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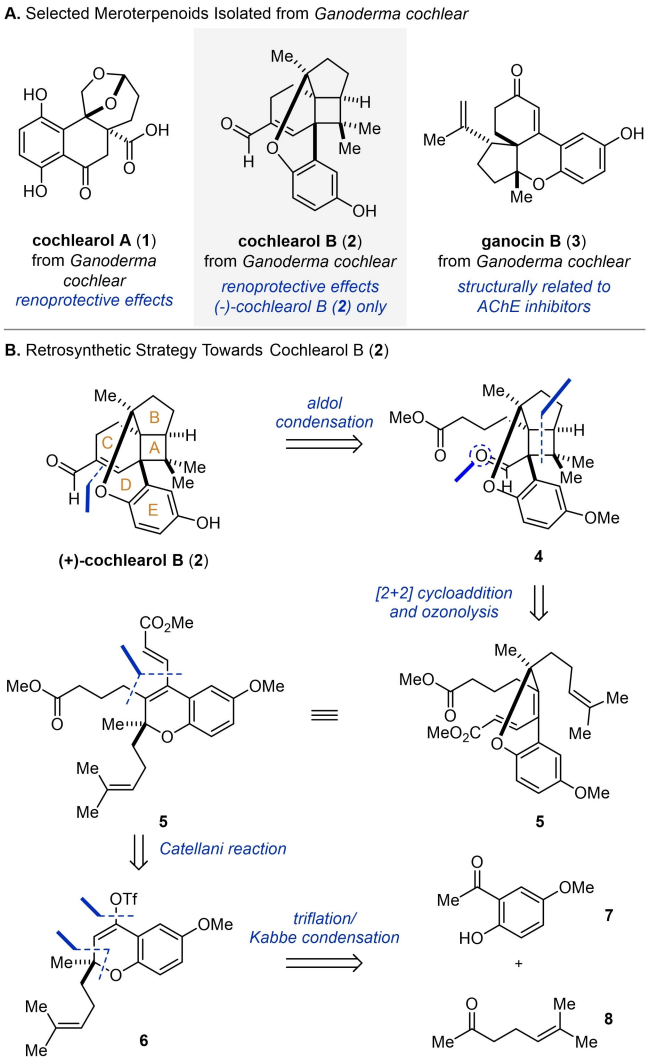
Natural Products Synthesis

Total Synthesis of (+)-Cochlearol B by an Approach Based on a Catellani Reaction and Visible-Light-Enabled [2+2] Cycloaddition**

*Alistair D. Richardson, Trenton R. Vogel, Emily F. Traficante, Kason J. Glover, and Corinna S. Schindler**

Abstract: A 14-step synthesis of (+)-cochlearol B is reported. This renoprotective meroterpenoid features a unique core structure containing a densely substituted cyclobutane ring with three stereocenters. Our strategy employed an organocatalytic Kabbe condensation in route to the key chromenyl triflate. A subsequent Catellani reaction incorporated the remaining carbon atoms featured in the skeleton of cochlearol B. An ensuing visible-light-mediated [2+2] photocycloaddition closed the cyclobutane and formed the central bicyclo-[3.2.0]heptane core. Notably, careful design and tuning of the Catellani and photocycloaddition reactions proved crucial in overcoming undesired reactivity, including cyclopropanation reactions and [4+2] cyclo-additions.

In 2014, Cheng and co-workers reported the isolation of cochlearol A (**1**) together with cochlearol B (**2**) from *Ganoderma cochlear* (Scheme 1A).[1] Their studies were initially inspired by the known pharmacological effects of *Ganoderma* extracts, which are used in traditional Chinese medicine for the prevention and treatment of cancer, hypertension, chronic bronchitis, and asthma.[2] In addition to cochlearol A and B, a number of other structurally diverse meroterpenoids have been isolated from *Ganoderma cochlear*, including ganocin B (**3**, Scheme 1A).[3] In comparison to cochlearol B (**2**), cochlearol A (**1**) is structurally less complex, incorporating a dioxaspiro[4.5]decane moiety. The structure of cochlearol B (**2**) was originally deduced based on NMR and HRMS analysis that showed a 4/5/6/6/6-fused polycyclic ring system with a central hepta-substituted cyclobutane core, which includes three stereogenic centers and three quaternary carbon atoms. Both cochlearol B (**2**) and ganocin B (**3**) contain a common chromane core; however ganocin B possesses a structurally distinct spiro[4,5]decane ring.[3] Notably, both cochlearol A (**1**) and cochlearol B (**2**) were isolated as racemates and tested for renoprotective effects on renal fibrosis by inhibiting upregulation of



