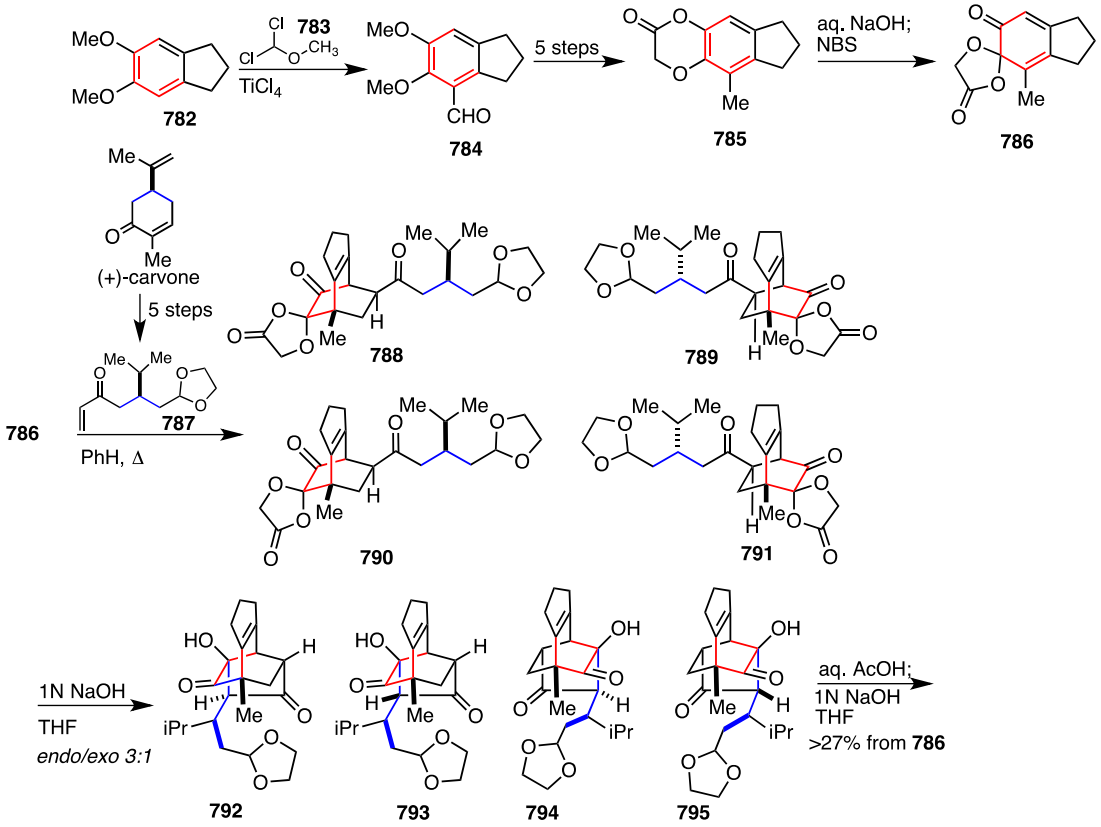


Scheme 95. Total Synthesis of (+)-Gibberellic Acid (Corey, 1978).

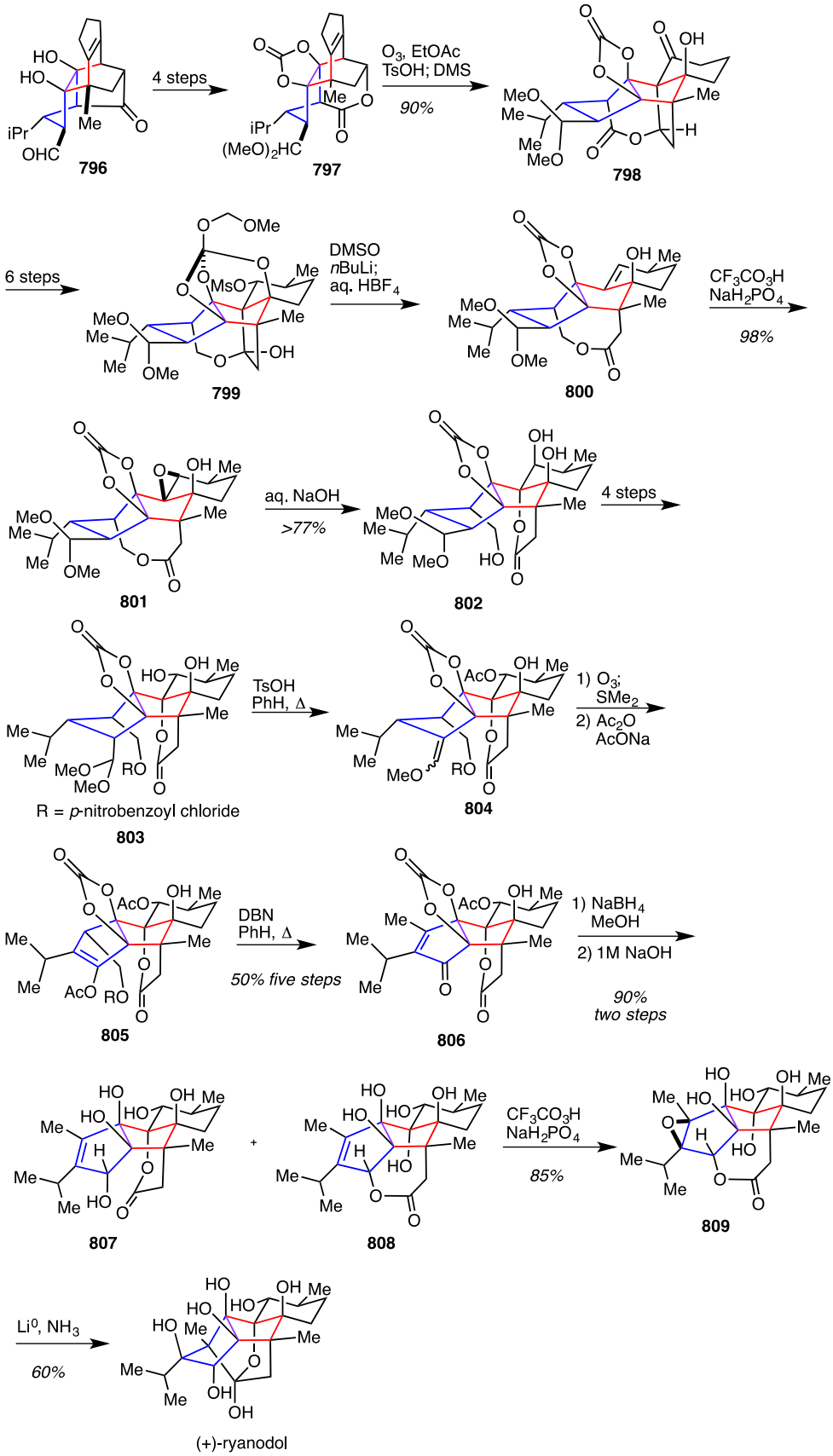
installed the primary ammonium group and Boc deprotection with TFA delivered **852**. Advanced intermediate **852** was a versatile synthetic intermediate that was used in the synthesis of the (−)-axinellamines, (−)-palau'amine, and (−)-massadine.

The first synthesis of (±)-pallambins C and D by Wong[162] employs a Grob fragmentation-intramolecular aldol cyclization sequence to construct a fully functionalized cyclopentane (Scheme 100). The synthesis commences with a reduction of the Wieland-Miescher ketone (**853**) to diol **854**. Benzyl protection of the diol was followed by epoxidation. Nucleophilic opening of the oxirane with methyl Grignard occurs at the less substituted carbon to give **855**. Displacement of the hydroxyl with chloride and subsequent elimination delivers **856**. Hydroboration-oxidation proceeds stereoselectively to give the *trans*-decalin. Acylation of the resulting hydroxyl group and hydrogenolysis of the benzyl ethers provides **857**. Oxidation to a diketone using Jones reagent was followed by selective conversion of the less hindered ketone to the diethyl ketal **858**. The acetyl protecting group was removed and a Bamford–Stevens-type iodination gave the vinyl iodide **859**. Benzyl protection of the secondary alcohol and transketalization was followed by a palladium-catalyzed alkoxycarbonylation to deliver ester **860**. Ester reduction and protection of the resulting alcohol as the MOM ether gives **861**. Hydroboration-oxidation on the less hindered alkene face, and acylation of the resulting alcohol delivered **862**. This material was advanced over five steps to intermediate **863**. Upon treatment with potassium *tert*-butoxide, a Grob fragmentation gave 1,6-ketoaldehyde **864** as an intermediate. A subsequent aldol cyclization occurred to give **865**. The constraints of the intramolecular tether ensure the aldehyde approaches on one diastereoface of the enolate, and the secondary alcohol stereocenter is inconsequential. At this stage, a fully functionalized cyclopentane has been synthesized, but the secondary alcohol must be converted to a tertiary alcohol. Introduction of the methyl group on the more hindered face of the molecular architecture required multiple steps.[163] Intermediate **865** was advanced five steps to homoallylic alcohol **866**. Substrate directed epoxidation was accomplished using the method of Sharpless, and fragmentation of the C–O bond was performed with $LiAlH_4$. Advanced intermediate **867** contains a fully functionalized cyclopentane with appropriate functional groups for the synthesis of (±)-pallambins C and D. The synthesis was completed in an additional six steps.

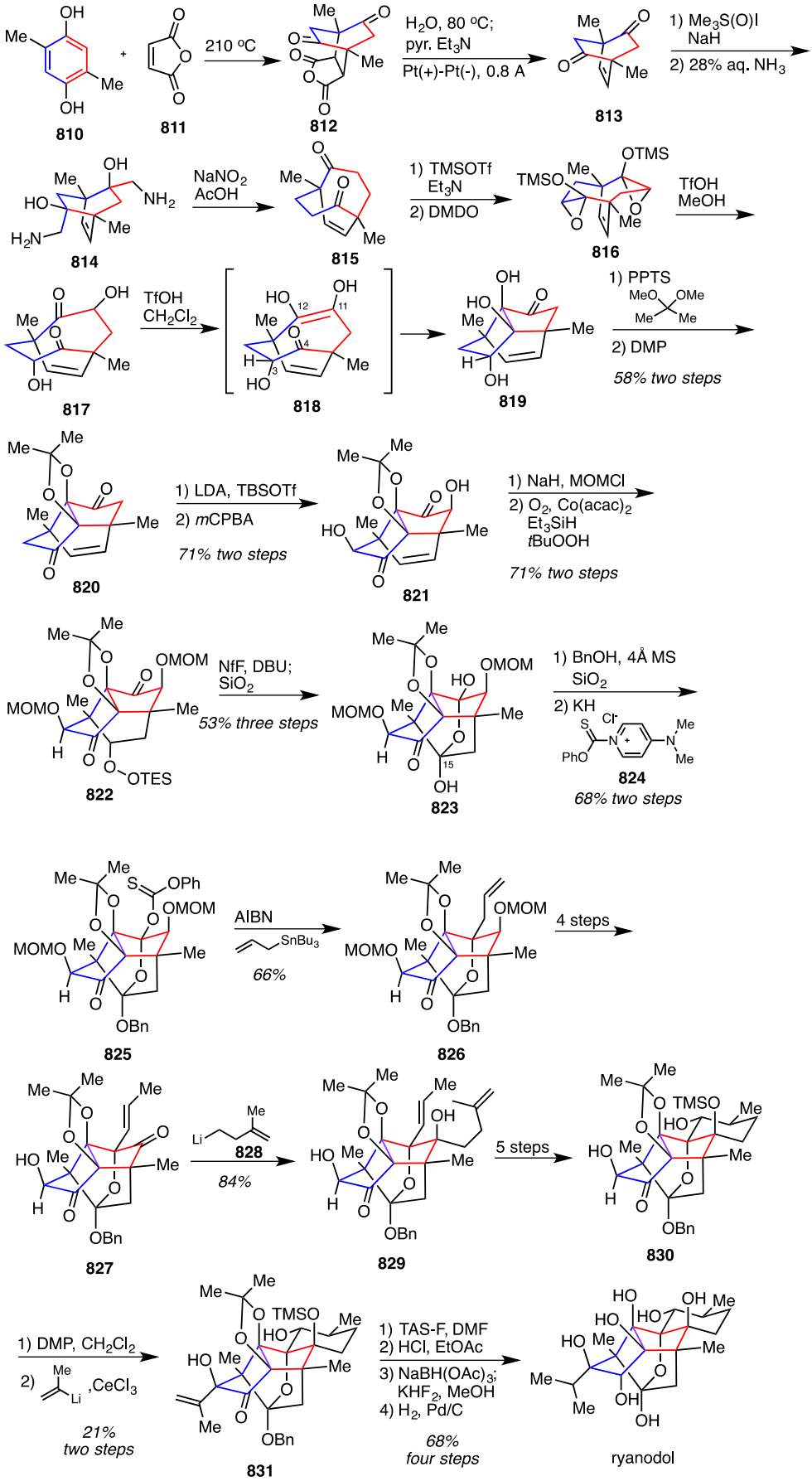
The total synthesis of (±)-pallambins C and D was completed by Baran[164] in eleven steps (Scheme 101). The cyclopentane was constructed with an intramolecular Mukaiyama aldol. The route commences with furfuryl alcohol (**868**). An Eschenmoser–Claisen rearrangement with *N,N*-dimethylpropionamide dimethyl acetal (**869**) and subsequent silyl hydride reduction of the resulting amide produces aldehyde **870**. A Robinson annulation with ethylvinyl ketone (**871**) yielded cyclohexenone **872**. Conjugate addition of vinyl cuprate and enolate trapping with TMS chloride delivers silyl enol ether **873**. Oxidative ring-opening of the furan gave keto-aldehyde **874**. This sensitive material was carried forward without chromatography into the aldol reaction. Lewis acid promoted Mukaiyama aldol reaction assembles the bicyclo[3.2.1]octane containing the functionalized five-membered ring. The reaction proceeds with complete stereocontrol to give **875** as a single stereoisomer. The stereochemistry of the tertiary alcohol is the result of bidendate chelation of the Lewis acid with the ketone and aldehyde carbonyls and suppression of any retro-aldol, aldol processes. The tetrahydrofuran could be assembled by treatment with trifluoroboron etherate and trimethylorthoformate. The reaction is thought to proceed through an acetal, which eliminates to an oxocarbenium ion. Nucleophilic conjugate addition of methanol occurring from the top face results in an unproductive intermediate



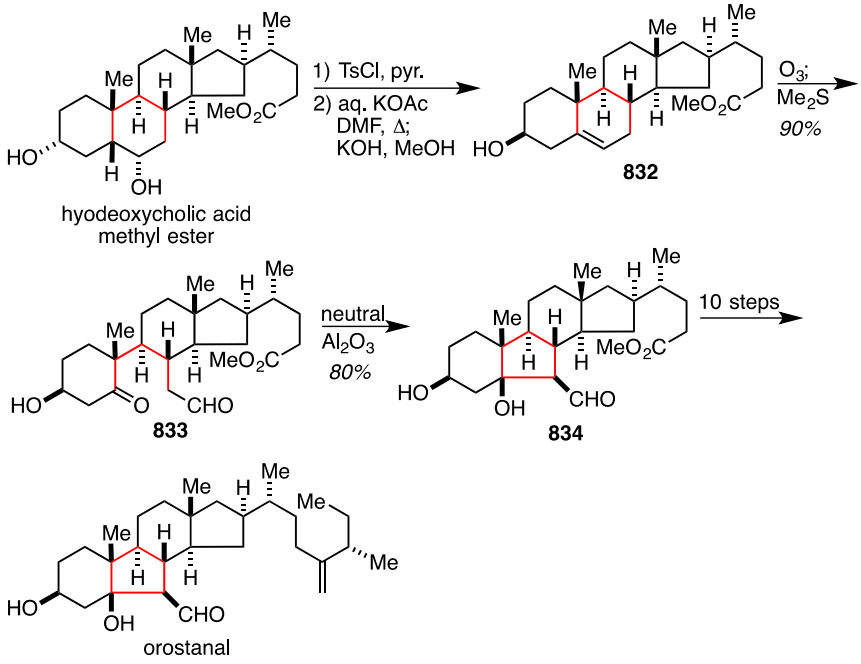
Scheme 96. Total Synthesis of (+)-Ryanodol (Deslongchamps, 1979).



Scheme 96. (*continued*).



Scheme 97. Total Synthesis of (±)-Ryanodol (Inoue, 2014).



Scheme 98. Total Synthesis of Orostanal (Zhou, 2002).

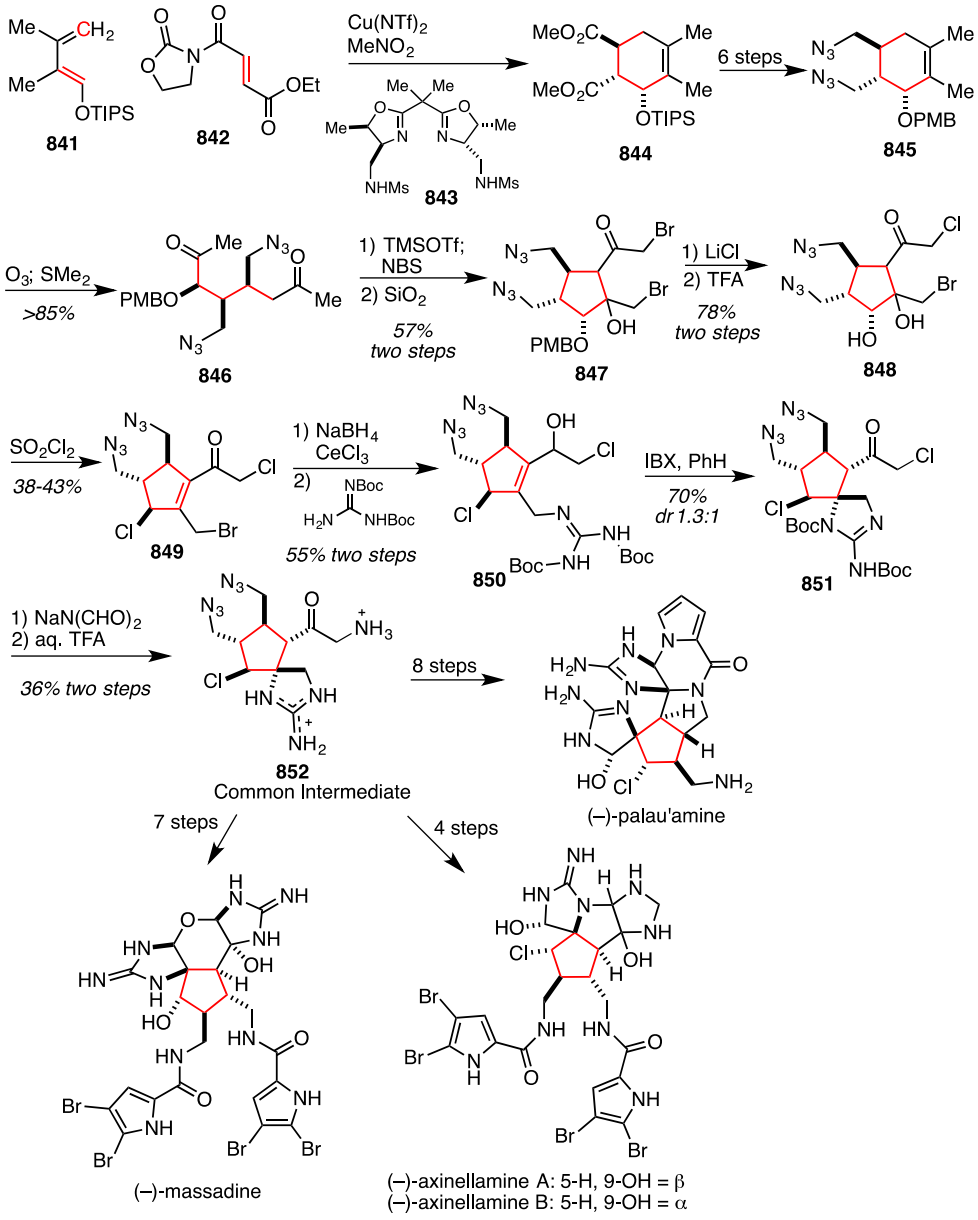
as cyclization would deliver the higher energy *trans*-fused bicycle. Upon conjugate addition of methanol to the bottom face, cyclization with the hydroxyl group delivers the *cis*-fused tetrahydrofuran ring **876**. This material was directly subjected to bromination with acetyl bromide to furnish **877**. Reduction of the bromide using Stille conditions gave **878**, which contains a fully functionalized cyclopentane with the required substitution and stereochemistry for pallambins C and D. Completion of the synthesis required an additional four steps.

In the total synthesis of (±)-rocaglamide by Dobler,[165] addition of a cyanohydrin anion to a benzofuranone assembles the key five-membered ring (Scheme 102). The synthesis commences with an addition of benzofuranone **880** to (*E*)-cinnamaldehyde (**881**) to give desired diastereomer of **882** with modest selectivity. Aldehyde **882** was transformed to the corresponding cyanohydrin **883**. The cyanohydrin could be deprotonated with LDA, and an aldol-like addition to the ketone occurred and an acyloin (**884**) was isolated upon elimination of the nitrile. The diastereoselectivity is the result of preferential formation of the *cis*-fused bicycle. Following earlier precedent, carboxylation with Stiles[166] reagent occurred on the concave face of the ring system opposite the two aryl substituents. Hydrolysis to the β-keto-acid, and amide formation delivered dimethylamide **885**. Substrate directed hydride reduction completed the synthesis of (±)-rocaglamide.

The asymmetric synthesis of (+)-gelsemine was completed by Zhai and Qiu,[167] and the fully functionalized cyclopentane is constructed with an aldol addition of a 1,6-ketoaldehyde (Scheme 103). The route commences with an enantioselective organocatalytic Diels–Alder reaction of dihydropyridine **887** and dienophile **888** to give desired *endo* product **891** after reduction.[168,169] Surprisingly, intermediate **890** was also isolated from the reaction mixture, which may suggest dienophile double bond isomerization under the reaction conditions. This material could be converted to the desired cycloadduct **891** by heating with DBU. Reduction with DIBAL gave a lactol, which upon Wittig reaction delivered a methyl enol ether that was converted to acetal **892**. Ozonolysis of the alkene gave a 1,6-ketoaldehyde that undwerent aldol addition upon treatment with base to give fully functionalized cyclopentane **893**. This material was advanced over six steps to intermediate **894**. The final carbon substituent of the cyclopentane was installed with an enolate alkylation of the pendant oxindole moiety to give **895**. Removal of the MOM ether delivered (+)-gelsemine.

The squarate ester cascade is a reaction sequence developed by Paquette,[170] and it was used to efficiently assemble the triquinane framework of (±)-coriolin (Scheme 104). Lithiated cyclopentene **897** was added to squarate ester **896**, to which excess vinyl lithium was added. The two possible stereochemical outcomes of the organometallic additions are inconsequential due to independent pathways to the desired triquinane **904**. The product of *syn*-addition (**898**) undergoes a di-anionic oxy-Cope rearrangement to give **871**. Anti-addition induces a 4π-electrocyclic ring opening of the cyclobutane (**899**) to give **900**, which is followed by an 8π-electrocyclization to give **901**. After regeneration of the ketone (**902**), an intramolecular aldol furnishes the tricyclic intermediate **904**. Treatment with acid leads to ketone **905**. Deoxygenation of the tertiary alcohol occurred over two steps to give **906**. A dehydrative 1,3-carbonyl transposition was effected with $LiAlH_4$ and MOM protection of the secondary alcohol gave intermediate **907**. Enolate alkylation stereoselectively installed the quaternary stereocenter forming the energetically favorable *cis*-ring fusion in **908**. Nucleophilic addition of methyllithium and dehydration formed the exocyclic alkene. A Saegusa oxidation installed the final unsaturation and delivered **142**, which is an intermediate previously synthesized by Ikegami[38] in a synthesis of coriolin.

The first Danishefsky[43] synthesis of the sesquiterpene (±)-merrilactone A begins with a Diels–Alder reaction between 2,3-dimethylmaleic anhydride and diene **909** to afford cyclohexene **910** (Scheme 105). The *endo* selectivity of the cycloaddition gives the desired relative stereochemistry for the target molecule. This material was carried forward to lactone **911** over five steps. The alkene underwent ozonolysis to a 1,6-dialdehyde that cyclized upon treatment with mild acid to give enal **912**. Following reduction of the aldehyde, addition of triethyl orthoacetate and acid induced a Johnson–Claisen rearrangement to give ester **913** as a mixture of diastereomers favoring the desired stereoisomer. The ester was then hydrolyzed, and iodolactonization proceeded to give



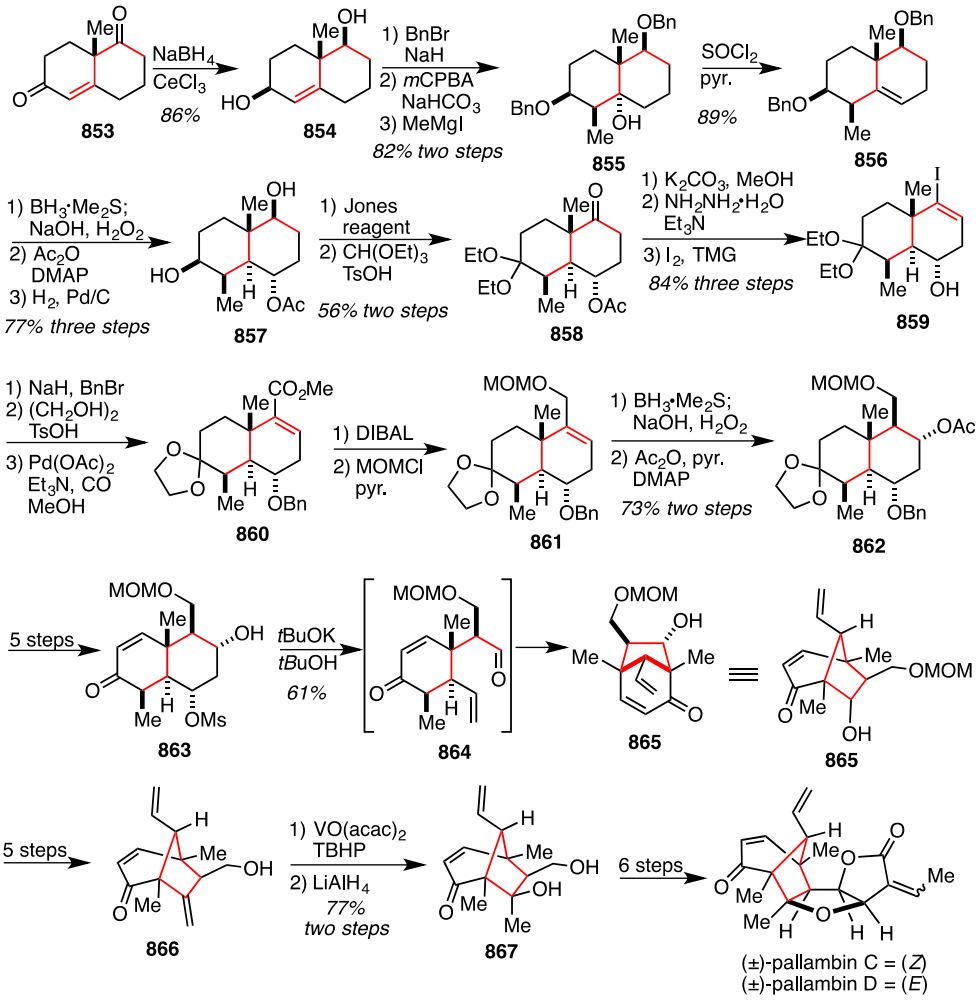
Scheme 99. Total Synthesis of (−)-Palau'amine, (−)-Massadine, (−)-Axinellamines A and B (Baran, 2008).

914, which contains a fully functionalized cyclopentane complete with the substituents and stereochemistry required for merrilactone A. The natural product was completed over an additional eight steps.

6.3. Henry reactions

In the synthesis of (±)-mannostatin A, Ogawa[171] constructs the cyclopentane by double addition of nitromethane to a dialdehyde (Scheme 106). The synthesis begins with an oxidative cleavage of *myo*-inositol derivative **915** to give a dialdehyde intermediate (**916**). Base-catalyzed double addition of nitromethane gives diol **917** as a complex mixture of diastereomers. This mixture was advanced to intermediate **918** and separated, with the major diastereomer having the desired configuration. This material was converted to **919** by selective *O*-acetate removal and sulfonate formation.[172,173] Heating in sodium acetate inverted the C1 and C4 configurations and resulted in a diol. Treatment of the diol with MsCl delivered racemic monomesylate **920**. Nucleophilic substitution with potassium thioacetate proceeded with inversion to set the final stereocenter for mannostatin A (**921**). This material was converted to mannostatin A over an additional three steps.

In the synthesis of (+)-trehazolin, Ogawa[174] constructs the cyclopentane by double addition of nitromethane to a dialdehyde (Scheme 107). The synthesis begins with intermediate **918** that was previously synthesized (see Scheme 106 above) in the route to mannostatin A. Conversion to the desired stereoisomer **922** was performed over five steps according to the protocol developed by Lichtenthaler.[172] Selective *O*-deacetylation with sodium methoxide in methanol was followed by formation of the *N,O*-isopropylidene to give **923**. A resolution of this racemic mixture was achieved by formation of a chromatographically separable diastereomeric mixture of (*S*)-acetylmandelates **925** and **926**. Ester cleavage of **926** and oxidation of the resulting secondary alcohol yields ketone (+)-**927**. Conversion to the *exo*-olefin was accomplished by conversion to a mixture of spiro-epoxides with diazomethane/DMSO



Scheme 100. Total Synthesis of (±)-Pallambins C and D (Wong, 2012).

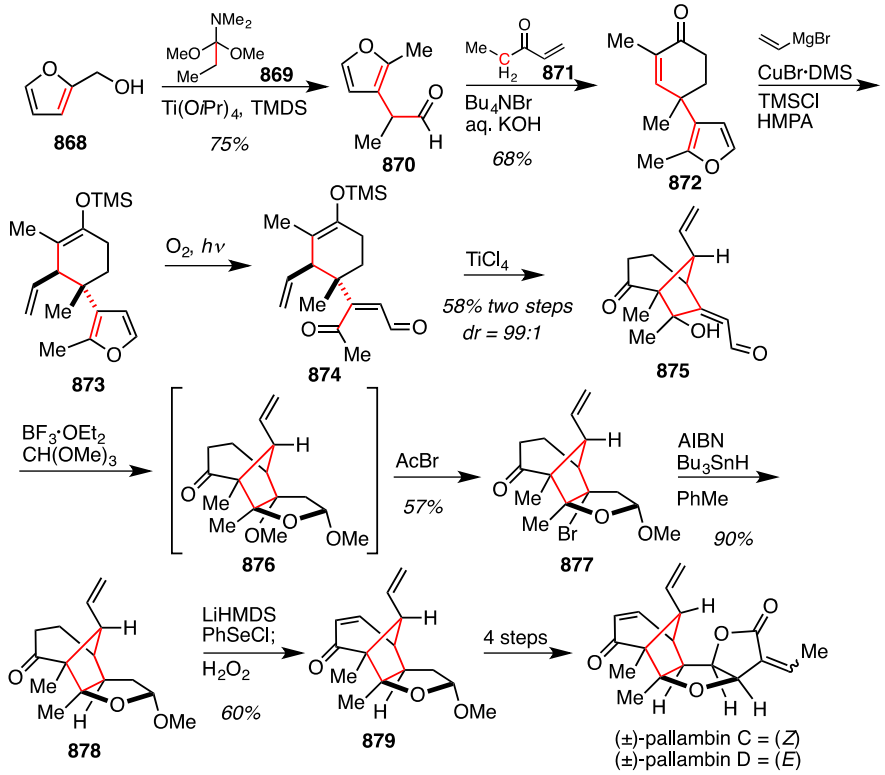
followed by reduction with trimethylphosphite to give **928**. To complete the synthesis of trehazolin, stereochemical inversion of C4′ was required. Hydrolysis of the ketal was followed by selective sulfonylation of the allylic alcohol. Acetate protection of the secondary alcohol delivered **929**. Substitution with sodium acetate successfully inverted the C4′ stereocenter and dihydroxylation from the less hindered face delivered **930**. This advanced intermediate contains a fully functionalized cyclopentane with the desired substitution and stereochemistry for (+)-trehazolin, which was completed in an additional four steps.

7. Mannich reactions

The Mannich reaction is a powerful C–C bond-forming reaction that is a mainstay of alkaloid total synthesis. The reaction is dependable in complex substrates. As a result, it is not surprising that the Mannich reaction has been employed in the creation of carbocycles that are part of fully functionalized cyclopentane natural products. Mannich reactions that form a five-membered ring require the substrate to contain a carbonyl and an iminium ion in a 1,6-relationship; however, the method by which the nucleophilic enol and the iminium are prepared vary widely.

The Mannich reaction gives products that display a 1,3-*N*,*O*-relationship (e.g. 3-amino ketone), and the Mannich reaction is well suited to targets with this functional group pattern. However, if such a relationship can be revealed through retrosynthetic simplification, then other C–C bonds may be targeted for the Mannich disconnection. For example, the central fully functionalized cyclopentane in gelsemine has been prepared using a Mannich reaction of **931** (eq. 1) to forge the C5–C16 bond of **932**, which is part of a 1,3-*N*,*O*-relationship in the natural product (Scheme 108). However, the C5–C6 bond becomes another Mannich disconnection if the target is simplified to a C7 carbonyl containing intermediate (**933** → **934**).

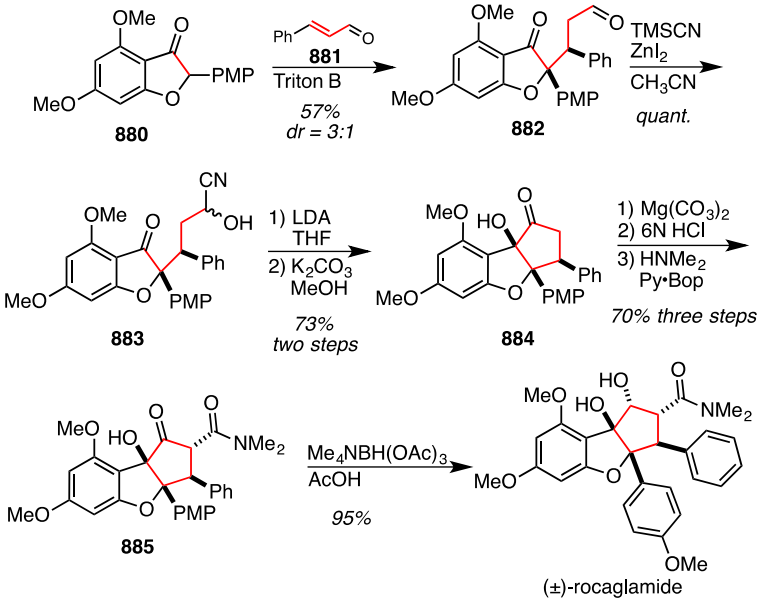
In the synthesis of (±)-gelsemine, Johnson[175] employs an intramolecular Mannich reaction to form the polycyclic molecular architecture (Scheme 109). The synthesis commences with a conjugate addition/chloride elimination of alcohol **935** to the vinyl diester **936** to deliver **937**. An intramolecular photochemical [2 + 2] cycloaddition provided tricyclic intermediate **938**. The stereochemistry of the product is a result of the suprafacial addition of both alkene components and the constraints of the intramolecular tether. This material was carried forward nine steps to cyclobutanone **939**. A retro-Claisen reaction was induced by addition of methylamine providing amido ester **940** as a single diastereomer. Conversion to the aldehyde was performed by an exhaustive reduction of the ester followed by oxidation to the corresponding aldehyde. Treatment with potassium carbonate epimerized the aldehyde and promoted cyclization to yield **941**. This material was carried forward five steps to the Mannich reaction precursor **942**.



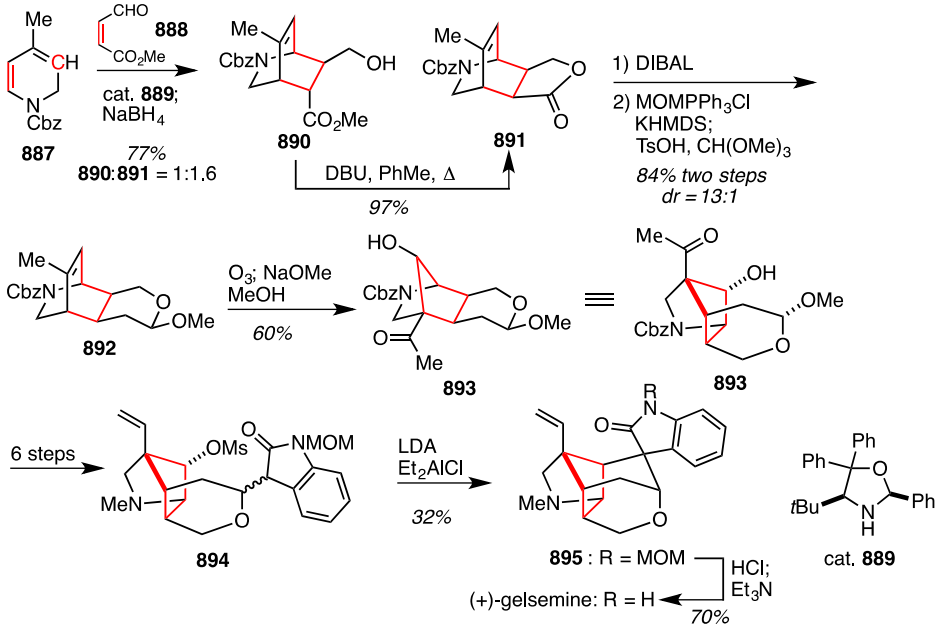
Scheme 101. Total Synthesis of (±)-Pallambins C and D (Baran, 2016).

Treatment of **942** with refluxing TFA generated the acyliminium ion, and the desired intramolecular Mannich reaction occurred to deliver fully functionalized cyclopentane **943**, and the natural product was completed in an additional nine steps.

The Speckamp[176] synthesis of (±)-gelsemine begins with a Diels–Alder reaction of *N*-methylmaleimide (**944**) and alcohol **945** (Scheme 110). The less hindered carbonyl of intermediate **946** was reduced and converted to the corresponding *N,O*-acetal **947**. Two additional transformations gave intermediate **948**.[177] Enolate formation and addition to 2-(phenylseleno)-ethanal gave a mixture of aldol products, which were advanced to the desired vinyl compound **931** as a mixture of silyl enol ether geometrical isomers. Exposure to Lewis acidic conditions promoted formation of an *N*-acyliminium ion, which cyclized to give aldehyde **932** as a 3:1 mixture with its C16 epimer. This establishes the fully functionalized cyclopentane with the desired functionality and



Scheme 102. Total Synthesis of (±)-Rocaglamide (Dobler, 2001).



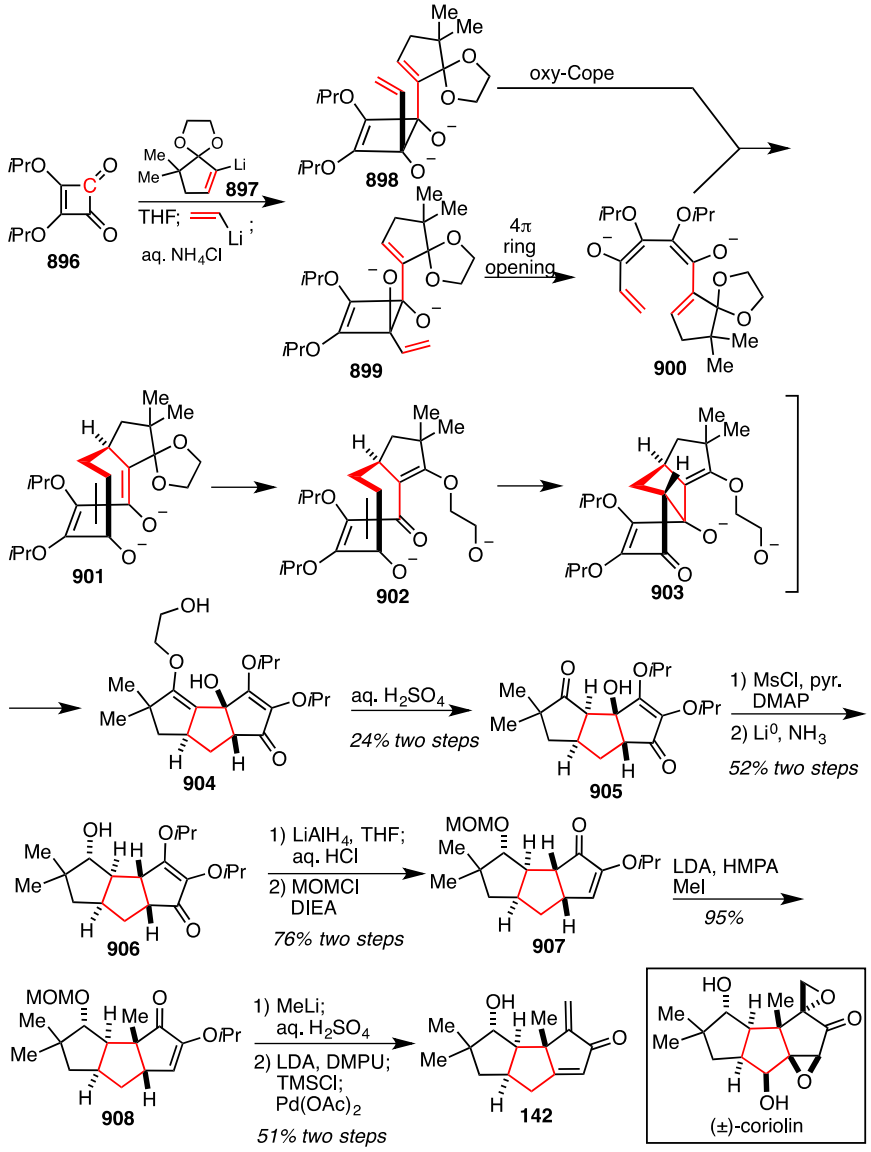
Scheme 103. Total Synthesis of (+)-Gelsemine (Zhai & Qiu, 2015).

stereochemistry for gelsemine. An additional 11 steps were used to complete the synthesis of (±)-gelsemine.

In the synthesis of (±)-gelsemine by Overman,[178] the azatricyclodecane ring system was constructed with an intramolecular Mannich reaction (Scheme 111). The synthesis commenced with the Diels–Alder reaction of siloxy cyclohexadiene **949** and methyl acrylate to give bicyclo[2.2.2]octene **950**. This material was functionalized over three steps to give **951**. A Curtius rearrangement sequence converted the carboxylic acid to primary amine **952**. Alkylation and TIPS removal delivered **953**. Treatment with potassium hydride and 18-crown-6 generated a formaldimine alkoxide (**954**), which participated in an anionic aza-Cope rearrangement. Quenching the reaction with methyl chloroformate delivered intermediate **956**. Selective removal of the carbonate group delivered *cis*-hexahydroisoquinolinone **957**. Bromination was envisioned as a means of installing a functional handle for the eventual hydroxymethyl group, and treatment of the enecarbamate with molecular bromine delivered monobrominated compound **933**. Exposure to TFA generated the acyliminium ion and promoted the intramolecular Mannich reaction to give azatricyclodecane **934**. In this cyclization, the tetrahydropyridine ring must exist in a boat conformation (as seen in **958**) in order to obtain the necessary overlap with the enol π-system. The thermodynamically favored C16 epimer delivers the tricyclic product with the bromine substituent on the *exo* face. At this stage a fully functionalized cyclopentane has been achieved, but the substitution does not match gelsemine. Seven steps were used to install the spirooxindole moiety of gelsemine (**959**). Aziridine formation was achieved by heating the bromide in refluxing cyanide to give **960**. The aziridine nitrogen was methylated, the aziridine was opened with cyanide at the less hindered position, and the ethoxy ethyl protecting group was removed to give **961**, which represents a fully functionalized cyclopentane with appropriate stereochemistry for gelsemine. Completion of the synthesis required an additional three steps.

