Notes

An Effective Synthesis of N-(9-Fluorenylmethyloxycarbonyl) α-Amino Aldehydes from S-Benzyl Thioesters

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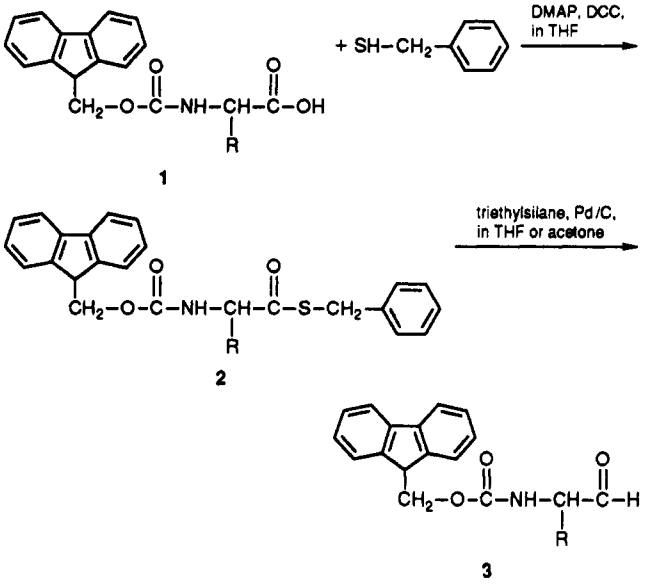
Optically active N-protected α-amino aldehydes are useful chiral building blocks and widely used in the synthesis of peptides, peptide analogues, and natural products.[1] In connection with our synthetic programs, we required an efficient method for the preparation of multifunctional *N*-(9-fluorenylmethyloxycarbonyl) (Fmoc) α-amino aldehydes.

In general, aldehydes have been prepared by oxidation of the corresponding alcohols.[2] Reduction of α-acylamino carboxylic esters with diisobutyl aluminum hydride at low temperature is also a useful method for preparation of α-amino aldehydes.[3] A two-step procedure involving the transformation of *N*-(*tert*-butyloxycarbonyl) (Boc) amino acids to the suitable amides followed by lithium aluminum hydride reduction has been a better methodology for the preparation of low racemization *N*-Boc-protected amino aldehydes.[4] However, these reactions are not suitable for the synthesis of multifunctional compounds, such as *N*-acylamino aspartyl aldehyde, because the carboxylic ester does not survive under these hydride reduction conditions. More recently, reduction of *S*-ethyl thioesters to the corresponding aldehydes with triethylsilane has been reported and demonstrated that a variety of functional groups have survived the essentially neutral conditions.[5] However, no application of this reductive procedure to the synthesis of Fmoc-protected α-amino aldehydes has been described. Here we would like to describe our results of triethylsilane reductive reaction on *N*-Fmoc-protected α-amino thioesters. We prepared the *S*-ethyl *N*-(9-fluorenylmethyloxycarbonyl)amino carboxylic thioesters and followed the reported reduction procedure.[5] However, the reduction of *S*-ethyl *N*-Fmoc-protected thioesters did not produce the expected results; products with the loss of *N*-(9-fluorenylmethyloxycarbonyl) gorup and a mixture of products were obtained. It has been observed that triethylsilane in the presence of palladium could attack the alkoxycarbonylamino group to give an amine.[6] Therefore, we assumed that the benzyl group of the thioester, as compared with the ethyl group, may be a better leaving group under the reductive conditions. Indeed the benzyl thioester was found to be more reactive toward the reducing reagent, and the desired product is formed.

Scheme I



We synthesized *S*-benzyl *N*-(9-flourenylmethyloxycarbonyl) α-amino carboxylic thioesters **2** by the reaction of the corresponding acids **1** with benzyl mercaptan and dicyclohexylcarbodiimide (DCC) in anhydrous tetrahydrofuran in the present of catalytic amount of 4-(dimethylamino)pyridine (DMAP). Reduction of **2** with triethylsilane in acetone or tetrahydrofuran with 10% palladium on activated carbon as a catalyst, after flash column chromatography, gave pure *N*-(9-fluorenylmethyloxycarbonyl) α-amino aldehydes **3** in satisfactory yield (Scheme I).

