

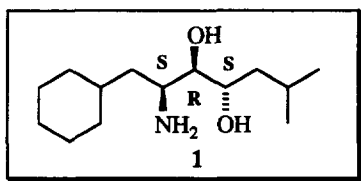
A Diastereoselective Synthesis of (2*S*, 3*R*, 4*S*)-2-Amino-1-cyclohexyl-6-methylheptane-3,4-diol, The Abbott Aminodiol.¹

Christopher W. Alexander and Dennis C. Liotta*

Department of Chemistry, Emory University, Atlanta, GA 30322 USA

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

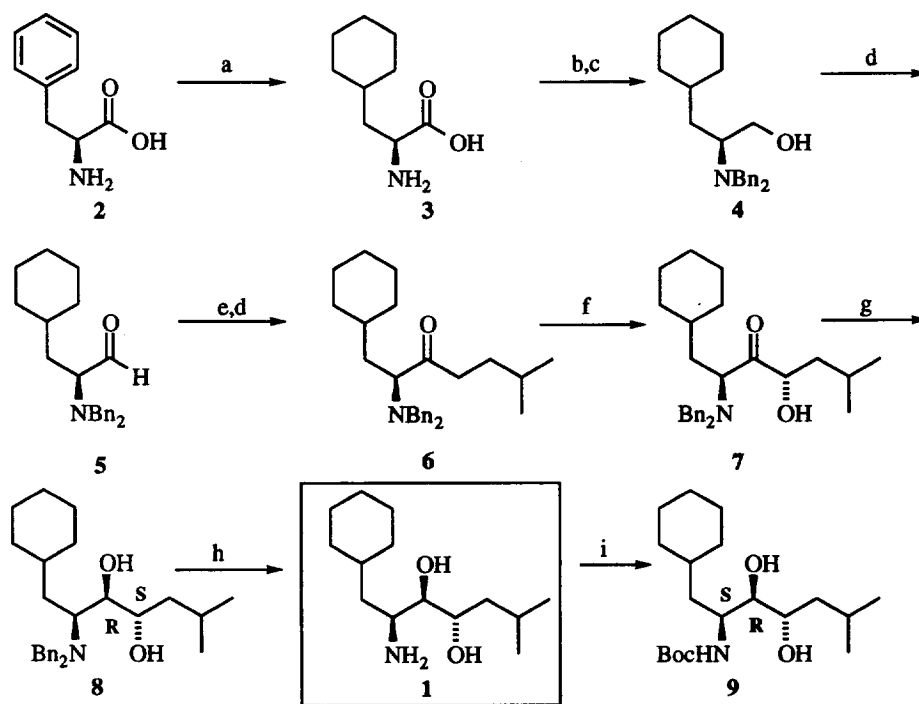
The design and synthesis of renin inhibitors has received a great deal of attention because of their potential as therapeutic agents for the treatment of hypertension. Structurally, these inhibitors are most often peptidic, and contain a core unit which is a peptide hydrolysis transition-state mimetic. 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**).



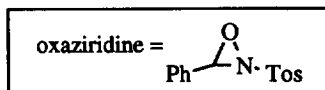
Amino acid derivatives have been a rich source of a variety of functionalized, chiral amines. The uniqueness of the *N,N*-dibenzyl protecting group has allowed for high degrees of facial selectivity in a variety of chemical transformations.⁴ Recently, our laboratories have explored the synthetic utility 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 LiAlH₄, 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 BrMgCH₂CH₂CH(CH₃)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 ¹H NMR analysis. α -Hydroxy ketone **7** was further reduced to the aminodiol using NaBH₄. 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 ¹H NMR.¹⁰ The free amine **1** was protected as the N-Boc diol **9** in 50% yield (not optimized) after chromatography.

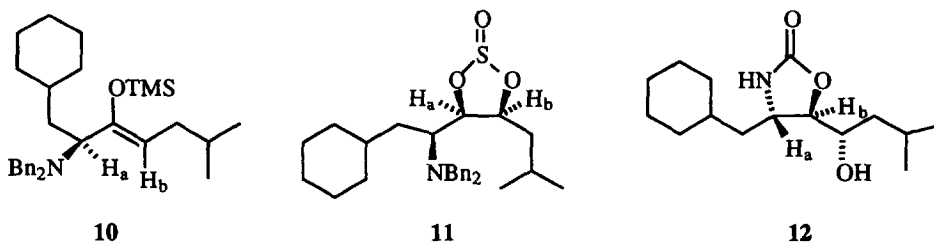


Scheme 11: Reagents: a) H₂, PtO₂, 40-50 psi, CH₃CO₂H, H₂O. b) NaOH, K₂CO₃, H₂O; PhCH₂Br, reflux. c) LiAlH₄, Et₂O, 0° C to rt. d) Swern oxidation [(COCl)₂/DMSO, CH₂Cl₂], -78° C. e) 2 eq. (CH₃)₂CHCH₂CH₂MgBr, Et₂O, 0° C. f) 1. 1.3 eq. NaHMDS, THF, -78° C, 3-5 h 2. 1.1 eq. oxaziridine, THF, -78° C. g) 2 eq. NaBH₄, MeOH, 0° C. h) 10% Pd/C, HCO₂NH₄, EtOH, reflux. i) Boc₂O, THF, H₂O, 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 corresponding 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



