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A VERSATILE AND STEREOSPECIFIC SYNTHESIS OF A DIHYDROXYETHYLENE DIPEPTIDE ISOSTERE OF RENIN INHIBITORS FROM D-RIBOSE

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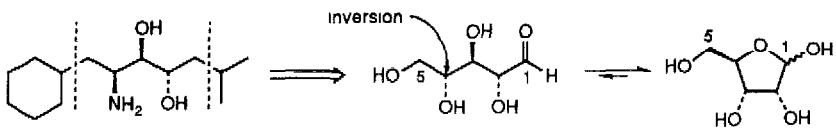
Summary: (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol, a dihydroxyethylene dipeptide isostere for renin inhibitors, was synthesized from D-ribose stereospecifically. This method can be readily adapted to other dihydroxyethylene isosteres.

Renin inhibitors have attracted a great deal of interest in medicinal chemistry due to their potential use as antihypertensive agents.[1] The dihydroxyethylene dipeptide isostere **1** found in a number of renin inhibitors was designed as a transition state mimic of the scissile Leu-Val bond in angiotensinogen.[2] Although several syntheses of this important molecule have been published,[3] they all involve asymmetric induction from an existing chiral center(s) which in some cases resulted in the formation of a mixture of diastereoisomers and hence complicated separations. Herein we report a stereospecific synthesis of the title compound from D-ribose **2** in which the three stereo centers of the sugar are incorporated into those of **1** by stereochemically well-defined reactions.

Our strategy takes advantage of the fact that the 2- and 3-OH groups in D-ribose **2** have the same absolute stereochemistry as the dihydroxyethylene moiety in **1**. The synthesis thus involves the replacement of the 4-OH group by an amine with inversion of configuration and the formation of two carbon-carbon bonds at C-1 and C-5 of **2** (Scheme 1). *The 4-OH group where the inversion of configuration is to take place can be distinguished from the other hydroxyl* groups by the preferential formation of the hemiacetal furanose form of D-ribose **2a**. Once in the cyclized form, the 2- and 3-OH groups can be easily protected as the acetonide.[4a] Furthermore the 5-OH group, being less hindered, can then be readily differentiated from the hemiacetal OH group.



