Asymmetric Synthesis of the C3α Fragment of 5,6-Dihydro-α-pyrone Nonpeptidic HIV-1 Protease Inhibitors

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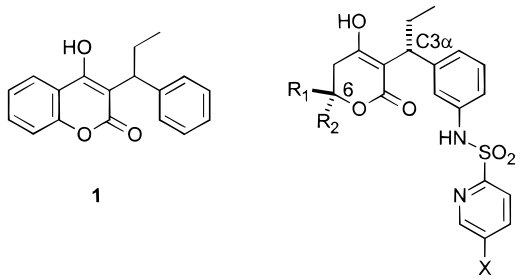
One promising strategy for the treatment of HIV infection is the administration of drugs that inhibit the virally encoded protease.[1] The most extensively studied inhibitors have been peptidomimetic compounds that contain transition-state inserts instead of the usual dipeptidic cleavage sites found in the substrates of HIV protease.[2] These types of compounds generally suffer from low oral bioavailability and rapid excretion. Extensive structure−activity relationship (SAR) studies in concert with structure-based design have led to the synthesis of inhibitors with reduced peptidic nature and correspondingly greater oral bioavailability. Several of these compounds have recently been approved by the FDA as therapeutic agents for the treatment of HIV infection. Previous reports from Pharmacia & Upjohn describe the identification of phenprocoumon (**1**) as a nonpeptidic lead HIV protease inhibitor.[3] Subsequent iterative cycles of structure-based design led to the discovery of three generations of clinical candidates.[4]

The third generation candidate was derived from a series of analogues of a 5,6-dihydro-4-hydroxy-2-pyrone template (e.g., **2**).[5] This template was attractive for exploring the steric and electronic requirements of the active site because of the ability of a C-6 disubstituted dihydropyrone to fill the S_2 and S_2' pockets[6] of the HIV protease enzyme active site. It was thought that exploiting these potential interactions with the enzyme would result in an increase in HIV protease inhibitory activity. The targetted analogues all possessed the same absolute configuration at the C3α side chain position, and some analogues contained an additional chiral center at C-6 of the dihydropyrone ring (**2**, $R_1 \neq R_2$). Three dihydropyrone compounds (e.g., **2a**−**c**) of this class were considered as potential third generation candidates, and just recently **2c**[7−10] was selected for clinical trials. To facilitate the synthesis of analogues, as well as to explore preparative scale syntheses of a potential drug candidate, we embarked upon an effort to streamline the synthesis of these substituted dihydropyrones.



1

2a R_1, R_2 = *n*-Pr; X = CF_3
2b R_1 = *n*-Pr; R_2 = -CH_2CH_2Ph; X = CF_3
2c R_1 = *n*-Pr; R_2 = -CH_2CH_2Ph; X = CN

Retrosynthetic analysis of **2** led to β-ketoester **3**, because conversion of β-ketoesters to dihydropyrones is well precedented (Scheme 1).[11,12] Because we were seeking a route amenable to large scale synthesis, we were pleased to note that this retrosynthetic analysis would likely allow for introduction of the stereogenic center at C3α by an efficient catalytic asymmetric hydrogenation of a substituted acrylic acid such as **5** or **6**. To examine this possibility, **7**[13] was subjected to Ru(II)(*R*)-BINAP-$(OAc)_2$-catalyzed hydrogenation (Scheme 2).[14] Although **7** possessed an aromatic nitro group, which is ordinarily highly sensitive to catalytic hydrogenation conditions, we were optimistic that the homogeneous Ru catalyst would provide the needed chemoselectivity owing to the antici-

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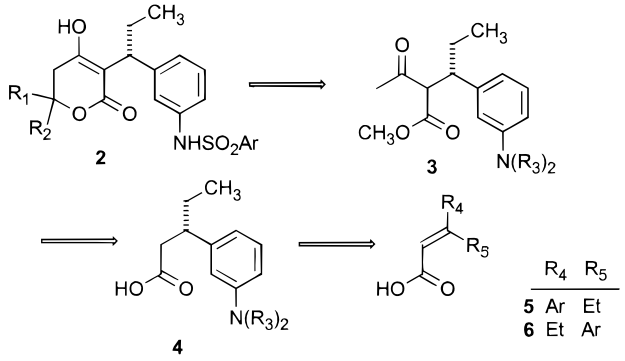
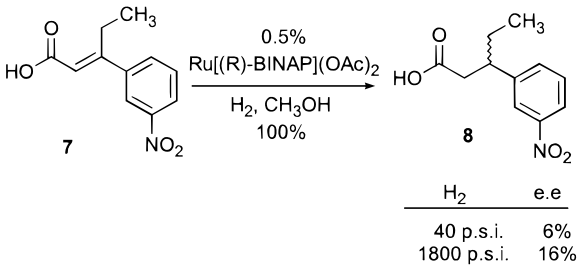
Scheme 1. Retrosynthetic Analysis



