A Stereodivergent Synthesis of Hydroxyethylene Dipeptide Isostere via Highly Diastereoselective Epoxidation

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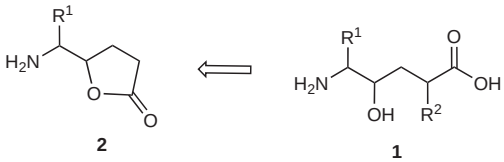
Abstract: Epoxidation of δ-amino-β,γ-unsaturated ester with trifluoroperacetic acid afforded its epoxide in a highly diastereoselective manner. Subsequent stereodivergent epoxide opening reactions provided synthetic routes towards both the *threo* and *erythro* hydroxyethylene peptide isostere.

Key words: hydroxyethylene isostere, diastereoselective epoxidation, stereodivergent, epoxide ring opening

As a transition state surrogate of the scissile amide bond with enhanced metabolic stability, hydroxyethylene dipeptide isostere **1** containing γ-hydroxy-δ-amino acid functionality has been exploited extensively as a key structural unit of many inhibitors of aspartyl proteases such as renin,[1] HIV,[2] and γ-secretase[3] (Scheme 1). Therefore, numerous synthetic routes have been devised particularly for the preparation of the common intermediate lactone **2** that was efficiently transformed to **1** via well-established enolate alkylation process.[4] The most common approach is based upon the reaction of an indium,[5] zinc,[6] titanium,[7] or magnesium[8] homoenolate equivalent with N-protected amino-aldehyde or amino acid derivatives as a key reaction. Other strategies include the use of an epoxide intermediate[9] prepared from N-protected amino-aldehyde; a radical intermediate;[10] a thiazolyl ketone intermediate;[11] a chiron approach starting from mannose[12] or glutamic acid;[13] asymmetric reactions such as Sharpless epoxidation,[14] dihydroxylation,[15] or aminohydroxylation;[16] and finally, strategically interesting olefin metathesis reaction[17] for the construction of the lactone ring. In addition to these approaches, many diverse synthetic routes[18] are also available. Herein, we disclose an alternative stereodivergent synthetic route towards a hydroxyethylene peptide isostere featuring the use of a highly diastereoselective epoxidation and subsequent stereodivergent ring-opening reactions as key transformations.

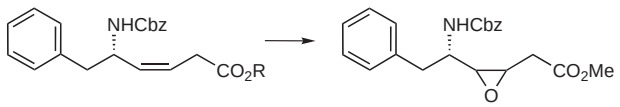
Ene-acid **3a**[19] was converted to its methyl ester **3b** in methanol in the presence of trimethylsilyl chloride in quantitative yield. Epoxidation of **3b** with MCPBA provided α-epoxide **4a** and β-epoxide **4b** in moderate 3:1 selectivity. As observed in the epoxidation of a similar



Scheme 1

δ-amino-(*Z*)-β,γ-unsaturated amide fragment,[20] a more electron-deficient peracid enhanced the diastereoselectivity through synergistic combination of the directing effect of the carbamate group and $A_{1,3}$-strain: use of permaleic acid increased the selectivity to 10:1 and the most electron deficient trifluoroperacetic acid[21] led to better than 150:1 selectivity (Table 1). Moreover, simple recrystallization of the crude product in methyl *tert*-butylether (MTBE) provided highly pure **4a** in better than 99% ee.[22]

Table 1 Influence of Epoxidation Reagents on the Diastereoselectivity



3a R = H
3b R = Me

4a α-epoxide
4b β-epoxide

Entry	Peracid	Selectivity (**4a**/**4b**)
1	MCPBA	3:1
2	Permaleic acid[a]	10:1
3	Trifluoroperacetic acid[a]	>150:1

[a] Epoxidation of **3b** was performed by peracid generated in situ by slow addition of the anhydride to the stirred mixture of urea hydrogen peroxide complex and Na_2HPO_4 (2 equiv) in CH_2Cl_2.

Treatment of the epoxide **4a** with DBU smoothly opened the epoxide ring to give **5**, a common intermediate for both hydroxyethylene and (*E*)-alkene dipeptide isosteres,[23] respectively. Chemoselective reduction of the α,β-unsaturated double bond of **5** by Ni_2B,[24] generated in situ, resulted in a mixture of lactone **6** and its open hydroxy-ester compound, which was exposed to *p*-TsOH in toluene at reflux resulting in only lactone **6**. Simple trituration of the crude product with hexane resulted in solidification and gave pure (1*S*,2′*S*)-**6**[25] in 80% overall yield (Scheme 2).

