Highly Stereoselective Conversion of Aryl Peptidyl Ketones into the Corresponding Peptide Alcohols

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In this paper we describe the conversion of aryl peptidyl ketones, by a hydride reduction, into the corresponding peptide alcohols. The developed methodology is highly stereoselective and represents a very important application in peptide chemistry for obtaining peptide alcohols. It provides peptide alcohols with definite stereochemistry and in moderate, but satisfactory, yields. The reducing procedure, performed with $NaBH_3CN$ and $TiCl_4$, probably proceeds via two diastereomeric cyclic intermediates that show different reactivity. The stereochemistry of the resulting alcohols was established after obtaining them by an alternative synthetic procedure. Furthermore, the methodology adopted keeps the urethane protecting group on the amino function of the N-terminal amino acid residue.

Introduction

Peptide alcohols are important synthetic intermediates of biologically and pharmaceutically active molecules.[1−5] Peptaibols, peptide analogues characterized by the presence of an alcoholic function at the C-terminal residue of the peptide chain, are receiving considerable attention because of their significant activity as antibiotics.[6−9] Peptide alcohols also serve as key synthetic precursors for a number of peptide aldehydes that are biologically active as enzymatic inhibitors.[10−13] Due to their importance in biology the stereoselective synthesis of peptide alcohols has become a goal for many research groups.[14,15] In the peptide alcohols, the stereochemistry of the carbon atom could be the key to their molecular activity, so stereochemical control in the synthesis of peptide alcohols is an important challenge in peptide chemistry and pharmacological research.

We report here a convenient and highly stereoselective synthesis of a class of peptide alcohols by hydride reduction of precursor aryl peptidyl ketones. The proposed procedure represents, in peptide chemistry, an interesting synthetic tool to obtain peptide alcohols with definite stereochemistry starting from peptide systems characterized by epimerization problems. A synthetic route to aryl peptidyl ketones is the acylation of aromatic substrates with *N*-protected amino acid derivatives. The perfect stereochemical control of the acylation reaction provides peptidyl ketones in which the configuration of the asymmetric centres is preserved.[16]

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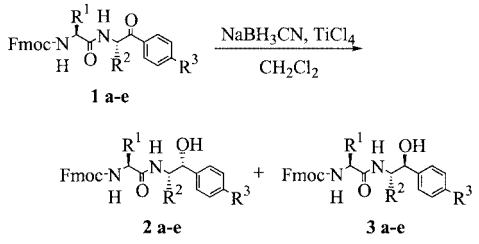
Results and Discussion

The aim of this work was the development of a stereoselective procedure to convert the carbonyl function of aryl peptidyl ketones into the alcohol function of peptide alcohols. For this purpose we prepared simple peptidyl ketones **1a**−**e**, made up of two amino acid residues, and studied their reduction by readily accessible reagents. In particular, the dipeptidyl ketone *N*-Fmoc-L-Ala-L-Ala-$C_6H_4CH_3$ (**1a**) was chosen as a model system to investigate the reduction reaction.

Reduction of the dipeptide **1a** with an excess of $LiAlH_4$ in dry THF provided two diastereomeric peptide alcohols **2a** and **3a** in a 1:1 molar ratio, characterized by the opposite configuration of the carbinol carbon atom. Under these conditions a preferential attack by the nucleophile on one of the two faces of the carbonyl group did not occur. However, the Fmoc group on the amino function was not affected by $LiAlH_4$, and side products due to the removal of the Fmoc group were not observed. The removal of the Fmoc group by $LiAlH_4$, under the conditions mentioned above, proceeds slowly, as confirmed by treating the *N*-Fmoc-L-valine methyl ester **4** with $LiAlH_4$. The reaction of **4** with an excess of $LiAlH_4$ in dry THF at room temperature for 17 h afforded, after work up and purification of the crude product by short column chromatography, *N*-Fmoc-L-valinol (**5**) in 84% yield, a small quantity of the starting material (5%) and traces of dibenzofulvene resulting from the removal of the Fmoc group under basic conditions. This experiment showed that the Fmoc group is not significantly affected by this kind of hydride reducing reagent.

