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Total Synthesis of Oxepin and Dihydrooxepin Containing Natural Products

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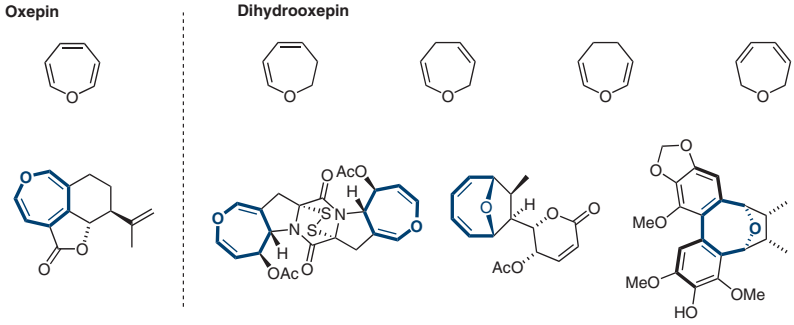

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Abstract The construction of oxepin and dihydrooxepin containing natural products represents a challenging task in total synthesis. In the last decades, a variety of synthetic methods have been reported for the installation of these structural motifs. Herein, we provide an overview of synthetic methods and strategies to construct these motifs in the context of natural product synthesis and highlight the key steps of each example.

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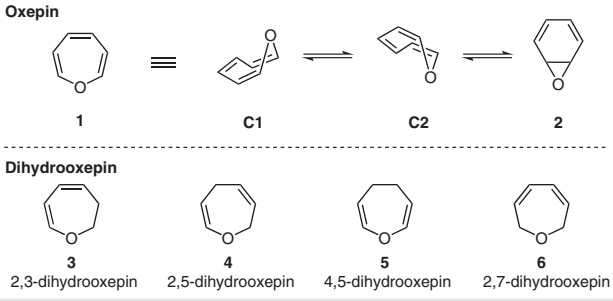
Key words oxepin, dihydrooxepin, natural product, total synthesis, heterocycles

1 Introduction

Oxepin is an unsaturated seven-membered heterocycle containing one oxygen and six carbon atoms. The antiaromatic character of oxepin **1** is demonstrated by its nonplanar boat conformations C1 and C2, shown in Scheme 1. Moreover, oxepin **1** exists in equilibrium with the corresponding arene oxide **2**, which is affected by the substitution pattern.[1] At low temperatures (–130 °C), the ^{1}H NMR spectrum shows peaks at 5.1 and 6.3 ppm (oxepin) and 4.0 and 6.3 ppm (arene oxide). These shifts also indicate the nonaromatic character with localized double bonds.[2]

Monohydrogenation of **1** yields the dihydrooxepin core, which exists as four different isomers **3–6**, depending on the arrangement of the two double bonds (Scheme 1).

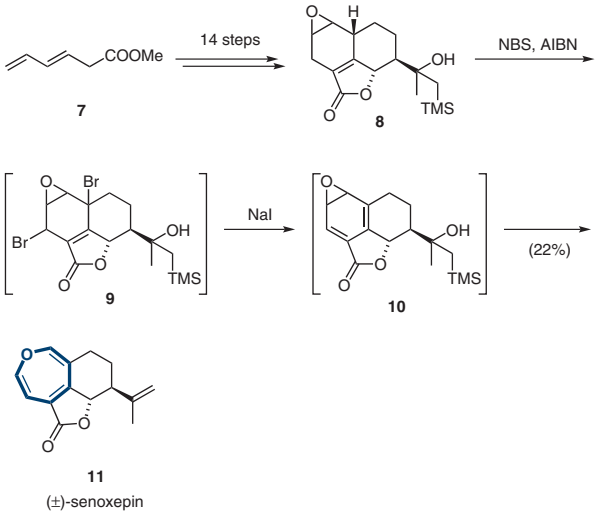


Scheme 1 Oxepin structures **1** and dihydrooxepin regioisomers **3–6**

In contrast to its five- and six-membered congeners, the seven-membered heterocyclic ring-system represents a relatively rare structural motif in nature. Nevertheless, several natural products bearing this structure have been isolated and demonstrated a variety of interesting biological activities.[3] For the syntheses of the heterocyclic core structure, a variety of methods have been developed.[4] A detailed description is beyond the scope of this short review. Here, we highlight synthetic strategies to access oxepin and dihydrooxepin containing natural products.

2 Oxepin Natural Products

Racemic senoxepin (**11**), a norsesquiternelactone found in *Senecio platyphylloides*, was the first oxepin-containing natural product obtained by total synthesis by Bohlmann in 1989 (Scheme 2).[5] Starting from methyl 3,5-hexadienoate (**7**), epoxide **8** was synthesized in 14 steps. Allylic bromination of **8** with azobisisobutyronitrile (AIBN) and *N*-bromosuccinimide (NBS) produced the dibromide **9**, which was directly subjected to Finkelstein conditions resulting in diene **10**. Spontaneous disrotatory electrocyclic rearrange-



Scheme 2 Arene oxide rearrangement for the construction of the oxepin motif in senoxepin **11** by Bohlmann

ment to the oxepin followed by Peterson olefination provided senoxepin (**11**). Initial attempts to install the *exo*-methylene group via Oshima methylenation (CH_2Br_2/Zn/$TiCl_4$) resulted in degradation of the oxepin to give a benzene core.

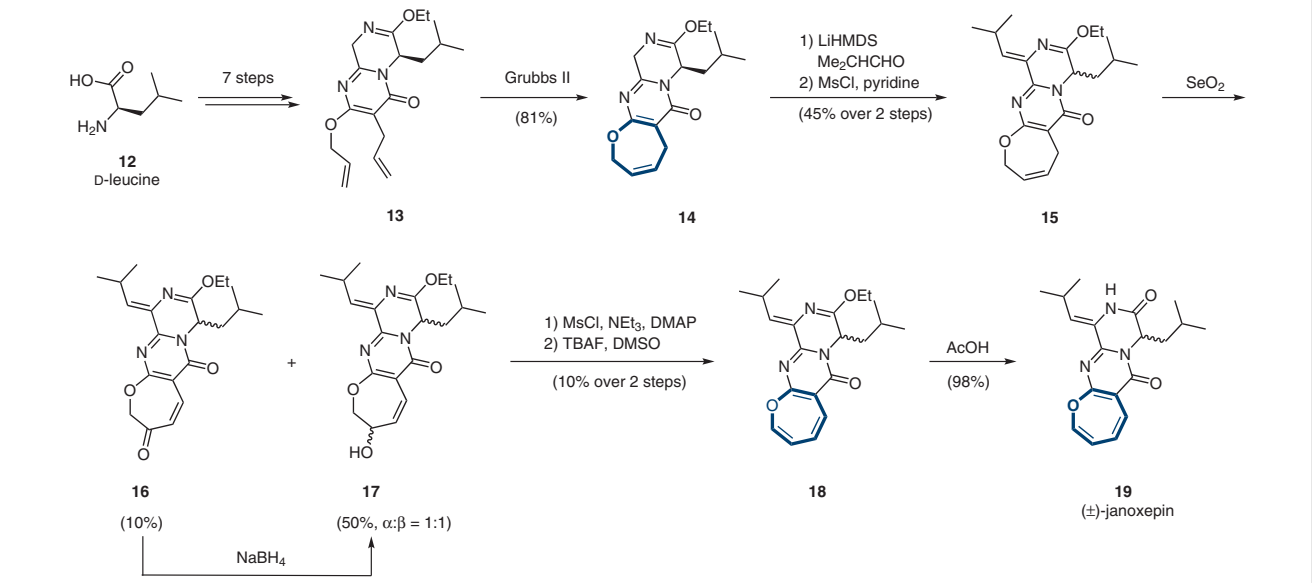
In 2012, Taylor reported the total synthesis of janoxepin (**19**), a leucine-derived oxepin-pyrimidinone-ketopiperazine natural product (Scheme 3).[6] Janoxepin (**19**) was isolated from the fungus *Aspergillus janus* and possesses antiplasmodial effects against the malaria parasite *Plasmodium falciparum* 3D7 strain. Diene **13** was generated in seven steps using leucine (**12**) as the starting material. Upon exposure to Grubbs second-generation catalyst, dihydrooxepin **14** was obtained in 81% yield. A two-step condensation procedure under basic conditions provided the desired isopropyl group in **15**. Nevertheless, during these steps, isomerization occurred with loss of stereoinformation. Riley oxidation afforded the desired alcohol **17** in 50% yield as an equimolar mixture of diastereomers together with the ketone **16** (10%). The latter was converted back into the alcohol **17** with sodium borohydride. While elimination proved challenging under various standard conditions, the alcohol **17** was transformed into the chloride using mesyl chloride. Tetrabutylammonium fluoride (TBAF) mediated dehydrohalogenation gave the desired oxepin **18** in low yield (10%) together with a mixture of unidentified byproducts. Final hydrolysis of the imidate functionality afforded janoxepin (**19**).

A more frequent structural motif in nature is benzoxepin, which does not undergo the previously described isomerization to the corresponding arene oxides. The benzoxepin salvianolic acid N (**25**) was isolated from Danshen, the dried root and rhizome of *Salvia miltiorrhiza Bunge* (Scheme 4).[7] Danshen is a traditional Chinese drug used for the treatment of coronary artery disease and is known to possess antiviral, antioxidant, and antitumor activities. The reported total synthesis began with aldehyde **20**, which was converted into bromide **21** via bromination and tosyl-

Biographical Sketches

Kevin Rafael Sokol was born in Munich, Germany. He completed his bachelor thesis under the supervision of Prof. Dirk Trauner at the Ludwig-Maximilians University Munich, working on azobenzene based molecules to control receptor functionality. For his master's degree he moved to the California Institute of Technology to develop novel nickel-catalyzed enantioselective reductive cross-coupling under the supervision of Prof. Sarah Reisman. End of 2016, he joined the research group of Prof. Thomas Magauer at the Ludwig-Maximilians University Munich and the University of Innsbruck for doctoral studies. In 2021, he moved to Vienna to join Boehringer Ingelheim as an Associate Principal Scientist.

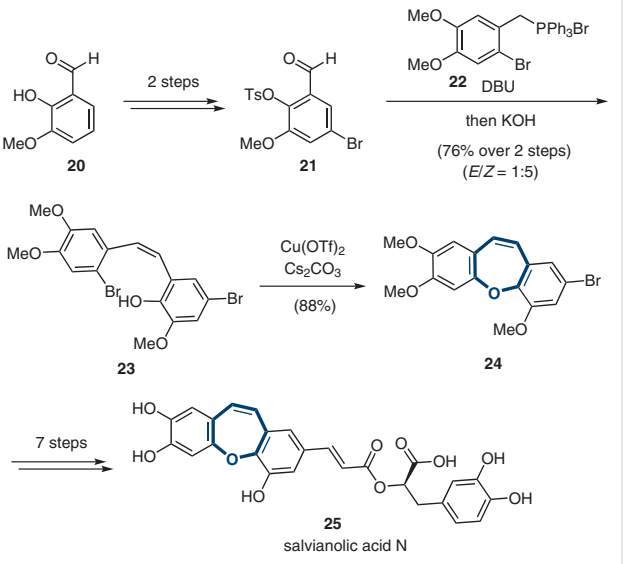
Thomas Magauer studied chemistry at the University of Vienna and joined the laboratories of Prof. Johann Mulzer in 2007. In 2009, he moved to Harvard University to begin postdoctoral studies with Prof. Andrew G. Myers. In 2012, he began his independent research as a FCI Liebig and a DFG Emmy Noether Group Leader at the Ludwig-Maximilians University Munich. In 2017, Tommy was awarded the Goering Visiting Professorship at the University of Wisconsin, Madison and in the same year he accepted a position as Full Professor of Synthesis and Synthetic Methods at the University of Innsbruck, Austria. His research program has been supported by the Austrian Science Fund (FWF), by an ERC Starting Grant (2017–2022) and an ERC Consolidator Grant (2022–2027).



