molecular sieves. The reaction mixture was filtered of resin, washed with 10% $KHCO_3$ (30 mL) and brine (30 mL), and dried (Na_2SO_4). The solution was concentrated and subjected to Kugelrohr distillation (75 °C 5 (mTorr)) to yield 2.37 g (90%) of the oxazoline **3b** as a clear oil: $[\alpha]^{24}_D$ +195° (*c* 1.63, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.42 (s, 3 H), 3.54 (dd, *J* = 6.1, 9.7 Hz, 1 H), 3.64 (dd, *J* = 4.2, 9.7 Hz, 1 H), 4.13 (dddd, *J* = 2.0, 4.2, 6.1, 7.1 Hz, 1 H), 5.29 (d, *J* = 7.1 Hz, 1 H), 7.02 (d, *J* = 2.0 Hz, 1 H), 7.26–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 59.19 (I), 73.40 (III), 73.81 (II), 82.22 (III), 125.43 (III), 128.16 (III), 128.67 (III), 140.21 (IV), 154.85 (III); IR (neat) ν 3064, 1631, 1102 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.94; H, 6.78; N, 7.33.

4(*S*)-Methyl-5(*R*)-phenyl-2-oxazoline (3c)[5] (Method A). (1*R*,2*S*)-Norephedrine, **1c** (10.0 g, 66.1 mmol), DMF-DMA (9.67 mL, 1.1 equiv), and TsOH (20 mg) in benzene (50 mL) were refluxed for 60 h in a flask equipped with a liquid/solid extraction apparatus containing 45 g of 4A molecular sieves. The reaction mixture was washed with 10% $KHCO_3$ (60 mL) and brine (60 mL) and dried (Na_2SO_4). The solution was concentrated and passed through a short column of silica gel with 30% ethyl acetate/hexane to remove residual formamidine. The residue was subjected to Kugelrohr distillation (80 °C (50 mTorr)) to yield 8.63 g (81%) of the oxazoline **3c** as a clear oil: $[\alpha]^{24}_D$ −228° (*c* 2.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 3 H), 4.43 (ddq, *J* = 2.0, 7.0, 10.0 Hz, 1 H), 5.56 (d, *J* = 10.0 Hz, 1 H), 7.02 (d, *J* = 2.0 Hz, 1 H), 7.19–7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.69 (I), 64.06 (III), 82.74 (III), 126.08 (III), 127.88 (III), 128.25 (III), 136.39 (IV), 153.80 (III); IR ($CDCl_3$) ν 3064, 3033, 1632, 1098 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.22; H, 6.90; N, 8.65.

2-Oxazoline 3d (Method A). (*S*)-Benzyltyrosinol, **1d** (2.50 g, 10.4 mmol), DMF-DMA (1.51 mL, 1.1 equiv), and TsOH (20 mg) in benzene (50 mL) were refluxed for 60 h in a flask equipped with a liquid/solid extraction apparatus containing 20 g of 4A molecular sieves. The reaction mixture was washed with 10% $KHCO_3$ (30 mL) and brine (30 mL) and dried (Na_2SO_4). The residue was subjected to Kugelrohr distillation (140–145 °C (5 mTorr)) to yield 2.04 g (74%) of the oxazoline **3d** as a clear oil that crystallized on standing. An analytical sample was recrystallized from ether: mp 61–62 °C; $[\alpha]^{24}_D$ −44.0° (*c* 1.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.62 (dd, *J* = 8.0, 13.9 Hz, 1 H), 3.01 (dd, *J* = 5.8, 13.9 Hz, 1 H), 3.91 (dd, *J* = 7.6, 8.5 Hz, 1 H), 4.14 (ddd, *J* = 0.5, 8.5, 9.5 Hz, 1 H), 4.33 (ddddd, *J* = 1.9, 5.8, 7.6, 8.0, 9.5 Hz, 1 H), 5.03 (s, 2 H), 6.80 (d, *J* = 1.9 Hz, 1 H), 6.90–7.42 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 40.76 (II), 66.71 (I), 70.04 (II), 70.53 (II), 114.95 (I), 127.48 (IV), 127.95 (I), 128.95 (I), 130.07 (I), 130.21 (I), 137.09 (IV), 154.74 (I), 157.57 (IV); IR ($CDCl_3$) ν 3035, 1630, 1511, 1114 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.54; H, 6.34; N, 5.27.

