A Novel, One-Pot Reductive Alkylation of Amines by *S*-Ethyl Thioesters Mediated by Triethylsilane and Sodium Triacetoxyborohydride in the Presence of Palladium on Carbon

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Received October 22, 1998

The reductive alkylation of primary amines with aldehydes or ketones is an important tool in the synthesis of wide variety of amines. We described here a novel, one-pot reductive alkylation method using multifunctional *S*-ethyl thioesters as a source for in situ generation of aldehydes to alkylate a range of multifunctional primary amines. The corresponding multifunctional secondary amines were obtained in good to excellent yields (mostly >90%). This one-pot reductive alkylation included the treatment of a mixture of protected *S*-ethyl thioester, primary amine, 10% Pd/C, and sodium triacetoxyborohydride in *N*,*N*-dimethylformamide with triethylsilane for 30 min at temperature lower than 20 °C. This method has special merit when the aldehyde is not stable enough to allow isolation and therefore does not lend itself to a stepwise strategy of reductive alkylation. This was the case with *tert*-butyl 1(*S*)-[(9-fluorenylmethoxycarbonyl)amino]-4-oxobutyrate (**10**) which could not be obtained from the α-*tert*-butyl γ-*S*-ethyl (*S*)-*N*-(9-fluorenylmethoxycarbonyl) thioglutamate (**9**). However, by our one-pot reductive alkylating method, treatment of 9-fluorenemethyl phenylalaninate (**6a**) with **9** afforded *tert*-butyl 2(*S*)-[(9-fluorenylmethoxycarbonyl)amino]-4-[[3-phenyl-1(*S*)-(9-fluorenylmethoxycarbonyl)propyl]amino]butyrate (**11**) in 76% yield. Furthermore, the acid labile *tert*-butyloxycarbonyl, and the hydogenation labile benzyloxycarbonyl and benzyl protecting groups, were stable in the one-pot reductive alkylation reaction. While the conjugated double bond is stable in these reaction conditions, the monosubstituted C−C double bond, as in the allyl protecting group in α-allyl β-cyclohexyl aspartate, was reduced to the corresponding propyl ester.

Introduction

The reductive alkylation of primary amines by carbonyl compounds, mostly aldehydes or ketones, in the presence of reducing agents is an important tool in the synthesis of secondary amines. A variety of reducing agents, such as hydrogenation in the presence of metal catalysts,[1] sodium cyanoborohydride ($NaBH_3CN$),[2] borane−pyridine complex,[3] borohydride exchange resin,[4] zinc−acetic acid,[5] sodium borohydride−magnesium chloride,[6] zinc borohydride−zinc chloride,[7] and recently sodium triacetoxyborohydride [$NaBH(OAc)_3$][8] and zinc borohydride − silica gel,[9] have been developed for this conversion. Among these, the most commonly used agents are hydrogen, $NaBH_3CN$, and $NaBH(OAc)_3$.

Generating the aldehydes, needed for the reductive alkylation, from the corresponding and readily available carboxylic acid requires their transformation into derivatives such as acid chlorides, esters, or amides. These can then be selectively reduced to the aldehydes. Alternatively, the carboxylic acid can be first reduced to the primary alcohol which then is oxidized to the corresponding aldehyde. Nevertheless, none of the above methods seems to be applicable to multifunctional compounds. Recently, reduction of *S*-ethylesters or *S*-benzylesters by triethylsilane to the corresponding aldehydes in either acetone or DCM in the presence of 10% Pd/C, under essentially neutral conditions, has been demonstrated.[10] Interestingly, under these mild conditions a variety of functional groups, including *O*-benzyl and carbon−carbon double bonds, are stable.[11]

Reductive alkylation is the synthetic route of choice to obtain pseudopeptides that include a reduced peptide bond. This frequently employed amide bond surrogate is readily generated by the reductive alkylation of a free α-amino, side chain protected peptide by an *N*-protected α-amino aldehyde.[12] In general, the most abundant methods to prepare simple α-amino acyl aldehydes are

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10.1021/jo982125g CCC: $18.00
Published on Web 03/02/1999

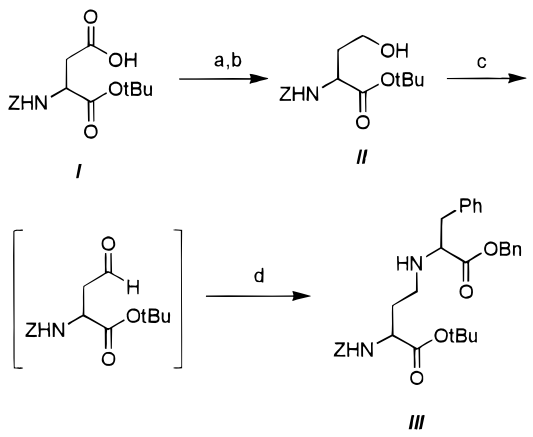
the following: reduction of α-amino acyl esters with diisobutyl aluminum hydride at low temperature,[13] reduction of *N*′-methoxy-*N*′-methyl-α-protected-carboxamides by $LiAlH_4$,[14] and oxidation of the *N*-protected amino alcohol via a modified Moffatt oxidation.[15] The *N*-protected amino alcohol is generated from the $NaBH_4$-mediated reduction of the mixed anhydride obtained from *N*-*tert*-butyloxycarbonyl-α-amino acid and isobutyl chloroformate. The reductive alkylation of a free α-amino side chain protected peptide is carried out by $NaBH_3CN$ in DMF in the presence of 1% acetic acid.[16]

Recently, we reported the preparation of a novel dipeptidomimetic synthon, the trisubstituted-1,2,5-hexahydro-3-oxo-1*H*-1,4-diazepine (DAP).[17] A low yield multistep procedure was used to generate the reduced peptide bond which is an essential feature in this structure. The *β*-carboxyl of *tert*-butyl *N*-α-benzyloxycarbonyl-aspartate was reduced to the alcohol and consecutively oxidized to the corresponding aldehyde. The later was subsequently used to reductively alkylate the free amino group of benzyl phenylalaninate. In this study we report the development of a general, efficient, one-pot reductive alkylation of multifunctional amines with multifunctional *S*-ethylthioesters by triethylsilane and $NaB(OAc)_3H$ in the presence of Pd/C.

Results and Discussions

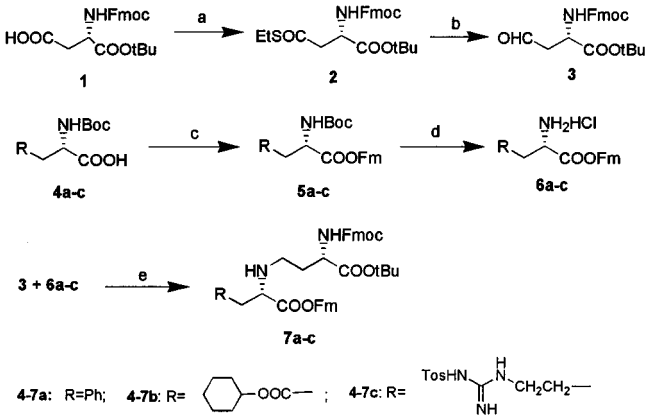
Stepwise Reductive Alkylation of α-*tert*-Butyl *β*-*S*-Ethyl (*S*)-*N*-Fmoc-thioaspartate. The potential application of DAP as a dipeptidomimetic and a molecular scaffold required an optimization of the synthesis described previously.[17] The reported yield for the *tert*-butyl 2(*S*)-benzyloxycarbonylamino-4-[2-phenyl-1(*S*)-benzyloxycarbonyl-ethylamino]butyrate (*III*) (Scheme 1), an essential intermidiate in the synthesis of DAP, starting from α-*tert*-butyl *N*-benzyloxycarbonyl-L-aspartate (*I*) and

Scheme 1[a]



[a] (a) *i*-BuOCOCl, Et_3N in THF; (b) $NaBH_4$ in H_2O; (c) PCC/silica gel in DMF; (d) HCl·*tert*-butyl (*S*)-phenylalaninate, $NaCNBH_3$ in AcOH−MeOH.

