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Editor's Choice

Total Syntheses of (+)-Sesamin and (+)-Sesaminol

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Total syntheses of (+)-sesamin (**1a**) and (+)-sesaminol (**1b**), which are major components of sesame lignans derived from *Sesamum indicum*, were accomplished in a highly stereocontrolled manner. Key steps include an L-proline-catalyzed cross-aldol reaction, which was accelerated with the aid of bifunctional urea **7**, and the construction of a furofuran lignan skeleton through a quinomethide intermediate.

The biologically active furofuran lignans (+)-sesamin (**1a**) and (+)-sesaminol (**1b**) (Figure 1), isolated from sesame seeds, have been reported to exhibit various biological activities, including antitumor, antioxidant, antiviral, and antihypertensive activity as well as inhibition of low-density lipoprotein oxidation.[1,2] Therefore, **1a** and **1b** and their derivatives are expected to be useful as lead compounds for drug development. Furthermore, there is a need for synthesis of probe molecules to identify their target proteins, as well for analysis of the in vivo kinetics of **1a** and **1b**.[3] There are a few reports on the synthetic study,[4] and total syntheses of symmetric **1a**.[5] However, there is no report on the synthesis of **1b**, which possesses a hydroxy group. Herein, we report an efficient and flexible total synthesis of (+)-sesamin (**1a**) and (+)-sesaminol (**1b**).

During the course of our synthetic investigations of polyphenols,[6] we found that the electronic properties of the phenol-protecting group can tune the reactivity at the benzylic position. For example, an electron-rich protecting group stabilizes the benzylic cation,[6c,6d] while an electron-deficient functionality enhances the reactivity of the carbonyl group and the stability to oxidation.[6d,6e] Recently, we accomplished the total synthesis of a hybrid neolignan natural product, hedyotol A,[7] by using our original diastereoselective C–H insertion reaction as a key step.[8] Furthermore, in the course of the total synthesis, we found that the stereoselective construction of an *exo–exo*-type furofuran can be accomplished through the quinomethide intermediate by acidic treatment of the benzyl alcohol. We envisioned that this background would provide the basis for the concise asymmetric total synthesis of **1a** and **1b**.

The heart of our synthetic plan for **1a** and **1b** is illustrated in Scheme 1. According to our recent total synthesis of furofuran lignin,[7] acid treatment of tetraol **2a** and **2b** would readily provide the desired furofuran skeleton of **1a** and **1b**. Incorporation of the two different aromatic rings into the core skeleton of **2a** and **2b** could be performed by stepwise aldol reactions: these compounds could be derived from diastereoselective aldol reaction of **3** with benzaldehyde derivatives **4a** and **4b**, obtained by catalytic asymmetric aldol reaction of aldehyde **5** with benzaldehyde derivative **6**.

As shown in Scheme 2, the total syntheses of **1a** and **1b** were commenced with a proline-catalyzed cross-aldol reaction[9] between aliphatic aldehyde **5**[10] and 3,4-dihydroxybenzaldehyde

