diisopropylamine and 0.35 g (4 mmol) LiBr in 15 mL anhydrous THF at 0 °C under argon) cooled to −78 °C was slowly added dropwise a solution of 0.95 g (2 mmol) hydrazone (*S*)-**2b** dissolved in 3–4 mL THF, and the reaction mixture was stirred at this temperature for 1–2 h. The resulting solution was cooled to −90 °C and 2.2 mmol of the aldehyde dissolved in 2 mL THF added slowly. The reaction mixture was held at −90 °C for 1–2 h, allowed to warm to −78 °C, stirred at this temperature for 1 h, and then hydrolyzed with 2 mL saturated NH_4Cl solution. The mixture was warmed to room temperature and diluted with 150 mL ether. The organic phase was washed with 10 mL water, buffer solution (pH 7), and saturated NaCl solution, and dried over $MgSO_4$. After removal of the solvent in vacuo the product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate 4:1). For the introduction of the benzyloxymethyl (BOM) protecting group, 1 mmol of the aldol product was dissolved together with 14 mg (0.1 mmol) nBu_4NI in 10 mL anhydrous CH_2Cl_2, and 0.52 g (4 mmol) *N*-ethyldiisopropylamine and 0.47 g (3 mmol) benzylchloromethylether were slowly added in that sequence. The resulting solution was heated at reflux for 12–15 h. After the reaction was complete the solution was treated with 2 mL methanol to quench the excess chloride, stirred for 2 h at room temperature, and concentrated. The residue was dissolved in 150 mL ether, the solution then washed with 10 mL of saturated NH_4Cl solution and 10 mL saturated NaCl solution, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate 95:5). For cleavage of the auxiliary, 1 mmol of the hydrazone was dissolved in ca. 50 mL CH_2Cl_2 and cooled to −78 °C under argon. Ozone was passed through the solution at this temperature until the reaction was complete. After removal of the excess ozone by purging with a stream of argon, the reaction mixture was warmed to room temperature, and concentrated. The product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate/2-propanol 90:10:1).

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[17] Suitable crystals for the X-ray structure analysis were obtained by crystallization from methanol at 2 °C. Monoclinic, space group $P2_1(4)$, $a = 10.940(1)$, $b = 15.822(2)$, $c = 23.817(4)$ Å, $\beta = 92.42(1)°$. From the cell volume of 4118.9 Å^3, two independent molecules in the asymmetric unit, and $M_r = 680.98$ a density of $\varrho_{calc} = 1.098$ g cm^{-3} can be calculated. Total electron count per unit cell $F(000) = 1488$. Enraf-Nonius CAD4 four-circle diffractometer, graphite monochromator, $\Omega/2\theta$ scans, −50 °C, $Cu_{K\alpha}$ irradiation ($\lambda = 1.54179$ Å), $\mu = 5.42$ cm^{-1}. A total of 7218 independent reflections ($\pm h + k + l$), of which 6518 were observed ($I > 2\sigma(I)$), $R_m = 0.008$, $\sin\theta/\lambda_{max} = 0.620$. The structure solution was obtained with direct methods (SHELXS-86[23]) and the refinement by application of the routines of the SDP program package[24]. The two independent molecules differ considerably in the conformation of the substituents at C3A,B of the five-membered ring. For the phenyl groups C12A,B-C17A,B the ideal positions were calculated because of disorder in the atoms C14A,B-C16A,B and the substituents refined isotropically as rigid groups. Hydrogen atom positions were calculated. For the refinement 783 parameters were used, $R = 0.089$ ($R_w = 0.120$). Isotropic extinction coefficient $a = 2.2 \times 10^{-6}$. Residual electron density is largely localized in the region of the phenyl groups C12A,B-C17A,B, maximum value 0.45 e Å^{-3}. Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information GmbH, D-W-7514 Eggenstein-Leopoldshafen 2 (FRG) on quoting the depository number CSD-56869, the names of the authors, and the journal citation.

