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Enantioselective synthesis of α,β-substituted β-amino acids

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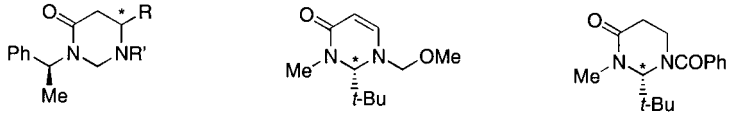
Abstract—Chiral derivative **3** was shown to be a precursor of α and β-substituted β-amino acids as well as α,β-disubstituted β-amino acids. The key steps of the procedure are a diastereoselective alkylation of synthon **3** by organocuprates reagents and a diastereoselective alkylation of the alkylated adduct.

β-Amino acids have attracted much attention in recent years, whether as analogues of α-amino acids to increase the resistance of peptides to enzymatic degradation[1] or as building blocks for the synthesis of β-lactam antibiotics.[2] In addition, β-amino acids derivatives are crucial structural components of numerous biologically active natural products.[3] Although many methods for synthesizing enantiomerically pure β-amino acids have been reported, great effort continues to be devoted towards more efficient enantioselective methods.[4] The most obvious strategy consists on directed conjugate addition of chiral amines to α,β-unsaturated esters.[5] Another strategy is based on stereoselective alkylation en route to enantiopure β-amino acids. Cardillo and Konopelski used substituted perhydropyrimidin-4-ones[6] **I** an **II** whose stereoselective alkylation and subsequent hydrolysis afforded substituted β-amino acids. Juaristi and Seebach showed the usefulness of chiral derivatives of 3-aminopropionic acids **III** (Scheme 1).[7] Moreover Juaristi alkylated heterocyclic compounds derived from aspartic acid[8] and Seebach made use of lithiated hydropyrimidines in order to synthesize α-branched β-amino acids.[9]

We have reported a new synthetic method that starts from chiral synthon **3** and allows to synthesize substituted enantiopure β-amino acids.[10] The key steps of this method consist in conjugate additions of different organocuprate reagents to this chiral Michael acceptor followed by α-alkylation of the resulting adduct with methyl iodide. Herein we report full details of our study concerning these reactions.

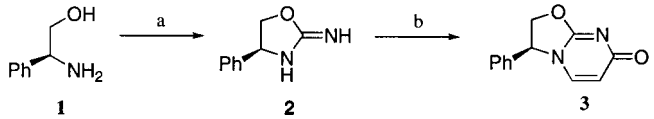
1. Results and discussion

Preparation of the chiral auxiliary: compound **3** was prepared in two steps. The reaction between (*S*)-phenylglycinol and cyanogen bromide afforded amino-oxazolidine **2**[11] and the condensation of this heterocycle with methyl propiolate gave bicyclic heterocycle **3** (Scheme 2).



I II III

Scheme 1.



1 2 3

Scheme 2. (a) BrCN, EtOH, reflux 12 h then NaOH, 98%. (b) Ethyl propiolate, EtOH, reflux, 12 h, 66%.

Keywords: asymmetric synthesis; conjugate addition; β-amino acids.

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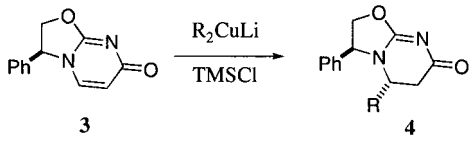
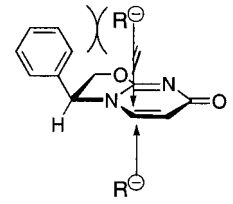
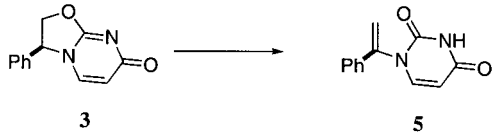
Table 1. Organocuprates addition to cyclic compound **3**



