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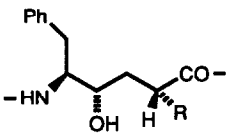
Stereoselective Synthesis of a Hydroxyethylene Dipeptide Isostere

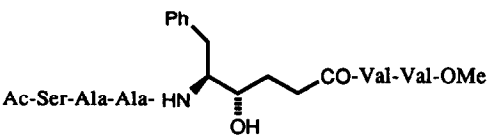
Ann M. Diederich and David M. Ryckman*
Synthetic Chemistry Department
SmithKline Beecham Pharmaceuticals
709 Swedeland Road
King of Prussia, Pennsylvania 19406

Abstract : *A stereoselective synthesis of a hydroxyethylene dipeptide isostere for Phe-Gly, (4S, 5S)-4-hydroxy-5-amino-6-phenylhexanoic acid, is described. The use of dibenzyl protecting groups on ketoamine* ***5*** *accounts for the selectivity on reduction. Also, the dibenzyl group plays a role in directing the introduction of a third chiral center.*

Currently there is active interest in the therapeutic action of enzyme inhibitors. In particular, aspartyl protease inhibitors are active against the HIV-1 virus in vitro.[1] For effective inhibition, attention has focused on the replacement of a hydrolyzable peptide bond with a non-hydrolyzable isostere that can mimic the transition state. One such structure, (*4S, 5S*)-4-hydroxy-5-amino-6-phenylhexanoic acid, **1**, is an isosteric analog of the dipeptide Phe-Gly. Substitution of this subunit for the labile Tyr-Pro dipeptide of oligopeptide enzyme substrate, as in peptide **2**, yields a potent inhibitor of HIV-1 protease. Since structure activity relationships have shown that the *4S, 5S* stereochemistry in **1** is essential for biological activity, a stereoselective synthesis is required.



1



2

Our effort, shown in Scheme I, relies on the chirality of L- phenylalanine to establish the new centers.[2] Thus, *N,N*-dibenzyl-L-phenylalanine **3**[3] was converted to dibenzyl-L-phenylalanine *N'*-methyl-*O*-methylcarboxamide **4** by reaction with N,O-dimethylhydroxylamine • HCl in DMF using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide • HCl (WSC), hydroxybenztriazole hydrate, DMAP, and Hunig's base in DMF. The reaction was quenched with 5 % $NaHCO_3$. The solution was stirred for 2h to allow the product to crystallize (mp. 65.0-66.0 °C, $[\alpha]_D$ = +55.5°, c=1.0 in $CHCl_3$,92% yield)[4]. Reaction with the Grignard reagents[5,6] derived from 2-(2-bromoethyl)-1,3-dioxolane or 2-(2-bromoethyl)-1,3-dioxane in THF gives aminoketones **5** and **6**, both in greater than 90% yield. The advantage of preparing ketone **6** is that it is a solid (mp. 66-68 °C, $[\alpha]_D$ = -68.1, c=0.74 in $CHCl_3$) and, therefore, may be crystallized, whereas ketone **5** is an oil ($[\alpha]_D$ = 108, c=1.0 in $CHCl_3$) and requires chromatography in order to separate it from impurities formed in the preparation of the Grignard reagent. Reduction of the carbonyl group in **5** and **6** with $NaBH_4$ in methanol at 0 °C provides diastereomeric alcohol pairs **7/8** and **9/10** respectively in 95% overall yield. The ratio of desired alcohols **8** and **10** to undesired **7** and **9** is 25:1 or better in both cases.[7] The diastereomers **7/8** are easily separated by flash chromatography. Since the six-membered acetal again imparts crystallinity, diastereomers **9** and **10** are easily separated by fractional crystallization. With a single recrystallization of the crude reaction mixture, the ratio is improved to 1/150 giving **10** in 80% isolated yield. Undesired diastereomers **7** and **9** may be cycled to **8** and **10** by an oxidation-reduction sequence.[8] The selectivity may be explained by examination of the Newman projection for the dibenzyl protected

aminoketones **5** and **6**, see Figure 1A.[9] Based on steric arguments, the conformer shown should be preferred. Consequently, the hydride is delivered from the least hindered (si) face. The relative stereochemistry in **8** was confirmed by X-ray crystallography on racemic **8**, see Figure 1B.[10(a)]

Treatment of **8** or **10** with 3N HCl in THF affords lactols **11** as an oily 1:1 mixture of epimers in 92% combined yield after basic extractive workup, see Scheme 1. Without separation, Jones oxidation of the mixtures gives aminolactone **12** (mp. 171.0-171.5 °C, $[\alpha]_D$ = +15.9°, c=1.1 in $CHCl_3$, 95% yield) in nearly quantitative yield after recrystallization from dichloromethane. The dibenzyl protecting groups are readily converted to a Boc group by catalytic transfer hydrogenolysis using Pd black in 5% formic acid/methanol. The reaction is almost instantaneous. Basic extractive workup followed by reaction with $(BOC)_2O$ in DMF and NEt_3 gives **15** (mp. 92.0-92.8 °C, $[\alpha]_D$ = +0.64°, c = 2.7 in $CHCl_3$, 50% yield).