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Diastereo- and Enantioselective Synthesis of C_2-Symmetrical HIV-1 Protease Inhibitors**

By *Dieter Enders*,* *Udo Jegelka*, and *Barbara Dücker*

Since the Center for Disease Control in Atlanta (USA) defined[1] the diagnostic term AIDS (Acquired Immunodeficiency Syndrome) in 1982 only three medications have been authorized for treatment of AIDS: 3′-azido-3′-deoxythymidine (AZT, Wellcome, 1987), 2′,3′-dideoxyinosine (DDI, Bristol Myers Squibb, 1992), and 2′,3′-dideoxycytosine (DDC, Hoffmann LaRoche, 1992), which was recently introduced for limited use. These drugs inhibit the enzyme reverse transcriptase of the human immunodeficiency virus (HIV). Nevertheless, they are only able to prolong somewhat the survival of patients with advanced cases of AIDS. They also lead to considerable side effects (bone marrow damage, neuropathy) and to the generation of more resistant strains of the virus.[2]

Since the solution of its structure in 1989[3] HIV-1 protease has become a new, highly favored target for chemotherapy.[4] This protease belongs to the class of acidic aspartate proteases and has an unusual homodimeric C_2-

[*] Prof. Dr. D. Enders, Dr. U. Jegelka, Dipl.-Chem. B. Dücker
Institut für Organische Chemie der Technischen Hochschule
Professor-Pirlet-Strasse 1, D-W-5100 Aachen (FRG)

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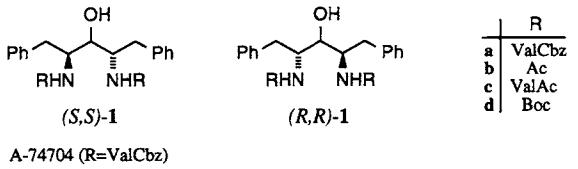
symmetrical structure. Starting from the Phe-Pro cleavage point most frequently preferred by the enzyme, Erickson and Kempf et al.[5] developed the C_2-symmetrical, highly selective HIV-1 protease inhibitor A-74704 (*S,S*)-**1a**. They demonstrated that the marked inhibiting effect of the inhibitor relies on its optimal fit in the active center of the C_2-symmetrical protease. Derivatives with other substituents at the amino group, for example (*S,S*)-**1b** and -**1c**,[6] are also active compounds.



A-74704 (R=ValCbz)

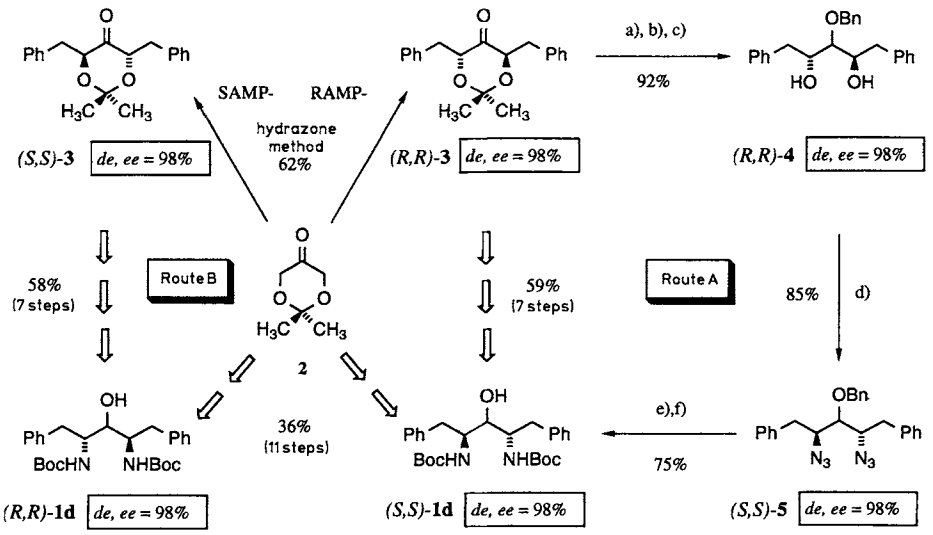
We report here on a new, highly diastereo- and enantioselective entry to C_2-symmetrical HIV-1 protease inhibitors of type **1**. To demonstrate the process both enantiomers of the *tert*-butyloxycarbonyl (Boc)-protected diaminoalcohol **1d** and the racemate *rac*-**1d** (dimethylhydrazone method[11]) were synthesized from the dibenzylated ketones (*R,R*)- and (*S,S*)-**3** (*de*, *ee* = 98%). The compounds (*R,R*)- and (*S,S*)-**3** were prepared from the dihydroxyacetone derivative **2**[7-9] according to the SAMP/RAMP-hydrazone method[10] in four steps and in over 60% yield.

