Asymmetric Synthesis of 1,2,3,4,5,6-Hexahydro-5-hydroxypyrimidin-2-ones as Potential HIV-Protease Inhibitors

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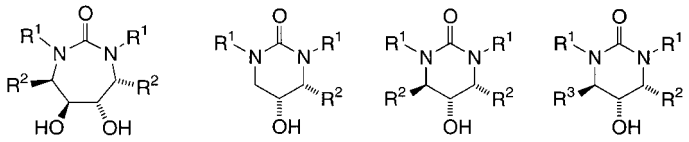
The first asymmetric synthesis of potential cyclic urea HIV protease inhibitors of *Type 2* is reported. The synthesis is short and highly versatile in the choice of the substitution pattern and absolute configuration of the products starting from readily available materials. Nonchiral central building block **5** was synthesized and subsequently asymmetrically alkylated under (*R*)-/(*S*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP/SAMP)-auxiliary control to provide **8a**–**e**. The alkylated ketones then were reduced to the target compounds **9a**–**e**, with good-to-excellent overall yields, as well as diastereoisomeric and enantiomeric purities.

Introduction. – An infection with the HI virus (*Human-Immunodeficiency Virus*) is the causal reason for the AIDS disease [1]. The *pol*-gene of the HI-1 virus encodes an aspartate protease (*HIV protease*), which proteolytically cleaves *gag*- and *gag-pol*-polyproteins into structural and functional proteins, which in turn play an important role in the function of the mature virus (for a review, see [2]). Inhibition of HIV-1 protease results in the production of non-infectious virions [3]. Therefore, the HIV protease is an interesting target for AIDS therapy [2][4].

Although already several HIV-1-protease inhibitors such as *Saquinavir*, *Ritonavir*, *Indinavir*, and *Nefinavir* have been developed, because of rapid development of viral resistance [5], there is always a great need for structurally new inhibitors. One important class of compounds are cyclic ureas, which replace a structural H_2O molecule bound at the active site of the HIV protease (for a review, see [6]). In recent years, many cyclic-urea-based inhibitors have been synthesized, examples of which are depicted below.



Structure-activity relationships (SAR) of the inhibitors based on seven-membered rings of type **I** have been intensively studied [6][7]. In the design of these drug molecules, the C_2 symmetry of the homodimeric HIV-1 protease was incorporated into the structure of the inhibitors. As may be seen from the X-ray crystal-structure analysis of enzyme-inhibitor complexes [8], the two substituents R^2 in the type-**I** inhibitor are in a *trans*-diaxial orientation, which seems to be important for their biological activity.

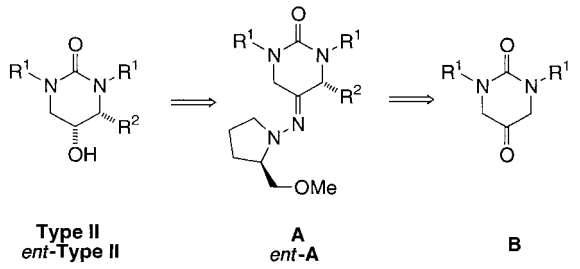
In addition, cyclic-urea inhibitors based on different ring sizes have been synthesized [9]. It was found that urea derivatives, which contain six-membered rings (types **II**–**IV**) had smaller, but still interesting, biological activities [8–10]. The reason for the reduced biological activity of the inhibitors based on six-membered rings of type **III** seems to be that the relative configuration of the two substituents R^2 in the 1,3-positions is *trans*, which means that one must be in an axial and the other in an equatorial position. To avoid this problem, instead of two $PhCH_2$ groups as R^2, a combination of a $PhCH_2$ and a $PhCH_2CH_2$ group were used. In this case, the $PhCH_2CH_2$ moiety can be rotated about the additional CH_2 group to adopt a pseudoaxial position, which leads to an increase in the biological activity of type-**IV** inhibitors [6][7].

Results and Discussion. – During our studies in the area of HIV-protease inhibitor synthesis [11], we became interested in developing a highly efficient synthesis of cyclic-urea inhibitors of type **II**. The synthesis described in [10] for type-**II** inhibitors is initiated with a 'chiral pool' of starting materials and, thus, does not allow for easy variation of substituents for generating a wide range of analogues to optimize new lead structures in SAR.

It was desired that our synthesis should be short, efficient, and allow a high versatility in the choice of the substituents R^1 and R^2, as well as free choice of the absolute configuration. We focused our efforts on the synthesis of the *cis*-stereoisomers, since researchers of *Dupont Merck* discovered that such stereoisomers exhibit better activities [10].

