with water. The organic layer was dried ($MgSO_4$) and concentrated, leaving the crude nitrile, which could be purified by flash chromatography.

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Registry No. 1, 126063-56-7; 2, 126063-57-8; 3 (n = 3), 126063-58-9; 3 (n = 4), 126063-59-0; 4 (n = 3), 126063-60-3; 4 (n = 4), 126063-61-4; $H_3C(CH_2)_5CH{=}NNMe_2$, 67660-53-1; $PhCH_2CH(Et)CH{=}NNMe_2$, 126063-54-5; $PhCH_2C(Me)_2CH{=}NNMe_2$, 126063-55-6; $4\text{-}MeOC_6H_4CH{=}NNMe_2$, 14371-13-2; $H_3C(CH_2)_5CN$, 629-08-3; $phCH_2CH(Et)CN$, 53244-13-6; $PhCH_2C(Me)_2CN$, 35863-45-7; $4\text{-}MeOC_6H_4CN$, 874-90-8; $H_3C(CH_2)_2CH{=}NNMe_2$, 10424-98-3; $PhCH_2$-(*S*)-CH(Et)-CH_2NHCO-(*R*)-C(Ph)(OMe)CF_3, 126063-62-5.

Lipase-Catalyzed Irreversible Transesterification Using Enol Esters: Resolution of Prostaglandin Synthons 4-Hydroxy-2-alkyl-2-cyclopentenones and Inversion of the 4*S* Enantiomer to the 4*R* Enantiomer

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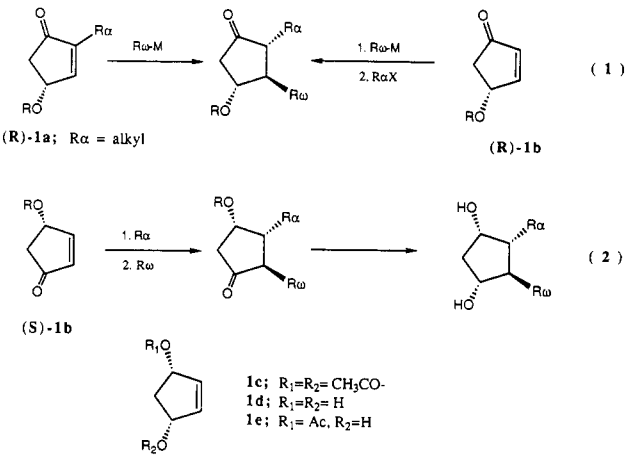
A common strategy for synthesis of prostaglandins (PGs) and their analogues is conjugate addition of ω-side chain (lower chain) to 4(*R*)-alkoxy-2-alkyl-2-cyclopentenones [(*R*)-**1a**][1] or to 4(*R*)-alkoxy-2-cyclopentenone [(*R*)-**1b**] followed by trapping with an electrophile (upper chain) suitable for construction of the α-side chain[2] (eq 1). A new strategy based on nucleophilic addition of the upper chain to the enantiomer of (*R*)-**1b** followed by electrophilic addition of the lower chain has recently been reported by Danishefsky et al. (eq 2).[3] Both (*R*)- and (*S*)-**1b** are available via enzyme-catalyzed enantioselective hydrolysis of the meso-diester **1c**[4] or transesterification of **1d**.[5] To



prepare enantiomerically pure **1a** with 4*R* absolute configuration, several methods are available which require either chemical resolution[6] or a lengthy process from a chiral intermediate.[7] As our interest in the development of an efficient method for the practical preparation of enantiomerically pure (4*R*)-**1a** from the corresponding racemates for use in synthesis of PGs,[8] we report here the enzymatic resolution of **1a** using lipases as catalyst and enol esters as solvents and as irreversible transesterification reagents. This irreversible enzymatic process has proven to be more efficient and often more enantioselective than other transesterification processes.[9] The high enantioselectivity of the process also allows conversion of the undesired *S* byproduct with high stereospecificity to the desired *R* enantiomer via Mitsunobu chemistry. With regard to the resolution strategy, transesterification instead of hydrolysis was chosen because the readily available starting materials contain an ester group which complicates the hydrolysis process (Scheme I).

Compounds **2a** and **2b** are appropriate intermediates for the synthesis of some PG analogues used for the treatment of peptic ulcer disease.[10] Several lipases, including that from Pseudomonas species (PSL), Candida cylindracea (CCL), porcine pancreas (PPL), and Aspergillus niger (ANL), and cholesterol esterase and subtilisin, all available commercially, were examined for the resolution of **2a**. It was found that all of the enzymes were selective in acylating the *R* isomer of the starting enone compound, and PPL gave the best enantioselectivity.

The resolution of **2b** was then undertaken. Of several lipases and organic solvents tested, it was found that PPL (free or immobilized on Amberlite XAD-8) in neat vinyl acetate gave the best result in terms of enantioselectivity

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(2) (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (b) Johnson, C. R.; Penning, T. D. *Ibid.* **1986**, *108*, 5655.

(3) Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.

(4) (a) Wang, Y.-F.; Chen, C. S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. (b) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875. (c) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255. (d) Sugai, T.; Mori, K. *Synthesis* **1988**, 19.

(5) Theil, F.; Ballschuh, S.; Schick, H.; Haupt, M.; Hafner, B.; Schwarz, S. *Synthesis* **1988**, 540. Jommi, G.; Orsini, F.; Sisti, M.; Verotta, L. *Gazz, Chim. Ital.* **1988**, *118*, 863. In these reports, the reaction was carried out in pyridine or triethylamine/THF using 2,2,2-trichloroethyl acetate as transesterification reagent.