Scheme 1

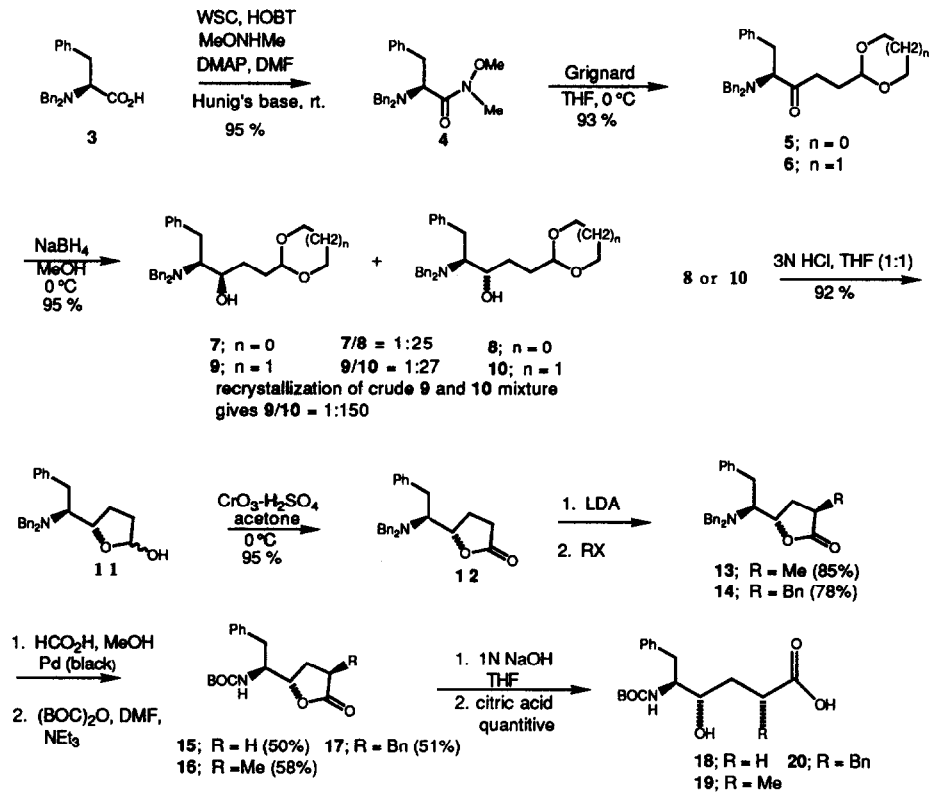
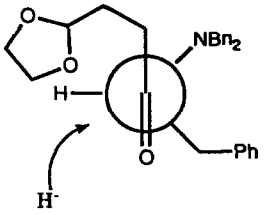
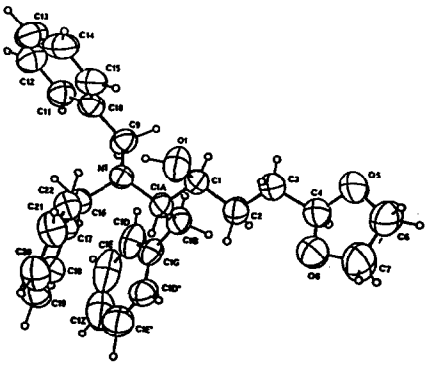


