VOLUME 74, NUMBER 13

JOC Featured Article

July 3, 2009

Catalytic, One-Pot Synthesis of β-Amino Acids from α-Amino Acids. Preparation of α,β-Peptide Derivatives

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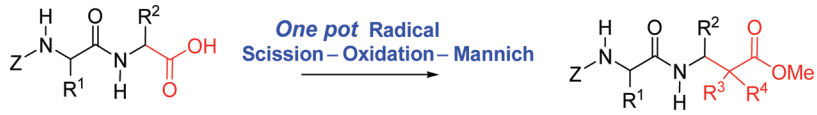
Received March 2, 2009



The one-pot conversion of readily available α-amino acid into β-amino acid derivatives was carried out in good yields. The method is a *sequential* process initiated by a *tandem* radical decarboxylation−oxidation reaction; the resulting acyliminium ion was trapped by silyl ketenes. Stoichiometric and catalytic versions of this reaction were developed and then applied to prepare modified di- and tripeptides. Interestingly, some tripeptides formed expanded β-turns in the solid state.

Introduction

The development of tandem and sequential processes has allowed shorter and more efficient procedures to obtain a variety of products, including drugs, catalysts, or synthetic intermediates.[1] Since several transformations are performed consecutively, and no purification of the intermediates is required, these processes save materials, energy, and time and decrease the amount of waste.

In previous work, we developed a one-step methodology to prepare bioactive products from readily available substrates (such as the amino sugar **1**, Scheme 1).[2] The method was a *sequential* process initiated by a *tandem* radical fragmentation−oxidation reaction. Remarkably, the radical scission step, which initiated the reaction cascade, took place at room temperature using visible light, such as sunlight or common lamps.[3] The scission generated a C-radical (such as **2**) which was trapped by iodine, affording an α-iodoacetal (e.g., compound **3**). The replacement of the iodo group by acetate ions from the reagent gave an *N*,*O*-acetal (such as product **4**). When a Lewis acid and a nucleophile were added, the acetal generated an acyliminium ion **5**,[2a] which was trapped by the nucleophile (for instance, the addition of phosphites afforded α-aminophosphonates **6**).[2b] In general, good yields were obtained, and the reaction conditions were mild, compatible with most functional groups.

We reasoned that this process could be applied to the direct transformation of amino acids into nonproteinogenic analogues and, moreover, to the selective transformation of peptides (Scheme 2). In a preliminary work, the conversion of α-amino

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(3) The radical scission can also be promoted by heating, but visible light irradiation allows milder reaction conditions. To set an irradiation standard, 80 W tungsten-filament lamps (from DIY shops) were used herein.

10.1021/jo9004487 CCC: $40.75 © 2009 American Chemical Society
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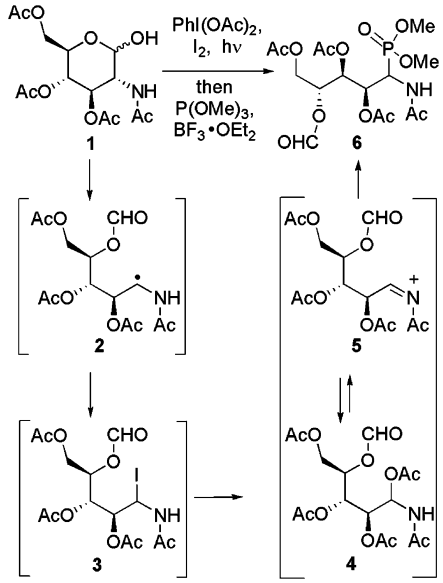
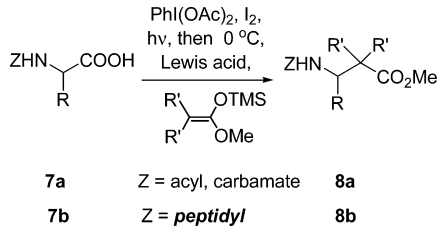
SCHEME 1. One-Pot Radical Fragmentation−Oxidation−Addition of Nucleophile Process



SCHEME 2. One-Pot Scission−Oxidation−Mannich Process for the Direct Conversion of α-Amino Acids into α-Substituted β-Amino Esters and the Selective Modification of Peptides



acids **7a** into substituted β-amino esters **8a** was studied.[4] The decarboxylation−oxidation was carried out, followed by addition of a silylketene[5] in the presence of a Lewis acid. A stoichiometric amount of the Lewis acid (BF_3•OEt_2 or TMSOTf) was required in the nucleophilic addition step. In this article, a catalytic system is reported, which affords similar results.

The sequential process would also allow the *selective transformation* of the C-terminal residue of peptides (conversion **7b→8b**, Scheme 2). In compound **7b**, the amino protecting group Z is a peptidyl chain which would act as a chiral auxiliary, and the reaction would be stereoselective. From a single α-peptide substrate, a library of hybrid α,β-peptides could be formed since the terminal β-amino acid could be mono-, di-, or unsubstituted in the α-position (R′ = H, alkyl, allyl, aryl, Hal, OR, NHR, etc.), and up to four different stereoisomers could be generated. Such procedure could be very useful in medicinal chemistry to obtain diversity from a single (or a few) bioactive α-peptide. The feasibility of this site-selective transformation will be commented on later.

In recent years, the formation of β-amino acid derivatives has received much interest, from both the synthetic[6,7] and medicinal[8] standpoints. Among the synthetic methodologies, the Arndt−Eistert homologation, the Curtius rearrangement, the conjugate addition of nitrogen nucleophiles to unsaturated esters, or the addition of carbon nucleophiles to imines have proven very useful.[6,7] For instance, Seebach and others have used the Arndt−Eistert homologation to prepare β-amino acids and β-peptides with high stereoselectivity.[9] This protocol also allows the synthesis of α-substituted α-amino acids but not α,α-disubstituted β-amino acids; it also presents problems for large-scale synthesis.[9f]

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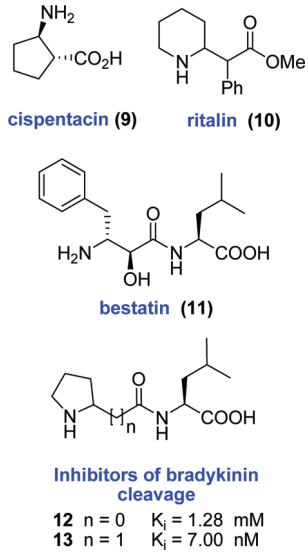


FIGURE 1. Bioactive β-amino acids and hybrid peptides.

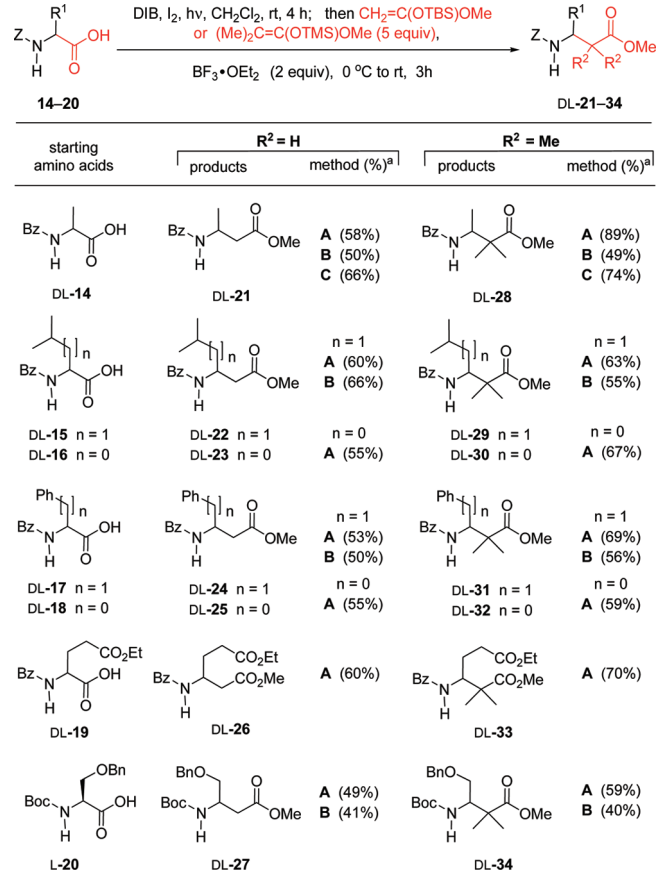
From the medicinal standpoint, the β-amino acid derivatives have displayed interesting biological properties (such as the antibiotic cispentacin **9**[10] and the β-lactams,[11] or the antihyperactivity drug ritalin **10**,[12] Figure 1). In other cases, they are components of bioactive products, such as bestatin (Ubenimex, **11**),[13] a microbial β,α-dipeptide which is under clinical studies to treat lymphomas, myeloid leukemias, and lung carcinoma. Other significant examples are the antitumoral paclitaxel,[14] the antifungal microscleroderms,[15] and the antihelmintic jasplakinolide.[16]

Besides, the replacement of α-amino acids by β-amino acids in bioactive peptides has produced derivatives with superior stability to proteases and with similar or increased activity.[17] For instance, the α-dipeptide **12** (Figure 1) is an inhibitor of bradykinin cleavage by aminopeptidase (APP) and thus a potential agent against cardiovascular diseases. However, its Pro−Leu amide bond is easily hydrolyzed by kidney peptidases. When the proline residue in peptide **12** was replaced by a β-homoproline, the modified β,α-peptide **13** displayed a 500-fold increase in inhibitory activity (from K_i = 1.28 mM to 7.0 nM); moreover, it was completely stable to peptidases in kidney membranes after 24 h.[17a]

Finally, the ability of many β-peptides or hybrid α,β- or β,γ-peptides to form turns, helices, β-sheets, or fibrils is rendering interesting applications to medicinal chemistry and materials science.[18] For example, the β-amino acids are used to generate turns in peptides in order to achieve bioactive conformations.[19]

The application of catalytic tandem−sequential processes to the synthesis of these interesting compounds is discussed below, with an emphasis on the preparation of hybrid α,β-peptides.

TABLE 1. One-Pot Scission−Oxidation−Silyl Ketene Addition: Preparation of β-Amino Acids



[a] Method A: The scission step uses DIB (1.5 equiv), I_2 (0.3 equiv). Method B: Scission step: DIB (2 equiv), I_2 (0.5 equiv). Method C: Scission step: DIB (2 equiv), I_2 (1.0 equiv).

