Filtration and removal of solvents under vacuum followed by separation on column (CH_2Cl_2) gave (−)-4 and (+)-5 (oils; 90–95% yield).

A reaction using 25 mmol of 4 (5.9 g), vinyl acetate (50 mL), and lipase PS (0.5 g) gave, after 13 d, 2.78 g (94%) of (−)-4 and 3.16 g (91%) of (+)-5 (both oils; for $[\alpha]_D$ see Table II). IR and NMR spectra of (−)-4 and (+)-5 were identical with those of racemic 4 and 5.

General Procedure for Direct Conversion of Chiral 4 or 5 to Chiral Propranolol (1). A mixture of chiral 4 or 5 (1 mmol), excess isopropylamine (2.5 mL), and 10% aqueous NaOH (0.44 mL, 1.1 mmol) was stirred at ambient temperature for 16 h. After excess isopropylamine was removed, water (2 mL) was added and the mixture was extracted with ether (2 × 10 mL). After the ether layer was dried over Na_2SO_4, dry HCl was bubbled into the solution for ca. 15 min to give colorless chiral propranolol hydrochloride in quantitative yields.

For example, (−)-4 obtained from the vinyl acetate reaction as described earlier ($[\alpha]^{25}_D$ −8.7°; 0.95 g, 4 mmol) after reaction with isopropylamine (10 mL) and 10% aqueous NaOH (1.76 mL) gave 1.2 g (100%) of crude (*S*)-(−)-propranolol hydrochloride, $[\alpha]^{25}_D$ −22.9° (1.15, EtOH); mp 188–190 °C. A single crystallization in MeOH–Et_2O provided optically pure (*S*)-1 HCl, mp 194–196 °C; $[\alpha]^{25}_D$ −25.5° (1.05, EtOH) (lit.[4] $[\alpha]^{21}_D$ −25.9° (1.06, EtOH)).

General Procedure for Conversion of Chiral 4 or 5 to Chiral Glycidyl 1-Naphthyl Ether (3). To a solution of chiral 4 or 5 (1 mmol) in isopropyl alcohol (5 mL) was added 20% aqueous NaOH (0.24 mL, 1.2 mmol for 4 or 0.5 mL, 2.5 mmol for 5), and the mixture was stirred at ambient temperature until TLC (CH_2Cl_2) showed complete conversion to 3 (ca. 1–2 h). Removal of solvent followed by CH_2Cl_2 (10 mL) extraction, water (2 mL) wash, drying, and removal of solvent afforded chiral 3 (77–85% yield) as an oil.

(+)-4 ($[\alpha]^{25}_D$ +9.0° (1.9, EtOH), obtained from BuOH–DIPE reaction, see Table II) gave (−)-3, $[\alpha]^{25}_D$ −33.9° (1.55, MeOH) (lit.[23] for *S*-(+)-3, $[\alpha]^{21}_D$ +31.4° (1.5, MeOH)).

(−)-5 ($[\alpha]^{25}_D$ −19.9 (2.4, EtOH), obtained from BuOH–DIPE reaction, see Table II) gave (+)-3, $[\alpha]^{25}_D$ +32.9° (1, MeOH) (lit.[23] $[\alpha]^{21}_D$ + 31.4° (1.5, MeOH)).

^1H NMR ($CDCl_3$) data for 3: δ 2.8 (m, 2 H, epoxide CH_2), 3.1–4.6 (m, 3 H, $ArOCH_2CH$), 6.75–8.5 (m, 7 H, aromatic).

Chiral Propranolol (1) from Chiral 3. A solution of chiral 3 (1 mmol) in excess isopropylamine (2.5 mL) and two drops of water was stirred at ambient temperature until TLC (CH_2Cl_2–MeOH) showed completion (16–20 h). Removal of solvent yielded crude propranolol (free base), which could be either purified by recrystallization in hexane or, more conventiently, converted directly to its hydrochloride as described earlier (85–90%).

(−)-3 ($[\alpha]^{25}_D$ −33.9° (1.55, MeOH) as obtained previously) gave *R*-(+)-1, $[\alpha]^{25}D$ +9.82° (1.6, EtOH) (lit.[24] $[\alpha]^{21}_D$ +10.6° (1.02, EtOH), mp 70 °C (lit.[24] 73 °C).

(+)-3 ($[\alpha]^{25}_D$ +32.9 (1, MeOH) as obtained previously) gave *S*-(−)-1, $[\alpha]^{25}_D$ −9.7° (1.5, EtOH) (lit.[24] $[\alpha]^{21}_D$ −10.2° (1.02, EtOH), mp 71 °C (lit.[24] 73 °C).

Spectral data for 1: IR (KBr) ν (cm^{-1}) 3425 (OH), 3280 (NH); ^1H NMR ($CDCl_3$) δ 1.1 (6 H, *J* = 6.2 Hz), 1.9 (2 H, br s) 2.9 (3 H, m), 6.8–8.3 (7 H, m).

Acknowledgment. Financial assistance for this work was provided by ICI India Limited. We thank Dr. B. N. Roy for encouragement and Amano Pharmaceutical Co. (Japan) for providing a free sample of Lipase PS.

Supplementary Material Available: ^1H NMR spectra of 1 and 3–5 (4 pages). Ordering information is given on any current masthead page.

