Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2233-2246, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00278-9

Enantioselective Synthesis of β-Amino Acids. 7. Preparation of Enantiopure α-Substituted β-Amino Acids from 1-Benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one.[1,2]

Eusebio Juaristi*, Delia Quintana, Margarita Balderas, and Enrique García-Pérez

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, D. F., México

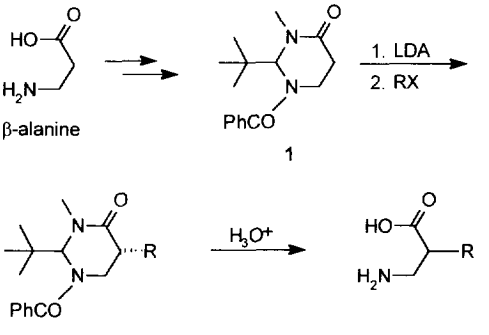
Abstract. Inexpensive natural α-amino acid L-asparagine was efficiently converted to either (*R*)- or (*S*)-α-alkylated β-amino acids in enantiomerically pure state. The key intermediate in this protocol is the enantiopure *N,N*-acetal pyrimidinone (*S*)-**1**, a masked chiral derivative of β-alanine.

Introduction

β-Amino acids are receiving increasing attention in view of their interesting pharmacological effects, both in free form or as constituents of peptides[3] and β-lactams.[4] Three recent reviews attest that the preparation of enantiomerically pure β-amino acids has emerged as an important and challenging synthetic endeavor.[5]

In this context, β-alanine (an achiral β-amino acid) was recently converted into racemic 2-*tert*-butylperhydropyrimidinone, *rac*-**1**, which was alkylated with high diastereoselectivity via its corresponding enolate.[6] The high stereoselectivity encountered in the reaction of **1**-Li with various electrophiles was ascribed to steric hindrance generated by the axial disposition of the *tert*-butyl group at C(2),[6,7] which directs approach to the electrophile from the enolate face opposite to this group. Hydrolysis of the alkylated products afforded the expected α-substituted β-amino acids in good yields (Scheme 1).

Scheme 1

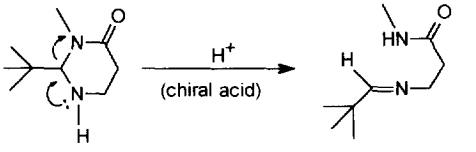


These observations paved the road for the development of a new method for the asymmetric synthesis of α-substituted β-amino acids, provided that an efficient protocol for the preparation of enantiopure pyrimidinone **1** could be developed.[8]

Results and Discussion

A. Attempted Resolution of the 2-*tert*-Butylpyrimidinone *rac*-2.

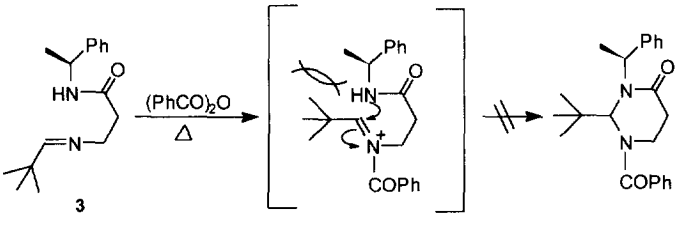
In 1986 Fitzi and Seebach[9] reported a convenient resolution procedure of racemic 2-*t*-butyl-3-methyl-1,3-imidazolidin-4-one with mandelic acid. A similar resolution protocol was envisaged for the six-membered ring analogue *rac*-2-*t*-butyl-3-methylperhydropyrimidin-4-one, (±)-**2**. Nevertheless, in contrast with the behavior exhibited by five-membered aminals, *rac*-**2** proved exceedingly unstable to acid, affording the open-chain imine instead of the expected diastereoisomeric salts (eq. 1).



(1)

B. Attempted Preparation of Enantiopure (*S*)-1 via the Separation of Diastereomeric Derivatives.

Recently, Juaristi, et al.[10] described an alternative route for the preparation of enantiopure 1,3-imidazolidin-4-ones via the separation of the diastereomeric mixture of (*R*,*S*)- and (*S*,*S*)-1-benzoyl-2-*tert*-butyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-ones. Unfortunately, analogous Schiff base (*S*)-**3** did not undergo cyclization under the normally employed conditions (benzoic anhydride and heating). Apparently, steric hindrance between the *tert*-butyl and phenethyl groups during ring formation is too high (eq. 2).

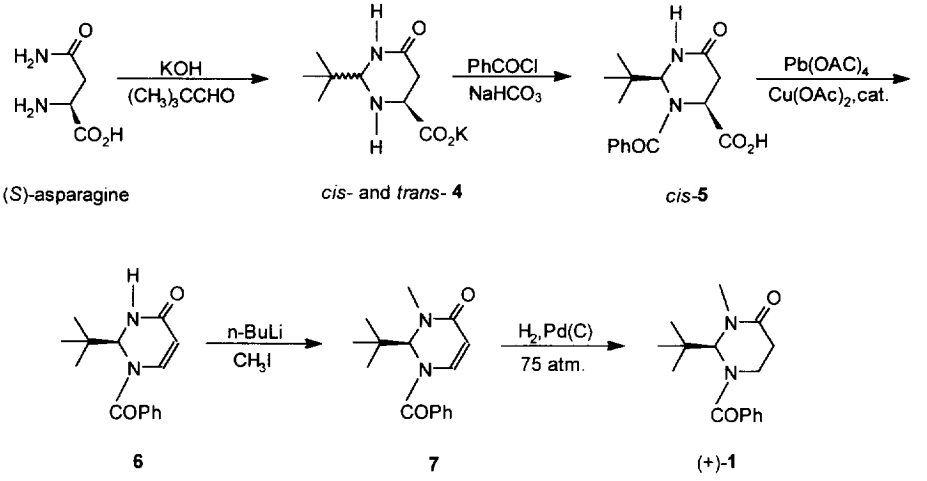


(2)

C. Successful Synthesis of Enantiopure (*S*)-1 from (*S*)-Asparagine.

(*S*)-Asparagine was condensed with pivalaldehyde according to the procedure described by Konopelski, et al.[11] Benzoylation of the amine funtion in **4** (PhCOCl, $NaHCO_3$) yielded **5** as a 86:14 cis/trans diastereomeric mixture. Slow addition of HCl resulted in the preferential precipitation of the main (cis) isomer in 74% yield from asparagine.[12] Treatment of *cis*-**5** with $Pb(OAc)_4$/catalytic $Cu(OAc)_2$ (oxidative decarboxylation[11a,13,14]) afforded enone **6** in 60% yield. Finally, *N*-methylation of **6** proceeded in 55% yield, and palladium-catalyzed hydrogenation yielded (+)-**1** in 98%. The overall yield of (+)-**1** from (*S*)-asparagine is 25% (Scheme 2).

