Sequential Acyl Halide−Aldehyde Cyclocondensation and Enzymatic Resolution as a Route to Enantiomerically Enriched β-Lactones

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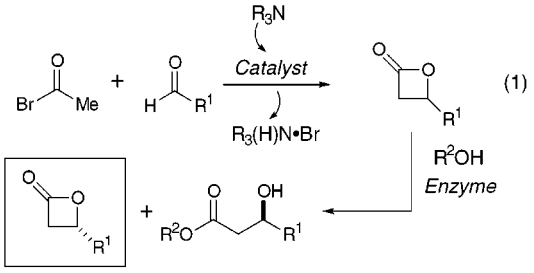
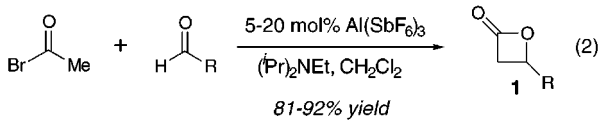
Substituted β-lactones constitute versatile intermediates for organic synthesis and are integral architectural features of a number of pharmacologically active natural products.[1,2] The utility of β-lactones as intermediates for asymmetric organic synthesis, however, has been impeded by the relatively limited number of methods for their preparation in enantiomerically pure form.[3,4] Recently, we have reported catalyzed acyl halide−aldehyde cyclocondensation (AAC) reactions as an efficient and operationally simple method for the synthesis of a variety of 4-substituted β-lactones.[5] The facile access to β-lactones afforded by the AAC reaction technology has led us to examine enzymatic resolution as a general means for obtaining enantiomerically enriched β-lactones (eq 1). Sequential application of the catalyzed AAC methodology and the enzymatic lactone resolution described herein represents an economical and easily executed synthesis of optically active β-lactones.



Catalyzed acyl halide−aldehyde cyclocondensation reactions involve the Al(III)-catalyzed reaction of acyl halides with enolizable aldehydes to deliver β-lactone products **1** in high yields (eq 2).[5] Under the optimized AAC reaction conditions, substoichiometric quantities of $Al(SbF_6)_3$ (5−20 mol %) catalyze the amine-mediated cyclocondensation of acetyl bromide and aliphatic aldehydes to afford the corresponding β-lactones as the exclusive reaction products (≥81% yield). To extend the utility of this reaction technology in synthesis activities, the preparation of optically active β-lactones by the enzymatic resolution of the racemic 4-substituted-2-oxetanones derived from the AAC reactions was explored.



Enantioselective cleavage of reactive ester linkages is among the transformations that have proven most amenable to enzymatic mediation.[6] The ring strain-induced lability of the C−O linkage in β-lactones, therefore, implicates racemic 2-oxetanones as candidates for enzyme-mediated resolution.[7] Indeed, Yamamoto has reported the successful enzymatic resolution of two 4-substituted-2-oxetanone substrates.[8] The routine preparation of 4-substituted β-propiolactones provided by the AAC reactions has allowed a detailed investigation of enzyme-mediated resolution as a general route to enantiomerically enriched β-lactones. Attempted resolution of the cyclohexanecarboxaldehyde-derived lactone **1** (R = c-C_6H_{11}) under the reported conditions using Lipase PS Amano, benzyl alcohol, and acetone solvent afforded poor conversion and resolution efficiency. Substituting isopropyl ether as the reaction solvent, however, resulted in dramatically improved reaction efficiency under otherwise identical resolution conditions (eq 3). Thus, commercially available Lipase PS Amano in conjunction with benzyl alcohol (BnOH) as the requisite nucleophile in $^iPr_2O$ affords both the resolved lactone **2a** and the β-hydroxy ester **3a** reaction product with high enantioselectivity and chemical yield.

(1) For a review of transformations involving β-lactones, see: Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−459.

(2) (a) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *62*, 4−5. (b) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308−5309. (c) Rzasa, R. M.; Shea, H. A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591−592. (d) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *Synthesis* **1998**, 1655−1661. (e) Yang, H. W.; Romo, D. *J. Org. Chem.* **1999**, *64*, 7657−7660.

