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A New Synthetic Route for the γ-Lactone Precursors of Hydroxyethylene Dipeptide Isosteres

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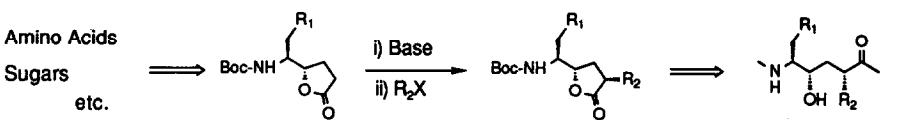
Abstract: *δ-Phthalimido-γ-ketoesters were obtained by the Pd catalyzed coupling reaction between acid chlorides and organozinc reagents derived from β-iodoesters, and were converted into the γ-lactone precursors of Phe-ψ[H.E.]-Ala and Phe-ψ[H.E.]-Pro (**15a,b-18a,b**).*

The hydroxyethylene dipeptide isostere mimics the tetrahedral intermediate formed when an aspartic proteinase hydrolyzes an amide bond. The peptides which possess this dipeptide isostere at the scissile site of substrates demonstrate strong inhibitory activity against the proteinases by virtue of the interaction of the hydroxyl group with the catalytic aspartic acids.[1] Therefore, the synthesis of hydroxyethylene dipeptide isosteres has drawn widespread attention and been extensively studied in many laboratories.[2] One of the most practical synthetic accesses to them is the stereoselective alkylation of γ-lactones **1**, which are derived from amino acids, sugars or other chiral sources, to yield *trans*-alkylated γ-lactones **2** as shown in Scheme 1.[3]



1 **2**

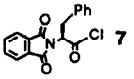
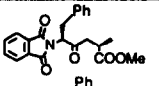
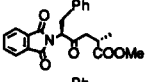
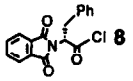
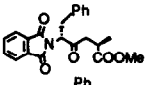
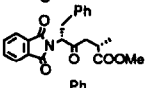
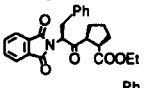
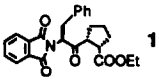
Scheme 1

In our early study of inhibitors of HIV-1 protease, which belongs to the aspartic proteinase, we were unable to utilize the above methodology. Since *cis*-alkylated γ-lactones and stereochemically defined phenylalanylproline hydroxyethylene dipeptide isosteres (Phe-ψ[H.E.]-Pro)[4] were necessary for the initial study of the structure-activity relationship, we developed a new synthetic route accessible to all stereoisomers of hydroxyethylene dipeptide isosteres. Herein, we report that the δ-amino-γ-ketoesters, which hitherto have required several steps for preparation,[5] were synthesized by one step utilizing Jackson's procedure.[6] Subsequent conversion to the γ-lactones by reduction of these δ-amino-γ-ketoesters gave the respective four diastereomers (**15a,b-18a,b**), the latter being precursors of phenylalanylalanine hydroxyethylene dipeptide isosteres (Phe-ψ[H.E.]-Ala) and Phe-ψ[H.E.]-Pro.

The β-iodoester starting materials **3** and **4** were prepared by the iodination of commercially available methyl (-)- and (+)-3-hydroxy-2-methylpropionates via the tosylates, respectively.[7] Ethyl (1*S*, 2*R*)-2-iodocyclopentanecarboxylate **5** was afforded by the substitution of *p*-nitrobenzenesulfonate of ethyl (1*R*, 2*S*)-2-hydroxycyclopentanecarboxylate, which was obtained by the assymetric reduction of ethyl 2-oxocyclopentanecarboxylate using baker's yeast,[8] with sodium iodide. Using sodium borohydride instead of baker's yeast gave racemic *trans* and *cis* ethyl 2-iodocyclopentanecarboxylates ((±)-**5** and (±)-**6**) after separation by silica gel column chromatography.

