An Efficient Synthesis of (2*S*,6*S*)- and *meso*-Diaminopimelic Acids via Asymmetric Hydrogenation

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Abstract: An efficient synthesis of the title compounds **1** and **2** has been successfully developed. The key step is the asymmetric hydrogenation of dehydroamino acid **7** using [Rh(I)(COD)-(*S*,*S*) or -(*R*,*R*)-Et-DuPHOS)]$^+$OTf$^-$ to produce the optically active, protected amino acid derivatives in high ee (>95%). The approach also can be used for the synthesis of other isomers and analogues.

Key words: amino acids, diaminopimelic acids, asymmetric hydrogenation, DuPHOS, DAP analogues

(2*S*,6*S*)-Diaminopimelic acid (DAP, **1**) (Figure) plays an important role in bacterial α-amino acid biosynthesis.[1,2] It is epimerized by LL-DAP epimerase to form *meso*-(2*S*,6*R*)-diaminopimelic acid (**2**) (*meso*-DAP, **2**), which is then stereoselectively decarboxylated at its (*R*)-stereogenic center by *meso*-DAP decarboxylase to afford the essential amino acid L-lysine.[3] In addition, *meso*-DAP (**2**) serves as a cross-linking constituent of many Gram negative and some Gram positive bacterial peptidoglycans.[4] Since mammals do not have the DAP biosynthetic pathway and require dietary intake of L-lysine, the inhibitors of the crucial biochemical pathway are potential antimicrobial and herbicidal agents with low toxicity.[1] Therefore, in recent years, the design and synthesis of DAP (**1**), *meso*-DAP (**2**), and their analogues has received considerable interest.[5–13] However, efficient methods are still needed to provide facile access to stereochemically pure DAPs and their derivatives.
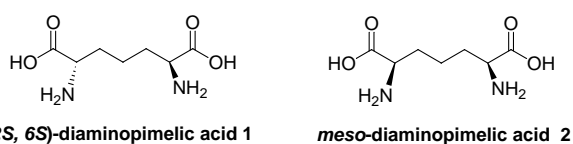

(2*S*, 6*S*)-diaminopimelic acid 1　　　*meso*-**diaminopimelic acid 2**

Figure　Chemical structures of **DAP 1** and *meso*-**DAP 2**

Our group has a long standing interest in the design and synthesis of novel unnatural amino acids.[14–23] We have demonstrated that the incorporation of these novel unnatural amino acids into biologically active peptides and peptidomimetics can significantly improve the potency and selectivities for their receptors.[14,15,24–27] Recently we have developed a convenient method for the synthesis of β-turn

mimetic indolizidinone amino acids using asymmetric hydrogenations of dehydroamino acids with Burk's catalyst, [Rh(I)(COD)-(*S*,*S*) or -(*R*,*R*)-Et-DuPHOS)]$^+$OTf$^-$,[28–31] in high stereoselectivity. It should be noted that Hiebl and coworkers have developed an efficient approach to the enantioselective synthesis of bis-amino acids using similar methods.[32] In this approach, many bis-amino acids with different lengths from readily available dialdehydes were synthesized in high optical purity (100% ee, ≥98.5% de). Unfortunately the method is limited to the preparation of (*S*,*S*)- or (*R*,*R*)-bis-amino acids. Herein we have employed this method for the synthesis of (2*S*,6*S*)-DAP (**1**) and *meso*-(2*S*,6*R*)-DAP (**2**). Furthermore, our method is a flexible, stereoselective route for the synthesis of DAPs with orthogonal protecting groups, allowing for the synthesis of their analogues.

