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ASYMMETRIC SYNTHESIS OF 4,6-DISUBSTITUTED 1,2,3,4,5,6-HEXAHYDRO-5-HYDROXYPYRIMIDIN-2-ONES AS POTENTIAL HIV-PROTEASE-INHIBITORS

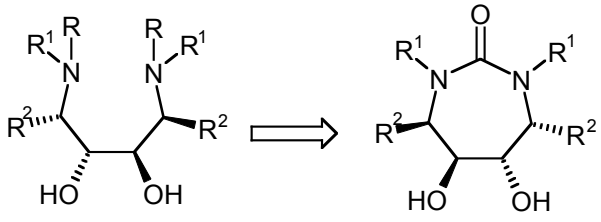
Dieter Enders* and Lars Wortmann

Institut für Organische Chemie der RWTH Aachen, Professor-Pirlet Straße 1, 52074 Aachen, Germany; Fax: +49(241)8092127, E-mail: Enders@RWTH-Aachen.de

Abstract - The first asymmetric synthesis of potential HIV protease inhibitors of **type III** and **IV** is described. Key step of the synthesis is an auxiliary based stereoselective alkylation by means of the RAMP-/SAMP-hydrazone method starting from a readily available key building block. The synthesis is short and highly versatile in the choice of the substitution pattern as well as the absolute configuration of the products.

Introduction

An infection with the HI virus (*Human Immunodeficiency Virus)* is the causal reason for the AIDS desease.[1] The HIV protease belongs to the class of aspartate proteases, which cleaves the *gag*- and *gag-pol*- polyproteins (encoded by the *pol*- gene of the virus) into structural and functional proteins, which in turn are required for function of the mature virus.[2] Inhibition of the HIV protease results in the production of non-infectious virions,[3] which makes the HIV protease an important drug target for the treatment of AIDS.[2, 4] Due to the fact that the HI virus rapidly develops resistance against new drug molecules there is an ongoing need for new chemical entities.[5]



Acyclic Inhibitor **Type I**

Scheme 1

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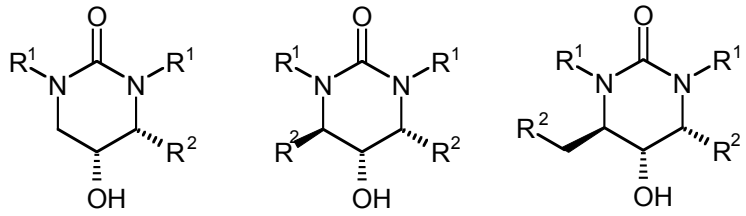
Dedicated to Professor A. I. Meyers on the occasion of his 70th birthday.

All HIV protease inhibitors of the first generation contained typical peptidomimetic structure elements. Coworkers of the *Merck Dupont* company could demonstrate that not only the acyclic molecules depicted in **Scheme 1** were excellent HIV protease inhibitors but also their corresponding cyclic analogues of **type I** if all stereogenic centers were inverted at the same time.[6]

According to the C_2-symmetry of the HIV protease active site **type I** inhibitors retain the same symmetry. It was shown that the *trans* diaxial arrangement of both R^2 residues was not only the preferred conformation of the free molecule but also crucial for good enzyme inhibition.

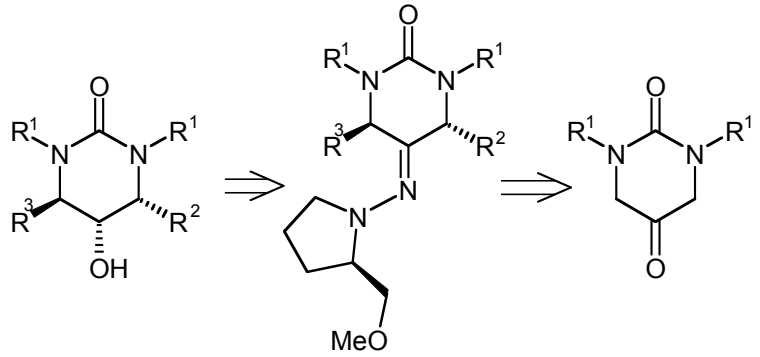


Scheme 2

Investigation of the influence of different ring sizes resulted in **type III** inhibitors with low potency (**Scheme 2**). As expected in the six membered ring case the residues R^2 cannot be arranged in a *trans* diaxial manner and therefore are responsible for the low affinity to the HIV protease. However it was possible to nearly retain potency by simply introducing an additional methylene group on one of the two R^2 groups (**type IV** inhibitors). This additional CH_2 group functions as a joint to turn R^2 into a pseudoaxial position.