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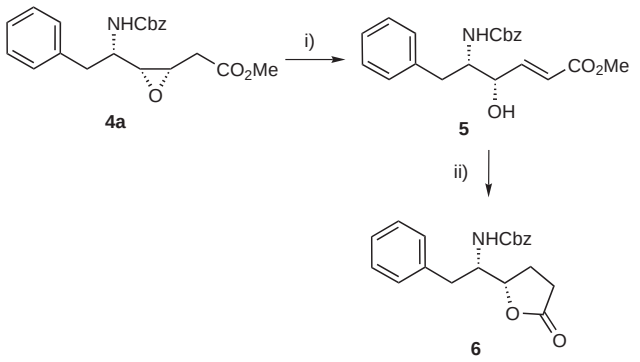
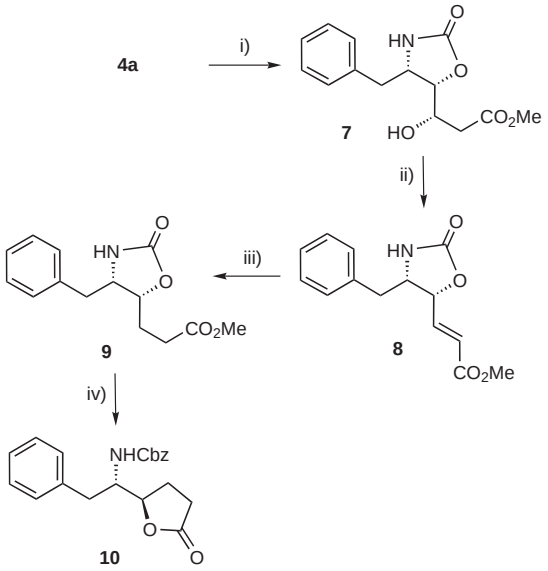


Scheme 2 *Reagents and conditions*: i) DBU, CH_2Cl_2; ii) (a) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH; (b) *p*-TsOH, toluene, reflux.



Scheme 3 *Reagents and conditions*: i) $ZrCl_4$ (2.5 equiv), CH_2Cl_2, reflux; ii) MsCl, Et_3N, CH_2Cl_2; iii) H_2, Pd/C, EtOAc; iv) (a) NaOH, EtOH–H_2O, CbzCl; (b) AcOH, toluene, reflux.

Alternative ring-opening of the epoxide moiety of **4a** was accomplished by the internal participation of the carbamate group in the presence of Lewis acids, among which $ZrCl_4$ turned out to be the optimal choice to afford the dihydroxyethylene intermediate **7** in 65% yield. Under the same conditions, $MgCl_2$ and $ZnCl_2$, showed only ca. 50% conversion, while $BF_3 \cdot OEt$[26] effected the reaction at ambient temperature to give **7**, however, in only 50% yield. One-pot mesylation of **7** and subsequent elimination gave the α,β-unsaturated intermediate **8**, which was hydrogenated using Pd/C in ethyl acetate to provide **9** in 75% yield overall. Interestingly, the hydrogenation reaction profile is very sensitive to reaction solvent: use of methanol as the reaction solvent led to significant contamination (ca. 30%) of the amino-ester side-product,[27] via hydrogenolysis of the allylic C–O bond of **8** followed by reduction. Reduction mediated by Ni_2B was also complicated by the formation of the same class of lactam side-product.[28] Hydrolysis of the oxazolidinone moiety of **9**, protection by the Cbz group, and final lactonization afforded (1*S*,2′*R*)-**10** in 90% yield (Scheme 3).[29]

In conclusion, we have developed efficient and stereodivergent synthetic routes towards diastereomeric **6** or **10** via the common intermediate **4a**. Particularly noteworthy are the highly diastereoselective epoxidation and subsequent stereodivergent ring-opening of the epoxide group of **4a**.

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(19) Ene-acid **3a** is available in multi-kg quantities (*Z*/*E* selectivity, 24:1; 83% ee); see ref. 20.