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Enzymes in Organic Synthesis. 48.[1,2] Pig Liver Esterase and Porcine Pancreatic Lipase Catalyzed Hydrolyses of 3,4-(Isopropylidenedioxy)-2,5-tetrahydrofuranyl Diesters

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Pig liver esterase (PLE) and porcine pancreatic lipase (PPL) catalyzed hydrolyses of 2,5-bis(methoxycarbonyl) and 2,5-bis(acetoxymethyl) meso-diester derivatives of 3,4-(isopropylidenedioxy)tetrahydrofuran proceed with enantiotopic selectivity to give monoester products of up to 72% ee. Transesterification of the 2,5-bis(hydroxymethyl) derivative with trifluoroethyl laurate promoted by PPL in ether also proceeds stereoselectively but in the opposite stereochemical sense from the hydrolysis of the corresponding diacetate. The data provide further examples of heteroatom and ester moiety induced reversals of stereoselectivity for the two enzymes.

Introduction

The use of enzymes as catalysts for the production of a broad structural range of chiral synthons is well-documented.[3] Hydrolytic enzymes such as pig liver esterase (PLE, E.C. 3.1.1.1)[4,5] and porcine pancreatic lipase (PPL, E.C. 3.1.1.3)[6] have proven particularly valuable in this regard, particularly with respect to their abilities to dis-

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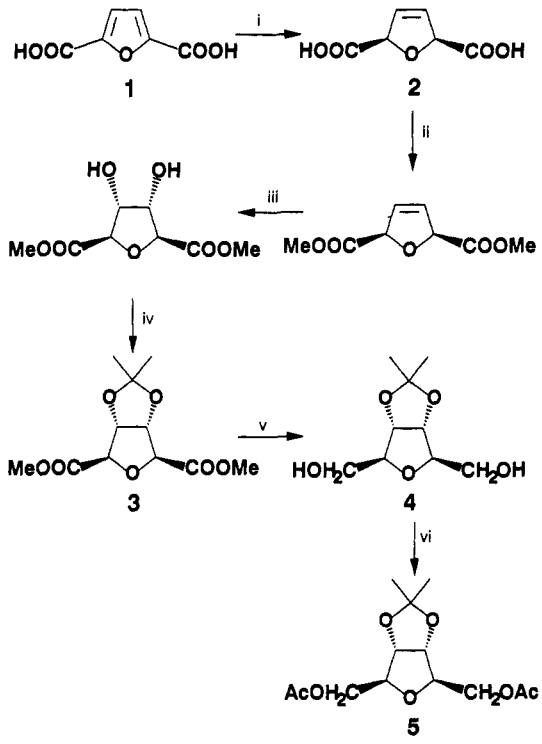
Scheme I[a]



[a] Reagents: (i) $Na/NH_3/i$-PrOH, 43%; (ii) MeOH, H^+, 89%; (iii) OsO_4/N-methylmorpholine oxide, 72%; (iv) acetone, $FeCl_3$, 58%; (v) $LiAlH_4$, THF, 25 °C, quantitative; (vi) Ac_2O, Et_3N, DMAP, 60%.

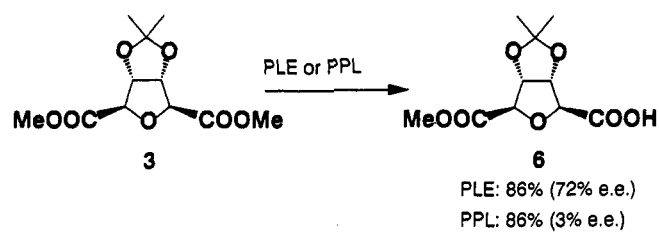
criminate between enantiotopic ester groups of symmetric diester substrates.[5-8]

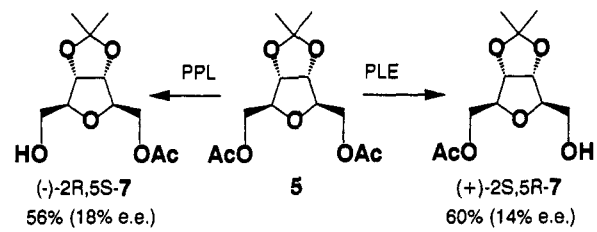
The stereoselectivities reported for PLE- and PPL-catalyzed hydrolyses of meso-2,5-disubstituted tetrahydrofuranyl diesters[5i,6a] producing chiral acid–ester products encouraged us to explore the preparations of more complex, carbohydrate-like, synthons via PLE- and PPL-mediated hydrolyses of diesters such as **3** and **5** and esterification of the diol **4**.

Results

The substrates **3–5** were prepared as outlined in Scheme I. The diesters **3** and **5** were subjected to PLE- and PPL-catalyzed hydrolyses. The results are summarized in Scheme II.

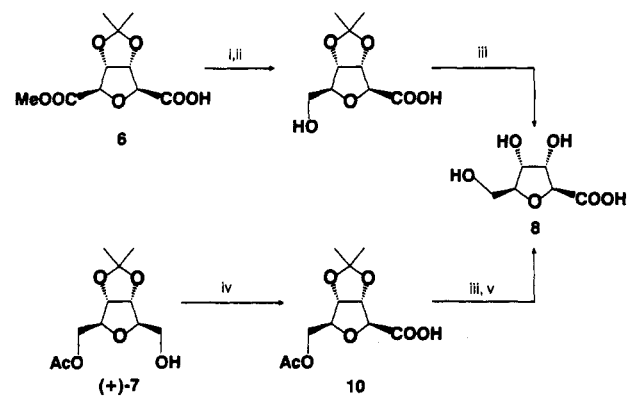
Scheme II[a]





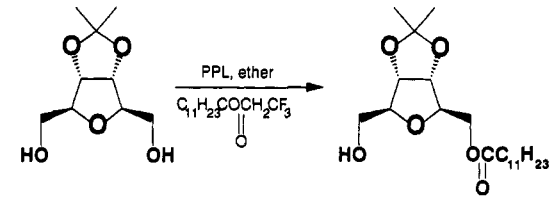
[a] Self-contained.