Results and Discussion

Development of the Radical Scission−Oxidation−Mannich Reaction. In a first stage, the sequential process was explored with simple substrates, derived from acylation or carbamoylation of commercial amino acids. Thus, compounds **14**−**20** (Table 1) were treated with the system (diacetoxyiodo)benzene and iodine,[2] in the presence of visible light, to induce the scission−oxidation steps, then BF_3•OEt_2 was added to generate an acyliminium intermediate, which was trapped by silylketenes. With unsubstituted ketenes (R^2 = H), the process afforded compounds **21**−**27** in moderate to good yields. Several reaction conditions were tried, showing that the amount of iodine was critical to obtain good yields. The scission did not take place

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without iodine, but an excess of iodine gave complex product mixtures. With 0.3−0.5 equiv, the reaction proceeded in reasonable yields.

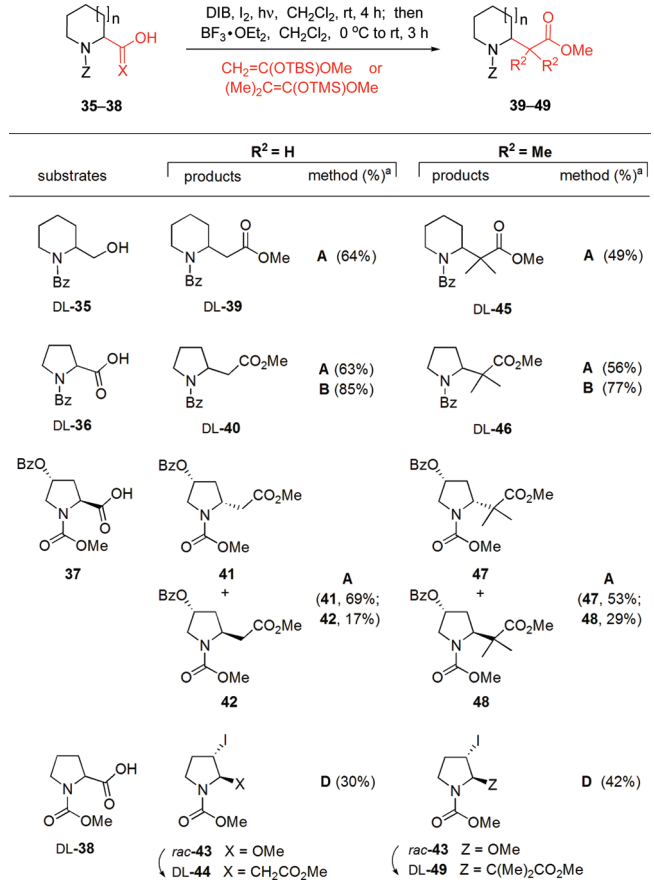
When the disubstituted ketene $Me_2C{=}C(OTMS)OMe$ was used, the yields improved, in particular, with Method A [DIB (1.5 equiv), iodine (0.3 equiv)],[20] which afforded compounds **28**−**34** in good yields. Hence, this methodology is an interesting alternative to the Arndt−Eistert homologation,[6c] not only due to the mild, relatively inexpensive and scalable conditions[9] but also due to the ready formation of α,α-disubstituted β-amino acids.

Similar results were obtained in the scission−alkylation of the cyclic amino alcohol **35** (Table 2) and the cyclic amino acids **36**−**38**. Although the scission of alcohols is less favored than the decarboxylation of amino acids,[21] the fragmentation of the amino alcohol **35** and the alkylation with $CH_2{=}C(OTBS)OMe$ proceeded in a satisfactory yield, affording compound **39**. Remarkably, products derived from possible side reactions, such as hydrogen abstraction, were not detected.

In a similar way, the decarboxylation−alkylation of proline derivative **36** afforded compound **40** in good yield. In the case of hydroxyproline substrate **37**, the stereogenic center on C-4 determined the stereoselectivity of the nucleophilic addition step. Surprisingly, the 2,4-*cis* product **41** predominated upon the 2,4-*trans* isomer **42**. This result could be explained according to the model reported by Woerpel for the addition of nucleophiles to five-membered ring oxocarbenium and iminium ions.[22]

By changing the reaction conditions, different derivatives can be obtained. For instance, when the reaction was carried out in acetonitrile and an excess of iodine was added, the proline carbamate **38** underwent a one-pot decarboxylation−oxidation−β-iodination process.[23a] The polar solvent favored the isomerization of the acyliminium intermediate to an encarbamate, which reacted with iodine affording a β-iodoacyliminium ion. This

TABLE 2. One-Pot Decarboxylation−Alkylation: Preparation of Cyclic β-Amino Acids



[a] Method A: DIB (1.5 equiv), I_2 (0.3 equiv), ketene (5 equiv). Method B: DIB (2.0 equiv), I_2 (0.5 equiv), ketene (5 equiv). Method D: DIB (2 equiv), I_2 (2 equiv), *hv*, CH_3CN, 4 h; MeOH (10 equiv), 0.5 h; solvent removal, then CH_3CN, 0 °C, ketene (5 equiv), $BF_3{\bullet}OEt_2$ (2 equiv), 3 h.

intermediate was trapped by addition of methanol, and a 2,3-*trans*-3-iodo-2-methoxy pyrrolidine **43**[23a] was formed. This compound was not purified, but the solvent was evaporated and the crude product mixture was redissolved, cooled to 0 °C, and treated with the nucleophile and the Lewis acid, yielding the iodinated β-amino ester **44**.[23b] The introduction of iodine in a previously unfunctionalized position is valuable since the iodo group can be replaced by other functionalities. Alternatively, the iodo derivative **43** could undergo elimination, and the resulting 3,4-alkene could be further functionalized.

When the nucleophile was the disubstituted silylketene $Me_2C{=}C(OTMS)OMe$, the α,α-dimethyl-β-amino esters **45**−**49** were isolated. In most cases, yields were similar or superior to

(17) (a) For recent reviews, see: Aguilar, M. I.; Purcell, A. W.; Devi, R.; Lew, R.; Rossjohn, J.; Smith, A. I.; Perlmutter, P. *Org. Biomol. Chem.* **2007**, *5*, 2884–2890. (b) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399–1408. (c) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366–1375. (d) For recent work on the subject, see: Sharma, G. V. M.; Manohar, V.; Dutta, S. K.; Subash, V.; Kunwar, A. C. *J. Org. Chem.* **2008**, *73*, 3689–3698. (e) Chakraborty, T. K.; Rao, K. S.; Kiran, M. U.; Jagadeesh, B. *Tetrahedron Lett.* **2008**, *49*, 2228–2231.

(18) (a) Wright, K.; Sarciaux, M.; de Castries, A.; Wakselman, M.; Mazaleyrat, J.-P.; Toffoletti, A.; Corvaja, C.; Crisma, M.; Peggion, C.; Formaggio, F.; Toniolo, C. *Eur. J. Org. Chem.* **2007**, 3133–3144. (b) Jiang, Z. X.; Yu, Y. B. *J. Org. Chem.* **2007**, *72*, 1464–1467. (c) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323–334. (d) Arvidsson, P. I.; Ryder, N. S.; Weiss, H. M.; Hook, D. F.; Escalante, J.; Seebach, D. *Chem. Biodiv.* **2005**, *2*, 401–420. (e) Cheng, R. P.; Gellman, S. H.; De Grado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.

(19) (a) For the expansion of β-turns with β- and γ-aa, see: Rai, R.; Vasudev, P. G.; Anandz, K.; Raghothama, S.; Shamala, N.; Karle, I. L.; Balaram, P. *Chem.—Eur. J.* **2007**, *13*, 5917–5926. (b) For turns in β-peptides, see: Abele, S.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1559–1571. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1–15. (d) For the biological importance of turns, see: Tyndall, J. D. A.; Pfeiffer, B.; Abbenante, G.; Fairlie, D. P. *Chem. Rev.* **2005**, *105*, 793–826. (e) Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Bioorg. Med. Chem.* **2005**, *13*, 11–16.

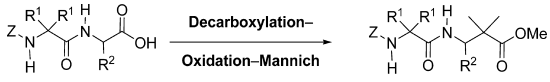
(20) Other methods were also tried, but they are not mentioned in the sake of clarity. For instance, a method using DIB (1.5 equiv) and iodine (0.5 equiv) gave similar results to Method A [DIB (1.5 equiv), iodine (0.3 equiv)].

(21) (a) Zhdankin, V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (b) Togo, H.; Katohgi, M. *Synlett* **2001**, 565–581. (c) Suárez, E.; Rodríguez, M. S. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 440−454. (d) Brun, P.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, pp 367−426 and references cited therein. (e) The decarboxylation of amino acids can also be induced electrochemically: Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401–425. (f) Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689–1691.

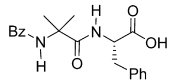
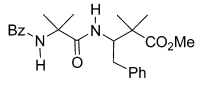
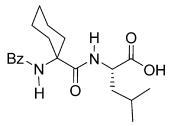
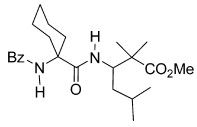
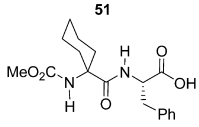
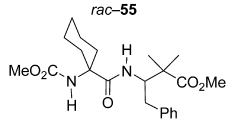
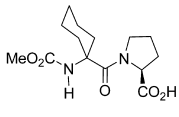
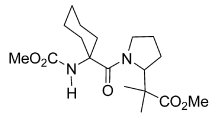
(22) (a) The ring adopts preferentially an envelope conformation, with the acetoxy group in a pseudoaxial position, and the nucleophile adds from the inside face of the envelope, giving the *cis* product. The attack from the outside face is disfavored, due to the eclipsing interactions developed between the substituents at C-2 and C-3 in the transition structure for the *trans* product. (b) For more information, see: Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209. (c) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149–14152. (d) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879–10884.

(23) (a) Boto, A.; Hernández, R.; León, Y.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 7796–7803. (b) The addition of methanol after the scission step was necessary to obtain good yields. If the fragmentation was followed by addition of the nucleophile and the Lewis acid, a complex product mixture was formed. The addition of methanol probably deactivated excess reagents from the first step and generated the stable *N*,*O*-acetal **43**, which was a good acyliminium precursor.

