Highly Diastereoselective Alkylation of Perhydropyrimidin-4-ones Directed toward the Synthesis of α-Substituted β-Amino Acids. 2

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Received June 14, 1994®

The alkylation of several enantiomerically pure perhydropyrimidin-4-ones at C_5 is described. For the methylation reaction, mixtures of 5,6-*trans*- and *cis*-disubstituted adducts were obtained with high diastereomeric ratios, whereas only the 5,6-*trans*-disubstituted products were obtained with larger alkylating agents. The dialkylation reaction at C_5 was also studied, and the 5,6-*cis*-trisubstituted product was preferentially formed. Acidic hydrolysis of 5,6-*trans*-disubstituted perhydropyrimidin-4-ones furnished the corresponding β-amino acid hydrochlorides in quantitative yield. On cyclization of the amino acids, 5,6-*trans*-disubstituted azetidin-2-ones were also synthesized.

Introduction

The past few years have brought increased interest in β-amino acids. This is due to the wide utility of these compounds, in that many classes of natural products, such as taxane alkaloids and depsipeptides from marine organisms, contain β-amino acids as active fragments.[1] Moreover, since the discovery of 1β-methyl carbapenem, much attention has been paid to the synthesis of enantiopure β-amino acids as starting materials for the synthesis of antibiotics. Only a few approaches to the synthesis of enantiomerically pure α-substituted β-amino acids, including enantioselective additions to imines[3] and the alkylation of perhydropyrimidin-4-ones, have been reported.[2-4] Recently, the highly stereoselective conjugate addition of lithium and magnesium chiral amides to esters, followed by electrophilic quenches, has been successfully performed.[5]

We have recently reported the alkylation of (1′*S*,6*R*)- and (1′*S*,6*S*)-3-(1′-phenylethyl)-6-methylperhydropyrimidin-4-ones, which produced 5-substituted 6-methylperhydropyrimidin-4-ones, useful precursors to α-substituted β-amino acids, with high 1,2-*trans* selectivity.[6] Furthermore, by means of difference NOE experiments performed on the starting material and on the alkylated products, the conformation of the heterocycles was established (Figure 1).

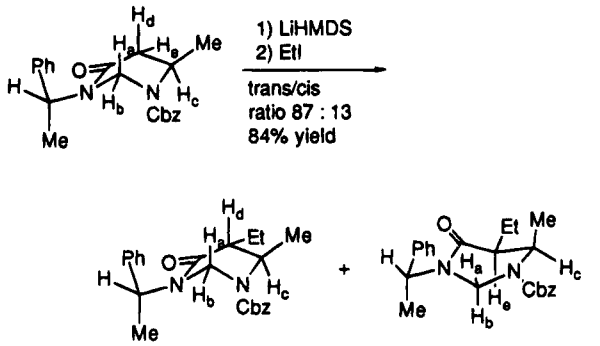

Figure 1.

Here we report details of a study wherein several 6-substituted perhydropyrimidin-4-ones were subjected to alkylation in order to analyze how the bulkiness of the substituent at C_6 and the electrophile affect the diastereoselectivity of the alkylation reaction. In particular, interesting results of the diastereoselective dialkylation at C_5 are described. Moreover, we describe a general method for the synthesis of *anti* α-substituted β-amino acids, which are easily transformed into the corresponding 3,4-*trans*-disubstituted azetidin-2-ones.

In exploring suitable ways to obtain the heterocyclic starting materials in multigram quantities, we chose the preparation of racemic β-amino acids by addition of 2 equiv of free hydroxylamine to alk-2-enoic acids in ethanol at reflux, following a well-known procedure described by Steiger for cinnamic acid.[7] The hydroxylamine behaves both as nucleophile and reducing agent for the 3-(hydroxylamino) intermediate. Although the reaction occurs with low yield, the availability of the reagents makes this old reaction still attractive (Scheme 1).[8]

Starting from pent-2-enoic acid, hex-2-enoic acid, and cinnamic acid, following this method, β-amino acids were obtained and protected at the nitrogen with benzyl chloroformate. The products **1a**, **1b**, and **1c** were transformed into the corresponding (*S*)-phenylethylamido

® Abstract published in *Advance ACS Abstracts,* November 1, 1994.

(1) See, for example: (a) Total and semi-synthetic approaches to Taxol. *Tetrahedron* **1992**, *48*, Symposia in Print no. 48, 6593. (b) Fredenhagen, A.; Tamura, S. Y.; Kenny, P. T. M.; Komura, H.; Naya, Y.; Nakanishi, K.; Nishiyama, K.; Sugiura, M.; Kita, H. *J. Am. Chem. Soc.* **1987**, *109*, 4409. (c) Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749.

(2) (a) Andrés, C.; Gonzàlez, A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*, 2895. (b) Feringa, B. L., de Lange B. *Tetrahedron Lett.* **1988**, *29*, 1303. (c) d'Angelo, J., Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.

(3) (a) Enders, D.; Klatt, M.; Funk, R. *Synlett* **1993**, 226. (b) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287. (c) Noyori, R.; Lubell, W. D.; Kitamura, M. *Tetrahedron: Asymmetry* **1991**, *2*, 543.

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(5) (a) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1660. (b) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Synlett* **1994**, 117. (c) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Walters, I. A. S. *Tetrahedron: Asymmetry* **1993**, *5*, 35. (d) Hawkins, J. M.; Lewis, T. *J. Org. Chem.* **1994**, *59*, 649.

(6) Amoroso, R.; Cardillo, G.; Tomasini, C. *Tetrahedron Lett.* **1992**, *33*, 2725.

(7) Steiger, R. E. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 664.

(8) On the other hand we have recently reported the addition of hydroxylamine to α,β-unsaturated amide, which exclusively affords the corresponding 3-hydroxylamino intermediate: Braschi, I.; Cardillo, G.; Tomasini, C. *Tetrahedron* **1994**, *50*, 2955.

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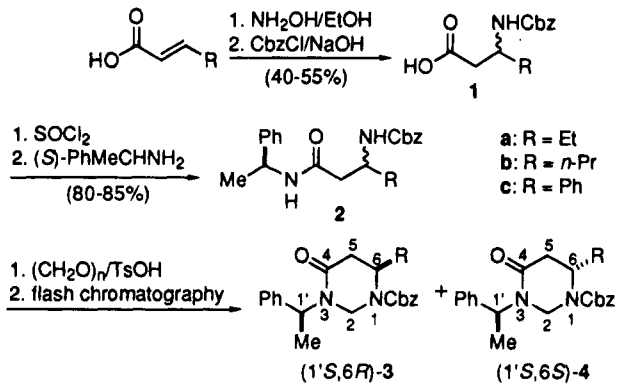
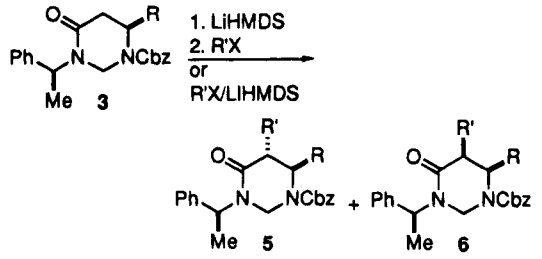
Scheme 1



Scheme 2



derivatives **2a**, **2b**, and **2c**. These steps occur in a short time with good yield and under mild conditions. The corresponding perhydropyrimidin-4-ones **3** and **4** were easily obtained by treatment with paraformaldehyde and *p*-toluenesulfonic acid in benzene at reflux[9] and fully separated by flash chromatography. Unfortunately, the separation of perhydropyrimidin-4-ones **3c** and **4c** failed, so the products were subjected to alkylation as a 1:1 diastereomeric mixture.