(6) Rappo, R.; Collins, P.; Jung, C. *Tetrahedron Lett.* **1973**, 943.

(7) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5591.

(8) The synthesis of PG analogues from **1a** rather than that from **1b** was carried out in large-scale process (see refs 2b and 10).

(9) (a) Wang, Y.-F.; Wong, C.-H. *J .Org. Chem.* **1988**, *53*, 3127. (b) Wang, Y.-F.; Lalonde, J. J.; Mommongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200. For earlier use of isopropenyl acetate in regioselective acylation of sugars, see: Sweers, H. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1986**, *108*, 6421 and the following subsequent presentations/publications: *Proceedings of Biotechnica '87*, Hannover; 194th ACS National Meeting; Symposium on Asymmetric Synthesis of Carbohydrates from Acyclic Precursors, 1987 (see ACS Symposium Series No. 386, p 318); *U.S. Japan Joint Biotechnology Conference*, Lake Biwa, 1986 (see *Bioproducts and Bioprocesses*; Fiechter, Okada, Tanner, Eds.; Springer-Verlag: Berlin, 1989; p 148). For the use of enol esters in lipase reaction with alcohols, see: Degueil-Castaing, M.; Jeso, B. D.; Drouillard, S.; Mailard, B. *Tetrahedron Lett.* **1987**, *28*, 953 (no enantioselective transformation was reported). Laumen, K.; Breitgoff, D.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1459.

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Scheme I

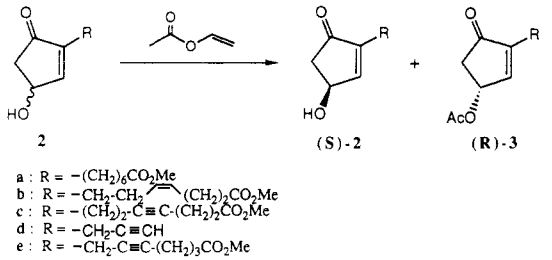
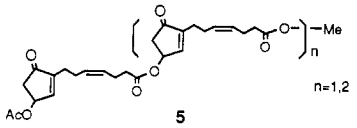


Table I. The Resolution of 2a–e and 1d with PPL in Vinyl Acetate[a]

substrate	% yield (% ee) acetate	% yield (% ee) alcohol	stereochemical preference
2a	46	41 (>98)	*R*
2b	43 (92)	35 (99.4)	*R*
2c	43	45 (96)	*R*
2d	35	48 (98)	*R*
2e	46	40 (92)	*R*
1d	52 (98)		1*S*,4*R*[b]

[a] All the reactions except that of **1d** was monitored by Chiracel HPLC column until the unreacted alcohol reached certain degree of enantiomeric excess. See the Experimental Section for details. [b] The product was (1*S*,4*R*)-4-hydroxy-2-cyclopentenyl acetate, **1e**.

and efficiency. Under this condition, the reaction proceeded smoothly at room temperature with no contamination of byproducts **5**.[11] As shown in Table I, compounds **2a–e**[12] and **1d** were successfully resolved or enantioselectively transformed under this condition. A 100-g-scale process was carried out for the resolution of **2b**.



It is worth noting that during the resolution process, the reaction was monitored by HPLC using a chiral stationary phase (chiracel OC or OD column). This process enables us to control the degree of conversion and at the same time to determine the ee of the unreacted alcohol. With this technique an enantiomeric excess as high as 99.9% can be determined. Typical chromatograms are shown in Figure 1.

Two critical challenges were considered: (a) enone (*S*)-**2b** with the undesired *S* configuration must be inverted with high stereospecificity to give the necessary (*R*)-enone (*R*)-**2b**; (b) over half of the product from the lipase reaction was (*R*)-**3b** with 92% ee. Methodology for enrichment of this material to usable optical purity (i.e. 98%) was desirable.

With respect to the first point, it was found that enone (*S*)-**2b** could be converted to (*R*)-**2b** via Mitsunobu chemistry[13] (see Scheme II).

In a representative case, when (*S*)-**2b** of 99.9% ee was submitted to Mitsunobu conditions using formic acid as

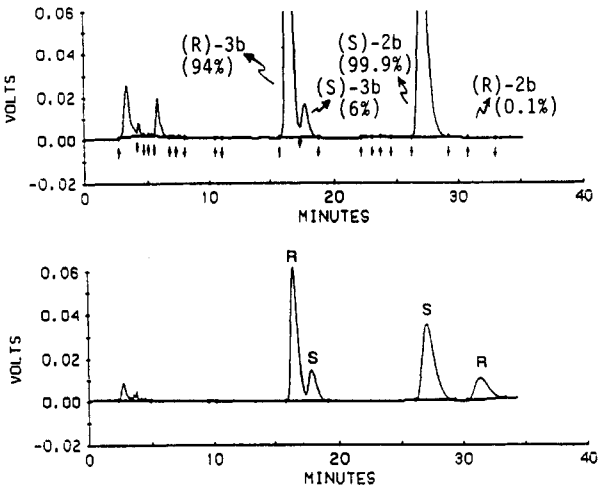
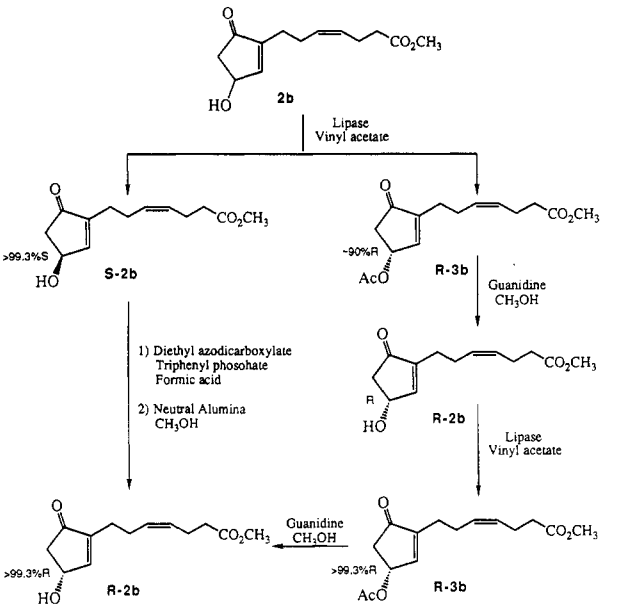