TABLE 3. One-Pot Decarboxylation−Oxidation−Mannich: Preparation of Modified Dipeptides



50–53 *rac*–**54–57**

starting peptides	products	method (%)[a]
 **50**	 *rac*–**54**	**A** (67%)
 **51**	 *rac*–**55**	**A** (58%)
 **52**	 *rac*–**56**	**A** (54%)
 **53**	 *rac*–**57**	**A** (44%)

[a] Method A: DIB (1.5 equiv), I_2 (0.3 equiv), *hν*, CH_2Cl_2, 4 h, then 0 °C, BF_3•OEt_2 (2 equiv), Me_2C═C(OTMS)OMe (5 equiv), 3 h.

those obtained with CH_2═C(OTBS)OMe. The resolution of the enantiomeric mixtures to form hybrid *β*,α-peptides will be commented on later.

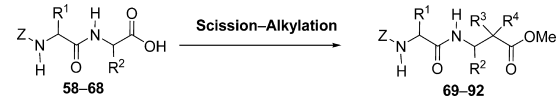
To determine whether the previous reaction conditions were appropriate for more complex substrates, the direct modification of α-dipeptides to give α,*β*-hybrids was explored. In order to simplify the study, a nonstereoselective scission−Mannich process was first carried out using substrates **50**−**53** (Table 3), whose N-terminal α,α-disubstituted amino acids were not chiral. Using Method A [DIB (1.5 equiv), iodine (0.3 equiv) for the scission step], the process afforded α,*β*-dipeptides **54**−**57** in moderate to good yields. Since both amino acids were α,α-disubstituted, the resulting peptides were unusually hydrophobic.

The stereoselective modification of dipeptides was then explored with substrates **58**−**68** (Table 4) which presented chiral N-terminal α-amino acids. Different reaction conditions were studied; only the optimized ones are described in the table. Due to differences in substrate solubility, reactivity, etc., the best conditions varied for each peptide.

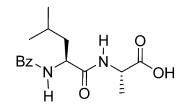
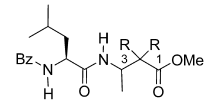
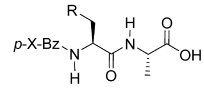
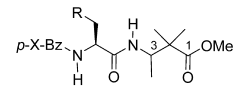
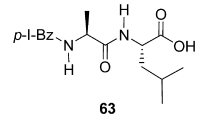
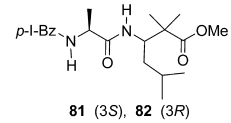
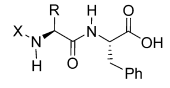
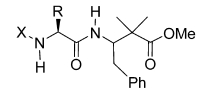
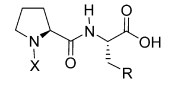
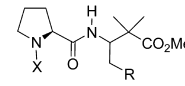
Substrate **58** underwent the scission−oxidation reaction and was then treated with the unsubstituted ketene CH_2═C(OTBS)OMe, affording dipeptides **69** and **70** in moderate yield (36%) and 1:1 diastereomeric ratio. However, when the process was repeated with the disubstituted ketene Me_2C═C(OTMS)OMe, giving dipeptides **71** and **72**, the yield and the diastereomeric ratio increased (77%; **71**:**72**, 2:1). The X-ray analysis of the crystalline derivative **71** showed that the major product retained the "natural" configuration (3*S*).

Since we were especially interested in peptides with α-disubstituted *β*-amino acids, we carried out the remaining experiments with the α,α-dimethyl silyl ketene. The scission−Mannich

TABLE 4. Synthesis of Modified Dipeptides



58–68 **69–92**

starting peptides	products	method,[a] yield (%)
 **58**	 R = H: **69** (3*S*), **70** (3*R*) R = Me: **71** (3*S*), **72** (3*R*)	**A** **69** (18), **70** (18) **A** **71** (51), **72** (26)
 **59** X = H, R = H **60** X = I, R = H **61** X = H, R = Ph **62** X = I, R = Ph	 **73** (3*S*), **74** (3*R*) **75** (3*S*), **76** (3*R*) **77** (3*S*), **78** (3*R*) **79** (3*S*), **80** (3*R*)	**C** **73:74** 5:3, (73) **C** **75:76** 5:3, (74) **C** **77** (45), **78** (27) **C**[b] **79** (30), **80** (11)
 **63**	 **81** (3*S*), **82** (3*R*)	**A** **81** (31), **82** (15)
 **64** X = Bz, R = CH_2Ph **65** X = Cbz, R = $CHMe_2$	 **83** (3*S*), **84** (3*R*) **85** (3*S*), **86** (3*R*)	**B**[c] **83** (49), **84** (14) **A** **85:86**, 5:4, (30)
 **66** X = Bz, R = $CHMe_2$ **67** X = Bz-p-I, R = $CHMe_2$ **68** X = Cbz, R = Ph	 **87** (3*S*), **88** (3*R*) **89** (3*S*), **90** (3*R*) **91** (3*S*), **92** (3*R*)	**A** **87** (36), **88** (22) **A** **89** (43), **90** (25) **A** **91:92**, 7:5, (72)

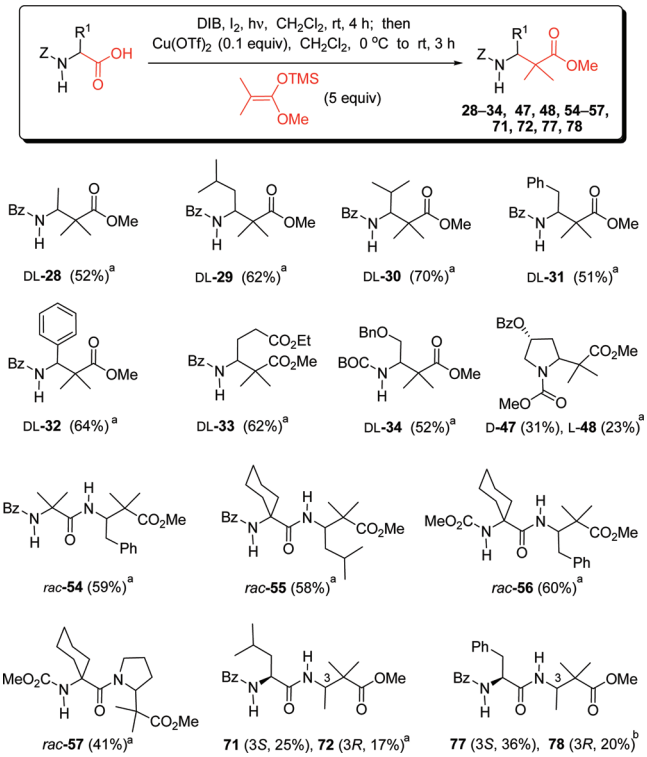
[a] Method A: DIB (1.5 equiv), I_2 (0.3 equiv). Method B: DIB (2.0 equiv), I_2 (0.5 equiv), I_2 (0.5 equiv). Method C: DIB (2 equiv), I_2 (1 equiv). [b] Method C, but using $CHCl_3$, reflux. [c] Method B, but using PhH, 26 °C.

of α-dipeptides **59**−**68** afforded the α,*β*-hybrids **73**−**92** in good global yields. The X-ray analysis of compounds **78**, **81**, **83**, and **90** showed that, in all of these cases, the major isomer possessed the "natural" configuration. In general, the minor isomers could be readily separated from the major ones. The isolation of the minor isomers is interesting for medicinal SAR studies in order to determine the influence of the stereochemistry in the biological activity.

Development of a Catalytic Mannich Step. In our previous reports,[2] the nucleophilic addition step required stoichiometric amounts of the Lewis acid (e.g., BF_3•OEt_2 or TMSOTf); if catalytic amounts were used, the process afforded very low product yields. For the first time, we report an efficient scission−nucleophilic addition process which only requires a catalytic amount of the Lewis acid. In the modified process (Scheme 3), the boron trifluoride (2 equiv) was replaced by the softer copper(II) triflate (0.1 equiv), affording satisfactory yields (41−70%) of the scission−Mannich products. In most cases, the yields were similar or slighty inferior to those obtained with the stoichiometric Lewis acid.

The catalytic process saves reagents and reduces the amount of acid waste to treat. Besides, this catalytic version will be further refined to allow the use of chiral Lewis acid catalysts,

SCHEME 3. Catalytic One-Pot Decarboxylation−Oxidation−Silyl Ketene Addition



[a] DIB (1.5 equiv), I_2 (0.3 equiv). [b] DIB (2.0 equiv), I_2 (1.0 equiv).

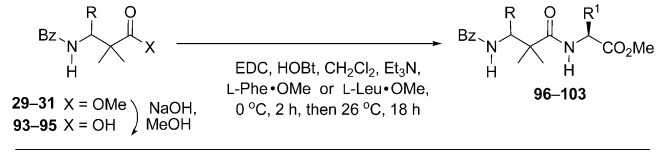
such as those derived from $Cu(OTf)_2$ and BOX ligands.[24] These catalysts, which are currently under study, will be used to increase the stereoselectivity in the generation of β-amino acids and hybrid α,β-dipeptides.

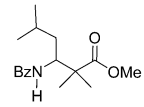
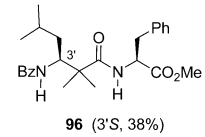
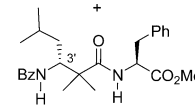
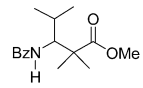
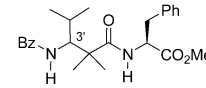
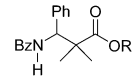
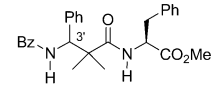
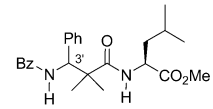
Separation of Isomer Mixtures: Enantiomeric β-Amino Acids or Diastereomeric α,β-Peptides. Once the reaction conditions were optimized, it was clear that the one-pot scission−oxidation−Mannich process was a useful methodology for the direct conversion of α- into β-amino acid derivatives. However, using simple α-amino acids as substrates gave racemic mixtures of β-amino esters since the scission generated an achiral acyliminium intermediate. These enantiomers were separated by formation of hybrid β,α-dipeptides (Table 5). Thus, the β-amino esters **29**−**31** were hydrolyzed to the acids **93**−**95**. Then, the β-homoleucine derivative **93** was coupled to a L-Phe•OMe residue with EDC/HOBt, affording the diastereomeric dipeptides **96** and **97**, which were easily separated (89% global yield). The stereochemistry of these compounds was determined by X-ray analysis.

