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Synthesis and Stereochemical Behaviour of 8-Alkyl-3-(1-phenylethyl)-7-oxa-1,3-diazabicyclo-[3.2.1]-octane-4,6-diones Directed Towards the Synthesis of α-Substituted β-Amino Acids

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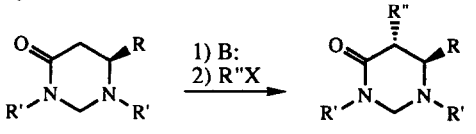
Abstract : A diastereoselective synthesis of enantiomerically pure α-hydroxymethyl β-amino acid derivatives is described starting from α,β-unsaturated acids. The unsaturated acids are transformed through simple steps into chiral perhydropyrimidin-4-ones that are diastereoselectively transformed into [3.2.1]-1,3-diaza-7-oxabicyclooctan-4,6-diones by reaction with LiHMDS. The bicycle **9b** is opened by reaction with methanol under acid catalysis and the product **10** is selectively reduced to afford the desired compound.

In a program directed towards the synthesis of enantiomerically pure α-substituted β-amino acids,[1] we describe herein a new route for the synthesis of *anti* α -hydroxymethyl β-amino acids with high diastereoselectivity, starting from [3.2.1]-3-(phenyl-1-yl)-8-(alkyl)-1,3-diaza 7-oxabicyclooctan-4,6-diones, easily obtained from chiral perhydropyrimidin-4-ones.

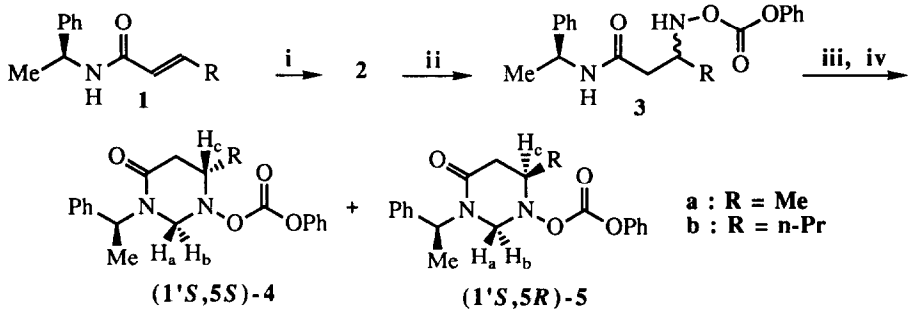
β-Amino acids are receiving increasing interest due to the importance of these compounds as components of natural products and as starting materials in the synthesis of antibiotics.[2] Not many methods are described for the synthesis of enantiomerically pure α-substituted β-amino acids [3] and among them the use of chiral perhydropyrimidin-4-ones as a masked form of β-amino acids appears particularly attractive,[4] because these heterocycles easily undergo alkylation and aldol condensation reactions [5] at C_5 in good yield and with high diastereoselectivity.



We obtained the perhydropyrimidin-4-ones by conjugate addition of hydroxylamine to α,β-unsaturated amides, followed by cyclisation with paraformaldehyde.[6] According to a well known procedure,[7] the addition of 2 equivalents of free hydroxylamine to alk-2-enoic acids at reflux affords β-amino acids, although in low yield. Here the hydroxylamine behaves both as nucleophile and as the reducing agent for the 3-hydroxylamino intermediate. On the other hand the conjugate addition of *N*-substituted hydroxylamines to

α,β-unsaturated esters [8] and sugar lactones [9] provides a short route to isoxazolidin-5-ones generally with good yield. Recently we described the highly diastereomeric addition of *O*-benzylhydroxylamine to the α,β-unsaturated imides of chiral imidazolidin-4-ones, promoted by Lewis acids[10] with the aim of obtaining enantiomerically pure β-amino acids.

In order to synthesise the enantiomerically pure 3-(1'-phenylethyl)-6-alkylperhydropyrimidin-4-ones **4** and **5** in good yield we reacted the free hydroxylamine with (*S*)-*N*-(1-phenylethyl)-2-alkenamides **1** in ethanol and water at reflux (Scheme 1). Reaction was complete in 3 hours and the addition products were recovered simply by removing the solvent. As observed for esters and lactones, the addition of hydroxylamine to the α,β-unsaturated amides **1** affords the corresponding 3-hydroxylamino derivatives **2**. The subsequent reaction with NaOH and benzyl chloroformate in water/acetone afforded exclusively the *O*-protected derivatives **3** in 70% yield. The IR absorption of **3a** and **3b** at 1758 and 1756 cm^{-1} respectively indicates the formation of a carbonate group. The reaction of **3** with paraformaldehyde under acid catalysis affords quantitatively the perhydropyrimidin-4-ones **4** and **5** which can be easily separated by flash chromatography.



