A Protocol for the Efficient Synthesis of Enantiopure β-Substituted β-Lactones

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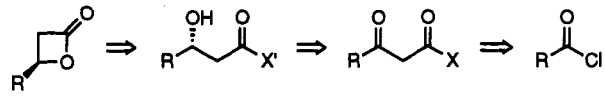
Introduction

In the course of an investigation on macrocyclization reactions by catalyzed cyclooligomerization of lactones,[1] we had the need of preparing enantiopure β-monosubstituted β-lactones as starting materials. Among the plethora of available lactonization methods,[2] we found that few were suitable for the synthesis of β-lactones,[3] due to their inherent lability. Furthermore, α-substitution is often a requirement; as a matter of fact, general methods, e.g. Adam's lactonization[4] of β-hydroxy acids with benzensulfonyl chloride and pyridine, failed for substrates lacking α-substituents, possibly because of ketene formation. The range of available methods further narrows when enantiopure compounds are desired, since this renders unsuitable those methods relying upon nucleophilic substitution at the β-carbon by the carboxylate anion, because of possible partial racemization. As a consequence, very few methods were left, despite the relevance of the β-lactone moiety in synthetic organic and natural product chemistry.[5] Apparently, only one method specifically describing the preparation of enantiopure β-monosubstituted β-lactones has been reported;[6] however, this method relies on a stoichiometric iron chiral auxiliary, $C_5H_5Fe(CO)(PPh_3)COCH_3$, whose noneconomical availability[7] discourages use for multigram preparations. Other interesting reactions affording enantiopure products have been reported, i.e., asymmetric cycloaddition of ketene and chloral[8] and asymmetric hydrogenation of diketene,[9] but they are confined to specific substrates and not amenable to general procedures. A convenient reaction that might be general has been described by D. Seebach and co-workers,[10] i.e. pyrolysis of an ortho ester of β-hydroxybutyric acid, which occurs with complete inversion at the stereocenter, but the low yields reported make it unappealing for multistep syntheses. It appears that, having to face such a synthetic problem, no practical methods are available.

Scheme I



In an attempt to fill this gap, we report the results of an investigation aimed at providing a convenient protocol for the preparation of enantiopure β-monosubstituted β-lactones that features versatility, high yields, accessible reagents, and simple procedures and that could be easily applied for producing multigram quantities.

Results and Discussion

To tackle the problem, we developed a synthetic strategy whose retrosynthetic pathway is reported in Scheme I. The strategy is based on two key steps, namely, a stereoconservative lactonization and the introduction of a stereocenter in enantiopure form. Lactonization of an enantiopure β-hydroxy acid by carboxyl activation appeared to be the most practical approach to the first critical step. Methods are available to manipulate the X′ group of the carboxyl without perturbing the stereochemistry at the stereocenter.[11] The generation of the latter, the second crucial step, can be achieved by asymmetric reduction of the corresponding keto ester, a large variety of which can in turn be accessed from commercially available carboxylic acids. The alternative way of building up the β-hydroxy acid framework, the frequently exploited aldol-type condensation of aldehydes and acetic esters, has been proved convenient in the preparation of di- and trisubstitued β-lactones with control of relative stereochemistry[5] but has not been developed for nonracemic monosubstituted products. On the other hand, asymmetric aldol condensation using chiral amines as auxiliaries for the synthesis of monosubstituted β-hydroxy thiolesters[12] affords good enantioselectivity but does not provide enantiopure compounds.

Being primarily interested in benzylic substituted β-lactones as building blocks for preparing macrocyclic polylactones with aromatic side arms, we focused on a set of phenylacetic acids as starting materials, whose chlorides 1 are readily available. The synthetic protocol is reported in Scheme II. Acylation of commercial Meldrum's acid by the Yonemitsu procedure[13] was the method of choice for the preparation of keto esters. Crude acylated Meldrum's acids **2**, formed in substantially quantitative yields in the presence of pyridine in CH_2Cl_2, were decomposed in boiling ethanol for 2 h to afford the desired ethyl β-keto esters in 80–83% yield of isolated pure product. Keto esters **3** could be obtained sufficiently pure for the subsequent step by simple filtration on silica gel in 86–93% yield with respect to the starting unpurified commercial acyl chloride. The introduction of the β-stereocenter in enantiomerically pure form was then achieved by Noyori's catalytic hydrogenation,[14] which proved to be extremely reliable and efficient, affording in all cases enantiopure β-hydroxy esters **4** in consistently excellent

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(1) (a) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901. (b) Roelens, S.; Dalla Cort, A.; Mandolini, L. *J. Org. Chem.* **1992**, *57*, 1472. (c) Roelens, S. *J. Chem. Soc., Chem. Commun.* **1990**, 58.

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(3) Pommier, A.; Pons, J. M. *Synthesis* **1993**, 441.

(4) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000.

(5) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176 and refereces cited therein.

(6) Case-Green, S. C.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1991**, 779.

(7) See ref 8 in Case-Green et al.[6]

(8) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.

(9) Ohta, T.; Miyake, T.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1725.

(10) Breitschuh, R.; Seebach, D. *Chimia* **1990**, *44*, 216.

