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PAPER

Preparation of modified peptides: direct conversion of α-amino acids into β-amino aldehydes†‡

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A direct method for the transformation of α-amino acids into β-amino aldehydes was developed, and applied to the modification of the C-terminal residue of peptides. The method takes place in good yields and under mild conditions. The application of this methodology to the preparation of small peptides with γ-amino alcohol units, which are precursors of analogues of peptaibol antibiotics, is also described.

Introduction

The replacement of amino acid residues in peptides by amino aldehyde units has provided several peptide analogues with remarkable biological activities.[1] Some derivatives presenting an α-amino aldehyde unit are potent inhibitors of proteases, such as papain, thrombin, trypsin, calpain, caspases and viral proteases. Their applications range from antiviral drugs to antithrombotic, anticataract or antitumoral agents.[2]

On the other hand, there are few examples of peptide derivatives with β-amino aldehyde units.[3] In most cases, an amino glyoxal residue[4] is introduced, as occurs with the caspase-3 inhibitor **1**[5a] (Fig. 1) and the collagen-degradation inhibitor **2**.[5b]

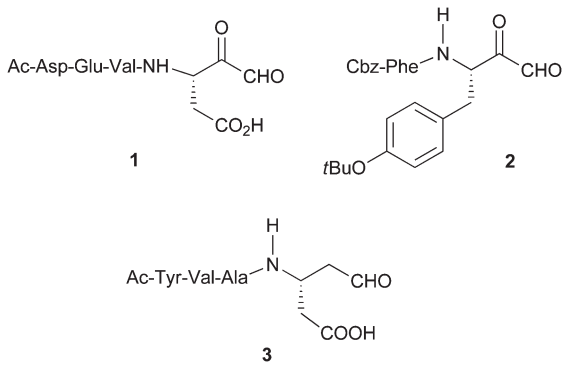
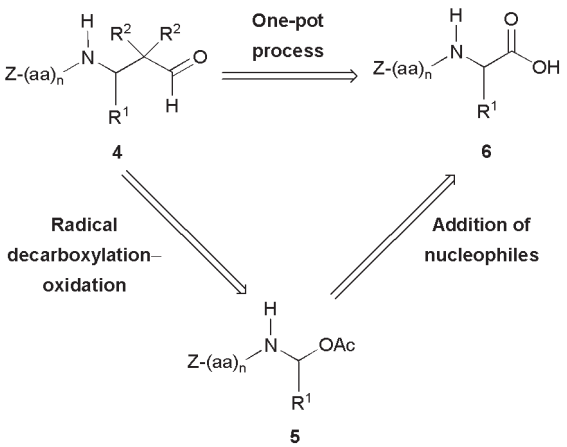


Fig. 1 Bioactive peptides with β-amino aldehyde units.

Some bioactive peptides also present α-unsubstituted β-amino aldehyde units,[6] such as product **3**, a potent inhibitor of interleukin 1-β converting enzyme, used as a drug lead for the treatment of inflammatory diseases.[6a]

The development of new derivatives, especially those with α-substituted β-amino aldehyde residues, could be useful to discover new drug leads. We reasoned that a peptide aldehyde **4** (Scheme 1) could be formed by addition of carbon nucleophiles (such as vinyl ethers or silylenol ethers) to the *N*,*O*-acetals **5**.[7] These acetals, in turn, could be generated by radical decarboxylation–oxidation of α-peptides such as substrate **6**.[8] The direct formation of peptide aldehydes **4** from α-peptides **6** would be particularly interesting. With the one-pot process, a single α-peptide **6** could be transformed into a variety of peptide aldehydes with different substituents, allowing the generation of libraries of derivatives **4** to study structure–activity relationships.

In previous work from our group,[8] the oxidative decarboxylation of α-amino acids followed by addition of different carbon nucleophiles had proven useful to obtain unnatural amino acids,



Scheme 1 Formation of peptide aldehydes from α-peptides.

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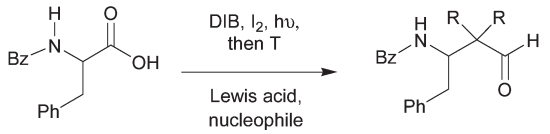
† Dedicated to Prof. Gerry Pattenden.

‡ Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of the amino acids **8**, **14**, **16**, **18**, **19**, **21**, **24**, and **26–29**, the peptide aldehydes **38–48** and the amino alcohol derivatives **52–57**. See DOI: 10.1039/c2ob25433f.

Table 1 One-pot oxidative radical decarboxylation–alkylation



7 **8** R= Me **9** R= H

Entry	DIB/I_2 (equiv)	Nucleophile/Lewis acid (equiv)[a]	T (°C)	Products (%)[b]
1	2.0/1.0	A (5)/$BF_3{\cdot}OEt_2$ (2)	0	**8** (38)
2	1.5/0.5	A (3)/$BF_3{\cdot}OEt_2$ (2)	0	**8** (53)
3	1.5/0.3	A (3)/$BF_3{\cdot}OEt_2$ (2)	0	**8** (61)
4	1.5/0.3	A (3)/TMSOTf (2)	0	**8** (58)
5	1.5/0.3	A (3)/$SnCl_4$ (2)	−78	**8** (51)
6	1.5/0.3	A (3)/$TiCl_4$ (2)	−78	**8** (25)
7	1.5/0.3	B (3)/$BF_3{\cdot}OEt_2$ (2)	0	**9** (41)
8	1.5/0.3	B (3)/TMSOTf (2)	0	**9** (40)
9	1.5/0.3	C (3)/$BF_3{\cdot}OEt_2$ (2)	0	**9** (60)

[a] A = (TMSO)–CH=C(Me)$_2$; B = (TMSO)CH=CH$_2$; C = (EtO)-CH=CH$_2$. [b] Yield for products purified by chromatography.

alkaloid precursors and α,β-peptide hybrids. In the current article, a variation of this methodology is described, to allow the direct conversion of α-amino acids or α-peptides into β-amino aldehydes or peptide β-aldehydes, under mild conditions and good overall yields.

Results and discussion

The initial studies on the one-pot decarboxylation–alkylation process were carried out with the DL-phenyl alanine derivative **7** (Table 1),[8e] which was treated with (diacetoxyiodo)benzene (DIB) and iodine under irradiation with visible light, to induce the oxidative decarboxylation.[8] The scission generated an *N*,*O*-acetal intermediate, which was not isolated, but treated with a Lewis acid and a nucleophile (entries 1–9). When 1-(trimethylsilyloxy)-2-methyl-1-propene was used as the nucleophile, the β-aminoaldehyde **8** was formed, while the use of 1-(trimethylsilyloxy)-1-ethene or ethyl vinyl ether as nucleophiles provided the β-amino aldehyde **9**.[9]

The amount of the scission reagents was important to obtain satisfactory yields (entries 1–3). The best result was obtained with a substrate/DIB/I_2 ratio of 1/1.5/0.3 (entry 3). Different Lewis acids were also tried (entries 3–6 and 7–8); boron trifluoride and TMSOTf provided the best yields. The nucleophiles B [1-(*tert*-butyldimethylsilyloxy)-1-ethene] and C [1-ethoxy-1-ethene] were then compared (entries 7 and 9), and the vinyl ether C proved superior to the silyl enol ether B, probably due to increased reagent stability.

The best conditions for each nucleophile were then used with other amino acids, such as DL-substrates **10–13**[8e,10] (Table 2), to afford the β-amino aldehyde derivatives **14–21**.[11]

Interestingly, the oxidative decarboxylation–alkylation of the ornithine derivative **13** (Table 2, entry 10) afforded the proline analogue **21**, probably due to intramolecular cyclization of the intermediate *N*,*O*-acetal to give the *N*,*N*-acetal **20**,[12] which then reacted with the Lewis acid to give a five-membered acyliminium ion, followed by the addition of the nucleophile.

Table 2 One-pot oxidative radical decarboxylation–alkylation[a]

Entry	Substrate	Nu (equiv)[b]	Products[c] (%)
1	Bz-Ala-OH **10**	A (3)	**14** R = Me (69)
2		B (3)	**15** R = H (45)
3		C (3)	**15** R = H (79)
4	Bz-Leu-OH **11**	A (3)	**16** R = Me (60)
5		B (3)	**17** R = H (55)
6		C (3)	**17** R = H (56)
7	Bz-Glu(OEt)-OH **12**	A (3)	**18** R = Me (66)
8		B (3)	**19** R = H (51)
9		C (3)	**19** R = H (45)
10	**13**	A (3)	**20** → **21** (83) **20** X = $NHCO_2Me$ **21** X = $C(Me)_2$-CHO

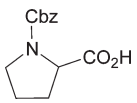
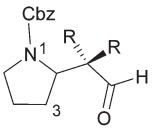
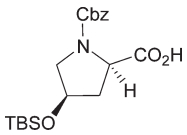
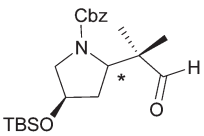
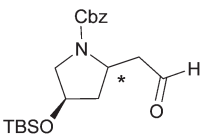
[a] DIB, I_2, *hν*, then 0 °C, nucleophile, Lewis acid. [b] A = (TMSO)–CH=C(Me)$_2$; B = (TMSO)CH=CH$_2$; C = (EtO)CH=CH$_2$; $BF_3{\cdot}OEt_2$ was used as the Lewis acid. [c] Yield for products purified by chromatography.

Similar products were obtained when the DL-proline and hydroxy L-proline derivatives **22**[13] (Table 3, entries 1–3) and **23**[14] (entries 4–6) underwent the decarboxylation–alkylation reaction. In the case of the proline derivative **22**, the process took place in 82–86% yields, affording products **24** (R = Me) or **25** (R = H).[15a–d] When hydroxyproline substrate **23** was used, the process afforded compounds **26–27** (R = Me) and **28–29** (R = H).[15e] Remarkably, the 2,4-*cis* products predominated over the 2,4-*trans* isomers, due to an stereoelectronic effect described by Woerpel and coworkers.[16]

The one-pot process was then tried with peptides, using compounds **30–36**[17] (Scheme 2) as substrates. Interestingly, with peptides TMSOTf proved superior to boron trifluoride as the Lewis acid (conversions **30** → **37** and **31** → **38**).

In the case of substrates **30** and **31**, whose N-terminal residue was an α,α-disubstituted amino acid, the process afforded a racemic mixture of the peptide aldehydes **37** and **38**, respectively. In the case of substrates **32–36**, the reacting residue was attached to a chiral amino acid, so the process was stereoselective (dr from 3 : 2 to 3 : 1), affording compounds **39–46** in good overall yields.

Table 3 One-pot oxidative radical decarboxylation–alkylation[a]

Entry	Substrate	Nu (equiv)[b]	Products[c] (%)
			
1	**22**	A (3)	**24** R = Me (86)
2		B (3)	**25** R = H (82)
3		C (3)	**25** R = H (85)
			
4	**23**	A (3)	**26** (2*R*) (63) **27** (2*S*) (19)
			
5	**23**	B (3)	**28** (2*R*) (34) **29** (2*S*) (20)
6	**23**	C (3)	**28** (2*R*) (27) **29** (2*S*) (13)

[a] DIB, I_2, *hν*, then 0 °C, nucleophile, Lewis acid. [b] A = (TMSO)–CH=C(Me)$_2$; B = (TMSO)CH=CH$_2$; C = (EtO)CH=CH$_2$. [c] Yield for products purified by chromatography.

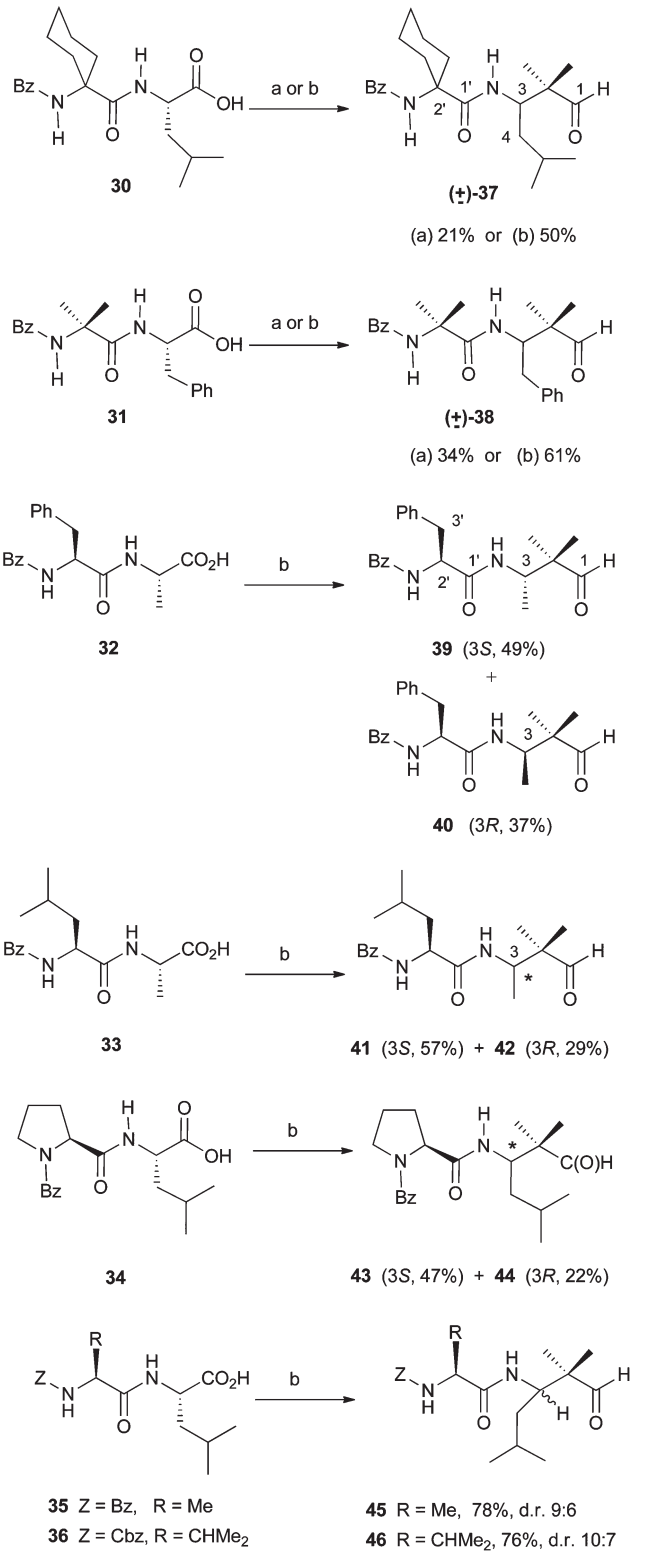
Their stereochemistry was unambiguously determined by correlation to known compounds, as will be commented later.

