Two Chiral Syntheses of *threo*-3-Hydroxylysine[1]

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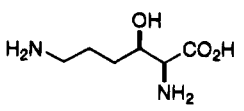
Two efficient chiral syntheses of 3-hydroxylysine, a naturally occurring amino acid and a putative intermediate in the synthesis of balanol, a potent protein kinase C inhibitor, are described. The synthesis of (2*R*,3*S*)-3-hydroxylysine utilizes Hayashi's chiral ferroceno gold catalyst. The synthesis of (2*S*,3*R*)-3-hydroxylysine demonstrates a β-hydroxy amino acid synthesis with the chirality derived from the Sharpless chiral *cis*-hydroxylation.

Introduction

Recently we required an efficient chiral synthesis of *threo*-3-hydroxylysine (**1**) for use as an intermediate in a chiral synthesis of the potent naturally occurring PKC inhibitor, balanol **2**.[2] We anticipated using 3-hydroxylysine in the synthesis of the azapine core of balanol. There are currently no commercial or viable natural sources for 3-hydroxylysine. An achiral synthesis of *threo*-3-hydroxylysine was reported by Stammer[3] in the 1960's and more recently a chiral synthesis was reported by Rapoport.[4] Structural elucidation of the potent phytotoxin, victorin, produced by the fungus *Cochliobolus victoriae*, revealed one component of the partially peptidic structure to be *threo*-3-hydroxylysine.[5] Because we anticipated the need to synthesize large quantities of the azapine for the synthesis of balanol and for the synthesis of analogues, we felt that a more efficient synthesis than those reported to date would be required.



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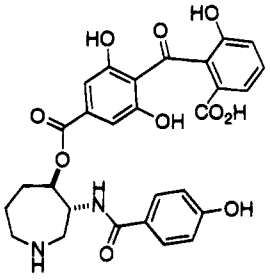

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Results

When we embarked on this endeavor we were attracted by the quickness with which we could assemble hydroxylysine with the required relative and absolute stereochemistry using the chiral catalyst of Hayashi.[6] The catalyst was available and being used in our laboratory in the synthesis of *threo*-dihydrosphingosine.[7] Although the Hayashi catalyst has been used for the synthesis of numerous β-hydroxy-α-amino acids,[8] the synthesis of 3-hydroxylysine by this method has not been reported. At this point we did not know the absolute stereochemistry of balanol and pursued the enantiomer derived from the catalyst in hand which, in our case, would ultimately produce (2*R*,3*S*)-3-hydroxylysine. Thus (Scheme 1), condensation of 4-phthalimidobutanal[9] with methyl isocyanoacetate in the presence of catalyst **4** (1 mol %) in methylene chloride at room temperature led after two days to a good yield of the desired oxazoline **3**. Analysis of the product after chromatography (90% yield) indicated a roughly 19:1 diastereomeric ratio. A single recrystallization (ethyl acetate/hexanes) gave product (73% overall) with none of the minor diastereomer detectable by ^{1}H-NMR (>98%). The product was hydrolyzed in refluxing 6 N HCl to give, after passing through Bio-Rad AG-1 (Cl^- form) and trituration in hot 2-propanol, (−)-(2*R*,3*S*)-3-hydroxylysine dihydrochloride (**1**) as a powder (75%).[10]

Subsequent analysis of a balanol derivative[1] indicated that the absolute configuration of balanol is that shown in structure **2** and its synthesis would require hydroxylysine with the configuration opposite to that obtained from the reaction using the ferrocene catalyst. Although the opposite enantiomer could be synthesized using the enantiomeric catalyst, we were interested in developing an alternative route which would not require catalyst synthesis and which might allow more flexibility in the choice of protecting groups.

A reliable alternative source of chirality is the Sharpless chiral *cis*-hydroxylation.[11] Replacement of the α-hydroxy of a 2,3-dihydroxy ester with an amine, with retention of configuration, would lead to the desired hydroxylysine. As shown in Scheme 2, 4-phthalimidobutanal was converted to *trans* 6-phthalimidohexenoate (**5**) with methyl (triphenylphosphoranylidene)acetate (97%). Chiral *cis*-hydroxylation gave the desired (2*S*,3*R*)-diol **6**

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(1) Dedicated to the memory of our late colleague, Jeffrey B. Nichols.