S-Benzyl *N*-(9-fluorenylmethyloxycarbonyl)amino carboxylic thioesters **2** with various side-chain functional groups have been converted into the corresponding aldehydes **3**. The reaction is generally completed in several hours at room temperature. Purification by flash column chromatography on silica gel eluted with organic solvents in the presence of 0.1% pyridine gives configurationally pure aldehyde. The generality of this effective procedure for the preparation of *N*-(9-fluorenylmethyloxycarbonyl) α-amino aldehydes **3** is apparent from the results shown in Table I. It is worth noting that the reaction conditions employed for the synthesis are sufficiently mild for acid- and base-sensitive compounds. Thus, a variety of functional groups such as alkyl carboxylic ester, *N*-(*tert*-

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(2) (a) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, 47, 3016. (b) Evans, D. A.; Takce, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371. (c) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, 104, 5719. (d) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. (e) Natarajan, S.; Condon, M. E.; Nakane, M.; Reid, J.; Gordon, E. M.; Cushman, D. W.; Ondetti, M. A. In *Peptides Synthesis-Structure-Function*; Rich, D. H.; Gross, E., Eds.; Pierce Chemical Co.; Rockford, IL **1981**; 429.

(3) Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, *J. Chem. Pharm. Perkin Trans.* **1982**, *1*, 307. (b) Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081. (c) Rich, D. H.; Sun, E. T.; Ulm, E. *J. Med. Chem.* **1980**, *23*, 27. (d) Gol Ebiowski, A.; Jacobsson, U.; Jurczak, J. J. *Tetrahedron* **1987**, *43*, 3063.

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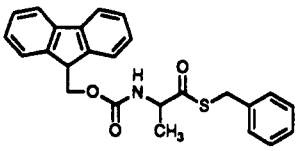
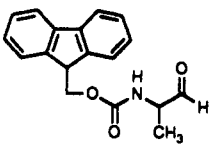
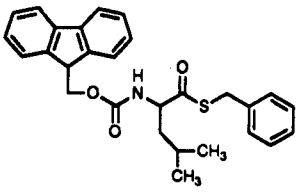
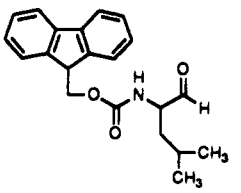
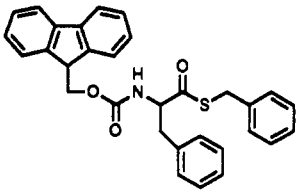
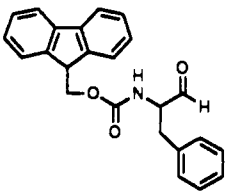
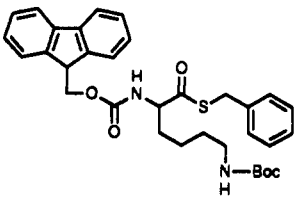
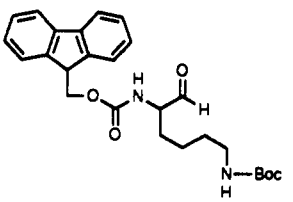
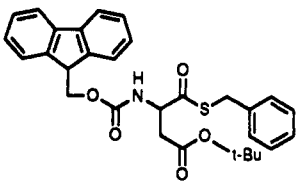
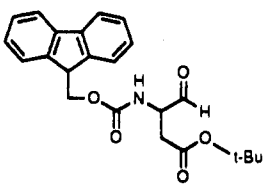
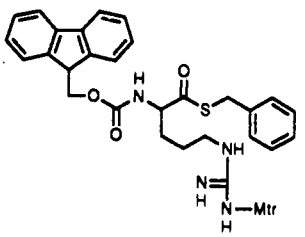
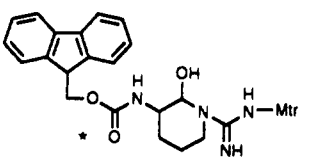
(5) Fukayama, T.; Shao-Cheng Lin; Leping Li. *J. Am. Chem. Soc.* **1990**, *112*, 1050.

