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# Backbone Stabilized Peptidomimetics Containing Statine-Like Structural Elements: Diastereospecific Synthesis of Trisubstituted Cyclic Ureas and 1,4-Diazepan-2-ones

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**Summary.** 2-Aminobenzyl substituted 4-amino-3-hydroxy-5-phenyl pentanoic acid (*AHPPA*) is the central structural element of highly active *HIV*-protease inhibitors. To obtain conformationally less flexible statine analogs, we stabilized *AHPPA via* ring formations, *e.g.* by reaction with 1,1′-carbonyl diimidazole to give six-membered ureas. Reaction of *AHPPA* with chloroacetyl chloride leads to 1,4-diazepan-2-ones, whereas *BOC* protected *AHPPA* is transformed in a two step sequence to 7(*S*)-benzyl-6-chloro-4-(4-methoxybenzyl)-2-oxo-[1,4]-diazepane-5(*S*)-carboxylic acid ethylester, likely assisted by transannular influence of N-4. *TBDMS* protection strategy allows the cyclization of 2-aminobenzyl substituted 4-amino-3-hydroxy-5-phenylpentanal to 7(*R*)-benzyl-6(*S*)-hydroxy-5(*R*)-hydromethyl-4-(4-methoxybenzyl)-(1,4)-diazepan-2-one and 4(*R*)-benzyl-5(*S*)-hydroxy-6(*R*)-hydroxymethyl-1-(4-methoxybenzyl)-tetrahydro-pyrimidino-2-one. In this way, backbone stabilized peptidomimetics containing statine-like structural elements are obtained. 3(*R*)-(7(*R*)-Benzyl-6(*S*)-hydroxy-4-(4-methoxybenzyl)-2-oxo-[1,4]-diazepan-5-yl)-acrylic acid ethylester showed the highest activity against *HIV*-protease in this series with a *Ki* value of about 600 n*M*.

**Keywords.** Diastereospecificity; *HIV*-Protease; Peptidomimetica; Statine.

**Stabilisierte Peptidomimetika mit statinanalogen Strukturelementen: Diastereospezifische Synthese von trisubstituierten zyklischen Harnstoffen und 1,4-Diazepan-2-onen**

**Zusammenfassung.** 2-Aminobenzylsubstituierte 4-Amino-3-hydroxy-5-phenyl-pentansäure (*AHPPA*) bildet das zentrale strukturelle Element von hochaktiven *HIV*-Proteaseinhibitoren. Um Derivate mit reduzierter konformeller Flexibilität, zu erhalten, stabilisierten wir *AHPPA* durch Ringbildung wie folgt: *AHPPA* wird mit 1,1′-Carbonyldiimidazol zu sechsgliedrigen Harnstoffen zyklisiert. Umsatz von *AHPPA* mit Chloracetylchlorid ergibt 1,4-Diazepan-2-on, wohingegen *BOC*-geschütztes *AHPPA* in einem Zweistufenprozess zu 7(*S*)-Benzyl-6-chloro-4-(4-methoxybenzyl)-2-oxo-[1,4]-diazepane-5(*S*)-carbonsäureethylester führt, wahrscheinlich durch transanulare Einflüsse des Stickstoffs in Position 4 begünstigt. *TBDMS*-Schutzgruppenstrategie erlaubt die Zyklisierung von Aminobenzylsubstituiertem 4-Amino-3-hydroxy-5-phenylpentanal zu 7(*R*)-Benzyl-6(*S*)-hydroxy-5(*R*)-hydroxymethyl-4-(4-methoxybenzyl)-(1,4)-diazepan-2-on und 4(*R*)-Benzyl-5(*S*)-

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hydroxy-6(*R*)-hydroxymethyl-1-(4-methoxybenzyl)-tetrahydro-pyrimidino-2-on. 3(*R*)-(7(*R*)-Benzyl-6(*S*)-hydroxy-4-(4-methoxybenzyl)-2-oxo-[1,4]-diazepan-5-yl)-acrylsäureethylester zeigte in dieser Serie mit einem *Ki*-Wert von etwa 600n*M* die beste Wirksamkeit gegen *HIV*-Protease.

## Introduction

*HIV* Protease, which is responsible for the maturation of infectious viral particles, proved to be an effective target to intervene viral replication in man, especially in combination therapies with reverse transcriptase inhibitors [1]. The chemotherapeutic treatment of AIDS has recently reached a milestone with the approval of Saquinavir (Roche), Indinavir (Merck) and Ritonavir (Abbott) by the FDA [2a, b]. These inhibitors are advanced open chain peptidomimetica containing transition state analogs located at the dipeptide cleavage site. Due to the seemingly limitless capacity of the AIDS retrovirus to develop drug resistance and the side effects of the above mentioned inhibitors due to drug-drug interactions [3] there still remains need to develop structurally unrelated orally available potent inhibitors of *HIV*-protease. Seven-membered cyclic and azacyclic ureas are such a highly promising class of inhibitors [4a, b], but there are still problems to obtain the necessary oral bioavailability profile [4b].

Work of our group has led to the synthesis of an open-chain peptidomimetic *HIV*-protease inhibitor containing 2-aminobenzyl-substituted 4-amino-3-hydroxy-5-phenylpentanoic acid (*AHPPA*; **1**) as inhibitor core displaying high antiviral activity and oral bioavailability and a good pharmacokinetic profile [5]. Molecular modeling docking studies indicated that **1**, cyclized *via* its two nitrogen atoms in positions 2 and 4 to ureas (**3**) or 1,4-diazepanones (**4**, **5**, Fig. 1), should fit nicely into the active site of the *HIV*-protease. These compound classes are related to the

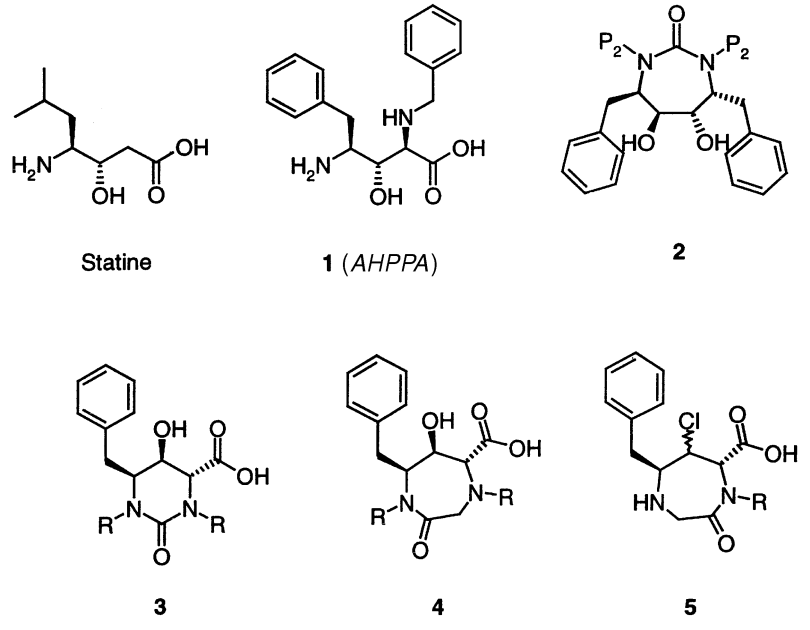



**Fig. 1.** Potential *HIV*-protease inhibitors

cyclic ureas **2** of the Dupont group [4]; however, they are, due to the substitution pattern and the positioning of the carbonyl groups, distinctively different (see Fig. 1). Therefore, we decided to synthesize these compounds starting from *L*- and *D*-phenylalaninal, because at that time it was not obvious from our modeling result which one would fit better into the active site of the *HIV*-protease. In addition, the substitution pattern of the heterocycles allows to develop these compounds further on into backbone stabilized peptidomimetica containing a statine-like structural element [6a, b].

## Results and Discussion

### *L-Series: 1,4-Diazepan-2-ones*

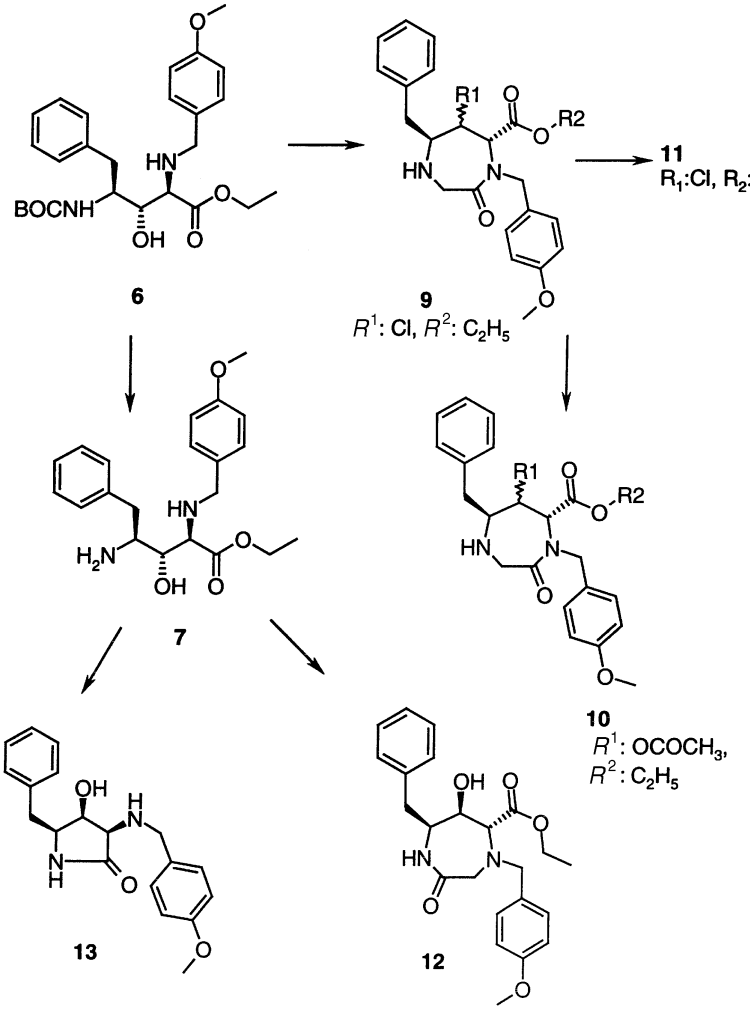
Compound **6**, which is easily obtainable from *BOC*-protected phenylalaninal by a *Wittig* reaction, epoxidation, and diastereoselecive epoxid opening [7], reacts with chloroacetyl chloride to give **8** which after deprotection with trifluoroacetic acid and neutralization with $NaHCO_3$ cyclized to **9**, accompanied by an additional nucleophilic substitution of the 6-OH group by Cl (Scheme 1). In an attempt to acetylate the basic nitrogen, only the O-acetylated product **10** was obtained, indicating a transannular influence of N-4 at position 6. This can be hypothesized to occur *via* an aziridine intermediate. Saponification of **9** with LiOH led to the 6-chloro acid **11** in good yield. Treatment of **6** with $HCl/Et_2O$ (cleavage of the *BOC*-group) and afterwards with *t*-butyldimethylsilylchloride (*TBDMSCl*)/imidazole (protection of the 6-hydroxy group) prior to cyclization with chloroacetylchloride gave **12** after deprotection. Due to the reduced basicity of the now amidic nitrogen, no additional substitution of 6-OH takes place. This reaction sequence has to be performed rather quickly; otherwise, intramolecular lactonization to **13** takes place (Scheme 1). All attempts to alkylate N2 of **12** to enhance the inhibitory activity by placing additional residues in the P2 side of the enzyme were unsuccessful.

