

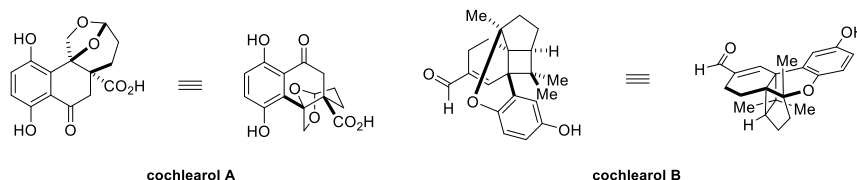
Synthetic Strategies Towards the Meroterpenoids Cochlearols A and B from *Ganoderma cochlear*

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Abstract. Since the first reports of their isolation, the meroterpenoids cochlearol A and B have attracted interest from the synthetic community for their unique structural features. This review describes the attempted and successful total syntheses of these natural products and provides a summary of the strategies developed in the years since their isolation.

- 1 Introduction
- 2 Overview of Cochlearol A Syntheses
- 3 Rongbiao's Approach Towards Cochlearol A
- 4 Liu and Qin's Total Synthesis of (±)-Cochlearol A
- 5 Ishigami's Formal Synthesis of (±)-Cochlearol A
- 6 Chandrasekhar's Formal Synthesis of (±)-Cochlearol A
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- 8 Schindler's Synthesis of (+)-Cochlearol B
- 9 Conclusions

Key words total synthesis, *ganoderma cochlear*, meroterpenoid, cochlearol

1 Introduction

Ganoderma ganodermataceae is a white rot fungus growing on wood logs and plants.¹ More than 70 distinct *Ganoderma* species are known of which *G. lucidum*, *G. sinense*, *G. capense*, *G. tsugae*, and *G. cochlear* are used in traditional medicinal applications.² However, only 22 *Ganoderma* species have been studied to date with respect to their chemical constituents and associated bioactivities.³ Among the chemical compounds isolated from *Ganoderma* species are *Ganoderma* meroterpenoids, which are natural products containing a 1,2,4-trisubstituted phenyl moiety together with an unsaturated terpene subunit known to display a range of desirable biological activities.⁴ Among others, anti-oxidant activity, anti-fibrotic, AChE (anti-Acetyl cholinesterase), cytotoxic, antimicrobial, and aldol reductase inhibitory activity have been reported.⁵ This review will focus on two *Ganoderma* meroterpenoids recently isolated from *Ganoderma cochlear* and associated efforts to develop efficient

synthetic routes towards these natural products.

In their efforts toward isolating natural products displaying activity toward chronic kidney disease, Cheng and coworkers reported the isolation of two new phenolic meroterpenoids, cochlearol A (**1**) and cochlearol B (**2**) in 2014 from the fungus *Ganoderma cochlear*.⁶ The structures and relative configurations of **1** and **2** were assigned using 2D NMR spectroscopy relying on ¹H-¹H COSY, HMBC, and ROESY experiments. Cochlearol A (**1**) was found to incorporate a 5/6/6/6 tetracyclic ring system and a structurally unique dioxaspiro[4.5]decane moiety. In comparison, cochlearol B (**2**) is structurally distinct and contains a 4/5/6/6/6 pentacyclic ring system featuring a hepta-substituted cyclobutane ring containing three contiguous stereocenters.

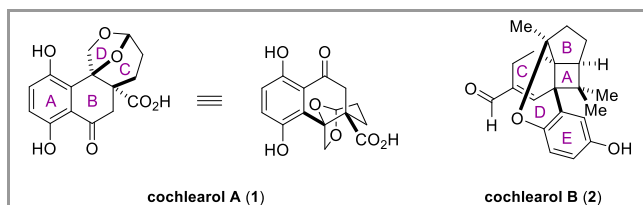


Figure 1 Meroterpenoids cochlearol A (**1**) and cochlearol B (**2**) isolated from *Ganoderma cochlear*.

Biological analysis of these complex meroterpenoid structures has shown that racemic **1** and **2** inhibited the upregulation of collagen I, fibronectin, and α-SMA suggesting renoprotective effects, especially on renal fibrosis, with **1** displaying more potent activity than **2**. Investigations using Western blot showed racemic **1** and **2** inhibited Smad2/3 phosphorylation, suggesting that both compounds exert antifibrotic action through the disruption of Smad activation.