In a similar way, the β-valine derivative **94** was coupled to L-Phe•OMe, giving dipeptides **98** and **99** (77% global yield), and the β-phenylalanine derivative **95** was coupled to L-Phe•OMe (affording the diastereomeric peptides **100** and **101**) or to L-Leu•OMe (giving dipeptides **102** and **103**). In both cases, good overall yields were obtained. The β,α-dipeptides were analogues of the potent antitumoral bestatin (Ubenimex). Since both possible diastereomers were obtained, it would be possible

(24) (a) Nakamura, S.; Nakashima, H.; Sugimoto, H.; Sano, H.; Hattori, M.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2008**, *14*, 2145–2152. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heilderberg, 1999. (d) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

TABLE 5. Resolution of β-Amino Acids: Formation of Modified β,α-Dipeptides



starting β-amino ester	acid (X = OH), yield (%)	amino ester for separation	dipeptides **96**–**103** (%)[a]
 DL-**29**	DL-**93** (90)	L-Phe•OMe	 **96** (3′*S*, 38%) +  **97** (3′*R*, 41%)
 DL-**30**	DL-**94** (90)	L-Phe•OMe	 **98** (3′*R*, 39%), **99** (3′*S*, 38%)
 DL-**31**	DL-**95** (92)	L-Phe•OMe	 **100** (3′*R*, 35%), **101** (3′*S*, 41%)
		L-Leu•OMe	 **102** (3′*R*, 50%), **103** (3′*S*, 43%)

[a] The diastereomeric dipeptides were readily separated by chromatography on silica gel.

to study the influence of the β-amino acid configuration on the biological activity.

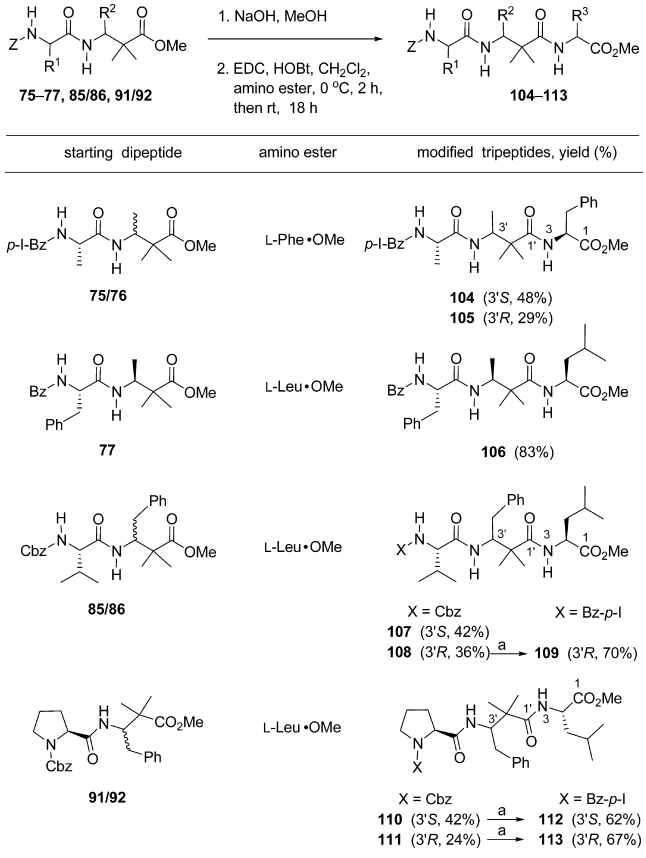
On the other hand, the diastereomeric α,β-peptides resulting from the scission-Mannich reaction were usually separated. In the few cases where unseparable diastereomer mixtures were obtained, we studied the formation of α,β,α-tripeptides (Table 6).

Thus, the mixture **75/76** was saponified and coupled to L-Phe•OMe, affording tripeptides **104** and **105** in 81% yield. These peptides were separated, and the X-ray analysis of compound **105** (Figure 2) showed that it possessed the "unnatural" configuration.

In a similar way, dipeptide **77** was transformed into tripeptide **106** in good yield, and the mixture of dipeptides **85/86** was converted into the α,β,α-tripeptides **107** and **108**. The latter underwent Cbz removal by hydrogenolysis and acylation with *p*-IBzCl, affording derivative **109**, which was suitable for X-ray analysis. Finally, the dipeptide mixture **91/92** was saponified and coupled to L-Leu•OMe, affording tripeptides **110** and **111**. Since their crystals were not appropriate for X-ray analysis, they were transformed into their *p*-iodobenzamides **112** and **113**. The X-ray analysis of compounds **112** and **113** showed that the major isomer presented the "natural" configuration.

These X-ray analysis also highlighted that, in the solid state, the α,β,α-tripeptides **105**, **109**, **112**, and **113** formed turns

TABLE 6. Separation of Diastereomeric α,β-Dipeptides: Formation of α,β,α-Tripeptides



[a] H_2, Pd (10% on carbon), THF/H_2O, then $NaHCO_3$, *p*-I-BzCl.

(Figure 2). In α-peptides, the generation of turns is favored by the presence of certain amino acids, such as proline, glycine, D-, or *N*-alkyl amino acids; in their absence, extended conformations are adopted.[25] None of these amino acids is present in the α,β-hybrids **105** and **109**, so the formation of an expanded β-turn is due to the introduction of the α,α-disubstituted β-amino acid.

The tripeptides whose β-amino acid unit has the "unnatural" configuration (compounds **105**, **109**, and **113**) adopted an expanded β-turn,[19] between the CO_i (benzamide) and the NH_{i+3} groups. Interestingly, these interactions are reinforced by a hydrogen bond between the NH_{i+2} group (from the β-amino acid) and the CO_{i+3} group (from the C-terminal amino acid).

In the case of peptide **112**, whose β-amino acid presents the "natural" configuration, the molecular conformation of the peptide is different. A hydrogen bond was formed between the β-amino acid CO and NH groups. An additional interaction was observed between the proline nitrogen lone pairs and the β-amino acid amine proton.

These interactions could be useful to design new peptide catalysts,[26] and we are currently carrying out additional studies to clarify the conformational effects in solution.

Conclusion

In summary, we have developed a one-pot radical scission−oxidation−Mannich process to transform α-amino acid into β-amino acid derivatives. This method is an interesting alternative to other homologation procedures, such as the Arndt−Eistert reaction, since it allows the easy generation of α,α-disubstituted β-amino esters. Some β-amino acid products were coupled to α-amino esters to form hybrid β,α-dipeptides since these compounds often display interesting biological activities.

Besides, this procedure allows the *selective modification* of the C-terminal residue in small peptides, which could be very useful in medicinal chemistry (a single bioactive α-peptide could be transformed into a library of hybrid α,β-peptides).

The method is a *sequential* process initiated by a *tandem* radical fragmentation−oxidation reaction, which generates an acyliminium ion. This intermediate reacts with silyl ketenes in the presence of a Lewis acid, affording β-amino esters or α,β-dipeptide derivatives. The process is operationally simple and saves materials and time since no purification of the intermediates is needed. The mild reaction conditions are compatible with most functional groups. Moreover, in the scission step, only a catalytic amount of iodine is needed.

When α-dipeptides were used as substrates, the N-terminal residue acted as a chiral auxiliary, and the reaction was stereoselective (predominating the isomer with the "natural" configuration). Some of the resulting α,β-dipeptides were transformed into α,β,α-tripeptides, whose molecular conformation was determined by the configuration of the β-amino acid unit. The "natural" configuration favored hydrogen bonds between the β-amino acid CO and NH groups, and an additional interaction was observed between the proline nitrogen lone pairs and the β-amino acid amine proton.

Interestingly, the unnatural configuration led to the formation of β-turns in the solid state, a structural feature found in some efficient peptide catalysts. Since two hybrid peptides (**105** and **109**) lacked turn-inducing α-amino acids (such as proline, glycine, D-, or *N*-alkyl amino acids), the generation of an expanded β-turn is probably due to the introduction of the α,α-disubstituted β-amino acid.

Finally, a new version of the scission−Mannich process was developed, which only required a catalytic amount of the Lewis acid [thus, boron trifluoride (2 equiv) was replaced by copper triflate (0.1 equiv)]. The modified process, which saves expensive reagents and reduces the acidic waste, took place in moderate to good yields (40−70%). The generation of chiral catalysts from $Cu(OTf)_2$ and chiral ligands is currently under study in order to prepare β-amino acids in high enantiomeric excess and to increase the stereoselectivity in the synthesis of α,β-hybrid peptides.

Experimental Section

General Procedures for the One-Pot Scission−Oxidation−Alkylation Sequence. Method A. To a solution of the starting amino acid or peptide (0.2 mmol) in dry dichloromethane (6 mL) were added iodine (15 mg, 0.06 mmol) and (diacetoxyiodo)benzene (DIB) (97 mg, 0.3 mmol). The reaction mixture was stirred at 26 °C for 4 h, under irradiation with visible light. Then the solution was cooled to 0 °C, and 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (218 μL, 188 mg, 1.0 mmol) or methyl trimethylsilyldim-

(25) (a) Sewald, N.; Jakubke, H. D. *Peptides: Chemistry and Biology*, Wiley-VCH: Weinheim, Germany, 2002; pp 311−337. (b) For applications, see: Blanchette, J. P.; Ferland, P.; Voyer, N. *Tetrahedron Lett.* **2007**, *48*, 4929–4933.

(26) (a) For reviews, see: Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812. (b) Berkessel, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3677–3679. (c) For recent work on the subject, see: Sánchez-Roselló, M.; Puchlopek, A. L. A.; Morgan, A. J.; Miller, S. J. *J. Org. Chem.* **2008**, *73*, 1774–1782. (d) Revell, J. D.; Wennemers, H. *Adv. Synth. Catal.* **2008**, *350*, 1046–1052. (e) Tsandi, E.; Kokotos, C. G.; Kousidon, S.; Ragoussis, V.; Kokotos, G. *Tetrahedron* **2009**, *65*, 1444–1449, and references cited therein.

