Bakers' Yeast-Mediated Synthesis of (*R*)-Aminoglutethimide

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Introduction

Enantiomerically pure forms of chiral β-hydroxy acid derivatives are important starting materials in organic synthesis.[1] In this context, we recently reported[2] on the bakers' yeast-mediated preparation of **1** and **3**, which can be regarded as the 2-formyl analogues of ethyl (*S*)- and (*R*)-3-hydroxy-2-methyl propionate.[3,4] The relative simplicity of the preparation of the above materials and their chemical features, *i.e.*, the presence in the C_5 molecule of four carbon atoms in different oxidation states, directly bound to the central carbon atom render this type of compounds of interest in the construction of optically active substances bearing an all-carbon-substituted quaternary center. In support of this view, we report now on the preparation of **2** and **4**, phenyl analogs of **1** and **3**, from **6** and **7** and on the use of **2** in the preparation of the (*R*) enantiomer **19** of the antimetastatic drug aminoglutethimide (Elipten, CIBA), which provides essentially all of the steroid synthesis inhibiting activity of the racemate.[5]

Results and Discussion

The starting material is ketolactone **5**, easily obtained by reacting gaseous formaldehyde at −20 °C in diethyl ether with diethyl α-phenyl oxalacetate in the presence of pyridine. Under these conditions, only a trace of ethyl α-phenylacrylate, previously reported as the unique noticeable transformation product of these reagents under basic conditions,[6,7] was obtained. Bakers' yeast reduction of **5** (4 g/L) affords two diastereoisomeric crystalline hydroxylactones, mp 82–83 and 103–104 °C, respectively, showing $[\alpha]^{20}_D$ −48.4 and +30.9 (*c* 1, $CHCl_3$). However, ^1H NMR studies in the presence of chiral shift reagents and HPLC analysis on Chiracel OD and comparison with the racemic materials obtained from **5** by $NaBH_4$ reduction indicate that the former material, which is the more mobile on TLC, is enantiomerically pure, whereas the second product shows 0.50 ee, respectively. We were unable to assign by NMR studies the relative stereochemistry of these materials. However, they possess (3*S*) and (3*R*) absolute configuration, respectively, as indicated by their conversion (see Figure 1) into the enantiomeric (*S*) and (*R*) aldehydes **2** and **4**.

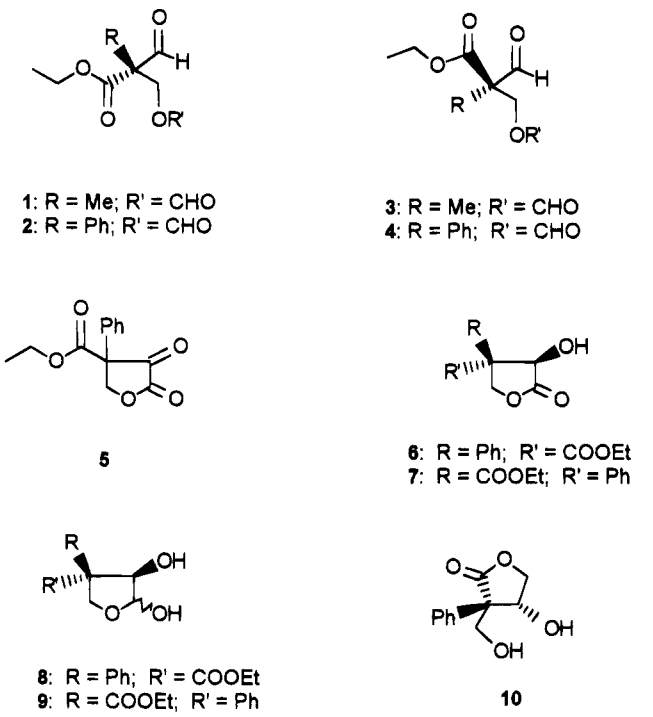

Figure 1.

Indeed, the former product gives rise (see Figure 1) to (*R*)-**19**,[5] which has been previously chemically correlated with 2-methyl-2-phenylbutanoic acid of known absolute configuration.[8] The assignement of the (2*R*) stereochemistry depicted in **6** and **7** is only made by analogy with the results of the bakers' yeast reduction of the methyl analog of **5**.[2] However, the assignment of this stereochemistry is not relevant in the present context of the synthesis of **2** and **4**.