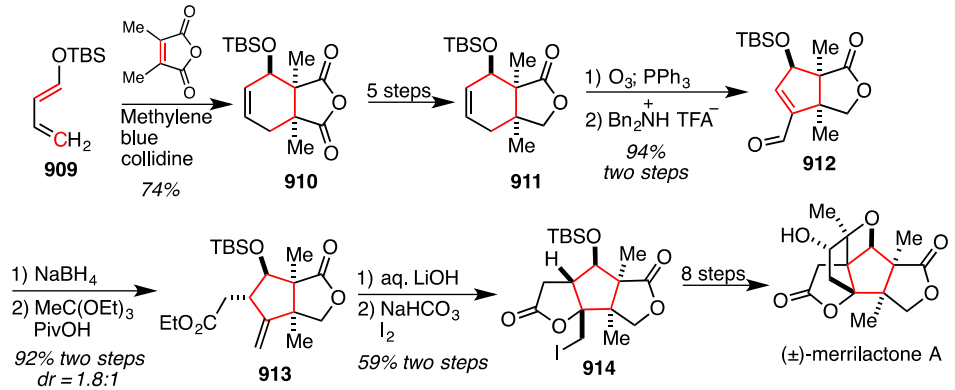
The synthesis of (−)-lepenine by Fukuyama[179] features an intramolecular Mannich reaction to form the key five-membered ring (Scheme 112). The synthesis begins with a Mitsunobu reaction with enantiopure lactic acid derivative (**963**) and guaiacol (**962**) to deliver **964** with complete inversion of stereochemistry. Reduction with DIBAL and addition of vinylmagnesium chloride provides **965** as a mixture of alcohol epimers. Heating the allylic alcohol in *p*-nitrophenol with triethyl orthoacetate promoted the Johnson–Claisen rearrangement to give the γ,δ-unsaturated ester **966**. This intermediate ester is also a Claisen substrate, and it undergoes a subsequent rearrangement to yield phenol **967**. The Claisen rearrangement cascade proceeds through the usual chair-like transition state and transfer of stereochemical information gives the expected stereoisomer in **967**. This material was advanced three steps to **968**. Saponification of the ethyl ester and Friedel–-Crafts acylation delivers **969**. Addition of vinylmagnesium chloride and elimination of the resulting alcohol gave diene **970**. Cleavage of the pivaloyl ester, esterification with methacrylic acid furnished cycloaddition substrate **971**. Heating in benzonitrile promoted the Diels–Alder cycloaddition furnishing tetracyclic intermediate **972** in good yield. Hydroboration-oxidation occurred on the convex face of the *cis*-6,6 ring system which gave complete diastereoselectivity to give alcohol **973**. The Mannich precursor **974** was prepared over three steps. Treatment of key substrate **974** with Pd(0) in acetic acid led to loss of the alloc protecting group. Intramolecular cyclization gave an iminium ion that underwent Mannich cyclization to give **975**. This material was advanced over three steps to *o*-quinone monoketal **976**. Heating in an ethylene atmosphere, a Diels–Alder reaction occurred with complete diastereoselectivity on the less hindered face of the diene to give cycloadduct **977**. This material was advanced three steps to **978**. The final stereocenter of the fully functionalized cyclopentane was set by hydroboration-oxidation of cyclopentene on the less hindered face to give **979**. Advanced intermediate **979** contains a fully functionalized cyclopentane and could be advanced to (−)-lepenine in four additional steps.

In Baran's[180] unified approach to the *ent*-atisane, atisine, and hetidine alkaloids, a fully functionalized five membered ring is synthesized via an azomethine ylide isomerization followed by a Mannich cyclization (Scheme 113). Beginning with the *ent*-

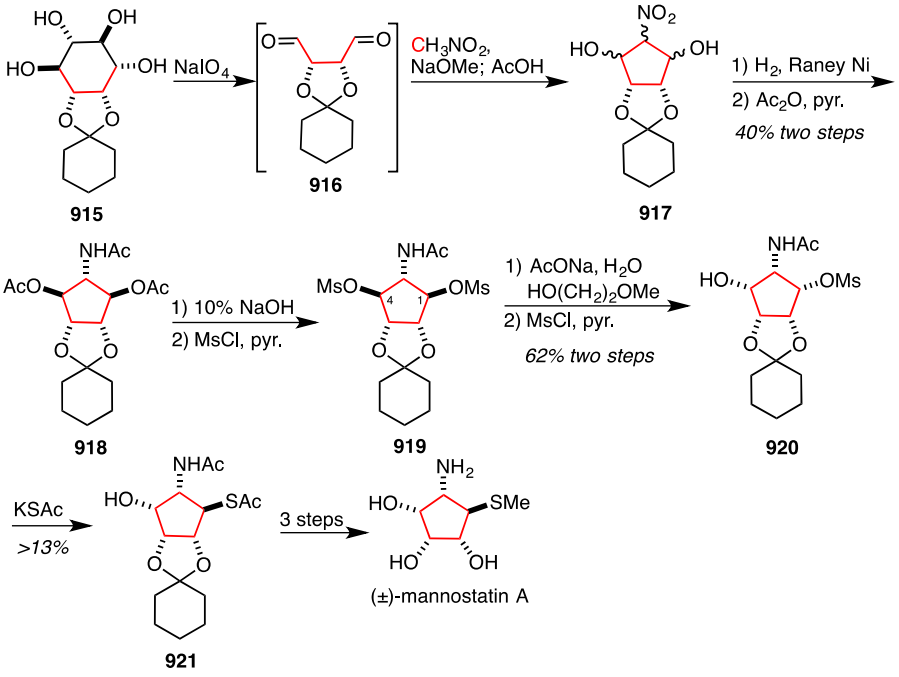


Scheme 104. Formal Synthesis of (±)-Coriolin (Paquette, 2002).

kaurane (−)-steviol, much of the required stereochemistry is present for the hetidine alkaloids. Amide formation introduced the requisite nitrogen for the Mannich reaction. Reduction to the amine and reaction with diethyl chlorophosphate provided phosphoramidate **980**. A three step sequence to form bicyclo [2.2.2]octane intermediate **981** begins with oxidative cleavage of

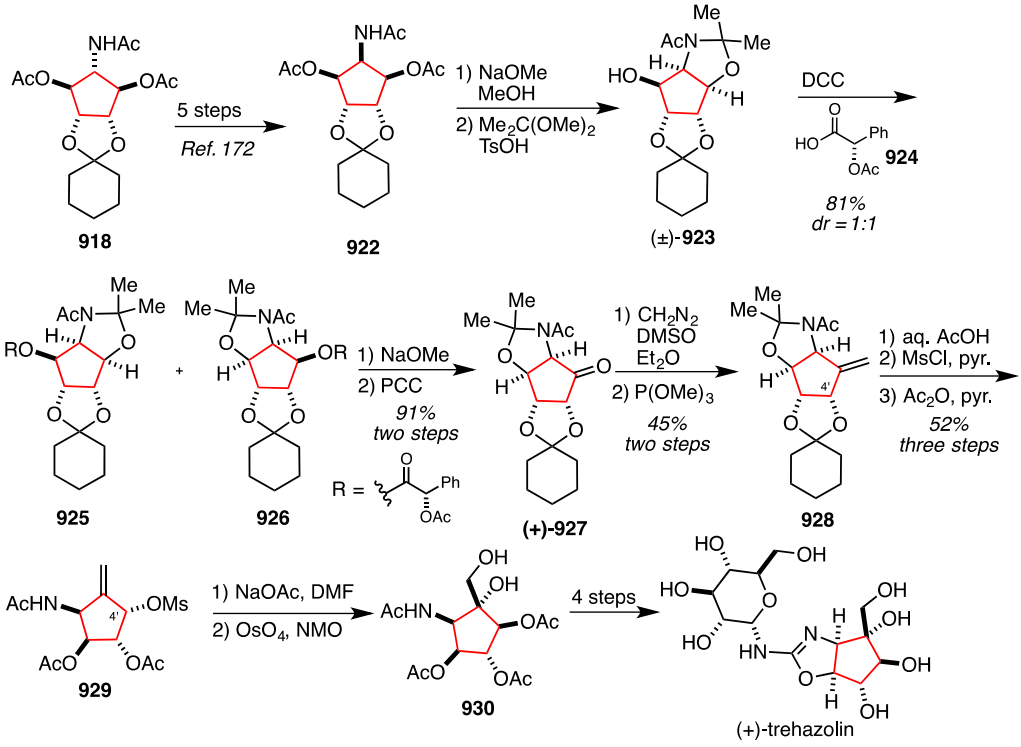


Scheme 105. Total Synthesis of (±)-Merrilactone A (Danishefsky, 2002).

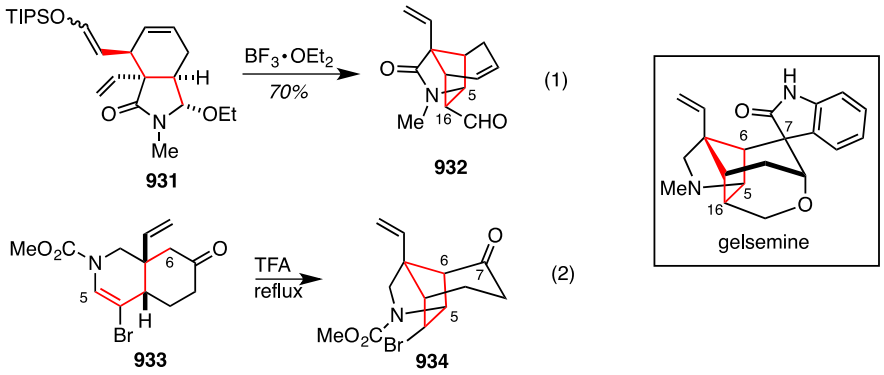


Scheme 106. Total Synthesis of (±)-Mannostatin A (Ogawa, 1994).

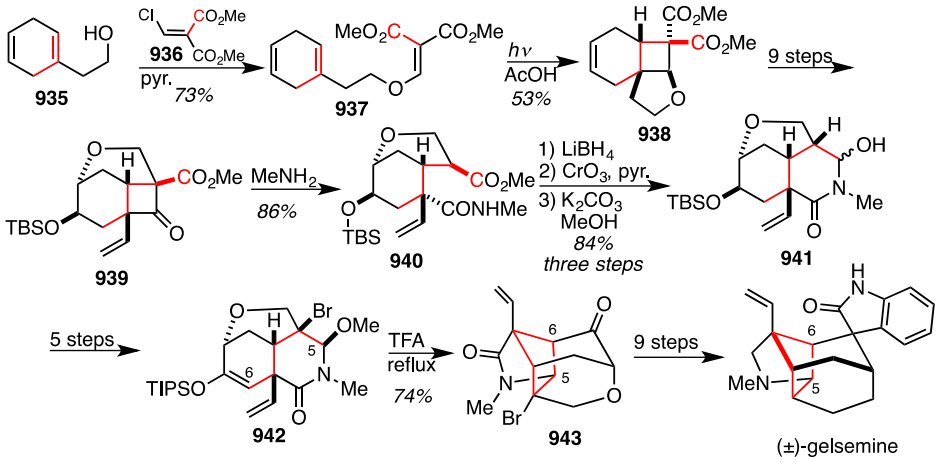
the alkene with cobalt acetoacetate to form a 1,5 dicarbonyl. Aldol cyclization delivers the bicyclo[2.2.2]octane and the resulting tertiary alcohol is protected as the acetate (**981**). Following the Suárez conditions,[181] C–H activation occurred selectively at C20. During the iodination, the phosphoramidate was also oxidized to the corresponding imine **982**. Treatment with allyl amine in methanol led to condensation and alkylation to give imminium ion **983**. Subsequent deprotonation to an azomethine imine, and re-protonation isomerized the imminium ion and triggered the Mannich cyclization to give hetidine skeleton **984**. While this structure is not a natural product, it contains the fully functionalized cyclopentane, all of the carbons, and the stereochemistry found in (−)-spirafine III and other structurally related natural products.



Scheme 107. Total Synthesis of (+)-Trehazolin (Ogawa, 1994).

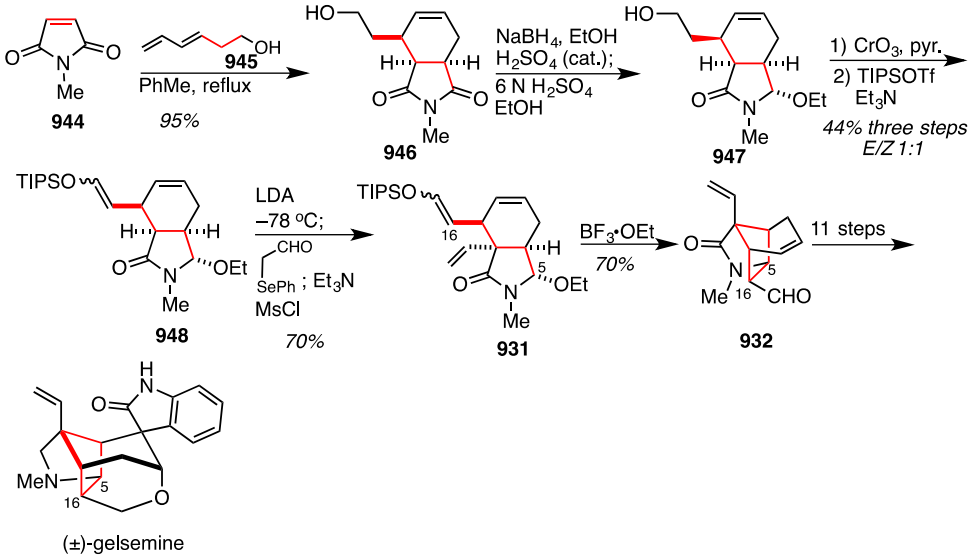


Scheme 108. Mannich Reactions in the Synthesis of Gelsemine.

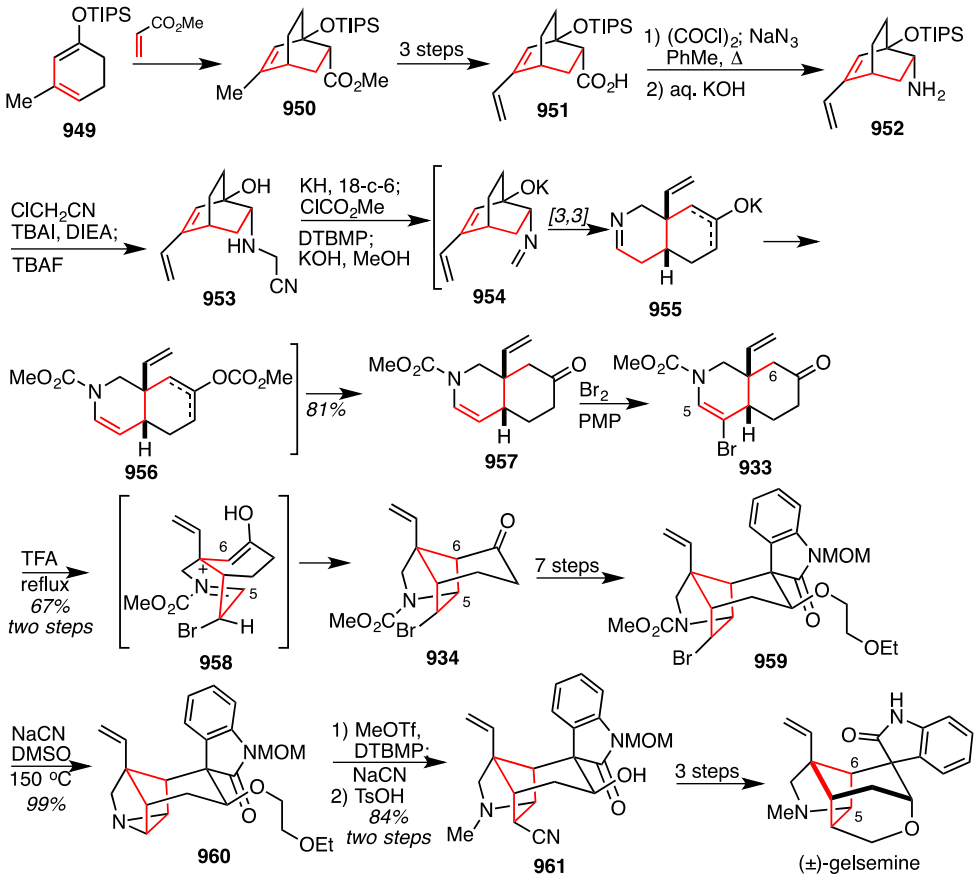


Scheme 109. Total Synthesis of (±)-Gelsemine (Johnson, 1994).

The synthetic effort towards palau'amine by Harran[182] seeks to take advantage of the symmetry present in the natural product (Scheme 114). The fully functionalized cyclopentane is constructed by a halogenative enamine Mannich-type reaction of **960**. The synthesis begins with tetrahydropyridazine **954** which could be advanced four steps to give key dimerization precursor **955**. Dienolate formation and subsequent oxidation gave meso-dimer **956** as the major product in a 3:1 ratio with its *trans*



Scheme 110. Total Synthesis of (±)-Gelsemine (Speckamp, 1994).



Scheme 111. Total Synthesis of (±)-Gelsemine (Overman, 1999).

diastereomer. A rhodium-catalyzed reduction provided **959** as a complex mixture of stereoisomers. This inconsequential mixture of diastereomers was treated with Cy_2BOTf and base, which induced a double fragmentation double tautomerization sequence to give **960**. The halogenative desymmetrization reaction proceeds with *t*BuOCl and magnesium chloride to give **961** as a mixture of C10 epimers thus completing the fully functionalized cyclopentane. This advanced intermediate contains many of the structural features found in palau'amine.

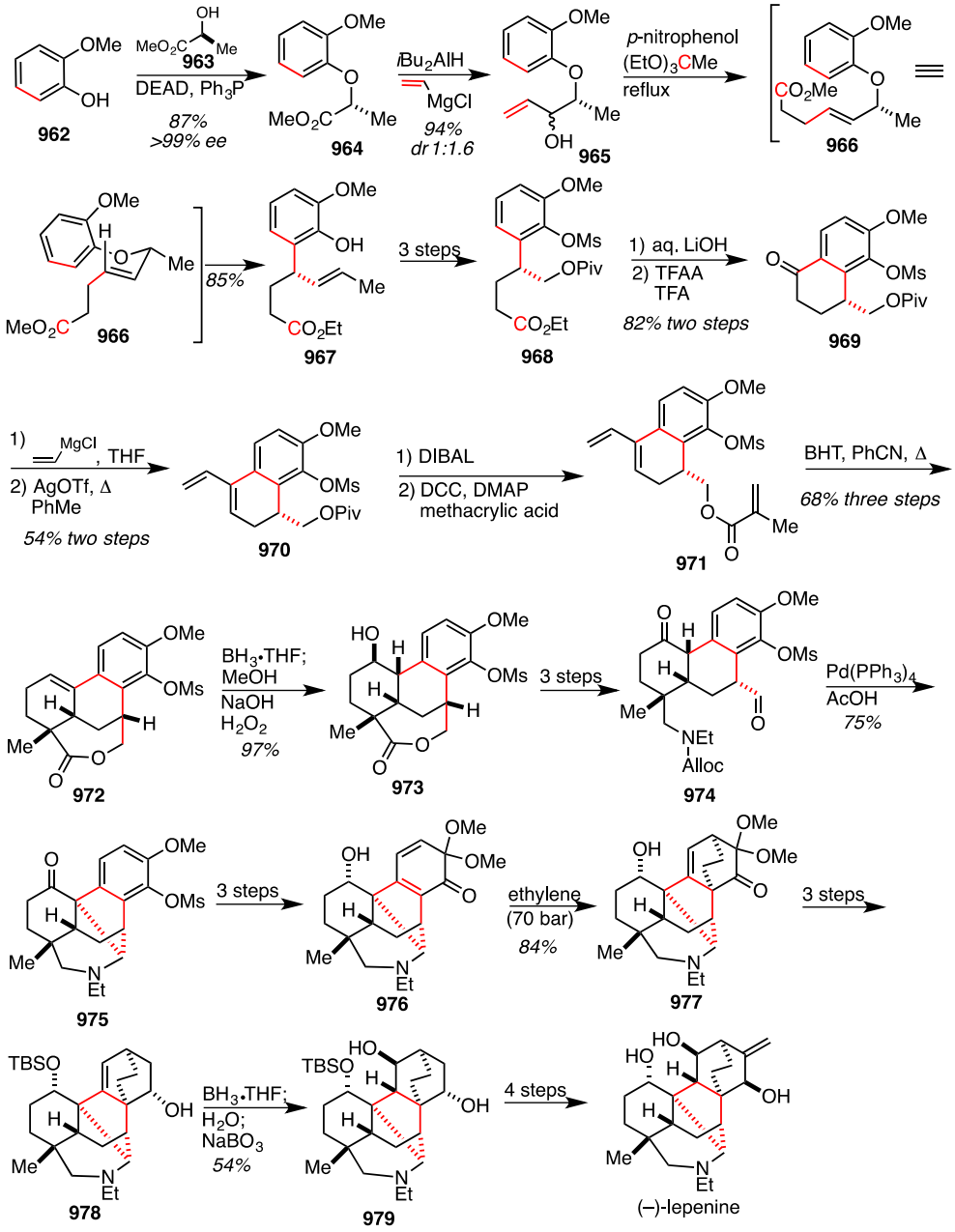
8. Conjugate addition reactions

This section describes syntheses where the fully funtionalized cyclopentane is created using a conjugate addition of an enolate (or related nucleophile) to an unsaturated carbonyl. Conjugate addition reactions, including the Michael reaction, inherently produce enolates; such enolates can be captured in a variety of creative ways. As a result, the reactions featured in this section are highly varied, and they contain many domino or cascade reactions of carbanions (e.g. tandem Michael–aldol reactions). We collect all relevant conjugate addition reactions and all cascade or tandem reactions involving conjugate additions in this section.

As mentioned above, the reactions in this section are particularly diverse. For example, there are two distinct syntheses of the complex alkaloid gelsemine (Scheme 115) that use enolate conjugate additions in markedly different strategies. The first (eq. 1) uses tandem nitronate and ester enolate (**993**) conjugate additions to divinyl ketone **994** to give a bicyclic product **995**. This reaction builds the key cyclopentane while creating the C5–C6 and C15–C16 bonds of the target molecule. In another gelsemine synthesis (eq. 2) an intramolecular reaction of a nitrile enolate and an unsaturated oxindole (**996**) creates the fully functionalized cyclopentane and the C6–C20 bond in **997**. The conjugate addition reactions shown were used to build a fully functionalized cyclopentane with good control of product stereochemistry; however, the reactions have little else in common. A feature of this section is the wide variety of creative uses and tandem tranformations that have been based on the conjugate addition reaction.

In the synthesis of (±)-gymnomitrol by Büchi,[183] a conjugate addition is followed by an intramolecular cyclization to construct the key five-membered ring (Scheme 116). The synthesis begins with quinone ketal **998**, which is obtained from 4,5-dimethoxy-2-methylbenzaldehyde in three steps. Condensation with 1,2-dimethylcyclopentene delivered **1001** as the major diastereomer. Mechanistically, the sequence begins with Lewis acid activation to give quinone derivative **999**. Conjugate addition of 1,2-dimethylcyclopentene is followed by trapping of the resulting carbocation by the tethered enol ether in **1000**. This cyclization sets four of the five stereocenters in gymnomitrol favoring the desired stereoisomer. The unpurified material was reduced with hydride to set the final stereocenter of gymnomitrol giving intermediate **1002**. Completion of the synthesis of (±)-gymnomitrol required five additional steps for the deletion of the enol ether functionality and olefination of the ketone.

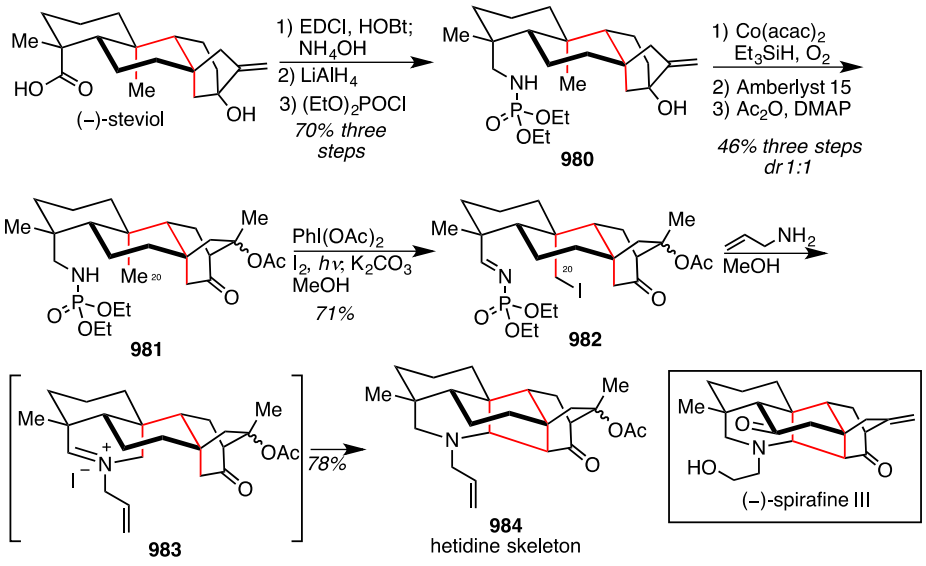
In the synthesis of coriolin by Danishefsky,[34] the key five-membered ring in the target was constructed in a cascade process featuring a Michael addition and an aldol condensation (Scheme 117). An addition of the enolate derived from **1003** to the



Scheme 112. Total Synthesis of (−)-Lepinine (Fukuyama, 2014).

Michael acceptor 5,5-dimethyl cyclopentenone (**1004**) was followed by refluxing in acid to deliver **1005**. A Diels–Alder reaction with diene **1006** gives the tricyclic **1007** as a single diastereomer. Addition from the bottom face of the cyclopentenone was controlled by formation of the energetically preferred *cis* fusion of the cyclopentanes. The enone functionality was installed by addition to phenylselenyl chloride and subsequent oxidation and elimination with $NaIO_4$ to give **1008**. Regiospecific addition of methyl to the enone carbonyl gave allylic alcohol **1009**. Diketone **1010** was accessed over the following steps: ozonolysis, Jones oxidation, decarboxylation with barium hydroxide, and lead acetate cleavage of the hydroxy acid. An aldol condensation of the 1,4-dicarbonyl delivered tricyclic product **1011**. Deconjugation of the α,β-enone to the β,γ-unsaturated ketone **1012** was completed with potassium *tert*-butoxide and acetic acid. Treatment with DIBAL resulted in reduction of the less-hindered ketone, and the more substituted ketone required dissolving metal reduction. These two steps resulted in the formation of diol **1013**. Epoxidation with *m*CPBA occurred stereoselectively by forming the favorable *cis* ring fusion of the cyclopentanes. Chromium oxidation provides ketone **1014**. Treatment of **1014** with LDA resulted in β-elimination of the epoxide and subsequent formation of an enolate that underwent sulfenylation to yield **1015**. The resulting thioether was oxidized with peracid to a sulfoxide that was eliminated upon reflux to give *exo*-methylene **130**. Double epoxidation of the divinyl ketone with peroxide completed the synthesis of (±)-coriolin.[184]

Considerations of the biosynthesis of shinjulactone C led Takahashi[185] to hypothesize that this natural product was biosynthetically related to the structurally similar compound ailanthone (Scheme 118). It was found that ailanthone could be converted into



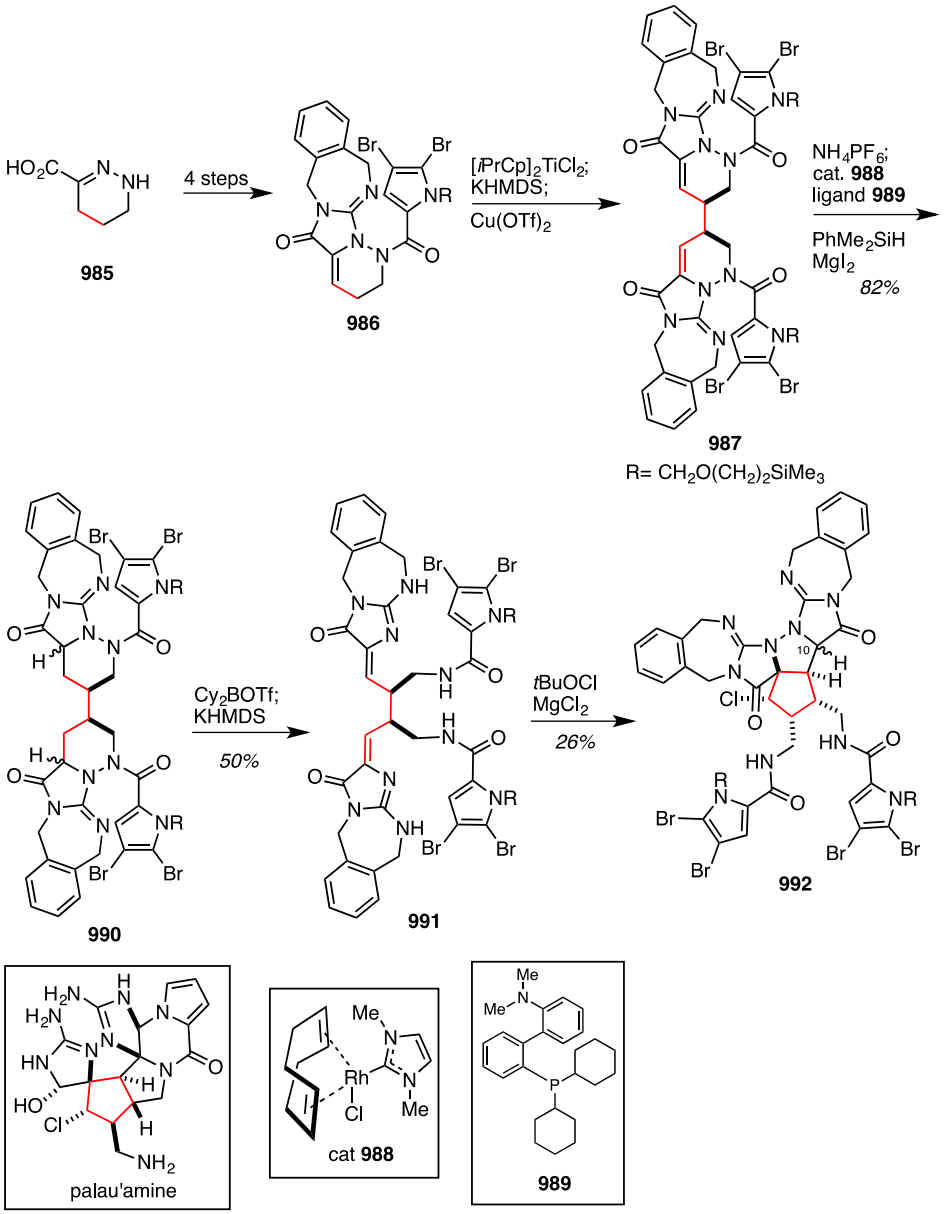
Scheme 113. Synthetic Studies Toward *ent*-Atisane, Atisine, and Hetidine Diterpenes (Baran, 2014).

shinjulactone C in low yield by prolonged reflux in pyridine. This spectacular reaction creates a decasubstituted cyclopentane embedded in the shinjulactone C architecture. Of the five contiguous fully substituted carbons, two of the quaternary carbons and both tertiary alcohols are forged in this transformation. With this discovery in hand additional effort was committed to a mechanistic investigation of the reaction. It was hypothesized that ailanthone undergoes oxidation at C1, hemiacetal fragmentation, isomerization of the *exo*-methylene, and epimerization at C9 to give presumed reactive intermediate **1017**. This intermediate would be deprotonated at C5 to form a dienolate nucleophile, which would undergo conjugate addition to the enone at C12. The conjugate addition presumably resulted in an enolate, nucleophilic at C13, which underwent cyclization by adding to the C1 carbonyl.

In order to investigate the mechanistic hypothesis shown above, ailanthone was converted to **1018**, which is a protected analog of reactive intermediate **1017**. Treatment of **1018** with refluxing pyridine resulted in the isomerization of the *exo*-methylene to give **1019**. Conversion of the TBS ether to the corresponding carbonyl gave **1020**. This molecule differs from reactive intermediate **1017** only in the configuration at C9 and the presence of two acetate protecting groups. Refluxing of this molecule in pyridine led to the formation of acetylated shinjulactone C (**1021**). The performance of this intermediate in the reaction cascade gives strong support for the mechanistic hypothesis.

In the first total synthesis of the quassinoid (±)-shinjulactone C, Grieco[186] utilizes the technology developed by Takahashi (see Scheme 118 above) to assemble a decasubstituted cyclopentane (Scheme 119). The route begins with Wieland-Miescher ketone **853**, which was stereoselectively reduced with hydride to give alcohol **1022**. This material was advanced over nine steps to cyclization precursor **1023**. A Diels–Alder cycloaddition with substituted diene **1024** using conditions developed by Grieco[187] produced tricyclic intermediate **1025**, which contains all five carbons of the eventual fully functionalized cyclopentane. This material was functionalized over four steps to give tetracyclic compound **1026**. A stereoselective hydroboration-oxidation reaction of the tertiary alkene was followed by alcohol oxidation to give ketone **1027**. This material was advanced over five steps to ketone **1028**. Treatment of **1028** with DIBAL reduced both carbonyl groups, and subsequent treatment with acidic methanol led to dehydration and acetal formation delivering **1029**. Oxidaton of the secondary alcohol provided ketone **1030**. Dihydroxylation and protection of the diol as the acetonide afforded **1031**. Oxidation of the ketone over three steps led to α-methoxy ketone **1032**. This material was advanced over seven steps to intermediate **1033**. Swern oxidation of the secondary alcohol gives a ketone. Treatment with acetic anhydride in DMAP forms the enol acetate (**1034**) while simultaneously acetylating the primary alcohol derived from the opening of the hemiketal. Cleavage of the methyl ether with boron tribromide was followed by Jones' oxidation to give cyclization precursor **1020**. Following the conditions developed by Takahashi, when **1020** was heated in pyridine (±)-shinjulactone C diacetate (**1021**) was produced in moderate yield. Ester hydrolysis gave the natural product.

In the Crimmins[188] synthesis of (±)-ginkgolide B, the five membered ring is assembled in an annulation involving a conjugate addition (Scheme 120). The route begins with furanyl aldehyde **1037**, which can be advanced to **1038** over three steps. Addition of ethynylmagnesium bromide delivered *syn* alcohol **1039** as the major product in a 1.2:1 diastereomer ratio. The undesired *anti* diastereomer could be converted to the desired **1039** via a Mitsunobu inversion. The alcohol was silylated and the alkyne was carboxylated to deliver **1040**. Treatment of acetylenic ester **1040** with the zinc-copper homoenolate **1041** delivered the cyclopentenone **1042**. Mechanistically, this transformation proceeds via a conjugate addition followed by a Dieckmann condensation. An intramolecular photocycloaddition resulted in formation of two contiguous quaternary carbon stereocenters on cyclopentanone **1043**. Desilylation, and activation of the alcohol as the sulfonate gave intermediate **1045**. Lactone formation under acidic conditions gave pentacyclic intermediate **1046**. The ketone was oxidized to the corresponding enone with standard conditions to give **1047**. Epoxidation of the enol ether with DMDO in the presence of aqueous acid resulted in spontaneous hydrolyis of the epoxide to a hemiacetal followed by fragmentation of the cyclobutane. Treatment with acidic methanol and trimethylorthoformate led to acetal formation giving **1048**. Barton deoxygenation[90] removed the secondary hydroxyl group to give **1049**. Modified conditions of a Davis procedure successfully led to α-hydroxylation of the β-dicarbonyl. Acylation with propionic anhydride delivered **1050**. Enolate addition to the cyclopentenone gave the undesired **1051** as the major

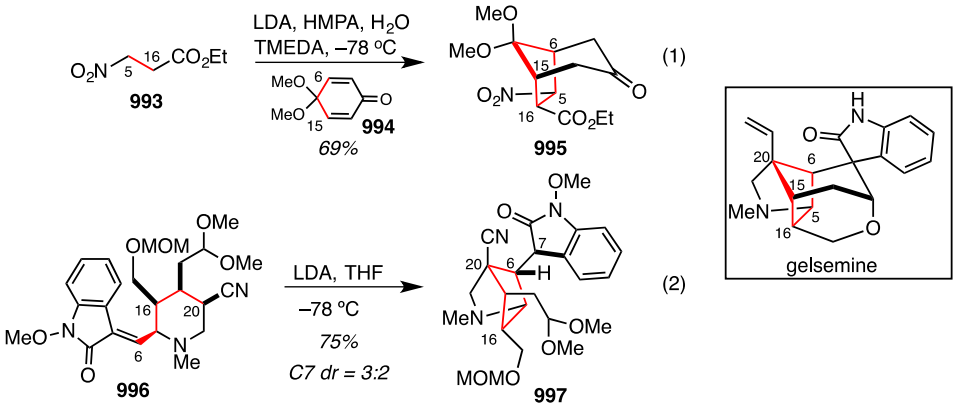


Scheme 114. Synthetic Studies Toward Palau'amine (Harran, 2009).

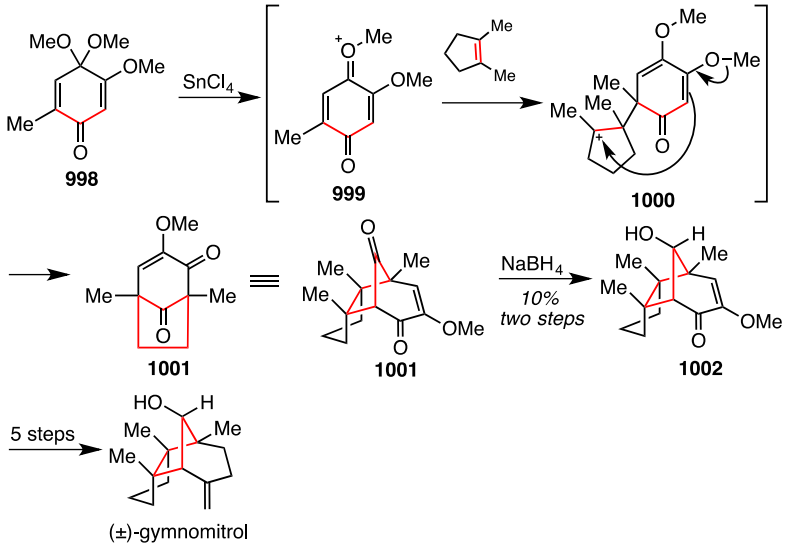
product. Epimerization of the methyl stereocenter with NaOMe/MeOH generated a 1:1 diastereomeric mixture with desired product **1052**. The undesired isomer could then be isolated and resubjected to epimerization conditions to obtain more of the desired material. Lactone cleavage was performed with camphorsulfonic acid and methanol to give **1053**. Heating the ketal with PPTS resulted in elimination of methanol and yielded enol ether **1054**. Epoxidation of the cyclopentene with concomitant intramolecular lactonization gave fully functionalized cyclopentane **1055** with the appropriate substitution and stereochemistry found in ginkgolide B. Two additional standard transformations were used to complete the synthesis of the natural product.

In the synthesis of (±)-longiborneol by Ihara,[189] a double Michael addition is used to assemble a fully functionalized cyclopentane (Scheme 121). The route begins with dicyclopentadiene derivative **1056** which was alkylated with iodide **1057** to give **1058**. A retro-Diels–Alder reaction releases cyclopentadiene to give cyclopentenone **1059**. Addition of methyllithium gave a tertiary alcohol and oxidative transposition with PCC gave enone **1060**. Silyl deprotection, alcohol oxidation and olefination gave cyclization precursor **1061**. The double Michael reaction proceeds with LHMDS, which constructs a fully functionalized cyclopentane as part of the core molecular architecture of the sesquiterpene natural products (**1062**); however, the natural products require conversion of the carbomethoxy substituent into a hydroxyl group. Basic hydrolysis of the ester gave **1063**. After much experimentation, radical decarboxylation conditions were found to deliver **1064** in good yield. This advanced intermediate contains the appropriate functionality and stereochemistry for (±)-culmorin, and ketone reduction completed the natural product. Intermediate **1063** was taken forward to (±)-longiborneol by exhaustive ketone reduction to give **1065** and an oxidative decarboxylation as discussed above.

The synthesis of (+)-rugulosin by Nicolaou[190] features two distinct cascade processes based on conjugate addition chemistry



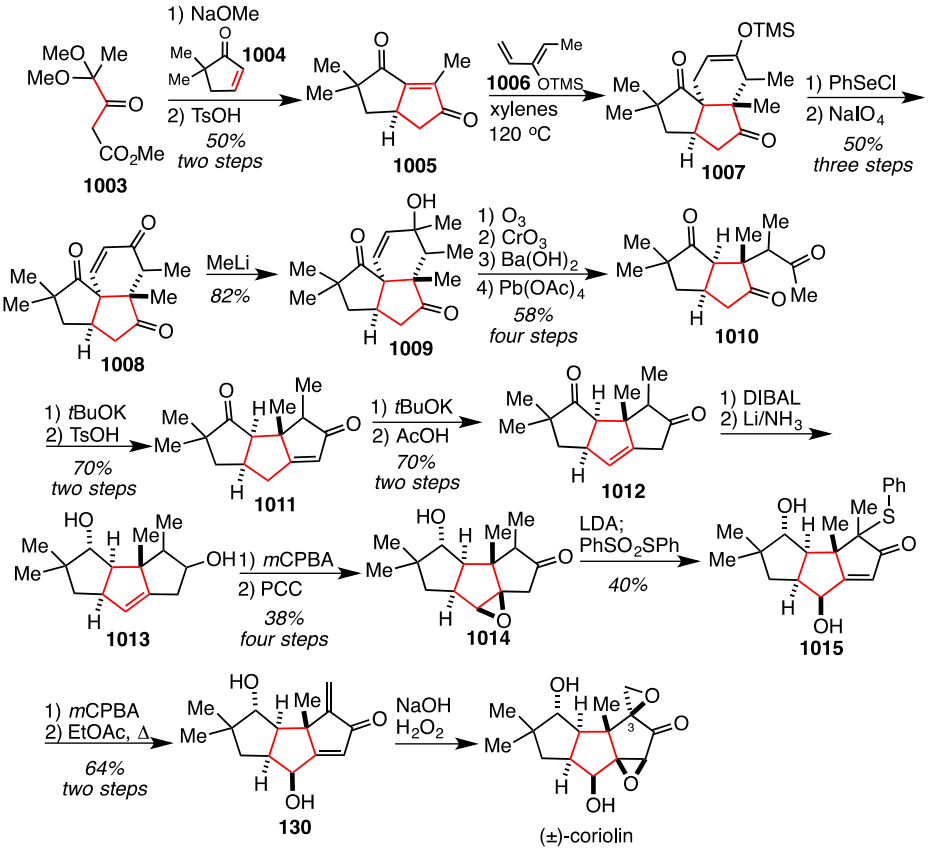
Scheme 115. Conjugate Addition Reactions in the Synthesis of Gelsemine.



