Synthesis of Optically Active 2-Alkyl-3,4-iminobutanoic Acids. *β*-Amino Acids Containing an Aziridine Heterocycle

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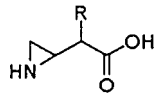
All four stereoisomers of 2-alkyl-3,4-iminobutanoic acid, a novel class of *β*-amino acids bearing a chemically versatile aziridine ring, were synthesized starting with aspartic acid. The synthetic strategy involves the introduction of an alkyl group at the *β*-position of fully protected optically active aspartic acid followed by the construction of an aziridine ring making use of the α-carboxylate and α-amino groups. The α-carboxylate was reduced to the corresponding alcohol, which was then subjected to cyclization to form an aziridine ring with the N-protected amino group. Removal of the protection groups yielded the target compounds.

Introduction

Three-membered heterocycles typified by oxirane display striking chemical property, which has its origin in the relief of ring strain that occurs when the ring is cleaved, and thus, they are extremely valuable chemical entities industrially and synthetically. Aziridine, which may be considered as a nitrogen analogue of oxirane, also bears high ring-strain energy comparable to that of oxirane.[1] Due to the high ring strain of the heterocycle, compounds having an aziridine ring would be valuable as synthetic intermediates[2] and are expected to exhibit varied biological activities.[3] The antineoplastic activity of mitomycin C, an aziridine-containing antibiotic produced by *Streptomyces caespitosus*, is known to be associated with the high reactivity of the strained heterocycle.[4] In connection with other projects, we needed 2-alkyl-3,4-iminobutanoic acids (**1**) in which an aziridine moiety is introduced in place of the amino group of *β*-amino acid. We wish to report herein the synthesis of all four diastereoisomers of **1** in an optically pure form. Although aziridine-2-carboxylic acid, which may be considered as an α-amino acid, has been known since 1966[5] and has attracted much attention,[6] its homologues such as **1** have been scarcely reported[7] despite their potential utility as intermediates for the synthesis of biologically active compounds.



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Results and Discussion

The initial strategy for the synthesis of **1** involved the introduction of an alkyl group at the *β*-position of fully protected aspartic acid by the protocol reported by Baldwin et al.[8] and subsequent construction of an aziridine ring making use of the α-carboxylate and α-amino groups of the aspartic acid as outlined in Scheme 1. The α-ester moiety in **3** was preferentially hydrolyzed according to the method described by Berger and Katchalski,[9] and the carboxylate moiety was reduced to hydroxymethyl via a mixed carboxylic−carbonic anhydride as described by Rodriguez et al.[10] The hydroxyl group thus formed was tosylated and subjected to cyclization reaction after the amino protection group was removed to obtain **7**. Unexpectedly, however, the attempted removal of the benzyl group in **7** to obtain the target compound under the hydrogenolysis conditions using Pd/C catalyst met with failure and resulted in the cleavage of the aziridine ring as well as the obtainment of 3-amino-2-benzylbutanoic acid, **8**, a literature compound.[11] It appears that the cleavage of aziridine ring to give an amine may be a

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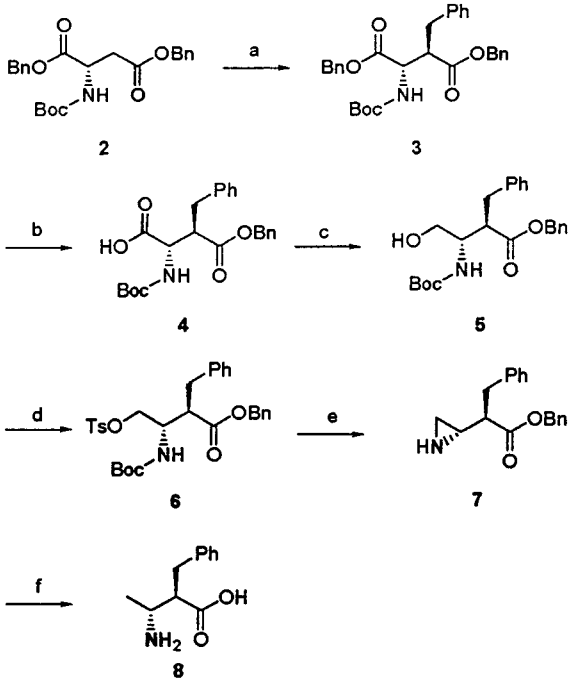
Scheme 1[a]

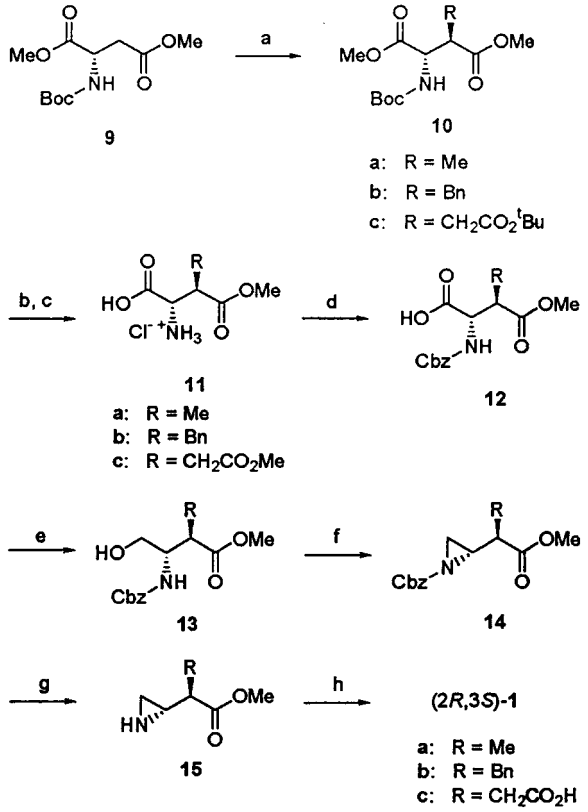


[a] Reagents, conditions, and (yields): (a) BnBr, LHMDS, THF, −78 °C (64%); (b) 0.1 N NaOH, dioxane/H_2O (94%); (c) (i) *i*-BuOCOCl, TEA, DME, (ii) $NaBH_4$, H_2O, −10 °C (75%); (d) TsCl, pyr, CH_2Cl_2 (62%), (e) (i) TFA, CH_2Cl_2, (ii) TEA, CH_2Cl_2 (60%), (f) H_2, Pd/C, MeOH (63%).

reflection of the property of aziridine ring tending to relieve its high strain energy through the ring opening. As can be seen later in the preparation of **15**, the aziridine survives hydrogenolysis under neutral conditions. Therefore, it appears that debenzylation of the benzyl ester moiety in **7** precedes the ring cleavage and the acid that generated facilitates the ring opening.[12] It was, therefore, thought that saponification of the ester under mild hydrolysis conditions would be advantageous, and we decided to make use of methyl ester, which is known to be hydrolyzed much more readily than the benzyl ester.

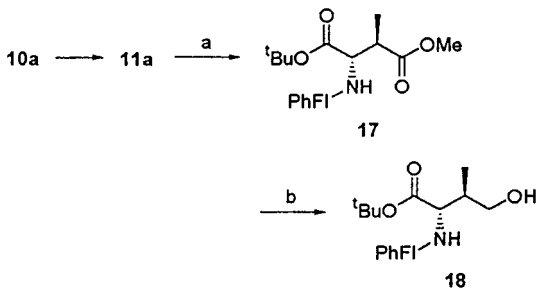
The successful synthetic route for the preparation of (2*R*,3*S*)-**1** is outlined in Scheme 2. The synthesis was started with fully protected (*S*)-aspartic acid **2**, which was prepared by treating the aspartic acid with methanol in the presence of thionyl chloride followed by treatment with $(Boc)_2O$. The enolate dianion that was obtained by treating (*S*)-**9** with 2 molar equiv of lithium hexamethyldisilazane (LHMDS) at −78 °C was allowed to react with alkyl halide to give **10**.[8] In the case of methylation, two products in a diastereoisomeric relationship were formed in about equal ratio. The mixture was readily separated by column chromatography. The compound having $[\alpha]_D = +15.5°$ was assigned to have the (2*S*,3*R*)-configuration on the basis of the NMR NOESY spectrum of 4-*N*-benzyloxycarbonylamino-3-methylbutyrolactone (**16**) obtained by the acid-catalyzed cyclization of **13a** (the discussion of the NOESY spectrum will be presented later). Furthermore, **18** that was obtained from **10a** by

Scheme 2[a]



[a] Reagents and conditions: (a) RX, LHMDS, THF, −78 °C; (b) HCl, MeOH; (c) $CuCO_3{\cdot}Cu(OH)_2$, EtOH/H_2O, 70 °C; (d) CbzCl, Na_2CO_3, H_2O; (e) (i) *N*-hydroxysuccinimide, DCC, DME, (ii) $NaBH_4$, THF, 0 °C to rt, (f) Ph_3P, DEAD, THF, (g) H_2, Pd/C, MeOH; (h) LiOH, MeOH/H_2O.

