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Stereoselective total synthesis of furofuran lignans through dianion aldol condensation

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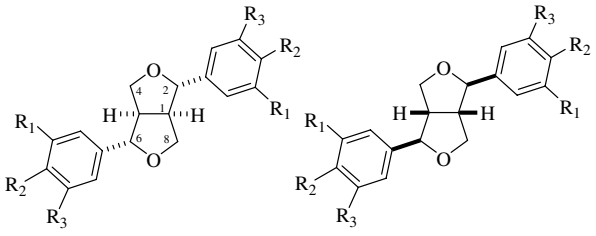
Abstract—Highly stereoselective total synthesis of (+)-eudesmin, (+)-yangambin, (−)-eudesmin, and (−)-yangambin is described. This method is useful to generate the core skeleton of furofuran rings utilizing modification of Evans asymmetric aldol condensation.

1. Introduction

Furofuran lignans have stimulated significant interest due to their wide range of intriguing biological activities[1] such as antitumor,[2] antimitomic,[3] antiviral,[4] antioxidant,[5] antihypertensive,[6] inhibition of platelet-activating factor (PAF),[7] and Ca^{2+} channels,[8] cAMP phosphodiesterase inhibitory,[9] sodium selective diuretic properties,[10] and microsomal monooxygenases inhibitory effects for insects.[11] Several elegant synthetic approaches have been reported[12] in the literature, most of these methods are substrate specific providing an entry to one particular stereochemical series and only a few approaches are applicable to the stereocontrolled synthesis of exo–exo furofuran (±)-sesamin, (±)-eudesmin, (±)-yangambin, and (±)-epiasarinin (Fig. 1).[12f,g]

We recently reported[13] an efficient asymmetric synthesis of (+)-sesamin and (−)-sesamin. Key steps include highly stereoselective aldol condensation of piperonal with the dianion of chiral auxiliary, followed by intramolecular ring cyclization of aldol product in high yield. In connection with our synthetic approaches, we have been interested in the asymmetric total synthesis of lignans of the furofuran series.



1a (+)-Sesamin R_1=H, R_2=R_3=-OCH_2O- **1b** (-)-Sesamin
2a (+)-Eudesmin R_1=H, R_2=R_3=-OCH_3 **2b** (-)-Eudesmin
3a (+)-Yangambin R_1=R_2=R_3=-OCH_3 **3b** (-)-Yangambin

Figure 1. Structures of furofuran lignans.

Herein, we described the efficient stereoselective total synthesis of (+)-eudesmin, (+)-yangambin, (−)-eudesmin, and (−)-yangambin by modification of asymmetric aldol condensation and intramolecular ring cyclization.

2. Results and discussion

The general features of our initial approach to the generation of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton of furofuran lignans are summarized in

Keywords: Furofuran lignans; (+)-Eudesmin; (+)-Yangambin; (−)-Eudesmin; (−)-Yangambin; Stereoselective aldol condensation; Intramolecular ring cyclization.
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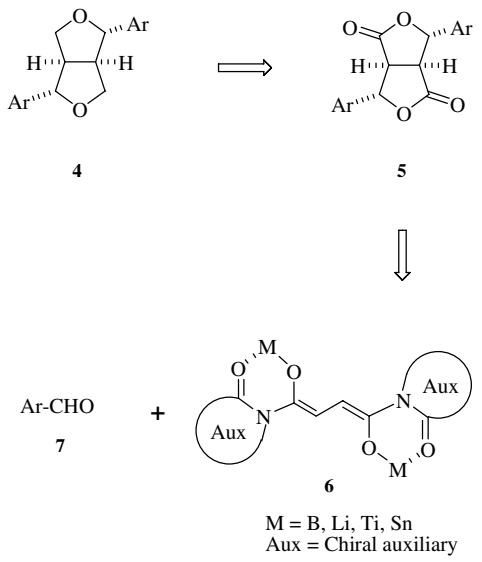


