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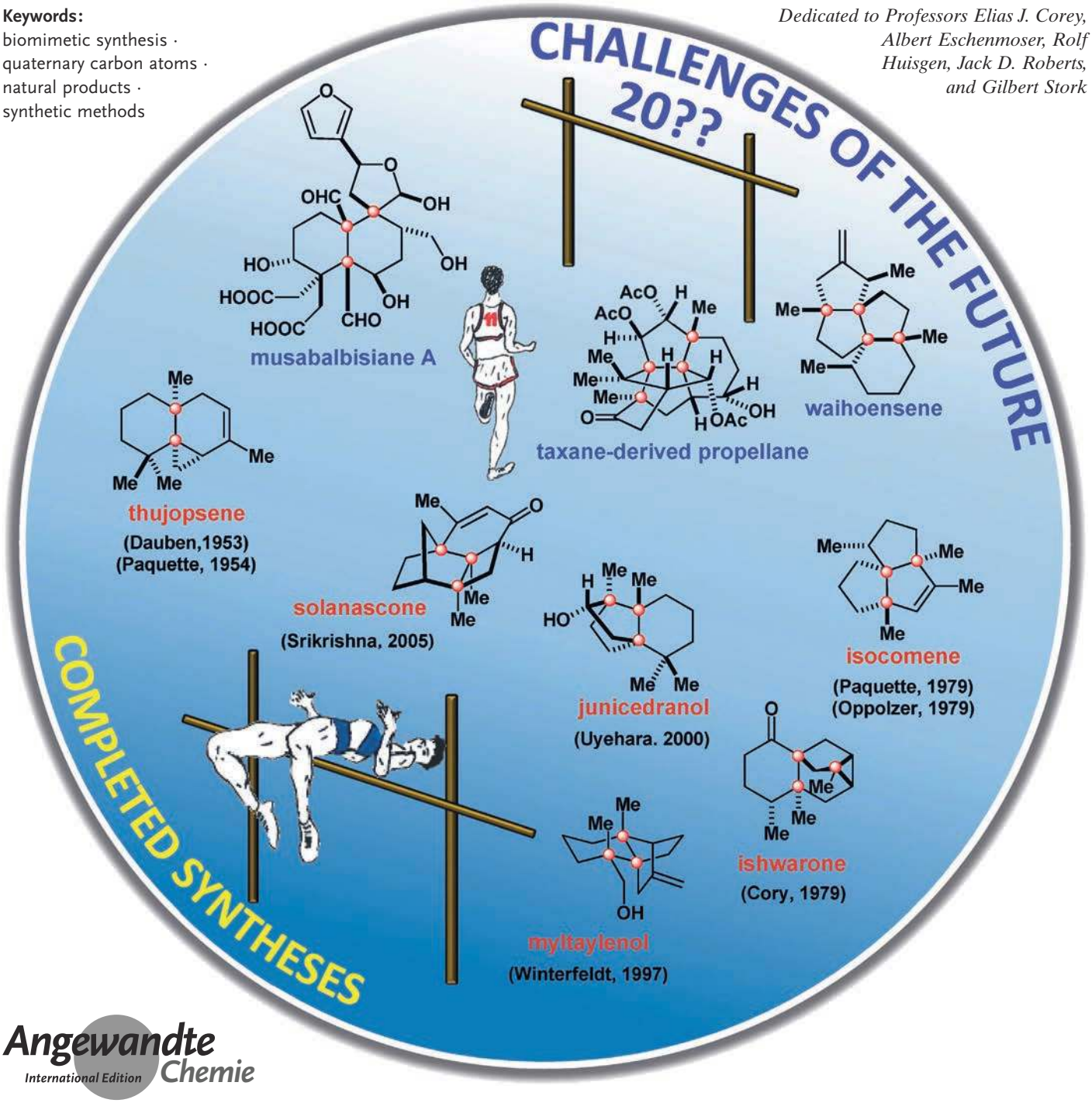
Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms

Martin Büschleb, Stéphane Dorich, Stephen Hanessian, Daniel Tao, Kyle B. Schenthal, and Larry E. Overman**

Keywords:
biomimetic synthesis · quaternary carbon atoms · natural products · synthetic methods

Dedicated to Professors Elias J. Corey, Albert Eschenmoser, Rolf Huisgen, Jack D. Roberts, and Gilbert Stork



Strategies for the total synthesis of complex natural products that contain two or more contiguous stereogenic quaternary carbon atoms in their intricate structures are reviewed with 12 representative examples. Emphasis has been put on methods to create quaternary carbon stereocenters, including syntheses of the same natural product by different groups, thereby showcasing the diversity of thought and individual creativity. A compendium of selected natural products containing two or more contiguous stereogenic quaternary carbon atoms and key reactions in their total or partial syntheses is provided in the Supporting Information.

From the Contents

1. Introduction

Long before the accidental synthesis of urea by Friedrich Wöhler, which is historically considered to be the first recorded synthesis of a "natural product",[1,2] humankind had already recognized the beneficial effects of plant extracts as remedies for its physical ills.[3] Anecdotal accounts of miraculous cures in the form of potions and the likes within some cultures, now known as nontraditional or alternative medicines, continue to perpetuate our fascination with natural products.[4] For millennia, nature has been the provider, the healer, and the enticer.[4,5] The variety of known chemical structures today is indeed overwhelming. Of these, only a minuscule number has been studied for their biological properties,[6] while only a mere fraction has been synthesized or chemically manipulated.[7] The choice of target molecules to synthesize has been justified, among other reasons, for their promise as potential therapeutic agents, a statement that is often found in the introductory paragraphs of published manuscripts. The total synthesis of many highly complex natural products had already been achieved during the second half of the twentieth century, thanks to continually evolving methods of stereoselective reactions,[8] separation techniques, and spectroscopic analyses. The incentive to undertake the total synthesis of architecturally challenging natural products continues to prevail to this day, as our understanding of the biological effects at the molecular level becomes more and more evident thanks to ground-breaking advances in genetics and molecular biology. More than ever, synthetic organic chemists are engaging in fruitful collaborations with scientists in other disciplines as a result of newly discovered activities of known natural products. Thus, biology-inspired and chemistry-driven projects also relying on structure-based organic synthesis is becoming widely acknowledged.[6] In this regard, the "what" and "why" of total synthesis[4] may no longer need to be justified, especially when the target molecules are expected to provide important answers to biologically relevant questions. Having decided on a given target molecule to synthesize, we are confronted with the highly subjective task of "how".[4] Past and present accomplishments have demonstrated the ingenuity, creativity, and resolve of synthetic organic chemists to initiate and complete the total synthesis of a plethora of natural products.[4,9] Among these are a small number that encompass quaternary carbon atoms on one or more stereogenic centers, which when embedded within the core structure of an intended target molecule presents a formidable challenge to a synthetic chemist. Creative solutions to such problems have been successfully addressed for natural products that only a few years ago would have been considered as beyond reach.[10]

In this Review, we present a selection of such successful syntheses by focusing on natural products that contain two and three quaternary carbon atoms, of which at least two are contiguous. Nature's ingenuity (and reasons) to create functionally and architecturally complex molecules that may contain up to four contiguous quaternary carbons atoms, none of which are methyl bearing, such as in the neo-clerodane diterpenoid musabalbisiane A,[11] illicits awe and fascination. Whether or not such molecules are biosynthesized for defense

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mechanisms against other natural predators may forever remain a mystery. However, the apparent facility with which nature constructs molecules of such high complexity is at first sight misleading. In fact, in many cases nature uses highly functionalized precursors that are "preorganized" to undergo intra- and intermolecular cyclizations, as in enzyme (and non-enzyme) catalyzed Diels–Alder reactions, to achieve its objectives.[12] These late-stage transformations in biosynthetic pathways take place in a timeframe that greatly contrasts the often much slower reaction times when similar cyclizations are attempted in the laboratory. Nevertheless, elegant "biomimetic" total syntheses under extremely mild reaction conditions have been reported which also rely on preorganization and proximity effects of reacting partners.

A brief introduction to each natural product is followed by a discussion of relevant and key reactions, especially when quaternary carbon atoms are introduced. Syntheses of one and the same natural product by more than one research group are presented to demonstrate different methods and strategies for creating stereogenic quaternary carbon atoms embedded in the structures of highly complex natural products. A particular challenge presents itself when the hindered quaternary stereocenters in a target molecule are adjacent. We have limited our discussion to a total of 12 natural products, which in our opinion combine the criteria of diversity of strategies with individual creativity. A compendium of selected natural products containing two or more contiguous stereogenic quaternary carbon atoms and key reactions in their total or partial syntheses is provided in the Supporting Information.

2. Sordaricin

Sordarin is a diterpene glycoside that was isolated from *Sordaria araneosa* and has been shown to possess antifungal properties with a unique mode of action.[13,14] It was established that sordaricin, the aglycone, is derived from the biosynthetic precursor cycloaraneosene, and it was proposed that the quaternary carbon centers arise from an intramolecular [4+2] cycloaddition.[15] Sordaricin is characterized by a complex and richly functionalized tetracyclic architecture that features an unprecedented presence of three contiguous quaternary centers, one being a bridgehead carbon atom. Key steps in the three total syntheses of sordaricin are highlighted below.[16]

2.1. The Kato Synthesis

In 1993, Kato et al. completed the first total synthesis of optically pure sordaricin as its methyl ester (Scheme 1).[17] The key reactions for the synthesis of the polycyclic core containing three contiguous quaternary centers were a Cope rearrangement and a bio-inspired intramolecular Diels–Alder cycloaddition. It was envisaged that two separate cyclopentane units, diol **1** and (*3S*)-1-iriden-7-al **2** (obtained by chemical resolution of an iridoid menthyl ester[18] originally synthesized from isoprene and methyl 2,4-dioxopentanoate), may be used as chiral building blocks for the synthesis of rings A and B (Scheme 1).

Thus, **3** and **4** (available from **1** and **2**, respectively) were coupled through a Nozaki–Hiyama–Kishi reaction to gener-

Martin Büschleb, born in Leinefelde (Germany), obtained his diploma (2008) and PhD (2012) in organic chemistry from Georg-August University in Göttingen under the supervision of Prof. Christian Ducho, where he studied the synthesis and application of epicapreomycidine in natural product synthesis. He pursued postdoctoral studies with Prof. Stephen Hanessian at Université de Montréal (Canada), working in the field of natural product synthesis. Currently, he is working in process development at Qiagen in Hilden (Germany).

Stephen Hanessian was born in Alexandria (Egypt) in 1935 and graduated from the University of Alexandria in 1956. After a year at the Starch Products Co., he obtained his PhD in 1960 with Prof. Melville Wolfrom (Ohio State University). From 1961 to 1968, he worked at Parke-Davis Research Laboratories in Ann Arbor, Michigan. He became Associate Professor at the Université de Montréal in 1969, and Full Professor in 1970. He currently holds the Ionis Pharmaceuticals Research Chair at the Université de Montréal, and is on the Faculty in the Departments of Pharmaceutical Sciences, Chemistry, and Pharmacology at the University of California, Irvine (USA), where he is the Director of the Medicinal Chemistry and Pharmacology Graduate Program.

Stéphane Dorich was born in Montréal and raised in Chertsey (Québec, Canada). He obtained a BSc with First-Class Honors at McGill University in 2006. He then joined the Hanessian group at the Université de Montréal and worked on diverse projects involving synthetic methodology and natural products with quaternary carbon centers. He completed his PhD in 2013 with Exceptional Honors, and has since then been working as a Research Scientist at OmegaChem.

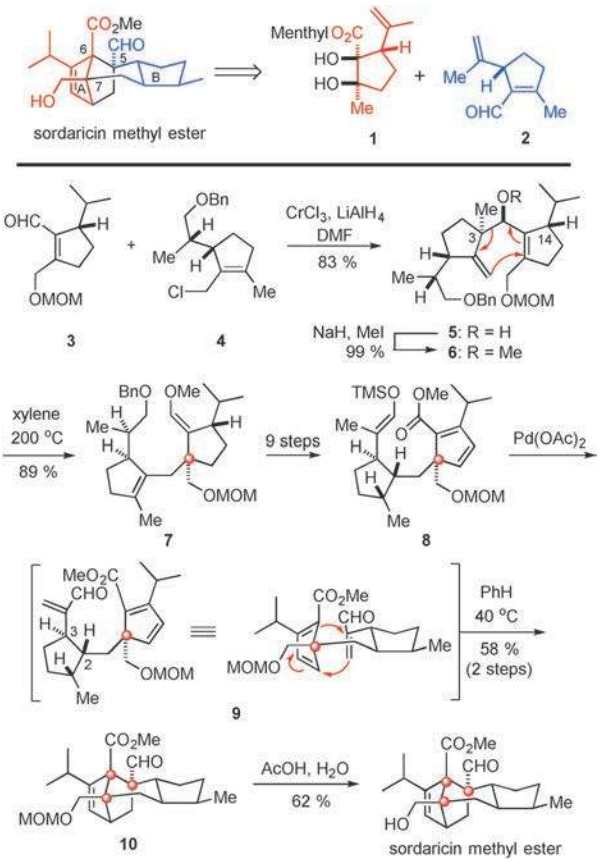
Daniel Tao was born in Lafayette (Indiana, USA). He obtained a BS in chemistry from Calvin College in 2010, during which he was awarded NSF fellowships under Prof. Stefan France at Georgia Institute of Technology and later Prof. John Montgomery at University of Michigan. He is currently a graduate student at the University of California, Irvine working in Prof. Larry Overman's laboratory on applying photoredox catalysis in natural product total synthesis.

ate secondary alcohol **5**, which was O-methylated to give **6**. An irreversible Cope rearrangement then led to the formation of the first quaternary center at C-7, as in **7**. It is noteworthy that, in developing a general strategy for the synthesis of related polyterpenes, Kato et al. had previously established that such a Cope rearrangement proceeded via a boat-transition state to avoid severe steric clash between the isopropyl group at C-14 and the methyl group at C-3.[18] Further functionalization of **7** afforded diene **8** which, under Saegusa conditions, yielded the Diels–Alder precursor **9**. The intended biomimetic cycloaddition[19] then proceeded smoothly, albeit slowly, to generate the remaining two contiguous quaternary centers. Cleavage of the MOM ether **10** afforded sordaricin methyl ester.

The biomimetically inspired total synthesis of sordaricin by Kato et al. features a late-stage intramolecular Diels–Alder cycloaddition that generates two contiguous quaternary carbon centers simultaneously next to an adjacent quaternary carbon atom. It is, therefore, impressive that this key cycloaddition could be achieved at a temperature as low as 40 °C.

2.2. The Mander Synthesis

In a later independent study, Mander et al. completed the total synthesis of (−)-sordaricin in an approach that featured a late-stage intramolecular Diels–Alder cycloaddition reaction to generate the same two quaternary centers, as in the Kato synthesis (Scheme 2).[20] Strategically, and considering the nature of the rings, Mander et al. chose norbornene intermediates **11** and **12** as starting materials, whose cyclopentane and cyclopentene rings could be further functionalized to eventually converge with rings A and B, respectively.



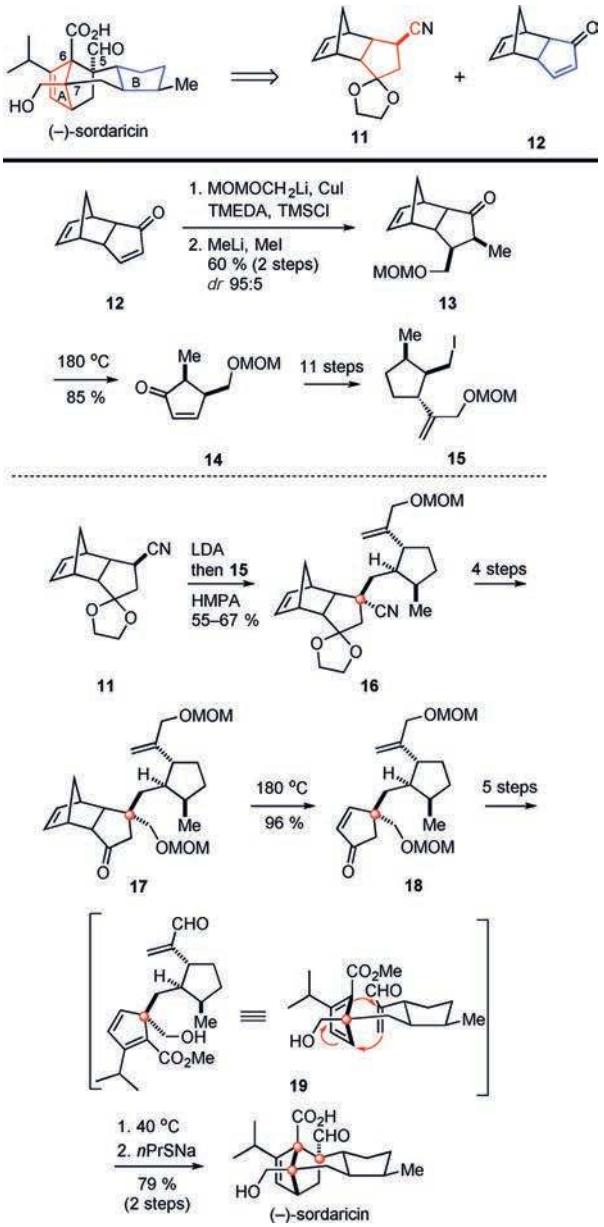
Scheme 1. Synthesis of sordaricin methyl ester by Kato and co-workers. Bn = benzyl, MOM = methoxymethyl, TMS = trimethylsilyl.

Kyle Schenthal was born in New Orleans (Louisiana, USA) in 1990 and raised in Destin, Florida. He obtained his AB from Princeton University in 2012, working in the lab of Prof. Erik Sorensen on the synthesis of complex natural products. He is currently a doctoral candidate in Prof. Larry Overman's laboratory investigating the photoredox-catalyzed construction of quaternary carbon atoms in biologically active systems.

Larry Overman was born in Chicago (Illinois, USA) in 1943 and raised in Hammond (Indiana, USA). He obtained a BA from Earlham College in 1965 and completed his PhD in 1969 with Prof. Howard Whitlock, Jr. at the University of Wisconsin. After a NIH postdoctoral fellowship with Prof. Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971, where he is now Distinguished Professor of Chemistry. His interests center on inventing new transformations and strategies in organic synthesis and the total synthesis of natural products and their congeners.

Intermediate **12**, which was obtained enantioselectively from cyclopentadiene,[21] was transformed to **13** in good yield and in excellent *exo* diastereoselectivity as a result of the shape of the molecule. Thermal retro-Diels–Alder ring opening of **13** led to extrusion of the norbornene moiety and afforded cyclopentenone **14** in good yield, which was further elaborated to trisubstituted cyclopentane **15**. Nitrile **11**, which was prepared in an expedient and convergent fashion from intermediate **12**,[22] was then combined with **15** by alkylation to generate the first quaternary center at C-7 as a single diastereoisomer **16**. Further transformations led to ketone **17**, which was subjected to a thermally induced cycloreversion to give cyclopentenone **18**. Subsequent transformations led to **19**, which underwent an intramolecular Diels–Alder cycloaddition smoothly at 40 °C, as in the Kato synthesis. In fact, cyclization proceeded slowly even at temperatures as low as 10 °C.

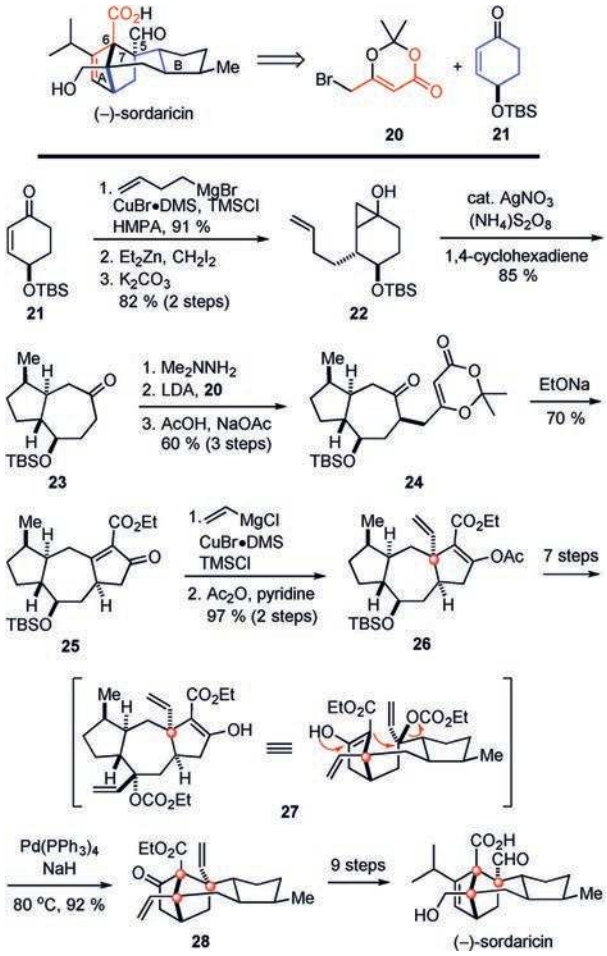
It is noteworthy that the Diels–Alder cycloaddition of the allylic alcohol equivalent of **19** (instead of the unsaturated ester) was also successful despite its unfavorable HOMO–LUMO interactions, although the reaction in this case had to be carried out at 100 °C. Final saponification yielded (−)-sordaricin. A more extensive study of the Diels–Alder reaction for the preparation of simplified intermediates of sordaricin was reported by Liang, Ciufolini, et al.[16,23]



Scheme 2. Synthesis of sordaricin by Mander and co-workers. HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, *n*Pr = *n*-propyl, TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine.

2.3. The Narasaka Synthesis

After having achieved a total synthesis of sordarin and sordaricin in racemic form in 2004,[24] Narasaka and co-workers completed an optimized, enantioselective total synthesis of both in 2006 (Scheme 3).[25] The key step in the synthesis was a Pd^0-catalyzed intramolecular nucleophilic displacement of an allylcarbonate by a β-keto ester enolate to generate two of the three contiguous quaternary centers in one step. Enantiomerically pure chiron **21**, prepared from quinic acid,[26] was utilized to generate an octahydroazulenone core **23** through a free-radical cyclization of cyclopropyl intermediate **22**. Alkylation of the dimethylhydrazone derivative of **23** with bromide **20** gave ketone **24**, which upon base-promoted cyclization, afforded tricyclic intermediate **25**. A conjugated cuprate addition generated the first quaternary center of **26** at C-7 as a single epimer in good yield. After further transformations, the allylic carbonate intermediate **27** was subjected to a modified intramolecular Tsuji–Trost allylation[27] to form the bicyclo[2.2.1]heptan-2-one core **28**, the structure of which was corroborated by X-ray analysis. Considering the steric environment of the reacting partners, this transformation occurred in an astounding 92% yield. In studying this reaction as a strategy to form the tetracyclic core of sordaricin, it was found that the presence of a stoichiometric quantity of NaH was critical, without which the diene formed by β-hydride elimination was the major product. A sequence of standard steps was then performed to transform the core structure **28** into (−)-sordaricin. The authors also completed the synthesis of sordarin by a glycosidation reaction.



Scheme 3. Synthesis of sordaricin by Narasaka and co-workers. DMS = dimethylsulfide, TBS = *tert*-butyldimethylsilyl.

The three total syntheses of sordaricin involved the use of enantiopure starting materials, which in the case of Kato and Narasaka also provided a good portion of the carbon skeleton of sordaricin. Unlike Kato and Mander, who used an intramolecular Diels–Alder reaction to set up the last two contiguous quaternary carbon atoms, the Narasaka synthesis is conceptually different in the use of a Pd^0-catalyzed

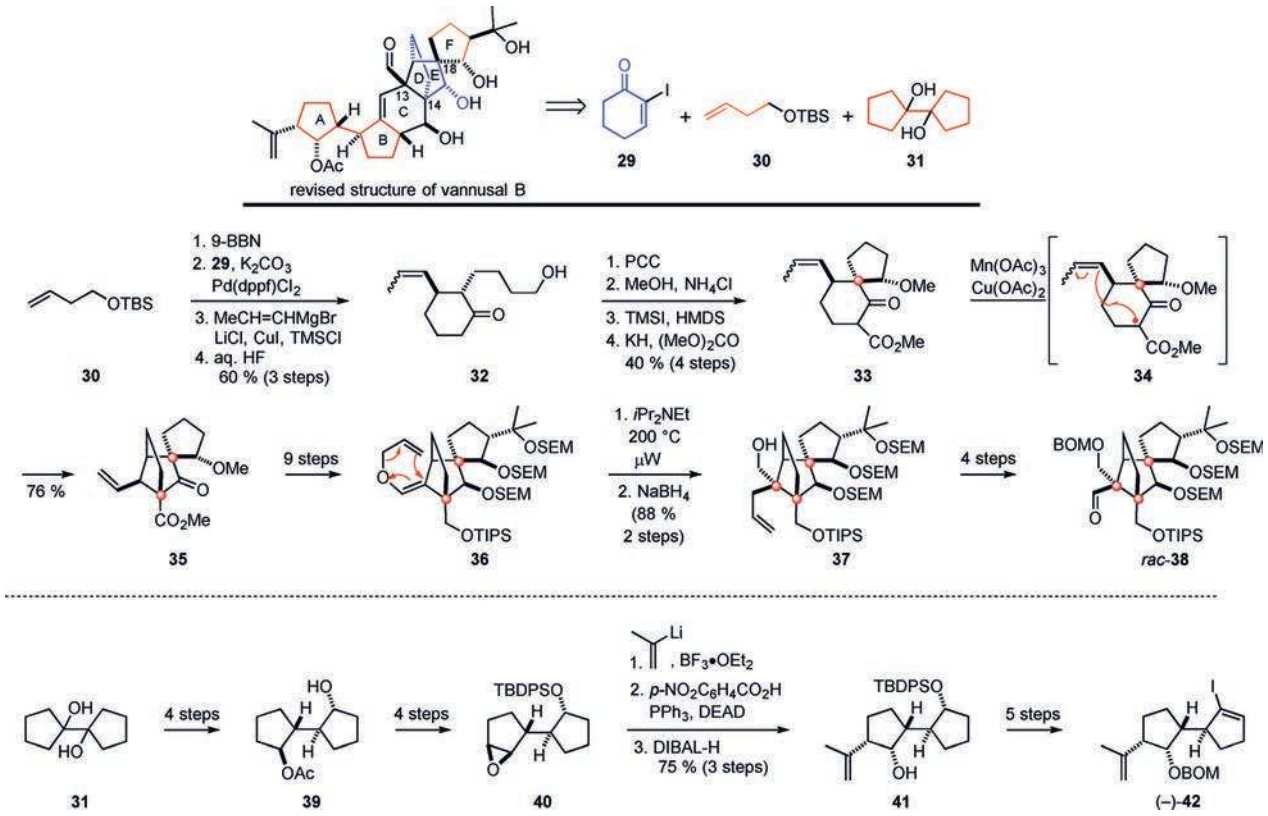
intramolecular ring closure to stereoselectively establish the last two quaternary centers.

3. Vannusals A and B

Highly oxygenated marine natural products from a structurally unique group of triterpenes called vannusal A and vannusal B (differing only in the presence or absence of the C-25 acetyl group), were isolated in 1999 by Guella et al.[28] as secondary metabolites from tropical interstitial ciliate *Euplotes vannus* strains Si121 and BUN3. Structure determination using mass spectrometry, NMR spectroscopic data, and chemical transformations revealed a complex steroid-like structure possessing a 30 carbon atom backbone containing seven rings and 13 stereogenic centers that harbor three quaternary carbon centers, two of which are contiguous.[29] The vannusals are biogenetically derived from farnesyl pyrophosphate, with hemivannusal being the key intermediate that leads to vannusal B through an intermolecular aldol reaction (dimerization) to set the contiguous quaternary centers.[28,30] Despite the intriguing and novel structure, no biological activity has been reported for the vannusals. The structurally most challenging feature is the presence of a spiroannulated cyclopentanol-norbornane subunit as part of a uniquely arranged triterpene architecture. Key steps in the total synthesis of vannusal B by Nicolaou et al. are highlighted below.

The enantioselective total synthesis of vannusal B in 2010 also confirmed its absolute configuration.[29] Only after a series of elegant and careful studies involving the synthesis and characterization of no less than eight diastereomers could the correct structure and absolute configuration of vannusal B be secured beyond doubt.[31] The complex 30 carbon atom backbone structure containing six carbocyclic rings, of which two are joined in a spirocyclic fashion was retrosynthetically disconnected into two readily available starting materials: α-iodocyclohexenone (**29**) and TBS-protected 3-butenol (**30**), which represents ring D (eventually ring F). Cyclopentanol dimer **31** would lead to rings A and B (Scheme 4).

For the preparation of the "northeastern" part of the molecule, **29** and **30** were coupled under Suzuki conditions, followed by a Cu-mediated Michael addition and silyl ether cleavage to give the racemic alcohol **32**, which was oxidized to the aldehyde. The corresponding dimethylacetal was cyclized in the presence of TMSI, and the product further functionalized to afford the spirocycle **33**.[32] Free-radical cyclization with $Mn(OAc)_3$ led to tricycle **35** through a single-electron oxidation by Mn^{III} (as shown in **34**[33]), followed by Cu^{II}-mediated single-electron oxidation to give the exocyclic vinyl group in **35**. This sequence led to the first quaternary center at C-14 in ring E, with control over the stereochemistry.[32] Further elaboration yielded allyl vinyl ether **36**, which was subjected to a microwave-assisted Claisen rearrangement followed by reduction of the resulting aldehyde to give alcohol **37** in excellent yield, thus generating the second



Scheme 4. Synthesis of the intermediates of vannusal B by Nicolaou et al. 9-BBN = 9-borabicyclo[3.3.1]nonane, BOM = benzyloxymethyl, DEAD = diethyl azodicarboxylate, DIBAL-H = diisobutylaluminum hydride, dppf = 1,1′-bis(diphenylphosphino)ferrocene, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, μW = microwaves, PCC = pyridinium chlorochromate, SEM = trimethylsilylethoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl.

contiguous quaternary center at C-13.[31] This rearrangement was controlled by the spatial orientation of the ethano bridge. Intermediate **37** was further converted into racemic building block *rac*-**38**.[31c]

The preparation of the "southwestern" part of vannusal B commenced with a double dehydration of **31**, followed by a double hydroboration, conversion into the diacetate, and enzymatic desymmetrization to give the enantiomerically enriched acetate **39**, which was further elaborated into epoxide **40** (Scheme 4).[31a] Regio- and diastereoselective epoxide opening with 2-propenyllithium, inversion of the resulting alcohol under Mitsunobu conditions, and ester cleavage yielded alcohol **41**, which was converted into the enantiomerically enriched vinyl iodide building block (−)-**42**.[31a]

Transmetalation of vinyl iodide (−)-**42** and addition to racemic aldehyde *rac*-**38**, followed by chromatographic separation of the diastereomers, and cleavage of the TIPS group gave the alcohols **43** and **44** in good yield and in a ratio of 1:1 (Scheme 5).[31c] Based on the extensive comparisons of natural vannusal B with products arising from other diastereomers, only the data from **44** corresponded to the required spectral characteristics for the "northeastern" part; this isomer was further elaborated into **45**. SmI_2-mediated[34] cyclization via ketyl radical **46** and anionic hexacycle **47** by two single-electron reductions and carbonate elimination furnished **48** as a single diastereomer in good yield. Further steps finally led to synthetic vannusal B, which was found to be identical to the proposed structure (Scheme 5).

