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Asymmetric Syntheses of (−)-Enterolactone and (7′*R*)-7′-Hydroxyenterolactone via Organocatalyzed Aldol Reaction

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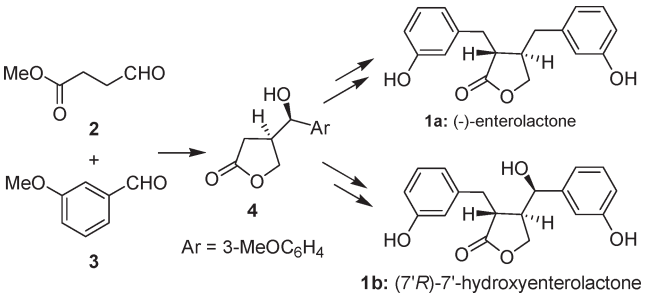
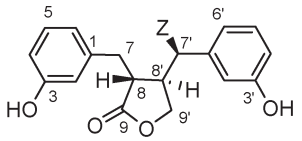


Short syntheses of (−)-enterolactone (**1a**) and (7′*R*)-7′-hydroxyenterolactone (**1b**) have been achieved utilizing organocatalyzed asymmetric cross-aldol reaction of aldehydes **2** and **3** and base-mediated alkylation of lactones **5** and **4**.

Lignan natural products have attracted much interest over the years because of their widespread occurrence in various plant species, varied biological activities, and use in folk medicine.[1] Among them, enterolactone (Z = H, Figure 1), unique in lacking *para* substitution, has been found in human and animal urine.[2] Enterolactone (**1a**) is also formed by the metabolism of plant lignans such as matairesinol, secoisolariciresinol, 7-hydroxymatairesinol, and lariciresinol by intestinal bacteria.[3] Enterolactone displays antiestrogenic and anticarcinogenic activities among other biological profiles.[4] Consequently, it has been the synthetic target of many research groups. The routes to synthesize enantiomerically pure enterolactone include (i) kinetic resolution,[5] (ii) chiral pool approach,[6] (iii) transformation of chiral *N*-alkyl-unsaturated-γ-lactams,[7] (iv) conjugate addition to chiral butenolides,[8] (v) chiral Rh(II)-catalyzed intramolecular insertion,[9] (vi) chemoenzymatic synthesis,[10] (vii) bacterial transformation,[11] (viii) chiral auxiliary directed alkylation,[12] (ix) asymmetric radical reaction,[13] (x) chemical conversion of natural lignans,[14] and (xi) Pd(0)-catalyzed malonate additions.[15] 7′-Hydroxyenterolactone **1b**, differing with enterolactone in carrying a hydroxyl group at the benzylic position of β-benzyl substitution (Figure 1, Z = OH), was detected and tentatively identified in human urine.[16] This mammalian lignan is also derived from the plant lignan 7′-hydroxymatairesinol. 7′-Hydroxyenterolactone has been synthesized by the Wähälä group.[17] Herein, we describe a short route for the asymmetric syntheses of (−)-enterolactone (**1a**) and (7′*R*)-7′-hydroxyenterolactone (**1b**).



1a: Z = H: (-)-enterolactone
1b: Z = OH: (7′*R*)-7′-hydroxyenterolactone

FIGURE 1. General structure of enterolactone and 7′-hydroxyenterolactone.

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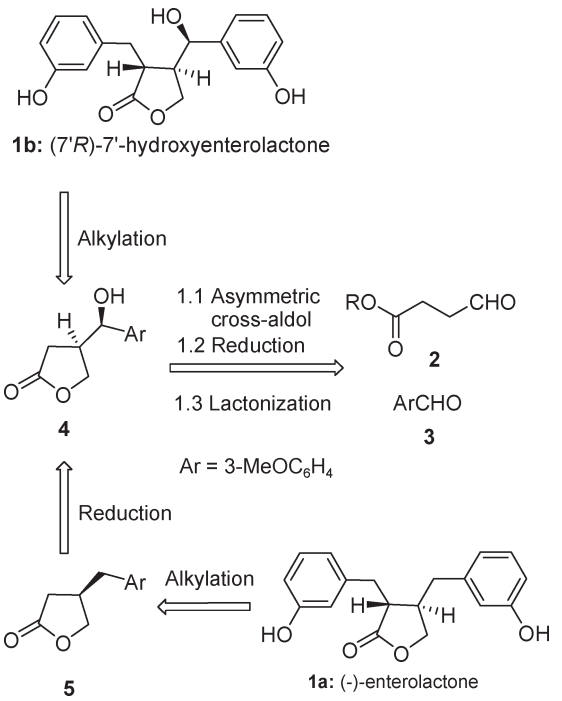
SCHEME 1. Retrosynthetic Analysis for (−)-Enterolactone and (7′*R*)-7′-Hydroxyenterolactone