In an additional experiment the dipeptide **1a** was treated with $NaBH_3CN$ in a methanol solution at pH = 3 using

methyl orange as indicator to monitor the change in pH. This reduction reaction gave the conversion of 81% of the starting ketone **1a** into the corresponding diastereomeric alcohols **2a** and **3a**, which were recovered by short column chromatography in the molar ratio 1:1. In light of the results obtained, the formation of chelate intermediates was attempted in order to achieve stereocontrol of the reduction process. With this result in mind the reduction reaction of **1a** was performed using titanium tetrachloride as the chelating agent and dichloromethane as the solvent. The reaction showed a different course; in fact, only about 50% of **1a** was converted into the corresponding diastereomeric alcohols **2a** and **3a** (Scheme 1).



Scheme 1

Moreover, the reaction was highly diastereoselective and the separation of the product mixture by short column chromatography afforded the two diastereomeric alcohols (**2a** and **3a**) in 47 and 2% yields, respectively (Scheme 1, Table 1).

Table 1. Synthesis of dipeptide alcohols **2a**−**e** and **3a**−**e**

	R^1	R^2	R^3	**2**[a]	**3**[a]
a	CH_3	CH_3	CH_3	47	2
b	$CH_3CH_2(CH_3)CH$	CH_3	CH_3	45	2
c	CH_3	$(CH_3)_2CH$	CH_3	47	1
d	CH_3	CH_3	H	45	2
e	$CH_3CH_2(CH_3)CH$	CH_3	H	46	2

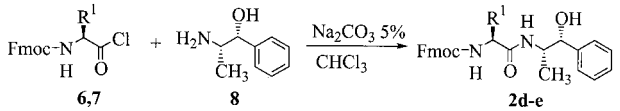
[a] Isolated yield (%).

In a further experiment the same reaction was performed at room temperature for 48 h with the aim of increasing the conversion of the starting ketone into the corresponding alcohol. The conversion of the starting material was still low. In fact, 45% of the peptidyl ketone **1a** was recovered unchanged by short column chromatography.

The diastereomers obtained from reduction of **1a** could be distinguished by ^{1}H NMR spectroscopy. For example the protons on the carbinol carbon atoms of **2a** and **3a** gave distinct signals at δ = 4.47 and 4.54 ppm in the ^{1}H NMR spectrum of the crude reaction product. The relative ratio of the diastereomers **2a** and **3a** was also determined by integration of these two ^{1}H NMR signals.

The reduction reaction was also extended to other systems. The aryl peptidyl ketones **1b**−**e** were treated with $NaBH_3CN$ and $TiCl_4$ under the same conditions as **1a** and afforded the corresponding peptide alcohols **2b**−**e** and **3b**−**e** with high stereoselectivity (Scheme 1, Table 1).

However, the ^{1}H NMR spectral differences could not be used to assign the exact stereochemistry of the new stereogenic centre generated in the reduction of the carbonyl function. It is very important to be able to assign the stereochemistry of the reduction reaction unambiguously, therefore we planned an alternative synthesis of the diastereomeric dipeptide alcohol **2d** resulting from the reduction of the dipeptidyl ketone **1d** and characterized by a definite configuration of the carbinol carbon atom (1*R*). The target dipeptide alcohol was obtained by treating *N*-Fmoc-L-alanine chloride (**6**) with (1*R*,2*S*)-norephedrine (**8**). In this way the configurations of the norephedrine asymmetric carbon atoms are unchanged (Scheme 2, Table 2).



6: $R^1 = CH_3$

7: $R^1 = CH_3CH_2(CH_3)CH$

Scheme 2

Table 2. Alternative synthesis of dipeptide alcohols **2d**−**e**

	R^1	**2**[a]
d	CH_3	85
e	$CH_3CH_2(CH_3)CH$	91

[a] Isolated yield (%).

TLC analysis of the reaction mixture showed the formation of the target dipeptidyl alcohol **2d**, which corresponded perfectly to that obtained, as the major product, by reduction of the peptidyl ketone **1d**. Furthermore, the ^{1}H NMR spectra of the two peptide alcohols, obtained by independent methods, are exactly alike. This result led us to the conclusion that reduction of the peptidyl ketone **1d** affords the corresponding alcohol **2d** as the major product.

