Enantioselective Synthesis of β-Amino Acids. 2. Preparation of the *like* Stereoisomers of 2-Methyl- and 2-Benzyl-3-aminobutanoic Acid

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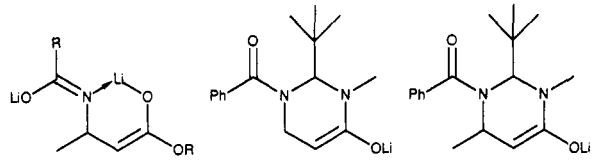
An improved procedure for the preparation of (*R*)- and (*S*)-3-aminobutanoic acids (**2a**) through diastereomer separation of the corresponding (1′*S*)-*N*-phenethyl derivatives **1** is reported. From **2a**, the four possible stereisomeric perhydropyrimidin-4-ones **4** were prepared through the amide **2c** and the Schiff base **3**. In the cyclization of **3**, the cis products **4** predominate ca. 95:5. These heterocycles can be alkylated (LDA, RX), as demonstrated by methylation and benzylation, with formation of a single diastereoisomer (**5**, **6**). Hydrolysis (6 N aqueous HCl) of these 5,6-dialkylperhydropyrimidin-4-ones leads to the free amino acids **7**–**10**.

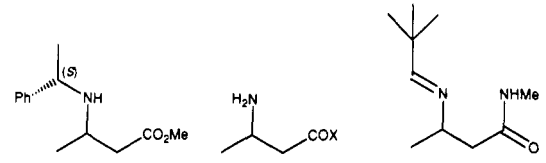
Introduction

In the course of our work on the synthesis of enantiopure β-amino acids[3-6] we have first prepared and α-alkylated 3-aminobutanoic acid through the dilithium derivative A.[3,4] The advantage of using heterocyclic monolithiated derivatives in the 3-hydroxybutanoic acid series[7] led us to study enolates B of perhydropyrimidinone derived from β-alanine,[5a] and we have now also prepared the precursors for the β-aminobutanoic acid derived enolate C.



A B C

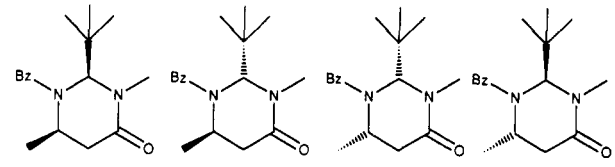
(*R*)- and (*S*)-3-aminobutanoic acids (**2a**) were prepared from methyl crotonate and (*S*)-1-phenylethylamine as described previously[4] (see also ref[8]); Michael addition of the amine to the α,β-unsaturated ester furnishes a 2:3 mixture of the 3*R*,1′*S* and 3*S*,1′*S* isomers which were now shown to be separable by simple flash chromatography if a gradient of the eluent solvent mixture is used (originally, we had done the separation by preparative HPLC); hydrogenolytic removal of the phenethyl group with concomitant ester hydrolysis gave the acid **2a**. Conversion



1 **2a** (X = OH) **2b** (X = OMe) **2c** (X = NHMe) 3

through the ester **2b** to the amide **2c** was followed by Schiff base formation with pivalaldehyde. The imine **3** was used for the cyclization step without purification, and it turned out that treatment with benzoyl chloride/DMAP gave much better yields of the perhydropyrimidinones **4** than with benzoic anhydride, which had been used in the preparation of the precursor for B.[5a]

The cis products (2*S*,6*R*)- and (2*R*,6*S*)-**4** predominated over the trans isomers (2*R*,6*R*)- and (2*S*,6*S*)-**4** in the product mixture (ca. 95:5). Chromatographic separation

