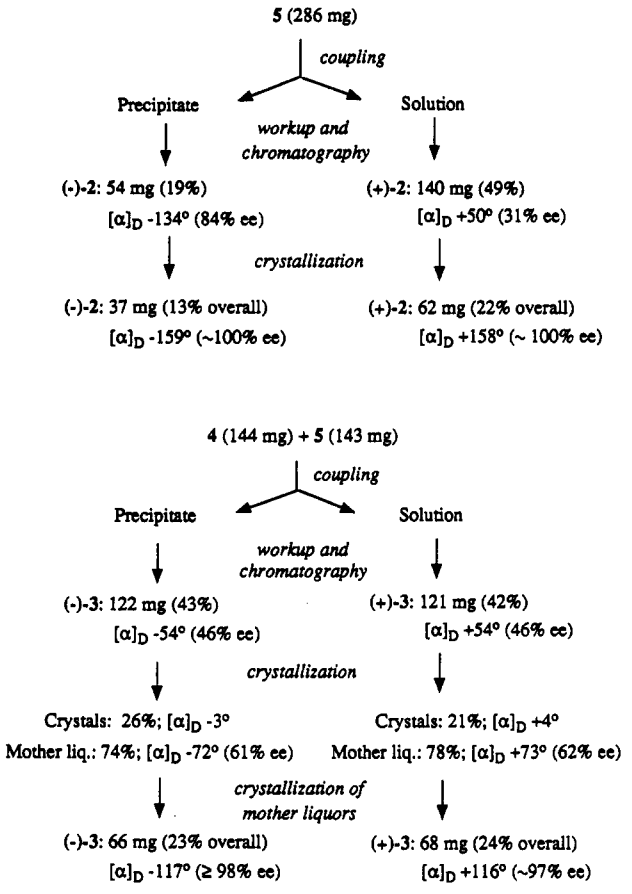
Scheme I. Optimized Procedures for Obtaining Pure Enantiomers of 2 and 3



at rt for 20 h under an argon atmosphere. Then concd HCl (5 mL) was added, followed by water (100 mL). The precipitate was filtered off, suspended in acetone with silica gel (20 g), and chromatographed on a silica gel column (40 g) using a light petroleum–ether mixture (1:1) as eluent. The eluate was evaporated to afford 1 (43 mg; 14%): mp 205–207 °C (no depression was observed for a mixture with an authentic sample of enantiomerically pure 1); $[\alpha]_D$ −34° (c 5.0, THF; 100% ee) (lit.[1i,j] mp 207–209 °C and $[\alpha]_D$ −35.5° or −33.4°, respectively, for optically pure compound and $[\alpha]_D$ +34.3° for the enantiomer.) Analogous workup of the solution furnished 1 (121 mg; 42%): mp 210–214 °C; $[\alpha]_D$ −6.8° (c 5.0, THF; 20% ee).

(B) By Deracemization of (±)-1. To a degassed solution of $CuCl_2 \cdot 4H_2O$ (200 mg; 1 mmol) in methanol (10 mL) was added a solution of (−)-sparteine (468; 2 mmol) in methanol (10 mL), and the mixture was stirred at rt for 10 min under argon. A solution of (±)-1 (286 mg; 1 mmol) in degassed methanol (10 mL) was added, and the mixture was stirred under argon at rt for 20 h. The mixture was then worked up as above to give 1 (267 mg; 94%): mp 212–214 °C; $[\alpha]_D$ −27.2° (c 5.0, THF; 80% ee). For further resolution, see the text.

(*R*)-(+)- and (*S*)-(−)-2,2′-Diamino-1,1′-binaphthyl (2). (A) By Coupling. A mixture of (−)-sparteine (702 mg; 3 mmol) and 2-naphthylamine (286 mg; 2 mmol) in degassed methanol (15 mL) was added to a solution of $CuCl_2 \cdot 4H_2O$ (400 mg; 2 mmol) in degassed methanol (15 mL), and the mixture was stirred under argon at rt for 4 h. The precipitate was filtered off, washed with methanol (5 mL), decomposed with concd HCl (3 mL), and then neutralized by concd aqueous ammonia (15 mL) and water (100 mL). The crude solid product (67 mg; 24%) was chromatographed as described for the first experiment to yield enriched (−)-2 (54 mg; 19%): mp 235–239 °C; $[\alpha]_D$ −134° (c 2.0, pyridine; 84% ee). On single crystallization from acetic acid, this crop gave enantiomerically pure (−)-2 (27 mg; 13% overall). The mother liquor from the reaction was worked up separately in the same way and furnished enriched (+)-2 (140 mg; 49%): mp 184–216 °C; $[\alpha]_D$ +50° (c 5.0, pyridine; 31% ee). Further resolution furnished enantiomerically pure (+)-2 (62 mg; 22% overall): mp 245–246 °C; $[\alpha]_D$ +158° (c 2.0, pyridine)[23] (lit.[3] mp 245–246 °C and $[\alpha]_D$ +159° for enantiomerically pure product).

(B) By Diastereoselective Crystallization of (±)-2. A hot solution of (±)-2 (284 mg; 1 mmol) in degassed methanol (30 mL; minimal amount) was added to a mixture of $CuCl_2 \cdot 4H_2O$ (200 mg; 1 mmol) and (−)-sparteine (234 mg; 1 mmol) in degassed methanol (5 mL), and the resulting mixture was stirred under argon at rt for 40 h and then worked up as described for the previous experiment. The precipitate and mother liquor were worked up separately, and the crude products were purified by chromatography as above. The precipitate afforded (−)-2 (51 mg; 18%): mp 231–239 °C; $[\alpha]_D$ −134° (c 2.0, pyridine; 84% ee). The mother liquor furnished (+)-2 (132 mg; 46%): mp 190–218 °C; $[\alpha]_D$ +72° (c 5.0, pyridine; 45% ee).

