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The Synthesis of Three Important Lactones *via* an Enzymatic Resolution Strategy that Improves ee's and Yields

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Abstract: Three important lactones have been synthesized in high enantiomeric purity by a complimentary, two-enantioselective-step strategy. In this approach, an enzymatic kinetic resolution is performed on a starting material that has been enriched in the faster-reacting enantiomer by an earlier enantioselective step. The results show that percent conversions, yields and ee's can be dramatically increased by this complimentary approach, and they illustrate how modestly enantioselective techniques can be combined with kinetic resolution procedures to yield optically pure compounds. The utility of many modestly enantioselective (and hence sometimes disregarded) techniques can be enhanced thereby.

Introduction

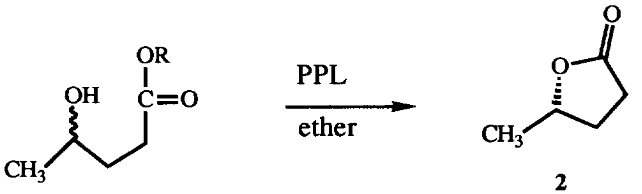
The need for methods that produce enantiomerically pure compounds is burgeoning.[1] Although numerous enantioselective methods exist,[2] pharmaceutical chemists criticize and avoid many of them[2b] because they produce only a predominance of one enantiomer (e.g. 70% ee). On the other hand, traditional synthetic organic chemists criticize pharmaceutical chemists for their frequent use of enzymatic kinetic resolution reactions (e.g. the enzymatic hydrolysis of racemic esters) to produce pure enantiomers. In these methods, one must stop the reaction prior to 50% conversion[3,4] (and hence waste >50% of the starting material) to avoid the onset of the undesired enantiomer.

We wish to popularize a strategy that alleviates the shortcomings of both methods and expands the options available to produce pure enantiomers: One can do an enantioselective step that produces predominantly the eutomer (the enantiomer that reacts fastest with the enzyme), followed by an enzymatic resolution to produce the pure enantiomer. This two-step approach would allow a host of previously unused, moderately enantioselective reactions to become useful in the synthesis of pure enantiomers. Another advantage of this combined, complementary approach is that greater than 50% conversion can be achieved in the resolution step because the starting material is already enriched in the eutomer. Although syntheses involving two enantioselective steps are well documented,[3-6] the general result has been to improve the ee at the expense of the chemical yield. For example, two consecutive resolutions have been done to improve enantiomeric purities.[3,5,6] But clearly the second resolution lowers the yield.

The efficacy of this complementary strategy is illustrated below by the high-ee synthesis of three synthetically important lactones.

Results and Discussion

The kinetic lactonization of γ-hydroxyesters by porcine pancreatic lipase (PPL) has been demonstrated by Gutman[7] and coworkers (eq. 1). In this case, the reaction gives an ee of 98% if it is carried out to 21% conversion, and the ee drops to 85% if it is carried out to 41% conversion. The reaction has been used in the synthesis of the Japanese beetle pheromone in 78% ee at 29% conversion.[5a] Clearly this chemistry has tremendous potential because of the importance of lactones in biologically active compounds.[8] However, it is restricted to very low yields if high enantiomeric purity is desired.



(1)

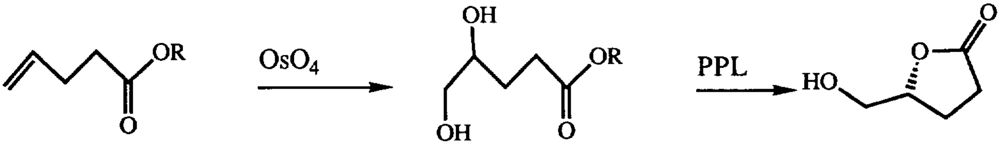
2

1a, R = CH_3
1b, R = CH_2CH_3

21% conversion (S, 98% *ee*)
41% conversion (S, 85% *ee*)

