Notes

A Practical Enantioselective Synthesis of α-Amino Dicarboxylates. Preparation of D- and L-α-Aminoadipate, α-Aminopimelate, and α-Aminosuberate

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Introduction

The longer homologues of the natural proteinogenic α-amino dicarboxylates, aspartic and glutamic acids, have received attention from chemists studying neuroscience, biosynthesis, organic synthesis, and peptide chemistry. For example, α-aminoadipic acid has been shown to exhibit selective antagonistic activity at the *N*-methyl-D-aspartate subtype of glutamate receptors.[1] It is also found in the tripeptide δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine, which serves as a biosynthetic precursor of penicillins and cephalosporins.[2] Dieckmann cyclization of α-aminoadipate has recently led to the synthesis of carbocyclic nucleoside precursors.[3] Synthesis of α-aminopimelic acid derivatives has attracted considerable interest because of the biological importance of 2,6-diaminopimelate, which is a cross-linking unit of bacterial cell wall peptidoglycan as well as a biosynthetic precursor of lysine.[4,5] The replacement of cystine by α-aminosuberic acid in macrocyclic peptides converts a reducible disulfide linkage into an ethylene chain, which may account for the enhanced metabolic stability and bioactivity of the desamino dicarba-analogues of somatostatin,[6] oxytocin,[7a] vasopressin,[7b] and calcitonin.[8]

Our laboratory recently reported a method to prepare 5-alkylprolines from glutamic acid via acylation of its γ-ester enolate and subsequent reductive amination.[9] Because extension of this methodology to α-amino dicarboxylates with longer carbon chain lengths could lead tothe synthesis of 6-alkylpipecolinic acids as well as larger alkyl-substituted heterocyclic amino acids, we sought to develop a general process in order to prepare a series of optically active α-amino dicarboxylates.

Previously published procedures to prepare α-amino dicarboxylic acids were insufficiently general to provide all three optically active amino acids of chain lengths from six to eight carbons.[3-5,10] A recent review of the preparations of L-(*S*)-α-aminoadipic acid illustrates that the state of the art uses the elaboration of proteinogenic amino acids, enzymatic methods, and diastereoselective synthesis in order to provide optically active α-amino dicarboxylate targets.[3] Prior to our work, enantioselective hydrogenation had not been used to prepare optically active α-amino dicarboxylic acids. A hydrogenation route offers potential for preparation of both L- and D-amino acid enantiomers in high optical purity from inexpensive prochiral substrates. Deuterium- and tritium-labeled amino acids for biosynthetic studies might also be prepared. Interest in the effects of double bond geometry and remote polar functionality on the BINAP–ruthenium(II)-catalyzed reduction of enamide substrates[11-14] prompted us to examine the hydrogenation of dehydro-α-amido diesters **4** with this Ru(II) catalyst in lieu of the more commonly used rhodium phosphine complexes.[15] Although hydrogenation of enamides in the presence of BINAP–ruthenium complexes proceeds normally with excellent enantioselectivity, only the α-amino acids alanine and phenylalanine were previously prepared using this catalyst.[13]

Our study demonstrates that enantioselectivity is augmented on increasing the temperature of the hydrogenation reaction. The importance of the double bond

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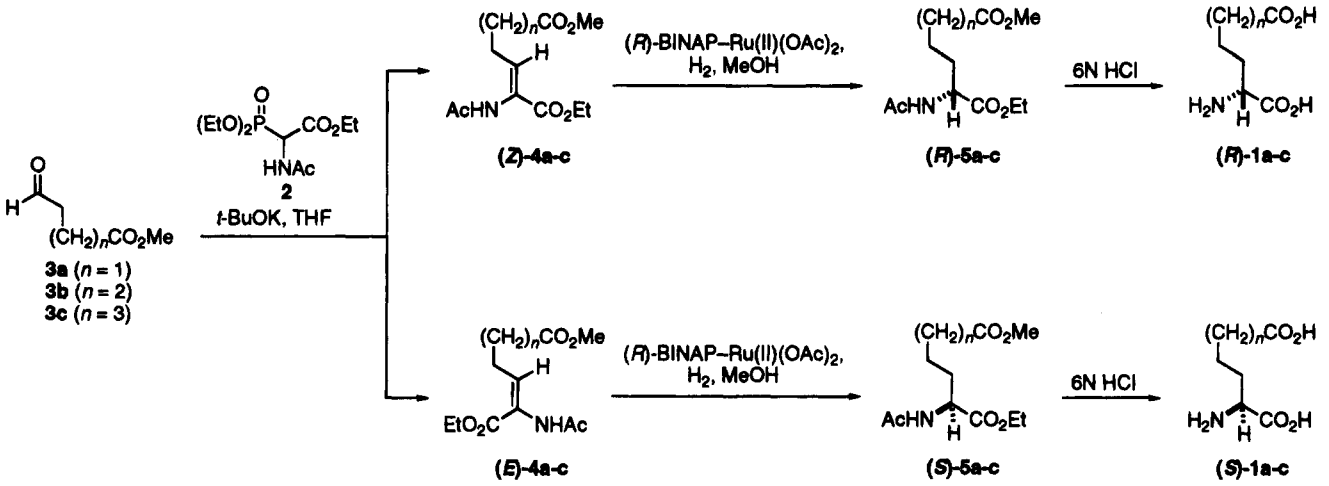
Scheme 1. Syntheses of (*R*)- and (*S*)-α-Aminoadipic Acid (1a), α-Aminopimelic Acid (1b) and α-Aminosuberic Acid (1c)