(*R*)-(+)- and (*S*)-(−)-2-Amino-2′-hydroxy-1,1′-binaphthyl (3). A solution of (*R*)-(+)-α-methylbenzylamine (1.21 g; 10 mmol) in degassed 2-propanol (10 mL) was added to a solution of $CuCl_2 \cdot 4H_2O$ (500 mg; 2.5 mmol) in degassed propanol (10 mL), the mixture was stirred for 10 min under argon, and then a solution of a mixture of 2-naphthylamine (143 mg; 1 mmol) and 2-naphthol (144 mg; 1 mmol) in degassed propanol (10 mL) was added. The mixture was stirred under argon at rt for 20 h. Both the precipitate and the mother liquor were worked up and chromatographed separately as above. The precipitate afforded (−)-3 (122 mg; 43%): mp 212–228 °C; $[\alpha]_D$ −54° (c 1.0, THF). The mother liquor yielded (+)-3 (121 mg; 42%); mp 212–230 °C; $[\alpha]_D$ +54° (c 1.0, THF). Further resolution by "kinetic" crystallization of the former product from benzene (see the text and Scheme I) afforded (−)-3 (66 mg; 23% overall): mp 171–173 °C; $[\alpha]_D$ −117° (ref 32); ^1H NMR 6.78 (1 H, *J* = 6.8, 1.4, 0.9, and 0.6 Hz), 6.96 (1 H, *J* = 6.8, 1.3, 1.1, and 0.5 Hz), 6.99 (1 H, *J* = 6.8, 6.8, and 1.7 Hz), 7.02 (1 H, *J* = 6.8, 6.8, and 1.4 Hz), 7.10 (1 H, *J* = 6.8, 6.8, and 1.4 Hz), 7.12 (1 H, *J* = 8.8 Hz), 7.17 (1 H, *J* = 8.0, 6.8, and 1.3 Hz), 7.26 (1 H, *J* = 8.8 Hz), 7.64 (1 H, *J* = 6.8, 1.7, 0.6, and 0.5 Hz), 7.65 (1 H, *J* = 8.8 and 0.5 Hz), 7.77 (1 H, *J* = 8.0, 1.4, 0.5, and 0.5 Hz), 7.81 (1 H, *J* = 8.8 and 0.5 Hz); ^{13}C NMR 110.71 (s), 115.87 (s), 119.33 (d), 119.45 (d), 122.20 (d), 123.79 (d), 124.43 (d), 125.34 (d), 126.93 (d), 127.13 (d), 128.80 (s), 128.80 (d), 128.97 (d), 130.06 (d), 130.18 (s), 130.46 (d), 134.80 (s), 135.55 (s), 145.55 (s) 154.04 (s); HRMS (EI 70 eV) *m/z* (relative intensity) 286 (27.5), 285 (100, $M^{\bullet+}$, $C_{20}H_{15}NO$), 284 (10.4), 268 (20, $C_{20}H_{13}N$), 267 (11.3, $C_{20}H_{12}O$), 256 (13), 239 (12.2), 143.5 (12.2), 142.5 (9.6 M^{2+}), 129.5 (15.6), metastable transitions $285^{\bullet+} \rightarrow 268^{\bullet+} + 17$, $285^{\bullet+} \rightarrow 267^{\bullet+} + 18$.

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Registry No. (*S*)-(−)-1, 18531-99-2; (*R*)-(+)-1, 18531-94-7; (*R*)-(+)-2, 18741-85-0; (*S*)-(−)-2, 18531-95-8; (*R*)-(+)-3, 137848-28-3; (*S*)-(−)-3, 137848-29-4; 4, 135-19-3; 5, 91-59-8; (−)-sparteine, 90-39-1; (*R*)-(+)-α-methylbenzylamine, 3886-69-9.

Supplementary Material Available: NMR spectra of the Mosher acid derivatives of (±)- and (−)-3 and IR spectra of (−)- and (±)-1, (−)- and (±)-2, and (−)- and (±)-3 (8 pages). Ordering information is given on any current masthead page.

Aldol Reactions of Pyroglutamates: Chiral Synthesis of 4α(*S*)- and 4β(*R*)-(Arylmethyl)pyroglutamates[1]

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Nonproteinogenic prolines are important because of their use in the synthesis of conformationally rigid

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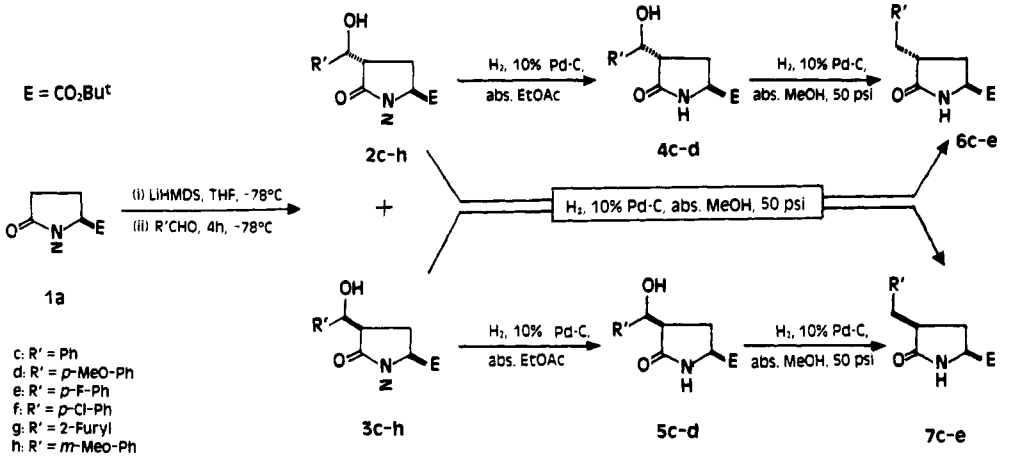
Scheme I



bioactive peptides,[2] angiotensin-converting enzyme inhibitors,[3] and as pharmacological probes.[4] For these reasons, chiral syntheses of prolines have received much attention in recent years. While good synthetic routes for the synthesis of 2,3,4β(*R*)- and 5-substituted prolines are available,[5] this is not the case with 4α(*S*)-substituted prolines.[6] Recently differentially protected glutamate γ-enolates have been alkylated and converted to 4-substituted prolines with a 3:1 predominance of the 4β-isomer.[5b] Chiral 4α-hydroxylation of a 2(*S*)-pyroglutamate-derived enolate has recently been described in the synthesis of (-)-bulgecinine.[7] As 4-substituted pyroglutamates can serve as precursors of the corresponding prolines,[5b,8] it was of interest to study the aldol behavior of pyroglutamate-derived enolates and subsequent transformations of the adducts. In the present paper we describe the chiral synthesis of 4α(*S*)- and 4β(*R*)-(arylmethyl)pyroglutamates and *tert*-butyl (2*S*)-4α-(phenylmethyl)prolinate.

Aldol condensation of the lithium enolate of **1a**, prepared by reacting the later with LiHMDS in anhyd THF at -78 °C, with benzaldehyde unexpectedly gave two isomeric compounds **2c** and **3c** in approximately a 3:1 ratio, which were separated by flash chromatography. Stereochemical assignments in **3c** were made on the basis of a positive NOE between H-3β and C*H*OH. No such NOE enhancements were observed in case of isomer **2c** which was at this stage presumed to be the α-isomer. These assignments were later confirmed by deprotection of **2c** and **3c** (H_2-10% Pd/C, absolute EtOAC, atmospheric pressure, 4 h) to yield **4c** and **5c**, respectively. ^{1}H NMR decoupling experiments on **4c** established 4α stereochemistry based on the observed coupling constant values ($J_{H_2-H_{3\alpha}}$ = 9 Hz, $J_{H_2-H_{3\beta}}$ = 3 Hz, $J_{H_4-H_{3\alpha}}$ = 8.6 Hz, $J_{H_4-H_{3\beta}}$ = 10.2 Hz). In the case of **5c**, however, the coupling constant values were not conclusive and NOE experiments were done. A weak positive NOE enhancement was observed between H-2 and H-4 and also between H-3β and C*H*OH, thus confirming the 4β assignments. In contrast, no such NOE was observed in the case of 4α-isomer **4c**. In a similar sequence of reactions **2d-h**, **3d-h**, **4d**, and **5d** were obtained. Lack of facial selectivity in aldol reactions of pyroglutamate-derived enolates as observed by us contrasts with their hydroxylations/alkylations, where exclusively 4α-products have been reported.[7,9] However, 4β-arylations of a pyroglutamate-derived enolate has been reported.[5b]

The 4-(hydroxyarylmethyl)pyroglutamates **4c-d** and **5c-d** were further hydrogenolyzed to 4α- and 4β-(arylmethyl)pyroglutamates **6c-d** and **7c-d**, respectively. Hydrogenolysis of **2c-e** and **3c-e** also yielded the corresponding 4-(arylmethyl)pyroglutamates **6c-e** and **7c-e** in one step.