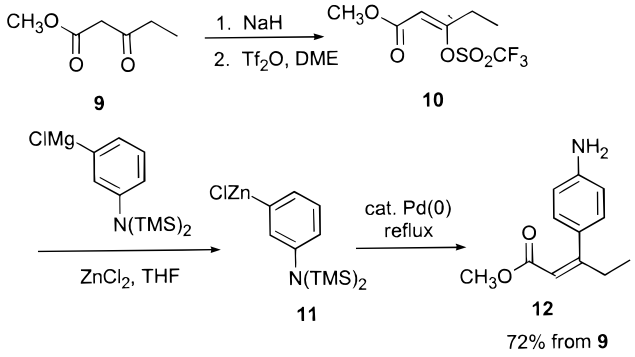
Scheme 2. First Asymmetric Hydrogenation Attempt



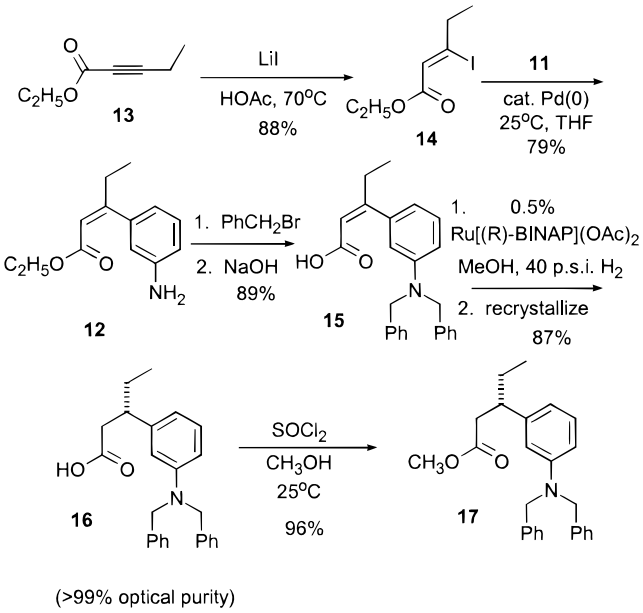
pated relatively poor coordinating ability of the nitro group. Indeed, hydrogenation of **7** at 40 psi cleanly afforded carboxylic acid **8** with no trace of other products by HPLC analysis; however, **8** was obtained in very poor optical yield (6% ee). Furthermore, although it has been demonstrated that the hydrogen pressure can exert a large influence on the optical yield for certain substituted acrylic acids,[15] only a slight improvement (16% ee) was found when the reaction was repeated using 1800 psi hydrogen pressure.[16]

At this point, we decided to pursue the asymmetric hydrogenation of the geometrical isomer of the acrylic acid. To prepare **10** (Scheme 3), the roles of the coupling partners were reversed. Methyl propionyl acetate (**9**) was cleanly converted to enol triflate **10**,[17] which smoothly underwent Pd(0)-catalyzed coupling with **11**[18] to provide

Scheme 3. Approaches To Obtain Stereochemically Pure 12



Scheme 4. Final Synthetic Route To Obtain Optically Pure 17



stereochemically pure **12** in an overall yield of 72% from **9**. Although this procedure worked well, it relied on the relatively costly and hazardous triflic anhydride, which was undesirable for large scale synthesis. A search for an alternative to enol triflate **10** led to a straightforward procedure for the stereoselective trans addition of H−I to alkynoates.[19] Simply stirring ethyl pent-2-ynoate (**13**) with lithium iodide in acetic acid at 70 °C for 5 h afforded an 88% yield of *Z*-alkenyliodide **14**[20] (Scheme 4). This iodoalkene reacted cleanly with **11** under Pd(0) catalysis to afford **12** in 79% yield on a multigram scale.[21] Careful dibenzylation of the aniline nitrogen followed by saponification of the ester gave crystalline **15** in 89% yield. Subjecting **15** to 0.5% Ru(II)(*R*)-BINAP catalyst at 40 psi hydrogen pressure afforded **16** in a 95:5 (*R*)/(*S*) enantiomeric ratio, upgraded to >99% optical purity by a single recrystallization (87% chemical yield on a 53 g scale).[16]

(13) Compound **7** was synthesized from commercially available ethyl 3-nitrobenzoyl acetate, which was converted to the (*Z*)-enolphosphate under kinetic conditions with sodium hydride and chlorodiethyl phosphate according to the method of Weiler and Sum (*Can. J. Chem.* **1979**, *57*, 1431−1441). This reaction afforded a 94% yield of stereochemically pure enolphosphate. Pd-catalyzed cross-coupling reaction of the enol phosphate with diethylzinc provided stereochemically pure **7** in 85% yield after saponification to the ester and crystallization (multigram scale).

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(16) The % ee was determined by reducing the carboxylic acid to the alcohol with borane methyl sulfide and analyzing the alcohol by HPLC using a Chiracel OD-H column (2-propanol/hexane). No attempt was made to determine the absolute configuration of the major isomer of **8**.

