An Efficient Synthesis of γ-Lactones as Precursors of Hydroxyethylene Dipeptide Isostere

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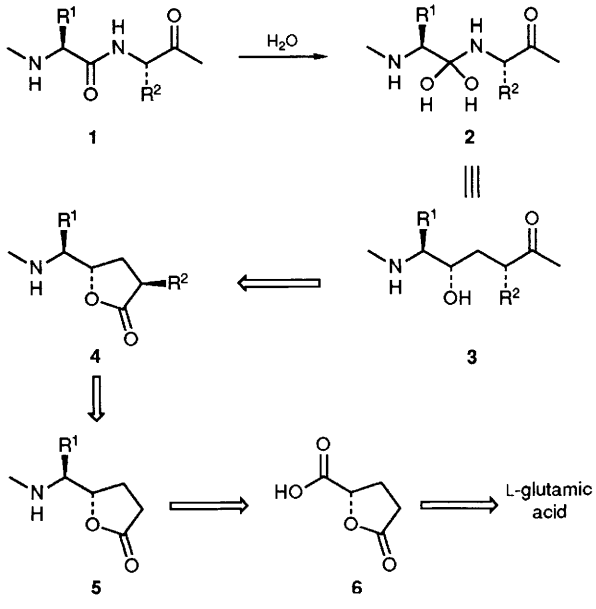
An efficient and stereocontrolled synthesis of γ-lactones as precursors of the hydroxyethylene dipeptide isostere has been developed, starting from readily available 5-oxotetrahydrofuran-2-carboxylic acid **6**.

Hydroxyethylene dipeptide isostere **3** is an attractive synthetic target in the field of medicinal chemistry.[1] This unit is chemically stable and mimics the tetrahedral intermediate **2** formed during hydrolysis of the peptide **1** by an aspartic proteinase. Thus, compounds which incorporate this unit at the cleavage site demonstrate strong inhibition against aspartic proteinases such as renin and human immunodeficiency virus type-1 (HIV-1) protease.[2]

Herein we report an efficient and stereocontrolled synthesis of γ-lactones **4** and **5**, which can be readily converted into the hydroxyethylene dipeptide unit **3**, the most potent configuration for inhibiting renin and HIV-1 protease. Stereoselective alkylation of γ-lactone **5** at C-2 from the opposite side to that of the substituent at C-4 affords γ-lactone **4**.[1c,e] Our synthesis of γ-lactone **5** employed (*S*)-(+)-5-oxotetrahydrofuran-2-carboxylic acid **6**, which is available from the cheap L-glutamic acid,[3] as a starting material (Scheme 1).

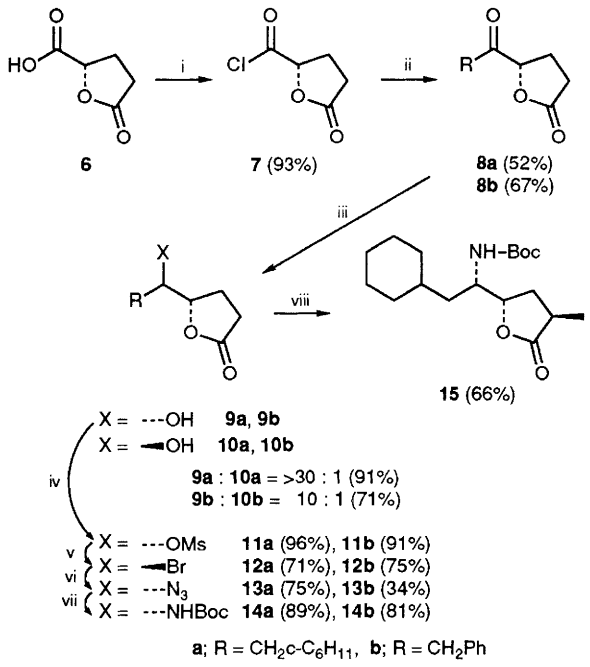
The first stage of our synthesis was to obtain *syn*-hydroxy γ-lactones by reducing the corresponding ketones diastereoselectively† (Scheme 2). Carboxylic acid **6** was converted into acid chloride **7** using thionyl chloride, which was then treated with Grignard reagents to give the ketones **8a** {m.p. 56–58 °C, $[\alpha]_D^{25}$ + 21.3 (*c* 1.0 MeOH)} and **8b** {m.p. 53–54 °C, $[\alpha]_D^{25}$ + 15.7 (*c* 1.0 $CHCl_3$)}.‡ The reduction of these ketones was then studied. Reduction with sodium borohydride afforded a *ca.* 1:2 mixture of *syn*- and *anti*-alcohols, whereas *syn*-alcohols **9a** {m.p. 71–72 °C, $[\alpha]_D^{20}$ + 16.0 (*c* 1.0 MeOH)} and **9b** {oil, $[\alpha]_D^{25}$ + 61.7 (*c* 0.7 $CHCl_3$); lit.,[4] $[\alpha]_D^{21}$ + 59.8 (*c* 1.04 $CHCl_3$)} were diastereoselectively obtained by reducing with L-Selectride (*syn*:*anti* = >30:1