While this work was in progress, the synthesis and X-ray data of *tert*-butyl *N*-Boc-4α-(phenylmethyl)pyroglutamate (**8b**) were reported.[10] The product obtained after the removal of the Boc group from **8b** with TFA in CH_2Cl_2 was presumed to be *tert*-butyl 4α-(phenylmethyl)pyroglutamate. The ^{1}H NMR data as reported for *tert*-butyl 4α-(phenylmethyl)pyroglutamate did not match with that of **6c** prepared by us. We observed H-3 and H-3′ both as close multiplets between δ 2.10 and 2.25, while the reported positions were δ 1.75-1.95 (H-3) and 2.35-2.85 (H-3′, H-4, and C*H*Ph). On the other hand, in the case of 4β-isomer **7c**, we have observed H-3 and H-3′ centered at δ 1.84 and 2.43, respectively. We also performed a COSY experiment which validated our assignments. To confirm further that our compound is indeed the 4α-isomer, we synthesized **8a** and **8b** by alkylation of *tert*-butyl *N*-Z-pyroglutamate (**1a**) and *tert*-butyl *N*-Boc-pyroglutamate (**1b**), respectively, with benzyl bromide according to the procedure described in the literature.[10] The ^{1}H NMR spectrum and other data for **8b** were found to agree closely with the reported values for this compound. Deprotection of both **8a** and **8b** gave the same product identical to **6c** (R_f, ^{1}H NMR, mp). All the samples of **6c** (prepared from **2c**, **4c**, **8a**, and **8b**) were reconverted to their *N*-Boc derivatives, which were found to be identical with **8b**, thus confirming that no epimeri-

(1) Communication No. 4714 from Central Drug Research Institute, Lucknow 226001, India.

(2) (a) Thaisrivongs, S.; Pals, D. T.; Turner, S. R.; Kroll, L. T. *J. Med. Chem.* **1988**, *31*, 1369. (b) Yu, K. L.; Rajakumar, G.; Srivastava, L. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1988**, *31*, 1430.

(3) (a) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; Deforrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwartz, J.; Natrajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31*, 1148. (b) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; Deforrest, J. M.; Dejeneka, T.; Lee, V. G.; Loots, M. J.; Petrillo, E. W. *J. Med. Chem.* **1990**, *33*, 1459.

(4) (a) McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic acid as a tool in Neurobiology*; Ravan Press: New York, 1978. (b) Deshong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979.

(5) (a) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229. (b) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859 and references cited therein.

(6) Thottahil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140.

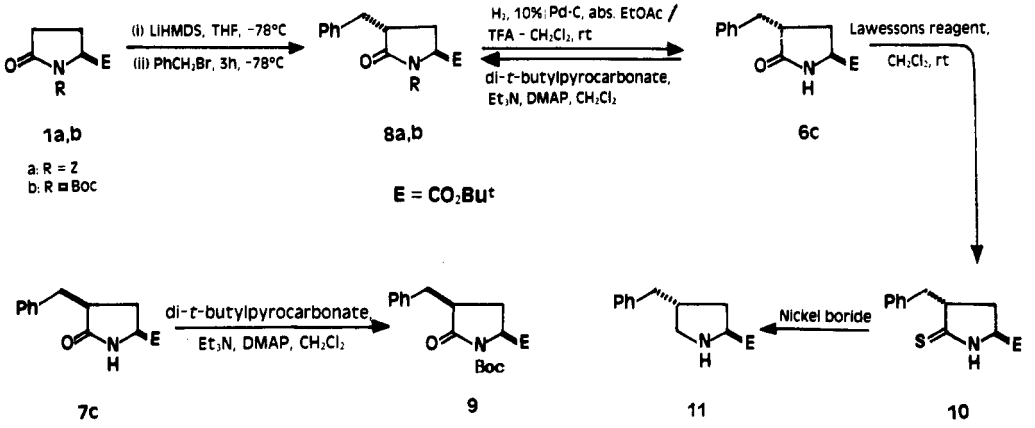
(7) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329.

(8) (a) Monteiro, H. J. *Synthesis* **1974**, 137. (b) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.

(9) Bowler, A. N.; Doyle, P. M.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett.* **1991**, *32*, 2679.

(10) Baldwin, J. E.; Miranda, T.; Moloney, M.; Hokelek, T. *Tetrahedron* **1989**, *45*, 7459.

Scheme II



zation occurred during the deprotection sequences. It is important to note that a similar conversion of **7c** to its *N*-Boc derivative gave **9**, whose data were markedly different from those of **8b**. We therefore conclude that the ^{1}H NMR assignments of **6c** as reported are in error.[11]

Lawesson's reagent was used to convert *tert*-butyl 4α-(phenylmethyl)pyroglutamate (**6c**) to its thioxo derivative **10**, which was reduced to *tert*-butyl (2*S*)-4α-(phenylmethyl)prolinate **11** using nickel boride.[12]

Experimental Section

Melting points are uncorrected. THF and Et_2O were distilled over sodium benzophenone ketyl. Anhydrous N_2 was used in an inert atmosphere reactions. Glassware was flame-dried in an inert atmosphere.

General Procedures: *tert*-Butyl (2*S*)-*N*-(Benzyloxycarbonyl)pyroglutamate (1a). Compound **1a** was prepared by reaction of isobutylene (200 mL) with *N*-(benzyloxycarbonyl)-pyroglutamic acid (10 g) dissolved in 200 mL of dry CH_2Cl_2 in the presence of 1 mL of concd H_2SO *in* a Parr SS vessel. Flash chromatographic purification (hexane–30% EtOAc) gave **1a** as a white solid (EtOAc–hexane) (8.1 g, 67%): mp 59–61 °C; $[\alpha]^{25}_D$ –45.7° (*c* 1.0, MeOH); IR (KBr) 1735, 1800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 [9 H, s, OC(CH_3)$_3$], 1.98–2.02 (1 H, m, H-3), 2.28–2.32 (1 H, m, H-3′), 2.55 (2 H, m, H-4 and H-4′), 4.52 (1 H, dd, *J* = 2.5, 10.5 Hz, H-2), 5.25 (2 H, s, CH_2Ph), 7.28 (5 H, m, Ar*H*); MS *m*/*z* 319 (M$^+$, 43) 263 (25), 91 (100).

