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Review

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Total Synthesis of Natural Products Containing the Tetralone Subunit

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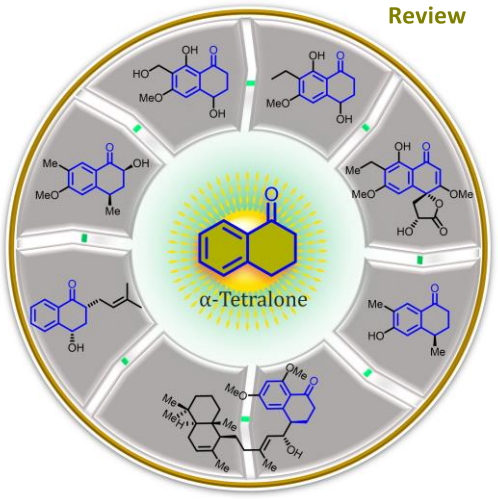
This work is dedicated to Professor Samir Z. Zard

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Abstract

Tetralone and its derivatives are unique structural motifs found in a wide range of natural products and serve as key scaffolds for the development of new drugs that target various biological end points. The tetralones have received a lot of interest because of their chemical features and their potential as lead molecules in the pharmaceutical sector. The goal of this review is to present the total synthesis of natural products bearing the 1-tetralone subunit, as well as to highlight key transformations for the synthesis of 1-tetralone. It summarizes the total syntheses of several natural products containing the tetralone subunit, such as 10-norparvulenone, catalponol, aristelegone-A, perenniporide A, and actinoranone.



Keywords: α-Tetralone, Natural products, Total synthesis, Friedel-Crafts reaction.

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1. Introduction

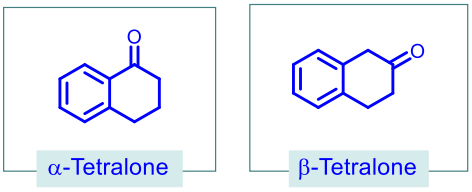


Figure 1. Structures of α-tetralone and β-tetralone.

Tetralones are a class of aromatic bicyclic compounds that include a 3,4-dihydro-1*H*-naphthalen-1-one (α-tetralone) or 3,4-dihydro-1*H*-naphthalen-2-one (β-tetralone) unit (Figure 1). These compounds have received a lot of interest because of their distinctive chemical features and potential as lead molecules in the pharmaceutical sector. Chemists around the world have been interested in isolating, synthesizing, and modifying tetralones and their derivatives since the early twentieth century, recognizing their importance in the synthesis of bioactive compounds such as steroids, prostaglandin analogs, dyes, heterocycles, and pharmaceuticals, including novel drug candidates.[1, 2, 3, 4, 5, 6]

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1-Tetralone (α–tetralone) features a characteristic bicyclic ring system, which consists of a cyclohexanone ring fused with a benzene ring. The tetralone structure is encountered in diverse bioactive natural products and represents a valuable target in synthetic organic and medicinal chemistry (for instance, 10-norparvulenone (antiviral), *O*-methylasparvenone (nitrogen-free serotonin receptor antagonists), aristelegone-A and B (natural metabolites), catalponol, isocatalponol (antitermitic), perenniporide A (inhibits the larva of the phytophagous weevil), actinoranone (cytotoxic against HCT-116 human colon cancer cells, LD50 = 2.0 µg/mL), hamigeran A and B (cytotoxic antiviral), celahypodiol (*anti*-tumor), nimbiol (antiseptic agent), octahydroeuclein (gram-positive bacterial inhibitors), isosclerone, shinanolone, isoshinanolone, prealnumycin B, phaeochromycin B, rubiginone B_2, cladosporone A and many others (Figure 2)).

Some creative methods and more conventional approaches for the preparation of this valuable bicyclic nucleus have been developed. However, although few excellent reviews devoted to the related tetralones have been published[7, 8, 9, 10, 11] the chemistry of natural products containing α-tetralones has not been reviewed to date.

This review article focuses on the total synthesis of several natural products, namely 10-norparvulenone, *O*-methylasparvenone, aristelegone-A, aristelegone-B, catalponol, perenniporide A, and actinoranone. We have excluded discussing the remaining molecules in Figure 2 due to either the absence of any synthesis reports or previous reviews in the literature.[12] The content of this review is intended to be informative for organic chemists as well as a contribution to the current body of literature in this field.

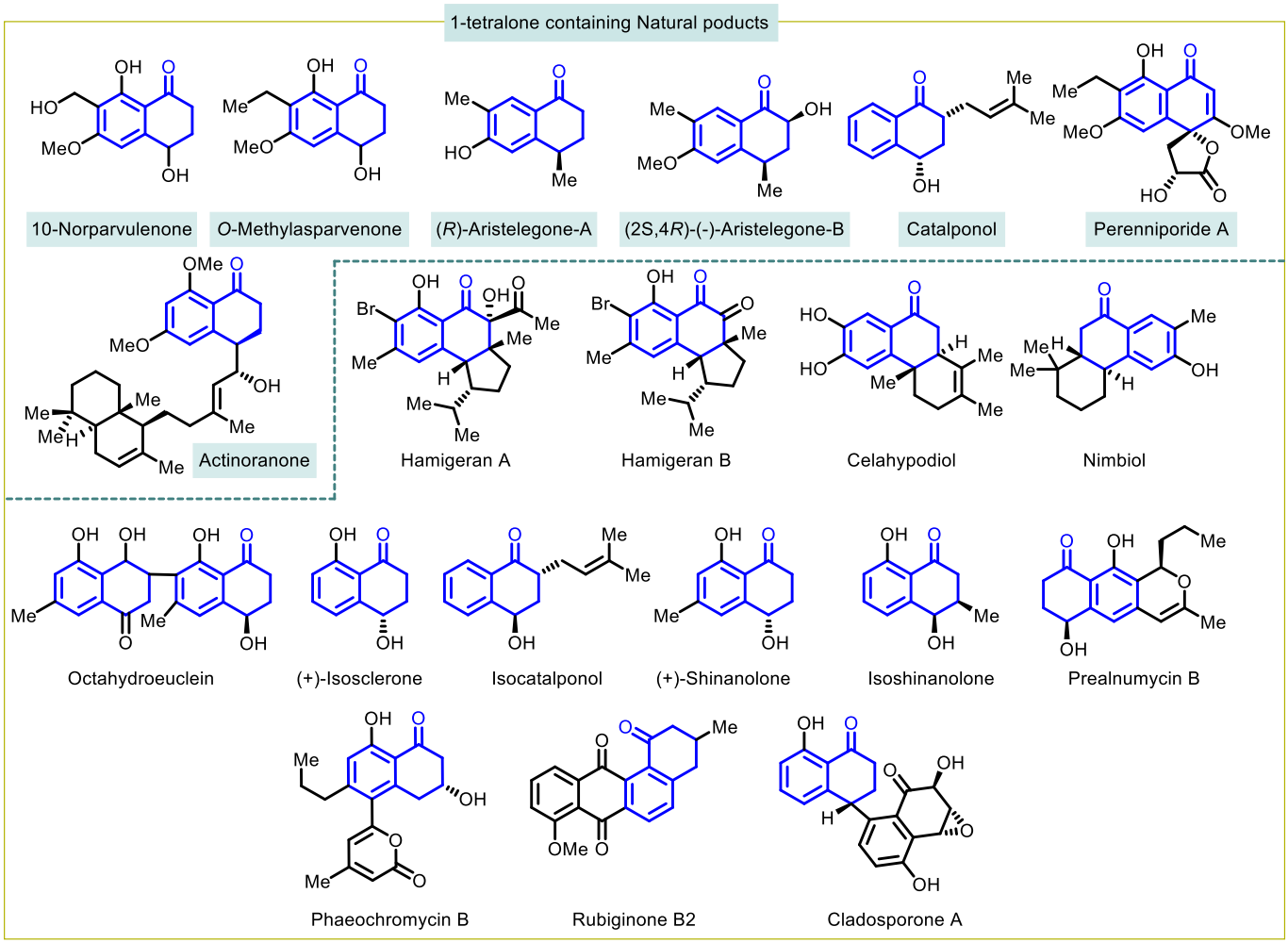
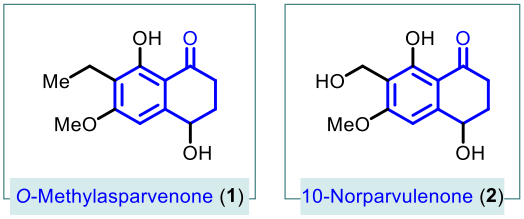


Figure 2. Natural products containing α–tetralone scaffold.