### *L-Series: Six-membered cyclic ureas*

Reaction of *TBDMS* protected **7** with 1,1′-carbonyl diimidazole (*Staab* reagent) gave **14** (Scheme 2). **14** can be *N*-alkylated with allyl and benzyl bromides (**15**, **21**), but not with halogenides such as 1-iodobutane or 2-chloro-(4-methoxyphenyl)-ethane. In both cases, prolonged reaction times led only to transesterification (**19a**, **b**), probably *via* intermediate nucleophilic substitution of the halide to the corresponding alcohol (Scheme 3). Reduction of **15** with $NaBH_4$/LiCl and deprotection gave **18**.

### *D-series: 1,4-Diazepan-2-ones*

Due to the unsatisfactory results with simple esters and the side reactions leading to five-membered lactones we decided to reduce ester **23** to alcohol **24** prior to cyclization (Scheme 4). **23** is obtained analogously to **6** using *D*-phenylalanine as starting material. Removal of the *BOC*-group, protection of the two hydroxyl groups with *TBDMS*, and reaction with chloroacetylchloride gave **26**. Selective

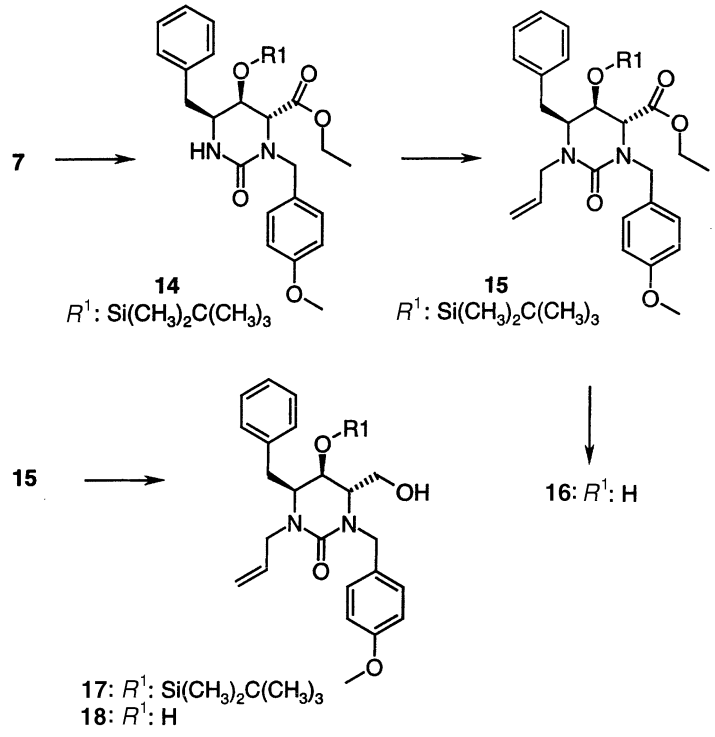



**Scheme 1**

deprotection results in **27** which was transformed further in a one-pot reaction to **33**. Standard deprotection conditions gave **28**.

*D-series: Six-membered cyclic ureas*

The same deprotection-protection sequence as above was applied to **24**, and cyclization with 1,1′-carbonyl diimidazole (*Staab* reagent) gave **29** which can be deprotected selectively to **30** and **31** (Scheme 4). **29** was alkylated to **34** (Scheme 5); selective deprotection gave **35** which was transformed to **36** using the one-pot procedure oxidation/*Wittig* reaction [7]. Deprotection with fluoride ion gave **37**. As shown in Scheme 6, **36** reacts with $H_2/O_2$/benzonitrile diastereospecifically to **38** (performed with the hope to create a suicide inhibitor). Saponification of **37** with LiOH leads to **39** which offers additional possibilities for amide and ester formation using classical acid activation conditions (N-ethyl-N′-(3-dimethyla-




**Scheme 2**

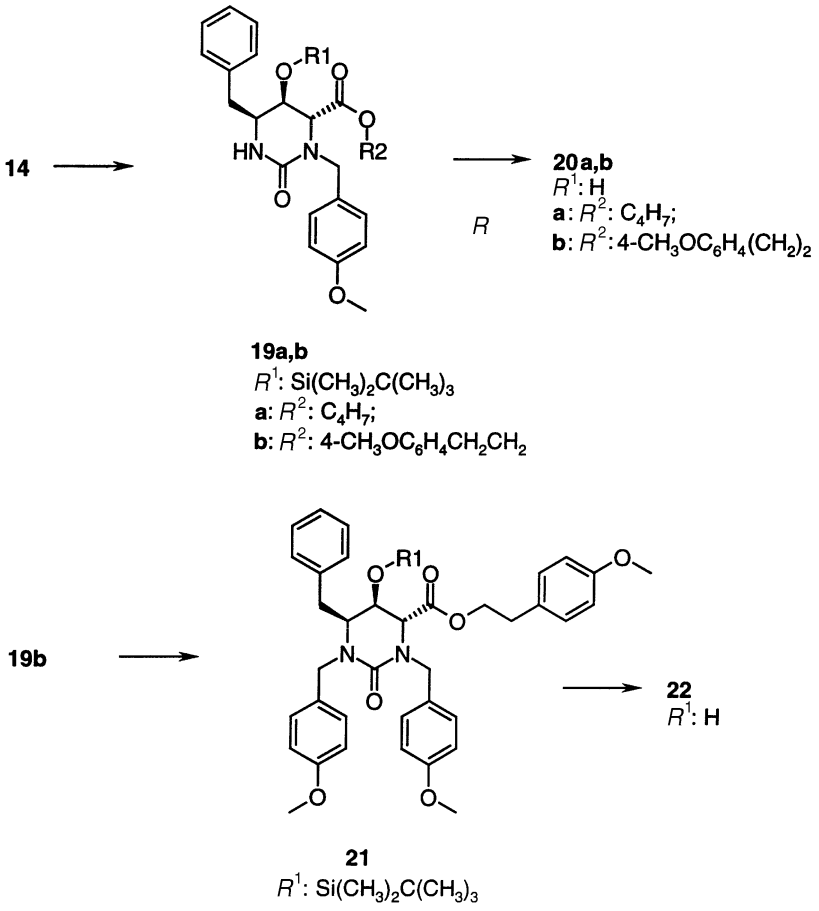
mino)-propyl)-carbodiimide hydrochloride, the water soluble carbodiimide). **39** contains a vinylogous statine-like element.

*Biological test results*

All compounds were tested in an enzymatic assay using *HIV*-1 protease as described in Res. [7]. **33** showed a *Ki* value of 616 n*M* and **28** a *Ki* of 923 n*M*; all other compounds were inactive up to a concentration of 12.5 μ*M*. None of them showed any activity in an assay measuring the *HIV*-1 IIIB induced cytopathic effect in MT4 cells [7] up to a concentration of 3 μ*M*.

*Conclusions*

The data demonstrate that cyclic *AHPPA* analogs are clearly less active than their open chain counterparts. This may be due to their unsymmetrical characteristics, which seems to be much more important in these cases than with open chain inhibitors. Their rigid structure does not allow even small conformational changes for optimal interactions with the P1 and P2 pocket of the enzyme. Therefore, small misfits have a much bigger influence on the activity than in the case of the open chain analogs. Similar results were observed in an attempt to alter the symmetry of cyclic ureas [4b]. On the other hand, expedient flexible reaction sequences were developed which led to conformationally rigidified peptidomimetics containing



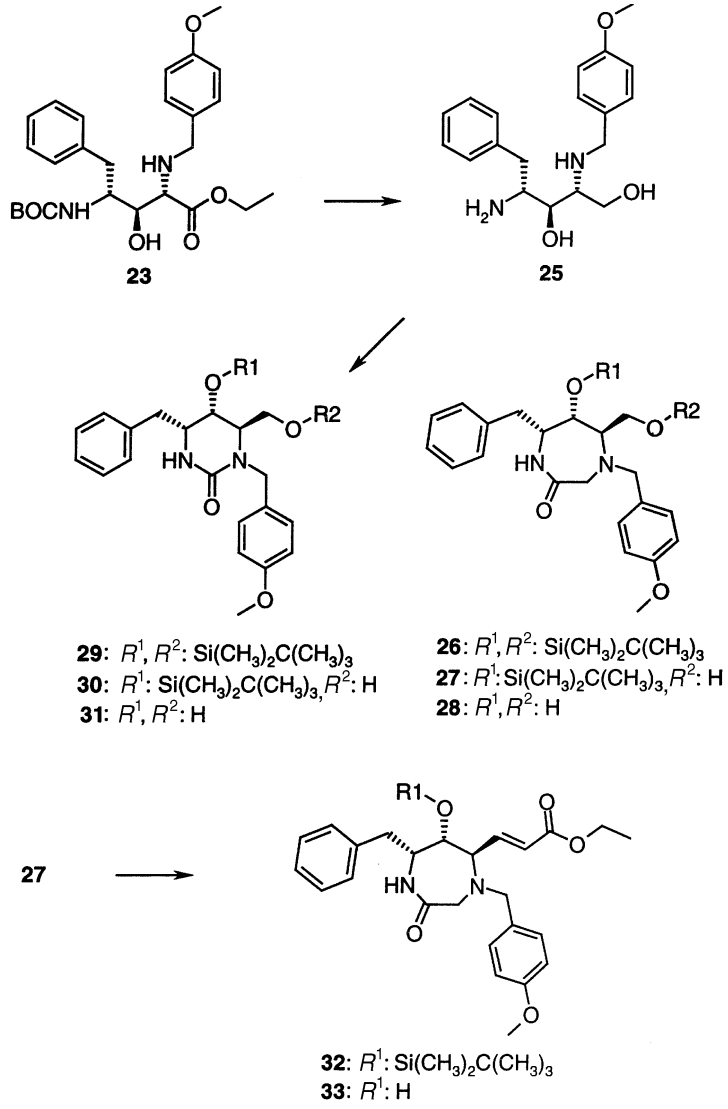

**Scheme 3**

statine-like structural elements. Due to the flexibility in the substitution pattern and the highly diastereospecific reactions, they might be useful building blocks for inhibitors of other aspartic proteases.