(6) Birkofer, L.; Bierstein, E.; Ritter, F. *Chem. Ber.* **1961**, *94*, 821.

0022-3263/93/1958-2313$04.00/0

Table I. Reduction of *S*-Benzyl Thioester to Aldehyde[a]

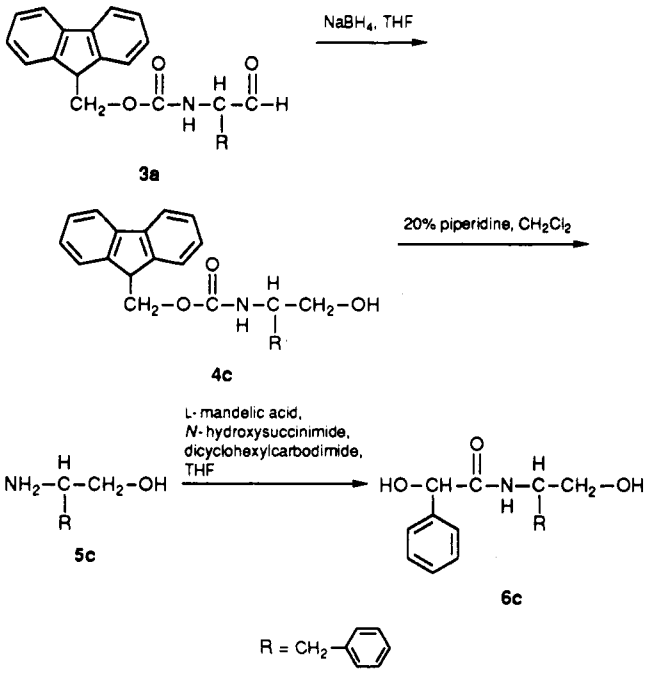
entry	substrate	product	isolated yield, %	$[\alpha]_D$, deg
I	 **2a**	 **3a**	77	−11.5°
II	 **2b**	 **3b**	72	+26.1
III	 **2c**	 **3c**	70	+49.6
IV	 **2d**	 **3d**	75	+11.3
V	 **2e**	 **3e**	75	−1.40
VI	 **2f**	 **3f**	67	−23.2

[a] Boc = *tert*-butyloxycarboxyl; *t*-Bu = *tert*-butyl; Mtr = (4-methoxy-2,3,6-trimethylphenyl)sulfonyl; $[\alpha]_D$ (*c* 1.0 in $CHCl_3$) for L-amino aldehydes; *Note ref 7.

butyloxycarbonyl) and 4-methoxy-2,3,6-trimethylphenylsulfonyl survives under these practically neutral conditions and the aldehydes **3** were obtained in good yields (Scheme II).

To find out whether *N*-(fluorenylmethyloxycarbonyl) α-amino aldehydes **3** significantly ramcemized during their preparation and purification on silica gel column, we selected *N*-(fluorenylmethyloxycarbonyl)phenylalaninal (**3c**) since aromatic aldehydes were reported as the most sensitive to acid-catalyzed racemization.[3b] Thus, *N*-(fluorenylmethyloxycarbonyl)phenylalaninal (**3c**) (L- or D-form) was first reduced by sodium borohydride to the corresponding alcohol **4c**. Removal of the fluorenylmethyloxycarbonyl group with piperidine, after purification, yielded the crystalline phenylalaninol **5c**: mp 89 °C, $[\alpha]$ −25.9° (*c* 1.2, 1 N HCl) for L-form and mp 90 °C, $[\alpha]$ +25.5° (*c* 1.2, 1 N HCl) for D-form. This study demonstrated that our methodology produces no significant racemization and gives high optical purity of α-amino aldehydes **3**. Furthermore to test the enantiomeric purity of **3** prepared under our conditions, we use L-mandelic acid to prepare separately both L-mandeloyl-L-phenylalaninol and L-mandeloyl-D-phenylalaninol (**6c**) from the amino alcohol **5c** (L- or D-form).[8] HPLC analysis of the L,L amide **6c** showed a single major component (99+%) with retention time (t_R) of 24.1 min, along with a minor fraction (less than

Scheme II



1%) with retention time of 25.2 min for L,D amide, and L,D amide **6c** also showed the expected major component (approximate 99%) with retention time 25.2 min, along with a minor peak (approximate 1%) with retention time of 24.1 min. All of these experiments proved that α-amino aldehydes **3** obtained by reduction of *S*-benzyl thioester **2** undergo little or insignificant racemization.