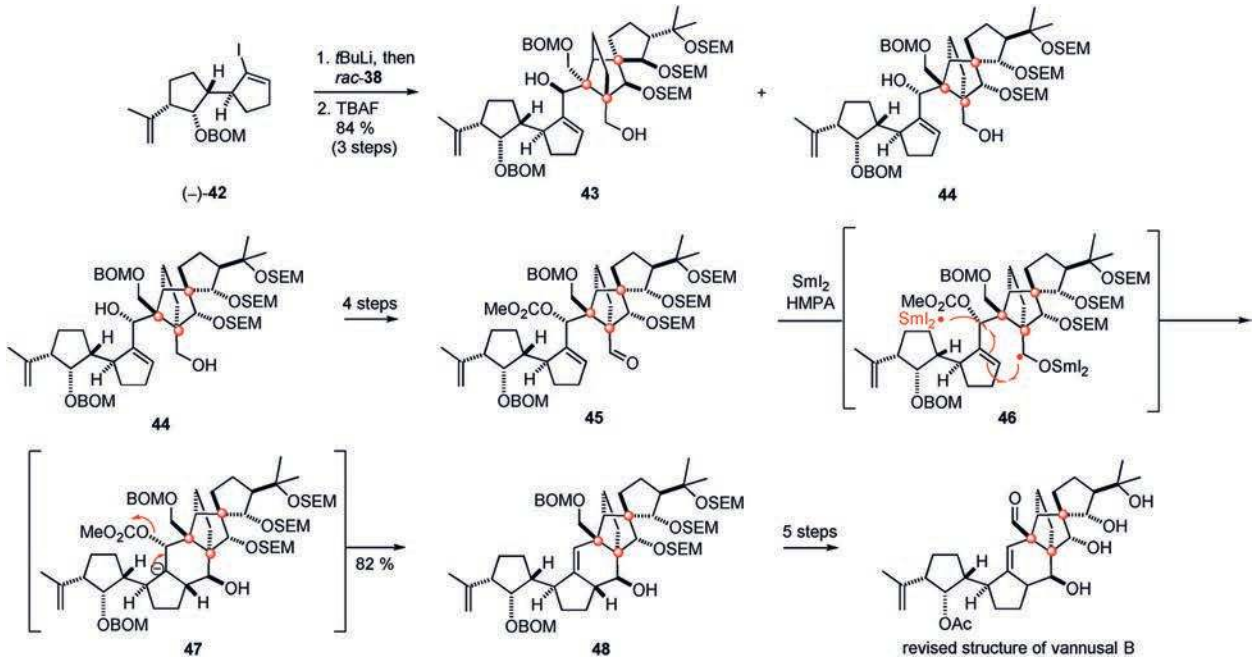
A noteworthy feature of the Nicolaou synthesis of vannusal B and its diastereomers is a Suzuki coupling and cuprate addition that selectively gives the *trans* product **32**; this strategy was later developed into a catalytic asymmetric three-component 1,4-addition/aldol reaction.[35] Other remarkable features are the spirocyclization and the Mn- and Cu-mediated oxidative free-radical cyclization to generate the highly complex spirocyclopentanol-norbornane subunit. The SmI_2-mediated cyclization and elimination that completes the elaboration of the vannusal core structure is remarkable in its selectivity and efficiency.

4. Acutumine

Acutumine, a chlorine-containing alkaloid belonging to the hasubanan family was isolated in 1929 by Goto and Sudzuki[36] as a minor component of the medicinal herb *Sinomenium acutum*. Its structure, determined nearly 50 years later by Tomita et al.[37] using X-ray crystallography, revealed a highly oxygenated tetracyclic skeleton containing four contiguous stereogenic carbon atoms, of which two are quaternary. Other structurally intriguing features are the presence of a spiroannulated cyclopentenone-chlorocyclopentane subunit as part of an oxidized hexahydroindole ring and an azapropellane core. Acutumine is believed to biosynthetically arise from two units of tyrosine, which are further elaborated to a tetracyclic intermediate closely related to acutumine.[38] Acutumine is known to have analgesic properties and is reported to selectively inhibit human T-cell growth with potential memory-enhancing properties.[39] Two total syntheses of acutumine that have adopted entirely different strategies have been reported. Key steps are highlighted below.

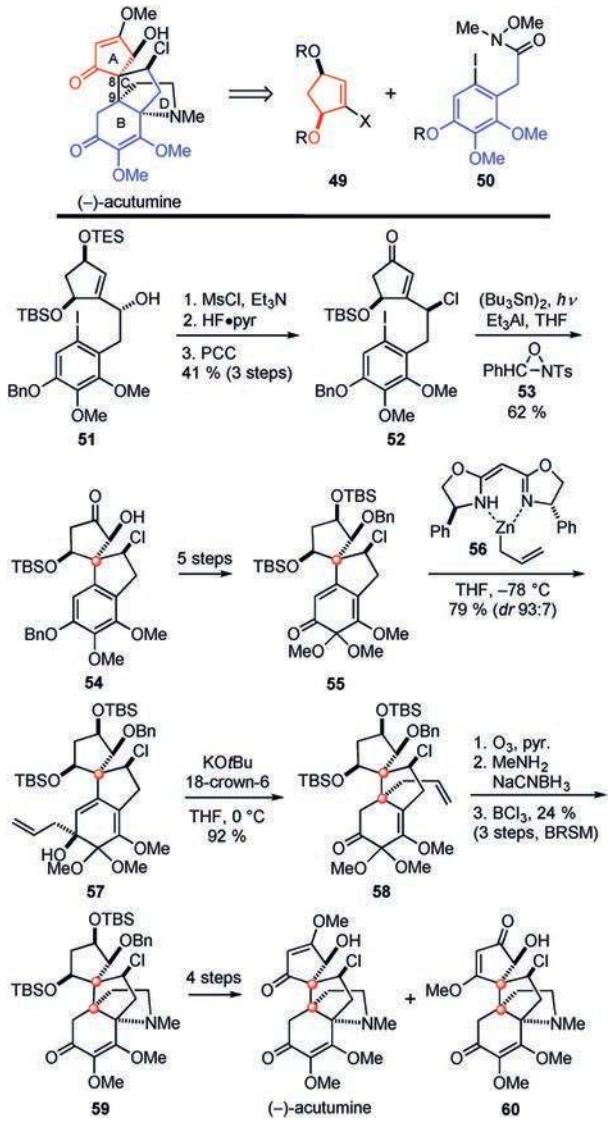
4.1. The Castle Synthesis

The first enantioselective synthesis of (−)-acutumine was reported by Castle and co-workers in 2009 (Scheme 6).[40,41] The key reaction leading to a highly stereoselective spiroan-



Scheme 5. Completion of the synthesis of the revised structure of vannusal B by Nicolaou et al. TBAF = tetra-*n*-butylammonium fluoride.

nulation and the creation of the first of two quaternary centers at C-8 was based on a radical-polar cross-over reaction.[42] Retrosynthetic disconnection of the complex tetracyclic structure led Castle and co-workers to select the readily available, enzymatically desymmetrized chiron **49** and aryl iodide **50** as suitable starting materials to produce **51**, which was converted into the allylic chloride **52** with inversion of configuration. Treatment with hexabutyldistannane under photolysis conditions (irradiation with a sun lamp), and trapping the resulting α-keto radical intermediate with the Davis oxaziridine reagent **53**[43] led to spirocyclic product **54** as the major stereoisomer. Further steps afforded quinone **55**, which was stereoselectively allylated with the Nakamura reagent **56**[44] to give **57**. Exposing allylic alcohol **57** to KO*t*Bu and 18-crown-6 led to the oxy-Cope product **58**, thus generating the second contiguous quaternary carbon center at C-9. Oxidative cleavage of the allylic double bond, followed by reductive amination and treatment with BCl_3 triggered a Lewis acid promoted cyclization to give **59**. Further steps led to acutumine and its enol ether regioisomer **60**.



Scheme 6. Synthesis of acutumine by Castle and co-workers. BRSM = based on recovered starting material, Ms = methanesulfonyl, Pyr = pyridine, TES = triethylsilyl, Ts = toluene-4-sulfonyl.

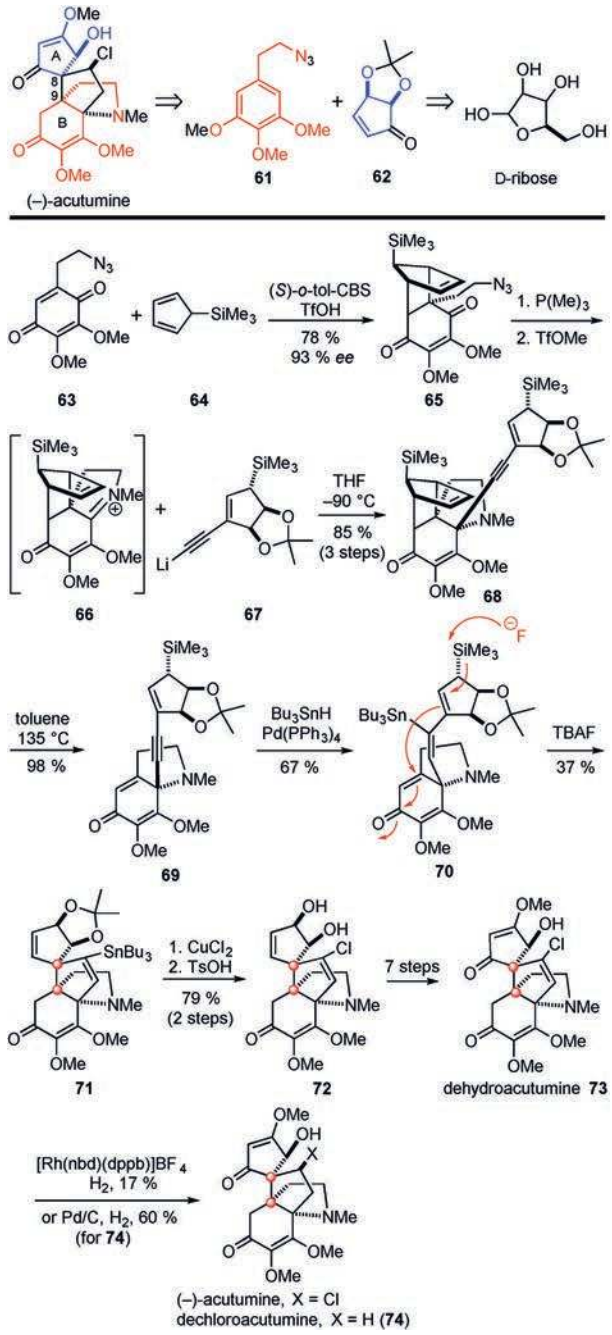
Noteworthy features of the Castle synthesis of (–)-acutumine include an intramolecular tin radical mediated conjugate addition of an aryl iodide onto a cyclopentenone and in situ hydroxylation with high stereoselectivity, thereby generating the unique spirocyclic motif. Another remarkable feature is the creation of a highly congested contiguous quaternary center based on an anion-accelerated oxy-Cope rearrangement, which was realized in 92% yield even at 0°C. Since the direct 1,4-conjugate addition of an allyl group was not successful with model compounds, it was not attempted in the total synthesis. Thus, the successful implementation of the anionic oxy-Cope rearrangement to obtain **58**, which harbors the second quaternary carbon center, was a most welcome alternative. A detailed account of the synthesis of acutumine by Castle and co-workers[41] provides further insights into the various strategies employed.[45]

4.2. The Herzon Synthesis

Retrosynthetic disconnection of acutumine into subunits representing rings A and B led Herzon and co-workers[46] to enantioenriched cyclopentenone **62**, which is readily available from D-ribose in gram quantities, and the aromatic azide **61** as suitable starting materials (Scheme 7).

An intermolecular Diels–Alder reaction between quinone **63** and trimethylsilylcyclopentadiene **64** in the presence of the triflate salt of the Corey–Bakshi–Shibata (CBS) oxazaborolidine reagent,[47] led to *endo* product **65** in excellent enantioselectivity.[48] Conversion into an amine through a Staudinger reaction, followed by N-methylation, gave iminium intermediate **66**, which was treated with lithium acetylide **67** (prepared from **61** in four steps) to give 1,2-adduct **68** in excellent yield as a single diastereomer. Thermal extrusion of silylcyclopentadiene provided the retro-Diels–Alder product **69** in a remarkable 98% yield. Pd-catalyzed hydrostannylation led to the vinylstannane **70**, which upon treatment with TBAF triggered an intramolecular conjugate addition, according to the Hosomi–Sakurai approach,[49] to provide spirocyclic intermediate **71** as a single diastereomer, thereby securing the contiguous quaternary centers at C-8 and C-9 in a highly stereoselective manner in one synthetic operation. Exposure of **71** to cupric chloride promoted smooth destannylation, and subsequent treatment with *p*-TsOH led to tetracyclic vinyl chloride **72**. Adjusting its oxidation level over several steps led to dehydroacutumine (**73**). A Rh-catalyzed homogeneous hydrogenation gave acutumine, whereas reduction with Pd/C and H_2 gave (–)-dechloroacutumine (**74**).

Interestingly, the Castle and Herzon approaches to acutumine started with enantiopure chirons which set the relative and absolute configurations early in their respective syntheses. However, the strategies used for the crucial spiroannulation reaction are conceptually very different. Castle and co-workers used a photochemically induced and highly stereoselective radical-polar cross-over reaction.



Scheme 7. Synthesis of acutumine by Herzon and co-workers. CBS = Corey–Bakshi–Shibata oxazaborolidine reagent, dppb = 1,1′-bis-(diphenylphosphino)butane, nbd = 2,5-norbornadiene, TsOH = *p*-toluenesulfonic acid, TfOH = trifluoromethanesulfonic acid, *o*-tol = *o*-tolyl.

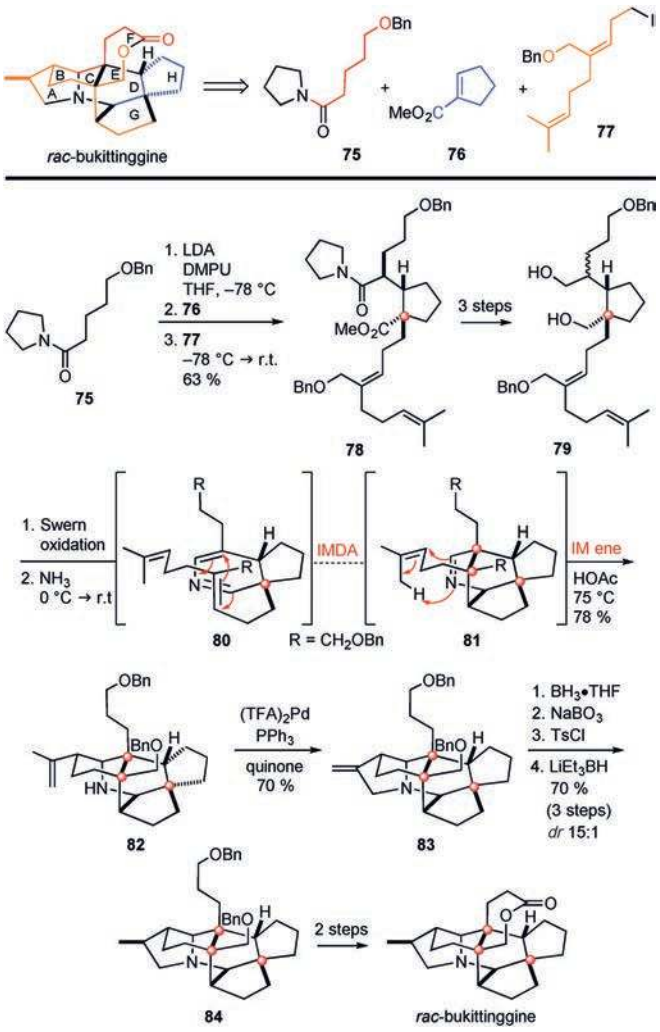
Herzon and co-workers, on the other hand, succeeded in generating the two contiguous quaternary carbon centers in acutumine through an intramolecular conjugated cascade reaction triggered by attack of fluoride on a distal trimethylsilyl group. Whereas D-ribose was the original source of the hydroxy group in ring A of the Herzon synthesis, Castle and co-workers resorted to a stereoselective hydroxylation. It is also of interest how and when the chlorine atom was introduced in the two syntheses.

5. Bukittinggine

A lactone-containing alkaloid belonging to the *Daphniphyllum* family named bukittinggine was isolated in 1990 by Arbain et al.[50] as the major component from the leaves and branches of *Sapium baccatum*. Its structure, as determined by Gibbons and Trotter using X-ray crystallography,[51] revealed a heptacyclic skeleton containing nine contiguous stereogenic carbon atoms, of which two are contiguous and quaternary. Another structurally intriguing feature within the azapolycyclic framework is the presence of a δ-lactone and an octahydroindolizidine subunit bearing a methyl substituent. As a consequence of the close structural relationship with the *daphniphyllum* alkaloids,[52] bukittinggine is believed to arise biosynthetically from squalene dialdehyde, which is produced from DL-mevalonic acid.[53,54] It is known for its anti-inflammatory activity, with a presumed mechanism of action similar to that of acetylsalicylic acid.[55] The strategy toward the total synthesis of bukittinggine was inspired by a previously established biomimetic approach to the pentacyclic seco-daphniphylline alkaloids pioneered by the Heathcock group.[54]

The first synthesis of racemic bukittinggine was reported by Heathcock et al. as part of synthetic investigations on several related *daphniphyllum* alkaloids.[56] They selected amide **75** (part of lactone ring F), cyclopentenyl methyl ester **76** (ring H), and homogeranyl iodide **77** (a part of ring G) as readily available building blocks (Scheme 8).

Sequential deprotonation of amide **75** with LDA, followed by a Michael reaction with α,β-unsaturated ester **76**, and trapping of the generated amide enolate with iodide **77** yielded racemic allylic ether **78** in an overall yield of 63% in one operation. Other stereoisomers and unalkylated Michael product were obtained in yields of 13% and 20%, respectively. The addition of DMPU as an additive was necessary to reduce the amount of additional by-products resulting from the reduction of iodide **77**. Sequential reduction of the ester and amide functions in **78** led to diol **79**, which set the stage for a one-pot tetracyclization reaction. Thus, Swern oxidation of **79** to the corresponding dialdehyde, and formation of the dihydropyridine **80** upon addition of ammonia, was followed by a biomimetic cascade reaction in the presence of acetic acid and heating at 75 °C. The first step is an intramolecular, inverse-electron-demand hetero-Diels–Alder reaction involving the 2-aza-diene and the internal double bond of the geranyl side chain, which results in the formation of the imine **81**.[54] In the second step of this cascade reaction sequence, an intramolecular formal ene or aza-Prins reaction of imine **81** resulted in ring closure to reveal ring B in the racemic pentacycle **82** in high yield and as the only diastereomer (note: the hetero-Diels–Alder and ene reactions might also take place from the protonated pyridinium or iminium species). Ring A was formed by a Pd^{II}-catalyzed oxidative cyclization of **82** to yield hexacycle **83** in good yield as a single diastereomer. According to the mechanism of this reaction developed independently by the groups of Trost and Hegedus,[57] a π-allyl complex is first formed, which is attacked by the internal amine to give the fused octahydroindolizidine **83**. Normally, non-aromatic amines are tightly coordinated to Pd



Scheme 8. Synthesis of bukittinggine by Heathcock and co-workers. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone, IM-Ene = intramolecular ene reaction, IMDA = intramolecular Diels–Alder reaction, TFA = trifluoroacetate.

and, as a consequence, are not sufficiently nucleophilic to participate in reactions of this type. Such coordination may be less important in the case of the secondary amine in **82**, because of its sterically congested nature. A number of hydrogenation methods, including diimide reduction, proved to be problematic, affording **84** only with modest diastereoselectivity. Alternatively, a hydroboration/oxidation procedure with **83** led to the desired primary alcohol, which was converted into the tosylate, and the latter reduced with triethylborohydride to give **84** in very good yield and diastereoselectivity. Removal of the benzyl protecting groups, and oxidation of the resulting 1,4-diol with the Fétizon reagent,[58] afforded racemic bukittinggine as a single regioisomer.

Noteworthy features in the Heathcock synthesis include the Michael reaction/alkylation sequence to assemble all the necessary carbon atoms in one operation and leading to a single diastereomer. Most remarkable is the one-pot biomimetic cascade reaction to give pentacycle **82** from **79**, which features a hetero-Diels–Alder reaction to generate the contiguous quaternary stereocenters of bukittinggine. Adopting this key biomimetic strategy, Heathcock was able to synthesize a large number of related *daphniphyllum* alkaloids.[54]

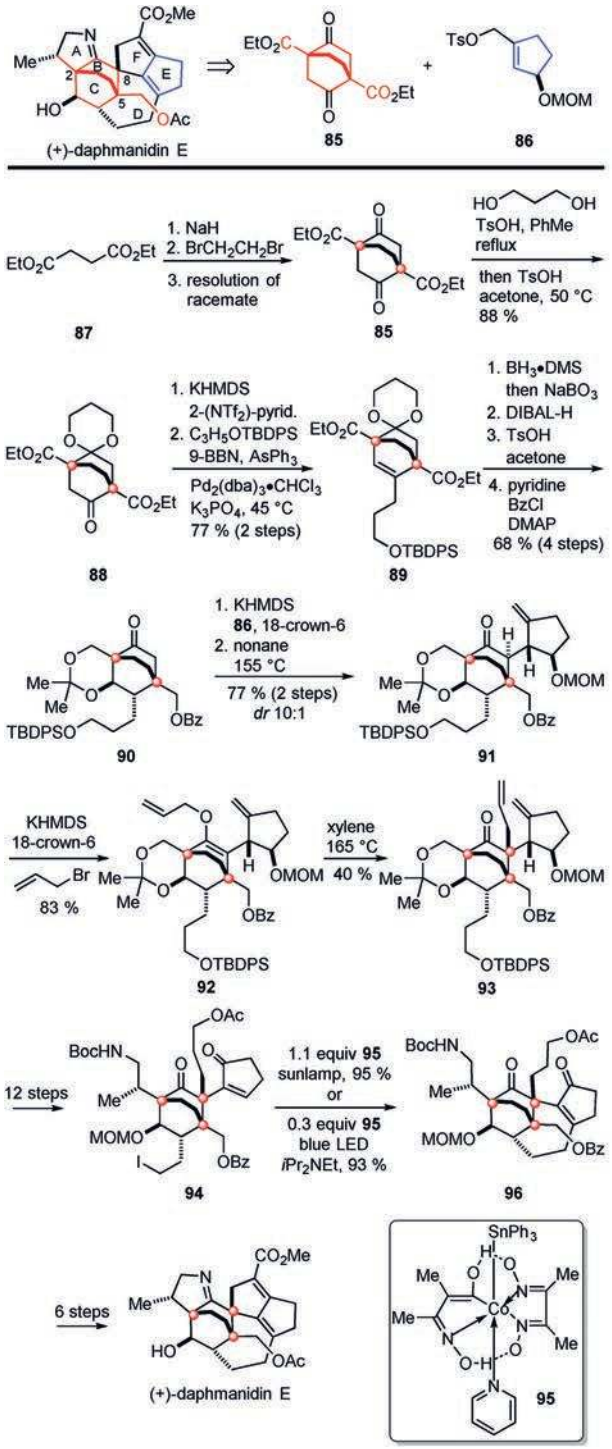
6. Daphmanidin E

A new class of hexacyclic *daphniphyllum* alkaloids represented by daphmanidin E was isolated by Kobayashi and co-workers from leaves of *Daphniphyllum teijsmanni* in 2006.[52e,59] Its structure, as determined by NOESY spectroscopy and a modified Mosher method, revealed a hexacyclic ring system containing six contiguous stereogenic carbon atoms, of which three are quaternary, including two that are contiguous. Another structurally intriguing feature is the bicyclo[2.2.2]octane core surrounded by a fused dihydropyrrole and a decahydrocyclopentazulene ring. As a member of the daphniphyllum alkaloid family,[52] daphmanidin E is believed to arise biosynthetically from squalene dialdehyde.[53,54] Daphmanidin E showed moderate vasorelaxant activity.[52e,59] Key steps in the enantioselective total synthesis of daphmanidin E are highlighted below.

Weiss and Carreira reported the only total synthesis of (+)-daphmanidin E in 2011 (Scheme 9).[60] Retrosynthetic analysis led to the readily available starting materials bicyclo[2.2.2]octane **85**, which corresponds to rings B and C and contains two C_2-symmetrically disposed quaternary centers, and cyclopentene **86**, which corresponds to ring E.

Diethyl succinate (**87**) was converted through two Claisen condensations with dibromoethane into the corresponding racemic β-ketoester **85**. Resolution of the corresponding diastereomeric hydrazones of **85** by chromatographic separation or enzymatic saponification of the esters[61] gave the enantioenriched variant of β-ketoester **85**. As a result of its symmetry, the carbonyl groups in **85** are homotopic, and one could be selectively functionalized to give monoketone **88**, which after formation of the enol triflate and Suzuki coupling yielded olefin **89**. Stereocontrolled hydroboration, reduction, acetalization, and introduction of a benzoyl protecting group afforded **90**. Enolate O-alkylation of **90** with cyclopentene triflate **86** followed by Claisen rearrangement gave ketone **91** in good yield and high diastereoselectivity. Formation of the enolate with KHMDS and treatment with allyl bromide gave allyl vinyl ether **92**. The second quaternary center at C-8 was then generated by another Claisen rearrangement to give **93** in moderate yield as a single diastereomer. Further functionalization of **93** gave **94**, which harbors a β-iodoethyl side chain, thereby setting the stage for ring closure of the seven-membered ring D. The novel alkyl-Heck cyclization could be carried out using stoichiometric or catalytic (equimolar Hunig's base necessary) cobaloxime **95**[62] under irradiation with a sun lamp or blue LED to give tetracycle **96**. In subsequent steps, an aldol reaction and a ketone-amine condensation constructed rings F and A, respectively. Final protecting group manipulations completed the first total synthesis of (+)-daphmanidin E.

Noteworthy features of the Carreira synthesis of daphmanidin E include the early installation of two quaternary



Scheme 9. Synthesis of daphmanidin E by Carreira and Weiss. Boc = *tert*-butoxycarbonyl, Bz = benzoyl, dba = *trans*,*trans*-dibenzylideneacetone, DMAP = 4-dimethylaminopyridine, KHMDS = potassium hexamethyldisilazide.

centers within the bicyclo[2.2.2]octane core in one step with suitable handles for further functionalization. Furthermore, two Claisen rearrangements were conducted with very good diastereoselectivities, first to connect ring E to the core subunit B/C, and secondly to create the second quaternary center at C-8. Finally, the seven-membered ring D was obtained in a remarkably effective and mild Co-catalyzed alkyl-Heck cyclization under irradiation with visible light.

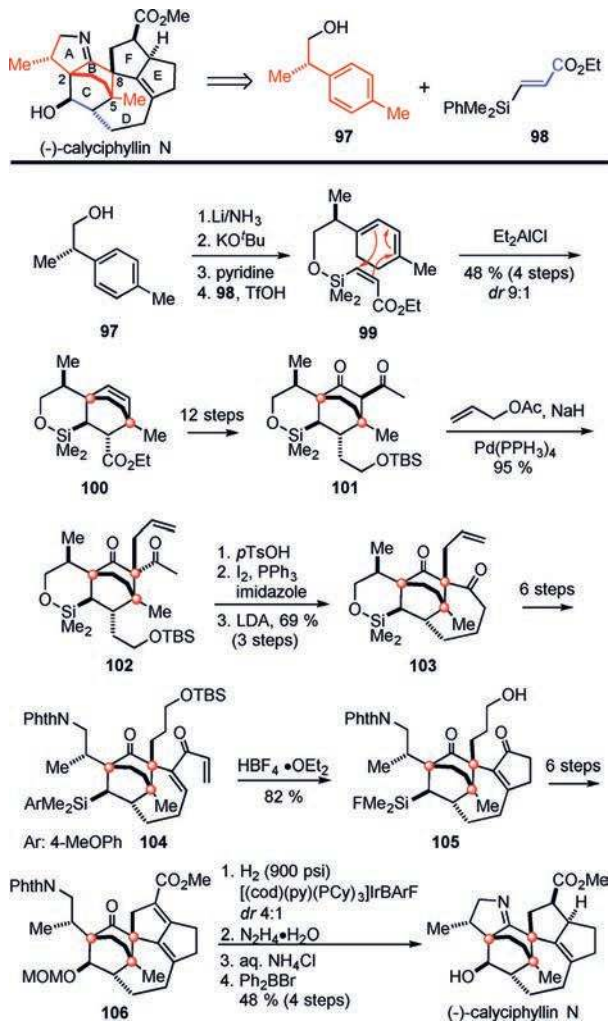
7. Calyciphylline N

Calyciphylline N, another member of the A-type daphmanidin family, was isolated in 2008 by Kobayashi and coworkers from leaves of *Daphniphyllum calycinum*, and its structure was determined by NOESY spectroscopy.[63] Calyciphylline N showed the same skeletal features as discussed for daphmanidin E, except for the absence of unsaturation in ring F and the presence of a methyl substituent on the quaternary carbon atom at the junction of rings B/C and D instead of the CH_2OAc group in daphmanidin E. Of the eight stereogenic carbon atoms, six are contiguous, two are adjacent quaternary centers, and an additional quaternary center joining rings B/C and A is also present. Key steps in the enantioselective total synthesis of calyciphylline N are highlighted below.

The first enantioselective total synthesis of (−)-calyciphylline N was reported by Shvartsbart and Smith in 2014 (Scheme 10).[64] In contrast to Carreira's synthesis of daphmanidin E, which started with the bicycle[2.2.2]octane core, Shvartsbart and Smith disconnected the complex hexacyclic structure into the readily available enantioenriched alcohol **97**, formally representing ring B and all the carbon atoms including one stereogenic center bearing the methyl group in ring A. The other building block was α,β-unsaturated silyl ester **98**, which would provide a C_3 tether as part of ring B.