Results of the coupling reactions between the organozinc reagents derived from these β-iodoesters and *N*-phthaloylphenylalanyl chloride in the presence of catalytic $(Ph_3P)_2PdCl_2$ under sonication are shown in Table 1.[9] The objective δ-phthalimido-γ-ketoesters were isolated in moderate to good yields. Comparisons of both the optical rotations of compounds **9** and **12** and the 270 MHz ^{1}H-NMR spectra of crude compounds **9** and **10** reveal that neither racemization nor epimerization occurs during this reaction. Interestingly, ethyl (1*S*, 2*R*)-2-iodocyclopentanecarboxylate **5** yielded the *cis*-substituted cyclopentane **13** without the production of the *trans*-substituted cyclopentane. The stereochemistry of compound **13** was established by X-ray crystallography.[10] The racemic *trans* and *cis* β-iodoesters ((±)-**5** and (±)-**6**) also gave only compounds **13** and **14** in the ratio of *ca* 2:3. We presume that exclusive formation of the *cis*-substituted cyclopentane system may be ascribed to a stable organozinc species which can be chelated with the oxygen of cyclopentanecarboxylate, but the detailed mechanism of this selectivity is now under investigation.

Table 1 Preparation of δ-Phthalimido-γ-ketoesters[a)]

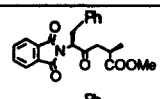
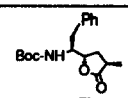
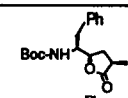
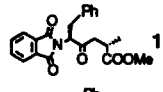
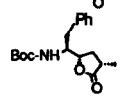
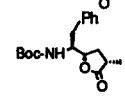
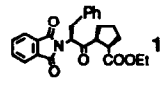
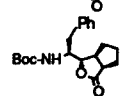
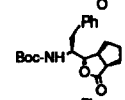
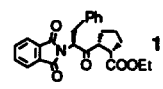
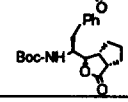
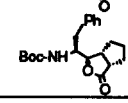
Entry	Iodide	Acid Chloride	Products[11]	(Isolated Yield[b)]; $[\alpha]_D^{25}$, CH_3Cl)
1	 **3**	 **7**		**9** (47%; -155.0°, c = 0.95)
2	 **4**	**7**		**10** (62%; -161.4°, c = 1.07)
3	**3**	 **8**		**11** (61%; +158.0°, c = 1.09)
4	**4**	**8**		**12** (57%; +150.2°, c = 1.06)
5	 **5**	**7**		**13** (27%; -180.4°, c = 1.04)
6	 (±)-**5**	**7**	**13** (23%) + 	**14** (33%; -119.2°, c = 1.01)
7	 (±)-**6**	**7**	**13** (13%) + **14** (22%)	

a) Reaction condition: iodide (1eq), Zn-Cu (1.7eq), benzene-DMF (15:1), sonication, 40min, 30°C, then $(Ph_3P)_2PdCl_2$ (0.05eq), acid chloride (1.05eq), sonication, 40min, 35°C. (Ref. 9) b) unoptimized.

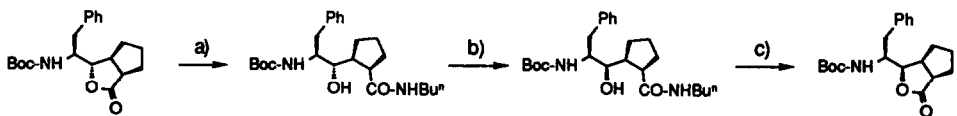
Subsequently, these δ-phthalimido-γ-ketoesters were converted into the *N*-Boc-γ-lactones (Table 2). Initially, reduction of the γ-ketoesters with sodium borohydride followed by acid hydrolysis and amino

protection afforded the objective *N*-Boc-γ-lactones (method A). However, compounds **9** and **10** were only partially hydrolyzed, resulting in low yields of the γ-lactones. Therefore, after sodium borohydride reduction, the resultant alcohols were subjected to ring closure to form the γ-lactones, which were further oxidized with PCC to give phthalimido-γ-lactones. Deprotection of the phthaloyl group by methylamine[12] and protection with $(Boc)_2O$ followed by acid treatment afforded the objective γ-lactones in good yield (method B). On the other hand, since only a slight amount of compound **17b** was obtainable, compound **17a** was transformed into **17b** in 35% overall yield as shown in scheme 2.

