Enantioselective Synthesis of β-Amino Acids. 4. 1,2 Asymmetric Induction in the Alkylation of 1-Benzoyl-3,6(*S*)-dimethylperhydropyrimidin-4-one. Preparation of the Like and Unlike Stereoisomers of 2-Methyl- and 2-Benzyl-3(*S*)-aminobutanoic Acid[1]

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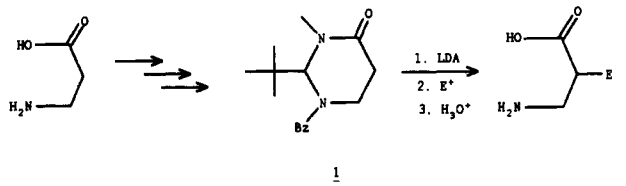
The title perhydropyrimidin-4-one (*S*)-4 was prepared from (*S*)-3-aminobutanoic acid via the Schiff base (*S*)-8. This heterocycle was alkylated (LDA, methyl iodide, or benzyl bromide) to afford the like and unlike diastereomeric products in a 80:20 ratio. Separation and hydrolysis (6 N aqueous HCl) of these 5,6-dialkylperhydropyrimidin-4-ones leads to the free, enantiomerically pure, amino acids 11–14.

Introduction

The highly diasteroselective addition of the enolate 1–Li, derived from β-alanine, to several electrophiles was described recently.[2] The hydrolysis of the resulting adducts proceeds with 6 N hydrochloric acid to afford α-substituted β-amino acids in good yields (Scheme I). Furthermore, an efficient method for the conversion of (*S*)-asparagine into *scalemic*[3] (*S*)-1 was recently described and applied to the enantioselective synthesis of (*R*)-α-methyl-β-alanine,[1] as well as other α-substituted β-amino acids.[4] In this regard, the diastereoselectivity found in the alkylation of 1–Li (Scheme I) varied in the range of 86–>96% and is the result of the steric hindrance generated by the axial disposition of the *tert*-butyl group at C(2), which directs addition from the enolate face opposite to this group.[2,5]

More recently, (*R*)- and (*S*)-β-aminobutyric acids were efficiently converted to enantiomerically pure 1-benzoyl-2(*S*)-*tert*-butyl-3,6(*R*)- and 1-benzoyl-2(*R*)-*tert*-butyl-3,6-(*S*)-dimethylperhydropyrimidin-4-ones, 2. A totally stereoselective reaction was observed in the addition of enolates 2–Li to methyl iodide and benzyl bromide.[6] Both the *tert*-butyl group at C(2) and the (cis) methyl group at C(6) hinder attack on the syn face, leading to the exclusive formation of the trans products. Hydrolysis of the resulting adducts affords the desired, enantiomerically pure α,β-disubstituted β-amino acids in good yields[6] (Scheme II).

Scheme I



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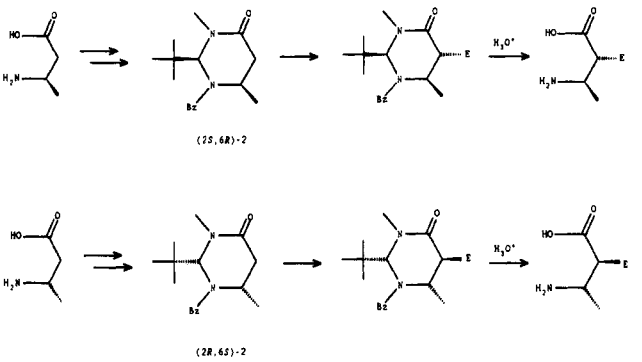
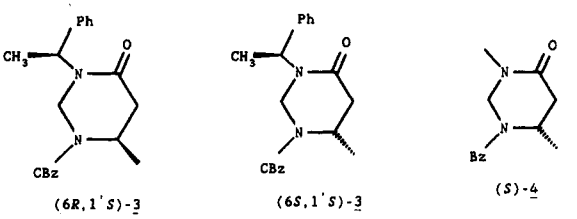
Scheme II



