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N-Methyl-*N*-nosyl-β^3-amino Acids

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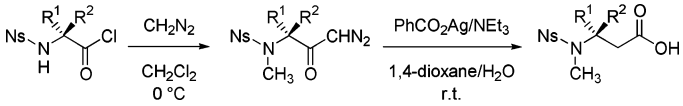

N-Methyl-β^3-amino acids are important building blocks in the synthesis of biologically active molecules. A very simple and efficient approach to transform natural α-amino acids into their corresponding *N*-methyl-β^3-amino acids is here presented. In the method, the key intermediates *N*-methyl-*N*-nosyl-α-aminoacyldiazomethanes are prepared in only one step, by a simple treatment of the corresponding *N*-nosyl-α-aminoacyl chlorides with diazomethane. The synthetic route takes advantage from the use of the nosyl group. This N-masking moiety activates the NH function, and the N-methylation can directly occur during the acylation step of diazomethane, rendering useless a second step that instead is shown to be necessary in all the classical procedures already reported for the preparation of *N*-methyl-β^3-amino acids. The Wolff rearrangement of *N*-methyl-*N*-nosyl-α-aminoacyldiazomethanes provides the corresponding *N*-methyl-*N*-nosyl-β^3-amino acids with total retention of the chiral configuration of the starting α-amino acids. No epimerization of the chiral carbon atom is observed also when *N*-methyl-*N*-nosyl-β^3-amino acids are transformed into chlorides and coupled with α-amino acid methyl esters to achieve model scaffolds for biologically important modified peptides.

Introduction

β^3-Amino acids are widely encountered in nature, especially in compounds having marine origin, and they are representative building blocks in the design of biologically active substances having peptidic morphology.

Pharmaceutical target molecules, such as peptide structure-based drugs, many natural products,[1] and a vast array of metabolites,[2] contain optically active β-amino acid residues. Furthermore, β^3-amino acids are considered as the ideal precursors of β-lactam antibiotics.[3]

Numerous studies dealing with peptides and other biologically active substances containing a β^3-amino acid framework are reported in the literature.[4] These molecules, the β-peptides, are able to fold into well-defined three-dimensional structures.[5]

β-Peptides have shown increased stability against the degrading action of mammalian proteases,[6] due to the inability of proteolytic enzymes to cleave the amide bonds adjacent to the β^3-amino acid.[7] Another peculiar aspect lies in the fact that β^3-amino acids are nonmutagenic. All these features confer to β-peptides valuable characteristics to be promising candidates in pharmaceutical applications as peptidomimetics.

Due to the importance of β^3-amino acids, their *N*-methyl derivatives are potentially useful amino acid surrogates for incorporation in lead therapeutic agents having β-peptide

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(1) (a) Bewley, C. A.; Faulkner, D. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2162−2178. (b) Berks, A. H. *Tetrahedron* **1996**, *52*, 331−375.

(2) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117−128.

(3) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563−572.

(4) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (c) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111−1239. (d) Stephens, O. M.; Kim, S.; Welch, B. D.; Hodson, M. E.; Kay, M. S.; Schepartz, A. *J. Am. Chem. Soc.* **2005**, *127*, 13126−13127. (e) Schmitt, M. A.; Choy, S. H.; Guzei, I. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 13130−13131.

(5) (a) Fernandéz-Santin, J. M.; Muñoz-Guerra, S.; Rodriguez-Galan, A.; Aymami, J.; Lloveras, J.; Subirana, J. A.; Giralt, E.; Ptak, M. *Macromolecules* **1987**, *20*, 62−68. (b) Fernandéz-Santin, J. M.; Aymami, J.; Rodriguez-Galan, A.; Muñoz-Guerra, S.; Subirana, J. A. *Nature* **1984**, *311*, 53−54. (c) Iverson, B. L. *Nature* **1997**, *385*, 113−115. (d) Koert, U. *Angew. Chem., Int. Ed.* **1997**, *36*, 1836−1837. (e) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905−925. (f) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022.