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2. *O*-Methylasparvenone and 10-Norparvulenone

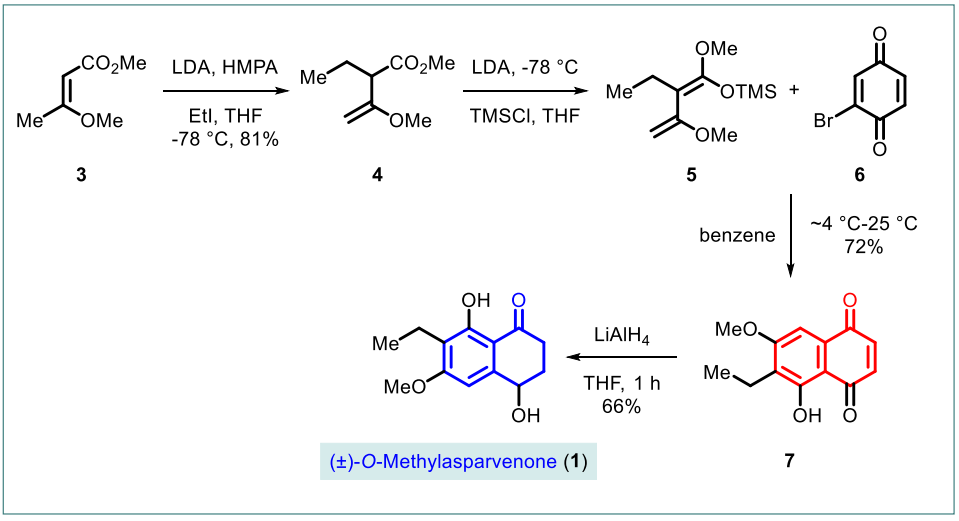
The natural products *O*-methylasparvenone and 10-norparvulenone both possess an α-tetralone subunit. *O*-Methylasparvenone is a rare type of serotonin receptor antagonist that lacks nitrogen and was discovered as a 5-HT2c antagonist[13] during a microbial screening for 5-HT2c ligands from the endophytic fungus *Aspergillus parvulus* Smith broth. On the other hand, 10-norparvulenone was first isolated in 2000 by Fukami *et al*. in the laboratory from *Microsphaeropsis sp*.[14] There is promising preliminary data from in vitro assays that suggest 10-norparvulenone may become a significant antiviral drug in the future. Both natural products contain a bicyclic carbon framework with a carbonyl function (1-tetralone), one methoxy group, and 2 or 3 hydroxyl groups as part of their structures.



To date, four total syntheses of *O*-methylasparvenone have been reported, while only one total synthesis of 10-norparvulenone has been documented.

2.1 Brassard's Total Synthesis of (±)-*O*-Methylasparvenone (1991):

Brassard's first total synthesis of *O*-methylasparvenone in 1991 utilized the Diels-Alder cycloaddition process and began with the preparation of diene **5** (Scheme 1). Methyl 3-substituted crotonate (**3**) underwent LDA-mediated alkylation to form ester **4**, which was further deprotonated with LDA and the anion trapped with TMSCl to yield enolsilylated diene **5**. The reaction of diene **5** with benzoquinone **6** via Diels-Alder cycloaddition in benzene at 4 °C to 25 °C produced the bicyclic skeleton juglone **7** in 72% yield. Direct reduction of juglone **7** with $LiAlH_4$ led to the desired natural product, *O*-methylasparvenone (**1**), in 66% yield.[15]

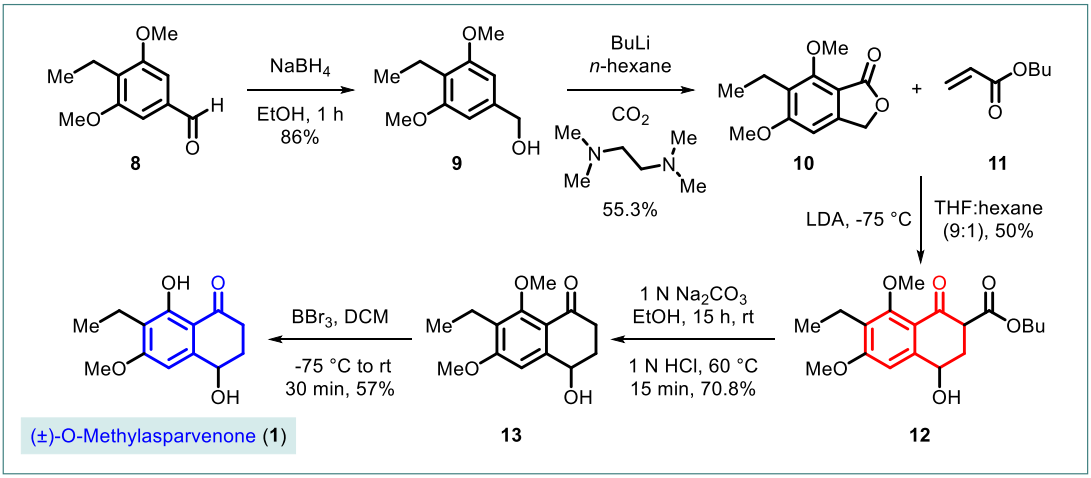


Scheme 1. Brassard's total synthesis of *O*-methylasparvenone.

2.2 Bös's Total Synthesis of (±)-*O*-Methylasparvenone (1997):

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In 1997, Bös and coworkers reported an impressive synthesis of (±)-*O*-methylasparvenone (**1**) utilizing a tandem Michael-Dieckmann reaction to construct the tetralone scaffold (Scheme 2). The synthesis began with the formation of 6-ethyl-5,7-dimethoxy-3*H*-isobenzofuran-1-one **10**, which was accessed from known aldehyde **8**. Aldehyde **8** was reduced using sodium borohydride to give benzylic alcohol **9** (86%), and then treated with *n*-BuLi and CO_2 to provide **10** in 55% yield. The carbanion of **10** was formed with LDA and added to butyl acrylate **11**, which furnished the Michael-product tetralone **12**. The butyl ester group from **12** was hydrolyzed using Na_2CO_3 followed by decarboxylation, resulting in compound **13**. Finally, selective demethylation of **13** delivered (±)-*O*-methylasparvenone **1**.[16]

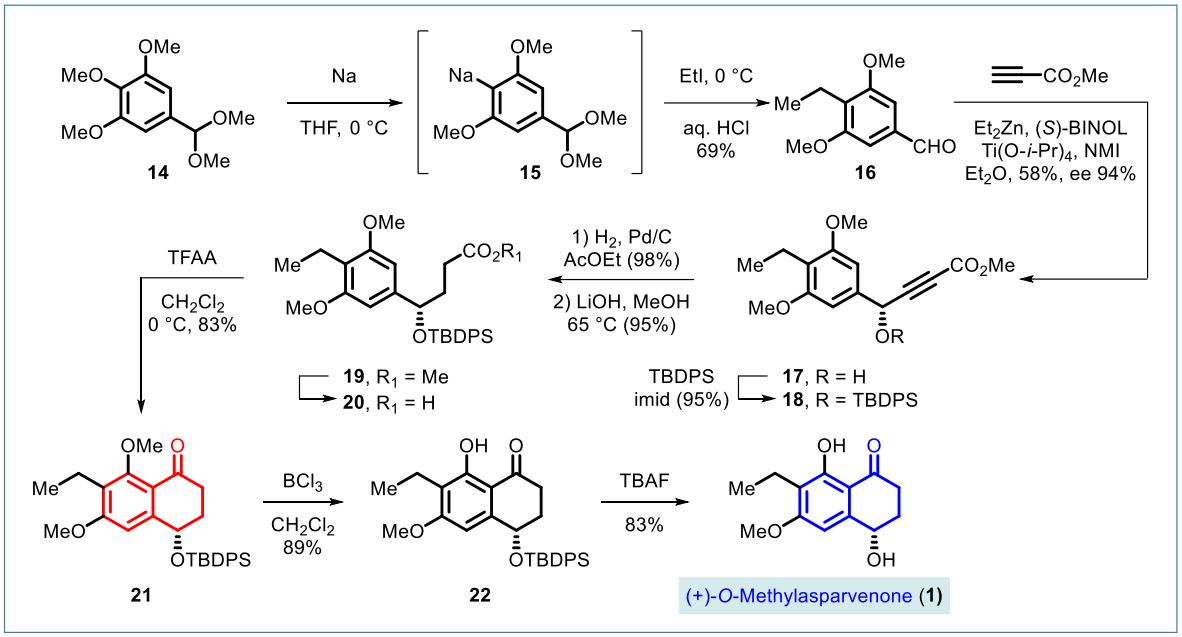


Scheme 2. Bös's total synthesis of (±)-*O*-methylasparvenone.

2.3 Boukouvalas's Total Synthesis of (+)-*O*-Methylasparvenone (2016):

The Boukouvalas's group reported the first asymmetric total synthesis of (+)-*O*-methylasparvenone (**1**) in 2016, using a new enantioselective approach to construct the 4-hydroxy-1-tetralone ring. The synthesis began with the preparation of aldehyde **16** (Scheme 3). Commercially available 3,4,5-trimethoxybenzaldehyde dimethyl acetal **14** was converted to **16** through regioselective reductive alkylation with Na/THF and ethyl iodide at 0 °C, followed by acetal hydrolysis. Aldehyde **16** underwent enantioselective alkynylation using methyl propiolate to provide alkyne **17** in moderate yield (58%) with high enantiomeric purity (ee 94%). Next, silyl protection of the benzylic alcohol, alkyne saturation under H_2/Pd-C conditions, and ester hydrolysis delivered acid **20** in an overall yield of 80%.