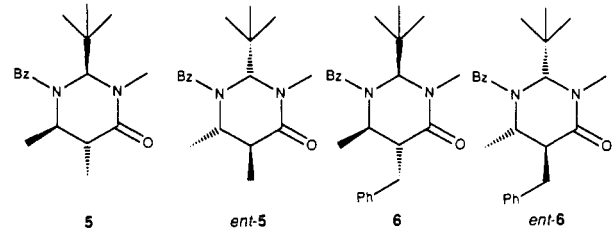


(2*S*, 6*R*)-4 (2*R*, 6*R*)-4 (2*R*, 6*S*)-4 (2*S*, 6*S*)-4

(Bz = PhCO)

and recrystallization gave pure samples of all four stereoisomers. The configuration follows from two X-ray crystal structure determinations of alkylation products (see below). There is an interesting difference between the ^{1}H NMR spectra of the two diastereomers: the cis compound shows several broad signals at room temperature, typical of amide rotamers equilibrating slowly on the NMR time scale, while the trans isomer exhibits only sharp signals. Since we do not know whether the cyclization of the intermediate *N*-benzoyliminium ion is subject to kinetic or thermodynamic control, we cannot discuss its mechanism.

The major isomers of cyclization were deprotonated with LDA under standard conditions to give yellow solutions of the Li enolates C which were alkylated with methyl iodide and benzyl bromide to give the cis, trans products **5**, *ent*-**5**, **6**, and *ent*-**6** in yields of chromatographically purified samples ranging from 75 to 95%. No second



5 *ent*-5 6 *ent*-6

diastereoisomer could be detected in the crude products by ^{1}H-NMR spectroscopy. The trans configuration of the vicinal stereogenic centers was first concluded from a coupling constant between the ring hydrogens of 12 Hz (determined by decoupling the 5- and 6-methyl groups in

(1) (a) Instituto Politécnico Nacional. (b) ETH Zürich.
(2) Part of the projected Ph.D. Theses of J.E. and B.L.
(3) Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103-3106.
(4) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824-1839.
(5) (a) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553-2557. (b) For an independent, related study, see: Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355-1357.
(6) Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.*, in press.
(7) Seebach, D.; Misslitz, U.; Uhlmann, P. *Chem. Ber.* **1991**, *124*, 1845-1852. Pietzonka, T.; Seebach, D. *Ibid.* **1991**, *124*, 1837-1843.
(8) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *3*, 183-186.

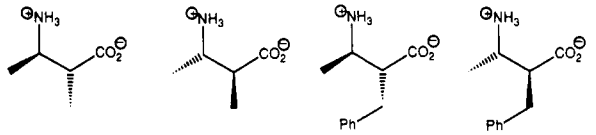
0022-3263/92/1957-2396$03.00/0

rac-**5**). Final proof for the configuration of both the products of methylation and benzylation comes from the X-ray crystal structure determination of *rac*-**5** and *rac*-**6**.[9,10]

The essentially complete diastereoselectivity of methylation and benzylation compares favorably with the values observed with the open-chain dilithium derivative A: 80% ds with MeI[11] and 97% ds with $PhCH_2Br$. Thus, the same improvement of diastereoselectivity results on going from open-chain to cyclic derivatives as in the case of the corresponding hydroxybutanoic acid.[12]

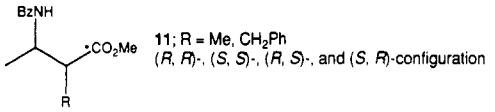
It is interesting to note that the trans isomer **4** failed to react with the alkyl halides when subjected to exactly the treatment which led to the products **5** and **6** with the cis isomer. This contrasting behavior is explained by the fact that in this substrate both faces of the pyrimidinone are hindered: one by the *tert*-butyl and the other by the methyl group.[13]

The final step of the overall conversion of 3-aminobutanoic acid to 2-alkyl-3-aminobutanoic acid, the hydrolysis of the heterocycles **5** and **6**, was achieved by heating with 6 N HCl in a sealed tube. The free amino acids **7**–**10** were purified by chromatography on an ion-



7 **8** **9** **10**

exchange column; the yields were ca. 50% of the methylated compounds **7** and **8** and ca. 90% of the benzyl derivatives **9** and **10**. Both the specific rotations and the ^{13}C-NMR chemical shifts of the free amino acids were sensitive to conditions of measurement, as evident from discrepancies between the values obtained with different enantiomers (see the Experimental Section) and between measured and previously reported[4] values. Therefore, the nonhygroscopic *N*-benzoyl methyl esters **11** were prepared for characterization and comparison with the literature values.



