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# *N*-(4-Nitrophenylsulfonyl)- and *N*-(Fluorenylmethoxycarbonyl)-*N*-ethyl Amino Acid Methyl Esters – A Practical Approach

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An efficient one-pot preparation of *N*-ethyl-*N*-4-nitrophenylsulfonyl (nosyl) amino acid methyl esters was accomplished by a simple *N*-ethylation reaction by using triethyloxonium tetrafluoroborate in the presence of *N*,*N*-diisopropylethylamine. The *N*-ethylated amino acid methyl esters are obtained with total retention of stereochemistry at the original chiral centers. To further broaden the scope of this methodology, the *N*-ethylated nosyl-protected compounds are easily converted in the more practical fluorenylmethyloxycarbonyl (Fmoc)-protected derivatives. The cleavage of methyl ester by using a mild and neutral method enables the preparation of *N*-ethyl amino acids that are building blocks suitable for introduction into a peptide chain. The methodology works well with both nosyl- and Fmoc-based solution-phase peptide synthesis.

## Introduction

*N*-Alkyl α-amino acids are constituents of a large number of naturally occurring peptides and proteins.[1] The substitution of *N*-alkyl α-amino acids into biologically active peptides and, in particular, *N*-methylation has resulted in analogues with enhanced pharmacological properties as a consequence of conformational modifications.[2,3] Enhanced potencies have been observed when higher *N*-alkyl substitutions are employed.[4] *N*-Ethyl amino acids can be widely applied as building blocks for the synthesis of *N*-ethylated peptides. A substitution of *N*-methyl-leucine of cyclosporin A by various *N*-ethyl amino acids was performed with the aim of blocking the main metabolic degradation pathways. The corresponding *N*-ethyl derivative resulted in analogues of cyclosporine A exhibiting nonimmunosuppressive and anti-HIV activity.[5] Various protocols have been developed for the synthesis of *N*-methyl amino acids.[2] At the present time, however, only a few methods for the synthesis of *N*-ethylated amino acids and their derivatives are available in the literature.[6] Furthermore, the general *N*-alkylation of amino acids with nonmethyl alkylating agent seems tricky mostly due to the steric hindrance of longer carbon chains.[7] Papaioannou and co-workers have described a Mitsunobu-type *N*-ethylation of tosylamino esters with excess ethanol.[8] However, the detosylation procedure is a drawback of this method. The *N*-ethylation of amino acids has been generally achieved by transforming the N–H function of amino acids into iminic or aminoacetalic systems. In recent years, the reductive amination, by using sodium cyanoborohydride, of imines derived from amino acids and acetaldehyde has constituted an efficient approach for the *N*-ethylation of amino acids,[9,10] but over alkylation readily occurs and is of major concern.[11,12] In addition, the *N*-ethylation can be achieved smoothly by starting from α-amino acids with hexafluoroacetone as the protecting and activating agent; the subsequent reaction with a cuprate prepared from copper(I) cyanide and one equivalent of methyllithium gave the corresponding *N*-ethyl compounds.[13] Nevertheless, traces of the *N*-methyl analogues were also detected. In the attempt to obtain protected *N*-ethyl amino acids, an important development has been the reduction of the *N*-Fmoc-oxazolidinones (Fmoc = fluorenylmethyloxycarbonyl) of various amino acids to their corresponding *N*-ethyl *N*-Fmoc derivatives.[14] An alternative route for the synthesis of *N*-ethyl amino acids was provided by the reduction of *O*-alkyl acetohydroxamate obtained from amino acids.[15] Another approach describes the *N*-ethylation of carbobenzyloxy (Z)- and *tert*-butoxycarbonyl (Boc)-protected amino acids by starting from the generation of a dianion derivative at the oxygen and nitrogen atoms that is subsequently alkylated with ethyl iodide.[16] However, Hansen and co-workers[17] suggest that this procedure affords only a trace of ethylated product because a β-elimination reaction of the alkylating agent preferentially occurs. Moreover, the necessity of maintaining the reaction temperature at –78 °C may make the reaction inconvenient. Thus, they posit that for a successful reaction the dianion had to be initially generated by using *tert*-butyl-

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lithium as a strong non-nucleophilic base and then treated with the powerful alkylating agent triethyloxonium tetrafluoroborate.

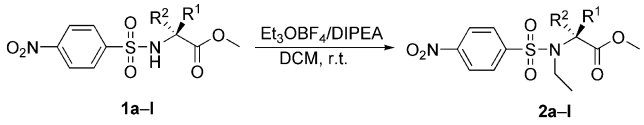
In the light of this, a novel and concise method for the synthesis of *N*-ethylated amino acids is needed.

## Results and Discussion

Our attention was devoted to the development of a synthetic procedure that had to respond to the following requirements: (1) A one-pot process without the need of a low reaction temperature would be preferred. (2) Any possible side reactions responsible for a decrease in yield should be avoided. (3) The use of a weak or dilute base is preferred to avoid racemization. (4) A proper protecting group for the aminic function had to be selected to suppress the formation of diethylated product and to enhance the acidity of the N–H proton. (5) A synthetic method compatible with widely used Fmoc-based chemistry[18] would complement this approach, especially for amino acids containing functionalities incompatible with Boc chemistry.

In this regard, the 4-nitrophenylsulfonyl (nosyl) protecting group, firstly described by Fukuyama,[19] seemed to be the most promising group for our purpose. Thanks to its strong electron-withdrawing character, the nosyl group acts as both an activating and protecting group and enhances the reactivity of the N–H function towards various alkylating agents.[20,21] In addition, the compatibility of the nosyl group with the more practical Fmoc protecting group, commonly used in peptide and amino acid synthesis has been well documented.[20–22]

On the basis of the above considerations, we initially subjected the *N*-nosyl-alanine methyl ester, (**1a**) chosen as a model system, to treatment with 2.5 equivalents of triethyloxonium tetrafluoroborate and 3.5 equivalents of *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane at room temperature (Scheme 1, Table 1). To our delight, the reaction was complete in only ten minutes and TLC analysis clearly showed the total conversion of **1a** into a single product; subsequently, a simple workup afforded the corresponding *N*-ethylated product **2a** in excellent yield. No additional chromatographic purification procedure was required.




Scheme 1. Direct *N*-ethylation of **1a**–**l**.

Encouraged by this promising result, we tested the *N*-ethylation reaction with other amino acids. Compounds **1b**–**f** were subjected to the above described reaction conditions to afford the *N*-ethylated derivatives in almost quantitative yields (Scheme 1, Table 1).

It is worth noting that the triethyloxonium tetrafluoroborate could react with the functional groups of side-chain-functionalized amino acids. For this purpose, we next investigated the scope of the reaction with respect to amino acids containing functionalized side chains with acid-labile protecting groups (e.g. Boc, *t*Bu, benzyl) to make the adopted procedure more general. The *N*-nosyl-glutamic acid methyl ester protected on the side-chain carboxylic function with a *tert*-butyl group (**1g**), was chosen as a model system. It was subjected to the ethylation reaction as described above and gave the *N*-ethylated derivative **2g** in 85% yield. The method works well also for preparing *N*-ethyl derivatives of other amino acids with functionalized side chains as indicated in Table 1 by entries **2h**–**l**.