3 **4**

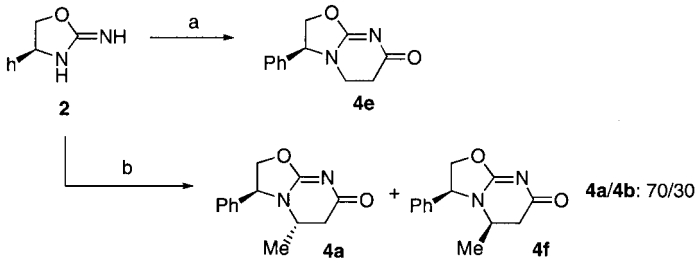
	R	Yield (%)	de (%)
4a	Me	86	>95
4b	*n*-Bu	93	>95
4c	Vinyl	75	>95
4d	Ph	81	>95





3 **5**

Scheme 3.



2 **4e** **4a** **4f**

Scheme 4. (a) Methyl acrylate, MeOH, reflux, 12 h, 76%. (b) Ethyl crotonate, EtOH, reflux 12 h, 25%.

Bicyclic compound **3** was used in Michael additions with different organocuprate reagents. In all cases, these reactions afforded compounds **4a–d** as pure diastereoisomers in high yields (Table 1).

The observed stereoselectivity corresponds to an attack of the nucleophile in an *anti* orientation with respect to the phenyl group. It is interesting to note that, in order to achieve Michael addition, the use of trimethylsilylchloride is necessary. The utility of TMSCl in similar 1,4-addition on enone using organocuprate reagents is well established.[12] Thus, in the absence of TMSCl, product **5** was formed via a β-elimination process that involves the abstraction of the benzylic hydrogen (Scheme 3). Pyrimidine **5** could also be obtained quantitatively by treatment of product **3** with an equimolar quantity of sodium hydride.

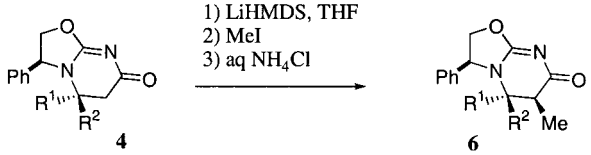
Chiral intermediates **4** were used in asymmetric α-alkylation processes. Condensation of the aminooxazolidine **2** with methylacrylate and ethyl crotonate afforded respectively compound **4e** and a 70/30 mixture of compounds **4a** and **4f** (Scheme 4).

Enolates derived from product **4** were generated by reaction with LiHMDS for 15 min at −10°C in THF. The electrophile was added at −10°C or at −50°C and the reaction mixture was stirred for 2 h at this temperature and further hydrolyzed with a saturated aqueous ammonium chloride solution (Table 2).

The overall yields of alkylation range from 88 to 96% when the reactions were conducted at −10°C. At −50°C the yields drop due incomplete conversion. The results reported in Table 2 show that electrophiles attack the chiral enolates derived from compounds **4** from the β-face, i.e. in a *syn* relationship with respect to the phenyl group. This stereochemical course is surprising since this alkylation takes place on the apparently most hindered β side of the enolate intermediate. The presence of a methyl or a *n*-butyl substituent on the α-face produces an enhancement of the stereoselectivity (compare entries 2, 3 and 5). In order to rationalize this stereoselectivity, specially when no substituent is present on the α-side (i.e. in substrate **4e**), the geometry of the enolate derived from susbstrate **4e**, shown in Fig. 1, was optimized by AM1 calculations.[13]

It is worth noting that the β-nitrogen atom is pyramidal and that the electron lone pair is located on the α-side of the enolate. An unfavorable field interaction occurs between this lone pair and the enolate β-electrons on the α-face.[14] This electronic effect may account for the observed stereoselectivity. The *S* absolute configuration of the α center in adducts **6** was established by NOE ^{1}H NMR experiments in the case of the α,β-dialkylated compounds **6a**, **b**, **f**. Adduct **6e** and **6b** led, respectively to the known (*S*)-3-amino-2-methylpropanoic acid **8b** and to (2*S*, 3*S*)-3-amino-2-methylheptanoic acid **8c**. The absolute configuration of the created stereocenter of compound **4a** was confirmed by synthesizing the already described (*S*)-3-aminobutanoic acid **8a** starting

Table 2. α-Alkylation of intermediates **4**



4 **6**

Entry	Product	R^1	R^2	Temp (°C)	Yield (%)[a]	Ratio (%)[b]
1	**6e**	H	H	−50	30	80:20
2	**6e**	H	H	−10	95	74:24
3	**6a**	Me	H	−10	88	>97:3
4	**6f**	H	Me	−10	93	57:43
5	**6b**	*n*-Bu	H	−10	96	>97:3

[a] Combined yields of the two diastereoisomers.
[b] Determined by ^{1}H NMR of the crude reaction mixture.