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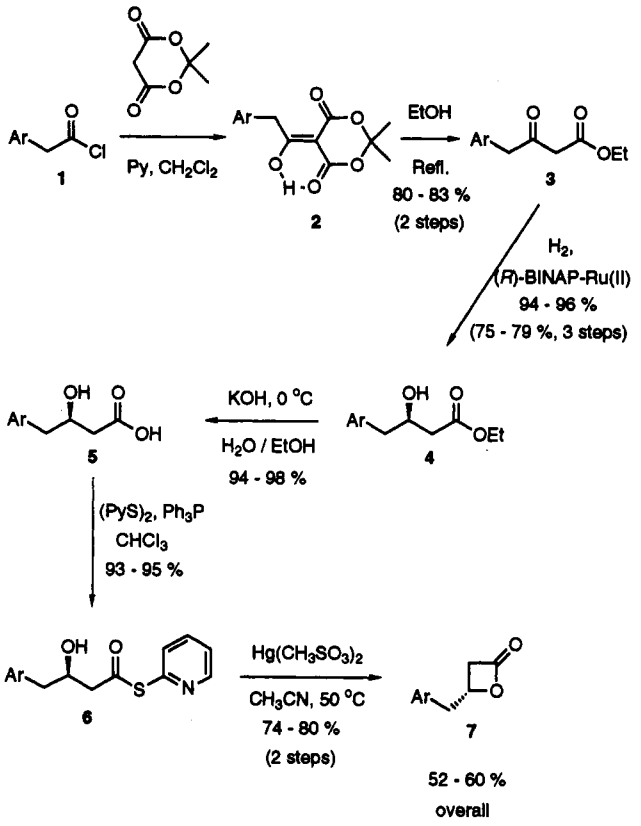
(14) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

0022-3263/93/1958-7932$04.00/0

Scheme II



1-7a Ar = $PhCH_2$

1-7b Ar = 4-MeO-$PhCH_2$

1-7c Ar = 3,4-$(MeO)_2$-$PhCH_2$

isolated yields (94–96%). Overall yields of the three steps from the starting unpurified acyl chloride were good (75–79%). Noyori's asymmetric hydrogenation is particularly convenient since the BINAP-Ru(II) catalyst is commercially available in both enantiomeric forms, has very high catalytic efficiency, and gives products of predictable absolute configuration.[15] Enantiopure materials **4** have also been obtained by bakers' yeast reduction,[16] but the low yield (37–38%; 60–62% max conversion), the impractical procedure, and, most of all, the low amount of substrate that can be reduced in a laboratory-scale process renders the method noncompetitive. Furthermore, only the *S* enantiomer can be obtained in this way.

Concerning the lactonization key step, a modified Masamune procedure,[17] featuring mercury(II) promoted cyclization of β-hydroxy benzene thiolesters, gave the best results. This method exploits a substantial acceleration of the lactonization reaction induced by the combined activation of the hydroxyl and the thio leaving group to achieve fast ring closure even at 0 °C.[18] Although the original reaction was not described for enantiopure compounds, no loss of enantiomeric purity was observed in any case.[19] Replacement of the benzene thiolester activating group with the 2-pyridine thiolester moiety was introduced in the procedure and resulted in reproducibly high lactone yields. The 2-pyridine thiolester **6** can be conveniently prepared from the parent β-hydroxy acid **5** by the Mukaiyama reagent (2,2′-dipyridyl disulfide and triphenylphosphine).[20] A major advantage is that **6** need not be isolated: the solution of **6**, obtained by mixing the reagents in chloroform[21] at room temperature, is cyclized by addition to a stirred suspension of $Hg(CH_3SO_3)_2$ in acetonitrile at 50 °C over 10 min.[22] We also found that with **6** the phosphate buffer of the original procedure is not necessary, the β-lactones being stable in the reaction medium. The overall yield of the two steps was good (74–80% of isolated pure lactone), in the first of which **6** was obtained in 93–95% yield. This explains the improvement obtained with respect to the benzene thiolester derivative, since the latter required purification before use and could be obtained in two steps from **5** through the imidazolide[23] in yields not greater than 60%. The imidazolide itself did not cyclize satisfactorily to the β-lactone.[24] The one-step conversion of **4** to the benzene thiolester by the method of Weinreb[25] was unprofitable, because yields not greater than 30% were obtained with the present substrates. Asymmetric hydrogenation of β-keto benzene thiolesters, potentially a very convenient shortcut, was unsuccessful because of complete lack of desired hydrogenation products. The β-hydroxy acids **5** were instead quantitatively (94–98% isolated yield) obtained from the corresponding ethyl esters by careful alkaline hydrolysis at 0 °C, which sets the overall yield of the synthetic protocol to 52–60% of isolated, chemically and enantiomerically pure lactones. The 2-pyridine thiolester moiety has been frequently employed after Corey and Nicolau to perform macrolactonization reactions in the so called "double activation method";[26] for β-lactones, however, catalysis is required to avoid decomposition caused by prolonged heating. In our hands, Masamune's mercury(II) methanesulfonate behaved as a superior catalyst, compared to silver(I) and copper(I) and -(II) salts.[27] Attempts to avoid the use of mercury by different activating group–metal ion combi-

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(16) Seebach, D.; Sutter, M. A.; Weber, R. H.; Züger, M. F. *Org. Synth.* **1985**, *63*, 1.

(17) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874.

