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Stereocontrolled Synthesis of Pseudo C_2-Symmetric 1,3-Diamino-2-propanol Core Units of HIV Protease Inhibitors

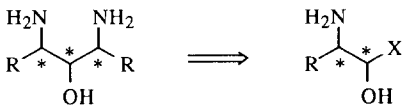
Alessandro Dondoni * and Daniela Perrone

Dipartimento di Chimica, Laboratorio di Chimica Organica , Università, Ferrara, Italy.

Abstract: The synthesis of the pseudo C_2-symmetric dibenzyldiamino alcohol (*S,S*)-**1** and the two *meso* stereoisomers **1a** and **1b** (R = $PhCH_2$) is described by stereocontrolled benzylmagnesium chloride addition to the nitrones **3** derived from chiral β–amino-α-hydroxy aldehydes **2** that in turn were obtained from phenylalanine; the overall yield of (*S,S*)-**1** is 23% from *N*-Boc L-phenylalaninal; the antipode (*R,R*)-**1** can be prepared in a similar way starting from the D-isomer of the same α-amino aldehyde.

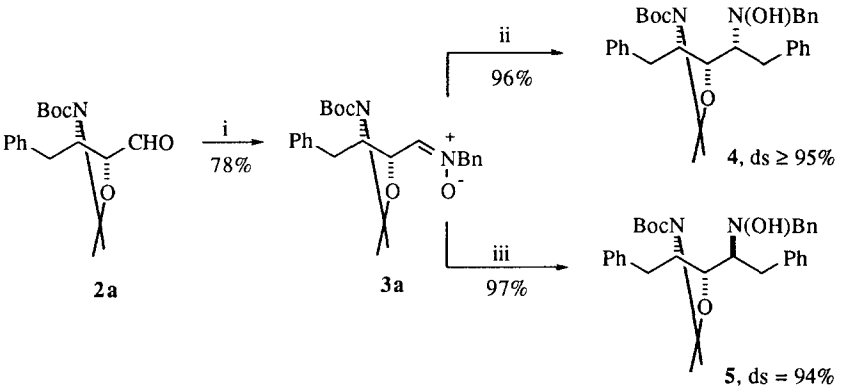
The recognition that the aspartic proteinase encoded by the human immunodeficiency virus of type 1 (HIV-1) exists in its active form as a two-fold symmetric homodimer has stimulated in recent years the design and synthesis of C_2 symmetric inhibitors of that enzyme.[1] The 1,3-diamino-2-propanol moiety **1** proved to be the key core unit of very potent and selective inhibitors of both protease activity and acute HIV-1 infection in vitro. For instance, the *N*-ValCbz derivative of (*S,S*)-**1** (R = benzyl, A74074) developed by Erickson and Kempf[1b] et al. at Abbott Laboratories in US was at least 10,000-fold more potent against HIV-1 protease than against related enzymes. Derivatives of type **1** with other susbstituents at the amino group and at the propanol moiety were also active compounds. Stereoselective syntheses of these pseudo C_2-symmetrical core units have been reported[2] starting from phenylalanine and therefore exploiting the configuration of the α-amino acid for the stepwise construction of the new stereocenters.[3] A recent asymmetric approach to both stereoisomers (*S,S*)- and (*R,R*)-**1** described by Enders is based on the SAMP/RAMP-hydrazone method for the enantioselective construction of chiral intermediates which are then diastereoselectively converted into the target products.[4]

We report here on a new, highly diastereoselective entry to the two chiral pseudo C_2 symmetric and the two *meso* stereoisomers **1** (R = benzyl) that develops from the ready access to β-amino-α–hydroxy aldehydes **2** through the thiazole-based homologation of amino acids.[5] The method involves the installation of the amino group by stereocontrolled alkylation of the aldehyde nitrones **3**. This new method of introduction of the amino group at a saturated carbon center by stereoselective addition of organometals to chiral nitrones proved to be very useful in amino sugar,[6] polyalkoxy α-amino acid,[7] and carbon linked glyco α-amino acid[8] synthesis.



1 **2**, X = CHO
3, X = CH=N(O$^-$)$^+$R'

We first focussed on the synthesis of (*S,S*)-**1** featured by A74074. The protected 3-amino-2-hydroxy phenylbutanal **2a** was prepared from *N*-Boc L-phenylalaninal by the stereoselective thiazole aldehyde synthesis[9] in 42% yield. Crude **2a** was readily converted into the stable and crystalline *N*-benzyl nitrone **3a** [mp 125-126 °C; $[\alpha]_D$ + 17.7° (*c* 0.6, $CHCl_3$)] by reaction with *N*-benzylhydroxylamine (Scheme 1).[10] The benzylmagnesium chloride addition to **3a** in diethyl ether at -55 °C occurred with high selectivity to give *syn* and *anti N*-benzylhydroxylamines **4** and **5** in 95 : 5 ratio. The configuration of the newly formed stereocenter of the major adduct **4** was tentatively assigned on the basis of earlier addition reactions of organometallic reagents to chiral nitrones.[6-8] When the Grignard reagent was added under the same conditions (Et_2O, -78 °C) to the nitrone **3a** precomplexed with 1 equiv. of diethylaluminum chloride, the reaction still showed high stereoselectivity but in the opposite direction since the *syn* and *anti* adducts **4** and **5** were obtained in a 6 : 94 ratio. In both cases the *syn : anti* ratio remained unchanged by lowering the reaction temperature down to -100 °C. Pure hydroxylamines **4** and **5** were isolated in 90 and 87% respectively by flash chromatography (silica, cyclohexane-EtOAc 9:1) of their crude reaction mixtures.