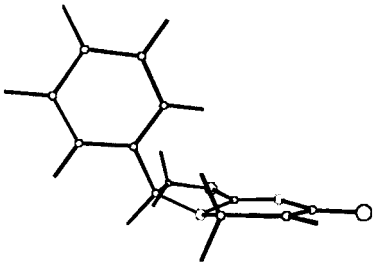
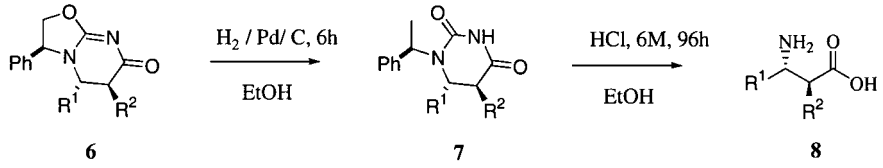


Figure 1. AM1 modelization of enolate derived from compound **4e**.



6 **7** **8**

Scheme 5.

from compound **4e**. As depicted on Scheme 5, the chemical sequence used for this synthesis involved two steps (Tables 3 and 4).

The first step is a selective hydrogenolysis of the homobenzylic C–O bond.[15] Reaction with hydrogen in presence of palladium on carbon, platinum oxide or palladium hydroxyde in acidic, basic or neutral medium gave products **7a**–**d**. The experimental conditions of base-catalysed hydrolysis[16] could be used in the case of the synthesis of β-substituted β-amino acid. Thus, (*S*)-3-aminobutanoic acid **8a**[17] was obtained in two steps from **7a** (i.e. hydrolysis of pyrimidinone **7a** followed by hydrogenolysis of the benzylic C–N bond). In contrast, compounds **7b** and **7c**, submitted to the base-catalysed conditions which were used in the hydrolysis of β-substituted β-amino acids, gave rise, in the present case, to epimerization of the created stereocenter of compound **7b** and **7c** which is in these cases α to carbonyl group. However, strong acidic conditions afforded optically pure (*S*)-3-amino-2-methylpropanoic acid **8b**[18] and (2*S*, 3*S*)-3-amino-2-methylheptanoic acid **8c** after chromatography on an acidic cation exchanger.

In conclusion, we have developed a novel and highly diastereoselective method for the asymmetric synthesis of α-, β- and α,β-substituted β-amino acids starting from chiral synthon **3**. Heterocycles derived from compound **3** are currently used in the asymmetric synthesis of 1,3-diamines, tetrahydropyrimidinones.

Table 3. Hydrogenolysis of compounds **6**

	R^1	R^2	Yield (%)
7a	Me	H	93
7b	H	Me	98
7c	*n*-Bu	Me	95
7d	*n*-Bu	H	95

Table 4. Hydrolysis of compounds **7**

	R^1	R^2	Yield (%)
8a	Me	H	61
8b	H	Me	68
8c	*n*-Bu	Me	81

2. Experimental

2.1. General comments

^{1}H and ^{13}C Spectra were respectively recorded on a Bruker ARX 250 spectrometer at 250 MHz and 62.9 MHz; chemical shifts are reported in ppm from TMS. Column chromatography were performed on silica gel, 230–400. TLC were run on Merck Kieselgel 60F_{254} plates. THF was distilled from sodium/benzophenone ketyl.