Scheme 3[a]



[a] Reagents, conditions, and (yields): (a) (i) propylene oxide, EtOH, (ii) TMSCI (1.05 equiv), TEA (2.1 equiv), $Pb(NO_3)_2$ (0.67 equiv), PhFlBr (1.3 equiv), $ChCl_3$, 3 d, (iii) *O-tert*-butyl-*N*,*N*′-diisopropylisourea (3 equiv), CH_2Cl_2, rt, 2 d (52%); (b) DIBAL (3 equiv), THF, −30 °C, 5 h (80%).

the sequence of reactions depicted in Scheme 3 was identical with the compound prepared by the literature method.[13]

In the *β*-methylation reaction of **9** under the conditions reported by Baldwin et al., no stereoselectivity resulted, giving a 1:1 mixture of diastereoisomers, but sterically demanding alkylating reagents such as benzyl bromide and *tert*-butyl bromoacetate provided diastereoselectivity in the ratios of 4:1 and 7:1, respectively, in favor of the trans alkylation with respect to the BocNH group, when

(12) Under the analogous conditions oxirane was reported to undergo a similar ring cleavage reaction: Dragovich, P. S.; Prins, T. J.; Zhou, R. *J. Org. Chem.* **1995**, *60*, 4922−4924.

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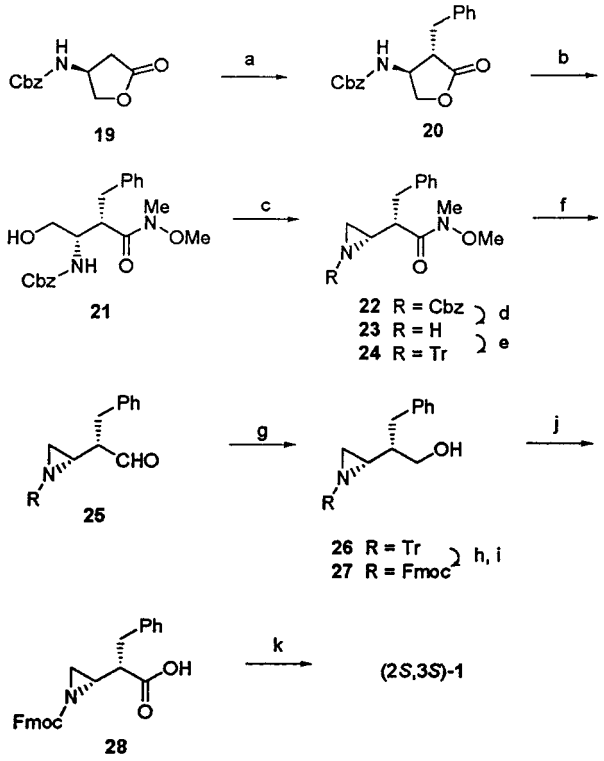
the product was examined by HPLC.[14] Rapoport and associates observed the similar trend that bulkier groups prefer the anti-alkylation in the aspartate alkylation reactions.[13]

Treatment of **10** with methanolic hydrochloride solution provided the N-deprotected product, the α-methyl ester that was then regioselectively hydrolyzed by the method reported by Gmeiner et al.[15] using $CuCO_3$·$Cu(OH)_2$ in an ethanol/water mixture to give **11** as a hydrochloride salt. In the case of **10c**, the *tert*-butyl ester moiety was converted into methyl ester under the reaction conditions. The amino group in the half-ester of (*S*)-aspartic acid derivative thus obtained was then protected to give **12**. The conversion of the α-carboxylate in **12** into the hydroxymethyl group to yield **13** was accomplished in good yield by sodium borohydride reduction of the active ester that was formed by treating **12** with *N*-hydroxysuccinimide in the presence of DCC as reported by Humphrey et al.[16] The aziridine ring formation to yield **14**, the key step in the present synthesis, was effected in 82% yield (for **14b**) under the Mitsunobu conditions using triphenylphosphine in the presence of DEAD following the procedure reported by Wipf and Miller.[17] The remaining steps to the target compound (**1**) having (2*R*,3*S*)-configuration involve removal of the Cbz group from the aziridine nitrogen and hydrolysis of the methyl ester moiety, which were effected by the hydrogenolysis in the presence of Pd/C and treatment with methanolic lithium hydroxide solution,[18] respectively.[16] In the case of compound **1** having (2*S*,3*R*)-configuration we have synthesized only **1b** starting with (*R*)-aspartic acid in overall yield of 13% by the synthetic path that is parallel to that used for the preparation of (2*R*,3*S*)-**1**.

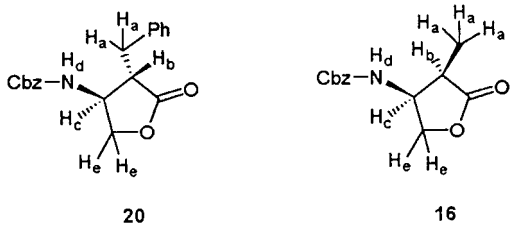
An alternative route had to be sought for the synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-**1** because the precursor to the key intermediate, namely, the compound that corresponds to **13** in the synthesis of (2*S*,3*R*)-**1**, has a strong tendency to cyclize to form a *δ*-lactone. Thus, instead of methyl ester, the Weinreb amide that resists lactonization but still can be readily converted to carboxylate via aldehyde moiety was employed.[19] The synthetic route for the preparation of (2*S*,3*S*)-**1** is outlined in Scheme 4. Lactone **19** that was prepared from (*S*)-aspartic acid as described in the literature[20] was subjected to benzylation in a solution of THF and HMPA using 2 equiv of lithium diisopropylamide (LDA) to give a diastereoisomeric mixture, from which **20** was obtained in 73% yield. Alkylation of *γ*-lactone such as **19** via its dianion is known to give a mixture of diastereoisomers, in which the anti-alkylated product predominates, especially when the alkylating reagent is bulky.[21] Nevertheless, we have ascertained the stereochemical assignment for **20** as well as **16** by 2D ^{1}H NMR NOESY experiments: Thus, strong NOEs were

Scheme 4[a]



[a] Reagents, conditions, and (yields): (a) BnBr, LDA, THF−HMPA, −78 °C (73%); (b) HCl·NHM(Me)OMe, $AlMe_3$, CH_2Cl_2 (87%); (c) Ph_3P, DEAD, THF (86%); (d) H_2, Pd/C, MeOH; (e) TrCl, TEA, $CHCl_3$, (73% from **23**); (f) LAH, THF, −78 °C; (g) LAH, THF, 0 °C to rt (72%); (h) TFA−$CHCl_3$−MeOH; (i) FmocCl, Na_2CO_3, H_2O (80%); (j) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (65%); (k) 10% piperidine in DMF.

observed between H_a−H_c and H_b−H_d in the case of **20** but **16** showed strong NOEs between H_a−H_d and H_b−H_c, which are in good agreement with the respective stereochemical assignments. Accordingly, **10a** from which **16** was derived is established to have the (2*S*,3*R*)-configuration. The lactone obtained from **10b** in a fashion analogous to the preparation of **16** from **10a** was found to be a diastereoisomer of **20**, indicating the **10b** to have the (2*S*,3*R*)-configuration. The assignments for the chemical shift of each proton in **16** and **20** were made from the respective NMR COSY spectrum.



The lactone **20** was readily converted into **21** by treatment with *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminum.[22] The aziridine ring formation was then effected by the intramolecular Mitsunobu-

(14) Racemization at the 2-position of **9** does not appear to take place to any appreciable extent under the reaction conditions: Thus, when the crude products obtained from the methylation of (*R*)- and (*S*)-**9** under the identical reaction conditions were analyzed using chiral HPLC column (ChiraCel OD column), it was shown that each product is a 1:1 binary mixture of optically pure diastereoisomers.

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type reaction to yield **22**.[17] Attempts at selective reduction of the Weinreb amide moiety in **22** to aldehyde were unsuccessful, so we converted the Cbz protecting group into a bulkier trityl to obtain **24**, which was then readily reduced by lithium aluminum hydride to give aldehyde **25**.[19] The aldehyde **25** appeared unstable to observe a change of color on the exposure to air, so it was not isolated but directly reduced further to hydroxymethyl again with lithium aluminum hydride to give **26**. Furthermore, there is a potential danger of the aldehyde undergoing racemization during workup and purification. Nonetheless, we tried direct conversion of the Weireb amide in **24** to the hydroxymethyl with lithium aluminum hydride but met with failure, affording only the aldehyde **25**. It appears that the reduced amide carbonyl forms an intramolecular complex with the lithium ion, which resists further reduction.[23] At this stage, the trityl moiety on the aziridine nitrogen atom was replaced with 9-fluorenylmethyl carbamate (Fmoc), which bears excellent acid stability because we thought that the trityl group would not survive the oxidation conditions of converting the primary alcohol group to carboxylate.[24] Ruthenium tetraoxide catalyzed periodate oxidation[25] of **27** followed by deprotection of the Fmoc group with piperidine in DMF produced (2*S*,3*S*)-**1b**. (2*R*,3*R*)-**1b** was similarly synthesized in an overall yield of 4% starting with (*R*)-aspartic acid.

Conclusion

Stereospecific synthesis of all four stereoisomers of 2-alkyl-3,4-iminobutanoic acid (**1**) have been reported. These compounds constitute a novel class of amino acids bearing an aziridine ring. The aziridine moiety is highly susceptible to ring cleavage reaction under a variety of conditions because of the high strain energy the heterocycle possesses and thus the 2-alkyl-3,4-iminobutanoic acids are expected to bring about versatile chemical transformations that can be useful for the synthesis of biologically active compounds. The biological activity shown by these compounds will be the subject of forthcoming report.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300 MHz) instrument using tetramethylsilane as the internal standard. IR spectra were recorded on a Bruker Equinox 55 FT-IR spectrophotometer. Mass spectra were obtained with a Micro Mass Platform II 8410E spectrometer. Flash chromatography was performed on silica gel 60 (230−400 mesh) from Merck. Elemental analyses were performed at the Center for Biofunctional Molecules, Pohang University of Science and Technology, Korea. Optical rotations were measured on a Rudolph Research Autopol III digital polarimeter. All chemicals were of reagent grade obtained from Aldrich Chemical Co., and solvents were purified before use.