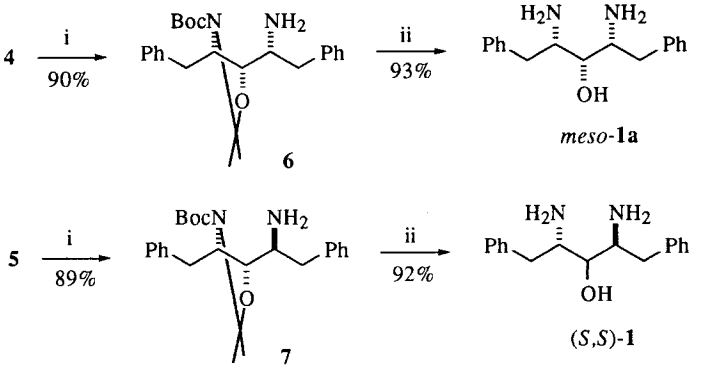


Scheme 1. Reagents and conditions: (i) $PhCH_2NHOH$, $MgSO_4$, CH_2Cl_2, 30 min; (ii) $PhCH_2MgCl$, Et_2O, -55 °C, 3 h; (iii) Et_2AlCl, Et_2O, rt, 30 min, then $PhCH_2MgCl$, -78 °C, 3 h.

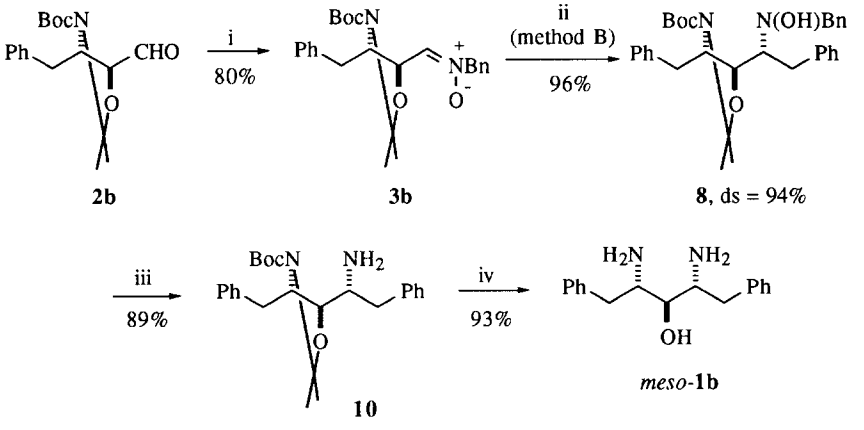
The conversion of **4** and **5** to amines **6** and **7** was efficiently carried out by low pressure hydrogenolysis over $Pd(OH)_2$ (Scheme 2). This method appeared operatively more simple and gave products in higher yields (ca. 90%) than the earlier procedure[6-8] employing $TiCl_3$. Finally, the simultaneous removal of the isopropylidene and *t*-butoxycarbonyl protective groups by acid treatment of amines **6** and **7** afforded the free diamino alcohols *meso*-**1a** and (*S,S*)-**1** respectively which were isolated by flash chromatography (silica, CH_2Cl_2-MeOH-NH_4OH 89:10:1) in excellent yields. The ^1H NMR spectra of these compounds were fully consistent with their structure as were their physical properties with the available literature data.[11] The calculated overall yield (23%) of isolated (*S,S*)-**1** from *N*-Boc L-phenylalaninal is comparable to that reported[2a] from *N*-Boc L-phenylalanine methyl ester (26%). Quite obviously the antipode (*R,R*)-**1** can be obtained in a similar way starting from the *R* enantiomer of the same α-amino aldehyde.