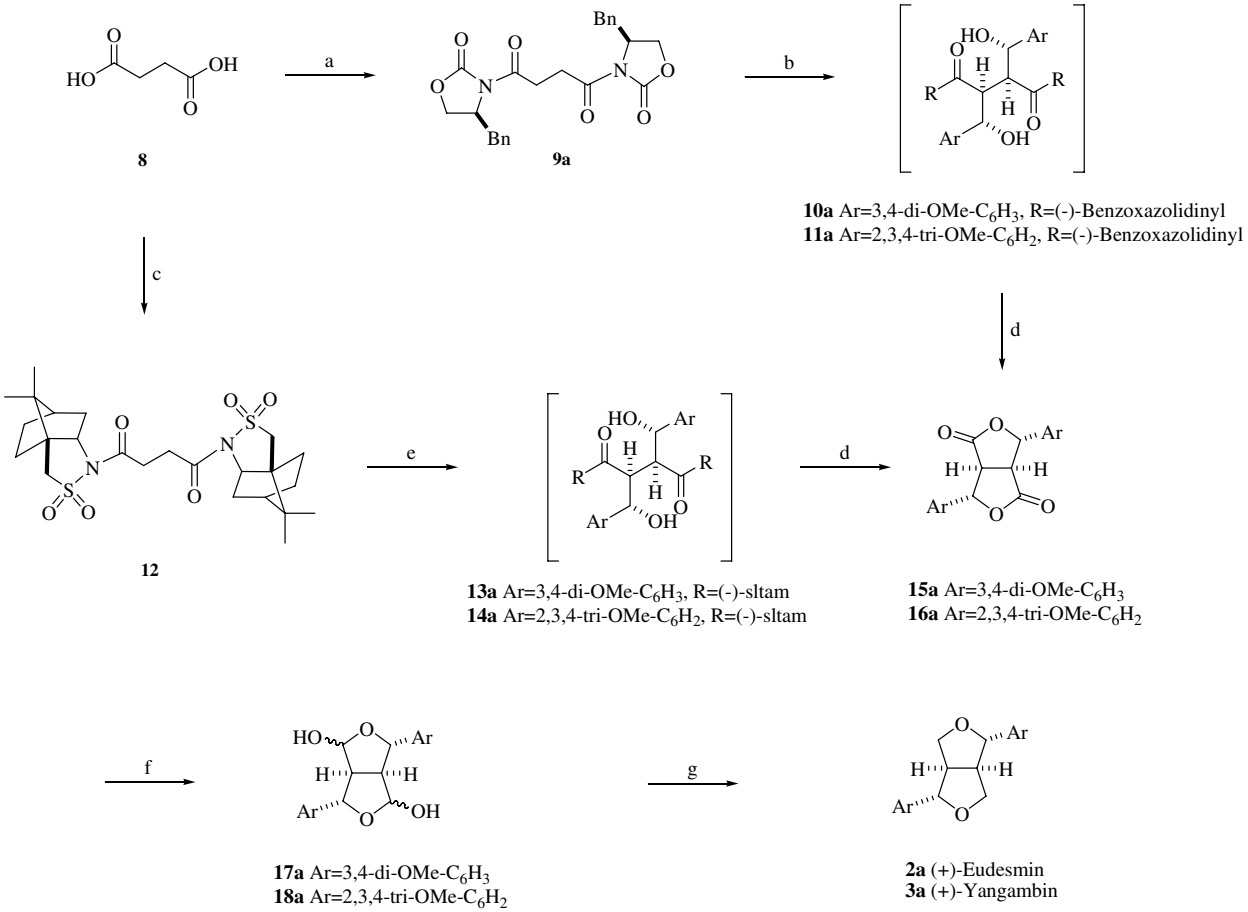
4 5 6

Scheme 1. Retrosynthetic analysis of eudesmin and yangambin.

Scheme 1. The chelated metal complex **6** (derived from **9a** or **12** with enolating agents) would be served as a key intermediate according to the retrosynthetic analysis of the furofuran lignans shown in Scheme 1. A diastereoselective double aldol condensation of chelated metal complex **6** and aldehyde **7**, followed by intramolecular ring cyclization and double-reduction to complete the synthesis of furofuran lignans **4**.

The synthesis of (+)-eudesmin (**2a**) and (+)-yangambin (**3a**) was accomplished as shown in Scheme 2. Thus, succinic acid (**8**) was treated with thionyl chloride to give succinyl chloride, which was reacted with freshly prepared (*S*)-(−)-4-benzyl-2-oxazolidinone and (*S*)-(−)-2,10-camphorsultam as chiral auxiliaries [(*S*)-(−)-4-benzyl-2-oxazolidinone was prepared[14] from (*S*)-phenylalaniol, diethyl carbonate, and sodium bicarbonate in 80% yield; (*S*)-(−)-2,10-camphorsultam was obtained from (+)-camphor-10-sulfonic acid with thionyl chloride, ammonium hydroxide, and sodium borohydride in a 65% three steps yield[15]] in the presence of *n*-BuLi (1.6 M soln, in hexane) at 0 °C to afford the required 1,4-bis[4-(*S*)-benzyl-2-oxazolidin-3-yl]butane-1,4-dione (**9a**) and (*S*)-(−)-sultam (**12**) in 85% and 88% yields, respectively.