Aldol Reaction of 1a. *n*-BuLi (1 equiv of a 2.5 M solution in hexane) was added to a solution of hexamethyldisilazane (1.2 equiv) in THF (25 mL) at –35 °C under a N_2 atmosphere. After 30 min the reaction mixture was cooled to –78 °C and a solution of **1a** (0.95 g, 3 mmol) in THF (50 mL) was added dropwise using a cannula. After the reaction mixture was stirred at –78 °C for 1.5 h, aryl aldehyde (3 mmol) in THF (10 mL) was added, and stirring was continued for an additional 4 h. The reaction mixture was quenched with saturated citric acid solution at –78 °C. THF was partly removed under reduced pressure without heating, water was added, and the mixture was extracted with Et_2O. The combined organic phases were washed with dilute $NaHCO_3$ and H_2O, dried (Na_2SO_4), and concentrated. The products were separated by flash chromatography using 30% EtOAc–hexane as eluent.

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4α-(hydroxyphenylmethyl)pyroglutamate (2c):** white solid (EtOAc–hexane) (565 mg, 45%); mp 115–117 °C; $[\alpha]^{25}_D$ –17.24° (*c* 0.6, MeOH); IR (KBr) 1758, 1800, 3500, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 [9 H, s, OC(CH_3)$_3$], 1.65–1.72 (1 H, m, H-3), 2.45–2.72 (1 H, m, H-3′), 3.03 (1 H, m, H-4), 4.49 (1 H, m, H-2), 5.26 (2 H, s, PhCH_2O), 5.43 (1 H, d, *J* = 3.5 Hz, C*H*OH), 7.32 (10 H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.7, 49.7, 57.7, 68.2, 70.3, 82.4, 125.4, 127.5, 128.1, 128.3, 128.5, 134.9, 141.5, 150.7, 170.2, 173.6; MS *m*/*z* 425 (M$^+$, 22), 368 (45), 318 (51), 263 (62), 91 (100). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.76; H, 6.35; N, 3.3. Found: C, 68.14; H, 6.32; N, 3.25.

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4α-(hydroxy(*p*-methoxyphenyl)methyl)pyroglutamate (2d):** white solid (EtOAc–hexane) (600 mg, 44%); mp 125–126 °C; $[\alpha]^{25}_D$ –11.16° (*c* 1.0, MeOH); IR (KBr) 1756, 1799, 3550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 [9 H, s, OC(CH_3)$_3$], 1.63 (1 H, m, H-3), 2.36 (1 H, m, H-3′), 2.79 (1 H, m, H-4), 3.73 (3 H, s, OCH_3), 4.09 (1 H, s, OH), 4.41 (1 H, m, H-2), 5.18 (2 H, s, PhCH_2O), 5.28 (1 H, d, *J* = 3.5 Hz, C*H*OH), 6.78 (2 H, m, *p*-MeOAr*H*), 7.28 (7 H, m, Ar*H* + *p*-MeOAr*H*); ^{13}C NMR ($CDCl_3$) δ 21.6, 27.7, 49.7, 55.2, 57.7, 68.2, 70.0, 82.4, 113.8, 126.6, 128.1, 128.3, 128.5, 133.5, 134.9, 150.7, 158.9, 170.3, 173.7; MS *m*/*z* 455 (M$^+$, 18), 318 (59), 91 (100). Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.41; N, 3.07. Found: C, 66.30; H, 6.70; N, 2.95.

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4α-(hydroxy(*p*-fluorophenyl)methyl)pyroglutamate (2e):** white solid (EtOAc–hexane) (558 mg, 42%); mp 102–106 °C; $[\alpha]^{25}_D$ –7.58° (*c* 0.35, MeOH); IR (KBr) 1750, 1795, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 [9 H, s, OC(CH_3)$_3$], 2.04 (1 H, m, H-3), 2.47 (1 H, m, H-3′), 2.97 (1 H, m, H-4), 4.43 (1 H, m, H-2), 5.20 (2 H, s, PhCH_2O), 5.35 (1 H, d, *J* = 3.4 Hz, C*H*OH), 7.03 (2 H, m, *p*-FAr*H*), 7.25 (7 H, m, Ar*H* + *p*-FAr*H*); MS *m*/*z* 443 (M$^+$, 20), 386 (42), 318 (50), 263 (51), 91 (100). Anal. Calcd for $C_{24}H_{26}NO_6F$: C, 65.0; H, 5.91; N, 3.16. Found: C, 65.08; H, 6.19; N, 3.06.

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4α-(hydroxy(*p*-chlorophenyl)methyl)pyroglutamate (2f):** white solid (EtOAc–hexane) (575 mg, 42%); mp 119–125 °C; $[\alpha]^{25}_D$ –5.68° (*c* 0.45, MeOH); IR (KBr) 1752, 1800, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 [9 H, s, OC(CH_3)$_3$], 1.61–1.75 (1 H, m, H-3), 2.36 (1 H, m, H-3′), 2.86 (1 H, m, H-4) 4.46 (1 H, m, H-2), 5.24 (2 H, s, PhCH_2O), 5.38 (1 H, d, *J* = 3.4 Hz, C*H*OH), 7.28 (7 H, m, *p*-ClAr*H* + Ar*H*), 7.67 (2 H, m, *p*-ClAr*H*); MS *m*/*z* 459 (M$^+$, 38), 402 (12), 318 (41), 263 (25), 91 (100). Anal. Calcd for $C_{24}H_{26}NO_6Cl$: C, 62.75; H, 5.66; N, 3.05. Found: C, 63.04; H, 6.05; N, 2.95.

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4α-(hydroxy-2-furylmethyl)pyroglutamate (2g):** colorless oil (471 mg, 38%); $[\alpha]^{25}_D$ –2.94° (*c*, 2.0, $CHCl_3$); IR (neat) 1740, 1800, 3540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 [9 H, s, OC(CH_3)$_3$], 1.84–2.50 (2 H, m, H-3 and H-3′), 3.09 (1 H, m, H-4), 4.50 (1 H, m, H-2), 5.19 (2 H, s, PhCH_2O), 5.26 (1 H, d, *J* = 3.5 Hz, C*H*OH), 6.25 (2 H, m, furyl-*H*), 7.25 (6 H, m, Ar*H* + furyl); MS *m*/*z* 415 (M$^+$, 20), 319 (42), 224 (70), 91 (100).