The synthesis starts from commercially available α-Boc-glutamic acid α-*tert*-butyl ester **3** (Scheme 1). Esterification of the free γ carboxyl group in **3** was carried out using dicyclohexylcarbodiimide (DCC) as an activating agent with methanol in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) and triethylamine (TEA) in 70% yield (Scheme 1). The direct reduction of the methyl ester in **4** using diisobutylaluminum hydride (DIBAL) at –78 °C to the corresponding aldehyde gave a complex mixture, which was difficult to purify, presumably due to the interference of nitrogen.[33] Therefore, a second Boc protecting group was introduced by reaction of **4** with di-*tert*-butyldicarbonate [(Boc)$_2$O] in the presence of a catalytic amount of DMAP in acetonitrile to give the bis-Boc protected methyl ester **5** in 89% yield as an oil after chromatography. Then the methyl ester in **5** was reduced to aldehyde **6** {[α]$_D^{29}$ –24.0 (*c* = 1.34, CHCl$_3$), Lit.[33] [α]$_D^{29}$ –23.1 (*c* = 0.805, CHCl$_3$)} in excellent yield (91%) using DIBAL in anhydrous diethyl ether at –78 °C for about 15 minutes.[33] Horner–Emmons olefination of the resulting aldehyde **6** with phosphonate (MeO)$_2$P(O)CH(NH-Cbz)CO$_2$Me (Cbz: benzyloxycarbonyl) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave the dehydroamino acid **7** with *Z*-configuration as the major product (*Z/E* = >95:5).[34] Asymmetric hydrogenation of isolated *Z*-dehydroamino acid **7** using [Rh(I)(COD)-(*S*,*S*)-Et-DuPHOS)]$^+$OTf$^-$ and [Rh(I)(COD)-(*R*,*R*)-Et-DuPHOS)]$^+$OTf$^-$ afforded **8** and **9** in 88 and 94% yields, respectively.[28] It should be noted that compounds **8** and **9** have different protecting groups on the two amino (Boc and Cbz) and carboxyl (methyl and *t*-butyl) functions. These protecting groups can be selectively cleaved for the prepara-

tion of DAP derivatives. The new absolute configurations were assigned as *S* in **8** and *R* in **9** based on the selectivity of the (*S,S*)-Et-DuPHOS and (*R,R*)-Et-DuPHOS ligands, respectively.[28]

To determine the optical purity of **8** and **9** (Scheme 2), the Cbz protecting groups were cleaved by Pd-catalyzed hydrogenations. The resulting free amino groups were coupled with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's agent) using DCC and HOBt (1-hydroxybenzotriazole) as coupling activating agents in the presence of TEA and a catalytic amount of DMAP in CH$_2$Cl$_2$.[35] The two Mosher's amide derivatives **10** and **11** were characterized by both ^{1}H and ^{19}F NMR spectra, which showed a single isomer for both. Therefore the optical purity in both cases is more than 95% ee. Removal of the protecting groups in **8** and **9** was readily accomplished by refluxing with 30% HBr in AcOH and PhOH to give

crude products which were purified by ion-exchange chromatography affording **1** and **2** in 53 and 62% yields, respectively. Under the reaction conditions no racemization was observed by comparison of the optical rotation of **1** {[α]$_D^{25}$ +41.4 (*c* = 0.98, 1 N HCl)} with literature values {Lit.[12] [α]$_D^{23}$ +42.7 (*c* = 1.1, 1 N HCl)}.

In summary, we have successfully developed an efficient method for the asymmetric synthesis of DAP (**1**) and *meso*-DAP (**2**) from the readily prepared didehyroamino acid **7** which underwent asymmetric hydrogenations with Burk's catalysts in high ee and overall chemical yields. This method is a flexible, stereoselective route for the synthesis of DAPs with orthogonal protecting groups. This synthetic approach can be used not only to prepare these compounds, but also the other isomers of DAPs and their analogues.
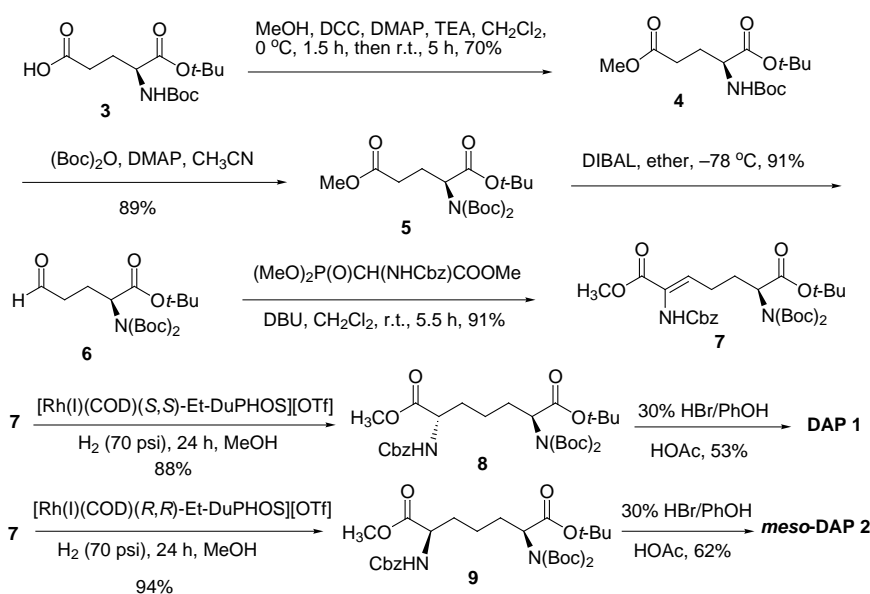
Scheme 1
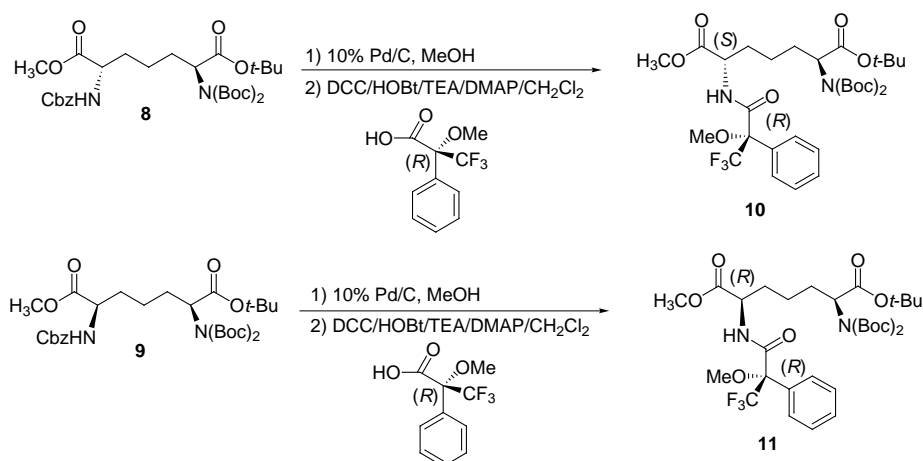
Scheme 2

