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Solid-Phase Synthesis of *N*-Nosyl- and *N*-Fmoc-*N*-Methyl-α-amino Acids

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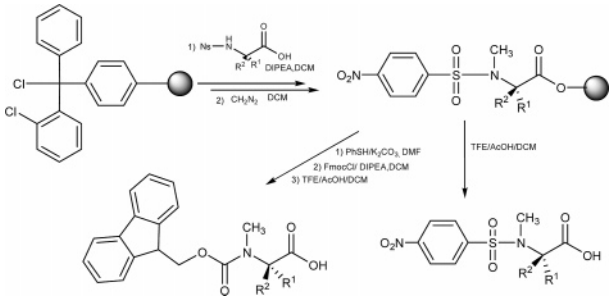

We report here a convenient and simple solid-phase synthesis of *N*-nosyl-*N*-methyl-α-amino acids and *N*-Fmoc-*N*-methyl-α-amino acids, important building blocks for the synthesis of conformationally restricted and protease-resistant natural peptides and peptide analogues. The methodology involves the use of 2-chlorotrityl chloride resin to temporarily protect the carboxylic group of α-amino acids and of diazomethane as the reagent to methylate the sulfonamidic function. The approach developed is particularly efficient also with α-amino acids bearing appropriately protected functionalized side chains.

Introduction

N-Fmoc-protected *N*-methyl-α-amino acids are widely used building blocks in peptide synthesis.[1] *N*-Nitrobenzenesulfonyl-protected *N*-methyl-α-amino acids are also used in peptide synthesis both in solution and solid phase.[2]Incorporation of *N*-methylamino acids into synthetic peptides is useful, as it induces conformational modification of the peptide backbone. Furthermore, it has been shown to be responsible for increased resistance to proteolysis, membrane permeability, receptor selectivity, potency, and bioavailability.[3−5]

We perceived a need for developing general solution or solid-phase methodologies for the acquisition of *N*-Fmoc-*N*-methyl-α-amino acids and *N*-nosyl-*N*-methyl-α-amino acids. Various methods for the synthesis of *N*-methylamino acids have been developed over the years; however, many of these procedures suffer from limitations in terms of yield or racemization or use of a large excess of, often, expensive reagents.[6] The reported methodologies also have shown limited or no application to *N*-methylamino acids with functionalized side-chains and are incompatible with Fmoc-SPPS side-chain protecting groups.[6] Other procedures report the preparation of esters of *N*-methylamino acids that require additional elaboration for their use in peptide synthesis.[6] A solid-phase approach currently available involves the amine activation of solid-supported amino acids by an *o*-nitrobenzenesulfonyl group, followed by Mitsunobu reaction on the activated nitrogen. The removal of the sulfonamide group, the subsequent Fmoc

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SCHEME 1

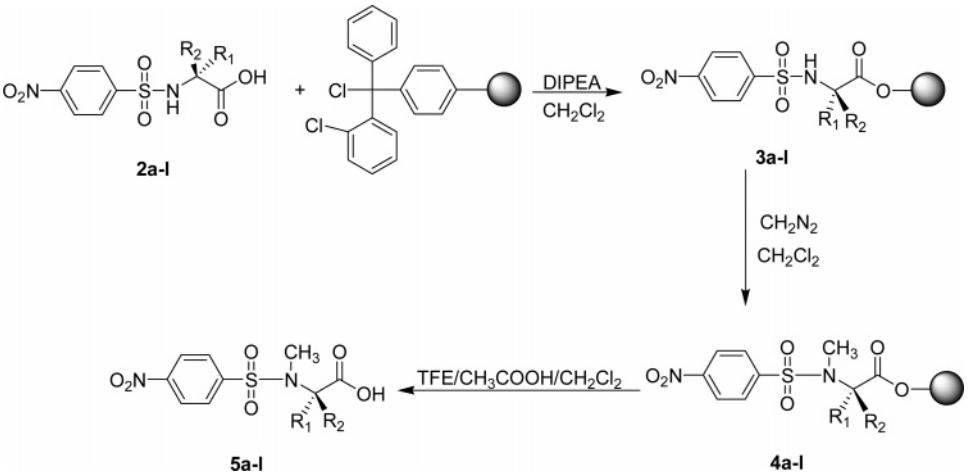

TABLE 1. Results of the Solid-Phase Synthesis of *N*-Nosyl-*N*-methyl-α-amino Acids 5a−l

