Pergamon

Tetrahedron Vol. 51, No. 43, pp. 11831-11840, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00744-X

Synthesis of Enantiomerically Pure *syn* and *anti* α-Hydroxy β-Amino Acids through Diastereoselective Hydroxylation of Perhydropyrimidin-4-ones

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Abstract : The diastereoselective hydroxylation at C_5 of chiral 6-substituted perhydropyrimidin-4-ones is described. The diastereoselection depends on the base and the hydroxylating agent utilised and on the absolute configuration of the exocyclic phenylethyl moiety. The acid hydrolysis of 5-hydroxy-6-methyl perhydropyrimidin-4-ones furnishes the enantiomerically pure L-isothreonine and D-alloisothreonine.

A variety of biologically interesting compounds containing α-hydroxy β-amino acids are promising anti-cancer, anti-AIDS or antihypertensive agents.[1]

In addition to the separation of racemic mixtures of esters of α-hydroxy β-amino acids, successfully performed by enzymatic resolution,[2] in the recent years some synthetic methods have been developed to obtain α-hydroxy β-amino acids in enantiomerically pure form, by means of hydroxylation of β-amino acids,[3] addition of a vinyl organometal compound to chiral α-amino acids [4] and hydrolysis of chiral 2-hydroxy azetidin-4-ones.[5]

We have recently developed the use of chiral perhydropyrimidin-4-ones for the synthesis of β-amino acids and α-substituted β-amino acids.[6] Perhydropyrimidin-4-ones can be obtained by addition of hydroxylamine to α,β-unsaturated acids followed by transformation of the adduct in the desired heterocycles. The chiral moiety (*S*)-phenylethylamine has been used to separate the diastereomeric mixture of perhydropyrimidin-4-ones and is a support for the determination of the configuration of C_6 of the heterocycle.[6b]

Our approach consists in the oxidation at C_5 of chiral 6-substituted perhydropyrimidin-4-ones by reaction with a base and an hydroxylating agent. Indeed 5-hydroxy perhydropyrimidin-4-ones furnish the corresponding α-hydroxy β-amino acids after a simple acid hydrolysis. With this method we have obtained the enantiomerically pure (2*S*,3*R*)-L-isothreonine, which is the side chain of the glycopeptide 1-*N*-(*D*-threo-3-amino-2-hydroxybutanoyl-2',3'-dideoxykanamicin A,[7] a good antibacterial agent.[8]

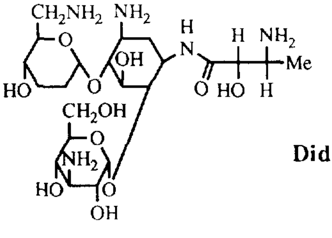


Figure 1

Dideoxykanamicin A

Recently many reagents which are able to donate a positive hydroxyl group have been prepared. They belong to two families: the oxaziridine derivatives [9] and the peroxomolybdenum derivatives.[10] We have performed the C_5-hydroxylation with several reagents, in order to compare the diastereoselectivities and yields of the reactions and to find the hydroxylating agent of choice for this class of compounds.

The enolates of (1'*S*,6*R*)-1'-phenylethyl-6-alkyl perhydropyrimidin-4-ones **1a** and **1b** [11] were treated with the complex MoO_5-pyridine-HMPT (MoOPH), (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine and (-)- and (+)-(camphorsulfonyl)oxaziridine (Scheme 1). The results are reported in Table 1.

Scheme 1.

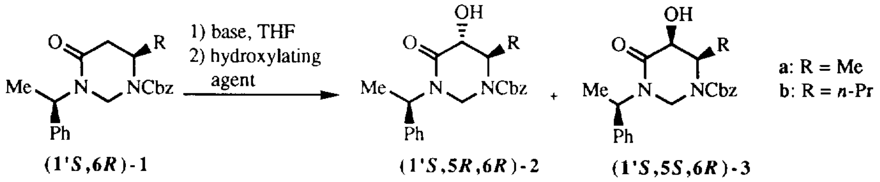


Table 1. Diastereomeric Products Ratios and Yields for the Hydroxylation Reaction of Perhydropyrimidin-4-ones **1a** and **1b**.

