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Enantiopure Synthesis of Side Chain-Modified α-Amino Acids and 5-*cis*-Alkylprolines‡

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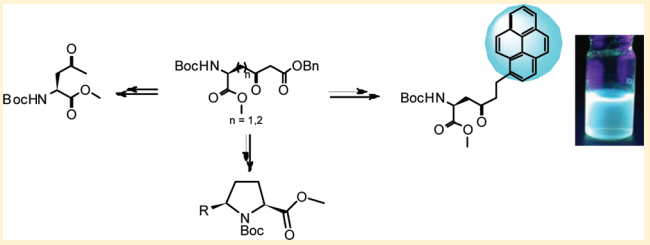
Supporting Information

ABSTRACT: A short, concise synthesis of enantiopure, side chain-modified α-amino acids such as 4-oxo-L-norvaline, 6-oxo-L-homonorleucine, and 5-*cis*-alkyl prolines is described. Knoevenagel condensation of L-aminocarboxylate-derived β-ketoesters with aldehydes followed by reductive decarboxylation results in unnatural α-amino acids in good yield. A fluorescent amino acid is synthesized using a similar protocol. These studies show that aminocarboxylate-derived β-ketoesters are very useful intermediates and the method employed is both general and practical for the preparation of γ(δ)-oxo α-amino acids and alkylprolines.



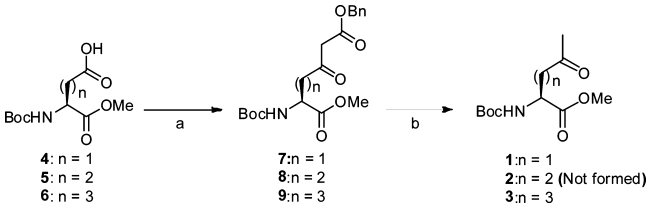
Naturally occurring and chemically synthesized nonnatural amino acids are gaining significance as useful and important tools for modern drug discovery research. Unnatural amino acids are used as chiral building blocks and molecular scaffolds for constructing molecular libraries because of their structural diversity and functional versatility. Some of these unnatural amino acids play a vital role in pharmaceuticals and lead development in drug discovery. Nongenetically coded amino acids, particularly non-natural α-amino acids, have contributed strongly in the area of peptide research. These amino acids play a significant role in peptide analogues to limit conformational flexibility, to enhance enzymatic stability, and to improve pharmacodynamics and bioavailability.[1−5] Side chain conformational restrictions deliver a practical approach in peptidomimetics to understand the interactions of peptides with proteins, nucleic acids, lipids, and sugars in biological systems.[6]

Since reactions utilizing these modified α-amino acids as organocatalysts[7,8] and/or scaffolds for building of peptidomimetics[9] are gaining importance, there is a need to synthesize such scaffolds in a novel way. For this reason, syntheses and use of some unnatural α-amino acids have been reported using different protocols.[10]

Herein, we wish to report a general, convenient, and concise synthesis of enantiopure side chain-modified amino acids and *cis*-5-alkylproline derivatives in good yields.

Coupling of *N*-Boc-L-aspartic acid 1-methyl ester[11] **4** with Meldrum's acid in the presence of DCC and DMAP gave the corresponding acyl Meldrum's acid as an intermediate. Subsequent treatment with benzyl alcohol afforded β-keto ester **7** in 61% yield using a procedure reported for similar compounds.[12] We then considered its use in syntheses of very useful keto-amino acids such as protected 4-oxo-L-norvaline **1**. Hydrogenolysis of **7** using Pd/C and triethylsilane smoothly gave the corresponding protected 4-oxo-L-norvaline **1** in 89% yield (Scheme 1).

Scheme 1[a]



[a]Reagents and conditions: (a) Meldrum's acid, DMAP, DCC, CH_2Cl_2 then BnOH, benzene, 80 °C, 53−63%; (b) Pd/C, triethylsilane, MeOH, rt, 83−89%.

Similarly, *N*-Boc-6-oxo-L-homonorleucine methyl ester **3** was prepared from *N*-Boc-L-homoglutamic acid 1-methyl ester **6** in one pot in 83% yield (Scheme 1).[13] An earlier synthesis of a protected L-homonorleucine (6-oxo α-amino acid) involved the reaction of the acid chloride with a zinc reagent from iodoalanine, which itself was derived from serine in four steps.[14] A different route to protected L-homonorleucine involved olefin metathesis of protected allyl glycine.[15] The method we have employed for the preparation of **1** and **3** promises to be general and high yielding for the preparation of oxo α-amino acids.

While the L-glutamic acid derived β-keto ester **8** did not give the anticipated protected 5-oxo-L-norleucine **2** on treatment with Pd/C and triethylsilane, instead we obtained 5-methyl-*N*-Boc-L-proline methyl ester **10** exclusively in 79% yield, which

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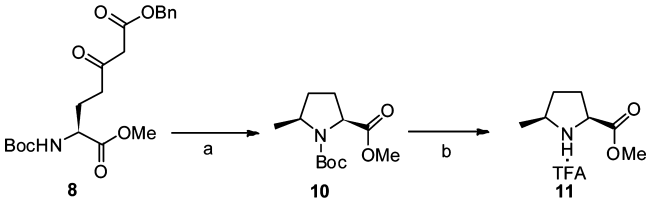
on treatment with trifluoroacetic acid gave 5-methylproline methyl ester **11** (Scheme 2).

Scheme 2[a]



[a]Reagents and conditions: (a) Pd/C, triethylsilane, MeOH, rt, 79%; (b) TFA, CH_2Cl_2, 1.5 h, 98%.

