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Enantioselective synthesis of β-amino acids. Part 10: Preparation of novel α,α- and β,β-disubstituted β-amino acids from (*S*)-asparagine[1]

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Abstract

Perhydropyrimidinone (*S*)-**1** is alkylated with very high diastereoselectivity to give *trans* products (2*S*,5*R*)-**3**, (2*S*,5*R*)–**4** and (2*S*,5*R*)-**5**. Dialkylation of (*S*)-**1** also proceeds with complete stereoselectivity to afford adducts (2*S*,5*R*)-**6**, (2*S*,5*S*)-**6**, (2*S*,5*R*)-**7** and (2*S*,5*S*)-**7**. Hydrolysis (6N HCl, 100°C) of monoalkylated derivative (2*S*,5*R*)-**3** gives enantiopure α-substituted β-amino acid (*R*)-**8**. Hydrolysis of dialkylated adducts **6** and **7** affords enantiopure α,α-disubstituted β-amino acids (*R*)- or (*S*)-**9** and (*R*)- or (*S*)-**10**. Related iminoester (2*S*,6*S*)-**2** is alkylated with complete diastereoselectivity to give products (2*S*,6*S*)-**11**–**13** whose hydrolysis under relatively mild conditions (2N CF_3CO_2H, CH_3OH, 100°C) affords enantiopure *N*-benzoylated β,β-disubstituted β-amino acid esters (*S*)-**14**–**16**, with intact double bonds in the olefinic substituents.

1. Introduction

In recent years, the preparation of enantiopure α,α-dialkylated α-amino acids has deserved substantial attention owing to the interesting chemical and biological properties exhibited by these compounds.[2–6] It can be anticipated that analogous α,α- and β,β-disubstituted β-amino acids will also exhibit interesting chemical properties.[7] Furthermore, incorporation of such *gem*-branched β-amino acids into unnatural peptides is likely to confer peculiar conformational properties to the macromolecule.[8,9]

Aspartic acid derivatives are also interesting subjects for study in view of their relevant role in physiological events. In particular, α-alkylated aspartic acids are a relevant class of β,β-disubstituted β-amino acids, whose enantioselective synthesis has been reported by several groups.[10]

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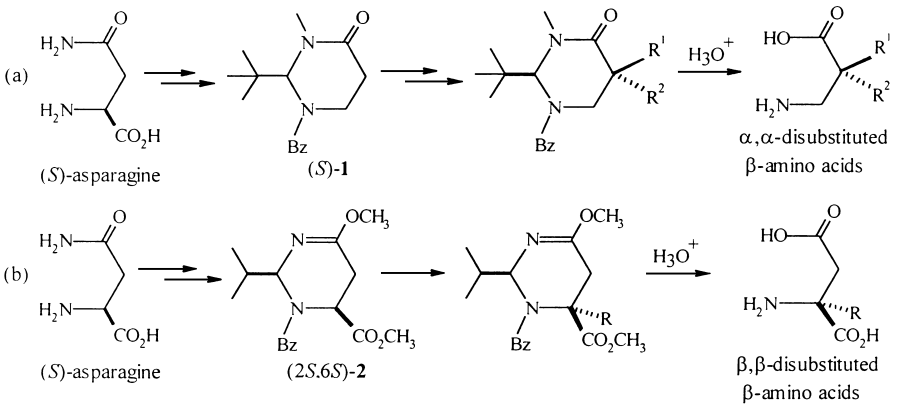
Very recently, we described the conversion of (*S*)-asparagine into chiral heterocycles (*S*)-**1** and (2*S*,6*S*)-**2**, which proved to be convenient precursors of α,α- (Scheme 1a) and β,β-disubstituted β-amino acids (Scheme 1b).[1,10a]



Scheme 1.

In the present paper, application of pyrimidinone (*S*)-**1** to the preparation of four novel α,α-disubstituted β-amino acids is reported. Furthermore, iminoester (2*S*,6*S*)-**2** was alkylated with three olefinic electrophiles to give the expected products, which were hydrolyzed under mild conditions to afford the desired unsaturated β,β-disubstituted β-amino acids.

2. Results and discussion

*2.1. Diastereoselective alkylation of (*S*)-**1***

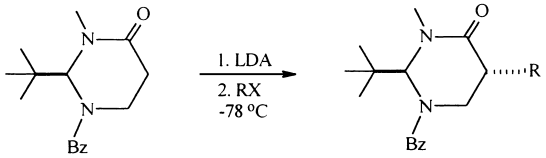
Pyrimidinone (*S*)-**1** was prepared as described in the literature,[11] and enolate (*S*)-**1**-Li was generated upon treatment of the heterocycle with lithium diisopropylamide (LDA), in THF solvent and under nitrogen atmosphere. The electrophile (ethyl iodide, benzyl bromide or *n*-hexyl iodide) was then added at −78°C to afford the *trans* alkylated products in 95% or higher diastereoselectivity (Table 1).

The high stereoselectivity achieved in the addition of (*S*)-**1**-Li to electrophiles is explained in terms of a reactive enolate conformation with the *tert*-butyl group occupying the axial position,[12] which sterically hinders one enolate face (the *syn* face, relative to the *tert*-butyl group) for reaction with electrophiles. The alkylated products (2*S*,5*R*)-**3**–**5** are all solids. Stereochemically pure materials were readily obtained by recrystallization.