As shown in Scheme 1 (Route A), ketone (*R,R*)-**3** was reduced with lithium aluminum hydride to provide the alcohol, which was then protected as the benzylether, and hydrolyzed under acidic conditions to release diol (*R,R*)-**4** (*de*, *ee* = 98%, overall yield 92%). Attempts to obtain bisazide (*S,S*)-**5** via a bismesylate, itself available quantitatively, with sodium azide in dimethylformamide (20 h, 90 °C), gave **5** and the corresponding HN_3-elimination product in the unfavorable ratio of 1:1. We produced (*S,S*)-**5** with double inversion in 85% yield (*de*, *ee* = 98%) by converting **4** into the bistriflate with trifluoromethanesulfonic acid anhydride (Tf_2O) and substituting with tetramethylguanidinium azide[12] in dichloromethane. In both cases the elimination product could be separated easily by chromatography. The bisazide was ultimately converted to the Boc_2-protected diamine by hydrogenation in the presence of a catalytic amount of Pd/C and 2.4 equivalents of Boc_2O. When ethyl acetate was employed as solvent, then the completely *N*-Boc- and *O*-Bn-protected diaminoalcohols were obtained in 75% yield. Subsequent hydrogenation in methanol led quantitatively to (*S,S*)-**1d** in almost diastereo- and enantiomerically pure form; (*R,R*)-**1d** was prepared by use of the corresponding auxiliary SAMP (Route B). The overall yield of **1d**, best characterized as the 3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (MTPA) ester,[13] is 58–59% starting from **3** and 36% based on **2** (Scheme 1).

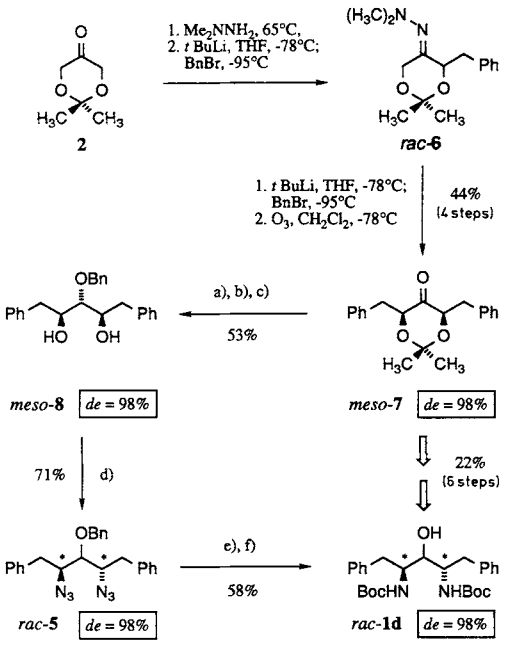
When the hydrogenation of (*S,S*)-**5** was conducted in methanol, a 75% yield of the unprotected diaminoalcohol (*S,S*)-**1** (R = H) was obtained, which can be converted into the C_2-symmetrical HIV-1 protease inhibitor A-74704 (*S,S*)-**1a** according to Kempf et al.[6] and Dreyer et al.[14] Since in the previously described syntheses either L-phenylalanine[6] or D-arabitol[14] were incorporated into the final product, Route A described here provides an entry to the first asymmetric synthesis of A-74704, and at the same time Route B allows a flexible and efficient access to its enantiomer.