Scheme 2[a]



[a] (a) EtSH, DCC, DMAP in CH_2Cl_2, rt, 30 min, 96%; (b) Et_3SiH, 10% Pd−C in acetone, ice bath, 30 min, 93%; (c) FmOH, DCC, DMAP in CH_2Cl_2, rt, 30 min. **5a**: 95%; **5b**: 92%; **5c**: 95%; (d) HCl−EtOAc, **6a**: 87%; **6b**: 91%; **6c**: 93%; (e) $NaBH(OAc)_3$ in DMF, 30 min, **7a**: 94%; **7b**: 92%; **7c**: 95%.

benzyl L-phenylalaninate (*II*) was less than 25%.[17] Therefore, our initial goal in this study was to optimize the reductive alkylation leading to multifunctional secondary amines.

Instead of reducing the *β*-carboxyl to alcohol and oxidizing it to the corresponding aldehyde, we reduced the *S*-ethyl thioesters with triethylsilane and a catalytic amount of 10% palladium on carbon in acetone (slightly lower yields were obtained in dichloromethane). This reaction was reported to afford the corresponding aldehyde in high yield with none or negligible racemization.[10] The high yield (93%) of this reaction was obtained provided the reaction temperature was kept below 20 °C. The *S*-ethyl thioesters were prepared by *N*,*N*′-dicyclohexylcarbodiimide (DCC)-mediated esterification of the carboxylic acids with ethanethiol in DMF in the presence of 0.1 equiv of 4-*N*,*N*-(dimethylamino)pyridine (DMAP) as previously reported.[10c] On the basis of previous reports, $NaB(OAc)_3H$ in DCM was chosen for the reduction of the in situ formed imine.[8a−c] No advantage was observed when 2% AcOH in DMF was used as solvent.[12] Scheme 2 summarizes three examples of stepwise reductive alkylations in which *tert*-butyl 2(*S*)-4-oxo-9-fluorenylmethoxycarbonylamino-butyrate (**3**) was used to reduc-

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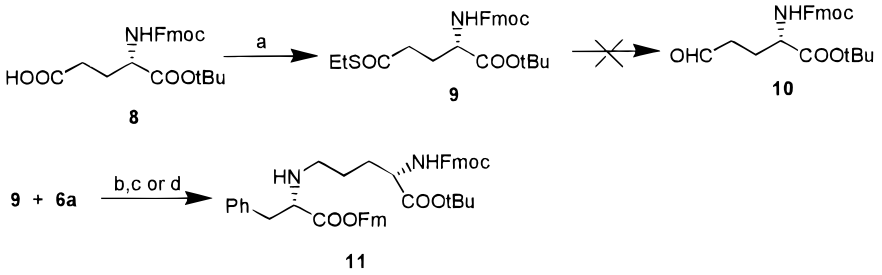
Scheme 3[a]



[a] (a) EtSH, DCC, DMAP in CH_2Cl_2, rt, 30 min, 95%; (b) method A: a mixture of **9**, 10% Pd−C in DMF at 4 °C was treated with Et_3SiH followed by the addition of **6a**. After 5 min, a solution of $NaBH(OAc)_3$ in DMF was added, 30 min at room temperature, 33% yield; (c) method B: a mixture of **9**, **6a**, and 10% Pd−C in DMF at 4 °C was treated with Et_3SiH. After 5 min, a solution of $NaBH(OAc)_3$ in DMF was added, 30 min at room temperature, 45% yield; (d) method C: a mixture of **9**, **6a**, and 10% Pd−C in DMF at 4 °C was treated with a solution of $NaBH(OAc)_3$ in DMF, After 5 min, Et_3SiH was added, 30 min 10−20 °C, 76−83% yield.

tively alkylate the hydrochlorides of 9-fluorenylmethyl esters (OFm) of L-Phe, L-Asp(*β*-OcHex), and L-Arg(N^G-Tos) (**6a**−**c**, respectively). Each of the individual steps in the above syntheses was carried out with yields greater than 90%.

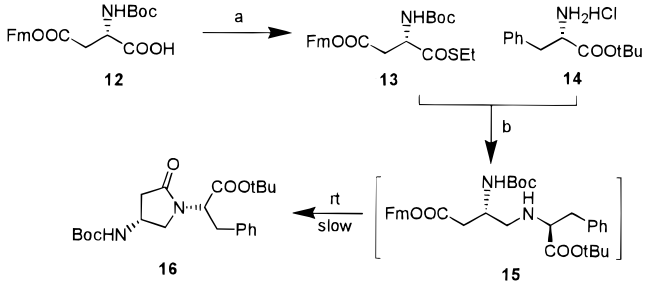
Attempts to carry out a $NaBH_3CN$-mediated reductive alkylation of L-Phe-OFm (**6a**) with aldehyde **3** in methanol/water resulted in only 34% yield of **7a**. More than 50% of aldehyde **3** was reduced to *tert*-butyl 2(*S*)-4-hydroxy-2-(9-fluorenylmethoxycarbonylamino)butyrate, and the 9-fluorenylmethyl ester of **3** was partially hydrolyzed. Replacement of methanol/water with either DMF or 2% AcOH in DMF prevented the reduction of the aldehyde. However, the reaction was slowed, and a partial loss of the 9-fluorenylmethyl ester was observed. Trial reductions of the in situ formed imine with $Zn(BH_4)_2$ proceeded very slowly. Less than 30% conversion to the reductively alkylated product **7a** was observed after 2 days at room temperature, and the 9-fluorenylmethyl ester was mostly removed.

The difficulty to purify the thiobenzyl esters corresponding to **2** from the excess of benzylmercaptan and the sustained repelling stench of the latter discouraged us from employing these esters in our syntheses.

In summary, the stepwise reductive alkylations used in this study are compatible with synthetic strategies employing Fmoc/Boc and OFm/O-*tert*-butyl as orthogonal protecting groups.

One-Pot Reductive Alkylation of α-*tert*-Butyl γ-*S*-Ethyl (*S*)-*N*-(9-Fluorenylmethyloxycarbonyl)thioglutamate (9). The urgency to develop a novel, one-pot reductive alkylation followed failed attempts to obtain aldehyde **10** (Scheme 3) by the method used successfully to synthesize of the homologous aldehyde **3** (see Scheme 2). Addition of triethylsilane to an ice-cooled mixture of thioester **9** in DMF and 10% Pd/C was followed by the addition of the amine **6a**. After 5 min $NaBH(OAc)_3$ was added and allowed to react for 30 min (method A), yielding 33% yield of the anticipated reductive alkylation product **11**. Alternatively, modifying the reaction by including amine **6a** in the ice-cold mixture of the thioester **9** and 10% Pd/C in DMF prior the addition of triethylsilane (method B) led to a slightly improved yield (45%) of the secondary amine **11**. Finally, adding $NaBH(OAc)_3$ to an ice-cold mixture of the thioester **9**, 10% Pd/C, and the amine **6a** in DMF, followed, after 5 min, by the additon of triethylsilane (method C) resulted in the highest yield (76%) of **11**. However, when thioester **2** was used, irrespective of the version of one-pot reductive alkylation method used, the secondary amine **7a** was always obtained in very high yields (90−95%). These results clearly suggest that the aldehyde, generated in situ, is trapped by the primary amine to form the imine which is subsequently reduced irreversibly to form the anticipated secondary amine. Evidently, when the in situ generated aldehyde is inherently unstable, e.g. aldehyde **10**, reduction of the thioester in the presence of all the other reactants results in the highest yield (method C). The order of adding the reactants did not make any difference when the in situ generated aldehyde is stable, e.g. aldehyde **3**. In such a case, the reductive alkylation product, the secondary amine **7a**, was always obtained in high yield. Importantly, a reaction temperature higher than 20 °C caused dramatic decrease in the yield of **11**. The secondary amine **11** decomposes slowly upon storage at room temperature.