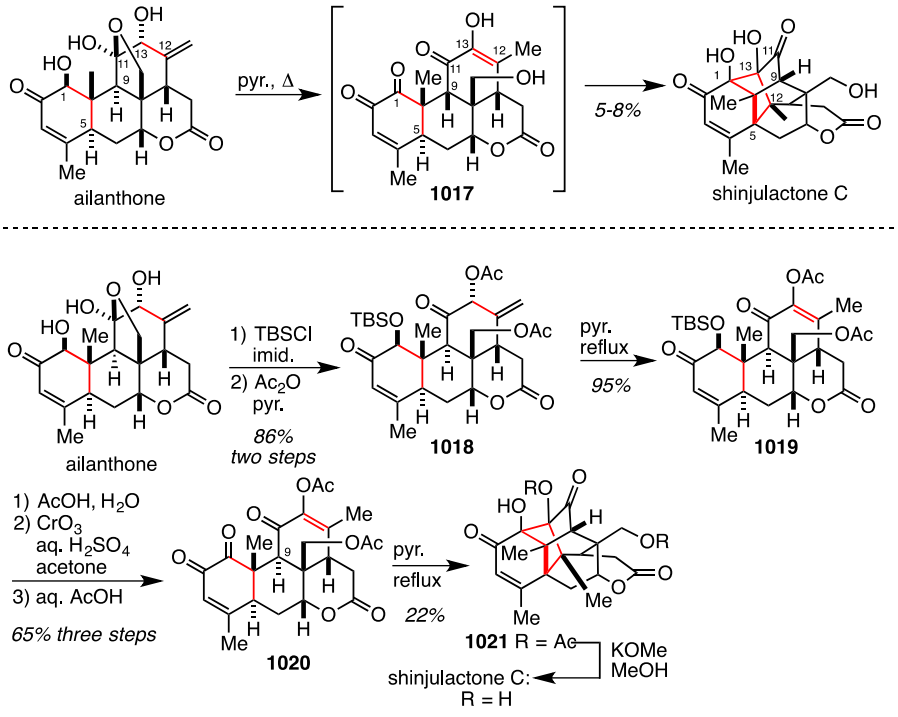
Scheme 116. Total Synthesis of (±)-Gymnomitrol (Buchi, 1979).

that construct two fused fully functionalized cyclopentanes (Scheme 122). The synthesis begins with cyclohexenone **1068**, which was synthesized from the known diacetate **1066** in four standard steps including an enzymatic desymmetrization. Nitrile **1070**[191] was stirred with LHMDS followed by addition of cyclohexenone **1068** to give anthradihydroquinone **1071**. When this material was treated with manganese dioxide (1.5 wt equiv) in CH_2Cl_2 intermediate **1073** was formed. This reactivity has been studied by both Nicolaou and Snider[192] and mechanistically it could be viewed as sequential conjugate addition reactions or as a hetero-Diels–Alder reaction. A tenfold dilution of intermediate **1073** with CH_2Cl_2 and treatment with additional managanese dioxide formed **1075**. Finally, warming the solution in the presence of triethylamine delivered **1077**. The cascade reaction (termed cytoskyrin cascade) involves two sequential Michael reactions to deliver the cage-like structure of rugulosin (**1074** → **1077**). Experimentally, it was found that the entire transformation of **1071** to **1077** could occur in a single flask without isolation of intermediates. This single elegant biomimetic transformation builds two fused fully functionalized cyclopentanes with complete control of stereochemical configuration. Acidic removal of the MOM protecting groups completed the synthesis of (+)-rugulosin.

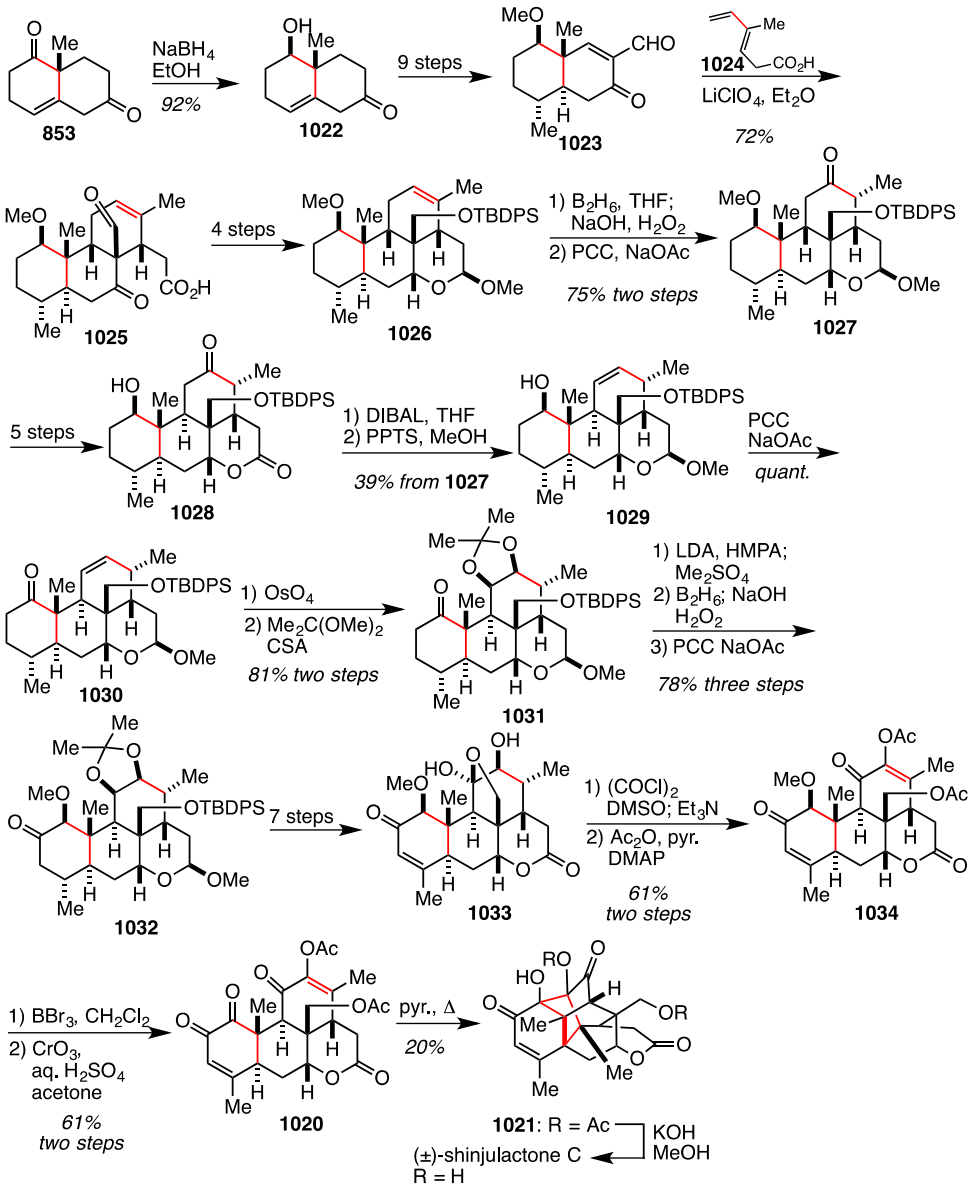
In the asymmetric synthesis of (+)-gelsemine by Qin,[193] the cyclopentane ring is constructed by a Michael addition of a nitrile enolate and an oxindole (Scheme 123). The synthesis begins by conversion of (*R,R*)-**1078** into the alkyne **1080** by reduction, tosylation, and addition of the lithiated acetylide (**1079**). This material was advanced to *cis*-olefin **1081** over eight steps. Condensation of the acid and hydroxyl groups delivered oxepinone **1082**. The first of two intramolecular Michael additions gave a mixture of inseparable diastereomers in a 66% yield favoring the desired **1083**. Reductive cleavage of the lactone was followed by acetal formation and oxidation of the primary alcohol to give aldehyde **1084**. Condensation with *N*-methoxyindole **1085** and subsequent dehydration of the resulting alcohol with thionyl chloride gave a mixture of alkenes **1086** and **996** in a 1.5:1 ratio. This mixture underwent the second Michael addition, which constructed the fully functionalized cyclopentane yielding **1088** and **1089** as a pair of C7 epimers. This transformation successfully synthesized the C20 quaternary stereocenter on the fully functionalized cyclopentane, but led to the undesired (*S*)-configuration at C6. To invert the configuration at C6, the oxindole was deprotonated, and the resulting enolate was treated with PhSeCl. Oxidative elimination gave an alkene, which was hydrogenated over the Lindlar catalyst to produce two diastereomers favoring the desired C7 epimer (**1090**) in a 2:1 ratio. This advanced intermediate contains a fully



Scheme 117. Total Synthesis of (±)-Coriolin (Danishefsky, 1980).



Scheme 118. Biomimetic Conversion of Alianthone to Shinjulactone C (Takahashi, 1983).

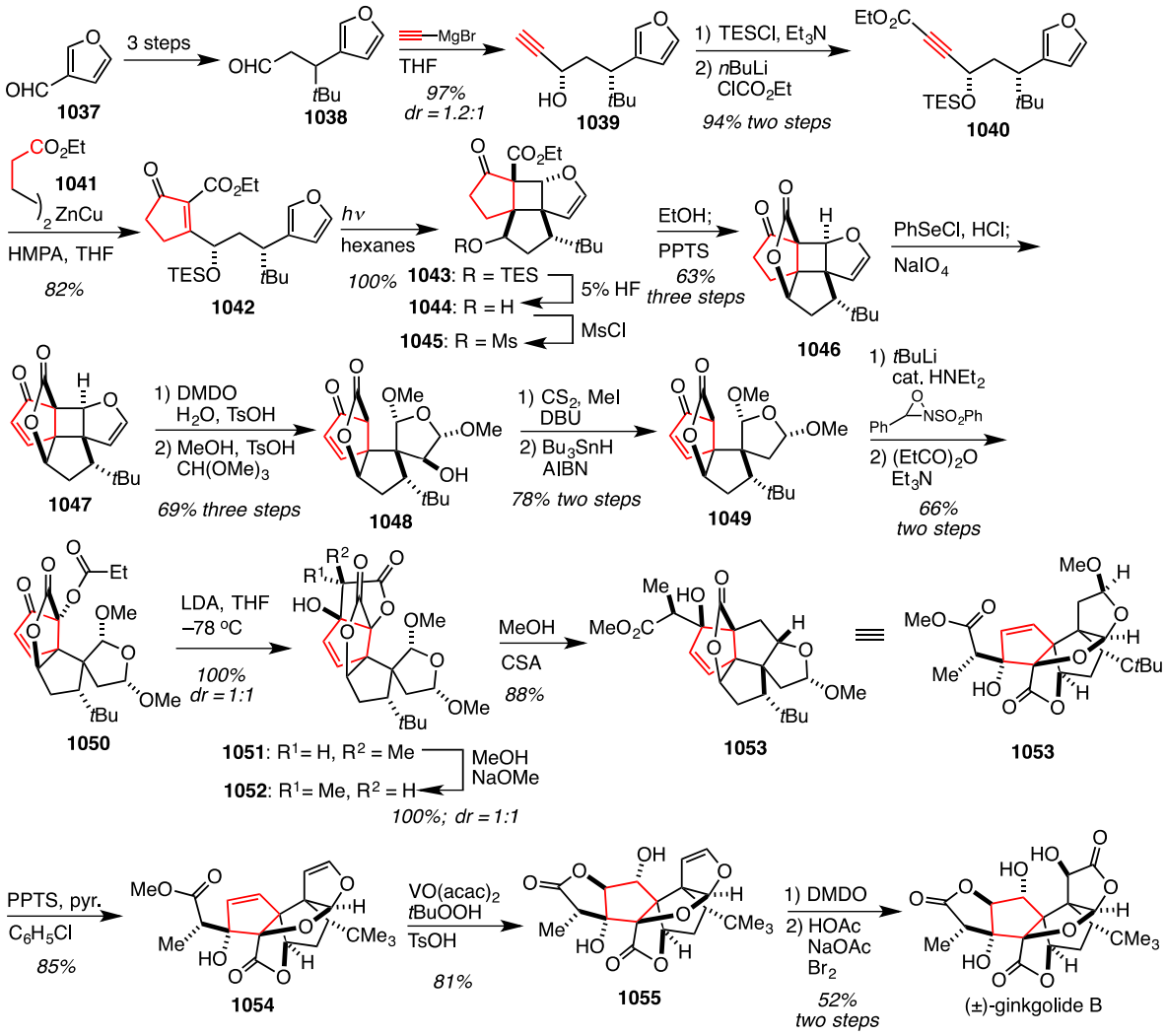


Scheme 119. Total Synthesis of (±)-Shinjulactone C (Grieco, 1990).

functionalized cyclopentane, and four additional steps were used to complete the synthesis of (+)-gelsemine.

In a formal synthesis of (±)-gelsemine, Aubé[194] performed a double conjugate addition to construct a bicyclo [3.2.1] octanone containing a fully functionalized cyclopentane (Scheme 124). In the first step of the synthesis, the dianion of ethyl 3-nitropropionate (**1061**) was generated with LDA. This was reacted with *p*-benzoquinone dimethyl ketal (**963**) to afford bicycle **964** as an inconsequential mixture of diastereomers. Treatment of the diastereomeric mixture **964** with DBU led to a single unsaturated ester **1062**. Introduction of the spirooxindole was achieved over six steps to give **1063**. Ketal removal and Horner-Wadsworth-Emmons reaction with *tert*-butyl diethylphosphonoacetate (**1064**) delivered **1065** predominantly as the desired *E*-isomer (*E*/*Z* = 3:1). Conjugate addition of methylamine on the less hindered face, alloc-protection, reduction with lithium borohydride, and acetylation furnished **1066**. This intermediate has previously been taken to (±)-gelsemine by Fukuyama.[97]

Synthetic efforts towards the hetidine and hetisine diterpenoid natural product frameworks (e.g. kobusine), were reported by Sarpong[195] (Scheme 125). These skeletons have dense polycyclic structures where the cyclopentane displays four carbon stereocenters, two of which are quaternary. The synthesis begins with alkylation of commercially available β-ketoester **1097** with known iodoalkyne **1098**. Saponification and decarboxylation delivered indanone **1099**. Hydride reduction of the ketone and alcohol elimination with PPTS gave indene **1100**. Cycloisomerization with gallium(III) iodide provided benzannulated cycloheptadiene **1101**. Selective reduction of the disubstituted alkene was performed with diimide. Treatment with ceric ammonium nitrate oxidized the benzylic position to give an enone, which underwent stereoselective hydrogenation furnishing **1102**. Allylation gave a mixture of *O*- and *C*-allylation products; heating the mixture resulted in a Claisen rearrangement simplifying the mixture to **1103**. Simultaneous reduction of the ketone and nitrile was followed by Boc-protection of the resulting amine to give **1104**. Treatment of the



Scheme 120. Total Synthesis of (±)-Ginkgolide B (Crimmins, 1999).

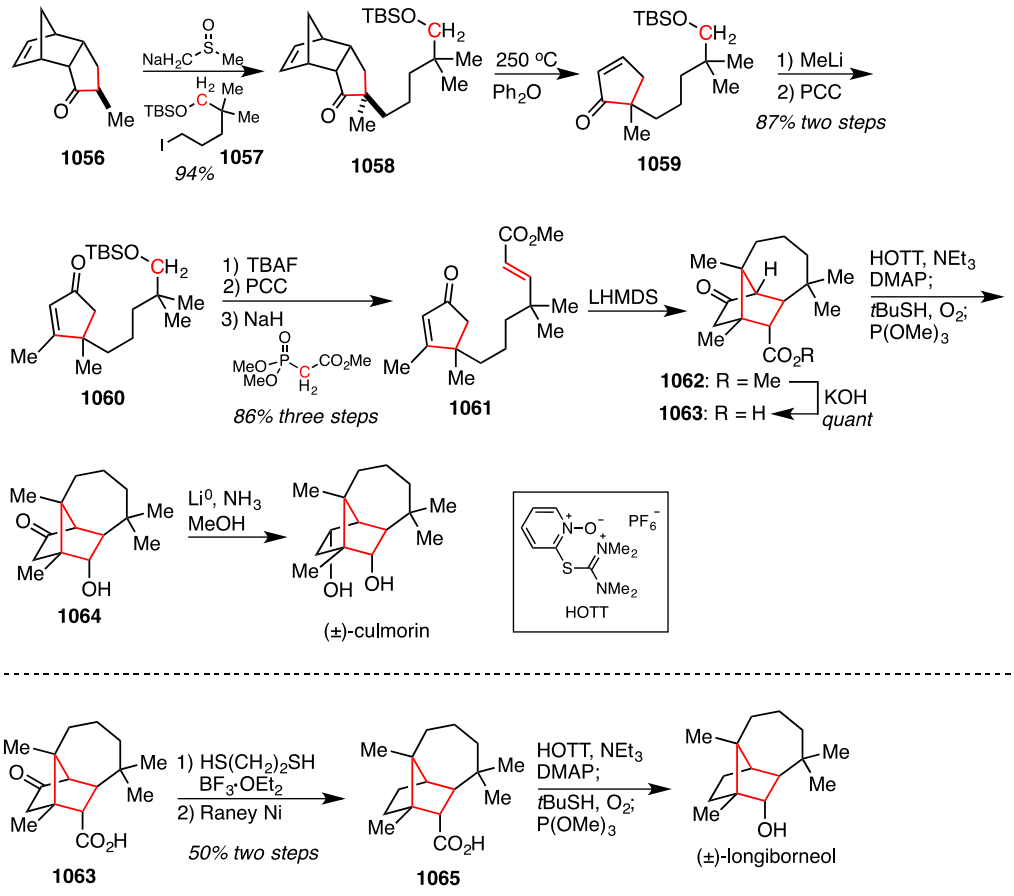
hydroxyl **1104** with thionyl chloride resulted in chlorination and spontaneous substitution by the tethered carbamate to give **1105**. Demethylation with sodium ethanethiolate yielded **1106**. Oxidative dearomatization performed with [bis(trifluoroacetoxy)iodo]benzene gave cyclohexadienone **1107**. Finally, oxidative cleavage yielded a ketoaldehyde which cyclized via a conjugate addition upon stirring in silica gel to furnish **1108**. This advanced intermediate contains many of the structural features of hetidine and hetisine-type alkaloids including a fully functionalized cyclopentane with the appropriate stereochemical configuration.

9. Friedel–Crafts and related reactions of nucleophilic alkenes

The intramolecular Friedel–Crafts acylation is a reliable process for the formation of five-membered carbocycles as part of fused polycyclic architectures. The Friedel–Crafts acylation has been used in two distinct strategies for the synthesis of gibberellin natural products; both approaches used the reaction to build the core dodecahydrofluorane substructure. In the first approach (Scheme 126, eq. 1), Lewis acid-promoted cyclization of **1109** led to the formation of the tetrahydrofluorenone **1110**. In the second strategy, Brønsted acid mediated cyclization of **1111** gave tetrahydrofluorene **1112**.

The strategic use of the Friedel–Crafts reaction benefits from the wide range of substituted benzenoid starting materials that may be employed in a regioselective bond-forming reaction. As seen in the above examples, the dodecahydrofluorene core of the gibberellins is expeditiously constructed. After the Friedel–Crafts cyclization, the six carbons of the benzene undergo functionalization to reveal the substituted cyclohexane present in the natural product. The products of the Friedel–Crafts cyclization (**1110** and **1112**) displayed functional handles for further manipulations, and both strategies provided intermediates that could be transformed to the gibberellins. One potential limitation of such Friedel–Crafts reactions in the synthesis of fully functionalized cyclopentanes is the requirement that the product five-membered ring contain (at least) two sp^2-hybridized carbon atoms. These carbons must undergo additional transformations en route to the fully saturated (sp^3-hybridized) carbocycle.

Two approaches to the natural product cyclosativene have used a cyclization of a substituted norbornene to build the fully functionalized cyclopentane. Activation of the suitably substituted starting material **1113** leads to an electrophilic intermediate **1114**



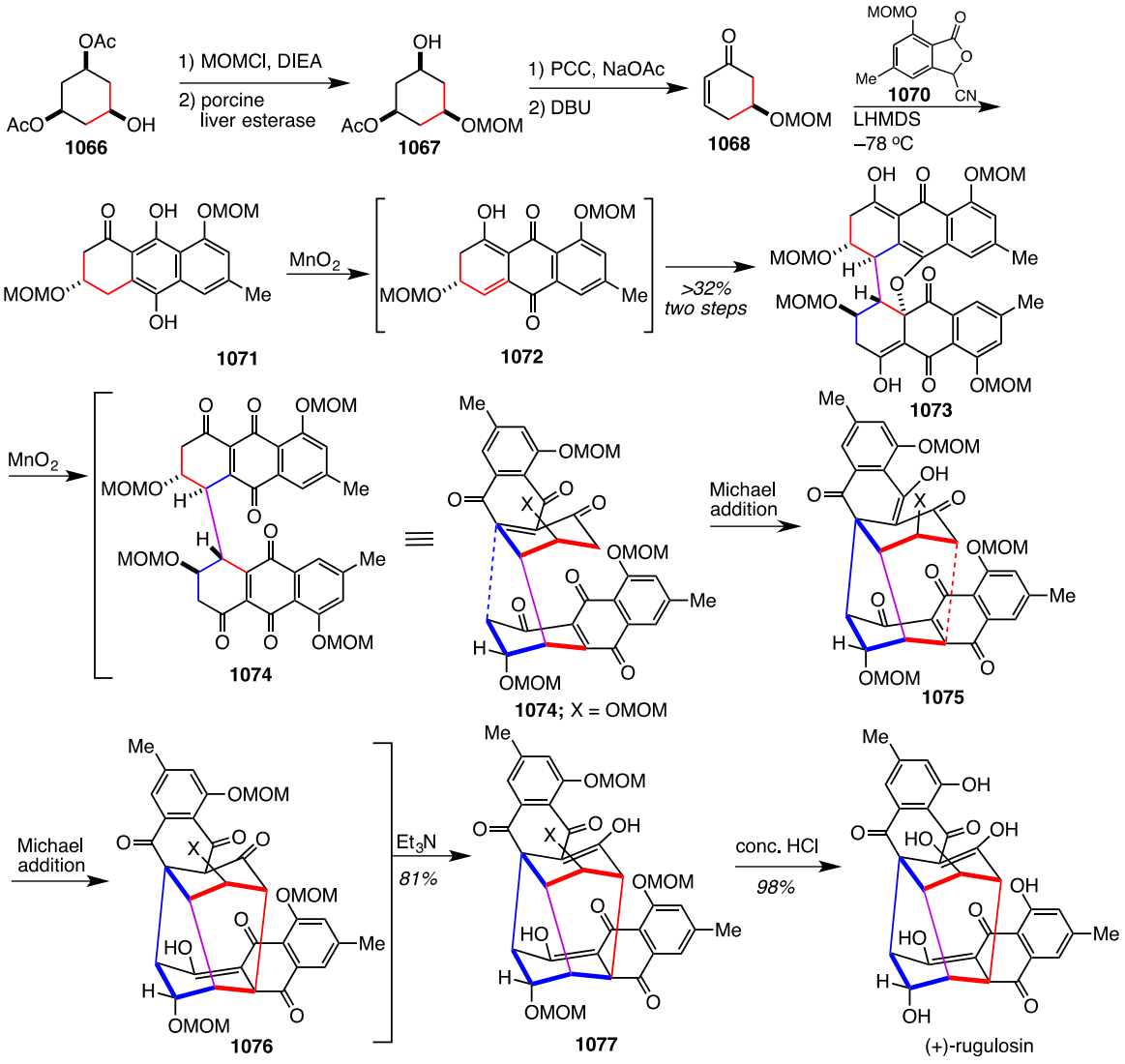
Scheme 121. Total Synthesis of (±)-Culmorin and (±)-Longiborneol (Ihara, 2000).

(Scheme 127). The electrophilic (i.e. carbocationic) carbon is trapped by the nearby alkene with concomitant introduction of a nucleophile. The nucleophile may be tethered to the substrate, or it may be an external reagent. The structure of these cyclization products displays the same tricyclo[2.2.1.0^{2,6}]hexane core as cyclosativene, and as a result the reactions are a good fit for the topology of this interesting target.

In the progress towards the synthesis of (±)-gibberelic acid (GA_3), Nakanishi[196] constructs a cyclopentane using an intramolecular Friedel-Crafts acylation (Scheme 128). The synthesis commences with a Diels–Alder reaction between diene **1116** and acrylate **1117** to give adduct **1118** as a mixture of *endo*/*exo* diastereomers. Hydrolysis of the esters and nitrile was accompanied by a decarboxylation to yield dicarboxylic acid **1119**. Heating in acetic anhydride delivered the cyclic anhydride **1109**. The intramolecular Friedel-Crafts cyclization occurred upon treatment with $AlCl_3$ in benzene to give cyclopentenone **1110**. Epoxidation with peracid and subsequent opening by the tethered carboxylic acid resulted in a lactone **1121**. This hydrofluorene derivative was the most advanced intermediate obtained by Nakanishi.

Completion of the synthesis from intermediate **1121** was accomplished by Yamada[197] approximately twenty years later. The secondary alcohol was protected as the TMS ether (**1122**). A Corey–Chaykovsky epoxidation was followed by treatment with boron trifluoroetherate to give an aldehyde on the less hindered face of **1123**. Seven additional steps were required to advance **1123** to intermediate **1124**. Cyclohexenone **1125** was obtained through a dissolving metal reduction of the phenyl ring, acidic hydrolysis of the enol ether and double bond isomerization. A photochemical [2 + 2] cycloaddition with allene gave tetracyclic adduct **1126** with a *syn* ring fusion. This material was advanced over five steps to intermediate **1127**. Fluoride removal of the SEM ether, activation as the sulfonate and elimination with DBU gave alkene **1128**, which could be advanced over twelve steps to **1129**. Iodolactonization of **1129** installs the oxygen-containing stereocenter on the cyclopentane ring. Removal of the MOM protecting group and elimination of the iodide with DBU delivers GA_3.

In a second generation synthesis of (±)-gibberellic acid by Mander,[198] the key five-membered ring is constructed using an intramolecular Friedel–Crafts acylation (Scheme 129). The synthesis commences with benzyl iodide derivative **1130**. Alkylation with enediolate **1131** delivers the hydrofluorene precursor **1111**. The Friedel–Crafts reaction was induced with polyphosphoric acid, and a simultaneous decarboxylation furnishes cyclopentadiene **1112**. This material was advanced over the next three steps to diazo ketone **1132**. Acid-catalyzed cyclization delivered tetracyclic ketone **1133**. Standard functional group transformations over the next three steps delivered **1134**. Carboxylation of the benzylic position was accomplished by first deprotonation followed by stirring in a carbon dioxide suspension in ether. The configuration of the carboxy bearing benzylic stereocenter was undesired for the synthesis of gibberellic acid, and would require later epimerization. Hydrogenation of the cyclohexene gives the *cis*-fused ring system in **1135**. This material was advanced four steps to cyclohexadiene **1136**. The methyl ester was converted to the corresponding carboxylic acid under nucleophilic conditions, and bromolactonization gave cyclized product **1137**. This unstable intermediate was immediately subjected to chromium-based reduction conditions, which gave



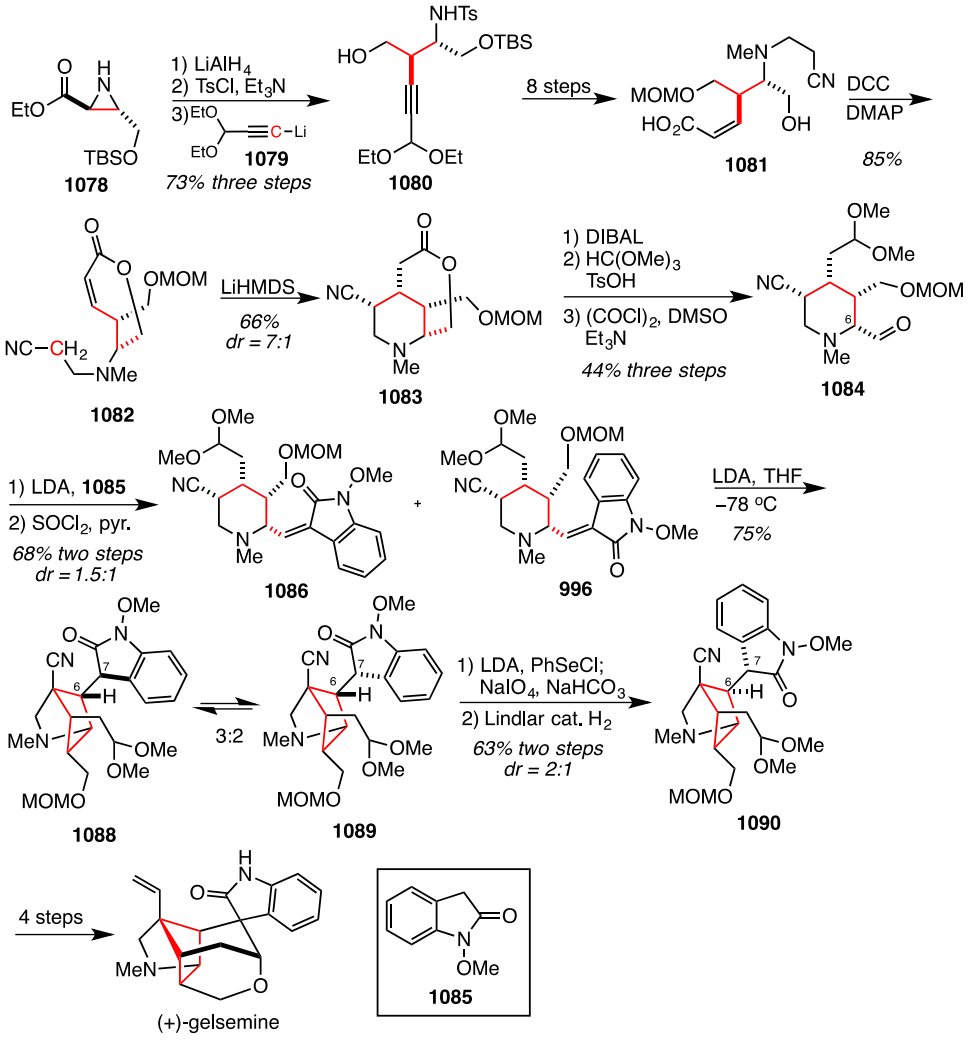
Scheme 122. Total Synthesis of (+)-Rugulosin (Nicolaou, 2005).

1138. Epimerization of the benzylic carboxylate was performed in DBU to correct the stereochemistry for the natural product. A two-step transesterification delivered compound **1139** which had previously been taken to gibberellic acid by Mander.[109]

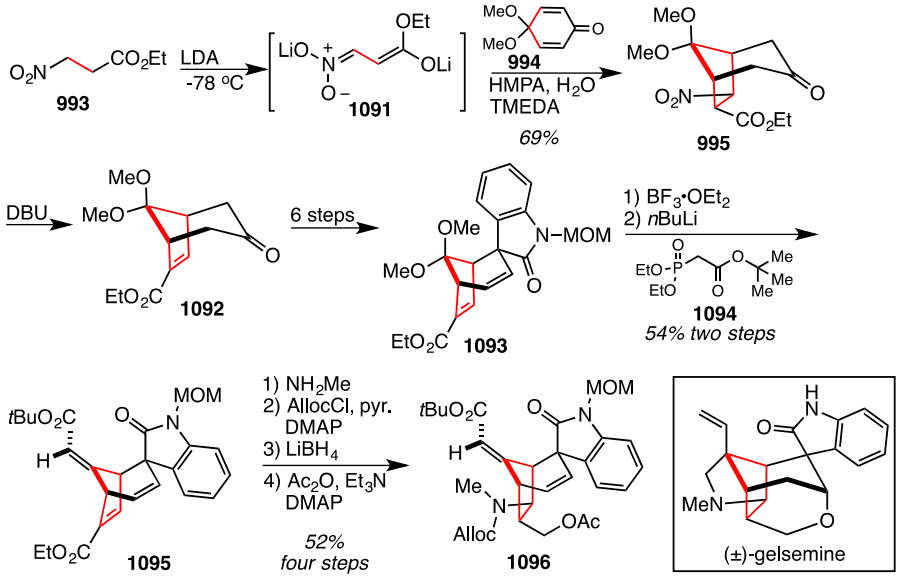
The formal synthesis of cyclosativene by Riehl[199] creates a fully functionalized cyclopentane with an intramolecular cyclization reaction (Scheme 130). The synthesis commences with a Diels–Alder cycloaddition between cyclopentadiene (**11**) and citraconic anhydride to give **1140**. Reductive cleavage of the anhydride **1140** and sulfonylation of the resulting diol delivers **1141**. Reaction with excess lithium bromide gives homoallylic bromide **1142**. Nucleophilic substitution with sodium cyanide delivers cyclization precursor **1143**. Upon treatment with benzenesulfenyl chloride, cyclization occurs to give tricyclic compound **1144** and creates a fully functionalized cyclopentane. This material was advanced over eight steps to carbomethoxy sulfone **1145**. A Dieckmann-type reaction delivered β-keto sulfone **1146**. Removal of the sulfone over three steps delivers **1147**. This intermediate was previously taken forward to cyclosativene by Yoshikoshi.[200]

Synthesis of (±)-cyclosativene was completed by Baldwin[201] wherein a fully functionalized cyclopentane was constructed with an intramolecular cyclization of a homoallylic carbocation (Scheme 131). The norbornene scaffold was assembled with a Diels–Alder cycloaddition of propynal and 2,3-dimethylcyclopentadiene (**1149**; generated in situ from **1148**) to give **1150**. Conjugate addition of allyl alcohol to the unpurified aldehyde delivered ether **1151**. Aldehyde reduction and bromination of the resulting alcohol was followed by displacement with lithium acetylide to give **1152**. Ether cleavage and subsequent activation of the resulting alcohol as the tosylate gave cyclization precursor **1153**. Solvolysis of **1153** led to a carbocation, which was trapped by the alkene giving the key five-membered ring; the resulting carbocation was intercepted by the tethered alkyne leading to intermediate **1154**. Hydrolytic workup gave ketone **1155**, which contains the fully functionalized cyclopentane of cyclosativene. The natural product was completed in an additional three steps.

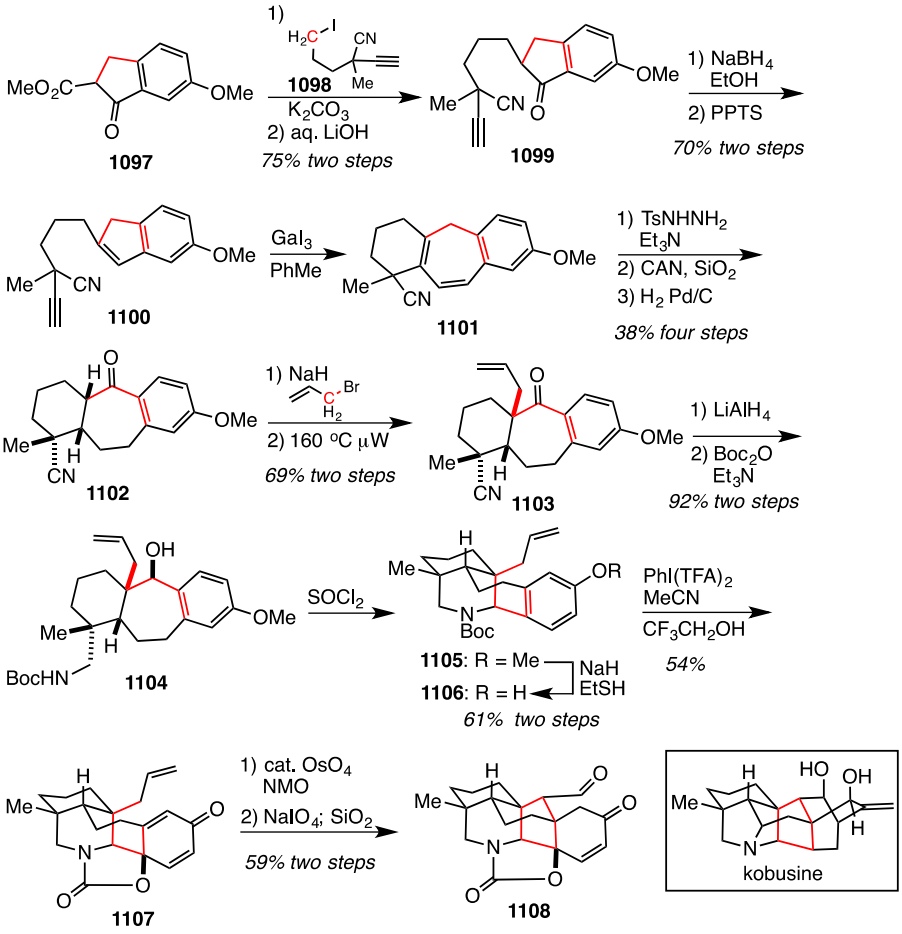
In the synthesis of (±)-nominine by Muratake and Natsume,[202] a Lewis acid-catalyzed Prins reaction[203] is used to form a fully functionalized cyclopentane (Scheme 132). The route commences with a palladium-catalyzed intramolecular α-arylation of **1156** to give **1157** as a mixture of diastereomers favoring the undesired *cis* isomer (4.2:1). Acetal formation under standard conditions gave **1158**. Under the conditions of the acetal formation, an epimerization occurred which decreased the *cis*:*trans* ratio to 2:1. The desired



Scheme 123. Total Synthesis of (±)-Gelsemine (Qin, 2012).



Scheme 124. Formal Synthesis of (±)-Gelsemine (Aubé, 2007).

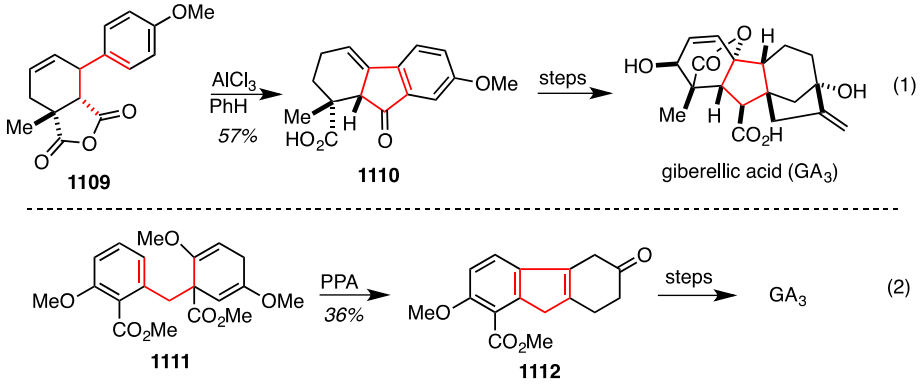


Scheme 125. Synthetic Studies Towards the Hetidine and Hetisine Skeletons (Sarpong, 2013).

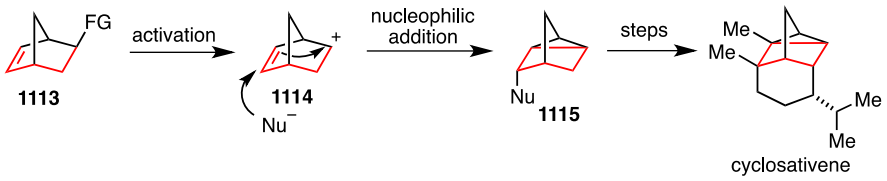
trans isomer was isolated and the *cis* isomer was recycled by re-establishing the equilibrium. Birch reduction of the arene gives predominantly the undesired β,γ-enone **1159**, but this could be isomerized with NaOMe to the desired α,β-enone **1160**. Luche reduction of **1160** gives allyl alcohol **1161** as the sole isomer. Eschenmoser–Claisen rearrangement of the allylic alcohol was followed by amide reduction and protection to give **1162**. Treatment of **1162** with Lewis acid initiates opening of the acetal to give an oxocarbenium ion, which is intercepted by the nearby alkene to form a fully functionalized cyclopentane (**1163**). This material was advanced over 17 steps to intermediate **1164**. Removal of the Cbz protecting group was followed by chlorination of the alcohol and subsequent cyclization to furnish *O*-acetylnominine. Acetate cleavage with base delivered the natural product.

10. Radical reactions

Radical cyclizations represent versatile C–C bond formations that can lead to cyclopentane formation with concomitant formation of stereogenic carbon atoms, including quaternary carbon



Scheme 126. Friedel–Crafts Acylations in the Synthesis of Gibberellic Acid.

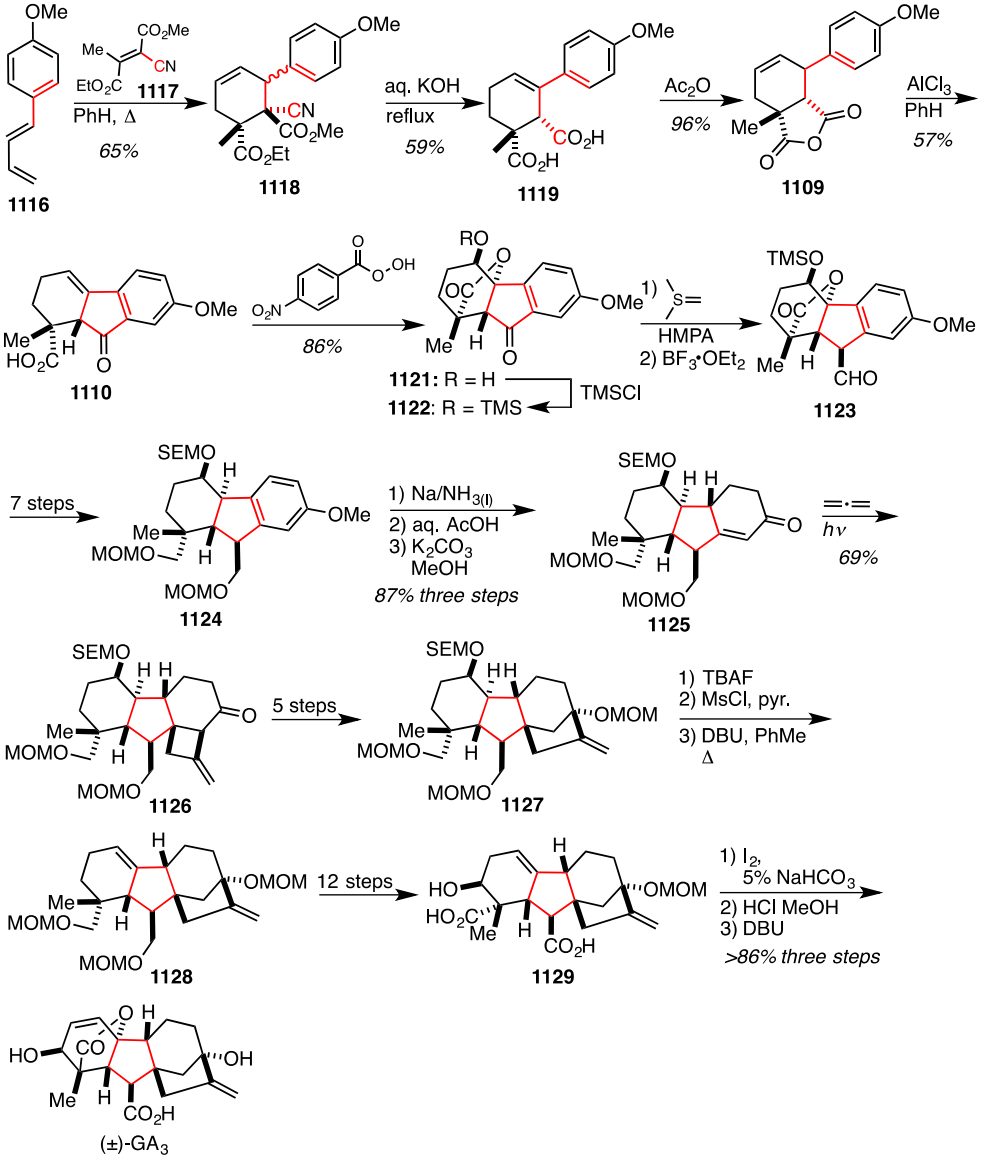


Scheme 127. Alkene Cyclizations in the Synthesis of Cyclosativene.

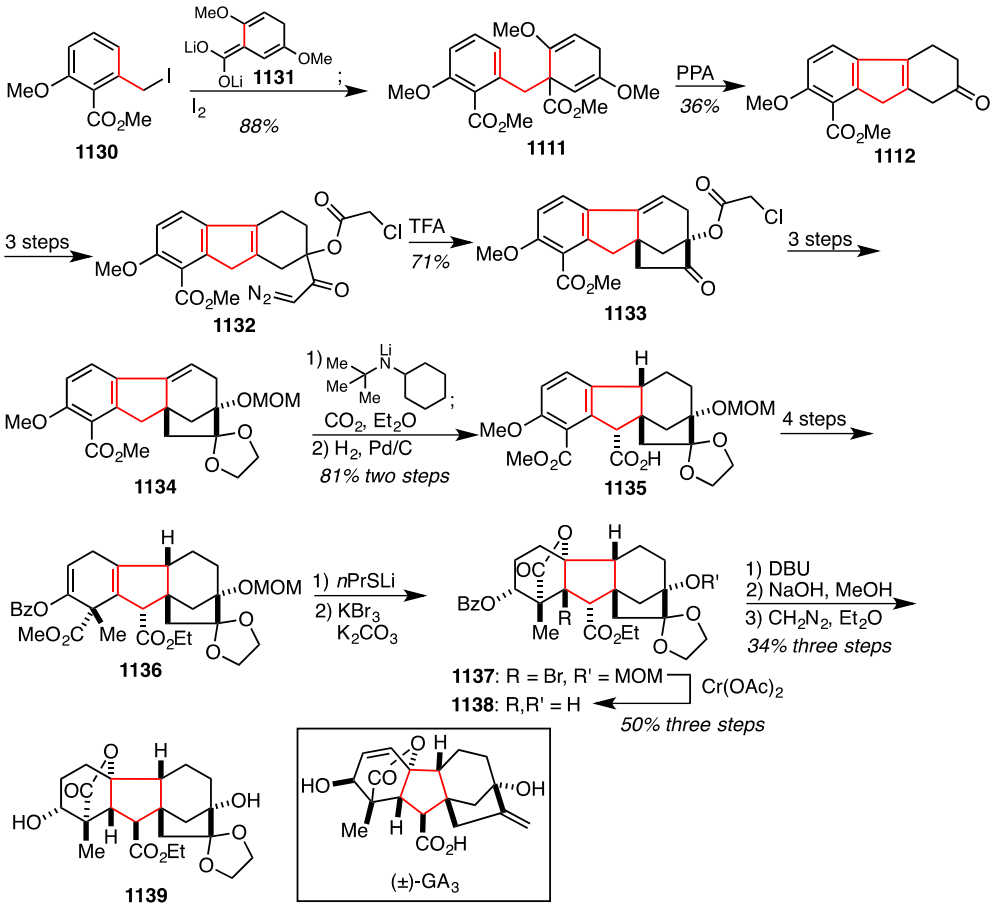
stereocenters. Such reactions are tolerant of steric crowding, and they are commonly used to form stereodiad strucutral motifs as part of larger arrays of contiguous stereocenters.