entry	R^1	R^2	yield (%)[a]
5a	$CH(CH_3)CH_2CH_3$	H	81
5b	CH_3	H	79
5c	$CHCH_2(CH_3)_2$	H	80
5d	$CH(CH_3)_2$	H	83
5e	H	CH_2Ph	78
5f	$(CH_2)_4NH$-(Boc)	H	70
5g	CH_2O-(*t*-Bu)	H	77
5h	$CH_2C_6H_4O$-(*t*-Bu)	H	73
5i	CH_2S-CH_2Ph	H	70
5l	CH_2CONH-(Trt)	H	76

[a] Isolated yield.

protection, and the final cleavage enable the recovery of *N*-Fmoc-*N*-methylamino acids.[7] This represents a reliable method for the solid-phase conversion of amino acids to their N-methylated analogs in high yield, but the procedure is based on the use of resin-bound amino acids and no control of any possible racemization process, as a consequence of the use of basic reagents, is reported.

Tentatively, another procedure for the N-methylation of resin-supported amino acids has been developed on the basis of the Matteson's 1,2-carbon-to-nitrogen migration of boron in α-aminoalkylboronic esters.[8] The N-methylated derivatives, however, are obtained after an oxidative resin wash using excess hydrogen peroxide to repair overalkylated sites: this step limits the methodology to amino acids not sensitive to oxidation. Also some methods for selective N-methylation of the desired amino acid on solid-phase during peptide synthesis have been reported[6,9] but compatibility of the procedures with every common amino acid is still unclear.

We recently described an efficient method for the preparation in solution of *p*-nitrobenzenesulfonyl (nosyl)-protected *N*-methyl-α-amino acid methyl esters under neutral conditions of diazomethylation.[10] This approach affords the N-methylated compounds exploiting both the acidity of the sulfonamidic *N*-H and the basic behavior of diazomethane that enables the formation of the methylating species, the methyldiazonium ion. The N-methylated compounds were obtained as methyl esters derivatives.[10,12]

Results and Discussion

The main objective of this work was the development of a methodology to obtain *N*-methyl-α-amino acids not protected on the carboxylic function that represent useful building blocks both in solution- and solid-phase peptide synthesis. To this aim, it was necessary to temporarily mask the carboxylic moiety with an easily removable protective group. Therefore, we considered the possibility of performing the synthesis using a solid support as a carboxylic protecting group, providing at the same time the advantages of solid-phase peptide synthesis.

The first step of our work was the selection of a suitable solid support. The highly acid-labile 2-chlorotrityl chloride resin (Barlos)[13] was chosen, as it offers a number of exemplary features: in comparison to alcohol-based resins the attachment of α-amino acids to this resin is free of racemization;[14] moreover, it is highly compatible with the base-labile protecting groups (Fmoc and nosyl), and its cleavage conditions are mild enough to retain all acid-sensitive side chain protecting groups. Most of the procedures reported in literature are based on the use of preloaded amino acids often bearing the Fmoc group for the protection of the α-amino function. In these cases, the initial removal of the Fmoc protecting group and the successive reprotection with the nosyl group is necessary.[2b,7]

