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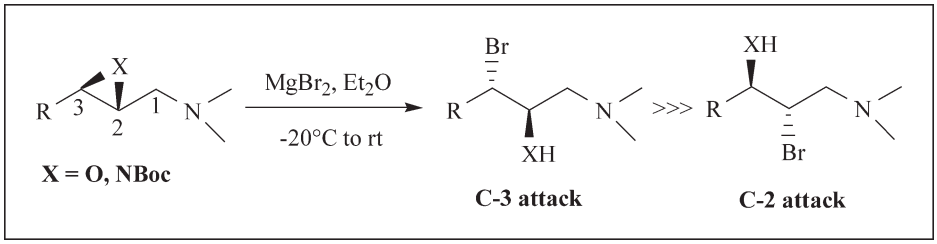

Regio- and stereo-controlled opening of 2,3-epoxy amines and 2,3-aziridine amines by the commercially available $MgBr_2$ is described. As reported, this new method could represent a general and useful approach for the preparation of promising intermediates. Moreover, in particular cases, the reaction evolves toward an interesting oxazolidin-2-one structure.

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INTRODUCTION

The human immunodeficiency virus (HIV) is the causative agent of the acquired immunodeficiency syndrome (AIDS); the HIV-protease (PR) is one of the essential viral enzymes to its maturation and infectivity. Actually, synergy of the two RT and PR inhibitors represents the most efficacious therapy for the treatment of this disease called Highly Active Antiretroviral Therapy (HAART). All the same, the widespread diffusion of the disease and the development of numerous mutant resistant viruses to this therapy have prompted the research toward new and selective inhibitors of HIV-PR, see review [1].

In this field, we synthesized two analogues of Saquinavir **1**, where the anti stereochemistry of the hydroxyethylene isoster core (anti HEA) was substituted with a syn one, as shown in Figure 1 [2].

Among the methods already reported for obtaining syn amino alcohols, see review [3], certainly the multisteps strategy largely used by us consisting in (1) Sharpless AE of allylic alcohols, (2) regio- and stereoselective opening of oxirane ring with halides, (3) substitution of the halogen with azide, and (4) catalytic hydrogenation to amine, represents, despite the number of steps, a very general and flexible route to build up the chiral β-amino alcohols. Following up this approach, we considered the epoxy amine **3**, having the Saquinavir characteristic

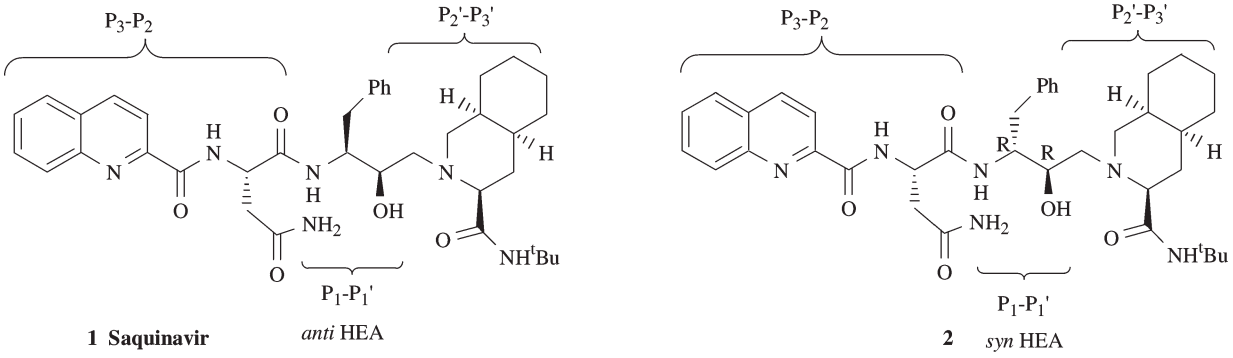
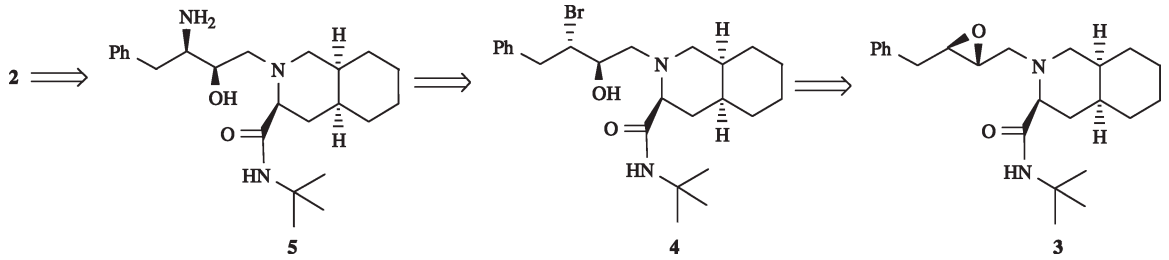


