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An efficient asymmetric synthesis of furofuran lignans: (+)-sesamin and (−)-sesamin

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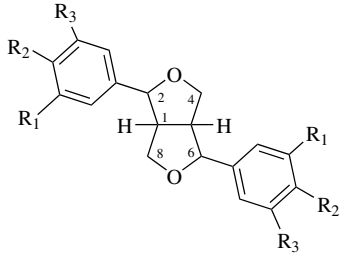
Abstract—An efficient synthesis of (+)-sesamin **1a** and (−)-sesamin **1b** is described. The key reactions include highly stereoselective aldol condensation of piperonal **7** with the dianion of chiral oxazolidinone **8**, followed by intramolecular ring cyclization of aldol product **11** in high yield.

1. Introduction

Lignans have evoked a great deal of interest due to their widespread occurrence in nature[1] and use in traditional medicines.[2] Furofurans, one of the major subclasses of the lignan family, exhibit a wide variety of biological activities including antitumor, antimitomic, antiviral,[3] antioxidant, antihypertensive,[4] inhibition of platelet-activating factor (PAF),[5] and Ca^{2+} channels.[6] Of the furofurans, these compounds containing chiral bis-tetrahydrofuran rings such as (±)-sesamin **2**, (±)-eudesmin **3** and (±)-yangambin **4**, have generated considerable and continued interest due to their unique structural characteristics and stereochemical diversity (Fig. 1). Significantly, (+)-sesamin **1a** and (−)-sesamin **1b** have been the target of extensive synthetic research for many years.[7]



2 (±)-sesamin R_1=H, R_2=R_3=-OCH_2O-
3 (±)-eudesmin R_1=H, R_2=R_3=-OCH_3
4 (±)-yangambin R_1=R_2=R_3=-OCH_3

Figure 1. Structures of furofuran lignans.

Since the synthesis of racemic (±)-sesamin **2** was first achieved by Beroza and Schechter,[8] several alternative synthetic routes for the racemate have been developed.[9] However, few methods have been reported for the asymmetric synthesis of the sesamins including Takano's asymmetric synthesis[9c] and Ogasawara's diastereodivergent chiral synthesis.[9g] Recently, Brown and co-workers[10a] reported an enantioselective synthesis using an Mn(III)-mediated intramolecular cyclopropanation and an C–H insertion reaction. Steel and co-workers[10b] generated the furofuran skeleton by diastereocontrolled cationic cyclization and stereoselective reduction. Roy and co-workers[10c] treated an epoxy ether with a titanium(III) adduct to afford the furano rings by intramolecular radical cyclization.

In connection with our synthetic studies for biologically active compounds, we herein report an efficient asymmetric synthesis of (+)-sesamin **1a**[11] and (−)-sesamin **1b**.[12] Key reactions include a stereoselective aldol condensation followed by intramolecular ring cyclization.

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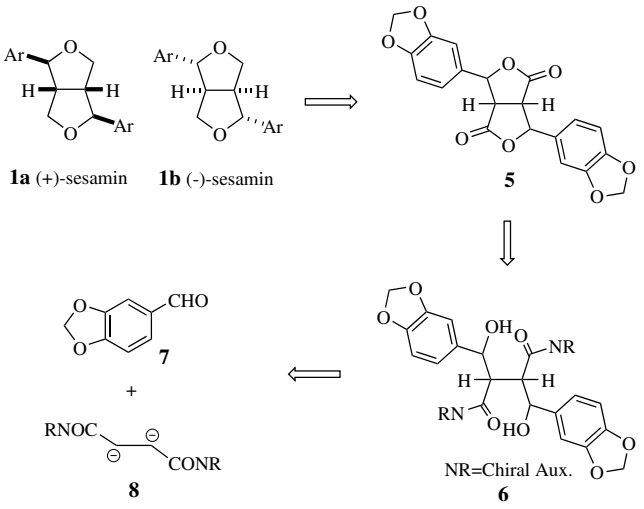
2. Results and discussion