*2.2. Stereoselective alkylation of (2*S*,5*R*)-**3**,-**4** and -**5***

Enolates (2*S*)-**3**-Li, (2*S*)-**4**-Li and (2*S*)-**5**-Li were generated upon treatment of the appropriate heterocycle with LDA, in THF solvent and under nitrogen atmosphere. The electrophile (benzyl bromide, *n*-hexyl iodide or ethyl iodide) in solvent *N*,*N*′-dimethylpropyleneurea (DMPU) was then added at −78°C to afford the dialkylated products in high diastereoselectivity (no NMR spectroscopic evidence for minor diastereomeric product was recorded[13]) and good to excellent yields (Table 2). The use of DMPU as co-solvent was necessary to achieve the dialkylation in high yield.[14] That addition of the electrophile takes place from the face opposite to the *tert*-butyl group was confirmed by X-ray crystallography [see, for example, Fig. 1 for (2*S*,5*S*)-**6**] and by chemical correlation.[1]

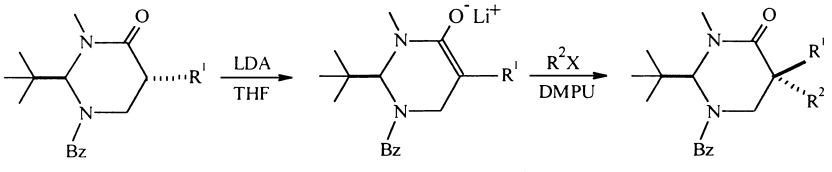
Table 1
Diastereoselectivity of enolate (*S*)-**1**-Li alkylations



(*S*)-**1** (2*S*,5*R*)-**3**-**5**

RX	Product	ds (%)	mp (°C)	$[\alpha]_D^{28\,°C}$	yield (%)
EtI	(2*S*,5*R*)-**3**	>95	85-86	+27.5	80.0
n-$C_6H_{13}I$	(2*S*,5*R*)-**4**	95	70-71	+31.2	80.0
$PhCH_2Br$	(2*S*,5*R*)-**5**	>96	173-174	-64.0	80.0

Table 2
Diastereoselectivity of enolate (2*S*)-**3**-Li, (2*S*)-**4**-Li and (2*S*)-**5**-Li alkylations



(2*S*,5*R*)-**3**, -**4**, -**5** (2*S*)-**3**-Li, -**4**-Li, -**5**-Li **6** or **7**

R^1	R^2	Product	ds (%)	mp (°C)	$[\alpha]_D^{28\,°C}$	yield (%)
Et	$PhCH_2$	**6**	>95	a	-11.6	95.3
$PhCH_2$	Et	*epi*-**6**	>95	106-107	-35.3	76.0
n-C_6H_{13}	$PhCH_2$	**7**	>95	a	-29.0	80.0
$PhCH_2$	*n*-C_6H_{13}	*epi*-**7**	>95	a	-11.3	63.0

[a] Viscous oil

*2.3. Hydrolysis of the C(5) alkylated pyrimidinone derivatives **3**, **6** and **7** to give enantiopure α-alkylated and α,α-dialkylated β-amino acids*

The final step of the overall conversion of (*S*)-asparagine to 2-ethyl-3-aminopropionic acid, the hydrolysis of the heterocycle (2*S*,5*R*)-**3**, was achieved by heating during 12 h with 6N HCl in a sealed tube at 100°C (Scheme 2).

Hydrolysis of (2*S*,5*S*)-**6**, (2*S*,5*R*)-**6**, (2*S*,5*R*)-**7** and (2*S*,5*S*)-**7** required heating with 6N HCl in a sealed tube at 100°C for two days. *p*-Dioxane was used as co-solvent in order to improve the solubility of the substrate in the aqueous medium. While the drastic conditions employed for hydrolysis may not be

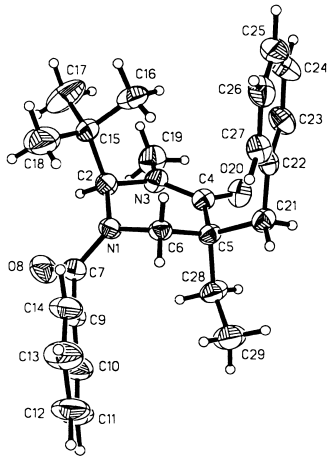
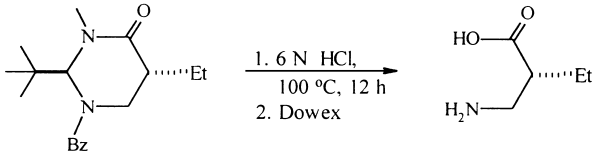


Figure 1. Structure and solid-state conformation of (2*S*,5*S*)-1-benzoyl-2-*tert*-butyl-3-methyl-5-benzyl-5-ethylperhydropyrimidin-4-one [(2*S*,5*S*)-**6**]



(2*S*,5*R*)-**3** (*R*)-**8**

Scheme 2.

tolerated by sensitive amino acids,[15] they proved harmless to the α,α-disubstituted β-amino acids **9** and **10**. Enantiopure (*S*)-**9**, (*R*)-**9**, (*R*)-**10** and (*S*)-**10** were purified by chromatography on an ion-exchange column (Table 3 and Experimental).