11; R = Me, CH_2Ph
(*R*, *R*)-, (*S*, *S*)-, (*R*, *S*)-, and (*S*, *R*)-configuration

Experimental Section

General. For a description of general experimental data, see ref 5a.

(3*R*,1′*S*)- and (3*S*,1′*S*)-3-[(1′-Phenylethyl)amino]butanoic Acid Methyl Esters [(*R*,*S*)- and (*S*,*S*)-1]. Methyl crotonate (10.0 g, 100 mmol), 14.04 g (116 mmol) of (*S*)-(−)-1-phenylethylamine, and 40 mL of methanol was heated at reflux for 4 d and then concentrated on a rotary evaporator. The residue was distilled in a Kugelrohr apparatus [100–103 °C (0.4 mm); lit.[4] bp 90–96 °C (0.2 mm)] to afford 19.01 g (86% yield) of a colorless liquid, which according to ^1H NMR consisted of a 2:3 mixture of the two diastereomers. Separation of the mixture (4.0 g) was accomplished by gradient flash chromatography (eluent: hexane–ethyl acetate, 19:2 → 1:1) on a column of 5.5 cm × 42 cm to yield pure fractions of 1.20 g of (*R*,*S*)-1 and 0.91 g of (*S*,*S*)-1.

(*R*,*S*)-1: $[\alpha]^{28}_D$ = −39.1° (*c* = 0.97, $CHCl_3$) [lit.[4] $[\alpha]^{RT}_D$ = −41.0° (*c* = 1.31, $CHCl_3$)].

(*S*,*S*)-1: $[\alpha]^{28}_D$ = −49.6° (*c* = 1.25, $CHCl_3$) [lit.[4] $[\alpha]^{RT}_D$ = −37.6° (*c* = 0.98, $CHCl_3$)].

(*R*)- and (*S*)-3-Aminobutanoic Acids [(*R*)- and (*S*)-2a]. A mixture of 9.50 g (43 mmol) of 1 (either diastereoisomer), 100 mL of wet ethanol, 0.90 g of Pd/C catalyst, and 10–15 drops of glacial acetic acid was stirred and pressurized to 30 bar of hydrogen and heated at 50 °C for 20 h. Filtration of the mixture through Celite and concentration on a rotatory evaporator afforded 4.03 g (91% yield) of the desired amino acid.

(*R*)-**2a**: mp 212–214 °C (lit.[14] mp 210–212 °C); $[\alpha]^{28}_D$ = −33.6° (*c* = 1.13, H_2O) [lit.[14] $[\alpha]^{23}_D$ = −38.5° (*c* = 0.8, H_2O)].

(*S*)-**2a**: mp 208–210 °C (lit.[14] mp 210–212 °C); $[\alpha]^{28}_D$ = +32.2° (*c* = 0.9, H_2O) [lit.[14] $[\alpha]^{23}_D$ = +37.2° (*c* = 0.3, H_2O)].

(*R*)- and (*S*)-3-Aminobutanoic Acid Methyl Ester Hydrochlorides [(*R*)- and (*S*)-2b·HCl]. (*R*)- or (*S*)-3-aminobutanoic acid (3.91 g, 38 mmol) was suspended in 40 mL of methanol, and the mixture was cooled to 0 °C. Chlorotrimethylsilane (10.8 mL, 83.6 mmol) was then added dropwise, and the reaction mixture was then stirred at 0 °C for 1 h and at ambient temperature for 8 h. Concentration of the mixture on a rotatory evaporator afforded 5.68 g (97% yield) of the desired ester hydrochloride.

(*R*)-Enantiomer: mp 206–208 °C; $[\alpha]^{28}_D$ = −37.0° (*c* = 0.73, H_2O).

(*S*)-Enantiomer: mp 218–222 °C; $[\alpha]^{28}_D$ = +34.0° (*c* = 0.88, H_2O).