Typically, a molecule with a 1,5-relationship between sp^2-hybridized carbons will undergo an intramolecular pinacol-type coupling to give a substituted cyclopentane (Scheme 133). For example, a 1,5-ketoaldehyde (**1165**) reacts with SmI_2 to give ketyl radical **1166**. The ketyl radical undergoes 5-*exo*-trig cyclization, followed by single electron reduction and protonation to give the diol **1167**. Yields are good and the diastereomeric ratio can be quite high.

In general for such radical cyclizations, the stereochemical outcome at the forming stereocenters is rationalized by considering the most stable chair-like transition state that places the resident substituents in an equatorial position. Reductive cyclization gives the *syn*-1,2-diol. The preference for the formation of the *syn* diol in these substituted cases, and in other unsubstituted dialdehydes (e.g. adipaldehyde), has been explained by a chelate



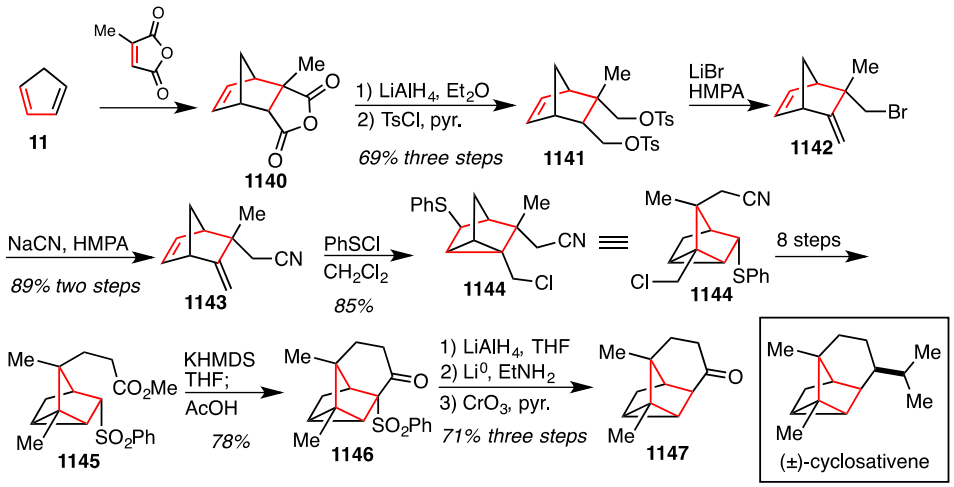
Scheme 128. Total Synthesis of (±)-Gibberellic Acid (Nakanishi, 1969; Yamada, 1989).



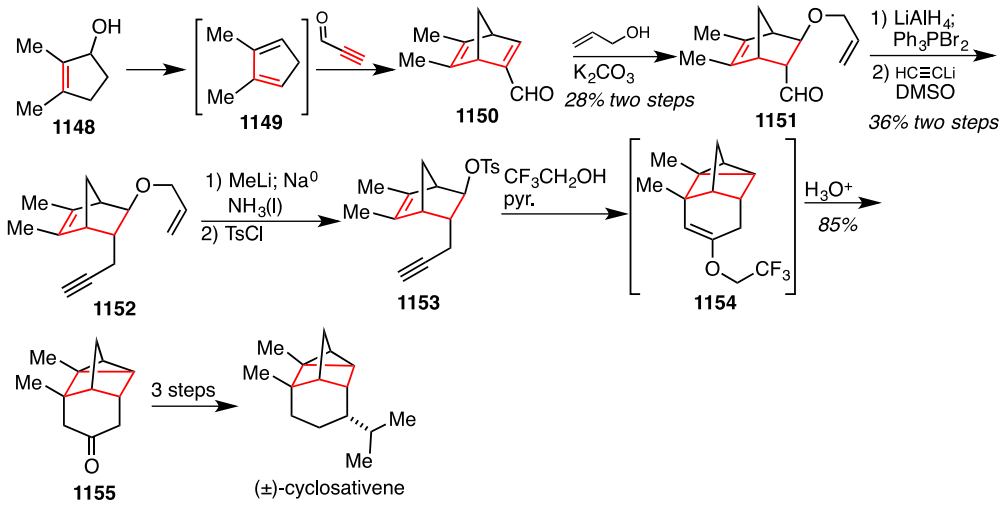
Scheme 129. Total Synthesis of (±)-Gibberellic Acid (Mander, 1975).

with samarium.[204] The adjacent alkoxy substituent forces the emerging diol to be *anti* with respect to the alkoxide.[205] However, not all cases follow this trend and other factors may complicate this stereochemical model (see discussions of individual syntheses below).

The starting material is not limited to ketoaldehdyes, and a variety of functional group patterns participate in this type of reaction, provided the two sp^2-hybridized carbons exist in a 1,5-reationship. For example, 1,5-ketoesters, 1,5-ketonitriles, 1,5-ketooxime ethers, and δ,ε-unsaturated aldehydes all perform well in this type of reaction. Such flexibility in starting material allows for strategic placement of a variety of functionality (alcohols, amines, ketones, alkenes, etc.) in the product for subsequent transformations.



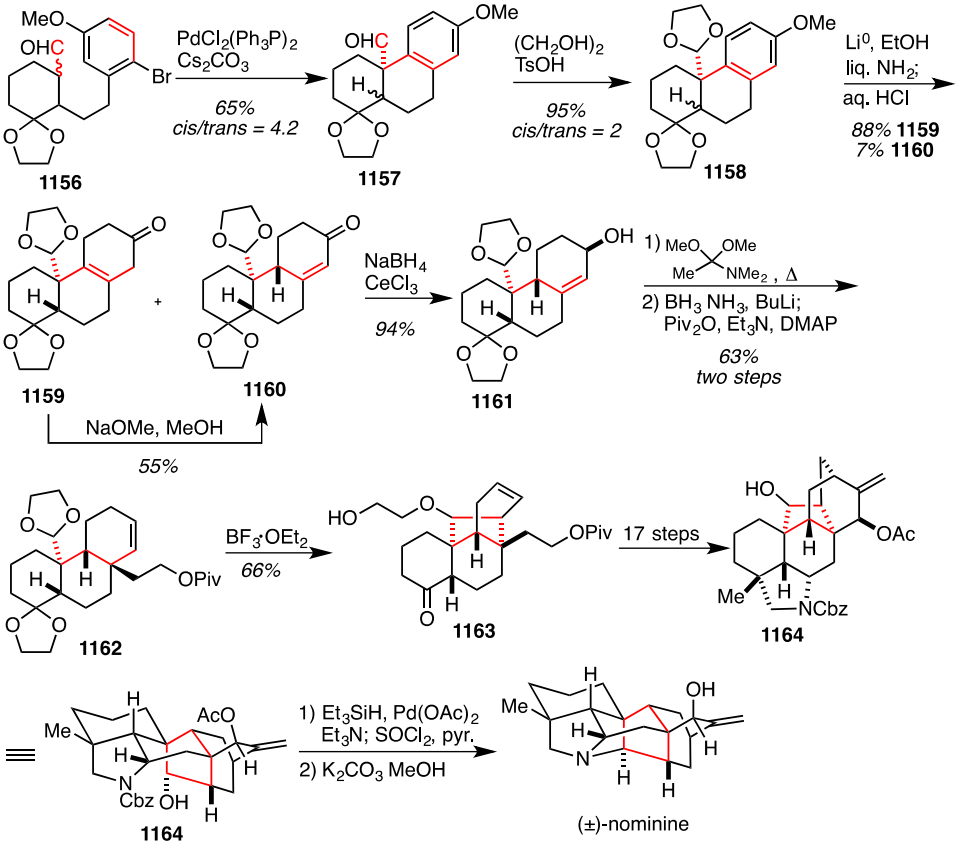
Scheme 130. Formal Synthesis of (±)-Cyclosativene (Riehl, 1976).



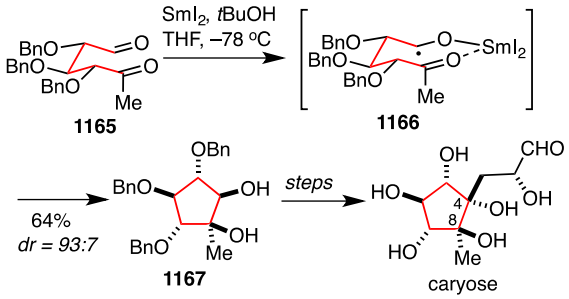
Scheme 131. Total Synthesis of (±)-Cyclosativene (Baldwin, 1980).

Particularly powerful examples of radical cyclizations in the context of this review form σ-bonds between a fully substituted stereocenter and a heteroatom-bearing stereocenter (e.g. C4–C8 in caryose, Scheme 133). The diastereoselectivity is often high, and this method has been used in elegant syntheses of tertiary alcohol stereocenters.

A second theme in this section involves homolysis of a sigma bond to form a carbon-centered radical that undergoes 5-*exo*-trig cyclization of a tethered alkene (Scheme 134, eq. 1). A suitable starting material **1168** undergoes bond homolysis to give radical **1169**. Cyclization of radical **1169** over a tethered alkene gives a new radical (**1170**) that abstracts a hydrogen atom to give the product **1171**. The initial σ-bond homolysis varies widely, and in the context of this review C–S, C–Hg, C–O, and C–H bonds have been cleaved to provide reactive radical intermediates. This strategy is exemplified by a key cyclization in the Hart synthesis of (±)-gelsemine (eq. 2). Homolysis of *N*,*S*-acetal **1172** gave an α-amino radical that cyclized to give intermediate **1173**.



Scheme 132. Total Synthesis of (±)-Nominine (Muratake and Natsume, 2004).

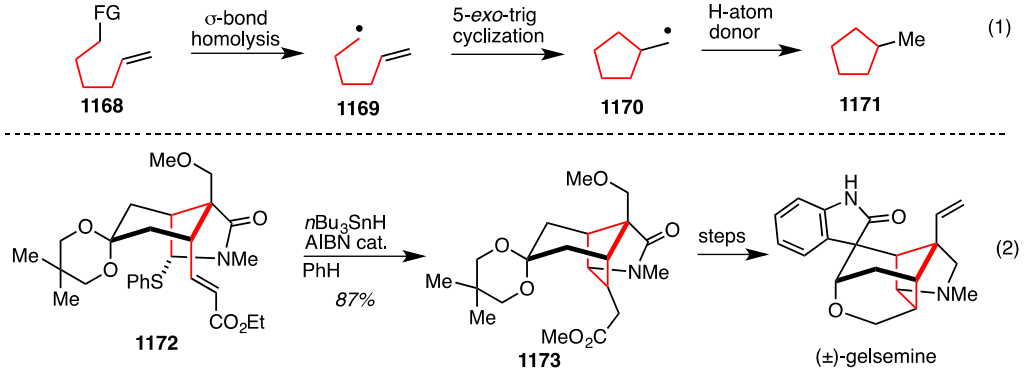


Scheme 133. Pinacol Couplings in the Synthesis of Fully Functionalized Cyclopentanes.

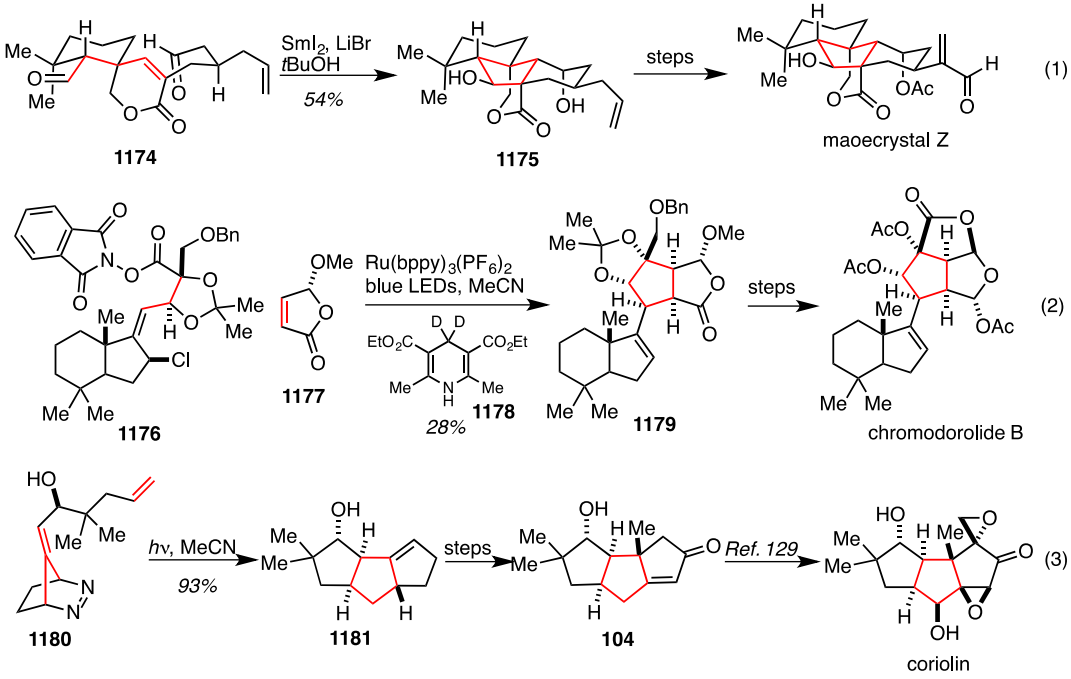
Radical reactions are well-suited to cascade processes that create multiple bonds. This review contains three unique reactions that deviate from the typical themes discussed above and create multiple new rings in a single step (Scheme 135). Reisman reported a reductive cyclization of substrate **1174** to give the molecular architecture of maoecrystal V (eq. 1). Second, Overman reported an elegant radical addition-cyclization-fragmentation cascade reaction between **1176** and radical acceptor **1177** (eq. 2). Finally, Little reported a fragmentation-cyclization of **1180** to give triquinane **1181**. Intermediate **1181** was advanced to complete a formal synthesis of coriolin[129] (eq. 3).

10.1. Pinacol-type reactions of carbon-heteroatom double bonds

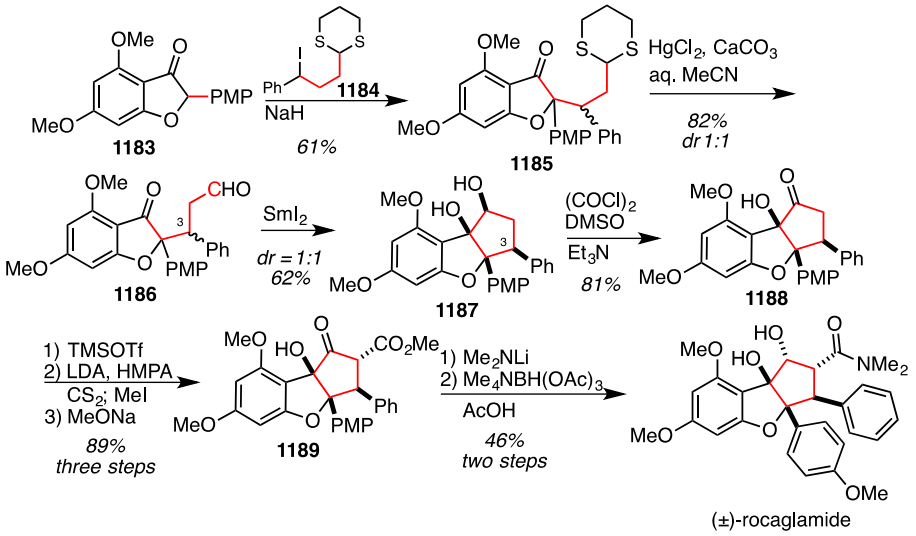
In the synthesis of (±)-rocaglamide by Taylor,[206] the fully functionalized cyclopentane was constructed with a radical-mediated pinacol coupling (Scheme 136). The route commences with alkylation of benzofuranone **1183** with iodide **1184** under standard conditions to give **1185** as a 1:1 mixture of diastereomers. Hydrolysis of the dithiane produced aldehyde **1186**. Upon treatment with samarium iodide, the pinacol coupling occurred delivering **1187** as a 1:1 mixture of diastereomers (epimeric at C3). Coordination of samarium between the oxygens of the ketoaldehyde during the formation of the ketyl radical is thought to result in



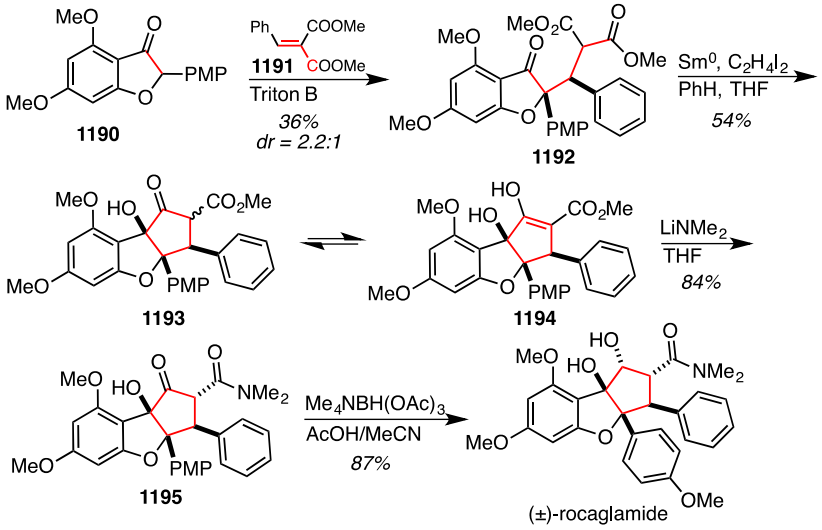
Scheme 134. σ-Bond Homolysis-5-*exo*-trig Cyclizations in the Synthesis of Fully Functionalized Cyclopentanes.



Scheme 135. Radical Cyclizations Forming Multiple Rings.



Scheme 136. Total Synthesis of (±)-Rocaglamide (Taylor, 1991).

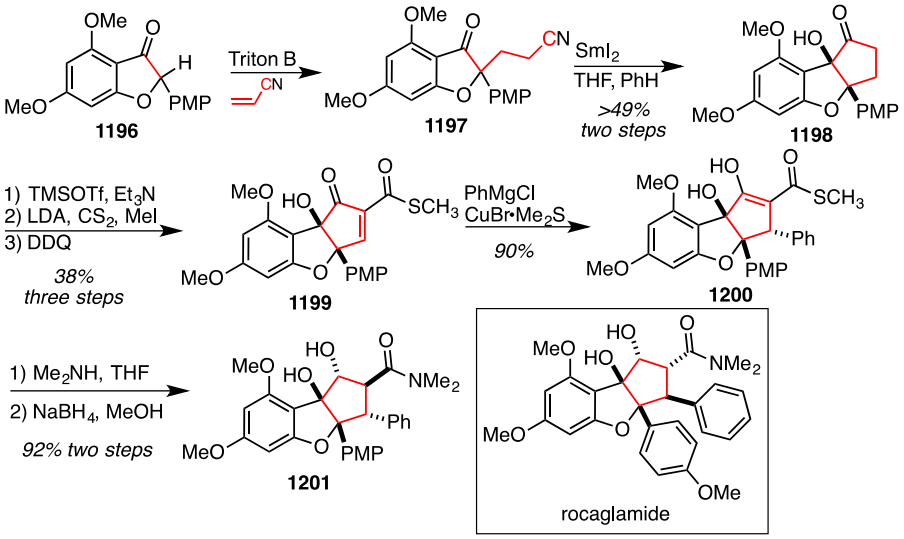


Scheme 137. Total Synthesis of (±)-Rocaglamide (Qin, 2008).

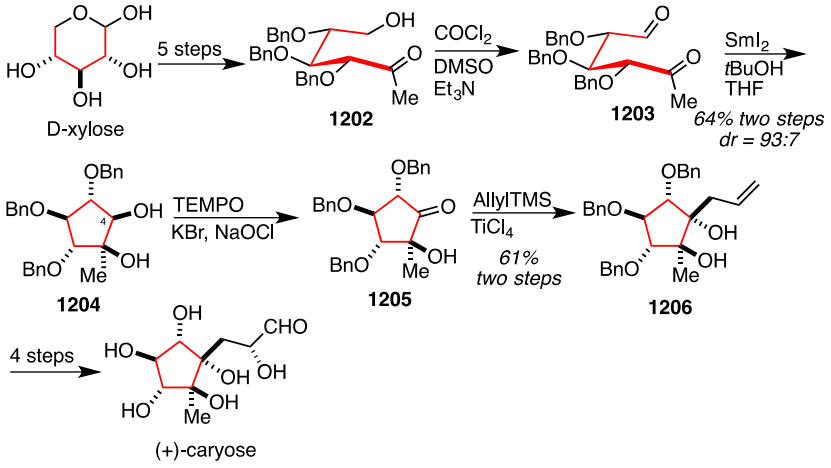
the *cis*-relationship in diol **1187**. However, the target rocaglamide bears an *anti*-diol relationship, so an inversion of the secondary alcohol would ultimately be required. A Swern oxidation delivered ketone **1188**. Conversion of the ketone to the β-ketoester **1189** was accomplished over three steps following the conditions of Kraus[207] discussed above. Ester **1189** was converted to the corresponding amide and a stereoselective ketone reduction was directed by the vicinal hydroxyl group to complete (±)-rocaglamide.

In the Qin[77] synthesis of (±)-rocaglamide, a radical cyclization was employed for constructing the fully functionalized cyclopentane (Scheme 137). The synthesis began with a Michael addition of benzofuranone **1190** with α-methoxycarbonylcinnamate (**1191**) to furnish the desired intermediate **1192** in modest yield and modest dr. The radical cyclization with samarium metal and 1,2-diiodoethane delivered cyclopentanone **1193**, which is in equilibrium with its enol tautomeric form (**1194**). The radical cyclization gave a single diastereomer of **1194** resulting from the preferential formation of the *cis*-fused bicycle. Amidation of the mixture of **1193** and **1194** was performed with lithium dimethylamide, and the product **1195** was formed as a single diastereomer in which the enol tautomer was not observed. It was shown that this diastereomer is the thermodynamic product of the reaction. Finally, ketone reduction proceeds with internal delivery of hydride directed by the vicinal hydroxyl group to give the desired diasteromer completing the synthesis of (±)-rocaglamide.

In the synthetic efforts towards rocaglamide, Kraus[207] constructs a functionalized cyclopentanone using a samarium-mediated cyclization of a ketonitrile (Scheme 138). Conjugate addition of ketone **1196** to acrylonitrile delivered **1197** as a racemic mixture. Treatment with samarium iodide induces a radical cyclization exclusively furnishing the *cis* ring fusion in ketone **1198**. This intermediate was converted to the corresponding acyl cyclopentenone **1199** over three steps. Conjugate addition of phenyl cuprate was expected to occur from the convex face to deliver a *syn* relationship of the two aromatic substituents. However, addition of the organometallic occurred away from the *p*-methoxyphenyl substituent to deliver **1200**. Amide formation and ketone reduction with sodium borohydride delivered a fully functionalized



Scheme 138. Synthetic Studies Towards Rocaglamide (Kraus, 1989).

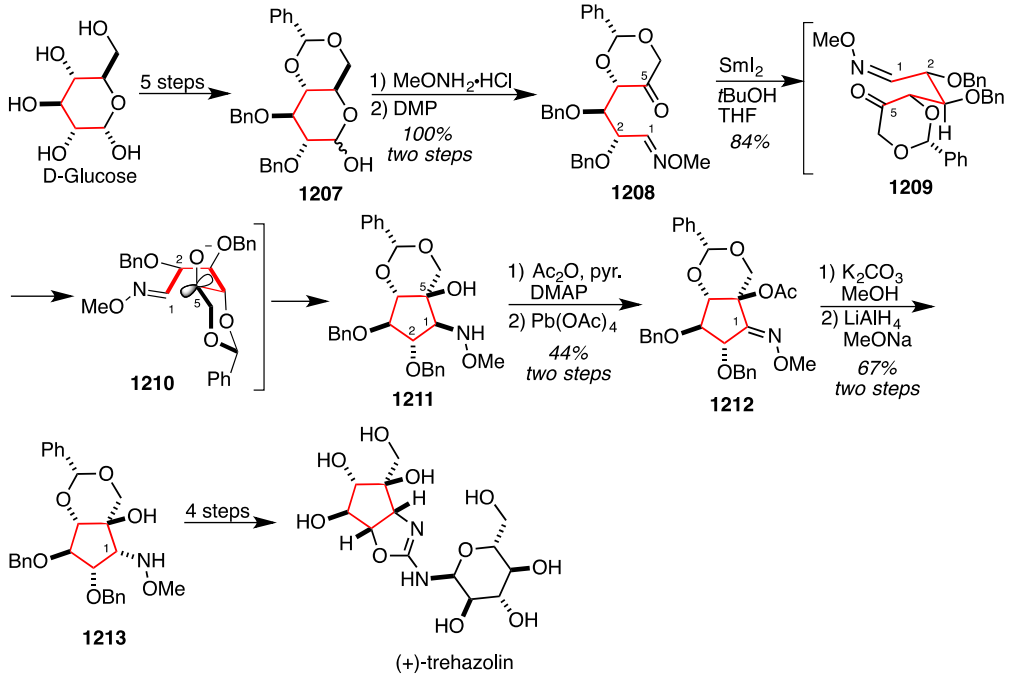


Scheme 139. Total Synthesis of (+)-Caryose (Iadonisi, 1997).

cyclopentane **1201**. Unfortunately, it was discovered that this intermediate did not display the desired relative stereochemistry of rocaglamide when compared with an authentic sample of the natural product.

The synthesis of the unusual monosaccharide (+)-caryose was completed by Iadonisi,[208] and it used a radical cyclization of a ketoaldehyde to construct the fully functionalized cyclopentane (Scheme 139). The route begins with **1202**, a compound synthesized from D-xylose in five steps. Swern oxidation yields the ketoaldehyde cyclization precursor **1203**. Exposure to samarium iodide promotes the expected cyclization to give **1204** as the major product in a 23:1 diastereomer ratio. As expected, the *syn*-diol diastereomer is formed (*trans* with respect to the vicinal benzyloxy substituents) likely as a result of a samarium chelate during the cyclization.[204] At this stage, a fully functionalized cyclopentane has been synthesized, but the completion of caryose requires further functionalization. The secondary alcohol was oxidized giving ketone **1205**. Addition of allyltrimethylsilane and $TiCl_4$ gave homoallylic alcohol **1206** with good selectivity. The authors hypothesize that the stereoselectivity of the addition can be attributed to complexation of the reagents to the adjacent hydroxyl and internal *syn*-delivery of the allyl group. The fully functionalized cyclopentane now displays all the appropriate stereocenters for the natural product (+)-caryose. The natural product was completed in an additional four steps.

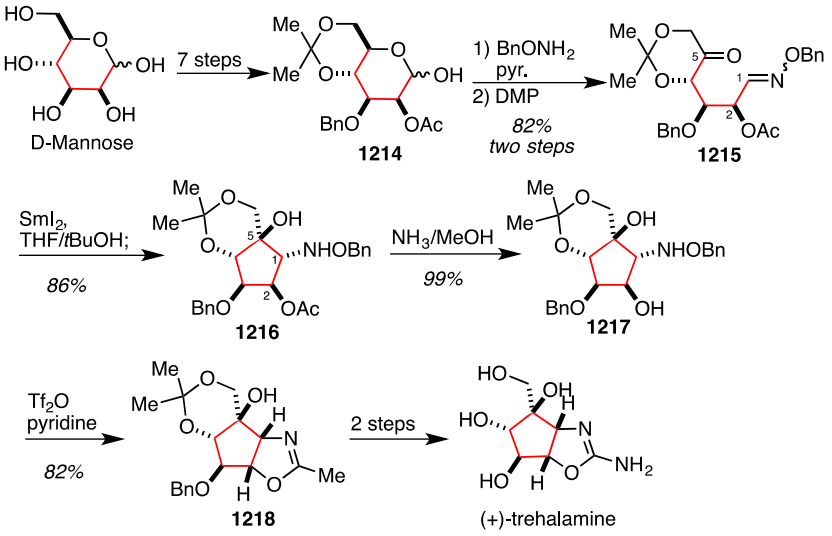
In the synthesis of (+)-trehazolin by Giese,[209] a pinacol-type coupling using samarium iodide was used to synthesize the fully functionalized cyclopentane (Scheme 140). Intermediate **1207** was prepared in five steps from D-glucose using standard synthetic transformations. Ring opening of the pyranose with methoxyamine hydrochloride delivers an oxime, and oxidation gives **1208**. Radical cyclization of keto-oxime **1208** occurs stereoselectively to form the *cis*-amino alcohol **1211** as a single diastereomer. In a departure from the stereochemical model invoked in the samarium-chelated pinacol coupling of dicarbonyls, experiments by Giese with **1208** and congeners suggested that interactions between tether substituents can favor either *syn* or *anti* products. The cyclic acetal protecting group in **1208** was designed to favor conformation **1209**, which has a *syn* co-planar relationship of the ketone and oxime double bonds. Reduction of **1209** gives radical anion **1210**, which leads to formation of the C5,C1 *syn* amino alcohol **1211**. Cyclization product **1211** had the desired configuration of the tertiary alcohol



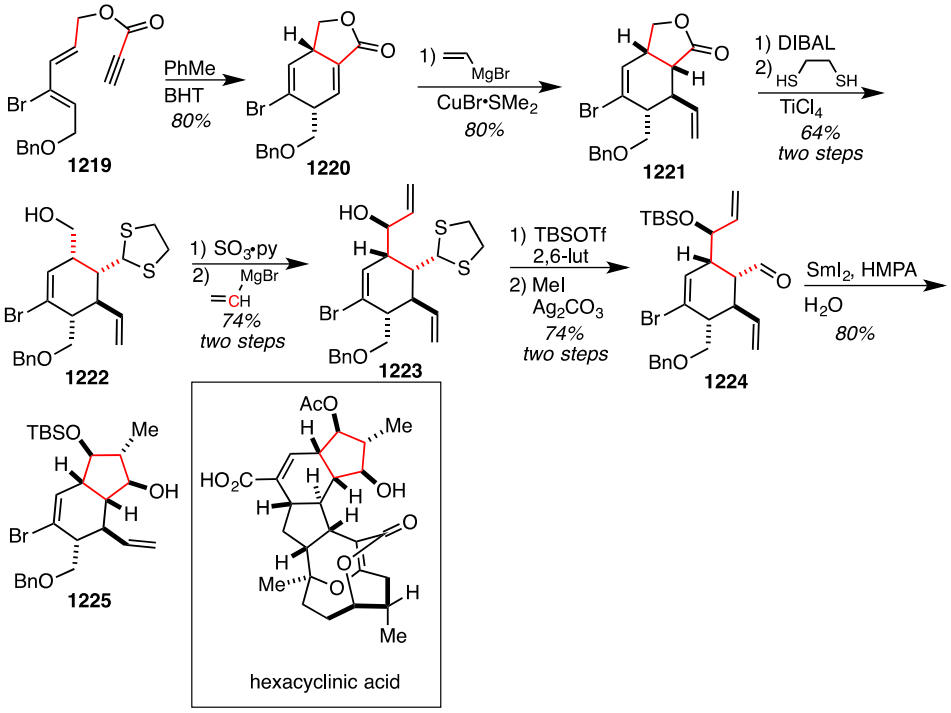
Scheme 140. Total Synthesis of (+)-Trehazolin (Giese, 1998).

stereocenter, but the amine-bearing stereocenter required stereochemical inversion. Interestingly, some substrates gave C5,C1 *trans*-configured amino alcohol products; however, no substrates were found that gave the appropriate *trans*,*trans*-diastereomer with respect to C5, C1 and C2. Although not commented upon by the authors, all cyclizations led to formation of the *trans* relationship between the emerging amine-bearing stereocenter at C1 and the resident alkoxy substituent at C2.[210] The inversion of the C1 stereocenter began with ester protection of the tertiary alcohol and oxidation of the hydroxylamine ether to the oxime ether **1212**. The acetate was removed, and stereoselective reduction of the oxime ether delivered **1213**. Selectivity of the hydride addition may be explained by complexation of the $LiAlH_4$ by the adjacent hydroxyl group promoting delivery from the convex face of the bicycle. The fully functionalized cyclopentane now bears all of the stereocenters contained in (+)-trehazolin, and the natural product was completed in an additional four steps.

In the synthesis of (+)-trehalamine by Chiara,[211] a similar stereoselective ketone-oxime ether reductive cyclization constructs a fully functionalized cyclopentane (Scheme 141). The synthesis begins with **1214**, which was prepared from D-mannose in seven steps. Conversion to the radical cyclization precursor **1215** occurs over two steps. Radical cyclization is promoted by treatment with samarium iodide. Substrate **1215** contains a cyclic acetal protecting group, similar to the cyclization substrate **1208** used by Giese. However, a C5,C1 *trans*-amino alcohol diastereomer was observed in **1216**. Also similar to the Giese synthesis, the amino alcohol formed displays a *trans* relationship between the emerging amine



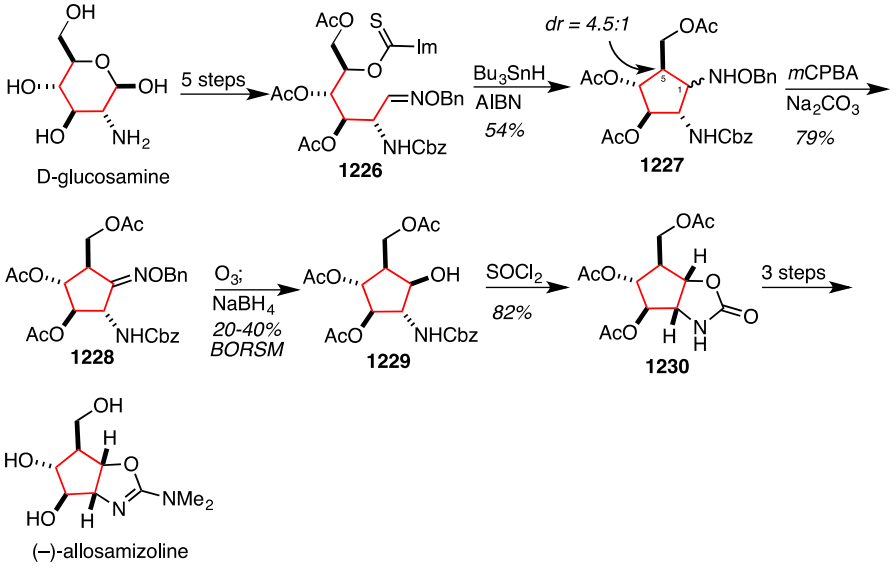
Scheme 141. Total Synthesis of (+)-Trehalamine (Chiara, 1999).



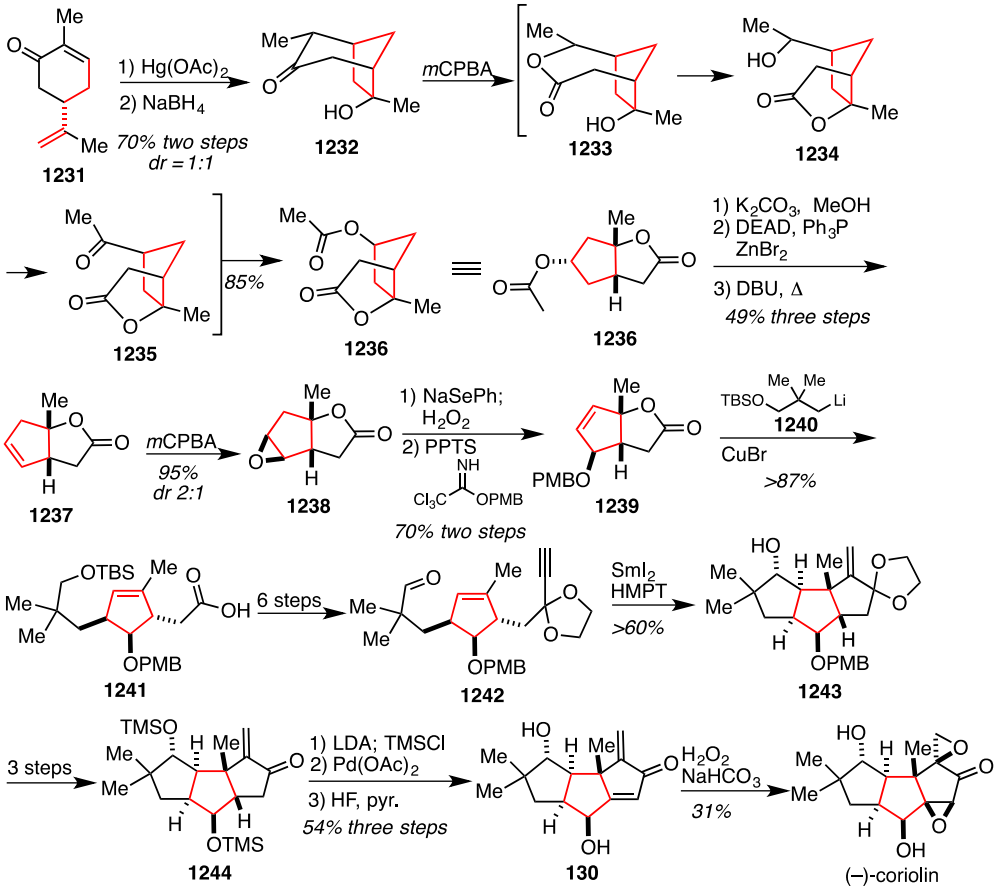
Scheme 142. Synthetic Studies Towards Hexacyclinic Acid (Clarke, 2009).

bearing stereocenter at C1 and the resident substituent at C2. The stereochemical result was attributed to minimization of allylic 1,3 strain in the cyclization transition state.[212] As a result of the stereochemistry present in the D-mannose starting material, intermediate **1216** requires stereochemical inversion of the alcohol bearing stereocenter at C2. The acetate protecting group was removed with ammonia and methanol to give **1217**. Triflation of the secondary alcohol induces an intramolecular substitution to form the oxazoline **1218**. An additional two steps were required to complete the synthesis of (+)-trehalamine.

In the synthetic studies toward hexacyclinic acid, Clarke[213] uses a reductive radical cyclization to build a fully functionalized cyclopentane (Scheme 142). The synthesis begins with an intramolecular Diels–Alder reaction of diene-yne **1219** to yield bicyclic lactone **1220**. Conjugate addition of a vinyl cuprate occurs on the diastereoface opposite the benzyloxy methyl substituent. After an aqueous workup, *cis*-fused bicycle **1221** is obtained. Lactone reduction and thioacetal formation gave intermediate **1222**. Oxidation of the primary alcohol was followed by addition of vinylmagnesium bromide to give **1223**. The desired diastereomer was obtained in a 30:1 ratio and can be rationalized by Felkin-Anh analysis. The alcohol was protected as the silyl ether and the



Scheme 143. Total Synthesis of (−)-Allosamizoline (Simpkins, 1992).



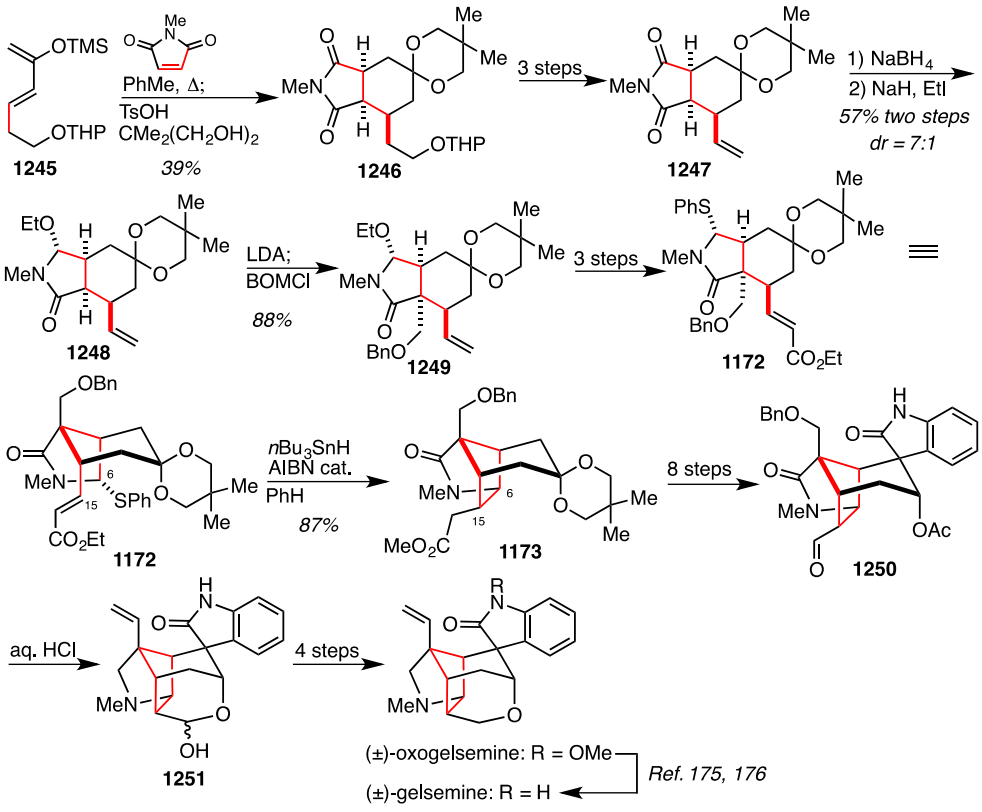
Scheme 144. Total Synthesis of (±)-Coriolin (Weinges, 1993).

dithiolane protecting group was removed to give aldehyde **1224**. With three stereocenters in place, the key reductive cyclization was investigated. The 5-*exo*-trig cyclization proceeded in a solution of HMPA and water to give fully functionalized cyclopentane **1225**. It was hypothesized that the two newly formed stereocenters in this all *trans* diastereomer is a result of repulsion of the anionic oxygen and carbon atoms in the transition state. Advanced intermediate **1225** contains a fully functionalized cyclopentane with substituents and stereochemistry found in the natural product.

10.2. σ-Bond homolysis–5-exo-trig cyclizations

In the Simpkins[214] synthesis of (−)-allosamizoline, the aglycone of allosamidin, a carbon-centered radical adds to an oxime ether constructing a fully functionalized cyclopentane (Scheme 143). Akin to other aminocyclitol syntheses, stereochemical information in the carbohydrate glucosamine is transferred to the cyclopentane scaffold. Radical precursor **1226** is obtained from D-glucosamine in five standard transformations. Treatment of **1226** with the tributyltin radical induces C–O bond homolysis to give an alkyl radical, which adds to the oxime ether. The major product **1227** was isolated as an inconsequential epimeric mixture at C1. The major C5 diastereomer arises from a preferred chair-like transition state with equatorial tether substituents.[215] The benzyloxyamino group was oxidized to an oxime ether (**1228**). Oxidative cleavage with reductive workup delivers alcohol **1229** in modest yield based on the recovered oxime. Treatment of **1229** with thionyl chloride leads to alcohol activation and cyclization of the tethered carbamate to give *cis*-fused bicycle **1230**. This advanced intermediate contains the appropriate substitution and stereochemistry for (−)-allosamizoline, and the natural product was completed using an additional two transformations.