Figure 1. Saquinaver and *syn* HEA analog.

Scheme 1



residue (*S*,*S*,*S*)-decahydroisoquinoline-3-carboxylamide residue (DIQ) already introduced in the molecule, a straightforward precursor for our purpose. In fact, its stereo- and regioselective opening by halide, followed by steps (3) and (4), would have furnished the suitable syn amino alcohol **5**, as shown in retrosynthetic Scheme 1.

Apart from selected examples [4], to our best knowledge, the regio- and stereo-controlled opening of 2,3-epoxy amines by halides has never been exploited; therefore, we decided to better study this particular reactivity of these compounds.

RESULTS AND DISCUSSION

During our studies, we have extensively investigated the metal halides-mediated opening of epoxy alcohols, esters (see review [5]), and aldehydes [6]. In every case, we established that the freshly prepared MgI_2, or the commercially available $MgBr_2$, as well as LiX/Amb15 system were able to direct the halide in C-3 position through a previously postulated chelated complex between the metal (Mg^{2+}, Li^{+}) and the two oxygen of the epoxide derivative. At this point, we hypothesized that also in the case of 2,3-epoxy amines, a possible chelate between metal, epoxide oxygen, and the nitrogen atom occurred, leading to a C-3 regioselective nucleophilic ring opening, Figure 2.

Our preliminary studies were restricted, for convenience, to racemic compounds; the 2,3-epoxy amines were synthesized in satisfactory yield from the corresponding 2,3-epoxy alcohols through the sequence described in Scheme 2: (1) transformation of the hydroxyl function in a good leaving group such as the mesilate (2) nucleophilic substitution with the suitable amine.

The prepared 2,3-epoxy amines were then submitted to the $MgBr_2$-mediated opening reaction employing dry Et_2O as solvent at low temperature [7]. As shown in Table 1, the results confirmed our hypothesis: the nucleophilic attack of the bromine occurred preferentially in the C-3 position, as expected for chelation-controlled ring opening reactions. The regiochemistry of the products was assigned by spin–spin decoupling experiments carried out on the corresponding acetyl derivatives, whereas the anti stereochemistry was assigned in accordance with the S_N2 mechanism of the opening reaction.

As expected, the same reaction conditions applied to the 2,3-epoxy amine **3** afforded the desired bromoderivative **4**, in good yield and excellent regioselectivity (entry 5); the further elaboration of bromine carried out to our desired target, the syn amino alcohol **5**.

For the sake of completeness and for our interest on these compounds, the study was extended on 2,3-aziridine amines. Also in this case very few examples [8], regarding essentially aziridine-fused heterocycles, are already reported in literature. Likewise 2,3-aziridino alcohols [9], also for 2,3-aziridine amines, a cyclic chelate may be invoked to control the regioselectivity in the ring opening reaction by metal halides, Figure 3.

An expeditious sequence was employed to prepare the starting substrates, consisting on the direct introduction of the amines on C-1 position, followed by the usual transformation to the aziridine ring (Scheme 3) [10]. In this case, the chosen amines have been once again piperidine and, for our specific interest regarding the synthesis of D-*treo*-PDMP, morpholine [11].

