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Lipase-Catalyzed Preparation of Optically Active γ-Substituted-methyl-γ-butyrolactones

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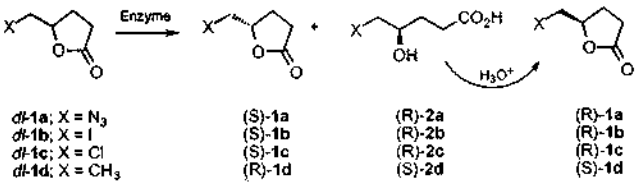
Optically active γ-substituted-methyl-γ-butyrolactones, especially γ-azido-, γ-iodo- and γ-chloromethyl-γ-butyrolactones, are valuable not only as synthons for various types of compounds[1] but as useful chiral auxiliaries.[2] A few methods toward the synthesis of optically active γ-substituted-methyl-γ-butyrolactones have been reported, *i.e.*, asymmetric iodolactonization[3] with the aid of a chiral auxiliary and asymmetric reduction of γ-ketobutyric acid followed by lactonization.[4] Another method based on chiral glutamic acid as a chiral pool has also been reported.[5] All of them requires multi-step reaction sequences to elaborate the synthesis of both enantiomers. Due to the usefulness of γ-substituted-methyl-γ-butyrolactones, resolution of racemates has been adopted as a method of rapid preparation of both enantiomers. Though the enzymatic hydrolysis[6] of γ-alkyl-γ-butyrolactones has been studied to a certain extent, preparation of synthetically more valuable γ-substituted-methyl-γ-butyrolactones remains to be investigated.[7,8] We report herein the results and characteristics of the enzyme-mediated resolution of γ-substituted-methyl-γ-butyrolactones with azide (**1a**), iodine (**1b**), chlorine (**1c**) and methyl (**1d**) substituents. This appears to be the first example to prepare these lactones by lipase-mediated resolution, though ample examples[9] have been reported for the preparation of other types of γ-lactones *via* lipase-reactions. This study also provides an insight into the effects of the substituents located at four bonds away from the reaction center.

The racemic substrates of γ-chloro- and γ-azidomethyl-γ-butyrolactones were prepared by chlorination and azidation of γ-iodomethyl-γ-butyrolactone with LiCl and NaN_3 respectively. The resolutions were carried out with several different hydrolytic enzymes such as *Porcine pancrease* lipase (PPL), Lipase Amano AY of *Candida* sp. (AYL), Lipase Amano PS of *Pseudomonas* sp. (PSL) and Pig liver esterase (PLE).



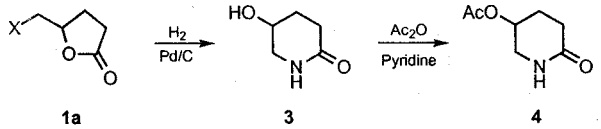
Scheme 1.

At first intensive studies were carried out with γ-azidomethyl-γ-butyrolactone (**1a**) as a substrate due to its wide applicability by changing solvent, enzyme, and reaction time. The reaction of azidolactone with PPL proceeded in phosphate buffer (pH 7.2) without significant discrimination of one enantiomer from the other (entries 1 and 2). In the pure organic solvents of hexane reaction proceeded much faster with similar enantioselectivity as in buffer (entry 3). Addition of acetone to phosphate buffer (1/1, v/v) stopped the reaction completely due to possible destruction of the enzyme. Addition of hexane into the phosphate buffer accelerated the PPL-mediated reaction with better enantioselectivity (entries 4-7). With enzymes of AYL or PSL in the mixed media of buffer and hexane (1 : 3, v/v) resolution was not successful either by retarded reaction rate or by poor selectivity. (entries 8 and 9) The reaction with the esterase enzyme of PLE proceeded faster than with PPL in phosphate buffer (entry 10). But the resolution was poor. The best result was obtained with PPL in the mixed solvent of phosphate buffer and hexane (1 : 3, v/v) (entries 6 and 7). (S)- and (R)-**1a** from entries 6 and 7 were hydrogenated with Pd C followed by acetylation to afford 5-acetyloxy-2-oxopiperidine (**4**).[5a] Enantioselectivity was re-evaluated with the resolved acetyl peaks of 5-acetyloxy-2-oxopiperidine in the NMR in the presence