The aldehydes are not only potential drug candidates, but also useful precursors of other compounds, such as diamines, amino alcohols, *etc.* Especially interesting are the amino alcohol derivatives (Scheme 3) which are precursors of analogues of the peptaibol antibiotics.[18] The peptaibols present a short peptidic chain with a C-terminal β-amino alcohol unit. The presence of non-proteinogenic amino acids (in particular Aib, α-amino isobutyric acid) is key for their potent activity against bacteria and fungi. These antibiotics present interesting folding patterns which can allow the creation of holes in the bacterial membrane.

Our scission–alkylation methodology, followed by mild reduction of the aldehydes, would allow the preparation of precursors of peptaibol analogues, such as compounds **47–56** (Scheme 3). These precursors present unusual C-terminal β,β-dimethyl γ-amino alcohol units (instead of the peptaibol β-amino alcohol units), and with their β,β-substitution they also resemble an Aib-derived amino alcohol. This new terminal residue could modify the conformational and biological properties of the derivatives, and thus be useful to understand SAR relationships.

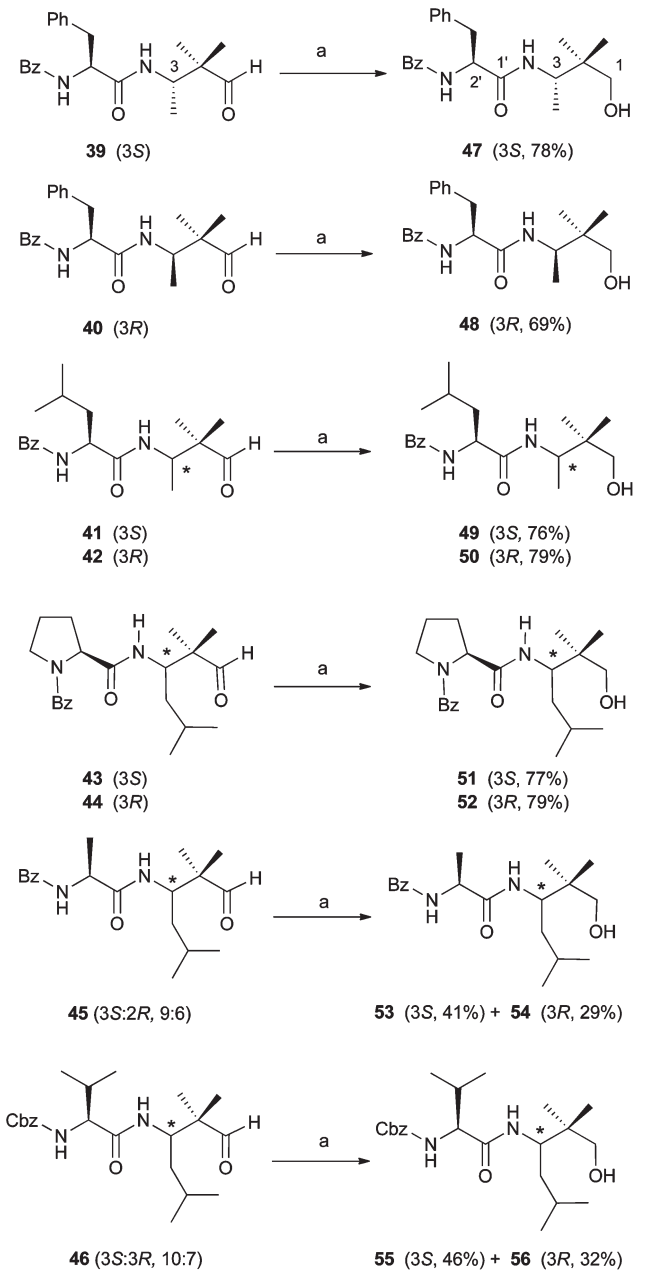
The reduction of peptide aldehydes **39–46** was tried under different conditions (DIBAL-H, $NaBH_4$, or $LiBH_4$ in different solvents), and the best results were obtained with $LiBH_4$ in ^{i}PrOH, affording the amino alcohols in good yields (69–79%).

To our satisfaction, in the case of aldehyde mixtures, such as compounds **45** and **46**, the reduction allowed the separation of the diastereomeric products.

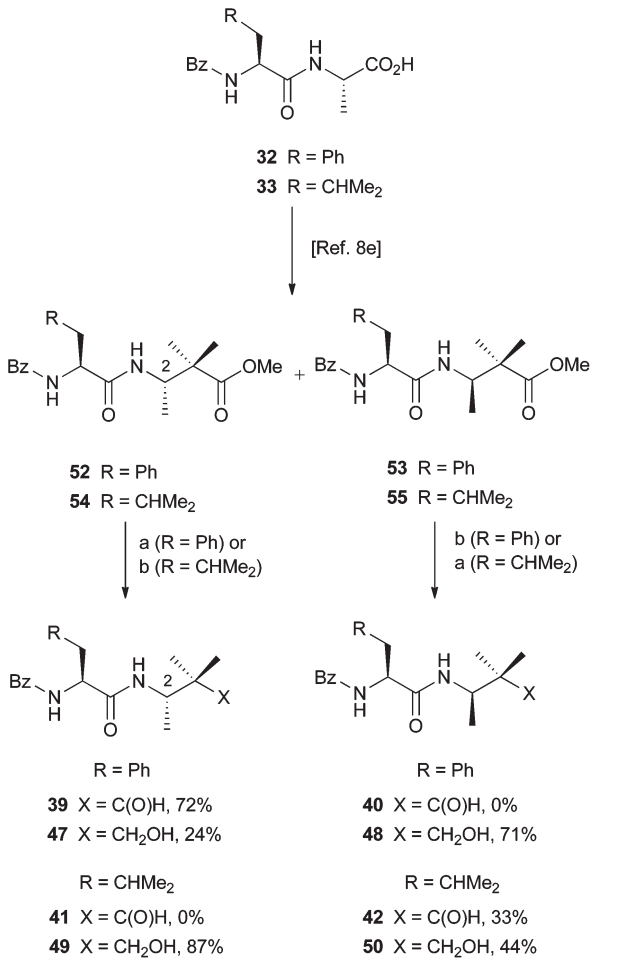


Scheme 2 Conversion of α-dipeptides into derivatives with a C-terminal β-amino aldehyde. Reaction conditions: [a] DIB, I_2, *hν*, then 0 °C, $BF_3{\cdot}OEt_2$, (TMSO)CH=C(Me)$_2$; [b] DIB, I_2, *hν*, then 0 °C, TMSOTf, (TMSO)CH=C(Me)$_2$.

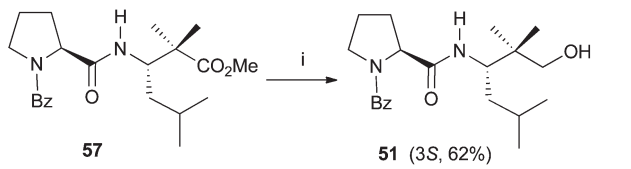
The stereochemistry of the amino aldehydes and the amino alcohols was determined by correlation to known compounds



Scheme 3 Conversion of dipeptides with a β-amino aldehyde unit into alcohol derivatives. Reaction conditions: [a] $LiBH_4$, ^iPrOH.



Scheme 4 Determination of the stereochemistry of the aldehydes by correlation to known compounds. Reaction conditions: [a] DIBAL-H, CH_2Cl_2, −78 °C; [b] DIBAL-H, CH_2Cl_2, 0 °C.



Scheme 5 Determination of the stereochemistry of the aldehydes by correlation to known compounds. Reaction conditions: [i] DIBAL-H, CH_2Cl_2, 0 °C.

(Scheme 4).[8e] Thus, the acids **32** and **33** were transformed into the known β-amino esters **52–53** and **54–55**, respectively, using a sequential scission–alkylation process.[8e]

The known esters **52–55** were then reduced with DIBAL-H to give the corresponding aldehydes **39–42** or the amino alcohols **47–50**,[19] confirming the assigned stereochemistries. In a similar way, the amino ester **57**[8e] (Scheme 5) was reduced to give the γ-amino alcohol derivative **51**. In all the cases, the major isomer presented the "natural" (3*S*) configuration.

The formation of peptaibol analogues from these simpler precursors is under way, and together with their conformational properties, will be reported in due course.

Conclusions

An efficient and mild one-pot process for the conversion of α-amino acid derivatives into β-amino aldehydes has been developed, and applied to the *selective modification* of the C-terminal residue in small peptides, giving peptide aldehydes in good overall yields. With this procedure, a single α-peptide could be transformed into a library of α,β-peptidyl aldehydes with different α-substituents. The aldehydes are useful precursors of other compounds, as illustrated by transformation of several peptide aldehydes into precursors of peptaibol analogues, which present γ-hydroxyamino units.

Experimental section

General remarks

Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use.[20] All reactions involving air- or moisture-sensitive materials were carried out under nitrogen atmosphere. Three alternative spray reagents for TLC analysis were used: (a) 0.5% vanillin in H_2SO_4–EtOH (4 : 1); (b) 0.25% ninhydrin in ethanol; and (c) Fleet's reagent [$Ce(SO_4)_2$ (0.5 g) and ammonium phosphomolybdate hydrate (2.5 g) in H_2SO_4 (5 mL) and water (65 mL)]. Once sprayed, the TLC was heated until development of color. Merck silica gel 60 PF_{254} and 60 (0.063–0.2 mm) were used for rotatory chromatography and column chromatography, respectively. Melting points were determined with a hot-stage apparatus and are uncorrected; the term "net" is used for crystals resulting from evaporation of the chromatography eluents. Optical rotations were measured at the sodium line at ambient temperature (26 °C). NMR spectra were determined at 500 or 400 MHz for ^1H and 125.7 or 100.6 MHz for ^{13}C in $CDCl_3$ as solvent and at 25 °C (δ_H 7.26; δ_C 77.0), unless otherwise stated.

Amino aldehyde derivatives **9**, **15**, **17**, and **25** are known but some are partially described; for comparison purposes their spectroscopic and physical data are also included.

General procedures for the scission–oxidation–alkylation sequence

Method A. To a solution of the starting amino acid or peptide (0.2 mmol) in dry dichloromethane (8 mL) were added iodine (15 mg, 0.06 mmol, 0.3 equiv) and (diacetoxyiodo)benzene (DIB) (97 mg, 0.3 mmol, 1.5 equiv). The reaction mixture was stirred at 25–26 °C for 4 h, under irradiation with visible light. Then the solution was cooled to 0 °C, and 2-methyl-1-(trimethylsilyloxy)-1-propene (110 μL, 86 mg, 0.6 mmol, 3 equiv) or vinyloxytrimethylsilane (89 μL, 70 mg, 0.6 mmol, 3 equiv) or ethyl vinyl ether (86 μL, 65 mg, 0.6 mmol, 3.0 equiv) was injected, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (51 μL, 57 mg, 0.4 mmol, 2 equiv). 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 over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes–EtOAc) to give the products.

Method B. As in Method A but using trimethylsilyl triflate (TMSOTf) (72 μL, 89 mg, 0.4 mmol, 2 equiv) as the Lewis acid.

