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Synthesis of (*R*)-3,4-Diaminobutanoic Acid by Desymmetrization of Dimethyl 3-(Benzylamino)glutarate through Enzymatic Ammonolysis

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Abstract: Lipase B from *Candida antarctica* is shown to be a highly efficient catalyst for the desymmetrization of dimethyl 3-(benzylamino)glutarate (**1**) through aminolysis and ammonolysis reactions. Using this procedure, enantiopure monoamides are obtained in high yield. The synthetic value of these compounds is demonstrated by the preparation of an enantiopure nonnatural amino acid, i.e. (*R*)-3,4-diaminobutanoic acid [(+)-**12**].

The enzymatic desymmetrization of meso and prochiral compounds has been widely recognized and constitutes an elegant approach to the synthesis of enantiomerically pure compounds.[1] This methodology avoids the inherent 50% yield limit and the difficult separations often encountered in the resolution of racemates. The desymmetrization strategy has been successfully utilized in the synthesis of biologically active compounds, such as pharmaceuticals, pesticides, flavors, and fragrances.[1]

Hydrolysis, transesterification, or lactonization processes have been largely applied to prochiral diesters and diols to prepare chiral synthons of high optical purity.[1,2] However, the potential of enzymes, especially lipases, to catalyze the aminolysis and ammonolysis of prochiral substrates has been recently reported by us.[3] Lipase B from *Candida antarctica* (CALB) has been shown to catalyze the aminolysis and ammonolysis of dimethyl 3-hydroxyglutarate. The ammonolysis product is a useful starting material for the synthesis of (*R*)-4-amino-3-hydroxybutanoic acid [(*R*)-GABOB].[3a]

Following on from these studies, we set out to examine the aminolysis and ammonolysis of dimethyl 3-(benzylamino)glutarate (**1**). This substrate was chosen in view of potential further applications of the resulting products. Chiral derivatives of **1** are valuable substrates for the synthesis of biologically active compounds, for example (*R*)- and (*S*)-3-aminoglutaric acid monoalkyl esters are starting materials in the synthesis of 4-substituted-2-azetidinones,[4] (+)-Negamycin,[5] and various *cis*- and *trans*-Carbapenem antibiotics.[6,7] Moreover, products derived from the aminolysis and ammonolysis of **1** could serve as versatile chiral synthons of biologically active amino acids and amino alcohols. To illustrate the synthetic value of these compounds, we also introduce herein a new chemoenzymatic method for the synthesis of (*R*)-3,4-diaminobutanoic acid [(+)-**12**] starting with amido ester (−)-**3c** obtained through ammonolysis of **1**. Optically active 4-aminobutanoic acid (GABA) analogues, such as (*R*)-GABOB, (*R*)-baclofen (4-*p*-chlorophenyl-GABA), and (*R*)-4-phenyl-GABA, are used clinically for different purposes.[8] These observations support that (*R*)-3,4-diaminobutanoic acid could be of interest not only as a chiral building block but also as a nonnatural amino acid itself.

Starting material **1** was prepared by a Michael-type addition of benzylamine to dimethyl glutaconate. We chose CALB as the biocatalyst, since it has exhibited high efficiency in both the desymmetrization of dimethyl 3-hydroxyglutarate[3] and the resolution of chiral esters[9] as well as chiral monoamines and diamines[10] through aminolysis and ammonolysis processes. The enzymatic reactions were run in dry 1,4-dioxane, which is known to be a good solvent for this type of transformation, using an equimolar amount of diester **1** and amines **2a** and **2b**,