geometry in ruthenium-catalyzed hydrogenations of enamides has also been revealed. Using only one enantiomer of the chiral phosphine ligand we prepared both the L- and D-amino acids of high enantiomeric purity by hydrogenation of either (*E*)- or (*Z*)-enamide substrate. The syntheses of the L- and D-enantiomers of α-aminoadipate (**1a**), α-aminopimelate (**1b**), and α-aminosuberate (**1c**) have thus been accomplished by the economical convergent three-step process presented in Scheme 1.

Results and Discussion

Preparation of Substrates and Determination of Product Enantiomeric Purity. The required enamido diester substrates **4** were synthesized by a modified Wadsworth–Horner–Emmons olefination in which the potassium salt of *N*-acetyl-α-diethylphosphonylglycine ethyl ester (**2**) was reacted with an appropriate ω-formyl ester **3**.[16] Phosphonylglycinate **2** was prepared by modification of the literature method involving radical bromination of ethyl *N*-acetylglycinate and subsequent Arbuzov reaction with triethyl phosphite.[17] Methyl ω-formyl esters **3a** and **3b** were prepared in good yields by reduction of the corresponding acid chlorides with triethylsilane in the presence of palladium-on-carbon.[18,19] Methyl ω-formyl ester **3c** was prepared by ozonolysis of cyclohexene in methanol followed by dehydration of the α-alkoxy hydroperoxide intermediate with acetic anhydride and triethylamine according to the published procedure.[20]

Table 1. Preparation of Enamido Diesters 4 *E*:*Z* Ratio vs Bath Temperature during Aldehyde Addition

			chemical shifts (ppm)			
4	temp, °C	*Z* vs *E*	H-β	H-γ	H-β	H-γ
4a	−78	90:10	6.5	2.5		
	25	12:88			7.0	3.0
4b	−78	90:10	6.6	2.2		
	−40	83:17				
	25	12:88			7.2	3.6
4c	−78	92:8	6.6	2.4		
	25	14:86			7.1	3.4

Olefination was performed by treatment of a solution of potassium *tert*-butoxide in THF with **2** at −78 °C and subsequent addition of aldehyde **3**. Enamido diesters **4a–c** were obtained as mixtures of double bond isomers that were separable by fractional crystallization and by chromatography on silica gel. The temperature of the potassium salt solution of **2** during the addition of aldehyde **3** influenced the double bond configuration of the dehydro-2-amido diester products such that the (*E*)-**4**(*Z*)-**4** ratio was usually augmented from 1:9 at −78 °C up to 9:1 at 25 °C (Table 1).

The double bond configuration of the (*E*)- and (*Z*)-enamido diesters **4a–c** was assigned by examination of the vinylic and allylic proton chemical shift values and correlation with literature compounds.[21] The (*E*)-**4** isomer exhibited signals 0.5–1.4 ppm downfield relative to those of the (*Z*)-**4** isomer (Table 1). The assignments for dehydropimelate **4b** were confirmed by measuring the coupling constants between the vinyl proton and α-ester carbon which were J^3_{HC} = 4.7 Hz for (*Z*)-**4b** and J^3_{HC} = 12 Hz for (*E*)-**4b**.[22] Furthermore, a significant nuclear Overhauser effect was observed at the α-ester carbon signal on saturation of the vinyl proton signal of isomer (*Z*)-**4b**.[23]

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(17) *N*-Acetyl-α-(diethylphosphonyl)glycine ethyl ester (**2**, mp 83–85 °C, lit. mp 84–85 °C) was prepared from glycine by (a) *N*-acetylation according to Herbst, R. M.; Shemin, D. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 11. (b) Esterification according to: Hanby, W. E.; Waley, S. G.; Watson, J. *J. Chem. Soc.* **1950**, 3239. (c) Bromination according to: Easton, C. J.; Scharfbillig, I. M. *J. Org. Chem.* **1990**, *55*, 384. (d) Arbuzov reaction according to: Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599.

