First Total Synthesis of (±)-6'-Methoxyretrojusticidin B Utilizing Regiocontrolled Benzannulation: Structural Inconsistency with Procumphthalide A and Its Revision to 5'-Methoxyretrochinensin

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Abstract: We achieved the first total synthesis of a novel (±)-6'-methoxyretrojusticidin B, which was proposed as procumphthalide A, utilizing regiocontrolled benzannulation of an aryl(aryl')-2,2-dichlorocyclopropylmethanol as the key step. ^{1}H NMR spectral data suggested that the structure of the synthesized product, 6'-methoxyretrojusticidin B, was inconsistent with that of natural procumphthalide A. A computational study of the rotational barrier rationally supports the existence of a rigid chiral axis in 6'-methoxyretrojusticidin B. The revised structural elucidation of natural procumphthalide A was concluded to be 5'-methoxyretrochinensin.

Key words: total synthesis, natural product, annulation**,** lignan lactone, revised structure

Highly substituted α-arylnaphthalene lignans are attracting considerable attention due to their widespread distribution in nature and their multiple significant biological activities.[1] Procumphthalide A, recently isolated from *Justicia procumbens*,[2] has significant anti-platelet effects on the adrenaline-induced platelet aggregation of human platelet-rich plasma.[3] The reported structure of procumphthalide A is equivalent to the 6'-methoxy analogue of parent natural retrojusticidin B[4] (Figure 1). Though axial chirality of procumphthalide A has not been pointed out in previous studies, the *ortho*-MeO substituent of the pendant aryl group would confer a rigid chiral axis.[5] Nonetheless, there has been no previous discussion with regard to this axial chirality issue.

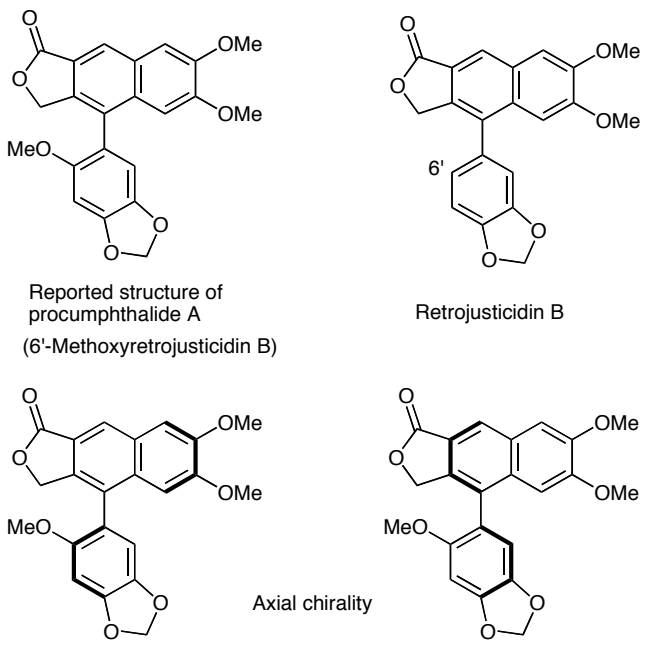
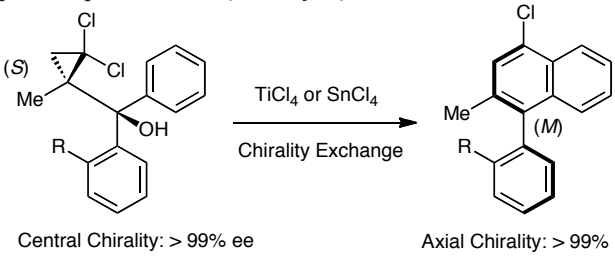


