Stereoselective Synthesis of *meso*-2,6-Diaminopimelic Acid and Its Selectively Protected Derivatives

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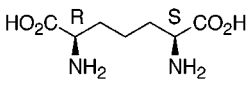
Four synthetic routes to selectively protected derivatives and isomers of *meso*-diaminopimelic acid (DAP) (**1a**), a key constituent of bacterial peptidoglycan, were investigated. *N*-(*tert*-butyloxycarbonyl)-D-allylglycine (**2**) and *N*-(benzyloxycarbonyl)-L-allylglycine (**4**) were esterified to ethylene glycol and cyclized via olefin metathesis to a protected derivative **7** of 2,7-diaminosuberic acid. Analogous linking of propane-1,3-diol with **2** and potential precursors of *N*-(benzyloxycarbonyl)-L-vinylglycine moieties, such as *N*-(benzyloxycarbonyl)-L-glutamate or *N*-(benzyloxycarbonyl)-L-methionine sulfoxide, gave **12** or **15**, both of which produced the α,*β*-unsaturated ester **14** upon attempted generation of the vinylglycine precursor for olefin metathesis to DAP derivatives. An alternative route, based on $SnCl_4$-catalyzed ene reaction of methyl *N*-(benzyloxycarbonyl)-L-allylglycinate (**18**) with glyoxylate esters of phenylcyclohexanol isomers as chiral auxiliaries, gave ca. 85:15 ratios of diastereomeric alcohols (**19** or **20**). These could be transformed to DAP derivatives in a series of steps employing azide displacement of corresponding mesylates to introduce the second nitrogen. A third method, involving reduction of pure dimethyl (*6S*)-2-keto-6-[*N*-(benzyloxycarbonyl)amino]pimelate (**32**) to the corresponding alcohol **33** with (*S*)-binaphthol−ruthenium catalyst as the key step, gives a 79:21 isomeric ratio. The fourth route employs the bis(oxazoline)−copper complex **41** as a chiral catalyst for the ene reaction of methyl (*S*)-4-(phenylthio)allylglycinate (**39**) and methyl glyoxylate to afford **42** in 94:6 isomeric ratio. Nickel boride removal of sulfur and the double bond in the presence of the Cbz group gives the desired alcohol, dimethyl (2*S*,6*S*)-6-[*N*-(benzyloxycarbonyl)amino]-2-hydroxyheptane-1,7-dioate (**33**). The required selectively protected second nitrogen is introduced using Mitsunobu inversion with *N*-*tert*-butyl [[2-(trimethylsilyl)-ethyl]sulfonyl]carbamate (**34**) as a key step.

The biosynthesis of the peptidoglycan cell wall layer in bacterial cells provides numerous potential targets for development of new antibiotics.[1,2] Among these is *meso*-diaminopimelic acid (DAP) (**1a**), the key cross-linking



meso-DAP (**1a**)

amino acid in this essential structural polymer in Gram-negative bacteria and a precursor to L-lysine, which is used for this purpose by many Gram-positive organisms.[3] Since mammals lack the DAP biosynthetic pathway, require L-lysine in their diet, and usually excrete DAP unchanged (except ruminants), there has been substantial interest in the specific inhibition of enzymes involved in its biosynthesis.[3,4] DAP also occurs in physiologically active peptidoglycan fragments that act as bacterial toxins, sleep-inducing factors, or antitumor agents.[5] Hence, considerable previous effort has focused on the synthesis of DAP isomers and their analogues,[6] as well as on the mechanism and genetic organization of DAP-related enzymes.[3,7] However, improved methods are still needed to provide facile access to stereochemically pure

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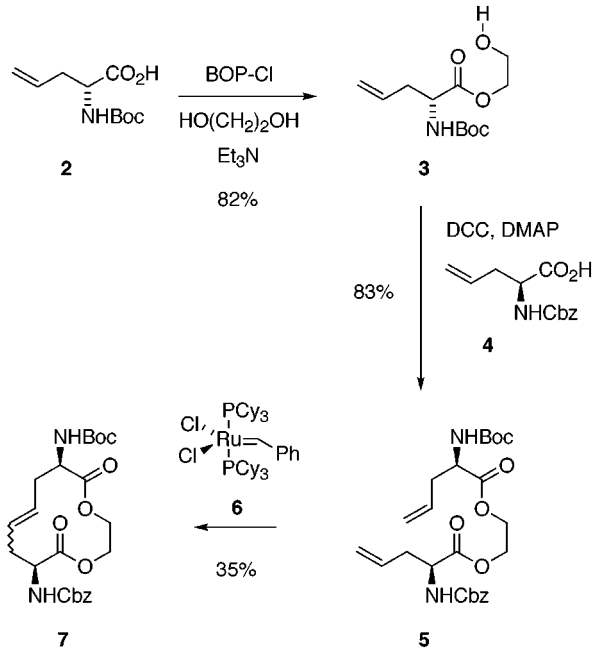
DAP derivatives with different protecting groups on the two amino and/or carboxyl functions. Ideally, complete orthogonal protection would permit individual manipulation of each of these four functionalities for synthesis of enzyme inhibitors or peptidoglycan-derived peptides. In the present work, we examine several approaches to selectively protected *meso*-DAP using optically pure L-allylglycine as a starting material. One route, potentially applicable to a variety of unusual molecules with amino acid moieties at either end, employs a ring-closing olefin metathesis reaction.[8] Several alternative methods reported herein are based on the ene reaction. In earlier studies, we[4a] and others[9,10] had employed nonstereoselective ene reactions to assemble the DAP skeleton. In addition to other approaches, we now describe the use of chiral auxiliaries and catalysts in such ene condensations.

Results and Discussion

Olefin Metathesis Approach to DAP and 2,7-Diaminosuberic Acid.[11] The successful application of olefin metathesis reactions to the synthesis of cyclic peptide derivatives by Grubbs and co-workers[8] suggested this methodology as a possible avenue to selectively protected DAP. Since 12-membered rings can often be formed quite readily, it appeared that linking two differentially N-protected amino acids bearing terminal olefins as esters of the appropriate chosen diol would permit metathesis cyclization with desired concomitant carbon−carbon bond formation. To test this, *N*-(*tert*-butyloxycarbonyl)-D-allylglycine (**2**) and *N*-(benzyloxycarbonyl)-L-allylglycine (**4**) were sequentially esterified onto ethylene glycol to form diester **5** (Scheme 1). Reaction with the Grubbs catalyst **6** produces the cyclic olefin **7**, a protected derivative of 2,7-diaminosuberic acid in modest (35%, not optimized) yield. Presumably, ester

Scheme 1



hydrolysis and hydrogenation under standard conditions[4a] would generate (2*S*,7*R*)-2-[*N*-(*tert*-butyloxycarbonyl)amino]-7-aminooctanedioic acid, although this was not done for this model system. LL-Diaminosuberic acid [(2*S*,7*S*)-2,7-diaminooctanedioic acid] has been extensively employed as a nonreducible isosteric replacement for cystine in biologically active peptides.[11,12]

This encouraging result suggested that similar cyclization of the propanediol diester of *N*-(benzyloxycarbonyl)-L-vinylglycine and *N*-(*tert*-butyloxycarbonyl)-D-allylglycine could produce a differentially protected DAP derivative. Although N-protected vinylglycine esters are quite sensitive to isomerization of the double bond from the β,γ- to the α,β-position, they can be made by lead tetraacetate decarboxylation of glutamate derivatives[13] or by elimination of methionine sulfoxides.[14] Both routes were investigated with a strategy of generating the vinylglycine moiety just before attempted metathesis cyclization (Scheme 2). Conversion of the known glutamate derivative **8**[15] to its (trimethylsilyl)ethyl ester **9** followed by reaction with 1,3-propanediol affords **10**, which is readily linked to *N*-(*tert*-butyloxycarbonyl)-D-allylglycine (**2**) to give **11**. Deprotection quantitatively generates the acid **12**. Unfortunately, attempts to generate the vinylglycine moiety via lead tetraacetate decarboxylation[13] of **12** produce only the conjugated compound **14** and none of the desired vinylglycine derivative **13**. An analogous approach provides the propanediol diester **15** of methionine sulfoxide and **2** (54% overall yield for three steps from *N*-(benzyloxycarbonyl)-L-methionine). However, attempted elimination under conditions known to normally give vinylglycine esters[14] again generates the undesired conjugated **14** rather than **13**. The reason for the unexpectedly rapid isomerization of presumed intermediate **13** is unknown but may involve deprotonation

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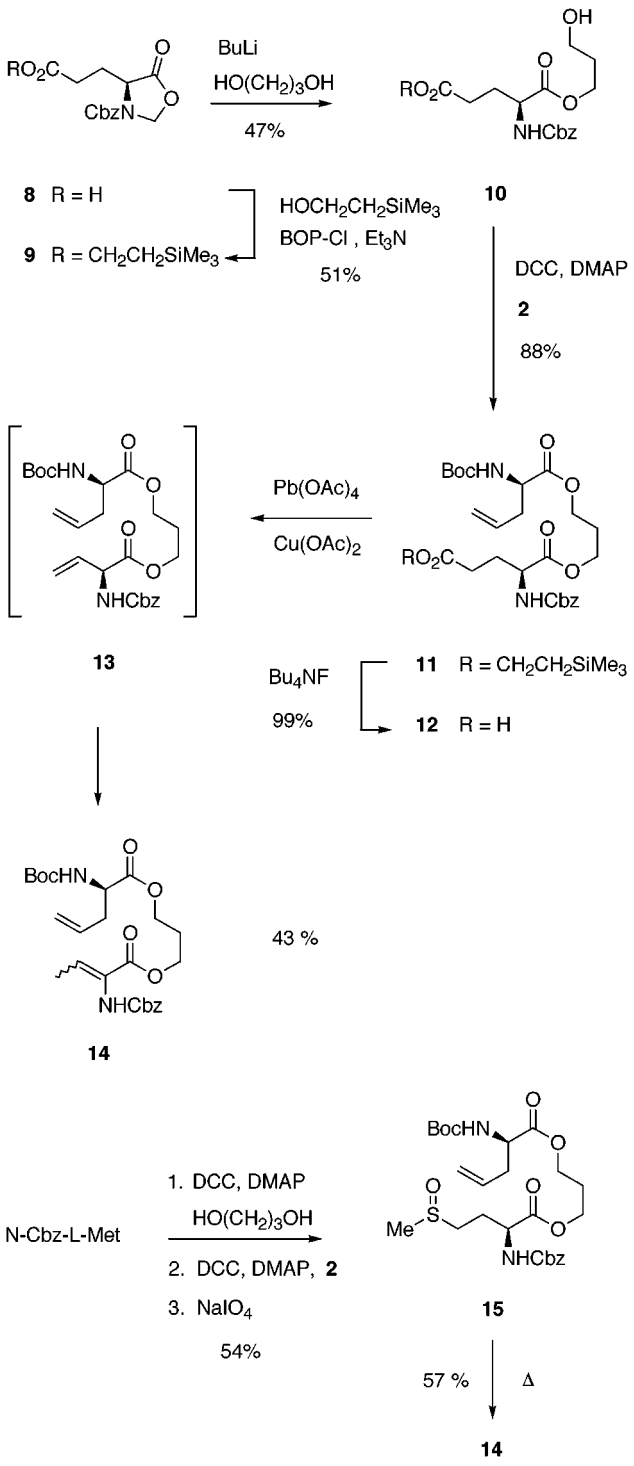
Scheme 2



at the α-carbon by a remote functional group in the allylglycine moiety. Nevertheless, the formation of **7** indicates that this approach could be a viable route to a number of compounds bearing orthogonally protected amino acid moieties at opposite ends of a central chain.[11]