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Table 2. Hydrogenation of (Z)-4 and (E)-4 with $Ru(O_2CCH_3)_2$[(R)-BINAP][a]

				product 5		
entry	substrate	H_2 (atm)	T (°C)	% conversion	% ee	confign
1	(Z)-4a	6	100	100	82	R
2	(Z)-4a	16	100	100	85	R
3	(E)-4a	2	100	100	81	S
4	(E)-4a	1	100	100	83	S
5[b]	(Z)-4b	6	25	<5	–	–
6	(Z)-4b	6	35	46	–	–
7	(Z)-4b	6	50	100	96	R
8	(Z)-4b	6	100	100	98	R
9	(Z)-4b	2	50	100	87	R
10	(Z)-4b	2	100	100	90	R
11	(E)-4b	6	25	100	70	S
12	(E)-4b	6	50	100	75	S
13	(E)-4b	6	100	100	86	S
14	(E)-4b	2	50	100	84	S
15	(E)-4b	2	100	100	96	S
16	(Z)-4c	6	100	100	94	R
17	(E)-4c	2	100	100	90	S

[a] Reactions were performed in MeOH for 56 h with 0.4 M solution of the substrate in the presence of 0.5 mol % of $Ru(O_2CCH_3)_2$(BINAP). [b] Reaction time was 48 h.

2-*N*-Acetylamino diesters **5a–c** obtained from hydrogenation of enamides **4a–c** with palladium-on-carbon and with BINAP–Ru(II) diacetate complex were directly convertible to α-amino dicarboxylates **1a–c** on treatment with 6 N HCl and purification on an ion-exchange resin. At first the extent of asymmetric induction in the hydrogenation of enamido ester **4** was ascertained after conversion of **1** into its corresponding *N*-(phenylsulfonyl)-prolylamide dimethyl ester **6** via esterification of **1** with methanolic HCl and *N*-acylation with *N*-(phenylsulfonyl)-L-prolyl chloride.[4a] The α-methyl ester singlets of amides **6a–c** from racemic amino acids **1a–c** were clearly resolved and of equal intensity in the proton NMR spectrum. The amides **6b** from α-aminopimelate were separable by analytical HPLC[4a] and gave diasteromeric ratios identical to the NMR values. Direct determination of the enantiomeric purity of α-amino dicarboxylates **1a–c** was later performed using a chiral crown ether HPLC column.[24]

Hydrogenation. The hydrogenation was studied using 0.5 mol % of (*R*)-BINAP–Ru(II) diacetate complex in methanol.[25a] The reaction conditions were first optimized on 2-(*N*-acetylamino)-2,3-didehydropimelate diester **4b** ($n = 2$) and then employed on didehydroadipate **4a** ($n = 1$) and didehydrosuberate **4c** ($n = 3$, Scheme 1 and Table 2).[25b] (*Z*)-α-Ethyl ω-methyl 2-(*N*-acetylamino)-2,3-didehydropimelate ((*Z*)-**4b**) did not react at 25 °C under 6 atm of hydrogen; however, warming the mixture to 50 °C resulted in quantitative conversion of (*Z*)-**4b** to 2-(*N*-acetylamino)pimelate **5b** after 56 h. The enantiomeric purity of (*R*)-amidopimelate **5b** obtained at 50 °C was 96% ee and could be increased to 98% ee on raising the reaction temperature to 100 °C. Decreasing the hydrogen pressure to 2 atm provided (*R*)-α-amidopimelate (*R*)-**5b** of lower enantiomeric purity. (*Z*)-Didehydroadipate (*Z*)-**4a** and (*Z*)-didehydrosuberate (*Z*)-**4c** reacted similarly at 100 °C under 6 atm of H_2 for 56 h to yield quantitatively the desired (*R*)-α-amidoadipate (*R*)-**5a** and (*R*)-α-amidosuberate (*R*)-**5c** of 82% ee and 94% ee, respectively.

(*E*)-α-Ethyl ω-methyl 2-(*N*-acetylamino)-2,3-didehydropimelate ((*E*)-**4b**) reacted at lower temperature in the presence of (*R*)-BINAP–Ru(II) diacetate complex under 6 atm of hydrogen and was completely converted to α-amidopimelate **5b** at 25 °C; however, elevated temperatures again provided pimelate **5b** of greater enantiomeric purity. In contrast to the (*Z*)-double bond isomer (*Z*)-**4b**, (*E*)-enamide (*E*)-**4b** was hydrogenated with improved enantioselectivity under 2 atm of H_2 (Table 2). (*E*)-Didehydroadipate (*E*)-**4a**, (*E*)-didehydropimelate (*E*)-**4b**, and (*E*)-didehydrosuberate (*E*)-**4c** all reacted quantitatively at 100 °C under 2 atm H_2 after 56 h to furnish, respectively, the desired (*S*)-α-acetamido dicarboxylates (*S*)-**5a–c** of 81% ee, 96% ee, and 90% ee.