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(19) Enantiomeric purity was assessed by ^1H NMR using a chiral shift reagent [Eu(hfc)$_3$]. Signals selected for the enantiomeric purity measurements, the downfield α proton or the downfield aromatic protons depending on the shift induced on the specific substrate, were chosen from control spectra on racemic compounds; the latter were prepared from β-hydroxy acids obtained by $NaBH_4$ reduction and hydrolysis of the β-keto esters. The *S* enatiomer was undetectable. The lower limit of detection of the undesired enantiomer was estimated as 1–2%.

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(21) 2-Pyridine thiolester **6** cannot be prepared in acetonitrile because of very fast decomposition, probably polymerization, which could not be controlled to achieve direct lactonization. Chloroform turned out to be an useful solvent for preparation and subsequent cyclization in mixed medium with acetonitrile.

(22) Major byproducts were cyclic and linear oligomers, whose relative amount varied with concentration as expected, higher dilution favoring the β-lactone. The described conditions represent a practical compromise between high yield and convenient amount of product, in a range of concentration where hydrolysis due to adventitious moisture, the major side reaction, is limited.

(23) (a) Bates, G. S.; Diakur, J.; Masamune, S. *Tetrahedron Lett.* **1976**, 4423. (b) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984; p 149.

(24) This finding had been already observed. See: Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7875, ref 14.

(25) Hatch, R. P.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 3960.

(26) (a) Corey, E. J.; Nicolau, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Corey, E. J.; Nicolau, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 653. (c) Corey, E. J.; Nicolau, K. C.; Toru, T. *J. Am. Chem. Soc.* **1975**, *97*, 2287.

(27) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W.-K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.

nations [imidazolide-Zn(II); phenyl ester or catechol ester-Fe(III)] met with disappointment. Purification could be achieved by flash column chromatography at room temperature with no appreciable decomposition,[28] although simple filtration on silica gel was effective in satisfactorily removing byproducts. It is noteworthy that only the β-hydroxy esters **4**, in the whole protocol, need to be of good purity. All other intermediates require either simple filtration on silica gel or no purification at all.

In conclusion, enantiopure β-substituted β-lactones of either absolute configuration can now be conveniently accessed in good overall yields by the described synthetic protocol. Thus, a reliable method is now available which fills a gap in the preparative literature of a useful class of lactones. The procedure employs readily available materials, can be applied on a multigram scale, and is likely to be general.

Experimental Section

General Methods. Meldrum's acid (Aldrich, 98%), phenylacetyl chloride (Fluka, >98%), 4-methoxyphenylacetyl chloride (Fluka, 97%), 3,4-dimethoxyphenylacetyl chloride (Aldrich, 98%), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]-chloro(*p*-cymene)ruthenium chloride) [(*R*)-BINAP-Ru(II)] (Aldrich), quinine anhydrous (Fluka, 99%), 2,2′-dipyridyl disulfide (Aldrithiol-2, Aldrich, >98%), triphenylphosphine (Merck, >98%), mercuric acetate (Fluka, >99%), methanesulfonic acid (Fluka, >99%), pyridine (Carlo Erba, RPE ACS), anhydrous ethanol, ethanol 95%, KOH (Carlo Erba RPE), and silica gel 60 for column chromatography (ICN-Biomed.) were commercial products used without further purification. Anhydrous, ethanol-free dichloromethane and chloroform were obtained by washing several times with water, drying overnight on $CaCl_2$, filtering, and storing on activated 13X molecular sieves; acetonitrile was refluxed overnight over P_2O_5, distilled, and kept under argon over activated 3-Å molecular sieves. Melting point determinations are uncorrected; ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 and 50 MHz, respectively; unambiguous NMR signal assignments were achieved from COSY, HETCOR, and long-range HETCOR 2-D spectra; *J* values are given in hertz; enantiomeric purity measurements were performed by ^1H NMR using tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato]europium(III), [Eu(hfc)$_3$], (Aldrich, 99+%); IR spectra were measured as neat liquid film; and mass spectra (EI) were determined at 70 eV.

Preparation of Mercury(II) Methanesulfonate.[17] Mercury(II) methanesulfonate was prepared by adding methanesulfonic acid (2 equiv) to a hot solution (80 °C) of mercuric acetate (1 equiv) in acetic acid (1 M solution) and stirring the resulting suspension at 80 °C for 1 h. Filtering, washing several times with dry diethyl ether, and drying the precipitate at 80 °C under reduced pressure gave the desired product as a white nonhygroscopic solid in 96% yield, which correctly analyzed for $C_2H_6O_6S_2Hg$.

General Procedure. The protocol described hereafter for the synthesis of **7b** has been successfully applied in the same preparative scale to all substrates of this paper.

