

Asymmetric Synthesis of 2,6-Diamino-6-(hydroxymethyl)pimelic Acid: Assignment of Stereochemistry

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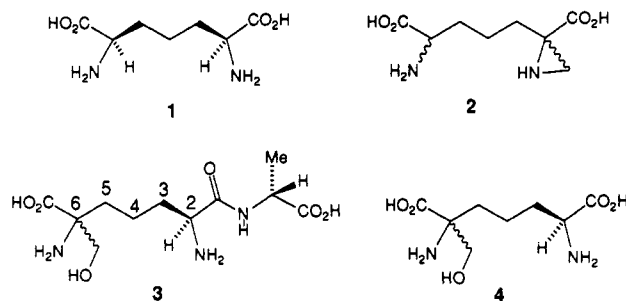
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Abstract: The asymmetric synthesis of (2*S*,6*R*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**17**) and (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**) has been accomplished. Sequential enolate alkylation of (5*S*,6*R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**9**) with 1-iodo-3-butene and bromomethyl methyl ether gave the α,α -disubstituted lactone in ~100% de; subsequent ozonolysis gave the quaternary aldehyde **19**. Aldol condensation with the enol borane of (5*S*,6*R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**9**) gave the dilactone **20**. Barton deoxygenation, reductive cleavage of the oxazinones, and demethylation gave (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**). Synthesis of the 2*S*,6*R* isomer followed the same protocol, only starting with (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**5**). Comparison of these two amino acids reveals that the 2*S*,6*S* isomer **4** is the constituent of natural *N*-[2,6-diamino-6-(hydroxymethyl)pimel-1-yl]-L-alanine (**3**), a natural antibiotic produced by *Micromonospora chalybeata*.

Introduction

2,6-Diaminopimelic acid (**1**, DAP) is an important, naturally occurring amino acid biosynthesized in bacteria and higher plants.¹ L,L- and *meso*-DAP serve as the penultimate biosynthetic precursors of the essential amino acid L-lysine. *meso*-DAP functions as a cross-linking constituent of virtually all Gram-negative and some Gram-positive bacterial peptidoglycans, and also serves to anchor various membrane-associated macromolecules, such as lipoprotein, to the cell wall. Recognition of the pivotal roles DAP plays in microbial metabolism² and cell wall structure has resulted in an increased level of interest in possible means to selectively disrupt the DAP biosynthetic pathway. A flurry of recent papers³ on the synthesis of DAP and, more significantly, structural analogues of DAP that can function as substrate-based inhibitors of key biosynthetic transformations attests to the potential importance of the DAP/lysine pathway as a viable target for antibiotic design. Recent studies in several laboratories demonstrate that a number of compounds that inhibit the formation or metabolism of 2,6-diaminopimelic acid in bacteria possess antibiotic activity.⁴ Since mammals lack the diaminopimelate pathway and require L-lysine in their diet,⁵ specific inhibitors of the enzymes along this route are potential antimicrobial agents that should display low mammalian host toxicity.

Despite the apparent simplicity of this amino acid, there exist no stereochemically unambiguous syntheses of *meso*-DAP nor asymmetric synthesis of L,L-DAP. Two very recent exceptions



are the synthesis of β -fluoro DAP by Vederas and Gelb^{6a} and β -hydroxy DAP by Bold and associates.^{6b} The potential importance of inhibiting the DAP pathway through the design and synthesis of functionalized DAP analogues renders this class of amino acids an attractive and worthy synthetic problem. A recent example is the (stereorandom) preparation of the aziridino DAP **2** that was shown⁷ to be a potent inhibitor of L,L-DAP epimerase and exhibits antimicrobial activity. In this paper, we report a stereochemically unambiguous asymmetric synthesis of two stereoisomers of the only known natural DAP homologue, 2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**).⁸

N-[2,6-Diamino-6-(hydroxymethyl)pimel-1-yl]-L-alanine (**3**) was isolated from the culture extracts of a microorganism identified as *Micromonospora chalybeata* by the Shionogi Co. in Japan.⁸ The dipeptide **3** exhibits limited antimicrobial activity against *Escherichia coli* on a synthetic medium, and this activity is synergistically enhanced by several cell wall synthesis inhibitors such as penicillin G, phosphonomycin, cycloserine, chloro-D-alanine, macarbomycin, and cephaloridine.

The structure of **3** was determined by spectroscopic methods and chemical degradation.⁸ The natural substance was assumed to be a dipeptide composed of an unknown amino acid and alanine. This was established by hydrolysis and subsequent analysis of the hydrolysate by an automatic amino acid analyzer. Specific optical rotation and ORD spectra proved that the alanine isolated from the hydrolysate has the L configuration. Elemental analysis indicated that the molecular formula of the unknown amino acid is C₈H₁₆N₂O₅. Furthermore, ¹H and ¹³C NMR spectroscopic data

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(2) Certain bacteria bypass the L,L form of DAP by means of *meso*-DAP D-dehydrogenase: (a) Bartlett, A. T. M.; White, P. J. *J. Gen. Microbiol.* **1985**, *131*, 2145. (b) Misono, H.; Ogasawara, M.; Nagasaki, S. *Agric. Biol. Chem.* **1986**, *50*, 2729.

(3) (a) Berges, D. A.; Dewolf, W. E., Jr.; Dunn, G. L.; Grappel, S. F.; Newman, D. J.; Taggart, J. J.; Gilvarg, C. *J. Med. Chem.* **1986**, *29*, 89. (b) Berges, D. A.; DeWolf, W. E., Jr.; Dunn, G. L.; Newman, D. J.; Schmidt, S. J.; Taggart, J. J.; Gilvarg, C. *J. Biol. Chem.* **1986**, *261*, 6160. (c) Kelland, J. G.; Arnold, L. D.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.* **1986**, *261*, 13216. (d) Girodeau, J.-M.; Agouridas, C.; Masson, M.; Pineau, R.; LeGoffic, F. *J. Med. Chem.* **1986**, *29*, 1023. (e) Lam, L. K. P.; Arnold, L. D.; Kalantar, T. H.; Kelland, J. G.; Lane-Bell, P. M.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.* **1988**, *263*, 11814. (f) Baumann, R. J.; Bohme, E. H.; Wiseman, J. S.; Vaal, M.; Nichols, J. S. *Antimicrob. Agents Chemother.* **1988**, *32*, 1119. (g) Bohme, E. H.; Gerhart, F.; Higgins, W. U.S. Patent 4,730,006, 1988.

(4) See also references in: Lin, Y.; Myhrman, R.; Schrag, M. L.; Gelb, M. H. *J. Biol. Chem.* **1988**, *263*, 1622.