Table 1. Synthesis of *N*-ethyl-*N*-nosyl amino acid methyl esters **2a**–**l**.

| Entry | $R^1$ | $R^2$ | % Yield[a] |
|---|---|---|---|
| **2a** | $CH_3$ | H | 96 |
| **2b** | $CH(CH_3)_2$ | H | 89 |
| **2c** | $CHCH_2(CH_3)_2$ | H | 97 |
| **2d** | $CH(CH_3)CH_2CH_3$ | H | 95 |
| **2e** | H | $CH(CH_3)CH_2CH_3$ | 96 |
| **2f** | $CH_2Ph$ | H | 99 |
| **2g** | $CH_2CH_2CO_2tBu$ | H | 85 |
| **2h** | $CH_2S(Bn)$ | H | 87 |
| **2i** | $CH_2C_6H_4O(Bn)$ | H | 91 |
| **2l** | $(CH_2)_4NH(Boc)$ | H | 94 |

[a] Isolated yield.

It was observed that the use of a stoichiometric quantity of base could halve the reaction yield. To demonstrate this assumption, one equivalent of *N*-nosyl-alanine methyl ester **1a** was treated with 2.5 equivalents of triethyloxonium tetrafluoroborate in the presence of an equivalent amount of base. The starting compound **1a** was still detected in the reaction mixture even after 3 h. Thus, the mixture was washed with water at first and then with a NaOH aqueous solution. Final evaporation of the solvent gave the *N*-ethyl-*N*-nosyl-alanine methyl ester **2a** in 50% yield. The reaction conducted on the starting compounds **1b**–**f** proceeded analogously affording the *N*-ethylated derivatives **2b**–**f** in 50% yields.

The necessity of conducting the ethylation reaction by adding an excess of base is justified by the presence of $BF_3$ and $F^-$ arising from the decomposition of the tetrafluoroborated anion.[23] The fluoride ion represents the counteranion of the diisopropylammonium species, whereas $BF_3$ coordinates the aminic function of the nosyl-protected amino acid restraining its ability to interact with the electrophile.

Our next effort was devoted to the demonstration that the chiral integrity of the starting α-amino acids had been maintained throughout the synthetic process. To address this issue, the alkylating reaction described above was repeated with both *N*-nosyl-isoleucine methyl ester (**1d**) and *N*-nosyl-D-alloisoleucine methyl ester (**1e**). The resulting *N*-ethylated derivatives **2d** and **2e** were obtained in 95 and 96% yields, respectively. The two crude reaction products were analyzed by GCMS analysis. The GCMS analysis (Figure 1) revealed the detection of only one diastereoisomer in each of the gas chromatograms, thus confirming that

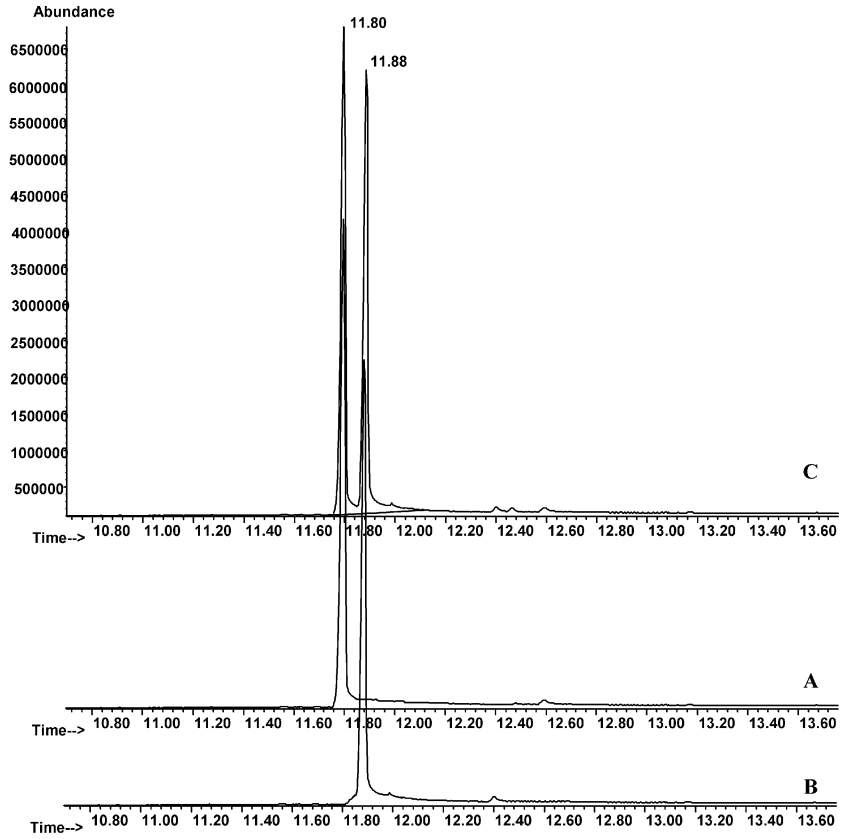



Figure 1. GCMS analyses of the *N*-ethyl-*N*-nosyl-amino acid methyl esters: (A) *N*-Ethyl-*N*-nosyl-L-Ile-OMe (**2d**, r.t., 11.80 min). (B) *N*-Ethyl-*N*-nosyl-D-alloIle-OMe (**2e**, r.t., 11.88 min). (C) A mixture of **2d** and **2e**.

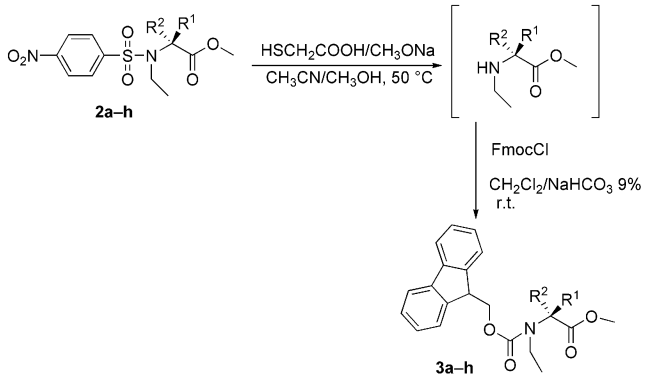
the alkylation reaction occurred with retention of configuration of the original stereocenters. The complete separation of **2d** and **2e** was confirmed by performing the GCMS analysis (Figure 1) of an opportunely prepared mixture of **2d** (25 mg) and **2e** (25 mg).

The final test of this methodology required the demonstration of the compatibility of our developed procedure with standard Fmoc chemistry. Thus, we planned the removal of the nosyl protective group and the subsequent introduction of the Fmoc group to obtain the desired *N*-ethyl-*N*-Fmoc-amino acid methyl esters.

The removal of the nosyl group from the intermediate *N*-ethylated sulfonamide **2a**–**h** was accomplished by an aromatic nucleophilic substitution (SNAr) by treatment with the reagent system mercaptoacetic acid/sodium methoxide in acetonitrile/methanol (Scheme 2) by following a procedure already described in our previous paper for *N*-methylated amino acids.[22] Lastly, the amino function was reprotected with the Fmoc group by treatment with Fmoc chloride.[22]

The reaction was complete in 90 min and the Fmoc-*N*-ethyl-amino acid methyl esters **3a**–**h** were afforded in 71–94% overall yields (Table 2).

At this point methyl ester cleavage was required to make these compounds available as building blocks for Fmoc-based chemistry. To avoid racemization during the saponification step,[24] methyl ester cleavage was easily realized by




Scheme 2. Removal of nosyl group and reprotection of the amino function with a Fmoc group.