Scheme III[a]



[a] Reagents: (i) LiOH, H_2O; (ii) $LiBH_4$, THF, reflux; (iii) 9:1 CF_3COOH/H_2O; (iv) $RuO_2/NaIO_4$; (v) NaOH, H_2O.

Scheme IV[a]



[a] Self-contained.

The absolute configurations of the acid–ester **6** as 2*R*,5*S* and of (+)-**7** as 2*S*,5*R* were determined by their conversion (Scheme III) to (−)-(2*S*,5*S*)-anhydroallonic acid **8**, the (+)-2*R*,5*R* enantiomer of which has been described.[9] The 2*R*,5*S* configuration of (−)-**7** was then assigned from the sign of its optical rotation.

PPL-promoted transesterification of diol **4** with trifluoroethyl laurate in ether afforded the hydroxy ester **9** with modest enantiotopic selectivity (Scheme IV). Surprisingly, however, the acylation occurred preferentially adjacent to the 2*R* center of **4**, rather than on the 5(*S*)-CH_2OH as would have been forecast by analogy with the stereoselectivity of PPL-catalyzed hydrolysis of **5**. The

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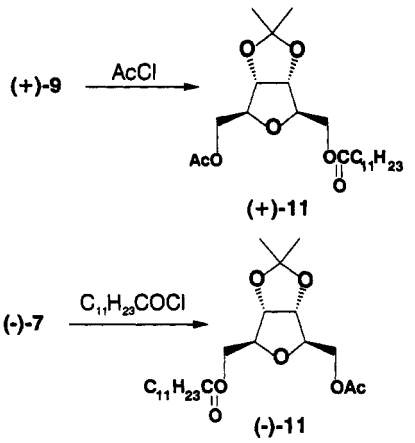
Scheme V[a]



[a] Self-contained.

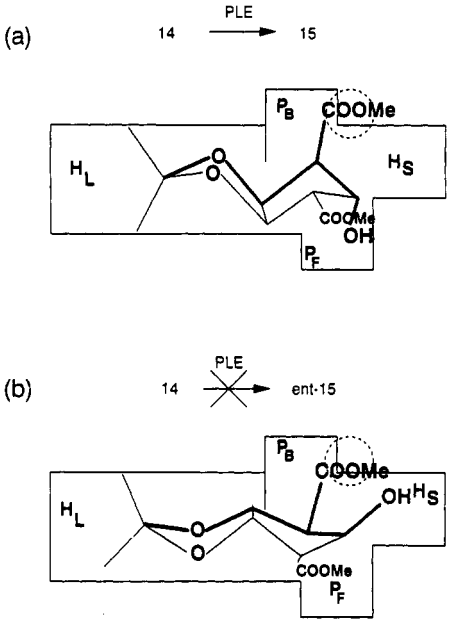
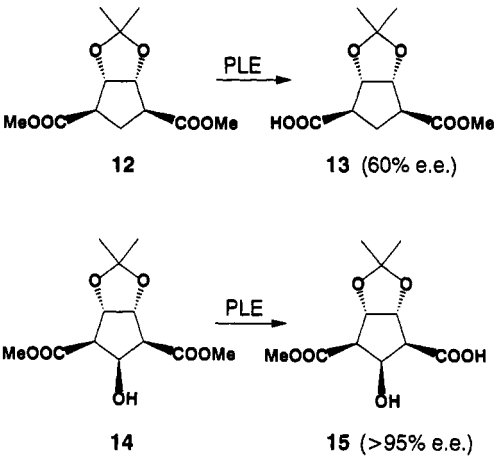


Figure 1. Details of the specification of the active site model, shown here from its top perspective, are given in ref 1. Analysis of the PLE-catalyzed 14 → 15 hydrolysis reported by Zemlicka et al.[7d] is shown. That of the less stereoselective 3 → 6 hydrolysis is completely analogous. (a) This is a preferred binding mode, with *S*-center ester located in the serine nucleophile region (dotted sphere) as required for hydrolysis. The remainder of the substrate can then locate in the allowed space, with the bicyclic portion accommodated in the large hydrophobic pocket (H_L), the *R*-center ester in the front polar pocket (P_F), and the hydroxyl group in the empty region above P_F. It is this favored ES complex that leads to the observed product 15. (b) In order for the enantiomer of 15 to be formed, the *R*-center ester would have to locate in the serine nucleophile zone. Such ES-complex orientations would place the polar hydroxyl group in the small hydrophobic pocket (H_S), which is a strongly disfavored situation, and thus hydrolysis via this ES complex does not take place. In the corresponding active site binding analysis of the diester 12, which lacks the C-2 OH group, the converse is true because fitting the nonpolar C-2 methylene group into H_S, in a binding mode analogous to that depicted in (b), becomes the favored situation, giving rise to 13 as the predominant product.

2*R*,5*S* configuration of the monolaurate (+)-9 followed from the (+)-9 → (+)-11 and (−)-7 → (−)-11 correlations summarized in Scheme V.