(3) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977−1979. (c) Tamai, Y.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1549−1550. (d) Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc. Chem. Commun.* **1994**, 2281−2282. (e) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 1053−1054. (f) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006−8007. (g) Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K.; Yang, H. W.; Zhao, C.; Wright, G. D. *Bioorg. Med. Chem.* **1998**, *6*, 1255−1272 and references therein. (h) Yang, H. W.; Romo, D. *Tetrahedron Lett.* **1998**, *39*, 2877−2880. (i) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743.

(4) For a comprehensive review of asymmetric β-lactone syntheses, see: H. W. Yang, D. Romo, *Tetrahedron* **1999**, *55*, 6403−6434.

(5) Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535−6540.

(6) For reviews of enzyme-mediated asymmetric reactions, see: (a) Poppe, L.; Novak, L. *Selective Biocatalysis*; VCH: Weinheim, Germany, 1992. (b) Halgas, J. *Biocatalysis in Organic Synthesis*; Elsevier: New York, 1992. (c) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071−1140. (d) Wong, C.-H., Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994. (e) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; VCH: Weinheim, Germany, 1995. (f) Schoffers, E.; Grisenti, P.; Manzocchi, A.; Johnson, C. R. *Tetrahdron* **1996**, *52*, 3796−3826. (g) Faber, K. *Biotransformations in Organic Chemistry*, 3rd ed.; Springer-Verlag: Heidelberg, Germany, 1997. (h) Roberts, S. M.; Williamson, N. M. *Curr. Org. Chem.* **1997**, *1*, 1−20.

(7) For some examples of asymmetric enzyme-mediated lactone ring-opening, see: (a) Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Poli, S.; Gardini, F.; Guerzoni, M. E. *Tetrahedron: Asymmetry* **1992**, *3*, 107−114. (b) Gelo, M.; Sunjic, V. *Tetrahedron* **1992**, *48*, 6511−6520. (c) Fellous, R.; Lizzanicuvelier, L.; Loiseau, M. A.; Sassy, E. *Tetrahedron: Asymmetry* **1994**, *5*, 343−346. (d) Ha, H.-J.; Yi, D.-G.; Yoon, K.-N.; Song, C.-W. *Bull. Kor. Chem. Soc.* **1996**, *17*, 544−547. (e) Viazzo, P.; Alphand, V.; Furstoss, R. *Tetrahedron Lett.* **1996**, *37*, 4519−4522. (f) Onakunle, O. A.; Knowles, C. J.; Bunch, A. W. *Enzyme Microb. Technol.* **1997**, *21*, 245−251. (g) Enzelberger, M. M.; Bornscheuer, U. T.; Gatfield, I.; Schmid, R. D. *J. Biotechnol.* **1997**, *56*, 129−133. (h) Ha, H.-J.; Yoon, K.-N.; Lee, S.-Y.; Park, Y.-S.; Lim, M.-S.; Yim, Y.-G. *J. Org. Chem.* **1998**, *63*, 8062−8066.

(8) (a) Koichi, Y.; Suginaka, K.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1645−1646. See also: (b) Adam, W.; Groer, P.; Saha-Moller, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 833−836. (c) Ito, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* **1998**, 54, 5523−5530.

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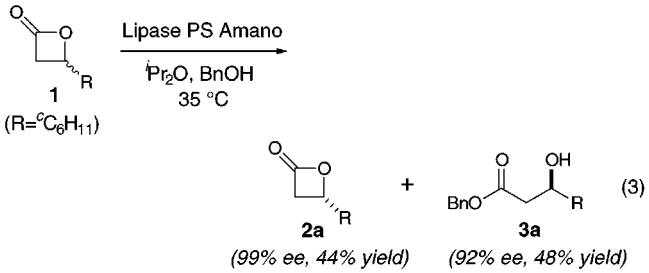
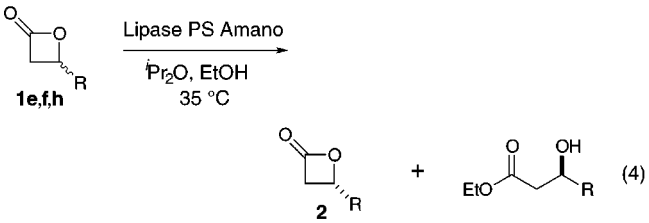


