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A Stereoselective Synthesis of Hydroxyethylene and *erythro*-Dihydroxyethylene Dipeptide Isosteres: A Facial Selective *anti*-Aldol Reaction

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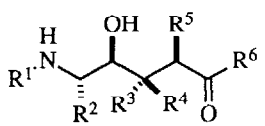
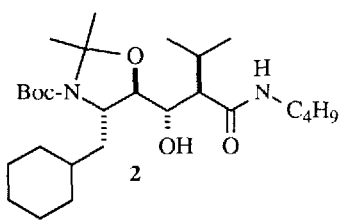
Key Words: hydroxyethylene isostere; *anti*-aldol; aspartic proteinase; renin inhibitor; facial selective

Abstract: *A Lewis-acid catalyzed anti-aldol reaction of aldehyde 4 afforded diol 6a (95% de). Aminolysis of the corresponding β-lactone provided erythro-dihydroxyethylene dipeptide isostere 2 while the lactone-protected hydroxyethylene dipeptide isostere 3 was obtained through selective deoxygenation and acidic deprotection.*

Tight-binding inhibitors of aspartic proteinases substitute, for the scissile amide bond, a mimic of the putative tetrahedral transition state such as the well known hydroxyethylene dipeptide isostere **1a**.[1] Also of interest has been the *threo*-dihydroxyethylene dipeptide isostere **1b** which has been incorporated into inhibitors of renin.[2] Previous syntheses of **1a** have either been not stereoselective at one or more centers,[3] or have required the use of a chiral auxiliary.[4] No syntheses of *erythro*-dihydroxyethylene dipeptide isosteres **1c** have been reported. We now describe a synthesis of the (cyclohexyl)alanine-valine *erythro*-dihydroxyethylene dipeptide isostere **2** utilizing an *anti*-aldol reaction which is facial selective in the absence of chiral auxiliaries, and the efficient conversion of aldol product **6a** to the lactone-protected hydroxyethylene dipeptide isostere **3**.



1a $R^3 = R^4 = H$
1b $R^3 = H$, $R^4 = OH$
1c $R^3 = OH$, $R^4 = H$



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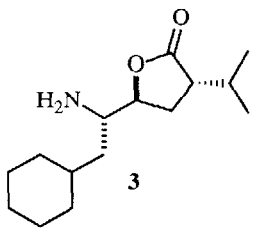
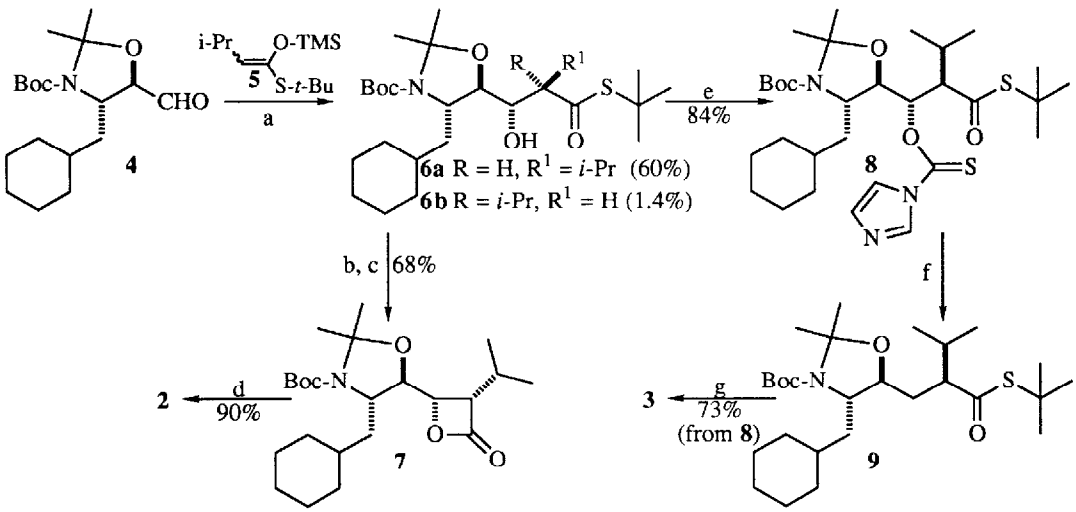


3

Aldehyde **4** (8:1 mixture of 5*R*:5*S* diastereomers)[5] was reacted with thioester silyl ketene acetal **5**[6] in the presence of $BF_3{\cdot}Et_2O$ according to the method of Gennari *et al.*[7] to afford *anti*-aldol product **6a**[8] in 60% isolated yield. While the readily separable *syn*-aldol product **6b**[9] was also obtained (1.4%, de = 95%), no other aldol products were detected. The moderate yield of the condensation was most likely due to the acid lability of the Boc and acetal protecting groups as neither **4** nor **6a** was stable to the reaction conditions. Use of other Lewis acids (Et_2AlCl, $EtAlCl_2$, $SnCl_4$) resulted in lower yields although the anti:syn ratios remained largely unchanged. Hydrolysis of the thioester and carbodiimide mediated cyclization via the hydroxybenzotriazole active ester afforded β-lactone **7**, which was opened with butyl amine to provide N-protected *erythro*-dihydroxyethylene dipeptide isostere **2**.

Alternately, **6a** was deoxygenated to thioester **9** via intermediate **8** using conditions similar to those previously reported.[4a] Without purification, **9** was converted to crystalline lactone-protected hydroxyethylene dipeptide isostere **3** suitable for further elaboration.[3e] Incorporation of *erythro*-dihydroxyethylene dipeptide isostere **2** into renin inhibitors provided compounds with good activity compared to the corresponding hydroxyethylene dipeptide isostere containing compounds. Complete results from these structure-activity studies will be described in a subsequent report.



Reagents: (a) **5** (150 mol%), $BF_3{\cdot}Et_2O$ (100 mol%), CH_2Cl_2, -78 °C, 1 h; pH 7 phosphate buffer. (b) LiOH (200 mol%), THF, H_2O, RT, 18 h; $NaHSO_4$. (c) EDC (140 mol%), 1-hydroxybenzotriazole (150 mol%), N-methylmorpholine (300 mol%), DMF, 0 °C, 24 h. (d) butyl amine (neat), 0 °C to RT, 16 h. (e) thiocarbonyldiimidazole (200 mol%), DMAP (25 mol%), 1,2-dichloroethane, 50 °C, 18 h. (f) Bu_3SnH (200 mol%), toluene, reflux, 20 h. (g) 4 **M** HCl/ethanol, RT, 1 h; Na_2CO_3.

References and Notes

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8. mp 65-67 °C; ^{1}H-NMR ($CDCl_3$) 4.27-4.08 (m, 1 H), 3.73-3.53 (m, 3 H), 2.67 (br d, 1 H), 2.32-2.15 (m, 1 H), 1.53 (br s, 6 H), 1.50 (s, 9 H), 1.47 (s, 9 H), 1.03 (d, 3 H), 1.01 (d, 3 H).
9. Identified by comparison to a sample prepared by an alternate procedure: Boyd, S. A.; Mantei, R. A. Unpublished results.

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