On the other hand, "removal" of the *tert*-butyl group at C(2) and substitution of the *N*-3-methyl group by (*S*)-α-phenylethyl [to give (6*R*,1′*S*)- and (6*S*,1′*S*)-3] affords a pyrimidinone system which is alkylated with 85–97% diastereoselectivity; the main product arises from trans addition relative to the configuration at C(6).[7,8]



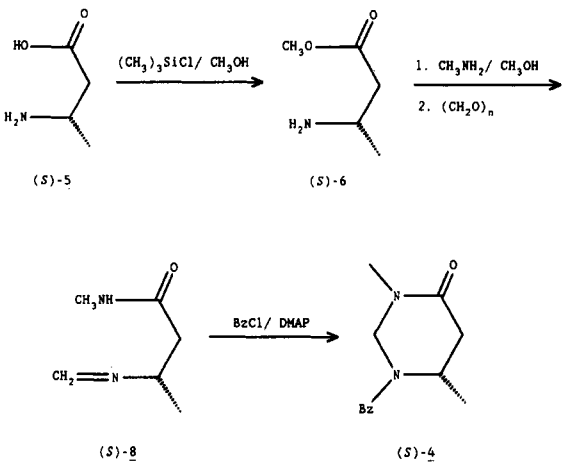
(6*R*,1′*S*)-3 (6*S*,1′*S*)-3 (*S*)-4

The present paper describes the diastereoselectivity observed in the alkylation of 1-benzoyl-3,6(*S*)-dimeth-

(1) For part 3, see: Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723–726.
(2) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553–2557.
(3) The term *scalemic* is being proposed to describe materials that are enantiomerically enriched: Heathcock, C. H. *Chem. Eng. News* **1991**, Feb 4, 3.
(4) Quintana, D. Unpublished results.
(5) 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* **1992**, *75*, 913–934.
(6) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396–2398.
(7) Amoroso, R.; Cardillo, G.; Tomasini, C. *Tetrahedron Lett.* **1992**, *33*, 2725–2728.
(8) Also, N(1) is protected with a carbobenzoxy (CBz) rather than a benzoyl (Bz) group.

0022-3263/93/1958-2282$04.00/0

Scheme III

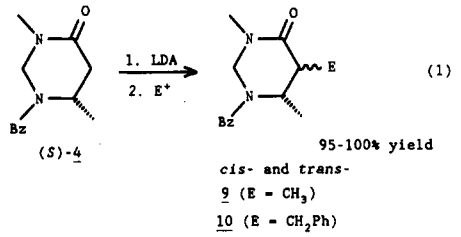


ylperhydropyrimidin-4-one [(*S*)-4], where the asymmetric induction is due exclusively to the stereogenic center at C(6).[9]

Results and Discussion

A. Synthesis of 1-Benzoyl-3,6(*S*)-dimethylperhydropyrimidin-4-one [(*S*)-4]. (*S*)-3-Aminobutanoic acid [(*S*)-5] was resolved through diastereomer separation of the corresponding (1′*S*)-*N*-phenethyl derivative.[6,10] Conversion through the ester (*S*)-6 to the amide (*S*)-7 was followed by Schiff base formation with paraformaldehyde. Imine (*S*)-8 was used for the cyclization step without purification: treatment with benzoyl chloride/DMAP gave excellent yields of the desired perhydropyrimidinone (*S*)-4 (Scheme III).

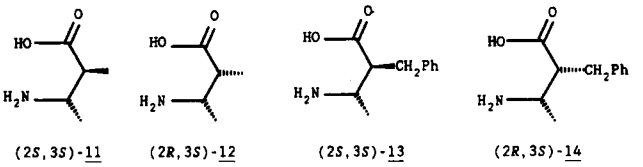
B. Diastereoselectivity of Alkylation of Enolate (*S*)-4–Li. The alkylation products **9** and **10** were formed by treatment of the enolate (*S*)-4–Li, generated with lithium diisopropylamide (LDA) in THF, with methyl iodide and benzyl bromide at −75 °C (eq 1).



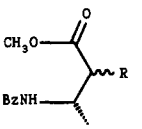
(1)

^{13}C NMR analysis of the crude products indicated the formation of two products in a 4:1 ratio. That the major product corresponds to the isomer of trans relative configuration [(5*S*,6*S*)-**9** or (5*S*,6*S*)-**10**, depending on the starting material] was ascertained by chemical correlation with the known α,β-disubstituted β-amino acids (see section C).