Figure 1

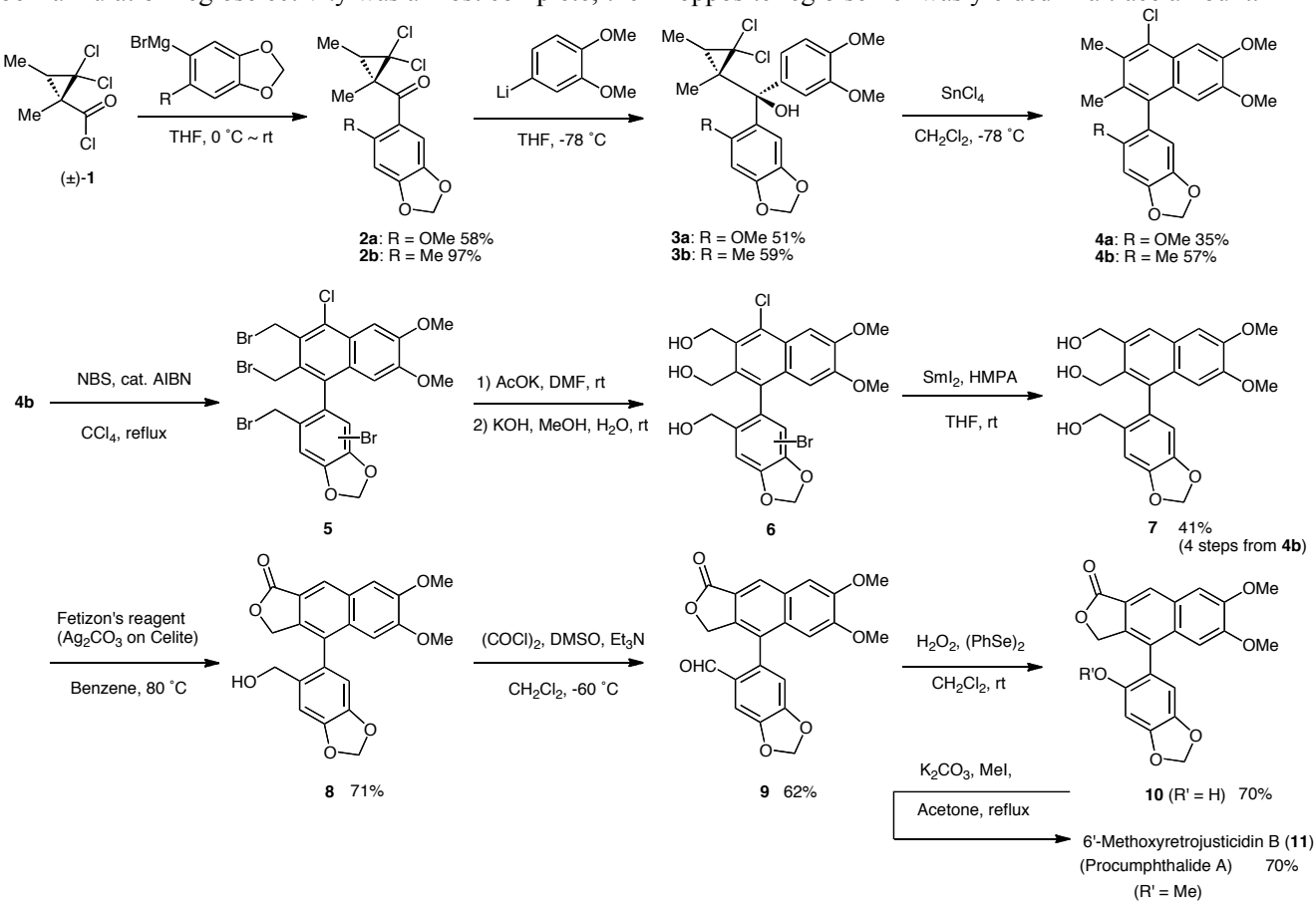
Our continuing interest in regiocontrolled and chirality exchange benzannulations[5,6] led us to envisage a total synthesis of procumphthalide A (Scheme 1), because of its specific structure based on 6'-substituent among various known lignan lactones. As the first stage of the synthetic study, we herein disclose the first total synthesis of unnatural (±)-6'-methoxyretrojusticidin B, the proposed structure of procumphthalide A. Note that the ^{1}H NMR spectral data of this rationally synthesized product, however, inconsistent with those of natural procumphthalide A (*vide infra*).



Scheme 1

Scheme 2 outlines the synthetic route, which basically follows the previous strategy.[6b] (±)-2,2-Dichlorocyclopropanecarbonyl chloride **1**[7] was converted to (±)-aryl(aryl')-2,2-dichlorocyclopropylmethanol (AACM) **3a** with high diastereoselectivity by a sequential condensation-addition with ArMgBr [Ar = 3,4-(-OCH_2O-)-2-$(MeO)C_6H_2$] (58%) and Ar'Li [Ar' = 3,4-$(MeO)_2C_6H_3$] (51%) via intermediary ketone **2a**.[8] $SnCl_4$-promoted regiocontrolled benzannulation of **3a** proceeded to give the desired α-arylnaphthalene **4a** as a sole isomer, but only in 35% yield.[9] The poor yield, compared with many hitherto reported examples, may be ascribed to undesirable coordination of $SnCl_4$ with the *ortho*-MeO substituent of the pendant Ar group. To solve this crucial problem, we switched the AACM from **3a** to **3b**, which bears an *ortho*-Me substituent. Gratifyingly, the yields of all three steps leading to α-arylnaphthalene **4b** markedly increased overall to 32%. As expected,

benzannulation regioselectivity was almost complete; the opposite regioisomer was yielded in a trace amount.