The synthesis of (−)-coriolin by Weinges[216] uses an oxymercuration-radical cyclization sequence of *R*-(−)-carvone to construct functionalized cyclopentane **1232** (Scheme 144). The alkyl mercury species, generated after oxymercuration, is reduced to a mercury hydride species that undergoes C–Hg σ-bond homolysis and a 5-*exo*-trig radical cyclization. Treatment with peracid induces an oxidative sequence leading to acetate **1236**. The reaction is thought to proceed via Baeyer–Villiger oxidation (to **1233**), *trans*-esterification (to **1234**), alcohol oxidation (to **1235**) and a subsequent Baeyer–Villiger reaction yielding **1236**. Acetate hydrolysis, Mitsunobu bromination, and elimination under basic conditions delivers a mixture of disubstituted alkenes with cyclopentene **1237** isolated as the major regioisomer (5:1). Epoxidation occurs preferentially from the convex face of the ring system to give **1238** as the major diastereomer. The epoxide was opened with phenylselenide, which was followed by elimination to give an allylic alcohol. The alcohol was then protected as the PMB-ether to furnish **1239**. Intermediate **1239** is a related compound to a coriolin precursor published by Curran,[217] but **1239** is non-racemic and it has the eventual secondary hydroxyl of coriolin installed and masked as a PMB-ether. However, many of the following transformations resemble those used in the Curran (±)-coriolin synthesis. Specifically, organocuprate-mediated allylic substitution occurred following Curran's precedent to give **1241**. This intermediate was elaborated to enyne **1242** over six steps. Radical-based cyclization with samarium iodide, again following Curran's route, constructs



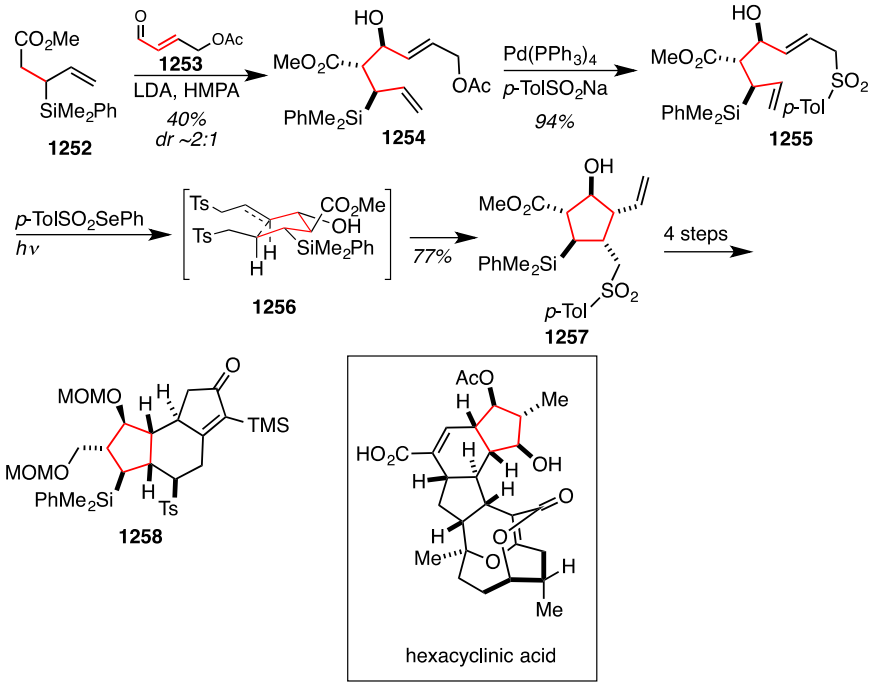
Scheme 145. Total Synthesis of (±)-Gelsemine (Hart, 1994).

the triquinane core of (−)-coriolin (**1243**). Protecting group manipulation over three steps gives enone **1244**. A Saegusa oxidation, and silyl deprotection gives common coriolin intermediate **130**. Nucleophilic epoxidation gave coriolin as a 2:1 mixture with its spiro-oxirane epimer.

In the synthesis of (±)-gelsemine by Hart,[218] a free radical is used to construct the tricyclic core and a fully functionalized cyclopentane (Scheme 145). All of the carbon atoms for the cyclopentane were installed with a Diels–Alder cycloaddition of diene **1245** and *N*-methylmaleimide yielding **1246**. This material underwent functional group manipulation over three steps to deliver alkene **1247**. Reduction of the imide with sodium borohyride occurs from the convex face of the ring system to give a carbinol lactam, which was alkylated with ethyl iodode to yield a mixture of isomeric ethoxy lactams favoring the desired **1248** in a 7:1 ratio. The lithium enolate generated from **1248** was alkylated on the convex face using MOMCl to deliver **1249**. This material was advanced over three steps to thioether **1172**. Treatment with standard radical conditions led to carbon-sulfur bond homolysis and cyclization with the tethered α,β-unsaturated ester to give the tricyclic core of gelsemine (**1173**). This key transformation leads to a fully functionalized cyclopentane, but requires inversion of configuration at C15. Intermediate **1173** was converted over eight steps to aldehyde **1250**. Treatment with aqueous acid removed the acetate group and spontaneous lactol formation delivered **1251** with the appropriate substitution and stereochemistry for gelsemine. This advanced intermediate was converted to (±)-gelsemine over an additional five steps.

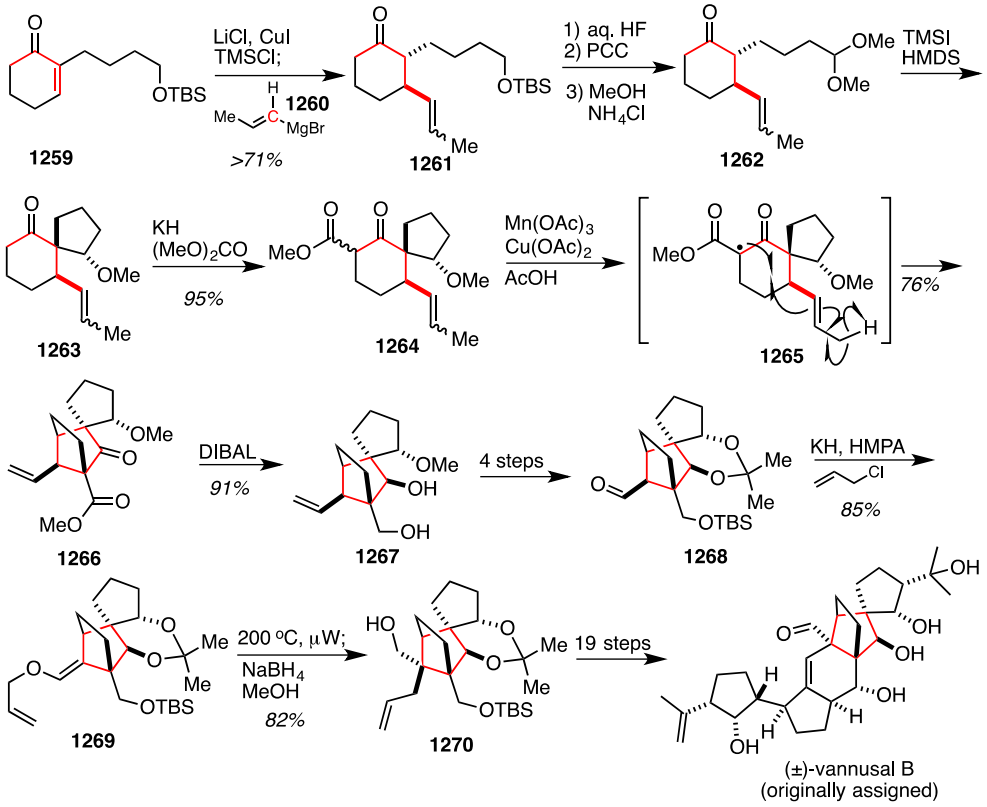
The core of hexacyclinic acid was stereoselectively synthesized by Landais[219] using a 5-*exo*-trig radical cyclization of a 1,6-diene (Scheme 146). The synthetic route commences with an aldol reaction between racemic ester **1252** and aldehyde **1253**. The major stereoisomer (**1254**) results from a combination of direction from the silyl substituent and Zimmerman–Traxler considerations.[220] A palladium-catalyzed sulfonylation delivered the radical cyclization substrate **1255** as a mixture of alkene isomers (*E*/*Z* 95:5). The radical cyclization was performed photochemically in the presence of catalytic *p*-TolSO$_2$SePh furnishing fully functionalized cyclopentane **1257**. The stereochemical outcome is rationalized by the authors with a chair-like transition state **1256**, which places all large substituents pseudo-equatorial. Intermediate **1257** contains a fully functionalized cyclopentane with substitution and stereochemistry corresponding to many of the structural features of hexacyclinic acid. It was advanced four steps to **1258**, which displays the ABC ring system of the natural product.

In the synthesis of the reported structures of (±)-vannusals A and B by Nicolaou,[221,222] a transannular radical cyclization forms a cyclopentanone substituted at each of the four sp^3-hybridized carbons (Scheme 147). Beginning with enone **1259**, conjugate addition of the vinyl cuprate derived from **1260** delivers **1261** as an inconsequential mixture of geometric alkene isomers that were advanced through the synthesis. The silylated alcohol was converted to acetal **1262** over the three steps shown. Intramolecular spirocyclization via a Mukaiyama-type aldol reaction occurred by exposure to excess TMSI and HMDS giving **1263**. The cyclization proceeded stereoselectively with the electrophile approaching opposite the vinyl group. Acylation of the ketone was performed using standard conditions to deliver keto-ester **1264** as a mixture of diastereomers. Treatment of **1264** with conditions developed by Snider[223] induced the ring closure to form cyclopentanone **1266** via the radical pathway shown. The product was obtained as a single diastereomer unaffected by either the ester stereochemistry or the alkene geometry. At this stage, three of the stereocenters have the desired configuration for vannusal B. A stereoselective ketone

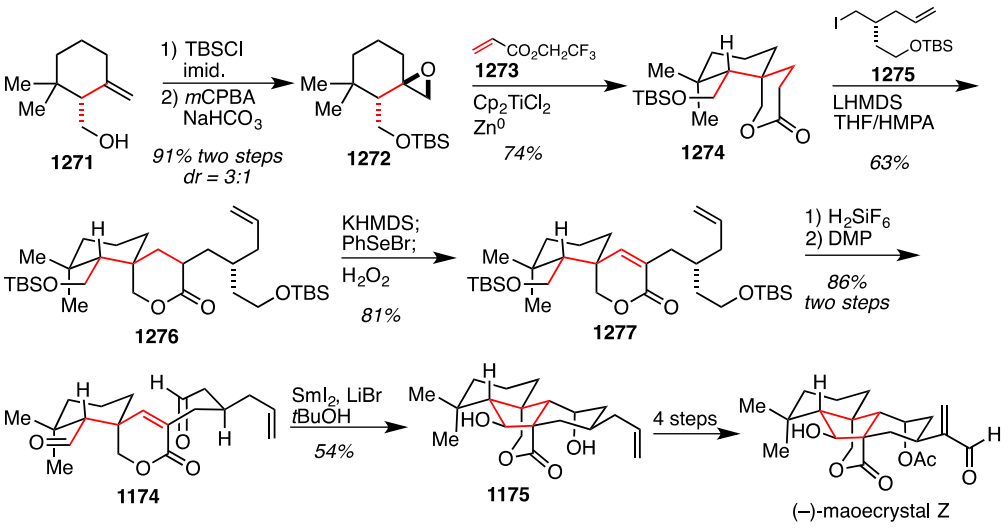


Scheme 146. Synthetic Studies Towards Hexacyclinic Acid (Landais, 2005).

reduction with DIBAL delivers alcohol **1267**. Presumably, the hydride approaches on the less hindered face away from the ethylene bridge. Functional group transformations delivered intermediate **1268** over four steps. The aldehyde was converted to allyl vinyl ether **1269**. The desired *E*-geometry of the enol ether was expected based on steric considerations. Microwave heating induced a Claisen rearrangement which established the quaternary stereocenter. Reduction of the aldehyde gave advanced intermediate



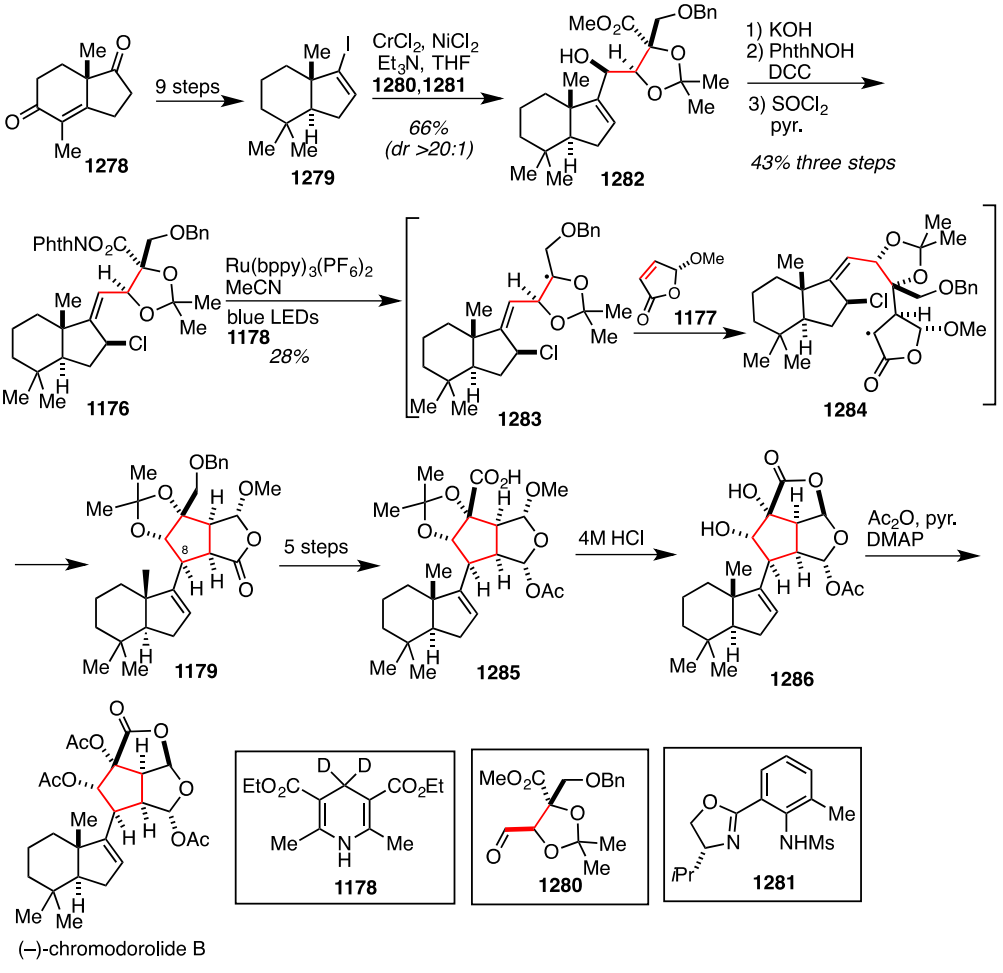
Scheme 147. Total Synthesis of (±)-Vannusals A and B (Nicolaou, 2010).



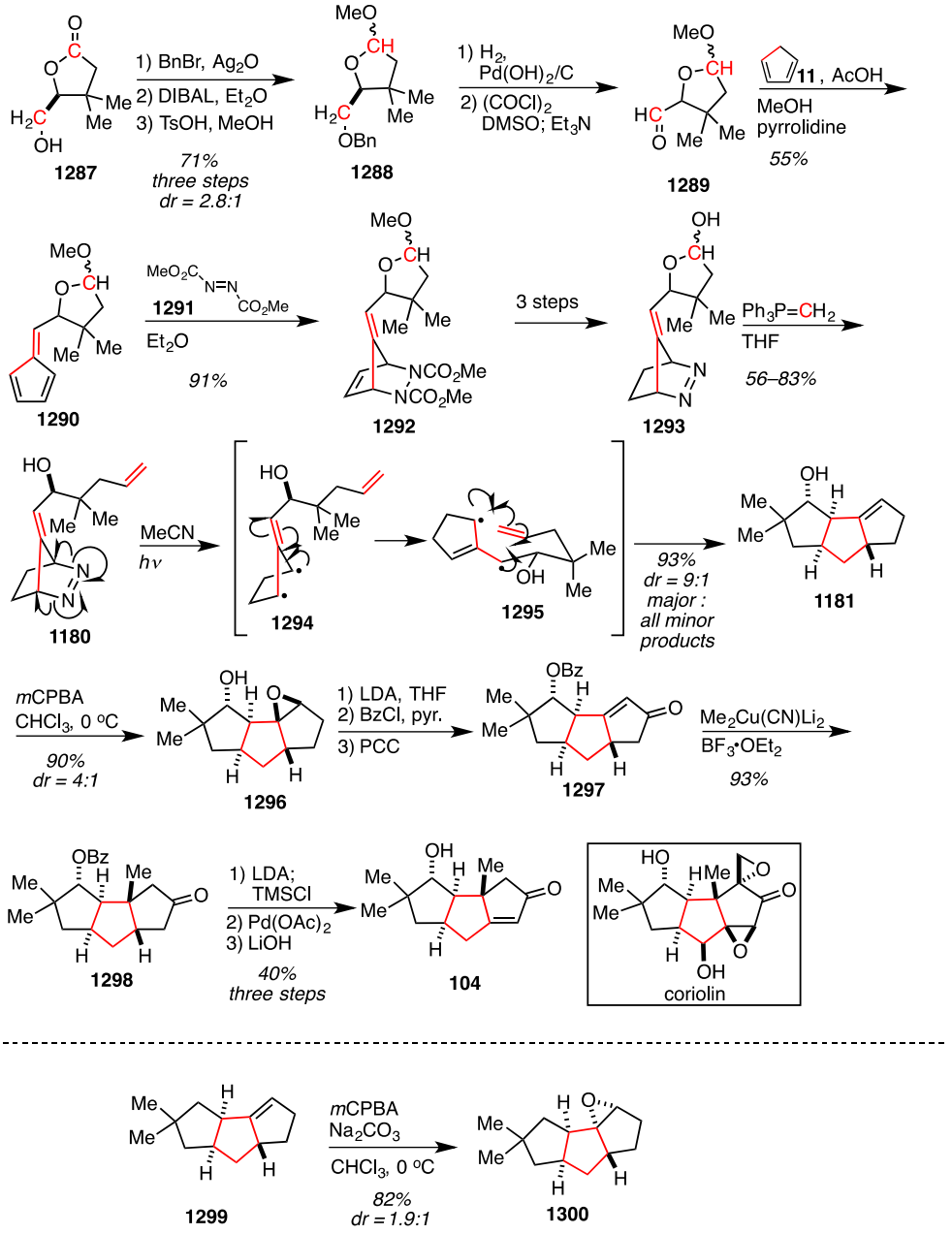
Scheme 148. Total Synthesis of (−)-Maoecrystal Z (Reisman, 2011).

1270. At this stage a fully functionalized cyclopentane with all the required stereochemistry and substituents for vannusal B has been created. An additional 19 steps were required to complete the reported structure of the natural product.

In the first synthesis of (−)-maoecrystal Z, Reisman[224] uses a samarium-mediated reductive cascade cyclization reaction to construct a fully functionalized cyclopentane (Scheme 148). The synthesis begins with silation of (−)-γ-cyclogeraniol (**1271**)



Scheme 149. Total Synthesis of (−)-Chromodorolide (Overman, 2016).

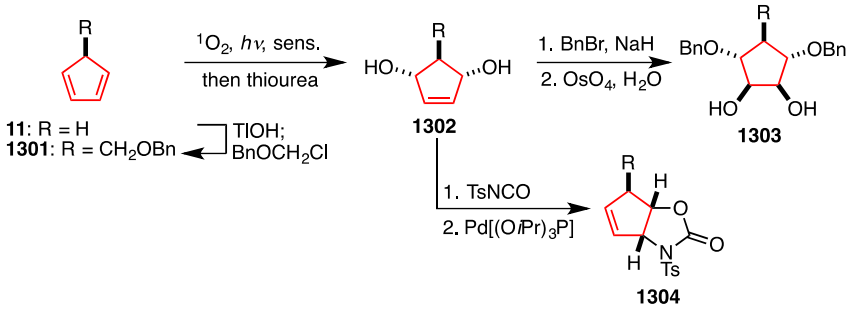


Scheme 150. Formal Synthesis of (±)-Coriolin (Little, 1987).

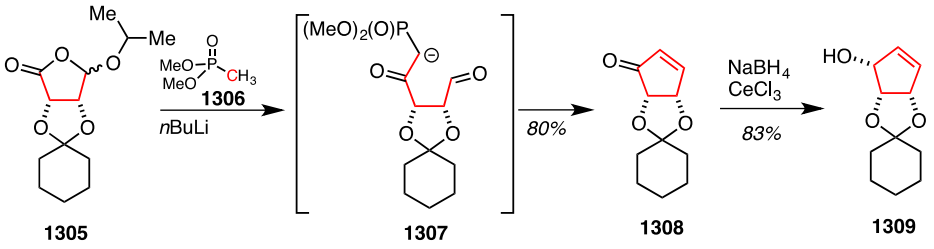
followed by epoxidation to give **1272** as the major product. A reductive epoxide coupling with acrylate ester **1273** following Gansäuer's method[225] delivered spirolactone **1274** as a single diastereomer. Alkylation with iodide **1275** (prepared from *S,S*-pseudoephedrine) delivered **1276** as an inconsequential mixture of epimers, which was further transformed to enoate **1277** by selenation/selenoxide elimination. Removal of the silyl ethers was followed by oxidation of the diol to dialdehyde **1174**. When radical substrate **1174** was subjected to samarium iodide and LiBr, the fully functionalized cyclopentane **1175** was obtained. The stereochemical configuration of the alcohols in the product is believed to be the result of a reactive conformation that minimizes steric interactions of the aldehyde carbonyls and the cyclohexane ring. Advanced intermediate **1175** contains a fully functionalized cyclopentane that was converted to the natural product in four additional steps.

10.3. Radical cyclizations that form multiple rings

In the first total synthesis of (−)-chromodorolide B, Overman[226] builds a fully functionalized cyclopentane using a novel radical addition/cyclization/fragmentation cascade (Scheme 149). The cascade brings together a butenolide and *trans* hydrindane fragment while constructing three stereocenters. The route begins by elaborating known enedione **1278** over nine steps to vinyl iodide **1279**. The hydrindane fragment was coupled with aldehyde **1280**[227] using a modified Nozaki–Hiyama–Kishi reaction in the presence of ligand **1281**. The allylic alcohol **1282** was isolated as a single alcohol epimer. Hydrolysis of the methyl ester was followed by esterification with *N*-hydroxyphthalimide. Suprafacial allylic chlorination with thionyl chloride proceeded regio- and stereoselectively delivering chloride **1176**.[228] The key radical cyclization



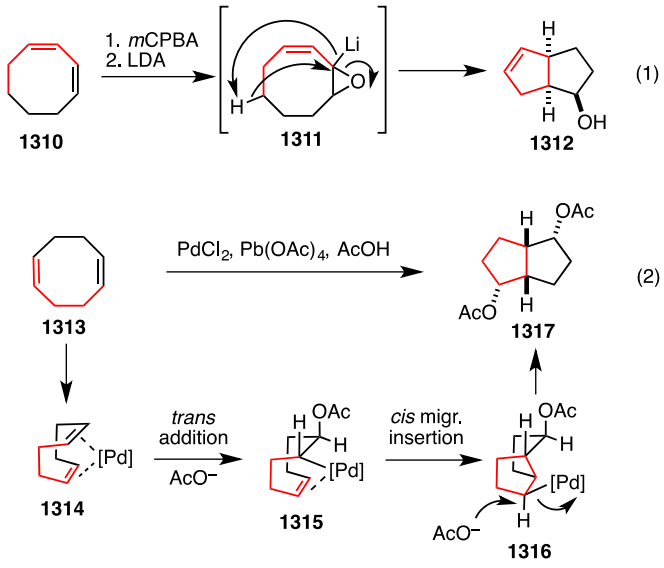
Scheme 151. Application of Cyclopentadiene Reactivity in the Synthesis of Fully Functionalized Cyclopentanes.



Scheme 152. Preparation of Allylic Alcohol **1309**.

was performed with blue LEDs in the presence of a ruthenium bipyridyl complex. After much experimentation, optimized conditions were realized with *d2*-Hantzch ester (**1178**) to give desired compound **1179** in a 1:1.3 ratio with the C8 epimer in a combined 65% yield (28% of desired **1179**). Use of the dideuterio Hantzch ester was to decrease the rate of hydrogen atom transfer to intermediates **1284**. The reaction proceeds via the radical cascade mechanism shown. Although the diastereoselectivity and chemical yield was somewhat modest, an impressive increase in molecular complexity transpires over the course of this reaction, and nearly the entire oxygenated moiety of the natural product has been constructed. Moreover, the fully functionalized cyclopentane is delivered in a single step from the coupling of relatively simple functional groups. The benzyl ether was functionalized to carboxylic acid **1285** over five steps. Treatment with 4 M HCl resulted in acetonide deprotection and lactonization to form lactol **1286**. Global acetyl protection delivered (−)-chromodorolide B.

In the formal synthesis of (±)-coriolin by Little[132] an intramolecular reaction of an alkene with a 1,3-diyl (i.e. alkyl 1,3-diradical) was used to assemble the cyclopentane (Scheme 150). The synthesis begins with benzyl protection of the commercially available furanone **1287**. The lactone was reduced and methylated under acidic conditions to give acetal **1288**. The benzyl group was removed and a Swern oxidation gave aldehyde **1289**. Condensation of **1289** with cyclopentadiene (**11**) delivered fulvene **1290**. The bicyclic skeleton of diazene **1292** was formed using a Diels–Alder reaction with dimethylazodicarboxylate (**1291**). This was advanced to diazene **1293** over three steps. A Wittig reaction with triphenylphosphonium methylide opens the lactol to give cyclization precursor **1180**. Photodeazetation of diazene **1180** formed the triquinane **1181**. Mechanistically, photolysis leads to 1,3-diyl **1294**, which undergoes intramolecular cyclization with the tethered alkene via a favored chair-like transition state (**1295**) with an equatorial alcohol substituent and suprafacial addition to the diyl. Epoxidation was accomplished with peracid to deliver **1296** in good yield and a 4:1 diastereomer ratio. Interestingly, the minor diastereomer is the product of epoxidation to give a *trans*-diquinane substructure. This minor diastereomer was confirmed by X-ray crystallographic studies. There are many examples in this review which demonstrate that conversion of similarly unsaturated diquinanes to *cis*-bicyclo[3.3.0]octanes proceeds reliably with complete diastereocontrol. This is the only example where the *trans*-diastereomer was observed even as a minor component. Even more interesting, deletion of the alcohol functional group in **1181** was anticipated to prevent Henbest delivery of oxygen to the α-face of the alkene; however, the deoxygenated substrate **1299** delivered **1300** with the *trans*-bicyclo[3.3.0]octane substructure as the major product. The reason for this diastereoselectivity is unknown. Epoxide **1296** underwent elimination with LDA, selective protection of the secondary alcohol as the benzoate ester and chromium oxidation with transposition of oxygen to deliver enone **1297**.



Scheme 153. Application of Cyclooctadiene Reactivity in the Synthesis of Fully Functionalized Cyclopentanes.

Conjugate addition using a higher order cuprate successfully installed the angular methyl group, leading to a *cis*-fused diquinane substructure (**1298**). Saegusa oxidation and ester hydrolysis let to intermediate **104**, which intersects an intermediate prepared by Trost[129] in a synthesis of (±)-coriolin.

11. Functionalization of five-membered carbocyclic starting materials

A common strategy for constructing fully functionalized cyclopentanes involves the functionalization of simple five-membered carbocyclic starting materials. With dozens of simple building blocks available, and a variety of transformations in the chemist's toolbox, it is somewhat surprising that many syntheses in this section are represented by a few well-defined patterns.

Cyclopentadiene is an inexpensive starting material common to many syntheses of natural products with fully functionalized cyclopentane architectures. Alkylation of cyclopentadiene gives substituted cyclopentadienes with functionality at all five carbons. A common strategy is to alkylate with an alkoxymethylene group (**11** → **1301**) (shown in Scheme 151); however, dialkylations are also known.[244] These cyclopentadienes undergo facile Diels–Alder cycloaddition on the diene face opposite the substituent. The most common dienophile for this sequence is singlet oxygen; however, nitroso and alkene dienophiles have also participated to give nitrogen- and carbon-substituted cyclopentenes, respectively. Subsequent fragmentation of the O–O sigma bond reveals an all *trans* 1,2,3-trisubsituted cyclopentene (**1302**). Cyclopentene **1302** may undergo 1,2-alkene difunctionalization such as dihydroxylation to give **1303**, epoxidation, or bromohydrin formation to reveal the fully functionalized cyclopentane. Depending on the choice of conditions, this 1,2-alkene difunctionalization may occur on the less hindered face, or it may be directed by the substrate to give oxygenation *syn* to the diol.

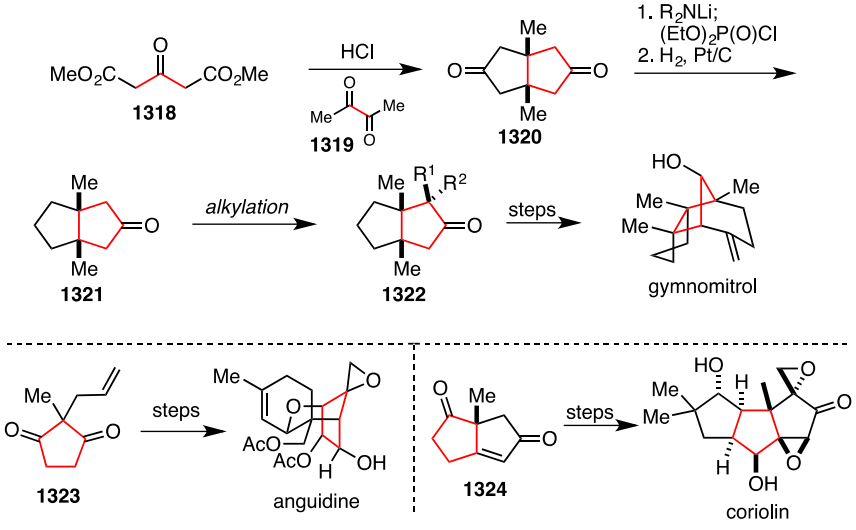
Another common pattern is for **1302** to first undergo intramolecular S_N2'-type cyclization, often via a carbamate intermediate (**1304**).[233] A subsequent 1,2-difunctionalization of the transposed alkene leads to substitution at all positions of the cyclopentane. In this strategy, both the Diels-Alder reaction and 1,2-alkene functionalization perform reliably with heteroatom reagents (e.g. $^1O_2$ and OsO_4, respectively); as a result, many of the natural products (trehazolin, mannostatin A, allosamizoline) made with this synthetic strategy display multiple heteroatom substituents on the fully functionalized cyclopentane.

Acyl acetal **1305** is a readily available intermediate derived from D-mannose. Addition of phosphonate **1306** under basic conditions gives **1308** (Scheme 152).[229] Intermediate carbanion **1307** cyclizes via intramolecular Horner–Wadsworth–Emmons olefination to give enone **1308**. The enone can be reduced under Luche conditions to form allylic alcohol **1309**. Hydride delivery occurs on the less hindered ketone diastereoface to give **1309** as a single diastereomer. Intermediate **1309** has been used in multiple syntheses of targets with a fully functionalized cyclopentane.

Cyclooctadienes may undergo transannular ring contraction to give *cis*-bicyclo[3.3.0]octane architectures. The two common starting materials prepared in this strategy are shown in Scheme 153. 1,3-Cyclooctadiene (**1310**, eq. 1) is oxidized to the corresponding epoxide (**1311**). Lithiation of the more acidic allylic position is followed by transannular ring closure to give **1312**.[230] Alternatively, 1,5-cyclooctadiene (**1313**) undergoes Pd-catalyzed cyclization in the presence of acetate to give C_2-symmetric starting material **1317** (eq. 2).[231] This intermediate can be processed in a variety of ways, including an enantioselective enzymatic desymmetrization (see below).

Cyclopentanones have also been used as building-block starting materials for fully functionalized cyclopentane natural products. Four separate syntheses of gymnomitrol begin with cyclopentanone **1321** (Scheme 154). This intermediate is prepared from dimethyl-3-ketoglutarate (**1318**).[232] Acid promoted condensation with 2,3-butandione (**1319**) gives **1320**. Deoxygenation gives **1321**. Ketone **1321** undergoes subsequent transformations that result in a dialkyated ketone intermediate of general structure **1322**. This material is advanced to gymnomitrol. Other than ketone **1321**, cyclopentane **1323** was used in an anguidine synthesis, and **1324** was used in a synthesis of coriolin.

Contrasting with the strategic patterns discussed above for cyclopentadienes and cyclopentanones, the strategic use of cyclopentenone starting materials represents the most varied tactic to approach to fully functionalized cyclopentanes (Fig. 3). Many substituted cyclopentenone starting materials have been used, and the enone functional group allows for a wide variety of standard transformations including enolate alkylations, additions to the carbonyl, Baylis–Hillman additions, conjugate additions, and Stork–Danheiser-type sequences.



Scheme 154. Cyclopentanone Starting Materials Used in the Synthesis of Fully Functionalized Cyclopentanes.

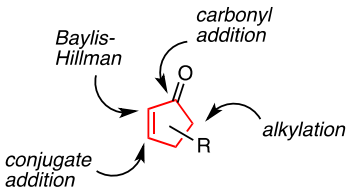


Fig. 3. Cyclopentenone Reactivity.

11.1. Cyclopentadiene functionalizations

The Trost[233,234] synthesis of (±)-allosamizoline was achieved alongside a general desymmetrization strategy for aminocyclopentitols (Scheme 155). This method of desymmetrizing *meso* alkenediols involves a palladium-catalyzed ionization/cyclization reaction to prepare chiral oxazolidinones. The synthesis of allosamizoline begins with *meso* diol **1325** (derived from cyclopentatdiene). Premixing diol **1325** with *p*-toluenesulfonylisocyanate followed by exposure to a Pd(0) catalyst promoted conversion to oxazolidin-2-one **1326** as a single product. An additional three steps were used to convert tosyl oxazolidinone **1326** to amino oxazoline **1328**. Alkene **1328** was particularly unreactive, but after much experimentation epoxidation was found to be most successful with peroxytrifluoroacetic acid giving the epoxide on the convex face of the bicycle. Acidic hydrolysis gave a *trans*-diol, which was the final required substituent on the fully functionalized cyclopentane. Hydrogenolysis of the benzyl group completed the synthesis of (±)-allosamizoline.

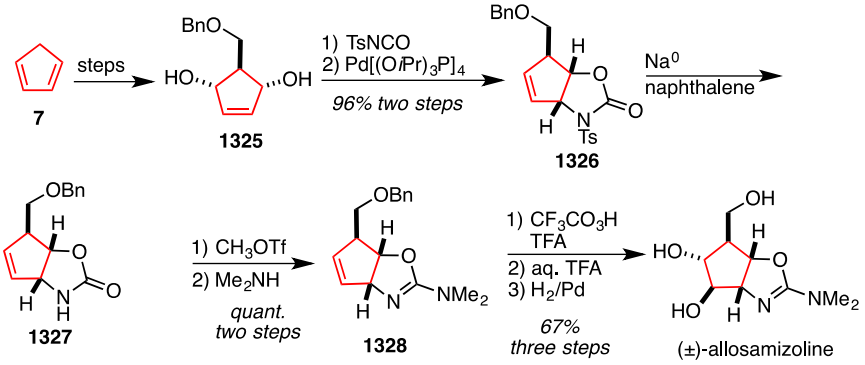
The Danishefsky[235] synthesis of (−)-allosamidin (Scheme 156) began with *meso*-diacetate **1329** (derived from cyclopentadiene). An enzymatic desymmetrization[236] with electric eel acetylcholinesterase delivers chiral alcohol **1330** with excellent enantioselectivity. Standard functional group manipulations were used to convert **1330** to carbamate **1331**. Cyclization in the presence of triethylamine and trifluoroacetic anhydride gave oxazolidinone **1327**. This material was also an intermediate in the Trost allosamizoline synthesis, and following the precedent of Trost[233] underwent aminooxazoline formation (**1328**), epoxidation and hydrolysis to give diol **1332**. An additional four steps were used to convert this intermediate to (−)-allosamidin complete with its disaccharide moiety.

In the synthesis of (±)-allosamizoline, Ganem[237] also uses a desymmetrization of a substituted cyclopentene (Scheme 157). The synthesis begins with exposure of **1333** (derived from cyclopentadiene) to NBS in wet DMSO to deliver a single bromohydrin stereoisomer **1334**. Mechanistically, bromonium ion formation occurs on the face *syn* to the hydroxyl groups.[238] Backside opening of the bromonium ion positions the incoming hydroxyl on the face *anti* to the resident hydroxyl groups of the substrate. Ring closure was performed with methanolic sodium carbonate to give epoxide **1335**. This two-step epoxidation sequence leads to formation of the diastereomer with the epoxide positioned *anti* to the diol; note that peracid oxidation would lead to the *syn* diastereomer. Nucleophilic epoxide opening with sodium azide and subsequent reduction delivered aminotriol and fully functionalized cyclopentane **1336**. An additional three steps were used to convert this material to (±)-allosamizoline.

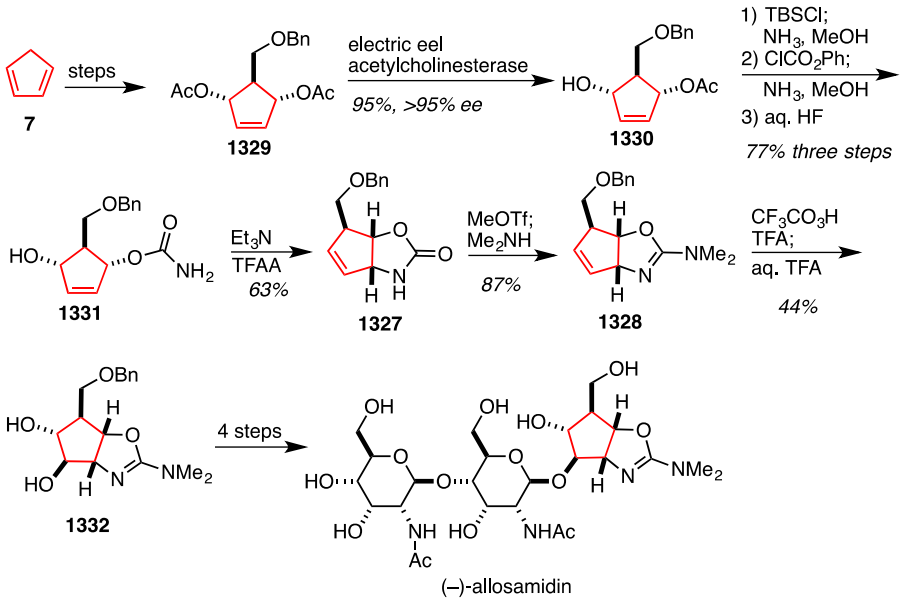
In the synthesis of (−)-allosamidin, Imperiali[239] uses the enzymatic desymmetrization developed by Danishefsky[235] to obtain synthetic intermediate **1338** (Scheme 158). An addition reaction of dimethylcyanamide delivers aminoimidate **1339**. This material was cyclized via a Hg(II) mediated ring closure which successfully transfers the stereochemistry to the newly formed center in the desired oxazoline **1341**. Oxidative demercuration with radical oxygen conditions leads to hydroxyl formation on the convex face of the bicycle to furnish a fully functionalized cyclopentane.[240] The target (−)-allosamidin was completed in an additional four steps.

In the synthesis of (−)-allosamizoline, Iwata[241] desymmetrizes *meso*-diol **1342** with a chiral auxiliary containing stereogenic sulfoxides (Scheme 159). The synthesis commences with benzyl protection of **1325** (derived from cyclopentadiene **11**) followed by dihydroxylation on the less hindered alkene face to deliver **1342** with good dr. Conversion of *meso* diol **1342** to chiral acetal **1344** was accomplished in two steps using chiral sulfoxide **1343** and Lewis acid conditons. Treatment with KHMDS and benzyl bromide induces elimination followed by benzylation to give **1345** with high diastereoselectivity. Acidic hydrolysis of the chiral auxiliary yields **1346**. Activation of the alcohol as a sulfonate, displacement with azide, and reduction produces fully functionalized aminocyclopentatol **1347** with the required stereochemistry for the target. This material was advanced to **1348** over four steps which is an intermediate previously taken to (−)-allosamizoline by Tatsuta.[23]

In the synthesis of (+)-mannostatin A, Ganem[242] constructs the fully functionalized cyclopentane by desymmetrizing 1-(methylthio)cyclopentadiene (**1349**, Scheme 160). The synthesis begins with a hetero-Diels–Alder reaction of **1319** and the chiral acylnitroso compound derived from oxidation of **1350**. This step delivers **1351** with three stereocenters, each appropriately functionalized for mannostatin A. Reduction of the N–O bond with aluminum amalgam and subsequent acetyl protection delivers **1352**. Dihydroxylation of **1352** proceeded with complete facial selectivity to give a fully functionalized cyclopentane. Such dihydroxylations have been studied,[243] and the major diastereomer is believed to be the result of a directing effect on osmium from the



Scheme 155. Total Synthesis of (±)-Allosamizoline (Trost, 1990).



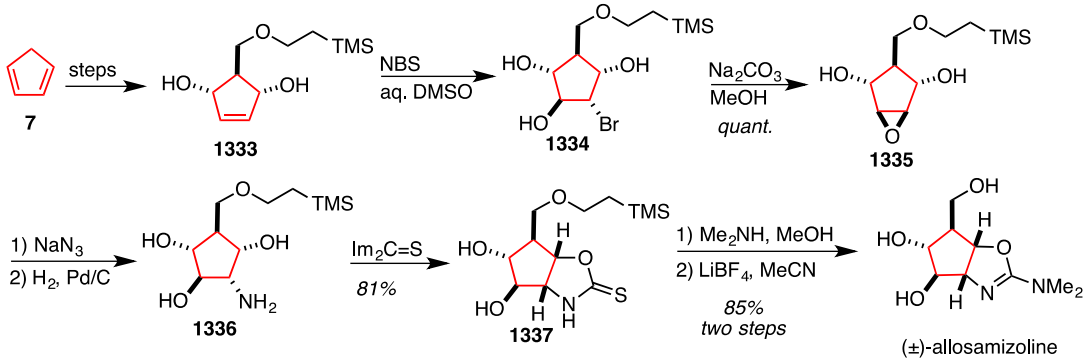
Scheme 156. Total Synthesis of (−)-Allosamidin (Danishefsky, 1991).

neighboring heteroatoms. Acetylation of the diol furnishes **1353**. Hydrolysis of the amide under acidic conditions provided (+)-mannostatin A as the hydrochloride salt.