2.1.1. (4*S*)-4-Phenyl oxazolidin-2-ylidene amine 2. To a solution of (*S*)-phenylglycinol **1** (2 g; 14.6 mmol) in EtOH (20 mL) was added, at room temperature, cyanogen bromide (1.77 g; 16.7 mmol). After 12 h at reflux, ethanol was evaporated under reduced pressure and the residue was dissolved in a 1 M aqueous solution of NaOH (30 mL) and extracted with dichloromethane (3×20 mL). The organic phase was concentrated at reduced pressure to afford quantitatively compound **2** as a white solid. Mp: 114°C. $[\alpha]_D^{20}=+11$ (*c* 1.0, $CHCl_3$). MS-CI/NH_3: 163 ($M+H^+$, 100). IR ν (cm^{-1}): 3425–1682. NMR ^{1}H ($CDCl_3$, 250 MHz): 4.17 (dd, 1H, *J*=7.3–8.0 Hz,), 4.74 (dd, 1H, *J*=8.0–9.0 Hz), 4.95 (ls, 2H), 5.13 (dd, 1H, *J*=7.3–9.0 Hz), 7.22 (m, 5H). NMR ^{13}C ($CDCl_3$, 65.2 MHz): 65.7, 75.6, 126.3, 127.7, 128.7, 142.2, 162.1.

2.1.2. (3*S*)-3-Phenyl-2,3-dihydro oxazolo [3,2-*a*] pyrimidin-7-one 3. To a solution of **2** (800 mg; 4.94 mmol) in ethanol (15 mL) was added, at room temperature, ethyl propiolate (0.88 mL; 9.88 mmol). After 12 h at reflux, ethanol was evaporated under reduced pressure and the residue was chromatographed on silica gel (MeOH/EtOAc: 10/90) to afford product **3** as a white solid (0.7 g; 3.27 mmol, yield 66%). Mp: 186°C. $[\alpha]_D^{20}=-18$ (*c* 0.4, MeOH). HRMS: calc for $C_{12}H_{10}O_2N_2+H^+=215.0821$, obs=215.0816. IR ν (cm^{-1}): 1632–1528–1477. NMR ^{1}H ($CDCl_3$, 250 MHz): 4.49 (dd, 1H, *J*=7.8–9.2 Hz), 5.01 (t, 1H, *J*=9.2 Hz), 5.23 (dd, 1H, *J*=7.8–9.2 Hz), 5.95 (d, 1H, *J*=7.5 Hz), 6.90 (d, 1H, *J*=7.5 Hz), 7.27 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 61.9, 74.0, 109.8, 127.1, 129.7, 130.0, 135.0, 135.8, 161.0, 175.0.

2.2. General procedure for Michael addition

To a solution of compound **3** (0.93 mmol) in THF (10 mL) were successively added, at −78°C, trimethylsilylchloride (0.93 mmol) and a solution of alkyl organocuprate (1.4 mmol, 0.15 M in diethyl ether, prepared by addition,

at −10°C, of a solution of commercially organolithium (2.8 mmol) to a suspension of CuI (1.4 mmol) in diethyl ether). The reaction was allowed to reach room temperature within 1 h and the mixture was stirred at rt for 2 h. An aqueous solution saturated with ammonium chloride (15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2×20 mL). After evaporation the residue was chromatographed (EtOAc/MeOH).

2.2.1. (4*S*,4′*S*)-4-(2-Imino-4-phenyl oxazolidin-3-yl)-pentan-2-one 4a. (86%). $[\alpha]_D^{20}=+119$ (*c*1, $CHCl_3$). MS-CI/NH_3: 231 ($M+H^+$, 100). ^1H NMR (250 MHz, $CDCl_3$): 1.20 (d, *J*=6.4 Hz, 3H), 2.35 (dd, *J*=15.9, 6.6 Hz, 1H), 2.59 (dd, *J*=15.9, 6.9 Hz, 1H), 3.39–3.44 (m, 1H), 4.32 (dd, *J*=8.9, 6.3 Hz, 1H), 4.81 (t, *J*=8.9 Hz, 1H), 5.03 (dd, *J*=8.6, 6.2 Hz, 1H), 7.22–7.39 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 17.2, 37.1, 45.5, 60.3, 73.2, 126.9, 128.6, 129.7, 135.5, 167.2, 178.1.