Experimental Section

All chemicals are commercially available. THF was distilled from benzophenone and sodium under argon before use. Anhydrous acetone is commercially available and was used without further purification. DMF was dried over molecular sieve 4A before use. NMR spectra were recorded on a Varian 60-MHz spectrometer with TMS as an internal standard. Melting points are uncorrected and were taken on a Mettler Fb-62 capillary tube apparatus. Infrared spectrum were recorded on a Perkin-Elmer 1420 spectrophotometer in KBr or $CHCl_3$. Optical rotation were recorded on a Perkin-Elmer 241. Elemental analysis were performed at Galbraith Laboratories Inc. HPLC were performed on a Shimadzu LC-6A C-R4A, with Chemcosorb C-18, 5 μm, 4.6 × 250 mm column.

Preparation of *S*-Benzyl *N*-(Fluorenylmethyloxycarbonyl)amino Thioesters 2. General Procedure. To a stirred solution of *N*-(fluorenylmethyloxycarbonyl)-L-amino acid **1** (0.032 mol) and benzyl mercaptan (0.064 mol) in anhydrous tetrahydrofuran (300 mL) at room temperature under argon atmosphere was added 4-(dimethylamino)pyridine (0.0032 mol) and dicyclohexylcarbodiimide (0.035 mol). The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue which was dissolved in 400 mL of ethyl acetate was washed with 1 N HCl (2 × 300 mL). The organic solution was dried over sodium sulfate anhydrous. Filtration and removal of solvent gave the crude product which was crystallized from ethyl ether to yield the pure *S*-benzyl-*N*-(fluorenylmethyloxycarbonyl)amino thioesters **2**.

***N*-(Fluorenylmethyloxycarbonyl)-L-alanine *S*-benzyl thioester (2a)**: yield 80%; mp 136–137 °C; $[\alpha]_D$ −11.5° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.3 (d, 3 H, CH_3), 4.0 (s, 2 H, SCH_2), 4.3 (m, 4 H, CH), 5.3 (d, 1 H, NH), 7.5 (m, 13 H, aromatic-H); IR (KBr) 3200, 3000, 1700, 1690, 1530 cm^{-1}. Anal. Calcd for $C_{25}H_{23}NO_3S$ (417.5): C, 71.92; H, 5.55; N, 3.35. Found: C, 71.90; H, 5.56; N, 3.39.

***N*-(Fluorenylmethyloxycarbonyl)-L-leucine *S*-benzyl thioester (2b)**: yield 75%; mp 126–128 °C; $[\alpha]_D$ −25.6° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 0.9 (d, 6 H, CH_3), 1.4 (t, 2 H, CH_2), 1.6 (m, 1 H, CH), 4.0 (s, 2 H, SCH_2), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, NH), 7.4 (m, 13 H, aromatic-H); IR (KBr) 3500, 2900, 1725, 1645, 1530 cm^{-1}. Anal. Calcd for $C_{28}H_{29}NO_3S$ (459.6): C, 73.17; H, 6.36; N, 3.05. Found: C, 73.06; H, 6.34; N, 3.04.

***N*-(Fluorenylmethyloxycarbonyl)-L-phenylalanine *S*-benzyl thioester (2c)**: yield 74%; mp 135–137 °C; $[\alpha]_D$ −51.7° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 3.0 (d, 2 H, CH_2), 4.0 (s, 2 H, SCH_2), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, NH), 7.4 (m, 18 H, aromatic-H); IR (KBr) 3400, 3000, 1710, 1680, 1540 cm^{-1}. Anal. Calcd for $C_{31}H_{27}NO_3S$ (493.6): C, 75.43; H, 5.51; N, 2.83. Found: C, 75.50; H, 5.10; N, 2.82.