(2*S*,3*R*)-*N*-*tert*-Butyloxycarbonyl-3-benzylaspartic Acid Dibenzyl Ester (3). To a solution of hexamethyldisilazane (39.6 mL, 188 mmol) in THF (150 mL) was added 1.6 M of *n*-butyllithium in hexane (109 mL, 175 mmol) at 0 °C under nitrogen atmosphere, and the mixture was stirred for 20 min and then cooled to −78 °C. A solution of (*S*)-*N*-Boc-aspartic acid dibenzyl ester **2** (31 g, 75 mmol) in THF (125 mL) was added slowly to the mixture, and the reaction mixture was allowed to stir for 2 h at the same temperature. After addition of benzyl bromide (17 mL, 143 mmol), the reaction mixture was stirred for an additional 12 h. The reaction mixture was quenched by addition of 3 N HCl solution to pH ∼3. The aqueous layer was saturated with sodium chloride and then extracted with EtOAc (200 mL × 2). The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give an oily residue. Purification by column chromatography (silica gel, EtOAc/hexane = 1:10) gave the product as a white solid. The product was recrystallized from diethyl ether−petroleum ether to afford white crystalline **3b** (24 g, 64%): mp 78−80 °C; $[\alpha]_D = +1.0°$ (c = 1.0, $CHCl_3$); IR (KBr) 3396 (NH), 1733, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35−7.18 (m, 15H), 5.60 (d, J = 9.9 Hz, 1H), 4.95−5.11 (m, 4H), 4.52 (dd, J = 9.9, 3.7 Hz, 1H), 3.45 (t, J = 8.3, 3.7 Hz, 1H), 3.12 (dd, J = 13.8, 7.2 Hz, 1H), 2.86 (dd, J = 13.8, 8.3 Hz, 1H), 1.48 (s, 9H); MS m/z (FAB) 504.21 (M + 1). Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.61; N, 2.78. Found: C, 71.60; H, 6.58; N, 2.72.

(2*S*,3*R*)-*N*-*tert*-Butyloxycarbonyl-3-benzylaspartic Acid 4-Benzyl Ester (4). To a stirred solution of **3** (16.1 g, 32 mmol) in dioxane (600 mL) and water (204 mL) was added 1 N NaOH solution (32 mL) over 2 h at room temperature. The mixture was stirred for 24 h and evaporated under reduced pressure to remove the dioxane. The resultant residue was acidified with 3 N HCl solution to pH 2−3 and then extracted with EtOAc (200 mL × 3). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give an oily residue. Purification by column chromatography (silica gel, EtOAc/hexane = 4:10−2:1) gave **4** (11 g, 94%) as a white solid that was recrystallized from benzene−petroleum ether: mp 108−110 °C; $[\alpha]_D = +14.2°$ (c = 1.0, $CHCl_3$); IR (KBr) 3400, 1741, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38−7.18 (m, 10H), 5.70 (d, J = 8.4 Hz, 1H), 5.08 (s, 2H), 4.44 (m, 2H), 3.42 (m, J = 8.8, 6.4, 3.6 Hz, 1H), 3.13 (dd, J = 13.6, 6.4 Hz, 1H), 2.88 (dd, J = 13.8, 8.8 Hz, 1H), 1.45 (s, 9H); MS m/z (FAB) 414.15 (M + 1). Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 67.12; H, 6.55; N, 3.37.

(2*R*,3*S*)-2-Benzyl-3-(*tert*-butyloxycarbonylamino)-4-hydroxybutanoic Acid Benzyl Ester (5). To an ice-chilled stirred solution of **4** (1.6 g, 3.9 mmol) in DME (20 mL) were added dropwise triethylamine (0.54 mL, 3.9 mmol) and isobutylchloroformate (0.5 mL, 3.9 mmol), and then the resulting mixture was stirred for 30 min. To this mixture was added a solution of $NaBH_4$ in water (5 mL) within 2 min. After vigorous gas evolution, an excess of water (150 mL) was added to decompose the residual hydride. The mixture was acidified to pH 3−4 with 3 N HCl solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a resin. Purification by column chromatography (silica gel, EtOAc/hexane = 4:10) gave **5** (1.05 g, 75%) as a white solid that was recrystallized in diethyl ether−petroleum ether: mp 78−80 °C; $[\alpha]_D = +24.5°$ (c = 1.0, $CHCl_3$); IR (KBr) 3431, 3365, 1707, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34−7.15 (m, 10H), 5.65 (d, J = 8.6 Hz, 1H), 5.03 (s, 2H), 3.87 (m, 1H), 3.61 (m, 2H), 3.12−2.88 (m, 3H), 2.25 (br, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$)_δ 174.8, 156.7, 138.7, 135.8, 129.2, 128.9, 128.6, 127.0, 125.7, 80.1, 67.0, 64.6, 53.7, 48.2, 36.4, 28.8; MS m/z (FAB) 400.29 (M + 1). Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.38; H, 7.18; N, 3.57.

(2*R*,3*S*)-2-Benzyl-3-(*tert*-butyloxycarbonylamino)-4-*p*-toluenesulfonyloxybutanoic Acid Benzyl Ester (6). To a stirred solution of **5** (1.27 g, 3.2 mmol) in CH_2Cl_2 (10 mL) were added TsCl (1.2 g, 3.3 mmol) and pyridine (1.5 mL) over 30 min. The resultant mixture was stirred for 15 h, diluted with CH_2Cl_2 (10 mL), and washed with 1 N HCl solution. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give an oil. Purification by column chromatography (silica gel, EtOAc/hexane = 1:4) gave **6** (1.1 g, 62%) as a white solid that was recrystallized in EtOAc−petroleum ether: mp 82−83 °C; $[\alpha]_D = +1.2°$ (c = 1.0, $CHCl_3$); IR (KBr) 3408, 1730, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J

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= 8.2 Hz, 2H), 7.35−7.18 (m, 10H), 7.11 (d, *J* = 7.0 Hz, 2H), 5.63 (d, *J* = 8.6 Hz, 1H), 5.00 (dd, *J* = 40.2, 12.2 Hz, 2H), 4.04−4.02 (m, 3H), 3.02−2.83 (m, 3H), 2.44 (s, 3H), 1.44 (s, 9H); MS *m*/*z* (FAB) 554.17 (M + 1). Anal. Calcd for $C_{30}H_{35}NO_7S$: C, 65.08; H, 6.37; N, 2.53. Found: C, 65.37; H, 6.43; N, 2.29.

(2*R*,3*S*)-2-Benzyl-3,4-iminobutanoic Acid Benzyl Ester (7). To an ice-chilled stirred solution of **6** (1.1 g, 2 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL) slowly, and then the mixture was stirred overnight at 4 °C. The mixture was evaporated to give a yellowish resin, which was dissolved in CH_2Cl_2 (40 mL), and washed with 5% aqueous $NaHCO_3$ solution (40 mL). To the organic layer was added triethylamine (0.42 mL, 3 mmol) and the mixture stirred for 20 h. The solvent and triethylamine was removed under reduced pressure, and the resultant residue was purified by column chromatography (silica gel, EtOAc/hexane = 1:1) to give **7** (334 mg, 60%) as an oil: $[\alpha]_D = -13°$ (*c* = 1.0, $CHCl_3$); IR (film) 3446, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.12 (m, 10H), 5.08 (m, 2H), 3.07 (m, 2H), 2.30 (m, 2H), 1.76 (m, 1H), 1.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 174.2, 139.0, 138.8, 136.2, 129.3 128.9, 128.8, 128.5, 126.9, 66.8, 52.4, 37.1, 31.9, 25.0; MS *m*/*z* (FAB) 282.01 (M + 1).

(2*R*,3*R*)-2-Benzyl-3-aminobutanoic Acid (8). To a stirred solution of **7** (140 mg, 0.5 mmol) in methanol (5 mL) was added 10% palladium on carbon (Pd/C, 20 mg). The mixture was stirred under hydrogen atmosphere overnight, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/MeOH = 1:1) to give **8** (60 mg, 63%) as a white solid: mp 232−234 °C dec; $[\alpha]_D = +9.3°$ (*c* = 1.0, MeOH); IR (KBr) 3396, 1701 cm^{-1}; ^1H NMR (CD_3OD) δ 7.29−7.17 (m, 5H), 3.24 (dt, *J* = 11.7, 6.6 Hz, 1H), 3.03 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.92 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.56 (dd, *J* = 11.9, 6.8 Hz, 1H), 1.32 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (CD_3OD) δ 182.8, 143.3, 133.8, 133.4, 132.0, 131.4, 56.6, 39.9, 22.3, 20.6; MS *m*/*z* (FAB) 194.07 (M + 1). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.14; H, 7.98; N, 7.08.