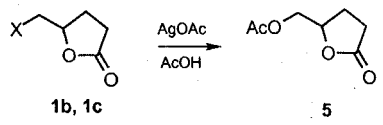
Table 1. Results of the enzyme-mediated resolution of racemic γ-substituted-methyl-γ-butyrolactones **1a**, **1b**, **1c** and **1d**

Entry	Subst.	Reaction conditions[a]					Unreacted lactone[b]			Lactone from Acid[b]			E[f]
		Enz.	Subst./Enz.[c]	Solvent[d]	RxnTime (h)	Convn.[e] (%)	Yield (%)	e.e.	Conf.	Yield (%)	e.e.	Conf.	
1	(±)-**1a**	PPL	3.0	Buffer	8	27	67	23	S	22	63	R	4
2	(±)-**1a**	PPL	3.0	Buffer	24.5	61	39	34	S	40	22	R	6
3	(±)-**1a**	PPL	3.0	Hexane	1	36	43	38	S	20	68	R	5
4	(±)-**1a**	PPL	3.0	Buffer:Hexane=1:1	4	36	60	41	S	30	73	R	7
5	(±)-**1a**	PPL	3.0	Buffer:Hexane=3:1	8	41	54	49	S	34	70	R	7
6	(±)-**1a**	PPL	3.0	Buffer:Hexane=1:3	8	55	37	76(78)[g]	S	51	62	R	8
7	(±)-**1a**	PPL	3.0	Buffer:Hexane=1:3	1	25[e]	–	–	–	21	81(80)[g]	R	7
8	(±)-**1a**	AYL	3.0	Buffer:Hexane=1:3	21.5	10[e]	78	5	S	–	–	–	–
9	(±)-**1a**	PLE	3.0	Buffer:Hexane=1:3	3.7	51[e]	47	30	S	–	–	–	–
10	(±)-**1a**	PPL	3.0	Buffer	8	40	56	32	S	31	49	R	4
11	(±)-**1b**	PPL	3.0	Buffer	4.3	61	35	61	S	38	39	R	9
12	(±)-**1b**	PPL	3.0	Buffer:Hexane=1:3	1.5	54	43	81(86)[g]	S	44	74	R	12
13	(±)-**1b**	PPL	3.0	Buffer:Hexane=1:3	1	35[e]	–	–	–	28	86(85)[g]	R	12
14	(±)-**1c**	PPL	3.0	Buffer	26	57	26	43	S	33	33	R	5
15	(±)-**1c**	PPL	3.0	Buffer:Hexane=1:3	6	55	31	70(72)[g]	S	37	58	R	7
16	(±)-**1c**	PPL	3.0	Buffer:Hexane=1:3	1	25[e]	–	–	–	19	78(81)[g]	R	8
17	(±)-**1d**	PPL	3.0	Buffer	12	39	52	36	R	28	57	S	5
18	(±)-**1d**	PPL	3.0	Buffer:Hexane=1:3	4	51	41	71	R	43	68	S	8
19	(±)-**1d**	PPL	3.0	Buffer:Hexane=1:3	5.5	60	25	82	R	55	53	S	10

[a]All reactions were carried out at 30 °C. [b]The absolute configurations and e.e. values were deduced from their optical rotations and comparison with those of the known. [c]Weight/weight. [d]Buffer solution (Na_2HPO_4, 0.1 M, pH=7.2), n-Hexane; volume/volume. [e]Conv. was calculated by ee (unreacted lactone/[ee(unreacted lactone)+ee (lactone from acid)]. [f]E value=ln[1-conv.(1+$ee_{product}$)]/ln[1-conv.(1-$ee_{product}$)]. [g]Conv. rate was determined by the NaOH consumption. [h]The e.e. value in the bracket was obtained from the NMR analysis in the presence of 0.3 mol equiv. of Eu(hfc)$_3$ after conversion to 5-acetyloxy-2-oxopiperidine. [i]The e.e. values in the bracket were obtained from the NMR analysis in the presence of 0.3 mol equiv. of Eu(hfc)$_3$ after conversion to γ-acetoxymethyl-γ-butyrolactones.



Scheme 2.



Scheme 3.

of 30 mol% of Eu(hfc)$_3$.

The same condition to resolve γ-azidomethyl-γ-butyrolactone was applied to other substrates. Successful resolutions of γ-iodomethyl-γ-butyrolactone (**1b**) and γ-chloromethyl-γ-butyrolactone (1c) with ≥70% e.e. were achieved in moderate yields under the same conditions of mixed solvents (entries 12, 13, 15 and 16). Resolved (R)- and (S)-halolactones were converted to γ-(acetyloxy)methyl-γ-butyrolactone (**5**) by the reaction with AgOAc in AcOH. Enantioselectivity was re-evaluated with the resolved acetyl peaks of this compound in the NMR in the presence of 30 mol% of Eu(hfc)$_3$.

