bicarbonate, and one portion of saturated brine. After being dried over magnesium sulfate, the solvent was evaporated and the oily product purified by distillation in vacuo, bp 65–70 °C/0.1 mm. ^{1}H NMR ($CDCl_3$): δ 2.59 (dd, J = 4.8, 2.6 Hz, 1 H), 2.72 (d, J = 5.79 Hz, 2 H), 2.86 (t, J = 4.4 Hz, 1 H), 3.35 (m, 1 H), 4.78 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ_C 168.4, 94.6, 73.9, 47.3, 46.2, 37.5. Anal. Calcd for $C_6H_7Cl_3O_3$: C, 30.87; H, 3.02. Found: C, 31.53; H, 3.15.

Preparation of the Poly(ethylene glycol) Substrate. PEG of molecular weight 1300–1600 (Aldrich) was chosen because of its solubility and melting point characteristics. Very low molecular weight oligomers were removed by the following procedure. To 200 mL of anhydrous isopropyl ether under a dry nitrogen atmosphere was added 25 g of PEG. The mixture was stirred and warmed to ~45 °C. During the 2 h the mixture was held at this temperature, the polymer melted and formed a separate phase at the bottom of the reaction vessel. Upon cooling to 0 °C in an ice/water bath, the PEG solidified and some dissolved polymer precipitated. The solid PEG was fractured into a relatively fine powder by rapid stirring. The powder was recovered by filtration, washed with additional cold isopropyl ether, and dried under vacuum at room temperature. The procedure yielded 24.2 g of PEG.

Resolution of 2,2,2-Trichloroethyl (*R*,*S*)-3,4-Epoxybutanoate [(*R*,*S*)-1]. To 100 mL of anhydrous isopropyl ether in a 300-mL three-necked round-bottom flask equipped with a magnetic stirrer and a dry nitrogen inlet was added 16 g (11.0 mmol) of the previously prepared PEG. The mixture was heated to ~45 °C with stirring and then 4.0 g (17.1 mmol) of (*R*,*S*)-1 and 4.3 g of PPL (35% protein, activity = 35–70 units per mg, Sigma), which had been dried for 3 days in vacuo over phosphorus pentoxide as we have described elsewhere,[17] were added in rapid succession. After 4.5 h, VPC analysis indicated that 50% of the starting ester had been consumed and the reaction was stopped by rapidly cooling the reaction vessel in an ice/water bath. The mixture of PPL and esterified PEG was filtered from the cold mixture and washed with cold isopropyl ether. The filtrate was concentrated by evaporation to yield 1.72 g (86%) of 2,2,2-trichloroethyl (*R*)-(+)-3,4-epoxybutanoate [(*R*)-1], $[\alpha]^{25}_D$ +5.05° (c = 4, $CHCl_3$); the ^{1}H and ^{13}C NMR spectra were identical with those described above for the racemic material.

The recovered PEG was dissolved in CH_2Cl_2 and freed of the insoluble PPL by suction filtration using a fritted glass funnel. The recovery was 15.82 g (94.6%) of a solid. (The theoretical yield of acylated polymer was estimated as 16.73 g by assuming that the acyl portion from one half the starting (*R*,*S*)-1 becomes bound to the polymer. Alternatively, it may be estimated as 16.83 g by assuming the acyl portion of all unrecovered 1 became bound to the polymer. In this case, the recovery would be 94.0%.) ^{1}H NMR ($CDCl_3$): δ 3.62 (s) and 2.6 (br s) were strong absorptions arising from the PEG; δ 2.54 (ddd), 2.80 (t), 3.25 (m) comprise a weak set of absorptions from the 3,4-epoxybutyrate. There is no absorption near δ 4.8 for the methylene of a trichloroethyl ester.

Isolation of (*S*)-3,4-Epoxybutanoate as the Methyl Ester. To 100 mL of anhydrous isopropyl ether was added 14.5 g (9.4 mmol) of the recovered PEG and the mixture was stirred and heated to 50 °C. In rapid succession 8.25 g (250 mmol) of anhydrous methanol and 2.2 g of PPL were added to the mixture. After approximately 30 h, the reaction was stopped by cooling the reaction vessel in an ice/water bath; then the solidified PEG was collected by filtration and washed with cold isopropyl ether. The filtrate was concentrated by evaporation to yield 0.91 g (92%) of methyl (*S*)-(−)-3,4-epoxybutanoate; $[\alpha]^{20}_D$ −11.61° (c = 1.8, $CHCl_3$) [lit.[22] $[\alpha]^{r.t.}_D$ +10.67° (c = 1.8 $CHCl_3$) for the unchanged enantiomer from the enzymatic hydrolysis]; the proton NMR spectrum was identical with that described previously[21] and the TLC and VPC behaviors were identical with those of a racemic, authentic sample.

Conversion of 2,2,2-Trichloroethyl (*R*)-3,4-Epoxybutanoate [(*R*)-1] to (*R*)-(−)-Carnitine Chloride (3). 2,2,2-Trichloroethyl (*R*)-3,4-epoxybutanoate [(*R*)-1] (1.5 g, 6.42 mmol) was suspended in 15 mL of 0.1 M phosphate buffer that had been adjusted to pH 7.8. To this mixture was added 200 mg of the lipoprotein lipase Amano P from *Pseudomonas* sp. (AMANO Int'l Enzyme Co. Troy, VA), and the mixture stirred at ambient temperature while maintaining the pH near 7.5 by slow addition of 1 M aqueous NaOH. After ~4 h, the consumption of base ceased and the reaction mixture was extracted with 2 × 10 mL of methylene chloride to remove the trichloroethanol that had been freed. Following the method of Bianchi et al.,[19] the aqueous solution of (*R*)-3,4-epoxybutanoate was converted to (*R*)-(−)-carnitine chloride (4) in 72% yield, $[\alpha]^{25}_D$ −22.9° (c = 1, H_2O) (lit.[20] $[\alpha]^{25}_D$ −23.7°); mp 146 °C dec (lit.[20] 142 °C dec). ^{1}H NMR (D_2O): δ 2.51 (two dd, 2 H), 3.06 (s, 9 H), 3.34 (m, 2 H), 4.52 (m, 1 H). The enantiomeric excess as determined by comparison of the optical rotation with the literature value is 96.6%.

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Lipase-Catalyzed Preparation of Optically Active γ-Butyrolactones in Organic Solvents

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Lipases in anhydrous organic solvents catalyze the lactonization of esters of γ-hydroxy carboxylic acids with a high degree of stereospecificity. Under these conditions the lipases exhibit both enantioselectivity and prochiral selectivity. We exploited the enzymes' enantioselectivity for synthesis of chiral lactones from racemic γ-hydroxy esters and their prochiral stereospecificity, i.e. the ability to discriminate between enantiotopic groups of a prochiral molecule, for the enantioconvergent lactonization of symmetrical γ-hydroxy diesters. This approach was used to develop a convenient, high-yielding, and stereoselective route to several optically active γ-substituted γ-butyrolactones.