^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer. The chemical shifts were expressed in ppm (δ) downfield from tetramethylsilane as an internal standard. Mass spectral analyses were conducted by the Department of Chemistry, University of Arizona Mass Spectrum Laboratory. Optical rotations were measured on a Jacso P1020 polarimeter. Column chromatography was performed with 200–400 mesh size silica gel purchased from Aldrich Chemical Co. TLC was performed with Kodak F-254 silica gel plates. CH_2Cl_2 was distilled from CaH_2 and THF from Na and benzophenone ketyl under a N_2 atmosphere. All other chemicals were purchased from Aldrich Chemical Co. or Bachem Bioscience, Inc. and used as received. All new compounds were characterized by ^{1}H and ^{13}C NMR, and by high-resolution mass spectroscopy (HRMS).

(S)-(–)-1-*tert*-Butyl-5-methyl-[(2-*tert*-butoxycarbonyl)-amino]-pentanedioate (4)

To a solution of **3** (2.424 g, 8 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon was added DCC (2.14 g, 10.4 mmol). After 3–4 min at 0 °C, MeOH (0.65 mL, 16 mmol), Et_3N (1.45 mL, 10.4 mmol) and DMAP (0.1 g, 0.8 mmol) were added to the above mixture. After the reaction was stirred for 1.5 h at 0 °C and 5 h at r.t., the white solid was removed by filtration. The solution was concentrated under reduced pressure. The residue was redissolved in EtOAc (180 mL), then the organic solution was washed with 1 N HCl (35 mL), aq sat. $NaHCO_3$ (35 mL) and brine (35 mL), dried ($MgSO_4$) and concentrated to give an oil. The purification of the crude product by flash column chromatography, eluting with EtOAc–hexanes (1:8 then 1:6) afforded **4** (1.78g, 70%) as a clear oil. The data for compound **4** are similar to those reported in the literature;[33] $[\alpha]^{25}_D$ –28.5 (c = 1.14, MeOH) {Lit.[33] $[\alpha]^{20}_D$ –28.2 (c = 1.52, MeOH)}.

^{1}H NMR (CDCl_3): δ = 1.44 (s, 9 H), 1.47 (s, 9 H), 1.85–1.98 (m, 1 H), 2.14–2.18 (m, 1 H), 2.23–2.49 (m, 2 H), 3.68 (s, 3 H), 4.20 (m, 1 H), 5.08 (d, J = 8.1 Hz, 1 H).