Figure 1



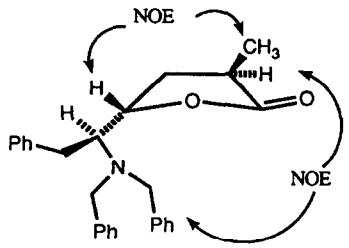
1A Felkin-Ahn Model for **5**



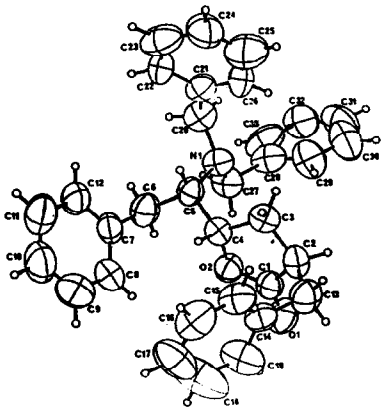
1B X-ray Structure of **8**

A third chiral center is readily introduced in a stereoselective manner[11]. Treatment of the lactone **12** with 1 equivalent of LDA at -78 °C for 30 min followed by the addition of methyl iodide gives alkylated lactone **13** (mp. 127.2-127.6 °C, $[\alpha]_D$ = +15.2°, c = 0.95 in $CHCl_3$, 77% yield) exclusively. The observed selectivity may be explained by coordination of the lone pair electrons on nitrogen to the lithium enolate, thus blocking the bottom face toward electrophillic attack. The stereochemistry of the alkylated product was readily determined by N.O.E. difference spectroscopy. An observed N.O.E. between the C2 methyl group and the C4 methyne proton indicates a cis relationship. Secondly, on irradiation of the C2 methyne proton, a strong N.O.E. was observed in the aromatic region, indicating a cis relationship with the aryl side group, see Figure 2A. In the same manner, a benzyl group may be introduced stereoselectively. The alkylation may be conducted at 0 °C with no loss in selectivity to give lactone **14** (mp. 113.0-113.2 °C, $[\alpha]_D$ = -18.2°, c = 0.96 in $CHCl_3$, 82.% yield). The stereochemistry was confirmed by X-ray diffraction analysis, Figure 2B.[10(b)] The transfer of the protecting groups may be accomplished as above to give lactones **16** (mp. 129-130 °C, $[\alpha]_D$ =+9.25°, c = 1.05 in $CHCl_3$, 58% yield) and **17** (mp. 89-91 °C, $[\alpha]_D$ = -17.3 °, c = 1.2 in $CHCl_3$, 51% yield). The lactones **15**, **16**, and **17** can be opened by basic hydrolysis[12] to give structures **18** (mp. 111-113 °C), **19** (mp. 126-127 °C), and **20** (mp. 124-125 °C) analogous to **1**.

Figure 2



2A



2B X-ray Structure of **14**

In conclusion, we have demonstrated a synthesis of the key hydroxy-ethylene isostere required for a potent HIV-1 protease inhibitor. An advantage of this route is the high selectivity in the non-chelation controlled reduction of the carbonyl group in **5** or **6**. Furthermore, the resultant diastereomers **9** and **10** are easily separated by crystallization making chromatography unnecessary. The route makes further use of the dibenzyl protecting groups to control the stereochemistry on introduction of a third chiral center. Since this synthesis relies on the chirality of the starting amino acid for the introduction of the subsequent centers, the enantiomers are readily available from D-phenylalanine.

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Notes and References.

1. Dreyer, G.B.; Lambert, D. M.; Meek, T.D.; Carr, T.J.; Tomaszek, T. A., Jr.; Fernandez, A. V.; Bartus, H.; Cacciavillani, E.; Hassel, A. M.; Minnich, M.; Petteway, S. R., Jr.; Metcalf, B. W. *Biochemistry* **1992**, *31*, 6646 and references cited therein for previous syntheses of molecules of this type.
2. D-phenylalanine was subjected to the same set of chemical transformations. Racemization was not detected at any step by comparative HPLC analysis. Conditions; Chiralcel OD column (25 cm x 0.46cm), isocratic elution with 30:70 2-propanol-hexane at 0.5 mL/min gave baseline separation of enantiomers at ambient. The detector was set at 230 nm.
3. Reetz, M.T.; Drewes, M.W.; Matthews, B.R.; Lennick, K. *J. Chem. Soc. Chem. Commun.* **1989**, 1474.
4. All new compounds gave satisfactory spectroscopic and microanalytical (or high resolution mass spectral) data.
5. Goel, O.P.; Krolls, U.; Stier, M.; Kresten, S. *Org. Syn.* **1988**, 67, 69.
6. Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217.
7. As determined by HPLC analysis, **8**:**7** or **10**:**9** is 25:1.
8. Swern oxidation of **7** to give **5**, then reduction as before.
9. For a discussion of chelation and non-chelation controlled reductions in series similar to this, see; Reetz, M.T.; Drewes, M.W.; Schmitz, A. *Angew. Chem.* **1987**,*99*, 1186.; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141.
10. (a) rac-**8**: $C_{28}H_{33}NO_3$. Irregular prism, space group P1 triclinic #2, a = 10.236(7) Å, b = 11.291(6) Å, c = 12.394(10) Å, α = 87.27(5)°, β = 71.20(6)°, γ = 63.23(5)°, V = 1202.4(13) A^3, Z = 2, ρ (calc) = 1.192 g cm^{-3}, μ = 5.693 cm^{-1}, F(000) = 464. (b) **14**: $C_{33}H_{33}NO_2$. Needles, space group $P2_12_12_1$ orthorhombic #19, a = 9.22(2) Å, b = 15.57(3) Å, c=18.88(5) Å, V = 2713(1) $Å^3$, Z = 4, ρ (calc) = 1.164 g cm^{-3}, μ = 0.666 cm^{-1}, F(000) = 1016. The structures were determined using a Enraf-Nonius CAD 4 diffractometer. The structures were solved by direct methods using the SHELXS program series. Further details are available upon request.
11. Alkylation of an NBOC protected lactone, albeit in lower yield, has been reported in a similar series, Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828.
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