Entry	S.M.	R	Base	Hydroxylating agent (equiv.)	Temp. (°C)	Time (h)	yield (%)	d. r. **2/3**
1	**1a**	Me	LiHMDS	MoOPH (2)	-78-r.t.	16 h	61	80 : 20
2	**1a**	Me	NaHMDS	MoOPH (2)	-78-r.t.	16 h	66	76 : 24
3	**1b**	*n*-Pr	LiHMDS	MoOPH (2)	-78-r.t.	16 h	40	99 : 1
4	**1a**	Me	LiHMDS	(±)-phenylox. (2)	-78-r.t.	16 h	41[a]	47 : 53
5	**1a**	Me	NaHMDS	(±)-phenylox. (2)	-78-r.t.	16 h	77	25 : 75
6	**1b**	*n*-Pr	NaHMDS	(±)-phenylox. (2)	-78-r.t.	16 h	7	99 : 1
7	**1a**	Me	LiHMDS	(-)-camphor. (1.2)	-78-r.t.	16 h	66	78 : 22
8	**1a**	Me	NaHMDS	(-)-camphor. (1.2)	-78-r.t.	16 h	27	90 : 10
9	**1b**	*n*-Pr	LiHMDS	(-)-camphor. (1.2)	-78-r.t.	16 h	23	>99 : 1
10	**1b**	*n*-Pr	NaHMDS	(-)-camphor. (1.2)	-78-r.t.	16 h	-	-
11	**1b**	*n*-Pr	LiHMDS	(-)-camphor. (1.2)	-20-r.t.	16 h	29	>99 : 1
12	**1a**	Me	LiHMDS	(+)-camphor. (1.2)	-78-r.t.	16 h	78	66 : 34
13	**1b**	*n*-Pr	LiHMDS	(+)-camphor. (1.2)	-78-r.t.	16 h	40	>99 : 1
14	**1b**	*n*-Pr	LiHMDS	(+)-camphor. (1.2)	-20-r.t.	16 h	72	>99 : 1

[a] The corresponding condensation product with *N*-benzylidenebenzensulfonamide was obtained in 38% yield.

As Table 1 shows, different results have been obtained by changing both the base and the hydroxylating agents. Furthermore the influence of the reaction temperature has been reported. Indeed when MoOPH was utilised as hydroxylating agent (entries 1, 2 and 3) an excess of the 5,6-*trans* derivatives **2** was obtained, confirming the high 5,6-*trans* selectivity previously achieved in the alkylation [6d,12] and in the aldol condensation [13] of these substrates. With this hydroxylating agent, a very small variation of diastereoselection was observed on replacing the lithium with the sodium counterion (entry 1 *versus* entry 2).

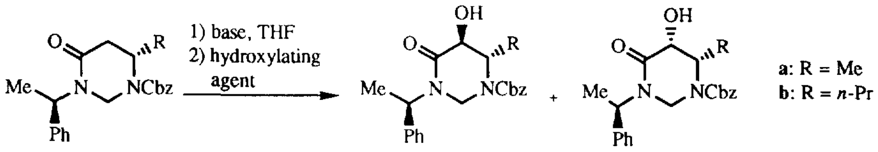
On the other hand, when (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine was used as hydroxylating agent, the base had a tremendous effect (entry 4 *versus* entry 5), indeed with LiHMDS a considerable amount of condensation product was obtained. This result was previously observed by Evans,[14] owing to the reaction of the lithium enolate with the imine by-product of the hydroxylation and can be avoided by using NaHMDS as base. Surprisingly the reaction of the sodium enolate of **1a** with (±)-phenyloxaziridine afforded an excess of the 5,6-*cis* derivative, while the sodium enolate of **1b** was unreactive.

Finally, to eliminate the problem of the condensation by-product, (-)- and (+)-(camphorsufonyl)oxaziridine were employed as hydroxylating agents. In this case the LiHMDS was demonstrate to be the base of choice, as it furnished better yield than NaHMDS (entries 7, 8, 9 and 10). Furthermore both enantiomers afforded complete diastereoselection in the hydroxylation of **1b**, but (+)-(camphorsulfonyl)oxaziridine furnished better yield, mainly when the hydroxylation was performed at higher temperature (entry 14). The configuration of the newly formed asymmetric centre at C_5 was determined by means of ^1H NMR analysis. Indeed the 5,6-*trans* derivatives present a H_5-H_6 coupling constant ($J_{H5,H6}$ = 9-11 Hz) always larger than the 5,6-*cis* derivative ($J_{H5,H6}$ = 6-7 Hz).