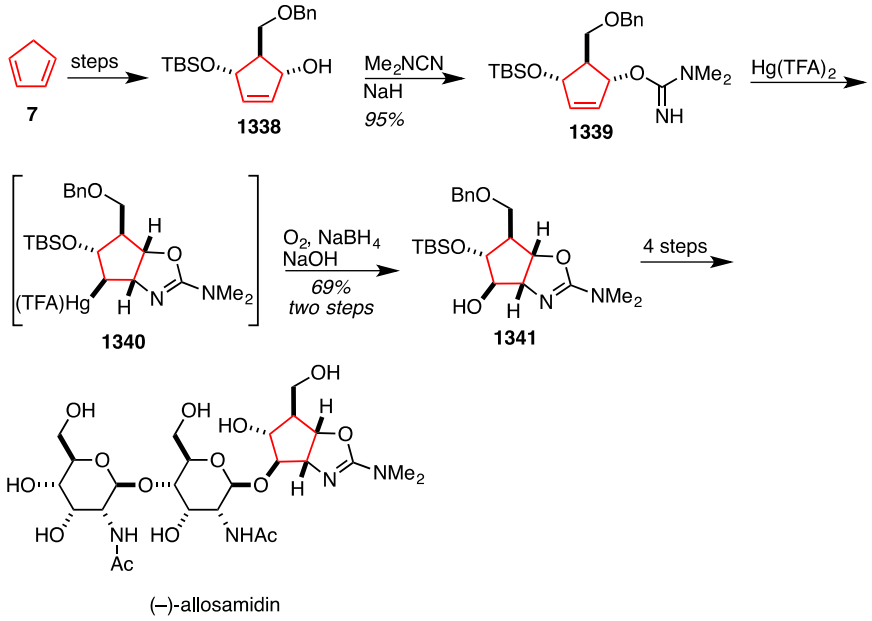
In the Trost synthesis of (±)-mannostatin A[234], the desymmetrization strategy developed for (±)-allosamizoline[233] was applied (Scheme 161). Beginning with *meso* diol **1354** (derived from cyclopentadiene) and toluenesulfonyl isocyanate, a palladium-catalyzed ionization/cyclization reaction was performed to deliver oxazolidinone **1355**. Allylic oxidation with selenium dioxide introduced the required hydroxyl group found in the mannostatin A structure. The crude mixture was oxidized with Dess-Martin periodinane to an enone. Luche reduction of this enone delivers the desired α-alcohol **1356** in a 7:1 mixture with the undesired stereoisomer. Opening of the carbamate with base delivers amino diol **1357**. The diol was protected as the acetonide, and substrate directed epoxidation with peroxytrifluoroacetic acid furnished **1358**. Treatment with lithium methanethiolate opened the epoxide to **1359**, which completes the fully functionalized cyclopentane. The regioselectivity in the epoxide opening was explained by stereoelectronic considerations. The acetonide protecting group leads to a more rigidified bicyclo[3.3.0]octane structure, and Furst–Plattner-type considerations favor pseduoaxial attack of the thiolate nucleophile with the observed regioselectivity. Removal of the sulfonate and acetonide protecting groups completes the synthesis of (±)-mannostatin A.

In the synthesis of (+)-trehazolin, Carreira[244] begins with lithium cyclopentadienide (**163**), which undergoes double addition with (*R*)-epichlorohydrin (**164**) to deliver **1360** as a pure enantiomer (Scheme 162). Treatment with sodium hydride and Cl_3CCN delivered trichloroacetimidate **1362**. Iodocyclization presumably gave the allylic iodide **1364** which underwent S_N2' addition with water to yield the observed allylic alcohol product **1365**. Sillylation of the secondary alcohol and nucleophilic opening of the imidate furnishes cyclopropylcarbinyl bromide **1366**. Epoxidation from the less hindered top face with dimethyldioxirane delivers **1367**. Epoxide opening with the tethered trichloroacetamide occurs under Lewis acid conditions to give **1368**. Radical fragmentation of the cyclopropane to give alkene **1369** proceeded with partial reduction of the trichloromethyl group. This material was advanced four steps to phenyl ketone **1370**. A Norrish Type II cleavage of the aryl ketone gave alkene **1371**. The unpurified material was dihydroxylated with OsO_4 furnishing **1372** which displays the desired functionality and stereochemistry for the target. This material was advanced to (+)-trehazolin over three steps.

The Ganem[245] synthesis of (+)-trehazolin capitalizes on the desymmetrization approach developed for their mannostatin



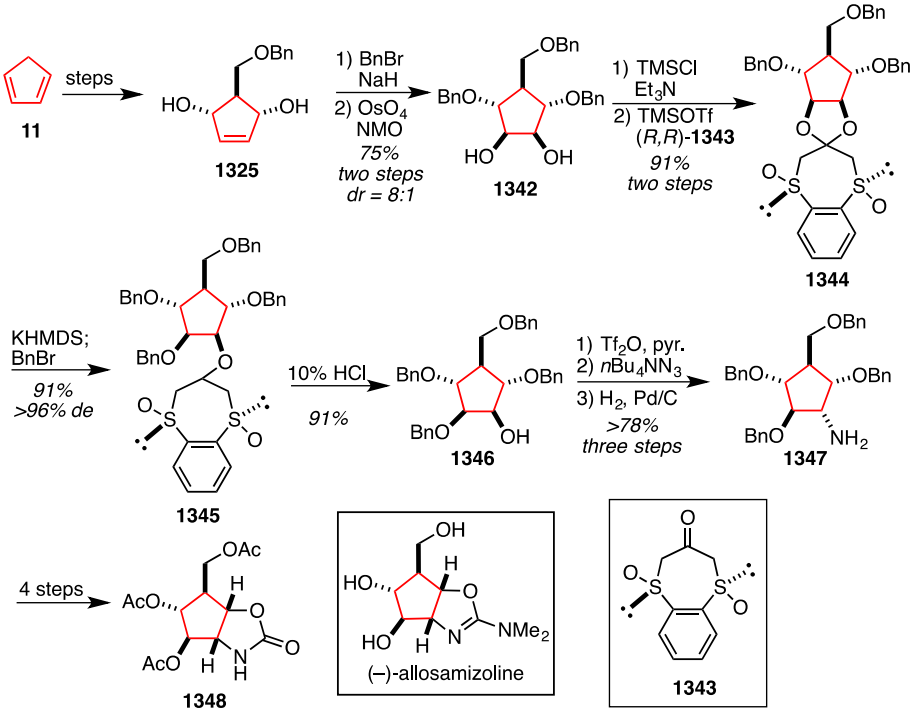
Scheme 157. Total Synthesis of (±)-Allosamizoline (Ganem, 1994).



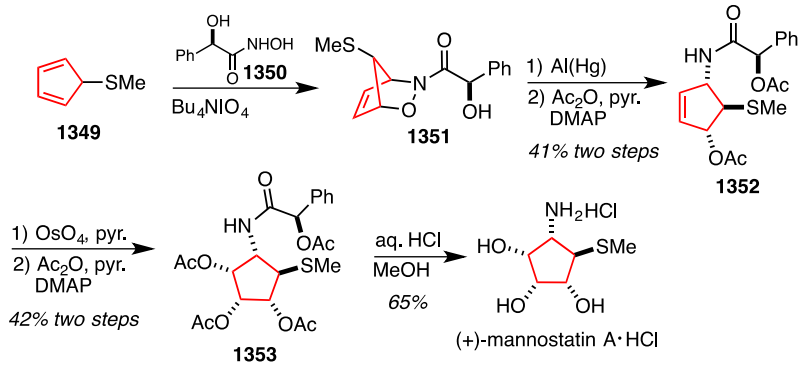
Scheme 158. Total Synthesis of (−)-Allosamidin (Imperiali, 1996).

synthesis discussed above (Scheme 163). Specifically, the Diels–Alder reaction of cyclopentadiene **1301** with the chiral nitroso species derived from **1373** gave the bicyclic product **1374**. Reduction of the N–O bond was performed with sodium amalgam, and the product (**1375**) was separated from its diastereomer. Cyclopentene **1375** was epoxidized to give **1376**. As before, epoxidation results in the *syn* diastereomer as a result of peracid coordination to the substrate. Hydrolysis of the epoxide was slow, but could be promoted using 2:1 H_2O/TFA to furnish a diol albeit in a 1:1.6 ratio in favor of the undesired diastereomer. The diol was converted to the corresponding acetate **1377**. At this stage, a fully functionalized cyclopentane has been constructed, but the tertiary alcohol has yet to be installed. Intermediate **1377** was converted to exocyclic alkene **1378** using Grieco's method.[42] Stereoselective dihydroxylation avoiding steric interactions with the adjacent substituents furnished diol **1379**. This advanced intermediate has been synthesized by Shiozaki[27] in a synthesis of trehazolin.

The Carreira[246] synthesis of the pallambins uses two distinct processes to create each of the fully functionalized carbocycles, and this synthesis could fall into either Section 11 or **4** of this review



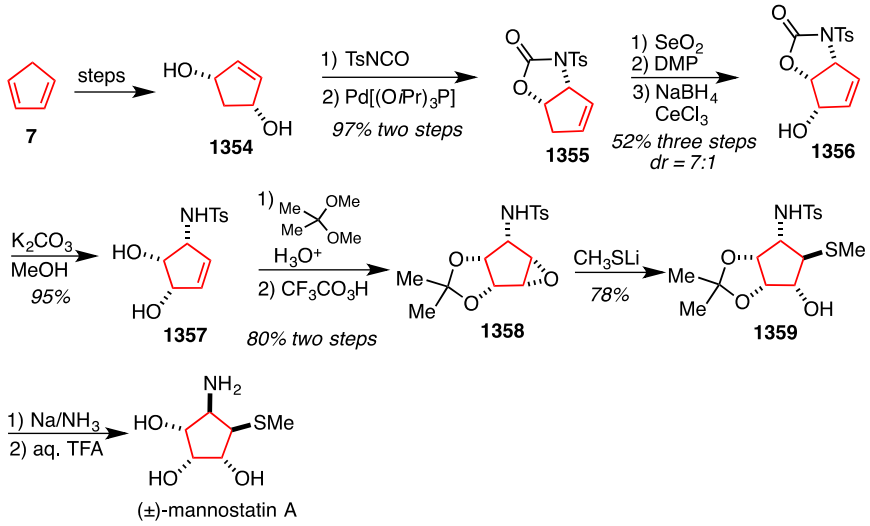
Scheme 159. Total Synthesis of (−)-Allosamizoline (Iwata, 1998).



Scheme 160. Total Synthesis of (+)-Mannostatin A (Ganem, 1991).

(Scheme 164). The first cyclopentane begins as fulvene and the second cyclopentane is created in a rhodium catalyzed C–H insertion reaction. We choose to discuss the synthesis here because more than half of the fused 5,5 fully functionalized system is installed with the fulvene. The route begins with a Diels–Alder reaction of methyl acrylate with fulvene (**1381**), the latter of which was generated in situ by a reduction and Hoffman elimination of the bench-stable dimethylaminofulvene (**1380**). Cyclopropanation with conditions developed by Denmark[247] delivered a tricyclic intermediate. The exocyclic olefin could be stereoselectively hydrogenated with Wilkinson's catalyst to give **1383** as the only product. Installation of the ketone in **1384** was accomplished by a three-step sequence involving α-hydroxylation, ester reduction, and oxidative cleavage of a diol. Methylation of ketone **1384** was followed by a Mukaiyama aldol reaction with acetaldehyde and Dess–Martin oxidation of the resulting β-hydroxy ketone to form 1,3-diketone **1385**. Formation of the diazoketone **1387** was performed with conditions developed by Danheiser.[248] Unpurified **1387** was subjected directly to rhodium conditions, which resulted in C–H insertion to deliver desired tetracycle **1388**. This C–H insertion reaction sets the final substitution on one fully functionalized cyclopentane and constructs the carbocyclic structure of the second key five-membered ring. The structure of pallambins A and B required that the C8 carbonyl served as a functional handle for the installation of the remaining substitution on the five-membered ring. This is a particularly demanding requirement due to the steric hindrance present in the substrate and the presence of two distinct ketone carbonyls. In the event, enolization of the acidic ketone was followed by formation of an enol triflate and subsequent Negishi cross-coupling to give **1389**. Dipolar cycloaddition with bromonitrile oxide approached from the convex face resulting in the desired stereochemistry. This advanced intermediate (**1390**) contains both fully functionalized cyclopentanes with the appropriate stereochemistry for the synthesis of (±)-pallambins A and B. An additional six steps was required to complete the natural products.

Schoop[249] reported synthetic studies toward rocaglamide wherein the key five-membered carbocycle was forged using an unusual alkylation-olefination[250] sequence (Scheme 165). Alkylation of phosphorane **1391** with bromoketone **1392** and subsequent deprotonation and intramolecular Wittig olefination delivers functionalized cyclopentadiene **1392**. Enol ether hydrolysis under acidic conditions furnishes cyclopentenone **1394**. Hydride reduction of the ketone to **1395** occurs stereoselectively. This two-step method results in three stereocenters appropriately set for rocaglamide. Oxidative cyclization with ceric ammonium nitrate and 1,3-cyclohexanedione provided dihydrofuran **1396**. The cyclization results in a fully functionalized cyclopentane, but the product does not possess the tertiary alcohol found in rocaglamide. Oxidative aromatization of this intermediate in the presence of methanol gave **1397**. A two-step oxidation/reduction sequence was used to invert the alcohol stereocenter to give advanced intermediate **1399**.



Scheme 161. Total Synthesis of (±)-Mannostatin A (Trost, 1993).

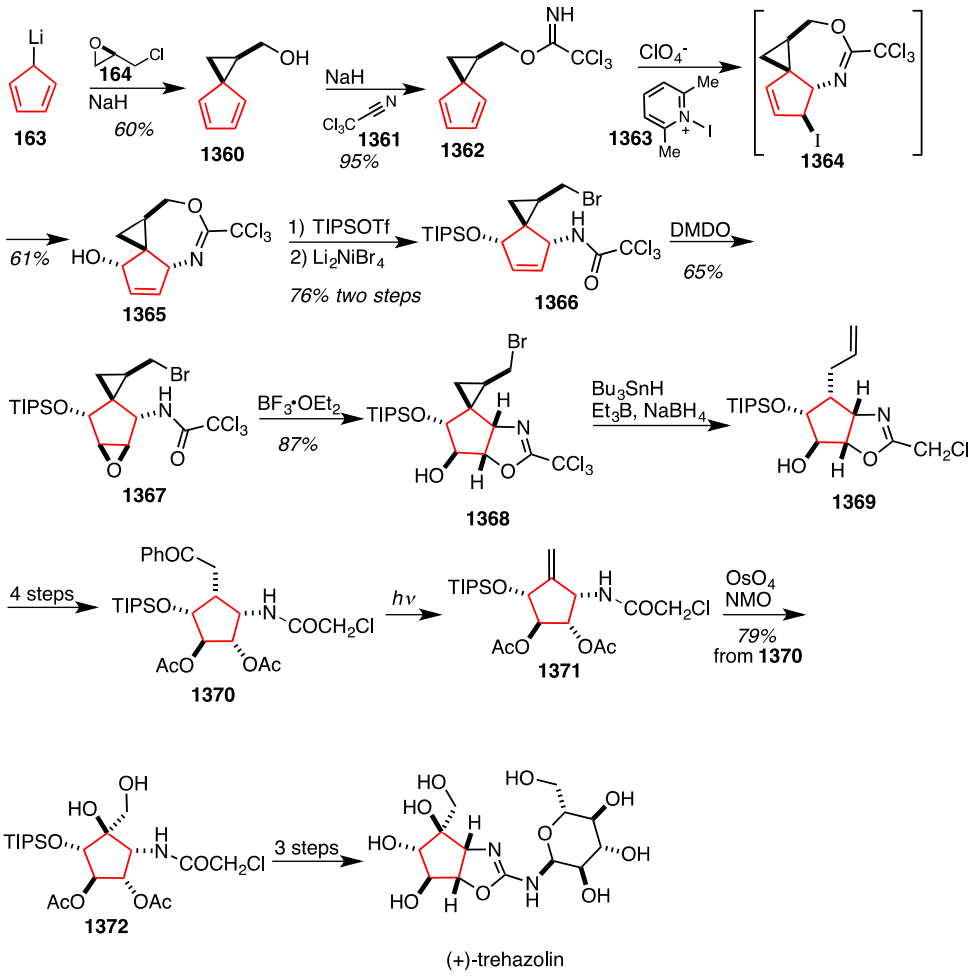
This rocaglamide intermediate contains many of the structural features found in the natural product; however, it lacks the tertiary alcohol and methyl ether.

11.2. Cyclopentene functionalizations

The Ikegami[38] synthesis of (±)-coriolin begins with a substituted cyclopentene derived from 1,3-cyclooctadiene (**1312**) (Scheme 166). Benzylation of the alcohol and bromination with *N*-bromosuccinimide resulted in the regio- and stereoselective formation of a bromohydrin. Hydrogenation of the benzyl ether gave **1400**. Chemoselective oxidation was possible due to the steric hindrance of the bromohydrin. Silylation of the unreacted hydroxyl furnished bromoketone **1401**. Elimination of bromide with DBU yields enone **1402**. Conjugate addition from the convex face and subsequent enolate protonation delivered the *cis*-fused ring system of **1403**. This material was advanced over four steps to intermediate **1404**. Silyl deprotection and oxidation of the resulting alcohol gave ketone **1405**. Formation of the thermodynamic enolate and addition to allyl bromide on the convex face gave **1406**, which sets the quaternary stereogenic carbon in coriolin. A Wacker-Tsuji oxidation with $PdCl_2$ and CuCl delivered a methyl ketone. The 1,4-dicarbonyl underwent an aldol condensation upon treatment with potassium *tert*-butoxide furnishing **1407** and the tricyclic core of coriolin. The α-methylene functionality was installed by enolate addition to methyl iodide followed by selenation and oxidation with peroxide. Acidic removal of the pyranyl ether delivers **142**. Deconjugation of the enone with *tert*-butoxide affords the β,γ-unsaturated carbonyl. Epoxidation with peracid occurred with facial selectivity favoring the *cis* fusion of the five membered rings in **1408**. Elimination with DBU provided the γ-hydroxy enone **130**, which intersects an intermediate previously taken to coriolin by Danishefsky[34] and Tatsuta.[35]

In the synthesis of (+)-mannostatin A by Knapp,[251] the route begins with known cyclopentene **1309** (Scheme 167), which is obtained from D-ribonolactone as discussed in the beginning of this section. This material could be advanced over two steps to imidothioate **1409**. Iodocyclization gave oxazolidinone **1410**. Removal of the PMB protecting group and substitution with methyl thiolate gave **1411**, which contains a fully functionalized cyclopentane. Substitution reaction proceeded with retention of configuration, likely as a result of anchimeric assistance from the vicinal nitrogen atom. Hydrolysis of the oxazolidinone and ketal groups over two steps completed the synthesis of (+)-mannostatin A.

Fuchs[252] synthesized (+)-mannostatin A using the same cyclopentene intermediate (**1309**) as Knapp[251] (Scheme 168). The allylic alcohol **1309** was converted to a trichloroacetimidate. After substantial experimentation, it was found that addition of DIEA and methanesulfenyl triflate in portions led to the isolation of *N*-sulfenylimidate **1412**. Resubjection of **1412** to similar conditions led to cyclization delivering **1413**. While cyclized product **1413** could be



Scheme 162. Total Synthesis of (+)-Trehazolin (Carreira, 1995).

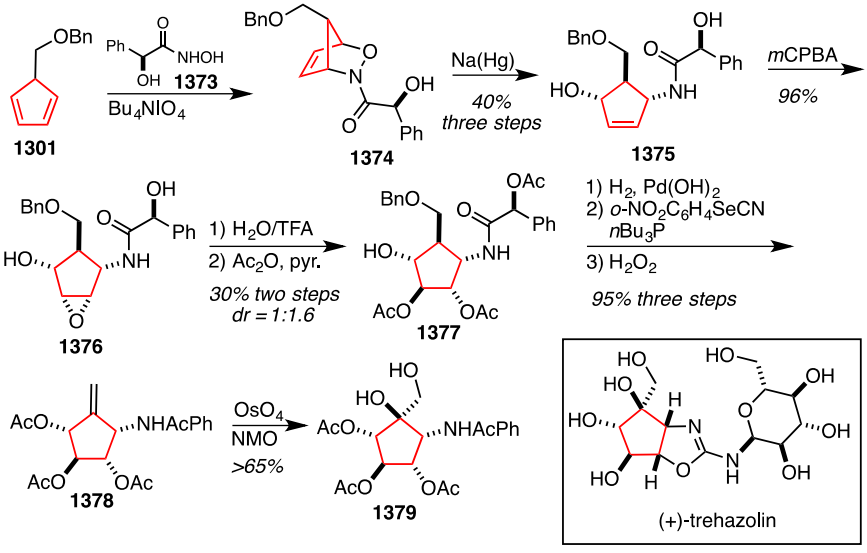
achieved from the acetimidate in a single step, superior yields were obtained if performed as a two-step transformation. Acidic methanolysis of **1413** delivered (+)-mannostatin A as the hydrochloride salt.

The Mehta[253] synthesis of (+)-kelsoene begins with chiral diacetate **1317** (Scheme 169), which is available from 1,5-cyclooctadiene (**1313**) as discussed in the intro. Acetate hydrolysis and oxidation of the corresponding diol gave dione **1414**. Wittig olefination desymmetrizes the diketone and hydrogenation occurs from the convex face of the diquinane to deliver **1415**. Enolization under kinetic conditions and silylation gave the corresponding enol ether, which underwent Saegusa oxidation to give enone **1416**. Subjection of **1416** to methyllithium gave the 1,2-addition product, and treatment with PCC led to oxidation with allylic transposition (**1417**). A [2 + 2]-photocycloaddition with *trans*-1,2-dicholoroethylene from the convex face of the diquinane furnishes tricyclic intermediate **1418**. Three additional steps featuring a reductive dechlorination were used to form intermediate **1419**. Homologation of the ketone by olefination following Kluge's method[62] (to **1420**) and hydrolysis gave aldehyde **1421**. The favored diastereomer positions the aldehyde on the less hindered face of the polycyclic framework. Four additional steps were required to complete the synthesis of (+)-kelsoene.

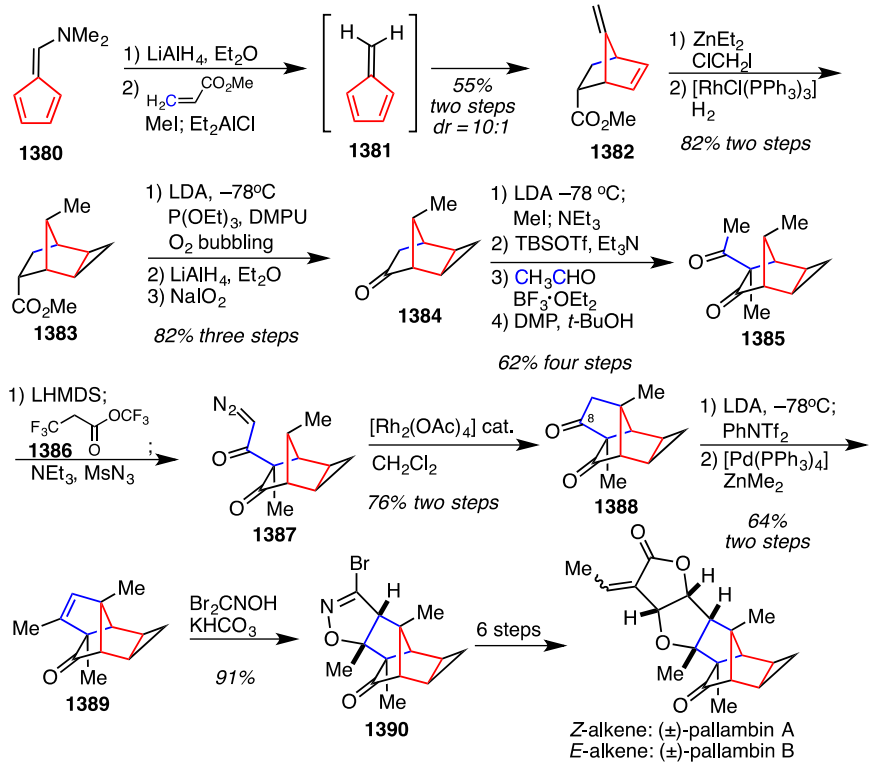
A synthesis of (−)-kelsoene was completed by Schulz[254] beginning with Mehta's intermediate **1419** (Scheme 170).[255] A Corey-Chaykovsky epoxidation delivered **1422**. Hydrogenation the cyclobutene proceeded with concomitant epoxide pinacol rearrangement to give aldehyde **1423** as the major stereoisomer. Addition of methyllithium and oxidation of the resulting alcohol gave methyl ketone **1424**. Treatment with base epimerized the ketone stereocenter delivering a fully functionalized cyclopentane containing the desired stereochemistry for the natural product. Olefination with the Petasis reagent completed (−)-kelsoene.

The Danishefsky[256] synthesis of (±)-gelsemine begins with epoxidation of the bicyclo[2.2.1]heptadiene **1425** to give **1426** (Scheme 171). Alumina-promoted rearrangement delivers the aldehyde **1427**. Through a divinylcyclopropane-Cope rearrangement, the carbocyclic core of gelsemine (**1430**) was established. Three of the cyclopentane stereocenters have been set at this point in the synthesis. Hydroboration-oxidation of the cyclopentene proceeded with complete chemoselectivity and excellent regioselectively to deliver **1431**. The chemoselective preference arises from the greater strain in the cyclopentene double bond. The regiochemical preference arises from homo-allylic stabilization of partial carbocation character at C16 that developed during an asynchronous hydroboration. Swern oxidation of the resulting alcohol delivers a ketone. Formation of the silyl enol ether and treatment with Eschenmoser's salt gives β-amino ketone **1432**, and a subsequent Hofmann elimination delivers enone **1433**. Luche reduction from the less hindered face gives an allylic alcohol, and a second hydroboration-oxidation sequence generates diol **1434**. Selective activation of the primary alcohol was followed by oxetane formation (**1435**). Ether cleavage and Swern oxidation gave cyclopentanone **1436**. A Horner-Wadsworth-Emmons olefination of the ketone led to a mixture of separable alkene isomers (3:2 favoring the *Z*-alkene). Both alkene isomers were independently reduced with DIBAL to give **1437**. A Johnson–Claisen rearrangement was performed to install the quaternary stereocenter of intermediate **1438**. Formation of the acyl azide and subsequent Curtius rearrangement (Shiori modification[257]) gave rise to carbamate **1439**. The oxetane was activated with boron trifluoride etherate and addition by the carbamate nitrogen delivered **1440**. This advanced intermediate contains the fully functionalized cyclopentane found in (±)-gelsemine. An additional 17 steps were used to complete the synthesis of the natural product.

In the synthesis of (−)-sulcatine G (Scheme 172), Mehta[258] utilizes a similar strategy developed for their kelsoene synthesis discussed above. Desymmetrization of the ring system **1441** was accomplished over five steps to give cyclopentanol **1442**. Alcohol oxidation yielded ketone **1443**. Acylation with dimethyl carbonate, selenation, and oxidation provides enone **1444**. The required methyl group for sulcatine G was introduced by cuprate addition, and the resulting diketone was re-oxidized to form **1445**. Cyclobutane **14146** was obtained by a [2 + 2]-photocycloaddition with *trans*-1,2-dichloroethylene. Addition occurred exclusively from the less hindered convex face of the diquinane ring system to deliver tricyclic intermediate **14146**. Treatment of the diastereomeric chloride mixture with DIBAL resulted in ketone reduction with low



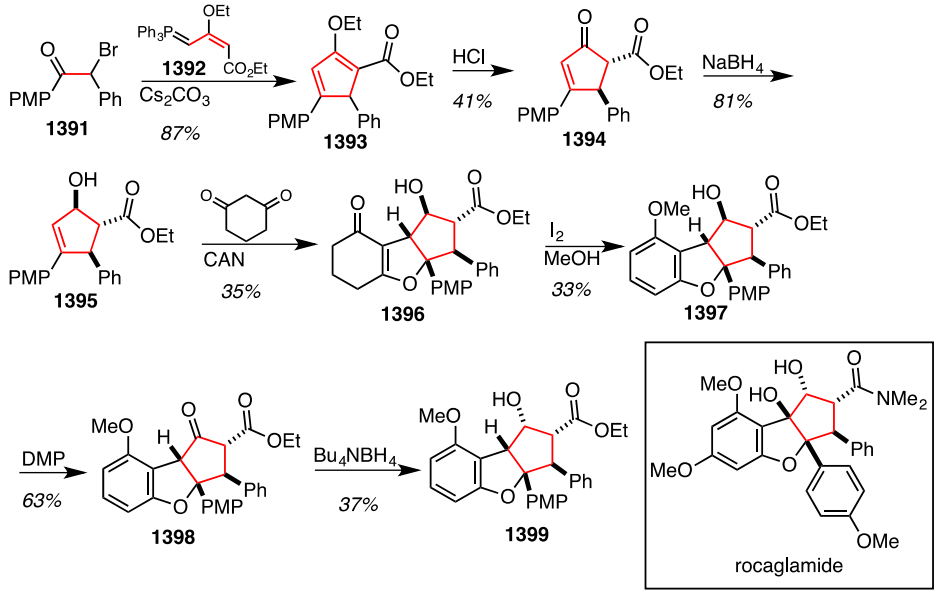
Scheme 163. Total Synthesis of (+)-Trehazolin (Ganem, 1998).



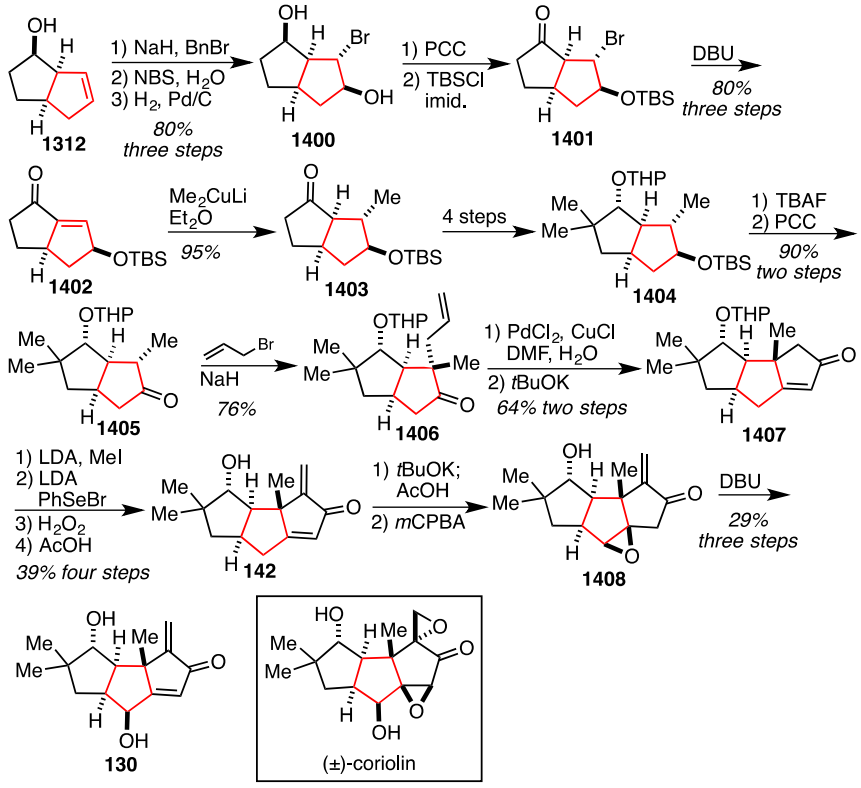
Scheme 164. Total Synthesis of (±)-Pallambins A and B (Carreira, 2015).

diastereoselectivity (*dr* = 55:45). The complicated mixture of diastereomers was subjected to reductive dechlorination and hydrogenation to produce a mixture of alcohol epimers **14147**. Selective silylation of the primary alcohol was followed by acetate formation, at which time the desired diastereomer (**1448**) could be purified. Advanced intermediate **1448** contains the fully functionalized cyclopentane with the desired stereochemistry for (−)-sulcatine G. An additional eight steps was required to complete the synthesis of the natural product.

The synthesis of epoxyqueuosine by Carell[259,260] begins with cyclopentene intermediate **1309** (Scheme 173). A Mitsunobu reaction with hydrazoic acid followed by a Staudinger reduction delivers allyl amine **1449**. Protection of the nitrogen as the trichloroacetimide was followed by acetonide cleavage and silylation with TBSCl to give **1450**. Epoxidation occurs on the diastereoface opposite the silyl ethers to furnish fully functionalized cyclopentane **1451**. This intermediate could be advanced to epoxyqueuosine over an additional three steps.



Scheme 165. Synthetic Studies Towards Rocaglamide (Schoop, 2000).

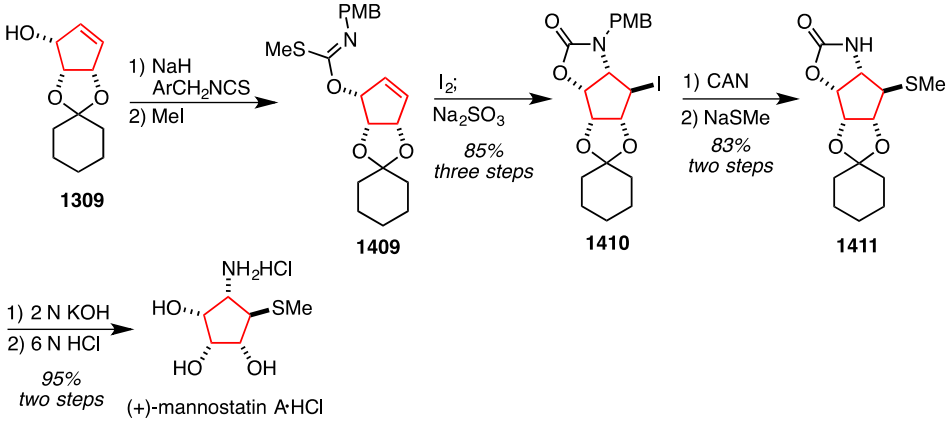


Scheme 166. Total Synthesis of (±)-Coriolin (Ikegami, 1981).

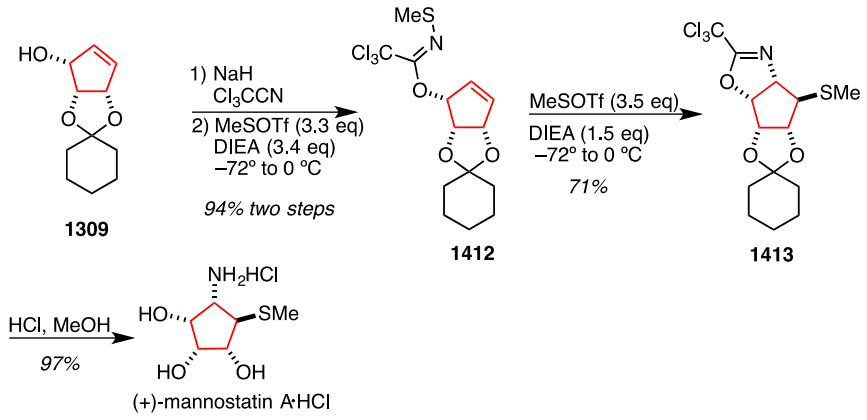
11.3. Cyclopentanone functionalizations

The sesquiterpene (±)-gymnomitrol was synthesized by Paquette[261] beginning with ketone **1321** (Scheme 174). Methylenation was accomplished by heating with formalin and *N*-methylanilinium trifluoroacetate to give **1452**. Copper-catalyzed conjugate addition of the vinyl Grignard species **1453** was followed by methylation on the convex face of the bicycle to obtain **1454**. Epoxidation gave silyl-oxirane **1455**, which was hydrolyzed to aldehyde **1456**. Aldol addition of the keto-aldehyde gave the tricyclic scaffold of gymnomitrol. The secondary alcohol stereocenter was then oxidized to diketone **1457**. Methylation of the less hindered ketone was followed by dehydration with $POCl_3$ to give an exocyclic alkene. Finally, stereoselective reduction of the ketone delivered a fully functionalized cyclopentane and completed the synthesis of (±)-gymnomitrol.

In the synthesis of (±)-gymnomitrol by Coates,[121] a condensation of cyclopentanone **1321** with ethyl formate delivered intermediate **1458** (Scheme 175). Reaction with hydroxylamine in sodium methoxide led to formation of the α-cyano ketone **1459** as an epimeric mixture. Upon heating with acrolein diethyl acetal (**1460**), alkylation occurred from the convex face of the bicycle yielding the ethoxyallyl ketone **1461**. Refluxing with ethylene glycol and acid afforded 1,3-dioxolane **1462**. Reductive decyanation was accomplished with lithium in liquid ammonia, and the resulting enolate ion was trapped as its silyl ether. Regeneration of the lithium enolate with methyllithium was followed by stereoselective methylation again on the convex face to give **1463**, which contains



Scheme 167. Total Synthesis of (+)-Mannostatin A (Knapp, 1991).



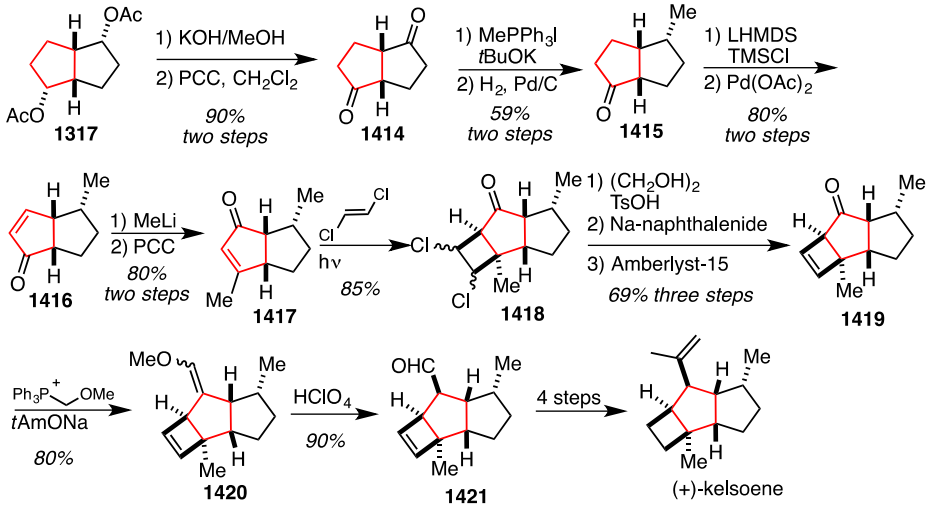
Scheme 168. Total Synthesis of (+)-Mannostatin A (Fuchs, 1994).

the three vicinal quaternary carbon stereocenters of gymnomitrol. Acid catalyzed removal of the acetal gave an aldehyde, which was resistant to a planned aldol cyclization. Chromium oxidation gave the corresponding carboxylic acid **1464**. Lactonization occurred upon treatment with acetic anhydride to deliver **1465**. Reduction of the ester carbonyl with DIBAL gave an aluminum hemiacetal, which fragmented to an aluminum enolate and a tethered aldehyde. Aldol cyclization successfully occurred under these conditions, presumably due to the enhanced reactivity of the enolate (compared with the unsuccessful aldol reaction of **1463** under acidic conditions) Oxidation of the aldol product delivered bridged diketone **1466**. A regioselective methylation, dehydration and carbonyl reduction completed the synthesis of (±)-gymnomitrol.

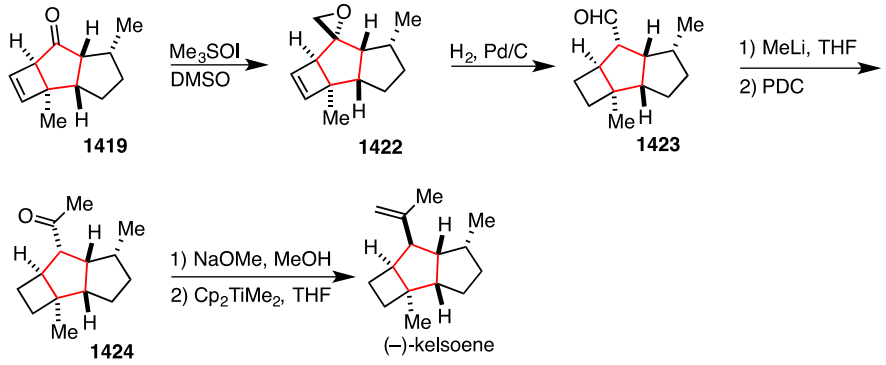
Synthetic efforts towards gymnomitrol and related compounds was performed by Imanishi (Scheme 176).[262] Beginning with cyclopentanone starting material **1321**, the lithium enolate was formed and added to diphenyldisulfide. Reformation of the lithium enolate and *O*-allylation delivers allyl vinyl ether **1467**. Heating in toluene gave rise to a Claisen rearrangement, which occurred on the convex face to afford **1468** as a single product. Desfulfurization was accomplished with dissolving metal conditions to give the corresponding enolate. Methyl iodide approaches the generated enolate on the less hindered convex face to give a single diastereomer **1469**. Ozonlysis gives an aldehyde that was protected as the acetal (**1470**). Reduction of the ketone, mesylate formation and elimination gave cyclopentene **1471**. A four-step sequence converted the protected aldehyde to a diazoketone (**1472**). Upon exposure to copper(II) acetylacetonate, cyclopropanation occurred yielding **1473**. Cleavage of the cylopropane ring with sulfuric acid in methanol gave fully functionalized cyclopentane **1474** bearing the desired stereochemistry found in gymnomitrol.

The synthesis of (±)-gymnomitrol by Snider[263] begins with ketone **1321** (Scheme 177). Alkylation of the bicyclic ketone with LHMDS and 1-iodo-2-butyne (**1475**) delivers a mixture of monoalkylated epimers along with some dialkylated material. Treatment of the mixture with standard alkylation conditions gave **1476** in good yield over the two steps. Exposure to potassium 3-aminopropanamide (**1477**) induces an alkyne-zipper isomerization, and silylation of the acetylide gives **1478**. The key step in the synthesis is an oxidative free-radical cyclization to establish the tricyclic architecture of gymnomitrol. The oxidative cyclization of **1478** with $Mn(OAc)_3$ gives **1479** as a mixture of (*E*)- and (*Z*)-vinyl silanes. Desilylation of the mixture was effected by treatment with hot acetic acid to give exocyclic alkene **1480**. Completion of (±)-gymnomitrol is accomplished by ketone reduction with sodium borohydride delivering the fully functionalized cyclopentane.

In the synthesis of anguidine by Brooks,[264] a 1,3-cyclopentanedione (**1323**) is desymmetrized by enantioselective



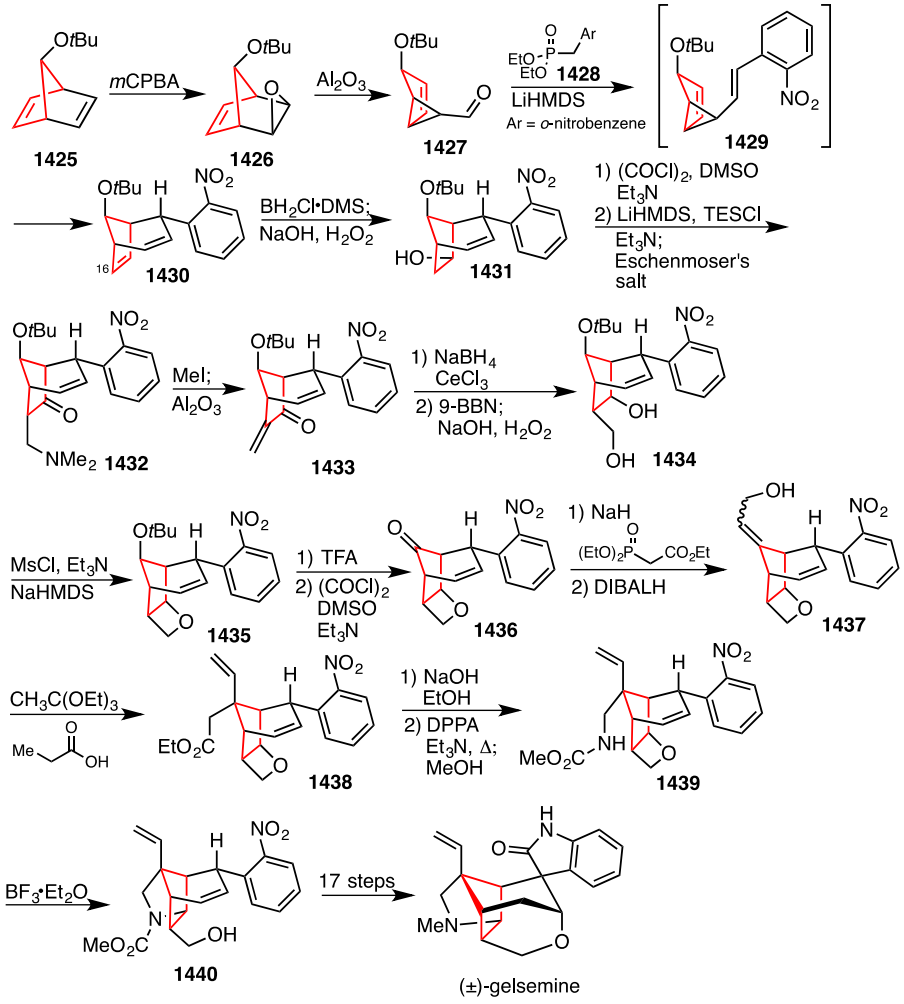
Scheme 169. Total Synthesis of (+)-Kelsoene (Mehta, 2001).