Scheme 4[a]

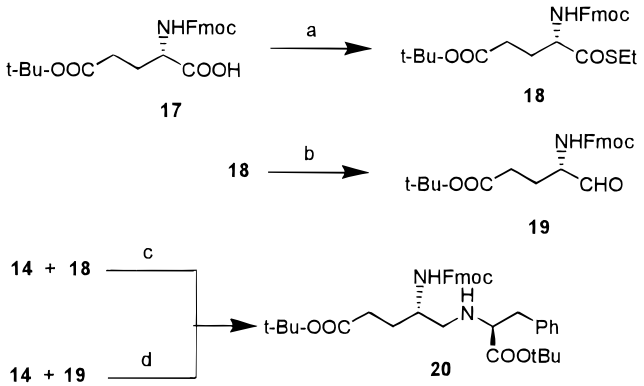


[a] (a) EtSH, DCC, DMAP in CH_2Cl_2, rt, 30 min, 93%; (b) Et_3SiH, $NaBH(OAc)_3$, 10% Pd−C in DMF, 30 min 4 °C, 87%.

Scope and Limitation of the Novel One-Pot Reductive Alkylation. Starting from α-*tert*-butyl *β*-*S*-ethyl (*S*)-*N*-Fmoc-thioaspartate (**2**), all three secondary amines **7a**−**c**, synthesized by the stepwise manner described above (Scheme 2), could also be prepared by the one-pot reductive alkylation in very high yields, 90−95%.

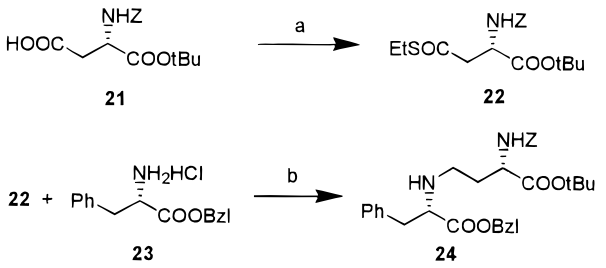
Due to the importance of the *tert*-butyloxycarbonyl (Boc) protecting group in peptide chemistry, we tested whether this group is compatible with the one-pot reductive alkylation conditions described above. The thioesterification of *β*-9-fluorenylmethyl L-*N*-Boc-aspartate (**12**) yielded 93% of the thioester **13** (Scheme 4). One-pot reductive alkylation of the *tert*-butyl L-phenylalaninate hydrochloride **14** with **13** resulted in 87% yield of the anticipated secondary amine **15**. Interestingly, amine **15** was unstable at room temperature. After several days it cyclized spontaneously to the corresponding 1-[[1(*S*)-(*tert*-butyloxycarbonyl)-2-phenyl]ethyl]-4(*S*)-[(*tert*-butyloxycar-

Scheme 5[a]



[a] (a) EtSH, DCC, DMAP in CH_2Cl_2, rt, 30 min 4 °C, yield 95%; (b) Et_3SiH, 10% Pd−C in acetone, 30 min, 95%; (c) Et_3SiH, $NaBH(OAc)_3$, 10% Pd−C in DMF, 30 min 4 °C, yield 94%; (d) $NaBH(OAc)_3$ in DMF, 30 min 4 °C, yield 95%.

Scheme 6[a]



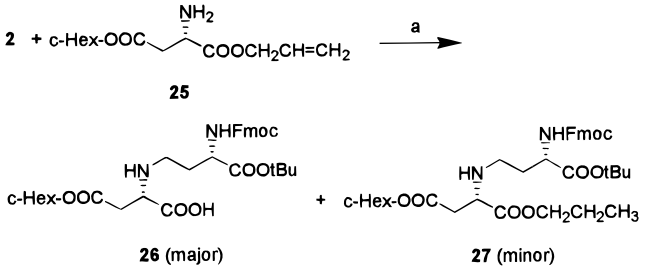
[a] (a) EtSH, DCC, DMAP in CH_2Cl_2, rt, 30 min, 96%; (b) Et_3SiH, $NaBH(OAc)_3$, 10% Pd−C in DMF, 30 min 4 °C, yield 94%.

bonyl)amino]pyrrolidin-2-one (**16**) (Scheme 4). This synthesis also demonstrates that similar to β- and γ-thioesters (**2** and **9**, respectively) α-thioesters also are compatible with the novel, one-pot reductive alkylation procedure.

Comparison of the stepwise versus the one-pot synthesis in which an α-thioester is the precursor for the aldehyde was addressed in the reductive alkylation of *tert*-butyl L-phenylalaninate hydrochloride **14** by γ-*tert*-butyl α-*S*-ethyl *N*-Fmoc-L-thioglutamate **18** (Scheme 5). The yield of the *S*-ethyl thioester **18** was 92%. Reduction of the thioester **18** to the corresponding aldehyde **19** was carried out with triethylsilane in acetone in the presence of 10% Pd/C at room temperature. Both the stepwise and the one-pot reductive alkylations resulted in the secondary amine **20** obtained in very high yields of 95% (Scheme 5). Unlike the inherent instability of the secondary amine **15** the secondary amine **20** was stable. Apparently, compared to the facile cyclization of **15** to form the pyrrolidone (Scheme 4), the steric hindrance of the γ-*tert*-butyl ester **20** does not allow the cyclization to the corresponding piperidinone.

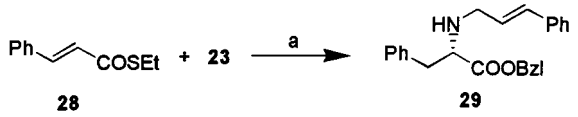
Benzyloxycarbonyl and benzyl esters are two common protecting groups on the amino and carboxyl functions, respectively. These groups are orthogonal to the Boc/*tert*-butyl and Fmoc/9-fluorenylmethyl protecting groups and therefore very useful in syntheses employing multifunctional building blocks. One-pot reductive alkylation of benzyl L-phenylalaninate hydrochloride (**23**) with α-*tert*-butyl β-*S*-ethyl *N*-benzyloxycarbonyl-L-thioaspartate (**22**) yielded 94% of the anticipated secondary amine **24** (Scheme 6). Both benzyloxycarbonyl and benzyl ester protecting groups are stable under the reaction conditions used in the one-pot reductive alkylation. This synthesis

Scheme 7[a]



[a] (a) $NaB(OAc)_3H$, 10% Pd−C, Et_3SiH in DMF, 30 min 4 °C.