The high diastereoselection of **1b** with (+)-(camphorsufonyl)oxaziridine is in accord with what was recently obtained by Escalante and Jauristi [15] in the hydroxylation of the lithium enolate of 1-benzoyl-3-methyl-6(*S*)-phenylperhydropyrimidin-4one with (+)-(camphorsulfonyl)oxaziridine in the synthesis of the 2(*R*)-hydroxy-3(*R*)-*N*-benzoylamino-3-phenylpropionic acid, the *like* stereoisomer of Taxol's side chain.

Also (1'*S*,6*S*)-1-phenylethyl-6-alkyl perhydropyrimidin-4-ones **4a** and **4b** [11] were hydroxylated at C_5 under the same conditions (Scheme 2). The results are shown in Table 2.

Scheme 2.



(1'*S*,6*S*)-4 (1'*S*,5*S*,6*S*)-5 (1'*S*,5*R*,6*S*)-6

A global comparison of these results with what we obtained in Table 1 shows that the hydroxylation of (1'*S*,6*S*)-perhydropyrimidin-4-ones **4** proceeds with different diastereoselection from (1'*S*,6*R*)-perhydropyrimidin-4-ones **1**. This is a quite surprising result, because the two diastereoisomers behaved in the same way in the previously examined reactions. This dissimilarity can be probably attributed to the steric hindrance of the hydroxylating agents, which are bulkier than the analysed alkylating agents [6d,12] and aldehydes.[13] Thus these reagents interact probably both with the substituent at C_6 of the heterocycle and with the phenylethyl group at $C_{1'}$.

Table 2. Diastereomeric Products Ratios and Yields for the Hydroxylation Reaction of Perhydropyrimidin-4-ones **4a** and **4b**.

Entry	S.M.	R	Base	Hydroxylating agent (equiv.)	Temp. (°C)	Time (h)	yield (%)	d.r. **5/6**
1	**4a**	Me	LiHMDS	MoOPH (2)	-78-r.t.	16 h	63	72 : 28
2	**4b**	*n*-Pr	LiHMDS	MoOPH (2)	-78-r.t.	16 h	44	67 : 33
3	**4a**	Me	LiHMDS	(±)-phenylox. (2)	-78-r.t.	16 h	-	-
4	**4a**	Me	NaHMDS	(±)-phenylox. (2)	-78-r.t.	16 h	44	8 : 92
5	**4b**	*n*-Pr	NaHMDS	(±)-phenylox. (2)	-78-r.t.	16 h	-	-
6	**4a**	Me	LiHMDS	(-)-camphor. (1.2)	-78-r.t.	16 h	75	29 : 71
7	**4a**	Me	NaHMDS	(-)-camphor. (1.2)	-78-r.t.	16 h	15	1 : 99
8	**4b**	*n*-Pr	LiHMDS	(-)-camphor. (1.2)	-78-r.t.	16 h	6	82 : 18
9	**4b**	*n*-Pr	LiHMDS	(-)-camphor. (1.2)	-20-r.t.	16 h	35	99 : 1
10	**4a**	Me	LiHMDS	(+)-camphor. (1.2)	-78-r.t.	16 h	78	45 : 55
11	**4b**	*n*-Pr	LiHMDS	(+)-camphor. (1.2)	-78-r.t.	16 h	31	72 : 28
12	**4b**	*n*-Pr	LiHMDS	(+)-camphor. (1.2)	-20-r.t.	16 h	60	83 : 17

The hydroxylation of **4a** and **4b** furnished the 5-hydroxy-6-alkyl-perhydropyrimidin-4-ones **5** and **6** with lower diastereoselection than **1a** and **1b** (Table 2).When MoOPH was utilised (entries 1 and 2), the 5,6-*trans* derivative was preferentially obtained, despite a decrease of the diastereoselection, which is more evident with the increase of the alkyl group at C_6. On the other hand the reaction of the sodium enolate of **4a** with phenyloxaziridine afforded preferentially the 5,6-*cis* derivative **5a**.

(-)- And (+)-(camphorsulfonyl)oxaziridine provide different results, thus showing a strong matching/mismatching effect.[16] Indeed the reaction of (-)-(camphorsulfonyl)oxaziridine afforded preferentially the 5,6-*cis* derivative with the lithium enolate of **4a** and reacted with very low yield with **4b**, while (+)-(camphorsulfonyl)oxaziridine reacted with no diastereoselection with **4a** and furnished with **4b** preferentially the 5,6-*trans* adduct **5b**.