Preparation of β-Keto Esters 3. Ethyl 3-Oxo-4-(4-methoxyphenyl)butanoate (3b). To an ice-cold, magnetically stirred solution of Meldrum's acid (7.81 g, 54.19 mmol) in anhydrous dichloromethane (37 mL) in a dried Schlenk tube, pyridine (8.57 g ,108.32 mmol) and 4-methoxyphenylacetyl chloride (**1b**) (10.0 g, 54.17 mmol) in anhydrous dichloromethane (34 mL) were subsequently added at 0 °C under a nitrogen atmosphere. Stirring was continued for 1 h at 0 °C and 2 h at room temperature. The mixture was then transferred to a separatory funnel, washed twice with 3% hydrochloric acid and twice with water, dried over Na_2SO_4, and evaporated under reduced pressure to give 15.53 g of crude acylated Meldrum's acid (**2b**) as a dark red oil that slowly solidifies; the latter was identified by its ^1H NMR spectrum and found to be present in enolic form completely[12] [^1H NMR ($CDCl_3$) δ 1.72 (s, 6H, Me_2), 3.79 (s, 3H, OMe), 4.35 (s, 2H, CH_2), 6.82–6.90 (m, 2H, H-3, H-5 Ar), 7.29–7.35 (m, 2H, H-2, H-6 Ar), 15.31 (br s, 1H, OH enol)]. The crude **2b** was refluxed 3 h in anhydrous ethanol (80 mL), during which time CO_2 evolution was observed. Evaporation of the solvent to dryness afforded 12.62 g of crude **3b** as a red oil, 6.83 g of which was purified by flash column chromatography on silica gel 60 (0.032–0.063 mm, 20 × 4 cm diameter, eluant petroleum ether/ethyl acetate 2:1) to give 5.53 g of pure **3b** as a pale yellow oil, yield 80% with respect to the unpurified **1b**: ^1H NMR (0.2 M in $CDCl_3$) keto 1.25 (t, *J* = 7.2, 3 H, CH_3), 3.43 (s, 2H, CH_2COO), 3.75 (s, 2H, CH_2Ar), 3.78 (s, 3H, OMe), 4.16 (q, *J* = 7.2, 2H, CH_2), 6.82–6.90 (app d, 2H, H-3, H-5 Ar), 7.07–7.14 (app d, 2H, H-2, H-6 Ar); enol 4.88 (s, 1H, CH), 12.11 (s, 1H, OH); keto/enol = 9:1; ^{13}C NMR (0.2 M in $CDCl_3$) δ 14.09 (CH_3), 48.14 (CH_2COO), 49.17 (CH_2Ar), 55.27 (OMe), 61.41 (CH_2), 114.28 (C-3, C-5 Ar), 125.22 (C-1 Ar), 130.63 (C-2, C-6 Ar), 158.88 (C-4 Ar), 167.24 (COO), 200.99 (CO); MS (EI) *m/z* (rel int) no M^+, 164 (29.2, $M^+ - OCH_2CH_2CO$), 122 (10.7), 121 (100, $M^+ - COCH_2COOEt$), 91 (16.3, $C_7H_7^+$), 78 (24.0), 77 (24.4, $C_6H_5^+$), 43 (11.9). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.98; H, 6.93.

In a different run, 16.20 g of crude **3b** was "filtered" on a short column of silica gel (10 × 4 cm diameter, same eluant) under pressure to give 13.54 g of practically pure product (82% yield). Extensive decomposition was observed when attempting purification by distillation under reduced pressure.

Ethyl 3-oxo-4-phenylbutanoate (3a):[29] yield 86% (by silica gel filtration); pale yellow oil; ^1H NMR (0.2 M in $CDCl_3$) keto δ 1.26 (t, *J* = 7.1, 3H, CH_3), 3.45 (s, 2H, CH_2COO), 3.83 (s, 2H, CH_2Ar), 4.17 (q, *J* = 7.1, 2H, CH_2), 7.18–7.39 (m, 5H, Ar); enol 4.92 (s, 1H, CH), 12.14 (s, 1H, OH); keto/enol = 9:1; ^{13}C NMR (0.2 M in $CDCl_3$) δ 14.10 (CH_3), 48.31 (CH_2COO), 50.06 (CH_2Ar), 61.44 (CH_2), 127.38 (C-4 Ar), 128.88 (C-3, C-5 Ar), 129.59 (C-2, C-6 Ar), 133.22 (C-1 Ar), 167.14 (COO), 200.55 (CO); MS (EI) *m/z* (rel int) 206 (25.5, M^+), 161 (3.8, $ArCH_2COCH_2CO^+$), 131 (10.8), 119 (13.1, $ArCH_2CO^+$), 118 (79.6), 115 (39.2, $CH_3CH_2OCOCH_2CO^+$), 92 (25.5), 91 (100, $C_7H_7^+$), 89 (27.1), 87 (32.6), 84 (18.4), 77 (13.3, $C_6H_5^+$), 69 (18.3), 65 (53.3), 63 (13.9), 55 (13.4), 51 (10.4), 45 (11.2), 43 (78.4), 41 (14.4), 39 (23.1). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.69; H, 6.93.