Scheme 1

† All new compounds gave satisfactory spectral data and elemental analyses.

‡ Although Larchevêque *et al.* reported that the ketones corresponding to **8a** or **8b** were rapidly racemized,[5] our compounds **8a** and **8b** were stable and showed the same optical rotations after standing over four months at room temperature.



Scheme 2. *Reagents and conditions*: i, $SOCl_2$, reflux; ii, cyclo-$C_6H_{11}CH_2MgBr$ or $PhCH_2MgCl$, THF, −78 °C; iii, L-Selectride, THF, −78 °C; iv, MsCl, Et_3N, CH_2Cl_2, 0 °C; v, LiBr, THF, reflux; vi, NaN_3, DMPU, room temp.; vii, H_2, Pd/C, $(Boc)_2O$, AcOEt, room temp.; viii, LDA, THF, −78 °C, then MeI

and 10 : 1).[5] The configuration of the new asymmetric carbon was confirmed by comparison with reported spectral data.[4]

The next stage was to convert these *syn*-alcohols into the desired *syn*-amino γ-lactones. Mesylation of the *syn*-alcohols **9a** and **9b** with mesyl chloride and triethylamine followed by two S_N2 processes, substitution with LiBr and azidation with NaN_3, yielded the azides **13a** and **13b**, respectively. While the yield of **13a** was good, only a modest yield of **13b** was achieved, because a large amount of elimination product (61%) was produced during treatment of **12b** with NaN_3. Catalytic hydrogenation of the azides **13a** and **13b** over Pd/C in the presence of $(Boc)_2O$§ afforded the desired *N*-Boc-γ-lactones **14a** {m.p. 62–64 °C, $[\alpha]_D^{20}$ −28.6 (*c* 1.0 MeOH); lit.,[1g] $[\alpha]_D^{23}$ −28.0 (*c* 2.48 $CHCl_3$)} and **14b** {m.p. 94–95 °C, $[\alpha]_D^{25}$ +1.2 (*c* 0.85 $CHCl_3$); lit.,[1h] m.p. 95 °C}, respectively.[6] These intermediates were chemically stable and did not show decomposition after storage at room temperature for several months. Further, deprotonation of **14a** by LDA followed by addition of MeI gave the *trans*-methylated γ-lactone predominantly. After purification by silica gel chromatography, pure *trans*-γ-lactone **15** {m.p. 80–82 °C, $[\alpha]_D^{20}$ −24.5 (*c* 1.0 $CHCl_3$)} was easily obtained. Although a small amount of dimethylated γ-lactone (4%) was also obtained, the *cis*-methylated γ-lactone could not be isolated.

In conclusion, we have succeeded in an efficient synthesis of hydroxyethylene dipeptide isostere precursors, γ-lactones, utilizing the chirality of L-glutamic acid. This method will also serve in the preparation of hydroxyethylene dipeptide isosteres with non-proteinogenic side chains by choosing appropriate Grignard and alkylating reagents.

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§ *Abbreviations*: Boc = *tert*-butoxycarbonyl, LDA = lithium diisopropylamide, Ms = methanesulfonyl, DMPU = *N*,*N*′-dimethylpropyleneurea.

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