The different results obtained in the hydroxylation of perhydropyrimidin-4-ones (1'*S*,6*R*)-**1** and (1'*S*,6*S*)-**4** lead us to presume that the (*S*)-phenylethyl moiety at $C_{1'}$ plays a role in the reaction diastereoselectivity.[17]

The most stable conformations of the (*S*)-phenylethyl moiety have been previously calculated for related molecules by molecular mechanics methods [18] and two preferential conformations have been obtained, with the hydrogen coplanar and antiperiplanar with the carbonyl of the heterocycle. For all the analysed molecules, the conformation with the hydrogen coplanar with the carbonyl results to be the more populated one.

In a similar way we have calculated the preferred conformations [19] of the (*S*)-phenylethyl moiety for (1'*S*,6*R*)-**1**, Li-(1'*S*,6*R*)-**1**, Na-(1'*S*,6*R*)-**1**, (1'*S*,6*S*)-**4**, Li-(1'*S*,6*S*)-**4** and Na-(1'*S*,6*S*)-**4**. The energies, as a function of the dihedral angle α between the $C_{1'}$-H bond and the N_3-C_4 bond, are reported in Table 3.

Table 3. Dihedral Angles α, Energies and Populations for **1**, **4** and Their Lithium and Sodium Enolates.

Entry	Molecule	Dihedral Angle	Energy (Kcal/mol)	Population (%)
1	(1'*S*,6*R*)-**1**	18.7°	-1.13	99
2	(1'*S*,6*R*)-**1**	-170.5°	1.59	1
3	Li-(1'*S*,6*R*)-**1**	22.1°	9.16	97.1
4	Li-(1'*S*,6*R*)-**1**	-170.7°	11.76	1.2
5	Li-(1'*S*,6*R*)-**1**	-69.1°	11.55	1.7
6	Na-(1'*S*,6*R*)-**1**	21.4°	7.80	97.2
7	Na-(1'*S*,6*R*)-**1**	-173.8°	10.45	1.1
8	Na-(1'*S*,6*R*)-**1**	-77.1°	9.97	1.7
9	(1'*S*,6*S*)-**4**	4.4°	15.99	91.5
10	(1'*S*,6*S*)-**4**	-177.0°	17.39	8.5
11	Li-(1'*S*,6*S*)-**4**	8.2°	22.17	85.8
12	Li-(1'*S*,6*S*)-**4**	-168.9°	23.23	14.2
13	Na-(1'*S*,6*S*)-**4**	7.6°	20.78	85.4
14	Na-(1'*S*,6*S*)-**4**	-168.8°	21.82	14.6

The results reported show that the more populated conformations of **1** and **4** are nearly the same for the neutral molecules and for the corresponding enolates and display the (*S*)-phenylethyl moiety at $C_{1'}$ with the $C_{1'}$-H bond almost coplanar with the carbonyl of the heterocycles (Figure 2).

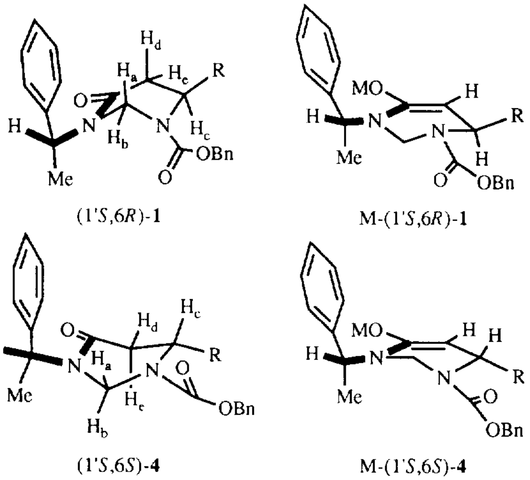


Figure 2

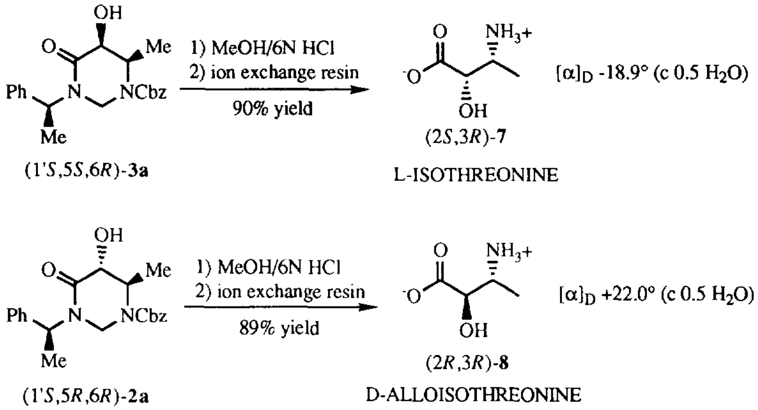
M = Li, Na

Owing to these preferential conformations, for (1'*S*,6*R*)-**1** and its enolates, the bulky phenyl group lies in the same side of the molecule with the C_6 substituent, while it lies on the other side for (1'*S*,6*S*)-**4** and its enolates. Thus the hydroxylation of **1a** and **1b** furnishes preferentially the corresponding 5,6-*trans* derivatives with good to high diastereoselection. The only reaction of **1a** with racemic phenyloxaziridine (Table 1 entries 4 and 5) is not clarified.

