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Enzymatic Resolution of 5-Phenylselanyltetrahydro-2-furanone. Enantioselective Preparation of (*R*) and (*S*)-γ-Valerolactone

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ABSTRACT

Lipase-catalyzed lactonization of (**2**) provides both (*R*) and (*S*) enantiomers of 5-phenylselenyltetrahydro-2-furanone (**1**) in good enantiomeric excess. The kinetic resolution was examined using PPL (Porcine pancreatic lipase), PSL (Amano PS, *Pseudomonas* sp. lipase), MML (*Mucor miehei* lipase), CRL (*Candida rugosa* lipase), CAL-B (*Candida Antarctica* lipase, type B) and Novozym 435 (immobilized *C. antarctica* lipase type B) in different solvents. A tributyltin hydride reduction of enantiomerically enriched **1** gave both (*R*) and (*S*) enantiomers of *S*-4-pentanolide (γ-valerolactone).

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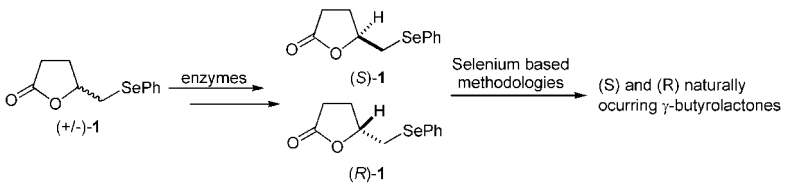
INTRODUCTION

The production of chiral building blocks, which could be used in the synthesis of a wide range of biologically active substances, is in the forefront of the synthetic organic chemistry.[1] The biocatalysis has been one of the methods of choice to meet this goal.[2] Among the chiral fragments often present in natural products of practical importance is the γ-butyrolactone backbone. This unity is present in many substances such as aromas,[3] insect pheromones[4] and plants growth regulators.[5] An easy way to access the γ-butyrolactone unity is the selenolactonization route,[6] which was recently made chiral by using chiral selenium electrophiles.[7]

In view of the already well established carbon–carbon bond formation methodology involving free radical intermediates derived from selenolactones,[8] the availability of chiral selenolactones enhances the synthetic potential of this class of selenium compounds. A drawback of the published methodologies to produce chiral selenolactones is that the expensive chiral selenogroups would be lost during the free radical generation step. A possible solution to this problem would be the enzymatic kinetic resolution of a phenylselenolactone (Sch. 1). To our knowledge only a brief report on the application of biocatalysis to prepare enantiopure selenium compounds was published to date.[9]

With the aim of combining the synthetic potential of the biocatalysis with that of the organoselenium chemistry, in this paper we present our preliminary results on the use of enzymes to produce enantiomerically enriched (*R*) and (*S*)-phenylselenolactones (**1**) starting from racemic phenylselenoesteres (**2**) (Sch. 2). A tributyltin hydride reduction of enantiomerically enriched (*R*) and (*S*)-**1** gave both enantiomers of γ-valerolactone (**6**), which has been widely used as intermediate in the natural products synthesis[10] and in biosynthetic studies.[10]



Scheme 1.

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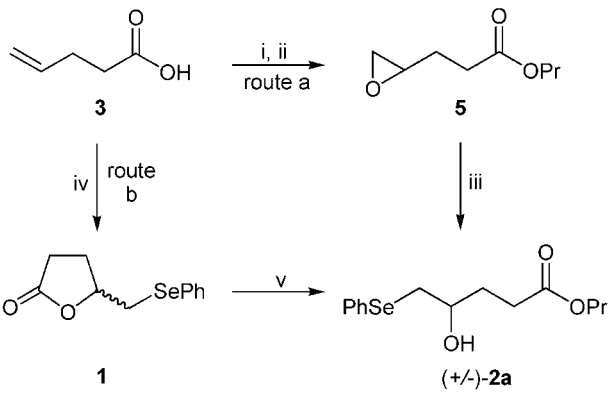


Reagents and conditions: (i) $SOCl_2$, 1 h; n-PrOH, 1 h, 76%; (ii) **4**, MCPBA, CH_2Cl_2, 17 h, 77%; (iii) PhSeNa, -40°C, 2 min, 57 %; (iv) PhSeBr, THF, -78°C⁻ 20°C, 17 h, 75 %; (v) KOH, H_2O, reflux 4 h; n-PrBr, DMF, r.t., 24 h, 75 %.