Figure 1. Column: Chiralcel OD, 25 cm × 4.6 mm. Mobile phase: 93/7 hexane/2-propanol. Flow rate: 0.7 mL/min. Detection: 215 nm.

Scheme II



nucleophile and then immediate hydrolysis of the formate ester intermediate, a 91–94% chromatographed yield of inverted enone (*R*)-**2b** was obtained with 99.3–99.6% ee. This product was then converted to its triethyl silyl derivative, (*R*)-**4b** in 94% yield after chromatography. Again, HPLC analysis on Chiracel OD column showed this material to be of identical optical purity to its precursor (99.3% ee).

This enzymatic resolution method, coupled with the Mitsunobu alcohol inversion technology described here, enables the preparation of either antipodes of the optically pure alcohol desired. With respect to the second point, a two-step process in which the acetate is removed by a purely chemical means and the recovered alcohol then resubmitted to the lipase acylation conditions was found to be most advantageous.

Referring to Scheme II, when (*R*)-**3b** was treated with 2 equiv of guanidine in CH_3OH,[14] very rapid, clean conversion to the desired compound (*R*)-**2b** was observed in less than 5 min at 0 °C. In fact, when only 0.25 equiv of guanidine were employed, the reaction profile and rate

(11) The contamination is mainly due to enzymatic reaction at the carboxy ester.

(12) For preparation of racemic enones, see: (a) For compounds **2b** and **2c**: Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786. (b) For **2d**: Collins, P. W.; Kramer, S. W.; Gasiecki, A. F.; Weier, R. M.; Jones, P. H.; Gullikson, G. W.; Bianchi, R. G.; Bauer, R. F. *Ibid.* **1987**, *30*, 193. (c) For **2a**: Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *Ibid.* **1977**, *10*, 1152. Kieczykowski, G. R.; Pagonowski, C. S.; Richman, J. E.; Schlessinger, R. H. *J. Org. Chem.* **1977**, *42*, 175.

(13) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427.

(14) Kunesch, N.; Miet, C.; Poisson, J. *Tetrahedron Lett.* **1987**, 3569.

were identical with those of the stoichiometric case, and compound (*R*)-**2b** (93% R) was recovered in 75–77% yield after chromatography. When this material was resubmitted to the action of PPL in vinyl acetate for 2 days, a 90% yield of compound (*R*)-**3b** was obtained with an enantiomeric excess of 99.6% (this represents a 98% conversion of available alcohol (*R*)-**2b**). Deacylation via guanidine in methanol as described above provided the target enone (*R*)-**2b**. HPLC showed *no* racemization during acetate removal. These results allow for complete conversion of both antipodes of **2b** into an enantiomerically pure enone, and all recovered nonenriched intermediates can be recycled to high optical purity (see Scheme II).

Experimental Section

Column chromatography separations were performed by using Merck SiO_2 60 with ethyl acetate/hexane mixtures as eluants. TLC analyses were performed on Merck SiO_2 60 F254 precoated glass plates and were visualized by charring with phosphomolybdic acid in ethanol. Melting points (differential scanning calorimetry) were obtained on a Dupont 9900 Thermal Analyzer. NMR were recorded at room temperature in $CDCl_3$. HPLC analyses were performed on Chiralcel OD, OA, or OC columns employing a chiral stationary phase (Daicel Chemical Industries) on a Gilson HPLC Instrument (Model 302 pump, Model 116 detector). The detector wavelength was set at 215 nm for monitoring. IR spectra were recorded as solutions in chloroform. UV spectra were recorded in CH_3OH.

Diethyl azodicarboxylate, triphenylphosphine, formic acid, guanidine carbonate, triethylsilyl chloride, and sodium spheres were purchased from Aldrich and used without purification. Candida cylindracea lipase (CCL), crude porcine pancreatic lipase (PPL), and cholesterol esterase (Ch.E) were purchased from Sigma Chemical Co. Pseudomonas lipase (PSL) was purchased from Amano Co. Isopropenyl acetate and vinyl acetate were purchased from Aldrich and fractionally distilled prior to use. All solvents were purchased from Burdick and Jackson and were reagent grade. Methanol was distilled from Mg. Dimethylformamide (DMF) was distilled at reduced pressure from magnesium sulfate, benzene and toluene were azeotropically distilled, chloroform was distilled from P_2O_5, and *tert*-butyl methyl ether was distilled from benzophenone ketyl (all under inert atmosphere).