Scheme 3 Ring-closing metathesis for the construction of the oxepin motif in janoxepin (**19**) by Taylor

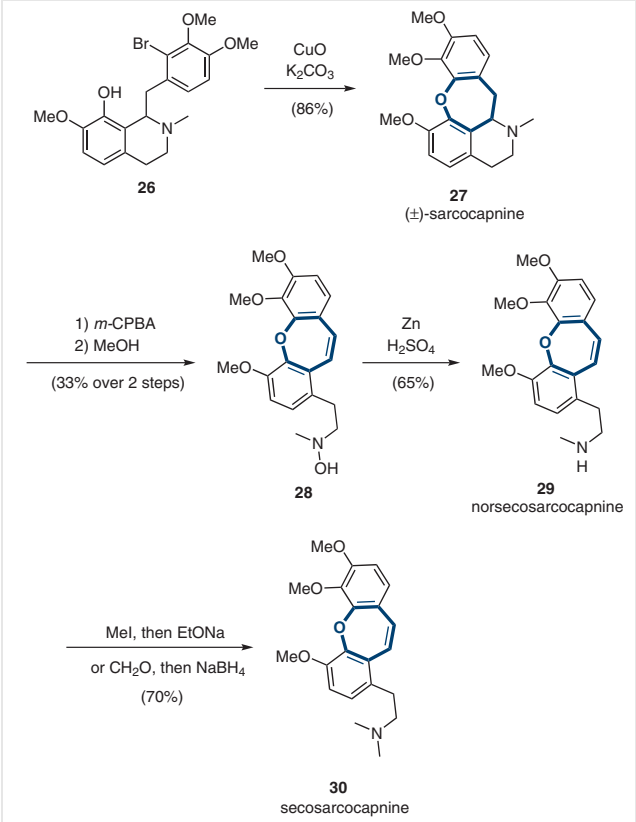
ation. Protection of the phenol as its tosylate proved to be essential to obtain the required *Z*-selectivity with ylide **22** (ratio 5:1) for stilbene formation. Intramolecular Ullmann coupling under optimized conditions (copper(I)triflate, caesium carbonate) afforded oxepin **24** in 88% yield. Completion of the synthesis of salvianolic acid N (**25**) was achieved in a further seven steps.

In 1991, Castedo reported the synthesis of norsecosarcocapnine (**29**), which also gave access to secosarcocapnine (**30**) via an intramolecular Ullmann coupling (Scheme 5).[8]



Scheme 4 Ullmann coupling for the construction of the oxepin motif in salvianolic acid N (**25**) by Zhang

Subsequent Cope elimination of the piperidine motif gave the desired oxepin structure. Reduction of the hydroxylamine moiety with zinc and sulfuric acid gave norsecosar-

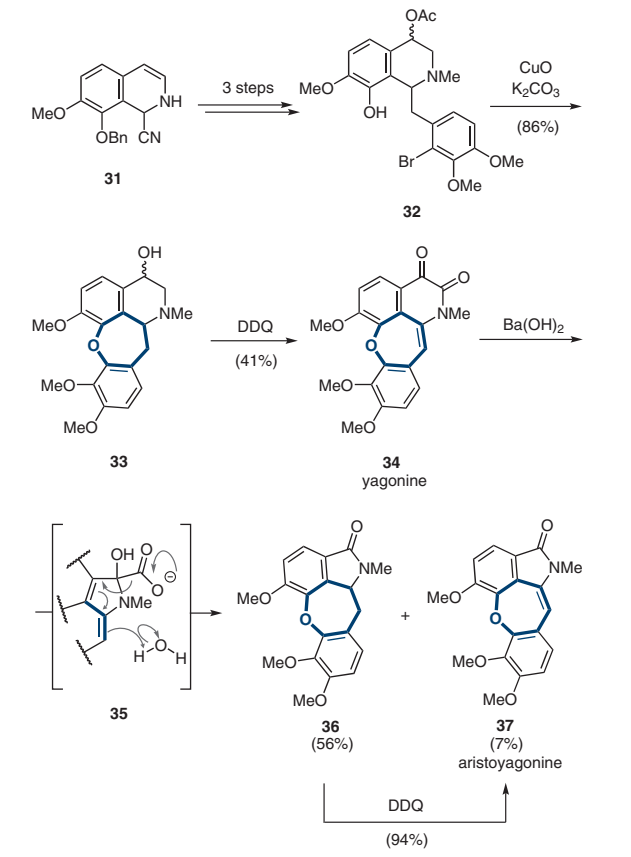


Scheme 5 Ullmann coupling for the construction of the oxepin motif in secosarcocapnine (**30**) by Castedo

cocapnine (**29**), which was then methylated with either methyl iodide followed by treatment with sodium ethanolate or by reductive amination using formaldehyde and sodium borohydride to give secosarcocapnine (**30**).

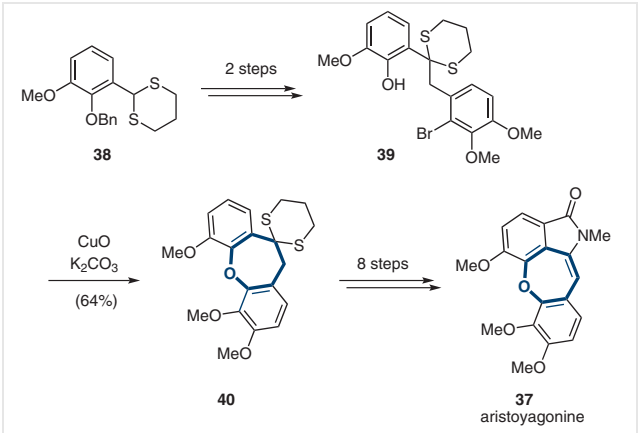
Exposure of phenol **32**, itself derived from dihydroisoquinoline **31** in three steps, to the same Ullmann coupling conditions gave an undetermined diastereomeric mixture of dihydrooxepin **33** (Scheme 6).[9] Subsequent oxidation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the natural product yagonine (**34**).

Exposure of **34** to barium hydroxide induced the formation of dihydrooxepin **36** (56%) and aristoyagonine (**37**) (7%) via benzilic-acid type ring-contraction. Oxidation of the undesired dihydrooxepin **36** with DDQ provided aristoyagonine (**37**) in excellent yield (Scheme 6).[9]



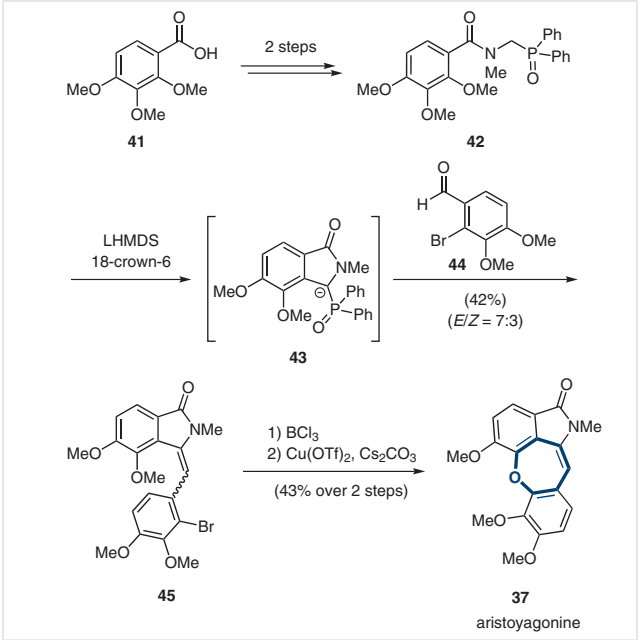
Scheme 6 Ullmann coupling for the construction of the oxepin motif in aristoyagonine (**37**) by Castedo

The first total synthesis of aristoyagonine (**37**) was reported by Domínguez in 1995 (Scheme 7).[10] The first part of the synthesis involved the conversion of thioacetal **38** into phenol **39**. Again, an Ullmann coupling was applied to produce the dihydrooxepin **40**. The presence of the thioacetal group turned out to be beneficial as other functionalities caused significant formation of side products. Finally, the lactam of aristoyagonin (**37**) was assembled in eight further steps.



Scheme 7 Ullmann coupling for the construction of the oxepin motif in aristoyagonine (**37**) by Domínguez

An additional total synthesis of aristoyagonine (**37**) was accomplished by Grandclaudon in 2004 and allowed shortening of the route to five steps (Scheme 8).[11]

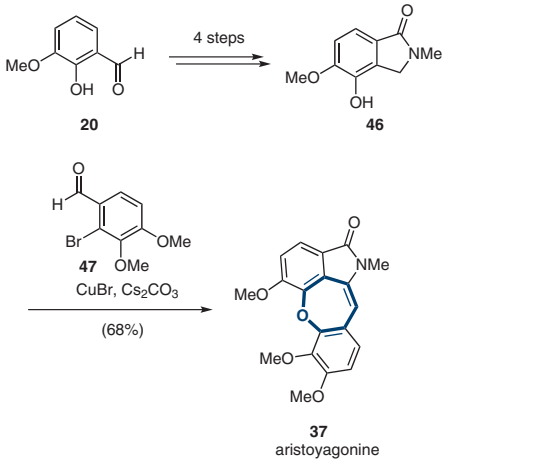


Scheme 8 Ullmann coupling for the construction of the oxepin motif in aristoyagonine (**37**) by Grandclaudon

Carboxylic acid **41** was converted into phosphorylated-isoindolinone **42** in two steps. Wittig type reaction employing lithium bis(trimethylsilyl)amide (LHMDS) and 18-crown-6 yielded alkene **45**. During demethylation with boron trichloride, full isomerization of the alkene was observed,

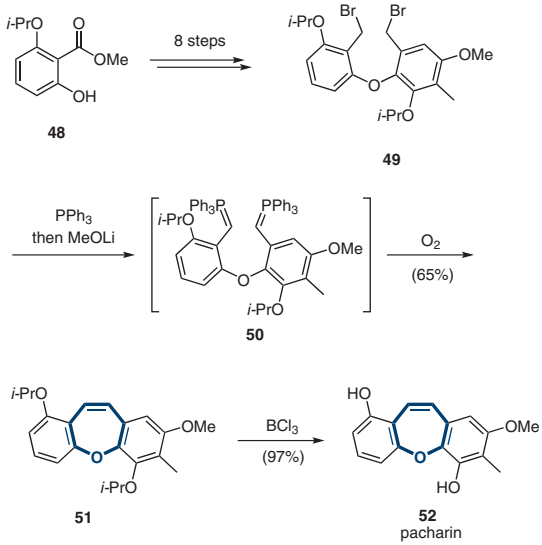
yielding only the *Z*-isomer, which was directly annulated under Ullmann coupling conditions to give aristoyagonine (**37**).

In 2013, aristoyagonine (**37**) was synthesized by Ho in five steps from aldehyde **20** (Scheme 9).[12] The one-pot cascade reaction of isoindoline **46** directly afforded the dibenzoxepin lactam aristoyagonine (**37**) via a one-pot sequence in 68% yield.