The similar results were observed with γ-caprolactone (**1d**) (entries 17-19). As seen in the entry 19, 82% e.e. of unreacted lactone was obtained at 60% conversion in the mixed solvents. With the same substrate the reaction was retarded in phosphate buffer with poorer enantioselectivity. The PPL-catalyzed reactions of γ-substituted-methyl-γ-butyrolactones in phosphate buffer proceeded slower than in the mixed or pure hexane medium with comparably lower enantioselectivity possibly due to insolubility of the substrate (entries 1, 2, 11, 14 and 17). The reaction time to reach about 51-55% conversion in the mixed solvent of the phosphate buffer and hexane (1/3, v/v) depended on the substituents, *i.e.*, 8, 1.5, 6 and 4 h with the substituents of N_3, I, Cl, and CH_3 respectively. At this point unreacted lactones were obtained with 78, 86, 72 and 71% e.e. (entries 6, 12, 15 and 18). The similar enantioselectivities of 72%, 60% and 76% e.e. were reported for the compounds with the substituents of X=C_2H_5, C_4H_9, and C_6H_{13}, respectively at 55% conversion of PPL-mediated resolution.[7] This observation gives some insights into the PPL-mediated hydrolytic reactions of γ-substituted-methyl-γ-butyrolactones. On the view point of enantioselectivity no significant deviation was observed from the difference in electronic characteristics and bulkiness of substituents at γ-methyl position while there is a noticeable difference on the reaction rate. In conclusion, we have successfully achieved

the PPL enzyme-mediated resolution of synthetically useful γ-substituted-methyl-γ-butyrolactones in good yields.

Experimental

^1H, ^{13}C NMR spectra were recorded on a Gemini 200 (200 MHz for ^1H and 50.3 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as internal standard. Elemental analysis was taken on a Perkin-Elmer 240 DS elemental analyzer. Optical rotations were measured with Rudolph Research Autopole 3 spectrometer. γ-Caprolactone (**1a**) was purchased from Aldrich. All other reagents and solvents were purchased from commercial sources. PLE and PPL were purchased from Sigma and AYL and PSL were obtained from Amano Pharmaceutical Co., Ltd.

Enzymatic Resolution of Racemic γ-Lactones. -Specified amount of the crude enzyme on the table was added to a stirred solution of γ-substituted-methyl-γ-butyrolactone (**1**) (0.72 mmol) in the specified solvent (15 mL). The resulting solution was stirred well at 35 ℃ while pH of the solution was maintained to 7.2 by adding NaOH solution (0.1 M). After the conversion of the reaction reached at certain percentage according to NaOH consumption, the reaction was quenched by adding celite and ice. The cake was filtered through Celite with water and EtOAc. Unreacted starting lactone was extracted with EtOAc. Hydroxy acid (**2**) in aqueous layer was acidified with c-HCl to pH 1.0 and stirred overnight to convert to γ-butyrolactone. After the conversion was complete the product was extracted with EtOAc. The combined organic layer was washed with water twice, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give product. For analysis the products were purified by flash chromatography on silica gel.

dl-γ-Iodomethyl-γ-butyrolactone dl-1b. -Aqueous $NaHCO_3$ (0.6 M, 250 mL, 0.15 mol) was added to 4-pentenoic acid (5 g, 0.05 mol) and the resultant solution was stirred until effervesce disappeared. Potassium iodide solution (49.8 g, 0.3 mol) in water (150 mL) was added dropwise at room temperature and stirred in the dark. After 4 h water (100 mL) and CH_2Cl_2 (300 mL) were added. To this solution was added $Na_2S_2O_3$ until the color of this solution was discharged. The two phases were separated. The aqueous layer was extracted with CH_2Cl_2 twice (100 mL×2). The combined organic layer was washed with water twice, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give crude product. Purification by flash chromatography gave 10.1 g of colorless oily product in 89% yield. δ_H ($CDCl_3$; J/Hz) 1.88-2.07 (1H, m), 2.38-2.53 (1H, m), 2.48-2.66 (2H, m), 3.47 (2H, d, J=11.2), 4.58 (1H, quin, J=5.4); δ_C ($CDCl_3$) 9.23, 27.6, 28.6, 78.1, 176.0.