Table 2. Synthesis of *N*-Fmoc-*N*-ethyl amino acid methyl esters **3a**–**h**.

| Entry | $R^1$ | $R^2$ | % Yield[a] |
|---|---|---|---|
| **3a** | $CH_3$ | H | 90 |
| **3b** | $CH(CH_3)_2$ | H | 91 |
| **3c** | $CHCH_2(CH_3)_2$ | H | 80 |
| **3d** | $CH(CH_3)CH_2CH_3$ | H | 94 |
| **3f** | $CH_2Ph$ | H | 90 |
| **3g** | $CH_2CH_2CO_2tBu$ | H | 76 |
| **3h** | $CH_2S(Bn)$ | H | 71 |

[a] Isolated yield.

an $S_N2$ dealkylation according to the efficient procedure described by Biron and Kessler.[25] Treatment of *N*-ethyl-*N*-Fmoc-L-isoleucine methyl ester (**3d**), chosen as a model system, with lithium iodide in refluxing ethyl acetate, afforded after 20 h the corresponding *N*-ethyl-*N*-Fmoc-L-isoleucine (**4**) in 94% yield, which could be directly used without further purification. The cleavage reaction did not involve racemization as shown by $^1$H NMR spectroscopic analysis of **4**. The *N*-ethyl-*N*-Fmoc amino acid **4** was now suitable for incorporation into a peptide chain. To demonstrate the application of this method, we prepared a dipeptide under the standard peptide coupling conditions by using *N*,*N*-dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBt).[26] The *N*-ethyl-*N*-Fmoc-isoleucine **4** was coupled with the amino-free L-valine methyl ester hydrochloride by using DCC, HOBt, and *N*-methylmorpholine in THF for 1 h. The resulting dipeptide *N*-ethyl-*N*-Fmoc-L-ile-L-valOMe (**5**) was isolated in 90% yield and only one diastereoisomer was observed by $^1$H NMR spectroscopic analysis.

Our methodology can readily be accommodated to the standard Fmoc and nosyl-based peptide synthetic strategy. In an additional experiment, in fact, we successfully prepared a nosyl-protected dipeptide containing an *N*-ethyl amino acid. Thus, the *N*-ethyl-*N*-nosyl-L-isoleucine methyl ester (**2d**) was subjected to the above described $S_N2$ dealkylation reaction with LiI. Also in this case, the corresponding *N*-ethyl-*N*-nosyl-L-isoleucine (**6**) was afforded in excellent yield (96%) and without the need for chromatographic purification. The *N*-ethylated nosyl-protected amino acid **6** was finally activated and coupled with valine methyl ester hydrochloride by means of DCC/HOBt as the coupling reagents.

The dipeptide *N*-ethyl-*N*-nosyl-L-ile-L-valOMe (**7**) was recovered after 1 h in high yield (92%) and without purification. Also in this case, no racemization was observed as shown by the $^1$H NMR spectrum of the crude product of **7**.

## Conclusions

A mild and efficient method for the preparation of *N*-ethylated amino acids has been described. The *N*-ethyl amino acids were obtained by a one-pot process of monoethylation of amino acids specifically acquired by using the nosyl group as an excellent protecting group. The chiral integrity of nosyl-protected amino acids during base-induced *N*-alkylation has also been investigated. The thus-obtained *N*-ethyl derivatives of isoleucine and D-alloisoleucine do not show any detectable racemization.

The *N*-ethyl-*N*-nosyl-amino acid methyl esters prepared by this method can be further converted into the corresponding *N*-Fmoc protected derivatives. The de-esterification is easily performed by using an $S_N2$ dealkylation reaction. The corresponding *N*-protected *N*-ethyl amino acids are efficiently incorporated into dipeptides under standard coupling conditions. The *N*-nosyl- and *N*-Fmoc-protected *N*-ethyl amino acids prepared by our procedure represent building blocks that are useful for solution-phase peptide synthesis.

The present procedure has the advantages of mild reaction conditions, short reaction times, high yields of products, and simple experimental workup procedures.

## Experimental Section

**General:** Solvents were purified and dried by standard procedures and distilled prior to use. Commercially available reagents were purchased from Aldrich Chemical Co. The $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker Avance 300 spectrometer by using $CDCl_3$ as the solvent. Chemical shifts ($\delta$) are reported in ppm. Coupling constants ($J$) are reported in Hertz (Hz). Reaction mixtures were monitored by TLC by using Merck Silica gel 60-$F_{254}$ precoated glass plates.

GCMS analyses were performed by HP-5MS (30 m × 0.25 mm, PhMesiloxane capillary column). The mass detector was operated in the electron-impact ionization mode (EIMS) with an electron energy of 70 eV. The injection port was heated to 250 °C. The oven-temperature program was initially set at 100 °C with a hold of 2 min and ramped to 280 °C at 14 °C/min with a hold of 10 min. Methane gas at a pressure of ca. 2 Torr was used as the CI reagent gas. The *N*-nosyl α-amino acid methyl esters were prepared as described previously.[20]

**Synthesis of *N*-Ethyl-*N*-nosyl Amino Acid Methyl Esters 2a–l. General Procedure:** DIPEA (3.5 mmol) and solid triethyloxonium tetrafluoroborate (2.5 mmol) were added to a solution of **1a**–**l** (150 mg, 1 mmol) in $CH_2Cl_2$ (20 mL) under an inert atmosphere. The reaction mixture was stirred at room temperature for 10 min. The mixture was quenched with a 1 N HCl solution (or a 10% citric acid solution for compounds **1g** and **l**) and then washed with a 1 N NaOH solution. The organic layer was extracted with $CH_2Cl_2$ (2 × 10 mL) and dried with $Na_2SO_4$. Evaporation of the solvent afforded the corresponding *N*-ethyl-*N*-nosyl amino acid methyl esters **2a**–**l** as yellow oils in 85–99% overall yields.

***N*-Ethyl-*N*-nosyl-L-alanine Methyl Ester (2a):** By following the general procedure, treatment of a solution of *N*-nosyl-alanine methyl ester (**1a**) (150 mg, 0.52 mmol) in dry $CH_2Cl_2$ (20 mL) with DIPEA (0.32 mL, 1.82 mmol) and triethyloxonium tetrafluoroborate (222 mg, 1.3 mmol) afforded **2a** (144 mg, 96% yield) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.34 (d, $J$ = 9 Hz, 2 H, *o*-$NO_2$), 8.01 (d, $J$ = 9 Hz, 2 H, *m*-$NO_2$), 4.71 (q, $J$ = 7.2 Hz, 1 H, α-C*H*), 3.54 (s, 3 H, OC$H_3$), 3.39 (m, 1 H, NC$H_2$CH$_3$), 3.19 (m, 1 H, NC$H_2$CH$_3$), 1.51 (d, $J$ = 7.5 Hz, 3 H, C$H_3$), 1.25 (t, $J$ = 7.1 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 171.2, 149.9, 145.7, 127.8, 123.9, 55.7, 52.3, 41.2, 17.1, 16.6 ppm. MS (EI) (rel. intensity%): $m/z$ = 257 (100), 229 (10), 186 (25), 122 (17), 56 (14). $C_{12}H_{16}N_2O_6S$ (316.07): calcd. C 45.56, H 5.10, N 8.86, O 30.35, S 10.14; found C 45.47, H 5.08, N 8.88.