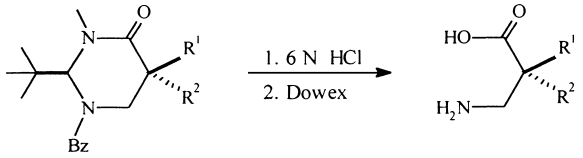
In summary, monoalkylation and double alkylation of chiral β-aminopropionic acid derivative (*S*)-**1** proceeds with very high stereoselectivity. Acid hydrolysis of the alkylated adducts affords enantiopure alkylated β-amino acids in good yields.

2.4. Diastereoselective alkylation of iminoester (2S,6S)-2

Enantiopure (2*S*,6*S*)-**2** was prepared according to the procedure recently described in the literature.[10a] Enolate (2*S*,6*S*)-**2**-Li was then generated by treatment of the heterocycle with LDA, in THF solvent and under nitrogen atmosphere. The olefinic electrophile (allyl bromide, 4-bromo-2-methyl-2-butene or *trans*-1-bromo-2-pentene) was then added at −78°C to afford the *trans*-alkylated products, apparently with complete diastereoselectivity.[16] The *trans* configuration of the alkylated products (Table 4) was assigned by chemical correlation to the known α-methyl and α-benzyl aspartic acids.[10a] Furthermore, an X-ray crystallographic structure of allylic derivative (2*S*,6*S*)-**11** (Fig. 2) confirms the *trans* relative configuration between the allyl and isopropyl groups. Table 4 summarizes the chemical yields and diastereoselectivities observed in the alkylation reaction, as well as some physical properties of the isolated products.

It is interesting that addition of (2*S*,6*S*)-**2**-Li, with an axial isopropyl group at the stereoinducing C(2) center, proceeds with stereoselectivities comparable with those obtained when a bulkier *tert*-butyl group is present. Thus, at least in this system, inexpensive isobutyraldehyde can efficiently replace the much costlier pivalaldehyde in the preparation of the chiral heterocycles.

Table 3
Hydrolysis of C(5) dialkylated products **6** and **7**

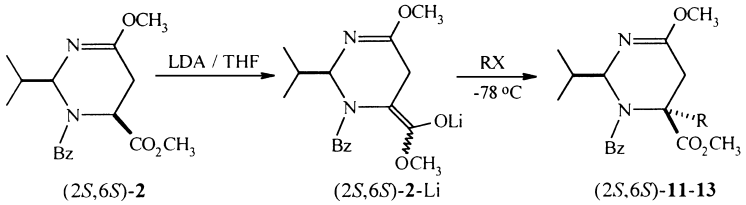


(2*S*,5*R*)-**6** or -**7**
or (2*S*,5*S*)-**6** or -**7**

(*R*)-**9** or -**10**
(*S*)-**9** or -**10**

R^1	R^2	Product	mp (°C)	$[\alpha]_D^{28\,°C}$	yield (%)
$PhCH_2$	Et	(*S*)-**9**	240-242	+11.5	88.0
Et	$PhCH_2$	(*R*)-**9**	240-242	-11.5	85.0
$PhCH_2$	*n*-C_6H_{13}	(*S*)-**10**	173-175	+8.0	87.0
n-C_6H_{13}	$PhCH_2$	(*R*)-**10**	173-175	-8.0	87.0

Table 4
Diastereoselectivity of enolate (2*S*,6*S*)-**2**-Li alkylations



(2*S*,6*S*)-**2** (2*S*,6*S*)-**2**-Li (2*S*,6*S*)-**11**-**13**

RX	Product	ds (%)	mp (°C)	$[\alpha]_D^{28\,°C}$	yield (%)
CH_2=$CHCH_2Br$	(2*S*,6*S*)-**11**	>97	151-152	-21.5	90.0
$(CH_3)_2C$=$CHCH_2Br$	(2*S*.6*S*)-**12**	>97	a	+24.0	54.0
t-CH_3CH_2CH=$CHCH_2Br$	(2*S*,6*S*)-**13**	>97	a	+16.0	58.0

[a]Viscous oil.

2.5. *Hydrolysis of olefinic adducts (2*S*,6*S*)-**11**–**13***

The hydrolysis of the alkylated heterocycles (2*S*,6*S*)-**11**–**13** was achieved under relatively mild conditions (2N CF_3CO_2H, 100°C, 72 h). This was important, as more drastic conditions would probably result in intramolecular amino group addition to the olefin.[15] The *N*-benzoylated amino acid esters (*S*)-**14**–**16** were purified by flash chromatography (Table 5).

Sections 2.4 and 2.5 demonstrate that (*S*)-asparagine is efficiently converted to enantiopure pyrimi-

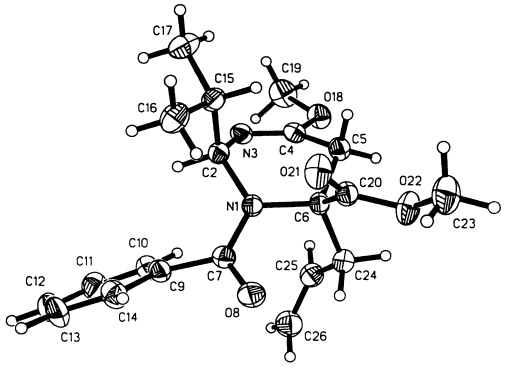
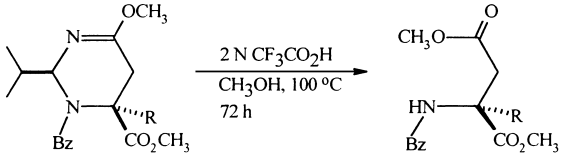


