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Stereoselective synthesis of aminoethylamine aspartyl protease transition state isosteres

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Abstract—A stereoselective synthesis of aminoethylamine aspartyl protease transition state isosteres **10** and **14** is described. The synthetic approach was designed to allow the introduction of functionality at the central core of the inhibitors, which should enable the identification of small molecule inhibitors of diverse aspartyl protease targets.

Proteases, which catalyze the hydrolysis of amide bonds in peptides and proteins, play essential roles in numerous biological processes and are important therapeutic targets in different diseases including cancer, viral infections, inflammation and cardiovascular diseases.[1] The aspartyl protease family includes the extremely important drug targets, HIV protease[2] and β secretase,[3] implicated in Alzheimer's disease. A common strategy in the design of aspartyl protease inhibitors is the replacement of the substrate scissile amide bond with a tetrahedral intermediate isostere, typically a secondary alcohol or an amine. Three common hydroxyl containing inhibitor scaffolds include hydroxyethylene, hydroxyethylamine and statine motifs.[4] Amine containing inhibitor scaffolds such as aminostatine,[4] aminoethylamine,[5] and aminoethylene[6] motifs have also been described (Fig. 1).

The two compounds described in this letter containing the aminoethylamine motif have been previously claimed as inhibitors of the beta-secretase enzyme; however, their published synthesis was not based on a stereoselective route and required the separation of each isomer by chiral chromatography at the final step.[5] In this letter, an alternative stereoselective synthesis to the aminoethylamine motif was investigated due to its possible use as isostere in other different aspartyl proteases. Both stereochemistries in the amino group were considered important based on the published crystal structures of several hydroxyl-containing aspartyl protease inhibitors.[7,8] Those pharmacophores, which differ from one another by the stereochemistry (*S*) and (*R*) on the hydroxyl group, engage either one or both of the catalytic aspartates of the enzyme via hydrogen bonds in a different manner. Due to this difference in the stereochemistry of the secondary alcohol depending on the isostere, both stereochemistries in the aminoethylamine motif have been pursued to keep both possibilities for the hydrogen bond pattern proposed for interaction with the two active-site aspartyl residues.

The synthesis of the two NH_2-isomers in the aminoethylamine isostere described herein utilized easily accessible amino epoxides **1** (Scheme 1),[9] and **2** (Scheme 3)[10] as the starting materials for the achievement of the primary amine central core.

Aziridine **3** was obtained in two steps by the treatment of (*S*)-epoxide **1** with NaN_3 which afforded the intermediate hydroxymethylazide that was closed immediately to the desired aziridine in the presence of PPh_3 with an inversion of configuration.

For ease of synthesis, the protection of the aziridine with Boc would be the best choice since removal in the last step with HCl to form the hydrochloride salt would facilitate isolation of the product. However, it is well known that the reactivity of aziridines decreases according to the decreased electron-withdrawing ability of the substituent on the nitrogen atom of aziridine. Based on this fact, Reider and co-workers[11] reported that nosylaziridines are highly reactive electrophiles towards a variety of nucleophiles and that the resulting primary