In our approach the amino acid of interest was attached to the resin as a *p*-nitrobenzensulfonyl-protected amino acid. We have synthesized a number of *N*-nosyl-α-amino acids (**2a**−**e**) using the Schotten−Baumann conditions.[15] Initially lipophilic amino acids were chosen as model systems to investigate the entire procedure. The nosyl-α-amino acids **2a**−**e** were loaded on the 2-chlorotrityl chloride resin in the presence of diisopro-

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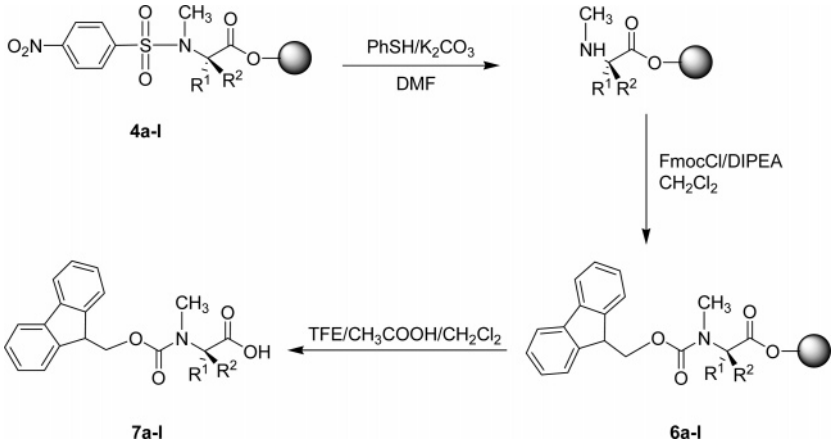
SCHEME 2



pylethylamine (DIPEA) in dichloromethane (DCM) for 2 h (Scheme 1). Unreacted remaining trityl chlorides were converted to the corresponding inert methyl ethers by washing the resin with a solution of DCM/MeOH/DIPEA (80:15:5).[16] N-Methylation of the resulting resin-bound sulfonamides was then performed using 8 equiv of diazomethane[10,11] in a dichloromethane solution for 4 h (Scheme 1).

Cleavage from the resin was, at this stage, the most comprehensive method to test the efficacy of the methodology. Treatment with trifluoroethanol (TFE)/acetic acid (AcOH)/DCM (1:1:3)[17] afforded the crude products **5a**−**e** in 78−83% yields (Scheme 1, Table 1). GC/MS and ^{1}H NMR analysis revealed the presence of *N*-nosyl-*N*-methyl-α-amino acids **5a**−**e** as the sole reaction products.

In light of these results, we then planned the removal of the nosyl protective group and the subsequent introduction of the Fmoc group in order to obtain the desired *N*-Fmoc-*N*-α-methylamino acids. To this end, the nosyl-protected lipophilic amino acids were attached to the 2-chlorotrityl chloride resin in the presence of DIPEA in dichloromethane: in a second step N-methylation was achieved with diazomethane. The removal of the nosyl group from the intermediate N-methylated sulfonamide **4a**−**e** was accomplished via aromatic nucleophilic substitution (SNAr) by treatment with thiophenol/potassium carbonate[2c] in DMF (Scheme 2).

Deprotection was easily followed by simple visual inspection of the released yellow chromophore.[2c] The reaction was also monitored by the chloranil test that enables a reliable qualitative detection of secondary amino groups.[18] The reaction went to completion in 2 h. The procedure was repeated once more to ensure complete deprotection in every case.

The Fmoc protecting group was introduced by treatment with FmocCl (4 equiv) and DIPEA (6 equiv) in DCM for 2 h. The *N*-Fmoc-*N*-methyl-α-amino acids **7a**−**e** were cleaved from the resin under the usual acidic conditions (Scheme 2, Table 2).