Enzymes are widely exploited as catalysts in asymmetric synthesis and resolution.[1] It is now well established that hydrolytic enzymes such as lipases, esterases, and proteases can function also in organic solvents and can be used for certain types of transformations which are difficult or impossible to do in water.[2] The most common reactions

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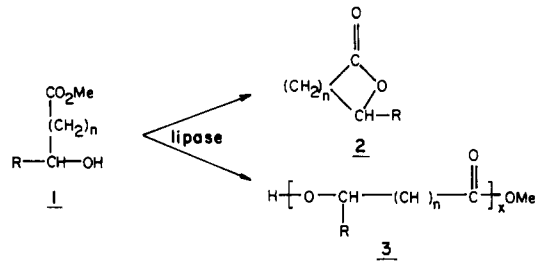
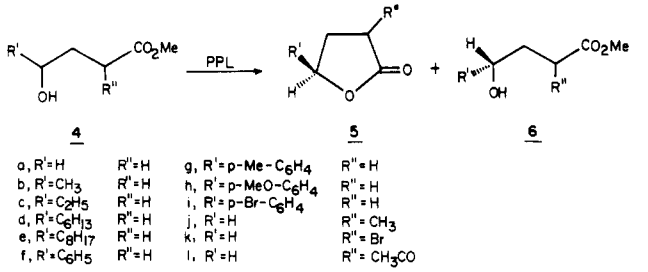
Scheme I



Scheme II



are lipase- and protease-catalyzed esterifications and transesterifications, which were extensively used for the preparative resolution of racemic acids and alcohols.[3] More recently, several reports were published on lipase-catalyzed preparation of macrocyclic lactones under carefully controlled kineteic conditions.[4,5]

Before the publication of these reports, we have investigated the catalytic potential of some commercially available lipases (triacylglycerol hydrolases EC 3.1.1.3) in organic solvents toward esters of ω-hydroxy acids, and we found that porcine pancreatic lipase (PPL) has a broad substrate specificity to this class of compounds.[6] Since hydroxy esters are bifunctional molecules, they undergo condensation by two alternative routes: *intramolecular*, to give the corresponding lactone, or *intermolecular*, to give oligomerization products (Scheme I). The outcome depended on the chain length and degree of substitution of the substrate. In the case of β-hydroxy esters (n = 1), the reaction proceeded in an *intermolecular* fashion to form the polyester (**3**, n = 1, R = H or R = Me). If a five-membered lactone can be formed (from γ-hydroxy esters, n = 2), this was the exclusive product.[7] For δ-hydroxy esters the outcome depended on substitution in position δ: if unsubstituted (**1**, n = 3, R = H), oligomerization was predominant, while in the case of δ-methyl-δ-hydroxy ester (**1**, n = 3, R = Me), the balance was tipped in favor of lactonization, and the corresponding δ-methylvalerolactone (**2**, n = 3, R = Me) was the exclusive product.[6]

Lactonic functionality is present in a large variety of natural products and biologically active compounds. Lactone derivatives are very common flavor components[8] used in the perfume and food industry. They have also been reported to be sex attractant pheromones of different insects[9] and to be plant-growth regulators,[10] and they are useful intermediates in the synthesis of natural products. Most of them are chiral, and the physiological activity often depends on the absolute configuration.[11] Even the optical purity of the substance, like in the case of some pheromones,[12] can determine the biological activity.

Owing to the importance of this class of compounds, in recent years, many optically active lactones have been the targets of an increasing number of synthetic efforts. Their synthesis in chiral form often depends on complicated multistep transformations starting from chiral natural products[13] or, in cases of some γ- and δ-lactones, on enzymatic[14] or microbial[15] reductions of appropriate keto acids followed by chemical lactonization. In several isolated cases it was possible to induce chirality by the use of a chiral chemical reagent.[16] Very recently, lipase-catalyzed asymmetric resolution of lactones via hydrolysis in aqueous solutions was reported.[17] However, while all these methods were shown to be useful for the synthesis of certain chiral lactones, they generally suffered from important drawbacks: transformation from a natural optically active compound is often very complicated and lengthy; enzymatic reduction involves an expensive cofactor (NADH), which has to be regenerated during the reaction—a very costly and hard to scale-up procedure; microbial reduction is restricted only to specific compounds which happen to be utilized as growth substrates, and, therefore, the substrate specificity and stereochemical outcome are unpredictable; use of chiral reagents[16] required critical control of the reaction conditions and have given products of relatively low optical purity, and the resolution

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via enzymatic hydrolysis[17] resulted in modest enantiomeric excesses and sometimes proceeded with difficulties, apparently because the resultant hydroxy acids inhibit the enzyme. Our approach with enzymes in organic solvents has significant advantages and provides a useful alternative for the preparation of chiral γ- and δ-lactones.

Results and Discussion

A preliminary report[7] describes our approach to enantioselective enzymatic lactonization of γ-hydroxy esters in organic solvents. Very recently we reported a strategy for lipase-catalyzed enantioconvergent lactonization of symmetrical prochiral γ-hydroxy diesters.[18] In the present work we undertook to study the potential of lipases in organic solvents for the synthesis of optically pure γ-butyrolactones from esters of racemic γ-hydroxy esters, and from prochiral symmetrical γ-hydroxy diesters. Our novel approach provides a convenient and highly stereoselective preparative route to this class of compounds.

Exploiting the Enzymes' Enantioselectivity. Since γ-hydroxy acids themselves undergo spontaneous lactonization, we investigated the lactonization of their methyl esters (**4a–4l**) with suspensions of porcine pancreatic lipase (PPL) in organic solvents (Scheme II). The racemic α- and γ-substituted γ-hydroxy esters were prepared by adaptation of known synthetic methods as described in the Experimental Section. PPL was our first choice of enzyme because it is stable and inexpensive[19] and has been shown to be effective in transesterification reactions.[3] The experiments were straightforward. The powdered commercial preparation of PPL was added to a solution of γ-hydroxy ester in dry hexane or in another anhydrous solvent, and the suspension (PPL is totally insoluble in organic solvents) was vigorously shaken on a reciprocal shaker at a chosen temperature. In several cases the hydroxy esters are poorly soluble in hexane, but the lactones are, so progressive dissolusion occurs as lactonization proceeds. Reaction progress (Scheme II) was monitored by IR, comparing the 1770 cm^{-1} lactone carbonyl absorption of product and the 1730 cm^{-1} ester carbonyl absorption of the starting material, or by 400-MHz NMR spectroscopy. Reactions were terminated simply by filtering off the enzyme. Lactonization was catalyzed in a variety of organic solvents, and, as expected,[20] the rate depended on the hydrophobicity of the solvent: thus for **4a** the initial reaction rate in hexane was double of that in ether or THF, and 4 times higher than that in chloroform.