***N*-Ethyl-*N*-nosyl-L-valine Methyl Ester (2b):** By following the general procedure, treatment of a solution of *N*-nosyl-valine methyl ester (**1b**) (150 mg, 0.47 mmol) in dry $CH_2Cl_2$ (20 mL) with DIPEA (0.29 mL, 1.64 mmol) and triethyloxonium tetrafluoroborate (200 mg, 1.2 mmol) afforded **2b** (134 mg, 89% yield) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.33 (d, $J$ = 8.7 Hz, 2 H, *o*-$NO_2$), 8.03 (d, $J$ = 8.7 Hz, 2 H, *m*-$NO_2$), 4.13 (d, $J$ = 10.5 Hz, 1 H, α-C*H*), 3.51 (m 1 H, NC$H_2$CH$_3$), 3.45 (s, 3 H, OC$H_3$), 3.30 (m, 1 H, NC$H_2$CH$_3$), 2.10 [m, 1 H, C*H*(CH$_3$)$_2$], 1.23 (t, $J$ = 7.7 Hz, 3 H, NCH$_2$C$H_3$), 1.07 [d, $J$ = 6.6 Hz, 3 H, CH-

($CH_3$)$_2$], 0.95 [d, $J$ = 6.6 Hz, 3 H, CH($CH_3$)$_2$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 170.6, 149.5, 145.9, 128.7, 123.9, 65.9, 51.6, 40.6, 28.6, 19.7, 16.2 ppm. MS (EI) (rel. intensity%): $m/z$ = 301 (28), 285 (100), 186 (19), 158 (5), 122 (10), 56 (12). $C_{14}H_{20}N_2O_6S$ (344.10): calcd. C 48.83, H 5.85, N 8.13, O 27.87, S 9.31; found C 48.71, H 5.86, N 8.10.

***N*-Ethyl-*N*-nosyl-L-leucine Methyl Ester (2c):** Following the general procedure, treatment of a solution of *N*-Nosyl-leucine methyl ester **1c** (150 mg, 0.45 mmol) in dry $CH_2Cl_2$ (20 mL) with DIPEA (0.27 mL, 1.59 mmol) and triethyloxonium tetrafluoroborate (192 mg, 1.12 mmol) afforded **2c** (146 mg, 97% yield) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.33 (d, $J$ = 8.7 Hz, 2 H, $o$-$NO_2$), 8.01 (d, $J$ = 8.7 Hz, 2 H, $m$-$NO_2$), 4.65 (m, 1 H, α-C$H$), 3.48 (s, 3 H, OC$H_3$), 3.35 (m, 1 H, NC$H_2$CH$_3$), 3.20 (m, 1 H, NC$H_2$CH$_3$), 1.80–1.61 [m, 3 H, C$H_2$CH(CH$_3$)$_2$ + CH$_2$C$H$-(CH$_3$)$_2$], 1.26 (t, $J$ = 7.7 Hz, 3 H, NCH$_2$C$H_3$), 1.01 [d, $J$ = 6.3 Hz, 3 H, CH$_2$CH(C$H_3$)$_2$], 0.98 [d, $J$ = 6.3 Hz, 3 H, CH$_2$CH(C$H_3$)$_2$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 171.4, 149.9, 145.5, 128.7, 123.9, 58.5, 52.1, 42.2, 41.1, 39.2, 24.4, 22.9, 21.3, 16.6 ppm. MS (EI) (rel. intensity%): $m/z$ = 299 (100), 243 (11), 186 (11), 122 (7), 56 (7). $C_{15}H_{22}N_2O_6S$ (358.12): calcd. C 50.27, H 6.19, N 7.82, O 26.78, S 8.95; found C 50.39, H 6.17, N 7.80.

***N*-Ethyl-*N*-nosyl-L-isoleucine Methyl Ester (2d):** By following the general procedure, treatment of a solution of *N*-nosyl-isoleucine methyl ester (**1d**) (150 mg, 0.45 mmol) in dry $CH_2Cl_2$ (20 mL) with DIPEA (0.28 mL, 1.57 mmol) and triethyloxonium tetrafluoroborate (192 mg, 1.12 mmol) afforded **2d** (153 mg, 95%) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.33 (d, $J$ = 9 Hz, 2 H, $o$-$NO_2$), 8.01 (d, $J$ = 9 Hz, 2 H, $m$-$NO_2$), 4.21 (d, $J$ = 10.5 Hz, 1 H, α-C$H$), 3.54 (m, 1 H, NC$H_2$CH$_3$), 3.43 (s, 3 H, OC$H_3$), 3.30 (m, 1 H, NC$H_2$CH$_3$), 1.92–1.71 [m, 2 H, CH(CH$_3$)C$H_2$CH$_3$], 1.28–1.12 [m, 4 H, NCH$_2$C$H_3$ + C$H$(CH$_3$)CH$_2$CH$_3$], 0.86–0.98 [m, 6 H, CH(C$H_3$)CH$_2$CH$_3$ + CH(CH$_3$)CH$_2$C$H_3$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 170.7, 149.9, 145.5, 128.6, 123.9, 64.7, 51.5, 40.6, 34.8, 25.3, 16.4, 15.4, 10.8 ppm. MS (C.I.): $m/z$ (%) = 387 (9) [M + $C_2H_5$]$^+$, 359 (7) [M + H]$^+$, 329 (2), 299 (100), 269 (4), 172 (3), 156 (3), 114 (2). $C_{16}H_{24}N_2O_6S$ (358.12): calcd. C 51.60, H 6.50, N 7.52, O 25.78, S 8.61; found C 51.72, H 6.48, N 7.54.

***N*-Ethyl-*N*-nosyl-D-alloisoleucine Methyl Ester (2e):** By following the general procedure, treatment of a solution of *N*-nosyl-D-alloisoleucine methyl ester (**1e**) (150 mg, 0.45 mmol) in dry $CH_2Cl_2$ (20 mL) with DIPEA (0.28 mL, 1.57 mmol) and triethyloxonium tetrafluoroborate (192 mg, 1.12 mmol) afforded **2e** (154 mg, 96%) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.34 (d, $J$ = 9 Hz, 2 H, $o$-$NO_2$), 8.04 (d, $J$ = 9 Hz, 2 H, $m$-$NO_2$), 4.23 (d, $J$ = 7.0 Hz, 1 H, α-C$H$), 3.53 (m, 1 H, NC$H_2$CH$_3$), 3.46 (s, 3 H, OC$H_3$), 3.31 (m, 1 H, NC$H_2$CH$_3$), 2.03–1.90 [m, 2 H, CH(CH$_3$)C$H_2$CH$_3$], 1.30–1.13 [m, 4 H, C$H$(CH$_3$)CH$_2$CH$_3$ + NCH$_2$C$H_3$], 0.99–0.83 [m, 6 H, CH(C$H_3$)CH$_2$CH$_3$ + CH(CH$_3$)CH$_2$C$H_3$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 170.5, 149.7, 145.3, 128.7, 123.9, 63.7, 51.5, 40.2, 34.0, 25.7, 16.3, 15.2, 11.1 ppm. MS (C.I.): $m/z$ (%) = 387 (8) [M + $C_2H_5$]$^+$, 359 (6) [M + H]$^+$, 329 (5), 299 (100), 269 (11), 172 (9), 156 (10), 114 (8). $C_{16}H_{24}N_2O_6S$ (358.12): calcd. C 51.60, H 6.50, N 7.52, O 25.78, S 8.61; found C 51.70, H 6.51, N 7.49.