Based on the results with ketone **1d**, we inferred that the reduction of the dipeptidyl ketones **1a**−**e** gave the corresponding alcohols **2a**−**e** with high stereoselectivity. The diastereomers **3a**−**e** were obtained in trace amounts with yields lower than 5%. As a further confirmation of the stereochemical assignments the dipeptide alcohol **2e** was also prepared in an alternative way by treating *N*-Fmoc-L-isoleucine chloride (**7**) with (1*R*,2*S*)-norephedrine (**8**; Scheme 2, Table 2). In this case also the TLC analysis and ^{1}H NMR spectrum of the obtained product are identical to those of the major product formed by the reduction of the dipeptidyl ketone **1e** with $NaBH_3CN$ and $TiCl_4$.

This reduction reaction is characterized by an incomplete conversion of the starting ketone into the corresponding alcohol and a high diastereoselectivity. The conversion of the starting material into the dipeptide alcohol did not improve with increased reaction times. The diastereoselectivity can be explained by the diastereomeric cyclic intermediates **A** and **B**, formed from starting material and $TiCl_4$. We pro-

pose that $TiCl_4$ coordinates to the amide nitrogen atom and the carbonyl oxygen atom of the aryl peptidyl ketone, forming the intermediates **A** and **B** in an equimolar ratio (Figure 1).

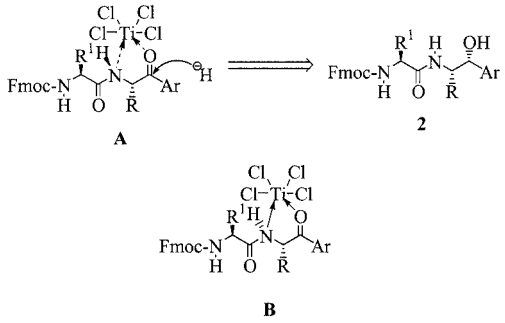


Figure 1. Diastereomeric cyclic intermediates **A** and **B** formed from acryl peptidyl ketones and $TiCl_4$

For chelate **A**, hydride attack on the accessible face of the carbonyl group produces the major diastereomer **2**, characterized by the (*R*) configuration of the carbinol carbon atom. For chelate **B**, both faces of the carbonyl groups are sterically blocked by the group containing titanium and by the substituent at the α-position. Therefore, chelate **A** appears to be the reactive intermediate.

The proposed model explains the reaction yields, which are about 50% for all used systems, and the high stereoselectivity as well.

Conclusion

The reduction of aryl peptidyl ketones represents a general method for the preparation of aryl peptide alcohols. The reduction reaction, performed using $NaBH_3CN/TiCl_4$ as the reagent system, shows a remarkably high stereoselectivity. These results suggest that chelation of the ketone oxygen atom and the amide nitrogen atom to titanium tetrachloride is the key to the stereochemical control. Our results also show that, under the reaction conditions used, the peptide alcohols obtained keep the Fmoc protecting group on the amino function. The most important aspect of the proposed methodology is the highly stereoselective formation of peptide alcohols using modified peptide systems as starting materials.

Experimental Section

General Remarks: All solvents were purified and dried by standard procedures and distilled prior to use. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained using KBr pellets. ^1H NMR spectra were recorded with a Bruker Avance 300 instrument at 300 MHz. Unless otherwise indicated, [D_6]DMSO was used as the NMR solvent. Mass spectra were recorded with a Vacuum Generators ZAB-2F spectrometer, using 3-nitrobenzyl alcohol as matrix, by fast-atom bombardment (FAB^+ MS), with a neutral Xenon beam operating at 8 keV and a total current of 10 μA. Reaction mixtures were monitored by TLC using silica gel 60-F_{254} precoated glass plates. Short column flash chromatography (SCFC) was performed on Kieselgel 60 H without gypsum. When required, the reactions were carried out under N_2.

Synthesis of 2a−e and 3a−e with $NaBH_3CN/TiCl_4$: A 1 M solution of $TiCl_4$ in CH_2Cl_2 (2 mmol, 2 mL) and a 1 M methanol solution of $NaBH_3CN$ (6 mmol, 6 mL) were added to a magnetically stirred solution of the dipeptide **1a−e** (2 mmol) in dry CH_2Cl_2 (5 mL). The resulting reaction mixture was maintained at room temperature and under N_2 for 20−24 h. A 2 N NaOH solution was added and the basified solution was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and the solvents evaporated under vacuum. Subsequent chromatographic purification (chloroform/methanol, 98:2 v/v) afforded the corresponding alcohols **2a−e** (45−47%) and **3a−e** (1−2%).