(17) Attempts to couple the (*Z*)-enolphosphate prepared from **9** with the arylzinc reagent **11** were unsuccessful because **11** reacted sluggishly under Pd(0)-catalyzed cross-coupling conditions and the reaction could not be driven to completion. Cu(I) catalysis with copper(I) bromide (1:1) left the enol phosphate unchanged.

(18) Prepared in situ from the commercially available Grignard reagent (Aldrich) and $ZnCl_2$.

(19) A report indicating that nonterminal alkynes were poor substrates: Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643−1644. A subsequent report that nonterminal alkynes did indeed work well: Marek, I.; Allexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1991**, *32*, 5329−5332.

(20) Stable after several months of storage.

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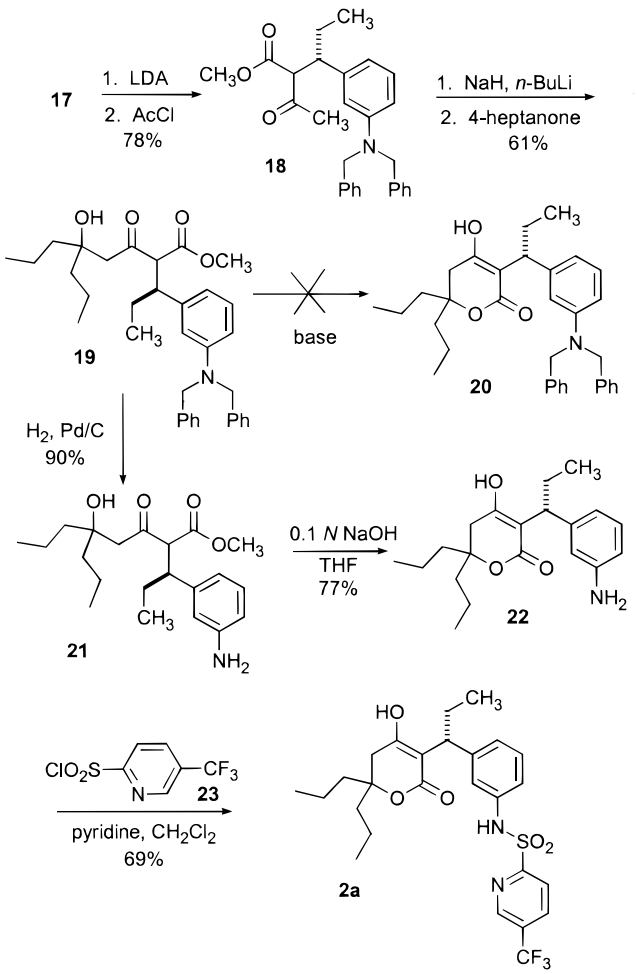
Scheme 5. Conversion of 17 to 2a (PNU-140135)



The absolute configuration of **16** was determined by X-ray diffraction analysis of the hydrogen bromide salt. With enantiomerically pure **17** possessing the requisite C3α stereochemistry in hand, we turned our attention to devising a method for incorporating this intermediate into the dihydropyrone ring.

Careful acylation of **17** via deprotonation with LDA and addition to excess acetyl chloride afforded **18** in 78% yield (Scheme 5). Treatment of the β-ketoester with sodium hydride followed by *n*-butyllithium formed the dianion, which was quenched with 3-heptanone to provide **19** in 61% yield. Lactonization was attempted using standard conditions of 0.1 N sodium hydroxide but afforded the desired dihydropyrone **20** in dismal yields (17−21%). A variety of other bases, such as potassium *t*-butoxide, sodium carbonate, potassium carbonate, sodium methoxide, and sodium hexamethyldisilazide, in various solvents and at various temperatures, were examined, but all favored the retro-aldol product **18** rather than hydrolysis and lactonization of the dihydropyrone. Because this cyclization worked well in a model system lacking the bis(benzyl)amine substitutent on the C3α phenyl ring, we hypothesized that the benzylamine protecting groups were in some way sterically inhibiting lactonization. Fortunately, removal of the benzyl protecting groups allowed lactonization to proceed uneventfully. Thus, treatment of **21** with 0.1 N sodium hydroxide provided dihydropyrone **22** in 77% yield. Finally, treatment of aniline **22** with sulfonyl chloride **23**[4] provided **2a** (PNU-140135) in 69% yield. Thus, PNU-140135 (**2a**) was prepared in five steps from optically pure ester **17** in 23% yield, resulting in a 12% overall yield of **2a** from commercially available **13** (unoptimized).

Conclusion

A synthetic process that affords HIV protease inhibitor **2a** (PNU-140135) in 11 steps and 12% overall yield from commercially available material was developed. The synthesis relied on an efficient asymmetric hydrogenation of a stereochemically pure β-substituted (*Z*)-cinnamic acid to set the C3α stereocenter. This methodology is potentially useful in the search for an economical route to the clinical candidate PNU-140690, which contains the identical C3α substitution.