Ethyl 3-oxo-4-(3,4-dimethoxyphenyl)butanoate (3c): yield 93% (by silica gel filtration, 86% purity); pale yellow oil; ^1H NMR (0.2 M in $CDCl_3$) keto δ 1.25 (t, *J* = 7.1, 3H, CH_3), 3.43 (s, 2H, CH_2COO), 3.75 (s, 2H, CH_2Ar), 3.856, 3.857 (s, 6H, OMe), 4.16 (q, *J* = 7.1, 2H, CH_2), 6.69–6.84 (m, 3H, Ar); enol δ 4.90 (s, 1H, CH), 12.12 (s, 1H, OH); keto/enol = 9:1; ^{13}C NMR (0.2 M in $CDCl_3$) 14.10 (CH_3), 48.05 (CH_2COO), 49.66 (CH_2Ar), 55.88 [$(OMe)_2$], 61.43 (CH_2), 111.38 (C-5 Ar), 112.44 (C-6 Ar), 121.80 (C-2 Ar), 125.61 (C-1 Ar), 148.33 (C-3, Ar), 149.13 (C-4 Ar), 167.20 (COO), 200.93 (CO); MS (EI) *m/z* (rel int) 266 (35.3, M^+), 220 (12.4, $ArCH_2COCHCO^+$), 178 (36.9, $ArCHCO^+$), 165 (15.7), 152 (17.8), 151 (100, $ArCH_2^+$), 118 (10.1), 117 (14.0), 107 (20.9), 106 (15.6), 105 (15.9), 92 (10.5), 91 (32.9), 90 (19.0), 89 (13.4), 87 (10.0), 78 (10.0), 77 (15.2), 65 (12.5), 51 (11.1), 50 (17.6), 43 (23.5), 42 (32.6), 41 (19.8). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.38; H, 7.02.

Preparation of Enantiopure β-Hydroxy Esters 4.[30] **(*R*)-(−)-Ethyl 3-Hydroxy-4-(4-methoxyphenyl)butanoate (4b).** Anhydrous ethanol was distilled over Mg turnings under a stream of Ar directly into a dried Schlenk tube over **3b** (3.15 g, 13.33 mmol) up to an 8 mL volume. The solution was degassed by three freeze–thaw cycles and the catalyst [(*R*)-(+)-2,2′-bis-(diphenylphsphino)-1,1′-binaphtylchloro(*p*-cymene)ruthenium chloride) [(*R*)-BINAP-Ru(II)] (50 mg, 0.054 mmol, 0.4% mol) added under Ar.[31] After three more freeze–thaw cycles, the

(28) It has been reported that β-lactones with cation-stabilizing substituents at the β position may decompose unless the chromatographic purification is carried out at −20 °C; Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1178. In our cases, yields detected in the mixture by NMR were in good agreement with isolated yields.

(29) Wierenga, W.; Skulnick, H. I. *J. Org. Chem.* **1979**, *44*, 311.

(30) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1.

(31) The catalyst oxidizes on the air, the solution quickly turning from brown to green.

homogeneous solution was transferred into a stainless steel Parr apparatus previously saturated with Ar and hydrogen was introduced into the autoclave up to 100–110 atm of pressure. Four atmospheres of hydrogen are described to be sufficient at 100 °C; higher pressure has been chosen only for the purpose of shortening reaction times. The solution was stirred at 80 °C until hydrogen consumption stops, usually 2–6 h depending on substrate's purity. Traces of acidic impurities have been shown to speed up the reaction.[32] The orange solution was evaporated under reduced pressure and purified by flash column chromatography on silica gel 60 (0.032–0.063 mm, 20 × 3 cm diameter, eluant petroleum ether/ethyl acetate 2:1) to give 3.05 g (96% yield) of pure **4b** as a pale yellow oil: $[\alpha]_D^{19}$ (c = 1.54 in $CDCl_3$) −12.7°; $[\alpha]_{546}^{19}$ (c = 1.54 in $CDCl_3$) −14.6°; ^1H NMR (0.03 M in $CDCl_3$) δ 1.26 (t, J = 7.1, 3H, CH_3), 2.34–2.57 (m, 2H, CH_2COO), 2.65–2.87 (m, 2H, CH_2Ar), 3.79 (s, 3H, OMe), 4.16 (q, J = 7.1, 2H, CH_2), 4.18 (m, 1H, CHO), 6.81–6.88 (app d, 2H, H-3, H-5 Ar), 7.10–7.16 (app d, 2H, H-2, H-6 Ar); ^{13}C NMR (0.2 M in $CDCl_3$) δ 14.16 (CH_3), 40.46 (CH_2COO), 42.01 (CH_2Ar), 55.27 (OMe), 60.74 (CH_2), 69.24 (CHO), 113.99 (C-3, C-5 Ar), 129.65 (C-1 Ar), 130.41 (C-2, C-6 Ar), 158.37 (C-4 Ar), 172.83 (COO); IR (cm^{-1}) 3457 (m, br, OH), 2939 (m), 2837 (m), 1726 (s, CO), 1612 (m, Ar), 1511 (s), 1246 (s), 1177 (s), 1033 (s); MS (EI) m/z (rel int) 238 (M^+, 1.4) 220 (53.3), 175 (22.1), 147 (28.2), 122 (63.5), 121 (100), 117 (31.8), 107 (17.2), 91 (21.1), 89 (23.9), 78 (27.5), 77 (31.0), 71 (38.0), 43 (20.4). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.34; H, 7.90.

The absolute configuration has been assigned on the basis of prediction of the configuration expected from the [(*R*)-BINAP-Ru(II)] catalyst[14] and is in agreement with the assignment based on comparison with the product obtained from bakers' yeast reduction the (*S*)-(+) enantiomer. No *S* enantiomer could be detected by ^1H NMR using Eu(hfc)$_3$.