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4α-(hydroxy(*m*-methoxyphenyl)methyl)pyroglutamate (2h):** oil (560 mg, 41%); IR (neat) 1745, 1800, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 [9 H, s, OC(CH_3)$_3$], 1.74–2.12 (2 H, m, H-3 and H-3′), 3.03 (1 H, m, H-4), 3.79 (3 H, s, OMe), 4.50 (1 H, m, H-2), 5.32 (2 H, s, PhCH_2O), 5.45 (1 H, d, *J* = 3.5 Hz, C*H*OH), 6.95 (2 H, m, *m*-MeOAr*H*), 7.20–7.40 (7 H, m, Ar*H* + *m*-MeOAr*H*); MS *m*/*z* 455 (M$^+$, 4), 398 (15), 318 (21), 91 (100).

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4β-(hydroxyphenylmethyl)pyroglutamate (3c):** white solid (EtOAc–hexane) (242 mg, 19%); mp 97–101 °C; $[\alpha]^{25}_D$ +1.55° (*c* 0.95, MeOH); IR (KBr) 1775, 1800, 3550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 [9 H, s, OC(CH_3)], 1.78 (1 H, m, H-3), 2.08 (1 H, m, H-3′), 2.82 (1 H, m, H-4), 4.27 (1 H, dd, *J* = 7, 9 Hz, H-2), 4.75 (1 H, d, *J* = 9.5

(11) In a personal communication Dr. Moloney has acknowledged the inadvertant inclusion of the wrong set of ^{1}H NMR data for **6c**.

(12) Guziec, F. S., Jr.; Wasmund, L. M. *Tetrahedron Lett.* **1990**, *31*, 23.

Hz, CHOH), 5.0 (1 H, s, OH), 5.19 (2 H, s, PhCH$_2$O), 7.25 (10 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 24.7, 27.6, 48.7, 57.7, 68.5, 74.9, 82.6, 126.8, 128.1, 128.3, 128.5, 128.6, 134.6, 140.0, 150.5, 169.7, 175.2; MS m/z 425 (M^+, 15), 319 (44), 219 (57), 91 (100). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.76; H, 6.35; N, 3.3. Found: C, 68.11; H, 6.49; N, 3.21.

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4β-(hydroxy(*p*-methoxyphenyl)methyl)pyroglutamate (3d)**: oil (245 mg, 18%); $[\alpha]^{25}_D$ + 2.86° (*c* 1.0, $CHCl_3$); IR (neat) 1745, 1800, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 [9 H, s, OC(CH$_3$)$_3$], 1.90 (1 H, m, H-3), 2.18 (1 H, m, H-3′), 2.90 (1 H, m, H-4), 3.79 (3 H, s, OCH$_3$), 4.36 (1 H, dd, *J* = 7, 9 Hz, H-2), 4.76 (1 H, d, *J* = 9.5 Hz, CHOH), 5.28 (2 H, s, PhCH$_2$O), 6.84 (2 H, m, *p*-MeOArH), 7.35 (7 H, m, *p*-MeOArH + ArH); ^{13}C NMR ($CDCl_3$) δ 24.5, 27.5, 48.6, 54.9, 57.5, 68.3, 74.2, 82.3, 113.8, 127.9, 128.3, 132.1, 134.5, 150.4, 159.4, 169.6, 175.1; MS m/z 455 (M^+, 32), 319 (57), 219 (45), 174 (43), 91 (100).

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4β-(hydroxy(*p*-fluorophenyl)methyl)pyroglutamate (3e)**: oil (212 mg, 16%); $[\alpha]^{25}_D$ +3.77° (*c* 0.55, $CHCl_3$); IR (neat) 1750, 1805, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 [9 H, s, OC(CH$_3$)$_3$], 1.50 (1 H, m, H-3), 2.12 (1 H, m, H-3′), 2.89 (1 H, m, H-4), 4.36 (1 H, dd, *J* = 7, 9 Hz, H-2), 4.85 (1 H, d, *J* = 9.4 Hz, CHOH), 5.29 (2 H, s, PhCH$_2$O), 7.05 (2 H, m, *p*-FArH), 7.38 (7 H, m, *p*-FArH + ArH); ^{13}C NMR ($CDCl_3$) δ 24.8, 27.7, 48.8, 57.8, 68.7, 74.3, 82.8, 115.5, 115.9, 128.3, 128.6, 135.9, 150.6, 163.9, 169.7, 175.1; MS m/z 443 (M^+, 5), 319 (20), 263 (51), 91 (100).

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4β-(hydroxy(*p*-chlorophenyl)methyl)pyroglutamate (3f)**: oil (205 mg, 15%); $[\alpha]^{25}_D$ +1.39° (*c* 1.4, $CHCl_3$); IR (neat) 1750, 1805, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 [9 H, s, OC(CH$_3$)$_3$], 1.60 (1 H, m, H-3) 2.05 (1 H, m, H-3′), 2.78 (1 H, m, H-4), 4.28 (1 H, dd, *J* = 7, 9 Hz, H-2), 4.75 (1 H, d, *J* = 9.5 Hz, CHOH), 5.19 (2 H, s, PhCH$_2$O), 6.86 (2 H, m, *p*-ClArH), 7.24 (5 H, m, ArH), 7.57 (2 H, m, *p*-ClArH); ^{13}C NMR ($CDCl_3$) δ 24.7, 27.7, 48.8, 57.7, 68.7, 74.3, 82.8, 128.2, 128.5, 128.8, 134.2, 134.6, 138.6, 150.5, 169.7, 174.9; MS m/z 459 (M^+, 15), 319 (35), 263 (55), 91 (100).

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4β-(hydroxy-2-furylmethyl)pyroglutamate (3g)**: oil (200 mg, 16%); $[\alpha]^{25}_D$ +1.4° (*c* 2.1, $CHCl_3$); IR (neat) 1740, 1795, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 [9 H, s, OC(CH$_3$)$_3$], 1.73 (1 H, m, H-3), 2.24 (1 H, m, H-3′), 3.08 (1 H, m, H-4), 3.55 (1 H, s, OH), 4.36 (1 H, dd, *J* = 7, 9 Hz, H-2), 4.84 (1 H, d, *J* = 9.5 Hz, CHOH), 5.20 (2 H, s, PhCH$_2$O), 6.25 (2 H, m, furyl), 7.26 (6 H, m, ArH + furyl); MS m/z 415 (M^+, 32), 319 (59), 218 (52), 91 (100).

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4β-(hydroxy(*m*-methoxyphenyl)methyl)pyroglutamate (3h)**: oil (230 mg, 17%); IR (neat) 1750, 1805, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 [9 H, s, OC(CH$_3$)$_3$], 1.84 (1 H, m, H-3), 2.09 (1 H, m, H-3′), 2.89 (1 H, m, H-4), 3.73 (3 H, s, OCH$_3$), 4.35 (1 H, dd, *J* = 7, 9 Hz, H-2), 4.76 (1 H, d, *J* = 9.5 Hz, CHOH), 5.08 (1 H, s, OH), 5.27 (2 H, s, PhCH$_2$), 6.87 (2 H, m, *m*-MeOArH), 7.30 (7 H, m, *m*-MeOArH + ArH); MS m/z 455 (M^+, 11), 319 (22), 263 (37), 91 (100).