4(*S*)-Isopropyl-2-oxazoline (3e) (Method B). With a water bath to moderate the exotherm, (*S*)-valinol, **1e** (9.50 g, 92.0 mmol), and DMF-DMA (14.7 mL, 1.2 equiv) were combined, neat. After the mixture was stirred for 4 h, the volatiles were removed by rotory evaporation and the mixture was twice azeotropically concentrated with the addition of a 30-mL portion of hexane (rotary evaporator). TsOH (40 mg) was added to the resultant formamidine, and the mixture was diluted with hexanes (50 mL), fitted with a liquid/solid extraction apparatus containing 30 g of 4A molecular sieves and refluxed for 48 h. The solution was washed with 10% $KHCO_3$ (30 mL) and brine (30 mL) and dried (Na_2SO_4). The hexanes were removed by distillation through a 10-cm helices column at atmospheric pressure. The mixture was then distilled at reduced pressure (69–70 °C (67 Torr)) to yield 6.96 g (67%) of the oxazoline **3e** as a clear liquid: $[\alpha]^{24}_D$ −117° (*c* 1.18, $CHCl_3$), −127° (*c* 3.09, EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86, 0.94 (d, *J* = 6.7 Hz, 3 H), 1.70 (d heptet, *J* = 6.7, 6.7 Hz, 1 H), 3.84–3.91 (m, 2 H), 4.17 (m, 1 H), 6.78 (d, *J* = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.13 (I), 18.52 (I), 32.32 (III), 68.75 (II), 71.22 (III), 154.05 (III); IR (neat) ν 1632, 1386, 1368, 1094 cm^{-1}. Anal. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.42; H, 9.89; N, 12.73.

4(*S*)-*tert*-Butyl-2-oxazoline (3f) (Method B). With a water bath to moderate the exotherm, (*S*)-*tert*-leucinol, **1f** (10.2 g, 86.8 mmol), and DMF-DMA (13.8 mL, 1.2 equiv) were combined, neat. After the mixture was stirred for 4 h, the volatiles were removed by rotory evaporation and the mixture was twice evaporated with the addition of a 30-mL portion of hexane (rotary evaporator). TsOH (40 mg) was added to the resultant formamidine, and the mixture was diluted with hexanes (50 mL), fitted with a liquid/solid extraction apparatus containing 30 g of 4A molecular sieves, and refluxed 48 h. The solution was washed with 10% $KHCO_3$ (30 mL) and brine (30 mL) and dried (Na_2SO_4). The hexanes were removed by distillation through a 10-cm helices column at atmospheric pressure. The mixture was then distilled at reduced pressure (74–75 °C (56 Torr)) to yield 7.19 g (65%) of the oxazoline **3f** as a clear liquid: $[\alpha]^{24}_D$ −104° (*c* 1.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 9 H), 3.86 (ddd, *J* = 2.0, 8.4, 10.4 Hz, 1 H), 4.00 (dd, *J* = 8.4, 8.4 Hz, 1 H), 4.14 (dd, *J* = 8.4, 10.4 Hz, 1 H), 6.82 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.74 (I), 33.25 (IV), 67.32 (II), 74.92 (I), 154.10 (I); IR (neat) ν 1635, 1395, 1366, 1102 cm^{-1}. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 65.95; H, 10.23; N, 11.02.