***N*-(Fluorenylmethyloxycarbonyl)-*N*-ε-(*tert*-butyloxycarbonyl)-L-lysine *S*-benzyl thioester (2d)**: yield 82%; mp 99–101 °C; $[\alpha]_D$ −17.7° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.3 (s, 9 H, CH_2), 1.6 (m, 6 H, CH_2), 3.0 (d, 2 H, CH_2N), 4.0 (s, 2 H, SCH_2), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, NH), 7.4 (m, 13 H, aromatic-H); IR (KBr) 3350, 3000, 1710, 1680, 1540 cm^{-1}. Anal. Calcd for $C_{33}H_{38}N_2O_3S$ (574.7): C, 68.96; H, 6.66; N, 4.87. Found: C, 68.91; H, 6.67; N, 4.89.

***N*-(Fluorenylmethyloxycarbonyl)-L-aspartic acid β-*tert*-butyl ester *S*-benzyl thioester (2e)**: yield 85% mp 126–127 °C; $[\alpha]_D$ +1.1° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.4 (s, 9 H, CH_3), 2.8 (d, 2 H, CH_2), 4.0 (s, 2 H, SCH_2), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, NH), 7.4 (m, 13 H, aromatic-H); IR (KBr) 3360, 3000, 1720, 1680, 1510 cm^{-1}. Anal. Calcd for $C_{30}H_{31}NO_5S$ (517.6): C, 69.61; H, 6.03; N, 2.70. Found: C, 69.60; H, 5.57; N, 2.70.

***N*-(Fluorenylmethyloxycarbonyl)-*N*-γ-[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]-L-arginine *S*-benzyl thioester (2f)**: yield 82%; mp 76–77 °C; $[\alpha]_D$ −23.2° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.6 (m, 4 H, CH_2), 2.0 (s, 3 H, CH_3), 2.5 (s, 3 H, CH_3), 2.6 (s, 3 H, CH_3), 3.6 (t, 2 H, CH_2N)) 3.8 (s, 3 H, CH_3), 4.0 (s, 2 H, SCH_2), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, NH), 6.4 (s, 1 H, aromatic-H), 6.6 (s, 2 H, NH), 7.4 (m, 13 H, aromatic-H); IR (KBr) 3350, 3000, 1720, 1670, 1510 cm^{-1}. Anal. Calcd for $C_{38}H_{42}N_4O_6S_2$ (714.9): C, 63.84; H, 5.92; N, 2.84. Found: C, 63.85; H, 6.16; N, 2.83.

Preparation of *N*-(Fluorenylmethyloxycarbonyl)amino Aldehydes 3. General Procedure. To a stirred solution of *N*-(fluorenylmethyloxycarbonyl)amino *S*-benzyl thioester **2** (0.0115 mol) and 10% Pd on carbon (25% by weight) in anhydrous acetone (150 mL) or tetrahydrofuran (100 mL) at room temperature under argon atmosphere was slowly added a solution of triethylsilane (0.0345 mol) in anhydrous acetone (5.5 mL). After the reaction mixture was stirred for 2 h and if the reaction was not completed, a second portion of triethylsilane (0.0345 mol) was added. The reaction mixture was stirred for additional 2 h and filtered through a layer of Celite. Removal of solvent under reduced pressure yielded the crude product which was purified by flash column chromatography eluted with 20% ethyl acetate in petroleum ether in the present of 0.1% pyridine (by volume). Crystallization from ethyl ether/petroleum ether gave pure *N*-(fluorenylmethyloxycarbonyl)amino aldehydes **3**.

***N*-α-(Fluorenylmethyloxycarbonyl)alaninal (3a)**: yield 77%; mp 136–137 °C; $[\alpha]_D$ −11.5° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.3 (d, 3 H, CH_3), 4.3 (m, 4 H, CH), 5.3 (d, 1 H, NH), 7.5 (m, 8 H, aromatic-H), 9.4 (s, 1 H, CHO); IR (KBr) 3350, 2970, 1740, 1690, 1530 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_3$ (295.3): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.22; H, 5.79; N, 4.73.

