



Electrochemical asymmetric dimerization of cinnamic acid derivatives and application to the enantioselective syntheses of furofuran lignans



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ABSTRACT

A new electrochemical method for the asymmetric oxidative dimerization of cinnamic acid derivatives has been developed. This method enabled the enantioselective syntheses of furofuran lignans, yangambin, sesamin and eudesmin.

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1. Introduction

There are a number of lignans¹ in plants and furofuran lignans, one of the largest subclass of them, have various biological activities such as antitumor, antimetabolic, antiviral and antimicrobial activities. The diversity of their bioactivities has attracted the attention of chemists, and the stereocontrolled synthesis of the substituted 3,7-dioxabicyclo[3,3,0]octane skeleton has also been a challenging target to synthetic chemists.² Furofuran lignans in our research interests are shown in Fig. 1. Yangambin was first obtained as a dimethylated derivative of lirioidesinol-B³ isolated from tulip tree, *Liriodendron tulipifera* L., and then isolated from Chinese medicinal plant, *Magnolia fargesii*.⁴ Yangambin displays selective inhibition against platelet activating factor,⁵ protective effects against cardiovascular collapse and anaphylactic shock, anti-allergic properties, analgesic activity, depressant effect in the central nervous system⁶ and apoptosis induction.⁷ Sesamin,⁸ which is a major constituent of sesame seed, is very famous of its antihypertensive,⁹ anticancer¹⁰ and antioxidant^{9d} properties. Eudesmine has been isolated from *Araucaria angustifolia*,¹¹ *Humbertia madagascariensis*¹² and the bark of *Mangolia kubus*¹³ up to the present. It

shows selective inhibition against platelet activating factor,¹⁴ T-cell proliferation,¹⁵ antioxidant¹⁶ and neuritogenic¹⁷ activities. Concise enantioselective syntheses of yangambin, sesamin and eudesmin have been reported by several research groups.¹⁸

We have previously developed an asymmetric oxidative dimerization of 3,4,5-trimethoxycinnamic acid derivative **1a** by using Yuzikhin's condition¹⁹ (PbO₂, TFA, CH₂Cl₂) (Scheme 1) and applied it to the efficient syntheses of furofuran lignans, yangambin (5 steps, 30% yield, 100% e.e.) and caruilignan A (6 steps, 30% yield, 100% e.e.).²⁰ Although other substrates (**1b** ~ **d**) with less oxygen atom on the benzene ring were subjected to the same condition, it was found that a trace amount of the desired bislactones (**2b** ~ **d**) was obtained along with an innegligible amount of aldehyde **3**, which was produced by oxidative cleavage of the double bond. Therefore, we proposed electrochemical oxidation²¹ as an alternative method to suppress the generation of **3** by setting factors such as solvent, supporting electrolyte, volumes of electric current and voltage suitable for each substrate. Herein, we report a new electrochemical method for the asymmetric oxidative dimerization of cinnamic acid derivatives and the enantioselective syntheses of furofuran lignans, yangambin, sesamin and eudesmin.

2. Results and discussion

Four substrates (**1a** ~ **d**) for electrochemical oxidation were

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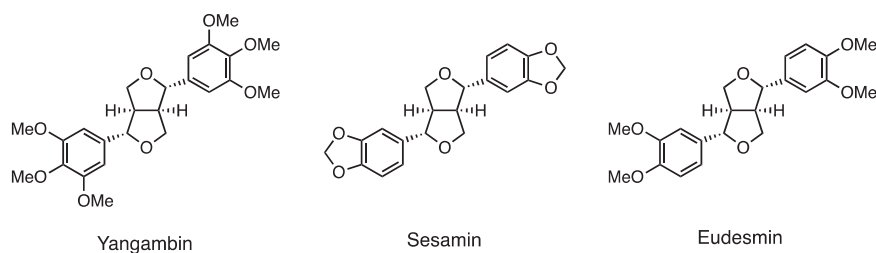
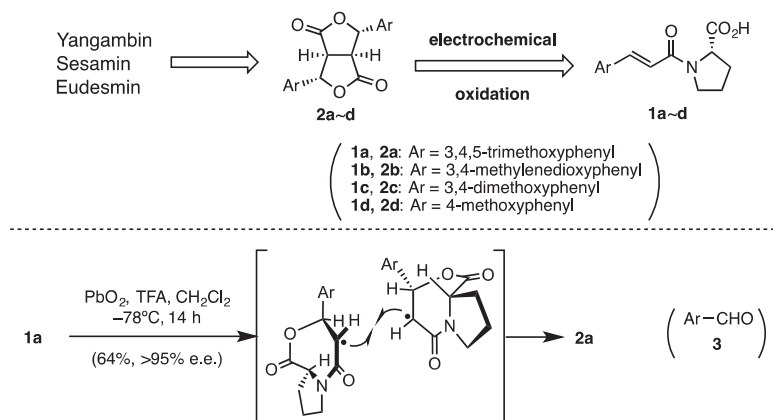


Fig. 1. Structures of furofuran lignans.