Every γ-substituted γ-hydroxy ester (Scheme II) that was submitted to PPL under those conditions proved to be a useful substrate for the enzyme in as far as reaction rates and stereospecificities were concerned. The γ-alkyl-substituted compounds (**4b–e**) reacted approximately 1 order of magnitude faster than the γ-aryl-substituted ones (**4f–i**), but even with the latter the reactions proceeded at a rate acceptable for preparative purposes. In all cases the kinetic profile of lactonization showed a marked slow-down near 50% conversion. Since no inactivation of the enzyme was observed during the reaction,[21] evidently the lipase-catalyzed lactonization is stereospecific, in a sense that one enantiomer of the racemic mixture undergoes lactonization in preference to the other. However, in all cases the reaction proceeded also beyond the 50% conversion stage, indicating that the unfavored enantiomer of the hydroxy ester reacted but at a much slower rate.

Table I. PPL-Catalyzed Lactonization of Racemic γ-Hydroxy Esters in Organic Solvents

substrate	initial rate, μmol/min per g	% conv[a]	chiral product	$[\alpha]^{28}_D$, deg (c CH_2Cl_2)	ee,[b] %
4a, R = H	1.4	100	**5a**	–	–
4b, R = CH_3	1.1	21	*S*-**5b**	−32.3[c]	>98
4c, R = C_2H_5	2.0	41	*S*-**5c**	−48.6[d]	88
4d, R = C_6H_{13}	3.7	48	*S*-**5d**	−33.7[e]	82
4e, R = C_8H_{17}	4.6	43	*S*-**5e**	−34.0[f]	91
4f, R = C_6H_5	0.23	31	*R*-**5f**	+31.0[g]	92
4g, R = Me-C_6H_4	0.17	30	*R*-**5g**	+11.0	94
4h, R = MeO-C_6H_4	0.31	34	*R*-**5h**	+4.9	88
4i, R = Br-C_6H_4	0.37	28	*R*-**5i**	+14.4	94

[a] Reaction progress was monitored by periodic examination of aliquots from the reaction mixture by IR or NMR, as described in the text. [b] The values for enantiomeric excess were determined by NMR spectra of the diols, obtained from the MeLi reaction of the lactone in the presence of the chiral shift reagent (+)-Eu(tfc)$_3$ as described in ref 23. [c] Literature $[\alpha]_D$ = −29.6° (c = 1.29, CH_2Cl_2), ref: Mori, K. *Tetrahedron* **1975**, *31*, 3011. [d] Literature $[\alpha]_D$ = −51.3° (c = 0.99, MeOH), ref: Francotte, E.; Lohmann, D. *Helv. Chem. Acta* **1987**, *70*, 1569. [e] Literature $[\alpha]_D$ = −39.2° (c = 0.4, MeOH), ref 13g. [f] Literature $[\alpha]_D$ = −32.8° (c = 1.6, MeOH), ref: Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. [g] Literature $[\alpha]_D$ = +32.5° (c = 4.3, $CHCl_3$), ref 15c.

Following the general theory of enzyme-catalyzed kinetic resolutions,[22] in order to optimize the optical purity of the lactones (**5**) the reaction was usually stopped at an early stage of conversion (Table I), and conversely in order to optimize the optical purity of the hydroxy ester (**6**) the reaction was terminated at a relatively late stage of conversion. In all cases the experiments were very "clean" in that no byproducts were detected and the lactones were separated from the unreacted hydroxy esters by silica gel chromatography. The significant discrimination in reaction rates of the two enantiomers enabled us to carry out an efficient kinetic resolution and to prepare several optically active γ-substituted γ-butyrolactones (Table I). The absolute configurations of the lactones were deduced from their optical rotations and comparison with those in the literature. Noteworthy, in all cases the absolute configuration of the γ-lactone was the same with the bulky substituent in position γ sticking out toward us (as shown in Scheme II). The apparent change in configuration on going from alkyl substitution to aryl substitution is simply due to the formal assignment of priorities of substituents.

Because of the very weak coordinating capabilities of both the carbonyl and the etheric moieties of the lactone function, there was not sufficient binding between the substrate and the Eu atom, and therefore the enantiomeric excess values could not be determined by a direct chiral shift reagent approach. Hence the optically active lactones were first converted into the corresponding diols by treatment with 3 equiv of methyllithium, and the ee values of these diols were readily determined by 400-MHz NMR spectroscopy in the presence of the chiral shift reagent (+)-Eu(tfc)$_3$ using the Jones method.[23]

The opposite enantiomeric lactone can be accessed by allowing the reactions to proceed to a late stage of con-

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Table II. Enantioconvergent Lactonization of γ-Hydroxypimelates with Lipases in Organic Solvents

prochiral substrate	enzyme	time, h	conv[a] %	chiral product	$[\alpha]_D^{28}$, deg (c in CH_2Cl_2)	% ee
8b	PPL	21	100	*R*-**9b**	−57.41 (c 2.26)	>95[c,d]
8c	PPL	44	100	*R*-**9c**	−60.86 (c 0.58)	>98[e]
8c	PF	44	100	*S*-**9c**	+6.61 (c 1.10)	32[e]
8d	PPL	68	33	*R*-**9d**	−26.85 (c 0.51)	46[e]
8d	PF	68	36	*S*-**9d**	+5.82 (c 0.80)	10[e]
8e	PPL	52	100	*R*-**9e**	−40.86 (c 0.74)	>95[f]
8e[b]	PF	48	100	*R*-**9e**	−18.02 (c 0.95)	45[f]

[a] Reaction progress was followed by ^1H NMR spectroscopy, comparing the relative intensities of the C-4 protons in hydroxydiesters **8b–e** at 3.65 ppm and in the corresponding lactones **9b–e** at 4.48 ppm. [b] The substrate **8e** is poorly soluble in hexane, but the lactone **9e** is soluble, so progressive dissolution occurs as lactonization proceeds. [c] Taken into consideration that **8b** contained ca. 15% of racemic lactone. [d] Enantiomeric excess was determined by comparison of optical rotation with data published in ref 15b for the (+)-*S* enantiomer: $[\alpha]_D$ = +61.98°. [e] Optical purity determination was based on a difference in the ^1H NMR chemical shifts in the two enantiomers for the methylene or methyne protons of the alcohol moiety in the presence of the chiral solvating reagent, (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol, as previously described.[15b] [f] Enantiomeric excess was determined by comparison of optical rotation with data published in ref 13e: for (−)-*R* enantiomer, $[\alpha]_D$ = 29.28°, for the (+)-*R* enantiomer, $[\alpha]_D$ = +25.50°.

version, and the unreacted γ-hydroxy ester is isolated and chemically lactonized. Thus, when the enzymatic lactonization of **4b** was stopped at 60% conversion, the (*R*)-(−)-γ-hydroxy-γ-methylbutyrate (**6b**) was obtained, and, as expected, its acid-catalyzed lactonization[24] gave the (*R*)-(+)-γ-methylbutyrolactone (**5b**), $[\alpha]_D$ = +31.6° (*c* = 2.3, CH_2Cl_2). The very high optical purity (ee >95%) indicates that also the hydroxy ester isolated from the 60% conversion experiment was of very high optical purity.