***N*-α-(Fluorenylmethyloxycarbonyl)leucinal (3b)**: yield 72%; mp 78–79 °C; $[\alpha]_D$ +26.1° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 0.9 (d, 6 H, CH_3), 1.4 (t, 2 H, CH_2), 1.6 (m, 1 H, CH), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, NH), 7.4 (m, 8 H, aromatic-H), 9.5 (s, 1 H, CHO); IR (KBr) 3330, 2960, 1730, 1690, 1530 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_3$ (337.4): C, 74.75; H, 6.87; N, 4.15. Found: C, 74.77; H, 5.87; N, 4.15.

***N*-α-(Fluorenylmethyloxycarbonyl)-L-phenylalaninal (3c)**: yield 70%; mp 129–130 °C; $[\alpha]_D$ +49.6° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 3.0 (d, 2 H, CH_2), 4.2 (m, 4 H, CH), 5.2 (d, 1

(7) The structure of Cbz-*N*-γ-nitroargininal was reported as a cyclic carbinolamine instead of a free aldehyde group by Shimizu B.; Saito, A.; Ito, A.; Tokawa, K.; Maeda, K.; Umezawa, H. *J. Antibiotics (Tokyo)*, 1971, *25*, 515. The ^1H NMR of our Fmoc-(*N*-γ-Mtr)argininal (see Experimental Section) agrees with their observation.

(8) Rapoport, H.; Lubell, W. D. *J. Am. Chem. Soc.* 1987, *109*, 236.

H, NH), 7.4 (m, 13 H, aromatic-H), 9.5 (s, 1 H, CHO); IR (KBr) 3400, 2970, 1725, 1690, 1530 cm^{-1}. Anal. Calcd for $C_{24}H_{21}NO_3$ (371.4): C, 77.60; H, 5.70; N, 3.77. Found: C, 77.60; H, 5.73; N, 3.75.

***N*-α-(Fluorenylmethyloxycarbonyl)-*N*-ε-(*tert*-butyloxycarbonyl)-L-lysinal (3d)**: yield 75%; mp 114–116 °C; $[\alpha]_D$ +11.3° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.3 (s, 9 H, CH_3), 1.6 (m, 6 H, CH_2), 3.0 (d, 2 H, CH_2N), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, NH), 7.4 (m, 8 H, aromatic-H), 9.5 (s, 1 H, CHO); IR (KBr) 3360, 2950, 1730, 1690, 1530 cm^{-1}. Anal. Calcd for $C_{26}H_{32}N_2O_5$ (452.5): C, 69.00; H, 7.13; N, 6.19. Found: C, 68.92; H, 7.21; N, 6.02.

***N*-α-(Fluorenylmethyloxycarbonyl)-L-aspart-α-al β-*tert*-butyl ester (3e)**: yield 75%; mp 61–62 °C; $[\alpha]_D$ −1.4° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.4 (s, 9 H, CH_3), 2.8 (d, 2 H, CH_2), 4.3 (m, 4 H, CH), 5.2 (d, 1 H, NH), 7.4 (m, 8 H, aromatic-H), 9.5 (s, 1 H, CHO); IR (KBr) 3360, 2990, 1730, 1725, 1680, 1510 cm^{-1}. Anal. Calcd for $C_{23}H_{25}NO_5$ (395.4): C, 69.86; H, 6.37; N, 3.54. Found: C, 69.88; H, 6.44; N, 3.53.