4(*R*)-Phenyl-2-oxazoline (3g) (Method B). With a water bath to moderate the exotherm, (*R*)-phenylglycinol, **1g** (1.76 g, 12.9 mmol), and DMF-DMA (2.22 mL, 1.3 equiv) were combined, neat, and 5 mL of $CHCl_3$ was added to dissolve the solid. After the mixture was stirred for 16 h, the volatiles were removed by rotory evaporation and the mixture was twice azeotropically evaporated with the addition of a 20-mL portion of hexane. TsOH (20 mg) was added to the resultant formamidine, and the mixiture was diluted with hexanes (50 mL), fitted with a liquid/solid extraction apparatus containing 10 g of 4A molecular sieves, and refluxed 48 h. The solution was washed with 10% $KHCO_3$ (15 mL) and brine (15 mL) and dried (Na_2SO_4). The hexanes were removed by rotary evaporation, and the mixture was then subjected to Kugelrohr distillation (40–45 °C (50 mTorr)) to yield 1.43 g (75%) of the oxazoline **3g** as a clear liquid: $[\alpha]^{24}_D$ +133° (*c* 1.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.03 (dd, *J* = ~8.4, ~8.4 Hz, 1 H), 4.55 (ddd, *J* = 0.4, 8.7, 10.4 Hz, 1 H), 5.18 (ddd, *J* = 2.1, 8.3, 10.4 Hz, 1 H), 7.02 (d, *J* = 2.1 Hz, 1 H), 7.22–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 68.56 (III), 73.22 (II), 126.39 (III), 127.47 (III), 128.58 (III), 141.60 (IV), 155.28 (III); IR ($CDCl_3$) ν 3063, 3030, 1627, 1099 cm^{-1}. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.29; H, 6.15; N, 9.57.

Acknowledgment. This work was supported by the National Institutes of Health. A NSRA-NIH Postdoctoral Fellowship (W.R.L.) and a Merck Fellowship (J.L.R.) are gratefully acknowledged.

An Enantioselective Synthesis of SK&F 93505, a Key Intermediate for Preparing Cardiotonic Agents

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Received August 20, 1990

A variety of 6-phenyl-5-substituted-4,5-dihydro-3-(2*H*)-pyridazinones (Figure 1) have demonstrated significant inhibitory activity against cardiac PDE III, making them attractive candidates for the treatment of congestive heart failure.[1] SK&F 95654 (Figure 2) has been found to be a potent inhibitor in this class. Approaches to racemic 6-phenyl-5-methyl-4,5-dihydro-3(2*H*)-pyridazinones based on the hydrazine condensation of 3-benzoylcrotonic acid derivatives **2** have been described in the literature.[1-3] The 3-benzoylcrotonic acid derivatives were prepared in about

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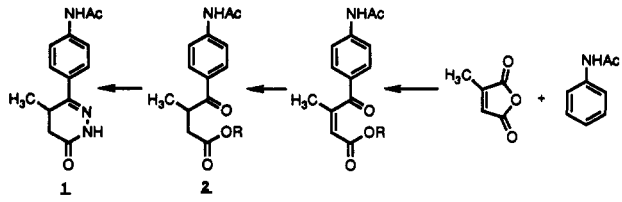

Figure 1.

18% yield from a Friedel–Crafts acylation of acetanilide with citraconic anhydride, followed by reduction with zinc dust[2] (Figure 1).

It had been demonstrated earlier at SmithKline Beecham that the (*R*)-(−) isomer of SK&F 95654 is approximately 80–100 times more active toward inhibition of PDE III than its enantiomer. We therefore sought to develop an economical synthetic method suitable for the large-scale production of optically active SK&F 95654 based on an enantioselective synthesis of key acyclic intermediate **3**. One retrosynthetic analysis developed for key intermediate **3** started from an optically active 2-halopropionic acid, as illustrated in Figure 2. Such an approach offered the advantage of using starting materials readily available from the chiral pool, such as lactic acid or alanine, and other inexpensive reagents. To be successful, however, synthetic methods needed to be carefully designed in order to minimize racemization of the chiral center through enolization; in particular, effecting a clean S_n2 displacement at a highly acidic halo ketone (**4**) was viewed as being potentially quite difficult. Considerations included identification of a suitable acetate anion equivalent and leaving group α to the aryl ketone.

Since the Friedel–Crafts acylation of optically active acid chlorides with aromatics had been reported to produce α-halopropiophenones in high enantiomeric purity,[4] it was anticipated that this method would serve as a starting point for our synthesis. Enantiomerically pure acid chlorides **7a** and **7b** (Figure 3) were prepared in two steps from L-alanine according to literature methods.[5,6] Alternatively (*R*)-(−)-2-chloropropionyl chloride could be prepared from (*R*)-(+)-2-chloropropionic acid by distillation from benzoyl chloride.[7] Friedel–Crafts acylation of acetanilide with **7a** (3 equiv of $AlCl_3$/trichlorobenzene/80 °C/2 h) produced bromo ketone **8a** in 79% yield, but with only 20% ee according to NMR analysis.[8] Attempts to alkylate **8a** with the sodium salt of dimethyl malonate or Meldrum's acid led to completely racemic malonate derivatives.