Scheme 2



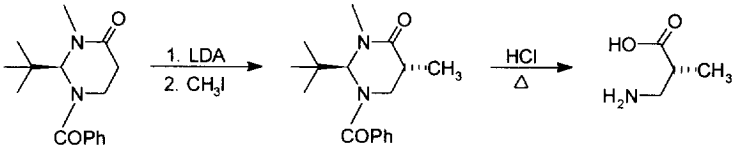
(*S*)-asparagine *cis*- and *trans*- **4** *cis*-**5**

6 **7** (+)-**1**

D. Assignments of Configuration.

It is well-established that addition of **1**-Li, the enolate derived from pyrimidinone **1**, to electrophiles takes place from the enolate face opposite to the *tert*-butyl group.[6] Thus, observation that hydrolysis of (+)-**8**, the product of methylation of (+)-**1**, affords (-)-α-methyl-β-alanine, i.e., (*R*)-(-)-**9**,[15] allows the assignment of the absolute configuration of (+)-**1** as (*S*).[16] (Scheme 3).

Scheme 3

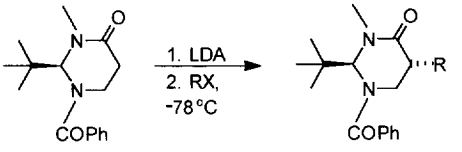


(+)-**1** (+)-**8** (-)-**9**

E. Stereoselective Alkylation of (*S*)-1.

Fully characterized, enantiopure pyrimidinone (*S*)-**1** was then examined as a potentially general, convenient substrate for the enantioselective synthesis of α-substituted β-amino propionic acids. To this end, enolate (*S*)-**1**-Li was generated upon treatment of the heterocycle with lithium diisopropylamide (LDA), in THF solvent and under nitrogen atmosphere. The electrophile (methyl iodide, *n*-butyl iodide, *n*-hexyl iodide, or benzyl bromide) was then added at -78°C to afford the *trans*-alkylated products in high diastereoselectivity and good yields (Table I). The trans configuration of the alkylated products (**8**, **10-12**) was assigned by comparison with the ^{1}H and ^{13}C NMR spectra of the racemic materials.[6]

Table I. Diastereoselectivity of Enolate (*S*)-**1**-Li Alkylations



(*S*)-**1** **8**, **10-12**

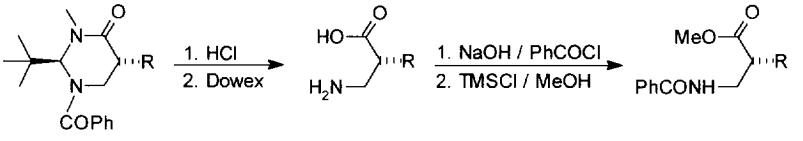
Product	RX	ds (%)	mp (°C)	$[\alpha]_D^{29°C}$	isolated yield (%)
8	CH_3I	>96	121-122	+39.5	77
10	*n*-C_4H_9I	95	80-81	+26.7	75
11	*n*-$C_6H_{13}I$	95	70-71	+31.2	80
12	$PhCH_2Br$	>96	173-174	-64.0	80

The high selectivity encountered in the addition of (*S*)-**1**-Li to electrophiles is explained in terms of a reactive enolate conformation with an axial *tert*-butyl group,[6,7] which sterically hinders one enolate face for reaction with electrophiles. The alkylated products, **8** and **10-12**, are all solids; stereochemically pure materials were readily obtained by recrystallization.

F. Hydrolysis of the Pyrimidinone Adducts 8 and 10-12 to Give the Enantiopure α-Substituted β-Amino Acids.

The final step of the overall conversion of β-alanine to 2-alkyl-3-aminopropanoic acid, the hydrolysis of the heterocycles **8** and **10-12**, was achieved by heating with 6 N HCl in a sealed tube at 90-100°C. The free amino acids **9** and **13-15** were purified by chromatography on an ion-exchange column, and converted to the nonhygroscopic *N*-benzoyl methyl esters **16-19**[17] (Table II).

Table II. Hydrolysis of Products **8** and **10-12**, and conversion to *N*-Benzoyl Methyl Esters (*R*)-**16-19**.



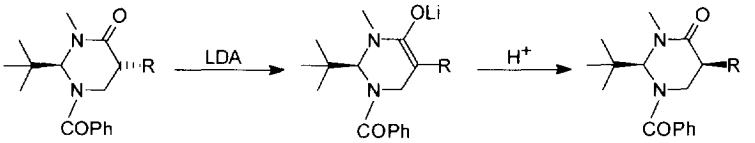
8,**10-12** (*R*)-**9**, **13-15** (*R*)-**16-19**

R	yield of free amino acids	mp of (*R*)-**9**, **13-15**	$[\alpha]_D^{29°C}$ of (*R*)-**9**, **13-15**	mp of (*R*)-**16-19**	$[\alpha]_D^{29°C}$ of (*R*)-**16-19**
CH_3	80	185-186	-11.8	70-71	-20.2
n-C_4H_9	80	170-171	+5.3	67-68	+8.5
n-C_6H_{13}	80	219-220	+6.6	65-66	+11.3
$PhCH_2$	85	225-226	+11.3	78-79	+15.6

G. Epimerization of Adducts 8 and 10-12, and Hydrolysis to Give the Enantiomeric α-Alkylated β-Aminopropionic Acids.

In principle, α-amino acids of opposite configuration, (*S*)-**9** and **13-15**, can be obtained when enantiomeric pyrimidinone (*R*)-**1** is used as the starting material, following the reaction sequence described above (Sections **E** and **F**). Nevertheless, an efficient and practical alternative consisted in the epimerization of trans adducts **8** and **10-12** to afford the cis diastereoisomers **20-23** (Table III). Hydrolysis of *cis*-**20-23** provided then the desired α-alkylated β-amino acids (Table IV).

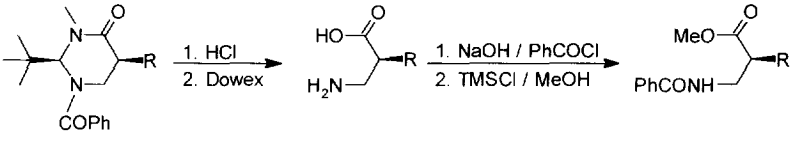
Table III. Epimerization of Pyrimidinone Adducts **8** and **10-12**.