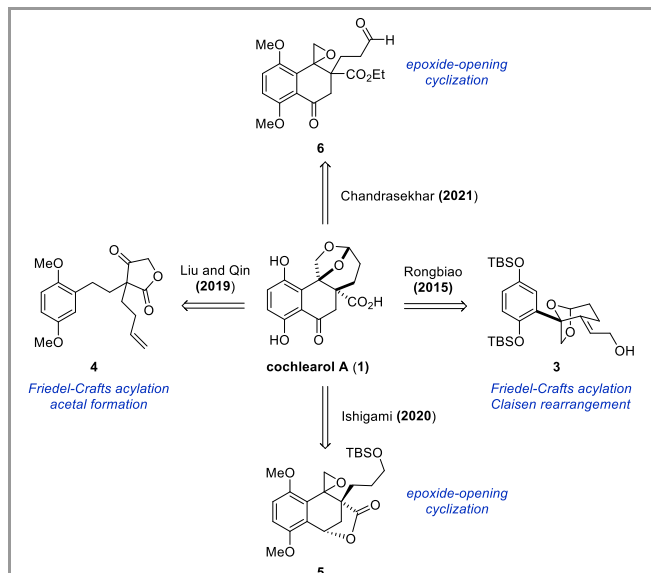
The enantiomers of **1** and **2** were separated and independently evaluated for renoprotective effects in renal proximal tubular cells using PCR and Western blot. Both enantiomers of **1** displayed no apparent inhibitory activity and demonstrated

toxic effects to cell viability in MTT assays. However, (-)-**2** displayed potent antifibrotic efficacy by a dose-dependent manner while the other enantiomer was shown to be inactive. MTT assays of both enantiomers of **2** demonstrated no effect on cell viability.

Due to the inherent structural complexity and promising biological activity displayed by both cochlearol A (**1**) and cochlearol B (**2**), they have piqued interest in the synthetic community and have been the subjects of several total syntheses. Given the unique polycyclic structures of these natural products, there are several obstacles in their syntheses. A key challenge in the synthesis of cochlearol A (**1**) is the diastereoselective construction of the *cis*-6,6 B/C ring scaffold, which is generally less stable relative to the *trans* isomer and contains two quaternary carbons at the bridgehead sites. Moreover, the unusual dioxaspiro[4.5]decane C/D ring motif presents an additional synthetic challenge due to the labile acetal. Similarly, the ring construction of cochlearol B's (**2**) core presents challenges as the highly substituted cyclobutane ring is unprecedented and must be constructed in a diastereoselective manner. Herein, the known syntheses of cochlearol A and cochlearol B are described.

2 Overview of Cochlearol A Syntheses

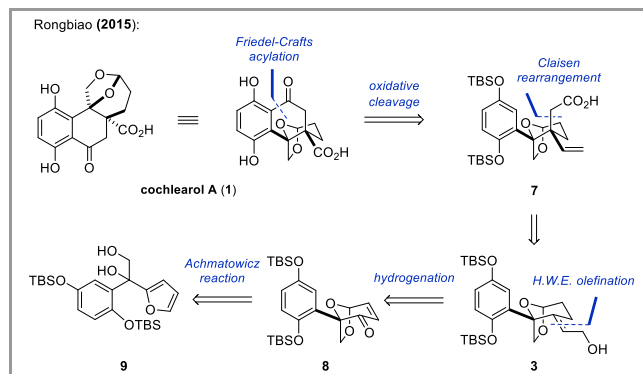
Cochlearol A has been targeted by four groups, with one total synthesis and two formal syntheses reported to date. Highlighting the complexity of cochlearol A's core structure, each synthetic route utilizes a different approach to build the 5/6/6/6 tetracyclic scaffold. While each route is unique, both Rongbiao et al. and Liu and Qin et al. rely on a Friedel-Crafts acylation from intermediates **3** and **4**, respectively, while Ishigami et al. and Chandrasekhar et al. employ a ring-opening cyclization from epoxides **5** and **6** as a key transformation in the synthesis of cochlearol A (Scheme 1).