Conclusions

We have found that increasing the reaction temperature augments reactivity and enantioselectivity in the BINAP–Ru(II)-catalyzed hydrogenation of α-*N*-acetylenamino diesters **4a–c**.[26] Enamido diesters (*Z*)- and (*E*)-**4a–c** hydrogenated, respectively, with (*R*)-BINAP–Ru catalyst to give (*R*)- and (*S*)-α-amido dicarboxylates **5a–c** as major products. Double bond isomerization of **4** was not observed during the hydrogenation reaction. Increased hydrogen pressure improved the enantioselectivity of the reduction with the (*Z*)-double bond isomer (*Z*)-**4** and diminished enantioselectivity with the (*E*)-isomer (*E*)-**4**. Similar effects of hydrogen pressure were previously observed in the BINAP–Ru(II)-catalyzed reductions of enamides[11–14] and α,β-unsaturated acids.[27] The direction of hydrogen delivery by the BINAP–Ru(II) complex to the (*E*)- and (*Z*)-double bond substrates **4a–c** is consistent with the reported examples of hydrogenation of (*Z*)-enamides,[13,14] (*E*)-2-alkylidene-γ-butyrolactones,[28] as well as (*E*)- and (*Z*)-α,β-unsaturated acids,[27] and allylic alcohols.[29] On the other hand, this face selectivity is opposite to that observed in the BINAP–Ru(II)-catalyzed hydrogenations of (*Z*)-2-alkylidene-γ-butyrolactones,[28] (*E*)-*N*-benzoyldidehydrophenylalanine,[13b,c] and (*E*)-β-acetamidoacrylic esters.[11]

These results comply with the generally accepted ruthenium and rhodium phosphine-catalyzed hydrogenation mechanisms in which the transition metal first complexes to the amide oxygen and then to the carbon–carbon double bond before hydrogen is transferred from the metal to the olefin.[30] In the case of enamides **4a–c**

(24) Amino acids **1a–c** were analyzed on a 150 × 4.0 mm Crownpak CR(+) column from Chiral Technologies Inc. using an eluant of 70% perchloric acid (16.3 g) diluted with distilled water to 1 L (pH 1) and the detector at 200 nm. The retention times were as follows: (*R*)-**1a**, 4.54 min; (*S*)-**1a**, 5.28 min (flow rate = 0.1 mL/min); (*R*)-**1b**, 3.88 min; (*S*)-**1b**, 4.75 min (flow rate = 0.4 mL/min); (*R*)-**1c**, 4.88 min; (*S*)-**1c**, 6.28 min (flow rate = 0.4 mL/min).

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(26) The influence of temperature on the enantioselectivity and reactivity of rhodium–phosphine-catalyzed hydrogenations of enamido esters has previously been reported in (a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (b) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728. (c) Sinou, D. *Tetrahedron Lett.* **1981**, *22*, 2987.

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the face selectivity of hydrogen delivery by BINAP–Ru(II) catalyst depends on the double bond configuration. A configuration dependence is in accordance with most BINAP–Ru(II)-catalyzed hydrogenations of enamides, α,β-unsaturated acids, allylic alcohols, and 2-alkylidene-γ-butyrolactones. The discrepancies seen between the configuration-dependent examples and the face selectivity observed in the addition of hydrogen to (*E*)-enamides possessing β-aryl and β-methoxycarbonyl groups may result from double bond isomerization prior to product formation. β-Aryl and β-methoxycarbonyl groups may reduce the barrier to double bond isomerization via mechanisms in which the transition metal functions as a Lewis acid and in which migratory insertion of the metal hydride into the double bond is followed by rotation and subsequent β-hydrogen elimination.[30] Isomerization of (*Z*)- to (*E*)-2-alkylidene-γ-butyrolactones has been observed and suggested to account for the preparation of the same enantiomeric product independent of the substrate's double bond configuration.[28] It should be noted that hydrogenations catalyzed by rhodium–phosphine complexes provide products with the same absolute configuration from both (*Z*)- and (*E*)-enamide substrates.[15a,30]

We have developed an efficient three-step enantioselective synthesis of D- and L-α-amino dicarboxylates in high purity. This process allows the preparation of α-aminoadipate, α-aminopimelate, and α-aminosuberate of 82–98% ee with good overall yields from glycine and simple hydrocarbons. Our synthesis offers an efficient and economical route to these interesting and useful unnatural amino acids.

Experimental Section

General. Unless otherwise noted all reactions were run under argon atmosphere and distilled solvents were transferred by syringe. Solutions were degassed under vacuum after freezing with liquid nitrogen. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately before use; CH_2Cl_2, CCl_4, and acetic anhydride were distilled from P_2O_5; 2-methoxyethyl ether (diglyme) was distilled from Na; methanol (MeOH) was distilled from Mg. [(*R*)-2,2′-Bis[diphenylphosphino)-1,1′-binaphthyl]ruthenium diacetate was prepared with commercial (*R*)-BINAP according to the literature procedure.[25] Final reaction mixture solutions were dried over Na_2SO_4. Chromatography was on 230–400 mesh silica gel; TLC on aluminum-backed silica plates. Melting points are uncorrected. Mass spectral data and HRMS (EI), were obtained by the Université de Montréal Mass Spec. facility. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. ^1H and ^{13}C NMR of α-amino dicarboxylates **1a–c** were recorded in D_2O (pH ≈ 5) with 1,4-dioxane (δ 3.6; 67) as internal reference. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$).