The enantiomeric excess of 6 was determined from its ^{1}H NMR spectrum in the presence of (+)-α-methylbenzylamine.[5k] The ee of (+)-7 was determined similarly after its conversion to 10. The ee of (−)-7 was then estimated from the magnitude of its optical rotation. The ee

Scheme VI[a]



[a] Self-contained.

of the monolaurate ester 9 was measured by the Mosher ester procedure.[10] In all cases, the ^{1}H NMR spectrum of the corresponding racemates were used as reference standards.

Discussion

The synthesis of the substrates was straightforward. Reduction of furan-2,5-dicarboxylic acid 1 to the dihydro derivative 2 had been achieved with mercury amalgam.[11] However, the problems of handling large amounts of mercury in this step were avoided by applying Birch reduction conditions. Although alkylfurans fragment under dissolving metal conditions,[12] and other 2-furanoic acid have afforded ca. 1:1 mixtures of cis and trans products,[13] the desired acid 2 predominated in the 95:5 cis/trans product mixture. To our knowledge, this represents the first time such a high degree of stereoselection has been observed in such reductions. Attempted determination of the relative stereochemistry of the diester 3 by ^{1}H NMR gave ambiguous results. The structure was therefore confirmed by X-ray crystallographic analysis.[14] Chiral synthons such as 6, 7, and 9 are useful precursors for the sugar moieties of C-nucleosides,[15] but the ee levels of the enzymically derived products are presently too low to be of asymmetric synthetic value. However, it should be possible to raise the ee's to acceptable levels using the reaction conditions control approach.[5d,h,16]

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Among the interesting questions raised by this study are the stereoselectivity reverals observed within structurally related series of substrates. For example, the *S*-center ester enantiotopic selectivity in the PLE-catalyzed hydrolysis of 3 → 6 is opposite to that observed by Ohno and coworkers[17] for PLE-mediated hydrolysis of the analogous carbocyclic diester 12, in which the product 13 results from preferential *R*-center ester cleavage (Scheme VI). This stereoselectivity-reversing influence of heteroatoms has been noted previously for monocyclic substrates.[5i] The generality of this effect is further substantiated by the behavior of the 14 → 15 process,[7d] for which a hydroxyl substituent on the carbocyclic ring once again induces 3- rather than 12-like behavior with PLE (Scheme VI).

This heteroatom effect on stereoselectivity is interpretable in terms of the PLE active site model for methyl ester hydrolyses proposed recently.[1] The analysis for the most highly stereoselective case, that of the 14 → 15 reaction, is shown in Figure 1. The stereoselectivity analysis for the 3 → 6 conversion is completely analogous.

Although the stereoselectivites of the PPL-catalyzed reactions were lower than for PLE, novel reversals of stereoselectivities are also manifest, with the stereoselectivity of the 4 → 9 transesterification reaction being unexpectedly opposite to that forecast from the 5 → (-)-7 hydrolysis. In this case, the size of the acyl group appears to be the determining factor, an effect that has been documented previously for tetrahydrofuranyl diacetate and dibutanoate substrates.[18] It has also been suggested that another enzyme fraction in the crude PPL preparations used may be responsible for catalysis of transesterification in organic solvents.[19]

Experimental Section

General Methods. Chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, of Caledon Laboratories Ltd., Georgetown, Ont., and were used as received unless otherwise noted. THF and diethyl ether were distilled from sodium/benzophenone before use. PLE (Esterase Type I, Lot no. 50F-8045) and PPL (Type II, Lot no. 82F-0636) were purchased from Sigma Corp., St. Louis, MO, and were used as received. Preparative-scale enzyme-mediated hydrolyses were performed with the aid of a pH-stat. High-performance liquid chromatography (HPLC) was performed using a Waters μBondapak C18 reversed-phase column, 30 × 0.39 cm. Melting points are uncorrected. Boiling points are given as uncorrected Kugelrohr-oven temperatures.

Preparation of Substrates. 2,5-Bis(methoxycarbonyl)-3,4-(isopropylidenedioxy)tetrahydrofuran (3). In a modification of the procedure of Kinoshita et al.,[20] furan-2,5-dicarboxylic acid (1; 50 g, 0.32 mol) and 2-propanol (200 mL) were placed in a 5-L three-necked flask fitted with a dry-ice condenser and a stopcock gas inlet. Ammonia (3 L) was distilled into the flask. To this was added, with stirring, Na metal (16.2 g, 0.704 mol) in several portions over 0.5 h. The mixture was stirred for 0.5 h more before being quenched with solid NH_4Cl (45.2 g). The flask was then opened and the ammonia was allowed to evaporate under a stream of air overnight. The solid residue was taken up in distilled H_2O (200 mL) and washed with Et_2O (3 × 100 mL), and the aqueous layer was adjusted to pH 2 with HCl gas. It was then continuously extracted with EtOAc for 2 days. The dried ($MgSO_4$) organic extracts yielded on evaporation ***cis*-2*H*,5*H*-dihydrofuran-2,5-dicarboxylic acid** (2;[18,11b] 21.51 g, 43%), mp 144–148 °C (lit.[11b] mp 147–148 °C): ^1H NMR (DMSO-d_6) δ 5.43 (2 H, s), 6.20 (2 H, s).