To illustrate our approach to alleviate this limitation, we prepared (R)-dihydro-5-(hydroxymethyl)-2(3H)-furanone (**5**, eq. 2). Compound **5** is a valuable synthetic intermediate,[9] and it has been used in the synthesis of anti-AIDS drugs.[10] We reasoned that it could be prepared from a diol precursor (**4** ---> **5**) by Gutman's method,[7] assuming a preference for five-membered ring formation. This diol precursor was synthesized by standard catalytic osmylation[11] of **3**, and the resulting racemic diol was treated with various enzymes to promote lactonization. PPL, Candida cylindracea lipase and pig liver esterase were tried. PPL was the most effective enzyme tried and ether was the most effective solvent (better yields and ee's).[7]

As Table 1 shows, an ee of 61% was obtained when the PPL lactonization was carried out to 28% conversion, and at 51% conversion, the ee was 24% (as determined by chiral capillary GC). We then prepared **4b** by asymmetric osmylation[12] and obtained the (R)- diol ester in 80% ee. This scalemic mixture was treated with PPL, and ee's of 91% and 97% were obtained (Table 1) at 57% and 37% conversion, respectively (it is important to note that yields were always similar to percent conversions). Clearly, a dramatic increase in



(2)

3a, R = Et
3b, R = 1-octyl

4a, R = Et
4b, R = 1-octyl

5

yield and ee has been achieved by this two-step, complimentary process, and no additional synthetic step was used. It was somewhat surprising that the octyl ester reacted almost as fast as the ethyl ester.

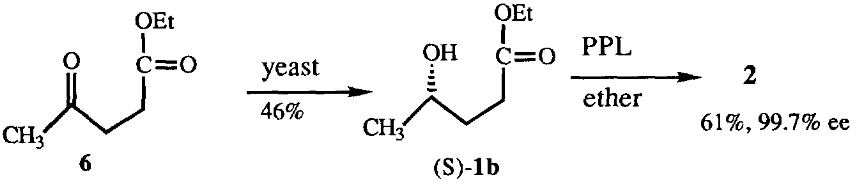
Table 1. Reactions of 1-Octyl 4,5-dihydroxypentanoate (**4b**) with PPL in Ether[a]

%ee of 4b	Reaction time, h	% conversion	NMR yield of 5	%ee of 5
80	142.5	67	65[b]	90
86	113.5	57	56	91
88	47.5	37	35	97
87	94.75	70	42	94
8	20.5	51	52	24
0	162.5	28	15[c]	61
0	56.5	30	19[c]	60

a. A 200 mg sample of **4b** and 1.0 g of PPL was stirred at room temperature in 10 mL of ether for the indicated time. b. Yield adjusted for removal of several aliquots. c. Isolated yield after liquid chromatography purification

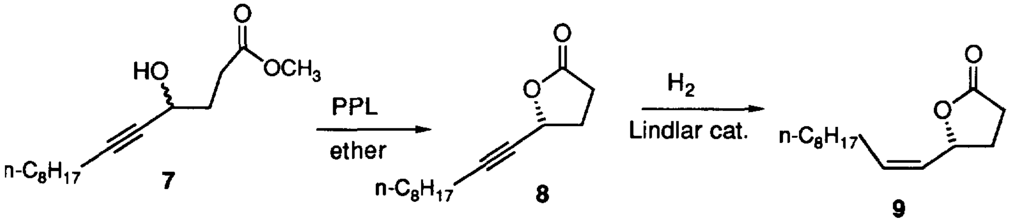
The methyl and ethyl esters of **4** were subject to spontaneous lactonization. For example, when the **4a** was treated with OsO_4 and N-methylmorpholine oxide[13] (NMO), 11% of the resulting diol ester product had lactonized. The use of the octyl ester and another osmylation technique[11] (using tetraethylammonium acetate and tert-butylhydroperoxide) gave no lactone along with **4b**. Care must be taken to avoid lactonization when doing the asymmetric osmylation;[12] the pH should not get below 6 or above approximately 11.