Synthesis of DAP Derivatives Using Chiral Auxiliaries for Ene Reaction. The ene reaction of protected allylglycines with esters of glyoxylic acid provides rapid access to a variety of unusual amino acids and has been successful for production of DAP derivatives as isomeric mixtures[9a,b] as well as for generation of stereochemically pure derivatives of substituted α-aminopimelic acids.[4a,10b] An earlier investigation of ene condensation of achiral glyoxylate esters with optically pure dipeptides having an L-allylglycine moiety reported relatively low diastereomeric excess (25%) at the newly generated hydroxyl-bearing carbon.[10a] Since elegant work by Whitesell and co-workers had previously shown that pure isomers of 2-phenylcyclohexyl glyoxylate undergo ene reaction with high diastereoselection,[16] we investigated the use of such auxiliaries to form selectively protected DAP isomers. Thus, optimized condensation of the known esters **16** and **17**[16b] (as their aldehyde hydrates) with *N*-(benzyloxycarbonyl)-L-allylglycine methyl ester (**18**)[4a,e] using tin tetrachloride at −23 °C affords the corresponding functionalized alcohols **19** and **20**, respectively (Scheme 3). Initial NMR (^{1}H and ^{13}C) examination suggested isomeric ratios of 84:16 and 86:14, respectively, at the newly generated asymmetric center. However, because of extensive spectral overlap and the possibility that epimerization at the α-amino center could occur during the ene reaction, each isomer mixture was further transformed to DAP for additional stereochemical analysis to confirm this.

Hydrogenation in the presence of *tert*-butoxypyrocarbonate (Boc anhydride) affords saturated alcohols **21** and **22**, which upon mesylation, azide displacement, and a second hydrogenation generate the selectively protected DAP derivatives **27** and **28**, respectively. Basic hydrolysis removes both ester functionalities to give **29** and **30**. Deprotection of **29** with trifluoroacetic acid provides a 84:16 mixture of LL-DAP (**1b**) and *meso*-DAP (**1a**), whereas the same procedure with **30** gives a 86:14 mixture of **1a** and **1b**. The stereochemistry was confirmed by conversion of these DAP isomer mixtures to the corresponding bis-*N*-(*S*)-camphanamide dimethyl esters **31a** and **31b** (Scheme 4). ^{1}H NMR comparison (particularly the methyl ester region) with stereochemically pure samples **31a**−**c** made from pure LL-, *meso*- and DD-DAP isomers, obtained by literature separation−enzymatic resolution procedures,[17] verifies the initial stereochemical outcome of the ene reactions and indicates that no significant epimerization occurs in subsequent transformations. The absence of DD-DAP derivative **31c** from the camphanamides obtained via the ene condensation route confirms that no epimerization occurs at the amino center derived from L-allylglycine.

Although other auxiliaries could in principle provide better diastereoselection in the ene reaction, this approach was not investigated further. Primary reasons include the extra steps necessary for attachment and disconnection of the chiral auxiliary, the lack of selectivity during removal of groups from the carboxyl moieties of DAP, and the development of more expedient approaches involving chiral catalysis (see below).

Synthesis of DAP Derivatives Using Chiral Catalysts for Reduction or for Ene Reaction. We had previously prepared optically pure dimethyl (6*S*)-2-keto-6-[*N*-(benzyloxycarbonyl)amino]pimelate (**32**) by a short

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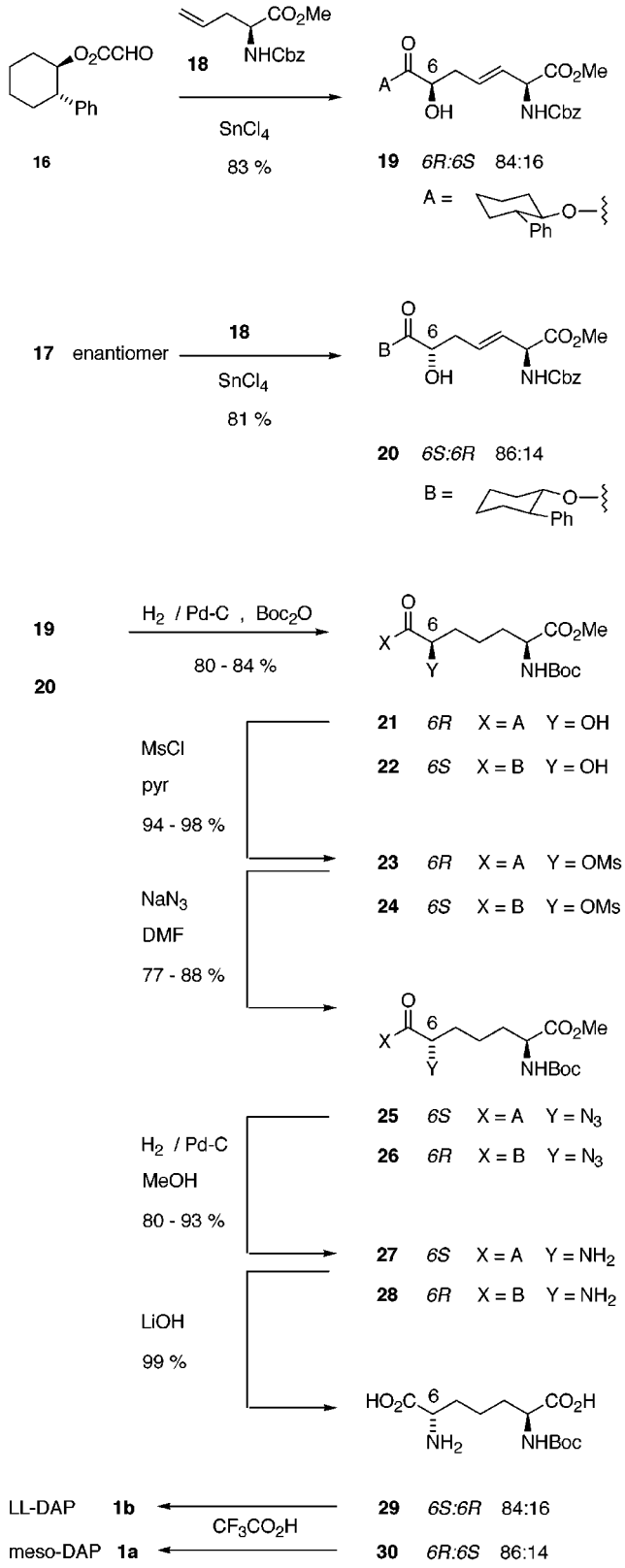
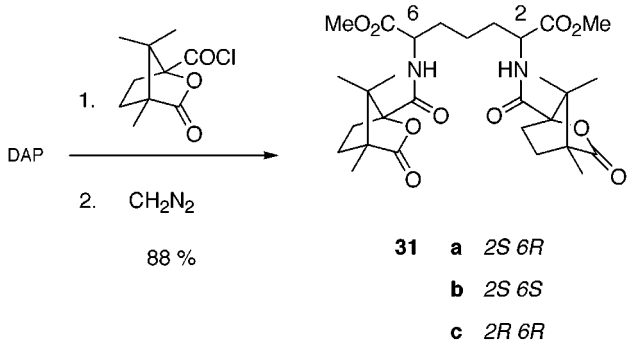
Scheme 3

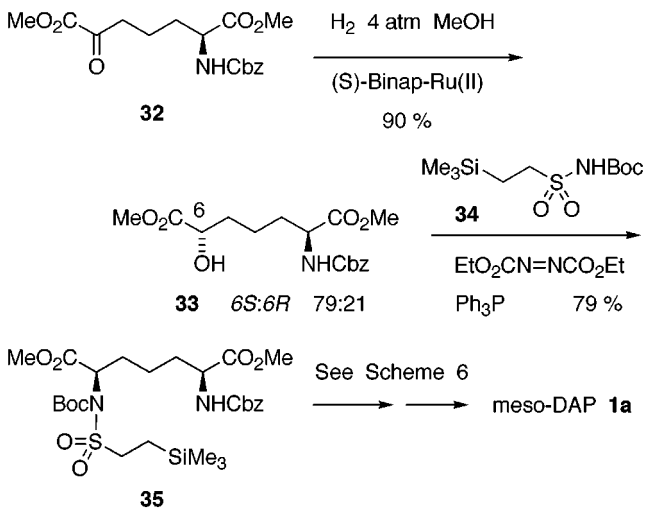


sequence using nonselective ene reaction of methyl *N*-(benzyloxycarbonyl)-L-allylglycinate (**18**) and methyl glyoxylate.[4a] It seemed that enantioselective hydrogenation of the keto group of **32** with the (*S*)-binaphtholruthenium (Binap−Ru) catalyst developed by Noyori et al.[18] would provide an attractive alternative entry to stereochemically pure 2-amino-6-hydroxypimelic acid derivatives,[10] whose hydroxyl group could then be substituted

Scheme 4



Scheme 5



with nitrogen to make DAP analogues (Scheme 5). However, after considerable effort to obtain high selectivity, the best reduction conditions afford only a 79:21 ratio of 6*S*:6*R* isomers of **33**. Since the α-hydroxy esters are prone to epimerization, the product mixture was directly transformed to *meso*-DAP (**1a**) using Mitsunobu substitution with *N*-*tert*-butyl [[2-(trimethylsilyl)ethyl]sulfonyl]-carbamate (**34**)[19] to give **35** followed by deprotection. Conversion to the bis-Mosher amides and HPLC analysis confirmed the isomeric ratio. Although fairly short, this route lacks the desired level of stereoselection in the hydrogenation of the oxo functionality. Attempts to discover a better catalyst for this process or to accomplish this reduction on the parent keto acid using various dehydrogenases have not been successful thus far.

Numerous recent reports of ene reactions facilitated by chiral catalysts[20,21] suggest that such reagents could

(18) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134−9135.