***N*-α-(Fluorenylmethyloxycarbonyl)-*N*-γ-[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]-L-argininal (3f)**: yield 67%; mp 76–77 °C; $[\alpha]_D$ −23.2° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.6 (m, 4 H, CH_2), 2.0 (s, 3 H, CH_3), 2.5 (s, 3 H, CH_3), 2.6 (s, 3 H, CH_3), 3.6 (t, 2 H, CH_2N), 3.7 (s, 3 H, OCH_3), 4.2 (m, 4 H, CH), 5.2 (d, 1 H, OH, exchanged with D_2O), 5.6 (m, 1 H, NCHO), 6.4 (s, 1 H, aromatic-H), 6.7 (br s, 2 H, NH, exchanged with D_2O), 7.4 (m, 8 H, aromatic-H), 8.4 (d, 1 H, NH, exchanged with D_2O); IR (KBr) 3300, 2940, 1720, 1630, 1520 cm^{-1}. Anal. Calcd for $C_{31}H_{36}N_4O_6S$ (592.0): C, 62.82; H, 6.12; N, 9.45. Found: C, 62.90; H, 6.10; N, 9.43.

Preparation of L-Mandeloylphenylalaninol (6c). *N*-(Fluorenylmethyloxycarbonyl)phenylalaninol (4c). A mixture of *N*-(fluorenylmethyloxycarbonyl)phenylalaninal (**3c**) (D- or L-) (0.4 g, 1.1 mmol) and sodium borohydride (0.15 g, 2.1 mmol) in 10 mL of anhydrous tetrahydrofuran was stirred at 0 °C. After 2 h of stirring, the solution was diluted with 80 mL of ethyl ether and washed with 2.5% aqueous sodium bicarbonate solution (2 × 50 mL), aqueous 1 N HCl (1 × 50 mL) and water. The organic solution was dried over sodium sulfate anhydrous. Filtration and removal of the solvent gave the crude product which was then crystallized from ethyl ether to yield the pure *N*-(fluorenylmethyloxycarbonyl)phenylalaninol (**4c**) [yield: (D-**4c**) 95%, (L-**4c**) 93%] L-**4c**: mp 161–162 °C; $[\alpha]_D$ −20.1° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 2.8 (d, 2 H, CH_2), 3.2 (s, 1 H, OH, exchanged with D_2O), 3.5 (d, 2 H, CH_2O), 4.2 (m, 4 H, CH), 6.7 (d, 1 H, NH, exchanged with D_2O), 7.4 (m, 13 H, aromatic-H); IR (KBr) 3340, 3000, 1700, 1550 cm^{-1}. Anal. Calcd for $C_{24}H_{23}NO_3$ (373.4): C, 77.19; H, 6.20; N, 3.75. Found: C, 76.96; H, 6.18; N, 3.79.

D-**4c**: mp 162–163 °C; $[\alpha]_D$ +20.5° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 2.8 (d, 2 H, CH_2), 3.2 (s, 1 H, OH, exchanged with D_2O), 3.5 (d, 2 H, CH_2O), 4.2 (m, 4 H, CH), 6.7 (d, 1 H, NH, exchanged with D_2O), 7.4 (m, 13 H, aromatic-H); IR (KBr) 3340, 3000, 1700, 1550 cm^{-1}. Anal. Calcd for $C_{24}H_{23}NO_3$ (373.4): C, 77.19; H, 6.20; N, 3.75. Found: C, 76.05; H, 6.19; N, 3.73.

Phenylalaninol (5c). To a solution of compound **4c** [D- or L-](0.37 g, 1.0 mmol) in 20 mL of CH_2Cl_2 was added 4 mL of piperidine under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h, after which time, removal of solvent under high vacuum at 35 °C gave the crude product **5c** which was purified by preparative silica gel TLC plate and eluted with 18% methanol in CH_2Cl_2. Crystallization from CH_2Cl_2 and petroleum ether gave the pure α-amino alcohol **5c**. [yield: (D-**5c**) 82%, (L-**5c**) 85%]. L-**5c**: mp 88–89 °C; $[\alpha]_D$ −25.9° (*c* 1.2, 1 N HCl) [lit. mp 92–94 °C, $[\alpha]$ −22.8° (*c* 1.2, 1 N HCl)]; H-NMR ($CDCl_3$) δ 2.8 (d, 2 H, CH_2), 3.2 (s, 1 H, OH, exchanged with D_2O), 3.5 (d, 2 H, CH_2O), 4.2 (m, 1 H, CH), 6.7 (d, 1 H, NH, exchanged with D_2O), 7.4 (m, 5 H, aromatic-H); IR (KBr) 3340, 3000, 1700, 1550 cm^{-1}. Anal. Calcd for $C_9H_{13}NO$ (151.21): C, 71.48; H, 8.67; N, 9.26. Found: 71.43; H, 8.61; N, 9.25.