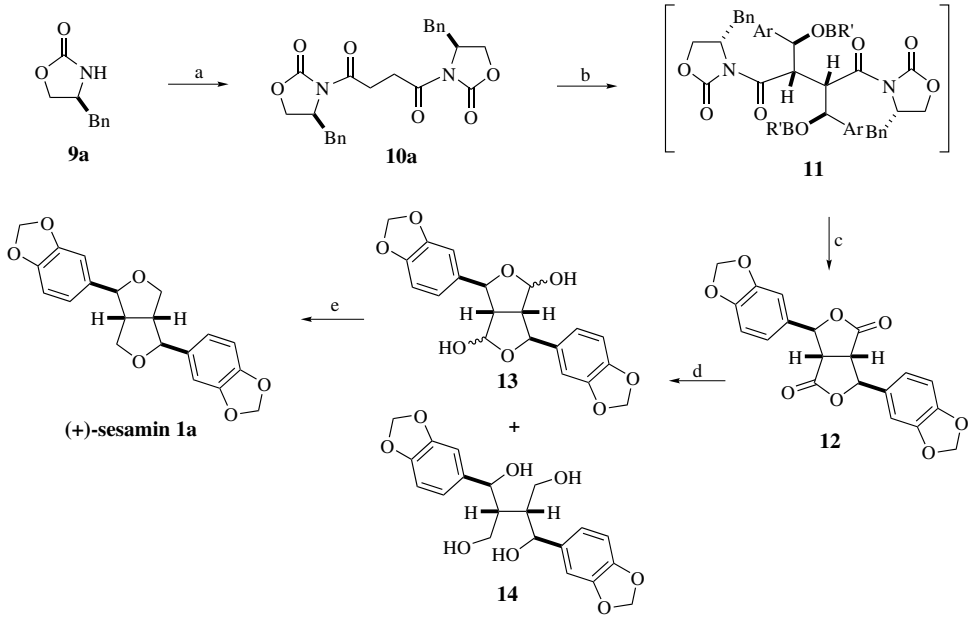
The retrosynthetic analysis for (+)-sesamin **1a** and (−)-sesamin **1b** is summarized in Scheme 1. We envisioned that the sesamins could be synthesized in five steps. The key synthetic steps involve stereoselective aldol condensation of piperonal **7** with dianion **8** and construction of the bicyclooctane skeleton of **5** through intramolecular ring cyclization of aldol product **6**. Reduction of dilactone **5** followed by removal of the dihydroxyl groups of the intermediate dilactol would give (+)-sesamin **1a**[13] and (−)-sesamin **1b**.



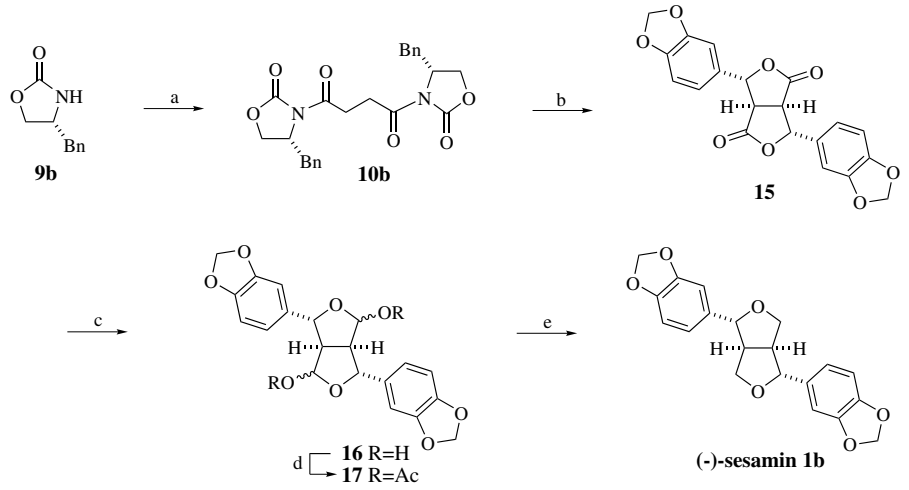
Scheme 1. Retrosynthetic analysis of **1a** and **1b**.