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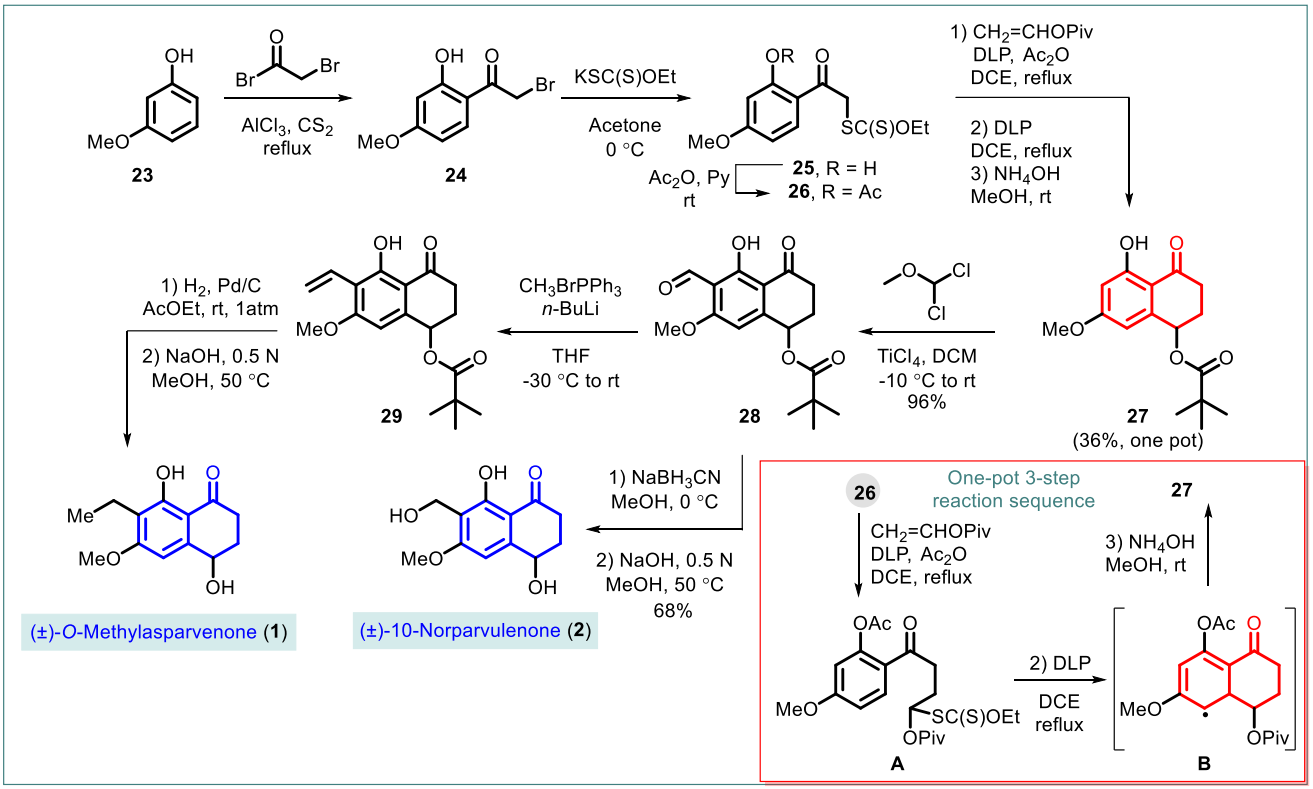
Scheme 3. Boukouvalas's total synthesis of (+)-*O*-methylasparvenone.

Treatment of **20** with freshly distilled trifluoroacetic anhydride unusually resulted in an excellent yield of tetralone **21**. Selective demethylation of the methoxy ether ortho to the carbonyl, followed by silyl deprotection using TBAF, produced the desired natural product (+)-*O*-methylasparvenone **1** in 83% yield.[17]

2.4 Zard's Total Synthesis of (±)-10-Norparvulenone and (±)-*O*-Methylasparvenone (2003):

Zard and coworkers achieved the total synthesis of (±)-10-norparvulenone **2** and (±)-*O*-methylasparvenone **1** in 2003 by utilizing a xanthate-mediated free radical addition-cyclization sequence to construct the challenging tetralone component of these compounds (Scheme 4). The synthesis of (±)-10-norparvulenone **2** began with the preparation of tetralone subunit **27**. Commercially available *m*-methoxyphenol **23** was acylated with bromoacetyl bromide to produce bromoacetophenone **24**. Treatment of **24** with potassium ethyl xanthate in acetone at 0 °C, followed by addition of acetic anhydride, afforded the desired radical precursor **26** in quantitative yield. Next, **26** underwent a three-step, one-pot reaction sequence involving radical addition of the xanthate onto vinyl pivalate using dilauroyl peroxide (DLP) as the initiator under acetic anhydride medium (**26** to **A**), followed by refluxing with DLP in DCE (**A** to **B**), and finally, treatment with ammonium hydroxide, resulting in the bicyclic tetralone intermediate **27** in an overall 36% yield (**B** to **27**). After optimizing reaction conditions, the formyl group on the aromatic ring of **28** was introduced by treating a cold solution of **27** with $TiCl_4$ and dichloromethyl methyl ether in 96% yield. Finally, chemoselective reduction of the aldehyde, followed by saponification of the trimethylacetyl ester group, produced (±)-10-norparvulenone **2** in 68% yield.

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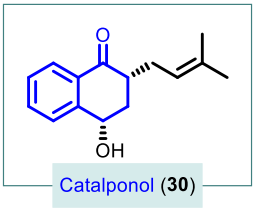


Scheme 4. Zard's total synthesis of 10-norparvulenone and of *O*-methylasparvenone.

Due to the close relationship between (±)-10-norparvulenone **2** and (±)-*O*-methylasparvenone **1**, Zard opted to synthesize **1** using the common intermediate aldehyde **28**. Aldehyde **28** was subjected to Wittig olefination to afford olefin **29** in a moderate yield. The olefin was then hydrogenated, followed by saponification to complete the synthesis of *O*-methylasparvenone **1**.[18]

3. Catalponol

Catalponol was first extracted from the wood of *Catalpa ovata* (also known as Kisasage in Japanese) by Inouye *et al*. in 1971.[19] McDaniel has shown that this natural substance possesses significant antitermitic properties.[20] Furthermore, Lee has also demonstrated that catalponol has the ability to promote dopamine biosynthesis and protect a variety of PC12 cells against the cytotoxicity caused by L-DOPA.[21] To date, the groups of Kündig and Sasai have each reported a total synthesis of catalponol.

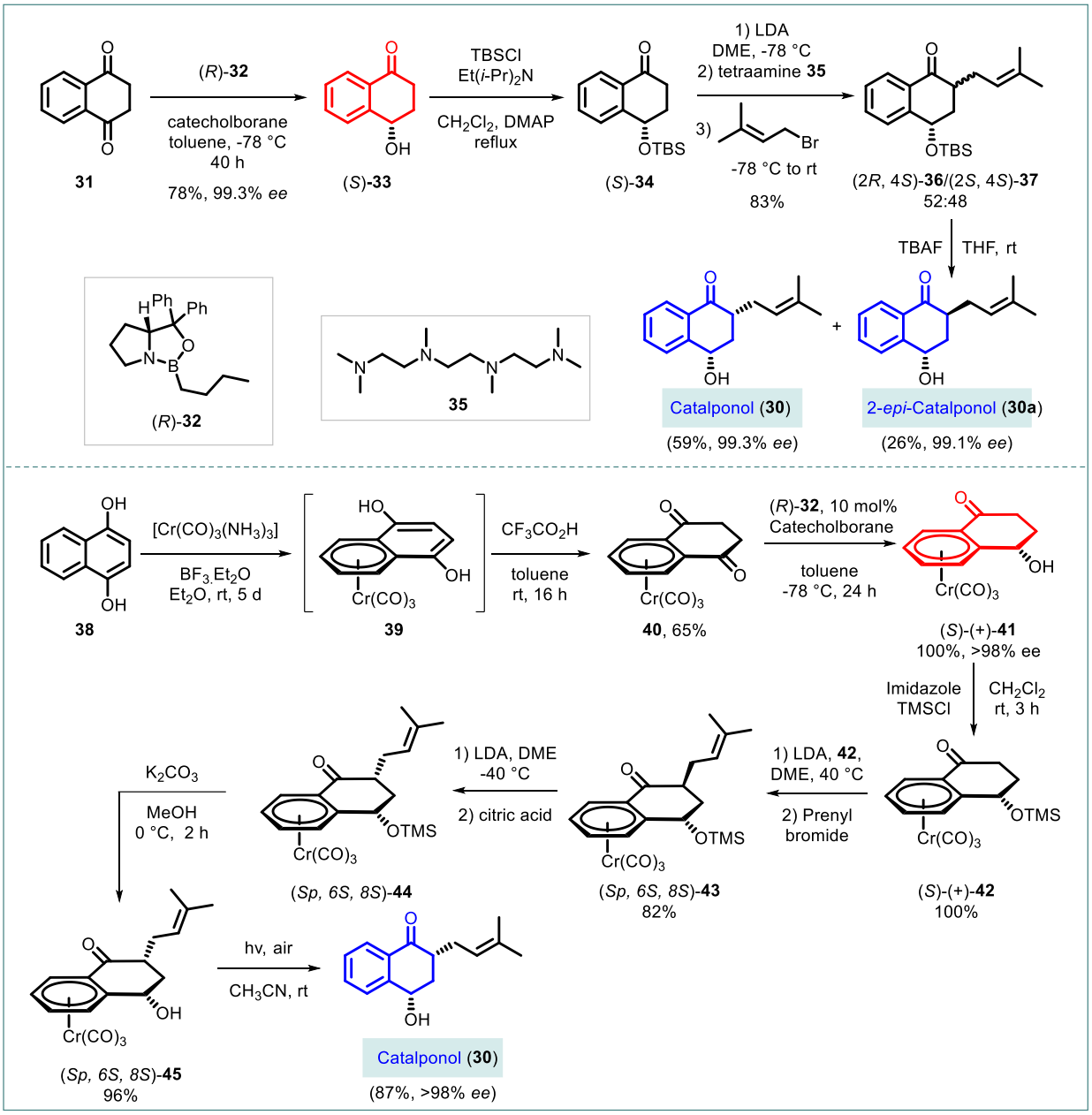


3.1 Kündig's Total Synthesis of Catalponol (2010):

In 2010, Kündig and coworkers reported the first total synthesis of catalponol **30**. They devised two unified approaches to access catalponol, utilizing: 1) a novel, efficient one-step enantioselective monoreduction of

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tetralin-1,4-dione to form 4-hydroxy-1-tetralone, and 2) a more selective enantioselective route involving planar chromiumtricarbonyl complexes of hydroxytetralone.



Scheme 5. Kündig's total synthesis of catalponol.