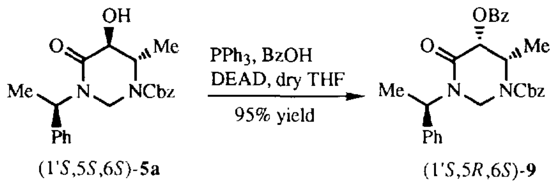
In contrast, the preferential conformation of **4** and its lithium and sodium enolates displays the two bulky substituents at $C_{1'}$ and at C_6 on different faces of the (1'*S*,6*S*)-perhydropyrimidin-4-ones. This accounts for a variety of results in the hydroxylation of **4a** and **4b**, indeed a wide variation of 5,6-*cis*/*trans* ratios are obtained, as a function of the C_6 substituent and of the hydroxylating agent.

Moreover the 2-hydroxy-3-amino acids L-isothreonine **7** and D-alloisothreonine **8** can be easily obtained by acid hydrolysis of the corresponding 5-hydroxy perhydropyrimidin-4-ones, utilizing the same method previously described for 6-alkyl and 5,6-dialkyl perhydropyrimidin-4-ones [6] (Scheme 3). Thus, by reaction of pyrimidin-4-ones (1'*S*,5*S*,6*R*)-**3a** and (1'*S*,5*R*,6*R*)-**2a** with 6N HCl at reflux for 30 hours complete hydrolysis of the heterocyclic rings was achieved with no racemisation. (2*S*,3*R*)-L-isothreonine **7** and (2*R*,3*R*)-D-alloisothreonine **8** were obtained pure after chromatography on a cation-exchange resin, as confirmed by ^{1}H NMR analysis and by the comparison of the $[\alpha]_D$ values with the data reported in the literature.[4b]

Scheme 3.



Finally a complete inversion of the absolute configuration at C_5 can be obtained by means of the Mitsunobu reaction.[20] Indeed (1'*S*,5*S*,6*S*)-5-hydroxy-6-methyl-perhydropyrimidin-4-one **5a** was treated with triphenylphosphine, benzoic acid and DEAD in dry THF for 6 hours at room temperature (Scheme 4). The benzoate derivative of the C_5-epimer **9** was readily obtained with high yield and total inversion of configuration.



Scheme 4

These results demonstrate that the hydroxylation at C_5 of (1'*S*)-phenylethyl-6-alkyl-perhydropyrimidin-4-ones affords the desired hydroxy derivative with high yield and good diastereoselection, if the reaction conditions are carefully studied for each substrate.

In this paper we have described the diastereoselective hydroxylation at C_5 of chiral 6-substituted perhydropyrimidin-4-ones. The diastereoselection depends on the hydroxylating agent. Furthermore the exocyclic (*S*)-phenylethyl moiety strongly influences the diastereoselection. This effect has never been observed in the past for functionalisations at C_5 and have been rationalised by molecular mechanics calculations. The acid hydrolysis of 5-hydroxy-6-methyl perhydropyrimidin-4ones furnished enantiomerically pure L-isothreonine and D-alloisothreonine.

EXPERIMENTAL SECTION

General: ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz 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. LiHMDS and NaHMDS were purchased as 1M solutions in THF. For the preparation of MoOPH see ref. 21. For the preparation of (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine see ref. 22.

General Procedure for the Hydroxylation of Perhydropyrimidin-4-ones 1 and 4 with the complex MoO_5-pyridine-HMPT (MoOPH)

To a stirred solution of perhydropyrimidin-4-one (**1**) or (**4**) (1 mmol) in dry THF (20 mL) LiHMDS or NaHMDS (1M sol. in THF, 1 mmol, 1 mL) was added in one portion under argon at 0 °C. For the preparation of the lithium enolate, the reaction mixture was stirred for 1h at 0 °C, while for the preparation of the sodium enolate the reaction mixture was stirred for 2 h at room temperature. Then the mixture was cooled at -78 °C and solid MoOPH was added in one portion. The reaction was vigorously stirred for 16 h while the temperature was slowly raising till room temperature. Then the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$, the organic 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.