In contrast, Friedel–Crafts acylation of acetanilide with (*R*)-(−)-2-chloroprionyl chloride (**7b**), afforded α-chloro ketone **8b** in 80% yield with about 90% ee.[8] α-Chloro ketone **8b** was found to be stable toward S_n2 attack by chloride under typical alkylation conditions, since no measurable loss of enantiomeric purity was observed after treatment with sodium chloride in DMF at room temperature. Treatment with 4 equiv of sodium dimethyl malonate in DMF at room temperature afforded malonate derivative **9a** in 40% yield with about 80% ee.[8] Base-catalyzed enolization of **8b** was occurring, as evidenced by the recovery of about 28% starting material which had only 50% ee. Attempts to push the alkylation to completion by using higher temperatures or longer reaction times produced **9a** with lower enantiomeric purity. Decarboxymethylation of **9a** under acidic conditions (6 M HCl/reflux/6 h) or nucleophilic conditions[9] (NaCl/H_2O/DMSO/160 °C) resulted in complete racemization. Complete retention of enantiomeric purity[10] could be achieved, however, by selective demethylation with pig liver esterase (pH 8.0/33 °C/1.5 h) to afford half-acid **9b**. Further efforts to thermally decarboxylate **9b** (165 °C/neat/45 min) gave ester **10c** with about a 10% loss in enantiomeric purity.

In light of the poor volume efficiency of the esterase-based hydrolysis, we continued to search for an acetate anion equivalent that could be more easily unmasked. Reaction of an excess of the sodium salt of di-*tert*-butyl malonate with **8b** afforded a 78% yield of **9d**, but with only 10% ee. Treatment of **8b** (90% ee) with excess sodium dibenzyl malonate (4 equiv/DMF/room temperature/22 h) afforded the corresponding malonate derivative **9e** in 70% yield and 86% ee. Some enolization of the starting material was still occurring, as evidenced by a loss of enantiomeric purity of the recovered starting material. Hydrogenolysis of **9e** (H_2/Pd on C/EtOAc/room temperature) proceeded quantitatively to diacid **9c** with no apparent loss of enantiomeric purity.[10] Attempts to thermally decarboxylate **9c** (neat/165 °C) provided monoacid **10a** in good yield, but again resulted in a significant racemization to 6% ee.[10] However, decarboxylation could also be effected in boiling water to afford, after treatment with diazomethane, esters **10b** and **10c** with 62% ee and 72% ee, respectively.

Interestingly, hydrazine cyclization (20% N_2H_4 in MeOH/reflux/2 h) of **10b** afforded (*R*)-(−)-SK&F 93505 with 56% ee, in contrast to the cyclization of **10c**, which afforded the same product with only 44% ee. The cyclization conditions apparently resulted in greater base-catalyzed enolization and racemization of acetanilide derivative **10c**, compared to **10b**, the corresponding aniline derivative. This can be rationalized by the effect of the *p*-acetylamino group, which would be expected to increase the acidity of ketone **10c** relative to that of **10b**, which can be considered as a vinylogous amide.

On the basis of these findings, a greater retention of enantiomeric purity was anticipated from basic reactions performed on the free aniline series of derivatives. Hydrolysis of ketone **8b** (1 N H_2SO_4/MeOH:H_2O, 1:1/reflux/2 h/91%) afforded aniline **8c** with 86% ee. As an added bonus, the enantiomeric purities of all the aniline series derivatives could be directly measured by HPLC.[11] Subsequent treatment of **8c** with excess sodium dimethyl malonate (4 equiv/DMF/room temperature/144 h/98%) afforded a nearly quantitative yield of **9f** with no loss of enantiomeric purity.