Our retrosynthetic plan was to synthesize inhibitors of type **II** by auxiliary-directed asymmetric enolate alkylation *via* hydrazone **A**, starting from the corresponding pyrimidine-2,5-dione **B**. The advantage of this methodology is the diversity in the choice of the residue R^2 by the application of the corresponding electrophile, as well as the possible choice of the absolute configuration, by employing either of two readily available enantiomeric auxiliaries (*Scheme 1*).

Scheme 1



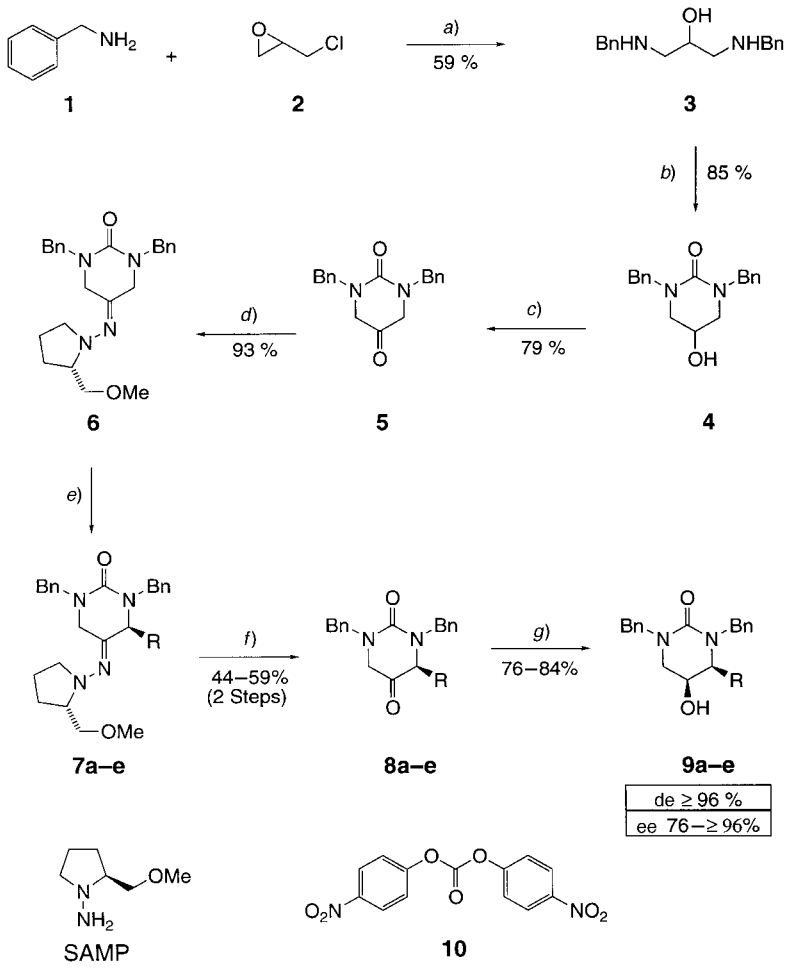
The method of choice in this case was the (*R*)-/(*S*)-1-amino-2-(methoxymethyl)-pyrrolidine (RAMP-/SAMP)-hydrazone method, which has been frequently applied in asymmetric enolate alkylations with a large variety of electrophiles [12].

One further advantage is that this method has already been used in C_2-symmetrical and pseudo-C_2-symmetrical alkylations to synthesize highly substituted dioxanone

derivatives (for a review, see [13]). By analogy, it would also be possible to synthesize inhibitors of type **III** and **IV** with the same retrosynthetic methodology, starting from the same chiral building block (*S*)-**6** or (*R*)-**6** (*Scheme 2*).

We started the synthesis of the achiral building block **5** (*Scheme 2*) by reacting benzylamine (**1**) with (chloromethyl)oxirane **2**. With the choice of **1** as primary-amine residue, R^1 is determined. Diamino alcohol **3** could thus be easily synthesized in one step and purified *via* recrystallization of the corresponding hydrochloride salt. Cyclization of **3** with a phosgene equivalent proved to be most effective with bis(4-nitrophenyl) carbonate **10** [14], since only the desired, thermodynamically favored, six-

