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THE SYNTHESIS OF (2S,4S,5S) -5-(N-BOC)-AMINO-6-CYCLOHEXYL-4-HYDROXY-2-ISOPROPYL-HEXANOIC ACID LACTONE, AN HYDROXYETHYLENE DIPEPTIDE ISOSTERE PRECURSOR

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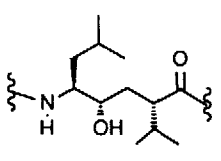
Abstract: A synthetic approach to the butyrolactones of (2SR,4SR)-5(S)-(N-Boc)-amino-6-cyclohexyl-4-hydroxy-2-isopropyl hexanoic acid from (L)-phenylalanine and the preparation of the n-butyl amide of the 2(S),4(S),5(S) acid is presented.

The design and synthesis of transition-state mimics for the hydrolysis of peptide bonds has attracted considerable interest.[2] One such transition-state mimic is the "hydroxy" peptide bond isostere **1** introduced by Szelke (Figure 1).[3] The hydroxy group may serve as a mimic of the tetrahedral intermediate for hydrolysis. The "hydroxy" isostere **1** of Leu-Val (and analogues thereof) has yielded potent inhibitors of the aspartic protease renin when used to replace the scissile Leu-Val peptide bond in substrate analogs.[4] Recently the hydroxy isostere **2** has also been incorporated into renin inhibitors.[5] We wish to report a flexible and efficient synthetic route to the precursor of the isostere **2**, the lactone **3**, via a novel application of the Wadsworth-Emmons reaction and its conversion to the N-butyl amide **2**.



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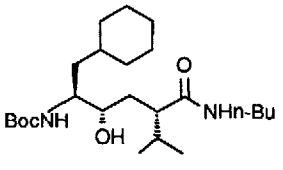

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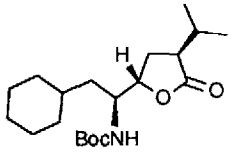

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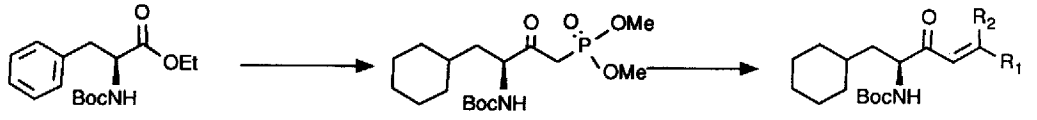
Figure 1

The ketophosphonate **4** (Scheme 1) is readily available from Boc-L-phenylalanine methyl ester by reduction (H_2, PtO_2, 95%), followed by Claisen condensation with lithio-dimethyl methylphosphonate (6eq., THF, 95%)(Scheme 1).[6,7] The ketophosphonate undergoes Wadsworth-Emmons reaction with benzaldehyde, isobutyraldehyde and acetone to give the olefins **5, 6** and **7** in 68%, 78% and 73% yield respectively (K_2CO_3, 18-Crown-6, CH_2Cl_2/H_2O). The E stereochemistry of **5** and **6** was assigned by ^{1}H-NMR (J=18.9Hz trans vinyl CH). Attempted Wadsworth-Emmons reaction with β-keto esters under a

variety of conditions (K_2CO_3, 18-Crown-6, CH_2Cl_2/H_2O; NaH/THF; NaOMe/MeOH; DBU/$PhCH_3$) gave either none or only very low yields of olefinic products. However, generation of the di-lithio ketophosphonate from **4** using 2.0 equivalents of n-BuLi in THF at 0°C followed by addition of ethyl 3-methyl-2-oxobutanoate gave a single olefin **8** in 72-88% yield.[8]