(6) (a) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734−739. (b) Werder, M.; Hauser, H.; Abele, A.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774−1783. (c) Huang, L.; Lee, A.; Ellman, J. A. *J. Med. Chem.* **2002**, *45*, 676−684.

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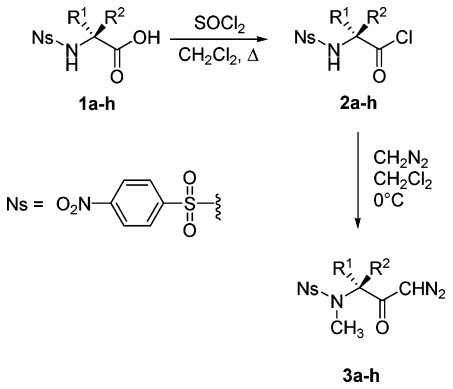
SCHEME 1



structure and characterized by an increased lipophilicity and bioavailability. The resulting conformational rigidity of N-methylated peptides[8] may produce compounds with improved binding characteristics and new receptor subtype selectivity.[9] Furthermore, N-methylation of optically pure β^3-amino acids could be straightforward in making available monomers useful for the developments of new foldamers,[10] as well as in the synthesis of biologically active peptidomimetic drugs.[11] For example, it is known[12] that introduction of an *N*-methyl-β^3-amino acid at the fourth position of tetrapeptide analogues of dermorphin, a potent natural analgesic with long-lasting opioidlike activity, provides molecules stable to proteolytic enzymes. Substitution also improves receptor affinity, selectivity, and analgesic activity.

N-Methyl-β^3-amino acids could also generate appropriate modified β-peptide scaffolds useful to enlighten the mechanisms regulating the gastrointestinal high-affinity carrier system of β^3-amino acids in human and mammalian organisms.[13] Consequentially, it is crucial to provide optically pure *N*-methyl-β^3-amino acids with a large supply. However, only a few methods have been developed for the synthesis of *N*-methyl-β^3-amino acids.[14] Some of these approaches are characterized by harsh reaction conditions or numerous synthetic steps.

TABLE 1. Synthesis of *N*-Methyl-*N*-nosyl-α-aminoacyldiazomethanes 3a−h

compd	R^1	R^2	yield (%)
3a	H	CH_3	78
3b	CH_3	H	81
3c	H	$CH(CH_3)_2$	73
3d	H	$CH_2(C_6H_5)$	77
3e	H	$CH(CH_3)CH_2CH_3$	81
3f	$CH(CH_3)CH_2CH_3$	H	89
3g	H	$CH_2CH(CH_3)_2$	77
3h	H	$(CH_2)_4NHFmoc$	69

Recently we have developed a very simple and efficient approach for preparing *N*-methyl-α-amino acid methyl esters using the nosyl group to protect the starting α-amino acid methyl esters.[15] The methylation reaction simply requires the treatment of nosyl derivatives with an ethereal solution of diazomethane. In addition, this procedure has been successfully employed for site-specific N-methylation of the terminal amino function of *N*-nosyl peptides.[16]

Furthermore, in a previous work, we have realized the direct homologation of *N*-Fmoc-α-amino acids into the corresponding β^3-amino acids, according to the Arndt−Eistert procedure and using Fmoc-amino acid chlorides as starting materials.[17]

On the other hand, the stability of the nosyl group toward acids allows the activation of carboxyl function as chloride;[16] therefore, the *N*-nosyl-α-aminoacyl chlorides could be the ideal starting substrates in the Arndt−Eistert reaction. The nosyl group enhances the acidity of the NH function, so that *N*-nosyl-α-aminoacyl chlorides should react with diazomethane at both the NH moiety and the carbonyl group, achieving in only one step the formation of the *N*-methyldiazoketones.