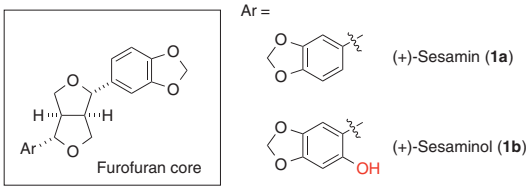
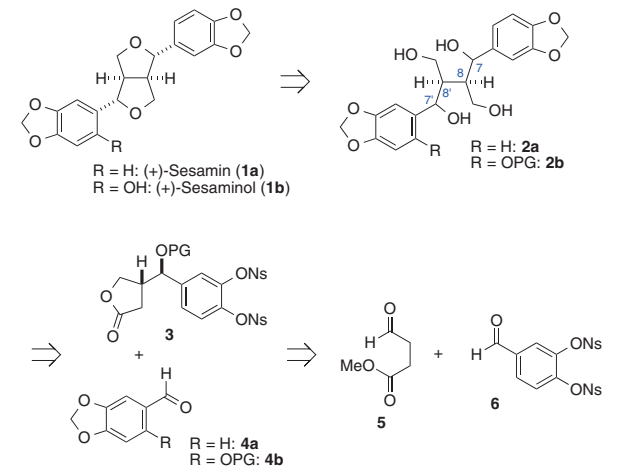
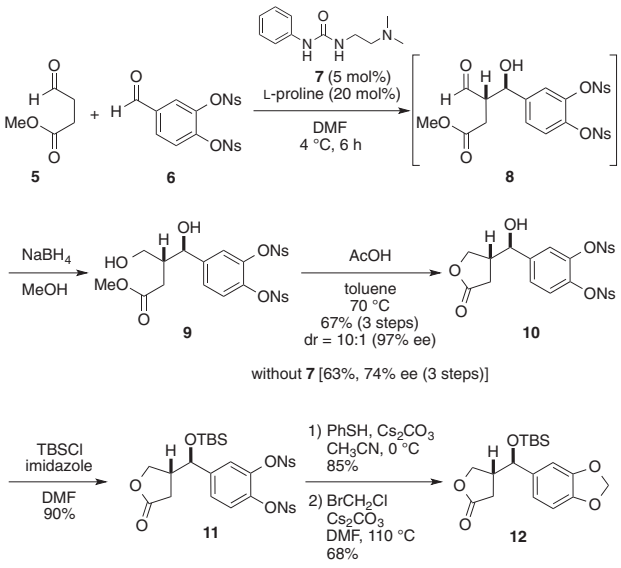


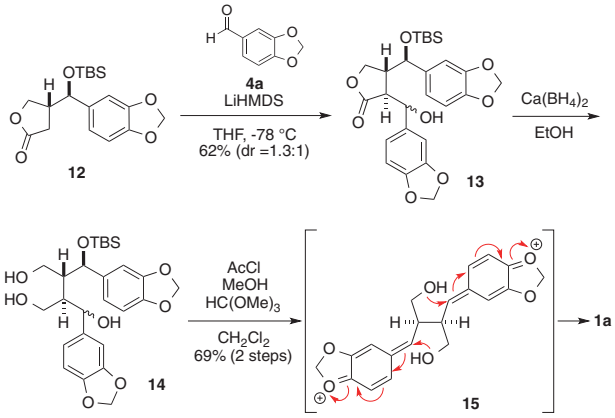
Figure 1. Structures of sesamin (**1a**) and sesaminol (**1b**).



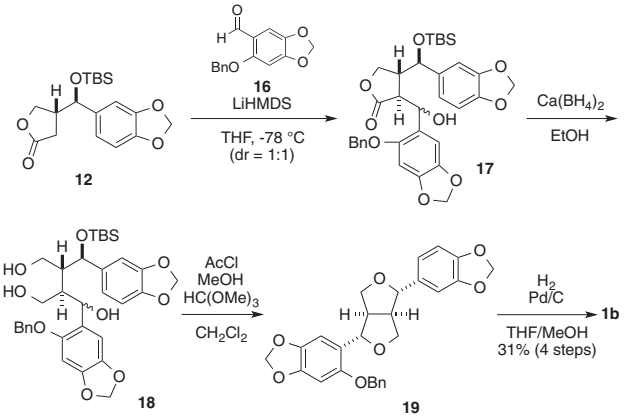
Scheme 1. Retrosyntheses of sesamin (**1a**) and sesaminol (**1b**).



Scheme 2. Synthesis of lactone **12**.



Scheme 3. Completion of total synthesis of (+)-sesamin (**1a**).