Experimental Section

All reactions were run under an atmosphere of nitrogen, unless otherwise indicated. Methyl 2-pentynoate was obtained from Farchan Chemical Co.; methyl propionyl acetate, 3-[bis-(trimethylsilyl)amino]phenylmagnesium chloride, and etheral anhydrous zinc chloride were obtained from Aldrich Chemical Co.; bis(triphenylphosphine)palladium chloride and anhydrous zinc chloride were obtained from Strem Chemical Co.; and (*R*)-BINAP was obtained from T.C.I.

Methyl (*Z*)-3-Trifluoromethylsulfonyloxy-2-pentenoate (10). A three neck flask was fitted with an overhead stirrer, and DME or toluene (500 mL) was added to sodium hydride (7.080 g of a 60% dispersion in oil, 177.1 mmol) that had been washed with pentane (2×). This slurry was cooled to 0 °C, and methyl 3-oxopentoate (20.19 g, 161.0 mmol) was added over 10 min, with hydrogen gas evolution. The resulting slurry was cooled to −30 °C, and trifluoromethanesulfonic anhydride (50.0 g, 177 mmol) was added by syringe. Stirring was continued for 30 min, at which point the slurry was allowed to warm to 25 °C and stir overnight. Optionally, the slurry could be filtered through diatomaceous earth before extractive workup. The slurry was cooled to 0 °C, diluted with aqueous sodium bicarbonate, and extracted with MTBE. The organic layer was washed with water (2×) and brine and dried over sodium sulfate. Solvent removal at 40 °C afforded 27.1 g (103 mmol, 64% yield) of a dark liquid, pure by NMR and HPLC, which was carried forward without further purification. An aliquot was shown to be unchanged by stirring overnight with aqueous sodium bicarbonate, showing it to be hydrolytically stable; likewise, storage for several days at 25 °C also resulted in no change. ^{1}H NMR ($CDCl_3$): δ 1.16 (t, 3H, 7 Hz), 2.44 (q, 2H, 7 Hz), 3.78 (s, 3H), 5.77 (s, 1H). IR (thin film): 1738, 1684, 1427, 1298 cm^{-1}. HRMS calcd for $C_7H_9F_3O_5S$: 262.0123, found 262.0110.

Ethyl (*Z*)-3-Iodopentenoate (14). Lithium iodide (39.0 g, 291 mmol) was placed in a flask with ethyl 2-pentynoate (33.1 g, 263 mmol) and fitted with a mechanical stirrer. Acetic acid (30 mL) was added, and the slurry was heated to 70 °C with stirring. After 5 h, analysis by HPLC indicated that no starting material remained and that a single new peak was present. The slurry was cooled, water and ether were added, and the mixture was extracted. The organic layer was washed with water (3X), saturated aqueous sodium bicarbonate, and brine. Solvent removal afforded a liquid that was pure by ^{1}H NMR analysis. The liquid was filtered through a plug of silica gel with ethyl acetate/hexane (5:95), and the solvent was removed to afford 58.8 g of a clear liquid (88%), pure by HPLC analysis. The liquid was stored at 25 °C for three months with no noticeable decomposition. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (s, 1H), 4.02 (q, 2H, 7 Hz), 2.74 (q, 2H, 7 Hz), 1.27 (t, 3H, 7 Hz), 1.15 (t, 3H, 7 Hz). IR (thin film): 1731, 1666, 1437, 1370 cm^{-1}. HRMS calcd for $C_7H_{11}O_2I$: 266.0919, found 266.0921. Anal. Calcd for $C_7H_{11}O_2I$: C, 33.09; H, 4.36. Found: C, 32.77; H, 4.27.

Methyl (*Z*)-3-(3-Aminophenyl)pentenoate (12). Method 1. A flask containing bis(triphenylphosphine)palladium chloride (3 mol %, 6.42 g) and triphenylphosphine (3 mol %, 2.4 g) was flushed with nitrogen. THF (200 mL) was added, and the slurry was cooled to 0 °C. DIBAL-H (6 mol %, 18.3 mL of a 1.0 M

