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An efficient asymmetric synthesis of (–)-wodeshiol

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Abstract. An efficient synthesis of (–)-wodeshiol **1** is described. The key reactions include highly stereoselective aldol condensation of piperonal with the dianion of chiral oxazolidinone, subsequent intramolecular ring cyclization of the aldol product **8** and a diastereocontrolled oxygenation of dilactone **7** in good yield.

Keywords. (–)-Wodeshiol; stereoselective aldol condensation; diastereocontrolled oxygenation; intramolecular ring cyclization.

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 plateletactivating 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] Of the furofurans, these compounds containing 4 contiguous stereogenic centers and one or two tertiary hydroxy functions at the bridgehead position such as (–)-wodeshiol **1**,[12] (+)-paulownin **2**,[13] (+)-isogmelinol **3**,[14] (+)-isopaulownin **4**,[13] and (+)-gmelinol **5**,[15] have generated considerable and continued interest due to their unique structural characteristics and stereochemical diversity (figure 1). The only synthesis published for (–)-wodeshiol **1** is that of Corey and Han[16] who synthesized it from the α, β-enone using a chiral oxazaborolidine for catalytic control of absolute configuration.

(–)-Wodeshiol **1** was isolated from *Cleistanthus collinus* or *Kigelia pinnata* by Anjaneyulu group[17] and Inoue group,[18] respectively. These spectra indicated the equatorial disposition of the two aryl groups and showed that positions C–1 and C–5 with dihydroxyl group. In preliminary communications,[19] we reported a method for efficient synthesis of furofuran lignans using highly stereoselective aldol condensation of piperonal and intramolecular ring cyclization of aldol product. As part of our continuing interest in the asymmetric synthesis of furofuran lignans for potential use as anticancer and anti-inflammatory agents, we established a stereoselective aldol condensation and a diastereocontrolled oxygenation to accomplish asymmetric synthesis of (–)-wodeshiol **1**. In this report, we describe an efficient asymmetric synthesis of (–)-wodeshiol **1** through 3 step route from the key starting material dilactone.

2. Results and discussion

The retrosynthetic analysis for (–)-wodeshiol **1** is summarized in scheme 1. We envisioned that (–)-wodeshiol **1** could be synthesized from the key intermediate **7** in 3 steps, which has been prepared, during our synthesis of (+)-sesamin and (–)-sesamin.[20] This precursor was synthesized by intramolecular ring cyclization of chiral complex **8** which was derived from piperonal and 1,4-*bis*-[4-(*S*)-benzyl-2-oxo-oxazolidin-3-yl]butane-1,4-dione through a diastereoselective double aldol condensation in the presence of dibutylboron triflate. The diastereocontrolled oxygenation of inter-

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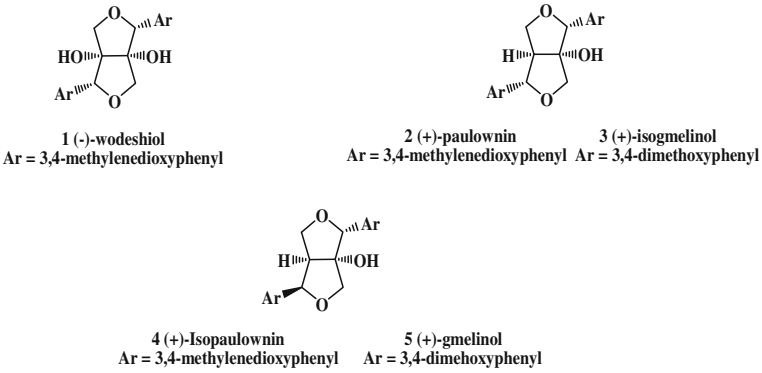
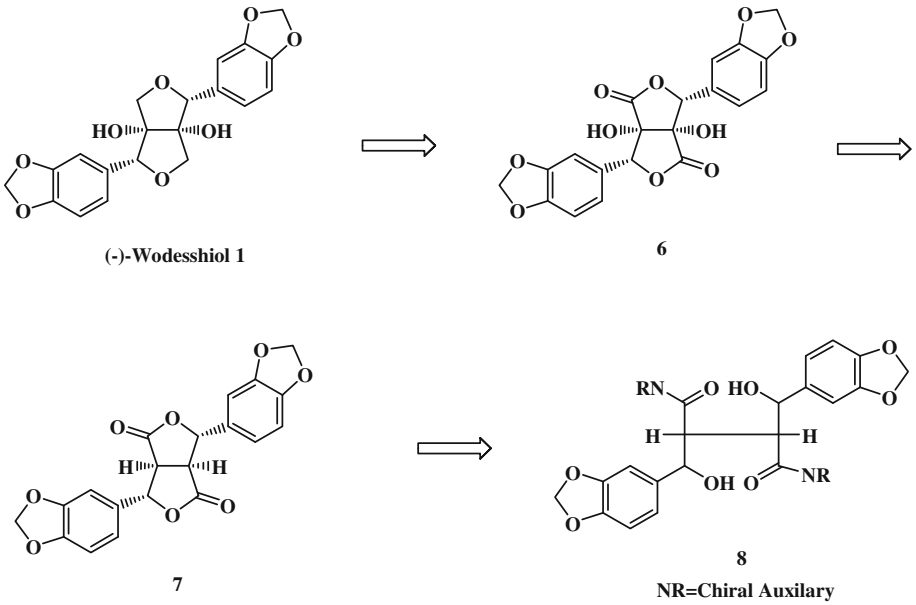


