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A Diastereoselective Synthesis of *(2S, 3R, 4S)*-2-Amino-1-cyclohexyl-6-methylheptane-3,4-diol, The Abbott Aminodiol.[1]

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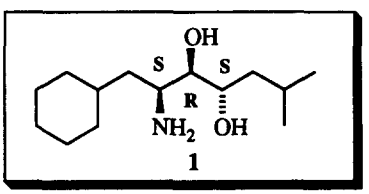
Abstract: An efficient asymmetric synthesis of the Abbott aminodiol, **1**, is described beginning with the readily-available starting material, L-phenylalanine.

The design and synthesis of renin inhibitors has received a great deal of attention because of the their potential as therapeutic agents for the treatment of hypertension. Structurally, these inhibitors are most often peptidic, and contian a core unit which is a peptide hydrolysis transition-state mimetic. One of the most common and efficacious core mimetics is the so-called Abbott Aminodiol, 2*S*, 3*R*, 4*S*,-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol (**1**).[2,3] Herein, we report an expeditious synthesis of **1**, starting from commercially available L-phenylalanine (**Scheme 1**).



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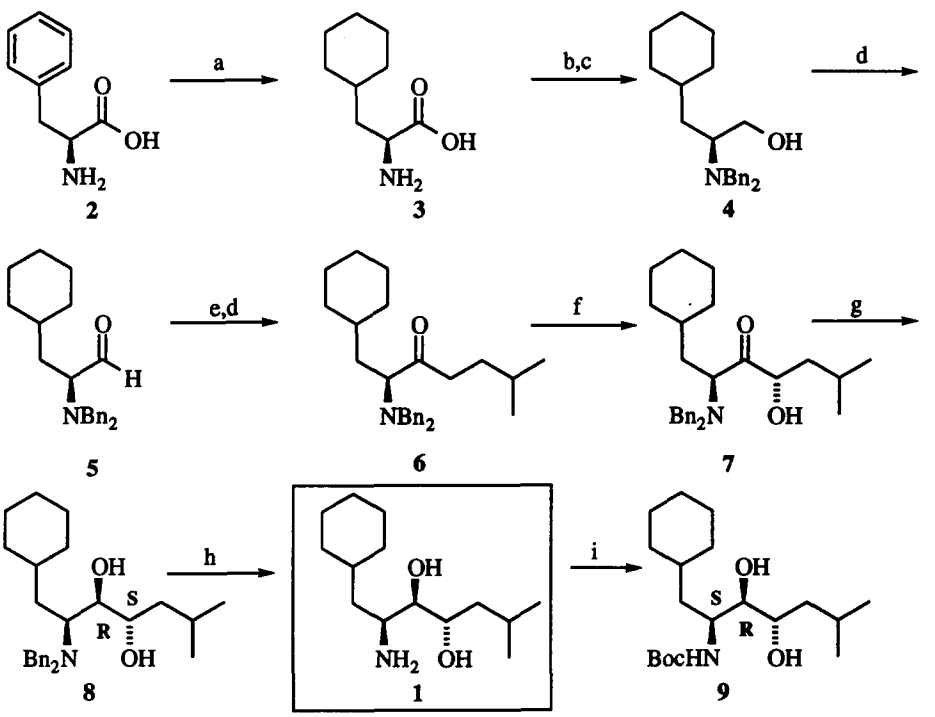
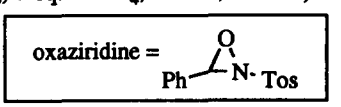
Amino acid derivatives have been a rich source of a variety of functionalized, chiral amines. The uniqueness of the N,N-dibenzyl protecting group has allowed for high degrees of facial selectivity in a variety of chemical transformations.[4] Recently, our laboratories have explored the synthetic utility of the N,N-dibenzyl group as a simple, but powerful moiety for controlling the stereochemistry in asymmetric aldol reactions.[5] Based on this precedent, the goal was to explore and examine the efficacy of this directing group in the asymmetric synthesis of the Abbott amino diol **1** and develop a general protocol for the potential synthesis of hydroxyethylene peptidomimetic isosteres for transition-state inhibitors of aspartic proteases.

Reduction of L-phenyl alanine with Adam's catalyst in the presence of hydrogen afforded cyclohexyl-L-alanine **3** in ≥95% yield.[6] Exhaustive benzylation of **3** using benzyl bromide, followed by reduction of the crude intermediate with $LiAlH_4$, gave the N,N-dibenzyl alcohol **4** in 73% yield for two steps after chromatography (Note: compound **4** is also commercially available). Amino alcohol **4** was oxidized to aldehyde **5** under Swern conditions and the resulting crude aldehyde was used without further purification.[7] Treatment of **5** with $BrMgCH_2CH_2CH(CH_3)_2$ afforded the intermediate addition product which was directly oxidized under Swern conditions to yield the α-N,N-

dibenzylamino ketone **6** in 65% yield for 3 steps after flash column chromatography.[5,8] α-Hydroxy ketone **7** was prepared by generation of the kinetic enolate of **6** and subsequent oxygenation with 3-phenyl-2-(toluene-4-sulfonyl)-oxaziridine affording **7** in 71% yield.[9] The hydroxylation appeared to give only one product according to ^{1}H NMR analysis. α-Hydroxy ketone **7** was further reduced to the aminodiol using $NaBH_4$. De-benzylation of the aminodiol was achieved using catalytic hydrogen transfer conditions (Pd/C and ammonium formate) affording **1** in 89-93% yield based on unpurified product which appeared clean by ^{1}H NMR.[10] The free amine **1** was protected as the N-Boc diol **9** in 50% yield (not optimized) after chromatography.