It was found that the α-substituted γ-hydroxy esters (**4j–l**) are very poor substrates for the enzyme in as far as reaction rates and stereospecificities are concerned. Thus, in the case of α-methyl substitution (**4j**) the initial rate of lactonization was 50 times lower than for the unsubstituted **4a** and in the case of α-bromo (**4k**) and α-acetyl (**4l**) 200 times lower. It has been recently reported[25] that also under aqueous hydrolytic conditions α-substituted esters are very poor substrates for PPL-catalyzed hydrolysis; this similarity of behavior in aqueous and organic solvents provides further support to the hypothesis[26] that the active-site conformation of an enzyme suspended in an organic solvent can be similar to that in water.

Exploiting the Enzymes' Prochiral Selectivity. The above experiments rely on the enantiospecificity of enzymatic conversions and amount to kinetic resolutions of racemic hydroxy esters, which may enable the isolation of the desired chiral lactones in yields not higher than 50%. This problem may be avoided when it is possible to exploit the enzymes' prochiral stereospecificity, i.e. their ability to discriminate between enantiotopic groups or faces of a prochiral molecule. Several lipases and proteases were shown to exhibit prochiral selectivity under aqueous conditions, for example when hydrolyzing symmetrical C-3-substituted glutarate diesters,[27] and more recently also in organic solvents, for example when acylating symmetrical C-2-substituted 1,3-propanediols.[28]

In this work we extended the concept of prochiral selectivity to enzymatic lactonization in organic solvents. In principle, the enzymatic cyclization of prochiral hydroxy diesters or of dihydroxy monoesters (Figure 1) will be enantioconvergent and may convert *all* of the precursor into a single enantiomer of the appropriate chiral lactone.

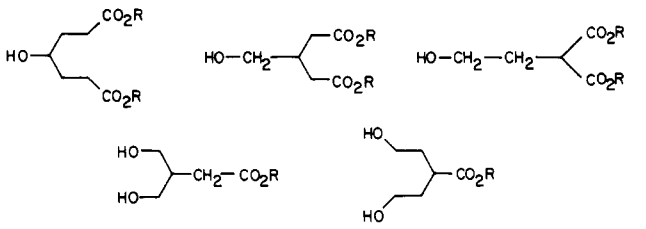
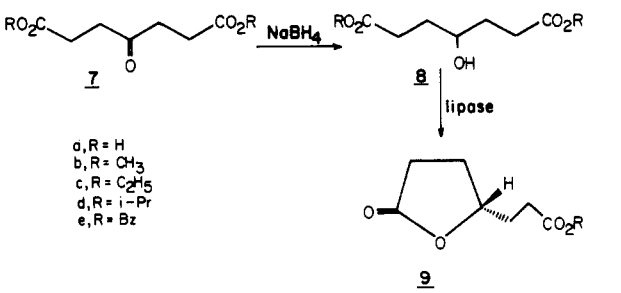


Figure 1.

Scheme III



In order to check the feasibility of this idea we undertook to prepare as possible substrates several symmetrical prochiral diesters of γ-hydroxypimelic acid (**8b–e**).

With that in mind the $NaBH_4$ reduction of the readily available γ-ketopimelates (**7b–e**) was studied. This turned out to be not straightforward, as under the usual reaction and workup conditions[29] spontaneous lactonization occurred, and it was not possible to isolate the desired γ-hydroxy diesters. However, we overcame this problem by modifying the reaction and workup procedures so as to carry out the reduction at low temperature and to rigorously avoid any acidic conditions during workup and purification. Under such mild nonacidic conditions the γ-hydroxypimelate diesters (**8b–e**) were obtained in nearly quantitative yields and, when necessary, were purified by silica gel chromatography. They could be stored for prolonged periods at 0 °C and were shown not to undergo spontaneous lactonization in organic solvents in the absence of enzymes.

Each of the substrate hydroxy diesters (**8b–e**) in hexane was submitted to the action of seven commercially available lipase and two protease preparations. Examination of aliquots from the enzymatic experiments by IR revealed that two enzymes, PPL and PF (lipase from *Pseudomonas fluorescens*), catalyzed lactonization. No lactonization was observed with lipases from *Aspergillus Mucor*, and *Rhi-*

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zopus (from Amano); with lipases from *Candida cylindracea* and from wheat germ (Sigma); and with the proteases subtilisin Carlsberg from *Bacillus subtilis* and protease from *Streptomyces griseus* (Sigma).

For both enzymes lactonization was enantioconvergent, but the stereospecificity was strikingly different (Table II): PPL gave the *S* enantiomer with high enantiomeric excess, while PF gave the *R* enantiomer in lower optical yield. For PPL the selectivity was strongly dependent on the ester alcohol, the best results being obtained for the faster reacting methyl, ethyl, and benzyl esters, and markedly lower enantiomeric excess with the more bulky isopropyl ester. The optical purity of **9c–d** was determined by NMR spectra in the presence of the chiral solvating reagent, (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

Palladium oxide catalyzed hydrogenation of the enzymatically produced benzyl ester **9e** in glacial acetic acid afforded in quantitative yield the crystalline (*S*)-(−)-lactonic acid **9a**, $[\alpha]^{28}_D$ −39.86° (*c* 0.77, H_2O). This value is considerably higher than that reported by Fuji et al.[16e] ($[\alpha]^{25}_D$ −26.5°), and it suggests that in our hands the lactonic acid **9a** had an ee >95%. Possessing two readily distinguishable functional groups, optically pure lactonic acid **9a** provides a versatile chiral building block for the synthesis of biologically active natural products such as pheromones and antifungal metabolites.[30]