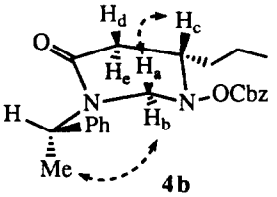
Scheme 1. *Reagents and conditions:* i NH_2OH (2 equiv.), ETOH/H_2O, reflux, 3h; ii NaOH (1.1 equiv), CbzCl (1.1 equiv.), acetone/water, r.t., 1h; iii paraformaldehyde (5 equiv.), TsOH (0.3 equiv.), benzene, reflux, 1h; iv flash chromatography.

The configuration of the asymmetric centre at C_6 of the pure heterocycles was attributed by means of ^1H NMR analysis, utilising the (*S*)-phenylethyl moiety as reference point. In earlier work [12] we have hypothesised that this chiral group assumes a rigid conformation with the hydrogen eclipsing the adjacent carbonyl group. This observation has been confirmed by MMP2 [13] calculations and by the analysis of all the heterocycles yet studied, containing this moiety. As a result of this conformation, the phenyl group exerts a shielding effect on the hydrogens above the heterocycle, so that H_a is always more shielded than H_b (Table 1) and H_c is more shielded in **4a** and **4b** than in **5a** and **5b** (Figure 1).

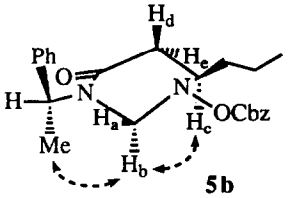
Table 1. ^1H NMR Data of Perhydropyrimidin-4-ones 4 and 5.

Product	δH_a	δH_b	δH_c	δH_d,H_e
(1'*S*,6*S*)-**4a**	4.00	4.40	3.41	2.48
(1'*S*,6*R*)-**5a**	4.22	4.44	3.50	2.53
(1'*S*,6*S*)-**4b**	3.99	4.39	3.20	2.48
(1'*S*,6*R*)-**5b**	4.24	4.41	3.31	2.54

NOEDIFF experiments performed on samples of **4b** and **5b**, confirmed the stereochemical assignment. Thus irradiation of the methyl at $C_{1'}$ in **4b** (δ 1.41) produces an enhancement of the doublet at δ 4.39, assigned to H_b, while irradiation of H_c (δ 3.20) produces an enhancement of the doublet at δ 3.99, assigned to H_a. Moreover the NOEDIFF experiments performed on **5b** confirmed the *R* configuration assigned to C_6. Irradiation of the d at δ 1.51, assigned to the methyl on $C_{1'}$, causes an enhancement of H_b (δ 4.41) and *vice versa*. Finally on irradiation of H_b an enhancement of H_c (δ 3.31) is observed and *vice versa*.



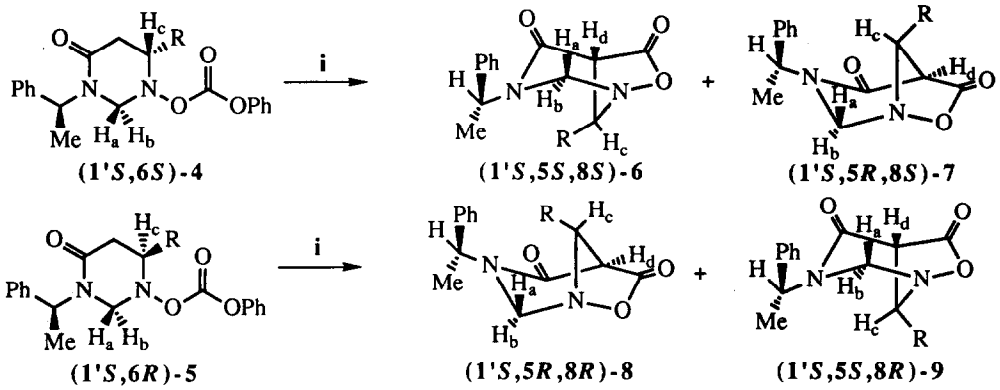
4b



5b

Figure 1.

The synthesis of the bicycles **6-9** can be accomplished readily by reacting compounds **4** or **5** with 1 equivalent of LiHMDS in THF at -78 °C. The cyclisation reaction is complete in 30 min and the products are recovered in high yield after the usual workup (Scheme 2).



Scheme 2. *Reagents and conditions:* i LiHMDS (1 equiv.), dry THF, -78 °C, 30 min. **a : R = Me**
b : R = *n*-Pr

The reaction shows good diastereoselectivity when **4a** and **5a** are reacted under the reported conditions, affording preferentially the trans isomers **6a** and **8a** (Table 2). At -78 °C a small amount of the *cis* derivatives **7a** and **9a** is observed and increases if the reaction takes place at a higher temperature (i. e. -20 °C). On the other hand with larger substituents on **4b** and **5b**, like the *n*-propyl group, no *cis* derivative is recovered even if the reaction is carried out at -20 °C.

The bicycles **6-9** show peculiar chemical and spectroscopic behaviour and are far more polar than the starting materials **4-5**, showing a R_f 0.1-0.3 in pure ethyl acetate, and thus are easily obtained pure by flash chromatography on silica gel.