2.2.2. (3*S*,5*R*)-5-Butyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-*a*] pyrimidin-7-one 4b. (93%). $[\alpha]_D^{20}=+109$ (*c* 0.5, $CHCl_3$). MS-CI/NH_3: 273 ($M+H^+$, 100). NMR ^1H ($CDCl_3$, 250 MHz): 0.69 (t, 3H, *J*=7.0 Hz), 1.10 (m, 2H), 1.39 (m, 2H), 1.69 (m, 2H), 2.33 (dd, 1H, *J*=5.5–16.0 Hz), 2.50 (dd, 1H, *J*=7.0–16.0 Hz), 3.21 (m, 1H), 4.26 (dd, 1H, *J*=6.0–9.0 Hz), 4.75 (t, 1H, *J*=9.0 Hz), 4.90 (dd, 1H, *J*=6.0–9.0 Hz), 7.14–7.34 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 13.7, 22.3, 26.5, 30.8, 34.4, 49.3, 60.6, 73.2, 126.7, 129.7, 135.8, 167.3, 178.1.

2.2.3. (3*S*,5*S*)-5-Vinyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-*a*] pyrimidin-7-one 4c. (75%). NMR ^1H ($CDCl_3$, 250 MHz): 2.55 (dd, 1H, *J*=5.7–16.0 Hz), 2.73 (dd, 1H, *J*=7.0–16.0 Hz), 3.80 (m, 1H), 4.90 (m, 1H), 4.92 (m, 1H), 5.03 (dd, 1H, *J*=17.1–1.2 Hz), 5.28 (dd, 1H, *J*=10.0–1.2 Hz), 5.70 (m, 1H), 3.35 (m, 5H).

2.2.4. (3*S*,5*R*)-3,5-Diphenyl-2,3,5,6-tetrahydro oxazolo [3,2-*a*] pyrimidin-7-one 4d. (81%). Mp: 90°C $[\alpha]_D^{20}=+96$ (*c* 0.5, $CHCl_3$). MS-CI/NH_3: 293 ($M+H^+$, 100). NMR ^1H (250 MHz, $CDCl_3$): 2.67 (dd, 1H, *J*=7.4–16.2 Hz), 2.85 (dd, 1H, *J*=7.1–16.2 Hz), 4.25 (dd, 1H, *J*=7.1–7.4 Hz), 4.40 (dd, 1H, *J*=5.8–8.8 Hz), 4.59 (dd, 1H, *J*=5.8–8.8 Hz), 4.80 (t, 1H, *J*=8.8 Hz), 7.03 (m, 5H), 7.32 (m, 5H). NMR ^{13}C (62.5 MHz, $CDCl_3$): 37.6, 54.4, 60.7, 73.1, 126.8, 127.1, 129.1, 129.4, 129.6, 129.8, 135.4, 137.0, 167.7, 177.4.

2.2.5. (3*S*)-3-Phenyl-2,3,5,6-tetrahydro oxazolo [3,2-*a*] pyrimidin-7-one 4e. To a solution of **2** (1 g; 6.21 mmol) in ethanol (60 mL) was added, at room temperature, methyl acrylate (0.87 mL; 9.3 mmol). After 12 h at reflux, ethanol was evaporated under reduced pressure and the residue is chromatographed on silica gel (MeOH/EtOAc: 10/90) to afford product **4e** as a white solid (1.02 g; 4.71 mmol, yield 76%). $[\alpha]_D^{20}=+93$ (*c* 0.6, $CHCl_3$). Mp: 183°C. MS-CI/NH_3: 217 ($M+H^+$, 100). NMR ^1H (250 MHz, $CDCl_3$): 2.57 (t, 2H, *J*=8.3 Hz), 3.16 (m, 1H), 3.27 (m, 1H), 4.33 (m, 1H), 4.86 (m, 2H), 7.33 (m, 5H). NMR ^{13}C (62.5 MHz, $CDCl_3$): 29.4, 39.3, 63.2, 73.5, 127.0, 129.6, 129.8, 135.1, 168.3, 178.1.