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SCHEME 1

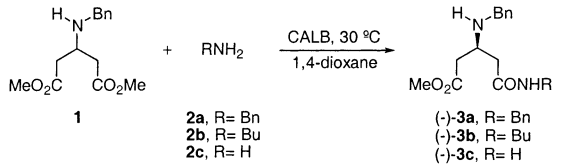


TABLE 1. CALB "Novozym 435"-Catalyzed Aminolysis and Ammonolysis of 1

product	R	time (days)	yield (%)[a]	$[\alpha]^{20}_D$	ee (%)[b]
(−)-**3a**	Bn	2	92	−14.5 (*c* 1.1, $CHCl_3$)	>99
(−)-**3b**	Bu	2	79	−14.2 (*c* 1.0, $CHCl_3$)	>99
(−)-**3c**	H	3	85	−11.5 (*c* 1.0, $CHCl_3$)	>99

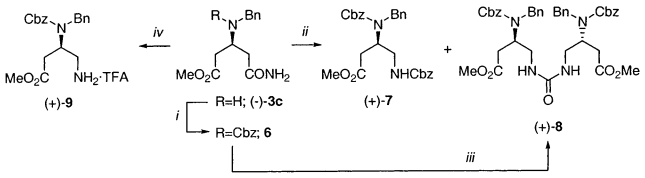
[a] After column chromatography. [b] Determined by chiral HPLC.

or a freshly prepared solution of ammonia at 30 °C (Scheme 1) until the conversion reached its maximum (as seen by ^{1}H NMR). With these conditions in hand, three different CALB preparations, namely "Chirazyme L-2, c-f, lyo", "Chirazyme L-2, c-f, C3, lyo", and CALB "Novozym 435" were tested, of which the latter turned out to be the best catalyst for the asymmetric aminolysis and ammonolysis of **1** giving enantiopure monoamides (−)-**3a**−**c** in high yield (Table 1). The smooth differences in yields are due to different percent conversion depending on the nucleophile. In all cases, the reaction stopped at the stage of the amido ester and diamides were not detected.

Independent of the nucleophile used, CALB "Novozym 435" only reacted with the *pro-R* ester group of **1**, yielding amido esters **3** with the *S* configuration. In the case of (−)-**3c**, the absolute stereochemistry was determined by its transformation into amino acid (+)-**12**, whose specific rotation matched the literature value of (*R*)-(+)-**12**.[11] The absolute configuration of the enzymatically prepared amido esters (−)-**3a,b** has been tentatively assigned on the basis of three convergent criteria: (a) the enantiotopic preference displayed by CALB in the aminolysis and ammonolysis of dimethyl 3-hydroxyglutarate,[3] as well as in the ammonolysis of **1** (vide supra); (b) using Mosher's method for primary amines[12] (compounds (−)-**3a**,**b** and (±)-**3a,b** were first *N*-deprotected using HCO_2H/Pd-black in MeOH), the MTPA amides derived from compounds (±)-**3a,b** showed two well-resolved peaks for the methyl ester group in their ^{1}H NMR spectra, whereas the MTPA amides derived from products (−)-**3a,b** showed only the high-field signal; and (c) when eluted from a chiral column, "Chiralcel OD-H", the enantiomer obtained through enzyme catalysis, exhibited the longer retention time in all cases (see the Experimental Section).

The synthesis of (*R*)-3,4-diaminobutanoic acid (+)-**12** from compound (−)-**3c** involved a Hofmann rearrangement of the amide function as the key step. After surveying the literature, we decided to use polyvalent iodoorganic compounds[8i,13] to promote the rearrangement. These reagents have several advantages, e.g. mild reaction conditions, facile product isolation, high yields, and avoidance of the use of heavy metal-based reagents, which are frequently used to carry out the rearrangement.[3a]

SCHEME 2[a]



[a] Reagents and conditions: (i) CbzCl, Na_2CO_3, H_2O, DCM, 86%; (ii) PIDA, BnOH, THF, rt, 61% **7**; (iii) PIDA, H_2O, THF, rt, 86%; (iv) PIFA, H_2O, MeCN, rt, 100%.