(S)-(-)-γ-Iodomethyl-γ-butyrolactone (S)-1b. -To a stirred solution of (S)-(+)-γ-Mesyloxymethyl-γ-butyrolactone[5c] (0.5 g, 2.57 mmol) in CH_3CN KI (0.85 g, 5.12 mmol) and 18-crown-6 (0.13 g) was added. The resultant solution was refluxed for 12 h for the reaction to be completed. The reaction product was extracted with EtOAc (3×80 mL). The organic layer was washed successively with water and brine twice, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give crude product. It was further purified by column chromatography to give 0.42 g of pure product in 72% yield. $[\alpha]_D^{20}=-19.9$ (c=0.2, $CHCl_3$) (lit.[2] $[\alpha]_D^{20}=-15.4°$ (c=1.75, $CHCl_3$)).

dl-γ-chloromethyl-γ-butyrolactone dl-1c. -Lithium chloride (0.75 g, 17.7 mmol) was added to γ-iodomethyl-γ-butyrolactone (2.0 g, 8.85 mmol) in DMF (20 mL). The resulting solution was refluxed under N_2 atmosphere for 3 hours. EtOAc (200 mL) was added and the solution was washed with brine three times to remove DMF. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give crude product. Purification by flash chromatography gave 1.09 g of a colorless oil in 92% yield. δ_H ($CDCl_3$; J/Hz) 2.07-2.28 (1H, m), 2.34-2.53 (1H, m), 2.58-2.72 (2H, m), 3.70 (1H, dd, J=9.6, 4.6), 3.79 (1H, dd, J=9.2, 4.6), 4.78-4.84 (1H, m); δ_C ($CDCl_3$) 24.3, 27.8, 45.9, 78.0, 176.4.

(S)-(+)-γ-chloromethyl-γ-butyrolactone (S)-1c. -This was prepared from (S)-(-)-γ-iodomethyl-γ-butyrolactone in the same way for the synthesis of racemates. $[\alpha]_D^{20}=+12.5°$ (c=0.2, $CHCl_3$) (lit.[5a] $[\alpha]_D^{27}=-12.9°$ (c=3.03, $CHCl_3$) for (R)-(+)-γ-chloromethyl-γ-butyrolactone).

dl-γ-azidomethyl-γ-butyrolactone dl-1a. -Sodium azide (8.63 g, 133 mmol) was added to γ-iodomethyl-γ-butyrolactone (**1b**) (10 g, 44.2 mmol) in DMF (100 mL) and stirred at room temperature under N_2 atmosphere. After 48 hours CH_2Cl_2 (200 mL) was added and the solution was washed brine three times to remove DMF. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give crude product. Purification by flash chromatography gave 5.77 g of colorless oily product in 92% yield. δ_H ($CDCl_3$; J/Hz) 1.97-2.12 (1H, m), 2.21-2.43 (1H, m), 2.45-2.68 (2H, m), 3.42 (1H, dd, J=13.1, 4.6), 3.81 (1H, dd, J=13.1, 3.2), 4.58-4.73 (1H, m); δ_C ($CDCl_3$) 24.5, 28.3, 54.2, 78.6, 176.9.

(S)-(-)-γ-Azidomethyl-γ-butyrolactone (S)-1a. -This was prepared from the reported method.[5(c)] $[\alpha]_D^{20}=+98.4°$ (c=0.2, $CHCl_3$) (lit.[5(c)] $[\alpha]_D^{20}=+98.2°$ (c=2.0, $CHCl_3$)).