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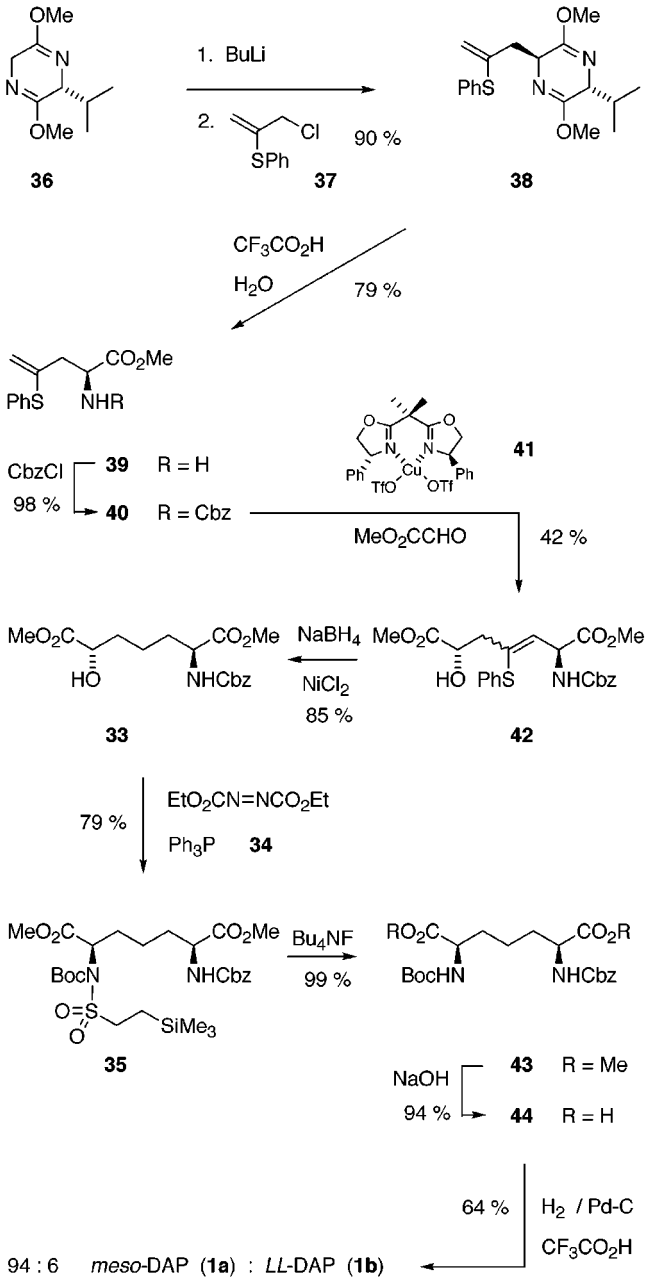
accomplish stereoselective condensation of *N*-(benzyloxycarbonyl)-L-allylglycine methyl ester (**18**) with simple glyoxylate esters. However, a large variety of chiral catalysts fail because their activation of the aldehyde carbonyl is insufficient to promote bond formation with the unreactive terminal olefin of **18**. To circumvent this difficulty, a sulfur substituent was temporarily introduced at the terminus of the allylglycine residue (Scheme 6). Thus, alkylation of the anion of commercially available Schöllkopf bis-lactim ether (**36**)[22] with the known 2-(phenylthio)-3-chloropropene (**37**)[23] affords **38**, which hydrolyzes to L-valine methyl ester and (*S*)-4-(phenylthio)allylglycine methyl ester (**39**) (≥98% ee by NMR analysis of the corresponding camphanamides). This is then protected as the *N*-Cbz derivative **40** prior to ene condensation with methyl glyoxylate.

Attempted conversion of **40** using chiral binaphthol−titanium complexes[20] as Lewis acids fails and leads only to recovery of starting material. However, the bis(oxazoline)−copper complex **41**,[21] which was initially used for asymmetric Diels−Alder reactions and was reported to produce undesired ene side products,[21d] catalyzes the desired reaction between **40** and methyl glyoxylate to give alcohol **42** in modest (42%) yield. The diastereomeric excess on the newly generated center could not be easily determined at this stage because this product is somewhat unstable. The olefinic bond and the phenylthio group of **42** are simultaneously removed by $NiCl_2$−sodium borohydride (nickel boride)[24] to generate saturated alcohol **33** in good yield. Other desulfurization reagents such as Raney-Ni, tributyltin hydride, and lithium in ammonia give primarily undesired overreduction. Mitsunobu substitution of the hydroxy group of **33** using **34**[19] as before inverts the chiral center to give a protected DAP derivative **35** with the desired *meso* stereochemistry. Removal of the silyl-containing group proceeds quantitatively with tetrabutylammonium fluoride to form **43**. Saponification of the diester generates a selectively *N*-protected analogue **44** in high yield. The Boc and Cbz protecting groups can then be selectively removed as desired. Hydrogenation (1 atm) with 10% Pd/C catalyst followed by acidic cleavage of the Boc group affords *meso*-DAP (**1a**). ^{1}H NMR analysis of the corresponding Mosher's diamide derivative as above shows the stereochemistry to be 94% (2*R*,6*S*) (**1a**) and 6% (2*S*,6*S*) (**1b**). Since earlier studies show that there is usually no isomerization under the deprotection conditions, and the Mitsunobu process usually occurs with clean inversion,[25] this suggests that the key ene reaction proceeds with ca. 88% diastereomeric excess.

Summary. The stereoselective synthesis of selectively protected derivatives of *meso*-DAP (**1a**) has been investigated using four approaches: olefin metathesis skeleton assembly, ene reaction employing chiral 2-phenylcyclohexyl auxiliaries, stereospecific reduction of 2-keto-6-

Scheme 6



aminopimelic derivatives (obtained via nonselective ene processes[4a]) with Binap−ruthenium catalyst, and ene reaction using chiral copper oxazoline catalysts. Although the metathesis cyclization is useful for generation of diaminosuberic acid derivatives,[11] problems with isomerization of vinylglycine moieties blocked this route to DAP. Both the chiral phenylcyclohexyl auxiliary ene route and the stereospecific reduction successfully lead to the desired DAP derivatives, but the best isomer ratio (94:6) and the most facile method employ chiral copper catalyst for ene condensation of methyl glyoxylate with methyl *N*-(benzyloxycarbonyl)-L-allylglycinate (**18**). Mitsunobu insertion of the nitrogen functionality then affords the target protected DAP derivatives. This synthetic approach can be used not only to produce these compounds, but also other DAP analogues useful for enzyme mechanism and inhibition studies. Additional studies on DAP enzymes and their inhibitors as potential antibiotic drug candidates are in progress.

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Experimental Section

General Methods. Common experimental procedures and instrumentation have been described previously.[4a,e] The procedure of Whitesell and co-workers[16b] was used to prepare (1*R*,2*S*)-*trans*-2-phenylcyclohexyl oxoacetate (**16**). The optical purity of this starting material was determined to ≥98% ee by conversion to its (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid ester (Mosher ester) using the corresponding acid chloride, followed by comparison to the diastereomeric product derived from the (1*S*,2*R*) -*trans*-2-phenylcyclohexyl oxoacetate (**17**) by ^{1}H NMR spectrometry. The bis-lactim ether **36**[22] was purchased from Merck Schuchardt (Hohenbrunn, Germany).

***N*-(*tert*-Butoxycarbonyl)-D-allylglycine (2).** To a solution of D-allylglycine[26] (0.61 g, 5.3 mmol) in saturated aqueous $NaHCO_3$ (60 mL) and 1,4-dioxane (10 mL) was added Boc_2O (1.4 g, 6.4 mmol). After being stirred for 5 h, the solution was washed with EtOAc (20 mL), acidified to pH 1 with 2 M HCl, and extracted with EtOAc (3 × 30 mL). The organic extracts were dried and evaporated to give **2** as an oil (0.68 g, 61%): R_f 0.67 (70% EtOAc in hexane); $[\alpha]_D$ −13.33° (*c* 1.08 $CHCl_3$); IR ($CHCl_3$ cast) 3340−3000, 1736, 1712, 1620, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9 H), 2.42−2.62 (m, 2 H), 4.32−4.44 (m, 1 H), 5.02−5.21 (m, 2 H), 5.65−5.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.27, 36.40, 52.76, 80.30, 119.36, 132.14, 155.53, 176.61; CI MS *m*/*z* (NH_3) 233 (80, [M + 18]$^+$). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.36; H, 8.17; N, 6.42.

***N*-(*tert*-Butoxycarbonyl)-D-allylglycine, 2-Hydroxyethyl Ester (3).** Condensation of **2** and ethylene glycol analogous to preparation of **9** below gave **3** in 82% yield: R_f 0.28 (40% EtOAc in hexane); IR ($CHCl_3$ cast) 3428, 3215, 1770, 1729, 1620, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9 H), 2.41−2.59 (m, 2 H), 3.79 (t, 2 H, *J* = 4.5 Hz), 4.20−4.32 (m, 3 H), 5.08−5.21 (m, 4 H), 5.63−5.74 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.26, 36.40, 53.13, 60.60, 66.73, 80.26, 119.21, 132.37, 155.64, 172.26; CI MS *m*/*z* (NH_3) 277 (62, [M + 18]$^+$). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.81; H, 8.36; N, 5.14.

2-[(2*R*)-2-[[(*tert*-Butoxycarbonyl)amino]-4-pentenoyl]oxy]ethyl *N*-(Benzyloxycarbonyl)-L-allylglycinate (5). Condensation of **3** and methyl *N*-(benzyloxycarbonyl)-L-allylglycinate (**4**) analogous to preparation of **9** below gave **5** in 83% yield: R_f 0.60 (30% EtOAc in hexane); $[\alpha]_D$ −3° (*c* 0.5 $CHCl_3$); IR ($CHCl_3$ cast) 3347, 1747, 1716, 1642, 1518 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.41 (s, 9 H), 2.39−2.62 (m, 4 H), 4.21−4.38 (m, 5 H), 4.40−4.44 (m, 1 H), 4.97−5.08 (m, 1 H), 5.08−5.14 (m, 4 H), 5.35 (d, 1 H, *J* = 7.5 Hz), 5.59−5.72 (m, 2 H), 7.27−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.29, 36.54, 52.86, 53.27, 61.87, 62.58, 62.83, 67.04, 80.00, 119.27, 119.53, 128.11, 128.21, 128.53, 131.91, 132.18, 136.23, 155.10, 155.76, 171.48, 171.84; CI MS *m*/*z* (NH_3) 492 (27, [M + 1]$^+$). Anal. Calcd for $C_{25}H_{34}N_2O_8$: C, 61.21; H, 6.99; N, 5.71. Found: C, 61.39; H, 7.06; N, 5.47.

(6*R*,11*S*)-11-[*N*-(Benzyloxycarbonyl)amino]-6-[*N*-(*tert*-butoxycarbonyl)amino]-5,12-dioxo-1,4-dioxacyclododec-8-ene (7). All reagents and solvents were dried and degassed. A round-bottomed flask charged with catalyst bis(tricyclohexylphosphine)benzylidineruthenium dichloride (**6**) (17 mg, 0.021 mmol) (Strem Chemicals, Newburyport, MA) was evacuated and filled with Ar three times before the addition of **5** (50.8 mg, 0.104 mmol) in degassed CH_2Cl_2 (15 mL) by an airtight syringe. The resulting orange solution was stirred under Ar for 1.5 h and then stirred for 2 h exposed to the air. The solution color changed from orange to dark black. Removal of the solvent in vacuo gave an oily residue that was purified by flash chromatography (25% EtOAc in hexane) to afford **7** as an equal mixture of double bond isomers (17 mg, 35%): R_f 0.09 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9 H), 2.27−2.48 (m, 2 H), 2.48−2.68 (m, 2 H), 4.22−4.59 (m, 6 H), 5.12 (s, 2 H), 5.42−5.50 (m, 2 H), 7.30−7.42 (m, 5 H); MS CI *m*/*z* (NH_3) 480 (33, [M + 18]$^+$), 463 (41, [M + 1]$^+$).