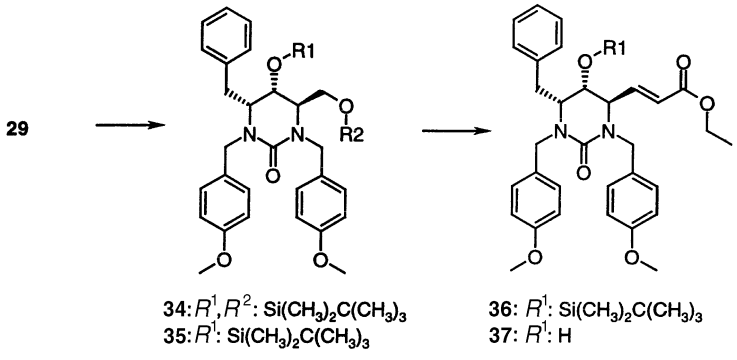
## Experimental

*General*

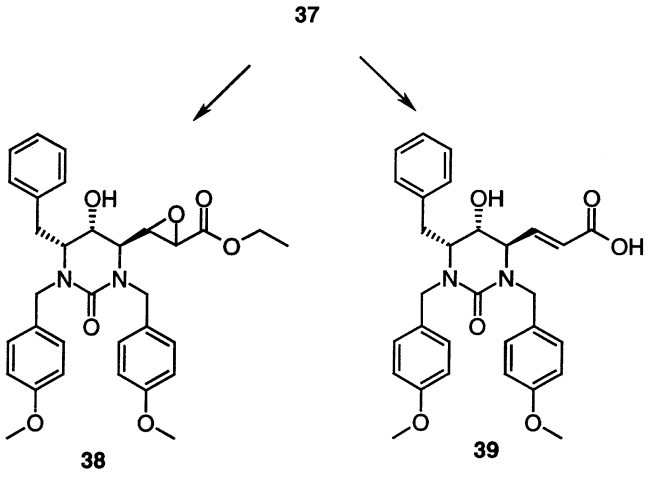
$^1$H NMR spectra were recorded on Bruker WC-250 or AMX-500 spectrometers; chemical shifts are reported in ppm ($\delta$) relative to internal *TMS*. Elemental analysis were performed by the Analytical Department of Novartis, Basle, Switzerland. Their results are in satisfactory agreement with the calculated values. Analytical thin-layer chromatography was performed on silica gel 60 $F_{254}$ glass plates (HPTLC, Merck). Preparative column chromatography was performed on silica gel (40–63 μm) under pressure (≈0.2 mPa). Solvents were AR grade and were used without further purification. All reagents were obtained from commercial suppliers and were used without further purification. Evaporations were carried out *in vacuo* with a rotary evaporator. Melting points were determined with a thermovar apparatus (Reichert-Jung) and are not corrected.




**Scheme 4**




**Scheme 5**




**Scheme 6**

*General procedure for the cleavage of the dimethyl t-butyl silyl protecting group*

The dimethyl *t*-butyl silyl protected compound (*e.g.* **19a**) (0.3 mmol) was dissolved in 5 $cm^3$ acetonitrile. Then, 1 $cm^3$ (20 mmol) 40% HF was added, and the solution was stirred at room temperature until all starting material was consumed (2–10 d). Subsequently, 400 $mm^3$ methanol were added, the reaction solution was diluted with $CH_2Cl_2$, washed with $H_2O$, dried, the solvent evaporated, and the residue chromatographed on silica gel.

*4(S)-Amino-3(S)-hydroxy-2(R)-(4-methoxybenzylamino)-5-phenyl-pentanoic acid ethylester dihydrochloride* (**7**; $C_{21}H_{20}N_2O_4Cl_2$)

To a solution of 2 g (4.23 mmol) **6** [7] in 20 $cm^3$ of $CH_2Cl_2$, 4.23 $cm^3$ (12.69 mmol) 3 *N* HCl were added, and the reaction mixture stirred at room temperature for 1 h. Evaporation of the solvent gave 1.84 g of **7** (97%).

Colorless crystals; m.p.: 118–121°C; $^1$H NMR ($CD_3OD$, $\delta$, 250 MHz): 1.37 (s, 2H, $CH_2CH_3$), 3.07 (ABX, 2H, $CH_2C_6H_5$), 3.80 (s, 3H, $OCH_3$), 3.79–3.84 (m, 1H, $NH_2CH$), 4.21 (AB, $NHCH_2$), 4.35 (q, 2H, $OCH_2$), 4.22–4.41 (m, 2H, CHNH, CHOH), 7.01 (d, 2H, aromatic H), 7.23–7.58 (m, 7H, aromatic H) ppm; MS (ESI): $m/z = 373.5$ [$MH^+$].

*(N-4(S)-((t-Butoxycarbonyl)amino)-3(S)-hydroxy-2(R)-((N-4-methoxybenzyl-N-chloroacetyl)-amino-5-phenyl)-heptanoic acid ethylester* (**8**; $C_{28}H_{37}ClN_2O_7$)

To a solution of 236 mg (0.5 mmol) of **6** [7] in 10 $cm^3$ $CH_2Cl_2$, 210 mg (2.5 mmol) solid $NaHCO_3$ were added and subsequently at 0°C 48 $mm^3$ (0.6 mmol) chloroacetyl chloride dissolved in 0.2 $cm^3$ of $CH_2Cl_2$. The reaction mixture was stirred for 2 h at room temperature and then extracted with $H_2O$, dried, and evaporated. Chromatographic separation of the residue (silica gel, toluene/ethyl acetate = 4/1) gave 239 mg (87%) of **8**.

White foam; $^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 1.18 (t, 3H, $OCH_2CH_3$), 1.34 (s, rotamer 22%, $C(CH_3)_3$), 1.41 (s, rotamer 78%, $C(CH_3)_3$), 2.90 (ABX, 2H, $CH_2C_6H_5$), 3.63 (d, 1H, CHCOO), 3.81 (s, 3H, $OCH_3$), 3.87 (q, 1H, NHCH), 4.04 (q, 2H, $OCH_2$), 4.05 (s, 2H, $CH_2Cl$), 4.31 (1/2AB, 1H, $NCH_2C_6H_4$), 4.38 (s, 1H, OH), 4.42 (d, 1H, CHOH), 4.81 (1/2AB, 1H, $NCH_2C_6H_4$), 5.03 (bd, rotamer 22%, NH), 5.17 (bd, rotamer 78%, NH), 6.83 (d, 2H, aromatic H), 7.15–7.30 (7H, aromatic H) ppm; MS (FAB): $m/z = 549$ [$MH^+$].

*7(S)-Benzyl-6-chloro-4-(4-methoxybenzyl)-2-oxo-1,4-diazepane-5(S)-carboxylic acid ethylester* (**9**; $C_{23}H_{27}ClN_2O_4$)

129 mg (0.23 mmol) of **8** were dissolved in 2 $cm^3$ of $CH_2Cl_2$, 230 $mm^3$ trifluoroacetic acid were added, and after standing for 3 h at room temperature the solvent was evaporated. The residue was dissolved in 25 $cm^3$ *THF*, 300 mg (3 mmol) solid $NaHCO_3$ were added, and the reaction mixture was stirred 4 h at room temperature. Filtration, evaporation of the solvent, and chromatography of the residue (silica gel, ethyl acetate/methanol = 95/5) gave 84 mg (86%) of **9**.

M.p.: 48–52°C (amorphous); $^1$H NMR (*DMSO*-$d_6$/310°K, $\delta$, 500 MHz): 1.04 (t, 3H, $OCH_2CH_3$), 3.01 (ABX, 2H, $CH_2C_6H_5$), 3.20–3.31 (m, 1H, NHC*H*), 3.71–3.74 (m, 1H, CHCl), 3.73 (s, 3H, $OCH_3$), 3.81 (s, 1H, CHCOO), 2.89–4.07 (m, 2H, $OCH_2$), 4.26 (AB, 2H, $CH_2CO$), 4.35 (1/2AB, 1H, $NCH_2C_6H_4$), 4.75 (1/2AB, 1H, $NCH_2C_6H_4$), 5.36 (bd, 1H, NH), 6.88 (d, 2H, aromatic H), 7.17–7.38 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 431$ [$MH^+$].

*6-O-Acetyl-5(S)-benzyl-7(R)-carboxyethyl-1-(4-methoxybenzyl)-2-oxo-1,4-diazacycloheptan* (**10**; $C_{25}H_{30}N_2O_6$)

100 mg (0.23 mmol) **9** were dissolved in 2 $cm^3$ $CH_2Cl_2$; 29 $mm^3$ (0.26 mmol) N-methylmorpholine, 23 $mm^3$ (0.24 mmol) acetic anhydride, and 10 mg dimethylaminopyridine were added at 0°C, and the reaction mixture was stirred for 1 h. Dilution with 20 $cm^3$ $CH_2Cl_2$, extraction with $H_2O$, drying evaporation of the solvent, and chromatographic separation of the residue (silica gel, toluene/ethyl acetate = 1/1) afforded 101 mg (92%) **10**.

