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Diastereoselective Synthesis of the Hydroxyethylene Dipeptide Isostere of Leu-Val

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The synthesis of hydroxyethylene dipeptide isostere of Leu-Val, a transition-state mimic, is described. The key steps of this synthetic approach are the homogeneous asymmetric hydrogenation of γ-keto esters by BINAP-Ru(II) complex, and the construction of a 2(S)-isopropyl unit.

Renin is an aspartic proteinase responsible for cleaving a decapeptide fragment from angiotensinogen and participates in the regulation of blood pressure. The search for renin inhibitors has intensified in recent years for control of hypertension. Numerous approaches to the design of renin inhibitors have been investigated. The most notable approach has been based upon the concept of a transition-state analogues,[1] such as the statine analogue (1)[2] and the hydroxyethylene dipeptide isostere at the scissile site (2)[3] (Fig. 1).

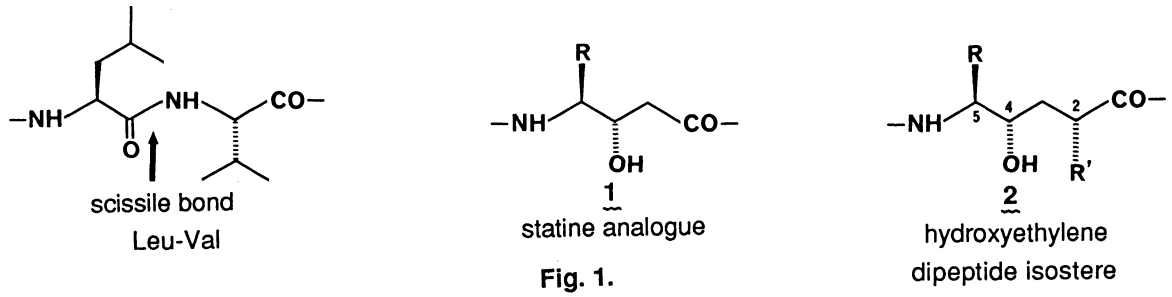


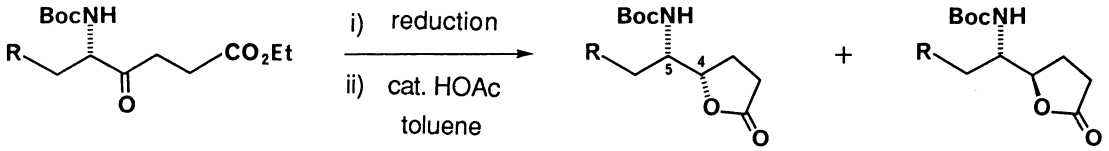
Fig. 1.

For the stereoselective introduction of the 2(S)-isopropyl unit, syn-γ-lactones (4a,b) are apparently useful precursors, since stereoselective trans alkylation at C-2 could be expected.[4] In our previous report, syn-γ-lactones were prepared starting from diacetone-D-glucose as the chiral building block, although this synthetic route required a number of steps.[5]

We report here an alternative synthetic route to syn-γ-lactones based on the reduction of the γ-keto esters (3a,b). The γ-keto esters (3a,b) were obtained in good yield from the corresponding N-Boc-L-amino aldehyde in three steps.[6] As shown in Table 1, reduction of γ-keto esters (3a,b) with reagents followed by cyclization produced the corresponding γ-lactones (4a,b and 5a,b). Several reducing reagents under various conditions were tried for the stereoselective reduction. Reduction with the periodic trend of borohydride reagents (runs 1-5) provided the undesired anti-γ-lactone as the major product regardless of the reagent. Further, reduction with bulky reagents resulted in low yield with low stereoselectivity

(runs 6-8). We turned our attention on the homogeneous asymmetric hydrogenation. In our previous report, diastereoselective hydrogenation of N-Boc-γ-amino β-keto esters catalyzed by BINAP-Ru(II) complex provided an efficient entry to the statine analogues with high enantiomeric purities.[2] Using the same conditions as reported, hydrogenation did not proceed even at room temperature. Reduction was successfully accomplished using ethanol as the solvent under 100 atm of hydrogen at 100 °C in the presence of 0.2 mol% of BINAP-Ru(II) complex.[7] Thus obtained hydroxy esters were not isolated but lactonized directly in refluxing toluene containing acetic acid. The desired 4a,b were the major products in high yield (runs 9-10).
To examine these enantiomeric purities, amino protecting group of 4a,b were removed to the corresponding free base and was condensed with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) by the reported method.[8] HPLC analysis of the resulting thioureas indicated them to be >98% e.e. (4a; column, Senshu Pak silica-1251-N 4.6 i.d. x 250 mm; eluent, 96 : 4 hexane–2-propanol mixture; flow rate, 1.5 ml/min; t_R of (4S,5S)-isomer, 44.0 min; t_R of (4R,5R)-isomer, 40.4 min. 4b; eluent, 97 : 3 hexane–2-propanol mixture; t_R of (4S,5S)-isomer, 44.2 min; t_R of (4R,5R)-isomer, 40.6 min).

