Diastereoselective Electrophilic Amination of Chiral 1-Benzoyl-2,3,5,6-tetrahydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one for the Asymmetric Syntheses of α-Substituted α,β-Diaminopropanoic Acids[1])

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The chiral compounds (*R*)- and (*S*)-1-benzoyl-2,3,5,6-tetrahydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one ((*R*)- and (*S*)-**1**), derived from (*R*)- and (*S*)-asparagine, respectively, were used as convenient starting materials for the preparation of the enantiomerically pure α-alkylated (alkyl = Me, Et, Bn) α,β-diamino acids (*R*)- and (*S*)-**11**–**13**. The chiral lithium enolates of (*R*)- and (*S*)-**1** were first alkylated, and the resulting diastereoisomeric products **5**–**7** were aminated with 'di(*tert*-butyl) azodicarboxylate' (DBAD), giving rise to the diastereoisomerically pure (≥ 98%) compounds **8**–**10**. The target compounds (*R*)- and (*S*)-**11**–**13** could then be obtained in good yields and high purities by a hydrolysis/hydrogenolysis/hydrolysis sequence.

1. Introduction. – The enantioselective synthesis of amino acids is receiving increased attention, owing in great part to their relevant role in biological systems. Indeed, an impressive number of new synthetic procedures have been developed for the asymmetric synthesis of both natural and unnatural amino acids [2]. Some relevant topics in this regard are the preparation of peptidomimetics [3], the synthesis of peptides and proteins that are more resistant to hydrolytic reactions [4], and the development of amino acid analogs as enzyme inhibitors [5].

α,β-Diamino acids are particularly attractive synthetic targets in view of the various biologically relevant activities exhibited by these compounds [6]. One example is (*S*)-2,3-diaminopropanoic acid, which is present in nature as a peptidic residue in several antibiotic cyclopeptides [7]. In other cases, diamino acids have been used to induce specific conformations in peptide segments [8], or as precursors of imidazoline derivatives with therapeutic activity and increased resistance to hydrolysis [9]. Furthermore, several diamino acids are convenient precursors of β-lactams presenting antibiotic activity [10].

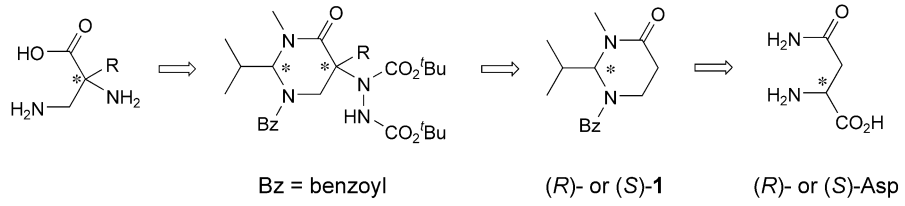
Several procedures have been described for the enantioselective synthesis of α,β-diamino acids [11]. Most of these methods are based on the diastereoselective alkylation of enolates of chiral glycine equivalents, *e.g.*, chiral imidazolidinones [12], oxazolidinones [13], and bis-lactims [14]. Some α,β-diamino acids have also been prepared from suitable β-lactams [15].

Given the importance of chiral α,β-diamino acids, and taking into account our experience concerning the application of chiral pyrimidinones derived from (*R*)- or

[1]) Enantioselective Syntheses of β-Amino Acids: Part 15. For Part 14, see [1].

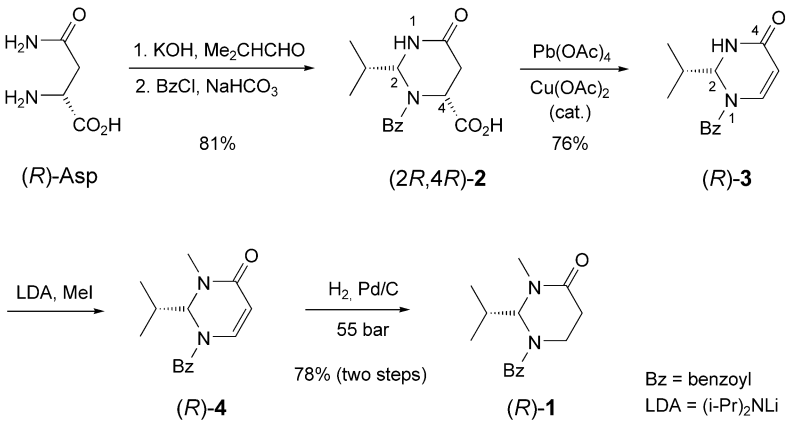
(*S*)-asparagine for the preparation of enantiomerically pure β-amino acids [16], we decided to undertake an enantioselective synthesis of (2*R*)- and (2*S*)-2-alkyl-2,3-diaminopropanoic acids, following the retrosynthetic strategy presented in *Scheme 1*.