Colorless syrup; $^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 1.08 (t, 3H, $OCH_2CH_3$), 2.05 (s, 3H, $COCH_3$), 2.97 (ABX, 2H, $CH_2C_6H_5$), 3.57–3.64 (m, 1H, NHC*H*), 3.81 (s, 3H, $OCH_3$), 3.93 (d, 1H, CHCOO), 4.00–4.21 (m, 2H, $OCH_2$), 4.23 (1/2AB, 1H, $NCHC_6H_4$), 4.28 (s, 2H, $NCH_2CO$), 4.97 (t, 1H, $CHOCOCH_3$), 5.00 (1/2AB, 1H, $NCHC_6H_4$), 6.81–6.87 (m, 2H, aromatic H), 7.17–7.39 (m, 7H, aromatic H) ppm; MS(FAB): $m/z = 455$ [$MH^+$].

*7(S)-Benzyl-6-chloro-4-(4-methoxybenzyl)-2-oxo-1,4-diazepane-5(S)-carboxylic acid* (**11**; $C_{21}H_{23}N_2O_4Cl$)

50 mg (0.12 mmol) of **9** were dissolved in 3 $cm^3$ of ethanol, and 3 mg (0.132 mmol) LiOH dissolved in 1 $cm^3$ $H_2O$ were added. After the reaction mixture was stirred for 24 h at room temperature the solution was acidified ($pH = 1$–2) with 1 *N* HCl. 5 $cm^3$ $H_2O$ were added, and the volume of the solution was reduced under vacuum to 1/3. The precipitating white crystals were collected and dried yielding. 20 mg (44%) of **11**.

M.p.: 192–198°C; $^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 2.97 (ABX, 2H, $CH_2C_6H_5$), 3.67–3.73 (m, 1H, CHNH), 3.70 (s, 3H, $OCH_3$), 3.88 (d, 1H, CHCOO), 4.07 (t, 1H, CHCl), 4.40 (1/2AB, 1H, NHC*H*), 4.43 (AB, 2H, $CH_2CO$), 4.90 (1/2AB, 1H, NHC*H*), 6.85 (d, 2H, aromatic H), 7.15–7.29 (m, 7H, aromatic H) ppm; MS(FAB): $m/z = 403$ [$MH^+$].

*7(S)-Benzyl-6(S)-hydroxy-4-(4-methoxybenzyl)-2-oxo-1,4-diazepan-5(S)-carboxylic acid ethylester hydrochloride* (**12**; $C_{22}H_{27}N_2O_5$)

444.6 mg (1 mmol) **7** were dissolved in 10 $cm^3$ $CH_2Cl_2$; 280 $mm^3$ (2 mmol) triethylamine and afterwards 87 $mm^3$ (1.1 mmol) chloroacetylchloride and 308 $mm^3$ (2.2 mmol) triethylamine were added at 0°C. The reaction mixture was stirred for 30 min, washed twice with $H_2O$, dried, and the solvent was evaporated. After chromatography (silica gel, toluene/ethyl acetate = 1/1) the residue gave 115 mg (28%) **12** as a syrup.

$^1$H NMR ($CD_3Cl$, $\delta$, 500 MHz): 1.29 (t, 3H, $OCH_2CH_3$), 2.87 (ABX, 2H, $CH_2C_6H_5$), 3.22 (d, 1H, CHCOO), 3.60 (AB, 2H, $NCH_2CO$), 3.75 (dd, 1H, CHOH), 3.79 (s, 3H, $OCH_3$), 3.92 (s, 2H,

NC$H_2$C$_6$H$_4$), 4.18 (dq, 2H, OC$H_2$), 4.39 (dq, 1H, NC$H$C$H_2$), 6.82 (d, 2H, aromatic H), 6.95 (bd, 1H, NH), 7.18–7.37 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 449$ [MH$^+$HCl].

*5(S)-Benzyl-4(S)-hydroxy-3(R)-(4-methoxybenzyl)-pyrrolidine-2-one* (**13**, $C_{19}H_{22}N_2O_3$)

891 mg (2 mmol) **7** (dihydrochloride) and 205 mg (3 mmol) imidazole were dissolved in 50 cm$^3$ of $CH_2Cl$. The reaction mixture was stirred for 12 h at room temperature, the organic phase washed with 30 cm$^3$ 1 *N* HCl and $H_2O$, and dried. Chromatographic separation (silica gel, toluene/ethyl acetate 1/1) gave 532 mg **13**.

Amorphous powder; m.p.: 134–138°C; $^1$H NMR ($CD_3Cl$, $\delta$, 250 MHz): 2.87 (1/2ABX, 1H, $J_{12} = 13.6$ Hz, C$H$C$_6$H$_5$), 3.00 (1/2ABX, 1H, $J_{12} = 13.6$ Hz, C$H$C$_6$H$_5$), 3.38 (d,1H, $J = 4.7$ Hz, CHCO), 3.68–3.72 (m, 1H, C$H$NH), 3.74 (1/2AB, $J_{12} = 13.3$, NHC$H$C$_6$H$_4$), 3.80 (s, 3H, OC$H_3$), 3.87 (1/2AB, $J_{12} = 13.3$, NHC$H$C$_6$H$_4$), 3.97–3.99 (m, 1H, CHO), 5.54 (bs, 1H, OH), 6.88 (d, 2H, aromatic H), 7.19–7.38 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 327$ [MH$^+$].

*6(S)-Benzyl-5(S)-O-t-butyl-dimethylsilyl-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid ethylester* (**14**; $C_{28}H_{40}N_2O_5Si$)

To a solution of 6.71 g (15.1 mmol) **7** in 130 cm$^3$ of $CH_2Cl_2$, 3.08 g (45.3 mmol) imidazole and 4.55 g (30.2 mmol) *t*-butyldimethylsilyl-chloride (*TBDMS*Cl) were added. The reaction mixture was stirred at room temperature for 20 h, then washed twice with $H_2O$, dired, and filtered. Imidazole was added to the filtrate to obtain a *pH* of 7–8, followed by 3.84 g (15 mmol) of 1,1′-carbonyl diimidazole (*Staab* reagent). The reaction mixture was stirred for 1 h at room temperature, the solvent was evaporated, and the residue was chromatographed on silica gel (eluent: toluene/ethyl acetate = 3/1) giving 5.82 g (76%) of **14** as colorless syrup.

$^1$H NMR ($CDCl_3$, $\delta$, 250 MHz): 0.18 (s, 3H, SiC$H_3$), 0.04 (s, 3H, SiC$H_3$), 0.85 (s, 9H, SiC(C$H_3$)$_3$), 1.25 (t, 3H, CH$_2$C$H_3$), 2.73 (ABX, 2H, C$_6$H$_5$C$H_2$), 3.58–3.62 (m, 1H, NHC$H$C$H_2$), 3.78 (s, 3H, OC$H_3$), 3.82 (1/2AB, 1H, NC$H$C$_6$H$_4$), 3.70 (d, 1H, NC$H$COO), 4.10–4.11 (m, 1H, CHOSi), 4.15–4.21 (m, 2H, OC$H_2$), 5.15 (1/2AB, 1H, NC$H$C$_6$H$_4$), 6.83 (d, 2H, aromatic H), 7.14–7.18 (m, 2H, aromatic H), 7.21 (d, 2H, aromatic H), 7.24–7.29 (m, 1H, aromatic H), 7.30–7.34 (m, 2H, aromatic H) ppm; MS (FAB): $m/z = 513$ [MH$^+$].

*1-Allyl-6(S)-benzyl-5(R)-O-t-butyldimethylsilyl-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid ethylester* (**15**; $C_{31}H_{44}N_2O_5Si$)

256 mg (0.5 mmol) **14** were dissolved in 1 cm$^3$ *DMF* and added to 24 mg (1 mmol) NaH suspended in 1 cm$^3$ *DMF*. After 5 min, 85 mm$^3$ (1 mmol) allyl bromide were added at 0°C. The reaction mixture was stirred for 40 min at room temperature; then, acetic acid was added (*pH* adjusted to 4–5), and the mixture was diluted with $CH_2Cl_2$, extracted with $H_2O$, dried, evaporated, and the residue chromatographed on silica gel (eluent: toluene/ethyl acetate = 5/1), yielding 167 mg (61%) of **15** as a colorless syrup.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.18 (s, 3H, SiC$H_3$), 0.08 (s, 3H, SiC$H_3$), 0.9 (s, 9H, C(C$H_3$)$_3$), 1.29 (t, 3H, CH$_2$C$H_3$), 2.21–2.36 (m, 2H, =CHC$H$, C$_6$H$_5$C$H$), 2.95 (dd, 1H, $J_{11} = 2.8$, $J_{12} = 13.4$, C$_6$H$_5$C$H$), 3.31–3.39 (m, 1H, CHN), 3.61 (d, 1H, $J_{11} = 14.99$, NC$H$C$_6$H$_4$), 3.80 (s, 3H, OC$H_3$), 3.82 (d, 1H, CHCOO), 4.07–4.25 (m, 3H, CHOSi, OC$H_2$), 4.41–4.52 (dm, 1H, =CCH), 4.82 (dm, 1H, =CH), 5.04 (dm, 1H, =CH), 5.28 (d, 1H, $J_{11} = 14.99$, NC$H$C$_6$H$_4$), 5.47–5.65 (m, 1H, CH$_2$C$H$=), 6.84–6.92 (m, 2H, aromatic H), 7.03–7.10 (m, 2H, aromatic H), 7.21–7.38 (m, 5H, aromatic H) ppm; MS (FAB): $m/z = 553$ [MH$^+$].

*1-Allyl-6(S)-benzyl-5(R)-hydroxy-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid ethylester* (**16**, $C_{25}H_{30}N_2O_5$)

120 mg (0.22 mmol) **15** were dissolved in 4 $cm^3$ *THF* and cooled to −10°C; 230 $mm^3$ (0.23 mmol) tetrabutylammonium fluoride dissolved in 1 $cm^3$ *THF* were added. After stirring for 30 min, the reaction mixture was diluted with $CH_2Cl_2$, extracted with $H_2O$, dried, the solvent was evaporated, and the residue chromatographed on silica gel (eluent: toluene/ethyl acetate = 2/3) yielding 77 mg (81%) of **16**.