Table 1. Reduction of γ-keto esters **3a,b**



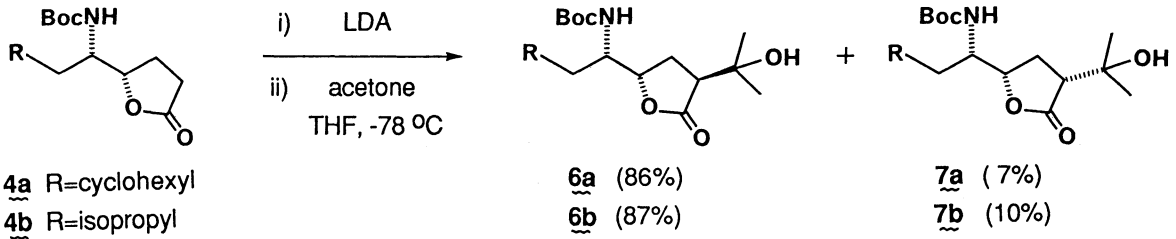
3a, R=cyclohexyl **4a** **5a**
3b, R=isopropyl **4b** **5b**

Run	Substrate	Reducing reagent	Conditions	Yield of 4+5/%[a]	ratio of 4:5[b]
1	**3a**	$NaBH_4$	EtOH,0 °C,30 min	92	27 : 73
2	**3a**	$NaBH_4$	THF,0 °C,30 min	73	44 : 56
3	**3a**	$LiBH_4$	THF,-78 °C,4 h	51	35 : 65
4	**3a**	KBH_4	EtOH,0 °C,6 h	98	23 : 77
5	**3a**	$Zn(BH_4)_2$	Et_2O,0 °C,2 h	93	30 : 70
6	**3a**	$LiAlH(O^tBu)_3$	THF,-78 °C,2 h	75	37 : 63
7	**3a**	K-Selectride	THF,-78 °C,2 h	low yield	-
8	**3a**	LS-Selectride	THF,-78 °C,2 h	low yield	-
9	**3a**	H_2/$RuBr_2$[(*R*)-binap][7]	EtOH,100 °C,3 d	98	85 : 15
10	**3b**	H_2/$RuBr_2$[(*R*)-binap]	EtOH,100 °C,3 d	97	87 : 13

a) Isolated yield. b) The ratios of diastereoisomers were determined by gas chromatography (2% OV-225 chromosorb W, column temp 180-215 °C).

Several attempts to introduce an isopropyl unit into 4a,b using isopropyl halides were unsuccessful. Finally acetone was examined as an electrophile to give desired product as a mixture of diastereomers. As expected, reaction occurred with high stereoselectivity from the less hindered face to give the β-substituted γ-

lactones (6a,b) in good yield (Scheme 1).[9] The diastereomers 6 and 7 can be conveniently separated by column chromatography on SiO_2.



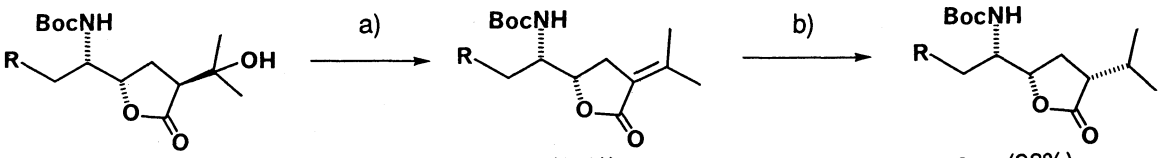
4a R=cyclohexyl
4b R=isopropyl

6a (86%)
6b (87%)

7a (7%)
7b (10%)

Scheme 1.

At first we examined the conversion of 6 and 7 into 11 by an initial dehydration and subsequent hydrogenation of 6a,b. Treatment of 6a,b with $POCl_3$ in pyridine followed by a catalytic hydrogenation of 8a,b by Pd on $BaSO_4$ gave undesired diastereomers 9a,b[9] (Scheme 2). Whose structures were determined by X-ray crystallographic analysis. Attempts to epimerize the isopropyl unit of 9a,b with DBU/DMF at 100 °C was not satisfactory to give a mixture of equilibrium products in a ratio of β/α isomers (1 : 2).



6a R=cyclohexyl
6b R=isopropyl

8a (89%)
8b (86%)

9a (98%)
9b (97%)

a) $POCl_3$, pyridine, 0 °C. b) H_2(4 atm)/ Pd on $BaSO_4$, AcOEt.

Scheme 2.