Results and Discussion

By use of previously published procedures,[16] *N*-nosyl-α-amino acids **1a**−**g** were prepared from the corresponding α-amino acids and *p*-nitrobenzenesulfonyl chloride and then treated with thionyl chloride to give the corresponding *N*-nosyl-α-aminoacyl chlorides **2a**−**g** in quantitative yields (Scheme 1).

N-Nosyl-α-aminoacyl chlorides **2a**−**g** were transformed into *N*-methyl-*N*-nosyl-α-aminoacyldiazomethanes **3a**−**g** upon treatment with a methylene chloride solution of diazomethane. Reaction was complete after 50−70 min, and **3a**−**g** were recovered in 73−89% overall yields, after column chromatography (Scheme 1, Table 1). The one-step formation of compounds **3a**−**g**, due to the methylation of the protected NH function that simultaneously occurs during the acylation of diazomethane, was confirmed by NMR spectroscopy. ^{1}H NMR spectrum of each compound showed singlets resonating in the ranges of 2.81−2.92 and 5.50−5.83 ppm, attributable to the NCH_3 and CHN_2 protons, respectively.

With the protected precursors **3a**−**g** in hand, we evaluated their conversion into the corresponding *N*-methyl-*N*-nosyl-β^3-homoamino acids. The homologation reaction was performed initially under experimental conditions already reported in the

(7) (a) Hintermann, T.; Seebach, D. *Chimia* **1997**, *50*, 244−247. (b) Franckenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445−455.

(8) (a) Mark, J. E.; Goodmann, M. *Biopolymers* **1967**, *5*, 809−814. (b) Fairlie, D. P.; Abbenante, G.; March, D. R. *Curr. Med. Chem.* **1995**, *2*, 654−686.

(9) (a) Rajeswaran, W. J.; Hocart, S. J.; Murphy, W. A.; Taylor, J. E.; Coy, D. H. *J. Med. Chem.* **2001**, *44*, 1305−1311. (b) Rajeswaran, W. J.; Hocart, S. J.; Murphy, W. A.; Taylor, J. E.; Coy, D. H. *J. Med. Chem.* **2001**, *44*, 1416−1421.

(10) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011.

(11) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V., Eds.; John Wiley & Sons: New York, 2005.

(12) (a) Ogawa, T.; Miyamae, T.; Murayama, K.; Okuyama, K.; Okayama, T.; Hagiwara, M.; Sakurada, S.; Morikawa, T. *J. Med. Chem.* **2002**, *45*, 5081−5089. (b) Ogawa, T.; Miyamae, T.; Okayama, T.; Hagiwara, M.; Sakurada, S.; Morikawa, T. *Chem. Pharm. Bull.* **2002**, *50*, 771−780. (c) Masakatsu, E. *Med. Res. Rev.* **2004**, *24*, 182−212.

(13) Munck, L. K.; Grøndahl, M. L.; Skadhauge, E. *Biochim. Biophys. Acta* **1995**, *1238*, 49−56.

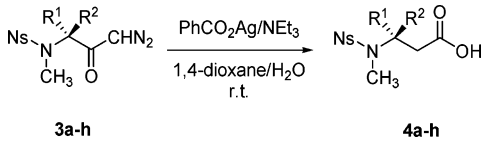
(14) (a) Hintermann, T.; Mathes, C.; Seebach, D. *Eur. J. Org. Chem.* **1998**, 2379−2387. (b) Farràs, J.; Ginesta, X.; Sutton, P. W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665−7674. (c) Govender, T.; Arvidsson, P. I. *Tetrahedron Lett.* **2006**, *47*, 1691−1694. (d) Hughes, A. B.; Sleebs, B. E. *Aust. J. Chem.* **2005**, *58*, 778−784. (e) Hughes, A. B.; Sleebs, B. E. *Helv. Chim. Acta.* **2006**, *89*, 2611−2637. (f) Gademann, K.; Ernst, M.; Seebach, D.; Hoyer, D. *Helv. Chim. Acta* **2000**, *83*, 16−33. (g) Matthews, J. L.; Overhand, M.; Kühnle, F. N. M.; Ciceri, P. E.; Seebach, D. *Liebigs Ann./Rec.* **1997**, 1371−1379.