Table 2. Diastereomeric Ratios for the Cyclisation of 4 and 5 at -78 °C.

R	6/7 ratio[a]	8/9 ratio[a]
Me	86/14	87/13
n-Pr	> 99/1	> 99/1

[a] Determined by ^{1}H NMR analysis.

The configuration of the newly formed asymmetric centre at C_5 was attributed by means of the ^{1}H NMR spectra of the product. In this respect the coupling constants $J_{Hc,Hd}$ of **6**, **7**, **8** and **9** are diagnostic and account for the required stereochemistry (Table 3). In fact products **6** and **8** have $J_{Hc,Hd}$ larger than products **7** and **9** (5.4-6.1 Hz *versus* 1.9-2.4 Hz). Furthermore owing to the rigid conformation of the molecule, the hydrogens abutting the phenyl of the (*S*)-phenylethyl moiety are strongly shielded (i. e. H_c in **7** and CH_3 in **8**, see Table 3). A 1,5 long range coupling constant (1.5-2.0 Hz) was also recorded between H_d and H_a (products **7** and **8**) or H_d and H_b (products **6** and **9**) depending on the molecular structure.

Table 3. ^{1}H NMR Data of Bicycles 6-9.

Product	δ_{Ha}	δ_{Hb}	δ_{Hc}	δ_{Hd}	δ_{CH3}	$J_{Hc,Hd}$	$J_{Ha,Hd}$	$J_{Hb,Hd}$
(1'*S*,5*S*,6*S*)-**6a**	4.06	3.96[a]	2.35	2.87	1.22	5.4	-	1.5
(1'*S*,5*R*,6*S*)-**7a**	3.85[a]	4.47	1.60	2.58	1.18	1.9	1.9	-
(1'*S*,5*R*,6*R*)-**8a**	3.64[a]	4.49	2.21	2.82	0.72	5.5	1.6	-
(1'*S*,5*R*,6*R*)-**9a**	4.06	4.15[a]	1.83	2.58	1.25	2.4	-	1.8
(1'*S*,5*S*,6*S*)-**6b**	4.08	3.99[a]	2.26	2.91	-	6.1	-	1.8
(1'*S*,5*R*,6*R*)-**8b**	3.70[a]	4.49	2.09	2.83	-	6.1	2.0	-

[a] These signals show a long-range coupling with H_d.

The NOEDIFF experiments performed on **6a**, **7a** and **8b** are in agreement with the assigned structures (Figure 2). In **6a**, irradiation of the methyl on $C_{1'}$ causes enhancement of H_b and of the methyl at C_6, and *vice versa*. On the other hand, irradiation of the methyl on $C_{1'}$ of **7a** causes enhancement of H_b, while on irradiation of H_d the methyl at C_6 is enhanced. Furthermore irradiation of H_a causes enhancement of H_c and *vice versa*. Finally in **8b** on irradiation of H_b, the signals of H_d and of the methyl at $C_{1'}$ are enhanced, while on irradiation of H_a the signals of the *n*-propyl side chain are enhanced.

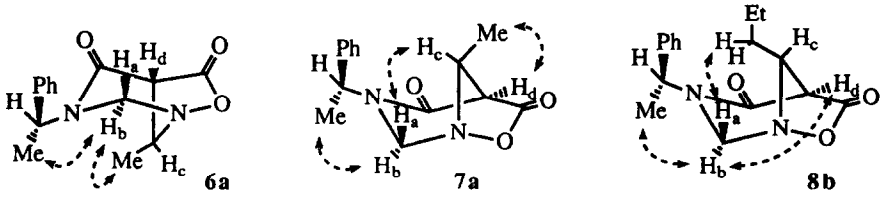
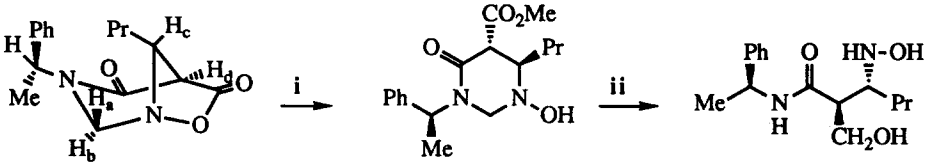


Figure 2.

In order to synthesise the optically active α-hydroxymethyl β-amino acid derivative **11**, the bicycle (1'*S*,5*R*,6*R*)-**8b** was easily transformed in high yield by treatment with dry methanol in the presence of Amberlyst A-26 at reflux for 3 h to the ester **10** which was selectively reduced into the corresponding primary alcohol **11** with $LiAlH_4$ at 0 °C in THF (Scheme 3). Compound **11** was fully characterised and can be easily

transformed into the corresponding amino acids by known synthetic methods: reduction of the N-O bond [14] and hydrolysis of the amide group.[4c,d,5b]



(1'*S*,5*R*,8*R*)-8b **(1'*S*,5*R*,6*R*)-10** **(1'*S*,2*S*,3*R*)-11**

Scheme 3. *Reagents and conditions:* i Amberlyst H-15 (2 equiv.), dry MeOH, reflux 3h; ii $LiAlH_4$ (1.5 equiv.), dry THF, 0 °C, 30 min.