General Procedure of PPL-Catalyzed Transesterification. A mixture of **2**, PPL, and distilled vinyl acetate was vigorously stirred at room temperature. The course of the reaction was monitored via HPLC on chiracel OD or OC until the ee of unreacted alcohol reached the desired point. The crude mixture was then treated with diatomaceous earth and filtered through a bed of diatomaceous earth. The filter cake was washed with methylene chloride. The combined filtrates were concentrated under reduced pressure to give the product mixture. The product was chromatographed on silica gel using a solvent gradient of 50–100% ethyl acetate in hexane to give *R*-enriched acetate (*R*)-**3** and *S*-unreacted alcohol (*S*)-**2**. Assignments of the absolute stereochemistry for (*S*)-**2** and (*R*)-**3** were based on the rotations and CD/ORD spectra as compared to the reported values of related PG-enones.[6,15]

Preparation of Methyl 7-[3(*R*)-(Acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4(*Z*)-heptenoate [(*R*)-3b] and Methyl 7-(3(*S*)-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate [(*S*)-2b] via Enzymatic Resolution. A mixture of 100.0 g (0.42 mol) of (±)-methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4-(*Z*)-heptenoate, **2b**, 100 g of porcine pancreatic lipase (this crude preparation contains ~0.1% lipase, the cost of 100 g is $8.80), and 2.5 L of distilled vinyl acetate were vigorously stirred at room temperature for 4 days. An additional 50-g portion of porcine pancreatic lipase was added, and the mixture was stirred for 1 more day. The course of the reaction was monitored by HPLC on Chiralcel OD using 93:7 hexane–2-propanol as eluant until the enantiomeric excess of unreacted alcohol was >99.8%. The crude mixture was then worked up as described in the general procedure to give 50.5 g (43%) of *R*-enriched methyl 7-[3(*R*)-(acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4(*Z*)-heptenoate, (*R*)-**3b** [^{1}H NMR ($CDCl_3$) δ 7.10 (m, 1 H, 2-H), 5.67 (m, 1 H, 3-H), 5.30 (m, 2 H, olefinic H), 3.68 (s, 3 H, OCH_3), 2.86 (dd, 1 H, 4-Hβ, J = 6.5, 18.5 Hz), 2.36 (dd, 1 H, 4-Hα, J = 2.1, 18.5 Hz), 2.4–2.25 (m, 8 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 204.3, 173.1, 170.3, 151.8, 148.8, 129.4, 128.6, 71.3, 51.3, 41.3, 33.7, 24.7, 24.3, 22.6, 20.7 ppm; IR ($CHCl_3$) 3030, 3010, 1735, 1720, 1440, 1370, 1230 cm^{-1}; $[\alpha]^{20}_D$ +45.4° (−634.3° at 365 nm) (*c* 1.080, $CHCl_3$); UV (CH_3OH) λ_{max} = 220 nm. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.24; H, 7.32], and 35.1 g (35%) of methyl 7-(3(*S*)-hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate, (*S*)-**2b**: ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 1 H, 2-H), 5.24 (m, 2 H, olefinic), 4.93 (m, 3-H, 1 H), 4.05 (b, 1 H, OH), 3.68 (s, 3 H, OCH_3), 2.80 (dd, 1 H, 4-Hβ, J = 6.0, 18.5 Hz), 2.4–2.2 (m, 4-Hα + CH_2's, 9 H); ^{13}C NMR δ 207.1, 174.1, 157.6, 146.9, 130.1, 128.8, 68.5, 51.9, 45.1, 34.2, 25.4, 24.6, 23.0 ppm; IR ($CHCl_3$) 3610, 3480 (broad), 3030, 3010, 1715 (shoulder at ~1730), 1440, 1230 cm^{-1}; $[\alpha]^{20}_D$ −14.9° (*c* 0.867, $CHCl_3$) (+1202° at 365 nm); UV (CH_3OH) λ_{max} = 221 nm; CD $[\vartheta]^{25}$ (nm) −11 900 (320), +64 909 (224) (CH_3OH). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 64.78; H, 7.74. HPLC (Chiralcel OD using 93:7 hexane in 2-propanol as eluant) indicated that purified acetate (*R*)-**3b** was of 92% ee in the *R* isomer and that recovered alcohol (*S*)-**2b** was 99.4% ee in the *S* isomer.

Enzymatic Resolution of Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)heptanoate (2a) via PPL in Vinyl Acetate. A mixture of 240 mg (1.0 mmol) of the title enone and 240 mg of crude porcine pancreatic lipase in 3 mL of distilled vinyl acetate was sealed and stirred at room temperature for a total of 9 days. Analysis on HPLC using chiralcel OC at 50 °C using hexane–2-propanol (9:1 v/v) as eluant indicated that the remaining alcohol was >99.8% *S* isomer. Resolution of the corresponding acetate was not possible under a variety of conditions. The reaction mixture was then worked up to give 269 mg of crude residue, which was purified by PTLC on silica gel (2000 μm) using 65% ethyl acetate in hexane as eluant [R_f(ROH) = 0.30 and R_f(ROAc) = 0.61]. In this manner, 130 mg (46%) of methyl 7-[3(*R*)-(acetyloxy)-5-oxo-1-cyclopenten-1-yl]heptanoate was isolated: ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 2-H, 1 H), 5.66 (dm, 3-H, 1 H), 3.68 (s, OCH_3, 3 H), 2.87 (dd, 4-Hβ, 1 H, J = 6, 19.0 Hz), 2.38 (dd, 4-Hα, 1 H, J = 2.0, 19 Hz), 2.31 (t, CH_2, 2 H, J = 7.5 Hz), 2.21 (bt, 2 H, J = 7.5 Hz), 2.10 (s, OAc, 3 H), 1.62 (m, 2 H), 1.35 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 204.5, 173.8, 170.3, 151.4, 149.6, 70.2, 51.2, 41.3, 33.7, 28.7, 28.5, 26.9, 24.5, 24.3, 20.6 ppm; IR ($CHCl_3$) 3020, 3010, 1715 (shoulder at 1735), 1435, 1370, 1240, 1025 cm^{-1}; UV (CH_3OH) λ_{max} = 221 nm; $[\alpha]^{20}_D$ +47.6° (*c* 0.871, $CHCl_3$) (−649.3° at 365 nm); CD $[\varphi]^{25}$ (nm) −7556 (315) (negative maximum), +49 533 (224) (positive maximum). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.80; H, 7.86. Found: C, 63.32; H, 7.91. The unreacted alcohol (*S*)-**2a** was obtained in 41% yield (99 mg): mp = 60.1 °C (DSC); the ^{1}H and ^{13}C NMR, IR, and UV spectra were identical with those of the racemic alcohol **2a**: $[\alpha]^{20}_D$ −9.8° (*c* 1.072, $CHCl_3$) (+1216.5° at 365 nm); CD $[\varphi]^{25}$ (nm) −175 176 (225) (negative maximum), +24 731 (314) (positive maximum) (CH_3OH). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.78; H, 8.52.