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(8) Enantiomeric purities of all acetanilide derivatives were measured by chiral solvent shift 270-MHz NMR using 3–10 equiv of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol in $CDCl_3$ and are accurate to about ±5%. See, the following: Weisman, G. R. In *Asymetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, Chapter 8. Pirkle, W. H.; Sikkenga, D. L. *J. Org. Chem.* **1977**, *42*, 1370.
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(10) Enantiomeric purity was measured by conversion back to the corresponding methyl ester by treatment with excess diazomethane in ethyl acetate at room temperature and measurement by NMR as described in ref 9.
(11) LKB Enantiopak HPLC column using an α-acid glycoprotein stationary phase; eluent was 0.1 M NaCl adjusted to pH 6.8 with 16 mM Na_2HPO_4/NaH_2PO_4. Resolution could be further enhanced by the addition of 0.5–3% 2-propanol to the mobile phase, 0.3–0.5 mL/min, UV detection at 280 nm.

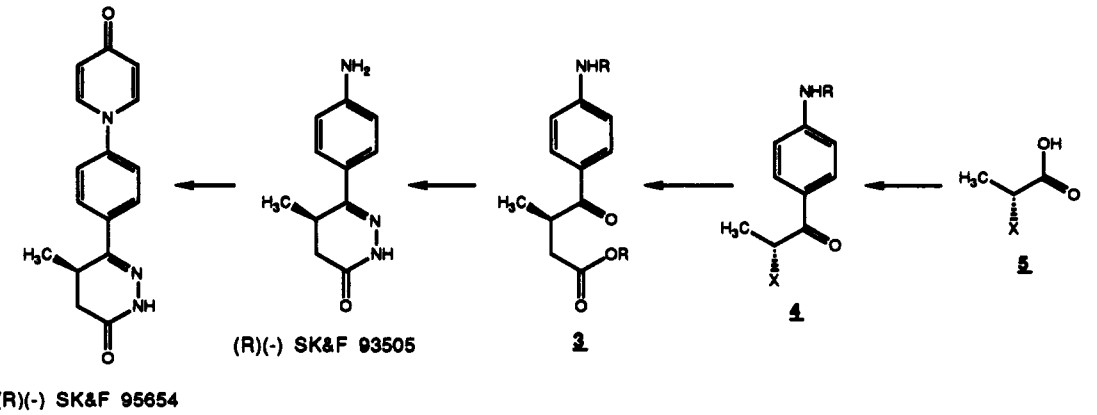

Figure 2.

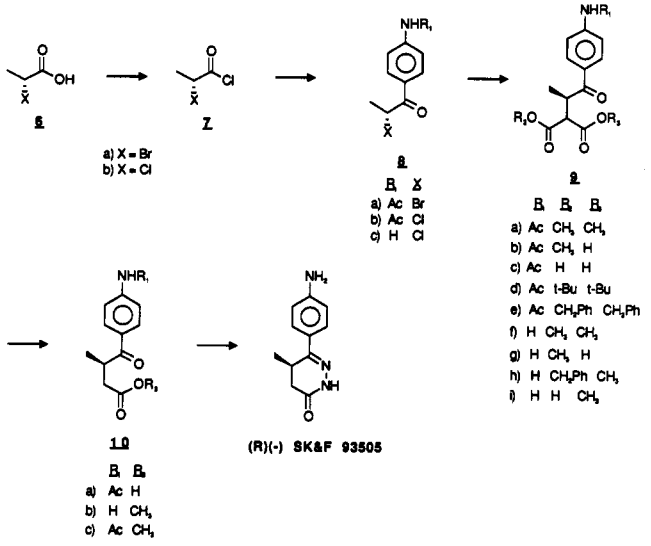

Figure 3.

Attempts to effect the decarboxymethylation[9] of **9f** using NaCl/H_2O/DMSO/160 °C or LiI/phenol/DMF/150 °C again resulted in substantial losses of enantiomeric purity. Such decarboxymethylation reactions have been described as occurring under "essentially neutral" conditions.[12] More recently they have been thought to proceed by nucleophilic cleavage of the methyl group to afford a carboxylate salt, which subsequently decarboxylates to an ester enolate. This enolate can then deprotonate water to generate 1 equiv of hydroxide ion.[13] We therefore reasoned that performing such reactions in the presence of a suitable buffer should inhibit base-catalyzed enolization and racemization of the chiral center of **10b**. Indeed, treatment of **9f** with the standard Krapcho conditions[9] in the presence of phosphate buffer (1.1 NaCl/2 H_2O/1 NaH_2PO_4/1.56 Na_2HPO_4/DMSO/170 °C/2.75 h) afforded aryl ketone **10b** with no significant loss of enantiomeric purity, but in only 38% yield.