To investigate the stereochemical aspects of the entire methodology the L-isoleucine was subjected to the adopted procedure affording the *N*-nosyl-*N*-methylisoleucine (**5a**) and *N*-Fmoc-*N*-methylisoleucine (**7a**). GC/MS analysis performed on the *N*-nosyl-*N*-methylisoleucine revealed **5a** as the single product; moreover, ^{1}H NMR analysis performed on **5a** and **7a** clearly showed the presence of signals corresponding to one diastereoisomer only thus excluding any possible racemization process of the chiral substrates during the entire synthetic process. Moreover, ^{1}H NMR analysis performed on **7a** was identical to that of a commercially available authentic sample.

TABLE 2. Results of the Solid-Phase Synthesis of *N*-Fmoc-*N*-methyl-α-amino Acids 7a−l

entry	R^1	R^2	yield (%)[a]
7a	$CH(CH_3)CH_2CH_3$	H	89
7b	CH_3	H	82
7c	$CHCH_2(CH_3)_2$	H	75
7d	$CH(CH_3)_2$	H	77
7e	H	CH_2Ph	76
7f	$(CH_2)_4NH$-(Boc)	H	70
7g	CH_2O-(*t*-Bu)	H	76
7h	$CH_2C_6H_4O$-(*t*-Bu)	H	73
7i	CH_2S-CH_2Ph	H	75
7l	CH_2CONH-(Trt)	H	72

[a] Isolated yield.

The applicability of this method was then tested for a set of amino acids containing functionalized side chains with acid-labile protecting groups (e.g., Boc, *t*-Bu, trityl) to make the adopted procedure general. The initial preparation of the nosyl-protected derivatives required particular attention to the acid-sensitive side chain protecting groups. Therefore, the protection of the α-amino function with the nosyl group was realized by treatment of the side chain-protected amino acids **1f**−**l** with nosyl chloride in a dioxane/water solution in the presence of a large excess of triethylamine. Workup was performed with a 5% solution of $KHSO_4$ to avoid undesired removal of the acid-sensitive side chain protecting groups (Scheme 3, Table 3).

Attachment of side-chain-protected N^{α}-nosyl-α-amino acids **2f**−**l** to the 2-chlorotrityl chloride resin was performed under the adopted conditions and then the obtained products were treated with diazomethane to provide the resin-bound N-

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SCHEME 3

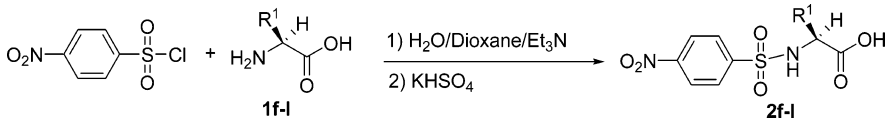

TABLE 3. Results of the Synthesis of 2f−l

entry	R^1	yield (%)[a]
2f	$(CH_2)_4NH$-(Boc)	78
2g	CH_2O-(*t*-Bu)	76
2h	$CH_2C_6H_4O$-(*t*-Bu)	74
2i	CH_2S-CH_2Ph	77
2l	CH_2CONH-(Trt)	80

[a] Isolated yield.

methylated sulfonamides (Scheme 1). Cleavage from the resin at this stage afforded the side-chain-protected N^{α}-nosyl-*N*-methyl amino acids **5f−l** in 70−77% yields (Table 1). Alternatively, removal of the nosyl protective group, subsequent Fmoc introduction, and final cleavage from the resin using TFE/AcOH/DCM furnished the N^{α}-Fmoc-*N*-methyl-α-amino acids **7f−l** in 70−76% yields.

Analysis of **7f−l** accomplished by ^{1}H NMR and ^{13}C NMR showed that the methodology is compatible with different amino acids including those bearing functionalized side chains with side chain acid-labile protecting groups. In fact all the products obtained maintain intact, at the end of the process, side chain acid-labile protective groups.