Enzymatic Resolution of Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4-heptynoate (2c) via PPL in Vinyl Acetate. A mixture of 116 mg (0.49 mmol) of title compound and 116 mg of crude porcine pancreatic lipase (PPL) in 3 mL of distilled vinyl acetate was sealed and stirred at room temperature. After 4 days, HPLC showed that the remaining alcohol was of 96% ee in *S* isomer. The product acetate could not be resolved by HPLC. Purification by PTLC on 2000-μm silica plates (R_f(ROAc) = 0.55 and R_f(ROH) = 0.28) using 65% ethyl acetate/hexane as eluant gave 58 mg (43%) of methyl 7-[3(*R*)-(acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4-heptynoate [^{1}H NMR ($CDCl_3$) δ 7.25 (m, 2-H, 1 H), 5.80 (dm, 3-H, 1 H), 3.70 (s, OCH_3, 3 H), 2.88 (dd, 4-Hβ, 1 H, J = 6.5, 19 Hz), 2.55–2.3 (m, 4CH_2 + 4-Hα, 9 H), 2.10 (s, OAc, 3 H); ^{13}C NMR ($CDCl_3$) δ 204.7, 172.4, 170.5, 152.8, 147.8, 79.4, 70.4, 41.7, 41.4, 33.7, 24.1, 20.9, 16.8, 14.6 ppm; IR ($CHCl_3$) 3020, 3010, 1735, 1717, 1437, 1370, 1240, 1027 cm^{-1};

(15) Jarosjewski, J. W.; Olafsdottir, E. S. *Tetrahedron Lett.* **1986**, 5297.

(16) We thank Dr. Paul Collins for providing us with samples of racemic enones **2c**, **2d**, and **2e** as well as for his technical assistance.

(17) The identity of all new compounds has been established by IR, NMR, and mass spectroscopy. The purity and elemental composition were verified by elemental analysis or HRMS. Compounds **2b**-*d*, **3b**-*d*, and **4b** are liquids.

$[\alpha]^{20}_D$ +41° (c 0.976, $CHCl_3$) (−606.4° at 365 nm); CD $[\vartheta]^{25}$ (nm) −6022 (315) (negative maximum), +46 668 (220 nm) (positive maximum)] and 51 mg (45%) of methyl 7-(3(*S*)-hydroxy-5-oxo-1-cyclopentenyl)-4-heptynoate whose TLC, ^1H and ^{13}C NMR, IR were identical with those of the racemic alcohol; $[\alpha]^{20}_D$ −16.7° (c 0.927, $CHCl_3$) (+984.4° at 365 nm); CD $[\vartheta]^{25}$ (nm) +7690 (312), −55 275 (225) (CH_3OH).

Enzymatic Resolution of 3-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)propyne (2d) via PPL in Vinyl Acetate. A mixture of 166 mg (1.22 mmol) of the title alcohol and 166 mg of crude porcine pancreatic lipase in 4 mL of distilled vinyl acetate was sealed and stirred at room temperature for a total of 7 days. HPLC indicated that the remaining (*S*)-alcohol was of 98% ee. The product acetate could not be resolved by HPLC. The crude product (205 mg) was purified by PTLC on 2000-μm silica gel plates using 65% ethyl acetate in hexane as eluant (R_f(ROAc) = 0.60 and R_f(ROH) = 0.37) to give 76 mg (35%) of 3-[2(*R*)-(acetyloxy)-5-oxo-1-cyclopenten-1-yl]propyne [^1H NMR ($CDCl_3$) δ 7.44 (q, 2-H, 1 H, *J* = 2.1 Hz), 5.75 (m, 3-H, 1 H), 3.13 (q, CH_2, 2 H, *J* = 2.1 Hz), 2.93 (dd, 4-Hβ, 1 H, *J* = 2.2, 19.0 Hz), 2.21 (t, C≡C*H*, 1 H, *J* = 5.3 Hz), 2.11 (s, OAc, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.6, 170.2, 153.5, 144.7, 78.8, 71.2, 69.8, 41.6, 20.7, 15.2 ppm; IR ($CHCl_3$) 3300, 3020, 3010, 1740, 1720, 1640, 1410, 1370, 1240, 1025 cm^{-1}; UV (CH_3OH) λ_{max} = 219 nm; $[\alpha]^{20}_D$ +52.2° (c 0.928, $CHCl_3$) (−713° at 365 nm); CD $[\vartheta]^{25}$ (nm) −3968 (319), +27 494 (216) (CH_3OH)] and 65 mg of 3-(2(*S*)-hydroxy-5-oxo-1-cyclopenten-1-yl)propyne whose ^1H NMR, IR, and UV were identical with those of the racemic alcohol **2d**: $[\alpha]^{20}_D$ −8.7° (c 0.863, $CHCl_3$) (+1693° at 365 nm); CD $[\vartheta]^{25}$ (nm) +9923 (318 nm), −50 781 (224) (CH_3OH).