Scheme 1 Cochlearol A retrosyntheses

3 Rongbiao's Approach Towards Cochlearol A

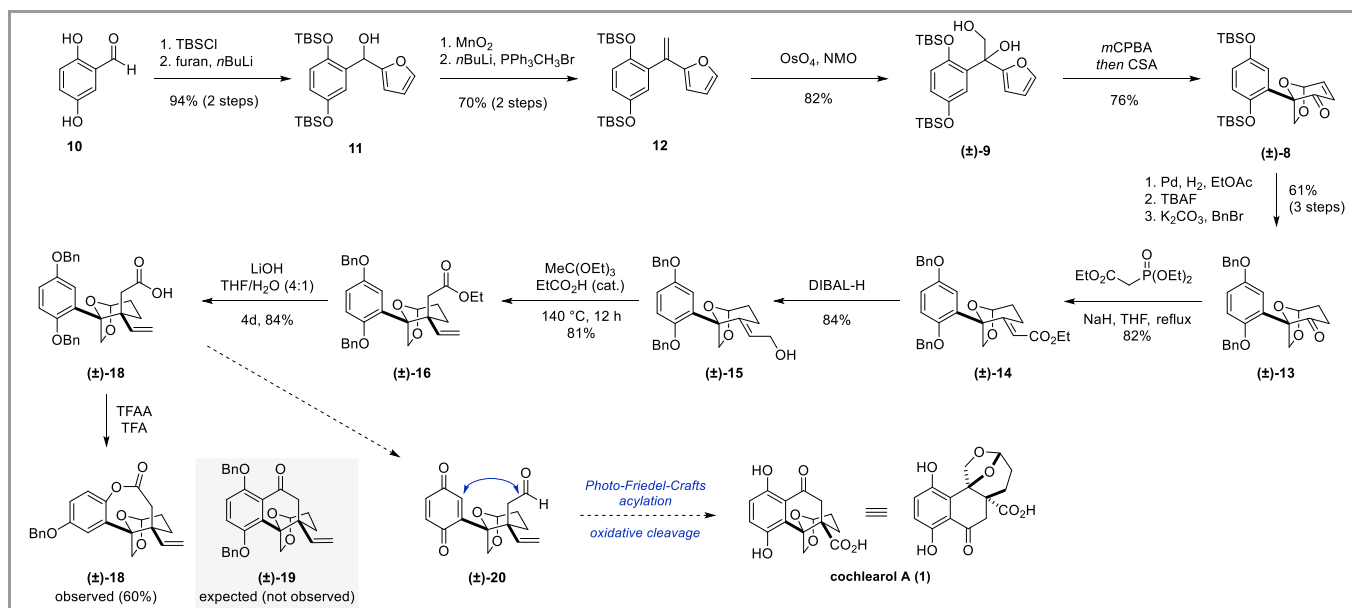
The authors envisaged that ring B in cochlearol A (**1**) could be formed via Friedel-Crafts acylation and oxidative cleavage from carboxylic acid **7** (Scheme 2).⁷ The γ , δ -unsaturated acid moiety could be constructed by Claisen-type rearrangement of a corresponding allylic alcohol **3**. This allylic alcohol can be



Scheme 2 Rongbiao's retrosynthetic strategy towards cochlearol A (**1**) relying on a key Achmatowicz reaction.

accessed from unsaturated pyranone **8** by hydrogenation and Horner-Wadsworth-Emmons (H.W.E.) olefination. The unsaturated pyranone could be formed by Achmatowicz rearrangement⁸ of the corresponding 2-substituted furan **9** followed by acetal formation, offering a one-step entry to the A/C/D ring scaffold. The necessary diol precursor, **9**, for the Achmatowicz reaction can be accessed by sequential 1,2-addition, Wittig olefination, and dihydroxylation.

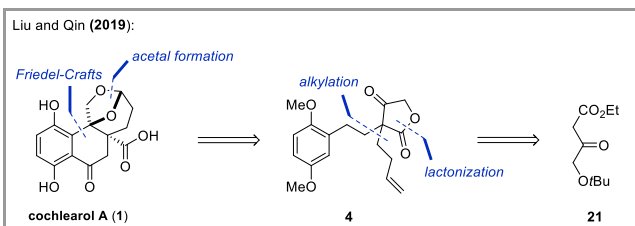
In a forward sense, Rongbiao's strategy commenced with commercially available benzaldehyde **10**, which upon global silyl protection followed by nucleophilic addition of furan afforded furfuryl alcohol **11** in 94% yield over 2 steps (Scheme 3). Alcohol **11** was converted in 70% yield over 2 steps to the corresponding olefin **12** via oxidation to the analogous aryl ketone followed by a Wittig reaction. To obtain the precursor of the Achmatowicz rearrangement, Upjohn dihydroxylation of the alkene furnished furfuryl diol **9** in 82% yield. Treatment of **9** with *m*CPBA followed by CSA afforded the desired core C/D bicyclic framework **8** in 76% via Achmatowicz reaction⁸ and subsequent bicyclopentalization. Routine Pd-catalyzed hydrogenation of the Achmatowicz product **8** afforded the saturated pyranone. Envisioning the silyl protection groups would be intolerant of the acidic Friedel-Crafts acylation conditions, this pyranone was converted to globally benzyl protected **13** by deprotection followed by etherification in 61% yield over 3 steps. Upon isolating the benzyl protected substrate **13**, it was subjected to H.W.E. olefination to afford the unsaturated ethyl ester **14** in 82% yield. Reduction of the ester to the corresponding allylic alcohol **15** in 84% yield gave access to the necessary precursor for the key Johnson-Claisen rearrangement using catalytic propionic acid and triethyl orthoacetate. This transformation led to the desired γ , δ -unsaturated ester **16** in 81% yield, which was hydrolyzed under basic conditions to the corresponding carboxylic acid **17** in 84% yield. Unfortunately, when a range of traditional Friedel-Crafts acylation conditions were evaluated to close ring B, only lactone **18** was observed in up to 60% yield rather than desired cyclohexanone **19**. The authors hypothesized that the bicyclic ketal and benzyl protecting groups were still too labile towards acidic Friedel-Crafts conditions, and instead envisioned a photo-Friedel-Crafts strategy that would avoid substrate incompatibility. In this revised approach, conversion of the Johnson-Claisen product to quinone **20** would provide a compound analogous to previously described intermolecular photo-Friedel-Crafts acylation products.⁹



Scheme 3 Rongbiao and coworkers strategy towards the synthesis of cochlearol A (1).