Scheme 9 Ullmann coupling for the construction of the oxepin motif in aristoyagonine (**37**) by Ho

While intramolecular Ullmann coupling was shown to be an attractive and powerful method for the synthesis of seven-membered oxacycles, Sargent reported the synthesis of pacharin (**52**) via an intermolecular Ullmann coupling (Scheme 10).[13] An eight-step sequence gave access to diaryl ether **49**. Treatment of **49** with triphenylphosphine generated bisylide **50**. Upon exposure of **50** to oxygen, the desired oxepin **51** was formed. A final deprotection step using boron trichloride allowed for selective removal of the isopropyl groups to afford pacharin (**52**).



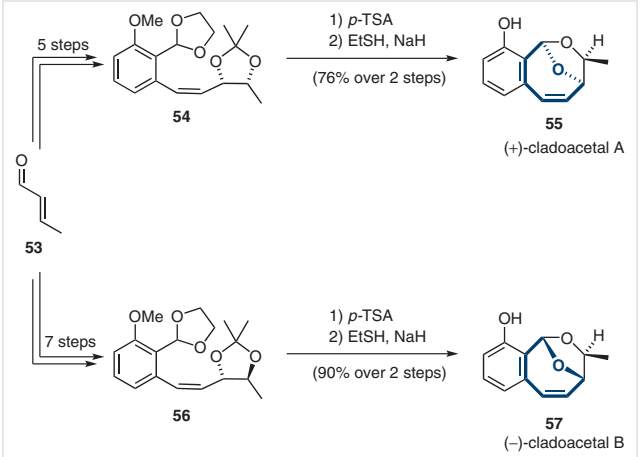
Scheme 10 Wittig type reaction for the construction of the oxepin motif in pacharin (**52**) by Sargent

3 Dihydrooxepin Products

In contrast to oxepin, the dihydrooxepin structure is more frequently found in natural products. Due to the different possibilities for the arrangement of the double bonds, there are significantly more options available for the construction of these heterocycles. In the following, we have ordered the syntheses according to the different strategies employed to build up the seven-membered ring system.

3.1 Brønsted or Lewis Acid Catalyzed Cyclization

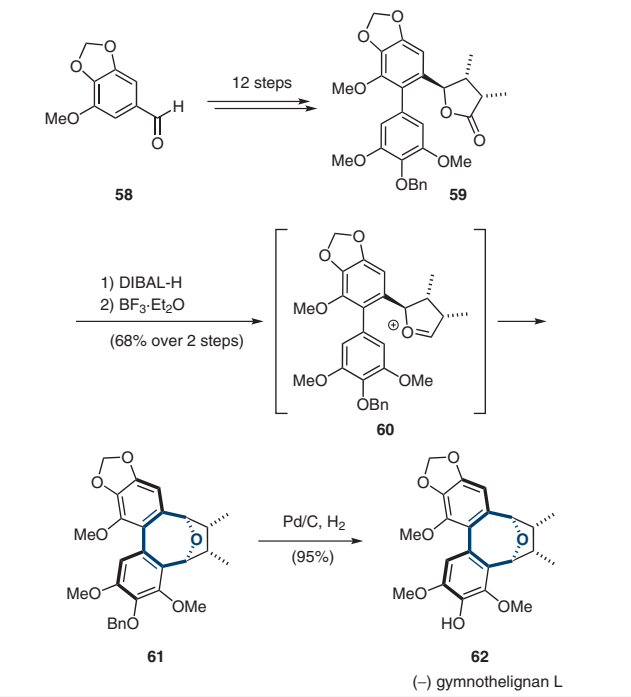
Cladoacetal A (**55**) and B (**57**) were isolated from solid-substrate fermentation cultures of an unidentified fungicolous isolate (NRRL 29097) resembling *Cladosporium* species. So far, only cladoacetal A (**55**) demonstrated antibacterial activity. While the relative configurations were determined by NMR spectroscopy shortly after the isolation, the absolute configurations were only determined by the first total synthesis by Lin in 2012. Enantioselective syntheses of cladoacetal A (overall yield: 16%) and B (overall yield: 34%) proceeded in nine and seven steps, respectively, employing crotonaldehyde (**53**) as the starting material (Scheme 11).[14] The dihydrooxepin core of both natural products was synthesized from bisoxolane **54** and **56** via intramolecular acetalization promoted under thermal (70 °C) acidic conditions (*p*-TSA). Final methyl deprotection with freshly pre-



Scheme 11 Acid catalyst acetalization for the construction of the dihydrooxepin motif in (+)-cladoacetal A (**55**) and (–)-cladoacetal B (**57**) by Lin

pared sodium ethanethiolate afforded (+)-cladoacetal A (**55**) in 76% and (–)-cladoacetal B (**57**) in 90% yield over two steps, respectively.

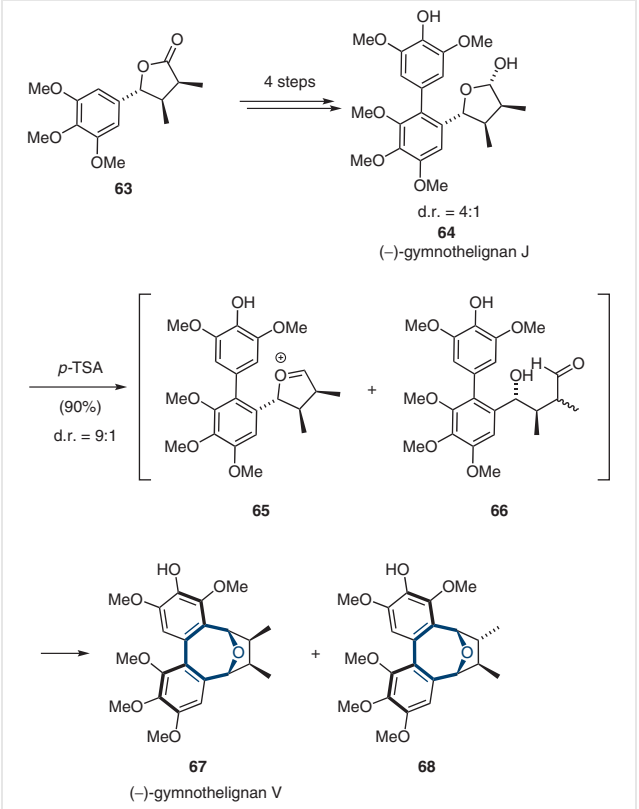
In 2018, She published a bioinspired total synthesis of the natural product (–)-gymnothelignan L (**62**), which was isolated from *Gymnotheca chinensis Decne*, a widely used perennial Chinese herb (Scheme 12).[15] Structurally, **62** is classified as a dibenzocyclooctene-type lignin natural product in which the chiral axial biphenyl scaffold is fused to the THF ring, to form a bridged dihydrooxepin backbone.



Scheme 12 Lewis acid mediated Friedel–Crafts alkylation for the construction of the dihydrooxepin motif in (–)-gymnothelignan L (**62**) by She

The aldehyde **58** served as the starting point of the synthesis and was converted into lactone **59** in twelve steps. The adjacent stereocenters of the lactone were introduced by an asymmetric Evans aldol reaction and the second methyl group by α-methylation of the corresponding lactone. With enantiomerically pure material in hand, the [4.2.1]-bicyclic ether core was constructed via an intramolecular transannular Friedel–Crafts reaction. Diisobutylaluminium hydride (DIBAL-H) mediated reduction of the γ-butyrolactone **59** afforded the corresponding lactol. Subsequent treatment with boron trifluoride–diethyl etherate at –78 °C generated oxocarbenium cation **60**, which underwent the Friedel–Crafts cyclization upon slow warming of the reaction mixture to –30 °C to give dihydrooxepin **61** in 68% yield over two steps. Finally, reductive cleavage of the benzyl group with a catalytic amount of palladium on charcoal furnished the natural product (–)-gymnothelignan L (**62**).

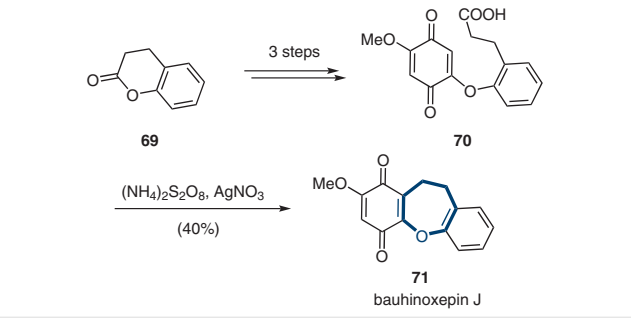
Similar to the already described synthesis of (–)-gymnothelignan L (**62**), a route to (–)-gymnothelignan V (**67**) was published by Reutrakul in the same year under slightly modified conditions (Scheme 13).[16] Starting from enantiopure lactone **63**, four further steps yielded the natural product gymnothelignan *J* (**64**) as a mixture of two diastereomers (d.r. = 4:1). Upon treatment of **64** with a catalytic amount of *p*-TSA, both diastereomers generated the same oxocarbenium cation **65**, which readily underwent stereoselective intramolecular Friedel–Crafts cyclization to afford (–)-gymnothelignan V (**67**) together with its *epi*-isomer (**68**) as an inseparable mixture (90%, d.r. = 9:1). The formation of **68** was proposed to proceed through the lactol ring-opening under acidic conditions followed by epimerization of the α-methyl group of aldehyde **66**. Separation of the diastereomers was accomplished by using the TBS-protected phenol derivative of **64**, which after desilylation gave pure (–)-gymnothelignan V (**67**).



Scheme 13 Friedel–Crafts alkylation for the construction of the dihydrooxepin motif in (–)-gymnothelignan V (**67**) by Reutrakul

3.2 Radical Cyclisation

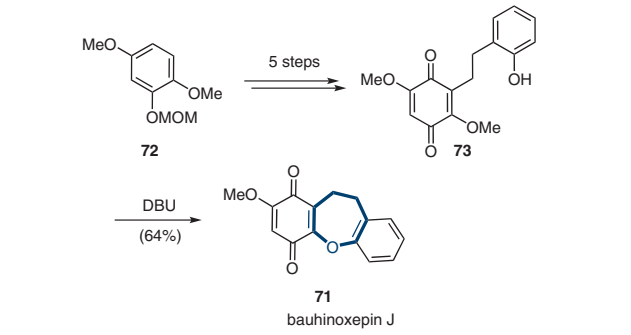
In recent years, numerous tricyclic dibenzo[*b*,*f*]oxepin natural products such as bauhinoxepin *J* (**71**) were isolated from plants belonging to the *Bauhinia* genus, in particularly *Bauhinia purpurea*. After its isolation in 2007, **71** was found to exhibit remarkable biological activities including antimycobacterial, antimalarial, and tumor growth inhibitory activity, making bauhinoxepin *J* (**71**) an interesting target for synthesis. The first total synthesis was accomplished by Kraus in 2009 (Scheme 14).[17] The synthesis began with chromanone **69**, which was converted into carboxylic acid **70** in three steps. The key radical intramolecular cyclisation step was based on work of DeKimpe and was promoted by the addition of ammonium persulfate to **70**. This gave bauhinoxepin *J* (**71**) in 40% isolated yield and an overall yield of 22% over four steps.