In conclusion this work describes a simple route to a totally diastereoselective synthesis of bicycles **7** and **9** for substituents larger than the methyl groups. These compounds exhibit peculiar chemical and spectroscopic behaviour and can be easily transformed through few easy steps into enantiomerically pure α-hydroxymethyl β-amino acids.

EXPERIMENTAL SECTION

General Methods. ^1H 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. Infrared spectra were recorded with a NICOLET 205 FT infrared spectrometer. Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with silica gel 60 (230-400 mesh). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Methylene chloride was distilled over CaH_2 and stored over molecular sieves. Other solvents were used as purchased.

(*S*)-*N*-(1-Phenylethyl)-alk-2-enamide (1)

To a stirred solution of (*S*)-phenylethylamine (40 mmol, 5.16 ml) and triethylamine (60 mmol, 8.36 ml) in dry CH_2Cl_2 (100 ml) 2-butenoyl or 2-hexenoyl chloride (40 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise at 0 °C under inert atmosphere. The mixture was stirred at rt for 1 h, then washed with water and with a saturated solution of Na_2CO_3. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. After flash chromatography (cyclohexane/ethyl acetate 8:2) the product was recovered as a waxy solid in 92% yield.

(1a) : Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.07; H, 7.93; N, 7.43; $[\alpha]_D$ = -121.4 (c 1.8, $CHCl_3$); IR (film) 3436, 3310, 1675, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (d, 3H, *J* = 7.2 Hz, N-CH-C*H*$_3$), 1.79 (dd, 3H, *J* = 6.9, 1.6 Hz, HC=CH-C*H*$_3$), 5.16 (apparent quintet, 1H, *J* = 7.2 Hz, N-C*H*-CH_3), 5.86 (dd, 1H, *J* = 15.2, 1.6 Hz, *H*C=CH-CH_3), 6.54 (d, 1H, *J* = 7.2 Hz, NH), 6.79 (dq, 1H, *J* = 6.9, 15.2 Hz, HC=C*H*-CH_3), 7.31 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 17.5, 21.6, 48.4, 125.1, 126.0, 127.0, 128.4, 139.6, 143.3, 165.1.

(1b) : Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.41; H, 8.83; N, 6.44; $[\alpha]_D$ = -101.0 (c 1.1, $CHCl_3$); IR (film) 3420, 3345, 1672, 1636, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, *J* = 7.3 Hz, =CH-CH_2-CH_2-C*H*$_3$), 1.45 (m, 2H, =CH-CH_2-C*H*$_2$-CH_3), 1.47 (d, 3H, *J* = 7.4 Hz, N-CH-C*H*$_3$), 2.11

(apparent quartet, 1H, J = 7.1, =CH-C*H*$_2$-CH$_2$-CH$_3$), 5.18 (apparent quintet, 1H, J = 7.4 Hz, N-C*H*-CH$_3$), 5.82 (d, 1H, J = 15.3 Hz, OC-*H*C=CH), 6.32 (d, 1H, J = 7.4 Hz, NH), 6.83 (dt, 1H, J = 7.1, 15.3 Hz, OC-HC=C*H*), 7.28 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.6, 21.4, 21.6, 34.0, 48.5, 121.6, 123.6, 126.1, 127.1, 128.5, 143.2, 144.7, 165.2.

[*S*,(*S*,*R*)]-*N*-(1-Phenylethyl)-3-hydroxylaminoalkanamide (2)

A hot solution of sodium ethoxide was prepared from Na (0.92 g, 40 mmol) and absolute EtOH (50 ml) under argon. A hot solution of hydroxylamine hydrochloride (2.78 g, 40 mmol) in distilled H_2O (4 ml) was added with 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 to it pure amide (**1**) (20 mmol) was added. The mixture was refluxed 3 h and then concentrated under reduced pressure. The residue was chromatographed with ethyl acetate as eluant, and the compound (**2**) was obtained as a waxy solid in 70% yield.

(**2a**) : Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.78; H, 8.09; N, 12.53; IR (film) 3305, 3236, 1652, 1558 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of diastereoisomers) δ 1.05 and 1.10 (d, 3H, J = 6.6 Hz, ON-CH-C*H*$_3$), 1.44 (d, 3H, J = 6.8 Hz, N-CH-C*H*$_3$), 2.27 (dd, 1H, ON-CH-C*H*H, J = 5.0, 14.5 Hz), 2.40 (dd, 1H, J = 7.1, 14.5 Hz, ON-CH-CH*H*), 3.34 (m, 1H, ON-CH), 5.05 and 5.06 (apparent quintet, 1H, J = 6.8 Hz, N-C*H*-CH$_3$), 5.90 (bs, 1H, OH), 6.83 (d, 1H, J = 6.8 Hz, NH), 7.28 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) (mixture of diastereoisomers) δ 17.9, 22.2 and 22.3, 40.1, 48.9, 54.8, 126.4, 127.4, 128.8, 143.7, 171.2.