The diacid 2 (21.5 g, 0.14 mol) in MeOH (250 mL) containing concentrated HCl (5 drops) and trimethylorthoformate (10 mL) was stirred overnight at 20 °C. Evaporation of the solvent and Kugelrohr distillation of the residue gave ***cis*-2,5-bis(methoxycarbonyl)-2*H*,5*H*-dihydrofuran**[18,21] (22.55 g, 89%), bp 76 °C (0.05 Torr) [lit.[18] bp 70 °C (0.2 Torr)]: ^1H NMR ($CDCl_3$) δ 3.83 (6 H, s), 5.36 (2 H, s), 6.25 (2 H, s); ^{13}C NMR ($CDCl_3$) δ 169.55, 126.94, 85.05, 51.90.

Following the method of VanRheenan et al.,[22] a solution of OsO_4 in *t*-BuOH (30 mL, 150 mg, 0.59 mmol) was added to *N*-methylmorpholine *N*-oxide (9.04 g, 59 mmol) in acetone (200 mL) and water (30 mL) at 0 °C. To this mixture was added the above dihydrofuran diester (10.1 g, 53 mmol) in acetone (100 mL), and the reaction was stirred overnight at 20 °C. A mixture of Florisil (5 g) and $NaHSO_3$ (3 g) was added, and the slurry was stirred for 10 min before being filtered. The filtrate was acidified with 3 M HCl (20 mL), and the solution was concentrated by 75%. This was saturated with NaCl and extracted with EtOAc (12 × 75 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give ***anti*,*syn*,*anti*-2,5-bis(methoxycarbonyl)-3,4-dihydroxytetrahydrofuran** (9.6 g, 82%): IR (film) ν 3700–3064, 1754–1731, 1288, 1221 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (6 H, s), 3.9 (2 H, s), 4.4–4.73 (4 H, m).

According to the method of Singh et al.,[23] the above diester–diol (9.6 g, 43.6 mmol) in freshly dried acetone (250 mL) was treated with anhydrous $FeCl_3$ (2 g). The mixture was stirred overnight under N_2. The solvent was then evaporated, and the residue was dissolved in 10% aqueous K_2CO_3 (50 mL) and extracted with Et_2O (11 × 75 mL). The dried ($MgSO_4$) extracts afforded on evaporation **2,5-bis(methoxycarbonyl)-3,4-(isopropylidenedioxy)-tetrahydrofuran** (3; 6.6 g, 58%). Recrystallization from water gave an analytical sample, mp 85–86 °C: IR (KBr) ν 1759, 1731, 1226, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.363 (3 H, q, J = 0.7 Hz), 1.537 (3 H, q, J = 0.6 Hz), 3.767 (6 H, s), 4.681 (2 H, d, J = 0.58 Hz), 5.084 (2 H, d, J = 0.73 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 169.88, 113.73, 84.47, 83.12, 52.39, 26.65 25.09. Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.18; H, 6.12.

2,5-Bis(hydroxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran (4). To a suspension of $LiAlH_4$ (265 mg, 7 mmol) in dry THF (25 mL) at 0 °C was slowly added a solution of the diester 3 (1.22 g, 4.7 mmol) in THF (20 mL). The ice bath was removed, and the solution was stirred for 1.5 h. The reaction was quenched with 2 M NaOH (1 mL) followed by the addition of water with rapid stirring to break up the pasty precipitate. The suspension was filtered through Celite, and the filter pad was washed with THF (4 × 10 mL). The combined organic filtrate was dried ($MgSO_4$) and evaporated to give 4, (960 mg, quantitative), bp 70–80 °C (0.05 Torr); IR (film) ν 3708–3037, 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.53 (3 H, s), 3.67–3.87 (4 H, m), 4.06 (2 H, br s), 4.6–4.73 (2 H, m); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 113.71, 84.97, 81.23, 62.68, 27.30, 25.30.

2,5-Bis(acetoxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran (5). Diol 4 (960 mg, 4.7 mmol) in CH_2Cl_2 (50 mL) at 0 °C containing Et_3N (2 mL) and DMAP (30 mg) was slowly treated with Ac_2O (1.1 mL, 11.75 mmol). The cooling bath was removed and stirring continued overnight. The solution was then diluted with Et_2O (50 mL) and washed with 1 M HCl (3 × 10 mL), saturated aqueous Na_2CO_3 (3 × 10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and evaporated. Flash column chromatography (4:1 hexanes/EtOAc) of the residue gave 5 (815 mg, 60%), bp 85–90 °C (0.025 Torr): IR (film) ν 1746, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, s), 1.56 (3 H, s), 2.1 (6 H, s), 4.2 (6 H, s), 4.5–4.6 (2 H, m).

PLE-Catalyzed Hydrolyses. General Procedure. (2*R*,5*S*)-2-(Methoxycarbonyl)-5-carboxy-3,4-(isopropylidenedioxy)tetrahydrofuran (6). The following basic method was used for all enzyme-promoted hydrolyses. The diester 3 (400 mg, 1.54 mmol) was suspended in water (20 mL) and treated

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with PLE (200 μL, 1200 units). The pH was held at 7.00 by the pH-stat controlled addition of 0.5 M NaOH. The reaction was stopped after 1 equiv of base had been added (50 min). The filtered solution was adjusted to pH 8 with solid $NaHCO_3$, and the solution was washed with EtOAc (3 × 15 mL). Concentrated HCl was added to adjust the pH to 2, and the solution was extracted with EtOAc (7 × 20 mL). These extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by Kugelrohr distillation (90–110 °C (0.05 Torr)) to afford the acid–ester **6** (325 mg, 86%, 72% ee): $[\alpha]^{25}_D$ 19.15° (*c* 5.5, $CHCl_3$); IR (film) ν 3600–2400, 1760–1730, 1376, 1212, 864 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.55 (3 H, s), 3.8 (3 H, s), 4.75 (2 H, br s), 4.9 (2 H, m), 10.1 (1 H, br s); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 172.44, 171.32, 114.32, 85.14, 84.90, 83.92, 83.14, 53.25, 26.71, 25.04. Anal. Calcd for $C_{10}H_{14}O_7$: C, 48.78, H, 5.73. Found: C, 48.52, H, 5.84.

