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Versatile Synthetic Routes to Enantiomeric Dihydroxyethylene Dipeptide Isosteres *via* Intramolecular Amidation

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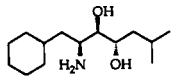
Since the aspartic protease renin catalyzes the hydrolysis of angiotensinogen to angiotensin I,[1] its inhibitors are expected to be of potential use in the treatment of hypertension and congestive heart failure.[1,2] Based on the transition state mimic of the scissile Leu-Val amide bond in angiotensinogen, the dihydroxyethylene dipeptide (DHED) isostere **1** was designed as a prospective C-terminal component for the development of renin inhibitors.[3] Several synthetic approaches to **1** have been described by employing stereoselective alkylation of imines,[4] one-pot reductive amination of epoxy ketone,[5] ring-opening of epoxides with sodium azide,[6] diastereoselective dihydroxylation of allylic amines[7] and enzymatic resolution.[8] Recently we have reinvestigated the electrophile promoted cyclization of trichloroacetimidates from allylic and homoallylic alcohols to attain a highly stereoselective amidation.[9] In this paper we report a divergent synthetic route to **1** and its enantiomer *ent*-**1** by extending the cyclization protocol to the stereocontrolled intramolecular amidation of trichloroacetimidates from (3R, 4S)-3,4-dihydroxy-6-methyl-1-heptene **4** and (2R,3S)-1,2,3-trihydroxy-5-pentene **9**.



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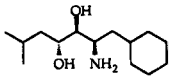
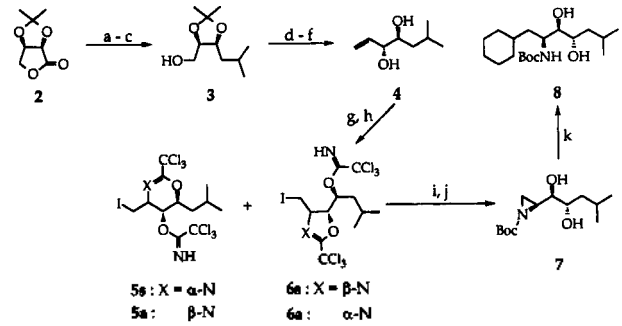
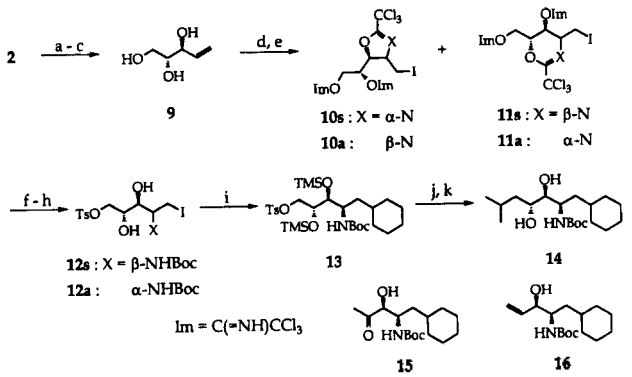


ent - **1**

The synthesis of DHED isostere **1** was initiated with DIBAL reduction of the known lactone **2**[10] followed by Wittig isopropylenation and hydrogenation to give alcohol **3** in 87% overall yield (Scheme 1). Swern oxidation[11] of **3** and the subsequent methylenation provided the volatile methylenic acetonide in 69% yield. Its acidic hydrolysis afforded (3*R*, 4*S*)-3,4-dihydroxy-6-methyl-1-heptene **4**, mp 55-56 °C, $[\alpha]_D^{15}$ −13.5 ($CHCl_3$, *c* 1.00) in 88% yield, of which the physical constants were appreciably higher than the reported values.[4,12] For the intended functionalization of the olefinic double bond in **4**, it reacted with trichloroacetonitrile and DBU, and the generated bis(trichloroacetimidate) was cyclized using iodine in the presence of sodium bicarbonate in acetonitrile at 0 °C to furnish a 3.7 : 1 mixture of dihydro-1, 3-oxazines **5** and oxazolines **6** in 89% combined yield. While the isomeric ratio of **5** turned out to be 28 : 1 in favor of **5s**, mp 93-95 °C, $[\alpha]_D^{10}$ +22.5 ($CHCl_3$, *c* 1.10), only *trans* isomer **6s**, mp 81-82 °C, $[\alpha]_D^{18}$ −87.4 ($CHCl_3$, *c* 1.04) was found in the case of **6**. The structures of **5s** and **6s** were corroborated from the following C=N stretching band frequencies[13] and proton-proton coupling constants : for **5s** : 1672 cm^{-1}, $J_{H4,H5}$=3.1 Hz and $J_{H5,H6}$=0 Hz. For **6s** : 1666 cm^{-1} and $J_{H4,H5}$=5.9 Hz. The assignments were supported by the derivatization of **5s** and **6s** into the identical Boc-aziridine **7** (*vide infra*).



Scheme 1. [a] DIBAL/CH_2Cl_2/ − 78 °C. [b] $Me_2CH^+PPh_3I^-$/*n*-BuLi/HMPA/THF/0 °C → rt. [c] H_2/10% Pd-C/$NaHCO_3$/MeOH/rt. [d] Swern ox. [e] $Me^+PPh_3I^-$/*n*-BuLi/HMPA/THF/0 °C. [f] AcOH/H_2O/45 °C. [g] Cl_3CCN/DBU/MeCN/0 °C. [h] I_2/$NaHCO_3$/MeCN/0 °C. [i] 6 N HCl/MeOH/rt. [j] $NaHCO_3$/MeOH/rt; Boc_2O/rt. [k] TMSOTf/HMDS/THF/ − 40 °C; *c*-HxMgCl/Li_2CuCl_4/ − 30 °C; acidic work-up (pH=2-3).