The NMR spectra of the N^{α}-Fmoc-*N*-α-methyl amino acids obtained in this study are of special interest because they are complicated at ambient temperature by rotamers of the trisubstituted amides. The presence of the bulky Fmoc protecting group gives rise to rotational isomers as a result of hindered rotation around the C−N bond. These rotamers are detectable at room temperature, as has been previously reported for N,N-disubstituted amides.[19] In fact, in the ^{1}H NMR spectrum of N^{α}-Fmoc-*N*-methyl-L-valine (**7d**) we can clearly observe two sets of signals, one for each rotamer (Figure 1). Doubling of the corresponding signals of most of the carbon atoms in the ^{13}C NMR spectra of compounds **7a−l** was also observed.

It is well-known that the duplicate resonances for the rotamers coalesce at higher temperatures where the rate of interconversion is much greater. To this end we performed, selecting the N^{α}-Fmoc-*N*-methylvaline (**7d**) as a model compound, a number of NMR experiments at different temperatures: the coalescence of the signals corresponding to the two rotamers of the N^{α}-Fmoc-*N*-methylvaline was observed at a temperature equal to 50 °C (Figure 2).

One of the important features of our approach is the economy of the synthetic process. In fact, the 2-chlorotrityl chloride resin after cleavage of the *N*-Nosyl- or *N*-Fmoc-*N*-methyl-α-amino acids is transformed into the corresponding alcohol and can be easily regenerated allowing the reuse of the resin.[20] To this aim, we reactivated the resin, converting the trityl alcohol moiety in trityl chloride so that the solid support could be reused. It is possible to reactivate the resin after the cleavage by treatment with thionyl chloride in dichloromethane at room temperature.[20b] To test the regenerated resin, the *N*-nosylphenylalanine **2e** was attached to the same resin, under the previously described conditions, and subsequently cleaved from the resin. GC/MS analysis of the crude product obtained confirmed the presence of *N*-nosylphenylalanine **2e** recovered in 60% yield. This result demonstrated the efficiency of the procedure for the regeneration of the resin.

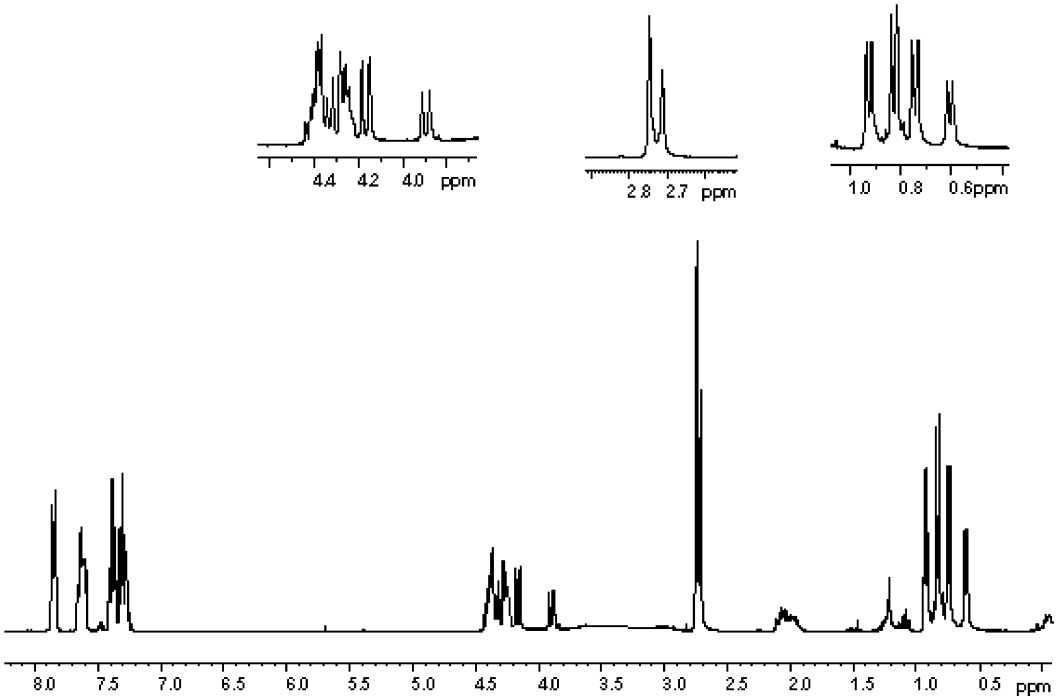

FIGURE 1. Rotamers in the ^{1}H NMR spectrum of N^{α}-Fmoc-*N*-methyl-L-valine (**7d**).