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(10) The hydrolysis was generally quantitative and the lower yield reflects loss on crystallization. This sample was isolated as an 2-propanol solvate. Although the 2-propanol solvate was less hygroscopic and more easily handled, we were not able to obtain the 2-propanol solvate reproducibly.

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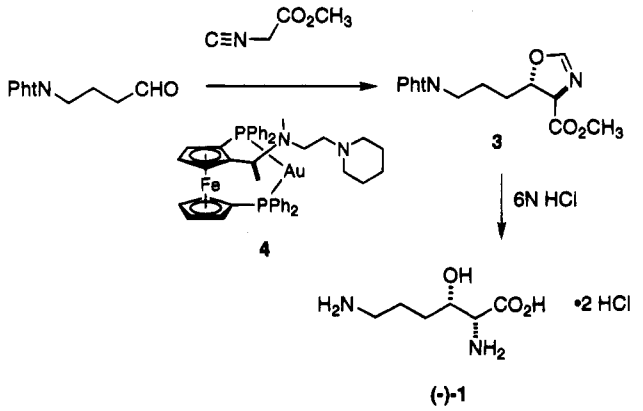
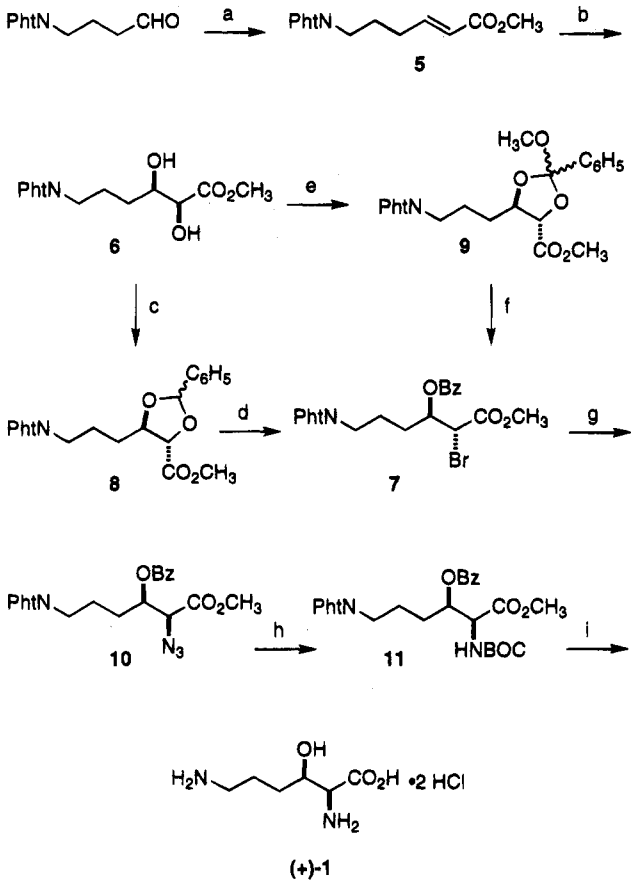
Scheme 1



Scheme 2



[a] (a) $Ph_3P{=}CHCO_2CH_3$, CH_2Cl_2; (b) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2$–PHAL, $K_2Os(OH)_3$, H_2O, $(CH_3)_3COH$; (c) C_6H_5CHO, $BF_3{\cdot}OEt_2$; (d) NBS, CH_2Cl_2; (e) $C_6H_5C(OCH_3)_3$, $BF_3{\cdot}OEt_2$; (f) CH_3COBr, NEt_3; (g) NaN_3, DMSO; (h) H_2, 10% Pd on carbon, EtOAc, $(BOC)_2O$, EtOH; (i) 6 N HCl, reflux.