The two-step conversion of **6** and **7** into aldehydes **2** and **4** first involves $LiBH_4$ reduction to furanoses **8** and **9** and occurs with 73% yield overall. Occasionally, overreduction takes place, but the 1,2-diols are not isolated, the hydroxy lactone **10** and its diastereisomer being obtained instead, as the result of an internal transesterification reaction catalyzed by the basic conditions of the reduction. The subsequent periodate oxidation of **8** and **9** to the desired aldehydes **2**, $[\alpha]^{20}_D = -92.1$, and **4**, $[\alpha]^{20}_D = +47$ (both *c* 1, $CHCl_3$), proceeds in quantitative yields.

In order to both determine the absolute configuration of **2** and **4** and explore the synthetic utility of this pair of yeast-generated optically active products[9] we converted enantiomerically pure **2** into **19**, which is the biologically active enantiomeric form of aminoglutethimide.[5] The two enantiomers of this drug, actually marketed as racemate, bearing an all-carbon-substituted quaternary chiral center, have been previously obtained by optical resolution of the final product with tartaric acids or of advanced acidic intermediates with optically active natural alkaloids.[5]

The synthesis of **19** from **2** (Scheme 1) involves, as relevant steps, two chain elongations by one- and two-carbon units, respectively. These have been achieved by two aldehyde–olefination reactions. In the first, the aldehyde **2** is converted into the unsaturated ester **11**.

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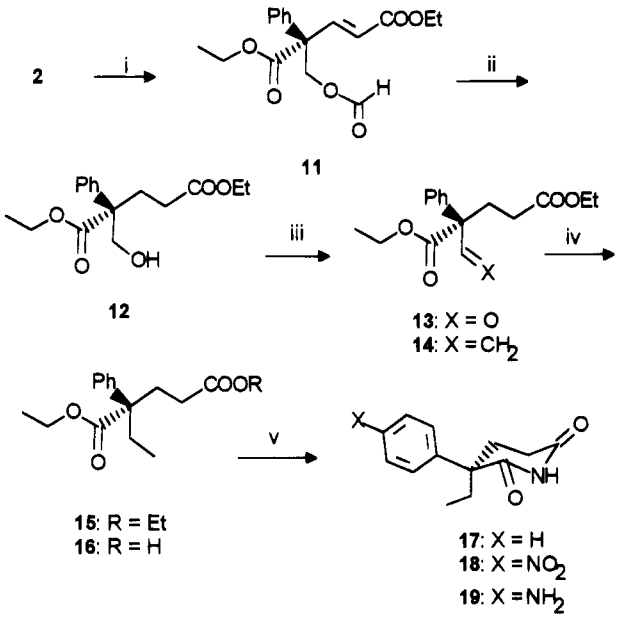
0022-3263/95/1960-5693$09.00/0

Scheme 1



[a] Key: (i) PhP_3P=CHCOOEt; (ii) H_2/Pd, then HCl/EtOH; (iii) PCC, $CH_2I_2/Me_3Al/Zn$; (iv) H_2/Pd, H_2O/OH^-; (v) NH_3/Δ, HNO_3/H_2SO_4, H_2/Pd.

This material, upon catalytic hydrogenation, hydrolysis of the formate ester, followed by pyridinium chlorochromate oxidation affords **13**, the second aldehyde of the sequence. The latter material, upon treatment with $CH_2I_2/Me_3Al/Zn$,[10] affords **14**, yielding, in turn, upon hydrogenation, the diester **15**, containing the complete carbon framework of **19**, in 29% overall yield from **2**. The synthetic sequence to **19** was completed,[11] converting the diester **15** into the glutethimide **17** by treatment of the related diacid **16** with ammonia and subsequent ring closure of the ammonium salt. The latter material by nitration and catalytic hydrogenation affords **19**, showing $[\alpha]^{20}_D$ = +162.9, well in agreement with the value reported in the literature[5] for the (*R*) enantiomer. Unfortunately, the modest enantiomeric purity of yeast-generated **4** prevents a direct access to the (*S*) enantiomer of aminoglutethimide through the above sequence. However, this material should be conceivably accessible from enantiomerically pure **2** merely by inverting the sequence in the two olefin-forming reactions.