Results and Discussion

A. Alkylation of Perhydropyrimidin-4-ones 3 and 4. α-Methyl β-amino acids are becoming of great interest because they are components of a number of molecules that display interesting biological properties. For instance, (2*S*,3*R*)-2-methyl-3-aminopentanoic acid has been isolated as a hydrolysis fragment of several biologically interesting natural products: the marine peptide antifungal agents majuscolamide C and 57-normajascolamide C and the antitumor agents dolastatins 11 and 25.[5b,10] Thus, we have studied the methylation reaction at C_5 of perhydropyrimidin-4-ones in some detail.

Perhydropyrimidin-4-one **3a** was submitted to the methylation reaction (Scheme 2) under the different reaction conditions reported in Table 1.

For **3a**, while with method A (entry 1) the diastereomeric ratio is more satisfactory than with method B (entry 2), the reaction yield proved to be poorer. Perhydropyrimidin-4-one **3b** (entry 3) has the same behavior as **3a** (entry 2), while **3c** gives rise to better diastereoselection but a lower yield (entry 4). A variety of reaction conditions (temperature, time, equivalents of alkylating agents) were explored for this alkylation, but none led to greater selectivity and/or reaction yield than those reported in Table 1. Moreover, by reacting a *trans/cis* diastereomeric mixture with LiOH in methanol at reflux for 2 h, only 5,6-*trans* disubstituted products were obtained.

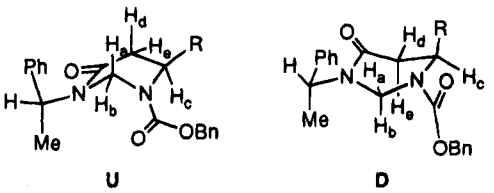


Figure 2.

Establishing the structural and stereochemical assignments of mono- and disubstituted perhydropyrimidin-4-ones proved to be a major part of the work. In previous publications, we developed a useful technique to assign the absolute configuration of C_6 of perhydropyrimidin-4-ones by means of ^1H NMR spectroscopy and difference NOE analysis.[11] We noticed that the semirigid heterocycle can assume two different half-boat conformations, U and D, depending on the ring substituents (Figure 2). Thus, we observed that H_a is always more shielded than H_b when the half-boat has U conformation, while H_b is always more shielded than H_a in the D conformation. Moreover, the window for H_a and H_b is larger for U than for D. As a consequence of these observations, the relative configuration of C_6 can be deduced.

In order to determine the relative configuration of C_5 after the alkylation reaction, three methods can be utilized. First, if both isomers are obtained, the coupling constants $J_{Hc,Hd}$ and $J_{Hc,He}$ can be compared. In fact, the *cis* coupling constant is always smaller than the *trans* coupling constant, which is usually greater than 6 Hz. Moreover, the chemical shift of H_d and/or H_e is always diagnostic. In fact, in every perhydropyrimidin-4-one, owing to the effect of the vicinal side chain, the hydrogen at C_5 *cis* to the substituent at C_6 is always more shielded than the *trans* hydrogen, regardless of the nature of the substituent at C_6 and the conformation of the heterocycle.

Finally, by means of difference NOE experiments, the configuration can usually be established. For instance, for products **5a** and **6a**, difference NOE experiments furnished the following results (Figure 3): on irradiation of Me at C_5 a large NOE enhancement (5.4%) of H_c occurred, indicating the *cis* relation between Me and H_c for **5a**. Likewise, on irradiation of H_d in **5a**, a small enhancement (2.0%) was observed for H_c, while a large NOE enhancement (5.4%) of H_c was observed on irradiation of H_e for **6a**.

Table 1. Diastereomeric Products Ratios and Chemical Yields for the Methylation Reaction of Perhydropyrimidin-4-ones 3a, 3b, and 3c

entry	starting material	products	R	R′	temp[a] (°C)	time[a] (h)	alkylating agent (equiv)	yield (%)	*trans/cis* ratio **5/6**
1	**3a**	**5a + 6a**	Et[b]	Me	−78 to rt	20	MeI (6)	60	84:16
2	**3a**	**5a + 6a**	Et[c]	Me	−20	2	Me_2SO_4 (2)	80	78:22
3	**3b**	**5b + 6b**	*n*-Pr[c]	Me	−20	2	Me_2SO_4 (2)	81	78:22
4	**3c**	**5c + 6c**	Ph[c]	Me	−20	2	Me_2SO_4 (2)	50	92:8

[a] Time and temperature refer to the alkylation. [b] The formation of the enolate was performed with 1 equiv of LiHMDS at 0 °C for 1 h, and then the alkylating agent was introduced (method A). [c] The base (LiHMDS) was introduced in the presence of the alkylating agent (method B).

Table 2. Diastereomeric Products Ratios and Chemical Yields for the Methylation Reaction of Perhydropyrimidin-4-ones 4a, 4b, and 4c

entry	starting material	products[a]	R	R'	time (h)	alkylating agent (equiv)	yield (%)	*trans/cis* ratio **7/8**	dialkylated (%)
1	**4a**	**7a + 8a**	Et	Me	2	Me_2SO_4 (2)	66	80:20	3
2	**4a**	**7a + 8a**	Et	Me	3	Me_2SO_4 (2)	80	82:18	7
3	**4b**	**7b + 8b**	*n*-Pr	Me	2	Me_2SO_4 (2)	86	77:23	
4	**4c**	**7c + 8c**	Ph	Me	2	Me_2SO_4 (2)	50	92:8	

[a] The base (LiHMDS) was always introduced in the presence of the alkylating agent at −20 °C in dry THF (method B).

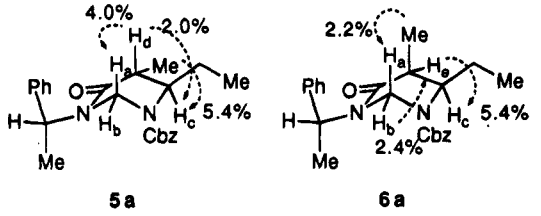
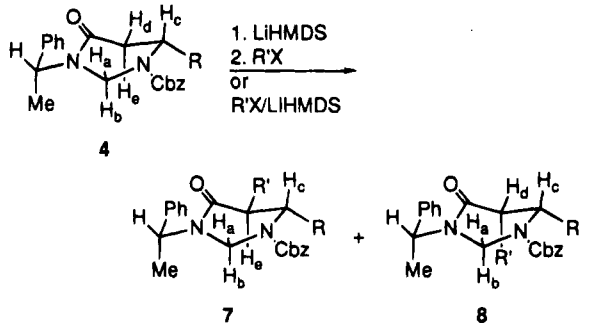
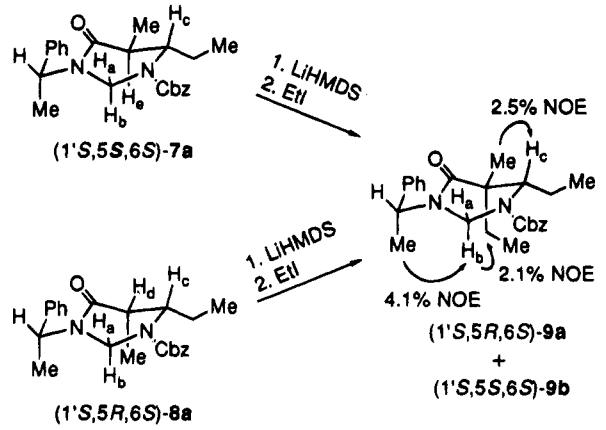


Figure 3.

Scheme 3



Scheme 4



The behavior of perhydropyrimidin-4-ones **4** is quite similar to that of compounds **3**. In Scheme 3, the general structure of compounds **4**, **7**, and **8** are shown in the preferred D conformation, as was indicated by ^1H NMR study and difference NOE experiments performed. Table 2 shows the results of the alkylation of **4a**, **4b**, and **4c**.