(90%).[12] Conversion to the α-bromo compound **7** could be accomplished by either of two methods. In our initial approach, the diol was converted to the benzaldehyde acetal **8** followed by conversion to **7** on treatment with N-bromosuccinimide.[13] However, it proved more efficient to use the methodology described recently by Sharpless[14] for the conversion of diols to bromohydrins. Thus,

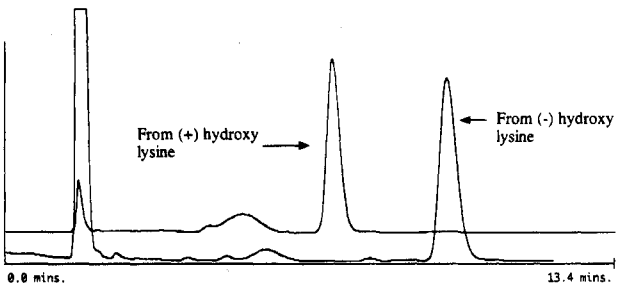


Figure 1.

treatment of diol **6** with trimethyl orthobenzoate and catalytic boron trifluoride etherate gave the mixed ortho-ester **9**. The ortho ester was converted to bromohydrin **7** by treatment with acetyl bromide. After workup, the crude bromide was converted to azide **10** by treatment with sodium azide (2 equiv) in DMSO. Again, after workup, the crude azide was converted to BOC amide **11** by hydrogenation (H_2 @ 1 atm, 10% Pd/C) of the azide in the presence of BOC anhydride.[15] Chromatography gave the desired protected hydroxylysine **11** in 80% yield from the diol. The product was hydrolyzed in refluxing 6 N HCl to give, after filtration, concentration, and passage through Bio-Rad AG-1 (Cl-form), and trituration in 2-propanol, (+)-(2*S*,3*R*)-3-hydroxylysine dihydrochloride (**1**) as an amorphous powder (74%).

To complete this work, it was necessary to determine the chiral purity of the synthetic (+) and (−) hydroxylysines. Both were condensed with excess (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate to give the bis-ureas. Analysis by HPLC revealed no separation on reverse phase; however, the diastereomers were cleanly separated on silica gel (90/10/0.5 methylene chloride/methanol/acetic acid). Analysis (Figure 1) indicated the optical purities of both amino acids to be greater than 99% ee.

Conclusion

Two complimentary and efficient chiral syntheses of *threo*-3-hydroxylysine, capable of providing multigram quantities, are described. One route demonstrates the application of Hayashi's chemistry to a new amino acid. The other route represents a new approach to the synthesis of β-hydroxy-α-amino acids. Although we have not used this chemistry for the synthesis of other amino acid targets, we believe it should be generally applicable. The use of (2*S*,3*R*)-3-hydroxylysine in the chiral synthesis of balanol is in progress and will be reported in due course.

Experimental Section

Starting compounds were obtained from Aldrich and used without further purification. Baker silica gel (40 μM) was used for flash chromatography.

(4*R*,5*S*)-4-(Methoxycarbonyl)-5-[(4-phthalimido)butyl]-oxazoline (3). The ferrocene ligand (*SR*-BPPF-[(methylamino)ethyl]piperidine,[5,16] 140 mg, 0.194 mmol) and the gold ($[Au(c\text{-}C_6H_{11}NC)_2]BF_4$,[17] 105 mg, 0.194 mmol) were dissolved in CH_2Cl_2 (25 mL) to generate the gold catalyst *in situ*. Methyl isocyanoacetate (384 mg, 350 μL, 3.9 mmol) was then added,

(12) Conditions as described in ref 8 were used except that, on the suggestion of H. Kolb of the Sharpless lab, the quantities of ligand and osmium were doubled. We felt the faster rate gave better yields by limiting competing ester or phthalimide hydrolysis. When the reaction was allowed to run for extended periods (>16 h), yields were substantially lower (<50%).

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followed by 4-phthalimidobutanal (870 mg, 5.01 mmol) in CH_2Cl_2 (10 mL). After stirring at rt for 2 d, TLC analysis (aldehyde $R_f = 0.47$, product $R_f = 0.15$ in 40% EtOAc in hexanes) showed complete reaction. The reaction mixture was chromatographed (4.1 × 13 cm, 100% EtOAc) to give the title compound (1.14 g, 90%) as a crystalline solid. A sample was recrystallized from EtOAc/hexanes for spectral analysis: mp 126–127 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.69–1.88 (4H, m), 3.74 (2H, t, J = 6.95 Hz), 3.77 (3H, s), 4.29 (1H, dd, J = 2, 7 Hz), 4.68 (1H, dd, J = 7, 13 Hz), 6.88 (1H, d, J = 2 Hz), 7.70 (2H, dd, J = 3, 5.3), 7.84 (2H, dd, J = 3, 5.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 24.46, 32.613, 37.52, 52.63, 72.37, 81.10, 123.48, 132.21, 134.23, 156.60, 168.53, 171.21; IR (KBr) 3462, 3056, 2949, 1772, 1737, 1772, 1620, 1400, 1112, 720 cm^{-1}; $[\alpha]^{25}_D$ = −178° (c = 2.145 in EtOAc). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.76; H, 5.1; N, 8.86. Found: C, 61.05; H, 5.15; N, 8.92.