1 **2** **2a**

Scheme 1

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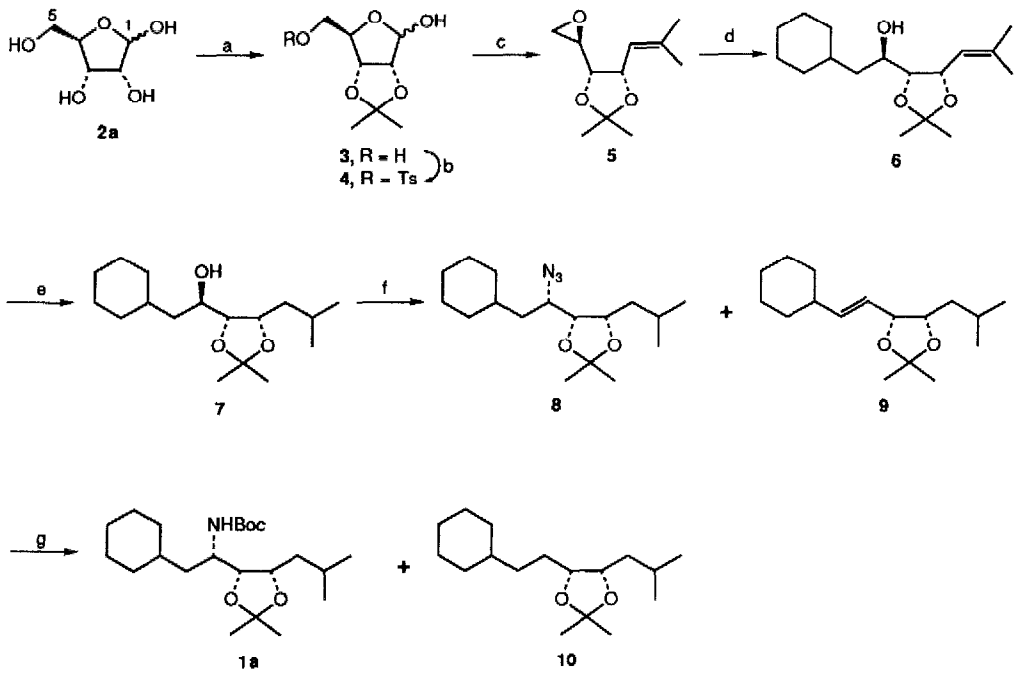
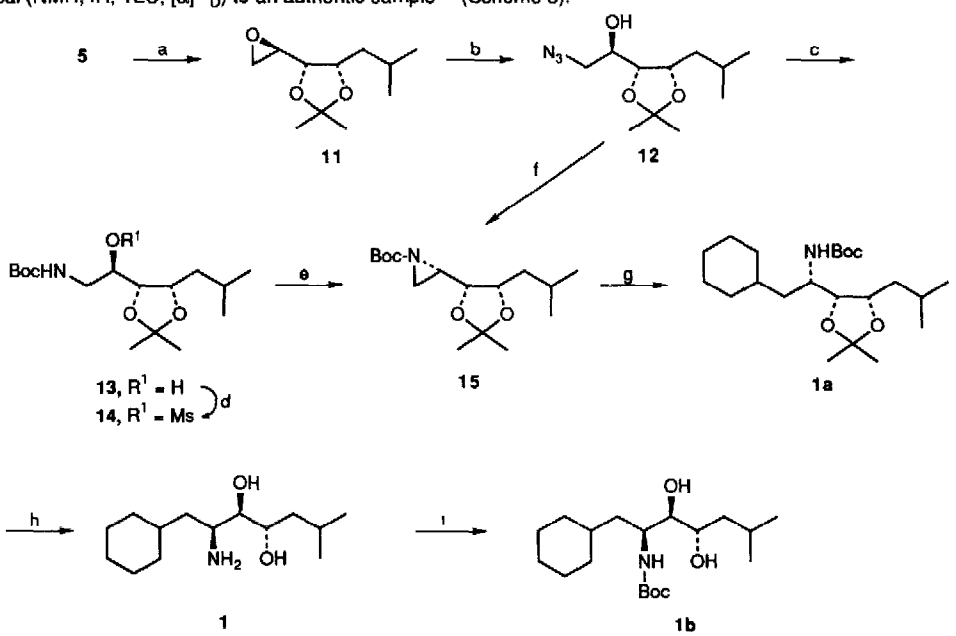
The 2- and 3-OH groups of D-ribose **2** were protected as the furanose acetonide **3** according to a literature method [4b] The crude acetonide **3** was converted into the 5-tosylate **4**[5a,b] selectively , m p 92 5-94 °C, $[\alpha]^{25}_D$ +1 5° (c=1.00, MeOH) in 69% overall yield from **2** On treatment with 2 2 equivalents of the ylide derived from isopropyltriphenylphosphonium iodide[6] at 0 °C, the epoxyalkene **5**,[5a,b] $[\alpha]^{25}_D$ +28 1° (c=1 00, MeOH) was obtained directly from **4** (62% yield) To the best of our knowledge, the simultaneous formation of an epoxide and an olefin directly from a ribose derivative is not well precedented in the literature.[7] The epoxide **5** was then opened with cyclohexyl magnesium chloride using CuI as a catalyst[8] (THF -20 °C, 72%) to give the alcohol **6**,[5a,b] m.p 84-6 °C, $[\alpha]^{25}_D$ +48 6° (c=1.18, MeOH) which was hydrogenated to give the saturated alcohol **7**,[5a,b] m.p. 50-2 °C, $[\alpha]^{24}_D$ -3 4° (c=1 12, MeOH) quantitatively. Conversion of the hydroxyl group in **7** into the azide **8** turned out to be exceptionally difficult, presumably due to its sterically hindered environment Under most conditions, the elimination product **9** predominated The best result was obtained under Mitsunobu conditions with diphenylphosphoryl azide[9] (Ph_3P, DEAD, THF), which gave ca 40% yield of a 1.1 mixture of the azide **8** and the olefin **9** This mixture was hydrogenated in the presence of di-tert-butyl dicarbonate (10% Pd/C, EtOAc) to afford the fully protected isostere **1a**[5a,b] and the acetonide **10**[5a] in 35 and 40% yield respectively (Scheme 2)



Scheme 2

Reagents and conditions a) Ref 4b; b) TsCl, pyridine, CH_2Cl_2, 25 °C, 24 h, 69% from **2a**; c) 2.2 equi $(CH_3)_2CHPPh_3^+ I^-$, 2.2 equi BuLi, THF, 0-25 °C, 3 h, 62%; d) c-$C_6H_{11}MgCl$, cat. CuI, THF, -40 °C, 2 h, 72%, e) H_2, Pd/C, MeOH, 25 °C, 3 h, 100%; f) $(PhO)_2P(O)N_3$, Ph_3P, DEAD, THF, 24 h, 40%, ca. 1 1 mixture; g) H_2, Pd/C, 1.5 equi $(t\text{-BuOCO})_2O$, EtOAc, 14 h