Birch reduction of **97** and alkylation of the major cyclohexadiene isomer with the silyl triflate derived from **98**[65] led to the silicon-tethered triene **99**. A thermal intramolecular Diels–Alder reaction gave all the possible diastereoisomers of tricycle **100** bearing the methyl-containing quaternary center at C-5. In constrast, the Et_2AlCl-promoted cyclization yielded **100** with good diastereoselectivity (9:1), presumably as a result of the spatial orientation of the methyl group enabling attack from the opposite side. Further functionalization yielded β-diketone **101**, which could be C-allylated to give **102** by using a Tsuji–Trost reaction,[66] thereby generating the second quaternary center at C-8 in excellent yield and as a single stereoisomer. The seven-membered ring D was formed by transannular enolate alkylation using LDA to give tetracycle **103**, which upon further elaboration gave dienone **104**. Nazarov cyclization and protodesilylation to enable functionalization of the silicon moiety were achieved with $HBF_4{\cdot}OEt_2$ in one operation to give tetracycle **105**.[67,68] Cyclization to give pentacycle **106** was accomplished by an intramolecular aldol reaction in the same way as in Carreira's synthesis of daphmanidin E. The remaining two stereogenic centers in rings E and F were generated by a selective 1,4-reduction using a cationic Ir-based modified Crabtree catalyst to give a 4:1 diastereomeric mixture of products in favor of the desired isomer.[69] Hydrazinolysis of the phthalimido group, formation of the imine, and cleavage of the MOM group completed the total synthesis of (−)-calyciphylline N.

Noteworthy features of the Smith synthesis of (−)-calyciphylline N include a diastereoselective (substrate-con-



Scheme 10. Synthesis of calyciphylline N by Shvartsbart and Smith. BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, cod = cycloocta-1,5-dienyl, Cy = cyclohexyl, py = pyridyl.

trolled) intramolecular Diels–Alder reaction with a silicon-tethered dienophile to generate the bicyclo[2.2.2]octane motif harboring two quaternary centers. Other remarkable features are a Tsuji–Trost C-allylation to generate the second contiguous quaternary center (despite the highly congested bridged core subunit) and a transannular enolate alkylation to create a seven-membered ring. Nazarov cyclization and a diastereo- and chemoselective hydrogenation of a conjugated diene ester are further highlights.

8. Bilobalide

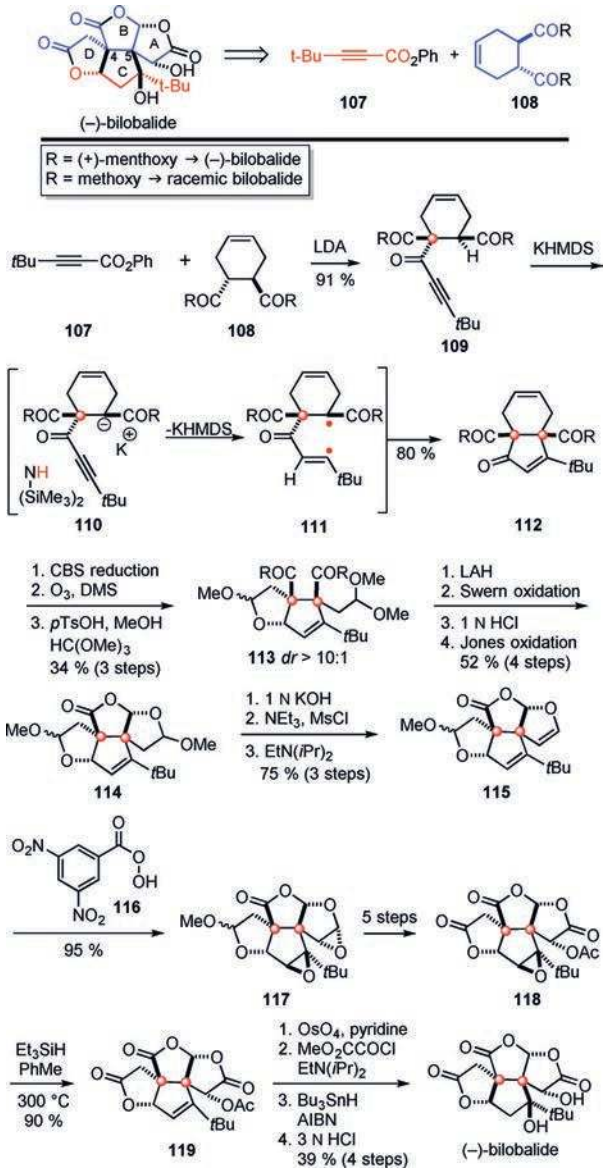
A terpenoid named bilobalide that contains a *tert*-butyl group and belongs to the ginkgolide family was isolated in 1971 by Nakanishi et al.[70] from *ginkgo biloba* extracts. The structure of the tetracyclic C-15 trilactone containing six stereogenic carbon atoms, of which two are contiguous and quaternary, was determined spectroscopically. A structurally unique feature in this class of ginkgolides is the presence of a *tert*-butylcarbinol group. The bilobalides are biosynthesized by degradation of the related ginkgolides, which in turn are formed from geranylgeranyl pyrophosphate, prepared by condensation of isopentenyl pyrophosphate and dimethylallyl pyrophosphate.[71,72] Ginko plants have long been known in Chinese folk medicine for their therapeutic benefit, as evidenced by their use in some European countries to treat cerebrovascular and peripheral circulatory problems in the elderly.[73] Ginkgolides act as a very effective anti-platelet-activating factor (PAF) antagonist to treat cardiovascular diseases.[71,72] Furthermore, bilobalide is known for its neuroprotective effects,[74] and is a negative allosteric modulator of some GABA receptors.[75] Two total syntheses of bilobalide based on entirely different strategies to create the contiguous quaternary centers have been reported. Key steps are highlighted below.

8.1. The Corey Synthesis

The only enantioselective synthesis of (−)-bilobalide was reported by Corey and Su in 1988.[76] Their approach was based on a strategy used for the synthesis of the racemic natural product a year earlier.[77] Analysis of the tetracyclic structure led Corey and Su to alkyne **107** and (+)-*trans*-1,2-cyclohexene dicarboxylic acid dimenthoxy ester (chiron **108**) as starting materials, which would end up in a bicylic intermediate bearing all the requisite carbon atoms of the target compound (Scheme 11). It is of interest that chiron **108** shows no visually evident overlap with any of the rings in bilobalide. Alkyne **107**[78] would eventually provide a segment of ring C, while the chiron **108** would be the source of the contiguous quaternary carbon atoms, albeit after some functional adjustments.

In the enantioselective synthesis of (−)-bilobalide, chiron **108** was prepared by the Diels–Alder reaction of butadiene and the (+)-menthol diester of fumaric acid catalyzed by diisobutylaluminum chloride according to Yamamoto and coworkers.[79] The first quaternary center at C-4 was installed by reaction of the monolithium enolate of **108** with **107** to yield Claisen product **109** diastereoselectively. Remarkably, and despite severe steric congestion, the intramolecular Michael reaction of the lithium enolate of **109** led to the bicyclic compound **112** now harboring the second quaternary center at C-5 in good yield and as a single diastereomer.

According to the authors, after initial deprotonation to form potassium enolate **110**, an electron is transferred to the ynone moiety to afford the diradical **111**, which undergoes ring closure to **112**. This reaction can also be performed using **108** and two equivalents of LDA, as was done in the original synthesis of racemic bilobalide.[77,80] Ketone **112** was reduced to the corresponding allylic alcohol (> 10:1) by CBS reduction. Sequential oxidative cleavage by ozonolysis and acetal formation yielded diester **113** in good yield. A series of oxidation/reduction and acetalization steps gave lactone **114**. Functionalization of the A-ring ketal was achieved by base-catalyzed opening of the lactone ring and elimination via the mesylate ester to give diene **115**. Stereoselective epoxidation using peroxy-3,5-dinitrobenzoic acid (**116**) yielded diepoxide **117**. As a reductive epoxide opening was not feasible, an



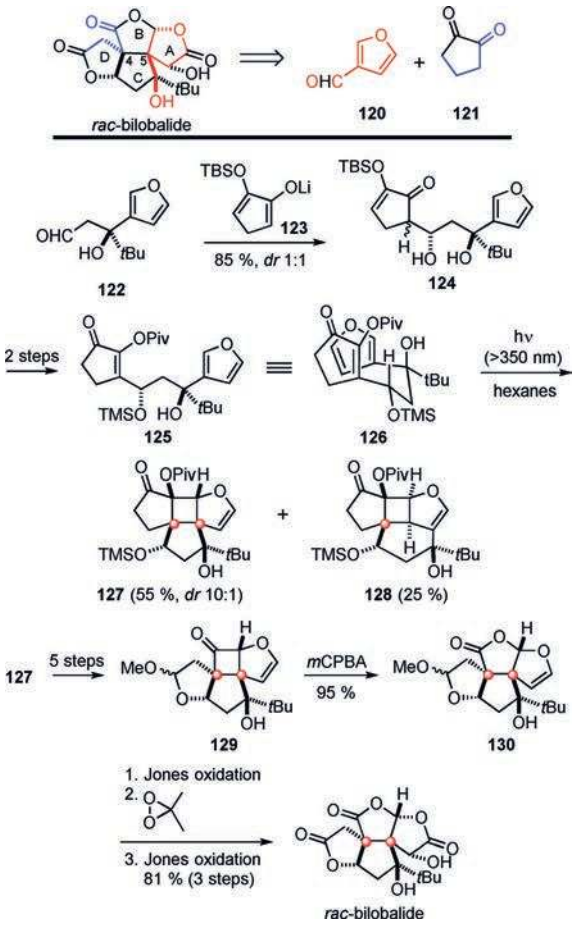
Scheme 11. Synthesis of bilobalide by Corey and Su. AIBN = 2,2′-azobis(2-methylpropionitrile), Ms = methanesulfonyl.

alternative approach was pursued involving the acid-mediated formation of a diol from **117**, acetylation, and further conversion into α-acetoxy trilactone monoepoxide **118**. The intermediate was deoxygenated to give trilactone **119** in remarkably good yield, presumably through a free-radical mechanism. Subsequently, **119** was dihydroxylated with osmium tetroxide. The less-hindered secondary hydroxy group was then activated as the corresponding half oxalate ester and deoxygenated under free-radical conditions. Acidic deprotection yielded (−)-bilobalide.

Noteworthy features in the synthesis of (−)-bilobalide by Corey and Su include an early two-step generation of the contiguous quaternary centers by stereoselective Claisen and intramolecular Michael reactions, the latter probably proceeding through a diradical mechanism.

8.2. The Crimmins Synthesis

In their approach toward the total synthesis of racemic bilobalide, Crimmins et al. chose 3-furaldehyde (**120**, to represent ring A) and 1,2-cyclopentanedione (**121**, later to become a segment of ring D) as suitable starting materials (Scheme 12).[81] Addition of tBuCeCl$_2$ to **120**[82] and oxidation to the ketone was followed by addition of lithioacetonitrile, and conversion into aldehyde **122**. An aldol reaction with 2.2 equivalents of lithium enolate **123**,[83] derived from **121**, gave a 1:1 diastereomeric mixture of products **124**, which was of no consequence because of the subsequent enolization of the ketone. Interestingly, the diastereomers showed the same desired *anti* relationship between the secondary and tertiary hydroxy groups, which can be explained by a chairlike six-membered Li-enolate transition state with the *tert*-butyl group occupying an equatorial position and the enolate attacking from the preferred pseudoequatorial face. Protecting-group manipulations and selective formation of enol ester **125** set the stage for the crucial intramolecular [2+2] photocycloaddition to establish the contiguous quaternary centers. In the event, photocyclization of **125** (uranium glass filter, $\lambda >$ 350 nm) proceeded via transition state **126**, which has the *tert*-butyl and (trimethylsilyl)oxy groups of the newly formed ring C in pseudoequatorial positions, to give the photo-



Scheme 12. Synthesis of bilobalide by Crimmins and co-workers. *m*CPBA = *meta*-chloroperoxybenzoic acid, Piv = pivaloyl.

cycloadduct **127** in 55% yield as a 10:1 mixture of diastereomers favoring the "up"-disposed cyclopentyl isomer. A regioisomer of **127** was isolated in 25% yield from cycloaddition with the less substituted furan double bond (**128**, which has one quaternary center). The photocycloadduct **127** was functionalized by hydroxylation with LDA and MoOPh,[84] oxidative degradation of the hydroxy ketone, and manipulation of the oxidation state to yield ketone **129**. A regioselective Baeyer–Villiger oxidation with *m*CPBA gave the desired lactone **130** in excellent yield after 5 min, whereas H_2O_2 or $tBuO_2H$ in the presence of Triton B led exclusively to the undesired lactone. Finally, oxidation of the acetal, diastereoselective epoxidation with dimethyldioxirane,[85] and a second Jones oxidation gave racemic bilobalide.

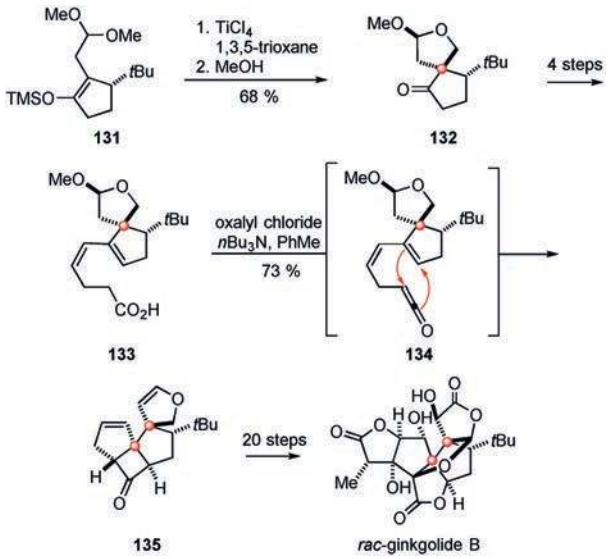
One of the key aspects of the Crimmins synthesis is the *anti*-stereoselective aldol reaction of the lithium enolate of **123** with aldehyde **122** to secure the desired configuration of the hydroxy group in ring D, as well as its *anti* relationship with the *tert*-butylcarbinol group. Most noteworthy is the stereoselective intramolecular [2+2] photo-cycloaddition, which was also utilized in the synthesis of other ginkgolides,[86–88] of **125** to generate the contiguous quaternary stereocenters at C-4 and C-5 in **127**. Other remarkable features include the regioselective Baeyer–Villiger oxidation of **129** and other selective late-stage oxidations.

Adopting a different approach to generate the quaternary centers, Corey and co-workers reported total syntheses of ginkgolides A[89] and B[90] (Scheme 13). Thus, a titanium tetrachloride mediated Mukaiyama aldol reaction with silyl enol ether **131** generated ketone **132**, which harbors the first quaternary center. Further functionalization led to **133** and set the stage for an intramolecular ketene-olefin cycloaddition with in situ generated ketene **134**[91] to give the contiguous quaternary centers in cyclobutanone **135**, an intermediate that was converted into racemic ginkgolide A[89] and ginkgolide B.[90,92]

The Corey and Crimmmins approaches toward the synthesis of bilobalide are conceptually different in their disconnection to simpler building blocks and in setting up the quaternary centers within the core cyclopentane structure. In the Corey and Su synthesis, the unsaturated indanone, which already bears two quaternary carbon atoms, was oxidatively cleaved to the corresponding diester, thus providing a highly substituted cyclopentene core. Crimmins, on the other hand, used a photochemical [2+2] cyclization to introduce the two contiguous quaternary carbon centers within a tetracyclic core structure, which was subjected to a series of steps to achieve the desired oxidation level present in bilobalide.

9. Maoecrystal V

Maoecrystal V is a pentacyclic *ent*-kaurenoid norditerpenoid that shows cytotoxicity towards HeLa cells.[93] First isolated from *Isodon eriocalyx* in 1994, its structure was not elucidated until 2004[93] by a combination of NMR spectroscopy and single-crystal X-ray analysis. Maoecrystal V is characterized structurally by a bicyclo[2.2.2]octan-2-one



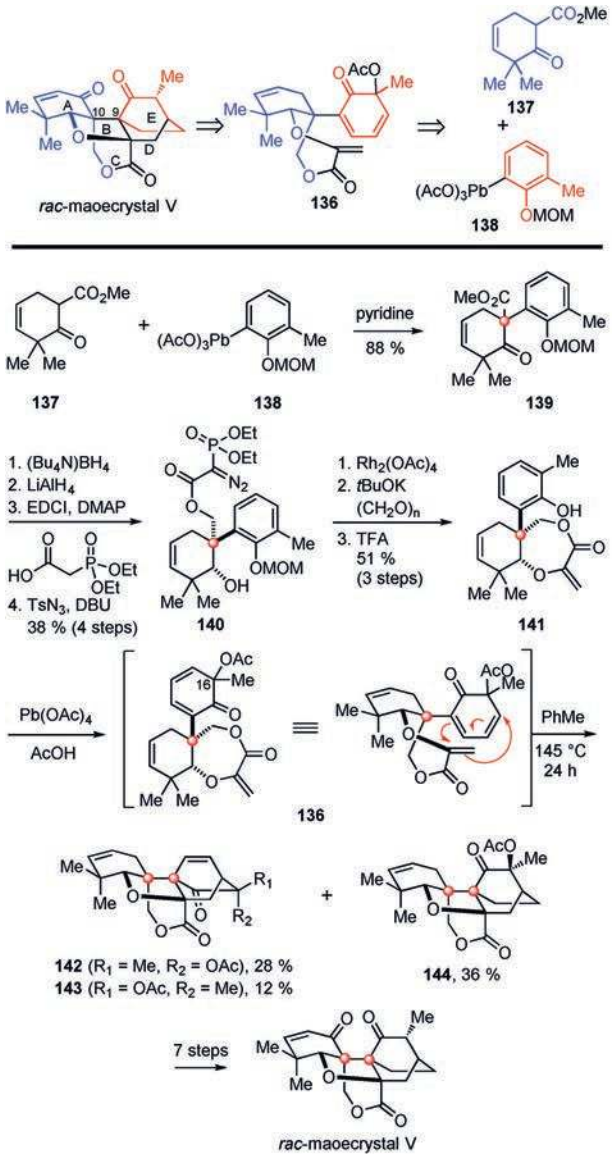
Scheme 13. Synthesis of ginkgolide B by Corey and Su.

core fused to a δ-lactone and a strained bridging tetrahydrofuran ring, with two contiguous quaternary stereocenters (C-9 and C-10) common to four and three separate rings, respectively. It is speculated that maoecrystal V arises biosynthetically from the tetracyclic diterpene *epi*-eriocalyxin A, which lacks the tetrahydrofuran ring of maoecrystal V.[93] Total syntheses of maoecrystal V have been completed by four research groups. Key steps in four of these syntheses are highlighted below.

9.1. The Yang Synthesis

In 2010, Yang and co-workers reported the first total synthesis of racemic maoecrystal V.[94] It was envisioned that the complete ring system would be constructed by an intramolecular Diels–Alder reaction of tetraene **136**, which in turn would arise from the coupling of β-ketoester **137** and aryl-lead intermediate **138** (Scheme 14).[95]

After preparing **137** from 2,2-dimethyl-1,3-cyclohexandione,[96] it was α-arylated to give **139** in 88% yield. Subsequent reduction of both the ketone and ester functionalities with $LiAlH_4$ was low yielding and proved inferior to a two-step reduction using $(Bu_4N)BH_4$ followed by $LiAlH_4$. Steglich esterification of the resulting primary alcohol using EDCI successfully appended the diethyl phosphonate. Reaction of ketoester **139** with tosyl azide under basic conditions led to isolation of the desired diazo ester **140** in 38% yield. Subjecting diazo ester **140** to catalytic rhodium(II) acetate generated the rhodium carbenoid, which underwent intramolecular OH insertion to assemble the 3-oxa-ε-lactone. A Horner–Wadsworth–Emmons reaction with paraformaldehyde and MOM cleavage gave enoic ester **141**. To set the stage for the intramolecular Diels–Alder reaction, phenol **141** was subjected to a Wessely oxidative acetoxylation[97] to yield cyclohexadienone **136** as a mixture of C-16 epimers. Without purification, **136** was heated in toluene at 145°C to afford a mixture of three cycloadducts **142–144**, from which the



Scheme 14. Synthesis of *rac*-maoecrystal V by Yang and co-workers. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

desired *endo*-cycloadduct **144** was isolated in 36% yield. After several additional steps, *rac*-maoecrystal V was obtained from Diels–Alder adduct **144**. Although no stereoselectivity was realized in the pivotal intramolecular Diels–Alder step, this inaugural total synthesis of maoecrystal V was accomplished in a highly concise fashion.

9.2. The Danishefsky Synthesis

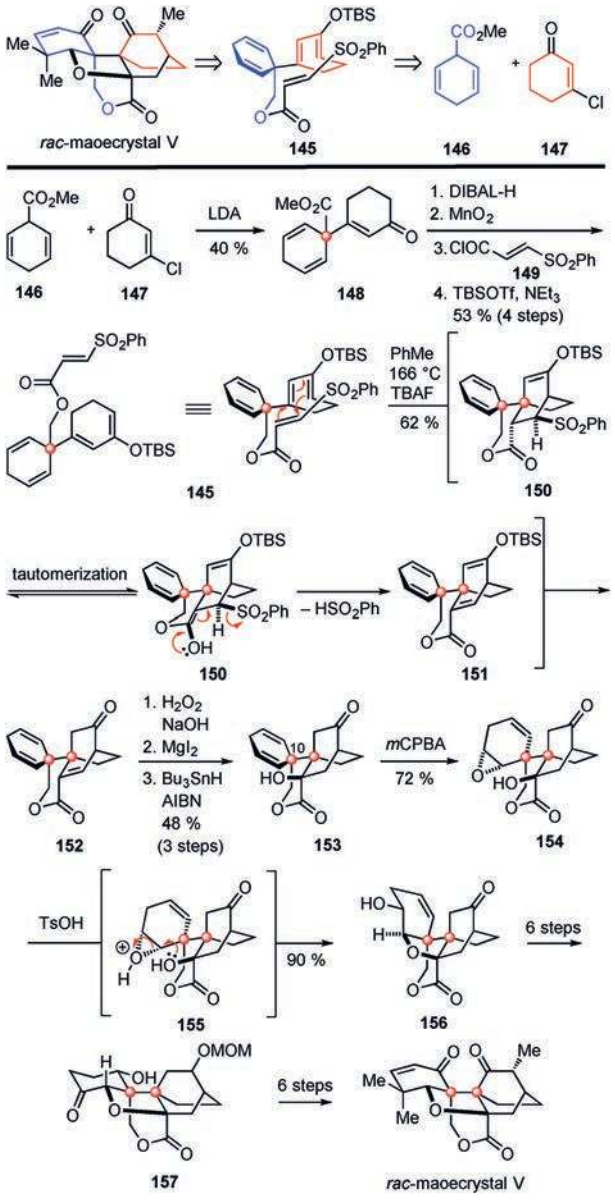
Peng and Danishefsky also utilized an intramolecular Diels–Alder strategy to synthesize racemic maoecrystal V.[98] After initially examining an approach in which the stereocenters of ring A were present in the Diels–Alder precursor,[99] the authors developed a successful strategy in which the pivotal intramolecular Diels–Alder reaction was accomplished with an achiral substrate. In this retrosynthetic analysis, maoecrystal V was disconnected to Diels–Alder precursor **145**, which would arise from the coupling of dienoate **146** (the product of the Birch reduction of methyl benzoate) and 3-chlorocyclohexenone (**147**; Scheme 15).

Reaction of the lithium enolate of ester **146** with chloroenone **147** gave substitution product **148**. Both the ester and ketone of **148** were reduced with DIBAL-H, and the allylic alcohol derived from the ketone was selectively oxidized with MnO_2. Acylation of the primary alcohol with acid chloride **149**, followed by enol silylation, afforded Diels–Alder precursor **145**. Heating this intermediate at 166 °C gave cycloadduct intermediate **150**, which subsequently lost phenylsulfinic acid. Desilylation of intermediate **151** furnished tetracyclic ketoester **152** in 62% yield. Nucleophilic epoxidation of the enone double bond of **152** took place exclusively from the less-hindered β-face, thereby giving rise to alcohol **153** after selective iodide-mediated ring opening at the secondary carbon atom and successive dehalogenation with Bu_3SnH. Differentiation of the two diastereotopically related double bonds in **153** to form the bridging tetrahydrofuran ring and generate the required relative configuration of the C-10 quaternary stereocenter was achieved by hydroxy-directed epoxidation with *m*-chloroperoxybenzoic acid to give epoxide **154**, which cyclized when exposed to *p*-toluenesulfonic acid via intermediate **155** to deliver tetrahydrofuran **156**. Elaboration of pentacyclic intermediate **156** to *rac*-maoecrystal V, which required isomerization of the A/B ring junction to give intermediate **157** and further functional group modification, was accomplished in a number of steps.

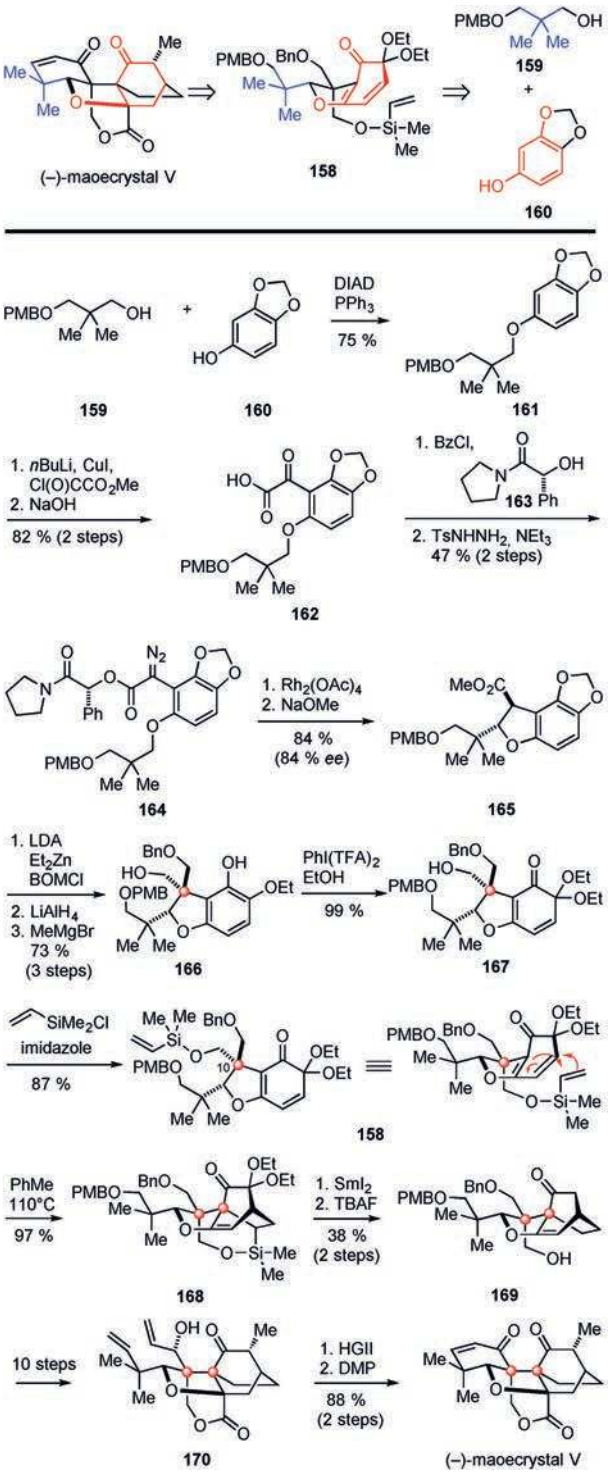
9.3. The Davies–Zakarian Synthesis

Zakarian and co-workers reported the third total synthesis of *rac*-maoecrystal V in 2013.[100] One year later, in a collaboration with the Davies group, a related strategy was employed to complete the first enantioselective synthesis of (−)-maoecrystal V.[101] With the challenge of forming the strained tetrahydrofuran ring in mind, this ring was constructed early. Thus, maoecrystal V was disconnected to Diels–Alder precursor **158** (Scheme 16). Intermediate **158** was designed with a removable silyl tether to control facial selectivity and exploit intramolecularity in the cycloaddition. Dienone **158** was seen to arise from a dihydrobenzofuran intermediate that would be constructed by using catalytic enantioselective C–H insertion chemistry developed earlier in the Davies group,[102] with sesamol (**160**) being the ultimate starting material.

To achieve high enantioselectivity in the Rh-catalyzed C–H insertion step, it was ultimately found that an auxiliary-based approach was preferable to enantioselective catalysis. Sesamol (**160**) was O-alkylated with primary alcohol **159** under Mitsunobu conditions to afford phenolic ether **161**. Directed *ortho*-metalation of **161** and addition of methyl chloroxoacetate led to pyruvic acid **162** in high yield after saponification. After esterification of **162** with mandelamide derivative **163**, conversion into the tosylhydrazone and reaction with Et_3N to eliminate tosyl sulfinate provided



Scheme 15. Synthesis of *rac*-maoecrystal V by Danishefsky and Peng. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.



Scheme 16. Synthesis of (−)-maoecrystal V by Davies, Zakarian, and co-workers. BOM = benzyloxymethyl, DIAD = diisopropyl azodicarboxylate, DMP = Dess–Martin periodinane, HGII = Hoveyda–Grubbs II catalyst, PMB = *para*-methoxybenzyl.

