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AN EFFICIENT SYNTHESIS OF THE γ-LACTONE CORRESPONDING TO A HYDROXYETHYLENE DIPEPTIDE ISOSTERE USING STEREOSELECTIVE BROMOLACTONISATION OF A CHIRAL ACYLOXAZOLIDINONE

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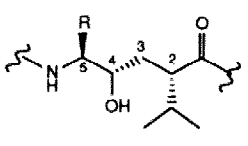
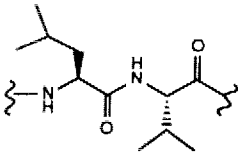
Abstract: An efficient synthetic route is described to the γ-lactone **11** corresponding to the dipeptide isostere (2S,4S,5S)-5-amino-6-cyclohexyl-4-hydroxy-2-isopropylhexanoic acid, in which stereochemical control is achieved by participation of chiral acyloxazolidinone **6** in a stereoselective bromolactonisation reaction.

In the design of transition state inhibitors of the aspartyl protease renin, a key enzyme in the regulation of blood pressure[1], the hydroxyethylene isostere **1a** has been increasingly used[2] as a mimetic of the dipeptide fragment Leu-Val **2**. By analogy with inhibitors containing the dipeptide replacement statine[3], changing the isobutyl group of **1a** to cyclohexylmethyl (isostere **1b**) results in significantly more potent compounds[4]. For effective binding of inhibitors to the enzyme, the S-configuration is required at each of the 3 stereocentres of these isosteres[5].



1a; R = Isobutyl
1b; R = Cyclohexylmethyl



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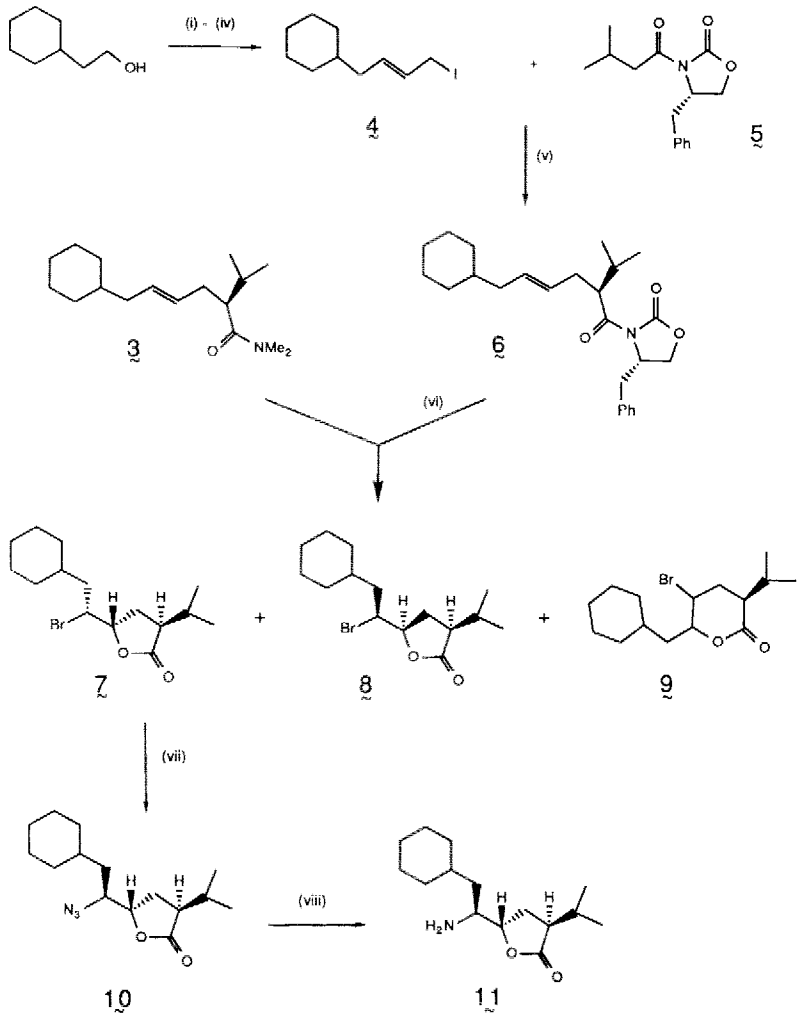
Whilst several syntheses of hydroxyethylene isosteres have been described[2a,4,6], the majority exhibit shortcomings in stereochemical control. Of note, however, is the most recent publication[6a] in this area reporting effective control of relative configuration by stereoselective bromolactonisation of γ,δ-unsaturated carboxamide **3** (Scheme). Consistent with the regio- and stereochemical outcome observed previously[7] for halolactonisation of α-substituted γ,δ-unsaturated amides, a strong preference was evident in favour of the desired *trans* γ-lactone **7** relative to the corresponding *cis* lactone **8** and δ-lactone **9**. The required absolute stereochemistry was derived by preparation of the optically pure S carboxylic acid precursor of amide **3**, either by resolution or by induction using an oxazolidinone chiral auxiliary. In light of this publication, we wish to report related

work, which we had already completed, involving participation of chiral acyloxazolidinone 6 in a stereoselective bromolactonisation reaction.