(**2b**) : Anal. Calcd. for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.07; H, 8.86; N, 11.21; IR ($CHCl_3$) 3436, 3286, 1656, 1509 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of diastereoisomers) δ 0.89 (t, 3H, J = 7.0 Hz, ON-CH-CH$_2$-CH$_2$-C*H*$_3$), 1.35 (m, 4H, ON-CH-C*H*$_2$-C*H*$_2$-CH$_3$), 1.43 (d, 3H, J = 7.1 Hz, N-CH-C*H*$_3$), 2.38 (m, 2H, ON-CH-C*H*$_2$), 3.16 (m, 1H, ON-CH), 5.08 (apparent quintet, 1H, J = 7.1 Hz, N-C*H*-CH$_3$), 5.51 (bs, 1H, OH), 6.91 (d, 1H, J = 7.1 Hz, NH), 7.29 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) (mixture of diastereoisomers) δ 14.0, 19.1 and 19.2, 21.8 and 21.9, 33.7, 38.2, 48.6, 58.8, 126.0, 127.1, 128.5, 143.4, 171.0.

[*S*,(*S*,*R*)]-*N*-(1-Phenylethyl)-3-O-benzyloxycarbonylhydroxylaminoalkanamide (3)

To a stirred solution of amide (**2**) (30 mmol) and NaOH (1.32 g, 33 mmol) in distilled water (25 ml) was added a solution of benzyl chloroformate (5.2 ml, 33 mmol) in acetone (25 ml) 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. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (cyclohexane/ethyl acetate 6:4 for (**2a**) and 8:2 for (**2b**) as eluant) and to give the product as a liquid in 70% yield.

(**3a**) : Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.33; H, 6.75; N, 7.83; IR (film) 3290, 3236, 1758, 1643, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of diastereoisomers) δ 1.11 and 1.16 (d, 3H, J = 6.5 Hz, ON-CH-C*H*$_3$), 1.45 and 1.46 (d, 3H, J = 7.0 Hz, N-CH-C*H*$_3$), 2.31 (d, 2H, J = 4.5 Hz, ON-CH-C*H*$_2$), 3.53 (dq, 1H, J = 4.5, 6.5 Hz, ON-CH), 5.10 (apparent quintet, 1H, J = 7.0 Hz, N-C*H*-CH$_3$), 5.19 and 5.21 (s, 2H, OC*H*$_2$Ph), 7.12 (d, 1H, J = 7.0 Hz, NH), 7.32 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) (mixture of

diastereoisomers) δ 18.6 and 18.7, 23.1, 40.4, 49.8, 55.0, 71.3, 127.2, 128.1, 129.6, 129.7, 129.8, 135.8, 144.6 and 144.7, 157.1, 170.9.

(3b) : Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.71; H, 7.28; N, 7.23; IR (film) 3296, 1756, 1644, 1544 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of diastereoisomers) δ 0.87 and 0.90 (t, 3H, *J* = 6.9 Hz, ON-CH-CH_2-CH_2-CH_3), 1.35 (m, 4H, ON-CH-CH_2-CH_2-CH_3), 1.45 and 1.46 (d, 3H, *J* = 7.0 Hz, N-CH-CH_3), 2.33 (ABX, 2H, *J* = 4.0, 6.9, 15.2 Hz, ON-CH-CH_2), 3.37 (m, 1H, ON-CH), 5.10 (apparent quintet, 1H, *J* = 7.0 Hz, N-CH-CH_3), 5.18 and 5.21 (s, 2H, OCH_2Ph), 7.12 (d, 1H, *J* = 7.0 Hz, NH), 7.28 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) (mixture of diastereoisomers) δ 13.8, 18.9, 21.9, 33.4 and 33.5, 37.6 and 37.7, 48.6, 58.2, 70.2, 126.0, 126.7, 128.3, 128.5, 134.6, 143.5, 155.9, 169.8.

1-Benzyloxycarbonylhydroxyl-3-(1'-Phenylethyl)-6-alkylperihydropyrimi-din-4-ones (4) and (5)

To a stirred solution of amide **(3)** (20 mmol) in benzene (50 ml) was added paraformaldehyde (3.0 g, 100 mmol) and *p*-toluenesulfonic acid monohydrate (1.14 g, 6 mmol). 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*S*)-**(4)** (1'*S*,6*R*)-**(5)** were obtained pure, after flash chromatography of the residue on silica gel (cyclohexane/ethyl acetate 65:35 for **(4a)** and **(5a)** and 9:1 **(4b)** and **(5b)** as eluant).