2-(Trimethylsilyl)ethyl (4*S*)-3-[3-*N*-(Benzyloxycarbonyl)-5-oxazolidinon-4-yl]propanoate (9). To a stirred solution of compound **8**[15] (233 mg, 0.789 mmol), 2-(trimethylsilyl)-ethanol (113 μL, 0.789 mmol), and *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (201 mg, 0.789 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (220 μL, 1.58 mmol). After 10 h, the solvent was evaporated in vacuo to give a residue that was purified by flash chromatography (30% EtOAc in hexane) to afford **9** as an oil (158 mg, 51%): R_f 0.92 (60% EtOAc in hexane); IR ($CHCl_3$ cast) 1802, 1724, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.03 (s, 9 H), 0.91 (t, 2 H, *J* = 8.6 Hz), 2.01−2.38 (m, 4 H), 4.07 (t, 2 H, *J* = 8.6 Hz), 4.29 (t, 1 H, *J* = 5.8 Hz), 5.16 (s, 2 H), 5.21 (m, 1 H), 5.40 (m, 1 H), 7.19−7.28 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ −1.92, 16.88, 25.55, 29.08, 53.63, 62.39, 67.44, 77.42, 127.82, 128.08, 128.23, 135.15, 152.60, 171.37, 171.70; CI MS *m*/*z* (NH_3) 411 (35, [M + 18]$^+$). Anal. Calcd for $C_{19}H_{27}NO_6Si$: C, 57.99; H, 6.92; N, 3.56. Found: C, 58.10; H, 7.21; N, 3.26.

***N*-(Benzyloxycarbonyl)-L-glutamic Acid, α-(3-Hydroxypropyl) γ-(2-Trimethylsilyl)ethyl Ester (10).** Propane-1,3-diol (34 μL, 0.47 mmol) in THF (10 mL) was treated with 2.5 M *n*-BuLi in hexane (188 μL, 0.47 mmol). After being stirred at room temperature for 10 min, this solution was transferred to a solution of **9** (154 mg, 0.392 mmol) in THF (20 mL) via cannula. The resulting mixture was stirred for 12 h, and the solvent was removed in vacuo. The residue was redissolved in EtOAc (40 mL), washed with water (10 mL), dried, and evaporated in vacuo to give an oil. Purification by flash chromatography (60% EtOAc in hexane) afforded **10** as a yellow oil (80 mg, 47%): R_f 0.43 (60% EtOAc in hexane); $[\alpha]_D$ = +6.7° (*c* 7.2 $CHCl_3$); IR (Nujol) 3079−2853, 1642, 1611, 1586, 1559, 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.01 (s, 9 H), 0.97 (t, 2 H, *J* = 8.4 Hz), 1.85 (t, 2 H, *J* = 5.9 Hz), 2.05 (m, 1 H), 2.17 (m, 1 H), 2.38 (m, 2 H), 3.67 (t, 2 H, *J* = 5.9 Hz), 4.16 (t, 2 H, *J* = 8.4 Hz), 4.27 (t, 2 H, *J* = 5.9 Hz), 4.37 (m, 1 H), 5.15 (s, 2 H), 5.42 (d, 1 H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −1.58, 17.24, 27.35, 30.21, 31.34, 53.47, 58.76, 62.51, 63.02, 67.03, 128.04, 128.15, 128.49, 136.12, 155.96, 172.14, 172.89; FAB MS *m*/*z* (Cleland) 440 (2.6, [M + 1]$^+$). Anal. Calcd for $C_{21}H_{33}NO_7Si$: C, 57.38; H, 7.57; N, 3.19. Found: C, 57.29; H, 7.62; N, 3.15.

***N*-(Benzyloxycarbonyl)-L-glutamic Acid, α-3-[[(2*R*)-2-[*N*-tert-Butoxycarbonyl)amino]-4-pentenoyl]oxy]propyl γ-2-(Trimethylsilyl)ethyl Ester (11).** A flask was charged with dicyclohexylcarbodiimide (DCC) (60 mg, 0.32 mmol), 4-(dimethylamino)pyridine (DMAP) (59 mg, 0.48 mmol), and DMAP·HCl (51 mg, 0.32 mmol) in CH_2Cl_2 (20 mL). The resulting solution was brought to reflux, and a solution of **10** (70 mg, 0.16 mmol) and (*R*)-*N*-(*tert*-butoxycarbonyl)allylglycine (**2**) (34 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) was added. After 16 h, the solution was cooled to room temperature and washed with 1 M HCl (10 mL) and saturated aqueous $NaHCO_3$ solution. Hexane (10 mL) was added, and the resulting suspension was filtered, the filtrate being evaporated in vacuo to give an oily residue that was purified by flash chromatography (30% EtOAc in hexane) to afford **11** (90 mg, 88%): R_f 0.28 (20% EtOAc in hexane); $[\alpha]_D$ = +0.33 (*c* 0.3 $CHCl_3$); IR ($CHCl_3$ cast) 3353, 1724, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 9 H), 0.95 (t, 2 H *J* = 8.5 Hz), 1.42 (s, 9 H), 1.98 (m, 3 H), 2.40 (m, 1 H), 2.31−2.60 (m, 4 H), 4.15 (t, 2 H, *J* = 8.5 Hz), 4.18−4.26 (m, 4 H), 5.07 (d, 1 H, *J* = 7.8 Hz), 5.10 (s, 2 H), 5.13−5.17 (m, 2 H), 5.48 (d, 1 H, *J* = 7.8 Hz), 5.48−5.73 (m, 1 H), 7.27−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −1.52, 17.30, 27.47, 27.88, 28.30, 30.36, 36.69, 52.91, 53.48, 61.61, 62.05, 63.01, 67.07, 79.96, 119.18, 128.11, 128.20, 128.54, 132.27, 136.20, 155.23, 155.98, 171.80, 172.00, 172.77; FAB MS *m*/*z* (Cleland) 637 (2, [M + 1]$^+$). Anal. Calcd for $C_{31}H_{48}N_2O_{10}Si$: C, 58.47; H, 7.60; N, 4.40. Found: C, 58.78; H, 7.54; N, 4.21.

***N*-(Benzyloxycarbonyl)-L-glutamic Acid, α-3-[[(2*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-pentenoyl]oxy]propyl Ester (12).** To a solution of **11** (83 mg, 0.13 mmol) in

(26) D-Allylglycine was obtained by resolution of the racemate as previously reported in ref 4a.

THF (10 mL) was added a 1 M solution of TBAF in THF (400 μL, 0.4 mmol). The resulting red solution was stirred for 45 min and then evaporated in vacuo. The residue was dissolved in Et_2O (45 mL), and the ethereal solution was washed with 1 M HCl (20 mL), dried, and evaporated in vacuo to give **12** as a gray oil (70 mg, quantitative): R_f 0.62 (EtOAc); IR ($CHCl_3$ cast) 3200−2800, 1773, 1760, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) 1.42 (s, 9 H), 1.96−2.15 (m, 3 H), 2.15−2.22 (m, 1 H), 2.40−2.48 (m, 4 H), 4.16−4.30 (m, 4 H), 4.30−4.45 (m, 2 H), 5.07−5.18 (m, 5 H), 5.56 (d, 1 H, J = 7.8 Hz), 5.61−5.78 (m, 1 H), 7.26−7.40 (m, 5 H); CI MS m/z (NH_3) 537 (42, $[M + 1]^+$).

Lead Tetraacetate Oxidation of 12 To Generate 14. To a solution of **12** (70 mg, 0.13 mmol) in benzene (20 mL) was added cupric acetate monohydrate (8 mg, 0.0373 mmol), and the suspension was stirred under Ar for 1 h. Freshly prepared lead tetraacetate (132 mg, 0.299 mmol) was added, and the resulting suspension was stirred for 1 h at room temperature then 15 h at reflux. The suspension was then cooled and diluted with EtOAc (20 mL). The mixture was washed with water (3 × 20 mL) and brine (15 mL), dried, and evaporated in vacuo. The resulting syrup was purified by flash chromatography (30% EtOAc in hexane) to give **14** (28 mg, 43%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9 H), 1.80 (d, 3 H, J = 7.2 Hz), 1.94−2.11 (m, 2 H), 2.41−2.59 (m, 2 H), 4.12−4.27 (m, 5 H), 5.03 (d, 1 H, J = 7.8 Hz), 5.09−5.18 (m, 5 H), 5.65−5.76 (m, 1 H), 6.74 (q, 1 H, J = 7.2 Hz), 7.26−7.40 (m, 5 H).

***N*-(Benzyloxycarbonyl)-L-methionine Sulfoxide, 3-[[(2*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-pentenoyl]-oxy]propyl Ester (15).** To a solution of L-methionine (1.0 g, 6.7 mmol) in saturated aqueous $NaHCO_3$ (20 mL) solution was added benzyl chloroformate (1.11 mL, 7.4 mmol) dropwise over 2 min. After being stirred at room temperature for 2 h, the solution was washed with EtOAc (20 mL), acidified to pH 2 with 2 M HCl, and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried and evaporated in vacuo to give *N*-(benzyloxycarbonyl)-L-methionine as an oil (1.2 g, 63%). A solution of this oil (721 mg) and propane-1,3-diol (968 mg, 12.74 mmol) in CH_2Cl_2 (10 mL) was transferred to a solution of DCC (524 mg, 2.55 mmol), DMAP (310 mg, 2.55 mmol), and DMAP·HCl (405 mg, 2.55 mmol) in CH_2Cl_2 (20 mL) at reflux. After 6 h at reflux, the solution was cooled and washed with 1 M HCl (2 × 20 mL). The organic layer was dried and evaporated in vacuo to give a residue that was purified by flash chromatography (40% EtOAc in hexane) to afford *N*-(benzyloxycarbonyl)-L-methionine 3-hydroxypropyl ester (685 mg, 79%): R_f 0.14 (40% EtOAc in hexane); IR ($CHCl_3$ cast) 3400−2900, 1721, 1523 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58−1.98 (m, 4 H), 2.09 (s, 3 H), 2.55 (t, 2 H, J = 7.6 Hz), 3.69 (t, 2 H, J = 5.9 Hz), 4.34 (m, 2 H), 4.45 (m, 1 H), 5.12 (s, 2 H), 5.41 (d, 1 H, J = 7.8 Hz), 7.26−7.38 (m, 5 H); CI MS m/z (NH_3) 359 (25, $[M + 18]^+$). Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10. Found: C, 56.64; H, 6.97; N, 3.98.

The method used above to make **11** transformed *N*-(benzyloxycarbonyl)-L-methionine 3-hydroxypropyl ester and **2** to *N*-(benzyloxycarbonyl)-L-methionine, 3-[[(2*R*)-2-[*N*-(*tert*-butyloxycarbonyl)amino]-4-pentenoyl]oxy]propyl ester in 84% yield: R_f 0.63 (40% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9 H), 1.86−2.41 (m, 7 H), 2.37−2.60 (m, 4 H), 4.04−4.26 (m, 4 H), 4.35 (m, 1 H), 4.48 (m, 1 H), 5.00−5.18 (m, 4 H), 5.42 (d, 1 H, J = 7.8 Hz), 5.54 (d, 1 H, J = 7.8 Hz), 5.60−5.71 (m, 1 H), 7.26−7.40 (m, 5 H); CI MS m/z (NH_3) 556 (34, $[M + 18]^+$), 539 (20, $[M + 1]^+$).