Scheme 8[a]



[a] (a) $NaB(OAc)_3H$, 10% Pd−C, Et_3SiH in DMF, 30 min, 4 °C.

demonstrates the significant improvement of our novel, one-pot reductive alkylation over the previously published stepwise synthesis of an identical secondary amine *III* (*III* and **24** are identical) which was obtained in less than 25% overall yield starting from alcohol *Ia* (Scheme 1).[17]

Unfortunately, the allyl ester is susceptible to the reductive conditions used in the one-pot reductive alkylation (Scheme 7). The reductive alkylation of β-cyclohexyl α-allyl (*S*)-aspartate (**25**) by the thioester **2** resulted in two reductively alkylated products, none of them containing the original allyl ester moiety. The predominant product (87% yield) was the free acid **26** which was obtained in the presence of minute amount of the *n*-propyl ester **27**. We assume that the reduction of the allyl ester to the *n*-propyl one was followed by a fast hydrolysis leading to the accumulation of the free acid (Scheme 7).

Reduction of thioethyl esters containing α,β-unsaturated carbonyl moieties and trisubstituted carbon−carbon double bonds with triethylsilane and Pd/C in acetone yielded the corresponding aldehydes.[10a] Under these conditions the di- and trisubstituted carbon−carbon double bonds remained intact. Reductive alkylation of α-amino esters by *N*-allyloxycarbonyl (Alloc) protected α-alaninal with $NaBH_3CN/ZnCl_2$ in methanol yielded 59% of the corresponding Alloc-protected secondary amine.[8d] In our novel, one-pot reductive alkylation of benzyl L-phenylalninate hydrochloride (**23**) by *S*-ethyl *trans*-thiocinnamate (**28**) we obtained the secondary amine **29** in 92% yield (Scheme 8). Therefore, under these conditions, conjugated carbon−carbon double bonds are stable. However, Alloc/allyl protecting groups are susceptible and should be avoided.

Previous reports demonstrated that the reduction of *N*-protected α-amino thioesters to the corresponding aldehydes[10a−c] and the following reductive alkylation[12c] proceed with retention of optical purity. LC−ESI-MS analysis of the crude products **20** and **15**, obtained through our one-pot reductive alkylation of **14** with α-amino protected thioethyl esters **18** or **13**, respectively, could not identify any detectable racemization. LC−ESI-MS analysis revealed the presence of only one component with molecular mass corresponding to the anticipated product (results not shown). LC−ESI-MS analysis of

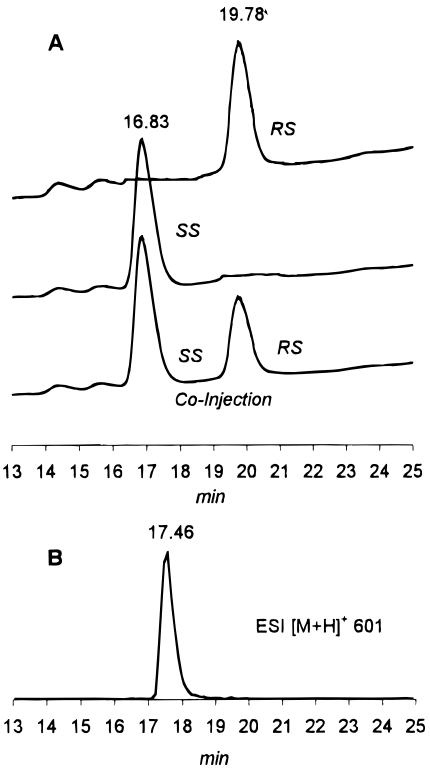


Figure 1. LC−ESI-MS analysis of the one-pot reductive alkylation reaction mixtures obtained from *tert*-buty (*S*)-phenylalaninate·HCl and either the (*S*)- or (*R*)-isomers of α-*S*-ethyl *β*-(9-fluorenemethyl) *N*-(*tert*-butyloxycarbonyl)thioaspartate (**13**). Panel A: RP-HPLC (C18, 0.2 mL/min, 220 nm, linear gradient of 45−55% A in B in 30 min) tracings of the reaction mixture generating either the (*SS*)- or the (*RS*)-diastereomers t_R =19.78 and 16.83 min (upper and middle tracings), respectively. The lowest tracing represents a coinjection of reaction mixtures generating either the (*SS*)- or (*RS*)-diastereomers. Panel B: The electron spray ionization mass spectra of the reaction mixture generating the (*SS*)-isomer whose M + H^+ mass corresponds to *m*/*z* = 601.

crude reaction mixtures of the diastereomers (*SS*)-**15** and (*RS*)-**15**, which eluted at distinct retention times, could detect only one diastereomer (Figure 1). We therefore conclude that there is no significant racemization of either α-thioester or the in situ generated α-aldehyde under the conditions employed in the one-pot reductive alkylation synthesis reported above.

Conclusions

We report here a novel, one-pot reductive alkylation method of polyfunctionalized primary amines by *S*-ethyl thioesters with sodium triacetoxyborohydride and triethylsilane in the presence of Pd−C. The results presented above indicate that this method is very general, efficient, and powerful with good to excellent yields. Many protecting groups which are sensitive to acid (*tert*-butyloxycarbonyl and *tert*-butyl) or base (*9*-fluorenylmethoxycarbonyl and *9*-fluorenemethyl) or hydrogenation (benzyl, benzyloxycarbonyl and conjugated double bond) can withstand these conditions. This method is not compatible with compounds containing monosubstituted double carbon−carbon bonds. The most important advantage of this method is the use of the stable thioesters instead of the labile aldehydes as the starting materials. Thus, reductive alkylation can be carried out effectively with *S*-ethyl thioesters as precursors of unstable aldehydes generated in situ.

Experimental Section

General Methods. Thin-layer chromatography (TLC) was performed on plastic plates coated with (0.20 mm) silica gel 60 F254 (Aldrich). Open column chromatography was carried out on silica gel 60 (200−400 mesh, Aldrich). Final organic solutions were dried over $MgSO_4$. Analytical reverse-phase high performance liquid chromatography (RP-HPLC) was carried out on a Waters 100 RP-18 column (5 μm, 19 × 150 mm) at a flow rate of 1 mL/min. Preparative RP-HPLC was carried out on Vydac 300 A C18 (15−20 μm, 47 × 300 mm) at a flow rate of 70 mL/min. The solvent system used in RP-HPLC included the following: solvent A, 0.1% (v/v) TFA in H_2O; solvent B, 0.1% TFA in CH_3CN. The effluent was monitored at 220 nm. Melting points were determined with a capilliary melting point apparatus and are uncorrected. Elementary microchemical analysis was carried out at E+R Microanalytical Laboratory, Inc, NY 11368. Analytical results were within 0.3% of the theoretical values. Mass spectroscopy was performed at the Mass Spectra Laboratory of the Chemistry Department at Harvard University using a fast atom bombardment (FAB) ion source or in our laboratory using an electron-spray ionization (ESI) source in-line with a liquid chromatograph (LC−ESI-MS). *N*,*N*-Dimethylformamide (DMF) was dried with 4 Å molecular sieve for 48 h before use. Other commercially available chemicals were used without further treatment. Catalytic hydrogenations were carried out in the presence of 10% Pd/C.

To avoid the strong stench from the mercaptans used during the synthesis of the thioesters **2**, **9**, **13**, **22**, and **28**, all the manipulations were carried out in the hood. All the generated waste was treated overnight with Clorox.