Next, deoxygenation of 6a,b was studied to obtain 11a,b. Mild conditions were required in this reaction, because the retro-aldol reaction could easily occur under basic conditions.[10] Finally, this was accomplished via 2 step sequence of reactions reported by Dolan and MacMillan.[11] Treatment of 6a,b with methyl oxalyl chloride gave 10a,b in good yield. Then reaction of 10a,b with tributyltin hydride and AIBN in refluxing toluene gave the desired 2(S)-isopropyl-γ-lactones (11a,b).[9] The γ-lactones 11a,b were readily converted to hydroxyamides 12a,b by treatment with methylamine in good yield as shown in Scheme 3.[9] In conclusion, starting from γ-keto esters (3a,b), a short and diastereoselective synthetic route to the hydroxyethylene dipeptide isostere of Leu-Val was established. The biological activities of low molecular-weight renin inhibitors which contain these fragment will be reported elsewhere.

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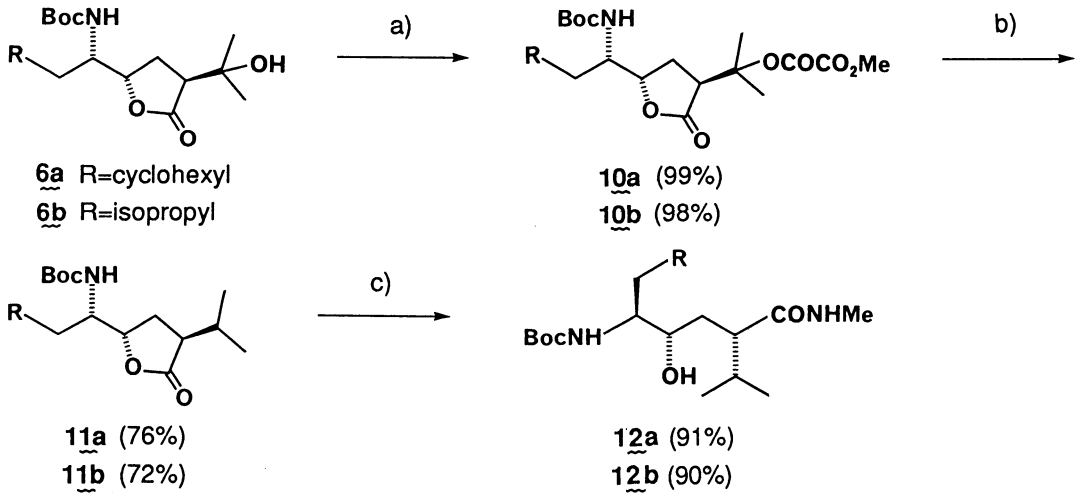

a) MeOCOCOCl, NEt_3, cat. DMAP, THF, 0 °C.b) *n*-Bu_3SnH, AIBN, PhMe.c) $MeNH_2$,MeOH.

Scheme 3.

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6) i) lithium ethyl propiolate, THF, -78 °C, ii) H_2(4 atm)/Pd on $BaSO_4$, AcOEt, iii) PCC, molecular sieves 3A, CH_2Cl_2.
7) R.Noyori, T.Ohkuma, M.Kitamura, H.Takaya, N.Sayo, H.Kumobayashi, and S.Akutagawa, J.Am.Chem.Soc., 109, 5856 (1987).
8) N.Nimura, H.Ogura, and T.Kinoshita, J.Chromatogr., 202, 375 (1980).
9) Satisfactory spectral (NMR,IR,MS) and analytical data were obtained for all new compounds.
6a, mp 123-125 °C, $[\alpha]_D^{20}$ -20.6°(c 1,MeOH). 6b, mp 93-95 °C, $[\alpha]_D^{20}$ -27.5°(c 1, MeOH). 7a, mp 141-143 °C, $[\alpha]_D^{20}$ -30.4°(c 1,MeOH). 7b, mp 113-115 °C, $[\alpha]_D^{20}$ -35.1°(c 1,MeOH). 9a, mp 133-134 °C, $[\alpha]_D^{20}$ -23.4°(c 1,MeOH). 9b, mp 94-96 °C, $[\alpha]_D^{20}$ -32.0°(c 1,MeOH). (lit.[3] mp 94-96 °C, $[\alpha]_D^{20}$ -32.4°(c 1,EtOH).) 11a, mp 114-116 °C, $[\alpha]_D^{20}$ -30.6°(c 1,MeOH). 11b, mp 144-146 °C, $[\alpha]_D^{20}$ -36.6°(c 1,MeOH). (lit.[3] mp 146-148 °C, $[\alpha]_D^{20}$ -39.4°(c 1,EtOH).) 12a, mp 154-157 °C, $[\alpha]_D^{20}$ -42.0° (c 0.75,MeOH). 12b, mp 149-151 °C, $[\alpha]_D^{20}$ -51.9°(c 1,MeOH).
10) We examined Barton's method (NaH,CS_2,MeI); however the retro-aldol reaction predominated, and the other modification methods were unsuccessful.
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