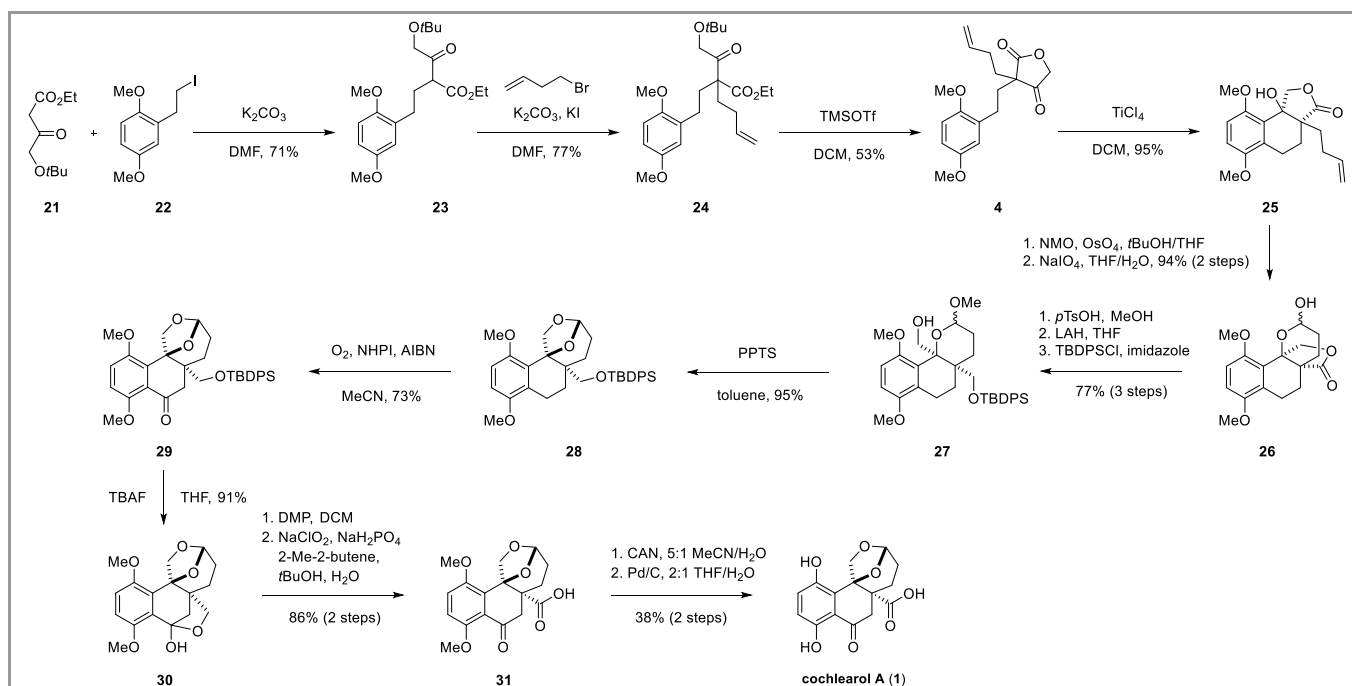
4 Liu and Qin's Total Synthesis of (±)-Cochlearol A

In 2019, Liu, Qin and coworkers disclosed the first total synthesis of cochlearol A (1), proposing a key disconnection for the C/D bicyclic ketal ring junction from a methyl-protected 6-membered cyclic hemiacetal and primary alcohol (Scheme 4).¹⁰



Scheme 4 Liu and Qin's retrosynthetic disconnections towards cochlearol A (1).