8, **10-12** **20-23**

starting material	R	product	mp (°C)	$[\alpha]_D^{29°C}$	isolated yield
8	CH_3	**20**	108-109	+33.5	85
10	*n*-C_4H_9	**21**	64-65	+18.7	85
11	*n*-C_6H_{13}	**22**	94-95	+20.7	90
12	$PhCH_2$	**23**	98-98.5	-6.4	88

Table IV. Hydrolysis of Epimerized Adducts *cis*-**20-23** to Give β-Amino Acids (*S*)-**9** and (*S*)-**13-15**, and Preparation of *N*-Benzoylated Methyl Esters (*S*)-**16-19**.



20-23 (*S*)-**9**, **13-15** (*S*)-**16-19**

R	yield of free amino acids	mp of (*S*)-**9**, **13-15**	$[\alpha]_D^{29°C}$ of (*S*)-**9**, **13-15**	mp of (*S*)-**16-19**	$[\alpha]_D^{29°C}$ of (*S*)-**16-19**
CH_3	80	184-185	+11.6	69.5-71	+19.7
n-C_4H_9	80	169-170	-5.0	66.5-68	-8.3
n-C_6H_{13}	85	219-220	-6.3	65-66	-10.6
$PhCH_2$	85	224-225	-11.0	77.5-79	-15.0

Clearly, protonation (aqueous NH_4Cl) of the enolates generated from **8** and **10-12** takes place on the face opposite to the *tert*-butyl group, and this reaction is also highly stereoselective.

Conclusions.

L-Asparagine, an inexpensive chiral amino acid, was converted into the enantiopure pyrimidinone (*S*)-**1**.

Enantiopure α-alkylated β-aminopropionic acids of (*R*) configuration were obtained by diastereoselective alkylation of enolate (*S*)-**1**-Li, followed by hydrolysis with 6 N aqueous HCl.

α-Alkylated β-aminopropionic acids of (*S*) configuration were conveniently prepared via epimerization of the trans adducts **8** and **10-12** (to afford the cis isomers **20-23**) and subsequent acid hydrolysis.

This work demonstrates the utility of chiral *N,N*-acetals derived from β-alanine[6] in the enantioselective synthesis of α-substituted β-amino acids.

Experimental Section

General. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for ca. 12 h at 120°C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[18] The *n*-butyl lithium employed was titrated according to the method of Juaristi, et al.[19]

TLC: Merck-DC-F_{254} plates; detection by UV light. Flash column chromatography:[20] Merck silica gel (0.040-0.063 nm). Melting points: Mel-Temp apparatus; not corrected. IR spectra: Nicolet MX-1 FT spectrometer. ^1H NMR spectra: Jeol PMX-60 (60 MHz) and Jeol GSX-270 (270 MHz) spectrometers. ^{13}C NMR spectra: Jeol FX-90Q (22.49 MHz) and Jeol GSX-270 (67.8 MHz). Chemical shifts (δ) in ppm downfield from internal TMS reference; the coupling constants (J) are given in Hz. Elemental analyses were obtained at Galbraith Laboratories, Inc., TN.

General Procedure for the Alkylation of Perhydropyrimidinones. In a dry two-necked round-bottom flask, provided with addition funnel, rubber septa, and thermometer, was placed under nitrogen diisopropylamine (4.4 mmol) in 50 mL of THF, which was then cooled to -20°C before the slow addition of 4.8 mmol of *n*-BuLi (ca. 1.8 M in *n*-hexane). The resulting solution was stirred at -20°C for 20 min and then cooled to -78°C before the dropwise addition of 4.0 mmol of the heterocycle in 30 mL of THF. Stirring was continued for 1 h at -78°C in order to secure the complete formation of the enolate. The alkylating agent (4.6 mmol, 15% excess) was then added dropwise via syringe, and the reaction mixture was stirred at -78°C until no further changes were detected by TLC (2-3 h). At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution, allowed to warm to ambient temperature, and extracted with two portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in a rotary evaporator.

***cis*- and *trans*-2-*tert*-Butyl-6(*S*)-potassium carboxylate-perhydropyrimidin-4-one (*cis*- and *trans*-4).** In a 500 mL round-bottom flask was placed 13.3 g (0.1 mol) of (*S*)-asparagine in 150 mL of dry methanol. A methanolic solution of KOH [6.3 g (0.1 mol) in 35 mL of CH_3OH] was added and the resulting solution was heated to reflux for 1.5 h. The reaction flask was submerged in an ice-water bath before the addition of 11.2 mL (0.1 mol) of pivalaldehyde. The cooling bath was removed and the reaction mixture was heated to reflux for 8 h. The solvent was then removed at reduced pressure to give a pale-yellow oil, which crystallized under vacuum into a hygroscopic solid in quantitative yield. NMR spectroscopy showed two sets of signals corresponding to an 86:14 diastereoisomeric mixture, where the cis isomer is prediminant.

cis-**4**: ^{1}H NMR (DMSO-d_6, 270 MHz) δ 0.90 (s, 9 H), 2.06 (dd, J_1 = 16.4 Hz, J_2 = 10.9 Hz, 1 H), 2.35 (dd, J_1 = 16.4 Hz, J_2 = 5.2 Hz, 1 H), 3.12 (dd, J_1 = 10.9 Hz, J_2 = 5.2 Hz, 1 H), 3.8 (s, 1 H), 3.9 (bs, 1 H), 7.45 (s, 1 H); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ 25.1, 34.1, 36.5, 56.2, 74.6, 172.3, 175.6.

trans-**4**: ^{1}H NMR (DMSO-d_6, 270 MHz) δ 0.86 (s, 9 H), 2.06 (dd, J_1 = 16.4 Hz, J_2 = 10.9 Hz, 1 H), 2.35 (dd, J_1 = 16.4 Hz, J_2 = 5.2 Hz, 1 H), 3.12 (dd, J_1 = 10.9 Hz, J_2 = 5.2 Hz, 1 H), 3.6 (s, 1 H), 3.74 (bs, 1 H), 7.35 (s, 1 H); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ 25.3, 34.1, 35.2, 54.4, 72.0, 176.3.