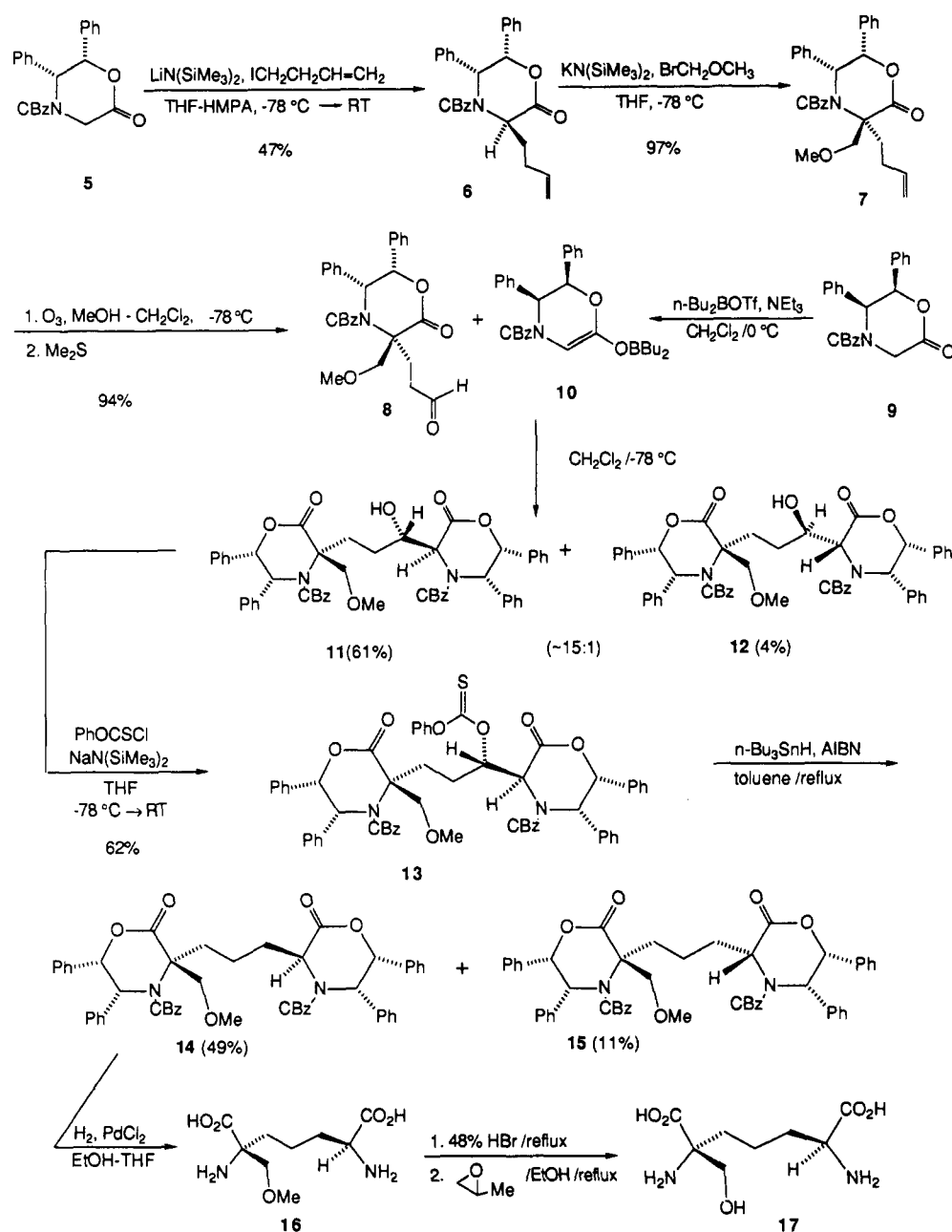
(5) Jouanneau, J.; Stragier, P.; Bouvier, J.; Pate, J.-C.; Yaniv, M. *Eur. J. Biochem.* **1985**, *146*, 173 and references therein.

(6) (a) Gelb, M. H.; Lin, Y.; Pickard, M. A.; Song, Y.; Vederas, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4932. (b) Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 497.

(7) Gerhart, F.; Higgins, W.; Tardif, C.; Duce, J.-B. *J. Med. Chem.* **1990**, *33*, 2157.

(8) Shoji, J.; Hinoo, H.; Kato, T.; Nakauchi, K.; Matsuura, S.; Mayama, M.; Yasuda, Y.; Kawamura, Y. *J. Antibiot.* **1981**, *34*, 374.

Scheme 1



suggested that the unknown amino acid should be 2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**). This was further corroborated by chemical degradation. Amino acid **4** was acetylated with acetic anhydride in a dilute sodium bicarbonate solution, and then treated sequentially with NaIO_4 in a dilute alkaline solution followed by oxidation with KMnO_4 ; subsequent hydrolysis furnished L- α -amino adipic acid. Thus, the new amino acid proved to be 2,6-diamino-6-(hydroxymethyl)pimelic acid with the L configuration at the C-2 stereogenic center. Employment of the Scheinblatt method⁹ established the connectivity shown in **3**. However, the relative and absolute stereochemistry at C-6 remained unknown.

In spite of the weak biological activity exhibited by **3**, we decided to synthesize this natural product in a stereochemically unambiguous manner. In this way, we hoped to be able to assign the stereochemistry at C-6 and develop methodology that would be generally applicable to the 2,6-diaminopimelic acid (DAP) family of amino acids. In addition, **4** and stereoisomeric derivatives would appear to be ideal precursors for unambiguously preparing all individual stereoisomers of the biologically active aziridine **2**.