Scheme 2.

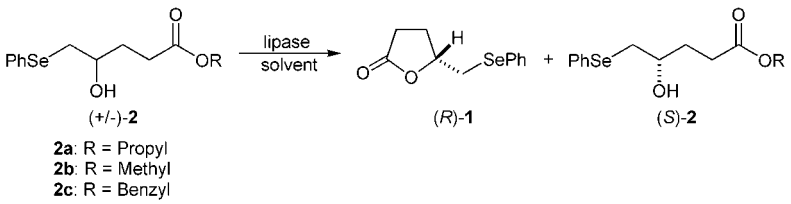
RESULTS AND DISCUSSION

In the search for methodologies to prepare the phenylselenoesteres (**2**), propyl-4-hydroxy-5-phenylselanylpentanoate (**2a**) was synthesized by two different routes as shown in Sch. 2.

By route *a* compound **2a** was obtained in 33% overall yield from 4-pentenoic acid (**3**) by reacting epoxide **5** with the phenylselenolate anion at $-40^{\circ}C$ for 2 min. At room temperature and at reaction times superior to 3 min, the main product formed was the selenolactone **1**. Even at low temperature the lactone **1** was formed, being separated from **2** by column chromatography on silica gel impregnated with triethylamine. By route *b* compound **3** was initially transformed into racemic 5-phenylselenyltetrahydro-2-furanone **1** through a selenolactonization with phenylselanil bromide. Hydrolysis of **1** with KOH followed by an esterefication with propyl bromide afforded **2a** in 56% overall yield from **3**. Since route *b* showed to be a superior method to prepare **2**, it was chosen to synthesize compounds **2b** and **2c**. Care must be taken to manipulate **2**, since heating and trace of acids can lactonize it.

With racemic **2** in hand we performed a systematic evaluation of solvent and lipases to promote the kinetic resolution (Sch. 3).

In a typical experiment, a solution containing 0.2 g of the substrate and 0.2 g of the enzyme in organic solvent (10 mL) were stirred at 30°C. The progress of the reaction was monitored by HPLC and it was stopped when the conversion into lactone **1** reached ca. 50%. Then, the lipase was removed by



Scheme 3.

centrifugation and the resulting solution concentrated. The organic residues were subjected to silica gel chromatography to obtain **1** and unreacted compound **2**. The enantiomeric excesses (e.e.) of **1** were determined by HPLC equipped with an amilose tris(3,5-dimethylphenylcarbamate) chiral phase column, prepared as reported by Cass and Batigalhia.[12] The *E* (enantiomeric ratio) values were calculated from the e.e. of products and the conversion values (c) according to Sih, Sharples and Fajan's equation ($E = \ln [1 - c(1 + e.e._p)/\ln [1 - c(1 - e.e._p)]$).[13] The absolute stereochemistry of the (*R*) and (*S*) phenylselenolactones could be attributed by comparing the $[\alpha]_D$ values of the products obtained by us with those of the literature.[14] The results obtained in the enzymatic lactonizations are summarized in Table 1.

Initially, In order to determine the best enzyme to perform the kinetic lactonization of the racemic phenylselenoesteres **2**, reaction of compound **2a** was examined using PPL (Sigma's porcine pancreatic lipase), PSL (Amano's PS–*Pseudomonas* sp. lipase), MML (Novozyme's *Mucor miehei* lipase), CRL (Sigma's *Candida rugosa* lipase), CAL-B (Roche's *C. antarctica* lipase, type B) and Novozym 435® (Novozyme's immobilized *Candida Antarctica* lipase type B) in diethyl ether. It was observed that the most efficient enzyme to perform this lactonization was Novozym 435® which after 3 hours led to 97% conversion, but with no enantiomeric excess (Table 1, Entry 6). The best enzyme in terms of enantioselectivity was found to be PPL, which transformed **2a** into (*R*)-**1** in 74% e.e. (Table 1, Entry 3).