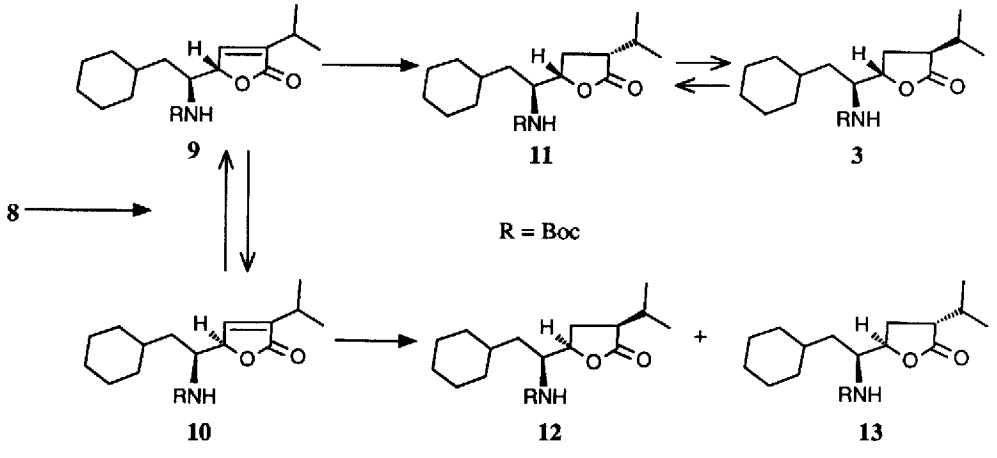


4

5. R_1 = Ph R_2 = H
6. R_1 = i-Pr R_2 = H
7. R_1 = Me R_2 = Me
8. R_1 = COOEt R_2 = i-Pr

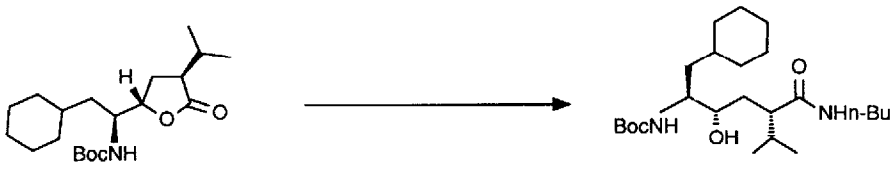
Scheme 1

Reduction of **8** with $NaBH_4$ (MeOH, 0.5 equiv., -30°C) gave a 3:2 mixture of the lactones **9** and **10** (85% yield), which were separated by silica gel chromatography (5:4:1 hexane:dichloromethane:ethyl acetate) (Scheme 2). Formation of the lactones **9** and **10** during reduction of **8** confirmed the Z olefin geometry assigned to **8**. Reduction of lactone **9** (H_2, 10% Pd/C, 93%) gave a single lactone **11** while a 3:1 mixture of lactones **12** and **13** resulted from reduction of **10**. An X-ray crystal structure determination confirmed the C-4(R) stereochemistry assigned to **12**.[9] Consequently, the desired C-4(S) configuration must be present in **9**, the C-4 diastereomer of **10**. It was expected that reduction of the sterically hindered lactones **9** and **10** would occur preferentially from the least hindered face of the lactone olefin, and this was observed in the reduction of **10**. Thus the C-2(R) absolute configuration was assigned to **11**.



Scheme 2

A satisfactory method for improving the yield of **9** was obtained by C-4 epimerisation of **10** (1.0 eq.DBU, DMF, 90°C,95%) to give a 2:1 mixture of **9**:**10**. Likewise, treatment of **11** with DBU/DMF at 90°C gave a 3:7 mixture of lactones **3** and **11** in quantitative yield. Repetitive recycling of **10** and **11** provided a means of preparing multi-gram quantities of the desired lactone **3**.



3 2

Scheme 3

The lactone **3** may be readily converted to hydroxyamides by application of the Weinreb amidation reaction (Scheme 3).[10] For example, addition of **3** to two equivalents of a 1:1 mixture of n-butyl amine and $(CH_3)_3Al$ in CH_2Cl_2 followed by heating at reflux for 3 hours gave rise to amide **2** (60% yield). Treatment of **2** with acid (TFA, CH_2Cl_2, 0°C) removes the Boc protecting group without lactone formation, providing the free amine after neutralization for incorporation into peptide structures.[11]

This work constitutes an alternative method for preparing a hydroxyethylene isostere from an amino acid precursor. The methodology should be applicable to other hydroxyethylene isosteres derived from amino acid precursors.