Figure 2. Structure and solid-state conformation of 1-benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-(2-propenyl)-6(*S*)-carbomethoxy-(1,2),(5,6)-tetrahydropyrimidin-4-one [(2*S*,6*S*)-**11**]

Table 5
Hydrolysis of products (2*S*,6*S*)-**11**–**13** to give *N*-benzoylated amino acid esters (*S*)-**14**–**16**



(2*S*,6*S*)-**11**-**13** (*S*)-**14**-**16**

R	Product	$[\alpha]_D^{28\,°C}$	yield (%)
$CH_2CH{=}CH_2$	(*S*)-**14**	-29.4	96.0
$CH_2CH{=}C(CH_3)_2$	(*S*)-**15**	-37.5	62.0
t-$CH_2CH{=}CHCH_2CH_3$	(*S*)-**16**	-24.0	89.0

dinone iminoester (2*S*,6*S*)-**2**, which is alkylated with very high diastereoselectivity. Hydrolysis of the olefinic derivatives (2*S*,6*S*)-**11**–**13** proceeds under mild conditions to afford enantiopure β,β-disubstituted β-amino acid esters (*S*)-**14**–**16**, with preservation of the olefinic double bond.

3. Experimental[17]

*3.1. 1-Benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one [(*S*)-**1**]*

The procedure described by Juaristi et al.[11] was followed.

*3.2. 1-Benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-carbomethoxy-(1,2),(5,6)-tetrahydro-1,3-pyrimidine [(2*S*,6*S*)-**2**]*

The procedure described by Juaristi et al.[10a] was followed.

3.3. General procedure for the alkylation of perhydropyrimidinone (S)-**1**

In a dry two-necked round-bottom flask provided with addition funnel, rubber septa and thermometer was placed under nitrogen diisopropylamine (4.4 mmol) in 50 mL of THF, which was then cooled to −20°C before the slow addition of 4.8 mmol of *n*-BuLi (ca. 1.8 M in *n*-hexane). The resulting solution was stirred at −20°C for 20 min and then cooled to −78°C before the dropwise addition of 4.0 mmol of the heterocycle in 30 mL of THF. Stirring was continued for 1 h at −78°C in order to secure the complete formation of the enolate. The alkylating agent (4.6 mmol, 15% excess) was then added dropwise via syringe and the reaction mixture was stirred at −78°C until no further changes were detected by TLC (silica gel 60 F_{254}, 2–3 h). At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution, allowed to warm to ambient temperature and extracted with two portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in a rotary evaporator.

3.4. 1-Benzoyl-2(S)-tert-butyl-3-methyl-5(R)-ethylperhydropyrimidin-4-one [(2S,5R)-**3**]

The general procedure (Section 3.3) was followed for the alkylation of 1.0 g (3.6 mmol) of (*S*)-**1** with 0.31 mL (4.36 mmol) of ethyl iodide. Purification of the crude product by flash chromatography on silica gel, 230–400 mesh (*n*-hexane:ethyl acetate 7:3) (TLC: *n*-hexane:ethyl acetate 2:3, R_f=0.33) afforded 0.89 g (80% yield) of (2*S*,5*R*)-**3**, mp 85–86°C. $[\alpha]_D^{28}$=+27.5 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.60 (t, J=6.2 Hz, 3H), 1.15 (s, 9H), 1.35 (m, 1H), 1.72 (m, 1H), 2.29 (br, 1H), 3.10 (s, 3H), 3.50 (d, J=13.8 Hz, 1H), 3.75 (dd, J^1=13.8 Hz, J^2=6.4 Hz, 1H), 5.78 (s, 1H), 7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 11.2, 24.8, 28.4, 37.7, 39.2, 41.3, 45.7, 73.7, 126.6, 128.6, 130.1, 135.0, 167.5, 170.4. Anal. calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67. Found: C, 71.47; H, 8.81.

3.5. 1-Benzoyl-2(S)-tert-butyl-3-methyl-5(R)-n-hexylperhydropyrimidin-4-one [(2S,5R)-**4**]

The procedure described by Juaristi et al.[11] was followed.

3.6. 1-Benzoyl-2(S)-tert-butyl-3-methyl-5(R)-benzylperhydropyrimidin-4-one [(2S,5R)-**5**]

The procedure described by Juaristi et al.[11] was followed.

3.7. General procedure for the alkylation of α-substituted perhydropyrimidinones

In a dry two-necked round-bottom flask equipped with an addition funnel, rubber septa and thermometer was placed, under nitrogen, diisopropylamine (1.1 mmol) in 15 mL of THF. This was then cooled to −20°C before the slow addition of 1.1 mmol of *n*-BuLi (ca. 2.3 M in *n*-hexane). The resulting solution was stirred at −20°C for 30 min before the dropwise addition of 1.0 mmol of monoalkylated heterocycle in 10 mL of THF. Stirring was continued for 1 h at −20°C in order to secure the complete formation of the enolate, before the reaction temperature was lowered to −78°C. The alkylating agent (1.1 mmol, 10% excess) and DMPU (1.1 mmol) was then added dropwise via syringe, and the reaction mixture was stirred at −78°C until no further changes were detected by TLC (silica gel 60 F_{254}). At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution, allowed to warm to ambient temperature and extracted with two portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in a rotary evaporator.