(*R*)- and (*S*)-3-[(2′,2′-Dimethylpropylidene)amino]-*N*-methylbutanamide [(*R*)- and (*S*)-3]. (*R*)- or (*S*)-3-aminobutanoic acid methyl ester hydrochloride (5.53 g, 36 mmol) and 50 mL of methanol were cooled to 0 °C and treated dropwise with 8.4 mL (109 mmol) of a 40% aqueous solution of methylamine. The reaction mixture was stirred at 0 °C for 14 h and then concentrated on a rotatory evaporator to afford a quantitative yield of the intermediate amide–amine, which was redissolved in 40 mL of CH_2Cl_2 and 7.27 g (10.0 mL, 72 mmol) of triethylamine. This solution was treated dropwise with 6.16 g (7.8 mL, 72 mmol) of pivalaldehyde, and the reaction mixture was heated at 40 °C for 6 h with azeotropic removal of water. The triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated to afford 4.1–4.4 g (63–67% yield) of the desired imine as a brownish oil, which was immediately used for the formation of pyrimidinones **4**.

(*R*)-**3**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.0 (s, 9 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 2.4 (d, *J* = 6 Hz, 2 H), 2.75 (d, *J* = 6 Hz, 3 H), 3.55 (tq, *J*, *J*′ = 6.3 Hz, 1 H), 6.9 (bs, 1 H), 7.58 (s, 1 H); ^{13}C (22.49 MHz, $CDCl_3$) δ 21.8, 25.7, 26.7, 35.9, 44.6, 62.2, 171.2, 172.0.

(*S*)-**3**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 1.16 (d, *J* = 6.3 Hz, 3 H), 2.4 (d, *J* = 6 Hz, 2 H), 2.76 (d, *J* = 6 Hz, 3 H), 3.56 (tq, *J*, *J*′ = 6.3 Hz, 1 H), 7.18 (bs, 1 H), 7.6 (s, 1 H).

1-Benzoyl-2(*R*)-*tert*-butyl-3,6(*S*)- and 1-Benzoyl-2(*S*)-*tert*-butyl-3,6(*S*)-dimethylperhydropyrimidin-4-one [(2*R*,6*S*)- and (2*S*,6*S*)-4]. (*S*)-3-[(2′,2′-Dimethylpropylidene)amino]-*N*-methylbutyramide [(*S*)-**3**; 2.94 g, 16 mmol] and 100 mL of toluene were treated with 1.80 g (14.4 mmol) of DMAP and 2.7 mL (22.8 mmol) of benzoyl chloride (dropwise addition) and heated at reflux for 24 h. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated on a rotatory evaporator to afford 3.95 g (86% yield) of the crude product, consisting of a 95:5 mixture of the cis and trans diastereoisomeric heterocycles. This mixture was separated by flash chromatography (hexane–ethyl acetate, 9:1 → 1:1) to afford 2.74 g of *cis*-(2*R*,6*S*)-**4** and 0.16 g of *trans*-(2*S*,6*S*)-**4**.

cis-(2*R*,6*S*)-**4**: mp 104–105 °C; $[\alpha]^{28}_D$ = +95.0° (*c* = 1.01, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.08 (9 H, bs), 1.32 (3 H, d, *J* = 7.5 Hz), 2.73 (2 H, d, *J* = 11 Hz), 3.15 (3 H, s), 4.45 (1 H, m), 5.62 (1 H, bs), 7.15–7.7 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 21.8, 27.8, 36.8, 37.5, 39.2, 47.6, 78.5, 125.7, 128.1, 128.8, 136.3, 169.0, 171.5. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.68; H, 8.50; N, 9.69.

(9) See the supplementary material.

(10) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta*, in press.

(11) The selectivity of the methylation could be increased to >99% by performing the reaction in the presence of 1 equiv of LiCl.

(12) Sutter, M. A.; Seebach, D. *Liebigs Ann. Chem.* **1983**, 939–949. Zimmermann, J.; Seebach, D.; Ha, T.-K. *Helv. Chim. Acta* **1988**, *71*, 1143–1155.

