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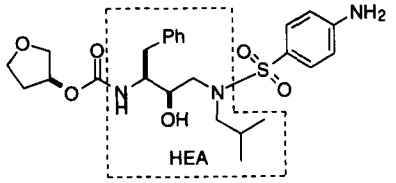
An Expeditious Synthesis of (2*R*,3*S*)-3-*tert*-Butoxycarbonylamino-1-isobutylamino-4-phenyl-2-butanol, a Key Building Block of HIV Protease Inhibitors

Norio Shibata, Tadashi Katoh, and Shiro Terashima*

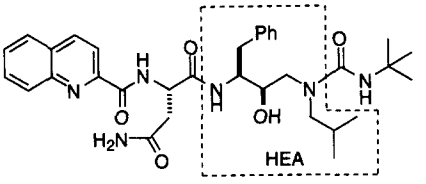
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Abstract: The title synthesis was achieved by the diastereoselective addition of an anion produced from *N*-nitroso-*N*-methylisobutylamine with (*S*)-2-*N*,*N*-dibenzylamino-3-phenylpropanal as a key step.

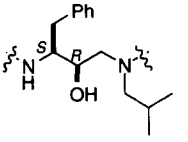
Protease inhibitors such as VX-478[1] and SC-52151[2] involving the hydroxyethylamine (HEA) moiety are very promising therapeutic agents for the treatment of acquired immunodeficiency syndrome (AIDS).[3] These compounds emerged from the drug design based on the transition state mimetic concept and prevent the cleavage of viral polyproteins into active proteins. The cleaving reaction occurs during the process by which the human immunodeficiency virus (HIV) replicates.



VX-478 (Vertex - Glaxo Wellcome)



SC-52151 (Searle - Monsanto)



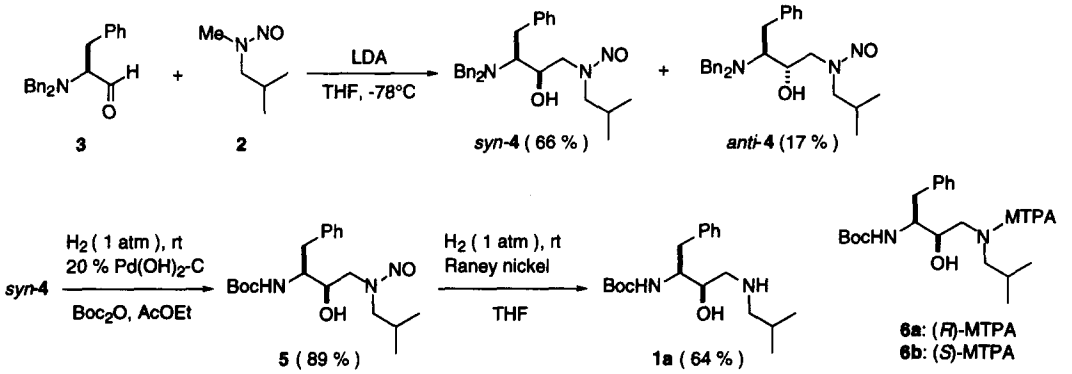
1

Since it appears that the (*R*)-configuration of the hydroxyethyl moiety in HEA isostere (**1**) is crucial for maximum activity, a stereoselective synthesis of **1** has been required. Conceptually, the simplest strategy to construct **1** involves the addition of a carbanion of the methylisobutylamine synthon to the *N*-protected (*S*)-phenylalaninal derivative. However, this straightforward strategy has never been reported for synthesizing **1**.[1b,2,4] Incidentally, *N*-nitrosoalkylmethylamine is synthetically of great potential and its usefulness as the amino carbanion synthon was studied intensively in the 1970s.[5] We, therefore, examined the use of *N*-nitorso-*N*-methylisobutylamine (**2**) as the amino carbanion synthon in the aldol reaction with the *N*-protected (*S*)-phenylalaninal derivative.

The explored synthetic scheme starts with (*S*)-2-*N*,*N*-dibenzylamino-3-phenylpropanal (**3**) prepared from (*S*)-phenylalanine in 3 steps.[4b,c] Treatment of **3** and lithiomethyl-*N*-nitrosoisobutylamine generated *in situ* from **2** with lithium diisopropylamide (LDA) at -78 ℃ furnished the crystalline *syn*-adduct (*syn*-**4**)[6] in 66 % yield along with the *anti*-adduct (*anti*-**4**)[6] (17% yield) after extractive isolation (hexane/AcOEt=1/1) followed by separation with a silica gel column (0-25% AcOEt in hexane). The stereochemistry of the newly generated chiral center involved in *syn*-**4** was determined unambiguously by X-ray crystallography.[7] The observed diastereoselectivity favoring the formation of *syn*-**4** is consistent with the Felkin non-chelation rule for asymmetric induction. The major isomer *syn*-**4** was isolated in more than 40 % yield by single recrystallization from the crude extract.

The dibenzyl groups of *syn*-**4** were subsequently exchanged with a Boc group by hydrogenolysis over Pearlman's catalyst[8] in the presence of Boc_2O. Finally, the *N*-nitroso function of the Boc derivative **5**[6] was

removed in quantitative yield by a Raney nickel catalyst under hydrogen atmosphere.[9] Recrystallization of the crude product from hexane gave the title compound **1a** [mp 107-109 °C, $[\alpha]_D^{20}$ +10.6° (c=0.77, $CHCl_3$)][10] in 64 % yield, which can be utilized as a key intermediate for the synthesis of VX-478[1b] and SC-52151.[2] The optical integrity of **1a** was examined by converting to the corresponding (*R*)- and (*S*)-Mosher amides (**6a** and **6b**) on treatment with (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) in the presence of triethylamine, respectively. Neither of the diastereomers was detected in the 400 MHz ^{1}H-NMR spectra of **6a** and **6b**. Thus, **1a** was obtained as a pure enantiomer.



As described above, we have succeeded in developing an expeditious synthetic route to **1a** by using the diastereoselective addition of an anion of **2** to **3**. The explored overall process may serve as one of the most practical synthetic methods of **1** because of its directness and operational simplicity.

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References and Notes:

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6. The ^{1}H-NMR spectra of **4** and **5** showed two sets of signals due to the *N*-nitroso group, indicating that they consisted of mixtures of (*E*)/(*Z*)-isomers. The ratios of (*E*)/(*Z*)-isomers were found to change under the conditions for purification, i.e., recrystallization or silica gel column chromatography.
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10. The physical data of **1a** were not reported.[1b]

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