Conclusions

This study provides a new addition to the synthetic utility of lipases in organic solvents. It has been shown that lipases in organic solvents can act as practical, highly stereoselective catalysts for lactonization of γ-hydroxy esters. This approach provided a convenient, high-yielding, and enantioselective route to several optically active γ-substituted γ-lactones. This study shows that prochiral selectivity can be achieved by enzymes in organic solvents and that optically pure γ-lactones may be obtained in quantitative yields from readily available symmetrical starting materials. The chiral γ-butyrolactone γ-3-propionates (**9b–e**), and the lactonic acid **9a** are versatile chiral building blocks in the synthesis of biologically active natural products. Considering the broad substrate specificity of lipases, this approach is expected to be synthetically useful for asymmetric preparation of other optically pure γ- and δ-lactones from symmetrical hydroxy dicarboxylates and dihydroxy monocarboxylates. It is noteworthy that this approach can work only in organic solvents and is not possible in aqueous solutions, where enzymatic hydrolysis of lactones such as **9** would produce a symmetrical molecule resulting in the loss of chirality.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AM 400-MHz spectrometer in $CDCl_3$. All chemical shifts were reported in ppm with tetramethylsilane as internal or external standard. IR spectra were taken on a Perkin-Elmer spectrometer Model 298 in $CHCl_3$. Optical rotations were determined on a JASCO polarimeter. Distillations were performed on a glass tube oven Büchi GKR-50. The shaker used for enzymatic experiments was an environmental shaker incubator from New Bronswick Scientific Co.

All solvents were redistilled before use. Thin-layer chromatography (TLC) were performed on plates coated with 0.25-mm thickness on silica gel 60F-254 (E. Merck). Preparative-layer chromatography (PLC) were performed on plates coated with 1-mm thick layer of silica gel 60 PF 254. Column chromatography was performed on silica gel kieselgel 40, 0.063–0.200 mm. Solvent extracts of aqueous solutions were dried over anhydrous Na_2SO_4. Solutions were concentrated under reduced pressure on a rotary evaporator.

The lipases from porcine pancreas (PPL, Type II), *Candida cylindracea* (CCL Type VII), and wheat germ were obtained from Sigma Chemical Co. Lipases from *Pseudomonas fluorescens*, *Aspergillus*, *Mucor*, and *Rhizopus* were obtained from Amano Pharmaceutical Co. Proteases subtilisin Carlsberg from *Bacillus subtilis* and protease from *Streptomyces griseus* were obtained from Sigma Chemical Co. Unless otherwise stated, materials were obtained from commercial suppliers and were used without further purification.

Synthesis of Racemic γ-Substituted γ-Hydroxy Esters. Methyl γ-hydroxybutyrate (4a) was prepared by acid-catalyzed methanolysis of the commercially available γ-butyrolactone according to the published method:[31] ^{1}H NMR δ 3.67 (3 H, s), 3.65 (2 H, m), 2.40 (2 H, t, *J* = 7.2 Hz), 1.83 (2 H, m); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-hydroxy-γ-methylbutyrate (4b) was obtained from the commercially available γ-valerolactone in 91% yield via the silver salt of the γ-hydroxy-γ-methylbutyric acid according to the published method.[32] The product was purified by chromatography on silica gel, eluting with dichloromethane: ^{1}H NMR δ 3.80 (1 H, m), 3.64 (3 H, s), 2.41 (2 H, t, *J* = 7.0 Hz), 2.11 (1 H, br s), 1.73 (2 H, m), 1.17 (3 H, d, *J* = 6.0 Hz); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-ethyl-γ-hydroxybutyrate (4c) was obtained from γ-caprolactone in 86% yield via the silver salt as described for **4b**: ^{1}H NMR δ 3.64 (3 H, s), 3.52 (1 H, m), 2.38 (2 H, m), 2.03 (1 H, br s), 1.80 (1 H, m), 1.65 (1 H, m), 1.43 (2 H, m), 0.94 (3 H, t, *J* = 7.0 Hz); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-hexyl-γ-hydroxybutyrate (4d) was obtained from γ-nonalactone in 78% yield via the silver salt as described for **4b** and purified by chromatography on silica gel, eluting with hexane–dichloromethane, 1:9: ^{1}H NMR δ 3.65 (3 H, s), 3.56 (1 H, m), 2.43 (2 H, t, *J* = 7.4 Hz), 1.82 (2 H, m), 1.73 (1 H, br s), 1.66 (1 H, m), 1.42 (3 H, m), 1.25 (6 H, br s), 0.87 (3 H, t, *J* = 6.7 Hz); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-hydroxy-γ-octylbutyrate (4e) was prepared as above from the corresponding γ-octylbutyrolactone, which was obtained by a published procedure.[33] Chromatography as above afforded pure **4e**: ^{1}H NMR δ 3.64 (3 H, s), 3.57 (1 H, m), 2.44 (2 H, t, *J* = 7.4 Hz), 1.83 (1 H, m), 1.72 (1 H, br s), 1.66 (1 H, m), 1.41 (3 H, m), 1.24 (11 H, br s), 0.86 (3 H, t, *J* = 6.0 Hz); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-hydroxy-γ-phenylbutyrate (4f) was prepared by $NaBH_4$ reduction of the corresponding methyl γ-oxo-γ-phenylbutyrate. The latter was obtained in 90% yield by methyl esterification of the commercially available 3-benzoylpropanoic acid. The $NaBH_4$ reduction was carried by a modification of the published procedure.[29] To a solution of the keto ester (8 g, 44 mmol) dissolved in a 1:1 mixture of diethyl ether and methanol (140 mL) was added a solution of sodium borohydride (815 mg, 22 mmol) in water (3 mL) with ice cooling. After stirring at 0–4 °C for 2 h, excess of $NaBH_4$ was decomposed with a 1% solution of $NaHCO_3$. The reaction mixture was extracted with ether, washed with water, and dried, and the solvent was evaporated to give a yellowish oil (6.1 g, 74% yield). Chromatography on silica gel, eluting with ethyl acetate–dichloromethane, 1:9, afforded pure **4f** as a colorless oil (4.8 g, 60%): ^{1}H NMR δ 7.30 (5 H, m), 4.76 (1 H, t, *J* = 7.2 Hz), 3.65 (3 H, s), 2.42 (2 H, t, *J* = 7.4 Hz), 2.32 (1 H, br s), 2.08 (2 H, m); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-hydroxy-γ-tolylbutyrate (4g) was prepared by $NaBH_4$ reduction of the corresponding methyl γ-oxo-γ-tolylbutyrate, which was obtained in 76% yield by a Friedel–Crafts reaction between succinic anhydride and toluene.[34] The $NaBH_4$