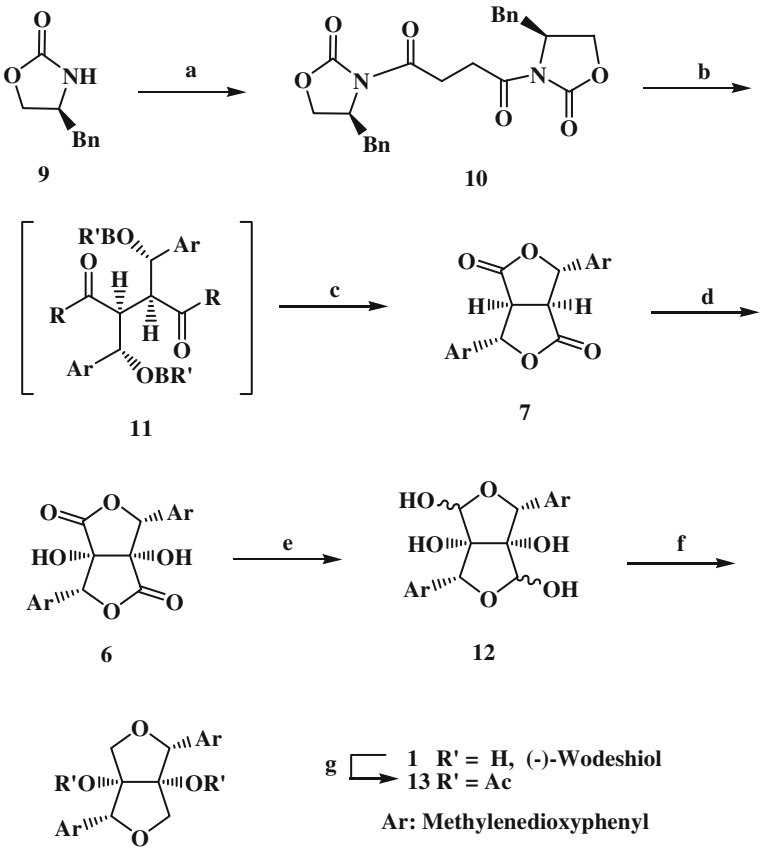
Figure 1. Structures of furofuran lignans with tertiary hydroxy function at the bridge-head position.



Scheme 1. Retrosynthetic analysis of (–)-wodeshiol **1**.

mediate **7** would give the compound **6** which has two –OH groups at α position of bridge-head carbon. Reduction of compound **6** with DIBAL-H, followed by removal of the dihydroxyl groups of the dihydroxy dilactol **12** would give (–)-wodeshiol **1**.