(2*S*,3*R*)-*N*-*tert*-Butyloxycarbonyl-3-benzylaspartic Acid Dimethyl Ester ((2*S*,3*R*)-10b). To a stirred solution of hexamethyldisilazane (HMDS, 36 mL, 169 mmol) in THF (300 mL) was added 10 M of *n*-butyllithium in hexane (10 M, 17 mL, 170 mmol) at 0 °C under nitrogen atmosphere, and the mixture was stirred for 20 min and then cooled to −78 °C. A solution of (*S*)-**9** (20 g, 76.6 mmol) in THF (100 mL) was added slowly to the mixture, and the reaction mixture was allowed to stir for 2 h at the same temperature. After the addition of benzyl bromide (11.0 mL, 91.9 mmol), the reaction mixture was stirred for an additional 6 h and quenched by addition of 3 N HCl solution to pH ∼3. The aqueous layer was saturated with sodium chloride and then extracted with EtOAc (200 mL × 2). The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give an oily residue. Purification by column chromatography (silica gel, EtOAc/hexane = 1:10) gave (2*S*,3*R*)-**10b** (15 g, 56%) as an oil: $[\alpha]_D = +32.2°$ (*c* = 1.0, $CHCl_3$); IR (film) 3429, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19−7.35 (m, 5H), 5.58 (d, *J* = 9.9 Hz, 1H), 4.47 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.42−3.35 (m, 1H), 3.11 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.85 (dd, *J* = 13.7, 8.3 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.8, 172.2, 156.1, 138.4, 129.4, 129.0, 127.2, 53.9, 52.9, 52.5, 49.1, 35.1, 28.7, 22.1; MS *m*/*z* (FAB) 352.13 (M + 1).

(2*R*,3*S*)-*N*-*tert*-Butyloxycarbonyl-3-benzylaspartic acid dimethyl ester ((2*R*,3*S*)-10b) was obtained as an oil in 61% yield from (*R*)-**9** following the procedure used for the preparation of (2*S*,3*R*)-**10b**: $[\alpha]_D = -31.5°$ (*c* = 0.9, $CHCl_3$).

(2*S*,3*R*)-*N*-*tert*-Butyloxycarbonyl-3-methylaspartic Acid Dimethyl Ester ((2*S*,3*R*)-10a). (2*S*,3*R*)-**10a** was prepared from (*S*)-**9** following the procedure used for the preparation of (2*S*,3*R*)-**10b**. The product was found to be a 1:1 mixture of (2*S*,3*R*)- and (2*S*,3*S*)-**10a**. The mixture was separated by column chromatography (silica gel, EtOAc/hexane = 1:15). (2*S*,3*R*)-**10a** (320 mg, 38%) was eluted first as an oil: $[\alpha]_D = +15.5°$ (*c* = 1.0, $CHCl_3$); IR (film) 3436, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.44 (d, *J* = 9.4 Hz, 1H), 4.53 (dd, *J* = 9.6, 3.8 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.27−3.23 (m, 1H), 1.47 (s, 9H), 1.26 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.6, 171.9, 156.4, 80.4, 55.7, 52.9, 52.5, 41.8, 28.5, 13.9; MS *m*/*z* (FAB) 276.12 (M + 1).

(2*S*,3*S*)-**10a** (oil, 245 mg, 29%): $[\alpha]_D = +36.0°$ (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.26 (d, *J* = 8.5 Hz, 1H), 4.65 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.98 (m, 1H), 1.44 (s, 9H), 1.25 (d, *J* = 7.2 Hz, 3H).

(2*S*,3*R*)-*N*-Butyloxycarbonyl-3-(*tert*-butyloxycarbonylmethyl)aspartic Acid Dimethyl Ester ((2*S*,3*R*)-10c). This compound was obtained as an oil in 73% yield from (*S*)-**9** following the procedure used for the preparation of (2*S*,3*R*)-**10b**: $[\alpha]_D = +23.9°$ (*c* = 1.0, $CHCl_3$); IR (film) 3435, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.31 (d, *J* = 9.3 Hz, 1H), 4.65 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.65−3.59 (m, 1H), 2.71 (dd, *J* = 16.9, 7.8 Hz, 1H), 2.52 (dd, *J* = 16.9, 6.8 Hz, 1H), 1.46 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 172.9, 171.6, 170.6, 156.0, 81.6, 80.6, 54.3, 53.0, 52.6, 43.9, 34.6, 28.6, 28.4; MS *m*/*z* (FAB) 376.19 (M + 1).

(2*S*,3*R*)-*N*-Benzyloxycarbonyl-3-benzylaspartic Acid 4-Methyl Ester ((2*S*,3*R*)-12b). To an ice-chilled stirred solution of (2*S*,3*R*)-**10b** (8 g, 23 mmol) in MeOH (30 mL) was added acetyl chloride (3.2 g, 40 mmol) in MeOH (70 mL, both components were premixed at 0 °C and stirred in an ice bath for 30 min). The mixture was stirred for 3 h at the same temperature and then evaporated under reduced pressure. The residue was dissolved in water (70 mL), basic cupric carbonate ($CuCO_3 \cdot Cu(OH)_2$, 6.1 g, 27.6 mmol) was added, and the mixture was stirred vigorously at 70 °C for 3 h. The mixture was then filtered through a Celite pad, and the filter pad was rinsed with copious water. Hydrogen sulfide was then bubbled into the solution until an aliquot filtered through a Celite pad was colorless. After the remaining black mixture was filtered through a Celite pad, the resultant colorless solution was concentrated under vacuum at 50 °C to provide (2*S*,3*R*)-**11b**: IR (film) 3400−2400 1720, 1624 cm^{-1}; ^1H NMR (D_2O) δ 8.83 (br, 1H), 7.27−7.40 (m, 5H), 4.33 (d, *J* = 3.5 Hz, 1H), 3.66 (s, 3H), 3.16 (dd, *J* = 14, 9.0 Hz, 1H), 3.04 (m, 1H), 2.97 (dd, *J* = 14, 7.8 Hz, 1H); MS *m*/*z* (FAB) 238.12 (M − Cl^-).

The crude (2*S*,3*R*)-**11b** was dissolved in water (30 mL), and sodium carbonate (7.3 g, 69 mmol) and benzyl chloroformate (3.6 mL, 27 mmol) were added at 0 °C. The mixture was stirred for 4 h at room temperature and then extracted with diethyl ether. The aqueous layer was acidified to pH 2−3, washed with ether several times, dried over $MgSO_4$, and evaporated to give (2*S*,3*R*)-**12b** (5.8 g, 68%). The oily product was used in the next step without further purification: IR (film) 3600−2400 (br), 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.84 (br, 1H), 7.42−7.15 (m, 10H), 5.95 (d, *J* = 9.8 Hz, 1H), 5.19 (d, *J* = 9.2 Hz, 2H), 4.52 (dd, *J* = 9.8, 3.3 Hz, 1H), 3.67 (s, 3H), 3.48−3.43 (m, 1H), 3.16 (dd, *J* = 13.8, 5.9 Hz, 1H), 2.82 (dd, *J* = 13.8, 9.3 Hz, 1H); MS *m*/*z* (FAB) 372.12 (M + 1).

(2*R*,3*S*)-*N*-Benzyloxycarbonyl-3-benzylaspartic acid 4-methyl ester ((2*R*,3*S*)-12b) was obtained as an oil in 67% yield from (2*R*,3*S*)-**10b** following the procedure used for the preparation of (2*S*,3*R*)-**12b** and used in the next step without further purification.

(2*S*,3*R*)-*N*-Benzyloxycarbonyl-3-methylaspartic acid 4-methyl ester ((2*S*,3*R*)-12a) was obtained as an oil in 74% yield from (2*S*,3*R*)-**10a** following the procedure used for the preparation of (2*S*,3*R*)-**12b** and used in the next step without further purification. **(2*S*,3*R*)-11a**: IR (film) 3400−2400, 1717, 1618 cm^{-1}; ^1H NMR (D_2O) δ 4.27 (d, *J* = 3.6 Hz, 1H), 3.72 (s, 3H), 3.36 (dq, *J* = 11, 3.8 Hz, 1H), 1.30 (d, *J* = 7.3 Hz, 3H); MS *m*/*z* (FAB) 162.12 (M − Cl^-). **(2*S*,3*R*)-12a**: IR (film) 3500−2500 (br), 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.12 (br, 1H), 7.43−7.16 (m, 5H), 5.47 (d, *J* = 9.4 Hz, 1H), 5.06 (d, *J* = 3.8 Hz, 2H), 4.53 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.26 (dq, *J* = 7.2, 3.7 Hz, 1H), 1.26 (d, *J* = 7.3 Hz, 3H); MS *m*/*z* (FAB) 296.12 (M + 1).

(2*S*,3*R*)-*N*-Benzyloxycarbonyl-3-(methyloxycarbonylmethyl)aspartic acid 4-methyl ester ((2*S*,3*R*)-12c) was obtained as an oil in 56% yield from (2*S*,3*R*)-**10c** following the procedure used for the preparation of (2*S*,3*R*)-**12b** and used in the next step without further purification. **(2*S*,3*R*)-11c**: IR (film) 3400−2400, 1726, 1619 cm^{-1}; ^1H NMR (D_2O) δ 4.37 (d, *J* = 3.9 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.51 (m, 1H), 2.87 (d. *J* = 6.7 Hz, 2H); MS *m*/*z* (FAB) 220.12 (M − Cl^-). **(2*S*,3*R*)-12c**: IR (film) 3500−2500 (br), 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ

9.04 (br, 1H), 7.42−7.27 (m, 5H), 5.30 (d, J = 11.2 Hz, 1H), 5.11 (d, J = 3.9 Hz, 2H), 4.80 (dd, J = 9.0, 2.9 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.65−3.48 (m, 1H), 2.83 (dd, J = 17.2, 6.9 Hz, 1H), 2.69−2.60 (dd, J = 17.3, 7.3 Hz, 1H); MS *m*/*z* (FAB) 354.12 (M + 1).