Entries 1 and 2 show different diastereomeric ratios, together with traces of dialkyl derivative. Previously,[6] we hypothesized that the dialkylation occurs faster on the 5,6-*cis*- than on the 5,6-*trans*-disubstituted pyrimidin-4-one strongly affecting the diastereomeric ratio. In order to demonstrate this assumption and to further investigate the possibility of synthesizing enantiomerically pure α,α-disubstituted β-amino acids, products **7a** and **8a** were easily isolated and submitted separately to alkylation with ethyl iodide (Scheme 4, Table 3).

Table 3. Diastereomeric Products Ratios and Chemical Yields for the Dialkylation Reaction of Perhydropyrimidin-4-ones 7a and 8a

entry	starting material	temp[a] (°C)	time[a] (h)	diastereomeric ratio **9a/9b**	yield (%)
1	**7a**	0	1	96:4	5
2	**7a**	rt	1	91:9	35
3	**7a**	rt	72	90:10	47
4	**8a**	0	1	91:9	99

[a] Time and temperature refer to the alkylation. The formation of the enolate was always performed with 1 equiv of LiHMDS at 0 °C for 1 h in dry THF (method A).

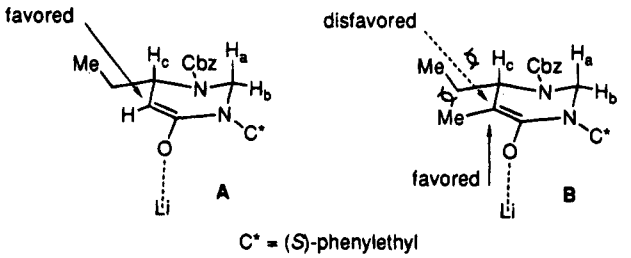


Figure 4.

The results reported in Table 3 confirm our hypothesis. In fact, while the alkylation of the lithium enolate of 5,6-*trans*-**7a** with ethyl iodide affords the dialkyl derivatives **9a** and **9b** in 5% overall yield (entry 1), the alkylation of 5,6-*cis*-**8a** produces a mixture of **9a** and **9b** in quantitative yield (entry 4). This outcome establishes that the relative configuration of C_5 and C_6 of the heterocycle strongly influences the dialkylation rate and, thus, the diastereomeric ratio of the monoalkylation.

Moreover, **9a** was obtained as the major product, whether starting from **7a** or **8a**. The absolute configuration of the major isomer **9a** was established by means of difference NOE experiments and shows that the preferred isomer is obtained from the attack of the ethyl group from the same side, at C_6 (see Scheme 4).

This behavior may be explained by considering the possible attack directions of the electrophile, as shown in Figure 4. Recently, the nonvertical attack has been shown to be preferred in the enolate−electrophile reaction.[12] Thus, for enolate **A**, derived from **3a**, owing to the *S* configuration of C_6, the preferred nonvertical attack direction is from the *si*-face, leading to a 5,6-*trans*-disubstituted product. On the other hand, the methyl group at C_5 and the pseudoaxial hydrogen at C_6 disfavor any attack from the *si*-face in the enolate **B**, derived from **7a** or **8a**, and lead to the 5,6-*cis* derivative by means of vertical attack from the *re*-face.

In order to test how the bulkiness of the alkylating agent affects the diastereomeric ratio, the pyrimidin-4-ones **3a**, **3b**, **3c**, **4a**, **4b**, and **4c** were submitted to alkylation with ethyl iodide and/or benzyl bromide (Table 4).

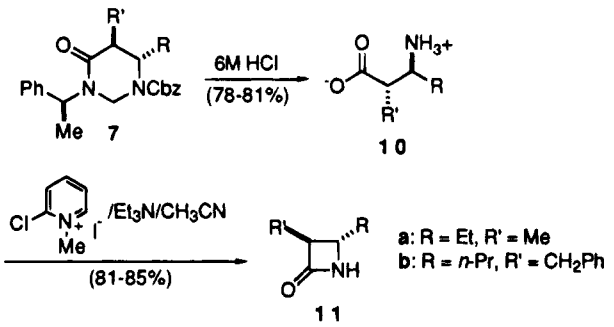
The reaction is highly diastereoselective, and only entry 1 shows the presence of traces of 5,6-*cis*-disubsti-

Table 4. Diastereomeric Products Ratios and Chemical Yields for the Alkylation of 3 and 4 with Ethyl Iodide and Benzyl Bromide, Following Method A

entry	starting material	products	R	R'	alkylating agent (1.5 equiv)	yield[a] (%)	*trans/cis* ratio
1	**3a**	**5d + 6d**	Et	Et	EtI	78	96:4
2	**3b**	**5f**	*n*-Pr	Et	EtI	90	>99:1[b]
3	**3b**	**5g**	*n*-Pr	CH_2Ph	$PhCH_2Br$	85	>99:1[b]
4	**3c**	**5h**	Ph	Et	EtI	96	>99:1[b]
5	**4a**	**7e**	Et	CH_2Ph	$PhCH_2Br$	95	>99:1[b]
6	**4b**	**7f**	*n*-Pr	Et	EtI	92	>99:1[b]
7	**4b**	**7g**	*n*-Pr	CH_2Ph	$PhCH_2Br$	88	>99:1[b]
8	**4c**	**7h**	Ph	Et	EtI	80	>99:1[b]

[a] No traces of dialkyl derivative were detected. [b] No traces of *cis* derivative were detected.

Scheme 5



tuted product. All the reactions were performed utilizing method A, and products **5** and **7** were obtained with satisfactory yields.

B. Hydrolysis of Perhydropyrimidin-4-ones and Synthesis of 3,4-*trans*-Disubstituted Azetidin-4-ones. To show the versatility of this synthetic method, the compounds **7a** and **7g** were transformed into the corresponding β-lactams **11a** and **11g**. The hydrolysis was performed under acidic conditions; thus, **7a** and **7g** were suspended in 6 M HCl and refluxed for 24 h, delivering a mixture of the corresponding β-amino acid hydrochlorides **10a** and **10g** and (*S*)-phenylethylamine hydrochloride (Scheme 5).

The (*S*)-1-phenylethylamine was separated during the workup, and the purification of the amino acid from sodium chloride was performed on a column of cation exchange resin using NH_4OH 1.5 M as eluant. The α-substituted β-amino acids were obtained pure in high yield, and the $[\alpha]_D$ and the melting point of compound **10a** coincided with reported values.[10]

Moreover, the β-amino acids were submitted to cyclization with 2-chloro-1-methylpyridinium iodide in the presence of triethylamine, following the procedure described by Mukayama.[13] The corresponding 3,4-*trans*-disubstituted β-lactams **11** were obtained pure in high yield after silica gel chromatography. Analysis of the crude reaction mixtures by ^1H and ^{13}C NMR spectroscopy and MS–GC chromatography showed the presence of a single stereoisomer. The 3,4-*trans* relationship of the substituents was confirmed by means of ^1H NMR analysis, and in fact the coupling constants $J_{H3,H4}$ of 2.0 Hz for **11a** and 1.9 Hz for **11g** are typical for the 3,4-*trans*-disubstituted azetidin-2-ones.

Conclusions

In conclusion, this work describes the synthesis and the conformational analysis of 5,6-*trans*-disubstituted perhydropyrimidin-4-ones, which were obtained in high yield and good diastereomeric ratio. These compounds are easily hydrolyzed to enantiomerically pure *anti* α-substituted β-amino acids and transformed into the corresponding 3,4-*trans*-disubstituted azetidin-2-ones.

Moreover, the dialkylation at C_5 of perhydropyrimidin-4-ones has been studied in some detail.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$, defined to be δ 7.27. Infrared spectra were recorded with an FT-IR spectrometer. Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from P_2O_5.