General Procedure for the Hydroxylation of Perhydropyrimidin-4-ones 1 and 4 with (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, (-) or (+)-(camphorsulfonyl)oxaziridine

To a stirred solution of perhydropyrimidin-4-one (**1**) or (**4**) (1 mmol) in dry THF (20 mL) LiHMDS or NaHMDS (1M sol. in THF, 1 mmol, 1 mL) was added in one portion under argon at 0 °C. For the preparation of the lithium enolate, the reaction mixture was stirred for 1h at 0 °C, while for the preparation of the sodium enolate the reaction mixture was stirred for 2 h at room temperature. Then the mixture was cooled at -78 °C or -20 °C (see Tables) and the oxaziridine in dry THF (5 ml) was added dropwise. The reaction was vigorously stirred for 16 h while the temperature was slowly raising till room temperature. Then the reaction was quenched with a saturated solution of NH_4Cl, the organic 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*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-hydroxy-6-methyl-perhydropyrimidin-4-one (2a). IR (film) 3400, 1707, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50° C) δ 1.44 (d, 3H, J = 6.1 Hz, C*H*$_3$-CH-CH-OH); 1.52 (m, 3H, C*H*$_3$-CH-Ph); 3.70 (m, 1H, CH_3-C*H*-CH-OH); 3.83-4.03 (bs, 1H, OH); 3.93 (d, 1H, J = 9.3 Hz, C*H*-OH), 3.99 (d, 1H, J = 14.1 Hz, H_a); 5.09 (m, 1H, H_b); 5.19 (AB, 2H, J = 12.3 Hz, O-C*H*$_2$-Ph); 5.71 (q, 1H, J = 6.8 Hz, CH_3-C*H*-Ph); 7.37 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50° C) δ 16.4, 19.1, 50.7, 51.6, 54.5, 67.9, 71.5, 127.2, 127.9, 128.1, 128.3, 128.5, 128.6, 128.8, 136.0, 139.4, 154.0, 170.7; $[\alpha]_D$ -81.9 (c 0.16, $CHCl_3$). Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.36; H, 6.61; N, 7.52.

(1'*S*,5*R*,6*R*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-hydroxy-6-*n*-propyl-perhydropyrimidin-4-one (2b). IR (film) 3420, 1709, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.88 (t, J = 7.2 Hz, 3H, C*H*$_3$-CH_2-CH_2), 1.10-1.90 (m, 7H, CH_3-C*H*$_2$-C*H*$_2$ + C*H*$_3$-CH-Ph), 3.77 (m, 1H, CH_3-C*H*-CH-OH), 3.90 (d, 1H, J = 13.6 Hz, H_a), 3.92 (bs, 1H, OH), 4.04 (d, 1H, J = 10.3 Hz, C*H*-OH); 5.07 (d, 1H, J = 13.6 Hz, H_b), 5.18 (AB, 2H, J = 12.2 Hz, O-C*H*$_2$-Ph); 5.68 (q, 1H, J = 7.0 Hz, CH_3-C*H*-Ph); 7.3 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.0, 16.4, 17.6, 26.7, 35.6, 51.7, 57.9, 68.0, 69.9, 127.3, 128.0, 128.4, 128.6, 128.8, 136.0, 139.4, 154.2, 171.0; $[\alpha]_D$ -71.2 (c 0.26, $CHCl_3$). Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.75; H, 7.10; N, 7.03.

(1'*S*,5*S*,6*R*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-hydroxy-6-methyl-perhydropyrimidin-4-one (3a). IR (film) 3400, 1707, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C), δ 0.99 (m, 3H, C*H*$_3$-CH-CH-OH); 1.56 (d, 3H, J = 7.2 Hz, C*H*$_3$-CH-Ph); 3.6-3.9 (bs, 1H, OH); 4.30 (d, 1H, J = 7.2 Hz, C*H*-OH); 4.43 (m, 1H, CH_3-C*H*-CH-OH), 4.63 (d,1H, J = 11.8 Hz, H_b); 4.73 (m, 1H, H_a); 5.13 (m, 2H, O-C*H*$_2$-Ph); 5.93 (q, 1H, J = 7.2 Hz, CH_3-C*H*-Ph); 7.3 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50° C) δ 13.4, 16.4, 50.3, 51.3, 52.0, 67.7, 68.2, 127.2, 127.9, 128.1, 128.2, 128.6, 128.7, 136.1, 138.9, 154.1, 170.5; $[\alpha]_D$ -37.0 (c 0.1, $CHCl_3$). Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.52; H, 6.56; N, 7.49.

