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Total Synthesis of *ent*-Plagiochianin B

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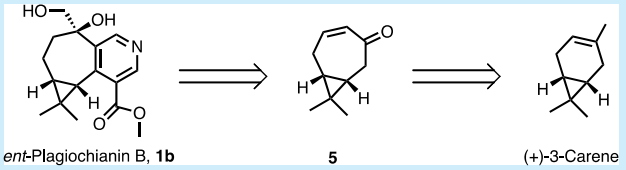
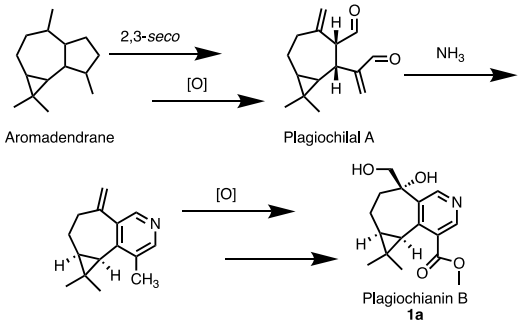
ABSTRACT: An enantioselective total synthesis of plagiochianin B is described that employs (+)-3-carene as its point of departure and delivers the enantiomer of the natural product. Key features of the synthesis include a palladium-mediated regioselective oxidative cleavage of an olefin residing on a pyridine derived from a 6π-azatriene electrocyclization.



Plagiochianin B (**1a**) was isolated in 2018 from the Chinese liverwort *Plagiochila duthiana* and possesses a unique 6/7/3 pyridine-containing tricyclic structure.[1] Biosynthetically, plagiochianin B is the first example of a sesquiterpene alkaloid isolated from liverworts and, as illustrated in Scheme 1, is

Scheme 1. Plausible Biosynthetic Pathway

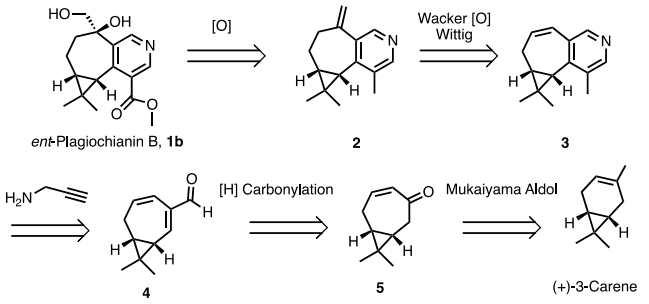


believed to arise from aromadendrane via a ring-opening event followed by a succession of oxidations that deliver plagiochilal A, a natural product which has been isolated from the genus *Plagiochila*. Condensation of plagiochilal A with ammonia forms an intermediate pyridine which, upon further oxidation, furnishes plagiochianin B.

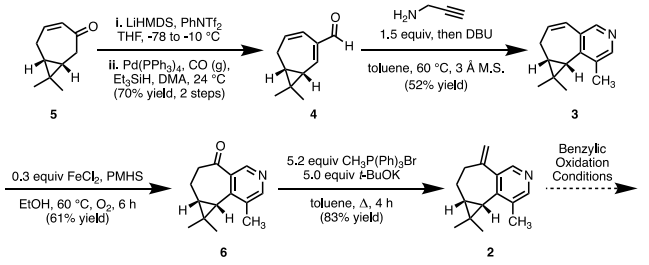
From a retrosynthetic perspective (Scheme 2), we initially envisioned *ent*-plagiochianin B as arising from exomethylene **2** via a sequence of late-stage oxidations. We believed **2** could be derived from methylpyridine (**3**) through a Wacker-type oxidation and Wittig olefination. To deliver the requisite **3** we planned to advance enal **4** by condensation with propargyl amine followed by 6π-azatriene electrocyclization. Access to **4** would be gained by reductive carbonylation of known enone **5**[2] which is derived from commercially available (+)-3-Carene. Given the inherent stereochemistry of (+)-3-Carene we anticipated producing *ent*-plagiochianin B (**1b**).

In a forward sense (Scheme 3), kinetic deprotonation of enone **5** and trapping with McMurry's reagent furnished an enol triflate which, without purification, was advanced in good

Scheme 2. Initial Retrosynthetic Analysis



Scheme 3. Initial Synthetic Route



yield to enal **4** by employing a slightly modified reductive carbonylation procedure reported by Stoltz.[3] Targeting enal **4** as an intermediate was inspired by recent efforts from Zhai who demonstrated that condensation of cinnamaldehyde with propargyl amine followed by treatment with DBU delivers the corresponding 3-methyl pyridine via 6π-azatriene electrocyclization of an intermediate allenyl imine.[4a] Gratifyingly we found that condensation of **4** with propargylamine and

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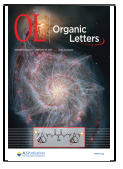