Recently,[12] there has been interest in producing by enzymic methods compounds containing asymmetric quaternary carbon centers, a topic of current interest in synthetic organic chemistry.[13,14] Our procedure, based on bakers' yeast reduction of **5** and of its 3-methyl analog[2] and leading to enantiomerically pure **1** and **2**, might be of interest due to the presence in these molecules of four carbon atoms in different oxidation states linked to a central carbon atoms, which allows a facile synthetic utilization, as indicated here by the straightforward obtainment of **19** from **2**.

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Experimental Section

Uncorrected melting points were determined on a microstage block. ^1H (250 MHz) NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise noted. The chemical shift scale (8) is based on internal TMS. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns.

Synthesis of Ketolactone 5. To a mixture of 60 g of diethyl α-phenyloxalacetate and 30 mL of pyridine in 300 mL of dry diethyl ether cooled at −20 °C was added gaseous formaldehyde until the ester disappeared (30−45 min). The mixture was poured in ice−HCl, extracted with diethyl ether, washed several times with brine, and then dried on Na_2SO_4. The residue was purified on a silica gel column (hexane−ethyl acetate) to give 44 g (78%) of ketolactone **5**: ^1H NMR δ 1.22 (t, 3H), 4.25 (q, 2H), 5.00 (d, 1H, *J* = 10 Hz), 5.52 (d, 1H, *J* = 10 Hz), 7.4 (s, 5H).

Yeast Transformation of Ketolactone 5. In a 30-L glass jar a mixture was made up composed of 5 kg of commercial moist bakers' yeast and 2 kg of D-glucose in 20 L of tap water at 32 °C. As the fermentation started, 80 g of ketolactone **5** in 80 mL of ethanol was added under stirring. After 16 h at 23 °C, 2 kg of Celite was added, the reaction mixture was filtered on a large Buchner funnel, the solid pad was washed with 2 L of ethyl acetate, and the filtrate was extracted twice with 2 L portions of ethyl acetate. The dried organic phase was evaporated, leaving a residue of *ca.* 80 g. Fifty g of this mixture was chromatographed on 400 g of silica gel with hexane−ethyl acetate as eluent (95:5 to 70:30), giving carbinol **6** (10 g, 20%): mp 82−83 °C (from hexane−ethyl acetate); $[\alpha]^{20}_D$ = −48.4 (*c* 1, $CHCl_3$). ^1H NMR δ 1.22 (t, 3H, CH_3), 4.23 (m, 3H, OCH_2CH_3 + OH)), 4.38 (d, 1H, $-OCH_aH_b$, *J* = 9.4 Hz), 4.73 (d, 1H, CHOH, *J* = 6.5 Hz), 5.03 (d, 1H, $-OCH_aH_b$, *J* = 9.4 Hz), 7.50−7.34 (m, 5H, C_6H_5). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.24; H, 5.34. Subsequently, **7** was eluted: 22 g (44%); mp 103−104 °C (from hexane−ethyl acetate); $[\alpha]^{20}_D$ = 30.9 (*c* 1, $CHCl_3$); ^1H NMR δ 1.26 (t, 3H, CH_3), 2.39 (d, 1H, OH), 4.28 (q, 2H, OCH_2CH_3), 4.63 (d, 1H, $-OCH_aH_b$, *J* = 10.3Hz), 4.89 (d, 1H, $-OCH_aH_b$); 5.08 (d, 1H, CHOH, *J* = 4.9 Hz), 7.45−7.24 (m, 5H, C_6H_5). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.26; H, 5.23. ^1H NMR studies on **6** and **7** in the presence of Eu(hfc)$_3$ and comparison with racemic materials obtained from **5** upon $NaBH_4$ reduction indicated that the compounds are of 0.99 and 0.5 ee, respectively.

Furanoses 8 and 9. To a solution of carbinol **6** (2.5 g, 0.01 mol) in anhydrous THF (15 mL) at 5−10 °C was added dropwise a 1.4 M solution of $LiBH_4$ (3.6 mL) in THF. The reaction mixture was allowed to warm to room temperature and then poured into ice−HCl. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate, washed with brine, dried on Na_2SO_4, and evaporated to dryness. The oily residue (2.5 g) was used in the next step without further purification.