(2*R*,3*S*)-2-Benzyl-3-(benzyloxycarbonylamino)-4-hydroxybutanoic Acid Methyl Ester ((2*R*,3*S*)-13b). To an ice-chilled stirred solution of (2*S*,3*R*)-**12b** (10.4 g, 28 mmol) and *N*-hydroxysuccinimide (3.4 g, 29.4 mmol) in DME (50 mL) was added DCC (6.1 g, 29.4 mmol). The mixture was stirred overnight and then filtered through a Celite pad, and the filtrate was concentrated to give the active ester as a white solid. To an ice-chilled stirred solution of the crude active ester in THF (26 mL) was added $NaBH_4$ (3.40 g, 90 mmol). After 18 h, the mixture was poured into an ice-chilled, vigorously stirred solution of 1 M citric acid buffer (600 mL, pH 4). The resultant mixture was extracted twice with ether, and the combined extracts were washed with water and and brine, dried over $MgSO_4$, and concentrated to give an oil. Purification by column chromatography (silica gel, EtOAc/hexane = 1:1) gave (2*R*,3*S*)-**13b** (7.3 g, 73%) as an oil: $[\alpha]_D = -69.0°$ (c = 0.5, $CHCl_3$); IR (film) 3304, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.10 (m, 10H), 5.51 (d, J = 9.0 Hz, 1H), 5.11 (d, J = 7.8 Hz, 2H), 3.88 (m, 1H), 3.67−3.39 (m, 2H), 3.56 (s, 3H), 2.94 (m, 2H), 2.75(m, 1H); MS *m*/*z* (FAB) 358.15 (M + 1).

(2*S*,3*R*)-2-Benzyl-3-(benzyloxycarbonylamino)-4-hydroxybutanoic acid methyl ester ((2*S*,3*R*)-13b) was obtained as an oil in 75% yield from (2*R*,3*S*)-**12b** following the procedure used for the preparation of (2*R*,3*S*)-**13b**: $[\alpha]_D$ = +67.2° (c = 1.0, $CHCl_3$).

(2*R*,3*S*)-3-(Benzyloxycarbonylamino)-4-hydroxy-2-methylbutanoic acid methyl ester ((2*R*,3*S*)-13a) was obtained as an oil in 69% yield from (2*S*,3*R*)-**12a** following the procedure used for the preparation of (2*R*,3*S*)-**13b**: $[\alpha]_D = +31.4°$ (c = 1.0, $CHCl_3$); IR (thin film) 3329, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46−7.25 (m, 5H), 5.41 (d, J = 9.3 Hz, 1H), 5.07 (d, J = 2.5 Hz, 2H), 3.75 (m, 1H), 3.70 (s, 3H), 3.64 (dd, J = 11, 5.5 Hz, 1H), 3.60 (dd, J = 11, 5.5 Hz, 1H), 2.86 (dq, J = 6.4, 5.5 Hz, 1H), 1.22 (d, J = 6.5 Hz, 3H); MS *m*/*z* (FAB) 282.12 (M + 1).

(2*R*,3*S*)-3-(Benzyloxycarbonylamino)-4-hydroxy-2-(methyloxycarbonylmethyl)butanoic acid methyl ester ((2*R*,3*S*)-13c) was obtained as an oil in 64% yield from (2*S*,3*R*)-**12c** following the procedure used for the preparation of (2*R*,3*S*)-**13b**: $[\alpha]_D = +42.7°$ (c = 1.0, $CHCl_3$); IR (film) 3331, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.21 (m, 5H), 5.38 (d, J = 9.5 Hz, 1H), 5.02 (d, J = 2.2 Hz, 2H), 3.81 (m, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.59 (m, 1H), 3.54 (m, 1H), 2.77 (m, 2H), 2.64 (m, 1H); MS *m*/*z* (FAB) 340.14 (M + 1).

(2*R*,3*S*)-2-Benzyl-3,4-(benzyloxycarbonylimino)-butanoic Acid Methyl Ester ((2*R*,3S)-14b). To a stirred solution of (2*R*,3*S*)-**13b** (3.84 g, 10.8 mmol) in dry THF (20 mL) was added triphenylphosphine (5.64 g, 21.5 mmol). After the mixture was cooled in an ice bath, DEAD (3.4 mL, 21.5 mmol) was added dropwise over 20 min. The mixture was stirred for 3 h at 0 °C and then concentrated to give an oil. Purification by column chromatography (silica gel, EtOAc/hexane = 1:4) gave (2*R*,3*S*)-**14b** (3.0 g, 82%) as an oil: $[\alpha]_D = +14.7°$ (c = 0.8, $CHCl_3$); IR (film) 1729, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.12 (m, 10H), 5.08 (s, 2H), 3.57 (s, 3H), 3.04 (dd, J = 13.7, 7.7 Hz, 1H), 2.88 (dd, J = 13.7, 7.7 Hz, 1H), 2.74−2.68 (m, 1H), 2.44 (q, 1H), 2.28 (d, J = 6.8 Hz, 1H), 1.80 (d, J = 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.4, 163.1, 138.4, 136.0, 129.3, 128.9, 128.8, 128.7, 128.5, 127.1, 68.7, 52.3, 50.6, 39.0, 36.1, 31.3; MS *m*/*z* (FAB) 340.17 (M + 1).

(2*S*,3*R*)-2-Benzyl-3,4-(benzyloxycarbonylimino)butanoic acid methyl ester ((2*S*,3*R*)-14b) was obtained as an oil in 79% yield from (2*S*,3*R*)-**13b** following the procedure used for the preparation of (2*R*,3*S*)-**14b**: $[\alpha]_D = -14.6°$ (c = 0.7, $CHCl_3$).

(2*R*,3*S*)-3,4-(Benzyloxycarbonylimino)-2-methylbutanoic acid methyl ester ((2*R*,3S)-14a) was obtained as an oil in 83% yield from (2*R*,3*S*)-**13a** following the procedure used for the preparation of (2*R*,3*S*)-**14b**: $[\alpha]_D = +15.0°$ (c = 1.0, $CHCl_3$); IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.31 (m, 5H), 5.10 (s, 2H), 3.62 (s, 3H), 2.73−2.68 (m, 1H), 2.41−2.35 (m, 1H), 2.37 (d, J = 6.2 Hz, 1H), 2.06 (d, J = 3.8 Hz, 1H), 1.17 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 163.3, 136.1, 128.9, 128.7, 128.5, 68.6, 52.3, 42.3, 39.8, 30.2, 13.8; MS *m*/*z* (FAB) 264.15 (M + 1).

(2*R*,3*S*)-3,4-(Benzyloxycarbonylimino)-2-(methyloxycarbonylmethyl)butanoic acid methyl ester ((2*R*,3*S*)-14c) was obtained as an oil in 76% yield from (2*R*,3*S*)-**13c** following the procedure used for the preparation of (2*R*,3*S*)-**14b**: $[\alpha]_D = +11.6°$ (c = 1.0, $CHCl_3$); IR (film) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.24 (m, 5H), 5.04 (s, 2H), 3.68 (s, 3H), 3.65 (s, 3H), 2.83 (m, 1H), 2.70 (m, 1H), 2.63 (m, 1H), 2.46 (m, 1H), 2.35 (d, J = 6.1 Hz, 1H), 2.09 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 175.0, 172.6, 163.1, 135.6, 129.6, 128.5, 128.3, 68.7, 53.2, 50.8, 43.3, 39.4, 31.4, 27.9; MS *m*/*z* (FAB) 322.13 (M + 1).

(2*R*,3*S*)-2-Benzyl-3,4-iminobutanoic Acid Methyl Ester ((2*R*,3*S*)-15b). To a stirred solution of (2*R*,3*S*)-**14b** (2.8 g, 8.25 mmol) in methanol (60 mL) was added 10% Pd/C (200 mg). Under hydrogen atmosphere the mixture was stirred for 2 h and then filtered through a Celite pad, and the filtrate was evaporated to give (2*R*,3*S*)-**15b** (1.6 g, 95%) as an oil: $[\alpha]_D = -3.54°$ (c = 0.5, $CHCl_3$); IR (film) 3341, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32−7.17 (m, 5H), 3.68 (s, 3H), 3.09 (dd, J = 13.7, 7.3 Hz, 1H), 2.95 (dd, J = 13.7, 6.6 Hz, 1H), 2.30−2.19 (m, 2H), 1.80 (d, J = 5.3 Hz, 1H), 1.22 (d, J = 2.8 Hz, 1H), 1.19 (m, 1H); MS *m*/*z* (FAB) 206.11 (M + 1).

(2*S*,3*R*)-2-Benzyl-3,4-iminobutanoic acid methyl ester ((2*S*,3*R*)-15b) was obtained in 97% yield from (2*S*,3*R*)-**14b** following the procedure used for the preparation of (2*R*,3*S*)-**15b**: $[\alpha]_D = +3.57°$ (c = 0.5, $CHCl_3$).