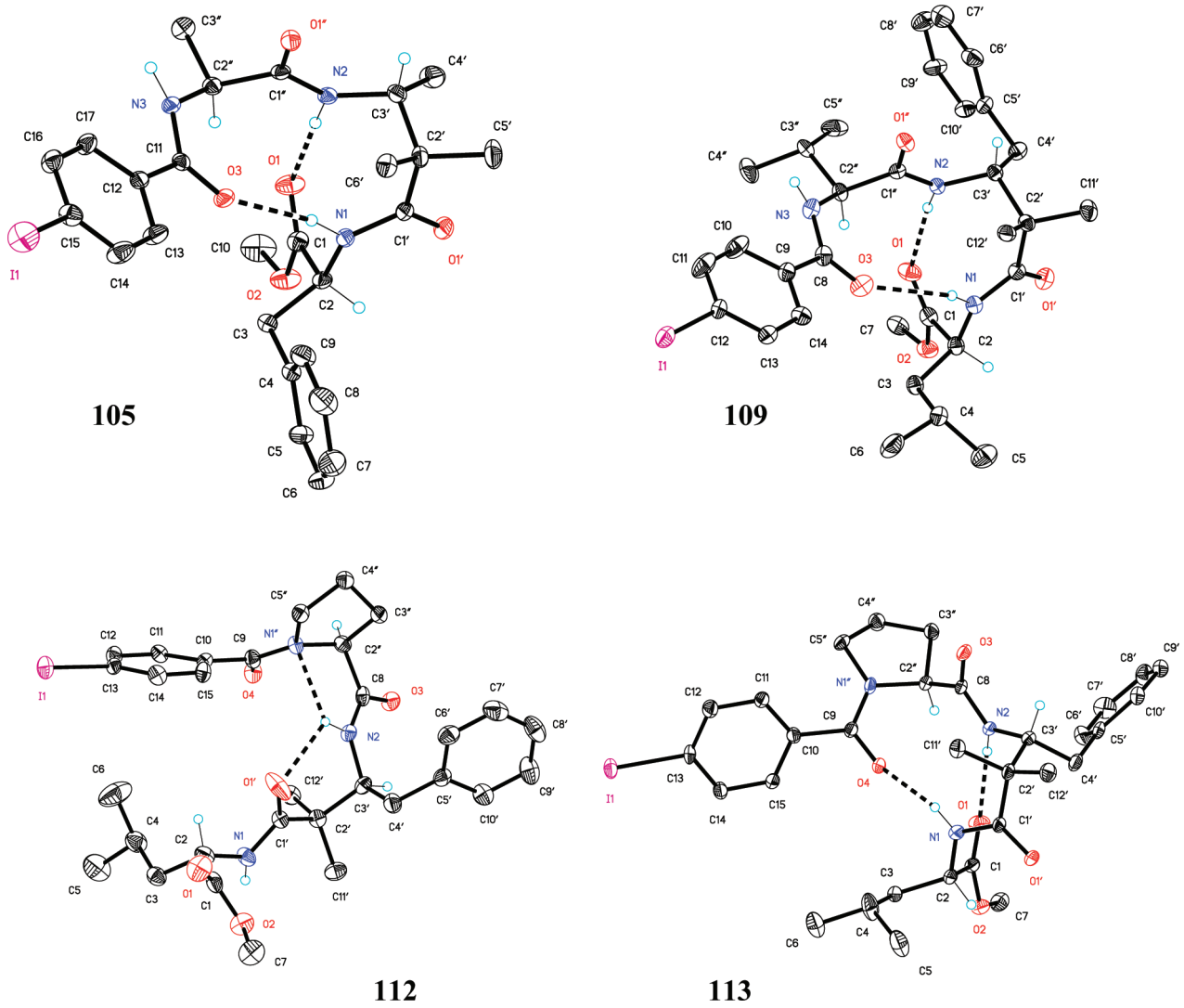


FIGURE 2. Molecular conformation of peptides **105**, **109**, **112**, and **113** in crystals. Intramolecular hydrogen bonds are shown as dotted lines.

ethylketene acetal (203 μL, 174 mg, 1.0 mmol) was injected, followed by dropwise addition of BF_3•OEt_2 (51 μL, 57 mg, 0.4 mmol). The mixture was allowed to reach room temperature and stirred for 3 h; then it was poured into 10% aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1:1, 10 mL) and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate mixtures) to give the products.

Method B. To a solution of the starting amino acid (0.2 mmol) in dry dichloromethane (6 mL), under nitrogen atmosphere, were added iodine (25 mg, 0.1 mmol) and (diacetoxyiodo)benzene (DIB) (129 mg, 0.4 mmol) and treated as in Method A.

Method C. To a solution of the starting amino acid or peptide (0.2 mmol) in dry dichloromethane (6 mL) were added iodine (51 mg, 0.2 mmol) and (diacetoxyiodo)benzene (DIB) (129 mg, 0.4 mmol) and treated as in Method A.

Method D. To a solution of starting material (0.2 mmol) in dry acetonitrile (6 mL) were added iodine (102 mg, 0.4 mmol) and (diacetoxyiodo)benzene (DIB) (129 mg, 0.4 mmol). The reaction mixture was stirred at 24−26 °C for 4 h, under irradiation with visible light. Then dry methanol (1 mL) was added, and the stirring was continued for 1 h. The mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum, and the residue was dissolved in dry acetonitrile (6 mL). The solution was cooled to 0 °C, and 1-*tert*-(dimethylsilyloxy)-1-methoxyethene (218 μL, 188 mg, 1.0 mmol) or methyl trimethylsilyldimethylketene acetal (203 μL, 174 mg, 1.0 mmol) was injected, followed by dropwise addition of BF_3•OEt_2 (51 μL, 57 mg, 0.4 mmol). The mixture was allowed to reach room temperature and stirred for 3 h; then it was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate mixtures) to give the products.

One-Pot Catalytic Scission−Oxidation−Alkylation Sequence. The procedures were similar to previously described Methods A−D, but replacing boron trifluoride by copper(II) triflate (0.1 equiv).

Resolution of *β*-Amino Acids. Formation of Modified Dipeptides. General Procedure for the Generation of Acids 93−95. A solution of esters **29**, **30**, or **31** (0.20 mmol) in methanol (6 mL) at 0 °C was treated with 2 N aqueous NaOH (2 mL). The reaction mixture was allowed to reach rt and stirred overnight. Then it was cooled to 0 °C, poured into 5% aqueous HCl, and extracted with EtOAc. The organic layer was dried and evaporated as usual.

Decarboxylation of Dipeptides Oxidation−Alkylation. The process was carried out according to previously described Method A, B, or C.

Separation of Dipeptides by Formation of Tripeptides: *N*-(*p*-Iodobenzoyl)-L-alanyl-[α,α-dimethyl-L-*β*-homoalanyl]-L-phenylalanine Methyl Ester (104) and *N*-(*p*-Iodobenzoyl)-L-alanyl-[α,α-dimethyl-D-*β*-homoalanyl]-L-phenylalanine Methyl Ester (105). To a solution of the mixture of dipeptides **75/76** (118 mg, 0.26 mmol) in methanol (6 mL) at 0 °C was slowly added 2

N aqueous NaOH (3 mL). The reaction mixture was allowed to reach rt and stirred for 64 h, then it was cooled to 0 °C, diluted with water, poured into 5% HCl, and extracted with EtOAc. The organic layer was dried and evaporated, and the residue was dissolved in dry CH_2Cl_2 (3 mL) and treated with L-phenylalanine methyl ester hydrochloride (57 mg, 0.26 mmol). The solution was cooled to 0 °C, and Et_3N (37 μL, 27 mg, 0.26 mmol), EDC (56 mg, 0.29 mmol), and HOBt (39 mg, 0.29 mmol) were added. The reaction mixture was stirred at 0 °C for 2 h, then it was allowed to reach room temperature and stirred for 18 h and finally was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. After usual drying and solvent removal, the residue was purified by rotatory chromatography (hexanes/EtOAc, 3:2 and 1:1), affording compounds **104** (48%) and **105** (29%).

Compound 104: Syrup; $[\alpha]_D$ +53 (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 3438, 3401, 3089, 3062, 1738, 1652, 1503, 1477 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.08 (3H, d, $J = 6.6$ Hz), 1.14 (3H, s), 1.15 (3H, s), 1.49 (3H, d, $J = 7.0$ Hz), 3.08 (1H, dd, $J = 6.3$, 13.9 Hz), 3.17 (1H, dd, $J = 6.0$, 13.9 Hz), 3.76 (3H, s), 3.89 (1H, dddd, $J = 6.9$, 6.9, 6.9, 9.3 Hz), 4.59 (1H, dddd, $J = 7.0$, 7.0, 7.0, 7.0 Hz), 4.79 (1H, ddd, $J = 6.0$, 6.3, 7.3 Hz), 6.16 (1H, d, $J = 7.6$ Hz), 7.08 (2H, d, $J = 6.6$ Hz), 7.12 (1H, d, $J = 7.0$ Hz), 7.25−7.35 (3H, m), 7.42 (1H, d, $J = 9.2$ Hz), 7.54 (2H, d, $J = 8.5$ Hz), 7.76 (2H, d, $J = 8.6$ Hz); ^{13}C NMR (125.7 MHz) δ_C 16.7 (CH_3), 19.3 (CH_3), 22.7 (CH_3), 24.8 (CH_3), 37.4 (CH_2), 45.0 (C), 49.6 (CH), 52.4 (CH_3), 52.7 (CH), 52.8 (CH), 98.5 (C), 127.3 (CH), 128.7 (4 × CH), 129.1 (2 × CH), 133.6 (C), 135.6 (C), 137.6 (2 × CH), 165.9 (C), 171.3 (C), 171.9 (C), 176.3 (C); MS *m/z* (rel intensity) 593 (M^+, 2), 319 (M^+ − CH(Me)NHBz-*p*-I, 55), 249 (M^+ + H − CH(Me)NHCOCH(Me)NHBz-*p*-I, 59), 231 ([*p*-I-PhCO]$^+$, 100); HRMS calcd for $C_{26}H_{32}IN_3O_5$, 593.1387; found, 593.1407; calcd for C_7H_4IO, 230.9307; found, 230.9301. Anal. Calcd for $C_{26}H_{32}IN_3O_5$: C, 52.62; H, 5.43; N, 7.08. Found: C, 52.79; H, 5.63; N, 7.09. **Compound 105**: Crystalline solid; mp 143−144 °C (from EtOAc/*n*-hexane); $[\alpha]_D$ +33 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3437, 3370, 3090, 3068, 1730, 1655, 1507, 1477 cm^{-1}; ^1H NMR (500 MHz) $\delta_H = 1.11$ (3H, d, $J = 7.0$ Hz), 1.14 (3H, s), 1.19 (3H, s), 1.55 (3H, d, $J = 7.3$ Hz), 3.18 (1H, dd, $J = 9.9$, 13.9 Hz), 3.22 (1H, dd, $J = 5.4$, 13.9 Hz), 3.79 (3H, s), 4.00 (1H, dddd, $J = 6.6$, 6.6, 6.6, 10.1 Hz), 4.43 (1H, dddd, $J = 7.0$, 7.0, 7.0, 7.0 Hz), 4.78 (1H, ddd, $J = 5.4$, 8.2, 9.8 Hz), 7.22 (1H, d, $J = 7.9$ Hz), 7.25 (1H, m), 7.34−7.36 (4H, m), 7.42 (2H, d, $J = 8.6$ Hz), 7.62 (2H, d, $J = 8.5$ Hz), 7.67 (1H, d, $J = 10.1$ Hz), 7.83 (1H, d, $J = 6.3$ Hz); ^{13}C NMR (125.7 MHz) δ_C 16.3 (CH_3), 17.2 (CH_3), 22.5 (CH_3), 23.9 (CH_3), 36.5 (CH_2), 46.7 (C), 51.2 (CH), 52.0 (CH), 52.7 (CH_3), 54.5 (CH), 98.7 (C), 126.9 (CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.2 (2 × CH), 132.5 (C), 137.0 (C), 137.5 (2 × CH), 166.7 (C), 172.7 (C), 174.7 (C), 175.2 (C); MS *m/z* (rel intensity) 593 (M^+, 2), 249 (M^+ + H − CH(Me)NHCOCH(Me)NHBz-*p*-I, 43), 231 ([*p*-I-PhCO]$^+$, 100); HRMS calcd for $C_{26}H_{32}IN_3O_5$, 593.1387; found, 593.1467; calcd for C_7H_4IO, 230.9307; found, 230.9318. Anal. Calcd for $C_{26}H_{32}IN_3O_5$: C, 52.62; H, 5.43; N, 7.08. Found: C, 52.62; H, 5.63; N, 6.99. **X-ray Analysis**: $C_{27}H_{33}Cl_3IN_3O_5$, M_r = 712.81, colorless plate crystal (0.24 × 0.19 × 0.11 mm^3) from EtOAc/*n*-hexane (mp 143−144 °C); orthorhombic, space group $P2_12_12$ (no. 18), $a = 34.192(2)$ Å, $b = 8.269(1)$ Å, $c = 11.228(1)$ Å, $V = 3174.5(5)$ $Å^3$, $Z = 4$, $\rho_{calcd} = 1.491$ g cm^{-3}, $F(000) = 1491$, $\mu = 1.300$ mm^{-1}; 57 660 measured reflections, of which 4044 were unique ($R_{int} = 0.0286$); 420 refined parameters, final $R_1 = 0.0382$, for reflections with $I > 2\sigma(I)$, $wR_2 = 0.1136$ (all data), GOF = 1.030. Flack parameter = 0.015(15). The max/min residual electron density: +0.589/−0.449 e·$Å^{-3}$.