(1'*S*,6*S*)-(4a): Yield 39%, oil. Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.40; H, 6.53; N, 7.62; $[\alpha]_D$ = -42.6 (c 2.7, $CHCl_3$); IR (film) 2975, 1773, 1646, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, *J* = 6.8 Hz, ON-CH-CH_3), 1.45 (d, 3H, *J* = 7.1 Hz, N-CH-CH_3), 2.48 (m, 2H, ON-CH-CH_2), 3.41 (m, 1H, H_c), 4.00 (d, 1H, *J* = 14.1 Hz, H_a), 4.40 (d, 1H, *J* = 14.1 Hz, H_b), 5.18 (s, 2H, OCH_2Ph), 6.08 (q, 1H, *J* = 7.1 Hz, N-CH-CH_3), 7.28 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 17.7, 19.1, 34.9, 49.3, 56.6, 70.7, 127.8, 128.1, 128.8, 128.9, 129.0, 129.1, 129.2, 132.3, 135.1, 139.4, 155.3, 166.6; M(m/e): 368 (M^+), 352, 324, 216, 174, 120, 105, 91, 79, 77, 44.

(1'*S*,6*R*)-(5a): Yield 35%, oil. Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.36; H, 6.50; N, 7.58; $[\alpha]_D$ = -20.1 (c 3.0, $CHCl_3$); IR (film) 2975, 1773, 1685, 1650, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3H, *J* = 6.6 Hz, ON-CH-CH_3), 1.50 (d, 3H, *J* = 7.2 Hz, N-CH-CH_3), 2.53 (m, 2H, ON-CH-CH_2), 3.50 (m, 1H, H_c), 4.22 (d, 1H, *J* = 12.1 Hz, H_a), 4.44 (d, 1H, *J* = 12.1 Hz, H_b), 5.05 (s, 2H, OCH_2Ph), 6.12 (q, 1H, *J* = 7.2 Hz, N-CH-CH_3), 7.29 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 16.8, 19.7, 35.5, 49.4, 57.4, 71.2, 128.1, 128.5, 129.4, 129.6, 129.7, 129.8, 135.7, 140.3, 155.5, 167.4; M(m/e): 368 (M^+), 324, 307, 216, 174, 120, 105, 91, 79, 77, 44.

(1'*S*,6*S*)-(4b): Yield 41%, oil. Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.63; H, 7.14; N, 7.14; $[\alpha]_D$ = -61.6 (c 1.0, $CHCl_3$); IR (film) 2968, 1771, 1739, 1645, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.1 Hz, ON-CH-CH_2-CH_2-CH_3), 1.38 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 1.41 (d, 3H, *J* = 7.0 Hz, N-CH-CH_3), 1.62 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 2.48 (m, 2H, ON-CH-CH_2), 3.20 (m, 1H, H_c), 3.99 (d, 1H, *J* = 14.2 Hz, H_a), 4.39 (d, 1H, *J* = 14.2 Hz, H_b), 5.20 (s, 2H, OCH_2Ph), 6.07 (q, 1H, *J* = 7.1 Hz, N-CH-CH_3), 7.31 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.8, 18.8, 26.9, 33.2, 35.1, 48.8, 60.2, 70.2, 127.6, 128.3, 128.6 128.7, 134.7, 138.9, 154.6, 166.3; M(m/e): 396 (M^+), 380, 352, 315, 258, 244, 201, 139, 120, 105, 97, 91, 79.

(1'*S*,6*R*)-(5b): Yield 35%, solid. Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.58; H, 7.10; N, 7.05; p.f. = 101-102 °C; $[\alpha]_D$ = -56.7 (c 1.2, $CHCl_3$); IR (film) 2960, 2932, 1772, 1737, 1649, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, *J* = 7.1 Hz, ON-CH-CH_2-CH_2-CH_3), 1.42 (m, 2H, ON-CH-CH_2-

CH_2-CH_3), 1.51 (d, 3H, J = 7.3 Hz, N-CH-CH_3), 1.58 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 2.54 (m, 2H, ON-CH-CH_2), 3.31 (m, 1H, H_c), 4.24 (d, 1H, J = 13.9 Hz, H_a), 4.41 (d, 1H, J = 13.9 Hz, H_b), 5.06 (s, 2H, OCH_2Ph), 6.11 (q, 1H, J = 7.3 Hz, N-CH-CH_3), 7.31 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.7, 15.6, 18.7, 26.8, 33.1, 34.9, 48.3, 60.2, 70.0, 126.9, 127.3, 128.2, 128.3, 128.5, 134.6, 139.2, 154.2, 166.4; M(m/e): 396 (M^+), 352, 335, 244, 201, 139, 120, 105, 97, 91, 79.

General Procedure for the Synthesis of 8-Alkyl-3-(1-phenylethyl)-7-oxa-1,3-diazabicyclo-[3.2.1]-octane-4,6-diones (6-9)

To a stirred solution of perihydropyrimidin-4-one (**4**) or (**5**) (1 mmol) in dry THF (10 ml) under an inert atmosphere LiHMDS (1 mmol, 1 ml of 1 M solution in THF) was added in one portion at -78 °C. After 30 min MeOH (1 ml) was added and the solvent was removed under reduced pressure. Then ethyl acetate was added and the mixture was washed with water. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/cyclohexane 8:2 for (**6-9a**) and 1:1 for (**6b**) and (**8b**) as eluant) and the products were obtained as colourless liquids.