When we submitted compounds **16–19** to $MgBr_2$ reaction, only one product was detected (Table 2); also

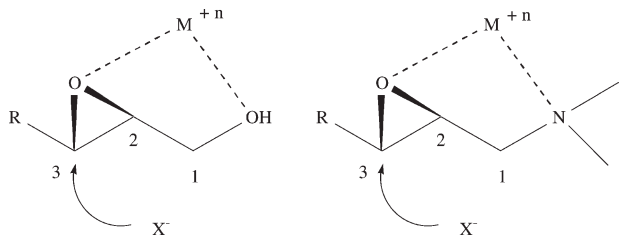
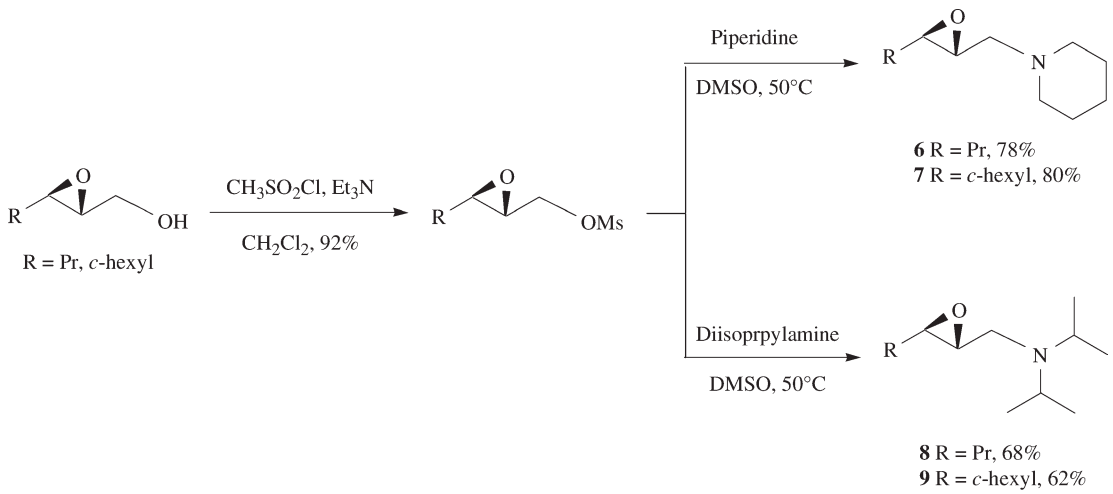
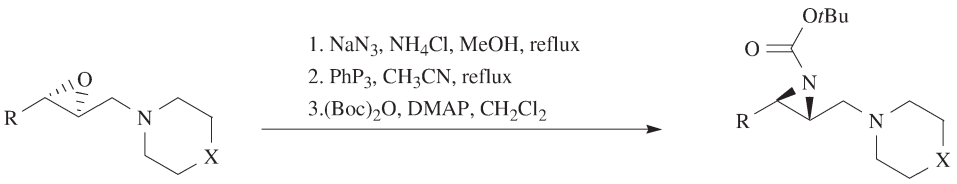


Figure 2. Possible cyclic chelate.

Scheme 2



Scheme 3

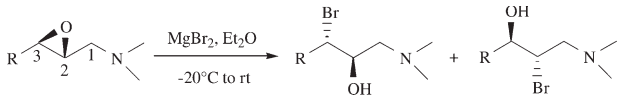


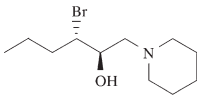
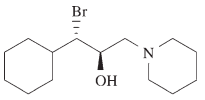
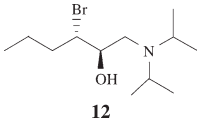
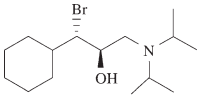
6 R = Pr; X = CH_2, 92%
14 R = Pr; X = O, 88%
7 R = *c*-hexyl; X = CH_2, 93%
15 R = *c*-hexyl; X = O, 91%

16 R = Pr; X = CH_2, 72% from **6**
17 R = Pr; X = O, 70% from **14**
18 R = *c*-hexyl; X = CH_2, 69% from **7**
19 R = *c*-hexyl; X = O, 73% from **15**

Table 1

Controlled opening of 2,3-epoxy amines.



2,3-Epoxy amine	Main haloderivative	Yield (%)	Ratio[a] C-3/C-2
6	 **10**	92	98:2
7	 **11**	65	90:10
8	 **12**	86	95:5
9	 **13**	69	90:10
3	4	68	95:5

[a] Regioisomeric ratio was determined by ^{1}H NMR spectra.