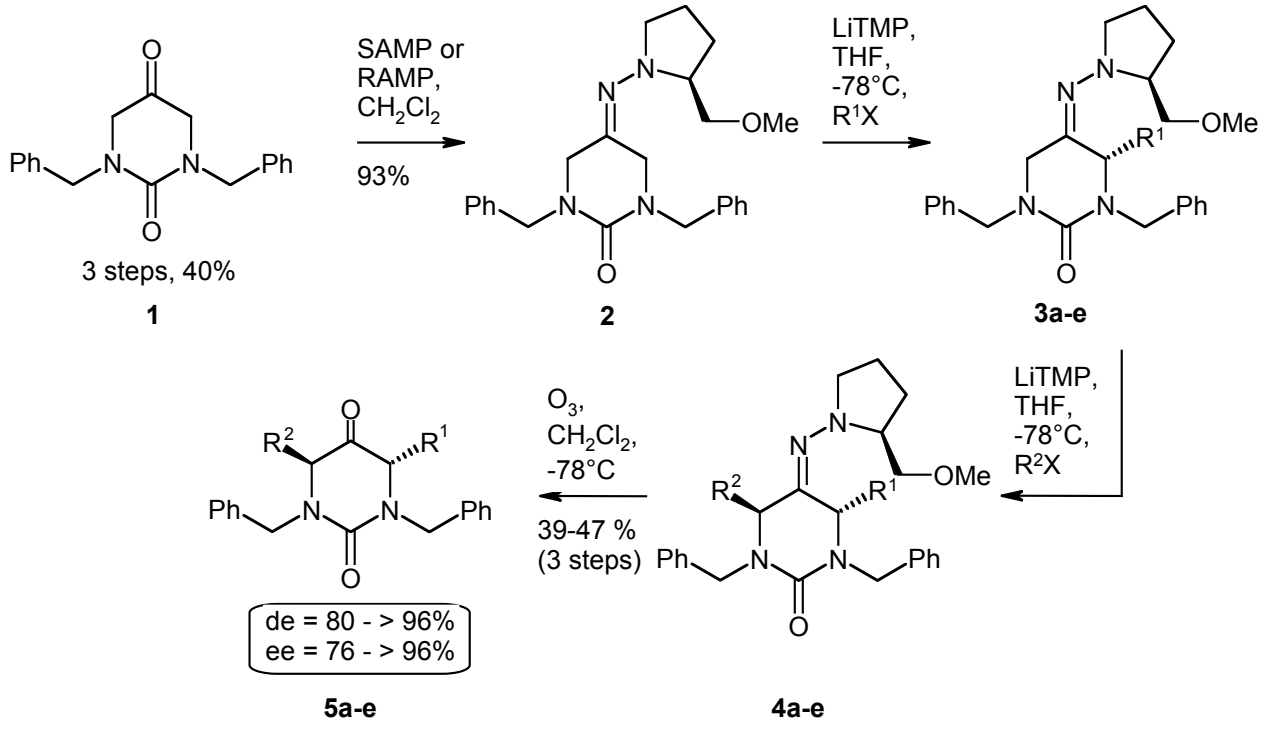
Retrosynthesis: After our efforts to develop a new asymmetric synthesis of an acyclic HIV protease inhibitor[7] we became interested in sythesizing **type II-IV** inhibitors. It was desired that our synthesis should be short, efficient, and allow a high versatility in the choice of the substitution pattern as well as free choice of the absolute configuration. Our retrosynthetic strategy was to utilize one central key building block to built up inhibitors of **type II**, **III** and **IV**. Based on our results of the double alkylation of dioxanones leading to C_2-symmetrical chiral 1,3-diols[8] we wanted to apply this idea in the double alkylation of corresponding nitrogen containing heterocycles (**Scheme 3**). Recently we described the first

asymmetric synthesis of **type II** inhibitors as well as an efficient and practical synthesis of key building block **B**.[9]



Scheme 3

The method of choice for the auxiliary directed double alkylation of central building block **B** was the RAMP-/SAMP-hydrazone method.[10] This methodology has proven to have an enormous scope to use even unreactive electrophiles such as organic halides with α-oxygen or β-branching.