***N*-Ethyl-*N*-nosyl-L-phenylalanine Methyl Ester (2f):** By following the general procedure, treatment of a solution of *N*-nosyl-phenylalanine methyl ester (**1f**) (150 mg, 0.41 mmol) in dry $CH_2Cl_2$ (20 mL) with DIPEA (0.25 mL, 1.44 mmol) and triethyloxonium tetrafluoroborate (175 mg, 1.02 mmol) afforded **2f** (148 mg, 99% yield) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.20 (d, $J$ = 8.7 Hz, 2 H, $o$-$NO_2$), 7.75 (d, $J$ = 8.7 Hz, 2 H, $m$-$NO_2$), 7.18–7.30 (m, 5 H, CH$_2$C$_6H_5$), 4.88 (dd, $J$ = 6.6, 8.7 Hz, 1 H, α-C$H$), 3.58 (s, 3 H, OC$H_3$), 3.25–3.50 (m, 3 H, C$H_2$Ph + NCH$_2$C$H_3$), 2.99 (m, 1 H, C$H_2$Ph), 1.19 (t, $J$ = 7.0 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 170.8, 149.7, 145.8, 136.4, 129.1, 128.8, 128.5, 127.1, 123.9, 61.4, 52.4, 40.9, 36.5, 15.6 ppm. MS (EI) (rel. intensity%): $m/z$ = 333 (25), 301 (100), 186 (17), 122 (12), 91 (14), 56 (12). $C_{18}H_{20}N_2O_6S$ (392.10): calcd. C 55.09, H 5.14, N 7.14, O 24.46, S 8.17; found C 54.96, H 5.16, N 7.13.

***N*-Ethyl-*N*-nosyl-L-glutamic Acid γ-*tert*-Butyl Methyl Diester (2g):** By following the general procedure, treatment of a solution of *N*-nosyl-glutamic acid (O*t*Bu) methyl ester (**1g**) (150 mg, 0.37 mmol) in dry $CH_2Cl_2$ (20 mL), with DIPEA (0.23 mL, 1.29 mmol) and triethyloxonium tetrafluoroborate (176 mg, 0.92 mmol) afforded **2g** (135 mg, 85% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.34 (d, $J$ = 9 Hz, 2 H, $o$-$NO_2$), 8.02 (d, $J$ = 9 Hz, 2 H, $m$-$NO_2$), 4.66 (dd, $J$ = 10.5, 4.8 Hz, 1 H, α-C$H$), 3.51 (s, 3 H, OC$H_3$), 3.38 (m, 1 H, NC$H_2$CH$_3$), 3.14 (m, 1 H, NC$H_2$CH$_3$), 2.48–2.43 (m, 2 H, γ-C$H_2$), 2.33 (m, 1 H, β-C$H_2$), 1.92 (m, 1 H, β-C$H_2$), 1.47 (s, 9 H, *t*Bu), 1.24 (t, $J$ = 7.2 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 171.7, 170.6, 149.9, 145.5, 128.7, 123.9, 80.9, 59.6, 52.3, 42.2, 31.2, 28.1, 25.3, 14.1 ppm. $C_{18}H_{26}N_2O_8S$ (430.14): calcd. C 50.22, H 6.09, N 6.51, O 29.73, S 7.45; found C 50.32, H 6.07, N 6.49.

***N*-Ethyl-*N*-nosyl-*S*-benzyl-L-cysteine Methyl Ester (2h):** By following the general procedure, treatment of a solution of *N*-nosyl-cysteine (SBn) methyl ester (**1h**) (150 mg, 0.36 mmol) in dry $CH_2Cl_2$ (20 mL), with DIPEA (0.22 mL, 1.26 mmol) and triethyloxonium tetrafluoroborate (171 mg, 0.90 mmol) afforded **2h** (138 mg, 88% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.32 (d, $J$ = 9.0 Hz, 2 H, $o$-$NO_2$), 8.14 (d, $J$ = 9.0 Hz, 2 H, $m$-$NO_2$), 7.40–7.25 (m, 5 H, SCH$_2$C$_6H_5$), 4.62 (t, $J$ = 7.8 Hz, 1 H, α-C$H$), 3.76 (s, 2 H, SC$H_2$Ph), 3.60 (s, 3 H, OC$H_3$), 3.30 (m, 1 H, NC$H_2$CH$_3$), 3.18 (m, 1 H, NC$H_2$CH$_3$), 3.03 (dd, $J$ = 13.8, 7.2 Hz, 1 H, C$H_2$SBn), 2.71 (dd, $J$ = 13.8, 8.2 Hz, 1 H, C$H_2$SBn), 1.13 (t, $J$ = 7.0 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 169.8, 151.6, 145.4, 137.2, 129.0, 128.7, 128.6, 127.4, 124.0, 59.6, 52.5, 41.2, 36.4, 31.5, 15.7 ppm. $C_{19}H_{22}N_2O_6S_2$ (438.09): calcd. C 52.04, H 5.06, N 6.39, O 21.89, S 14.62; found C 51.98, H 5.08, N 6.38.

***N*-Ethyl-*N*-nosyl-*O*-benzyl-L-tyrosine Methyl Ester (2i):** By following the general procedure, treatment of a solution of *N*-nosyl-tyrosine (OBn) methyl ester (**1i**) (150 mg, 0.32 mmol) in dry $CH_2Cl_2$ (20 mL) with DIPEA (0.19 mL, 1.12 mmol) and triethyloxonium tetrafluoroborate (136 mg, 0.8 mmol) afforded **2i** (136 mg, 91% yield) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.23 (d, $J$ = 9 Hz, 2 H, $o$-$NO_2$), 7.79 (d, $J$ = 9 Hz, 2 H, $m$-$NO_2$), 7.49–7.32 (m, 5 H, OCH$_2$C$_6H_5$), 7.10 (d, $J$ = 8.7 Hz, 2 H, $m$-OBn), 6.88 (d, $J$ = 8.7 Hz, 2 H, $o$-OBn), 5.03 (s, 2 H, OC$H_2$Ph), 4.81 (dd, $J$ = 7.2, 8.4 Hz, 1 H, α-C$H$), 3.56 (s, 3 H, OC$H_3$), 3.50–3.25 (m, 3 H, C$H_2$PhOBn + NCH$_2$C$H_3$), 2.93 (m, 1 H, C$H_2$PhOBn), 1.20 (t, $J$ = 7.2 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 170.8, 157.8, 149.6, 146.7, 130.2, 128.5, 128.3, 128.1, 127.6, 123.9, 115.1, 70.1, 61.6, 52.3, 40.9, 35.7, 15.8 ppm. MS (EI) (rel. intensity%): $m/z$ = 281 (32), 225 (100), 207 (60), 91 (8). $C_{25}H_{26}N_2O_7S$ (498.15): calcd. C 60.23, H 5.26, N 5.62, O 22.46, S 6.43; found C 60.37, H 5.24, N 5.63.

***N*$^{\alpha}$-Ethyl-*N*$^{\alpha}$-nosyl-*N*$^{\varepsilon}$-(*tert*-butyloxycarbonyl)-L-lysine Methyl Ester (2l):** By following the general procedure, treatment of a solution of *N*$^{\alpha}$-nosyl-lysine (Boc) methyl ester (**1l**) (150 mg, 0.34 mmol) in dry $CH_2Cl_2$ (20 mL), with DIPEA (0.21 mL, 1.19 mmol) and triethyloxonium tetrafluoroborate (161 mg, 0.85 mmol) afforded **2l** (150 mg, 93% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.34 (d, $J$ = 9.0 Hz, 2 H, $o$-$NO_2$), 8.00 (d, $J$ = 9.0 Hz, 2 H, $m$-$NO_2$),

4.54 (dd, $J$ = 9.9, 5.4 Hz, 1 H, α-C$H$), 3.49 (s, 3 H, OC$H_3$), 3.34 (m, 1 H, NC$H_2$CH$_3$), 3.22–3.09 (m, 3 H, NC$H_2$CH$_3$ + ε-C$H_2$), 1.98 (m, 1 H, β-C$H_2$), 1.78–1.65 (m, 2 H, δ-C$H_2$ + β-C$H_2$), 1.56–1.48 (m, 3 H, γ-C$H_2$ + δ-C$H_2$), 1.44 (s, 9 H, *t*Bu), 1.23 (t, $J$ = 7.2 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 170.9, 168.2, 156.0, 150.3, 128.6, 123.9, 80.0, 60.2, 52.2, 41.6, 34.0, 29.8, 29.4, 28.4, 23.2, 16.4 ppm. $C_{20}H_{31}N_3O_8S$ (473.18): calcd. C 50.73, H 6.60, N 8.87, O 27.03, S 6.77; found C 50.88, H 6.59, N 8.89.