First, amido ester (−)-**3c** was protected with benzyl chloroformate (Scheme 2) to eliminate the posibility of an intramolecular nucleophilic addition of the amine functionality to the isocyanate, which would give rise to a cyclic urea. Reaction of (−)-**6** with *I*,*I*-bis(acetoxy)-iodobenzene (PIDA) in THF in the presence of benzyl alcohol led to a mixture of benzyl carbamate (+)-**7** (61%) and chiral urea (+)-**8** (accounting for the mass balance). This byproduct is obtained when the intermediate isocyanate and the amine that is subsequently formed from it react under catalysis of the acetic acid liberated from PIDA. Substituted ureas have received considerable attention due to their wide range of applications, including the use as herbicides, corrossion inhibitors, artificial receptors, antioxidants in gasoline, and pharmaceuticals.[14] Encouraged by this, we tried to obtain compound (+)-**8** as the main product replacing benzyl alcohol with an equimolar amount of water. Under these conditions, we were able to prepare the C_2 symmetric urea in 86% yield. Coming back to our initial goal, we tested some other conditions, this time, in an attempt to decrease the yield of (+)-**8**. However, formation of the urea seems to be highly favored in the presence of acetic acid. Hence, we considered changing the iodoorganic compound to *I*,*I*-bis(trifluoroacetoxy)iodobenzene (PIFA). The solvent effect on the yield of reactions with this reagent has been studied by Longqin Hu et al., finding that acetonitrile is the solvent of choice.[13d] Thus, we carried out the reaction with PIFA in acetonitrile which afforded product (+)-**9** in quantitave yield. The trifluoroacetic acid released during the course of the reaction can both catalyze the attack of water onto the isocyanate and protonate the resulting amine, thereby preventing it from participating in the formation of the urea.

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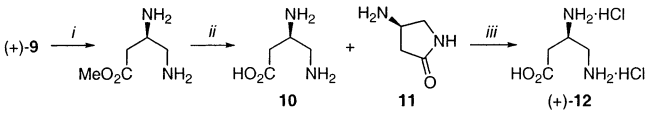
SCHEME 3[a]



[a] Reagents and conditions: (i) HCOOH, "Pd-black", MeOH; (ii) MeOH, 1 M NaOH, rt; (iii) 6M HCl, 85 °C. 74% over 3 steps.

Hydrogenation and subsequent hydrolysis of rearranged product (+)-**9** led to a mixture of diamino acid **10** and γ-lactam **11** (Scheme 3). When this residue was treated with 6 M hydrochloric acid at 85 °C for 12 h, the γ-lactam was converted into the desired amino acid, which was isolated as its dihydrochloride salt (+)-**12**.

In summary, the desymmetrization of dimethyl 3-(benzylamino)glutarate by enzymatic aminolysis and ammonolysis has been accomplished using lipase B from *Candida antarctica* as the biocatalyst. This procedure gives access to valuable enantiopure polyfunctionalized synthons in high yield. Hofmann rearragement of the ammonolysis product allows the preparation of an optically pure C_2 symmetric urea and a novel chemoenzymatic synthesis of (*R*)-3,4-diaminobutanoic acid.

Experimental Section

General. Lipase B from *Candida antarctica* (CALB) "Novozym 435" was donated by Novo Nordisk Co. and the preparations "Chirazyme L-2, c-f, lyo" and "Chirazyme L-2, c-f, C3, lyo" were obtained from Roche Diagnostics. All reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran and 1,4-dioxane were freshly distilled from sodium and benzophenone ketyl under nitrogen atmosphere. Methanol and acetonitrile were dried by distillation from calcium hydride under nitrogen atmosphere. Thin layer chromatography was performed on aluminum plates coated with Merck silica gel $60F_{254}$. Column chromatography was carried out on Merk silica gel 60/230−400 mesh at increased pressure (hand-held bellows). Melting points are uncorrected. Chemical shifts are quoted in ppm on the scale using tetramethylsilane as internal standard. Coupling constants are given in hertz. Mass spectra were recorded using electrospray ionization. The enantiomeric excess was determined by chiral HPLC analysis using a "Chiralcel OD-H" column.