(2*R*,3*S*)-2-Methyl-3,4-iminobutanoic acid methyl ester ((2*R*,3*S*)-15a) was obtained in 94% yield from (2*R*,3*S*)-**14a** following the procedure used for the preparation of (2*R*,3*S*)-**15b**: $[\alpha]_D = -5.61°$ (c = 0.6, $CHCl_3$); IR (film) 3339, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H), 2.27−2.21 (m, 1H), 2.07−1.96 (m, 1H), 1.86 (d, J = 5.9 Hz, 1H), 1.40 (d, J = 3.5 Hz, 1H), 1.24 (d, J = 7.2 Hz, 3H), 1.13 (dd, J = 15.7, 7.1 Hz, 1H); MS *m*/*z* (FAB) 130.12 (M + 1).

(2*R*,3*S*)-2-Methyloxycarbonylmethyl-3,4-iminobutanoic acid methyl ester ((2*R*,3*S*)-15c) was obtained in 85% yield from (2*R*,3*S*)-**14c** following the procedure used for the preparation of (2*R*,3*S*)-**15b**: $[\alpha]_D = -4.76°$ (c = 1.0, $CHCl_3$); IR (film) 3340, 1735, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.69 (s, 3H), 2.85 (m, 1H), 2.72 (m, 1H), 2.42 (m, 1H), 2.23 (m, 1H), 1.84 (d, J = 5.4 Hz, 1H), 1.46 (d, J = 3.4 Hz, 1H), 1.15 (m, 1H); MS *m*/*z* (FAB) 188.09 (M + 1).

(2*R*,3*S*)-2-Benzyl-3,4-iminobutanoic Acid ((2*R*,3*S*)-1b). To an ice-chilled stirred solution of (2*R*,3*S*)-**15b** (1.2 g, 5.85 mmol) in methanol (20 mL) and water (10 mL) was added dropwise 1 N LiOH in water (6 mL), and the mixture was stirred at the same temperature for 4 h and then evaporated to give (2*R*,3*S*)-**1b** as a lithium salt (1.02 g, 85%). The lithium salt was converted to the corresponding free acid by carefully neutralizing its aqueous solution with a small amount of acetic acid followed by addition of ethanol and ether: mp 237−239 °C dec; $[\alpha]_D = +5.9°$ (c = 1.0, MeOH); IR (KBr) 3330−2300 (br), 1698 cm^{-1}; ^1H NMR (CD_3OD) δ 7.31−7.13 (m, 5H), 2.87 (m, 2H), 2.09 (m, 1H), 1.89 (dd, J = 15.6, 7.6 Hz, 1H), 1.65 (d, J = 5.9 Hz, 1H), 1.13 (d, J = 3.4 Hz, 1H); ^{13}C NMR (CD_3OD) δ 182, 140.6, 129.2, 128.2, 126.0, 54.6, 38.1, 32.4, 24.1; MS *m*/*z* (FAB) 192.13 (M + 1). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.85; H, 7.01; N, 7.12.

(2*S*,3*R*)-2-Benzyl-3,4-iminobutanoic acid ((2*S*,3*R*)-1b) was obtained (80% yield as a lithium salt) from (2*S*,3*R*)-**15b** following the procedure used for the preparation of (2*R*,3*S*)-**1b**: $[\alpha]_D = -5.8°$ (c = 1.0, MeOH).

(2*R*,3*S*)-2-Methyl-3,4-iminobutanoic acid ((2*R*,3*S*)-1a) was obtained (83% yield as a lithium salt) from (2*R*,3*S*)-**15a** following the procedure used for the preparation of (2*R*,3*S*)-**1b**: mp 223−225 °C dec; $[\alpha]_D = +7.62$ ° (c = 0.5, $CHCl_3$); IR (KBr) 3356 (br), 1691 cm^{-1}; ^1H NMR (CD_3OD) δ 2.27−2.21 (m, 1H), 2.07−1.96 (m, 1H), 1.76 (d, J = 6.5 Hz, 1H), 1.30 (d, J = 6.0 Hz, 1H), 1.10 (d, J = 7.1 Hz, 3H); MS *m*/*z* (FAB) 116.15 (M + 1). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.04; H, 7.67; N, 12.05.

(2*R*,3*S*)-2-Hydroxycarbonylmethyl-3,4-iminobutanoic acid ((2*R*,3*S*)-1c) was obtained (85% yield as a lithium salt)

from (2*R*,3*S*)-**15c** following the procedure used for the preparation of (2*R*,3*S*)-**1b**: mp 200−202 °C dec; $[\alpha]_D = +5.70°$ (c = 0.4, $CHCl_3$); IR (KBr) 3238 (br), 1695 cm^{-1}; ^1H NMR (CD_3OD) δ 2.57 (m, 1H), 2.39 (m, 1H), 2.24 (m, 1H), 1.99 (m, 1H), 1.84 (d, J = 5.7 Hz, 1H), 1.30 (d, J = 3.3 Hz, 1H); MS m/z (FAB) 160.09 (M + 1). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.01; H, 5.86; N, 8.52.

(3*R*,4*S*)-3-Methyl-4-*N*-(benzyloxycarbonylamino)butyrolactone ((3*R*,4*S*)-16). To a stirred solution of **13a** (300 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) was added *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol). The reaction mixture was stirred for 2 h and then washed with saturated aqueous $NaHCO_3$ solution and with brine. The organic layer was dried over $MgSO_4$ and evaporated to give (3*R*,4*S*)-**16** (252 mg, 95%) as a white solid that was recrystallized from EtOAc−ether: mp 116−118 °C; $[\alpha]_D = -57.2°$ (c = 0.9, $CHCl_3$); IR (film) 3331, 1756, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17−7.40 (m, 5H), 5.95 (d, J = 8.5 Hz, 1H) 5.04 (s, 2H), 4.49 (m, 1H), 4.27 (dd, J = 10, 8.5 Hz, 1H), 4.10 (m, H), 2.65 (m, 1H), 1.11 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.2, 136.4, 128.9, 128.6, 126.3, 72.6, 67.7, 52.1, 38.5, 9.3; MS m/z (FAB) 250.16 (M + 1).

(2*S*,3*R*)-*N*-(9-Phenylfluoren-9-yl)-3-methyl-aspartic Acid 1-*tert*-Butyl 4-Methyl Diester ((2*S*,3*R*)-17). To a solution of (2*S*,3*R*)-**11a** (0.9 g, 4.5 mmol) in dry EtOH (5 mL) was added propylene oxide (1 mL), and then the solution was refluxed for 6 h to liberate the free amino acid. The mixture was cooled, and the precipitate was filtered and dried. The white solid was suspended in dry $CHCl_3$ (10 mL), and TMSCl (1.2 mL, 9.2 mmol) was added. After 2 h, triethylamine (2.7 mL, 9.2 mmol) was added and the mixture stirred for 20 min. $Pb(NO_3)_2$ (1.0 g, 6 mmol) and 9-bromo-9-phenylfluorene (3.9 g, 12 mmol) in dry $CHCl_3$ (10 mL) were added separately. The mixture was stirred for 3 days, and MeOH (4 mL) was added. After 20 min, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 10% aqueous citric acid (30 mL) and extracted with ether (40 mL × 3). The extract was washed with brine (30 mL), dried, and concentrated to 5 mL. The concentrated solution was chilled in an ice bath, and the precipitate was filtered and washed with diethyl ether (10 mL). Concentration of the filtrate yielded a second crop to give 2.1 g of the product in total (67%): ^1H NMR ($CDCl_3$) δ 7.70 (m, 2H), 7.19−7.44 (m, 11H), 3.65 (s, 3H), 3.21 (m, 1H), 2.96 (m, 1H), 2.47 (m, 1H), 1.09 (d, J = 7.3 Hz, 3H).

The pale yellow solid (2.0 g, 5 mmol) was dissolved in CH_2Cl_2 (60 mL), and *O*-*tert*-butyl-*N*,*N*'-diisopropylisourea (3.0 g, 15 mmol) in CH_2Cl_2 (15 mL) was added at room temperature. After the mixture was stirred for 2 days, water (10 mL) was added, and the stirring was kept for 1 h. The reaction mixture was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and with water (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/hexane = 1:10) gave (2*S*,3*R*)-**17** (3.5 g, 73%): IR (film) 3314, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (m, 2H), 7.17−7.40 (m, 11H), 3.60 (s, 3H), 3.18 (m, 1H), 2.92 (m, 1H), 2.4 (m, 1H), 1.15 (s, 9H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.4, 173.1, 149.5, 145.5, 141.5, 128.6, 128.5, 128.1, 127.5, 126.5, 126.3, 120.2, 81.7, 73.2, 58.9, 51.9, 45.5, 28.3, 12.8.