***N*-(Benzoyl)-L-phenylalanyl-[α,α-dimethyl-L-β-homoalanyl]-L-leucine Methyl Ester (106).** It was synthesized from dipeptide **77** following the previous coupling procedure. The residue was purified by rotatory chromatography (hexanes/EtOAc, 3:2), affording compound **106** (83%) as a crystalline solid: mp 97−98 °C (from EtOAc/*n*-hexane); $[\alpha]_D$ +10 (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) 3437, 3382, 3088, 3067, 1740, 1654, 1508, 1483 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.89 (3H, d, $J = 6.3$ Hz), 0.92 (3H, d, $J = 6.3$ Hz), 0.99 (3H, s), 1.07 (3H, d, $J = 6.6$ Hz), 1.20 (3H, s), 1.52−1.66 (3H, m), 3.19 (1H, dd, $J = 7.3$, 13.9 Hz), 3.23 (1H, ddd, $J = 6.3$, 13.9 Hz), 3.71 (3H, s), 3.87 (1H, dddd, $J = 6.6$, 6.6, 6.6, 9.2 Hz), 4.46 (1H, ddd, $J = 5.0$, 8.0, 8.5 Hz), 4.87 (1H, ddd, $J = 6.9$, 7.0, 7.3 Hz), 6.04 (1H, d, $J = 7.9$ Hz), 6.71 (1H, d, $J = 7.3$ Hz), 7.21 (1H, m), 7.26−7.30 (4H, m), 7.40 (2H, dd, $J = 7.3$, 7.9 Hz), 7.48 (1H, dd, $J = 7.3$, 7.6 Hz), 7.51 (1H, d, $J = 8.9$ Hz), 7.71 (2H, d, $J = 7.8$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 16.7 (CH_3), 21.9 (CH_3), 22.7 (CH_3), 22.9 (CH_3), 24.6 (CH_3), 25.0 (CH), 38.6 (CH_2), 41.1 (CH_2), 44.7 (C), 50.7 (CH), 52.3 (CH_3), 53.0 (CH), 55.0 (CH), 127.0 (3 × CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.4 (2 × CH), 131.6 (CH), 134.1 (C), 136.5 (C), 167.1 (C), 170.1 (C), 173.3 (C), 176.6 (C); MS *m/z* (rel intensity) 509 (M^+, 2), 418 (M^+ − CH_2Ph, 2), 365 (M^+ − NHCH(CH_2CHMe_2)CO_2Me, 4), 105 ([PhCO]$^+$, 100), 77 ([Ph]$^+$, 25); HRMS calcd for $C_{29}H_{39}N_3O_5$, 509.2890; found, 509.2880; calcd for C_7H_5O, 105.0340; found, 105.0339. Anal. Calcd for $C_{29}H_{39}N_3O_5$: C, 68.34; H, 7.71; N, 8.25. Found: C, 68.41; H, 7.89; N, 8.18.

***N*-(Benzyloxycarbonyl)-L-valyl-[α,α-dimethyl-L-β-homophenylalanyl]-L-leucine Methyl Ester (107) and *N*-(Benzyloxycarbonyl)-L-valyl-[α,α-dimethyl-D-β-homophenylalanyl]-L-leucine Methyl Ester (108).** They were synthesized from a mixture of dipeptides **85/86** following the previous coupling procedure. The residue was purified by rotatory chromatography (hexanes/EtOAc, 7:3 and 1:1), affording compounds **107** (42%) and **108** (36%). **Compound 107**: Syrup; $[\alpha]_D$ −49 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3435, 3090, 3067, 1728, 1667, 1499 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.64 (3H, d, $J = 6.6$ Hz), 0.83 (3H, d, $J = 6.6$ Hz), 0.94 (3H, d, $J = 6.6$ Hz), 0.96 (3H, d, $J = 7.0$ Hz), 1.24 (3H, s), 1.34 (3H, s), 1.55−1.75 (3H, m), 2.02 (1H, m), 2.54 (1H, dd, $J = 11.3$, 13.3 Hz), 2.97 (1H, dd, $J = 4.1$, 14.2 Hz), 3.76 (3H, s), 3.87 (1H, dd, $J = 7.9$, 7.9 Hz), 4.20 (1H, ddd, $J = 3.8$, 10.1, 10.4 Hz), 4.58 (1H, ddd, $J = 5.4$, 8.2, 8.5 Hz), 5.01 (1H, d, $J = 8.2$ Hz), 5.10 (2H, s), 6.18 (1H, d, $J = 7.6$ Hz), 7.06−7.15 (6H, m), 7.31−7.38 (5H, m); ^{13}C NMR (125.7 MHz) δ_C 17.1 (CH_3), 19.3 (CH_3), 21.9 (CH_3), 22.7 (CH_3), 23.4 (CH_3), 24.8 (CH_3), 25.0 (CH), 30.4 (CH), 37.2 (CH_2), 41.0 (CH_2), 45.6 (C), 50.8 (CH), 52.4 (CH_3), 57.7 (CH), 60.7 (CH), 66.9 (CH_2), 126.2 (CH), 128.1 (2 × CH), 128.2 (3 × CH), 128.5 (2 × CH), 129.2 (2 × CH), 136.3 (C), 138.4 (C), 156.2 (C), 170.6 (C), 173.4 (C), 176.8 (C); MS *m/z* (rel intensity) 567 (M^+, 1), 476 (M^+ − CH_2Ph, 6), 368 (M^+ − CH_2Ph − $HOCH_2Ph$, 12), 91 ([CH_2Ph]$^+$, 100); HRMS calcd for $C_{32}H_{45}N_3O_6$, 567.3308; found, 567.3286; calcd for C_7H_7, 91.0548; found, 91.0547. Anal. Calcd for $C_{32}H_{45}N_3O_6$: C, 67.70; H, 7.99; N, 7.40. Found: C, 67.74; H, 8.11; N, 7.25. **Compound 108**: Syrup; $[\alpha]_D$ +19 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 3438, 3374, 3336, 1725, 1710, 1680, 1658, 1508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.26 (3H, d, $J = 6.7$ Hz), 0.76 (3H, d, $J = 6.9$ Hz), 0.95 (3H, d, $J = 6.6$ Hz), 0.97 (3H, d, $J = 6.6$ Hz), 1.13 (3H, s), 1.36 (3H, s), 1.60−1.69 (2H, m), 1.76−1.82 (1H, m), 1.92 (1H, ddd, $J = 4.5$, 11.7, 13.6 Hz), 2.39 (1H, dd, $J = 12.3$, 14.5 Hz), 3.12 (1H, dd, $J = 3.5$, 14.5 Hz), 3.33 (1H, dd, $J = 7.9$, 8.8 Hz), 3.82 (3H, s), 4.22 (1H, ddd, $J = 3.5$, 10.4, 12.3 Hz), 4.70 (1H, ddd, $J = 4.1$, 8.5, 11.7 Hz), 5.01 (1H, d, $J = 12.6$ Hz), 5.08 (1H, d, $J = 12.3$ Hz), 5.18 (1H, d, $J = 7.9$ Hz), 7.10−7.16 (4H, m), 7.21 (2H, dd, $J = 7.3$, 7.3 Hz), 7.27−7.35 (5H, m), 7.51 (1H, d, $J = 10.4$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 18.4 (CH_3), 18.9 (CH_3), 21.1 (CH_3), 23.1 (CH_3), 23.2 (CH_3), 23.3 (CH_3), 25.2 (CH), 29.3 (CH), 35.7 (CH_2), 39.1 (CH_2), 47.4 (C), 51.7 (CH), 52.7 (CH_3), 57.4 (CH), 62.8 (CH), 66.9 (CH_2), 126.1 (CH), 127.7 (2 × CH), 128.2 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 129.2 (2 × CH), 136.1 (C), 138.9 (C), 156.8 (C), 171.7 (C), 175.3 (C), 176.4 (C); MS *m/z* (rel intensity) 567 (M^+, 1), 476 (M^+ − CH_2Ph, 2), 368 (M^+ − CH_2Ph − $HOCH_2Ph$, 9), 91 ([CH_2Ph]$^+$, 100); HRMS calcd for $C_{32}H_{45}N_3O_6$, 567.3308; found, 567.3311; calcd for C_7H_7, 91.0548; found, 91.0549. Anal. Calcd for $C_{32}H_{45}N_3O_6$: C, 67.70; H, 7.99; N, 7.40. Found: C, 67.83; H, 7.95; N, 7.15.