Dimethyl 3-(Benzylamino)glutarate (1). Benzylamine (15 mmol) was added to dimethyl glutaconate (15 mmol) under nitrogen and the reaction mixture was stirred at room temperature for 3 days. The crude residue was purified by column chromatography on neutral silica gel using DCM as the eluent affording the title compound as a colorless oil in 68% yield: IR (neat) 3350, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.95 (br s, 1H, NH), 2.60 (d, J = 6.2 Hz, 4H), 3.40−3.52 (m, 1H), 3.69 (s, 6H), 3.82 (s, 2H), 7.20−7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.3, 50.6, 50.9, 51.4, 126.8, 127.9, 128.2, 139.7, 172.0; MS (%) *m*/*z* 288 [(M + Na)$^+$, 25], 266 [(M + H)$^+$, 100]. Elemental Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.26; H, 7.43; N, 5.12,.

General Procedure for the Aminolysis of Dimethyl 3-(Benzylamino)glutarate. The corresponding amine, **2a** or **2b** (0.5 mmol), was added to a suspension of dimethyl 3-(benzylamino)glutarate (0.5 mmol) and CALB (60 mg) in 1,4-dioxane (2 mL) under nitrogen atmosphere. Solvent was previously dried to avoid the competitive enzymatic hydrolysis. The mixture was shaken at 30 °C at 250 rpm for 2 days. Afterward, the enzyme was filtered off and washed with DCM and the combined organics were evaporated under reduced pressure. Products (−)-**3a,b** were purified by column chromatography on silica using ethyl acetate as the eluent.

Methyl (*S*)-(−)-3-(Benzylamino)-4-(*N*-benzylcarbamoyl)-butanoate [(−)-3a]. Yield, 92%; oil; $[\alpha]^{20}_D$ −14.5 (*c* 1.1, $CHCl_3$); IR (neat) 3285, 1734, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.31 (br s, 1H), AB portion of an ABX system (δ_A 2.41, δ_B 2.54, J_{AB} = 15.9 Hz, J_{AX} = 7.8 Hz, J_{BX} = 4.2 Hz, 2H), 2.61 (d, J = 5.8 Hz, 2H), 3.37−3.45 (m, 1H), 3.69 (s, 3H), AB system (δ_A 3.73, δ_B 3.81, J_{AB} = 12.6 Hz, 2H), AB portion of an ABX system (δ_A 4.41, δ_B 4.46, J_{AB} = 14.8 Hz, J_{AX} = 5.7 Hz, J_{BX} = 5.6 Hz, 2H), 7.13−7.38 (m, 10H), 8.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.4, 39.1, 43.0, 50.2, 51.2, 51.5, 127.0, 127.1, 127.6, 128.0, 128.3, 128.4, 138.2, 138.8, 170.8, 171.9; MS (%) *m*/*z* 379 [(M + K)$^+$, 8], 363 [(M + Na)$^+$, 12], 341 [(M + H)$^+$, 100]. Elemental Anal. for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.36; H, 7.28; N, 8.14.

Methyl (*S*)-(−)-3-(Benzylamino)-4-(*N*-butylcarbamoyl)-butanoate [(−)-3b]. Yield, 79%; oil; $[\alpha]^{20}_D$ −14.2 (*c* 1.0, $CHCl_3$); IR (neat) 3296, 1737, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.2 Hz, 3H), 1.27−1.39 (m, 2H,), 1.42−1.52 (m, 2H), 2.25 (s, 1H), AB portion of an ABX system (δ_A 2.35, δ_B 2.49, J_{AB} = 15.6 Hz, J_{AX} = 7.4 Hz, J_{BX} = 4.2 Hz, 2H), 2.60 (d, J = 6.1 Hz, 2H), 3.23 (q, J = 6.6 Hz, 2H), 3.35−3.43 (m, 1H), 3.69 (s, 3H), AB system (δ_A 3.79, δ_B 3.85, J_{AB} = 12.8 Hz, 2H), 7.26−7.38 (m, 5H), 7.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 20.0, 31.4, 37.5, 38.7, 39.2, 50.3, 51.3, 51.6, 127.2, 128.0, 128.4, 139.0, 170.9, 172.1; MS (%) *m*/*z* 354 [(M + K)$^+$, 3], 329 [(M + Na)$^+$, 15], 307 [(M + H)$^+$, 100]. Elemental Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.49; H, 8.82; N, 8.91.