Scheme 1



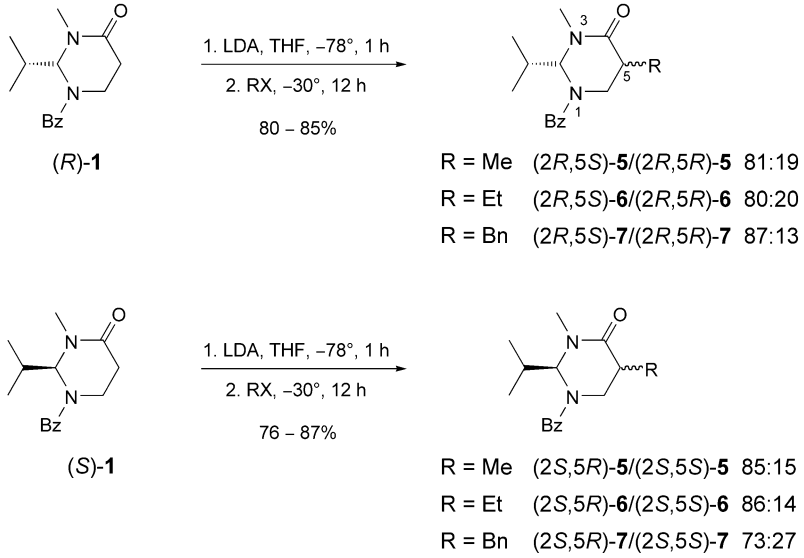
2. Results and Discussion. – 2.1. *Synthesis of (*R*)-***1*** from (*R*)-Asparagine*. The general procedure developed by *Konopelski et al.* [17] was followed, with isobutyraldehyde instead of pivalaldehyde. As indicated in *Scheme 2*, (2*R*,4*R*)-**2** was obtained in 81% yield. This product was subjected to oxidative decarboxylation with $Pb(OAc)_4$ under $Cu(OAc)_2$ catalysis [17][18], resulting in (*R*)-**3** (76%). The latter was then *N*-methylated [19] to (*R*)-**4**, which was hydrogenated catalytically with Pd on charcoal [18], affording (*R*)-**1** in 78% yield for the two steps (*Scheme 2*). The enantiomer (*S*)-**1** was prepared by a similar synthetic strategy, and according to literature procedures [20].

Scheme 2



2.2. *Electrophilic Alkylation/Amination of (*R*)- and (*S*)-***1***.* As expected [16][21], addition of various alkyl halides to the chiral enolate of either (*R*)- or (*S*)-**1** proceeded predominantly on the enolate's face opposite to the i-Pr group. As shown in *Scheme 3*, all reactions proceeded in good yield and with high diastereoselectivity.

Scheme 3



The alkylated products **5**–**7** (diastereoisomeric mixtures) were treated with lithium diisopropylamide (LDA) to give the corresponding enolates, which were immediately aminated with di-(*tert*-butyl) azodicarboxylate[2]) (DBAD) [22] (*Scheme 4*). Most gratifyingly, ^{1}H-NMR analyses of the crude amination products **8**–**10** showed a single set of signals, indicating a diasteroisomeric purity of $\geq 98\%$.

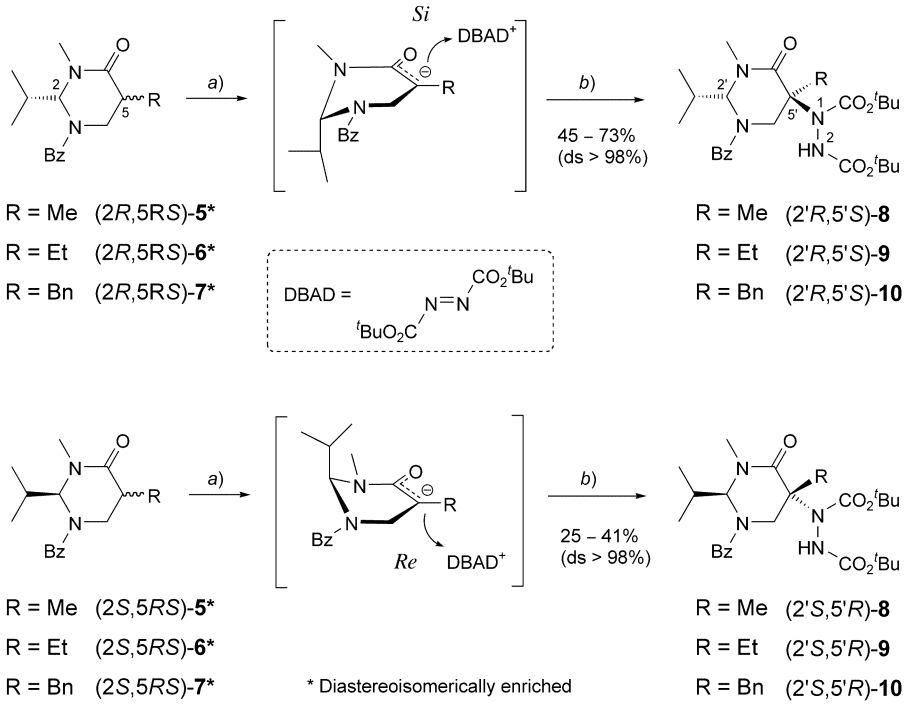
Chemical correlation with known α-alkylated α,β-diamino acids (*vide infra*) confirmed that the addition of the electrophilic reagent took place from the enolate's face opposite to the isopropyl group (*Scheme 4*). The very high diastereoselectivity observed is, thus, induced by the pseudoaxial orientation adopted by the isopropyl group [21][23], which effectively hinders the approach of the bulky DBAD reagent from the *syn* face.

2.3. *Isolation of the α-Alkylated α,β-Diamino Acids (*R*)- and (*S*)-***11***–***13***.* The final part in the synthesis consisted of a hydrolysis/hydrogenolysis/hydrolysis sequence of reactions (*Scheme 5*) that gave the expected diamino acids (*R*)- and (*S*)-**11**–**13** from the intermediates (2′*S*,5′*R*)-**8**–**10** and (2′*R*,5′*S*)-**8**–**10**, respectively. The final products could be readily purified by silica-gel column chromatography, with MeOH/i-PrOH/aq. NH_3 as eluent [24].

3. Conclusions. – The chiral pyrimidinones (*R*)- and (*S*)-**1** are convenient starting materials for the preparation of the enantiomerically pure α-alkylated α,β-diamino acids (*R*)- and (*S*)-**11**–**13**. The chiral enolates (*R*)- and (*S*)-**1**–Li are readily prepared by treatment of the starting heterocycle with lithium diisopropylamide (LDA). Although the subsequent alkylation of (*R*)- and (*S*)-**1**–Li with various alkyl halides is not fully diastereoselective, treatment of the resulting alkylated products **5**–**7**

[2]) Systematic name: di(*tert*-butyl) (*E*)-diazene-1,2-dicarboxylate.