Scheme 2. *Synthesis of the HIV-Protease Inhibitors of Type* **II**



a) 0°, Reflux. *b*) Bis(4-Nitrophenyl) carbonate **10**, CH_2Cl_2, reflux. *c*) *Dess-Martin* reagent. *d*) SAMP, CH_2Cl_2, molecular sieves (3 Å), r.t. *e*) 2,2,6,6-Tetramethylpiperidine, BuLi, THF, electrophile RX. *f*) Dimethyldioxirane, acetone, MeCN, H_2O, r.t., or $CuCl_2$, THF, H_2O, r.t.; yields over 2 steps from **6**: **8a**: 53%, **8b**: 59%, **8c**: 44%, **8d**: 57%, **8e**: 56%. *g*) $LiAlH_4$, Et_2O, 0° – r.t.

membered urea could be detected, and not the kinetically favored, five-membered ring carbamate as by-product. Up to this step, all products could be purified by simple recrystallization. Subsequent *Dess-Martin* oxidation [15] gave rise to the achiral building block **5**, which could be prepared on a multigram scale. By simply stirring the dione **5** with SAMP or RAMP [16], the corresponding SAMP- or RAMP-hydrazones (*S*)-**6** or (*R*)-**6** were obtained in excellent yields, and thus the synthesis of the important chiral building block **6** was completed. By choice of the alkyl halide as electrophile in the auxiliary-directed aza-enolate alkylation, the residue R^2 is introduced. X-Ray crystal-structure analysis of **7c**[1]) confirmed the configuration at the newly formed stereogenic center, with the sense of asymmetric induction assenting to our SAMP/RAMP alkylation model [12a] (*Fig. 1*).

Without further purification, the alkylated hydrazones **7a**–**e** were cleaved directly to give rise to the desired ketones **8a**–**e**. The best results were obtained by the method of *Curci* and co-workers [18] with dimethyldioxirane as the cleavage reagent. Lower yields were obtained by the copper(II) chloride method [19]. After column chromatography on silica gel, the α-alkylated ketones **8a**–**e** were reduced to the desired *cis*-alcohols **9a**–**e** with $LiAlH_4$ with excellent diastereoselectivities. The relative configuration was confirmed by X-Ray crystal-structure analysis of the allyl derivative **9c**[2]) (*Fig. 2*).

Since most of the target molecules **9a**–**e** are crystalline, they could easily be further purified *via* simple recrystallization. The enantioselectivities of this synthesis were good to excellent (*Table*)

Conclusions. – With our asymmetric synthesis, we have developed a highly efficient route to HIV-protease inhibitors of type **II**. The synthesis is short and provides the *cis*-alcohols **9a**–**e** in good yields as well as in good stereoselectivities. The synthesis for inhibitors of type **III** and **IV**, starting from building block **6**, is currently under investigation.

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[1]) *X-Ray Crystal-Structure Analysis of* **7c** (Deposition No. CCDC-116037). Crystals were obtained from CH_2Cl_2. Compound **7c** ($C_{27}H_{34}O_2N_4$, $M_{calc.} = 446.6$, crystal size *ca.* $0.3 \times 0.3 \times 0.3$ mm) crystallizes in orthorhombic space group $P2_12_12_1$ (No. 19), $a = 7.7066(5)$, $b = 10.5628(6)$, $c = 30.780(2)$ Å, $Z = 4$, $V = 2505.6$ Å^3, $D_{calc.} = 1.184$ gcm^{-3}. *Enraf-Nonius CAD4* diffractometer, CuK_α radiation (graphite monochromator, $\lambda = 1.54179$ Å). The structure was solved by direct methods (GENSIN, GENTAN as implemented in Xtal 3.4. [17]). Some of the H-atoms could be located, the others were calculated. All parameters were kept constant in the refinement. The allyl group is disordered (C(7) and C(6) occur in two components (0.75 : 0.25), which could be refined isotropically with constant occupation numbers). 2552 observed reflections ($I > 2\sigma(I)$) in the final full-matrix least-squares refinement of 296 parameters, terminating at $R = 0.064$, $R_w = 0.040$ ($w = \sigma^{-2}$) and residual electron density of $-0.29/+0.29$ eÅ^{-3}.