Methyl 4-Oxobutanoate (3a). A 25-mL round-bottom flask was charged with β-carbomethoxypropionyl chloride (18.3 g, 125 mmol),[31] 10 wt % Pd/C (400 mg), and 24 mL (150 mmol) of Et_3SiH. After some bubbling, the flask became hot and was cooled in a water bath. The reaction mixture was stirred at room temperature for 1 h. The solution was filtered on a pad of Celite and the filtrate was evaporated. The residue was dissolved in ether (125 mL) and extracted with saturated aqueous $NaHCO_3$ (5 × 30 mL). The combined aqueous layer was acidified with 1 M NaH_2PO_4 to pH ≈ 5–6. The aqueous layer was then extracted with Et_2O (3 × 125 mL) and the combined organic extractions were dried and evaporated to an oil that was stored in a dessicator for 24 h over P_2O_5. Aldehyde **3a** (10.2 g, 70%) was obtained as a colorless liquid: ^1H NMR δ 2.3 (m, 4 H), 3.4 (s, 3 H), 9.2 (s, 1 H); ^{13}C NMR δ 28.9, 29.6, 51.4, 173.6, 177.4; HRMS calcd for $C_5H_8O_3$ (M^+) 116.0473, found 116.1065.

Methyl 5-Oxopentanoate (3b) was prepared according to the procedure described for **3a** starting with γ-carbomethoxybutyryl chloride (41.2 g, 250 mmol, prepared from glutaric anhydride by the procedure in ref 31). Aldehyde **3b** (24.8 g, 72%) was obtained as a colorless liquid: ^1H NMR δ 2 (t, 2 H, *J* = 7.32 Hz), 2.4 (t, 4 H, *J* = 6.7 Hz), 3.7 (s, 3 H), 9.8 (s, 1 H); ^{13}C NMR δ 17.1, 19.6, 32.8, 51.5, 178.9, 180; HRMS calcd for $C_6H_{10}O_3$ (M^+) 130.0630, found 130.0576.

General Procedure for the Synthesis of (1*Z*)-α-Ethyl ω-Methyl 2-Acetamido-2,3-didehydro Dicarboxylates ((*Z*)-4a–c). A solution of *N*-acyl-α-(diethylphosphonyl)glycine ethyl ester (**2**, 1.4 g, 3 mmol)[17] in CH_2Cl_2 (4.4 mL) was added dropwise to a −78 °C solution of potassium *tert*-butoxide (0.34 g, 3 mmol) in CH_2Cl_2 (0.6 mL). The solution was stirred at −78 °C for 15 min and then a solution of aldehyde **3** (3 mmol) in CH_2Cl_2 (0.6 mL) was added. The cooling bath was removed and the mixture was allowed to warm to room temperature with stirring for 2 h. The reaction mixture was concentrated on a rotary evaporator, redissolved in 16.5 mL of ethyl acetate, and extracted with water (3 × 3 mL) and 1 M NaH_2PO_4 (2 × 2 mL), dried, concentrated to a residue that was left to sit overnight. Unreacted **2** which crystallized from the residue was removed by filtration and washed with cold hexanes. The filtrate and washings were combined and evaporated to a residue that was crystallized from hexane to give (*Z*)-enamido diesters (*Z*)-**4a–c**.

(1*Z*)-α-Ethyl ω-Methyl 2-Acetamido-2,3-didehydroadipate ((*Z*)-4a): 63%, mp 42–45 °C; R_f = 0.17 (60:40, EtOAc:hexane); ^1H NMR δ 1.3 (t, 3 H, *J* = 7.1 Hz), 2.1 (s, 3 H), 2.4 (q, 2 H, *J* = 7.1 Hz), 2.5 (t, 2 H, *J* = 7.1 Hz), 3.7 (s, 3 H), 4.2 (q, 2 H, *J* = 7.1 Hz), 6.5 (t, 1 H, *J* = 7.5 Hz), 7.5 (br s, 1 H); ^{13}C NMR δ 13.9, 23.2, 23.7, 32.1, 51.6, 61.4, 127, 134, 164.2, 168, 173.1; IR ($CHCl_3$) 3692, 3155, 2985, 2901, 1794, 1737, 1643, 1602, 1561, 1216, 1167; HRMS calcd for $C_{11}H_{17}NO_5$ (M^+) 243.1107, found 243.1095. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.3; H, 7.0; N, 5.8. Found: C, 54.3; H, 7.4; N, 5.3.