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reduction was carried out as described for the preparation of **4f**. The oily product was purified by chromatography on silica gel, eluting with dichloromethane to give pure **4g** as a colorless oil: ^{1}H NMR δ 7.21 (2 H, d, J = 8.6 Hz), 7.14 (2 H, d, J = 8.6 Hz), 4.70 (1 H, t, J = 8.1 Hz), 3.64 (3 H, s), 2.77 (1 H, br s), 2.41 (2 H, t, J = 8.0 Hz), 2.32 (3 H, s), 2.04 (2 H, m); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-hydroxy-γ-(*p*-methoxyphenyl)butyrate (4h) was prepared in three steps following the same route as for the preparation of **4g**, i.e. Friedel–Crafts acylation of succinic anhydride with anisole, followed by esterification with methanol afforded the precursor γ-keto ester, methyl 3-(*p*-methoxybenzoyl)propionate,[34] which was reduced with $NaBH_4$ as before to give after chromatography the desired material as a colorless oil: ^{1}H NMR δ 7.25 (2 H, d, J = 9.6 Hz), 6.86 (2 H, d, J = 9.6 Hz) 4.67 (1 H, t, J = 7.4 Hz) 3.77 (3 H, s), 3.63 (3 H, s), 2.41 (2 H, t, J = 7.8 Hz), 2.04 (2 H, m), 1.85 (1 H, br s); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Methyl (±)-γ-(*p*-bromophenyl)-γ-hydroxybutyrate (4i) was prepared in the same way as **4h**, starting from succinic anhydride and bromobenzene. The product was characterized by its spectrascopic properties: ^{1}H NMR δ 7.44 (2 H, d, J = 7.8 Hz), 7.20 (2 H, d, J = 7.8 Hz), 4.69 (1 H, t, J = 6.2 Hz), 3.65 (3 H, s), 2.81 (1 H, br s), 2.39 (2 H, t, J = 7.2 Hz), 1.99 (2 H, m); IR 3440 (broad OH), 1730 cm^{-1} (C=O, ester).

Synthesis of γ-Hydroxypimelate Diesters. (a) Preparation of γ-Keto Esters (7b–e). Dimethyl γ-oxopimelate (7b) was prepared by esterification of the diacid **7a** with methanol and sulfuric acid (Fischer conditions) in 55% yield: ^{1}H NMR δ 3.65 (6 H, s), 2.76 (4 H, t, J = 6 Hz), 2.59 (4 H, t, J = 6 Hz); IR 1735 (C=O, ester), 1720 cm^{-1} (C=O, ketone).

Diethyl γ-oxopimelate (7c) was prepared from furylacrylic acid by a modification of a published procedure.[35] Dry ethanol (250 mL, 4.27 mol) in a 0.5-L flask was cooled by an ice–water bath, and thionyl chloride (35 mL, 0.48 mol) was added dropwise with stirring. After the addition of thionyl chloride was complete, the mixture was allowed to warm up to room temperature, and furylacrylic acid (17.3 g, 0.125 mole) was added. The reaction mixture was refluxed for 3 h, cooled, and evaporated. The residue was dissolved in CH_2Cl_2 (100 mL), and the organic solution was washed with a 5% solution of $NaHCO_3$ (50 mL) and water (50 mL), dried over Na_2SO_4, and evaporated. The product **7c** was isolated by vacuum distillation (bp 115 °C, 0.6 mmHg) as a clear, colorless liquid (25 g, 87% yield): ^{1}H NMR δ 4.13 (4 H, q, J = 6 Hz), 2.75 (4 H, t, J = 6 Hz), 2.55 (4 H, t, J = 6 Hz), 1.22 (6 H, t, J = 6 Hz); IR 1735 (C=O, ester), 1720 cm^{-1} (C=O, ketone).

Diisopropyl γ-oxopimelate (7d) was prepared by esterification of the diacid **7a** with 2-propanol and sulfuric acid (Fischer conditions) in 82% yield. ^{1}H NMR δ 4.95 (2 H, m), 2.74 (4 H, t, J = 6 Hz), 2.54 (4 H, t, J = 6 Hz), 1.2 (12 H, d, J = 6 Hz); IR 1735 (C=O, ester), 1720 cm^{-1} (C=O, ketone).

Dibenzyl γ-oxopimelate (7e) was prepared from the cesium salt of the diacid **7a** by an adaptation of a published procedure.[36] **7a** (2.5 g, 14.4 mmole) was dissolved in a mixture of methanol (5 mL) and water (20 mL). The solution was titrated with a 20% aqueous solution of Cs_2CO_3 (ca. 34 mL) to pH 8.5 and evaporated to dryness. To remove traces of water, the gummy residue was treated twice with dry DMF (70 mL) and reevaporated. The solid cesium salt obtained was stirred with benzyl bromide (5.34 g, 31.2 mmol) in DMF (70 mL) for 10 h at 50 °C. The inorganic salt was filtered off, the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (70 mL), washed with water (30 mL), dried, and evaporated. The crude product was chromatographed on a silica gel column with hexane–ethyl acetate, 70:30, to give a pure fraction of **7e** as a solid crystalline material (3 g, 59% yield): ^{1}H NMR δ 7.31 (10 H, s), 5.08 (4 H, s), 2.75 (4 H, t, J = 6 Hz), 2.65 (4 H, t, J = 6 Hz); IR 1735 (C=O, ester), 1720 cm^{-1} (C=O, ketone).

(b) $NaBH_4$ Reduction of γ-Keto Diesters 7b–e into the Corresponding γ-Hydroxy Diesters 8b–e. Diethyl γ-Hydroxypimelate (8c). The foregoing keto diester **7c** (3 g, 13 mmol) was dissolved in a 1:1 mixture of diethyl ether and ethanol (42 mL), and the solution was cooled to −20 °C. A solution of sodium borohydride (0.25 g, 6.5 mmol) in water (15 mL) was added, and the reaction mixture was stirred at −20 °C for 3 h. The reaction was terminated by adding a 5% aqueous solution of $NaHCO_3$ (10 mL), and the cold reaction mixture was extracted with diethyl ether (3 × 40 mL), which was precooled to 0 °C. The combined cold ether extracts were dried over Na_2SO_4 and evaporated in vacuo without heating to give crude **8c** as a colorless oil (2.5 g, 82% yield). Before the enzymatic reaction the material was purified by silica gel chromatography, eluting with hexane–diethyl ether, 60:40. During chromatography and consequent handling of the material acidic conditions were rigorously avoided by freshly redistilling all solvents and prewashing all glassware with a 1% solution of $NaHCO_3$: ^{1}H NMR δ 4.11 (4 H, q, J = 7 Hz), 3.62 (1 H, m), 2.44 (4 H, t, J = 4 Hz), 1.74 (4 H, m), 1.23 (6 H, t, J = 7 Hz); IR 3500 (broad, OH), 1735 cm^{-1} (C=O, ester).