***N*-Benzoyl-α,α-dimethyl-DL-β-homophenylalaninal (8).** Obtained from *N*-benzoyl-DL-phenylalanine (**7**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 90 : 10), giving the aldehyde (±)-**8** (61%) as a crystalline solid; Mp 133–134 °C (EtOAc–*n*-hexane); ν_{max}/cm^{-1} 3439, 3083, 3067, 1724, 1660; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, s, 2-Me_a), 1.31 (3H, s, 2-Me_b), 2.75 (1H, dd, J = 11.2, 14.6 Hz, 4-H_a), 3.10 (1H, dd, J = 4.1, 14.2 Hz, 4-H_b), 4.69 (1H, ddd, J = 4.1, 10.2, 10.8 Hz, 3-H), 6.38 (1H, d, J = 9.8 Hz, NH), 7.18 (1H, dd, J = 6.8, 6.8 Hz, Ar), 7.23–7.28 (4H, m, Ar), 7.36 (2H, dd, J = 7.5, 7.8 Hz, Ar), 7.45 (1H, dd, J = 7.1, 7.8 Hz, Ar), 7.52 (2H, d, J = 7.1 Hz, Ar), 9.59 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 19.5 (CH_3), 20.1 (CH_3), 36.7 (CH_2), 50.5 (C), 54.7 (CH), 126.7 (3 × CH), 128.5 (4 × CH), 128.9 (2 × CH), 131.3 (CH), 134.6 (C), 137.8 (C), 167.4 (C), 205.3 (CH); *m/z* 295 (M^+, <1%), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1580; calcd for C_7H_5O 105.0340, found 105.0343. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74%. Found: C, 77.18; H, 7.43; N, 4.74.

***N*-Benzoyl-DL-β-homophenylalaninal (9).**[9] *N*-Benzoyl-DL-phenylalanine (**7**) was treated as in Method A, using ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 60 : 40), giving the aldehyde (±)-**9** (60%) as a syrup; ν_{max}/cm^{-1} 3437, 3065, 1723, 1657; δ_H (500 MHz, $CDCl_3$) 2.73 (1H, ddd, J = 1.6, 6.0, 17.3 Hz, 2-H_a), 2.77 (1H, ddd, J = 1.3, 5.4, 17.7 Hz, 2-H_b), 2.97 (1H, dd, J = 7.6, 13.6 Hz, 4-H_a), 3.09 (1H, dd, J = 6.9, 13.6 Hz, 4-H_b), 4.76 (1H, m, 3-H), 6.58 (1H, d, J = 8.2 Hz, NH), 7.21–7.25 (3H, m, Ar), 7.32 (2H, dd, J = 7.3, 7.6 Hz, Ar), 7.40 (2H, dd, J = 7.6, 7.6 Hz, Ar), 7.48 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.68 (2H, d, J = 7.6 Hz, Ar), 9.77 (1H, dd, J = 0.6, 0.9 Hz, CHO); δ_C (125.7 MHz, $CDCl_3$) 40.1 (CH_2), 46.7 (CH_2), 46.9 (CH), 126.9 (3 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.2 (2 × CH), 131.6 (CH), 134.3 (C), 137.3 (C), 167.0 (C), 201.2 (CH); *m/z* 268 (M^+ + H, 12%), 176 (69, M^+ − $PhCH_2$), 105 (100, $[PhCO]^+$), 91 (37, $[PhCH_2]^+$), 77 (81, $[Ph]^+$); HRMS calcd for $C_{17}H_{18}NO_2$ 268.1338, found 268.1327; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0708; calcd for C_7H_5O 105.0340, found 105.0341; calcd for C_7H_7 91.0548, found 91.0549; calcd for C_6H_5 77.0391, found 77.0388. $C_{17}H_{17}NO_2$ requires C, 76.38; H, 6.41; N, 5.24%. Found: C, 76.38; H, 6.41; N, 5.03.

***N*-Benzoyl-α,α-dimethyl-DL-β-homoalaninal (14).** Obtained from *N*-benzoyl-DL-alanine (**10**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 70 : 30), giving the aldehyde (±)-**14** (69%) as a syrup; ν_{max}/cm^{-1} 3439, 3081, 1725, 1650, 1519, 1487; δ_H (500 MHz, $CDCl_3$) 1.14 (3H, s, 2-Me_a), 1.18 (3H, s, 2-Me_b), 1.23 (3H, d, J = 6.9 Hz, 3-Me), 4.43 (1H, m, 3-H), 6.58 (1H, d, J = 8.8 Hz, NH), 7.41 (2H, dd, J = 7.3, 7.6 Hz, Ar), 7.48 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.73 (2H, d, J = 6.9 Hz, Ar), 9.54 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 16.3 (CH_3), 18.9 (CH_3), 20.0 (CH_3), 49.4 (CH), 49.9 (C), 126.8 (2 × CH), 128.6 (2 × CH), 131.5 (CH), 134.5 (C), 166.8 (C), 205.9 (CH); *m/z* 220 (M^+ + H, 6%), 219 (M^+, <1%), 148 (32, M^+ − H − Me_2CCHO), 105 (100, $[PhCO]^+$), 77 (36, $[Ph]^+$). HRMS calcd for $C_{13}H_{18}NO_2$ 220.1338, found 220.1333; calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1270; calcd for $C_9H_{10}NO$ 148.0762, found 148.0764; calcd for C_7H_5O 105.0340, found 105.0339; calcd for C_6H_5 77.0391, found 77.0394. $C_{13}H_{17}NO_2$ requires C, 71.21; H, 7.81; N, 6.39%. Found: C, 71.10; H, 8.04; N, 6.51.

***N*-Benzoyl-DL-β-homoalaninal (15).**[11a,b] *N*-Benzoyl DL-alanine (**10**) was treated as in Method A, using ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 50 : 50), giving the aldehyde (±)-**15**

(79%) as an oil; ν_{max}/cm^{-1} 3440, 3063, 1724, 1656, 1517; δ_H (500 MHz, $CDCl_3$) 1.36 (3H, d, J = 6.8 Hz, 3-Me), 2.74 (1H, dd, J = 5.7, 17.3 Hz, 2-H_a), 2.80 (1H, ddd, J = 1.9, 5.7, 17.3 Hz, 2-H_b), 4.61 (1H, m, 3-H), 6.56 (1H, br b, NH), 7.40 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.48 (1H, dd, J = 7.6 Hz, Ar), 7.73 (2H, d, J = 8.2 Hz, Ar), 9.81 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 20.5 (CH_3), 41.6 (CH), 49.6 (CH_2), 126.9 (2 × CH), 128.5 (2 × CH), 131.5 (CH), 134.3 (C), 166.8 (C), 201.1 (CH); m/z 191 (M^+, <1%), 163 (2, $M^+ - CO$), 121 (4, $[PhCONH_2]^+$), 105 (100, $[PhCO]^+$), 77 (75, $[Ph]^+$); HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0941; calcd for $C_{10}H_{13}NO$ 163.0997, found 163.1004; calcd for C_7H_7NO 121.0528, found 121.0524; calcd for C_7H_5O 105.0340, found 105.0344; calcd for C_6H_5 77.0391, found 77.0389. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32%. Found: C, 69.23; H, 7.02; N, 7.43.

***N*-Benzoyl-α,α-dimethyl-DL-β-homoleucinal (16).** Obtained from *N*-benzoyl DL-leucine (**11**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 9 : 1), giving the aldehyde (±)-**16** (60%) as an oil; ν_{max}/cm^{-1} 3440, 3081, 3065, 1725, 1706, 1657, 1519; δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, J = 6.7 Hz, 5-Me_a), 0.95 (3H, d, J = 6.7 Hz, 5-Me_b), 1.13 (3H, s, 2-Me_a), 1.17 (3H, s, 2-Me_b), 1.30 (1H, ddd, J = 2.6, 9.8, 14.4 Hz, 4-H_a), 1.46 (1H, ddd, J = 3.6, 11.4, 14.0 Hz, 4-H_b), 1.64 (1H, m, 5-H), 4.44 (1H, ddd, J = 2.6, 9.8, 11.0 Hz, 3-H), 6.29 (1H, br d, J = 9.3 Hz, NH), 7.42 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.49 (1H, dd, J = 7.2, 7.8 Hz, Ar), 7.74 (2H, d, J = 7.2 Hz, Ar), 9.54 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 19.2 (CH_3), 19.6 (CH_3), 21.4 (CH_3), 23.8 (CH_3), 25.2 (CH), 39.8 (CH_2), 50.5 (C), 51.9 (CH), 126.8 (2 × CH), 128.6 (2 × CH), 131.5 (CH), 134.5 (C), 167.3 (C), 205.8 (CH); m/z 262 (M^+ + H, 3%), 190 (31, $M^+ - H - Me_2CCHO$), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{16}H_{24}NO_2$ 262.1807, found 262.1801; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1223; calcd for C_7H_5O 105.0340, found 105.0344. $C_{16}H_{23}NO_2$ requires C, 73.53; H, 8.87; N, 5.36%. Found: C, 73.43; H, 9.09; N, 5.27.

***N*-Benzoyl-DL-β-homoleucinal (17).**[11c] *N*-Benzoyl DL-leucine (**11**) was treated as in Method A, using ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 70 : 30), giving the aldehyde (±)-**17** (56%) as a oil; ν_{max}/cm^{-1} 3437, 3065, 1704, 1655, 1518, 1486; δ_H (500 MHz, $CDCl_3$) 0.94 (3H, d, J = 6.6 Hz, 5-Me_a), 0.95 (3H, d, J = 6.9 Hz, 5-Me_b), 1.42 (1H, ddd, J = 5.0, 10.1, 15.1 Hz, 4-H_a), 1.67 (1H, m, 4-H_b), 1.68 (1H, m, 5-H), 2.72 (1H, ddd, J = 2.2, 5.9, 17.3 Hz, 2-H_a), 2.78 (1H, br dd, J = 5.5, 17.3 Hz, 2-H_b), 4.61 (1H, m, 3-H), 6.50 (1H, br d, J = 8.8 Hz, NH), 7.40 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.48 (1H, dd, J = 7.6, 7.8 Hz, Ar), 7.73 (2H, d, J = 7.0 Hz, Ar), 9.80 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 22.0 (CH_3), 22.9 (CH_3), 25.2 (CH), 43.7 (CH_2), 44.0 (CH), 48.8 (CH_2), 126.9 (2 × CH), 128.6 (2 × CH), 131.5 (CH), 134.4 (C), 167.0 (C), 201.4 (CH); m/z 234 (M^+ + H, 3%), 233 (M^+, <1%), 190 (3, $M^+ - CH_2CHO$), 105 (100, $[PhCO]^+$), 77 (53, $[Ph]^+$). HRMS calcd for $C_{14}H_{20}NO_2$ 234.1494, found 234.1502; calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1419; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1228; calcd for C_7H_5O 105.0340, found 105.0345; calcd for C_6H_5 77.0391, found 77.0394. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%. Found: C, 72.23; H, 8.24; N, 6.01.

Ethyl 4-benzamido-5,5-dimethyl-6-oxo hexanoate (18). Obtained from Bz-Glu(OEt)-OH (**12**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotary chromatography (hexanes–EtOAc, 85 : 15), giving the aldehyde (±)-**18** (66%) as an oil; ν_{max}/cm^{-1} 3428, 1725, 1658, 1519; δ_H (500 MHz, $CDCl_3$) note: the usual numbering (CHO as C-1) is used, not the one given by IUPAC nomenclature: 1.13 (3H, dd, J = 6.7, 7.0 Hz, Et), 1.15 (3H, s, 2-Me_a), 1.20 (3H, s, 2-Me_b), 1.81 (1H, m, 4-H_a), 1.96 (1H, dddd, J = 3.2, 6.9, 6.9, 13.9 Hz, 4-H_b), 2.30–2.45 (2H, m, 5-H_2), 3.94–4.08 (2H, m, Et), 4.35 (1H, ddd, J = 3.2, 9.8, 12.9 Hz, 3-H), 6.55 (1H, d, J = 9.8 Hz, NH), 7.41 (2H, dd, J = 7.3, 7.6 Hz, Ar), 7.48 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.74 (2H, d, J = 7.5 Hz, Ar), 9.53 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 14.1 (CH_3), 19.1 (CH_3), 19.8 (CH_3), 25.0 (CH_2), 31.3 (CH_2), 50.3 (C), 53.6 (CH), 60.6 (CH_2), 126.9 (2 × CH), 128.6 (2 × CH), 131.7 (CH), 133.9 (C), 167.3 (C), 173.6 (C), 205.4 (CH); m/z 306 (M^+ + H, 1%), 234 (43, $M^+ - Me_2CCHO$), 105 (100, $[PhCO]^+$), 77 (48, $[Ph]^+$). HRMS calcd for $C_{17}H_{24}NO_4$ 306.1705, found 306.1714; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1131; calcd for C_7H_5O 105.0340, found 105.0343; calcd for C_6H_5 77.0391, found 77.0388. $C_{17}H_{23}NO_4$ requires C, 66.86; H, 7.59; N, 4.59%. Found: C, 66.63; H, 7.77; N, 4.58.