Scheme 4



a) $^{i}Pr_2NLi$ (LDA), THF, $-78°$, 2 h. *b*) DBAD, $-78°$, r.t., 12 h.

(diastereoisomeric mixture) with a second equivalent of LDA affords the corresponding Li enolates, which are now aminated with DBAD with complete (>98%) diastereoselectivity. A hydrolysis/hydrogenolysis/hydrolysis sequence finally provides the desired α,β-diamino acids in enantiomerically pure form.

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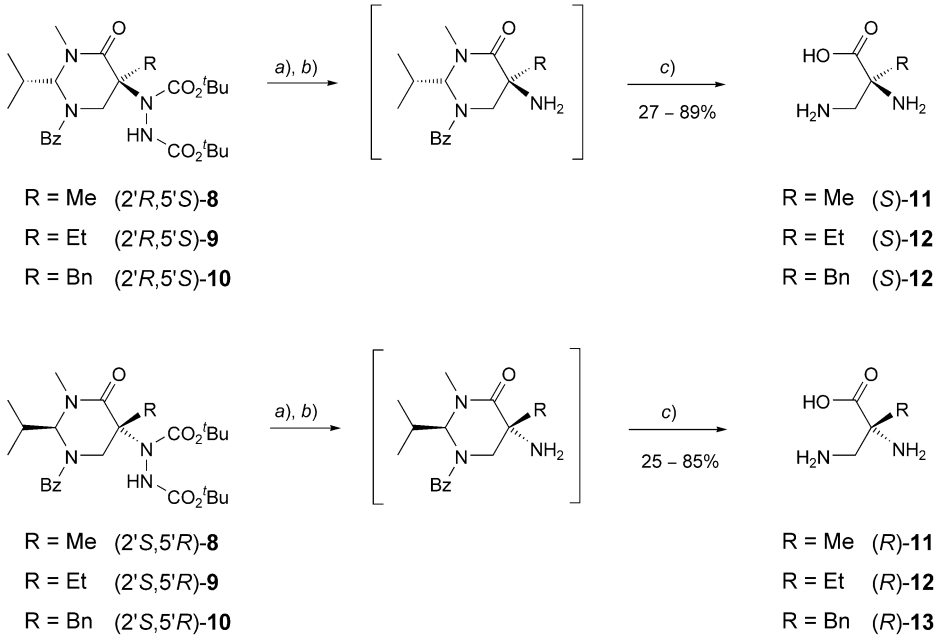
Experimental Part

General. All commercial reagents were used as received. Anhydrous (anh.) solvents were obtained by distillation. Flash-column chromatography (FC) was performed on silica gel (*Merck 60*, 230–400 mesh). Reactions were monitored by thin-layer chromatography (TLC; aluminium-backed plates (0.2 mm), *Merck* silica-gel *60* F_{254}). Melting points (m.p.) were determined on a *Mel Temp* apparatus, and are uncorrected. Optical rotations were measured on a *Perkin-Elmer-241* polarimeter ($\lambda = 589$ nm). ^{1}H- and ^{13}C-NMR Spectra were recorded on *Jeol Eclipse-400* (400/100 MHz), *Bruker Ultra-Shield* (300/75 MHz), and *Jeol GSX-270* (270/67.5 MHz) spectrometers; chemical shifts δ in ppm rel. to $SiMe_4$ (=0 ppm) as internal reference, coupling constants *J* in Hz. Elemental analyses were determined by the combustion method with a *Thermo-Finnigan-Serie-Flash-1112* apparatus.

*(2*R*,4*R*)-3-Benzoyl-1,2,3,4,5,6-hexahydro-2-(1-methylethyl)-6-oxopyrimidine-4-carboxylic Acid* ((2*R*,4*R*)-**2**). In an *Erlenmeyer* flask (1000 ml), equipped with a magnetic bar, KOH (13.2 g, 0.2 mol) was dissolved in distilled H_2O (300 ml). Then, under stirring, (*R*)-asparagine monohydrate (30 g, 0.2 mol) and isobutyraldehyde

Scheme 5



a) CF_3COOH, CH_2Cl_2, r.t., 30 min. *b*) *Raney* Ni/H_2 (69 bar), MeOH, r.t., 27 h. *c*) 6N HCl, 90°, 36–56 h.

(36.3 ml, 0.4 mmol) were added, and the mixture was vigorously stirred for 6 h at r.t. Then, the mixture was cooled to 0° in an ice bath, and $NaHCO_3$ (8.4 g, 0.1 mol) and benzoyl chloride (BzCl; 11.6 ml, 0.1 mol) were added. After 30 min of stirring, additional portions of $NaHCO_3$ and BzCl (8.4 g and 11.6 ml, resp.) were added, and the resulting mixture was stirred at 0° for 1 h, and then at r.t. for 1 h. Unreacted isobutyraldehyde and BzCl were removed by extraction with CH_2Cl_2 (200 ml). The aq. phase was adjusted to pH 2.0 with 10% aq. HCl soln., an the desired product was extracted with CH_2Cl_2 (3 × 500 ml). The org. layers were combined, dried (Na_2SO_4), and concentrated in a rotary evaporator at reduced pressure. The resulting crude solid was recrystallized from hexane/acetone 8:2 to afford pure (2*R*,4*R*)-**2**: 47.0 g (81%). M.p. 191–192°. $[\alpha]_0^{25} = +149$ (*c* = 1, MeOH). ^{1}H-NMR (300 MHz, (D_6)DMSO, *T* = 120°): 0.87 (*d*, *J* = 6.7, 3 H); 0.96 (*d*, *J* = 6.6, 3 H); 2.10 (*m*, 1 H); 2.64 (*dd*, *J* = 16.7, 8.3, 1 H); 2.80 (*dd*, *J* = 16.7, 8.9, 1 H); 4.80 (*t*, *J* = 8.6, 1 H); 4.93 (*d*, *J* = 10.0, 1 H); 7.38–7.45 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, *T* = 120°): 18.1; 18.5; 31.4; 32.9; 52.4; 69.5; 126.2; 127.7; 128.8; 135.3; 166.3; 169.8; 171.0. Anal. calc. for $C_{15}H_{18}N_2O_4$ (290.31): C 62.06, H 6.25, N 9.65; found: C 61.84, H 6.25, N 9.65.