Scheme 2. [a] DIBAL/CH_2Cl_2/−78 °C. [b] $Me^+PPh_3I^-$/*n*-BuLi/HMPA/THF/0 °C→rt. [c] AcOH/H_2O/50 °C. [d] Cl_3CCN/DBU/MeCN/−30 °C. [e] I_2/$NaHCO_3$/MeCN/0 °C→rt. [f] 6 N HCl/MeOH/rt. [g] Boc_2O/$NaHCO_3$/MeOH/0 °C. [h] TsCl/DMAP/Et_3N/CH_2Cl_2/0 °C. [i] TMSOTf/HMDS/THF/0 °C; LDA/−20 °C; *c*-HxMgCl/Li_2CuCl_4/−30 °C. [j] K_2CO_3/MeOH/0 °C. [k] $Me_2CHMgCl/Li_2CuCl_4$/THF/−20 °C.

After chromatographic removal of **5a**, the mixture of **5s** and **6s** was completely deprotected with methanolic HCl, and the resulting amino iodide was sequentially treated with sodium bicarbonate and di-*t*-butyl dicarbonate to produce Boc-aziridine **7**, $[\alpha]_D^{17}$ −39.5 ($CHCl_3$, *c* 1.16) in 77% overall yield. Since it was necessary to protect the hydroxy groups in **7** for the regioselective opening of its aziridine ring, they were silylated with hexamethyldisilazane (HMDS) and trimethylsilyl triflate (TMSOTf).[14] The protected aziridine was subjected to cyclohexylmagnesium chloride in the presence of dilithium tetrachlorocuprate and the ensuing acidic work-up provided the desired Boc-protected DHED isostere **8**[7a], mp 128.5-130 °C, $[\alpha]_D^{18}$ −64.8 ($CHCl_3$, *c* 1.00) in 81% overall yield.[15]

For the preparation of the enantiomeric DHED isostere *ent*-**1**, lactone **2** was reduced with DIBAL, methylenated and then hydrolyzed in aqueous acetic acid to afford trihydroxypentene **9**, $[\alpha]_D^{19}$ −28.4 (MeOH, *c* 1.01) in 77% overall yield (Scheme 2). After converting **9** into tris(trichloroacetimidate), its olefinic double bond was intramolecularly iodoaminated with iodine to furnish a 2-3 : 1 mixture of oxazolines **10** and dihydro-1,3-oxazines **11**. The major isomers **10** and **11** were determined to be **10s**, $[\alpha]_D^{17}$ +56.5 ($CHCl_3$, *c* 1.00) and **11s**, $[\alpha]_D^{17}$ +6.8 ($CHCl_3$, *c* 1.07), respectively, based on the C=N stretching band frequencies and proton-proton coupling constants as follows: for **10s**: 1669 cm^{-1} and $J_{H4,H5}$=5.5 Hz. For **11s**: 1673 cm^{-1}, $J_{H4,H5}$=3.3 Hz and $J_{H5,H6}$=1.6 Hz.

Since its separation was not facile, the mixture was completely hydrolyzed with methanolic HCl, and the unmasked amino and primary hydroxy groups were derivatized into *t*-butyl carbamate and tosylate, respectively, to produce a readily separable 38 : 1 mixture of iodide **12s**, mp 103.5-104 °C, $[\alpha]_D^{16}$+22.9 ($CHCl_3$, *c* 1.05) and **12a** in 70% combined yield. Although cyclohexylcuprate reaction of **12s** did not proceed, the substitution reaction could be accomplished with the corresponding Boc-aziridine, of which the hydroxy groups should be protected for the complete regioselectivity. Accordingly **12s** was silylated, cyclized with LDA and substituted with cyclohexylmagnesium chloride in the presence of dilithium tetrachlorocuprate in one pot to give tosylate **13**, $[\alpha]_D^{11}$ +24.3 ($CHCl_3$, *c* 0.97) in 71% overall yield. Desilylation and the following epoxide formation were effected in 89% yield by methanolic potassium carbonate at 0 °C. The resultant epoxide, mp 106.5-107.5 °C, $[\alpha]_D^{18}$ +72.3 ($CHCl_3$, *c* 1.02) was exposed to isopropylmagnesium chloride in the presence of dilithium tetrachlorocuprate to provide another desired Boc-protected DHED isostere **14**[16], mp 128.5-130 °C, $[\alpha]_D^{19}$ +67.8 ($CHCl_3$, *c* 1.01) in 74% yield along with 8% of ketone **15** and 3% of alkene **16**.

In summary we have established enantioselective synthetic routes to DHED isosteres **1** and *ent*-**1** *via* the intramolecular amidation of olefinic trichloroacetimidates, of which the stereoselectivity was higher than 94% ee.

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12. The reported mp. and $[\alpha]_D^{25}$: 42-46 °C and −9.8 ($CHCl_3$, *c* 1.0).[4]
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15. Cyclohexylcuprate reaction of the unprotected aziridine **7** yielded 72% of **8** along with 8-10% of the corresponding regioisomer.
16. All new compounds showed satisfactory spectral data.