Scheme 2

Further functional transformations leading to the target compound were performed as follows. Note that the present process involves a novel protocol for converting the functional group from –CHO to –OH. Radical bromination of **4b** using 10 equiv of NBS did not give the expected tribromide being reacted with three Me groups, but instead afforded overbrominated product **5**[10] due to the inherently reactive pendant Ar group bearing 2-Me and 3,4-(-OCH_2O-) substituents. Decreased amounts of NBS resulted in a complex mixture of di- and tribromides and tetrabromide **5**. The obtained crude compound **5** was converted to triol **6** using a conventional method with AcOK and KOH.[6b,7a] A bromine remaining on the benzene nucleus of **6** was smoothly removed using SmI_2[11] to give the key triol **7** from **4b** in 41% overall yield. Oxidation-lactonization of **7** using Fetizon's reagent (Ag_2CO_3-Celite),[12] followed by separation of the undesirable regioisomers, produced lactone **8** in 71% yield.[13] Swern oxidation of the hydroxyl group in **8** gave aldehyde **9**, which was subjected to an effective Dakin oxidation promoted by a $(PhSe)_2$–H_2O_2 reagent[14] to afford the corresponding phenolic compound **10** in 43% overall yield. The final methylation of **10** produced the target product **11** in 70% yield.

The ^{1}H NMR spectra of synthesized compound **11**, (±)-6'-methoxyretrojusticidin B (I), however, was not consistent with the reported data of procumphthalide A (II), as depicted in Figure 2. The most notable difference is two pairs of methylene protons on C-10 and C-7' (I-a and I-c), which showed clear geminal couplings for **11**, whereas those of II exhibit singlet patterns (II-a and II-c). We speculate that these couplings attribute to a rigid chiral axis that prevents free rotation of the pendant aryl group, consistent with the notion of Charlton group's study,[15a] which strongly suggests that compound **11** has an atropisomer.

MO calculations were performed using Gaussian 03 at the *ab initio* level [RB3LYP/6-31G(d) with QST2] instead of Spartan at the AM1 level, which was performed by Charlton's group.[15b] Figure 3 depicts two optimized stable structure and one planer transition state structure. The calculated energy barrier of **11** was 28.4 kcal/mol, which is sufficient to give rise to stable atropisomers.[16] This result also supports the rigid skeleton of **11**. Therefore, the structure of the synthesized (±)-6'-methoxyretrojusticidin B is inconsistent with that of procumphthalide A.

Based on a careful review of the reported structure of procumphthalide A (II), we concluded that the data were consistent with 5'-methoxyretrochinensin,[17] which was previously synthesized by Takano's,[18] Charlton's,[19] and our groups.[6b] Thus, the regiocontrolled benzannulation strategy contributed to a rational structure determination of these unsymmetrically substituted lignan lactones.

In conclusion, we achieved the first total synthesis of (±)-6'-methoxyretrojusticidin B, which was first proposed to be procumphthalide A, utilizing a key regiocontrolled benzannulation. Spectral data and computational studies revealed that the synthesized 6'-

methoxyretrojusticidin B did not correspond to the natural procumphthalide A. The structure of procumphthalide A should thus be revised to 5'-methoxyretrochinensin. Further investigations into the synthesis of chiral 6'-methoxyretrojusticidin B utilizing a chirality exchange benzannulation are in progress.