*(*R*)-1-Benzoyl-2,3-dihydro-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((*R*)-**3**). In a round-bottom flask, equipped with a magnetic stirrer, was placed (2*R*,4*R*)-**2** (20.0 g, 68.9 mmol) in toluene (200 ml) and THF (300 ml), and this soln. was treated with pyridine (10 ml) and $Cu(OAc)_2$ (0.5 g, 2.4 mmol). The resulting mixture was stirred at r.t. for 2 h. Then, the flask was placed in an ice bath, and $Pb(OAc)_4$ (54.0 g, 121.8 mmol) was added. The ice bath was removed, and the mixture was heated to reflux for 18 h. The resulting suspension was filtered, and the filtrate was concentrated *in vacuo*. The crude product was washed with H_2O (200 ml) and extracted with AcOEt (250 ml). The org. extracts were combined, dried (Na_2SO_4), and evaporated to a viscous oil, which was purified by FC (SiO_2; hexane/AcOEt 1:1) to afford (*R*)-**3**: 12.8 g (76%). White solid. M.p. 159–160°. $[\alpha]_D^{25} = -490$ (*c* = 1, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO, *T* = 120°): 0.88 (*d*, *J* = 6.9, 3 H); 0.96 (*d*, *J* = 6.7, 3 H); 2.22 (*m*, 1 H); 5.12 (*d*, *J* = 8.01, 1 H); 5.42 (*dd*, *J* = 7.26, 1.5, 1 H); 7.09 (*dd*, *J* = 8.1, 1.6, 1 H); 7.04–7.11 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, *T* = 120°): 16.9; 17.5; 32.2; 68.0; 104.6; 127.0; 128.0; 130.2; 133.0; 136.3; 161.5; 167.6. Anal. calc. for $C_{14}H_{16}N_2O_2$ (244.29): C 68.83, H 6.60, N 11.47; found: C 69.11, H 6.52, N 11.54.

*(*R*)-1-Benzoyl-2,3-dihydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((*R*)-**4**) In a dried, 100-ml round-bottom flask, equipped with a magnetic stirrer, were placed anh. THF (15.0 ml) and (i-Pr)$_2$NH (1.14 ml,

8.1 mmol), and the resulting soln. was cooled to −20°. Then, BuLi (2.37M in hexane, 3.11 ml, 7.4 mmol) was added. The resulting LDA (lithium diisopropylamide) soln. was stirred for 20 min, and then cooled to −78° (dry-ice/acetone bath). To this soln., a cooled (−78°) soln. of (*R*)-**3** (1.8 g, 7.4 mmol) in anh. THF (15.0 ml) was added, and the mixture was stirred for 1 h at this temp. Then, MeI (0.55 ml, 8.8 mmol) was added, the temp. was allowed to come to −30°, and stirring was continued at this temp. for 4 h. Then, sat. aq. NH_4Cl soln. (3.0 ml) was added, and the mixture was extracted with AcOEt (3 × 15 ml). The org. extracts were combined, dried (Na_2SO_4), and concentrated to afford crude (*R*)-**4** as a yellowish solid, which was purified by FC (SiO_2; hexane/AcOEt 3:7): 15.6 g (82.0%). White solid. M.p. 104–105°. $[\alpha]_D^{25} = -511$ ($c = 1$, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO, $T = 120°$): 0.92 (*d*, $J = 6.9$, 3 H); 1.00 (*d*, $J = 6.8$, 3 H); 2.38 (*m*, 1 H); 3.02 (*s*, 3 H); 5.22 (*d*, $J = 7.87$, 1 H); 5.60 (*dd*, $J = 7.3, 1.6$, 1 H); 7.05 (*dd*, $J = 7.9, 1.7$, 1 H); 7.49–7.52 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, $T = 120°$): 17.7; 18.2; 32.0; 34.0; 73.9; 105.3; 127.0; 128.0; 130.3; 132.8; 135.6; 160.8; 167.5. Anal. calc. for $C_{15}H_{18}N_2O_2$ (258.31): C 69.74, H 7.02, N 10.84; found: C 69.95, H 6.98, N 10.95.

*(*R*)-1-Benzoyl-2,3,5,6-tetrahydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((*R*)-**1**). In a hydrogenation flask was placed Pd/C (0.2 g) under a stream of anh. N_2 gas. MeOH (20 ml) and (*R*)-**4** (2.0 g, 7.8 mmol) were added, and the flask was pressurized with H_2 (55 bar) and shaken at r.t. for 12 h. The catalyst was removed by filtration over *Celite*, the solvent was evaporated under reduced pressure, and the crude (*R*)-**1** was purified by FC (SiO_2; AcOEt/hexane 9:1): 1.9 g (95%). White solid. M.p. 99–100°. $[\alpha]_D^{25} = -25.0$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR (400 MHz, (D_6)DMSO, $T = 120°$): 0.95 (*d*, $J = 6.6$, 3 H); 1.00 (*d*, $J = 6.6$, 3 H); 2.35 (*m*, 1 H); 2.50 (*m*, 2 H); 2.95 (*s*, 3 H); 3.58 (*qt*, $J = 13.9, 7.7$, 1 H); 3.86 (br. *t*, $J = 7.0$, 1 H); 5.15 (*d*, $J = 7.0$, 1 H); 7.39–7.48 (*m*, 5 H). ^{13}C-NMR (100 MHz, (D_6)DMSO, $T = 120°$): 19.2; 19.2; 30.4; 33.3; 35.5; 39.5; 74.8; 127.2; 128.9; 130.2; 136.2; 167.5; 170.3. Anal. calc. for $C_{15}H_{20}N_2O_2$ (260.33): C 69.20, H 7.74, N 10.76; found: C 69.20, H 7.67, N 10.79.