(1'*S*,5*S*,6*S*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-hydroxy-6-methyl-perhydropyrimidin-4-one (5a). IR (film) 3400, 1708, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 1.43 (d, 3H, J = 6 Hz, C*H*$_3$-CH-CH-OH); 1.56 (d,3H, J = 7.2 Hz, C*H*$_3$-CH-Ph); 3.63 (bs, 1H, OH), 3.91 (m, 1H, CH_3-C*H*-CH-OH), 3.97 (d, 1H, J = 9.4 Hz, C*H*-OH); 4.34 (d, 1H, J = 12.8 Hz, H_b), 5.0 (d, 1H, J = 12.8 Hz, H_a); 5.15 (m, 2H, O-C*H*$_2$-Ph); 5.77 (q, 1H, J = 7.2 Hz, CH_3-C*H*-Ph); 7.3 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ 17.1, 18.9, 50.8, 51.8, 54.1, 67.5, 71.3, 127.0, 127.6, 127.9, 128.1, 128.4, 128.7, 136.0, 139.4, 170.9; $[\alpha]_D$ -28.8 (c 0.17, $CHCl_3$). Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.39; H, 6.50; N, 7.59.

(1'*S*,5*S*,6*S*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-hydroxy-6-*n*-propyl-perhydropyrimidin-4-one (5b). IR (film) 3450, 1709, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H, C*H*$_3$-CH_2-CH_2), 1.10-1.90 (m, 4H, CH_3-C*H*$_2$-C*H*$_2$), 1.55 (d, 3H, J = 7.2 Hz, C*H*$_3$-CH-Ph), 3.74 (bs, 1H, OH), 3.91 (m, 1H, CH_3-C*H*-CH-OH), 4.10 (d, 1H, J = 9.0 Hz, C*H*-OH), 4.28 (d, 1H, J = 12.6 Hz, H_b), 4.99 (d, 1H, J = 12.6 Hz, H_a), 5.16 (m, 2H, O-C*H*$_2$-Ph); 5.74 (q, 1H, J = 7.2 Hz, CH_3-C*H*-Ph); 7.3 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.1, 17.1, 17.4, 29.7, 35.1, 51.8, 57.3, 67.6, 69.5, 127.1, 127.8, 127.9, 128.2, 128.4, 128.6, 135.9, 139.4, 151.7, 171.1; $[\alpha]_D$ -19.3 (c 0.15, $CHCl_3$). Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.66; H, 7.16; N, 7.05.

(1'*S*,5*R*,6*S*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-hydroxy-6-methyl-perhydropyrimidin-4-one (6a). IR (film) 3500, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.15 (d, 3H, J = 6.3 Hz, C*H*$_3$-CH-CH-OH); 1.59 (d,3H, J = 6.9 Hz, C*H*$_3$-CH-Ph); 3.82 (bs, 1H, OH), 4.32 (d, 1H, J = 6 Hz, C*H*-OH); 4.2-4.6 (m, 2H, H_b + CH_3-C*H*-CH-OH); 4.82 (m, 1H, H_a); 5.15 (m, 2H, O-C*H*$_2$-Ph); 5.89 (q, 1H, J = 6.9 Hz, CH_3-C*H*-Ph), 7.30 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ 15.8, 29.7, 50.7, 51.5, 52.3, 67.7, 68.2, 127.1, 127.9, 128.1, 128.3, 128.6, 128.9, 136.1, 138.9, 155.3, 170.6; $[\alpha]_D$ -72.5 (c 0.1, $CHCl_3$). Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.42; H, 6.50; N, 7.65.

(1'*S*,5*R*,6*S*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-hydroxy-6-*n*-propyl-perhydropyrimidin-4-one (6b). IR (film) 3440, 1710, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H, C*H*$_3$-CH_2-CH_2), 1.10-1.90 (m, 4H, CH_3-C*H*$_2$-C*H*$_2$), 1.60 (d, 3H, J = 7.1 Hz, C*H*$_3$-CH-Ph), 3.77 (bs, 1H, OH), 4.24 (d, 1H, J = 6.0 Hz, C*H*-OH), 4.50 (m, 2H, CH_3-C*H*-CH-OH + H_a), 4.66 (d, 1H, J = 12.6 Hz, H_b), 5.10 (m, 2H, O-C*H*$_2$-Ph); 5.88 (q, 1H, J = 7.2 Hz, CH_3-C*H*-Ph); 7.30 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ 13.9, 15.5, 19.1, 29.5, 31.9, 51.4, 53.7, 67.9, 68.4, 127.2, 128.0, 128.2, 128.6, 128.8, 135.9, 138.8, 170.8; $[\alpha]_D$ -27.5 (c 0.4, $CHCl_3$). Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.64; H, 7.11; N, 7.11.

