Total Synthesis

An Asymmetric Total Synthesis of Tupichilignan A using Donor– acceptor Cyclopropanes: A Structural Revision of Tupichilignan A

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This paper is dedicated to Prof. Dennis P. Curran in celebration of his recovery and 64th birthday.

Abstract: An asymmetric total synthesis of tupichilignan A was achieved using enantioenriched donor–acceptor (D–A) cyclopropanes. The key steps include an asymmetric cyclopropanation using the Hayashi–Jørgensen catalyst, an oxy-homo-Michael reaction of a bicyclic D–A cyclopropane, an α-benzylation of a γ-lactone, a decarboxylation furnishing a trans-α,β-dibenzyl-γ-lactone, a configurational inversion of a hydroxy chiral center via oxidation, and a final reduction, all of which occur with high stereoselectivity. The spectral data of the diastereomers previously identified in the literature as tupichilignan A were found to be inconsistent with the reported data for the natural product. On the basis of the spectral data of both of the synthesized diastereomers, the structure of tupichilignan A was revised, and the absolute configuration of the 7 position of tupichilignan A was changed from R to S.

Lignans have attracted considerable attention owing to their widespread presence in plants and their diverse bioactivity.[1–3] For example, 7-hydroxy-dibenzyllignan lactones, such as 7S-hydroxymatairesinol, exert a statistically significant inhibitory effect on tumor growth and thus represent promising candidates for anticancer drugs (Figure 1).[2a–c] In 2006, tupichilignan A, which exhibits a similar absolute configuration to that of 7R-hydroxymatairesinol, was isolated from Tupistra chinensis Baker, traditionally used in Chinese folk medicine for the treatment of rheumatic diseases and snake bites.[3] However, the total synthesis of tupichilignan A has not yet been reported, to the best of our knowledge, and the absolute configuration of the carbon atom bearing an OH group at the 7 position has become a matter of interest in structure–activity relationship (SAR) studies.[2]

On the other hand, a new golden age for donor–acceptor (D–A) cyclopropanes has begun in organic synthesis, based on recent synthetic developments.[4,5] During the course of our synthetic studies using cyclopropanes,[6,7] we have already reported the oxy-homo-Michael addition of alcohols to bicyclic D–A cyclopropanes[7c] with inversion[7d] and the asymmetric total synthesis of yatein.[7e] Herein, we report an asymmetric total synthesis of tupichilignan A and its 7S-isomer using an oxy-homo-Michael reaction of an enantioenriched bicyclic D–A cyclopropane as the key step. Moreover, the inversion of the 7R-hydroxy chiral center of tupichilignan A to its 7S analogue is described.

Initially, the asymmetric cyclopropanation of ary1propenal 1 with dimethyl α-bromomalonate (2) using the Hayashi–Jørgensen catalyst afforded enantioenriched cyclopropane 3 in high yield and ee (Scheme 1).[7f,g] Reduction of aldehyde 3 with NaBH₄ and subsequent lactonization furnished bicyclic lactone 4. As expected, the highly stereoselective oxy-homo-Michael addition[7h] of benzyl alcohol to 4 afforded the desired lactone 5 in high yield and d.r., resulting in a stereospecific inversion at the γ carbon atom. On the basis of spectral data, the absolute configuration of 5 was determined by analogy with a similar lactone bearing a 3,4,5-trimethoxyphenyl group instead of the 3,4-dimethoxyphenyl that was assigned by X-ray crystallographic analysis in our previous report.[7i] Subsequently, the enolate generated from benzoxylactone 5 successfully attacked 3,4-dimethoxybenzyl bromide from the less hindered side to generate the desired product 6 as a single isomer. The trans-α,β-disubstituted lactone 7 was obtained via decarboxylation of 6, followed by protonation. An enol–keto tautomerization afforded the thermodynamically favored trans product 7 with excellent d.r. (Scheme 2).

Although diastereoselectivities were high (d.r. = 93:7–98:2) during the similar oxy-homo-Michael reaction, α-benzylation...
and decarboxylation in our previous total synthesis of ya-
tein (7b)\(^7\) the excellent diastereoselectivity (d.r. > 99:1) was
observed in the transformation of 5 to 7 owing to a bulky
 substitutions in the configuration at the 7 position of 8 was attempted via a Mitsu-

Scheme 3. Comparison of diastereomeric ratio (trans/cis) during a transform-

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<th>Scheme 1. Asymmetric total synthesis of tupichilignan A.</th>
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| Scheme 2. Proposed stereochemistry of intermediates 5, 6, and 7. |

under an atmosphere of hydrogen furnished tupichilignan A (8) in high yield. However, the spectral data of the synthesized 7R isomer (8), which had previously been reported as tupichilignan A, were inconsistent with the reported data of the isolated natural product (Table 1).\(^3\) The chemical shifts of H-7, H-8, H-9, H-7', and H-8' in the \(^1\)H NMR spectrum were significantly different from those reported in the literature. On the basis of the reported spectral data of 7S- and 7R-hydroxymatairesinol,\(^9\) we speculated that the structure of natural tupichilignan A should be that of the 7S isomer (Figure 1), that is, the epimer of 8.

In order to verify our hypothesis, we tried to synthesize the corresponding 7S analogue (10). Initially, the inversion of the configuration at the 7 position of 8 was attempted via a Mitsunobu reaction, which resulted in the formation of a 10:1 mix-

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<th>Table 1. Comparison of the (^1)H NMR spectral data of tupichilignan A with those of the synthesized 7R and 7S isomers.</th>
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[A] For an easier comparison between the observed and the previously re-
ported spectral data, the signal at 3.85 ppm (6H, s) is described here as
two signals at 3.85 ppm (3H, s).
In contrast, treatment of ketone \(9\), derived from alcohol, with \(\text{L-selectride}\) afforded it in good yield with high stereoselectivity (d.r. = 4:96). The \(^1\)H NMR spectral data of the thus obtained 75 analogue were in good agreement with those of natural tupichilignan A (Table 1). In addition, the \(^{13}\)C NMR spectral data of the 75 analogue were also fully consistent with those of tupichilignan A (Table 2).

Consequently, the structure of natural tupichilignan A was confirmed to be that of the 75 isomer \(10\) (Scheme 5).

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### Conflict of interest

The authors declare no conflict of interest.

### Keywords:

asymmetric synthesis · donor–acceptor cyclopropane · lignans · oxy-homo-Michael reaction · total synthesis · tupichilignan A

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**Scheme 4.** Inversion of the configuration at the 7 position from the \(7\)R isomer \(8\) to the \(7\)S isomer \(10\) via ketone \(9\). DEAD = diethyl azodicarboxylate.

**Scheme 5.** Revised structure of tupichilignan A.


[11] In this case, the Mitsunobu reaction was not effective for the inverse reaction (from 7S to 7R), see ref. 9.
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