2a: White solid (47% yield), m.p. 166−170 °C. IR (KBr): ν̃= 3310, 3061, 2978, 1685, 1654, 1559, 1254, 759, 739 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 0.97 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCHOH), 1.03 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCONH), 2.25 (s, 3 H, C*H*$_3$C$_6$H$_4$), 3.80−4.05 (m, 2 H, C*H*CH$_2$O and C*H*CHOH), 4.13−4.30 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.47 (dd, *J* = 4.6 and *J* = 5.1 Hz, 1 H, C*H*OH), 5.37 (d, *J* = 4.6 Hz, 1 H, O*H*), 7.03−7.98 (m, 14 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 459 (13) $[M + H]^+$, 441 (20), 338 (9), 281 (6), 221 (5), 179 (100), 178 (48), 165 (33), 164 (15). $C_{28}H_{30}N_2O_4$ (458.2): calcd. C 73.34, H 6.59, N 6.11; found C 73.31, H 6.61, N 6.13.

3a: White solid (2% yield), m.p. 187−191 °C. IR (KBr): ν̃= 3312, 3060, 2977, 1673, 1652, 1560, 1262, 760, 741 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 0.99 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CHCHOH), 1.06 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCONH), 2.23 (s, 3 H, C*H*$_3$CHCONH), 3.81−4.05 (m, 2 H, C*H*$_3$C$_6$H$_4$), 4.14−4.32 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.54 (dd, *J* = 4.1 and *J* = 4.6 Hz, 1 H, C*H*OH), 5.42 (d, *J* = 4.1 Hz, 1 H, O*H*), 7.04−7.98 (m, 14 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB^-MS (+, NBA): *m*/*z* (%) = 459 (15) $[M + H]^+$, 441 (25), 338 (7), 281 (5), 221 (6), 179 (100), 178 (46), 165 (32), 164 (17). $C_{28}H_{30}N_2O_4$ (458.2): calcd. C 73.34, H 6.59, N 6.11; found C 73.32, H 6.61, N 6.12.

2b: White solid (45% yield), m.p. 193−196 °C. IR (KBr): ν̃= 3313, 3059, 2976, 1681, 1657, 1557, 1250, 760, 740 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 0.66 [d, *J* = 6.1 Hz, 3 H, CH$_3$CH$_2$(C*H*$_3$)CH], 0.74 [dd, *J* = 6.9 and *J* = 7.8 Hz, 3 H, C*H*$_3$CH$_2$(CH$_3$)CH], 0.97 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CHCHOH), 1.19−1.30 [m, 2 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.60 [m, 1 H, CH$_3$CH$_2$(CH$_3$)C*H*], 2.25 (s, 3 H, C*H*$_3$C$_6$H$_4$), 3.83 (dd, *J* = 7.8 and *J* = 8.6 Hz, 1 H, C*H*CH$_2$O), 3.95 (m, 1 H, C*H*CHOH), 4.15−4.36 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.47 (dd, *J* = 4.3 and *J* = 5.2 Hz, 1 H, C*H*OH), 5.30 (d, *J* = 4.3 Hz, 1 H, O*H*), 7.01−7.92 (m, 14 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 501 (18) $[M + H]^+$, 483 (31), 380 (8), 279 (6), 179 (100), 178 (58), 165 (13), 164 (8). $C_{31}H_{36}N_2O_4$ (500.3): calcd. C 74.37, H 7.25, N 5.60; found C 74.34, H 7.27, N 5.61.