(*R*)-(−)-Ethyl 3-hydroxy-4-phenylbutanoate (4a): yield 94%; pale yellow oil; $[\alpha]_D^{25}$ (c = 1.0 in $CDCl_3$) −15.1°; $[\alpha]_D^{20}$ (c = 1.0 in $CDCl_3$) −15.5° (lit.[33] $[\alpha]_D^{20}$ −14.5, ee 97%); enantiopure by ^1H NMR [Eu(hfc)$_3$]; ^1H NMR (0.2 M in $CDCl_3$) δ 1.26 (t, J = 7.1, 3H, CH_3), 2.36–2.58 (m, 2H, CH_2COO), 2.71–2.93 (m, 2H, CH_2Ar), 3.03 (s, 1H, OH), 4.15 (q, J = 7.1, 2H, CH_2), 4.26 (m, 1H, CHO), 7.20–7.36 (m, 5H, Ar); ^{13}C NMR (0.2 M in $CDCl_3$) δ 14.19 (CH_3), 40.53 (CH_2COO), 42.95 (CH_2Ar), 60.76 (CH_2), 69.08 (CHO), 126.63 (C-4 Ar), 128.56 (C-3, C-5 Ar), 129.47 (C-2, C-6 Ar), 137.71 (C-1 Ar), 172.76 (COO); MS (EI) m/z (rel int) no M^+, 190 (27.2), 145 (12.8), 117 (59.0), 92 (44.9), 91 (100), 89 (30.6), 77 (10.7), 75 (10.9), 71 (62.2), 65 (28.0), 43 (24.4). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.43; H, 7.94.

(*R*)-(−)-Ethyl 3-hydroxy-4-(3,4-dimethoxyphenyl)butanoate (4c): yield 94% (81% from a 86% pure **3c**); white solid, mp 58.5–59.0 °C; $[\alpha]_D^{25}$ (c = 1.0 in $CDCl_3$) −9.3°; $[\alpha]_D^{20}$ (c = 1.0 in $CDCl_3$) −8.8°; enantiopure by ^1H NMR [Eu(hfc)$_3$]; ^1H NMR (0.2 M in $CDCl_3$) δ 1.24 (t, J = 7.1, 3H, CH_3), 2.34–2.56 (m, 2H, CH_2COO), 2.64–2.84 (m, 2H, CH_2Ar), 2.96 (s, 1H, OH), 3.84, 3.86 (s, 6H, OMe), 4.14 (q, J = 7.1, 2H, CH_2), 4.22 (m, 1H, CHO), 6.70–6.82 (m, 3H, Ar); ^{13}C NMR (0.2 M in $CDCl_3$) δ 14.18 (CH_3), 40.53 (CH_2COO), 42.50 (CH_2Ar), 55.83, 55.89 $(OMe)_2$, 60.74 (CH_2), 69.14 (CHO), 111.22 (C-5 Ar), 112.50 (C-6 Ar), 121.39 (C-2 Ar), 130.17 (C-1 Ar), 147.75, 148.88 (C-3, C-4 Ar), 172.76 (COO); MS (EI) m/z (rel int) 268 (15.5, M^+), 250 (28.2), 205 (15.1), 177 (20.2), 152 (43.5), 151 (100), 137 (54.5), 121 (19.0), 117 (21.9), 107 (19.0), 106 (13.6), 105 (14.1), 91 (12.0), 89 (18.1), 77 (14.5), 71 (21.9), 65 (13.2). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.50; H, 7.81.

Preparation of Enantiopure β-Hydroxy Acids 5. (*R*)-(−)-3-Hydroxy-4-(4-methoxyphenyl)butanoic Acid (5b). A solution of KOH (574 mg, 8.70 mmol) in water (9 mL) cooled to 0 °C was added to a cold solution (0 °C) of **4b** (2.07 g, 8.70 mmol) in ethanol (15 mL), vigorously shaken and kept 24 h in refrigerator at 0 °C. The solution was cautiously[34] acidified under stirring at 0 °C with 3% HCl, added with brine, extracted several times with diethyl ether, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give **5b** as a white solid (1.76 g, yield 96%): mp 91.5–93 °C; recrystallized from benzene: white crystals, mp 94–95 °C; $[\alpha]_D^{18}$ (c = 0.8 in $CDCl_3$) −4.2°; $[\alpha]_D^{18}$ (c = 1.9 in $CDCl_3$) −4.5°; enantiopure by ^1H NMR (measured as quinine salt in $CDCl_3$);[35] ^1H NMR (0.2 M in $CDCl_3$) δ 2.39–2.62 (m, 2H, CH_2COO), 2.66–2.86 (m, 2H, CH_2Ar), 3.78 (s, 3H, OMe), 4.22 (m, 1H, CHO), 6.64 (br s, 2H, OH), 6.81–6.88 (app d, 2H, H-3, H-5 Ar), 7.08–7.16 (app d, 2H, H-2, H-6 Ar); ^{13}C NMR (0.2 M in $CDCl_3$) δ 40.30 (CH_2COO), 41.98 (CH_2Ar), 55.28 (OMe), 69.15 (CHO), 114.06 (C-3, C-5 Ar), 129.29 (C-1 Ar), 130.42 (C-2, C-6 Ar), 158.44 (C-4 Ar), 177.65 (COO); MS (EI) m/z (rel int) 210 (42.8, M^+), 192 (53.7, M^+-H_2O), 147 (14.7), 123 (15.3), 122 (82.4), 121 (100), 107 (47.8), 91 (46.0), 90 (13.9), 89 (32.2), 79 (13.1), 78 (51.8), 77 (65.1), 71 (17.6), 65 (12.7), 52 (12.2), 51 (17.6). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.01; H, 6.94.