The simple lactone (S)-**2** has been used in the synthesis of sulcatol,[14] Geodiamolide A[15] and (-)-botryococcene.[16] Interestingly, the eutomer in the PPL-promoted lactonization of **1** can be prepared by Baker's yeast reduction[17] of keto ester **6**. We repeated the Baker's yeast reduction of **6** and obtained a reproducible yield of 46% in 90-96% ee. This product [predominantly (S)-**1**] was treated with PPL to 61% conversion (eq. 3), which gave a product that was measured by capillary GC to be 99.7% ee. This conversion was almost triple that of the original procedure (that gave 98% ee), and still a better enantiomeric purity resulted. Also, the synthesis of pure **6** by other methods is not trivial.[18] A one-pot synthesis of **6** ---> **1** ---> **2** was performed by doing the yeast reduction in water and then directly adding PPL in several portions. Although the reaction time was one month, a 21% yield of product (98% ee) was obtained.



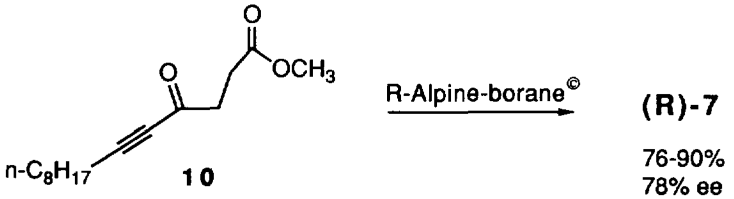
(3)

As mentioned above, the Japanese beetle sex pheromone (**9**) has been prepared by using the PPL lactonization (eq. 4) of Gutman et al.[7] as the enantioselective step (eq 4).[5a] When the reaction was carried out to 29% conversion, a 78% ee resulted.[5a] Again, the yield is low, and the level of enantiomeric purity



(4)

would reduce the effectiveness of this pheromone product at attracting the beetles.[19] However, the hydroxyester (7, eq. 4) can be made by a chiral organoborane method, also in 78% ee, and in 76-90% chemical yield.[20,21] We made (R)-7 (70-78% ee)[20] by this method and then treated it with PPL in ether. Reduction of **8** produced in this way, using hydrogen and Lindlar catalyst,[5a] gave the pheromone. When the lipase reaction was carried out on optically active 7 to 45% conversion, the ee of **8** was 99.2%, and when the lactonization was carried out to 34% conversion (30% yield) with purified PPL,[22] the ee was 94.8% (as shown by chiral capillary GC).[23] Although we were unable to determine the ee's of the pheromone products,[23] it is reasonable to assume that they are the same as those of the unhydrogenated precursor **8**.



(5)

The above methods show the advantage of using a starting material that is enriched in the eutomer involved in an enzymatic kinetic resolution reaction. Both the yield and enantiomeric purities can be improved dramatically in this way. Also, it is important to note that no additional steps were added to the syntheses of these molecules: An enantioselective step was merely substituted for a nonselective step. The results also show how modestly enantioselective methods can be used advantageously to produce products of high enantiomeric purity.

Experimental Section

Enzymes and chemicals: PPL was purchased from ICN as steapsin and purified forms. Other enzymes were purchased from Sigma Chemical Co. The ether used came straight from a reagent can (ether dried by distillation from sodium/benzophenone ketyl did not work in the PPL lactonization reaction, and when significant amounts of water were added, low ee's resulted).

Analysis: The compounds used in this study have been reported in the literature.[24,25] NMR (75 MHz ^{13}C and 300 MHz ^{1}H) spectra (performed in CDCl3) of the compounds described were provided for editorial review. Enantiomeric excesses of the lactones were determined by capillary GC using β–DEX 120 (Supelco) and Chiraldex™ G-TA (Astec) columns. Yields were calculated as isolated yields after distillation or liquid chromatography purification, or were determined by NMR using 1,3,5-trimethylbenzene or benzene as an internal standard. Percent conversions were determined by ^{1}H NMR using the relative integration areas of signals from the lactone versus the hydroxyester starting materials (since the yields and percent conversions were very similar, this procedure was valid). TLC was done on precoated silica gel plates and the spots were visualized by *p*-anisaldehyde spray. The products described below were >96% pure unless otherwise noted. IR spectra were carried out on NaCl disks.