Ethyl 4-benzamido-6-oxohexanoate (19). Obtained from Bz-Glu(OEt)-OH (**12**) according to Method A, using vinyloxytrimethylsilane as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 50 : 50), giving the aldehyde (±)-**19** (51%) as a oil; ν_{max}/cm^{-1} 3434, 1724, 1658, 1518; δ_H (500 MHz, $CDCl_3$) 1.18 (3H, dd, J = 6.9, 7.3 Hz, Et), 1.97 (1H, m, 4-H_a), 2.06 (1H, m, 4-H_b), 2.38–2.51 (2H, m, 5-H_2), 2.75 (1H, dd, J = 5.7, 17.1 Hz, 2-H_a), 2.83 (1H, ddd, J = 1.9, 5.7, 17.3 Hz, 2-H_b), 4.01–4.11 (2H, m, Et), 4.51 (1H, m, 3-H), 6.94 (1H, d, J = 8.2 Hz, NH), 7.40 (2H, dd, J = 7.8, 7.9 Hz, Ar), 7.47 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.75 (2H, d, J = 7.3 Hz, Ar), 9.79 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 14.0 (CH_3), 28.9 (CH_2), 31.2 (CH_2), 45.7 (CH), 48.5 (CH_2), 60.7 (CH_2), 126.9 (2 × CH), 128.5 (2 × CH), 131.6 (CH), 133.9 (C), 167.0 (C), 173.7 (C), 200.8 (CH); m/z 278 (M^+ + H, 6%), 234 (12, $M^+ - CH_2CHO$), 172 (99, $M^+ - PhCO$), 144 (60, $M^+ - PhCO - CHO$), 105 (100, $[PhCO]^+$), 77 (99, $[Ph]^+$); HRMS calcd for $C_{15}H_{20}NO_4$ 278.1392, found 278.1395; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1123; calcd for $C_8H_{14}NO_3$ 172.0974, found 172.0976; calcd for $C_7H_{14}NO_2$ 144.1025, found 144.1020; calcd for C_7H_5O 105.0340, found 105.0344; calcd for C_6H_5 77.0391, found 77.0393. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%. Found: C, 64.98; H, 6.96; N, 5.19.

***N*-Methoxycarbonyl-α,α-dimethyl-DL-β-homoprolinal (21).** Obtained from the ornithine derivative **13** according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 60 : 40), giving the aldehyde (±)-**21** (83%) as a syrup; ν_{max}/cm^{-1} 1719, 1690, 1454, 1386; δ_H (500 MHz, $CDCl_3$, 70 °C) 1.00 (3H, s, 2-Me_a), 1.01 (3H, s, 2-Me_b), 1.74–1.90 (3H, m, 4-H_a + 5-H_2), 2.00 (1H, m, 4-H_b), 3.19

(1H, m, 6-H_a), 3.65 (3H, s, OMe), 3.71 (1H, m, 6-H_b), 4.14 (1H, m, 3-H), 9.53 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) 16.3 (CH_3), 20.0 (CH_3), 24.4 (CH_2), 27.1 (CH_2), 47.9 (CH_2), 50.5 (C), 52.2 (CH_3), 62.0 (CH), 156.4 (C), 203.4 (CH); *m/z* 200 (M^+ + H, <1%), 199 (M^+, <1%), 128 (100, M^+ − Me_2CCHO). HRMS calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1284; calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1199; calcd for $C_6H_{10}NO_2$ 128.0712, found 128.0717. $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.60; N, 7.03%. Found: C, 59.99; H, 8.61; N, 7.36.

***N*-Benzyloxycarbonyl-α,α-dimethyl-DL-β-homoprolinal (24).** Obtained from DL-proline benzyl carbamate (**22**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 70 : 30), giving the aldehyde (±)-**24** (86%) as a syrup; ν_{max}/cm^{-1} 1689, 1451, 1416; δ_H (500 MHz, $CDCl_3$, 70 °C) 1.01 (3H, s, 2-Me), 1.02 (3H, s, 2-Me), 1.74–1.90 (3H, m, 3-H_a + 4-H_2), 1.98 (1H, m, 3-H_b), 3.24 (1H, m, 5-H_a), 3.75 (1H, m, 5-H_b), 4.18 (1H, m, 2-H), 5.06 (1H, d, *J* = 12.4 Hz, OCH_aPh), 5.12 (1H, d, *J* = 12.3 Hz, OCH_bPh), 7.25–7.36 (5H, m, Ar), 9.54 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) 16.5 (CH_3), 20.1 (CH_3), 22.4 (CH_2), 27.1 (CH_2), 47.9 (CH_2), 50.5 (C), 62.1 (CH), 67.2 (CH_2), 128.0 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.9 (C), 155.9 (C), 203.5 (CH); *m/z* 275 (M^+, <1%), 204 (80, M^+ − Me_2CCHO), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1512; calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1026; calcd for C_7H_7 91.0548, found 91.0548. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%. Found: C, 69.62; H, 7.75; N, 5.13.

***N*-Benzyloxycarbonyl-DL-β-homoprolinal (25).**[15a–d] Obtained from the proline derivative **22** according to Method A, using 2-ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 50 : 50), giving the aldehyde (±)-**25** (85%) as a syrup; ν_{max}/cm^{-1} 1717, 1692, 1420; δ_H (500 MHz, $CDCl_3$, 70 °C) 1.69 (1H, m, 3-H_a), 1.81–1.92 (2H, m, 4-H_2), 2.14 (1H, m, 3-H_b), 2.50 (1H, ddd, *J* = 1.9, 7.9, 16.4 Hz, 1′-H_a), 2.90 (1H, br b, 1′-H_b), 3.43 (1H, ddd, *J* = 5.4, 6.9, 10.7 Hz, 5-H_a), 3.49 (1H, m, 5-H_b), 4.30 (1H, m, 2-H), 5.13 (2H, s, OCH_2Ph), 7.28–7.35 (5H, m, Ar), 9.75 (1H, br s, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) 23.5 (CH_2), 31.5 (CH_2), 46.6 (CH_2), 48.9 (CH_2), 53.0 (CH), 66.9 (CH_2), 128.0 (2 × CH), 128.5 (3 × CH), 137.0 (C), 154.8 (C), 200.0 (CH); *m/z* 247 (M^+, 2%), 204 (27, M^+ − CH_2CHO), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1205; calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1027; calcd for C_7H_7 91.0548, found 91.0546. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%. Found: C, 68.35; H, 7.14; N, 5.30.

(2*R*,4*R*)-Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-methyl-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (26) and (2*S*,4*R*)-benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-methyl-1-oxo propan-2-yl)pyrrolidine-1-carboxylate (27). Obtained from hydroxyproline derivative **23** according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 90 : 10), giving the 2,4-*cis* product **26** (63%) and the 2,4-*trans* isomer **27** (19%).

Product ***26***. Syrup; $[\alpha]_D$ +8 (*c* 1.05 in $CHCl_3$); ν_{max}/cm^{-1} 1724, 1691, 1471; δ_H (500 MHz, $CDCl_3$, 70 °C) note: the usual numbering (CHO as C-1) is used, not the one given by IUPAC nomenclature: 0.07 (3H, s, $SiMe_a$), 0.08 (3H, s, $SiMe_b$), 0.91 (9H, s, *t*Bu), 1.00 (3H, s, 2-Me_a), 1.07 (3H, s, 2-Me_b), 1.72 (1H, ddd, *J* = 7.6, 7.6, 13.2 Hz, 4-H_a), 2.27 (1H, ddd, *J* = 7.5, 7.5, 13.2 Hz, 4-H_b), 2.96 (1H, dd, *J* = 7.9, 11.3 Hz, 6-H_a), 3.99 (1H, dd, *J* = 7.3, 11.1 Hz, 6-H_b), 4.19 (1H, dd, *J* = 8.0, 8.1 Hz, 3-H), 4.24 (1H, dddd, *J* = 7.4, 7.5, 7.5, 7.6 Hz, 5-H), 5.04 (1H, br d, *J* = 12.6 Hz, OCH_aPh), 5.13 (1H, d, *J* = 12.3 Hz, OCH_bPh), 7.30–7.35 (5H, m, Ar), 9.56 (1H, br b, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) −4.8 (2 × CH_3), 16.0 (CH_3), 18.0 (C), 20.2 (CH_3), 25.8 (3 × CH_3), 36.3 (CH_2), 50.2 (C), 54.6 (CH_2), 60.7 (CH), 67.3 (CH_2), 69.7 (CH), 128.1 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 136.7 (C), 155.7 (C), 203.2 (CH); *m/z* 334 (14, M^+ − Me_2CCHO), 290 (41, M^+ − $Me_3CSi(Me)_2$), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{18}H_{28}NO_3Si$ 334.1838, found 334.1823; calcd for $C_{16}H_{20}NO_4$ 290.1392, found 290.1378; calcd for C_7H_7 91.0548, found 91.0545. $C_{22}H_{35}NO_4Si$ requires C, 65.15; H, 8.70; N, 3.45%. Found: C, 65.02; H, 8.82; N, 3.56.

Product ***27***. Syrup; $[\alpha]_D$ −37 (*c* 0.18 in $CHCl_3$); ν_{max}/cm^{-1} 1722, 1694, 1469, 1415; δ_H (500 MHz, $CDCl_3$, 70 °C) 0.04 (3H, s, $SiMe_a$), 0.06 (3H, s, $SiMe_b$), 0.86 (9H, s, *t*Bu), 1.00 (6H, s, 2-Me_2), 1.86 (1H, ddd, *J* = 3.5, 7.9, 13 Hz, 4-H_a), 1.97 (1H, m, 4-H_b), 3.20 (1H, dd, *J* = 3.6, 11.9 Hz, 6-H_a), 3.77 (1H, m, 6-H_b), 4.33 (1H, m, 5-H), 4.38 (1H, br dd, *J* = 7.6, 7.9 Hz, 3-H), 5.06 (1H, m, OCH_aPh), 5.14 (1H, m, OCH_bPh), 7.28–7.34 (5H, m, Ar), 9.56 (1H, br b, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) −4.8 (2 × CH_3), 15.9 (CH_3), 18.0 (C), 20.0 (CH_3), 25.7 (3 × CH_3), 37.0 (CH_2), 50.0 (C), 56.8 (CH_2), 61.0 (CH), 67.3 (CH_2), 70.8 (CH), 128.0 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.9 (C), 156.8 (C), 203.5 (CH); *m/z* 334 (5, M^+ − Me_2CCHO), 290 (20, M^+ − $Me_3CSi(Me)_2$), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{18}H_{28}NO_3Si$ 334.1838, found 334.1850; calcd for $C_{16}H_{20}NO_4$ 290.1392, found 290.1400; calcd for C_7H_7 91.0548, found 91.0548. $C_{22}H_{35}NO_4Si$ requires C, 65.15; H, 8.70; N, 3.45%. Found: C, 65.45; H, 8.88; N, 3.67.

(2*R*,4*R*)-Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxoethyl) pyrrolidine-1-carboxylate (28) and (2*S*,4*R*)-benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (29). Obtained from hydroxyproline derivative **23** according to Method A, using vinyloxytrimethylsilane as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 90 : 10), giving the 2,4-*cis* product **28** (34%) and the 2,4-*trans* isomer **29** (20%).

Product ***28***. Colorless oil; $[\alpha]_D$ +5 (*c* 0.63 in $CHCl_3$); ν_{max}/cm^{-1} 1694, 1417; δ_H (500 MHz, $CDCl_3$, 70 °C) note: the usual numbering (CHO as C-1) is used, not the one given by IUPAC nomenclature: 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, *t*Bu), 1.78 (1H, br d, *J* = 13.2 Hz, 4-H_a), 2.24 (1H, ddd, *J* = 5.2, 8.4, 13.5 Hz, 4-H_b), 2.85 (1H, m, 2-H_a), 3.09 (1H, m, 2-H_b), 3.37 (1H, br d, *J* = 12.6 Hz, 6-H_a), 3.64 (1H, m, 6-H_b), 4.37 (1H, m, 3-H), 4.39 (1H, m, 5-H), 5.13 (1H, d, *J* = 12 Hz, OCH_aPh), 5.16 (1H, d, *J* = 11.5 Hz, OCH_bPh), 7.30–7.36 (5H, m, Ar), 9.77 (1H, br b, CHO); δ_C (100.6 MHz, $CDCl_3$, 25 °C) A mixture of rotamers was observed: −5.0 (CH_3), −4.9 (CH_3), 17.9 (C), 25.7 (3 × CH_3), 39.7/40.4 (CH_2), 49.2/49.9 (CH_2), 51.9/52.5 (CH), 55.2/55.7 (CH_2), 66.9/67.1 (CH_2), 70.6/71.3 (CH), 127.9 (2 × CH),

128.1 (CH), 128.5 (2 × CH), 136.5/136.7 (C), 154.5/154.8 (C), 201.1/201.2 (CH); *m/z* 320 ($M^+ - Me_3C$, 9%), 292 (11, $M^+ - Me_3C - CO$), 276 (15, $M^+ - Me_3C - CH_2CHO$), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{16}H_{22}NO_4Si$ 320.1318, found 320.1320; calcd for $C_{15}H_{22}NO_3Si$ 292.1369, found 292.1363; calcd for C_7H_7 91.0548, found 91.0544. $C_{20}H_{31}NO_4Si$ requires C, 63.63; H, 8.28; N, 3.71%. Found: C, 63.59; H, 8.15; N, 3.78.