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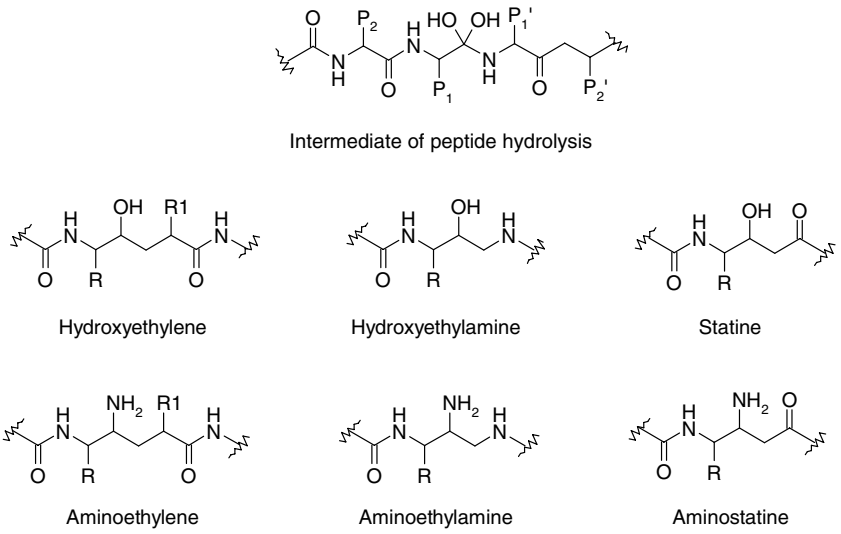
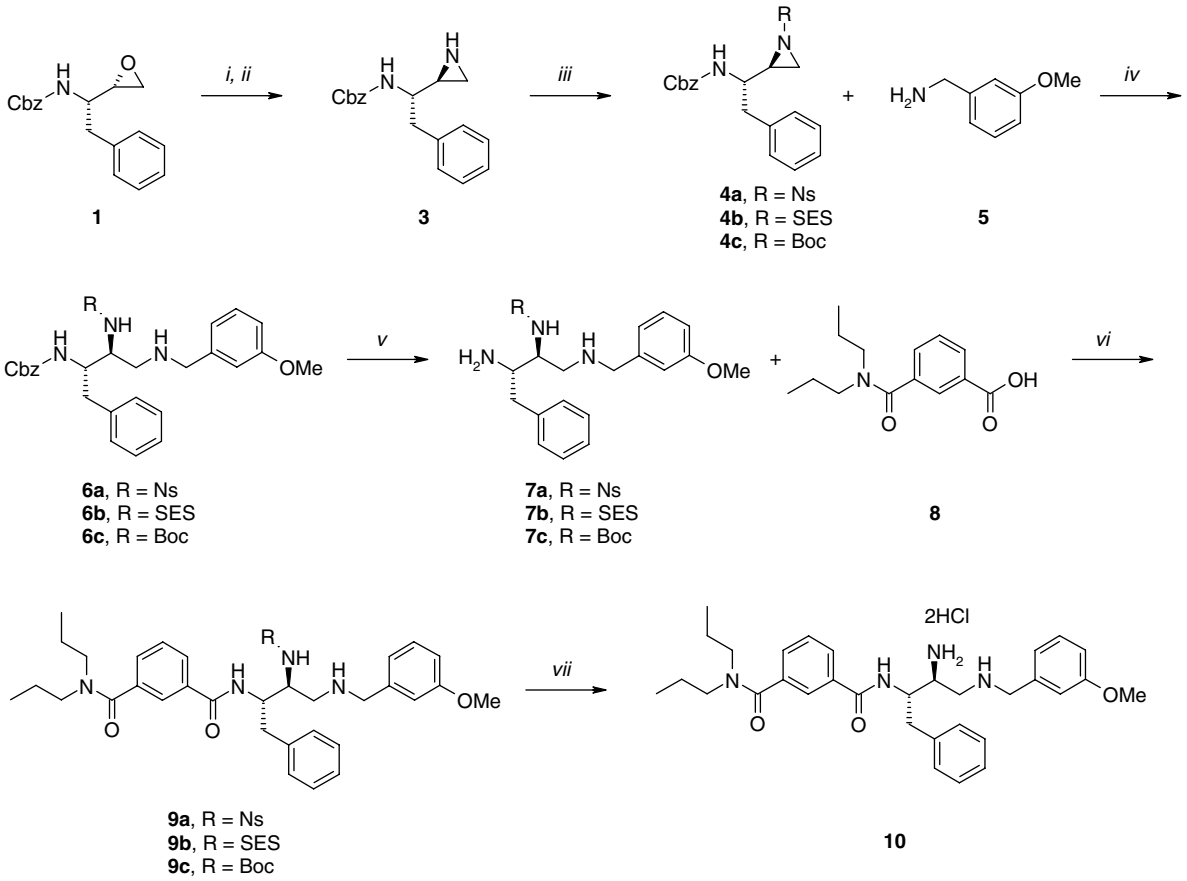


Figure 1. Aspartyl protease inhibitor core motifs.



Scheme 1. Reagents and conditions: (i) NH_4Cl, NaN_3, MeOH, 64 °C, 3 h; (ii) PPh_3, CH_3CN, reflux, 1 h, 66% both steps; (iii) 4-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, −20 °C to 10 °C, 30 min, 75% for **4a**, β-trimethylsilylethanesulfonyl chloride, Et_3N, DMF, 35% for **4b**, $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, overnight, 80% for **4c**; (iv) Bu_3P, CH_3CN, rt, 2 h, 76% yield for **6a**, 78% yield for **6b**, CH_3CN, 85 °C, sealed tube, 20 h, 40% yield for **6c**; (v) H_2, Pd/C, EtOH, rt, 3 h, 98 %; (vi) EDC·HCl, HOBt, DMAP, Et_3N, CH_2Cl_2, rt, 50% yield for **9a**, 58% yield for **9b**, 60% yield for **9c** and (vii) HCl 4.0 M in dioxane, rt, 1 h, 55% after trituration with Et_2O for **9c**.