Results and Discussion

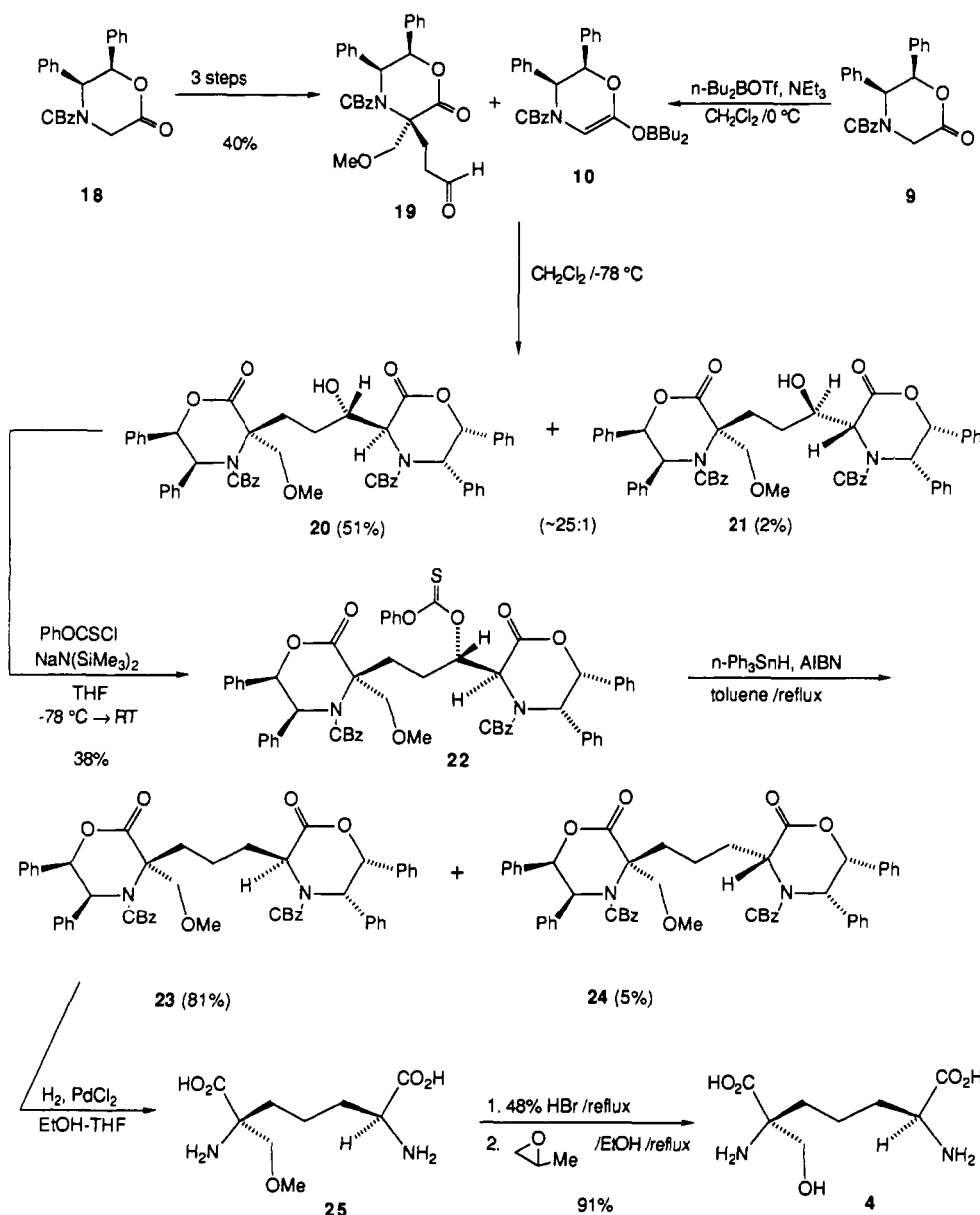
We have previously reported¹⁰ on the utility of the diphenyloxazinones **5** as versatile templates from which both electrophilic¹¹ and nucleophilic¹² C-C bond-forming strategies can be employed to access a variety of nonproteinogenic α -amino acids. In selecting a strategy to accomplish the key coupling of two optically pure glycines to a three-carbon tether, we examined a variety of C-C

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(11) (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (c) Sinclair, P. J. Ph.D. Thesis, Colorado State University, Fort Collins, CO, 1987. (d) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021. (e) Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.* **1988**, *110*, 482. (f) Williams, R. M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5425. (g) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501. (h) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723.

(12) (a) Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1989**, *29*, 6075. (b) Details of dialkylations of **5** and **9** and the X-ray crystal structure of a dialkylation product (from **9**, alkylating sequentially with methyl iodide and benzyl bromide) will be published elsewhere: Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.*, in press.

Scheme II



bond-forming reactions between two oxazinones, one carrying the activated three-carbon tether and the other, unsubstituted. Attempted enolate couplings to various 3'-halo derivatives all met with complete failure. Similarly, attempted electrophilic couplings between metallo-alkynylated^{11f} substrates also failed to give the desired homologies. Finally, we found that employment of the enol borane aldol couplings reported by Miller¹³ on these oxazinone systems proved to be effective. Initially, we attempted to synthesize the 2*S*,6*R* isomer. As shown in Scheme I, the commercially available¹⁴ lactone **5** was treated with homoallyl iodide in the presence of lithium bis(trimethylsilyl)amide to give the homoallyloxazinone **6** in 47% yield. After extensive experimentation, it was found that enolate alkylation of **6** could be carried out in high yield by the following procedure. To a solution of **6** in THF at -78°C was added potassium bis(trimethylsilyl)amide; after 5 min, bromomethyl methyl ether was added. The (methoxymethyl)homoallyloxazinone **7** was obtained in 97% yield ($\sim 100\%$ de) after chromatography. We could not detect any of the epimeric alkylation product in the crude reaction mixture by ^1H NMR analysis. Approach of the electrophile to the least hindered

face of the enolate has been corroborated^{12b} through single-crystal X-ray analysis of a related dialkylation on **5**. The homologated oxazinone **7** was ozonized and then quenched with dimethyl sulfide to afford the aldehyde **8** in 94% yield.

Preparation of the boron enolate of **9** according to Miller¹³ followed by aldol condensation with the aldehyde **8** gave the β -hydroxy dilactone **11** (61%) as the major product and **12** (4%) as the minor product. It is assumed that the relative stereochemistry of the minor diastereomer **12** at the α -position is syn to the two phenyl rings (*R*) because of the characteristic^{11c} relative difference in chemical shifts of methine protons at the benzylic positions of the oxazinone ring. For the anti diastereomer **11**, the difference in chemical shift ($\Delta\delta$) for the benzylic methines in the monosubstituted lactone ring is 1.26 ppm while $\Delta\delta$ for the syn diastereomer **12** is 0.47 ppm. This assignment is based on the additional assumption that both the syn and anti diastereomers have similar chemical shift differences for the methines in the quaternary lactone system. These relative chemical shift differences are in accord with empirical observations first discussed by Sinclair.^{11c} Although ultimately unimportant for the synthesis of **4**, the diastereoselectivity of the aldol condensation appears to be excellent. Out of a total of four possible diastereoisomers, only two were observable in the crude reaction mixture. The small vicinal coupling constants (~ 1.9 Hz) for the C-2/C-3 (DAP numbering) methines for each diastereomer (**11** and **12**) are in

(13) Reno, D. S.; Lotz, B. T.; Miller, M. J. *Tetrahedron Lett.* 1990, 31, 827.

(14) Lactones **5** and **9** are commercially available from Aldrich Chemical Co.; **5**: catalog # 33, 185-6; **9**: catalog # 33, 187-2.

accord with the anti selectivity observed by Miller¹³ in related aldolizations.

Next, we examined reductive functional transformation of the β -hydroxy group to obtain the requisite deoxygenation product. This proved to be very difficult since this alcohol moiety is very hindered and is prone to α,β -elimination. Many attempts at activating the hydroxyl for hydride displacement resulted in either no reaction or α,β -dehydrogenation.¹⁵

After examining a multitude of reductive activation possibilities, we established conditions to prepare a Barton reaction¹⁶ precursor. As shown in Scheme I, treatment of the alcohol **11** with phenyl chlorothionoformate in the presence of sodium bis(trimethylsilyl)amide furnished the thionoformate **13** in 62% yield. Standard procedures¹⁷ to prepare phenyl thionoformates afforded either the α,β -unsaturated lactone or unreacted starting material, depending on the reaction conditions. Several attempts to prepare other Barton reaction precursors failed, leading to no reaction. Among several bases examined ($n\text{BuLi}$, $\text{LiN}(\text{SiMe}_3)_2$, $\text{NaN}(\text{SiMe}_3)_3$, $\text{KN}(\text{SiMe}_3)_2$, sodium bis(trimethylsilyl)amide gave the best result for the conversion of **11** to **13**.