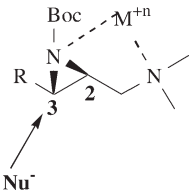


Figure 3. Possible cyclic chelate.

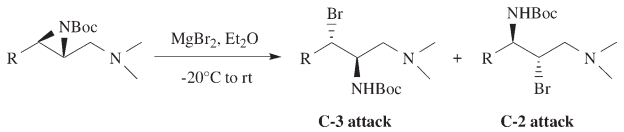
in this case, the ring opening occurred with an excellent C-3 regioselectivity (as demonstrated through spin–spin decoupling experiments), according to the proposed cyclic chelate model.

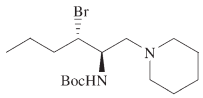
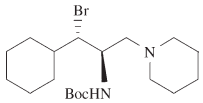
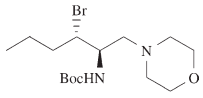
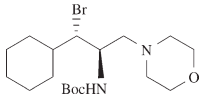
An unexpected behavior was observed when the C-3 position of the substrate was very reactive, as for **24** and **25**; in this case, the initial 3-bromo derivative underwent a rearrangement during the time (4–5 h), giving a new product, the physical data of which were in agreement with a 2-oxazolidinone structure (Scheme 4). This transformation could be explained through an intramolecular nucleophilic substitution of the bromine in benzylic and allylic position (Fig. 4).

In conclusion, the described new method represents a general and useful approach to the preparation of promising intermediates, due to the possible elaboration of the bromine [12]. Moreover, also when the reaction

Table 2

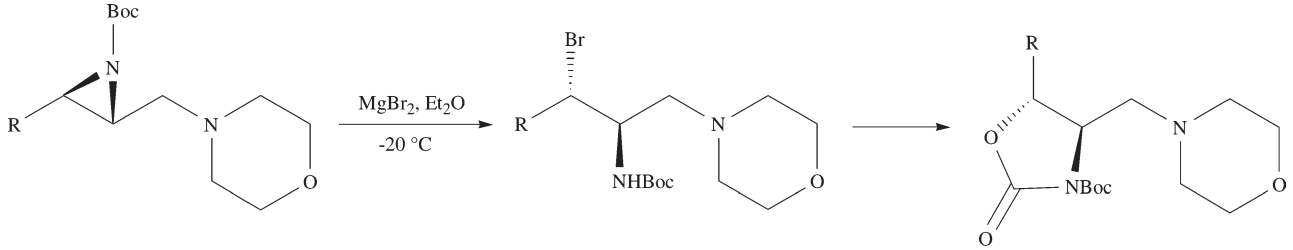
Controlled opening of 2,3-aziridine amines.



2,3-Aziridine amine	Main haloderivative	Yield (%)	Ratio[a] C-3/C-2
16	 **20**	81	>95:5
17	 **21**	78	>95:5
18	 **22**	78	>95:5
19	 **23**	69	>90:10

[a] Regioisomeric ratio was determined by ^1H NMR spectra.

Scheme 4



24 R = Ph
25 R = CH_3CH=CH

26 R = Ph 86%
27 R = CH_3CH=CH

28 R = Ph 86%
29 R = CH_3CH=CH

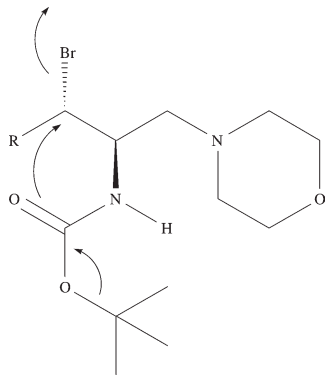


Figure 4. Proposed intramolecular cyclization.

evolves toward oxazolidin-2-ones, it could be of interest, considering the importance of oxazolidinones in the stereoselective synthesis of natural products and pharmaceuticals [13].