Removal of Benzyloxycarbonyl Groups from 2c–d and 3c–d. H_2 gas was bubbled through a solution of **2** or **3** (**c**–**e**) (0.5 mmol) in dry EtOAc (50 mL) in the presence of 10% Pd–C (0.5 g) for 4 h. Filtration of the catalyst and concentration of the filtrate, followed by flash chromatographic separation (40% EtOAc–hexane), gave **4c–d** or **5c–d**.

***tert*-Butyl (2*S*)-4α-(hydroxyphenylmethyl)pyroglutamate (4c)**: white solid (EtOAc–hexane) (105 mg, 73%); mp 110–111 °C; $[\alpha]^{25}_D$ −1.95° (*c* 0.75, MeOH); IR (KBr) 1690, 1730, 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 [9 H, s, OC(CH$_3$)$_3$], 1.95 (1 H, ddd, *J* = 14, 10.2, 3 Hz, H-3β), 2.53 (1 H, ddd, *J* = 14, 8.6, 9 Hz, H-3α), 2.88 (1 H, ddd, *J* = 10.2, 8.6, 3 Hz, H-4), 3.15 (1 H, d, *J* = 5.5 Hz, OH), 4.02 (1 H, dd, *J* = 3.0, 9.0 Hz, H-2), 5.35 (1 H, dd, *J* = 3.0, 5.5 Hz, CHOH), 6.6 (1 H, s, NH), 7.34 (5 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 24.2, 27.7, 48.4, 55.0, 70.3, 81.9, 125.4, 126.8, 128.1, 142.4, 171.8, 178.7; MS m/z 291 (M^+, 29), 235 (54), 190 (59), 185 (44) 105 (100). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.80. Found: C, 65.90; H, 7.2; N, 4.45.

***tert*-Butyl (2*S*)-4α-(hydroxy(*p*-methoxyphenyl)-methyl)pyroglutamate (4d)**: white solid (EtOAc–hexane) (110 mg, 68%); mp 168–169 °C; $[\alpha]^{25}_D$ −4.16° (*c* 0.6, MeOH); IR (KBr) 1710, 1740, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 [9 H, s, OC(CH$_3$)$_3$], 1.95 (1 H, m, H-3), 2.45 (1 H, m, H-3′), 2.80 (1 H, m, H-4), 3.76 (3 H, s, OCH$_3$), 3.99 (1 H, dd, *J* = 3.5, 9.5 Hz, H-2), 5.25 (1 H, d, *J* = 3.5 Hz, CHOH), 6.50 (1 H, s, NH), 6.84 (2 H, m, *p*-MeOArH), 7.26 (2 H, m, *p*-MeOArH); ^{13}C NMR ($CDCl_3$) δ 24.7, 27.9, 47.8, 54.8, 55.2, 70.8, 82.3, 113.8, 126.8, 134.1, 158.8, 171.5, 178.3; MS m/z 321 (M^+, 35), 264 (48), 220 (44), 185 (51), 129 (100). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.85; H, 7.26; N, 4.02.

***tert*-Butyl (2*S*)-4β-(hydroxyphenylmethyl)pyroglutamate (5c)**: oil (102 mg, 71%); $[\alpha]^{25}_D$ +21.34° (*c* 1.65, $CHCl_3$); IR (neat) 1695, 1720, 3250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 [9 H, s, OC(CH$_3$)$_3$], 1.88 (1 H, m, H-3), 2.1 (1 H, m, H-3′), 2.65 (1 H, m, H-4), 3.90 (1 H, t, *J* = 7.5 Hz, H-2), 4.62 (1 H, d, *J* = 9.5 Hz, CHOH), 5.20 (1 H, s, OH), 6.29 (1 H, s, NH), 7.20 (5 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 27.8, 28.3, 47.1, 54.3, 75.7, 82.6, 126.7, 128.1, 128.4, 140.8, 170.1, 179.1; MS m/z 291 (M^+, 25) 275 (40), 234 (45), 185 (51), 105 (100).

***tert*-Butyl (2*S*)-4β-(hydroxy(*p*-methoxyphenyl)-methyl)pyroglutamate (5d)**: oil (125 mg, 77%); $[\alpha]^{25}_D$ +2.78° (*c* 0.72, $CHCl_3$); IR (neat) 1710, 1740, 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 [9 H, s, OC(CH$_3$)$_3$], 1.75 (1 H, m, H-3), 2.04 (1 H, m, H-3′), 2.71 (1 H, m, H-4), 3.76 (3 H, s, OCH$_3$), 3.98 (1 H, t, *J* = 8 Hz, H-2), 4.62 (1 H, d, *J* = 9.5 Hz, CHOH), 5.25 (1 H, s, OH), 6.66 (1 H, s, NH), 6.82 (2 H, m, *p*-MeOArH), 7.24 (2 H, m, *p*-MeOArH); ^{13}C NMR ($CDCl_3$) δ 27.9, 28.6, 47.2, 54.3, 55.2, 75.4, 82.8, 113.9, 128.0, 129.7, 133.0, 159.5, 170.1, 179.0; MS m/z 321 (M^+, 34), 264 (50), 220 (69), 185 (64).

Preparation of *tert*-Butyl (2*S*)-4-(Arylmethyl)pyroglutamates 6c–e and 7c–e from 2c–e and 3c–e. Compounds **2**/**3**(**c**–**e**) (0.5 mmol) were hydrogenated in absolute MeOH (50 mL) at 50–60 psi in the presence of 10% Pd–C (0.5 g) for 6 h. The usual workup followed by chromatographic purification (40% EtOAc–hexane) gave *tert*-butyl (2*S*)-4-(arylmethyl)pyroglutamates **6** or **7** (**c**–**e**).

***tert*-Butyl (2*S*)-4α-(phenylmethyl)pyroglutamate (6c)**: white solid (EtOAc–hexane) (95 mg, 69.2%); mp 107–109 °C; $[\alpha]^{25}_D$ −4.26° (*c* 0.95, MeOH); IR (KBr) 1725, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 [9 H, s, OC(CH$_3$)$_3$], 2.10–2.25 (2 H, m, H-3 and H-3′), 2.61–2.86 (2 H, m, H-4 + PhCH), 3.19 (1 H, dd, *J* = 5, 12.5 Hz, PhCH′), 3.88 (1 H, dd, *J* = 5.2, 8.5 Hz, H-2), 5.95 (1 H, s, NH), 7.25 (5 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 27.8, 30.3, 36.5, 41.5, 54.3, 82.0, 126.3, 128.4, 128.9, 138.8, 171.2, 179.2; MS m/z 275 (M^+, 10), 174 (75), 91 (100). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79, H, 7.64; N, 5.08. Found: C, 70.11; H, 7.94; N, 4.95.