The stereoselective aldol condensation of aldehydes (3,4-dimethoxybenzaldehyde, 2,3,4-trimethoxybenzaldehyde) and chiral auxiliaries **9a**, **12** into the dichloro-



8 **9a**

10a Ar=3,4-di-OMe-C_6H_3, R=(-)-Benzoxazolidinyl
11a Ar=2,3,4-tri-OMe-C_6H_2, R=(-)-Benzoxazolidinyl

12

13a Ar=3,4-di-OMe-C_6H_3, R=(-)-sltam
14a Ar=2,3,4-tri-OMe-C_6H_2, R=(-)-sltam

15a Ar=3,4-di-OMe-C_6H_3
16a Ar=2,3,4-tri-OMe-C_6H_2

17a Ar=3,4-di-OMe-C_6H_3
18a Ar=2,3,4-tri-OMe-C_6H_2

2a (+)-Eudesmin
3a (+)-Yangambin

Scheme 2. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, reflux, 1 h; then (*S*)-(−)-4-benzyl-2-oxazolidinone, *n*-BuLi/THF, 0 °C, 2 h, 85%; (b) Bu_2BOTf, DIPEA/CH_2Cl_2, −78 °C, 3,4-dimethoxybenzaldehyde, 20 min; (c) $SOCl_2$, CH_2Cl_2, reflux, 1 h; then (*S*)-(−)-2,10-camphorsultam, *n*-BuLi/THF, 0 °C, 2 h, 88%; (d) KH_2PO_4 (aq), H_2O_2 (28%)/MeOH, 25 °C, 8 h, 84% for **15a**, 81% for **16a**; (e) Bu_2BOTf, DIPEA/CH_2Cl_2, −78 °C, 2,3,4-trimethoxybenzaldehyde, 20 min; (f) DIBAL-H/THF, −25 °C, 1 h, 42% for **17a**, 45% for **18a**; (g) Et_3SiH, $BF_3{\cdot}Et_2O$/CH_2Cl_2, −78 °C, 1 h, 55% for **2a**, 58% for **3a**.

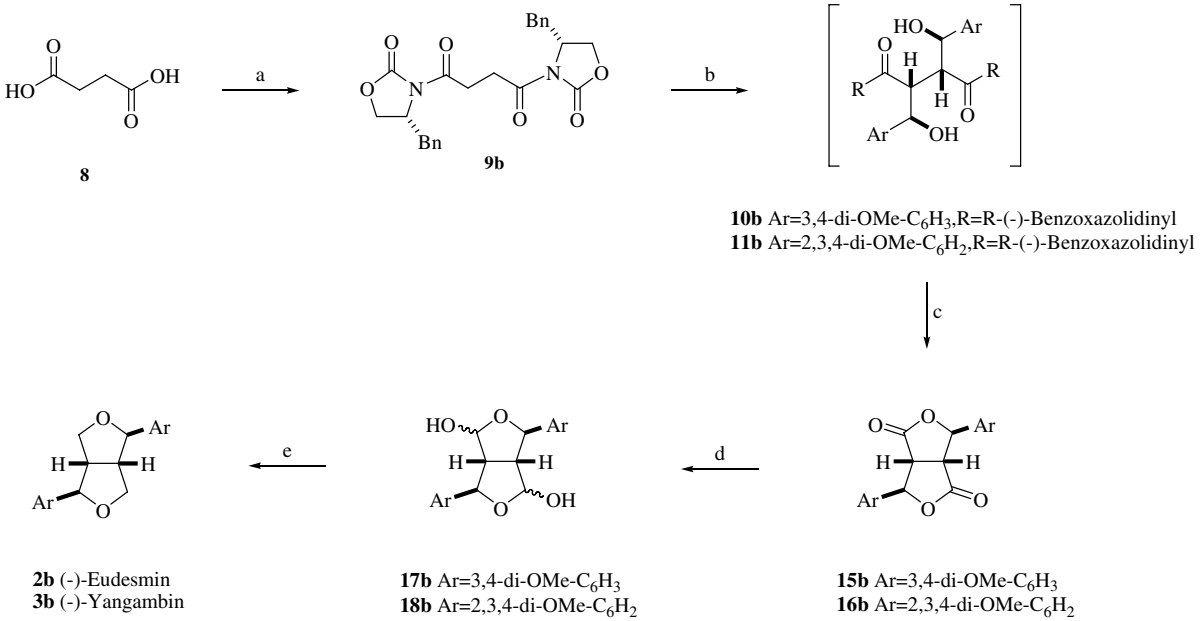
methane was performed with dibutylboron triflate at −78 °C. The resultant dihydroxyl compounds **13a** and **14a** were unstable and we were not able to isolate them in sufficient purity or yield. Compounds **13a** and **14a** were subjected to intramolecular ring cyclization using KH_2PO_4 and H_2O_2 (28%) in MeOH to yield dilactone **15a** and **16a** in 84% and 81% two step yields, with 18:1, 20:1 diasteromeric selectivity, respectively. Conversion of **15a** and **16a** was achieved by reduction using DIBAL–H in THF, followed dehydroxylation of dilactols **17a** and **18a** to generate (+)-eudesmin (**2a**) and (+)-yangambin (**3a**) (Scheme 2).