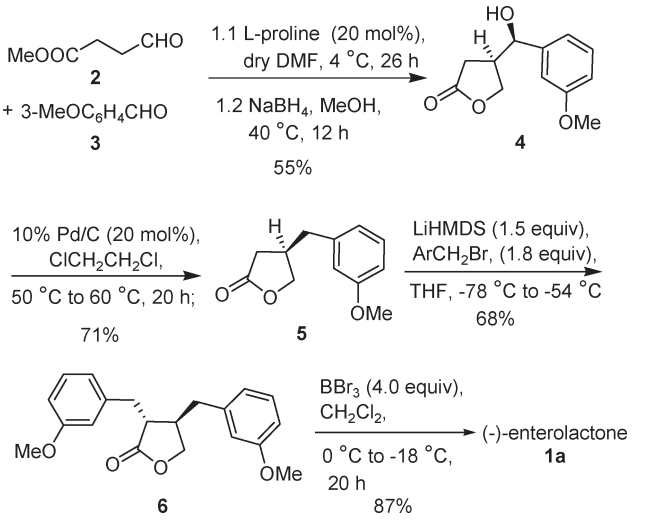


Recently, we reported organocatalytic and enantioselective one-pot syntheses of 4-(hydroxyalkyl)-γ-butyrolactones,[18] which are important synthons for the asymmetric synthesis of γ-butyrolactone-containing natural products,[19] such as dibenzylbutyrolactone lignans and 7′-hydroxybutyrolactones. Thus, we planned a short and divergent route for the asymmetric syntheses of enterolactone **1a** and (7′*R*)-7′-hydroxyenterolactone **1b** utilizing organocatalyzed asymmetric cross-aldol reaction and alkylation as the key steps (Scheme 1).

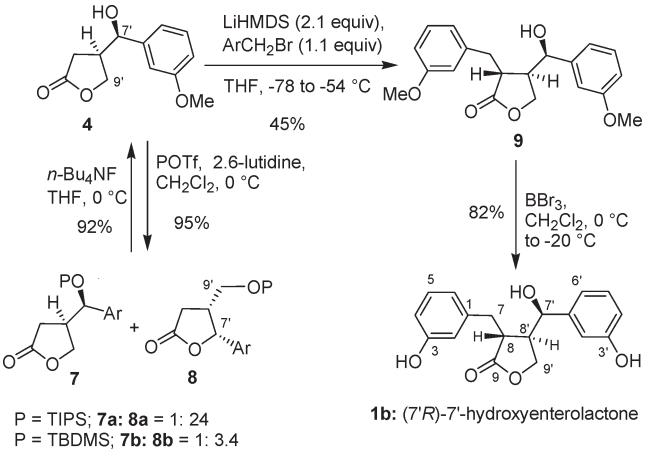
For this purpose, a cross-aldol reaction was carried out by slow addition over 22 h of 4-oxobutyrate **2** (1.0 equiv) to a solution of 3-methoxybenzaldehyde **3** (2.5 equiv) and L-proline (20 mol %) in dry DMF at 4 °C under an argon atmosphere. After an additional 4 h of stirring, the resulting mixture was diluted with methanol at 4 °C. $NaBH_4$ was then added portion wise. This addition was followed by stirring at 35−40 °C for 10 h. Workup of the reaction mixture afforded the desired β-substituted-γ-butyrolactone **4** with high diastereo- (dr > 24:1) and enantioselectivity (ee = 97%) in 55% yield (Scheme 2).