***(S,R)*-3-((Benzyloxycarbonyl)amino)alkanoic Acid 1.** A hot solution of sodium ethoxide was prepared from Na (40 mmol, 0.92 g) and absolute EtOH (40 mL) under argon. A hot solution of hydroxylamine hydrochloride (40 mmol, 2.78 g) in distilled H_2O (4 mL) was added while stirring, the resulting suspension was cooled quickly and then filtered under reduced pressure. The residue of sodium chloride was washed with small portions of absolute EtOH, the filtrate was returned to the flask and pure α,β-unsaturated acid (20 mmol) was added. The mixture was refluxed for 9 h and then concentrated under reduced pressure. The resulting β-amino acid was obtained as a waxy solid and directly protected without any further purification.

To the stirred solution of the residue and NaOH (42 mmol, 1.68 g) in distilled water (25 mL) a solution of benzyl chloroformate (22 mmol, 3.47 mL) in acetone (25 mL) was added dropwise at 0 °C. The mixture was stirred at rt for 1 h, the acetone was removed under reduced pressure and the residue was extracted twice with ethyl acetate. Then 2M HCl was added to the aqueous layer until the solution reached pH = 1 and the mixture was extracted twice with ethyl acetate. The second organic layer was dried over Na_2SO_4 and concentrated. Compounds **1a** and **1b** were obtained as an oil in about 50% overall yield.

Acid **1c** was soluble in organic solvents even at basic pH, so the aqueous mixture was extracted only once and the organic layer which was dried over Na_2SO_4 and concentrated, was purified by flash chromatography (ethyl acetate as eluant).

1a: 55% yield, solid; IR (film) 3317, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.2 Hz), 1.60 (m, 2H), 2.59 (d, 2H, J = 4.1 Hz), 3.92 (m, 1H), 5.11 (s, 2H), 5.31 (d, 1H, J = 9.3 Hz), 7.36 (m, 5H), 10.46 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 10.5, 11.9, 38.4, 49.4, 66.7, 127.9, 128.0, 128.4, 136.4, 156.0, 176.9; mp 111 °C. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.12; H, 6.82; N, 5.58. Found: C, 62.14; H, 6.80; N, 5.50.

(9) Amoroso, R.; Cardillo, G.; Mobbili, G.; Tomasini, C. *Tetrahedron: Asymmetry* **1993**, *4*, 2241 and references cited therein.
(10) Bates, R. B.; Gangwar, S. *Tetrahedron: Asymmetry* **1993**, *4*, 69 and references cited therein.
(11) (a) Amoroso, R.; Cardillo, G.; Tomasini, C.; Tortoreto, P. *J. Org. Chem.* **1992**, *57*, 1082. (b) Amoroso, R.; Cardillo, G.; Tomasini, C. *Heterocycles* **1992**, *34*, 349.
(12) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 25–29 and references cited therein.
(13) Huang, H.; Iwasawa, N.; Mukayama, T. *Chem. Lett.* **1984**, 1465.

1b: 52% yield, oil; IR (film) 3293, 1694, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.1 Hz), 1.37 (m, 2H), 1.53 (m, 2H), 2.59 (m, 2H), 4.00 (m, 1H), 5.10 (s, 2H), 5.27 (d, 1H, J = 9.0 Hz), 7.35 (m, 5H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.3, 36.4, 38.8, 47.7, 66.7, 128.0, 128.1, 128.5, 136.3, 155.9, 176.6. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.42; H, 7.16; N, 5.23.

1c: 40% yield, oil; IR ($CHCl_3$) 3616, 3420, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (dd, 1H, J = 5.7 Hz, J = 16.8 Hz), 2.99 (dd, 1H, J = 8.1 Hz, J = 16.8 Hz), 4.65 (dd J = 5.7 Hz, J = 8.1 Hz) 5.17 (m, 2H), 7.35 (m, 10H), 9.47 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 37.9, 61.4, 70.2, 126.1, 127.1, 127.4, 127.7, 128.1, 128.3, 128.4, 128.5, 128.6, 134.4, 137.7, 155.7, 175.7. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.20; H, 5.73; N, 4.68. Found: C, 68.29; H, 5.77; N, 4.75.

[*S*,(*S*,*R*)]-*N*-(1-Phenylethyl)-3-*N*-(benzyloxycarbonyl)-alkanamide 2. To a stirred solution of acid (**1**) (10 mmol) in dry CH_2Cl_2 (50 mL), a solution of $SOCl_2$ (20 mmol, 1.47 mL) in dry CH_2Cl_2 (20 mL) was added dropwise at room temperature. The mixture was stirred for 30 min and the excess of $SOCl_2$ and the solvent were gently removed under vacuum. A waxy solid was obtained, and dry CH_2Cl_2 (20 mL) was added. The solution was added dropwise to a stirred solution of (*S*)-1-phenylethylamine (10 mmol, 1.32 mL) and triethylamine (48.2 mmol, 6.7 mL) in dry CH_2Cl_2 (10 mL) at 0 °C and stirred at room temperature for 1 hour. Then the mixture was washed twice with water, dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography (cyclohexane/ethyl acetate 8:2 as eluant) of the residue afforded (**2**) in about 80% overall yield.

2a: 82% yield, oil; IR (film) 3320, 1693, 1681, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of diastereoisomers) δ 0.87 (t, 3H, J = 6.8 Hz), 1.39 (m, 2H), 1.57 (d, 3H, J = 6.6 Hz), 2.38 (m, 2H), 3.80 (m, 1H), 5.03 (m, 3H), 5.76 (bs, 1H), 6.75 (bs, 1H), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) (mixture of diastereomers) δ 10.5, 21.4 and 21.7, 27.6, 48.7, 51.4, 66.4, 126.6, 127.7, 127.9, 128.3, 128.4, 128.7, 136.5, 139.7, 156.2, 170.0. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.15; H, 7.40; N, 7.91. Found: C, 71.19; H, 7.42; N, 7.50.

2a: 80% yield, oil; IR (film) 3320, 1695, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of diastereoisomers) δ 1.13 and 1.14 (t, 3H, J = 7.1 Hz), 1.67 (d, 3H, J = 6.9 Hz), 1.72 (m, 4H), 2.67 (m, 2H), 4.16 (m, 1H), 5.32 (m, 2H), 5.37 (pseudoquintet, 1H, J = 7.7 Hz), 5.77 (d, 1H, J = 10.9 Hz), 6.48 (bs, 1H), 7.58 (m, 10H); ^{13}C NMR ($CDCl_3$) (mixture of diastereoisomers) δ 13.7 and 14.2, 19.4, 21.7, 25.4, 36.7, 40.8, 48.6 and 48.7, 66.6, 126.1, 127.3, 127.8 and 128.0, 128.4, 128.6, 136.5, 138.0, 156.2, 169.9. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.70; H, 7.66; N, 7.61. Found: C, 71.79; H, 7.62; N, 7.57.

2c: 85% yield, oil; IR (film) 3323, 1689, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of diastereoisomers) δ 1.38 and 1.49 (d, 3H, J = 7.1 Hz), 2.70 (m, 2H), 5.10 (m, 4H), 5.63 (bs, 1H), 6.39 (bs, 1H), 7.32 (m, 15H); ^{13}C NMR ($CDCl_3$) (mixture of diastereoisomers) δ 21.4 and 21.7, 42.9 and 43.0, 48.7 and 48.8, 52.7, 66.8, 126.1, 126.2, 127.4, 128.0, 128.4, 128.6, 128.7, 128.9, 136.7, 142.7, 155.8, 169.2. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.59; H, 6.52; N, 6.96. Found: C, 74.70; H, 6.48; N, 7.01.