Spectroscopic data for compound **1** were in a close agreement with reported values.[16] In order to ascertain the enantiopurity of the *N*-Boc 4-oxo-L-norvaline methyl ester **1**, its enantiomer *N*-Boc 4-oxo-D-norvaline methyl ester **1a** and the racemic mixture *N*-Boc 4-oxo-DL-norvaline methyl ester **1b** were synthesized.[17] HPLC[18] showed that compound **1** was indeed optically pure, and importantly, no trace of racemization could be detected in the preparation of **1** from *N*-Boc-L-aspartic acid 1-methyl ester **4**. Earlier, protected 4-oxo-L-norvaline has been prepared via reduction of 5-diazo-4-oxo-L-norvaline,[19] by ozonolysis of 4,5-dehydroleucine from serine,[10b,c,20] by insertion of diazoalkyl into aldehyde derived from homoserine using diazomethane,[10d] and by alkylation using strong base such as LiHMDS.[21]

The optical and spectroscopic data of compound **10** were in a close agreement with reported data.[22] The *cis*-stereochemistry of **11** was unambiguously assigned by NOE studies.[23] It is important to note that we synthesized *cis*-*N*-Boc-5-methylproline methyl ester **10** in one pot from *N*-Boc-L-glutamic acid β-ketoester **8** under relatively mild conditions in contrast to the harsh conditions and longer route used earlier.[22] It is also interesting that the Boc-protected amine reacts with a β-ketoester, which is expected to exist largely in the enol form. A plausible mechanism involves β-keto decarboxylation[24] of compound **8** under hydrogenolytic conditions (Pd/C, TES)[25] giving rise to keto intermediate **2**, which then cyclizes to **10** via enamine intermediate III (Scheme 3).

Brimble[26a] and Sutherland[26b] have reported the formation of a similar six-membered enamine intermediate in their syntheses of pipecolic acid derivatives by intramolecular condensation of homoglutamic acid ω-semialdehyde with a protected amine.

The synthetic strategy that we employed for the synthesis of **1**, **3**, and **11** is short and practical and also avoids the use of explosive hazards, such as diazomethane and ozonolysis, and the use of expensive starting materials.

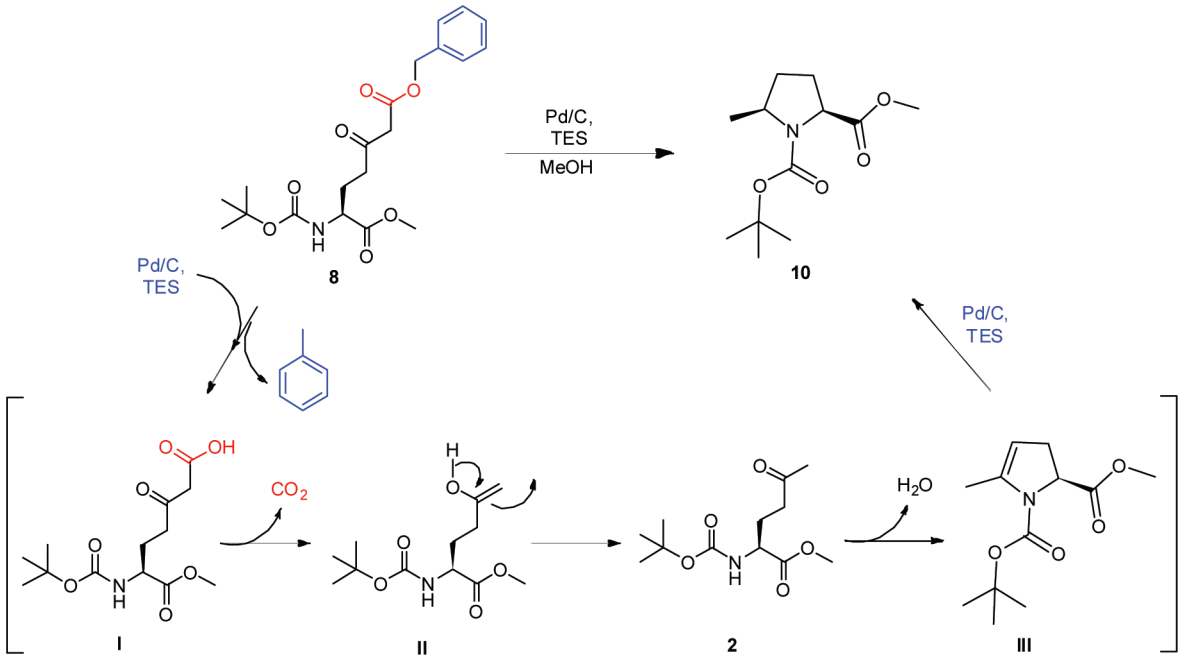
Encouraged by this initial success, we next employed a related strategy to synthesize additional keto amino acids based on aspartic and glutamic acids (Scheme 4).

We earlier reported the use of aminocarboxylate-derived β-ketoesters in the synthesis of piperidine derivatives.[27] We now planned to use aminodicarboxylate-derived β-ketoesters **7** and **8** for Knoevenagel condensation with aldehydes to synthesize various keto-amino acids. β-Ketoesters **7** and **8** condense with aldehydes to give the corresponding unsaturated β-ketoesters **12**–**14**. These on treatment with Pd/C and triethylsilane gave the novel keto α-amino acids **16**–**18** (Scheme 4).

Interestingly, although compound **18** on subjection to hydrogenolytic conditions did not give the corresponding proline derivative, treatment with $B(C_6F_5)_3$ and triphenylsilane did give compound **20** in 82% yield (Scheme 5).