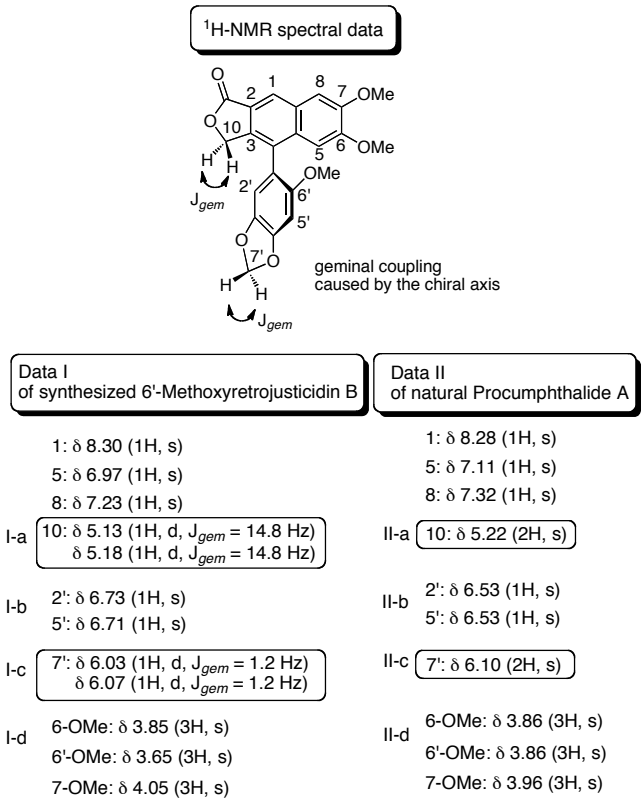


Figure 2

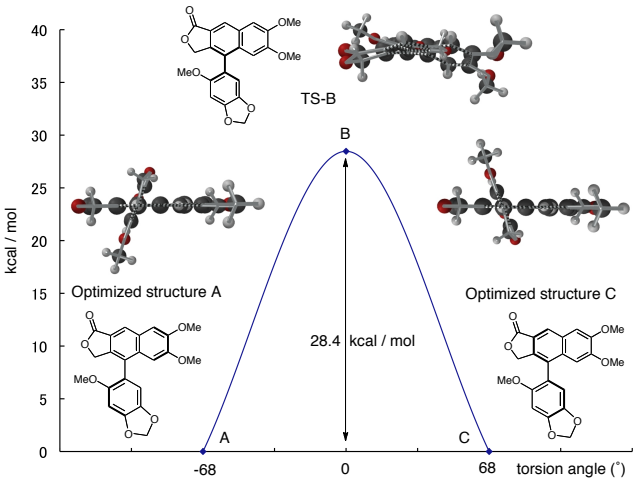


Figure 3

Acknowledgment

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Experimental

Experimental procedures and spectral data were described in supporting information, which is available electronically on the Thieme Chemistry Journal Web site, http://www.thieme-chemistry.com/products/journals/synlett.html.

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(8) The addition proceeded with high *syn*-diastereoselectivity (>95 : 5) according to the reported method:[6b] ArLi attacked the less hindered side of the preferential *s-cis* conformer of ketone **2a** or **2b** following the Cram's rule.

(9) AACM **3a** was completely consumed but inseparable complex by-products were yielded.

(10) Tetrabrominated product **5** was obtained as inseparable regioisomers and the structure was difficult to be determined due to a complex ^{1}H NMR spectrum.

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(13) Undesirable counter regioisomer was yielded in ca. 10%. The regioselectivity favors the synthesis of retro-type lignan lactones.

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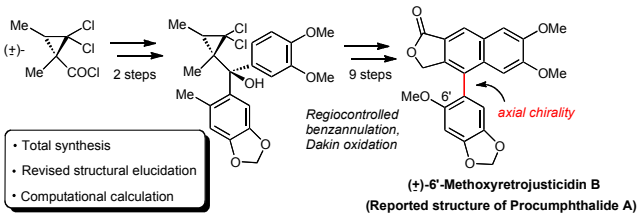
(15) (a) Charlton, J. L.; Oleschuk, C. J.; Chee, G-L.; *J. Org. Chem*. **1996**, *61*, 3452. For lignan lactones such as Justicidin A and B, retrojusticidin B, helioxanthin, and retrohelioxanthin, ^{1}H NMR of both methylene groups in the methylenedioxy substituent and in the lactone moiety exhibit AB coupling patterns, because these protons become diastereotopic due to the slow axis rotation. The rotation barriers are calculated by AM1 level (Spartan). (b) MO calculations were performed in a similar manner to the Charlton's report.



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(16) Selected data of calculations were described in the supporting information.
(17) Data in Ref. 6b; ^{1}H NMR (400 MHz) δ 3.87 (3Hx2, s), 3.96 (3H, s), 5.22 (2H, s), 6.10 (2H, s), 6.54 (1Hx2, s), 7.11 (1H, s), 7.31 (1H, s), 8.27 (1H, s).
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