1-Benzoyl-2(*S*)-*tert*-butyl-6(*S*)-carboxy-perhydropyrimidin-4-one [(2*S*,6*S*)-5]. In a 500-mL round-bottom flask provided with magnetic stirrer, was placed 23.8 g (0.1 mol) of the 86:14 cis-trans mixture of diastereoisomeric **4** in 50 mL of distilled water. An aqueous solution of sodium bicarbonate (8.4 g $NaHCO_3$ in 100 mL of water, 0.1 mol) was added and the reaction flask was submerged in an ice-water bath before the dropwise addition of 12.7 mL (0.11 mol) of benzoyl chloride. The reaction mixture was stirred at 0°C for 1 h and then at ambient temperature for 8 h. Addition of 19 mL of 6 N HCl induced the precipitation of 22.5 g (74% yield) of the *N*-benzoylated cis isomer as an amorphous solid, mp 202-203°C. $[\alpha]_D^{29°C}$ = -107.0 (c = 1, EtOH); ^{1}H NMR (DMSO-d_6, 270 MHz, 100°C) δ 0.94 (s, 9 H), 2.68 (m, 2 H), 4.79 (t, J = 8.9 Hz, 1 H), 5.45 (s, 1 H), 7.44 (bs, 6 H), 8.2 (bs, 1 H); ^{13}C NMR (DMSO-d_6, 67.8 MHz, 100°C) δ 26.3, 31.4, 38.9, 54.0, 68.9, 126.6, 128.4, 129.4, 136.2, 167.4, 171.2, 172.3; MS, *m/z* 304 (M^+), 247, 219, 142, 105, 77.

Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.13; H, 6.63. Found: C, 63.04; H, 6.72.

1-Benzoyl-2(*S*)-*tert*-butyl-2,3-dihydro-4(1H)-pyrimidin-4-one [(*S*)-6]. In a 2-L round-bottom flask provided with magnetic stirrer, 12.48 g (40.77 mmol) of (2*S*,6*S*)-**5** was dissolved in 800 mL of toluene containing 5 mL of pyridine. The resulting solution was treated with 1.64 g (8.2 mmol) of copper diacetate monohydrate in 60 mL of tetrahydrofuran, and the mixture was stirred at ambient temperature for 2 h. The reaction flask was then submerged in an ice-water bath before the addition of 27.3 g (1.5 equiv.) of lead tetra acetate. The cooling bath was removed and the reaction mixture was heated to reflux at 80-90°C for 12 h. The precipitate was removed by filtration, and the filtrate was concentrated to afford a yellow oil. The desired product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give 6.36 g (60% yield) of (*S*)-**6** as a white solid, mp 204-205°C. $[\alpha]_D^{29°C}$ = + 564.5 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.04 (s, 9 H), 5.23 (d, J = 7.9 Hz, 1 H), 5.85 (s, 1 H), 7.15 (d, J = 7.9 Hz, 1 H), 7.50 (s, 5 H), 8.20 (bs, 1 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 25.8, 40.9, 70.3, 104.8, 127.9, 128.9, 131.3, 133.4, 138.7, 164.5, 169.5.

Anal. calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02. Found: C, 69.72; H, 6.94.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-2,3-dihydro-4(1H)-pyrimidin-4-one [(*S*)-7]. In a 250-mL round-bottom flask, provided with magnetic stirrer and under nitrogen atmosphere, 1.65 g (6.38 mmol) of (*S*)-**6** was dissolved in 150 mL of THF. The solution was cooled to -78°C (dry ice/acetone bath) before the dropwise addition of 6.1 mL of 1.15 M *n*-BuLi (7.01 mmol, 1.1 equiv.), and the resulting solution was stirred at -78°C for 2 h and then treated with 0.60 mL (9.57 mmol, 1.5 equiv.) of methyl iodide. The reaction mixture was stirred at -78°C for 2 h and at ambient temperature for 6 h, before quenching with 2.0 mL of aqueous 10% NH_4Cl. The usual workup procedure afforded the crude product which was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give 0.96 g (55% yield) of the pure product as a white solid, mp 137-138°C. $[\alpha]_D^{29°C}$ = +558.0 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.06 (s, 9 H), 3.19 (s, 3 H), 5.31 (d, J = 7.9 Hz, 1 H), 5.82 (s, 1 H), 7.02 (d, J = 7.9 Hz, 1 H), 7.49 (s, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 27.3, 37.6, 41.7, 76.5, 106.8, 127.9, 128.8, 131.3, 133.2, 136.8, 162.9, 169.1. MS, *m/z* 272 (M^+), 215, 105, 77, 42.

Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.55; H, 7.40. Found: C, 70.70; H, 7.45.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one [(*S*)-1]. Heterocycle (*S*)-**7** (2.18 g, 8.0 mmol), 45 mL of ethyl acetate, 0.436 g of 5% Pd(C), and 0.2 mL of acetic acid were placed in a hydrogenation flask. The reaction mixture was pressurized to 75 atm of hydrogen, heated to 45°C, and stirred for 24 h. The catalyst was then removed by filtration over celite, the filtrate was washed with aqueous, saturated $NaHCO_3$, dried over anh. Na_2SO_4, filtered, and evaporated at reduced pressure to give 2.15 g (98% yield) of the desired product, which crystallyzed into a solid, mp 98-99°C. $[\alpha]_D^{29°C}$ = + 50.0 (c = 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz) δ 1.17 (s, 9 H), 2.54 (m, 2 H), 3.17 (s, 3 H), 3.77 (m, 2 H), 5.87 (s, 1 H), 7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 28.0, 29.8, 37.6, 39.0, 41.7, 73.7, 126.6, 128.6, 130.1, 135.0, 167.0, 170.4; MS, *m/z* 274 (M^+), 217, 203, 105, 77.

Anal. calcd for $C_{16}H_{22}N_2O_2$: C, 70.04, H, 8.08. Found: C, 70.15; H, 8.13.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*R*)-methylperhydropyrimidin-4-one [(2*S*,5*R*)-8]. The general procedure was followed for the alkylation of 1.0 g (3.6 mmol) of (*S*)-**1** with 0.26 mL (4.14 mmol) of CH_3I. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 7:3) afforded 0.8 g (77% yield) of (2*S*,5*R*)-**8**, mp 121-122°C. IR 1650, 1458, 1283 cm^{-1}; $[\alpha]_D^{29°C}$ = + 39.5 (c = 1, $CHCl_3$): ^1H NMR ($CDCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.10 (d, J = 7.3 Hz, 3 H), 1.19 (s, 9 H), 2.64 (m, 1 H), 3.15 (s, 3 H), 3.40 (dd, J_1 = 13.2 Hz, J_2 = 4.6 Hz, 1 H), 3.90 (dd, J_1 = 13.2 Hz, J_2 = 7.3 Hz, 1 H), 5.92 (s, 1 H), 7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 17.6, 28.4, 34.7, 37.9, 39.5, 49.4, 74.4, 126.9, 128.7, 130.1, 135.5, 171.1, 171.6; MS, *m/z* 288 (M^+), 231, 105, 77.