Fluorescent amino acids are widely applied as labels in biology and medicine and are also valuable in combinatorial chemistry and chemical biology. Thus, attention has been directed to the design and development of nonnatural α-amino acids that have a fluorophore in their side chain.[28] We therefore embarked on the synthesis of the pyrene-derived fluorescent amino acid **19**. Hydrogenolysis of **15** led to the formation of the desired compound **19** (Scheme 4). The absorption and

Scheme 3. Plausible Mechanism for the Formation of 10



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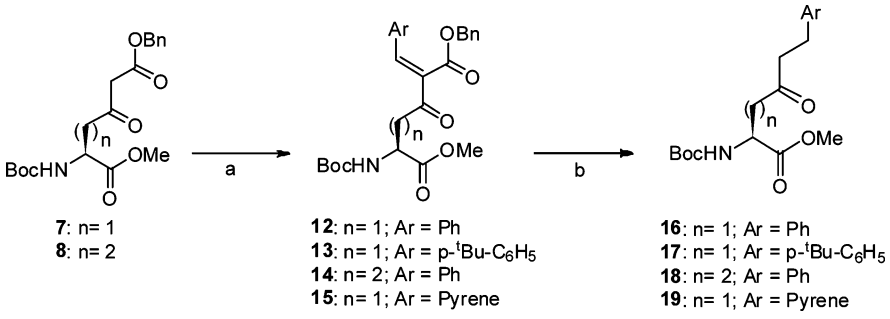
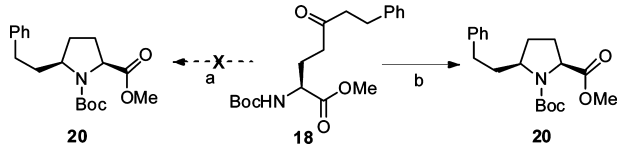
Scheme 4[a]



[a]Reagents and conditions: (a) ArCHO, condensation, 69−77%; (b) Pd/C, triethylsilane, MeOH, rt, 54−77%.

Scheme 5[a]



[a]Reagents and conditions: (a) Pd/C, triethylsilane, MeOH, rt; (b) $B(C_6F_5)_3$, triphenylsilane, −78 °C to rt, 82%.

fluorescence properties of compound **19** in dichloromethane resemble those of pyrene (Figure 1).

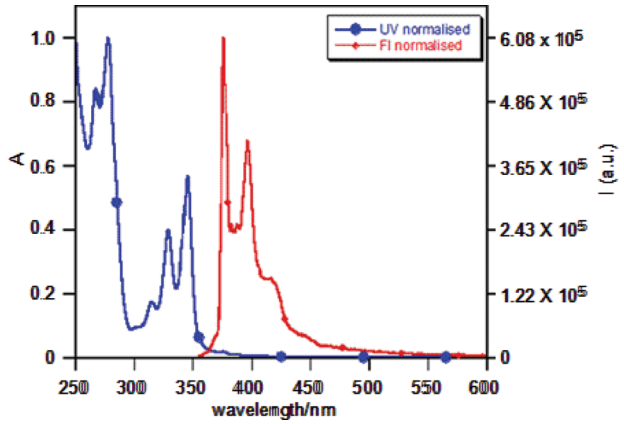


Figure 1. Normalized absorption (blue) and fluorescence (red) spectrum of **19**.

Using this protocol, any fluorescent aldehyde may easily be condensed with aminodicarboxylate-derived β-ketoesters, and series of different fluorescent nonnatural amino acids can be synthesized according to need. This result is encouraging because compound **19** and similar fluorescent amino acids can be inserted into peptides to be excited at long wavelength without excitation of tryptophan, tyrosine, or phenylalanine.

In summary, we have developed a general and efficient approach for the preparation of protected $\gamma(\delta)$-keto α-amino acids. In addition, a concise synthesis of a *cis*-5-methylproline derivative is described. The protocol thus developed should be applicable to a wide variety of keto peptides since the approach is general, useful, and simple. It has been especially exemplified by the synthesis of new fluorescent α-amino acid. The penultimate step affords protected unsaturated β-keto ester that has high potential for incorporation into peptides and proteins. Further work investigating the synthesis of various solvatochromic fluorescent amino acids and their application is underway.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm). ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ and MeOH-d_4. Chemical shifts in ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard; J values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and MeOH-d_4. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF and MALDI TOF/TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride or KBr discs and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Enantioselectivities were determined by HPLC analysis, and enantiomeric excess was determined using Chiralpak IA column with *n*-hexane and 2-propanol as eluents.

(*S*)-3-(*tert*-Butoxycarbonylamino)-4-methoxy-4-oxobutanoic Acid (4).[11] White solid (12.2 g, 45% yield): mp = 88−90 °C; R_f = 0.2 DCM/MeOH (90:10); $[\alpha]^{22}_D$ −19.2 (*c* 1, MeOH); IR (KBr) cm^{-1} 3310, 1711, 1735; δ_H (400 MHz, $CDCl_3$) 9.12 (bs, 1H), 5.55 (d, J = 8 Hz, 1H), 4.59 (t, J = 4 Hz, 1H), 3.75 (s, 3H), 3.08−3.03 (m, 1H), 2.89−2.84 (m, 1H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 176.3, 171.6, 155.6, 80.6, 52.9, 49.8, 36.7, 28.4; HRMS (ESI TOF) m/z calcd for $C_{10}H_{17}NO_6Na$ $[M + Na]^+$ 270.0954, found 270.0957.

(*R*)-3-(*tert*-Butoxycarbonylamino)-4-methoxy-4-oxobutanoic Acid (4a).[11] White solid (8.2 g, 43% yield): mp = 88−89 °C; R_f = 0.2 DCM/MeOH (90:10); $[\alpha]^{23}_D$ + 18.3 (*c* 1, MeOH); IR (Neat) cm^{-1} 3300, 1705, 1740; δ_H (400 MHz, $CDCl_3$) 9.1 (bs, 1H), 5.55 (d, J = 8 Hz, 1H), 4.60 (quintet, J = 4 Hz, 1H), 3.75 (s, 3H), 3.08−3.02 (m, 1H), 2.89−2.83 (m, 1H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 176.3, 171.6, 155.6, 80.6, 52.9, 49.8, 36.7, 28.4; HRMS (ESI TOF) m/z calcd for $C_{10}H_{17}NO_6Na$ $[M + Na]^+$ 270.0954, found 270.0955.