3b: White solid (2% yield), m.p. 180−182 °C. IR (KBr): ν̃= 3311, 3060, 2980, 1683, 1657, 1555, 1250, 759, 740 cm^{-1}. ^1H NMR: δ = 0.67 [d, *J* = 6.3 Hz, 3 H, CH$_3$CH$_2$(C*H*$_3$)CH], 0.78 [dd, *J* = 6.8 and *J* = 7.6 Hz, 3 H, C*H*$_3$CH$_2$(CH$_3$)CH], 0.99 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CHCHOH), 1.20−1.27 [m, 2 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.61 [m, 1 H, CH$_3$CH$_2$(CH$_3$)C*H*], 2.23 (s, 3 H, C*H*$_3$C$_6$H$_4$), 3.83 (dd, *J* = 7.7 and *J* = 8.7 Hz, 1 H, C*H*CH$_2$O), 3.95 (m, 1 H, C*H*CHOH), 4.15−4.36 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.52 (dd, *J* = 4.3 and *J* = 4.7 Hz, 1 H, C*H*OH), 5.41 (d, *J* = 4.3 Hz, 1 H, O*H*), 7.02−7.95 (m, 14 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm.

FAB-MS (+, NBA): *m*/*z* (%) = 501 (23) [M + H]$^+$, 483 (27), 380 (10), 279 (5), 179 (100), 178 (67), 165 (22), 164 (12). $C_{31}H_{36}N_2O_4$ (500.3): calcd. C 74.37, H 7.25, N 5.60; found C 74.33, H 7.27, N 5.62.

2c: White solid (47% yield), m.p. 168−171 °C. IR (KBr): ṽ= 3316, 3060, 2958, 1689, 1654, 1559, 1251, 760, 738 cm^{-1}. ^{1}H NMR: δ = 0.80 [d, *J* = 6.8 Hz, 6 H, (C*H*$_3$)$_2$CH], 0.90 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CH), 2.10 [m, 1 H, (CH$_3$)$_2$C*H*], 2.25 (s, 3 H, C*H*$_3$C$_6$H$_4$), 3.85−3.92 (m, 2 H, C*H*CH$_2$O and C*H*CONH), 4.10−4.30 (m, 3 H, C*H*CHOH and CHC*H*$_2$O), 4.34 (dd, *J* = 4.1 and *J* = 5.3 Hz, 1 H, C*H*OH), 5.28 (d, *J* = 4.1 Hz, 1 H, O*H*), 7.02−7.94 (m, 14 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 487 (11) [M + H]$^+$, 469 (30), 366 (10), 276 (6), 179 (100), 178 (69), 165 (32), 164 (14). $C_{30}H_{34}N_2O_4$ (486.3): calcd. C 74.05, H 7.04, N 5.76; found C 74.02, H 7.06, N 5.77.

3c: White solid (1% yield), m.p. 178−180 °C. IR (KBr): ṽ= 3313, 3065, 2964, 1687, 1650, 1558, 1245, 762, 739 cm^{-1}. ^{1}H NMR: δ = 0.82 [d, *J* = 6.8 Hz, 6 H, (C*H*$_3$)$_2$CH], 0.93 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CH), 2.14 [m, 1 H, (CH$_3$)$_2$C*H*], 2.24 (s, 3 H, C*H*$_3$C$_6$H$_4$), 3.84−3.92 (m, 2 H, C*H*CH$_2$O and C*H*CONH), 4.13−4.31 (m, 3 H, C*H*CHOH and CHC*H*$_2$O), 4.39 (dd, *J* = 4.0 and *J* = 5.7 Hz, 1 H, C*H*OH), 5.37 (d, *J* = 4.0 Hz, 1 H, O*H*), 7.02−7.94 (m, 14 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 487 (10) [M + H]$^+$, 469 (35), 366 (8), 276 (5), 179 (100), 178 (77), 165 (46), 164 (18). $C_{30}H_{34}N_2O_4$ (486.3): calcd. C 74.05, H 7.04, N 5.76; found C 74.02, H 7.06, N 5.77.

2d: White solid (45% yield), m.p. 181−183 °C. IR (KBr): ṽ= 3313, 3060, 2981, 1686, 1653, 1557, 1258, 761, 738 cm^{-1}. ^{1}H NMR: δ = 1.01 (d, *J* = 6.8 Hz, 6 H, C*H*$_3$CHCONH and C*H*$_3$CHCHOH), 3.91−4.08 (m, 2 H, C*H*CH$_2$O and C*H*CHOH), 4.17−4.28 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.50 (dd, *J* = 4.9 and *J* = 5.0 Hz, 1 H, C*H*OH), 5.46 (d, *J* = 4.9 Hz, 1 H, O*H*), 7.19−7.94 (m, 15 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 445 (26) [M + H]$^+$, 427 (31), 338 (8), 267 (4), 207 (3), 179 (100), 178 (63), 165 (29), 164 (14). $C_{27}H_{28}N_2O_4$ (444.2): calcd. C 72.95, H 6.35, N 6.30; found C 72.93, H 6.36, N 6.31.