1-(Benzyloxycarbonyl)-3-(1′-phenylethyl)-6-(alkyl or aryl)perhydropyrimidin-4-ones (1′*S*,6*R*)-3 and (1′*S*,6*S*)-4. To a stirred solution of amide (**2**) (10 mmol) in benzene (50 mL) paraformaldehyde (50 mmol, 1.5 g) and *p*-toluenesulfonic acid monohydrate (3 mmol, 0.57 g) were added. The mixture was refluxed for 1 h in a flask equipped with a Soxhlet apparatus, washed with aqueous Na_2CO_3, dried over Na_2SO_4 and concentrated. (1′*S*,6*R*)-**3** and (1′*S*,6*S*)-**4** were obtained pure, after flash chromatography of the residue on silica gel (cyclohexane/ethyl acetate 9:1 as eluant). Compounds **3c** and **4c** were not separated by flash chromatography, but used as a 1:1 mixture in the following reactions.

(1′*S*,6*R*)-3a: 45% yield, oil; IR (film) 1707, 1669, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 0.85 (t, 3H, J = 7.4 Hz), 1.47 (d, 3H, J = 7.1 Hz), 1.65 (m, 2H), 2.36 (dd, 1H, J = 7.7, 15.9 Hz), 2.71 (dd, 1H, J = 6.6 Hz, J = 15.9 Hz), 4.02 (d, 1H, J = 12.9 Hz), 4.06 (m, 1H), 4.99 (d, 1H, J = 12.9 Hz), 5.16 (AB, 2H, J = 12.2 Hz), 5.85 (q, 1H, J = 7.1 Hz), 7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 9.3, 16.1, 27.2, 36.8, 48.8, 52.0, 52.1, 67.6, 127.1, 127.5, 127.9, 128.2, 128.3, 128.5, 136.1, 139.8, 154.9, 168.6; MS (*m/e*) 366 (M^+), 275, 261, 171, 146, 120, 105, 91; $[\alpha]_D$ −61.3 (*c* 0.75, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.09; H, 7.16; N, 7.65. Found: C, 72.10; H, 7.20; N, 7.69.

(1′*S*,6*S*)-4a: 43% yield, oil; IR (film) 1708, 1666, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 0.91 (t, 3H, J = 7.5 Hz), 1.53 (d, 3H, J = 7.1 Hz), 1.75 (m, 2H), 2.45 (dd, 1H, J = 6.1, 15.8 Hz), 2.75 (dd, 1H, J = 6.5, 15.8 Hz), 4.10 (m, 1H), 4.44 (d, 1H, J = 12.5 Hz), 4.83 (d, 1H, J = 12.5 Hz), 5.03 (m, 2H), 5.93 (q, 1H, J = 7.1 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 9.5, 16.2, 26.7, 36.5, 49.9, 51.2, 51.8, 67.3, 127.1, 127.3, 127.5, 127.7, 127.8, 127.9, 128.3, 128.4, 136.1, 139.8, 155.8, 168.4; MS (*m/e*) 366 (M^+), 275, 247, 171, 146, 120, 105, 91; $[\alpha]_D$ −52.9 (*c* 1.29, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.09; H, 7.16; N, 7.65. Found: C, 72.15; H, 7.10; N, 7.59.

(1′*S*,6*R*)-3b: 42% yield, oil; IR (film) 1708, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 0.87 (t, 3H, J = 7.1 Hz), 1.49 (d, 3H, J = 7.1 Hz), 1.55 (m, 4H), 2.36 (dd, 1H, J = 7.5, 15.9 Hz), 2.74 (dd, 1H, J = 6.7, 15.9 Hz), 4.02 (d, 1H, J = 12.8 Hz), 4.16 (m, 1H), 4.98 (d, 1H, J = 12.8 Hz), 5.17 (AB, 2H, J = 12.3 Hz), 5.87 (q, 1H, J = 7.1 Hz), 7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.6, 16.1, 18.3, 36.5, 37.4, 49.9, 50.5, 52.0, 67.7, 127.6, 128.1, 128.2, 128.5, 128.6, 136.1, 139.8, 168.6; MS (*m/e*) 380 (M^+), 289, 275, 231, 185, 146, 120, 105, 91; $[\alpha]_D$ −63.5 (*c* 1.77, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.59; H, 7.42; N, 7.37. Found: C, 72.50; H, 7.33; N, 7.39.

(1′*S*,6*S*)-4b: 40% yield, oil; IR (film) 1708, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 0.92 (t, 3H, J = 7.1 Hz), 1.34 (m, 2H), 1.54 (d, 3H, J = 7.1 Hz), 1.69 (m, 2H), 2.42 (dd, 1H, J = 5.7, 16.2 Hz), 2.75 (dd, 1H, J = 6.4, 16.2 Hz), 4.18 (m, 1H), 4.44 (d, 1H, J = 12.5 Hz), 4.82 (d, 1H, J = 12.5 Hz), 5.03 (m, 2H), 5.94 (q, 1H, J = 7.1 Hz), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.6, 16.1, 18.5, 35.8, 36.9, 49.9, 50.2, 51.9, 67.3, 127.0, 127.4, 127.7, 128.0, 128.3, 128.4, 136.1, 139.8, 154.0, 168.3; MS (*m/e*) 380 (M^+), 289, 207, 185, 146, 120, 105, 91; $[\alpha]_D$ −57.0 (*c* 1.54, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.59; H, 7.42; N, 7.37. Found: C, 72.49; H, 7.43; N, 7.41.

(1′*S*,6*R*)-3c and **(1′*S*,6*S*)-4c**: 88% overall yield. For the analytical and spectroscopic data see ref. 11a.

General Procedure for the Alkylation of Perhydropyrimidin-4-ones 3 and 4. Method A. To a stirred solution of perhydropyrimidin-4-one **3** or **4** (1 mmol) in dry THF (10 mL) LiHMDS (1M sol. in THF, 1 mmol, 1 mL) was added in one portion under argon at 0 °C. After 30 min the alkylating agent was added at the proper temperature. After the scheduled reaction time (see Table), the reaction was quenched with MeOH (1 mL), the solvent was removed under reduced pressure, replaced with ethyl acetate which was washed twice with water. The organic layer was dried over Na_2SO_4, concentrated and chromatographed on silica gel (cyclohexane/ethyl acetate 9:1 as eluant). All the products were obtained as oils.

Method B. To a stirred solution of perhydropyrimidin-4-one **3** or **4** (1 mmol) and of the alkylating agent in dry THF (10 mL) LiHMDS (1M sol. in THF, 1 mmol, 1 mL) was added in one portion under argon at −20 °C. The mixture was stirred at −20 °C for 2 hours, then quenched with MeOH (1 mL). The solvent was removed under reduced pressure, replaced with ethyl acetate which was washed twice with water. The organic layer was dried over Na_2SO_4, concentrated and chromatographed on silica gel (cyclohexane/ethyl acetate 9:1 as eluant). All the products were obtained as oils.

(1′*S*,5*R*,6*R*)-5a: IR (film) 1711, 1667, 1662 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C), δ 0.85 (t, 3H, J = 7.1 Hz), 1.28 (d, 3H, J = 6.9 Hz), 1.53 (d, 3H, J = 6.9 Hz), 1.75 (m, 2H), 2.48 (pseudoquintet, J = 6.9 Hz), 3.79 (m, 1H), 3.95 (d, 1H, J = 12.5 Hz), 5.06 (d, 1H, J = 12.5 Hz), 5.17 (AB, J = 12.1 Hz), 5.87 (q, 1H, J = 6.9 Hz), 7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 9.0, 10.3, 16.1, 25.5, 40.2, 50.1, 52.1, 57.9, 67.8, 127.3, 127.6, 128.3, 128.6, 128.7, 136.2, 140.6, 154.6, 171.3; MS (*m/e*) 380 (M^+) 289, 275, 231, 185, 162, 120, 105, 91; $[\alpha]_D$ −56.0 (*c* 0.27, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.69; H, 7.43; N, 7.40.