The reduction of **13** with tributyltin hydride in the presence of AIBN in refluxing toluene provided the deoxygenated product **14** in 60% yield along with an epimer **15** in 15% yield (major:minor $\sim 5:1$). Formation of the unexpected minor isomer **15** can be explained mechanistically as follows: the initially formed secondary β -radical from tin hydride removal of the thionoformate is quenched with tributyltin hydride to afford the major diastereomer **14**. However, a more stable tertiary radical at the α -position of the monosubstituted lactone can be formed by two pathways: (1) 1,2-hydrogen migration of the β -radical, or (2) abstraction of the α -hydrogen in the initially formed dilactone **14** by the secondary β -radical or from a stannane radical. Hydrogen-atom transfer from tributyltin hydride to the putative tertiary radical is expected to proceed from the least hindered face (anti to the phenyl rings), leading to the minor product **5**. It is unlikely that 1,2 hydrogen atom migration occurs because this process is not allowed by orbital symmetry theory. The latter explanation is therefore the most plausible.

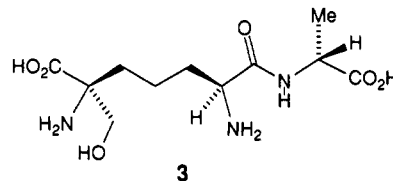
Finally, **14** was smoothly converted into (2*S*,6*R*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**17**). Dilactone **14** was hydrogenated to give the amino acid **16**, which was directly converted into **17** in 95% yield by demethylation in refluxing 48% HBr and subsequent scavenging of HBr with propylene oxide in refluxing ethanol.

Measurement of the specific optical rotation of **17** indicates that the 6*R* stereochemistry is not that of the natural amino acid $[[\alpha]^{25}_D +22.5^\circ$ (c 0.6, 5 N HCl), lit.⁸ $[\alpha]^{25}_D +8.1 \pm 1.0^\circ$ (c 0.506, 5 N HCl)]. Since the stereochemistry at C-2 of the natural

product had been assigned by the oxidative degradation to L- α -aminoadipic acid, preparation of the 2*S*,6*S* isomer starting with the antipodal lactone **18** (Scheme II) was carried out.

Following the identical protocol used to prepare **7**, the antipodal quaternary lactone aldehyde **19** was prepared. As shown in Scheme II, aldol condensation of **10** with **19** provided the hydroxy dilactone **20** as the major diastereomer (51%) plus **21** as the minor isomer (2%). Again, as in the case above for **11** and **12**, excellent diastereoselectivity in the aldol reaction was observed. The vicinal coupling constants for the C-2/C-3 system were 0 and 2.4 Hz for **20** and **21**, respectively. We could not detect the corresponding anti (aldol) diastereomers in the crude reaction mixture by NMR analysis. Both sets of aldolizations support a Zimmerman-Traxler chair-type transition state predominantly from the face of the oxazinone anti to the two phenyl rings with the aldehyde methine oriented toward the inside of the oxazinone ring. The major isomer **20** was converted into the thionoformate **22** by the method described above for **13**. The reduction of **22** with tributyltin hydride gave the dilactone **23** (60%), and the minor syn isomer **24** was obtained in 10% yield. Employment of triphenyltin hydride instead of tri-*n*-butyltin hydride enhanced the yield of reduction, giving the major isomer **23** in 81% yield and the minor isomer **24** in 5%. Catalytic hydrogenolysis and demethylation produced (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid (**4**) in 91% overall yield from **23**. Measurement of the specific rotation of synthetic **4** demonstrates that the natural product possesses the 2*S*,6*S* relative and absolute stereochemistry $[[\alpha]^{25}_D +7.1^\circ$ (c 0.55, 5 N HCl) lit.⁸ $[\alpha]^{25}_D +8.1 \pm 1.0^\circ$ (c 0.506, 5 N HCl)]. The synthetic amino acid **4** proved to be identical (¹H NMR, TLC) with an authentic sample of **4** obtained from hydrolytic cleavage¹⁸ of the natural product **3** obtained from Shionogi & Co. Since the diastereoisomeric purity of **19** is ca. 100% de, the enantiomeric purity of the synthetic amino acid **4** is similarly ca. 100% ee.

Thus the complete stereostructure for the natural dipeptide **3** is (2*S*,6*S*)-*N*-(2,6-diamino-6-(hydroxymethyl)pimel-1-yl)-L-alanine:



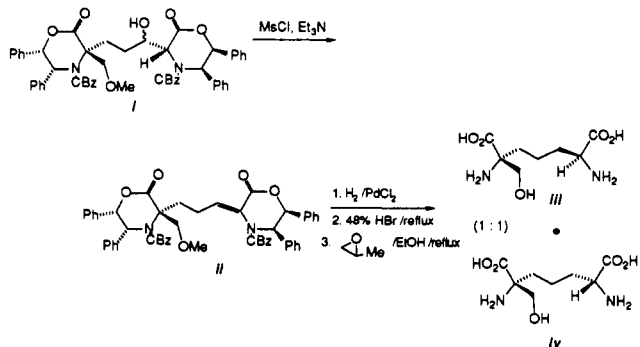
We have examined the biological activity of both amino acids **4** and **17** against nine microorganisms (*Bacillus subtilis*, *Staphylococcus aureus*, *Micrococcus luteus*, *Candida albicans*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Saccharomyces cerevisiae*, and *Serratia marcescens*) and find that neither compound displays significant antimicrobial activity up to 1 mg/mL.

In summary, we have developed an asymmetric and stereochemically defined construction of an α -functionalized diamino-pimelic acid system and have assigned, through total synthesis, the stereochemistry at the quaternary center of the natural product **3**. The availability¹⁴ of both optical antipodes of the oxazinone systems renders this chemistry adaptable to preparing all possible diastereoisomers of substances based on the DAP skeleton in optically pure form. Efforts to extend this methodology to construct other functionalized DAP systems, particularly those with potential antimicrobial activity, are being pursued in these laboratories and will be reported on in due course.

Experimental Section

General Information. ¹H NMR spectra were obtained on the following instruments: Bruker WP-200SY 200-MHz spectrometer, Bruker WP-270S 270-MHz spectrometer, or Bruker AC 300-MHz spectrometer. ¹⁹F NMR spectra were recorded on the Bruker WP-200 SY 200 MHz spectrometer. Chemical shifts are reported in parts per million downfield from the internal standard. Infrared spectra were recorded on

(15) The reaction of **i** with mesyl chloride in the presence of triethylamine and subsequent treatment with excess triethylamine furnished the alkene **ii**. Unfortunately, sequential hydrogenation, hydrolytic deprotection of the methyl ether, and scavenging of acid with propylene oxide produced the amino acids **iii** and **iv** as a 1:1 mixture of diastereomers.



(16) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* 1975, 1574. (b) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. I* 1977, 1718.

(17) (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* 1981, 103, 932. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. 1983, 105, 4059.