To complete the synthesis of (−)-enterolactone (**1a**) (Scheme 2), dihydrofuran-2-one **4** was subjected to hydrogenolysis at atmospheric pressure of hydrogen over 10% Pd/C in dichloroethane at 50−60 °C for 20 h to produce the compound **5**.[14] The specific rotation $\{[\alpha]^{27}_D$ +6.4 (*c* 1.00, $CHCl_3)\}$[5,7,12] of compound **5** supported, in part, our previously established stereochemistry for β-(hydroxyalkyl)-γ-butyrolactones.[18] Alkylation[9,13] of **5** on successive treatment with LiHMDS and 3-methoxybenzyl bromide afforded lactone **6** with >95:5 *trans*-selectivity. Spectral data and optical rotation, $[\alpha]^{27}_D$ −41.1 (*c* 1.00, $CHCl_3$) {lit.[9b,13] $[\alpha]^{25}_D$ −39.2 (*c* 0.78, $CHCl_3$), $[\alpha]^{25}_D$ −38.8 (*c* 1.06, $CHCl_3$)}, of compound **6** were compared with the literature data. It was converted to the (−)-enterolactone (**1a**) by demethylation using BBr_3 (4.0 equiv) in 87% yield.[9] The specific rotation $\{[\alpha]^{27}_D$ −38.5 (*c* 0.50, $CHCl_3)\}$ of compound **1a** was comparable to reported value.[2c,7,8,13,14] The overall yield for the (−)-enterolactone (**1a**) was 23% from **2** (Scheme 2).

SCHEME 2. Synthesis of (−)-Enterolactone



SCHEME 3. Synthesis of (7′*R*)-7′-Hydroxyenterolactone



En route to the synthesis of (7′*R*)-7′-hydroxyenterolactone **1b** (Scheme 3), the dihydrofuran-2-one **4** was silylated by treating with TIPSOTf and 2,6-lutidine in dichloromethane at 0 °C for 1 h.[20] However, the reaction delivered the rearranged lactone **8a** exclusively in 95% yield, as suggested by spectral data. NMR data of compound **8a** were seen to be comparable with those of the similar type of compounds.[21] In ^1H NMR of lactone **4**, H-7′ appeared as a doublet at δ 4.6 (J = 7.5 Hz), whereas for silylated lactone **8a**, it was found as a doublet at δ 5.63 (J = 6.4 Hz) and two H-9′ of **4** appeared as a multiplet at δ 4.4, but those of compound **8a** came as a doublet at δ 3.36 (J = 5.2 Hz). *cis*-Stereochemistry of rearranged lactone **8a** was suggested by assuming that there was

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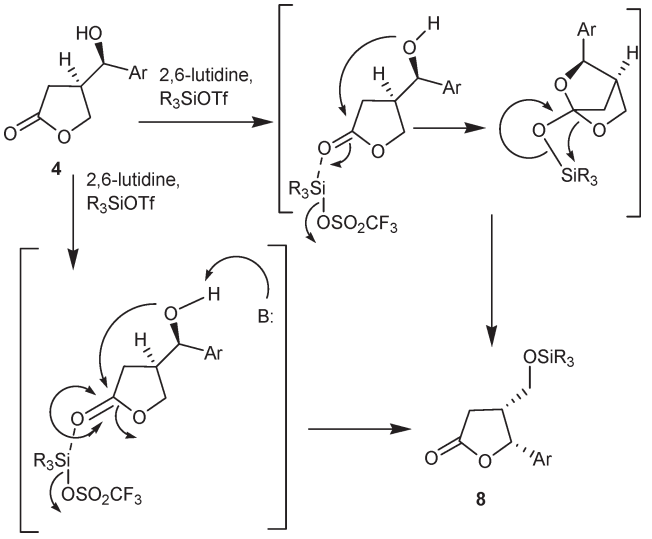
SCHEME 4. Plausible Pathways for Translactonization