In an attempt to improve the e.e. of the enzymatic reactions, compound **2a** was allowed to react with PPL in hexane, cyclohexane, toluene, *t*-butyl methyl ether, but these reactions presented inferior results. As observed for substrate **2a**, the *E* values obtained in the enzymatic lactonization of **2b** and **2c** showed that the PPL/diethyl ether is the most efficient combination to perform this transformation. In addition, the similar *E* values calculated for **2a–c** showed that the enantioselectivity of these enzymatic lactonizations was not dependent on the size of the substituents attached to the ester group.

Starting from unreacted (*S*)-**2a**, an acid-catalyzed lactonization using *p*-toluenesulphonic acid (PTSA) was firstly attempted to synthesize (*S*)-**1**.

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Table 1. Lipase-catalyzed kinetic lactonization of **2**.

Entry	Enzyme	R	Solvent	Time (h)	Conversion (%)	R-(−)-**1** ee (%)	*E*-value
1	*Pseudomonas* sp.	Propyl	Diethyl ether	180	31	32	2.2
2	*M. miehei*	Propyl	Diethyl ether	14	47	43	3.6
3	P. pancreas	Propyl	Diethyl ether	39	46	74	12
4	C. rugosa	Propyl	Diethyl ether	160	4	0	—
5	*C. antartia*, B	Propyl	Diethyl ether	160	11	22	1.6
6	Novozym 435	Propyl	Diethyl ether	3	97	0	—
7	P. pancreas	Propyl	Hexane	50	40	61	6.1
8	P. pancreas	Propyl	Toluene	42	42	70	9.3
9	P. pancreas	Propyl	Cyclohexane	40	47	68	9.6
10	P. pancreas	Propyl	^{t}BuME	40	50	64	8.6
11	P. pancreas	Propyl	Diethyl ether	33	43	71	10
12	P. pancreas	Methyl	Cyclohexane	16	47	64	7.9
13	P. pancreas	Benzyl	Diethyl ether	13	49	66	9.2
14	P. pancreas	Benzyl	Cyclohexane	14	50	64	8.6
15	P. pancreas	Benzyl	Hexane	15	43	64	7.8

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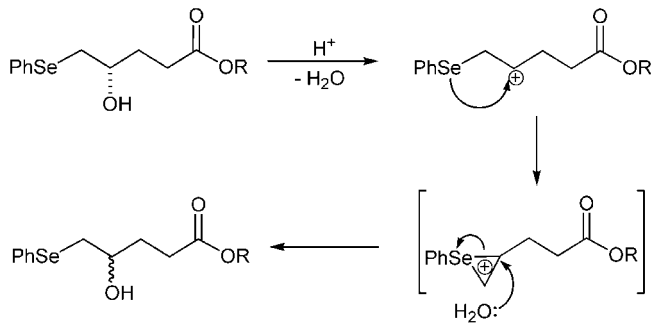


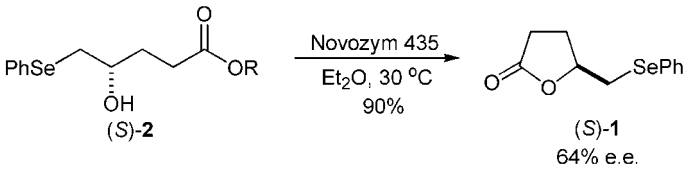
Scheme 4.

However, under these conditions only racemic **1** was obtained, probably formed through the mechanistic pathway shown in Sch. 4.

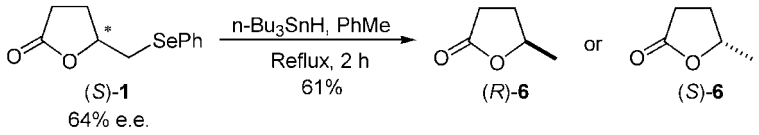
In view of the high reactivity of Novozym 435® (Table 1, Entry 6) we used this lipase to perform the lactonization of (*S*)-**2a**. Under these conditions *S*-phenylselanyltetrahydro-2-furanone **1** was obtained with 64% enantiomeric excess (Sch. 5).

Both racemic and chiral **1** were then submitted to tributyltin hydride reduction leading to γ-valerolactone **6** (Sch. 6). According to the literature[8] this reaction can be performed without free-radical initiator. However, it was observed that the use of catalytic amount of the 1,1′-azo-*bis*-(ciclohexane-carbonitrile) reduced the reaction time and afforded **6** in a better yield.

