



Ni-promoted reductive cyclization cascade enables a total synthesis of (+)-aglacin B

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Letter

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Abstract

The total synthesis of bioactive (+)-aglacin B was achieved. The key steps include an asymmetric conjugate addition reaction induced by a chiral auxiliary and a nickel-promoted reductive tandem cyclization of the elaborated β -bromo acetal, which led to the efficient construction of the aryltetralin[2,3-*c*]furan skeleton embedded in this natural product.

Introduction

Proksch and co-workers isolated aglacins A, B, C, and E (**1–4**, Figure 1) from the methanolic extract of stem bark of *Aglaia cordata* Hiern from the tropical rain forests of the Kalimantan region (Indonesia) [1,2]. These cyclic ether natural products belong to the typical aryltetralin lignans, which have already attracted broad attention from the synthetic community [3–5]. Zhu and co-workers disclosed a concise synthesis of (\pm)-aglacins B (**2**) and C (**3**), featuring a visible light-catalyzed radical cation cascade for the formation of the C8–C8' and C2–C7' bonds [6]. Subsequently, they improved the reaction conditions to achieve the racemic synthesis of aglacins A (**1**) and E (**4**) as well [7]. In 2021, the Gao group described the total synthesis of both enantiomers of aglacins A (**1**), B (**2**), and E (**4**) by asymmetric photoenolization/Diels–Alder reactions as the key steps for the construction of the C7–C8 and C7'–C8' bonds [8].

During the past decade, we had developed nickel-catalyzed or -promoted reductive coupling/cyclization reactions for the formation of inter- or intramolecular carbon–carbon bonds under mild conditions [9–12], and strategically applied this method for the divergent syntheses of some natural products [13–17]. Herein, we report our recent advance to a total synthesis of (+)-aglacin B (**2**), which relies on a non-photocatalysis approach.

Results and Discussion

Retrosynthetic analysis of (+)-aglacin B

Based on the retrosynthetic analysis shown in Scheme 1, both C8'–C8 and C7–C1 bonds in (+)-aglacin B (**2**) could be constructed in one-step from the β -bromo acetal **5** by a Ni-promoted tandem radical cyclization, and a subsequent

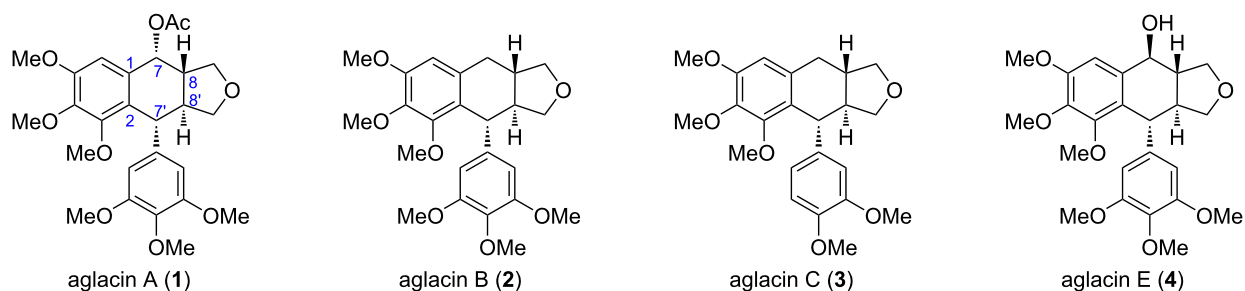
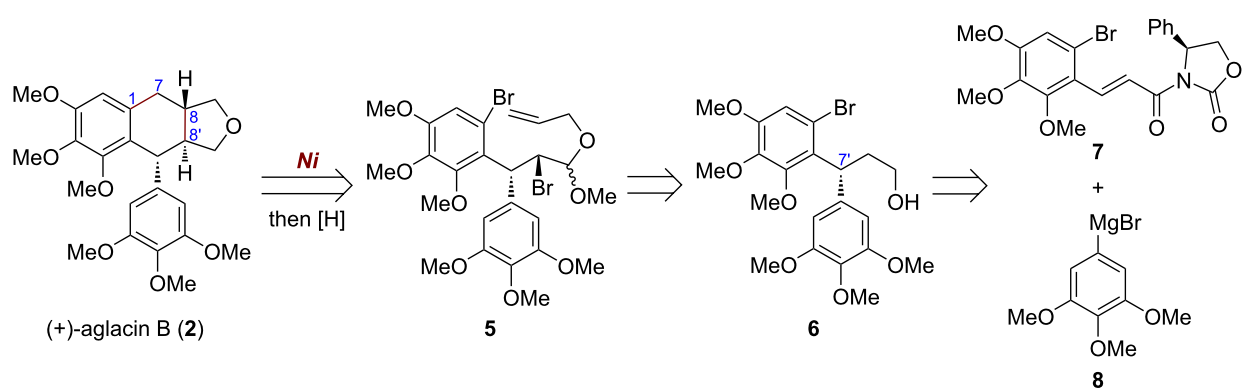


Figure 1: The structures of aglacin A, B, C, and E.