3d: White solid (2% yield), m.p. 175−177 °C. IR (KBr): ṽ= 3318, 3063, 2984, 1690, 1655, 1555, 1252, 760, 738 cm^{-1}. ^{1}H NMR: δ = 1.02 (d, *J* = 6.8 Hz, 6 H, C*H*$_3$CHCONH and C*H*$_3$CHCHOH), 3.89−4.07 (m, 2 H, C*H*CH$_2$O and C*H*CHOH), 4.18−4.30 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.55 (dd, *J* = 4.6 and *J* = 5.4 Hz, 1 H, C*H*OH), 5.54 (d, *J* = 4.6 Hz, 1 H, O*H*), 7.21−7.95 (m, 15 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 445 (22) [M + H]$^+$, 427 (33), 338 (6), 267 (4), 207 (4), 179 (100), 178 (60), 165 (31), 164 (12). $C_{27}H_{28}N_2O_4$ (444.2): calcd. C 72.95, H 6.35, N 6.30; found C 72.93, H 6.36, N 6.31.

2e: White solid (46% yield), m.p. 190−192 °C. IR (KBr): ṽ= 3312 cm^{-1}, 3060, 2983, 1687, 1654, 1559, 1251, 760, 738 cm^{-1}. ^{1}H NMR: δ = 0.63 [d, *J* = 6.8 Hz, 3 H, CH$_3$CH$_2$(C*H*$_3$)CH], 0.74 [dd, *J* = 6.8 and *J* = 7.8 Hz, 3 H, C*H*$_3$CH$_2$(CH$_3$)CH], 0.99 (d, *J* = 5.9 Hz, 3 H, C*H*$_3$CHCHOH), 1.18−1.30 [m, 2 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.59 [m, 1 H, CH$_3$CH$_2$(CH$_3$)C*H*], 3.82 (dd, *J* = 7.8 and *J* = 8.7 Hz, 1 H, C*H*CH$_2$O), 3.97 (m, 1 H, C*H*CHOH), 4.19−4.35 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.52 (dd, *J* = 3.9 and *J* = 4.8 Hz, 1 H, C*H*OH), 5.40 (d, *J* = 3.9 Hz, 1 H, O*H*), 7.18−7.93 (m, 15 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 487 (25) [M + H]$^+$, 469 (19), 380 (11), 279 (6), 179 (100), 178 (63), 165 (28), 164 (14). $C_{30}H_{34}N_2O_4$ (486.3): calcd. C 74.05, H 7.04, N 5.76; found C 74.01, H 7.06, N 5.77.

3e: White solid (2% yield), m.p. 175−177 °C. IR (KBr): ṽ= 3311, 3058, 2985, 1685, 1659, 1562, 1257, 761, 739 cm^{-1}. ^{1}H NMR: δ = 0.66 (d, *J* = 6.8 Hz, 3 H, CH$_3$CH$_2$(C*H*$_3$)CH], 0.76 [dd, *J* = 6.8 and *J* = 7.8 Hz, 3 H, C*H*$_3$CH$_2$(CH$_3$)CH], 0.98 (d, *J* = 5.9 Hz, 3 H, C*H*$_3$CHCHOH), 1.20−1.31 (m, 2 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.57 [m, 1 H, CH$_3$CH$_2$(CH$_3$)C*H*], 3.80 (dd, *J* = 7.8 and *J* = 8.7 Hz, 1 H, C*H*CH$_2$O), 4.01 (m, 1 H, C*H*CHOH), 4.19−4.32 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 4.58 (dd, *J* = 4.3 and *J* = 5.0 Hz, 1 H, C*H*OH), 5.40 (d, *J* = 4.3 Hz, 1 H, O*H*), 7.17−7.93 (m, 15 H, CON*H*CHCHOH, FmocN*H* and Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 487 (21) [M + H]$^+$, 469 (15), 380 (10), 279 (6), 179 (100), 178 (73), 165 (32), 164 (12). $C_{30}H_{34}N_2O_4$ (486.3): calcd. C 74.05, H 7.04, N 5.76; found C 74.01, H 7.06, N 5.77.