Enzymatic Resolution of Methyl 7-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)-5(*Z*)-heptenoate (2e) via PPL in Vinyl Acetate. A mixture of 83 mg (0.35 mmol) of the title alcohol and 83 mg of crude porcine pancreatic lipase in 3.0 mL of distilled vinyl acetate was sealed and stirred at room temperature for a total of 7 days. HPLC indicated that the remaining (*S*)-alcohol had a 92% ee. The acetate product could not be resolved by HPLC. Purification of the product (86 mg) with PTLC on 2000-μm silica gel phase using 65% ethyl acetate in hexane as eluant gave 45 mg (R_f = 0.61, 46%) of methyl 7-[3(*R*)-(acetyloxy)-5-oxo-1-cyclopentene-1-yl]-5(*Z*)-heptenoate [^1H NMR ($CDCl_3$) δ 7.12 (m, C_2H, 1 H), 5.72 (dm, 3-H, 1 H), 5.47 (m, olefinic H, 2 H), 3.68 (s, OCH_3, 3 H), 2.96 (, bis allylic CH_2), 2.89 (dd, 4-Hβ, 1 H, *J* = 6.5, 19.0 Hz), 2.48 (dd, 4-Hα, 1 H, *J* = 6.5, 19.0 Hz), 2.48 (dd, 4-Hβ, 1 H, *J* = 2.1, 19.0 Hz), 2.31 (t, CH_2CO_2, 2 H, *J* = 10.1 Hz), 2.10 (m, 2 H), 2.10 (s, OAc, 3 H), 1.70 (quint, isolated CH_2, 2 H, *J* = 7.5 Hz); IR ($CHCl_3$) 3020, 3010, 1715 (shoulder at ~1735), 1435, 1370, 1240, 1025 cm^{-1}; $[\alpha]^{20}_D$ +47.1° (c 0.935, $CHCl_3$) (−649.2° at 365 nm); UV (CH_3OH) λ_{max} = 218 nm; CD $[\vartheta]^{25}$ (nm) −4339 (314), +29 793 (218) (CH_3OH). Anal. Calcd for $C_{15}H_{20}O_5$: C, 63.81; H, 7.14. Found: C, 63.65; H, 7.04] and 33 mg (R_f = 0.34, 40%) of methyl 7-(3(*S*)-hydroxy-5-oxo-1-cyclopenten-1-yl)-5(*Z*)-heptenoate whose ^1H NMR, IR, TLC were identical with those of racemic alcohol **2e**: $[\alpha]^{20}_D$ −19° (c 0.627, $CHCl_3$) (+1031° at 365 nm); CD $[\vartheta]^{25}$ (nm) +4561 (312), −25 707 (221) (CH_3OH).

Enzymatic Acetylation of *cis*-2-Cyclopentene-1,4-diol (1d) via PPL in Vinyl Acetate. A mixture of 100 mg (1.0 mmol) of the title alcohol and 100 mg of crude PPL in 4.0 mL of distilled vinyl acetate was sealed and stirred at room temperature for a total of 5 days. Purification of the crude product (188 mg) with silica gel column chromatography afforded monoacetate 88 mg (52%); $[\alpha]^{25}_D$ −66.0° (c 1.0, $CHCl_3$). The optical purity of product was determined to be 98% (calculated from optical rotation) [lit.[5] $[\alpha]^{20}_D$ −66.3° (c 1, $CHCl_3$)]. ^1H NMR was identical with that of the reported value.[5]

Mitsunobu Inversion of Methyl 7-(3(*S*)-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate [(*S*)-2b]. To a mixture of 7.14 g (30.0 mmol) of the title alcohol and 15.7 g (60.0 mmol) of triphenylphosphine in THF (100 mL) under argon was added 2.26 mL, 2.76 g (60.0 mmol), of formic acid via syringe. The solution was cooled to ~10 °C in an ice bath. The reaction mixture was maintained at ≤15 °C while 10.44 g (9.49 mL, 60.0 mmol) of diethyl azodicarboxylate was added dropwise via syringe. The pale yellow solution was warmed to room temperature and stirred at room temperature overnight. TLC (80% ethyl acetate/hexane on silica gel) showed complete consumption of starting alcohol. The solvents were removed at reduced pressure to give a viscous oil. This was dissolved in 200 mL of *tert*-butyl methyl ether (TBME), and to this was slowly added 400 mL of hexane, and the mixture stirred at room temperature for 20 min. The mixture was filtered. The filter pad was washed with two 100-mL portions of 1:1 TBME–hexane. The combined filtrates were concentrated at reduced pressure to give 12.80 g of an amber oil, which was dissolved in 300 mL of absolute methanol and stirred mechanically. To this was added gradually 200 g of Woelm Super 1 (neutral) alumina. The mixture was stirred at room temperature for 5 h to hydrolyze the formate ester intermediate. The mixture was filtered through a glass-fritted funnel, and the filter cake was washed with three 100-mL portions of CH_3OH. The combined filtrates were concentrated at reduced pressure to give ~12 g of residue, which was purified by flash chromatography on silica gel using gradient elution (30–75% ethyl acetate in hexane) to give 8.22 g of product which still contains 6–10% of 1,2-dicarboxyhydrazine (determined by ^1H NMR), which is removed in the subsequent step. An analytical sample was obtained by PTLC on 2000-μm silica gel plates using two elutions of 65% ethyl acetate in hexane. The twice purified sample was identical to (4*S*)-alcohol by normal phase HPLC, TLC, ^1H and ^{13}C NMR, UV and IR spectroscopy: $[\alpha]^{25}_D$ +16.6° (c 1.024, $CHCl_3$) (−1174° at 365 nm); CD $[\vartheta]^{25}$ (μm) −11 900 (320) (negative maximum), +64 909 (224) (positive maximum) (CH_3OH). HPLC on Chiracel OD using 93/7 hexane–2-propanol as eluant indicated that the ratio of (4*R*)- to (4*S*)-alcohols was 99.4/0.6.