The best results with an acetate anion equivalent were achieved by treatment of **8c** (90% ee) with excess sodium benzyl methyl malonate (4 equiv/DMF/room temperature/84%) to afford **9h**. Catalytic hydrogenolysis (H_2/10% Pd on C/EtOA/room temperature) readily afforded half-acid **9i** with virtually no racemization at the key chiral center.[10] Decarboxylation in diglyme at reflux afforded key intermediate **10b** in 60% yield and 84% ee. (*R*)-(-) SK&F 93505 was prepared in high yield under nearly neutral conditions (20% aqueous N_2H_4/HOAc/pH 6.5/reflux/90%) with 82% ee. The enantiomeric purity of (*R*)-(-) SK&F 93505 could be further enhanced to >96% ee by recrystallization from ethyl acetate.

Thus by judicial choice of reaction pathway and conditions, such that the base-catalyzed displacement of chloro ketone **8** was carried out on the less acidic free amine **8c**, (*R*)-(-) SK&F 93505 was produced in seven synthetic steps in 12% overall yield from (*R*)-(+)-2-chloropropionic acid. This synthesis has been used to produce over 10 g of (*R*)-(-) SK&F 93505 with 97.2% ee. (*R*)-(-) SK&F 93505 can be readily converted into a variety of cardiotonic agents by further functionalization of the *p*-amino group. For example, (*R*)-(-) SK&F 95654 has been prepared in 80% yield with 96% ee by treatment of (*R*)-(-) SK&F 93505 with 4-pyridone in aqueous hydrochloric acid.[14]

Experimental Section

General Section. Unless stated elsewhere, experiments were performed under a slight static pressure of nitrogen. Tetrahydrofuran was freshly distilled from sodium under a nitrogen atmosphere, using benzophenone as an indicator. Flash chromatography[15] was performed with J.T. Baker silica, unless otherwise stated. Nuclear magnetic resonance spectra were obtained on a Bruker AM 400, a Bruker WM 360, or a Varian EM-360L spectrometer for 400 MHz, 360 MHz, and 60 MHz spectra, respectively, using deuteriotrichloromethane as solvent and tetramethylsilane as a reference. Enantiomeric purities of all acetanilide derivatives were measured by 270-MHz NMR.[8] Enantiomeric purities of all anilide derivatives were measured with an LKB Enantiopak HPLC column using an α-acid glycoprotein stationary phase; eluent was 0.1 M NaCl adjusted to pH 6.8 with 16 mM Na_2HPO_4/NaH_2PO_4. Resolution could be further enhanced by the addition of 0.5–3% 2-propanol to the mobile phase, 0.3–0.5 mL/min, UV detection at 280 nm. Infrared spectra were measured with a Nicolet 20 SXB FT-IR instrument, using a DTGS detector, or with a Perkin-Elmer Model 1320 infrared spectrophotometer. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C CHN analyzer.

Preparation of 8b. A 4-L jacketed glass reaction vessel equipped with a mechanical stirrer, an immersion thermometer, and a gas outlet was charged with 1 L of 1,2,4-trichlorobenzene, 200.0 g (1.5 mol) of acetanilide, and 592.0 g (4.5 mol) of aluminum trichloride. The solution was warmed to 70 °C, and 200.0 g (1.6 mol) of (*R*)-(-)-2-chloropropionyl chloride[5,6] (96% ee) (**7b**) was added as rapidly as possible while maintaining a controlled evolution of HCl. The resulting black solution was warmed to 80 °C and stirred for 1 h, during which some tar deposited on the side of the flask. The heat source was removed, and the reaction