To eventually achieve a *cis* 6,6 B/C ring fusion, Friedel-Crafts alkylation from ketolactone 4 was proposed to afford the desired A/B ring fusion product. Sequential alkylation of β-ketoester 21 followed by lactonization could give access to the desired ketolactone 4. Base-mediated alkylation of the commercially available β-ketoester 21 with aryl iodide 22 afforded the desired mono-alkylation product 23 in 71% yield (Scheme 5). A subsequent base-mediated alkylation with 4-bromo-1-butene furnished the substituted β-ketoester 24 in 77% yield. With 24 in hand, a Lewis-acid catalyzed lactonization was carried out to afford 4 in 53% yield. However, no *in situ* Friedel-Crafts alkylation was observed, thus a stronger Lewis acid, TiCl₄, was employed to give access to 25 in 95% yield. Two step oxidative cleavage of the pendant alkene afforded cyclic hemiacetal 26 in 94% yield. Methyl protection of the hemiacetal, reduction of the lactone to the corresponding diol, and

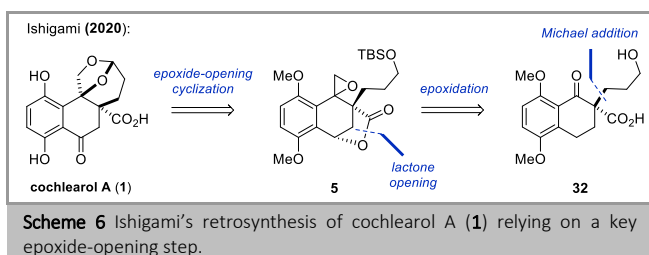


Scheme 5 First reported total synthesis of cochlearol A (1) by Liu and Qin

regioselective silyl protection afforded the *cis*-oxadecalin B/C ring scaffold **27** in 77% yield over 3 steps. Upon accessing **27**, an acid-catalyzed acetalization via hemiacetal ring opening gave the bridged acetal C/D ring scaffold **28** in 95% yield.

Selective benzylic oxidation of **28** furnished the desired aryl ketone **29** in 73% yield and subsequent deprotection of the primary silyl ether to afford the cyclic hemiacetal **30** in 91% yield. The hemiacetal was oxidized in two steps with Dess-Martin periodinane (DMP) and Pinnick oxidation conditions to afford the corresponding carboxylic acid **31** in 86% overall yield. Finally, CAN-mediated global oxidative demethylation and hydrogenation afforded cochlearol A (**1**) in 38% yield. Overall, the synthesis was completed with a longest linear sequence of 16 steps from commercial β -ketoester **21**.

5 Ishigami's Formal Synthesis of ($\pm$)-Cochlearol A



The year following the first total synthesis of cochlearol A by Liu, Qin et al., Ishigami and co-workers reported their formal synthesis of racemic cochlearol A (**1**) (Scheme 6).¹⁰ Their 16-step approach to precursor **31** utilizes a distinct approach to build the C/D ring system, as they were the first group to report an epoxide opening cyclization to access the tetracyclic core of cochlearol A (**1**). In addition to this key step, Ishigami's route utilized a late-stage lactone opening and epoxidation, as well as a Michael addition to install a masked aldehyde necessary for the epoxide-opening cyclization to occur (**32**).

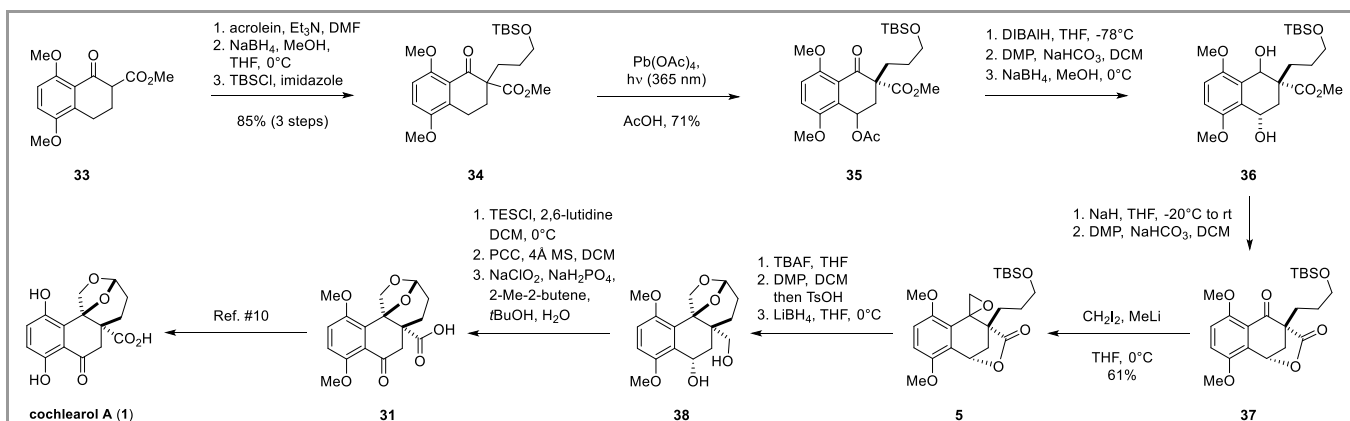
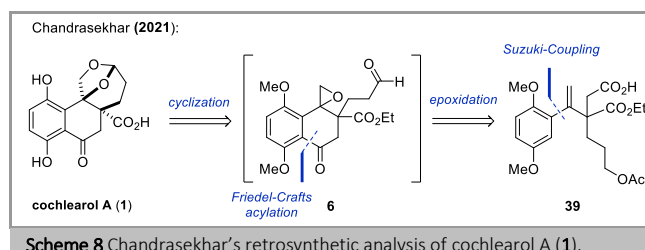
Starting from **33**, which is known to be accessed in one step from 5,8-dimethoxytetralone,¹² Ishigami et al. aimed to construct key intermediate **5** which serves as the precursor to the C/D ring formation in cochlearol A (**1**) (Scheme 7). This was initiated by a Michael addition between **33** and acrolein which proceeded in 96% yield. Regioselective reduction of the aldehyde to a primary alcohol followed by silyl protection with TBSCl formed **34** in 89% yield over 2 steps. Following literature