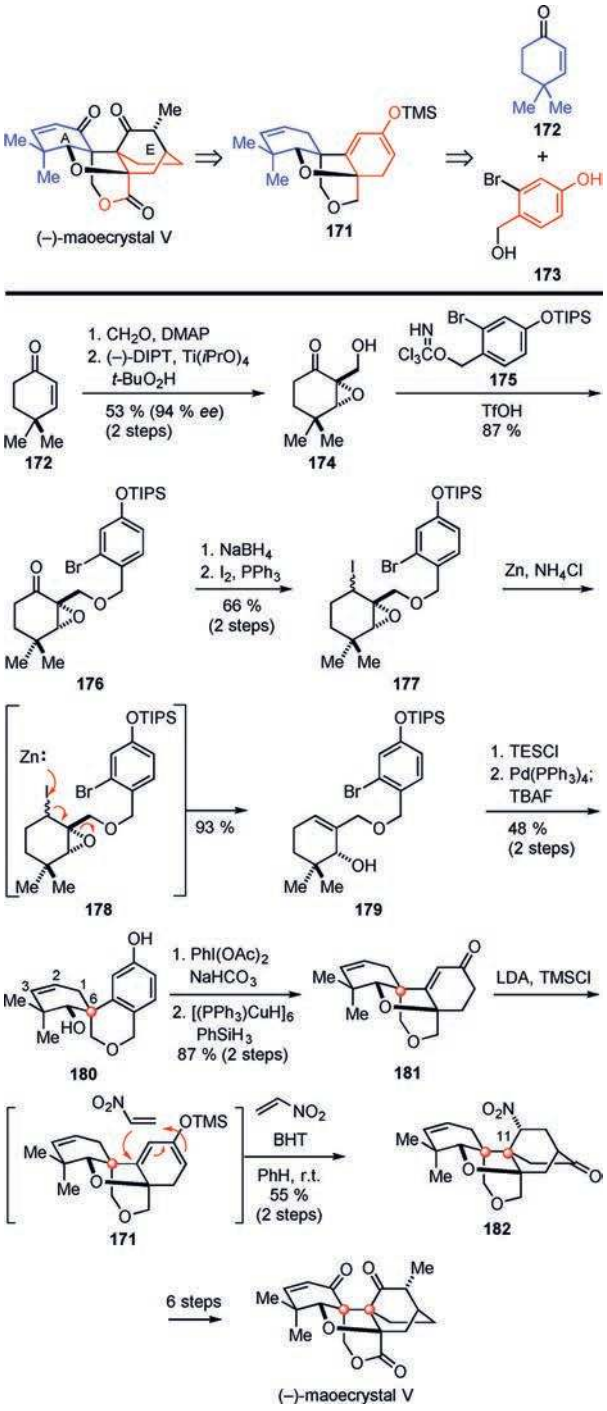
diazoester **164**. Intramolecular C–H insertion of **164** catalyzed by $[Rh_2(OAc)_4]$ gave, after base-promoted isomerization of the initially produced mixture of ester epimers, dihydrobenzofuran **165** in 84 % yield and 84 % *ee*. Installation of the C-10 quaternary stereocenter by alkylation of the zinc enolate of ester **165** took place in 95 % yield and >20:1 diastereoselectivity from the face opposite the adjacent side chain. Reduction of the ester and ring opening of the dioxolane gave dihydrobenzofuran **166**. Oxidative dearomatization of **166** provided dienenone **167**, which was coupled with chlorodimethylvinylsilane to give Diels–Alder precursor **158**. Heating this in refluxing toluene promoted intramolecular cycloaddition to provide tetracyclic product **168** and form the second of the contiguous quaternary stereocenters in near quantitative yield. Reductive removal of the diethoxy acetal upon reaction with SmI_2 and discharge of the silicon tether delivered tricycle **169**, which was advanced in several steps to intermediate **170**. Ring-closing metathesis using the Hoveyda–Grubbs II catalyst and oxidation with Dess–Martin periodinane yielded (−)-maoecrystal V.

9.4. The Thomson Synthesis

Shortly after the Davies–Zakarian synthesis appeared, a synthesis of (−)-maoecrystal V was disclosed by Thomson and co-workers.[103] In their approach, maoecrystal V was disconnected to dioxatetracyclic intermediate **171**, with the aim of fashioning the bicyclo[2.2.2]octan-2-one fragment using a bimolecular Diels–Alder reaction (Scheme 17). Disconnection of tetracyclic intermediate **171** led Thomson and co-workers to select 4,4-dimethylcyclohexenone (**172**) and bromophenol **173** as the precursors to rings A and E.

The synthesis began with the Baylis–Hillman reaction of cyclohexenone **172** with formaldehyde, followed by an asymmetric Sharpless epoxidation of the resulting allylic alcohol to give **174** in moderate yield and high enantiopurity.[104] Reaction of the product with benzyl trichloroacetimidate **175** in the presence of TfOH produced benzylic ether **176**. After reduction of the carbonyl group of **176** with $NaBH_4$, the resulting alcohol was converted under Appel conditions into alkyl iodide **177** as an inconsequential mixture of epimers. β-Iodoepoxide **177**, was reduced with elemental zinc, as depicted in **178**, to supply allylic alcohol **179**. The first quaternary stereocenter at C-6 was installed by a diastereoselective intramolecular Heck reaction of **179** from the face opposite the silyloxy substituent to give oxaspirotricyclic product **180** after removal of the silyl protecting groups. Predominant formation of the isomer with the 2,3-double bond resulted from isomerization of the intermediate Pd-hydride complex formed upon initial spirocyclization. Hypervalent iodide mediated cyclo-dearomatization of **180** formed the dienone, which was selectively reduced with Stryker's reagent to yield tetracyclic enone **181**. After formation of dienoxysilane **171**, the Diels–Alder reaction with nitroethylene took place at room temperature exclusively from the less-hindered β-face of the diene to give cycloadduct **182**, which harbors the second quaternary center at C-11, in 55% yield after acidic workup. With the pentacyclic ring system constructed, Thomson and co-workers carried cycloadduct **182** forward to complete (−)-maoecrystal V.

From a strategic point of view, it is not surprising that a Diels–Alder reaction was employed to construct the bicyclo[2.2.2]octan-2-one fragment of maeocrystal V in each synthesis. In all but the Thompson synthesis, an intramolecular Diels–Alder reaction was used. Only in the Davis–Zakarian synthesis is this reaction performed on an enantioenriched precursor that allows the stereochemical relationship of the contiguous quaternary stereocenters at C-9 and C-10 to be established with high selectivity in this step. The Thompson synthesis is distinctive in utilizing a bimolecular Diels–Alder reaction to construct the bicyclo[2.2.2]octan-2-one fragment and establish the stereochemical relationship between the contiguous quaternary stereocenters. The highly reactive cycloaddends used in this step (Danishefsky-type diene and nitroethylene) and the fact that the strained tetrahydrofuran ring was already in place are undoubtedly responsible for the cycloaddition of **171** taking place at room temperature.



Scheme 17. Synthesis of (−)-maoecrystal V by Thomson and co-workers. (−)-DIPT = (−)-diisopropyl tartrate, BHT = 2,6-di-*tert*-butyl-4-hydroxyphenol.

10. Hyperforin

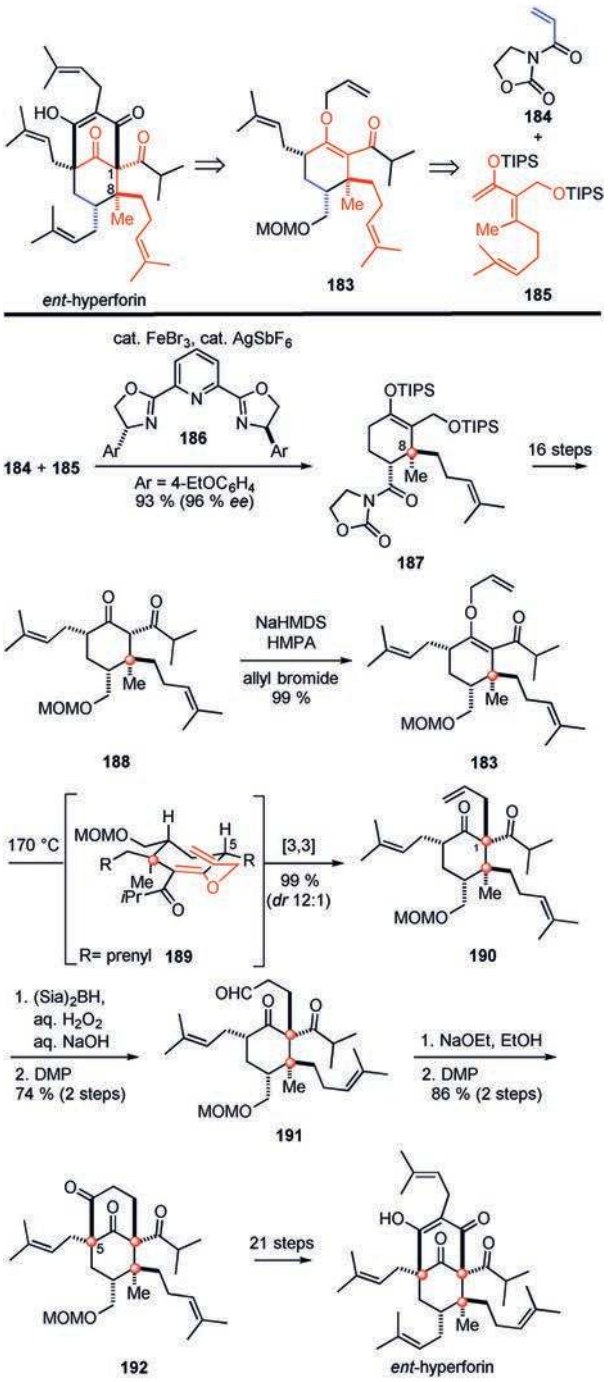
Hyperforin, a member of the polycyclic polyprenylated acylphloroglucinols (PPAPs), was isolated in 1971 from St. John's wort (*Hypericum perforatum*).[105] Its structure and absolute configuration were confirmed by X-ray crystallography in 1983.[106] Like many PPAPs, hyperforin contains a heavily substituted bicyclo[3.3.1]nonane unit. Embedded on

this skeleton are four prenyl side chains and three quaternary stereocenters, two of which are contiguous. The C-8 stereocenter incorporates a prenyl unit, a feature not found in other PPAPs—they contain a geminal dimethyl functionality at this site. Hyperforin is proposed to arise biosynthetically from the alkylation of a substituted acylphloroglucinol with geranyl pyrophosphate and prenyl pyrophosphate.[107] Hyperforin, the primary active ingredient in the popular nutraceutical St. John's wort, is responsible for the plant's well-known antidepressant property[108] as well as other biological activities.[109] Herein, we present three of the five total syntheses of hyperforin to date that employ different strategies. In the 2014 total synthesis of *rac*-hyperforin by Bellavance and Barriault,[110] the quaternary centers were introduced through a series of enolate alkylation and conjugate addition reactions. In the shortest total synthesis of racemic hyperforin to date, Ting and Maimone[111] started with 2-methyl-cyclopentenone, and effected a series of stereocontroled C–C functionalizations to reach the target in 10 steps.

10.1. The Shibasaki Synthesis

The first enantioselective synthesis was reported by Shibasaki and co-workers in 2010 and delivered *ent*-hyperforin.[112] Central to the synthesis was a catalytic enantioselective Diels–Alder reaction previously developed by the Shibasaki group.[113] Shibasaki and co-workers envisioned *ent*-hyperforin being constructed by late-stage functionalization and Claisen rearrangement of allyl vinyl ether **183**, with the cyclohexanone core of **183** being formed from a [4+2] cycloaddition between acryloyl oxazolidinone **184** and triene **185** (Scheme 18).

The Shibasaki synthesis began with an enantioselective Diels–Alder reaction between dienophile **184** and triene **185**, catalyzed by $FeBr_3$, $AgSbF_6$, and (*R*,*R*)-pybox ligand **186**, to provide *exo*-cycloadduct **187** in high yield and enantioselectivity. The geometry and steric bulk of the tetrasubstituted double bond of **185** dictates the facial approach of dienophile **184** to favor the *exo* cycloaddition mode, thereby setting the initial quaternary stereocenter at C-8.[114] Following acylation and prenylation of **187**, β-diketone **188** was selectively O-allylated to provide allyl vinyl ether **183**. Shibasaki and co-workers had previously examined the diastereoselectivity of the Claisen rearrangement in related systems and discovered strong directing effects by allylic substituents at C-5.[114] Rearrangement of allyl vinyl ether **183**, via chair transition structure **189** with the pseudoequatorial C-5-prenyl substituent, delivered β-diketone **190** in quantitative yield, thereby securing the second of the contiguous quaternary stereocenters with 12:1 diastereoselectivity. β-Diketone **190** was elaborated to aldehyde **191** in two steps, and the aldehyde smoothly underwent intramolecular aldol cyclization to form the bicyclo[3.3.1]nonane ring system as a single diastereomer now harboring the final quaternary stereocenter at C-5. After oxidation of the resulting alcohol, bicyclo[3.3.1]nonatrione **192** was carried forward to complete the total synthesis of *ent*-hyperforin.



Scheme 18. Synthesis of *ent*-hyperforin by Shibasaki and co-workers. NaHMDS = sodium hexamethyldisilazide, Sia = bis(1,2-dimethylpropyl).

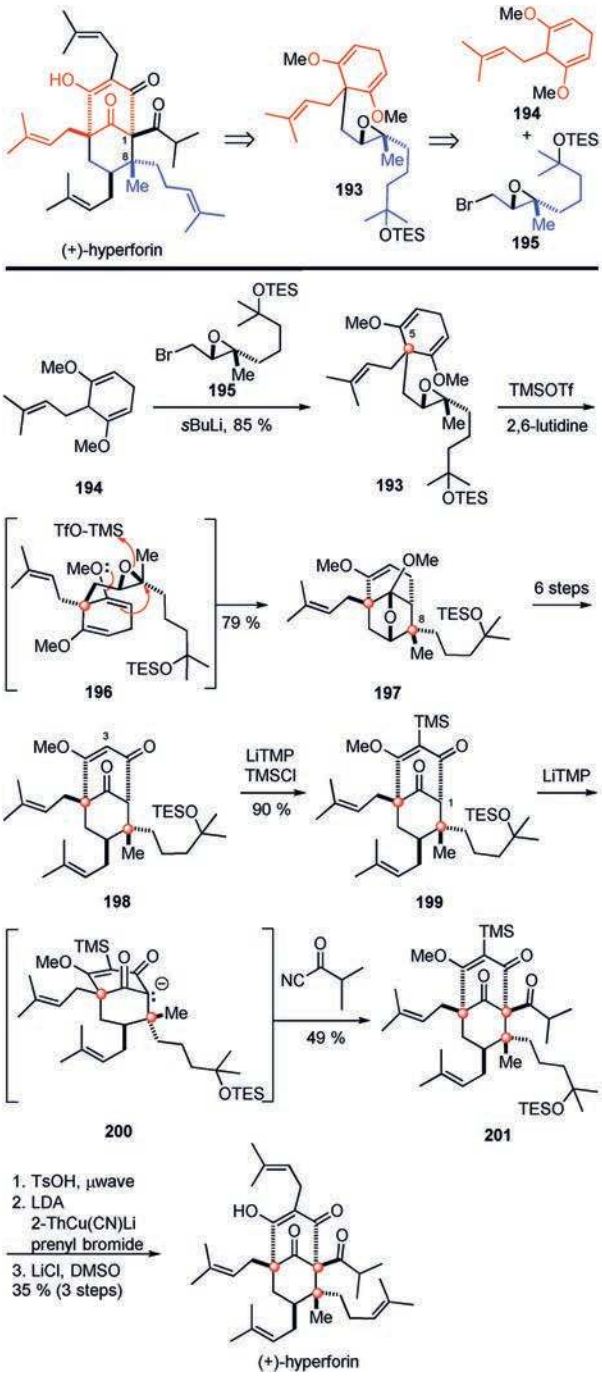
10.2. The Shair Synthesis

The second enantioselective synthesis of hyperforin by Shair and co-workers took inspiration from its proposed biosynthesis.[115] Whereas nature constructs the C-1/C-8 linkage between the contiguous quaternary stereocenters by alkylation of an acyl phoroglucinol with geranyl pyrophosphate, Shair and co-workers planned to form this bond by an epoxide-opening cyclization of **193**. This functionalized

intermediate would then be accessible by coupling diene **194** with geraniol-derived bromide **195** (Scheme 19).

The synthesis commenced with construction of diene **194** by Birch reduction and alkylation of 1,3-dimethoxybenzene. The other coupling partner, enantioenriched bromide **195**, was synthesized in four steps from geraniol, using Sharpless epoxidation to access the desired enantiomer. Base-mediated coupling of triene **194** with bromoepoxide **195** led to epoxide **193** with a prochiral quaternary center at C-5. Exposure of this intermediate to trimethylsilyl triflate at low temperature promoted diastereoselective cyclization to form exclusively bicyclo[3.3.1]nonane ketal **197** by way of the proposed chair transition structure **196**. This step both desymmetrizes the prochiral quaternary carbon atom of **193** and incorporates the quaternary stereocenter at C-8. Oxatricyclic ketal **197** was elaborated to diketone **198** with the aim of forming the second of the contiguous quaternary stereocenters by acylation of a bridgehead carbanion intermediate. To accomplish this transformation, the kinetically more acidic vinylic hydrogen atom (H-3) of **198** required masking with a trimethylsilyl group. Subsequent lithiation of 1,3-diketone **199** with lithium tetramethylpiperidide (LiTMP) and trapping with isobutyryl cyanide delivered triketone **201** in 49% yield via anion **200**.

Bridgehead functionalizations to construct contiguous quaternary carbon atoms of other PPAPs have been notoriously difficult as a result of poor overlap of the adjacent carbonyl groups and steric congestion at the bridgehead carbon atom.[110,116] Removal of protecting groups and installation of the last prenyl unit completed this synthesis of (+)-hyperforin.

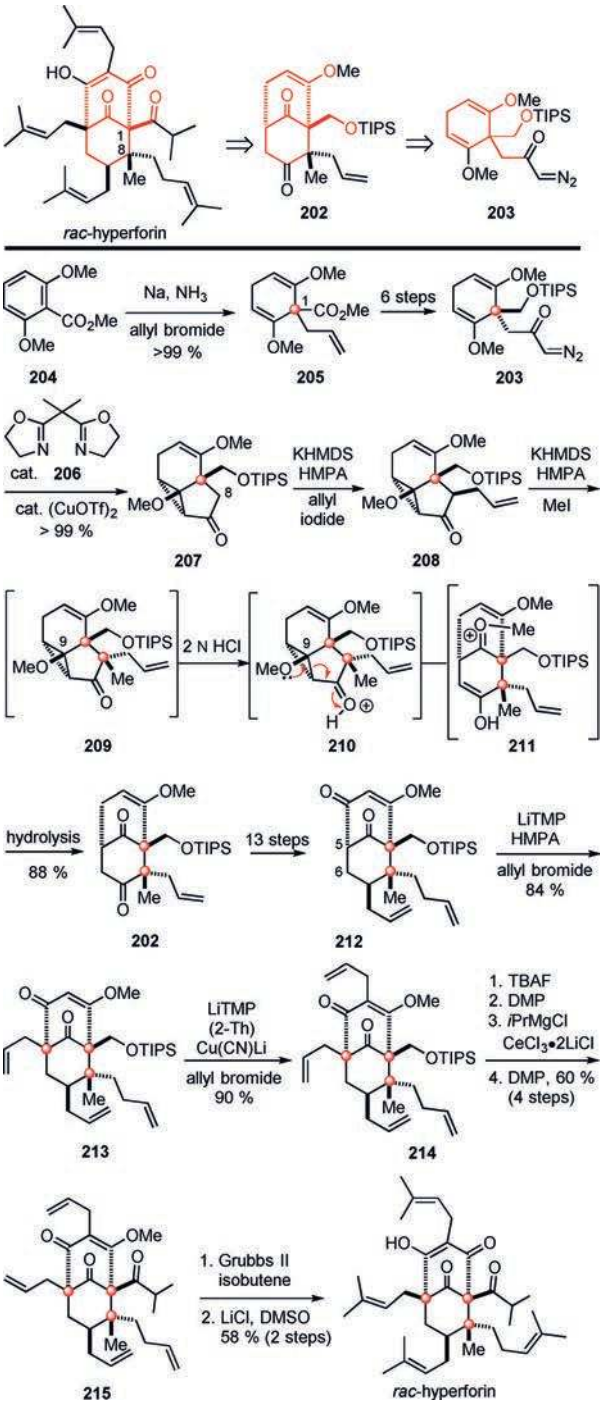


Scheme 19. Synthesis of (+)-hyperforin by Shair and co-workers. TMSOTf = trimethylsilyl trifluoromethanesulfonate, TMP = tetramethylpiperidide.

10.3. The Nakada Synthesis

Uwamori and Nakada described the synthesis of *rac*-hyperforin[117] shortly after Shair and co-workers published their enantioselective synthesis. This synthesis featured a cyclopropane ring-opening reaction previously developed in the Nakada group for the total synthesis of nemorosone.[118] In targeting hyperforin, they aimed for the late-stage installation of four prenyl groups on bicyclo[3.3.1]nonendione intermediate **202** (Scheme 20). The bicyclic scaffold of **202** would then be constructed from cyclopropanation and ring opening of their nemorosone intermediate **203**.

The synthesis of *rac*-hyperforin began by accessing α-diazoketone **203** from dimethoxybenzoate **204**.[118] In this sequence, the first quaternary center at C-1 was installed by Birch reduction of **204** and alkylation with allyl bromide to give cyclohexadiene **205**. After functionalization to α-diazoketone **203**, a copper-catalyzed intramolecular cyclopropanation with ligand **206** formed tricyclic cyclopropane **207**. The synthetic sequence to hyperforin then diverged from the nemorosone route through the use of a stepwise alkylation strategy to introduce the quaternary stereocenter at C-8. Relying on facial bias, intermediate **207** was alkylated first with allyl iodide to give ketone **208** and then methyl iodide to form product **209**, which contains the second of the contiguous quaternary stereocenters of hyperforin, in high yield and excellent stereoselectivity. Quenching the second alkylation reaction with strong acid induced opening of the cyclopropane ring (**210**) to give **211**, which upon hydrolysis provided bicyclo[3.3.1]nonane **202** in 88% yield from cyclopropane precursor **208**. Elaboration of **202** to diketone **212** and alkylation of the bridgehead position by reaction with LiTMP and allyl bromide installed the third quaternary stereocenter of **213** at C-5. This bridgehead alkylation proceeded in high yield (84%), presumably because of the absence of an adjacent quaternary stereocenter. Subsequent



Scheme 20. Synthesis of *rac*-hyperforin by Nakada and co-workers. 2-Th = 2-thienyl.

C-3 allylation required (2-Th)Cu(CN)Li and LiTMP to obtain a good yield of diallyl ketone **214**. A four-step sequence to install the isopropyl ketone then afforded triketone **215**, and the four allyl fragments were then simultaneously converted into prenyl units through cross-metathesis with isobutene. Deprotection of the resulting methyl ether completed the synthesis of *rac*-hyperforin.

The three total syntheses of hyperforin are conceptually different in the manner with which the quaternary centers were introduced. Noteworthy features of the Shibasaki synthesis are the use of a catalytic enantioselective Diels–Alder reaction to construct the cyclohexanone ring and two stereocenters, one being the C-8 quaternary stereocenter, and the reliable Claisen rearrangement to form the adjacent quaternary stereocenter at C-1. Whereas the Shibasaki synthesis constructs the bicyclo[3.3.1]nonane framework at a late stage, the Shair synthesis constructs this scaffold early on. Of particular note in Shair's short synthesis of hyperforin is an epoxide-initiated alkene cyclization that directly constructs the C-8 quaternary stereocenter while desymmetrizing the C-5 quaternary stereocenter in the process. The Nakada synthesis is noteworthy for its use of an intramolecular catalytic enantioselective cyclopropanation reaction to form a tricyclic intermediate, whose pronounced facial bias allows the C-8 quaternary stereocenter to be formed by reliable enolate alkylation reactions, with the cyclopropane ring ultimately cleaving to reveal the bicyclo[3.3.1]nonendione ring system of hyperforin.

11. Scopadulcic Acids A and B

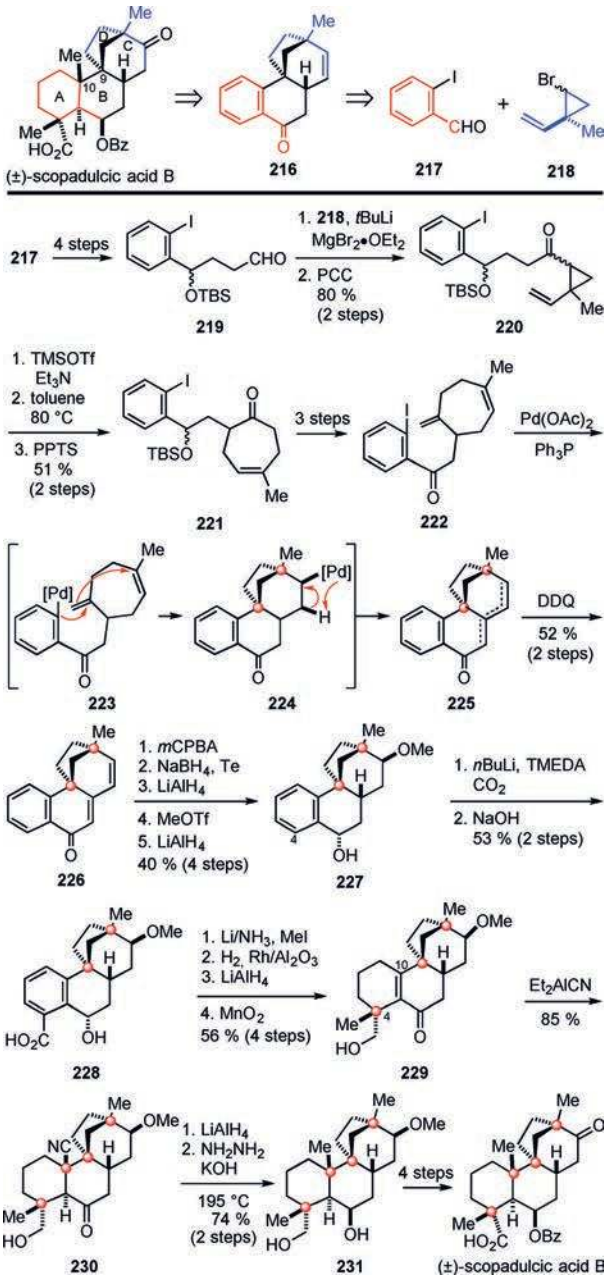
Two structurally unique tetracyclic diterpenoid acids, scopadulcic acids A and B, were reported by Hayashi et al. in 1987 from *Scoparia dul*cis *L*.[119] This flowering plant is widely distributed in the tropics and subtropics and is considered by several native populations to possess various medicinal properties.[120] Subsequent studies showed that scopadulcic acid B is a powerful inhibitor of H^+,K^+-ATPase (the proton pump for gastric acid secretion) as well as an inhibitor of herpes simplex virus type 1 and of bone resorption by osteoclast cells.[121] The structure of scopadulcic acid A was established by X-ray crystallography;[122] the absolute configuration of these diterpenoid acids was suggested on the basis of circular dichroism (CD) measurements and later confirmed by enantioselective synthesis.[123] The bicyclo-[3.2.1]octane subunit of scopadulcic acids A and B is also found in tetracyclic diterpenes such as aphidicolin and stemarin. The structural feature unique to the scopadulcic acids is the presence of this fragment on a tricyclic hydrophenanthrene backbone.

11.1. The Overman Synthesis of rac-Scopadulcic Acid B

The synthesis of *rac*-scopadulcic acid B, the first total synthesis of a scopadulan diterpene, was reported by Overman et al. in 1993 (Scheme 21).[124] The plan deferred construction of the contiguous C-10 quaternary center to a late stage, hence scopadulcic acid was disconnected to tetracyclic intermediate **216**. A cascade intramolecular Heck reaction was envisaged to construct rings B, C, and D of the scopadulan ring system. As sequential Heck cyclizations of structurally simple dienes had only been described recently,[125] a simple benzene ring was chosen for the ring A fragment to allow the pivotal cascade cyclization to be quickly evaluated. The cycloheptene ring of the Heck cyclization precursor was seen to arise from a divinylcyclopropane

rearrangement, thus 2-iodobenzaldehyde (**217**) and vinylcyclopropyl bromide **218** were identified as the starting materials.

Bromide **218** was available in two steps from isoprene as a 3:2 mixture of epimers favoring the required *cis* stereoisomer. Coupling of aldehyde **219** (available in four steps from **217**) with the cyclopropyl Grignard reagent generated from **218** and oxidation of the alcohol product delivered cyclopropyl ketone **220**. Enol silylation of **220** and subsequent heating to 80 °C promoted divinylcyclopropane rearrangement to give, after desilylation, cycloheptenone **221**. After advancing this product to iodide **222**, the cascade Heck cyclization was accomplished in 80–85 % yield to form a mixture of tetracyclic alkene products **225** bearing two quaternary centers via carbopalladium intermediates **223** and **224**, which converged to dienone **226** after dehydrogenation of the crude Heck product with DDQ. The required oxidation in the C ring and the *trans*-C/D ring fusion was then installed by way of the epoxide formed by electrophilic epoxidation of the distal double bond of dienone **226**. The pseudoequatorial alcohol of the resulting tetracyclic intermediate **227** was then exploited to regioselectively carboxylate ring A at C-4, thereby allowing the aromatic ring to be dearomatized and the C-4 quaternary center introduced by Birch reduction and methylation of the resulting 3-carboxypentadienyl anion intermediate. After modification of the oxidation state, enone **229** was formed in 56 % overall yield from hydroxy acid **228**. At this point, the severe challenge of constructing the second of the contiguous quaternary stereocenters at C-10 was encountered. Although Me_2CuLi added in high yield to a structurally related tetrasubstituted decalin enone, this reagent, and many other regents commonly used for conjugate addition, failed to introduce a methyl substituent at C-10 of enone **229**.



Scheme 21. Synthesis of *rac*-scopadulcic acid B by Overman and coworkers. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, PPTS = pyridinium *p*-toluenesulfonate.