Alternative Synthesis of 2d−e: (1*R*,2*S*)-Norephedrine (1 mmol) in an aqueous 5% solution of Na_2CO_3 (5 mL) was added to a solution of *N*-Fmoc-L-alanine chloride (**6**; 1 mmol) or *N*-Fmoc-L-isoleucine chloride (**7**; 1 mmol) in ethanol-free chloroform (10 mL). The resulting mixture was stirred at room temperature for 1 h, and then HCl (1 N) was added. The chloroform layer was separated and the acidified aqueous solution was extracted with two additional portions of chloroform (2 × 5 mL). The combined chloroform extracts were washed with brine, dried with Na_2SO_4 and the solvents evaporated under vacuum to afford the corresponding aryl peptide alcohols **2d−e** in 84−88% yields. The compound characterization data for **2d−e** are identical to those obtained with the $NaBH_3CN$/$TiCl_4$ procedure.

Synthesis of Aryl Peptidyl Ketones 1a−e: Aryl peptidyl ketones **1a−c** were synthesised as reported in the literature.[16] Peptides **1d**,**e** were obtained as follows: $AlCl_3$ (3 mmol) was added to a magnetically stirred solution of *N*-Fmoc-L-alanine chloride (1 mmol) in dry benzene (15 mL). The reaction mixture was maintained at room temperature under N_2 for 5 h. HCl (1 N) was added, and the acidified solution was extracted with diethyl ether (3 × 10 mL). The aqueous phase was basified with saturated aqueous Na_2CO_3. The basic liquors, containing the α-aminoalkyl phenyl ketone, were treated with a solution of *N*-Fmoc-L-alanine chloride (1 mmol) or *N*-Fmoc-L-isoleucine chloride (1 mmol) in ethanol-free chloroform (10 mL). The resulting mixture was stirred at room temperature for 1 h, and then the chloroform layer was separated. The aqueous phase was extracted with three additional portions of chloroform (3 × 10 mL). The combined chloroform extracts were dried with Na_2SO_4 and the solvents evaporated under vacuum to afford the aryl peptidyl ketones in 84−87% yields.

1d: White solid (84% yield), m.p. 125−127 °C. IR (KBr): ṽ= 3294, 3059, 2986, 1719, 1690, 1640, 1549, 1260, 760, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.40 (d, *J* = 7.4 Hz, 6 H, C*H*$_3$CHCONH and C*H*$_3$CHCOC$_6$H$_5$), 4.22 (m, 1 H, C*H*CH$_2$O), 4.39−4.48 (m, 3 H, CHC*H*$_2$O and C*H*CONH), 5.51 (m, 1 H, C*H*COC$_6$H$_5$), 5.64 (d, *J* = 7.4 Hz, 1 H, FmocN*H*), 7.14 (d, *J* = 6.9 Hz, 1 H, CON*H*CHCOC$_6$H$_5$), 7.25−7.95 (m, 13 H, Ar-H) ppm. FAB-MS (+, NBA): *m*/*z* (%) = 443 (35) [M + H]$^+$, 337 (7), 294 (4), 265 (5), 223 (13), 179 (100), 178 (75), 165 (38), 164 (22). $C_{27}H_{26}N_2O_4$ (442.2): calcd. C 73.28, H 5.92, N 6.33; found C 73.25, H 5.93, N 6.34.

