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SYNTHESIS OF THE LACTONE PRECURSOR TO HYDROXYETHYLENE DIPEPTIDE ISOSTERE FROM 3,4,6-TRI-O-ACETYL-D-GLUCAL

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Summary: (2S,4S,5S)-5-Amino-6-cyclohexyl-4-hydroxy-2-isopropyl hexanoic acid lactone (5) was synthesized from 3,4,6-tri-O-acetyl-D-glucal in an efficient manner.

In recent years there has been a growing interest in the use of enzyme inhibitors as therapeutic agents. It is well known that many inhibitors of the enzymes for conversion from angiotensin I to II are effective for the medical treatment of the high blood pressure, as are inhibitors of aspartyl proteases (ex. renin). To date, many statine derivatives and hydroxyethylene dipeptide isosteres have been reported as aspartyl protease inhibitors.[1]

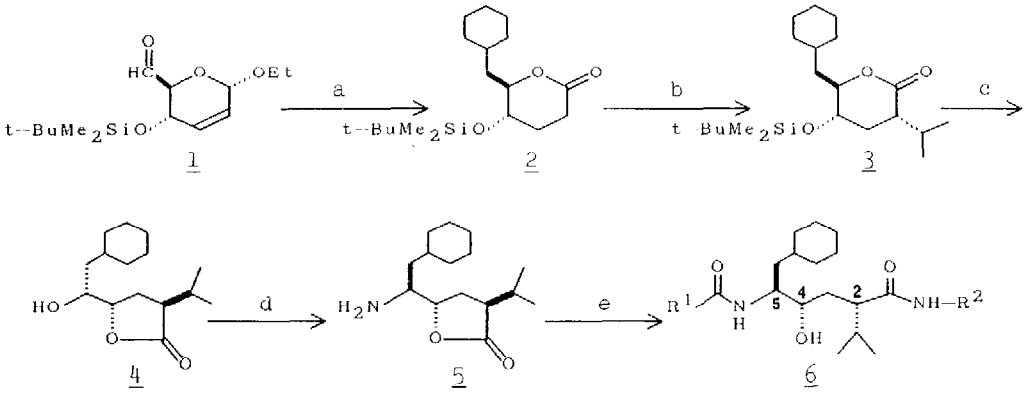
In view of the practical synthesis of hydroxyethylene dipeptide isostere and its analogues,[2] stereocontrolled construction of C4 and C5 functional groups is an important problem to be solved. An approach, which allows for broad variations in introducing two side chains at C2 and C5, was the use of 3,4,6-tri-O-acetyl-D-glucal as a starting material.

3,4,6-Tri-O-acetyl-D-glucal was converted to the aldehyde 1 by a modified method of Valverde et al.[3] Wittig reaction (cyclohexyltriphenylphosphorane) of 1, followed by Jones oxidation and then hydrogenation gave 2 (33%, mp 76-78°C, $[\alpha]_D^{24}$ +86.8° (c 1.0, $CHCl_3$)). Since the introduction of an isopropyl group into 2 with isopropyl iodide and $LiN(TMS)_2$ was not successful, this was carried out in the following sequence of reactions. Aldol condensation (acetaldehyde), dehydration and methylation of 2 gave a 1:1 mixture of diastereomers 3 and 3' (C2 epimer of 3) (81%). Although this mixture could not be separated on a silica gel column, fractional recrystallization of this mixture from cold methanol gave 3 (mp 91-92°C, $[\alpha]_D^{24}$ +68.7° (c 1.0, $CHCl_3$)). (2R)-Isomer 3' (mp 45-47°C) remained in the mother liquor. The mixture rich in 3' was equilibrated by the use of 1.1 equiv of $LiN(TMS)_2$ at -78°C for 5 min, to give a 1:1 mixture of 3 and 3' in a quantitative yield. Thus, the undesired stereoisomer 3' was converted to 3 in a good yield by repeating this procedure. Desilylation of 3 gave 4 (94%, mp 88-90°C, $[\alpha]_D^{24}$ +13.8° (c 1.0, $CHCl_3$)). The alcohol 4 was converted to 5 (86%, mp 48-49°C) by Mitsunobu reaction (diphenylphosphoryl azide), followed by

reduction of the obtained azide, with the complete inversion of the original configuration. The structure was confirmed by X-ray crystallographic analysis.[4] The lactone amine 5 was further converted to the hydroxyethylene dipeptide isostere 6.

Thus the present synthetic route to isostere via key intermediates (1 and 2) would allow for versatile variations of C2- and 5-substituents.

Scheme 1.



Reagents and conditions: (a) (i) 2 equiv cyclohexyltriphenylphosphorane/THF, 25°C, 1.5 h; (ii) Jones reagent/acetone, 0°C, 10 min; (iii) H_2/EtOAc, 10% Pd/C, 1 atm; (b) (i) $LiN(TSM)_2$-MeCHO/THF, -78°C, 10 min; (ii) MsCl/pyridine, then DBN/THF, 25°C; (iii) Me_2CuLi/THF, -78°C, 10 min; (c) MeOH-4N HCl (5:1), refluxed, 20 min; (d) (i) diethyl azodicarboxylate-PPh_3, 5 min, then $(PhO)_2P(O)N_3$/THF, 25°C, 1.5 h; (ii) H_2/EtOAc, 10% Pd/C, 1 atm; (e) (i) R^1COOH, $(EtO)_2P(O)CN$-Et_3N/THF, 25°C, 15 h; (ii) R^2NH_2 (liquid), 20-25°C, 15 h.

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3. S. Valverde, B. Herradon, R. M. Rabmal, and M. Martin-Romas, Can. J. Chem., 65, 339 (1987). [(i) BF_3-ether/EtOH; (ii) MeOH/cat. KOH; (iii) pivaloyl chloride/pyridine; (iv) t-$BuMe_2SiCl$/Et_3N; (v) $LiAlH_4$; (vi) DCC-DMSO/cat. H_3PO_4].
4. The X-ray data are abailable from the Director of the Cambridge Crystallographic Centre.

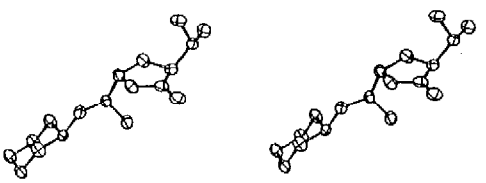

Fig. 1. Perspective View of 5.

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