(1*Z*)-α-Ethyl ω-Methyl 2-Acetamido-2,3-didehydropimelate ((*Z*)-4b): 64%, mp 35–38 °C; R_f = 0.15 (60:40, EtOAc:hexane); ^1H NMR δ 1.3 (t, 3 H, *J* = 7.1 Hz), 1.8 (q, 2 H, *J* = 7.4 Hz), 2.1 (s, 3 H), 2.20 (q, 2 H, *J* = 7.4 Hz), 2.3 (t, 2 H, *J* = 7.3 Hz), 3.7 (s, 3 H), 4.2 (q, 2 H, *J* = 7.1 Hz), 6.6 (t, 1 H, *J* = 8.1 Hz), 7.1 (s, 1 H); ^{13}C NMR δ 13.1, 24.3, 24.4, 28, 34, 51.1, 62, 126, 135.5, 164, 168, 173; IR ($CHCl_3$) 3692, 3598, 3521, 1735, 1714, 1602, 1560, 1175, 1137; HRMS calcd for $C_{12}H_{19}NO_5$ (M^+) 257.1263, found 257.1251.

(1*Z*)-α-Ethyl ω-Methyl 2-Acetamido-1-didehydrosuberate ((*Z*)-4c): 62%, mp 29 °C; R_f = 0.22 (60:40, EtOAc:hexane); ^1H NMR δ 1.4 (t, 3 H, *J* = 7 Hz), 1.8 (m, 2 H), 2.1 (s, 3 H), 2.2 (q, 2 H, *J* = 7 Hz), 2.3 (t, 2 H, *J* = 7.2 Hz), 3.7 (s, 3 H), 4.2 (q, 2 H, *J* = 7.1 Hz), 6.6 (t, 1 H, *J* = 7.1 Hz), 6.8 (s, 1 H); ^{13}C NMR δ 14, 24.5, 25, 28, 29, 34, 52, 62, 127, 138, 164, 168, 174; IR ($CHCl_3$) 3420, 3160, 2980, 1720, 1700, 1470, 1370, 1270; HRMS calcd for $C_{13}H_{21}NO_5$ (M^+) 271.1420, found 271.1463. Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.56; H, 7.80; N, 5.16. Found: C, 57.40; H, 7.79; N, 5.29.

General Procedure for the Synthesis of (1*E*)-α-Ethyl ω-Methyl 2-Acetamido-2,3-didehydro Dicarboxylates (*E*)-4a–c. A solution of *N*-acyl-α-diethylphosphonylglycine ethyl ester (**2**, 1.4 g, 3 mmol)[17] in CH_2Cl_2 (4.4 mL) was added dropwise to a −78 °C solution of potassium *tert*-butoxide (0.34 g, 3 mmol) in CH_2Cl_2 (0.6 mL). The solution was stirred for 10 min and allowed to reach room temperature. A solution of aldehyde **3** (3 mmol) in CH_2Cl_2 (0.6 mL) was then added. The mixture was stirred for 2 h, concentrated on a rotary evaporator, and redissolved in 16.5 mL of ethyl acetate. The organic phase was extracted with water (3 × 3 mL) and 1 M NaH_2PO_4 (2 × 2 mL), dried, concentrated to a residue that was left to sit overnight. Unreacted **2** which crystallized from the residue was filtered and washed with cold hexanes. The combined organic filtrate and washings were evaporated to a residue that was purified by chromatography with an eluant of 60:40 EtOAc:hexanes. Evaporation of the collected fractions then provided (*E*)-**4a–c** as oils.

(1*E*)-α-Ethyl ω-Methyl 2-Acetamido-2,3-didehydroadipate ((*E*)-4a): 65%, R_f = 0.28 (60:40, EtOAc:hexane); ^1H NMR δ 1.38 (t, 3 H, *J* = 7 Hz), 2.16 (s, 3 H), 2.50 (t, 2H, *J* = 7.1 Hz), 2.90 (q, 2 H, *J* = 7.1 Hz), 3.7 (s, 3 H), 4.30 (q, 2 H, *J* = 7.1 Hz), 7.1 (t, 1 H, *J* = 7.5 Hz), 7.4 (br s, 1 H); ^{13}C NMR δ 14.1, 23.6, 24.5,

(31) Cason, J. *Org. Synth.* **1945**, *25*, 19.

33.7, 51.8, 61.8, 126, 129, 164.4, 168, 173.5; IR ($CHCl_3$) 3030, 2930, 2856, 1764, 1736, 1632, 1462, 1397, 1360, 1231.