Guided by the above results, we sought the oportunity for an alternative approach to (*S,S*)-**1** via *syn* stereoselective addition of benzyl magnesium chloride to the *N*-benzyl nitrone **3b** in the absence of a precomplexing agent. The absolute configuration at the nitrone α-carbon is unimportant in this synthesis since this is lost in the target pseudo C_2-symmetric product.[3] Also the nitrone **3b**, a stable and crystalline compound

[mp 153-154 °C; $[\alpha]_D$ -108.9° (*c* 0.3, $CHCl_3$)] was obtained in good yield by the *N*-benzylhydroxylamine method from the corresponding aldehyde **2b**[12] (Scheme 3). Unexpectedly, the addition of the Grignard reagent to this nitrone in Et_2O at -78 °C (method A) turned out to be unselective since it produced a mixture of *anti* and *syn N*-benzylhydroxylamines **8** and **9** in ca 1:1 ratio.[13] In spite of the failure of this approach to (*S,S*)-**1**, the nitrone **3b** proved to be a useful vehicle for the synthesis of the remaining forth stereoisomer *meso*-**1b**. The precomplexation of **3b** with diethylaluminum chloride followed by the addition of benzyl magnesium chloride (method B) afforded the *anti*-adduct **8** with high diastereoselectivity. Pure hydroxylamine **8** was isolated in 90% yield by flash chromatography (silica, cyclohexane-EtOAc 9:1) and then converted into *meso*-**1b** through the amine **10** as detailed in Scheme 3. The ^1H NMR of *meso*-**1b** was consistent with its structure.[14]



Scheme 2. Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2$, AcOH/EtOH (90%), 15 h; (ii) HCl/dioxane (4.8 M), 0 °C then rt, 20 h.



Scheme 3. Reagents and conditions: (i) $PhCH_2NHOH$, $MgSO_4$, CH_2Cl_2, 30 min; (ii), method A : $PhCH_2MgCl$, -78 °C, 3 h; method B : Et_2AlCl, Et_2O, rt, 30 min, then $PhCH_2MgCl$, -78 °C, 3 h; (iii) H_2 (1 atm), $Pd(OH)_2$, AcOH/EtOH (90%), 15 h; (iv) HCl/dioxane (4.8 M), 0 °C then rt, 20 h.

In conclusion, the results presented here provide practical, stereoselective syntheses of the four possible stereoisomers of the dibenzyl substituted 1,3-diamino-2-propanol unit **1**. The reactions were scaled up to produce gram quantities of the final products. These include the chiral stereoisomer (*S,S*)-**1**, and consequently

(*R,R*)-**1**, whose relevance as precursors to HIV-1 inhibitors has been already demonstrated. Given the access to various chiral β-amino-α-hydroxy aldehydes by the thiazole-aldehyde synthesis,[5] this new synthetic method should be amenable to the production of pseudo C_2-symmetric compounds **1** with a wide range of substituents.

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References and Notes

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3. By virtue of its symmetrical characteristics, the central carbon becomes nonstereogenic in the final product.
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9. Three steps : 1) addition of 2-(trimethyl)silylthiazole to the aldehyde (ref. 5d); 2) isolation of the *syn* adduct through the formation of the oxazolidine derivative (DMP / CSA, toluene, 120 °C, 14 h) ; 3) thiazolyl-to-formyl conversion (Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275). Crude aldehyde **2a** was judged to be 90% pure by ^{1}H NMR analysis.
10. All new compounds reported in this and the following Schemes gave satisfactory elemental analysis (C, H, N) and ^{1}H and ^{13}C NMR spectra (300 MHz).
11. *meso*-**1a**: mp: 106-107 °C; ^{1}H NMR ($CDCl_3$) δ: 2.59 (dd, 2 H, *J* = 9.0, 13.5 Hz), 2.92 (dd, 2 H, *J* = 5.0, 13.5 Hz), 3.09 (ddd, 2 H, *J* = 3.5, 5.0, 9.0 Hz), 3.31 (t, 1 H, *J* = 3.5 Hz), 7.15-7.40 (m, 10 H).
(*S,S*)-**1**: mp: 138-139 °C; [lit.[2a] mp 135-137 °C]; $[\alpha]_D$ -11.1° (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.50 (dd, 1 H, *J* = 10.1, 13.4 Hz), 2.65 (dd, 1 H, *J* = 9.6, 13.4 Hz), 2.91 (dd, 1 H, *J* = 4.6, 13.4 Hz), 3.01 (dd, 1 H, *J* = 3.2, 13.4 Hz), 3.08-3.20 (m, 1 H), 3.31-3.43 (m, 2 H), 7.15-7.45 (m, 10 H).
12. The aldehyde **2b** was obtained in 50% yield by acetonization (2-methoxypropene, CSA, toluene, 80 °C) of its thiazole masked precursor (compound *anti*-**23** in ref. 5d) and the usual thiazolyl-to-formyl deblocking sequence (ref. 9). The purity of **2b** was judged to be 90% by ^{1}H NMR.
13. Compounds **8** and **9** (the latter is not shown in Scheme 3) were not separated.
14. *meso*-**1b**: mp 131-133 °C; ^{1}H NMR ($CDCl_3$) δ: 2.52 (dd, 2 H, *J* = 10.1, 13.5 Hz), 3.17 (dd, 2 H, *J* = 3.0, 13.5 Hz), 3.29 (ddd, 2 H, *J* = 3.0, 5.7, 10.1 Hz), 3.39 (t, 1 H, *J* = 5.7 Hz), 7.17-7.40 (m, 10 H).

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