(18) Natural **3** was hydrolyzed and separated according to the procedure detailed in reference 8 to provide an authentic comparison sample of **4**.

Perkin-Elmer 1600 Series FTIR and are reported as $\lambda_{\max}$ in cm^{-1} . Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter at wavelength 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1 mL. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at the specified temperature and the concentration (*c*) given in grams per 100 mL in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are accurate to within the calculated values by $\pm 0.4\%$. High-resolution mass spectra were carried out by Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska—Lincoln, Lincoln, NE. Thin-layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel glass plates. Visualization on TLC was achieved with ultraviolet light, an I_2 developing chamber, and/or heating of TLC plates submerged in a 5% solution of phosphomolybdic acid in 95% ethanol. Preparative chromatography was performed by the following methods. Column chromatography was performed with Merck silica gel grade 60, 230–400 mesh, 60 Å. Radial chromatography was done on 1-, 2-, and 4-mm silica gel plates using E. Merck silica gel 60 PF-254 containing gypsum on a Harrison Research Chromatotron Model 7924. Reagents and solvents were commercial grades and were used as supplied with the following exceptions. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dry methylene chloride and carbon tetrachloride were obtained by distillation over CaH_2 . DMF and HMPA were dried over activated 4-Å molecular sieves. All moisture-sensitive reactions were carried out in glassware that was flame-dried under high vacuum (0.5–2.0 mmHg) and then purged with N_2 . The term “concentrated” refers to solvent removal using a Buchi Rotavapor. The amino acids furnished crude from the hydrogenation were always obtained in greater than the theoretical amount due to a certain fraction of HCl salt resulting from the PdCl_2 catalyst. To ascertain the exact amount of amino acid by weight in the residue, the mixture was dissolved in D_2O with a known amount of leucine (purity titrated against ultrapure acetamide), and ^1H NMR integration of a well-resolved resonance of the amino acid against the nine-proton singlet of leucine was carried out, averaged, and calculated to give the adjusted chemical yields.

(3S,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3'-butenyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (6). To a stirred solution of **5** (3 g, 7.744 mmol, 1 equiv) and 4-iodobutene (4.2 mL, 39.35 mmol, 5.1 equiv) in warm THF (90 mL) and HMPA (9 mL) was added lithium bis(trimethylsilyl)amide (13.9 mL, 13.9 mmol, 1.8 equiv, 1 M solution in THF) dropwise via syringe at -78°C . After 10 min the dry ice bath was removed. After an additional 1 h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 1.59 g (46.5%) of **6** as a white solid. The antipode was obtained from **9** in 48.5% yield. Data for **6**: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 2.18–2.31 (4 H, m), 4.81–5.16 (5 H, m), 5.27 (1 H, d, $J = 2.93$ Hz), 5.77–5.95 (1 H, m), 6.22 (1 H, d, $J = 3.02$ Hz), 6.54–6.59 (2 H, m), 7.02–7.24 (13 H, m); IR (NaCl, CH_2Cl_2) 1747, 1704 cm^{-1} ; mp 146–147 $^\circ\text{C}$; $[\alpha]_D^{25} +44.1^\circ$ (*c* 0.49, CH_2Cl_2), antipode (from **9**) -45.2° (*c* 0.42, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2 /hexanes) Calcd for $\text{C}_{28}\text{H}_{27}\text{NO}_4$: C, 76.17; H, 6.17; N, 3.17. Found: C, 76.07; H, 6.36; N, 3.20.

(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3'-butenyl)-3-(methoxymethyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (7). To a stirred solution of **6** (1.1 g, 2.49 mmol, 1 equiv) in THF (15 mL) was added potassium bis(trimethylsilyl)amide (8.9 mL, 12.46 mmol, 5 equiv, 1.4 M solution in THF) dropwise via syringe at -78°C . After 5 min bromomethyl methyl ether (2 mL, 24.9 mmol, 10 equiv) was added to the reaction mixture at -78°C . After an additional 50 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 1.17 g (96.7%) of **7** as a colorless oil. The antipode was obtained in 88.5% yield. Data for **7**: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.29–1.43 (1 H, m), 1.51–1.70 (1 H, m), 2.09–2.38 (2 H, m), 3.32 (3 H, s), 3.64 (1 H, $1/2$ AB q, $J = 9.76$ Hz), 4.37 (1 H, $1/2$ AB q, $J = 9.79$ Hz), 4.65–4.79 (2 H, m), 5.15 (1 H, $1/2$ AB q, $J = 12.31$ Hz), 5.24 (1 H, $1/2$ AB q, $J = 12.07$ Hz), 5.41–5.64 (1 H, m), 5.72 (1 H, d, $J = 3.32$ Hz), 6.35 (1 H, d, $J = 3.28$ Hz), 7.07–7.31 (15 H, m); IR (NaCl, CH_2Cl_2) 1746, 1702 cm^{-1} ; $[\alpha]_D^{25} -49.4^\circ$ (*c* 0.35, CH_2Cl_2), antipode $+48.7^\circ$ (*c* 0.39, CH_2Cl_2); exact mass (FAB) calcd for $\text{C}_{30}\text{H}_{31}\text{N}_2\text{O}_5$ 492.236228, found 492.2381.

(3R,5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(2'-carbonyl-ethyl)-3-(methoxymethyl)-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (8). Ozone was bubbled through a solution of **7** (316 mg, 0.651 mmol, 1 equiv) in $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (10 mL, 1:1) until the solution turned blue (ca.

5 min). Nitrogen gas was then passed through the reaction mixture to remove excess ozone until the solution became colorless. The resulting solution was quenched with excess dimethyl sulfide. After 15 h the reaction mixture was concentrated and separated by radial chromatography on silica gel to afford 319 mg (96%) of **8** as a colorless oil. The antipode **19** was obtained in 94% yield. Data for **8**: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.69–1.84 (1 H, m), 1.95–2.10 (1 H, m), 2.28–2.60 (2 H, m), 3.32 (3 H, s), 3.68 (1 H, $1/2$ AB q, $J = 9.79$ Hz), 4.38 (1 H, $1/2$ AB q, $J = 9.81$ Hz), 5.14 (1 H, $1/2$ AB q, $J = 12.35$ Hz), 5.24 (1 H, $1/2$ AB q, $J = 12.35$ Hz), 5.72 (1 H, d, $J = 3.40$ Hz), 6.35 (1 H, d, $J = 3.44$ Hz), 7.14–7.32 (15 H, m), 9.32 (1 H, s); IR (NaCl, CH_2Cl_2) 1745, 1722 (shoulder), 1701 cm^{-1} ; $[\alpha]_D^{25} -79.9^\circ$ (*c* 1.2, CH_2Cl_2), antipode **19** $+80.4^\circ$ (*c* 0.7, CH_2Cl_2); exact mass (FAB) calcd for $\text{C}_{29}\text{H}_{30}\text{NO}_6$ 488.207314 ($\text{M}^+ + \text{H}$), found 488.2070.