For synthesis of the racemate of **1d** the *meso* compound **7** was first prepared in four steps from **2** by the dimethylhydrazone method[11] with an overall yield of 44%. In contrast to the *trans* double alkylation of simple cyclic ketones via the *N,N*-dimethylhydrazone (DMH) derivatives, the α,α-dibenzylation of **2** via *rac*-**6** provided the *cis* product and thereby *meso*-**7** (*de* = 98%) diastereoselectively. After conversion to the mono-protected triol *meso*-**8** (*de* = 98%) analogous to that shown in Scheme 1, bisazide *rac*-**5** was obtained in 71% yield by a Mitsunobu reaction in the presence of zinc azide and diisopropylazidocarboxylate.[15] In this Mitsunobu reaction only one stereogenic center is generated by inversion and the other with retention. This can be explained by invoking an S_Ni reaction: initially, the 1,3-diol is converted into an oxetane ring, which is opened by azide with assistance by Zn^{2+} (retention). The azidoalcohol formed then undergoes substitution with inversion to give the bisazide.[16] After subsequent hydrogenation in the presence of Boc_2O in analogy to that in Scheme 1, *rac*-**1d** was obtained (*de* = 98%) (Scheme 2).

The asymmetric syntheses described here provide an efficient and stereochemically flexible entry to C_2-asymmetric HIV-1 protease inhibitors. The inhibiting effect and the pharmacological properties of these new agents may possibly be improved further for the treatment of AIDS, as certain properties can be varied almost at will:[17] the stereogenic center, which can be selected by the choice of the



Scheme 1. Enantioselective synthesis of C_2-symmetrical protease inhibitors. a) $LiAlH_4$, Et_2O, room temperature (RT), 99%; b) NaH, BnBr, Bu_4NI, THF, 15 h, quant.; c) 3 N HCl, MeOH, RT, 93%; d) 1. Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h, 2. tetramethylguanidinium azide, CH_2Cl_2, −78 → 0 °C; e) H_2, Pd/C, Boc_2O, EtOAc, RT, 12 h, 75%; f) H_2, Pd/C, MeOH, RT, quant.



Scheme 2. Synthesis of the racemic protease inhibitor *rac*-**1d**. a), b), c), e), f) as in Scheme 1; d) $Zn(N_3)_2 \cdot Py$, Ph_3P, $iPrO_2C-N=N-CO_2iPr$, toluene, RT, 5 h.

auxiliary (SAMP/RAMP); the side chain (here $PhCH_2$), by the choice of electrophile;[7-9] and the substituents on the amino group.[3, 6]