Scheme 5 outlines the synthetic approach to catalponol. Initially, catalytic enantioselective asymmetric monoreduction of tetralin-1,4-dione using (*R*)-**32** as the catalyst and catecholborane gave 4-hydroxy tetralone (*S*)-**33** with excellent enantioselectivity. Compound **33** was then subjected to silyl protection to furnish **34**. Compound **34** was transformed to its mono-prenylated derivative, resulting in the formation of *cis* **36** and *trans* **37** diastereoisomers in 83% yield with a 52:48 diastereomeric ratio, along with a minor diprenylated product. Treatment of the mixture of diastereoisomers **36** and **37** with TBAF afforded catalponol (**30**) and 2-*epi*-catalponol (**30a**). However, this route failed to demonstrate higher selectivity for catalponol as anticipated.[22]

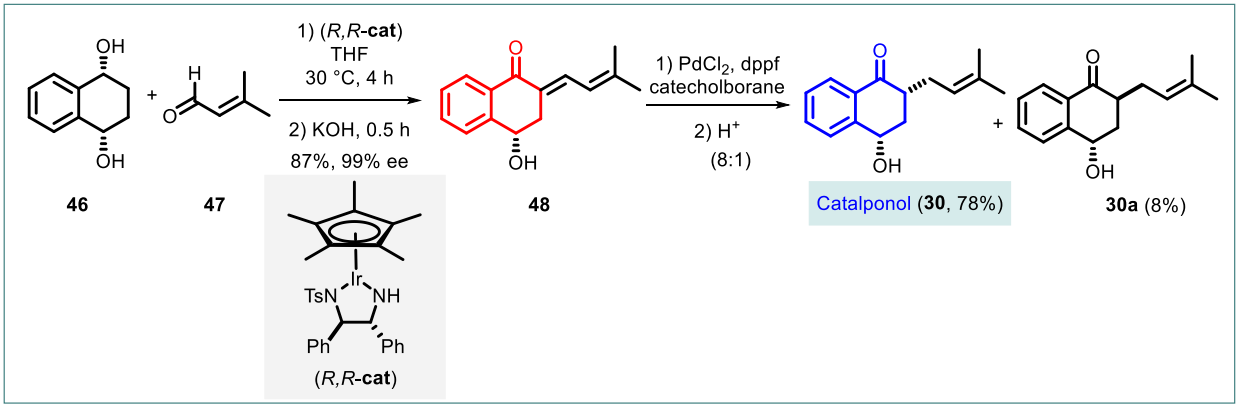
Kündig's second approach is based on a more diastereoselective strategy, utilizing chromium complexes [Cr(arene)$(CO)_3$]. In this approach, the author prepared the chromium complex **40** of the widely available 1,4-

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dihydroxynaphthalene precursor **38** through tautomer **39**. Next, complex **40** was subjected to enantioselective reduction to install the appropriate chiral benzylic hydroxyl group, which was then protected as a TMS to afford **42**. The LDA-mediated enolate formation and prenylation of the $Cr(CO)_3$ complex resulted in the formation of a single diastereomer of *exo*-complex **43**. This *exo*-complex was transformed into *endo*-complex **44** by enolate formation and *exo*-protonation with citric acid. Finally, ether hydrolysis and decomplexation yielded enantiomerically pure catalponol.

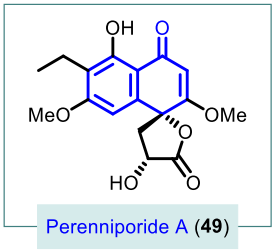
3.2 Suzuki's Total Synthesis of Catalponol (2015):

Suzuki and colleagues developed a straightforward one-pot method for synthesizing benzylidene-hydroxytetralones from *meso*-diols using chiral iridium-catalyzed tandem asymmetric hydrogen transfer oxidation/aldol condensation (Scheme 6). When *meso*-1,4-tetralinediol (**46**) was treated with 3-methyl-2-butenal (**47**) in the presence of catalyst (*R,R*)-**cat**, followed by the addition of KOH, the desired dienone **48** was obtained in an 87% yield with 99% ee. After multiple experiments on the achiral conjugate reduction of unsaturated carbonyl compounds, the authors were able to complete the total synthesis of catalponol **30** in a 78% yield by utilizing $PdCl_2$, dppf, and catecholborane, along with an undesired minor isomer **30a** in 8%.[23]



Scheme 6. Suzuki's total synthesis of catalponol.

4. Perenniporides

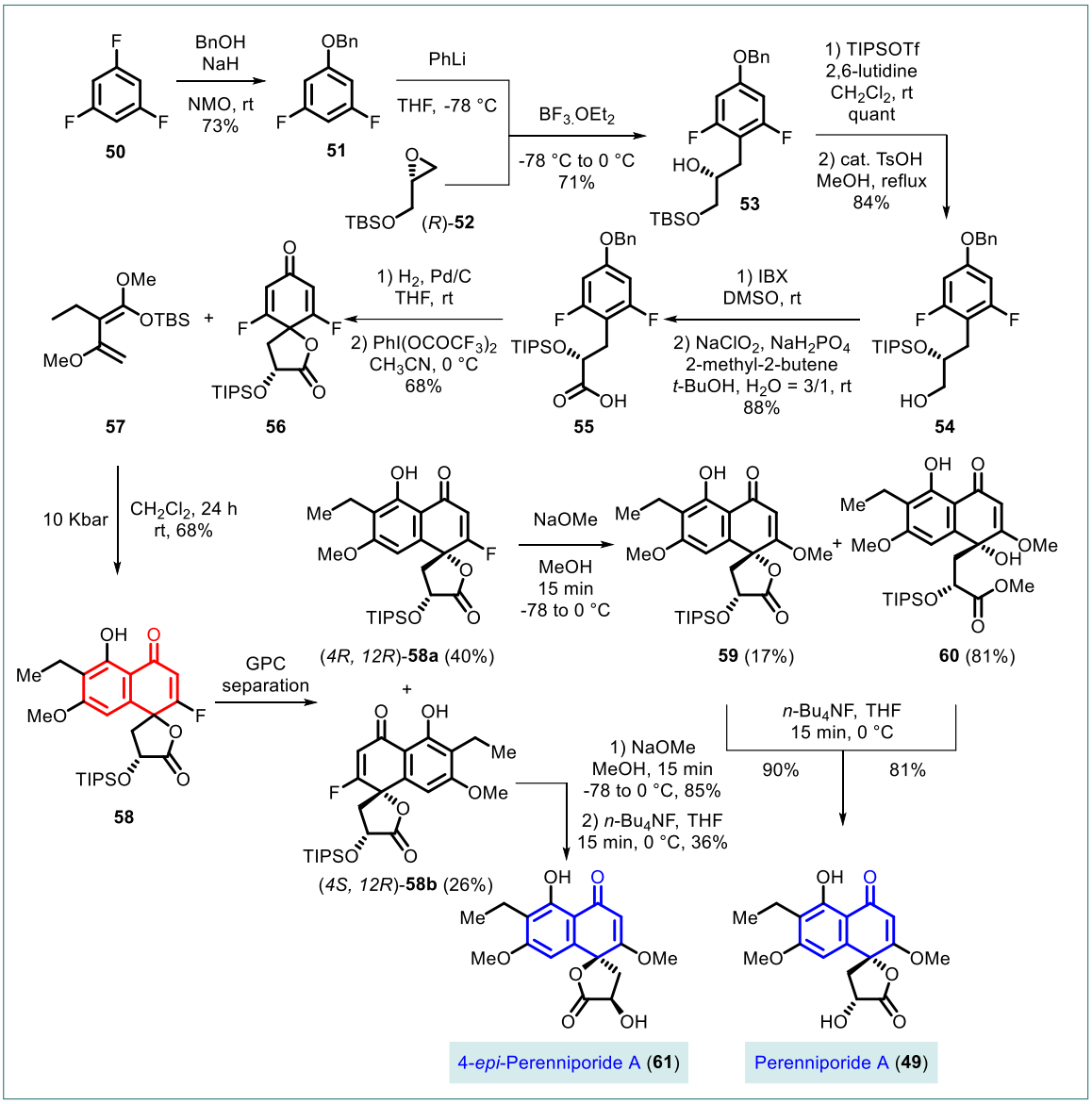


Perenniporides A-D are a class of natural products that were isolated by Liu and Che in 2012 from the fungus *Perenniporia sp.* found in the larva of the phytophagous weevil, *Euops chinesis*.[24] Among these compounds, Perenniporide A (**49**) has been found to exhibit a strong inhibitory effect on various plant pathogens. Its structure features α-tetralone skeleton with a 2-hydroxypropanoic acid appendage. So far, only one total synthesis of **49** has been reported in the literature.

4.1 Ohmori, and Suzuki's Total Synthesis of Perenniporides (2015):

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In 2015, Ohmori and Suzuki achieved the first total synthesis of perenniporide A (**49**), utilizing a remarkable high-pressure cycloaddition reaction to efficiently build the tetralone core of the molecule.



Scheme 7. Ohmori and Suzuki's total synthesis of perenniporides

The synthesis began with the preparation of the crucial cycloaddition precursor, difluorodienone (**56**), starting from 1,3,5-trifluorobenzene (**50**) (Scheme 7). Compound **50** underwent a SNAr reaction with benzyl alkoxide, resulting in the formation of the single-substituted difluoride **51**. This compound was then lithiated regioselectively using PhLi and added to epoxide **52** in the presence of $BF_3.OEt_2$, providing compound **53**. TIPS protection of the secondary alcohol and selective removal of the TBS group under specified conditions gave primary alcohol **54** in 84% yield over two steps. The primary alcohol was transformed into carboxylic acid functionality by IBX oxidation, which was then followed by Kraus-Pinnick oxidation, yielding acid **55** in 88% yield (two steps). Compound **55** underwent H_2, Pd/C-promoted removal of the benzyl ether, followed by oxidative dearomatization of the resulting labile phenol using $PhI(OCOCF_3)_2$, giving difluorodienone **56** in 68% yield.