3.8. (2S,5R)-1-Benzoyl-2-tert-butyl-3-methyl-5-benzyl-5-ethylperhydropyrimidin-4-one [(2S,5R)-6]

The general procedure was followed for the alkylation of 0.97 g (3.2 mmol) of (2*S*,5*R*)-**3** with 0.42 mL (3.5 mmol, 1.1 equiv.) of benzyl bromide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 9:1) (TLC: *n*-hexane:ethyl acetate 1:1, R_f=0.42) afforded 1.2 g (95.3% yield) of (2*S*,5*R*)-**6** as a yellowish oil. $[\alpha]_D^{28}$=−11.6 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J=7.5 Hz, 3H), 0.86 (s, 9H), 1.84 (m, 2H), 2.50 (d, J=13.2 Hz, 1H), 2.73 (d, J=13.2 Hz, 1H), 2.95 (s, 3H), 3.81 (dd, J=14.3 Hz, 2H), 5.78 (s, 1H), 7.20 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 8.4, 27.4, 28.8, 37.4, 38.0, 38.8, 43.7, 45.3, 74.0, 126.6, 127.6, 128.2, 128.5, 130.2, 130.6, 134.7, 137.3, 170.0, 173.4. HRMS calcd *m*/*z* for $C_{25}H_{33}N_2O_2$ (M^+ +1): 393.2542. Found: 393.2551.

3.9. (2S,5S)-1-Benzoyl-2-tert-butyl-3-methyl-5-benzyl-5-ethylperhydropyrimidin-4-one [(2S,5S)-6]

The general procedure was followed for the alkylation of 0.80 g (2.38 mmol) of (2*S*,5*R*)-**5** with 0.21 mL (2.62 mmol, 1.1 equiv.) of ethyl iodide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 9:1) (TLC: *n*-hexane:ethyl acetate 1:1, R_f=0.43) afforded 1.1 g (76% yield) of (2*S*,5*S*)-**6** as white crystals, mp 106–107°C. $[\alpha]_D^{28}$=−35.3 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.50 (t, J=7.5 Hz, 3H), 0.70 (s, 9H), 1.41 (m, 1H), 1.65 (m, 1H), 2.14 (d, J=13.4 Hz, 1H), 3.20 (s, 3H), 3.35 (d, J=13.4 Hz, 1H), 3.61 (dd, J=14.3 Hz, 2H), 5.78 (s, 1H), 7.32 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.4, 28.0, 31.3, 37.7, 38.2, 38.8, 47.3, 47.4, 73.7, 126.7, 127.3, 128.3, 128.7, 130.2, 131.2, 134.9, 137.2, 170.7, 172.1. Anal. calcd for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.21. Found: C, 76.39; H, 8.36. X-Ray crystallographic structure, see Fig. 1.

3.10. (2S,5R)-1-Benzoyl-2-tert-butyl-3-methyl-5-benzyl-5-n-hexylperhydropyrimidin-4-one [(2S,5R)-7]

The general procedure was followed for the alkylation of 0.87 g (2.43 mmol) of (2*S*,5*R*)-**4** with 0.38 mL (2.9 mmol, 1.1 equiv.) of *n*-hexyl iodide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 9:1) (TLC: *n*-hexane:ethyl acetate 1:1, R_f=0.50) afforded 0.80 g (80% yield) of (2*S*,5*R*)-**7** as colorless oil. $[\alpha]_D^{28}$=−29.0 (c=1.1 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, J=7.3 Hz, 3H), 1.17 (s, 9H), 1.29 (m, 8H), 1.73 (m, 2H), 2.54 (d, J=13.3 Hz, 1H), 2.73 (d, J=13.4 Hz, 1H), 2.92 (s, 3H), 3.90 (dd, J=14.3 Hz, 2H), 5.98 (s, 1H), 7.25 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.5, 23.8, 24.2, 28.8, 29.9, 31.7, 37.9, 39.8, 40.3, 44.0, 45.2, 74.2, 126.5, 127.4, 128.2, 128.6, 130.2, 130.5, 134.6, 136.2, 169.9, 173.5. HRMS calcd *m*/*z* for $C_{29}H_{40}N_2O_2$: 449.3168. Found: 449.3168.

3.11. (2S,5S)-1-Benzoyl-2-tert-butyl-3-methyl-5-benzyl-5-n-hexylperhydropyrimidin-4-one [(2S,5S)-7]

The general procedure was followed for the alkylation of 1.0 g (2.97 mmol) of (2*S*,5*R*)-**5** with 0.48 mL (3.26 mmol, 1.1 equiv.) of *n*-hexyl iodide. Purification of the crude product by flash chromatography (*n*-hexane:ethyl acetate 9:1) (TLC: *n*-hexane:ethyl acetate 1:1, R_f=0.52) afforded 0.82 g (63% yield) of (2*S*,5*S*)-**7** as a colorless oil. $[\alpha]_D^{28}$=−11.3 (c=1 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.63 (s, 9H), 0.84 (t, J=6.9 Hz, 3H), 1.20 (m, 10H), 2.15 (d, J=13.3 Hz, 1H), 2.90 (s, 3H), 3.33 (d, J=13.3 Hz, 1H), 3.61 (dd, J=14.3 Hz, 2H), 5.75 (s, 1H), 7.10 (m, 5H), 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.1, 22.7, 23.6, 25.0, 28.0, 29.9, 31.7, 37.3, 38.0, 39.4, 40.0, 47.3, 73.7, 126.7, 127.4, 128.2, 128.6, 130.2, 131.2, 134.9, 137.2, 170.6, 172.2. HRMS calcd *m*/*z* for $C_{29}H_{40}N_2O_2$: 449.3168. Found: 449.3150.