(13) We have been so far unable to metallate-alkylate *trans*-**4**.

(14) Keglevic, D.; Ladesic, B. *Croat. Chem. Acta* **1959**, *31*, 57–66.

trans-(2*S*,6*S*)-**4**: mp 168–168.5 °C; $[\alpha]^{28}_D$ = −126° (*c* = 0.82, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.0 (3 H, d, *J* = 6.7 Hz), 1.08 (9 H, s), 2.28 (1 H, dd, J_1 = 16.5 Hz, J_2 = 2 Hz), 3.13 (1 H, dd, J_1 = 16.5 Hz, J_2 = 5.5 Hz), 3.16 (3 H, s), 4.42 (1 H, m), 5.82 (1 H, s), 7.4–7.6 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 22.6, 28.2, 38.0, 38.7, 41.9, 50.0, 76.4, 127.3, 128.7, 130.5, 136.7, 169.6, 173.3. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.50; H, 8.45; N, 9.73.

1-Benzoyl-2(*S*)-*tert*-butyl-3,6(*R*)- and 1-Benzoyl-2(*R*)-*tert*-butyl-3,6(*R*)-dimethylperhydropyrimidin-4-one [(2*S*,6*R*)- and (2*R*,6*R*)-4]. The same conditions described above were used to cyclize 3.0 g of (*R*)-**3**. A combined yield of 58% of a 95:5 mixture of the desired cis and trans heterocycles (2.65 g and 0.19 g, respectively) was obtained, which were recrystallized from hexane–ethyl acetate (9:1).

cis-(2*S*,6*R*)-**4**: 104–105 °C; $[\alpha]^{28}_D$ = −94.6° (*c* = 1.3, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.08 (9 H), 1.32 (3 H), 2.73 (2 H), 3.15 (3 H), 4.45 (1 H), 5.62 (1 H), 7.15–7.7 (5 H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 21.7, 27.7, 36.8, 37.3, 39.1, 47.5, 78.5, 125.6, 128.0, 128.7, 136.4, 168.7, 171.4. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39. Found: C, 71.09; H. 8.51.

trans-(2*R*,6*R*)-**4**: mp 169–170 °C; $[\alpha]^{28}_D$ = +124° (*c* = 0.8, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.0 (3 H), 1.08 (9 H), 2.23 (1 H), 3.14 (1 H), 3.16 (3 H), 4.42 (1 H), 5.82 (1 H), 7.4–7.6 (5 H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 22.6, 28.2, 38.1, 38.7, 42.0, 50.0, 76.5, 127.4, 128.7, 130.6, 136.8, 169.6, 173.4. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.79; H, 8.53; N, 9.73.

General Procedure for the Reaction of Perhydropyrimidinone Enolates C with Electrophiles. A solution of $(i\text{-Pr})_2NH$ (0.15 mL, 1.1 mmol) in 10 mL of anhydrous THF was cooled to −78 °C before the slow addition of 0.45 mL (1.1 mmol) of *n*-BuLi in hexane (2.4 M). The resulting solution was stirred at −78 °C for 30 min and then treated with 287 mg (1 mmol) of pyrimidinone **4** in 8 mL of THF. The yellow solution formed was stirred at −78 °C for 1 h before the addition of the electrophile (1.2 mmol). The reaction mixture was stirred at this temperature for 1 h and at ambient temperature for 5 min. The mixture was then treated with 3 mL of saturated ammonium chloride solution and then with 7 mL of water. The aqueous phase was extracted with five 5-mL portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product.