(1′*S*,5*S*,6*R*)-6a: IR (film) 1708, 1671, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C), δ 0.75 (t, 3H, J = 6.1 Hz), 1.22 (d, 3H, J = 7.1 Hz), 1.36 (m, 2H), 1.53 (d, 3H, J = 7.1 Hz), 2.75 (dq, J = 5.4 Hz, J = 7.1 Hz), 4.10 (m, 1H), 4.21 (d, 1H, J = 11.4 Hz), 4.88

(d, 1H, J = 11.4 Hz), 5.12 (s, 2H), 6.01 (q, 1H, J = 7.1 Hz), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 10.4, 12.2, 15.9, 21.7, 40.4, 49.9, 52.2, 56.2, 67.6, 127.3, 127.7, 127.9, 128.6, 128.7, 136.3, 139.6, 154.7, 161.6; MS (*m/e*) 380 (M^+), 289, 275, 231, 185, 162, 120, 105, 91; $[\alpha]_D$ −38.0 (*c* 0.09, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.55; H, 7.38; N, 7.30.

(1′*S*,5*R*,6*R*)-5b: IR (film) 1710, 1660, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C), δ 0.88 (t, 3H, J = 7.3 Hz), 1.28 (d, 3H, J = 6.9 Hz), 1.52 (m, 4H), 1.55 (d, 3H, J = 7.1 Hz), 2.44 (pseudoquintet, J = 6.9 Hz), 3.85 (m, 1H), 3.93 (d, 1H, J = 13.1 Hz), 5.04 (d, 1H, J = 13.1 Hz), 5.16 (AB, J = 12.3 Hz), 5.89 (q, 1H, J = 7.1 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 15.0, 15.8, 16.1, 18.2, 35.3, 41.1, 50.1, 56.2, 56.8, 67.7, 127.3, 128.2, 128.4, 128.5, 128.6, 128.7, 129.6, 136.2, 140.0, 154.3, 171.2; MS (*m/e*) 394 (M^+), 303, 289, 245, 199, 176, 120, 105, 91; $[\alpha]_D$ −54.9 (*c* 0.41, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.11; H, 7.71; N, 7.05.

(1′*S*,5*R*,6*S*)-5c: IR (film) 1715, 1683, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 1.14 (d, 3H, J = 6.6 Hz), 1.55 (d, 3H, J = 7.1 Hz), 2.79 (dq, J = 6.6, 9.9 Hz), 4.41 (d, 1H, J = 13.4 Hz), 4.47 (d, 1H, J = 9.9 Hz), 5.10 (1H, J = 13.5 Hz), 5.15 (m, 2H), 5.87 (q, 1H, J = 7.1 Hz), 7.31 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 12.8, 16.4, 42.7, 50.5, 53.2, 62.0, 67.7, 126.8, 127.3, 127.6, 127.8, 128.1, 128.4, 128.5, 128.7, 135.9, 140.1, 141.7, 154.2, 171.0; MS (*m/e*) 428 (M^+), 380, 323, 279, 233, 149, 120, 105, 91; $[\alpha]_D$ −73.7 (*c* 0.38, $CHCl_3$). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.75; H, 6.58; N, 6.58.

(1′*S*,5*R*,6*R*)-5d: IR 1707, 1667, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixtures of conformers) δ 0.78 and 0.85 (t, 3H, J = 7.2 Hz), 0.99 and 1.06 (t, 3H, J = 7.3 Hz), 1.49 and 1.55 (d, 3H, J = 7.1 Hz), 1.58 (m, 2H), 1.76 (m, 2H), 2.25 and 2.31 (dt, 1H, J = 5.9, 8.8 Hz), 3.85 and 3.94 (d, 1H, J = 12.1 Hz) 3.97 and 4.07 (m, 1H), 4.88 and 5.03 (d, 1H, J = 12.1 Hz), 5.15 (s, 2H), 5.95 and 6.02 (q, 1H, J = 7.1 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) (mixture of conformers) δ 9.8 and 9.9, 12.1, 15.6, 23.3 and 23.6, 25.5, 47.4 and 47.9, 49.4 and 49.5, 51.3, 54.2 and 54.4, 67.6, 127.2, 127.4, 127.6, 127.9, 128.2, 128.5, 128.6, 136.0, 139.4, 154.3 and 155.0, 170.1 and 170.5; MS (*m/e*) 394 (M^+), 303, 289, 245, 199, 120, 105, 91; $[\alpha]_D$ −36.2 (*c* 0.39, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.11; H, 7.68; N, 7.12.

(1′*S*,5*R*,6*R*)-5f: IR (film) 1706, 1668, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.82 (t, 3H, J = 6.5 Hz), 1.02 (t, 3H, J = 5.7 Hz), 1.25 (m, 2H), 1.43 (d, 3H, J = 7.0 Hz), 1.48 (m, 2H), 1.78 (m, 2H), 2.24 (m, 1H), 3.92 (d, 1H, J = 11.0 Hz), 4.12 (m, 1H), 4.99 (d, 1H, J = 11.0 Hz), 5.16 (s, 1H), 6.01 (q, 1H, J = 7.0 Hz), 7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 12.1, 13.7, 15.7, 18.8, 23.7, 35.1, 48.6, 49.6, 51.5, 52.9, 67.7, 127.4, 127.6, 128.0, 128.3, 128.5, 128.6, 136.2, 139.7, 159.7, 170.3; MS (*m/e*) 408 (M^+), 317, 303, 259, 213, 176, 120, 105, 91; $[\alpha]_D$ −36.2 (*c* 0.50, $CHCl_3$). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.89; N, 6.86. Found: C, 73.58; H, 7.93; N, 6.89.

(1′*S*,5*R*,6*R*)-5g: IR (film) 1706, 1667, 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.67 (t, 3H, J = 6.4 Hz), 1.05 (m, 2H), 1.31 (m, 2H), 1.57 (d, 3H, J = 7.0 Hz), 2.60 (pseudo dt, J = 3.6, 9.6 Hz), 2.70 (dd, 1H, J = 9.6, 13.2 Hz), 3.21 (dd, 1H, J = 3.6, 13.2 Hz), 3.92 (d, 1H, J = 11.8 Hz), 4.08 (m, 1H), 5.03 (d, 1H, J = 11.8 Hz), 5.16 (s, 2H), 6.08 (q, 1H, J = 7.0 Hz), 7.30 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.4, 15.4, 18.5, 34.9, 36.9, 49.1, 49.8, 51.5, 52.0, 67.7, 126.3, 127.3, 127.6, 128.1, 128.2, 128.3, 128.4, 128.5, 129.2, 136.0, 139.1, 139.4, 154.7, 169.5; MS (*m/e*) 470 (M^+), 379, 365, 321, 275, 176, 105, 91; $[\alpha]_D$ −66.6 (*c* 1.56, $CHCl_3$). Anal. Calcd for $C_{30}H_{34}N_2O_3$: C, 76.57; H, 7.28; N, 5.95. Found: C, 76.61; H, 7.33; N, 5.98.