no epimerization during rearrangement. This idea was supported when lactone **8a** was desilylated with *n*-Bu_4NF to give lactone **4**. It is also worth mentioning that a minor amount of lactone **8** (P = H) was detected in the ^{1}H NMR of the crude reaction mixture during the synthesis of lactone **4**, in particular, prior to stirring of the reaction mixture at 40 °C (Scheme 2). When the silylating reagent was changed from TIPSOTf to TBDMSOTf, both the lactone **7b** and rearranged lactone **8b** were obtained as an inseparable mixture in 1:3.4 ratio as depicted from ^{1}H NMR. Protection of **4** with nonsilylating agent, such as 3,4-dihydropyran (DHP), provided an inseparable and uncharacterized mixture of compounds. There was no reaction of **4** with MOMCl. To circumvent the lactone rearrangement, a direct alkylation of the unprotected **4** was performed with 2.1 equiv of LiHMDS at −78 °C followed by treatment with 1.1 equiv of 3-methoxybenzyl bromide. It provided the desired alkylated product **9** in 45% yield along with recovery of 30% of lactone **4**. Stereochemistry of compound **9** was assigned by analogy[9,22] and spectral analysis. It is known in the literature[17a] that the H-7′*S* signal of ^{1}H NMR for 7′-hydroxybutyrolactone lignans appears at δ 4.6, while that of H-7′*R* is at δ 4.4, irrespective of the aromatic substitutions. In the ^{1}H NMR spectrum of **9**, the H-7′*R* signal appeared at δ 4.39 as a doublet (J = 6.0 Hz), which is in good agreement with literature data for similar compounds.[17a] Formation of corresponding *cis*-alkylated product and rearranged lactone[17a] was not observed. Demethylation of **9** using BBr_3 afforded (7′*R*)-7′-hydroxyenterolactone **1b** in 82% yield. The specific rotation of **1b** was found as $[\alpha]^{25}_D$ −13.0 (*c* 1.5, acetone), and overall yield for the hydroxyenterolactone was 20% from **2**. It is to be noted that the ^{1}H NMR data of compound **1b** did not match with the spectral data of the racemic compound reported by Wähälä et al.,[17a] but the ^{13}C NMR matched perfectly.

Formation of the rearranged lactone **8a** may be explained via the pathways as shown in Scheme 4, where chelation of carbonyl oxygen with R_3SiOTf activates it toward translactonization via either stepwise or a concerted mechanism.

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In conclusion, we have developed an efficient, short, and divergent route for the asymmetric syntheses of (−)-enterolactone **1a** and (7′*R*)-7′-hydroxyenterolactone **1b** via organocatalytic asymmetric cross-aldol reaction and alkylation as the key steps.

Experimental Section

(4*R*,4′*R*)-4-[4′-Hydroxyl-(3-methoxyphenyl)methyl]dihydrofuran-2-one (4). 3-Methoxybenzaldehyde **3** (0.88 g, 6.46 mmol, 2.5 equiv) was taken in dry DMF (3.5 mL) under argon atmosphere and cooled to 4 °C. L-Proline (0.058 g, 0.52 mmol, 0.2 equiv) was added and stirred for 2 min. Methyl 4-oxobutyrate (**2**) (0.30 g, 2.58 mmol, 1.0 equiv) dissolved in dry DMF (1.5 mL) was added slowly over 22 h through a syringe pump. After an additional 4 h, dry methanol (1.5 mL) was added to the reaction mixture followed by portion wise addition of sodium borohydride (0.152 g, 4.01 mmol). Low-temperature bath was removed, and the reaction mixture was stirred at 35−40 °C for 10 h. It was quenched with saturated ammonium chloride solution (30 mL) and extracted with dichloromethane (3 × 75 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. HPLC analysis revealed the enantiomeric ratios, where enantiomers were identified on comparing with HPLC analysis of the same reaction catalyzed by D-proline. Diastereomeric ratios were measured from ^{1}H NMR spectrum analysis. Purification by flash column chromatography of the crude using petroleum ether and EtOAc as an eluent afforded 0.316 g (55%) of β-(hydroxyphenylmethyl)-γ-butyrolactone **4**: $[\alpha]^{27}_D$ +46.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30−7.22 (m, 1H), 6.95−6.85 (m, 3H), 4.6 (d, J = 7.5 Hz, 1H), 4.45−4.3 (m, 2H), 3.8 (s, 3H), 3.0−2.8 (m, 1H), 2.5−2.3 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.8, 159.5, 143.1, 129.5, 117.6, 113.1, 111.3, 74.53, 69.8, 54.8, 41.9, 30.9; HPLC analysis, Chiralpak AD-H (hexane/*i*-PrOH = 93/7, flow rate = 1.0 mL/min, 230 nm, 25 °C); t_R 26.7 min and t_R 41.2 min (ee 97%); HRMS found m/z 245.0786 $[M + Na]^+$, calcd for $C_{12}H_{14}O_4Na$ 245.0790; FTIR ($CHCl_3$) υ_{max} 3445, 1763, 1655, 1610, 1491, 1459, 1260, 1188, 1020, 789, 705 cm^{-1}.