Product ***29***. Colorless oil; $[\alpha]_D$ −35 (*c* 0.26 in $CHCl_3$); ν_{max}/cm^{-1} 1694, 1416, 1357; δ_H (500 MHz, $CDCl_3$, 70 °C) 0.06 (3H, s, $SiMe_a$), 0.07 (3H, s, $SiMe_b$), 0.88 (9H, s, *t*Bu), 1.77 (1H, ddd, *J* = 4.7, 7.3, 12.0 Hz, 4-H_a), 2.17 (1H, m, 4-H_b), 2.58 (1H, br dd, *J* = 6.9, 16.0 Hz, 2-H_a), 2.96 (1H, m, 2-H_b), 3.46 (1H, dd, *J* = 4.4, 11.4 Hz, 6-H_a), 3.50 (1H, m, 6-H_b), 4.37 (1H, m, 5-H), 4.41 (1H, m, 3-H), 5.12–5.18 (2H, m, OCH_2Ph), 7.29–7.35 (5H, m, Ar), 9.75 (1H, br b, CHO); δ_C (100.6 MHz, $CDCl_3$, 25 °C) A mixture of rotamers was observed: −4.9 (CH_3), −4.8 (CH_3), 17.9 (C), 25.7 (3 × CH_3), 40.9/41.8 (CH_2), 48.5/49.4 (CH_2), 51.3/51.9 (CH_2), 55.0/55.3 (CH), 66.8/67.0 (CH_2), 69.5/70.0 (CH), 127.8 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 136.8 (C), 155.4 (C), 200.3/200.5 (CH); *m/z* 292 ($M^+ - Me_3C - CO$, 33%), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{15}H_{22}NO_3Si$ 292.1369, found 292.1364; calcd for C_7H_7 91.0548, found 91.0544. $C_{20}H_{31}NO_4Si$ requires C, 63.63; H, 8.28; N, 3.71%. Found: C, 63.61; H, 8.28; N, 3.70.

***N*-(*N*-Benzoyl-1-aminocyclohexanecarbonyl)-α,α-dimethyl-DL-β-homoleucinal (37).** Obtained from the dipeptide **30** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 70 : 30), giving product **37** (50%) as a syrup; ν_{max}/cm^{-1} 3433, 1724, 1662, 1515; δ_H (500 MHz, $CDCl_3$) 0.86 (3H, d, *J* = 6.6 Hz, 5-Me), 0.88 (3H, d, *J* = 6.3 Hz, 5-Me), 1.02 (3H, s, 2-Me), 1.05 (3H, s, 2-Me), 1.15 (1H, ddd, *J* = 2.5, 11.8, 13.3 Hz, 4-H_a), 1.33 (1H, ddd, *J* = 3.2, 11.7, 14.1 Hz, 4-H_b), 1.38 (1H, m, 5′-H_a), 1.46 (2H, m, 4′-H_a + 6′-H_a), 1.56 (1H, m, 5-H), 1.66 (1H, m, 5′-H_b), 1.70 (2H, m, 4′-H_b + 6′-H_b), 1.96 (2H, m, 3′-H_a + 7′-H_a), 2.25 (2H, dd, *J* = 13.2, 13.2 Hz, 3′-H_b + 7′-H_b), 4.23 (1H, ddd, *J* = 2.2, 9.8, 11.8 Hz, 3-H), 6.05 (1H, s, NH), 7.45 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.50 (1H, d, *J* = 7.6 Hz, NH), 7.53 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.73 (2H, d, *J* = 7.0 Hz, Ar), 9.46 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 18.0 (CH_3), 18.6 (CH_3), 21.4 (CH_3), 21.6 (CH_2), 21.7 (CH_2), 23.8 (CH_3), 25.0 (CH), 25.2 (CH_2), 32.2 (CH_2), 32.5 (CH_2), 39.4 (CH_2), 50.6 (CH), 50.8 (C), 61.1 (C), 126.8 (2 × CH), 128.8 (2 × CH), 131.9 (CH), 134.8 (C), 168.5 (C), 173.8 (C), 205.1 (CH); *m/z* 387 (M^+ + H, <1%), 230 (21, M^+ − NH-CH(CH_2CHMe_2)-C($Me)_2$-CHO), 202 (73, M^+ − CONH-CH(CH_2CHMe_2)-C($Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{23}H_{35}N_2O_3$ 387.2648, found 387.2641; calcd for $C_{14}H_{16}NO_2$ 230.1181, found 230.1183; calcd for $C_{13}H_{16}NO$ 202.1232, found 202.1235; calcd for C_7H_5O 105.0340, found 105.0341. $C_{23}H_{34}N_2O_3$ requires C, 71.47; H, 8.87; N, 7.25%. Found: C, 71.36; H, 8.97; N, 6.93.

***N*-(*N*-Benzoyl-2-methylalanyl)-α,α-dimethyl-β-α,α-dimethyl-β-homophenylalaninal (38).** Obtained from the dipeptide **31** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 60 : 40), giving product **38** (61%) as a crystalline solid; Mp 138–139 °C (EtOAc–*n*-hexane); ν_{max}/cm^{-1} 3439, 3088, 1722, 1671, 1512, 1484; δ_H (500 MHz, $CDCl_3$) 1.19 (3H, s, 2-Me or 2′-Me), 1.21 (3H, s, 2-Me or 2′-Me), 1.37 (3H, s, 2-Me or 2′-Me), 1.41 (3H, s, 2-Me or 2′-Me), 2.59 (1H, dd, *J* = 11.7, 14.2 Hz, 4-H_a), 2.98 (1H, dd, *J* = 4.1, 14.2 Hz, 4-H_b), 4.48 (1H, ddd, *J* = 4.1, 9.8, 11.7 Hz, 3-H), 6.62 (1H, br s, NH), 7.07 (1H, br d, *J* = 9.8 Hz, NH), 7.13–7.20 (5H, m, Ar), 7.42 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.50 (1H, dd, *J* = 7.6, 7.8 Hz, Ar), 7.70 (2H, d, *J* = 6.9 Hz, Ar), 9.50 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 19.1 (CH_3), 19.5 (CH_3), 24.6 (CH_3), 25.3 (CH_3), 36.4 (CH_2), 50.5 (C), 54.2 (CH), 57.8 (C), 126.5 (CH), 126.9 (2 × CH), 128.3 (2 × CH), 128.6 (2 × CH), 129.0 (2 × CH), 131.6 (CH), 134.7 (C), 137.9 (C), 167.5 (C), 173.9 (C), 204.8 (C); *m/z* 381 (M^+ + H, 5%), 309 (6, M^+ − Me_2CCHO), 190 (64, M^+ − NHCH(CH_2Ph)-C($Me)_2$-CHO), 162 (70, M^+ − CONHCH(CH_2Ph)-C($Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{23}H_{29}N_2O_3$ 381.2178, found 381.2170; calcd for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1616; calcd for $C_{11}H_{12}NO_2$ 190.0868, found 190.0861; calcd for $C_{10}H_{12}NO$ 162.0919, found 162.0925; calcd for C_7H_5O 105.0340, found 105.0343. $C_{23}H_{28}N_2O_3$ requires C, 72.61; H, 7.42; N, 7.36%. Found: C, 72.77; H, 7.68; N, 7.07.

***N*-(*N*-Benzoyl-L-phenylalanyl)-α,α-dimethyl-L-β-homoalaninal (39) and *N*-(*N*-benzoyl-L-phenylalanyl)-α,α-dimethyl-D-β-homoalaninal (40).** Obtained from the dipeptide **32** according to Method B, but using DIB (0.4 mmol) and iodine (0.1 mmol) in the scission step, and 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile in the addition step. The reaction mixture was purified by chromatography (hexanes–EtOAc, 75 : 25), giving the diastereomeric products **39** (49%) and **40** (37%), in 86% overall yield.

Product ***39***. Crystalline solid; Mp 133–134 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −8 (*c* 0.24 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 3310, 1723, 1653, 1512; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, s, 2-Me_a), 0.94 (3H, s, 2-Me_b), 1.02 (3H, d, *J* = 6.9 Hz, 3-Me), 3.12 (1H, dd, *J* = 7.9, 13.9 Hz, 3′-H_a), 3.21 (1H, dd, *J* = 6.6, 13.9 Hz, 3′-H_b), 4.17 (1H, m, 3-H), 4.86 (1H, ddd, *J* = 6.6, 7.6, 7.9 Hz, 2-H), 6.43 (1H, d, *J* = 9.5 Hz, NH), 6.91 (1H, d, *J* = 7.6 Hz, NH), 7.21–7.30 (5H, m, Ar), 7.40 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.71 (2H, d, *J* = 7.3 Hz, Ar), 9.35 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 16.1 (CH_3), 18.4 (CH_3), 19.0 (CH_3), 38.3 (CH_2), 49.0 (CH), 49.6 (C), 55.2 (CH), 127.0 (2 × CH), 127.1 (CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.3 (2 × CH), 131.8 (CH), 133.7 (C), 136.5 (C), 167.4 (C), 170.5 (C), 204.8 (CH); *m/z* 366 (M^+, 1%), 224 (17, M^+ − CONHCH(Me)-C($Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{22}H_{26}N_2O_3$ 366.1943, found 366.1944; calcd for $C_{15}H_{14}NO$ 224.1075, found 224.1074; calcd for C_7H_5O 105.0340, found 105.0338. $C_{22}H_{26}N_2O_3$ requires C, 72.11; H, 7.15; N, 7.64%. Found: C, 72.24; H, 7.35; N, 7.76.

Product ***40***. Syrup; $[\alpha]_D$ −13 (*c* 0.21 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 3310, 1723, 1648, 1510; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, d, *J* = 6.9 Hz, 3-Me), 0.93 (3H, s, 2-Me_a), 0.95 (3H, s, 2-Me_b), 3.12 (1H, dd, *J* = 8.2, 13.6 Hz, 3′-H_a), 3.24 (1H, dd, *J* = 6.3, 13.6, 3′-H_b), 4.15 (1H, m, 3-H), 4.88 (1H, ddd, *J* = 6.9, 7.9, 7.9 Hz, 2′-H), 6.59 (1H, br b, NH), 7.16 (1H, m, Ar), 7.20–7.30 (5H, m, Ar + NH), 7.39 (2H, dd, *J* = 6.8, 7.3 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.72 (2H, d, *J* = 8.1 Hz, Ar), 9.32 (1H,

br b, CHO); δ_C (125.7 MHz, $CDCl_3$) 15.6 (CH_3), 18.0 (CH_3), 18.7 (CH_3), 38.3 (CH_2), 48.5 (CH), 49.6 (C), 55.2 (CH), 127.0 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.3 (2 × CH), 131.8 (CH), 133.7 (C), 136.7 (C), 167.6 (C), 170.6 (C), 204.3 (CH); *m/z* 366 (M^+, 5%), 224 (18, M^+ − CONHCH(Me)-C(Me)$_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{22}H_{26}N_2O_3$ 366.1943, found 366.1948; calcd for C_7H_5O 105.0340, found 105.0343. $C_{22}H_{26}N_2O_3$ requires C, 72.11; H, 7.15; N, 7.64%. Found: C, 72.23; H, 6.89; N, 7.77.

***N*-(*N*-Benzoyl-L-leucyl)-α,α-dimethyl-L-β-(41) and *N*-(*N*-benzoyl-L-leucyl)-α,α-dimethyl-D-β-homoalaninal (42).** The products were generated from dipeptide **33** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 80 : 20), affording compounds **41** (57%) and **42** (29%).

Compound 41. Crystalline solid; Mp 184–185 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −22 (*c* 0.43 in $CHCl_3$); ν_{max}/cm^{-1} 3428, 1723, 1656, 1517; δ_H (500 MHz, $CDCl_3$) 0.95 (6H, d, *J* = 6.3 Hz, 4′-Me_2), 1.05 (3H, d, *J* = 8.2 Hz, 3-Me), 1.06 (3H, s, 2-Me_a), 1.07 (3H, s, 2-Me_b), 1.67–1.72 (3H, m, 3′-H_2 + 4′-H), 4.23 (1H, dddd, *J* = 6.8, 6.8, 6.8, 9.4 Hz, 3-H), 4.67 (1H, ddd, *J* = 7.5, 7.5, 7.5 Hz, 2′-H), 6.87 (1H, br b, NH), 6.94 (1H, d, *J* = 7.9 Hz, NH), 7.40 (2H, dd, *J* = 7.7, 7.7 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.78 (2H, d, *J* = 7.5 Hz, Ar), 9.45 (1H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 15.8 (CH_3), 17.9 (CH_3), 19.2 (CH_3), 22.2 (CH_3), 22.8 (CH_3), 25.0 (CH), 41.4 (CH_2), 48.6 (CH), 50.0 (C), 52.5 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.8 (C), 167.6 (C), 171.9 (C), 204.7 (CH); *m/z* 333 (M^+ + H, 1%), 190 (100, M^+ − CONHCH(Me)CMe_2CHO), 105 (91, $[PhCO]^+$); HRMS calcd for $C_{19}H_{29}N_2O_3$ 333.2178, found 333.2181; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1239. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.49; N, 8.43%. Found: C, 68.90; H, 8.35; N, 8.14.