To a cooled solution (0 °C) of *N*-(benzyloxycarbonyl)-L-methionine, 3-[[(2*R*)-2-[*N*-(*tert*-butyloxycarbonyl)amino]-4-pentenoyl]oxy]propyl ester (150 mg, 0.28 mmol) in methanol (10 mL) was added a solution of $NaIO_4$ (63 mg, 0.29 mmol) in water (10 mL) dropwise over a period of 2 h through an addition funnel. The mixture was then stirred at 4 °C for 12 h. The product was filtered through a bed of Celite, and the filtrate was extracted with chloroform (6 × 50 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried, and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc) to give **15** (127 mg, 82%) as an oil: R_f 0.12 (EtOAc); IR ($CHCl_3$ cast) 3340, 1770, 1720, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9 H), 1.97 (m, 2 H), 2.15 (m, 1 H), 1.93−2.50 (m, 3 H), 2.54 (s, 3 H), 2.77 (t, 2 H, J = 7.6 Hz), 4.10−4.26 (m, 4 H), 4.33 (m, 1 H), 4.46 (m, 1 H), 5.08 (s, 2 H), 5.11−5.19 (m, 2 H), 5.60−5.78 (m, 1 H), 5.83 (d, 1 H, J = 8.0 Hz), 5.89 (d, 1 H, J = 7.8 Hz), 7.37−7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 27.87, 28.33, 32.27, 36.63, 38.54, 50.07, 52.95, 53.21, 61.52, 62.32, 67.20, 80.01, 119.20, 128.19, 128.29, 128.57, 132.31, 136.14, 155.30, 156.13, 171.19, 172.06; CI MS m/z (NH_3) 572 (23, $[M + 18]^+$), 555 (17, $[M + 1]^+$). Anal. Calcd for $C_{26}H_{38}N_2O_9S$: C, 56.30; H, 6.91; N, 5.05. Found: C, 56.71; H, 6.77; N, 5.17.

1-Methyl 7-[(1*R*,2*S*)-*trans*-2-Phenylcyclohexyl] (2*S*,6*R*)-2-[*N*-(Benzyloxycarbonyl)amino]-6-hydroxy-3-heptenedioate (19). $SnCl_4$ (10.0 mL, 86.7 mmol) was added over 2 min to a stirred solution of **16**[16b] (5.01 g, 20.0 mmol) in dry CH_2Cl_2 (125 mL) at approximately −55 °C. The solution was cooled to −78 °C and stirred for 5 min, and **18** (5.86 g, 22.3 mmol) in dry CH_2Cl_2 (40 mL) was added over 15 min. The solution was warmed to −23 °C and was stirred for 3 h. The mixture was quenched with ether (500 mL) and washed with saturated $NaHCO_3$ (2 × 250 mL) and water (250 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give a pale yellow oil. Purification by flash chromatography (EtOAc 40%/hexane 60%) gave 8.20 g (83%) of **19** as a clear oil: $[\alpha]_D$ +28.1° (c = 1.88, $CHCl_3$); IR ($CHCl_3$ cast) 3420, 3360, 2936, 1726, 1271, 1208 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44−7.10 (m, 10H), 5.55 (d, 1H, J = 7.9 Hz), 5.25−4.92 (m, 5H), 4.75−4.64 (m, 1H), 3.96 (dd, 1H, J = 11.0, 6.0 Hz), 3.68 (s, 3H) 2.90 (br s, 1H), 2.65 (m, 1H), 2.18−2.00 (m, 1H) 2.00−1.18 (m, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.3, 171.0, 155.4, 142.8, 136.2, 128.5, 128.3, 127.55, 127.5, 126.8, 78.0, 69.3, 67.0, 55.3, 52.5, 49.8, 36.5, 33.7, 32.1, 25.6, 24.6; exact mass 495.2259 (495.2257 calcd for $C_{28}H_{33}NO_7$). Anal. Calcd for $C_{28}H_{33}NO_7$: C, 67.86; H, 6.71; N, 2.83. Found: C, 67.55; H, 6.88; N, 2.90.

1-Methyl 7-[(1*S*,2*R*)-*trans*-2-Phenylcyclohexyl] (2*S*,6*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-6-hydroxy-3-heptenedioate (20). The previous procedure was adapted to condense **17**[16b] (1.05 g, 4.20 mmol) and **18** (1.01 g, 3.84 mmol) to give an 81% yield of **20**: $[\alpha]_D$ +24.4° (c = 0.85, $CHCl_3$); IR ($CHCl_3$ cast) 3420, 3360, 2936, 1726, 1265, 1209 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34−7.06 (m, 10H), 5.54 (d, 1H, J = 8.3 Hz), 5.25−4.90 (m, 5H), 4.72−4.64 (m, 1H), 4.04−3.96 (m, 1H), 3.68 (s, 3H) 2.90 (d, 1H, J = 6.0 Hz), 2.65 (ddd, 1H, J = 12.2, 11.0, 3.7 Hz), 2.18−2.00 (m, 1H) 2.05−1.22 (m, 9H); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 173.4, 171.1, 155.4, 142.8, 136.2, 128.5, 128.3, 127.8, 127.52, 127.48, 127.4, 127.3, 126.8, 78.1, 69.4, 67.0, 55.4, 52.5, 49.8, 36.5, 33.8, 32.2, 25.6, 24.6; exact mass 495.2256 (495.2257 calcd for $C_{28}H_{33}NO_7$). Anal. Calcd for $C_{28}H_{33}NO_7$: C, 67.86; H, 6.71; N, 2.83. Found: C, 68.02; H, 6.93; N, 2.96.

1-Methyl 7-[(1*R*,2*S*)-*trans*-2-Phenylcyclohexyl] (2*S*,6*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-hydroxyheptanedioate (21). The procedure of Sakaitani *et al.*[27] was adapted. To a solution of **19** (2.68 g, 5.41 mmol) and di-*tert*-butyl pyrocarbonate (1.56 g, 7.06 mmol) in MeOH (20 mL) was added 5% Pd on carbon (0.0479 g) in MeOH (5 mL). The suspension was stirred under H_2 (1 atm) for 20 h and then filtered through Celite. The Celite was washed with MeOH, and the combined filtrates were concentrated in vacuo to give a colorless oil. Purification by flash chromatography ($CHCl_3$ followed by 3% MeOH/$CHCl_3$ 97%) afforded 2.10 g (84% yield) of **21** as a colorless oil: $[\alpha]_D$ −8.3° (c = 0.579, $CHCl_3$); IR (CH_3OH cast) 3480 br, 3410 br, 2935, 2865, 2858, 1742, 1716 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36−7.12 (m, 5H), 5.03 (ddd, 1H, J = 11.0, 10.4, 4.3 Hz), 4.87 (br d, 1H, J = 7.9 Hz), 4.12 (m, 1H), 3.94 (m, 1H), 3.73 (s, 3H), 2.74−2.60 (m, 2H), 2.24−2.18 (m, 1H), 2.01−1.70 (m, 3H), 1.66−1.05 (m, 8H), 1.46 (s, 9H), 1.00−0.78 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 173.1, 155.2, 142.8, 128.2, 127.4, 127.3, 126.6, 126.5, 79.4, 77.7, 69.8, 53.1, 52.0, 49.8, 33.8, 33.3, 32.1, 32.0, 28.2, 25.5, 24.5, 20.3; exact mass 463.2547 (463.2570 calcd for $C_{25}H_{37}NO_7$). Anal. Calcd

(27) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983−2984.

for $C_{25}H_{37}NO_7$: C, 64.78; H, 8.05; N, 3.02. Found C, 64.55; H, 7.69; N, 2.94.

1-Methyl 7-[(1*S*,2*R*)-*trans*-2-Phenylcyclohexyl] (2*S*,6*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-hydroxyheptanedioate (22). Alcohol **22** was prepared in 80% yield from **20** (0.512 g, 1.03 mmol) by the same procedure used for the synthesis of **21**, employing Boc anhydride (99%, 0.291 g, 1.32 mmol) and 5% Pd on carbon (0.109 g) in 11 mL of MeOH: $[\alpha]_D$ +17.7 (c = 1.30, $CHCl_3$); IR ($CHCl_3$ cast) 3380, 2936, 1737, 1719, 1253, 1210, 1165, 1113 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34−7.16 (m, 5H), 5.10 (ddd, 1H, J = 11.0, 10.4, 4.3 Hz), 4.85 (d, 1H, J = 8.6 Hz), 4.18−4.08 (m, 1H), 3.99−3.90 (m, 1H), 3.74 (s, 3H), 2.74−2.64 (m, 1H), 2.62 (d, 1H, J = 5.5 Hz), 2.22−2.10 (m, 1H), 2.00−1.87 (m, 3H), 1.66−0.70 (m, 10H), 1.45 (s, 9H); ^{13}C NMR δ 174.2, 173.0, 155.2, 142.6, 128.2, 128.1, 127.2, 126.64, 126.58, 79.5, 77.6, 69.6, 53.0, 51.9, 49.7, 33.6, 33.1, 32.0, 31.8, 28.1, 25.5, 24.5, 19.7; exact mass 404.2426 ($M^+ - C_2H_3O_2$). Anal. Calcd for $C_{25}H_{37}NO_7$: C,64.78; H, 8.05; N, 3.02. Found: C, 64.83; H, 7.75; N, 2.83.

1-Methyl 7-(1*R*,2*S*)-*trans*-2-Phenylcyclohexyl (2*S*,6*R*)-2-(*N*-(*tert*-Butoxycarbonyl)amino]-6-[(methylsulfonyl)-oxy]heptanedioate (23). Methanesulfonyl chloride (98%, 0.220 mL, 2.75 mmol) was added to a stirred solution of **21** (0.965 g, 2.08 mmol) in dry pyridine (20 mL) under argon. The mixture was stirred for 1.75 h and was then quenched by the addition of 20% $CuSO_4 \cdot 5H_2O$ solution (30 mL). The solution was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were washed with 2 M HCl (3 × 30 mL), dried over Na_2SO_4, and then concentrated in vacuo to yield 1.05 g (94%) of **23** as an oil: $[\alpha]_D$ +14.00° (c = 1.35, $CHCl_3$); IR ($CHCl_3$ cast) 3380, 2935, 2860, 1746, 1714, 1365, 1208, 1176 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36−7.17 (m, 5H), 5.06 (ddd, 1H, J = 11.0, 10.4, 4.3 Hz), 4.90 (br d, 1H, J = 8.6 Hz), 4.76 (dd, 1H, J = 6.1, 5.5 Hz), 4.22−4.12 (m, 1H), 3.75 (s, 3H), 2.95 (s, 3H), 2.77−2.66 (m, 1H), 2.23−2.15 (m, 1H), 2.03−1.78 (m, 3H), 1.70−0.90 (m, 10H), 1.48 (s, 9H); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 172.9, 168.1, 155.2, 142.8, 128.5, 128.4, 127.6, 127.4, 126.7, 79.8, 78.1, 77.3, 52.9, 52.2, 49.8, 38.7, 34.1, 32.1, 31.8, 31.0, 28.2, 25.5, 24.6, 20.3; exact mass 482.2206 (482.2206 calcd for $M^+ - C_2H_3O_2$), MS (Pos FAB, Cleland) 542.53 (542.23 calcd for MH^+). Anal. Calcd for $C_{26}H_{39}NO_9S$: C, 57.65; H, 7.26; N, 2.58; S, 5.92. Found: C, 57.53; H, 7.15; N, 2.70; S, 5.66.