Scheme 1. A) *Ganoderma* meroterpenoids including cochlearol B (**2**). B) Retrosynthetic strategy towards cochlearol B (**2**) relying on Catellani and [2+2] cycloaddition reactions. Proceeds through an EDBAC ring formation sequence.

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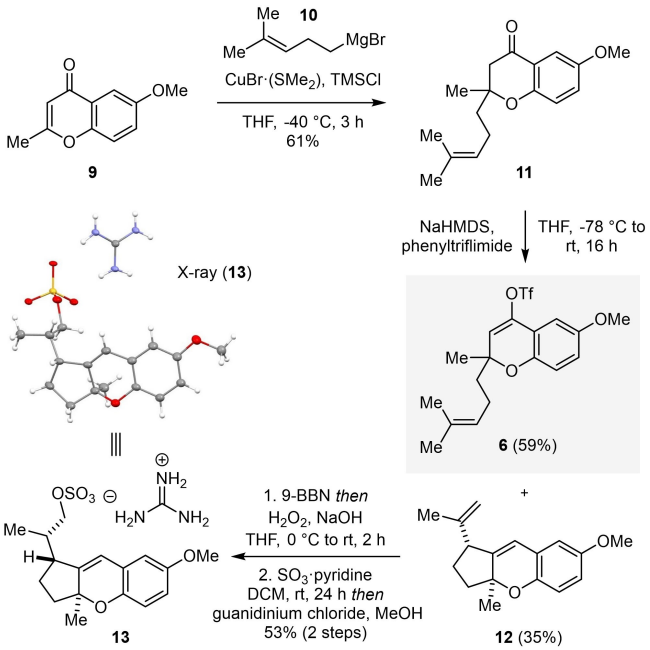
collagen I, fibronectin, and α-SMA.[1] Interestingly, only (−)-cochlearol B (**2**) demonstrated potent antifibrotic efficacy while (−)-**1**, (+)-**1**, and (+)-**2** were found to be inactive. Furthermore, additional studies suggested that (−)-**2** efficiently inhibits the phosphorylation of Smad2 (Small Mothers Against Decapentaplegic) and Smad3 and consequently disrupts Smad2 and Smad3 activation whereas (+)-**2** does not. While both cochlearol A (**1**) and ganocin B (**3**) have been the target of multiple established synthetic strategies[4,5] only one approach to cochlearol B (**2**) has been reported[6] despite its unique architecture.

The start of our retrosynthetic analysis of cochlearol B (**2**) relied on an intramolecular aldol condensation to form the α,β-unsaturated aldehyde moiety from cyclobutane **4** (Scheme 1B). We envisioned building both the A and B ring systems simultaneously in an intramolecular, visible-light-mediated [2+2] cycloaddition of chromene **5**. Introduction of the two methyl ester fragments in **5** could proceed concomitantly in a palladium- catalyzed Catellani reaction[7–9] of triflate **6**. This represents one of the more complex precursors used in this class of transformations to date.[10–23] Triflate **6** is accessible through a two-step sequence of triflation preceded by Kabbe condensation[24] of commercially available precursors phenol **7** and sulcatone (**8**).