1-Benzoyl-2(*S*)-*tert*-butyl-3,5(*R*),6(*R*)-trimethylperhydropyrimidin-4-one (5). The general procedure was followed for the alkylation of 0.50 g (1.7 mmol) of *cis*-(2*S*,6*R*)-**4** with 0.13 mL of CH_3I. Purification of the crude product by flash chromatography (hexane–ethyl acetate, 19:1 → 3:2) afforded 0.52 g (89% yield) of **5**: mp 150–150.5 °C; $[\alpha]^{28}_D$ = −36.4° (*c* = 0.8, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.05 (9 H, s), 1.2 (3 H, d, *J* = 6 Hz), 1.45 (3 H, bd, *J* = 6 Hz), 2.7 (1 H, m), 3.15 (3 H, s), 4.00 (1 H, m), 5.49 (1 H, bs), 7.2–7.7 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 14.1, 20.8, 28.1, 37.8, 39.2, 54.9, 78.6, 125.9, 128.3, 129.0, 136.5, 171.2, 171.3. Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67. Found: C, 71.64; H, 8.86.

1-Benzoyl-2(*R*)-*tert*-butyl-3,5(*S*),6(*S*)-trimethylperhydropyrimidin-4-one (*ent*-5). The general procedure was followed for the alkylation of 0.05 g (1.7 mmol) of (2*R*,6*S*)-**4** with 0.13 mL of CH_3I. Purification of the crude product by flash chromatography (hexane–ethyl acetate, 19:1 → 3:2) afforded 0.45 g (85% yield) of *ent*-**5**: mp 149.5–150 °C; $[\alpha]^{28}_D$ = +35.0° (*c* = 0.65, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.02 (9 H), 1.25 (3 H), 1.45 (3 H), 2.7 (1 H), 3.15 (3 H), 4.01 (1 H), 5.47 (1 H), 7.3–7.7 (5 H). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67. Found: C, 71.79; H, 8.59.

1-Benzoyl-2(*S*)-*tert*-butyl-3,6(*R*)-dimethyl-5(*R*)-benzylperhydropyrimidin-4-one (6). The general procedure was followed for the alkylation of 0.80 g (2.8 mmol) of (2*S*,6*R*)-**4** with 0.4 mL of benzyl bromide. Purification of the crude product by flash chromatography (hexane–ethyl acetate, 19:1 → 65:35) afforded 0.99 g (95% yield) of **6**: $[\alpha]^{28}_D$ = −137° (*c* = 1.01, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.04 (9 H, s), 1.28 (3 H, d, *J* = 7 Hz), 2.6–3.3 (3 H, m), 3.11 (3 H, s), 3.82–4.25 (1 H, m), 5.60 (1 H, bs), 7.05–7.45 (10 H, m). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.37; H, 7.99; N, 7.42. Mp of the racemic form: 108–108.5 °C.

1-Benzoyl-2(*R*)-*tert*-butyl-3,6(*S*)-dimethyl-5(*S*)-benzylperhydropyrimidin-4-one (*ent*-6). The general procedure was followed for the alkylation of 0.80 g (2.8 mmol) of (2*R*,6*S*)-**4** with 0.4 mL of benzyl bromide. Purification of the crude product by flash chromatography (hexane–ethyl acetate, 19:1 → 65:35) afforded 0.79 g (75% yield) of *ent*-**6**: $[\alpha]^{28}_D$ = +130° (*c* = 0.8, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.04 (9 H), 1.20 (3 H), 2.95 (1 H), 3.1 (2 H), 3.15 (3 H), 4.04 (1 H), 5.60 (1 H), 7.05–7.45 (5 H), 7.25 (5 H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 21.3, 28.1, 34.2, 38.3, 39.2, 46.2, 52.1, 78.5, 125.9, 126.1, 128.4, 129.0, 129.2, 136.4, 139.5, 170.5, 171.3. Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.37; H, 7.99; N, 7.42.

General Procedure of the Hydrolysis of the Alkylated Pyrimidinones 5 and 6. A suspension of 1.0 mmol of the adduct in 10 mL of 6 N HCl was heated in a sealed ampoule to 115–120 °C for 6 h. The solution was then allowed to cool to ambient temperature, and the precipitated benzoic acid was filtered. The filtrate was evaporated at reduced pressure to afford a 1:1 mixture of the amino acid hydrochloride and methylamine hydrochloride, which was adsorbed on an acidic ion-exchange resin (Dowex 50W X 8). The resin was washed with distilled water until the washings were neutral, and then the free amino acid was eluted with 1.5 M aqueous NH_4OH. Evaporation afforded the crystalline amino acid, which was dried under high vacuum at 40 °C.