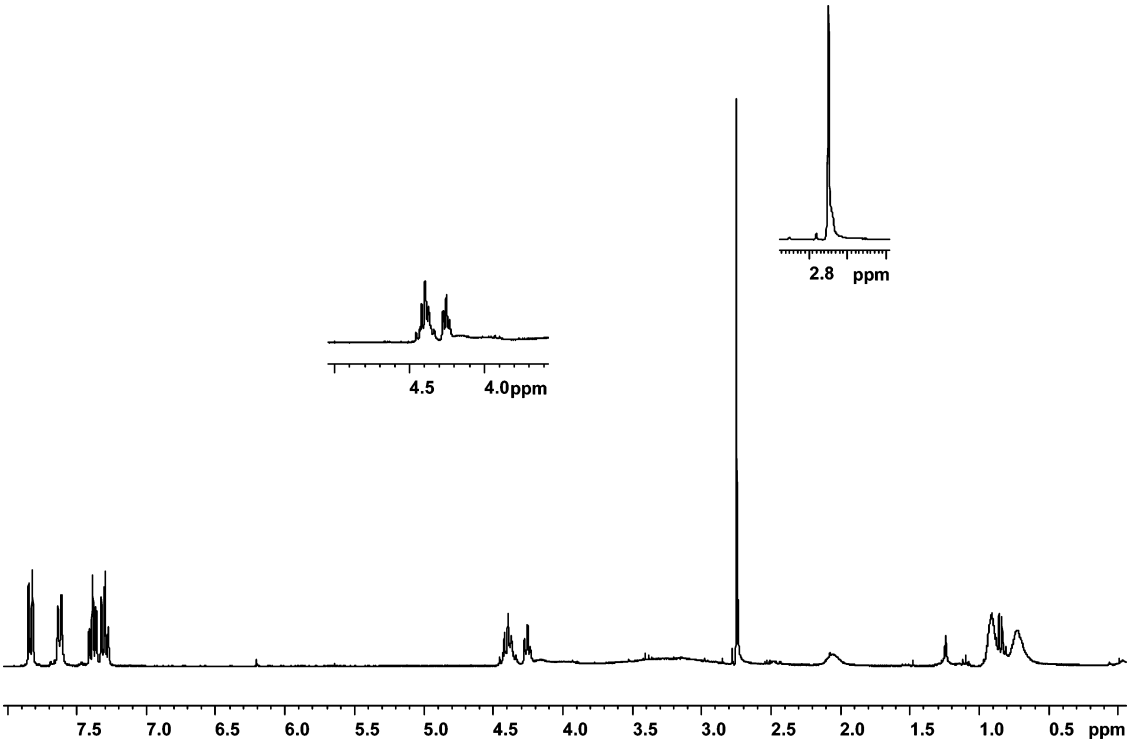

FIGURE 2. ^{1}H NMR spectrum of N^{α}-Fmoc-*N*-methyl-L-valine (**7d**) at the coalescence temperature (50 °C).

Conclusions

In conclusion we have presented a simple and efficient method for the production of *N*-nosyl- and *N*-Fmoc-*N*-methyl-α-amino acids with the COOH function unmasked and therefore directly employable in peptide synthesis. The procedure is based on the use of diazomethane as methylating reagent and on the use of the 2-chlorotritylchloride resin acting both as solid support and as a temporary protecting system of the carboxylic function. The simple use of a dichloromethane solution of diazomethane enables the direct methylation of the sulfonamidic function of resin bound *N*-nosyl-α-amino acids. Our approach combines the features of simplicity and generality also when the synthesis involves amino acids bearing functionalized side chains. Furthermore, the recycling of the resin makes the procedure economically advantageous.