Scheme 14 Radical cyclization for the construction of the dihydrooxepin motif in bauhinoxepin *J* (**71**) by Kraus

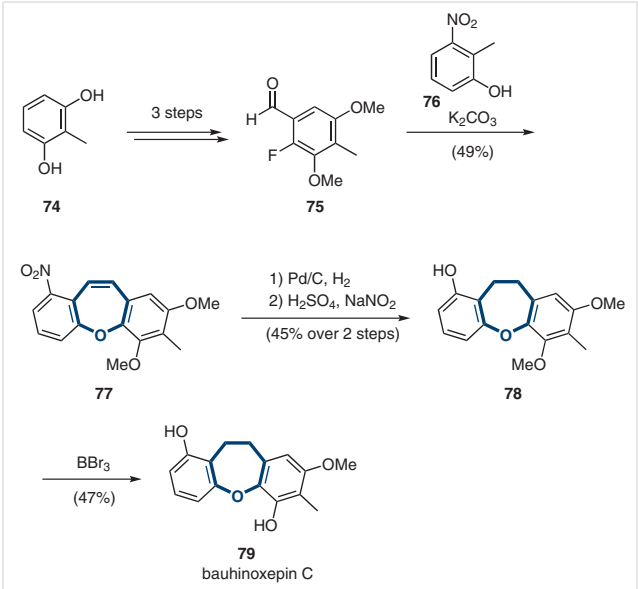
3.3 Substitution and Addition Cyclization

A second route to bauhinoxepin *J* (**71**) was published by Katoh. Starting from trioxybenzene **72** the synthesis proceeded in 33% yield over six steps (Scheme 15).[18] The final cyclization of the seven-membered dihydrooxepin ring was accomplished under mild basic conditions and involved intramolecular nucleophilic 1,4-addition of phenol **73** and subsequent elimination to give bauhinoxepin J (**71**).



Scheme 15 1,4-Addition/elimination for the construction of the dihydrooxepin motif in bauhinoxepin J (**71**) by Katoh

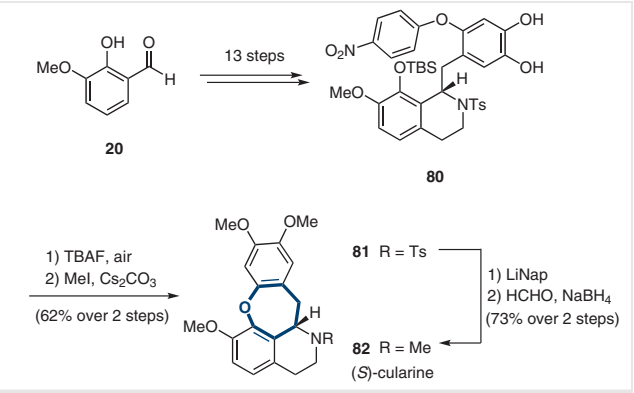
A further member of this natural product family, bauhinoxepin C (**79**), was synthesized via a one-pot sequence developed by Ngernmeesri in 2021 (Scheme 16).[19] 2-Methylresorcinol (**74**) was converted into aldehyde **75** in three steps. Under optimized conditions, oxepin **77** was synthesized in 49% yield, by reaction with nitro-phenol **76** under basic conditions. In the proposed reaction mechanism biaryl ether formation occurred via an intermolecular nucleophilic aromatic substitution reaction. A subsequent intramolecular Knoevenagel reaction afforded the oxepin substructure. Upon exposure of **77** to palladium on charcoal under an atmosphere of hydrogen gas, reduction of the nitro group and the C10–11 double bond occurred. The obtained aniline was directly used in a diazotization–substitution sequence to produce phenol **78** in 45% yield over two steps. Regioselective demethylation with boron tribromide was proposed to occur via coordination of the oxygen in the seven-membered ring to yield bauhinoxepin C (**79**) in 47% yield.



Scheme 16 Nucleophilic aromatic substitution and Claisen condensation cascade for the construction of the oxepin motif in bauhinoxepin C (**79**) by Ngernmeesri

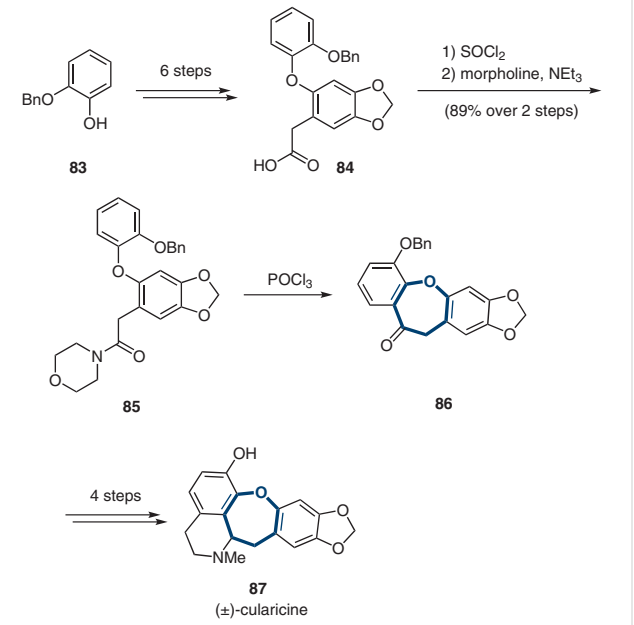
The synthesis of benzyltetrahydroisoquinoline based natural product cularine (**82**) was reported by Lumb in 2021. The first enantioselective synthesis of (*S*)-cularine (**82**) was accomplished by initially using aldehyde **20** as the starting material.[20] The utilization of Ellman's chiral sulfonamide and modification of the Pomeranz–Fritsch cyclization held promise to generate the C4-C4a bond and reveal the isoquinoline. Within twelve further steps, phenol **80** was accessible. The use of a 4-nitrophenyl leaving group was required for the substitution reaction of the *o*-quinone generated in situ. Simple removal of the silyl protecting group with TBAF in the presence of air induced *o*-quinone

formation and intramolecular substitution. The instable product was treated with methyl iodide to yield dihydrooxepin **81** in 62% yield over two steps. Deprotection of the tosyl group (lithium naphthalenide) and reductive methylation (formaldehyde and sodium borohydride) completed the total synthesis of (*S*)-cularine (**82**) (Scheme 17).



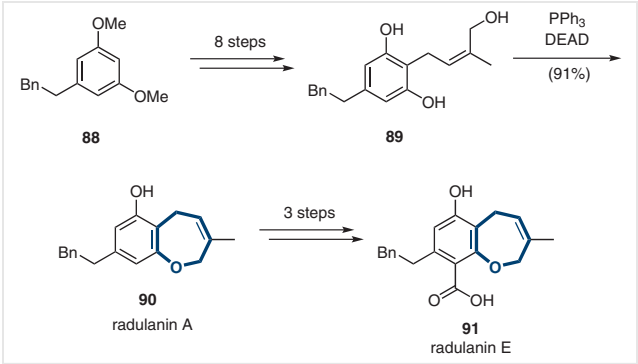
Scheme 17 Redox-neutral substitution for the construction of the dihydrooxepin motif in (*S*)-cularine (**82**) by Lumb

(±)-Cularicine (**87**) an alkaloid of *Corydalis claviculata* (L.) DC, was isolated by Manske in 1940. Starting with phenol **83**, Maclean published a racemic synthesis of cularicine (**87**), as shown in Scheme 18.[21] Attempts to cyclize **84** under various acidic conditions turned out to be unsuccessful. Cyclization under Friedel–Crafts conditions with the corresponding acid chloride were reported to give complex product mixtures arising from debenzylation of the ether by the Lewis acid. However, when the acid chloride was converted into amide **85**, cyclization to the enamine was observed upon treatment with phosphoryl chloride. After hydrolysis, ketone **86** was obtained. The final four steps of the synthesis were required to build up the piperidine ring system.



Scheme 18 Friedel–Crafts cyclization for the construction of the dihydrooxepin motif in (±)-cularicine (**87**) by Maclean

In 2000, Yamaguchi reported the synthesis of 2,5-dihydro-1-benzoxepins employing a Mitsunobu cyclization as the key step (Scheme 19).[22] This strategy was applied to the total synthesis of the radulanins, a family of bicyclic benzoxepins. Starting from readily available 1,3-dimethoxy-5-(2-phenylethyl)benzene **88**, triol **89** was accessible via eight steps. Exposure of **89** to standard Mitsunobu conditions (DEAD, PPh_3) allowed for efficient ring-closure to furnish radulanin A (**90**).

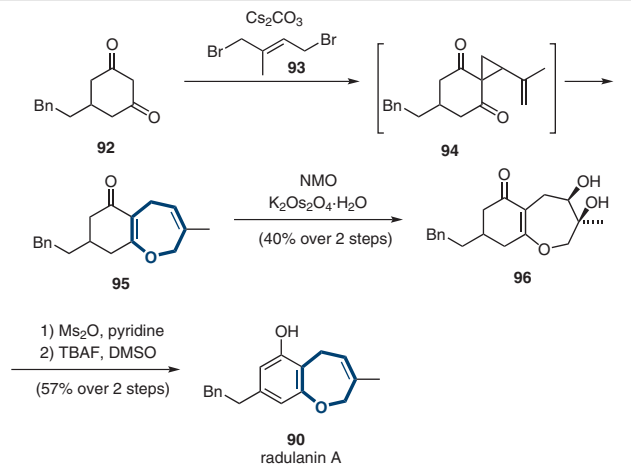


Scheme 19 Mitsunobu reaction for the construction of the dihydrooxepin motif in radulanin A (**90**) and radulanin E (**91**) by Yamaguchi

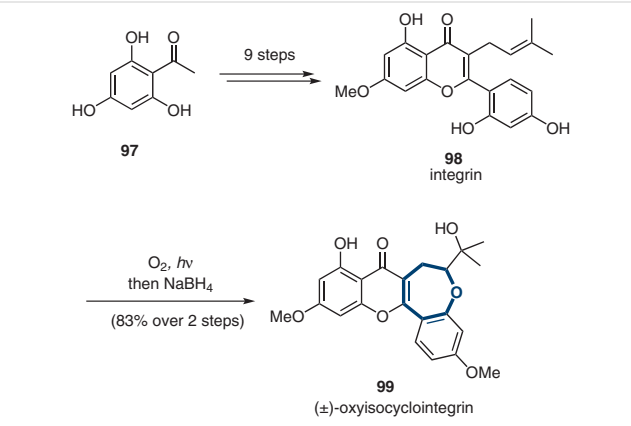
The developed strategy was later further expanded to the synthesis of radulanin E (**91**) via a three-step sequence (temporary protection, Vilsmeier formulation and selective oxidation).[23]

3.4 Sigmatropic Rearrangement

In 2019, Nay published a one-pot synthesis of 2,5-dihydrooxepines through retro-Claisen rearrangements and applied this strategy to the synthesis of radulanin A (**90**) (Scheme 20).[24] Theoretical studies were performed to explain the experimental results and the difference in reactivity observed between substrates derived from cyclic or linear 1,3-diketones. Reaction of diketone **92** with 1,4-dibromo-2-methyl-2-butene (**93**) under basic conditions afforded **94**, which underwent retro-Claisen rearrangement to afford dihydrooxepin **95**. Subsequent dihydroxylation under standard conditions (NMO, K_2OsO_4) allowed preparation of diol **96**. To complete the synthesis, diol **96** was treated with mesyl anhydride. TBAF promoted elimination of both mesylates and isomerization provided radulanin A (**90**).