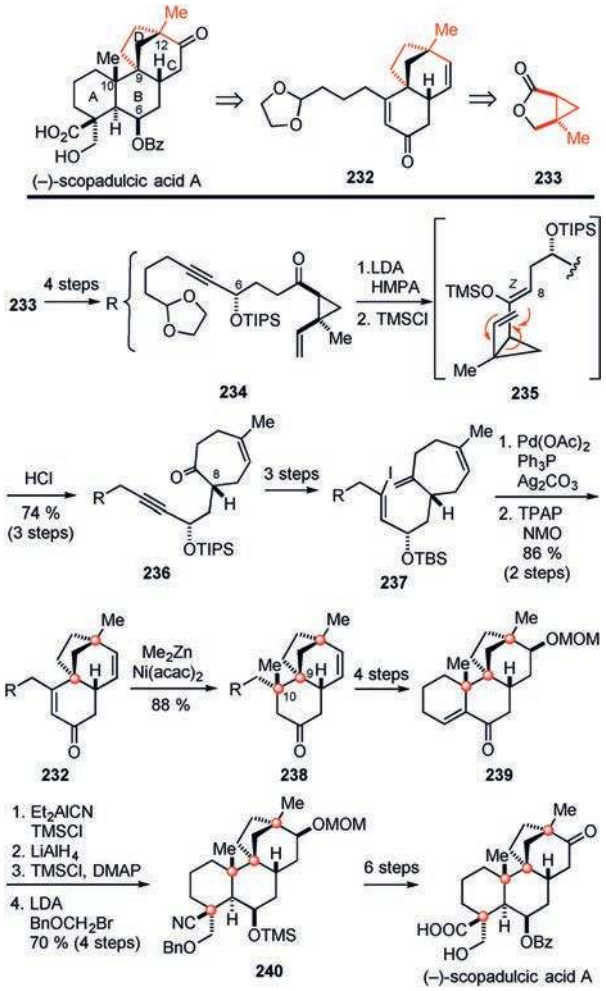
Overman and co-workers also reported in 1993 a second-generation approach to the scopadulcic acids, culminating in the synthesis of *rac*-scopadulcic acid A.[127] In 1999, this strategy was adapted to synthesize both natural (−)-scopadulcic acid A and its enantiomer.[123] To allow the contiguous quaternary center relationship to be formed directly while avoiding the multistep sequence required in their earlier approach to functionalize ring A, (−)-scopadulcic acid A was disconnected to tricyclic dienone **232** (Scheme 22). As in their inaugural synthesis, rings B–D would be formed by an intramolecular cascade Heck cyclization. The cycloheptene ring of the bicyclization precursor would again be constructed by a divinylcyclopropane rearrangement, thus (1*S*,5*R*)-5-methyloxabicyclo[3.1.0]hexanone (**233**), whose synthesis by catalytic enantioselective intramolecular cyclopropanation had been reported previously,[128] was identified as the starting material.

The synthesis began by converting enantiomerically pure lactone **233** into cyclopropyl ketone **234**. The cycloheptenone ring and critical C-8 stereocenter were formed by stereoselective enolization of ketone **234** and O-silylation to form (*Z*)-

11.2. The Overman Synthesis of (−)-Scopadulcic Acid A

enoxysilane intermediate **235**, which rearranged upon warming to give cycloheptenone **236** in high yield. After elaborating **236** to trienyl iodide **237**, a Pd-catalyzed cascade cyclization and oxidation of the tricyclic alcohol product gave dienone **232** in 86% yield. In stark contrast to tetracyclic enone **229** (Scheme 21), **232** reacted successfully with Me_2CuLi to install the methyl group at C-10. However, this procedure was found to be less reliable than the Ni-catalyzed conjugate addition of Me_2Zn,[129] which reliably gave tricycle **238**, which contains the contiguous C-9 and C-10 quaternary stereocenters, in 88% yield. The success in adding a methyl group to enone **232**, and the failure of identical reactions with the tetrasubstituted enone **229**, likely reflects the more facile coordination of the less-hindered enone double bond of **232** with transition metals. After introduction of oxygen functionality in ring C, ring A was formed by intramolecular aldolization/dehydration to provide tetracyclic intermediate **239**. The final quaternary center was then incorporated by conjugate addition of cyanide, again using the Nagata reagent, followed by selective equatorial-face reduction of the ring B ketone. After protection of the resulting alcohol, the hydroxymethyl substituent was installed by alkylation of the α-cyanolithium intermediate from the face opposite the angular methyl group to give **240** in good overall yield. The enantioselective total synthesis of (−)-scopadulcic acid A was completed from this intermediate by routine functional-group modifications.

In addition to the efficient intramolecular Heck cyclization cascade of this second-generation approach, the strategic choice of chiron **233** is noteworthy, as neither of the stereogenic centers of this precursor are retained in the natural product target, although two carbon atoms of this fragment become the C-9 and C-12 quaternary stereocenters of the bicyclo[3.2.1]octane unit. The stereocenters of cyclopropane **234** regulate the formation of the C-8 stereocenter, which subsequently controls the evolution of the four quaternary stereocenters of scopadulcic acid A. A noteworthy feature of the strategy employed in this synthesis was the opportunity to also fashion the unnatural enantiomer of scopadulcic acid A by rearrangement of the divinylcyclopropane moiety of the (*E*)-enoxysilane intermediate formed upon soft enolization of the C-6 epimer of cyclopropyl ketone **235** with trimethylsilyl triflate and triethylamine.[123]

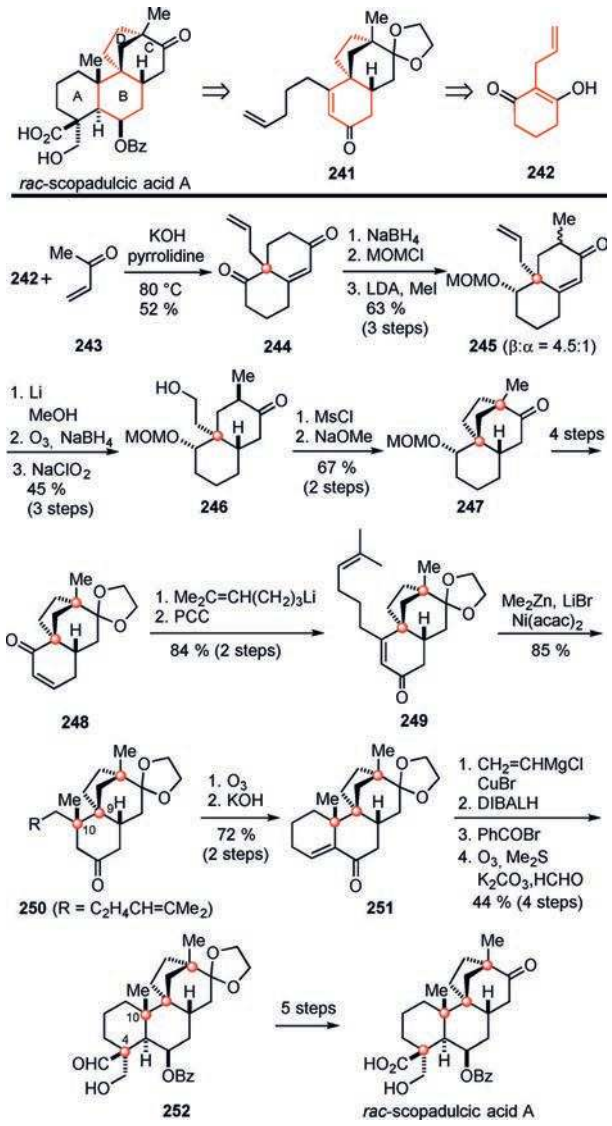


Scheme 22. Synthesis of (−)-scopadulcic acid A by Overman and coworkers. acac = acetylacetonate, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

11.3. The Ziegler Synthesis of rac*-Scopadulcic Acid A*

Ziegler and Wallace reported their total syntheses of *rac*-scopadulcic acids A and B two years after Overman and coworkers published the inaugural total syntheses of racemic scopadulcic acids A and B.[130] As in the Overman synthesis, these authors disconnected scopadulcic acid A to an enone intermediate containing rings B, C, and D. This intermediate, **241**, was further disconnected to 2-allylcyclohexan-1,3-dione **242** (Scheme 23).

Robinson annulation of dione **242** with methyl vinyl ketone (**243**) gave decalin dione **244**,[131] whose nonconjugated ketone carbonyl group was masked by reduction and protection of the resulting alcohol as a methoxymethyl ether. Methylation of the kinetically favored enolate of this product gave bicyclic intermediate **245** as a mixture of methyl epimers. The major isomer with a pseudoequatorial β-methyl substituent underwent stereoselective conjugate reduction to install the *trans*-C/D ring fusion. Three steps, terminating with selective oxidation of the secondary alcohol, advanced **245** to decalone **246**. Intermediate **247**, containing rings B, C, and D of scopadulcic acid A, was then formed in 74% yield by intramolecular alkylation of the keto mesylate generated from **246** upon reaction with sodium methoxide and methanol. The tricyclic product resulting from cyclization of the alternate, less-substituted, enolate intermediate was produced only as a minor product. In four routine steps, **247** was advanced to enone **248**. The addition of 4-pentenyllithium and oxidative transposition of the allylic alcohol gave tetracycle **241** (Scheme 23, top line). The authors were surprised to find that the C-10 quaternary stereocenter was not incorporated upon reaction of **241** with Me_2CuLi, $Me_2CuCNLi_2$/$BF_3{\cdot}Et_2O$ or $Me_3Al/[Ni(acac)_2]$. As this result stood in stark contrast to a closely related success in the Overman synthesis, the authors conjectured that the failure of the Ni-mediated methylation was the result of coordination of the terminal vinyl group of **241** with a Ni intermediate. To minimize such



Scheme 23. Synthesis of *rac*-scopadulcic acid A by Ziegler and Wallace.

an interaction, the related enone **249** containing a pendant trisubstituted double bond was prepared in a similar fashion and in 84% yield from **248**. As hoped, enone **249** underwent conjugate addition of a methyl nucleophile in high yield upon reaction with Me_3Al and [$Ni(acac)_2$]. The resulting product **250**, now harboring the contiguous quaternary centers at C-9 and C-10, was elaborated to *rac*-scopadulcic acid A following the general strategy of the earlier Overman synthesis. In this case, tetracyclic enone **251** was fashioned from **250** by oxidative cleavage of the alkene, intramolecular aldol cyclization, and dehydration. Introduction of the final quaternary stereocenter at C-4 was accomplished by conjugate addition of vinylcuprate to enone **251**, stereoselective reduction of the carbonyl group on ring B, and benzoylation. In a noteworthy one-pot process, the vinyl group of the resulting intermediate was cleaved with ozone to afford the corresponding aldehyde, which—after purging with nitrogen to remove excess ozone—was exposed to K_2CO_3 and formaldehyde to give aldol product **252** in 44% yield from **251**. The stereoselectivity in introducing this final quaternary stereocenter was the result of the aldol condensation occurring from the enolate face opposite the angular C-10 methyl group. The β-hydroxyaldehyde intermediate **252** served as a precursor of *rac*-scopadulcic acid A (as depicted in Scheme 23), and also of *rac*-scopadulcic acid B and *rac*-scopadulciol.

All three syntheses postponed installing the C-10 stereocenter until after construction of a tricyclic BCD fragment and relied on conjugate addition to enones to fashion the C-4 and C-10 quaternary stereocenters. A noteworthy aspect of the Ziegler synthesis is the rapid construction of the tricyclic BCD fragment containing two quaternary stereocenters, with the first arising from a classical Robinson annulation reaction. Overman, on the other hand, used a cascade Heck cyclization to construct a related tricyclic BCD fragment. Also notable in Overman's second-generation approach and Ziegler's synthesis is the success realized in introducing the methyl substituent at the quaternary atom C-10 by conjugate addition of a methyl nucleophile to an enone intermediate with a trisubstituted double bond, whereas related conjugate addition reactions to enone intermediates having tetrasubstituted double bonds failed.

12. Crinipellins A and B

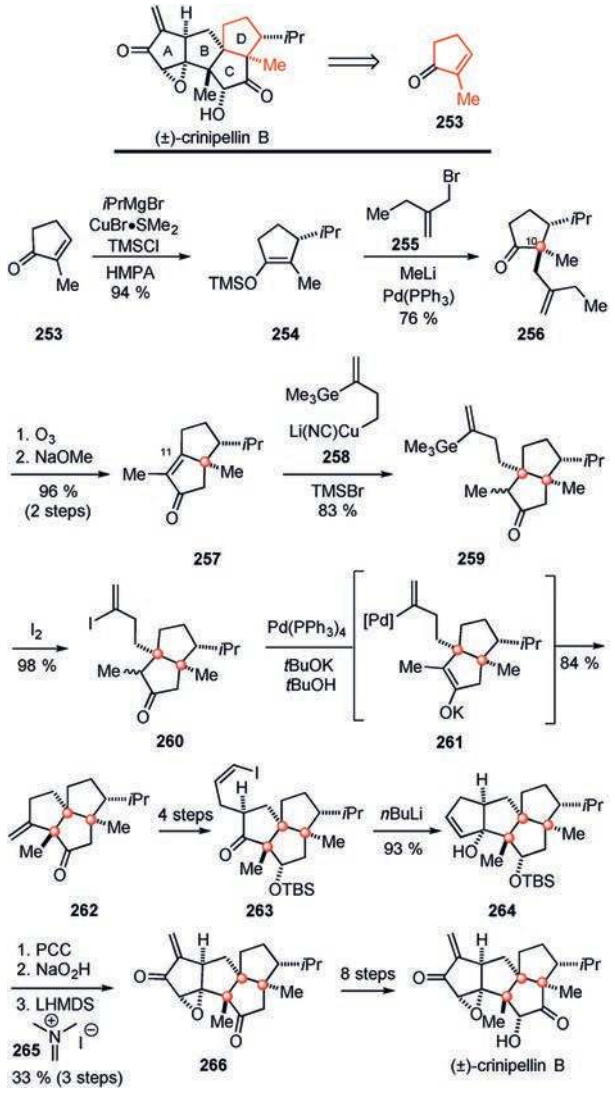
The first natural products containing a tetraquinane skeleton, crinipellins A and B, were described by Steglich and co-workers in 1985 from cultures of the fungus *Crinipellis stipitaria*.[132] The potent antibiotic activity of what turned out to be the O-acetyl derivative of crinipellin B had been described six-years earlier.[133] The relative configuration of crinipellin B was defined by X-ray crystallography, although the absolute configuration of the crinipellins had to wait almost 30 years for elucidation by total synthesis.[134] Crinipellins A and B feature four rings containing both linear and angular triquinane motifs as well as eight contiguous stereocenters, three of which are contiguous quaternary stereocenters at the junctures of rings B, C, and D. The crinipellins also contain a variety of oxygenation states: epoxide, alcohol, and two ketone carbonyl groups. Only one total synthesis of *rac*-crinipellin A and one of (−)-crinipellin B have been reported. Key steps of these syntheses are highlighted below.

12.1. The Piers Synthesis

Piers and Renaud reported in 1993 the synthesis of *rac*-crinipellin B, the first total synthesis of a crinipellin natural product.[135] They constructed rings C, B, and A in sequential fashion starting with 2-methyl-cyclopent-2-one (**253**; Scheme 24).

The synthesis began with copper-mediated conjugate addition of isopropylmagnesium bromide to **253**. The enoxysilane product **254** was converted into the corresponding lithium enolate, which underwent stereoselective Pd-mediated coupling with allylic bromide **255** to give cyclopentanone **256**, which contains the first of the three contiguous quaternary stereocenters at C-10. Ozonolysis to reveal the 1,4-

diketone and cyclization with NaOMe in MeOH delivered pentalenone **257** as a prelude to a second conjugate addition to form the quaternary stereocenter at C-11. Despite the presence of the adjacent C-10 quaternary carbon atom and the β-disubstitution of the enone, Lewis acid mediated addition of cuprate **258**[136] to enone **257** proceeded in excellent yield to form ketone **259**. As previously discovered by Piers and Marais, this conjugate addition occurred exclusively from the convex face to form the *cis*-pentalene product.[136b] Following germanium–iodide exchange, vinyl iodide **260** underwent Pd-catalyzed enolate vinylation[136b] to yield triquinane **262** by way of vinylpalladium enolate intermediate **261**. Subsequent functionalization of triquinane **262** gave vinyl iodide **263**. Lithium–iodide exchange of **263** and intramolecular addition of the vinyllithium intermediate to the carbonyl group fashioned ring A, thereby giving tetracyclic alcohol **264**. Exposure of the tertiary allyl alcohol **264** to excess pyridinium chlorochromate formed the rearranged enone and unexpectedly transformed the siloxy ether of ring B to a carbonyl group. Epoxidation of this product under basic conditions and introduction of the α-methylene group with Eschenmoser's salt (**265**) gave epoxide **266**, which upon additional oxidation and functional-group modification yielded *rac*-crinipellin B.



Scheme 24. Synthesis of *rac*-crinipellin B by Piers and Renaud. LHMDS = lithium hexamethyldisilazide.

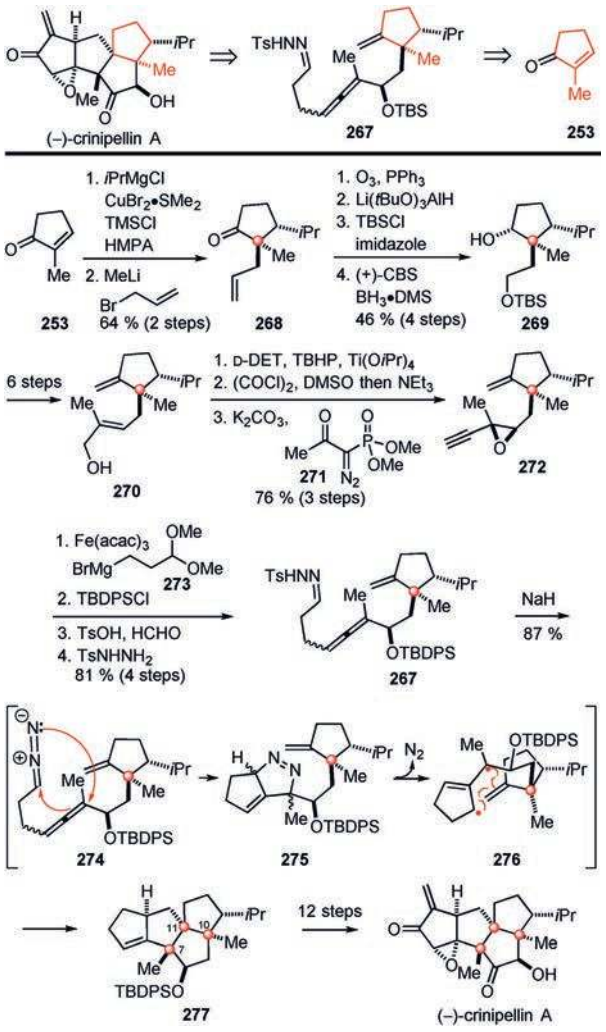
The most noteworthy feature of the Piers synthesis is the construction of triquinane **262**, which has three contiguous quaternary stereocenters, in only 7 steps and 47 % overall yield from 2-methyl-2-cyclopentenone (**253**). Key to this remarkable sequence was the facility of cuprate conjugate additions to five-membered enones, which even took place in high yield to construct contiguous quaternary stereocenters with an enone substrate **257** containing a tetrasubstituted double bond. Also noteworthy was this early use of a palladium-catalyzed coupling of a basic enolate and a vinyl halide to fashion the third ring and third contiguous quaternary carbon center.

12.2. The Lee Synthesis

Lee and co-workers reported the enantioselective total synthesis of (−)-crinipellin A in 2014.[134] In their approach (Scheme 25), the tetraquinane framework of the diterpenoid would be constructed from monocyclic tosylhydrazone **267** by a cascade sequence involving the intermediacy of a trimethylenemethane diyl.[137] Synthesis of tosylhydrazone **267** was foreseen to arise from cyclopentenone **253** in a fashion similar to the opening steps of the Piers synthesis.

The Lee synthesis commenced by converting cyclopentenone **253** into enantioenriched cyclopentanol **269** by a known seven-step sequence featuring CBS reduction for enantioenrichment.[138,139] Thereby, the first quaternary center at C-10 was installed by cuprate addition to cyclopentenone **253**, enolization, and alkylation with allyl bromide to yield cyclopentanone **268**. Further functionalization and chemical racemate resolution of ketone **268** via alcohol **269** led to allylic alcohol **270**. Sharpless asymmetric epoxidation of allylic alcohol **270** followed by oxidation and Seyferth–Gilbert homologation with the Ohira–Bestmann reagent (**271**) provided alkynyl epoxide **272**.

The allene was introduced as a 1:1 mixture of stereoisomers by an Fe-promoted reaction of **272** with Grignard reagent **273**. Subsequent functional-group modification led to tosyl hydrazone **267**, which upon heating with NaH in refluxing toluene gave tetraquinane **277** in 87 % yield. This remarkable stereoselective transformation is believed to occur by a base-promoted elimination to generate alkyl diazo intermediate **274**, which cycloadds to the distal allene double bond to yield dihydropyrazole **275**. Loss of nitrogen from **275** generates a diyl intermediate, which undergoes formal [3+2] cycloaddition via the favored chair conformer **276** to yield tetraquinane **277**, thereby forming three C–C bonds as well as the A, B, and C rings. The last step of this sequence constructs the two final quaternary stereocenters of the crinipellin skeleton (C-7 and C-11). Although diastereoselectivity in forming the C-11 stereocenter is influenced by the adjacent C-10 stereocenter, Lee and co-workers note that the relative configuration of the oxygen substituent and its bulky TBDPS protecting group are necessary to realize high



Scheme 25. Synthesis of (−)-crinipellin A by Lee and co-workers. D-DET = D-diethyl tartrate, TBHP = *tert*-butylhydroperoxide.

stereoselection in the formation of tetraquinane **277**. Introduction of the three remaining oxygen substituents and the exocyclic methylene group completed the enantioselective synthesis of (−)-crinipellin A.

The strategy of the Lee synthesis provides a striking contrast to the linear approach to ring formation utilized by Piers. In the approach by Lee and co-workers, three of the four five-membered rings are fashioned in the one-step conversion of a tosylhydrazone into a tetraquinane. In this remarkable transformation, the ultimate 1,3-diyl–alkene cycloaddition step forms two rings and two of the three contiguous quaternary carbon atoms of the tetraquinane target.

13. Chimonanthines

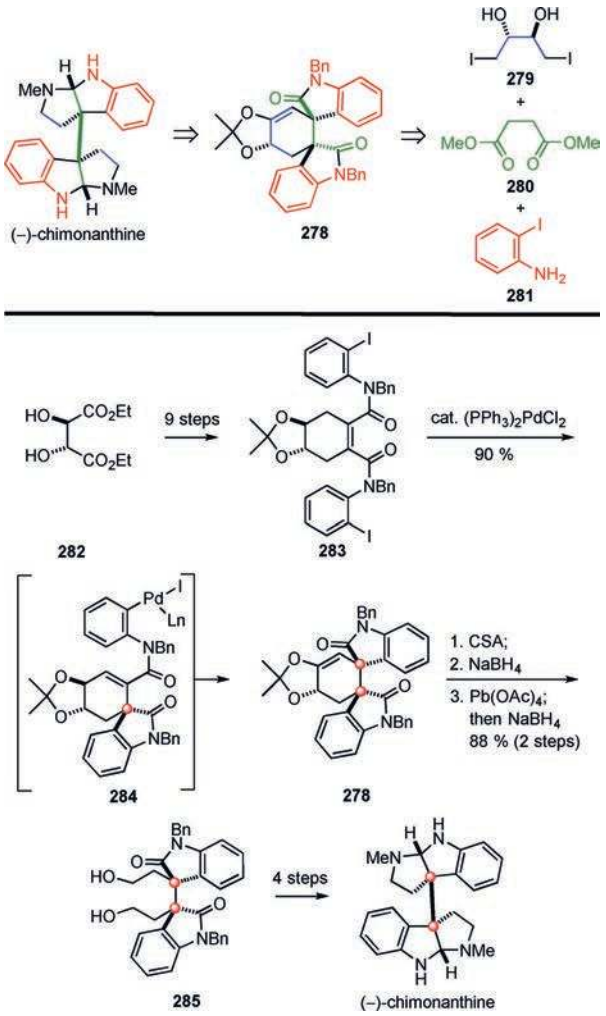
The chimonanthines have a distinctive hexacyclic structure in which two pyrrolidino[2,3-*b*]indoline (cyclotryptamine) subunits are linked at the benzylic quaternary carbon atoms. They were first isolated from plants,[140] and subsequently identified in fungi and Colombian poison-dart frogs.[141] All three possible stereoisomers—*meso* and a pair of C_2-symmetric enantiomers—are found in nature. Hexacyclic chimonanthine fragments are core units in many larger polyindoline alkaloids such as hodgkinsine and the quadrigemines. The structure of (−)-chimonanthine was settled in 1962 by an early application of X-ray crystallography.[142] The chimonanthines are undoubtedly biosynthesized from two tryptophan units, although details of the biosynthetic pathway, in particular how the contiguous quaternary carbon atoms are linked, are not known. The challenges involved in linking two cyclotryptophan fragments to form the weak C-3a/C-3a′ bond that links the two contiguous quaternary carbon atoms has been discussed in some detail.[143] Although non-stereocontrolled syntheses of chimonanthines were reported as early as 1964,[144] the first stereocontrolled synthesis, that of *meso*-chimonanthine, was not reported until 1996.[145] Soon thereafter, stereo- and enantiocontrolled syntheses of the C_2-symmetric enantiomers were developed. Key steps in four of these enantioselective syntheses are discussed.

13.1. The Overman Syntheses of (−)- and (+)-Chimonanthine

The first enantioselective syntheses of a C_2-symmetric chimonanthine was published in 1999 by Overman et al.[146] In this approach, (−)-chimonanthine was disconnected retrosynthetically to hexacyclic precursor **278**, with the aim of elaborating the oxindole rings to cyclotryptamine fragments in a classical fashion[147] after cleavage of the central six-membered ring (Scheme 26). It was visualized that **278** would then arise from a diastereoselective double Heck cyclization, and that the Heck cascade precursor could be constructred from tartrate-derived diiodide **279**, dimethyl succinate (**280**), and 2-iodoaniline (**281**).

Early exploration of this approach showed that the desired *anti* arrangement of the spirooxindole units in Heck product **278** was obtained when the *trans*-cyclohexene diol was masked as an acetonide. The synthesis began with diethyl L-tartrate (**282**), which after transformation to the acetonide variant of diiodide **279**, was dialkylated with diester **280** and the resulting cyclohexane product advanced to diamide **283**. Cascade Heck cyclization of this diiodide gave a single pentacyclic product **278** in 90% yield via tricyclic palladium intermediate **284**, thereby constructing both contiguous quaternary stereocenters in a single step. Removal of the acetonide group of **278**, reduction of the ketone, andcleavage of the resulting six-membered ring diol with $Pb(OAc)_4$, and hydride reduction gave diol **285** in high yield. In five additional steps, **285** was advanced to (−)-chimonanthine.

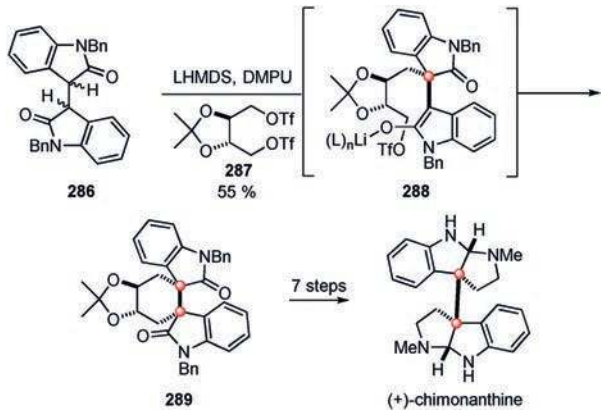
The subtle factors that control the stereoselection in the cascade Heck cyclization of diiodide **283** were subsequently studied in detail.[148] The acetonide plays an essential role, as protection of the oxygen substituents as benzyl ethers yields a major cyclization product having *syn*-oriented spirooxindole units, with this product being a precursor of *meso*-chimonanthine.[146]



Scheme 26. Synthesis of (−)-chimonanthine by Overman et al. using a diasteroselective Heck cyclization cascade. CSA = camphorsulfonic acid.

One year later, Overman et al. reported a second construction of C_2-symmetric chimonanthines.[149] The strategy was similar to that depicted in Scheme 26, but in this approach a cyclohexane intermediate having *anti*-oriented spirooxindole units was fashioned by dialkylation of dioxindole **286** with L-tartrate-derived dielectrophile **287** (Scheme 27).

This synthesis began with the preparation of dioxindole **286** in three steps and 71% yield from oxindole and isatin. Choice of the counterion and reaction conditions was critical to the success of the diastereoselective dialkylation reaction. To favor the second alkylation proceeding as depicted in representation **288,** chelation of the enolate counterion with the carbonyl group of the initially formed 3,3-dialkylspirooxindole had to be prevented. Use of a lithium counterion and the additive 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU), known to tightly bind lithium cations, was found to be essential. Under the optimized conditions depicted in Scheme 27, C_2-symmetric product **289** and its *meso* stereoisomer were formed in a 2.8:1 ratio. Factors that govern the diastereoselection in the first alkylation to generate intermediate **288** with high selectivity remain poorly understood.



Scheme 27. Synthesis of (+)-chimonanthine by Overman et al. by using a diasteroselective dialkylation strategy.

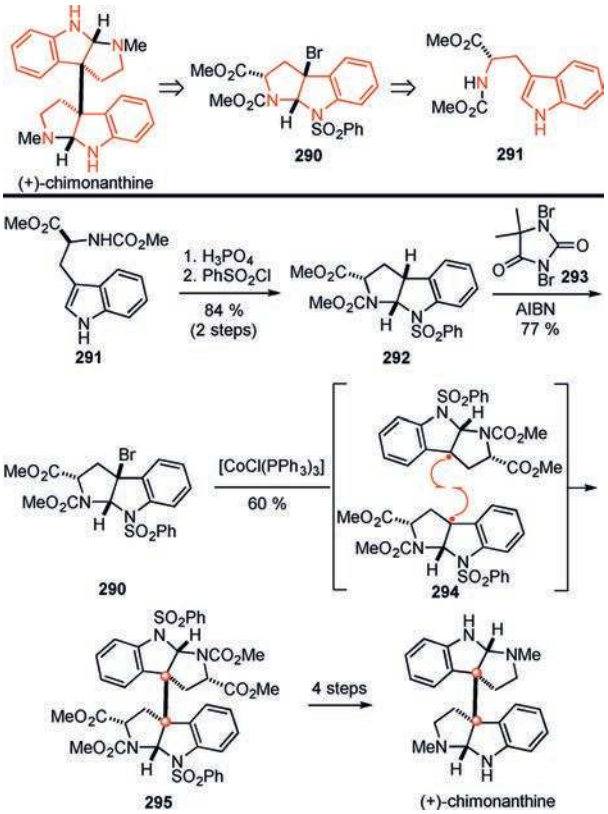
13.2. The Movassaghi Synthesis of (+)-Chimonanthine

In 2007, Movassaghi and Schmidt disclosed a convergent, efficient strategy to synthesize (+)-chimonanthine.[150] A variation of this strategy was subsequently employed by Ma and co-workers to prepare (−)-chimonanthine.[151] In the approach by Movassaghi and Schmidt, the bond connecting the contiguous quaternary stereocenters is retrosynthetically disconnected—in a fashion mimicking a plausible biosynthetic dimerization of cyclotryptamine tertiary radicals—to give tertiary bromide **290** (Scheme 28). To allow rapid access to the cyclotryptamine unit of **290** in enantiomerically enriched form, it would be assembled from a derivative of natural tryptophan **291**.