Under these resolution conditions, the lipase enzyme is relatively insensitive to the structure of the lactone β-substituent (Table 1). Lactones incorporating α-branched (entries a and b), straight chain (entries c−e), β-branched (entry f), and functionalized (entries g and h) alkyl side chains all represent effective substrates for the enzyme. High enantioselectivity, and good chemical yields in all but one trial, are obtained for all of the recovered lactones **2a**−**h** (84−99% ee).[9] The isolated yield of the isobutyraldehyde-derived lactone **2b** is uncharacteristically low (5.4%) due to the volatility of this lactone; the yield of the β-hydroxy ester reaction product **3b** (52%) would suggest that this resolution reaction is relatively efficient and is compromised only by lactone volatility. In some instances, highly enantiomerically enriched β-hydroxy ester products are also obtained (**3a**, **f**, and **h**; 88−96% ee) although ester enantiomeric purity is considerably more variable than that obtained for the unreacted lactones.

The lipase is equally insensitive to the structure of the alcohol reagent employed in the resolutions. In fact, resolutions employing ethanol afford enantioselectivities superior to those reactions using benzyl alcohol (eq 4). Resolutions using ethanol rather than benzyl alcohol offer the additional advantage of allowing the excess alcohol reagent to be removed by evaporation prior to purification. For each lactone substrate, the enantiomerically enriched lactone is separated from the corresponding β-hydroxy ester product by routine column chromatography.



Alkyl group (R)	%ee **2** (% yield)
$^{n}C_3H_7$—	96 (43)
Me_2CHCH_2—	99 (44)
$BnOCH_2$—	94 (37)

Catalyzed AAC reactions and the accompanying lactone resolution provide a general and easily executed synthesis of optically active 4-substituted β-propiolactones. The facile access to enantiomerically enriched β-lactones provided by this methodology is expected to facilitate the integration of β-lactones as intermediates in asymmetric organic synthesis.

(9) See Experimental Section for stereochemical assignment of resolved β-lactones.

Table 1. Enzymatic Resolution of Racemic β-Lactones Using BnOH

entry	β-lactone **1** (R)	% ee **2** (% yield, config)[a,b]	% ee **3** (% yield)[b,d]
a	c-C_6H_{11}	99 (44, *S*)	92 (48)
b	Me_2CH	99 (5.4, *S*)[c]	62 (53)
c	$PhCH_2CH_2$	93 (38, *R*)[d]	32 (61)
d	$CH_3(CH_2)_3$	97 (42, *R*)	74 (51)
e	$CH_3CH_2CH_2$	98 (26, *R*)	27 (62)
f	Me_2CHCH_2	90 (40, *R*)	88 (52)
g	$CH_2CH(CH_2)_8$	99 (32, *R*)	50 (60)
h	$BnOCH_2$	84 (44, *S*)[d]	96 (48)

[a] Enantiomer ratios determined by chiral capillary GC (Chiraldex G-TA column) unless otherwise specified. [b] Reported yields are for chromatographically purified materials. [c] Yield reflects lactone volatility. [d] Enantiomer ratio determined by chiral HPLC (Chiralcel OD-H column).

Experimental Section

Proton NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ 7.26 ppm); proton-decoupled ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). Analytical gas−liquid chromatography (GLC) was performed using a flame ionization detector and a Chiraldex G-TA column (20 m × 0.25 mm) (Advanced Separation Technologies Inc.). Analytical high performance liquid chromatograph (HPLC) was performed using a Daicel Chiralcel OD-H column (250 × 4.6 mm) (Daicel Inc.).

All experiments were carried out under a nitrogen atmosphere in oven- or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Diisopropyl ether ($^{i}Pr_2O$), benzyl alcohol, and ethanol were distilled from CaH_2 under N_2. Lipase PS Amano (=30000 u/g) was purchased from Amano Enzyme USA Co. All other commercially obtained reagents were used as received. The racemic β-lactone substrates **1a**−**h** were prepared according to the procedure in ref 5.