Methyl (*S*)-(−)-3-(Benzylamino)-4-carbamoylbutanoate [(−)-3c]. Ammonia was bubbled through 1,4-dioxane at 5−10 °C for 30 min under nitrogen. Then, 8 mL of this solution were added to a mixture of dimethyl 3-(benzylamino)glutarate (2 mmol) and CALB (240 mg). The reaction mixture was shaken at 30 °C and 250 rpm for 3 days, whereupon the enzyme was filtered and washed with dichloromethane and the combined organic solvents were evaporated. Purification by column chromatography on silica using ethyl acetate as the eluent gave the title compound as a colorless oil in 85% yield: $[\alpha]^{20}_D$ −11.5 (*c* 1.0, $CHCl_3$); IR (neat) 3335, 3193, 1727, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ AB portion of an ABX system (δ_A 2.35, δ_B 2.50, J_{AB} = 15.7 Hz, J_{AX} = 6.9 Hz, J_{BX} = 4.6 Hz, 2H), 2.37 (s, 1H), 2.59 (d, J = 6.2 Hz, 2H), 3.32−3.44 (m, 1H), 3.67 (s, 3H), 3.79 (s, 2H), 6.18 (br s, 1H), 7.20−7.37 (m, 5H), 7.61 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.5, 38.9, 50.4, 51.1, 51.5, 127.0, 127.9, 128.3, 139.0 172.0 173.8; MS (%) *m*/*z* 289 [(M + K)$^+$, 14], 273 [(M + Na)$^+$, 26], 251 [(M + H)$^+$, 100]. Elemental Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.54; H, 7.13; N, 11.32.

Determination of the Enantiomeric Excess of (−)-3a−c. (a) General Procedure for the Synthesis of Racemic Compounds (±)-3a,b. A small amount of (±)-**3a,b** could be obtained when the corresponding amine, **2a** or **2b** (0.5 mmol), was added to a suspension of dimethyl 3-(benzylamino)glutarate (0.5 mmol) in MeOH (1 mL) under nitrogen atmosphere, and the mixture was stirred at room temperature for 4 days. Afterward, the solvent was evaporated. Compounds (±)-**3a,b** were purified by column chromatography using ethyl acetate as the eluent.

A sample (20 μL) of a solution of (±)-**3a** or (−)-**3a** (0.5 mg) in a mixture of hexane/EtOH (4/1) (2 mL) was analyzed by HPLC (Chiralcel OD-H, 0.5 mL/min, 35 °C, 18 kgf/cm^2, 210 nm), showing two peaks (t_R 13.479 and 22.906) for (±)-**3a** and one peak (t_R 22.949) for (−)-**3a**.

A sample (20 μL) of a solution of (±)-**3b** or (−)-**3b** (0.5 mg) in a mixture of hexane/EtOH (19/1) (2 mL) was analyzed by HPLC (Chiralcel OD-H, 0.5 mL/min, 30 °C, 15 kgf/cm^2, 210 nm), showing two peaks (t_R 21.875 and 24.169) for (±)-**3b** and one peak (t_R 24.197) for (−)-**3b**.