General Procedure (*GP1*) *for the Alkylation of (*R*)-***1** *and (*S*)-***1** (*Scheme 2*). A soln. of (i-Pr)$_2$NH (1.0 ml, 7.3 mmol) in anh. THF (15 ml) was cooled to −20° under N_2 gas. Then, BuLi (2.4M in hexane; 2.75 ml, 6.6 mmol) was added, and the resulting mixture was stirred for 20 min at this temp. Then, the temp. was lowered to −78° (dry-ice/acetone bath), and a cooled (−78°) soln. of (*R*)- or (*S*)-**1** (1.7 g, 6.6 mmol) in anh. THF (20 ml) was added slowly. The resulting soln. was stirred at this temp. for 2 h. Then, the electrophile (MeI, EtI, or BnBr; 7.2 mmol, 1.1 equiv.) was added slowly. The temp. was raised to −30°, and stirring was continued for 3–7 h, until no starting material was visible by TLC. An aq. sat. soln. of NH_4Cl (3 ml) was then added to quench the reaction, the resulting mixture was washed with brine (10 ml), and extracted with AcOEt (3 × 20 ml). The combined org. extracts were driede (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the crude product, which was analyzed by ^{1}H-NMR to determine the diastereoisomeric ratio. The crude diastereoisomerically enriched products **5**–**7** were purified by FC (SiO_2; AcOEt/hexane 7:3).

*(2*R*,5*S*)- and (2*R*,5*R*)-1-Benzoyl-2,3,5,6-tetrahydro-3,5-dimethyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((2*R*,5*S*)-**5** and (2*R*,5*R*)-**5**, resp.). Prepared according to *GP1*. Yield: 80%; diastereoisomer ratio: (2*R*,5*S*)/(2*R*,5*R*) 81:19.

*Data for (2*R*,5*S*)-***5** (major product, *trans*-isomer): ^{1}H-NMR (300 MHz, (D_6)DMSO, $T = 120°$): 0.94 (*d*, $J =$ 6.8, 3 H); 0.98 (*d*, $J = 6.7$, 3 H); 1.03 (*d*, $J = 6.8$, 3 H); 2.38 (*m*, 1 H); 2.72 (*m*, 1 H); 2.94 (*s*, 3 H); 3.40 (*dd*, $J = 7.0$, 13.0, 1 H); 3.8 (*dd*, $J = 7.8, 13.0$, 1 H); 5.19 (*d*, $J = 8.8$, 1 H); 7.35–7.46 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, $T = 120°$): 14.9; 18.1; 18.3; 32.4; 33.2; 34.5; 46.4; 74.2; 126.1; 127.8; 129.0; 135.3; 169.2; 169.8.

*Data for (2*R*,5*R*)-***5** (minor product, *cis*-isomer): ^{1}H-NMR (300 MHz, (D_6)DMSO, $T = 120°$): 0.94 (*d*, $J =$ 6.8, 3 H); 1.00 (*d*, $J = 7.7$, 3 H); 1.05 (*d*, $J = 7.2$, 3 H); 2.28 (*m*, 1 H); 2.72 (*m*, 1 H); 2.94 (*s*, 3 H); 3.19 (*dd*, $J = 11.0$, 14.0, 1 H); 4.03 (*dd*, $J = 8.0$, 13.4, 1 H); 5.22 (*d*, $J = 7.5$, 1 H); 7.35–7.46 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, $T = 120°$): 13.9; 17.6; 18.0; 32.3; 34.0; 34.7; 44.9; 72.8; 125.9; 127.8; 129.1; 134.9; 168.7; 169.5.

*(2*S*,5*R*)- and (2*S*,5*S*)-1-Benzoyl-2,3,5,6-tetrahydro-3,5-dimethyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((2*S*,5*R*)-**5** and (2*S*,5*S*)-**5**, resp.). Prepared according to *GP1*. Yield: 76%; diastereoisomer ratio: (2*S*,5*R*)/(2*S*,5*S*) 85:15. The spectral data of the (2*S*,5*R*)- and the (2*S*,5*S*)-isomers were identical with those of enantiomeric (2*R*,5S)-and (2*R*,5*R*)-**5**, resp. (see above).

*(2*R*,5*S*)- and (2*R*,5*R*)-1-Benzoyl-5-ethyl-2,3,5,6-tetrahydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((2*R*,5*S*)-**6** and (2*R*,5*R*)-**6**, resp.). Prepared according to *GP1*. Yield: 83%; diastereoisomer ratio: (2*R*,5*S*)/(2*R*,5R) 80:20.

*Data for (2*R*,5*S*)-***6** (major product, *trans*-isomer): ^{1}H-NMR (270 MHz, (D_6)DMSO, $T = 120°$): 0.79 (*t*, $J =$ 7.4, 3 H); 0.96 (*d*, $J = 6.7$, 3 H); 1.00 (*d*, $J = 6.7$, 3 H); 1.40 (*m*, 1 H); 1.72 (*m*, 1 H); 2.30 (*m*, 1 H); 2.38 (*m*, 1 H); 2.95 (*s*, 3 H); 3.62 (*dd*, $J = 13.0, 18.8$, 1 H); 3.75 (*dd*, $J = 7.7, 13.6$, 1 H); 5.23 (*d*, $J = 7.8$, 1 H); 7.38–7.50 (*m*, 5 H). ^{13}C-NMR (67.5 MHz, (D_6)DMSO, $T = 120°$): 11.4; 19.3; 19.2; 24.0; 33.4; 35.6; 41.0; 43.7; 73.9; 127.3; 129.0; 130.3; 136.4; 170.0; 170.3.