toluene solution) was slowly added. The cold bath was removed, and the dark slurry was allowed to stir for 30 min to generate the palladium(0) catalyst. During this time, 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride (1.2 equiv, 366 mL of a 1.0 M THF solution) was added at 0 °C to an ether solution of anhydrous zinc chloride (1.2 equiv, 366 mL of a 1.0 M solution), and a white slurry formed. Methyl (*Z*)-3-trifluoromethylsulfonyloxypentenoate (**10**) (1.0 equiv, 80.5 g, 307 mmol) was added to the arylzinc slurry followed by cannula transfer of the palladium catalyst. The reaction was allowed to stir at 0 °C, and the ice was allowed to melt. After a total of 1 h at 25 °C, the reaction was cooled to 0 °C, and 2 N aqueous hydrochloric acid (300 mL) was carefully added, followed by water (1 L). MTBE was added, and the reaction was partitioned. The organic layer was back-extracted with additional water. The aqueous layers were combined and washed with MTBE, and then concentrated ammonium hydroxide was added followed by MTBE. Filtration through diatomateous earth at this point circumvents a potential emulsion problem. The solvent mixture was partitioned, and the organic layer was washed with water (2×) and brine. Drying over sodium sulfate and solvent removal afforded the product as a liquid in 46.2 g crude yield (225 mmol, 73%), contaminated only by a trace amount of aniline, as judged by HPLC and ^{1}H NMR analysis. This material was carried on as is. An analytical sample was purified by chromatography with ethyl acetate/hexane (25:75). ^{1}H NMR ($CDCl_3$): δ 1.04 (t, 3H, 7 Hz), 2.41 (q, 2H, 7 Hz), 3.46 (s, 3H), 5.83 (s, 1H), 6.48 (s, 1H), 6.53 (d, 1H, 7 Hz), 6.62 (d, 1H, 7 Hz), 7.14 (d, 1H, 7 Hz). IR (thin film): 1721, 1602 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.37; N, 6.83. Found: C, 70.21; H, 7.37; N, 6.78.

Ethyl (*Z*)-3-(3-Aminophenyl)pentenoate (12). Method 2. The procedure used above for the enol triflate was applied to **14** (5.20 g, 19.6 mmol), except that it was necessary to reflux the THF solution, and afforded 3.00 g (15.6 mmol, 80%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 1.04 (t, 3H, 7 Hz), 1.26 (t, 3H, 7 Hz), 2.41 (q, 2H, 7 Hz), 4.19 (q, 2H, 7 Hz), 5.83 (s, 1H), 6.48 (s, 1H), 6.53 (d, 1H, 7 Hz), 6.62 (d, 1H, 7 Hz), 7.14 (d, 1H, 7 Hz). IR (thin film): 1723, 1600 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.41; H, 7.81; N, 6.39. Found: C, 71.57; H, 8.13; N, 6.12.

Methyl (*Z*)-3-(3-*N*,*N*-Dibenzylaminophenyl)pentenoate. Compound **12** (77.0 g, 375 mmol) was dissolved in acetonitrile (500 mL) with diisopropylethylamine (131 mL) and cooled to 0 °C. Benzylbromide (2.1 equiv, 94.1 mL) was added, and the solution was stirred overnight. When HPLC analysis ascertained that all of the primary and secondary amines were consumed, the solution was cooled to 0 °C, and a solution of 25% aqueous trimethylamine was added to scavenge the excess benzylbromide. After 60 min at 25 °C, the solution was diluted with MTBE and washed with saturated aqueous ammonium hydroxide and water. The organic layer was washed with water (2×) and brine. Drying over sodium sulfate and solvent removal afforded a liquid, which was filtered through a plug of silica gel with ethyl acetate/hexane (15:85). Solvent removal afforded 128 g (334 mmol, 89%) of pure product. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, 7 Hz), 2.31 (q, 2H, 7 Hz), 3.52 (s, 3H), 4.61 (s, 1H), 6.49 (d, 1H, 8 Hz), 6.51 (s, 1H), 6.68 (d, 1H, 7 Hz), 7.14 (t, 1H, 8 Hz), 7.34−7.23 (m, 11 H). IR (thin film): 1728, 1640, 1598 cm^{-1}. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.00; H, 7.06; N, 3.64. Found: C, 80.68; H, 6.85; N, 3.50.

(*Z*)-3-(3-*N*,*N*-Dibenzylaminophenyl)pentenoic Acid (15). Methyl (*Z*)-3-(3-*N*,*N*-dibenzylaminophenyl)pentenoate (110 g, 286 mmol) was added to a solution of sodium hydroxide (45 g) in water (400 mL), methanol (400 mL), and THF (300 mL). This was stirred at 25 °C overnight and then heated to reflux for 2 h. The solvent was removed in vacuo, and water was added (500 mL). The solution was cooled in an ice bath, acidified to pH 6 with 6 N aqueous hydrochloric acid, and extracted with MTBE. The organic layer was washed with water and brine. Drying over sodium sulfate and solvent removal afforded 106 g (285 mmol, 100%) of a crystalline solid (mp 130 °C), pure by HPLC and ^{1}H NMR. ^{1}H NMR ($CDCl_3$): δ 0.960 (t, 3H, 7 Hz), 2.34 (q, 2H, 7 Hz), 4.60 (s, 4H), 5.75 (s, 1H), 6.50 (m, 2H), 6.68 (d, 1H, 8 Hz), 7.32−7.11 (m, 11 H), 10.5 (bs, 1H). IR (Nujol): 1695, 1671, 1600 cm^{-1}. HRMS calcd for $C_{25}H_{25}NO_2$: 371.1885, found 371.1885. Anal. Calcd for $C_{25}H_{25}NO_2$·HCl: C, 73.45; H, 6.40; N, 3.77. Found: C, 73.45; H, 6.40; N, 3.63.

