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Organocatalytic and Enantioselective Synthesis of β-(Hydroxyalkyl)-γ-Butyrolactones

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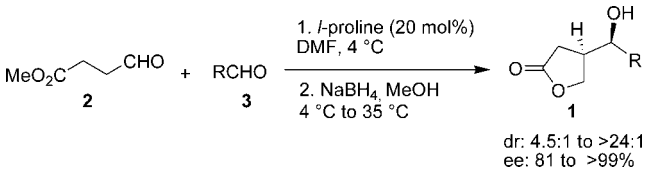
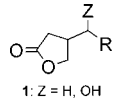


Organocatalytic cross-aldol reaction of methyl 4-oxobutyrate (**2**) and a variety of aldehydes **3** followed by reduction with $NaBH_4$ has provided a one-pot, general and efficient method for the synthesis of 4-(hydroxyalkyl)-γ-butyrolactones **1** with high diastereo- (dr > 24:1) and enantioselectivity (ee > 99%).

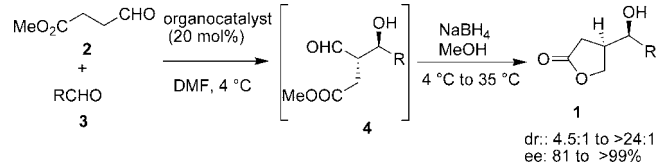
β-Substituted-γ-butyrolactones are important structural motifs of a wide range of natural products and pharmaceuticals.[1] Consequently, the asymmetric synthesis of the lactones with general structure **1** constitutes an active area in organic synthesis. A number of strategies have been developed for the asymmetric



1: Z = H, OH

synthesis of **1** (Z = H). These include (i) diastereoselective conjugate addition to chiral butenolides,[2] (ii) asymmetric radical reaction,[3] (iii) dichloroketene addition to optically active alkenyl sulfoxide,[4] (iv) chiral auxiliary directed alkylation,[5] from L-malic acid via chiral *N*-alkyl-unsaturated-γ-lactams[6] and from L-glutamic acid,[7] and (v) enzymatic resolution.[8] Catalytic asymmetric hydrogenation of itaconic acid derivatives followed by chemoselective reduction-lactonization[9] and chiral Rh(II)-catalyzed enantioselective intramolecular C−H insertion of alkyl diazoacetates[10] are the catalytic asymmetric synthesis of **1** (Z = H). On the contrary, that of β-(hydroxyalkyl)-γ-butyrolactone **1** (Z = OH) is achieved only by enzymatic resolution[11] and from L-glutamic acid via a number of steps.[12] Herein, we report one-pot synthesis of β-(hydroxyalkyl)-γ-butyrolactones **1** (Z = OH) with high enantioselectivity (ee: 81 to >99%) and moderate to good diastereoselectivity (dr: 4.5:1 to >24:1) via an organocatalytic cross-aldol reaction of methyl 4-oxobutyrate (**2**) with acceptor aldehydes **3** followed by $NaBH_4$ reduction (Scheme 1).

SCHEME 1. Organocatalytic One-Pot Synthesis of Lactone 1



Asymmetric organocatalysis[13,14] and organocatalytic aldol reactions[15,16] are a vigorously active area. Among the organocatalysts, proline and its derivatives have become very attractive because of their efficiency, simplicity and wide applicability.[14]

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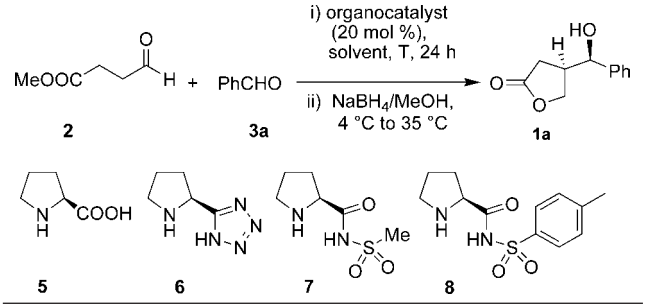
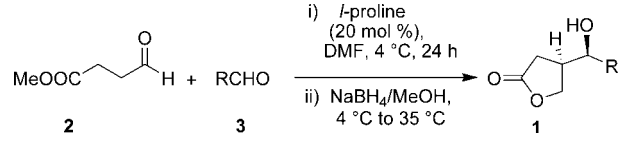
TABLE 1. Synthesis of Lactone 1a by Sequential Cross-Aldol Reaction and Reduction



entry	cat.	temp. (°C)	solvent	dr[a]	ee[b]	yield[c] (%)
1	**5**	4	DMF	10:1	90	47
2	**5**	12	DMF	>24:1	58	55
3	**5**	4	DCM/THF	–	–	–
4	**6**	4	DMF	15:1	84	50
5	**7**	4	DMF	6:1	26[d]	25
6	**8**	4	DMF	–	–	<5

[a] The dr's were determined by the analysis of ^{1}H NMR spectra. [b] The ee's were measured by HPLC (Chiralpak AD-H column) using 2-propanol and *n*-hexane as solvents. Enantiomers of lactone **1a** were identified by HPLC analysis of the reactions with L-proline and D-proline. [c] Combined isolated yield of all isomers of lactone **1a** after flash chromatography. [d] Reverse enantioselectivity, i.e., opposite enantiomer as a major one.