Compound 42. Crystalline solid; Mp 152–153 °C (net); $[\alpha]_D$ −28 (*c* 0.60 in $CHCl_3$); ν_{max}/cm^{-1} 3428, 1721, 1656, 1517; δ_H (500 MHz, $CDCl_3$) 0.96 (3H, d, *J* = 6.5 Hz, 4′-Me_a), 0.97 (3H, d, *J* = 6.3 Hz, 4′-Me_b), 1.00 (3H, s, 2-Me_a), 1.03 (3H, s, 2-Me_b), 1.13 (3H, d, *J* = 6.9 Hz, 3-Me), 1.63–1.82 (3H, m, 3′-H_2 + 4′-H), 4.24 (1H, dddd, *J* = 6.9, 6.9, 6.9, 9.5 Hz, 3-H), 4.61 (1H, ddd, *J* = 6.0, 6.3, 8.2 Hz, 2′-H), 6.67 (1H, d, *J* = 8.2 Hz, NH), 6.75 (1H, d, *J* = 9.8 Hz, NH), 7.43 (2H, dd, *J* = 7.4, 7.4 Hz, Ar), 7.50 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.78 (2H, d, *J* = 6.9 Hz, Ar), 9.43 (1H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 16.0 (CH_3), 17.9 (CH_3), 19.0 (CH_3), 22.3 (CH_3), 22.9 (CH_3), 25.0 (CH), 40.4 (CH_2), 48.4 (CH), 50.1 (C), 52.2 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.9 (C), 167.9 (C), 171.3 (C), 204.8 (CH); *m/z* 333 (M^+ + H, 2%), 190 (86, M^+ − CONHCH(Me)CMe_2CHO), 105 (100, $[PhCO]^+$); HRMS calcd $C_{19}H_{29}N_2O_3$ 333.2178, found 333.2177; calcd for C_7H_5O 105.0340, found 105.0340. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.49; N, 8.43%. Found: C, 68.80; H, 8.32; N, 8.10.

***N*-(*N*-Benzoyl-L-prolyl)-α,α-dimethyl-L-β-homoleucinal (43) and *N*-(*N*-benzoyl-L-prolyl)-α,α-dimethyl-D-β-homoleucinal (44).** The products were generated from dipeptide **34** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 80 : 20), affording compounds **43** (47%) and **44** (22%).

Compound 43. Syrup; $[\alpha]_D$ −85 (*c* 0.65 in $CHCl_3$); ν_{max}/cm^{-1} 3300, 1723, 1674, 1610, 1536; δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.92 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.96 (3H, s, 2-Me_a), 1.05 (3H, s, 2-Me_b), 1.18 (1H, ddd, *J* = 2.2, 9.8, 12.6 Hz, 4-H_a), 1.32 (1H, ddd, *J* = 3.5, 11.3, 13.0 Hz, 4-H_b), 1.65 (1H, m, 5-H), 1.81 (1H, m, 4′-H_a), 1.91–2.04 (2H, m, 4′-H_b + 3′-H_a), 2.50 (1H, m, 3′-H_b), 3.37 (1H, m, 5′-H_a), 3.50 (1H, m, 5′-H_b), 4.26 (1H, dd, *J* = 10, 11.7 Hz, 3-H), 4.82 (1H, m, 2′-H), 7.26 (1H, d, *J* = 9.8 Hz, NH), 7.41 (3H, m, Ar), 7.54 (2H, m, Ar), 9.47 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 17.0 (CH_3), 18.9 (CH_3), 21.4 (CH_3), 23.8 (CH_3), 25.0 (CH), 25.2 (CH_2), 26.3 (CH_2), 38.6 (CH_2), 50.0 (CH_2), 50.5 (CH), 51.0 (C), 59.5 (CH), 126.8 (2 × CH), 128.5 (2 × CH), 130.1 (CH), 136.3 (C), 170.7 (C), 171.5 (C), 204. 7 (CH); *m/z* 358 (M^+, 3%), 202 (50, M^+ − NHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 174 (95, M^+ − CONHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{21}H_{30}N_2O_3$ 358.2256, found 358.2262; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0858; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0921; calcd for C_7H_5O 105.0340, found 105.0341. $C_{21}H_{30}N_2O_3$ requires C, 70.36; H, 8.44; N, 7.81%. Found: C, 70.48; H, 8.42; N, 8.10.

Compound 44. Syrup; $[\alpha]_D$ −97 (*c* 0.34 in $CHCl_3$); ν_{max}/cm^{-1} 3424, 3303, 1725, 1674, 1660, 1602, 1420; δ_H (500 MHz, $CDCl_3$) 0.83 (3H, d, *J* = 6.9 Hz, 5-Me_a), 0.90 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.07 (3H, s, 2-Me_a), 1.08 (3H, s, 2-Me_b), 1.16 (1H, m, 4-H_a), 1.31 (1H, m, 4-H_b), 1.56 (1H, m, 5-H), 1.83 (1H, m, 4′-H_a), 1.99–2.08 (2H, m, 4′-H_b + 3′-H_a), 2.43 (1H, m, 3′-H_b), 3.45 (1H, m, 5′-H_a), 3.53 (1H, m, 5′-H_b), 4.24 (1H, dd, *J* = 9.5, 9.8 Hz, 3-H), 4.76 (1H, dd, *J* = 4.8, 7.3 Hz, 2′-H), 7.11 (1H, br d, *J* = 9.8 Hz, NH), 7.40–7.50 (5H, m, Ar), 9.49 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 18.4 (CH_3), 18.7 (CH_3), 21.5 (CH_3), 23.8 (CH_3), 25.2 (CH), 25.4 (CH_2), 27.1 (CH_2), 39.6 (CH_2), 50.4 (CH_2), 50.5 (C), 51.0 (CH), 59.9 (CH), 126.9 (2 × CH), 128.5 (2 × CH), 130.3 (CH), 136.2 (C), 170.9 (C), 171.5 (C), 205.2 (CH); *m/z* 358 (M^+, 2%), 202 (27, M^+ − NHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 174 (74, M^+ − CONHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{21}H_{30}N_2O_3$ 358.2256, found 358.2251; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0863; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0925; calcd for C_7H_5O 105.0340, found 105.0336. $C_{21}H_{30}N_2O_3$ requires C, 70.36; H, 8.44; N, 7.81%. Found: C, 70.19; H, 8.43; N, 7.76.

***N*-(*N*-Benzoyl-L-alanyl)-α,α-dimethyl-DL-β-homoleucinal (45).** The products were generated from dipeptide **35** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 75 : 25), affording compound **45** (78%) as a 9 : 6 mixture of diastereomers; ν_{max}/cm^{-1} 3422, 3307, 1724, 1676, 1645, 1514; δ_H (500 MHz, $CDCl_3$) major isomer: 0.90 (3H, d, *J* = 6.8 Hz, 5-Me_a), 0.91 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.98 (3H, s, 2-Me_a), 1.01 (3H, s, 2-Me_b), 1.14 (1H, m, 4-H_a), 1.39 (1H, m, 4-H_b), 1.49 (3H, d, *J* = 6.9 Hz, 2′-Me), 1.61 (1H, m, 5-H), 4.24 (1H, m, 3-H), 4.81 (1H, m, 2′-H), 7.07 (1H, br d, *J* = 10.4 Hz, NH), 7.22 (1H, br d, *J* = 7.6 Hz, NH), 7.40 (2H, dd, *J* = 7.8, 7.8 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.5 Hz, Ar), 7.79 (2H, d, *J* = 8.1 Hz, Ar), 9.46 (1H, s, CHO); minor

isomer: 0.75 (3H, d, J = 6.7 Hz, 5-Me_a), 0.84 (3H, d, J = 6.5 Hz, 5-Me_b), 1.08 (3H, s, 2-Me_a), 1.09 (3H, s, 2-Me_b), 1.12 (1H, m, 4-H_a), 1.34 (1H, m, 4-H_b), 1.50 (3H, d, J = 6.9 Hz, 2′-Me), 1.51 (1H, m, 5-H), 4.24 (1H, m, 3-H), 4.81 (1H, m, 2′-H), 7.04 (1H, br d, J = 10.4 Hz, NH), 7.24 (1H, br d, J = 8.2 Hz, NH), 7.40 (2H, dd, J = 7.8, 7.8 Hz, Ar), 7.49 (1H, dd, J = 7.3, 7.5 Hz, Ar), 7.76 (2H, d, J = 7.5 Hz, Ar), 9.51 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) major isomer: 18.2 (CH_3), 18.4 (CH_3), 18.6 (CH_3), 21.2 (CH_3), 23.8 (CH_3), 25.1 (CH), 39.1 (CH_2), 49.4 (CH), 50.7 (C), 50.9 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 131.8 (CH), 133.7 (C), 167.6 (C), 172.5 (C), 204.9 (CH); minor isomer: 18.0 (CH_3), 18.4 (CH_3), 19.1 (CH_3), 21.2 (CH_3), 23.6 (CH_3), 24.9 (CH), 38.8 (CH_2), 49.4 (CH), 50.7 (C), 50.9 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 131.8 (CH), 133.8 (C), 167.4 (C), 172.5 (C), 204.8 (CH); m/z 333 (M^+ + H, 1%), 176 (31, M^+ − NHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 148 (55, M^+ − CONHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{19}H_{29}N_2O_3$ 333.2178, found 333.2166; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0706; calcd for $C_9H_{10}NO$ 148.0762, found 148.0763; calcd for C_7H_5O 105.0340, found 105.0345. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.49; N, 8.43%. Found: C, 68.50; H, 8.61; N, 8.69.

***N*-(*N*-Benzyloxycarbonyl-L-valyl)-α,α-dimethyl-DL-β-homoleucinal (46).** The products were generated from dipeptide **36** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 85 : 15), affording compound **46** (76%) as a 10 : 7 mixture of diastereomers: syrup; ν_{max}/cm^{-1} 3426, 1714, 1672, 1506, 1469; δ_H (500 MHz, $CDCl_3$) major isomer: 0.86–0.90 (9H, m, 5-Me_2 + 3′-Me_a), 0.95 (3H, d, J = 6.6 Hz, 3′-Me_b), 1.01 (3H, s, 2-Me_a), 1.06 (3H, s, 2-Me_b), 1.16 (1H, m, 4-H_a), 1.32 (1H, m, 4-H_b), 1.52 (1H, m, 5-H), 2.14 (1H, m, 3′-H), 3.92 (1H, ddd, J = 8.8, 8.8, 8.9 Hz, 2′-H), 4.21 (1H, br dd, J = 12.0, 12.0 Hz, 3-H), 5.08 (1H, d, J = 12.0 Hz, OCH_aPh), 5.11 (1H, d, J = 12.5 Hz, OCH_bPh), 5.37 (1H, br b, NH), 6.11 (1H, br d, J = 9.8 Hz, NH), 7.30–7.35 (5H, m, Ar), 9.44 (1H, s, CHO); minor isomer: 0.85 (3H, d, J = 6.6 Hz, 5-Me_a), 0.86–0.90 (6H, m, 5-Me_b + 3′-Me_a), 0.95 (3H, d, J = 6.5 Hz, 3′-Me_b), 1.01 (3H, s, 2-Me_a), 1.03 (3H, s, 2-Me_b), 1.15 (1H, m, 4-H_a), 1.32 (1H, m, 4-H_b), 1.52 (1H, m, 5-H), 2.14 (1H, m, 3′-H), 3.92 (1H, ddd, J = 8.8, 8.8, 8.9 Hz, 2′-H), 4.21 (1H, br dd, J = 12.0, 12.0 Hz, 3-H), 5.09–5.15 (2H, m, OCH_2Ph), 5.38 (1H, br b, NH), 6.14 (1H, br d, J = 12.0 Hz, NH), 7.30–7.35 (5H, m, Ar), 9.45 (1H, s, CHO); major isomer: δ_C (125.7 MHz, $CDCl_3$) 17.7 (CH_3), 18.7 (CH_3), 19.0 (CH_3), 19.4 (CH_3), 21.1 (CH_3), 23.8 (CH_3), 24.9 (CH), 30.3 (CH), 39.3 (CH_2), 50.3 (C), 51.0 (CH), 61.0 (CH), 67.1 (CH_2), 128.0 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 136.2 (C), 156.5 (C), 171.2 (C), 205.0 (CH); minor isomer: δ_C (125.7 MHz, $CDCl_3$) 17.7 (CH_3), 18.5 (CH_3), 18.7 (CH_3), 19.4 (CH_3), 21.2 (CH_3), 23.7 (CH_3), 25.0 (CH), 30.1 (CH), 39.4 (CH_2), 50.4 (C), 51.2 (CH), 61.0 (CH), 67.1 (CH_2), 128.0 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 136.2 (C), 156.6 (C), 171.2 (C), 204.9 (CH); m/z 391 (M^+ + H, <1%), 390 (M^+, <1%), 319 (8, M^+ − C(Me)$_2$-CHO), 234 (12, M^+ − NHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{22}H_{34}N_2O_4$ 390.2518, found 390.2519; calcd for $C_{18}H_{27}N_2O_3$ 319.2022, found 319.2027; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1122; calcd for C_7H_7 91.0548, found 91.0552. $C_{22}H_{34}N_2O_4$ requires C, 67.66; H, 8.78; N, 7.17%. Found: C, 67.57; H, 8.93; N, 7.11.