(1*E*)-α-Ethyl ω-Methyl 2-Acetamido-2,3-didehydropimelate ((*E*)-4b): 62%, R_f = 0.20 (60:40, EtOAc:hexane); ^1H NMR δ 1.35 (t, 3 H, *J* = 7.5 Hz), 1.8 (q, 2 H, *J* = 7.5 Hz), 2.1 (s, 3 H), 2.35 (t, 2 H, *J* = 7.5 Hz), 2.6 (q, 2 H, *J* = 7.5 Hz), 3.7 (s, 3 H), 4.3 (q, 2 H, *J* = 7.1 Hz), 7.1 (t, 1 H, *J* = 8.1 Hz), 7.4 (s, 1 H); ^{13}C NMR δ 13.7, 24.3, 24.4, 27.3, 33.1, 51.1, 61.4, 125.1, 130.4, 164, 168.2, 173.4; IR ($CHCl_3$) 3405, 3025, 1723, 1677, 1513, 1436, 1374, 1231.

(1*E*)-α-Ethyl ω-Methyl 2-Acetamido-2,3-didehydrosuberate ((*E*)-4c): 55%, R_f = 0.27 (60:40, EtOAc:hexane); ^1H NMR δ 1.3 (t, 3 H, *J* = 7.1 Hz), 1.5 (quintet, 2 H, *J* = 7 Hz), 1.7 (q, 2 H, *J* = 7 Hz), 2.13 (s, 3 H), 2.15 (t, 2 H, *J* = 7.3 Hz), 2.3 (q, 2 H, *J* = 7.3 Hz), 3.67 (s, 3 H), 4.2 (q, 2 H, *J* = 7.1 Hz), 7.1 (t, 1 H, *J* = 7.2 Hz), 7.5 (s, 1 H); ^{13}C NMR δ 14, 20, 24.2, 32.1, 33, 35.7, 51.7, 61.8, 129, 134, 164, 171, 174; IR ($CHCl_3$) 3413, 3008, 2952, 1724, 1692, 1492, 1372, 1272.

(2*RS*)-, (2*R*)-, and (2*S*)-α-Ethyl ω-Methyl 2-(*N*-Acetylamino) Dicarboxylates 5a–c. Racemic samples were prepared as follows. Enamido diester **4** (542 mg, 2 mmol) was dissolved in 15 mL of acetone, treated with 100 mg of 10 wt% Pd/C, and stirred under 4 atm of hydrogen for 24 h at room temperature. The solution was filtered on Celite and evaporated, and the residue was concentrated under vacuum to give **1** (540 mg, 99%) as a viscous yellow oil.

Optically active samples were prepared as follows. A degassed solution of enamido diester **4** (271 mg, 1.0 mmol) in 2.5 mL of MeOH was treated with $Ru(OCOCH_3)_2$[(*R*)-BINAP] (2 mg, 0.0025 mmol)[25] and the homogeneous mixture was degassed. The solution was transferred under a positive pressure of argon via cannula into a hydrogenation vessel that was filled, vented, and refilled with a hydrogen atmosphere five times. The solution was then stirred for the specified length of time at the temperature and H_2 pressure indicated in Table 2. Methanol was then evaporated and the residue was concentrated under vacuum to give an oil.

(2*R*)-α-Ethyl ω-Methyl 2-(*N*-(Acetylamino)adipate (5a): 99%, R_f = 0.2 (60:40, EtOAc: hexane); ^1H NMR δ 1.26 (t, 3 H, *J* = 7.1 Hz), 1.6–1.9 (m, 4 H), 2.0 (s, 3 H), 2.35 (t, 2 H, *J* = 7.1 Hz), 3.7 (s, 3 H), 4.2 (q, 2 H, *J* = 7.1 Hz), 4.6 (q, 1 H, *J* = 7.1 Hz), 6.3 (d, 1 H, *J* = 7.5 Hz); ^{13}C NMR δ 17.1, 27.6, 32.3, 32.7, 34, 51.46, 51.5, 60.3, 169.7, 173.2, 174.3; HRMS calcd for $C_{11}H_{20}NO_5$ (M + 1) 246.1341, found 246.1270.

(2*R*)-α-Ethyl ω-Methyl 2-(*N*-Acetylamino)pimelate (5b): 99%, R_f = 0.19 (60:40, EtOAc:hexane); ^1H NMR δ 1.1 (t, 3 H, *J* = 7.1 Hz), 1.2 (m, 2 H), 1.48 (m, 4 H), 1.9 (s, 3H), 2.1 (t, 2 H, *J* = 7.3 Hz), 3.5 (s, 3 H), 4 (q, 2 H, *J* = 7.1 Hz), 4.3 (q, 1 H, *J* = 7.1 Hz), 6.7 (d, 1 H); ^{13}C NMR δ 14, 23, 24.3, 24.6, 32.1, 33.5, 51.4, 52, 61.3, 169.7, 172.5, 173.7; HRMS calcd for $C_{12}H_{22}NO_5$ (M + 1) 260.1498, found 260.1480.