Experimental Section

Solid-Phase Synthesis of N^{α}-Nosyl-*N*-methyl-α-amino Acids 5a-l. General Procedure A: (1) Attachment of the *N*-Nosylamino Acid to 2-Chlorotrityl Chloride Resin. In a peptide vessel 2-chlorotrityl chloride resin (1.8 mmol/g, 200 mg) was covered with DMF (3−6 mL/g) and allowed to swell for 4 h. *N*-Nosyl-α-amino acids **2a**−**l** (2 equiv relative to resin capacity) were dissolved in DCM (10 mL/g resin). The solution was added to the resin followed by 8 equiv (relative to resin capacity) of DIPEA. The mixture was mechanically stirred at room temperature for 2 h. After filtration, the remaining trityl chloride groups were capped by a solution of DCM/MeOH/DIPEA (80:15:5 v:v:v) for 10 min. The resin was drained and washed with DCM (3×), DMF (3×), DCM (3×). **(2) N-Methylation.** The resin-bound N^{α}-nosyl-α-amino acids **3a**−**l** were mixed with diazomethane[10,11] (8 equiv) in a dichloromethane solution for 4 h. The resin was then washed with DCM (3×), MeOH(3×), DCM (3×). **(3) Cleavage from the Resin.** The resin-bound N^{α}-nosyl-*N*-methyl-α-amino acids **4a**−**l** were stirred for 2 h in 5 mL of 2,2,2-trifluoroethanol/AcOH/DCM (1:1:3). The reaction mixture was filtered, and the resin was rinsed with 2,2,2-trifluoroethanol/AcOH/DCM and then washed with DCM (3×). The filtrates were pooled, and the solvents were evaporated under vacuum to furnish the N^{α}-nosyl-*N*-methylamino acids **5a**−**l** as yellow solids in 70−83% overall yields. The yields were based on the 2-chlorotritylchloride resin initial loading (1.8 mmol/g). The solid support synthesis overall yield was evaluated after cleavage from the resin.

***N*-Nosyl-*N*-methyl-L-isoleucine (5a):** yellow solid (81%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, 2H, J = 9.3 Hz), 8.00 (d, 2H, J = 9.3 Hz), 4.26 (d, 1H, J = 10.4 Hz), 2.92 (s, 3H), 1.92 (m, 1H), 1.59 (m, 1H), 1.19 (m, 1H), 0.98−0.87 (m, 6H). MS (EI) *m*/*z* (rel intensity %): 285 (100%), 229 (31), 186 (30), 122 (29), 42 (59). Anal. Calcd. for $C_{13}H_{18}N_2O_6S$: C, 47.26; H, 5.49; N, 8.48; S, 9.71. Found: C, 47.44; H, 5.47; N, 8.49; S, 9.68.

Solid-Phase Synthesis of N^{α}-Fmoc-*N*-Methyl-α-amino Acids 7a-l. General Procedure B: (1) Removal of Nosyl Protecting Group. A 20 equiv amount of K_2CO_3 and 15 equiv of thiophenol were mixed in DMF (2 mL/100 mg of resin) for 10 min, and then the K_2CO_3 was allowed to sediment. The deprotection solution obtained, containing the soluble potassium thiophenolate, was added to the resin-bound *N*-nosyl-*N*-methylamino acids **4a**−**l**, swollen in DMF, prepared according the above-described general procedure A. The mixture was agitated at rt for 2 h, and this procedure was repeated once more, monitoring the progress of the deprotection reaction by the chloranil test. The resin was drained and washed with DMF (3×), MeOH (3×), DCM (3×). **(2) Introduction of Fmoc Protecting Group.** The resin was swollen in DCM and then treated with DIPEA (6 equiv) and FmocCl (4 equiv). The mixture was agitated for 2 h, monitoring the progress of the reaction by the chloranil test. The resin was drained and washed with DCM (3×), MeOH (3×), DCM (3×). **(3) Cleavage from the Resin.** The resin-bound *N*-Fmoc-*N*-methylamino acids **6a**−**l** were treated with a TFE/AcOH/DCM (1:1:3) solution for 2 h. The resin was washed with the cleavage mixture and then with DCM. The combined filtrates and washings were evaporated to dryness at reduced pressure to afford the desired *N*-Fmoc-*N*-methylamino acids **7a**−**l** as white solids in 70−89% yields.