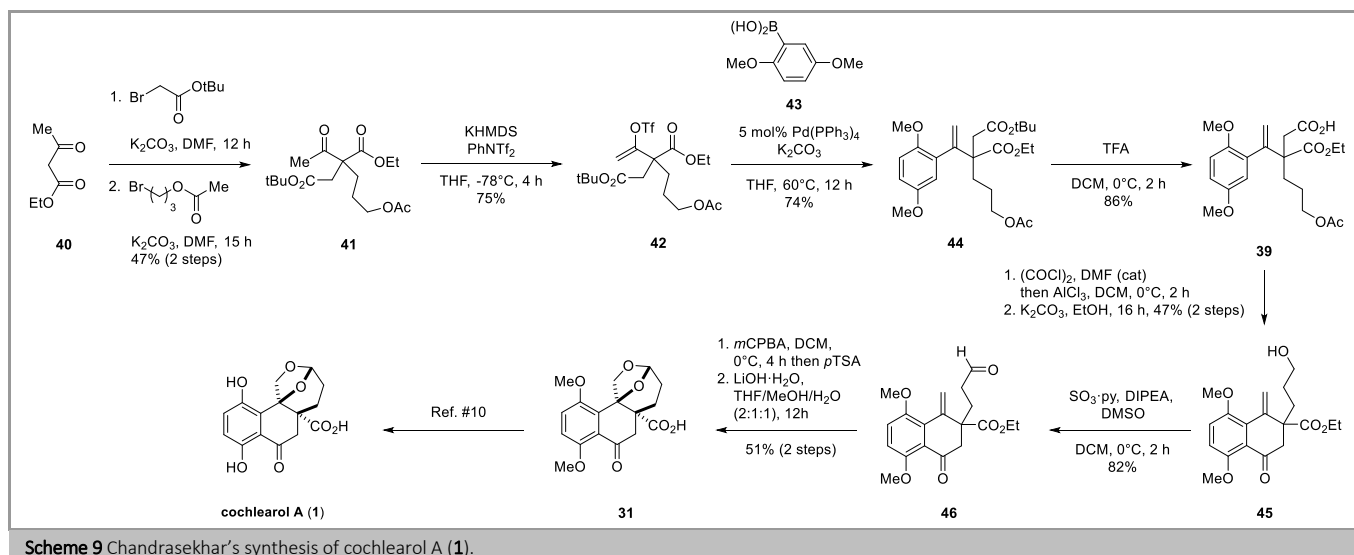
precedent from Nicolaou¹³, a photochemical benzylic oxidation with lead(IV) acetate was conducted to afford **35** in 71% yield. Subsequent DIBALH reduction resulted in removal of the acetyl group and concomitant reduction of the tetralone ketone, thus yielding a diol that was selectively oxidized gamma to the ester subunit with DMP in 47% yield over 2 steps. Reformation of the diol as a single diastereomer (**36**) was achieved by a NaBH₄ reduction thus allowing lactone formation upon subjection to sodium hydride. DMP oxidation of the alcohol then afforded **37** with a 90% yield over 3 steps.

With **37** in hand, epoxide **5** was formed using Concellon's conditions¹⁴ of diiodomethane and methylolithium in 61% yield. To unmask the aldehyde for subsequent bicyclization, the silyl protected alcohol was deprotected by TBAF then oxidized to the corresponding aldehyde with Dess-Martin periodinane. Upon addition of TsOH, the bicyclic acetal was formed and the lactone was reduced to the ring-opened diol **38** with LiBH₄. Thus, the tetracyclic core of cochlearol A (**1**) was constructed. Diol **38** was subsequently oxidized to known cochlearol A precursor **31**. From this intermediate, Liu, Qin and coworkers report a 2 step oxidative demethylation utilizing CAN followed by a Pd/C mediated reduction sequence to cochlearol A¹⁰, completing the formal synthesis.