1-Methyl 7-(1*S*,2*R*)-*trans*-2-Phenylcyclohexyl (2*S*,6*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-[(methylsulfonyl)-oxy]heptanedioate (24). Mesylate **24** was prepared from **22** (1.47 g, 3.23 mmol) in 94% yield in the same manner as **23** was prepared from **21**, using methanesulfonyl chloride (98%, 0.330 mL, 4.18 mmol), in dry pyridine (20 mL): $[\alpha]_D$ +2.9° (c = 1.0, $CHCl_3$); IR ($CHCl_3$ cast) 3380, 2936, 1749, 1715, 1365, 1210, 1176 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36−7.18 (m, 5H), 5.06 (ddd, 1H, J = 11.0, 10.4, 4.3 Hz), 4.90 (br d, 1H, J = 8.0 Hz), 4.82−4.76 (m, 1H), 4.22−4.14 (m, 1H), 3.74 (s, 3H), 2.95 (s, 3H), 2.77−2.66 (m, 1H), 2.23−2.15 (m, 1H), 2.03−1.78 (m, 3H), 1.70−0.90 (m, 10H), 1.47 (s, 9H); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 172.9, 168.1, 155.2, 142.8, 128.4, 127.3, 126.7, 79.7, 78.1, 77.8, 52.9, 52.1, 49.7, 38.6, 34.0, 32.0, 31.4, 30.8, 28.1, 25.5, 24.5, 19.9; exact mass 482.2206 (482.2206 calcd for $M^+ - C_2H_3O_2$), MS (Pos FAB, Cleland) 542.27 (542.23 calcd for MH^+). Anal. Calcd for $C_{26}H_{39}NO_9S$: C, 57.65; H, 7.26; N, 2.58; S, 5.92. Found: C, 57.82; H, 7.25; N, 2.48; S, 5.67.

1-Methyl 7-(1*R*,2*S*)-*trans*-2-Phenylcyclohexyl (2*S*,6*S*)-2-[*N*-(Butoxycarbonyl)amino]-6-azidoheptanedioate (25). Mesylate **23** (0.819 g, 1.51 mmol) and NaN_3 (0.400 g, 6.16 mmol) were dissolved in dry DMF (15 mL) and stirred under Ar for 28 h. The DMF was removed in vacuo, and the residue was taken up in CH_2Cl_2 (75 mL) and washed with brine (2 × 30 mL). The organic layer was dried over Na_2SO_4 and then concentrated in vacuo to give a red oil that was purified by flash chromatography (EtOAc 25%/hexane 75%) to afford 0.647 g (88% yield) of **25** as a colorless oil: $[\alpha]_D$ −4.1° (c = 2.18, $CHCl_3$); IR ($CHCl_3$ cast) 3375, 2936, 2861, 2107, 1739, 1717 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H), 5.06 (ddd, 1H, J = 11.0, 10.4, 4.3 Hz), 4.94 (br d, 1H, J = 8.6), 3.73 (s, 3H), 3.47 (dd, 1H, J = 7.3, 6.7 Hz), 2.72 (ddd, 1H, J = 12.2, 11.0, 3.7 Hz), 2.16−2.10 (m, 1H), 2.02−1.73 (m, 3H), 1.72−1.02 (m, 10H), 1.45 (s, 9H); ^{13}C NMR (MHz, $CDCl_3$) δ 172.9, 169.3, 155.2, 142.5, 128.4, 127.5, 126.7, 79.8, 77.7, 61.7, 52.9, 52.2, 49.9, 33.8, 32.1, 31.8, 30.5, 28.2, 25.6, 24.7, 21.3; MS (Pos FAB glycerol) 463.36 (463.27 calcd for MH^+). Anal. Calcd for $C_{25}H_{36}N_4O_6$: C, 61.46; H, 7.43; N, 11.47. Found: C, 61.65; H, 7.70; N, 11.40.

1-Methyl 7-[(1*S*,2*R*)-*trans*-2-Phenylcyclohexyl] (2*S*,6*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-azidoheptanedioate (26). Azide **26** was prepared from **24** (1.12 g, 2.06 mmol) in 77% yield by the same method as employed for the preparation of **25** from **23**, using NaN_3 (0.552 g, 8.49 mmol) in dry DMF (20 mL): $[\alpha]_D$ +25.3° (c = 1.44, $CHCl_3$); IR ($CHCl_3$ cast) 3375, 2936, 2861, 2107, 1739, 1717 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38−7.16 (m, 5H), 5.06 (ddd, 1H, J = 11.0, 10.4, 4.3 Hz), 4.94 (br d, 1H, J = 8.6 Hz), 3.74 (s, 3H), 3.45 (dd, 1H, J = 7.9, 6.7 Hz), 2.72 (ddd, 1H, J = 11.0, 11.0, 3.7 Hz), 2.22−2.12 (m, 1H), 2.04−1.78 (m, 3H), 1.78−1.06 (m, 10H), 1.45 (s, 9H); ^{13}C NMR (MHz, $CDCl_3$) δ 172.9, 169.3, 155.2, 142.5, 128.3, 127.5, 126.7, 79.9, 77.7, 61.7, 53.0, 52.2, 49.8, 33.7, 32.1, 31.9, 30.5, 28.2, 25.6, 24.7, 21.3; MS (Pos FAB glycerol) 463.36 (463.27 calcd for MH^+). Anal. Calcd for $C_{25}H_{36}N_4O_6$: C, 61.46; H, 7.43; N, 11.47. Found: C, 61.28; H, 7.62; N, 11.50.

1-Methyl 7-[(1*R*,2*S*)-*trans*-2-Phenylcyclohexyl] (2*S*,6*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-aminoheptanedioate (27). Azide **25** (0.645 g, 1.32 mmol) in MeOH (10.0 mL) was added to 5% Pd on carbon (0.0805 g) moistened with MeOH. The mixture was then stirred under H_2 (1 atm) for 1.5 h. It was filtered through Celite, and the Celite was washed with MeOH. The combined filtrates were concentrated in vacuo to give 0.485 g (80% yield) of **27** as an oil: $[\alpha]_D$ −4.7° (c = 0.867, $CHCl_3$); IR ($CHCl_3$ cast) 3370, 2934, 1743, 1716, 1166 cm^{-1}; ^1H NMR (360 MHz $CDCl_3$) δ 7.38−7.12 (m, 5H), 5.16−4.89 (m, 2H), 4.25−4.08 (m, 1H), 3.73 (s, 3H), 2.73−2.59 (m, 1H), 2.18−0.80 (m, 16H), 1.43 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.2, 172.8, 155.0, 142.5, 127.9, 127.1, 126.1, 76.0, 53.7, 52.8, 51.6, 49.4, 33.2, 31.8, 31.6, 27.9, 25.3, 24.3, 20.9; exact mass 462.2734 (462.2730 calcd for $C_{25}H_{38}N_2O_6$).

1-Methyl 7-[(1*S*,2*R*)-*trans*-2-Phenylcyclohexyl] (2*S*,6*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-aminoheptanedioate (28). Amine **28** was prepared from **26** (0.775 g, 1.59) in 93% yield in a manner analogous to the synthesis of **27** from **25**, using 5% Pd on carbon (0.489 g) in MeOH (15 mL): $[\alpha]_D$ +23.1° (c = 1.21, $CHCl_3$); IR ($CHCl_3$ cast) 3370, 2973, 2931, 2858,1741, 1714, 1165 cm^{-1}; ^1H NMR (360 MHz $CDCl_3$) δ 7.36−7.18 (m, 5H), 5.20−5.00 (m, 2H), 4.45−4.10 (m, 3H), 3.76 (s, 3H), 2.76−2.66 (m, 1H), 2.23−1.00 (m, 14H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 172.8, 155.0, 142.5, 127.9, 127.2, 126.2, 79.2, 76.0, 53.7, 52.8, 51.6, 49.5, 33.2, 31.8, 31.6, 27.9, 25.3, 24.3, 20.9; exact mass 462.2731 (462.2730 calcd for $C_{25}H_{38}N_2O_6$).

(2*S*,6*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-aminoheptanedioic Acid (29). $LiOH \cdot H_2O$ (0.0999 g, 2.38 mmol) was added to a stirred solution of **27** (0.275 g, 0.595 mmol) in 3:1 THF/H_2O (20.0 mL), and the solution was stirred at room temperature for 4.5 h. The THF was removed in vacuo, and the aqueous solution was washed with CH_2Cl_2 (3 × 10 mL). It was then acidified to pH 4 with 5.7 M HCl. Lyophilization yielded **29** as its lithium salt in the form of a hygroscopic white foam (0.259 g): IR (CH_3OH cast) 3360, 3040, 1687, 1601 cm^{-1}; ^1H NMR (360 MHz, CD_3OD) δ 4.08−3.83 (m, 1H), 3.78−3.55 (m, 1H), 2.10−1.12 (m, 6H) 1.47 (s, 9H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 179.4, 174.8, 157.8, 80.4, 56.7, 55.9, 33.6, 31.9, 28.8, 22.4; MS (Pos FAB glycerol/HCl) 291.02 (291.16 calcd for $C_{11}H_{20}N_2O_6Li_2$), 297.03 (297.18 calcd for $C_{11}H_{20}N_2O_6Li_3$). Acidic deprotection with trifluoroacetic acid and standard cation-exchange chromatography (AG50) gave LL-DAP (**1b**) and *meso*-DAP (**1a**) in a ratio of 84:16. The ratio was determined by conversion to corresponding camphanamide derivatives **31a**,**b** (see below).

(2*S*,6*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-6-aminoheptanedioic Acid (30). The procedure used for the conversion of **27** to **29** was utilized to prepare **30** as its lithium salt (0.216 g) from **28** (0.209 g, 0.452 mmol), employing $LiOH \cdot H_2O$ (0.0765

g, 1.82 mmol) in 3:1 THF/H_2O (20.0 mL) over 5 h: IR (CH_3-OH cast) 3400, 3040, 1686, 1602 cm^{-1}; ^1H NMR (360 MHz, CD_3OD) δ 4.08−3.83 (m, 1H), 3.78−3.55 (m, 1H), 2.10−1.12 (m, 6H) 1.47 (s, 9H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 179.3, 174.6, 157.8, 80.2, 56.8, 56.0, 33.9, 32.0, 28.8, 22.7; MS (Pos FAB glycerol/HCl) 297.03 (297.18 calcd for $C_{11}H_{20}N_2O_6Li_3$). Acidic deprotection with trifluoroacetic acid and standard cation-exchange chromatography (AG50) gave *meso*-DAP (**1a**) and LL-DAP (**1b**) in a ratio of 86:13. The ratio was determined by conversion to corresponding camphanamide derivatives **31a**,**b**.

Stereochemical Analysis of DAP Isomers: Dimethyl (2*S*,6*S*)-2,6-Bis[[(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane(carbonylamino)heptanedioate (31b), Its (2*R*,6*R*)-Isomer 31c, and Its (2*S*,6*R*)-Isomer 31a. NMR spectral comparison, particularly of the methyl ester region (δ 3.7−3.8), of DAP derivatives **31** allows determination of stereochemical purity to ±2%. LL-DAP (**1b**) (1.93 mg, 0.0102 mmol) was dissolved in 1 M $NaHCO_3/Na_2CO_3$ buffer, pH 10.4 (2 mL). Toluene (1 mL) was added followed by (1*S*,4*R*)-(−)-camphanic chloride (10.2 mg, 0.0469 mmol), and the mixture was stirred vigorously at room temperature for 2.5 h. The solution was acidified to pH 1 with 5.7 M HCl. It was then diluted to 5 mL with water and extracted with dichloromethane (3 × 10 mL). The combined organic fractions were dried over Na_2SO_4 and were concentrated in vacuo. The residue was taken up in ether (2 mL). This was treated with a solution of CH_2N_2 in ether until a yellow color persisted. The ether was evaporated to give 17.1 mg of a waxy solid, which was heated at 65−70 °C for 5 h at 0.4 mmHg to remove methyl camphanoate and give 5.16 mg (88%) of a colorless oil: $[\alpha]_D$ −4.7° (c = 1.25, $CHCl_3$); IR ($CHCl_3$ cast) 3416, 3365, 2965, 1793, 1745, 1674, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (br d, J = 8.2 Hz, 2H, 2 N*H*), 4.63−4.57 (m, 2H, 2 C*H*NH), 3.75 (s, 6H, OCH_3), 2.53−2.42 (m, 2H, 2 CH_aHCR$_2$CON), 1.99−1.82 (m, 6H, 2 CH_aHCR$_2$CON, 2 CH_aHCR$_2$CO$_2$, 2 CH_aHCHN), 1.78−1.47 (m, 4H, 2 CHH_bCR$_2$CO$_2$, 2 CHH_bCHN), 1.46−1.32 (m, 2H, CH_2), 1.12 (s, 6H, 2 CH_3), 1.11 (s, 6H, 2 CH_3), 0.92 (s, 6H, 2 CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.9 (*C*O$_2$R), 171.6 (*C*O$_2$R), 167.1 (*C*ONH), 92.2 (N*C*O), 77.2 (*C*HNH), 55.3 (OCH_3), 53.9 (*C*R$_4$), 52.6 (*C*R$_4$), 51.6 (*C*H$_3$), 32.0 (*C*H$_2$), 31.8 (*C*H$_2$), 30.4 (*C*H$_2$), 29.1 (*C*H$_2$), 21.5 (*C*H$_2$), 16.7 (*C*H$_3$), 16.6 (*C*H$_3$), 9.7 (*C*H$_2$); exact mass 578.2824 (578.2839 calcd for $C_{29}H_{42}N_2O_{10}$).

