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A Convenient Synthesis of 1-(S)-[1'-(S)-(*t*-Butyloxycarbonylamino)-2'-phenylethyl]oxirane. A Useful Building Block in the Synthesis of HIV Protease Inhibitors.

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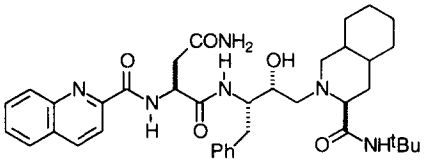
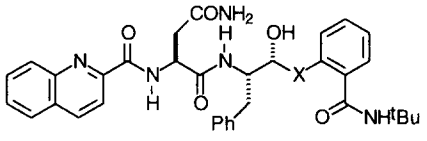
Abstract: A new short route to epoxide **6b**, a pivotal intermediate for the preparation of hydroxyethylamine dipeptide isosteres has been developed. Opening of the epoxide by anthranilic acid, followed by extensions in the P2/P3-region gave the target compounds which were evaluated as HIV-1 protease inhibitors.

The aspartyl protease encoded by the human immunodeficiency virus type 1 (HIV-1) has emerged as an attractive target for chemotherapeutic intervention against the acquired immunodeficiency syndrome (AIDS).[1] HIV-1 protease is intimately involved in viral replication and is essential for the formation of new infectious virus particles.[2] The first HIV protease inhibitor to enter clinical trials, Ro 31-8959, Saquinavir (**1**),[3] has recently been approved for clinical treatment of HIV (Figure 1). In efforts to reduce the structural complexity, P-1' replacements lacking stereogenic centers have been examined. These include LY289612 (**2**),[4] **3**[5] and **4**.[5b] However, to our knowledge, the corresponding nitrogen analogue **5b** has not been previously reported.



1 (Saquinavir)

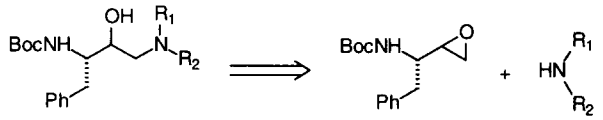


2 X = CH_2 **4** X = CH_2O
3 X = CH_2S **5b** X = CH_2NH

Figure 1

Hydroxyethylamine (HEA) dipeptide isosteres are usually prepared by a convergent approach involving opening of chiral α-aminoalkyl epoxides with amines (Scheme 1).[6] The configuration of the hydroxyl group in the HEA-moiety is usually crucial for maximum antiviral activity. With a few exceptions, the isostere obtained from the 2*S*-isomer **6b** is the more potent. While the 2*R*-isomer **6a** is conveniently

prepared by epoxidation of the corresponding olefin,[7] there is no obvious route to **6b**. Consequently, several synthetic approaches to **6b** have appeared in the literature, however many of these are either lengthy or use inappropriate reagents (i.e. diazomethane).[6,8] In this communication we present an alternative approach to epoxide **6b** from Boc-L-phenylalanine which is short and proceeds in a high overall yield. Epoxides **6a** and **b** were reacted with anthranilic acid *tert*-butylamide to produce some hydroxyethylamine isosteres which were evaluated as HIV protease inhibitors.

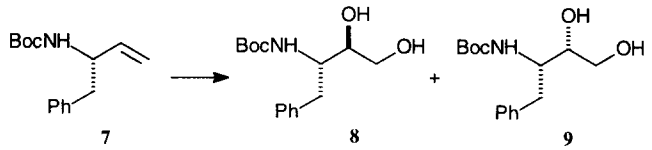


Hydroxyethylamine (HEA) dipeptide isostere

6a (2*R*)
6b (2*S*)

Scheme 1

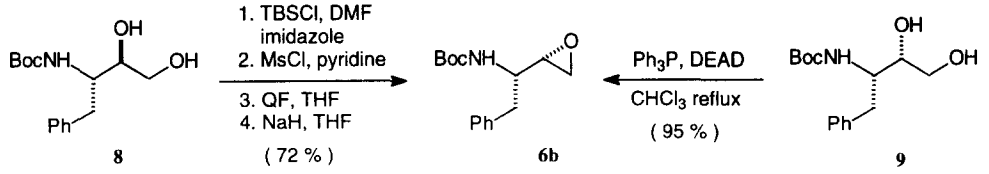
Olefin **7** is readily prepared from Boc-L-phenylalanine methyl ester by DIBAL reduction and Wittig olefination.[9] Dihydroxylation of the olefinic bond in **7** using a catalytic amount of osmium tetraoxide with *N*-methylmorpholine *N*-oxide as reoxidant gave a 1:1.5 mixture of **8** and **9** in an almost quantitative yield (Scheme 2). In contrast to the osmylation of chiral allylic alcohols, which has been thoroughly investigated and usually proceeds with high diastereoselection, osmylations of the corresponding allylamines are much less studied.[10] Our efforts to increase the selectivity have included change of solvent or amino protecting group[11] and double diastereoselection using chiral ligands.[10,12] We were surprised to find that AD-mix α and β,[12] which are expected to give complementary diastereomeric ratios of **8** and **9** characteristic of double diastereoselection, instead generated product mixtures of equal ratios hardly distinguishable from the OsO_4 / MMO reaction. To our knowledge, such anomalous selectivity is rare and have only been observed in a few cases.[13]