(*RS*)-3-(*tert*-Butoxycarbonylamino)-4-methoxy-4-oxobutanoic Acid (4b).[11] White solid (4.3 g, 44% yield): mp = 88 °C; R_f = 0.2 DCM/MeOH (90:10); IR (KBr) cm^{-1} 3318, 1713, 1739, 685; δ_H (400 MHz, $CDCl_3$) 9.11 (bs, 1H), 5.55 (d, J = 8 Hz, 1H), 4.59 (t, J = 4 Hz, 1H), 3.75 (s, 3H), 3.08−3.03 (m, 1H), 2.89−2.83 (m, 1H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 176.3, 171.6, 155.6, 80.6, 52.9, 49.7, 36.7, 28.4; HRMS (ESI TOF) m/z calcd for $C_{10}H_{17}NO_6Na$ $[M + Na]^+$ 270.0954, found 270.0962.

(*S*)-6-Benzyl 1-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxohexanedioate (7). To a well stirred mixture of (*S*)-3-((*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoic acid **4** (2.5 g, 10 mmol), Meldrum's acid (1.5 g, 10 mmol), DMAP (1.6 g, 13 mmol) in anhydrous dichloromethane (40 mL) at 0 °C was added portion-wise

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dicyclohexyl carbodiimide (DCC) (2.7 g, 13 mmol) over 10 min at 0 °C. The reaction mixture was allowed to warm to rt and stirred 5 h. The precipitate formed was removed by filtration through sintered glass funnel. Filtrate was washed with aq 1 M $KHSO_4$ solution (2 × 70 mL) and then brine (2 × 75 mL), dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The yellowish residue was dissolved in dry benzene (30 mL), benzyl alcohol (1.5 mL, 13 mmol) was added, the mixture was refluxed 4 h, and solvent was removed under reduced pressure to give crude product, which was purified by column chromatography over silica gel eluting with petroleum ether/EtOAc (97:5 to 90:30) to give **7** as a light yellow oil (2.3 g, 63% yield): R_f = 0.4 petroleum ether/EtOAc (50:50); $[\alpha]^{25}_D$ −12.3 (*c* 0.33, MeOH); IR (Neat) cm^{-1} 1739, 1711, 1156; δ_H (400 MHz, $CDCl_3$) 7.38−7.34 (m, 5H), 5.45 (d, *J* = 8 Hz, 1H), 5.17 (s, 2H), 4.52 (quintet, *J* = 4 Hz, 1H), 3.71 (s, 3H), 3.51 (s, 2H), 3.29−3.23 (m, 1H), 3.11−3.05 (m, 1H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 200.8, 171.6, 166.5, 155.6, 135.2, 128.8, 128.7, 128.6, 80.3, 67.5, 52.9, 49.5, 49.2, 45, 28.4; HRMS (ESI TOF) *m*/*z* calcd for $C_{19}H_{25}NO_7Na$ $[M + Na]^+$ 402.1529, found 402.1537.

(*R*)-6-Benzyl 1-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxohexanedioate (7a). Compound **7a** was prepared from (*R*)-3-((*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoic acid (D-aspartic acid derivative) **4a**, following the experimental procedure described for **7** above. Light yellow oil (1.3 g, 53% yield): R_f = 0.4 petroleum ether/EtOAc (50:50); $[\alpha]^{25}_D$ + 12.9 (*c*, MeOH); IR (Neat) cm^{-1} 1742, 1721, 1150, 962; δ_H (400 MHz, $CDCl_3$) 7.37−7.30 (m, 5H), 5.44 (d, *J* = 8 Hz, 1H), 5.15(s, 2H), 4.52 (quintet, *J* = 4 Hz, 1H), 3.68 (s, 3H), 3.49(s, 2H), 3.26−3.20 (m, 1H), 3.09−3.03 (m, 1H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 200.8, 171.6, 166.5, 155.5, 135.2, 128.7, 128.6, 128.5, 80.3, 67.4, 52.8, 49.4, 49.1, 44.9, 28.4; HRMS (ESI TOF) *m*/*z* calcd for $C_{19}H_{25}NO_7Na$ $[M + Na]^+$ 402.1529, found 402.1525.

(*RS*)-6-Benzyl 1-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxohexanedioate (7b). Compound **7b** was prepared from racemic-(*RS*)-3-((*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoic acid (DL-aspartic acid derivative) **4b** using a similar experimental procedure to that described for **7**.

Light yellow oil (1.45 g, 59% yield): R_f = 0.4 petroleum ether/EtOAc (50:50); IR (Neat) cm^{-1} 1738, 1712, 1149; δ_H (400 MHz, $CDCl_3$) 7.38−7.33 (m, 5H), 5.46 (d, *J* = 8 Hz, 1H), 5.16 (s, 2H), 4.54 (quintet, *J* = 4 Hz, 1H), 3.69 (s, 3H), 3.50 (s, 2H), 3.27−3.22 (m, 1H), 3.10−3.04 (m, 1H), 1.43 (s, 9H); δ_C (100 MHz, $CDCl_3$) 200.8, 171.6, 166.5, 155.6, 135.2, 128.8, 128.7, 128.5, 80.3, 67.4, 52.8, 49.4, 49.1, 45, 28.4; HRMS (ESI TOF) *m*/*z* calcd for $C_{19}H_{25}NO_7Na$ $[M + Na]^+$ 402.1529, found 402.1532.

(*S*)-7-Benzyl 1-Methyl 2-((*tert*-Butoxycarbonyl)amino)-5-oxoheptanedioate (8). Experimental procedure similar as described for (**7**). Light yellow oil (1.7 g, 53% yield): R_f = 0.5 petroleum ether/EtOAc (50:50); $[\alpha]^{25}_D$ −7.1 (*c* 1, MeOH); IR (Neat) cm^{-1} 2960, 2874, 1723, 1456, 1285; δ_H (400 MHz, $CDCl_3$) 7.37−7.34 (m, 5H), 5.17 (s, 2H), 5.08 (d, *J* = 8 Hz, 1H), 4.26 (d, *J* = 4 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 2H), 2.72−2.56 (m, 2H), 2.18−2.13 (m, 1H), 1.92−1.83 (m, 1H), 1.43 (s, 9H); δ_C (100 MHz, $CDCl_3$) 201.5, 172.8, 166.9, 155.6, 135.4, 128.8, 128.6, 128.5, 80.2, 67.3, 52.7, 52.6, 49.4, 38.9, 28.4, 26.2; HRMS (ESI TOF) *m*/*z* calcd for $C_{20}H_{27}NO_7Na$ $[M + Na]^+$ 416.1685, found 416.1681.