Complete or partial spectroscopic data for the following compounds has been reported previously:

(*S*)-4-cyclohexyloxetan-2-one (**2a**),[3g] (*S*)-4-(1-Methylethyl)oxetan-2-one (**2b**),[8a] (±)-4-(2-phenylethyl)oxetan-2-one (**2c**),[2a] (*R*)-4-butyloxetan-2-one (**2d**),[3g] (*R*)-4-propyloxetan-2-one (**2e**),[8a] (±)-4-(benyloxymethyl)oxetan-2-one (**2h**),[2a] and (*R*)-3-cyclohexyl-3-hydroxypropionic acid, benzyl ester (**3a**).[10]

General Procedure for the Lipase PS-Mediated Resolution of β-Lactones. To a mixture of Lipase PS Amano [~30 u/mg of **1**; 1:1 mass ratio lipase:lactone **1**] and β-lactone **1** in $^{i}Pr_2O$ (6 mL/g of substrate) was added BnOH or EtOH (0.8 equiv to β-lactone), and the resulting heterogeneous mixture was heated at 35 °C for 30−72 h. Progress of the resolution was monitored by removing reaction aliquots and assaying the enantiomeric purity of the unreacted lactone by chiral HPLC (Chiracel OD-H, 90:10 hexanes:^{i}PrOH, 1 mL/min) or chiral GC (Chiraldex G-TA column, flow rate 0.5 mL/min, method: 100 °C for 10.00 min, ramp @ 10.00 °C/min to 130 °C for 8.00 min, ramp @ 10.00 °C/min to 160 °C for 5.00 min). Upon cooling to ambient temperature, the reaction mixture was eluted through a silica gel pad with EtOAc, and the eluent was concentrated in vacuo. The products were isolated by flash chromatography (hexanes:ethyl acetate).

(*S*)-4-Cyclohexyloxetan-2-one (2a).[3g] The general procedure was followed employing 250 mg of 4-cyclohexyloxetan-2-one (**1a**) and 140 mg of benzyl alcohol (72 h reaction time). Column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 110 mg of the title compound (44%). Separation of the enantiomers by chiral GC (Chiraldex G-TA column, flow rate 0.5 mL/min, method: 100 °C for 10.00 min, ramp @ 10.00 °C/min to 130 °C for 8.00 min, ramp @ 10.00 °C/min to 160 °C for 5.00 min, T_r 22.1 (*S*) and 24.3 (*R*) min)

(10) Mukaiyama, T.; Kobayashi, S.; Sano, T. *Tetrahedron* **1990**, *46*, 4653−4662.

determined the enantiomeric excess to be greater than 99% (other enantiomer not observed). $[\alpha]_D$ +14.7° (*c* 4.0, CH_2Cl_2).

(*R*)-3-Cyclohexyl-3-hydroxypentanoic Acid, Benzyl Ester (3a).[10] From the resolution of **1a** described above, column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 204 mg of the title compound (48%). Separation of the enantiomers by chiral HPLC (Daicel Chiracel OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane T_r 25.5 (*S*) and 26.7 (*R*) min) determined the enantiomer ratio to be 24:1 (92% ee). $[\alpha]_D$ +20.4° (*c* 6.0, CH_2Cl_2).

(*S*)-4-(1-Methylethyl)oxetan-2-one (2b).[8a] The general procedure with the following modifications was followed employing 1.0 g of 4-(1-methylethyl)oxetan-2-one (**1b**) and 759 mg of benzyl alcohol (72 h reaction time). After the resolution was complete, the reaction mixture was eluted through a silica gel pad with ethyl ether. The filtrate was concentrated in vacuo and the products separated by column chromatography (90% pentane, 10% ether) to afford 54 mg of the title compound (5.4%). Separation of the enantiomers by chiral GC (Chiraldex G-TA column, flow rate 0.5 mL/min, method: 100 °C for 10.00 min, ramp @ 10.00 °C/min to 130 °C for 8.00 min, ramp @ 10.00 °C/min to 160 °C for 5.00 min, T_r 9.9 (*S*) and 10.6 (*R*) min) determined the enantiomeric excess to be 99%. $[\alpha]_D$ +20.1° (*c* 3.9, CH_2Cl_2). IR (NaCl): 1822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (ddd, J = 8.0, 5.7, 4.4 Hz, 1H), 3.44 (dd, J = 16.3, 5.6 Hz, 1H), 3.09 (dd, J = 16.3, 4.4 Hz, 1H), 1.94 (m, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 75.4, 40.4, 32.0, 17.1, 16.2; MS (CI, isobutane): m/z 115 [M + H]$^+$, 97, 71.