In initial studies towards cochlearol B (**2**), we were able to access 6-methoxy-2-methyl-4*H*-chromen-4-one (**9**) via a one-pot acylation, Baker–Venkataraman rearrangement,[25] and condensation of **7** using conditions developed by Brown and co-workers.[26] A subsequent 1,4-conjugate addition[27] of **9** with homoprenyl magnesium bromide (**10**) in the presence of catalytic amounts of CuBr·(SMe_2) initially gave rise to chromanone **11** in 34 % yield. Forming the corresponding pyrilium ion of **9** upon addition of stoichiometric amounts of TMSCl[28] proved beneficial and increased the yield of **11** to 61 % (Scheme 2). The subsequent triflation of chromanone **11** proved more challenging than expected. In addition to isolating 59 % of vinyl triflate **6**, cyclopentylchromene **12** was isolated in 35 % yield. The structure of **12** was unambiguously confirmed via X-ray crystallographic analysis of guanidinium sulfate derivative **13**.[29,30] This tricyclic structure is also featured in ganocin B (**3**), as well as related natural products ganocins A and C.[3] To overcome this undesired reactivity, Comins' reagent[31] was evaluated as an alternative to phenyltriflimide. This more reactive triflating agent enabled the reaction to proceed at cryogenic temperatures in shorter reaction times, eliminated the formation of **12**, and improved the yield of **6** up to 86 % (Scheme 5).

Vinyl triflate **6** was subsequently subjected to Catellani conditions[9] to enable concomitant *ortho* and *ipso* functionalization to provide tetrasubstituted alkene **5** in 31 % yield (Scheme 3A). However, efforts to optimize this transformation could not overcome the formation of undesired byproduct **15**, which forms in up to 11 % yield, likely through a thermal [4+2] cycloaddition. Importantly, further studies confirmed that **15** forms exclusively upon heating of **16** to 100 °C in dioxane, which is consistent with the [4+2] cycloaddition hypothesis. Compound **16** likely forms in situ via a direct Heck reaction[32] of vinyl triflate **6** and methyl acrylate



Scheme 2. Triflation of chromanone **11** yields unexpected cyclopentylchromene **12**, which is also found in ganocin B (**3**). TMSCl = trimethylsilyl chloride, NaHMDS = sodium bis(trimethylsilyl)amide, 9-BBN = 9-borabicyclo[3.3.1]nonane.

that competes with the desired Catellani reaction. Unfortunately, when tetrasubstituted alkene **5** was subjected to visible-light-mediated [2+2] cycloaddition conditions using [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]-(PF_6)](**17**) as a photocatalyst,[33,34] none of the desired cyclobutane **18** was formed. The only product isolated was identified as cyclopropane **19** in 85 % yield (Scheme 3B).[35] We hypothesize that this unexpected product arises upon initial photochemical excitation of the styrenyl olefin in **5** to its excited state **20**. The resulting biradical subsequently reacts with the homoprenyl subunit to form ring B (**21**). From there, instead of forming the desired cyclobutane (ring A) by radical recombination, an addition to the electrophilic carbon of the methyl acrylate fragment occurs, resulting in a second five-membered ring (**22**) and ultimately providing cyclopropane **19** upon radical recombination (Scheme 3C). Notably, the evaluation of multiple photocatalysts exhibiting distinct triplet energies[36] (e.g. [Ru(bpy)$_3$](PF_6)$_2$, [Ir(dF(CF_3)ppy)$_2$(dtbbpy)](PF_6) (**17**)), as well as direct excitation with UV light, did not provide cyclobutane **18**; rather cyclopropane **19** remained the exclusive product. To gain support for this mechanistic hypothesis, as well as investigate how to overcome this undesired reactivity, we next evaluated the role of the steric and electronic effects of the substituents by subjecting **16** to the conditions for [2+2] cycloadditions (Scheme 4). Although **16** is electronically comparable to **5**, no formation of cyclopropane **23** was observed. Instead, a mixture of the [2+2] and [4+2] cycloadducts **24** and **15** + **25** were isolated in 29 % and 32 % yield, respectively. These results suggest that steric constraints of the methyl acrylate and methyl butyrate chains favor the formation of cyclopropane **19** over cyclo-