Preparation of Methyl 7-[5-Oxo-3(*R*)-[(triethylsilyl)-oxy]-1-cyclopenten-1-yl]-4(*Z*)-heptenoate [(*R*)-4b]. To a 10 °C solution of 34.6 g (0.136 mmol) of 94% pure alcohol (*R*)-**2b**, 34.3 g (0.34 mmol) of triethylamine, and 4.76 g (0.07 mmol) of imidazole in 100 mL of DMF under nitrogen was added dropwise via syringe 24.0 g (26.7 mL, 0.16 mmol) of triethylsilyl chloride. The mixture was warmed to room temperature for 4 h. TLC (silica gel with 1:1 ethyl acetate–hexane as eluant) showed complete conversion of alcohol (R_f = 0.60). The mixture was poured into 300 mL of 1:1 toluene–hexane, and this was washed with 300 mL of water followed by three 100-mL portions of water and then 50 mL of brine and dried over sodium sulfate. Removal of solvent at reduced pressure followed by in vacuo treatment of 2×10^{-2} Torr at 50 °C for 2 h gave 44.76 g of crude product, which was purified by chromatography on silica gel using a step gradient of 10–20% ethyl acetate in hexane; 40.2 g (84%) of purified TES-enone was obtained in this manner. HPLC on Chiralcel OD using 93:7 hexane–2-propanol indicated an enantiomer ratio (*R*/*S*) of 99.3:0.7: ^1H NMR ($CDCl_3$) δ 7.04 (m, 1 H, C_2H), 5.34 (m, 2 H, cis olefin), 4.90 (m, 1 H, 3-H), 3.68 (s, 3 H, OCH_3), 2.75 (dd, 1 H, 4-Hβ, *J* = 6.0, 18.0 Hz), 2.29 (dd, 1 H, 4-Hα, obscured), 2.4–2.2 (m, 8 H, CH_2), 1.0 (t, 9 H, $3CH_3$, *J* = 8.0 Hz), 0.67 (q, 6 H, $3CH_2$, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 206.3, 173.7, 157.3, 146.8, 130.3, 129.0, 69.1, 51.9, 45.9, 34.4, 25.4, 24.8, 23.2, 7.1, 5.1 ppm; IR ($CHCl_3$) 3020, 3010, 1735, 1710, 1440, 1355, 1235, 1080 cm^{-1}; UV (CH_3OH) λ_{max} = 222 nm; $[\alpha]^{20}_D$ +12.3° (c 0.814 g/dL, $CHCl_3$) (−1018.4° at 365 nm); CD $[\vartheta]^{25}$ (nm) −12 166 (315) (negative maximum); +66 507 (224) (positive maximum) (CH_3OH). Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.75; H, 9.15. Found: C, 64.67; H, 9.20.

Preparation of Methyl 7-(3(*R*)-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate [(*R*)-2b] from Methyl 7-[3-(*R*)-(Acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4(*Z*)-heptenoate [(*R*)-3b] via Deacylation. A stock solution of 0.5 M guanidine in CH_3OH was prepared by adding 1.78 g (77.4 mmol) of hexane (3×) washed sodium spheres to ice-cooled CH_3OH (154 mL) under argon atmosphere. When all the sodium had reacted, 14.2 g (79.0 mmol) of guanidine carbonate was added. This solution was stirred at room temperature for 25 min, and the mixture was allowed to stand to settle out precipitated salts. In a separate flask was placed 12.8 g (45.6 mmol) of (*R*)-**3b** (93:7 *R*/*S* ratio) in 50 mL of absolute CH_3OH under argon. This was cooled to 0 °C in an ice bath, and to it was added via syringe 100 mL of 0.5 M guanidine in CH_3OH prepared above, over ~5 min. This mixture was stirred at ~10 °C for 5 min. TLC (80% ethyl acetate in hexane on silica gel) showed complete consumption of acetate. To the reaction mixture was then added 2.86 mL (3.0 g, 50.0 mmol) of glacial acetic acid to neutralize the guanidine. After the mixture was stirred for 5 min, solvent was removed at reduced pressure to give a thick slurry. The residue was partitioned between 100

mL of water and 100 mL of toluene–ethyl acetate (1:1 v/v). The aqueous layer was further extracted with two 50-mL portions of ethyl acetate. The combined organic layers were washed with two 50-mL portions of water and 50 mL of brine and dried over sodium sulfate. Removal of solvent at reduced pressure gave a deep amber oil, which was purified by flash chromatography on silica gel with 50% ethyl acetate in hexane to give 8.06 g of (*R*)-**2b** (77%) after exhaustive removal of solvent. ^{1}H and ^{13}C NMR were identical with previously isolated pure (*S*)-**2b**. HPLC on Chiracel OD using hexane–2-propanol (93:7) as eluant indicated a 93:7 *R*/*S* mixture of alcohols which showed that *no* racemization had taken place during deacylation.