α-*tert*-Butyl *β*-*S*-Ethyl (*S*)-*N*-(9-Fluorenylmethoxycarbonyl)thioaspartate (2). *N*,*N*′-Dicyclohexylcarbodiimide (DCC) (2.27 g, 11 mmol) was added to a solution of α-*tert*-butyl (*S*)-*N*-(fluorenylmethoxycarbonyl)aspartate (3.15 g, 10 mmol), ethanthiol (0.81 mL, 11 mmol), and 4-*N*,*N*-(dimethylamino)-pyridine (DMAP) (122 mg, 1 mmol) in dichloromethane (DCM) (10 mL) and stirred at room temperature for 30 min and then filtered and concentrated in vacuo. Purification on silica gel column afforded 4.37 g of **2** (96% yield) as a colorless oil which solidified at room temperature: mp 69−70 °C; R_f = 0.46 (EtOAc/hexane, 20:80); $[\alpha]^{20}_D$ −18.7° (*c* = 0.88, MeOH); ^{1}H NMR ($CDCl_3$) (δ in ppm) 7.33−7.79 (m, 8H), 5.68 (d, *J* = 8.7 Hz, 1H), 4.53 (m, 1H), 4.39 (m, 2H), 4.35 (t, *J* = 7 Hz, 1H), 2.92 (dd, *J* = 4.5, 8.7 Hz, 1H), 2.93 (q, *J* = 7.4 Hz, 2H), 1.49 (s, 9H), 1.28 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR 197.1, 169.6, 156.0, 144.1, 141.5, 127.9, 127.3, 125.4, 120.2, 83.0, 67.4, 51.6, 47.4, 45.6, 28.1, 23.8, 14.9; FAB-MS *m*/*z* = 456 (M + H)$^+$. Anal. Calcd for $C_{25}H_{29}NO_5S$: C, 65.91; H, 6.42; N 3.07. Found: C, 66.07; H, 6.58; N, 3.04.

***tert*-Butyl 4-Oxo 2(*S*)-[(9-Fluorenylmethoxycarbonyl)-amino]butyrate (3).** Triethylsilane (0.80 mL, 5 mmol) was added to a solution of thioester **2** (455 mg, 1 mmol) and 10% Pd−C (20 mg) in ice cold acetone (2 mL). Stirring was maintained for 30 min at 10−20 °C and then filtered through a Celite bed which was then washed with acetone. The combined filtrates were concentrated in vacuo and purified on a silica gel column to give 367 mg of **3** (93% yield) as colorless oil which solidified at room temperature: mp 68−69 °C; R_f = 0.28 (EtOAc/hexane, 30:70). $[\alpha]^{20}_D$ −28.4° (*c* = 0.69, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.25−7.75 (m, 8H), 5.71 (d, *J* = 8.7 Hz, 1H), 4.54 (m, 1H), 4.40 (m, 2H), 4.22 (t, *J* = 7 Hz, 1H), 3.07 (dd, *J* = 4.5, 8.7 Hz, 1H), 3.00 (dd, *J* = 4.5, 8.7 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR 199.5, 169.8, 156.1, 144.0, 143.8, 141.5, 127.9, 127.2, 125.3, 120.2, 83.2, 67.4, 49.8, 47.3, 46.3, 28.0; FAB-MS *m*/*z* = 396 (M + H)$^+$. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.57; H, 6.35; N, 3.48.

9-Fluorenemethyl (*S*)-Phenylalaninate Hydrochloride (6a). DCC (2.27 g, 11 mmol) was added to a solution of *N*-(*tert*-

butyloxycarbonyl)-(*S*)-phenylalanine (2.65 g, 10 mmol), 9-fluorenemethanol (2.16 g, 11 mmol), and DMAP (122 mg, 1 mmol) in DCM (10 mL) and stirred at room temperature for 30 min and then filtered and concentrated in vacuo to give 4.21 g of **5a** (95% yield) as a white solid. Crystallization from EtOAc/hexane afforded white crystals: mp 125−126 °C (lit.[18] 125−126 °C); $[\alpha]^{20}_D$ −6.3° (*c* 0.93, $CHCl_3$) [lit.[19] $[\alpha]^{20}_D$ −6° (*c* 0.84, $CHCl_3$)]. ESI-MS $m/z = 444$ $(M + H)^+$.

Crude **5a** was dissolved in EtOAc (30 mL), saturated with HCl (gas), and left overnight at room temperature. The precipitate was filtered off and washed with EtOAc for three times to give 3.30 g of **6a** (87% yield) as white crystals: mp 169−170 °C; ^{13}C NMR 169.8, 144.1, 143.8, 141.5, 135.5, 130.2, 129.4, 128.6, 128.0, 126.0, 125.9, 120.9, 107.7, 67.8, 54.0, 46.7, 36.5. ESI-MS $m/z = 344$ $(M + H)^+$.

α-(9-Fluorenemethyl) *β*-Cyclohexyl L-Aspartate Hydrochloride (6b). DCC (2.27 g, 11 mmol) was added to a solution of *β*-cyclohexyl-*N*-(*tert*-butyloxycarbonyl)-L-aspartic acid (3.15 g, 10 mmol), 9-fluorenemethanol (2.16 g, 11 mmol), and DMAP (122 mg, 1 mmol) in DCM (10 mL) and stirred at room temperature for 30 min and then filtered and concentrated in vacuo. Purification by silica gel column afforded 4.53 g (92% yield) of **5b** as a white solid. Crystallization from EtOAc/hexane gave white crystals: mp 87−88 °C; $R_f = 0.51$ (EtOAc/hexane, 20:80); ^{1}H NMR ($CDCl_3$) δ 7.25−7.77 (m, 8H), 5.56 (d, $J = 9$ Hz, 1H), 4.75 (m, 1H), 4.70 (m, 1H), 4.42 (m, 2H), 4.22 (t, $J = 7$ Hz, 1H), 3.00 (dd, $J = 4.5$, 17.0 Hz, 1H), 2.80 (dd, $J = 4.5$, 17.0 Hz, 1H), 1.20−1.79 (m, 19H); ^{13}C NMR 171.5, 170.6, 155.6, 143.8, 143.7, 141.4, 128.0, 127.4, 125.3, 120.2, 80.4, 73.9, 68.0, 50.2, 46.9, 31.7, 28.5, 25.4, 23.9; FAB-MS $m/z = 494$ $(M + H)^+$. Anal. Calcd for $C_{29}H_{35}NO_6$: C, 70.57; H, 7.15; N, 2.84. Found; C, 70.77; H, 7.00; N, 2.72.

5b was dissolved in EtOAc (30 mL), saturated with HCl (gas), and left overnight at room temperature. The residue obtained after evaporation solidified under vacuum. Treatment of the residue with ether afforded 3.30 g of **6b** (91% yield) as white powder: mp 102−103 °C; ^{13}C NMR 168.4, 143.2, 127.9, 127.2, 125.3, 120.2, 73.3, 67.6, 48.4, 46.0, 34.3, 30.9, 24.8, 23.1. ESI-MS $m/z = 394$ $(M + H)^+$.

α-(9-Fluorenemethyl)-N^G-*p*-Tosyl L-Argininate Hydrochloride (6c). Preparation followed the procedure described above for **6b** and afforded 4.54 g of **6c** (93% yield) as white powder: mp 88−90 °C; ^{1}H NMR (d_6-DMSO) δ 8.63 (s, 2H), 7.28−7.90 (m, 12H), 6.95 (broad, 1H), 5.22 (broad, 3H), 4.73 (dd, $J = 5.5$, 5.8 Hz, 1H), 4.52 (dd, $J = 5.5$, 5.8 Hz, 1H), 4.33 (t, $J = 5.8$ Hz, 1H), 3.94 (m, 1H), 2.94 (m, 2H), 3.31 (s, 3H), 1.12−1.71 (m, 4H); ^{13}C NMR 169.5, 156.8, 143.4, 143.2, 140.9, 129.1, 127.9, 127.8, 127.3, 127.2, 125.7, 125.3, 125.1, 120.2, 66.7, 51.5, 46.2, 27.3, 24.4, 21.0; ESI-MS $m/z = 507$ $(M + H)^+$.