3.12. General procedure for the hydrolysis of monoalkylated pyrimidinone **3** and dialkylated pyrimidinones **6** and **7**

A suspension of 0.8 mmol of adduct **3** in 20 mL of 6N HCl was heated in a sealed ampoule to 100°C until complete reaction (see Sections 3.14–3.19). The solution was then allowed to cool to ambient temperature and the precipitate of benzoic acid was removed by filtration. The filtrate was extracted with three 20 mL portions of EtOAc and the aqueous phase was concentrated at reduced pressure to afford a 1:1 mixture of the amino acid hydrochloride and methylammonium chloride, which was adsorbed onto acidic ion-exchange resin Dowex 50WX8. The resin was washed with distilled water until the washings emerged neutral, and then the free amino acid was recovered with 1N ammonium hydroxide. Evaporation afforded the free amino acid, which was dried under high vacuum at 40°C.

3.13. (R)-(+)-2-Ethyl-3-aminopropionic acid [(R)-**8**]

Derivative (2*S*,5*R*)-**3** (0.21 g, 0.71 mmol) was hydrolyzed according to the general procedure (100°C, 12 h) to afford 74 mg (89.3% yield) of pure, free amino acid (*R*)-**8**, mp 206–207°C. $[\alpha]_D^{28}$=+4.6 (c=1, H_2O). ^{1}H NMR (D_2O, 270 MHz) δ 0.83 (t, J=7.6 Hz, 3H), 1.52 (m, 2H), 2.4 (m, 1H), 2.95 (dd, J^1=12.7 Hz, J^2=5.2 Hz, 1H), 3.04 (dd, J^1=12.7 Hz, J^2=8.7 Hz, 1H). ^{13}C NMR (D_2O, 67.8 MHz) δ 10.7, 23.2, 40.9, 47.0, 181.1.

3.14. (R)-(−)-α-Benzyl-α-ethyl-β-aminopropionic acid [(R)-**9**]

erivative (2*S*,5*R*)-**6** (0.12 g, 0.305 mmol) was hydrolyzed according to the general procedure (100°C, 48 h) to afford 63 mg (85% yield) of pure, free amino acid (*R*)-**9**, mp 240–242°C. $[\alpha]_D^{28}$=−11.5 (c=1, 1 N HCl). ^{1}H NMR (D_2O, 300 MHz) δ 0.65 (t, J=7.5 Hz, 3H), 1.43 (m, 2H), 2.62 (d, J=13.8 Hz, 1H), 2.73 (d, J=13.8 Hz, 1H), 2.83 (dd, J^1=13.8 Hz, J^2=16.15 Hz, 2H), 7.0 (m, 5H). ^{13}C NMR (D_2O, 75.5 MHz) δ 7.7, 25.9, 39.8, 41.9, 49.4, 127.5, 128.7, 130.2, 135.8, 177.8.

3.15. (S)-(+)-α-Benzyl-α-ethyl-β-aminopropionic acid [(S)-**9**]

erivative (2*S*,5*S*)-**6** (0.12 g, 0.305 mmol) was hydrolyzed according to the general procedure (100°C, 48 h) to afford 58 mg (88% yield) of pure, free amino acid (*S*)-**9**, mp 240–242°C. $[\alpha]_D^{28}$=+11.5 (c=1, 1 N HCl). ^{1}H and ^{13}C NMR spectra were similar to those reported for (*R*)-**9**.

3.16. (R)-(−)-α-Benzyl-α-n-hexyl-β-aminopropionic acid [(R)-**10**]

erivative (2*S*,5*R*)-**7** (0.20 g, 0.447 mmol) was hydrolyzed according to the general procedure (100°C, 48 h) to afford 0.10 g (87% yield) of pure, free amino acid (*R*)-**10**, mp 173–175°C. $[\alpha]_D^{28}$=−8.0 (c=1, 1 N HCl). ^{1}H NMR (D_2O, 270 MHz) δ 0.5 (t, J=7.2 Hz, 3H), 0.52 (m, 8H), 0.90 (m, 2H), 2.27 (dd, J=13.8 Hz, 2H), 2.90 (dd, J=6.9 Hz, 2H), 6.90 (m, 5H). ^{13}C NMR (D_2O, 75.5 MHz) δ 13.6, 22.2, 23.3, 29.0, 31.1, 33.1, 40.2, 42.6, 49.2, 127.7, 128.9, 130.3, 135.9, 178.0.

3.17. (S)-(+)-α-Benzyl-α-n-hexyl-β-aminopropionic acid [(S)-**10**]

erivative (2*S*,5*S*)-**7** (0.11 g, 0.248 mmol) was hydrolyzed according to the general procedure (100°C, 48 h) to afford 56 mg (86.5% yield) of pure, free amino acid (*S*)-**10**, mp 173–175°C. $[\alpha]_D^{28}$=+8.0 (c=1, 1 N HCl). ^{1}H and ^{13}C NMR spectra were similar to those reported for (*R*)-**10**.