C. Hydrolysis of the Pyrimidinone Adducts 9 and 10 To Give the α,β-Disubstituted β-Amino Acids. The final step of the overall conversion of (*S*)-3-aminobutanoic acid to (2*S*,3*S*)- and (2*R*,3*S*)-2-alkyl-3-aminobutanoic acids, the hydrolysis of the heterocycles **9** and **10**, was achieved by heating the acid to 115–120 °C with 6 N HCl in a sealed tube. The free amino acids **11**–**14** were purified by chromatography on an ion-exchange column; the yields were ca. 84% of the dimethylated compounds **11** and **12** and ca. 70% of the benzyl derivatives **13** and **14**.



Both the specific rotations and the melting points of the free amino acids were sensitive to conditions of measurement, as evident from discrepancies between measured and previously reported[6] values (see the Experimental Section). Therefore, the nonhygroscopic *N*-benzoyl methyl esters **15**–**18** were prepared for characterization and comparison with the literature values.



15: (2*S*,3*S*), R = CH_3
16: (2*R*,3*S*), R = CH_3
17: (2*S*,3*S*), R = CH_2Ph
18: (2*R*,3*S*), R = CH_2Ph

At this point, the specific rotations, the melting points, and the ^1H and ^{13}C NMR spectra of **15** and **17** were found to be essentially identical with those already present in the literature.[6] This chemical correlation permits the assignment of the relative configuration of the main product during alkylation (see section B) as trans. The lower diastereoselectivity observed in the alkylation of **5**–Li, relative to that observed with **1**–Li, **2**–Li and **3**–Li (see the Introduction), suggests the relative ability of the *tert*-butyl, methyl, and phenethyl groups as stereodirecting entities when located, respectively, on the stereogenic centers C(2), C(6), and C(1′) of the 1,3-perhydropyrimidin-4-one system. This sort of information is quite relevant in the design of chiral substrates for the development of asymmetric synthesis.[11]

Experimental Section

General. For a description of general experimental data, see ref 2. Microanalyses were performed by Galbraith Laboratories, TN. The purity of compounds (*S*)-**4**, *cis*-**9**, *trans*-**9**, *cis*-**10**, *trans*-**10**, **12**, and **14**, for which elemental analyses are not provided, was judged to be >95%, as evidenced by ^1H and ^{13}C NMR spectra (see supplementary material).

(*S*)-3-(Methylideneamino)-*N*-methylbutanamide [(*S*)-8]. (*S*)-3-Aminobutanoic acid methyl ester hydrochloride[6] (2.60 g, 17 mmol) and 25 mL of methanol were cooled to 0 °C and treated dropwise with 4.2 mL (54.5 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 30 mL of CH_2Cl_2 and 3.41 g (4.7 mL, 34 mmol) of triethylamine. This solution was treated dropwise with 0.76 g (25.5 mmol) of paraformaldehyde, and the reaction mixture was heated at 40 °C for 6 h with azeotropic removal of water. The

(9) For a discussion on 1,2-asymmetric induction, see: Nógrádi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1987; p 131. Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley-Interscience: New York, 1991; p 178.

(10) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824–1839.

(11) See, for example: Morrison J. D., Ed. *Asymmetric Synthesis*; Academic Press: Orlando, FL, 1983–1985; Vols. 1–5.

triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated to afford 1.71 g (78.6% yield) of the desired imine as a brownish oil, which was immediately used for the formation of pyrimidinone 4: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.15 (d, J = 6 Hz, 3 H), 1.88–2.6 (m, 3 H), 2.85 (s, 3 H), 2.9–3.3 (m, 1 H), 4.15 (s, 2 H); ^{13}C (22.49 MHz, $CDCl_3$) δ 20.4, 29.6, 39.4, 47.5, 63.0, 166.9.