(*R*)-4-(2-Phenylethyl)oxetan-2-one (2c).[2a] The general procedure was followed employing 500 mg of 4-(2-phenylethyl)-oxetan-2-one (**1c**) and 246 mg of benzyl alcohol (30 h reaction time). Column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 189 mg of the title compound (38%). Separation of the enantiomers by chiral HPLC (Daicel Chiracel OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane T_r16.2 (*S*) and 17.9 (*R*) min) determined the enantiomeric excess to be 93%. $[\alpha]_D$ +37.8° (*c* 2.4, CH_2Cl_2).

(*R*)-4-Butyloxetan-2-one (2d).[3g] The general procedure was followed employing 1.0 g of 4-isopropyloxetan-2-one (**1d**) and 676 mg of benzyl alcohol (72 h reaction time). Column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 422 mg of the title compound (42%). Separation of the enantiomers by chiral GC (Chiraldex G-TA column, flow rate 0.5 mL/min, method: 100 °C for 10.00 min, ramp @ 10.00 °C/min to 130 °C for 8.00 min, ramp @ 10.00 °C/min to 160 °C for 5.00 min, T_r 11.3 (*R*) and 11.9 (*S*) min) determined the enantiomeric excess to be 97%. $[\alpha]_D$ +21.5° (*c* 5.9, CH_2Cl_2). IR (NaCl): 1826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.51 (ddt, J = 7.4, 5.9, 4.4 Hz, 1H), 3.51 (dd, J = 16.3, 5.8 Hz, 1H), 3.07 (dd, J = 16.3, 4.3 Hz, 1H), 1.86 (m, 1H), 1.78 (m, 1H), 1.39 (m, 4H), 0.93 (t, J = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 71.0, 42.4, 34.0, 26.6, 21.9, 13.5; MS (CI, isobutane): m/z 129 [M + H]$^+$, 111.

(*R*)-4-Propyloxetan-2-one (2e).[8a] The general procedure was followed employing 1.0 g of 4-isopropyloxetan-2-one (**1e**) and 759 mg of benzyl alcohol (72 h reaction time). Column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 261 mg of the title compound (26%). Separation of the enantiomers by chiral GC (Chiraldex G-TA column, flow rate 0.5 mL/min, method: 100 °C for 10.00 min, ramp @ 10.00 °C/min to 130 °C for 8.00 min, ramp @ 10.00 °C/min to 160 °C for 5.00 min, T_r 10.5 (*R*) and 11.2 (*S*) min) determined the enantiomeric excess to be 98%. $[\alpha]_D$ +25.9° (*c* 3.2, CH_2Cl_2). IR (NaCl): 1826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.53 (ddt, J = 7.4, 5.8, 4.4 Hz, 1H), 3.52 (dd, J = 16.2, 5.7 Hz, 1H), 3.07 (dd, J = 16.2, 4.3 Hz, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.46 (m, 2H), 0.99 (t, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 70.8, 42.4, 36.2, 17.9, 13.2; MS (CI, isobutane): m/z 115 [M + H]$^+$, 97, 73.