(15) Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2003**, *68*, 7416−7421.

(16) Di Gioia, M. L.; Leggio, A.; Liguori, A. *J. Org. Chem.* **2005**, *70*, 3892−3897.

(17) Leggio, A.; Liguori, A.; Procopio, A.; Sindona, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1969−1971.

SCHEME 2



literature.[17,18] In particular, 1 mmol of *N*-methyl-*N*-nosyl-alanyldiazomethane **3a**, chosen as model system, was dissolved in a 1,4-dioxane/water mixture and subjected to treatment with catalytic amounts of silver benzoate, at 70 °C. After 5 h, the catalyst was filtered off and the solvent was removed. Hydrolytic workup of the crude mixture afforded *N*-methyl-*N*-nosyl-β^3-homo-L-alanine (**4a**) in only 30% total yield. Unexpectedly, the main reaction product was *N*-methyl-4-nitrobenzenesulfonamide.

After a careful optimization of the reaction conditions, we found that yields and kinetic of the homologation were significantly improved when silver benzoate was dissolved in triethylamine and the resulting homogeneous solution was added to a 1,4-dioxane/water system containing *N*-methyl-*N*-nosyl-alanyldiazomethane (**3a**). The use of excess triethylamine together with catalytic amounts of silver benzoate at room temperature for 20 min led to the rearrangement product **4a** in higher yield (78%). Probably silver benzoate dissolved in triethylamine acts as a homogeneous catalyst.[19] On the other hand, it was recently demonstrated that triethylamine helps the formation of silver nanoclusters,[20] which are the species responsible for the catalysis in the Wolff rearrangement of diazoketones.[21] In principle, the presence of the coreagent triethylamine favors the formation of *N*-methyl-*N*-nosyl-β^3-amino acid rather than *N*-methyl-4-nitrobenzenesulfonamide. The catalyst system triethylamine/silver benzoate produces only traces of the sulfonamide in the reaction mixture.

In light of the excellent results obtained with **3a**, treatment with silver benzoate and triethylamine in 1,4-dioxane/water was then extended to the other *N*-methyldiazoketones **3b**−**g**. In all cases, the reaction performed at room temperature was complete in a few minutes and the corresponding *N*-methyl-*N*-nosyl-β^3-amino acids **4b**−**g** were recovered pure without need of chromatography, and in yields variable between 65% and 83% (Scheme 2, Table 2).

For completeness, we investigated the application of the described procedure to *N*-nosyl-L-lysine protected on the ϵ-amino function with the Fmoc group. The selection of the base-labile masking group in the side chain of lysine was necessary as a protection compatible with the developed methodology. In fact, the Fmoc group is stable under the acidic conditions required for preparation of amino acid chlorides.

The starting N^{α}-nosyl-N^{ϵ}-Fmoc-L-lysine (**1h**) was prepared by treatment of commercial N^{ϵ}-Fmoc-α-L-amino acid with *p*-nitrobenzensulfonyl chloride in a 1,4-dioxane/water solution containing triethylamine. Reaction of **1h** with thionyl chloride furnished **2h** (Scheme 1), which was in turn converted into the corresponding *N*-methyldiazoketone **3h** under experimental conditions similar to those used for the preparation of **3a**−**g** (Scheme 1, Table 1). Column chromatography was necessary to recover pure **3h** in 69% yield. Homologation of **3h** under the catalytic conditions optimized as previously described proceeded at room temperature for 20 min, giving the desired N^{α}-methyl-N^{α}-nosyl-N^{ζ}-Fmoc-β^3-homo-L-lysine (**4h**) in 62% yield, without need of chromatography (Scheme 2, Table 2).