Scheme 20 Retro-Claisen rearrangement for the construction of the dihydrooxepin motif in radulanin A (**90**) by Nay

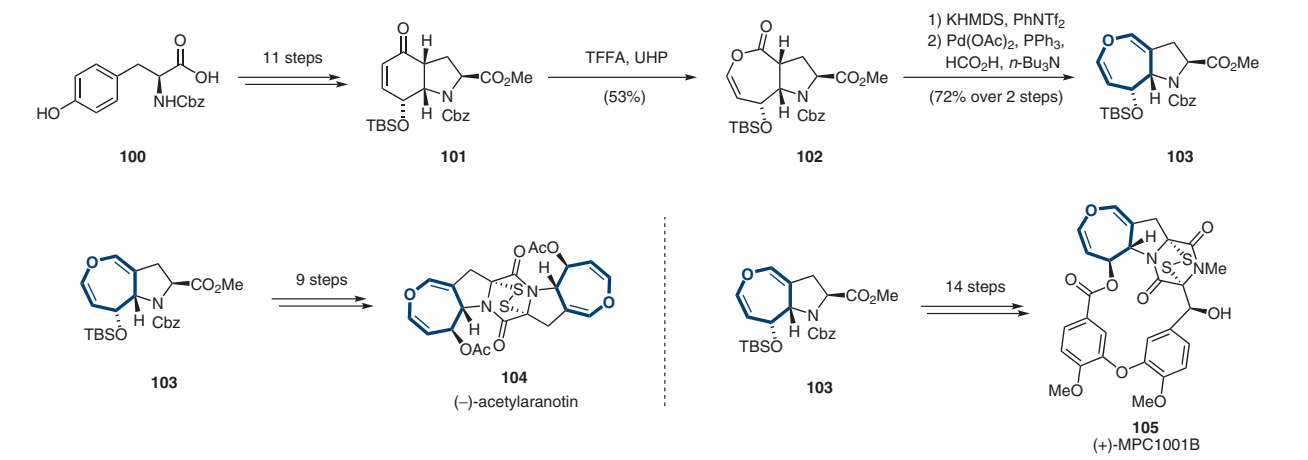


Scheme 21 Oxidative cyclization for the construction of the dihydrooxepin motif in (±)-oxyisocyclointegrin (**99**) by Hawkins

3.5 Oxidative Methods

The oxidation of cyclohexanone derivatives via the Baeyer–Villiger rearrangement is a powerful method for the synthesis of simple seven-membered ring systems. The oxidation of linear alkenes or similar functionalities was also reported as a valuable strategy to access these systems. An example for the use of a linear precursor is the synthesis of oxyisocyclointegrin (**99**) from integrin (**98**) (Scheme 21).[25] To date, it is still unclear if oxyisocyclointegrin (**99**) exists as a racemate or a single enantiomer as no optical data nor any biological activity of either **98** or **99** were reported during their isolation. The total synthesis of both natural products was disclosed in 2019 by Hawkins starting from ketone **97**. Nine steps were required to accomplish the synthesis of integrin (**98**), which, upon irradiation in the presence of oxygen with a high-pressure mercury lamp, provided oxyisocyclointegrin (**99**) and its hydroperoxide. The crude residue was then treated with sodium borohydride in methanol to give racemic oxyisocyclointegrin (**99**) in 84% yield. Biological evaluation of **99** revealed moderate to weak activity against *Staphylococcus aureus* and prostate cancer cells.

Owing to their unique structural and biological properties, epidithiodiketopiperazines represent an important class of natural products. Among them, acetylaranotin (**104**) features a dihydrooxepin moiety fused to a pyrrolidine epidithiodiketopiperazine, which renders it a challenging target for synthetic chemists. In 2012, Tokuyama reported the total synthesis of (–)-acetylaranotin (**104**) featuring a regioselective Baeyer–Villiger oxidation to efficiently form the proline-fused dihydrooxepin ring (Scheme 22).[26] The synthesis of enone **101** began with L-Cbz-tyrosine (**100**). Further screening of a variety of oxidation conditions revealed a combination of trifluoroacetic anhydride (TFAA) and urea hydrogen peroxide (UHP) as the combination of choice. This gave enol lactone **102** as a single isomer

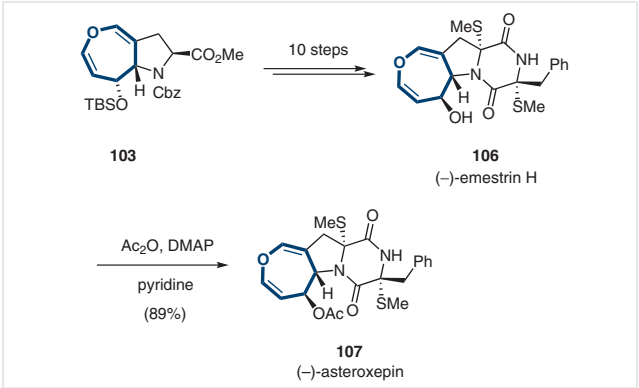


Scheme 22 Bayer–Villiger oxidation for the construction of the dihydrooxepin motif in (–)-acetylaranotin (**104**) and (+)-MPC1001B (**105**) by Tokuyama

in 53% yield. After conversion into an enol triflate, subjection to palladium-catalyzed reduction conditions gave dihydrooxepin **103** in excellent yield with the Cbz group still intact. Nine further steps, including dimerization of the monomer units, were required to finish the synthesis of (–)-acetylaranotin (**104**).

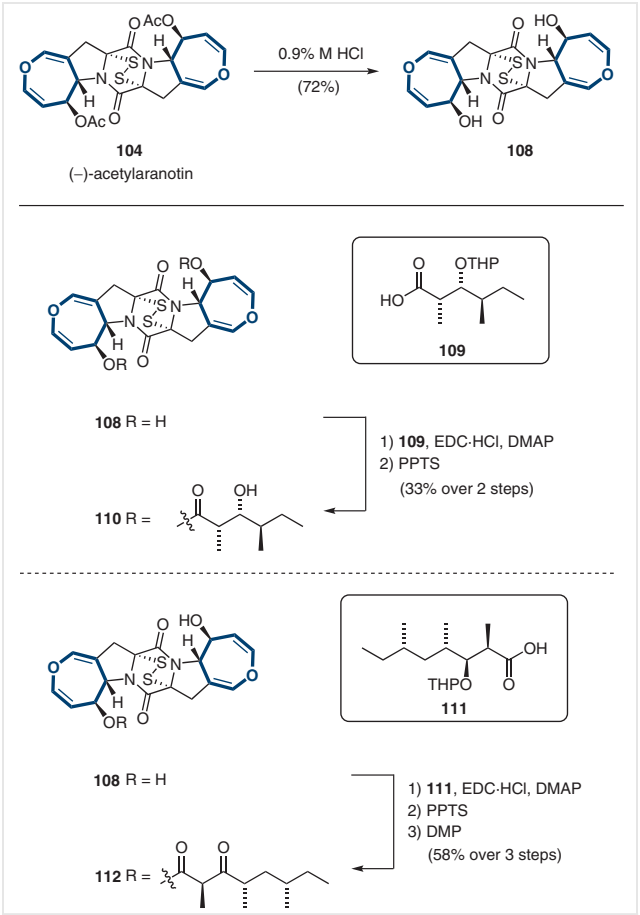
Four years later, Tokuyama used the same strategy to complete the total synthesis of (+)-MPC1001B (**105**). The greatest challenges in the synthesis of MPC1001B (**105**) were the diastereoselective assembly of the characteristic 15-membered ring as well as the labile aldol substructure of the dithiodiketopiperazine.[27]

In 2020, with dihydrooxepin **103** already in hand, Tokuyama reported the total syntheses of (–)-emestrin H (**106**) and (–)-asteroxepin (**107**) (Scheme 23).[28] A major breakthrough during this synthesis was the discovery of the allyloxymethyl (Allom) group as a protecting group for the amide nitrogen of the diketopiperazine core. Most importantly, this group was fully stable under Nicolaou's sulfenylation conditions and cleavable under mild conditions (tetrakis(triphenylphosphin)palladium ($Pd(PPh_3)_4$) and *N*,*N*-dimethylbarbituric acid) without affecting the acid-sensitive dihydrooxepin structure.



Scheme 23 Synthesis of (–)-emestrin H (**106**) and (–)-asteroxepin (**107**) from dihydrooxepin **103** by Tokuyama.

In 2017, Isaka reported the semi-synthesis of SCH 64874 (**110**) and hirsutellomycin (**112**) (Scheme 24).[29] Due to the limited availability of hydrooxepin **108**, readily available **104** was chosen as the starting material and hydrolysed to **108**. The C2-symmetric epidithiodiketopiperazine alkaloid SCH 64874 (**110**), was synthesized by condensation of the (–)-deacetylaranotine scaffold with two equivalent of carboxylic acid **109**, uncovering the relative stereochemistry of SCH 64874 (**110**). The relative stereochemistry of the β-keto carboxylic acid chain of the analogous alkaloid hirsutellomycin (**112**) was determined in a stepwise manner. The C4′–C6′ *syn* relationships were predicted by comparing the NMR data of the corresponding ester fragments with that of hirsutellomycin (**112**). The relative stereochemistry of the entire molecule, including the epimerizable C2′ stereocenter was determined by introduction of four diastereomeric side chains into the deacetylaranotin core **108**.

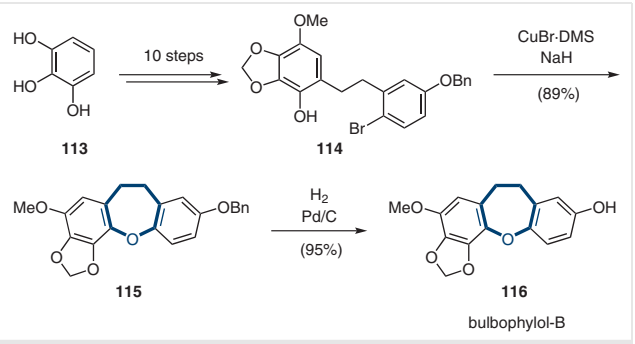


Scheme 24 Semi-synthesis of SCH 64874 (**110**) and hirsutellomycin (**112**) by Isaka

3.6 Transition-Metal-Catalyzed Cyclization

The natural polyoxygenated dihydrodibenz[*b*,*f*]oxepin bulbophylol-B (**116**) was isolated from *Bulbophyllum kwangtungense Schltr* (Orchidaceae) by Wu and was shown to display significant cytotoxicity against human epithelial carcinoma (HeLa) and human erythromyeloblastoid leukemia (K562) cells. Additionally, Kitanaka postulated that bulbophylol-B (**116**) exhibits radical-scavenging activity. Synthesis of bromide **114** commenced with the commercially available benzene-1,2,3-triol (**113**) and required ten steps (Scheme 25).[30] Exposure of **114** to different copper catalysts (Cu, Cu_2O, CuCl, or CuBr) and potassium carbonate or sodium hydride as base in pyridine at 130 °C only allowed for partial conversion into **115**. However, when using soluble copper(I) dimethylsulfide complex as the catalyst at 120 °C, dihydrooxepin **115** was obtained in 89% yield. Cleavage of

the benzyl protecting group of **115** via hydrogenolysis employing palladium on charcoal gave the natural product in near-quantitative yield.