(*S*)-3-(3-*N*,*N*-Dibenzylaminophenyl)pentanoic Acid (16). All solvents were sparged with argon before use. Compound **15** (53.0 g, 143 mmol) was placed in a large Parr bottle, flushed with nitrogen, and diluted with methanol (300 mL). Freshly prepared [(*R*)-BINAP]ruthenium acetate (0.005 equiv) was added by syringe as a methanol (50 mL)/THF (10 mL) solution. The Parr bottle was repeatly flushed with hydrogen and then allowed to shake under a 40 psi (2.7 atm) atmosphere of hydrogen. Careful removal of an aliquot after 3 d showed the reduction to be complete (^{1}H NMR analysis). The solvent was removed in vacuo, at which point the residue solidified. Reduction of a sample to the alcohol with borane methyl sulfide, followed by examination by chiral HPLC on a Chiracel OD-H column (2.5% 2-propanol/hexane) showed the product to be a 95:5 ratio of enantiomers. Cyclohexane, acetonitrile, and acetic acid were all judged to be suitable recrystallation solvents to upgrade the optical purity; recrystallization from acetic acid (35 mL)/water (10 mL) afforded 47.0 g (124 mmol, 87% yield) of pure **16**, as judged by reverse phase HPLC, ^{1}H NMR, and examination of the alcohol by chiral column HPLC (vide supra); mp 120 °C, $[\alpha]^{25}_D = +11°$ (c = 0.904, CH_3OH). X-ray diffraction analysis of the HBr salt (crystallized from CH_3OH) showed the product to be the (*S*)-enantiomer. ^{1}H NMR ($CDCl_3$): δ 0.69 (t, 3H, 7 Hz), 1.48 (m, 1H), 1.61 (m, 1H), 2.53 (d, 2H, 7 Hz), 2.83 (m, 1H), 4.62 (s, 4H), 6.52, (d, 1H, 8 Hz), 6.53, (s, 1H), 6.58 (d, 2H, 8 Hz), 7.09 (t, 1H, 8 Hz), 7.33−7.22 (m, 10H), 11.4 (bs, 1H). IR (mineral oil): 2710, 1700, 1600 cm^{-1}. MS (*m*/*e*): 373, 296, 283, 223. Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: C, 80.57; H, 7.46; N, 3.71.

(*S*)-Methyl 3-(3-*N*,*N*-Dibenzylaminophenyl)pentanoate (17). Thionyl chloride (20.0 g, 169 mmol) was added dropwise to methanol (220 mL) at 0 °C. The ice bath was removed, **16** (42.0 g, 113 mmol) was added, and the solution was allowed to stand overnight. The solvent was removed in vacuo, and the residue was placed in a separatory funnel with MTBE and water. Concentrated ammonium hydroxide was added, and the mixture was extracted. The organic layer was washed with water and brine and dried over sodium sulfate, and the solvent was removed in vacuo to afford a liquid (42 g, 96% yield). $[\alpha]^{25}_D = +16°$ (c = 0.994, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.69 (t, 3H, 7 Hz), 1.48 (m, 1H), 1.55 (m, 1H), 2.50 (d, 2H, 7 Hz), 2.83 (m, 1H), 3.57 (s, 3H), 4.62 (s, 4H), 6.51 (d, 1H, 8 Hz), 6.53 (s, 1H), 6.58 (d, 1H, 8 Hz), 7.08 (t, 1H, 8 Hz), 7.34−7.16 (m, 10H). IR (thin film): 1737, 1600, 1494 cm^{-1}. HRMS calcd for $C_{26}H_{29}NO_2$: 387.2198, found 387.2203. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.42; H, 7.41; N, 3.65.