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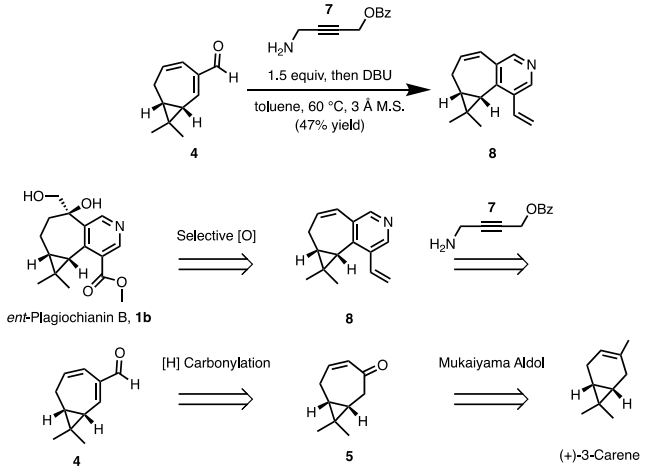
subsequent addition of DBU furnished fused pyridine **3** in good yield.

Having completed the tricyclic core, we turned attention to the remaining largely oxidative modifications of the periphery. To this end, we attempted to advance **3** via palladium-mediated Wacker type oxidations but did not observe any appreciable product formation. After considerable experimentation, we discovered an iron-catalyzed variant recently developed by Han to be very effective in delivering the corresponding ketone (**6**).[5] With ketone **6** in hand, the stage was set for a seemingly simple methylenation to **2**. However, typical Wittig olefination conditions using cryogenic temperatures and strong bases led to consistently low yields of the desired product and the predominant return of starting material. Presuming ketone enolizability as the culprit, we turned to conditions originally developed by Conia (employing sodium *tert*-amylate), and effectively deployed by Dauben to overcome issues with both substrate sterics and acidity.[6] In the event, exposure of **6** to methyltriphenylphosphonium bromide and potassium *tert*-butoxide in toluene at reflux furnished the desired exocyclic methylene (**2**) in good yield.[7] Unfortunately, efforts to install the vicinal hydroxyl unit were met with little or extraordinarily sluggish reactivity.[8] Additionally, oxidation of the methylpyridine on compounds **3** and **6** also proved remarkably challenging, resulting in either undesirable or no reactivity.[9]

Unable to advance methylpyridine substrates to the corresponding ester, we decided to modify our plan. As illustrated in Scheme 4, we focused on altering the 6π-azatriene

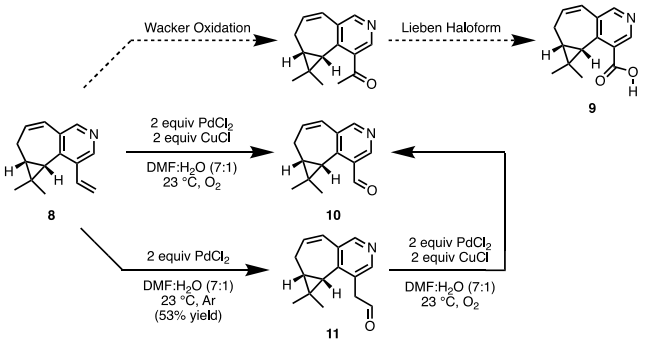
Scheme 4. Synthesis of Vinyl Pryidine (8) and Revision of Retrosynthesis



electrocyclization substrate so as to deliver a more malleable vinylpyridine intermediate (**8**), an approach that was advantaged by continued efforts from Zhai.[4b] Selective oxidations of the external and internal olefins would then deliver **1b**. While implementing this revised strategy, it was found that exposure of enal **4** to benzoyloxy propargylamine (**7**), with minor alteration to conditions reported by Zhai, delivered the corresponding vinylpyridine (**8**) in useful yields.

With the vinyl pyridine **8** in hand, we turned toward effecting a selective oxidation of the terminal olefin in the presence of the presumably more electron-rich internal one. Precedent regarding electrophilic oxidation strategies such as ozonolysis[10] suggested the internal olefin would likely react first. However, our experiences in the methyl pyridine series suggested that the internal olefin would be inert to traditional Wacker oxidation conditions and led to our speculation that it would be possible to convert the exocyclic olefin of **8** to a methyl ketone which, in turn, might then be elaborated to carboxylic acid **9** via a Lieben Haloform reaction (see Scheme 5).

Scheme 5. Evolution of an Oxidation Strategy



Much to our chagrin, it was found that exposure of **8** to traditional Wacker oxidation conditions resulted in no reaction. Efforts to push this chemistry led to the serendipitous discovery that exposure of **8** to 2 equiv of $PdCl_2$, under an atmosphere of O_2, results in the selective cleavage of the external olefin giving rise to pyridinecarboxaldehyde **10**; neither oxidation to the corresponding acid nor reaction of the internal olefin was observed under these conditions. Intrigued by this reactivity we explored the literature for similar observations and discovered pioneering work performed by Spencer and Gaunt, who, when working on styrene-type compounds, found that 2 equiv of $PdCl_2$ were able to effect anti-Markovnikov selectivity in the Wacker oxidation.[11] Further, Spencer noted spontaneous degradation of the anti-Markovnikov aldehydes to analogous benzaldehydes in the presence of O_2. Indeed, exposure of **8** to Spencer's conditions using degassed solvents and an inert atmosphere produced anti-Markovnikov aldehyde **11** (see Scheme 5). Isolation of **11** and resubmission to the original, oxygenated, reaction conditions again furnished **10**. Notably, conditions akin to those used by Spencer and Gaunt (2 equiv of $PdCl_2$ in the presence of O_2) were also found to produce **10**; however, the efficiency of this transformation was increased by incorporation of CuCl.