**Synthesis of *N*-Ethyl-*N*-Fmoc Amino Acid Methyl Esters 3a–h. General Procedure:** Mercaptoacetic acid (3 mmol) was added to a solution of **2a**–**h** (1 mmol) in dry acetonitrile (10 mL) and the reaction mixture was maintained at 50 °C. Sodium methoxide (8 mmol) was then gradually added to the solution with a variable amount of methanol to facilitate the sodium methoxide solubilization. The resulting mixture was stirred for 30 min and the conversion of the precursors **2a**–**h** was monitored by TLC ($Et_2O$/petroleum ether = 6:4). A 1 N HCl solution (or a 10% citric acid solution for compound **2g**) was then added and the mixture extracted with EtOAc (3 × 10 mL). The aqueous phase was basified with saturated aqueous $NaHCO_3$ (pH 8). The basic phase, containing the deprotected product, was then treated with a solution of Fmoc chloride (1 mmol) in dry $CH_2Cl_2$ (10 mL). The reaction mixture was stirred at room temperature for 1 h and then the organic layer was separated. The aqueous phase was extracted with three additional portions of $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried with $Na_2SO_4$ and the solvents evaporated under vacuum to afford the corresponding *N*-ethyl-*N*-Fmoc-amino acid methyl esters as oils in 71–94% overall yields.

***N*-Ethyl-*N*-Fmoc-L-alanine Methyl Ester (3a):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-alanine methyl ester (**2a**) (200 mg, 0.63 mmol) with the reagent system mercaptoacetic acid (0.13 mL, 1.89 mmol)/sodium methoxide (272 mg, 5.04 mmol), and subsequently with Fmoc chloride (163 mg, 0.63 mmol), afforded **3a** as a colorless oil (200 mg, 90% yield).$^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.81–7.28 (m, 8 H, Fmoc-Ar$H$), 4.61–4.10 (m, 4 H, Fmoc-C$H$, Fmoc-C$H_2$, α-C$H$), 3.70 and 3.60 (2 s, 3 H, OC$H_3$), 3.43–3.29, 3.24–3.05 (2 m, 2 H, NC$H_2$), 1.44, 1.33 (2 d, $J$ = 7.2 Hz, 3 H, CHC$H_3$), 1.15, 1.06 (2 t, $J$ = 7.2 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 171.5, 155.2, 143.8, 141.4, 127.7, 127.0, 124.9, 119.9, 67.3, 54.9, 52.2, 47.3, 40.8, 15.4, 14.9 ppm. $C_{21}H_{23}NO_4$ (353.16): calcd. C 71.37, H 6.56, N 3.96, O 18.11; found C 71.56, H 6.54, N 3.97.

***N*-Ethyl-*N*-Fmoc-L-valine Methyl Ester (3b):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-valine methyl ester (**2b**) (200 mg, 0.58 mmol) with the reagent system mercaptoacetic acid (0.12 mL, 1.74 mmol)/sodium methoxide (250 mg, 4.64 mmol), and subsequently with Fmoc chloride (150 mg, 0.58 mmol), afforded **3b** as a colorless oil (201 mg, 91% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.78–7.30 (m, 8 H, Fmoc-Ar$H$), 4.59–4.40 (2 m, 2 H, Fmoc-C$H_2$), 4.34 (d, $J$ = 10.5 Hz, 1 H, α-C$H$), 4.26 (t, $J$ = 6 Hz, 1 H, Fmoc-C$H$), 3.71, 3.65 (2 s, 3 H, OC$H_3$), 3.40–3.07 (2 m, 2 H, NC$H_2$), 2.18, 2.06 [2 m, 1 H, C$H$(CH$_3$)$_2$], 1.10 (t, $J$ = 7.0 Hz, 3 H, NCH$_2$C$H_3$), 0.99–0.83 [m, 6 H, CH(C$H_3$)$_2$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 173.4, 157.2, 144.0, 142.7, 141.4, 128.2, 127.7, 127.3, 125.1, 124.8, 120.0, 119.9, 71.6, 64.0, 51.9, 47.4, 39.2, 27.7, 19.8, 18.8, 14.1, 13.5 ppm. $C_{23}H_{27}NO_4$ (381.19): calcd. C 72.42, H 7.13, N 3.67, O 16.78; found C 72.51, H 7.14, N 3.65.

***N*-Ethyl-*N*-Fmoc-L-leucine Methyl Ester (3c):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-leucine methyl ester (**2c**) (200 mg, 0.56 mmol) with the reagent system mercaptoacetic acid (0.11 mL, 1.68 mmol)/sodium methoxide (242 mg, 4.48 mmol), and subsequently with Fmoc chloride (145 mg, 0.56 mmol), afforded **3c** as a colorless oil (176 mg, 80% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.80–7.27 (m, 8 H, Fmoc-Ar$H$), 4.74, 4.64 (2m, 1 H, α-C$H$), 4.58–4.42 (2m, 1 H, Fmoc-C$H_2$), 4.35–4.22 (2m, 1 H, Fmoc-C$H$), 3.70, 3.60 (2 s, 3 H, OC$H_3$), 3.48–3.25 (2 m, 1 H, NC$H_2$CH$_3$), 1.90–1.46 [2m, 3 H, C$H_2$CH(CH$_3$)$_2$ + CH$_2$C$H$(CH$_3$)$_2$], 1.24–1.12 (2 m, 3 H, NCH$_2$NC$H_3$), 1.08–0.94 [2 m, 6 H, CH$_2$CH(C$H_3$)$_2$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 172.3, 156.2, 144.0, 141.3, 128.3, 128.0, 127.6, 127.4, 125.0, 124.8, 120.3, 120.1, 67.3, 67.0, 57.4, 52.1, 50.3, 47.2, 46.7, 40.9, 40.1, 38.4, 38.2, 24.7, 23.1, 21.8, 14.6, 13.9 ppm. $C_{24}H_{29}NO_4$ (395.21): calcd. C 72.89, H 7.39, N 3.54, O 16.18; found C 72.93, H 7.40, N 3.55.