TABLE 2. L-Proline Catalyzed Enantioselective One-Pot Synthesis of Butyrolactones 1



entry	R (equiv. of aldehyde)	product	dr[a]	ee[b]	yield[c] (%)
1	C_6H_5 (5.0)	**1a**	10:1	90	47
2	4-$NO_2C_6H_4$ (2.5)	**1b**	10:1	92[d]	59
3	3-$NO_2C_6H_4$ (2.5)	**1c**	9:1	92[d]	63
4	3-BrC_6H_4 (2.5)	**1d**	4.5:1	81	41
5	4-FC_6H_4 (2.5)	**1e**	12:1	94	47
6	2-naphthyl (2.5)	**1f**	5.5:1	94	50[d]
7	4-$MeOC_6H_4$ (5.0)	**1g**	–	–	<5
8	4-$BzOC_6H_4$ (2.5)	**1h**	16:1	88	55[e]
9	*i*-Pr (5.0)	**1i**	>24:1	>99	50
10	*c*-C_6H_{11} (5.0)	**1j**	12.5:1	>99	55
11	*n*-C_5H_{11}[f]	**1k**	Mixture of products		

[a] The dr's were determined by the analysis of ^{1}H NMR spectra. [b] The ee's were measured by HPLC (Chiralpak AD-H column) using 2-propanol and *n*-hexane as solvents. Enantiomers were confirmed by HPLC analysis of all corresponding lactones obtained by both L-proline and D-proline catalyzed reactions. [c] Combined isolated yield of all isomers of lactone **1** after flash chromatography. [d] The ee's were measured after benzoyl protection of OH. [e] Complete lactonization was obtained on treatment with PPTS. [f] Using 1−5 equiv under different conditions.[19]

The present investigation began with the reaction of methyl 4-oxobutyrate (**2**)[17] and benzaldehyde (**3a**) in the presence of L-proline as a catalyst (Table 1). It was carried out with 4-oxobutyrate **2** (1.0 equiv) and benzaldehyde **3a** (5.0 equiv) in dry DMF containing of L-proline (20 mol %) at 4 °C under an argon atmosphere. Addition of 4-oxobutyrate **2** to the reaction mixture was performed through a microsyringe pump during 22 h to avoid its self-aldol reaction.

After an additional 4 h of stirring, the resulting mixture was diluted with methanol at 4 °C. $NaBH_4$ (0.5 equiv) was then added portionwise. This was followed by stirring at 35−40 °C for 1 h. Work up of the reaction mixture afforded β-hydroxy-phenylmethyl-γ-butyrolactone **1a** with high diastereo-(dr 10:1) and enantioselectivity (ee 90%) in 47% yield (Table 1, entry 1). When conducted at higher temperature (12 °C), a slight increase in yield (55%) and diastereoselectivity at the cost of ee (Table 1, entry 2) was observed. The change of reaction medium gave inferior results with respect to the yields (Table 1, entry 3). We also studied aldol reactions with few L-proline derived catalysts **6**−**8**, which are relatively more soluble in a range of organic solvents.[18] Tetrazole catalyst **6** furnished comparable results with that of L-proline (Table 1, entry 4). Interestingly, catalyst **7** showed inverse enantioselectivity, but with low selectivity and yield (Table 1, entry 5). *N*-Tosyl amide catalyst **8** did not bring about the aldol reaction (Table 1, entry 6), even with more reactive 4-nitrobenzaldehyde under different reaction conditions. Since the intermediate aldol adduct **4a** could not be isolated in pure form, the crude aldol adduct was submitted to reduction with $NaBH_4$ (0.5 equiv) in MeOH to provide **1a** in 22% yield. Thus, proline was found to be the best among all the catalysts studied for the synthesis of lactones **1**. The synthesis was generalized with several substituted aromatic and aliphatic aldehydes (Table 2). Proline-catalyzed reaction of 4-oxobutyrate **2** with aromatic aldehydes **3b**−**e** and 2-naphthaldehyde **3f** followed by in situ reduction provided the lactones **1b**−**f** with 81−94% of ee and moderate-to-good diastereoselectivity (dr: 4.5:1 to 12:1) and yields (entries 2−6).