2.2.6. (4*R*,4′*S*)-4-(2-Imino-4-phenyl oxazolidin-3-yl)-pentan-2-one 4f. To a solution of **2** (1 g; 6.21 mmol) in methanol (60 mL) was added, at room temperature, ethyl crotonate (3.54 mL; 31 mmol). After 12 h at reflux, ethanol was evaporated under reduced pressure and the residue is chromatographed on silica gel (MeOH/EtOAc: 10/90) to afford product **4f** as a white solid (0.357 g; 1.55 mmol, yield 25%). $[\alpha]_D^{20}=+83$ (*c* 1.0, $CHCl_3$). MS-CI/NH_3: 231 ($M+H^+$, 100). Mp: 162°C. NMR ^1H ($CDCl_3$, 250 MHz): 0.74 (d, 3H, *J*=6.6 Hz), 2.30 (dd, 1H, *J*=8.75–15.9 Hz), 2.59 (dd, 1H, *J*=6.5–15.9 Hz), 3.71 (m, 1H), 4.11 (m, 1H), 4.28 (m, 1H), 4.90 (m, 1H), 7.37 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 20.2, 38.4, 49.5, 62.9, 73.6, 126.8, 128.5, 129.5, 137.7, 168.7, 178.5.

2.3. General procedure for the α-alkylation

To a solution of compound **4** (1 mmol) in THF (10 mL) was added, at −10°C, LiHMDS (1.1 mL of a 1 M solution in THF, 1.1 mmol) and after 15 min, at −10°C, methyl iodide (0.09 mL, 1.5 mmol) was added. The reaction mixture was stirred 2 h at −10°C and further quenched by a saturated NH_4Cl aqueous solution and extracted with CH_2Cl_2 (2×20 mL). After evaporation, the residue was chromatographed (EtOAc/MeOH).

2.3.1. (3*S*,5*S*,6*S*)-5,6-Dimethyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-*a*] pyrimidin-7-one 6a. (88%). $[\alpha]_D^{20}=+62$ (*c* 0.8, $CHCl_3$). HRMS: calc for $C_{14}H_{16}O_2N_2+H^+=245.1290$, obs=245.1290. NMR ^1H ($CDCl_3$, 250 MHz): 1.14 (d,3H, *J*=6.6 Hz), 1.19 (d, 3H, *J*=6.6 Hz), 2.29 (quint, 1H, *J*=6.6 Hz), 3.03 (quint, 1H, *J*=6.6 Hz), 4.33 (q, 1H, *J*=6.3–8.9 Hz), 4.84 (t, 1H, *J*=8.9), 5.02 (q, 1H, *J*=6.3–8.9 Hz), 7.31 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 14.8, 16.7, 40.9, 51.7, 60.2, 73.0, 126.8, 128.4, 129.5, 135.5, 165.9, 181.4.

2.3.2. (3*S*,5*S*,6*S*)-5-butyl-6-methyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-α] pyrimidin-7-one 6b. (96%). $[\alpha]_D^{20}=+95$ (*c* 0.2, $CHCl_3$). MS-CI/NH_3: 287 ($M+H^+$, 100). NMR ^1H ($CDCl_3$, 250 MHz): 0.81 (t, 3H, *J*=6.7 Hz), 1.08 (d, 3H, *J*=7.2 Hz), 1.22 (m, 4H), 1.50 (m, 2H), 2.46 (qd, 1H, *J*=3.5–7.2 Hz), 2.90 (m, 1H), 4.36 (dd, 1H, *J*=6.9–8.9 Hz); 4.88 (t, 1H, *J*=8.9 Hz), 5.01 (dd, 1H, *J*=6.9–8.9 Hz), 7.32 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 13.6, 16.5, 22.4, 26.1, 29.8, 38.1, 55.6, 60.4, 73.1, 127.1, 129.4, 129.6, 135.4, 165.8, 182.0.