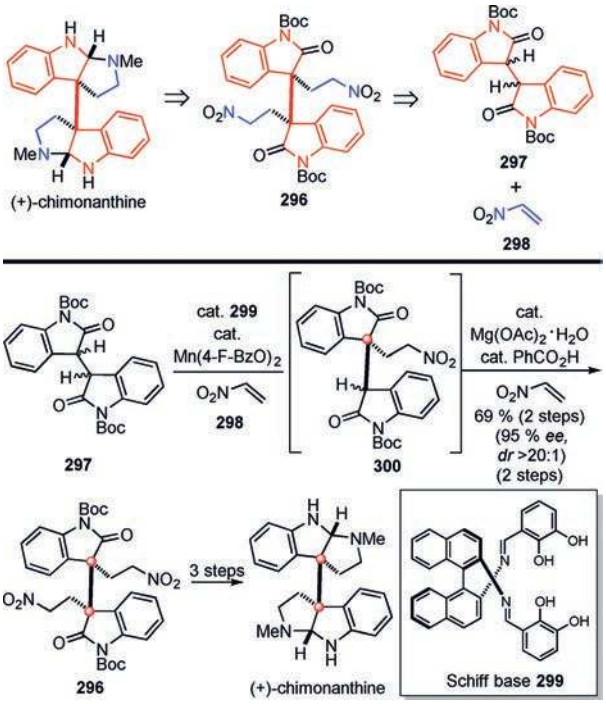
The synthesis commenced by a known diastereoselective isomerization of commercially available tryptophan derivative **291** to its cyclotryptophan isomer, followed by protection of the indoline nitrogen atom to give **292** in high yield.[152] Stereoselective halogenation at the benzyl position using dibromohydantoin **293**[153] then delivered bromide **290** in three steps and 65% overall yield from **291**. In the key step, the reaction of bromide **290** with $[CoCl(PPh_3)_3]$ generated tertiary radical **294,** which upon dimerization gave bis(pyrrolidinoindoline) product **295** in a remarkable 60% yield. The high diastereoselectivity observed in forming the contiguous quaternary stereocenters is a result of dimerization occurring from the more accessible convex face of each cyclotryptophan fragment. In four additional steps, the ester group was removed and the methyl groups were installed to yield (+)-chimonanthine in a notably concise sequence.

13.3. The Kanai–Matsunaga Synthesis of (+)-Chimonanthine

Kanai, Matsunaga, and co-workers reported the synthesis of (+)-chimonanthine in 2012 by a strategy quite different from those discussed thus far, in which enantioselective catalysis plays a key role.[154] In this approach, chimonanthine was retrosynthetically disconnected to dioxindole **296**, which would be formed from dioxindole precursor **297** by two Michael additions to nitroethylene (**298**; Scheme 29).[155] In this key step, the first Michael reaction would dictate the



Scheme 28. Synthesis of (+)-chimonanthine by Movassaghi and Schmidt.



Scheme 29. Synthesis of (+)-chimonanthine by Kanai, Matsunaga, and co-workers.

enantioselectivity and the second Michael reaction would dictate the diastereoselectivity.

With access to dioxindole **297** in two steps from commercial materials, initial studies focused on accomplishing the double Michael addition in a single step to form C_2-symmetric product **296**. Using a manganese co-catalyst and the Schiff base **299**, the double-Michael product **296** was obtained in both modest yield (44%) and diastereoselectivity (5:1). The authors proposed that steric congestion created by the first quaternary stereocenter limits the efficacy of the second Michael addition. A two-step sequence was then developed, in which product **300** of the first enantioselective Michael addition (after filtration to remove the catalysts) was treated with a more reactive catalyst to facilitate the second highly diastereoselective Michael addition, thereby giving dioxindole product **296** in 69% yield and 95% *ee* with >20:1 diastereoselectivity. Dioxindole **296** was subsequently advanced to complete an especially short synthesis of (+)-chimonanthine.

Although both contiguous quaternary stereocenters are formed in a single step (or a one-pot sequence in the Kanai–Matsunaga synthesis) in these four syntheses, the strategies employed by the three research groups are notably different. In the Overman syntheses, the contiguous quaternary carbon atoms are formed by diastereoselective reactions in which stereocontrol in the critical first C–C bond-forming step is dictated by two oxygen-containing stereocenters that are not found in the chimonanthine products. The Movassaghi synthesis, in which the key step is dimerization of a persistent tricyclic tertiary-benzylic radical intermediate,[156] illustrates the ultimate in convergent synthesis strategy. The notably short Kanai–Matsunaga synthesis exploits enantioselective catalysis to incorporate the contiguous quaternary stereocenters on a readily available dioxindole precursor. The fact that the second catalytic enantioselective Michael reaction of intermediate **300** required more forcing conditions than the first, provides yet another example of the challenge in forming contiguous quaternary carbon atoms.

14. Epilogue

When the target molecule of a chemical synthesis endeavor contains multiple quaternary carbon stereocenters, how to construct such highly functionalized segments becomes a central focus of synthesis planning.[10] When these quaternary carbon atoms are contiguous and stereogenic, the hindered environment surrounding them renders such constructions in a stereoselective manner unusually difficult.[10e] The syntheses of natural products of extraordinary structural complexity highlighted in this Review reveal how this challenge can be met successfully. The remarkable creativity of synthetic chemists to address such challenges in various ways over the past six decades is striking.[4,9] A compendium of selected natural products with two or more contiguous stereogenic quaternary carbon atoms that have been previously synthesized (as well as key reaction types) is provided in the Supporting Information.

Several insights emerge from examining how the second or third quaternary center of a set of contiguous quaternary

stereocenters within a molecule was formed in the syntheses discussed in this Review. Considering the serious steric challenge, it is not surprising that intramolecuar C–C bond constructions were utilized in two thirds of the syntheses. In fact, pericyclic reactions exemplified by cycloadditions and sigmatropic rearrangements account for half of the C–C bond-forming reactions in the syntheses, with enolate alkylations and conjugate additions being utilized in just over a third. Completing the list are other creative C–C bond-forming methods involving free-radical reactions and photochemical transformations. Considering the remarkable progress recorded during the past decade in forming quaternary carbon atoms by using enantioselective catalysis,[10a] it seems assured that these methods will begin to play a larger role in the chemical synthesis of structurally more intricate molecules.

Numerous future opportunities and challenges in this area will emerge through creative thinking and inspiration from biogenetic principles. In particular, we envisage the invention of C–C bond-forming methods in which multiple stereogenic centers, including quaternary ones, can be created in a single operation through cascade or sequential bond-forming steps. Complex molecules containing three and four contiguous quaternary stereocenters such as musabalbisiane,[11] waihoensene,[157] and the taxane-derived propellane,[158] which are depicted in the frontispiece and yet to be synthesized, are excellent incentives to test the feasibility of newly developed synthetic methods. Associating such complex molecules with interesting biological activities would further heighten interest in their total synthesis, thus heralding numerous opportunities for future innovation.

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Supporting Information

Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms

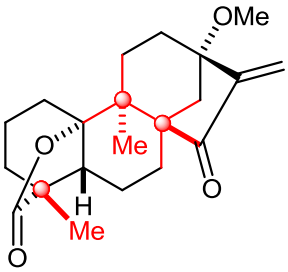
Martin Büschleb, Stéphane Dorich, Stephen Hanessian, Daniel Tao, Kyle B. Schenthal, and Larry E. Overman**

anie_201507549_sm_miscellaneous_information.pdf

Supporting Information

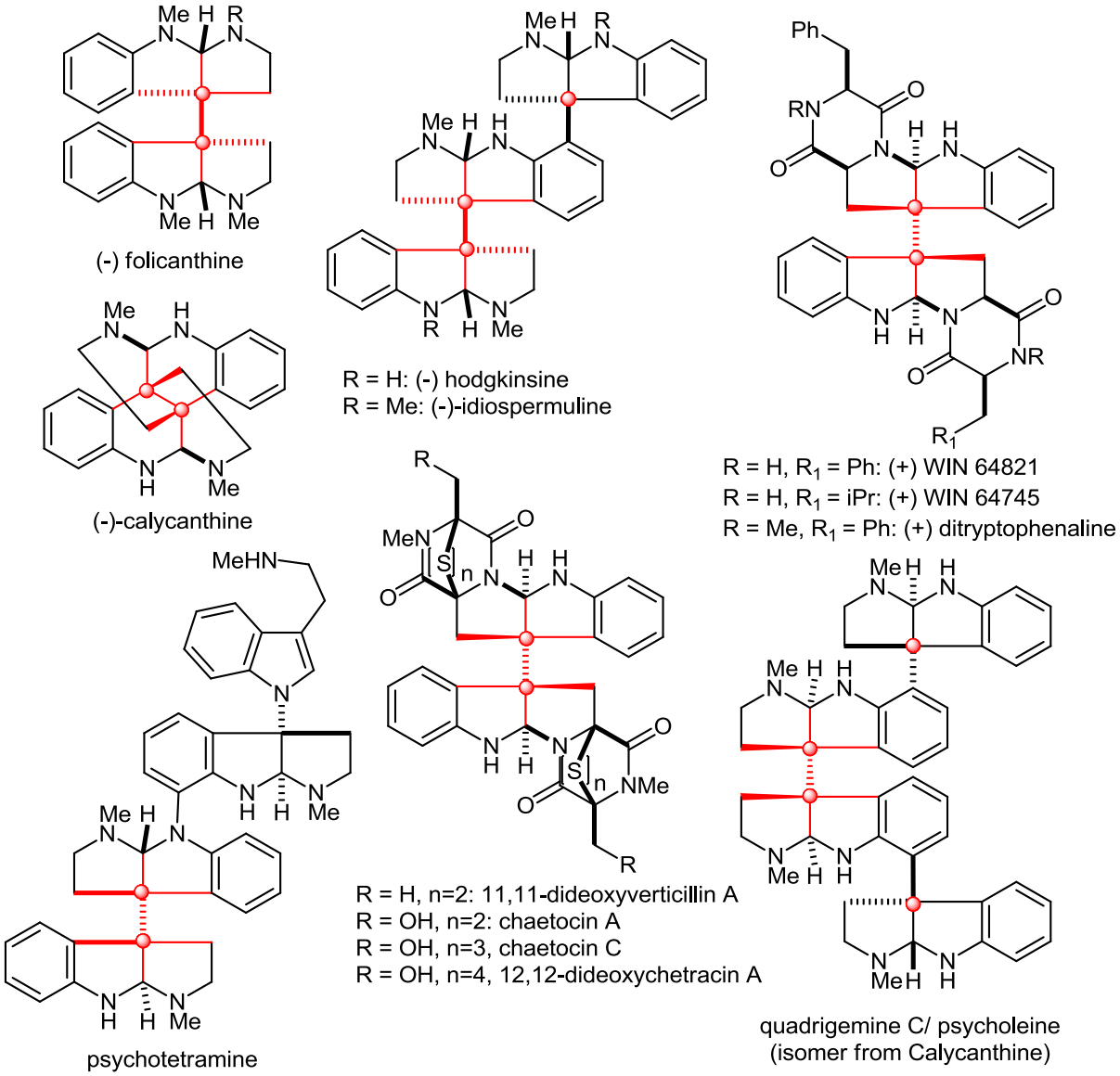
General information. The Supporting Information contains a non-exhaustive list of natural products featuring at least two contiguous quaternary centers in their structures. Only *total* and *formal* syntheses, but not partial syntheses, have been included. The key reactions or general strategies involved in the formation of the contiguous quaternary centers are indicated in blue.

13-Methoxy-15-oxozoapatlin:



R. A. Britton, E. Piers, B. O. Patrick, *J. Org. Chem.* **2004**, *69*, 3068–3075 (**1. Michael addition, 2. Heck cyclization**)

3a,3a'-Bispyrrolidino[2,3-b]indoline based natural products



WIN 64821/WIN 64745/Ditryptophenaline:

M. Movassaghi, M. A. Schmidt, J. A. Ashenhurst, *Angew. Chem. Int. Ed.* **2008**, *47*, 1485–1487 (**Reductive radical dimerization**)

L. E. Overman, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 9465–9467 (**Alkylation**)

S. Tadano, Y. Mukaeda, S. Ishikawa, *Angew. Chem. Int. Ed.* **2013**, *52*, 7990–7994 (**Oxidative dimerization**)

C. Pérez-Balado , A. R. de Lera, *Org. Lett.* **2008**, *10*, 3701–3704 (**Reductive radical dimerization**)

11,11-Dideoxyverticillin A:

J. Kim, J. A. Ashenhurst, M. Movassaghi, *Science* **2009**, *324*, 238–241 (**Reductive radical dimerization**)

Chaetocins:

E. Iwasa, Y. Hamashima, S. Fujishiro, F. Higuchi, A. Ito, M. Yoshida, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4078–4079; E. Iwasa, Y. Hamashima, S. Fujishiro, D. Hashizume, M. Sodeoka, *Tetrahedron* **2011**, *67*, 6587–6599 (**Reductive radical dimerization**)

J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2010**, *132*, 14376–14378 (**Reductive radical dimerization**)

Idiospermuline:

L. E. Overman, E. A. Peterson, *Angew. Chem. Int. Ed.* **2003**, *42*, 2525–2528; L. E. Overman, E. A. Peterson, *Tetrahedron* **2003**, *59*, 6905–6919 (**1. and 2. Alkylation**)

Hodgkinsine A/B (isomers):

J. J. Kodanko, L. E. Overman, *Angew. Chem. Int. Ed.* **2003**, *42*, 2528–2531; J. J. Kodanko, S. Hiebert, E. A. Peterson, L. Sung, L. E. Overman, V. de Moura Linck, G. C. Goerck, T. A. Amador, M. B. Leal, E. Elisabetsky, *J. Org. Chem.* **2007**, *72*, 7909–7914 (**1. and 2. Alkylation**) (+), (–)

R. H. Snell, R. L. Woodward, M. C. Willis, *Angew. Chem. Int. Ed.* **2011**, *50*, 9116–9119; R. H. Snell, M. J. Durbin, R. L. Woodward, M. C. Willis, Chem. Eur. J. 2012, 18, 16754–16764 (**1. and 2. Oxidative dimerization**) (–)

Quadrigemine C:

D. Lebsack, J. T. Link, L. E. Overman, B. A. Stearns, *J. Am. Chem. Soc.* **2002**, *124*, 9008–9009 (**1. and 2. Alkylation**)

Psychotetramine:

K. Foo, T. Newhouse, I. Mori, H. Takayama, P. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 2716–2719 (**Reductive radical dimerization**) (+)

Calycanthine:

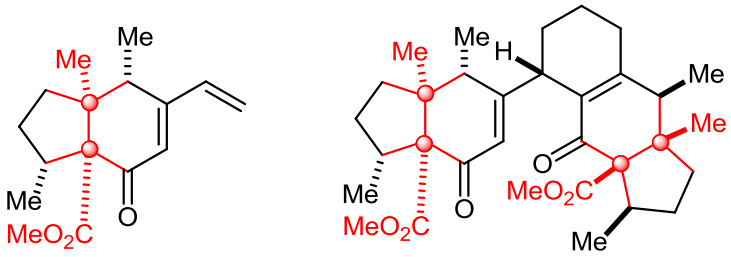
M. Movassaghi, M. A. Schmidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 3725–3728 (**Reductive radical dimerization**) (–)

Folicanthine:

Y.-X. Li, H.-W. Wang, X.-F. Xia, Y.M. Liang, *Chem. Commun.* **2012**, *48*, 2343–2345 (**oxidative dimerization**) (*rac.*)

C.-L. Fang, S. Horne, N. Taylor, R. Rodrigo, *J. Am. Chem. Soc.* **1994**, *116*, 9480–9486 (**Radical anionic dimerization**) (*rac.*)

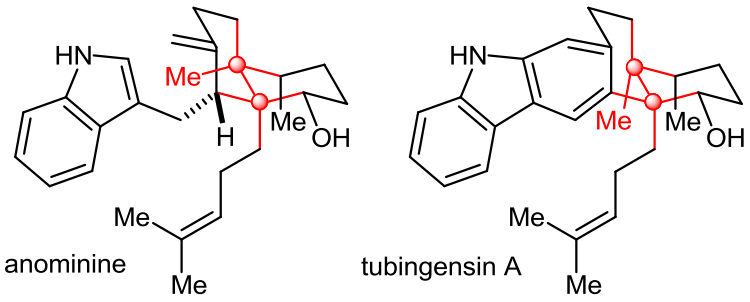
Acutifolone A/Bisacutifolone:



M.-T. Hsieh, H.-J. Liu, T. W. Ly, K.-S. Shia, *Org. Biomol. Chem.* **2009**, *7*, 3285–3290 (**1. Conjugate addition, 2. Pd(II)–mediated annulation**) (*rac.*)

J. Moineau, G. Pozzi, S. Quici, D. Sinou, *Tetrahedron Lett.* **2005**, *46*, 7683–7686; J. Shiina, M. Oikawa, K. Nakamura, R. Obata, S. Nishiyama, *Eur. J. Org. Chem.* **2007**, *31*, 5190–5197 (**1. Intramolecular Diels–Alder, 2. Mukaiyama aldol reaction**)

Anominine/Tubingensin:



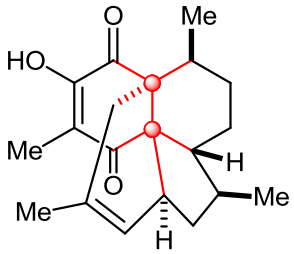
B. Bradshaw, G. Etxebarria–Jardí, J. Bonjoch, *J. Am. Chem. Soc.* **2010**, *132*, 5966–5967 (**1. Michael addition, 2. Conjugate addition**)

M. Bian, Z. Wang, X. Xiong, Y. Sun, C. Matera, K. C. Nicolaou, A. Li, *J. Am. Chem. Soc.* **2012**, *134*, 8078–8081 (**1. Michael addition, 2. Radical cyclization**)

A. E. Goetz, A. L. Silberstein, M. A. Corsello, N. K. Garg, *J. Am. Chem. Soc.* **2014**, *132*, 3036–3039 (**1. Conjugate addition, 2. benzyne cyclization**)

Colombiasin A:

Biosynthesis: *Natural Product Synthesis II: Targets, Methods, Concepts*, (Ed. J. H. Mulzer), Springer, **2005**; b) A. D. Rodríguez, E. González, S. D. Huang, *J. Org. Chem.* **1998**, *63*, 7083–7091.



K. C. Nicolaou, G. Vassilikogiannakis, W. Mägerlein, Remp, Kranich, *Chem. Eur. J.* **2001**, *7*, 5359–5371 (**Intramolecular Diels–Alder**)

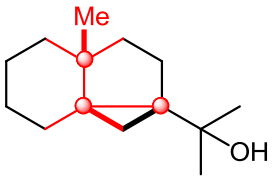
A. I. Kim, S. D. Rychnovsky, *Angew. Chem. Int. Ed.* **2003**, *42*, 1267–1270 (**Intramolecular Diels–Alder**)

D. C. Harrowven, D. D. Pascoe, D. Demurtas, H. O. Bourne, *Angew. Chem. Int. Ed.* **2005**, *44*, 1221–1222 (**Intramolecular Diels–Alder**)

A. A. Boezio, E. R. Jarvo, B. M. Lawrence, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6046–6050 (**Tandem dehydration–intramolecular Diels–Alder**)

H. M. L. Davies, X. Dai, M. S. Long, *J. Am. Chem. Soc.* **2006**, *128*, 2485–2490 (**Intramolecular Diels–Alder**)

Cycloeudesmol:

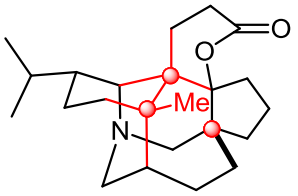


(α,β–isomer)

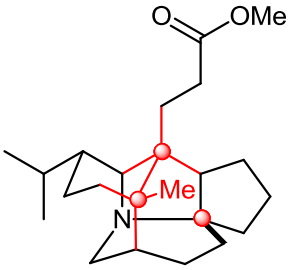
M. Ando, K. Wada, K. Takase, *Chem. Lett.* **1979**, 191–194; M. Ando, K. Wada, K. Takase, *Tetrahedron Lett.* **1985**, *26*, 235–238 (**1. Robinson annulation, 2. Cyclopropanation**)
R. A. Moss, E. Y. Chen, J. Banger, M. Matsuo, *Tetrahedron Lett.* **1978**, 19, 4365–4368; R. A. Moss, E. Y. Chen, *J. Org. Chem.* **1981**, *46*, 1466–1469 (**1. Robinson annulation, 2. Cyclopropanation**)

Daphniphyllum alkaloids:

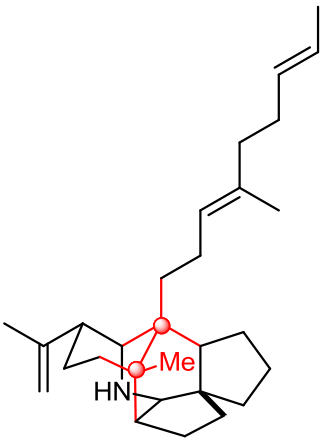
Biosynthesis: J. Kobayashi, T. Kubota *Nat. Prod. Rep.* **2009**, *26*, 936–962.



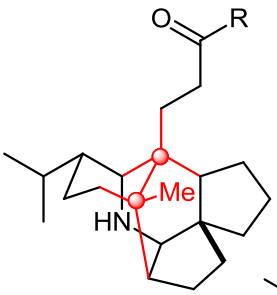
daphnilactone A

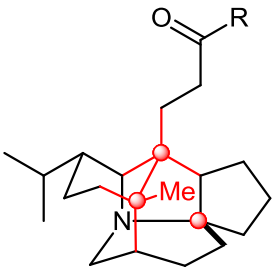


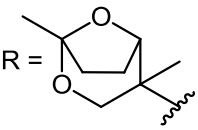
methyl homodaphniphyllate



protodaphniphylline





secodaphniphylline R =  = R: (+)-codaphniphylline

R = OMe methyl homosecodaphniphyllate

Daphnilactone A:

R. B. Ruggeri, K. F. McClure, C. H. Heathcock, *J. Am. Chem.* Soc. **1989**, *111*, 1530–1531; C. H. Heathcock, R. B. Ruggeri, K. F. McClure, *J. Org. Chem.* **1992**, *57*, 2585–2594 (**1. Alkylation. 2. Intramolecular Diels–Alder**) (*rac.*)

Methyl homosecodaphniphyllate:

R. B. Ruggeri, M. M. Hansen, C. H. Heathcock, *J. Am. Chem.* Soc. **1988**, *110*, 8734–8736; C. H. Heathcock, M. M. Hansen, R. B. Ruggeri, J. C. Kath, *J. Org. Chem.* **1992**, *57*, 2544–2553 (**1. Alkylation. 2. Intramolecular Diels–Alder**) (*rac.*)

Methyl homodaphniphyllate:

C. H. Heathcock, S. K. Davidsen, S, Mills, M. A. Sanner, *J. Am. Chem.* Soc. **1986**, *108*, 5650–5651 (**2 x Michael annulation**) (+);C. H. Heathcock, R. B. Ruggeri, K. F. McClure, *J. Org. Chem.* **1992**, *57*, 2585–2594 (**Intramolecular Diels–Alder**) (*rac.*)

Secodaphniphylline:

C. H. Heathcock, J. A. Stafford, *J. Org. Chem.* **1992**, *57*, 2566–2574; J. A. Stafford, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 5433–5434 (**1. Alkylation. 2. Intramolecular Diels–Alder**)

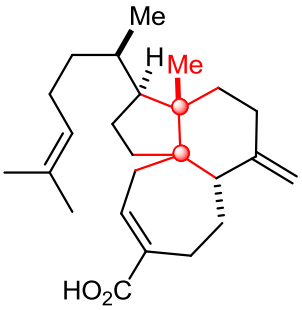
Protodaphniphylline:

S. Piettre, C. H. Heathcock, *Science* **1990**, *248*, 1532–1534 (**1. Alkylation. 2. Intramolecular Diels–Alder**)

Codaphniphylline:

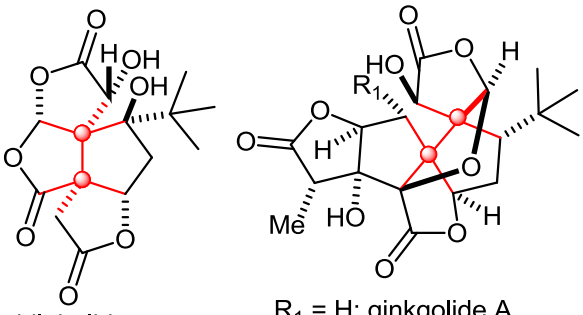
C. H. Heathcock. J. C. Kath, R. B. Ruggeri, *J. Org. Chem.* **1995**, *60*, 1120–1130 (**1. Alkylation. 2. Intramolecular Diels–Alder**)

Gascardic acid (rac.):



G. Bérubé, A. G. Fallis, *Tet. Lett.* **1989**, *30*, 4045–4048 (**1. Intramolecular Diels–Alder, 2. Oxy-Cope rearrangement**)

Ginkgolides:



Ginkgolide A:

E. J. Corey, A. K. Ghosh, *Tetrahedron Lett.* **1988**, *29*, 3205–3206 (**1. Mukaiyama aldol, 2. Intramolecular ketene [2 + 2]**) (*rac.*)

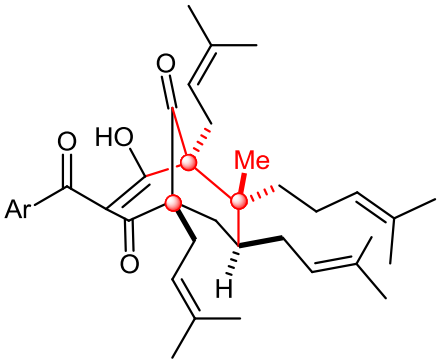
Ginkgolide B:

E. J. Corey, M. C. Kang, M. C. Desai, A. K. Ghosh, I. N. Houpis. *J. Am. Chem. Soc.* **1988**, *110*, 649–651 (**1. Mukaiyama aldol, 2. Intramolecular ketene [2 + 2]**) (*rac.*)

M. T. Crimmins, J. M. Pace, P. G. Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, A. S. Wagman, *J. Am. Chem. Soc.* **1999**, *121*, 10249–10250; M. T. Crimmins, J. M. Pace, P. G.

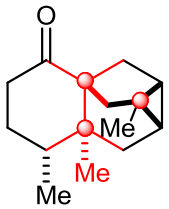
Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, A. S. Wagman, *J. Am. Chem. Soc.* **2000**, *122*, 8453–8463 (**Intramolecular [2 + 2] photocycloaddition**) (*rac.*)

Guttiferone:



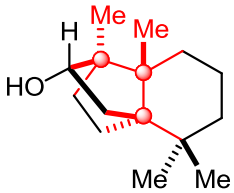
F. Horeischi, N. Biber, B. Plietker, *J. Am. Chem. Soc.* **2014**, *136*, 4026–4030 (**1. Conjugate addition, 2. Pd-catalyzed decarboxylative Tsuji–Trost allylation**)

Ishwarone:



R. M. Cory, D. M. T. Chan, F. R. McLaren, M. H. Rasmussen, R. M. Renneboog, *Tetrahedron Lett.* **1979**, *20*, 4133–4136 (**1. Conjugate addition, 2. Intramolecular epoxide-opening alkylation**) (rac.)

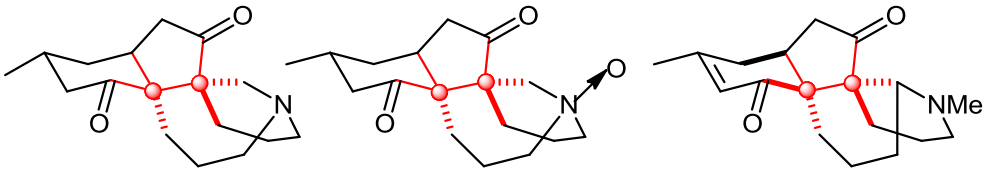
Junicedranol:



T. Uyehara, Y. Sato, H. Ishizuka, Y. Sakiyama, M. Ueno, T. Sato, *Tetrahedron Lett.* **2000**, *41*, 1939–1942 (**1. Starting material, 2. and 3. Diels–Alder, 4. Alkylation**) (rac.)

Lycopodium alkaloids:

Biosynthesis: a) W. A. Ayer, Y. Fukazawa, P. P. Singer, B. Altenkirk, *Tetrahedron. Lett.* **1973**, *50*, 5045–5048; b) H. Li, X. Wang, B. Hong, X. Lei, *J. Org. Chem.* **2013**, *78*, 800–821.



lycoflexine lycoflexine *N*-oxide lycojaponicumin C

Lycoflexine and lycoflexine–N–oxide:

K. Xu, B. Cheng, Y. Li, T. Xu, C. Yu, J. Zhang, Z. Ma, H. Zhai, *Org. Lett.* **2014**, *16*, 196–199 (**1. Intermolecular Diels–Alder, 2. Mannich reaction**)

J. Ramharter, H. Weinstabl, J. Mulzer, *J. Am. Chem. Soc.* **2010**, *132*, 14338–14339 (**1. Alkylation, 2. Mannich reaction**) (+)

Y.-R. Yang, L. Shen, J.-Z. Huang, T. Xu, K. Wei, *J. Org. Chem.* **2011**, *76*, 3684–3690 (**1. Helquist annulation, 2. Mannich reaction**) (+)

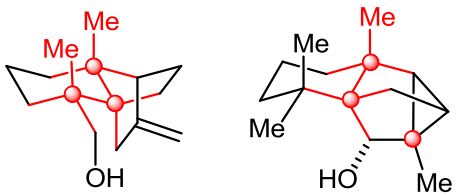
G. Pan, R. M. Williams, *J. Org. Chem.* **2012**, *77*, 4801–4811 (**1. Intermolecular Diels–Alder, 2. Mannich reaction**) (*rac.*)

N. Itoh, T. Iwata, H. Sugihara, F. Inagaki, C. Mukai, *Chem. Eur. J.* **2013**, *19*, 8665–8672 (**1. Radical cyclization, 2. Mannich reaction**) (*rac.*)

Lycojaponicumin C:

S.-H. Hou, Y.-Q. Tu, L. Liu, F.-M. Zhang, S.-H. Wang, X.-M. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 11373–11376 (**1. Intramolecular carbenoid cyclopropanation, 2. Tsuji–Trost allylation**) (–)

Myltaylanols:



myltaylenol cyclomyltaylanol

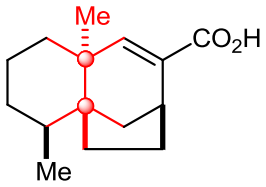
Cyclomyltaylanol:

H. Sakai, H. Hagiwara, Y. Ito, T. Hoshi, T. Suzuki, M. Ando, *Tetrahedron Lett.* **1999**, *40*, 2965–2968 (**1. Robinson annulation, 2. Claisen rearrangement**) (+)

Myltaylenol:

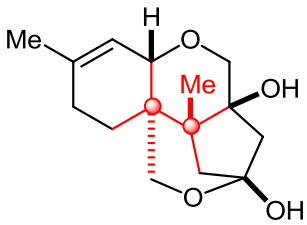
S. Doye, T. Hotopp, E. Winterfeldt, *Chem. Commun.* **1997**, 1491–1492 (**1. Robinson annulation, 2. Intramolecular Diels–Alder**) (–)

Nudenoic acid:



T.-L. Ho, C.-Y. Su, *J. Org. Chem.* **2000**, *65*, 3566–3568 (**1. Robinson annulation, 2. Johnson–Claisen rearrangement**) (*rac.*)

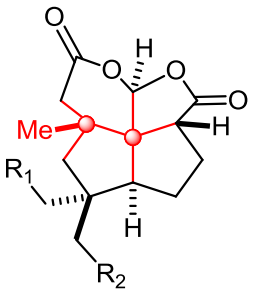
Paecilomycine A:



S.-J. Min, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2007**, *46*, 2199–2202 (**1. Intermolecular Diels–Alder, 2. Cyclopropanation**) (*rac.*)

Penifulvin:

Biosynthesis: a) *Asymmetric Synthesis II: More Methods and Applications*, (Eds. M. Christmann, S. Brase), Wiley–VCH, Weinheim, 2012; b) S. H. Shim, J. B. Gloer, D. T. Wicklow, *J. Nat. Prod.* **2006**, *69*, 1601–1605.