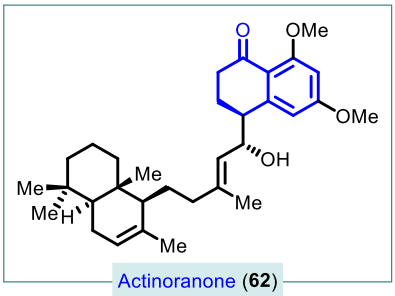
After obtaining the key intermediate **56**, the Diels-Alder reaction with siloxy diene **57** was investigated. After extensive optimization of reaction conditions, the siloxy diene **57** and difluorodienone **56** were subjected

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to ultra-high-pressure conditions (10 Kbar, DCM, rt, 24 h) to yield the Diels-Alder adduct (α-tetralone) **58** in a 68% yield as a 3/2 inseparable mixture (simple chromatography conditions). This mixture was separated using gel permeation chromatography (YMC-GPC T4000+T2000, AcOEt) to afford **58a** and **58b** in 40% and 26% yield, respectively. The relative stereochemistry was assigned using 2D NMR analysis. Next, the fluorine atom in **58a** was replaced by a methoxy group, yielding compounds **59** and **60**, which, upon treatment with tetrabutylammonium fluoride, afforded the natural product perenniporide A. Similarly, **58b** was transformed into 4-*epi*-perenniporide A **61**.[25]

5. Actinoranone

Actinoranone is a meroterpene natural compound that was isolated from a marine-derived actinomycete by Fenical and colleagues in 2013.[26] This natural product possesses an unusual scaffold composed of diterpene and polyketide (containing tetralone functionality) and has been demonstrated to exhibit significant in vitro cytotoxicity against HCT-116 human colon cancer cells, with an LD_{50} value of 2.0 μg/mL.



Actinoranone (**62**)

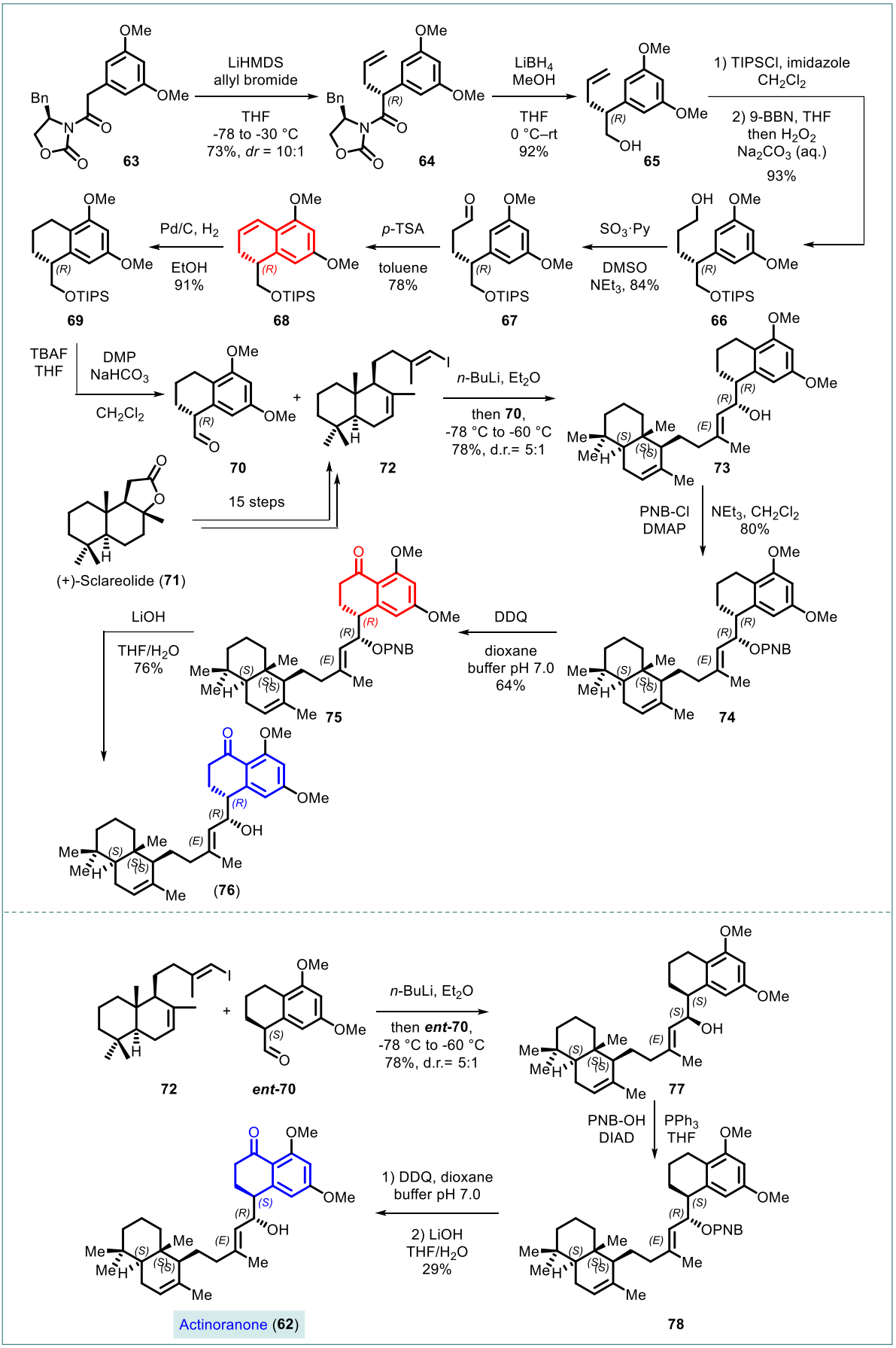
To date, the research teams of Xu/Ye, has completed a total synthesis. Pastre, and Christmann have secured formal syntheses of actinoranone.

5.1 Xu/Ye's Total Synthesis of Actinoranone (2017):

In 2017, the Xu/Ye research group accomplished the first total synthesis of actinoranone **62** and successfully assigned its stereochemistry. The construction of the core skeleton was achieved through the use of an intramolecular Friedel-Crafts reaction and a benzylic C-H oxidation reaction (Scheme 8).

To synthesize actinoranone, aldehyde **70** was prepared from (*R*)-oxazolidinone imide **63**. Allylation of **63** with allyl bromide gave allylated amide **64**, which was reduced using $LiBH_4$ to afford primary alcohol **65**. TIPS protection of the primary alcohol followed by hydroboration of the terminal olefin to obtain the monosilylated diol **66**. Oxidation of alcohol **66** under Parikh-Doering conditions led to the aldehyde, which was then subjected to a Friedel-Crafts reaction and dehydration with catalytic p-toluenesulfonic acid to produce bicycle **68**. This was hydrogenated, and the primary alcohol was desilylated to produce aldehyde **70** through Dess-Martin oxidation. The vinyl iodide coupling partner **72** was prepared from commercial (+)-sclareolide **71** in 15 steps, allowing for efficient synthesis of actinoranone.

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Scheme 8. Xu/Ye's total synthesis of actinoranone.

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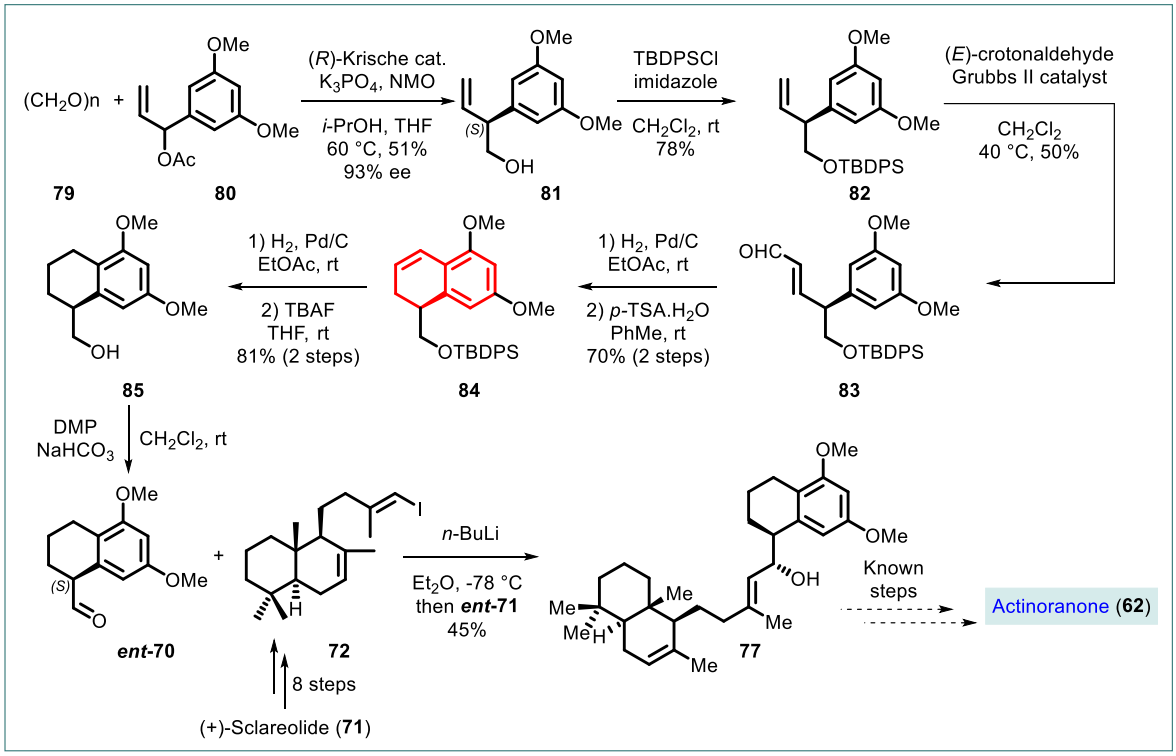
The *n*-BuLi-mediated coupling of **72** and **70** proceeded smoothly, producing secondary alcohol **73** in a 78% yield with reasonable selectivity (Felkin/anti-Felkin = 5:1). The resulting diastereomers were separated using column chromatography, and the stereochemistry at the secondary hydroxyl group was determined using Mosher's ester.