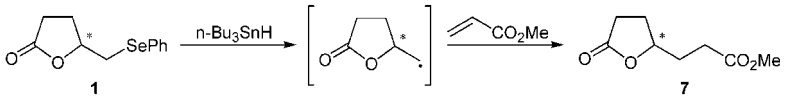
It is well-known that there are occasional difficulties in removing tin species from the products of stannane mediated radical reactions, particularly when excess of the hydride is used to improve the rate of reduction.[15] Both distillation and chromatographic separations, performed over silica-gel using different solvent systems, were not efficient to purify γ-valerolactone **6**. The best work-up procedure was found by dissolving the dry residue of the reduction reaction in acetonitrile and then washing several times with dry hexane to remove organotins, as previously reported by Hamon and Richards.[16] The organice extract was then concentrated and compound **6**



Scheme 5.



Scheme 6.



Scheme 7.

purified by column chromatography. The γ-valerolactone **6** was separated into its enantiomers by means of gas chromatography using a β-cyclodextrin column.

Since the selenium removal should not affect the stereogenic center, the absolute stereochemistry of the γ-valerolactones could be confirmed by comparing the $[\alpha]_D$ values of the products obtained by us with those of the literature. In particular, the $[\alpha]_D$ of compound (*S*)-**6** obtained in 74% e.e. was −26.7, close to −29.6, the reported value for the enantiomerically pure (−)-(*S*)-γ-valerolactone.[17]

In conclusion, the first kinetic resolution of a phenylselenolactone promoted by enzymes was performed, opening the perspective for a more economical route to these interesting building blocks which, as shown for (*R*) and (*S*)-γ-valerolactone, could be used in the enantioselective synthesis of biologically active γ-butyrolactones, by means of well known selenium methodologies,[8,18] in particular the free radical mediated chain elongation (Sch. 7).[8a]

EXPERIMENTAL

General

The NMR spectra were recorded on Bruker DRX-500 and Varian FT-300 spectrometers using TMS as internal reference (^{1}H NMR) and the central peak of the $CDCl_3$ signal (^{13}C NMR). IR spectra were obtained with a Perkin-Elmer 1600 grating infrared spectrophotometer. The GC analyses were performed on a Hewlett-Packard 5890(II) and on a Shimadzu GC-17 (chiral analysis). The

mass spectra were performed on Shimadzu GC-MS QP5050. Optical rotations were measured on a Jasco DIP 370 digital polarimeter. The enzymatic reactions were monitored in a Shimadzu LC10AD HPLC.

Propyl-4-hydroxy-5-phenylselanylpentanoate (2a)

To a solution of diphenyl diselenide (1.72 g, 5.5 mmol) in ethanol (30 mL) was added solid sodium borohydride in small portions until the characteristic yellow color of the diphenyl diselenide faded. The resulting sodium phenylselenolate solution was cooled to -40°C and epoxide **5** (1.58 g, 10 mmol) was added. After stirring for 2 min, ethyl acetate (150 mL) was added and the mixture was washed with 10% $NaHCO_3$ aqueous solution (3×20 mL). The residue was purified by flash silica gel column chromatography eluting with hexane/ethyl acetate (7 : 3) to give **2a** (1.78 g, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (t, $J = 7.44$ Hz; 3H), 1.64 (qui, $J = 7.44$ Hz; 2H), 1.73–1.97 (m, 2H), 2.4 (t, $J = 6.85$ Hz; 2H), 2.76 (d, $J = 3.94$; 2H), 2.88–2.95 (m, 2H), 3.59–3.76 (m, 1H), 4.01 (t, $J = 7.44$ Hz; 1H), 7.20–7.23 (m, 2H); 7.51–7.57 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.4, 21.9, 30.7, 31.5, 36.1, 66.0, 69.4, 125.9, 129.1, 129.8, 132.6, 173.8. IR (KBr) (cm^{-1}): 3431, 2967, 1739. Anal. Calcd for $C_{14}H_{20}O_3Se$: C, 53.34; H, 6.39. Found: C, 53.35; H, 6.22.