(b) General Procedure for the Synthesis of Racemic Compound (±)-3c. Ammonia was bubbled through 1,4-dioxane at 5−10 °C for 30 min under nitrogen. A small amount of (±)-**3c** could be obtained when 1 mL of the previous solution was added to dimethyl 3-(benzylamino)glutarate (0.5 mmol) under nitrogen atmosphere and the mixture was stirred at 5−10 °C

for 2 days. The solvent was evaporated and compound (−)-**3c** was purified by flash chromatography using ethyl acetate as the eluent.

A sample (20 μL) of a solution of (±)-**3c** or (−)-**3c** (0.5 mg) in a mixture of hexane/EtOH (9/1) (2 mL) was analyzed by HPLC (Chiralcel OD-H, 0.5 mL/min, 35 °C, 15 kgf/cm^2, 210 nm) showing two peaks (t_R 27.218 and 30.487) for (±)-**3c** and one peak (t_R 30.468) for (−)-**3c**.

Methyl (*S*)-(−)-3-[(*N*-Benzyl-*N*-benzyloxycarbonyl)amino]-4-carbamoylbutanoate [(−)-6]. Compound (−)-**3c** (1 mmol) was dissolved in water (2 mL) and Na_2CO_3 (1.2 mmol) was added. Immediately after this, the mixture was cooled to 0 °C and vigorously stirred. Then, benzyl chloroformate (1.2 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 h, followed by extraction of the aqueous solution with DCM. The combined organics were dried over Na_2SO_4, filtered, and evaporated in vacuo. Column chromatography of the residue, on silica using ethyl acetate as the eluent, gave the title compound as a white solid in 86% yield: mp 103−105 °C; $[\alpha]^{20}_D$ −5.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3427, 3178, 1731, 1691, 1653 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz, T = 65 °C) δ 2.56 (d, J = 7.0 Hz, 2H), AB portion of an ABX system (δ_A 2.64, δ_B 2.72, J_{AB} = 15.6 Hz, J_{AX} = 6.2 Hz, J_{BX} = 8.1 Hz, 2H), 3.56 (s, 3H), 4.54 (s, 2H), 4.55 (m, 1H), 5.19 (s, 2H), 5.73 (br s, 2H) 7.26−7.39 (m, 10H); ^{13}C NMR (CD_3CN, 75 MHz, T = 65 °C) δ 38.9, 40.1, 51.9, 52.2, 54.2, 68.1, 128.2, 128.8, 128.9, 129.0, 129.5, 129,. 138.3, 140.0, 157.2, 172.5, 173.3; MS (%) *m*/*z* 423 [(M + K)$^+$, 100], 407 [(M + Na)$^+$, 64], 385 [(M + H)$^+$, 44]]. Elemental Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.37; H, 6.13; N, 7.17.

Hofmann Rearrangement of Methyl (*S*)-3-[(*N*-Benzyl-*N*-benzyloxycarbonyl)amino]-4-carbamoylbutanoate. Methyl (*R*)-(+)-3-[(*N*-Benzyl-*N*-benzyloxycarbonyl)amino]-4-(*N*-benzyloxycarbonylamino)butanoate [(+)-7]. *I*,*I*-bis-(acetoxy)iodobenzene (1.4 mmol) and benzyl alcohol (2.0 mmol) were added to a solution of amido ester (−)-**6** (1 mmol) in THF (10 mL) under nitrogen atmosphere at room temperature. After being stirred for 12 h, the mixture was heated at 60 °C for 30 min to decompose the remaining PIDA. Afterward, the solvent was evaporated. Column chromatography of the residue on silica using hexane/ethyl acetate (3/2) as the eluent gave the corresponding title compound as a colorless oil in 61% yield: $[\alpha]^{20}_D$ +6.8 (*c* 0.7, $CHCl_3$); IR (neat) 3344, 1692−1738 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz, T = 65 °C) δ AB portion of an ABX system (δ_A 2.61, δ_B 2.74, J_{AB} = 15.9 Hz, J_{AX} = 6.1 Hz, J_{BX} = 7.8 Hz, 2H), AB portion of an ABX system (δ_A 3.37, δ_B 3.45, J_{AB} = 13.8 Hz, J_{AX} = 6.4 Hz, J_{BX} = 6.9 Hz, 2H), 3.58 (s, 3H), 4.33−4.43 (m, 1H), AB system (δ_A 4.49, δ_B 4.59, J_{AB} = 16.1 Hz, 2H), 5.10 (s, 2H), 5.22 (s, 2H), 5.49 (br s, H) 7.29−7.42 (m, 15H); ^{13}C NMR (CD_3CN, 75 MHz, T = 65 °C) δ 36.9, 44.3, 51.7, 52.4, 56.7, 67.4, 68.3, 128.4, 128.85, 128.97, 129.04, 129.08, 129.1, 129.7, 138.4, 138.7, 140.1, 157.6, 172.5; MS (%) *m*/*z* 529 [(M + K)$^+$, 100], 513 [(M + Na)$^+$, 79], 491 [(M + H)$^+$, 12]. Elemental Anal. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.32; H, 6.35; N, 5.56.