The key step in our synthesis involved the stereoselective aldol coupling of enolizable substrates **9a** and **12** with aldehydes **7**. The primary goal in a reaction of this type is to obtain maximum diastereoselectivity. Therefore, we sought to determine the conditions necessary to achieve this goal by varying the enolizable substrate, and the reaction conditions for the aldol condensation. In our original report,[13] oxazolidinine **9a** was used as an enolizable substrate resulting in a 19:1 diastereomeric ratio of dilactones as (+)-, (−)-sesamin precursors in good yield. Having pure enolizable substrate **9a** and **12** in hand, we tested several enolating agents[16] such as Et_2BOTf/CH_2Cl_2, Bu_2BOTf/CH_2Cl_2, *n*-BuLi, $ZnCl_2$/THF, LDA/THF, $TiCl_4/CH_2Cl_2$, $TiCl(OiPr)_3/CH_2Cl_2$, and $SnOTf/CH_2Cl_2$ under standard conditions.[17] The best results were obtained with Bu_2BOTf/CH_2Cl_2 at −78 °C to 0 °C for 1 h, regarding diastereoselectivity and yield (Table 1). Although stereoselectivity was enhanced, the reaction failed to go to completion. Aldol reactions with lithium, titanium, and tin failed to enhance the stereoselectivity. Also, the enhancement in diastereoselectivity was not sufficient to compensate for the low yields in both aldol condensation and intramolecular ring cyclization. We have found that our original reaction conditions using the chelated boron complex of chiral auxiliaries **9a** and **12**, followed by intramolecular ring cyclization with KH_2PO_4 and

Table 1. Stereoselective aldol condensation and intramolecular ring cyclization of **10a** and **11a** to form dilactones **15a** and **16a**

Entry	Substrate	Enolization conditions	Temp (°C)	Time (h)	Selectivity; yield (%)	
					15a	**16a**
1		Et_2BOTf, DIPEA/CH_2Cl_2	−78 to 0	1	15:1[a] (48)[b]	10:1 (33)
2		Bu_2BOTf, DIPEA/CH_2Cl_2	−78 to 0	1	18:1 (61)	9:1 (28)
3		*n*-BuLi, $ZnCl_2$/THF	−40 to 0	1	20:1 (45)	25:1 (35)
4	**9a** or **12**	LDA/THF	−78	0.5	5:1 (34)	10:1 (37)
5		$TiCl_4/CH_2Cl_2$	−78 to 0	2	10:1 (38)	—[c]
6		$TiCl(OiPr)_3/CH_2Cl_2$	−78 to 0	2	10:1 (30)	—[c]
7		$Sn(OTf)_2/CH_2Cl_2$	−78 to 0	1	5:1 (22)	—[c]

[a] Stereoselectivity was determined by HPLC analysis.
[b] Yield was isolated yield.
[c] No isolation.