(S)-(–)-1-*tert*-Butyl-5-methyl-2-[bis(*tert*-butoxycarbonyl)-amino]pentanedioate (5)

DMAP (0.132 g, 1.085 mmol) was added to a solution of **4** (1.72 g, 5.43 mmol) in MeCN (20 mL) under N_2. To this mixture, a solution of di-*tert*-butyl dicarbonate (2.368 g, 10.85 mmol) in MeCN (10 mL) was added dropwise via a syringe pump over 20 min, and the mixture was stirred for 18 h at r.t. The solvent was removed on a rotary evaporator under reduced pressure and the residue was further dried using an oil pump. The crude product was purified by flash column chromatography (EtOAc–hexanes, 1:10) to afford 2.00 g of **5** in 89% yield as a colorless oil. The data for compound **5** are similar to those reported in the literature;[33] $[\alpha]^{25}_D$ –23.8 (c = 0.87, MeOH) {Lit.[33] $[\alpha]^{20}_D$ –24.5 (c = 1.46, MeOH)}.

^{1}H NMR (CDCl_3): δ = 1.45 (s, 9 H), 1.50 (s, 18 H), 2.12–2.21 (m, 1 H), 2.36–2.46 (m, 3 H), 3.67 (s, 3 H), 4.67–4.81 (m, 1 H).

(S)-(–)-1-*tert*-Butyl-2-[bis(*tert*-butoxycarbonyl)amino]-5-oxo-pentanoate (6)

DIBAL (1.0 M in hexanes, 5.2 mL, 5.2 mmol) was added dropwise to a –78 °C cooled solution of **5** (1.97 g, 4.72 mmol) in anhyd Et_2O (60 mL) under argon over 3 min. The mixture was stirred for 15 min, then quenched with H_2O (1.2 mL) and allowed to warm to r.t. The resulting white thick suspension was filtered through Celite and washed with Et_2O (3 × 35 mL). The filtrate was concentrated and the remaining trace amount of H_2O was removed azeotropically using toluene (2 × 35 mL) on a rotary evaporator. The residue was purified by flash column chromatography (EtOAc–hexanes, 1:10) to afford 1.664 g of **6** in 91% yield as a clear oil. The data of compound **6** are similar to those reported in the literature;[33] $[\alpha]^{29}_D$ –24.0 (c = 1.34, CHCl_3) {Lit.[33] $[\alpha]^{20}_D$ –23.1 (c = 1.52, CHCl_3)}.

^{1}H NMR (CDCl_3): δ = 1.45 (s, 9 H), 1.51 (s, 18 H), 2.05–2.18 (m, 1 H), 2.40–2.59 (m, 3 H), 4.74 (dd, J = 9.6, 5.2 Hz, 1 H), 9.77 (s, 1 H).

tert-Butyl (2S)-[Bis(*tert*-butoxycarbonyl)amino]-(6Z)-[(benzyl-oxycarbonyl)amino]-7-(methoxycarbonyl)hept-5-enoate (7)

To a solution of 2-(benzyloxycarbonyl)amino-2-(dimethyloxyphosphoryl)acetate (1.165 g, 3.52 mmol) in anhyd CH_2Cl_2 (8 mL) was added DBU (0.48 mL, 3.22 mmol) at r.t. under argon. After 10 min, a solution of **6** (1.134 g, 2.93 mmol) in anhyd CH_2Cl_2 (10 mL) was added to the above mixture. After stirring at r.t. for 5.5 h, the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (120 mL), the EtOAc layer was washed with aq 5% citric acid solution (2 × 30 mL) and brine (35 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give an oil. The crude compound was purified by flash column chromatography (EtOAc–hexanes, 1:8 then 1:6) to afford **7** (Z-isomer, 1.591 g, 91%) as an oil; $[\alpha]^{25}_D$ –13.7 (c = 1.094, CHCl_3).

^{1}H NMR (CDCl_3): δ = 1.43 (s, 9 H), 1.49 (s, 18 H), 1.97–2.01 (m, 1 H), 2.18–2.35 (m, 3 H), 3.74 (s, 3 H), 4.62 (dd, J = 4.2, 9.9 Hz, 1 H), 5.13 (dd, J = 12.3, 13.5 Hz, 2 H), 6.57 (m, 2 H), 7.30–7.37 (m, 5 H).

^{13}C NMR (CDCl_3): δ = 25.4, 27.8, 28.1, 28.2, 52.5, 58.6, 65.7, 81.6, 83.8, 118.4, 128.4, 128.7, 129.6, 136.3, 136.7, 152.9, 154.5, 165.2, 169.6.