Dimethyl (3*R*,3′*R*)-(+)-3,3′-Bis[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]-4,4′-ureylenedibutanoate [(+)-8]. To a solution of compound (−)-**6** (0.2 mmol) in THF (2 mL) were added *I*,*I*-bis(acetoxy)iodobenzene (0.28 mmol) and H_2O (0.4 mmol). After being stirred for 12 h, the mixture was heated at 60 °C for 30 min to decompose the remaining PIDA. Afterward the solvent was evaporated. Column chromatography of the residue (ethyl acetate as eluent) gave the title compound as a colorless oil in 86% yield: $[\alpha]^{20}_D$ +25.9 (*c* 1.0, $CHCl_3$); IR (neat) 3378, 1737, 1694 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz, T = 65 °C) δ AB portion of an ABX system (δ_A 2.54, δ_B 2.67, J_{AB} = 15.9 Hz, J_{AX} = 6.0 Hz, J_{BX} = 8.1 Hz, 4H, 2CH−CH_2−CO_2Me), 3.26−3.32 (m, 4H), 3.54 (s, 6H), 4.26−4.34 (m, 2H), AB system (δ_A 4.46, δ_B 4.54, J_{AB} = 16.1 Hz, 4H), 4.83 (br s, 2H) 5.19 (s, 4H), 7.26−7.38 (m, 20H); ^{13}C NMR (CD_3CN, 75 MHz, T = 65 °C) δ 36.9, 43.4, 51.4, 52.3, 57.1, 68.2, 128.3, 128.8, 129.0, 129.1, 129.6, 129.7, 138.4, 140.3, 157.6, 159.0, 172.7; MS (%) *m*/*z* 777 [(M + K)$^+$, 19], 761 [(M + Na)$^+$, 50], 739 [(M + H)$^+$, 100]. Elemental Anal. Calcd for $C_{41}H_{46}N_4O_9$: C, 66.65; H, 6.28; N, 7.59. Found: C, 66.48; H, 6.49; N, 7.34.