***tert*-Butyl (2*S*)-4α-((*p*-methoxyphenyl)methyl)pyroglutamate (6d)**: white solid (EtOAc–hexane) (90 mg, 58.5%); mp 129–130 °C; $[\alpha]^{25}_D$ −3.26° (*c* 0.92, MeOH); IR (KBr) 1720, 1745, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 [9 H, s, OC(CH$_3$)$_3$], 2.11–2.26 (2 H, m, H-3 and H-3′), 2.63–2.78 (2 H, m, H-4 + *p*-MeOPhCH), 3.09 (1 H, m, *p*-MeOPhCH′), 3.79 (3 H, s, OCH$_3$), 3.81–3.87 (1 H, m, H-2), 5.88 (1 H, s, NH), 6.81–6.90 (2 H, m, *p*-MeOArH), 7.15 (2 H, m, *p*-MeOArH): ^{13}C NMR ($CDCl_3$) δ 27.9, 30.2, 35.6, 41.6, 54.2, 55.2, 82.3, 113.9, 130.0, 130.7, 158.3, 171.2, 178.9; MS m/z 305 (M^+, 9). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.88; H, 7.59; N, 4.59. Found: c, 66.75; H, 7.36; N, 4.88.

***tert*-Butyl (2*S*)-4α-((*p*-fluorophenyl)methyl)pyroglutamate (6e)**: white solid (EtOAc–hexane) (90 mg, 62%); mp 109–110 °C; $[\alpha]^{25}_D$ −2.26° (*c* 1.6, MeOH); IR (KBr) 1710, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 [9 H, s, OC(CH$_3$)$_3$], 1.85–2.20 (2 H, m, H-3 and H-3′), 2.55–2.95 (2 H, m, H-4) + *p*-FPhCH), 3.07 (1 H, m, *p*-FPhCH′), 3.79 (1 H, m, H-2), 5.75 (1 H, s, NH), 6.97 (2 H, m, *p*-FArH), 7.18 (2 H, m, *p*-FArH); MS m/z 293 (M^+, 24), 236 (51), 192 (100), 185 (44). Anal. Calcd for $C_{16}H_{20}NO_3F$: C, 65.53; H, 6.87; N, 4.78. Found: C, 65.70; H, 6.65; N, 4.55.

***tert*-Butyl (2*S*)-4β-(phenylmethyl)pyroglutamate (7c)**: white solid (EtOAc–hexane) (94 mg, 69%); mp 135–136 °C; $[\alpha]^{25}_D$ +10.71° (*c* 0.30, MeOH); IR (KBr) 1680, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 [9 H, s, OC(CH$_3$)$_3$], 1.84 (1 H, m, H-3), 2.43 (1 H, m, H-3′), 2.54–2.78 (2 H, m, H-4 + PhCH), 3.33 (1 H, dd, *J* = 3.9, 11.8 Hz, PhCH′), 4.05 (1 H, t, *J* = 7.8 Hz, H-2), 6.07 (1 H, s, NH), 7.25 (5 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 27.9, 30.8, 36.7, 43.1, 54.3, 82.3, 126.3, 128.5, 128.8, 139.2, 170.8; MS m/z 275 (M^+, 34), 219 (52), 175 (43), 174 (22), 91 (100). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.64; N, 5.08. Found: C, 69.71; H, 7.70; N, 4.91.

***tert*-Butyl (2*S*)-4β-((*p*-methoxyphenyl)methyl)pyroglutamate (7d)**: white solid (EtOAc–hexane) (92 mg, 60%); mp 118–120 °C; $[\alpha]^{25}_D$ +3.61° (*c* 0.83, MeOH); IR (KBr) 1720, 1745

cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 [9 H, s, OC(CH_3)$_3$] 1.75 (1 H, m, H-3), 2.20–2.30 (1 H, m, H-3′), 2.50–2.75 (2 H, m, H-4 and *p*-MeOPhC*H*), 3.18 (1 H, m, *p*-MeOPhC*H*′), 3.75 (3 H, s, OCH_3), 3.98 (1 H, t, J = 7.7 Hz, H-2), 5.88 (1 H, s, NH), 6.76 (2 H, m, *p*-MeOAr*H*), 7.15 (2 H, m, *p*-MeOAr*H*); MS m/z 305 (M$^+$, 31), 249 (49), 248 (22), 205 (100). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.89; H, 7.59; N, 4.59. Found: C, 66.98; H, 7.32; N, 4.45.

***tert*-Butyl (2*S*)-4β-((*p*-fluorophenyl)methyl)pyroglutamate (7e)**: white solid (EtOAc–hexane) (95 mg, 65%); mp 105–106 °C; $[\alpha]^{25}_D$ +31.8° (c 0.66, MeOH); IR (KBr) 1720, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 [9 H, s, OC(CH_3)$_3$], 1.70–1.80 (1 H, m, H-3), 2.32–2.40 (1 H, m, H-3′), 2.50–2.68 (2 H, m, H-4 and *p*-FPhC*H*), 3.15 (1 H, dd, J = 3.9, 11.8 Hz, *p*-FPhC*H*′), 4.02 (1 H, t, J = 7.6 Hz, H-2), 6.05 (1 H, s, N*H*), 7.02 (2 H, m, *p*-FAr*H*), 7.13 (2 H, m, *p*-FAr*H*); MS m/z 293 (M$^+$, 20), 238 (9), 192 (100). Anal. Calcd for $C_{16}H_{20}NO_3F$: C, 65.53; H, 6.87; N, 4.78. Found: C, 65.84; H, 6.62; N, 4.59.

Alkylation of 1a or 1b with Benzyl Bromide. Compounds **1a** (0.95 g, 3 mmol) and **1b** (285 mg, 1 mmol) were benzylated with benzyl bromide according to the procedure described in the literature[10] to give **8a** and **8b**, respectively.

***tert*-Butyl (2*S*)-1-(benzyloxycarbonyl)-4α-(phenylmethyl)pyroglutamate (8a)**: white solid (EtOAc–hexane) (430 mg, 35%); mp 112–114 °C; $[\alpha]^{25}_D$ −59.2° (c 1.75, $CHCl_3$); IR (KBr) 1740, 1792 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 [9 H, s, OC(CH_3)$_3$], 1.95–2.10 (2 H, m, H-3 and H-3′), 2.55–3.05 (2 H, m, H-4 and PhC*H*), 3.25 (1 H, dd, J = 2.5, 12 Hz, PhC*H*′), 4.35 (1 H, dd, J = 4.5, 6.5 Hz, H-2), 5.25 (2 H, s, PhCH_2O), 7.30 (10 H, m, Ar*H*); MS m/z 410 (M + 1, 20), 409 (M$^+$, 35), 353 (30), 319 (11), 275 (35), 265 (20), 264 (15); 91 (100). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.41; H, 6.6; N, 3.42. Found: C, 70.82; H, 6.92; N, 3.1.