***tert*-Butyl 2(*S*)-[(9-Fluorenylmethoxycarbonyl)amino]-4-[[2-Phenyl-1(*S*)- (9-Fluorenylmethoxycarbonyl)ethyl]-amino]butyrate (7a). Stepwise Procedure.** To a stirred solution of aldehyde **3** (395 mg, 1 mmol) and amine **6a** (527 mg, 1.1 mmol) in DMF (2 mL) at room temperature was added sodium triacetoxyborohydride (424 mg, 2 mmol) in DMF (2 mL). After 30 min the reaction mixture was diluted with ether (30 mL), washed with diluted $NaHCO_3$ (3 × 5 mL), water (10 mL), and brine (5 mL), dried, and concentrated in vacuo. Purification on silica gel column afforded 678 mg of **7a** (94% yield) as a colorless oil. An aliquot of the oil was dissolved in H_2O-CH_3CN-TFA (30:70:0.1, v/v/v) and lyophilized to afford a white powder: mp 56−57 °C; $R_f = 0.34$ (EtOAc/hexane = 30:70). $[\alpha]^{20}_D$ −17.5° (*c* = 0.84, MeOH); ^{1}H NMR ($CDCl_3$) 7.44−7.77 (m, 21 H), 6.06 (d, $J = 8.6$ Hz, 1H), 4.05−4.46 (m, 8H), 3.53 (m, 1H), 2.90 (dd, $J = 4.5$, 8.6 Hz, 1H), 2.85 (dd, $J = 4.5$, 8.6 Hz, 1H), 2.67 (m, 1H), 2.46 (m, 1H), 1.73−1.91 (m, 2H), 1.47 (s, 9H); δ ^{13}C NMR 174.9, 17.4, 156.5, 144.1, 144.0, 143.7, 143.5, 141.5, 141.4, 129.4, 128.9, 128.8, 128.5, 128.1, 127.9, 127.5, 127.4, 127.2, 125.3, 125.1, 125.0, 120.2, 120.1, 82.5, 67.2, 66.7, 62.7, 53.1, 47.3, 47.0, 44.2, 31.6, 28.2; ESI-MS $m/z = 723$ $(M + H)^+$. Anal. Calcd for $C_{46}H_{46}N_2O_6 \cdot {}^1/_8$TFA: C, 75.36; H, 6.31; N, 3.79. Found: C, 75.78; H, 6.18; N, 3.39.

One-Pot Reductive Alkylation. Method A. Triethylsilane (0.80 mL, 5 mmol) was quickly added to an ice cold solution of thioester **2** (455 mg, 1 mmol) and 10% Pd−C (35 mg) in DMF (5 mL), followed by the addition of **6a** (527 mg, 1.1 mmol) and, after 5 min, sodium triacetoxyborohydride (424 mg, 2 mmol) in DMF (2 mL). The resulting mixture was stirred at room temperature for 30 min and then filtered through a Celite bed which was washed with ether (30 mL). Following the workup procedure described above afforded 672 mg of **7a** as a viscous oil (93% yield).

Method B: Triethylsilane (0.80 mL, 5 mmol) was quickly added to an ice-cold mixture of thioester **2** (455 mg, 1 mmol), amine **6a** (527 mg, 1.1 mmol), and 10% Pd−C (35 mg) in DMF (5 mL). After 5 min sodium triacetoxyborohydride (424 mg, 2 mmol) in DMF (2 mL) was added, and the resulting mixture was stirred at room temperature for 30 min. Workup procedure, as described in method A, afforded 665 mg of **7a** (92% yield).

Method C. Sodium triacetoxyborohydride (424 mg, 2 mmol) was added to an ice-cold mixture of amine **6a** (527 mg, 1.1 mmol), thioester **2** (455 mg, 1 mmol), and 10% Pd−C (35 mg) in DMF (5 mL), followed by quick addition of triethylsilane (0.8 mL, 5 mmol). The resulting mixture was stirred at 10∼20 °C for 30 min. The workup procedure described above afforded **7a** with 90−95% yield.

***tert*-Butyl 2(*S*)-[(9-Fluorenylmethoxycarbonyl)amino]-4-[1(*S*)-(9-Fluorenylmethoxycarbonyl)-2-(cyclohexyloxycarbonyl)ethylamino]butyrate (7b).** Synthesis followed method C, described above for **7a**, and afforded 733 mg of **7b** (95% yield) as a viscous oil. An aliquot of the oil was dissolved in H_2O-CH_3CN-TFA (30:70:0.1, v/v/v) and lyophilized to afford a white powder: mp 81−82 °C; $R_f = 0.35$ (EtOAc/hexane, 30:70); $[\alpha]^{20}_D$ −18.4° (*c* = 0.77, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.75−7.24 (m, 16 H), 5.96 (d, $J = 8$ Hz, 1 H), 4.76 (m, 1H), 4.12−4.52 (m, 8 H), 3.61 (m, 1H), 2.32−2.74 (m, 4H), 1.80 (m, 2H), 1.21−1.75 (m, 19H); ^{13}C NMR 199.4, 171.4, 170.0, 169.7, 156.1, 144.0, 143.8, 143.5, 141.5, 128.0, 127.9, 127.4, 127.2, 125.4, 125.0, 120.1, 83.2, 73.9, 67.3, 67.1, 60.6, 57.6, 52.9, 49.8, 47.3, 47.0, 46.3, 31.6, 25.4, 23.8, 21.2. ESI-MS $m/z = 773$ $(M + H)^+$. Anal.Calcd for $C_{47}H_{52}N_2O_8 \cdot {}^1/_6$TFA: C, 71.79; H, 6.64; N, 3.54. Found: C, 71.48; H, 6.47; N, 3.56.

***tert*-Butyl (*S*)-[(9-Fluorenylmethoxycarbonyl)amino]-4-[4-(N^G-*p*- tosylguanidino)-1(*S*)-(9-Fluorenylmethoxycarbonyl)butylamino]butyrate (7c).** Synthesis followed method C, described above for **7a**, and afforded 733 mg of **7c** (95% yield) as a viscous oil. An aliquot was dissolved in H_2O-CH_3CN-TFA (30:70:0.1, v/v/v) and lyophilized to afford a white solid: mp 79−80 °C; $R_f = 0.48$ (EtOAc/hexane: MeOH, 45:48:7); $[\alpha]^{20}_D$ −21.1° (*c* = 0.88, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.14−7.74 (m, 20H), 6.36 (m, 1H), 6.08 (s, 1H), 6.94 (m, 1H), 5.29 (s, 1H), 4.11−4.55 (m, 8H), 3.04 (m, 2H), 2.56 (m, 1H), 2.01−2.33 (m, 4H), 1.82−1.91 (m, 2H), 1.43 9S, 9H); ^{13}C NMR 175.8, 171.2, 157.1, 156.7, 143.8, 143.3, 142.0, 141.5, 129.3, 128.1, 127.8, 127.3, 126.0, 125.2, 124.7, 120.1, 82.8, 67.3, 66.4, 60.4, 52.6, 47.1, 47.0, 44.1, 28.0, 21.5; ESI-MS $m/z = 887$ $(M + H)^+$. Anal. Calcd for $C_{50}H_{55}N_5O_8S \cdot {}^1/_6$TFA: C, 66.79; H, 6.14; N, 7.74. Found: C, 66.52; H, 6.20; N, 7.61.