Anal. calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39. Found: C, 70.62; H, 8.59.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*R*)-*n*-butylperhydropyrimidin-4-one [(2*S*,5*R*)-10]. The general procedure was followed for the alkylation of 1.0 g (3.6 mmol) of (*S*)-**1** with 0.47 mL (4.1 mmol) of *n*-BuI. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 7:3) afforded 0.9 g (75% yield) of (2*S*,5*R*)-**10**, mp 80-81°C. $[\alpha]_D^{29°C}$ = + 26.7 (c = 1, $CHCl_3$) IR 1542, 1433, 1200 cm^{-1}; ^1H NMR

($CDCl_3$, 270 MHz) δ 0.74 (t, J = 7.3 Hz, 3 H), 0.8-1.15 (m, 6 H), 1.19 (s, 9 H), 2.36 (m, 1 H), 3.13 (s, 3 H), 3.63 (dd, J_1 = 13.5 Hz, J_2 = 3.2 Hz, 1 H), 3.82 (dd, J_1 = 13.5 Hz, J_2 = 6.6 Hz, 1 H), 5.89 (s, 1 H), 7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 13.7, 22.3, 28.4, 28.9, 31.4, 37.7, 39.1, 40.3, 45.7, 73.7, 126.9, 128.6, 130.0, 135.1, 170.7, 171.2; MS, *m/z* 330 (M^+), 273, 105, 77.

Anal. calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15. Found: C, 72.71; H, 9.25.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*R*)-*n*-hexylperhydropyrimidin-4-one (2*S*,5*R*)-11]. The general procedure was followed for the alkylation of 0.69 g (2.5 mmol) of (*S*)-**1** with 0.43 mL (4.1 mmol) of *n*-$C_6H_{13}I$. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 7:3) afforded 0.72 g (80.0% yield) of (2*S*,5*R*)-**11**, mp 70-71°C. $[\alpha]_D^{29°C}$ = + 31.2 (c = 1, $CHCl_3$): IR 1642, 1466, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.83 (t, J = 6.7 Hz, 3 H), 0.92-1.42 (m, 8 H), 1.19 (s, 9 H), 1.68 (m, 2 H), 2.35 (m, 1 H), 3.13 (s, 3 H), 3.64 (dd, J_1 = 13.9 Hz, J_2 = 3.7 Hz, 1 H), 3.81 (dd, J_1= 13.9 Hz, J_2 = 5.9 Hz, 1 H), 5.89 (s, 1 H), 7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 13.9, 22.4, 26.8, 28.3, 28.9, 31.4, 31.6, 37.7, 39.1, 40.3, 45.6, 73.6, 126.9, 128.5, 130.0, 135.1, 170.7, 171.2; MS, *m/z* 358 (M^+), 301, 197, 105, 83.

Anal. calcd for $C_{22}H_{34}N_2O_2$: C, 73.69; H, 9.55. Found: C, 73.55; H, 9.80.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*R*)-benzylperhydropyrimidin-4-one [(2*S*,5*R*)-12]. The general procedure was followed for the alkylation of 0.75 g (2.73 mmol) of (*S*)-**1** with 0.38 mL (3.14 mmol) of benzyl bromide. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 7:3) afforded 0.73 g (80% yield) of (2*S*,5*R*)-**12**, mp 173-174°C. $[\alpha]_D^{29°C}$ = -64.0 (c = 1, $CHCl_3$); IR 1550, 1425, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.17 (s, 9 H), 2.31 (m, 1 H), 2.66 (m, 1 H), 3.19 (s, 3 H), 3.25 (m, 1 H), 3.62 (m, 2 H), 5.94 (m, 1 H), 6.61 (m, 2 H), 7.05 (m, 3 H) 7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 28.2, 37.7, 37.9, 39.1, 42.1, 45.0, 73.8, 126.2, 127.5, 128.3, 128.6, 128.8, 130.3, 134.7, 138.6, 170.2, 170.5; MS, *m/z* 364 (M^+), 307, 167, 105, 83.

Anal. cald for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74. Found: C, 75.75; H, 7.83.

General Procedure for the Epimerization at C(5) of Pyrimidin-4-ones 8, 10-12 → 20-23. Lithium diisopropylamide solution is prepared according to the procedure described above for the alkylation of pyrimidinones, and then one equivalent of the alkylated pyrimidinone (**8**, **10-12**) in THF is added at -78°C. The resulting solution of the enolate is stirred at this temperature for 2 h and then 20% aqueous NH_4Cl is added. The usual workup procedure affords the epimerized product (**20-23**), which is purified by flash chromatography.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*S*)-methylperhydropyrimidin-4-one [(2*S*,5*S*)-20]. The epimerization procedure was followed with 1.16 g (3.5 mmol) of (2*S*,5*R*)-**8** and 0.51 mL (3.6 mmol) of diisopropylamine. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to afford 0.85 g (85% yield) of (2*S*,5*S*)-**20**, mp 108-109°C. $[\alpha]_D^{29°C}$ = + 33.5 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.17 (s, 9 H), 1.25 (d, J = 7.3 Hz, 3 H), 2.40 (m, 1 H), 3.15 (s, 3 H), 3.42 (dd, J_1 = 13.2 Hz, J_2 = 4.6 Hz, 1 H), 3.86 (dd, J_1 = 13.2 Hz, J_2 = 7.3 Hz, 1 H), 5.86 (s, 1 H), 7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.6, 28.4, 29.7, 37.5, 40.3, 46.2, 73.5, 126.3, 128.6, 134.9, 140.0, 171.1, 171.6.

Anal. calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39. Found: C, 70.62; H, 8.59.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*S*)-*n*-butylperhydropyrimidin-4-one [(2*S*,5*S*)-21]. The epimerization procedure was followed with 1.0 g (3.0 mmol) of (2*S*,5*R*)-**10** and 0.45 mL (3.18 mmol) of diisopropylamine. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to afford 0.85 g (85% yield) of (2*S*,5*S*)-**21**, mp 64-65°C. $[\alpha]_D^{29°C}$ = + 18.7 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.84 (t, J = 6.8 Hz, 3 H), 1.14 (m, 6 H), 1.17 (s, 9 H), 2.43 (m, 1 H), 3.14 (s, 3 H), 3.40 (m, 1 H), 3.86 (m, 1 H), 5.82 (s, 1 H), 7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 13.5, 22.1, 28.2, 28.4, 29.1, 37.2, 37.6, 40.1, 46.0, 73.3, 126.6, 128.4, 129.7, 134.6, 169.6, 170.2.