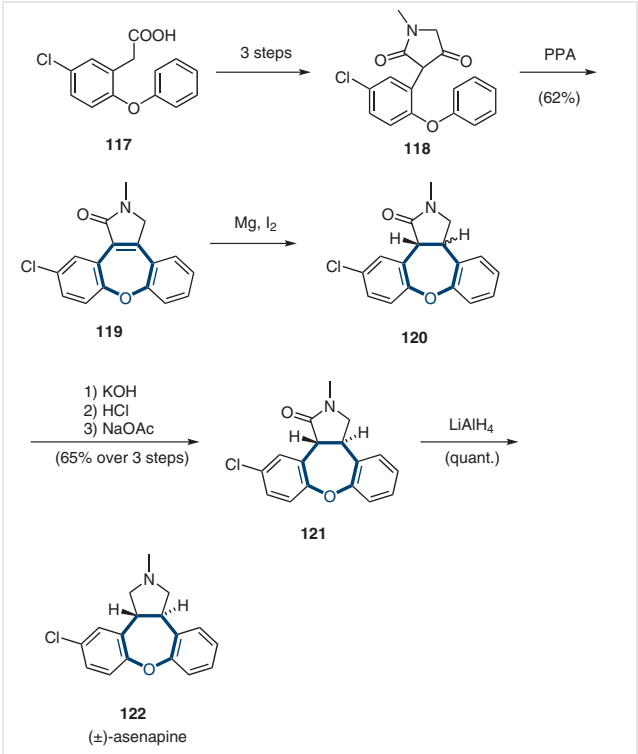


Scheme 25 Ullmann coupling for the construction of the dihydrooxepin motif in bulbophylol-B (**116**) by Kitanaka

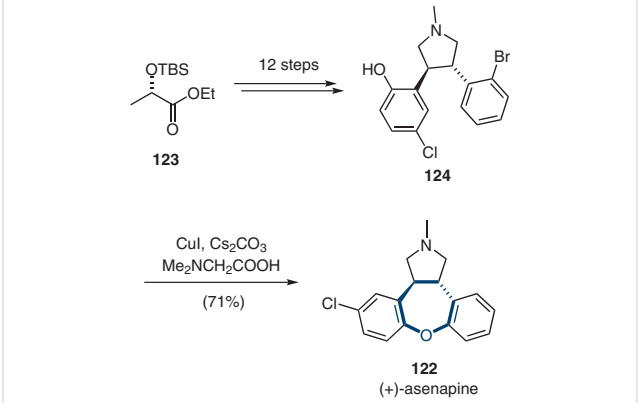
Asenapine **122** was discovered and developed by Organon and later co-developed in collaboration with Pfizer. Asenapine (**122**) is an active ingredient of Saphris® (USA) and Sycrest® (Europe) for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorders. Since the FDA approved the market launch of racemic asenapine in 2009, the most patented and public domain protocols involve the total synthesis of racemic asenapine (**122**). However, studies of the metabolism and pharmacokinetics of the individual enantiomers of asenapine (**122**) revealed that the (+)-isomer was found in higher concentrations within the blood plasma compared to the (–)-isomer.

Several synthetic routes for the preparation of asenapine are known today, and the largest reported process scale route is described in Scheme 26.[31] 5-Chloro-2-phenoxyphenylacetic acid (**117**) was first converted into amide **118**. An intramolecular Friedel–Crafts alkylation-dehydration sequence was then performed by subjecting **118** to polyphosphoric acid to afford unsaturated lactam **119** in 62% yield. Reduction of **119** with magnesium in methanol and a catalytic amount of iodine gave a 4:1 diastereomeric mixture of **120** in quantitative yield. Ring-opening of **120** in the presence of potassium hydroxide in refluxing ethanol resulted in concomitant epimerization of the corresponding *cis*-amino acid to the *trans*-amino acid **121**. Treatment with sodium acetate in refluxing toluene regenerated *trans*-lactam as a single isomer in 65% yield over three steps. Final lithium aluminum hydride mediated reduction of **121** provided asenapine (**122**).

In 2016, Chandrasekhar published a synthesis of asenapine (**122**) in optically pure form employing a Ireland–Claisen rearrangement as the key step (Scheme 27).[32] Starting from commercially available (*S*)-ethyl lactate **123**, chiral pyrrolidine **124** was obtained in twelve steps. The dihydrooxepin ring was closed under Ullmann conditions to afford the desired natural product (+)-asenapine (**122**) in 71% yield and 94% ee.



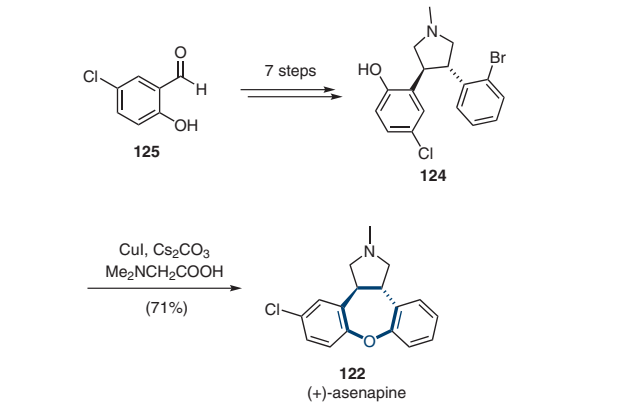
Scheme 26 Industrial Friedel–Crafts cyclization for the construction of the dihydrooxepin motif in (±)-asenapine (**122**)



Scheme 27 Ullmann coupling for the construction of the dihydrooxepin motif in (+)-asenapine (**122**) by Chandrasekhar

In 2019, Mlynarski published a shortened asymmetric synthesis of (+)-asenapine (**122**) (Scheme 28).[33] Their key step included an organocatalytic Michael addition using aldehyde **125**. The final cyclization under the reported Ullmann conditions with pyrrolidine **124** yielded asenapine

122 with >94% ee. The main drawbacks of this approach are the relatively long synthetic process and the need for diazomethane and osmium tetroxide.



Scheme 28 Ullmann coupling for the construction of the dihydrooxepin motif in (+)-asenapine (**122**) by Mlynarski

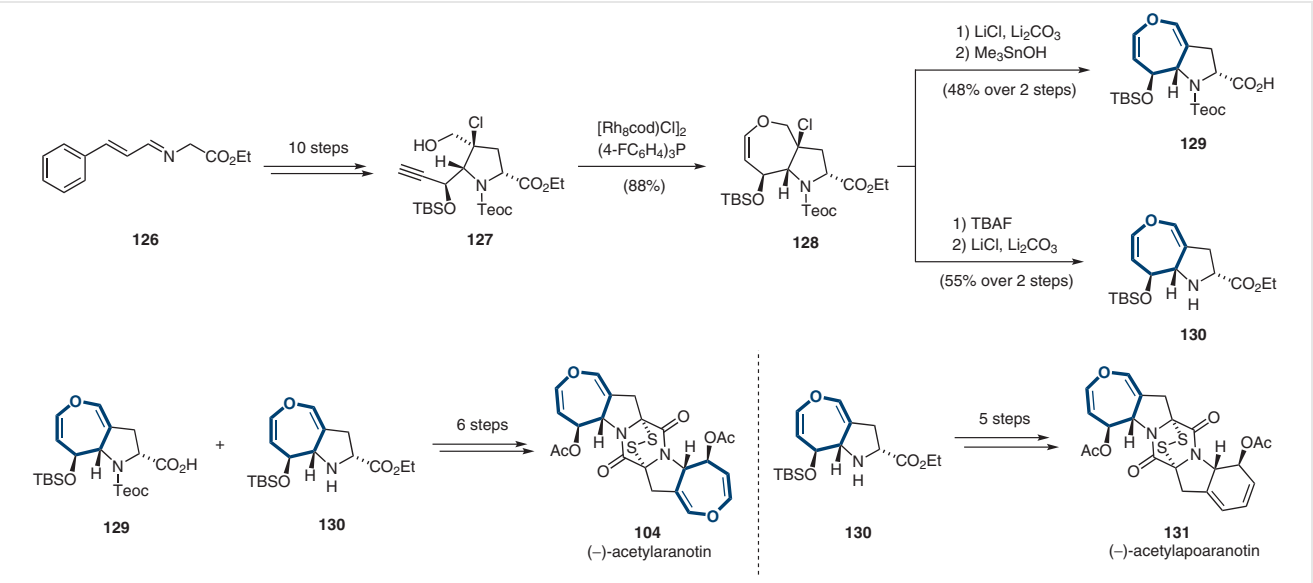
The first total synthesis of the dihydrooxepin epidithiodiketopiperazine (–)-acetylaranotin (**104**) was reported by Reisman and features a rhodium-catalyzed cycloisomerization as the key step (Scheme 29).[34] At the outset, alkyne **127** was synthesized in ten steps from cinnamaldimine **126**. After screening several catalysts and solvents, it was found that exposure of alcohol **127** in *N*,*N*-dimethylformamide (DMF) to catalytic bis(1,5-cyclooctadien)dirhodium(I)-dichloride [Rh(cod)-Cl]$_2$ and tris(4-fluorophenyl)phosphine provided the corresponding chlorotetrahydrooxepin **128** in 88% yield. Since all attempts to achieve dimerization of two identical monomers proved to be challenging, a stepwise approach was followed. Elimination was realized by using lithium chloride and lithium carbonate at 100 °C in DMF, yielding the desired dihydrooxepin core.

Subsequent hydrolysis of the ester functionality yielded carboxylic acid **129**. In parallel, chemoselective cleavage of the Teoc group in the presence of the TBS ether was achieved by the use of TBAF and allowed for clean formation of the free amine functionality. Subjection of the amine to the previously optimized chloride elimination conditions delivered dihydrooxepin **130** in 55% yield over two steps. Both fragments were combined using classical amide coupling conditions and an additional five steps were required to complete the first enantioselective total synthesis of (–)-acetylaranotin (**104**).

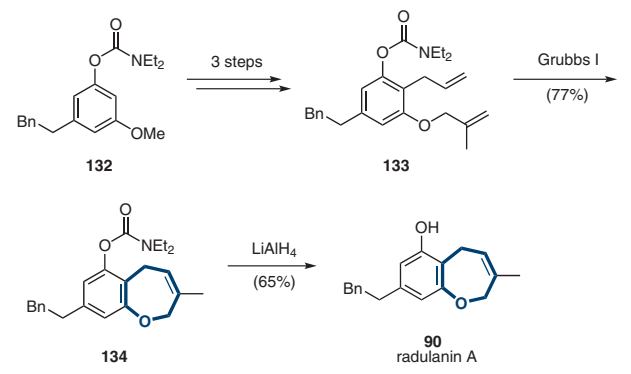
Further investigations directed toward the implementation of these strategies and methods for the synthesis of related dihydrooxepin-containing natural products resulted in the synthesis of (–)-acetylapoaranotin (**131**).[35]

The first dihydrooxepin synthesis using a ring-closing metathesis (RCM) was reported by Snieckus in 1998 (Scheme 30).[36] Carbamate **132** was converted into the desired diene **133** in three steps, which underwent cyclization at high dilution in the presence of Grubbs first-generation catalyst to yield dihydrooxepin **134**. A final lithiumaluminium hydride reduction afforded radulanin A (**90**) in 65% yield.

In 2007, the first synthesis of heliannuol B (**138**) was reported by Venkateswaran. Heliannuol B (**138**) features a unique benzoxepane ring system and belongs to a novel group of allelopathic sesquiterpenes isolated from the cultivar sunflowers *Helianthus annus*. The synthesis was initiat-

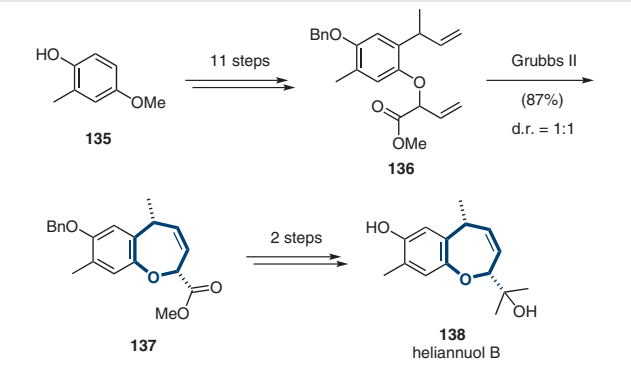


Scheme 29 Rhodium-catalyzed cycloisomerization for the construction of the dihydrooxepin motif in (–)-acetylaranotin (**104**) and (–) acetylapoaranotin (**131**) by Reisman



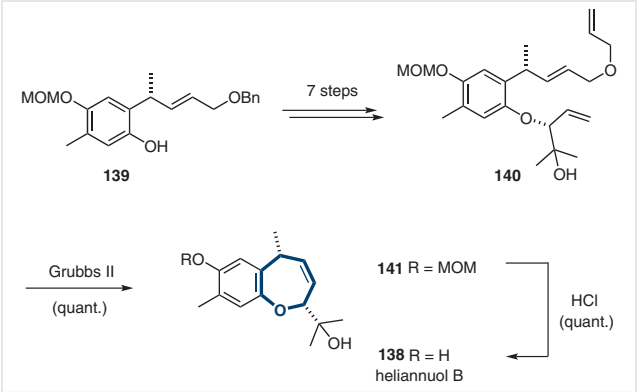
Scheme 30 Ring-closing metathesis for the construction of the dihydrooxepin motif in radulanin A (**90**) by Snieckus

ed with phenol **135**, which was converted into diene **136** in eleven steps (Scheme 31).[37] Subsequent RCM yielded the dihydrooxepin **137** in good yield as a mixture of two diastereomers. The crude mixture was directly subjected to an excess of methyl lithium to afford, after chromatographic purification, benzyl protected heliannuol B. Finally, debenzylation using sodium in *n*-butanol furnished heliannuol B (**138**).