With pyridinecarboxaldehyde **10** in hand, we employed a standard Pinnick oxidation followed by treatment with $TMSCHN_2$ to provide the requisite methyl ester (**12**) (Scheme 6).[12] Based on previous success, we turned to the iron-catalyzed Wacker-type oxidation to produce ketone **13** which, with this substrate, was accompanied by a mixture of diastereomeric alcohols (**14**) that were isolated and converted to **13** via a Swern oxidation.[13] A modification of the Wittig olefination was employed to furnish exomethylene **15**.[6,7] Lastly, dihydroxylation, with potassium osmate dihydrate and NMO,[14] provided a 1:3 mixture of diastereomers favoring the undesired diastereomer of *ent*-plagiochianin B (**16**).[15] Separation of the diastereomers allowed for comparison of NOESY data which supported the isolation chemist's proposed relative stereochemistry of plagiochianin B. Furthermore, analysis of the optical rotation of our synthetic product aided

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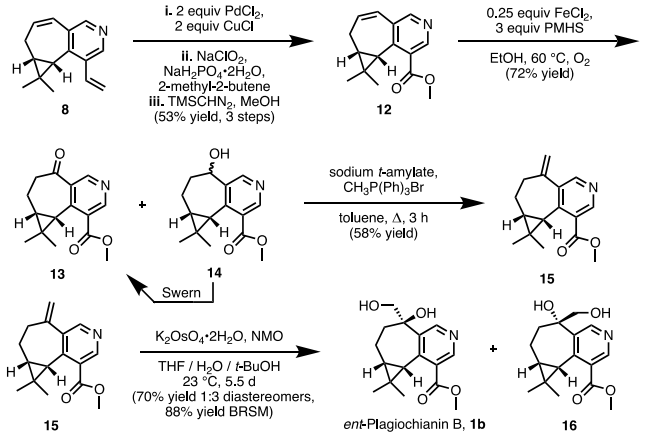
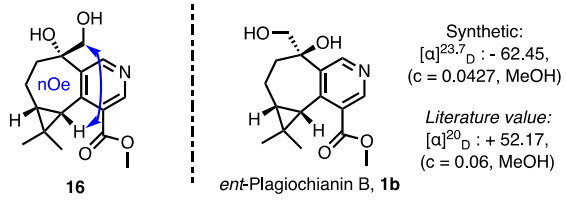
Scheme 6. Completion of the Total Synthesis



in confirmation of the absolute stereochemistry found in the natural product. As anticipated, our synthetic product bears an optical rotation of similar magnitude but opposite sign to plagiochianin B (see Scheme 7).

Scheme 7. NOESY Correlation and Optical Rotation



The total synthesis of *ent*-plagiochianin B (**1b**) has been completed. Introduction of the pyridine ring was accomplished by a 6π-azatriene electrocyclization with propargylamine **7** and enal **4**. Differentiation of the two olefins found in the resultant vinylpyridine (**8**) was enabled by orthogonal reactivity between iron and palladium mediated Wacker-type oxidations. The latter conditions led to oxidative cleavage of the exocyclic olefin to selectively furnish a pyridinecarboxaldehyde (**10**). Subsequent iron-catalyzed Wacker-type oxidation then set the stage for synthesis completion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04219.

General information; Experimental Section; NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1b**–**16**, and **SI 1**-**SI 9** (ZIP)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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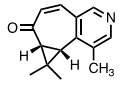
(8) Dihydroxylation of (**2**) proved sluggish, and efforts to advance small quantities of the corresponding diol acetonide by oxidation of the methyl pyridine with chromium (V) failed. For similar successful pyridine oxidations with chromium, see: Schuppe, A. W.; Huang, D.; Chen, Y.; Newhouse, T. R. Total Synthesis of (−)-Xylogranatopyridine B via a Palladium-Catalyzed Oxidative Stannylation of Enones. *J. Am. Chem. Soc.* **2018**, *140*, 2062−2066.

(9) Although not fully delineated, undesired allylic oxidation of **3** to enone (**i**) appeared to be the predominant reaction event, whereas no oxidation was observed with ketone (**6**).



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(15) Efforts to improve the selectivity in the dihydroxylation with chiral ligands were met with limited success. In particular, no reaction was observed with addition of AD Mix β and, with $(DHQD)_2AQN$, <50% conversion was observed after 6 days with a moderate improvement in stereoselectivity (1:1.6).

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