1-Benzoyl-3,6(*S*)-dimethylperhydropyrimidin-4-one. [(*S*)-4]. (*S*)-3-(Methylideneamino)-*N*-methylbutanamide [(*S*)-8; 1.32 g, 10.3 mmol] and 15 mL of benzene were treated with 0.80 g (9.2 mmol) of DMAP and 1.21 mL (14.6 mmol) of benzoyl chloride (dropwise addition) and heated at reflux for 6 h. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated on a rotatory evaporator. The residue was separated by flash chromatography (hexane–ethyl acetate (90:10 → 30:70)) to afford 2.2 g (92% yield) of (*S*)-4 as a viscous oil: $[\alpha]_D^{28}$ = +17.6° (*c* =1.25, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (3 H, d, J = 7.2 Hz), 2.38 (1 H, dd, J_1 = 19.2 Hz, J_2 = 3.9 Hz), 2.60 (1 H, dd, J_1 = 19.2 Hz, J_2 = 6.6 Hz), 2.85 (3 H, s), 4.50 (1 H, m), 4.56 (1 H, d, J = 13.5 Hz), 5.12 (1 H, J = 13.5 Hz), 7.4 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 18.3, 31.7, 37.8, 46.5, 57.4, 126.5, 128.5, 130.2, 134.6, 167.3, 170.1; HRMS calcd for $C_{13}H_{15}N_2O_2$ 231.1134, found 231.1136.

General Procedure for the Reaction of Perhydropyrimidinone Enolate (*S*)-4-Li with Electrophiles. A solution of (*i*-Pr)$_2$NH (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 232 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-3,5(*S*),6(*S*)-trimethylperhydropyrimidin-4-one and 1-Benzoyl-3,5(*R*),6(*S*)-trimethylperhydropyrimidin-4-one [(5*S*,6*S*)- and (5*R*,6*S*)-9]. The general procedure was followed for the alkylation of 0.2 g (0.9 mmol) of (*S*)-4 with 0.07 mL (1.2 mmol) of CH_3I to afford 0.21 g (95% yield) of the crude product, consisting of a 1:4 mixture of the cis and trans diastereoisomeric heterocycles. This mixture was separated by flash chromatography (hexane–ethyl acetate (5:5 → 1:9)) to afford 0.04 g (95% recovery) of *cis*-(5*R*,6*S*)-9 and 0.152 g (91% recovery) of *trans*-(5*S*,6*S*)-9 as viscous oils.

trans-(5*S*,6*S*)-9: $[\alpha]_D^{28}$ = +20.6° (*c* = 1.5, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.27 (3 H, d, J = 7.2 Hz), 1.37 (3 H, d, J = 6.9 Hz), 2.36 (1 H, m), 2.90 (3 H, s), 4.13 (1 H, m), 4.60 (1 H, d, J = 14.4 Hz), 5.15 (1 H, d, J = 14.4 Hz), 7.40 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 15.5, 17.7, 31.5, 42.1, 52.3, 57.1, 126.1, 128.1, 129.6, 134.5, 169.9, 170.3; HRMS calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1369.

cis-(5*R*,6*S*)-9: $[\alpha]_D^{28}$ = −4.1° (*c* = 1.7, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.10 (3 H, d, J = 8.1 Hz), 1.24 (3 H, d, J = 8.1 Hz), 1.97 (1 H, m), 2.90 (3 H, s), 4.35 (1 H, m), 4.58 (1 H, d, J = 13.8 Hz), 5.15 (1 H, d, J = 13.8 Hz), 7.4 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 12.3, 13.7, 32.0, 40.3, 126.7, 128.8, 130.5, 134.9, 170.1, 170.5 (note: signals for C(2) and C(6) are obscured by base line noise); HRMS calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1369.