Reagent	ratio 8 / 9	tot. yield
OsO_4	1 : 1.5	97 %
AD-mix α	1 : 1.5	95 %
AD-mix β	1 : 1.5	44 %

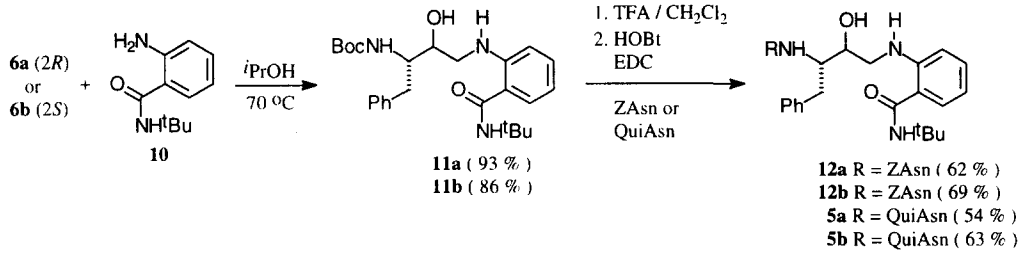
Scheme 2

In contrast to epoxides **6a** and **b**, diols **8** and **9** were easily separated either by column chromatography, or, more conveniently for large scale preparations, by fractional crystallization from toluene. It is noteworthy that, although the stereoselectivity of the osmylation reaction was low, both **8** and **9** were easily converted to the desired isomer **6b**, thus giving a high total yield for the process (Scheme 3). The major isomer **9** was converted to **6b** in 95 % yield using a modified Mitsunobu procedure.[14] For the minor isomer **8**, the primary hydroxyl group was silylated and the secondary hydroxyl mesylated. Desilylation and subsequent treatment with NaH gave **6b** in 72 % yield from **8**.[15] This methodology conveniently provided us with gram quantities of epoxide **6b** for further elaboration.



Scheme 3

Anthranilic acid *tert*-butylamide (**10**) was prepared from anthranilic acid in 62 % yield using standard DCC coupling methodology. Heating **10** with epoxide **6a**[7] in isopropanol overnight gave **11a** in 93 % yield (Scheme 4). Compound **11b** was prepared analogously from epoxide **6b**, or, from **11a** by Mitsunobu inversion of the hydroxyl group. Treatment of **11a** with TFA / dichloromethane (1:1) followed by coupling with Z-Asn or N-(quinolinylcarbonyl)-Asn (QuiAsn) using EDC and HOBt gave **12a** and **5a**[16] in 62 % and 54 % yield, respectively. Compounds **12b** and **5b** were prepared analogously from **11b** in 69 % and 63 % yield, respectively.[17]



Scheme 4

Evaluation of the anti HIV protease activity of the target substances was performed as previously reported.[18] In this test system, compound **5b** was found to be almost as potent as Saquinavir against the HIV protease but its antiviral activity in cell culture was reduced (Table 1).

Compound	Hydroxyl configuration	Enzyme inhibition I_{50} (μM)	Antiviral activity ED_{50} (μM)
11a	*S*	8	na
11b	*R*	2	20
12a	*S*	1.5	na
12b	*R*	0.5	5
5a	*S*	0.2	8
5b	*R*	0.02	1
1 (Saquinavir)	*R*	0.01	0.02

Table 1. HIV protease inhibition (I_{50}) and HIV-inhibition in cell culture (ED_{50}), (na = not active). All values are average of two or more determinations.

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15. Epoxide **6b** had analytical data (^{1}H NMR and ^{13}C NMR) in excellent agreement with those previously reported[8g], $[\alpha]^{20}_D$ -8.5 (c=1.0, MeOH); -8.1 (c=1, MeOH)[6]; -8.6 (c=1, MeOH)[8g].
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17. Satisfactory spectral data were obtained for all new compounds. Structure and purity determinations were based on ^{1}H NMR, ^{13}C NMR and elemental analysis. Compound **5b**: ^{1}H NMR (250 MHz, $CDCl_3$) 1.43 (s, 9H), 2.10 (b, 1H), 2.74 (dd, J = 7.4, 15.2 Hz, 1H), 2.80-3.06 (m, 2H), 3.15-3.44 (m, 2H), 3.95-4.15 (m, 2H), 4.25-4.41 (m, 1H), 4.90-5.02 (m, 1H), 5.89 (b, 1H), 5.96 (b, 2H), 6.46 (b, 1H), 6.57 (t, J = 7.4 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1 H), 6.83-7.06 (m, 2H), 7.11-7.38 (m, 4H), 7.59 (t, J = 8.0 Hz, 1H), 7.73 (dt, J = 1.4, 7.0 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H), 8.09-8.29 (m, 3H), 9.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) 28.9 ($(CH_3)_3$), 35.5 (CH_2), 37.3 (CH_2), 46.3 (CH_2), 50.2 (CH), 51.6 (C), 54.4 (CH), 71.5 (CH), 112.3-149.0 (aromatic C), 164.7 (CO), 169.6 (CO), 170.8 (CO), 173.2 (CO). Anal. Calcd for $C_{35}H_{40}O_5N_6$: C, 67.29; H, 6.45; N, 13.45. Found: C, 67.60; H, 6.18; N, 13.22.
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