The synthesis of (+)-sesamin **1a** was accomplished as depicted in Scheme 2. Succinyl chloride was treated with freshly prepared (*S*)-(−)-4-benzyl-2-oxazolidinone **9a** to form the chiral auxiliary [reduction of (*S*)-phenylalanine with sodium borohydride gave (*S*)-phenylalaninol, which on treatment with anhydrous sodium carbonate in diethyl carbonate gave an oxazolidinone, 80% two steps yield][14] in the presence of *n*-BuLi to afford 1,4-bis-[4-(*S*)-benzyl-2-oxo-oxazolidin-3-yl]butane-1,4-dione **10a**[13] in 89% yield. Aldol condensation of boron (*Z*)-enolate[15] (generated by treatment of *N*-acyloxazolidinone **10a** with dibutylboron triflate[16] and DIPEA in CH_2Cl_2 at −78 °C), followed by treatment with piperonal **7**, afforded the condensation product **11** as an unstable key intermediate, which was not isolated but instead subjected to intramolecular ring cyclization [KH_2PO_4 and H_2O_2 (28%) in MeOH] to give dilactone **12** with 95:5 diasteromeric selectivity, which was determined on the basis of HPLC analysis (91% combined yield, two steps). After intramolecular ring cyclization of **11**, the pure chiral auxiliary **9a** was recovered in 75% yield. Reduction of dilactone **12** with DIBAL-H afforded dilactol **13** (1:1 cis/trans ratio, 45% combined yield).[17] Interestingly, exposure of dilactone **12** to excess DIBAL-H (4 equiv) for longer reaction times (3 h) gave a mixture of the desired dilactol **13** and tetralol **14** as an over reduction product in 32% and 9% yields, respectively. Also, the reduction of dilactone **12** with excess of $LiAlH_4$ in ether gave teteralol **14** in quantitative yield. Dilactol **13** was reduced by treatment with Et_3SiH and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to afford (+)-sesamin **1a** in 60% yield,[18] whereas attempts to convert side product tetralol **14** to (+)-sesamin **1a** via treatment with mesyl chloride in the presence of Et_3N and DMAP in CH_2Cl_2 failed.

As shown in Scheme 3, a synthetic route for (−)-sesamin **1b** was achieved using a similar route to the synthetic route for (+)-sesamin **1a**. Freshly prepared **9b** was deprotonated with *n*-BuLi at −78 °C, followed by treatment with succinyl chloride in dry THF to give *N*-acyloxazolidinone **10b** in 86% yield. Enolizable substrate



Scheme 2. Reagents and conditions: (a) *n*-BuLi, succinyl chloride/THF, 0 °C, 2 h, 89%; (b) Bu_2BOTf, DIPEA/CH_2Cl_2, −78 °C, **7**, 20 min; (c) KH_2PO_4(aq), H_2O_2 (28%)/MeOH, rt, 8 h, 91% (two steps); (d) DIBAL-H/THF, −25 °C, 1 h, 45%; (e) Et_3SiH, $BF_3{\cdot}Et_2O/CH_2Cl_2$, −78 °C, 1 h, 60%.



Scheme 3. Reagents and conditions: (a) *n*-BuLi, succinyl chloride/THF, 0 °C, 2 h, 86%; (b) (i) Bu_2BOTf, DIPEA/CH_2Cl_2, −78 °C, **7**, 20 min; (ii) KH_2PO_4(aq), H_2O_2 (28%)/MeOH, rt, 8 h, 88% (two steps); (c) DIBAL-H/THF, −25 °C, 1 h, 45%; (d) Ac_2O/pyridine, 48 h, 70%; (e) Et_3SiH, $BF_3{\cdot}Et_2O/CH_2Cl_2$, −78 °C, 1 h, 58%.

10b was treated with dibutylboron triflate (Bu_2BOTf)[16] in the presence of DIPEA in CH_2Cl_2 to generate the (*Z*)-enolate,[15] which in situ was reacted stereoselectively with piperonal **7** at −78 °C for 20 min.