(1'*S*,5*S*,8*S*)-(6a): Yield 80%. Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.55; H, 6.23; N, 10.73; $[\alpha]_D$ = -61.5 (c 1.6, $CHCl_3$); IR (film) 2990, 2932, 1693, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 3H, J = 6.2 Hz, ON-CH-CH_3), 1.46 (d, 3H, J = 7.2 Hz, N-CH-CH_3), 2.35 (dq, 1H, J = 5.4, 6.2 Hz, H_c), 2.87 (dd, 1H, J = 1.5, 5.4 Hz, H_d), 3.96 (dd, 1H, J = 1.5, 9.0 Hz, H_b), 4.06 (d, 1H, J = 9.0 Hz, H_a), 5.33 (q, 1H, J = 7.2 Hz, N-CH-CH_3), 7.32 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 7.5, 17.7, 37.1, 45.1, 50.1, 61.5, 128.0, 128.9, 129.7, 139.9, 169.1; M(m/e): 216 (M^+ - CO_2), 134, 118, 111, 105, 77, 56.

(1'*S*,5*R*,8*S*)-(7a): Yield 13%. Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.64; H, 6.15; N, 10.68; $[\alpha]_D$ = -190.3 (c 0.2, $CHCl_3$); IR (film) 2981, 2932, 1738, 1697, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 3H, J = 5.5 Hz, ON-CH-CH_3), 1.55 (d, 3H, J = 7.3 Hz, N-CH-CH_3), 1.60 (dq, 1H, J = 1.9, 5.5 Hz, H_c), 2.58 (apparent triplet, 1H, J = 1.9 Hz, H_d), 3.85 (dd, 1H, J = 1.9, 8.3 Hz, H_a), 4.47 (d, 1H, J = 8.3 Hz, H_b), 5.31 (q, 1H, J = 7.3 Hz, N-CH-CH_3), 7.27 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.8, 16.9, 39.9, 45.6, 48.5, 66.2, 127.8, 128.6, 128.7, 139.8, 170.3; M(m/e): 216 (M^+ - CO_2), 134, 118, 111, 105, 77, 56.

(1'*S*,5*R*,8*R*)-(8a): Yield 77%. Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.59; H, 6.17; N, 10.67; $[\alpha]_D$ = -197.0 (c 1.7, $CHCl_3$); IR (film) 2995, 2948, 1742, 1692, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3H, J = 6.1 Hz, ON-CH-CH_3), 1.52 (d, 3H, J = 7.2 Hz, N-CH-CH_3), 2.21 (dq, 1H, J = 5.5, 6.1 Hz, H_c), 2.82 (dd, 1H, J = 1.6, 5.5 Hz, H_d), 3.64 (dd, 1H, J = 1.6, 8.8 Hz, H_a), 4.49 (d, 1H, J = 8.8 Hz, H_b), 5.28 (q, 1H, J = 7.2 Hz, N-CH-CH_3), 7.28 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 5.7, 15.8, 36.1, 43.9, 49.2, 60.4, 127.1, 127.9, 128.4, 139.0, 167.9; M(m/e): 216 (M^+ - CO_2), 134, 118, 111, 105, 77, 56.

(1'*S*,5*S*,8*R*)-(9a): Yield 11%. Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.63; H, 6.25; N, 10.67; $[\alpha]_D$ = -93.4 (c 0.2, $CHCl_3$); IR (film) 2975, 2931, 1694, 1647, 1433 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 5.5 Hz, ON-CH-CH_3), 1.45 (d, 3H, J = 7.2 Hz, N-CH-CH_3), 1.83 (dq, 1H, J = 2.4, 5.5 Hz, H_c), 2.58 (dd, 1H, J = 1.8, 2.4 Hz, H_d), 4.06 (d, 1H, J = 8.5 Hz, H_a), 4.15 (dd, 1H, J = 1.8, 8.5 Hz, H_b), 5.29 (q, 1H, J = 7.2 Hz, N-CH-CH_3), 7.28 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 16.8, 17.0, 41.1, 45.8, 48.7, 66.5, 127.0, 127.9, 128.7, 139.8, 170.6; M(m/e): 216 (M^+ - CO_2), 134, 118, 111, 105, 77, 56.

(1'*S*,5*S*,8*S*)-(6b): Yield 92%. Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.60; H, 6.89; N, 9.70; $[\alpha]_D$ = -29.3 (c 0.9, $CHCl_3$); IR (film) 2975, 2932, 1697, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00

(t, 3H, J = 7.2 Hz, ON-CH-CH_2-CH_2-CH_3), 1.42 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 1.50 (d, 3H, J = 7.1 Hz, N-CH-CH_3), 1.56 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 2.26 (apparent quartet, 1H, J = 6.1 Hz, H_c), 2.91 (dd, 1H, J = 1.8, 6.1 Hz, H_d), 3.99 (dd, 1H, J = 1.8, 9.0 Hz, H_b), 4.08 (d, 1H, J = 9.0 Hz, H_a), 5.35 (q, 1H, J = 7.1 Hz, N-CH-CH_3), 7.32 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.9, 16.5, 20.6, 23.2, 41.0, 43.9, 49.0, 60.8, 126.9, 127.8, 128.5, 138.7, 168.1; M(m/e): 244 (M^+ - CO_2), 215, 188, 139, 134, 105, 97, 83, 77.