6 Chandrasekhar's Formal Synthesis of ($\pm$)-Cochlearol A

In 2021, Chandrasekhar and co-workers reported a formal synthesis of racemic cochlearol A in which they synthesized **31**, a known precursor to cochlearol A (**1**), in 10 steps from ethyl acetoacetate (**40**) (Scheme 8).¹⁵ Their approach allows for ($\pm$)-cochlearol A to be accessed in a longest linear sequence of 12 steps, the shortest to date. Retrosynthetically, the tetracyclic core of cochlearol A would be constructed via an epoxide-opening cyclization (**6**) to introduce the acetal and form the C/D 6/5 ring system preceded by an intramolecular Friedel-Crafts acylation from **39** giving rise to the tetralone core. Key





Scheme 9 Chandrasekhar's synthesis of cochlearol A (1).

intermediate **39** was envisaged to be accessible via sequential α -alkylation and a Suzuki-coupling.

Starting from ethyl acetoacetate, base mediated alkylation with *t*-butyl 2-bromoacetate followed by 3-bromo-1-propyl acetate afforded **41** in 47% yield over 2 steps. To convert **41** into the alkenyl triflate coupling partner required for the Suzuki-Coupling with (2,5-dimethoxyphenyl)boronic acid, treatment of **41** with KHMDS followed by phenyl triflimide gave **42** in 75% yield (Scheme 9). With the necessary functional handles in place, the palladium-catalyzed Suzuki-coupling with **43** successfully afforded **44** in 74% yield which, upon selective deprotection of the *t*-butyl ester with trifluoroacetic acid, provided the key carboxylic acid moiety of **39** in 86% yield. Capitalizing on this deprotection strategy, transformation of the acid into an acyl chloride with oxalyl chloride and catalytic amounts of DMF allowed for the tetralone core to be constructed via AlCl_3 -mediated intramolecular Friedel-Crafts acylation in 60% yield.

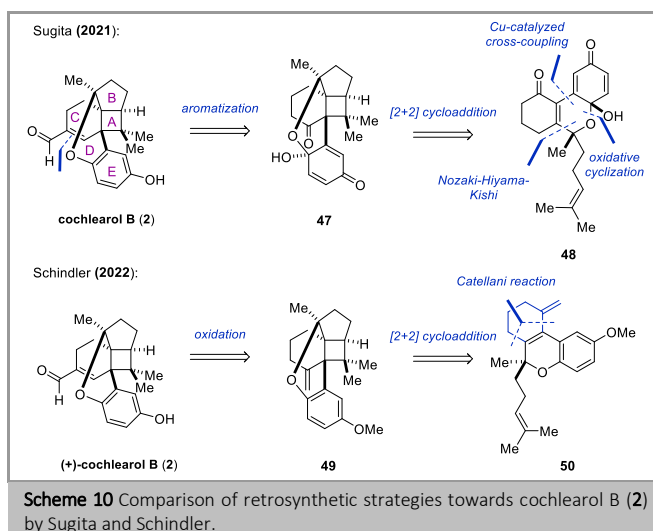
With two of the four rings of cochlearol A (**1**) constructed, Chandrasekhar and co-workers transitioned to their epoxide-opening ring formation strategy.¹² This approach relied on the conversion of the acetyl group of **39** into aldehyde **46** in a 64% yield via deprotection and $\text{SO}_3\cdot\text{py}$ oxidation of **45**. From here, the critical C/D ring system was built in a 60% yield via conversion of the alkene to an epoxide with *m*CPBA followed by addition of pTSA, which resulted in epoxide-opening, acetal formation, and the construction of the final two rings of cochlearol A (**1**) in a single step. With an 85% yield, the ethyl ester was converted via saponification to the corresponding carboxylic acid **31**. To reach cochlearol A (**1**) from **31**, the dimethoxyarene follows deprotection to the hydroquinone as previously reported by Liu, Qin and coworkers in the first total synthesis of racemic cochlearol A (**1**)¹⁰, thus completing Chandrasekhar's synthesis.

7 Sugita's Synthesis of ($\pm$)-Cochlearol B

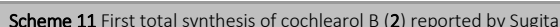
The first total synthesis of cochlearol B (**2**) was reported by Sugita and coworkers in 2021 and relies on a key [2+2]-cycloaddition strategy (Scheme 10).¹⁶ The authors' retrosynthetic analysis builds on accessing the phenol moiety through aromatization of quinone monohemiacetal **47**. The cyclobutane could be formed through an intramolecular [2+2] photocycloaddition of quinone **48**, which was expected to result

upon a copper-catalyzed cross-coupling and Nozaki-Hiyama-Kishi reaction followed by an oxidative dearomative cyclization.