In order to improve the yield of the synthesis, we elect to invert the C-4 chiral center (ribose numbering) by means of a proximal nitrogen nucleophile before the cyclohexyl group is introduced Accordingly, the epoxide **5** was hydrogenated to give **11**,[5a,b] b p 120-5 °C (bath)/1.5 torr, $[\alpha]^{24}_D$ +7.4° (c=1 04, MeOH) and opened with azide ion[10] (NaN_3, NH_4Cl, $EtOCH_2CH_2OH/H_2O$, reflux 1h, 85%) at the less hindered position to afford the azidoalcohol **12**[5a,b], $[\alpha]^{24}_D$ -27.8° (c=1.04, MeOH) exclusively The azide **12** was reduced (H_2, 10% Pd/C) to the corresponding amine and was protected *in situ* as the t-butoxycarbonyl (Boc) derivative **13**,[5a,b] $[\alpha]^{24}_D$ +2.9° (c=1 00, MeOH) in 92% overall yield. After conversion of the alcohol **13** into the mesylate **14**,[5a,b] m p 109 5-111 °C, $[\alpha]^{24}_D$ +48.6° (c=1 00, MeOH), cyclization took place smoothly in DMF in the presence of sodium hydride to form the N-Boc aziridine **15**[5a], $[\alpha]^{24}_D$ -17.0° (c=1 03, MeOH) in 83% yield. Thus, the stereochemistry at C-4 was inverted in this S_N2 reaction. It is interesting to note that **14** failed to cyclize under identical conditions in THF even at boiling temperature. Alternatively and more efficiently, the azidoalcohol **12** was reacted with Ph_3P in refluxing toluene to give the N-unsubstituted aziridine directly[11] which on acylation with di-tert-butyl dicarbonate gave **15** in 75% overall yield from **12**. The spectroscopic properties and optical rotation of the product **15**[13b] obtained in this case is identical to that obtained through the mesylate, thus indicating that an inversion of configuration has occurred at C-2. The cyclohexyl group was introduced via a cuprate opening[12] of the N-Boc aziridine **15** (lithium dicyclohexyl cuprate, THF, -40 °C) to give the fully protected dihydroxyethylene isostere **1a**, $[\alpha]^{24}_D$ -38 4° (c=1.14, MeOH)[13a] in 80% yield The title compound **1** was obtained by hydrolysis of **1a** as a viscous oil which without purification was converted to the N-Boc amino diol **1b**. Compound **1b** is identical (NMR, IR, TLC, $[\alpha]^{24}_D$) to an authentic sample[3a] (Scheme 3).



Scheme 3

Reagents and conditions a) H_2, 10% Pd/C, EtOAc, 25 °C, 2 h, 91%; b) NaN_3, NH_4Cl, $MeOCH_2CH_2OH/H_2O$, reflux, 1 h, 85%, c) H_2, 10% Pd/C, EtOAc, $(t\text{-BuOCO})_2O$, 25 °C, 2 h, 92%, d) MsCl, Et_3N, CH_2Cl_2, 0 °C; e) NaH, DMF, 25 °C, 2 h, 82% for two steps, f) Ph_3P, toluene, reflux, 6 h; then $(t\text{-BuOCO})_2O$, 85% overall from **12**; g) $(c\text{-}C_6H_{11})_2CuMgX$, THF, -40 °C, 2 h, 80%; h) TFA/H_2O, 25 °C, 16 h, 55 °C, 1 h; i) $(t\text{-BuOCO})_2O$, CH_2Cl_2/H_2O, 2 h.

Thus, we have developed a versatile synthesis of the protected amino diol **1b** from D-ribose in 22% overall It is noteworthy that the key reactions used in this synthesis are regio- and stereospecific and hence no diastereoisomers were formed This synthesis can be readily adapted to a wide variety of dihydroxyethylene isosteres simply by changing the Wittig reagent and the organocuprate used

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13. Spectral data:
   a) Compound **1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75-2 0 (H, m), 0 93 (6H, app t, J = 6 Hz), 1 35 (3H, s), 1.45 (9H, s), 1 49 (3H, s),3.7-3.8 (1H, m), 3,99 (1H, br d, J = 6 Hz), 4 23 (1H, ddd, J = 4, 7.5, 10 5 Hz), 4 67 (1H, br d, J = 9 Hz), CIMS *m/z* 384 (M+1, 100%), 328 (16), 310 (14), 284 (17), HRMS calcd for $C_{22}H_{42}NO_4$+H: 384.3114, found: 384 3106;
   b) Compound **15**: ^{1}H NMR (300 MHz, $CDCl_3$). δ 0 94 (3H, d, J = 6 6 Hz), 0.98 (3H, d, J = 6 6 Hz), 1.3-1.4 (1H, m), 1.36 (3H, s), 1.46 (9H, s), 1.55 (3H, s), 1 65-1 85 (2H, m), 1 99 (1H, d, J = 3 8 Hz, *cis* N-C<u>H</u>$_2$), 2 30 (1H, d, J = 6 3 Hz; *trans* N-C<u>H</u>$_2$), 2.51 (1H, ddd, J = 3.8, 6.3 and 8 5 Hz, N-C<u>H</u>), 3 55 (1H, dd, J = 5 7, 8.5 Hz, CH_2-C<u>H</u>-O) and 4.23 (1H, ddd, J = 4, 5.7, 9.6 Hz; CH-C<u>H</u>-O), CIMS, *m/z* 300 (M+1, 100%), 200 (55%); HRMS calcd for $C_{16}H_{29}NO_4$+H 300 2175, found. 300.2180

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