(1'*S*,5*R*,8*R*)-(8b): Yield 89%. Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.67; H, 6.93; N, 9.69; $[\alpha]_D$ = -148.7 (c 1.6, $CHCl_3$); IR (film) 2961, 2939, 1694, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.65 (t, 3H, J = 7.4 Hz, ON-CH-CH_2-CH_2-CH_3), 0.85 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 1.24 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 1.52 (d, 3H, J = 7.3 Hz, N-CH-CH_3), 2.09 (apparent quartet, 1H, J = 6.1 Hz, H_c), 2.83 (dd, 1H, J = 2.0, 6.1 Hz, H_d), 3.70 (dd, 1H, J = 2.0, 9.0 Hz, H_a), 4.49 (d, 1H, J = 9.0 Hz, H_b), 5.32 (q, 1H, J = 7.2 Hz, N-CH-CH_3), 7.28 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.4, 15.5, 20.3, 22.6, 41.1, 43.7, 49.0, 60.7, 127.1, 127.9, 128.4, 139.1, 167.9; M(m/e): 244 (M^+ - CO_2), 215, 139, 134, 105, 97, 83, 77.

(1'*S*,5*R*,6*R*)-1-Hydroxyl-3-(1'-phenylethyl)-5-methoxycarbonyl-6-propylperhydropyrimidin-4-one (10)

To a stirred solution of bicycle **(8b)** (0.175 g, 0.6 mmol) in dry methanol (10 ml) was added Amberlyst H-15 (0.94 g, 2 equiv., 4.7 meq/g). The mixture was refluxed for 3 hours, the resin was filtered off and the organic layer was concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate as eluant) and product **(10)** was obtained pure in 85% yield as a liquid.

Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.75; H, 7.52; N, 8.74; $[\alpha]_D$ = -122.6 (c 0.1, $CHCl_3$); IR (film) 3691, 3605, 1720, 1692, 1532 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz, ON-CH-CH_2-CH_2-CH_3), 1.32-1.58 (m, 3H, ON-CH-CH_2-CH_2-CH_3 + OC-CH-CO), 1.62 (d, 3H, J = 7.3 Hz, N-CH-CH_3), 1.77 (m, 2H, ON-CH-CH_2-CH_2-CH_3), 3.63 (s, 3H, CO_2CH_3), 3.86 (m, 1H, ON-CH-CH_2-CH_2-CH_3), 4.16 (bs, 1H, OH), 4.47 (d, 1H, J = 6.7 Hz, H_a), 4.85 (d, 1H, J = 6.7 Hz, H_b), 5.47 (q, 1H, J = 7.3 Hz, N-CH-CH_3), 7.31 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.8, 16.4, 18.4, 32.6, 50.3, 55.1, 57.6, 58.4, 61.1, 126.8, 128.3, 128.9, 137.9, 165.8.

(1'*S*,2*S*,3*R*)-*N*-(1-Phenylethyl)-2-hydroxymethyl-3-hydroxylaminohexanamide (11)

To a stirred solution of compound **(10)** (100 mg, 0.31 mmol) in dry THF (5 ml), was added $LiAlH_4$ (1M solution in THF, 0.45 mmol, 0.45 ml) in one portion at 0 °C under argon. The mixture was stirred for 30 min at 0 °C, then methanol and water were added. The organic solvents were removed under reduced pressure and the residue was extracted twice with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated and chromatographed on silica gel (ethyl acetate as eluant). The product **(11)** was obtained pure in 75% yield as a waxy solid.

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.17; H, 9.17; N, 10.59; $[\alpha]_D$ = -39.8 (c 0.2, $CHCl_3$); IR ($CHCl_3$) 3436, 3286, 1656, 1509 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, J = 7.0 Hz, ON-CH-CH_2-CH_2-CH_3), 1.34-1.45 (m, 5H, ON-CH-CH_2-CH_2-CH_3 + OC-CH), 1.52 (d, 3H, J = 7.1 Hz, N-CH-CH_3), 3.21 (m, 1H, ON-CH), 3.65 (m, 2H, CH_2OH), 5.11 (apparent quintet, 1H, J = 7.1 Hz, N-CH-CH_3), 7.28 (m, 5H, Ph), 8.06 (d, 1H, J = 7.1 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.6, 22.1, 29.7, 33.3, 35.1, 57.9, 66.5, 126.1, 127.1, 128.5, 143.3, 169.8; M(m/e): 279 (M^+ - 1), 246, 192, 161, 141, 130, 120, 105, 98, 87.

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