2.3.3. (3*S*,6*S*)-6-Methyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-*a*] pyrimidin-7-one 6e. (35%). $[\alpha]_D^{20}=+60$ (*c* 0.6, $CHCl_3$). HRMS: calc for $C_{13}H_{14}O_2N_2+H^+=231.1134$, obs=231.1128. NMR ^1H ($CDCl_3$, 250 MHz): 1.23 (d, 3H, *J*=6.9 Hz), 2.84 (m, 1H), 2.88 (dd, 1H, *J*=9.2–11.7 Hz), 3.36 (dd, 1H), 4.46 (m, 1H,), 4.91 (m, 2H), 7.35 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5M Hz): 14.6, 33.5, 45.5, 62.9, 73.5, 127.0, 129.6, 129.7, 135.3, 167.2, 181.4.

2.3.4. (3*S*,5*R*,6*R*)-5,6-Dimethyl-3-phenyl-2,3,5,6-tetrahydro oxazolo [3,2-α] pyrimidin-7-one 6f. (35%). $[\alpha]_D^{20}=+34$ (*c* 0.2, $CHCl_3$). MS-CI/NH_3: 245 ($M+H^+$, 100). NMR ^1H ($CDCl_3$, 250 MHz): 0.78 (d, 3H, *J*=7.2 Hz), 1.18 (d, 3H, *J*=7.2 Hz), 2.27 (quint, 1H, *J*=7.2 Hz), 3.33 (quint, 1H, *J*=7.2 Hz), 4.33 (m, 1H,), 4.84 (m, 2H,), 7.29 (m, 5H,). NMR ^{13}C ($CDCl_3$,

62.5 MHz): 14.6, 19.5, 42.3, 55.6, 63.5, 73.5, 127.2, 129.4, 129.7, 137.8, 167.3, 181.4.

2.4. General procedure for hydrogenolysis of compounds 6

To a solution of compound **6** (1 mmol) in ethanol (10 mL) and under hydrogen atmosphere was added 0.75 equiv. of Pd/C. The reaction mixture was stirred 6 h at room temperature and then filtered over celite and after evaporation compounds **7** were obtained and used, without purification, for the next step.

2.4.1. (1′*R*,6*S*)-6-Methyl-1-(1′-phenyl ethyl) dihydro pyrimidine-2,4-dione 7a. (93%). $[\alpha]_D^{20}=+69$ (*c* 0.5, $CHCl_3$). MS-CI/NH_3: 250 ($M+NH_4^+$, 100). NMR ^1H ($CDCl_3$, 250 MHz): 0.47 (d, 3H; *J*=6.7 Hz), 1.45 (d, 3H, *J*=7.1 Hz), 2.24 (m, 1H), 2.55 (dd, 1H, *J*=6.0–16.4 Hz), 3.52 (m, 1H), 5.70 (q, 1H, *J*=7.1 Hz), 7.22 (m, 5H), 8.76 (ls, 1H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 16.5, 18.8, 38.8, 43.9, 51.5, 127.8, 127.9, 128.4, 139.2, 151.9, 169.8.

2.4.2. (1′*R*,5*S*)-1-(1′-Phenyl ethyl)-5-methyl dihydro pyrimidine-2,4,dione 7b. (98%). $[\alpha]_D^{20}=+90$ (*c* 0.3, $CHCl_3$) HRMS: calc pour $C_{13}H_{16}O_2N_2+H^+=233.1290$, obs=233.1287. NMR ^1H ($CDCl_3$, 250 MHz): 1.18 (d, 3H, *J*=7.0 Hz), 1.60 (d, 3H, *J*=7.3 Hz), 2.48 (m, 1H), 3.02 (m, 2H), 5.83 (q, 1H, *J*=7.3 Hz), 7.36 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 12.6, 15.4, 35.2, 43.1, 51.3, 127.1, 127.8, 128.7, 139.6, 153.6, 172.5.