***N*-Ethyl-*N*-Fmoc-L-isoleucine Methyl Ester (3d):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-isoleucine methyl ester (**2d**) (200 mg, 0.56 mmol) with the reagent system mercaptoacetic acid (0.11 mL, 1.68 mmol)/sodium methoxide (242 mg, 4.48 mmol), and subsequently with Fmoc chloride (145 mg, 0.56 mmol), afforded **3d** as a colorless oil (208 mg, 94% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.75–7.28 (m, 8 H, Fmoc-Ar$H$), 4.64–4.42 (m, 2 H, Fmoc-C$H_2$), 4.25 (t, $J$ = 5.9 Hz, 1 H, Fmoc-C$H$), 4.15 (m, 1 H, α-C$H$), 3.68 (s, 3 H, OC$H_3$), 3.44–3.11 (m, 2 H, NC$H_2$), 1.93 [m, 1 H, C$H$(CH$_3$)CH$_2$CH$_3$], 1.42–1.32 [m, 2 H, CH(CH$_3$)C$H_2$CH$_3$], 1.13 (t, $J$ = 6.6 Hz, 3 H, NCH$_2$C$H_3$), 0.96–0.81 [m, 6 H, CH(C$H_3$)CH$_2$CH$_3$, CH(CH$_3$)CH$_2$C$H_3$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 171.9, 156.9, 144.1, 141.5, 127.4, 127.3, 125.1, 119.9, 67.3, 63.1, 51.8, 47.5, 39.4, 33.8, 24.8, 15.9, 14.2, 10.9 ppm. $C_{24}H_{29}NO_4$ (395.21): calcd. C 72.89, H 7.39, N 3.54, O 16.18; found C 73.08, H 7.37, N 3.53.

***N*-Ethyl-*N*-Fmoc-L-phenylalanine Methyl Ester (3f):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-phenylalanine methyl ester (**2f**) (200 mg, 0.51 mmol) with the reagent system mercaptoacetic acid (0.11 mL, 1.53 mmol)/sodium methoxide (220 mg, 4.08 mmol), and subsequently with Fmoc chloride (132 mg, 0.51 mmol), afforded **3f** as a colorless oil (198 mg, 90% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.82–7.13 (m, 13 H, Fmoc-Ar$H$ + $C_6H_5$), 4.81–3.99 (m, 4 H, Fmoc-C$H$, Fmoc-C$H_2$, α-C$H$), 3.74, 3.47 (2 s, 3 H, OC$H_3$), 3.36 (dd, $J$ = 14.1, 5.4 Hz, 1 H, C$H_2$Ph), 3.19 (2 m, 1 H, NC$H_2$CH$_3$), 2.97 (dd, $J$ = 14.1, 5.4 Hz, 1 H, C$H_2$Ph), 2.79 (2 m, 1 H, NC$H_2$CH$_3$), 0.87–0.79 (2 m, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 171.4, 155.8, 144.4, 141.5, 137.9, 129.2, 128.5, 127.6, 127.0, 126.6, 125.1, 120.1, 67.2, 65.2, 62.1, 61.6, 52.3, 50.3, 47.3, 43.3, 42.9, 35.6, 35.3, 13.7, 13.0 ppm. $C_{27}H_{27}NO_4$ (429.51): calcd. C 75.50, H 6.34, N 3.26, O 14.90; found C 75.36, H 6.35, N 3.24.

***N*-Ethyl-*N*-Fmoc-L-glutamic Acid γ-*tert*-Butyl Methyl Diester (3 g):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-glutamic acid (O*t*Bu) methyl ester (**2g**) (200 mg, 0.46 mmol) with the reagent system mercaptoacetic acid (0.097 mL, 1.39 mmol)/sodium methoxide (198 mg, 3.68 mmol), and subsequently with Fmoc chloride (119 mg, 0.46 mmol), afforded **3g** as a colorless oil (164 mg, 76% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.80–7.28 (m, 8 H, Fmoc-Ar$H$), 4.66–4.38 (2 m, 3 H, Fmoc-C$H_2$ + α-C$H$), 4.29–4.18 (2 m, 1 H, Fmoc-C$H$), 3.70, 3.52 (2 s, 3 H, OC$H_3$), 3.48–3.27 (2 m, 2 H, NC$H_2$CH$_3$), 3.15–3.01 (2 m, 2 H, NC$H_2$CH$_3$), 2.36–2.24 (m, 2 H, β-C$H_2$), 2.11–2.02 (m, 2 H, γ-C$H_2$), 1.45 (s, 9 H, *t*Bu), 1.12 (2 t, $J$ = 7.1 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 172.2, 168.0, 156.7, 143.9, 141.2, 136.2, 135.1, 127.9, 127.6, 127.3, 127.0, 125.2, 124.9, 120.0, 119.9, 80.6, 67.3, 65.1, 59.0, 58.5, 52.3, 52.2,

47.3, 41.7, 31.9, 31.7, 28.1, 24.9, 24.7, 14.2, 13.7 ppm. $C_{27}H_{33}NO_6$ (467.23): calcd. C 69.36, H 7.11, N 3.00, O 20.53; found C 69.17, H 7.13, N 2.98.

***N*-Ethyl-*N*-Fmoc-(*S*)-benzyl-L-cysteine Methyl Ester (3h):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-cysteine (SBn) methyl ester (**2h**) (200 mg, 0.45 mmol) with the reagent system mercaptoacetic acid (0.095 mL, 1.37 mmol)/sodium methoxide (194 mg, 3.59 mmol), and subsequently with Fmoc chloride (116 mg, 0.45 mmol), afforded **3h** as a colorless oil (154 mg, 71% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.82–7.24 (m, 13 H, Fmoc-Ar*H* + $SCH_2C_6H_5$), 4.58–4.16 (m, 4 H, Fmoc-C$H_2$ + FmocC*H* + α-C*H*), 4.06, 4.03 (2 s, 2 H, SC$H_2$Ph), 3.96 (s, 3 H, OC$H_3$), 3.54–3.04 (m, 3 H, NC$H_2$CH$_3$ + C$H_2$SBn), 2.93 (m, 1 H, C$H_2$SBn), 0.91 (t, $J$ = 6.9 Hz, 3 H, NCH$_2$C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 170.5, 165.8, 145.0, 144.5, 142.7, 141.5, 141.3, 128.5, 128.2, 127.3, 127.2, 125.1, 125.0, 123.8, 120.2, 120.0, 71.6, 65.1, 50.4, 44.7, 38.8, 36.7, 32.1, 13.3 ppm. $C_{28}H_{29}NO_4S$ (475.18): calcd. C 70.71, H 6.15, N 2.95, O 13.46, S 6.74; found C 70.58, H 6.13, N 2.96.

**Synthesis of *N*-Ethyl-*N*-Fmoc-L-isoleucine (4) and *N*-Ethyl-*N*-nosyl-L-isoleucine (6). General Procedure:** The *N*-ethyl-*N*-Fmoc-isoleucine methyl ester (**3d**) or the *N*-ethyl-*N*-nosyl-L-isoleucine methyl ester (**2d**) (1 mmol) and LiI (5 mmol) were dissolved in ethyl acetate (5 mL). The reaction mixture was heated at reflux for 24 h and the conversion of the precursors **3d** and **2d** was monitored by TLC. A saturated aqueous $Na_2CO_3$ solution was then added and extracted with ethyl acetate. The aqueous phase was acidified with 1 M HCl and extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with brine. The organic phase was dried with $Na_2SO_4$ and the solvents evaporated under vacuum to afford the corresponding amino acids **4** and **6** as oils in 94 and 96% yields, respectively.