(*R*)-(−)-3-Hydroxy-4-phenylbutanoic acid (5a): yield 98%; white solid; recrystallized from toluene; white crystals, mp 83–83.5 °C; $[\alpha]_D^{20}$ (c = 1.0 in $CDCl_3$) −5.3°; enantiopure by ^1H NMR (measured as quinine salt in $CDCl_3$); ^1H NMR (0.2 M in $CDCl_3$) 2.42–2.62 (m, 2H, CH_2COO), 2.73–2.93 (m, 2H, CH_2Ar), 4.27 (m, 1H, CHO), 7.22 (br s, 2H, OH), 7.19–7.37 (m, 5H, Ar); ^{13}C NMR (0.2 M in $CDCl_3$) 40.34 (CH_2COO), 42.88 (CH_2Ar), 69.02 (CHO), 126.79 (C-4 Ar), 128.66 (C-3, C-5 Ar), 129.45 (C-2, C-6 Ar), 137.31 (C-1 Ar), 177.76 (COO); MS (EI) m/z (rel int) no M^+, 162 (64.3, M^+ − H_2O), 120 (18.1), 117 (34.5), 115 (15.7), 91 (100), 89 (36.5), 88 (32.9), 71 (22.4), 70 (37.7), 65 (29.0), 64 (36.9), 63 (11.8), 62 (23.7), 52 (33.3), 50 (58.0), 47 (12.3), 45 (17.6), 44 (36.5). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.99; H, 6.95.

(*R*)-(−)-3-Hydroxy-4-(3,4-dimethoxyphenyl)butanoic acid (5c): white solid; yield 94%; recrystallized from benzene; white crystals, mp 122.5–123.5 °C; $[\alpha]_D^{20}$ (c = 1.0 in $CDCl_3$) −1.0°; enantiopure by ^1H NMR (measured as quinine salt in $CDCl_3$); ^1H NMR (0.1 M in $CDCl_3$) δ 2.42–2.64 (m, 2H, CH_2COO), 2.67–2.86 (m, 2H, CH_2Ar), 3.85, 3.86 (s, 6H, OMe), 4.24 (m, 1H, CHO), 6.70 (br s, 2H, OH), 6.72–6.83 (m, 3H, Ar); ^{13}C NMR (0.1 M in $CDCl_3$) δ 40.34 (CH_2COO), 42.49 (CH_2Ar), 55.88 $[(OMe)]_2$, 69.05 (CHO), 111.30 (C-5 Ar), 112.47 (C-6 Ar), 121.42 (C-2 Ar), 129.75 (C-1 Ar), 147.88 (C-3 Ar), 148.96 (C-4 Ar), 177.54 (COO); MS (EI) m/z (rel int) 240 (44.3, M^+), 222 (11.4, M^+ − H_2O), 152 (51.4), 151 (100), 138 (10.4), 137 (77.7), 135 (14.5), 121 (16.5), 108 (12.3), 107 (33.3), 106 (21.4), 105 (20.8), 91 (17.9), 90 (14.9), 89 (16.6), 79 (10.1), 78 (15.9), 77 (23.8), 71 (12.3), 65 (21.5), 51 (13.4), 45 (10.0), 43 (25.9). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.95; H, 6.85.

Preparation of Enantiopure β-Lactones. (*R*)-(+)-4-(4-Methoxybenzyl)oxetan-2-one (7b). In a dried Schlenk tube 2,2′-dipyridyl disulfide (1.65 g, 7.5 mmol) and triphenylphosphine (2.10 g, 8.0 mmol) were dissolved in anhydrous chloroform (50 mL) at room temperature under a nitrogen atmosphere. **5b** (1.05 g, 5.0 mmol) was then slowly added portionwise under stirring until complete dissolution. The 0.1 M solution of **6b** thus obtained [(yield 95% by ^1H NMR; δ 2.68–2.86 (m, 2H, CH_2COO), 2.84–2.87 (m, 2H, CH_2Ar), 3.76 (s, 3H, OMe), 4.33 (m, 1H, CHO), 6.78–6.88 (app d, 2H, H-3, H-5 Ar), 7.05–7.15 (m, 2H, H-2, H-6 Ar), 8.59 (ddd, 1H, H-*o* Pyr)] was added dropwise in 10 min to a vigorously stirred suspension of $Hg(CH_3SO_3)_2$ (3.91 g, 10 mmol) in anhydrous acetonitrile (120 mL) at 50 °C under an Ar atmosphere. After 10 more min at 50 °C, the mixture was filtered and the precipitate was washed several times with $CHCl_3$. By evaporation of the solvent under reduced pressure, 5.05 g of crude mixture were obtained, which was purified by flash column chromatography on silica gel 60[36] (0.032–0.063 mm, 15 × 4 cm diameter, eluant petroleum ether/ethyl acetate 2:1) to give 765 mg (yield 80%) of pure **7b** as a pale yellow oil; $[\alpha]_D^{20}$ (c = 1.0 in $CDCl_3$) +2.2°; $[\alpha]_D^{25}$ (c = 1.0 in $CDCl_3$) +2.4°; enantiopure by ^1H NMR [Eu(hfc)$_3$]; ^1H NMR (0.2 M in $CDCl_3$) δ 2.94–3.19 (m, 3H, H-α, H-γ, H-γ′), 3.40–3.51 (dd, 1H, H-α′), 3.79 (s, 3H, OMe), 4.69 (m, 1H, H-β), 6.83–6.90 (app d, 2H, H-3, H-5 Ar), 7.10–7.17 (app d, 2H, H-2, H-6 Ar); ^{13}C NMR (0.2 M in $CDCl_3$) δ 39.56 (CH_2COO), 42.31 (CH_2Ar), 55.29 (OMe), 70.99 (CHO), 114.25

(32) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

(33) Glänzer, B. I.; Faber, K.; Griengl, H.; Röhr, M.; Wöhrer, W. *Enzyme Microb. Technol.* **1988**, *10*, 744.