[2]) *X-Ray Crystal-Structure Analysis of* **9c** (Deposition No. CCDC-116038). Crystals were obtained from CH_2Cl_2/Et_2O. Compound **9c** ($C_{21}H_{24}O_2N_2$, $M_{calc.} = 336.4$, crystal size *ca.* $0.3 \times 0.3 \times 0.3$ mm) crystallizes in orthorhombic space group $P2_12_12_1$ (No. 19), $a = 7.1682(7)$, $b = 12.019(2)$, $c = 21.592(3)$ Å, $Z = 4$, $V = 1860.3$ Å^3, $D_{calc.} = 1.201$ g cm^{-3}. *Enraf-Nonius CAD4* diffractometer, CuK_α radiation (graphite-monochromator, $\lambda = 1.54179$ Å). Direct methods (GENSIN, GENTAN from Xtal 3.4.[17]) were used to solve the structure. Some of the H-atoms could be located, the others were calculated. H-Parameters were not refined. Final full-matrix least-squares refinement of 226 parameters (1745 observed reflections ($I > 2\sigma(I)$) converged at $R = 0.061$, $R_w = 0.062$ ($w = (\sigma(F)^2 + 0.0004 \cdot F^2)^{-1}$) and a final residual electron density of $-0.29/+0.37$ eÅ^{-3}.

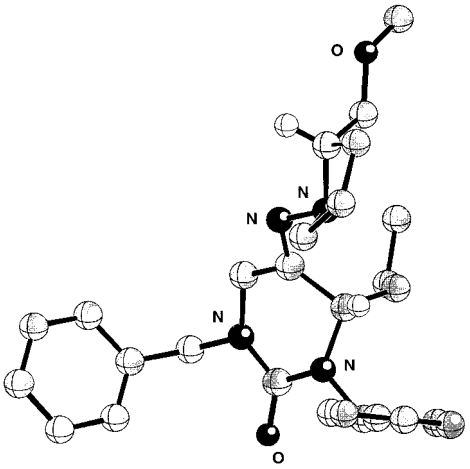

Fig. 1. *Crystal structure of* **7c**

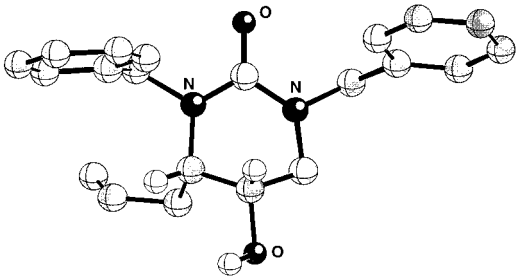

Fig. 2. *Crystal structure of* **9c**

Table. *Yields and Diastereoselectivities*[a]) *for the Reduction of the Alkylated Diones* **8a**–**e** *As Well As Enantiomeric Excesses of the* cis*-Configured Alcohols* **9a**–**e**[b])

9	R	Yield [%]	de [%]	ee [%]
9a	Me	76	≥ 96	76
9b	Bu	80	≥ 96	≥ 96
9c	CH_2=CH–CH_2	79	≥ 96	80
9d	$PhCH_2$	84	≥ 96	76
9e	$PhCH_2CH_2$	83	≥ 96	86

[a]) Diastereoisomeric excesses were determined from ^{1}H-NMR spectra. [b]) Enantiomeric excesses were determined *via* ^{1}H-NMR shift experiments with (–)-*Pirkle* alcohol as shift reagent.

Experimental Part

Synthesis of 1,3-Bis(benzylamino)propan-2-ol (**3**). *Benzylamine* **1** (120 ml, 1.1 mol, 3.5 equiv.) was cooled to 0°, and (*chloromethyl)oxirane* (**2**; 20 ml, 0.31 mol, 1 equiv.) was added. The mixture was stirred for 5 h at 0°, and then refluxed for 4 h. After cooling, a colorless solid precipitated. Aq. NaOH was added until the precipitate disappeared. After extraction with CH_2Cl_2, the solvent and benzylamine (**1**) were removed by distillation. The mixture was dissolved in EtOH, then crystallized as the hydrochloride salt by addition of conc. aq. HCl, and

recrystallized from EtOH. The colorless solid was stirred with conc. aq. NaOH (aq), extracted with Et_2O, dried ($MgSO_4$), and evaporated: **3** was isolated in 59% yield (175.2 g) as yellow oil.

Synthesis of 1,3-Dibenzyl-1,2,3,4,5,6-hexahydro-5-hydroxypyrimidin-2-one (**4**). *Bis(4-nitrophenyl) carbonate* (**10**; 10 g, 32.87 mmol, 1 equiv.) and **3** (15 g, 55.56 mmol, 1.7 equiv.) were refluxed in CH_2Cl_2 (2.5 l) for 24 h. The mixture was extracted once with citric acid and five times with aq. NaOH. After evaporation, the product was recrystallized from Et_2O and CH_2Cl_2: **4** was isolated in 85% yield (8.3 g) as a colorless solid. M.p. 115°.