Experimental Procedure

(*S,S*)- and (*R,R*)-**1d**: Compound **3** [9] (1.50 g, 4.8 mmol) was dissolved in 3 mL Et_2O and added dropwise to a suspension of 0.5 equiv (0.09 g) lithium aluminum hydride in 25 mL Et_2O at room temperature (RT). After 3 h the reaction mixture was hydrolyzed with 100 mL water, stirred for 15 min, and extracted with ether (3 × 200 mL). The organic phase was washed with saturated solutions of $NaHCO_3$ and NaCl, then dried over $MgSO_4$. After removal of the solvent and chromatography (silica gel, ether/petroleum ether 1:2), 1.50 g (99%) of the alcohol was obtained. This compound was dissolved in 60 mL THF, and treated with 2 equiv NaH and 0.02 equiv Bu_4NI at 0°C. After the reaction mixture was allowed to warm to RT, 4.9 mmol benzylbromide was added dropwise. After 15 h, 9.6 mL of a 20% KOH solution and a spatula tip of SiO_2 were added. The gelatinous precipitate was removed by filtration, the aqueous phase extracted with ether, and the combined organic phases dried over $MgSO_4$. After concentration and chromatography (silica gel, ether:petroleum ether 1:20), 1.93 g (100%) of the benzylether was obtained. This was dissolved in 10 mL methanol, stirred for 0.5 h with 10 mL of 3N HCl, and then neutralized with solid $NaHCO_3$. After the crude mixture was extracted with ether, the organic phase was dried over $MgSO_4$ and concentrated. Chromatographic purification (silica gel, ether/petroleum ether 2:1) gave 1.61 g (93%) **4**. After dissolution in 22 mL CH_2Cl_2, **4** was treated with 2.0 mL trifluoromethanesulfonic acid anhydride (Tf_2O) at −78°, then 5 min later with 1.5 mL 2,6-lutidine. The reaction mixture was stirred for 30 min, before a further 0.2 mL Tf_2O and 0.15 mL 2,6-lutidine were added. After a further 30 min a solution of tetramethylguanidinium azide (4.1 g dissolved in 22 mL CH_2Cl_2) was added dropwise. The reaction mixture was left to stand for 15 min, allowed to warm to 0°C, and stirred at this temperature for a further 2 h. The crude mixture was filtered through silica gel and evaporated to dryness. Chromatography (silica gel, ether/petroleum ether 1:10) gave 1.54 g (85%) **5** as a colorless oil. To a mixture of 0.05 g Pd/C (10%) in 1 mL ethyl acetate at RT under hydrogen was added dropwise a solution of 0.24 mmol **5** and 2.4 equiv Boc_2O in 4 mL ethyl acetate. After stirring for 12 h, filtration through Celite, and chromatography (silica gel, ether/petroleum ether 1:4), 0.1 g (75%) of the triply protected diaminoalcohol was obtained as colorless crystals, m.p. 125°C (petroleum ether); $[\alpha]_D^{23}$ + 23.5 (*c* = 1.0, $CHCl_3$) for the compound with (*R,R*) configuration. Subsequent debenzylation by hydrogenation [0.05 g Pd/C (10%), H_2, 5 mL MeOH, 3 h] gave 0.08 g **1d** (quantitative); MTPA derivative [18]: colorless oil, $[\alpha]_D^{23}$ +19.39 (*c* = 0.98, $CHCl_3$) (*R,R*).

rac-**1d**: Compound **2** (26.0 g, 0.2 mol) was heated with 3 equiv *N,N*-dimethylhydrazine under reflux at 65°C for 20 h. The reaction mixture was concentrated and dissolved in 400 mL ether and washed with water. The organic phase was dried over $MgSO_4$, the solvent removed, and the residue purified by distillation to give 29.9 g (87%) of the DMH derivative of **2** (pale yellow oil, b.p. 57°C/2.25 Torr). This compound (20 mmol) was treated with *t*BuLi and BnBr (under the conditions given ref. [9] for the SAMP hydrazones) and the crude α,α-bisalkylated product oxidatively cleaved with ozone in CH_2Cl_2 at −78°C. After chromatography (silica gel, ether/petroleum ether 1:30), 2.94 g (44% based on **2**) of *meso*-**7** (*de* = 98%) was obtained as a colorless oil. Conversion into *meso*-diol **8** was achieved in similar manner to that described for **4**. For the substitution with zinc azide according to Mitsunobu [16] 0.63 g (1.71 mmol) *meso*-**8** was used. Chromatographic purification gave 0.42 g (71%) of *rac*-**5** (*de* = 98%) as colorless crystals, m.p. 91°C (petroleum ether). Conversion to *rac*-**1d** followed in similar fashion to that used for (*R,R*)-**1d**; 0.33 g (58%).

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Silylamines with Pyramidal Coordination at Nitrogen**

By *Karin Ruhlandt-Senge, Ruth A. Bartlett, Marilyn M. Olmstead*, and *Philip P. Power**

The nature of the Si–N bond in silylamines has been a subject of considerable interest[1] since the planar structure of $N(SiH_3)_3$ was originally established in 1951.[2] For several

[*] Prof. P. P. Power, Dr. K. Ruhlandt-Senge, R. A. Bartlett, Dr. M. M. Olmstead
Department of Chemistry, University of California
Davis, CA 95616 (USA)

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