Scheme



Reagents: (i) $P_2O_5/Et_3N/DMSO/CH_2Cl_2/0\rightarrow20^oC$; (ii) $CH_2=CHMgBr/THF/-15^oC$; (iii) $SOCl_2/Et_2O/20^oC$; (iv) $NaI/Me_2CO/20^oC$; (v) LDA/THF/0°C; (vi) $NBS/H_2O/DME/0\rightarrow20^oC$; (vii) $NaN_3/DMPU/20^oC$; (viii) $H_2/Pd/C/EtOH$

In a similar fashion to the recent disclosure,[6a] we prepared 6[8] in 73% yield by alkylation of the lithium enolate of acyloxazolidinone 5[9], derived from (S)-(-)-4-benzyl-2-oxazolidinone, with the allyl iodide 4, readily obtained on a large scale in 4 steps from 2-cyclohexylethanol. As expected[10] greater than 99% diastereoselectivity was seen for induction of the required S stereochemistry at the newly formed asymmetric centre. Treatment of 6 with N-bromosuccinimide in aqueous dimethoxyethane gave[11] directly in 67%

yield after chromatography an 82:18 mixture of trans γ-lactone **7** and a regioisomeric δ-lactone **9**[12] of undetermined configuration, from which the desired γ-lactone **7** enriched to ca 95% purity[12] could be obtained by a single recrystallisation from hexane. By analysis of appropriate chromatographic fractions, formation of a minor amount of the diastereoisomeric cis γ-lactone **8** could also be inferred.[12] Bromolactonisation of **6** thus shows regio- and stereoselectivity similar to that displayed by amide **3**. However, compared with the use of **3**, the more direct cyclisation of **6** has the advantage of avoiding the need for cleavage of the oxazolidinone chiral auxiliary and subsequent amide formation. To our knowledge, there are no previously reported examples of participation of an acyloxazolidinone in a halolactonisation reaction. Stereoselective halolactonisation of this type of chiral substrate is of potential general applicability for simultaneous induction of both absolute and relative configuration in trans 3,5-disubstituted γ-lactones.

Bromolactone **7** was readily converted to aminolactone **11** corresponding to isostere **1b** in 2 high yielding steps via azidolactone **10**[6a]. An X-ray crystal structure determination confirmed the relative stereochemistry expected for **11**[13]. We have employed this sequence routinely to provide multigram quantities of **11** for use in the preparation of renin inhibitors by means of N-acylation, followed by opening of the lactone ring with amines[6c].

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11. NBS (13.7 g, 77.0 mmol) was added to 6 (27.9 g, 70.0 mmol) in 1:1 aq. dimethoxyethane (150 ml) stirred at 0°C. The mixture was stirred at 0°C for 10 mins and then at ambient temperature overnight. Work-up by addition of water (500 ml), and extraction with ether (3 x 250 ml), followed by flash chromatography on silica (Merck Art. 9385), eluting with ethyl acetate/hexane on a gradient from 1:9 v/v to 3:17 v/v, gave a ca 82:18 mixture[12] of **7** and **9** (14.7 g, 67%). Recrystallisation from hexane (70 ml) provided 10.1 g of material enriched to ca 95% in **7**. A further recrystallisation from hexane gave material containing no detectable[12] amount of **9**, m.p. 94.5-95°C (Lit[6a] m.p. 95-95.5°C), $[\alpha]_D^{22}$ + 31.9° (c, 1.0 $CHCl_3$) (Lit[6a] $[\alpha]_D^{25}$ + 35.6° (c, 1.2 $CHCl_3$)). Further elution of the chromatography column with methanol/ethyl acetate (1:9 v/v) resulted in recovery of the chiral auxiliary (S)-(-)-benzyl-2-oxazolidinone (7.0 g, 57%).
12. The presence of side-products **8** and **9** was detected by analysis of ^1H NMR spectra (cf data since presented in ref 6a).
13. Suitable crystals were obtained from hexane with orthorhombic space group symmetry of $P2_1P2_1P2_1$ and cell constants of a = 18.613(4)°A, b = 13.168(3)°A, c = 6.265 (2)°A, calculated density = 1.09 g/cm^3. 659 Reflections were used ($I>2\sigma I$) on a Philips PW1100 automatic four circle diffractometer equipped with MoK-alpha radiation. Direct solution methods located the hydrogen atoms attached to nitrogen. Other hydrogens were located at calculated positions (C-H bond length 1.08°A). The best hydrogen atom located was used to define methyl group orientations. Nitrogen and oxygen atoms were assigned anisotropic temperature factors, whilst carbon atoms were assigned isotropic temperature factors. All hydrogen atoms were assigned fixed isotropic thermal parameters equal to 0.01 A^{o2}. The final R-factor was 0.0993 for the θ range 3° to 23°. The atomic coordinates are available from the Director of the Cambridge Crystallographic Centre.

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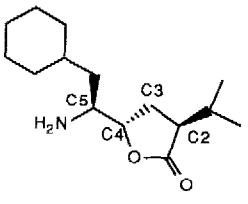

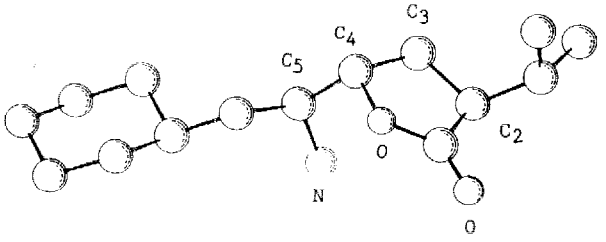

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