Scheme 1. Synthetic strategies for furofuran lignans.

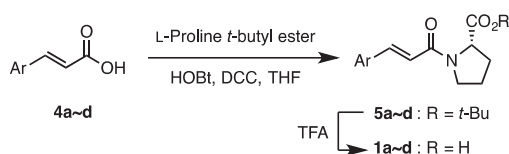
prepared by the same method reported previously²⁰ (Scheme 2). Cinnamic acid derivatives (**4a–d**) were condensed with *L*-proline *t*-butyl ester followed by treatment with TFA to give desired carboxylic acids (**1a–d**).

After screening suitable reaction conditions, oxidative dimerization of each substrate was found to proceed under Ronlan's electrochemical conditions²² (Pt anode, *n*-Bu₄NBF₄, CH₂Cl₂/TFA) without the formation of aldehyde **3**. So we examined chemical yield and enantiomeric excess of bislactones (**2a–d**), which could be obtained under Ronlan's conditions (Table 1). Since chemical yield of **2a** was almost the same between CH₂Cl₂/TFA = 5:1 and 2:1 at 0 °C, solvent ratio was set to CH₂Cl₂/TFA = 5:1 to avoid crystallization of TFA at lower temperature, and same volumes (1.8 mA/cm³) of electric current flowed. Enantiomeric excess was determined by chiral HPLC analysis of **7a–d** (**7a**: yangambin, **7b**: sesamin, **7c**: eudesmin), which were obtained from **2a–d** by reduction with Ca(BH₄)₂ and subsequent ether formation. At first, the reaction of 3,4,5-trimethoxycinnamic acid derivative **1a** was performed at various temperatures (r.t., 0 °C, –20 °C, –40 °C), and it became clear that chemical yield as well as enantiomeric excess were higher at lower temperature. Since electric current was sometimes hard to be kept the same flow at –40 °C in spite of getting the best result (52% yield, 91% e.e.), reactions of other substrates were carried out at 0 °C or –20 °C. On 3,4-methylenedioxcinnamic acid derivative **1b**, chemical yield

decreased compared to those of 3,4,5-trimethoxycinnamic acid derivative **1a**, but was better (24%) than that of Yuzikhin's racemic synthesis¹⁹ (15%). On the other hand, bislactones **2c** and **2d** were obtained in low chemical yield (8–10%), while enantiomeric excess of 3,4-dimethoxycinnamic acid derivative **2c** was tolerable (85–87% e.e.). The low chemical yields of **2c** and **2d** were due to decompositions of the starting materials **1c** and **1d** during the reactions. Interestingly, in our experiments, chemical yields were better in the case of the substrates with more oxygenated benzene ring, which was opposite to the results of Yuzikhin's racemic synthesis.¹⁹

Next, we searched for more effective supporting electrolytes and protonic acids in the reaction of 3,4-dimethoxycinnamic acid derivative **1c**. Seven supporting electrolytes were tested and the results were summarized in Table 2. Although the desired bislactone **2c** was obtained with the use of Et₄NClO₄, Et₄NOTFA, *n*-Bu₄NPF₆ or *n*-Bu₄NHSO₄, chemical yield could not be improved dramatically (entry 1–4). Tetraalkylammonium salts with halide ion were not effective to this reaction (entry 5–7). Furthermore, other protonic acids (TfOH, HSO₃F, MsOH, HClO₄, HBF₄·Et₂O) were also tested, but a trace amount of desired bislactone **2c** was obtained only when TfOH was used.

In summary, we have developed a new electrochemical method for the asymmetric oxidative dimerization of cinnamic acid derivatives. Three natural furofuran lignans, yangambin, sesamin and eudesmin could be synthesized with high enantiomeric excess by this electrochemical method.



Scheme 2. Preparation of the substrates.

3. Experimental

3.1. General

Optical rotations were recorded with a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-230

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