TABLE 2. Synthesis of *N*-Methyl-*N*-nosyl-β^3-homoamino Acids 4a−h

compd	R^1	R^2	yield (%)
4a	H	CH_3	83
4b	CH3	H	82
4c	H	$CH(CH_3)_2$	60
4d	H	$CH_2(C_6H_5)$	70
4e	H	$CH(CH_3)CH_2CH_3$	65
4f	$CH(CH_3)CH_2CH_3$	H	68
4g	H	$CH_2CH(CH_3)_2$	74
4h	H	$(CH_2)_4NHFmoc$	62

TABLE 3. Synthesis of *N*-Methyl-*N*-nosyldipeptides 6a,b

compd	R^1	R^2	yield (%)
6a	H	CH_3	75
6b	CH_3	H	64

In order to exploit the stereochemical features of the novel synthetic approach here proposed, we synthesized the diastereomers *N*-methyl-*N*-nosyl-L-isoleucyldiazomethane (**3e**) and *N*-methyl-*N*-nosyl-D-*allo*-isoleucyldiazomethane (**3f**). Compounds **3e,f** were obtained in 81% and 89% total yields, respectively, by the described procedure (Scheme 1, Table 1). The ^1H and ^{13}C NMR analysis of each compound showed resonances attributable to only one diastereomer,[22] proving that the stereochemistry of the original chiral carbon atom is totally retained during the preparation of diazoketones **3e,f**. The spectroscopic analysis performed on a mixture of the two compounds **3e,f** showed instead the presence of all spin systems attributable to both products.[22]

In addition, we investigated if racemization could occur during the conversion of diazomethane derivatives into the corresponding β^3-amino acids. In analogy to the spectral study performed on **3e,f**, ^1H and ^{13}C NMR spectroscopies were able to determine the presence of the corresponding unwanted diastereomer in the samples of *N*-methyl-*N*-nosyl-β^3-homo-L-isoleucine (**4e**) and its epimer **4f**. The spectral information led to the conclusion that also homologation is not affected by racemization. Gas chromatographic−mass spectrometric (GC-MS) analysis of the single products **4e,f**, injected after their conversion into the corresponding methyl esters by treatment with a methylene chloride solution of diazomethane, definitively confirmed the presence of only one diastereomer in both samples. As expected, GC-MS analysis of a sample containing a mixture of the two methyl esters clearly showed the presence of only two distinguishable peaks corresponding to the couple of diastereomeric methyl esters.[22]

We completed our studies by verifying the possible applications of *N*-methyl-β^3-amino acids as building blocks in the synthesis of modified peptides. *N*-methyl-*N*-nosyl-β^3-homoamino acids **4a,b** were converted quantitatively into the corresponding acyl chlorides **5a,b** by treatment with thionyl chloride,

(18) Babu, V. V. S.; Gopi, H. N.; Ananda, K. *J. Pept. Res.* **1999**, *53*, 308−313.

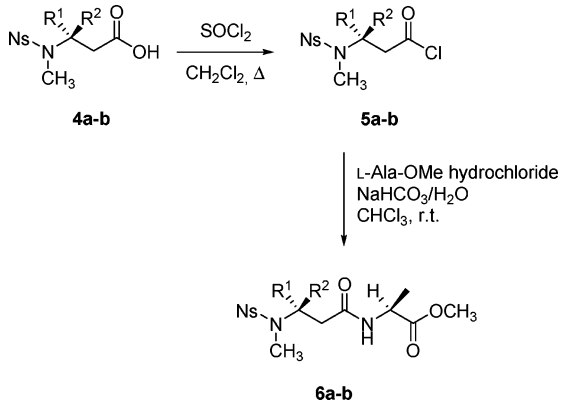
(19) Newman, M. S.; Beal, P. F. *J. Am. Chem. Soc.* **1950**, *72*, 5163−5165.