$^1$H NMR (CDCl, $\delta$, 500 MHz): 1.17 (t, 3H, $CH_2CH_3$), 2.81–2.86 (m, 2H, $CH_2C_6H_5$), 3.24–3.56 (m, 2H, $CH_2CH$=), 3.76–3.82 (m, 1H, $CHCO_2$), 3.76 (s, 3H, $OCH_3$), 3.82 (bs, 2H, $CH_2C_6H_4$), 3.98–3.82 (m, 1H, $CHCO_2$), 3.76 (s, 3H, $OCH_3$), 3.82 (bs, 2H, $CH_2C_6H_4$), 3.98–4.10 (m, 2H, $OCH_2$), 4.61–4.73 (m, 1H, CHOH), 5.11 (dq, 1H, NCH), 5.18–5.21 (m, 2H, $CH_2$=), 5.62–5.86 (m, 1H, CH=), 6.82 (d, 2H, aromatic H), 7.14–7.30 (m, 7H, aromatic H) ppm; MS (El): $m/z = 438$ [$M^+$].

*1-Allyl-6(S)-benzyl-5(R)-O-t-butyldimethylsilyl-4(S)-hydroxymethyl-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine* (**17**; $C_{29}H_{42}N_2O_4Si$)

34 mg (0.92 mmol) $NaBH_4$ and 30 mg (0.92 mmol) LiCl were dissolved in 3 $cm^3$ of a 3:2 mixture of ethanol/*THF* and stirred for 30 min at room temperature. Then, 126 mg (0.23 mmol) **15** dissolved in 1 $cm^3$ of the above mixture were added, and the reaction mixture was stirred for 2 d. Two more equivalents of $NaBH_4$/LiCl were added, and stirring was continued for another 2 d. After neutralization with acetic acid, the reaction mixture was diluted with $CH_2Cl_2$, washed with $H_2O$, dried, the solvent was evaporated, and the residue was chromatographed on silica gel (eluent: toluene/ethyl acetate = 3/2 → 1/1) yielding 64 mg (58%) of **17** as a colorless syrup.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 0.13 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$), 0.92 (s, 9H, $C(CH_3)_3$), 2.26–2.38 (m, 2H, =CCH, $C_6H_5CH$), 2.97 (dd, 1H, $C_6H_5CH$), 3.08 (d, 1H, $CHCH_2OH$), 3.35–3.40 (dm, 1H, CHN), 3.51–3.58 (m, 1H, $CH_\beta$ OH), 3.80 (s, 3H, $OCH_3$), 3.91 (dd, 1H, $CH_\alpha OH$), 4.14 (dd, 1H, CHOH), 4.25 (1/2AB, 1H, $CHC_6H_4$), 4.48 (dm, 1H, =CCH), 4.84 (d, 1H, =CH), 4.99 (1/2AB, 1H, $CHC_6H_4$), 5.02 (d, 1H, =CH), 5.50–5.60 (m, 1H, $CH_2CH$=), 6.87–6.92 (m, 2H, aromatic H), 7.12–7.15 (m, 2H, aromatic H), 7.24–7.48 (m, 5H, aromatic H) ppm; MS (FAB): $m/z = 511$ [$MH^+$].

*1-Allyl-6(S)-benzyl-5(R)-hydroxy-4(S)-hydroxymethyl-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine* (**18**; $C_{23}H_{28}N_2O_4$)

336 mg (0.66 mmol) **17** were dissolved in 10 $cm^3$ *THF*, and 700 $mm^3$ (0.7 mmol) tetrabutylammonium fluoride was added at −10°C. The reaction mixture was stirred for 6 h and then diluted with $CH_2Cl_2$, extracted with $H_2O$, dried, evaporated, and chromatographed on silica gel (eluent: $CH_2Cl_2$/$CH_3OH$ = 95/5) yielding 227 mg (87%) **18** as a syrup.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 2.45 (1/2ABX, 1H, $CHC_6H_5$), 2.63 (1/2ABX, 1H, $CHC_6H_5$), 2.95 (dd, 1H, CHOH), 3.10–3.29 (m, 2H, $CH_2CH$=), 3.41–3.48 (m, 1H, $CHCH_2OH$), 3.68–3.87 (m, 2H, $CH_2OH$), 3.76 (s, 3H, $OCH_3$), 4.01 (bs, 2H, $NCH_2$), 4.40 (dm, 1H, NCH), 4.97–5.18 (m, 2H, =$CH_2$), 5.47–5.63 (m, 1H, CH=), 6.82 (d, 2H, aromatic H), 7.10–7.38 (m, 7H aromatic H) ppm; MS (AP+): $m/z = 397.3$ [$MH^+$].

*6(S)-Benzyl-5(R)-O-t-butyl-dimethylsilyl-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid butylester* (**19a**; $C_{30}H_{44}N_2O_5Si$)

48 mg (2 mmol) NaH were suspended in 4 $cm^3$ *DMF*; then, 512 mg (1 mmol) **14** dissolved in 2.5 $cm^3$ *DMF* and, after 10 min, 230 $mm^3$ (2 mmol) 1-iodobutane were added at −20°C. The suspension was stirred to 0°C overnight, diluted with $CH_2Cl_2$, acidified with acetic acid to *pH* 4–5, washed with

$H_2O$, dried, evaporated, and chromatographed on silica gel (eluent: toluene/ethyl acetate) = 2/1), yielding 194 mg (34%) of **19a** as colorless syrup.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.18 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.93 (t, 3H, $CH_2CH_3$), 1.36 (sext, 2H, $CH_2CH_2CH_3$), 1.61 (quint, 2H, $CH_2CH_2CH_2$), 2.73 (ABX, 2H, $C_6H_5CH_2$), 3.60 (dm, 1H, CHCOO), 3.78 (s, 3H, $OCH_3$), 3.82 (1/2AB, 1H, $NCHC_6H_4$), 3.88 (d, 1H, CHOSi), 4.09–4.11 (m, 1H, HNCH), 4.13 (q, 2H, $OCH_2$), 4.38 (bs, 1H, NH), 5.18 (1/2AB, 1H, $NCHC_6H_4$), 6.81 (dm, 2H, aromatic H), 7.14 (d, 2H, aromatic H), 7.20 (dm, 2H, aromatic H), 7.25–7.29 (m, 1H, aromatic H), 7.33 (t, 2H, aromatic H) ppm; MS (FAB): $m/z = 541$ [$MH^+$].

*6(S)-Benzyl-5(R)-O-t-butyl-dimethylsilyl-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid 2-(4-methoxyphenyl) ethyl ester* (**19b**, $C_{35}H_{46}N_2O_6Si$)

112 mg (4.68 mmol) NaH were suspended in 4 cm$^3$ *DMF*; then, 1.20 g (2.34 mmol) **14** dissolved in 2.5 cm$^3$ *DMF* and, after 10 min, 707 mm$^3$ (4.68 mmol) 1-(2-chloroethyl)-4-methoxybenzene were added at 0°C. After addition of 200 mg potassium iodide, the reaction mixture heated for 4 d to 65°C. Then was diluted with $CH_2Cl_2$, acidified with acidic acid to *pH* 4–5, washed with $H_2O$, dried, evaporated, and chromatographed on silica gel (eluent: toluene/ethyl acetate = 7/3), yielding 458 mg (30%) of **19a** as yellowish syrup and 290 mg recovered starting material.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.18 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.82 (s, 9H, $SiC(CH_3)_3$), 2.63 (ABX, 2H, $C_6H_5CH_2$), 2.89 (t, 2H, $CH_2C_6H_4$), 3.41–3.45 (m, 1H, CHCOO), 3.60 (1/2AB, 1H, $NCHC_6H_4$), 3.73 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.81–3.83 (m, 1H, CHOSi), 3.91–3.93 (m, 1H, NHCH), 4.22–4.48 (m, 3H, NH, $OCH_2CH_2$), 5.14 (1/2AB, 1H, NCH), 6.78–6.87 (m, 4H, aromatic H), 7.03–7.35 (m, 9H, aromatic H) ppm; MS (FAB): $m/z = 619$ [$MH^+$].

*6(S)-Benzyl-5(S)-hydroxy-3(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid butyl ester* (**20a**, $C_{24}H_{30}N_2O_5$)

141 mg (0.26 mmol) of **19a** were deprotected using the general procedure. The eluent for chromatography was toluene/ethyl acetate = 1/2.

Yield: 105 mg (95%); $^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 0.86 (t, 3H, $CH_2CH_3$), 1.25 (sext, 2H, $CH_2$), 1.51 (quint, 2H, $CH_2$), 2.86 (ABX, 2H, $C_6H_5CH_2$), 3.58 (dt, 1H, CHOH), 3.78 (s, 3H, $OCH_3$), 3.92–3.95 (m, 1H, NHCH), 3.97 (1/2AB, 1H, NCH), 4.00 (d, 1H, CHCOO), 4.45 (dq, 2H, $OCH_2$), 5.11 (1/2AB, 1H, NCH), 6.84 (dm, 2H, aromatic H), 7.16–7.33 (m, 7H, aromatic H) ppm; MS (ESI): $m/z = 427$ [$MH^+$].

*6(S)-Benzyl-5(R)-hydroxy-3-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid-2-(4-methoxyphenyl)ethyl ester* (**20b**, $C_{29}H_{32}N_2O_6$)

80 mg (0.13 mmol) of **19b** were deprotected using the general procedure. The eluent for chromatography was toluene/ethyl acetate = 4/1.

Yield: 56 mg (86%); amorphous; m.p.: 172–178°C; $^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 2.62–2.87 (m, 4H, $C_6H_5CH_2$, $C_6H_5CH_2$), 3.38–3.47 (m, 1H, NHCH), 3.75 (s, 3H, $C_6H_4CH_2$), 3.78 (s, 3H, $C_6H_4CH_2$), 3.81–3.84 (m, 1H, CHOH), 3.85 (1/2AB, 1H, NCH), 4.16–4.33 (m, 2H, $COCH_2$), 4.60 (bs, 1H, NH), 5.08 (1/2AB, 1H, NCH), 6.80–6.85 (m, 4H, aromatic H), 7.04–7.18 (m, 5H, aromatic H), 7.22–7.38 (m, 4H, aromatic H) ppm; MS (FAB): $m/z = 504$ [$MH^+$].