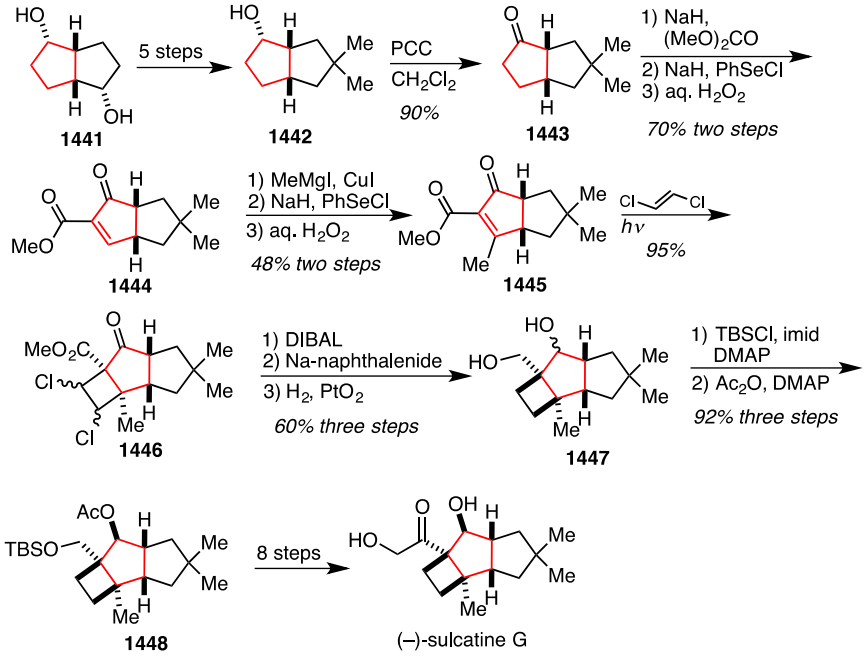
Scheme 170. Total Synthesis of (−)-Kelsoene (Schulz, 2001).

carbonyl reduction with Baker's yeast to give chiral ketol **1481** (Scheme 178).[265] Hydroxyl inversion occurred over two steps to give **1482**. This material was converted to ester **1483** over three steps. Bromination occurred following the method of Marquet,[266] and subsequent elimination gave cyclopentene **1484**. The cyclopentene was dihydroxylated to give the desired diastereomer in a 5:1 ratio (**1485**). Presumably the stereoselectivity results from the steric size of the adjacent silyl ether. Treatment of this intermediate with base induced lactonization; the regioselectivity can be attributed to reaction of the less hindered hydroxyl group. Intermediate **1486** was advanced 12 steps to intermediate **1487**. A Wititig olefination and removal of the silyl group yielded **1488**. Finally, epoxidation with peracid delivered the fully functionalized cyclopentane (**1489**) of anguidine. Completion of the synthesis required an additional two transformations.

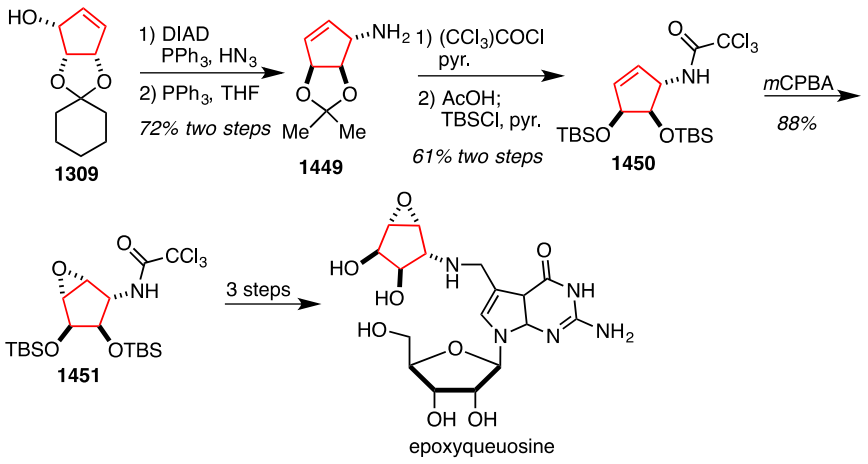
In a synthesis of (±)-coriolin, Trost begins the synthesis with



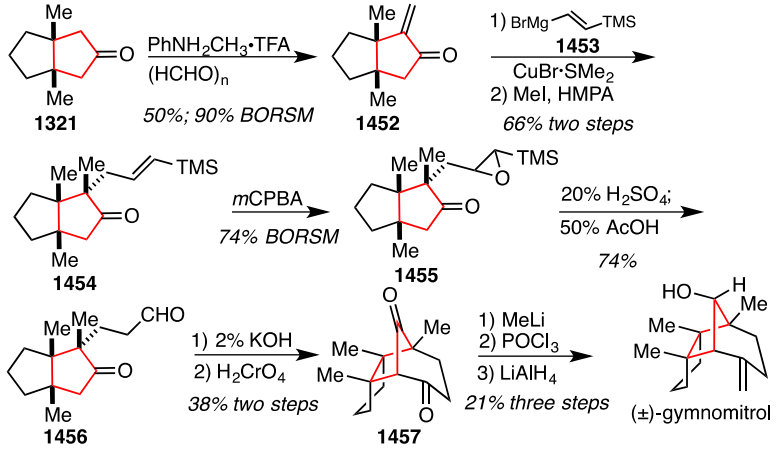
Scheme 171. Total Synthesis of (±)-Gelsemine (Danishefsky, 2002).



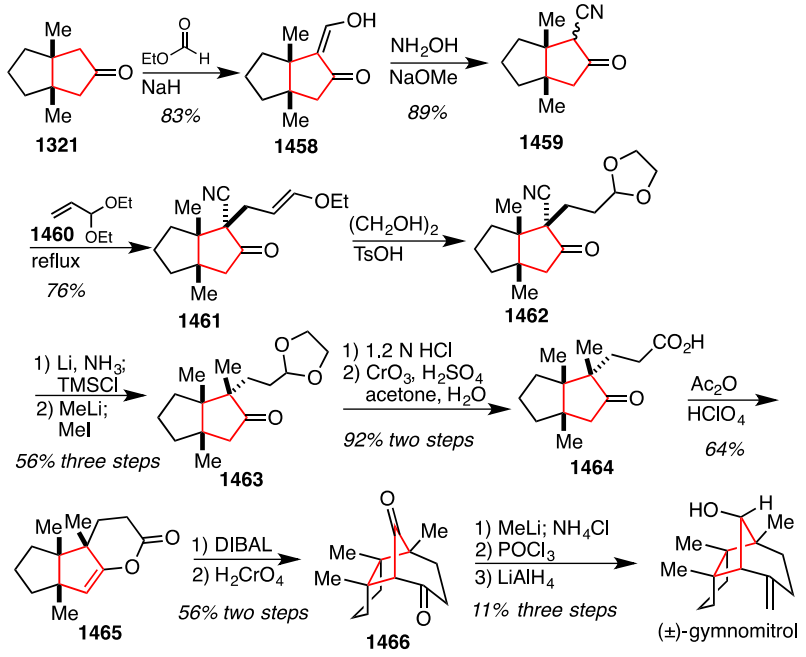
Scheme 172. Total Synthesis of (−)-Sulcatine G (Mehta, 2002).



Scheme 173. Total Synthesis of Epoxyqueuosine (Carell, 2013).

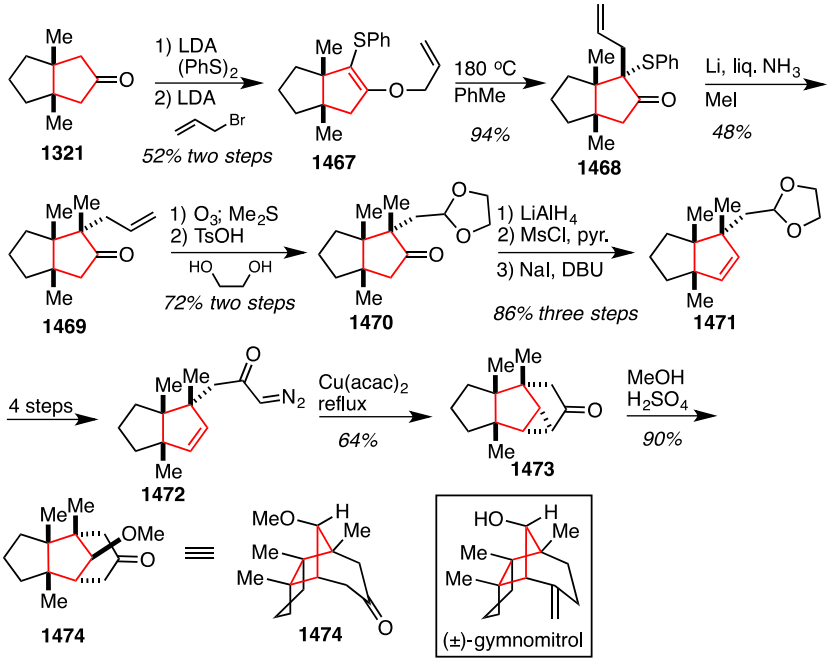


Scheme 174. Total Synthesis of (±)-Gymnomitrol (Paquette, 1979).

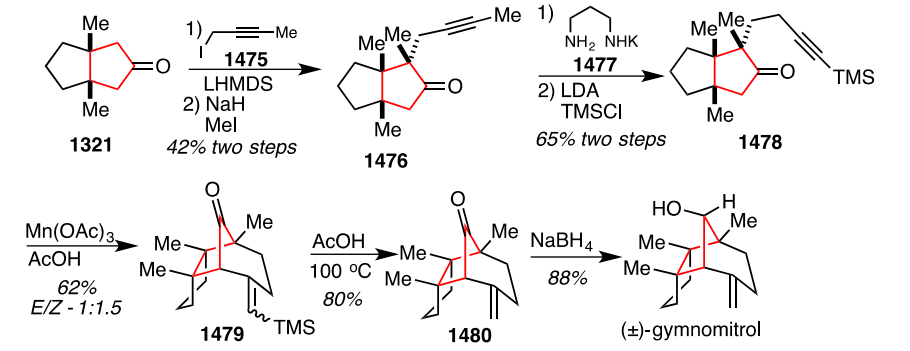


Scheme 175. Total Synthesis of (±)-Gymnomitrol (Coates, 1982).

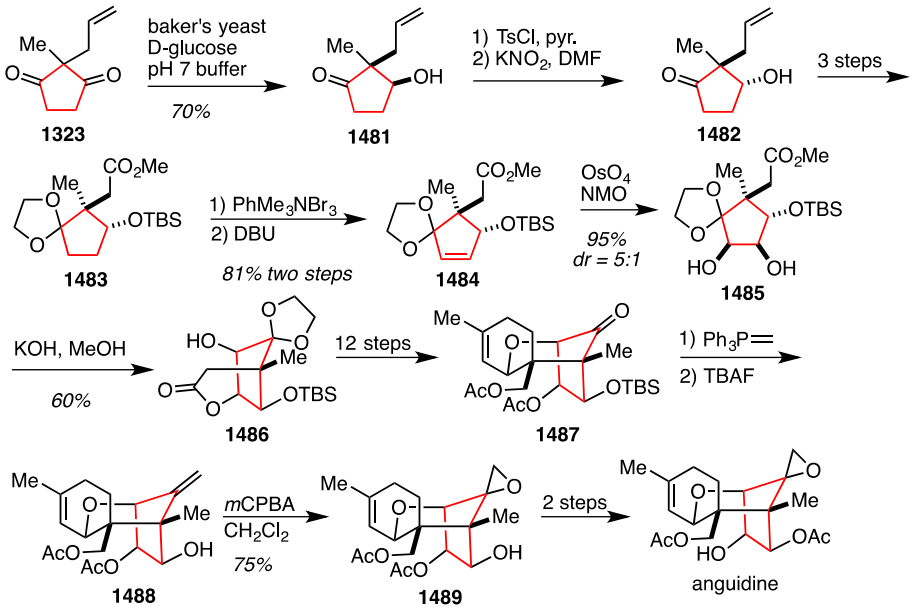
enedione starting material **1490**, which has become an important building block in chemical synthesis[267] (Scheme 179). The enone functionality was masked as a thioether by conjugate addition of methanethiol. A chemoselective ketalization protected the less hindered ketone. Finally, monosulfenylation using dimethyl disulfide occurred to give **1491**. Alkylation with the substituted allyl iodide **1492** gives **1493**. Peracid oxidation of the sulfides to the corresponding sulfones yielded **1494**. Treatment with fluoride promoted allyl silane addition to the ketone giving triquinane **1495**. This material was advanced three steps to intermediate **1496**, which was epoxidized with peracid to give **1497**. The stereoselectivity of the epoxidation can be explained by the preferential formation of the *cis* diquinane substructure. Acetal hydrolysis and elimination of the sulfones gave dienone **1498**. Reductive opening of the epoxide gives a mixture of isomeric products, and subsequent treatment with DBU delivers a single dienone alcohol **1499**. Conjugate reduction with lithium in liquid ammonia gave an 80:20 mixture of β,γ- and α,β-unsaturated ketones. Epoxidation of this crude mixture was followed by isomerization with DBU to give the allylic alcohol **129**. This material was advanced four steps to



Scheme 176. Synthetic Studies Towards Gymnomitrol (Imanishi, 1993).



Scheme 177. Total Synthesis of (±)-Gymnomitrol (Snider, 1997).



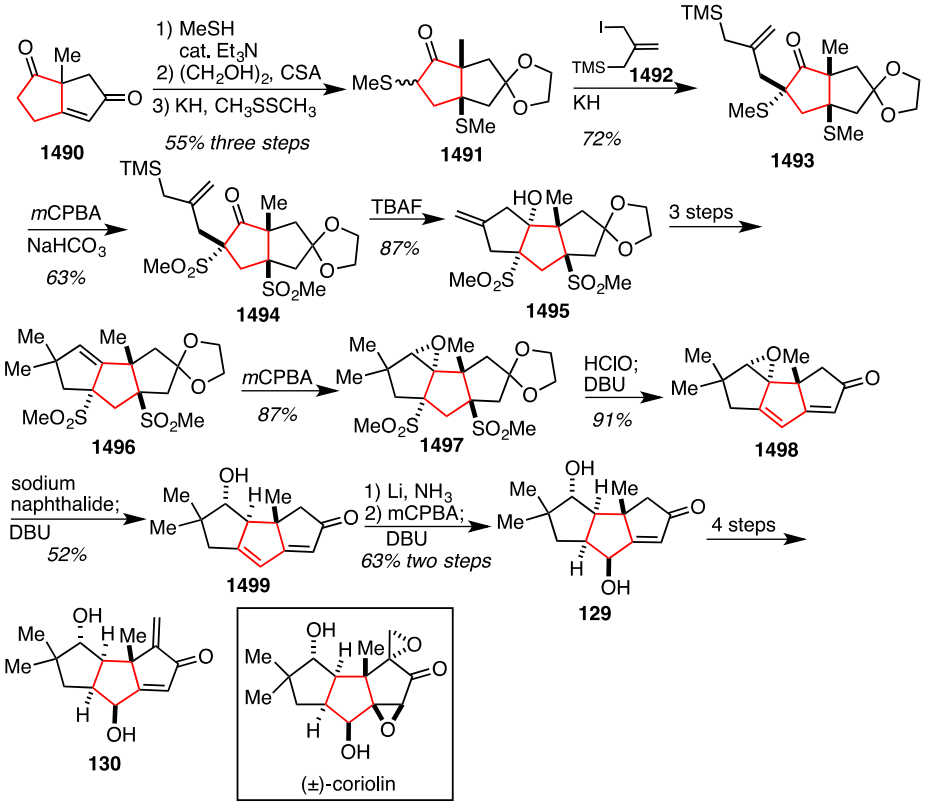
Scheme 178. Total Synthesis of Anguidine (Brooks, 1983).

intermediate **130**, which is an intermediate previously taken to the natural product by Danishefsky.[34]

The formal synthesis of (±)-coriolin by Curran[217] begins with 2-methylcyclopentenone (**1500**) (Scheme 180). This material was advanced using an Ireland–Claisen rearrangement, selenolactonization and elimination to give bicyclic intermediate **1505**. Treatment of **1505** with the cuprate derived from **1473** induced substitution with opening of the bicycle furnishing **1507**. Functional group manipulations over five steps occurred to give **1508**. An elegant cascade radical cyclization was promoted by treatment with samarium iodide to give the desired triquinane ring system with *cis* ring fusions. Hydrolysis of the ketal furnishes **1509**. Conversion to the cross-conjugated dienone **142** was accomplished by formation of the silyl enol ether and oxidation with DDQ. This advanced intermediate was previously prepared and taken to coriolin by Danishefsky[34] and Tatsuta.[35]

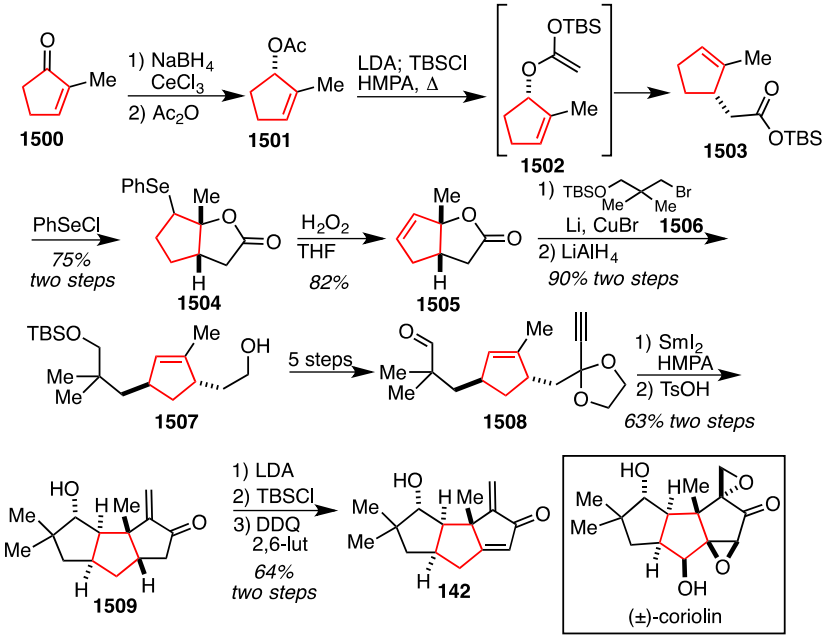
11.4. Cyclopentenone functionalizations

In the synthesis of (±)-coriolin, Koreeda[268] uses a one-step aldol-alkylation to construct a bicyclo[3.3.0]octenone system (Scheme 181). The dialkylation reaction begins with a substituted cyclopentenone **1510**, which was treated with base to generate dianionic intermediate (**1511**). This intermediate undergoes double addition to 3-iodo-2,2-dimethylpropanal (**1512**), and the aldol functional group is protected as its MOM ether to give bicyclic product **1513**. The regioselectivity of the alkylation is the result of a more reactive anion at C5; reaction of the C5 anion leaves a fully conjugated enolate intermediate, which undergoes subsequent alkylation. Alternatively, initial alkylation at C4 would leave a less stable cross-conjugated anion. Addition of methyllithium to enone **1513** and elimination upon acidic workup delivered enone **1514**. A conjugate addition of the cuprate derived from **1515** occurred from the convex face of the bicycle. Acid-catalyzed acetal removal and subsequent aldol cyclization delivered triquinane scaffold **1516**. Alcohol protection and elimination delivers enone **1517**. A stereoselective and regioselective carbonyl reduction was performed under Luche conditions. Interestingly, the diastereomer formed in the Luche reduction arises from hydride addition to the concave face of the bicycle. After evaluating other hydride reducing reagents and substrates, it was postulated that the steric size of the benzoate group is responsible for the unexpected diastereoselectivity. A subsequent acetylation gave **1518**. A Salmond[269] oxidation installs the carbonyl yielding cyclopentenone **1519**. Reductve removal of the acetate and benzoyl deprotection furnishes intermediate **104**, which has been taken forward to (±)-coriolin by Trost.[129]

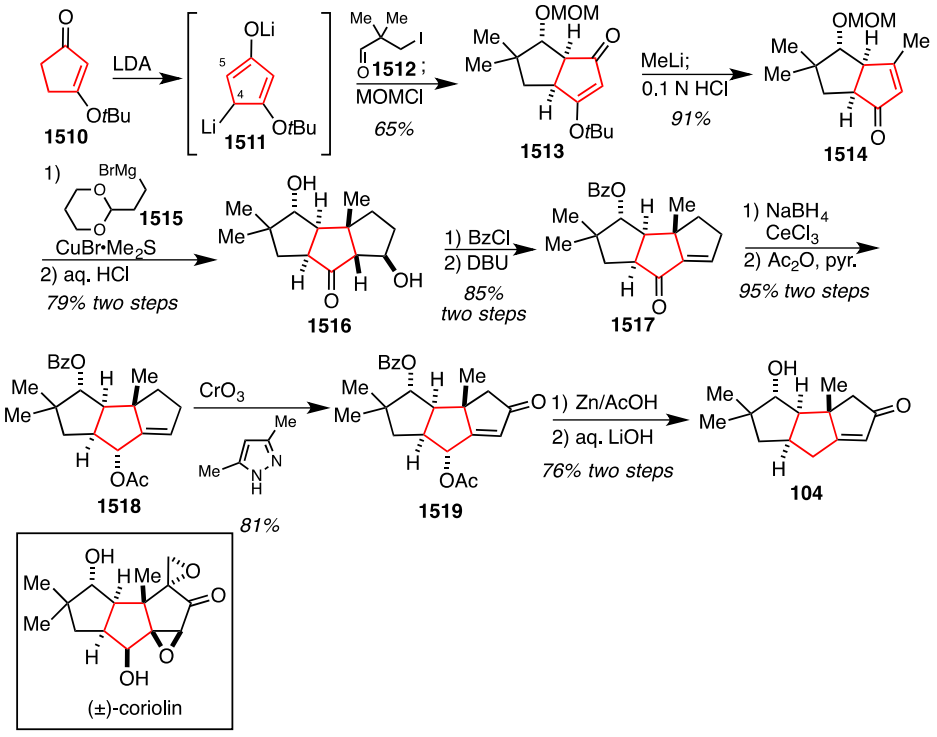


Scheme 179. Formal Synthesis of (±)-Coriolin (Trost, 1981).

The synthesis of (±)-kelsoene by Piers[270] begins with cyclopentenone (**1520**). Conjugate addition of the lower order heterocuprate **1521** delivers **1522** (Scheme 182). Intramolecular alkylation delivered the *cis*-fused bicyclo[3.3.0]octane substructure of kelsoene. Hydrogenation using Crabtree's catalyst[271] occurred from the less hindered face of the bicycle to give **1523** with good diastereoselectivity. Selenium based oxidation of ketone **1523** gave cyclopentenone **1524**. Addition of methyllithium formed a tertiary alcohol that could be oxidized with PCC on alumina to give the transposed enone **1525**. A [2 + 2] photocycloaddition with ethylene proceeded stereoselectively from the less hindered face of the bicycle furnishing **1526** and completing the tricyclic core of kelsoene.



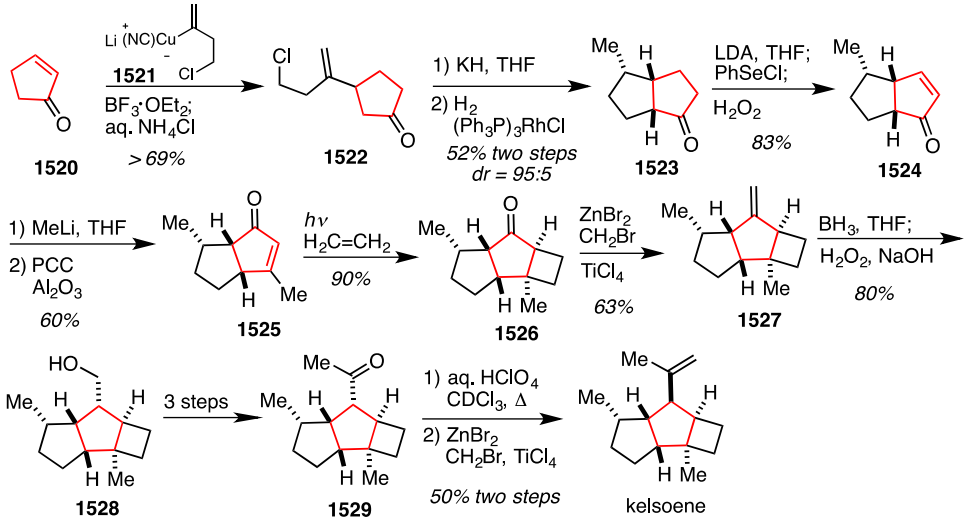
Scheme 180. Formal Synthesis of (±)-Coriolin (Curran, 1988).



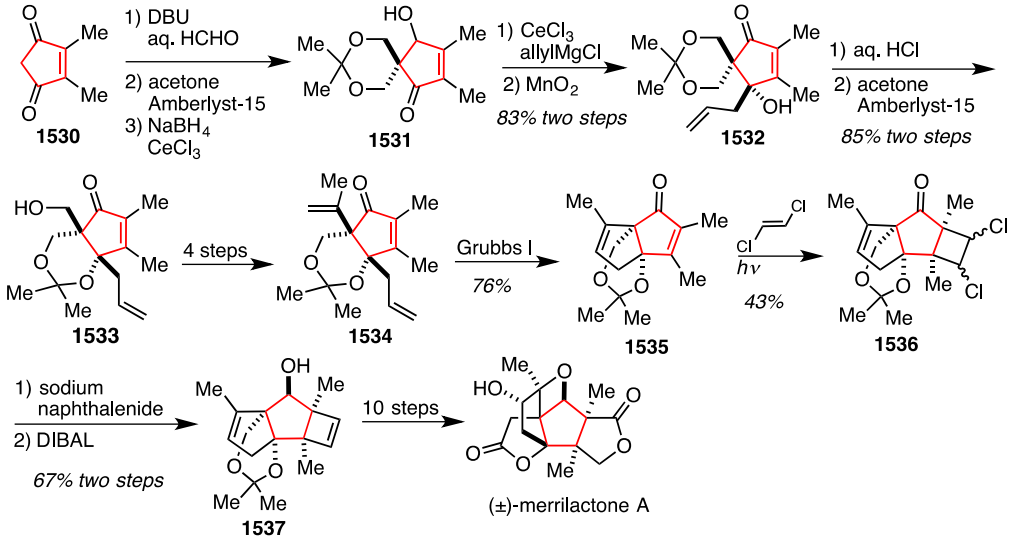
Scheme 181. Total Synthesis of (±)-Coriolin (Koreeda, 1983).

After many unsuccessful attempts at olefination of the ketone, the Lombardo[272] reagent was effective at delivering alkene **1527**. Hydroboration-oxidation delivered fully functionalized cyclopentene **1528**. This material was advanced to the methyl ketone **1529** over three transformations. Treatment with acid induced ketone epimerization, which established the desired stereochemistry for the target. Finally, olefination with the Lombardo reagent completed the synthesis of (±)-kelsoene.

In the synthesis of (±)-merrilactone A, Mehta[273] begins with a substituted cyclopentene-1,3-dione (Scheme 183). Desymmetrization of **1530** was performed over three steps requiring double hydroxymethylation, protection of the diol as the acetonide and Luche reduction to give **1531**. A 1,2-addition of an allylcerium reagent was followed by hydroxyl oxidation with manganese dioxide to give hydroxyenone **1532**. A two-step transketalization sequence delivered the desired acetonide **1533** in a 1:1 ratio with **1532**, which could be recycled. This material was advanced four steps to diene **1534**. Ring closing metathesis[274] delivered tricyclic intermediate **1535**. A [2 + 2] cycloaddition with *trans*-dichloroethylene was successful in promoting the formation of vicinal quaternary stereocenters as a complex mixture of diastereomers. The cycloaddition proceeds with modest facial selectivity ($dr = 2{:}1$) with respect to the enone because the acetonide blocks the α-diastereoface. The desired major isomer **1536** was isolated as an inconsequential mixture of chloride diastereomers. Reductive dehalogenation was followed by ketone reduction with DIBAL,



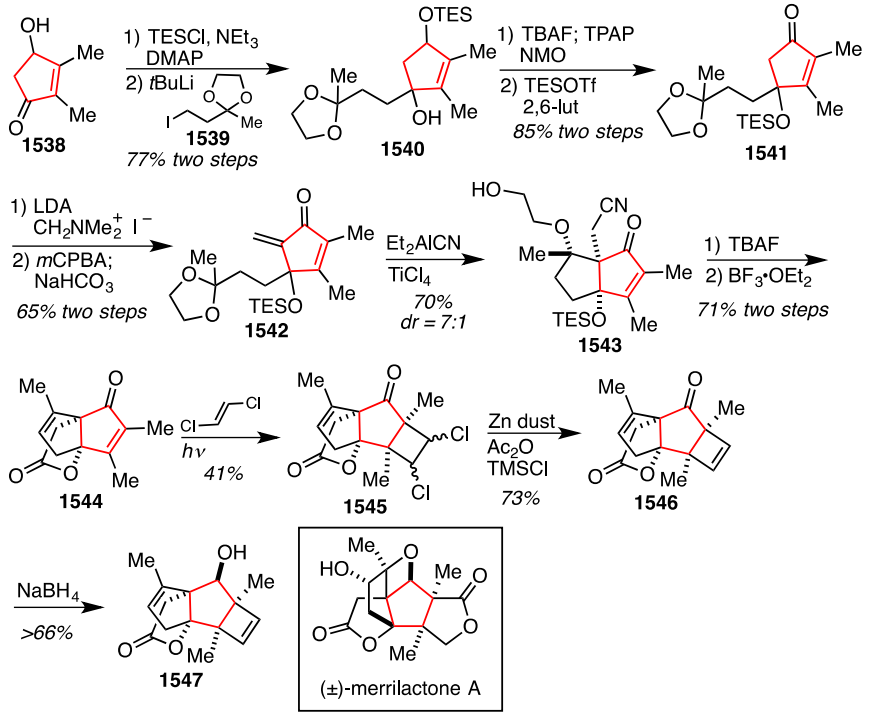
Scheme 182. Total Synthesis of (±)-Kelsoene (Piers, 2001).



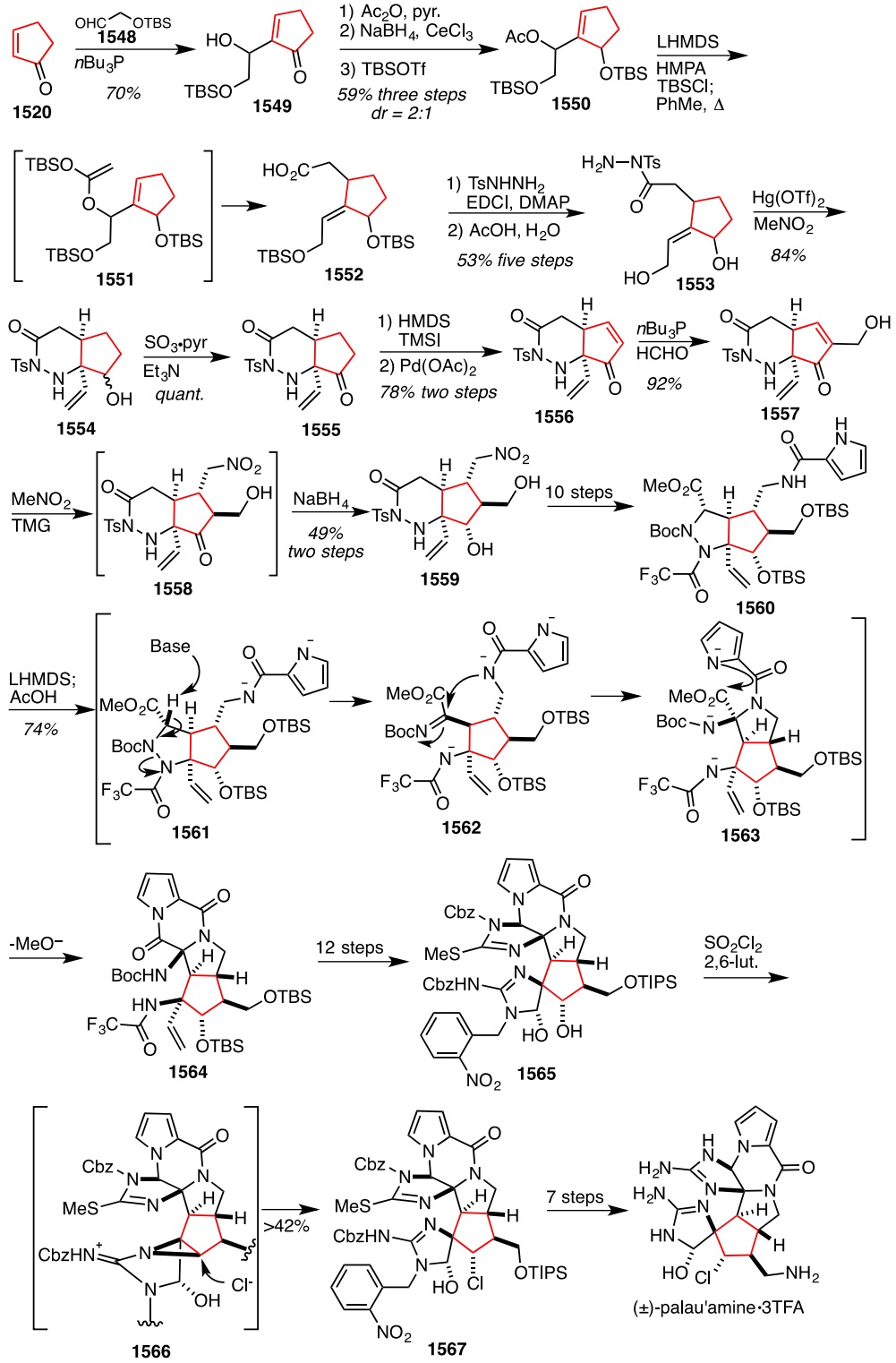
Scheme 183. Total Synthesis of (±)-Merrilactone A (Mehta, 2006).

which proceeds with complete diastereoselectivity to give **1537**. It was speculated that the diastereoselective ketone reduction is the result of either the steric bias of the polycyclic architecture or coordination of the hydride reagent to the acetonide oxygens. The resulting fully functionalized cyclopentane contains all the desired stereochemistry for (±)-merrilactone A, and the natural product was completed over an additional ten steps.

In a formal synthesis of (±)-merrilactone A, Greaney[275] begins with functionalized cyclopentenone **1538** (Scheme 184). Silylation of the alcohol was followed by a 1,2-addition of the organolithium derived from **1539** furnishing **1540**. Fluoride deprotection and oxidation gave a cyclopentenone. The tertiary alcohol was then protected as a silyl ether to give **1541**. A two-step sequence involving Eschenmoser's reagent yielded **1542**. The key conjugate addition–aldol process was promoted by Et_2AlCN and $TiCl_4$, and **1543** is obtained as the major diastereomer (dr = 7:1). Mechanistically, addition of cyanide gives a cyclic *E*-configured ketone enolate. The aldol reaction presumably proceeds through a closed titanium-chelated transition state leading to the favored *anti*-aldol diastereomer. Desilylation and treatment with boron trifluoride furnished the oxatriquinane core **1544**. Using a similar approach to Mehta,[273] photocycloaddition with dichloroethylene proceeded to give a mixture of diastereomers favoring addition on the β-diastereoface of the enone (**1545**). Dechlorination with zinc



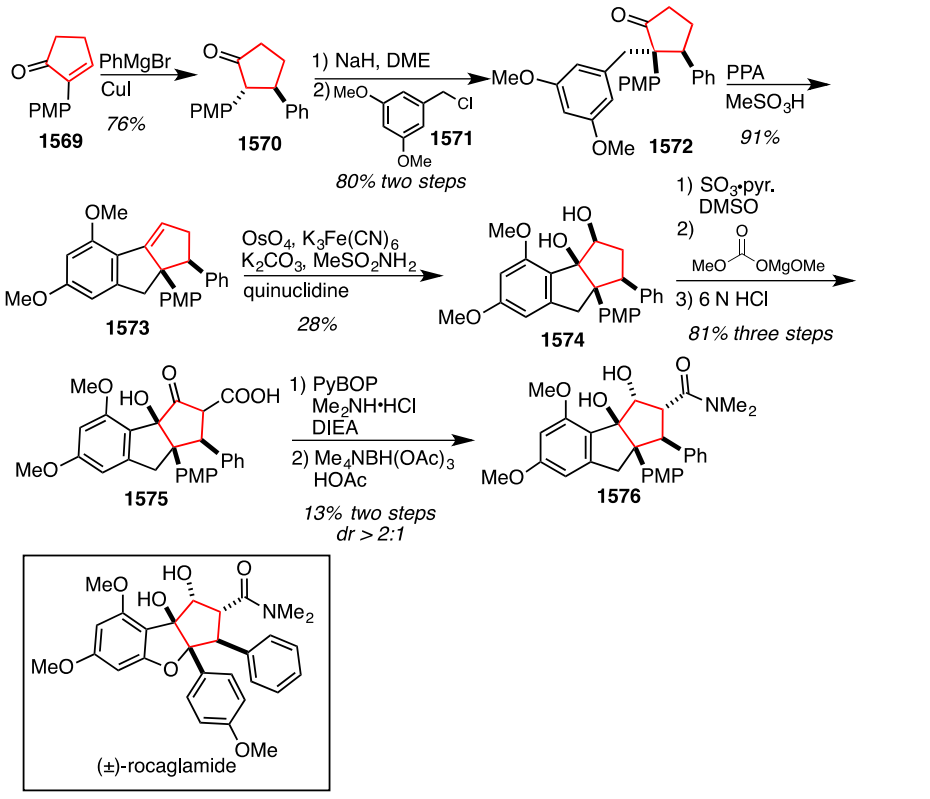
Scheme 184. Formal Synthesis of (±)-Merrilactone A (Greaney, 2012).



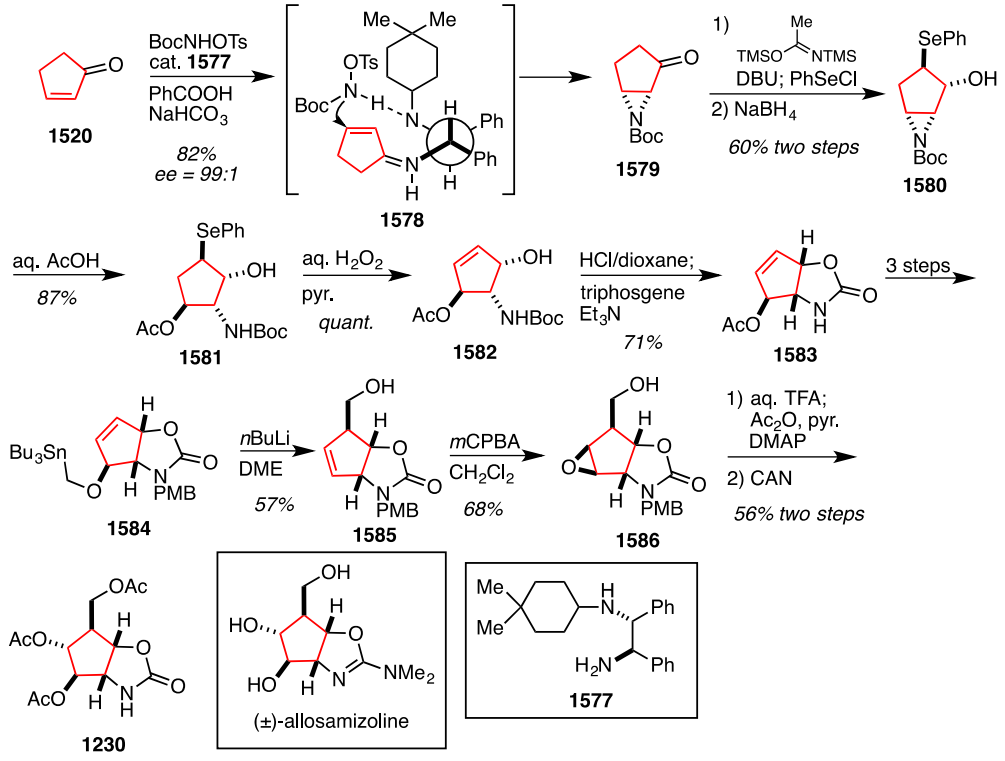
Scheme 185. Total Synthesis of (±)-Palau'amine (Namba, Nishizawa, Tanino, 2015).

dust gave cyclobutene **1546**. A stereoselective ketone reduction delivered fully substituted cyclopentane **1547**, which is an intermediate previously prepared in the total syntheses of (±)-merrilactone A by Mehta and Singh.[273]

The synthesis of (±)-palau'amine accomplished by Namba, Nishizawa and Tanino[276,277] begins with cyclopentenone (**1520**, Scheme 185). A Morita–Baylis–Hilman reaction with TBS-protected glycolaldehyde (**1548**) delivers **1549**. Acetylation, Luche reduction, and TBS protection delivers a 2:1 mixture of diastereomers (**1550**). This diastereomeric mixture was carried several steps through the synthesis. This mixture was subjected to an Ireland–Claisen rearrangement to give **1552**. The geometry



Scheme 186. Synthetic Studies Towards (±)-Rocaglamide (Bruce, 1999).



Scheme 187. Formal Synthesis of (−)-Allosamizoline (Nemoto, 2016).

of the trisubstituted alkene is the result of a favored chair-like transition state with equatorial positioning of the silyloxymethyl group. The carboxylic acid was converted to the acyl tosylhydrazide, and the silyl ethers were cleaved under acidic conditions furnishing diol **1553**. Cyclization of **1553** was catalyzed by $Hg(OTf)_2$ to give **1554** exclusively as the *cis*-fused bicycle; however, the product remained an inconsequential mixture of alcohol diastereomers. Alcohol oxidation simplified the diastereomer mixture giving good yields of ketone **1555**. Saegusa–Ito oxidation provided **1556**. A second Morita–Baylis–Hilman reaction with formaldehyde delivered alcohol **1557**. Conjugate addition of nitromethane under basic conditions occurred from the convex face of the bicycle to deliver **1558**. The unpurified material was subjected to hydride reduction to yield a fully functionalized cyclopentane **1559**. Interestingly, the hydride addition occurred from the concave face of the bicycle; no explanation was offered for this diastereoselectivity, but it may result from a greater steric demand of the vinyl and nitro methyl groups compared with the cyclic acyl hydrazide. This material was advanced ten steps to intermediate **1560**. The central ring architecture of palau'amine was then constructed in a cascade reaction initiated by treatment of **1560** with LHMDS. Deprotonation induces β-elimination of a trifluoromethyl amide, which simultaneously cleaves the N–N bond and generates an imine (**1562**). Intramolecular nucleophilic addition to the activated imine delivers the *trans*-bicyclo[3.3.0]octane ring system. The cascade continues with the addition of the tethered pyrrole to the methyl ester to form diketopiperizine **1564**. This intermediate was advanced over 12 steps to alcohol **1565**. The activation of the secondary alcohol as the chloride proceeded with retention of stereochemistry and induced a cyclization with the guandine nitrogen to form an intermediate aziridine (**1566**). Subsequent backside attack of chloride resulted in **1567**, which has the required stereogenic chloride configuration and the fully functionalized cyclopentane found in (±)-palau'amine. The natural product was completed in an additional seven steps.

In the Bruce[278] synthesis of a (±)-rocaglamide analog, the opening synthetic sequence capitalizes on the rich reactivity of the enone functional group (Scheme 186). Specifically, conjugate addition of phenyl cuprate to enone **1569** gives an *anti*-diarylcyclopentanone **1570** after an aqueous workup. Thermodynamic enolate formation and alkylation with chloride **1571** delivered trisubstituded cyclopentanone **1572** with control of diastereoselectivity. Intramolecular electrophilic aromatic substitution was followed by an acid promoted dehydration to give the fused tricyclic intermediate **1573**. Dihydroxylation of the trisubstituted alkene in **1573** was problematic, but a 28% yield of **1574** was obtained using optimized conditions. Steric crowding from the nearby aryl groups hinders the convex face of the ring system making formation and/or cleavage of the osmate ester low yielding. Oxidation of the secondary alcohol, α-carboxylation with the Stiles reagent,[166] and methyl ester hydrolysis delivers β-ketoacid **1575**. Formation of the ketoamide was performed with dimethylamine hydrochloride, and the product existed exclusively in the keto form with the amide substituent *anti* to the vicinal phenyl group. Finally, hydride reduction of the ketone gave target compound **1576** with modest diastereoselectivity. This final product contains a fully functionalized cyclopentane, and it is an analog of (±)-rocaglamide where the furanyl oxygen has been replaced with a methylene group.