(*R*)-4-(2-Methylpropyl)oxetan-2-one (2f). The general procedure was followed employing 500 mg of 4-(2-methylpropyl)-oxetan-2-one (**1f**) and 338 mg of benzyl alcohol (72 h reaction time). Column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 200 mg of the title compound (40%). Separation of the enantiomers by chiral GC (Chiraldex G-TA column, flow rate 0.5 mL/min, method: 100 °C for 10.00 min, ramp @ 10.00 °C/min to 130 °C for 8.00 min, ramp @ 10.00 °C/min to 160 °C for 5.00 min, T_r 12.4 (*R*) and 13.2 (*S*) min) determined the enantiomer ratio to be 20:1 (90% ee). $[\alpha]_D$ +37.2° (*c* 5.8, CH_2Cl_2). IR (NaCl): 1828 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54−4.59 (m, 1H), 3.54 (dd, J = 16.3, 5.9 Hz, 1H), 3.04 (dd, J = 16.3, 4.3 Hz, 1H), 1.75−1.86 (m, 2H), 1.56−1.73 (m, 1H), 0.96 (d, J = 6.50, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 70.4, 43.7, 43.6, 25.5, 22.9, 22.3; MS (EI, 70 eV): m/z 128 (M$^+$), 113, 109, 104, 95, 91, 85, 71, 56. HRMS (FAB) m/z cacld for $C_7H_{12}O_2$: 128.0837. Found: 128.0835.

(*S*)-3-Hydroxy-5-methylhexanoic Acid, Benzyl Ester (3f). From the resolution of **1f** described above, column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 478 mg of the title compound (52%). Separation of the enantiomers by chiral HPLC (Daicel Chiracel OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane T_r 5.9 (*R*) and 7.6 (*S*) min) determined the enantiomer ratio to be 16:1 (88% ee). $[\alpha]_D$ +10.3° (*c* 6.5, CH_2Cl_2); IR (NaCl) 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.17 (s, 2H), 4.12 (m, 1H), 2.75 (br s, 1H), 2.56 (dd, J = 16.5 and 3.3 Hz, 1H), 2.45 (dd, J = 16.5 and 8.7 Hz, 1H), 1.80 (m, 1H), 1.49 (ddd, J = 14.0, 8.9, and 5.5 Hz, 1H), 1.18 (ddd, J = 13.4, 8.7, and 4.4 Hz, 1H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C δ 172.5, 135.4, 128.4, 128.0 (2C), 66.2, 65.9, 45.4, 41.8, 24.4, 23.1, 21.7; TLC R_f 0.31 (20% ethyl acetate, 80% hexane); MS (EI, 70 eV): m/z: 236 (M$^+$). HRMS (FAB) m/z cacld for $C_{14}H_{20}O_3$: 236.1413. Found: 236.1418.

(*R*)-4-(9-Decylenyl)oxetan-2-one (2g). The general procedure was followed employing 200 mg of 4-(9-decylenyl)oxetan-2-one (**1g**) and 82 mg of benzyl alcohol (72 h reaction time). Column chromatography (90% hexane, 10% ethyl acetate) of the crude reaction mixture afforded 64 mg of the title compound (32%). Separation of the enantiomers by chiral GC (Chiraldex G-TA column, flow rate 0.5 mL/min, method: 100 °C for 10.00 min, ramp @ 5.00 °C/min to 130 °C for 12.00 min, ramp @ 10.00 °C/min to 160 °C for 15.00 min, T_r 38.5 (*R*) and 39.7 (*S*) min) determined the enantiomeric excess to be greater than 99% (other enantiomer not observed). $[\alpha]_D$ +21.8° (*c* 4.7, CH_2Cl_2). IR (NaCl): 3075, 1828, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76−5.85 (m, 1H), 4.90−5.02 (m, 2H), 4.46−4.52 (m, 1H), 3.50 (dd, J = 16.2, 5.6 Hz, 1H), 3.05 (dd, J = 16.2, 4.3 Hz, 1H), 2.00−2.05 (m, 2H), 1.73−1.86 (m, 2H), 1.29−1.45 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 139.2, 114.3, 71.4, 43.0, 34.8, 33.8, 29.4 (2C), 29.2, 29.1, 29.0, 25.0; MS (EI, 70 eV): m/z 167, 150, 135, 121, 109, 95, 81, 67. HRMS (FAB) m/z cacld for $C_{13}H_{22}O_2$: 210.1620. Found: 210.1626.