Scheme 31 Ring-closing metathesis for the construction of the dihydrooxepin motif in heliannuol B (**138**) by Venkateswaran

In 2014, the first enantioselective total synthesis of heliannuol B (**138**) was reported by Shishido (Scheme 32).[38] The key steps include chirality transfer through a Lewis acid-promoted Claisen rearrangement to obtain the tertiary C7 stereocenter and a RCM for assembling the dihydrobenzo[*b*]oxepin backbone of the natural product. Initial attempts did not give the expected cyclized product but only led to recovered starting material. Same results were obtained in different solvents and at higher temperature. Attempts to reduce the steric bulk by exchanging the carbinol unit with an ester function were unsuccessful. As shown for the synthesis of **141**, the limitations of standard RCM protocols forced them to use a relay ring-closing metathesis. Selective debenzylation of **139** followed by allylation of the resulting alcohol provided the allyl ether **140**. The addition of Grubbs second-generation catalyst (5 mol%) to a solution of **140** in dichloromethane delivered the functionalized dihydrobenzo[*b*]oxepin **141** in quantitative yield. Exposure of **141** to aqueous hydrogen chloride yielded heliannuol B (**138**).

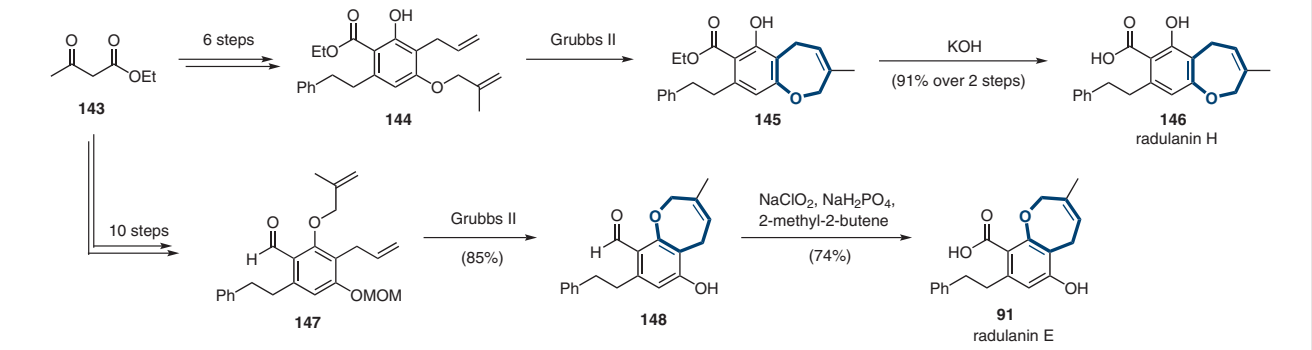


Scheme 32 Ring-closing metathesis for the construction of the dihydrooxepin motif in heliannuol B (**138**) by Shishido

Radulanins H (**146**) and E (**91**) were isolated by Asakawa from the liverwort *Radula perrottetii* and *Radula variabilis*. Radulanin H (**146**) was reported to exhibit calmodulin and cyclooxygenase inhibitory activities. Shishido described a concise total synthesis of radulanin H (**146**) and the proposed structure of radulanin E (**91**), utilizing an intramolecular condensation, sequential regioselective allylations, and RCM as the key steps (Scheme 33).[39] Both routes proceeded by forming the aromatic core from ethyl acetoacetate **143**, which was converted into diene **144** in six additional steps. Diene **147** was synthesized in ten steps. Exposure of **144** to RCM using Grubbs second-generation catalyst followed by hydrolysis of the ethyl ester moiety in aqueous potassium hydroxide solution produced radulanin H (**146**) in 91% yield over two steps.

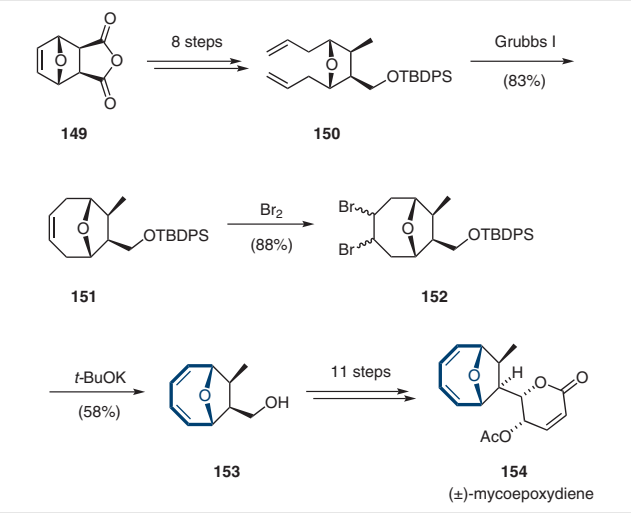
For the synthesis of **91**, exposure of **147** to Grubbs second-generation catalyst afforded the desired dihydrooxepin **148** in 85% yield. Final Pinnick oxidation provided the proposed structure of radulanin E (**91**) in 74% yield. The structure of **91** was unambiguously confirmed by single-crystal X-ray analysis.

Mycoepoxydiene (**154**) was isolated from the fermentation of a rare fungus designated as OS-F66617 in 1999. Its structure and relative stereochemistry were determined by spectral and X-ray crystallographic analyses, but the absolute stereochemistry is still unknown. Tadano published the first synthesis in 2002 via a RCM reaction (Scheme 34).[40] Starting from racemic anhydride **149** (the Diels–Alder adduct of furan and maleic anhydride), the diene **150** was obtained in eight steps. With diene **150** in hand, the RCM reaction was examined. Treatment of **150** with Grubbs first-generation catalyst (four additions, each of 5 mol% over a period of 20 h) in refluxing benzene furnished the desired oxygen-bridged cyclooctene derivative **151** in 83% yield.



Scheme 33 Ring-closing metathesis for the construction of the dihydrooxepin motif in radulanin H (**146**) and E (**91**) by Shishido

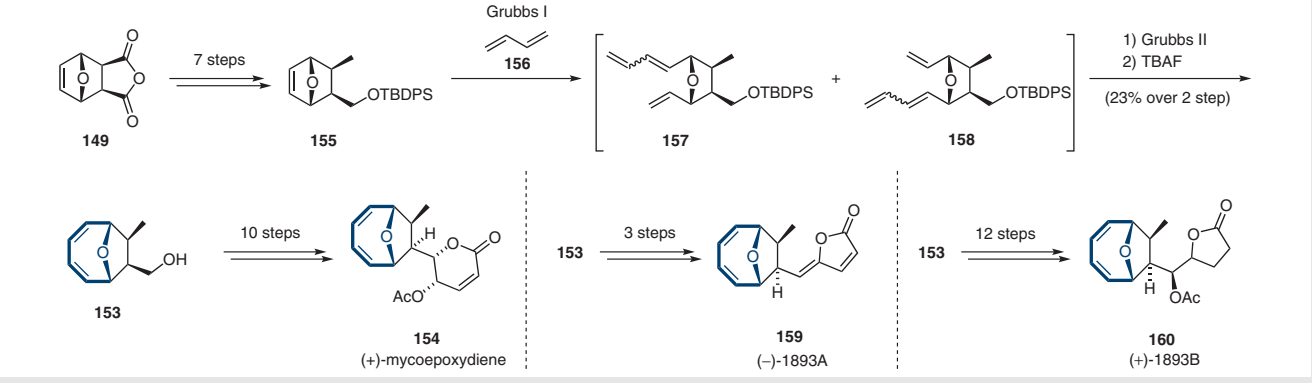
Bromination of **151** followed by exposure of the resulting diastereomeric dibromo adduct **152** to potassium *tert*-butoxide, provided 9-oxabicyclo[4.2.1]nona-2,4-diene derivative **153**. The pyranone core was accessed in a further eleven steps and completed the total synthesis of racemic mycoepoxydiene (**154**).



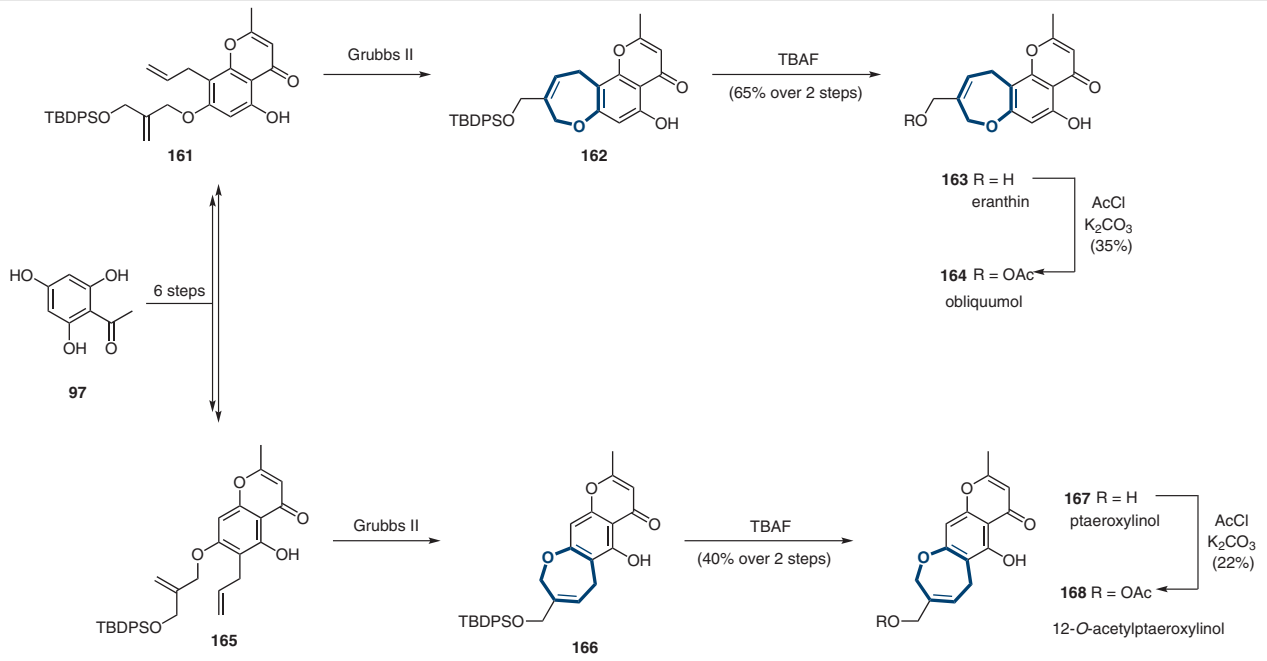
Scheme 34 Ring-closing metathesis for the construction of the dihydrooxepin motif in (±)-mycoepoxydiene (**154**) by Tadano

The asymmetric total syntheses of (+)-mycoepoxydiene (**154**) and the related natural products (–)-1893A (**159**) and (+)-1893B (**160**) were reported by Tadano via a one-pot ring-opening/cross/ring-closing metathesis to construct the 9-oxabicyclo[4.2.1]nona-2,4-diene skeleton (Scheme 35).[41] Starting with the same anhydride, enantioenriched material was obtained by desymmetrization of *meso*-compounds **149**. Intermediate **149** was then converted into alkene **155**, which underwent the first ring-opening reaction. Employing Grubbs first-generation catalyst in benzene at 23 °C, the reaction proceeded smoothly to give a mixture of trienes favoring a mixture of the *Z*-isomers **157** and **158**. This mixture was used directly without further purification for the next ring-closing reaction. Interestingly, the Grubbs second-generation catalyst preferentially produced the undesired *E*-isomers in a diminished yield.