*Data for (2*R,5R*)*-**6** (minor product, *cis*-isomer): ^{1}H-NMR (270 MHz, (D_6)DMSO, $T = 120°$): 0.84 (*t*, *J* = 7.4, 3 H); 0.96 (*d*, *J* = 6.7, 3 H); 1.06 (*d*, *J* = 6.7, 3 H); 1.50 (*m*, 1 H); 1.72 (*m*, 1 H); 2.35 (*m*, 1 H); 2.40 (*m*, 1 H); 2.93 (*s*, 3 H); 3.28 (*dd*, *J* = 11.0, 14.0, 1 H); 4.02 (*dd*, *J* = 7.7, 13.6, 1 H); 5.14 (*d*, *J* = 7.9, 1 H); 7.38–7.52 (*m*, 5 H). ^{13}C-NMR (67.5 MHz, (D_6)DMSO, $T = 120°$): 11.1; 18.9; 19.2; 23.1; 33.5; 35.4; 42.2; 44.0; 75.0; 127.1; 129.0; 130.3; 136.0; 170.2; 170.3.

*(2*S,5R*)- and (2*S,5S*)-1-Benzoyl-5-ethyl-2,3,5,6-tetrahydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((2*S*,5*R*)-**6** and (2S,5*S*)-**6**, resp.). Prepared according to *GP1*. Yield: 82%; diastereoisomer ratio: (2*S*,5*R*)/(2*S*,5S) 86:14. The spectral data of the (2*S*,5*R*)- and the (2*S*,5*S*)-isomers were identical with those of enantiomeric (2*R*,5S)-and (2*R*,5*R*)-**6**, resp. (see above).

*(2*R,5S*)- and (2*R,5R*)-1-Benzoyl-5-benzyl-2,3,5,6-tetrahydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((2*R*,5*S*)-**7** and (2*R*,5*R*)-**7**, resp.). Prepared according to *GP1*. Yield: 85%; diastereoisomer ratio: (2*R*,5*S*)/(2*R*,5R) 87:13.

*Data of (2*R,5S*)*-**7** (major product, *trans*-isomer): ^{1}H-NMR (400 MHz, (D_6)DMSO, $T = 120°$): 0.91 (*d*, *J* = 6.6, 3 H); 0.99 (*d*, *J* = 6.9, 3 H); 2.37 (*m*, 1 H); 2.56 (*dd*, *J* = 13.9, 8.8, 1 H); 2.80 (*m*, 1 H); 2.98 (*s*, 3 H); 3.10 (*m*, 1 H); 3.13 (*dd*, 1 H); 3.59 (*dd*, *J* = 7.2, 13.0, 1 H); 5.16 (*d*, *J* = 7.4, 1 H); 7.03–7.50 (*m*, 5 H). ^{13}C-NMR (100 MHz, (D_6)DMSO, $T = 120°$): 19.3; 19.4; 33.4; 35.3; 36.7; 41.8; 44.2; 75.2; 127.4; 128.6; 128.9; 129.2; 129.4; 130.3; 136.1; 139.5; 169.9; 170.1.

*Data of (2*R,5R*)*-**7** (minor product, *trans*-isomer): ^{1}H-NMR (400 MHz, (D_6)DMSO, $T = 120°$): 0.79 (*d*, *J* = 6.9, 3 H); 0.91 (*d*, *J* = 6.9, 3 H); 1.91 (*m*, 1 H); 2.38 (*dd*, *J* = 14.0, 8.8, 1 H); 2.90 (*m*, 1 H); 2.94 (*s*, 3 H); 3.12 (*m*, 1 H); 3.80 (*dd*, 1 H); 4.06 (*dd*, *J* = 7.6, 13.5, 1 H); 5.14 (*d*, *J* = 7.6, 1 H); 7.03–7.42 (*m*, 5 H). ^{13}C-NMR (100 MHz, (D_6)DMSO, $T = 120°$): 18.6; 19.1; 33.3; 35.5; 35.9; 42.1; 43.1; 73.9; 126.5; 126.6; 126.9; 128.6; 129.4; 130.2; 135.2; 138.8; 169.9; 170.1.

*(2*S,5R*)- and (2*S,5S*)-1-Benzoyl-5-benzyl-2,3,5,6-tetrahydro-3-methyl-2-(1-methylethyl)pyrimidin-4(1*H*)-one* ((2*S*,5*R*)-**7** and (2*S*,5*S*)-**7**, resp.). Prepared according to *GP1*. Yield: 87%; diastereoisomer ratio: (2*S*,5*R*)/(2*S*,5*S*) 73:27. The spectral data for (2*S*,5*R*)-and (2*S*,5*S*)-**7** were identical with those of the corresponding enantiomers (2*R*,5*S*)- and (2*R*,5*R*)-**7**, resp.

General Procedure (*GP2*) *for the Electrophilic Amination of Compounds* **5**–**7** (*Scheme 4*). To a cooled (−20°) soln. of (i-Pr)$_2$NH (1.2 mmol) in anh. THF (15 ml) was added under N_2 atmosphere BuLi (2.3M soln. in hexane; 0.43 ml, 1.0 mmol). The resulting LDA soln. was stirred at −20° for 20 min. Then, the temp. was lowered to −78° (dry-ice/acetone bath), and a cooled (−78°) soln. of the substrate (**5**, **6** or **7**; 1.0 mmol) in anh. THF (20 ml) was added dropwise. The resulting soln. was stirred at −78° for 2 h. Then, a cooled (−78°) soln. of di(*tert*-butyl)azodicarboxylate (DBAD; 1.5 mmol[2]) in anh. THF (1.5 ml) was added. The mixture was stirred at −78° for 6 h, and then at r.t. for another 3–6 h, until no more substrate was detected (TLC). The reaction was then quenched with sat aq. NH_4Cl soln. (4 ml), treated with brine (15 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. extracts were combined, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to afford the crude products, wich were analyzed by ^{1}H-NMR (determination of diastereoisomer ratio). Only one set of signals was observed, indicating diastereoisomer purities of ≥ 98%. The compounds were purified by FC (SiO_2; AcOEt/hexane 6:4), affording the desired pure products **8**–**10** as white foams.