(2*R*,3*S*)-2,6-Diamino-3-hydroxyhexanoic Acid Dihydrochloride ((−)-1). (4*R*,5*S*)-4-(Methoxycarbonyl)-5-[(4-phthalimido)butyl]oxazoline (**3**) (1 g, 3.16 mmol) was slurried in 6 N HCl and heated at reflux for 16 h. TLC analysis (product R_f = 0.05 in 4/1/1 n-BuOH/AcOH/H_2O) showed complete reaction. The mixture was concentrated and then passed through an anion-exchange resin (Bio-Rad AG-1, Cl^- form). The ninhydrin active fractions, which eluted at the solvent front, were combined and concentrated. The residue was recrystallized from MeOH/IPA to give the title compound (0.71g, 76%), an 2-propanol solvate, as a white powder: ^{1}H-NMR (300 MHz, D_2O) δ 1.17 (6H, d, from IPA), 1.58–1.95 (4H, m), 3.07 (2H, t), 3.93 (1H, d, J = 4.4 Hz), 4.02 (1H, hpt, from IPA), 4.20 (1H, m); ^{13}C-NMR (75 MHz, D_2O) δ 23.90 24.27 (IPA), 30.56, 39.60, 58.36, 64.84 (IPA), 69.04, 171.20; IR (KBr) 3391, 2974, 1739, 1595, 1499, 1310, 1012 cm^{-1}; $[\alpha]^{25}_D$ = −13.15° (c = 1.64 in CH_3OH). Anal. Calcd for $C_6H_{14}N_2O_3{\cdot}2HCl{\cdot}C_3H_8O$: C, 36.62; H, 8.19; N, 9.49. Found: C, 36.99; H, 8.49; N, 9.28.

Methyl 6-Phthalimidohex-2-enoate (5). 4-Phthalimidobutanal (19.5 g, 89.6 mmol) was dissolved in CH_2Cl_2 (100 mL) and treated with methyl (triphenylphosphoranylidene)-acetate (30 g, 89.6 mmol) in CH_2Cl_2 (100 mL). After 1 h, the mixture was concentrated to about 75 mL in volume, poured onto a silica gel column (7 × 14 cm, packed in and eluted with 30% EtOAc in hexanes), and chromatographed to give after concentration, the product (23.7 g, 97%) as a white solid. An aliquot was recrystallized in EtOAc and hexanes: mp 87–88 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.81 (2H, p, $J \approx$ 7.1 Hz), 2.23 (2H, m), 3.67 (3H, s), 3.70 (2H, t, J = 7.1 Hz), 5.84 (1H, d, J = 15.5 Hz), 6.92 (1H, dt, J = 15.5, 6.8 Hz), 7.71 (2H, m), 7.81 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.11, 29.73, 37.58, 51.64, 121.89, 123.49, 132.26, 134.20, 147.82, 167.01, 168.56; IR (KBr) 3456, 2943, 1773, 1702, 1397, 719 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.12. Found: C, 65.76; H, 5.38; N, 5.09.