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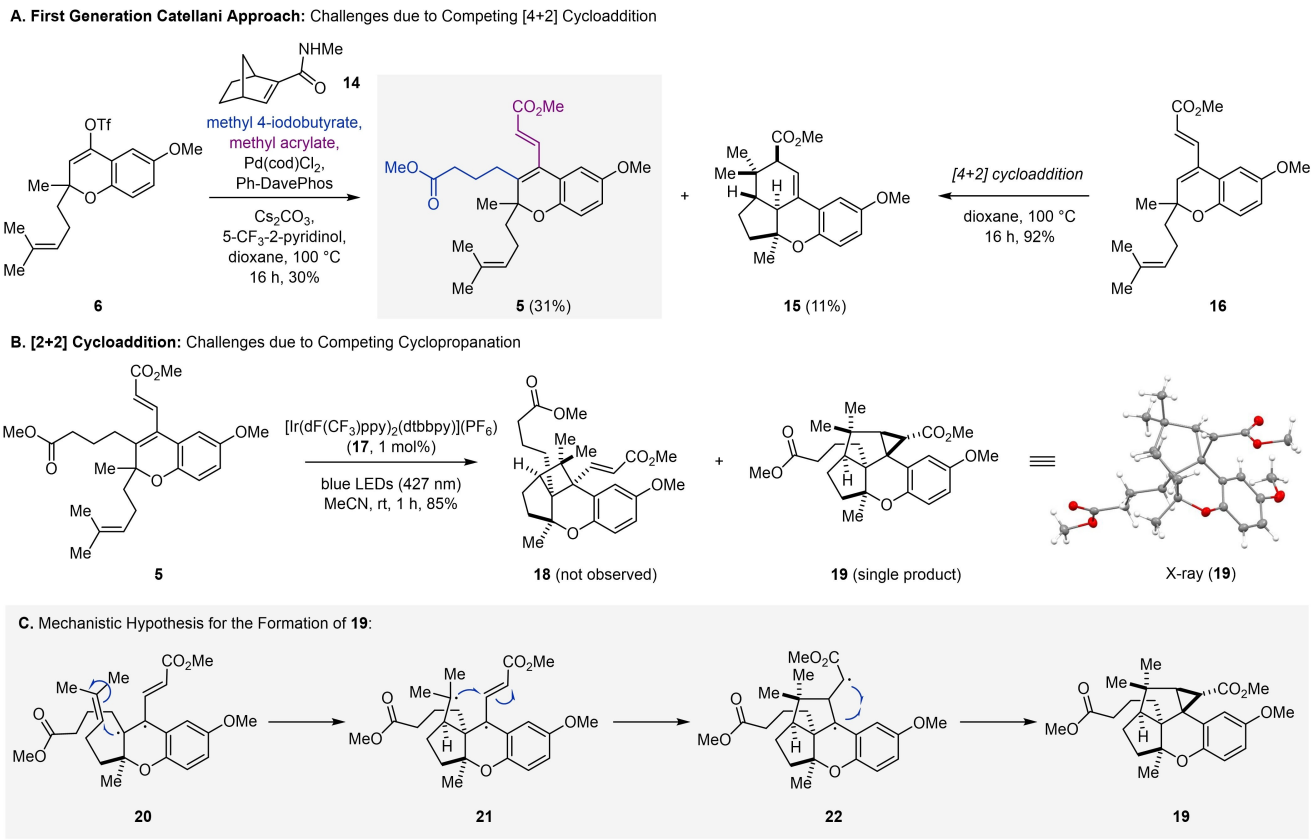
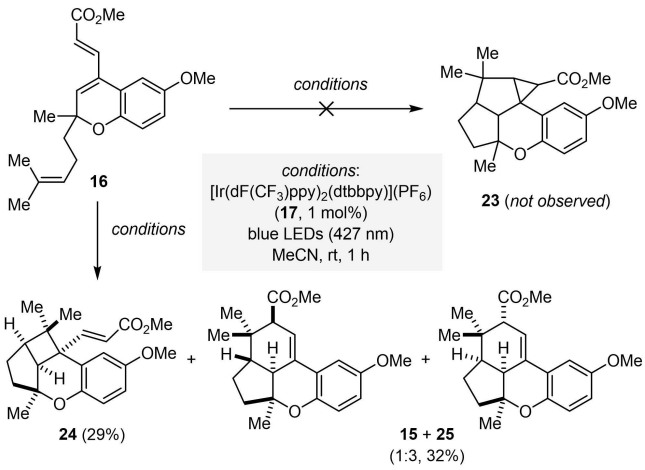