(*S*)-Methyl 2-[1-(3-Bis(phenylmethyl)aminophenyl)propyl] Acetoacetate (18). To a mixture of 14.77 g (38.16 mmol) of **17** in 100 mL of freshly distilled THF at −78 °C under nitrogen was added 21.0 mL of 2.0 M lithium diisopropyl amide via syringe over 1 min. After stirring for 10 minutes, this mixture (anion solution) was added to a solution of 26.0 mL of acetyl chloride in 100 mL of freshly distilled THF stirring at −78 °C under nitrogen via cannula, followed by THF rinse (60 mL) over 9 min. This mixture was then allowed to stir for 3 min and then allowed to stir at 0 °C. After 2 min at 0 °C, 200 mL of ice-cold water was added. The mixture was stirred for 6 min and then poured into 200 mL of saturated aqueous sodium bicarbonate, and the resulting layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate. The pH of the aqueous layer was adjusted from 1 to 8 with solid sodium bicarbonate, and then the aqueous layer was extracted with ethyl acetate (3×). All of the organic layers were then combined, dried ($MgSO_4$), and concentrated in vacuo to provide 21.66 g of crude material as a yellow oil. The crude was taken up into a mixture of methylene chloride and hexane and placed on a 36 cm × 5.5 cm, 40−63 μm silica MPLC column and eluted with ethyl acetate in hexane (1 L each 2%, 4%, 6%, 8%, 10%, 12%, 20%). Collection of 40 mL fractions provided 12.76 g (78% yield) of **18** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 4 H), 7.25 (m, 6 H), 7.08 (t, J = 8.0 Hz, 1H), 6.61 (m, 1 H), 6.53 (m, 2 H), 4.62 (s, 4 H), 3.72 (m, 3.5 H), 3.40 (s, 0.5 H), 3.10 (m, 1 H), 2.25 (s, 0.5 H), 1.80 (s, 2.5 H), 1.62 (m, 1 H), 1.43 (m, 1 H), 0.63 (m, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.90, 12.07, 27.16, 27.78, 30.07, 30.12, 47.77, 48.20, 52.47, 52.78, 54.75, 54.93, 66.55, 67.10, 111.87, 111.97, 113.47, 113.56, 117.00, 127.17, 127.24, 127.28, 127.32, 128.96, 129.02, 129.48, 129.78, 139.01,

139.10, 141.61, 141.96, 149.54, 168.93, 169.73, 202.89, 203.20. IR (mull): 1740 (s), 1715 (m), 1596 (s) cm^{-1}. MS (EI) *m*/*z* (rel intensity): 429 (M^+, 94), 352 (11), 338 (9), 222 (10), 208 (7). Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.22; H, 7.28; N, 3.40. $[\alpha]^{25}_D = +32°$ (*c* = 0.8844, MeOH).

(*S*)-Methyl 2-[1-(3-Bis(methylphenyl)aminophenyl)propyl]-5-hydroxy-3-oxo-5-propyl Octoate (19). To a mixture of 5.68 g (13.2 mmol) of **18** in 35.0 mL of freshly distilled THF under nitrogen was added 895 mg (22.4 mmol) of 60 wt % sodium hydride. Only slight effervescence was noticed. The mixture was heated to 45 °C for 5 h, cooled to 0 °C, and stirred for 20 min. Then, 10.0 mL of 1.6 M *n*-butyllithium (16 mmol) was added over 2 min, providing a reddish brown mixture. This mixture was then stirred for 30 min at 0 °C. The mixture was cooled to −78 °C, and after 7 min, 3.80 mL (27.2 mmol) of 4-heptanone was added. After the mixture stirred for 18 min at −78 °C, it was warmed to 0 °C. After 25 min, the color had changed to yellow, and the mixture was slowly quenched with 10 mL of ice water. The mixture was then partitioned between brine and ethyl acetate. The resulting layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The combined ethyl acetate layers were dried ($MgSO_4$) and concentrated in vacuo to provide 8.46 g of crude yellow oil. The crude was dissolved in methylene chloride, placed upon a 36 cm × 5.5 cm, 40−63 μm silica MPLC column, and eluted with ethyl acetate in hexane (1 L each 2%, 4%, 6%, 8%, 10%, 12%, 20%). Collection of 50 mL fractions provided 4.38 g (61% yield) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 10 H), 7.06 (m, 1 H), 6.50 (m, 3 H), 4.61 (s, 4 H), 3.73 (m, 2.6 H), 3.44 (s, 0.5 H), 3.39 (s, 1.4 H), 3.24 (s, 0.5 H), 3.12 (m, 1 H), 2.73 (d, *J* = 18 Hz, 0.5 H), 2.65 (d, *J* = 18 Hz, 0.5 H), 2.39 (d, *J* = 18.0 Hz, 1 H), 2.18 (d, *J* = 18.0 Hz, 1 H), 1.56−1.11 (m, 10 H), 0.860 (m, 6 H), 0.61 (m, 3 H). MS (EI) *m*/*z* (rel intensity): 543 (M^+, 34), 544 (13), 429 (15), 328 (10), 314 (10). Anal. Calcd for $C_{35}H_{45}NO_4$: C, 77.31; H, 8.34; N, 2.58. Found: C, 77.32; H, 8.31; N, 2.76.