1-Octyl-4,5-dihydroxypentanoate (4b). To an ice-cooled mixture of 1-octyl 4-pentenoate[24] (**3b**, 412 mg; 1.94 mmol), 134 mg (0.51 mmol) of Et_4NOAc, 0.05 mL of 70% *tert*-butyl hydroperoxide and 4 mL of acetone was added 0.4 mL of 1% OsO_4 in *tert*-butanol.[11] After stirring 35 min, 0.43 mL *t*-BuOOH (3.4 mmol total) was added, and the mixture was stirred at room temperature for 15 3/4 h. The mixture was cooled with an ice-bath, and 4 mL of ether and 0.5 mL of 20% $NaHSO_3$ were added. After 1 h, 1 mL of saturated NaCl was added and the mixture was saturated with NaCl. The organic layer was collected and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* leaving 484 mg (100% crude yield) of **4b**, which was pure to ^{13}C NMR: IR 3600-3200, 1766 and 1734 cm^{-1}; ^1H NMR δ 0.9 (t, J = 7 Hz, 3H), 1.2-1.5 (m, 10H), 1.6-1.8 (m, 5H), 2.4-2.6 (m, 2H), 3.4-3.8 (m, 3H), 4.1 (t, J = 7 Hz, 2H overlapping with 2 O$\underline{H}$); ^{13}C NMR δ 14.6, 23.1, 26.4, 28.5, 29.1, 29.67, 29.75, 31.0, 32.3, 65.4, 66.9, 71.9, 174.8.

1-Octyl-(R)-4,5-dihydroxypentanoate[25] [**(R)-4b)**]. To a 636 mg (3 mmol) sample of **3b** in 15 mL of *tert*-butanol (cooled with an ice bath) was added 4.2 g of AD-mix-α.[12] After 6.5 h, no starting material was present by TLC, and 4.5 g of Na_2SO_3 was added and the mixture was stirred 0.5 h. CH_2Cl_2 (30 mL) was added and the mixture was stored in the freezer overnight. The resulting organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried and concentrated *in vacuo* to give 694 g (94%) of crude (pure by ^{13}C NMR) **(R)-4b**. Spectral data are the same as above. The product could be isolated by low-temperature recrystalization from MeOH (mp 23.5-24.5 °C). Samples obtained by these procedures were treated in MeOH with *p*-toluenesulfonic acid (*p*-TsOH) to give **5b**, and determination of the ee was done on the lactone by chiral GC. A typical procedure[26] was to treat 12 mg of **4b** in 2 mL of MeOH with a few crystals of *p*-TsOH and overnight stirring followed by neutralization ($CaCO_3$) and filtration. The ee of the crude **4b** was 80%, and recrystallized product had an ee of up to 88%.

(R)-Dihydro-5-(hydroxymethyl)-2(3H)-furanone (5). A mixture of 200 mg of **4b** (0.81 mmol), 2.0 g of PPL (steapsin grade) and 10 mL of ether was stirred magnetically for three days, and the reaction was followed by NMR (after filtration of aliquots and evaporation of the ether). Additional PPL (0.35 g) was added and the mixture was stirred three more days. The reaction mixture was filtered and the solid residue was washed twice with ether. The combined organic layers were dried ($MgSO_4$) and concentrated. NMR yield of the product was 59%, and starting with **4b** that had an ee of 80% gave **5** that had a 90% ee. Other results are given in Table 1. The yield was verified by isolating the product by silica gel flash chromatography (95:5 ether:MeOH). Isolated yields were within a few percent of the NMR yields. The product gave the same spectral and chromatographic data as those of a commercial sample:[27] ^1H NMR δ 2.0-2.2 (m, 1H), 2.2-2.4 (m, 1H), 2.4-2.7 (m, 2H), 3.6-3.8 (m, 1H), 3.8-4.0 (m, 1H), 4.2-4.4 (s, 1H), 4.6-4.8 (m, 1H); ^{13}C NMR δ 23.2, 28.7, 63.9, 81.3, and 178.7; MS 116 (M^+), 85 (100), and 57 (23); $[\alpha]_D^{22} = -44.7$ (c =.015, $CHCl_3$), lit.[27,9b] $[\alpha]_D^{20} = -56$ (c = 3, $CHCl_3$). The ee was determined on the β-DEX column, and the values are listed in Table 1.