3.18. General procedure for the reaction of pyrimidine enolate [(2S,6S)-2-Li] with electrophiles

ithium chloride (6 equiv.) was placed in a 100 mL round-bottom flask provided with stirring bar and under nitrogen. Diisopropylamine (1.0 equiv.) in THF was added, and the resulting mixture was cooled to −20°C before the slow addition of 1.0 equiv. of *n*-BuLi (ca. 1.8 M in hexane). The resulting solution was stirred at −20°C for 20 min and then cooled to −78°C before the dropwise addition of 1.0 equiv. of imino ester (2*S*,6*S*)-**2** in THF. Stirring was continued for 1 h at −78°C in order to secure the complete formation of the enolate. The alkylating agent (1.15 equiv.) was then added dropwise via syringe, and the reaction mixture was stirred at −78°C for 2 h and at ambient temperature overnight. At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with three portions of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure, maintaining the temperature below 30°C.

3.19. 1-Benzoyl-2(S)-isopropyl-4-methoxy-6(S)-carbomethoxy-6(S)-(2-propenyl)-(1,2),(5,6)-tetrahydro-1,3-pyrimidine [(2S,6S)-11]

he general procedure was followed with 1.30 g (4.09 mmol) of iminoester (2*S*,6*S*)-**2** in 40 mL of THF and 0.42 mL (4.90 mmol) of allyl bromide. The crude product was purified by flash column chromatography (*n*-hexane:ethyl acetate 9:1) (TLC: *n*-hexane:ethyl acetate 3:1; R_f=0.43) to give 1.46 g (90% yield) of (2*S*,6*S*)-**11** as a white, crystalline solid, mp 151–152°C. $[\alpha]_D^{28}$=−21.5 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (d, J=6.6 Hz, 6H), 1.96 (m, 1H), 2.50 (d, J=16.1 Hz, 1H), 2.62 (dd, J^1=14.5 Hz, J^2=7.7 Hz, 1H), 2.84 (d, J=16.1 Hz, 1H), 3.33 (dd, J^1=14.5 Hz, J^2=7.7 Hz, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 5.07 (s, 1H), 5.10 (d, J=10.6 Hz, 1H), 5.33 (d, J=9.2 Hz, 1H), 5.75 (m, 1H), 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 19.9, 34.0, 35.6, 40.0, 52.6, 53.1, 62.1, 77.7, 119.3, 128.1, 128.4, 129.9, 132.3, 136.4, 163.3, 170.9, 173.3. Anal. calcd for $C_{20}H_{26}N_2O_4$: C, 67.01; H, 7.31. Found: C, 67.15; H, 7.44.

3.20. 1-Benzoyl-2(S)-isopropyl-4-methoxy-6(S)-carbomethoxy-6(S)-(3-methyl-2-butenyl)-(1,2),(5,6)-tetrahydro-1,3-pyrimidine [(2S,6S)-12]

The general procedure was followed with 0.61 g (1.90 mmol) of iminoester (2*S*,6*S*)-**2** in 40 mL of THF and 0.28 mL (2.40 mmol) of 1-bromo-3-methyl-2-butene. The crude product was purified by flash chromatography (*n*-hexane:ethyl acetate 9:1) (TLC: *n*-hexane:ethyl acetate 3:1; R_f=0.45) to give 0.48 g (54% yield) of (2*S*,6*S*)-**12** as a viscous oil. $[\alpha]_D^{28}$=+24.0 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (d, J=6.6 Hz, 3H), 0.70 (d, J=6.6 Hz, 3H), 1.47 (s, 3H), 1.61 (s, 3H), 1.88 (m, 1H), 2.32 (d, J=15.9 Hz, 1H), 2.53 (dd, J^1=14.9 Hz, J^2=8.2 Hz, 1H), 2.70 (d, J=15.9 Hz, 1H), 3.19 (dd, J^1=14.9 Hz, J^2=7.5 Hz, 1H), 3.59 (s, 3H), 3.70 (s, 3H), 4.98 (t, J=8.1 Hz, 1H), 5.24 (d, J=9.4 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 19.4, 19.9, 26.3, 33.8, 34.0, 35.5, 52.5, 53.1, 62.8, 77.7, 118.5, 128.1, 128.3, 129.9, 135.5, 136.5, 163.7, 170.8, 173.7. HRMS calcd *m*/*z* for $C_{22}H_{30}N_2O_4$: 387.2271. Found: 387.2284.

*3.21. 1-Benzoyl-2(*S*)-isopropyl-4-methoxy-6(*S*)-carbomethoxy-6(*S*)-(2(*E*)-pentenyl)-(1,2),(5,6)-tetrahydro-1,3-pyrimidine [(2*S*,6*S*)-**13**]*

The general procedure was followed with 0.55 g (1.73 mmol) of iminoester (2*S*,6*S*)-**2** in 40 mL of THF and 0.24 mL (2.07 mmol) of 1-bromo-2(*E*)-pentene. The crude product was purified by flash column chromatography (*n*-hexane:ethyl acetate 9:1) (TLC: *n*-hexane:ethyl acetate 3:1; R_f=0.44) to give 0.47 g (58% yield) of (2*S*,6*S*)-**13** as a viscous oil. $[\alpha]_D^{28}$ =+16.0 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77 (d, J=6.6 Hz, 6H), 0.88 (t, J=7.3 Hz, 3H), 1.97 (m, 1H), 2.01 (m, 2H), 2.40 (d, J=15.7 Hz, 1H), 2.68 (dd, J^1=15.0 Hz, J^2=8.4 Hz, 1H), 2.80 (d, J=15.7 Hz, 1H), 3.28 (dd, J^1=13.2 Hz, J^2=7.3 Hz, 1H), 3.66 (s, 3H), 3.78 (s, 3H), 5.27 (m, 1H), 5.32 (d, J=9.2 Hz, 1H), 5.48 (m, 1H), 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 19.3, 19.9, 20.6, 32.9, 34.0, 35.6, 52.5, 52.9, 62.4, 77.7, 122.4, 128.1, 128.3, 129.8, 135.4, 136.4, 163.4, 170.8, 172.5.