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(22) Preparation of **4a**: To a stirred mixture of **3b** (660 mg, 1.87 mmol), urea hydrogen peroxide (790 mg, 8.40 mmol), and Na_2HPO_4 (1.12 g, 7.89 mmol) in CH_2Cl_2 (10 mL) was added $(CF_3CO)_2O$ (784 mg, 3.73 mmol) at 0 °C. The mixture was allowed to warm to r.t. and stirred for 4 h. The reaction mixture was washed with a sat. aq solution of $NaHCO_3$, a 5% solution of $NaHSO_3$, and finally H_2O. The separated organic layer was concentrated and MTBE (15 mL) was added to the residue. The mixture was stirred for 5 h. The solid formed was filtered and washed with MTBE (2 mL). The cake was dried over a stream of nitrogen to give **4a** (615 mg, 86.1%) as a white solid; **4a** t_R 31.4 min, ***ent*-4a** t_R 40.8 min (Chiralpak® AD-H; 35 °C; 10% *i*-PrOH–hexane; 1 mL/min; 250 nm); ee of isolated **4a** ≥99.9%, while the ee of the filtrate was 50%, which reflects highly selective recrystallization. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38–7.18 (10 H, m), 5.12 (1 H, d, *J* = 12.4 Hz), 5.09 (1 H, d, *J* = 12.4 Hz), 4.95 (1 H, br), 3.71 (1 H, m), 3.67 (3 H, s), 3.32 (1 H, m), 3.07 (1 H, m), 3.01 (1 H, dd, *J* = 8.0, 4.4 Hz), 2.85 (1 H, dd, *J* = 13.2, 8.0 Hz), 2.38 (1 H, dd, *J* = 16.8, 7.6 Hz), 2.03 (1 H, dd, *J* = 17.2, 4.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.8, 155.8, 136.6, 136.5, 129.6, 128.7, 128.6, 128.2, 128.1, 127.0, 67.0, 57.6, 53.6, 52.0, 51.8, 39.5, 33.3.

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(25) **Benzyl (1*S*)-1-[(2′*S*)-5′-oxotetrahydrofuran-2′-yl]-2-phenylethylcarbamate (6)**: $[\alpha]_D^{25}$ = –9.6 ($CHCl_3$, *c* 1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.34–7.25 (10 H, m), 5.09 (1 H, d, *J* = 12.4 Hz), 5.05 (1 H, d, *J* = 12.4 Hz), 4.87 (d, 1 H, *J* = 10.0Hz), 4.48 (1 H, t, *J* = 7.8 Hz), 4.07 (dd, 1 H, *J* = 17.5, 8.7 Hz), 2.98 (1 H, dd, *J* = 13.3, 6.9 Hz), 2.90 (1 H, dd, *J* = 13.3, 8.7 Hz), 2.48 (dd, 2 H, *J* = 9.7, 7.4 Hz), 2.16–2.03 (2 H, m); ^{13}C NMR ($CDCl_3$,125 MHz): δ = 177.2, 156.7, 137.1, 136.4, 129.4, 128.8, 128.6, 128.2, 128.0, 126.9, 79.9, 54.9, 39.3, 28.7, 24.1; MS: *m*/*z* = 340 [M + H].

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(27) **Amino-ester side-product** (Figure 1): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.28 (5 H, m), 3.57 (3 H, s), 3.51 (1 H, m), 3.24 (1 H, dd, *J* = 13.6, 5.6 Hz), 2.95 (1 H, dd, *J* = 13.6, 8.8 Hz), 2.32 (2 H, m), 1.95–1.69 (4 H, m); MS: *m*/*z* = 222 [M + H].

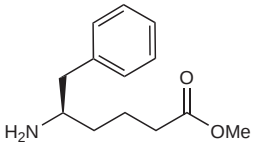

Figure 1

(28) **Lactam side-product** (Figure 2): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.17 (5 H, m), 5.65 (1 H, br), 3.61 (1 H, m), 2.88 (1 H, dd, *J* = 13.6, 5.2 Hz), 2.62 (1 H, dd, *J* = 13.6, 9.2 Hz), 2.43–2.29 (2 H, m), 1.94 (2 H, m), 1.68 (1 H, m), 1.47 (1 H, m); MS: *m*/*z* = 190 [M + H] .

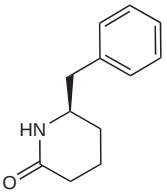

Figure 2

(29) **Benzyl (1*S*)-1-[(2′*R*)-5′-oxotetrahydrofuran-2′-yl]-2-phenylethylcarbamate (10)**: $[\alpha]_D^{25}$ = –8.6 ($CHCl_3$, *c* 0.02); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.18 (10 H, m), 5.04 (2 H, s), 4.66 (1 H, br), 4.40 (1 H, m), 4.05 (1 H, m), 3.03 (1 H, dd, *J* = 14.4, 4.4 Hz), 2.90 (1 H, m), 2.52 (2 H, m), 2.25 (1 H, m), 2.11 (1 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.6, 165.9, 136.1, 132.7, 129.5, 128.8, 128.6, 128.3, 128.0, 127.0, 80.4, 60.4, 50.0, 30.9, 28.2, 24.7; MS: *m*/*z* = 340 [M + H] .