(2*S*,5*R*)-2-(Acetoxymethyl)-5-(hydroxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran ((+)-7). The diacetate **5** (400 mg, 1.39 mmol) in water (20 mL) was treated with PLE (200 μL, 1200 units). The reaction was complete in 2.5 h. Workup by extraction with EtOAc (5 × 50 mL) at pH 7 yielded a mixture of starting diacetate **5**, monoacetate (+)-**7**, and diol **4**, which was separated by Chromatotron chromatography (2:1 hexanes/EtOAc + 1% v/v methanol) to give (+)-**7** (207 mg, 60%, 14% ee): $[\alpha]^{25}_D$ 1.17° (*c* 5.29, $CHCl_3$); IR (film) ν 3701–3137, 1744, 1241, 1216, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3 H, s), 1.57 (3 H, s), 2.13 (3 H, s), 2.83 (1 H, t, J = 6 Hz), 3.75 (2 H, d, J = 6 Hz), 4.0–4.33 (4 H, m), 4.5–4.83 (2 H, m); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 170.82, 114.17, 85.04, 82.46, 81.77, 81.56, 64.33, 62.67, 27.28, 25.34, 20.67. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65, H, 7.37. Found: C, 53.20, H, 7.65.

PPL-Catalyzed Hydrolyses. (2*R*,5*S*)-2-(Methoxycarbonyl)-5-carboxy-3,4-(isopropylidenedioxy)tetrahydrofuran (6). The diester **3** (260 mg, 1 mmol) was treated with PPL (27 mg, 324 units) in water (20 mL). The reaction was stopped after 31 h, at 89% conversion. Workup as described above for PLE-derived **6** gave, from the pH 8 extracts, recovered **3** (55.2 mg, 21%). Acidification of the same extracts to pH 2 followed by reextraction gave **6**, (169.6 mg, 86%, ~3% ee): $[\alpha]^{25}_D$ 0.925° (*c* 4, $CHCl_3$). The sample was spectroscopically identical with PLE-derived **6**.

(2*R*,5*S*)-2-(Acetoxymethyl)-5-(hydroxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran ((−)-7). Diacetate **5** (405 mg, 1.4 mmol) was treated with PPL (100 mg, 1200 units) in water (20 mL). After 3 h, it was noted that the enzyme was being inhibited. Therefore, more PPL (100 mg) was added. A third portion (100 mg) was added after 25 h. The reaction was stopped at 96% conversion, after 31 h. Extraction of the solution with EtOAc (8 × 25 mL) and evaporation of the dried ($MgSO_4$) extracts gave a clear oil (344 mg, quantitative). Chromatotron chromatography (2:1 hexanes/EtOAc + 1% v/v methanol) afforded (−)-**7** (184 mg, 56%, ~18% ee): $[\alpha]^{25}_D$ −0.96° (*c* 4.7, $CHCl_3$). The sample was spectroscopically identical with the (+)-**7** obtained with PLE.

PPL-Catalyzed Transesterification. (2*R*,5*S*)-2-[(Lauroyloxy)methyl]-5-(hydroxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran (9). According to the method of Stokes and Oehlschlager,[24] a sample of P (of activity 12 units/mg) was washed with several portions of acetone at −20 °C under a blanket of N_2. It was then stored in a desiccator over P_2O_5 at 0.2 Torr for 1 week.

The diol **4** (371 mg, 1.82 mmol) in dry Et_2O (10 mL) was mixed with dried PPL (600 mg), with vigorous stirring. Trifluoroethyl laurate (571 mg, 1.87 mmol) in dry Et_2O (2 mL) was added. The reaction was halted after 2 days. The mixture was filtered, and the solvent was evaporated. Column chromatography on silica (hexane/Et_2O/EtOH 6:3:1) afforded dilaurate ester (129 mg, 12%), the monolaurate **9** (182 mg, 26%, 48% ee), and starting diol (80 mg, 21%). The monolaurate crystallized on standing for several days, mp 40–44 °C: $[\alpha]^{25}_D$ 2.03° (*c* 2.2, $CHCl_3$); IR (film) ν 3701–3617, 2925, 2854, 1739, 1212, 1159, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.851 (3 H, t, J = 6.9 Hz), 1.227 (14 H, br s), 1.257 (2 H, m), 1.323 (3 H, s), 1.518 (3 H, s), 1.577–1.613 (2 H, m), 2.297–2.335 (3 H, m, incl OH), 3.626 (1 H, m, J_{gem} = 12 Hz), 3.782 (1 H, m, J_{gem} = 12 Hz), 4.099 (1 H, m, J_1 = 3.7 Hz, J_2 = 6.8 Hz), 4.159–4.198 (2 H, m), 4.249–4.296 (1 H, m), 4.490 (1 H, dd, J_1 = 6.8 Hz, J_2 = 4.2 Hz), 4.673 (1 H, dd, J_1 = 6.6 Hz, J_2 = 3.7 Hz). Anal. Calcd for $C_{21}H_{38}O_6$: C 65.52, H 9.91. Found: C, 65.47, H 9.81.