***N*-Ethyl-*N*-Fmoc-L-isoleucine (4):** By following the general procedure, treatment of *N*-ethyl-*N*-Fmoc-isoleucine methyl ester (**3d**) (200 mg, 0.51 mmol) with LiI (339 mg, 2.53 mmol) afforded **4** as a colorless oil (182 mg, 94% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.82–7.27 (m, 8 H, Fmoc-Ar*H*), 4.57 (d, $J$ = 6.0 Hz, 2 H, Fmoc-C$H_2$), 4.25 (t, $J$ = 5.5 Hz, 1 H, Fmoc-C*H*), 4.10 (m, 1 H, α-C*H*), 3.31 (2 m, 1 H, NC$H_2$), 3.06 (m, 1 H, NC$H_2$), 2.15 [m, 1 H, C*H*(CH$_3$)CH$_2$CH$_3$], 1.45–1.31 [m, 2 H, CH(CH$_3$)-C$H_2$CH$_3$], 1.30–1.08 (2 m, 3 H, NCH$_2$C$H_3$), 1.01–0.82 [m, 6 H, CH(C$H_3$)CH$_2$CH$_3$, CH(CH$_3$)CH$_2$C$H_3$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): (rotamers) $\delta$ = 177.2, 155.8, 141.4, 134.3, 127.8, 127.1, 124.7, 120.0, 67.7, 65.1, 47.3, 43.3, 33.2, 25.2, 15.7, 13.8, 10.8 ppm. $C_{23}H_{27}NO_4$ (381,19): calcd. C 72.42, H 7.13, N 3.67, O 16.78; found C 72.23, H 7.12, N 3.66.

***N*-Ethyl-*N*-nosyl-L-isoleucine (6):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-isoleucine methyl ester (2**d**) (200 mg, 0.56 mmol) with LiI (374 mg, 2.79 mmol) afforded **6** as a colorless oil (186 mg, 96% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.32 (d, $J$ = 9 Hz, 2 H, *o*-NO$_2$), 8.00 (d, $J$ = 9 Hz, 2 H, *m*-NO$_2$), 4.14 (d, $J$ = 10.2 Hz, 1 H, α-C*H*), 3.48–3.24 (m, 2 H, NC$H_2$CH$_3$), 1.84 [m, 1 H, CH(CH$_3$)C$H_2$CH$_3$], 165 [m, 1 H, CH(CH$_3$)C$H_2$CH$_3$], 1.23 (t, $J$ = 7.05 Hz, 3 H, NCH$_2$C$H_3$) 1.11 [m, 1 H, C*H*(CH$_3$)CH$_2$CH$_3$], 0.97–0.86 [m, 6 H, CH(C$H_3$)CH$_2$CH$_3$ + CH(CH$_3$)CH$_2$C$H_3$] ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 25 °C): $\delta$ = 174.9, 149.9, 145.3, 128.6, 124.0, 64.7, 40.7, 34.6, 25.4, 16.2, 15.4, 10.7 ppm. $C_{14}H_{20}N_2O_6S$ (344,10): calcd. C 48.83, H 5.85, N 8.13, O 27.87, S 9.31; found C 48.75, H 5.86, N 8.10.

**Synthesis of Dipeptides 5 and 7. General Procedure:** Valine methyl ester hydrochloride (1 mmol), HOBt (1.1 mmol), *N*-methylmorpholine (1 mmol), and the *N*-ethyl-*N*-Fmoc-isoleucine or *N*-ethyl-*N*-nosyl-isoleucine were dissolved in dry THF (20 mL). The solution was stirred and cooled in an ice/water bath while DCC (1.15 mmol) was added. Stirring was continued for 1 h at 0 °C and an additional hour at room temperature whilst monitoring by TLC. *N*,*N*′-Dicyclohexylurea was removed by filtration and the solvent evaporated in vacuo. A mixture of ethyl acetate (30 mL) and a saturated solution of $NaHCO_3$ in water (10 mL) was added to the residue and the organic phase extracted with a 10% solution of citric acid in water (10 mL), again with saturated $NaHCO_3$ (10 mL), and then brine. The organic layer was dried with $Na_2SO_4$, filtered, and the solvents evaporated to dryness in vacuo to afford the *N*-ethylated dipeptides **5** and **7** as oils in 90 and 92% yields, respectively.

***N*-Ethyl-*N*-Fmoc-L-isoleucyl-L-valine (OMe) (5):** By following the general procedure, treatment of *N*-ethyl-*N*-Fmoc-isoleucine (**4**) (200 mg, 0.52 mmol) with valine methyl ester hydrochloride (88 mg, 0.52 mmol), HOBt (77 mg, 0.57 mmol), *N*-methylmorpholine (52 mg, 0.52 mmol), and DCC (124 mg, 0.60 mmol) afforded **5** as a yellow oil (232 mg, 90% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): (rotamers) $\delta$ = 7.87–7.28 (m, 9 H, Fmoc-Ar*H* + N*H*), 4.60–4.03 (m, 5 H, Fmoc-C$H_2$ + FmocC*H* + α-C*H*Ile + α-C*H*Val), 3.78, 3.60 (2 s, 3 H, OC$H_3$), 3.43–3.09 (m, 2 H, NC$H_2$), 2.16 [m, 1 H, C*H*(CH$_3$)$_2$], 1.69–1.60 [m, 3 H, C*H*(CH$_3$)CH$_2$CH$_3$ + CH(CH$_3$)-C$H_2$CH$_3$], 1.03–0.80 [m, 12 H, NCH$_2$C$H_3$ + CH(C$H_3$)$_2$ + CH(CH$_3$)CH$_2$C$H_3$] ppm. $C_{29}H_{38}N_2O_5$ (494.62): calcd. C 70.42, H 7.74, N 5.66, O 16.17; found C 70.59, H 7.72, N 5.67.

***N*-Ethyl-*N*-nosyl-L-isoleucyl-L-valineOMe (7):** By following the general procedure, treatment of *N*-ethyl-*N*-nosyl-isoleucine **6** (200 mg, 0.58 mmol) with valine methyl ester hydrochloride (97 mg, 0.58 mmol), HOBt (86 mg, 0.64 mmol), *N*-methylmorpholine (59 mg, 0.58 mmol), and DCC (137 mg, 0.67 mmol) afforded **7** as a yellow oil (243 mg, 92% yield). $^1$H NMR ($CDCl_3$, 300 MHz, 25 °C): $\delta$ = 8.35 (d, $J$ = 9 Hz, 2 H, *o*-NO$_2$), 8.02 (d, $J$ = 9 Hz, 2 H, *m*-NO$_2$), 6.70 (d, $J$ = 8.4 Hz, N*H*), 4.45 (dd, $J$ = 8.4, 4.8 Hz, 1 H, NHC*H*), 3.85 (d, $J$ = 10.8 Hz, C*H*CONH), 3.73 (s, 3 H, OCH$_3$), 3.55 (m, 1 H, NC$H_2$CH$_3$), 3.30 (m, 1 H, NC$H_2$CH$_3$), 2.18 [m, 1 H, C*H*(CH$_3$)$_2$], 1.91 [m, 1 H, C*H*(CH$_3$)CH$_2$CH$_3$], 1.29 (t, $J$ = 7.2 Hz, 3 H, NCH$_2$C$H_3$), 1.06 [m, 1 H, CH(CH$_3$)C$H_2$CH$_3$], 0.97–0.90 [m, 6 H, CH(C$H_3$)$_2$], 0.83 [d, $J$ = 6.3 Hz, 3 H, CH(C$H_3$)CH$_2$CH$_3$], 0.72 [t, $J$ = 7.3 Hz, 3 H, CH(CH$_3$)CH$_2$C$H_3$], 0.45 [m, 1 H, CH(CH$_3$)-C$H_2$CH$_3$] ppm. $C_{20}H_{31}N_3O_7S$ (457.54): calcd. C 52.50, H 6.83, N 9.18, O 24.48, S 7.01; found C 52.29, H 6.85, N 9.16.

**Supporting Information** (see also the footnote on the first page of this article): $^1$H and $^{13}$C NMR spectra of all compounds.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