Table 2 Conversion of γ-Ketoesters into *N*-Boc-γ-lactones

Entry	γ-ketoester	Products [a),13]		Method [b]	Isolated Yield[14] a	Isolated Yield[14] b
1	 **9**	 **15a**	 **15b**	A B	10.0% 7.4%	7.0% 43.4%
2	 **10**	 **16a**	 **16b**	A B	20.6% 54.7%	c) 5.5%
3	 **13**	 **17a**	 **17b**	A	55.6%	0.4%
4	 **14**	 **18a**	 **18b**	A	43.9%	12.9%

a) The stereochemistry of these products was determined by measuring NOE between C3 and C5 protons of γ-lactones. b) Method A; i) $NaBH_4$, ii) HCl, iii) $(Boc)_2O$. Method B; i) $NaBH_4$, ii) AcOH, iii) PCC, iv) $MeNH_2$, v) $(Boc)_2O$, vi) AcOH. c) not isolated.



17a → **19a** (100%) → **19b** (35%) + **19a** (45%) → **17b** (100%)

Scheme 2; a) *n*-butylamine, b) i) Dess-Martin Periodinane, ii) $NaBH_4$-$CeCl_3$, c) AcOH.

In conclusion, we succeeded in obtaining the respective four γ-lactone precursors of Phe-ψ[H.E.]-Ala and Phe-ψ[H.E.]-Pro. Compounds **17a,b** and **18a,b** were converted into the *trans*-substituted cyclopentanes by epimerization at the α carbon with base treatment after the lactone rings were opened with *n*-butylamine.[15] Thus, four diastereomers of Phe-ψ[H.E.]-Ala and eight diastereomers of Phe-ψ[H.E.]-Pro could be prepared. The stereochemistry-activity relationship of HIV-1 protease inhibitors containing these hydroxyethylene dipeptide isosteres will be reported separately.[15]

References and Notes

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Furukawa, Y.; *Tetrahedron Lett.* **1989**, *28*, 3369. e) Kano, S.; Yokomatsu, T. and Shibuya, S.; *Tetrahedron Lett.* **1991**, *32*, 233. f) Plata, D.J.; Leanna, M.R. and Morton, H.E.; *Tetrahedron Lett.* **1991**, *32*, 3623. g) D'Aniello, F.; Géhanne, S. and Taddei, M.; *Tetrahedron Lett.* **1992**, *33*, 5621.

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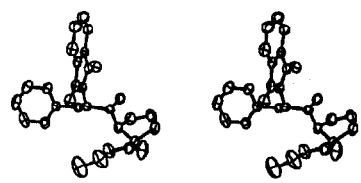
7. All the compounds gave satisfactory spectral data and elemental analyses.
8. Deol, B.S.; Ridley, D.D. and Simpson, G.W.; *Aust. J. Chem.* **1976**, *29*, 2459.
9. Typical experimental procedure: Under a nitrogen atmosphere, methyl (*S*)-3-iodo-2-methylpropionate **3** (2.00g, 8.77mmol) in benzene (5ml) was added to a suspension of zinc-copper couple (0.97g, 14.91mmol) in a mixture of benzene and *N,N*-dimethylformamide (11ml, 10:1), and the mixture was sonicated for 40 min at 30°C (Nihonseiki NS-200 sonicating bath). To this reaction mixture was slowly added a suspension of $(Ph_3P)_2PdCl_2$ (308mg, 0.44mmol) in benzene (5ml), and the mixture was stirred for 5 min at room temperature. *N*-Phthaloyl-L-phenylalanyl chloride (2.89g, 9.21mmol) in THF (5ml) was rapidly added, and the reaction mixture was sonicated for 40 min at 35°C. Quenched by the addition of AcOEt and 1N HCl, the reaction mixture was partitioned. The organic layer was washed with 1N HCl, 5% $NaHCO_3$ and brine, and then dried over Na_2SO_4. Evaporation and purification by silica gel chromatography (eluent: toluene→*n*-hexane:AcOEt=10:1→4:1) followed by crystallization from *n*-hexane afforded compound **9** (1.56g, 47%) as colorless crystals.
10. Crystallographic data for compound **13**: $C_{25}H_{25}NO_5$, monoclinic, $B2_1$, a = 16.193(2), b = 26.184(2), c = 10.600(1) Å, β = 92.14(1)°, V = 4491(1) Å^3, Z = 8, Dc = 1.24g/cm^3, μ(Cu-$K\alpha$) = 7.2 cm^{-1}, colorless prismatic crystals, 0.6 x 0.2 x 0.2 mm. Among the 3809 unique reflections collected, 3289 were considered to be observed at the 3 $\sigma(Fo)$ level. The structure was solved by the direct method with MULTAN[78] and refined by block-diagonal least-squares methods. Final refinements, with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms, lowered the R value to 0.053 (wR = 0.049). The final coordinates of this X-ray data are deposited at the Cambridge Crystallographic Data Centre.