Furanose **8** (1.9 g, 76%): oil, $[\alpha]^{20}_D$ = −11.4 (*c* 1, $CHCl_3$); ^1H NMR (mixture of two anomers in 8:2 ratio; major diastereoisomer) δ 1.20 (t, 3H, CH_3), 3.98 (d, 1H, OH-2, *J* = 8.32 Hz), 4.20 (m, 2H, CH_2CH_3), 4.21 (d, 1H, OH-3), 4.23 (d, 1H, H-5a, *J* = 9.2 Hz), 4.43 (dd, 1H, H-3, *J* = 3.7 and 6.4 Hz), 4.70 (d, 1H, H-5b, *J* = 9.2 Hz), 5.28 (dd, 1H, H-2, *J* = 3.7 and 8.3 Hz), 7.50−7.28 (m, 5H, C_6H_5); minor diastereoisomer (only some peaks are reported due to the overlapping with the signals of the major isomer) δ 1.21 (t, 3H, CH_3); 2.72 (d, 1H, OH-2, *J* = 5.9 Hz), 4.64 (d, 1H, H-5b, *J* = 9.1Hz), 5.37 (dd, 1H, H-2, *J* = 2.9 and 5.6 Hz), 4.20 (m, 2H, OCH_2CH_3). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.02; H, 6.27.

Hydroxy lactone **10** (0.2 g, 10%): oil; $[\alpha]^{20}_D$ = +62.4 (*c* 1, $CHCl_3$); ^1H NMR 1.62 (s, 1H, OH), 3.40 (s, 1H, OH), 3.51 (s, 1H, CHOH), 3.73 (d, 1H, $-CH_aH_b$, *J* = 12.5 Hz), 3.81 (d, 1H, $-CH_aH_bOH$), 4.20 (d, 1H, $-OCH_aH_b$, *J* = 15.5 Hz), 4.82 OCH_aH_b, *J* = 15.5 Hz). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.34; H, 5.88.

Similarly, furanose **9** was obtained from **7** (1.9 g, 7.6%): oil; $[\alpha]^{20}_D$ = +5.8 (*c* 1, $CHCl_3$); ^1H NMR (mixture of two anomers in 6:4 ratio), major diastereoisomer δ 1.17 (t, 3H, CH_3), 2.65 (s br, 1H, OH-3), 4.13 (m, 2H, CH_2CH_3), 4.30 (s br, 1H, OH-2), 4.42 (d, 1H, H-5a, *J* = 8.4 Hz), 4.62 (d, 1H, H-5b, *J* = 8.4 Hz), 4.95 (d, 1H, H-3, *J* = 3.4 Hz), 5.54 (s br, 1H, H-2), 7.43−7.21 (m, 5H,

C_6H_5); minor diastereoisomer δ 1.17 (t, 3H, CH_3), 1.91 (s br, 1H, OH-3), 3.68 (s br, 1H, OH-2), 4.13 (m, 2H, CH_2CH_3), 4.39 (d, 1H, H-5a, J = 8.6 Hz), 4.93 (d, 1H, H-5b, J = 8.6 Hz), 4.89 (s, 1H, H-3), 5.34 (s, 1H, H-2), 7.43–7.21 (m, 5H, C_6H_5). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.96; H, 6.45.

(*S*)-Ethyl 2-Formyl-2-[(formyloxy)methyl]phenylpropionate (2). Furanose **8** (2.5 g, 10 mmol) in 10 mL of THF was treated under stirring, at once, with H_5IO_6 (2.28 g, 10 mmol) in 15 mL of THF. After 10 min, a few drops of 1,2-ethanediol were added, and the reaction mixture was filtered, concentrated under vacuum, and partioned between water and AcOEt (100 mL). The organic layer was washed with a Na_2SO_3 solution and then evaporated to dryness. Silica gel chromatography of the organic residue afforded **2**; 1.8 g, oil, $[\alpha]^{20}_D = -92.1$ (*c* 1, $CHCl_3$), in 73% overall yield from carbinol **6**: ^{1}H NMR δ 1.32 (t, 3H), 4.35 (m, 2H), 4.75 (d, 1H, J = 10.5 Hz), 4.95 (d, 1H, J =10.5 Hz), 7.2 (m, 2H), 7.4 (m, 3H), 8.0 (s, 1H), 10.0 (s, 1H). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.12; H, 5.74.