To prevent a competing polymerization of the diene **155**, an excess of 1,3-butadiene (**156**) was employed. The RCM reaction of the mixture of trienes **157** and **158** with Grubbs second-generation catalyst in refluxing benzene afforded the desired dihydrooxepin system together with several unidentified byproducts. Exposure of the mixture to TBAF, gave alcohol **153**. To construct the 9-oxabicyclo-



Scheme 35 Ring-opening/cross/ring-closing metathesis cascade for the construction of the dihydrooxepin motif in (+)-mycoepoxydiene (**154**), (–)-1893A (**159**) and (+)-1893b (**160**) by Tadano



Scheme 36 Ring-closing metathesis for the construction of the dihydrooxepin motif in obliquumol (**164**) and 12-*O*-acetylptaeroxylinol (**168**) by Selepe

[4.2.1]nona-2,4-diene unit in a more efficient way, a ROM/CM/RCM one-pot sequence using the alkene **155** was studied. Treatment of **155** with 1,3-butadiene (**156**) (2 equiv) in the presence of Grubbs first-generation catalyst (2 mol%) in benzene initially produced trienes **157** and **158** at 23 °C. After full consumption of alkene **155**, excess 1,3-butadiene (**156**) was removed by sparging the solution with a stream of argon. Then each 2 mol% of Grubbs second-generation was added in five portions over a period of four days to the refluxing reaction mixture. Desilylation of the reaction mixture provided the key intermediate **153** in 23% yield. With alcohol **153** in hand, the total synthesis of (+)-mycoepoxydiene (**154**) was accomplished in a further ten steps, (–)-1893A (**159**) in three steps and (+)-1893B (**160**) in twelve steps, respectively. Both natural (+)-**154** and unnatural (–)-**154** were found to show cytotoxicity toward human tumor cells *in vitro* against human chronic myelogenous leukemia, K562, and against human hepatocellular carcinoma.

Moody reported the synthesis of eranthin (**163**) and ptaeroxylinol (**167**) in 2010, which was further used to accomplish the synthesis of the bioactive oxepinochromones obliquumol (**164**) (angular isomer) and 12-*O*-acetylptaeroxylinol (**168**) (linear isomer) by Selepe in 2020 (Scheme 36).[42] Both synthetic routes use the same strategic RCM reaction and only vary in the choice of different protecting groups. From ketone **97**, dienes **161** and **165** were synthesized through a Kostanecki–Robinson reaction, Williamson etherification, and a Claisen rearrangement. Subsequent RCM afforded the desired dihydrooxepins **162** and **166**, which then were converted into the natural products eranthin (**163**) and ptaeroxylinol (**167**) via desilylation. Acetylation of the free alcohol yielded obliquumol (**164**) and 12-*O*-acetylptaeroxylinol (**168**). The antifungal activities of these compounds were determined against *Candida albicans* and *Cryptococcus neoformans* and demonstrated a good to moderate activity against these pathogens.

4 Summary

In this review, we illustrated a variety of different natural products containing either an oxepin or a dihydrooxepin ring system. We highlighted different synthetic methods and strategies to access the seven-membered ring system and the challenges observed for the individual routes. Finally, we would also like to encourage others to work on these natural products, as we see great potential for them to act as lead structures for the pharmaceutical industry as well as academia. Many oxepin natural products have eluded their synthesis in the past and are still not accessible in sufficient amounts for extensive biological screening.

Conflict of Interest

The authors declare no conflict of interest.

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References

(1) Schleif, T.; Merini, M. P.; Sander, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 20318.
(2) (a) Ji Ram, V.; Sethi, A.; Nath, M.; Pratap, R. In *The Chemistry of Heterocycles*; Ji Ram, V.; Sethi, A.; Nath, M.; Pratap, R., Ed.; Elsevier: Oxford, **2019**, 393–425. (b) Tochtermann, W.; Olsson, G. *Chem. Rev.* **1989**, *89*, 1203. (c) Hayes, D. M.; Nelson, S. D.; Garland, W. A.; Kollman, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 1255.
(3) (a) Barbero, H.; Díez-Poza, C.; Barbero, A. *Mar. Drugs* **2017**, *15*, 361. (b) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631.
(4) (a) Siddiqi, Z.; Wertjes, W. C.; Sarlah, D. *J. Am. Chem. Soc.* **2020**, *142*, 10125. (b) Shim, S. Y.; Cho, S. M.; Venkateswarlu, A.; Ryu, D. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 8663. (c) Clark, D. L.; Chou, W. N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975. (d) Nicolaou, K. C.; Yu, R.; Shi, L.; Cai, Q.; Lu, M.; Heretsch, P. *Org. Lett.* **2013**, *15*, 1994. (e) Belen'kii, L. I. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Ed.; Elsevier: Oxford, **2008**, 45–95.
(5) Cleve, A.; Bohlmann, F. *Tetrahedron Lett.* **1989**, *30*, 1241.
(6) Doveston, R. G.; Steendam, R.; Jones, S.; Taylor, R. J. K. *Org. Lett.* **2012**, *14*, 1122.
(7) Wu, K.; Xie, Z. P.; Cui, D.-M.; Zhang, C. *Org. Biomol. Chem.* **2018**, *16*, 832.
(8) Tojo, E.; Dominguez, D.; Castedo, L. *Phytochemistry* **1991**, *30*, 1005.
(9) (a) Campello, M. J.; Castedo, L.; Dominguez, D.; de Lera, A. R.; Saá, J. M.; Suau, R.; Tojo, E.; Vidal, M. C. *Tetrahedron Lett.* **1984**, *25*, 5933. (b) De Lera, A. R.; Suau, R.; Castedo, L. *J. Heterocycl. Chem.* **1987**, *24*, 313.
(10) Garcia, A.; Castedo, L.; Domínguez, D. *Tetrahedron* **1995**, *51*, 8585.
(11) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2004**, *69*, 4527.
(12) Lim, H. S.; Choi, Y. L.; Heo, J.-N. *Org. Lett.* **2013**, *15*, 4718.
(13) Comber, M. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1371.
(14) Hsu, D.-S.; Lin, S.-C. *J. Org. Chem.* **2012**, *77*, 6139.
(15) Chen, P.; Huo, L.; Li, H.; Liu, L.; Yuan, Z.; Zhang, H.; Feng, S.; Xie, X.; Wang, X.; She, X. *Org. Chem. Front.* **2018**, *5*, 1124.
(16) Soorukram, D.; Pohmakotr, M.; Kuhakarn, C.; Reutrakul, V. *J. Org. Chem.* **2018**, *83*, 4173.
(17) Kraus, G. A.; Thite, A.; Liu, F. *Tetrahedron Lett.* **2009**, *50*, 5303.
(18) Narita, K.; Nakamura, K.; Abe, Y.; Katoh, T. *Eur. J. Org. Chem.* **2011**, 4985.
(19) Taweesak, P.; Thongaram, P.; Kraikruan, P.; Thanetchaiyakup, A.; Chuanopparat, N.; Hsieh, H.-P.; Uang, B.-J.; Ngernmeesri, P. *J. Org. Chem.* **2021**, *86*, 1955.
(20) Huang, Z.; Ji, X.; Lumb, J.-P. *Org. Lett.* **2021**, *23*, 236.
(21) Noguchi, I.; Maclean, D. B. *Can. J. Chem.* **1975**, *53*, 125.
(22) Yamaguchi, S.; Furihata, K.; Miyazawa, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **2000**, *41*, 4787.
(23) Yamaguchi, S.; Tsuchida, N.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2005**, *70*, 7505.
(24) Zhang, W.; Baudouin, E.; Cordier, M.; Frison, G.; Nay, B. *Chem. Eur. J.* **2019**, *25*, 8643.
(25) Smith, R. J.; Bower, R. L.; Ferguson, S. A.; Rosengren, R. J.; Cook, G. M.; Hawkins, B. C. *Eur. J. Org. Chem.* **2019**, 1571.
(26) Fujiwara, H.; Kurogi, T.; Okaya, S.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 13062.
(27) Kurogi, T.; Okaya, S.; Fujiwara, H.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 283.
(28) Umeki, K.; Ueda, Y.; Sakata, J.; Tokuyama, H. *Tetrahedron* **2020**, *76*, 131630.
(29) Tokuyama, H.; Yamada, K.; Fujiwara, H.; Sakata, J.; Okano, K.; Sappan, M.; Isaka, M. *J. Org. Chem.* **2017**, *82*, 353.
(30) Lin, J.; Zhang, W.; Jiang, N.; Niu, Z.; Bao, K.; Zhang, L.; Liu, D.; Pan, C.; Yao, X. *J. Nat. Prod.* **2008**, *71*, 1938.
(31) Liu, K. K. C.; Sakya, S. M.; O'Donnell, C. J.; Flick, A. C.; Li, J. *Bioorg. Med. Chem.* **2011**, *19*, 1136.
(32) Anugu, R. R.; Mainkar, P. S.; Sridhar, B.; Chandrasekhar, S. *Org. Biomol. Chem.* **2016**, *14*, 1332.
(33) Szcześniak, P.; Staszewska-Krajewska, O.; Mlynarski, J. *Org. Biomol. Chem.* **2019**, *17*, 3225.
(34) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 1930.
(35) Wang, H.; Regan, C. J.; Codelli, J. A.; Romanato, P.; Puchlopek-Dermenci, A. L. A.; Reisman, S. E. *Org. Lett.* **2017**, *19*, 1698.
(36) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808.
(37) Roy, A.; Biswas, B.; Sen, P. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2007**, *48*, 6933.
(38) Manabe, Y.; Kanematsu, M.; Yokoe, H.; Yoshida, M.; Shishido, K. *Tetrahedron* **2014**, *70*, 742.
(39) Yoshida, M.; Nakatani, K.; Shishido, K. *Tetrahedron* **2009**, *65*, 5702.
(40) Takao, K.-i.; Watanabe, G.; Yasui, H.; Tadano, K.-i. *Org. Lett.* **2002**, *4*, 2941.
(41) (a) Takao, K.-i.; Yasui, H.; Yamamoto, S.; Sasaki, D.; Kawasaki, S.; Watanabe, G.; Tadano, K.-i. *J. Org. Chem.* **2004**, *69*, 8789. (b) Yasui, H.; Hirai, K.; Yamamoto, S.; Takao, K.-i.; Tadano, K.-i. *J. Antibiot.* **2006**, *59*, 456.
(42) (a) Malefo, M. S.; Ramadwa, T. E.; Famuyide, I. M.; McGaw, L. J.; Eloff, J. N.; Sonopo, M. S.; Selepe, M. A. *J. Nat. Prod.* **2020**, *83*, 2508. (b) Bruder, M.; Haseler, P. L.; Muscarella, M.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2010**, *75*, 353.