(2*R*)-α-Ethyl ω-Methyl 2-(*N*-Acetylamino)suberate (5c): 99%, R_f = 0.25 (60:40, EtOAc:hexane); ^1H NMR δ 1.3 (t, 3 H, *J* = 7.1 Hz), 1.3 (m, 4 H), 1.6 (m, 4 H), 2.0 (s, 3 H), 2.3 (t, 2 H, *J* = 7.3 Hz), 3.7 (s, 3 H), 4.2 (q, 2 H, *J* = 7.1 Hz), 4.6 (q, 1 H, *J* = 7.1 Hz), 6.4 (d, 1 H); ^{13}C NMR δ 14.1, 23.1, 24.5, 24.7, 28.6, 32.3, 33.8, 51.4, 52, 61.4, 169.7, 172.6, 173.9; HRMS calcd for $C_{13}H_{24}NO_5$ (M + 1) 274.1654, found 274.1670.

Deprotection Procedure to Provide α-Amino Dicarboxylates 1a–c. The α-ethyl ω-methyl 2-(*N*-acetylamino) dicarboxylate **5** (2 mmol) was dissolved in 2 mL of diglyme and treated with 10 mL of 6 N HCl. The mixture was heated at a reflux for 48 h, cooled to room temperature, and evaporated to give a brown residue. The residue was redissolved in water and purified on the Dowex 1-X8 (20–50 Mesh) resin (hydroxide form) with a gradient of 0–0.5 M acetic acid as eluant. Evaporation of the ninhydrin-positive fractions gave **1** as a white crystalline solid.

(2*R*)-D-α-Aminoadipic acid ((*R*)-1a): 84%, mp 198–202 °C, lit.[3] 200–202 °C; ^1H NMR (D_2O) δ 1.44 (m, 2 H), 2.0 (m, 2 H), 2.39 (t, 2 H, *J* = 7.2 Hz), 4.08 (t, 1 H, *J* = 7.2 Hz); ^{13}C NMR (D_2O) δ 21.3, 22.6, 30.3, 50.6, 171, 173; **(*R*)-1a** of 85% ee $[\alpha]^{23}_D$ −21.0° (*c*, 0.7, 6 N HCl), lit.[3] $[\alpha]^{25}_D$ −25° (*c*, 0.7, 6 N HCl). **(2*S*)-L-α-Aminoadipic acid ((*S*)-1a)**: 86%, mp 200–204 °C; **(*S*)-1a** of 83% ee $[\alpha]^{23}_D$ 21.5° (*c*, 1, 6 N HCl).

(2*R*)-D-α-Aminopimelic acid ((*R*)-1b): 83%, mp 215–220 °C, lit.[4a] 218–220 °C; ^1H NMR (D_2O) δ 1.35 (m, 2 H), 1.6 (quint, 2 H, *J* = 7.1 Hz), 2 (m, 2 H), 2.43 (t, 2 H, *J* = 7.4 Hz), 4.14 (t, 1 H, *J* = 6.5 Hz); ^{13}C NMR (D_2O) δ 24.2, 24.3, 30, 33.8, 53.5, 172.8, 179.1; **(*R*)-1b** of 98% ee $[\alpha]^{23}_D$ −20.0° (*c*, 1, 5 N HCl); lit.[4a] $[\alpha]^{20}_D$ −20.5° (*c*, 1, 5 N HCl). **(2*S*)-L-α-Aminopimelic acid ((*S*)-1b)**: 83%, mp 215–220 °C; **(*S*)-1b** of 96% ee $[\alpha]^{23}_D$ 20.5° (*c*, 1, 5 N HCl).

(2*R*)-D-α-Aminosuberic acid ((*R*)-1c): 82%, mp 230–234 °C; ^1H NMR (D_2O) δ 1.35 (m, 4 H), 1.6 (quint, 2 H, *J* = 7.2 Hz), 1.85 (m, 2 H), 2.38 (t, 2 H, *J* = 7.3 Hz), 4.07 (t, 1 H, *J* = 6.3 Hz); ^{13}C NMR (D_2O) δ 24.36, 24.4, 28.2, 30.1, 34.1, 53.5, 172.8, 179.5; **(*R*)-1c** of 94% ee $[\alpha]^{23}_D$ −20.0° (*c*, 1, 5 N HCl); HRMS calcd for $C_8H_{16}NO_4$ (M + 1) 190.1085, found 190.1079. **(2*S*)-L-α-Aminosuberic acid ((*S*)-1c)**: 85%, mp 230–235 °C, lit.[32] 233–234 °C; **(*S*)-1c** of 90% ee $[\alpha]^{23}_D$ 20.0° (*c*, 1, 5 N HCl); lit.[10c] $[\alpha]^{25}_D$ 20.2° (*c*, 0.1, 5 N HCl).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of **1** and **3–5**, ^1H NMR spectra of **6b**, and IR spectra of **4** (40 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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