Scheme 3. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, reflux, 1 h; then (*S*)-(−)-4-benzyl-2-oxazolidinone, *n*-BuLi/THF, 0 °C, 2 h, 86%; (b) Bu_2BOTf, DIPEA/CH_2Cl_2, −78 °C, 3,4-dimethoxybenzaldehyde or 2,3,4-trimethoxybenzaldehyde, 20 min; (c) KH_2PO_4 (aq), H_2O_2 (28%)/MeOH, 25 °C, 8 h, 80% for **15b**, 83% for **16b**; (d) DIBAL–H/THF, −25 °C, 1 h, 42% for **17b**, 45% for **18b**; (e) Et_3SiH, $BF_3{\cdot}Et_2O/CH_2Cl_2$, −78 °C, 1 h, 51% for **2b**, 50% for **3b**.

H_2O_2 (28%) provided acceptable selectivity and yield for preparation of the furofuran lignans **4**.

Likewise, treatment of oxazolidinone **9b** with aldehydes (3,4-dimethoxybenzaldehyde, 2,3,4-trimethoxybenzaldehyde) in the presence of Bu_2BOTf in dry dichloromethane gave diastereomeric boron complex mixtures, which were subjected to intramolecular ring cyclization with KH_2PO_4 and H_2O_2 (28%) in MeOH to afford dilactones **15b** and **16b** in 80% and 83% yields, with 19:1 diastereomeric selectivity, respectively. Reduction of dilactones **15b** and **16b** with DIBAL-H in THF gave dilactols **17b** and **18b** in good yields, which were treated with Et_3SiH and $BF_3{\cdot}Et_2O$ in dichloromethane to give (−)-eudesmin (**2b**) and (−)-yangambin (**3b**) (Scheme 3). The properties of **2b** and **3b** were identical to the reported spectral and physical data for the these compounds.[12f,l]

In conclusion, we have developed a method for the efficient synthesis of (+)-, (−)-eudesmin and (+)-, (−)-yangambin. This method is useful to generate the core skeleton of furofuran rings by modification of asymmetric aldol condensation.

Acknowledgement

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17. *General procedure for the preparation of dilactones* **15a** *and* **16a**: To a stirred solution of substrates **9a** and **12** (2.2 mmol) in a specified solvent (12 mL) was added dropwise a specified enolizable reagent (4.8 mmol) and DIPEA (8.8 mmol, for boron aldol reagents) at −78 °C, and the reaction mixture was stirred at that temperature for 10 min. A solution of aldehydes (3,4-dimethoxybenzaldehyde, 2,3,4-trimethoxybenzaldehyde; 5.5 mmol) in solvent (THF or CH_2Cl_2; 2 mL) was added dropwise at −78 °C, and the resulting mixture was warmed to −40 or 0 °C for an appropriate reaction time (Table 1). The reaction mixture was quenched by the slow addition of satd aqueous NH_4Cl solution (5 mL). The mixture was warmed to room temperature, and diluted with dichloromethane (10 mL). The organic phase was separated, and the aqueous layer was extracted with dichloromethane (8 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the aldol products **10a** and **11a**,

which were treated with KH_2PO_4 (10 mL), H_2O_2 (10 mL, 28%), MeOH (15 mL), and the resulting mixture was vigorously stirred at room temperature for 8 h. The mixture was extracted with dichloromethane (3×30 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give dilactones, which were purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford pure dilactones **15a** and **16a**. Compound **15a**: Mp 203–204 °C (lit.,[12h,18] 199 °C); IR (neat, NaCl) 3045, 2987, 1780, 1490, 1242, 1045, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 4H), 6.79 (s, 2H), 5.89 (s, 2H), 3.90 (s, 6H), 3.87 (s, 6H), 3.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 149.6, 130.4, 116.7, 111.4, 107.9, 81.8, 56.1, 56.0, 48.4; HRMS calcd for $C_{22}H_{23}O_8$: 415.1393 $[M+H]^+$, found: 415.1398; **16a**: mp 170–171 °C; IR (neat, NaCl) 3030, 2975, 1778, 1600, 1520, 1261, 1045 cm^{-1}; ^1H NMR[12i] (400 MHz, $CDCl_3$) δ 6.51 (s, 4H), 5.87 (s, 2H), 3.87 (s, 12H), 3.81 (s, 6H), 3.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 153.9, 138.3, 133.6, 101.3, 81.6, 60.9, 56.3, 48.5; MS (ESI) (m/z) 475 $[M+H]^+$, 307, 154 (base peak); HRMS calcd for $C_{24}H_{27}O_{10}$: 475.1604 $[M+H]^+$, found: 475.1610.

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