(1′*S*,5*R*,6*S*)-5h: IR (film) 1714, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.99 (t, 3H, J = 7.3 Hz), 1.51 (d, 3H, J = 7.1 Hz), 1.79 (m, 2H), 2.70 (m, 1H), 4.31 (d, 1H, J = 12.9 Hz), 4.81 (m, 1H), 5.02 (d, 1H, J = 12.9 Hz), 5.11 (m, 2H), 5.91 (q, 1H, J = 7.1 Hz), 7.31 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 12.2, 16.2, 21.3, 48.9, 50.2, 52.8, 58.7, 67.8, 126.9, 127.4, 127.6, 127.8, 128.4, 128.5, 128.6, 136.0, 139.8, 154.2, 170.2; MS (*m/e*) 442 (M^+), 351, 337, 293, 247, 210, 159, 132, 105, 91, 65; $[\alpha]_D$ −6.7 (*c* 0.89, $CHCl_3$). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 76.03; H, 6.90; N, 6.37.

(1′*S*,5*S*,6*S*)-7a: IR (film) 1708, 1667, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.89 (t, 3H, J = 6.9 Hz), 1.28 (d, 3H, J = 6.4 Hz), 1.53 (d, 3H, J = 7.1 Hz), 1.61 (m, 2H), 2.53 (pseudoquintet, J = 6.4 Hz), 3.88 (m, 1H), 4.33 (d, 1H, J = 12.0 Hz), 4.92 (d, 1H, J = 12.0 Hz), 5.00 (m, 2H), 5.95 (q, 1H, J = 7.1 Hz), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 9.3, 15.8, 16.1, 25.2, 40.5, 49.9, 51.8, 57.4, 67.4, 127.1, 127.5, 127.7, 128.0, 128.4, 128.5, 136.2, 139.9, 154.6, 171.2; MS (*m/e*) 380 (M^+), 289, 275, 231, 185, 162, 120, 105, 91; $[\alpha]_D$ −63.7 (*c* 0.30, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.70; H, 7.38; N, 7.43.

(1′*S*,5*R*,6*S*)-8a: IR (film) 1707, 1673, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.91 (t, 3H, J = 7.4 Hz), 1.23 (d, 3H, J = 7.1 Hz), 1.41 (m, 2H), 1.55 (d, 3H, J = 7.1 Hz), 2.77 (dq, J = 5.4, 7.1 Hz), 4.15 (m, 1H), 4.58 (s, 2H), 5.09 (s, 2H), 6.01 (q, 1H, J = 7.1 Hz), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 8.9, 10.3, 12.1, 15.6, 40.0, 49.7, 51.7, 56.2, 67.3, 127.1, 127.6, 128.0, 128.1, 128.2, 128.5, 128.6, 136.0, 139.6, 148.2, 171.0; MS (*m/e*) 380 (M^+), 289, 231, 185, 162, 120, 105, 91; $[\alpha]_D$ −97.0 (*c* 0.71, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.53; H, 7.31; N, 7.33.

(1′*S*,5*S*,6*S*)-7b: IR (film) 1708, 1668, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.91 (t, 3H, J = 7.4 Hz), 1.20 (m, 2H), 1.28 (d, 3H, J = 7.0 Hz), 1.51 (m, 2H), 1.54 (d, 3H, J = 7.2 Hz), 2.51 (dq, 1H, J = 4.7, 7.1 Hz), 3.98 (m, 1H), 4.34 (d, 1H, J = 11.8, Hz), 4.90 (d, 1H, J = 11.8 Hz), 5.05 (m, 2H), 5.96 (q, 1H, J = 7.2 Hz), 7.29 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.9, 16.0, 16.2, 18.5, 34.8, 41.3, 50.0, 51.7, 56.0, 67.5, 127.2, 127.4, 127.6, 127.8, 128.1, 128.5, 128.6, 136.2, 140.0, 154.2, 171.1; MS (*m/e*) 394 (M^+), 303, 245, 199, 176, 120, 105, 91; $[\alpha]_D$ −44.6 (*c* 0.13, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.05; H, 7.70; N, 7.15.

(1′*S*,5*S*,6*R*)-7c: IR (film) 1713, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 1.17 (d, 3H, J = 6.5 Hz), 1.54 (d, 3H, J = 6.7 Hz), 2.85 (dq, 1H, J = 6.5, 9.0 Hz), 4.55 (m, 1H), 4.67 (d, 1H, J = 12.4 Hz), 4.85 (d, 1H, J = 12.4 Hz), 5.20 (m, 2H), 5.93 (q, 1H, J = 6.7 Hz), 7.28 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.4, 16.7, 42.4, 50.4, 53.0, 61.4, 67.4, 126.8, 127.3, 127.9, 128.4, 128.6, 136.0, 140.2, 154.1, 171.1; MS (*m/e*) 428 (M^+), 337, 279, 233, 118, 105, 91; $[\alpha]_D$ −27.3 (*c* 0.44, $CHCl_3$). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.66; H, 6.62; N, 6.54.

(1′*S*,5*S*,6*S*)-7e: IR (film) 1708, 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.84 (t, 3H, J = 7.2 Hz), 1.60 (m, 2H), 1.65 (d, 3H, J = 7.1 Hz), 2.73 (m, 2H), 3.26 (d, 1H, J = 9.7 Hz), 4.15 (m, 1H), 4.44 (d, 1H, J = 11.5 Hz), 4.90 (d, 1H, J = 11.5 Hz), 5.14 (m, 1H), 6.14 (q, 1H, J = 7.1 Hz), 7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 10.9, 15.2, 16.6, 38.3, 50.1, 51.0, 54.4, 68.6, 127.4, 128.2, 128.7, 128.8, 128.9, 129.1, 129.4, 129.6, 136.2, 140.6, 154.7, 170.6; MS (*m/e*) 456 (M^+), 365, 351, 307, 261, 236, 202, 160, 146, 105, 91; $[\alpha]_D$ −32.2 (*c* 0.24, $CHCl_3$). Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 76.33; H, 7.13; N, 6.17.

(1′*S*,5*S*,6*S*)-7f: IR (film) 1711, 1666, 1644; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.92 (t, 3H, J = 6.4 Hz), 1.03 (t, 3H, J = 6.4 Hz), 1.34 (m, 2H), 1.51 (m, 2H), 1.55 (d, 3H, J = 7.1 Hz), 1.76 (m, 2H), 2.29 (dt, J = 7.2, 9.6 Hz), 4.23 (m, 1H), 4.34 (d, 1H, J = 11.6 Hz), 4.75 (d, 1H, J = 11.6 Hz), 5.03 (m, 2H), 6.02 (q, 1H, J = 7.1 Hz), 7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 12.1, 13.8, 15.6, 19.0, 24.4, 34.9, 48.9, 49.7, 52.6, 67.5, 127.1, 127.6, 127.8, 128.5, 128.6, 136.2, 139.8, 154.6, 170.2; MS (*m/e*) 408 (M^+), 317, 303, 259, 213, 176, 120, 105, 91; $[\alpha]_D$ −67.5 (*c* 0.52, $CHCl_3$). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.89; N, 6.86. Found: C, 73.46; H, 7.91; N, 6.87.

(1′*S*,5*S*,6*S*)-7g: IR (film) 1708, 1665, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.78 (t, 3H, J = 7.1 Hz), 1.18 (m, 2H), 1.37 (m, 2H), 1.59 (d, 3H, J = 7.1 Hz), 2.65 (m, 2H), 3.18 (dd, 1H, J = 1.3, 11.2 Hz), 4.17 (m, 1H), 4.38 (d, 1H, J = 11.5 Hz), 4.82 (d, 1H, J = 11.5 Hz), 5.06 (m, 2H), 6.08 (q, 1H, J = 7.1 Hz), 7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.5, 15.6, 18.8, 34.6, 37.3, 49.4, 50.0, 51.6, 67.6, 126.4, 127.2, 127.7, 128.1, 128.4, 128.5, 128.6, 136.0, 139.0, 139.5, 154.5, 169.5; MS (*m/e*) 470 (M^+), 379, 365, 321, 275, 176, 105, 91; $[\alpha]_D$ −18.3 (*c* 0.86, $CHCl_3$). Anal. Calcd for $C_{30}H_{34}N_2O_3$: C, 76.57; H, 7.28; N, 5.95. Found: C, 76.60; H, 7.31; N, 5.98.

