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Synthesis of the Hydroxyethylene Dipeptide Isostere, (2S,4S,5S)-5-Amino-6-Cyclohexyl-4-Hydroxy-2-Isopropyl Hexanoic Acid n-Butyl Amide[1]

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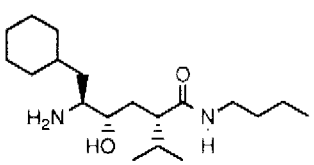
Key Words: aldol; furan; hydroxyethylene dipeptide isostere; renin

Abstract: *A stereoselective synthesis of the hydroxyethylene dipeptide isostere, (2S,4S,5S)-5-amino-6-cyclohexyl-4-hydroxy-2-isopropyl hexanoic acid n-butyl amide from Boc-L-phenylalanine is described.*

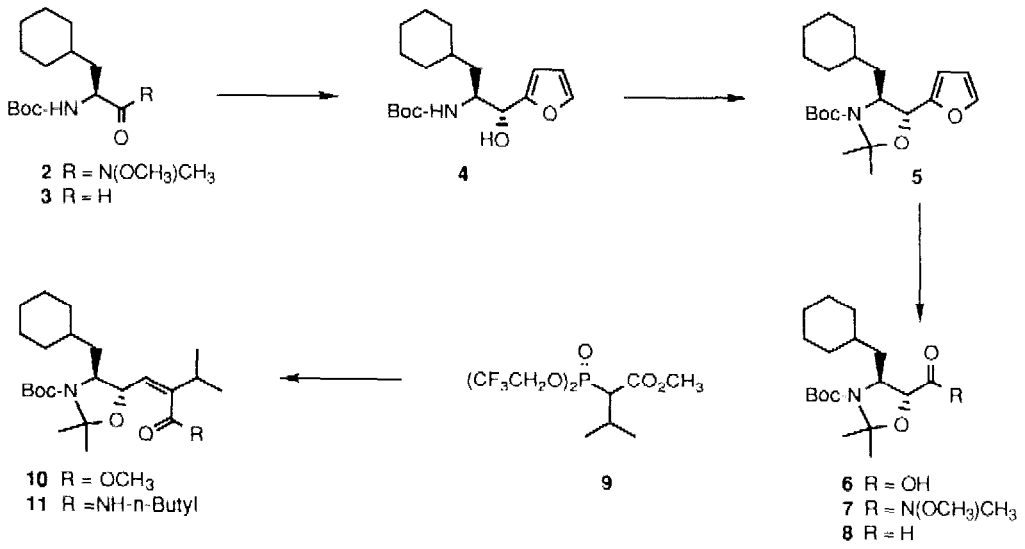
The hydroxyethylene dipeptide isostere, (2S,4S,5S)-5-amino-6-cyclohexyl-4-hydroxy-2-isopropyl hexanoic acid n-butyl amide, **1**, has been used in inhibitors of the aspartyl protease renin as a transition state analogue to replace the scissile dipeptidic Leu-Val portion of the renin substrate.[2] The hydroxyl group is believed to mimic the tetrahedral intermediate formed during hydrolysis of the Leu-Val amide bond. Syntheses of the hydroxyethylene dipeptide isostere were first described by Szelke[3] and Rich[4], and have been reported more recently by others.[5] We wish to describe a stereoselective synthesis of **1** starting from Boc-L-phenylalanine. In our synthesis, the stereochemistry of the hydroxyl group was set by a highly diastereoselective aldol addition with furan. Control of the stereochemistry of the isopropyl group was accomplished by heterogeneous catalytic hydrogenation.



1

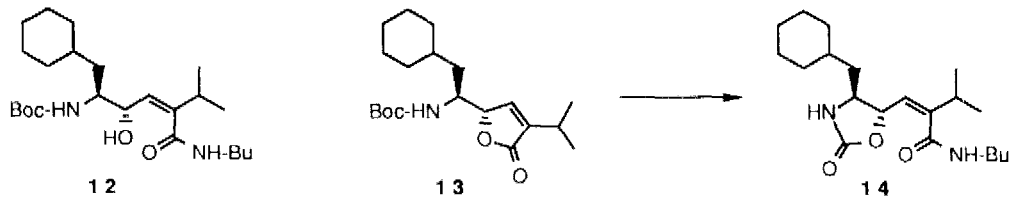
Figure 1

Amide **2**, (Scheme 1), was readily available from Boc-L-phenylalanine by reduction (H_2, PtO_2, EtOH, 98%) followed by amide formation (CH_3NHOCH_3, 1,1'-carbonyldiimidazole, Et_3N, THF, 95%).[6] Reduction (LAH, Et_2O, 93%) of amide **2**[7] provided aldehyde **3** which underwent smooth reaction with 2-furyllithium in the presence of zinc bromide (furan, n-BuLi, $ZnBr_2$, THF, 91%) to provide furyl alcohol **4**.[8] The aldol reaction proceeded with >10:1 diastereoselectivity and furnished predominantly the desired S-hydroxyl diastereomer.[9] In the absence of $ZnBr_2$, a 1:1 mixture of diastereomeric alcohols was obtained. The stereoselectivity can be explained by assuming coordination of the zinc with the aldehyde and the Boc group.