(*S*)-Methyl 2-[1-(3-Aminophenyl)propyl]-5-hydroxy-3-oxo-5-propyl Octoate (21). A mixture of 4.38 g (8.07 mmol) of **20** and 722 mg of 10% palladium on carbon in 50 mL of 20% methanol in ethyl acetate was shaken on the Parr under hydrogen (30 psi) for 5 h. The mixture was then evacuated, filled with nitrogen (3×), and filtered over Celite. The filtrate was concentrated in vacuo to provide 2.65 g (90%) of the title compound. ^{1}H NMR (300 MHz, MeOD): δ 7.02 (m, 1 H), 6.55 (m, 3 H), 4.00 (m, 1 H), 3.72 (s, 2 H), 3.38 (s, 1 H), 3.09 (m, 1 H), 2.77 (d, *J* = 16.6 Hz, 0.5 H), 2.70 (d, *J* = 16.6 Hz, 0.5 H), 2.55 (d, *J* = 17.8 Hz, 1 H), 2.32 (d, *J* = 17.9 Hz, 1 H), 1.62−1.06 (m, 10 H), 0.89 (m, 3 H), 0.73 (m, 6 H). MS (EI) *m*/*z* (rel intensity): 363 (M^+, 45), 270 (66), 206 (20), 202 (16), 174 (36). HRMS (EI) calcd for $C_{21}H_{33}NO_4$: 363.2409, found 363.2402. Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.30; H, 9.21; N, 4.04.

[3α(*R*)]-3-[1-(3-Aminophenyl)propyl]-5,6-dihydro-6,6-dipropyl-4-hydroxy-2*H*-pyran-2-one (22). A mixture of 2.42 g (6.67 mmol) of amine intermediate in 50 mL of THF and 170 mL of 0.1 N sodium hydroxide was stirred at room temperature for 4.5 h. It was then stirred at 0 °C for 20 min, and 25 mL of 1 N hydrochloric acid was added. The mixture became cloudy and then homogeneous again. The mixture was stirred at room temperature for 30 min, and then the pH was adjusted from 3 to 7 with solid sodium bicarbonate. The mixture became cloudy white while the pH was adjusted. The mixture was then partitioned between ethyl acetate (200 mL) and brine (150 mL). The resulting layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The combined ethyl acetate layers were dried ($MgSO_4$) and concentrated in vacuo to provide 1.70 g (77% crude yield) of the title compound as a foam. IR (mull): 2660 (b), 1606 (s), 1531, 1493 cm^{-1}. ^{1}H NMR (300 MHz, MeOH-d_4): δ 6.95 (t, *J* = 7.7 Hz, 1 H), 6.80 (s, 1 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 6.51 (dd, *J* = 1.2, 7.8 Hz, 1 H), 3.91 (dd, *J* = 6.6, 9.5 Hz, 1 H), 2.54 (s, 2 H), 2.19 (m, 1 H), 1.96 (m, 1 H), 1.62 (m, 4 H), 1.32 (m, 4 H), 0.89 (m, 9 H). MS (EI) *m*/*z* (rel intensity): 331 (M^+, 96), 202 (30), 192 (32), 191 (68), 174 (53). HRMS (EI) calcd for $C_{20}H_{29}NO_3$: 331.2147, found 331.2153. Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.48; H, 8.98; N, 4.03.

[3α(*R*)]-*N*-[3-[1−5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2*H*-pyran-3-yl]propyl]phenyl-5-triflurormethyl)-2-pyridinesulfonamide (2a). To a mixture of 534 mg (1.61 mmol) of **22** (crude) in 20 mL of methylene chloride and 0.26 mL (3.21 mmol) of pyridine at 0 °C was added 415 mg (1.69 mmol) of 5-trifluoromethyl pyridine-2-sulfonyl chloride (**23**) as a solid all at once. After 2 h, the mixture was added to 10 mL of 1 N hydrochloric acid. The resulting layers were separated, and the aqueous layer was extracted with additional methylene chloride (3×). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to provide 860 mg of crude as a dark oil. The crude was taken up into methylene chloride, placed upon a 24 cm × 2.5 cm, 40−63 μm silica MPLC column, and eluted with ethyl acetate in hexane (250 mL each 2%, 4%, 6%, 8%, 10%, 15%, 20%, 25%, 30%, 40%). Collection of 25 mL fractions provided 600 mg of **2a** as colorless oil (69%). Upon reconcentration from methylene chloride (2×) a tan foam was obtained. ^{1}H NMR (300 MHz, MeOH-d_4): δ 8.98 (s, 1 H), 8.26 (d, *J* = 8.2 Hz, 1 H), 8.05 (d, *J* = 8.2 Hz, 1 H), 7.20 (s, 1 H), 7.03 (m, 2 H), 6.92 (m, 1 H), 3.90 (m, 1 H), 2.53 (s, 2 H), 2.08 (m, 1 H), 1.86 (m, 1 H), 1.58 (m, 4 H), 1.26 (m, 4 H), 0.83 (m, 9 H). IR (mull): 1641 (m), 1608 (m), 1595 (m) cm^{-1}. MS (EI) *m*/*z* (rel intensity): 540 (M^+, 33), 401 (57), 383 (77), 343 (40), 197 (40), 174 (51), 146 (54), 145 (75). Anal. Calcd for $C_{26}H_{31}F_3N_2O_5S$: C, 57.77; H, 5.78; N, 5.18. Found: C, 57.67; H, 5.80; N, 5.19. $[\alpha]^{25}_D = +28°$ (*c* = 0.8397, MeOH).

Supporting Information Available: Ortep drawing and tables of X-ray data for compound **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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