Scheme 1: Retrosynthetic analysis of (+)-aglacin B (2).

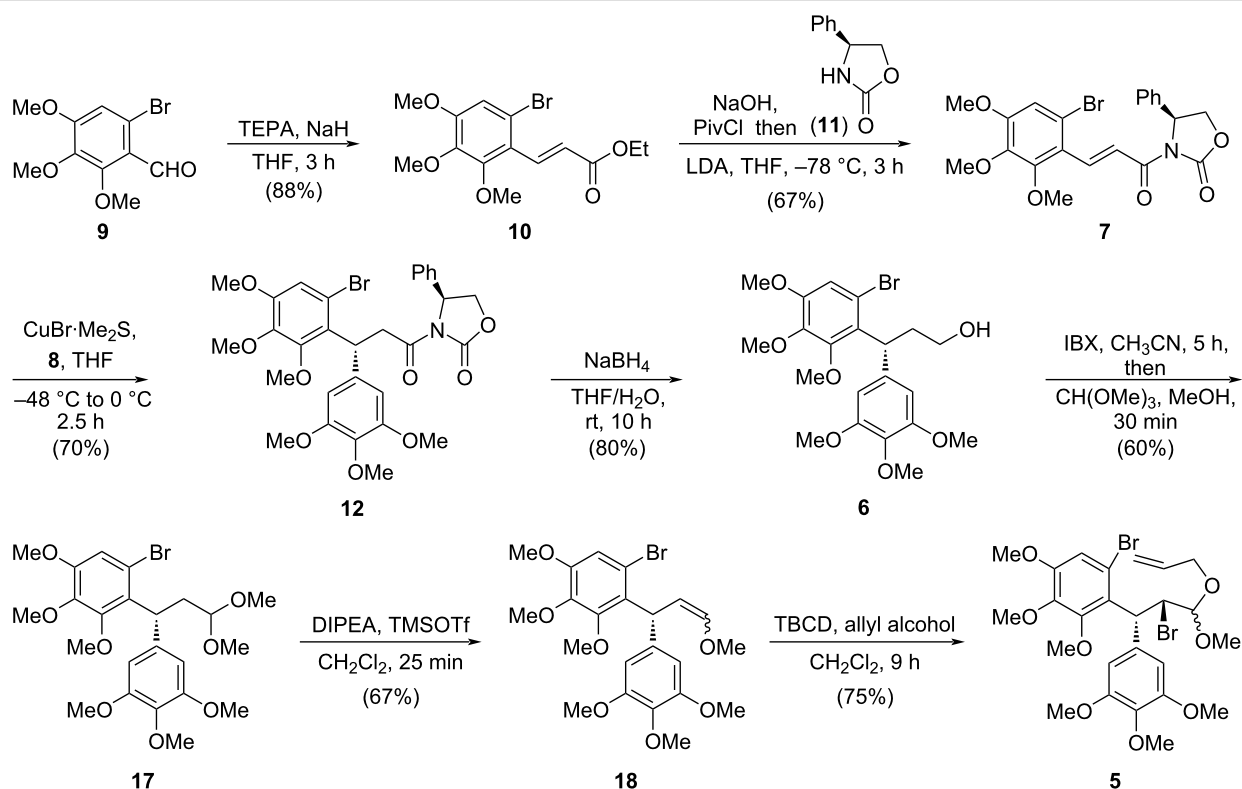
acetal reduction under acidic conditions then can complete the total synthesis of this molecule. The cyclization precursor **5** could be prepared from the primary alcohol **6** through transforming functional groups of the alkyl chain and installing an allyl group. It was envisioned that the diarylmethine stereocenter at C7' in **6** could be formed by an Evans' auxiliary-induced asymmetric conjugate addition of α,β -unsaturated acyl oxazolidinone **7** with 3,4,5-trimethoxyphenylmagnesium bromide (**8**). Both of these two building blocks could be conveniently prepared from commercially available 2,6-dimethoxyphenol [18,19].

Synthesis of cyclization precursor **5** and (+)-aglacin B

As shown in Scheme 2, the forward synthesis began with a triethyl phosphonoacetate-mediated Horner–Wadsworth–Emmons (HWE) reaction of *o*-bromobenzaldehyde **9** derived from 2,6-dimethoxyphenol (Supporting Information File 1). The generated ester **10** was then converted into the corresponding acyl chloride by saponification and subsequent reaction with pivaloyl chloride. The resulting acyl chloride was then trapped by (*S*)-4-phenyl-2-oxazolidinone (**11**) to produce the desired