(*S*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxopentanoate (1). To the stirred mixture of **7** (1 g, 2.64 mmol) and 10% Pd/C (10% w/w, 0.100 g) in dry MeOH (35 mL) at rt was added triethylsilane (TES) (4.2 mL, 26 mmol). The progress of the reaction was monitored by TLC. After completion of reaction (4−5 h), the solution was filtered through a Celite bed, the filtrate evaporated under reduced pressure, and the residue purified over silica gel eluting with petroleum ether/EtOAc (98:1 to 93:7) affording **1** as a colorless oil. (0.575 g, 89% yield): R_f = 0.2 petroleum ether/EtOAc (80:20); $[\alpha]^{22}_D$ = +32.2 (*c* 1, $CHCl_3$); IR (Neat) cm^{-1} 1708, 1499, 1157; δ_H (400 MHz, $CDCl_3$) 5.50 (d, *J* = 4 Hz, 1H), 4.51 (quintet, *J* = 4 Hz, 1H), 3.73 (s, 3H), 3.20−3.16 (m, 1H), 2.98−2.94 (m, 1H), 2.17 (s, 3H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 206.6, 171.8, 155.5, 79.9, 52.6, 49.4, 45.3, 29.8, 28.2; HRMS (ESI TOF) *m*/*z* calcd for $C_{11}H_{19}NO_5Na$ $[M + Na]^+$ 268.1161, found 268.1161.

(*R*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxopentanoate (1a). Compound **1a** was prepared starting from (*R*)-6-benzyl 1-methyl 2-((*tert*-butoxycarbonyl) amino)-4-oxohexanedioate **7a**, following similar experimental procedure described for **1** above (0.153 g, 93% yield). Colorless oil (0.153 g, 93% yield): R_f = 0.2 petroleum ether/EtOAc (80:20); $[\alpha]^{22}_D$ = −31.6 (*c* 1, $CHCl_3$); IR (Neat) cm^{-1} 1712, 1485, 1151, 679; δ_H (400 MHz, $CDCl_3$) 5.48 (d, *J* = 4 Hz, 1H), 4.47 (t, *J* = 4 Hz, 1H), 3.70 (s, 3H), 3.18−3.14 (m, 1H), 2.96−2.90 (m, 1H), 2.14 (s, 3H), 1.42 (s, 9H); δ_C (100 MHz, $CDCl_3$) 206.7, 171.9, 155.62, 80.2, 52.7, 49.5, 45.5, 30, 28.4; HRMS (ESI TOF) *m*/*z* calcd for $C_{11}H_{19}NO_5Na$ $[M + Na]^+$ 268.1161, found 268.1169.

(*RS*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxopentanoate (1b). Compound **1b** was prepared starting from racemic (*RS*)-6-benzyl 1-methyl 2-((*tert*-butoxycarbonyl) amino)-4-oxohexanedioate **7b**, following similar experimental procedure described for **1** above (0.15 g, 90% yield). Colorless oil (0.150 g, 90% yield): R_f = 0.2 petroleum ether/EtOAc (80:20); IR (Neat) cm^{-1} 1709, 1478, 1148, 684; δ_H (400 MHz, $CDCl_3$) 5.48 (d, *J* = 4 Hz, 1H), 4.47 (t, *J* = 4 Hz, 1H), 3.69 (s, 3H), 3.18−3.13 (m, 1H), 2.96−2.90 (m, 1H), 2.13 (s, 3H), 1.41 (s, 9H); δ_C (100 MHz, $CDCl_3$) 206.7, 171.9, 155.6, 80.1, 52.7, 49.5, 45.5, 30, 28.4; HRMS (ESI TOF) *m*/*z* calcd for $C_{11}H_{19}NO_5Na$ $[M + Na]^+$ 268.1161, found 268.1165.

(*S*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-6-oxoheptanoate (3). Experimental procedure similar as described for (**7** and **1**). Colorless oil (0.062 g, 83% yield): R_f = 0.3 petroleum ether/EtOAc (65:35); $[\alpha]^{23}_D$ + 8.2 (*c* 1, MeOH); IR (Neat) cm^{-1} 2954, 2360, 1746, 1715, 1517, 1163; δ_H (400 MHz, $CDCl_3$) 5.11(d, *J* = 8 Hz, 1H), 4.30 (q, *J* = 8 and 4 Hz, 1H), 3.74 (s, 3H), 2.61−2.45 (m, 2H), 2.14(s, 3H), 1.81−1.78 (m, 1H), 1.68−1.60 (m, 3H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.4, 173.3, 155.5, 80.1, 53.2, 52.5, 42.9, 32.1, 30.1, 28.4, 19.4; HRMS (ESI TOF) *m*/*z* calcd for $C_{13}H_{23}NO_5K$ $[M + K]^+$ 312.1213 found 312.1219.