(S)-4-hydroxypentanoate[17] [**(S)-1b**). Commercial ethyl levulinate (**6**) was treated with baker's yeast (Sigma Type II) by the method of Gopalan and coworkers.[17] Glucose (20 g) was dissolved in 200 mL of distilled water and the solution was warmed to 35 °C. Carefully, 20 g of yeast was added over 10 min, and foaming was controlled by stirring with a stirring rod. The reaction was continued for 45 min and 0.91 g (6.3 mmol) of **6** was added. The pH was kept at 7 by adding 1 M NaOH as needed, and the depletion of sugar was followed by indicator paper. Sugar was also added as needed. After one week of stirring at 32 °C on an orbit-shaker bath, the reaction was stopped by centrifuging off the yeast and washing the centrifugate twice with 50 mL portions of ether. After adding 10 g of NaCl to the aqueous layer, it was washed 5 times with 100 mL of ether . The combined ether layers were dried ($MgSO_4$) and rotary evaporated. After filtration through Supercel, the product was purified by flash liquid chromatography from a 60:40 mixture of hexane:ethyl acetate using silica gel that had been deactivated with 2% by weight water. Isolated yields were 40-46%, and NMR yields were 40-48%: IR 3600-3200, 1730 cm^{-1}; ^{1}H NMR δ 1.2 (d, J = 6 Hz, 3H), 1.26 (t, J = 7.3 Hz, 3H), 1.7-1.9 (m, 2H), 1.6-1.9 (s, OH), 2.4 (t, J = 7.3Hz, 2H), 3.8-3.9 (m, 1H), 4.1 (q, J = 7.3 Hz, 2H); ^{13}C NMR δ 14.7, 24.0, 31.4, 34.5, 61.1, 67.8, 174.8 (the spectra matched that of authentic compound[17]).

(S)-4-methyl-γ-butyrolactone[7,17] **(2)**. A 0.743 g sample (5.08 mmol) of **(S)-Ib** was dissolved in 520 mL of reagent-grade ether and 2.23 g of PPL (steapsin) was added to the solution. The mixture was magnetically stirred but no reaction was taking place, so two drops of water were added. After 48 hours, the reaction had gone to 60% completion. Some of the product was retained during silica gel chromatography, so it was carefully distilled by maintaining the bath temperature at 84-86 °C, bp 58 °C at 1.7 mm Hg (lit.[27] 207-208 °C), and 0.3108 g of 92% pure **2** (3.1 mmol, 61% yield) was obtained. The ee was carefully determined by chiral GC to be 99,7%; IR 1771 and 1175 cm^{-1}; ^{1}H NMR δ 1.41 (d, J = 6 Hz, 3H), 1.8-1.9 (m, 1H), 2.3-2.5 (sextet, J = 6 Hz, 1H), 2.5-2.6 (m, 2H), 4.6-4.7 (m, 1H); ^{13}C NMR δ 21.6, 29.6, 30.3, 77.9, 177.9; MS 100 (M^+), 85 (43), 56 (100), 41 (67).[7,17,28]

Methyl-(R)-4 Hydroxy-5-tetradecynoate [(R)-7]. This compound was prepared by reduction of ketone[21] **10** with commercial R-Alpine-borane© exactly as described by other workers.[20] It was purified by silica gel flash chromatography using an 80:20 mixture of petroleum ether and ethyl acetate. The yield was 76%, and the measured ee was 70-76% (78% was reported): IR 3600-3200, 2228, and 1726 cm^{-1};^{1}H NMR δ 0.9 (t, J = 7 Hz, 3H), 1.2-1.4 (m, 11H), 1.45-1.53 (m, 1H), 2.0 (q, J = 7 Hz, 2H), 2.2 (dt, J = 7.5 and 2 Hz, 2H), 2.55 (q, J = 7 Hz, 3 H with overlaping OH), 3.7 (s, 3H), 4.45 (m, 1H); ^{13}C NMR δ 14.7, 19.3, 23.3, 29.2, 29.5, 29.7, 29.8, 30.4, 32.4, 33.4, 52.4, 62.3, 80.9, 86.9, 174.8; MS 254 (0.9, M^+), 79 (96), 67 (62), 41 (100).[20,28]