Dimethyl γ-Hydroxypimelate (8b). This was obtained from **7b** as described for the preparation of **8c** from **7c**. However, after chromatography (hexane–diethyl ether, 55:45) the oily product contained ca. 15% lactone: ^{1}H NMR δ 3.65 (6 H, s), 3.65 (1 H, m), 2.45 (4 H, t, J = 4 Hz), 1.75 (4 H, m); IR 3500 (broad, OH), 1735 cm^{-1} (C=O, ester).

Diisopropyl γ-Hydroxypimelate (8d). This was prepared from **7d** as described for the preparation of **8c** from **7c**. Purification by chromatography (hexane–diethyl ether, 65:35) afforded pure **8d** as a colorless oil: ^{1}H NMR δ 4.88 (2 H, m), 3.62 (1 H, m), 2.41 (4 H, t, J = 4 Hz), 1.76 (4 H, m), 1.21 (12 H, d, J = 6 Hz); IR 3500 (broad, OH), 1735 cm^{-1} (C=O, ester).

Dibenzyl γ-Hydroxypimelate (8e). This was prepared from **7e** as described for the preparation of **8c** from **7c**. Purification by chromatography (hexane–diethyl ether, 50:50) afforded pure **8e** as a white solid material: ^{1}H NMR δ 7.33 (10 H, s), 5.10 (4 H, s), 3.65 (1 H, m), 2.50 (4 H, t, J = 4 Hz), 1.80 (4 H, m); IR 3500 (broad, OH), 1735 cm^{-1} (C=O, ester).

Enzymatic Lactonization of Racemic γ-Hydroxy Esters (4a–i) (Representative Procedure). Porcine pancreatic lipase (PPL) (600 mg) was added to a solution of the racemic γ-hydroxy ester (**4b**) (204 mg, 1.7 mmol) in dry diethyl ether (25 mL), and the suspension was shaken at 100 rpm at 26 °C in a conical flask equipped with a drying tube. Reaction progress was monitored by NMR, comparing the relative intensities of the γ-methyl protons in the hydroxy ester (**4b**) at 1.17 ppm and lactone (**5b**) at 1.39 ppm. The reaction was terminated by filtering off the enzyme after 12 h at 21% conversion. The lactone was separated from the unreacted hydroxy ester by chromatography on a preparative silica gel plate, eluting with dichloromethane–hexane, 9:1.

Using this procedure chiral lactones **5b–i** were obtained, and their structures and optical purities (for comparison of optical rotations with literature see footnotes to Table I) were confirmed by optical rotations and NMR analysis.

(*S*)-(−)-γ-Methyl-γ-butyrolactone (5b): ^{1}H NMR δ 4.60 (1 H, m), 2.53 (2 H, t, J = 8.4 Hz), 2.36 (1 H, m), 1.80 (1 H, m), 1.39 (3 H, d, J = 6.0 Hz); IR 1773 cm^{-1} (C=O, lactone); $[\alpha]_D$ = −32.3° (c = 1.20, CH_2Cl_2).

(*S*)-(−)-γ-Ethyl-γ-butyrolactone (5c): ^{1}H NMR δ 4.40 (1 H, m), 2.50 (2 H, t, J = 8.2 Hz), 2.26 (1 H, m), 1.49–1.91 (3 H, m), 0.96 (3 H, t, J = 7.5 Hz); IR 1766 cm^{-1} (C=O, lactone); $[\alpha]_D$ = −48.6° (c = 1.02, CH_2Cl_2).

(*S*)-(−)-γ-Hexyl-γ-butyrolactone (5d): ^{1}H NMR δ 4.42 (1 H, m), 2.48 (2 H, t, J = 8.0 Hz), 2.26 (1 H, m), 1.81 (1 H, m), 1.68 (1 H, m), 1.54 (1 H, m), 1.09–1.47 (8 H, m), 0.83 (3 H, t, J = 7.4 Hz); IR 1767 cm^{-1} (C=O, lactone); $[\alpha]_D$ = −33.7° (c = 1.03, CH_2Cl_2).

(*S*)-(−)-γ-Octyl-γ-butyrolactone (5e): ^{1}H NMR δ 4.45 (1 H, m), 2.52 (2 H, t, J = 7.0 Hz), 2.29 (1 H, m), 1.12–1.91 (15 H, m), 0.85 (3 H, t, J = 7.6 Hz); IR 1772 cm^{-1} (C=O, lactone); $[\alpha]_D$ = −34.0° (c = 2.15, CH_2Cl_2).

(*R*)-(+)-γ-Phenyl-γ-butyrolactone (5f): ^{1}H NMR δ 7.37 (5 H, m), 5.52 (1 H, t, J = 7.4 Hz), 2.52–2.71 (3 H, m), 2.18 (1 H, m); IR 1772 cm^{-1} (C=O, lactone); $[\alpha]_D$ = +31.0° (c = 0.675, CH_2Cl_2).

(*R*)-(+)-γ-Tolyl-γ-butyrolactone (5g): ^{1}H NMR δ 7.05–7.35 (4 H, m), 5.46 (1 H, t, J = 7.9 Hz), 2.53–2.68 (3 H, m), 2.34 (3 H,

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s), 2.18 (1 H, m); IR 1778 cm^{-1} (C=O, lactone); $[\alpha]_D$ = +11.0° (c = 1.30, CH_2Cl_2).

(*R*)-(+)-γ-(*p*-Methoxyphenyl)-γ-butyrolactone (5h): ^1H NMR δ 7.25 (2 H, d, J = 8.6 Hz), 6.89 (2 H, d, J = 8.6 Hz), 5.45 (1 H, t, J = 6.5 Hz), 3.79 (3 H, s), 2.54-2.88 (2 H, m), 2.11-2.31 (2 H, m); IR 1778 cm^{-1} (C=O, lactone); $[\alpha]_D$ = +4.9° (c = 1.30, CH_2Cl_2).

(*R*)-(+)-γ-(*p*-Bromophenyl)-γ-butyrolactone (5i): ^1H NMR δ 7.49 (2 H, d, J = 8.4 Hz), 7.18 (2 H, d, J = 8.4 Hz), 5.44 (1 H, t, J = 6.9 Hz), 2.61-2.88 (3 H, m), 2.09-2.16 (1 H, m); IR 1778 cm^{-1} (C=O, lactone); $[\alpha]_D$ = +14.4° (c = 1.30, CH_2Cl_2).