General Procedure for the Hydrolysis of Perhydropyrimidin-4-ones (2), (3), (4) and (5)

A solution of perhydropyrimidin-4-one (1 mmol) in 6N 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 6N 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 1.5N aqueous NH_4OH to recover the α-hydroxy β-amino acid, which was obtained after evaporation in the zwitterionic form.

L-Isothreonine, (2*S*,3*R*)-(7) 90% yield; mp 210-211 °C (lit. [4b] for D-isothreonine 215-217 °C); ^1H NMR (D_2O) δ 1.29 (d, 3H, J = 6.9 Hz, CH_3), 3.49 (dq, 1H, J = 5.0 Hz, 6.9 Hz, C*H*-NH_2), 3.98 (d, 1H, J = 5.0 Hz, C*H*-OH); ^{13}C NMR 14.8, 49.2, 73.1, 177.1; $[\alpha]_D$ -18.9 (c 0.5, H_2O), lit. [4b] for D-isothreonine $[\alpha]_D$ +22.2 (c 0.46, H_2O).

D-Alloisothreonine, (2*R*,3*R*)-(8) 89% yield; mp 238-239 °C (lit. [4b] for D-alloisothreonine 242-243 °C); ^1H NMR (D_2O) δ 1.20 (d, 3H, J = 6.8 Hz, CH_3), 3.60 (dq, 1H, J = 3.4 Hz, 6.8 Hz, C*H*-NH_2), 4.21 (d, 1H, J = 3.4 Hz, C*H*-OH); ^{13}C NMR (D_2O) δ 13.6, 48.8, 73.8, 177.7; $[\alpha]_D$ +23.0 (c 0.5, H_2O), lit. [4b] for D-isothreonine $[\alpha]_D$ -26.15 (c 0.11, H_2O).

(1'*S*,5*R*,6*S*)-Benzyloxycarbonyl-3-(1'-phenylethyl)-5-benzoyl-6-methyl-perhydropyrimidin-4-one (9)

To a stirring solution of (5a) (1 mmol, 0.37 g), solid triphenylphosphine (2 mmol, 0.52 g) and benzoic acid (2 mmol, 0.24 g) in dry THF (20 ml) was added dropwise a solution of diethyl azodicarboxylate (2 mmol, 0.35 g) in dry THF (10 ml) under nitrogen and at room temperature. The mixture was stirred at room temperature for 6 h, then the solvent was removed under reduced pressure and replaced with CH_2Cl_2. The mixture was washed with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, concentrated and chromatographed on silica gel (cyclohexane/ethyl acetate 9:1 as eluant).

IR (film) 1732, 1712, 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.38 (d, 3H, J = 6.3 Hz, C*H*$_3$-CH-CH-OBz), 1.60 (d, 3H, J = 7.1 Hz, C*H*$_3$-CH-Ph), 4.59 (m, 2H, C*H*-CH-OBz + H_a), 4.80 (m, 1H, H_b), 5.14 (m, 2H, O-C*H*$_2$-Ph); 5.74 (d, 1H, J = 4.7 Hz, CH-O), 5.95 (q, 1H, J = 7.1 Hz, CH_3-C*H*-Ph); 7.20-7.80 (m, 13H, Ph), 8.13 (d, 2H, J = 7.0 Hz, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ 14.7, 16.8, 50.5, 51.8, 65.1, 68.9, 70.6, 128.2, 128.9, 129.1, 129.3, 129.4, 129.6, 129.8, 130.5, 131.0, 133.1, 134.4, 136.9, 140.1, 166.3 ; $[\alpha]_D$ -87.5 (0.2, $CHCl_3$). Anal. Calcd. for $C_{28}H_{28}N_2O_4$: C, 71.17; H, 5.97; N, 5.93. Found: C, 71.20; H, 5.92; N, 5.89.

Acknowledgement 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 HPLC analysis.

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(*Received in UK* 17 *July* 1995; *revised* 4 *September* 1995; *accepted* 8 *September* 1995)