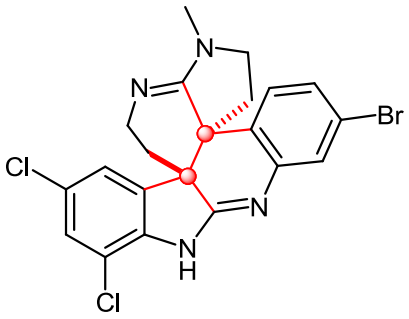


$R_1 = R_2 = H$: penifulvin A
$R_1 = H$, $R_2 = OH$: penifulvin B
$R_1 = OH$, $R_2 = H$: penifulvin C

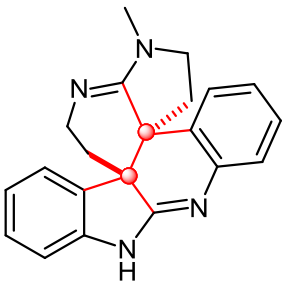
D. Das, R. Kant, T. K. Chakraborty, *Org. Lett.* **2014**, *16*, 2618–2621 (**1. Johnson-Claisen rearrangement, 2. Ti(III)-mediated cyclization**) (*rac.*)
T. Gaich, J. Mulzer, *J. Am. Chem. Soc.* **2009**, *131*, 452–453 (**Intramolecular photocycloaddition**)
T. Gaich, J. Mulzer, *Org. Lett.* **2010**, *12*, 272–275 (**Intramolecular photocycloaddition**)

Perophoramidine/Communesin:

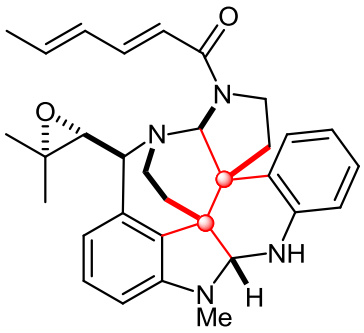
Biosynthesis (communesin): L. J. Wigley, P. G. Mantle, D. A. Perry, *Phytochemistry* **2006**, *67*, 561–569.



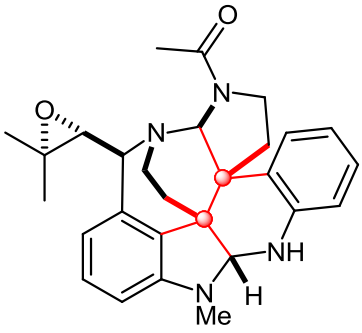
perophoramidine



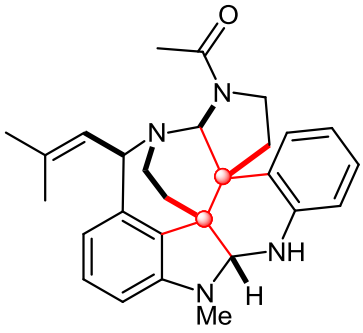
dehaloperophoramidine



communesin B



communesin A



communesin F

Perophoramidine:

J. R. Fuchs, R. L. Funk, *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069 (**Intermolecular cycloaddition**) (*rac.*)

H. Wu, F. Xue, X Xiao, Y. Qin, *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054; Y. Du, H. Wu, H. Song, Y. Qin, D. Zhang, *Chin. J. Chem.* **2012**, *30*, 1970–1973 (**Intermolecular hetero-Diels–Alder**) (+)

H. Zhang, L. Hong, H. Kang, R. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 14098–14101 (**Catalytic asymmetric alkylation**) (+)

S.-J. Han, F. Vogt, S. Krishnan, J. A. May, M. Gatti, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2014**, *16*, 3316–3319 (**1. Alkylation, 2. Decarboxylative Tsuji–Trost allylation**) formal

Dehaloperophoramidine:

T. Ishida, H. Ikota, K. Kurahashi, C. Tsukano, Y. Takemoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 10204–10207 (**Tandem dearomatizing arylation–allylation**) (*rac.*)

A. Sabahi, A. Novikov, J. D. Rainier, *Angew. Chem. Int. Ed.* **2006**, *45*, 4317–4320 (rac.) (**1. cationic cyclization, 2. Alkylation**) (*rac.*)

Communesin A/B:

Z. Zuo, D. Ma, *Angew. Chem. Int. Ed.* **2011**, *50*, 12008–12011 (**1. intramolecular oxidative coupling, 2. Alkylation**) (–)

Communesin F:

J. Belmar, R. L. Funk, *J. Am. Chem. Soc.* **2012**, *134*, 16941–16943 (**Intermolecular cycloaddition**) (*rac.*)

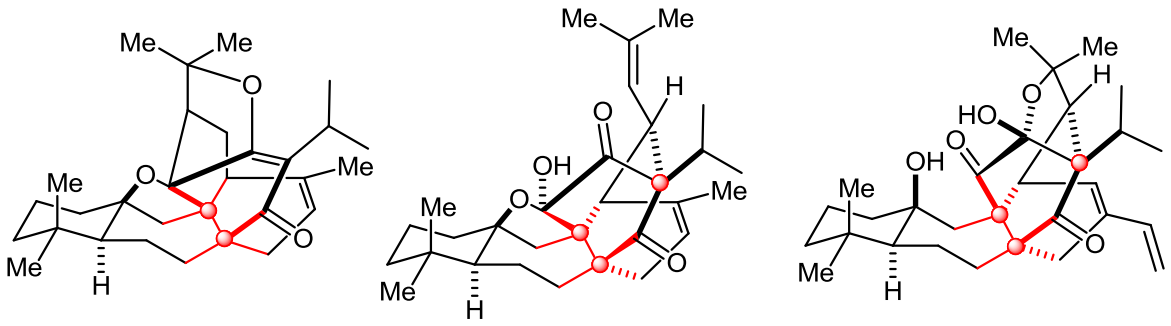
Z. Zuo, W. Xie, D. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228 (**1. intramolecular oxidative coupling, 2. Alkylation**) (–)

P. Liu, J. H. Seo, S. M. Weinreb, *Angew. Chem. Int. Ed.* **2010**, *49*, 2000–2003; *J. Org. Chem.* **2010**, *75*, 2667–2680 (**1. intramolecular tandem Heck cyclization/carbonylation, 2. Alkylation or Claisen rearrangement**) (*rac.*)

J. Yang, H. Wu, L. Shen, Y. Qin, *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795 (**1. cyclopropanation, 2. Claisen rearrangement**) (*rac.*)
S.-J. Han, F. Vogt, S. Krishnan, J. A. May, M. Gatti, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2014**, *16*, 3316–3319 (**1. Alkylation, 2. Decarboxylative Tsuji–Trost allylation**) formal

Perovskone/Salvadione A:

Biosynthesis: V. U. Ahmad, M. Zahid, M. S. Ali, M. I. Choudhary, F. Akhtar, Z. Ali, M. Z. Iqbal, *Tetrahedron Lett.* **1999**, *40*, 7561–7564.



Perovskone:

G. Majetich, Y. Zhang, *J. Am. Chem. Soc.* **1994**, *116*, 4979–4980 (*rac.*); G. Majetich, Y. Zhang, X. Tian, J. E. Britton, Y. Li, R. Phillips, *Tetrahedron* **2011**, *67*, 10129–10146 **1. and 2.** (**Intermolecular Diels–Alder**) (*rac.* & (+))

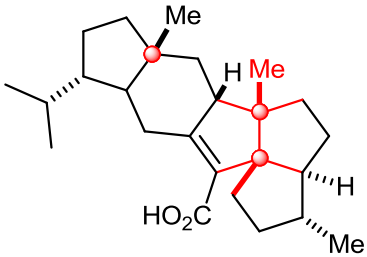
Salvadione A:

G. Majetich, Y. Wang, Y. Li, J. K. Vohs, G. H. Robinson, *Org. Lett*. **2003**, *5*, 3847–3850 (**1. and 2. Intermolecular Diels–Alder**) (*rac.* & (+))

Salvadione B:

G. Majetich, G. Zou, S. Hu, *Org. Lett.* **2013**, *15*, 4924–4927 (**1. and 2. Intermolecular Diels–Alder**) (+)

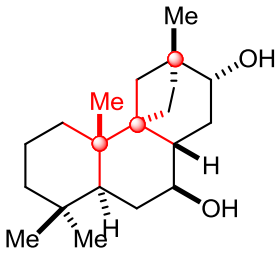
Retigeranic acid:



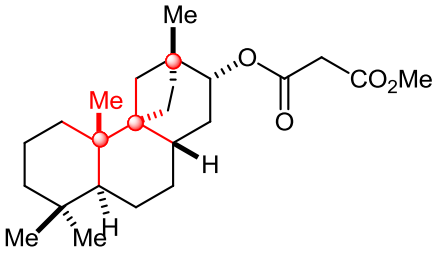
P. A. Wender, S. K. Singh, *Tetrahedron Lett.* **1990**, *31*, 2517–2520; P. A. Wender, R. Ternansky, M. deLong, S. Singh, A. Olivero, K. Rice, *Pure & Appl. Chem.* **1990**, *62*, 1597–1602 (**1. and 2. Intramolecular photocycloaddition**) (–)
E. J. Corey, M. C. Desai, T. A. Engler, *J. Am. Chem. Soc.* **1985**,*107*, 4339–4341 (**1. Conjugate addition, 2. Intermolecular Diels–Alder**) (rac.)
L. A. Paquette, J. Wright, G. J. Drtina, R. A. Roberts, *J. Org. Chem.* **1987**, *52*, 2960–2962; J. Wright, G. J. Drtina, R. A. Roberts, L. A. Paquette, *J. Am. Chem. Soc.* **1988**, *110*, *5806–5817* (**Marfat–Helquist annulation**) (–)

T. Hudlicky, L. Radesca–Kwart, L.-Q. Li, T. Bryant, *Tetrahedron Lett.* **1988**, *29*, 3283–3286; T. Hudlicky, R. P. Short, *J. Org. Chem.* **1982**, *47*, 1522–1527; T. Hudlicky, A. Fleming, L. Radesca, *J. Am. Chem. Soc*. **1989**, *111*, 6691–6707 (**1. and 2. Intermolecular [2+3] cycloaddition/thermal rearrangement**) (–)

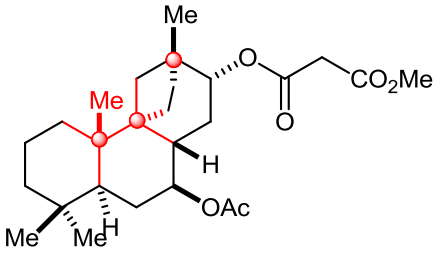
Scopadulan diterpenes:



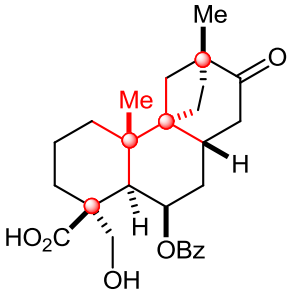
thyrsiflorin C



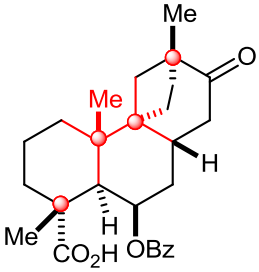
methyl thyrsiflorin A



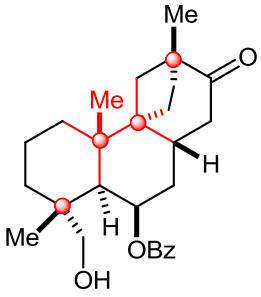
methyl thyrsiflorin B acetate



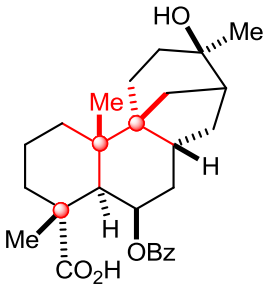
scopadulcic acid A



scopadulcic acid B



scopadulciol



scopadulin

Thyrsiflorin C, Methyl thyrsiflorin A, Methyl Thyrsiflorin B acetate:

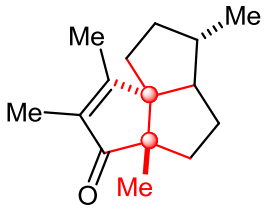
M. Arnó, M. A, González, M. L. Marín, R. J. Zaragozá, *J. Org. Chem.* **2000**, *65*, 840–846 (**1. Alkylation, 2. Intramolecular cyclopropanation**(–)

Scopadulin:

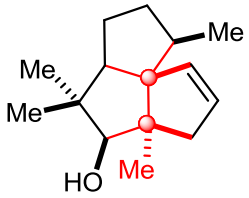
S. M. A. Rahman, H. Ohno, T. Murata, H. Yoshino, N. Satoh, K. Murakami, D. Patra, C. Iwata, N. Maezaki, T. Tanaka, *Org. Lett.* **2001**, *3*, 619–622; S. M. A. Rahman, H. Ohno, T. Murata, H. Yoshino, N. Satoh, K. Murakami, D. Patra, C. Iwata, N. Maezaki, T. Tanaka, *J. Org. Chem.* **2001**, *66*, 4831–4840 (**1. Spiroannulation, 2. Intermolecular conjugate addition**) (*rac.*)

Silphiperfolan/Silphinane–type Sesquiterpenes:

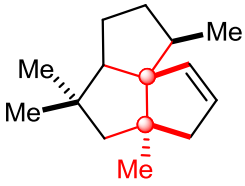
Biosynthesis : a) R. M. Coates, Z. Ho, M. Klobus, S. R. Wilson, *J. Am. Chem. Soc.* **1996**, *118*, 9249–9254; b) R. M. Coates, J. Z. Ho, M. Klobus, L. Zhu, *J. Org. Chem.* **1998**, *63*, 9166–9176.



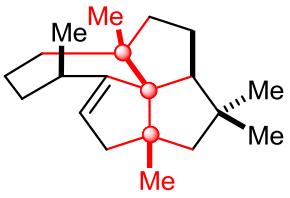
5-oxosilphiperfolene



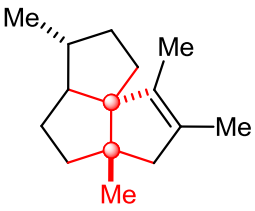
cameroonanol



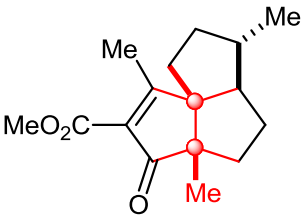
silphinene



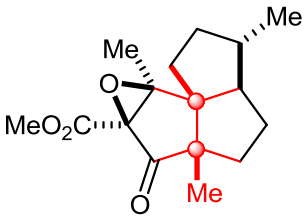
laurenene



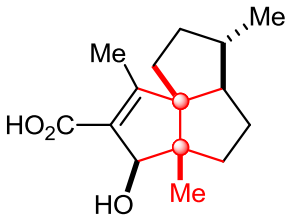
silphiperfolene



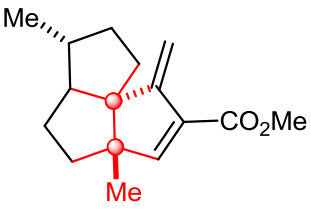
methyl cantabrenonate



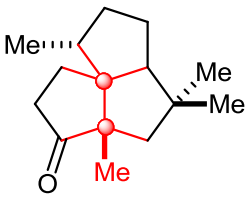
methyl epoxycantabronate



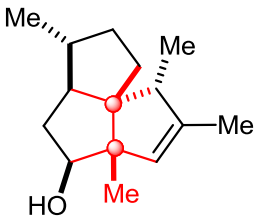
cantabrenolic acid



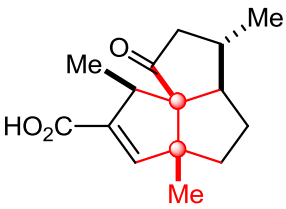
methyl Cantabradienate



3-oxosilphinene



silphiperfol-5-en-3-ol



subergorgic acid

Review: G. Mehta, A. Srikrishna, *Chem. Rev.* **1997**, *97*, 671–720.

5–Oxo–silphiperfol–6–en:

M. Demuth, W. Hinsken, *Angew. Chem. Int. Ed.* **1985**, *24*, 973–975; M. Demuth, W. Hinsken, *Helv. Chim. Acta* **1988**, *71*, 569–576 (**1. Robinson annulation, 2. Intermolecular Diels–Alder**) (–)

K. Kakiuchi, M. Ue, H. Tsukahara, T. Shimizu, T. Miyao, Y. Tobe, Y. Odaira, M. Yasuda, K. Shima, *J. Am. Chem. Soc.* **1989**, *111*, 3707–3712 (**1. [2 + 2] Photocycloaddition-rearrangement, 2. Alkylation**) (*rac.*)

C.-K. Sha, K. C. Santhosh, S.-H. Lih, *J. Org. Chem.* **1998**, *63*, 2699–2704 (**1. Radical cyclization, 2. Alkylation**) (–)

Silphiperfol–6–ene:

D. P. Curran, S. C. Kuo, *J. Am. Chem. Soc.* **1986**, *108*, 1106–1107; D. P. Curran, S. C. Kuo, *Tetrahedron* **1987**, *43*, 5653–5661 (**1. Alkylation, 2. Radical cyclization**) (*rac.*)

L. A. Paquette, R. A. Roberts, G. J. Drtina, *J. Am. Chem. Soc.* **1984**, *106*, 6690–6693 (**Marfat–Helquist annulation**) (–)

P. A. Wender, S. K. Singh, *Tetrahedron Lett.* **1985**, *26*, 5987–5590 (**Intramolecular photocycloaddition**) (*rac.*)

A. I. Meyers, B. A. Lefker, *Tetrahedron* **1987**, *43*, 5663–5676 (**1. Alkylation, 2. Radical cyclization**) (–)

C. E. Davis, B. C. Duffy, R. M. Coates, *J. Org. Chem.* **2003**, *68*, 6935–6943 (**1. Conjugate addition, 2. Wagner–Meerwein rearrangement**) (*rac.*)
T. J. Reddy, V. H. Rawal, *Org. Lett.* **2000**, *2*, 2711–2712 (**Intermolecular Diels–Alder**) (*rac.*)
K. Kakiuchi, M. Ue, H. Tsukahara, T. Shimizu, T. Miyao, Y. Tobe, Y. Odaira, M. Yasuda, K. Shima, *J. Am. Chem. Soc.* **1989**, *111*, 3707–3712 (**1. [2 + 2] photocycloaddition/ rearrangement, 2. Alkylation**) (*rac.*)
J. K. Dickson, B. Fraser–Reid, *J. Chem. Soc., Chem. Commun.* **1990**, 1440–1443 (**1. Alkylation, 2. Claisen rearrangement**) (–)
N. H. Vo, B. B. Snider, *J. Org. Chem.* **1994**, *59*, 5419–5423 (**Intramolecular [2 + 2] cycloaddition**) (–)

3–Oxosilphinene:

M. Ihara, A. Kawaguchi, M. Chihiro, K. Fukumoto, T. Kametani, *J. Chem. Soc, Chem. Commun.* **1986**, 671–672 (**1. and 2. Intramolecular Diels–Alder**) (*rac.*)
M. Ue, Y. Ohnishi, K. Kobiro, K. Kakiuchi, Y. Tobe, Y. Odaira, *Chem Lett.* **2006**, *19*, 149–150 (**1. and 2. [2 + 2] photocycloaddition**) (*rac.*)

Cameroonanol:

D. F. Taber, C. G. Nelson, *J. Org. Chem.* **2011**, *76*, 1874–1882 (**1. Intramolecular carbenoid C-H Insertion, 2. oxidative radical cyclization**) (–)
C. E. Davis, B. C. Duffy, R. M. Coates, *Org. Lett.* **2000**, *2*, 2717–2719; C. E. Davis, B. C. Duffy, R. M. Coates, *J. Org. Chem.* **2003**, *68*, 6935–6943 (**1. Conjugate addition, 2. Alkylation**) (*rac.*)
A. W. Schmidt, T. Olpp, S. Schmid, S. Goutal, A. Jäger, H.-J. Knölker, *Synlett* **2007**, 1549–1552; A. W. Schmidt, T. Olpp, S. Schmid, A. Jäger, H.-J. Knölker, *Tetrahedron* **2009**, *65*, 5484–5490 (**1. Conjugate addition, 2. [3 + 2] cycloaddition**) (*rac.*)

Silphinene:

L. A. Paquette, A. Leone–Bay, *J. Am. Chem. Soc.* **1983**, *105*, 7352–7358 (**1. Conjugate addition, 2. Intramolecular aldol**) (*rac.*)
J. K. Dickson, B. Fraser–Reid, *J. Chem. Soc., Chem. Commun.* **1990**, 1440–1443 (**1. Eschenmoser–Claisen rearrangement, 2. Alkylation**) formal
M. T. Crimmins, S. W. Mascarella, *J. Am. Chem. Soc.* **1986**, *108*, 3435–3438 (**1. Conjugate addition, 2. Intramolecular [2 + 2] photocycloaddition**) (*rac.*)
L. Fitjer, H. Monzo-Oltra, *J. Org. Chem.* **1993**, *58*, 6171–6173 (**1. and 2. Rearrangement**) (–)
Y. K. Rao, M. Nagarajan, *Tetrahedron Lett.* **1988**, *29*, 107–108; *J. Org. Chem.* **1989**, *54*, 5678–5683 (**1. Alkylation, 2. Radical cyclization**) formal
M. Franck–Neumann, M. Miesch, E. Lacroix, *Tetrahedron Lett.* **1989**, *30*, 3533–3536 (**1. Nazarov cyclization, 2. Alkylation**) (*rac.*)
S. Yamamura, Y. Shizuri, H. Shigemori, Y. Okuno, M. Ohkubo, *Tetrahedron* **1991**, *47*, 635–644; Y. Shizuri, M. Ohkubo, S. Yamamura *Tetrahedron Lett.* **1989**, *30*, 3797–3798 (**1. Anodic oxidation, 2. Conjugate addition**) formal
T. Tsunoda, M. Kodama, S. Itô, *Tetrahedron Lett.* **1983**, *24*, 83–86 (**1. Alkylation, 2. Conjugate addition, 2. Intramolecular aldol**) (*rac.*)

Silphiperfol–5–en–3ol:

J. Brendel, P. Weyerstahl, *Tetrahedron Lett.* **1989**, *30*, 2371–2374; P. Weyerstahl, J. Brendel, *Liebigs Ann. Chem. 1992*, 669–678 (**1. Conjugate addition, 2. Intramolecular aldol reaction**) (*rac.*)

Laurenene:

T. Tsunoda, M. Amaike, U. S. F. Tambunan, Y. Fujise, S. Itô, M. Kodama, *Tetrahedron Lett.* **1987**, *28*, 2537–2540 (**1. Conjugate addition, 2. Intramolecular aldol, 3. Claisen rearrangement**) (*rac.*)
M. T. Crimmins, L. D. Gould, *J. Am. Chem. Soc.* **1987**, *109*, 6199–6200 (**1. Conjugate addition, 2. and 3. Intramolecular [2 + 2] photocycloaddition**) (*rac.*)
L. A. Paquette, M. E. Okazaki, J. C. Caille, *J. Org. Chem.* **1988**, *53*, 477–481 (**1. Conjugate addition, 2. Intramolecular aldol, 3. Alkylation**) formal

P. A. Wender, T. W. von Geldern, B. H. Levine, *J. Am. Chem. Soc.* **1988**, *110*, 4858–4860 (**1. Alkylation, 2. and 3. Intramolecular photocycloaddition**) (*rac.*)

Methyl cantabrenonate/ Methyl epoxycantabronate:

E. Piers, J. Renaud, *J. Chem. Soc., Chem. Comm.* **1990**, 1324–1326; E. Piers, J. Renaud, *Synthesis* **1992**, 74–82 (**1. Conjugate addition, 2. Intramolecular Alkylation**) (*rac.*)

Methyl cantabradienate:

N. H. Vo, B. B. Snider: *J. Org. Chem.* **1994**, *59*, 5419–5423 (**Intramolecular [2 + 2] cycloaddition**) (–)

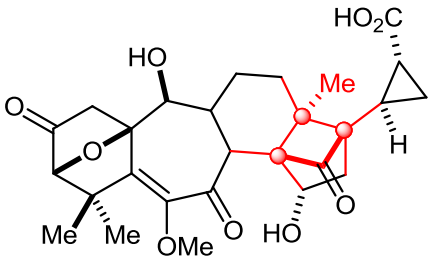
Subergorgic acid:

C. Iwata, Y. Takemoto, M. Doi, T. Imanishi, *J. Org. Chem.* **1988**, *53*, 1623–1628 (**1. Intramolecular diazoalkane-phenyl cyclization, 2. [2 + 2] photocycloaddition or Claisen rearrangement**) (*rac.*)

P. A. Wender, M. A. deLong, *Tetrahedron Lett.* **1990**, *31*, 5429–5432 (**Intramolecular photocycloaddition**)(*rac.*)

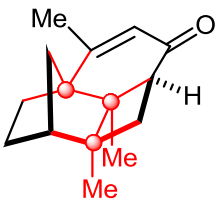
L. A. Paquette, P. G. Meister, D. Friedrich, D. R. Sauer, *J. Am. Chem. Soc.* **1993**, *115*, 49–56 (**1. Alkylation, 2. Conjugate addition**)(–)

Solanoeclepin A:

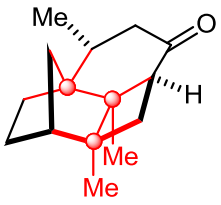


K. Tanino, M. Takahashi, Y. Tomata, H. Tokura, T. Uehara, T. Narabu, M. Miyashita, *Nat. Chem.* **2011**, *3*, 484–488 (**1. Michael addition, 2. Semi–pinacol rearrangement, 3. Intramolecular alkylation**)

Solanascone/Dehydrosolanascone:



solanascone

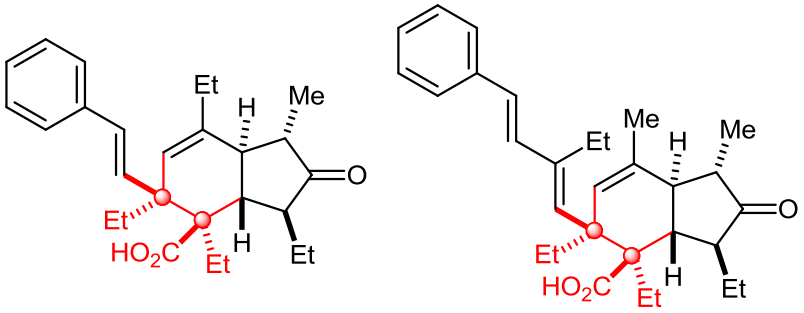


dehydrosolanascone

A. Srikrishna, S. S. V. Ramasastry, *Tetrahedron Lett.* **2005**, *46*, 7373–7376 (**1. Epoxide rearrangement, 2. and 3. Intramolecular [2 + 2] photocycloaddition**) (+)

Spiculoic acid/Zyggomphic acid:

Biosynthesis: A. Pinto, C. N. Boddy, *Bioorganic & Medicinal Chemistry Letters* **2012**, *22*, 5253–5256.



spiculoic acid zyggomphic acid

Spiculoic acid:

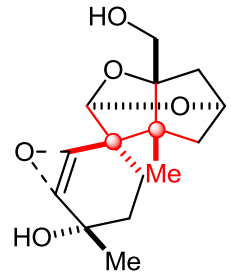
D. Matsymura, T. Toda, T. Hayamizu, K. Sawamura, K. Takao, K. Tadano, *Tetrahedron Lett.* **2009**, *50*, 3356–3358; K. Tadano, *Eur. J. Org. Chem.* **2009**, 4381–4394 (**Intramolecular Diels–Alder**) (+)

J. E. D. Kirkham, V. Lee, J. E. Baldwin, *Chem. Commun.* **2006**, 2863–2865 (**Intramolecular Diels–Alder**), (–)

Zyggomphic acid:

D. Matsumura, T. Takarabe, T. Toda, T. Hayamizu, K. Sawamura, K. Takao, K. Tadano, *Tetrahedron* **2011**, *67*, 6730–6745 (**Intramolecular Diels–Alder**) (+)

Spirotenuipesine:

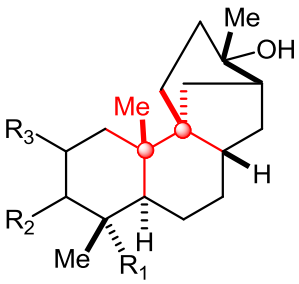


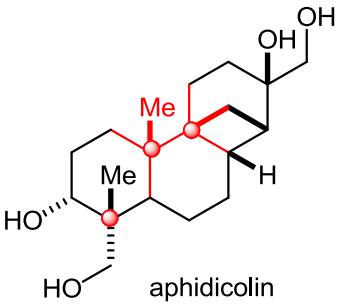
A: olefin; B: epoxide

M. Dai, S. J. Danishefsky, *J. Am. Chem. Soc.* **2007**, *129*, 3498–3499 (**1. Intramolecular cyclopropanation, 2. Intermolecular Diels–Alder**); M. Dai, I. J. Krauss, S. J. Danishefsky, *J. Org. Chem.* **2008**, *73*, 9576–9583 (**1. Intramolecular cyclopropanation/radical initiated fragmentation, 2. Intermolecular Diels–Alder**) (*rac.*)

Stemarane/Stemodane–diterpenes:

Biosynthesis: R. Fujii, A. Minami, T. Tsukagoshi, N. Sato, T. Sahara, S. Ohgiya, K. Gomi, H. Oikawa, *Biosci Biotechnol Biochem.* **2011**,75, 1813–1817.





aphidicolin

R_1= Me, R_2=R_3=H: desoxystemodinone
R_1=CH_2OH, R_2=R_3=H: stemodinol
R_1= Me, R_2= H, R_3=OH: stemodin
R_1= Me, R_2=H, R_3=O: stemodinone
R_1= Me, R_2=OH, R_3=H: maritimol

Review: M. Toyota, M. Ihara, *Tetrahedron* **1999**, *55*, 5641–5679.