Anal. calcd for $C_{20}H_{30}N_2O_2$: C, 72.68; H, 9.15. Found: C, 72.45; H, 9.07.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*S*)-*n*-hexylperhydropyrimidin-4-one [(2*S*,5*S*)-22]. The epimerization procedure was followed with 1.0 g (2.6 mmol) of (2*S*,5*R*)-**11** and 0.39 mL (2.75 mmol) of diisopropylamine. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to afford 0.9 g (90% yield) of (2*S*,5*S*)-**22**, mp 94-95°C. $[\alpha]_D^{29°C}$ = + 20.7 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.83 (t, J = 6.8 Hz, 3 H), 1.15 (m, 10 H), 1.17 (s, 9 H), 2.38 (m, 1 H), 3.12 (s, 3 H), 3.37 (t, J = 6.8 Hz, 1 H), 3.80 (dd, J_1 = 16.0 Hz, J_2 = 9.6 Hz, 1 H), 5.84 (s, 1 H), 7.38 (m, 2 H), 7.45 (m, 3 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.0, 22.5, 26.6, 28.6, 29.0, 29.7, 31.5, 37.5, 37.6, 40.4, 46.4, 73.7, 126.5, 128.8, 130.1, 135.0, 170.0, 170.7.

Anal. calcd for $C_{22}H_{34}N_2O_2$: C, 73.69; H, 9.55. Found: C, 73.70; H, 9.55.

1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*S*)-benzylperhydropyrimidin-4-one [(2*S*,5*S*)-23]. The epimerization procedure was followed with 1.0 g (2.74 mmol) of (2*S*,5*R*)-**12** and 0.4 mL (2.88 mmol) of diisopropylamine. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to afford 0.88 g (88% yield) of (2*S*,5*S*)-**23**, mp 98-98.5°C. $[\alpha]_D^{29°C}$ = -6.4 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99 (s, 9 H), 2.85 (m, 2 H), 3.14 (s, 3 H), 3.30 (m, 2 H), 3.58 (m, 1 H), 5.79 (s, 1 H), 7.13 (m, 2 H), 7.27 (m, 3 H), 7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 28.3, 34.8, 37.5, 37.6, 41.9, 45.3, 73.8, 126.2, 126.5, 128.4, 128.6, 128.9, 129.9, 134.6, 137.7, 169.6, 170.0.

Anal. calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74. Found: C, 75.83; H, 8.00.

General Procedure for the Hydrolysis of the Alkylated Pyrimidinones 8, 10-12, and 20-23. A suspension of 2.0 mmol of adduct in 15 mL of 6 N HCl was heated in a sealed ampule to 90-100°C for 8 h. The solution was then allowed to cool to ambient temperature and the precipitate of benzoic acid removed by filtration. The filtrate was extracted with two 30-mL portions of CH_2Cl_2 and the aqueous phase was concentrated at reduced pressure to afford a 1:1 mixture of the amino acid hydrochloride and methylammonium chloride, which was adsorbed to acidic ion-exchange resin Dowex 50W X8. The resin was washed with distilled water till the washings came out neutral, and then the free amino acid was recovered with 1 N ammonium hydroxyde. Evaporation afforded the free amino acid, which was dried under high vacuum at 40°C.

(R)-(-)-α-Methyl-β-aminopropionic Acid [(*R*)-9]. Derivative (2*S*,5*R*)-**8** (0.5 g, 1.73 mmol) was hydrolyzed according to the general procedure to afford 0.14 g (80% yield) of pure, free amino acid (*R*)-**9**, mp

185-186°C. $[\alpha]_D^{29°C}$ = -11.8 (c = 1, 1 N HCl); ^{1}H NMR (D_2O, 270 MHz) δ 1.10 (d, J = 7.3 Hz, 3 H), 2.51 (ddq, J_1 = 5.4 Hz, J_2 = 7.3 Hz, J_3 = 7.3 Hz, 1 H), 2.92 (dd, J_1 = 12.2 Hz, J_2 = 5.4 Hz, 1 H), 3.01 (dd, J_1 = 12.2 Hz, J_2 = 7.3 Hz, 1 H); ^{13}C NMR (D_2O, 67.8 MHz) δ 24.9, 49.0, 52.2, 191.4.

(*R*)-(+)-α-*n*-Butyl-β-aminopropionic Acid [(*R*)-13]. Derivative (2*S*,5*R*)-**10** (0.75 g, 2.27 mmol) was hydrolyzed according to the general procedure to afford 0.26 g (80% yield) of pure, free amino acid (*R*)-**13**, mp 170-171°C. $[\alpha]_D^{29°C}$ = +5.3 (c = 1, 1N HCl); ^{1}H NMR (D_2O, 90 MHz) δ 0.68 (m, 3 H), 1.10 (m, 6 H), 2.25 (m, 2 H), 2.80 (m, 2 H); ^{13}C NMR (D_2O, 22.49 MHz) δ 14.4, 23.1, 29.6, 30.8, 42.3, 46.5, 182.2.

(*R*)-(+)-α-*n*-Hexyl-β-aminopropionic Acid [(*R*)-14]. Derivative (2*S*,5*R*)-**11** (0.59 g, 1.54 mmol) was hydrolyzed according to the general procedure to afford 0.21 g (80% yield) of pure, free amino acid (*R*)-**14**, mp 219-220°C. $[\alpha]_D^{29°C}$ = + 6.6 (c =1, 1 N HCl); ^{1}H NMR (D_2O, 90 MHz) δ 0.72 (m, 3 H), 1.20 (m, 8 H), 1.57 (m, 2 H), 2.7 (m, 1 H), 3.10 (m, 2 H); ^{13}C NMR (D_2O, 22.49 MHz) δ 14.5, 23.0, 26.1, 29.3, 30.4, 31.9, 41.1, 43.8, 178.4.

(*R*)-(+)-α-Benzyl-β-aminopropionic Acid [(*R*)-15]. Derivative (2*S*,5*R*)-**12** (0.60 g, 1.65 mmol) was hydrolyzed according to the general procedure to afford 0.25 g (85% yield) of pure, free amino acid (*R*)-**15**, mp 225-226°C. $[\alpha]_D^{29°C}$ = + 11.3 (c = 1, 1 N HCl); ^{1}H NMR (D_2O, 270 MHz) δ 2.88 (m, 2 H), 3.04 (m, 3 H), 7.35 (m, 5 H); ^{13}C NMR (D_2O, 67.8 MHz) δ 46.0, 50.5, 56.8, 136.5, 138.5, 138.8, 148.4, 189.4.