To confirm the relative configuration of **8**, the diol was converted to its sulfite derivative **10** in 53% yield after preparative TLC using $\text{Et}_3\text{N} / \text{CH}_2\text{Cl}_2$, 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 $3R, 4S$ 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 $2S, 3R$ 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**.

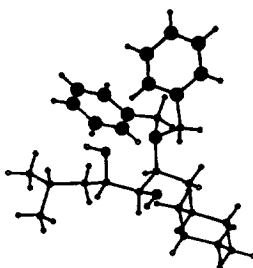


Figure 1: Chem3D Representation of the X-ray Structure of \pm **8**.

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, $[\alpha]_D = -61.78^\circ$ ($c = 0.00246$ g/mL, CHCl_3), which compared to the reported literature values $[\alpha]_D = -64.91^\circ$ ($c = 2.20$, CHCl_3)^{2a} and $[\alpha]_D = -67.4^\circ$ ($c = 1.17$, 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.

Acknowledgments: CWA would like to thank the Division of Endocrinology, Emory University, for an NIH NRSA Postdoctoral Training Fellowship. The authors would like to thank Ms. Xiaoyang Xia and Mr. A. Marcus Semones for obtaining the X-ray crystal structure of \pm **8**. Additionally, the authors would like to thank Dr. Shiow-Jyi Wey for assistance with NMR experiments and helpful suggestions as well as Ms. Jane Betty Goh for helpful discussions. The financial support by NIH and NSF for NMR and Mass Spectrometry facilities is gratefully acknowledged. This research was generously supported by the National Institutes of Health.

References and Notes.

1. This work was presented in part at the 209th ACS National Meeting at Anaheim, CA, April 2-6, 1995, ORGN 076.
2. (a) Luly, J. R.; Hsiao, C. -N.; BaMaung, N.; Plattner, J. J. *J. Org. Chem.* **1988**, *53*, 6109. (b) Wood, J. L.; Jones, D. R.; Hirschmann, R.; Smith, III, A. B. *Tetrahedron Lett.* **1990**, *31*, 6329. (c) Kobayashi, Y.; Matsumoto, T.; Takemoto, Y.; Nakatani, K.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2550. (d) Chan, M. F.; Hsiao, C. *Tetrahedron Lett.* **1992**, *33*, 3567. (e) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277. (f) Krysan, D. J.; Haight, A. R.; Menzia, J. A.; Welch, N. *Tetrahedron* **1994**, *50*, 6163. (g) Spero, D. M.; Kapadia, S.; Farina, V. *Tetrahedron Lett.* **1995**, *36*, 4543.
3. Kleinert, H. D.; Rosenburg, S. H.; Baker, W. R.; Stein, H. H.; Klinghofer, V.; Barlow, J.; Spina, K.; Polakowski, J.; Kovar, P.; Cohen, J.; Denissen, J. *Science* **1992**, *257*, 1940 and references cited therein.
4. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531.
5. (a) Goh, J. B.; Lagu, B. R.; Wurster, J.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 6029. (b) Lagu, B. R.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 4485. (c) Lagu, B. R.; Crane, H. M.; Liotta, D. C. *J. Org. Chem.* **1993**, *58*, 4191.
6. Schuda, P. F.; Greenlee, W. J.; Chakravarty, P. K.; Eskola, P. *J. Org. Chem.* **1988**, *53*, 873.
7. (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141. (b) Cooke, J. W. B.; Davies, S. G.; Naylor, A. *Tetrahedron* **1993**, *49*, 7955.
8. Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375.
9. (a) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774. (b) Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc. Perkin Trans. I*, **1994**, 2373.
10. Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.
11. Compounds **4**, **6** - **9**, and **11** were fully characterized by ¹H and ¹³C NMR, IR, MS, and C, H, N analysis.
12. Lohray, B. B. *Synthesis* **1992**, 1035.
13. Luly, J. R.; BaMuang, N.; Soderquist, J.; Fung, A. K. L.; Stein, H.; Kleinert, H. D.; Marcotte, P. A.; Egan, D. A.; Bopp, B.; Merits, I.; Bolis, G.; Greer, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1988**, *31*, 2264.
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 \pm **9**: 25.133 min and 27.662 min (broad peaks).