Maritimol:

A. Toró, P. Nowak, P. Deslongchamps, *J. Am. Chem. Soc.* **2000**, *122*, 4526–4527 (**Intramolecular Diels–Alder**)

E. Piers, B. F. Abeysekera, D. J. Herbert, I. D. Sucklin, *Can. J. Chem.* **1985**, *63*, 3418–3432 (**1. Robinson annulation, 2. Photochemical [2 + 2] cycloadditon**) (*rac.*)

E. E. van Tamelen, J. G. Carlson, R. K. Russell, S. R Zawacky, *J. Am. Chem. Soc.* **1981**, *103*, 4615–4616 (**1. LA mediated polyene cyclization, 2. Intermolecular Diels–Alder**) (*rac.*)

A. Lupi, M. Patamia, I. Grgurina, R. M. Bettolo, O. Di Leo, P. Gioia, S. Autnaroli, *Helv. Chim. Acta* **1984**, *67*, 2261–2263 (**1. Podocarpic acid or Robinson annulation**, **2. Allene photocycloaddition**) (*rac.*)

Stemodin:

J. Germanas, C. Aubert, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1991**, *113*, 4006–4008 (**Co-mediated [2 + 2 + 2] cycloaddition**) formal

M. Toyota, T. Seishi, K. Fukumoto, *Tetrahedron Lett.* **1993**, *34*, 5947–5950; *Tetrahedron* **1994**, *50*, 3673–3686 (**1. Intramolecular Diels–Alder, 2. Claisen rearrangement**) formal

E. Piers, B. F. Abeysekera, D. J. Herbert, I. D. Sucklin, *Can. J. Chem.* **1985**, *63*, 3418–3432 (**1. Robinson annulation, 2. Allene photochemical [2 + 2] cycloadditon**) (*rac.*)

A. Lupi, M. Patamia, I. Grgurina, R. M. Bettolo, O. Di Leo, P. Gioia, A. Antonaroli, *Helv. Chim. Acta* **1984**, *67*, 2261–2263 (**1. Podocarpic acid or Robinson annulation , 2. allene photocycloaddition**) (*rac.*)

(+)–18–Deoxystemarin/(+)–Stemarene:

F. Leonelli, F. Blesi, P. Dirito, A. Trombetta, F. Ceccacci, A. La Bella, L. M. Migneco, R. M. Bettolo, *J. Org. Chem.* **2011**, *76*, 6871–6876; M. Berettoni, R. M. Bettolo,V. MontanariT. Prencipe, S. Romeo, *Helv. Chim. Acta* **1991**, *74*, 1671–1678 (**1. Podocarpic acid or Robinson annulation** (G. Stork, A. Meisels, J. E. Davies, *J. Am. Chem. Soc.* **1963**, *85*, 3419–3425)**, 2. Allene photocycloaddition**)

2–desoxystemodinone:

R. B. Kelly, M. L. Harley, S. J. Alward, R. N. Rej, G. Gowda, A. Mukhopadhyay, P. S. Manchand, *Can. J. Chem.* **1983**, *61*, 269–275 (**1. Podocarpic acid or Robinson annulation ,** (G. Stork, A. Meisels, J. E. Davies, *J. Am. Chem. Soc.* **1963**, *85*, 3419–3425)**, 2. Allene photocycloaddition**) (*rac*, (+))

E. Piers, B. F. Abeysekera, D. J. Herbert, I. D. Sucklin, *Can. J. Chem.* **1985**, *63*, 3418–3432 (**1. Robinson annulation, 2. Allene photocycloadditon**) (*rac.*, formal)

J. D. White, T. C. Somers, *J. Am. Chem. Soc.* **1987**, *109,* 4424–4426; J. D. White, T. C. Somers, *J. Am. Chem. Soc.* **1994**, *116,* 9912–9920 (**1.LA–mediated cyclization, 2. Diels-Alder**) (*rac.*)

A. Lupi, M. Patamia, I. Grgurina, R. M. Bettolo, O. Di Leo, P. Gioia, A. Antonaroli, *Helv. Chim. Acta* **1984**, *67*, 2261–2263 2263 (**1. Podocarpic acid or Robinson annulation, 2. Allene photocycloaddition**) (*rac.*)

Aphidicolin:

J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser, M. A. Johnson, *J. Am. Chem. Soc.* **1979**, *101*, 1330–1332 (**1. Robinson annulation, 2. Claisen rearrangement**) formal

B. M. Trost, Y. Nishimura, K. Yamamoto, *J. Am. Chem. Soc.* **1979**, *101*, 1328–1330 (**1. Robinson annulation** (Y. Kitahara, A. Yoshikoshi, S. Oida, *Tetrahedron Lett.* **1964**, *5*, 1763–1770), **2. Alkylation**) formal

R. A. Holton, R. M. Kennedy, H. B. Kim, M. E. Krafft, *J. Am. Chem. Soc.* **1987**, *109*, 1597–1600 (**Michael Addition**) (+)

R. E. Ireland, J. D. Godfrey, S. Thaisrivongs, *J. Am. Chem. Soc.* **1981**, *103,* 2446–2448; *J. Org. Chem.* **1984**, *49*, 1001–1013. (**1. Alkylation, 2. Claisen rearrangement**) (*rac.*)

R. M. Bettolo, P. Tagliatesta, A. Lupi, D. Bravetti, *Helv. Chim. Acta* **1983**, *66,* 1922–1928; A. Lupi, M. Patamia, R. M. Bettolo, *Helv. Chim. Acta* **1988**, *71,* 872–875 (**1. Podocarpic acid or Robinson annulation**, **2. allene photocycloaddition**) (*rac.*)

E. E. van Tamelen, S. R. Zawacky, R. K. Russell, J. G. Carlson, *J. Am. Chem. Soc.* **1983**, *105,* 142–143 (**1. Polyene cyclization, 2. Intermolecular Diels–Alder**) formal

T. Tanaka, O. Okuda, K. Murakami, H. Yoshino, H. Mikamiyama, A. Kanda, S.-W. Kim, C. Iwata, *Chem. Pharm. Bull.* **1995**, *43*, 1407–1411 (**1. LA-catalyzed spiroannulation, 2. Conjugate addition**) (*rac.*, formal)

M. Toyota, Y. Nishikawa, K. Fukumoto, *Tetrahedron Lett.* **1994**, *35,* 6495–6498; M. Toyota, Y. Nishikawa, K. Fukumoto, *Tetrahedron* **1994**, *50,* 11153–11166, (**1. Heck cyclization, 2. Intramolecular Diels–Alder**) (*rac.*); M. Toyota, Y. Nishikawa, K. Fukumoto, *Tetrahedron Lett.* **1995**, *36,* 5379–5382; M. Toyota, Y. Nishikawa, K. Fukumoto, *Tetrahedron* **1996**, *52*, I0347–I0362 (**1. Pd–cat. Cycloisomerization, 2. Intramolecular Diels–Alder**) (+)

Stemodinone:

E. J. Corey, M. A. Tius, J. Das, *J. Am. Chem. Soc.* **1980**, *102*, 7612–7613 (**1. Hg(II) mediated polyene cyclization, 2. Robinson annulation**), (*rac.*, Stemodin, Aphidicolin).

A. Lupi, M. Patamia, I. Grgurina, R. M. Bettolo, O. Di Leo, P. Gioia, S. Autnaroli, *Helv. Chim. Acta* **1984**, *67*, 2261–2263 (**1. Podocarpic acid or Robinson annulation**, **2. Allene photocycloaddition**) (*rac.*)

E. Piers, B. F. Abeysekera, D. J. Herbert, I. D. Sucklin, *Can. J. Chem.* **1985**, *63*, 3418–3432 (**1. Robinson annulation, 2. Allene photocycloadditon**) (*rac.*)

A. J. Pearson, X. Fang, *J. Org. Chem*. **1997**, *62*, 5284–5292 (**1. and 2. Alkylation**) (*rac.*)

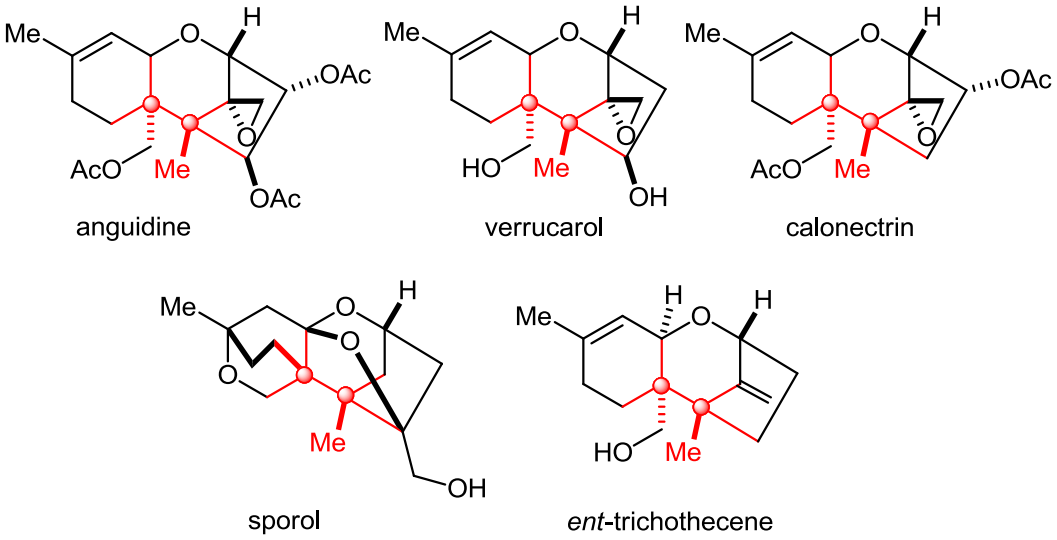
T. Tanaka, K. Murakami, A. Kanda, D. Patra, S. Yamamoto, N. Satoh, S.-W. Kim, S. M. A. Rahman, H. Ohno, C. Iwata, *J. Org. Chem.* **2001**, *66*, 7107–7112, T. Tanaka, O. Okuda, K. Murakami, H. Yoshino, H. Mikamiyama, A. Kanda, C. Iwata, *Tetrahedron Lett.* **1994**, *35*, 4125–4128; T. Tanaka, O. Okuda, K. Murakami, H. Yoshino, H. Mikamiyama, A. Kanda, S.-W. Kim, C. Iwata, *Chem. Pharm. Bull.* **1995**, *43*, 1017–1023 (**1. LA spiroannulation, 2. Intermolecular Diels–Alder**) (*rac.*)

(+)–stemodinol:

R. B. Kelly, M. L. Harley, S. J. Alward, R. N. Rej, G. Gowda, A. Mukhopadhyay, P. S. Manchand, *Can. J. Chem.* **1983**, *61*, 269–275 (**1. Podocarpic acid or Robinson annulation, 2. Allene photocycloaddition**)

Trichothecenes:

Biosynthesis: A. E. Desjardins, T. M. Hohn, S. P. McCormick, *Microbiological Reviews* **1993**, *57*, 595–604.



Anguidine:

D. W. Brooks, P. G. Grothaus, H. Mazdiyasni, *J. Am. Chem. Soc.* **1983**, *105*, 4472–4473 (**1. Alkylation, 2. Robinson annulation**) (enantioselective, formal)

Verrucarol:

M. Koreeda, D. J. Ricca, J. I. Luengo, *J. Org. Chem.* **1988**, *53*, 5586–5588 (**1. Wagner-Meerwein rearrangement, 2. Intramolecular Diels–Alder**) (rac., formal)

R. H. Schlessinger, R. A. Nugent, *J. Am. Chem. Soc.* **1982**, *104*, 1116–1118 (**1. Robinson annulation, 2. Intramolecular Diels–Alder**) (*rac.*)

B. M. Trost, P. G. McDougal, K. J. Haller, *J. Am. Chem. Soc.* **1984**, *106*, 383–395 (**1. Claisen rearrangement, 2. Intermolecular Diels–Alder**)

W. R. Roush, T. E. D'Ambra, *J. Am. Chem. Soc.* **1983**, *105,* 1058–1060 (**1. Rearrangement, 2. Diels–Alder**) (*rac.*)

Calonectrin:

G. A. Kraus, B. Roth, K. Frazier, M. Shimagaki, *J. Am. Chem. Soc.* **1982**, *104*, 1114–1116; G. A. Kraus, B. Roth *J. Org. Chem.* **1980**, *45*, 4820–4825 (**1. Intermolecular Diels–Alder, 2. Intramolecular alkylation**) (*rac.*)

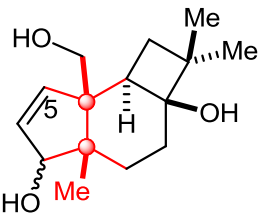
Sporol:

F. E. Ziegler, A. Nangia, G. Schulte, *Tetrahedron Lett.* **1988**, *29*, 1669–1672 (regioisomer); F. E. Ziegler, C. A. Metcalf III, A. Nangia, G. Schulte, *J. Am. Chem. Soc.* **1993**, *115*, 2581–2589 (*rac.*) (**Claisen rearrangement**)

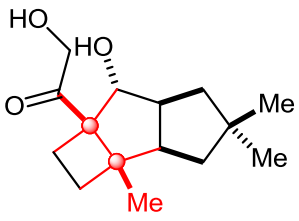
***Ent*–Trichothecene**:

J. C. Gilbert, R. D. Selliah, *Tetrahedron Lett.* **1992**, *33*, 6259–6262; *Tetrahedron* **1994**, *50*, 1651–1664 (**Ireland–Claisen rearrangement**) (+)

Tricyclic cyclobutane sesquiterpene:



punctatin A (5*R*)
punctatin D (5*S*)



sulcatine G

Punctatin A/D:

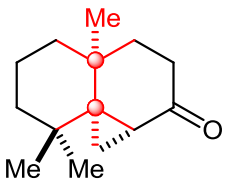
L. A. Paquette, T. Sugimura, *J. Am. Chem. Soc.* **1986**, *108*, 3841–3842 ((–)punctatin A), T. Sugimura, L. A. Paquette, *J. Am. Chem. Soc.* **1987**, *109*, 3017–3024 ((+)punctatin D), (**1. Robinson annulation, 2. Wittig–Still rearrangement**)

Sulcatine G:

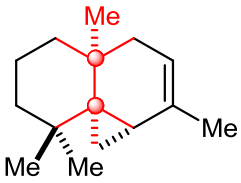
D. F. Taber, K. J. Frankowski, *J. Org. Chem.* **2005**, *70*, 6417–6421 (**1. Intramolecular carbenoid C–H insertion, 2. Intramolecular alkylation, 3. Cyclopropanation**) (+)

G. Mehta, K. Sreenivas, *Tetrahedron Lett.* **2002**, *43*, 3319–3321 (**1. Alkylation, 2. and 3. [2 + 2] Photocycloaddition**) (–)

Tricyclic cyclopropane sesquiterpenes:



dihydromayurone



thujopsene

Thujopsene:

C. X. Zhang, L. J. Fang, F. Q. Bi, Y. L. Li, *Chin. Chem. Lett.* **2008**, *19*, 256–258 (**1. Robinson annulation, 2. Cyclopropanation**) (–)

C. R. Johnson, M. R. Barbachyn, *J. Am. Chem. Soc.* **1982**, *104*, 4290–4291 (**1. Robinson annulation, 2. Cyclopropanation**) (*rac.*) (+) & (–)

A. Srikrishna, K. Anebouselvy, *J. Org. Chem.* **2001**, *66*, 7102–7106 (**1. Alkylation, 2. Intramolecular cyclopropanation**) (–) formal

W. G. Dauben, A. C. Ashcraft, *J. Am. Chem. Soc.* **1963**, *85*, 3673–3676 (**1. Robinson annulation, 2. Cyclopropanation**) (*rac.*)

G. Büchi, J. D. White, *J. Am. Chem. Soc.* **1964**, *86*, 2884–2887 (**1. Claisen rearrangement, 2. Intramolecular cyclopropanation**) (*rac.*)

K. Mori, M. Ohki, A. Kobayashi, M. Matsui, *Tetrahedron* **1970**, *26*, 2815–2819 (**1. Claisen rearrangement, 2. Intramolecular cyclopropanation)** (*rac.*)

J. E. McMurry, L. C. Blaszczak, *J. Org. Chem.* **1974**, *39*, 2217–2222 (**1. Robinson annulation, 2. Intramolecular cyclopropanation**) (*rac.*)

S. J. Branca, R. L. Lock, A. B. Smith III, *J. Org. Chem.* **1977**, *42*, 3165–3168 (**1. Wolff rearrangement, 2. Intramolecular cyclopropanation**) (*rac.*)

Dihydromayurone:

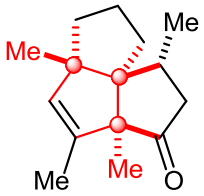
E. Lee, I.-J. Shin, T.-S. Kim, *J. Am. Chem. Soc.* **1990**, *112*, 260–264 (**1. Starting material, 2. Anionic oxy-Cope rearrangement, 3. Cyclopropanation**) (+)

C. R. Johnson, M. R. Barbachyn, *J. Am. Chem. Soc.* **1982**, *104*, 4290–4291 (**1. Robinson annulation, 2. Cyclopropanation**) (*rac.*) (+) & (–)

A. Srikrishna, K. Anebouselvy, *J. Org. Chem.* **2001**, *66*, 7102–7106 (**1. Alkylation, 2. Intramolecular cyclopropanation**) (–) formal

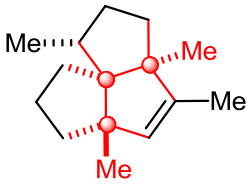
Angular Triquinane Sesquiterpene:

Arnicenone:

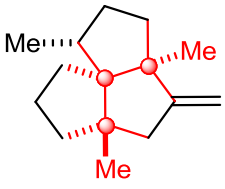


Y. Iura, T. Sugahara, K. Ogasawara, *Org. Lett.* **2001**,*3*, 291–293 (**1. Pauson–Khand reaction, 2. Conjugate addition, 3. Alkylation**)

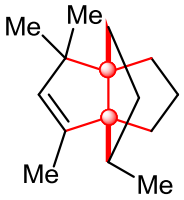
Isocomene–core:



isocomene



β-isocomene



modhephene

Isocomene (*rac.*):

W. G. Dauben, D. M. Walker, *J. Org. Chem.* **1981**, *46*, 1103–1108 (**1. and 2 . Weiss–Cook Condensation, 3. Alkylation**) formal

L. A. Paquette, Y. K. Han, *J. Org. Chem.* **1979**, *44*, 4014–4016; L. A. Paquette, Y. K. Han, *J. Am. Chem. Soc.* **1981**, *103*, 1835–1838 (**1. Henry reaction, 2. Conjugate addition, 3. Prins cyclization**) (*rac.*)

M. C. Pirrung, *J. Am. Chem. Soc.* **1981**, *103*, 82–87 (**Intramolecular [2 + 2] photocycloaddition**)

W. Oppolzer, K. Bättig, T. Hudlicky, *Helv. Chim. Acta* **1979**, *62*, 1493–1496 (**1. Robinson annulation, 2. Alkylation, 3. Ene**)

S. Chatterjee, *J. Chem. Soc., Chem. Comm.* **1979**, 620–621 (**1. Alkylation, 2. Acid–catalyzed transannular cyclization, 3. Conjugate addition**)

G. G. G. Manzardo, M. Karpf, A. S. Dreiding, *Helv. Chim. Acta* **1986**, *69*, 659–669 (**1. Starting material, 2. Conjugate addition, 3. thermolytic α–alkynone cyclization**) formal

L. Fitjer, A. Kanschik, M. Majewski, *Tetrahedron Lett.* **1988**, *29*, 5525–5528; L. Fitjer, M. Majewski, H. Monzó-Oltra, *Tetrahedron* **1995**, *51*, 8835–8852 (**1. Ketene photocycloaddition, 2. Meinwald Rearrangement, 3. Wagner-Meerwein Rearrangement**) (*rac.*)

B. B. Snider, R. B. Beal, *J. Org. Chem.* **1988**, *53*, 4508–4515 (**1. Carroll rearrangement (Claisen rearrangement), 2. Intramolecular ketene photocycloaddition**) formal

E. Wenkert, T. S. Arrhenius, *J. Am. Chem. Soc.* **1983**, *105*, 2030–2033 (**1. Robinson-like annulation, 2. Cyclopropanation, 3. Ring expansion**) (*rac.*)

H.-W. Lee, I.-Y. C. Lee, *Bull. Korean Chem. Soc.* **1990**, *11*, 273–274; H.-W. Lee, J.-H. Lee, I.-Y. C. Lee *Bull. Korean Chem. Soc.* **1991**, *12*, 392–397 (**1. Alkylation, 2. Conjugate addition, 3. Alkylation**) formal

T. Uyehara, T. Murayama, K. Sakai, K. Onda, M. Ueno, T. Sato, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 231–242 (**1. Pinacol rearrangement, 2. Oxa-di-π-methane rearrangement, 3. Intramolecular aldol**) formal

β–Isocomene/ Isocomene:

A. W. Schmidt, T. Olpp, E. Baum, T. Stiffel, H.-J. Knölker, *Synlett* **2007**, *15*, 2371–2374 (**1. Michael addition, 2. Ti(II)–mediated tandem cyclization**) (*rac.*)

N. D. Willmore, R. Goodman, H. H. Lee, R. M. Kennedy, *J. Org. Chem.* **1992**, *57*, 1216–1219 (**1. Ireland–Claisen rearrangement, 2. Alkylation, 3. Conjugate addition**) (*rac.*)

Y. Tobe, T. Yamashita, K. Kakiuchi, Y. Odaira, *J. Chem. Soc, Chem. Comm.* **1985**, 898–899 (**1. Alkylation, 2. and 3. Allene photocycloaddition**) (*rac.*)

V. H. Rawal, C. Dufour, A. Eschbach, *J. Chem. Soc., Chem. Commun.* **1994**, 1797–1798 (**1. Alkylation, 2. Alkylation, 3. Intramolecular Conjugate addition-radical or anionic**) (*rac.*) formal isocomene

R. P. Short, J.-M. Revol, B. C. Ranu, T. Hudlicky, *J. Org. Chem.* **1983**, *48*, 4453–4461; B. C. Ranu, M. Kavka, L. A. Higgs, T. Hudlicky, *Tetrahedron Lett.* **1984**, *25*, 2447–2450 (**1. Johnson–Claisen rearrangement, 2. and 3. Intramolecular cyclopropanation**) (*rac.*)

L. Fitjer, H. Monzo-Oltra, *J. Org. Chem.* **1993**, *58*, 6171–6173 (**1. Allene photocycloaddition, 2. Rearrangement, 3. Rearrangement**) (–)

Modhephene:

J. Wrobel, K. Takahashi, V. Honkan, G. Lannoye, J. M. Cook, S. H. Bertz, *J. Org. Chem.* **1983**, *48*, 139–141 (**1. and 2. Weiss–Cook reaction, 3. Alkylation**) (*rac.*)

W. Oppolzer, F. Marazza, *Helv. Chim. Acta* **1981**, *64*, 1575–1578; W. Oppolzer, K. Bättig, *Helv. Chim. Acta* **1981**, *64*, 2489–2491 (**1. Conjugate addition, 2. Ene, 3. Conjugate addition**) (*rac.*)

A. B. Smith III, P. J. Jerris, *J. Am. Chem. Soc.* **1981**, *103*, 194–195; A. B. Smith III, P. J. Jerris, *J. Org. Chem.* **1982**, *47*, 1845–1855 (**1. and 2. [2 + 2] Photocycloaddition, 3. Conjugate addition**) (*rac.*)

M. Karpf, A. S. Dreiding, *Tetrahedron Lett.* **1980**, *21*, 4569–4570; M. Karpf, A. S. Dreiding, *Helv. Chim. Acta* **1981**, *64*, 1123–1133 (**1. Conjugate addition, 2. Thermolytic α–alkynone cyclization, 3. Conjugate addition**) (*rac.*)

H. Schostarez, L. A. Paquette, *J. Am. Chem. Soc.* **1981**, *103*, 722–724; H. Schostarez, L. A. Paquette, *Tetrahedron* **1981**, *37*, 4431–4435 (**1. Nazarov cyclication, 2.Conjugate addition, 3. Conia-ene reaction**) (*rac.*)

P. A. Wender, G. B. Dreyer, *J. Am. Chem. Soc.* **1982**, *104,* 5805–5807 (**Arene-olefin photocycloaddition**) (*rac.*)

D. Wilkening, B. P. Mundy, *Tetrahedron Lett.* **1984**, *25*, 4619–4622 (formal); B. P. Mundy, D. Wilkening, K. B. Lipkowitz, *J. Org. Chem.* **1985**, *50*, 5727–5731 (**1. and 2. Tandem alkylation-aldol cyclization, 3. Conjugate addition**) (*rac.*)

L. Fitjer, A. Kanschik, M. Majewski, *Tetrahedron Lett.* **1988**, *29*, 5525–5528 (*rac.*); L. Fitjer, Monzo–Oltra, M. Noltemeyer, *Angew. Chem., Int. Ed.* **1991**, *30*, 1492–1494 (–),(+),L. Fitjer, M. Majewski, H. Monzó–Oltra, *Tetrahedron* **1995**, *51*, 8835–8852 (**1. Ketene Photocycloaddition, 2. Meinwald Rearrangement, 3. Ring expansion**) (*rac.*)

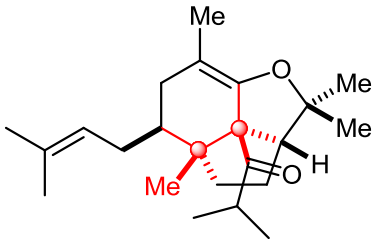
E. A. Mash, S. K. Math, C. J. Flann, *Tetrahedron Lett.* **1988**, *29*, 2147–2150 (+),E. A. Mash, S. K. Math, C. J. Flann, *Tetrahedron* **1989**, *45*, 4945–4950 (–) (**1. Nazarov cyclization, 2. Cyclopropanation, 3. Intramolecular Conia–ene**)

C.-K. Sha, T.-S. Jean, D.-C. Wang, *Tetrahedron Lett.* **1990**, *31*, 3745–3748; *J. Chin. Chem. Soc.* **1995**,*42*, 637–640 (**1. Nazarov cyclization, 2. Conjugate addition, 3. Radical cyclization**) (*rac.*)

C. P. Jasperse, D. P. Curran, *J. Am. Chem. Soc.* **1990**, *112*, 5601–5609 (**1. Alkylation, 2. Radical cyclization, 3. Cationic alkylation**) D. P. Curran, W. Shen, *Tetrahedron* **1993**, *49*, 755–770 (**1. Ireland–Claisen rearrangement, 2. and 3. Radical cyclization**) (*rac.*) + epimer

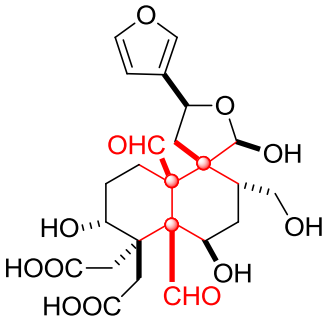
S. C. Suri, *Tetrahedron Lett.* **1993**, *34*, 8321–8324 (**1. Intermolecular Diels–Alder, 2. Rearrangement, 3. Alkylation**) formal
G. A. Kraus, J. Shi, *J. Org. Chem.* **1990**, *55*, 5423–5424; G. A. Kraus, J. Shi, *J. Org. Chem.* **1991**, *56*, 4147–4151 (**1. Michael addition, 2. Favorskii reaction, 3. Conjugate addition**) formal
G. Mehta, D. Subrahmanyam, *J. Chem. Soc., Chem. Commun.* **1985**, 768–769; G. Mehta, D. Subrahmanyam, *J. Chem. Soc., Perkin Trans. 1* **1991**, 395–401 (**1. and 2 Intermolecular Diels–Alder, 3. Oxa–di–π–methane rearrangement**) (*rac.*)
Y. Tobe, S. Yamashita, T. Yamashita, K. Kakiuchi, Y. Odaira, *J. Chem. Soc., Chem. Commun.* **1984**, 1259–1260 (**1. Nazarov cyclization, 2. and 3. Allene Photocycloaddition**) formal
M. S. Laxmisha, G. S. R. S. Rao, *Tetrahedron Lett.* **2000**, *41*, 3759–3761 (**1. Diels–Alder, 2. Alkylation, 3. Radical cyclization**) (rac.)
T. Uyehara, T. Murayama, K. Sakai, M. Ueno, T. Sato, *Tetrahedron Lett.* **1996**, *37*, 7295–7298; T. Uyehara, T. Murayama, K. Sakai, K. Onda, M. Ueno, T. Sato, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 231–242 (**1. and 2. Pinacol rearrangement, 3. Alkylation**) formal

Yezo'otogirin C:

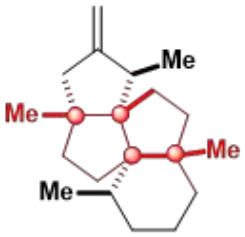


S. He, W. Yang, L. Zhu, G. Du, C.-S. Lee, *Org. Lett.* **2014**, *16*, 496–499 (**1. Conjugate addition, 2. Oxidative radical cyclization**) (*rac.*)

Representative Molecules with 4 and 5 contiguous quaternary stereocenters:

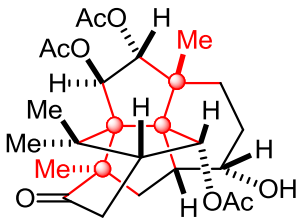


M. Ali, *Phytochemistry*, **1992**, *31*, 2173–2175.



waihoensene

D. B. Clarke, S. F. R. Hinkley, R. T. Weavers, *Tetrahedron Lett.* **1997**, *38*, 4297-4300.



taxane-derived propellane
'Canataxapropellane'

W. Q. Shi, F. Sauriol, Mamer, L. O. Zamir, *Chem. Comm.* **2012**, 68–69.

2003

see also TL 2007, 48, 2721