***N*-(*p*-Iodobenzoyl)-L-valyl-[α,α-dimethyl-D-β-homophenylalanyl]-L-leucine Methyl Ester (109).** To a solution of tripeptide **108**

(38 mg, 0.07 mmol) in a biphasic mixture (2:1 THF/H_2O, 9 mL) was added Pd (10% on carbon, 25 mg), and the reaction was stirred at room temperature and under hydrogen atmosphere (1 atm) for 16 h. Then the mixture was filtered through Celite, and the filtrate was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$ (6 mL) and 4-iodobenzoyl chloride (23 mg, 0.09 mmol). The mixture was allowed to reach rt and stirred for 16 h, then it was poured into 5% aqueous HCl and extracted with EtOAc. After usual drying, the residue were purified by rotatory chromatography (hexanes/EtOAc, 85:15), giving product **109** (31 mg, 70%) as a crystalline solid: mp 131−132 °C (from EtOAc/*n*-pentane); $[\alpha]_D$ +44 (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 3434, 3359, 3089, 1726, 1676, 1654, 1514 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.22 (3H, d, *J* = 6.7 Hz), 0.85 (3H, d, *J* = 6.7 Hz), 0.98 (3H, d, *J* = 6.3 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 1.20 (3H, s), 1.38 (3H, s), 1.66 (1H, ddd, *J* = 4.1, 10.1, 13.6 Hz), 1.84−1.95 (2H, m), 2.05 (1H, m), 2.46 (1H, dd, *J* = 12.7, 14.5 Hz), 3.15 (1H, dd, *J* = 3.5, 14.5 Hz), 3.69 (1H, dd, *J* = 7.6, 10.1 Hz), 3.83 (3H, s), 4.27 (1H, ddd, *J* = 3.5, 10.4, 12.5 Hz), 4.72 (1H, ddd, *J* = 3.8, 8.2, 12.1 Hz), 7.13 (1H, dd, *J* = 6.9, 7.0 Hz), 7.16−7.24 (4H, m), 7.415 (2H, d, *J* = 8.5 Hz), 7.416 (1H, d, *J* = 8.5 Hz), 7.55 (1H, d, *J* = 8.5 Hz), 7.65 (2H, d, *J* = 8.5 Hz), 7.80 (1H, d, *J* = 10.7 Hz); ^{13}C NMR (125.7 MHz) δ_C 18.3 (CH_3), 19.5 (CH_3), 21.1 (CH_3), 23.1 (CH_3), 23.2 (CH_3), 23.5 (CH_3), 25.2 (CH), 28.7 (CH), 35.6 (CH_2), 39.0 (CH_2), 47.4 (C), 51.9 (CH), 52.6 (CH_3), 57.4 (CH), 62.5 (CH), 98.9 (C), 126.1 (CH), 128.3 (2 × CH), 128.7 (2 × CH), 129.1 (2 × CH), 132.7 (C), 137.6 (2 × CH), 138.9 (C), 167.2 (C), 172.1 (C), 175.3 (C), 176.5 (C); MS *m*/*z* (rel intensity) 664 (M^+ + H, <1), 519 (M^+ − $NHCH(CH_2CHMe_2)CO_2Me$, 4), 449 (M^+ − $C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 3), 330 ($M^+$ − $NHCH(CH_2Ph)$ − $C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 11), 302 ($M^+$ − $CONHCH(CH_2Ph)$ − $C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 17), 243 ($M^+$ − HOMe − $CHMe_2$ − NHCOCH($CHMe_2$)NH-Bz-*p*-I, 100); HRMS calcd for $C_{31}H_{43}IN_3O_5$, 664.2247; found, 664.2260; calcd for $C_{15}H_{17}NO_2$, 243.1259; found, 243.1249. Anal. Calcd for $C_{31}H_{42}IN_3O_5$: C, 56.11; H, 6.38; N, 6.33. Found: C, 56.42; H, 6.60; N, 6.07. **X-ray Analysis**: $C_{31}H_{42}IN_3O_5$, M_r = 663.58, colorless prism crystal (0.42 × 0.23 × 0.22 mm^3) from EtOAc/*n*-pentane (mp 131−132 °C); trigonal, space group *R*3 (no. 146), *a* = *b* = 44.8052(13) Å, *c* = 8.8254(4) Å, γ = 120°, *V* = 15343.4(9) $Å^3$, *Z* = 18, ρ_{calcd} = 1.293 g cm^{-3}, *F*(000) = 6156, μ = 0.978 mm^{-1}; 91 627 measured reflections, of which 13 671 were unique (R_{int} = 0.0921); 783 refined parameters, final R_1 = 0.0442, for reflections with $I > 2\sigma(I)$, wR_2 = 0.1238 (all data), GOF = 1.028. Flack parameter = −0.033(13). The max/min residual electron density: +0.645/−0.750 e·$Å^{-3}$.

***N*-(Benzyloxycarbonyl)-L-prolyl-[α,α-dimethyl-L-β-homophenylalanyl]-L-leucine Methyl Ester (110) and *N*-(Benzyloxycarbonyl)-L-prolyl-[α,α-dimethyl-D-β-homophenylalanyl]-L-leucine Methyl Ester (111).** They were synthesized from a mixture of dipeptides **91/92** following the previous coupling procedure. The residue was purified by rotatory chromatography (hexanes/EtOAc, 75:25 and 3:2), affording compounds **110** (42%) and **111** (24%).

Compound 110: Syrup; $[\alpha]_D$ +14 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3448, 3415, 3090, 3067, 1739, 1696, 1684, 1664 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ_H 0.96 (3H, d, *J* = 6.2 Hz), 0.97 (3H, d, *J* = 6.3 Hz), 1.20 (3H, s), 1.30 (3H, s), 1.37 (1H, m), 1.55−1.75 (4H, m), 1.77−1.85 (2H, m), 2.52 (1H, dd, *J* = 11.4, 14.2 Hz), 3.00 (1H, dd, *J* = 4.1, 14.2 Hz), 3.26 (1H, ddd, *J* = 3.5, 9.3, 9.3 Hz), 3.37 (1H, ddd, *J* = 8.2, 8.5, 9.8 Hz), 3.75 (3H, s), 4.23 (1H, dd, *J* = 5.7, 5.7 Hz), 4.34 (1H, ddd, *J* = 4.1, 10.1, 11.0 Hz), 4.59 (1H, ddd, *J* = 5.4, 7.9, 8.5 Hz), 5.10 (1H, d, *J* = 12.3 Hz), 5.20 (1H, d, *J* = 12.6 Hz), 6.15 (1H, br b), 7.08 (1H, br b), 7.12 (1H, m), 7.13 (2H, d, *J* = 7.3 Hz), 7.18 (2H, dd, *J* = 6.3, 8.2 Hz), 7.29 (1H, dd, *J* = 6.9, 7.0 Hz), 7.30−7.40 (4H, m); ^{13}C NMR (125.7 MHz) δ_C 22.1 (CH_3), 22.8 (CH_3), 23.4 (CH_3), 23.5 (CH_3), 23.7 (CH_2), 25.3 (CH), 29.2 (CH_2), 37.2 (CH_2), 41.4 (CH_2), 46.5 (C), 47.1 (CH_2), 51.2 (CH), 52.1 (CH_3), 56.7 (CH), 61.1 (CH), 67.4 (CH_2), 126.2 (CH), 128.1 (2 × CH), 128.15 (CH), 128.2 (2 × CH), 128.5 (2 × CH), 129.2 (2 × CH), 136.7 (C), 138.9 (C), 155.8 (C), 171.4 (C), 173.4 (C), 176.3 (C); MS *m*/*z* (rel intensity) 566 (M^+ + H, 3), 474 (M^+ − CH_2Ph, 10), 303 (M^+ + H − CH_2Ph − $CONHCH(CH_2CHMe_2)CO_2Me$, 19), 215 ($C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$ + H, 28), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{32}H_{44}N_3O_6$, 566.3230; found, 566.3239; calcd for C_7H_7, 91.0548; found, 91.0544. Anal. Calcd for $C_{32}H_{43}N_3O_6$: C, 67.94; H, 7.66; N, 7.43. Found: C, 68.19; H, 7.76; N, 7.14. **Compound 111**: Syrup; $[\alpha]_D$ +65 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) ν 3364, 3090, 3067, 1726, 1685, 1657, 1552 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.94 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.3 Hz), 1.25 (3H, s), 1.35 (3H, s), 1.55 (1H, m), 1.61 (1H, ddd, *J* = 4.1, 9.4, 13.5 Hz), 1.68−1.91 (4H, m), 2.08 (1H, m), 2.44 (1H, dd, *J* = 12.3, 14.2 Hz), 3.10 (1H, dd, *J* = 3.5, 14.5 Hz), 3.40 (1H, ddd, *J* = 6.8, 7.0, 10.4 Hz), 3.54 (1H, ddd, *J* = 5.1, 7.3, 10.4 Hz), 3.80 (3H, s), 3.88 (1H, dd, *J* = 4.8, 7.3 Hz), 4.09 (1H, ddd, *J* = 3.5, 11.5, 12.0 Hz), 4.63 (1H, ddd, *J* = 3.8, 8.2, 11.7 Hz), 5.05 (1H, d, *J* = 12.6 Hz), 5.08 (1H, d, *J* = 12.6 Hz), 7.13−7.17 (3H, m), 7.24 (2H, dd, *J* = 7.6, 7.6 Hz), 7.27−7.34 (5H, m), 7.38 (1H, d, *J* = 8.2 Hz), 7.55 (1H, d, *J* = 10.4 Hz); ^{13}C NMR (100.6 MHz) δ_C 21.1 (CH_3), 22.8 (CH_3), 23.2 (CH_3), 23.8 (CH_3), 24.8 (CH_2), 25.2 (CH), 29.2 (CH_2), 35.6 (CH_2), 39.0 (CH_2), 46.9 (CH_2), 47.3 (C), 51.9 (CH), 52.6 (CH_3), 56.9 (CH), 61.1 (CH), 66.8 (CH_2), 125.8 (CH), 127.5 (2 × CH), 127.9 (CH), 128.0 (2 × CH), 128.4 (2 × CH), 129.0 (2 × CH), 136.5 (C), 139.2 (C), 154.8 (C), 172.0 (C), 175.6 (C), 176.6 (C); MS *m*/*z* (rel intensity) 566 (M^+ + H, 7), 474 (M^+ − CH_2Ph, 16), 303 (M^+ + H − CH_2Ph − $CONHCH(CH_2CHMe_2)CO_2Me$, 41), 215 ($C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$ + H, 53), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{32}H_{44}N_3O_6$, 566.3230; found, 566.3215; calcd for C_7H_7, 91.0548; found, 91.0547. Anal. Calcd for $C_{32}H_{43}N_3O_6$: C, 67.94; H, 7.66; N, 7.43. Found: C, 67.92; H, 7.72; N, 7.29.