*6(S)-Benzyl-5(R)-O-t-butyl-dimethylsilyl-1,3-bis-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid-2-(4-methoxyphenyl)ethyl ester* (**21**; $C_{43}H_{54}N_2O_7Si$)

28 mg (1.16 mmol) NaH were suspended in 1 cm$^3$ *DMF*. At 0°C, 284 mg (0.46 mmol) **19b** dissolved in 1 cm$^3$ *DMF* were added and, after 10 min, a solution of 374 mg (1.16 mmol) tetrabutyl ammonium

bromide, 119 mg (1.16 mmol) NaBr, and 157 $mm^3$ (1.16 mmol) 4-methoxy-benzylchloride in 2 $cm^3$ *DMF*. After 5 h at room temperature the reaction mixture was neutralized with acetic acid, diluted with $CH_2Cl_2$, washed with $H_2O$, dried, evaporated, and chromatographed on silica gel (eluent: toluene/ethyl acetate = 4/1), yielding 276 mg (81%) of as a syrup.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.38 (s, 3H, $SiCH_3$), −0.29 (s, 3H, $SiCH_3$), 0.78 (s, 9H, $SiC(CH_3)_3$), 2.24 (dd, 1H, $C_6H_4CH_\alpha$), 2.63 (d, 1H, NCH), 2.86 (dd, 1H, $C_6H_4CH_\beta$), 2.89–2.92 (m, 2H, $CH_2C_6H_5$), 3.10–3.24 (m, 1H, C*H*OH), 3.51 (d, 1H, NCH), 3.72 (d, 1H, $CHCO_2$), 3.74 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.85–3.90 (m, 1H, C*H*OH), 4.18–4.36 (m, 2H, $CO_2CH_2$), 5.10 (d, 1H, NCH), 5.27 (d, 1H, NCH), 6.72–7.35 (m, 17H, aromatic H) ppm; MS (FAB): $m/z = 739$ [$MH^+$].

*6(S)-Benzyl-5(R)-hydroxy-1,3-bis-(4-methoxybenzyl)-2-oxo-hexahydropyrimidine-4(S)-carboxylic acid-2-(4-methoxyphenyl)ethyl ester* (**22**; $C_{37}H_{40}N_2O_7$)

233 mg (0.32 mmol) **21** were desilylated using the general procedure yielding 170 mg (85%) amorphous **22**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 2.61–2.74 (m, 2H, $C_6H_4CH_2$), 2.74–2.81 (m, 2H, $C_6H_5CH_2$), 3.23–3.28 (m, 1H, CHN), 3.55 (d, 1H, NCH), 3.69–3.72 (m, 1H, C*H*OH), 3.75 (d, 1H, NCH), 3.78 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.80 (d, 1H, $CHCO_2$), 4.13–4.28 (m, 2H, $CO_2CH_2$), 5.31 (d, 1H, NCH), 5.35 (d, 1H, NCH), 6.79–7.25 (m, 17H, aromatic H) ppm; MS (FAB): $m/z = 625$ [$MH^+$].

*4(R)-((N-t-Butoxycarbonyl)amino)3-(R)-hydroxy-2(S)-(4-methoxy benzylamino)-5-phenyl pentanoic acid ethyl ester* (**23**; $C_{26}H_{36}N_2O_6$)

9.59 g (28.59 mmol) 4(*R*)-((N-*t*-butoxycarbonyl)amino)2(*R*),3(*S*)-epoxy-5-phenyl pentanoic acid ethyl ester [7] were dissolved in 130 $cm^3$ *THF*/ethanol (3/2), and 7.44 $cm^3$ (57.18 $cm^3$) 4-methoxy-benzylamine were added. The reaction mixture was kept at 60°C for 24 h, the solvent was evaporated under reduced pressure, and the residue chromatographed on silica gel (eluent: toluene/ethyl acetate = 5/1 → 2/1), yielding 10.0 g (74%) of **23** as a syrup.

$^1$H NMR ($CDCl_3$, $\delta$, 250 MHz): 1.23 (t, 3H, $CH_2CH_3$), 1.38 (s, 9H, $C(CH_3)_3$), 2.90 (ABX, 2H, $CH_2C_6H_5$), 3.28 (d, 1H, $CHCO_2$), 3.51 (1/2AB, 1H, $NHCHC_6H_5$), 3.67 (dd, 1H, C*H*OH), 3.71 (1/2AB, 1H, $NHCHC_6H_5$), 3.79 (s, 3H, $OCH_3$), 4.05 (bq, 1H, $CHCH_2$), 4.32–4.21 (m, 2H $OCH_2$), 4.79 (bd, 1H, *BOC*NH), 6.85 (d, 2H, aromatic H), 7.12–7.23 (m, 5H, aromatic H), 7.28 (d, 2H, aromatic H) ppm; MS (FAB): $m/z = 473$ [$MH^+$].

*4(R)-((N-t-Butoxycarbonyl)amino)-2(S)-(4-methoxybenzylamino)-5-phenyl-pentan-1,3(R)-diol* (**24**; $C_{33}H_{54}N_2O_4Si_2 \cdot HCl$)

571 mg (15.1 mmol) $NaBH_4$ and 640 mg (15.1 mmol) LiCl were dissolved in 60 $cm^3$ of ethanol/*THF* = 3/2 and stirred for 1 h at room temperature. Then, 3.57 g (7.55 mmol) **23** dissolved in 10 $cm^3$ of the above solvent mixture were added, and the reaction mixture was stirred for 1 d. After neutralization with acetic acid and dilution with $CH_2Cl_2$, the reaction mixture was washed with $H_2O$, dried, and the solvent evaporated. Chromatography on silica gel (eluent: $CH_2Cl_2$/methanol = 95/5) yielded 2.93 g (86%) foamy **24**.

$^1$H NMR ($CDCl_3$, $\delta$, 250 MHz): 1.28 (s, 9H, $C(CH_3)_3$), 2.61–2.70 (m, 1H, $CHC_6H_5$), 2.81–2.94 (m, 3H, $CHC_6H_5$, CHNH), 3.60–3.78 (m, 5H, $NHCH_2$, C*H*OH, $CH_2OH$), 3.79 (s, 3H, $OCH_3$), 3.95 (dq, 1H, $NHCHCH_2$), 4.95 (d, 1H, *BOC*NH), 6.80 (d, 2H, aromatic H), 7.08–7.30 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 431$ [$MH^+$].

*4(R)-Amino-2(S)-(4-methoxybenzylamino)-5-phenyl-pentan-1,3(R)-diol* (**25**; $C_{19}H_{25}N_2O_3$)

2.93 g (6.81 mmol) **24** were dissolved in 20 $cm^3$ $CH_2Cl_2$ and treated with 11 $cm^3$ (33 mmol) 3 *N* HCl (ethyl acetate). After 2 h the solvent was evaporated yielding 2.71 g (99%) crude hygroscopic **25**, which was pure enough to be used directly for further reactions.

$^1$H NMR ($CD_3OD$, $\delta$, 250 MHz): 3.08 (ABX, 2H, C*H*$_2$C$_6$H$_5$), 3.41–3.45 (m, 1H, C*H*CH$_2$OH), 3.76–3.81 (m, 1H, C*H*NH$_2$), 3.89 (s, 3H, OCH$_3$), 4.02 (ABX, 2H, C*H*$_2$OH), 4.26 (1/2AB, 1H, C*H*C$_6$H$_4$), 4.30 (t, 1H, C*H*OH), 4.33 (1/2AB, 1H, C*H*C$_6$H$_4$), 7.38–7.49 (m, 9H, aromatic H) ppm.

*7(R)-Benzyl-6(S)-O-t-butyldimethylsilyl-5(R)-((O-t-butyldimethylsilyl)-methyl)-4-(4-methoxybenzyl)-1,4-diazepan-2-one* (**26**; $C_{33}H_{54}N_2O_4Si_2 \cdot HCl$)

403 mg (1 mmol) **25** were dissolved in 5 $cm^3$ $CH_2Cl_2$. 544 mg (8 mmol) imidazole and 900 mg (6 mmol) *TBDMS*Cl dissolved in 2 $cm^3$ $CH_2Cl_2$ were added, and the reaction mixture was stirred for 12 h at room temperature. After washing with $H_2O$ and drying, 136 mg (2 mmol) imidazole and 158 $mm^3$ (2 mmol) chloroacetylchloride were added. After stirring for 30 min at room temperature the solution was washed with $H_2O$, dried, evaporated, and chromatographed on silica gel (eluent: toluene/ethyl acetate = 9/1), yielding 515 mg (81%) as a syrup. **26**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 0.06 (s, 3H, SiCH$_3$), 0.08 (s, 3H, SiCH$_3$), 0.11 (s, 3H, SiCH$_3$), 0.21 (s, 3H, SiCH$_3$), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.92 (s, 9H, SiC(CH$_3$)$_3$), 2.37–2.48 (1/2ABX, 1H, C*H*C$_6$H$_5$), 2.68 (dt, 1H, C*H*CH$_2$), 2.88–2.97 (1/2ABX, 1H, C*H*C$_6$H$_5$), 3.58 (1/2AB, 1H, NHC*H*C$_6$H$_4$), 3.71 (d, 1H, CHO), 3.73–3.81 (m, 3H, NHC*H*C$_6$H$_4$, CH$_2$O), 3.79 (s, 3H, OCH$_3$), 3.81 (d, 2H, CH$_2$O), 4.39–4.50 (m, 1H, NC*H*CH$_2$), 6.86 (d, 2H, aromatic H), 7.08–7.30 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 635$ [MH$^+$].