Aldol Adducts 11 and 12. To a stirred solution of **9** (445 mg, 1.15 mmol, 1 equiv) in CH_2Cl_2 (8 mL) was added dibutylboron triflate (2.3 mL, 2.30 mmol, 2 equiv, 1 M solution in CH_2Cl_2) followed by the addition of triethylamine (320 mL, 2.30 mmol, 2 equiv) at 0°C . After 20 min the reaction mixture was cooled to -78°C and a CH_2Cl_2 (11 mL) solution of aldehyde **8** (1.12 g, 2.297 mmol, 2 equiv) was added to it. After 30 min the reaction mixture was quenched with phosphate buffer solution (0.025 M, pH 6.9) and poured into water. The aqueous layer was extracted three times with CH_2Cl_2 . The combined organic solution was dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 613 mg (61%) of **11** as a white solid and 41 mg (4%) of **12** as a white solid.

11: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.32–1.55 (2 H, m), 2.36–2.47 (2 H, m), 3.34 (3 H, s), 3.65 (1 H, $1/2$ AB q, $J = 9.86$ Hz), 3.89–3.99 (1 H, m), 4.38 (1 H, $1/2$ AB q, $J = 9.74$ Hz), 4.52 (1 H, d, $J = 1.89$ Hz), 4.89 (1 H, $1/2$ AB q, $J = 12.66$ Hz), 4.98 (1 H, $1/2$ AB q, $J = 12.52$ Hz), 5.11 (1 H, $1/2$ AB q, $J = 12.47$ Hz), 5.18 (1 H, d, $J = 3.21$ Hz), 5.23 (1 H, $1/2$ AB q, $J = 12.39$ Hz), 5.56 (1 H, d, $J = 3.50$ Hz), 5.23 Hz), 5.63 (1 H, d, $J = 3.59$ Hz), 6.36 (1 H, d, $J = 3.50$ Hz), 6.44 (1 H, d, $J = 3.14$ Hz), 6.52 (2 H, d, $J = 6.76$ Hz), 6.93–7.34 (28 H, m); IR (NaCl, CH_2Cl_2) 3474, 1749, 1704 cm^{-1} ; mp 123–125 $^\circ\text{C}$; $[\alpha]_D^{25} -7.9^\circ$ (*c* 0.92, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2 /hexanes) Calcd for $\text{C}_{53}\text{H}_{50}\text{N}_2\text{O}_{10}$: C, 72.76; H, 5.76; N, 3.20. Found: C, 72.94; H, 6.02; N, 3.02.

12: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.41–1.59 (2 H, m), 1.96–2.11 (1 H, m), 2.39–2.55 (1 H, m), 3.35 (3 H, s), 3.54 (1 H, $1/2$ AB q, $J = 9.78$ Hz), 3.63–3.71 (1 H, m), 3.91 (1 H, d, $J = 4.79$ Hz), 4.33 (1 H, $1/2$ AB q, $J = 9.82$ Hz), 4.58 (1 H, d, $J = 1.96$ Hz), 5.11 (1 H, $1/2$ AB q, $J = 12.31$ Hz), 5.13 (1 H, $1/2$ AB q, $J = 12.43$ Hz), 5.20 (1 H, $1/2$ AB q, $J = 12.39$ Hz), 5.22 (1 H, $1/2$ AB q, $J = 12.33$ Hz), 5.61 (2 H, d, $J = 3.23$ Hz), 6.08 (1 H, d, $J = 3.29$ Hz), 6.31 (1 H, d, $J = 3.31$ Hz), 7.07–7.39 (30 H, m); IR (NaCl, CH_2Cl_2) 3483, 1746, 1702 cm^{-1} ; mp 101–103 $^\circ\text{C}$; $[\alpha]_D^{25} +11.1^\circ$ (*c* 0.56, CH_2Cl_2); exact mass calcd for $\text{C}_{53}\text{H}_{51}\text{N}_2\text{O}_{10}$ ($\text{M}^+ + \text{H}$) 875.35453, found 875.3521.

Phenyl Thionoformate 13. To a solution of **11** (237 mg, 0.271 mmol, 1 equiv) in THF (4 mL) was added phenyl chlorothionoformate (187 mL, 1.352 mmol, 5 equiv) followed by addition of sodium bis(trimethylsilyl)amide (298 mL, 0.298 mmol, 1.1 equiv, 1 M solution in THF) at -78°C . After 10 min the dry ice bath was removed. After further reaction for 3 h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 170 mg (62%) of **13** as a labile white solid. This compound was used directly after purification for the subsequent tin hydride reaction. Data for **13**: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.50–1.76 (2 H, m), 2.22–2.65 (2 H, m), 3.35 (3 H, s), 3.66 (1 H, $1/2$ AB q, $J = 9.56$ Hz), 4.38 (1 H, $1/2$ AB q, $J = 9.83$ Hz), 4.94 (1 H, d, $J = 1.66$ Hz), 4.94 (1 H, $1/2$ AB q, $J = 12.46$ Hz), 5.03 (1 H, $1/2$ AB q, $J = 12.79$ Hz), 5.17 (1 H, $1/2$ AB q, $J = 12.31$ Hz), 5.30 (1 H, $1/2$ AB q, $J = 12.27$ Hz), 5.31 (1 H, d, $J = 3.15$ Hz), 5.75 (1 H, d, $J = 3.32$ Hz), 5.77–5.85 (1 H, m), 6.00 (1 H, d, $J = 3.21$ Hz), 6.37 (1 H, d, $J = 3.34$ Hz), 6.56 (2 H, d, $J = 6.84$ Hz), 6.97–7.46 (33 H, m); IR (NaCl, CH_2Cl_2) 1754, 1704 cm^{-1} .

Reduction Products 14 and 15. To a solution of **13** (170 mg, 0.168 mmol, 1 equiv) in toluene (5 mL) was added AIBN (5.5 mg, 0.033 mmol, 0.2 equiv) followed by addition of tributyltin hydride (90 μL , 0.335 mmol, 2 equiv). The resulting solution was brought to reflux. After 3 h the toluene was evaporated off and the residue was separated by column chromatography on silica gel to afford 71 mg (49%) of **14** as a white solid and 16 mg (11%) of **15** as a white solid.

14: ^1H NMR (220 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.01–1.18 (1 H, m), 1.22–1.38 (1 H, m), 1.79–2.03 (2 H, m), 2.11–2.25 (1 H, m), 2.35–2.48 (1 H, m), 3.33 (3 H, s), 3.64 (1 H, $1/2$ AB q, $J = 9.78$ Hz), 4.37 (1 H, $1/2$ AB q, $J = 9.78$ Hz), 4.55 (1 H, dd, $J = 9.69$ Hz, $J = 4.62$ Hz), 4.90 (1 H, $1/2$ AB q, $J = 12.71$ Hz), 4.99 (1 H, $1/2$ AB q, $J = 12.75$

Hz), 5.13 (1 H, $1/2$ AB q, $J = 12.33$ Hz), 5.19 (1 H, d, $J = 3.32$ Hz), 5.22 (1 H, $1/2$ AB q, $J = 12.25$ Hz), 5.66 (1 H, d, $J = 3.48$ Hz), 6.08 (1 H, d, $J = 3.03$ Hz), 6.35 (1 H, d, $J = 3.45$ Hz), 6.50–6.54 (2 H, m), 7.01–7.34 (28 H, m); IR (NaCl, CH_2Cl_2) 1748, 1704 cm^{-1} ; mp 99–101 $^\circ\text{C}$; $[\alpha]_D^{25} -16^\circ$ (c 0.5, CH_2Cl_2); exact mass (FAB) calcd for $\text{C}_{33}\text{H}_{50}\text{N}_2\text{O}_9\text{Li}$ 865.367 637, found 865.3675.