D-**5c**: mp 89–90 °C; $[\alpha]_D$ +25.5° (*c* 1.2, 1 N HCl) [Lit. mp 92–94 °C, $[\alpha]$ −23° (*c* 1.2, 1 N HCl)]; H-NMR ($CDCl_3$) δ 2.8 (d, 2 H, CH_2), 3.2 (s, 1 H, OH, exchanged with D_2O), 3.5 (d, 2 H, CH_2O), 4.2 (m, 1 H, CH), 6.7 (d, 1 H, NH, exchanged with D_2O), 7.4 (m, 5 H, aromatic-H); IR (KBr) 3340, 3000, 1700, 1550 cm^{-1}. Anal. Calcd for $C_9H_{13}NO$ (151.21): C, 71.48; H, 8.67; 9.27. Found: C, 71.47; H, 8.65; 9.27.

L-Mandeloylphenylalaninol (6c). A solution of compound **5c** (D- or L-) (0.12 g, 0.79 mmol), L-mandelic acid (0.12 g, 0.87 mmol), and *N*-hydroxysuccinimide (0.1 g, 0.87 mmol.) in anhydrous THF (30 mL) was stirred under argon atmosphere, and dicyclohexylcarbodiimide (0.18 g, 0.87 mmol) was added to the mixture. The reaction mixture was stirred overnight at room temperature, after which time it was diluted with 150 mL of ethyl ether and washed with 2.5% aqueous sodium bicarbonate (2 × 150 mL), 1 N aqueous HCl (2 × 150 mL), and water. The organic solution was dried over sodium sulfate anhydrous. Filtration and removal of solvent gave the crude product which was loaded on preparative silica gel TLC and eluted with 30% ethyl acetate/petroleum ether. The pure L-mandeloylphenylalaninol (**6c**) (L,D- or L,L-) was obtained as an oil [L,D-**6c**) 77%, (L,L-**6c**) 80%].

L,L-**6c**: $[\alpha]_D$ +8.2° (*c* 1.0, MeOH); H-NMR ($CDCl_3$) δ 2.8 (d, 2 H, benzylic-H), 3.2 (br s, 1 H, OH, exchanged with D_2O), 3.3 (m, 2 H, OCH_2), 3.5 (s, 1 H, OH, exchanged with D_2O), 4.2 (m, 2 H, CH), 6.7 (d, 1 H, NH, exchanged with D_2O), 7.4 (m, 10 H, aromatic-H); IR (KBr) 3340, 3000, 1700, 1550 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_3$ (285.33): C, 71.55; H, 6.71; N, 4.91. Found: C, 71.65; H, 6.68; N, 4.89.

L,D–**6c**: $[\alpha]_D$ −8.0° (*c* 1.0, $CHCl_3$); H-NMR ($CDCl_3$) δ 2.8 (d, 2 H, benzylic-H), 3.2 (br s, 1 H, OH, exchanged with D_2O), 3.3 (m, 2 H, OCH_2), 3.5 (s, 1 H, OH, exchanged with D_2O), 4.2 (m, 2 H, CH), 6.7 (d, 1 H, NH, exchanged with D_2O), 7.4 (m, 10 H, aromatic-H); IR (KBr) 3340, 3000, 1700, 1550 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_3$ (285.33): C, 71.55; H, 6.71; N, 4.91. Found: C, 71.60; H, 6.79; N, 4.90.

HPLC analysis: Column is a Chemcosorb 5-μm C-18, 4.6 × 250 mm. The UV detector monitors at 214 nm. HPLC solvent system consists of buffer A: 0.1% TFA in H_2O; buffer B: 60% CH_3CN in buffer A. The gradient is 0–100% buffer B in 40 min. Retention time: (L,L-**6c**) 24.1 min, (L,D-**6c**) 25.2 min.