11. 270MHz ^{1}H-NMR in $CDCl_3$; δ ppm (J, Hz) **9**: 1.17(d, J=7.3, 3H), 2.47(dd, J=4.9, 17.6, 1H), 2.91(dd, J=8.3, 17.6, 1H), 3.03-3.10(m, 1H), 3.36(dd, J=11.2, 14.6, 1H), 3.57(dd, J=4.9, 14.6, 1H), 3.68(s, 3H), 5.04(dd, J=4.9, 11.2, 1H), 7.07-7.18(m, 5H), 7.69-7.74(m, 2H), 7.75-7.80(m, 2H). **10**: 1.20(d, J=7.3, 3H), 2.52-2.66(m, 1H), 2.94-3.09(m, 2H), 3.45(dd, J=11.2, 14.5, 1H), 3.58(dd, J=5.3, 14.5, 1H), 3.66(s, 3H), 5.04(dd, J=5.3, 11.2, 1H), 7.10-7.20(m, 5H), 7.67-7.80(m, 4H). **13**: 1.24(t, J=7.3, 3H), 1.56-1.68(m, 1H), 1.82-2.13(m, 5H), 3.01(q, J=7.8, 1H), 3.38-3.62(m, 3H), 4.11(q, J=7.3, 2H), 5.18(dd, J=4.9, 11.2, 1H), 7.07-7.18(m, 5H), 7.66-7.71(m, 2H), 7.73-7.78(m, 2H). **14**: 1.28(t, J=7.3, 3H), 1.51-1.67(m, 1H), 1.88-1.99(m, 4H), 2.05-2.20(m, 1H), 2.97(dd, J=7.8, 8.3, 1H), 3.29-3.37(m, 1H), 3.47-3.58 (m, 2H), 4.03-4.20(m, 2H), 5.22(dd, J=5.9, 10.3, 1H), 7.07-7.18(m, 5H), 7.65-7.72(m, 2H), 7.74-7.81(m, 2H).
12. Wolfe, S. and Hasan, S.K.; *Can. J. Chem.* **1970**, *48*, 3572.
13. mp and $[\alpha]_D^{25}$ (c, $CHCl_3$): **15a**; 133-134°C, +8.9°(0.30). **15b**; 105-106°C, -27.0°(0.24). **16a**; 129-130°C, -10.8°(1.04). **16b**; 131-133°C, -27.5°(0.98). **17a**; 142-143°C, -4.4°(0.23). **17b**; 180-183°C, -25.5°(0.14). **18a**; 173-174°C, +4.2°(0.24). **18b**; 129-130°C, -36.4°(0.14).
14. The final product ratios given in Table 2 do not precisely reflect the selectivity of the $NaBH_4$ reduction since several reactions were performed on the isomeric mixture thereafter.
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