1e: White solid (87% yield), m.p. 169−171 °C. IR (KBr): ṽ= 3296, 3060, 2974, 1718, 1687, 1644, 1545, 1258, 762, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.85−0.98 [m, 6 H, C*H*$_3$CH$_2$(C*H*$_3$)CH], 1.22 [m, 1 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.40 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CHCOC$_6$H$_5$), 1.50 [m, 1 H, CH$_3$C*H*$_2$(CH$_3$)CH], 1.89 [m, 1 H, CH$_3$CH$_2$(CH$_3$)C*H*], 4.16−4.25 (m, 2 H, C*H*CH$_2$O and C*H*CONH), 4.39−4.45 (m, 2 H, CHC*H*$_2$O), 5.52 (m, 1 H,

C*H*COC$_6$H$_5$), 5.75 (d, J = 8.6 Hz, 1 H, FmocN*H*), 7.12 (d, J = 7.8 Hz, 1 H, CON*H*CHCOC$_6$H$_5$), 7.22−7.92 (m, 13 H, Ar-H) ppm. FAB-MS (+, NBA): m/z (%) = 485 (31) [M + H]$^+$, 379 (2), 336 (3), 307 (9), 179 (100), 178 (67), 165 (34), 164 (18). Anal. Calcd. For $C_{30}H_{32}N_2O_4$ (484.2): calcd. C 74.36, H 6.66, N 5.78; found C 74.34, H 6.68, N 5.79.

Reduction of Aryl Peptidyl Ketone 1a with LiAlH$_4$: $LiAlH_4$ (3 mmol) was added to a magnetically stirred solution of aryl peptidyl ketone **1a** (1 mmol) in dry THF (10 mL). The resulting reaction mixture was maintained at room temperature under N_2 for 15 min, then 1 N $KHSO_4$ (5 mL) was added. The THF was evaporated under vacuum and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried with Na_2SO_4 and the solvents evaporated under vacuum. Subsequent chromatographic purification (chloroform/methanol, 98:2 v/v) afforded the corresponding alcohols **2a** and **3a** as a 1:1 diastereomeric mixture. The compound characterisation data for **2a** and **3a** are identical to those obtained with the $NaBH_3CN/TiCl_4$ procedure.

Treatment of *N*-Fmoc-valine Methyl Ester (4) with LiAlH$_4$: $LiAlH_4$ (3 mmol) was added to a magnetically stirred solution of *N*-Fmoc-valine methyl ester (1 mmol) in dry THF (10 mL). The resulting reaction mixture was maintained at room temperature and N_2 for 17 h. H_2O (10 mL) was added and the aqueous phase was extracted with diethyl ether (2 × 5 mL). The combined organic extracts were washed with 1 N HCl (1 × 5 mL) then dried with Na_2SO_4 and the solvents evaporated under vacuum. Subsequent chromatographic purification (chloroform/methanol, 95:5 v/v) afforded the corresponding alcohol **5** in 84% yield.

5: White solid (84% yield), m.p. 126−128 °C. IR (KBr): $\tilde{\nu}$= 3466, 3348, 3066, 2965, 1667, 1540, 1273, 763, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.98 [d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 1.03 [d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 1.93 [m, 1 H, *CH*(CH$_3$)$_2$], 3.55 (m, 1 H, C*H*NH), 3.66−3.80 (m, 2 H, C*H*$_2$OH), 4.29 (m, 1 H, C*H*CH$_2$O), 4.42−4.59 (m, 2 H, CHC*H*$_2$O), 5.10 (d, J = 9.2 Hz, 1 H, FmocN*H*), 7.35−7.88 (m, 8 H, Ar-H) ppm. FAB-MS (+, NBA): m/z (%) = 326 (18) [M + H]$^+$, 179 (100), 178 (87), 165 (23), 164 (8). $C_{20}H_{23}NO_3$ (325.2): calcd. C 73.82, H 7.12, N 4.30; found C 73.79, H 7.14, N 4.31.

Reduction of Aryl Peptidyl Ketone 1a with NaBH$_3$CN: $NaBH_3CN$ (1.1 mmol) was added to a magnetically stirred solution of aryl peptidyl ketone **1a** (1 mmol) in dry MeOH (5 mL). A trace of a 1 M ethanol solution of methyl orange was added and 2 M HCl in methanol was added dropwise to maintain the red colour. The resulting reaction mixture was maintained at room temperature under N_2 for 36 h, then the methanol was evaporated in vacuo. Brine was added and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried with Na_2SO_4 and the solvents evaporated in vacuo. The subsequent chromatographic purification (chloroform/methanol, 98:2 v/v) afforded the corresponding alcohols **2a** and **3a** as a 1:1 diastereomeric mixture.

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