***N*-(*p*-Iodobenzoyl)-L-prolyl-[α,α-dimethyl-L-β-homophenylalanyl]-L-leucine Methyl Ester (112).** To a solution of tripeptide **110** (98 mg, 0.17 mmol) in a biphasic mixture (2:1 THF/H_2O, 15 mL) was added Pd (10% on carbon, 50 mg), and the reaction was stirred at room temperature and under hydrogen atmosphere (1 atm) for 16 h. Then the mixture was filtered through Celite, and the filtrate was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$ (6 mL) and 4-iodobenzoyl chloride (69 mg, 0.26 mmol). The mixture was allowed to reach rt and stirred for 16 h, then it was poured into 5% aqueous HCl and extracted with EtOAc. After usual drying and purification by rotatory chromatography (hexanes/EtOAc, 3:2), product **112** was isolated (71 mg, 62%) as a crystalline solid: mp 169−170 °C (from EtOAc/*n*-pentane); $[\alpha]_D$ +80 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3447, 3362, 1739, 1659, 1504 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ_H 0.86 (3H, d, *J* = 6.2 Hz), 0.91 (3H, d, *J* = 6.3 Hz), 1.26 (3H, s), 1.34 (3H, s), 1.50−1.65 (5H, m), 1.80 (1H, m), 1.94 (1H, m), 2.66 (1H, dd, *J* = 11.5, 13.6 Hz), 3.02 (1H, dd, *J* = 4.5, 13.9 Hz), 3.28−3.36 (2H, m), 3.74 (3H, s), 4.29 (1H, ddd, *J* = 4.1, 9.8, 10.7 Hz), 4.47 (1H, ddd, *J* = 6.9, 7.2, 7.9 Hz), 4.57 (1H, m), 6.18 (1H, d, *J* = 7.9 Hz), 7.13 (1H, m), 7.18−7.21 (4H, m), 7.26 (2H, d, *J* = 8.2 Hz), 7.44 (1H, brb), 7.74 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 21.7 (CH_3), 22.7 (CH_3), 23.1 (CH_3), 24.6 (CH_3), 25.0 (CH + CH_2), 28.6 (CH_2), 36.5 (CH_2), 40.7 (CH_2), 46.2 (C), 50.3 (CH_2), 51.0 (CH), 52.3 (CH_3), 56.9 (CH), 60.8 (CH), 96.5 (C), 126.1 (CH), 128.1 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 135.7 (C), 137.4 (2 × CH), 138.9 (C), 170.0 (C), 170.8 (C), 173.7 (C), 176.9 (C); MS *m*/*z* (rel intensity) 661 (M^+, 1), 570 (M^+ − CH_2Ph, 6), 328 (M^+ − $NHCH(CH_2Ph)C(Me)_2$ − $CONHCH(CH_2CHMe_2)CO_2Me$, 99), 300 (M^+ − $CONHCH(CH_2Ph)C(Me)_2CO$ − $NHCH(CH_2CHMe_2)CO_2Me$, 57), 231 ($[p$-I-PhCO$]^+$, 100); HRMS calcd for $C_{31}H_{40}IN_3O_5$, 661.2013; found, 661.2015; calcd for C_7H_4IO, 230.9307; found, 230.9308. Anal. Calcd for $C_{31}H_{40}IN_3O_5$: C, 56.28; H, 6.09; N, 6.35. Found: C, 56.63; H, 6.43; N, 6.01. **X-ray Analysis**: $C_{31}H_{40}IN_3O_5$, M_r = 661.56, colorless needle crystal (0.15 × 0.11 × 0.10 mm^3) from EtOAc/*n*-pentane (mp 169−170 °C); orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.1613(3) Å, *b* = 15.2508(7) Å, *c* = 32.8063(17) Å, *V* = 3082.6(3) $Å^3$, *Z* = 4, ρ_{calcd} = 1.425 g cm^{-3}, *F*(000) = 1360, μ = 1.081 mm^{-1}; 35 963 measured reflections, of which 9373 were unique (R_{int} = 0.0737); 372 refined parameters, final R_1 = 0.0472, for reflections with $I > 2\sigma(I)$, wR_2 = 0.0945 (all data), GOF = 0.984. Flack parameter = 0.005(17). The max/min residual electron density: +1.126/−1.692 e·$Å^{-3}$.

***N*-(*p*-Iodobenzoyl)-L-prolyl-[α,α-dimethyl-D-*β*-homophenylalanyl]-L-leucine Methyl Ester (113).** A solution of tripeptide **111** (40 mg, 0.07 mmol) underwent hydrogenolysis of the Cbz group, followed by acylation with 4-iodobenzoyl chloride, as in the previous case. After purification by rotatory chromatography (hexanes/EtOAc, 85:15), product **113** was isolated (31 mg, 67%) as a crystalline solid: mp 162−163 °C (from EtOAc/*n*-pentane); $[\alpha]_D$ +19 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3354, 3089, 3065, 1725, 1683, 1655, 1620, 1558, 1425 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.90 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.7 Hz), 1.29 (3H, s), 1.36 (3H, s), 1.55−1.65 (2H, m), 1.71 (1H, m), 1.78−1.85 (2H, m), 1.92 (1H, ddd, J = 4.8, 11.4, 13.3 Hz), 2.01 (1H, m), 2.47 (1H, dd, J = 12.3, 14.2 Hz), 3.12 (1H, dd, J = 3.8, 14.2 Hz), 3.43 (1H, ddd, J = 4.4, 6.9, 10.5 Hz), 3.62 (1H, ddd, J = 6.6, 6.9, 10.4 Hz), 3.83 (3H, s), 4.09−4.16 (2H, m), 4.61 (1H, ddd, J = 4.1, 7.9, 11.4 Hz), 7.16 (1H, dd, J = 7.3, 8.5 Hz), 7.18 (2H, d, J = 7.3 Hz), 7.26 (2H, dd, J = 6.6, 7.9 Hz), 7.27 (2H, d, J = 8.5 Hz), 7.59 (1H, d, J = 7.9 Hz), 7.68 (1H, d, J = 10.4 Hz), 7.73 (2H, d, J = 8.2 Hz); ^{13}C NMR (125.7 MHz) δ_C 21.2 (CH_3), 22.8 (CH_3), 23.1 (CH_3), 24.0 (CH_3), 25.1 (CH), 25.7 (CH_2), 28.8 (CH_2), 35.6 (CH_2), 39.1 (CH_2), 47.3 (C), 50.6 (CH_2), 52.1 (CH), 52.6 (CH_3), 57.0 (CH), 61.7 (CH), 96.7 (C), 125.9 (CH), 128.1 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 135.5 (C), 137.3 (2 × CH), 139.3 (C), 168.3 (C), 171.6 (C), 175.8 (C), 176.8 (C); MS *m*/*z* (rel intensity) 661 (M^+, 1), 570 ($M^+ - CH_2Ph$, 2), 328 ($M^+ - NHCH(CH_2Ph)C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 44), 300 ($M^+ - CONHCH(CH_2Ph)C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 35), 231 ([*p*-I-PhCO]$^+$, 100); HRMS calcd for $C_{31}H_{40}IN_3O_5$, 661.2013; found, 661.1989; calcd for C_7H_4IO, 230.9307; found, 230.9314. Anal. Calcd for $C_{31}H_{40}IN_3O_5$: C, 56.28; H, 6.09; N, 6.35. Found: C, 56.60; H, 6.28; N, 5.95. **X-ray Analysis**: $C_{31}H_{40}IN_3O_5$, M_r = 661.56, colorless block crystal (0.41 × 0.35 × 0.24 mm^3) from EtOAc/*n*-pentane (mp 162−163 °C); triclinic, space group *P*1 (no. 1), a = 9.8375(13) Å, b = 10.8487(14) Å, c = 14.9223(18) Å, α = 95.264(4)°, β = 90.527(4)°, γ = 91.967(4)°, V = 1584.8(3) $Å^3$, Z = 2, ρ_{calcd} = 1.386 g cm^{-3}, $F(000)$ = 680, μ = 1.052 mm^{-1}; 42 926 measured reflections, of which 14 751 were unique (R_{int} = 0.0447); 743 refined parameters, final R_1 = 0.0589, for reflections with $I > 2\sigma(I)$, wR_2 = 0.1712 (all data), GOF = 1.060. Flack parameter = 0.02(2). The max/min residual electron density: +3.953/−2.157 e·$Å^{-3}$.

Acknowledgment. This work was supported by the Investigation Programmes CTQ2006-14260/PPQ and PPQ2003-01379 of the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Ministerio de Educación y Ciencia and Ministerio de Ciencia y Tecnología, Spain. We also acknowledge financial support from FEDER funds. C.J.S. thanks the CSIC for an I3P contract, and the Gobierno de Canarias-BIOSIGMA SL for a research contract.

Supporting Information Available: Experimental procedures to prepare substrates **37**, **50**−**53**, **58**−**64**, **66**, and **67**, and characterization of these compounds. Preparation and spectroscopic data of the scission−Mannich products **21**−**34**, **39**−**49**, **54**−**57**, and **69**−**92**. Synthesis and spectroscopic data of acids **93**−**95** and dipeptides **96**−**103**. X-ray analysis of compounds **71**, **78**, **81**, **83**, **90**, **96**, **98**−**101**, and **103**. ^1H and ^{13}C NMR spectra of the new compounds (**21**−**34**, **37**, **39**−**64**, **66**, **67**, **69**−**113**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO9004487