2.4.3. (1′*S*,5*S*,6*S*)-6-Butyl-5-methyl-1-(1-phenyl-ethyl)-dihydro-pyrimidin-2,4-dione 7c. (95%). NMR ^1H ($CDCl_3$, 250 MHz): 0.54 (t, 3H, *J*=7.2 Hz), 1.21 (d, 3H, *J*=4.9 Hz), 1.50 (d, 3H, *J*=7.1 Hz), 1.90 (m, 6H), 2.51 (m, 1H), 2.97 (m, 1H), 5.81 (q, 1H, *J*=7.1 Hz), 7.36 (m, 5H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 15.1, 17.9, 18.2, 23.6, 29.5, 34.3, 40.5, 53.1, 56.8, 129.7,130.2, 140.9, 152.9, 175.0.

2.4.4. (1′*S*,6*S*)-6-Butyl-1-(1-phenyl-ethyl)-dihydro-pyridin-2,4-dione 7d. (95%). $[\alpha]_D^{20}=+69$ (*c* 0.5, $CHCl_3$). MS-CI/NH_3: 292 ($M+NH_4^+$, 100). NMR ^1H ($CDCl_3$, 250 MHz): 0.56 (t, 3H, *J*=7.2 Hz), 0.86 (m, 4H), 1.12 (m, 2H), 1.52 (d, 3H, *J*=7.2 Hz), 2.51 (m, 2H), 3.32 (m, 1H), 5.73 (q, 1H, *J*=7.2 Hz), 7.36 (m, 5H), 2.51 (ls, 1H). NMR ^{13}C ($CDCl_3$, 62.5 MHz): 14.0, 17.2, 22.4, 28.4, 32.5, 35.9, 49.0, 52.7, 128.6, 129.5, 139.6, 152.1, 169.9.

2.5. General procedure for the hydrolysis of the alkylated pyrimidinones

A suspension of adduct **7** (180 mg, 0.870 mmol) in 10 mL of 8N HCl was heated at reflux for 96 h. The aqueous phase was concentrated at reduced pressure and the amino acid hydrochloride was adsorbed to acidic ion exchange resin Dowex 50W X8. The resin was washed with distilled water until the washing came out neutral, and then the free amino acid was recovered with 3% ammonium hydroxide.

2.5.1. (*S*)-3-Aminobutanoic acid 8a. (61%): $[\alpha]_D^{20}=+34$ (*c* 0.6, H_2O); [lit.[7a]: $[\alpha]_D^{28}=+32.2$ (*c*0.9, H_2O); lit.[18]: $[\alpha]_D^{23}=+37.2$ (*c*0.3, H_2O)]. Mp: 210°C. NMR ^1H (D_2O, 250 MHz): 1.26 (d, 3H, *J*=6.9 Hz), 2.25 (dd, 1H, *J*=8.4–16.6H), 2.39 (dd, 1H, *J*=4.7–16.6 Hz), 3.40 (m, 1H). NMR ^{13}C (CD_3OD, 62.5 MHz): 18.7, 41.2, 46.6, 177.5.

2.5.2. (2*S*,3*S*)-3-Amino-2-methylpropanoic acid 8b. (68%). $[\alpha]_D^{25}=+11$ (*c* 0.3, 1N HCl); [lit.[19]: $[\alpha]_D^{29}=+11.6$ (*c*1, 1N HCl). ^1H NMR (250 MHz, D_2O): 1.15 (d, *J*=7.3 Hz, 3H), 2.57 (m, 1H), 2.98 (dd, *J*=12.8, 5.3 Hz, 1H), 3.08 (dd, *J*=12.8–8.4 Hz, 1H). ^{13}C NMR (63 MHz, D_2O): 14.0, 38.1, 41.3, 180.3.

2.5.3. (*S*)-3-Amino-2-methylheptanoic acid 8c. (81%). $[\alpha]_D^{20}=+12$ (*c* 0.15, MeOH). NMR ^1H (MeOD, 250 MHz): 1.03 (t, 3H, *J*=7 Hz), 1.35 (d, 3H, *J*=7 Hz), 1.46 (m, 4H), 1.73 (m, 2H), 2.72 (m, 1H), 3.44 (m, 1H). NMR ^{13}C (MeOD, 62.5 MHz): 12.7, 13.6, 22.8, 26.8, 30.0, 41.8, 53.2, 175.5.

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