(20) Sudrik, S. G.; Maddanimath, T.; Chaki, N. K.; Chavan, S. P.; Chavan, S. P.; Sonawane, H. R.; Vijayamohanan, K. *Org. Lett.* **2003**, *5*, 2355−2358.

(21) (a) Sudrik, S. G.; Sharma, J.; Chavan, V. B.; Chaki, N. K.; Sonawane, H. R.; Vijayamohanan, K. P. *Org. Lett.* **2006**, *8*, 1089−1092. (b) Sudrik, S. G.; Chaki, N. K.; Chavan, V. B.; Chavan, S. P.; Chavan, S. P.; Sonawane, H. R.; Vijayamohanan, K. *Chem.*—Eur. J. **2006**, *12*, 859−864.

(22) See the Supporting Information.

SCHEME 3



under the same conditions adopted for the α-analogues[13] (Scheme 3). Dipeptides **6a,b** were then obtained by coupling of *N*-methyl-*N*-nosyl-β^3-homoamino acid chlorides **5a,b**, dissolved in ethanol-free methylene chloride, with L-alanine methyl ester hydrochloride dissolved in an aqueous basic solution (Scheme 3). The reactions proceeded at room temperature and went to completion in about 25−30 min. Dipeptides **6a,b** were isolated in 75% and 64% yields, respectively (Table 3) and in high purity.

The single diastereomeric dipeptides **6a,b**, and then a mixture of the two compounds, were characterized by GC-MS analysis. Each diastereomer showed a unique peak, while the mixture presented two peaks well resolved. ^{1}H NMR spectroscopy definitively excluded the formation of epimerized products in the coupling reaction.

Further elongation of dipeptide chain can be easily accomplished by removal of the sulfonamide group followed by a coupling with activated amino acids.[16]

Conclusions

We developed a highly efficient and simple methodology for the homologation of *N*-nosyl-protected α-amino acids into the corresponding *N*-methyl-β^3-amino acids. The nosyl protecting group is used straightforwardly in the synthetic method, since it offers great advantages in the preparation of *N*-methyl-β^3-amino acids. In fact, the sulfonamide masking group enhances the NH proton acidity, allowing the formation of diazoketones and the simultaneous methylation of the amino function during the treatment of *N*-nosyl-α-aminoacyl chlorides with diazomethane. *N*-Methyl-*N*-nosyl-α-aminoacyldiazomethanes are then smoothly converted into the corresponding β^3-amino acids by Wolff rearrangement. With respect to the other procedures already reported in the literature, our methodology allows us to easily obtain *N*-methyl-β^3-amino acids in a few synthetic steps and under very mild conditions. Another advantage is the efficient conversion of *N*-methyl-*N*-nosyl-β^3-amino acids into their corresponding chlorides, which can be used as building blocks in the synthesis of modified peptides. It is worth noting, moreover, that the entire synthetic procedure does not cause any detectable racemization of the stereocenters present in the precursors. Although synthesis of *N*-methyldiazoketones by the acid chloride method is not applicable when acid-labile groups are used to protect reactive amino acid side chains, the strategy can also be applied to functionalized α-amino acids bearing on side chains base-labile protecting groups compatible with the nosyl chemistry. The synthesis of functionalized *N*-methyl-β^3-amino acids with acid-labile groups in the side chain, through the homologation of the corresponding *N*-nosyl-protected α-amino acids, is now under investigation.

Experimental Section

Synthesis of *N*-Methyl-*N*-nosyl-α-aminoacyldiazomethanes 3a−h: General Procedure. A solution of the appropriate *N*-nosyl-α-aminoacyl chloride **2a−h** (1 mmol) in dry methylene chloride was added dropwise to a stirred 0.66 M methylene chloride solution of diazomethane (10 mmol) at 0 °C. The mixture was maintained under stirring for about 50−60 min, until thin-layer chromatogrtaphic (TLC) analysis (chloroform/diethyl ether 90:10 v/v) of the reaction mixture showed complete conversion of the precursor into the corresponding *N*-methyldiazoketone. The organic solvent was removed under vacuum and the oily residue was purified by column chromatography to afford the respective *N*-methyl-*N*-nosyl-α-aminoacyldiazomethane **3a−h** in 69−89% yield.