(2*S*,3*R*)-2-[(9-Phenylfluoren-9-yl)amino]-3-methyl-4-hydroxybutanoic Acid *tert*-Butyl Ester ((2*S*,3*R*)-18). (2*S*,3*R*)-**17** (411 mg, 0.9 mmol) was dissolved in dry THF (20 mL) and cooled to −30 °C. To the resulting mixture was added 1.0 M DIBAL in THF (2.8 mL, 2.8 mmol) and the mixture stirred for 6 h. Acetone (130 μL) was added to the reaction mixture and the mixture stirred for 10 min. Finally, MeOH (810 μL) was added, and the resulting mixture was warmed to room temperature. The mixture was diluted with ether (30 mL) and washed with 1 M K_3PO_4 solution (30 mL) and then with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/hexane = 1:4) gave (2*S*,3*S*)-**18** (300 mg, 80%): $[\alpha]_D = -217°$ (c = 1.2, $CHCl_3$); IR (film) 3440, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68−7.70 (m, 2H), 7.17−7.35 (m, 11H), 3.54 (dd, J = 11, 3.4 Hz, 1H), 3.40 (dd, J = 11, 8.4 Hz, 1H), 2.44 (d, J = 7.8 Hz, 1H), 1.85 (m, 1H), 1.15 (s, 9H), 0.64 (d, J = 0.7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 148.9, 144.4, 141.5, 140.8, 128.9, 128.3, 127.7, 126.7, 126.2, 120.3, 81.8, 73.3, 68.3, 61.8, 40.3, 28.3, 14.7; MS m/z (FAB) 430.3 (M + 1). The spectral data of this compound were identical with those of reference compound prepared by the literature method.[13]

(3*S*,4*S*)-3-Benzyl-4-(*N*-benzyloxycarbonylamino)-butyrolactone ((3*S*,4*S*)-20). Ice-chilled stirred solution of LDA (50 mmol) and HMPA (40 mL) in THF (40 mL) was further cooled to −78 °C. To the resulting mixture was added dropwise a solution of (*S*)-**19** (4.1 g, 20.4 mmol) in THF (50 mL). The mixture was stirred for 2 h at −78 °C, and then was added benzyl bromide (5.1 g, 30 mmol) over 30 min. The resulting mixture was stirred for 3 h and acidified with 10% aqueous citric acid to pH 3, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic layer was washed with 10% aqueous citric acid (100 mL × 3), brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/hexane = 1:10 to 1:4) gave (3*S*,4*S*)-**20** (4.33 g, 73%) as a white solid which was recrystallized from ether/hexane: mp 89−90 °C; $[\alpha]_D = -20.3°$ (c = 0.62, $CHCl_3$); IR ($CHCl_3$) 3369, 1773, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32−7.19 (m, 10H), 5.13 (d, J = 4.8 Hz, 1H), 5.02 (s, 2H), 4.24 (m, 2H), 3.90 (m, 1H), 3.19 (dd, J = 13.8, 4.5 Hz, 1H), 2.94 (dd, J = 13.9, 7.4 Hz, 1H), 2.83 (dd, J = 11.7, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 176.7, 156.0, 137.3, 136.3, 129.6, 129.2, 129.0, 128.8, 128.6, 127.5, 71.1, 67.5, 52.5, 47.1, 34.7; MS (FAB) m/z 326.11 (M + 1). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.87; H, 5.94; N, 4.08.

(3*R*,4*R*)-3-Benzyl-4-*N*-benzyloxycarbonylaminobutyrolactone ((3*R*,4*R*)-20) was obtained from (*R*)-**19** following the procedure used for the preparation of (3*S*,4*S*)-**20**: $[\alpha]_D = +21.0°$ (c = 0.5, $CHCl_3$).

(2*S*,3*S*)-*N*-Methoxy-*N*-methyl-2-benzyl-3-(benzyloxycarbonylamino)-4-hydroxybutanamide ((2*S*,3*S*)-21). To an ice-chilled slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (2.0 g, 20 mmol) in CH_2Cl_2 (20 mL) was added dropwise 2 M trimethylaluminum in hexane (20 mL) over 20 min, and the resultant solution was stirred for 30 min. A solution of (3*S*,4*S*)-**20** (6.5 g, 20 mmol) in dry CH_2Cl_2 (20 mL) was then added to the reaction mixture over 15 min. After being stirred for 1 h at room temperature, the solution was cooled to 0 °C, and then an ice-chilled 1 N HCl solution (100 mL) was slowly added. The resulting mixture was extracted twice with EtOAc, and the combined organic layer was washed once each with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a clear oil. Purification by column chromatography (silica gel, EtOAc/hexane = 1:2) gave (2*S*,3*S*)-**21** (6.7 g, 87%) as a white solid that was recrystallized from EtOAc/hexane: mp 144−146 °C; $[\alpha]_D = +9.69°$ (c = 0.5, $CHCl_3$); IR (film) 3304, 1704, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.16 (m, 10H), 5.70 (d, J = 6.6 Hz, 1H), 5.11 (dd, J = 33.3, 12.3 Hz, 2H), 4.17 (d, J = 12.2 Hz, 1H), 3.81 (br, 1H), 3.85−3.76 (m, 1H), 3.63 (dd, J = 12.1, 3.6 Hz, 1H), 3.13−2.98 (m, 2H), 2.85−2.78 (m, 1H), 2.77 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 156.5, 138.9, 137.0, 129.1, 128.9, 128.8, 128.5, 127.1, 126.3, 67.1, 60.8, 53.8, 46.1, 38.0, 37.3, 36.4; MS m/z (FAB) 369.25 (M − OH). Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 64.99; H, 6.84; N, 7.03.

(2*R*,3*R*)-*N*-Methoxy-*N*-methyl-2-benzyl-3-(benzyloxycarbonylamino)-4-hydroxybutanamide ((2*R*,3*R*)-21) was obtained from (3*R*,4*R*)-**20** following the procedure used for the preparation of (2*S*,3*S*)-**21**: $[\alpha]_D = -9.73°$ (c = 0.5, $CHCl_3$).

(2*S*,3*S*)-*N*-Methoxy-*N*-methyl-2-benzyl-3,4-(benzyloxycarbonylimino)-butanamide ((2*S*,3*S*)-22). To a stirred solution of (2*S*,3*S*)-**21** (4.28 g, 11.5 mmol) in dry THF (30 mL) was added triphenylphosphine (6.03 g, 23.0 mmol). After the mixture was cooled in an ice bath, DEAD (3.6 mL, 23 mmol) was added dropwise over 20 min. The mixture was stirred for 3 h at 0 °C and then concentrated to give an oil. Purification by column chromatography (silica gel, EtOAc/hexane = 1:4) gave (2*S*,3*S*)-**22** (3.6 g, 86%) as a colorless oil: $[\alpha]_D = +31.1°$ (c = 0.7, $CHCl_3$); IR (film) 3455, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.18 (m, 10H), 5.17 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H),

2.90−2.78 (m, 2H), 2.83 (s, 3H), 2.50 (s, 3H), 2.42 (d, J = 5.9 Hz, 1H), 2.14 (d, J = 3.4 Hz, 1H); MS m/z (FAB) 368.14 (M^+).

(2*R*,3*R*)-*N*-Methoxy-*N*-methyl-2-benzyl-3,4-(benzyloxycarbonylimino)butanamide ((2*R*,3*R*)-22) was obtained from (2*R*,3*R*)-**21** following the procedure used for the preparation of (2*S*,3*S*)-**22**: $[\alpha]_D$ = −30.6° (c = 0.7, $CHCl_3$).

(2*S*,3*S*)-*N*-Methoxy-*N*-methyl-2-benzyl-3,4-(triphenylmethylimino)butanamide ((2*S*,3*S*)-24). To a stirred solution of (2*S*,3*S*)-**22** (3.1 g, 8.4 mmol) in methanol (70 mL) was added 10% Pd/C (100 mg). Under hydrogen atmosphere the mixture was stirred for 2 h, filtered through a Celite pad, and the filtrate was concentrated to give (2*S*,3*S*)-**23**: IR (film) 3304, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28−7.17 (m, 5H), 3.11 (d, J = 7.9 Hz, 1H), 2.84 (m, 1H), 2.83 (s, 3H), 2.47 (s, 3H), 2.51−2.42 (m, 2H), 1.90 (d, J = 5.7 Hz, 1H), 1.42 (d, J = 2.9 Hz, 1H), 1.09 (m, 1H); MS m/z (FAB) 235.27 (M + 1).

To an ice-chilled stirred solution of (2*S*,3*S*)-**23** (1.04 g, 4.44 mmol) in chloroform (10 mL) were added triethylamine (700 μL, 5.0 mmol) and triphenylmethyl chloride (1.3 g, 4.4 mmol) in chloroform (5 mL). The mixture was stirred at 4 °C overnight and then diluted with chloroform and washed with water and with brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give a resin. Purification by column chromatography (silica gel, EtOAc/hexane = 1:5) gave (2*S*,3*S*)-**24** (1.5 g, 73%) as a white solid, which was recrystallized form ether/petroleum ether: mp 182−183 °C; $[\alpha]_D$ = +95.1° (c = 1.0, $CHCl_3$); IR (film) 3027, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55−7.51 (m, 5H), 7.29−7.12 (m, 15H), 3.04−2.81 (m, 3H), 2.76 (s, 3H), 2.49 (s, 3H), 1.73 (d, J = 3.0 Hz, 1H), 1.60−1.55 (m, 1H), 1.16 (d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 174.1, 144.9, 140.3, 130.0, 129.3, 128.7, 127.9, 127.1, 126.7, 74.6, 48.2, 39.5, 37.6, 37.1, 35.7, 26.4; MS m/z (FAB) 461.20 (M − CH_3). Anal. Calcd for $C_{32}H_{32}N_2O_2$: C, 80.64; H, 6.77; N, 5.88. Found: C, 80.62; H, 6.58; N, 5.79.