(R)-5-(1-Decynyl)-2-oxotetrahydrofuran (8) was prepared by Ohta's[5a] and Gutman's methods.[7] A 0.350 g sample of **7** (1.38 mmol) was dissolved in 30 mL of ether and 0.70 g of PPL was added to the solution. After 6 days of magnetic stirring, the solution was at 45% conversion. It was worked up and purified by liquid chromatography as described by Ohta[5a] et al. A chromatographic fraction of pure product (86 mg) was used in the next step. The ee of product was 99.2% (G-TA column, 145 °C). Another sample of **7** was treated with purified PPL (approximately 4 mg, 100,000 units) and after 18.5 hours, 29% conversion had occurred. The reaction stopped at that point, and even appeared to revert to 26% conversion.[22] Steapsin (0.4 g) was added twice over the next 5 days to achieve 34% conversion (30% NMR yield, ee 94.8%). After workup and flash liquid chromatography purification,[5a] spectra were the same as those reported in the literature:[5a,19] $[\alpha]_D^{21} = -5.27$ (c =.011, $CHCl_3$), lit.[19] $[\alpha]_D^{20} = -5.26$ (c = 3, $CHCl_3$) IR 2245, 1782, 1184, 1153, 1020 cm^{-1}; ^{1}H NMR δ 0.9 (t, J = 7 Hz, 3H), 1.2-1.4 (m, 13H), 1.4-1.6 (m, 1H), 2.2-2.3 (m, 2H), 2.4-2.6 (m, 1H), 2.6-2.8 (m, 1H), 5.1 (m, 1H), ^{13}C NMR δ 14.6, 19.3, 23.2, 28.5, 28.7, 28.9, 29.4, 29.6, 29.7, 30.8, 32.4, 70.3, 89.5, 176.8; MS 222 (0.5, M^+), 79 (88), 60 (61), 41 (100). A very pure sample formed a waxy solid, mp 39-42 °C, after drying.

(R)-5-(1-Decenyl)-2-oxotetrahydrofuran (9) was prepared by hydrogenation over Lindlar catalyst[5a19,20] (86%) as described earlier (some sample was purified by silica gel HPLC using 80:20 hexane:ether): $[\alpha]_D^{21} = -59$ (c = 0.009, $CHCl_3$), lit.[19] $[\alpha]_D^{20} = -69.9$ ($CHCl_3$); IR 3014, 1776, 1178, 723 cm^{-1}; ^1H NMR δ 0.88 (t, J = 7 Hz, 3H), 1.2-1.45 (m, 12 H), 1.9-2.1 (m, 1H), 2.1-2.2 (m, 2H), 2.3-2.5 (m, 1H), 2.5-2.6 (m, 2H), 5.2-5.3 (m, 1H), 5.4-5.55 (td, J = 10 and 1.5 Hz, 1H), 5.6-5.7 (dt, J = 10 and 7 Hz, 1H); ^{13}C NMR δ (central peak of $CDCl_3$ set at 77.0) 14.0, 22.6, 27.8, 28.9, 29.2, 29.3, 29.5, 31.8, 76.4, 127.3, 135.8, 177.0; MS 224 (6, M^+), 111 (100), 81 (51), 55 (69).[19,28]

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22. This reaction, performed with purified enzyme, stopped at 29% conversion and gave a lower ee. We have not repeated this reaction to determine if poorer results are consistently obtained with purified enzyme.
23. Independent work performed at Advance Separations Technologies, Inc (Astec). See Acknowledgment section. We were unable to separate the enantiomers of the pheromone with their G-TA column as reported in Koseki, K.; Ebata, T.; Kadokura, T.; Kawakami, H.; Ono, M.; Matsushita, H. *Tetrahedron* **1993**, *49*, 5961, but Astec was able to separate the enantiomers of the pheromone precursor **8**.

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28. Spectral data of these compounds were the same as those in the reference indicated.

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