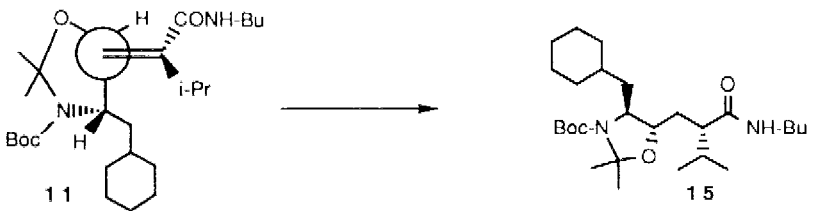
Scheme 1

Protection (2,2-dimethoxypropane, PpTSA, CH_2Cl_2, 78%) of the free hydroxyl in **4** as part of an oxazolidine ring provided compound **5**. The furanyl ring was then cleaved oxidatively ($RuCl_3$-H_2O, $NaIO_4$, H_2O, CH_3CN, CCl_4, 80%) to give acid **6**.[10] Conversion (CH_3NHOCH_3, 1,1'-carbonyldiimidazole, Et_3N, THF, 80%) of acid **6** to amide **7** followed by reduction (LAH, Et_2O, 95%) provided aldehyde **8**. Aldehyde **8** was then reacted ($KN(TMS)_2$, THF, 81%) with the phosphonate reagent **9** to furnish ester **10** (Z:E, 20:1), which was obtained as a single isomer after chromatography.[11] Phosphonate reagent **9** had been prepared from bis(2,2,2-trifluoroethyl)-(methoxycarbonyl-methyl)phosphonate and 2-iodopropane (DMSO, t-BuOK, 62%). Next, amide **11** was obtained from ester **10** by application of the Weinreb[12] amidation reaction (n-$BuNH_2$, $(CH_3)_3Al$, 1,2-dichloroethane, 88%).



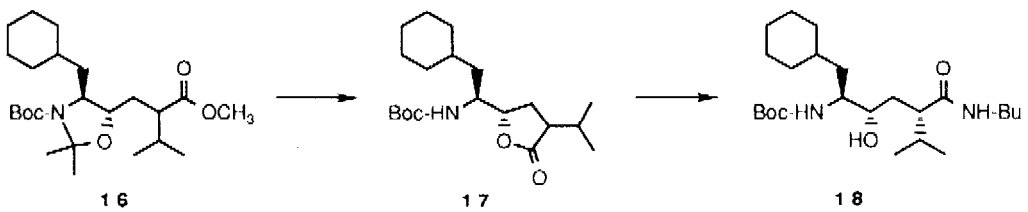
Scheme 2

Our original plans to control the stereochemistry of the isopropyl group involved hydroxyl directed hydrogenation of hydroxy amide **12**, (Scheme 2).[13] However, all efforts (HCl, dioxane, followed by Boc_2O, or 10% HCl, CH_3CO_2H, THF) to obtain hydroxy amide **12** from amide **11** failed and produced lactone **13** instead. We attempted to reopen lactone **13** using the Weinreb[12] amidation conditions, but the reaction required forcing conditions (n-$BuNH_2$, $(CH_3)_3Al$, 1,2-dichloroethane, 70°, 18 hrs, 61%) and produced carbamate **14.**



Scheme 3

Attention was then focused on finding alternative substrates for hydrogenation. Lactone **13** was not suitable since it was expected that hydrogenation of **13** would produce predominantly the wrong isopropyl stereochemistry.[14] Analysis of amide **11**, however, indicated that nonbonding interactions might influence the facial selectivity of hydrogenation to favor formation of the desired 2S isopropyl stereochemistry, (Scheme 3).[15] Indeed, hydrogenation (H_2, Rh/Al_2O_3, THF) of **11** provided a (7:3) mixture of diastereomers from which the major isomer, amide **15**, was isolated in 70% yield after purification by chromatography. Treatment of **15** with acid (HCl, dioxane, 84%) provided the hydroxyethylene dipeptide isostere **1**.



Scheme 4

To verify the stereochemistry of the isopropyl group in amide **15**, ester **10** was reduced (H_2, Rh/Al_2O_3, THF) to provide esters **16**, (Scheme 4). The hydrogenation produced a (1:1) mixture of diastereomers which were separated by chromatography (A 45%, B 33%). Treatment of esters **16** with aqueous acid (10% HCl, CH_3CO_2H, THF, A 83%, B 95%) gave lactones **17** which were used in NOE experiments to identify the diastereomer having the 2S configuration. 2S-**17** was then subjected to the Weinreb[12] amidation conditions (n-$BuNH_2$, $(CH_3)_3Al$, 1,2-dichloroethane) to furnish amide **18**. Amide **18** was also prepared by partial hydrolysis (10% HCl, CH_3CO_2H, THF, 89%) of amide **15**. The two products were identical which confirmed that the 2S diastereomer, **15**, was the major product produced by hydrogenation of amide **11**.

Acknowledgement: We thank Dr. Denis Ryono for helpful discussions.

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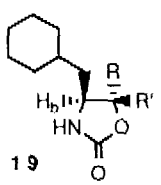

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Major Isomer: H_a, δ = 5.1 ppm; J_{ab} = 6.8 Hz (R = C_4H_3O, R' = H_a)
Minor Isomer: H_a, δ = 5.6 ppm; J_{ab} = 7.9 Hz (R = H_a, R' = C_4H_3O)

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