(2*S*,5*S*)-1-*tert*-Butyl 2-Methyl 5-Methylpyrrolidine-1,2-dicarboxylate (10). To a stirred mixture of **8** (0.650 g, 1.65 mmol) and Pd/C (10% w/w, 0.065 g) in dry MeOH (20 mL) at rt was added triethylsilane (TES) (2.64 mL, 16.52 mmol), and after 1 h an additional amount of TES (1.32 mL) was added. After completion of reaction (4 h), methanol was evaporated under vacuum, and the residue purified over silica gel eluting with petroleum ether/EtOAc (100:0 to 90:10) affording **10** as a colorless oil (0.280 g, 79% yield): R_f = 0.4 petroleum ether/EtOAc (80:20); $[\alpha]^{25}_D$ = −28.4 (*c* 1, MeOH); IR (Neat) cm^{-1} 1750, 1693, 1387, 1364, 1164; (rotamers) δ_H (400 MHz, $CDCl_3$) 4.35−4.33 (m, 1H), 4.22−4.19 (m, 1H), 4.01 (bs, 1H), 3.91 (bs, 1H), 3.73 (s, 6H), 2.19−2.16 (m, 2H), 2.05−2 (m, 4H), 1.63 (m, 2H), 1.47 (s, 9H), 1.41 (s, 9H), 1.27 (d, *J* = 6 Hz, 6H); (showed a mixture of carbamate isomers) δ_C (100 MHz, $CDCl_3$) 174.2, 173.9, 155.5, 154.4, 79.9, 60.3, 59.9, 54.2, 52.1, 32.6, 31.8, 28.9, 28.4, 20.7, 19.9; HRMS (MALDI TOF/TOF) *m*/*z* calcd for $C_{12}H_{21}NO_4Na$ $[M + Na]^+$ 266.1368 found 266.1369.

(2*S*,5*S*)-Methyl 5-Methylpyrrolidine-2-carboxylate (11). To a stirred solution of **10** (0.2 g, 0.82 mmol) in dry DCM (3 mL) at 0 °C was added acetic acid (TFA) (1.3 mL, 16 mmol), and gradually the reaction mixture was warmed to rt. After completion of reaction (1.5 h) DCM was evaporated under vacuum, and the residue precipitated with diethyl ether to give **11** as a white solid (0.115 g, 98% yield): mp = 114−116 °C ; IR (KBr) cm^{-1} 1742, 1676, 1438, 1205, 1143; δ_H (400 MHz, MeOH-d_4) 4.47 (t, *J* = 8 Hz, 1H), 3.85 (s, 3H), 3.77−3.72 (m, 1H), 2.45−2.37 (m, 2H), 1.75−1.68 (m, 1H), 1.45 (d, *J* = 4 Hz, 3H); δ_C (100 MHz, MeOH-d_4) 170.5, 60.7, 58.4, 53.9, 31.6, 28.2, 17.5; $[\alpha]^{25}_D$ −4.3 (*c* 0.3, MeOH); HRMS (ESI TOF) *m*/*z* calcd for $C_7H_{14}NO_2$ $[M + H]^+$ 144.1025, found 144.1027.

(*S*)-(*E*,*Z*)-1-Benzyl 7-Methyl 2-Benzylidene-6-((*tert*-butoxycarbonyl)amino)-3-oxoheptanedioate (14). To a stirred mixture of **8** (0.5 g, 1.27 mmol) and benzaldehyde (0.1 mL, 1.27 mmol) in benzene (65 mL) were added piperidine (0.013 mL, 0.127 mmol) and acetic acid (0.015 mL, 0.24 mmol). The reaction mixture was refluxed using Dean−Stark apparatus to remove the water. After completion of reaction (2.5−3 h), benzene was evaporated under vacuum, and the residue purified by flash chromatography over silica

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gel eluting with petroleum ether/EtOAc (98:2 to 70:30) giving **14** as a light yellow oil (0.480 g, 77% yield): (*E*:*Z* = 0.96:1); R_f = 0.6 petroleum ether/EtOAc (50:50); $[\alpha]^{25}_D$ −4.2 (*c* 1, MeOH); IR (Neat) cm^{-1} 1700, 1497, 1158; (mixture of *E* and *Z* isomers) δ_H (400 MHz, $CDCl_3$) 7.74 (s, 1H), 7.60 (s, 1H), 7.39−7.25 (m, 20H), 5.30−5.29 (m, 4H), 5.1 (bs, 1H), 4.94 (bs, 1H), 4.34 (bs, 1H), 4.21 (bs, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.84−2.82 (m, 2H), 2.66−2.62 (m, 2H), 2.05−1.96 (m, 2H), 1.94−1.91 (m, 2H), 1.44 (s, 9H), 1.40 (s, 9H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, $CDCl_3$) 204.3, 95.8, 172.8, 167.6, 164.3, 155.5, 141.8, 141.5, 135.5, 133.3, 132.9, 130.8, 129.8, 129.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 80.2, 79.9, 67.8, 67.4, 53.6, 52.6, 52.5, 39.7, 34.9, 28.4, 26.9, 26.6; HRMS (MALDI TOF/TOF) *m*/*z* calcd for $C_{27}H_{31}NO_7Na$ $[M + Na]^+$ 504.1998 found 504.2009.

(*S*,*Z*)-1-Benzyl 6-Methyl 2-Benzylidene-5-((*tert*-butoxycarbonyl)amino)-3-oxohexanedioate (12). Experimental procedure similar as described for (**14**). **12** was obtained as a pale yellow oil (0.210 g, 74% yield): (*E*:*Z* = 0.71:1); $[\alpha]^{25}_D$ −3.8 (*c* 0.8, MeOH); IR (Neat) cm^{-1}1714, 1477, 1165; (mixture of *E* and *Z* isomers) δ_H (400 MHz, $CDCl_3$) 7.77 (s, 1H, *E*), 7.61 (s, 1H, *Z*), 7.41−7.23 (m, 20H), 5.55−5.48 (m, 2H), 5.29−5.26 (m, 4H), 4.62 (quintet, *J* = 4 Hz, 1H), 4.51 (quintet, *J* = 4 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.51 (m, 1H), 3.35−3.25 (m, 2H), 3.16 (m, 1H), 1.45 (d, *J* = 8 Hz, 18H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, $CDCl_3$) 202.9, 194.6, 171.8, 171.7, 167.1, 164.1, 155.6, 142.7, 135.4, 134.6, 133.3, 132.6, 132.1, 131.1, 130.9, 130.1, 129.8, 129.2, 129, 128.9, 128.8, 128.7, 128.6, 128.4, 80.2, 80.1, 67.9, 67.4, 52.8, 52.6, 49.5, 49.1, 45.6, 41.2, 28.5, 28.4; HRMS (MALDI TOF/TOF) *m*/*z* calcd for $C_{26}H_{29}NO_7Na$ $[M + Na]^+$ 490.1841 found 490.1844.