(34) When temperature was not carefully controlled, extensive elimination and decarboxylation were observed.

(35) Eu(hfc)$_3$ did not provide useful signal separations with β-hydroxy acids.

(36) Because byproducts have a very low R_f, simple filtration on silica gel affords β-lactones of sufficient purity for most purposes.

(C-3, C-5 Ar), 126.82 (C-1 Ar), 130.28 (C-2, C-6 Ar), 158.86 (C-4 Ar), 167.82 (COO); IR (film, cm^{-1}) 2963 (m), 2837 (w), 1823 (s), 1610 (m), 1510 (s), 1246 (s); MS (EI) *m/z* (rel int) 192 (63.1, M^+), 148 (15.8, $M^+ - CO_2$), 147 (16.0), 122 (11.4), 121 (100, 4-MeOBz$^+$), 91 (17.5), 78 (20.7), 77 (27.8). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.48; H, 6.44.

(*R*)-(+)-4-Benzyloxetan-2-one (7a): yield 78%; colorless oil; $[\alpha]_D^{20}$ (c = 1.0 in $CDCl_3$) +6.3°; $[\alpha]_D^{20}$ (c = 1.1 in $CDCl_3$) +6.2°; enantiopure by ^1H NMR [Eu(hfc)$_3$]; ^1H NMR (0.2 M in $CDCl_3$) δ 3.00–3.27 (m, 3H, H-α, H-γ, H-γ'), 3.43–3.54 (dd, 1H, H-α'), 4.73 (m, 1H, H-β), 7.20–7.39 (m, 5H, Ar); ^{13}C NMR (0.2 M in $CDCl_3$) δ 40.50 (CH_2COO), 42.52 (CH_2Ar), 70.83 (CHO), 127.33 (C-4 Ar), 128.86 (C-3, C-5 Ar), 129.21 (C-2, C-6 Ar), 134.95 (C-1 Ar), 167.72 (COO); IR (film, cm^{-1}) 3030 (w), 2967 (w), 1824 (s), 1496 (w), 1264 (w), 1201 (w), 1133 (m); MS (EI) *m/z* (rel int) 162 (97.7, M^+), 118 (47.5, M^+-CO_2), 117 (43.5), 92 (35.7), 91 (100, Bz$^+$), 89 (14.0), 77 (11.5), 71 (52.2), 65 (47.8), 63 (17.8), 51 (22.2), 50 (12.0), 43 (50.6), 42 (11.5). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.03; H, 6.34.

(*R*)-(+)-4-(3,4-Dimethoxybenzyl)oxetan-2-one (7c): yield 74% of a viscous oil that slowly solidifies; white solid; mp 82–84.5 °C; $[\alpha]_D^{20}$ (c = 1.0 in $CDCl_3$) +11.7°; enantiopure by ^1H NMR [Eu(hfc)$_3$]; ^1H NMR (0.2 M in $CDCl_3$) δ 2.95–3.17 (m, 3H, H-α, H-γ, H-γ'), 3.41–3.52 [dd, 1H, H-α', J_{cis} = 5.6,[37] J_{gem} = 16.2 (simulated values), 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.71 (m, 1H, H-β), 6.73–6.84 (m, 3H, Ar); spin simulation (AMNXY) 4.72 (A), 3.47 (M), 3.14 (N), 3.13 (X), 3.01 (Y), J_{AM} 5.6, J_{AN} 4.4, J_{AX} 6.3, J_{AY} 5.9, J_{MN} 16.2, J_{XY} 14.1; ^{13}C NMR (0.2 M in $CDCl_3$) 39.99 (CH_2COO), 42.34 (CH_2Ar), 55.92 $(OMe)_2$, 70.99 (CHO), 111.41 (C-5 Ar), 112.37 (C-6 Ar), 121.29 (C-2 Ar), 127.43 (C-1 Ar), 148.30 (C-3 Ar), 149.10 (C-4 Ar), 167.82 (COO); IR (film, cm^{-1}) 2950 (w), 2820 (w), 1825 (s), 1580 (w), 1520 (m), 1260 (m), 1230 (m), 1025 (m); MS (EI) *m/z* (rel int) 222 (89.8, M^+), 178 (97.7, $M^+ - CO_2$), 163 (31.8), 151 (100, 3,4-$(MeO)_2$Bz$^+$), 147 (27.5), 135 (12.1), 107 (35.7), 105 (16.5), 103 (13.9), 91 (36.9), 79 (11.6), 78 (10.7), 77 (16.9), 65 (16.6), 43 (13.4). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.69; H, 6.42.

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(37) The assignment is based on J values for β-lactones: Pommier, A.; Pons, J. M. *Synthesis* **1993**, 443.