Methyl (2*S*,3*R*)-2,3-Dihydroxy-6-phthalimidohexanoate (6). Potassium ferricyanide (34.5 g, 105 mmol), potassium carbonate (14.5 g, 105 mmol), $(DHQD)_2$–PHAL[18] (544 mg, 698 μmol), and potassium osmate (51 mg, 139 μmol) were dissolved in t-BuOH and H_2O (175 mL each) and cooled to 0 °C in an ice bath. Methyl 6-phthalimidohex-2-enoate (**5**) (9.5 g, 35 mmol), dissolved in CH_2Cl_2 (25 mL), was added slowly and the vigorously stirred reaction mixture was allowed to warm in a slowly melting ice bath. After 4 h, the ice had melted and TLC analysis indicated complete reaction. The reaction mixture was treated with sodium sulfite (54 g, 428 mmol) and stirred for 30 min. The reaction mixture was then treated with CH_2Cl_2 (300 mL). The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (2 × 200 mL). The combined organic layers were concentrated (to 100 mL) and poured onto a silica gel column (7 cm diam. × 9 cm ht.) packed in CH_2Cl_2. The column was eluted with 1/1 CH_2Cl_2/EtOAc to give product in 250 mL fractions 2–6. After concentration, the product was dissolved in hot CH_2Cl_2 (150 mL) and treated with hot hexanes (250 mL) to effect crystallization. The product was collected and air-dried to give 9.56 g (89%). The mother liquor was concentrated and recrystallized to give a second crop, 780 mg (7.3%). An aliquot was again recrystallized from CH_2Cl_2/hexanes: mp 123–123.5 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.59–1.92 (4H, m), 2.50 (OH, d, J = 9 Hz), 3.23 (OH, d, J = 6 Hz), 3.73 (3H, t, J = 7 Hz), 3.79 (3H, s), 3.94 (1H, m), 4.07 (1H, m), 7.69 (2H, m), 7.80 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.26, 30.78, 37.82, 53.03, 72.29, 73.19, 123.45, 132.23, 131,17, 168.73, 174.00; IR (KBr) 3438, 3364, 1774, 1719, 1395, 1326, 1117, 1046, 718 cm^{-1}; $[\alpha]^{25}_D$ = +15.6° (c = 0.475 in CH_3OH). Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.43; H, 5.55; N, 4.60.

Methyl (2*S*,3*R*)-3-(Benzoyloxy)-2-[(*tert*-butyloxycarbonyl)amino]-6-phthalimidohexanoate (11). Methyl (2*S*,3*R*)-2,3-dihydroxy-6-phthalimidohexanoate (**6**) (17 g, 55.3 mmol) and trimethyl orthobenzoate (13.1 g, 12.4 mL, 71.9 mmol) were dissolved in CH_2Cl_2 (200 mL) and treated with $BF_3{\cdot}OEt_2$ (345 mg, 300 μL, 2.4 mmol). After stirring for 1 h, the mixture was concentrated and put under full vacuum (0.05 mmHg) for 30 min. The mixture was redissolved in CH_2Cl_2 (200 mL), cooled to 0 °C and treated sequentially with NEt_3 (296 mg, 403 μL, 2.9 mmol) and acetyl bromide (7.14 g, 4.3 mL, 58.1 mmol). After stirring for 4 h, the reaction mixture was treated with saturated $NaHCO_3$ solution (150 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were filtered through filter paper and concentrated to give the α-bromo β-benzoate as a glass: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.85 (2H, m), 2.05 (2H, m), 3.76 (2H, t, J = 7 Hz), 3.76 (3H, s), 4.58 (1H, d, J = 7 Hz), 5.60 (1H, m), 7.48 (2H, d, J = 7 Hz), 7.60 (1H, t, J = 7.5 Hz), 7.74 (2H, m), 7.85 (2H, m), 8.02 (2h, d, J = 7 Hz). The oil was dissolved in DMSO (70 mL) and treated with sodium azide (7.2 g, 111 mmol). After stirring for 4 h, the mixture was partitioned between H_2O and ether (300 mL each). The aqueous layer was again extracted with ether (200 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to an oil: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.79 (3H, m), 2.00 (1H, m), 3.72 (3H, s), 3.74 (2H, t, J = 7 Hz), 3.89 (1H, d, J = 3 Hz), 5.67 (1H, m), 7.41 (2H, d, J = 7 Hz), 7.55 (1H, t, J = 7.5 Hz), 7.69 (2H, m), 7.82 (2H, m), 7.99 (2h, d, J = 7 Hz). The oil was treated with di-*tert*-butyl dicarbonate (14.5 g, 66.4 mmol) and dissolved in EtOAc (120 mL). The mixture was treated with an EtOAc (30 mL) slurry of 10% palladium on carbon and EtOH (10 mL) and stirred in a H_2 atmosphere under balloon pressure. After 30 h the reaction was finished and the mixture was filtered through a Mitex filter, concentrated, and chromatographed (silica gel, 7 cm diam. × 13 cm ht., 7/3 hexanes/EtOAc) to give 22.6 g (80% from diol) of the product, methyl 3(R)-(Benzoyloxy)-2(*S*)-[(*tert*-butyloxycarbonyl)amino]-6-phthalimidohexanoate (**11**) in 250 mL fractions 6–10, as a glass after concentration: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (9H, s), 1.7–1.85 (4H, m), 3.67 (3H, s), 3.71 (2H, m), 4.58 (1H, dd, J = 2.5, 9.5 Hz), 5.28 (NH, d, J = 9.5 Hz), 5.57 (1H, m), 7.40 (2H, t, J = 7 Hz), 7.51 (1H, t, J = 7 Hz), 7.68 (2H, m), 7.79 (2H, m), 7.94 (2H, d, J = 7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.11, 28.79, 28.79, 38.00, 53.28, 56.18, 74.48, 80.92, 123.80, 129.01, 129.96, 130.31, 132.66, 133.87, 134.46, 156.25, 166.09, 168.84, 171.29; IR (KBr) 3432, 3369, 1713, 1271, 716 cm^{-1}. Anal. Calcd for $C_{27}H_{30}N_2O_8$: C, 63.52; H, 5.92; N, 5.49. Found: C, 63.04; H, 6.05; N, 5.34.