α-*tert*-Butyl *γ*-*S*-Ethyl (*S*)-*N*-(9-Fluorenylmethoxycarbonyl)thioglutamate (9). Preparation followed procedure described above for **2** and afforded 4.46 g of **9** (95% yield) as a colorless oil which solidified at room temperature. Crystallization from EtOAc/hexane afforded white crystals: mp 62−63 °C; $R_f = 0.41$ (EtOAc/hexane, 20:80); $[\alpha]^{20}_D$ −20.1° (*c* = 1.04, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.27−7.77 (m, 8H), 5.43 (d, $J = 8$ Hz, N*H*, 1H), 4.27−4.30 (m, 3H), 4.22 (t, $J = 6.8$ Hz, 1H), 2.87 (q, $J = 7.5$ Hz, 2H), 2.56−2.60 (m, 2H), 2.21 (m, 1H), 2.00 (m, 1H), 1.48 (s, 9H), 1.24 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR 198.8, 171.0, 156.1, 144.1, 143.9, 141.5, 127.9, 127.2, 125.3, 120.2, 82.8, 67.2, 53.9, 47.3, 40.0, 28.5, 28.2, 23.6, 14.9; ESI-MS $m/z = 470$ $(M + H)^+$. Anal. Calcd for $C_{26}H_{31}NO_5S$: C, 66.50; H, 6.65; N, 2.98. Found: C, 66.75; H, 6.95; N, 3.08.

***tert*-Butyl 2(*S*)-[(9-Fluorenylmethoxycarbonyl)amino]-5-[2-Phenyl-1(S)-(9-Fluorenylmethoxycarbonyl)ethylamino]-**

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caproate (11). Synthesis followed the described procedure for **7a**. The amine **11** was obtained as a viscous oil (33%, 45%, and 76% yields were achieved using methods A, B, and C respectively). An aliquot of the oil was dissolved in H_2O-CH_3CN-TFA (30:70:0.1, v/v/v) and lyophilized to afford a white powder: mp 53−54 °C; $R_f = 0.33$(EtOAc/hexane, 30:70); $[\alpha]^{20}_D$ −20.1° (c = 0.73, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.44−7.77 (m, 21 H), 6.05 (d, J = 8.6 Hz, 1H), 4.03−4.47 (m, 8H), 3.53 (m, 1H), 2.90 (dd, J = 4.5, 8.6 Hz, 1H), 2.85 (dd, J = 4.5, 8.6 Hz, 1H), 2.67 (m, 1H), 2.46 (m, 1H), 1.63−1.91 (m, 4H), 1.44 (s, 9H); ^{13}C NMR 174.9, 17.4, 156.5, 144.1, 144.0, 143.7, 143.5, 141.5, 141.4, 129.4, 128.9, 128.8, 128.5, 128.1, 127.9, 127.5, 127.4, 127.2, 125.3, 125.1, 125.0, 120.2, 120.1, 82.5, 67.2, 66.7, 62.7, 53.1, 47.3, 47.0, 44.2, 31.6, 28.2; ESI-MS m/z = 737 (M + H)$^+$. Anal. Calcd for $C_{47}H_{48}N_2O_6$: C, 76.61; H, 6.57; N, 3.80. Found: C, 76.38; H, 6.39; N, 3.85.

α-*S*-Ethyl *β*-(9-Fluorenemethyl) (*S*)-*N*-(*tert*-Butyloxycarbonyl)thioaspartate (13). Preparation followed the procedure described above for **2** and afforded 423 mg of **13** (93% yield) as a colorless oil which solidified at room temperature. Crystallization from EtOAc/hexane afforded white crystals: mp 109−110 °C; R_f = 0.42 (EtOAc/hexane, 20:80); ^{1}H NMR ($CDCl_3$) δ 7.25−7.77 (m, 8H), 5.48 (d, J = 8.5 Hz, 1H), 4.63 (m, 1H), 4.45 (m, 2H), 4.23 (t, J = 7 Hz, 1H), 3.20 (dd, J = 4.5, 17 Hz, 1H), 3.08 (dd, J = 4.5, 17 Hz, 1H), 2.87 (q, J = 7.5 Hz, 2H), 1.46 (s, 9H), 1.23 (t, J = 7.5 Hz, 3H,); ^{13}C NMR 197.5, 171.3, 155.6, 143.9, 143.8, 141.6, 128.2, 127.5, 125.4, 120.3, 80.6, 68.0, 50.7, 47.0, 45.6, 28.6, 23.9, 14.9; FAB-MS m/z = 456 (M + H)$^+$. Anal. Calcd for $C_{25}H_{29}NO_5S$: C, 65.91; H, 6.42; N 3.07. Found: C, 66.18; H, 6.50; N, 3.09.

9-Fluorenemethyl 3(*S*)-[(*tert*-Butyloxycarbonyl)amino]-4-[2-Phenyl-1(*S*)- (*tert*-Butyloxycarbonyl)ethylamino]butyrate (15) and 1-[1(*S*)-(*tert*-Butyloxycarbonyl)-2-Phenylethyl]-4(*S*)-[(*tert*-Butyloxycarbonyl)amino]pyrrolidin-2-one (16). Synthesis followed the procedure for method C described above for **7a**. The crude product purified on a silica gel column afforded 261 mg of **15** as a viscous oil (87% yield). R_f = 0.36 (EtOAc/hexane, 35:65); ESI-MS m/z = 601 (M + H)$^+$.

15 was unstable at room temperature and converted to **16** after a few days. Purification by semipreparative RP-HPLC on Vydac C-18, λ = 220 nm, employed a linear gradient of 0−40% (v/v) B in 15 min and followed by 40−80% B in 55 min, afforded 126 mg of a colorless oil; $[\alpha]^{20}_D$ −72.1° (c = 1.20, MeOH); ^{1}H NMR ($CDCl_3$) 7.17−7.32 (m, 5H), 5.15 (m, 1H), 4.95 (m, 1H), 4.00 (m, 1H), 3.43 (m, 1H), 3.20 (m, 1H), 2.96 (m, 1H), 2.52 (m, 1H), 1.79 (m, 1H), 1.45 (s, 9H); δ ^{13}C NMR 173.4, 169.3, 156.0, 136.4, 128.8, 128.6, 127.2, 82.7, 80.2, 56.1, 52.3, 41.9, 35.4, 28.7, 28.3, 28.1; ESI-MS m/z = 405. Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. Found: C, 70.87; H, 6.87; N, 5.19.

***γ*-*tert*-Butyl α-*S*-Ethyl (*S*)-*N*-(Fluorenylmethoxycarbonyl)thioglutamate (18).** Synthesis followed the procedure for **2** deiscribed above and afforded 444 mg of **18** (92% yield) as a white solid. Crystallization from EtOAc/hexane afforded white needles: mp 110−111 °C; R_f = 0.43 (EtOAc/hexane, 20:80); $[\alpha]^{20}_D$ −34.5° (c = 0.96, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.25−7.76 (m, 8H), 5.69 (d, J = 8.5 Hz, 1H), 4.49 (dd, J = 7, 10.5 Hz, 1H), 4.45 (m, 1H), 4.33 (dd, J = 7.5, 10.5 Hz, 1H), 4.22 (t, J = 7 Hz, 1H), 2.88 (q, J = 7.3 Hz, 2H), 2.34 (m, 2H), 2.18 (m, 1H), 1.94 (m, 1H), 1.45 (s, 9H), 1.25 (t, J = 7.3 Hz, 3H); ^{13}C NMR 200.9, 172.5, 156.1, 144.0, 143.8, 141.4, 127.9, 127.2, 125.3, 120.1, 81.2, 67.3, 60.8, 47.3, 31.7, 28.2, 27.7, 23.5, 14.6; FAB-MS m/z = 470 (M + H)$^+$. Anal. Calcd for $C_{26}H_{31}NO_5S$: C, 66.50; H, 6.65; N, 2.98. Found; C, 66.61; H, 6.77; N, 2.98.