Methyl (*R*)-(+)-4-Amino-3-[(*N*-benzyl-*N*-benzyloxycarbonyl) amino]butanoate as Its TFA Salt [(+)-9]. To a solution of compound (−)-**6** (0.4 mmol) in CH_3CN (4 mL) were added *I*,*I*-bis(trifluoroacetoxy)iodobenzene (0.56 mmol) and H_2O (0.8 mmol). After being stirred for 12 h, the mixture was heated at 60 °C for 30 min to decompose the remaining PIFA. The solvent was evaporated under reduced pressure, and the residue was filtered through silica and washed with ethyl acetate to remove iodobenzene. Then, the desired product was eluted from the silica with MeOH. Removal of the solvent gave the title compound as a white solid in quantitative yield: mp 139−141 °C; $[\alpha]^{20}_D$ +6.9 (*c* 1.1, CH_3OH); IR (KBr) 3450, 1731, 1688 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz, T = 50 °C) δ AB portion of an ABX system (δ_A 2.63, δ_B 2.73, J_{AB} = 16.8 Hz, J_{AX} = 7.1 Hz, J_{BX} = 6.8 Hz, 2H), A portion of an ABX system (δ_A 3.17, J_{AB} = 13.3 Hz, J_{AX} = 5.1 Hz, 1H), B portion of an ABX system (δ_B 3.34, 1H), 3.54 (s, 3H), 4.32−4.41 (m, 1H), AB system (δ_A 4.52, δ_B 4.62, J_{AB} = 15.9 Hz, 2H), AB system (δ_A 5.21, δ_B 5.26, J_{AB} = 12.3 Hz, 2H), 7.29−7.37 (m, 10H); ^{13}C NMR (CD_3OD, 75 MHz, T = 50 °C) δ 36.4, 42.5, 51.9, 52.2, 54.8, 69.0, 118.2 (q, $^2J_{CF}$ = 293 Hz, CF_3), 128.7, 128.9, 129.3, 129.5, 129.7, 137.4, 134.0, 157.9, 163.1 (q, $^3J_{CF}$ = 33 Hz, $COCF_3$), 172.3; MS (%) *m*/*z* 379 [{(M − HCO_2CF_3) + Na}$^+$, 10], 357 [{(M − HCO_2CF_3) + H}$^+$, 100]. Elemental Anal. Calcd for $C_{22}H_{25}N_2O_6F_3$: C, 56.17; H, 5.36; N, 5.95. Found: C, 56.23; H, 5.28; N, 5.78.

(*R*)-(+)-3,4-Diaminobutanoic acid dihydrochloride [(+)-12]. To compound (+)-**9** (0.2 mmol) was added 18 mL of a 4% HCO_2H solution in MeOH (purged with nitrogen prior to use), followed by Pd-black (100 mg), and the mixture was stirred vigorously. After 40−60 min (TLC monitoring) the reaction mixture was filtered through Celite and washed with MeOH. The solvent was evaporated and the crude residue was dissolved in MeOH (1.3 mL) under nitrogen, and subsequently treated with NaOH (1 N, 0.5 mL). After being stirred for 13 h, the solvent was removed and 2 mL of 6 M HCl was added. The mixture was heated at 85 °C for 12 h. The solvent was evaporated under reduced pressure and 2 mL of H_2O was added. The mixture was filtered and the filtrate purified on an ion-exchange column (Dowex 50WX 4-400). The desired product was eluted with a 4% aqueous ammonia solution and the fractions were evaporated to dryness. The residue was resuspended in H_2O (2 mL) and then acidified with 3 M HCl. Finally, the solvent was removed yielding the title compound as a white hygroscopic solid in 74% yield: $[\alpha]^{20}_D$ +12.2 (*c* 0.9, H_2O, pH 7.0); IR (KBr) 3423, 3023, 1618 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ AB portion of an ABX system (δ_A 2.92, δ_B 3.02, J_{AB} = 18.3 Hz, J_{AX} = 7.0 Hz, J_{BX} = 5.4 Hz, 2H), 3.43 (d, J = 6.3 Hz, 2H), 3.98−4.07 (m, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 34.4, 40.7, 46.0, 172.9; MS (%) *m*/*z* 141 [{(M − 2HCl) + Na}$^+$, 5], 119 [{(M − 2HCl) + H}$^+$, 100]. Elemental Anal. Calcd for $C_4H_{12}N_2O_2Cl_2$: C, 25.15; H, 6.33; N, 14.66. Found: C, 25.01; H, 6.57; N, 14.39.;

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**, (−)-**3a**, (−)-**3b**, (−)-**3c**, (−)-**6**, (+)-**7**, (+)-**8**, (+)-**9**, and (+)-**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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