(4′*R*,4*R*,3*R*)-4-[Hydroxy-(3-methoxyphenyl)methyl]-3-(3-methoxybenzyl)dihydrofuran-2-one (9). To a cold (−78 °C) solution of lactone **4** (0.20 g, 0.9 mmol, 1.0 equiv) in 4 mL of THF under argon atmosphere was added dropwise LiHMDS (1.9 mL, 1.0 M in THF, 1.89 mmol, 2.1 equiv) over a period of 5 min. After stirring at that temperature for 1 h, a solution of 3-methoxybenzyl bromide (0.99 mmol, 0.20 g, 1.1 equiv) in THF (2 mL) was added dropwise over a period of 5 min. The reaction mixture was then slowly warmed to −54 °C and stirred at this temperature for 20 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography using ethyl acetate/petroleum ether as eluent to afford 0.14 g of the alkylated product **9** as a light yellow oil in 45% yield along with recovery of 0.06 g of starting lactone **4** (30%): $[\alpha]^{25}_D$ −13.98 (*c* 3.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27−7.14 (m, 2H), 6.84−6.63 (m, 6H), 4.39 (d, J = 5.8 Hz, 1H), 4.32 (dd, J = 9.4 Hz, 7.4 Hz, 1H), 4.0 (dd, J = 9.2 Hz, 8.0 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.92−2.78 (m, 3H), 2.59−2.52 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.6, 159.9, 159.8, 143.3, 139.2, 129.8, 129.6, 121.5, 117.9, 114.7, 113.6, 112.4, 111.2, 73.3, 67.3, 55.2 (2C), 46.4, 42.9, 35.3. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.85; H, 6.62.

(3*R*,4′*R*,4*R*)-3-(3-Hydroxybenzyl)-4-[hydroxyl-(3-hydroxyphenyl)methyl]dihydrofuran-2-one (1b). To a rapidly stirred solution of lactone **9** (0.20 g, 0.58 mmol, 1.0 equiv) in 15 mL of anhydrous CH_2Cl_2 at 0 °C was added BBr_3 (2.90 mL, 1.0 M solution in CH_2Cl_2, 2.90 mmol, 5.0 equiv) dropwise during 5 min. Stirring was continued at 0 °C for 1 h and then at −18 °C. After 10 h, the reaction mixture was quenched with water (10 mL),

DCM layer was separated, and the aqueous layer was extracted three times with diethyl ether. DCM layer and ether layers were separately washed with brine, combined, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using diethyl ether/dichloromethane as eluent to provide 0.15 g of **1b** as a colorless semisolid in 82% yield: $[\alpha]^{25}_D$ −13.04 (*c* 1.50, acetone); ^{1}H NMR (200 MHz, acetone-d_6) δ 8.28 (br s, 1.6H), 7.64 (br s, 0.4H), 7.12 (m, 2H), 6.8−6.65 (m, 6H), 4.69 (d, J = 4.2 Hz, 1H), 4.51 (t, J = 4.2 Hz, 1H), 4.19 (t, J = 8.6 Hz, 1H), 3.87 (t, J = 8.6 Hz, 1H), 3.05−2.85 (m, 2H), 2.79 (t, J = 6.2 Hz, 1H), 2.66−2.57 (m, 1H); ^{13}C NMR (50 MHz, acetone-d_6) δ 179.1, 158.4 (2C), 146.0, 140.7, 130.3 (2C), 121.6, 117.8, 117.2, 115.2 114.5, 113.7, 73.0, 67.6, 47.3, 43.5, 35.6.

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Supporting Information Available: Synthetic details and characterization data for compounds **1a**, **1b**, **4**, **5**, **6**, **8a**, and **9** as well as copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1b**, **4**, **5**, **8a**, and **9** and HPLC chromatogram for compound **4** and its enantiomer. This material is available free of charge via the Internet at http://pubs.acs.org.