nosylamide adducts can be readily cleaved under mild conditions to provide the primary amines. For this reason, 4-nitrobenzene sulfonyl chloride (nosyl group, Ns), was the first choice as a protecting group for the aziridine in the proposed synthesis to obtain **4a**. Tributylphosphine in acetonitrile was used as an effective promoting agent for ring-opening of the aziridine to provide amine **6a** in 76% yield.[12] Removal of the Cbz group by hydrogenation followed by an amide coupling reaction with the isophthalamide carboxylic

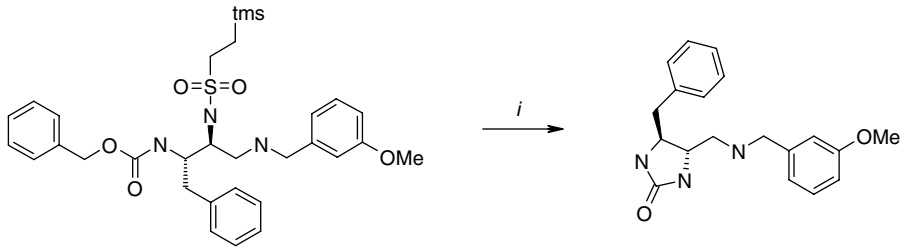
acid **8** afforded the desired N-protected compound **9a**. Unfortunately, attempts to remove the nosyl group with thiophenol in the presence of potassium carbonate in acetonitrile yielded unreacted starting material as the only isolated product.

The synthesis was then tried with the SES protecting group (β-trimethylsilylethanesulfonyl). This group was described as a useful reagent for the protection of amines as their sulfonamides, which are easily cleaved by heating with fluoride ion.[13] The protection of the aziridine to give **4b** and the following ring-opening step to obtain **6b** worked in acceptable yields. Once the ring was opened, we tried to exchange the protecting group from SES to Boc to avoid the last heating step. Unexpectedly, compound **11** was obtained (Scheme 2) which was formed after deprotection of the SES group and amine attack to the carbonyl group of the Cbz affording benzylalcohol as a secondary product.[14] When the removal of the SES group was postponed to the last step of the synthesis, after heating to 110 °C in the presence of fluoride anion, only the decomposition products were detected.

At this point, the Boc group (*tert*-butoxy carbonyl) was chosen to protect aziridine **3** even knowing that the desired aziridine ring-opening reaction will most likely proceed in lower yield than in the previous cases. As the Boc group is not an electron withdrawing group like the Ns group, the tributylphosphine did not appear to assist in the aziridine opening with 3-methoxybenzylamine and starting material was recovered. However, treatment of the Boc-aziridine with 3-methoxybenzylamine in CH_3CN in a sealed tube at 85 °C for 20 h gave the desired product **6c** in 40% yield. The two remaining steps in the synthetic route (hydrogenation to remove the Cbz protecting group and the amide coupling step) proceeded in good yields to give the *N*-Boc protected product **9c**. This intermediate was readily deprotected by treatment with 4.0 M HCl in dioxane at room temperature for 1 h to give the corresponding hydrochloride salt of (*S*)-aminoethylamine **10**.[15]

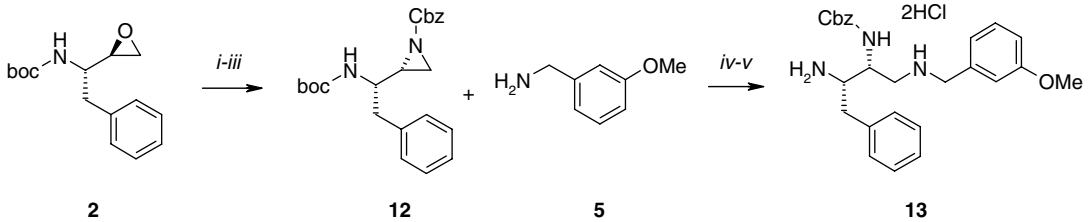
Available (*R*)-epoxide **2** served as the starting material to obtain the (*R*)-aminoethylamine (Scheme 3).[16] The aziridine was now protected with Cbz in order to distinguish between the two amino groups in the molecule. Following the same synthetic route described above, the desired product **14** was obtained in an overall yield of 7% from epoxide **2**.[15]