*Di(*tert*-butyl) 1-[(2*R,5S*)-1-Benzoyl-1,2,3,4,5,6-hexahydro-3,5-dimethyl-2-(1-methylethyl)-4-oxopyrimidin-5-yl]hydrazine-1,2-dicarboxylate* ((2′*R*,5′*S*)-**8**). Prepared according to *GP2*. White foam. Yield: 227 mg (45%). $[\alpha]_D^{25} = +2.0$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO, $T = 120°$): 0.93 (*d*, *J* = 6.7, 3 H); 1.02 (*d*, *J* = 6.6, 3 H); 1.31 (*s*, 9 H); 1.34 (*s*, 3 H); 1.36 (*s*, 9 H); 2.35 (br. *s*, 1 H); 2.91 (*s*, 3 H); 3.54 (br *s*, 1 H); 4.60 (br *s*, 1 H); 5.21 (br. *s*, 1 H); 7.38–7.45 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, $T = 120°$): 17.7; 17.8; 27.3; 32.1; 34.1; 47.1; 61.3; 73.7; 78.8; 79.9; 126.3; 126.6; 127.4; 128.6; 153.0; 154.5; 168.5; 169.1. Anal. calc. for $C_{26}H_{40}N_4O_6$ (504.62): C 61.88, H 7.99, N 11.10; found: C 62.10, H 8.39, N 10.70.

*Di(*tert*-butyl) 1-[(2*S,5R*)-1-Benzoyl-1,2,3,4,5,6-hexahydro-3,5-dimethyl-2-(1-methylethyl)-4-oxopyrimidin-5-yl]hydrazine-1,2-dicarboxylate* ((2′*S*,5′*R*)-**8**). Prepared according to *GP2*. White foam. Yield: 207 mg (41%). $[\alpha]_D^{25} = -1.9$ (*c* = 1.0, $CHCl_3$). The NMR-spectral data were identical with those of (2*R*,5*S*)-**8**. Anal. calc. for $C_{26}H_{40}N_4O_6$ (504.62): C 61.88, H 7.99, N 11.10; found: C 61.78, H 8.32, N 10.86.

*Di(*tert*-butyl) 1-[(2*R,5S*)-1-Benzoyl-5-ethyl-1,2,3,4,5,6-hexahydro-3-methyl-2-(1-methylethyl)-4-oxopyrimidin-5-yl]hydrazine-1,2-dicarboxylate* ((2′*R*,5′*S*)-**9**). Prepared according to *GP2*. White foam. Yield: 347 mg (67%). $[\alpha]_D^{25} = +2.3$ (*c* = 0.6, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO, $T = 120°$): 0.86 (*d*, *J* = 7.0, 3 H); 0.90 (*d*, *J* = 6.5, 3 H); 0.99 (*d*, *J* = 6.5, 3 H); 1.29 (*s*, 9 H); 1.36 (*s*, 9 H); 1.83 (br. *s*, 2 H); 2.31 (br. *s*, 1 H); 2.92 (*s*, 3 H); 3.63 (br. *s*, 1 H); 4.53 (br. *s*, 1 H); 5.35 (br. *s*, 1 H); 7.37–7.45 (*m*, 5 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, $T = 120°$): 7.9; 17.9; 18.0; 27.3; 27.4; 29.0; 32.0; 35.4; 49.9; 73.4; 79.0; 80.0; 126.8; 127.3; 128.7; 135.3; 153.4; 154.6; 167.1; 168.9. Anal. calc. for $C_{27}H_{42}N_4O_6$ (518.65): C 62.53, H 8.16, N 10.80; found: C 62.25, H 8.43, N 10.66.

Di(tert-*butyl*) *1-[(2*S,5R*)-1-Benzoyl-5-ethyl-1,2,3,4,5,6-hexahydro-3-methyl-2-(1-methylethyl)-4-oxopyrimidin-5-yl]hydrazine-1,2-dicarboxylate* ((2′*S*,5′*R*)-**9**). Prepared according to *GP2*. White foam. Yield: 192 mg (37%). $[\alpha]_D^{25} = -2.5$ ($c = 1.0$, $CHCl_3$). The NMR-spectral data were identical with those of (2′*R*,5′*S*)-**9**. Anal. calc. for $C_{27}H_{42}N_4O_6$ (518.65): C 62.53, H 8.16, N 10.80; found: C 62.30, H 8.45, N 10.68.

Di(tert-*butyl*) *1-[(2*R,5S*)-1-Benzoyl-5-benzyl-1,2,3,4,5,6-hexahydro-3-methyl-2-(1-methylethyl)-4-oxopyrimidin-5-yl]hydrazine-1,2-dicarboxylate* ((2′*R*,5′*S*)-**10**). Prepared according to *GP2*. White foam. Yield: 423 mg (73%). $[\alpha]_D^{25} = -11.5$ ($c = 0.99$, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO, $T = 120°$): 0.44 (br. *s*, 6 H); 1.34 (*s*, 9 H); 1.41 (*s*, 9 H); 2.05 (br. *s*, 2 H); 2.84 (br. *s*, 4 H); 2.98 (br. *s*, 1 H); 3.47 (br. *s*, 1 H); 4.88 (br. *s*, 1 H); 7.19–7.40 (*m*, 10 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, $T = 120°$): 17.0; 17.9; 18.3; 27.4; 27.4; 29.5; 31.9; 35.5; 46.5; 65.7; 79.0; 79.3; 80.0; 125.8; 126.3; 127.3; 127.4; 130.4; 135.1; 135.2; 153.1; 154.5; 165.0; 168.5. Anal. calc. for $C_{32}H_{44}N_4O_6$ (580.71): C 66.18, H 7.64, N 9.65; found: C 66.19, H 7.90, N 9.38.