(*S*)-(+)-α-Methyl-β-aminopropionic Acid [(*S*)-9]. Derivative (2*S*,5*S*)-**20** (0.49 g, 1.69 mmol) was hydrolyzed according to the general procedure to afford 0.14 g (80% yield) of pure, free amino acid (*S*)-**9**, mp 184-185°C. $[\alpha]_D^{29°C}$ = + 11.6 (c = 1, 1N HCl); ^{1}H NMR and ^{13}C NMR spectra are similar to those described for (*R*)-**9**.

(*S*)-(-)-α-*n*-Butyl-β-aminopropionic Acid [(*S*)-13]. Derivative (2*S*,5*S*)-**21** (0.46 g, 1.36 mmol) was hydrolyzed according to the general procedure to afford 0.16 g (80% yield) of pure, free amino acid (*S*)-**13**, mp 169-170°C. $[\alpha]_D^{29°C}$ = -5.0 (c = 1, 1 N HCl); ^{1}H and ^{13}C NMR spectra are similar to those described for (*R*)-**13**.

(*S*)-(-)-α-*n*-Hexyl-β-aminopropionic Acid [(*S*)-14]. Derivative (2*S*,5*S*)-**22** (0.50 g, 1.3 mmol) was hydrolyzed according to the general procedure to afford 0.19 g (85% yield) of pure, free amino acid (*S*)-**14**, mp 219-220°C. $[\alpha]_D^{29°C}$ = -6.3 (c = 1, 1 N HCl); ^{1}H and ^{13}C NMR spectra are similar to those described for (*R*)-**14**.

(*S*)-(-)-α-Benzyl-β-aminopropionic Acid [(*S*)-15]. Derivative (2*S*,5*S*)-**23** (0.54 g, 1.48 mmol) was hydrolyzed according to the general procedure to afford 0.22 g (85% yield) of pure, free amino acid (*S*)-**15**, mp 224-225°C. $[\alpha]_D^{29°C}$ = -11.0 (c = 1, 1 N HCl); ^{1}H and ^{13}C NMR spectra are similar to those described for (*R*)-**15**.

General Procedure for the *N*-Benzoylation and Esterification of β-Amino Acids 9 and 13-15. In a 25-mL round-bottom flask, provided with magnetic stirrer, was placed 2 mmol of the free amino acid in 3.0 mL of distilled water. The solution was cooled to 0°C, treated with 1.0 mL of 5 N NaOH, and stirred for 10 min before the simultaneous addition of 1.1 equiv. of benzoyl chloride and 1.5 mL of 2 N NaOH. The reaction

mixture was stirred at 0°C for 1 h and at ambient temperature for 5 h. The reaction was quenched by the addition of 6 N HCl to pH = 3, the *N*-benzoylated product was extracted with ethyl acetate and worked up the usual way. The crude product was dissolved in 5 mL of dry methanol and cooled to 0°C before the slow addition of 1.5 equiv. of chlorotrimethylsilane (TMSCl). The resulting solution was stirred at 0°C for 1.5 h and at ambient temperature for 6 additional hours. Evaporation afforded then the *N*-benzoylated methyl ester, which was purified by flash chromatography (*n*-hexane/ethyl acetate, 9:1).

Methyl *N*-benzoyl-2(*R*)-methyl-3-aminopropionate [(*R*)-16]. The general procedure was followed with 143 mg (1.38 mmol) of (*R*)-**9**, 0.18 mL of benzoyl chloride, and 0.26 mL of TMSCl to give 187 mg (75% yield) of (*R*)-**16**, mp 70-71°C. $[\alpha]_D^{29°C}$ = -20.2 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.25 (d, J = 7.3 Hz, 3 H), 2.85 (m, 1 H), 3.52 (m, 2 H), 3.71 (s, 3 H), 6.86 (b, 1 H), 7.46 (m, 3 H), 7.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.9, 39.4, 42.0, 51.9, 126.9, 128.5, 131.4, 134.4, 167.5, 176.2.

Methyl *N*-benzoyl-2(*S*)-methyl-3-aminopropionate [(*S*)-16]. The general procedure was followed with 139 mg (1.35 mmol) of (*S*)-**9**, 0.18 mL of benzoyl chloride, and 0.25 mL of TMSCl to give 175 mg (70% yield) of (*S*)-**16**, mp 69.5-71°C. $[\alpha]_D^{29°C}$ = + 19.7 (c = 1, $CHCl_3$); ^1H and ^{13}C NMR spectra are similar to those described for (*R*)-**16**.

Methyl *N*-benzoyl-2(*R*)-*n*-butyl-3-aminopropionate [(*R*)-17]. The general procedure was followed with 247 mg (1.7 mmol) of (*R*)-**13**, 0.22 mL of benzoyl chloride, and 0.33 mL of TMSCl to give 336 mg (75% yield) of (*R*)-**17**, mp 67-68°C. $[\alpha]_D^{29°C}$ = + 8.5 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.35 (m, 4 H), 1.65 (m, 2 H), 2.74 (m, 1 H), 3.59 (m, 2 H), 3.72 (s, 3 H), 6.73 (b, 1 H), 7.45 (m, 3 H), 7.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 13.9, 22.5, 29.2, 29.6, 40.6, 44.9, 51.9, 126.9, 128.6, 131.5, 134.5, 167.4, 176.1.

Anal. calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04. Found: C, 68.08; H, 8.06.

Methyl *N*-benzoyl-2(*S*)-*n*-butyl-3-aminopropionate [(*S*)-17]. The general procedure was followed with 152 mg (1.05 mmol) of (*S*)-**13**, 0.14 mL of benzoyl chloride, and 0.19 mL of TMSCl to give 133 mg (70% yield) of (*S*)-**17**, mp 66.5-68°C. $[\alpha]_D^{29°C}$ = -8.3 (c = 1, $CHCl_3$); ^1H and ^{13}C NMR spectra are similar to those described for (*R*)-**17**.

Anal. calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04. Found: C, 68.62; H, 8.25.