Synthesis of *N*-Methyl-*N*-nosyl-β^3-homoamino Acids 4a−h: General Procedure. A solution of silver benzoate (0.13 mol equiv) dissolved in freshly distilled triethylamine (the volume of triethylamine was adjusted to $^1/_8$ that of the 1,4-dioxane/water solution) was added dropwise to a solution (0.1 M) of the appropriate *N*-methyl-*N*-nosyl-α-aminoacyldiazomethane **3a−h** in 1,4-dioxane/water (4:1 v/v). The resulting mixture was stirred at room temperature for 20−30 min, until TLC analysis (chloroform/methanol 90:10 v/v) of the reaction mixture showed complete conversion of the precursor into the corresponding *N*-methyl-β^3-homoamino acid. The reaction mixture was filtered and the solvent was removed under vacuum. The residue was dissolved in saturated aqueous sodium hydrogen carbonate (20 mL) and washed with diethyl ether (3 × 10 mL). The aqueous layer was acidified to pH 2 by adding 1 N aqueous hydrochloric acid (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed once with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under vacuum afforded the respective *N*-methyl-*N*-nosyl-β^3-homoamino acid **4a−h** in 62−83% yield, without need of chromatography. The *N*-methyl-*N*-nosyl-β^3-homoamino acids **4a−g** were analyzed by GC-MS after their conversion into the corresponding methyl esters by treatment with a methylene chloride solution of diazomethane.

Synthesis of *N*-Methyl-*N*-nosyl-β^3-homoamino Acid Chlorides 5a,b: General Procedure. Thionyl chloride (12 mmol) was added to a solution of the appropriate *N*-methyl-*N*-nosyl-β^3-homoamino acid **4a,b** (1 mmol) dissolved in dry ethanol-free methylene chloride (15 mL). The resulting mixture was stirred under reflux for 20−30 min, until TLC analysis (chloroform/methanol 90:10 v/v) showed complete conversion of the precursor. Evaporation of the solvent under vacuum afforded the respective *N*-methyl-*N*-nosyl-β^3-homoamino acid chlorides **5a,b** in quantitative yield, each one as a yellowish amorphous solid.

Synthesis of *N*-Methyl-*N*-nosyldipeptides 6a,b: General Procedure. The appropriate *N*-methyl-*N*-nosyl-β^3-homoamino acid chloride **5a,b** (1 mmol) was dissolved in ethanol-free methylene chloride (10 mL) and treated with a solution of L-alanine methyl ester hydrochloride (1 mmol) in 5% aqueous sodium hydrogen carbonate (10 mL). The mixture was stirred at room temperature for 25−30 min, until TLC analysis (chloroform/methanol 95:5 v/v) showed complete conversion of the precursor. The organic layer was separated and the aqueous phase was extracted with methylene chloride (3 × 10 mL). The combined organic extracts were washed once with 1 N aqueous hydrochloric acid (10 mL) and once with brine (10 mL) and then dried over Na_2SO_4. The solvent was evaporated under vacuum to afford the corresponding *N*-nosyl-dipeptides **6a,b** in 64−75% yield.

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Supporting Information Available: Characterization of compounds **1h**, **3a**−**h**, **4a**−**h**, and **6a,b**; GC-MS analysis of the methyl esters of compounds **4a**−**g**; ^{1}H NMR spectra of compounds **3a**, **3c**−**h**, **4a**, **4c**−**h**, and **6a,b**; ^{1}H NMR spectra of a mixture of **3e** and **3f** and a mixture of **4e** and **4f**; ^{1}H NMR spectrum of a mixture of dipeptides **6a** and **6b**; GC-MS analysis of methyl esters of compounds **4e,f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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