Di(tert-*butyl*) *1-[(2*S,5R*)-1-Benzoyl-5-benzyl-1,2,3,4,5,6-hexahydro-3-methyl-2-(1-methylethyl)-4-oxopyrimidin-5-yl]hydrazine-1,2-dicarboxylate* ((2′*S*,5′*R*)-**10**). Prepared according to *GP2*. White foam. Yield: 145 mg (25%). $[\alpha]_D^{25} = +11.5$ ($c = 1.0$, $CHCl_3$). The NMR-spectral data were identical with those of (2′*R*,5′*S*)-**10**. Anal. calc. for $C_{32}H_{44}N_4O_6$ (580.71): C 66.18, H 7.64, N 9.65; found: C 66.29, H 7.97, N 9.45.

General Procedure (*GP3*) *for the Preparation of the Target Compounds* **11**–**13** (*Scheme 5*). To a soln. of compound **8**, **9**, or **10** (0.5 mmol) in CH_2Cl_2 (2.0 ml) was added CF_3COOH (TFA; 3 ml), and the resulting soln. was stirred at r.t. for 30 min. The soln. was then transfered to a hydrogenation flask, and treated with MeOH (25 ml) and *Raney* Ni (10 mol-%; 0.5 g). The flask was pressurized to 69 bar of H_2 and shaken for 24 h at r.t. The mixtrue was filtered over *Celite*, the solvent was removed at reduced pressure, and the remaining crude product was dissolved in H_2O (10 ml). Then, sat. aq. Na_2CO_3 soln (10 ml) was added, and the mixture was extracted with AcOEt (2 × 15 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford a crude intermediate, which was treated with 6M aq. HCl soln (3.0 ml). This mixture was placed in a sealed tube and heated to 90°, until the starting material had disappeared (typically after 36–96 h). The mixture was extracted with CH_2Cl_2 (2 × 15 ml), and the aq. phase was evaporated to afford the crude α,β-diamino acid (**11**, **12**, or **13**, resp.), which was purified by FC (SiO_2, 70–230 mesh; i-PrOH/MeOH/aq. NH_3 3:2:1) according to [24].

*(*S*)-2,3-Diamino-2-methylpropanoic Acid* ((*S*)-**11**). Prepared according to *GP3*. White solid. Yield: 224 mg (89%). M.p. 200–201° (dec.) (lit. 203–205° [8b]). $[\alpha]_D^{25} = +5.0$ ($c = 0.2$, MeOH) (lit. $[\alpha]_D^{25} = +5.0$ ($c = 0.2$, MeOH) [8b]). ^{1}H-NMR (300 MHz, D_2O): 1.40 (*s*, 3 H); 2.96 (*d*, *J* = 13.5, 1 H); 3.11 (*d*, *J* = 13.5, 1 H). ^{13}C-NMR (75 MHz, D_2O): 22.3; 47.4; 60.0; 178.6.

*(*R*)-2,3-Diamino-2-methylpropanoic Acid* ((*R*)-**11**). Prepared according to *GP3*. White solid. Yield: 214 mg (85%). M.p 203–205° (dec.) (lit. 202–204° [8b]). $[\alpha]_D^{25} = -4.8$ ($c = 0.2$, MeOH) (lit. $[\alpha]_D^{25} = -4.5$ ($c = 0.2$, MeOH) [8b]). The NMR-spectral data were identical with those of (*S*)-**11** (see above).

*(*S*)-2-Amino-2-(aminomethyl)butanoic Acid* ((*S*)-**12**). Prepared according to *GP3*. White solid. Yield: 194 mg (75%). M.p. 205–206°. $[\alpha]_D^{25} = +6.8$ ($c = 0.08$, H_2O). ^{1}H-NMR (300 MHz, D_2O): 0.98 (*t*, *J* = 7.5, 3 H); 1.79 (*dt*, *J* = 14.8, 7.3, 1 H); 3.20 (*d*, *J* = 11.0, 1 H); 3.28 (*d*, *J* = 3.3, 1 H). ^{13}C-NMR (75 MHz, D_2O): 7.7; 28.1; 44.3; 62.6; 175.3.

*(*R*)-2-Amino-2-(aminomethyl)butanoic Acid* ((*R*)-**12**). Prepared according to *GP3*. White solid. Yield: 145 mg (56%). M.p. 206–208°. $[\alpha]_D^{25} = -7.2$ ($c = 0.08$, H_2O). The NMR-spectral data were identical with those of (*S*)-**12** (see above).

*(*S*)-2,3-Diamino-2-benzylpropanoic Acid* ((*S*)-**13**). Prepared according to *GP3*. White solid. Yield: 78 mg (27%). M.p. 224–225°. $[\alpha]_D^{25} = +9.2$ ($c = 0.8$, H_2O). ^{1}H-NMR (300 MHz, D_2O): 2.95 (*d*, *J* = 14.3, 1 H); 3.26 (*d*, *J* = 14.3, 1 H); 3.35 (*d*, *J* = 1.3, 1 H); 3.37 (*d*, *J* = 1.2, 1 H); 7.10 (*m*, 5 H). ^{13}C-NMR (75 MHz, D_2O): 39.4; 42.7; 61.4; 129.0; 129.6; 130.4; 131.1; 170.0.

*(*R*)-2,3-Diamino-2-benzylpropanoic Acid* ((*R*)-**13**). Prepared according to *GP3*. White solid. Yield: 72.5 mg (25%). M.p 221–222° (lit. 222° (dec) [11a]). $[\alpha]_D^{25} = -9.8$ ($c = 0.6$, H_2O) (lit. $[\alpha]_D^{25} = -8.25$ ($c = 0.8$, H_2O) [11a]). The NMR-spectral data were identical with those of (*S*)-**13** (see above).

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