HRMS (FAB): m/z calcd for $C_{30}H_{45}N_2O_{10}$ 593.3074. Found 593.3085.

tert-Butyl (2S)-[Bis(*tert*-butoxycarbonyl)amino]-(6S)-[(benzyl-oxycarbonyl)amino]-7-(methoxycarbonyl)heptanoate (8)

A solution of **7** (550 mg, 0.92 mmol) in HPLC grade MeOH (15 mL) was purged with argon for 30 min, then (S,S)-Et-DuPHOS-based catalyst (1.3 mg, 0.00185 mmol) was added. After 5 vacuum/ H_2 cycles, the reaction bottle was pressurized to an initial pressure of 70 psig. After 24 h, the solvent was evaporated. The residue was passed through a short silica gel column, eluting with CH_2Cl_2– EtOAc (4:1) to give **8** (468 mg, 88%) as a clear oil; $[\alpha]^{25}_D$ –14.0 (c = 1.05, CHCl_3).

^{1}H NMR (CDCl_3): δ = 1.32–1.55 (m, 2 H), 1.44 (s, 9 H), 1.49 (s, 18 H), 1.71–1.92 (m, 3 H), 1.96–2.09 (m, 1 H), 3.74 (s, 3 H), 4.34 (dd, J = 7.8, 12.6 Hz, 1 H), 4.66 (dd, J = 5.1, 9.6 Hz, 1 H), 5.09 (s, 2 H), 5.30 (br s, 1 H), 7.28–7.41 (m, 5 H).

^{13}C NMR (CDCl_3): δ = 22.3, 28.1, 28.2, 28.9, 32.1, 52.6, 54.1, 58.5, 67.2, 81.5, 83.1, 128.0, 128.3, 128.7, 136.4, 152.7, 156.1, 169.8, 173.1.

HRMS (FAB): m/z calcd for $C_{30}H_{47}N_2O_{10}$ 595.3231. Found 595.3223.

tert-Butyl (2S)-[Bis(*tert*-butoxycarbonyl)amino]-(6R)-[(benzyl-oxycarbonyl)amino]-7-(methoxycarbonyl)heptanoate (9)

In a similar manner to the synthesis of **8**, compound **7** (800 mg, 1.34 mmol) was hydrogenated with (R,R)-Et-DuPHOS to give **9** (754 mg, 94%) as a clear oil; $[\alpha]^{25}_D$ –25.8 (c = 1.195, CHCl_3).

^{1}H NMR (CDCl_3): δ = 1.33–1.56 (m, 2 H), 1.44 (s, 9 H), 1.49 (s, 18 H), 1.62–1.74 (m, 1 H), 1.83–1.92 (m, 2 H), 1.99–2.11 (m, 1 H), 3.74 (s, 3 H), 4.34 (dd, J = 7.8, 12.6 Hz, 1 H), 4.66 (dd, J = 5.1, 9.6 Hz, 1 H), 5.09 (s, 2 H), 5.30 (br s, 1 H), 7.28–7.41 (m, 5 H).

^{13}C NMR (CDCl_3): δ = 22.2, 28.1, 28.2, 29.0, 32.3, 52.5, 53.9, 58.7, 67.2, 81.4, 83.0, 127.9, 128.3, 128.7, 136.4, 152.7, 156.1, 169.8, 173.0.

HRMS (FAB): m/z calcd for $C_{30}H_{47}N_2O_{10}$ 595.3231. Found 595.3228.

Methyl (2S)-{[(R)-(+)-α-Methoxyl-α-trifluoromethylphenyl-acetyl]amino}-(6S)-[bis(*tert*-butoxycarbonyl)amino]-7-(tert-butoxycarbonyl)heptanoate (10)

Compound **8** (140 mg, 0.23 mmol) in MeOH (8 mL) and in the presence of 10% Pd/C (20 mg) was hydrogenated for 1.5 h at an initial pressure of 58 psi. After removal of the catalyst by filtration, the so-

lution was concentrated by rotary evaporation under reduced pressure. The residue was used directly without purification for the preparation of Mosher's amide derivative.