*3.22. General procedure for the hydrolysis of the alkylated pyrimidines **11**–**13***

A solution of 1 mmol of adduct in 10 mL of methanolic 2 N CF_3CO_2H was heated in a sealed ampoule to 100°C for 72 h. The solution was then allowed to cool to ambient temperature, and was concentrated in a rotary evaporator. The residue was dissolved in 200 mL of CH_2Cl_2, washed three times with H_2O, dried over anh. Na_2SO_4 and concentrated in the rotary evaporator to afford the crude product that was purified by flash chromatography (*n*-hexane:ethyl acetate 9:1).

3.23. N-*Benzoyl dimethyl ester of (*S*)-α-(2-propenyl)-aspartic acid [(*S*)-**14**]*

Derivative (2*S*,6*S*)-**11** (200 mg, 0.55 mmol) was hydrolyzed according to the general procedure to afford 145 mg (96% yield) of (*S*)-**14** as a viscous oil (TLC: *n*-hexane:ethyl acetate 3:1; R_f=0.36). $[\alpha]_D^{28}$=−29.4 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (dd, J^1=13.8 Hz, J^2=7.5 Hz, 1H), 3.01 (d, J=16.7 Hz, 1H), 3.40 (ddt, J^1=13.9 Hz, J^2=7.3 Hz, J^3=1.1 Hz, 1H), 3.60 (s, 3H), 3.81 (d, J=16.7 Hz, 1H), 3.82 (s, 3H), 5.10 (m, 2H), 5.60 (m, 1H), 7.36 (br, 1H), 7.46 (m, 3H), 7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.3, 51.8, 53.1, 61.8, 119.7, 126.9, 128.6, 131.3, 131.7, 134.6, 166.6, 171.0, 172.9.

3.24. N-*Benzoyl dimethyl ester of (*S*)-α-(3-methyl-2-butenyl)-aspartic acid [(*S*)-**15**]*

Derivative (2*S*,6*S*)-**12** (418 mg, 1.08 mmol) was hydrolyzed according to the general procedure to afford 193 mg (62% yield) of (*S*)-**15** as a viscous oil (TLC: *n*-hexane:ethyl acetate 3:1; R_f=0.34). $[\alpha]_D^{28}$=−37.5 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (s, 3H), 1.60 (s, 3H), 2.53 (dd, J^1=14.5 Hz, J^2=7.7 Hz, 1H), 3.00 (d, J=16.5 Hz, 1H), 3.26 (dd, J^1=14.3 Hz, J^2=7.7 Hz, 1H), 3.55 (s, 3H), 3.77 (s, 3H), 3.80 (d, J=16.5 Hz, 1H), 4.91 (t, J=7.7 Hz, 1H), 7.33 (br, 1H), 7.40 (m, 3H), 7.72 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8, 25.9, 33.9, 39.1, 51.6, 52.9, 61.8, 116.8, 126.9, 128.5, 131.5, 134.8, 136.6, 166.6, 171.0, 173.1. HRMS calcd *m/z* for $C_{18}H_{23}NO_5$: 334.1654. Found: 334.1666.

3.25. N-*Benzoyl dimethyl ester of (*S*)-α-[(*E*)-2-pentenyl]-aspartic acid [(*S*)-**16**]*

Derivative (2*S*,6*S*)-**13** (102 mg, 0.26 mmol) was hydrolyzed according to the general procedure to afford 65 mg (86% yield) of (*S*)-**16** as a viscous oil (TLC: *n*-hexane:ethyl acetate 3:1; R_f=0.40). $[\alpha]_D^{28}$=−24.0 (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J=7.7 Hz, 3H), 1.98 (m, 2H), 2.59 (dd, J^1=14.3 Hz, J^2=7.7 Hz, 1H), 3.03 (d, J=16.5 Hz, 1H, 3.36 (dd, J^1=14.3 Hz, J^2=7.7 Hz, 1H), 3.59 (s,

3H), 3.80 (s, 3H), 3.85 (d, J=16.5 Hz, 1H), 5.13 (m, 1H), 5.50 (m, 1H), 7.36 (br, 1H), 7.40 (m, 3H), 7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 20.6, 32.9, 39.2, 51.7, 53.1, 61.7, 120.9, 126.9, 128.5, 131.6, 134.7, 136.5, 166.6, 171.0, 173.0. HRMS calcd *m/z* for $C_{18}H_{23}NO_5$: 334.1654. Found: 334.1653.

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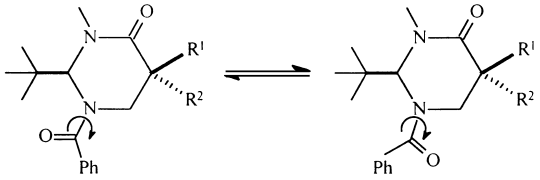
13. Slow rotation around the *N*-benzoyl group in the disubstituted heterocyclic products gives rise to two sets of signals for the corresponding isomers. A single set of signals is observed at T=145°C (DMSO-d_6).



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16. A single product was detected by both ^{1}H and ^{13}C NMR spectroscopy (400 and 100 MHz, respectively).
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