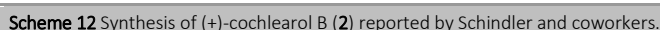
Sugita's efforts commenced with commercially available iodoarene **51** and 1,3-cyclohexadione (**52**), which were subjected to a copper catalyzed coupling giving enol **53** in 93% yield (Scheme 11). Appel conditions transformed **53** to vinyl iodide **54** in 89% yield. Subsequent Nozaki-Hiyama-Kishi coupling with aldehyde **55** afforded alcohol **56** in 78% yield. This newly formed alcohol was oxidized to the exocyclic ketone while subsequent regioselective reduction of the cyclic ketone to a cyclohexanol, 1,2-addition of MeMgBr into the exocyclic ketone afforded diol **57** in 69% yield over three steps. It is worth noting that Sugita and coworkers showed a CBS reduction of the cyclic ketone does lead to the enantioenriched cyclohexanol. Deprotection of the phenolic benzyl ether proceeded in 85% yield via lithium naphthalenide reduction. Swern oxidation of the cyclohexenol gave cyclic ketone **58** in 89% yield. Subjecting **58** to PIDA afforded a mixture of diastereomeric quinone monohemiacetals **48** (62% yield) and **59** (14% yield) upon oxidative dearomative cyclization. Stirring **59** in DCM resulted in epimeric equilibration producing the desired diastereomer **48** in 50% yield. Exposure of **48** to UV irradiation via a mercury lamp at -78°C promoted an intramolecular [2+2] photocycloaddition giving cyclobutane **47** in 74% yield. Luche reduction conditions



Scheme 10 Comparison of retrosynthetic strategies towards cochlearol B (**2**) by Sugita and Schindler.



This forward synthetic strategy commenced with a pyrrolidine-catalyzed Kabbe condensation between **63** and **64** to form chromanone **65** in 76% yield (Scheme 12). A chiral resolution of chromanone **65** with (*R*)-*tert*-butanesulfinamide (**66**) was employed and allowed for isolation of a single enantiomer of (**65**) in 38% yield and 95% *ee* over two steps. Chromanone (-)-**65** was



subjected to triflation conditions and afforded vinyl triflate **68** in 86% yield. Converting **68** and 5-iodo-1-pentene following Catellani reaction conditions allowed for concomitant ipso/ortho alkylation of the vinyl triflate resulting in ring C and afforded C/D/E tricycle **50** in 81% yield.¹⁹ Subsequently, tricycle **50** was subjected to visible-light enabled [2+2] photocycloaddition using photocatalyst **70**, affording the desired cyclobutane **49** and completing the pentacyclic core of cochlearol B (**2**) in 94% yield. The terminal alkene **49** was converted to ketone **71** in 40% overall yield via a two-step dihydroxylation and oxidative cleavage sequence. To introduce the desired enal moiety similar to Sugita's synthesis, ketone **71** was subjected to a condensation with DMF-DMA, giving enaminone **72** in 86% yield. Triflation of enaminone **72** and hydrolysis of the iminium ion upon aqueous workup, followed by a palladium catalyzed triflate reduction, afforded **73** in 76% yield over two steps. Completion of the synthesis of (+)-cochlearol B (**2**) required demethylation of the methyl aryl ether **73**, which proved challenging due to the molecule's instability under acidic and nucleophilic demethylation conditions. However, following a reduction of the aldehyde, demethylation of the phenol was achieved upon treatment with neat MeMgI at elevated temperatures under a reduced atmosphere.²⁰ Finally, a Swern oxidation completed the total synthesis of (+)-cochlearol B (**2**) in 25% yield over the last 3 steps. This synthesis accessed enantioenriched (+)-cochlearol B (**2**) in 14 overall steps and 1.2% overall yield from commercially available acetophenone **63** and sulcatone (**64**).

9 Conclusions

The uniquely challenging structures of cochlearols A (**1**) and B (**2**) have intrigued synthetic chemists since the first report of their isolation by Cheng and co-workers in 2014 and have resulted in substantial synthetic efforts from various research laboratories within less than ten years. Specifically, synthetic approaches towards cochlearol A (**1**) were reported within the past three years and feature distinct strategies, particularly with regards to construction of the dioxaspiro[4.5]decane subunit relying on Achmatowicz reactions, acetalization or epoxide opening procedures. However, Friedel Crafts acylation protocols play a key role in three of the four reported strategies towards cochlearol A (**1**) to construct the characteristic B ring. Notably, all reported synthetic approaches result in the formation of racemic cochlearol A (**1**). In comparison, the first strategy towards racemic cochlearol B (**2**) was reported in 2021 with a second approach towards (+)-cochlearol B (**2**) published in 2022. Both strategies rely on key photochemical [2+2]-cycloaddition reactions to build up the cyclobutane core, which are promoted by either UV- or visible light. A synthetic challenge for both of these approaches represented the incorporation of the enal moiety on the C-ring of cochlearol B (**2**), which could not be introduced as a structural part of the photocycloaddition precursors and consequently needed to be incorporated post cyclization.

Funding Information

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