The required major isomer was protected as a PNB ester, and benzylic C-H oxidation of **74** using DDQ gave tetralone **75**. Hydrolysis of ester **75** ultimately yielded actinoranone (**76**). However, upon comparison of the spectral data with natural actinoranone, considerable differences were observed. To determine the exact structure of actinoranone, the *ent*-**70** isomer of the aldehyde was prepared and coupled with vinyl iodide to form **77**. The Mitsunobu inversion of alcohol **77**, benzylic C-H activation, and ester hydrolysis were used to deliver the desired natural product, actinoranone **62**, in a 29% yield over 3 steps. All analytical data agreed with known data. [27]

5.2 Pastre's Formal Synthesis of Actinoranone (2017/2018):

In 2017, Pastre and coworkers reported a formal synthesis of actinoranone (**62**) that utilized similar chemistry to Xu's approach in constructing the tetralene scaffold. The synthesis of actinoranone began with the preparation of aldehyde ***ent*-70** and vinyl iodide **72**. Initially, vinyl iodide **72** was obtained from commercial (+)-sclareolide (**71**) in approximately 8 steps, using a sequence previously reported procedure.

The synthesis of the aldehyde fragment began with the enantioselective hydroxymethylation of allylic acetate **80** under an iridium catalyst, which provided a straightforward way of obtaining alcohol **81** (Scheme 9). The primary alcohol was protected as silyl ether, and the terminal olefin was converted into unsaturated aldehyde **83** using Grubbs cross metathesis with (*E*)-crotonaldehyde. Next, catalytic hydrogenation of the olefin, followed by Friedel-Crafts cyclization and dehydration, produced the bicycle with a new olefin **84**. Compound **84** was subjected to a second hydrogenation, followed by silyl deprotection and DMP oxidation, which delivered the required aldehyde fragment ***ent*-70**.

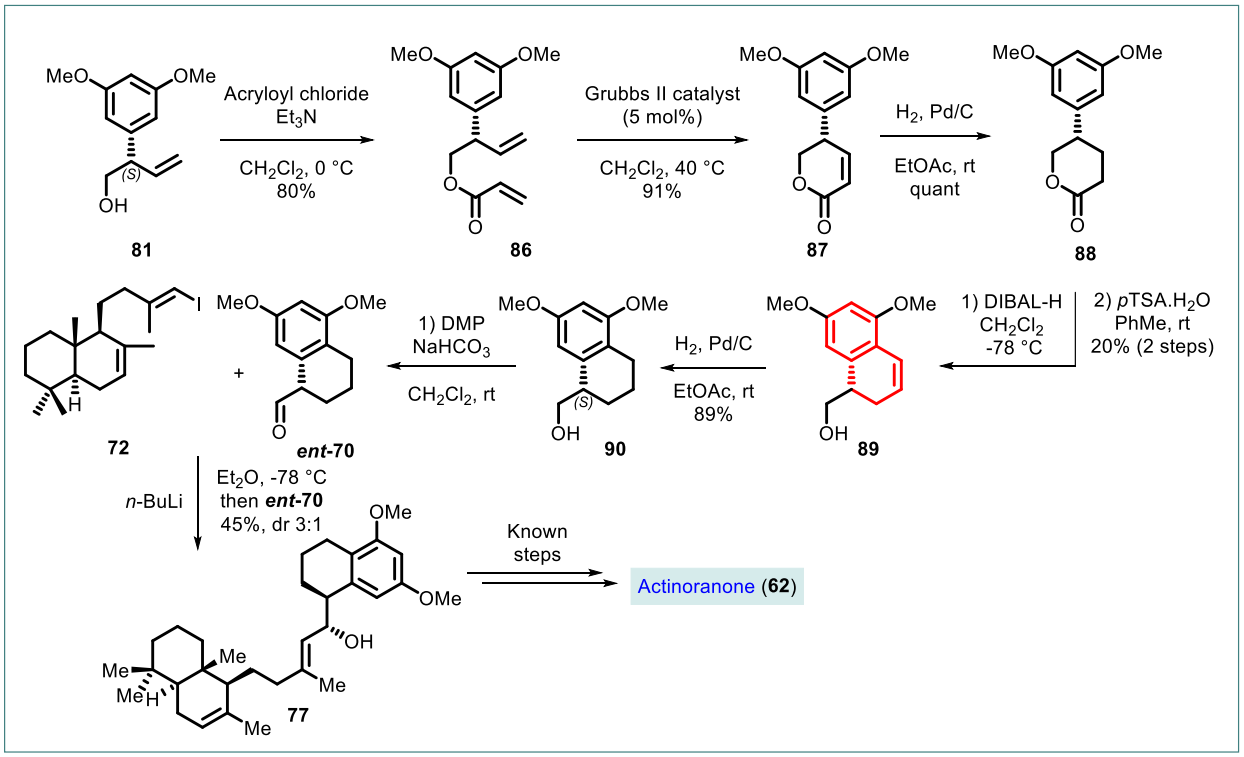


Scheme 9. Pastre's formal synthesis of actinoranone.

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Finally, the coupling of fragments **72** and ***ent*-70** was carried out using lithium halogen exchange to give alcohol **77**, which was an advanced intermediate in Xu/Ye's total synthesis, thus completing the formal synthesis of actinoranone (**62**).[28]

About a year later, the same group reported a full account of their efforts towards the formal synthesis of actinoranone (**62**) (Scheme 10).[29] The polyketide fragment was prepared using protecting group-free synthetic methods. The primary alcohol **81** was first transformed into an acrylate **86**, which was then metathesized and hydrogenated to yield the δ-valerolactone derivative **88**. DIBAL-H reduction of the lactone, followed by a subsequent Friedel-Crafts reaction of the resulting lactol, and hydrogenation produced compound **90**. The desired aldehyde fragment ***ent*-70** was obtained by oxidizing primary alcohol **90**. Finally, the coupling of ***ent*-70** and **72** using butyl lithium provided **77**, an intermediate in previous syntheses of actinoranone, thus accomplishing the formal synthesis of actinoranone (**62**).



Scheme 10. Pastre's formal synthesis of actinoranone.

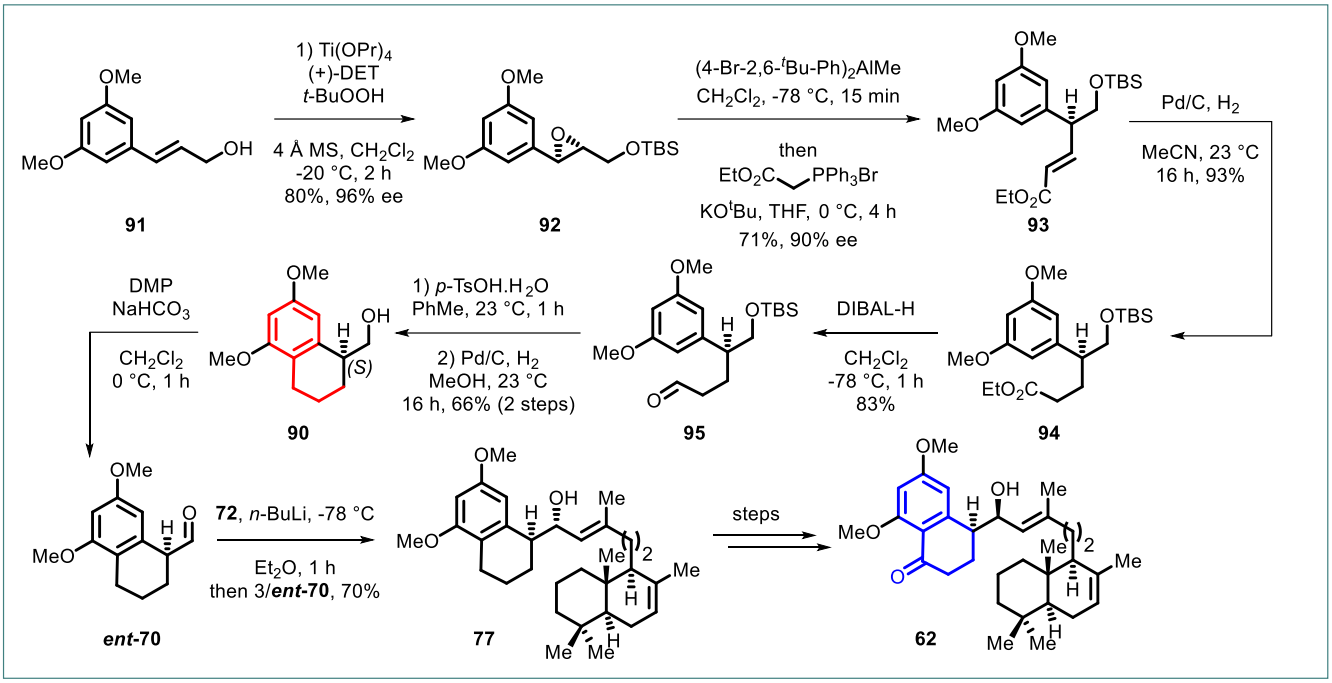
5.3 Menger and Christmann's Formal Synthesis of Actinoranone (2019):

In 2019, Menger and Christmann reported an approach to the synthesis of actinoranone (**62**) through intermediate **77** (Scheme 11).[30] The synthesis of **77** utilized a semipinacol rearrangement/Wittig reaction sequence and a chiral pool approach for the syntheses of the tetralone and octalin fragments, respectively.