5-*tert*-Butyl1-Oxo-2(*S*)-[(9-Fluorenylmethoxycarbonyl)-amino]caproate (19). Synthesis followed procedure described above for **3** and afforded 388 mg of **19** (95%) as a colorless oil which solidified at room temperature: mp 64−65 °C; R_f = 0.33 (EtOAc/hexane, 35:65). $[\alpha]^{20}_D$ −28.4° (c = 0.69, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.56 (s, 1H), 7.29−7.76 (m, 8H), 5.69 (d, J = 7 Hz, 1H), 4.18−4.24 (m, 4H), 1.85−2.36 (m, 4H), 1.44 (s, 9H); ^{13}C NMR 199.0, 172.5, 156.4, 143.9, 143.8, 141.4, 172.9, 127.2, 125.2, 120.2, 81.3, 67.2, 59.8, 47.3, 31.0, 28.2, 24.1; ESI-MS m/z = 410 (M + H)$^+$. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.17; H, 6.80; N, 3.24.

***tert*-Butyl 4(*S*)-[(9-Fluorenylmethoxycarbonyl)amino]-5-[[2-Phenyl-1(*S*)- (*tert*-butyloxycarbonyl)ethyl]amino]-caproate (20).** Preparation by either the stepwise or one-pot method C described above for **7a** afforded **20** as a colorless oil with 95% and 94% yields, respectively. An aliquot of the oil was dissolved in H_2O-CH_3CN-TFA (30:70:0.1, v/v/v) and lyophilized to afford a white powder: mp 34−36 °C; R_f = 0.41 (EtOAc/hexane = 40:60); $[\alpha]^{20}_D$ + 5.6° (c = 1.02, MeOH); ^{1}H NMR ($CDCl_3$) 6.95−7.50 (m, 13H), 6.37 (d, J = 7.5 Hz, 1H), 4.03 (d, J = 8 Hz, 2H), 3.92 (m, 1H), 3.81 (m, 1H), 3.72 (m, 1H), 3.10 (m, 2H), 2.92 (m, 1H), 2.79 (m, 1H), 2.07 (m, 1H), 1.56 (m, 1H), 1.16 (s, 9H), 1.05 (s, 9H); ^{13}C NMR 172.8, 167.2, 157.8, 144.1, 143.8, 141.4, 133.7, 129.6, 129.1, 128.0, 127.3, 125.5, 120.1, 85.2, 81.5, 67.8, 61.9, 51.2, 49.2, 47.1, 35.9, 31.7, 28.2, 27.8, 27.1; ESI-MS m/z = 615 (M + H)$^+$.

α-*tert*-Butyl *β*-*S*-Ethyl (*S*)-*N*-(Benzyloxycarbonyl)thioaspartate (22). Preparation followed the procedure describe for **2**. Purification of the crude product on silica gel column afforded 352 mg **22** (96% yield) as a colorless oil: R_f = 0.48 (EtOAc/hexane, 25:75); $[\alpha]^{20}_D$ −23.4° (c = 1.32, MeOH); ^{1}H NMR ($CDCl_3$) 7.35 (m, 5H), 5.72 (d, J = 8 Hz, 1H), 5.11 (s, 2H), 4.49 (m, 1H), 3.17 (dd, J = 4.5, 16.5 Hz, 1H), 3.15 (dd, J = 4.5, 16.5 Hz, 1H), 2.87 (m, J = 7.5 Hz, 2H), 1.44 (s, 9H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR 196.9, 169.5, 156.0, 136.4, 128.6, 128.2, 128.1, 82.7, 67.0, 51.4, 45.5, 28.0, 23.6, 14.8; ESI-MS m/z 368 (M + H)$^+$.

***tert*-Butyl 2(*S*)-[(Benzyloxycarbonyl)amino]-4-[[2-Phenyl-1(*S*)-(Benzyloxycarbonyl)ethyl]amino]butyrate (24).**[17] Prepared according to method C described above for **7a**. Purification of the crude product on a silica gel column afforded 513 mg of **24** (94% yield) as a colorless oil. An aliquot was dissolved in H_2O-CH_3CN-TFA (30:70:0.1, v/v/v) and lyophilized to afford a white powder: mp 42−43 °C; R_f = 0.46 (EtOAc/hexane, 35:65); $[\alpha]^{20}_D$ −10.5° (c = 1.14, MeOH); ESI-MS m/z = 547 (M + H)$^+$; ^{1}H and ^{13}C NMR were identical with those previously reported.[17]

***tert*-Butyl 2(*S*)-[(9-Fluorenylmethoxycarbonyl)amino]-4-[[(2-Cyclohexyloxycarbonyl)-1(*S*)-(Hydroxycarbonyl)-ethyl]amino]butyrate (26) and *tert*-Butyl 2(*S*)-[(9-Fluorenylmethoxycarbonyl)amino]-4-[[(2-Cyclohexyl-oxycarbonyl)-1(*S*)-(propyloxycarbonyl)ethyl]amino]-butyrate (27).** Preparation followed method C described above for **7a**. Purification of the crude product by preparative RP-HPLC on Vydac C-18, 220 nm (linear gradient of 0−30% (v/v) B in 20 min followed by 30−80% B in 65 min) and lyophilization of the pure fractions afforded 126 mg of **26** (87% yield) and 5 mg of **27** as white powders. **26**: mp 152−153 °C; $[\alpha]^{20}_D$ −2.2° (c = 1.89, MeOH); ^{1}H NMR (d_6-DMSO) δ 7.30−7.86 (m, 8H), 4.43 (m, 1H), 4.31 (m, 1H), 4.22 (m, 1H), 4.13 (m, 1H), 3.14 (m, 2H), 2.94 (m, 2H), 2.24 (m, 2H), 1.77 (m, 1H), 1.71 (m, 1), 1.32−1.45 (m, 20H); ^{13}C NMR 170.6, 168.3, 167.8, 155.4, 142.8, 142.6, 139.9, 126.6, 126.0, 124.1, 118.7, 80.8, 79.0, 64.9, 55.2, 49.0, 47.0, 46.0, 33.5, 30.2, 26.9, 26.7, 26.6; ESI-MS: MW calcd for $C_{32}H_{42}N_2O_8$: 582.6942, found: m/z = 583 (M + H)$^+$. **27**: mp 39−40 °C; ESI-MS m/z = 623 (M + H)$^+$.

Benzyl *N*-(3-Phenylallyl) (*S*)-Phenylalaninate (29). Preparation followed method C described above for **7a**. Purification of the crude product on a silica gel column afforded 343 mg of **29** (92% yield) as a colorless oil which upon lyophilization afforded a white powder: mp 105−106 °C; R_f = 0.42 (EtOAc/hexane, 6:4); $[\alpha]^{20}_D$ +3.7° (c = 2.68, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.09−7.38 (m, 15 H), 6.51 (d, J = 16 Hz, 1H), 6.23 (m, 1H), 5.06 (m, 1H), 4.08 (m, 1H), 3.80 (m, 1H), 3.42 (m, 1H), 3.22 (m, 1H), 2.60 (m, 1H), 2.05 (m, 1H); ^{13}C NMR 168.4, 139.2, 135.2, 134.2, 133.9, 129.4, 129.0, 128.9, 128.3, 127.8, 127.0, 126.6, 117.8, 68.2, 60.1, 48.9, 36.5, 36.5; ESI-MS m/z = 372 (M + H)$^+$.

JO982125G