(*R*)-Ethyl 2-Formyl-2-[(formyloxy)methyl]phenylpropionate (4). Similarly, the aldehyde **4** was obtained from **9**: 1.9 g; oil; $[\alpha]^{20}_D$ +47 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.32 (t, 3H), 4.35 (m, 2H), 4.75 (d, 1H, J = 10.5 Hz), 4.95 (d, 1H, J = 10.5 Hz), 7.2 (m, 2H), 7.4 (m, 3H), 8.0 (s, 1H), 10.0 (s, 1H). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.36; H, 5.69.

(*S*)-Diethyl 4-Phenyl-4-[(formyloxy)methyl]glutaconate (11). Aldehyde **2** (5 g, 0.02 mol) in 50 mL of $CHCl_3$ was stirred at room temperature for 1 h with triphenylphosphonium (carboxyethyl)methinylide (7.6 g, 0.022 mol). The reaction mixture was evaporated under reduced pressure and then chromatographed on silica gel to give 5 g of oily **11**: $[\alpha]^{20}_D$ −5.3 (*c* 1, $CHCl_3$); 75% yield; ^{1}H NMR δ 1.28 (m, 6H), 4.22 (m, 4H), 4.67 (d, 1H, J = 12.5 Hz), 4.88 (d, 1H, J = 12.5 Hz), 5.9 (d, 1H, J = 16 Hz), 7.35 (m, 6H), 8.02 (s, 1H). Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.94; H, 6.11.

(*S*)-Diethyl 2-Phenyl-2-(hydroxymethyl)glutarate (12). A suspension of diester **11** (5g, 16 mmol) and 5% Pd/C (0.5 g) in 100 mL of ethanol was stirred under a H_2 atmosphere. The reaction mixture was filtered, the ethanolic solution saturated with dry HCl, and the solvent removed under vacuum, partitioned between water and ethyl acetate, and washed with sodium hydrogen carbonate and brine. Removal of the solvent afforded 4.2 g of **12**: $[\alpha]^{20}_D$ −13.3 (*c* 1, $CHCl_3$); 91% yield; ^{1}H NMR δ 1.23 (m, 6H), 2.05 (m, 1H), 2.2–2.8 (m, 4H), 4.15 (m, 4H), 4.6 (d, 1H, J = 11 Hz), 4.95 (d, 1H, J = 11 Hz), 7.35 (m, 5H). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.32; H, 7.54.

(*S*)-Diethyl 2-Phenyl-2-formylglutarate (13). Compound **12** (4 g, 14 mmol) was added dropwise to a suspension of pyridinium chlorochromate (6 g, 28 mmol). The mixture was vigourously stirred overnight and then partitioned between water and CH_2Cl_2. Silica gel chromatography of the organic residue afforded oily **13** (2.9 g) $[\alpha]^{20}_D$ = + 87.6 (*c* 1, $CHCl_3$) in 73% yield accompanied by some unreacted starting material (1 g): ^{1}H NMR δ 1.25 (m, 6H), 2.1–2.6 (m, 4H), 4.1 (q, 2H), 4.32 (q, 2H), 7.2 (d, 2H), 7.4 (m, 3H), 9.9 (s, 1H). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.65; H, 6.93.

(*R*)-Diethyl 2-Phenyl-2-vinylglutarate (14). To a suspension of zinc dust (4.1 g, 63 mmol) and diiodomethane (5.6 g, 21 mmol) in dry THF (50 mL) was added a solution of trimethylaluminum in hexane (2 M, 2.1 mL, 4.2 mmol) at 25 °C under nitrogen. The mixture was stirred until the exothermic reaction had subsided (10 min). A solution of the aldehyde **13** (2 g, 7 mmol) in THF (10 mL) was added dropwise at 0 °C, and the mixture was stirred for 1 h. The mixture was diluted with ether (50 mL), and the organic solution was washed with 1 N HCl (70 mL) and brine. Chromatography on a silica gel column gave vinyl glutarate **14** (1.2 g) as an oil: $[\alpha]^{20}_D$ = −6.6 (*c* 1, $CHCl_3$); 61% yield; ^{1}H NMR δ 1.2 (m, 6H), 2.1–2.5 (m, 4H), 4.09 (q, 2H), 4.18 (q, 2H), 5.18 (d, 1H, J = 18 Hz), 5.47 (d, 1H, J = 10 Hz), 6.32 (q, 1H, J = 10 and 18 Hz), 7.3 (m, 5H). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.56; H, 7.65.