Determination of Absolute Configurations. (a) Of (+)-7. Following the method of Carlsen et al.,[25] alcohol–acetate (+)-**7** (114 mg, 0.46 mmol) in a mixture of CCl_4 (1.5 mL), CH_3CN (1.5 mL), and H_2O (2.2 mL) was vigorously stirred with RuO_2 (5 mg) and $NaIO_4$ (400 mg) for 1.75 h. It was then diluted with CH_2Cl_2 (10 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and swirled with solid $NaHSO_3$ (100 mg) before being filtered and evaporated. The residue was taken up in Et_2O (20 mL), decolorized with Norit, and reevaporated to afford **(2*S*,5*S*)-2-carboxy-5-(acetoxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran** (**10**; 109 mg, 91%): $[\alpha]^{25}_D$ −1.31° (*c* 6.64, $CHCl_3$); IR (film) ν 3695–2300, 1749–1716, 1236, 1116, 1074, 866 cm^{-1} ^1H NMR ($CDCl_3$, 200 MHz) δ 1.370 (3 H, s), 1.559 (3 H, s), 2.070 (3 H, s), 4.140–4.302 (2 H, ABX, J_{A-B} = 12 Hz, J_{A-X} = 4.5 Hz, J_{B-X} = 3.8 Hz), 4.444–4.497 (1 H, ABXX′, $J_{X-X'}$ = 2.2 Hz), 4.629 (1 H, d, J = 2.6 Hz), 4.664 (1 H, dd, J = 6.1 Hz, $J_{X-X'}$ = 2.2 Hz), 5.039 (1 H, dd, J_1 = 6.2 Hz, J_2 = 2.6 Hz), 9.008 (1 H, br s).

The acid–acetate **10** (109 mg, 0.42 mmol) was treated at 20 °C with 9:1 trifluoroacetic acid/water (10 mL) for 15 min and the solvent then evaporated. Trituration of the residue with CH_2Cl_2 (10 mL) produced **(2*S*,3*S*,4*S*,5*S*)-2-carboxy-3,4-dihydroxy-5-(acetoxymethyl)tetrahydrofuran** (91 mg, 99%): IR (film) ν 3715–2200, 1782–1650 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.03 (3 H, s), 4.0–4.45 (6 H, m), 5.94 (3 H, br s). The acetate group was hydrolyzed with 0.1 M NaOH (13.7 mL, 3.3 equiv) at 20 °C for 3.5 h. The solution was acidified by the addition of Dowex-50(H^+) resin, filtered, and evaporated. The residue was purified by HPLC (μBondapak C18 column, 30 × 0.39 cm, 1:1 methanol/water at 0.25 mL min^{-1}) to give **(2*R*,5*S*)-2,5-anhydroallonic acid** (**8**; 45.1 mg, 61%): $[\alpha]^{25}_D$ −0.24° (*c* 4.51, water) (lit. for 2*S*,5*R* enantiomer[8] $[\alpha]^{25}_D$ 9.9° (*c* 0.5, H_2O)); IR (film) ν 3754–2100, 1748–1560 cm^{-1}; ^1H NMR (D_2O, 400 MHz, ext dioxane as reference) δ 3.668 (1 H, ABX, J_{B-X} = 5.0 Hz), 3.803 (1 H, ABX, J_{A-B} = 12.4 Hz, J_{A-X} = 3.2 Hz), 4.007 (1 H, ABX), 4.071 (1 H, dd, J_1 = 4.9, J_2 = 6.3 Hz), 4.282 (1 H, dd, J_1 = 4.3, J_2 = 4.9 Hz), 4.355 (1 H, d, J = 4.3 Hz); ^{13}C NMR (D_2O, 100 MHz, ext dioxane as reference) δ 176.355, 84.416, 82.367, 75.077, 71.502, 62.023. This result showed that (+)-**7** had the 2*S*,5*R* configuration, while (−)-**7** had the 2*R*,5*S* configuration.

(b) Of 6. In a modification of the method of Cornforth et al.,[26] the acid–ester **6a** (95 mg, 0.39 mmol, from PLE method) in EtOH containing 3 drops of phenolphthalein solution was titrated to neutrality with 0.1 M aqueous LiOH. The solvent was then evaporated. The residue was dried at 50 °C (0.25 Torr) for 1 h before being dissolved in dry THF (20 mL), and brought to reflux under N_2. A solution of $LiBH_4$ in THF (2.0 M, 0.12 mL) was added via syringe, and refluxing was continued for 1.75 h. MeOH (10 mL) was added and refluxing continued for 10 min before distilling away 10 mL of the solution. More MeOH (10 mL) was added, and the process was repeated. A third addition of MeOH was followed by Dowex 50 H^+ (250 mg), and the mixture was stirred while it cooled to room temperature. Filtration and evaporation of the solvent afforded a yellow oil. Trituration with Et_2O (10 mL) and storage at 0 °C for 2 days precipitated a solid, which was removed by filtration. The filtrate was evaporated to yield **(2*S*,5*S*)-2-carboxy-5-(hydroxymethyl)-3,4-(isopropylidenedioxy)tetrahydrofuran** (83.5 mg, 98%): IR (film) ν 3700–2300, 1735–1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (3 H, s), 1.65 (3 H, s), 3.7–3.9 (2 H, m), 5.1–4.2 (4 H, m), 6.2 (2 H, br s). This alcohol–acid (83.5 mg, 0.38 mmol) in 9:1 trifluoroacetic acid/water was stirred at 20 °C for 15 min. Evaporation of the solvent gave an oil, which was purified by HPLC (μBondapak C18 column, H_2O, 0.5 mL min^{-1}) to give **(2*R*,5*S*)-2,5-anhydroallonic acid** (**8**; 11.4 mg, 17%): $[\alpha]^{25}_D$ −0.44° (*c* 1.14, D_2O), spectro-

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scopically identical with that described above.