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[7] Representative procedure for the ring opening of 2,3-three membered heterocyclic amines: To a cold (−20°C) stirred solution of 2,3-three membered heterocyclic amine (1 mmol) in Et_2O, $MgBr_2$ Et_2O (516.5 mg, 2 mmol) was added. The mixture was stirred for 6 h (TLC monitoring) and then filtered through a pad of Celite. The filtrate was diluted with EtOAc, washed with saturated aq. NaCl, dried over Na2SO4, and then evaporated in vacuum. The crude mixture was purified by column chromatography (petroleum ether/ethyl acetate 7/3). (3S*,2R*)-3-Bromo-2-hydroxy-1-piperidine-hexane, 10. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.31 (ddd, 1H, J 10.2 7.3 2.9 Hz, CHOH); 3.97 (ddd, 1H, J 9.2 7.3 2.9 Hz, CHBr); 3.41 (dd, 1H, J 13.2, 2.2 Hz, CH_AN); 3.35–2.99 (m, 6H, CH_BN+$2CH_2N$-piperidine+OH); 2.17–1.95 (m, 6H, $3CH_2$-piperidine); 1.93–1.15 (m, 4H, $2CH_2$); (t, 3H, J 7.3 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 68.0; 61.1; 58.1; 54.2; 36.1; 22.5; 21.3; 20.1;13.0. HR-MS (ES Q-TOF) Calcd for $C_{11}H_{23}BrNO$ $(M+H)^+$: 264.0963 Found 264.0968. (1R*,2S*)-2-Bromo-1-(1′-methylpiperidinyl)-pentyl carbamic acid *t*-butyl ester, 20. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.17–4.98 (bs, 1H, NHBoc); 4.48–4.34 (m, 1H, CHNHBoc); 3.88–3.67 (m, 1H, CHBr); 2.62–2.20 (m, 6H, CH_2N+$2CH_2N$-piperidine); 1.91–1.70 (m, 2H, CH_2CHBr); 1.5–1.18 (m, 8H, CH_2+$3CH_2$-piperidine); 1.44 (s, 9H, $C(CH_3)_3$); 0.93 (t, 3H, J 7.3 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.6; 78.7; 61.4; 60.7; 59.0; 53.9; 36.3; 28.3; 27.0; 24.5; 19.8; 12.9. HR-MS (ES Q-TOF) Calcd for $C_{16}H_{32}BrN_2O_2$ $(M+H)^+$: 363.1647 Found 363.1651. (2S,3R)-2-Bromo-2-phenyl-1-(1′-methylmorpholinyl) carbamic acid *t*-butyl ester, 26. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54–7.23 (m, 5H); 5.38 (bd, 1H, J 4.4 Hz, NHBoc); 4.96 (d, 1H, J 6.6 Hz, CHBr); 4.36-4.08 (m, 1H, CHNH); 3.71 (t, 4H, J 4.4 Hz, $2CH_2O$-morpholine); 2.78–2.29 (m, 6H, CH_2N+$2CH_2N$-morpholine); 1.40 (s, 9H, $C(CH_3)_3$). Calcd for $C_{18}H_{28}BrN_2O_3$ $(M+H)^+$: 399.1283 Found 399.1288. (4R,5R)-4-Morpholin-4-ylmethyl-5-phenyl-oxazolidin-2-one, 28. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.52–7.29 (m, 5H); 5.96 (bs, 1H, NH); 5.22 (d, 1H, J 5.9 Hz, CHO); 3.91–3.78 (m, 1H, CHNH); 3.67 (t, 4H, J 4.4 Hz, $2CH_2O$-morpholine); 2.66–2.33 (m, 6H, CH_2N+$2CH_2N$-morpholine). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158,7; 138,5; 128,8; 125,6; 81,5; 66,6; 62,5; 57,4; 53,8. Calcd for $C_{19}H_{27}N_2O_5$ $(M+H)^+$: 363.1920 Found 363.1924.

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[9] Bonini, C.; Righi, G.; Franchini, T. Tetrahedron Lett 1998, 39, 2385.

[10] Tanner, D.; He, H. M.; Somfai, P. Tetrahedron 1992, 48, 6069.

[11] Manuscript in preparation.

[12] Since in our precedent studies, we have extensively used LiBr/Amb15 system to open 2-functionalized three membered heterocyclic rings in regioselective fashion, we decided to test it also in this contest. As expected, the reaction performed on compounds 3, 6, 7, 18, and 24 carried out to the same bromo derivatives obtained by $MgBr_2$.

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