The mixture was then quenched with KH_2PO_4 to afford dilactone **15** in 95:5 dr selectivity (88% combined yield, two steps). Dilactone **15** was treated with DIBAL-H in THF at −25 °C to give dilactol **16** (1:1 cis/trans ratio, 45% combined yield).[17] Due to intermediate **16** being unstable, its isolation, and characterization were problematic. Acetylation of **16** with acetic anhydride gave diacetate **17** (70%),[9a] which could be easily isolated and characterized. Reduction of dilactol **16** with Et_3SiH and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 gave (−)-sesamin **1b** in 58% yield (Scheme 3).

3. Conclusion

In conclusion, a new and efficient method has been developed for the synthesis of (+)-sesamin **1a** and (−)-sesamin **1b** via a five-step route using a stereoselective aldol condensation in overall 22% and 20% yields, respectively. This synthetic method is superior to those reported in view of simplicity, enantiomeric excess, and overall yield and should be useful in the synthesis of lignans. All physical and spectral data for the synthetically prepared (+)-sesamin **1a** and (−)-sesamin **1b** were identical to those reported for the natural product.[11,12]

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13. Selected data: **10a**: mp 56–57 °C; $[\alpha]_D^{22} = +103.8$ (*c* 1.0, MeOH); IR (neat, NaCl) 3158, 1781, 1697, 1376, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.19 (m, 10H), 4.67 (br s, 2H), 4.16 (t, $J = 8.8$ Hz, 4H), 3.32 (s, 4H), 3.22 (d, $J = 13.3$ Hz, 2H), 2.82 (dd, $J = 12.9$, 9.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 154.0, 135.7, 129.9, 129.7, 129.3, 127.7, 66.8, 55.4, 38.0, 30.5; HRMS calcd for $C_{24}H_{24}N_2O_6$: 437.1713 $[M+H]^+$, found: 437.1663. (+)-Sesamin (**1a**): mp 121–122 °C (lit.,[9i] 118–120 °C); $[\alpha]_D^{22} = +68.0$ (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 2849, 1515, 1448, 1246, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.85–6.77 (m, 6H), 5.95 (s, 4H), 5.39 (s, 2H), 4.33–4.29 (m, 2H), 4.02–3.89 (m, 2H), 3.41–3.21 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 141.7, 133.8, 119.7, 110.1, 105.8, 102.3, 101.2, 82.6, 46.4. General procedure for the preparation of dilactone **12**: To a stirred solution of *N*-acyloxazolidinone **10a** (2.0 g, 4.6 mmol), DIPEA (1.5 g, 12.0 mmol) in CH_2Cl_2 (22 mL) was added dropwise Bu_2BOTf (10.0 mL, 10.0 mmol, 1.0 M solution in dichloromethane) at 0 °C and the mixture stirred for 30 min. Piperonal **7** (1.8 g, 12.0 mmol) was added dropwise to the reaction mixture at −78 °C and the resulting mixture stirred at same the temperature for 20 min. The reaction mixture was treated with KH_2PO_4 (18 mL), H_2O_2 (18 mL, 28%), MeOH (27 mL) and the resulting mixture vigorously stirred at room temperature for 8 h. The mixture was then extracted with dichloromethane (3×30 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give dilactone, which were purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford pure dilactone **12** (1.6 g, 91%, two steps) as a white solid. mp 188–189 °C (lit.[9b] 189–191 °C); IR (neat, NaCl) 3209, 1772, 1498, 1247, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 4H), 6.75 (s, 2H), 5.99 (s, 4H), 5.82 (s, 2H), 3.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 149.2, 149.0, 132.4, 119.2, 109.4, 105.9, 102.3, 82.5, 48.9; MS(ESI) (m/z) 383 $[M+H]^+$, 307, 154 (base peak); HRMS calcd for $C_{20}H_{14}O_8$: 383.0767 $[M+H]^+$, found: 383.0695.
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