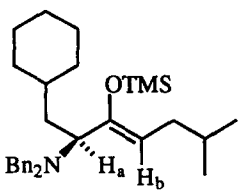


Scheme 1[11]: Reagents: a) H_2,PtO_2, 40-50 psi, CH_3CO_2H, H_2O. b) NaOH, K_2CO_3, H_2O; $PhCH_2Br$, reflux. c) $LiAlH_4$, Et_2O, 0° C to rt. d) Swern oxidation [$(COCl)_2$/DMSO, CH_2Cl_2], -78° C. e) 2 eq. $(CH_3)_2CHCH_2CH_2MgBr$, Et_2O, 0° C. f) 1. 1.3 eq. NaHMDS, THF, -78° C, 3-5 h 2. 1.1 eq. oxaziridine , THF, -78° C. g) 2 eq. $NaBH_4$, MeOH, 0° C. h) 10% Pd/C, HCO_2NH_4, EtOH, reflux. i) Boc_2O, THF, H_2O, rt.



The stereochemistry of α-hydroxyl ketone **7** was predicted to be *anti* relative to the N,N-dibenzyl moiety assuming the intermediacy of a *Z*-enolate and the steric bias of the dibenzyl moiety directing the hydroxylation reaction. A *Z*-enolate geometry was assigned based on an NOE

experiment on the correspponding silyl enol ether **10** (a 5.9% NOE difference between H_a and H_b was observed). This observation is consistent with the reported geometries of other enolates derived from α-N,N-dibenzyl ethyl ketones.[5a] The reduction of the hydroxy ketone **7** to give the *syn* aminodiol (*anti*-diol) **8** is based on Reetz's work wherein the N,N-benzyl moiety sterically directs a non-chelation controlled reduction of the α-amino ketone affording the major diastereomer with an (*S,S*) configuration.[8]



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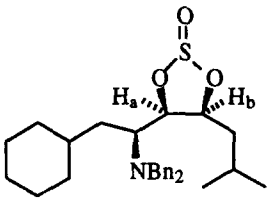

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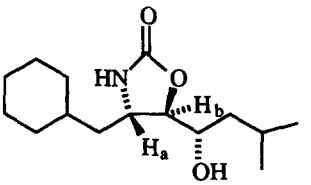

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To confirm the relative configuration of **8**, the diol was converted to its sulfite derivative **10** in 53% yield after preparative TLC using Et_3N / CH_2Cl_2, followed by $SOCl_2$.[12] The relative stereochemical arrangement of the diol was determined to be *syn* by NOE experiment. A 15% NOE difference for H_a and H_b was observed supporting a 3*R*, 4*S* configuration for the diol. To confirm the relative stereochemistry of **1**, the free amino diol was converted to the oxazolidinone derivative **12** using NaH / DMF.[13] From NOE experiment, the relative geometry of H_a and H_b was assumed to be *anti* because no NOE difference was observed. This is consistent with a 2*S*,3*R* configuration of the amino alcohol **1**. The relative stereochemistry of N,N-dibenzylamino diol **8** was unequivocally established by single crystal X-ray structure determination of racemic **8** (**Figure 1**). The X-ray data corroborates the NMR data for the overall stereochemical assignment of **1**.

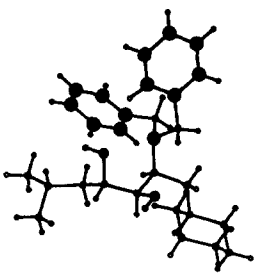

Figure 1: Chem3D Representation of the X-ray Structure of ± **8**.

The enantiopurity of **9** was determined using chiral HPLC analysis and was assayed to be >99% ee as compared to a racemic standard of **9**.[14] Additionally, the optical rotation of **9** was measured, $[\alpha]_D$ = -61.78° (c = 0.00246 g/mL, $CHCl_3$), which compared to the reported literature values $[\alpha]_D$ = -64.91° (c = 2.20, $CHCl_3$)[2a] and $[\alpha]_D$ = -67.4° (c = 1.17, $CHCl_3$).[2c]

In conclusion, an efficient stereoselective synthesis of (2*S*, 3*R*, 4*S*)-2-amino-1-cyclohexyl-6-methylheptane-3,4-diol **1** from L-phenylalanine has been achieved. This methodology demonstrates the value of the N,N-dibenzyl moiety as a powerful stereochemical directing group for asymmetric synthesis.

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14. The enantiopurity of the **9** was assayed by chiral HPLC analysis using a Shimadzu system, (LC-6A pumps, SPD-6A UV detector, and C-R6A integrator), equipped with a Daicel Chiralcel OD column (UV detector: 240 nm; solvent system: 99% hexanes : 1% 2-propanol; flow rate: 0.8 mL/min.; ambient temperature). Retention times: N-Boc diol **9**: 25.295 min (broad peak), and ± **9**: 25.133 min and 27.662 min (broad peaks).

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