5-Acetyloxy-2-oxopiperidine (R)-4. -To a stirred solution of γ-azidomethyl-γ-butyrolactone (11.5 mg, 0.08 mmol) obtained from PPL mediated resolution in MeOH (20 mL) was added Pd·C (2.5 mg). The reaction vessel was filled with H_2 under atmospheric pressure at room temperature. The resultant solution was stirred for 4 hr. The reaction mixture was filtered over Celite and concentrated under reduced pressure. This crude reaction product was recrystallized from methanol to give 6.1 mg of white crystalline product of 5-hydroxy-2-oxopiperidine (**3**) in 66% yield. δ_H ($CDCl_3$; J/Hz) 1.90-2.07 (2H, m), 2.28-2.58 (2H, m), 3.24 (1H, dd, J=14.0, 3.7), 3.46 (1H, dd, J=13.1, 3.7), 4.20 (1H, quin, J=3.9), 4.7 (2H, s); δ_C ($CDCl_3$) 27.7, 27.9, 49.0, 63.8, 176.9. Acetic anhydride (44.3 mg, 0.43 mmol) was added to 5-Hydroxy-2-oxopiperidine (6 mg, 0.05 mmol) in pyridine (1 mL) and stirred well to for 4 h at room temperature. After the reaction was complete methanol (1 mL) was added and stirred well for 1 hr. Then water (1 mL) was added and the mixture was stirred overnight. Pyridine (1 mL) was added and the resultant solution was distilled under reduced pressure. The reaction product was further purified by column chromatography to give 7.1 mg of pure crystalline product of 5-acetyloxy-2-oxopiperidine (**4**) in 90% yield. mp 100-102 ℃; δ_H ($CDCl_3$; J/Hz) 1.90-2.07 (2H, m), 2.07 (3H, s), 2.31-2.57 (2H,

m), 3.39 (1H, d, J=13.3), 3.54 (1H, dd, J=13.3, 2.8), 5.14 (1H, quin, J=3.6), 7.75 (1H, bs); δ_C ($CDCl_3$) 21.5, 25.4, 27.5, 46.2, 65.9, 170.8, 172.3. (Found: C, 53.6; H, 7.11, N, 8.89. Calc. for $C_7H_{11}NO_3$: C, 53.5; H, 7.05, N, 8.91%).

γ-(Acetyloxy)methyl-γ-butyrolactone dl-5. -Silver acetate (167 mg, 1.0 mmol) was added to γ-iodo- (**1b**) or γ-chloromethyl-γ-butyrolactone (**1c**) (0.2 mmol) obtained from PPL-mediated resolution in acetic acid (10 mL) and stirred at room temperature under N_2 atmosphere. After 1 hour no starting material was left on TLC. CH_2Cl_2 (100 mL) was added and the solution was washed with brine three times to remove acetic acid. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give crude product. Purification by flash chromatography gave colorless oily product (**3**) in 86 and 79% yield from γ-iodo- or γ-chloromethyl-γ-butyrolactone respectively. δ_H ($CDCl_3$; J/Hz) 1.91-2.07 (1H, m), 2.18 (3H, s), 2.24-2.46 (1H, m), 2.52-2.63 (2H, m), 4.13 (1H, dd, J=10.4, 6.2), 4.31 (1H, dd, J=10.4, 3.8), 4.63-4.80 (1H, m); δ_C ($CDCl_3$) 20.5, 23.7, 28.0, 65.2, 77.1, 170.6, 176.6.

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Synthesis of Intercalation Compounds between a Layered Double Hydroxide and an Anionic Dye

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Introduction

Layered double hydroxides (LDHs) are minerals and synthetic materials with positively charged brucite-type layers of mixed-metal hydroxides. Exchangeable anions located in the interlayer spaces compensate for the positive charge of the brucite-type layers. The chemical composition of the LDH is generally expressed as $[M^{2+}_{1-x}M^{3+}_x(OH)_2]^{x+}[(A^{n-})_{x/n}\ H_2O]^{x-}$ with $x=[M^{3+}]/([M^{2+}]+[M^{3+}])$. Here, $M^{2+}=Mg^{2+}$, Co^{2+}, Ni^{2+}, etc., $M^{3+}=Al^{3+}$, Cr^{3+}, etc., and A^{n-} is an interlayer exchangeable anion such as CO_3^{2-}, Cl^-, etc. These ionic layered materials also have been termed "hydrotalcite-like" compounds in the reference to the structural similarity to the mineral hydrotalcite, $[Mg_6Al_2(OH)_{16}][CO_3]\cdot 4H_2O$, or termed "anionic clays" in mirror image resemblance to the cationic clays whose negative charge of the aluminosilicate layers are counterbalanced by the intercalated cations. The preparations, properties, and applications of LDH materials have been studied extensively.[1~7] They are used as adsorbents, catalysts, catalyst precursors, aninoic exchangers, and antacid drugs.[8~11]

There have been several reports on the intercalation of organic anions into the LDH.[12,13] The main synthetic route has been performed by anionic exchange. Among the various organic substances used as the interlayer guest species, dyes are one of the most interesting materials because their host-guest interaction may provide unique structural features and physicochemical properties. Intercalation compounds between a LDH and an anionic dye are expected to have several