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was diluted by the careful addition of 1 L of methylene chloride so as to lower the temperature to about 55 °C. The warm solution was quenched into 4 L of a stirred ice–water slurry, and the resulting mixture was extracted with three 1-L portions of methylene chloride. The combined extracts were dried with magnesium sulfate and concentrated under reduced pressure. The resulting orange oil was triturated with 8 L of petroleum ether and chilled in ice water. The resulting crude yellow solid was collected by suction filtration and dried under vacuum. Purification by column chromatography (Merck Silica Gel 60, 40–63 μm, 5–10% acetone/methylene chloride) afforded 265 g (79% yield) of **8b** as a buff white solid, mp 110–112 °C: 90% ee;[9] $[\alpha]^{25}_D$ = –61.7° (c = 1.98, CH_2Cl_2); IR (KBr, cm^{-1}) 3400–3100, 3100–3000, 3000–2800, 1670, 1586, 1537, 1410, 1313, 858, 660; NMR 8.00 (2 H, d, 8.7 Hz), 7.65 (2 H, d, 8.7 Hz), 5.22 (1 H, m) 2.23 (3 H, s), 1.74 (3 H, d, 6.7 Hz). Anal. Calcd: C, 58.54; H, 5.36; N, 6.21; Cl, 15.71. Found: C, 58.35; H, 5.33; N, 6.11; Cl, 15.36.

Preparation of 8c. A 100-mL glass round-bottom flask equipped with a reflux condenser, immersion thermometer, and a mechanical stirrer was charged with 4.0 g (17.7 mmol) of **8b**, 100 mL of methanol, and 100 mL of 6 N sulfuric acid. The solution was heated at reflux for 2 h and then cooled to room temperature. The reaction solution was treated with excess aqueous saturated sodium carbonate to make it basic and then extracted with three 100-mL portions of diethyl ether. The combined organic extracts were washed with 50 mL of saturated aqueous sodium carbonate, dried over sodium sulfate, and concentrated under vacuum to yield 2.9 g (89% yield) of yellow solid **8c**: mp 101–104 °C; HPLC[12] 84% ee; $[\alpha]^{25}_D$ = –85.27° (c = 2.295, CH_2Cl_2); IR (KBr, cm^{-1}) 3411, 3329, 3212, 3100–3000, 3000–2800, 1664, 1643, 1589, 1564, 1348, 1261, 843, 615, 584; NMR 7.88 (2 H, d, 8.7 Hz), 6.66 (2 H, d, 8.7 Hz), 5.20 (1 H, q, 6.7 Hz), 4.21 (2 H, bs), 1.71 (3 H, d, 6.7 Hz). Anal. Calcd: C, 58.87; H, 5.49; N, 7.63; Cl, 19.31. Found: C, 59.03; H, 5.53; N, 7.58; Cl, 19.23.

Preparation of 9h. A 3-L flask equipped with a dropping addition funnel, inert gas inlet/outlet, and a mechanical stirrer was charged with 55.8 g (1.4 mol) of 60% sodium hydride dispersion in oil. The oil was removed under inert atmosphere by washing with three 150-mL portions of hexanes, and the residue was dried in vacuo. The hydride was suspended in 1.5 L of dimethylformamide and the suspension was chilled with an ice–water bath. With good stirring 305 g (1.5 mol) of neat benzyl methyl malonate was added via dropping addition funnel over 1 h so as to control the hydrogen evolution. The mixture was stirred at room temperature for 12 h, and a solution of 64 g (0.35 mol) of **8c** in 800 mL of dimethylformamide was added in one portion. The resulting brown suspension was stirred at room temperature for 25 h and quenched into 2 L of pH 7 phosphate buffer. About 20 mL of 10% aqueous HCl was added to raise the pH to 5.5. The mixture was extracted with three 500-mL portions of methylene chloride. The combined extracts were dried over magnesium sulfate and concentrated in vacuo to afford 300 g of a crude oil, which was subjected to column chromatography (Merck Silica Gel 60, 40–63 μm, 3:1 hexane/acetone) to afford 103.7 g (84% yield) of **9h** as a crude yellow oil, which was used directly in the next step.