Employing the same procedure, **31a** was prepared from *meso*-DAP (**1a**): IR ($CHCl_3$ cast) 3360, 2966, 1792, 1746, 1674, 1528 cm^{-1} ; ^1H NMR (360 MHz, $CDCl_3$) δ 6.92 (br d, J = 8.3 Hz, 1H, N*H*), 6.80 (br d, J = 8.0 Hz, 1H, N*H*), 4.65−4.51 (m, 2H, 2 C*H*NH), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.58−2.40 (m, 2H, 2 CH_aHCR$_2$CON), 2.05−1.82 (m, 6H, 2 CH_aHCR$_2$-CON, 2 CH_aHCR$_2$CO$_2$, 2 CH_aHCHN), 1.80−1.62 (m, 4H, 2 CHH_bCR$_2$CO$_2$, 2 CHH_bCHN), 1.45−1.30 (m, 2H, CH_2), 1.08 (m, 9H, 3 CH_3), 1.03 (s, 3H, CH_3) 0.93 (s, 3H, 2CH_3), 0.90 (s, 3H, 2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.0 (*C*O$_2$R), 177.8 (*C*O$_2$R), 171.62 (*C*O$_2$R), 171.55 (*C*O$_2$R), 167.0 (*C*ONH), 92.21 (N*C*O), 92.15 (N*C*O), 55.3 (*C*HNH), 55.2 (OCH_3), 54.1 (*C*R$_4$), 53.9 (*C*R$_4$), 52.5 (*C*R$_4$), 52.4 (*C*R$_4$), 51.53 (*C*H$_3$), 51.47 (*C*H$_3$), 51.4 (*C*H$_3$), 51.3 (*C*H$_3$), 31.9 (*C*H$_2$), 31.8 (*C*H$_2$), 31.4 (*C*H$_2$), 30.3 (*C*H$_2$), 29.0 (*C*H$_2$), 21.5 (*C*H$_2$), 16.6 (*C*H$_3$), 16.5 (*C*H$_3$), 16.4 (*C*H$_3$), 9.6 (*C*H$_2$); exact mass 578.2832 (578.2839 calcd for $C_{29}H_{42}N_2O_{10}$). Anal. Calcd for $C_{29}H_{42}N_2O_{10}$: C, 60.19; H, 7.32; N, 4.84. Found: C, 60.03; H, 7.59; N, 4.56.

Employing the same procedure, **31c** was prepared from DD-DAP (**1c**): $[\alpha]_D$ −13.5° (c = 0.11, $CHCl_3$); IR ($CHCl_3$ cast) 3365, 2965, 1790, 1745, 1672, 1528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (br d, J = 8.3 Hz, 2H, 2 N*H*), 4.63−4.57 (m, 2H, 2 C*H*NH), 3.75 (s, 6H, OCH_3), 2.64−2.50 (m, 2H, 2 CH_aHCR$_2$-CON), 2.02−1.85 (m, 6H, 2 CH_aHCR$_2$CON, 2 CH_aHCR$_2$CO$_2$, 2 CH_aHCHN), 1.85−1.62 (m, 4H, 2 CHH_bCR$_2$CO$_2$, 2 CHH_b-CHN), 1.50−1.38 (m, 2H, CH_2), 1.12 (s, 6H, 2 CH_3), 1.08 (s, 6H, 2 CH_3), 0.96 (s, 6H, 2 CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.1 (*C*O$_2$R), 171.8 (*C*O$_2$R), 167.2 (*C*ONH), 92.3 (N*C*O), 55.4 (OCH_3, *C*HNH)), 54.2 (*C*R$_4$), 52.5 (*C*R$_4$), 51.4 (*C*H$_3$), 31.5 (*C*H$_2$), 30.4 (*C*H$_2$), 29.1 (*C*H$_2$), 21.7 (*C*H$_2$), 16.7 (*C*H$_3$), 16.6 (*C*H$_3$), 9.7 (*C*H$_2$); exact mass 578.2836 (578.2839 calcd for $C_{29}H_{42}N_2O_{10}$).

Dimethyl (2*S*,6*S*)-6-[*N*-(Benzyloxycarbonyl)amino]-2-hydroxyheptane-1,7-dioate (33) from 32. The procedure of Noyori and co-workers[18] was adapted. All the reagents and solvents were predried and degassed. To a dry Schlenk tube charged with dimethyl (6*S*)-6-[*N*-(benzyloxycarbonyl)amino]-2-oxoheptane-1,7-dioate (**32**)[4a] (180 mg, 0.513 mmol) and methanol (5 mL) was added the in situ prepared (*S*)-Binap−Ru(II) complex (2 mg)[18] under a stream of Ar. The resulting yellow-orange solution was further degassed by two freeze−thaw cycles and transferred to a dry, argon-filled autoclave that was evacuated by vacuum and refilled with hydrogen five times. Finally, the system was kept at 4 atm hydrogen, 100 °C for 4 h. After the autoclave was cooled to room temperature and excess hydrogen was allowed to bleed off, the solution was evaporated in vacuo. The residue was separated by flash chromatography (40% EtOAc in hexane) to give **33** as an oil (163 mg, 90%). Conversion to DAP and NMR analysis of the corresponding Mosher amides (see Scheme 6 and below) showed an isomeric ratio 6*S*:6*R* of 79:21 (58% de): R_f 0.79 (EtOAc); IR (CH_2Cl_2 cast) 3356, 1790−1760, 1735, 1527 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.40−1.95 (m, 6 H), 3.70 (s, 3 H), 3.78 (s, 3 H), 4.08−4.20 (m, 1 H), 4.31−4.41 (m, 1 H), 5.17 (s, 2 H), 5.20−5.31 (br s, 1 H), 7.29−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.73, 32.36, 33.70, 52.43, 52.61, 53.68, 67.07, 70.13, 128.15, 128.23, 128.57, 136.24, 156.20, 172.81, 175.43; exact mass 353.1468 (7.3, M^+) (353.1474 calcd for $C_{17}H_{23}NO_7$). Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.42; H, 6.65; N, 3.87.

Dimethyl (2*S*,6*R*)-2-[*N*-(Benzyloxycarbonyl)amino]-6-[*N*-(*tert*-butoxycarbonyl)-*N*-[[2-(trimethylsilyl)ethyl]sulfonyl]amino]heptane-1,7-dioate (35). To a solution of Ph_3P (115 mg, 0.442 mmol), carbamate **34**[19] (116 mg, 0.414 mmol), and **33** (96 mg, 0.27 mmol) in 20 mL of THF at 0 °C was added dropwise diethyl azodicarboxylate (65 μL, 0.414 mmol) over a 5 min period. The solution was stirred for 5 h at room temperature, concentrated in vacuo, and purified by flash chromatography (25% EtOAc in hexane) to give **35** as an oil (132 mg, 79%): R_f 0.32 (30% EtOAc in hexane); IR ($CHCl_3$ cast) 3376, 1729, 1520 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 9 H), 1.02−2.22 (m, 17 H), 1.47 (s, 9 H), 3.40−3.60 (m, 2 H), 3.71 (s, 6 H), 4.30−4.40 (m, 1 H), 4.68−4.75 (m, 1 H), 5.09 (s, 2 H), 5.30−5.37 (m, 1 H), 7.26−7.38 (m, 5 H); CI MS m/z (NH_3) 634 (19, $[M + 18]^+$), 617 (1, $[M + 1]^+$). Anal. Calcd for $C_{27}H_{44}N_2O_{10}SSi$: C, 52.58; H, 7.19, N, 4.54. Found: C, 52.36; H, 7.02; N, 4.68.

(3*R*,6*S*)-3-Isopropyl-2,5-dimethoxy-6-[2-(phenylthio)-2-propenyl]-3,6-dihydropyrazine (38). The alkylating agent 3-chloro-2-thiophenylpropene (**37**) was prepared by a modification of the literature method[23] and was used without purification. Thus, allene (0.61 g, 15.2 mmol) was bubbled into a solution of dry THF (25 mL) at −30 °C at a constant flow rate. Sulfenyl chloride (1.871 g, 12.9 mmol) in THF (5 mL) was then added dropwise (10 min). The resulting solution was stirred at −30 to −20 °C for about 30 min to give a solution of **37** in THF. A cooled solution (−78 °C) of (*R*)-Schöllkopf bis-lactim ether **36** (2.32 mL, 12.9 mmol) in THF (20 mL) under Ar was treated with a 2.5 M solution of *n*-BuLi in hexane (5.2 mL, 12.9 mmol). After being stirred for an additional 10 min at −78 °C, the THF solution of **37** was added via cannula over 15 min and the resulting orange-black solution was stirred at −60 °C for 4 h. After another 12 h, while the temperature was gradually raised to room temperature, the solvent was removed in vacuo and the black residue was partitioned between Et_2O (20 mL) and water (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried and evaporated. The dark oily residue was purified by flash chromatography (5% EtOAc in hexane) to give **38** as an unstable oil (3.86 g, 90%): R_f 0.22 (10% EtOAc in hexane); IR ($CHCl_3$ cast) 1779, 1721, 1635, 1578 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 0.68 (d, 3 H, J = 6.9 Hz), 1.07 (d, 3 H, J = 6.9 Hz), 2.20−2.32 (m, 1 H), 2.52−2.81 (m, 2 H), 3.18 (s, 3 H), 3.21 (s, 3 H), 3.92−3.95 (t, 1 H, J = 3.5 Hz), 4.19−4.29 (m, 1 H), 4.92 (s, 1 H), 5.20 (s, 1 H), 7.20−7.47 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 16.66, 19.36, 31.99, 41.37, 61.17, 61.27, 116.46, 128.07, 129.55, 132.89, 133.22, 134.17,

142.11, 163.08, 164.13; CI MS *m/z* (NH_3) 333 (100, $[M + 1]^+$). Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43; S, 9.64. Found: C, 65.04; H, 7.24; N, 8.41; S, 9.97.