Enzymatic Lactonization of γ-Hydroxypimelates (8b-e) (Representative Procedure). Porcine pancreatic lipase (PPL) (360 mg) was added to a 100 mM solution of diethyl γ-hydroxypimelate (**8c**) (140 mg) in hexane (6 mL), and the suspension was shaken on a reciprocal shaker at 40 °C. Reaction progress was monitored by NMR, following the gradual replacement of the multiplet at 3.65 ppm (corresponding to the C-4 proton in the γ-hydroxy diester) by a multiplet at 4.48 ppm (corresponding to this proton in the lactone **9c**). The reaction was terminated after 44 h, by filtering off the enzyme and evaporating the solvent. The lactone was purified by preparative TLC eluting with diethyl ether-hexane, 80:20 (R_f = 0.45).

Using this procedure the lactones **9b-e** were obtained in ca. 80% yields. Their structures and absolute configurations were confirmed by NMR and measurements of optical rotation.

Methyl (*R*)-(-)-γ-Butyrolactone-γ-propionate (9b). The reaction proceeded to 100% conversion in 21 h: ^1H NMR δ 4.50 (1 H, m), 3.67 (3 H, s), 2.49 (5 H, m), 1.90 (3 H, m); IR 1770 (C=O, lactone), 1730 cm^{-1} (C=O, ester); $[\alpha]_D$ = -48.8° (c = 2.26, CH_2Cl_2). Considering that in this experiment the product contained ca. 15% of racemic lactone as a result of spontaneous reaction, the ee of enzymatic product is at least 93%.

Ethyl (*R*)-(-)-γ-Butyrolactone-γ-propionate (9c). The reaction proceeded to 100% conversion in 44 h: ^1H NMR δ 4.50 (1 H, m), 4.10 (2 H, q, J = 7 Hz), 2.48 (4 H, m), 2.35 (1 H, m), 1.88 (3 H, m), 1.26 (3 H, t, J = 7 Hz); IR 1770 (C=O, lactone), 1730 cm^{-1} (C=O, ester); $[\alpha]_D$ = -60.86° (c = 0.58, CH_2Cl_2). This corresponds to ee >98%.

Isopropyl (*R*)-(-)-γ-Butyrolactone-γ-propionate (9d). The reaction proceeded to 33% conversion in 68 h: ^1H NMR δ 5.00 (1 H, m), 4.52 (1 H, m), 2.49 (5 H, m), 1.94 (3 H, m), 1.22 (6 H, d, J = 6 Hz); IR 1770 (C=O, lactone), 1730 cm^{-1} (C=O, ester); $[\alpha]_D$ = -26.85° (c = 0.51, CH_2Cl_2). This corresponds to ee 46%.

Benzyl (*R*)-(-)-γ-Butyrolactone-γ-propionate (9e). The substrate **8e** is poorly soluble in hexane, but the lactone **9e** is soluble so progressive dissolution occurs as lactonization proceeds. The reaction proceeded to 100% conversion in 52 h: ^1H NMR δ 7.33 (5 H, s), 5.11 (2 H, s), 4.50 (1 H, m), 2.50 (4 H, m), 2.35 (1 H, m), 1.95 (3 H, m); IR 1770 (C=O, lactone), 1730 cm^{-1} (C=O, ester); $[\alpha]_D$ = -40.86° (c = 0.74, CH_2Cl_2). This corresponds to ee >95%.

(*S*)-(-)-Lactonic Acid (9a). The foregoing lactone benzyl ester (**9e**) (54 mg, 0.22 mmol) was dissolved in glacial acetic acid, mixed with activated palladium oxide on charcoal (32 mg, 10% Pd), and hydrogenated at atmospheric pressure for 3 h. Filtration of the catalyst and evaporation of the acetic acid in vacuum afforded the lactonic acid **9a** as white crystalline material (30 mg, 87% yield): ^1H NMR δ 4.54 (1 H, m), 2.53 (4 H, m), 2.34 (1 H, m), 1.91 (3 H, m); $[\alpha]_D$ = -39.86° (c = 0.77, H_2O).

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Registry No. **4a**, 925-57-5; **4b**, 126252-14-0; **4c**, 87241-91-6; **4d**, 126135-36-2; **4e**, 126135-37-3; **4f**, 126252-15-1; **4g**, 126135-38-4; **4h**, 126135-39-5; **4i**, 126135-40-8; **5a**, 96-48-0; *S*-**5b**, 19041-15-7; *R*-**5b**, 58917-25-2; **5c**, 41035-07-8; **5d**, 107797-27-3; **5e**, 69830-92-8; **5f**, 111138-03-5; **5g**, 126135-41-9; **5h**, 126135-42-0; **5i**, 126135-43-1; **6b**, 111043-99-3; **7a**, 502-50-1; **7b**, 22634-92-0; **7c**, 6317-49-3; **7d**, 117726-76-8; **7e**, 70957-27-6; **8b**, 126135-44-2; **5b** lactone derivative, 126252-16-2; **8c**, 58262-40-1; **8d**, 122950-94-1; **8e**, 122950-95-2; **9a**, 98611-83-7; **9b**, 111070-69-0; *R*-**9c**, 99438-12-7; *S*-**9c**, 99438-11-6; *R*-**9d**, 122950-97-4; *S*-**9d**, 122950-96-3; **9e**, 99393-14-3; PPL, 9001-62-1; methyl γ-oxo-γ-phenylbutyrate, 25333-24-8; methyl γ-oxo-γ-tolylbutyrate, 57498-54-1; methyl 3-(*p*-methoxybenzoyl)propionate, 5447-74-5; furylacrylic acid, 539-47-9.

A Novel Aromatic Iodination Method Using F_2

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A new method for direct aromatic iodination with IF, made in situ from the corresponding elements, is described. Depending on the reaction time and temperature, mono- or polyiodination can be achieved. Even deactivated aromatic rings can be directly iodinated without the presence of any Friedel-Crafts catalyst. Sensitive groups such as aromatic aldehydes are not affected by the reagent.

During the last 10 years elemental fluorine has gained increasing popularity as a fluorinating agent.[1] We and others have shown that F_2 can be a source of electrophilic,[2] nucleophilic,[3] and radical[4] fluorine species. Despite this remarkable versatility it was not anticipated that fluorine would also play a role in general organic chemistry by participating in the syntheses of fluorine-free compounds which are otherwise difficult to prepare. But it seems that this surprising element can indeed do just that, and, since we believe that F_2 has a considerable general synthetic potential, we have channeled most of our efforts toward this new area. Thus in the last few years we have used fluorine to activate alkanes by converting them to alkenes,[5] to substitute very resistant heterocyclic hydrogens by acetoxy,[6] chlorine, bromine, or various ethers,[7] to epoxidize a whole spectrum of olefins,[8] to hydroxylate molecules at regions remote from activating groups,[9] and to brominate

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