Preparation of 10b. A solution of **9h** (1.0 g, 2.8 mmol) in 29 mL of ethyl acetate was charged to a flask containing 40 mg of 10% Pd on carbon in 11 mL of ethyl acetate. The mixture was stirred under 1 atm of hydrogen at room temperature, and the reaction was complete after 2.5 h. The catalyst was removed by filtration through SuperCel, and the filtrate was concentrated under reduced pressure to afford 0.8 g of **9i** as a crude oil. This crude oil (0.7 g) was dissolved in 6 mL of diglyme and heated to reflux for 15 min. The solution was cooled and the solvent was removed in vacuo to afford a crude oil. The oil was purified by flash chromatography (hexane/acetone 3:1) to afford 300 mg (55% yield from **9h**) of **10h** as a white solid: mp 96–99 °C; HPLC[12] 86% ee; IR (KBr, cm^{-1}) 3436, 3346, 3244, 3100–3000, 3000–2800, 1728, 1654, 1643, 1590, 1345, 1175, 841; NMR 7.85 (2 H, d, 8.6 Hz), 6.66 (2 H, d, 8.6 Hz), 4.11 (2 H, bs) 3.86 (1 H, m), 3.64 (3 H, s), 291 (1 H, dd, 8.0 Hz and 16.6 Hz), 2.42 (1 H, dd, 6.2 Hz and 16.6 Hz), 1.21 (3 H, d, 7 Hz). Anal. Calcd: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.09; H, 6.90; N, 6.34.

Preparation of (*R*)-(–) SK&F 93505. A solution of **10b** (11.2 g, 50.6 mmol) dissolved in 90 mL of methanol was treated with with 860 mL of a solution of 1:9 v/v hydrazine/water, which was adjusted to pH 6.5 with glacial acetic acid. The reaction solution was heated at reflux for 1 h and cooled to room temperature. The solution was treated with 150 mL of saturated aqueous sodium carbonate and was extracted with 3 × 300 mL portions of ethyl acetate. The combined organic phases were washed with 100 mL of saturated sodium carbonate, dried over magnesium sulfate, and concentrated in vacuo to afford 9.34 g (91% yield) of (*R*)-(–) SK&F 93505 as a crude white solid: HPLC[12] 84% ee.

This crude solid was twice recrystallized by dissolving in ethyl acetate, boiling off solvent until the cloud point, and cooling. (*R*)-(–) SK&F 93505 was obtained in 50% overall recovery: mp 204–206 °C; HPLC[12] 98% ee; $[\alpha]^{25}_D$ = –469.4° (c = 1.14, MeOH); IR (KBr, cm^{-1}) 3367, 3333, 3219, 3100–3000, 3000–2800, 1664, 1609, 1593, 1520, 1349, 1307, 1185, 844; NMR 8.36 (bs, 1 H), 7.57 (d, 8.7 Hz, 2 H), 6.69 (d, 8.7 Hz, 2 H), 3.90 (bs, 2 H), 3.30 (m, 1 H), 2.68 (dd, 1 H, 6.7 Hz and 16.5 Hz), 2.43 (d, 1 H, 16.5 Hz), 1.23 (d, 3 H, 7.4 Hz). Anal. Calcd: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.89; H, 6.49; N, 20.62.

Acknowledgment. We would like to thank Dr. Charles DeBrosse and Mr. David Staiger of the Analytical Chemistry Department for chiral solvent shift NMR spectra and Drs. Yousef Hajikarimian, Jim Johnston, Norman Lewis, Michael McGuire, Michael Mitchell and Jay Sherbine for their assistance with specific experiments.

Amplification of Enantioselectivity in Biocatalyzed Kinetic Resolution of Racemic Alcohols

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Received August 15, 1990

Introduction

Recently, much effort in the field of asymmetric biocatalysis has been directed toward identifying lipases with useful enantioselectivity against a broad array of organic compounds.[1] For many unnatural substrates, the catalysis is often effected with low to moderate selectivity, yielding products with enantiomeric excess ranging from 0.5 to 0.8. To improve the enantiomeric discrimination, several strategies have been proposed which entail physical and/or chemical manipulations of enzyme preparations. Presumably, these treatments led to selectivity enhancement by diminishing competing reactions caused by contaminating enzymes[2] or by altering enzyme molecules to assume new conformation.[3] More recently, Sih and his co-workers have proposed a useful concept of "sequential biocatalytic resolution"[4] in the preparation of axially disymmetric diols such as binaphthol and *threo*-2,4-pentanediol with high optical purity. As these molecules possess two functional sites for enzymatic action, the synergistic coupling of two consecutive enantiospecific steps allows stereoselectivity enhancement.

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