5-Phenylselanyltetrahydro-2-furanone (1)

A solution of phenylselanil bromide (5.37 g, 22,7 mmol) in dry THF (70 mL) was added dropwise to a solution of 4-pentenoic acid **3** (2.0 g, 20 mmol) in dry THF (150 ml) at -78°C under nitrogen. Triethylamine (20 ml) was added and the mixture was stirred for 17 h at room temperature. Then, the solvent was concentrated under reduced pressure and NH_4Cl saturated solution (10 mL) was added. The mixture was extracted with AcOEt (3×50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt = 9 : 1) to give **1** (3.9 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.89–1.98 (m, 1H), 2.35–2.43 (m, 1H), 2.50–2.57 (m, 2H), 2.98–3.04 (m, 1H), 3,24–3.29 (m, 1H), 4.64 (dtd, $J = 7.36$ Hz, $J = 6.99$ Hz, $J = 4.78$ Hz, 1H), 7.26–7.30 (m, 2H), 7.51–7.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.4, 28.6, 31.7, 79.2, 127.5, 128.7, 133.0, 135.4 and 176.4. IR (film) (cm^{-1}): 2933, 1773, 730. MS (m/z) (% rel.): 43 (100%), 55 (51%), 77 (49%), 85 (97%), 157 (13%), 256 (11%). Anal. Calcd for $C_{11}H_{12}O_2Se$: C, 51.78; H, 4.74. Found: C, 51.67; H, 4.94. The analytical separation of the enantiomers of racemic and chiral 5-phenylselanyltetrahydro-2-furanone (**1**) were achieved in chiral HPLC;

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Stationary phase: amilose tris(3,5-dimethylphenylcarbamate) coated onto APS-Hypersil (5 μm particle size and 120 Å pore size, 20% w/w). Mobile phase: [Hexane : Ethanol (9 : 1)]. Flow rate: 0.5 mL/min.

Propyl-4-hydroxy-5-phenylselanylpentanoate (2a)

To the selenolactone **1** (1.01 g, 4 mmol) at r.t. was added an aqueous solution of KOH (12 mL, 0.28 g, 4.2 mmol) and the mixture was refluxed for 4 h. The water was removed by azeotropic distillation (three times) with DMF (30 mL). To the dried solid were added dry DMF (16 mL) and n-propyl bromide (0.72 mL, 8 mmol), and the mixture was stirred for 24 h at room temperature. Diethyl ether (50 mL) was added and the organic layer was washed with water (5 × 25 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography eluting with hexane/ethyl acetate (7 : 3) to give **2a** (0.94 g, 75%). The spectral data are agreement with those reported for compound **2a** prepared as described above.

Methyl-4-hydroxy-5-phenylselanylpentanoate (2b)

Following the same procedure described for the preparation of **2a**, compound **2b** was obtained in 76% yield using MeI as the alkylating agent. NMR ^{1}H (500 MHz, $CDCl_3$): δ (ppm) 1.5 (b, 1H); 1.9–2.0 (m, 1H); 2.37–2.45 (m, 1H); 2.47–2.62 (m, 2H); 3.05 (dd, $J = 13$ Hz, $J = 8$ Hz; 1H); 3.2 (dd, $J = 13$ Hz, $J = 4.5$ Hz; 1H), 3.5 (s, 3H); 4.62–4.68 (m, 1H); 7.26–7.30 (m, 3H); 7.54–7.56 (m, 2H). NMR ^{13}C (125 MHz, $CDCl_3$): δ (ppm) 26.7, 28.8, 31.9, 69.3, 79.4, 127.7, 129.4, 133.3, 174.2. I.R. (film) (cm^{-1}): 3467, 2948, 1730, 1580, 1437, 1171, 1062, 744. Anal. Calcd for $C_{12}H_{16}O_3Se$: C, 50.18; H, 5.61. Found: C, 50.29; H, 5.47.