*7(R)-Benzyl-6(S)-O-t-butyldimethylsilyl-5(R)-hydroxymethyl-4-(4-methoxybenzyl)-1,4-diazepan-2-one* (**27**; $C_{27}H_{40}N_2O_4Si \cdot HCl$)

394 mg (0.62 mmol) **26** were reacted according to the general procedure using 400 $mm^3$ 40% HF for 3d, yielding 220 mg (68%) syrupy **27**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 0.09 (s, 3H, SiCH$_3$), 0.21 (s, 3H, SiCH$_3$), 0.98 (s, 9H, SiC(CH$_3$)$_3$), 2.53–2.64 (1/2ABX, 1H, C*H*C$_6$H$_5$), 2.71 (dt, 1H, C*H*CH$_2$), 2.79–2.90 (1/2ABX, 1H, C*H*C$_6$H$_5$), 3.52–3.79 (m, 5H, NC*H*$_2$C$_6$H$_4$, C*H*$_2$OH, CHO), 3.79 (s, 3H, OCH$_3$), 3.86 (s, 2H, COCH$_2$), 4.85–4.46 (m, 1H, NHC*H*CH$_2$), 6.84 (d, 2H aromatic H), 7.11–7.32 (m, 7H, aromatic H), 7.80 (d, 1H, CONH) ppm; MS (FAB): $m/z = 522$ [MH$^+$].

*7(R)-Benzyl-6(S)-hydroxy-5(R)-hydroxymethyl-4-(4-methoxybenzyl)-1,4-diazepan-2-one* (**28**; $C_{21}H_{26}N_2O_4 \cdot HCl$)

200 mg (0.31 mmol) **26** were desilylated with 800 $mm^3$ (16 mmol) 40% HF for 6 d, using the general procedure yielding 92 mg (77%) syrupy **28**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 2.55–2.61 (m, 1H, C*H*CH$_2$), 2.89 (ABX, 2H, C*H*$_2$C$_6$H$_5$), 3.59–3.79 (m, 5H, NC*H*$_2$C$_6$H$_4$, C*H*$_2$OH, CHO), 3.79 (s, 3H, OCH$_3$), 3.89 (s, 2H, COCH$_2$), 4.22–4.38 (dq, 1H, NHC*H*CH$_2$), 6.84 (d, 2H, aromatic H), 7.04–7.25 (m, 8H, aromatic H, CONH) ppm; MS (FAB): $m/z = 407$ [MH$^+$].

*4(R)-Benzyl-5(S)-O-t-butyldimethylsilyl-6(R)-((O-t-butyldimethylsilyl)-methyl)-1-(4-methoxybenzyl)-tetrahydropyrimidin-2-one* (**29**; $C_{32}H_{52}N_2O_4Si_2$)

403 mg (1 mmol) **25** were dissolved in 3 $cm^3$ $CH_2Cl_2$, and 272 mg (4 mmol) imidazole and 452 mg (3 mmol) *TBDMS*Cl dissolved in 3 $cm^3$ $CH_2Cl_2$ were added; the reaction mixture was stirred for 1 d.

After washing with water and drying, 256 mg (1 mmol) 1,1′-carbonyldiimidazole (*Staab* reagent) were added to the filtrate, and stirring was continued for 30 min. Evaporation of the solvent and chromatograpy of the residue on silica gel (eluent: toluene/ethyl acetate = 3/1) yielded 470 mg (80%) syrupy **29**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.2 (s, 3H, $SiCH_3$), 0.01 (s, 9H, $3SiCH_3$), 0.81 (s, 9H, $SiC(CH_3)_3$), 0.82 (s, 9H, $SiC(CH_3)_3$), 2.79 (d, 2H, $CH_2C_6H_5$), 3.21–3.28 (m, 1H, $CHCH_2$), 3.40 (1/2ABX, 1H, CHOSi), 3.60 (1/2ABX, 1H, CHOSi), 3.72–3.80 (m, 1H, CHOSi), 3.79 (s, 3H, $OCH_3$), 4.08–4.12 (m, 1H, NHCH), 4.20 (1/2AB, 1H, $NCHC_6H_4$), 4.29 (bs, 1H, NH), 4.87 (1/2AB, 1H, $NCHC_6H_4$), 6.81 (d, 2H, aromatic H), 7.18–7.38 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 585$ [$MH^+$].

*4(R)-Benzyl-5(S)-O-t-butyldimethylsilyl-6(R)-hydroxymethyl-1-(4-methoxybenzyl)-tetrahydropyrimidin-2-one* (**30**; $C_{28}H_{38}N_2O_4Si$)

100 mg (0.17 mmol) **29** were reacted with 200 mm$^3$ 40% HF for 1 d following the general procedure yielding 77 mg (96%) **30**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.2 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 2.79 (ABX, 2H, $CH_2C_6H_5$), 3.22 (q, 1H, $CHCH_2OH$), 3.61 (d, 2H, $CH_2OH$), 3.80 (s, 3H, $OCH_3$), 3.77–3.82 (m, 1H, NHCH), 4.15 (1/2AB, 1H, $NCHC_6H_4$), 4.64 (1/2AB, 1H, $NCHC_6H_4$), 4.82 (bs, 1H, CONH), 6.82 (d, 2H, aromatic H), 7.15–7.32 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 363$ [$MH^+$].

*4(R)-Benzyl-5(S)-hydroxy-6(R)-hydroxymethyl-1-(4-methoxybenzyl)-tetrahydropyrimidin-2-one* (**31**; $C_{20}H_{24}N_2O_4$)

170 mg (0.036 mmol) **30** were desilylated with 720 mm$^3$ (14.4 mmol) 40% HF following the general procedure yielding 101 mg (79%) syrupy **31**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 2.82 (ABX, 2H, $CH_2C_6H_5$), 3.37 (t, 1H, $CHCH_2OH$), 3.51 (d, 2H, $CH_2OH$), 3.71–3.88 (m, 2H, CHOH, NHCH), 3.77 (s, 3H, $OCH_3$), 4.18 (1/2AB, 1H, $NCHC_6H_4$), 4.70 (bs, 1H, CONH), 4.82 (1/2AB, 1H, $NCHC_6H_4$), 6.82 (d, 2H, aromatic H), 7.15–7.32 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 357$ [$MH^+$].

*3(R)-(7(R)-Benzyl-6(S)-O-t-butyldimethylsilyl-4-(4-methoxybenzyl)-2-oxo-1,4-diazepan-5-yl)-acrylic acid ethylester* (**32**; $C_{31}H_{44}N_2O_5Si \cdot HCl$)

352 mg (0.73 mmol) **27** were dissolved in 2 cm$^3$ dry *DMSO*, 307 mm$^3$ (2.19 mmol) triethylamine and 349 mg (2.19 mmol) pyridinium sulfate were added, and the solution was stirred for 15 min at room temperature. Then, 763 mg (2.19 mmol) carboxyethyl triphenylphosphorane were added, and the reaction was worked up after 1 h by diluting with $CH_2Cl_2$, washing with $H_2O$, drying, and evaporating the solvent. The residue was chromatographed on silica gel (eluent: toluene/ethyl acetate = 9/1) yielding 267 mg (62%) syrupy **32**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 0.00 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.18 (s, 9H, $SiC(CH_3)_3$), 1.29 (t, 3H, $CH_3CH_3$), 2.54 (1/2ABX, 1H, $CHC_6H_5$), 2.82 (1/2ABX, 1H, $CHC_6H_5$), 3.21 (dd, 1H, CHCH=), 3.43 (1/2AB, 1H, $NCHC_6H_4$), 3.68 (dd, 1H, CHO), 3.72 (1/2AB, 1H, $NCHC_6H_4$), 3.80 (s, 3H, $OCH_3$), 3.89 (s, 2H, $COCH_2$), 4.22 (q, 2H, $CH_2CH_3$), 4.30–4.44 (m, 1H, $NHCHCH_2$), 5.88 (d, 1H, =CH), 6.67 (dd, 1H, CH=), 6.84 (d, 2H, aromatic H), 7.08–7.30 (m, 7H, aromatic H), 7.68 (d, 1H, CONH) ppm; MS (FAB): $m/z = 589$ [$MH^+$].

*3(R)-(7(R)-Benzyl-6(S)-hydroxy-4-(4-methoxybenzyl)-2-oxo-1,4-diazepan-5-yl)-acrylic acid ethylester* (**33**; $C_{25}H_{30}N_2O_5 \cdot HCl$)

84 mg (0.14 mmol) **32** were dissolved in 4 cm$^3$ *THF*, and 150 mm$^3$ (0.15 mmol) tetrabutylammonium fluoride (1 *M* in *THF*) were added at 15°C. After 2 h the reaction was quenched with 0.4 cm$^3$

methanol, the solvent evaporated, and the residue chromatographed on silica gel (eluent: toluene/ethyl acetate = 2/1 → 1/1), yielding 50 mg (79%) syrupy **33**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 1.28 (t, 3H, $CH_2CH_3$), 2.87 (d, 2H, $CH_2C_6H_5$), 3.11 (dd, 1H, CHCH=), 3.43 (1/2AB, 1H, $NCHC_6H_4$), 3.62 (dd, 1H, CHO), 3.62 (1/2AB, 1H, $NCHC_6H_4$), 3.79 (s, 3H, $OCH_3$), 3.89 (s, 2H, $COCH_2$), 4.20 (q, 2H, $CH_2CH_3$), 4.26 (dq, 1H, $NHCHCH_2$), 5.91 (d, 1H, =CH), 6.77 (dd, 1H, CH=), 7.02 (d, 1H, CONH), 7.16 (d, 2H, aromatic H), 7.19–7.35 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = 475$ [$MH^+$].