(2*S*,3*R*)-2,6-Diamino-3-hydroxyhexanoic Acid Dihydrochloride ((+)-1). Methyl (2*S*,3*R*)-3-(benzoyloxy)-2-[(*tert*-butyloxycarbonyl)amino]-6-phthalimidohexanoate (**11**) (22.1 g, 43.3 mmol) was slurried in 6 N HCl (300 mL) and heated at reflux for 20 h. TLC analysis (product R_f = 0.05 in 4/1/1 n-BuOH/AcOH/H_2O) showed complete reaction. The mixture was concentrated and then passed through an anion-exchange resin (Bio-Rad AG-1, Cl^- form, 2.1 × 30 cm) with water. The ninhydrin active fractions, which eluted at the solvent front, were combined and concentrated. The residue was triturated by stirring with IPA (200 mL) and a small amount of MeOH (≈30 mL). The resulting powder was filtered off under nitrogen, washed with IPA, and dried under nitrogen flow to give the title compound (7.4 g, 73%) as a white powder: mp 188–192 °C; ^{1}H-NMR (300 MHz, D_2O) δ 1.58–1.98 (4H, m), 3.07 (2H, t, J = 7.4 Hz), 4.05 (1H, d, J = 4.1 Hz), 4.23 (1H, dt,

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J = 3.8, 9.5 Hz); ^{13}C-NMR (75 MHz, D_2O) δ 23.30, 29.92, 38.98, 57.62, 66.51 (dioxane reference), 68.37, 170.44; IR (KBr) 3437, 1737, 1621, 1503 cm^{-1}; $[\alpha]^{25}_D$ = +16.9° (c = 1.83 in CH_3OH). Anal. Calcd for $C_6H_{14}N_2O_3 \cdot 2HCl$: C, 30.65; H, 6.86; N, 11.91. Found: C, 30.88; H, 6.93; N, 12.01.

Hydroxylysine Derivitization. (+)-3-Hydroxylysine (6 mg, 25 μmol) was dissolved in DMF (10 drops) and treated with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (Aldrich, 14 μL, 16 mg, 81 μmol) followed by NEt_3 (14 μL, 10.3 mg, 102 μmol). The mixture was allowed to sit for two days and an aliquot was withdrawn for HPLC analysis. The product was analyzed by chromatography on an Alltech silica gel column (Intersil Sil 5 μm, 4.6 × 15 cm) eluted with 180/20/1 CH_2Cl_2/MeOH/AcOH. The bis-urea eluted at 7.1 min. A sample of the product was purified for NMR analysis: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.36−1.39 (4H, m), 1.41−1.46 (6H, 2 d), 2.98 (2H, m), 3.90 (1H, m), 4.09 (1H, d, J = 7.7 Hz), 5.53 (2H, m), 5.8 (1H, br s), 5.98 (1H, d, J = 8.8 Hz), 6.42 (1H, m), 7.00 (1H, d, J = 7.6 Hz), 7.4−7.6 (8H, m), 7.80 (2H, d, J = 8.9 Hz), 7.92 (2H, d, J = 7.3 Hz), 8.1 (2H, m).

Analogous derivatization of (−)-hydroxylysine gives a bis-urea which elutes at 9.6 min.

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