Scheme 4

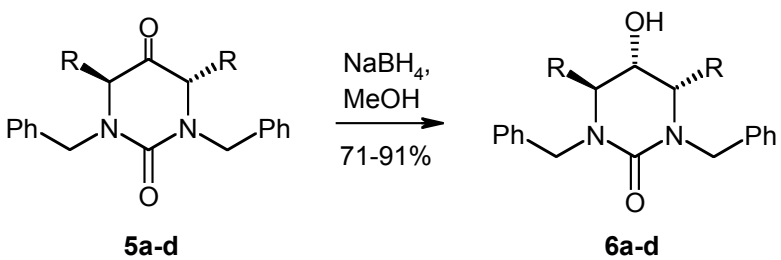
Results and Discussion

We started our synthesis from the achiral key building block (**1**) (**Scheme 4**), which can be readily prepared in three steps (40 percent yield) on multigram scale from commodity chemicals.[9] Simply stirring ketone (**1**) with either hydrazine SAMP or RAMP provides hydrazone (**2**) in almost quantitative yield.[10] The first alkylation is best carried out in THF at –78 °C with LiTMP (lithium tetramethylpiperidide) as base. The reaction was not allowed to reach ambient temperature but was quenched at –78 °C with saturated aqueous NH_4Cl solution. The diastereomeric excess of the reaction could not be determined on this step as one obtained a mixture of the (*E*)- and the (*Z*)-configured hydrazone (**3**). The second alkylation is carried out in the same manner to provide **4**. Attemps to alkylate **2** directly with two equivalents of base and electrophile failed and gave a complex mixture of products. To cleave the hydrazone auxiliary a number of useful methods are known.[11] The method of choice in our case was to ozonize **4** at –78 °C. The diastereomeric excess (de) of **5** has been determined by ^{1}H-NMR-analysis and lies in the range of 80 - > 96% (**Table 1**). The enantiomeric excess (ee) was determined by ^{1}H-NMR-shift experiments with (-)-*Pirkle* alcohol.[19]

Table 1

5	R^1	R^2	Electrophile	Yield over 3 steps [%]	de [%]	ee [%]
5a	i-Pr	i-Pr	i-PrI	43	>96	86
5b	n-Bu	n-Bu	n-BuI	39	>96	>96
5c	Bn	Bn	BnBr	40	>96	76
5d	PhEt	PhEt	PhEtI	47	>96	86
5e	Bn	PhEt	BnBr/PhEtI	34	80	76

The C_2-symmetrical ketones (**5a-d**) could be transformed into their corresponding alcohols (**6a-d**) using standard sodium borohydride reduction[13] (**Scheme 5**). The yields of the reduction are shown in **Table 2**. In this manner ,the synthesis of **type III** HIV protease inhibitors was completed.



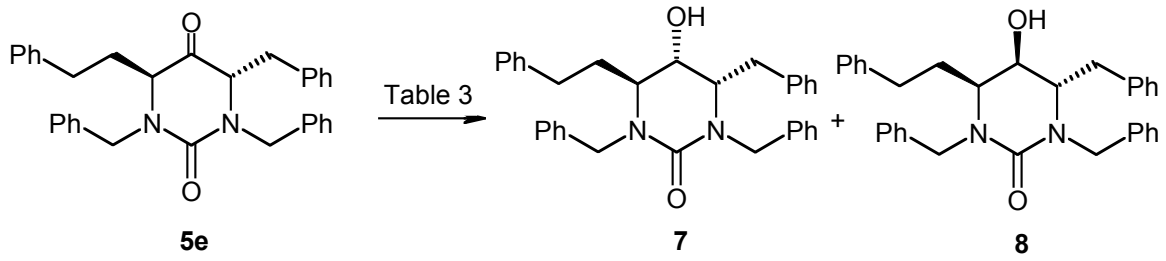
5a-d **6a-d**

Scheme 5

Table 2

6	Rest R	Yield [%] of the Reduction
6a	i-Pr	71
6b	n-Bu	85
6c	Bn	82
6d	PhEt	91

The reduction of the unsymmetrical system (**5e**) (**Scheme 6**) leads to a new stereogenic center. As the benzyl and the phenylethyl residue in **5e** have similar bulk it was ambitious to find an appropriate reduction reagent leading to a high diastereoselection.



5e **7** **8**

Scheme 6

The reagents which were examined for the diastereoselective reduction of **5e** leading to the two diastereomeric alcohols (**7** and **8**) are listed in **Table 3**.

Table 3

Reaction conditions	**Diastereomeric Ratio 7 : 8**
$LiAlH_4$, Ether, 0 °C[12]	1 : 2
$NaBH_4$, MeOH, 0 °C[13]	1 : 2
(L)-Selectride, THF, -78 °C to rt[14]	0 : 100
Superhydride, THF, Ether, -78 °C to rt[15]	1 : 8.7
Catecholborane, Ether, -78 °C to rt[16]	1.5 : 1
BH_3-SMe_2, THF, Ether, rt[17]	1.6 : 1

One can see that the best results were obtained with (L)-Selectride (minor diastereomer could not be detected by ^{1}H-NMR) in favour of diastereomer (**8**) (89% yield). The selectivity could be partly reversed if borane reagents were used, however the diastereomeric ratio (dr 1.6 : 1) was not very high. The relative stereochemistry could be elaborated by comparison with literature data.[18] Thus, the first asymmetric synthesis of inhibitors of **type IV** was completed.

Conclusion

With our asymmetric synthesis, we have developed a highly efficient route to HIV-protease inhibitors of **type III and IV** starting from one central building block. The synthesis is short and flexible with good to excellent diastereomeric and enantiomeric excesses.

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