The synthesis of (–)-wodeshiol **1** was accomplished as depicted in scheme 2. The key intermediate **7** was prepared according to the reactions as those used for the synthesis of (+)/(–)-sesamin.[20] Aldol condensation of boron (*Z*)-enolate[21] (generated by treatment of *N*-acyloxazolidinone **10** with dibuthylboron triflate[22] and DIPEA in CH_2Cl_2 at $-78°C$) and piperonal afforded the condensation product **11** as an unstable 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 **7** with 95:5 diastereomeric selectivity, which was determined on the basis of HPLC analysis (91% combined yield for two steps). The diastereocontrolled oxygenation[23] of dilactone **7** with MoOPH produced dihydroxy dilactone **6** in 58% yield. Interestingly, dihydroxy dilactone **6** was treated with benzyl bromide in the presence of bases such as NaH (60%), K_2CO_3, or DIPEA to generate benzyl protected compound. Unfortunately, these reactions failed to give desired product, giving starting material and/or mono-protected product. Reduction of the dihydroxy dilactone **6** with DIBAL-H yielded dihydroxy dilactol **12** (1:1 cis/trans ratio, 65% combined yield). The dihydroxy dilactol **12** was reduced by treatment with Et_3SiH and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to give (–)-wodeshiol **1** in 58% yield. (–)-Wodeshiol **1** could neither be acetylated in the usual way with Ac_2O/pyridine nor oxidized with Jones reagent. However, acetylation of (–)-wodeshiol **1** with Ac_2O/triethylamine in the presence of



Scheme 2. Reagents and conditions: (a) *n*-BuLi, succinyl chloride/THF, 0°C, 2 h, 86%; (b) Bu_2BOTf, DIPEA/CH_2Cl_2, –78°C, piperonal, 20 min; (c) KH_2PO_4(aq), H_2O_2 (28%)/MeOH, rt, 8 h, 88% (two steps); (d) LDA, MoOPH/THF, −78°C, 4 h, 58%; (e) DIBAL-H/THF, −25°C, 8 h, 65%; (f) Et_3SiH, $BF3{\cdot}Et_2O/CH_2Cl_2$, −40°C, 5 h, 58%; (g) Ac_2O, TEA, DMAP, rt, 2 h, 65%.

4-dimethylaminopyridine (DMAP) gave diacetate **13**,[24] which could be easily isolated and characterized.

3. Conclusion

In conclusion, a new and efficient method have been developed for the synthesis of (–)-wodeshiol **1** via a five-step route using a diastereocontrolled oxygenation in overall 10.4% yield. This synthetic method is better than the reported one in view of simplicity, enantiomeric excess and overall yield and should be useful in the synthesis of furofuran lignan which has two tertiary hydroxly groups at bride-head carbon.

Acknowledgement

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    Selected data; **7**: mp. 124–126°C $[\alpha]_D^{20}$ (c 1.0, MeOH); IR (neat, NaCl) 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, CDCl3) 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. (–)-Wodeshiol **1**: mp. 153–154°C (lit.[16] 152–153°C; lit.[12] 150–151°C); $[\alpha]_D^{20} = -11.2$ (c 0.7, $CHCl_3$), (lit.[16] $[\alpha]_D^{23} = -11.7$ in $CHCl_3$; lit.[12] $[\alpha]_D^{24} = -34.6$ in $CHCl_3$); IR (neat, NaCl) 3432, 1602, 1256, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.8–6.6 (m, 6H), 6.05 (s, 4H), 5.13 (s, 2H), 4.0–2.8 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 147.9, 128.3, 120.4, 108.8, 101.4, 87.3, 85.7, 76.3; HRMS calcd for $C_{20}H_{19}O_8$: 387.1080 $[M+H]^+$, found: 387.1091. General procedure for the preparation of dihydroxy dilactone **6**: To a stirred solution of diisopropylamine (0.25 mL, 1.87 mmol), n-BuLi (1.1 mL, 1.87 mmol) in THF (3 mL) at −78°C and dilactone 7 (300 mg, 0.83 mmol) was added to the reaction mixture at −78°C and the mixture was stirred at same the temperature for 1 h. The reaction mixture was treated with MoOPH (1.08 g, 2.49 mmol) at −78°C. As soon as the sparingly soluble reagent has resolved, the reaction was quenched with aqueous sodium sulfite and extracted with ether (3 × 10 mL). The organic phase was washed with 5% HCl and brine. The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give dihydroxy dilactone **6**, which were purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford pure dihydroxy dilactone **6** (199 mg, 58%) as a clean solution. IR (neat, NaCl) 3329, 1780, 1488, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.8 (m, 6H), 6.3 (s, 2H), 6.0 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 148.3, 147.3, 135.2, 120.9, 108.6, 101.4, 97.8, 83.7. HRMS calcd for $C_{20}H_{15}O_{10}$: 415.0665 $[M+H]^+$, found: 415.0652.
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