Methyl (2*S*)-4-(Phenylthio)allylglycinate (39). A solution of **38** (3.0 g, 9.3 mmol) in 0.4 N CF_3CO_2H (70 mL, 28 mmol) and THF (10 mL) was stirred at room temperature for 4 h. The THF was removed in vacuo, and the aqueous residue was washed with EtOAc (15 mL) before it was concentrated to a volume of 15−20 mL. The pH was adjusted to 8−9 by adding saturated aqueous Na_2CO_3 solution. The mixture was extracted with EtOAc (3 × 25 mL), and the combined organic extracts were washed with brine (15 mL). The organic solution was dried and evaporated in vacuo. The resulting oil was bulb-to-bulb distilled, and (*R*)-valine methyl ester was the forerun separated from the residue that yielded relatively unstable **39** (1.73 g, 79%): R_f 0.19 (EtOAc); $[\alpha]_D$ +21.31° (*c* = 1.60, $CHCl_3$); IR ($CHCl_3$ cast) 3379, 3316, 1739, 1607 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) 2.40−2.70 (m, 2 H), 3.65 (s, 3 H), 3.72−3.80 (m, 1 H), 5.02 (s, 1 H), 5.26 (s, 1 H), 7.30−7.49 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 42.45, 52.21, 54.58, 110.79, 128.46, 129.69, 133.12, 133.51, 142.05, 175.53; exact mass 237.0823 (11, M^+) (237.0823 calcd for $C_{12}H_{15}NO_2S$).

To determine the enantiomeric excess, a stirred solution of **39** (11.1 mg, 0.047 mmol) and (1*S*)-camphanic acid chloride (15.5 mg, 0.071 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (10 μL, 0.071 mmol). After 1 h, the solution was washed with 1 M HCl (10 mL), dried, and evaporated in vacuo to give a residue. ^1H NMR ($CDCl_3$, 360 MHz) analysis showed an ee ≥98%.

Methyl (2*S*)-*N*-(Benzyloxycarbonyl)-4-(phenylthio)allylglycinate (40). To a solution of **39** (1.72 g, 7.3 mmol) and benzyl chloroformate (Cbz-Cl) (1.25 mL, 8.76 mmol) in CH_2Cl_2 (40 mL) was added freshly distilled pyridine (0.71 mL, 8.76 mmol) over 5 min, and the mixture was stirred at room temperature for 4 h. The mixture was then washed with 1 M HCl (10 mL) and brine (10 mL). The organic layer was dried and evaporated in vacuo to afford an oil that was purified by flash chromatography (30% EtOAc in hexane) to obtain **40** as an oil (2.69 g, 98%): R_f 0.48 (30% EtOAc in hexane); $[\alpha]_D$ +16.22° (*c* 1.0 $CHCl_3$); IR ($CHCl_3$ cast) 3345, 1721, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.58−2.81 (m, 2 H), 3.72 (s, 3 H), 4.62 (m, 1 H), 4.95 (s, 1 H), 5.08−5.17 (m, 3 H), 5.48 (d, 1 H, *J* = 7.8 Hz), 7.25−7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 52.32, 52.96, 66.95, 38.69, 116.80, 128.03, 128.11, 128.18, 128.47, 129.26, 132.22, 133.24, 136.27, 140.33, 155.61, 171.75; CI MS *m/z* (NH_3) 372 (80, $[M + 1]^+$). Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.60; H, 5.49; N, 3.67; S, 8.90.

Dimethyl (2*S*,6*S*)-6-[*N*-(Benzyloxycarbonyl)amino]-2-hydroxy-4-(phenylthio)-4-heptene-1,7-dioate (42). To a dry flask under Ar containing copper trifluoromethanesulfonate (60 mg, 0.084 mmol) and (*R*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) (**41**) (61 mg, 0.084 mmol) was added dry CH_2Cl_2 (3 mL) under Ar, and the mixture was stirred for 2 h. The resulting green homogeneous solution was then treated with methyl gloxylate[28] (70 mg, 0.8 mmol) and **40** (315 mg, 0.84 mmol) in CH_2Cl_2 (1 mL) at room temperature. After 12 h, the solution was diluted by adding CH_2Cl_2 (20 mL), washed with brine (20 mL), dried, and evaporated in vacuo to give a yellow oil that was purified by flash chromatography (20% EtOAc in hexane) to give **42** as an oil (154 mg, 42%): R_f 0.22 (40% EtOAc in hexane); $[\alpha]_D$ = +82.91 (*c* 2.0 $CHCl_3$); IR ($CHCl_3$ cast) 3366, 1790, 1743, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.80−2.88 (m, 2 H), 3.78 (s, 6 H), 4.09 (d, 1 H, *J* = 6.8 Hz), 4.59 (m, 1 H), 5.11 (s, 2 H), 5.21 (dd, 1 H, *J* = 9.0, 6.2 Hz), 5.42 (d, 1 H, *J* = 9.0 Hz), 5.76 (d, 1 H, *J* = 6.2 Hz), 7.20−7.51 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 36.63, 52.40, 52.94, 53.10, 67.31, 69.22, 127.55, 128.07, 128.20, 128.30, 128.58, 129.37, 132.54, 135.98, 138.64, 155.62, 170.42, 173.89; FAB MS *m/z* (Cleland) 481 (26, $[M + Na]^+$), 460 (1, $[M + H]^+$). Anal. Calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H, 5.48; N, 3.05. Found: C, 59.60; H, 5.23; N, 2.98.

(28) (a) Hook, J. M. *Synth. Commun.* **1984**, *14*, 83−87. (b) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.

Dimethyl (2*S*,6*S*)-6-[*N*-(Benzyloxycarbonyl)amino]-2-hydroxyheptane-1,7-dioate (33) from 42. Compound **42** (150 mg, 0.327 mmol) and $NiCl_2 \cdot 6H_2O$ (0.53 g, 2.28 mmol) were dissolved in 9 mL of methanol and 3 mL of THF in a flask cooled in an ice bath with stirring. $NaBH_4$ (254 mg, 6.8 mmol) was added in portions over 15 min. The immediate formation of a black precipitate was observed, and the mixture was stirred for an additional 15 min. The precipitate was filtered through a bed of Celite, and the filtrate was evaporated to dryness in vacuo. Purification of the residue by flash chromatography (20% EtOAc in hexane) gave **33** as an oil (97 mg, 85%) with spectral and chromatographic properties in agreement with those for **33** prepared above from **32**. Conversion to DAP and NMR analysis of the corresponding Mosher amides (see Scheme 6 and below) showed an isomeric ratio 6*S*:6*R* of 94:6: $[\alpha]_D$ +37.23 (*c* = 0.5, $CHCl_3$).

Dimethyl (6*R*,2*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-6-[*N*-(*tert*-butoxycarbonyl)amino]heptane-1,7-dioate (43). To a solution of **35** (110 mg, 0.176 mmol) in 10 mL of THF was added a 1 M solution of *n*-Bu_4NF (TBAF) in THF (537 μL, 0.54 mmol). The resulting solution was stirred for 15 min and then diluted with 45 mL of Et_2O. The organic layer was washed with water (4 × 20 mL) followed by 15 mL of saturated aqueous $NaHCO_3$, dried, and concentrated *in vacuo*. The residue was purified by flash chromatography (50% EtOAc in hexane) to give **43** (78 mg, quantitative) as an oil: R_f 0.55 (50% EtOAc in hexane); $[\alpha]_D$ +5.45 (*c* = 0.5, $CHCl_3$); IR ($CHCl_3$ cast) 3348, 1741, 1716, 1521 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.70−2.15 (m, 15 H), 1.41 (s, 9 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 4.22−4.42 (m, 2 H), 5.09 (s, 2 H), 5.35 (m, 1 H), 7.27−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.17, 28.28, 31.90, 32.31, 52.27, 53.55, 67.06, 67.51, 79.99, 127.75, 128.16, 128.51, 136.21, 155.10, 172.79, 173.03; CI MS *m/z* (NH_3) 470 (51, $[M + 18]^+$), 453 (17, $[M + 1]^+$). Anal. Calcd for $C_{22}H_{32}N_2O_8$: C, 58.40; H, 7.13; N, 6.19. Found C, 58.00; H, 7.15; N, 6.13.

(2*S*,6*R*)-2-[*N*-(Benzyloxycarbonyl)amino]-6-[*N*-(*tert*-butoxycarbonyl)amino]-heptane-1,7-dioic Acid (44). A mixture of **43** (70 mg, 0.153 mmol) and 10% aqueous NaOH (340 μL, 0.82 mmol) was stirred vigorously for 4 h and then diluted with water (2 mL) and CH_3CN (3 mL). After an additional 14 h of stirring, the mixture was diluted with water (4 mL), washed with EtOAc (4 mL), acidified to pH 1 with 2 M HCl, and extracted with EtOAc (3 × 20 mL). The combined extracts were dried and evaporated in vacuo to give **44** (60 mg, 94%): IR ($CHCl_3$ cast) 3348, 1747, 1716, 1528 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.15−1.57 (m, 11 H), 1.41 (s, 9 H), 1.62−1.87 (m, 4 H), 4.21−4.44 (m, 4 H), 5.11 (s, 2 H), 7.28−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.17, 28.29, 31.90, 32.31, 52.85, 53.55, 57.06, 79.99, 127.76, 128.17, 128.51, 136.22, 153.50, 153.92, 172.79, 173.04; CI MS *m/z* (NH_3) 442 (92, $[M + 18]^+$), 425 (30, $[M + 1]^+$).

***meso*-Diaminopimelic Acid (1a) from 44.** To a solution of **44** (14 mg, 0.033 mmol) in methanol (15 mL) and glacial AcOH (1 mL) was added 10% Pd/C (10 mg). The suspension was stirred under 1 atm of H_2 for 14 h and then filtered through cotton wool. The filtrate was evaporated in vacuo to give a powder, to which was added a mixture of CF_3CO_2H (15 mL) and CH_2Cl_2 (15 mL). The resulting solution was stirred at room temperature for 15 min and then evaporated in vacuo. The residue was purified by ion-exchange chromatography (AG50W × 8, H^+ form, 5 mL), eluting with H_2O and 2% to 10% aqueous NH_4OH to give pure **1a** (3.9 mg, 64%) with chromatographic and spectral properties in agreement with those of a reference sample of *meso*-DAP obtained by classical resolution-separation procedures.[17]

Analysis of Diastereomeric Excess of DAP Isomers 1a, 1b, and 1c. In a typical procedure, to a saturated aqueous $NaHCO_3$ (2 mL) solution of **1a** (2.8 mg, 0.015 mmol) was added (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (11 mg, 0.033 mmol). After being stirred at room temperature for 1 h, the aqueous solution was washed with EtOAc (1 mL), acidified to pH 2 by adding 2 M HCl, and extracted with EtOAc (5 × 10 mL). The extracts were dried and evaporated in vacuo to give a residue that was purified by HPLC (the Mosher amides of different DAP isomers do not separate under these

conditions): (BioRad Model 400 system; solid phase−C_{18} Resolve 10 μm, two 8 mm × 10 cm columns in tandem; solvent A: 0.1% CF_3CO_2H in H_2O; solvent B: CH_3CN; method: gradient 5%-70% in 35 min, at 1 mL/min, detection at 254 nM; retention time: 27.71 min). ^{1}H NMR ($CDCl_3$, 500 MHz) analysis of the methoxy region allowed discrimination between all DAP isomers and provided the isomeric ratios of DAP synthesized by the various procedures.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1a**, **7**, **12**, **14**, **27**−**29**, **39**, and **44** (13 pages). This material is contained in 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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