In conclusion, a stereoselective route is reported for the synthesis of the aminoethylenamine-based aspartyl protease inhibitors **10** and **14** obtained from easily available

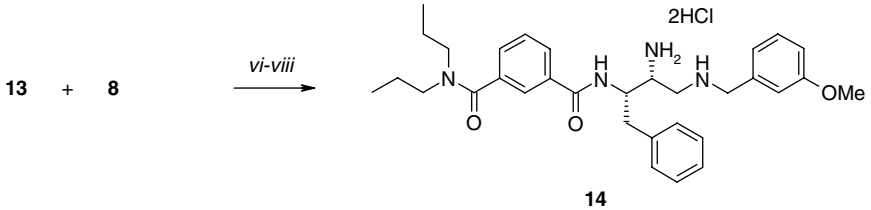


6b **11**

Scheme 2. Reagents and conditions: (i) TBAF 1.0 M in THF, dioxane, Et_3N, $(Boc)_2O$, 110 °C, overnight, 51%.



2 **12** **5** **13**



14

Scheme 3. Reagents and conditions: (i) NH_4Cl, NaN_3, MeOH, 64 °C, 3 h; (ii) PPh_3, CH_3CN, reflux, 3 h, 69% both steps; (iii) 4-benzyl chloroformate, Et_3N, CH_2Cl_2, rt, 3 h, 75%; (iv) Bu_3P, CH_3CN, rt, overnight, 35%; (v) 4.0 M HCl in dioxane, rt, 1 h, quantitative; (vi) EDC·HCl, HOBt, DMAP, Et_3N, CH_2Cl_2, rt, 71%; (vii) H_2, Pd/C, EtOH, rt, 2 h, 72% and (viii) 4.0 M HCl in dioxane, rt, 5 min, 72% after trituration with Et_2O.

starting materials in acceptable yields. Those cores should provide a new approach to aspartic protease inhibitors incorporating a number of functional different groups.

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14. Spectral data of by-product **11**: MS for $C_{19}H_{23}N_3O_2$: 326 (M^++H); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.4–7.2 (6H, m), 6.9–6.7 (3H, m), 4.52 (2H, s), 4.47 (1H, br s); 3.79 (3H, s), 3.75–3.65 (1H, m), 3.37 (1H, dd, $J = 11.7$, 2.8 Hz), 3.3–3.2 (1H, m), 3.1–3.0 (2H, m), 2.90 (1H, dd, $J = 13.3$, 5.6 Hz), 2.69 (1H, dd, $J = 13.3$, 9.1 Hz).
15. Spectral data of final compounds **10** and **14**: Compound **10**, MS for $C_{32}H_{42}N_4O_3$: 531 (M^++H); ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.9–7.5 (4H, m); 7.4–7.1 (8H, m), 7.01 (1H, d, $J = 8.5$ Hz); 4.8–4.6 (1H, m), 4.30 (2H, s), 4.10 (3H, s), 4.1–4.0 (1H, m), 3.9–3.7 (1H, m), 3.4–3.2 (4H, m), 3.1–2.9 (4H, m), 1.7–1.5 (2H, m), 1.4–1.3 (2H, m), 1.02 (3H, t, $J = 6.7$ Hz), 0.70 (3H, t, $J = 6.7$ Hz). Compound **14**, MS for $C_{32}H_{42}N_4O_3$: 531 (M^++H); ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.9–7.5 (4H, m); 7.4–7.1 (8H, m), 7.01 (1H, d, $J = 8.5$ Hz); 4.8–4.7 (1H, m), 4.36 (2H, s), 4.1–3.9 (1H, m), 3.84 (3H, s), 3.8–3.7 (1H, m), 3.6–3.4 (4H, m), 3.2–3.0 (4H, m), 1.8–1.6 (2H, m), 1.6–1.4 (2H, m), 1.02 (3H, t, $J = 6.7$ Hz), 0.70 (3H, t, $J = 6.7$ Hz).
16. Both protecting groups (Cbz and Boc) at the epoxide could be used to obtain both final compounds ((*S*)-aminoethylamine **10** and (*R*)-aminoethylamine **14**) starting from the appropriate configuration at the epoxide ((*S*) or (*R*)) following Schemes 1 and 3. For instance, the *N*-Boc (*S*,*S*) amino epoxide is now commercially available and the synthesis of **10** can be done following the same synthetic route as described for **14** (Scheme 3).