In the Nemoto[279] synthesis of (−)-allosamizoline, cyclopentenone **1520** undergoes an asymmetric aziridination using chiral diamine catalyst **1577** (Scheme 187). The key aziridination is believed to proceed through assembly **1578**, wherein the primary amine first forms an iminium cation intermediate and the secondary amine aids in delivery of the sulfonyloxy carbamate to the *Re*-face of the ring yielding **1579**. Selenation and ketone reduction each occurred stereoselectively from the convex face of **1579** to deliver **1580**. Treatment with aqueous acetic acid resulted in regioselective opening of the aziridine ring to furnish **1581**. Oxidative elimination of the selenide delivered cyclopentene **1582**. Acidic removal of the Boc protecting group and treatment with triphosgene produces cyclic carbamate **1583**. This material was advanced three steps to allyl ether **1584**. A suprafacial 2,3-Wittig rearrangement resulted in homo-allylic alcohol **1585**. Stereoselective epoxidation is thought to arise due to hydroxyl direction to deliver fully functionalized cyclopentane **1586**. Acidic opening of the epoxide and acetate protection of the resulting triol was followed by oxidative removal of the PMB ether delivering **1230**. Intermediate was previously prepared and taken to allosamizoline by Simpkins[214] and Tatsuta.[23]

12. Conclusion

This review has presented the syntheses of natural products containing fully-functionalized cyclopentanes. Substituted cyclopentanes are a common and central structural feature in many important synthetic target molecules, and this molecular feature has inspired and challenged synthetic chemists for decades. Strategies for constructing fully-functionalized cyclopentanes were organized into ten well-defined patterns. All major reaction types including pericyclic, ionic, and radical reactions have been used to prepare such molecular architectures. Cascade processes are often particularly powerful strategies used to create cyclic motifs with control of multiple stereogenic carbon atoms. Moreover, those cascade sequences that are biomimetic or bioinspired have been particularly useful in creating the most highly substituted cyclopentanes.

Acknowledgment

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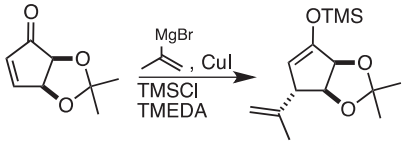
References

1. Heasley B. *Eur J Org Chem*. 2009:1477–1489.
2. Jung ME. *Tetrahedron*. 1976;32:3–31.
3. (a) Berecibar A, Grandjean C, Siriwardena A. *Chem Rev*. 1999;99:779–844;
(b) Gelsemine: Lin H, Danishefsky SJ *Angew Chem Int Ed*. 2003;42:36–51;
(c) Basler B, Brandes S, Spiegel A, Bach T. *Topics in Current Chemistry*. Springer-Verlag; 2005:1–42;
(d) Köck M, Grube A, Seiple IB, Baran PS. *Angew Chem Int Ed*. 2007;46:6586–6594;
(e) Li X–W, Ear A, Nay B. *Nat Prod Rep*. 2013;30:765–782.
4. For review, see: Crimmins MT, Reinhold TL *Org React*. 1993;44:297–588.
5. For reviews, see: (a) Pellissier H. *Adv Synth Catal*. 2011;353:189–218;
(b) Ylijoki KEO, Stryker JM. *Chem Rev*. 2013;113:2244–2266.
6. Note that we organized all metal-mediated [3 + 2] cycloadditions in this section rather than removing the transition metal catalyzed examples to Section 4.
7. Little RD. [3+2] cycloadditions-thermal. In: Trost BM, Fleming I, eds. *Comp. Org. Syn*. vol. 5. Oxford: Pergamon Press; 1991:239–270.
8. Ivchenko NB, Ivchenko PV, Nifant'ev IE. *Russ J Org Chem*. 2000;36:609–637.
9. Roush WR. Intramolecular Diels–Alder reations. In: Trost BM, Fleming I, Paquette LA, eds. *Comp. Org. Syn*. vol. 5. Oxford: Pergamon Press; 1991:513–550.
10. After this report was accepted, a synthesis of three denudatine natural products was reported using an intramolecular Diels–Alder reaction. See: Kou KGM, Li BX, Lee JC, et al *J Am Chem Soc*. 2016;138:10830–10833.
11. Corey EJ, Kang M-C, Desai MC, Ghosh AK, Houpis IN. *J Am Chem Soc*. 1988;110:649–651.
12. Bach T, Spiegel A. *Synlett*. 2002;8:1305–1307.
13. Tietze LF, Beifuss U, Ruther M, Rühlman A, Antel J, Sheldrick GM. *Angew Chem Int Ed Engl*. 1988;27:1186–1187.
14. Trost BM, Greenspan PD, Yang BV, Saulnier MG. *J Am Chem Soc*. 1990;112:9022–9024.

15. Trost BM, Chan DMT. *J Am Chem Soc*. 1983;105:2315–2325.
16. Trost BM, Yang B, Miller ML. *J Am Chem Soc*. 1989;111:6482–6484.
17. Mizuno H, Domon K, Masuya K, Tanino K, Kuwajima I. *J Org Chem*. 1999;64:2648–2656.
18. Porco used a similar synthetic strategy to prepare the related natural product rocaglamide, see: (a) Gerard B, Jones II G, Porco Jr JA. *J Am Chem Soc*. 2004;126:13620–13621;
(b) Gerard B, Sangji S, O'Leary DJ, Porco Jr JA. *J Am Chem Soc*. 2006;128:7754–7755.
19. Gerard B, Cencic R, Pelletier J, Porco Jr JA. *Angew Chem Int Ed*. 2007;46:7831–7834.
20. Baker W. *J Chem Soc*. 1933:1381–1389.
21. El Sous M, Khoo ML, Holloway G, Owen D, Scammells PJ, Rizzacasa MA. *Angew Chem Int Ed*. 2007;46:7835–7838.
22. Lajkiewicz NJ, Roche SP, Gerard B, Porco Jr JA. *J Am Chem Soc*. 2012;134:13108–13113.
23. Nakata M, Akazawa S, Kitamura S, Tatsuta K. *Tetrahedron Lett*. 1991;32:5363–5366.
24. Kitahara T, Suzuki N, Koseki K, Mori K. *Biosci Biotech Biochem*. 1993;11:1906–1909.
25. (a) Blattner R, Furneaux RH, Kemmit T, Tyler PC, Ferrier RJ, Tidén A-K. *J Chem Soc Perkin Trans*. 1994;1:3411–3421;
(b) Ferrier RJ, Ferneaux RH, Prasit P, et al. *J Chem Soc Perkin Trans*. 1983;1:1621–1628.
26. Herranz E, Biller SA, Sharpless KB. *J Am Chem Soc*. 1978;100:3596–3598.
27. Kobayashi Y, Miyazaki H, Shiozaki M. *J Org Chem*. 1994;59:813–822.
28. Funk RL, Bolton GL, Daggett JU, Hansen MM, Horcher LHM. *Tetrahedron*. 1985;41:3479–3495.
29. Gerlach H, Huong TT, Müller W. *J Chem Soc Chem Commun*. 1972:1215–1216.
30. Fétizon M, Golfier M, Louis J-M. *J Chem Soc D Chem Commun*. 1969:1102.
31. Matsumoto N, Tsujimoto T, Nakazaki A, Isobe M, Nishikawa T. *RSC Adv*. 2012;2:9448–9462.
32. Ito T, Tomiyoshi N, Nakamura K, et al. *Tetrahedron Lett*. 1982;23:1721–1724.
33. Yoshioka H, Takasaki K, Kobayashi M, Matsumoto T. *Tetrahedron Lett*. 1979;20:3489–3492.
34. Danishefsky S, Zamboni R, Kahn M, Etheredge SJ. *J Am Chem Soc*. 1980;102:2097–2098.
35. (a) Tatsuta K, Akimoto K, Kinoshita M. *J Antibiot*. 1980;33:100–102;
(b) Tatsuta K, Akimoto K, Kinoshita M. *Tetrahedron*. 1981;37:4365–4369.
36. Schuda PF, Heimann MR. *Tetrahedron*. 1984;40:2365–2380.
37. Mehta G, Murthy AN, Reddy DS, Reddy AV. *J Am Chem Soc*. 1986;108:3443–3452.
38. Iseki K, Yamazaki M, Shibasaki M, Ikegami S. *Tetrahedron*. 1981;37:4411–4418.
39. For the first generation synthesis see Scheme 100, reference Error! Bookmark not defined.
40. Meng Z, Danishefsky SJ. *Angew Chem Int Ed*. 2005;44:1511–1513.
41. (a) Denney DB, Sherman N. *J Org Chem*. 1965;30:3760–3761;
(b) Danishefsky SJ, Tsuzuki K. *J Am Chem Soc*. 1980;102:6891–6893.
42. Grieco PA, Gilman S, Nishizawa M. *J Org Chem*. 1976;41:1485–1486.
43. Birman VB, Danishefsky SJ. *J Am Chem Soc*. 2002;124:2080–2081.
44. Starr JT, Koch G, Carreira EM. *J Am Chem Soc*. 2000;122:8793–8794.
45. Bolm C, Gerlach A, Dinter CL. *Synlett*. 1999:195–196.
46. Abiko A, Roberts JC, Takemasa T, Masamune S. *Tetrahedron Lett*. 1986;27:4537–4540.
47. (a) Grootaert WM, De Clercq PJ. *Tetrahedron Lett*. 1982;23:3291–3294;
(b) Grootaert WM, De Clercq PJ. *Tetrahedron Lett*. 1986;27:1731–1734.
48. Bal BS, Childers WE, Pinnick HW. *Tetrahedron*. 1981;37:2091–2096.
49. Vosburg DA, Vanderwal CD, Sorensen EJ. *J Am Chem Soc*. 2002;124:4552–4553.
50. Evans DA, Starr JT. *J Am Chem Soc*. 2003;125:13531–13540.
51. Kiyooka S –i, Kuroda H, Shimasaki Y. *Tetrahedron Lett*. 1986;27:3009–3012.
52. Tanaka N, Suzuki T, Matsumura T, Hosoya Y, Nakada M. *Angew Chem Int Ed*. 2009;48:2580–2583.
53. Peese KM, Gin DY. *Chem Eur J*. 2008;14:1654–1665.
54. Nicolaou KC, Sarlah D, Wu TR, Zhan W. *Angew Chem Int Ed*. 2009;48:6870–6874.
55. Marigo M, Franzén J, Poulsen TB, Zhuang W, Jørgensen KA. *J Am Chem Soc*. 2005;127:6964–6965.
56. Uchiro H, Kato R, Arai Y, Hasegawa M, Kobayakawa Y. *Org Lett*. 2011;13:6268–6271.
57. Gao Y, Hanson RM, Klunder JM, Ko SY, Masamune H, Sharpless KB. *J Am Chem Soc*. 1987;109:5765–5780.
58. (a) Ohira S. *Synth Commun*. 1989;19:561–564;
(b) Müller S, Liepold B, Roth GJ, Bestmann HJ. *Synlett*. 1996:521–522.
59. Halvorsen GT, Roush WR. *Tetrahedron Lett*. 2011;52:2072–2075.
60. Ward DE, Souweha MS. *Org Lett*. 2005;7:3533–3536.
61. Reber KP, Tilley SD, Carson CA, Sorensen EJ. *J Org Chem*. 2013;78:9584–9607.
62. Kluge AF. *Tetrahedron Lett*. 1978;39:3629–3632.
63. Zhang W, Luo S, Fang F, et al. *J Am Chem Soc*. 2005;127:18–19.
64. Toyota M, Odashima T, Wada T, Ihara M. *J Am Chem Soc*. 2000;122:9036–9037.
65. Stellfeld T, Bhatt U, Kalesse M. *Org Lett*. 2004;6:3889–3892.
66. (a) Wender PA, Howbert JJ. *Tetrahedron Lett*. 1982;23:3983–3986;
(b) Wender PA, Howbert JJ. *Tetrahedron Lett*. 1983;24:5325–5328.
67. For a review of biomimetic electrocyclizations in synthesis, see: Beaudry CM, Malerich JP, Trauner D *Chem Rev*. 2005;105:4757–4778.
68. (a) Woodward RB, Hoffmann R. *Angew Chem Int Ed*. 1969;8:781–853;
(b) Hoffmann R, Woodward RB. *Acc Chem Res*. 1968;1:17–22.
69. (a) Nazarov IN, Zaretskaya II. *Zh. Obshch. Khim*. 1960;30:746–754;
(b) Habermas KL, Denmark SE, Jones TK. *Org React*. 1994;45:1–158.
70. (a) Denmark SE, Jones TK. *J Am Chem Soc*. 1982;104:2642–2645;
(b) He W, Sun X, Frontier AJ. *J Am Chem Soc*. 2003;125:14278–14279;
(c) Liang G, Gradl SN, Trauner D. *Org Lett*. 2003;5:4931–4934;
(d) Bee C, Leclerc E, Tius MA. *Org Lett*. 2003;5:4927–4930;
(e) Aggarwal VK, Beffield AJ. *Org Lett*. 2003;5:5075–5078;
(f) Occhiato EG, Prandi C, Ferrali A, Guarna A, Venturello P. *J Org Chem*. 2003;68:9728–9741.
71. (a) He W, Huang J, Sun X, Frontier AJ. *J Am Chem Soc*. 2007;129:498–499;
(b) He W, Huang J, Sun X, Frontier AJ. *J Am Chem Soc*. 2008;130:300–308.
72. (a) Malona JA, Cariou K, Frontier AJ. *J Am Chem Soc*. 2009;131:7560–7561;
(b) Malona JA, Cariou K, Spencer WT, Frontier AJ. *J Org Chem*. 2012;77:1891–1908.
73. Magnus P, Freund WA, Moorhead EJ, Rainey T. *J Am Chem Soc*. 2012;134:6140–6142.
74. Blanchette MA, Choy W, Davis JT, et al. *Tetrahedron Lett*. 1984;25:2183–2186.
75. Zhou Z, Tius MA. *Angew Chem Int Ed*. 2015;54:6037–6040.
76. Bresser T, Knochel P. *Angew Chem Int Ed*. 2011;50:1914–1917.
77. Li H, Fu B, Wang MA, et al. *Eur J Org Chem*. 2008:1753–1758.
78. Ling R, Mariano PS. *J Org Chem*. 1998;63:6072–6076.
79. Trost BM, Scanlan TS. *Tetrahedron Lett*. 1986;27:4141–4144.
80. Wipf P, Miller CP. *J Org Chem*. 1993;58:1575–1578.
81. Note that the Pd-catalyzed [3+2]-cycloaddition appears in Section 2.2.
82. Khand IU, Knox GR, Pauson PL, Watts WE, Foreman MI. *J Chem Soc Perkin Trans*. 1973;1:977–981.
83. For reviews, see: (a) Schore NE. *Org React*. 1991;40:1–90;
(b) Brummond KM, Kent JL. *Tetrahedron*. 2000;56:3263–3283.
84. For reviews, see: (a) Grubbs RH, Miller SJ, Ru GC. *Acc Chem Res*. 1995;28:446–452;
(b) Yet L. *Org React*. 2016;89:1–1304.
85. Su S, Rodriguez RA, Baran PS. *J Am Chem Soc*. 2011;133:13922–13925.
86. Chen J, Gao P, Yu F, Yang Y, Zhu S, Zhai H. *Angew Chem Int Ed*. 2012;51:5897–5899.
87. Chuang KV, Xu C, Reisman SE. *Science*. 2016;353:912–915.
88. (a) Exon C, Magnus P. *J Am Chem Soc*. 1983;105:2477–2478;
(b) Magnus P, Exon C, Albaugh–Robertson P. *Tetrahedron*. 1985;41:5861–5869.
89. Oppolzer W, Ando A. *Chimia*. 1992;46:122–125.
90. (a) Barton DHR, Dowlatshahi HA, Motherwell WB, Villemin DA. *J Chem Soc Chem Commun*. 1980:732–733;
(b) Barton DHR, Crich D, Motherwell WB. *Tetrahedron Lett*. 1983;24:4979–4982;
(c) Barton DHR, Crich D, Motherwell WB. *J Chem Soc Chem Commun*. 1983:939–941.
91. Donohoe TJ, Rosa CP. *Org Lett*. 2007;9:5509–5511.
92. Basha A. *Tetrahedron Lett*. 1988;19:2525–2526.
93. Keck GE, Enholm EJ, Yates JB, Wiley MR. *Tetrahedron*. 1985;41:4079–4094.
94. Toueg J, Prunet J. *Org Lett*. 2008;10:45–48.
95. For related examples, see: (a) Kishi Y, Wang W. *Org Lett*. 1999;7:1129–1132;
(b) Lebsack AD, Overman LE, Valentekovich RJ. *J Am Chem Soc*. 2001;123:4851–4852.

96. 

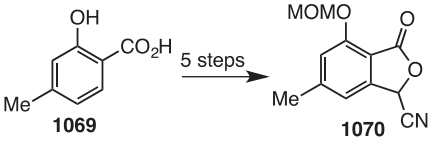
438

Interestingly, advanced intermediate 441 contains two fully functionalized cyclopentanes; however, the target hexacyclinic acid requires only one fully functionalized cyclopentane. The uncolored fully functionalized cyclopentane of 441 was constructed beginning with the cyclopentenone building block starting material shown above, by way of intermediate 438. See Section 11 for similar functionalizations of related enones.

97. Fukuyama T, Liu G. *J Am Chem Soc*. 1996;118:7426–7427.
98. Here we discuss Fukuyama's 1996 report of the synthesis of (±)-gelsemine. An enantioselective synthesis of (+)-gelsemine was published by Fukuyama in which intermediate 449 was prepared as a single enantiomer, see

Yokoshima S, Tokuyama H, Fukuyama T. *Angew Chem Int Ed*. 2000;39:4073–4075.
99. Kondo K, Umemoto T, Yako K, Tunemoto D. *Tetrahedron Lett*. 1978;19:3927–3930.
100. Pfitzner KE, Moffatt JG. *J Am Chem Soc*. 1965;87:5661–5670.
101. Taber DF, Frankowski KJ. *J Org Chem*. 2005;70:6417–6421.
102. Holmquist CR, Roskamp EJ. *J Org Chem*. 1989;54:3258–3260.
103. Trost BM, Chan DMT. *J Am Chem Soc*. 1983;105:2315–2325.
104. The ester may direct the hydride to the more hindered ketone face.
105. (a) Sung MJ, Lee C–W, Cha JK. *Synlett*. 1999:561–562;
(b) For the Kulinkovich reaction, see: Kulinkovich OG, de Meijere A *Chem Rev*. 2000;100:2789–2834.
106. For review of semipinacol rearrangements in synthesis, see: Song Z–L, Fan C–A, Tu Y–Q *Chem Rev*. 2011;111:7523–7556.
107. For a thorough microreview of the Wolff rearrangement, see: Kirmse W *Eur J Org Chem*. 2002:2193–2256.
108. For review of the di-π-methane and oxa-di-π-methane rearragnements, including a mechanistic analysis, see: Hixson SS, Mariano PS, Zimmerman HE *Chem Rev*. 1973;73:531–551.
109. Lombardo L, Mander LN, Turner JV. *J Am Chem Soc*. 1980;102:6626–6628.
110. Takahashi S, Terayama H, Kuzuhara H. *Tetrahedron Lett*. 1991;32:5123–5126.
111. Zhang L, Koreeda M. *Org Lett*. 2002;4:3755–3758.
112. Reetz MT, Kindler A. *J Organomet Chem*. 1995;502:C5–C7.
113. Hu G, Zimmerman M, Ramana CV, Vasella A. *Chem Comm*. 2003:952–953.
114. Hu G, Vasella A. *Helv Chim Acta*. 2004;87:2434–2446.
115. Ma Z, Wang X, Wang X, et al. *Science*. 2014;346:219–224.
116. Early publications in this area by Chen depict (*R*)-Garner's aldehyde and related intermediates that were transformed to diastereomers of 516. Investigations of the stereostructure of massadine, palau'amine and related alkaloids led to correction of the stereochemistry of 515 and 516. We depict the corrected structures based on personal communication with Prof. Chuo Chen.
117. Kinnel RB, Gehrken H–P, Swali R, Skoropowski G, Scheuer PJ. *J Org Chem*. 1998;63:3281–3286.
118. The Scheuer hypothesis has been investigated and experimentally validated by several groups. See: Romo, reference 123 Sivappa R, Hernandez NM, He Y, Lovely C. *J Org Lett*. 2007;9:3861–3864 (and references therin).
119. (a) Ma Z, Lu J, Wang X, Chen C. *Chem Commun*. 2011;47:427–429;
(b) Wang X, Ma Z, Lu J, Tan X, Chen C. *J Am Chem Soc*. 2011;133:15350–15353;
(c) Ma Z, Wang X, Ma Y, Chen C. *Angew Chem Int Ed*. 2016;55:4763–4766.
120. Kodama M, Kurihara T, Sasaki J, Itō S. *Can J Chem*. 1979;57:3343–3345.
121. Coates RM, Shah SK, Mason RW. *J Am Chem Soc*. 1982;104:2198–2208.
122. Clarke C, Fleming I, Fortunak JMD, et al. *Tetrahedron*. 1988;44:3931–3944.
123. Dilley AS, Romo D. *Org Lett*. 2001;3:1535–1538.
124. A second approach to a palau'amine-type intermediate was later published by Romo using a similar synthetic strategy. See: (a) Dransfield PJ, Wang S, Dilley A, Romo D. *Org Lett*. 2005;7:1679–1682;
(b) Dransfield PJ, Dilley AS, Wang S, Romo D. *Tetrahedron*. 2006;62:5223–5247;
(c) Wang S, Dilley AS, Poullennec KG, Romo D. *Tetrahedron*. 2006;62:7155–7161;
(d) Zancanella MA, Romo D. *Org Lett*. 2008;10:3685–3688.
125. (a) Breder A, Chinigo GM, Waltman AW, Carreira EM. *Angew Chem Int Ed*. 2008;47:8514–8517;
(b) Breder A, Chinigo GM, Waltman AW, Carreira EM. *Chem Eur J*. 2011;17:12405–12416.
126. Schreiber SL, Claus RE, Reagan J. *Tetrahedron Lett*. 1982;23:3867–3870.
127. Chinigo GM, Breder A, Carreira EM. *Org Lett*. 2011;13:78–81.
128. (a) Demuth M, Ritterskamp P, Weigt E, Schaffner K. *J Am Chem Soc*. 1986;108:4149–4154;
(b) Demuth M, Ritterskamp P, Schaffner K. *Helv Chim Acta*. 1984;67:2023–2027.
129. Trost BM, Curran DP. *J Am Chem Soc*. 1981;103:7380–7381.
130. Singh V, Alam SQ. *Chem Commun*. 1999:2519–2520.
131. Adler E, Holmberg K. *Acta Chem Scand B*. 1974;28:465–472.
132. Van Hijfte L, Little RD, Peterson JL, Moeller KD. *J Org Chem*. 1987;52:4647–4661.
133. (a) Bon DJ–YD, Banwell MG, Ward JS, Willis AC. *Tetrahedron*. 2013;69:1363–1368;
(b) Reekie TA, Austin KAB, Banwell MG, Willis AC. *Aust J Chem*. 2008;61:94–106;
(c) Bon DJ–YD, Banwell MG, Willis AC. *Tetrahedron*. 2010;66:7807–7814.
134. Corey EJ, Nozoe S. *J Am Chem Soc*. 1965;87:5733–5735.
135. Shi L, Meyer K, Greaney MF. *Angew Chem Int Ed*. 2010;49:9250–9253.
136. Rajan Babu TV, Nugent WA. *J Am Chem Soc*. 1994;116:986–997.
137. Bultman M,S, Ma J, Gin DY. *Angew Chem Int Ed*. 2008;47:6821–6824.
138. Story PR. *J Org Chem*. 1961;26:287–290.
139. (a) Piers E, Geraghty MB, Kido F, Soucy M. *Synth Commun*. 1973;3:39–43;
(b) Piers E, Geraghty MB, Soucy M. *Synth Commun*. 1973;3:401–405.
140. Hagiwara H, Miyashita M, Uda H, Yoshikoshi A. *Bull Chem Soc Jpn*. 1975;48:3723–3726.
141. Welch SC, Walters RL. *J Org Chem*. 1974;39:2665–2673.
142. Welch SC, Chayabunjonglerd S. *J Am Chem Soc*. 1979;101:6768–6769.
143. Colvin EW, Egan MJ, Kerr FW. *J Chem Soc Chem Commun*. 1990:1200–1202.
144. Inoue M, Sato T, Hirama M. *Angew Chem Int Ed*. 2006;45:4843–4848.
145. Hanessian S, Vakiti RR, Dorich S, Banerjee S, Deschnês-Simard B. *J Org Chem*. 2012;77:9458–9472.
146. Malinowski JT, Sharpe RJ, Johnson JS. *Science*. 2013;340:180–182.
147. Corey EJ, Smith JG. *J Am Chem Soc*. 1979;101:1038–1039.
148. (a) Wiesner K, Jay EWK, Tsai TYR, et al. *Can J Chem*. 1972;50:1925–1943;
(b) Wiesner K. *Pure Appl Chem*. 1979;51:689–703.
149. For related work on this class of alkaloids by Wiesner, see: (a) Wiesner K, Bickelhaupt F, Babin DR, Götz M. *Tetrahedron Lett*. 1959;3:11–14;
(b) Wiesner K. *Pure Appl Chem*. 1975;41:93–112;
(c) Wiesner K, Tsai TYR, Huber K, Bolton SE. *J Am Chem Soc*. 1974;96:4990–4992.
150. (a) Nagata W, Sugasawa T, Narisada M, Wakabayashi T, Hayase Y. *J Am Chem Soc*. 1963;85:2342–2343;
(b) Nagata W, Wakabayashi T, Narisada M, Hayase Y, Kamata S. *J Am Chem Soc*. 1971;93:5740–5758.
151. (a) Corey EJ, Danheiser RL, Chandrasekaran S, Siret P, Keck GE, Gras J–L. *J Am Chem Soc*. 1978;100:8031–8034;
(b) Corey EJ, Danheiser RL, Chandrasekaran S, et al. *J Am Chem Soc*. 1978;100:8034–8036.
152. Bélanger A, Berney DJF, Borschberg H–J, et al. *Can J Chem*. 1979;57:3348–3354.
153. Control experiments indicated that purified 792 underwent quantitative cyclization to 796; however, purified 794 did not undergo productive aldol addition under these conditions. Furthermore, it was not reported whether purified 793 underwent a retro-aldol–aldol addition with epimerization to give 796.
154. No rationale was given to explain the origin of diastereoselectivity in the epoxidation; however, it may arise from steric considerations or the Henbest effect.
155. (a) Hagiwara K, Himuro M, Hirama M, Inoue M. *Tetrahedron Lett*. 2009;50:1035–1037;
(b) Urabe D, Nagamoto M, Hagiwara K, Masuda K, Inoue M. *Chem Sci*. 2013;4:1615–1619;
(c) Nagamoto M, Koshimizu M, Masuda K, Tabuchi T, Urabe D, Inoue M. *J Am Chem Soc*. 2014;136:5916–5919.
156. For examples of two-directional strategies used in total synthesis, see: (a) Poss CS, Schreiber SL. *Acc Chem Res*. 1994;27:9–17.
157. Note that the two alkene carbons are symmetry related.
158. Liu B, Zhou B. *Tetrahedron Lett*. 2002;43:4187–4189.
159. Bharucha KR, Buckley GC, Cross CK, Rubin LJ, Ziegler P. *Can J Chem*. 1956;34:982–990.
160. (a) Yamaguchi J, Seiple IB, Young IS, O'Malley DP, Maue M, Baran PS. *Angew Chem Int Ed*. 2008;47:3578–3580;
(b) O'Malley DP, Yamaguchi J, Young IS, Seiple IB, Baran PS. *Angew Chem Int Ed*. 2008;47:3581–3583;
(c) Su S, Seiple IB, Young IS, Baran PS. *J Am Chem Soc*. 2008;130:16490–16491.
161. Lee reported a somewhat similar oxidative cleavage/1,6-dicarbonyl aldol cyclization in a synthesis of the carbocyclic core of massadine. See: Sun C, Lee H, Lee D *Org Lett*. 2015;17:5348–5351.
162. Xu X–S, Li Z–W, Zhang Y–J, Peng X–S, Wong HNC. *Chem Commun*. 2012;48:8517–8519.
163. Organometallic addition of methyl to the ketone derived from 865 led to the undesired tertiary alcohol diastereomer.
164. Martinez LP, Umemiya S, Wengryniuk SE, Baran PS. *J Am Chem Soc*. 2016;138:7536–7539.
165. Dobler MR, Bruce I, Cederbaum F, et al. *Tetrahedron Lett*. 2001;42:8281–8284.
166. Stiles M. *J Am Chem Soc*. 1959;81:2598–2599.
167. Chen X, Duan S, Tao C, Zhai H, Qiu FG. *Nat Commun*. 2015;6:7204.
168. Ahrendt KA, Borths CJ, MacMillan DWC. *J Am Chem Soc*. 2000;122:4243–4244.
169. Nakano H, Osone K, Takeshita M, et al. *Chem Commun*. 2010;46:4827–4829.
170. Paquette LA, Geng F. *J Am Chem Soc*. 2002;124:9199–9203.
171. (a) Ogawa S, Yuming Y. *J Chem Soc Chem Commun*. 1991:890–891;
(b) Ogawa S, Kimura H, Uchida C, Ohashi T. *J Chem Soc Perkin Trans*. 1995;1:1695–1705;
(c) Ogawa S, Yuming Y. *Bioorg Med Chem*. 1995;3:939–943.
172. Suami T, Tadano K, Nishiyama S, Lichtenthaler FW. *J Org Chem*. 1973;38:3691–3696.
173. Ahluwalia R, Angyal SJ, Luttrell BM. *Aust J Chem*. 1970;23:1819–1829.
174. (a) Ogawa S, Uchida C, Yuming Y. *J Chem Soc Chem Commun*. 1992:886–888;
(b) Uchida C, Yamagishi T, Ogawa S. *J Chem Soc Perkin Trans*. 1994;1:589–602;
(c) Ogawa S, Uchida C. *J Chem Soc Perkin Trans*. 1992;1:1939–1942.
175. (a) Sheikh Z, Steel R, Tasker AS, Johnson AP. *J Chem Soc Chem Commun*. 1994:763–764;
(b) Dutton JK, Steel RW, Tasker AS, Popsavin V, Johnson AP. *J Chem Soc Chem Commun*. 1994:765–766.
176. Newcombe NJ, Ya F, Vijn RJ, Hiemstra H, Speckamp WN. *J Chem Soc Chem Commun*. 1994:767–768.
177. Hiemstra H, Vijn RJ, Speckamp WN. *J Org Chem*. 1988;53:3882–3884.

178. (a) Madin A, O'Donnell CJ, Oh T, Old DW, Overman LE, Sharp MJ. *Angew Chem Int Ed*. 1999;38:2934–2936;
(b) Earley WG, Jacobsen EJ, Meier GP, Oh T, Overman LE. *Tetrahedron Lett*. 1988;29:3781–3784.
179. Nishiyama Y, Han-ya Y, Yokoshima S, Fukuyama T. *J Am Chem Soc*. 2014;136:6598–6601.
180. Cherney EC, Lopchuk JM, Green JC, Baran PS. *J Am Chem Soc*. 2014;136:12592–12595.
181. Francisco CG, Herrera AJ, Suárez EJ. *J Org Chem*. 2003;68:1012–1017.
182. Li Q, Hurley P, Ding H, Roberts AG, Akella R, Harran PG. *J Org Chem*. 2009;74:5909–5919.
183. Büchi G, Chu P–S. *J Am Chem Soc*. 1979;101:6767–6768.
184. The final transformation delivers a 7:5 ratio of the desired (±)-coriolin and its spiroepoxide epimer. A four-step stereoselective route was designed for the final transformation to (±)-coriolin, see: Danishefsky S, Zamboni R, Kahn M, Etheredge SJ *J Am Chem Soc*. 1981;103:3460–3467.
185. Ishibashi M, Tsuyuki T, Takahashi T. *Tetrahedron Lett*. 1983;24:4843–4846.
186. Collins JL, Grieco PA, Gross RS. *J Org Chem*. 1990;55:5816–5818.
187. Grieco PA, Garner P, He Z. *Tetrahedron Lett*. 1983;24:1897–1900.
188. (a) Crimmins MT, Pace JM, Nantermet PG, et al. *J Am Chem Soc*. 1999;121:10249–10250;
(b) Crimmins MT, Pace JM, Nantermet PG, et al. *J Am Chem Soc*. 2000;122:8453–8463.
189. Takasu K, Mizutani S, Noguchi M, Makita K, Ihara M. *J Org Chem*. 2000;65:4112–4119.
190. Nicolaou KC, Lim YH, Papageorgiou CD, Piper JL. *Angew Chem Int Ed*. 2005;44:7917–7921.
191. Nitrile 1070 was obtained from benzoic acid derivative 1069 over five steps.



1069 1070

192. Snider BB, Gao X. *J Org Chem*. 2005;70:6863–6869.
193. Zhou X, Xiao T, Iwama Y, Qin Y. *Angew Chem Int Ed*. 2012;51:4909–4912.
194. Grecian S, Aubé J. *Org Lett*. 2007;9:3153–3156.
195. Hamlin AM, Cortez F, de J, Lapointe D, Sarpong R. *Angew Chem Int Ed*. 2013;52:4854–4857.
196. Hori T, Nakanishi K. *J Chem Soc D Chem Commun*. 1969;10:528–529.
197. Nagaoka H, Shimano M, Yamada Y. *Tetrahedron Lett*. 1989;30:971–974.
198. Hook JM, Mander LN, Urech R. *J Org Chem*. 1984;49:3250–3260;
(a) For related studies, see: Hook JM, Mander LN, Urech R *J. Am. Chem. Soc*. 1980;102:6628–6629.
199. Heissler D, Riehl J–J. *Tetrahedron Lett*. 1980;21:4707–4710.
200. Kido F, Sakuma R, Uda H, Yoshikoshi A. *Tetrahedron Lett*. 1969;10:3169–3172.
201. Baldwin SW, Tomesch JC. *Tetrahedron Lett*. 1975;16:1055–1058.
202. (a) Muratake H, Natsume M. *Tetrahedron Lett*. 2002;43:2913–2917;
(b) Muratake H, Natsume M. *Angew Chem Int Ed*. 2004;43:4646–4649.
203. The authors describe this transformation as an acetal-ene reaction; however, we describe it as a Prins cyclization.
204. Chiara JL, Cabri W, Hanessian S. *Tetrahedron Lett*. 1991;32:1125–1128.
205. For an excellent review of the pinacol coupling, see: Chatterjee A, Joshi NN *Tetrahedron*. 2006;62:12137–12158.
206. Davey AE, Schaeffer MJ, Taylor RJK. *J Chem Soc Chem Commun*. 1991:1137–1139.
207. Kraus GA, Sy JO. *J Org Chem*. 1989;54:77–83.
208. Adinolfi M, Barone G, Iadonisi A, Mangoni L, Manna R. *Tetrahedron*. 1997;53:11767–11780.
209. Boiron A, Zillig P, Faber D, Giese B. *J Org Chem*. 1998;63:5877–5882.
210. This *trans* relationship may arise from the preferential pseudo-equatorial positioning of the oxime double bond and the C2 substituent.
211. Storch de Gracia I, Bobo S, Martin–Ortega MD, Chiara JL. *Org Lett*. 1999;1:1705–1708.
212. Alternatively, Giese's stereochemical model applied to substrate 1215 may give a reactive conformation that predicts the observed stereochemistry.
213. Clarke PA, Cridland AP, Rolla GA, et al. *J Org Chem*. 2009;74:7812–7821.
214. Simpkins NS, Stokes S, Whittle AJ. *J Chem Soc Perkin Trans*. 1992;1:2471–2477.
215. (a) Bartlett PA, McLaren KL, Ting PC. *J Am Chem Soc*. 1988;110:1633–1634;
(b) Rajanbabu TV. *J Am Chem Soc*. 1987;109:609–611.
216. (a) Weinges K, Braun R, Huber-Patz U, Irngartinger H. *Liebigs Ann Chem*. 1993:1133–1140;
(b) Weinges K, Reichert H. *Synlett*. 1991;11:785–786.
217. Fevig TL, Elliot RL, Curran DP. *J Am Chem Soc*. 1988;110:5064–5067.
218. Atarashi S, Choi J–K, Ha D–C, et al. *J Am Chem Soc*. 1997;119:6226–6241.
219. James P, Felpin F–X, Landais Y, Schenk K. *J Org Chem*. 2005;70:7985–7995.
220. Fleming I, Hill JHM, Parker D, Waterson D. *J Chem Soc Chem Commun*. 1985;6:318–320.
221. (a) Nicolaou NC, Jennings MP, Dagneau P. *Chem Commun*. 2002;21:2480–2481;
(b) Nicolaou KC, Ortiz A, Zhang H, et al. *J Am Chem Soc*. 2010;132:7138–7152.
222. A related enantioselective approach to the synthesis of the reported structure of vannusals A and B was also published. See: Nicolaou KC, Tang W, Dagneau P, Faraoni R *Angew Chem Int Ed*. 2005;44:3874–3879.
223. Snider BB. *Chem Rev*. 1996;96:339–364.
224. Cha JY, Yeoman JTS, Reisman SE. *J Am Chem Soc*. 2011;133:14964–14967.
225. Gansäuer A, Pierobon M, Bluhm H. *Angew Chem Int Ed*. 1998;37:101–103.
226. Tao DJ, Slutskyy Y, Overman LE. *J Am Chem Soc*. 2016;138:2186–2189.
227. Aldehyde 1252 was prepared in three steps from dimethyl 2,3-O-isopropylidene L-tartrate. See: Reference 226.
228. Ireland RE, Wrigley TI, Young WG. *J Am Chem Soc*. 1958;80:4604–4606.
229. Borcherding DR, Scholtz SA, Borchardt RT. *J Org Chem*. 1987;52:5457–5461.
230. Crandall JK, Chang L–H. *J Org Chem*. 1967;32:532–536.
231. Henry PM, Davies M, Ferguson G, Phillips S, Restivo R. *J Chem Soc Chem Commun*. 1974:112–113.
232. Weiss U, Edwards JM. *Tetrahedron Lett*. 1968;9:4855–4887.
233. Trost BM, Van Vranken DL. *J Am Chem Soc*. 1990;112:1261–1263.
234. Trost BM, Van Vranken DL. *J Am Chem Soc*. 1993;115:444–458.
235. Griffith DA, Danishefsky SJ. *J Am Chem Soc*. 1991;113:5863–5864.
236. Deardorf DR, Matthews AJ, McMeekin DS, Craney CL. *Tetrahedron Lett*. 1986;27:1255–1256.
237. Goering BK, Ganem B. *Tetrahedron Lett*. 1994;35:6997–7000.
238. (a) Bannard RAB, Casselman AA, Hawkins LR. *Can J Chem*. 1965;43:2398–2407;
(b) Langstaff EJ, Hamanaka E, Neville GA, Moir RY. *Can J Chem*. 1967;45:1906–1920;
(c) Bellucci G, Berti G, Ingrosso G, Mastrorilli E. *Tetrahedron Lett*. 1973;14:3911–3914.
239. Shrader WD, Imperiali B. *Tetrahedron Lett*. 1996;37:599–602.
240. Note that the oxidative demercurization process is likely not stereospecific. See: Hill CL, Whitesides GM *J Am Chem Soc*. 1974;96:870–876.
241. Maezaki N, Sakamoto A, Tanaka T, Iwata C. *Tetrahedron Asymmetry*. 1998;9:179–182.
242. King BS, Ganem B. *J Am Chem Soc*. 1991;113:5089–5090.
243. Trost BM, Kuo G–H, Benneche T. *J Am Chem Soc*. 1988;110:621–622.
244. Ledford BE, Carreira EM. *J Am Chem Soc*. 1995;117:11811–11812.
245. Li J, Lang F, Ganem B. *J Org Chem*. 1998;63:3403–3410.
246. Ebner C, Carreira EM. *Angew Chem Int Ed*. 2015;54:11227–11230.
247. Denmark SE, Edwards JP. *J Org Chem*. 1991;56:6974–6981.
248. Danheiser RL, Miller RF, Brisbois RG, Park SZ. *J Org Chem*. 1990;55:1959–1964.
249. Schoop A, Greiving H, Göhrt A. *Tetrahedron Lett*. 2000;41:1913–1916.
250. Hatanaka M, Himeda Y, Imashiro R, Tanaka Y, Ueda I. *J Org Chem*. 1994;59:111–119.
251. Knapp S, Dhar TGM. *J Org Chem*. 1991;56:4096–4097.
252. Li C, Fuchs PL. *Tetrahedron Lett*. 1994;35:5121–5124.
253. (a) Mehta G, Srinivas K. *Tetrahedron Lett*. 2001;42:2855–2857;
(b) Mehta G, Srinivas K. *Synlett*. 1999;5:555–556.
254. Fietz-Razavian S, Schulz S, Dix I, Jones PG. *Chem Commun*. 2001:2154–2155.
255. Concomitantly with the synthetic studies towards (−)-kelsoene, Schulz also published degradation studies that determined the absolute configuration of the natural product.
256. Ng FW, Lin H, Danishefsky SD. *J Am Chem Soc*. 2002;124:9812–9824.
257. Shiori T, Ninomiya K, Yamada S. *J Am Chem Soc*. 1972;94:6203–6205.
258. Mehta G, Sreenivas K. *Tetrahedron Lett*. 2002;43:3319–3321.
259. Thoma I, Carell T. *Eur J Org Chem*. 2013:4483–4485.
260. Epoxyqueuosine has not been isolated from natural sources; however, it is the anticipated biosynthetic precursor to the known natural product queuosine.
261. Paquette LA, Han Y–K. *J Am Chem Soc*. 1981;103:1831–1835;
(a) Han Y–K, Paquette LA. *J. Org. Chem*. 1979;44:3731–3733.
262. Imanishi T, Yamashita M, Hirokawa Y, Tanaka T, Miyashita K, Iwata C. *Chem Pharm Bull*. 1993;41:1695–1697.
263. O'Neil SV, Quickley CA, Snider BB. *J Org Chem*. 1997;62:1970–1975.
264. (a) Brooks DW, Grothaus PG, Palmer JT. *Tetrahedron Lett*. 1982;23:4187–4190;
(b) Brooks DW, Grothaus PG, Mazdiyasni H. *J Am Chem Soc*. 1983;105:4472–4473.
265. Brooks DW, Grothaus PG, Irwin WL. *J Org Chem*. 1982;47:2820–2821.
266. Marquet A, Duolaitsky M, Kogan HB, Mamlok L, Ouanees C, Jacques J. *Bull Soc Chim Fr*. 1962:90.
267. Trost BM, Curran DP. *J Am Chem Soc*. 1980;102:5699–5700.
268. Koreeda M, Mislankar SG. *J Am Chem Soc*. 1983;105:7203–7205.
269. Salmond WG, Barta MA, Havens JL. *J Org Chem*. 1978;43:2057–2059.
270. Piers E, Orellana A. *Synthesis*. 2001;14:2138–2142.
271. Suggs JW, Cox SD, Crabtree RH, Quirk JM. *Tetrahedron Lett*. 1981;22:303–306.
272. Lombardo L. *Tetrahedron Lett*. 1982;23:4293–4296.
273. Mehta G, Singh SR. *Tetrahedron Lett*. 2005;46:2079–2082.
274. Grubbs RH, Chang H. *Tetrahedron*. 1998;54:4413–4450.
275. Nazef N, Davies RDM, Greaney MF. *Org Lett*. 2012;14:3720–3723.
276. (a) Namba K, Kaihara Y, Yamamoto H, et al. *Chem Eur J*. 2009;15:6560–6563;
(b) Namba K, Takeuchi K, Kaihara Y, et al. *Nat Commun*. 2015;6:8731.
277. This synthesis was disclosed in two distinct manuscripts each depicting racemic intermediates in opposite enantiomeric series. Herein, we depict all the racemic intermediates from both papers in the same enantiomeric series
278. Bruce I, Cooke NG, Diorazio LJ, Hall RG, Irving E. *Tetrahedron Lett*. 1999;40:4279–4282.
279. Nemoto T, Muramoto R, Ruengsatra T, Hamada Y. *Tetrahedron*. 2016;72:1991–1997.

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