Synthesis of 1,3-Dibenzyl-1,2,3,4,5,6-hexahydropyrimidine-2,5-dione (**5**). The hydroxy ketone **4** (11.5 g, 38.85 mmol, 1 equiv.) and the freshly prepared *Dess-Martin* reagent (58.28 mmol, 1.5 equiv.) were stirred overnight in CH_2Cl_2 (100 ml) saturated with H_2O (TLC control). The reaction was quenched by addition of sat. aq. $NaHCO_3$ and aq. $Na_2S_2O_3$, and stirred until the precipitate completely dissolved. After extraction with CH_2Cl_2, drying ($MgSO_4$), and evaporation, the crude product was filtered through a short column of silica (Et_2O/pentane 1:1): **5** was isolated as a yellow oil in 79% (9.0 g), which crystallized after some time. M.p. 73°.

Synthesis of 1,3-Dibenzyl-1,2,3,4,5,6-hexahydro-5-{[2-(methoxymethyl)pyrrolidin-1-yl]imino}pyrimidine-2,5-dione (**6**). The dione **5** (9 g, 30.61 mmol, 1 equiv.) and SAMP or RAMP (4.48 ml, 33.67 mmol, 1.1 equiv.) were dissolved in CH_2Cl_2, and the mixture was stirred for 5 h at r.t. with molecular sieves (3 Å). After filtration and evaporation of the solvent, the crude product was filtered through a short column of silica gel (Et_2O): **6** was isolated in 93% yield (11.6 g) as a yellow oil.

Synthesis of the 4-Alkyl-1,3-dibenzyl-1,2,3,4,5,6-hexahydro-5-{[2-(methoxymethyl)pyrrolidin-1-yl]imino}-pyrimidine-2,5-diones **7a**–**e** (1–3 mmol-scale). 2,2,6,6-tetramethylpiperidine (1.3 equiv.) was dissolved in dry THF (20 ml) in a pre-dried *Schlenk* flask under Ar, and a BuLi soln. (1.2 equiv. of a 1.6M soln. in hexane) was added. The pale-yellow soln. was stirred for 10 min at r.t. and then cooled to −78°. A soln. of **6** (1 equiv., −78°) in THF (20 ml) was added slowly *via* a double-ended needle. After stirring for 10 min at −78°, a soln. of the electrophile in THF (5 ml) was added with a syringe pump (5 ml/h), and the mixture was stirred for a further 2 h at −78°, and then quenched with aq. NH_4Cl. After extraction with Et_2O and drying ($MgSO_4$), the solvent was removed. The crude products were used directly in the following cleavage reactions.

Synthesis of the 4-Alkyl-1,3-dibenzyl-1,2,3,4,5,6-hexahydropyrimidine-2,5-diones **8a**–**e**. *Method A:* Compounds **7a**–**e** were dissolved in acetone (20 ml) and H_2O (5 ml). A 0.1M soln. of dimethyldioxirane (5 equiv.) in acetone was added, and the mixture was stirred overnight (TLC control). After addition of H_2O, the mixture was extracted wtih Et_2O and dried ($MgSO_4$), and the solvent was removed. The product was purified by chromatography on silica gel (Et_2O/pentane 1:3) to afford **8a**–**e** in 44–59% yield.

Method B: The compounds **7a**–**e** were dissolved in THF (5 ml) and H_2O (1 ml). $CuCl_2$ (5 equiv.) was added, and the mixture was stirred overnight (TLC control). After addition of H_2O, the mixture was extracted with Et_2O, dried ($MgSO_4$), and the solvent was removed. The product was purified by chromatography on silica gel (Et_2O/pentane 1:3).

Synthesis of the 4-Alkyl-1,3-dibenzyl-1,2,3,4,5,6-hexahydro-5-hydroxypyrimidine-2,5-diones **9a**–**e**. A soln. of **8a**–**e** in THF (10 ml) was added to a suspension of $LiAlH_4$ (3 equiv.) in dry Et_2O (10 ml) at 0°. The mixture was stirred for 1 h (TLC control) at 0°, and the reaction was then quenched with aq. NH_4Cl, and the mixture was filtered and washed with CH_2Cl_2, dried ($MgSO_4$), and the solvent was removed. The pure hydroxy ketones **9a**–**e** were obtained after column chromatography on silica gel (Et_2O/pentane 1:1) in 76–84% yield. The de value of the reduction products was in all cases >96% (^{1}H-NMR). The enantioselectivities were determined by ^{1}H-NMR shift experiments with (−)-*Pirkle alcohol* (ee 76–>96%).

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