General procedure for the reduction of the amino aldehydes to the amino alcohols

To a solution of the starting β-peptide aldehydes (0.4 mmol) in dry ^{i}PrOH (12 mL) cooled at 0 °C, was added $LiBH_4$ (17 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 40 min. Then it was poured into saturated brine and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes–EtOAc) giving the γ-amino alcohol derivatives.

***N*-(*N*-Benzoyl-L-phenylalanyl)-α,α-dimethyl-L-β-homoalaninol (47).** Obtained by reduction of the peptide aldehyde **39** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 70 : 30), affording compound **47** (78%) as a crystalline solid: Mp 187–188 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −17 (c 0.27 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 1650, 1509, 1484; δ_H (500 MHz, $CDCl_3$) 0.47 (3H, s, 2-Me_a), 0.90 (3H, s, 2-Me_b), 1.01 (3H, d, J = 6.9 Hz, 3-Me), 2.91 (1H, d, J = 11.7 Hz, 1-H_a), 3.10 (1H, d, J = 11.7 Hz, 1-H_b), 3.15 (1H, dd, J = 8.5, 13.9 Hz, 3′-H_a), 3.25 (1H, dd, J = 6.3, 13.9 Hz, 3′-H_b), 3.93 (1H, dddd, J = 6.8, 6.8, 6.9, 8.7 Hz, 3-H), 4.92 (1H, ddd, J = 6.3, 7.9, 8.2 Hz, 2′-H), 6.34 (1H, br d, J = 9.0 Hz, NH), 6.85 (1H, brd, J = 7.3 Hz, NH), 7.24 (1H, m, Ar), 7.29–7.34 (4H, m, Ar), 7.42 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.51 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.72 (2H, d, J = 8.2 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 15.3 (CH_3), 18.3 (CH_3), 23.0 (CH_3), 38.5 (CH_2 + C), 49.6 (CH), 55.2 (CH), 69.6 (CH_2), 127.0 (2 × CH), 127.2 (CH), 128.6 (2 × CH), 128.9 (2 × CH), 129.3 (2 × CH), 131.9 (CH), 133.6 (C), 136.4 (C), 167.4 (C), 171.3 (C); m/z 368 (M^+, 1%), 350 (3, M^+ − H_2O), 252 (26, M^+ − NHCH(Me)C(Me)$_2CH_2OH$), 224 (21, M^+ − CONHCH(Me)C-(Me)$_2CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{22}H_{28}N_2O_3$ 368.2100, found 368.2107; calcd for $C_{22}H_{26}N_2O_2$ 350.1994, found 350.1985; calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1019; calcd for $C_{15}H_{14}NO$ 224.1075, found 224.1070; calcd for C_7H_5O 105.0340, found 105.0343. $C_{22}H_{28}N_2O_3$ requires C, 71.71; H, 7.66; N, 7.60%. Found: C, 71.79; H, 7.68; N, 7.68.

***N*-(*N*-Benzoyl-L-phenylalanyl)-α,α-dimethyl-D-β-homoalaninol (48).** Obtained by reduction of the peptide aldehyde **40** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 75 : 25), affording compound **48** (69%) as a crystalline solid: Mp 134–135 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −11 (c 0.19 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 1731, 1650, 1510; δ_H (500 MHz, $CDCl_3$) 0.54 (3H, s, 2-Me_a), 0.86 (3H, d, J = 6.9 Hz, 3-Me), 0.91 (3H, s, 2-Me_b), 2.92 (1H, d, J = 11.7 Hz, 1-H_a), 3.14 (1H, dd, J = 7.9, 13.2 Hz, 3′-H_a), 3.21 (1H, dd, J = 6.6, 13.3 Hz, 3′-H_b), 3.25 (1H, d, J = 12 Hz, 1-H_b), 3.87 (1H, dddd, J = 6.6, 6.6, 6.7, 9.1 Hz, 3-H), 4.02 (1H, OH), 4.99 (1H, ddd, J = 6.6, 8.2, 8.2 Hz, 2′-H), 6.95 (1H, br d, J = 9.5 Hz, NH), 7.19 (1H, m, Ar), 7.21–7.25 (4H, m, Ar), 7.35 (1H, brb, NH), 7.37 (2H, dd, J = 7.6, 7.8 Hz, Ar), 7.49 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.70 (2H, d, J = 8.2 Hz, Ar);

δ_C (100.6 MHz, $CDCl_3$) 14.8 (CH_3), 18.1 (CH_3), 22.9 (CH_3), 38.6 (C), 38.8 (CH_2), 49.0 (CH), 55.2 (CH), 69.7 (CH_2), 126.9 (CH), 127.1 (2 × CH), 128.5 (4 × CH), 129.4 (2 × CH), 131.8 (CH), 133.6 (C), 136.6 (C), 167.6 (C), 171.8 (C); *m/z* 368 (M^+, 1%), 350 (1, $M^+ - H_2O$), 252 (58, M^+ − NHCH(Me)C(Me)$_2$$CH_2OH$), 224 (44, M^+ − CONHCH(Me)C(Me)$_2$$CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{22}H_{28}N_2O_3$ 368.2100, found 368.2104; calcd for $C_{22}H_{26}N_2O_2$ 350.1994, found 350.1984; calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1014; calcd for $C_{15}H_{14}NO$ 224.1075, found 224.1072; calcd for C_7H_5O 105.0340, found 105.0341. $C_{22}H_{28}N_2O_3$ requires C, 71.71; H, 7.66; N, 7.60%. Found: C, 71.64; H, 7.48; N, 7.62.

***N*-(*N*-Benzoyl-L-leucyl)-α,α-dimethyl-L-β-homoalaninol (49).** Obtained by reduction of the peptide aldehyde **41** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 60 : 40), affording compounds **49** (76%) as a crystalline solid; Mp 186–187 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −35 (*c* 0.62 in $CHCl_3$); ν_{max}/cm^{-1} 3427, 1651, 1516; δ_H (500 MHz, $CDCl_3$) 0.69 (3H, s, 2-Me_a), 0.95 (6H, d, *J* = 6.6 Hz, 2 × Me), 0.96 (3H, s, 2-Me_b), 0.97 (3H, d, *J* = 6.3 Hz, Me), 1.71 (1H, m, 3′-H_a), 1.77 (1H, m, 4′-H), 1.82 (1H, m, 3′-H_b), 3.03 (1H, brdd, *J* = 9.1, 11.0 Hz, 1-H_a), 3.33 (1H, brd, *J* = 11.4 Hz, 1-H_b), 3.92 (1H, dddd, *J* = 6.6, 6.9, 6.9, 8.8 Hz, 3-H), 4.09 (1H, brb, OH), 4.89 (1H, ddd, *J* = 5.1, 5.4, 8.8 Hz, 2′-H), 7.34 (1H, dd, *J* = 7.3, 8.2 Hz, Ar), 7.46 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.44–7.50 (2H, brb, 2 × NH), 7.81 (1H, d, *J* = 8.0 Hz, Ar); δ_C (100.6 MHz, $CDCl_3$) 14.9 (CH_3), 18.4 (CH_3), 22.1 (CH_3), 22.9 (CH_3), 23.0 (CH_3), 25.0 (CH), 38.9 (C), 41.8 (CH_2), 49.0 (CH), 52.5 (CH), 69.8 (CH_2), 127.2 (2 × CH), 128.4 (2 × CH), 131.7 (CH), 133.8 (C), 167.6 (C), 173.4 (C); *m/z* 335 (M^+ + H, <1%), 261 (5, M^+ − C(Me)$_2$$CH_2OH$), 218 (66, M^+ − NHCH(Me)C(Me)$_2$$CH_2OH$), 190 (57, M^+ − CONHCH(Me)C(Me)$_2$$CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2339; calcd for $C_{15}H_{21}N_2O_2$ 261.1603, found 261.1592; calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1180; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1227; calcd for C_7H_5O 105.0340, found 105.0340. $C_{19}H_{31}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.59; H, 8.95; N, 8.48.

***N*-(*N*-Benzoyl-L-leucyl)-α,α-dimethyl-D-β-homoalaninol (50).** Obtained by reduction of the peptide aldehyde **42** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 60 : 40), affording compounds **50** (79%) as a crystalline solid; Mp 163–164 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −39 (*c* 0.66 in $CHCl_3$); ν_{max}/cm^{-1} 3425, 1654, 1510; δ_H (500 MHz, $CDCl_3$) 0.62 (3H, s, 2-Me_a), 0.95 (3H, d, *J* = 6.9 Hz, Me), 0.96 (3H, s, 2-Me_b), 0.97 (3H, d, *J* = 6.9 Hz, Me), 1.12 (3H, d, *J* = 6.9 Hz, Me), 1.67–1.75 (2H, m, 3′-H_a + 4′-H), 1.77 (1H, m, 3′-H_b), 2.94 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.25 (1H, d, *J* = 11.9 Hz, 1-H_b), 3.98 (1H, dddd, *J* = 6.6, 6.8, 6.9, 9.4 Hz, 3-H), 4.69 (1H, ddd, *J* = 6.0, 6.3, 7.9 Hz, 2′-H), 6.95 (1H, brd, *J* = 8.2 Hz, NH), 7.03 (1H, br d, *J* = 9.5 Hz, NH), 7.41 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.50 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.76 (2H, d, *J* = 8.0 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 15.3 (CH_3), 18.3 (CH_3), 22.4 (CH_3), 22.8 (CH_3), 23.1 (CH_3), 25.0 (CH), 38.9 (C), 40.7 (CH_2), 49.1 (CH), 52.5 (CH), 69.8 (CH_2), 127.1 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.8 (C), 167.9 (C), 172.7 (C); *m/z* 335 (M^+ + H, 1%), 261 (9, M^+ − C(Me)$_2$$CH_2OH$), 218 (97, M^+ − NHCH(Me)C(Me)$_2$$CH_2OH$), 190 (92, M^+ − CONHCH(Me)C(Me)$_2$$CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2343; calcd for $C_{15}H_{20}N_2O_2$ 260.1525, found 260.1515; calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1177; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1229; calcd for C_7H_5O 105.0340, found 105.0342. $C_{19}H_{31}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.06; H, 8.88; N, 8.41.

***N*-(*N*-Benzoyl-L-prolyl)-α,α-dimethyl-L-β-homoleucinol (51).** Obtained by reduction of the peptide aldehyde **43** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 1 : 1), affording compound **51** (77%) as a syrup; $[\alpha]_D$ −92 (*c* 0.41 in $CHCl_3$); ν_{max}/cm^{-1} 3426, 1656, 1613; δ_H (500 MHz, $CDCl_3$) 0.64 (3H, s, 2-Me_a), 0.89 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.94 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.00 (3H, s, 2-Me_b), 1.28–1.33 (2H, m, 4-H_2), 1.64 (1H, m, 5-H), 1.84 (1H, m, 4′-H_a), 2.03 (1H, m, 3′-H_a), 2.08 (1H, m, 4′-H_b), 2.48 (1H, m, 3′-H_b), 2.93 (1H, brb, OH), 3.01 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.30 (1H, d, *J* = 11.9 Hz, 1-H_b), 3.46 (1H, m, 5′-H_a), 3.55 (1H, m, 5′-H_b), 3.92 (1H, ddd, *J* = 3.5, 10.2, 10.7 Hz, 3-H), 4.80 (1H, m, 2′-H), 7.02 (1H, brd, *J* = 9.5 Hz, NH), 7.40–7.48 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.3 (CH_3), 21.3 (CH_3), 23.1 (CH_3), 23.9 (CH_3), 25.4 (CH), 25.5 (CH_2), 27.0 (CH_2), 38.1 (CH_2), 39.0 (C), 50.3 (CH_2), 51.2 (CH), 59.7 (CH), 70.3 (CH_2), 126.8 (2 × CH), 128.5 (2 × CH), 130.3 (CH), 136.0 (C), 171.2 (C), 172.4 (C); *m/z* 360 (M^+, 1%), 287 (73, M^+ − C(Me)$_2$$CH_2OH$), 202 (51, M^+ − NHCH(CH_2CHMe_2)C(Me)$_2$$CH_2OH$), 174 (54, M^+ − CONHCH(CH_2CHMe_2)C(Me)$_2$$CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{21}H_{32}N_2O_3$ 360.2413, found 360.2404; calcd for $C_{17}H_{23}N_2O_2$ 287.1760, found 287.1752; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0864; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0918; calcd for C_7H_5O 105.0340, found 105.0345. $C_{21}H_{32}N_2O_3$ requires C, 69.97; H, 8.95; N, 7.77%. Found: C, 70.13; H, 9.01; N, 7.83.