(*S*,*E*,*Z*)-1-Benzyl 6-Methyl 5-((*tert*-Butoxycarbonyl)amino)-2-(4-(*tert*-butyl)benzylidene)-3-oxohexanedioate (13). The experimental procedure is similar as described for **14**. Product **13** was obtained as a light yellow oil (0.335 g, 73% yield): (*E*:*Z* = 0.64:1); $[\alpha]^{25}_D$ −4.4 (*c* 0.9, MeOH);IR (Neat) cm^{-1} 2977, 1718, 1498, 1167; (mixture of *E* and *Z* isomers) δ_H (400 MHz, $CDCl_3$) 7.71 (s, 1H, *E*), 7.58 (s, 1H, *Z*), 7.38−7.31 (m, 14H), 7.26−7.25 (m, 4H), 5.55−5.50 (m, 2H), 5.30−5.26 (m, 4H), 4.62−4.56 (m, 2H), 3.73 (s, 3H), 3.66 (s, 3H), 3.50−3.19 (m, 4H), 1.43 (d, *J* = 4 Hz, 18H), 1.30 (d, *J* = 8 Hz, 18H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, $CDCl_3$) 203, 194.6, 171.9, 167.4, 155, 148.3, 142.7, 135.6, 134.8, 130.9, 130.3, 129.9, 129.7, 129.3, 128.8, 128.74, 128.7, 128.6, 128.55, 128.4, 126.1, 126, 125.7, 80.2, 67.8, 67.4, 52.8, 52.6, 45.6, 41.1, 35.1, 31.5, 31.22, 31.19, 28.53, 28.47; HRMS (MALDI TOF/TOF) *m*/*z* calcd for $C_{30}H_{37}NO_7Na$ $[M + Na]^+$ 546.2468 found 546.2479.

(*S*,*Z*)-1-Benzyl 6-Methyl-5-((*tert*-butoxycarbonyl)amino)-3-oxo-2-(pyren-1-ylmethylene)hexanedioate (15). The experimental procedure was similar to that described for **14** and gave product **15** as a light yellow oil (0.180 g, 69% yield): (*E*:*Z* = 1:0.86); $[\alpha]^{25}_D$ −5.9 (*c* 1, MeOH); IR (Neat) cm^{-1} 1715, 2927, 1593, 1498, 1366, 1209, 1165, 848; (mixture of *E* and *Z* isomers) δ_H (400 MHz, $CDCl_3$) 8.83 (s, 1H, *E*), 8.73 (s, 1H, *Z*), 8.28−7.99 (m, 16H), 7.87−7.82 (m, 3H), 7.47−7.37 (m, 5H), 7.14 (m, 1H), 7.03−6.90 (m, 3H), 5.64 (d, *J* = 8 Hz, 1H), 5.41−5.34 (m, 3H), 5.13 (s, 2H), 4.71 (quintet, *J* = 4 Hz, 1H), 4.39 (quintet, *J* = 4 Hz, 1H), 3.80 (s, 3H), 3.69−3.63 (m, 1H), 3.48−3.41 (m, 4H), 3.20−3.14 (m, 1H), 3.01−2.95 (m, 1H), 1.48 (s, 9H), 1.37 (s, 9H); (mixture of *E* and *Z* isomers) δ_C (100 MHz, $CDCl_3$) 202.5, 194.4, 171.9, 171.6, 164.2, 155.7, 155.5, 142.2, 141.6, 135.5, 135.1, 134.5, 134.2, 133.1, 131.3, 130.8, 130, 129.9, 129.13, 129.1, 129.05, 128.9, 128.7, 128.6, 128.4, 128.35, 127.4, 127.3, 127, 126.6, 126.56, 126.5, 126.43, 126.4, 126.36, 125.9, 124.8, 124.7, 124.5, 123.1, 123, 80.3, 80, 67.6, 67.5, 52.9, 52.5, 45.9, 41.9, 28.5, 28.4; HRMS (MALDI TOF/TOF) *m*/*z* calcd for $C_{36}H_{33}NO_7Na$ $[M + Na]^+$ 614.2155 found 614.2157.

(*S*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxo-6-phenylhexanoate (16). Experimental procedure as for (**1**); product **16** obtained as a white solid (0.116 g, 77% yield): mp = 62−63 °C; $[\alpha]^{25}_D$ −12.8 (*c* 1, MeOH); IR (KBr) cm^{-1} 2962, 1715, 1492, 1391, 1161; δ_H (400 MHz, $CDCl_3$) 7.29−7.26 (m, 2H), 7.21−7.15 (M, 3H), 5.49 (d, *J* = 8 Hz, 1H), 4.49 (quintet, *J* = 4 Hz, 1H), 3.71 (s, 1H), 3.12 (m, 1H), 2.94−2.86 (m, 3H), 2.77−2.72 (m, 2H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.1, 171.9, 155.6, 140.6, 128.6, 128.4, 126.3, 80.2, 52.8, 49.5, 44.8, 44.3, 29.6, 28.4; HRMS (MALDI TOF/TOF) *m*/*z* calcd for $C_{18}H_{25}NO_5Na$ $[M + Na]^+$ 358.1630 found 358.1614.