15: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 0.64–1.02 (3 H, m), 1.31–1.46 (1 H, m), 1.70–1.85 (1 H, m), 2.06–2.21 (1 H, m), 3.29 (3 H, s), 3.52 (1 H, $1/2$ AB q, $J = 9.77$ Hz), 4.24 (1 H, dd, $J = 9.66$ Hz, $J = 4.33$ Hz), 4.27 (1 H, $1/2$ AB q, $J = 9.83$ Hz), 5.02 (2 H, s), 5.07 (1 H, $1/2$ AB q, $J = 12.74$ Hz), 5.18 (1 H, $1/2$ AB q, $J = 12.34$ Hz), 5.62 (1 H, d, $J = 3.54$ Hz), 5.83 (1 H, d, $J = 2.76$ Hz), 5.88 (1 H, d, $J = 2.76$ Hz), 6.29 (1 H, d, $J = 3.48$ Hz), 7.03–7.43 (30 H, m); IR (NaCl, CH_2Cl_2) 1748, 1704 cm^{-1} ; mp 114–116 $^\circ\text{C}$; $[\alpha]_D^{25} -20.6^\circ$ (c 0.6, CH_2Cl_2); exact mass (FAB) calcd for $\text{C}_{33}\text{H}_{50}\text{N}_2\text{O}_9\text{Li}$ 865.367 637, found 865.3662.

(2S,6R)-2,6-Diamino-6-(hydroxymethyl)pimelic Acid (17). To a solution of **14** (66 mg, 0.077 mmol, 1 equiv) in THF and EtOH (3 mL, 1:1) was added palladium chloride (41 mg, 0.231 mmol, 3 equiv). The reaction mixture was hydrogenated at 50 psi for 48 h. The mixture was then purged with nitrogen and filtered through Celite to remove the catalyst. The filtrate was concentrated and dried in vacuo. The crude product **16** was dissolved in 48% HBr and refluxed for 3 h. The solvent was evaporated off and the residue was treated with excess propylene oxide for 20 min in refluxing EtOH. The white precipitate was filtered to give 16 mg (95%) of **17** as a white solid: ^1H NMR (300 MHz, D_2O , vs DSS) δ 1.26–1.45 (2 H, m), 1.65–1.90 (4 H, m), 3.66 (1 H, $1/2$ AB q, $J = 11.90$ Hz), 3.74 (1 H, m), 3.80 (1 H, $1/2$ AB q, $J = 11.80$ Hz); ^{13}C NMR (69.73 MHz, D_2O) δ (DSS) 21.3, 34.3, 56.8, 66.8, 68.7, 176.4, 176.6; IR (ZnS, H_2O) 3435, 3119, 1618 cm^{-1} ; mp 220–230 $^\circ\text{C}$ dec, $[\alpha]_D^{25} +22.5^\circ$ (c 0.6, 5 N HCl); exact mass calcd for $\text{C}_8\text{H}_{17}\text{N}_2\text{O}_5$ (M + H $^+$) 221.11375, found 221.1137.

Aldol Adducts 20 and 21. To a solution of **9** (407 mg, 1.05 mmol, 1 equiv) in CH_2Cl_2 (8 mL) was added dibutylboron triflate (2.1 mL, 2.1 mmol, 2 equiv, 1 M solution in CH_2Cl_2) followed by addition of triethylamine (293 μL , 2.1 mmol, 2 equiv) at 0 $^\circ\text{C}$. After 20 min the reaction mixture was cooled to -78 $^\circ\text{C}$ and a CH_2Cl_2 (10 mL) solution of **19** (1.024 g, 2.1 mmol, 2 equiv) was added to it. After 30 min the reaction mixture was quenched with a phosphate buffer solution (pH 6.9) and poured into water. The aqueous layer was extracted three times with CH_2Cl_2 . The combined organic solution was dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 465 mg (50.6%) of **20** as a white solid and 17 mg (2%) of **21** as a white solid.

20: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.34–1.69 (2 H, m), 2.19–2.64 (2 H, m), 3.34 (3 H, s), 3.64–3.71 (1 H, m), 3.91–4.02 (1 H, m), 4.40 (1 H, $1/2$ AB q, $J = 9.87$ Hz), 4.66 (1 H, s), 4.98 (2 H, s), 5.11 (1 H, $1/2$ AB q, $J = 12.38$ Hz), 5.13 (1 H, d, $J = 3.16$ Hz), 5.22 (1 H, $1/2$ AB q, $J = 12.58$ Hz), 5.40 (1 H, d, D_2O exch, $J = 5.22$ Hz), 5.64 (1 H, d, $J = 3.64$ Hz), 6.34 (1 H, d, $J = 3.43$ Hz), 6.42 (1 H, d, $J = 3.04$ Hz), 6.55–6.58 (2 H, m), 6.91–7.37 (28 H, m); IR (NaCl, CH_2Cl_2) 3477, 1749, 1704 cm^{-1} ; mp 92–94 $^\circ\text{C}$; $[\alpha]_D^{25} +3.6^\circ$ (c 0.94, CH_2Cl_2); exact mass calcd for $\text{C}_{33}\text{H}_{51}\text{N}_2\text{O}_{10}$ (M $^+$ + H) 875.354 53, found 875.3508.

21: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.27–1.45 (1 H, m), 1.58–1.76 (1 H, m), 2.05–2.41 (2 H, m), 3.31 (3 H, s), 3.56 (1 H, $1/2$ AB q, $J = 9.70$ Hz), 3.52–3.63 (1 H, m), 3.99 (1 H, d, D_2O exch, $J = 6.70$ Hz), 4.33 (1 H, $1/2$ AB q, $J = 9.75$ Hz), 4.47 (1 H, d, $J = 2.39$ Hz), 5.06 (1 H, $1/2$ AB q, $J = 12.64$ Hz), 5.17 (2 H, s), 5.18 (1 H, $1/2$ AB q, $J = 12.22$ Hz), 5.57 (1 H, d, $J = 3.49$ Hz), 5.60 (1 H, d, $J = 3.60$ Hz), 6.02 (1 H, d, $J = 3.45$ Hz), 6.30 (1 H, d, $J = 3.47$ Hz), 7.02–7.33 (30 H, m); IR (NaCl, CH_2Cl_2) 3488, 1747, 1704 cm^{-1} ; mp 105–107 $^\circ\text{C}$; $[\alpha]_D^{25} +56.9^\circ$ (c 0.36, CH_2Cl_2).