The epoxide **92** was synthesized from allylic alcohol **91** via catalytic Sharpless epoxidation, followed by silyl protection. The Yamamoto rearrangement of **92**, using stoichiometric quantities of (methylaluminum bis-(4-bromo-2,6-di-*tert*-butylphenoxide)), followed by direct addition of freshly produced Wittig reagent, resulted in the formation of unsaturated ester **93**. Olefin hydrogenation followed by ester reduction led to the formation of aldehyde **95**. Using *p*-TsOH as a catalyst, cyclization, silyl ether cleavage, and hydrogenation of the olefin provided the bicyclic alcohol **90**. The oxidation of alcohol **90** by Dess Martin periodinane yielded aldehyde fragment ***ent*-70**.

When aldehyde ***ent*-70** was combined with *in-situ* lithiated vinyl iodide **72**, the allylic alcohol **77** was obtained, completing the formal synthesis of actinoranone.

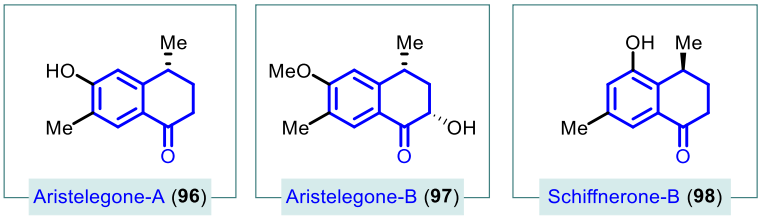
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Scheme 11. Menger and Christmann's formal synthesis of actinoranone.

6. Aristelegone-A, B and Schiffnerone B

Aristelegone-A and B are natural metabolites that were isolated by the Wu research group in 2002 from the root and stem of *Aristolochia elegans*.[31] Schiffnerone-B was isolated from the wood of *Dysoxylum schiffneri*.[32] To date, four total syntheses of aristelegone-A and B and one synthesis of schiffnerone-B have been reported.

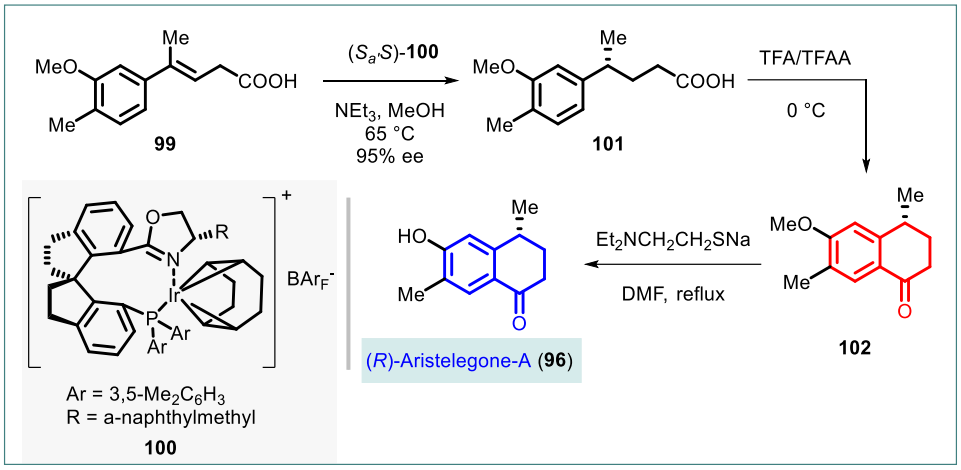


6.1 Zhou's Total Synthesis of Aristelegone-A (2012):

In 2012, Zhou's research group developed an expeditious method for the highly enantioselective iridium-catalyzed hydrogenation of 4-alkyl-4-aryl-3-butenoic acids. Using the iridium catalyst (**100**) (0.5 mol%), H_2 (3 atm), and Et_3N (1 equiv) in methanol at 65 °C, various chiral 4-alkyl-4-aryl butanoic acids were obtained with a broad substrate scope, functional group tolerability, and excellent enantioselectivity. This methodology was successfully applied for the total synthesis of aristelegone-A (**96**).

The concise total synthesis of aristelegone-A was accomplished by Friedel-Crafts reaction of chiral butanoic acid (**101**) and subsequent demethylation with $Et_2NCH_2CH_2SNa$ (Scheme 12).[33]

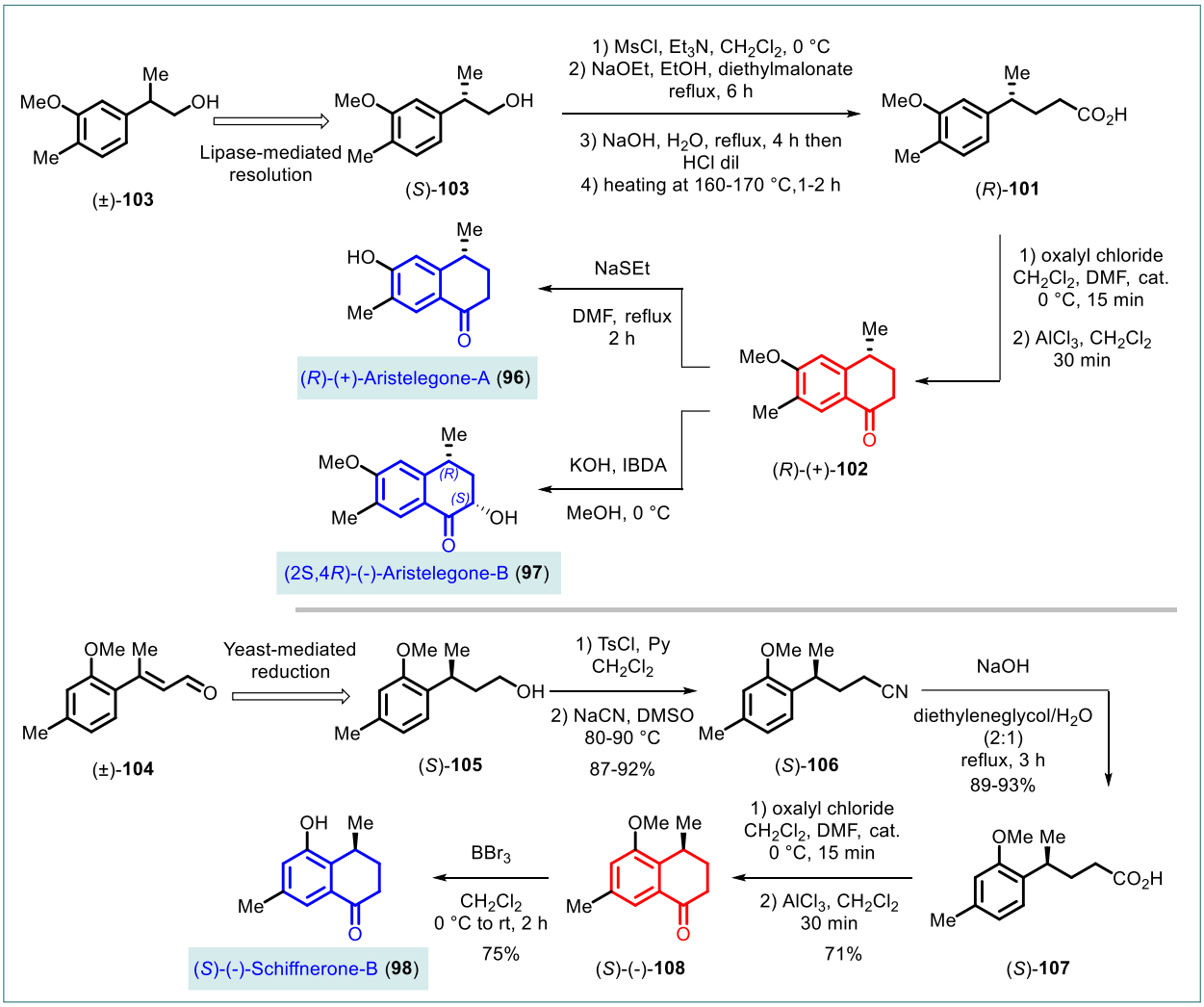
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Scheme 12. Zhou's total synthesis of aristelegone-A.

6.2 Serra's Total Synthesis of Aristelegone-A, B and Schiffnerone B (2013):

Serra in 2013 reported the enantioselective total synthesis of the most common trinorsesquiterpene tetralones (aristelegone-A and B and schiffnerone-B) using stereodivergent method and simple chemical transformations. The required tetralone core was achieved using a Friedel-Crafts reaction.[34]



Scheme 13. Serra's total synthesis of aristelegone-A, B and schiffnerone B.