(*S*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-6-(4-(*tert*-butyl)-phenyl)-4-oxohexanoate (17). Experimental procedure as for (**1**); product **17** obtained as a colorless oil (0.192 g, 72% yield): R_f = 0.5 petroleum ether/EtOAc (50:50); $[\alpha]^{25}_D$ −8.6 (*c* 1, MeOH); IR (Neat) cm^{-1} 2963, 1716, 1499, 1392, 1165; δ_H (400 MHz, $CDCl_3$) 7.31 (d, *J* = 8 Hz, 2H), 7.1 (d, *J* = 12 Hz, 2H), 5.51 (d, *J* = 12 Hz, 1H), 4.50 (quintet, *J* = 4 Hz, 1H), 3.71 (s, 3H), 3.18−3.12 (m, 1H), 2.96−2.71 (m, 5H), 1.44 (s, 9H), 1.30 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.8, 172.6, 155.1, 149.8, 138.2, 128.6, 126.2, 80.8, 53.4, 50.2, 45.3, 44.9, 35.1, 32.1, 29.6, 29.1; HRMS (ESI TOF) *m*/*z* calcd for $C_{22}H_{33}NO_5Na$ $[M + Na]^+$ 414.2256, found 414.2251.

(*S*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-5-oxo-7-phenylheptanoate (18). Experimental procedure as described for (**1**); product **18** obtained as a colorless oil (0.268 g, 77% yield): R_f = 0.5 petroleum ether/EtOAc (50:50); $[\alpha]^{25}_D$ −12.6 (*c* 1, MeOH); IR (Neat) cm^{-1} 1742, 1705, 1158; δ_H (400 MHz, $CDCl_3$) 7.30−7.26 (m, 2H), 7.21−7.16 (m, 3H), 5.10 (d, *J* = 8 Hz, 1H), 4.29 (q, *J* = 8 and 4 Hz, 1H), 3.73 (s, 3H), 3.90 (t, *J* = 8 Hz, 2H), 2.73 (t, *J* = 8 Hz, 2H), 2.55−2.42 (m, 2H), 2.15−2.10 (m, 1H), 1.19−1.84 (m, 1H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.8, 172.9, 155.6, 141, 128.6, 128.4, 126.3, 80.1, 52.9, 52.5, 44.5, 38.8, 29.8, 28.4, 26.6; HRMS (ESI TOF) *m*/*z* calcd for $C_{19}H_{27}NO_5Na$ $[M + Na]^+$ 372.1787, found 372.1787.

(*S*)-Methyl 2-((*tert*-Butoxycarbonyl)amino)-4-oxo-6-(pyren-1-yl)hexanoate (19). Experimental procedure as described for (**1**); product **19** obtained as a pale yellow oil (0.075 g, 54% yield): R_f = 0.2 petroleum ether/EtOAc (80:20); $[\alpha]^{25}_D$ −4.1 (*c* 1, MeOH); IR (Neat) cm^{-1} 1732, 1708; δ_H (500 MHz, $CDCl_3$) 8.22−8.10 (m, 5H), 8.03−8.00 (m, 3H), 7.86 (d, *J* = 8 Hz, 1H), 5.53 (d, *J* = 8 Hz, 1H), 4.52 (t, *J* = 4 Hz, 1H), 3.72 (s, 3H), 3.62 (t, *J* = 8 Hz, 2H), 3.19−3.13 (m, 1H), 3.00−2.93 (m, 3H), 1.44 (s, 9H); δ_C (100 MHz, $CDCl_3$) 208.1, 172.1, 155.7, 134.7, 131.5, 130.3, 128.6, 127.8, 127.6, 127.2, 127, 126.1, 125, 125.1, 122.9, 80.3, 52.8, 49.6, 44.9, 44.4, 28.4, 27.2; HRMS (MALDI TOF/TOF) *m*/*z* calcd for $C_{28}H_{29}NO_5Na$ $[M + Na]^+$ 482.1943 found 482.1937.

(2*S*,5*S*)-1-*tert*-Butyl 2-Methyl 5-Phenethylpyrrolidine-1,2-dicarboxylate (20). To a stirred mixture of **18** (0.558 g, 1.46 mmol) and $B(C_6F_5)_3$ (0.075 g) in dry DCM (10 mL) was added triphenylsilane (1.14 g) in dry DCM (3 mL) at −78 °C, and the reaction mixture was allowed to warm to rt. After completion of reaction (2 h), DCM was evaporated and the residue purified by flash chromatography over silica gel eluting with petroleum ether/EtOAc (100:0 to 90:10) to give **20** as a colorless oil (0.339 g, 82% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); $[\alpha]^{25}_D$ −4.4 (*c* 0.29, MeOH); IR (Neat) cm^{-1} 2973, 1751, 1697, 1392, 1169; (showed a mixture of carbamate isomers) δ_H (400 MHz, $CDCl_3$) 7.26−7.15 (m, 10H), 4.36 (t, *J* = 8 Hz, 1H), 4.22 (t, *J* = 8 Hz, 1H), 3.98 (bs, 1H), 3.83 (bs, 1H), 3.71 (s, 6H), 2.67−2.65 (m, 4H), 2.20−2.16 (m, 4H), 2.0−1.92 (m, 4H), 1.76−1.72 (m, 4H), 1.43 (s, 9H), 1.40 (s, 9H); (rotational isomers) δ_C (100 MHz, $CDCl_3$) 174.1, 153.8, 142.4, 142.1, 128.5, 128.4, 125.9, 125.8, 80.11, 80.02, 60.2, 59.8, 58.5, 58.2, 52.3, 52.11, 36.6, 36.2, 33.2, 33.1, 30.3, 29.6, 29.1, 28.6, 28.4, 28.3; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{27}NO_4Na$ $[M + Na]^+$ 356.1838, found 356.1831.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR, ^{13}C NMR spectra are provided for compounds **1**, **1a**, **1b**, **3**, **4**, **4a**, **4b**, **7**, **7a**, **7b**, **8**, **10**−**20**. HPLC chromatograms of **1**, **1a**, **1b** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

‡Dedicated to Prof. S. Chandrasekaran.

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(17) Compounds **1a** and **1b** were synthesized from derivatives of D-aspartic acid **4a** and DL-aspartic acid **4b** via β-keto ester intermediates **7a** and **7b**, respectively.
(18) HPLC was carried out using Chiralpak IA (5 μm, Dim: 4.6 × 250 mm ID), solvent system: 10% isopropyl alcohol in *n*-hexane.
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