Methyl *N*-benzoyl-2(*R*)-*n*-hexyl-3-aminopropionate [(*R*)-18]. The general procedure was followed with 187 mg (1.08 mmol) of amino acid (*R*)-**14**, 0.14 mL of benzoyl chloride, and 0.20 mL of TMSCl, to give 252 mg (80% yield) of (*R*)-**18**, mp 65-66°C. $[\alpha]_D^{29°C}$ = + 11.3 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (t, J = 7.0 Hz, 3 H), 1.27 (m, 8 H), 1.64 (m, 2 H), 2.78 (m, 1 H), 3.57 (m, 2 H), 3.71 (s, 3 H), 6.72 (b, 1 H), 7.46 (m, 3 H), 7.76 (m, 2 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.0, 22.5, 27.0, 29.1, 29.9, 31.6, 40.6, 44.9, 51.8, 126.9, 128.5, 131.4, 134.3, 167.5, 176.0.

Anal. calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65. Found: C, 69.97; H, 8.78.

Methyl *N*-benzoyl-2(*S*)-*n*-hexyl-3-aminopropionate [(*S*)-18]. The general procedure was followed with 158 mg (0.91 mmol) of amino acid (*S*)-**14**, 0.12 mL of benzoyl chloride, and 0.18 mL of TMSCl, to give

213 mg (80% yield) of (*S*)-**18**, mp 65-66°C. $[\alpha]_D^{29°C}$ = -10.6 (c = 1, $CHCl_3$); ^1H and ^{13}C NMR spectra are similar to those described for (*R*)-**18**.

Methyl *N*-benzoyl-2(*R*)-benzyl-3-aminopropionate [(*R*)-19]. The general procedure was followed with 236 mg (1.3 mmol) of amino acid (*R*)-**15**, 0.17 mL of benzoyl chloride, and 0.25 mL of TMSCl, to give 315 mg (80% yield) of (*R*)-**19**, mp 78-79°C. $[\alpha]_D^{29°C}$ = +15.6 (c =1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.90 (m, 1 H), 3.08 (m, 2 H), 3.62 (m, 2 H), 3.66 (s, 3 H), 6.67 (b, 1 H), 7.21 (m, 5 H), 7.41 (m, 3 H), 7.71 (m, 2 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 36.2, 40.5, 46.6, 51.9, 126.7, 126.9, 128.6, 128.6, 128.9, 131.5, 134.4, 138.1, 167.4, 175.0.

Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44. Found: C, 72.86; H, 6.62.

Methyl *N*-benzoyl-2(*S*)-benzyl-3-aminopropionate [(*S*)-19]. The general procedure was followed with 211 mg (1.18 mmol) of amino acid (*S*)-**15**, 0.15 mL of benzoyl chloride, and 0.23 mL of TMSCl, to give 279 mg (80% yield) of (*S*)-**19**, mp 77.5-79°C. $[\alpha]_D^{29°C}$ = -15.0 (c = 1, $CHCl_3$); ^1H and ^{13}C NMR spectra are similar to those described for (*R*)-**19**.

Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44. Found: C, 72.69; H, 6.57.

Acknowledgments. We are grateful to G. Uribe and V. González-Díaz for recording some of the NMR spectra, to the Comission of the European Communities (Contract No. CI1*.0558 ME-JR) and to CONACYT for financial support, and to Dr. M. Ordóñez for a careful revision of the manuscript.

References and Notes

1. For part 6, see: Escalante, J.; Juaristi, E. *Tetrahedron Lett.* **1995**, *36*, 4397.
2. A preliminary report of this work was published: Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723.
3. See, for example: (a) Spatola, A.F. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B. (Ed.) Marcel Dekker: New York, 1983; Vol. 7, pp 331-333. (b) Drey, C.N.C. In *Chemistry and Biochemistry of Amino Acids*; Barrett, G.C. (Ed.) Chapman and Hall: London, 1985.
4. See, for example: (a) Georg, G.I. (Ed.) *Organic Chemistry of β-Lactams*, VCH Publishers: New York, 1992. (b) Page, M.I. (Ed.) *The Chemistry of β-Lactams*, Chapman and Hall: London, 1992.
5. Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. (b) Cole, D.C. *Tetrahedron* **1994**, *50*, 9517. (c) Juaristi, E. (Ed.) *Enantioselective Synthesis of β-Amino Acids*, VCH Publishers: New York, in press.
6. Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553.
7. The axial orientation of the *tert*-butyl group in **1** is due to the so-called $A^{1,3}$ strain: 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.

8. Limited amounts of both enantiomers of **1** became first available via preparative resolution by recycling chromatography on *chiraspher*: Kinkel, J.; Gysel, U.; Blaser, D.; Seebach, D. *Helv. Chim. Acta* **1991**, *74*, 1622. We are grateful to these researchers for a sample of the resolved material.
9. (a) Fitzi, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 345. (b) See, also: Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.
10. Juaristi, E.; Rizo, B.; Natal, V.; Escalante, J.; Regla, I. *Tetrahedron: Asymmetry* **1991**, *2*, 821.
11. (a) Chu, K.S.; Negrete, G.R.; Konopelski, J.P.; Lakner, F.J.; Woo, N.-T.; Olmstead, M.M. *J. Am. Chem. Soc.* **1992**, *114*, 1800. (b) See also: Hardy, P.M.; Samworth, D.J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1954.
12. The 98% overall yield for these two steps reported in reference 2 is in error.
13. McMurry, J.E.; Blaszczack, L.C. *J. Org. Chem.* **1974**, *39*, 2217.
14. Alternatively, decarboxylation can be achieved by electrolysis: (a) Lakner, F.J.; Chu, K.S.; Negrete, G.R.; Konopelski, J.P. *Org. Synth.* **1995**, *73*, 201. (b) See, also: Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401. (c) Lamatsch, B.; Quintana, D. Unpublished results.
15. The absolute configuration of (-)-α-methyl-β-alanine is known: Balenovic, K.; Bregant, N. *Tetrahedron* **1959**, *5*, 44.
16. Further confirmation of the absolute configuration in (+)-**1** comes from the X-ray crystallographic structure of *cis*-**12**: Molins, E. Unpublished observations.
17. Specific rotations and physical and spectroscopic properties of the free amino acids are usually sensitive to conditions of measurement; see, for example: Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396.
18. Brown, H.C.; Kramer, G.W.; Levy, A.B.; Midland, M.M. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p 256.
19. Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J.S. *J. Org. Chem.* **1983**, *48*, 2603.
20. Still, W.C.; Kahn, M.; Mitra, A., *J. Org. Chem.* **1978**, *43*, 2923.

(*Received in USA* 26 *March* 1996; *accepted* 1 *June* 1996)