Scheme 3. Challenges observed in developing a Catellani and subsequent [2+2] cycloaddition approach towards cochlearol B (**2**).



Scheme 4. Proof-of-principle for a visible-light-enabled [2+2] cycloaddition strategy towards cochlearol B (**2**).

butane **18**. This is consistent with **19** being isolated as a single diastereomer with the cyclopropane and methyl butyrate chains on opposite faces. Furthermore, in addition to the steric constraints, we hypothesized that the electrophilic nature of the acrylate moiety in **21**, together with the high stability of the resulting biradical in **22**, favors the formation of cyclopropane **19**. To enable a synthesis of enantioenriched cochlearol B (**2**), we revised our synthetic strategy. Specifically, we postulated that a less reactive alkene could mitigate the competing Heck reaction in the Catellani step, while a conformationally restricted diene would be expected to prevent undesired [4+2] cycloadditions. Our final approach to (+)-cochlearol B (**2**) takes advantage of these insights and through a revised design for the Catellani reaction to ultimately enable a productive [2+2] cycloaddition by disfavoring competing Heck reaction, [4+2] cycloaddition, and cyclopropanation (Scheme 5). Additionally, a Kabbe condensation[24] was employed to access chromanone **11**, which reduced the overall number of steps.

Specifically, a pyrrolidine-catalyzed condensation between **7** and **8** formed chromanone **11** directly in 76 % yield. Conducting the transformation with chiral pyrrolidine and imidazolinone catalysts[37] provided enantioenriched (−)-**11** albeit with a modest enantioselectivity of 23 %.[38] In comparison, an approach relying on a chiral resolution of chromanone **11** with (*R*)-*tert*-butanesulfinamide[39] (**26**) proved superior resulting in the desired product in 95 % *ee*. Subsequent treatment with Comins' reagent provided triflate (+)-**6** in 86 % yield. Subjecting (+)-**6** to Catellani conditions with commercially available 5-iodo-1-pentene,[9] which functions as both the nucleophilic and electrophilic coupling partner, gives rise to chromene **28** establishing ring C of (+)-cochlearol B (**2**) as well as incorporating an s-trans diene. This intermediate was expected to exhibit distinct