Scheme 4. Completion of total synthesis of (+)-sesaminol (**1b**).

derivative **6**.[7] In this reaction, a significant enhancement of the reactivity of benzaldehyde **6** was produced by the incorporation of nitrobenzenesulfonate (–ONs) at the phenol group[11] as an electron-withdrawing group.[12] Addition of bifunctional urea **7**[13] greatly accelerated the aldol reaction. When **5** and **6** were reacted in the presence of L-proline and **7**, the desired aldol reaction proceeded smoothly to provide **8**, and the reaction was complete within 6 h, while the reaction in the absence of **7** required 26 h to achieve a similar chemical yield. Reducing the reaction time was advantageous for maintaining the high enantiomeric excess. Without isolation of the less-stable **8**, chemoselective reduction of the aldehyde by $NaBH_4$ and treatment with AcOH provided lactone **10** in 67% yield (three steps) in a highly enantioselective manner (dr = 10:1, 97% ee). After protection of the secondary alcohol of **10** with a TBS group and subsequent removal of the Ns groups of **11**, a key intermediate **12** was synthesized by treatment of the resultant catechol with bromochloromethane and Cs_2CO_3.

The second aromatic ring was incorporated by means of a strong base-mediated aldol reaction of lactone **12** with aldehyde **4a** (Scheme 3). Upon treatment of **12** and **4a** with LiHMDS, the alkylation reaction occurred from the less-hindered β-face of the lactone ring to afford **13** in 62% yield. Although the stereochemistry of the newly formed benzylic alcohol was in a 1.3:1 ratio, both diastereomers were converted to the same *exo–exo* furofuran ring. After reduction of lactone **13** with $Ca(BH_4)_2$,[14] treatment of **14** with anhydrous HCl, generated in situ from AcCl and MeOH, promoted smooth construction of the furofuran ring to provide (+)-sesamin (**1a**). Since a single diastereomer was obtained, it is likely that this cyclization reaction occurred through the biomimetic quinomethide intermediate **15** to furnish **1a** as a thermodynamically stable *exo–exo* furofuran ring. Furthermore, trimethoxy orthoformate played an important role in pushing this reaction forward by trapping the H_2O generated in the cyclization. All spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) of the synthetic **1a** were in full agreement with reported values.[5]

Having established the synthetic route to **1a**, we thought that this methodology should be applicable to the preparation of numerous asymmetric furofuran derivatives. As an example, the enantioselective synthesis of (+)-sesaminol (**1b**)[15] was demonstrated, as shown in Scheme 4. The LiHMDS-mediated addition reaction of **12** and **16**[16] and subsequent reduction with $Ca(BH_4)_2$ provided triol **18**. Acidic cyclization of **18** proceeded smoothly to give furofuran **19**. Finally, removal of the benzyl group under hydrogenolysis condition furnished (+)-sesaminol (**1b**). All spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) of synthetic **1b** were in full agreement with reported values.[15]

In conclusion, we have established an efficient and flexible synthetic method for furofuran lignans such as **1a** and **1b**. Our stereocontrolled synthesis features an L-proline-catalyzed cross-aldol reaction of an aliphatic and aromatic aldehyde and biomimetic construction of the *exo–exo* furofuran skeleton through the quinomethide intermediate. Considering the mildness of all the reaction conditions and the convergent nature of the synthetic route, our synthetic strategy is, in principle, suitable for the easy preparation of a furofuran library.[17] Furthermore, an electron-rich aromatic ring would be beneficial for the incorporation of a halogen atom, which can act as a handle for the installation of a linker group by cross-coupling reaction. Thus, the concise preparation of various probe molecules should be possible.[3a–3d] Further synthetic studies and biological investigations of other furofuran lignans, as well as development of probe molecules are in progress.

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Supporting Information is available electronically on J-STAGE.

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16 The aldol reaction with **16** was not affected by in the presence of *o*-substitution of the benzaldehyde derivatives.

17 Our synthetic strategy was also applicable for readily syntheses of (+)-demethoxyaschantin (**1c**) and (+)-5′-hydroxymethylpiperitol (**1d**).