***tert*-Butyl (2*S*)-1-(*tert*-butyloxycarbonyl)-4α-(phenylmethyl)pyroglutamate (8b)**: white crystalline solid (150 mg, 40%); mp 129–131 °C; $[\alpha]^{25}_D$ −34.09° (c 0.44, MeOH); IR (KBr) 1742, 1800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 [9 H, s, OC(CH_3)$_3$], 1.49 [9 H, s, C(CH_3)$_3$], 1.83–2.05 (2 H, m, H-3 and H-3′), 2.5–2.95 (2 H, m, H-4 and PhC*H*), 3.25 (1 H, dd, J = 2.5, 12 Hz, PhC*H*′), 4.30 (1 H, dd, J = 5, 6.6 Hz, H-2), 7.23 (5 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 27.9, 36.3, 43.3, 57.7, 82.2, 83.2, 126.5, 128.6, 128.9, 138.3, 149.4, 170.2, 174.3; MS m/z 375 (M$^+$, 5). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.2; H, 7.73; N, 3.73. Found: C, 67.05; H, 8.15; N, 3.68.

Removal of the Benzyloxycarbonyl Group from 8a. Removal of the benzyloxycarbonyl group from **8a** (0.4 g, 1 mmol) using a similar procedure as described for **4** or **5** gave **6c** (200 mg, 75%).

Removal of the *tert*-Butyloxycarbonyl Group from 8b. **8b** (0.23 g, 0.6 mmol) was deprotected with TFA–CH_2Cl_2 according to the literature procedure[10] to give **6c** (95 mg, 56%), identical in all respects to the product obtained by the aldol pathway.

Conversion of 6c and 7c to 8b and 9. To a solution of **6c** or **7c** (0.14 g, 0.5 mmol) in dry CH_2Cl_2 were added Et_3N (0.07 mL, 0.5 mmol), di-*tert*-butyl dicarbonate (0.22 g, 1 mmol), and DMAP (0.06 g, 0.5 mmol). The solution was stirred for 6–8 h at 25 °C under a N_2 atmosphere. The volatiles were removed, and the residue was chromatographed on a column of Florisil (30% EtOAc–hexane) to give **8b** and **9**, respectively.

***tert*-Butyl (2*S*)-1-(*tert*-butyloxycarbonyl)-4β-(phenylmethyl)pyroglutamate (9)**: white solid (EtOAc–hexane) (140 mg, 73%); mp 115–116 °C; $[\alpha]^{25}_D$ +3.57° (c 0.56, MeOH); IR (KBr) 1745, 1800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 [9 H, s, OC (CH_3)$_3$], 1.50 [9 H, s, C(CH_3)$_3$], 1.72 (1 H, m, H-3), 2.25 (1 H, m, H-3′), 2.46–2.75 (2 H, m, H-4 + PhC*H*), 3.28 (1 H, d, J = 12.4 Hz, Ph-C*H*′), 4.33 (1 H, dd, J = 5.9, 8.8 Hz, H-2), 7.18 (5 H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.9, 36.9, 44.5, 58.1, 82.2, 83.4, 126.6, 128.7, 128.9, 138.6, 149.5, 170.6, 174.6; MS m/z 375 (M$^+$, 4), 320 (43), 319 (65), 263 (15), 246 (22), 219 (40), 174 (35), 91 (100). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.20; H, 7.73; N, 3.73. Found: C, 66.95; H, 7.95; N, 3.45.

***tert*-Butyl (2*S*)-4α-(Phenylmethyl)-5-thioxoprolinate (10).** To a solution of **6c** (275 mg, 1 mmol) in dry THF was added Laweson's reagent (202 mg, 0.5 mmol). The solution was stirred for 4 h at 25 °C. The volatiles were removed, Et_2O (25 mL) was added, and the mixture was poured into cold saturated sodium bicarbonate solution. The Et_2O layer was separated, and the aqueous layer was extracted twice with Et_2O. The Et_2O extract was washed with water, dried over Na_2SO_4, concentrated, and chromatographed by flash chromatography using 20% EtOAc–hexane as eluent to afford compound **10** as a white crystalline solid (recrystallized from EtOAc–hexane) (195 mg, 67%); mp 88–91 °C; IR (KBr) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 [9 H, s, OC(CH_3)$_3$], 2.15 (2 H, m, H-3 and H-3′), 2.65 (1 H, m, PhC*H*), 2.95–3.18 (1 H, m, H-4), 3.35 (1 H, dd, J = 2.5, 12 Hz, PhC*H*′), 3.96 (1 H, dd, J = 5, 9 Hz, H-2), 6.43 (1 H, s, N*H*), 7.14 (5 H, m, Ar*H*); MS m/z 293 (M + 2, 5), 292 (M + 1, 20), 291 (M$^+$, 35), 237 (2), 236 (6), 235 (32), 234 (48), 202 (12), 91 (100). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.98; H, 7.21; N, 4.8. Found: C, 66.32; H, 7.17; N, 4.52.

***tert*-Butyl (2*S*)-4α-(Phenylmethyl)prolinate (11).** Sodium borohydride (912 mg, 24 mmol) was added in portions to a solution of **10** (290 mg, 1 mmol) and $NiCl_2$·$6H_2O$ (2.2 g, 8 mmol) in 50 mL of THF–MeOH (1:1) at 0 °C. The reaction mixture was stirred at room temperature until the starting material had disappeared as monitored by TLC; the reaction mixture was filtered through Celite, concentrated, and chromatographed on a column of alumina to afford **11** (130 mg, 50%); IR (neat) 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 [9 H, s, OC(CH_3)$_3$], 1.85 (1 H, ddd, J = 10, 9, 13 Hz, H-3α), 1.95 (1 H, ddd, J = 8, 5, 13 Hz, H-3β), 2.32 (2 H, m, H-4 and PhC*H*), 2.58 (1 H, dd, J = 8, 11 Hz, H-5α), 2.66 (1 H, dd, J = 2.5, 7 Hz, PhC*H*′), 3.16 (1 H, dd, J = 7, 11 Hz, H-5β), 3.72 (1 H, dd, J = 5.0, 9.0 Hz, H-2), 6.64 (1 H, s, NH), 7.12–7.30 (5 H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 27.8, 36.4, 39.4, 40.4, 52.5, 60.0, 80.9, 125.8, 128.2, 128.5, 140.7, 174.4; MS m/z 262 (M + 1, 44), 206 (9), 205 (4), 161 (35), 160 (95), 91 (90), 57 (100).

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Supplementary Material Available: ^{1}H NMR and in some cases ^{13}C NMR spectra for compounds for which elemental analyses were not obtained (19 pages). Ordering information is given on any current masthead page.

Efficient Preparative Separation of C_{60} and C_{70}. Gel Permeation Chromatography of Fullerenes Using 100% Toluene as Mobile Phase

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The scientific community is becoming increasingly interested in the chemistry and physics of the fullerene family of carbon allotropes.[1] A number of studies have uncovered interesting properties of C_{60}: rubidium- and potassium-doped C_{60} are high-temperature superconductors[2-5] and C_{60} thin films display a number of interesting

(1) Diederich, F.; Whetten, R. L. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 678–680.
(2) Chen, C.-C.; Kelty, S. P.; Lieber, C. M. *Science* **1991**, *253*, 886–888.

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