(1'S,5S,6R)-7h: IR (film) 1712, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.04 (t, 3H, J = 7.2 Hz), 1.49 (d, 3H, J = 7.2 Hz), 1.82 (m, 2H), 2.75 (pseudo q, J = 7.1 Hz). 4.48 (d, 1H, J = 12.1 Hz), 4.88 (m, 3H), 4.94 (d, 1H, J = 12.1 Hz), 5.97 (q, 1H, J = 7.2 Hz), 7.30 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 °C) δ 12.2, 16.1, 22.0, 48.7, 50.1, 52.5, 57.9, 67.6, 127.0, 127.1, 127.6, 127.8, 128.0, 128.4, 128.6, 136.0, 140.0, 154.2, 170.3; MS (*m/e*) 442 (M^+), 351, 337, 293, 247, 210, 159, 132, 105, 91; $[\alpha]_D$ −6.9 (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.91; H, 6.78; N, 6.31.

(1'S,5R,6S)-9a: IR (film) 1709, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of conformers) δ 0.84 and 0.85 (t, 3H, J = 7.4 Hz), 0.89 and 0.94 (t, 3H, J = 6.9 Hz), 1.13 and 1.17 (s, 3H), 1.39 (m, 2H), 1.54 and 1.56 (d, 3H, J = 7.1 Hz), 1.65 (m, 2H), 4.00 and 4.17 (dd, 1H, J = 3.9, 11.9 Hz), 4.29 and 4.30 (d, 1H, J = 11.2 Hz), 4.74 and 4.75 (d, 1H, J = 11.2 Hz), 5.03 and 5.10 (AB, J = 12.3 Hz), 6.07 (q, 1H, J = 7.1 Hz), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, mixture of conformers) δ 8.3 and 8.6, 10.3 and 10.5, 15.2, 18.4, 20.9 and 21.4, 31.0 and 31.6, 46.2 and 46.5, 49.3 and 49.5, 51.3 and 52.1, 57.2 and 57.8, 67.3 and 67.6, 127.1, 127.3, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 136.0, 139.6 and 139.7, 154.6 and 155.0, 172.8 and 173.0; MS (*m/e*) 408 (M^+), 317, 259, 213, 162, 120, 105, 91; $[\alpha]_D$ −45.4 (*c* 0.33, $CHCl_3$). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.89; N, 6.86. Found: C, 73.44; H, 7.98; N, 6.77.

General Procedure for the Isomerization of 5,6-*Cis* Derivatives. A stirred solution of perhydropyrimidin-4-ones **7a** and **8a** (1 mmol, 0.38 g) and $LiOH{\cdot}H_2O$ (5 mmol, 0.21 g) in MeOH (20 mL) was refluxed for 2 hours and the reaction was followed by means of TLC and GC. Then the reaction mixture was concentrated under reduced pressure, ethyl acetate was added and the organic layer was washed twice with water, dried over Na_2SO_4 and concentrated under reduced pressure. The ^1H NMR spectrum and the GC analysis of the crude reaction mixture showed the presence of only the perhydropyrimidin-4-ones (**7a**).

General Procedure for the Hydrolysis of Perhydropyrimidin-4-ones 5 and 7. A solution of perhydropyrimidin-4-one (1 mmol) in 6M HCl (5 mL) was refluxed for 30 h. The mixture was then concentrated and extracted with ethyl acetate/aqueous Na_2CO_3 to separate the (*S*)-1-phenylethylamine. To the aqueous layer 6M HCl was added until the reaction reached pH = 1. The solvent was eliminated and replaced with water (1 mL). The mixture was adsorbed on cation exchange resin and the resin was washed with distilled H_2O until the washing came out neutral, then with 1.5M aqueous NH_4OH to recover the β-amino acid. Evaporation of the aqueous solution afforded the β-amino acid (**10**) in the zwitterionic form.

(2S,3S)-2-Methyl-3-aminopentanoic acid (10a): 78% yield, solid; ^1H NMR (D_2O + DCl) δ 0.98 (t, 3H, J = 7.4 Hz), 1.27 (d, 3H, J = 7.3 Hz), 1.71 (m, 2H), 2.88 (dq, 1H, J = 7.3, 6.3 Hz), 3.44 (pseudo q, J = 6.3 Hz); ^{13}C NMR (D_2O + DCl) δ 8.2, 12.4, 22.6, 40.1, 54.1, 177.2. The hydrochloride **10a·HCl**: mp 240−243 °C (lit.[10] mp 244−246 °C); $[\alpha]_D$ +6.0 (c 0.01, H_2O) (lit.[10] for (2*R*,3*R*)-**10a·HCl** $[\alpha]_D$ −6.7 (*c* 0.2, H_2O).

(2S,3S)-2-Benzyl-3-aminohexanoic acid (10g): 81% yield, solid; ^1H NMR (D_2O + DCl) δ 0.74 (t, 3H, J = 7.1 Hz), 1.25 (m, 2H), 1.51 (m, 2H), 2.53 (m, 1H), 2.78 (d, 2H, J = 7.7 Hz), 3.21 (pseudo q, 1H, J = 4.4 Hz), 7.15, (m, 5H); ^{13}C NMR (D_2O + DCl) δ 12.5, 17.5, 32.3, 34.1, 48.0, 51.5, 126.6, 128.4, 137.0, 175.2; mp 173−175 °C; $[\alpha]_D$ −21.4 (*c* 0.44, H_2O).

General Procedure for the Synthesis of Azetidin-2-ones 11. 2-Chloro-1-methylpyridinium iodide (1.1 mmol, 0.28 g) and Et_3N (2.3 mmol, 0.32 mL) were added in one portion to a suspension of β-amino acid (**10**) (1 mmol) in CH_3CN (10 mL). The mixture was refluxed for 3 hours, then the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8:2 as eluant) and the azetidin-2-one **11** was obtained pure as an oil.

***trans*-(3S,4S)-3-Methyl-4-ethylazetidin-2-one (11a)**: 81% yield; IR (field) 3300, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, J = 7.4 Hz), 1.34 (d, 3H, J = 7.0 Hz), 1.67 (m, 2H), 2.81 (dq, 1H, J = 2.0, 7.0 Hz), 3.21 (dt, 1H, J = 2.0, 7.0 Hz), 5.87 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.2, 27.8, 51.0, 58.2, 171.6; MS (*m/e*) 113 (M^+), 97, 85, 71, 57; $[\alpha]_D$ −15.2 (*c* 0.01, $CHCl_3$). Anal. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.75; H, 9.73; N, 12.44.

***trans*-(3S,4S)-3-Benzyl-4-propylazetidin-2-one (11g)**: 85% yield; IR (film) 3225, 1751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, J = 7.4 Hz), 1.10 (m, 2H), 1.49 (m, 2H), 2.89 (dd, 1H, J = 8.9, 13.5 Hz), 3.03 (m, 1H), 3.14 (dd, 1H, J = 4.8, 13.5 Hz), 3.36 (dt, J = 1.9, 6.7 Hz), 5.92 (bs, 1H), 7.24 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.4, 34.5, 37.0, 54.5, 58.0, 126.5, 128.6, 128.8, 138.6, 170.3; MS (*m/e*) 204 (M^+ + 1), 174, 160, 131, 117, 104, 91, 77, 65; $[\alpha]_D$ +4.0 (*c* 0.20, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.85; H, 8.49; N, 6.93.

Acknowledgment. We thank Consiglio Nazionale delle Ricerche (Progetto Finalizzato 'Chimica Fine II') and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Fondi 40%) for financial support and Miss Micaela Fabbri for GC-MS analysis.