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Notes and references:

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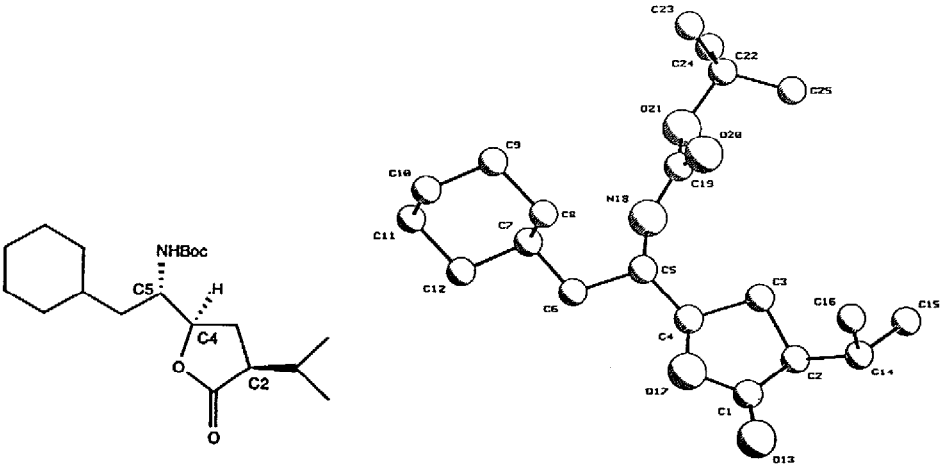
7. All yields are for chromatographically purified compounds. Satisfactory spectral and analytical data was obtained for all synthetic intermediates.
8. To a -10°C solution of 10.05 g (0.026 M) **4** in 100 ml of anhydrous THF under N_2 was added 10.1 ml of a 2.5 M solution of n-BuLi in hexanes (0.025 M) (Aldrich). After stirring for 1 hr 5.75

g (0.04 M) of ethyl 3-methyl-2-oxobutyrate was added and the reaction mixture was allowed to warm to room temperature and stirred for 1.5 hr Water (100 ml) was added, and the aqueous phase extracted with CH_2Cl_2 (3x50 ml). The combined organic phases were washed with water (2x25 ml) and sat. NaCl (2x25 ml) and dried over $MgSO_4$. The solution was filtered and conc. in vacuo. The residue was chromatographed over silica gel on a 5 cmx45 cm column with 12.5% EtAc/hexanes as eluant to give 8.6 g of **8** (83% yield).^{1}H-NMR ($CDCl_3$, 300 MHz): 0.92 (m, 1H), 1.1-1.75 (b.m., 11H), 1.62 (d, 6H, J=6.84Hz), 1.83 (t, 3H, J=7.05Hz), 1.41 (s, 9H), 1.88 (m, 1H), 2.66 (m, 1H), 4.28 (q, 2H, J=7.05Hz), 4.43 (m, 1H), 5.03 (b.d., 1H, 8.19Hz), 6.16 (s, 1H). Mass spectrum (FAB): observed 396 for M^++1 (M^+= $C_{22}H_{37}NO_5$). Anal. ($C_{22}H_{37}NO_5$) C, H, N.

9. Suitable crystals formed from hexane with space group symmetry of $P2_1$ and cell constants of a=10.736(2)^{o}A, b=9.667(9)^{o}A, c=11.646(9)^{o}A, β=114.08(5)^{o}A, calculated density= 1.064g./cm^3. 1616 reflections were measured, 1326 observed (I>3σI) on an automatic four circle diffractometer equipped with Cu radiation. The structure was solved with a direct methods approach and difference Fourier analysis and refined using full matrix least square techniques. Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\Sigma\omega(|F_o|-|F_c|)^2$ with $\omega=1/(\sigma F_o)^2$ was minimized to give an unweighted residual of .051. The atomic coordinates are available from the Director of the Cambridge Crystallographic Centre.



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11. The use of HCl/MeOH for deprotection results in relactonization, see ref. 4b.

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