2(*R*)-Methyl-3(*R*)-aminobutanoic Acid (7). Derivative **5** (289 mg, 0.96 mmol) was hydrolyzed according to the general procedure to afford 61 mg (53% yield) of pure **7**: mp 216–220 °C dec; $[\alpha]^{28}_D$ = −14.6° (*c* = 1.13, H_2O). *N*-Benzoyl methyl ester: mp 90–90.5 °C; $[\alpha]^{28}_D$ = +38.7°. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36: H, 7.28; N, 5.95. Found: C, 66.35; H, 7.50; N, 5.85.

2(*S*)-Methyl-3(*S*)-aminobutanoic Acid (8). Derivative *ent*-**5** (293 mg, 0.97 mmol) was hydrolyzed according to the general procedure to afford 60 mg (52% yield) of pure **8**: mp 208–218 °C dec; $[\alpha]^{28}_D$ = +15.5° (*c* = 0.9, H_2O). *N*-Benzoyl methyl ester: mp 90–90.5 °C; $[\alpha]^{28}_D$ = −37.3°. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.31; H, 7.48; N, 5.81.

2(*R*)-Benzyl-3(*R*)-aminobutanoic Acid (9). Derivative **6** (189 mg, 0.5 mmol) was hydrolyzed according to the general procedure to afford 92 mg (95% yield) of pure **9**: mp 229–231 °C dec; $[\alpha]^{28}_D$ = +26.0° (*c* = 1.23, H_2O). *N*-Benzoyl methyl ester: mp 128.5–129 °C; $[\alpha]^{28}_D$ = +81.9°. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.99; H, 6.93; N, 4.37.

2(*S*)-Benzoyl-3(*S*)-aminobutanoic Acid (10). Derivative *ent*-**6** (189 mg, 0.5 mmol) was hydrolyzed according to the general procedure to afford 86 mg (89% yield) of pure **10**: mp 214–221 °C dec; $[\alpha]^{28}_D$ = −36.9° (*c* = 0.65, H_2O). *N*-Benzoyl methyl ester: mp 130–130.5 °C; $[\alpha]^{28}_D$ = −78.0°. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.99; H, 6.89; N, 4.44.

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Registry No. (*R*,*S*)-**1**, 64838-60-4; (*S*,*S*)-**1**, 103123-51-9; (*R*)-**2a**, 3775-73-3; (*S*)-**2a**, 3775-72-2; (*R*)-**2b**·HCl, 139243-54-2; (*S*)-**2b**·HCl, 139243-55-3; (*R*)-**3**, 139243-56-4; (*S*)-**3**, 139243-57-5; (2*S*,6*R*)-**4**, 139243-58-6; (2*R*,6*S*)-**4**, 139243-59-7; (2*R*,6*R*)-**4**, 139243-60-0; (2*S*,6*S*)-**4**, 139243-61-1; **5**, 139243-62-2; *ent*-**5**, 139243-63-3; *rac*-**5**, 139344-71-1; **6**, 139243-64-4; *ent*-**6**, 139243-65-5; *rac*-**6**, 139344-72-2; **7**, 139344-67-5; **7** (*N*-benzoyl methyl ester), 121054-38-4; **8**, 139344-68-6; **8** (*N*-benzoyl methyl ester), 139344-73-3; **9**, 139344-69-7; **9** (*N*-benzoyl methyl ester), 139344-74-4; **10**, 139344-70-0; **10** (*N*-benzoyl methyl ester), 139344-75-5; $CH_3CH{=}CHCOOMe$, 18707-60-3; (*S*)-(−)-$PhCHMeNH_2$, 2627-86-3; Me_3CCHO, 630-19-3.

Supplementary Material Available: PLUTO representations of the crystal structures for *rac*-**5** and *rac*-**6** (2 pages). This material is contained in many 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.