***N*-Fmoc-*N*-Methyl-L-isoleucine (7a):** white solid (89%). mp 181−183 °C. ^{1}H NMR (300 MHz, DMSO-d_6), two conformers (67*:33): δ 7.90−7.25 (m, 8H), 4.50−4.30 (m, 3H), 3.95 and 4.25* (2d, 1H, J = 9.9 Hz), 2.70 (s, 3H), 1.80 (m, 1H), 1.25−1.05 (m, 2H), 0.90−0.70 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6), two conformers: δ 172.5, 156.4, 144.3, 144.1, 141.3, 128.1, 127.5, 125.4, 120.5, 67.2, 62.9, 62.7, 47.2, 47.1, 33.1, 30.4, 25.0, 24.8, 11.1, 10.9. Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.98; H, 6.85; N, 3.80.

Synthesis of *N*-Nosyl-α-amino Acids 2f-l. General Procedure C. The side-chain-protected α-amino acids **1f**−**l** (1 mmol) were dissolved in a dioxane/water solution and cooled to 0 °C. Dry triethylamine (20 mmol) and then a solution of *p*-nitrobenzenesulfonyl chloride (1.5−1.6 mmol) in dioxane were added slowly. The reaction mixture was stirred for 30−50 min, monitoring the conversion of **1f**−**l** by TLC (chloroform/methanol 90:10 v/v). The solvent was removed under reduced pressure, and the residue was basified with a 5% aqueous solution of Na_2CO_3 and extracted with diethyl ether (3 × 10 mL). The aqueous phase was acidified with a 5% aqueous solution of $KHSO_4$ (pH = 3−4) and extracted with ethyl acetate. The organic layer was washed with water and brine and then dried with Na_2SO_4. The solvent was evaporated to afford the corresponding side-chain-protected *N*-nosyl-α-amino acids **2f**−**l** as white solids in 74−80% overall yields.

***N*$^\alpha$-Nosyl-*N*$^\epsilon$-Boc-L-lysine (2f):** white solid (78%). mp 153−155 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.72 (br s, 1H), 8.58 (d, 1H, J = 8.7 Hz), 8.39 (d, 2 H, J = 8.4 Hz), 8.00 (d, 2H, J = 8.9 Hz), 6.75 (m, 1H), 3.70 (dd, 1H, J = 13.5, 8.4 Hz), 2.78 (m, 2 H), 1.60−1.40 (m, 2H), 1.34 (s, 9H), 1.27−1.10 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.0, 156.0, 149.8, 147.2, 144.8, 128.5, 124.8, 77.8, 56.1, 32.0, 29.2, 28.7, 22.8, 18.1. MS *m*/*z* (%) 453.8931 [(M + Na)$^+$, 100]. Anal. Calcd. for $C_{17}H_{25}N_3O_8S$: C, 47.32; H, 5.84; N, 9.74; S, 7.43. Found: C, 47.41; H, 5.86; N, 9.72; S, 7.40.

Supporting Information Available: General experimental methods and experimental details for the synthesis of compounds **5b**−**l**, **7b**−**l**, and **2g**−**l**. Copies of ^{1}H NMR spectra of compounds **5a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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