1-Benzoyl-3,6(*S*)-dimethyl-5(*S*)- and 1-Benzoyl-3,6(*S*)-dimethyl-5(*R*)-benzylperhydropyrimidin-4-one [(5*S*,6*S*)- and (5*R*,6*S*)-10]. The general procedure was followed for the alkylation of 0.65 g (2.8 mmol) of (*S*)-4 with 0.4 mL (3.2 mmol) of benzyl bromide to afford 0.90 g (100% yield) of the crude product, consisting of a 1:4 mixture of the cis and trans diastereoisomeric heterocycles. This mixture was separated by flash chromatography (hexane–ethyl acetate (5:5 → 1:9)) to afford 98.4 mg (55%) recovery) of *cis*-(5*R*,6*S*)-10 and 511 mg (71% recovery) of *trans*-(5*S*,6*S*)-10 as viscous oils.

trans-(5*S*,6*S*)-10: $[\alpha]_D^{28}$ = +67.7° (*c* = 1.3, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.26 (3 H, d, J = 7.8 Hz), 2.50 (1 H, m), 2.73 (1 H, bd, J = 10.8 Hz), 2.90 (3 H, s), 3.15 (1 H, d, J = 10.8 Hz), 4.35 (1 H, m), 4.55 (1 H, d, J = 14.1 Hz), 5.15 (1 H, bd, J = 14.1 Hz), 7.10 (5 H, m), 7.4 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 17.8, 31.3, 36.2, 47.9, 49.7, 56.3, 125.7, 126.2, 127.7, 127.9, 128.2, 129.7, 134.1, 138.1, 168.7, 169.3; HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1684.

cis-(5*R*,6*S*)-10: $[\alpha]_D^{28}$ = +3.6° (*c* = 1.1, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.15 (3 H, d, J = 8.4 Hz), 2.28 (1 H, m), 2.90 (3 H, s), 2.95 (1 H, bd, J_1 = 16.5 Hz), 3.50 (1 H, dd, J_1 = 16.5 Hz, J_2 = 5.4 Hz), 4.15 (1 H, m), 4.60 (1 H, d, J = 14.4 Hz), 5.20 (1 H, bd, J = 14.4 Hz), 7.13 (5 H, m), 7.3 (5 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 13.5, 31.9, 32.2, 47.3, 50.0, 57.0, 126.3, 126.3, 128.3, 128.6, 130.2, 134.6, 138.5, 169.3, 169.8; HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1677.

General Procedure of the Hydrolysis of the Alkylated Pyrimidinones 9 and 10. A suspension of 1.0 mmol of the adduct in 10 mL of 6 N HCl was heated in a sealed ampule 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 50WX8). 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(*S*)-Methyl-3(*S*)-aminobutanoic Acid (11). Derivative (5*S*,6*S*)-9 (80 mg, 0.32 mmol) was hydrolyzed according to the general procedure to afford 43.3 mg (86.7% yield) of pure 11: mp 208–218 °C dec (lit.[6] mp 208–218 °C); $[\alpha]_d^{28}$ = +8.6° (*c* = 1.4, H_2O) [lit.[6] $[\alpha]_D^{28}$ = +15.5° (*c* = 0.9, H_2O)]; ^{1}H NMR (60 MHz, D_2O) δ 1.20 (3 H, d, J = 8.1 Hz), 1.30 (3 H, d, J = 7.5 Hz), 2.55 (1 H, dq, $J_1 \approx J_2 \approx$ 7.5 Hz), 3.45 (1 H, dq, $J_1 \approx J_2 \approx$ 7.5 Hz); ^{13}C NMR (22.49 MHz, D_2O) δ 15.3, 17.4, 46.3, 51.0, 183.0.

N-Benzoyl methyl ester (15): mp 89–90 °C (lit.[6] mp 90–90.5 °C); $[\alpha]_D^{28}$ = −37.6° (*c* = 1.01, $CHCl_3$) [lit.[6] $[\alpha]_D^{28}$ = −37.3° (*c* = 1.02, $CHCl_3$)]; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.23 (6 H, d, J = 7.5 Hz), 2.71 (1 H, m), 3.68 (3 H, s), 4.38 (1 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 15.0, 19.4, 43.6, 47.3, 51.6, 126.7, 128.3, 131.2, 134.4, 166.6, 176.2.