Enzymatic Optical Enrichment of Methyl 7-(3(*R*)-Hydroxy-5-oxo-1-cyclopenten-1-yl)-4(*Z*)-heptenoate [(*R*)-2b]. Compound (*R*)-**2b** obtained above (7.5 g, 31.5 mmol) with 93:7 *R*/*S* ratio and 7.5 g of crude porcine pancreatic lipase in 180 mL of distilled vinyl acetate was stirred vigorously at room temperature for 45 h. HPLC of an aliquot on Chiralcel OD (using 93:7 hexane–2-propanol as solution system) showed excellent conversion of alcohol (*R*)-**2b** to the corresponding acetate (*R*)-**3b**. In fact, 98% of available (*R*)-alcohol had been consumed to give (*R*)-acetate with greater than 98.8% ee. The mixture was filtered through diatomaceous earth, and the filter cake washed with two 100-mL portions of methylene chloride. The combined filtrates were concentrated under reduced pressure to give 8.90 g of residue, which was purified by chromatography on silica with 20% ethyl acetate in hexane as eluant. By this technique, 7.53 g (85%) of (*R*)-**3b** was obtained in 98.8% ee, which was identical with the previously isolated (*R*)-acetate by ^{1}H and ^{13}C NMR, HPLC, and TLC.

Deacylation of Optically Enriched Methyl 7-[3(*R*)-(Acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4(*Z*)-heptenoate [(*R*)-3b]. To a room-temperature solution of 7.47 g (26.6 mmol) of (*R*)-**3b** (98.8% of ee) in 25 mL of absolute methanol under argon was added dropwise via syringe 5.2 mL (2.6 mmol) of stock 0.5 M guanidine in methanol prepared above. The reaction was stirred at room temperature for 30 min. TLC on silica gel with 80% ethyl acetate in hexane showed complete conversion of acetate to free alcohol. The solvent was removed at reduced pressure, and the residue was partitioned between 150 mL of 1:1 toluene–ethyl acetate and 50 mL of water. The aqueous layer was further extracted with 50 mL of ethyl acetate. The combined organic layers were washed with two 25-mL portions of water and 25 mL of brine and dried over sodium sulfate to give 6.25 g of crude residue. This was purified by flash chromatography on silica gel with gradient elution of 50–75% ethyl acetate in hexane to give 4.89 g (77%) of (*R*)-**2b**. HPLC on Chiracel OD using 93:7 hexane–2-propanol as eluant indicated a 98.8% ee for the desired product. This product was identical to previously prepared (4*R*)-alcohol by HPLC, ^{1}H and ^{13}C NMR, and TLC.

Molecular Recognition in Macroporous Polymers Prepared by a Substrate Analogue Imprinting Strategy

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Polymers showing molecular recognition properties can be obtained by a technique called molecular imprinting.[1-5] In principle, imprinting of small molecules is carried out as follows.

(a) Functionalized monomers are bound, covalently or noncovalently, to a print molecule or template.

(b) The resulting print assembly is copolymerized with an excess of a cross-linking agent in an inert solvent to form a rigid polymer.

(c) The polymer is freed from print molecules, in most cases by hydrolysis or extraction.

(d) In binding experiments, the polymers thus formed are able to recognize selectively print molecules used in the polymerization step. The recognition observed has been ascribed to the formation of binding sites containing functional groups attached to the polymer network at defined positions.

Previously, we have developed an imprinting procedure for amino acid derivatives based on noncovalent interactions both in step a and in step d.[2] Following this procedure, polymers showing a high selectivity for the print molecule applied in the imprinting step could be prepared.[3,4] In some cases it may be of interest to use a substrate analogue as print molecule, in particular if the latter is expensive or difficult to synthesize. Here we wish to report on an imprinting procedure employing a print molecule with its configuration inverted, compared with that of the substrate interacting most strongly with the polymer in the binding assays. To our knowledge, this is the first example of the use of a substrate analogue as print molecule leading to a polymer showing inverse stereoselectivity.

Table I. Distributions and Enantioselectivities Found for Polymers A and B Prepared by Molecular Imprinting with Derivative 1 and the Print Assembly PVB:L-*p*-NH_2PheOEt (2:1 Molar Ratio), Respectively[a]

polymer	K_D	α (K_D/K_L)
A	0.59	1.26 ± 0.10
B	0.46	0.83 ± 0.01

[a] Imprinted polymers were equilibrated with substrate at room temperature using a batch procedure. The substrates D- and L-*p*-NH_2PheO[C-1,^{14}C]Et were applied separately in the reaction mixtures and the same polymer was used in two or three binding experiments. After completion of a binding cycle, polymers were freed from bound substrate by extraction (see Experimental Section) and then reapplied in further binding experiments. The K_D given is the distribution coefficient (ratio of the amount of bound and free enantiomer) for the D form in the first binding experiment. It was found that the values of both K_D and K_L decreased on using the polymers repeatedly. The separation factor $\alpha = K_D/K_L$ represents an average value, and the error limits given are standard deviations.

Results and Discussion

The derivatized print molecule, N^2-propionyl-O^1-acryl-

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