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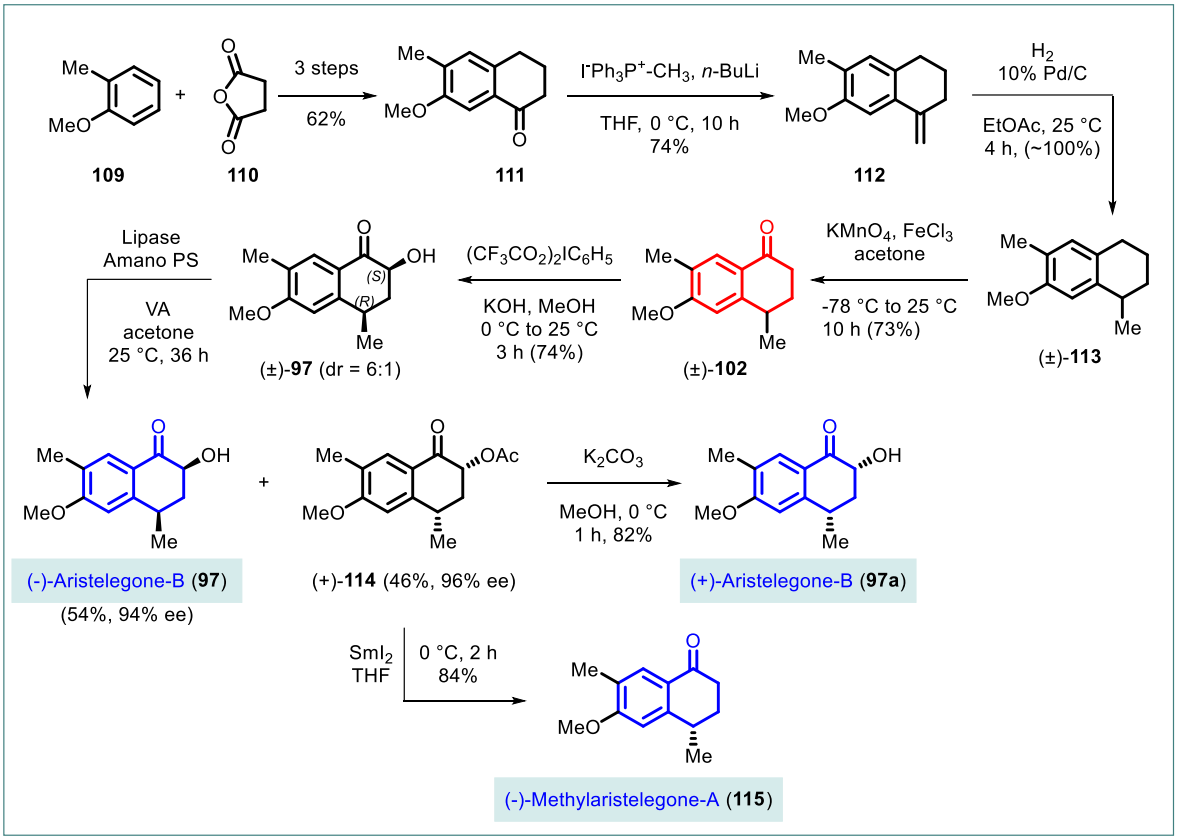
Initially, Serra proposed obtaining the tetralone scaffold via a Friedel-Crafts reaction from an open-chain acid, either (*R*)-**101** or (*S*)-**107** (Scheme 13). To this end, the synthesis of natural products **96** and **97** commenced with the substituted (*S*)-2-arylpropanol (*S*)-**103**, which was prepared from lipase-mediated resolution of racemic 2-arylpropanols (±)-**103**. The alcohol (S)-**103** underwent a four-step reaction sequence involving mesylation, alkylation of sodium salt of diethylmalonate, hydrolysis of diester, and decarboxylation to yield its homologous acid (*R*)-**101**. The acid (*R*)-**101** was then subjected to classic Friedel-Crafts reaction, leading to the desired chiral tetralone scaffold. Demethylation of this tetralone produced (*R*)-(+)-aristelegone-A (**96**), while KOH/IDBA (iodobenzene diacetate) mediated α-hydroxylation yielded (2*S*, 4*R*)-(–)-aristelegone B (**97**).

To synthesize compound **98**, (*S*)-3-arylbutanol (*S*)-**105** was utilized as the starting material. The (*S*)-3-arylbutanol was prepared through baker's yeast mediated reduction of substituted (*E*)-3-aryl-but-2-enal **104**. The alcohol (*S*)-**105** was converted into cyano functionality by first tosylating it and then displacing the tosylate group with sodium cyanide. The resulting nitrile was hydrolyzed using a refluxing solution of sodium hydroxide to produce the desired acid (*S*)-**107**. A regioselective Friedel-Crafts cyclization followed by demethylation then yielded (*S*)-(-)-schiffnerone-B (**98**).

6.3 Argade's Total Synthesis of Aristelegone B and Methylaristelegone A (2015):

In 2015, Batwal and Argade reported a chemoenzymatic total synthesis of various optically active terpenoids based on a tetralone scaffold. Their approach employed late-stage efficient enzymatic resolution, providing access to both enantiomers.

The synthesis began with the preparation of tetralone **111** from 2-methylanisole (**109**) and succinic anhydride (**110**) in three steps, including Friedel-Crafts acylation, Clemmensen reduction, and acid-promoted intramolecular cyclization (Scheme 14). Wittig olefination of ketone **111**, followed by hydrogenation of the resulting olefin, and benzyllic oxidation, yielded another tetralone, **102**.



Scheme 14. Batwal and Argade's total synthesis of aristelegone B and acylaristelegone B.

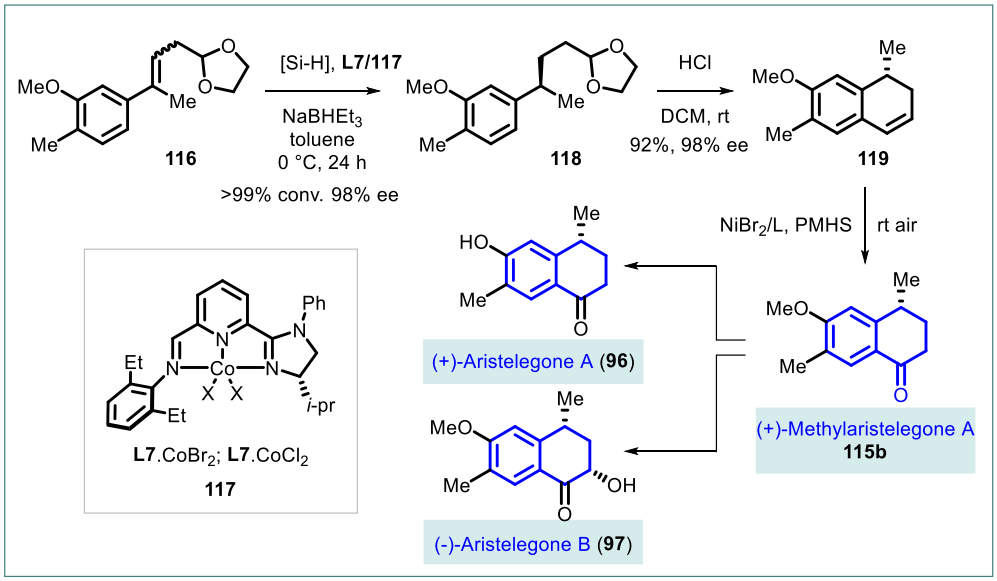
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Base-induced stereoselective α-hydroxylation of **102** with a hypervalent iodine reagent ((bis(trifluoroacetoxy) iodo)benzene) resulted in the formation of (±)-aristelegone B (**97**), which was then subjected to lipase Amano PS-catalyzed stereoselective acylation, providing optically active natural product (−)-aristelegone B (**97**) (54%, 94% ee) and (+)-acylaristelegone B (**114**) (46%, 96% ee). Upon acetate hydrolysis, compound **114** was transformed into (+)-aristelegone B (**97a**), and samarium iodide-mediated deacetoxylation converted this compound into (−)-methylaristelegone A (**115**).[35]

6.4 Hong/Lu's Total Synthesis of Aristelegone A and B (2022):

The research groups of Hong and Lu have developed an efficient cobalt-catalyzed enantioconvergent hydrogenation technique, which utilizes easily available, minimally functionalized *E/Z*-olefin mixtures. This technique was used for the formal total synthesis of aristelegone A and B.

The synthesis began with the enantioselective hydrogenation of trisubstituted olefin **116**, which delivered the chiral compound **118** in quantitative yield and 98% ee. Compound **118** was subsequently transformed into known intermediate methylaristelegone A (**115b**) in two stages via **119**. This completed the formal synthesis of **96** and **97** (Scheme 15).[36]



Scheme 15. Hong/Lu's total synthesis of aristelegone A and B.

7. Conclusions

The α-tetralone skeleton is a unique structural feature found in natural products with diverse biological activities, making them a subject of increasing interest in the organic synthetic community. This review provides a summary of the total syntheses of various natural products containing this scaffold, such as 10-norparvulenone, *O*-methylasparvenone, aristelegone-A, aristelegone-B, catalponol, perenniporide A, and actinoranone, achieved since 1991. To construct this tetralone framework, several general and concise synthetic strategies have been employed, including ring-formation reactions such as Diels-Alder and Friedel-Crafts acylation-cyclization, as well as radical cyclization reactions. Although several other natural products with this motif have been isolated, their syntheses have not yet been reported. The unique challenges associated with tetralones have spurred innovative solutions and novel chemical techniques. As new bioactive

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tetralones are discovered every year, the synthetic interest in this class of natural products is expected to grow. Therefore, it will be intriguing to witness the emergence of new strategies, alternative disconnections, and useful synthetic methods in the future.

8. Acknowledgements

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Mukund Sibi earned his PhD from the City University of New York. After postdoctoral studies, he began his independent career at North Dakota State University where he is currently a University Distinguished Professor. His research focus is on radical chemistry, development of enantioselective reactions, total synthesis, and green chemistry. Prof. Sibi has received the prestigious Arthur C. Cope Scholar Award from the American Chemical Society in 2008 in recognition of his contributions to the field of radical chemistry. In 2021 he was elected as a Fellow of AAAS for his contribution to radical chemistry as well as building biomedical research infrastructure.

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