Phenyl Thionoformate 22. To a solution of **20** (400 mg, 0.457 mmol, 1 equiv) in THF (4 mL) was added phenyl chlorothionoformate (316 μL , 2.284 mmol, 5 equiv) followed by addition of sodium bis(trimethylsilyl)amide (503 μL , 0.503 mmol, 1.1 equiv, 1 M solution in THF) at -78 $^\circ\text{C}$. After 3 h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous

magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel to afford 174 mg (38%) of **22** as a white solid and 135 mg (34%) of unreacted **22**: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.41–1.59 (1 H, m), 1.76–1.95 (1 H, m), 2.36–2.61 (2 H, m), 3.35 (3 H, s), 3.66 (1 H, $1/2$ AB q, $J = 9.77$ Hz), 4.39 (1 H, $1/2$ AB q, $J = 9.70$ Hz), 5.00 (2 H, s), 5.08 (1 H, $1/2$ AB q, $J = 12.32$ Hz), 5.09 (1 H, d, $J = 1.70$ Hz), 5.24 (1 H, $1/2$ AB q, $J = 12.44$ Hz), 5.31 (1 H, d, $J = 3.15$ Hz), 5.71 (1 H, d, $J = 3.54$ Hz), 5.73 (1 H, m), 6.01 (1 H, d, $J = 3.09$ Hz), 6.37 (1 H, d, $J = 3.40$ Hz), 6.60 (2 H, d, $J = 6.74$ Hz), 6.98–7.44 (33 H, m); IR (NaCl, CH_2Cl_2) 1748, 1705 cm^{-1} .

Reduction Products 23 and 24. To a solution of **22** (155 mg, 0.153 mmol, 1 equiv) in toluene (5 mL) was added AIBN (8 mg, 0.049 mmol, 0.3 equiv) followed by addition of triphenyltin hydride (269 mg, 0.766 mmol, 5 equiv). The resulting solution was brought to reflux. After 2.5 h the toluene was removed under reduced pressure and the residue was separated by column chromatography on silica gel to afford 107 mg (81%) of **23** as a white solid and 7 mg (5%) of **24** as a white solid.

23: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 1.09–1.32 (2 H, m), 1.88 (2 H, q, $J = 7.67$ Hz), 2.30 (2 H, t, $J = 8.07$ Hz), 2.91 (3 H, s), 3.65 (1 H, $1/2$ AB q, $J = 9.87$ Hz), 4.37 (1 H, $1/2$ AB q, $J = 9.78$ Hz), 4.58 (1 H, t, $J = 6.43$ Hz), 4.98 (2 H, s), 5.10 (1 H, $1/2$ AB q, $J = 12.31$ Hz), 5.19 (1 H, d, $J = 2.99$ Hz), 5.20 (1 H, $1/2$ AB q, $J = 12.42$ Hz), 5.63 (1 H, d, $J = 3.36$ Hz), 6.10 (1 H, d, $J = 3.02$ Hz), 6.35 (1 H, d, $J = 3.40$ Hz), 6.51–6.55 (2 H, m), 6.98–7.29 (28 H, m); IR (NaCl, CH_2Cl_2) 1750, 1705 cm^{-1} ; mp 98–100 $^\circ\text{C}$; $[\alpha]_D^{25} -8.8^\circ$ (c 0.5, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2 /hexanes) Calcd for $\text{C}_{33}\text{H}_{50}\text{N}_2\text{O}_9$: C, 74.11; H, 5.87; N, 3.26. Found: C, 74.18; H, 6.04; N, 3.08. Exact mass (FAB) calcd for $\text{C}_{33}\text{H}_{50}\text{N}_2\text{O}_9\text{Li}$ 865.367 637, found 865.3670.

24: ^1H NMR (200 MHz, $\text{DMSO}-d_6$, 393 K, vs TMS) δ 0.66–0.89 (2 H, m), 1.01–1.14 (1 H, m), 1.28–1.42 (1 H, m), 1.96 (2 H, t, $J = 8.28$ Hz), 3.30 (3 H, s), 3.53 (1 H, $1/2$ AB q, $J = 9.75$ Hz), 4.25 (1 H, t, $J = 4.61$ Hz), 4.27 (1 H, $1/2$ AB q, $J = 9.72$ Hz), 5.02 (1 H, $1/2$ AB q, $J = 12.87$ Hz), 5.08 (1 H, $1/2$ AB q, $J = 12.51$ Hz), 5.11 (1 H, $1/2$ AB q, $J = 12.86$ Hz), 5.19 (1 H, $1/2$ AB q, $J = 12.58$ Hz), 5.61 (1 H, d, $J = 3.56$ Hz), 5.84 (1 H, d, $J = 3.29$ Hz), 5.86 (1 H, d, $J = 3.32$ Hz), 6.29 (1 H, d, $J = 3.49$ Hz), 7.01–7.39 (30 H, m); IR (NaCl, CH_2Cl_2) 1749, 1705 cm^{-1} ; mp 88–90 $^\circ\text{C}$; $[\alpha]_D^{25} +12.9^\circ$ (c 0.22, CH_2Cl_2).

(2S,6S)-2,6-Diamino-6-(hydroxymethyl)pimelic Acid (4). To a solution of **23** (73 mg, 0.085 mmol, 1 equiv) in THF and EtOH (3 mL, 1:1) was added palladium chloride (90 mg, 0.508 mmol, 6 equiv). The reaction mixture was hydrogenated at 50 psi for 48 h. The mixture was then purged with nitrogen and filtered through Celite to remove the catalyst. The filtrate was concentrated and dried in vacuo. The crude product was dissolved in 48% HBr and refluxed for 3 h. The solvent was evaporated off and the residue was treated with excess propylene oxide for 20 min in refluxing EtOH. The white precipitate was filtered to give 17 mg (91%) of **4** as a white solid. This material proved to be indistinguishable by ^1H NMR and TLC from the authentic amino acid obtained by hydrolysis of natural **3** provided by Shionogi & Co. Data for **4**: ^1H NMR (300 MHz, D_2O , vs DSS) δ 1.29–1.39 (1 H, m), 1.43–1.57 (1 H, m), 1.62–1.90 (4 H, m), 3.64 (1 H, $1/2$ AB q, $J = 11.69$ Hz), 3.65 (1 H, m), 3.89 (1 H, $1/2$ AB q, $J = 11.83$ Hz); ^{13}C NMR (67.93 MHz, D_2O) δ DSS 21.7, 33.2, 34.6, 57.4, 66.7, 68.6, 176.4, 176.9; IR (ZnS, H_2O) 3395, 3109, 1614 cm^{-1} ; mp 235–245 $^\circ\text{C}$ dec, lit.⁸ mp 240–250 $^\circ\text{C}$ dec; $[\alpha]_D^{25} +7.1^\circ$ (c 0.55, 5 N HCl), lit.⁸ $+8.1 \pm 1.0^\circ$ (c 0.506, 5 N HCl).

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