To a solution of (*R*)-(+)-α-methoxy-α-trifluorophenylacetic acid (61 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added DCC (58 mg, 0.28 mmol). After 2–3 min, HOBt (48 mg, 0.35 mmol) was added. The mixture was stirred for ca. 15 min, followed by addition of the above amine, Et_3N (49 μL, 0.35 mmol) and DMAP (6 mg, 0.047 mmol). After stirring at 0 °C for 1.5 h and at r.t. for 15 h, the white solid was filtered off. The solvent was removed to give an oil. The oil was dissolved in EtOAc (60 mL) and the EtOAc layer was washed with 1 N HCl (20 mL), aq sat. $NaHCO_3$ (20 mL) and brine (20 mL), and dried ($MgSO_4$). Concentration of the EtOAc solution under reduced pressure gave an oil, which was purified by flash chromatography, eluting with EtOAc–hexanes (1:8) to provide **10** as a clear oil (112 mg, 70%); $[\alpha]^{25}_D$ –19.2 (*c* = 0.96, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.34–1.57 (m, 2 H), 1.44 (s, 9 H), 1.51 (s, 18 H), 1.75–2.12 (m, 4 H), 3.37 (br s, 3 H), 3.73 (s, 3 H), 4.62 (dd, *J* = 2.7, 7.8 Hz, 1 H), 4.68 (dd, *J* = 5.1, 9.6 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 1 H), 7.38–7.42 (m, 3 H). 7.53–7.56 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 22.4, 28.1, 28.2, 29.0, 31.8, 52.4, 52.6, 55.1, 58.7, 81.4, 83.0, 84.3 (q, $J_{C,F}$ = 26.1 Hz), 124.0 (q, $J_{C,F}$ = 287.4 Hz), 128.2, 128.7, 129.7, 132.1, 152.7, 166.3, 169.8, 172.3.

^{19}F NMR ($CDCl_3$/$CFCl_3$): δ = –70.21.

HRMS (FAB): *m/z* calcd for $C_{32}H_{48}F_3N_2O_{10}$ 677.3261. Found 677.3267.

Methyl (2*R*)-{[(*R*)-(+)-α-Methoxyl-α-trifluoromethylphenyl-acetyl]amino}-(6*S*)-[bis(*tert*-butoxycarbonyl)amino]-7-(*tert*-butoxycarbonyl)heptanoate (11)

In a similar manner to the synthesis of **10**, compound **9** (215 mg, 0.36 mmol) gave **11** (159 mg, 65%) as a clear oil; $[\alpha]^{25}_D$ –11.6 (*c* = 1.09, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.20–1.34 (m, 2 H), 1.44 (s, 9 H), 1.49 (s, 18 H), 1.61–2.08 (m, 4 H), 3.51 (s, 3 H), 3.75 (s, 3 H), 4.59–4.66 (m, 2 H), 7.12 (d, *J* = 8.1 Hz, 1 H), 7.40–7.45 (m, 3 H), 7.53–7.56 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 22.5, 28.1, 28.2, 29.1, 32.0, 52.2, 52.7, 55.4, 58.7, 81.5, 83.0, 84.1 (q, $J_{C,F}$ = 26.0 Hz), 123.8 (q, $J_{C,F}$ = 288.4 Hz), 127.6, 128.8, 129.7, 132.9, 152.6, 166.5, 169.7, 172.3.

^{19}F NMR ($CDCl_3$/$CFCl_3$): δ = –69.96.

HRMS (FAB): *m/z* calcd for $C_{32}H_{48}F_3N_2O_{10}$ 677.3261. Found 677.3270.

(2*S*, 6*S*)-(+)-Diaminopimelic Acid (1)

A mixture of **8** (260 mg, 0.44 mmol) in 30% HBr in AcOH (15 mL) and phenol (70 mg) was refluxed for 15 h. The mixture was cooled to 0 °C with an ice bath, and was washed with Et_2O (20 mL). The solution was concentrated to ca. 2 mL, and then was loaded on to a Dowex ion-exchange resin and eluted with H_2O (90 mL) followed by aq 10% NH_4OH solution (250 mL) to give 41 mg (53%) of **1**; $[\alpha]^{25}_D$ +41.4 (*c* = 0.98, 1 N HCl) {Lit.^{12} $[\alpha]^{23}_D$ +42.7 (*c* = 1.1, 1 N HCl)}.

^{1}H NMR (D_2O): δ = 1.24–1.33 (m, 2 H), 1.52–1.80 (m, 4 H), 3.52–3.61 (m, 2 H).

meso-(2*S*, 6*R*)-Diaminopimelic Acid (2)

In a similar manner as for the synthesis of **1**, compound **9** (340 mg, 0.57 mmol) in 30% HBr in AcOH and phenol (91 mg) gave **2** (62 mg, 62%) after purification.^{12}

^{1}H NMR (D_2O): δ = 1.33–1.54 (m, 2 H), 1.71–1.90 (m, 4 H), 3.88–3.92 (m, 2 H).

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