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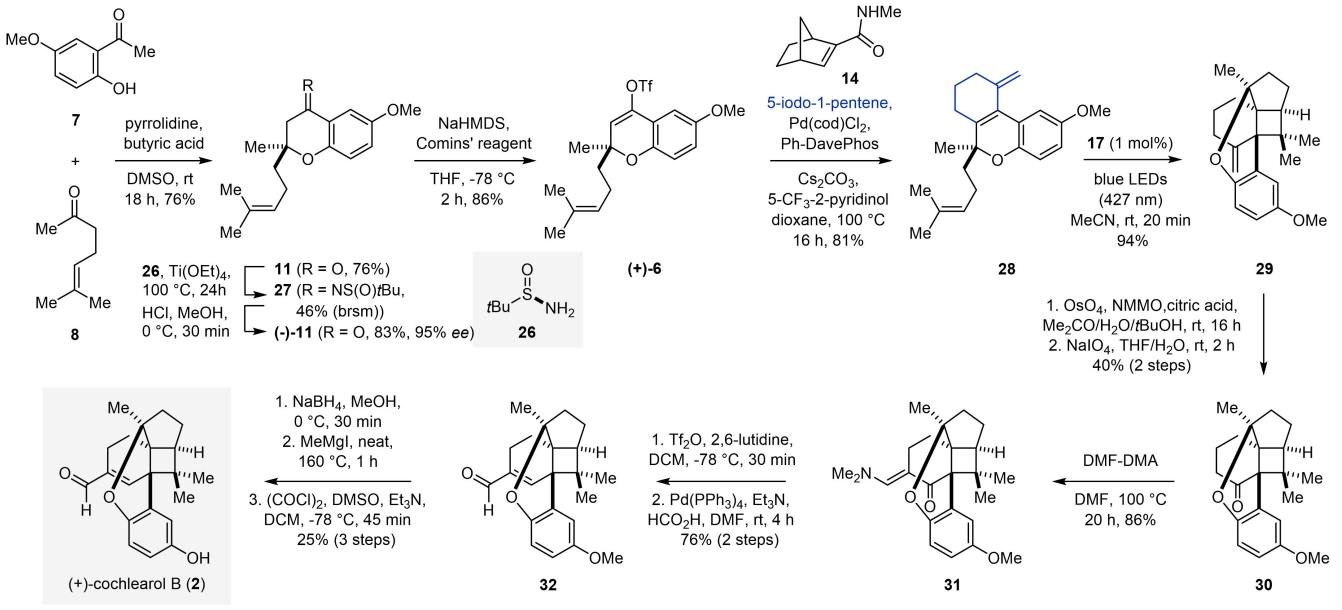

Scheme 5. Development of an efficient strategy towards cochlearol B (**2**) relying on a Catellani reaction and visible-light-mediated [2+2] cycloaddition. Comins' reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide), NMMO = *N*-methylmorpholine *N*-oxide, DMF-DMA = *N*,*N*-dimethylformaide dimethyl acetal.

advantages compared to chromene **5**. In particular: 1) the locked *s*-trans conformation of the diene in **28** prevents the formation of a competing thermal [4+2] cycloadduct under Catellani reaction conditions, while 2) the absence of a methyl acrylate moiety disfavors cyclopropanation, as the alkene is now less electrophilic and the resulting radical is no longer stabilized by an adjacent carbonyl; 3) forming ring C prior to the [2+2] cycloaddition reduces the steric constraints that previously precluded the formation of cyclobutane **18**. This also represents a change in our overall ring formation strategy, shifting from an EDBAC sequence to an EDCBA sequence. Importantly, the first supposition was reinforced with the isolation of chromene **28** as the exclusive product. Remarkably, this reaction was amenable to gram scale resulting in the formation of the desired product in 81 % yield. With a viable route to the photocycloaddition precursor established, diene **28** was subjected to visible-light-enabled [2+2] cycloaddition conditions giving rise to the pentacyclic cyclobutane **29** as the sole product in 94 % yield. Notably, irradiation of chromene **28** with UV-light in the absence of a photocatalyst failed to provide the desired product **29**. The terminal alkene in **29** was next converted in a two-step dihydroxylation[40] and oxidative cleavage[41] sequence to ketone **30** in 40 % overall yield. In order to incorporate the desired α,β-unsaturated aldehyde of cochlearol B (**2**), ketone **30** was first subjected to a condensation reaction with DMF-DMA,[42] giving enaminone **31** in 86 % yield. Tandem triflation and hydrolysis,[43] followed by a palladium catalyzed reduction,[44] provided **32** in 76 % yield over two steps. Completion of the synthesis of (+)-cochlearol B (**2**) required deprotection of the phenol in **32**, which proved challenging due to its instability under Lewis acidic and nucleophilic demethylation conditions. However, following a reduction of the aldehyde with $NaBH_4$, demethylation of the phenol was achieved upon treatment with neat MeMgI at elevated temperatures.[45] A final Swern oxidation completed the total synthesis of (+)-cochlearol B (**2**) in 25 % yield over the final 3 steps and in 14 overall steps from commercially available materials.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Catellani Reaction · Meroterpenoids · Total Synthesis · Visible Light · [2+2] Photocycloaddition

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