*4(R)-Benzyl-5(S)-O-t-butyldimethylsilyl-6(R)-((O-t-butylidimethylsilyl)-methyl)-1,3-bis-(4-methoxybenzyl)-tetrahydropyrimidin-2-one* (**34**; $C_{40}H_{60}N_2O_5Si_2$)

227 mg (9.48 mmol) NaH were dispersed in 20 cm$^3$ *DMSO* at 0°C. Then 2.77 g (4.74 mmol) **26** were added, and the reaction mixture was stirred for 15 min at 0°C. A solution of 3.056 g (9.48 mmol) tetrabutylammonium bromide, 975 mg (9.48 mmol) NaBr, and 1.29 cm$^3$ (9.48 mmol) 4-methoxybenzyl chloride dissolved in 20 cm$^3$ *DMSO* was added. After stirring for 12 h at 4°C the reaction mixture was acidified to *pH* 4–5 with acetic acid, diluted with $CH_2Cl_2$, washed with $H_2O$, the organic solvent was evaporated, and the residue was chromatographed on silica gel (eluent: toluene/ethyl acetate = 4/1) yielding 2.82 g (70%) syrupy **34**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.31 (s, 3H, $SiCH_3$), −0.18 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.81 (s, 9H, $SiC(CH_3)_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 2.41 (1/2ABX, 1H, $CHC_6H_5$), 2.57 (1/2AB, 1H, $NCHC_6H_4$), 2.88 (1/2ABX, 1H, $CHC_6H_5$), 3.12–3.18 (m, 1H, $NCHCH_2$), 3.51 (1/2ABX, 1H, CHOSi), 3.76 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 3.81–3.84 (m, 1H, CHOSi), 3.91 (1/2ABX, 1H, CHOSi), 5.10 (1/2AB, 1H, $NCHC_6H_4$), 5.60 (1/2AB, 1H, $NCHC_6H_4$), 7.16 (d, 2H aromatic H), 7.26–7.38 (m, 7H, aromatic H) ppm; MS (FAB): $m/z = [MH^+]$.

*4(R)-Benzyl-5(S)-O-t-butyldimethylsilyl-6(R)-hydroxymethyl)-1,3-bis-(4-methoxybenzyl)-tetrahydropyrimidin-2-one* (**35**; $C_{34}H_{46}N_2O_5Si$)

2.34 g (3.32 mmol) **34** were reacted with 1 cm$^3$ 40% HF for 4 d according to the general procedure yielding 1.12 g (56%) syrupy **35** after chromatography on silica gel (eluent: toluene/ethyl acetate = 6/4 → 8/1).

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.31 (s, 3H, $SiCH_3$), −0.18 (s, 3H, $SiCH_3$), 0.81 (s, 9H, $SiC(CH_3)_3$), 1.63 (1/2ABX, 1H, $CHC_6H_5$), 2.32 (1/2ABX, 1H, $CHC_6H_5$), 2.63 (1/2AB, 1H, $NCHC_6H_4$), 2.91 (1/2ABX, 1H, CHOH), 3.04 (d, 1H, $CHCH_2$), 3.10–3.19 (m, 1H, CHOSi), 3.49 (1/2ABX, 1H, CHOH), 3.75 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.92 (dt, 1H, $NCHCH_2$), 4.22 (1/2AB, 1H, $NCHC_6H_4$), 5.11 (1/2AB, 1H, $NCHC_6H_4$), 5.18 (1/2AB, 1H, $NCHC_6H_4$), 6.75–6.68 (m, 4H, aromatic H), 6.90 (d, 2H, aromatic H), 7.08–7.15 (m, 2H, aromatic H), 7.22–7.43 (m, 5H, aromatic H) ppm; MS (FAB): $m/z = 591 = [MH^+]$.

*3(R)-(6(R)-Benzyl-5(S)-O-t-butyldimethylsilyl-1,3-bis-(4-methoxybenzyl)-2-oxo-hexahydropyrimidin-4-yl)-acrylic acid ethylester* (**36**; $C_{38}H_{50}N_2O_6Si$)

200 mg (0.34 mmol) **35** were dissolved in 3 cm$^3$ $CH_2Cl_2$. 173 mg (0.408 mmol) *Dess-Martin* reagent and 53 mm$^3$ (0.68 mmol) pyridine were added, and after 1 h 284 mg (0.82 mmol) carboxyethyl triphenylphosphorane were added together with 4 cm$^3$ toluene. The reaction mixture was heated at 60°C for 1 h; then the solvent was evaporated and the residue chromatographed on silica gel (eluent: toluene/methanol = 95/5) to yield 172.5 mg (77%) syrupy **36**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): −0.31 (s, 3H, $SiCH_3$), −0.18 (s, 3H, $SiCH_3$), 0.79 (s, 9H, $SiC(CH_3)_3$), 1.32 (t, 3H, $CH_2CH_3$), 2.20 (1/2ABX, 1H, $CHC_6H_5$), 2.58 (1/2AB, 1H, $NCHC_6H_4$), 2.87 (1/2ABX, 1H, $CHC_6H_5$), 3.12–3.20 (m, 1H, $NCHCH_2$), 3.41 (dd, 1H, CHOSi), 3.61 (t, 1H, CHCH=),

3.72 (1/2AB, 1H, NC*H*$C_6H_4$), 3.78 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 4.26 (dq, 2H, $OCH_2$), 5.10 (1/2AB, 1H, NC*H*$C_6H_4$), 5.95 (1/2AB, 1H, NC*H*$C_6H_4$), 5.94 (d, 1H, =CH), 6.63 (dd, 1H, =CH), 6.72–6.84 (m, 4H, aromatic H), 6.89 (d, 2H, aromatic H), 7.01–7.10 (m, 2H, aromatic H), 7.22–7.40 (m, 5H, aromatic H) ppm; MS (FAB): $m/z = 659$ [$MH^+$].

*3(R)-(6(R)-Benzyl-5(S)-hydroxy-1,3-bis-(4-methoxybenzyl)-2-oxo-hexahydropyrimidin-4-yl)-acrylic acid ethylester* (**37**; $C_{32}H_{36}N_2O_6$)

120 mg (0.18 mmol) **36** were desilylated with 600 $mm^3$ 40% HF according to the general procedure yielding 91.2 mg (93%) syrupy **37** after chromatography on silica gel (eluent: toluene/ethyl acetate = 4/1).

$^1$H NMR ($CDCl_3$, $\delta$, 250 MHz): 1.31 (t, 3H, $CH_2CH_3$), 2.77 (ABX, 2H, $CH_2C_6H_5$), 3.23 (dt, 1H, NC*H*$CH_2$), 3.42 (1/2AB, 1H, NC*H*$C_6H_4$), 3.41–3.52 (m, 1H, C*H*CH=), 3.67 (1/2AB, 1H, NC*H*$C_6H_4$), 3.76–3.82 (m, 1H, C*H*OH), 3.79 (s, 6H, $2OCH_3$), 4.21 (q, 2H, $OCH_2$), 5.25 (1/2AB, 1H, NC*H*$C_6H_4$), 5.42 (1/2AB, 1H, NC*H*$C_6H_4$), 5.96 (dd, 1H, =CH), 6.58 (dd, 1H, CH=), 6.75–6.89 (m, 4H, aromatic H), 7.00–7.05 (m, 4H, aromatic H), 7.20–7.33 (m, 5H, aromatic H) ppm; MS (FAB): $m/z =$ [$MH^+$].

*3(R)-(6(R)-Benzyl-5(S)-hydroxy-1,3-bis-(4-methoxybenzyl)-2-oxo-hexahydropyrimidin-4-yl)-oxiran-carboxylic acid ethyl ester* (**38**; $C_{32}H_{36}N_2O_7$)

100 mg (0.18 mmol) **37**, 56 $mm^3$ benzonitrile, 8 mg (0.08 mmol) $KHCO_3$, and 110 $mm^3$ (0.36 mmol) 30% $H_2O_2$ were dissolved in 2 $cm^3$ ethanol and stirred for 4 d. Then, 1 $cm^3$ 40% $NaHSO_3$ was added, and the reaction mixture was taken up in $CH_2Cl_2$, washed, dried, evaporated, and chromatographed on silica gel (eluent: toluene/ethyl acetate = 3/1) to yield 74 mg (72%) **38**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 1.32 (t, 3H, $CH_2CH_3$), 2.69 (1/2ABX, 1H, C*H*$C_6H_5$), 2.92 (1/2ABX, 1H, C*H*$C_6H_5$), 2.96 (d, 1H, C*H*CHO), 3.08 (dd, 1H, $CHOCO_2$), 3.20 (d, 1H, C*H*OCH), 3.31 (1/2AB, 1H, NC*H*$C_6H_4$), 3.46–3.53 (m, NC*H*$CH_2$), 3.79 (s, 6H, $2OCH_3$), 3.76–3.82 (m, 1H, C*H*OH), 4.08 (1/2AB, 1H, NC*H*$C_6H_4$), 4.20–4.29 (q, 2H, $OCH_2$), 5.18 (1/2AB, 1H, NC*H*$C_6H_4$), 5.23 (1/2AB, 1H, NC*H*$C_6H_4$), 6.81–6.91 (m, 4H, aromatic H), 7.01 (m, 2H, aromatic H), 7.10–7.19 (m, 3H, aromatic H), 7.22–7.31 (m, 4H, aromatic H) ppm; MS (FAB): $m/z = 561$ [$MH^+$].

*5(S)-(Hydroxy-1,3-bis-(4-methoxybenzyl)-2-oxo-hexahydro-pyrimidin-4-yl)-acrylic acid* (**39**; $C_{30}H_{32}N_2O_6$)

212 mg (0.39 mmol) **37** were dissolved in 1.5 $cm^3$ *THF*, 10 mg (0.429 mmol) LiOH and 0.3 $cm^3$ $H_2O$ were added, and the reaction mixture was stirred for 1 d at room temperature. After acidification with 1 *N* HCl the solution was extracted with $CH_2Cl_2$. Evaporation of the organic solvent yielded 191 mg (95%) foamy **39**.

$^1$H NMR ($CDCl_3$, $\delta$, 500 MHz): 2.41 (1/2ABx, 1H, C*H*$C_6H_5$), 2.81 (1/2ABX, 1H, C*H*$C_6H_5$), 3.01 (1/2AB, 1H, NC*H*$C_6H_4$), 3.41 (dd, 1H, NC*H*$CH_2$), 3.61–3.80 (m, 2H, C*H*CH=, C*H*OH), 3.79 (s, 6H, $2OCH_3$), 3.90 (1/2AB, 1H, NC*H*$C_6H_4$), 4.97 (1/2AB, 1H, NC*H*$C_6H_4$), 5.22 (1/2AB, 1H, NC*H*$C_6H_4$), 5.96 (dd, 1H, =CH), 6.48 (dd, 1H, CH=), 6.80–7.38 (m, 13H, aromatic H) ppm; MS (FAB): $m/z = 517$ [$MH^+$].

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