***N*-(*N*-Benzoyl-L-prolyl)-α,α-dimethyl-D-β-homoleucinol (52).** Obtained by reduction of the peptide aldehyde **44** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 1 : 1), affording compound **51** (79%) as a syrup; $[\alpha]_D$ −130 (*c* 0.13 in $CHCl_3$); ν_{max}/cm^{-1} 3449, 1656, 1615; δ_H (500 MHz, $CDCl_3$) 0.68 (3H, s, 2-Me_a), 0.82 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.87 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.02 (3H, s, 2-Me_b), 1.26–1.32 (2H, m, 4-H_2), 1.52 (1H, m, 5-H), 1.85 (1H, m, 4′-H_a), 1.99–2.09 (2H, m, 3′-H_a + 4′-H_b), 2.50 (1H, m, 3′-H_b), 3.02 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.38 (1H, d, *J* = 11.6 Hz, 1-H_b), 3.47 (1H, m, 5′-H_a), 3.53 (1H, m, 5′-H_b), 3.89 (1H, ddd, *J* = 4.4, 9.4, 9.5 Hz, 3-H), 4.88 (1H, dd, *J* = 4.4, 7.3 Hz, 2′-H), 7.12 (1H, brd, *J* = 9.5 Hz, NH), 7.41–7.48 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.4 (CH_3), 21.3 (CH_3), 23.0 (CH_3), 23.8 (CH_3), 25.4 (CH_2), 25.5 (CH), 26.9 (CH_2), 38.3 (CH_2), 38.9 (C), 50.4 (CH_2), 51.5 (CH), 59.7 (CH), 70.3 (CH_2), 126.9 (2 × CH), 128.5 (2 × CH), 130.4 (CH), 136.0 (C), 171.7 (C), 172.3 (C); *m/z* 360 (M^+, 1%), 287 (7, M^+ − C(Me)$_2$$CH_2OH$), 202 (36, M^+ − NHCH(CH_2CHMe_2)C(Me)$_2$$CH_2OH$), 174 (55, M^+ − CONHCH(CH_2CHMe_2)C(Me)$_2$$CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for

$C_{21}H_{32}N_2O_3$ 360.2413, found 360.2415; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0875; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0924; calcd for C_7H_5O 105.0340, found 105.0344. $C_{21}H_{32}N_2O_3$ requires C, 69.97; H, 8.95; N, 7.77%. Found: C, 69.76; H, 8.87; N, 7.68.

***N*-(*N*-Benzoyl-L-alanyl)-α,α-dimethyl-L-β-homoleucinol (53) and *N*-(*N*-benzoyl-L-alanyl)-α,α-dimethyl-D-β-homoleucinol (54).** Obtained by reduction of the peptide aldehyde **45** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 60 : 40), affording compounds **53** (41%) and **54** (29%).

Product ***53***. Syrup; $[\alpha]_D$ +1 (*c* 0.29 in $CHCl_3$); ν_{max}/cm^{-1} 3421, 1653, 1647, 1512; δ_H (500 MHz, $CDCl_3$) 0.59 (3H, s, 2-Me_a), 0.87 (3H, d, *J* = 6.3 Hz, 5-Me_a), 0.90 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.98 (3H, s, 2-Me_b), 1.26 (1H, ddd, *J* = 2.5, 10.5, 13.3 Hz, 4-H_a), 1.41 (1H, ddd, *J* = 3.5, 11.3, 13.9 Hz, 4-H_b), 1.51 (3H, d, *J* = 6.9 Hz, 2′-Me), 1.62 (1H, m, 5-H), 2.92 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.26 (1H, d, *J* = 11.7 Hz, 1-H_b), 3.90 (1H, ddd, *J* = 2.5, 9.5, 12.0 Hz, 3-H), 4.88 (1H, dddd, *J* = 6.9, 6.9, 7.3, 7.3 Hz, 2′-H), 7.28 (1H, d, *J* = 9.5 Hz, NH), 7.38 (1H, d, *J* = 7.6 Hz, NH), 7.41 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.51 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.79 (2H, d, *J* = 7.8 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.3 (CH_3), 18.6 (CH_3), 21.0 (CH_3), 23.0 (CH_3), 23.9 (CH_3), 25.4 (CH), 37.8 (CH_2), 38.9 (C), 49.4 (CH), 51.4 (CH), 70.1 (CH_2), 127.1 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.5 (C), 167.6 (C), 174.0 (C); *m*/*z* 335 (M^+ + H, <1%), 316 (2, M^+ − H_2O), 176 (34, [BzNH-CH(Me)CO), 148 (45, [BzNH=CH(Me)]$^+$), 105 (96, $[PhCO]^+$), 86 (100, $[NH_2{=}CHCH_2CH(Me)_2]^+$), 77 (32, $[Ph]^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2351; calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2141; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0707; calcd for $C_9H_{10}NO$ 148.0762, found 148.0760; calcd for C_7H_5O 105.0340, found 105.0338; calcd for $C_5H_{12}N$ 86.0970, found 86.0973; calcd for C_6H_5 77.0391, found 77.0392. $C_{19}H_{30}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.44; H, 8.96; N, 8.30.

Product ***54***. Crystalline solid; Mp 158–159 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −40 (*c* 0.36 in $CHCl_3$); ν_{max}/cm^{-1} 3421, 1655, 1649, 1512, 1484; δ_H (500 MHz, $CDCl_3$) 0.71 (3H, s, 2-Me_a), 0.76 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.79 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.02 (3H, s, 2-Me_b), 1.25 (1H, m, 4-H_a), 1.31 (1H, ddd, *J* = 3.5, 11.0, 14.5 Hz, 4-H_b), 1.48 (1H, m, 5-H), 1.55 (3H, d, *J* = 6.9 Hz, 2′-Me), 3.05 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.35 (1H, d, *J* = 11.9 Hz, 1-H_b), 3.90 (1H, ddd, *J* = 2.5, 9.5, 11.7 Hz, 3-H), 4.88 (1H, dddd, *J* = 6.9, 6.9, 7.3, 7.3 Hz, 2′-H), 7.01 (1H, br d, *J* = 9.1 Hz, NH), 7.13 (1H, br d, *J* = 7.3 Hz, NH), 7.43 (2H, dd, *J* = 7.6, 7.8 Hz, Ar), 7.52 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.78 (2H, d, *J* = 8.2 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.6 (CH_3), 19.1 (CH_3), 21.1 (CH_3), 23.0 (CH_3), 23.7 (CH_3), 25.2 (CH), 37.9 (CH_2), 39.0 (C), 49.3 (CH), 51.5 (CH), 70.2 (CH_2), 127.0 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.6 (C), 167.4 (C), 173.7 (C); *m*/*z* 335 (M^+ + H, <1%), 316 (1, M^+ − H_2O), 176 (23, [PhCONH-CH(Me)CO]), 148 (37, [PhCONH=CH(Me)]$^+$), 105 (100, $[PhCO]^+$), 86 (100, $[NH_2{=}CHCH_2CH(Me)_2]^+$), 77 (31, $[Ph]^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2344; calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2156; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0711; calcd for $C_9H_{10}NO$ 148.0762, found 148.0760; calcd for C_7H_5O 105.0340, found 105.0336; calcd for $C_5H_{12}N$ 86.0970, found 86.0968; calcd for C_6H_5 77.0391, found 77.0391. $C_{19}H_{30}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.58; H, 9.10; N, 8.22.

***N*-(*N*-Benzoyloxycarbonyl-L-valyl)-α,α-dimethyl-L-β-homoleucinol (55) and *N*-(*N*-benzoyloxycarbonyl-L-valyl)-α,α-dimethyl-D-β-homoleucinol (56).** Obtained by reduction of the peptide aldehyde **46** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 85 : 15), affording compounds **55** (46%) and **56** (32%).

Product ***55***. Amorphous solid; $[\alpha]_D$ +2 (*c* 0.21 in $CHCl_3$); ν_{max}/cm^{-1} 3425, 1718, 1653, 1506; δ_H (500 MHz, $CDCl_3$) 0.61 (3H, s, 2-Me_a), 0.86 (3H, d, *J* = 6.3 Hz, 5-Me_a), 0.91 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.94 (3H, d, *J* = 6.9 Hz, 3′-Me_a), 0.97 (3H, d, *J* = 6.9 Hz, 3′-H_b), 0.98 (3H, s, 2-Me_b), 1.24–1.30 (2H, m, 4-H_2), 1.55 (1H, m, 5-H), 2.11 (1H, m, 3′-H), 2.95 (1H, d, *J* = 11.9 Hz, 1-H_a), 3.23 (1H, d, *J* = 11.7 Hz, 1-H_b), 3.87–3.95 (2H, m, 3-H + 2′-H), 5.07 (1H, d, *J* = 12.0 Hz, OCH_aPh), 5.12 (1H, d, *J* = 12.3 Hz, OCH_bPh), 5.40 (1H, d, *J* = 8.8 Hz, NH), 6.10 (1H, d, *J* = 9.5 Hz, NH), 7.31–7.37 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 17.9 (CH_3), 18.5 (CH_3), 19.4 (CH_3), 21.0 (CH_3), 23.1 (CH_3), 24.0 (CH_3), 25.3 (CH), 30.2 (CH), 38.2 (CH_2), 38.9 (C), 51.5 (CH), 61.1 (CH), 67.1 (CH_2), 70.0 (CH_2), 128.0 (2 × CH), 128.2 (CH), 128.6 (2 × CH), 136.1 (C), 156.6 (C), 172.8 (C); *m*/*z* 393 (M^+ + H, 1%), 319 (9, M^+ − $C(Me)_2$-CHO), 234 (14, M^+ − $NHCH(CH_2CHMe_2)$-$C(Me)_2$-CH_2OH), 108 (18, $[PhCH_2OH]^+$), 91 (100, $[PhCH_2]^+$), 86 (29, $[NH_2{=}CHCH_2CH(Me)_2]^+$). HRMS calcd for $C_{22}H_{37}N_2O_4$ 393.2753, found 393.2749; calcd for $C_{18}H_{27}N_2O_3$ 319.2022, found 319.2015; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1130; calcd for C_7H_8O 108.0575, found 108.0574; calcd for C_7H_7 91.0548, found 91.0549; calcd for $C_5H_{12}N$ 86.0970, found 86.0967. $C_{22}H_{36}N_2O_4$ requires C, 67.32; H, 9.24; N, 7.14%. Found: C, 67.34; H, 8.98; N, 7.29.

Product ***56***. Amorphous solid; $[\alpha]_D$ −30 (*c* 0.26 in $CHCl_3$); ν_{max}/cm^{-1} 3422, 1715, 1653, 1520, 1506; δ_H (500 MHz, $CDCl_3$) 0.63 (3H, s, 2-Me_a), 0.83 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.89 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.92 (3H, d, *J* = 6.6 Hz, 3′-Me_a), 0.99 (3H, d, *J* = 6.9 Hz, 3′-H_b), 1.00 (3H, s, 2-Me_b), 1.23–1.30 (2H, m, 4-H_2), 1.50 (1H, m, 5-H), 2.21 (1H, m, 3′-H), 3.01 (1H, br d, *J* = 11.5 Hz, 1-H_a), 3.34 (1H, br d, *J* = 12.0 Hz, 1-H_b), 3.89 (1H, m, 3-H), 3.96 (1H, m, 2′-H), 5.08 (1H, d, *J* = 12.3 Hz, OCH_aPh), 5.13 (1H, d, *J* = 12.3 Hz, OCH_bPh), 5.27 (1H, br b, NH), 6.03 (1H, br d, *J* = 8.8 Hz, NH), 7.32–7.38 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 17.7 (CH_3), 18.7 (CH_3), 19.5 (CH_3), 21.1 (CH_3), 23.1 (CH_3), 23.9 (CH_3), 25.2 (CH), 30.0 (CH), 38.3 (CH_2), 38.8 (C), 51.6 (CH), 61.0 (CH), 67.2 (CH_2), 70.0 (CH_2), 128.1 (2 × CH), 128.3 (CH), 128.6 (2 × CH), 136.0 (C), 156.5 (C), 172.4 (C); *m*/*z* 393 (M^+ + H, 1%), 319 (12, M^+ – $C(Me)_2$-CHO), 234 (20, M^+ − NHCH (CH_2CHMe_2)-$C(Me)_2$-CH_2OH), 91 (100, $[PhCH_2]^+$), 86 (21, $[NH_2{=}CHCH_2CH(Me)_2]^+$). HRMS calcd for $C_{22}H_{37}N_2O_4$ 393.2753, found 393.2743; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1138; calcd for C_7H_7 91.0548, found 91.0544; calcd for $C_5H_{12}N$ 86.0970, found 86.0967. $C_{22}H_{36}N_2O_4$ requires C, 67.32; H, 9.24; N, 7.14%. Found: C, 67.37; H, 9.13; N, 7.18.

General procedure for the reduction of the β-amino esters to the β-amino aldehydes

A solution of the β-amino ester (0.2 mmol) in methanol (8 mL), was cooled to −78 °C and DIBAL-H was added (1 M solution in dichloromethane, 2 mL, 2 mmol). The reaction mixture was stirred for 6 h; then the solution was poured into a saturated solution of Rochelle's salt and extracted with CH_2Cl_2. The organic layer was dried on anhydrous sodium sulfate, filtered and evaporated under vacuum. The residue was purified by column chromatography (hexanes–EtOAc) to give the β-amino aldehydes.

General procedure for the reduction of the β-amino esters to the γ-amino alcohols

A solution of the β-amino ester (0.2 mmol) in methanol (8 mL), was cooled to 0 °C; then DIBAL-H was added (1 M solution in dichloromethane, 2 mL, 2 mmol; except in the case of substrate **57**, where 0.6 mmol of the reducing agent were used). The reaction mixture was stirred for 3 h at 0 °C, and then was extracted, evaporated and purified as before to give the γ-amino alcohols.

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