2(*R*)-Methyl-3(*S*)-aminobutanoic Acid (12). Derivative (5*R*,6*S*)-9 (90 mg, 0.36 mmol) was hydrolyzed according to the general procedure to afford 35 mg (81.7% yield) of pure 12: mp 217–220 °C dec; $[\alpha]_D^{28}$ = +1.0° (*c* = 0.99, D_2O); ^{1}H NMR (60 MHz, D_2O) δ 1.20 (3 H, d, J = 8.1 Hz), 1.30 (3 H, d, J = 8.1 Hz), 2.52 (1 H, dq, $J_1 \approx J_2 \approx$ 7.5 Hz), 3.50 (1 H, dq, $J_1 \approx J_2 \approx$ 7.5 Hz); ^{13}C NMR (22.49 MHz, D_2O) δ 13.9, 16.5, 45.7, 50.6, 182.2.

N-Benzoyl methyl ester (16): mp 92.5–93.5 °C; $[\alpha]_D^{28}$ = −42.9° (*c* = 1.05, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.21 (6 H, d, J = 7.5 Hz), 2.78 (1 H, m), 3.69 (3 H, s), 4.43 (1 H, m), 6.60–7.90 (6 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 13.9, 16.4, 43.8, 47.4, 51.8, 126.8, 128.5, 131.4, 134.4, 166.4, 174.9. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found C, 66.22; H, 7.33.

2(*S*)-Benzyl-3(*S*)-aminobutanoic Acid (13). Derivative (5*S*,6*S*)-10 (200 mg, 0.68 mmol) was hydrolyzed according to the general procedure to afford 100 mg (75.8% yield) of pure 13: mp 214–218 °C dec (lit.[6] mp 214–221 °C); $[\alpha]_D^{28}$ = −43.05° (*c* = 0.72, D_2O) [lit.[6] $[\alpha]_D^{28}$ = −36.9° (*c* = 0.65, H_2O)]; ^{1}H NMR (60 MHz, D_2O) δ 1.32 (3 H, d, J = 6.6 Hz), 2.8 (1 H, m), 2.90 (2 H, s), 3.50 (1 H, m), 7.35 (5 H, m); ^{13}C NMR (22.49 MHz, D_2O) δ 18.1, 36.5, 49.6, 52.5, 127.8, 129.9, 139.8, 175.1.

N-Benzoyl methyl ester (17): mp 129.5–130 °C (lit.[6] 130.0–130.5 °C); $[\alpha]_D^{28}$ = −79.0° (*c* = 1.1, $CHCl_3$) [lit.[6] $[\alpha]_D^{28}$ = −78.0° (*c* = 1.0, $CHCl_3$)]; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.25 (3 H, d, J = 7.2 Hz), 2.9 (3 H, m), 3.59 (3 H, s), 4.38 (1 H, m), 7.0–8.0 (11 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 20.0, 36.5, 45.6, 51.8, 51.9, 126.6, 126.9, 128.5, 128.5, 128.8, 131.4, 134.4, 138.2, 166.6, 175.7.

2(*R*)-Benzyl-3(*S*)-aminobutanoic Acid (14). Derivative (5*R*,6*S*)-10 (80 mg, 0.24 mmol) was hydrolyzed according to the general procedure to afford 30 mg (62.6% yield) of pure 14: mp 220–224 °C dec; $[\alpha]_D^{28}$ = +6.3° (*c* = 0.79, D_2O); ^{1}H NMR (60 MHz, D_2O) δ 1.40 (3 H, d, J = 6.6 Hz), 2.86 (2 H, s), 2.90 (1 H, m), 3.6 (1 H, m), 7.35 (5 H, m); ^{13}C NMR (22.49 MHz, D_2O) δ 16.5, 35.3, 49.6, 54.3, 127.6, 129.7, 129.7, 140.0, 180.2.

N-Benzoyl methyl ester 18: mp 119.5–120 °C; $[\alpha]_D^{28}$ = −12.2° (*c* = 0.74, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (3 H, d, J

= 7.5 Hz), 3.0 (3 H, m), 3.69 (3 H, s), 4.48 (1 H, m), 7.0–8.0 (11 H, m); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 16.9, 34.9, 46.5, 51.3, 51.8, 126.4, 126.8, 128.5, 128.5, 130.1, 131.4, 134.4, 141.6, 166.6, 173.7. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80. Found C, 72.64; H, 6.75.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for (*S*)-**4**, *cis*-**9**, *trans*-**9**, *cis*-**10**, *trans*-**10**, **12**, and **14** (14 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.