(*S*)-4-(Benzyloxylmethyl)oxetan-2-one (2h).[2a] The general procedure was followed employing 250 mg of 4-(benzyloxylmethyl)oxetan-2-one (**1h**) and 113 mg of benzyl alcohol (72 h reaction time). Column chromatography (60% pentane, 30% ethyl ether, 10% toluene) of the crude reaction mixture afforded 110 mg of the title compound (44%). Separation of the enantiomers by chiral HPLC (Daicel Chiracel OD-H column, flow rate 0.9 mL/min, 15% ^{i}PrOH, 85% hexane T_r 14.1(*R*) and 23.0 (*S*) min) determined the enantiomer ratio to be 11.5:1 (84%ee). $[\alpha]_D$ +21.9° (*c* 5.3, CH_2Cl_2).

(*R*)-4-(Benzyloxy)-3-hydroxybutanoic Acid, Benzyl Ester (3h). From the resolution of **1h** described above, column chromatography (60% pentane, 30% ethyl ether, 10% toluene) of the crude reaction mixture afforded 187 mg of the title compound (48%). Separation of the enantiomers via chiral HPLC (Daicel Chiracel OD-H column, flow rate 0.9 mL/min, 15% ^{i}PrOH, 85% hexane T_r 12.8 (*S*) and 15.8 (*R*) min) determined the enantiomer ratio to be 50:1 (96% ee). $[\alpha]_D$ +6.8° (*c* 1.7, CH_2Cl_2); IR (NaCl) 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 10H), 5.31 (s, 2H), 4.56 (s, 2H), 4.27 (m, 1H), 3.53 (dd, J = 9.6 and 4.5 Hz, 1H) 3.48 (dd, J = 9.6 and 6.5 Hz, 1H) 2.90 (br s, 1H), 2.59 (dd, J = 18.6 and 6.3 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 171.9, 137.8, 135.5, 128.6, 128.4, 128.3, 128.2, 127.8, 127.7, 73.4, 73.0, 67.2, 66.5, 38.2; TLC R_f 0.15 (30% diethyl ether, 60% pentane, 10% toluene); MS (EI, 70 eV): m/z 300 (M$^+$). HRMS (FAB) m/z cacld for $C_{11}H_{13}O_4$ (M$^+$ − C_7H_7): 209.0814. Found: 209.0812.

Assignment of Stereochemistry. Stereochemical assignment of the enantiomerically enriched β-lactones **2c** and **2h** was made by their conversion to the corresponding 1,3-diol derivatives and comparison of the specific rotations to literature values. General procedure: Lithium aluminum hydride (2.0 equiv) was

added in portions to a 0 °C solution of lactone **2** in Et_2O (0.3 M). After the reactions were complete as monitored by TLC, water (*n* mL/*n* g LAH) was carefully added to the reaction followed by 3 N aqueous NaOH (*n* mL/*n* g LAH) and water (3*n* mL/*n* g LAH). The resulting granular precipitate was removed by filtration and washed with additional Et_2O. The combined filtrates were concentrated, and the diol product was isolated by column chromatography. Lactone **2c** afforded (*R*)-5-phenyl-1,3-pentanediol $[\alpha]_D$ +9.6° (*c* 2.3 EtOH) [lit. (*S*) $[\alpha]_D$ −7.2° (*c* 1.52, EtOH)];[11] lactone **2h** afforded (*S*)-1-*O*-benzyl-1,2,4-butanetriol $[\alpha]_D$ −8.4° (*c* 3.6 MeOH) [lit. $[\alpha]_D$ −7.56° (*c* 3.67, MeOH)].[12] Stereochemical assignment of the remaining lactones of unknown configuration (**2f** and **2g**) was made by analogy to these determinations. Resolved lactones **2a**, **2c**, and **2h** were converted to the corresponding *β*-hydroxy benzyl esters by reaction with BnOH (1.0 equiv) and $La(O^tBu)_3$ (5 mol %) in THF and shown by chiral HPLC to be enantiomeric to the analogous *β*-hydroxy esters derived from the resolution reactions.[5]

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(11) Nuñez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 2370−2374.

(12) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303−5305.