(*R*)-Diethyl 2-Phenyl-2-ethylglutarate (15). Vinyl glutarate **14** (1 g, 3.4 mmol) was dissolved in ethanol (10 mL) and stirred in the presence of 5% Pd/C (0.1 g). The reaction mixture was filtered and concentrated under vacuum to give glutarate **15** (0.95 g, 95%) as an oil: $[\alpha]^{20}_D$ = −10.8 (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.8 (t, 3H), 1.2 (m, 6H), 2.05 (m, 4H), 2.32 (m, 2H), 4.1 (m, 4H), 7.28 (m, 5H).

(*R*)-2-Phenyl-2-ethylglutaric Acid (16). A mixture of glutarate **15** (1 g, 3.4 mmol), EtOH (5 mL), NaOH (0.3 g, 7.5 mmol), and H_2O (10 mL) was boiled to reflux for 4 h. The reaction mixture was concentrated in vacuum, acidified with concd HCl, and extracted with ethyl acetate to give the solid glutaric acid **16** (0.72 g) in 89% yield: mp 108–110 °C; $[\alpha]^{20}_D$ = −13.7 (*c* 1, $CHCl_3$); ^{1}H NMR δ 0.85 (t, 3H), 2–2.5 (m, 6H), 7.3 (s, 5H), 11.3 (m, 2H). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.11; H, 6.85.

(*R*)-2-Phenyl-2-ethylglutarimide (17). Glutaric acid **16** (10 g, 0.042 mol) was treated with 30% NH_3(8.2 mL, 0,12 mol) with vigorous stirring. The resulting solution was heated to 180–200 °C for 1 h. The residue was partitioned between a saturated $NaHCO_3$ solution and ethyl acetate. The solid residue was crystallized from 2-propanol to afford the glutarimide **17** (7.4 g, 81%): mp 95–96 °C; $[\alpha]^{20}_D$ = +181 (*c* 1, MeOH); ^{1}H NMR δ 0.85 (t, 3H), 1.8–2.7 (m, 6H), 7.3 (m, 5H), 9.75 (m, 1H). Anal. Calcd for $C_{13}H_{15}O_2N$: C, 71.87; H, 6.96. Found: C, 71.98; H, 6.96.

(*R*)-2-(4-Nitrophenyl)-2-ethylglutarimide (18). To a solution of compound **17** (2.17 g, 0.01 mol) in concd sulfuric acid (5 mL) at −10 °C was added dropwise a mixture of concd sulfuric (1.1 g) and 63% nitric acid (1.1 g). The resulting reaction mixture was allowed to warm to room temperature and then poored into ice and extracted with CH_2Cl_2. The oily residue was crystallized from a mixture of hexane/ethyl acetate to afford 2.2 g of the expected nitrated **18** glutarimide (2.2 g, 85%): mp 130–133 °C; $[\alpha]^{20}_D$ = +136.6 (*c* 1, MeOH); ^{1}H NMR δ 0.9 (t, 3H), 1.9–2.2 (m, 2H), 2.3–2.5 (m, 3H), 2.7 (m, 1H), 7.5 (d, 2H, J = 10 Hz), 8.24 (d, 2H, J = 10 Hz), 8.45 (b, 1H). Anal. Calcd for $C_{13}H_{14}O_4N_2$: C, 59.54; H, 5.38. Found: C, 59.61; H, 5.50.

(*R*)-2-(4-Aminophenyl)-2-ethylglutarimide (19). Nitroglutarimide **18** (2 g, 7.6 mmol) was mixed with 5% Pd/C (0.2 g) in 20 mL of EtOH under a H_2 atmosphere. The reaction mixture was filtered and concentrated under vacuum and the oily residue crystallized from methanol to give **19** as white needles: mp 111–113 °C (1.7 g, 94% yield); $[\alpha]^{20}_D$ = +162.9 (*c* 1, MeOH); ^{1}H NMR δ 0.86 (t, 3H), 1.8–2.6 (m, 6H), 3.7 (b, 2H), 6.67 (d, 2H, J = 10 Hz), 7.05 (d, 2H, J = 10 Hz), 7.9 (b, 1H). Anal. Calcd for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94. Found: C, 67.52; H, 6.95.

Supporting Information Available: ^{1}H NMR spectra (250 MHz) for compounds **2, 6, 7,** and **11–19** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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