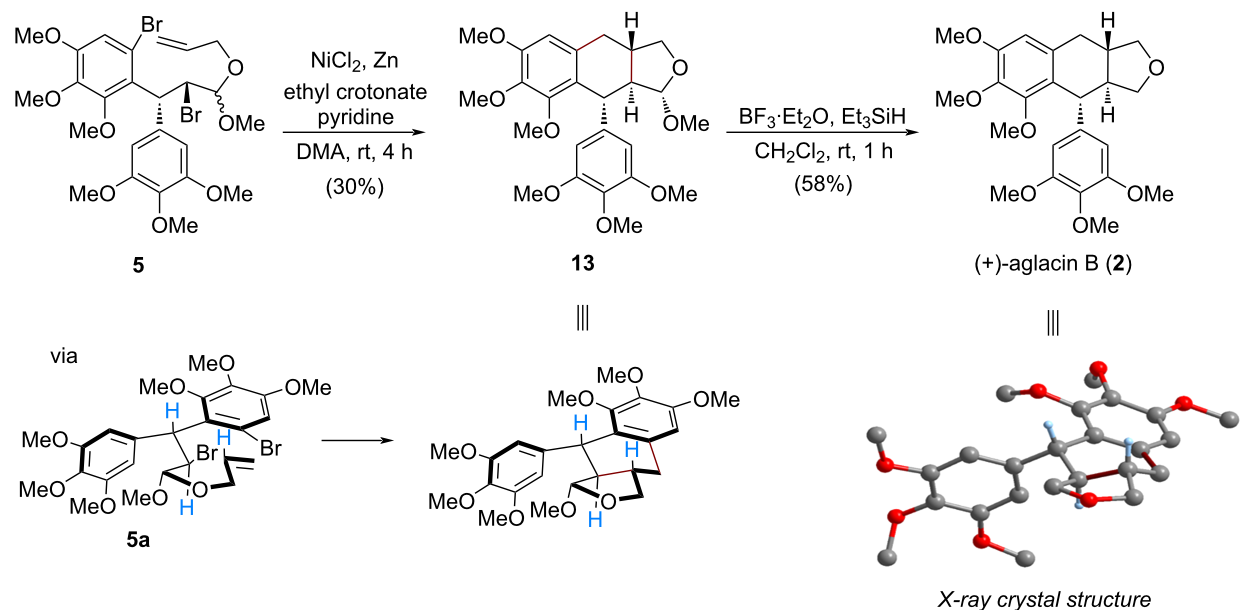
α,β -unsaturated amide **7**. Next, the asymmetric conjugate addition was carried out [20,21]. The in situ generated aryl–copper(I) species was obtained under the action of CuBr·Me₂S with Grignard reagent **8**, and then added to a THF solution of the α,β -unsaturated acyl oxazolidinone **7** at -48°C . This reaction demonstrated an excellent diastereocontrol for **12** (dr = 20:1), and could easily proceed on a scale of ten grams (Supporting Information File 1). For the reduction of the chiral auxiliary in **12**, NaBH₄ in THF/H₂O proved to be the optimal conditions, giving the primary alcohol **6** in 80% yield. Subsequently, oxidation of this alcohol by IBX followed by reaction with CH(OMe)₃ afforded acetal **17**, which was then subjected to a CH₂Cl₂ solution of TMSOTf and iPr₂NEt. A mixture of enol methyl ethers **18** were thus produced by an elimination reaction. Eventually, a site-selective bromination of the double bond over the electron-rich benzene rings with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD) in CH₂Cl₂ followed by reaction with allyl alcohol, provided β -bromo acetal **5** in 30% overall yield starting from alcohol **6**.

With a successful preparation of the cyclization precursor **5**, the designed nickel-promoted reductive tandem cyclization was



pursued (Scheme 3). By slightly modifying the reaction conditions of our previous studies [11,12], the expected bicyclization of **5** occurred smoothly, resulting in an efficient construction of

the *trans*-tetrahydronaphtho[2,3-*c*]furan skeleton embedded in **13**, which could be separated from the other diastereomer [14] by flash column chromatography in 30% yield. The stereocon-



trolled formation of aryltetralin **13** could be attributed to an adoption of a *pseudo*-half-chair conformation **5a**. Finally, the final step towards the total synthesis of (+)-aglacina B (**2**) was achieved by treatment with BF₃·Et₂O as the Lewis acid and Et₃SiH as the hydrogen source [22], affording this natural product in 58% isolated yield. NMR data of the synthetic sample were found to be in agreement with those of previous literature (Tables S1 and S2, Supporting Information File 1). Moreover, the newly synthesized (+)-aglacina B (**2**) formed single crystals, and a corresponding X-ray diffraction analysis (inset in Scheme 3, selected H atoms have been omitted for clarity, and Table S3, Supporting Information File 1) unambiguously confirmed its precise structure with three continuous chiral centers.

Conclusion

In summary, the total synthesis of (+)-aglacina B, a typical aryltetralin natural product [23,24], was completed from 2,6-dimethoxyphenol. The key Ni-promoted reductive cyclization cascade of a β-bromo acetal with an allyl tether, smoothly established the tetrahydronaphtho[2,3-*c*]furan core of this molecule in a new fashion.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, and copies of ¹H/¹³C NMR spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-21-197-S1.pdf>]

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

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