This result demonstrated that **6a,b** had the 2*R*,5*S* configuration.

(c) Of (+)-9. Monolaurate (+)-**9** (58 mg, 0.15 mmol, from the PPL-promoted transesterification of **4**), Et_3N (0.1 mL), and DMAP (5 mg) were dissolved in CH_2Cl_2 (5 mL) at 0 °C. Acetyl chloride (17.7 mg, 0.225 mmol) in CH_2Cl_2 (1 mL) was added dropwise, and the mixture was stirred at 0 °C for 30 min and then overnight at 25 °C. It was then washed with 1 M HCl at 0 °C and then with saturated aqueous $NaHCO_3$ and with water. The dried ($MgSO_4$) organic layer was concentrated and the residue purified by preparative TLC (hexane/Et_2O) to give (+)-**11** (30 mg, 47%): $[\alpha]^{25}_D$ 0.567° (*c* 3.0, $CDCl_3$); IR (film) ν 2962, 1746, 1237, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.841 (3 H, m), 1.22 (16 H, br s), 1.313 (3 H, s, acetonide), 1.509 (3 H, s, acetonide), 1.588 (2 H, m), 2.064 (3 H, s, acetyl), 2.309 (2 H, dd, not resolved), 4.15 (6 H, m), 4.494 (2 H, m). The 2*R*,5*S* configuration of this acetate–laurate (+)-**11** was established by its opposite optical rotation sign to that of the (−)-(2*S*,5*R*)-**11** characterized as follows. A mixture of monoacetate (−)-**7** (65 mg, 0.264 mmol), from PPL-mediated hydrolysis as described above, Et_3N (0.1 mL), and DMAP (5 mg) in CH_2Cl_2 (5 mL) was cooled to 0 °C. A solution of lauroyl chloride (87 mg, 0.4 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction was allowed to proceed for 30 min at 0 °C and then 3 h at 25 °C. The solution was washed successively with 1 M HCl, saturated aqueous $NaHCO_3$, and water. The organic layer was dried ($MgSO_4$) and concentrated. The residual oil was purified by preparative TLC (hexane/Et_2O (2:1)) to give (−)-**11** (62 mg, 55%): $[\alpha]^{25}_D$ −0.16° (*c* 3.7, $CDCl_3$) whose IR and ^1H NMR data matched those for (+)-**11** above.

Enantiomeric Excess Determinations. (a) Of 6 (from PLE) and (+)-7. The method of Schneider[5f] was used for these compounds. Samples of **6** or **10** (ca. 20 mg), as appropriate, were dissolved in $CDCl_3$ (~0.75 mL), and their 200- or 400-MHz ^1H NMR spectra were recorded. The samples were then treated with (+)- or (−)-α-phenylethylamine (10 μL) and shaken well and the spectra rerecorded. Signals arising from diastereomeric salts were integrated to yield the enantiomer ratios of the acids. The methyl ester group of **6** or the acetate methyl group of **10** were used as marker signals. In each case, the racemates were used for the reference spectra.

(b) Of 6 (from PPL) and (−)-7. Because of their low values, the enantiomeric excesses of (+)-**8** and (−)-**9** were determined by comparison of their optical rotations with those of the samples analyzed by NMR.

(c) Of (+)-9. The monolaurate was converted to its (+)-MTPA ester,[9] and the ^1H NMR spectrum was recorded in $CDCl_3$ solution. The signals due to the OCH_3 protons of the two diastereomers were used as markers.

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Supplementary Material Available: ^1H NMR spectra for **4**, **5**, and **10** and the ^{13}C NMR spectrum of **4** (4 pages). Ordering information is given on any current masthead page.

Peptide Conformational Distributions As Studied by Electron-Transfer Kinetics[1]

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The preparation and electron-transfer (ET) behavior of a homologous series of alanine oligomers bearing naphthoyl groups at the N-termini and biphenylylamide groups at the C-termini is described. Electron pulse radiolysis was used to generate the corresponding radical anions, and the rates of ET were monitored at 700 nm (decay of donor) and at 500 nm (growth of acceptor). Several systems displayed ET decays too fast to measure ($k_{et} > 10^{10}$), and in the others multiexponential decay kinetics were observed. The ET decay of dipeptide **3** could be fit to two exponential described by rate constants of 5.2×10^8 (22%) and 5.6×10^9 s^{-1} (78%). In the longer peptides, the fit of the rate constants (and their relative contributions to total intensity) becomes less well-defined, suggesting additional conformational diversity.

Introduction

Fluorescent probes, pioneered by Stryer,[2] have been a mainstay in providing important details on peptide and protein structure and conformational dynamics.[3-7] In view of the substantial current interest in electron transfer reactions within peptides[8-15] and redox proteins,[16-22] we sought to determine whether the electron-transfer behavior of donor (D)–acceptor (A) disubstituted peptides might

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