Benzyl-4-hydroxy-5-phenylselanylpentanoate (2c)

Following the same procedure described for the preparation of **2a**, compound **2c** was obtained in 74% yield using benzyl bromide as the alkylating agent. NMR ^{1}H (500 MHz, $CDCl_3$): δ (ppm) 1.75 (br, 1H); 1.9–2.0 (m, 1H); 2.36–2.45 (m, 1H); 2.47–2.62 (m, 2H); 3.0 (dd, $J = 13$ Hz, $J = 8$ Hz; 1H); 3.29 (dd, $J = 13$ Hz, $J = 5$ Hz; 1H), 4.62–4.68 (m, 1H); 4.69 (s, 2H); 7.24–7.38 (m, 8H); 7.52–7.58 (m, 2H). NMR ^{13}C (125 MHz, $CDCl_3$): δ (ppm) 26.6, 28.7, 31.9, 69.2, 79.4, 127, 127.6, 127.6, 128.7, 128.7, 129.3,

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133.2, 140.8, 176.6. I.R. (film) (cm^{-1}): 3461; 2925; 1944; 1724; 1580; 1154; 1079; 733. Anal. Calcd for $C_{18}H_{20}O_3Se$: C, 59.51; H, 5.55. Found: C, 59.40; H, 5.58.

Typical Procedure for the Lipase-Catalyzed Kinetic Lactonization of 2

To a solution of substrate **2** (0.2 g) in the dry organic solvent (10 mL) was added the lipase (0.2 g) and the mixture was stirred at 30°C. The progress of reaction was monitored by HPLC (Supelcosil LC-18 15 cm × 4.6 mm × 5 μm column. Mobile phase: Acetonitrile : H_2O 0.65 : 0.35. Flow rate: 1 mL/min) and it was stopped when conversion into lactone (*R*)-**1** reached ca. 50%. Then, the lipases were removed by centrifugation and the resulting solution concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography eluting with hexane/diethyl ether (1 : 1) as the eluent. From substrate 2a and PPL in diethyl ether (0.06 g, 37%) of compound (R)-**1**. [74% e.e., $[\alpha]_D^{25} = -0.5$, (c = 2.56)] and (0.10 g, 52%) of compound (*S*)-**2a** [64% e.e (estimated from the lactonized derivative), $[\alpha]_D^{25} = +16.14$, (c = 3.11)] were obtained. The spectral data for compounds (*R*)-**1** and (*S*)-**2** are in agreement with those of racemic **1** and **2**.

Typical Procedure for Lactonization of 2 with Novozym 435®

Compound (*S*)-**2** (1 g) was dissolved in dry diethyl ether (50 mL) and Novozym 435® (1 g) was added. The mixture was stirred for 6 h at 30°C, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography eluting with hexane/diethyl ether (1 : 1). Starting from (*S*)-**2a**, compound (*S*)-**1** (0.32 g, 90%) was obtained [64% e.e., $[\alpha]_D^{25} = +0.3$, (c = 2.31)]. The spectral data are in agreement with those of racemic **1**.

(*S*)-4-Pentanolide (γ-Valerolactone) (6)

In a round-bottomed flask, compound **1** (0.255 g, 1 mmol) was dissolved in toluene (3 mL). A reflux condenser was coupled and nitrogen was swept through the system for about 5 min. Then tributyltin hydride (0.54 mL, 0.58 g, 2 mmol) and catalytic amount of the 1,1′-azobis-(ciclohexanecarbonitrile) were added into the mixture and the flask was immersed into a preheated oil bath (120–130°C). The mixture was refluxed for 2 h and then cooled.

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Acetonitrile (10 mL) was added and the resulting mixture was washed with hexane (10 × 10 mL) and the solvent was evaporated. The residue was purified by flash silica gel column chromatography eluting with hexane/diethyl ether (1 : 1) to give *S*-4-pentanolide (γ-valerolactone) **6** (61 mg, 61%) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (d, $J = 6.3$ Hz, 3H), 1.78–1.91 (m, 1H), 2.54–2.59 (m, 2H), 4.6–4.71 (m, 1H). ^{13}C NMR (75 MHz, $CdCl_3$) δ: 21.0, 29.1, 29.8, 77.4, 177.6 IR (film) (cm^{-1}): 2998, 1777, 1432, 1130. MS (m/z) (%rel.): 41 (47%), 43 (34%), 56 (100%), 85 (45%) and 100 (8%). The analytical separation of the enantiomers of racemic and chiral γ-valerolactone was achieved in a gas chromatograph equipped with a CHIRASIL-DEX CD (CROMPACK®) chiral phase capillary column. Chiral separations were performed using the following gradient temperature program: 60°C (3 min) to 190°C (10 min) at 5°C/min. Carrier gas at 15 psi, the injector and detector temperatures were maintained at 230°C and 250°C, respectively.

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