4-Methoxybenzaldehyde **3g** did not provide the desired butyrolactone under the similar reaction conditions (entry 7), whereas 4-benzoyloxybenzaldehyde **3h** did undergo the reaction and provided the lactone **1h** with 88% of ee in moderate yield (entry 9). Aliphatic aldehydes, i.e., *iso*-butyraldehyde **3i** and cychlohexanecarboxaldehyde **3j**, yielded the lactone **1i** and **1j** with excellent enantioselectivity (>99% ee) and good diastereoselectivity (entries 9 and 10). However, enolizable aldehyde, such as *n*-hexanal, provided an inseparable mixture of products even under different reaction conditions.[19]

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(19) In addition to the general procedure, the reaction was carried out under different conditions, e.g., (a) to a suspension of L-proline in dry DMF at 4 °C, a solution of aldehydes **2** (1.0 equiv) and *n*-hexanal **3k** (1.0 equiv) was added over 22 h, (b) by changing the mole proportions such as using **2** (2.0 equiv) and **3k** (1.0 equiv), and (c) a solution of **2** (2.0 equiv), **3k** (1.0 equiv), and proline (0.2 equiv) in dry DMF was stirred at 4 °C for overnight. All of the attempts led to an inseparable mixture of products.

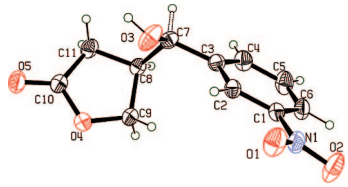

FIGURE 1. ORTEP diagram of lactone **1c**.

The stereochemistry of γ-butyrolactones **1** was established by the comparison with the literature reports[15,20] and the single crystal X-ray analysis of the lactone **1c** (Figure 1).[21]

In summary, we have developed an efficient organocatalyst-based asymmetric synthesis of β-(hydroxyalkyl)-γ-butyrolactones, in particular β-{hydroxyl(arylmethyl)}-γ-butyrolactones **1** with high diastereo-(>24:1) and enantioselectivity (>99%). Proline was found to be the best catalyst among all of the catalysts examined.

Experimental Section

General Procedure for the Synthesis of β-(Hydroxyalkyl)-γ-butyrolactones 1. To a solution of freshly distilled benzaldehyde **3a** (0.685 g, 6.46 mmol, 5.0 equiv) in dry DMF (1.1 mL), cooled to 4 °C, under an argon atmosphere L-proline (0.029 g, 0.26 mmol, 0.2 equiv) was added. The resulting mixture was stirred for 2 min. A solution of methyl 4-oxobutyrate (**2**) (0.15 g, 1.29 mmol, 1.0 equiv) in dry DMF (1.5 mL) was slowly added during 22 h through a syringe pump. After an additional 4 h, dry methanol (1.5 mL) was added to the reaction mixture followed by portionwise addition of sodium borohydride (0.152 g, 4.01 mmol). The reaction mixture was then allowed to stir at 35−40 °C for 1 h. It was quenched with a saturated ammonium chloride solution (50 mL) and extracted by dichloromethane (3 × 75 mL). The combined extracts were washed with water and brine, dried (Na_2SO_4), and concentrated under vacuum. The crude material was purified by flash column chromatography using petroleum ether (60−80)/EtOAc as an eluent to give 0.116 g of β-(hydroxyphenylmethyl)-γ-butyrolactone **1a** (47%; dr 10: 1)).

(4*R*,4′*R*)-4-(4′-Hydroxyphenylmethyl)dihydrofuran-2-one (1a). Gummy liquid, yield: 0.116 g (47%; dr 10:1); $[\alpha]_D^{27}$ +42.97 (c 1.00, $CHCl_3$); ee 90%. Enantioselectivity was determined by HPLC analysis using Chiralpak AD-H column (*n*-Hexane/*i*-PrOH = 90/10, flow rate: 0.75 mL/min, 210 nm, 25 °C) t_R 12.6 min and t_R 16.2 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.3 (m, 5H); 4.66 (d, *J* = 7.6 Hz, 1H); 4.5−4.35 (m, 2H); 3.0−2.82 (m, 1H); 2.40 (dd, *J* = 18.0, 8.8 Hz, 1H); 2.31 (dd, *J* = 18.0, 7.6 Hz, 1H); 2.236 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 141.7, 128.8 (2C), 128.4, 126.0 (2C), 75.1, 70.3, 42.4, 31.3. HRMS Found: *m*/*z* 215.0679 $[M + Na]^+$; Calc. for $C_{11}H_{12}O_3Na$ 215.0684. FTIR ($CHCl_3$) υ_{max} 3439, 2920, 1770, 1182, 1023, 767, 704 cm^{-1}.

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Supporting Information Available: Spectral data, spectra and chromatograph of lactones **1**, and CIF of **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Crystal data for **1c**: $C_{11}H_{11}NO_5$, MW = 237.21, *T* = 293(2) K, Monoclinic, *P*21, *a* = 6.0650(10) Å, *b* = 5.9654(9) Å, *c* = 14.695(2) Å, β = 91.142(5)°. *V* = 531.55(15) Å^3. *Z* = 2, ρ_{calcd} = 1.482 Mg/m^3, μ = 0.119 mm^{-1}, γ = 0.71073 Å, $2\theta_{max}$ = 56.64, reflection collected/unique = 7909/2797, R_{int} = 0.0264, *R1* = 0.0444, *wR2* = 0.1020 for 2150 reflections [$I > 2\sigma(I)$], Flack(×) parameter = 0.0(10).