(2*R*,3*R*)-*N*-Methoxy-*N*-methyl-2-benzyl-3,4-(triphenylmethylimino)butanamide ((2*R*,3*R*)-24) was obtained from (2*R*,3*R*)-**22** following the procedure used for the preparation of (2*S*,3*S*)-**24**: $[\alpha]_D$ = −95.9° (c = 1.0, $CHCl_3$).

(2*S*,3*S*)-2-Benzyl-3,4-(triphenylmethylimino)butan-1-ol ((2*S*,3*S*)-26). A solution of (2*S*,3*S*)-**24** (1.0 g, 2.1 mmol) in THF (30 mL) was cooled to −78 °C, and to this solution was added lithium aluminum hydride (80 mg, 2.1 mmol). The mixture was stirred at −78 °C for 4 h, and water (10 drops) was added to decompose the residual hydride. The mixture was dried over $MgSO_4$ and evaporated under reduced pressure to give (2*S*,3*S*)-**25** as a resin: ^1H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.46−7.50 (m, 5H), 7.18−7.30 (m, 15H), 3.02−3.15 (m, 1H), 2.85−3.05 (m, 2H), 1.86 (d, J = 3.1 Hz, 1H), 1.42−1.47 (m, 1H), 1.14 (d, J = 6.2 Hz, 1H).

The resultant resinous product was dissolved in ether (20 mL) and to this solution was added lithium aluminum hydride (60 mg, 1.5 mmol) at 0 °C. The mixture was stirred at the same temperature for 3 h, after which time 6 drops of water was added. The mixture was dried over $MgSO_4$ and evaporated under reduced pressure to give a resin. Purification by column chromatography (silica gel, EtOAc/hexane = 1:3) gave the desired product (2*S*,3*S*)-**26** (630 mg, 72%) as a solid which was recrystallized from EtOAc/hexane: mp 51−53 °C; $[\alpha]_D$ = −66.1° (c = 0.6, $CHCl_3$); IR (film) 3335, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (dd, J = 8.3, 1.7 Hz, 5H), 7.28−7.17 (m, 13H), 7.01 (dd, J = 8.3, 1.7 Hz, 2H), 3.62−3.54 (m, 2H), 2.63 (m, 1H), 2.49−2.31 (m, 2H), 2.08 (d, J = 3.5 Hz, 1H), 1.62−1.59 (m, 1H), 1.09 (d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.1, 139.7, 129.9, 129.2, 128.7, 128.0, 127.3, 126.5, 75.5, 65.1, 39.4, 37.3, 36.9, 23.0; MS m/z (FAB) 420.15 (M + 1). Anal. Calcd for $C_{30}H_{29}NO$: C, 85.88; H, 6.97; N, 3.34. Found: C, 85.74; H, 3.25; N, 3.76.

(2*R*,3*R*)-2-Benzyl-3,4-(triphenylmethylimino)-butan-1-ol ((2*R*,3*R*)-26) was obtained from (2*R*,3*R*)-**24** following the procedure used for the preparation of (2*S*,3*S*)-**26**: $[\alpha]_D$ = +65.6° (c = 0.6, $CHCl_3$).

(2*S*,3*S*)-2-Benzyl-3,4-(fluorenylmethyloxycarbonylimino)butan-1-ol ((2*S*,3*S*)-27). To an ice-chilled solution of (2*S*,3*S*)-**26** (400 mg, 0.95 mmol) in chloroform (2 mL) and methanol (1 mL) was added dropwise TFA (3 mL). The mixture was stirred for 4 h and then evaporated under reduced pressure to remove the excess TFA. The residue was diluted with ether (10 mL) and washed with water, and then the aqueous layer was basified by sodium carbonate to pH ∼10 and extracted with ether several times. The combined extracts were dried over $MgSO_4$ and evaporated to give a colorless oil: ^1H NMR ($CDCl_3$) δ 7.14−7.31 (m, 5H), 3.36−3.51 (m, 2H), 3.27 (br, 2H), 2.59−2.67 (m, 2H), 2.07−2.12 (m, 1H), 1.94−2.01 (m, 1H), 1.80 (d, J = 6.1 Hz, 1H), 1.65 (d, J = 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 140.1, 129.5, 128.8, 126.5, 63.4, 43.7, 36.7, 32.7, 22.5.

The oily product was dissolved in a mixture of aqueous sodium carbonate solution (2 M, 4 mL) and THF (1 mL), and to this solution was added 9-fluorenylmethyl chloroformate (270 mg, 1.0 mmol). The mixture was stirred at 0 °C for 3 h, after which time it was diluted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to give an oil. Purification by column chromatography (EtOAc/hexane = 1:2) gave product (2*S*,3*S*)-**27** (160 mg, 80%) as an oil: $[\alpha]_D$ = −28.3° (c = 0.7, $CHCl_3$); IR (film) 3347 (br), 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (d, J = 7.4 Hz, 2H), 7.63 (d, J = 7.4 Hz, 2H), 7.40−7.45 (t, 2H), 7.24−7.37 (m, 5H), 7.12−7.22 (m, 2H), 4.49−4.58 (m, 2H), 4.27 (t, J = 6.3 Hz, 1H), 3.47−3.56 (m, 2H), 2.75 (dd, J = 5.6, 13.9 Hz, 1H), 2.57 (dd, J = 9.1, 13.9 Hz, 1H), 2.37−2.43 (m, 1H), 2.30 (d, J = 6.3 Hz, 1H), 2.22 (d, J = 3.8 Hz, 1H), 2.11 (br, 1H), 1.89−1.99 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 164.0, 143.9, 141.8, 139.8, 129.4, 128.9, 128.3, 127.6, 126.3, 125.4, 120.4, 68.4, 63.2, 47.5, 43.7, 40.6, 34.8, 30.6; MS m/z (FAB) 400.12 (M + 1).

(2*R*,3*R*)-2-Benzyl-3,4-(fluorenylmethyloxycarbonylimino)butan-1-ol ((2*R*,3*R*)-27) was obtained from (2*R*,3*R*)-**26** following the procedure used for the preparation of (2*S*,3*S*)-**27**: $[\alpha]_D$ = +27.9° (c = 0.6, $CHCl_3$).

(2*S*,3*S*)-2-Benzyl-3,4-(fluorenylmethyloxycarbonylimino)butanoic Acid ((2*S*,3*S*)-28). To a mixture of (2*S*,3*S*)-**27** (200 mg, 0.64 mmol) and sodium periodate (560 mg, 2.6 mmol) in acetonitrile (1.5 mL), carbon tetrachloride (1.5 mL), and water (2 mL) was added ruthenium chloride hydrate (10 mg, 0.05 mmol) at room temperature. The resulting mixture was stirred overnight and extracted with EtOAc. The combined extracts were washed with water, dried over $MgSO_4$, and evaporated to give a resinous residue that was purified by column chromatography (EtOAc/hexane = 2:1) to give (2*S*,3*S*)-**28** in a resinous form (175 mg, 65%): $[\alpha]_D$ = −32.4° (c = 0.5, $CHCl_3$); IR (film) 3402 (br), 1694, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (d, J = 7.4 Hz, 2H), 7.60 (t, J = 7.5 Hz, 2H), 7.42−7.17 (m, 9H), 4.55 (d, J = 6.8 Hz, 2H), 4.28 (t, J = 6.6 Hz, 1H), 3.08 (dd, J = 14.2, 7.3 Hz, 1H), 2.89 (dd, J = 13.8, 7.5 Hz, 1H), 2.64 (m, 1H), 2.50 (dd, J = 15.3, 7.5 Hz, 1H), 2.22 (d, J = 6.1 Hz, 1H), 1.81 (d, J = 3.6 Hz, 1H); MS m/z (FAB) 414.17 (M + 1). Anal. Calcd for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.26; H, 5.52; N, 3.13.

(2*R*,3*R*)-2-Benzyl-3,4-(fluorenylmethyloxycarbonylimino)butanoic acid ((2*R*,3*R*)-28) was obtained from (2*R*,3*R*)-**27** following the procedure used for the preparation of (2*S*,3*S*)-**28**: $[\alpha]_D$ = +33.1° (c = 0.5, $CHCl_3$).

(2*S*,3*S*)-2-Benzyl-3,4-iminobutanoic Acid ((2*S*,3*S*)-1b). To a solution of (2*S*,3*S*)-**28** (300 mg, 0.73 mmol) in DMF (1 mL) was added piperidine (100 μL). The mixture was stirred for 20 min, diluted with water, and washed with ether. The aqueous layer was concentrated under vacuum to give (2*S*,3*S*)-**1b** as a solid (83 mg, 57%) that was recrystallized from EtOH−H_2O (0.1% AcOH): mp 209−211 °C dec; $[\alpha]_D$ = −4.71° (c = 0.5, MeOH); IR (film) 3305 (br), 1697 cm^{-1}; ^1H NMR (D_2O) δ 7.31−7.13 (m, 5H), 2.87 (m, 2H), 2.09 (m, 1H), 2.00 (m, 1H), 1.75 (d, J = 5.7 Hz, 1H), 1.24 (d, J = 3.4 Hz, 1H); MS m/z (FAB) 192.13 (M + 1). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.87; H, 7.03; N, 7.21.

(2*R*,3*R*)-2-Benzyl-3,4-iminobutanoic Acid ((2*R*,3*R*)-1b) was prepared from (2*R*,3*R*)-**28** by the same method as the preparation of (2*S*,3*S*)-**1b**: $[\alpha]_D$ = +4.65° (c = 0.5, $CHCl_3$). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.92; H, 6.91; N, 7.16.

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